Development of Synthetic Transformations Comprising C–H Functionalization and NHC Catalysis to Access Vital Scaffolds via C–C and C–N Bond Formation

by

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10CC15J26016

A thesis submitted to the
Academy of Scientific & Innovative Research
for the award of the degree of
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in
SCIENCE

Under the supervision of
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February 2021

Certificate

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22/02/2021

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(Research Student)

22/02/2021

Dr. Santosh B. Mhaske

(Research Supervisor)

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I, Amol B. Viveki, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC15J26016 hereby undertake that, the thesis entitled "Development of Synthetic Transformations Comprising C–H Functionalization and NHC Catalysis to Access Vital Scaffolds via C–C and C–N Bond Formation" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)".*

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Date : 22/ 02/ 2021
Place : CSIR-NCL, Pune

भारतीय जवान और किसान को समर्पित

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-Amol B. Viveki

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Abbreviations

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

Chemical Notations	
Ac	Acetyl
AcOH	Acetic Acid
ACN	Acetonitrile
Ar	Aryl
APS	Ammonium persulfate
BRSM	Based on recovered starting material
BHT	Butylated hydroxytoluene
CCDC	Cambridge Crystallographic Data centre
$CDCl_3$	Deuterated Chloroform
DCM	Dichloromethane
DCE	Dichloethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
Et	Ethyl
EtOH	Ethanol
EtOAc	Ethyl acetate
LAH	Lithium aluminium hydride
LCMS	Liquid chromatography–mass spectrometry
NBS	N-bromo succinimide
NHC	N-Heterocyclic carbene
Ph	Phenyl

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

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

General information

All reagents and solvents were used as received from commercial sources. All experiments were carried out under argon atmosphere unless otherwise noted. Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for thin layer chromatography (TLC). Visualization of the developed TLC plate was performed by irradiation with UV light. Column chromatographic purifications were carried out on flash silica gel (240−400 mesh) using petroleum ether and ethyl acetate or DCM and acetone as eluents unless otherwise noted. The ^{1}H, ^{13}C NMR spectra were recorded on 200/400/500 MHz, and 100/125 MHz NMR spectrometers, respectively in $CDCl_3$/DMSO-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. Infrared spectra were scanned on Bruker ALPHA spectrometer with sodium chloride optics and are measured in cm^{-1}.

Synopsis Report

AcSIR	**Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry**
Name of the Candidate	Amol Basagonda Viveki
Degree Enrollment No. & Date	Ph. D. in Chemical Sciences (10CC15J26016); January 2015
Laboratory	CSIR-National Chemical Laboratory, Pune
Title of the Thesis	Development of Synthetic Transformations Comprising C–H Functionalization and NHC Catalysis to Access Vital Scaffolds via C–C and C–N Bond Formation
Research Supervisor	Dr. Santosh B. Mhaske (AcSIR, CSIR-NCL, Pune)

Introduction: The present thesis describes the novel method developments involving metal-catalyzed C–H functionalization and *N*-heterocyclic carbene (NHC) catalysis to access biologically important scaffolds via C–C and C–N bond formation. The thesis also demonstrates our efforts to extend the developed methods towards the synthesis of natural products. The thesis is divided into three chapters. The first two chapters are based on the transition-metal-catalyzed C–H functionalization and the third chapter deals with the utilization of NHC based organocatalysis. Chapter 1 deals with the transition-metal-catalyzed C–H activation strategy for accessing novel bioactive scaffolds and our attempts to apply this concept in the synthesis of alkaloid natural products. It is divided into two sections. The first section describes the functionalization of unmasked quinazolinones with terminal alkynes utilizing Ruthenium catalysis to access new alkenylated quinazolinone products. The same protocol has been also extended by employing electron-deficient phenylacetylenes for the alkenylation followed by tandem hydroamidation of the newly generated *trans*-double bond to furnish novel quinazolinone alkaloids related to the Luotonine class of natural products. The second section covers the study towards the synthesis of Crispine and related natural alkaloids utilizing Palladium-catalyzed intramolecular tandem olefin amidation/C–H activation protocol. Chapter 2 encompasses the Copper-catalyzed *para*-selective C(sp^2)–H amidation/dimerization of anilides via a radical pathway. The radical pathway of the developed protocol was established by control experiments. Chapter 3 deals with the utilizati-

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on of NHC as a organocatalyst for the synthesis of biologically important scaffolds and study towards the synthesis of natural products. Chapter 3 is further divided into two sections. The first section describes the study towards the total synthesis of Coneicine utilizing NHC-catalyzed Stetter reaction. The second section deals with NHC-catalyzed, substrate selective synthesis of varyingly substituted isomaleimides and maleimides. An unusual reactivity of the α,β-unsaturated aldehyde provides a facile access to commercially important five membered imide heterocycles. Extension of this newly developed protocol towards the synthesis of natural product has been also studied.

Statement of the problem: Construction of bioactive scaffolds utilizing an atom and step economical processes is always in demand in organic synthesis and pharmaceuticals. We planned to exploit two of the most popular and contemporary synthetic tools viz C–H functionalization and NHC-catalysis to achieve this goal. Utilization of an inherent directing group for C–H functionalization avoids additional steps for installing and removing the directing group, which makes the process short and economically viable. In light of this, we aimed to develop a strategy for the late-stage derivatization of important bioactive scaffolds containing the inherent directing group utilizing the transition-metal-catalyzed C–H functionalization process. Additionally, we intended to use NHC catalysis to construct interesting scaffolds via novel processes and explore its application in the synthesis of bioactive natural products.

Methodology and result:

Chapter 1: Amide-Directed Transition-Metal-Catalyzed C–H Activation Protocols and Study of their Application in Natural Product Synthesis

In the recent years, C–H bond activation has become a powerful tool for the synthesis and functionalization of various bioactive molecules, natural products, and pharmaceuticals. The concept of C–H activation has gained significant attention from the synthetic community because it provides direct access and delivers more step and atom-economical paths in the synthesis of complex structures as compared to the traditional organic synthesis. The directing group plays a crucial role in the selective C–H bond activation process since organic molecule contains many hydrogen atoms. We have exploited this concept in the development

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of synthetically important transformantions. This chapter is devided into two sections.

Section 1 describes the Ruthenium-catalyzed regioselective alkenylation/tandem hydroamidative cyclization of unmasked quinazolinones using terminal alkynes. Ruthenium-catalyzed amide directed Csp^2–H activation of the quinazolinone scaffold furnished selective mono- or dialkenylated medicinally important stilbene containing quinazolinones in moderate to good yields (Scheme 1). Such type of quinazonlinone alkaloids containing a *trans*-stilbene moiety have been found to be two-fold more potent than the marketed drug Etoposide in the preliminary test against cancer cell lines. Electron-deficient phenylacetylenes facilitate alkenylation followed by tandem hydroamidation of the newly generated *trans*-double bond to provide novel quinazolinone alkaloids related to the Luotonine class of natural products (Figure 1).

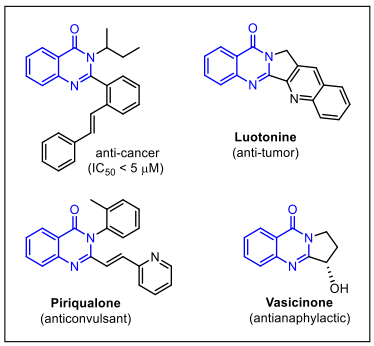
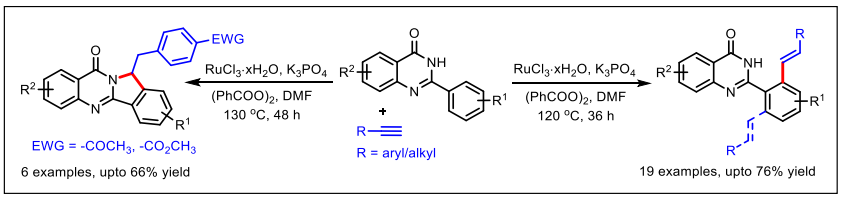


Figure 1. Selected bioactive quinazolinone molecule, drug, and natural products



Scheme 1. Alkenylation/tandem hydroamidative cyclization of quinazolinones

Terminal acetylenes have been utilized for first time in the alkenylation/ diversification of quinazolinones. The protocol provided nineteen new alkenylated and six new Luotonine class of cyclized quinazolinones. This novel protocol would be useful in the late-stage derivatization of bioactive quinazolinones and natural products for SAR studies.

Section 2 demonstrates the effort towards the synthesis of Crispine and related natural products (Figure 2). Metal-catalyzed difunctionalization of unactivated alkenes has gained considerable attention of chemists in the recent years. It is a single-step operation and considered as a powerful and practical strategy for constructing polycyclic ring skeletons. In this context, we have designed retrosynthesis of indolizidine based N-heterocycles considering the utilization of olefin activation with Pd-catalyzed, chelation assisted tandem cyclization strategy (Scheme 2).

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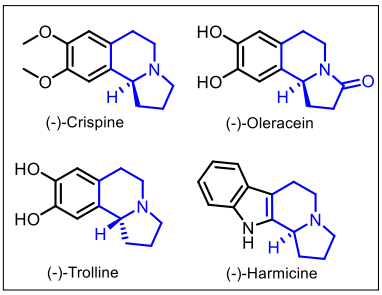
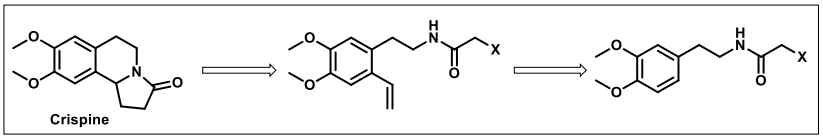
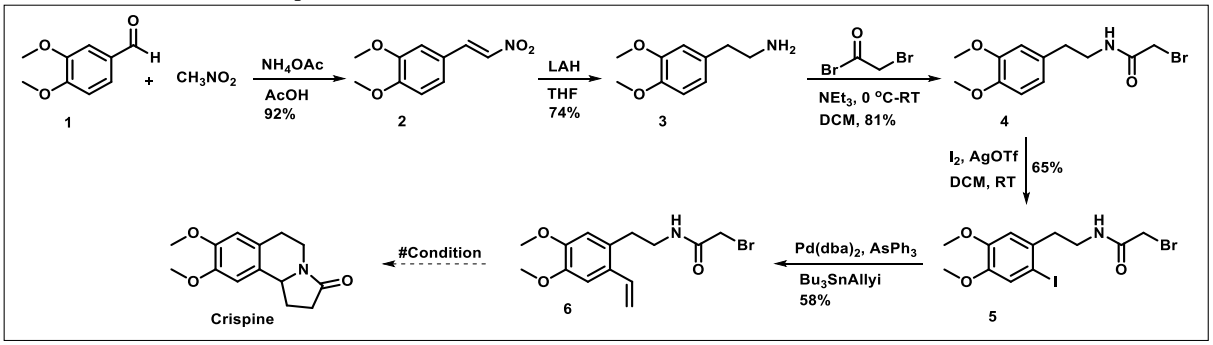


Figure 2. Selected examples of Indolizidine class of natural products



Scheme 2. Retrosynthetic strategy for Crispine natural product



Scheme 3. Synthetic route for the Crispine natural product

Here, we have attempted the synthesis of Crispine natural product utilizing double functionalization of unactivated alkene as a key-step. The alkene compound **6** was synthesized starting from the aldehyde **1** in five steps with good yields. However, we observed the formation of unexpected products when the alkene **6** was subjected to various known and new reaction conditions (Scheme 3). Our next target is to find a suitable condition for the required transformation. Alternately we plan to modify the subsrate to avoid the formation of undesired products. After getting the expected product in hand the process can be generalized for the synthesis of other alkaloids of the same class.

Chapter 2: *para*-Selective Copper-Catalyzed C(sp^2)–H Amidation/Dimerization of Anilides via a Radical Pathway

Chapter 2 describes the detail study of Copper-catalyzed *para*-selective amidation /dimerization of anilides. Single-step distal and regioselective functionalization of C–H bond has gained a considerable importance in the of synthetic organic chemistry, which otherwise requires a multistep process. Earlier approaches utilized the electronic or steric factors to reach at prerequisite position, which were not quite general. Later on, the directing group strategy came into practice, which requires two or more additional steps for installation and removal of the directing group. Hence, the process wherein the functional group itself acts as

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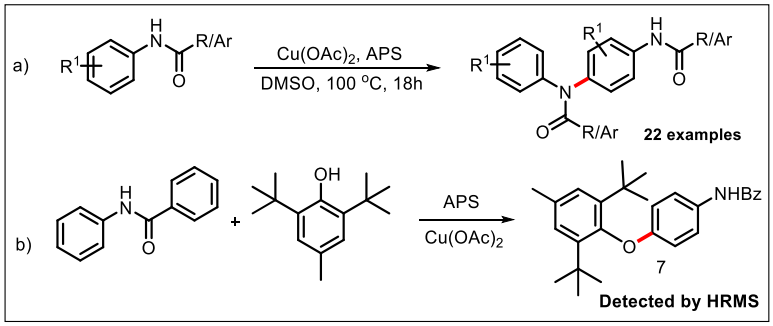
an inheret directing group is considered efficient and atom economical method for C–H functionalization. We have explored the *para*-selective functionalization of anilides via regioselective C(sp^2)–H activation. Copper-catalyzed *para*-selective amidation/dimerization of anilides is accomplished on the anilide aromatic ring via a radical pathway leading to C–N bond formation (Scheme 4). The regioselective amidation has been achieved in the presence of ammonium persulfate as a radical source/oxidant for the Copper catalyst.



Scheme 4: a) *para*-Selective amidation/dimerization of anilides
b) Experimental proof for radical pathway of the reaction

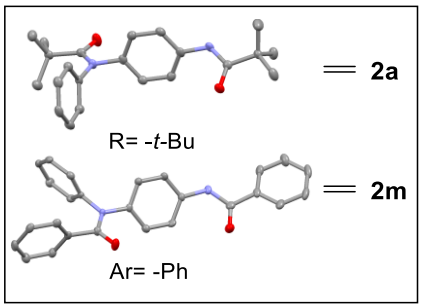


Figure 3: Single-crystal X-ray of **2a** & **2m**

The developed protocol tolerates a wide range of anilide substrates. We have successfully synthesized twenty-two dimerized products utilizing the newly developed protocol. The radical pathway of the reaction was confirmed by the radical quenching experiment, wherein the radical adduct compound **7** was observed with the inhibition of the expected product. The regioselectivity and structure of the product was further confirmed by single-crystal X-ray studies (Figure 3).

Chapter 3: N-Heterocyclic Carbene-Catalyzed Rapid Construction of Biologically Important Scaffolds

Chapter 3 deals with the development of new methods and their application in the synthesis of natural products utilizing NHC as an organocatalyst. NHC is an important class of organocatalysts, which has an unique property of reversing the reactivity (umpolung) of functional groups, particularly aldehydes or enals. We have utilized this property to construct important scaffolds. This chapter is divided into two sections.

Section 1 reveals the study towards the synthesis of Coniceine skeleton utilizing NHC-catalyzed Stetter reaction. Retrosynthetic analysis involves NHC catalyzed Stetter reaction as a key step (Scheme 5). Coniceine is the basic core of indolizidine alkaloids. Indolizidine class of natural products, isolated from skin secreations of several neotropical

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frogs, represent an important class of pharmacophore (Figure 4). We have studied different routes (Scheme 6) for the synthesis of the substrate **8,** which is required to perform the key Stetter reaction. We are currently preparing the required key substrate **8** in better quantities so as to optimize the NHC-catalyzed intramoleuclar Stetter reaction (Scheme 6). This will be followed by essential transformations to obtain the proposed natural products.

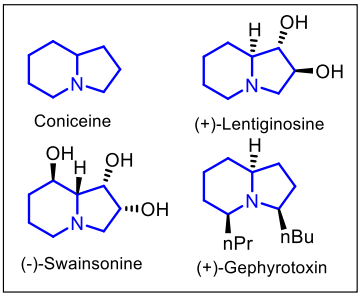
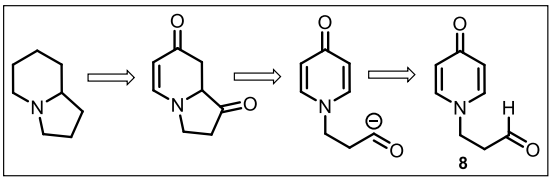
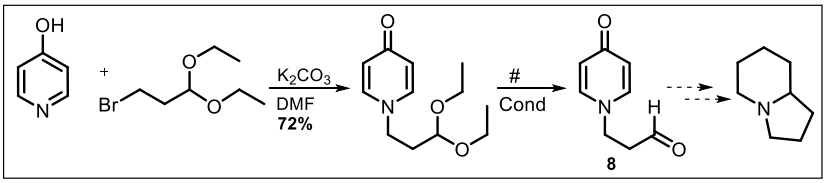


Figure 4. Selected examples of Coniceine class of natural product



Scheme 5: Retroynthetic strategy for Coniceine



Scheme 6: Synthetic route for Coniceine

Section 2 deals with the NHC-catalyzed novel and expeditious synthesis of important multifunctional heterocylic building blocks maleimides and isomaleimides starting from easily accessible cinnamaldehydes and carbamoylpropiolates (Scheme 7). Maleimides and isomaleimides are commonly used in the field of polymer chemistry and biochemistry as well as in organic synthesis as the key building blocks for the construction of natural products and drugs. Additionally, many natural products and drugs contain maleimide/isomaleimide basic core in their structure (Figure 5). The selective formation of maleimides or isomaleimides developed herein was controlled by varying the carbamoylpropiolate substituents.

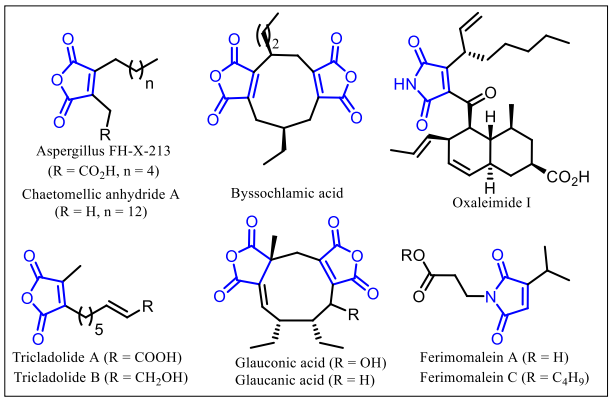


Figure 5. Selected examples of natural products containing maleic anhydreide and maleimide

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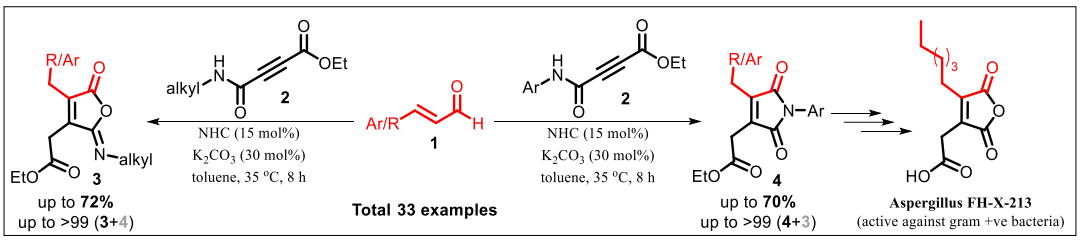

Scheme 7: NHC-Catalyzed synthesis of substituted maleimides and isomaleimides.

Electronically unbiased substrates provide their mixture in varying ratios, however heating the reaction mixture in acetic acid after completion of the reaction smoothly provides thermodynamically more stable maleimides. Intrestinlgy, the reaction proceeds via an unusual enolate pathway and it tolerates a wide range of substituents on both the reacting partners. The developed protocol will be utilized in the synthesis of related bioactive molecules and natural products.

Conclusions: In summary, we have developed the novel and efficient synthetic transformations utilizing transition metal and NHC as catalysts leading to new C–C and C–N bond formation for the efficient synthesis of biologically interesting scaffolds. We have also explored the synthesis of Crispine, Coniceine and maleic anhydride class of natural products. The work on the NHC-catalyzed rapid consutruction of maleimides and isomaleimides is noteworthy.

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1. **Viveki, A. B**.; Mhaske, S. B. *J. Org. Chem.* **2018**, *83*, 8906.
2. **Viveki, A. B**.; Garad, D. N.; Mhaske, S. B. *Chem. Commun*. **2020**, *56*, 1565.
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4. **Viveki, A. B**.; Pol, M. D.; Mhaske, S. B. et al. *Manuscript communicated*.

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Introduction

The present thesis describes the novel method developments involving metal-catalyzed C–H functionalization and *N*-heterocyclic carbene (NHC) catalysis to access biologically important scaffolds via C–C and C–N bond formation. The thesis also demonstrates our efforts to extend the developed methods towards the synthesis of natural products. The thesis is divided into three chapters. The first two chapters are based on the transition-metal-catalyzed C–H functionalization and the third chapter deals with the utilization of NHC based organocatalysis. Chapter 1 deals with the transition-metal-catalyzed C–H activation strategy for accessing novel bioactive scaffolds and our attempts to apply this concept in the synthesis of alkaloid natural products. It is divided into two sections. The first section describes the functionalization of unmasked quinazolinones with terminal alkynes utilizing Ruthenium catalysis to access new alkenylated quinazolinone products. The same protocol has been also extended by employing electron-deficient phenylacetylenes for the alkenylation followed by tandem hydroamidation of the newly generated *trans*-double bond to furnish novel quinazolinone alkaloids related to the Luotonine class of natural products. The second section covers the study towards the synthesis of Crispine and related natural alkaloids utilizing Palladium-catalyzed intramolecular tandem olefin amidation/C–H activation protocol. Chapter 2 encompasses the Copper-catalyzed *para*-selective C(sp^2)–H amidation/dimerization of anilides via a radical pathway. The radical pathway of the developed protocol was established by control experiments. Chapter 3 deals with the utilization of NHC as a organocatalyst for the synthesis of biologically important scaffolds and study towards the synthesis of natural products. Chapter 3 is further divided into two sections. The first section describes the study towards the total synthesis of Coneicine utilizing NHC-catalyzed Stetter reaction. The second section deals with NHC-catalyzed, substrate selective synthesis of varyingly substituted isomaleimides and maleimides. An unusual reactivity of the *α,β*-

unsaturated aldehyde provides a facile access to commercially important five membered imide heterocycles. Extension of this newly developed protocol towards the synthesis of natural product has been also studied.

This introduction is divided into two sections. The first section describes the overview about transition-metal-catalyzed C–H functionalization and second sections deals with NHC catalysis.

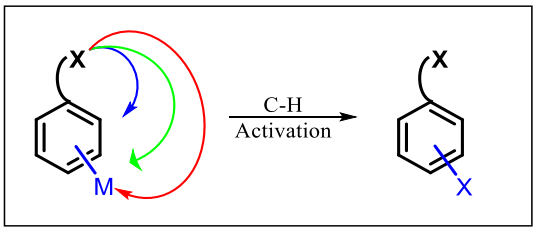
Section 1. Transition-metal-catalyzed C–H functionalization

Conversion of unreactive C–H bonds to C–C or C–X (X = N, O, S) by utilizing transition-metal catalyst leading to the desired product from simple starting materials preferably without necessary of prefunctionalization is basically known as C–H activation. This has been emerged as a powerful tool in the field of bioactive scaffolds synthesis. C–H bond functionalization has brought a paradigm shift from the traditional way of organic synthesis. It is step and atom economic.[1a] The strategy focuses on controlled and site selective activation of C–H bonds in the presence of more reactive functional groups. Diverse approaches have been developed for the activation of selective C–H bonds including electronic factor, steric factor, free radical way and directing group approach. Proximal C–H activation has been extensively studied in recent decades, whereas distal C–H functionalization and its application in the synthesis of natural products are not fully explored. Late stage functionalization of bioactive molecules opens up chances of larger library generation, which helps in search of the lead molecule. Keeping these facts in consideration, we planned to develop the methods for transition-metal-catalyzed C–H functionalization and its application in the synthesis of natural products.

0.1. C–H bond activation/functionalization

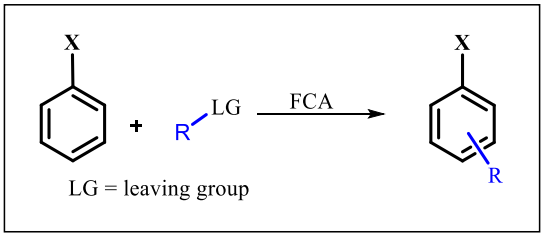
The terms C–H activation and C–H functionalization are used to describe the identical chemistry but sometimes can also be differentiated very finely based on the mechanism of reaction. The direct conversion of C–H bond to C–X bond (X = N, O, S or halogen) using transition-metal catalysis involves the first reaction of hydrocarbon with a transition-metal catalyst to form an organometallic complex, where the hydrocarbon coordinates to the inner-sphere of metal. It may lead via an intermediary alkane or arene complex or by formation of transition state leading to a M−C complex. The intermediate complex of the first step then undergoes the subsequent transformations to produce the expected functionalized product (Scheme 1).[1b]

Scheme 1. C–H activation



On the other hand, C–H functionalization deals with electrophilic/nucleophilic reaction on the aromatic ring leading to alkylation/arylation etc. In this kind of reaction the overall process is conversion of C–H bond to C–Y (Y = usually alkyl/acyl) bond, but the reaction follows the different mechanism. The first report of C–H functionalization reaction is Friedel-Crafts alkylation/acylation (FCA) reaction, named after their inventers Charles Friedel and James Crafts in 1877 (Scheme 2).[2] The Lewis acids such as $AlCl_3$, $FeCl_3$ of other MX_n are usually used as the catalyst in FCA reaction. In short C–H activation is subset of C–H functionalization.

Scheme 2. Friedel-Crafts reaction

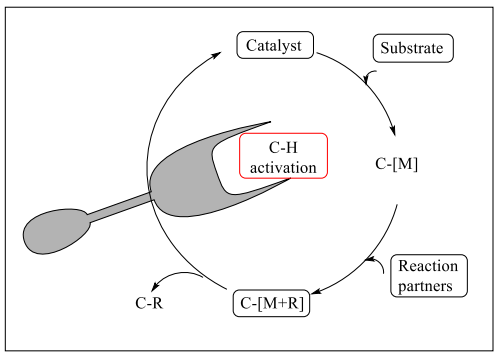


C–H activation/functionalization reactions are treated as clean, atom/step economic and cost effective reactions. They play a crucial role in the late stage functionalization of bioactive scaffolds at desired site for larger library generation. Due to the multiple advantages, the concept has gained immense attention of organic chemists in the recent years as a synthetic tool for synthesis of various bioactive scaffolds, natural products and pharmaceuticals.

0.2. Catalytic cycle

The catalytic cycle of the transition-metal-catalyzed C–H functionalization involves the first formation of organometallic complex via oxidative addition or C–H activation. It then forms complex with another coupling partner, which is followed by reductive elimination to give the expected product.[3] The catalytic cycle shown here represents the transformation which involves the transition-metal as catalyst (Figure 1).

Figure 1. Catalytic Cycle



0.3. Traditional cross coupling Vs. C–H activation

Cross-coupling reactions are the type of transformations used in the field of synthetic organic chemistry, where two fragments are combined together with the help of a transition-metal catalyst. In cross-coupling reaction, an organometallic partner of the type R–M (R = organic partner, M = metal partner) reacts with any organic halide of the type R'–X (X = halogen) with formation of the new carbon–carbon bond in the product R–R'. Cross-coupling reactions are a subclass of coupling reactions. Ideally, these types of reactions require additional steps for prefunctionalization which becomes low atom and step economic. It is often used in arylation or alkylation of organic compounds to obtain cross coupled product.[4]

On the other hand, C–H activation deals with breaking the C–H bond and making the new C–X (X = C, N, O) by using transition-metal catalyst. In this process, transition-metal catalyst plays a crucial role in the initial breaking of the C–H bond. C–H activation avoids pre-functionalization, thus making the process more atom/step economic, cost effective and ecofriendly.[5]

0.4. Features of C–H bond

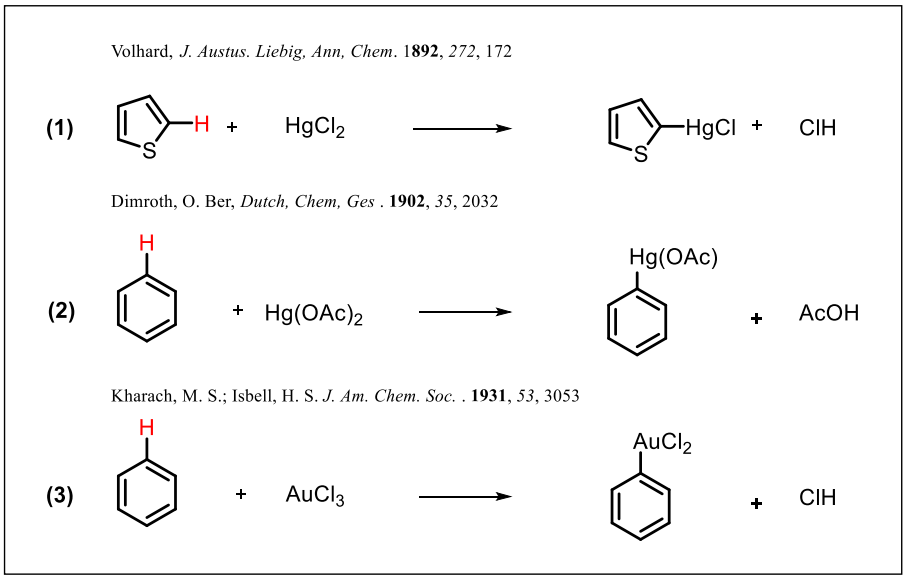
The concept of C–H bond functionalization revolves around the bond between carbon and hydrogen, which is found in nearly all the organic compounds. The C–H bond is a covalent bond, having bond length 1.09 Å and bond energy 413 kJ/mol. The C–H bond is about 20% stronger than C─C bond because of smaller bond length (about 1.09Å).[6] The difference between the electronegativity of these two atoms is 0.35, which shows that the bond is very much non-polar, thus it becomes unreactive. The C–H bond can be activated in presence of transition-metal catalyst, later which leads to the formation of different type of bonds. The relative rates of reac-

tivity for C─H bonds activity follows the trend $SP>SP^2>SP^3$.

0.5. History of C–H bond functionalization

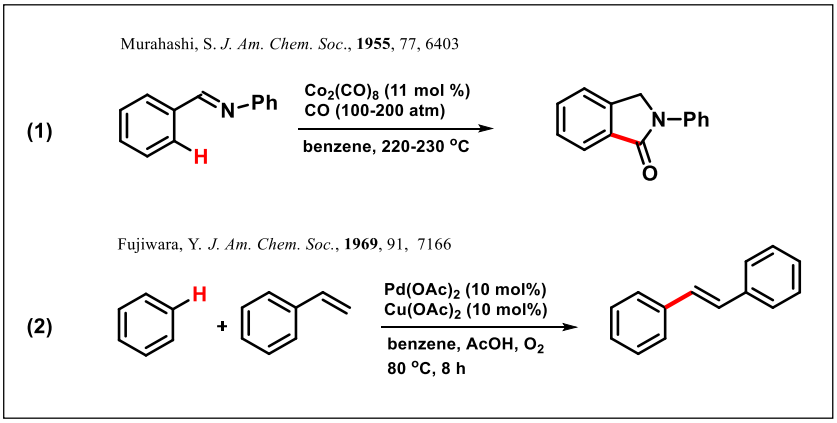
The C–H functionalization strategy came into the light in the late 18th century, when Volhard in 1892 and Dimroth in 1902 first time reported the mercuration of thiophene and benzene respectively (Scheme 3, eqn 1-2).[7a-b] Later, Kharach in 1931 reported Auration of benzene using $AuCl_3$ (Scheme 3, eqn 3) .[7c] These reports explained the realization of activation of C–H bond, but no further transformations reported. The pioneering work in the field of C–H activation was reported by Murahashi in 1955 using Cobalt catalysis during the synthesis of N-phenyl isoindolinone using carbon monoxide (CO) as a carbonyl source (Scheme 4, eqn 1).[8a] Later in

Scheme 3. History of C–H activation



1969, Fujiwara and co-workers reported Heck-type reaction using Pd/Cu catalytic system for synthesis of stilbene derivatives using C–H activation strategy (Scheme 4, eqn 2).[8b] Followed by these initial inventions, recent years have witnessed a substantial amount of research in the area of transition-metal catalyzed C–H bond functionalization.

Scheme 4. History of C–H activation

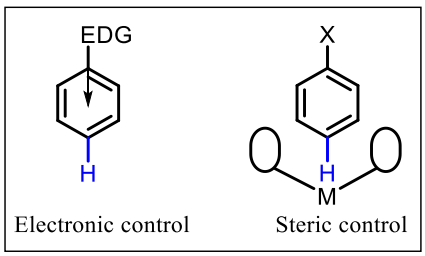


0.6. Control of regioselectivity

The regioselectivity is the primary challenge during transition-metal catalyzed C–H bond functionalization as the molecule comprises ubiquitous C–H bonds. Selective C–H functionalization can be generally achieved by using a directing-group or steric/electronic factors.

Regiocontrol by electronic/steric factor: Direct regioselective C–H bond functionalization of electron rich aromatic group has been the contemporary interest of synthetic organic chemists. Distal C–H functionalization has been always found more challenging than the proximal site. Distal C–H functionalization of electron rich aromatic ring works either by radical way or via

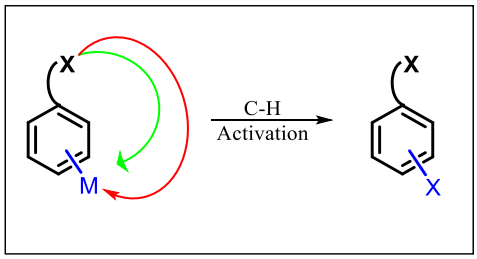
Scheme 5. Control of selectivity



para-quinone type intermediate using transition-metal catalysis. Selectivity can also be achieved by bulky ligand design on transition-metal (Scheme 5).[9] The regiocontrol by steric/electronic factor has some limitations during its application, as most of these are substrate specific.

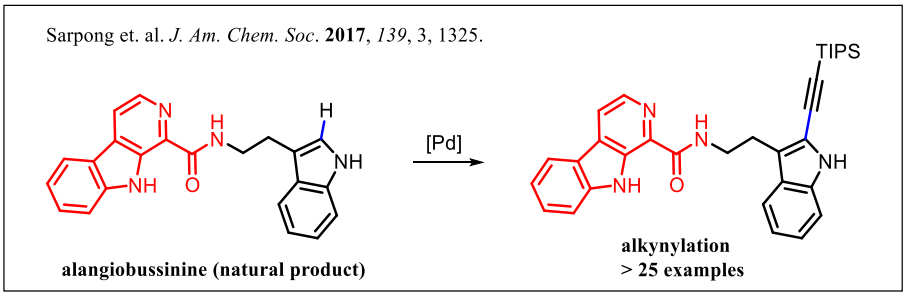
Regiocontrol by directing group: The directing group model has emerged as the most practical and useful method for site selective C–H functionalization of wide range of substrates among others reported (Scheme 6). It helps the transition-metal to reach at specific site to activate selective C–H bond usually by forming 5-7 membered transition state.[10a] Recently, large sized directing groups have been reported to reach selectively at *meta*/*para*- position, which makes the transition state larger than 10 membered during the functionalization of various aromatic rings.[11]

Scheme 6. Distal C–H activation



Sometimes, the molecule itself acts as a directing group, which is well known as inherent/intrinsic directing group (Scheme 7). Intrinsic directing group has many advantages, as it avoids the additional steps for installation and removal of directing group. Many functional groups such as imine, amide, ketone, aldehyde etc. are reported as directing group during metal chelation. Hence, the process wherein the functional group of the molecule itself acts as an inherent directing group is preferred over the earlier methods.[12]

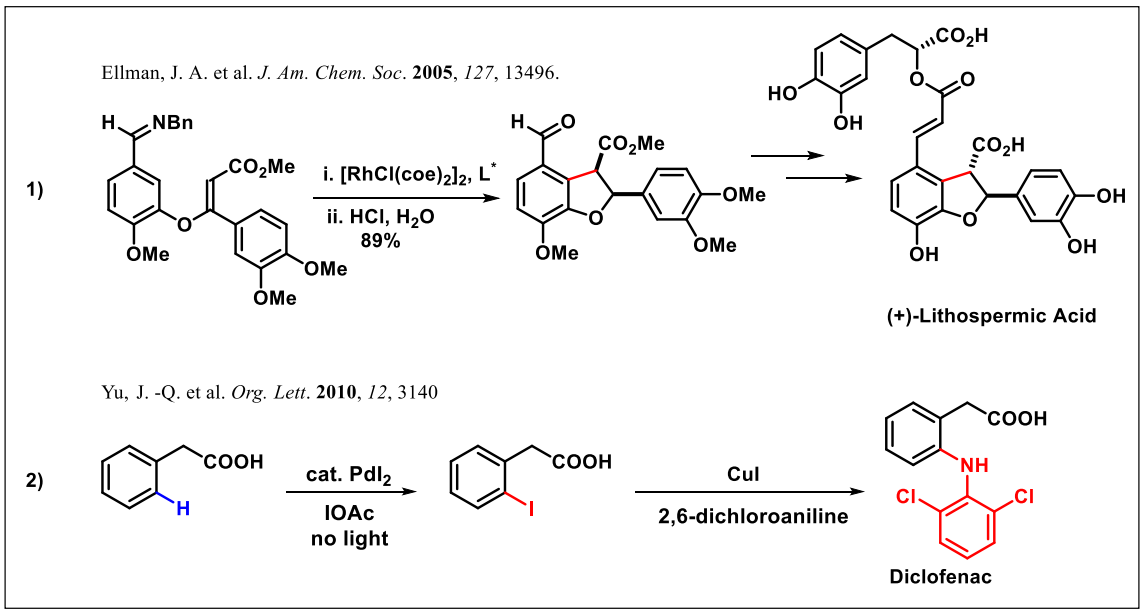
Scheme 7. Intrinsic C–H activation



0.7. C–H Activation in natural product and drug synthesis

In the recent past decades, C–H activation is one of the highly explored fields of the organic chemistry. Many reports have appeared in the various scientific journals based on methodology developments, using transition metal. Along with methodology development, in the recent years C–H activation strategy has been utilized in the synthesis of natural products, but it is not fully explored. Ellman and co-workers in 2005 have reported the elegant synthesis of (+)-lithospermic acid using Rh-catalyzed C–H activation by asymmetric intramolecular alkylation as the key step

Scheme 8. Application C–H activation in natural product and drug synthesis



(Scheme 8, eqn 1).[12a] Yu and co-workers in 2010 reported Pd-catalyzed *ortho*-C–H iodination in the total synthesis of drug Diclofenac (Scheme 8, eqn 2).[12b] Additionally, other known literature reports on synthesis of natural products and drugs using C–H bond activation demonstrates the importance of this technique.[13]

We believe that developing the newer methodology using transition-metal catalyst and its application in the total synthesis of natural product would be of great interest to organic and medicinal chemists. In this context, we have explored the alkenylation of quinazolinone using Ru-catalysis[14] and attempted synthesis of Crispine and related natural products in the first chapter. The second chapter deals with Copper catalyzed dimerization of anilides via radical pathway.[15]

Section 2. NHC catalysis

0.8. Introduction

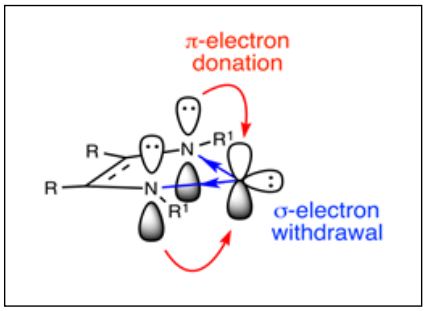
A small organic molecule which catalyzes the wide range of organic reactions is well known as organocatalyst, which contain carbon, hydrogen, nitrogen, oxygen or sulfur etc. Various metal-free catalysts are well documented in the literature to catalyze wide array of transformations with good chemo, regio and enantioselectivity. Organocatalyst offers a greener approach to chemists, which make it useful in wider context. The organocatalysis chemistry had started initially with simple transformations, and currently the focus has shifted towards the asymmetric catalysis using chiral organocatalysts.[16] Out of many, N-heterocyclic carbene (NHC) catalysis has emerged as one of the powerful synthetic tools in the development of novel transformations for the construction of bioactive and complex molecules from readily available starting materials. Reactions such as pyruvate decarboxylation and benzoin-type condensations catalyzed by

thiamine (vitamin B1) dependent enzymes were considered as some of the most mysterious transformations during the initial period of its investigation. Because of having multiple heterocyclic centers, it was challenging to find the exact reactive center until the Breslow's proposal of carbene involvement in 1958, which was the breakthrough in the field of NHC organocatalysis.[17] It became the most studied organocatalyst in the field of synthetic organic chemistry after the first reports of its isolation in stable form by Bertrand et al. in 1988 and Arduengo et. al. in 1991.[18] Thereafter, NHC has emerged as versatile catalyst in the field of organic chemistry, which works through different mechanisms, as well as also found equally useful as a ligand with transition-metal catalyst for homogeneous reactions.[19] NHC as organocatalysis has helped to address variety of synthetic transformations such as benzoin reaction, stetter reaction, annulation, cycloaddition reaction, annulation, halogenation, hydroacylation, redox esterification, redox amidation among others.[20] It has been also found very effective in the field of highly enantioselective conversions using chiral NHC-precatalyst for the construction of variety of natural products, bioactive scaffolds and important building blocks with diverse pharmaceutical activities.[21]

0.9. Structure of N-heterocyclic carbene

The carbene in NHC is divalent carbon planked between the two heterocycles, having at least one nitrogen. Π-donation from the electron pair of heterocycle into the empty orbital of carbene from the out-of-plane fashion stabilizes the electrophilic reactivity and σ withdrawal by the electronegative atoms stabilizes nucleophilic reactivity. The combined effect is to increase the singlet-triplet gap and stabilizes the singlet-state carbene over triplet-state carbene. In some cases the singlet carbenes are found thermodynamically stable in the absence of oxygen and moisture, and can also be isolated and stored indefinitely.

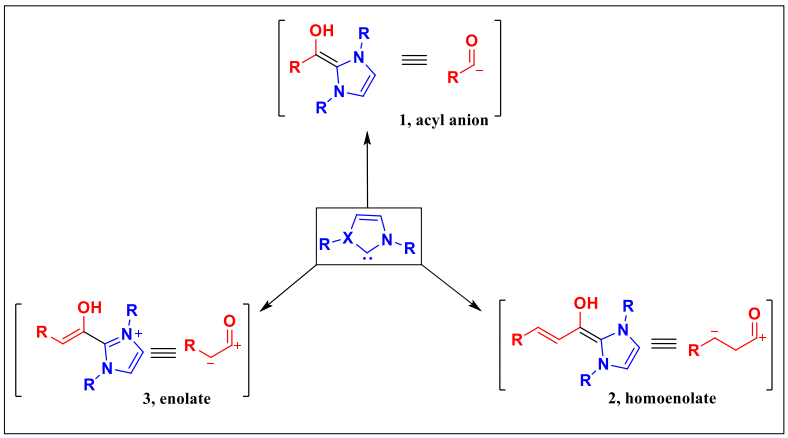
Figure 2. Structure of N-heterocyclic carbene



0.10. Modes of reactivity using N-heterocyclic carbene

NHC is widely known for Umpolung (reversal of reactivity) of aldehyde, where it converts the Breslow intermediate into different reactive intermediates based on the structure of substrate, NHC and reaction condition, such as 1) acyl anion, 2) homoenolate or 3) enolate

Figure 3. Modes of reactivity of NHC reaction



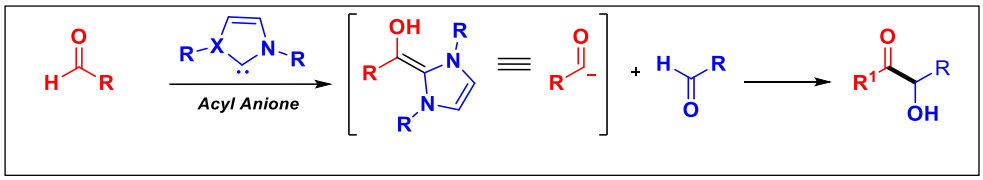
Reaction via acyl anion

Benzoin condensation was the first reaction ever reported using thiazolium salt as a catalyst in 1943 by Ukai.[22] This may be considered as an early example of organocatalysis utilizing an azolium salt. Breslow in 1958 depicted the role of NHC in the benzoin reaction and proposed the

mechanism.[17] He postulated the involvement of thiazolium zwitterion as an active species and hypothesized that, reaction occurs via enaminol intermediate and it is now popularly well-known as 'Breslow intermediate'.

The conversion of aromatic aldehyde into *α*-hydroxy ketone (benzoin), utilizing cyanide or thiazolium catalyst, is known as benzoin reaction. The reaction utilizes two molecules of aldehyde, where one molecule acts as acyl anion equivalent and another as carbonyl electrophile to afford α-hydroxy ketones (benzoins).

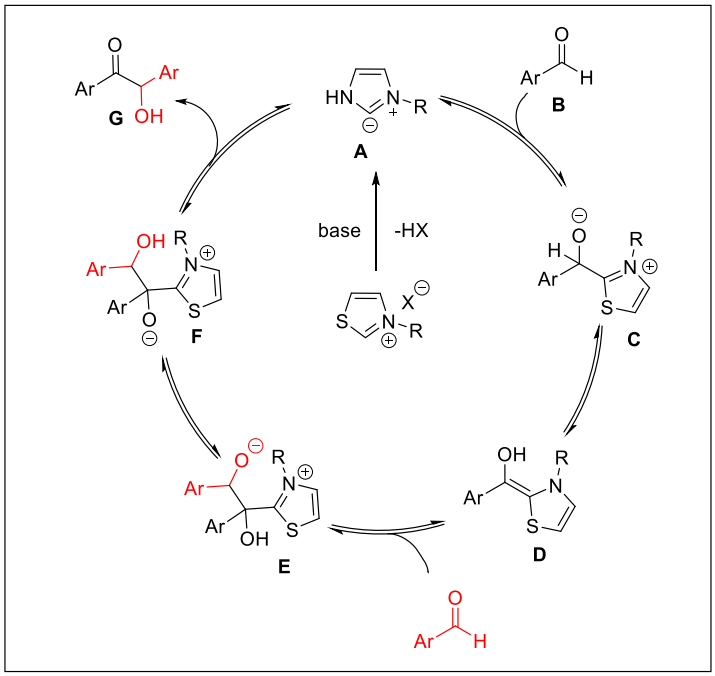
Scheme 9. Benzoin reaction



The mechanism of the reaction is explained as below, which is originally proposed by Breslow. Abstraction of proton from NHC precursor by base generates active catalyst **A**, which attacks on aldehyde **B** to generate tetrahedral intermediate **C**. It then undergoes a proton shift to form Breslow intermediate **D**, which is an active nucleophile. Reaction of ayl anion equivalent **D**, with another molecule of aldehyde **B** leads to the formation of alkoxide **E**. Later, proton transfer and subsequent expulsion of thiazolylidene **A** leads to the final product the α-hydroxy ketone **G**.[17]

The nucleophilic addition of NHC catalyzed acyl anion equivalents to various Michael acceptors has been illustrated as a powerful organocatalytic transformation, which is popularly known as Stetter reaction.[23] It is most studied reaction, which occurs through acyl anion equivalent. Roughly, stetter reaction is divided into two types ie. 1) intermolecular stetter reaction, 2) intramolecular stetter reaction.

Scheme 10. Mechanism of benzoin reaction

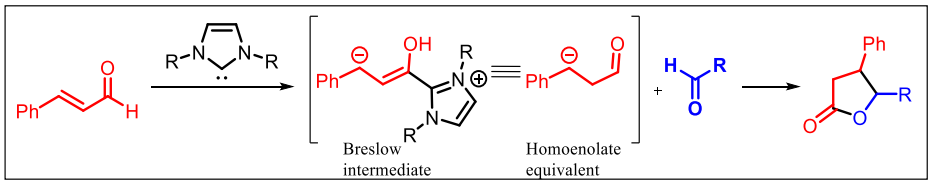


Reaction via homoenolate intermediate

Homoenolates are the type of nucleophilic intermediate that has *β*-nucleophilic center generated form the corresponding *α*-*β*-unsaturated aldehyde using NHC as organocatalyst. The term has been used in synthetic organic chemistry since 1980s, to describe the newly discovered class of nucleophile. Generation of Breslow intermediate from *α*-*β*-unsaturated aldehyde leads to generation of nucleophilic center at the *β*-position, which traps variety of electrophiles. The initial discovery of homoenolate generation by Bode and Glorius independently in 2004, paved the new synthetic route for *β*-functionalization of enal.[24] Glorius and Bode groups reported the synthesis of *γ*-lactones from cinnamaldehyde and aromatic aldehyde. The NHC and substrate were finely tuned to shepherd activity form *β*-position. These two seminal reports opened the new tool for organic chemists for derivatization at *β*-position using homoenolate intermediate. In absence of another aldehyde under the similar reaction condition, it leads to dimerization of

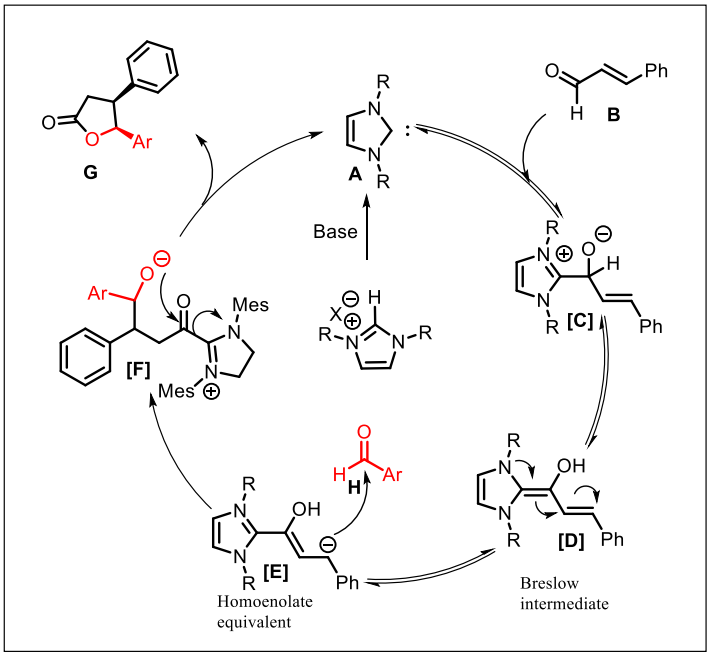
corresponding γ-lactone. In the following years the concept has been utilized in the synthesis of natural product and complex bioactive molecules.

Scheme 11. Generation of homoenolate from enal



The mechanism of the reaction involving homoenolate intermediate is explained as follows. Active NHC catalyst **A** which generates after abstraction of proton by base, first attacks on carbonyl of enal **B** to generate tetrahedral intermediate alkoxide **C**. After 1,2-proton delocalization it forms the corresponding nucleophilic Breslow intermediate **D**. This converts to active homoenolate **E** after electron migration and can react with variety of electrophiles. In the

Scheme 12. Plausible reaction mechanism

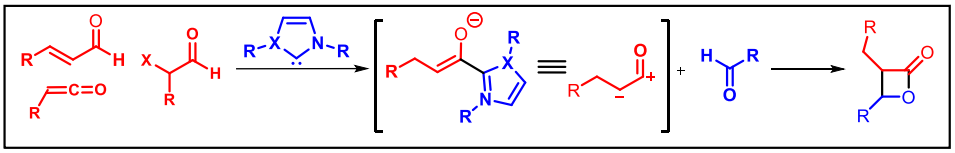


presence of aldehyde **H** as a electrophile, homoenolate equivalent **E** attacks on carbonyl. Finally, expulsion of NHC leads to the formation of the desired product lactam.

Reaction via enolate pathway

Enolates are organic nucleophiles derived by *α*-deprotonation of carbonyl compounds using suitable base. Such moiety leads to *α*-functionalization by reacting with various electrophiles. Synthesis of acyl anion equivalent (Breslow equivalent) is well established and its extension as homoenolate by taking *α*-*β*-unsaturated aldehyde is also explored since its realization. Bode and Glorius groups independently reported the new reactivity by NHC in 2006, which set a foundation of enolate chemistry.[25] In the following years Chi, Nair, Bode, Scheidt and others also explored this chemistry.[26] The strategy has been also expanded in the development of enantioselective protocols for the synthesis of complex and bioactive molecules. Protonation of *β*-anion or 1-3 migration of proton in homoenolate leads to generation of enolate intermediate. Enal, ketene or *α*-halo aldehydes are studied towards generation of enolate. Scheidt and co-workers in 2007 and Quio and co-workers in 2020 have demonstrated the intramolecular cyclization by using similar chemistry.[27]

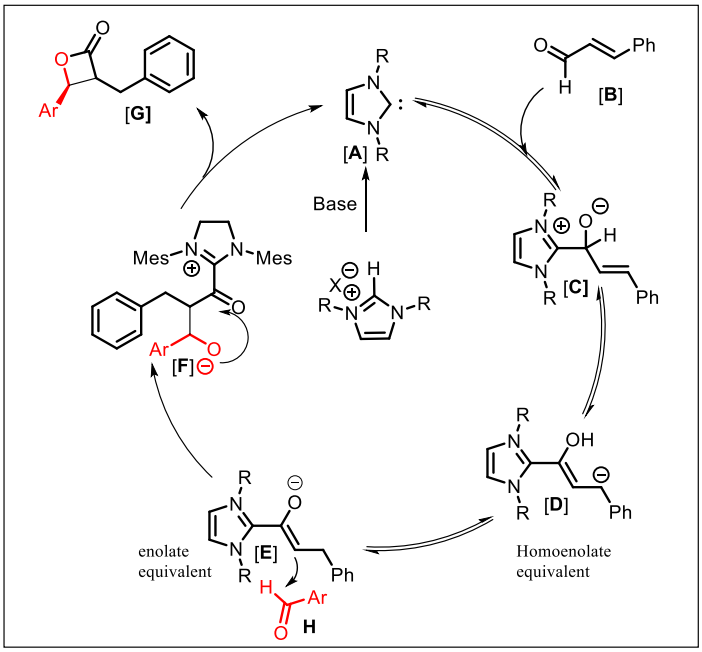
Scheme 12. Reaction involving homoenolate pathway



The mechanism of the reaction involving enolate intermediate is explained as follows. Active NHC catalyst **A** first attacks on carbonyl of enal **B** to generate tetrahedral intermediate alkoxide **C**. After 1,2-proton migration it forms *β*-nucleophilic center. In the presence of proton or after

1,4-proton migration it converts to corresponding enolate **E**, which reacts with various electrophiles. In the presence of aldehyde **H** as a electrophile, enolate equivalent **E** attacks on carbonyl. Finally, expulsion of NHC leads to the formation of the desired product lactam **G**.

Scheme 13. Plausible reaction pathway



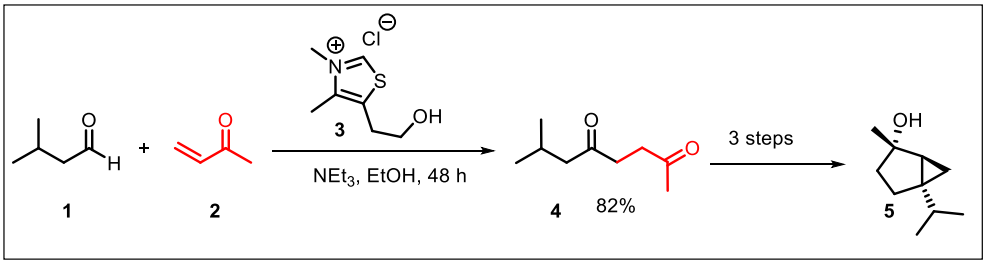
0.11. Application of NHC catalysis in the total synthesis of natural product

Successful application of the developed synthetic methodologies in the synthesis of natural products and bioactive compounds from readily available precursor is always fascinating and challenging task for the synthetic organic chemist. In the recent past years NHC has emerged as a potential organocatalyst for the synthesis of complex building blocks, bioactive molecules and natural product.[20,21] Different mode of reactivities of Breslow intermediate has enhanced the significance of the NHC catalysis. Recently, application of NHC chemistry in the total synthesis of natural product is reported by various groups.

Synthesis of (±)-*trans*-Sabinene hydrate[28]

trans-Sabinene is a natural product isolated from *Metha candicans* and it is commonly used as flavoring ingredient in a various essential oils. Galopin and co-workers in 2001 reported short and efficient synthesis of (±)-*trans*-Sabinene hydrate utilizing NHC catalyzed intermolecular Stetter reaction. The total synthesis was initiated by reacting Isovaleraldehyde 2 and methylvinylketone 1 in presence of thiazolium salt 3 to obtain 1,4-dicarbonyl compound **4** via intermolecular Stetter reaction. The synthesis of target molecule **5** was achieved by following three sequential transformations in 28% yield over three steps, starting from 1,4-diketone **4**.

Scheme 14. Synthesis of (±)-*trans*-Sabinene hydrate

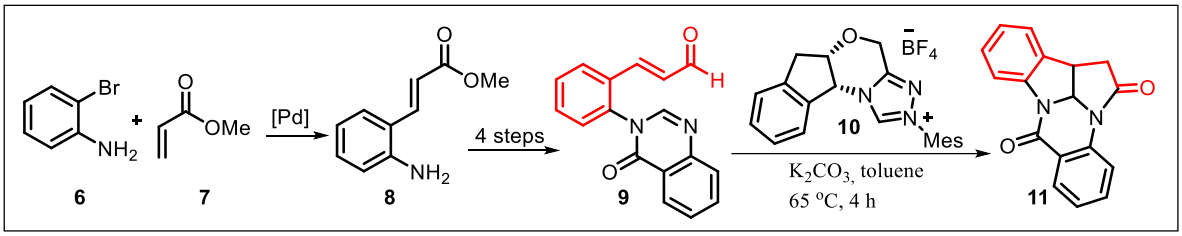


Synthesis of deoxy-Cruciferane using NHC catalysis[29]

Our group has also demonstrated the successful utilization of NHC catalysis in the construction of deoxy-cruciferane alkaloid. The synthesis of alkaloid started with the synthesis of the key intermediate quinazolinone-aldehyde. The methyl cinnamate derivative **8** was synthesized using the Heck coupling reaction of *ortho*-bromoaniline (**6**) and methyl acrylate (**7**). It was then reacted with benzoxazinone, which was synthesized from anthranilic acid. Reduction of the corresponding ester and oxidation of the resultant alcohol leads to the formation of key intermediate quinazolinone-aldehyde **9**. The synthesis was completed using NHC catalyzed [3+2] annulation via homoenolate pathway to achieve the scaffold of Cruciferane. The benzylic

oxidation of the obtained product **11** under various conditions however was not successful to obtain cruciferane alkaloid.

Scheme 15. Synthesis of deoxy-cruciferane using NHC catalysis



Considering the literature reports and importance of Stetter reaction and enolate pathway we planned to explore the synthesis of natural product Coniceine and utilize enolate pathway in the construction of isomaleimide/maleimide and its application in the synthesis of natural product.

0.12. Conclusion

The C–H bond functionalization protocol has emerged as a powerful synthetic tool for C–C and C–X (X = N, O, S etc.) bond construction in the recent past decades. Remarkable catalytic C–H functionalization processes have been developed using transition-metal catalysis, either by utilizing directing group or taking a benefit of steric/electronic factor. This chemistry found very useful in the construction of complex molecules, which otherwise would be difficult to synthesize from simple starting materials. However, there are very limited reports known in the literature, where C–H activation strategy has been successfully applied during the total synthesis of bioactive molecules, natural products and drugs. The fascinating efficient transformations possible using C–H activation protocol developed our interest in the application of C–H bond functionalization chemistry for the development of novel methodologies and its use in the total synthesis of natural product.

The NHC has emerged as one of the most studied catalyst in the field of organocatalysis since its isolation in the stable form. It has attracted the chemists because of its immense potential as organocatalysis, which reacts via various modes of reactivity. The NHC are well known to catalyze the reactions such as, benzoin reaction, stetter reaction, annulation, cycloaddition reaction, halogenation, hydroacylation, redox esterification, redox amidation among others. Enantioselective transformation leading to formation of complex molecule and its application in the synthesis of natural product though reported needs to be explored more.

The background report and importance of C–H functionalization and NHC-catalysis prompted us to take up further studies. All this work is presented in this thesis.

0.13. References

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Chapter 1

Amide-Directed Transition-Metal-Catalyzed C–H Activation Protocols and Study of their Application in Natural Product Synthesis

Amide-Directed Transition-Metal-Catalyzed C–H Activation Protocols and Study of their Application in Natural Product Synthesis

Introduction

Nitrogen containing heterocycles are the essential structural motifs in several biologically active compounds, natural products and drugs, which inspire organic chemists to develop novel strategies for their synthesis.[1] The regioselective activation of C–H bonds is one of the most attractive strategy due to the ubiquity of the C–H bonds in the organic compounds, but it is more challenging than it seems. In the recent past decades, directing group assisted C–H activation is one of the highly studied fields of the Organic Chemistry.[2] The site selective C–H bond activation was initially discovered for *ortho*-functionalization and later it has been successfully extended, wherein the directing groups are utilized to activate at *meta*- and *para*-positions selectively. The C–H functionalization, where organic molecule itself acts as a directing group is more favored because of the high atom and step economy. Out of many, amide is one of the potential functional groups as well as directing groups, which has been utilized enormously in chelation controlled functionalization using transition-metal catalysis.[3] The similar protocol also facilitates the late-stage diversification and synthesis of large number of bioactive molecules. In the recent past years this protocol also has been utilized in the synthesis of bioactive molecules, natural products and drugs. As compared to the methodology developments, utilization of the transition-metal catalysis in the total synthesis of the large organic molecules is not fully explored. In few of the recent reports, this concept has been utilized as a key-step in the synthesis of small organic molecule. Even though the field has grown enormously, still there are many voids which need to be fulfilled. This prompted us to explore newer possibilities of the synthetic transformations using transition-metal catalysis as a key-step.

We planned to explore the C–H activation protocol in the synthesis of quinazolinone and Crispine class of alkaloids. Several traditional synthetic routes are reported for the construction of quinazolinone, but very few strategies are known where quinazolinone compounds itself were functionalized by metal catalysis.[4] In this regard, we have developed the transition-metal-catalyzed amide directed functionalization of quinazolinones. We have also attempted the synthesis of natural product (±)-Crispine and its derivatives. The first section of Chapter-1 describes the functionalization of unmasked quinazolinones with terminal alkynes utilizing Ruthenium catalysis to access new alkenylated quinazolinone products. The same protocol has been also extended by employing electron-deficient phenylacetylenes for the alkenylation followed by tandem hydroamidation of the newly generated trans-double bond to furnish novel quinazolinone alkaloids related to the Luotonine class of natural products. The second section covers the study towards the synthesis of Crispine and related natural alkaloids utilizing Palladium-catalyzed intramolecular tandem olefin amidation/C–H activation protocol.

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Section 1: Ruthenium-Catalyzed Alkenylation/Tandem Hydroamidative Cyclization of Unmasked Quinazolinones Using Terminal Alkynes

Section 2: Studies Towards the Total Synthesis Crispine and Related Natural Products via Pd-Catalyzed Aminoalkylation Reaction

Chapter 1

Section 1

Ruthenium-Catalyzed Alkenylation/Tandem Hydroamidative Cyclization of Unmasked Quinazolinones Using Terminal Alkynes

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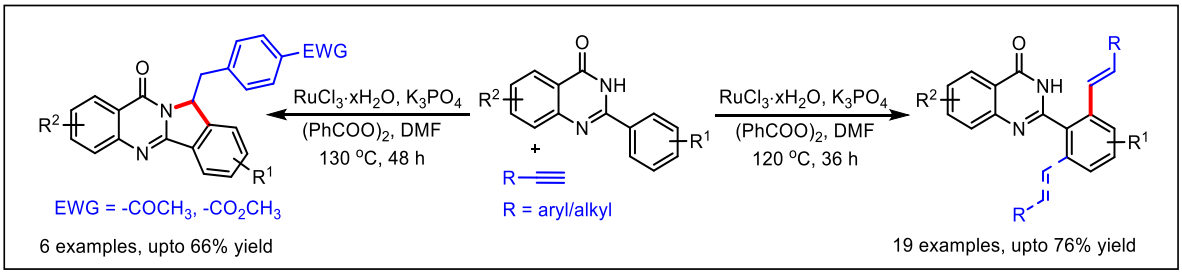
Section 1. Ruthenium-Catalyzed Alkenylation/Tandem Hydroamidative Cyclization of Unmasked Quinazolinones Using Terminal Alkynes

1.1.1. Abstract

Section 1 involves our study on highly regeoselective Ruthenium-catalyzed amide directed C_{sp2}–H activation of quinazolinone scaffold. This method leads to the selective mono- or di-alkenylation in moderate to good yields to achieve medicinally important stilbene containing quinazolinones. The terminal alkyne is utilized as a coupling partner, which resulted in the selective *trans*-alkene formation. Electron-deficient phenylacetylenes facilitate alkenylation followed by tandem hydroamidation of the newly generated *trans*-double bond to provide novel quinazolinone alkaloids related to Luotonine class of natural products. A broad substrate scope has been demonstrated for both quinazolinones as well as terminal alkynes.

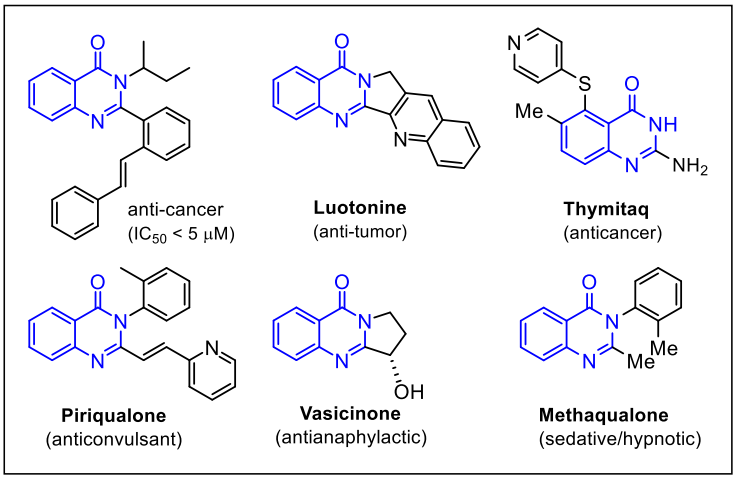


1.1.2. Introduction

Heteroatom containing organic compounds gained immense attention of organic chemists because of their diverse bioactivity**.** Around 70% of the marketed drugs contain at least one heteroatom as a part of their core structure. Quinazolinone is one of the most important building blocks found in many biologically active molecules, natural products as well as drug candidates.[1] Many marketed drugs containing quinazolinone or quinazoline as a basic core with various biological activities are known.[2] This privileged scaffold gained immense attention of synthetic as well as medicinal chemists because of their

ubiquitous fascinating structural architecture and wide range of biological properties such as anticancer, antianaphylatic, diuretic, antimalarial, antiinflammatory, antihypertensive, anticonvulsant, and antidiabetic among others.[1,2] Quinazonlinone alkaloids containing *trans*-stilbene moiety have been found to be two-fold more potent than the marketed drug Etoposide in the preliminary test against cancer cell lines (Figure 1).[3] Diversity-oriented late-stage functionalization of such biologically active scaffolds broaden the scope of the search for a lead molecule. Incorporating an easily functionalizable moiety, such as an alkene,[4] on an active scaffold improves the chances of larger library generation. Additionally, quinazolinone compounds with extra polar/non-polar functional groups may enhance their medicinal properties. Hence, the development of efficient and novel methods for their construction is always desired for drug discovery.[1,2]

Figure 1. Selected bioactive quinazolinone molecule, drug, and natural products.



Metal-catalyzed activation of neutral C─H bond leading to diverse functionalization is a wide area of chemistry, which can be utilized for this purpose. Late-stage diversification of bioactive molecules opens up a new avenue for synthetic chemistry as well as biology. In the recent past decades, directing group assisted C─H activation is one of the highly studied fields of the Organic Chemistry. The functional group directed C─H activation, in

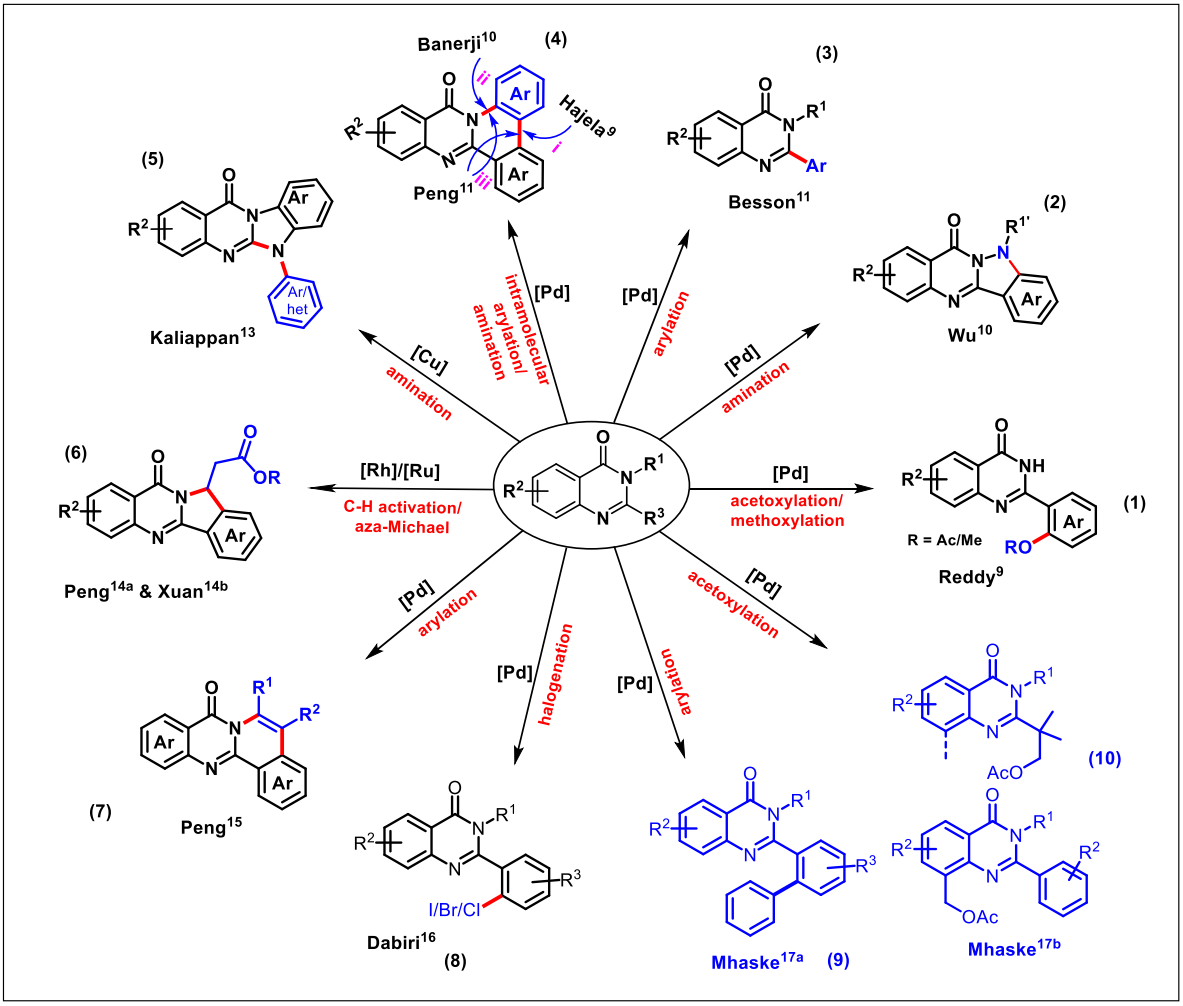
particular, alkenylation is often used for the construction of new C─C bond,[5] nevertheless, C─H bond activation using intrinsic directing group is more preferred since it avoids a number of steps to obtain the products with high atom economy.[6]

1.1.3. Literature review

The literature survey revealed that, heterocyclic compounds having various biological activities have gained immense attention of synthetic organic chemists. Particularly, quinazolinone is one of the important scaffolds with wide range of biological activity. Hence, several classical methods for the construction of quinazolinone basic core have been reported by many research groups. Though there are various conventional methods available for synthesizing novel quinazolinones,[7,8] late-stage derivatization of quinazolinone compounds itself by metal catalysis is not much explored. In 2012, Reddy et al. first time utilized quinazolinone as inherent directing group for Pd-catalyzed acetoxylation/methoxylation (Scheme 1, eq 1).[9] This report opened up the new way of generating the library of bioactive quinazolinone. Later in 2014, Wu and co-workers reported intramolecular aerobic oxidative C−H amination of quinazolinones and the potential utility of the obtained products has been demonstrated as a new class of blue fluorophores for fluorescent materials (Scheme 1, eq 2).[10] Ligand-free Pd-Catalyzed and Cu-Assisted regioselective C−H arylation of quinazolin-4-ones with aryl iodides was reported by Besson and co-workers. The reaction was performed under Microwave heating which tolerated wide range of both the partners (Scheme 1, eq 3).[11] A three different possible approaches were successfully utilized for the Pd-catalyzed construction of phenanthridine/benzoxazine fused quinazolinones. Intramolecular biaryl cross-coupling on two distinct skeletons by C–H bond activation with bromoarenes was reported. The Hajela group also demonstrated the utilization of formaldehyde as a single carbon source during synthesis of benzoxazine fused quinazolinones (Scheme 1, eq

4i).[12a] In the subsequent year 2016, Banerji et al. developed regioselective intramolecular oxidative C–H amination from cyclic strained amides of quinazolinones (Scheme 1, eq 4ii),[12b] Moreover, such fused molecules show excellent fluorescent properties and have great potential to be a new type of fluorophores for the use in medicinal and material science. In 2016, peng and co-workers reported the modular synthesis of quinazolinone fused phenanthridinones via cascade C–H/N–H arylation (Scheme 1, eq 4iii).[12c] Similar way few other metal catalysts such as Ru, Cu and Rh were also utilized for the functionalization of quinazolinones. Kaliappan and co-workers reported Cu-catalyzed cascade C−H functionalization leading to two-fold C−N bond formation

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



protocol for the syntheses of N-aryl benzimidazoquinazolinones (Scheme 1, eq 5).[13] A Ru/Rh-catalyzed oxidative coupling of 2-aryl-quinazolinones with olefins via C–H bond activation followed by an intramolecular aza-Michael reaction is described by Peng and Xuan groups independently. This strategy allowsthe direct and efficient construction of pyrrolo[2,1-b]quinazolin-9(1H)-one scaffolds (Scheme 1, eq 6).[14a,b] Additionally, the annulation reaction of quinazolinone with alkynes was reported by Peng and Cui groups independently (Scheme 1, eq 7).[15a-b] Dabiri and co-workers reported a Pd-catalyzed *ortho*-selective halogenation of quinazolinone scaffolds by utilizing *N*-halosuccinamides as a halogen source for selective functionalization (Scheme 1, eq 8).[16a] Direct diversification was also reported by Hong and co-authors.[16b] Prior to this current study, our group has reported two studies where quinazolinone itself acts as an inherent directing group for *ortho*-functionalization. Pd-catalyzed regioselective monoarylation of quinazolinone was reported utilizing diaryliodonium triflates as aryl source by C−H bond activation (Scheme 1, eq 9).[17a] Our group has also reported another study where C_{sp3}─H was activated using Pd-catalysis leading to acetoxylation. It was the first report where quinazolinone directed C_{sp3}─H was activated (Scheme 1, eq 10).[17b]

1.1.4. Origin of the work

It has been observed from the literature reports that the quinazonlinone alkaloids containing a *trans*-stilbene moiety have been found to be 2-fold more potent than the marketed drug Etoposide in the preliminary test against cancer cell lines.[3] Internal alkynes have been exploited more frequently in the nitrogen directed C─H activation to obtain alkenylated products[5b,15,18] as compared to terminal alkynes.[5c,19] Quinazolinone moiety has been reported as an inherent directing group for *ortho*-functionalization. Considering these facts and inspired by the importance of quinazolinone derivatives containing *trans*-stilbene moiety and Luotonine related

quinazolinone compounds as potential bioactive candidates,[1,2] we planned to develop a protocol for their synthesis using C─H activation protocol.

1.1.5. Objective of the work

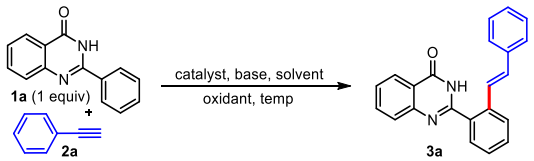
Due to the extensive occurrence of quinazolinone nucleus in bioactive organic compounds, and the literature precedence, we thought that the quinazolinone derivatives containing *trans*-stilbene moiety could of immense interest in search of lead molecule against cancer. Our objective was to develop a protocol wherein quinazolinone may act as an inherent directing group for the metal-catalyzed regioselective alkenylation, which would afford a library of novel quinazolinones featuring stilbene scaffold for structure-activity-relationship (SAR) studies. Herein, we report a protocol for Ruthenium-catalyzed regioselective alkenylation/tandem hydroamidative cyclization of unmasked quinazolinones using terminal alkynes.

1.1.6. Result and discussion

Our preliminary investigation commenced with the reaction of 2-phenylquinazolin-4(3H)-one (**1a**) with phenylacetylene (**2a**) in the presence of ruthenium catalyst ($RuCl_3.xH_2O$, 0.05 equiv), base (K_3PO_4, 2 equiv) and oxidant [dibenzoyl peroxide (75 % in water), 1.5 equiv] in NMP at 120 ^oC. To our delight, the desired alkenylated product **3a** was obtained in 15% yield (Table 1, entry 1). When the *N*-methyl protected quinazolinone was treated under the same condition, the reaction failed to give the expected product (Table 1, entry 2). We reasoned that the amide moiety of quinazolinone is acting as the directing group for ruthenium catalyst unlike imine (pyridine) reported by Zhang et al.[19f] Hence, we proceeded further with the unmasked quinazolinone **1a** for the optimization of the protocol. Heating the reaction for longer time, showed that 36 h is the ideal time with slight improvement in the yield (Table 1, entries 3-4). Change in the catalyst loading did not show much improvement in the yield (Table 1, entry 3).

Decrease in the reaction temperature did not lead to expected product formation, but increase in the temperature up to 150 ^{o}C showed multiple product formation (Table 1, entries 5-6). To improve the yield further, different solvents i.e. ACN, DCE and DMF were also screened (Table 1, entries 7-9). Out of the many, DMF was found to be better for this transformation (Table 1, entry 9). We were delighted to observe substantial improvement in the reaction yield up to 48%,

Table 1. Optimization of reaction condition[a]



Sr. no.	**2a** (equiv)	solvent	base	temp (^{o}C)	time (h)	yield[b] (%)
1	2	NMP	K_3PO_4	120	24	15
2[c]	2	NMP	K_3PO_4	120	24	NR
3[d]	2	NMP	K_3PO_4	120	36	19
4	2	NMP	K_3PO_4	120	48	12
5	2	NMP	K_3PO_4	100	36	trace
6	2	NMP	K_3PO_4	150	36	--[e]
7	2	ACN	K_3PO_4	120	36	10
8	2	DCE	K_3PO_4	120	36	NR
9	2	DMF	K_3PO_4	120	36	24
10	3	DMF	K_3PO_4	120	36	48
11	**4**	**DMF**	**K_3PO_4**	**120**	**36**	**72**
12	5	DMF	K_3PO_4	120	36	60
13	4	DMF	Cs_2CO_3	120	36	--[e]
14	4	DMF	K_2CO_3	120	36	45
15	4	DMF	Na_2CO_3	120	36	52
16[f]	4	DMF	K_3PO_4	120	36	35
17[g]	4	DMF	K_3PO_4	120	36	60
18[h]	4	DMF	K_3PO_4	120	36	NR
19[i]	4	DMF	--	120	36	45
20[j]	4	DMF	K_3PO_4	120	36	NR

[a]Reaction condition: **1a** (0.2 mmol), **2a**, $RuCl_3 \cdot xH_2O$ (0.05 equiv.), $(PhCOO)_2$ (0.3 mmol), base (0.4 mmol), solvent (1.4 mL) in glass tube with screw cap. [b]Isolated yield. [c]*N*-CH_3. [d]Catalyst used 2-10 mol %. [e]Multiple products. NR = No reaction. [f]$PhCO_3t$-Bu, [g]$PhCO_2H$, [h]$(t\text{-}BuO)_2$, [i,j]$PhCO_2Na$ as oxidant/additive.

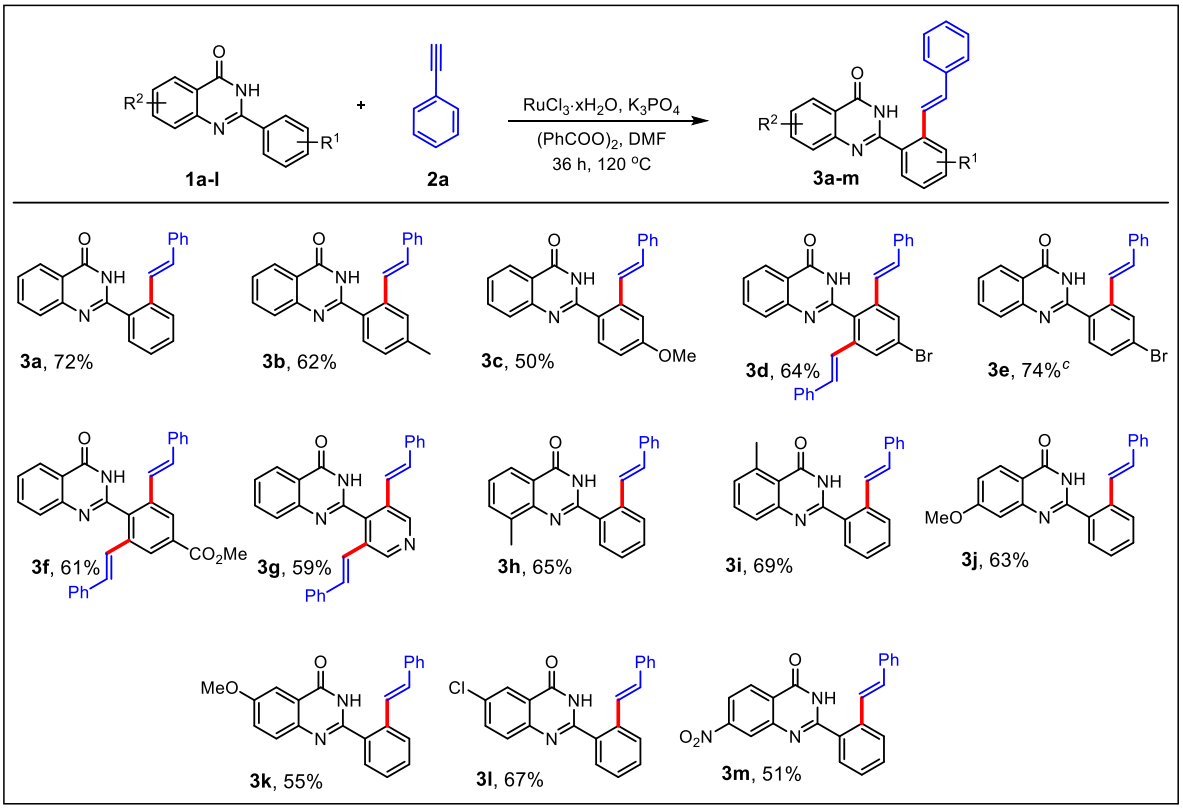
with 3 equivalents of 2a alkyne coupling partner (Table 1, entry 10). We tried the reaction with 4 equivalents of **2a** and we were pleased to observe a significant enhancement in the yield up to 72% (Table 1, entry 11). However, the use of 5 equivalents resulted in diminished yield and the formation of a trace amount (LC-MS) of dialkenylated product (Table 1, entry 12). Further attempts to improve the yield using various bases such as, Cs_2CO_3, K_2CO_3, Na_2CO_3 failed to meet our expectation, which either lead to complex reaction or diminished yield (Table 1, entries 13-15). Other oxidants such as $PhCO_3t$-Bu, $PhCO_2H$ and $(t\text{-BuO})_2$ also did help to improve the yield of the reaction (Table 1, entries 16-18). $PhCO_2Na$ as an oxidant/additive also resulted in either no product formation or decrease in the yield (Table 1, entries 19-20).

After having the optimized condition in hand (Table 1, entry 11), we turned our attention towards the generalization of the developed protocol on varyingly substituted quinazolinones (Scheme 2). Initially, the effect of substituents present on the phenyl ring of the quinazolinone substrate was studied. Electron donating substituents such as methyl and methoxy groups at the *para*-position of the phenyl ring provided products **3b** and **3c** respectively in good to moderate yields. Surprisingly, 4-bromo substituted compound provided dialkenylated product **3d** in good yield under the optimized reaction condition. It may be reasoned that quinazolinone substrate with electron withdrawing group is more active for such transformations as the reaction proceeds through deprotonation pathway. With slight modification (2 equivalent of **2a**, at 100 ^oC) in the optimized reaction condition, we could isolate the monoalkenylated product **3e** in very good yield. The carboxylate group substituted quinazolinone also resulted into the dialkenylated product **3f**, however our attempts to achieve only monoalkenylated product by modification in the reaction condition were not successful because of the high reactivity of the substrate. Similar to the carboxylate substituted quinazolinone, the presence of electron-deficient pyridine ring

on quinazolinone substrate provided only dialkenylated product **3g** in moderate yield.

Further, the scope of the alkenylation reaction was studied on substrates with different substituents on the quinazolinone core. Quinazolinone core with the methyl group at 3- and 6-positions provided the desired products **3h** and **3i** respectively in good yields. Substrates with electron donating methoxy group at 4- and 5- positions also worked well to provide the corresponding products **3j** and **3k**. Halogen substituent such as chlorine was also tolerated well to furnish the expected product **3l** in good yield. Nitro-substituted electron-deficient substrate provided the expected alkenylated product **3m** in moderate yield.

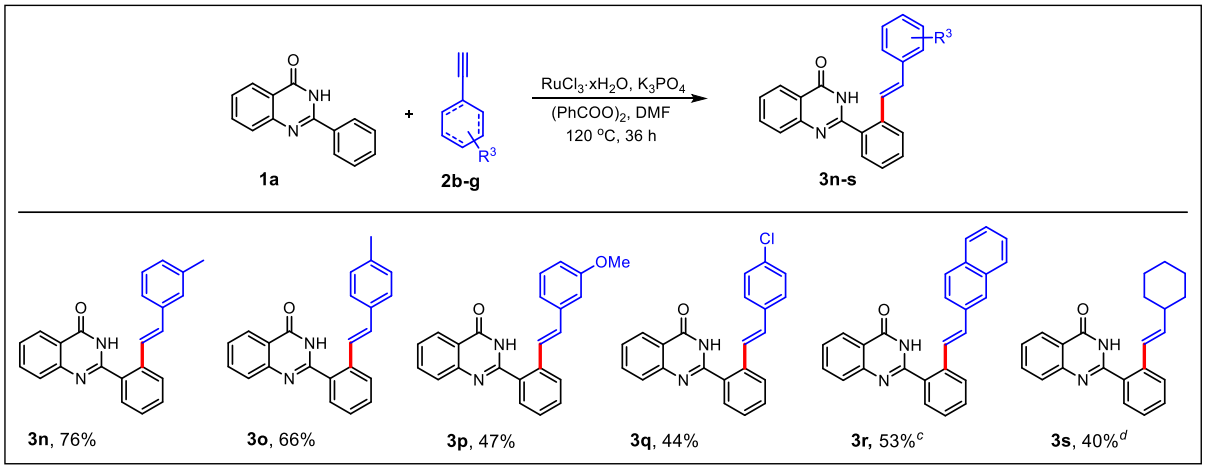
Scheme 2. Ruthenium-catalyzed alkenylation of various quinazolinones[a,b]



[a]Reaction condition: **1a-l** (0.2 mmol), **2a** (0.8 mmol), $RuCl_3 \cdot xH_2O$ (0.05 equiv), $(PhCOO)_2$ (0.3 mmol), K_3PO_4 (0.4 mmol), DMF (1.4 mL) in glass tube with screw cap for 36 h. [b]Isolated yield. [c]Reaction at 100 °C with 2a (2 equiv).

We also investigated the substrate scope of different terminal alkynes with quinazolinone **1a** (Scheme 3). 3/4-Methyl-substituted phenylacetylenes furnished the corresponding products **3n** and **3o** in very good yields. In the case of 3-methoxy and 4-chloro phenylacetylene, the expected products **3p** and **3q** were obtained in moderate yields. When the reaction was performed using 2-ethynylnaphthalene, the reaction took longer time and resulted into the expected product **3r** in moderate yield. It has been observed that aliphatic terminal alkyne was unreactive at 120 ^{o}C, but when the temperature was increased to 150 ^{o}C, the reaction went to completion and resulted in the corresponding alkenylated product **3s** (*trans*:*cis* = 7:1) though in low yield.

Scheme 3. Ruthenium-catalyzed alkenylation using various terminal alkynes[a,b]

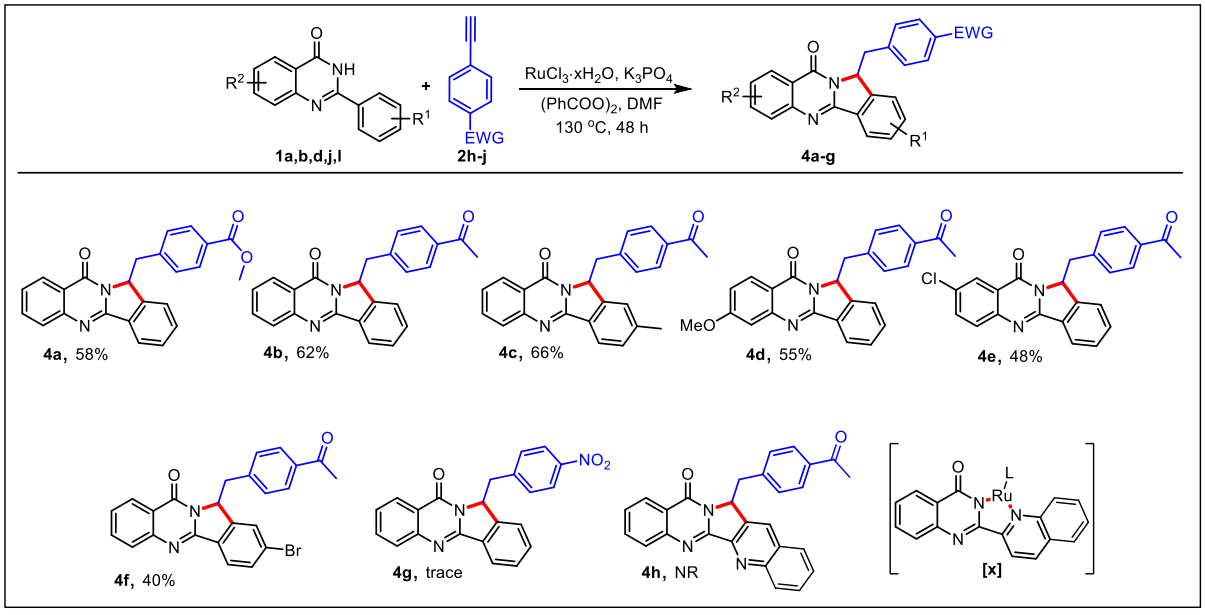


[a]Reaction condition: **1a** (0.2 mmol), **2b-g** (0.8 mmol), $RuCl_3 \cdot xH_2O$ (0.05 equiv), $(PhCOO)_2$ (0.3 mmol), K_3PO_4 (0.4 mmol), DMF (1.4 mL) in glass tube with screw cap for 36 h. [b]Isolated yield. [c]48 h. [d]150 ^{o}C, 48 h.

The results obtained during the substrate scope studies (Scheme 2 and 3) prompted us to investigate whether a presence of an electron-withdrawing group on the alkyne partner will induce the envisioned hydroamidative cyclization to obtain interesting compounds related to Luotonine class of natural products (Scheme 4). To our immense interest methyl 4-ethynylbenzoate reacted smoothly to provide the cyclized product **4a** in optimum yield at the higher temperature and longer reaction time. Interestingly, keto- substituted phenyl acetylene also worked similarly with various quinazolinone substrates providing the corresponding cycliz-

ed products **4b-f** in good to moderate yields. However, the nitro-substituted phenylacetylene remained unreactive under the optimized reaction conditions, and only a trace amount of product formation was observed (HRMS) at the higher temperature. Most probably the presence of the strong electron withdrawing nitro group did not facilitate the binding of the electron-deficient alkyne with the in situ generated quinazolinone-ruthenium complex. Hence the expected product **4g** was not observed. We then attempted the reaction of 2-(2-pyridyl)-substituted quinazolinone under our optimized condition, but the substrate remained unreactive though we tried variations in the reaction condition. It is interesting to note that the reaction worked well with pyridine substituted quinazolinone, where nitrogen is away from the reacting center (Scheme 1, **3g**). This result suggests that probably the formation of stable ruthenium complex (Scheme 4, **[x]**) inhibits the reaction, hence the formation of product **4h** is not observed.

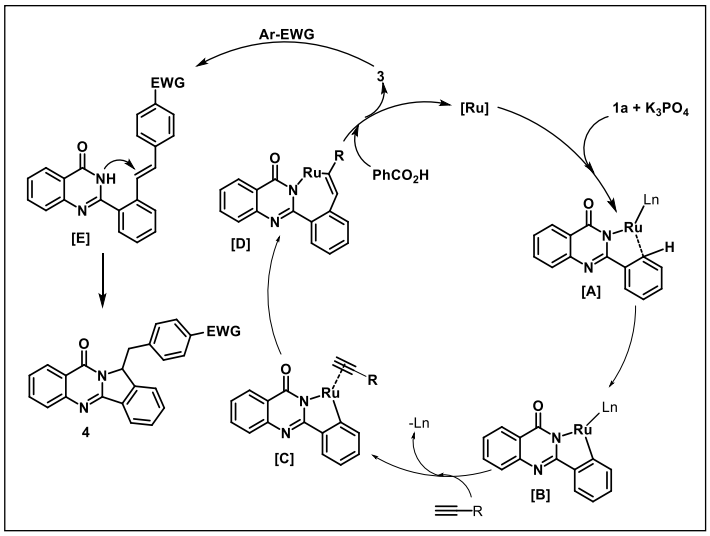
Scheme 4. Ruthenium-catalyzed alkenylation-hydroamidation[a,b]



[a]Reaction condition: **1a**,**b**,**d**,**j**,**l** (0.2 mmol), **2h-j** (0.8 mmol), $RuCl_3 \cdot xH_2O$ (0.05 equiv), $(PhCOO)_2$ (0.3 mmol), K_3PO_4 (0.4 mmol), DMF (1.4 mL) in glass tube with screw cap for 48 h. [b]Isolated yield.

Based on the reactivity pattern of various quinazolinone substrates and literature precedence,[15,19f,20] a plausible reaction mechanism for this transformation is depicted in Scheme 5.

Scheme 5. Plausible reaction pathway



Coordination of the ruthenium metal with the amide nitrogen in the presence of a base forms a transition state **[A]**. The abstraction of the acidic proton of the aromatic ring results into the intermediate **[B]**. Exchange of benzoic acid with terminal alkyne produces the complex **[C]**. The consequent migratory insertion of alkyne leads to the intermediate **[D]**, which culminates into the expected alkenylated products **3** by protodemetalation. In the case of electron-deficient phenyl acetylenes further hydroamidative cyclization directly furnishes cyclized products **4**.

1.1.7. Conclusion

In conclusion, we have achieved ruthenium-catalyzed direct C─H bond alkenylation of quinazolinones using terminal alkynes as alkene coupling partner in good to moderate yields. The developed protocol was successfully extended for the synthesis of Luotonine analogues. Quinazolinone is used as the inherent directing group, which allows late-stage diversification and synthesis of a library of medicinally important compounds that could be extended for SAR studies. Screening of the synthesized molecules for anticancer activity and regioselective functionalization of quinazolinone alkaloids using other metals is underway in our laboratory.

1.1.8. Experimental section

1. Additional Information: All quinazolinone starting materials were prepared[21] according to literature procedures starting from the corresponding 2-amino benzamide and aldehyde and the structures were confirmed by literature reports.[21-26] 4-Acetylphenylacetylene (**2i**) was prepared according to the previously reported procedure.[27]

2. Experimental Procedures

A] General procedure for alkenylation/tandem hydroamidation of quinazolinone (3a-s, 4a-g)

The oven dried screw cap glass tube equipped with a magnetic stirring bar was charged with quinazolinone (0.2 mmol, 1 equiv), phenylacetylene (0.8 mmol, 4 equiv), benzoyl peroxide (75 % in water, 0.3 mmol, 1.5 equiv), K_3PO_4 (0.4 mmol, 2 equiv), $RuCl_3.{}_XH_2O$ (0.05 mmol, 5 mol %) and DMF (1.4 mL). The reaction mixture was backfilled with argon and heated at 100-150 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC. After completion of the reaction (36-48 h), the reaction mixture was diluted with ethyl acetate and washed thrice with ice cold water. The organic layer was dried over Na_2SO_4, concentrated under vacuum and the crude residue was purified over flash column chromatography using 2% acetone in DCM to afford pure products **3a-s** and **4a-g**.

B] Typical experimental procedure for the preparation of representative product 3a

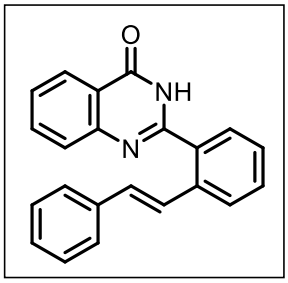
The oven dried screw cap glass tube equipped with a magnetic stirring bar was charged with quinazolinone **1a** (44.4 mg, 0.2 mmol, 1 equiv), phenylacetylene (**2a**) (87 μL, 0.8 mmol, 4 equiv), benzoyl peroxide (75 % in water, 97 mg, 0.3 mmol), K_3PO_4 (85 mg, 0.4 mmol, 2 equiv), $RuCl_3.{}_XH_2O$ (2 mg, 0.05 mmol, 5 mol %) and DMF (1.4 mL). The reaction mixture was backfilled with argon and heated at 120 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC. After completion of the reaction (36 h), the reaction mixture was diluted with ethyl acetate (25 mL) and washed thrice with ice cold water. The organic layer was dried over Na_2SO_4, concentrated under vacuum and the crude residue was purified over flash column chromatography using 2% acetone in DCM to afford pure quinazolinone product **3a** in 72% yield (46 mg).

C] Typical experimental procedure for the preparation of representative product 4c

The oven dried screw cap glass tube equipped with a magnetic stirring bar was charged with quinazolinone **1b** (47.2 mg, 0.2 mmol, 1 equiv), phenylacetylene **2i** (115 mg, 0.8 mmol, 4 equiv), benzoyl peroxide (75 % in water, 97 mg, 0.3 mmol, 1.5 equiv), K_3PO_4 (85 mg, 0.4 mmol, 2 equiv), $RuCl_{3.X}H_2O$ (2 mg, 0.05 mmol, 5 mol %) and DMF (1.4 mL). The reaction mixture was backfilled with argon and heated at 130 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC. After completion of the reaction (48 h), the reaction mixture was diluted with ethyl acetate (25 mL) and washed thrice with ice cold water. The organic layer was dried over Na_2SO_4, concentrated under vacuum and the crude residue was purified over flash column chromatography using 2% acetone in DCM to afford pure quinazolinone product **4c** in 66% yield (50 mg).

3. Characterization Data of Compounds:

(*E*)-2-(2-Styrylphenyl)quinazolin-4(3*H*)-one (**3a**):



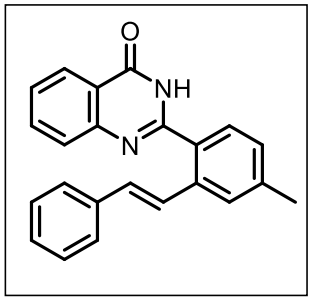
According to the general procedure, the title compound **3a** was obtained as a colorless solid (46 mg; 72% yield): reaction time 36 h/120 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 188−190 ^{o}C.

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 10.09 (s, 1H), 8.32 (d, *J* = 7.96 Hz, 1H), 7.84−7.80 (m, 3H), 7.69 (dd, *J* = 7.39 Hz, 0.95 Hz, 1H), 7.61−7.49 (m, 3H), 7.45−7.38 (m, 3H), 7.34−7.22 (m, 3H), 7.11 (d, *J* = 16.07 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.8, 152.9, 149.1, 136.9, 136.7, 134.9, 132.3, 132.2, 130.9, 129.5, 128.6, 128.0, 127.9, 127.8, 127.1, 126.9, 126.7, 126.4, 125.6, 120.8.

HRMS (ESI−TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{17}N_2O$; 325.1335, found 325.1336.

(*E*)-2-(4-Methyl-2-styrylphenyl)quinazolin-4(3*H*)-one (**3b**):



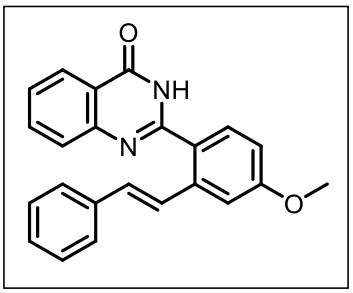
According to the general procedure, the title compound **3b** was obtained as a colorless solid (42 mg; 62% yield): reaction time 36 h/120 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 235−237 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.12 (s, 1H), 8.33 (d, *J* = 7.93 Hz, 1H), 7.83 (d, *J* = 3.05 Hz, 2H), 7.60 (apparent d, *J* = 7.93 Hz, 2H), 7.56−7.52 (m, 1H), 7.46 (d, *J* = 15.87 Hz, 1H), 7.40 (d, *J* = 7.32 Hz, 2H), 7.30 (d, *J* = 7.32 Hz, 2H), 7.26−7.22 (m, 2H) 7.09 (d, *J* = 15.87 Hz, 1H), 2.48 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.5, 152.8, 149.1, 141.2, 136.9, 136.5, 134.9, 132.1, 129.6, 129.4, 128.8, 128.7, 128.0, 127.9, 127.6, 127.0, 126.7, 126.5, 125.7, 120.7, 21.6.

HRMS (ESI−TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{19}N_2O$; 339.1492, found 339.1490.

(*E*)-2-(4-Methoxy-2-styrylphenyl)quinazolin-4(3*H*)-one (**3c**):



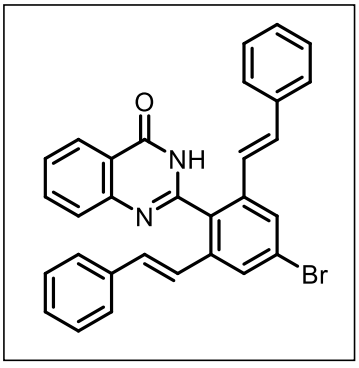
According to the general procedure, the title compound **3c** was obtained as a colorless solid (35 mg; 50% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 228−230 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.19 (s, 1H), 8.31 (d, *J* = 7.93 Hz, 1H), 7.81 (d, *J* = 3.66 Hz, 2H), 7.67 (d, *J* = 8.54 Hz, 1H), 7.54−7.52 (m, 1H), 7.49 (d, *J* = 15.87 Hz, 1H), 7.41 (d, *J* = 7.93 Hz, 2H), 7.31−7.21 (m, 4H), 7.08 (d, *J* = 15.87 Hz, 1H), 6.97 (dd, *J* = 8.54, 1.83 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.6, 161.5, 152.5, 149.2, 138.5, 136.7, 134.9, 132.5, 131.1, 128.7, 128.1, 127.8, 126.9, 126.8, 126.4, 125.8, 125.1, 120.6, 113.6, 112.1, 55.5.

HRMS (ESI−TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{19}N_2O_2$; 355.1441, found 355.1442.

2-(4-Bromo-2,6-di((*E*)-styryl)phenyl)quinazolin-4(3*H*)-one (**3d**):



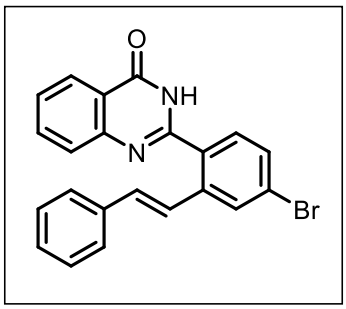
According to the general procedure, the title compound **3d** was obtained as a colorless solid (64 mg; 64% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 228−230 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.7 (s, 1H), 8.23 (d, *J* = 7.93 Hz, 1H), 8.07 (s, 2H), 7.86 (t, *J* = 7.62 Hz, 1H), 7.74 (d, *J* = 8.54 Hz, 1H), 7.61 (t, *J* = 7.32 Hz, 1H), 7.42−7.38 (m, 6H), 7.31−7.21 (m, 6H), 6.84 (d, *J* = 16.48, 2H).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 161.7, 152.3, 148.4, 138.3, 136.3, 134.7, 132.8, 131.3, 128.8, 128.4, 127.4, 127.1, 126.7, 126.6, 126.1, 123.7, 123.2, 121.3.

HRMS (ESI−TOF) *m/z* $[M+H]^+$ calcd for $C_{30}H_{22}N_2O^{79}Br$; 505.0910, found 505.0913.

(*E*)-2-(4-Bromo-2-styrylphenyl)quinazolin-4(3*H*)-one (**3e**):



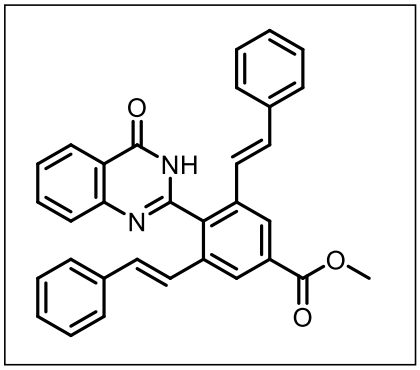
According to the general procedure, the title compound **3e** was obtained as a colorless solid (59 mg; 74% yield): reaction time 36 h/100 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 270−272 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.57 (s, 1H), 8.18 (d, *J* = 7.93 Hz, 1H), 8.15 (s, 1H), 7.85 (t, *J* = 7.32 Hz, 1H), 7.70 (d, *J* = 8.54 Hz, 1H), 7.62 (d, *J* = 7.93 Hz, 1H), 7.58−7.53 (m, 2H), 7.49 (d, *J* = 7.93 Hz, 2H), 7.37−7.31 (m, 4H), 7.26 (d, *J* = 7.32 Hz, 1H).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 161.8, 153.0, 148.6, 138.2, 136.6, 134.5, 132.2, 132.1, 131.9, 129.9, 128.8, 128.2, 128.1, 127.4, 126.83, 126.77, 125.8, 124.2, 123.9, 121.2.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{22}H_{16}N_2O^{79}Br$; 403.0441, found 403.0444.

Methyl 4-(4-oxo-3,4-dihydroquinazolin-2-yl)-3,5-di((*E*)-styryl)benzoate (**3f**):



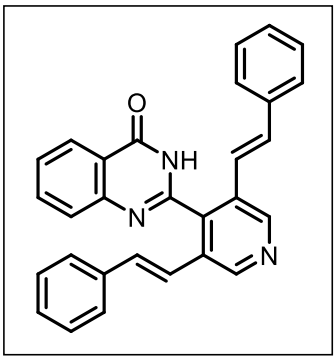
According to the general procedure, the title compound **3f** was obtained as a colorless solid (59 mg; 61% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 227−229 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.77 (s, 1H), 8.35 (s, 2H), 8.24 (d, *J* = 7.93 Hz, 1H), 7.87 (t, *J* = 7.32 Hz, 1H), 7.75 (d, *J* = 7.93 Hz, 1H), 7.62 (t, *J* = 7.62 Hz, 1H), 7.43 (d, *J* = 7.93 Hz, 4H), 7.37 (d, *J* = 16.48 Hz, 2H), 7.30 (t, *J* = 7.82 Hz, 4H), 7.24 (d, *J* = 7.32 Hz, 2H), 6.95 (d, *J* = 16.48 Hz, 2H), 3.98 (s, 3H).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 165.8, 161.5, 152.2, 148.4, 136.9, 136.3, 135.7, 134.7, 132.5, 131.1, 128.8, 128.3, 127.5, 127.2, 126.7, 126.0, 124.6, 123.8, 121.3, 52.6.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{32}H_{25}N_2O_3$; 485.1860, found 485.1860.

2-(3,5-di((*E*)-Styryl)pyridin-4-yl)quinazolin-4(3*H*)-one (**3g**):



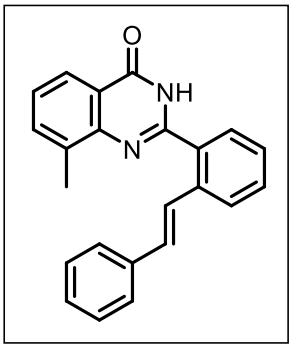
According to the general procedure, the title compound **3g** was obtained as a colorless solid (50 mg; 59% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (20% Acetone in DCM); mp 281−283 ^{o}C

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.77 (s, 1H), 9.06 (s, 2H), 8.23 (d, *J* = 7.93 Hz, 1H), 7.87 (t, *J* = 7.32 Hz, 1H), 7.74 (d, *J* = 8.54 Hz, 1H), 7.62 (t, *J* = 7.32 Hz, 1H), 7.44−7.39 (m, 6H), 7.33−7.23 (m, 6H), 6.95 (d, *J* = 16.48 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.5, 150.8, 148.4, 145.8, 137.4, 136.3, 134.7, 133.0, 130.6, 128.8, 128.4, 127.5, 127.3, 126.8, 126.1, 121.9, 121.6.

HRMS (ESI−TOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{22}N_3O$; 428.1757, found 428.1754.

(*E*)-8-Methyl-2-(2-styrylphenyl)quinazolin-4(3*H*)-one (**3h**):



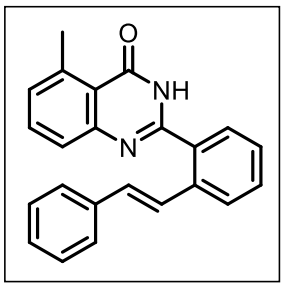
According to the general procedure, the title compound **3h** was obtained as a colorless solid (44 mg; 65% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 263−365 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.54 (s, 1H), 8.02 (d, *J* = 7.93 Hz, 1H), 7.94 (d, *J* = 7.32 Hz, 1H), 7.69 (d, *J*= 7.32 Hz, 1H)**,** 7.65 (d, *J* = 7.32 Hz, 1H), 7.59 (d, *J* = 7.32 Hz, 1H),7.55 (s, 1H), 7.49−7.41 (m, 4H), 7.34 (t, *J* = 7.63 Hz, 2H), 7.26−7.21 (m, 2H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 162.3, 152.4, 147.1, 137.0, 136.2, 135.5, 134.8, 133.0, 130.3, 130.1, 130.0, 128.7, 127.8, 127.3, 126.5, 126.4, 126.1, 126.0, 123.4, 120.9, 17.1.

HRMS (ESI−TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{19}N_2O$; 339.1492, found 339.1492.

(*E*)-5-Methyl-2-(2-styrylphenyl)quinazolin-4(3*H*)-one (**3i**):



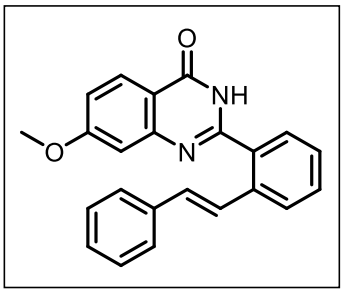
According to the general procedure, the title compound **3i** was obtained as a colorless solid (47 mg; 69% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 232−234 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.32 (s, 1H), 7.94 (d, *J* = 7.93 Hz, 1H), 7.65 (t, *J* = 7.62 Hz, 1H), 7.56 (t, *J* = 7.62 Hz, 2H), 7.50−7.39 (m, 5H), 7.34−7.23 (m, 5H); 2.83 (s, 3H).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 162.3, 153.6, 150.3, 140.0, 137.0, 135.7, 133.5, 133.0, 130.4, 130.1, 129.7, 129.0, 128.8, 127.8, 127.3, 126.5, 125.7, 125.6, 125.5, 119.4, 22.5.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{23}H_{19}N_2O$; 339.1492, found 339.1494.

(*E*)-7-Methoxy-2-(2-styrylphenyl)quinazolin-4(3*H*)-one (**3j**):



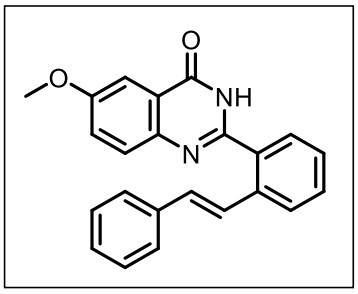
According to the general procedure, the title compound **3j** was obtained as a colorless solid (45 mg; 63% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 198−200 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.40 (s, 1H), 8.08 (d, *J* = 9.16 Hz, 1H), 7.94 (d, *J* = 7.93 Hz, 1H), 7.56 (t, *J* = 7.02 Hz, 2H), 7.48−7.41 (m, 3H), 7.38−7.31 (m, 3H), 7.27 (s, 1H), 7.24 (d, *J* = 7.32 Hz, 1H), 7.14−7.12 (m, 2H), 3.89 (s, 3H).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 164.1, 161.3, 154.6, 150.9, 136.9, 135.6, 133.3, 130.6, 130.2, 129.7, 128.8, 127.9, 127.5, 127.3, 126.6, 125.7, 125.6, 116.2, 114.5, 108.6, 55.7.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{23}H_{19}N_2O_2$; 355.1441, found 355.1442.

(*E*)-6-Methoxy-2-(2-styrylphenyl)quinazolin-4(3*H*)-one (**3k**):



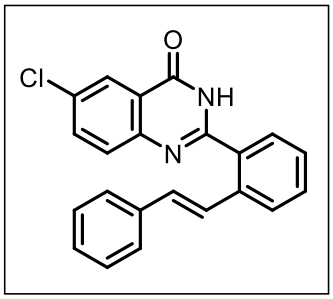
According to the general procedure, the title compound **3k** was obtained as a colorless solid (39 mg; 55% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 219−221 ^{o}C.

^{1}H NMR (500 MHz, DMSO−*d*$_6$) δ (ppm) 12.5 (s, 1H), 7.93 (d, *J* = 8.01 Hz, 1H), 7.65 (d, *J* = 8.77 Hz, 1H), 7.58−7.54 (m, 3H), 7.46−7.44 (m, 3H), 7.42 (s, 1H), 7.37 (d, *J* = 16.4 Hz, 1H), 7.32 (t, *J* = 7.63 Hz, 2H), 7.25 (s, 1H), 7.23 (d, *J* = 8.39 Hz, 1H), 3.90 (s, 3H).

^{13}C NMR (125 MHz, DMSO−*d*$_6$) δ (ppm) 161.6, 157.9, 151.6, 143.2, 137.0, 135.7, 133.3, 130.5, 130.1, 129.8, 129.1, 128.8, 127.9, 127.3, 126.5, 125.7, 123.97, 121.86, 105.9, 55.7 (one 'C' is merged in one of the above peaks).

HRMS (ESI−TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{19}N_2O_2$; 355.1441, found 355.1441.

(*E*)-6-Chloro-2-(2-styrylphenyl)quinazolin-4(3*H*)-one (**3l**):



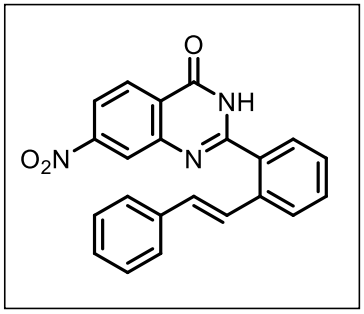
According to the general procedure, the title compound **3l** was obtained as a colorless solid (48 mg; 67% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 258−260 ^{o}C.

^{1}H NMR (400 MHz, DMSO−*d*$_6$) δ (ppm) 12.71 (s, 1H), 8.12 (d, *J* = 1.83 Hz, 1H), 7.95 (d, *J* = 7.93, 1H), 7.87 (dd, *J* = 8.55, 2.44 Hz, 1H), 7.72 (d, *J* = 8.55 Hz, 1H), 7.58 (t, *J* = 8.24 Hz, 2H), 7.49 (d, *J* = 7.93, 2H), 7.44 (d, *J* = 7.32 Hz, 1H), 7.39 (d, *J* = 16.48. 1H), 7.32 (d, *J* = 7.32 Hz, 2H), 7.27−7.23 (m, 2H).

^{13}C NMR (100 MHz, DMSO−*d*$_6$) δ (ppm) 160.9, 154.4, 147.4, 136.9, 135.8, 134.6, 133.0, 130.9, 130.6, 130.3, 129.8, 129.6, 128.7, 127.9, 127.3, 126.6, 125.7, 125.6, 124.8, 122.4.

HRMS (ESI−TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{16}N_2OCl$; 359.0946, found 359.0944.

(*E*)-7-Nitro-2-(2-styrylphenyl)quinazolin-4(3*H*)-one (**3m**):



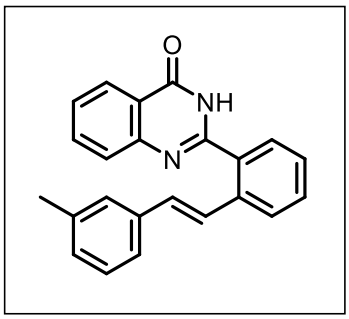
According to the general procedure, the title compound **3m** was obtained as a colorless solid (38 mg; 51% yield): reaction time 36 h/120 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 249−251 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.92 (s, 1H), 8.40 (d, *J* = 9.16 Hz, 2H), 8.27 (d, *J* = 9.16 Hz, 1H), 7.97 (d, *J* = 7.93 Hz, 1H), 7.62−7.58 (m, 2H), 7.52 (d, *J* = 7.32 Hz, 2H), 7.47−7.41 (m, 2H), 7.33−7.22 (m, 4H).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.0, 156.3, 151.2, 149.2, 136.9, 135.9, 132.7, 130.8, 130.5, 129.9, 128.7, 128.2, 127.9, 127.3, 126.7, 125.7, 125.5, 122.3, 120.2 (one 'C' is merged in one of the above peaks).

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{22}H_{16}N_3O_3$; 370.1186, found 370.1187.

(*E*)-2-(2-(3-Methylstyryl)phenyl)quinazolin-4(3*H*)-one (**3n**):



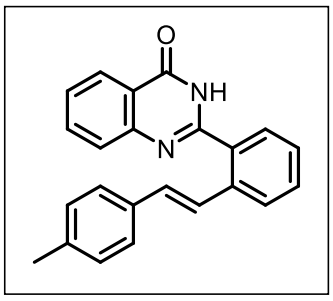
According to the general procedure, the title compound **3n** was obtained as a colorless solid (51 mg; 76% yield): reaction time 36 h/120 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 175−177 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ 12.54 (s, 1H), 8.19 (d, *J* = 7.93 Hz, 1H), 7.92 (d, *J* = 7.32 Hz, 1H), 7.84 (t, *J* = 7.32 Hz, 1H), 7.70 (d, *J* = 7.93 Hz, 1H), 7.60−7.55 (m, 3H), 7.44 (d, *J* = 7.93 Hz, 1H), 7.39 (d, *J* = 16.48 Hz, 1H), 7.26 (d, *J* = 8.55 Hz, 2H), 7.21−7.17 (m, 2H), 7.06 (d, *J* = 6.71 Hz, 1H), 2.25 (s, 3H)

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 161.8, 153.9, 148.7, 137.8, 136.9, 135.8, 134.5, 133.1, 130.7, 130.2, 129.8, 128.61, 128.57, 127.33, 127.25, 126.7, 125.8, 125.7, 125.6, 123.5, 121.1, 20.9 (one 'C' is merged in one of the above peaks).

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{23}H_{19}N_2O$; 339.1492, found 339.1488.

(*E*)-2-(2-(4-Methylstyryl)phenyl)quinazolin-4(3*H*)-one (**3o**):



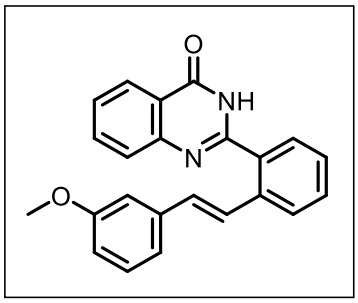
According to the general procedure, the title compound **3o** was obtained as a colorless solid (45 mg; 66% yield): reaction time 36 h/120 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 208−210 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.53 (s, 1H), 8.18 (d. *J* = 7.32 Hz, 1H), 7.92 (d, *J* = 7.32 Hz, 1H), 7.84 (t, *J* = 7.63 Hz, 1H), 7.69 (d, *J* = 7.93 Hz, 1H), 7.58−7.53 (m, 3H), 7.41 (t, *J* = 7.63 Hz, 1H), 7.36−7.30 (m, 3H), 7.20 (d, *J* = 16.48 Hz, 1H), 7.12 (d, *J* = 7.93 Hz, 2H), 2.26 (s, 3H).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 161.8, 153.9, 148.7, 137.3, 135.9, 134.5, 134.2, 133.1, 130.5, 130.2, 129.8, 129.3, 127.4, 127.1, 126.7, 126.5, 125.8, 125.6, 124.6, 121.1, 20.82.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{23}H_{19}N_2O$; 339.1492, found 339.1488.

(*E*)-2-(2-(3-Methoxystyryl)phenyl)quinazolin-4(3*H*)-one (**3p**):



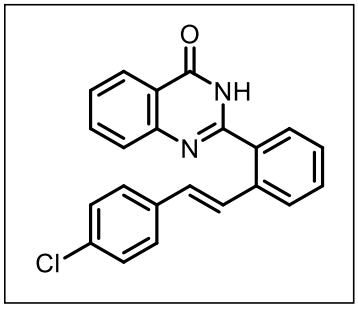
According to the general procedure, the title compound **3p** was obtained as a colorless solid (33 mg; 47% yield): reaction time 36 h/120 ^{o}C; R_f 0.4 (2% Acetone in DCM); mp 164−166 ^{o}C.

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.53 (s, 1H), 8.18 (d, *J* = 7.32 Hz, 1H), 7.92 (d, *J* = 7.93 Hz, 1H), 7.84 (t, *J* = 7.63 Hz, 1H), 7.70 (d, *J* = 7.93 Hz, 1H), 7.61−7.54 (m, 3H), 7.44−7.40 (m, 2H), 7.25−7.19 (m, 2H), 7.07−7.01 (m, 2H), 6.82 (dd, *J* = 7.93, 1.83 Hz, 1H), 3.70 (s, 3H).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 161.9, 159.5, 153.8, 148,7, 138.5, 135.7, 134.5, 133.1, 130.4, 130.2, 129.83, 129.78, 127.38, 127.33, 126.7, 126.2, 125.8, 125.8, 121.1, 118.9, 113.4, 112.1, 55.0.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{23}H_{19}N_2O_2$; 355.1441, found 355.1439.

(*E*)-2-(2-(4-Chlorostyryl)phenyl)quinazolin-4(3*H*)-one (**3q**):



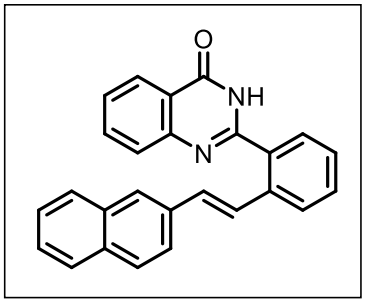
According to the general procedure, the title compound **3q** was obtained as a colorless solid (32 mg; 45% yield) reaction time 36 h/120 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 284−286 ^{o}C;

^{1}H NMR (400 MHz, DMSO−d_6) δ (ppm) 12.53 (s, 1H), 8.18 (d, *J* = 7.93 Hz, 1H), 7.94 (d, *J* = 7.32 Hz, 1H), 7.84 (t, *J* = 7.32 Hz, 1H), 7.68 (d, *J* = 7.93 Hz, 1H), 7.60−7.56 (m, 3H), 7.51 (d, *J* = 8.54 Hz, 2H), 7.46−7.37 (m, 4H), 7.25 (d, *J* = 16.48 Hz, 1H).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 161.8, 153.8, 148.7, 135.9, 135.6, 134.5, 133.3, 132.2, 130.2, 129.9, 129.2, 128.7, 128.2, 127.5, 127.4, 126.7, 126.6 125.81, 125.76 (one 'C' is merged in one of the above peaks);

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{22}H_{16}N_2OCl$; 359.0946, found 359.0942.

(*E*)-2-(2-(2-(Naphthalen-2-yl)vinyl)phenyl)quinazolin-4(3*H*)-one (**3r**):

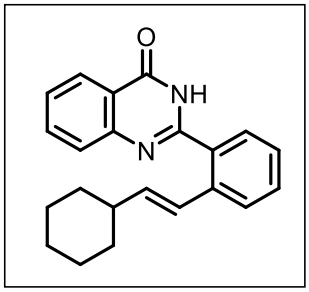


According to the general procedure, the title compound **3r** was obtained as a colorless solid (40 mg; 53% yield): reaction time 48 h/120 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 265−267 ^{o}C. **^{1}H NMR (400 MHz, DMSO−d_6)** δ (ppm) 12.58 (s, 1H), 8.2 (d, *J* = 7.32 Hz, 1H), 8.0 (d, *J* = 7.93 Hz, 1H), 7.95 (s,1H), 7.87−7.83 (m, 4H), 7.73−7.67 (m, 2H), 7.63−7.55 (m, 4H), 7.51−7.40 (m, 4H);).

^{13}C NMR (100 MHz, DMSO−d_6) δ (ppm) 161.9, 153.9, 148.8, 135.9, 134.6, 134.5, 133.23, 133.19, 132.6, 130.6, 130.3, 130.0, 128.1, 127.9, 127.6, 127.40, 127.39, 126.8, 126.7, 126.5, 126.3, 126.2, 125.9, 125.8, 123.4, 121.2.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{26}H_{19}N_2O$; 375.1492, found 375.1489.

(*E*)-2-(2-(2-Cyclohexylvinyl)phenyl)quinazolin-4(3*H*)-one (**3s**):



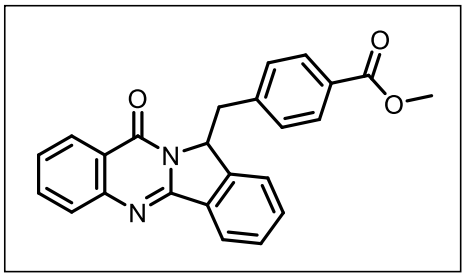
According to the general procedure, the title compound **3s** was obtained as a colorless solid (26 mg; 40% yield, *E*:*Z* 7:1): reaction time 48 h/150 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 119−121 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.36 (s, 1H), 8.33 (d, *J* = 7.96 Hz, 1H), 7.84−7.81 (m, 2H), 7.70 (dd, *J* = 1.33, 7.53 Hz, 1H), 7.59−7.51 (m, 2H), 7.50−7.44 (m, 1H), 7.40 (dd, *J* = 1.64, 7.33 Hz, 1H), 6.59 (d, *J* = 15.66 Hz, 1H), 6.18 (dd, *J* = 6.82, 15.92 Hz, 1H), 2.21−2.06 (m, 1H), 1.81−1.70 (m, 4H), 1.34−1.29 (m, 2H), 1.22−1.17 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.8, 153.0, 149.1, 141.9, 137.0, 134.8, 131.6, 130.9, 129.3, 127.9, 127.5, 127.4, 127.1, 126.4, 124.4, 120.8, 41.2, 32.6, 26.0, 25.9.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{22}H_{23}N_2O$; 331.1805, found 331.1805.

Methyl 4-((10-oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-12-yl)methyl)benzoate (**4a**):



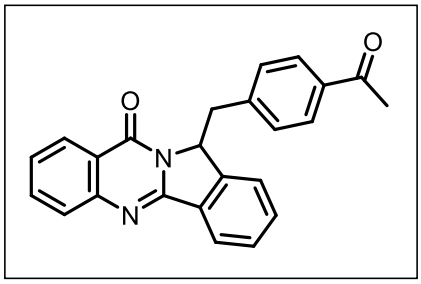
According to the general procedure, the title compound **4a** was obtained as a colorless solid (44 mg; 58% yield); reaction time: 48 h/130 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 249−251 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.93 Hz, 1H), 8.02 (d, *J* = 7.32 Hz, 1H), 7.83−7.72 (m, 4H), 7.61−7.52 (m, 3H), 7.31 (d, *J* = 7.32 Hz, 1H), 6.95 (d. *J* = 7.93 Hz, 2H), 5.85 (d, *J* = 6.10 Hz, 1H), 3.92-3.85 (m, 1H), 3.84 (s, 3H), 3.67 (dd, *J* = 7.32, 13.43 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.8, 161.0, 154.4, 149.2, 142.9, 140.1, 134.4, 132.2, 132.1, 129.7, 129.4, 129.2, 128.8, 127.4, 126.6, 123.5, 123.3, 120.9, 62.4, 52.0, 36.7 (one 'C' is merged in one of the above peaks).

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{24}H_{19}N_2O_3$; 383.1390, found 383.1373.

12-(4-Acetylbenzyl)isoindolo[1,2-b]quinazolin-10(12H)-one (**4b**):



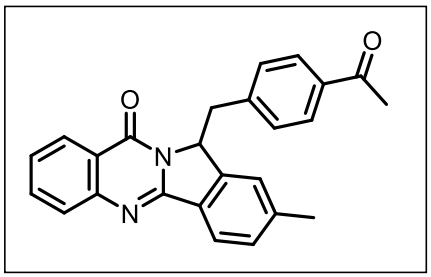
According to the general procedure, the title compound **4b** was obtained as a colorless solid (45 mg; 62% yield): reaction time 48 h/130 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 198−200 ^{o}C.

^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm) 8.44 (d, J = 7.71 Hz, 1H), 8.13 (d, J = 7.96 Hz, 1H), 7.88−7.77 (m, 2H), 7.66−7.52 (m, 5H), 7.35 (d, J = 7.07, 1H), 6.96 (d, J = 8.21 Hz, 2H), 5.89−5.84 (m, 1H), 3.90−3.67 (m, 2H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 197.7, 161.0, 154.4, 149.2, 142.9, 140.3, 135.8, 134.4, 133.5, 132.1, 129.9, 129.3, 128.5, 128.2, 127.4, 126.6, 123.5, 123.3, 120.91, 62.4, 36.6, 26.5.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{24}H_{19}N_2O_2$; 367.1441, found 367.1443.

12-(4-Acetylbenzyl)-2-methylisoindolo[1,2-b]quinazolin-10(12H)-one (**4c**):



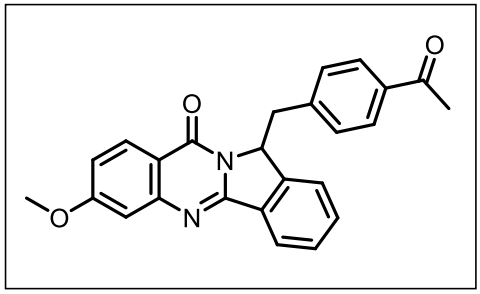
According to the general procedure, the title compound **4c** was obtained as a colorless solid (50 mg; 66% yield): reaction time 48 h/130 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 215−217 ^{o}C.

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.41 (d, J = 7.93 Hz, 2H), 8.09 (s, 1H), 7.85−7.79 (m, 1H), 7.65−7.57 (m, 3H), 7.42 (s, 1H), 7.23 (s, 1H), 6.91 (d, J = 7.32 Hz, 2H), 5.86 (s, 1H), 3.79 (s, 2H), 2.53 (s, 3H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 197.5, 159.8, 155.1, 145.5, 144.0, 142.0, 139.4, 136.1, 135.3, 131.1, 129.7, 128.3, 127.5, 127.4, 126.9, 125.6, 124.9, 123.6, 119.8, 63.32, 36.4, 26.5, 22.4.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{25}H_{21}N_2O_2$; 381.1598, found 381.1601.

12-(4-Acetylbenzyl)-7-methoxyisoindolo[1,2-b]quinazolin-10(12H)-one (**4d**):



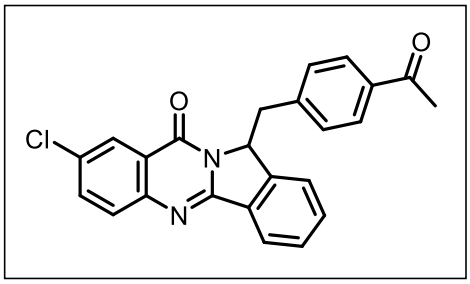
According to the general procedure, the title compound **4d** was obtained as a colorless solid (38 mg; 48% yield): reaction time 48 h/130 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 192−194 ^{o}C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23 (d, J = 8.84 Hz, 1H), 8.02 (d, J = 7.45 Hz, 1H), 7.57-7.42 (m, 4H), 7.28 (d, J = 7.33 Hz, 1H), 7.14 (s, 1H), 7.03 (dd, J = 8.84, 2.40 Hz, 1H), 6.86 (d, J = 8.21 Hz, 2H), 5.75 (dd, J = 6.32, 3.54 Hz, 1H), 3.87 (s, 3H), 3.79-3.60 (m, 2H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.6, 165.1, 159.7, 155.3, 143.5, 139.7, 135.9, 133.2, 129.8, 129.6, 128.2, 128.2, 124.8, 123.3, 117.4, 113.6, 106.6, 63.0, 55.9, 36.5, 26.5.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{25}H_{21}N_2O_3$; 397.1547, found 397.1548.

12-(4-Acetylbenzyl)-8-chloroisoindolo[1,2-b]quinazolin-10(12H)-one (**4e**):



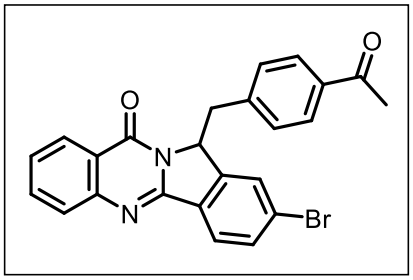
According to the general procedure, the title compound **4e** was obtained as a colorless solid (38 mg; 48% yield): reaction time 48 h/130 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 171−173 ^{o}C.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.40−8.37 (m, 2H), 7.97 (d, J = 8.72 Hz, 1H), 7.78−7.56 (m, 5H), 7.41 (d, J = 7.33 Hz, 1H), 6.91 (d, J = 8.08 Hz, 2H), 5.92−5.88 (m, 1H), 3.86−3.72 (m, 2H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.5, 159.1, 155.0, 143.3, 139.4, 136.0, 135.4, 133.4, 133.1, 130.2, 129.8, 129.7, 128.3, 127.5, 126.2, 125.1, 123.3, 121.4, 63.3, 36.4, 26.5.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{24}H_{18}O_2N_2Cl$; 401.1051, found 401.1055.

12-(4-Acetylbenzyl)-2-bromoisoindolo[1,2-b]quinazolin-10(12H)-one (**4f**):



According to the general procedure, the title compound **4f** was obtained as a colorless solid (36 mg; 40% yield): reaction time 48 h/130 ^{o}C; R_f 0.5 (2% Acetone in DCM); mp 213−215 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) 8.41 (d, *J* = 7.93 Hz, 1H), 8.02 (d, *J* = 7.93 Hz, 1H), 7.83 (s, 1H), 7.79 (t, *J* = 7.62 Hz, 1H), 7.72 (d, *J* = 7.93 Hz, 1H), 7.62 (t, *J* = 7.32 Hz, 1H), 7.56 (d, *J* = 7.93 Hz, 2H), 7.48 (d, *J* = 7.32 Hz, 1H), 6.80 (d, *J* = 7.93 Hz, 2H), 5.96 (s, 1H), 4.28 (d, *J* = 13.43 Hz, 1H), 3.80 (d, *J* = 13.43 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.4, 159.9, 152.7, 146.2, 138.1, 136.3, 135.7, 134.5, 130.2, 129.8, 128.5, 128.4, 128.3, 127.2, 127.1, 126.2, 124.7, 120.5, 97.2, 43.4, 29.7, 26.5.

HRMS (ESI−TOF) ***m/z*** $[M+H]^+$ calcd for $C_{24}H_{18}N_2O_2Br$; 445.0546, found 445.0538.

1.1.9. References

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1.1.10. Selected ^{1}H and ^{13}C NMR spectra

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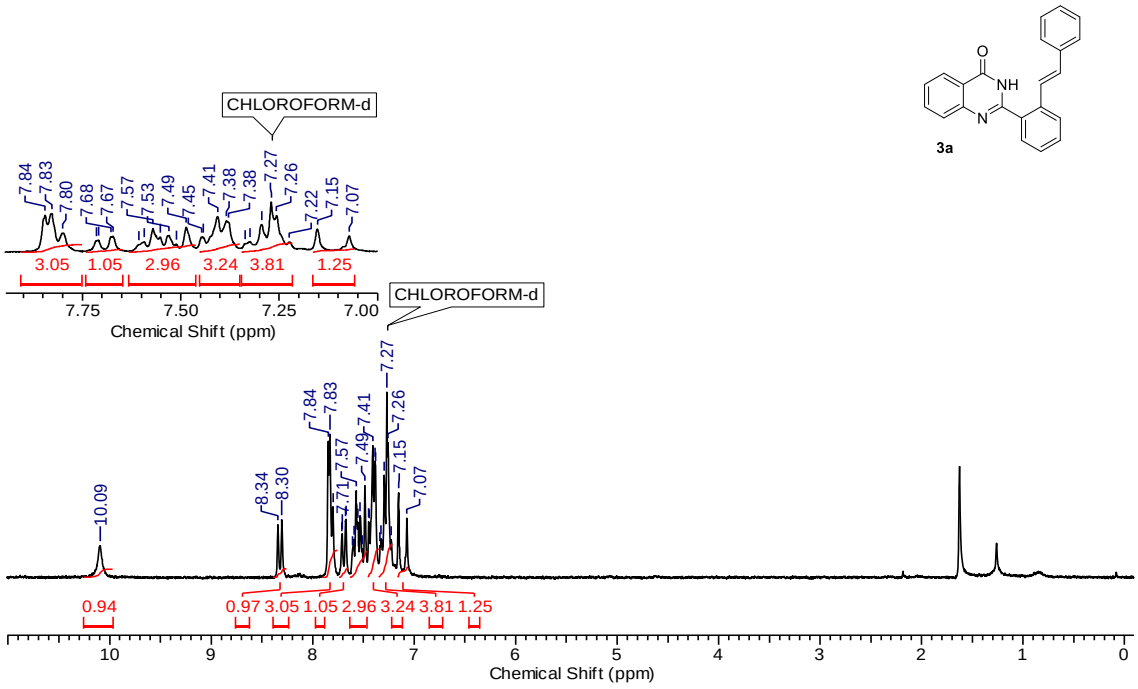

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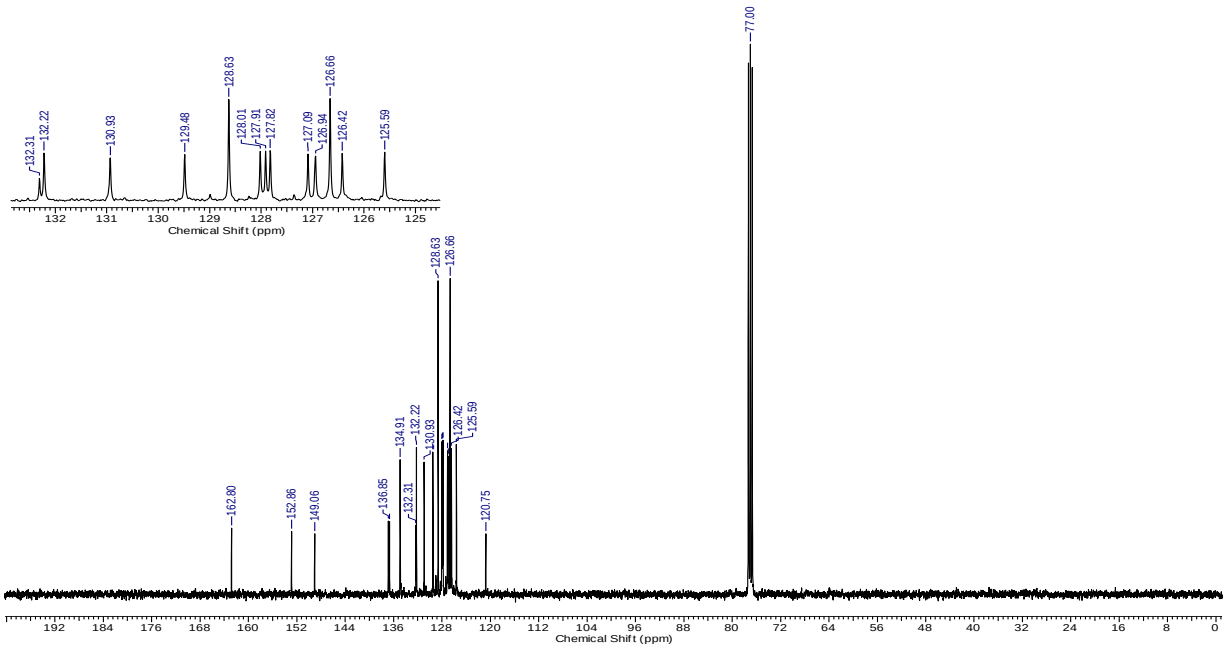

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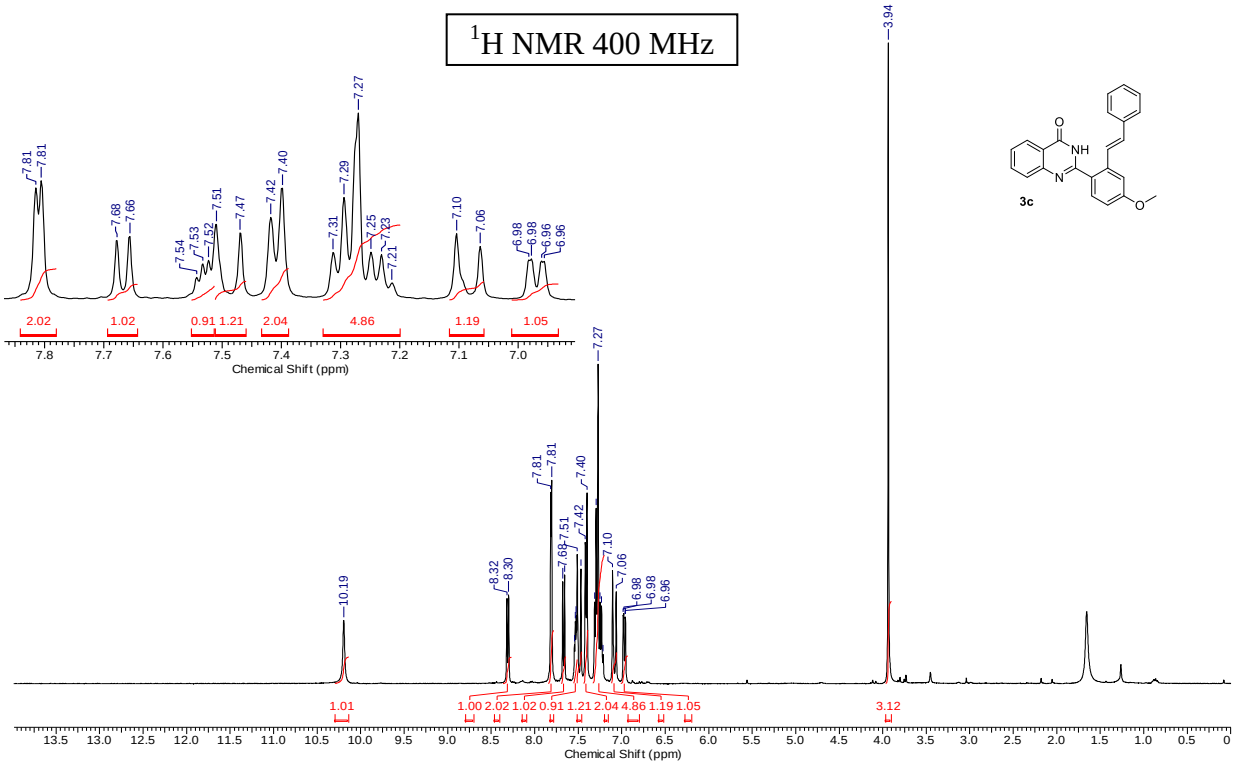

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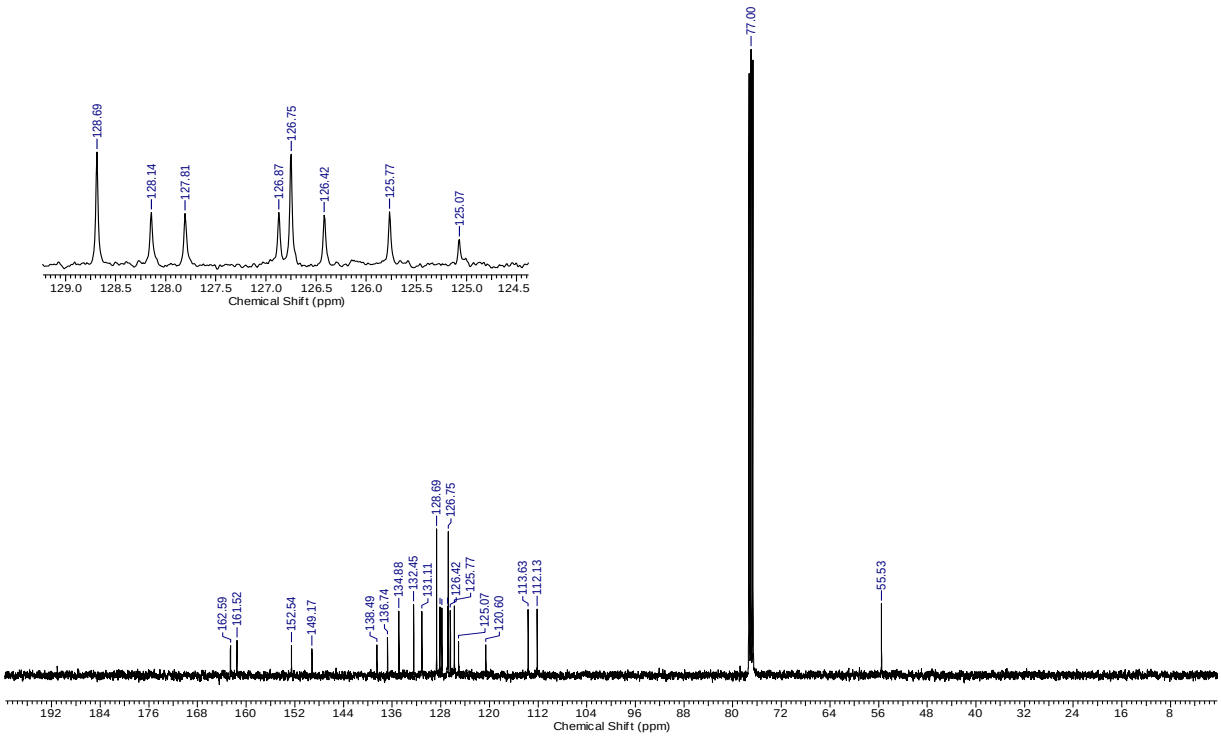

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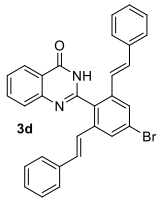

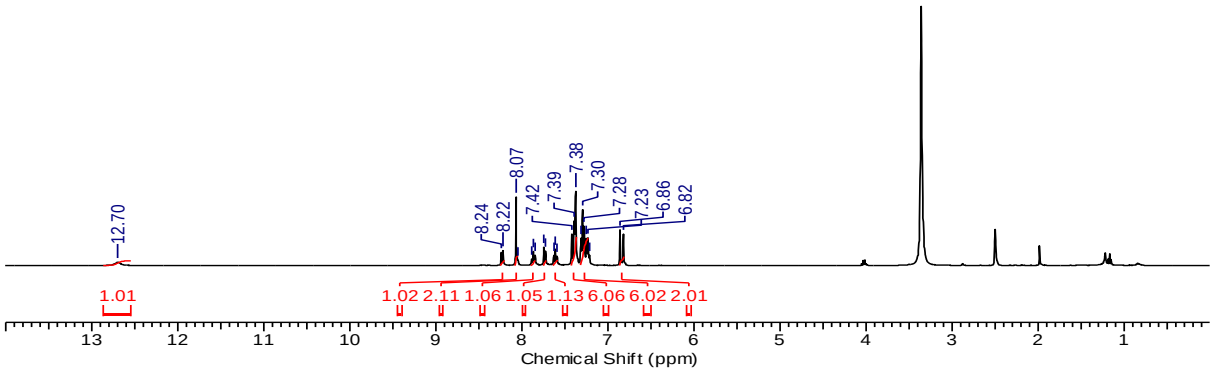

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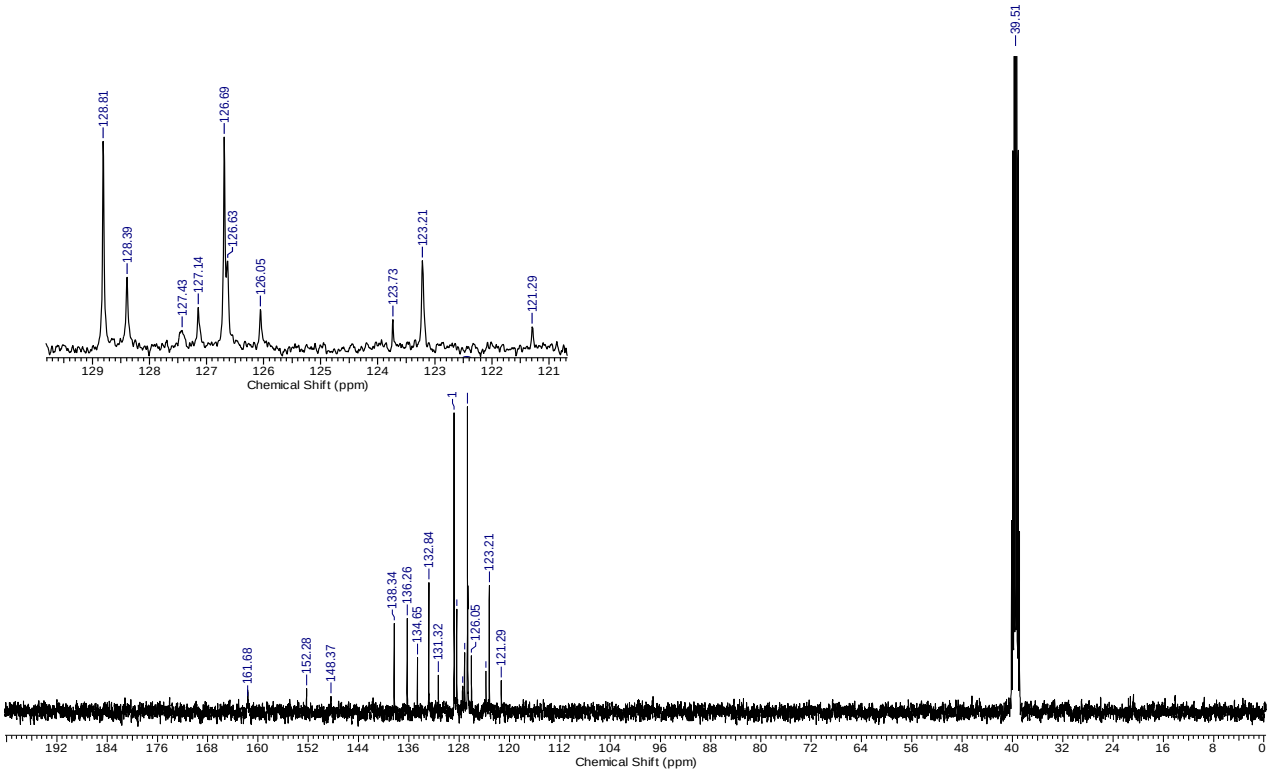

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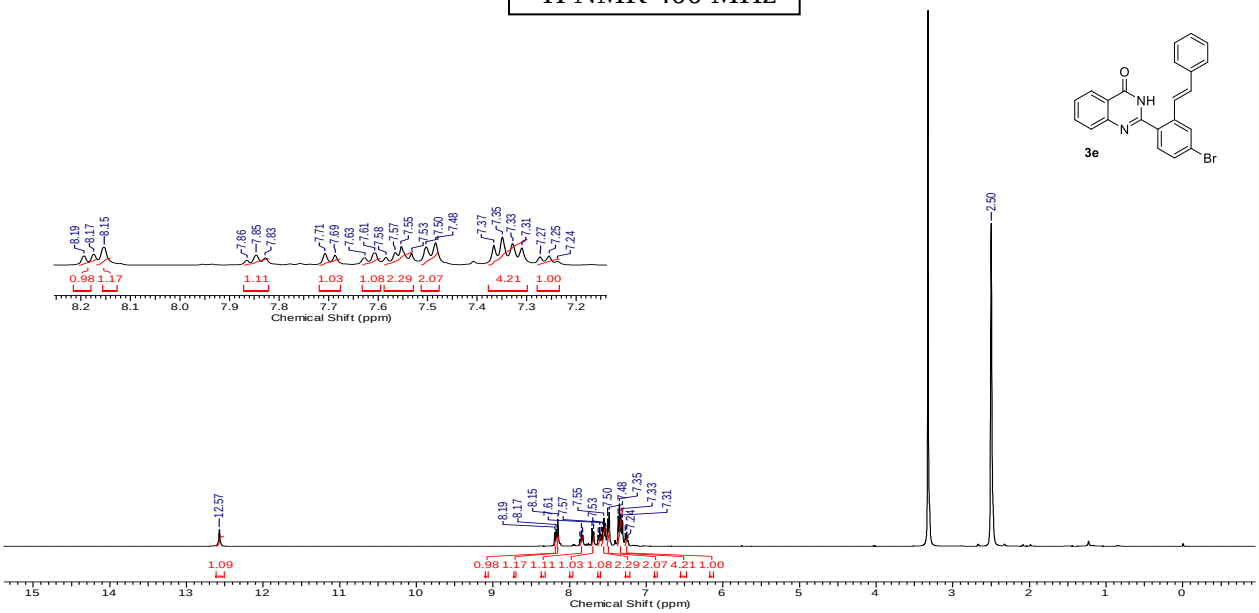

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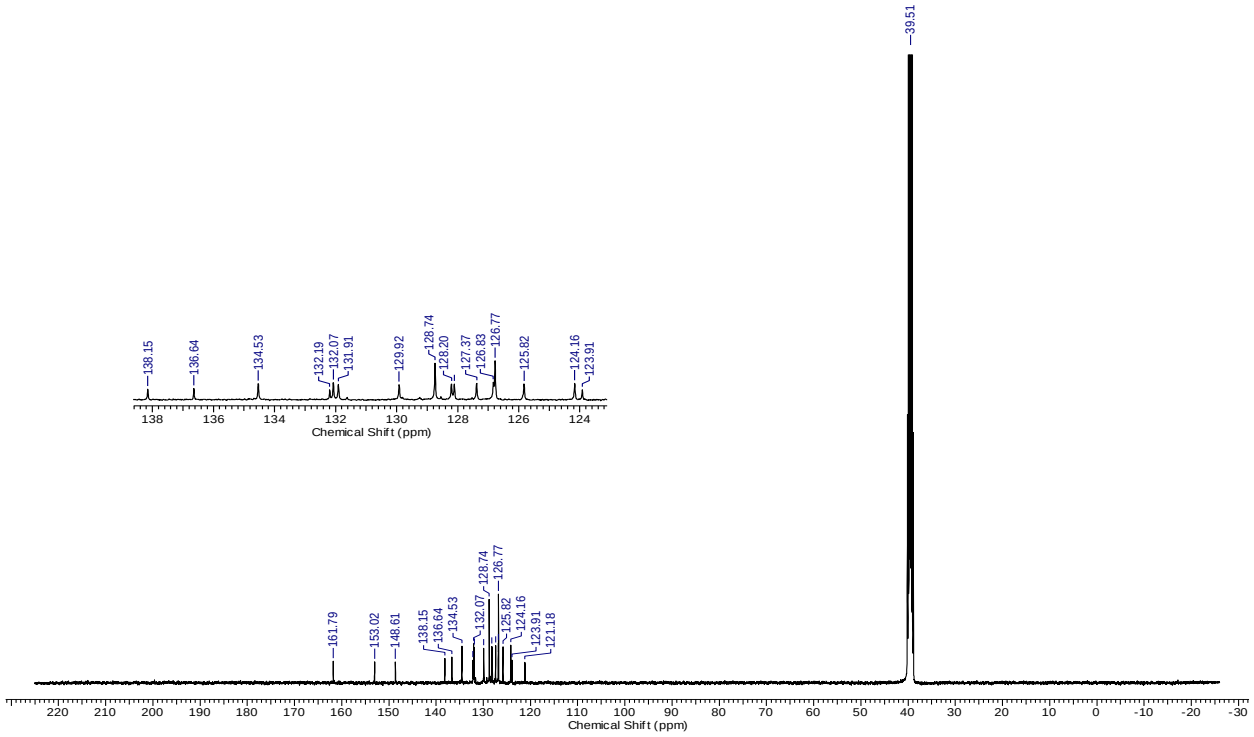

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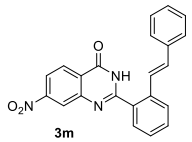

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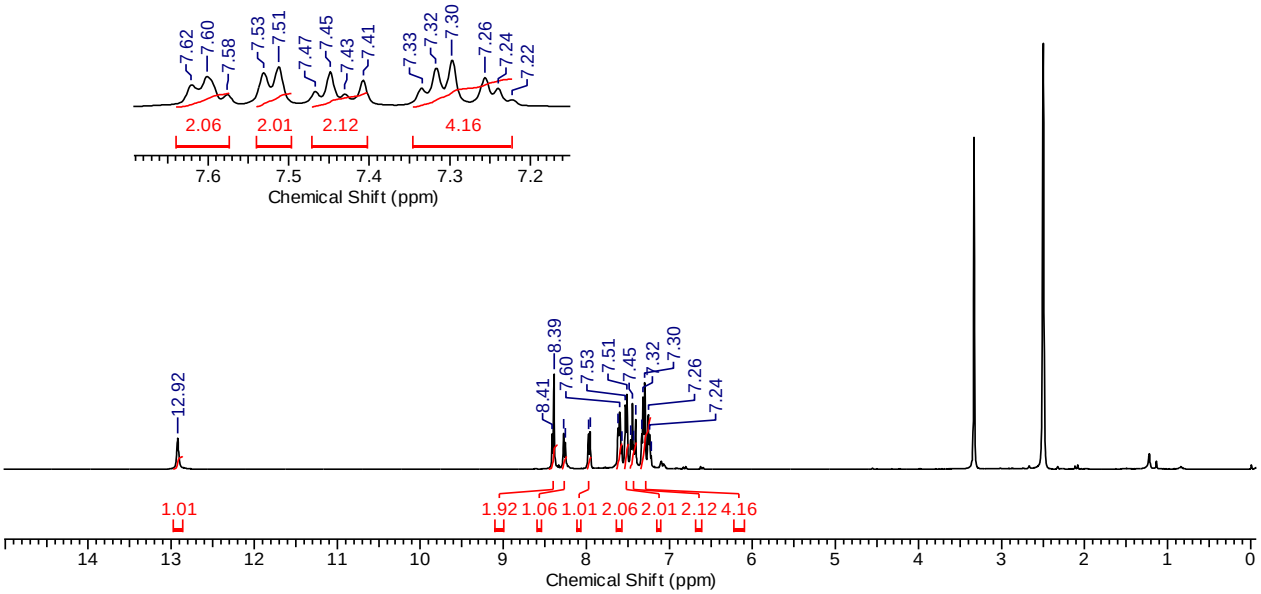

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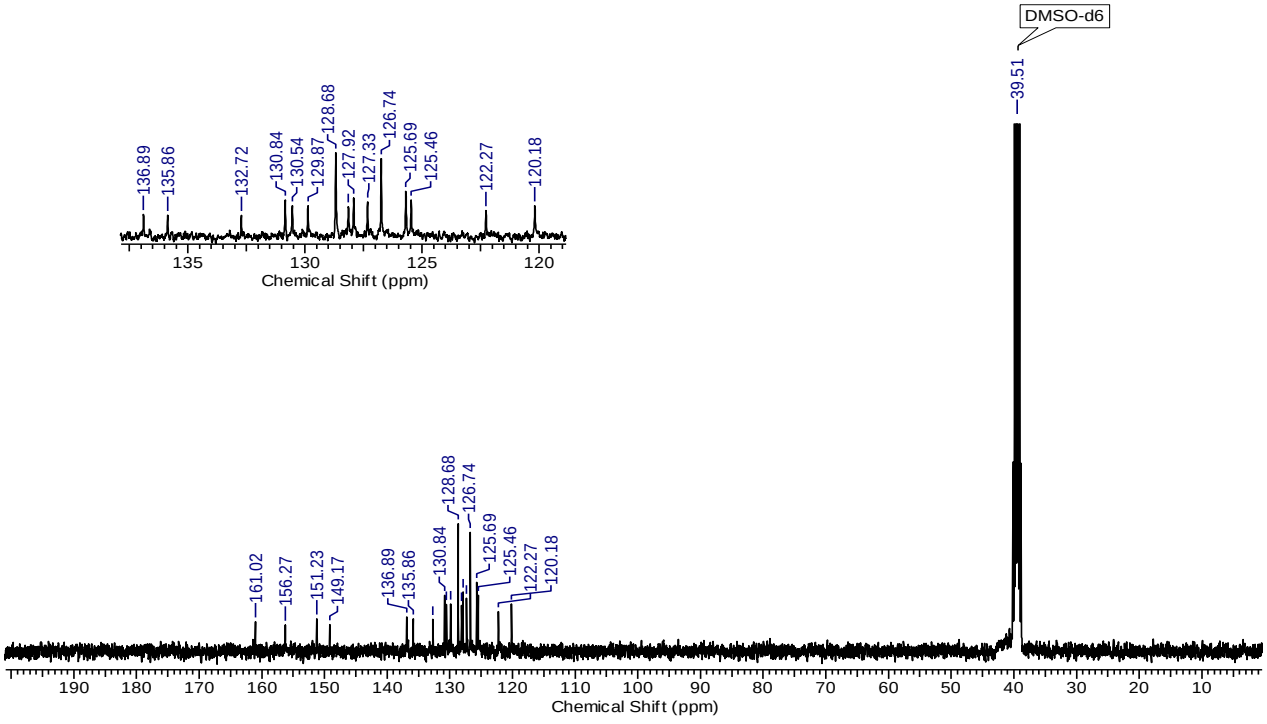

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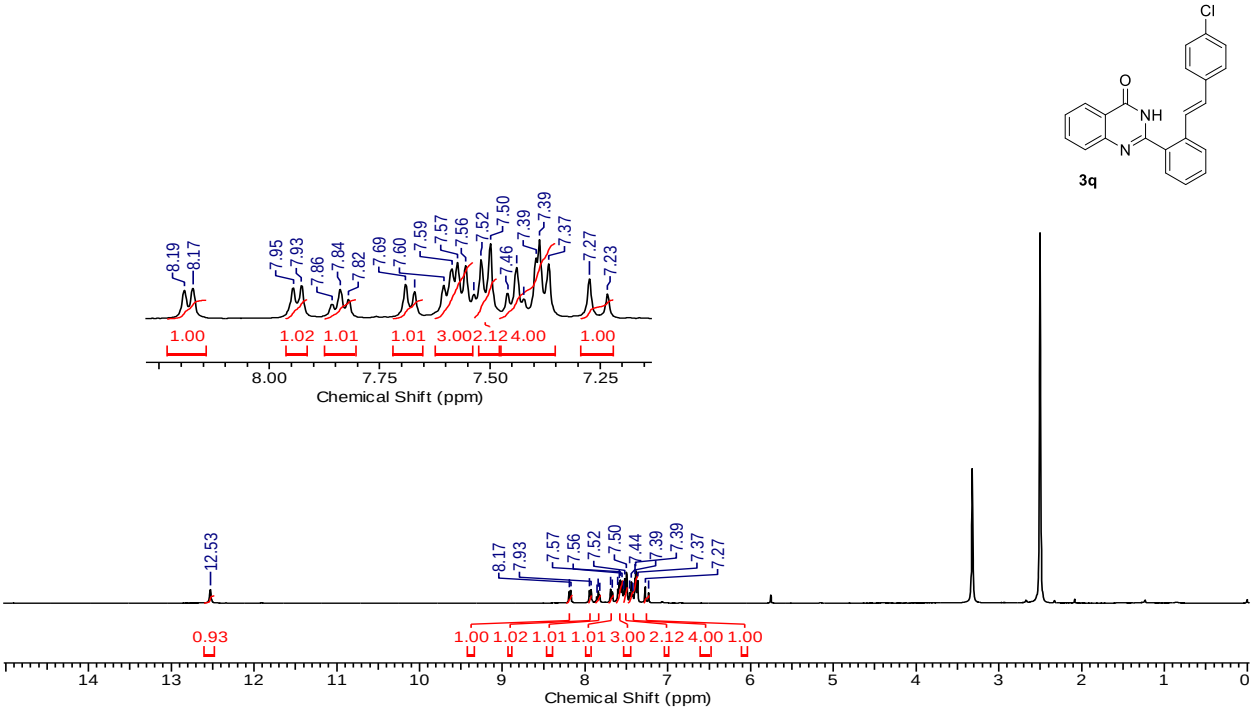

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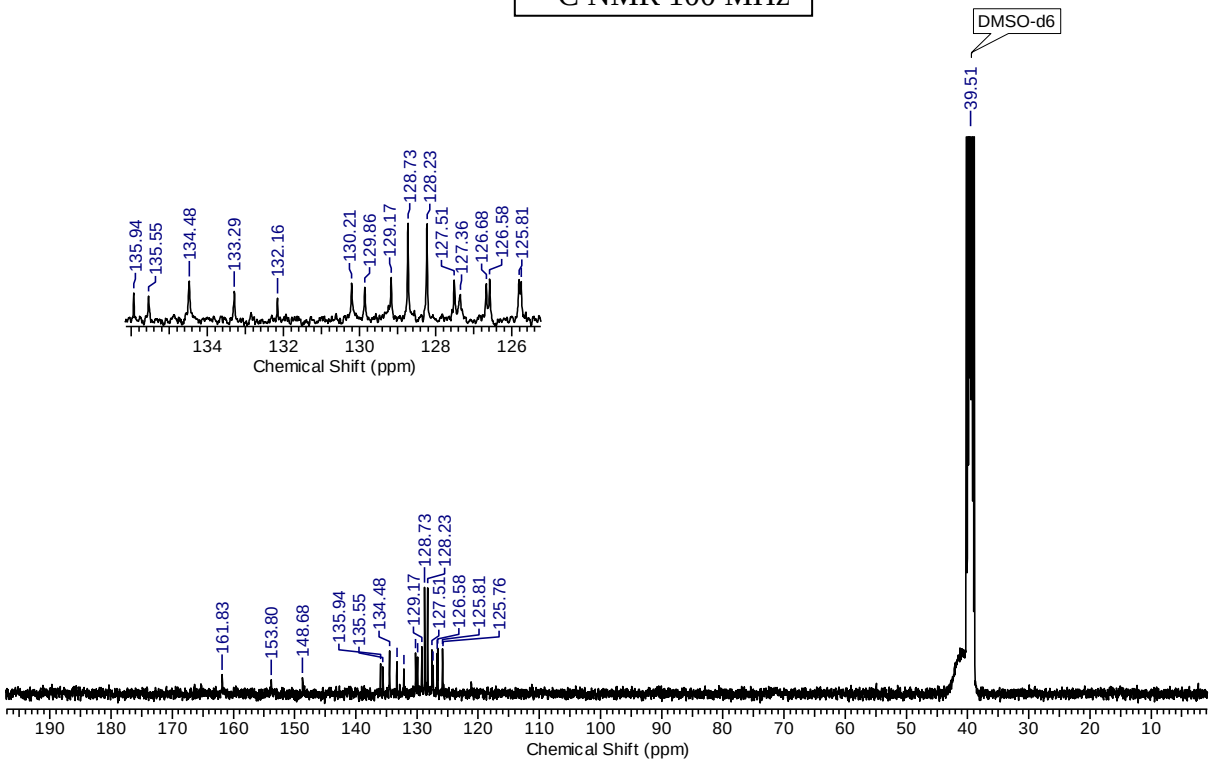

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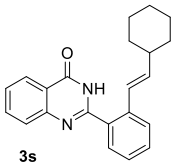

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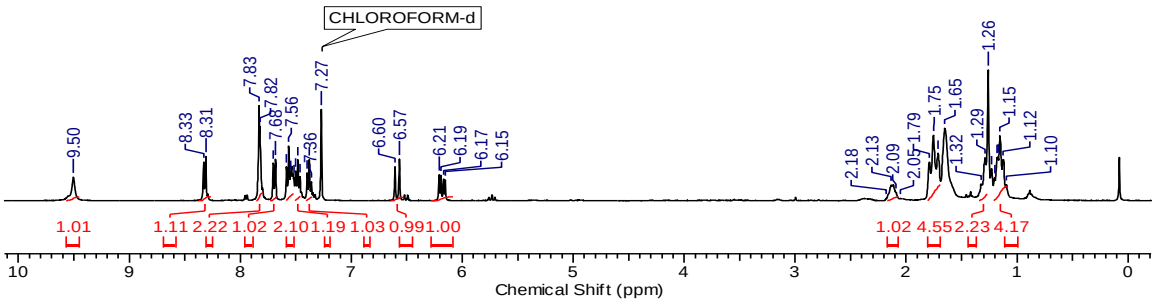

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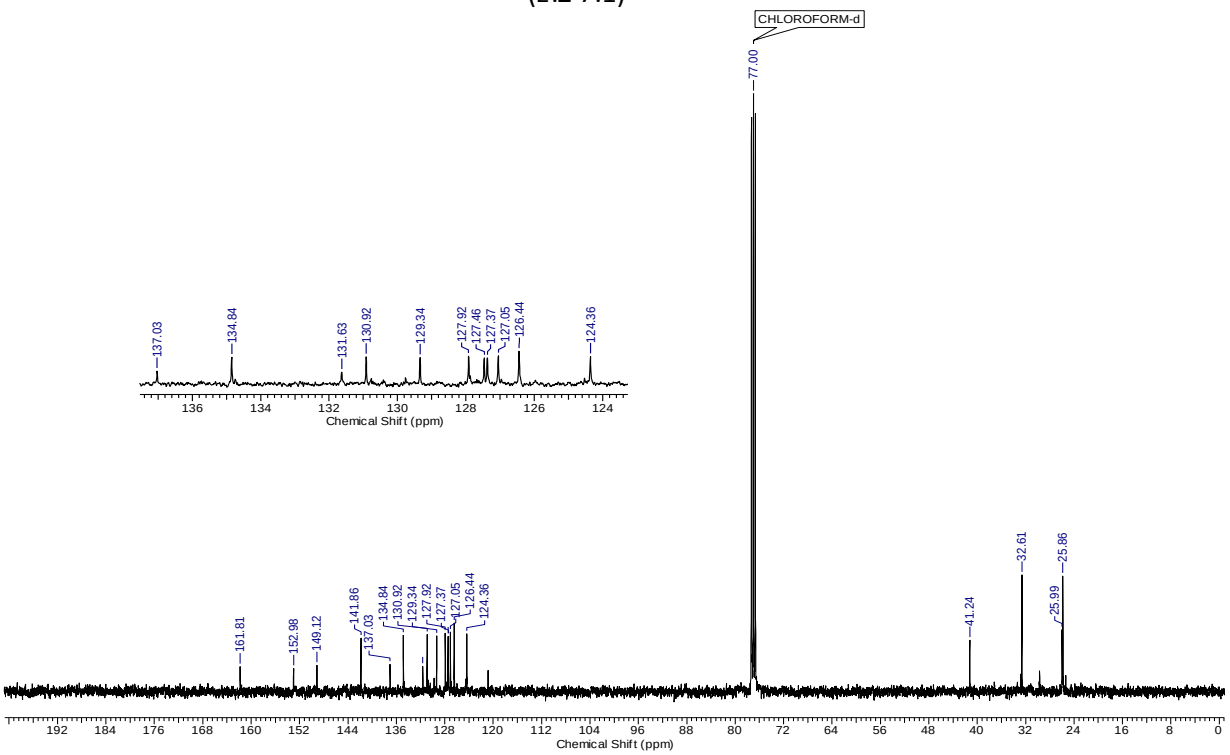

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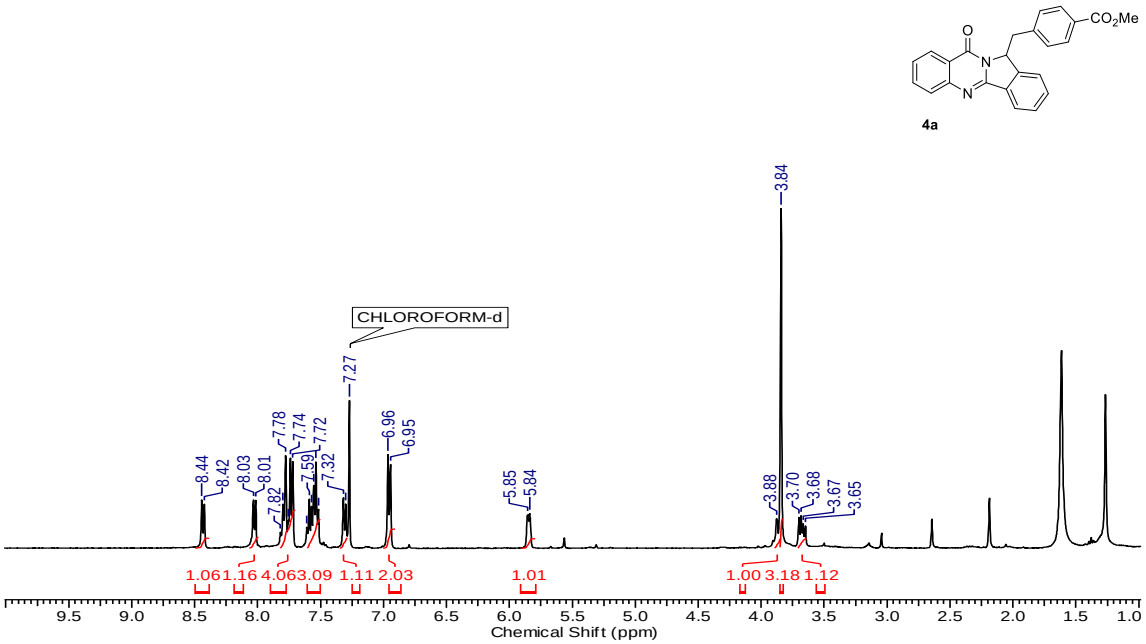

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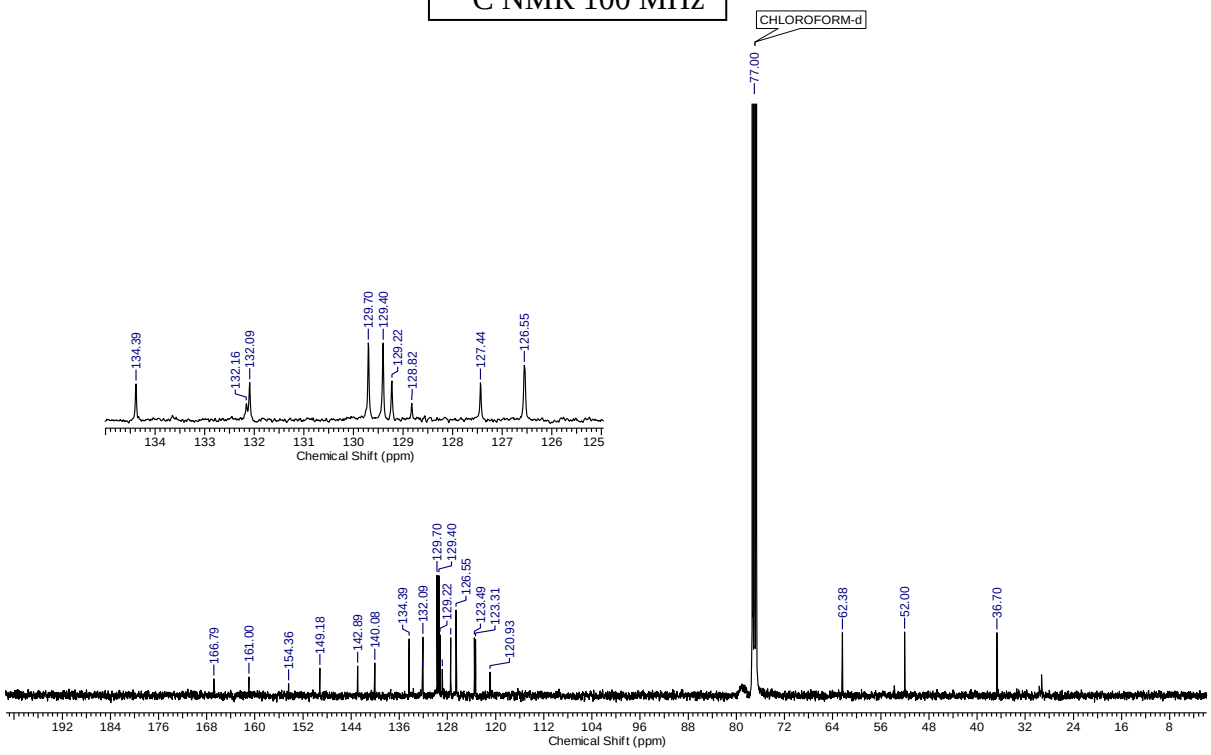

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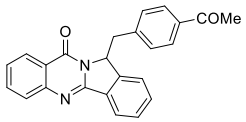
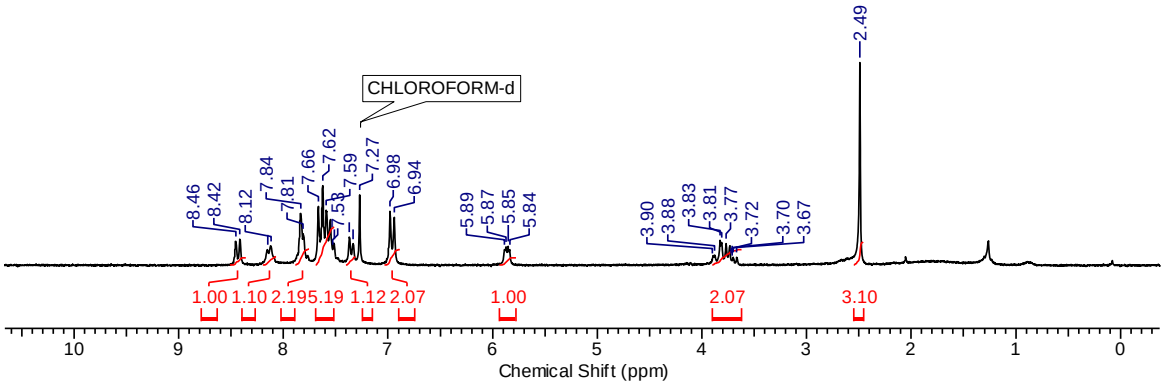


4b



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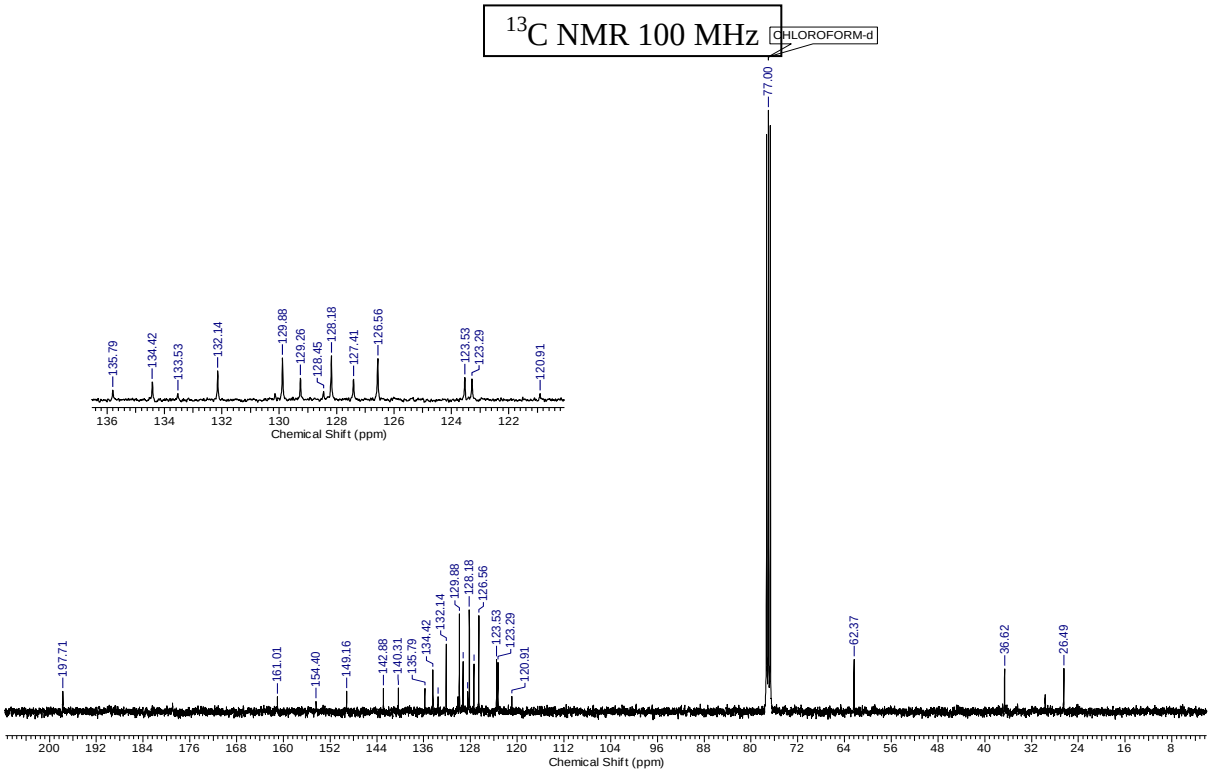

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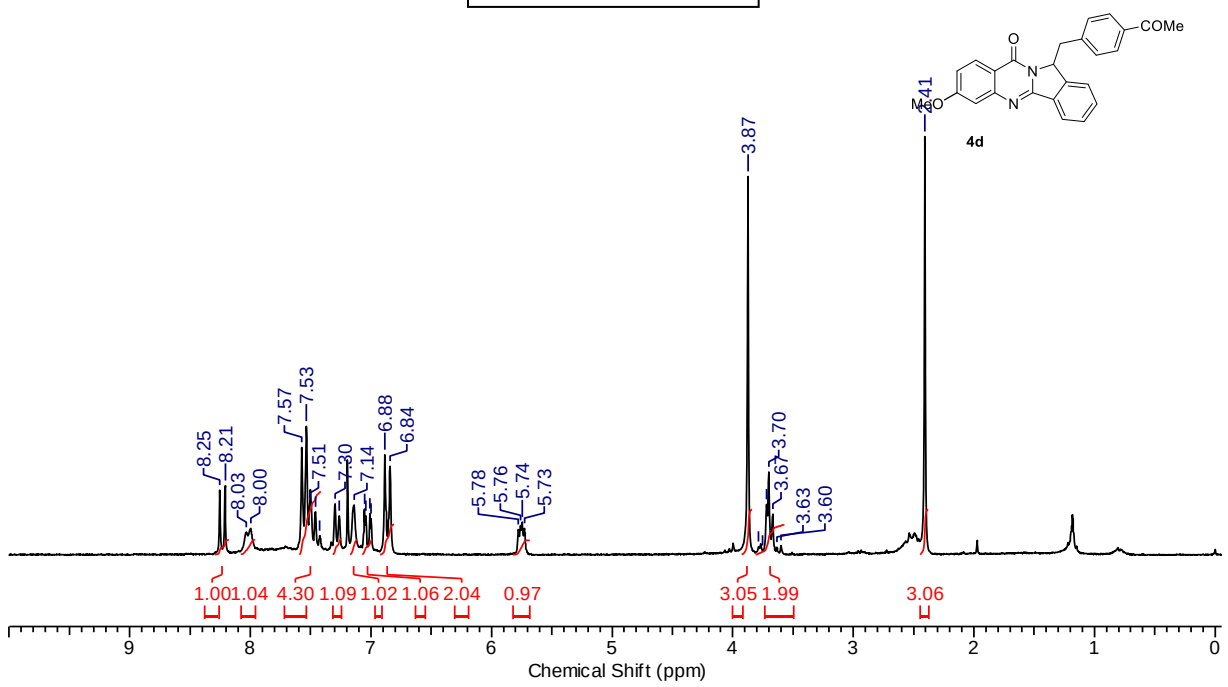

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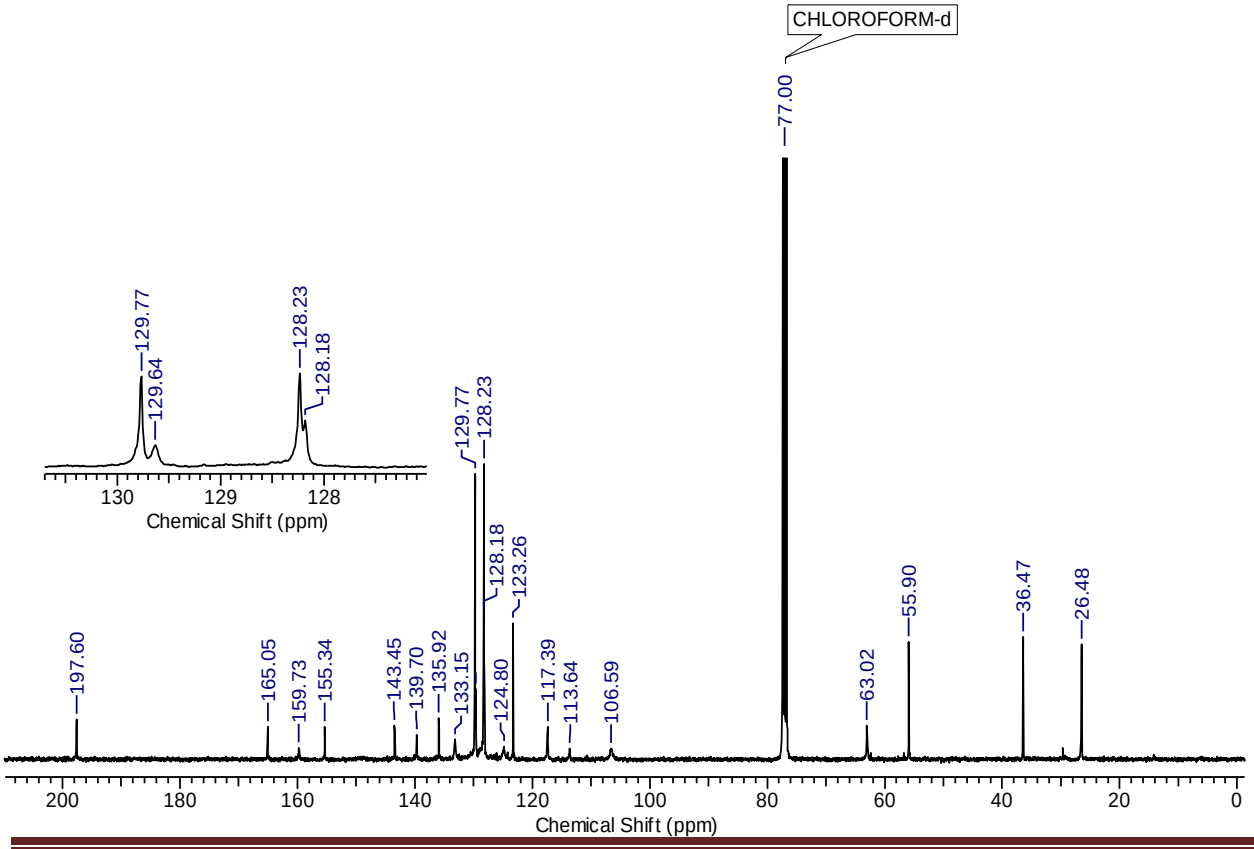


Section 2. Studies Towards the Total Synthesis of Crispine and Related Natural Products via Pd-Catalyzed Aminoalkylation Reaction

1.2.1. Abstract

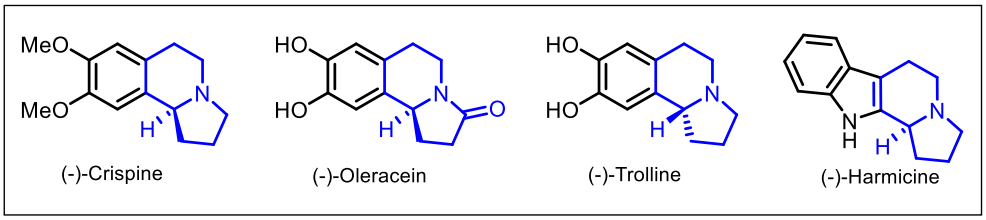
Herein, we describe our efforts towards the synthesis of Crispine and related natural products using C–H functionalization reaction as key step. We hypothesized to utilize Pd-catalyzed tandem aminoalkylation to construct [6+5] heterocyclic rings of Crispine. We have synthesized the required precursor for the key-step and observed either formation of unwanted product or unreacted stating material under various reaction conditions utilized. Appropriate catalyst system should provide the desired transformation

1.2.2. Introduction

Indolizidine containing natural products are found to be widely distributed in the nature. They possess good structural variation and diverse bioactivity (Figure 1).[1] The pyrroloisoquinoline alkaloid (+)-Crispine A, which was isolated by Zhao and co-workers in 2002 from *Carduus crispus*, shows significant biological activity against KB, SKOV3, and HeLa human cancer cell lines and since then it became the target of interest for the synthetic chemists.[1] Several synthetic reports have been published for the Crispine A natural product and the main focus remained on the construction of Indolizidine ring.[2] Interestingly, literature reports revealed that, the synthesis of this heterocycle is of the immense interest to chemists even before and after its isolation as natural product or it's naming as Crispine A.[3]

In the past three decades, a remarkable progress has been made towards the cascade C−C and C−heteroatom bond formations across the alkenes by the cross-coupling and C−H activation.[4] The development of cascade reactions involving the vicinal difunctionalization of

Figure 1. Indolizidine containing natural products



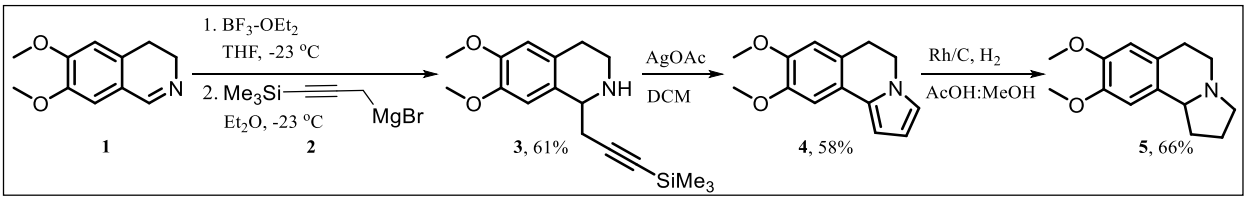
unactivated alkenes in single operation is particularly appealing and considered as powerful and practical strategies for constructing polycyclic ring skeletons.[5] In this context, Pd-catalyzed chelation assisted tandem cyclization strategy has emerged as a versatile and powerful tool to construct complex polycyclic natural products and diversely functionalized *N*-heterocycles as multiple stereo centers can be established in one step under mild conditions with great atom economy.[6-9] Although there is impressive progress in Palladium-catalyzed aminoarylation,[6] aminocarbonylation,[7] aminovinylation,[8] and aminoalkynylation,[9] the amino alkylation of unactivated alkenes is relatively little explored despite the fact that the reaction can have great advantage in forming heterocycles.[10] The recent advancements in such transformations[10] has been partially achieved using an expensive and/or sensitive ligand or an excess amount of external oxidant, which hampers the efficiency of the overall functionalization process. Thus, the development of an efficient Pd-catalyzed amino alkylation of unactivated alkenes under mild conditions with a simple operation has been a great challenge and highly desirable task. In this context, we envisioned synthesise of Crispine and related natural products using Pd-catalyzed aminoalkylation via C–H activation protocol.

1.2.3. Literature review

Since the isolation of Crispine natural product from *Carduus crispus*, it has gained enormous attention of organic chemists because of its diverse bioactivity. It has been synthesized via

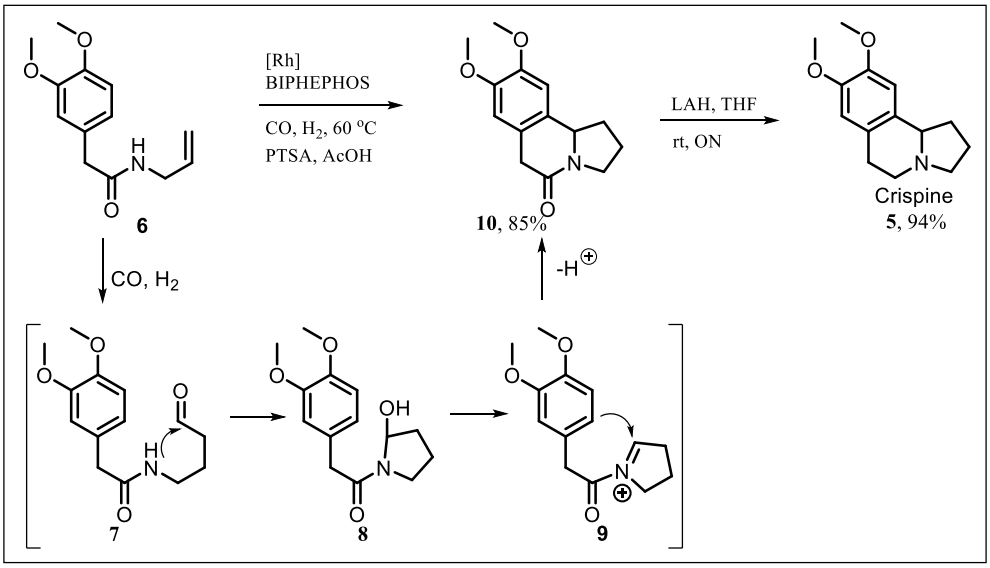
various methods before and after its isolation as natural product either in racemic or enantiomeric form. After the isolation Knolker and co-workers in 2005 reported the first synthesis of Crispine in racemic form using Silver (I)-mediated oxidative cyclization as key step.[2i] Compound **1** was synthesized on gram scale form *N*-formyl-3,4-dimethoxyphenylethylamine using Bischler–Napieralski cyclization. Boron trifluoride promoted addition of Grignard compound **2** to dimethoxysoquinoline **1** leads to the formation of propargyl compound **3** in 61% yield. Ag(I) promoted cyclization of **3** afforded dihydroisoquinolone compound **4** in 58% yield, which after chemo selective hydrogenation of pyrrole ring provided (±)-Crispine (Scheme 1).

Scheme 1. Crispine synthesis using Silver (I)-mediated oxidative cyclization



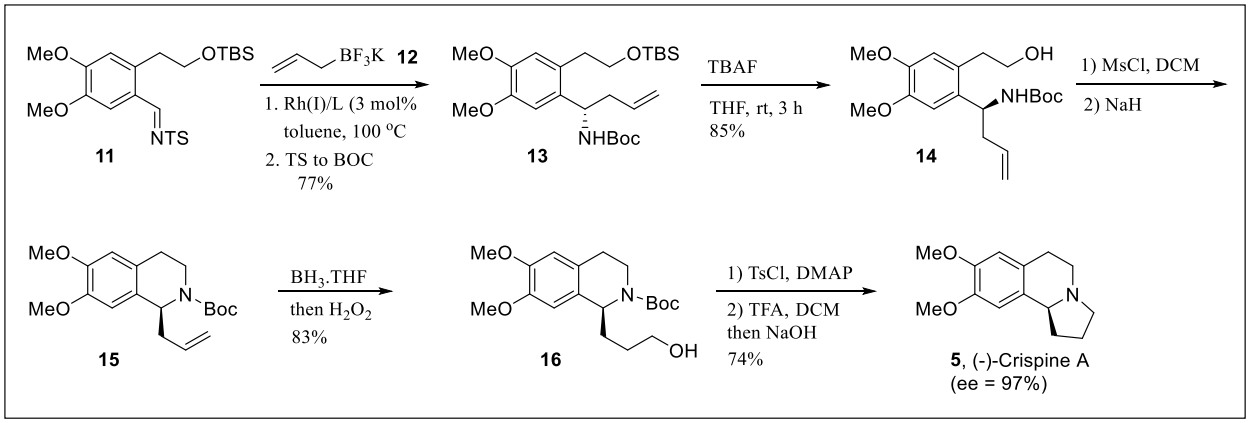
Chiou and co-workers in 2009 reported the synthesis of crispine A starting from the corresponding amide **6** via domino reaction process.[2f] This domino process commenced with selective hydroformylation of linear *N*-allylic amide of phenylacetic acid **6** to yield aldehyde [**7**.] It then undergoes the first intramolecular cyclization to form hemiaminal [**8**] in the presence of Bronsted acid PTSA. Dehydration of [**8]** generates an N-acyliminium ion [**9]**, followed by the Friedal-Craft alkylation type second cyclization with an electron-rich aromatic ring to afford bicyclization product **10**. Reduction of **10** with $LiAlH_4$ and Et_3N•HCl in THF gave Crispine A (**5**) in 94% yield (Scheme 2).

Scheme 2. Chiou's Crispine synthesis using Pd-catalyzed domino reaction



Wu and co-workers in 2018 reported the enantioselective synthesis of (-)-Crispine A using Rh-catalyzed allylation of N-tosylaldimines.[2a] The synthesis has started with enantioselective addition reaction of **12** with imine **11** in presence of Rh-catalysis which afforded adduct **13** in 77% yield with 99% ee. Protecting group switch from Ts to Boc afforded **13** in 87% for two steps. Alcohol was deprotected using TBAF to provide **14** in 85% yield. Alcohol was then converted to mesylated product followed by subsequent cyclization gave cyclic

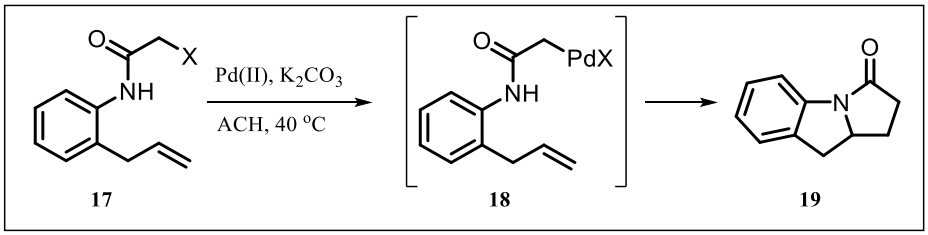
Scheme 3. Enantioselective synthesis of (-)-Crispine A



amine **15** in 83% yield over two steps. Hydroboration− oxidation transformed **15** into alcohol **16**. It was subjected to tosylation, Boc removal followed by basic cyclization to provide (−)-Crispine A in 74% yield (Scheme 3).

Transition-metal-catalyzed aminoalkylation has paved a new class of reaction leading to the formation of complex heterocyclic compounds, natural products or bioactive scaffolds. Yang and co-workers in 2017 reported the intramolecular aminoalkylation of unactivated alkenes using Pd-catalysis.[11] The method allowed synthesizing diverse *N*-heterocycles without use of external ligand and oxidant. *α*-Halo amide **17** when treated with [Pd], converts to intermediate **18**, which later leads to the formation of cyclized heterocyclic compound **19** (Scheme 4).

Scheme 4. Pd-catalyzed intramolecular aminoalkylation



1.2.4. Origin of the work

It has been observed from the literature reports that Crispine and its related natural analogs shows diverse bioactivity. Various efforts have been made towards the synthesis of Crispine natural product in the racemic as well as enantiomeric form after its isolation as a natural product. Synthesis of bioactive natural product and late stage derivatization is always desired in the field of drug discovery, as it helps in generating the library of compounds. In this context, herein we have described our efforts towards the synthesis of Crispine and related natural

products using intramolecular Pd-catalyzed aminoalkylation via tandem C–C and C–N bond formation.

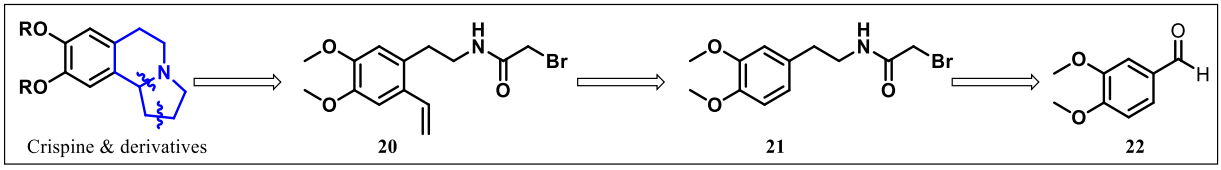
1.2.5. Objective of the work

The formation of C–C or C–X (X = N, S, O or halogen) bonds via site selective C–H activation is a challenge as well as opportunity for the organic chemists. Formation of multiple bonds in single step is always found to be step as well as atom economic, which helps during the construction of complex molecules from simple and readily available starting materials. The objective of the present work is to develop an efficient method for the synthesis of Crispine and related natural products utilizing Pd-catalyzed intramolecular aminoalkylation.

1.2.6. Result and discussion

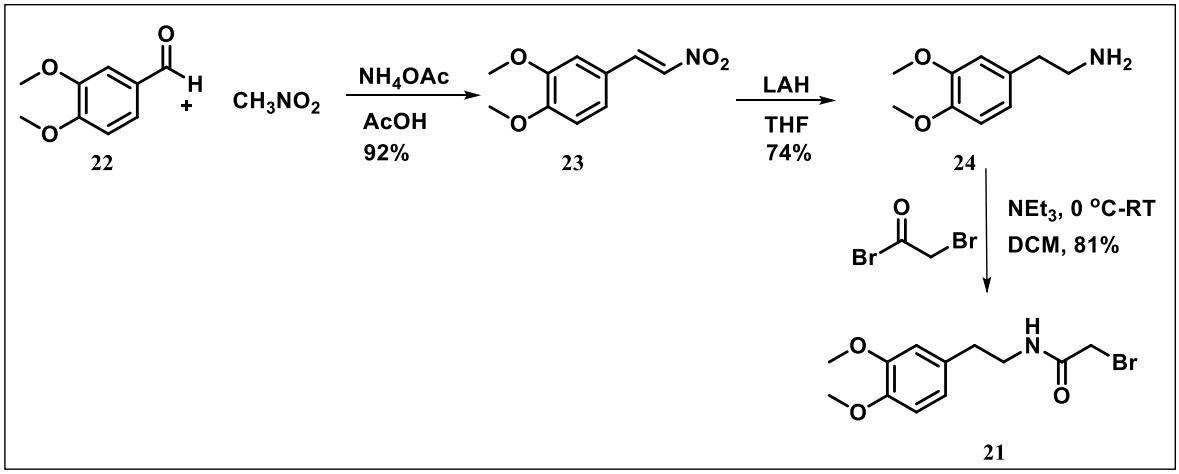
We planned to synthesize Crispine and related natural products using Pd-catalyzed aminoalkylation as a key-step via C–H activation protocol. Retrosynthetic analysis shows that Crispine could be achieved by reduction of the intermediate obtained from Pd-catalyzed aminoalkylation of α-halo amide compound **20**. Amide **20** could be readily prepared from corresponding amide **21** by halogenation followed by Stille-cross coupling using vinyl tributyltin as vinyl source. The synthesis could start from Henry reaction of veratraldehyde (**22**), followed by complete reduction and amidation using bromoacetyl bromide (Scheme 5).

Scheme 5. Retrosynthetic disconnection of Crispine and its derivatives



Our effort towards the synthesis of Crispine and related natural products started with the Henry reaction of veratraldehyde (**22**) with nitromethane in the presence of ammonium acetate to achieve nitro compound **23** in 92% yield. The complete reduction of nitro compound was achieved using 4 equivalents of LAH in THF to obtain amine **24**, which was utilized for the next step without further purification. Amine **24** was then reacted with bromoacetyl bromide the in presence of triethyl amine in DCM at rt to achieve bromo compound **21** in 81% isolated yield (Scheme 6).

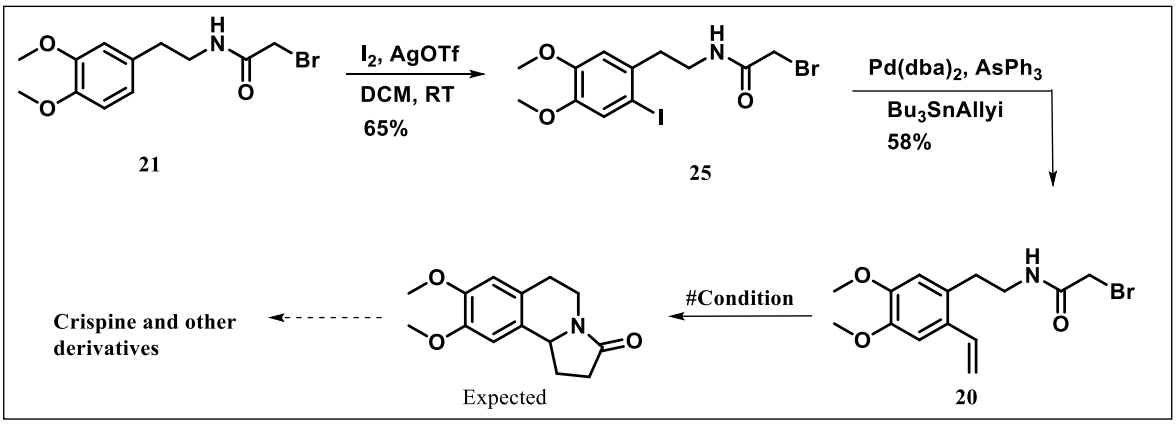
Scheme 6. Synthesis of bromo α-bromoamide



Iodination of the amide **21** by treatment with iodine and silver triflate in dark atmosphere furnished the iodo-amide **25** in good yield and excellent regioselectivity. The iodo-amide **25** was further treated with vinyl tributyltin under Stille cross coupling conditions catalyzed by $Pd_2(dba)_3$ and $AsPh_3$ as ligand to get vinyl-amide **20** in 58% yield, which was used as a precursor for aminoalkylation protocol (Scheme 7).

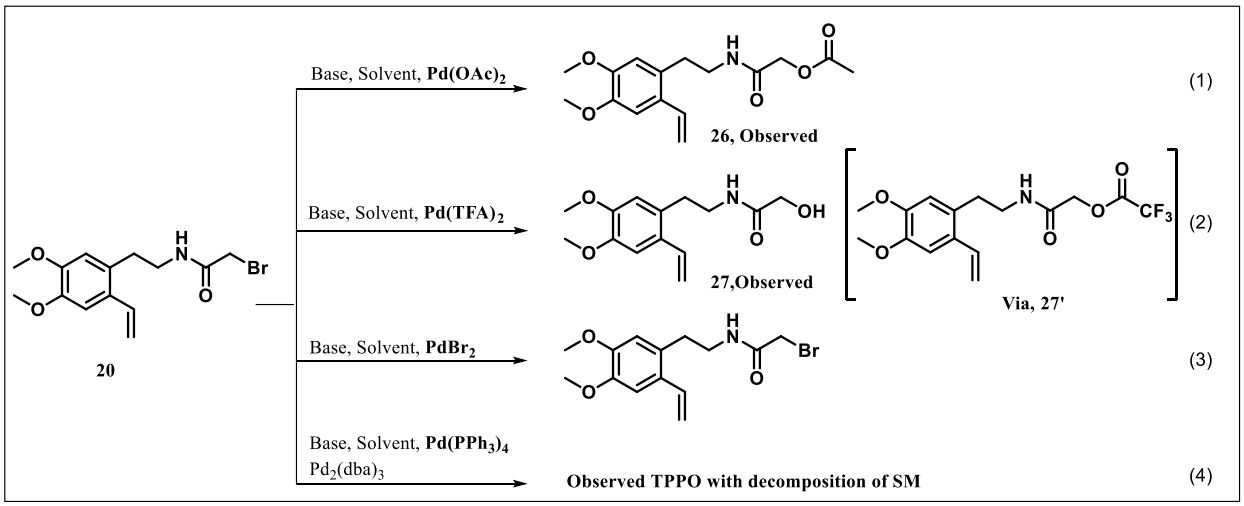
Next, various catalysts, solvents and bases were screened to obtain the aminoalkylated product. We initially tried the reaction by taking $Pd(OAc)_2$ as a catalyst along with combination of various bases such as K_2CO_3, Cs_2CO_3, NaOAc, NEt_3 or pyridine and solvents such as toluene,

Scheme 7. Synthesis of key intermediate



DMSO, DMF, DCM, DCE or ACN. In all the attempts made, we observed the formation of small amount of acetylated product **26**, which was confirmed by LCMS along with starting material unchanged (Scheme 8, eq. 1). Maybe the strong nucleophilic nature of acetate is responsible for the observed product. Here we thought to use less nucleophilic ligand (TFA) with Pd-catalyst and in this case we observed the formation of hydroxyl compound **27** (Scheme 8, eq. 2), which confirmed the sensitivity of bromo compound towards nucleophiles. The hydroxyl compound **27** might be formed from the corresponding compound **27'** after hydrolysis. When $PdBr_2$ was used as catalyst, all the starting material remained unreacted and no any other product formation was observed (Scheme 8, eq. 3). $Pd(PPh)_3$ also was not found useful during our effort to get the expected product (Scheme 8, eq. 4). In this case we observed the formation of TPPO along with decomposition of the starting material **20**. Now our next goal is to develop the suitable condition for aminoalkylation followed by required modifications to obtain Crispine and related natural products.

Scheme 8. Pd-catalyzed aminoalkylation



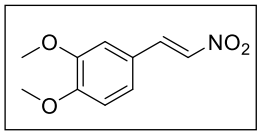
1.2.7. Conclusion

In summary, we have prepared the required precursor for Pd-catalyzed aminoalkylation leading to *N*-heterocyclic core of Crispine and related natural product starting from veratraldehyde. We have performed the different reactions using various combinations of base, solvent, catalyst and additives. In all the cases we either observed the unwanted product formation or starting material remained as it is. Our next target is to find the suitable reaction condition for the proposed transformation, which could be later converted into the other natural products of similar class.

1.2.8. Experimental Section

(E)-1,2-dimethoxy-4-(2-nitrovinyl)benzene[12] (**23**):

Oven dried 100 ml RB was filled with the mixture of veratraldehyde (**22**, 2.00 g, 12.05 mmol), ammonium acetate (0.93 g, 12.05 mmol), nitromethane (3.67 g, 60.23 mmol), and glacial AcOH (15 ml) was refluxed for 4 h. The reaction was cooled to room temperature and the crystalline product was filtered using Buchner funnel and washed with water and pet ether. The obtained solid compound was then recrystallized from EtOH to afford 1,2-dimethoxy-4- (2-nitro-vinyl)-benzene (**17**) yellow solid (2.316 g, 92%)**.**



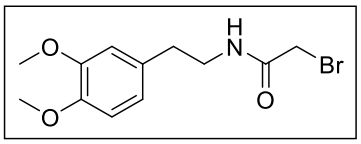
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.97 (d, *J* = 13.51 Hz, 1H), 7.53 (d, *J* = 13.51 Hz, 1H**)**, 7.18 (dd, *J* = 8.38, 2 Hz, 1H), 7.01 (d, *J* = 2 Hz, 1H), 6.92 (d, *J* = 8.25 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** *δ* (ppm) 152.8, 149.5, 139.3, 135.2, 124.6, 122.8, 111.3, 110.2, 58.1, 56.0.

2-Bromo-N-(3,4-dimethoxyphenethyl)acetamide[13] (**21**):

A solution of 1,2-Dimethoxy-4-(2-nitro-vinyl)-benzene **(23**, 2.09 g, 10.0 mmol) in THF (10 mL) was added dropwise to a stirred solution of $LiAlH_4$ (1.52 g, 40.0 mmol) in THF (30 mL). The reaction mixture was refluxed for 3 h followed by addition of aq KOH (20%) to destroy the excess $LiAlH_4$. The mixture was then extracted with EtOAc (3 x 20 mL), washed with brine (3 g x 20 mL), dried (K_2CO_3), concentrated in vacuo. The oily residue **24** was used directly in the next step without further purification (1.340 g, 74%).

2-(3,4-dimethoxyphenyl)ethan-1-amine (**24**) (1.34 g, 7.40 mmol) was dissolved in dry DCM (20 ml) and triethylamine (1.1mL, 8.14 mmol) was added to this solution. The solution was stirred at 0°C for 10 min after which bromoacetyl bromide (0.6 g, 8.14 mmol) was added drop wise to the

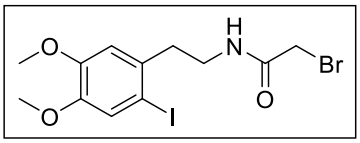
stirred solution over a period of 30 min. The reaction mixture was then stirred overnight. Subsequently, the reaction mixture was filtered to remove the hydro bromide salts, and the filtrate collected. The filtrate was washed with water (10 ml), dried over anhydrous sodium sulfate and then the solvent was removed under reduced pressure. 2-Bromo-N-[2-(4-methoxy-phenyl)-ethyl] acetamide (**21**) was obtained as a brown solid. The crude product thus obtained was recrystallized from DCM (1.878 g, 84%).



^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.83 (d, *J* = 8 Hz, 1H), 6.77-6.72 (m, 2H), 6.52 (brs, 1H), 3.89 (s, 3), 3.87 (s, 3H), 3.86 (s, 3H), 3.57-3.50 (m, 2H), 2.80 (t, *J* = 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** 165.2, 149.1, 147.8, 130.8, 120.7, 111.9. 111.4, 55.91, 55.85, 41.4, 35.0, 29.3.

2-Bromo-N-(2-iodo-4,5-dimethoxyphenethyl)acetamide (**25**):

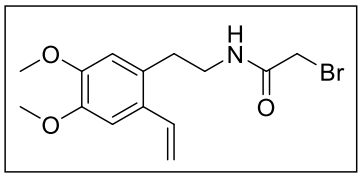
The iodo compound **25** was prepared according to literature procedure.[14] To a solution of amide **21** (1.5 g; 5.0 mmol) in DCM (30 mL) was added AgOTf (1.285 g; 5.0 mmol) and stirred at 25 °C for 2 min. The solution of iodine (1.265 g; 5.0 mmol) in DCM (30 mL) was added to the above solution drop-wise 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 **25** (1.39 g, 65% yield) as a colorless solid. R*f*: 0.5 (2:3 EtOAc:Pet. ether).



^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.23 (s, 1H), 6.74 (s, 1H), 6.55 (brs, 1H), 3.88 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.57-3.52 (m, 2H), 2.92 (t, *J* = 7.0 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** 165.4, 149.5, 148.4, 133.3, 121.8, 112.7, 88.0, 56.2, 56.0, 40.2, 39.5, 29.3.

2-Bromo-N-(4,5-dimethoxy-2-vinylphenethyl)acetamide (**20**):

The vinyl-amide **20** was prepared by using known procedure.[14] To a solution of compound **25** (1.0 g, 2.33 mmol) in 40 mL of DMF, tributyl(vinyl)tin (1.03 mL, 3.5 mmol), $Pd_2(dba)_3$ (213 mg, 0.233 mmol) and $AsPh_3$ (0.570 g, 1.86 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 (40 mL x 3). The organic layer was washed with water (20 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 **20** (0.444 g; 58% yield) as a colorless solid. R*f*: 0.6 (1:1 EtOAc:Pet. ether).



^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.04 (s, 1H), 6.93 (dd, *J* = 17.17, 11.06 Hz, 1H), 6.66 (s, 1H), 6.10 (brs, 1H), 5.59 (dd, *J* = 17.17, 0.76 Hz, 1H), 5.27 (dd, *J* = 10.68, 0.76 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.68 (s, 2H), 3.49-3.43 (m, 2H), 2.88 (t, *J* = 7.25 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** 166.6, 148.9, 148.0, 133.7, 129.1, 128.5, 114.2, 112.9, 108.7, 56.0, 55.9, 41.4, 32.1.

Pd-catalyzed aminoalkylation leading to heterocycle towards Crispine:

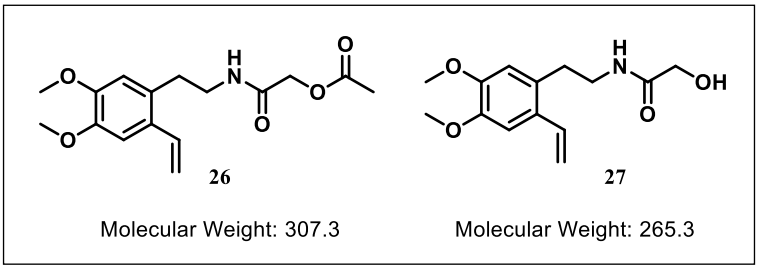
A oven dried Schlenk tube was filled with vinyl compound **20** (0.1 mmol), Pd(II)/Pd(0) and base (1 mL). To the reaction mixture, solvent was added and glass tube backfilled with argon and

stirred at various temperatures ranging from room temperature to 120 ^{o}C in preheated oil bath. The reaction was followed by TLC analysis and LCMS. In all the cases we either observed the formation of unwanted product formation or starting material recovered unchanged.

We confirmed the formation of side products by LCMS analysis

Observed ESI-LCMS^{+} (**26**) = 308.2

Observed ESI-LCMS^{+} (**27**) = 266.2



1.2.9. References

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10. a) Du, W.; Gu, Q.; Li, Z.; Yang, D. *J. Am. Chem. Soc*. **2015**, *137*, 1130. b) Hewitt, J. F.; Williams, M. L.; Aggarwal, P.; Smith, C. D.; France, D. *J. Chem. Sci*. **2013**, *4*, 3538. c) Xing, D.; Yang, D. *Org. Lett*. **2013**, *15*, 4370.
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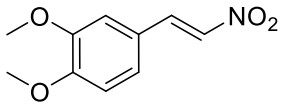
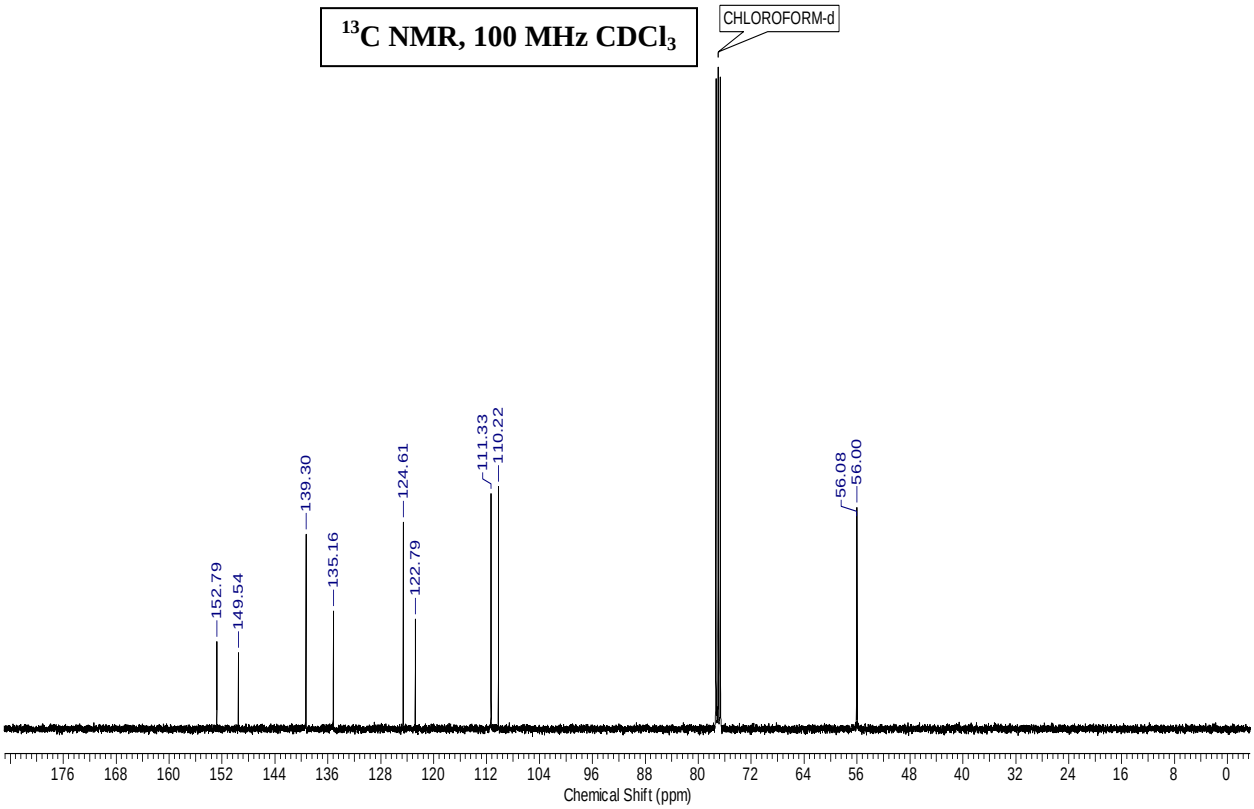
1.2.10. Selected ^{1}H and ^{13}C NMR spectra

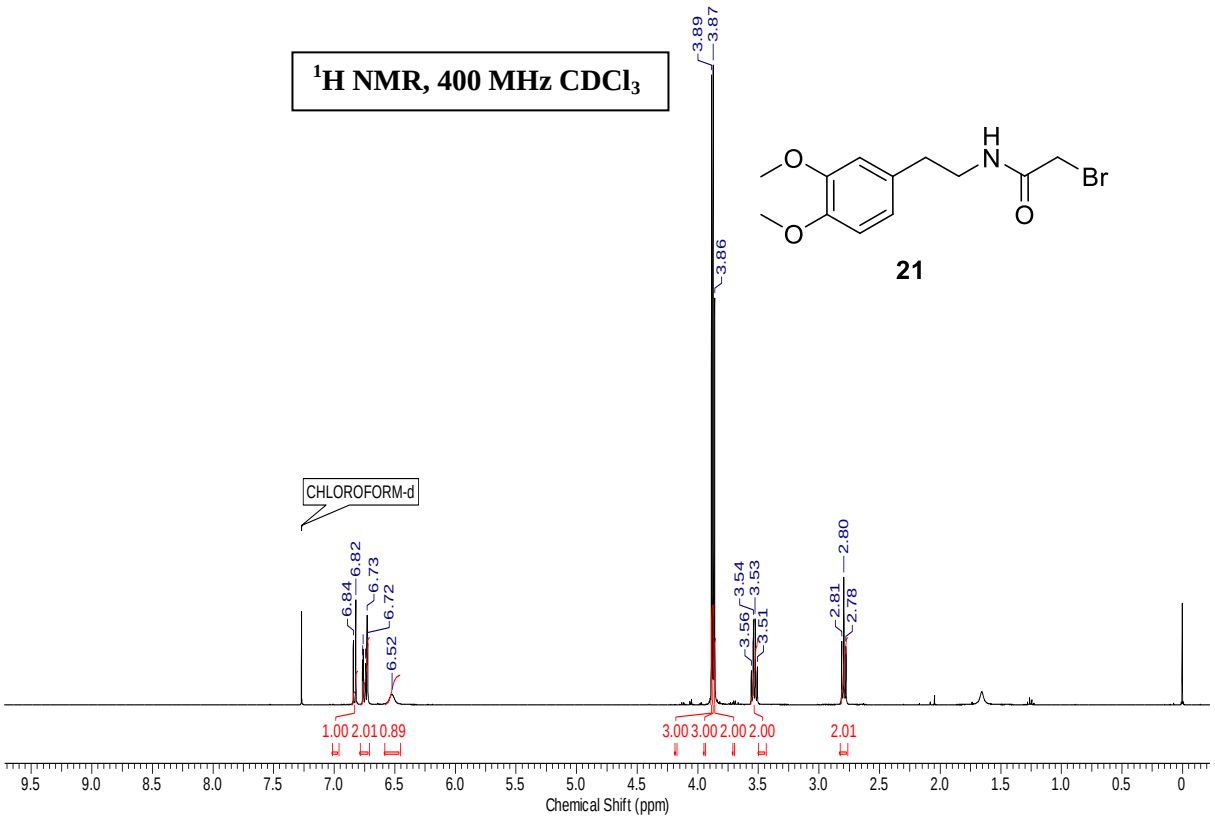
^{1}H NMR, 400 MHz $CDCl_3$



23

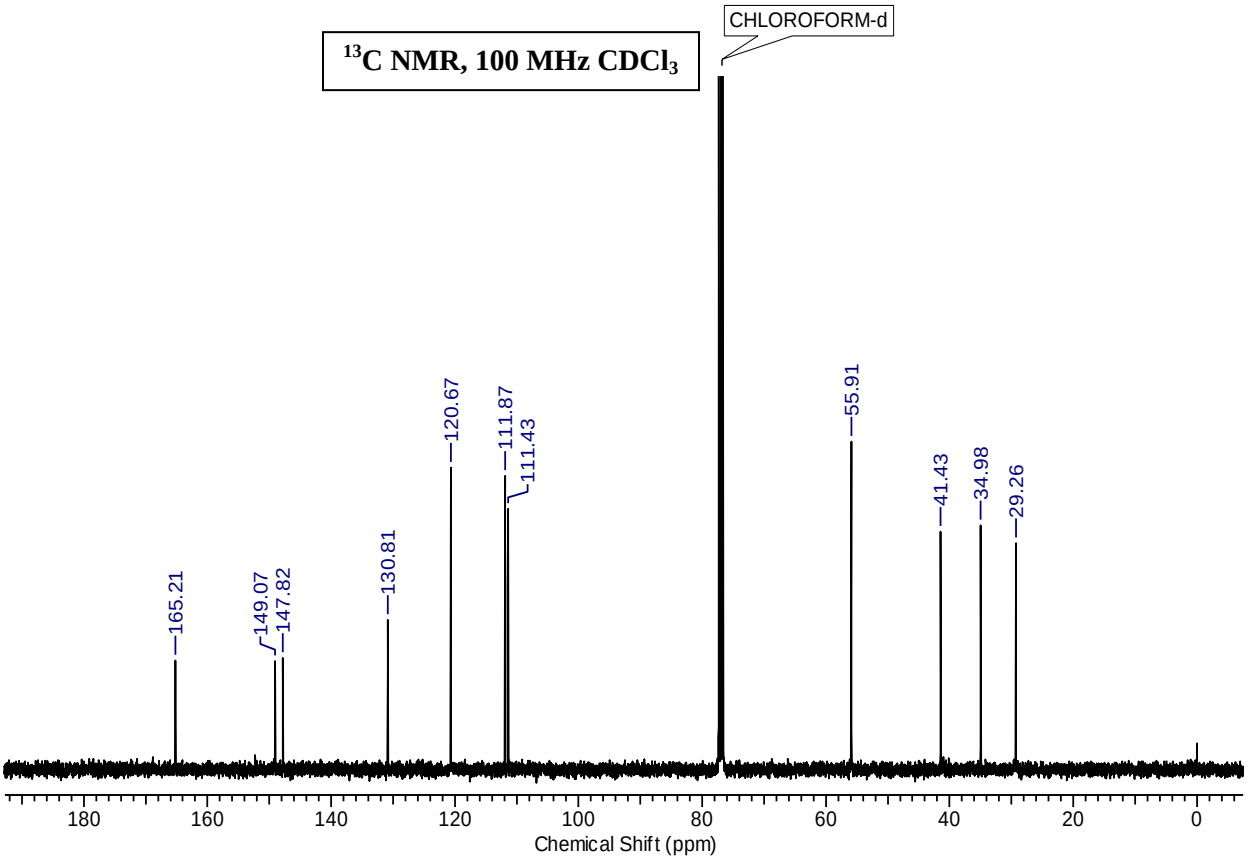
^{13}C NMR, 100 MHz $CDCl_3$

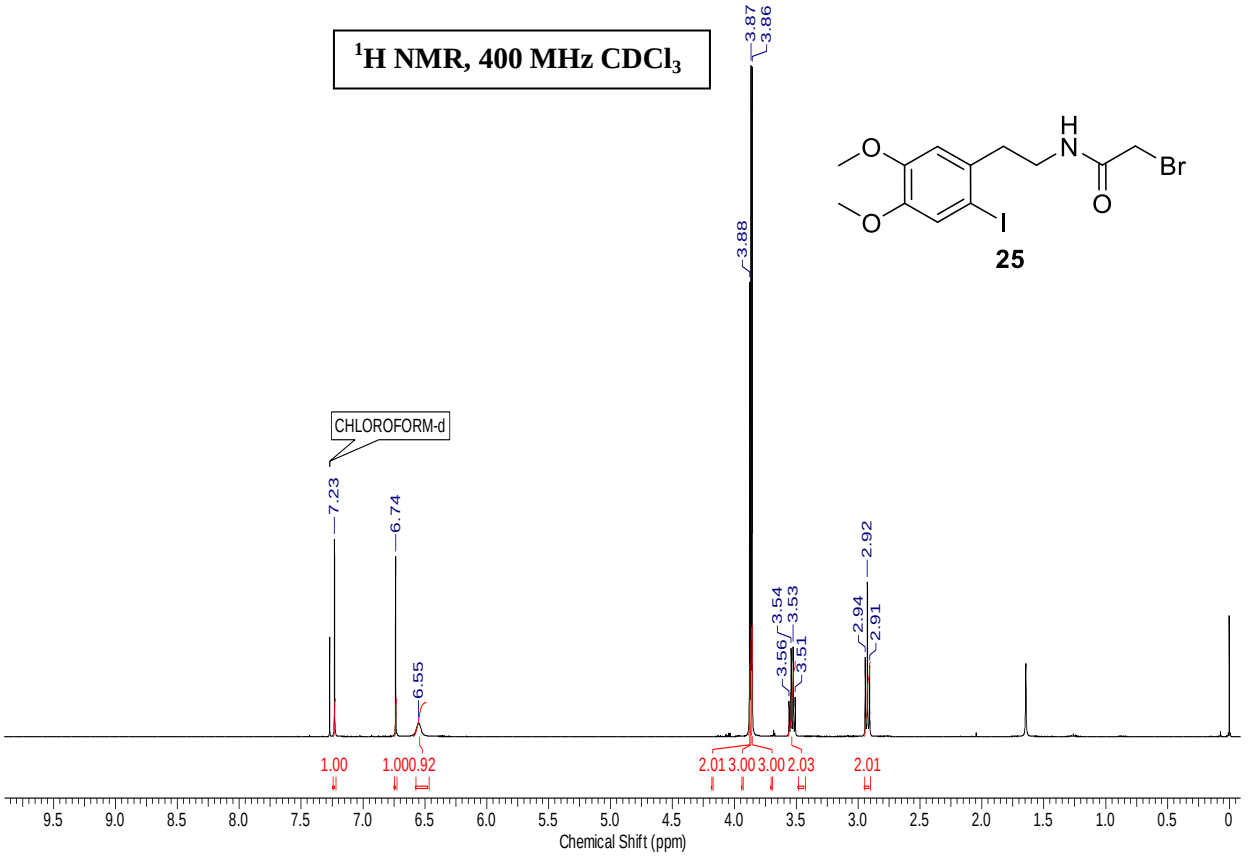



^{1}H NMR, 400 MHz CDCl$_3$
3.89
3.87
3.86
6.84
6.82
6.73
6.72
6.52
3.56
3.54
3.53
3.51
2.81
2.80
2.78
CHLOROFORM-d
1.00 2.01 0.89
3.00 3.00 2.00 2.00
2.01
Chemical Shift (ppm)

H
N
O
O
Br
O

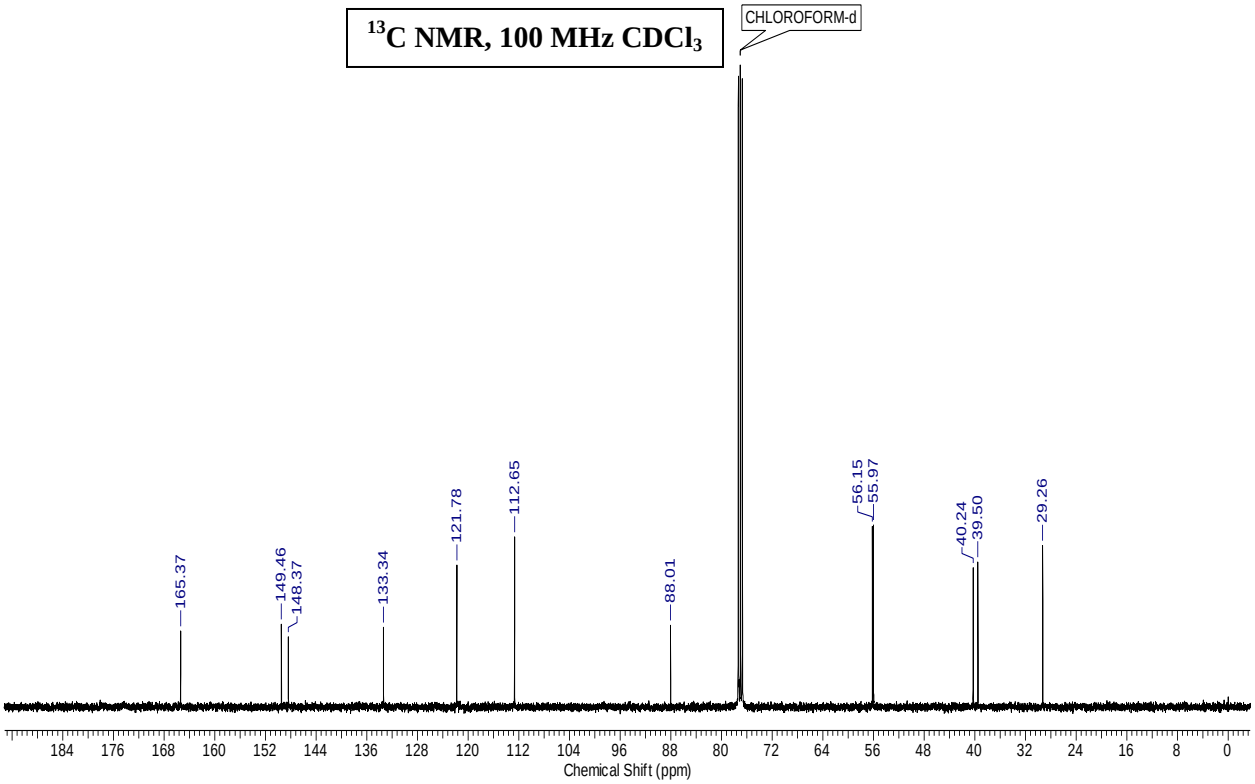
21


^{13}C NMR, 100 MHz CDCl$_3$
CHLOROFORM-d
165.21
149.07
147.82
130.81
120.67
111.87
111.43
55.91
41.43
34.98
29.26
Chemical Shift (ppm)

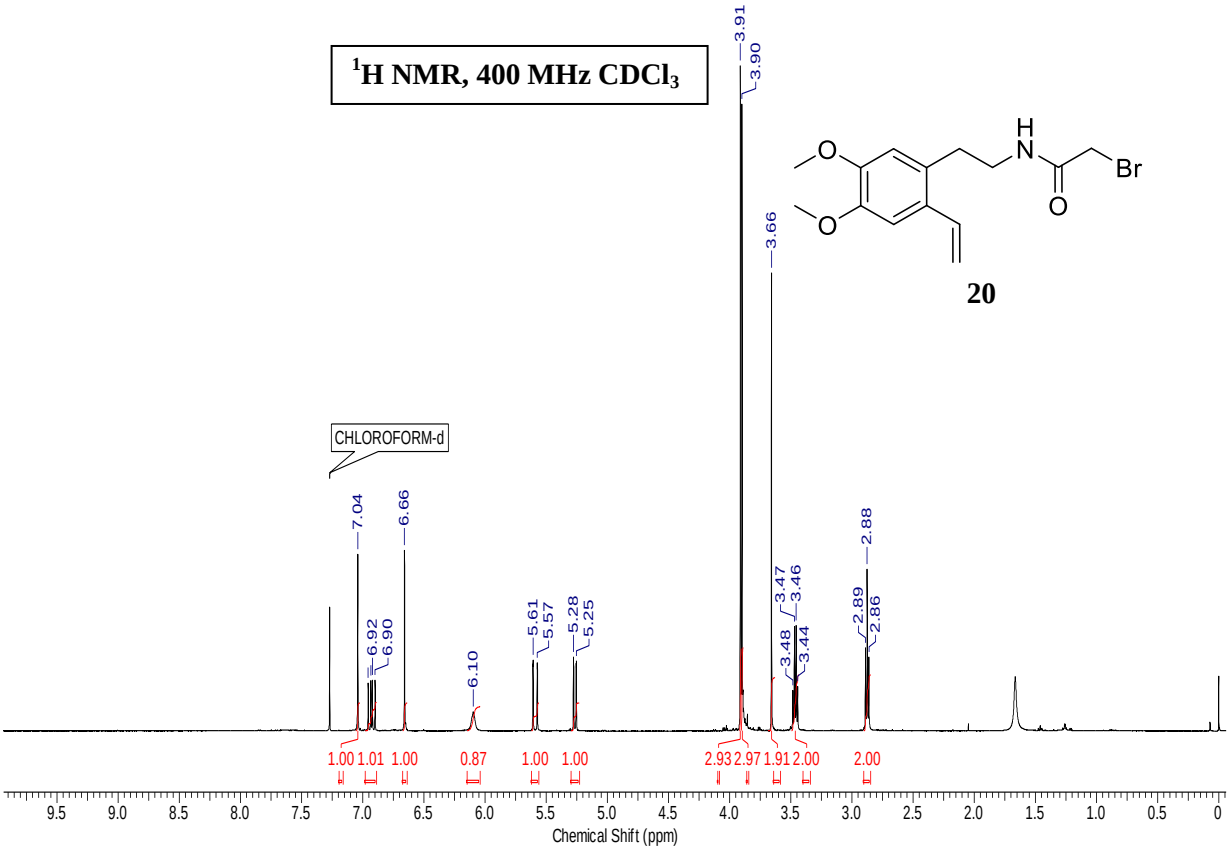

^{1}H NMR, 400 MHz $CDCl_3$
3.87
3.86
3.88
CHLOROFORM-d
7.23
6.74
6.55
3.56
3.54
3.53
3.51
2.94
2.92
2.91
1.00
1.00
0.92
2.01
3.00
3.00
2.03
2.01
Chemical Shift (ppm)

H
N
O
O
Br
O
I

25

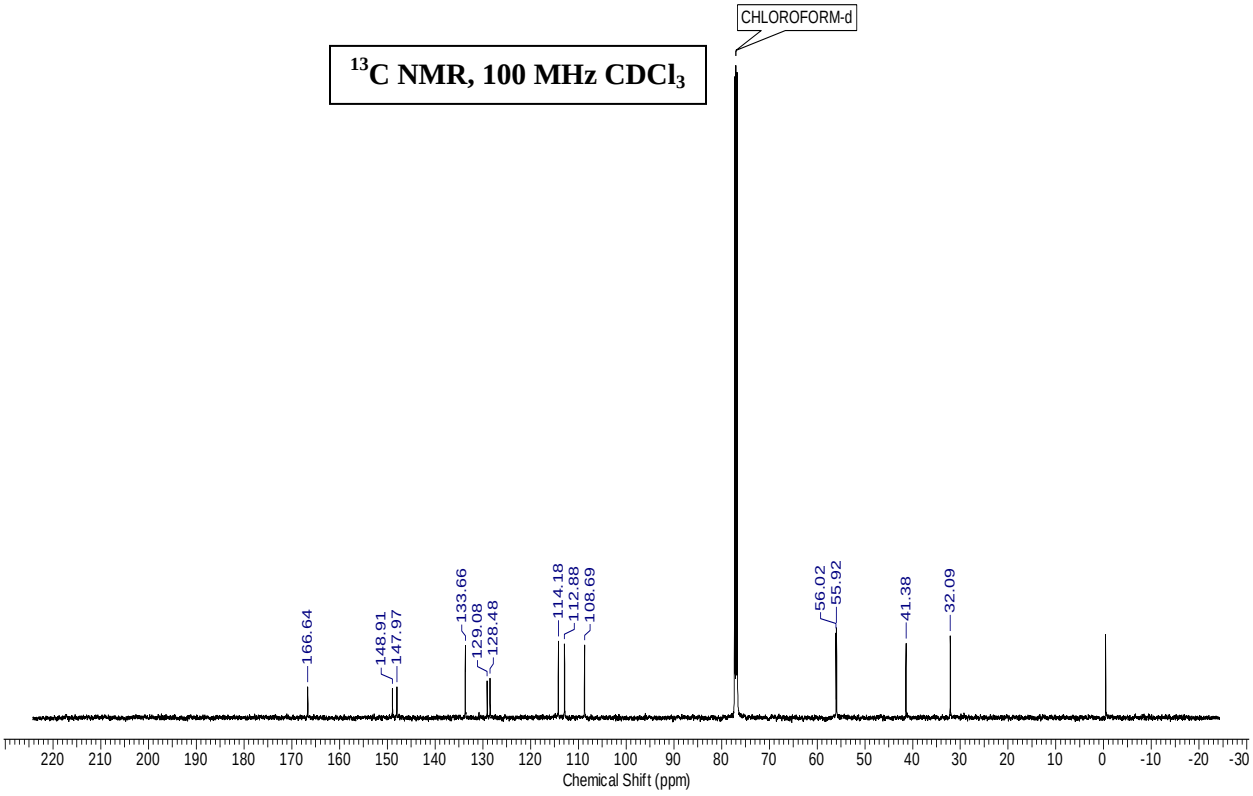

^{13}C NMR, 100 MHz $CDCl_3$
CHLOROFORM-d
165.37
149.46
148.37
133.34
121.78
112.65
88.01
56.15
55.97
40.24
39.50
29.26
Chemical Shift (ppm)

^{1}H NMR, 400 MHz $CDCl_3$



20

^{13}C NMR, 100 MHz $CDCl_3$



Chapter 2

para-Selective Copper-Catalyzed C(sp^2)–H Amidation/ Dimerization of Anilides via a Radical Pathway

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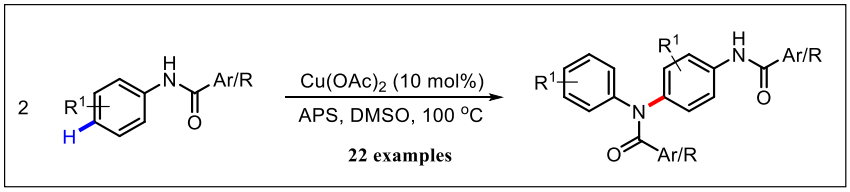
Citations:

1) Liu et al. *Synthesis* **2020**, *52*, 3211.
2) Dang et al. *Org. Lett.* **2020**, *22*, 9178.
3) Anilkumar et al. *RSC Adv.*, **2020**, *10*, 34429.
4) Qin et al. *Tetrahedron* **2020**, *76*, 131724
5) Sawamura et. al. *Science* **2020**, *369*, 970.

para-Selective Copper-Catalyzed C(sp^2)–H Amidation/ Dimerization of Anilides via a Radical Pathway

2.1. Abstract

Copper-catalyzed amidation/dimerization of anilides via regioselective C(sp^2)─H functionalization is achieved. The *para*-selective amidation is accomplished on the anilide aromatic ring via a radical pathway leading to C─N bond formation in the presence of ammonium persulfate (APS) as a radical source/oxidant for the Copper catalyst. The developed protocol tolerates a wide range of anilide substrates. The regioselectivity is confirmed by single-crystal X-ray.



2.2. Introduction

Transition-metal-catalyzed C─H bond functionalization has emerged as a prominent synthetic tool in organic chemistry over the past few decades.[1] It avoids the need for prefunctionalization of substrates and offers straightforward access to the desired scaffold in high atom and step-economy. Regioselective C─H functionalization to furnish C─C and C─X (X = O, N, S, etc.) bond formation is generally achieved either by using a directing-group or steric/electronic factors. The functionalization of arenes *ortho* to the directing-groups can be realized easily since the metal can reach readily to the desired site. Whereas, selectively reaching *meta*- or *para*-position is difficult because of many other factors.[2] The pioneering work in the field of *meta*- and *para*-selective C─H functionalization has been reported by Yu[3] and Maiti[4] groups respectively, employing

molecular template to direct a metal catalyst to a specific position. Despite of the many advantages of template-assisted site-selective C─H functionalization over the traditional methods, sometimes the template is larger than the substrate and additional steps are required to install or remove them, which makes the process lengthy, tedious and economically unviable. Hence, the process wherein the functional group of the molecule itself acts as an inherent directing group is preferred over the earlier.[5] We have previously utilized amide as an inherent directing group for the functionalization of quinazolinones as well as acrylamides using Ruthenium catalysis for alkenylation and cascade annulation respectively.[6]

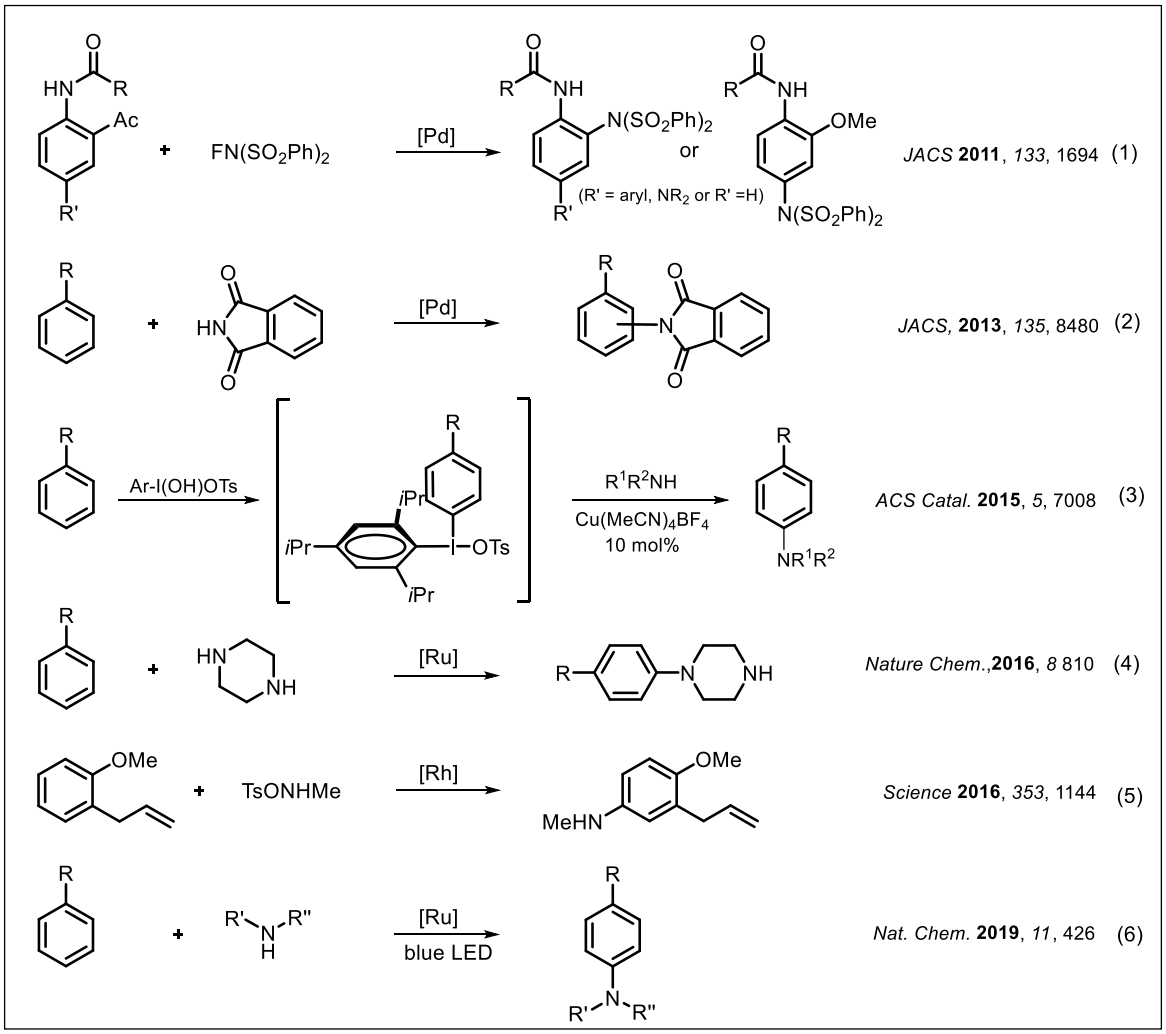
Amide is one of the potential functional group as well as directing group, which has been utilized enormously in chelation controlled functionalization using transition-metal catalysis.[7] In continuation of our interest in developing new methods utilizing amide as an inherent directing group for the C─H activation, we were exploring the functionalization of anilide derivatives. Interestingly, during the course of our investigation, we observed self-dimerization of anilide under one of our Cu-catalyzed reaction condition. After careful observation and characterization of the obtained product, we have confirmed the C─N bond formation at the *para*-position to the nitrogen of the electron-rich anilide ring.

2.3. Literature review

Upon confirmation of the structure and regioselectivity of the product obtained from the above mentioned reaction, we reviewed the literature to understand the importance and potential of the observed transformation. Interestingly, literature survey revealed that Masui et al. observed dimerization of benzanilides during anodic oxidation,[8] however, metal-catalyzed *para*-selective amidation/ dimerization of anilides through C─N bond

formation specifically on aniline aromatic ring as observed here is not reported until now. In 2011, Zhang and co-workers reported the amide-directed, Pd-catalyzed, highly selective, intermolecular, C–H aminations with the *N*-fluorobenzenesulfonimide. This methodology provided a new pathway for directed metal-catalyzed aromatic C–H amination (Scheme 1, eq 1).[9] In the subsequent year 2013, Hartwig and co-workers reported Pd-catalyzed sterocontrolled amination of arenes leading to *N*-aryl phthalimides (Scheme 1, eq 2).[10] A one-pot, two-step method has been reported for *para*-selective C−H amination of aromatic compounds, utilizing Cu(I) as an active catalyst by Suna and Co-workers in 2015 (Scheme 1, eq 3). The method has also been extended for synthesis of Linezolid by late stage amination.[11] Apart from directing group mediated/chelation controlled site selective C–H functionalization, Ritter and co-workers in 2016 demonstrated the charge-transfer-directed radical substitution enabled *para*-selective C–H functionalization. They have utilized Ru-catalysis for highly *para*-selective amination (Scheme 1, eq 4).[12] *para*-selective oxidation induced, C–H functionalization of iodobenzenes has been reported by Lei and co-workers, where oxygen based nucleophiles has been utilized as a coupling partner.[13] Falk group has published the mild di-Rhodium-catalyzed C–H amination for conversion of structurally diverse monocyclic and fused aromatics to the corresponding primary and *N*-alkyl arylamines using NH_2/NH(alkyl)-O-(sulfonyl)hydroxylamines as aminating agents and the relatively weak RSO_2O-N bond functions as an internal oxidant (Scheme 1, eq 5).[14] Leonori and co-workers reported the regioselective amination of arene using photocatalyst (Scheme 1, eq 7).[15] Apart from the sterically or electronically controlled site selective functionalization, in the recent past years template mediated directing group assisted meta- and para- functionalization has

Scheme 1. Selected metal-catalyzed *para*-amination/amidation



also been reported by many groups. Although, the template mediated functionalization requires additional steps, yet it holds good potential to access remote functionalization.[3,4]

Copper catalysts are one of the most desired transition-metal catalysts for C–H functionalization as they are robust, cost-effective, and provide practical alternative over the other expensive transition-metal catalysts such as [Pd], [Ru], [Ir] etc.[16b,g,18] Hence, we aimed at optimizing the protocol using a Copper catalyst. In this context, reported herein is a protocol for the *para*-selective amidation/dimerization of anilides using a Copper

catalyst and inexpensive ammonium persulfate (APS) as an oxidant/radical source.

2.4. Origin of the Work

It has been observed from the literature reports that *para*-selective C–H functionalization is always challenging. It requires harsh reaction conditions and costly metal catalysts. Regioelectivity is the major challenge in the field of distal C–H functionalization. The field of *para*-C–H functionalization is still immature, which demands more research for regioselective, economically viable and simple reaction condition. Metal-catalyzed dimerization leading to C–N bond formation is also not reported until now. In this context, we have explored serendipitous observation to overcome these challenges.

2.5. Objectives of the work

The formation of C–C or C–X (X= N, S, O or halogen) bonds via site selective C–H activation is a challenge as well as opportunity for the organic chemists. Amide is a Lewis basic coordinating functional group, which is often utilized in the site selective transition-metal catalyzed C–H activation.[7] The potential of the amide group inspired us to utilize it as a directing group for useful synthetic transformations. We initially aimed to functionalize anilides by utilizing amide directed transition-metal catalysis. Interestingly, during the course of our investigation, we observed the dimerized product formation. The objective of the present work is to explore and demonstrate the potential of observed transformation.

2.6. Result and Discussion

The optimization of the protocol commenced with the modifications in the previously perceived condition. Selected modifications are presented in Table 1. Though several variations in oxidant, catalyst, reaction concentration, time and temperature were tried,

the best yield achieved through optimization studies was 62% (Table 1, entry 9). However, 0.037 mmol of the starting material was recovered unchanged, and hence the

Table 1 Optimization of Reaction Conditions[a]

Sr. No.	Oxidant (equiv)	$Cu(OAc)_2$ (mol%)	Concen. (in M)	Yield[b] (%)
1	APS (1.5)	5	0.15	27
2	APS (1.0)	-	0.15	trace
3	-	5	0.15	NR
4	APS (2.0)	5	0.15	16
5	APS (1.0)	5	0.15	41
6	APS (0.75)	5	0.15	32
7	APS (1.0)	5	0.30	21
8	APS (1.0)	5	0.10	49
9	**APS (1.0)**	**10**	**0.10**	**62 (77)[c]**
10	$K_2S_2O_8$ (1.0)	10	0.10	46
11	$Na_2S_2O_8$ (1.0)	10	0.10	42
12	APS (1.0)/O_2	10	0.10	22
13	(*t*BuO)$_2$ (1.0)	10	0.10	NR
14[d]	APS (1.0)	10	0.10	40
15[e]	APS (1.0)	10	0.10	52

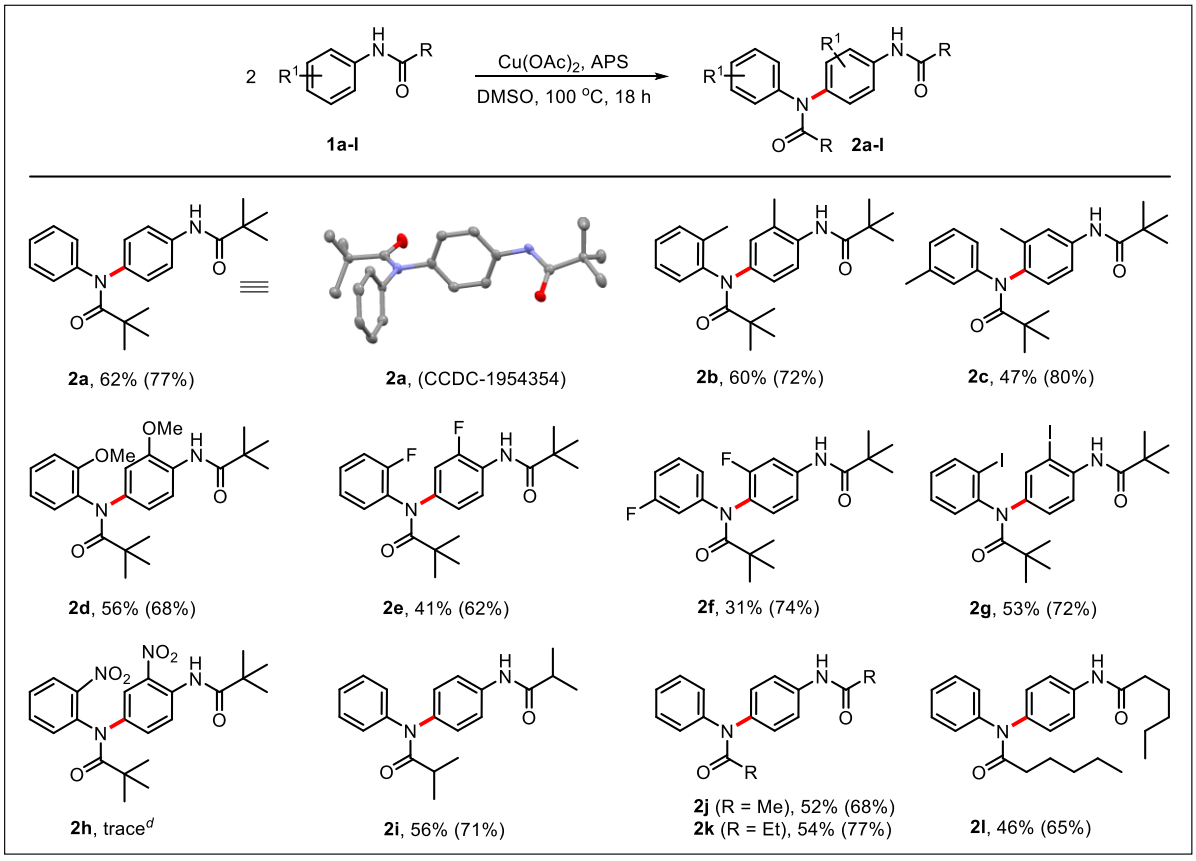
[a]Reaction conditions: **1a** (0.2 mmol), $Cu(OAc)_2$, oxidant-ammonium persulfate (APS) in DMSO at 100 ^{O}C for 18h, [b]Isolated yield. [c]Yield in the parentheses is based on the recovered starting material. [d]Additive: AcOH (1 equiv), [e]Additive: NaOAc (1 equiv).

actual yield based on the recovered starting material (brsm) was 77%. GC/GC-MS analysis of the crude reaction mixture, as well as purified product **2a**, confirms the formation of a single regioisomer. The *para* regioselectivity of **2a** was confirmed by X-ray crystallography (CCDC-1954354).

After optimizing the reaction condition, our next target was to generalize the scope of the developed protocol (Scheme 2). The study began with the variation of substituents on the aromatic part of the anilide **1a**. The substrates with methyl substituent *ortho* or *meta* to anilide nitrogen furnished the corresponding products **2b** and **2c** respectively in good

yields. Similarly, anilide with electron-donating methoxy group at the *ortho* position also worked smoothly to provide the expected compound **2d** in optimum yield. The fluoro substituted anilides resulted into the expected products **2e** and **2f** with comparatively lower yields. The *ortho*-substituted anilides (**1b**, **1e**) worked better than the corresponding *meta*-substituted anilides (**1c**, **1f**) probably because of the steric hindrance. Following the same trend, iodo-substituted anilide also provided the dimer **2g** in good yield. However, anilide with electron-withdrawing $-NO_2$ substituent failed to furnish the expected product **2h** under the optimized conditions. We reasoned that the amide group of the electron-

Scheme 2. Amidation/dimerization of *N*-arylalkylamide[a-c]



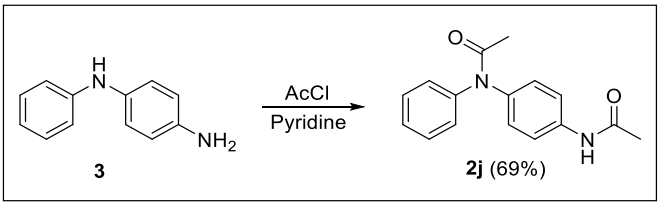
[a]Reaction conditions: **1a-l** (0.2 mmol), $Cu(OAc)_2$ (10 mol%), APS (0.2 mmol), DMSO (0.1M) in a screw cap glass tube at 100 ^{O}C for 18 h. [b]Isolated yields. [c]Yields in parentheses are based on the recovered starting material. [d]Starting material recovered unchanged.

deficient anilide fails to bind with the metal during the course of the reaction.

At this point, we decided to study the substrate scope by varying the aliphatic group of anilide **1a**. Accordingly, *N*-phenylisobutyramide was treated under the optimized reaction condition, which worked well leading to **2i**. *N*-phenylacetamide also resulted into the corresponding dimerized product **2j** in moderate yield. The reaction worked equally well with *N*-phenylpropionamide to obtain **2k**. However, the substrate *N*-phenylhexanamide having a long alkyl chain provided the corresponding dimer **2l** in relatively lower yield. Overall, the bulkiness of the aliphatic group had minimal effect on the yield.

The NMR spectra of compounds **2a-g** show clean countable proton/carbon peaks. However, peak broadening was observed for aromatic peaks in the ^{1}H and ^{13}C NMR spectra of **2i-l**. Scanning the sample at various concentrations in $CDCl_3$ and other deuterated solvents at different concentrations and even for a longer time (24 h) on a 700 MHz Bruker NMR instrument also did not change this peculiar pattern. However, scanning the ^{1}H NMR of a representative compound **2j** at higher temperature provided clean spectra. These compounds with the presence of proton on the carbon adjacent to the carbonyl group may have a different kind of inter or intramolecular interaction leading to such a pattern. To clarify the doubt about the structure, we prepared the same compound **2j** by acylation of the corresponding commercially available diamine **3** (Scheme 3). The peculiar peak broadening was observed in the NMR, but the spectral and analytical data was in complete agreement with the data of the compound **2j**

Scheme 3. Acylation of amine to form **2j**

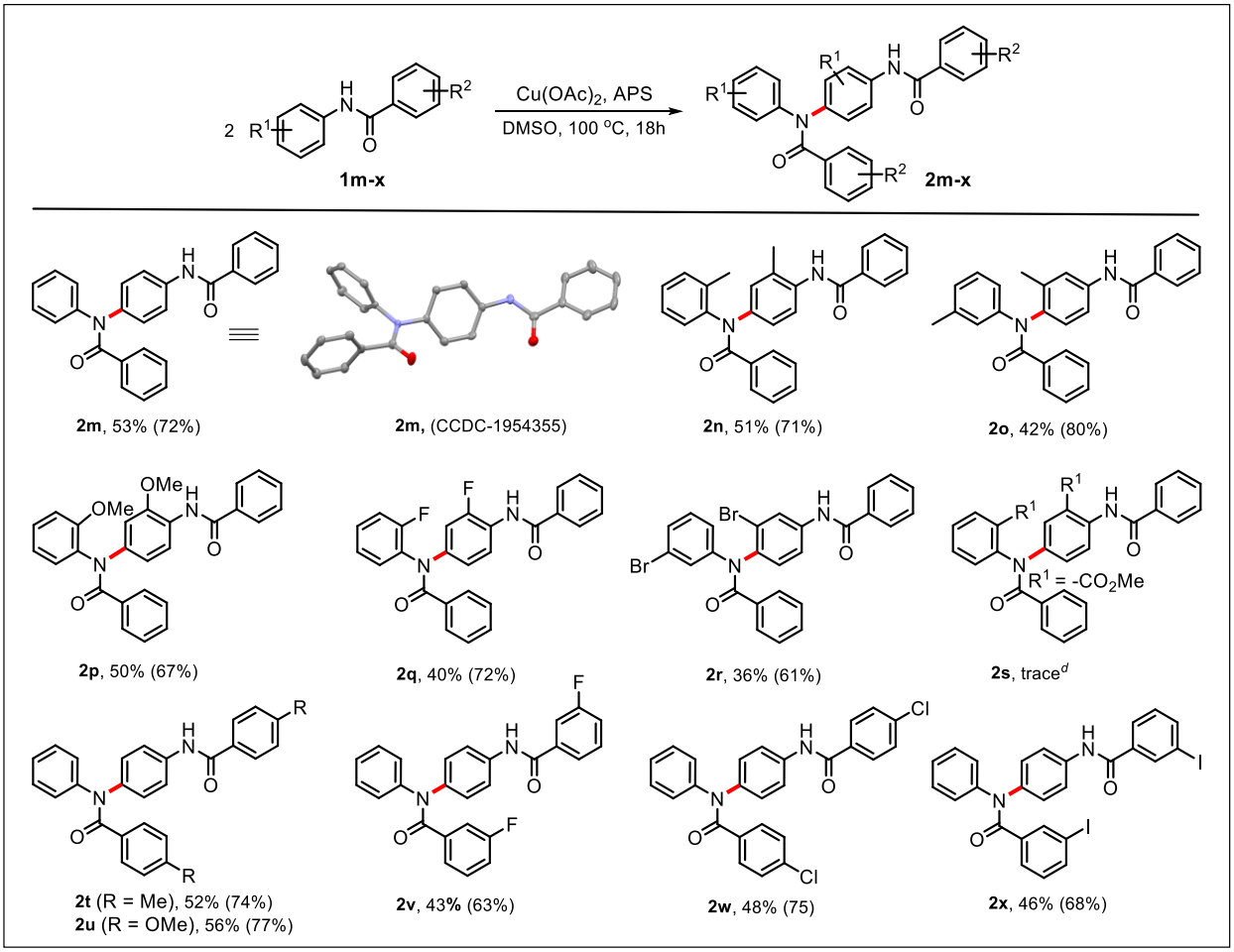


3 **2j** (69%)

synthesized by our protocol. The matching data also confirms the regioselectivity of our protocol.

The successful completion of the substrate scope study of *N*-arylalkylamides prompted us to demonstrate the generality of the protocol with varyingly substituted N-arylbenzamides (Scheme 4). The developed protocol was first applied on *N*-phenylbenzamide, and gratifyingly the product **2m** was obtained in a good yield. The regioselectivity of the product **2m** was also confirmed by single-crystal X-ray (CCDC-1954355). Initially, we studied the effect of

Scheme 4. Amidation/dimerization of *N*-arylbenzamides[a-c]



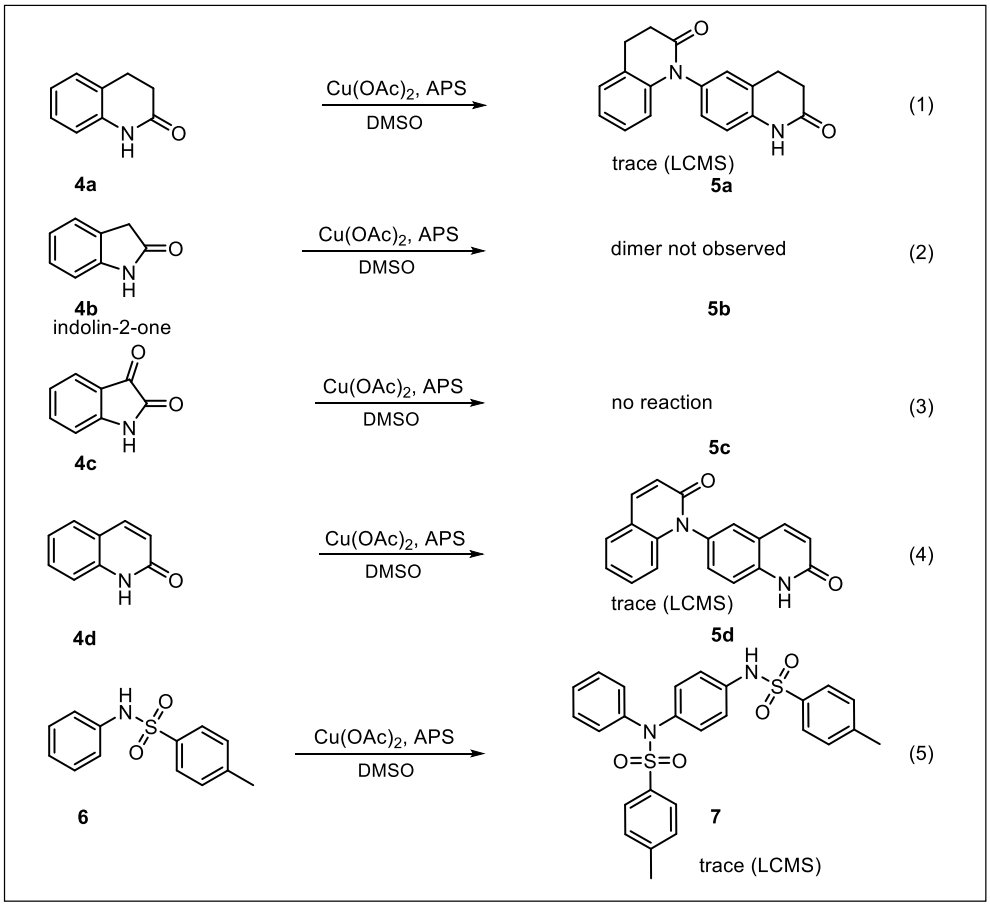
[a]Reaction conditions: 1m-x (0.2 mmol), $Cu(OAc)_2$ (10 mol%), APS (0.2 mmol), DMSO (0.1M) in a screw cap glass tube at 100 °C for 18 h. [b]Isolated yields. [c]Yields in parentheses are based on the recovered starting material. [d]Starting material recovered unchanged

substituents present on the electron-rich anilide aromatic ring. Two anilide substrates with electronically unbiased methyl substituent at *ortho* and *meta* position of the electron-rich aromatic ring worked well to provide **2n** and **2o**, respectively. The anilide substrate with electron-donating methoxy group furnished **2p** in moderate yield. The *ortho*-fluoro and *meta*-bromo-substituted anilides worked fine to provide the corresponding dimers **2q** and **2r**, respectively. However, as observed before, anilide having strong electron-withdrawing group failed to give the expected product **2s** under the developed protocol.

After the study of variation in the substituents present on the electron-rich aromatic ring of anilide, we targeted to study the effect of variation on electron-deficient aromatic ring of N-arylbenzamides. The substrate with methyl group at the *para*- position of the amide carbonyl did not affect the yield and **2t** was obtained in comparable yield with **2m**. Strong electron-donating methoxy group substituted anilide also worked well to furnish dimer **2u** decent yield. *meta*-Fluoro, *para*-chloro, and *meta*-iodo substituted anilides also worked fine to provide the corresponding desired products **2v**, **2w** and **2x** respectively in moderate yields.

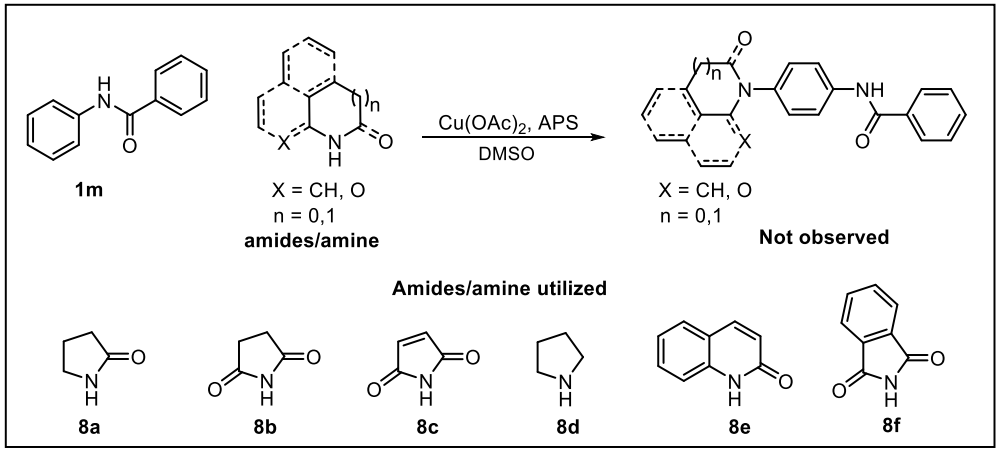
Overall, the developed protocol is quite general and many substituents, except highly electron-withdrawing groups, are well tolerated. Apart from anilides, we tested the feasibility of our developed protocol for the other amides/amines and sulphonamides. When we subjected dihydro-quinolone **4a** under the optimized reaction condition, a trace amount of dimer formation was observed, which was confirmed by LCMS analysis (Scheme 5, eq 1). We did not observe the formation of dimerized product in case of 2-indolone **4b**, and isatin (**4c**) as well (Scheme 5, eq 2-3). Trace amount of product formation was observed when quinolone **4d** and sulphonamides **5** was subjected under the optimized reaction condition (Scheme 5, eq 4-5), which confirms the protocol is highly selective for anilides. We neither observed cross-coupling

Scheme 5. Attempted dimerization reaction of other amides



products between anilides **1m** and aliphatic/aromatic amides/amines (**8a-f**) nor dimerization of other amides (**8a-f**) (Scheme 6).

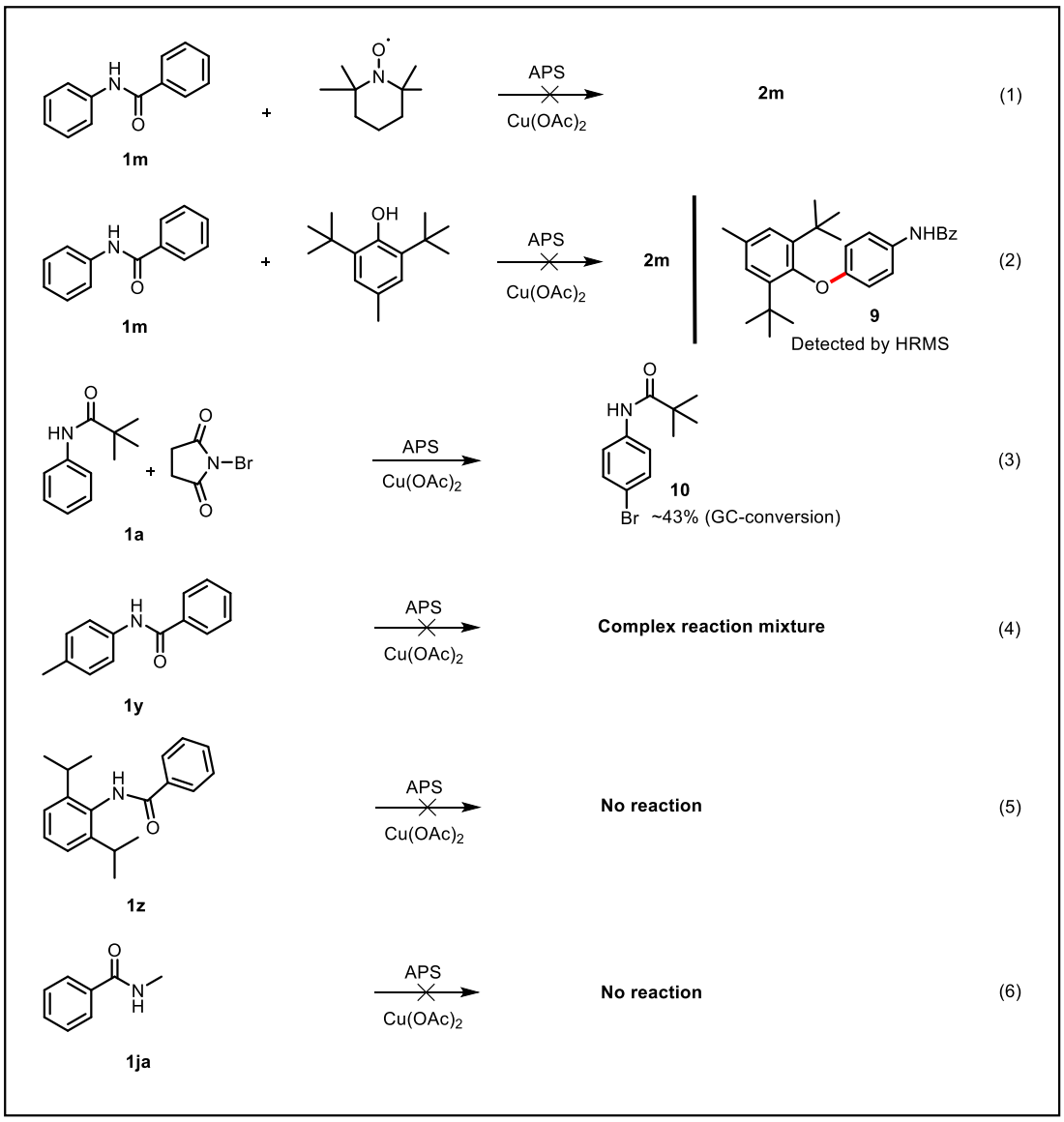
Scheme 6. Cross coupling/dimerization of anilides



Derivatives of the products **2a**-**2x** are commonly used in polymer/material chemistry,[19] and they would also be interesting precursors for the synthesis of the corresponding carbazoles or phenanthridinones via regioselective C─H activation strategy.

Few control experiments were performed for preliminary understanding of the mechanism of our protocol. The radical nature of the reaction was determined by performing the reaction of anilide **1m** under the standard reaction condition in the presence of radical scavengers such as TEMPO and BHT (Scheme 7, eq 1 and 2). Complete inhibition of reactions was observed in both cases. Interestingly, adduct **9** (Scheme 7, eq 2) was observed in HRMS of the crude reaction mixture, which confirms the radical pathway of the reaction. The formation of brominated product **10** instead of dimer **2a** in the presence of NBS also confirms the radical pathway (Scheme 7, eq 3). The reaction of anilide **1y** showed very less conversion and complex reaction mixture by TLC (Scheme 7, eq 4). The anilide substrate **1z** having bulky isopropyl substituent on both *ortho*-positions did not react under the standard reaction conditions though the *para*-position was available for the reaction. This observation indicates that probably the approach of Copper catalyst to the amide –NH is blocked due to the steric hindrance of isopropyl group leading to the failure of the reaction (Scheme 7, eq 5). We believe that the developed protocol works via a radical mechanism involving the formation of a *para*-quinone type of intermediate on aniline part of the anilide, which makes it highly regioselective. A tentative proof for our hypothesis of *para*-quinone type intermediate was realized when the substrate **1ja** (a structural isomer of **1j**) lacking the aniline part of the aromatic ring was subjected to our protocol (Scheme 7, eq 6). The reaction did not work because *para*-quinone type intermediate is not possible on benzamide aromatic ring.

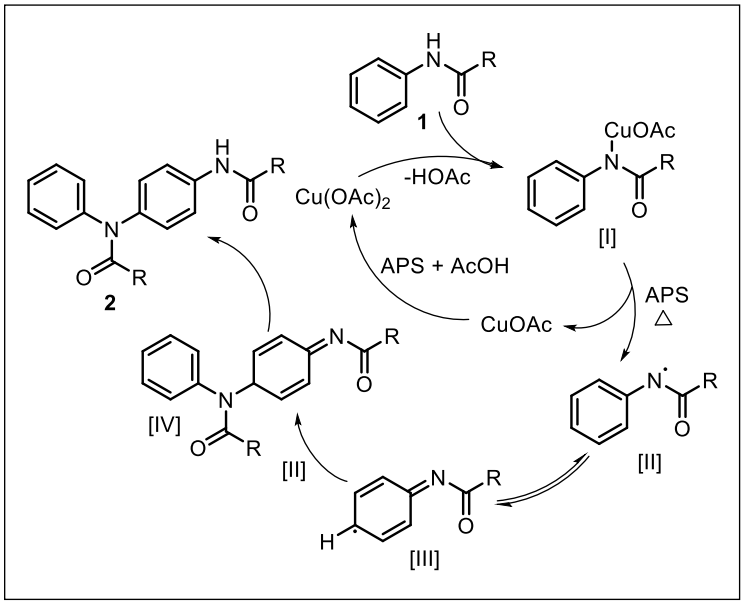
Scheme 7. Control Experiments



Based on the literature survey[9,16b, 20] and the control experiments (Scheme 7), a plausible mechanism via a radical pathway has been depicted in Scheme 8. Anilide **1** first chelates with a Copper catalyst to form complex [I], which converts to amidyl radical intermediate [II] in the presence of APS. The amidyl radical intermediate transforms to a stable *para*-quinone type imine radical intermediate [III]. A radical coupling between intermediates [II] and [III] provides the intermediate [IV], which on aromatization furnish the desired products 2. The Copper catalyst is

again regenerated in the presence of the oxidant APS. The proposed mechanism provides important starting points for a detailed investigation of the mechanism.

Scheme 8. Plausible Mechanism



2.7. Conclusion

In conclusion, we have developed a unique process for *para*-selective C─H functionalization leading to amidation /dimerization of anilide derivatives. The developed protocol is highly selective as the dimerization through C─N bond formation occurs specifically on aniline part of the anilide. Preliminary mechanistic investigation demonstrates that the reaction follows a radical pathway. A broad substrate scope has been demonstrated utilizing an inexpensive Copper catalyst. The obtained products are potential precursors for the synthesis of bioactive heterocyclic scaffolds. Currently, we are exploring the protocol for C─H functionalization of anilide derivatives with other reacting partners leading to C─C as well as C─X bond formation.

2.8. Experimental section

1. AdditionalInformation:

The NMR spectra of compounds **2a-g** show clean countable proton/carbon peaks. However, peak broadening was observed for aromatic peaks in the ^{1}H and ^{13}C NMR spectra of **2i-l**. Scanning the sample at various concentrations in $CDCl_3$ and other deuterated solvents at different concentrations and even for a longer time (24 h) on a 700 MHz Bruker NMR instrument also did not change this peculiar pattern. However, scanning the ^{1}H NMR of a representative compound **2j** at higher temperature provided clean spectra (see page nos. 37 and 38). These compounds with the presence of proton on the carbon adjacent to the carbonyl group may have a different kind of inter or intramolecular interaction leading to such a pattern. To clarify the doubt about the structure, we prepared the same compound **2j** by acylation of the corresponding commercially available diamine (page S4). The peculiar peak broadening was observed in the NMR, but the spectral and analytical data was in complete agreement with the data of the compound **2j** synthesized by our protocol. The matching data also confirms the regioselectivity of our protocol.

2. Experimental Procedures:

a] Synthesis of substrates 1a-z: The known substrates **1a-z** were prepared using the following procedure.[1-3] To a solution of amine (1 equiv) and NEt_3 (1.1 equiv) in dry CH_2Cl_2 was added the corresponding acid chloride (1.00 equiv) drop-wise over 30 min at 0 °C. The resulting reaction mixture was then allowed to warm to room temperature (rt) and stirred for 12-24 h. After completion of the reaction, the solution was transferred to a separatory funnel and washed three times with saturated aqueous $NaHCO_3$ and once with brine. The organic layer was dried over

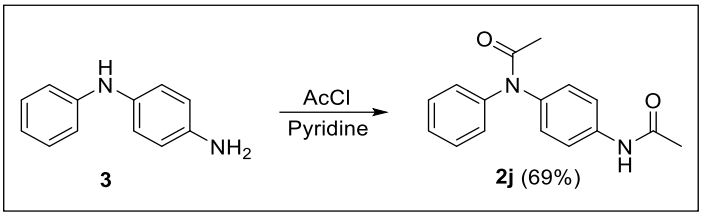
anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by recrystallization from EtOH.

b] General procedure for *para*-selective dimerization of anilides to obtain 2a-x: An oven-dried screw cap glass tube equipped with a magnetic stirring bar was charged with anilide **1a-x** (0.2 mmol, 1 equiv), ammonium persulfate (APS, 46 mg, 0.2 mmol, 1 equiv) and Copper acetate (3.6 mg, 0.02 mmol, 0.1 equiv) under argon atmosphere. To this mixture, DMSO (2.0 mL) was added and the glass tube was backfilled with argon and heated at 100 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC. After maximum conversion (18 h), the reaction mixture was diluted with ethyl acetate (40 mL) and washed with ice cold water (30 mL x 3). The organic layer was dried over Na_2SO_4, concentrated under vacuum, and the crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether as eluents.

c] Typical experimental procedure for the preparation of representative product 2a: An oven-dried screw cap glass tube, equipped with a magnetic stirring bar, was charged with *N*-phenylpivalamide (**1a**, 35.4 mg, 0.2 mmol, 1 equiv), APS (46 mg, 0.2 mmol, 1 equiv) and Copper acetate (3.6 mg, 0.02 mmol, 0.1 equiv) under argon atmosphere. To this mixture, DMSO (2.0 mL) was added and the glass tube was backfilled with argon and heated at 100 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC. After 18 h, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with ice cold water (30 mL x 3). The organic layer was dried over Na_2SO_4, concentrated under vacuum, and the crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether (1:4) to afford pure dimer product **2a** in 62% yield (22 mg) and 6.5 mg of **1a** was recovered

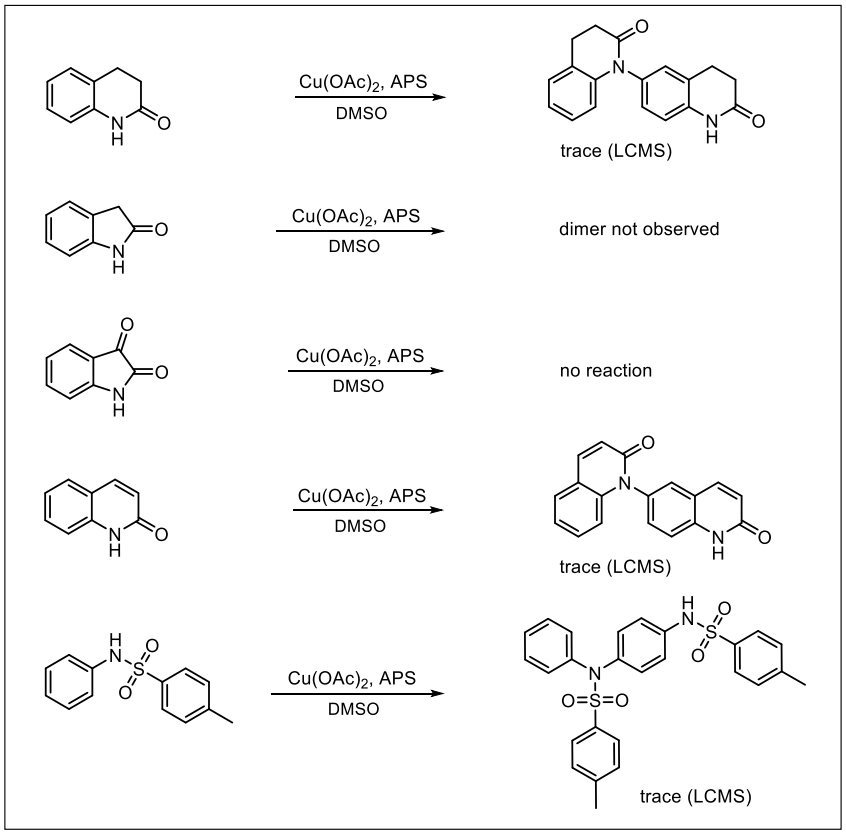
unchanged. Accordingly, the actual yield based on the recovered starting material (brsm) was 77%.

d] Alternate synthesis of product 2j: The procedure reported[4] for the acylation of amine was utilized. Acetyl chloride (86 µL, 1.2 mmol, 2.2 equiv) was added to a solution of commercially available amine **4** (100 mg, 0.55 mmol, 1 equiv) in dry pyridine (4 mL), and the reaction mixture was stirred for 1h at rt. After the removal of pyridine under vacuum, the residue was purified by silica gel column chromatography using ethyl acetate and petroleum ether (1:1) to afford **2j** in 69% yield (102 mg).



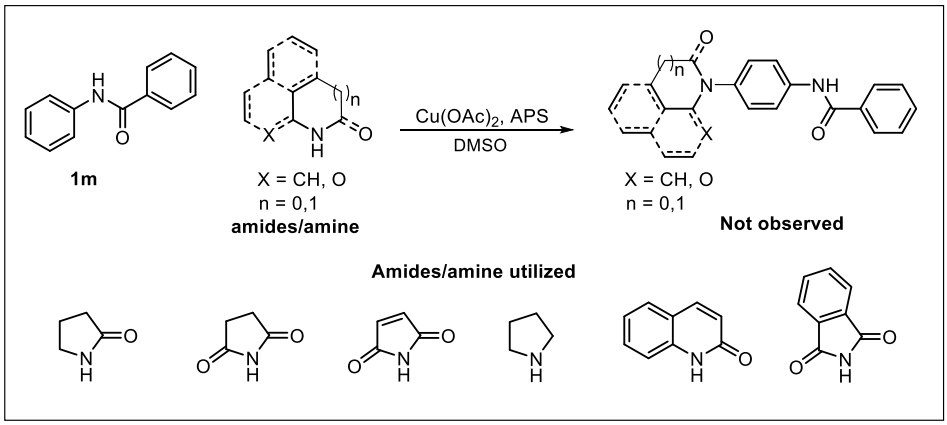
e) General procedure for the attempted dimerization reaction of other amides:

An oven-dried screw cap glass tube equipped with a magnetic stirring bar was charged with amides (0.2 mmol, 1 equiv), ammonium persulfate (APS, 46 mg, 0.2 mmol, 1 equiv) and Copper acetate (3.6 mg, 0.02 mmol, 0.1 equiv) under argon atmosphere. To this mixture, DMSO (2.0 mL) was added and the glass tube was backfilled with argon and heated at 100 ^{o}C in a preheated oil bath. The progress of the reaction was monitored using TLC. All the reactions failed to give an isolable quantity of dimer product. A trace amount of dimer product formation was observed (LCMS) in the crude reaction mixture of 3,4-dihydroquinolin-2(1H)-one, quinolin-2(1H)-one and 4-methyl-*N*-phenylbenzenesulfonamide.



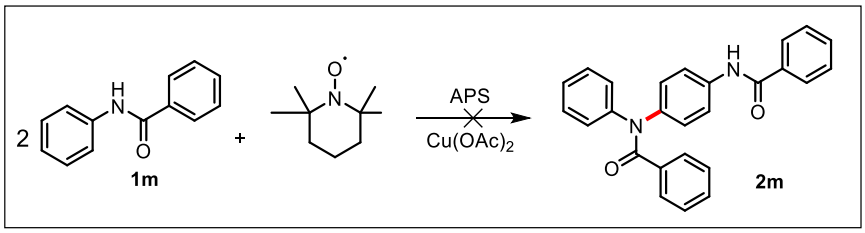
f) General procedure for attempted Cross-coupling reactions:

An oven-dried screw cap glass tube equipped with a magnetic stirring bar was charged with anilide **1m** (0.2 mmol, 1 equiv), other amide (0.4 mmol, 2 equiv), ammonium persulfate (APS, 46 mg, 0.2 mmol, 1 equiv), and Copper acetate (3.6 mg, 0.02 mmol, 0.1 equiv) under argon atmosphere. To this mixture, DMSO (2.0 mL) was added and the glass tube was backfilled with argon and heated at 100 ^{o}C in a preheated oil bath. The reaction was monitored using TLC. All the reactions failed to give cross-coupled product as confirmed by LCMS of the crude reaction mixture.



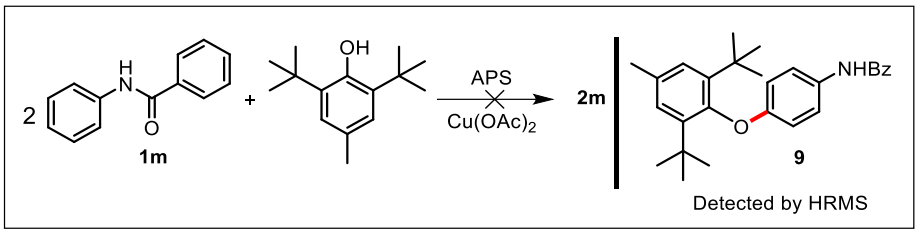
g) Radical trapping experiments:

An oven-dried screw cap glass tube, equipped with a magnetic stirring bar, was charged with anilide **1m** (20 mg, 0.1 mmol, 1 equiv), APS (23 mg, 0.1 mmol, 1 equiv), Copper acetate (1.8 mg, 0.02 mmol, 0.1 equiv) and TEMPO (31 mg, 0.2 mmol, 2 equiv) under argon atmosphere. To this mixture, DMSO was added (1.0 mL) and the glass tube was backfilled with argon and heated at 100 ^{o}C in a preheated oil bath. The progress of the reaction was monitored using TLC, however the formation of the product **2m** was not observed and most of the starting material remained unreacted. LC-MS of the crude reaction mixture did not show any TEMPO adduct formation.



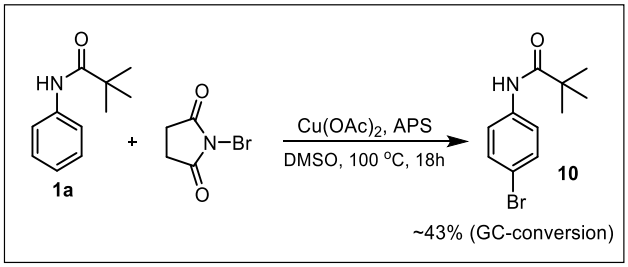
The same reaction was performed in the presence of BHT (44 mg, 0.2 mmol, 2 equiv) asa radical scavenger. In this case also, the formation of product **2m** was not observed. However, the peak corresponding to the molecular weight of BHT+**2m** was observed in LC-MS, which was reconfirmed by HRMS. HRMS of **3** (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{34}NO_2$, 416.2584 found, 416.2584.

Trapping of intermediate with BHT using the above mentioned procedure



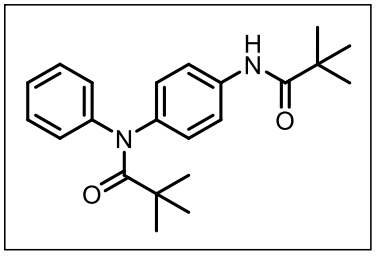
h) Bromination of anilide 1a with NBS under standard conditions:

An oven-dried screw cap glass tube, equipped with a magnetic stirring bar, was charged with *N*-phenylpivalamide (**1a**, 35.4mg, 0.2 mmol, 1 equiv), N-bromosuccinimide (71mg, 0.4 mmol, 2 equiv), APS (46 mg, 0.2 mmol, 1 equiv) and Copper acetate (3.6 mg, 0.02 mmol, 0.1 equiv) under argon atmosphere. To this mixture, DMSO (2.0 mL) was added and the glass tube was backfilled with argon and heated at 100 ^{o}C in a preheated oil bath. The progress of the reaction was monitored by GC and GC-MS. After 18 h, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with ice cold water (30 mL x 3). The organic layer was dried over Na_2SO_4, concentrated under vacuum, and the crude residue was passed through flash column chromatography using ethyl acetate and petroleum ether (1:3) to afford an inseparable mixture of **1a** and brominated product **4**. The ^{1}H NMR and GC/GC-MS analysis of inseparable mixture of **1a** and brominated product **4** shows 43% conversion.



Characterization Data of Compounds.

***N*-Phenyl-N-(4-pivalamidophenyl)pivalamide (2a)**:



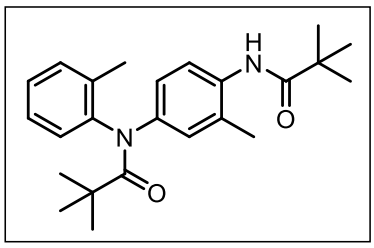
According to the general procedure, the title compound **2a** was obtained as a white solid (22 mg; 62% yield, [BRSM-77%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate: pet. ether, 1:2); mp: 170-172 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57-7.47 (m, 2H), 7.37-7.29 (m, 3H), 7.27-7.15 (m, 5H), 1.31 (s, 9H), 1.15 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 179.5, 176.6, 144.5, 140.2, 136.8, 129.1, 128.2, 126.7, 120.6, 41.6, 39.6, 29.7, 27.7.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{29}N_2O_2$, 353.2224; found, 353.2220.

***N*-(3-Methyl-4-pivalamidophenyl)-N-(o-tolyl)pivalamide (2b)**:



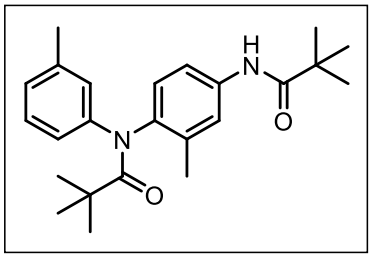
According to the general procedure, the title compound **2b** was obtained as a white solid (23 mg; 60% yield, [BRSM-72%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 140-142 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (d, J = 8.54 Hz, 1H), 7.24-7.12 (m, 5H), 7.05-7.96 (m, 2H), 2.23 (s, 3H), 2.21 (s, 3H), 1.33 (s, 9H), 1.14 (s, 9H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 179.5, 176.4, 142.7, 140.1, 135.7, 134.0, 131.4, 129.3, 129.2, 129.0, 127.6, 126.5, 125.9, 122.8, 41.7, 39.7, 29.5, 27.7, 18.6, 17.7.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{33}N_2O_2$, 381.2542; found, 381.2547.

***N*-(2-Methyl-4-pivalamidophenyl)-N-(m-tolyl)pivalamide (2c)**:



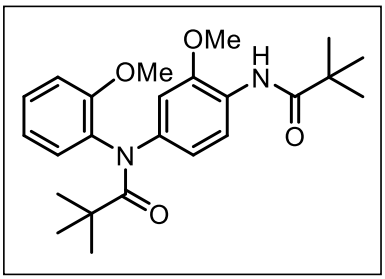
According to the general procedure, the title compound **2c** was obtained as a white solid (18 mg; 47% yield, [BRSM-80%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 85-87 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 (d, J = 2.29 Hz, 1H), 7.41-7.34 (m, 2H), 7.19-7.14 (m, 1H), 7.13 (d, J = 8.70 Hz, 1H), 6.98 (d, J = 7.33 Hz, 1H), 6.95-6.90 (m, 2H), 2.29 (s, 3H), 2.2 (s, 3H), 1.31 (s, 9H), 1.14 (s, 9H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 179.7, 176.6, 143.7, 138.6, 137.2, 136.7, 129.9, 128.5, 127.8, 127.0, 124.4, 122.5, 117.8, 41.8, 39.6, 29.5, 27.6, 21.4, 18.7.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{33}N_2O_2$, 381.2542; found, 381.2540.

***N*-(3-Methoxy-4-pivalamidophenyl)-N-(2-methoxyphenyl)pivalamide (2d)**:



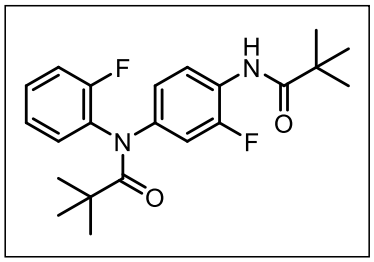
According to the general procedure, the title compound **2d** was obtained as a white solid (23 mg; 56% yield, [BRSM-68%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp113-115 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.33 (d, J = 8.70 Hz, 1H), 8.05 (s, 1H), 7.26-7.18 (m, 2H), 6.93-6.88 (m, 4H), 3.86 (s, 3H), 3.86 (s, 3H), 1.30 (s, 9H), 1.15 (s, 9H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 179.1, 176.4, 155.2, 147.9, 139.8, 133.5, 130.0, 128.7, 126.6, 120.83, 120.79, 119.3, 111.9, 110.3, 55.9, 55.4, 41.4, 40.0, 29.2, 27.6.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{33}N_2O_4$, 413.2440; found, 413.2439.

***N*-(3-Fluoro-4-pivalamidophenyl)-N-(2-fluorophenyl)pivalamide (2e)**:



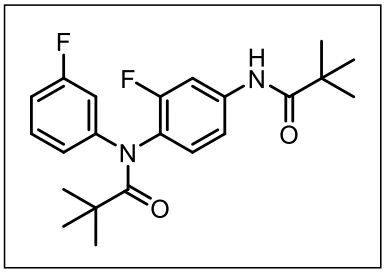
According to the general procedure, the title compound **2e** was obtained as a white solid (16 mg; 41% yield, [BRSM-62%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 139-141 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35 (t, *J* = 8.77 Hz, 1H), 7.60 (d, *J* = 2.29 Hz, 1H), 7.31-7.22 (m, 2H), 7.15-7.06 (m, 4H), 1.32 (s, 9H), 1.17 (s, 9H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 178.6, 176.6, 158.0 (d, *J* = 249.2 Hz), 152.0 (d, *J* = 243.5), 139.3 (d, *J* = 9.59 Hz), 132.0 (d, *J* = 12.46), 130.4, 129.4 (d, *J* = 7.67 Hz), 125.8 (d, 10.54 Hz), 124.6 (d, *J* = 3.83), 124.5, 121.4, 116.7 (d, *J* = 21.09 Hz), 115.1 (d, *J* = 20.13 Hz), 41.5, 40.0, 29.1, 27.5.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}N_2O_2F_2$, 389.2040; found, 389.2042.

***N*-(2-Fluoro-4-pivalamidophenyl)-N-(3-fluorophenyl)pivalamide (2f)**:



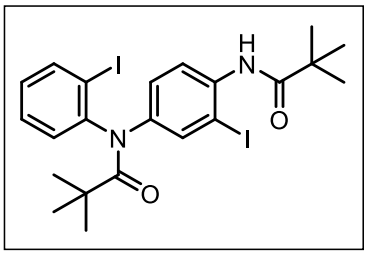
According to the general procedure, the title compound **2f** was obtained as a white solid (12 mg; 31% yield, [BRSM-74%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 136-138 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26 (m, 2H), 7.33-7.25 (m, 1H), 7.17 (d, *J* = 3.81 Hz, 2H), 7.06 (d, *J* = 7.63 Hz, 1H), 7.01-7.91 (m, 2H), 1.30 (s, 9H), 1.17 (s, 9H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 179.1, 176.8, 162.7 (d, *J* = 248.28 Hz), 159.1 (d, *J* = 249.2 Hz), 145.3 (d, *J* = 8.63 Hz), 139.3 (d, *J* = 10.54), 130.6, 130.1 (d, *J* = 8.63 Hz), 127.0 (d, *J* = 13.42 Hz), 123.7, 115.5 (d, *J* = 5.75 HZ), 115.2, 114.1 (d, *J* = 21.09), 108.5 (d, *J* = 25.88), 41.5, 39.7, 29.1, 27.5.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}N_2O_2F_2$, 389.2040; found, 389.2043.

***N*-(3-Iodo-4-pivalamidophenyl)-N-(2-iodophenyl)pivalamide (2g)**:



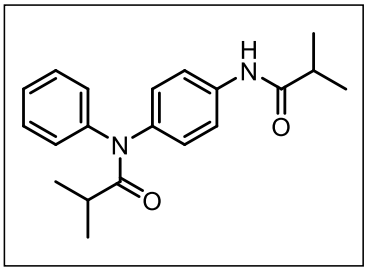
According to the general procedure, the title compound **2g** was obtained as a white solid (32 mg; 53% yield, [BRSM-72%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 132-134 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.30 (d, *J* = 8.70 Hz, 1H), 7.90 (d, *J* = 7.79 Hz, 1H), 7.82 (s, 1H), 7.80 (d, *J* = 2.29 Hz, 1H), 7.40-7.30 (m, 2H), 7.24 (d, *J* = 7.78 Hz, 1H), 7.03-6.98 (t, *J* = 7.56, 1H), 1.36 (s, 9H), 1.20 (s, 9H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 179.1, 176.7, 146.2, 140.5, 139.8, 138.0, 137.2, 130.2, 129.3, 129.1, 128.8, 120.8, 100.3, 88.9, 41.9, 40.2, 29.5, 27.6.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}N_2O_2I_2$, 605.0162; found, 605.0164.

***N*-(4-Isobutyramidophenyl)-N-phenylisobutyramide (2i)**:



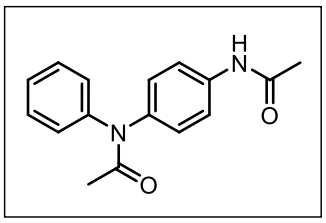
According to the general procedure, the title compound **2i** was obtained as a sticky solid (18 mg; 56% yield, [BRSM-71%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 140-142 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.59-7.29 (m, 5H), 7.26-7.05 (m, 4H), 2.79-2.67 (m, 1H), 2.55-2.44 (m, 1H), 1.22 (d, *J* = 6.71 Hz, 6H), 1.13 (d, *J* = 6.71 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 177.9, 175.5, 142.9, 138.6, 131-125 (5C's), 120.6, 36.4, 31.9, 19.6, 19.5.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_2$, 325.1916; found, 325.1919.

***N*-(4-Acetamidophenyl)-N-phenylacetamide (2j)**:



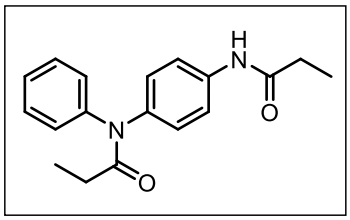
According to the general procedure, the title compound **2j** was obtained as a sticky solid (14mg; 52% yield, [BRSM-68%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77 (s, 1H), 7.55 (s, 1H), 7.45-7.32 (m, 4H), 7.28-7.23 (m, 2H), 7.22-7.14 (m, 2H); 2.14 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 170.8, 168.5, 129.7-126.4 (7C's), 120.6, 24.4, 23.7.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_2$, 269.1290; found, 269.1295.

***N*-Phenyl-N-(4-propionamidophenyl)propionamide (2k):**



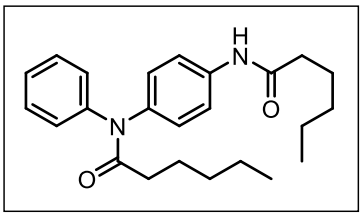
According to the general procedure, the title compound **2k** was obtained as a sticky solid (16mg; 54% yield, [BRSM-77%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (s, 1H), 7.57 (m, 2H), 7.41-7.31 (m, 2H), 7.31-7.22 (m, 3H), 7.18 (d, J = 7.93 Hz, 2H), 2.35 (q, J = 7.52 Hz, 2H), 2.28 (q, J = 7.32 Hz, 2H), 1.22 (t, J = 7.32 Hz, 3H), 1.13 (t, J = 7.62 Hz, 3H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 174.2, 172.2, 142.8, 138.5, 131-124 (5C's), 120.6, 30.6, 28.7, 9.7, 9.6.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_2$, 297.1603; found, 297.1605.

***N*-(4-Hexanamidophenyl)-N-phenylhexanamide (2l)**:



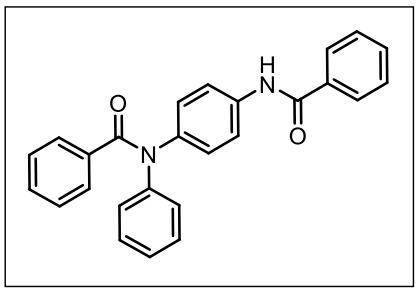
According to the general procedure, the title compound **2l** was obtained as a sticky solid (18 mg; 46% yield, [BRSM-65%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.65-7.30 (m, 5H), 7.23 (d, *J* = 7.32 Hz, 2H), 7.20-7.10 (m, 2H); 2.39-2.22 (m, 4H), 1.78-1.59 (m, 4H), 1.40-1.30 (m, 4H), 1.29-1.21 (m, 4H), 0.95-0.8 (m, 6H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 173.7, 171.7, 142.9, 138.5, 130-125 (5C's), 120.6, 37.5, 35.1, 33.7, 31.4, 29.7, 25.6, 22.4, 22.4, 13.9, 13.9.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{33}N_2O_2$, 381.2542; found, 381.2538.

***N*-(4-Benzamidophenyl)-N-phenylbenzamide (2m)**:



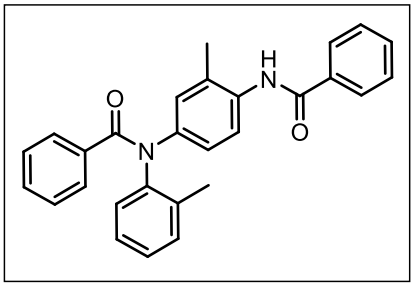
According to the general procedure, the title compound **2m** was obtained as a white solid (21 mg; 53% yield, [BRSM-72%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether 1:2); mp: 188-190 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.16 (s, 1H), 7.85 (d, *J* = 7.32 Hz, 2H), 7.58 (d, *J* = 8.54 Hz, 2H), 7.53 (d, *J* = 7.32 Hz, 1H), 7.49-7.42 (m, 4H), 7.35-7.27 (m, 2H), 7.26-7.16 (m, 4H), 7.16-7.06 (m, 4H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 170.8, 165.7, 143.8, 139.9, 136.3, 135.9, 134.8, 131.8, 130.3, 129.2, 129.1, 128.7, 127.9, 127.4, 127.1, 126.4, 120.8.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_2$, 393.1598; found, 393.1592.

***N*-(4-Benzamido-3-methylphenyl)-N-(o-tolyl)benzamide (2n)**:



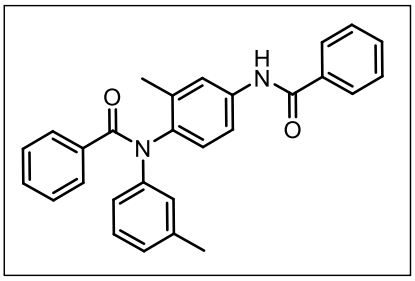
According to the general procedure, the title compound **2n** was obtained as a white solid (21mg; 51% yield, [BRSM-71%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 168-170 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) 7.91-7.82 (m, 3H), 7.68 (s, 1H), 7.62-7.52 (m, 2H), 7.52-7.44 (m, 4H), 7.30 (d, *J* = 7.32 Hz, 1H), 7.26-7.12 (m, 5H), 7.07 (d, *J* = 7.32 Hz, 1H), 6.97-6.92 (m, 1H), 2.29 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm); 170.4, 165.5, 142.1, 136.0, 135.4, 134.8, 133.5, 131.9, 131.4, 130.3, 130.1, 129.6, 129.3, 128.9, 128.4, 128.1, 127.9, 127.6, 127.0, 124.7, 123.1, 18.4, 17.9.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_2$, 421.1916; found, 421.1921.

***N*-(4-Benzamido-2-methylphenyl)-N-(m-tolyl)benzamide (2o)**:



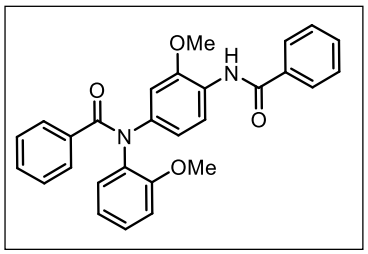
According to the general procedure, the title compound **2o** was obtained as a white solid (18 mg; 42% yield, [BRSM-80%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 138-140 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) 8.19 (s, 1H), 7.87 (d, *J* = 7.33 Hz, 2H), 7.57-7.41 (m, 8H), 7.32 (t, *J* = 7.33 Hz, 1H), 7.27-7.21 (m, 2H), 7.09 (t, *J* = 6.87 Hz, 1H), 7.0 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 7.33 Hz, 1H), 6.86-6.79 (m, 1H), 2.26 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm); 170.6, 165.8, 138.9, 138.3, 137.2, 136.1, 136.0, 134.9, 131.8, 130.3, 128.9, 128.7, 128.6, 127.9, 127.1, 126.8, 126.7, 123.6, 122.7, 118.8, 21.3, 18.5.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_2$, 421.1916; found, 421.1921.

***N*-(4-Benzamido-3-methoxyphenyl)-N-(2-methoxyphenyl)benzamide (2p)**:



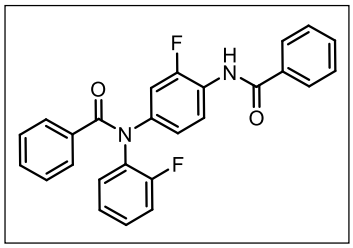
According to the general procedure, the title compound **2p** was obtained as a white solid (23 mg; 50% yield, [BRSM-67%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 152-154 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) 8.48 (s, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 7.88 (s, 1H), 7.86 (d, *J* = 1.34 Hz, 1H), 7.60-7.44 (m, 6H), 7.30-7.25 (m,1H), 7.24-7.17 (m, 4H), 6.91 (t, *J* = 7.56 Hz, 1H), 6.86 (s, 1H), 6.74 (dd, *J* = 8.70, 2.29 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 171.1, 165.1, 154.8, 148.1, 139.4, 136.4, 135.2, 132.6, 131.7, 129.9, 129.5, 128.8, 128.7, 128.5, 127.6, 127.0, 125.7, 121.1, 119.6, 118.8, 112.2, 109.3, 55.9, 55.5.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_4$, 453.1814; found, 453.1821.

***N*-(4-Benzamido-3-fluorophenyl)-N-(2-fluorophenyl)benzamide (2q)**:



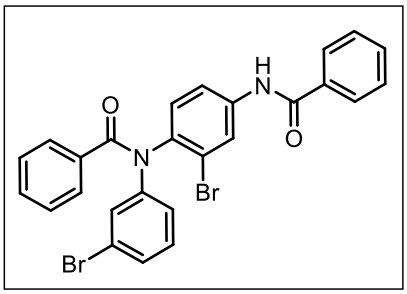
According to the general procedure, the title compound **2q** was obtained as a white solid (17 mg; 40% yield, [BRSM-72%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 162-164 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 8.41 (t, *J* = 8.77 Hz, 1H), 8.04 (s, 1H), 7.87 (d, *J* = 6.87 Hz, 2H), 7.61-7.5 (m, 1H), 7.54-7.47 (m, 4H), 7.37-7.31 (m, 1H), 7.31-7.22 (m, 3H), 7.22-7.16 (m, 1H), 7.16-7.03 (m, 3H), 7.98 (d, *J* = 8.39 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.5, 165.4, 157.6 (d, *J* = 251.12 Hz), 152.2 (d, *J* = 245.37 Hz), 139.0 (d, *J* = 10.54 Hz), 135.0, 134.2, 132.3, 131.0 (d, *J* = 12.46 Hz), 130.6, 129.8, 129.0 (d, *J* = 7.67 Hz), 128.9, 128.7, 128.0, 127.1, 124.9, 124.9 (d, *J* = 4.79 Hz), 122.8, 121.7, 116.8 (d, *J* = 20.13 Hz), 113.7 (d, *J* = 21.09 Hz).

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{19}N_2O_2F_2$, 429.1414; found, 429.1415.

N-(4-Benzamido-2-bromophenyl)-N-(3-bromophenyl)benzamide (2r):



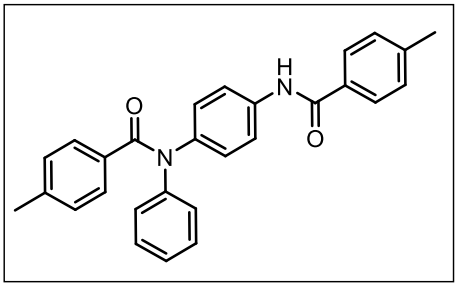
According to the general procedure, the title compound **2r** was obtained as a white solid (20 mg; 36% yield, [BRSM-61%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 202-204 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.37 (s, 1H), 7.96 (s, 1H), 7.88 (d, *J* = 7.32 Hz, 2H), 7.66 (d, *J* = 7.32 Hz, 1H), 7.60-7.52 (m, 3H), 7.50-7.43 (m, 2H), 7.41-7.36 (m, 1H), 7.33-7.26 (m, 3H), 7.22 (s, 1H), 7.10 (d, *J* = 7.93 Hz, 2H), 7.02 (s, 1H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 170.7, 165.8, 138.8, 137.5, 135.0, 134.7, 134.4, 132.1, 130.9, 130.1, 129.3, 129.1, 128.9, 128.7, 128.1, 127.2, 127.1, 125.2, 124.9, 123.2, 122.4, 120.3.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{19}N_2O_2{}^{79}Br_2$, 548.9813; found, 548.9824.

4-Methyl-N-(4-(4-methylbenzamido)phenyl)-N-phenylbenzamide (2t):



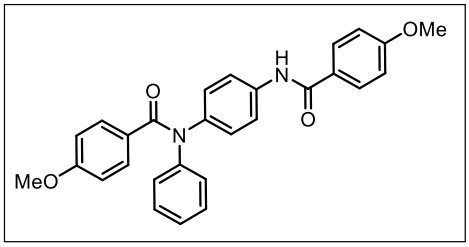
According to the general procedure, the title compound **2t** was obtained as a white solid (22 mg; 52% yield, [BRSM-74%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 162-164 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 8.02 (s, 1H), 7.78 (d, *J* = 5.95 HZ, 2H), 7.62-7.52 (m, 2H), 7.37 (d, *J* = 7.33 Hz, 2H), 7.32- 7.21 (m, 4H), 7.21-7.07 (m, 5H), 7.03 (d, *J* = 7.33 Hz, 2H), 2.42 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 170.9, 165.8, 144.1, 142.5, 140.7, 140.1, 136.4, 133.0, 132.0, 129.51, 129.48, 129.2, 128.7, 128.1, 127.5, 127.2, 126.4, 120.9, 21.6, 21.5.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_2$, 421.1911; found, 421.1907.

4-Methoxy-N-(4-(4-methoxybenzamido)phenyl)-N-phenylbenzamide (2u):



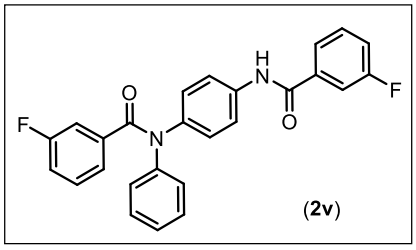
According to the general procedure, the title compound **2u** was obtained as a white solid (25 mg; 56% yield, [BRSM-77%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 190-192 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.99 (s, 1H), 8.83 (d, *J* = 8.55 Hz, 2H), 7.57 (d, *J* = 7.55 Hz, 2H), 7.45 (d, *J* = 9.16 Hz, 2H), 7.33-7.22 (m, 2H), 7.21-7.07 (m, 5H), 6.94 (d, *J* = 7.93 Hz, 2H), 6.73 (d, *J* = 8.55 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 170.4, 165.2, 162.5, 161.1, 144.2, 140.2, 136.2, 131.4, 129.1, 129.0, 127.9, 127.3, 126.9, 126.1, 120.8, 113.9, 113.2, 55.4, 55.2.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_4$, 453.1809; found, 453.1806.

3-Fluoro-N-(4-(3-fluorobenzamido)phenyl)-N-phenylbenzamide (2v):



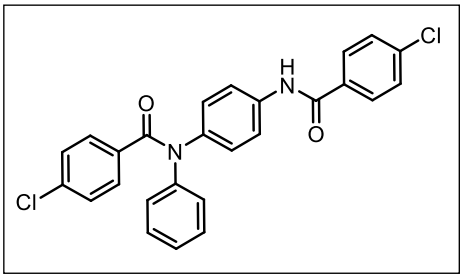
According to the general procedure, the title compound **2v** was obtained as a white solid (18 mg; 43% yield, [BRSM-63%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 162-164 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18 (s, 1H), 7.63 (d, *J* = 7.63 Hz, 1H), 7.58 (d, *J* = 8.39 Hz, 3H), 7.46-7.39 (m, 1H), 7.30 (d, *J* = 7.30 Hz, 1H), 7.26-7.16 (m, 6H), 7.15-7.07 (m, 4H), 7.04-7.98 (m, 1H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 169.4, 164.4, 162.7 (d, *J* = 248.24 Hz), 162.1 (d, *J* = 247.3 Hz), 143.3, 139.6, 138.0 (d, *J* = 7.67 Hz), 137.0 (d, *J* = 6.71 Hz), 136.3, 130.4 (d, *J* = 7.67 Hz), 129.6 (d, *J* = 7.67 Hz), 129.3, 127.8, 127.3, 126.8, 124.8 (d, *J* = 2.88 Hz), 122.6 (d, *J* = 2.88 Hz), 121.0, 118.9 (d, *J* = 21.09 Hz), 117.4 (d, *J* = 21.09 Hz), 116.2 (d, *J* = 23 Hz), 114.6 (d, *J* = 23 Hz).

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{19}N_2O_2F_2$, 429.1409; found, 429.1404.

4-Chloro-N-(4-(4-chlorobenzamido)phenyl)-N-phenylbenzamide (2w):



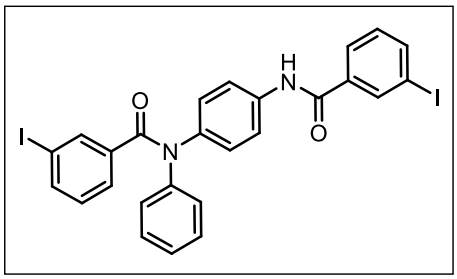
According to the general procedure, the title compound **2w** was obtained as a white solid (22 mg; 48% yield, [BRSM-75%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. Ether; 1:2); mp: 161-163 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (s, 1H), 7.80 (d, *J* = 8.24 Hz, 2H), 7.57 (d, *J* = 8.70 Hz, 2H), 7.41 (d, *J* = 7.41 Hz, 2H), 7.38 (d, *J* = 8.24 Hz, 2H), 7.33- 7.27 (m, 2H), 7.23-7.17 (m, 3H), 7.16-7.05 (m, 4H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 169.7, 164.7, 143.4, 139.7, 138.2, 136.4, 136.3, 134.2, 133.0, 130.6, 129.3, 129.0, 128.6, 128.3, 127.8, 127.3, 126.7, 121.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{19}N_2O_2Cl_2$, 461.0818; found, 461.0811.

3-Iodo-N-(4-(3-iodobenzamido)phenyl)-N-phenylbenzamide (2x):



According to the general procedure, the title compound **2x** was obtained as a white solid (30 mg; 46% yield, [BRSM-68%]): Reaction time 18h, 100 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 81-83 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21-8.17 (m, 1H), 8.06 (s, 1H), 7.89-7.86 (m, 1H), 7.86-7.84 (m, 1H), 7.84-7.80 (m, 1H), 7.65-7.62 (m, 1H), 7.58 (d, *J* = 9.16 Hz, 2H), 7.37-7.34 (m, 1H), 7.32-7.28 (m, 2H), 7.23-7.18 (m, 2H), 7.16-7.09 (m, 4H) 6.97-6.91 (m, 1H).

^{13}C NMR (100 MHz, CDCl3) δ (ppm) 168.9, 164.1, 143.3, 140.8, 139.6, 139.2, 138.1, 137.8, 136.7, 136.2, 136.1, 130.4, 129.5, 129.3, 128.1, 127.9, 127.4, 126.8, 126.3, 121.0, 94.4, 93.5.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{19}N_2O_2I_2$, 644.9530; found, 644.9526.

2.9. References

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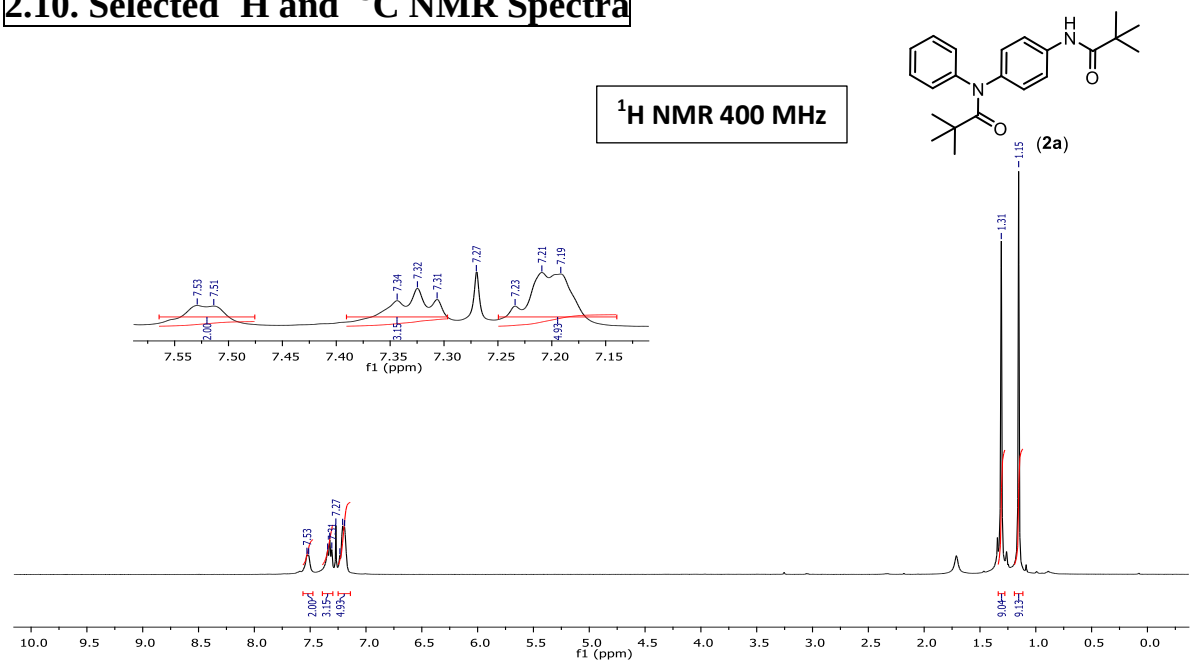
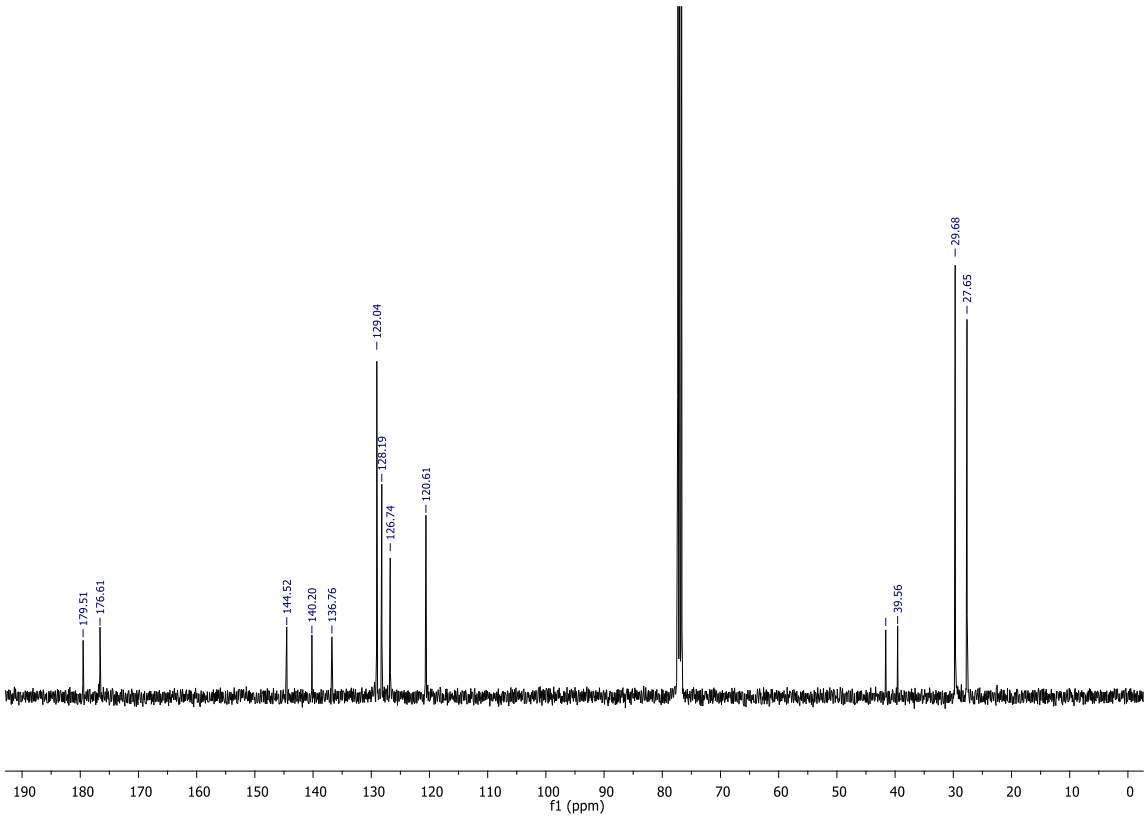
2.10. Selected ^{1}H and ^{13}C NMR Spectra





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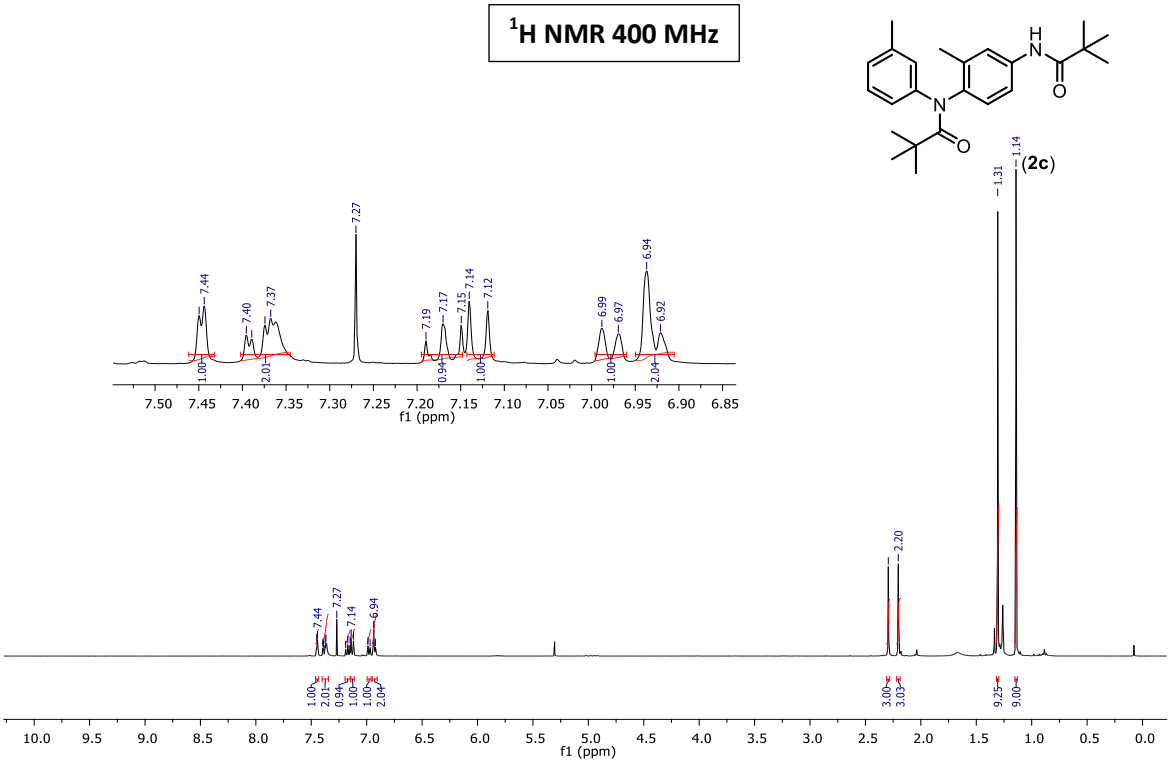

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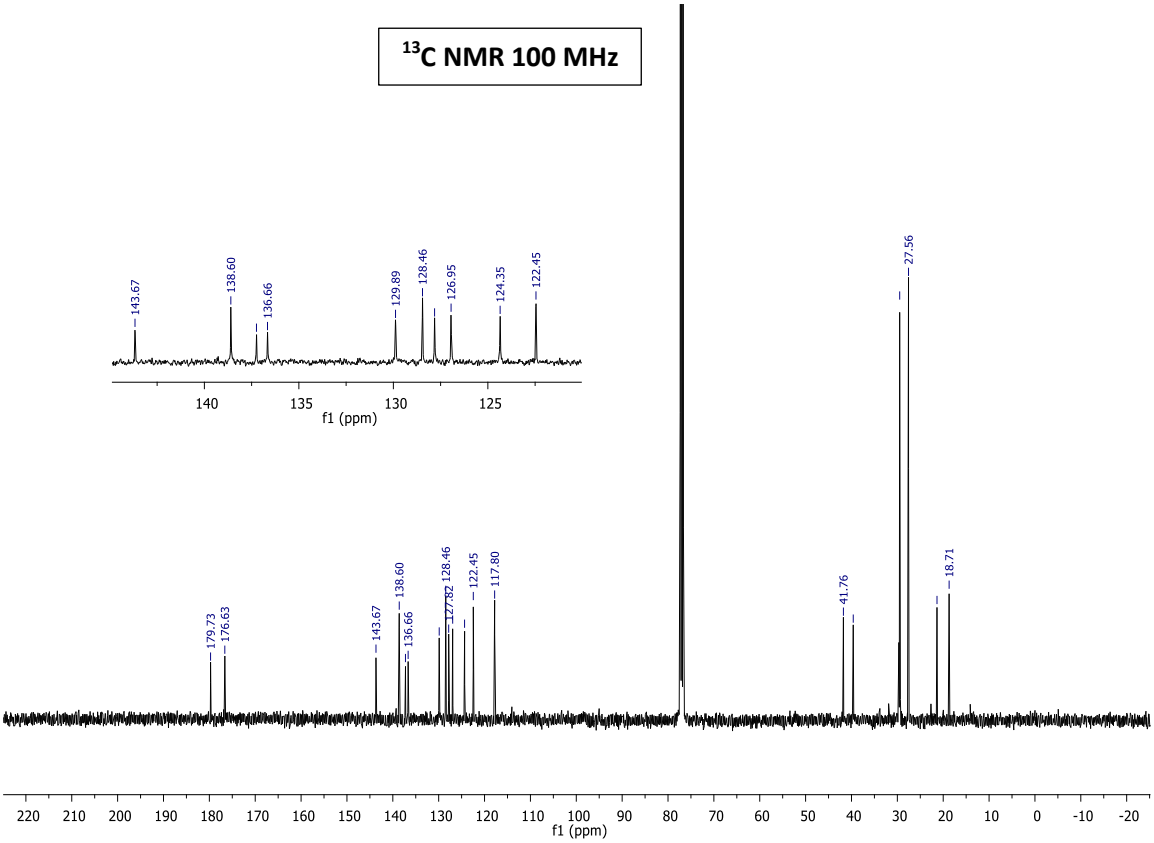

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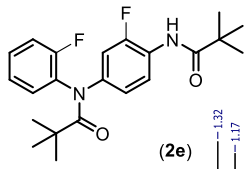

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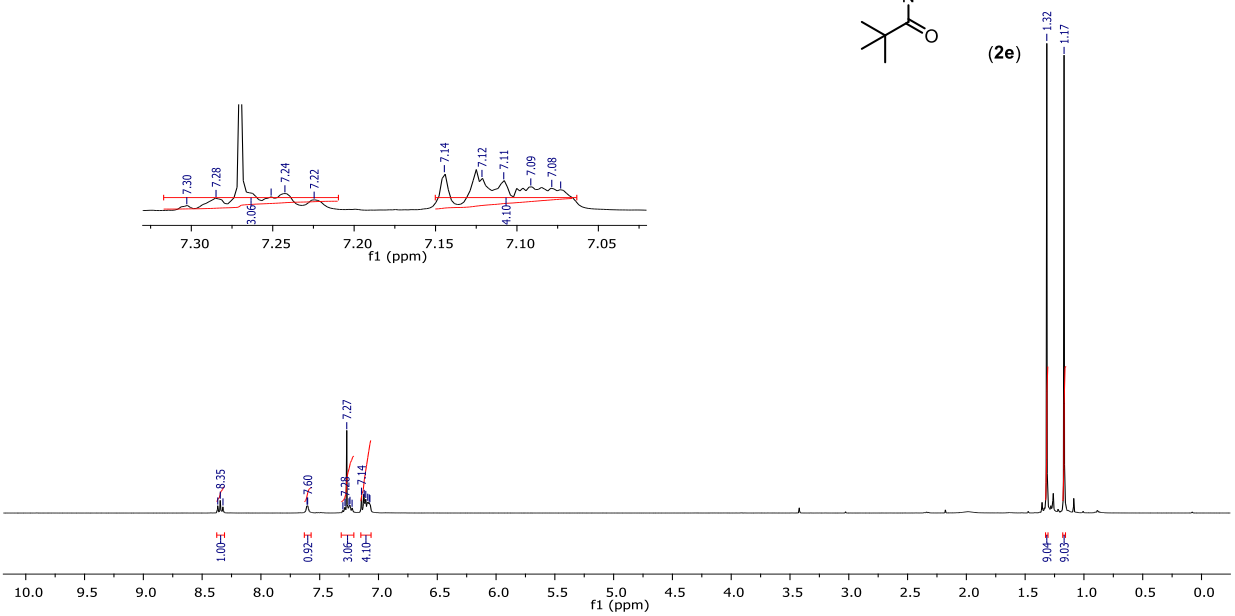

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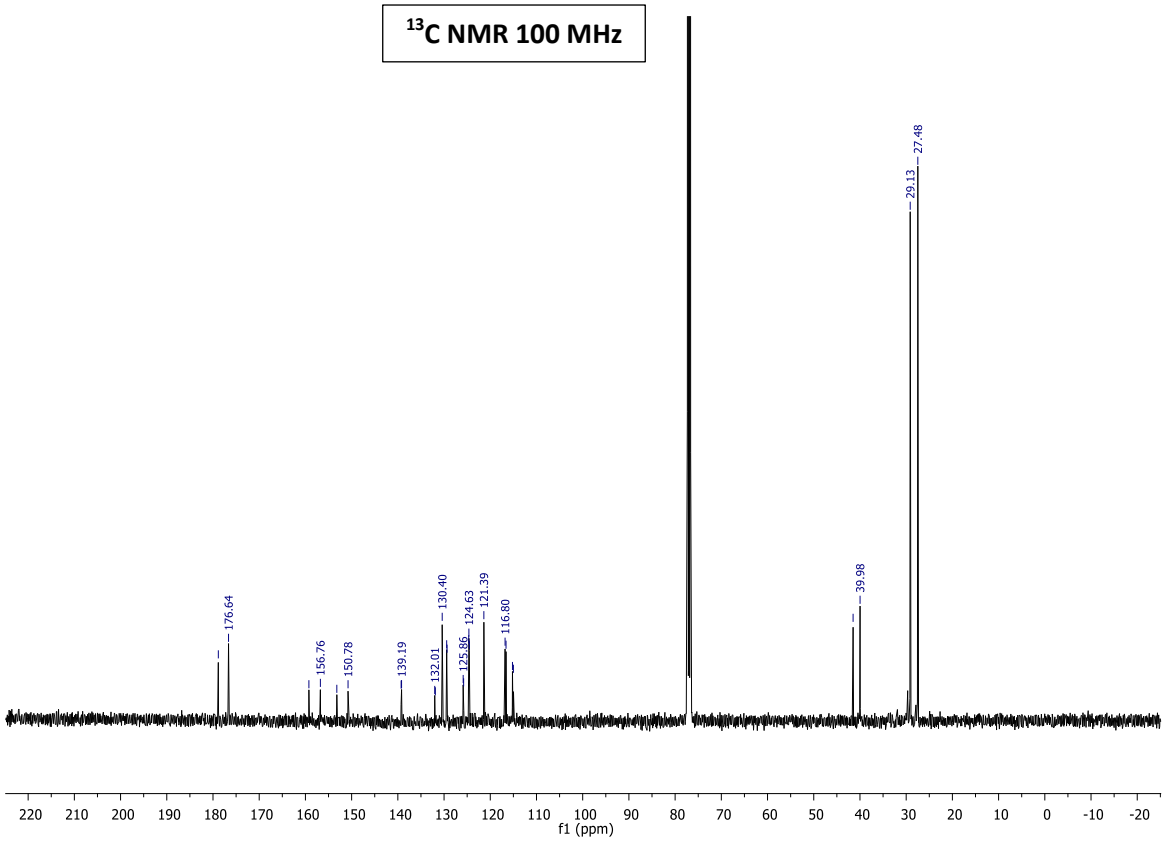

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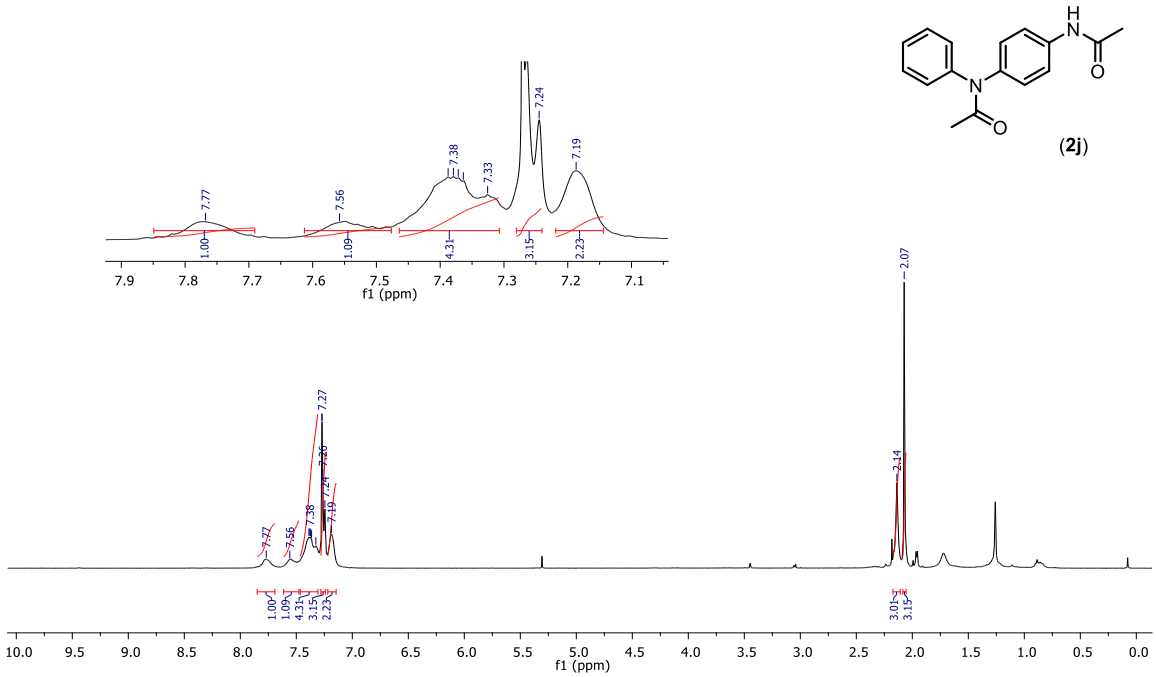

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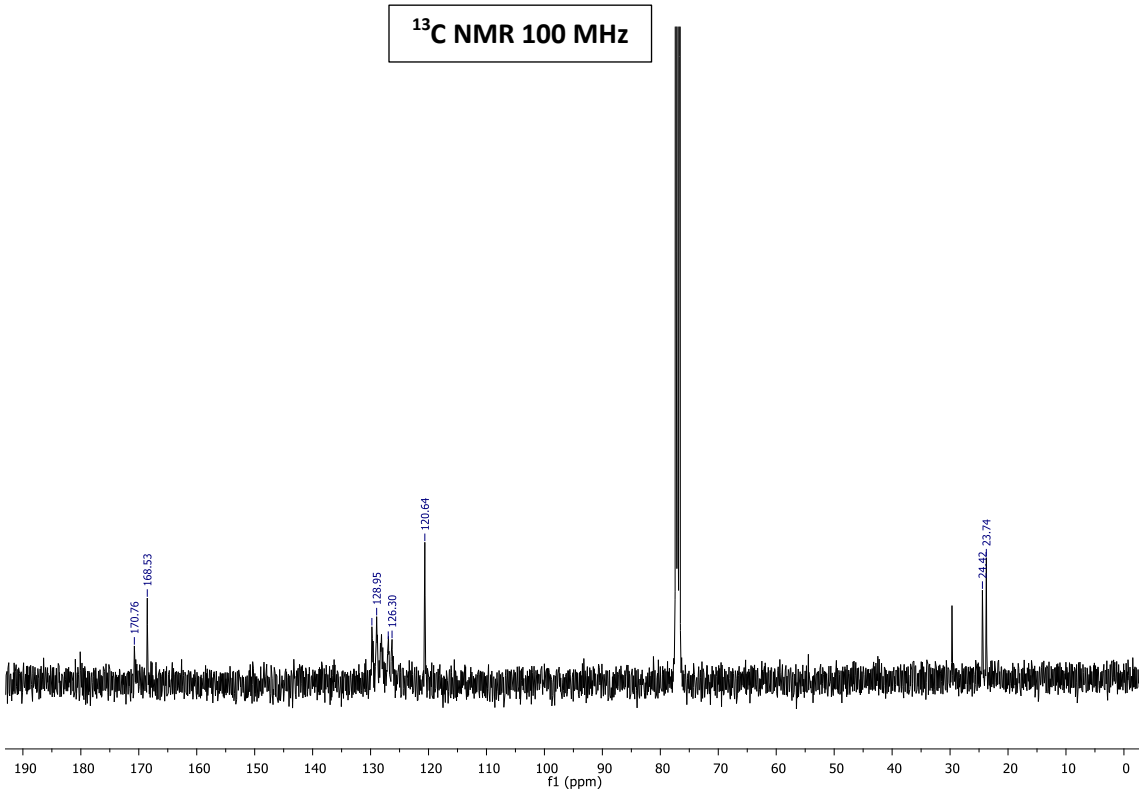

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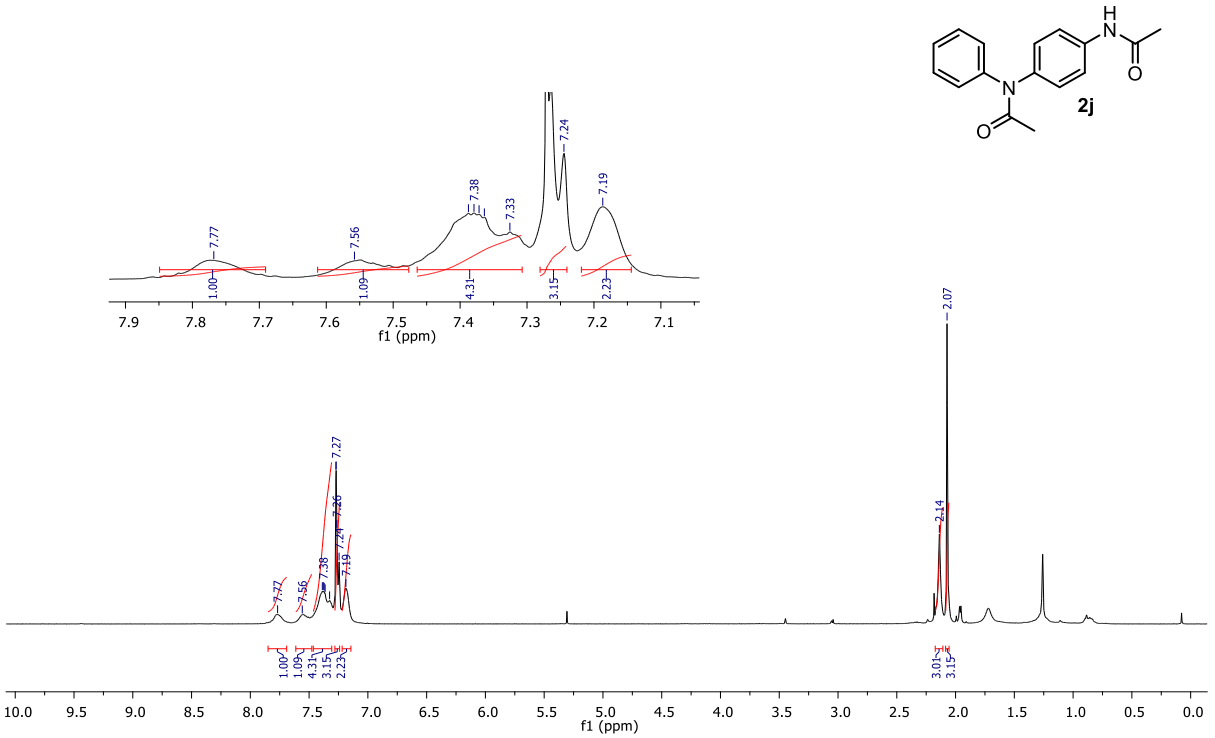

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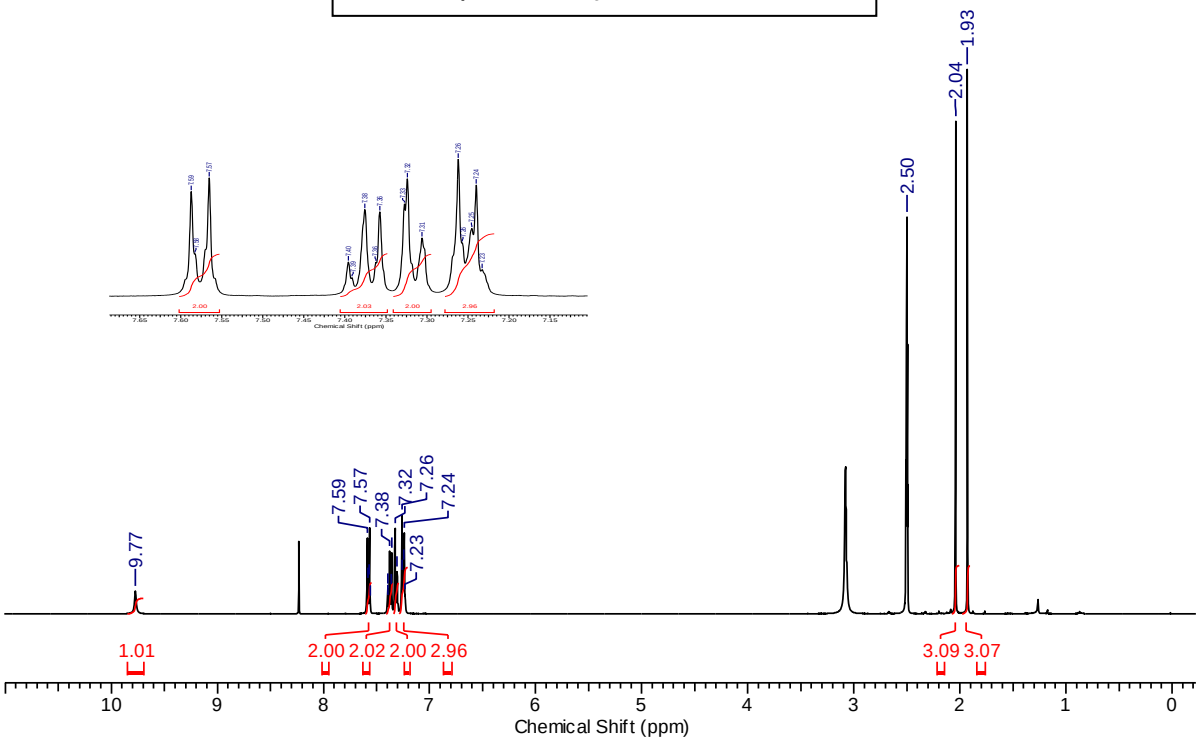

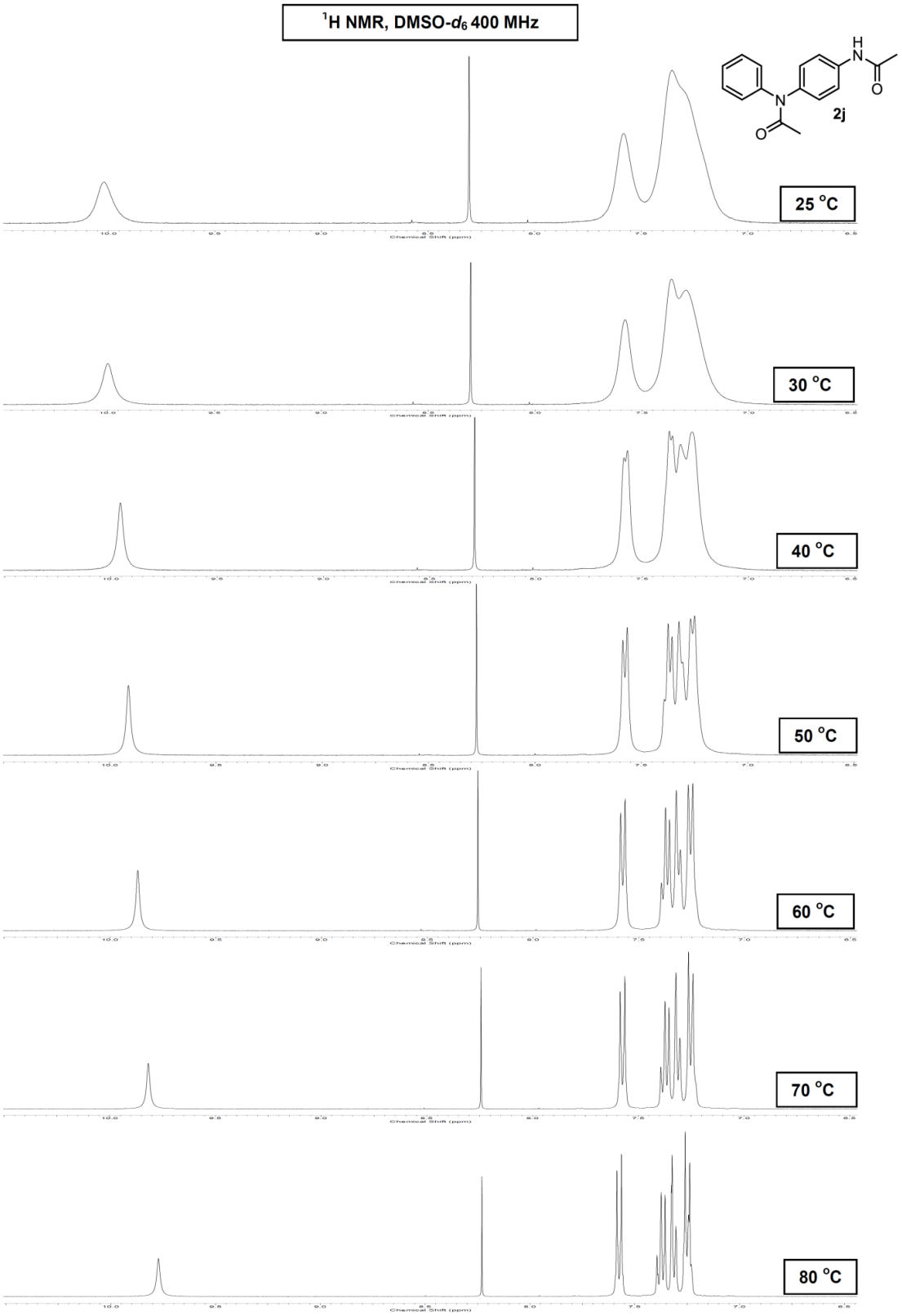
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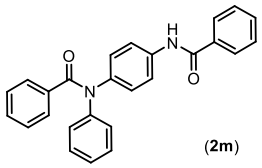
2j
25 °C
30 °C
40 °C
50 °C
60 °C
70 °C
80 °C

^{1}H NMR 400 MHz



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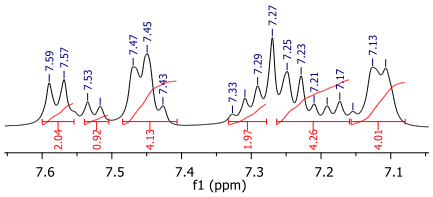

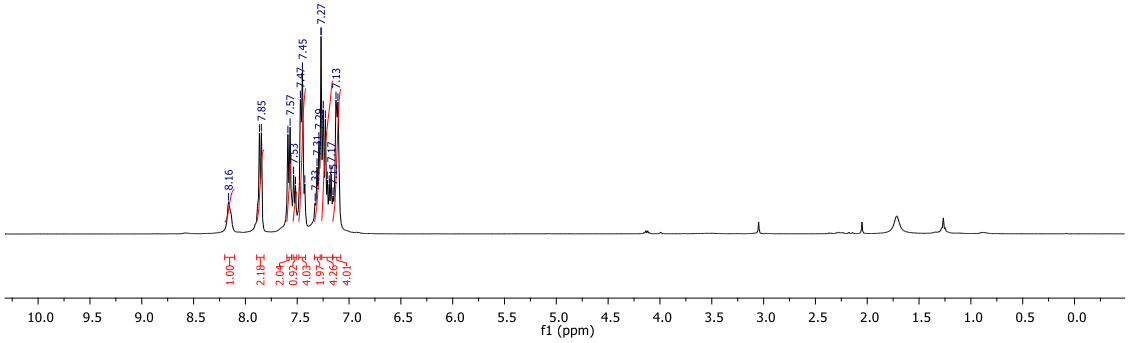

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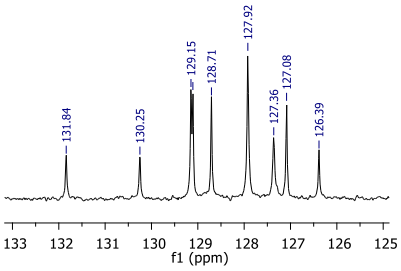

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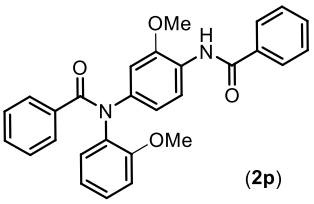

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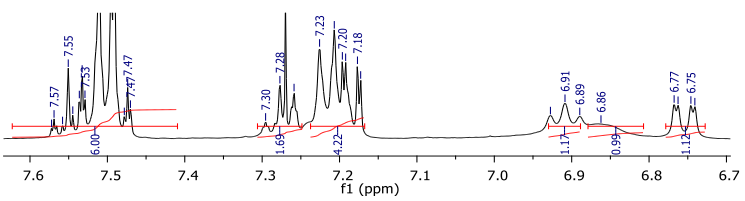

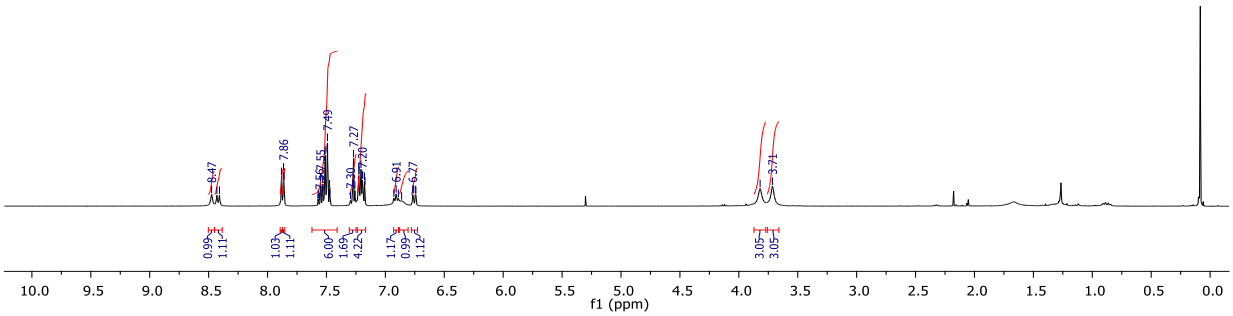

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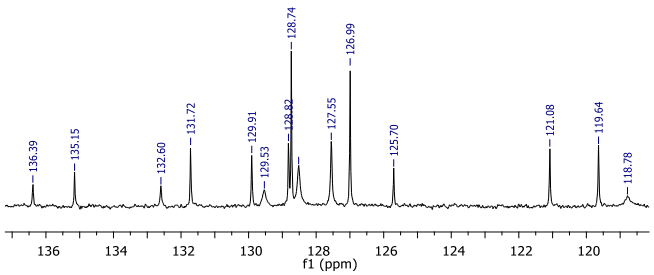

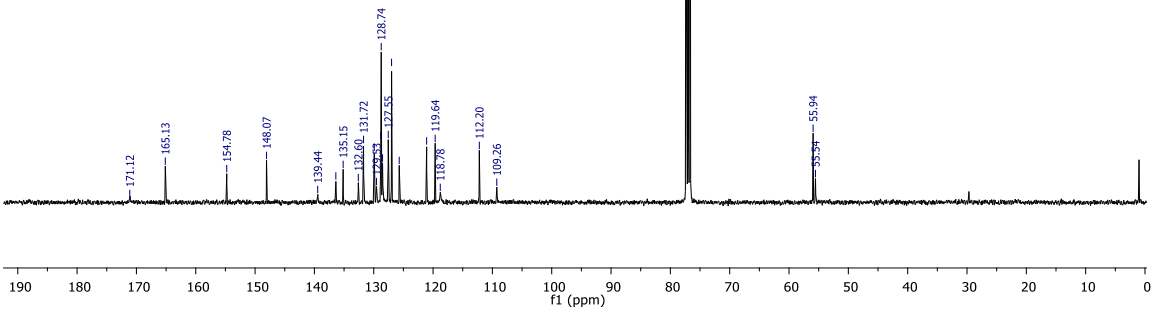

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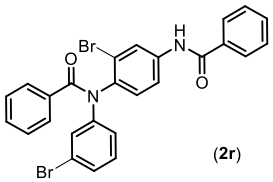

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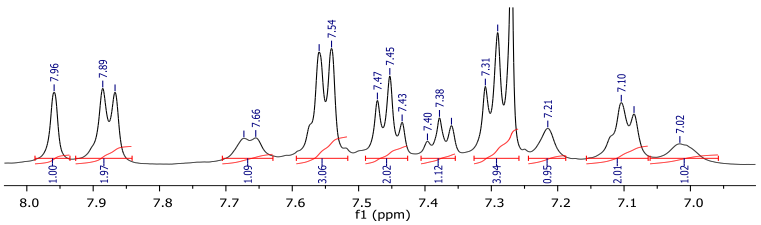

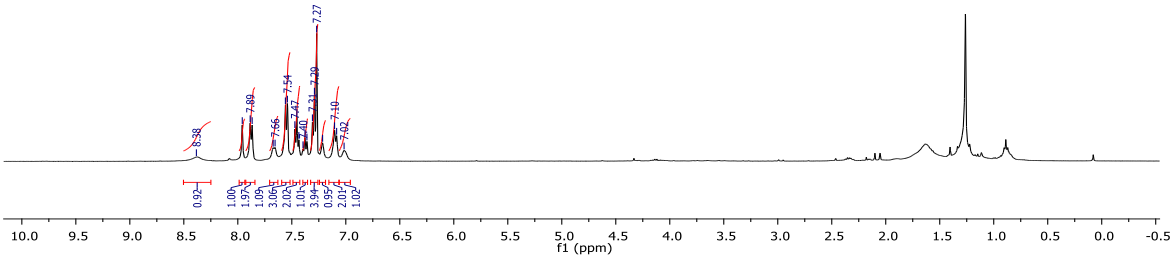

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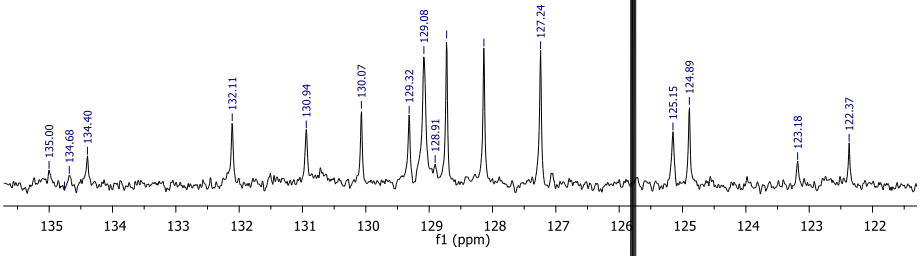

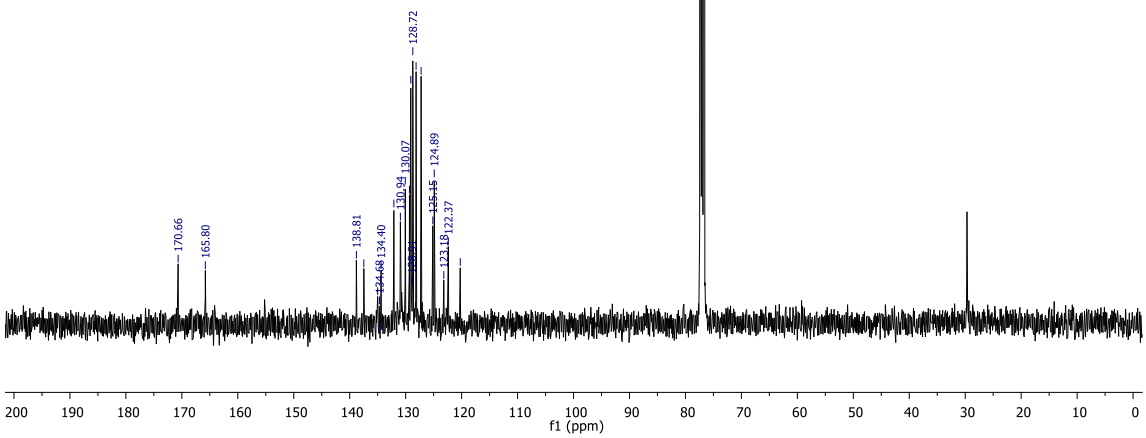

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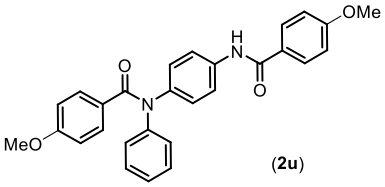

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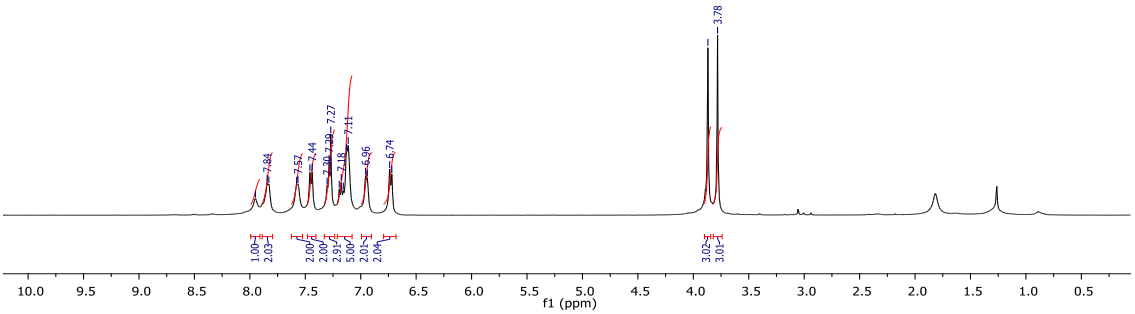

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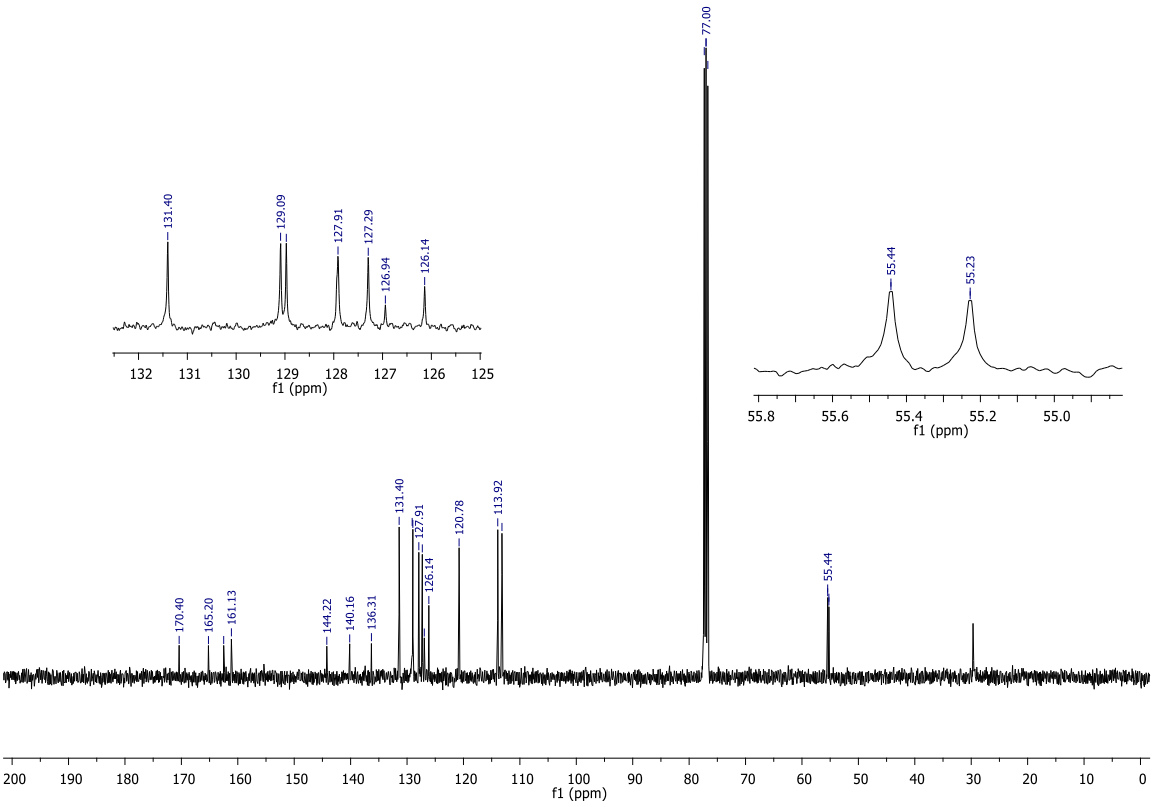

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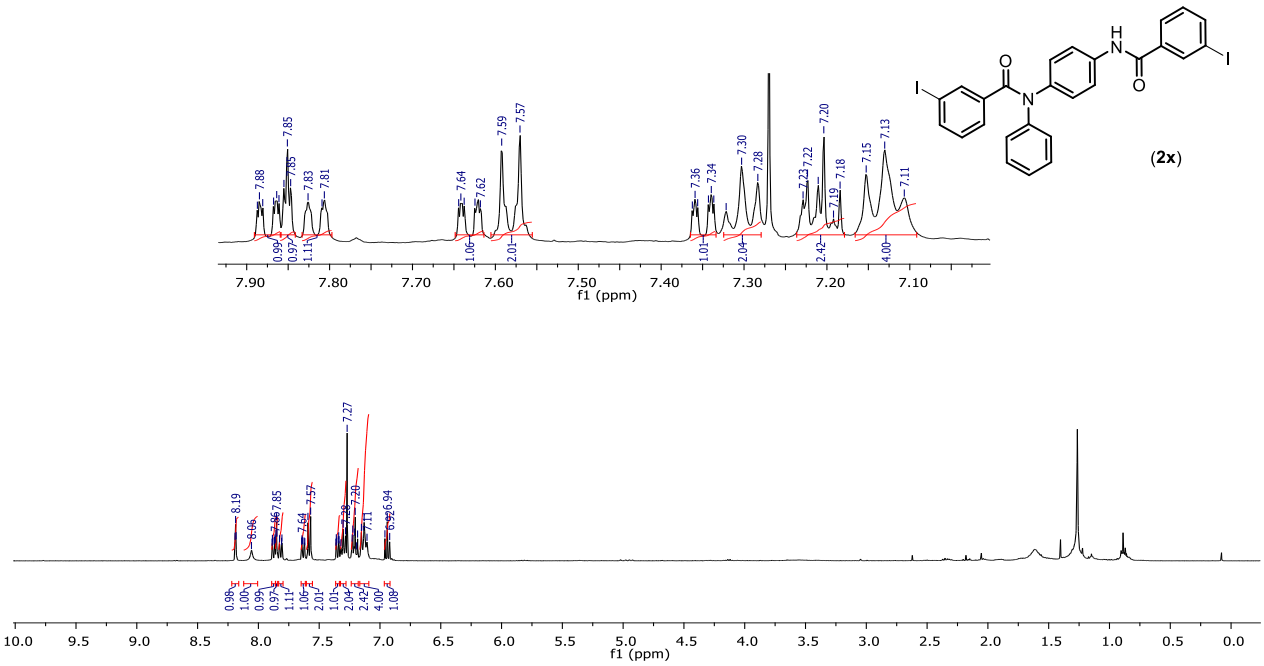

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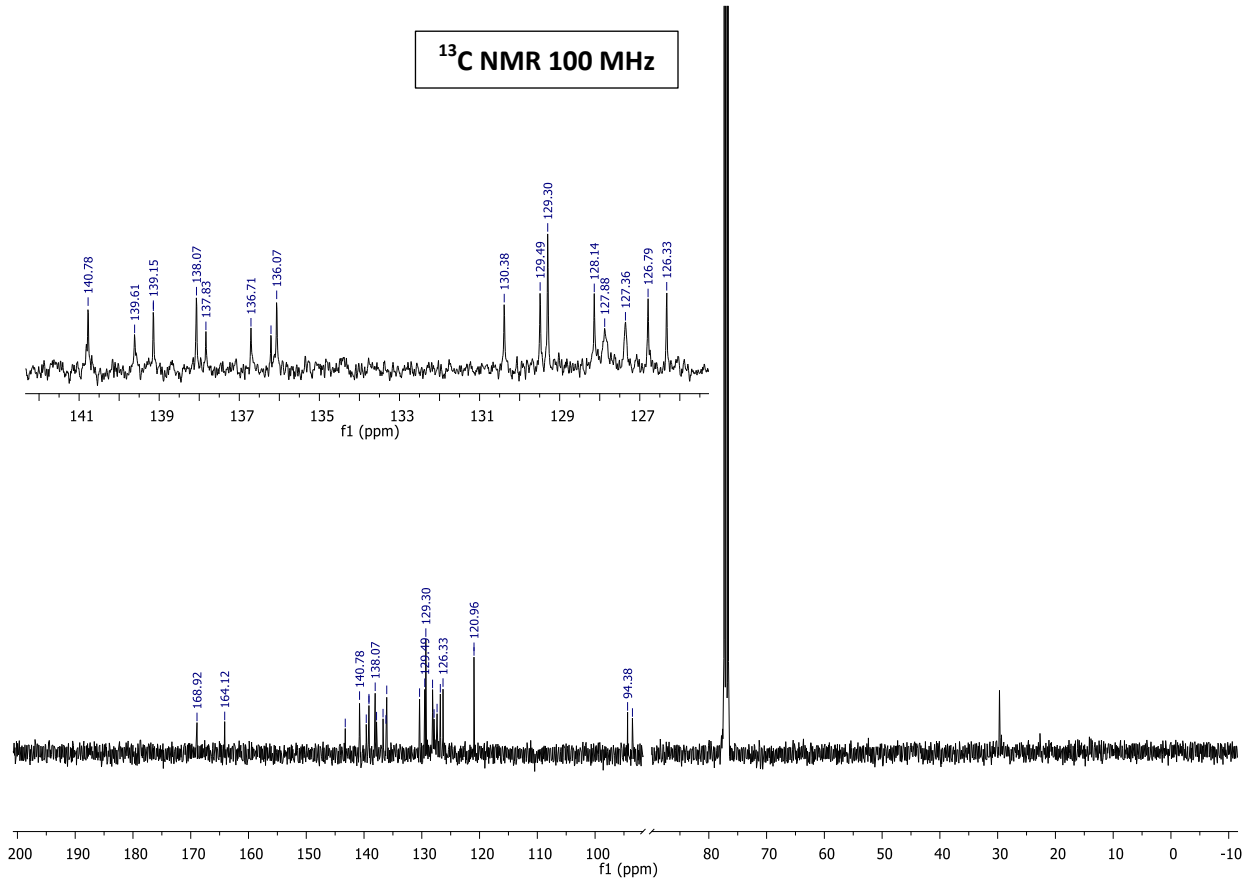
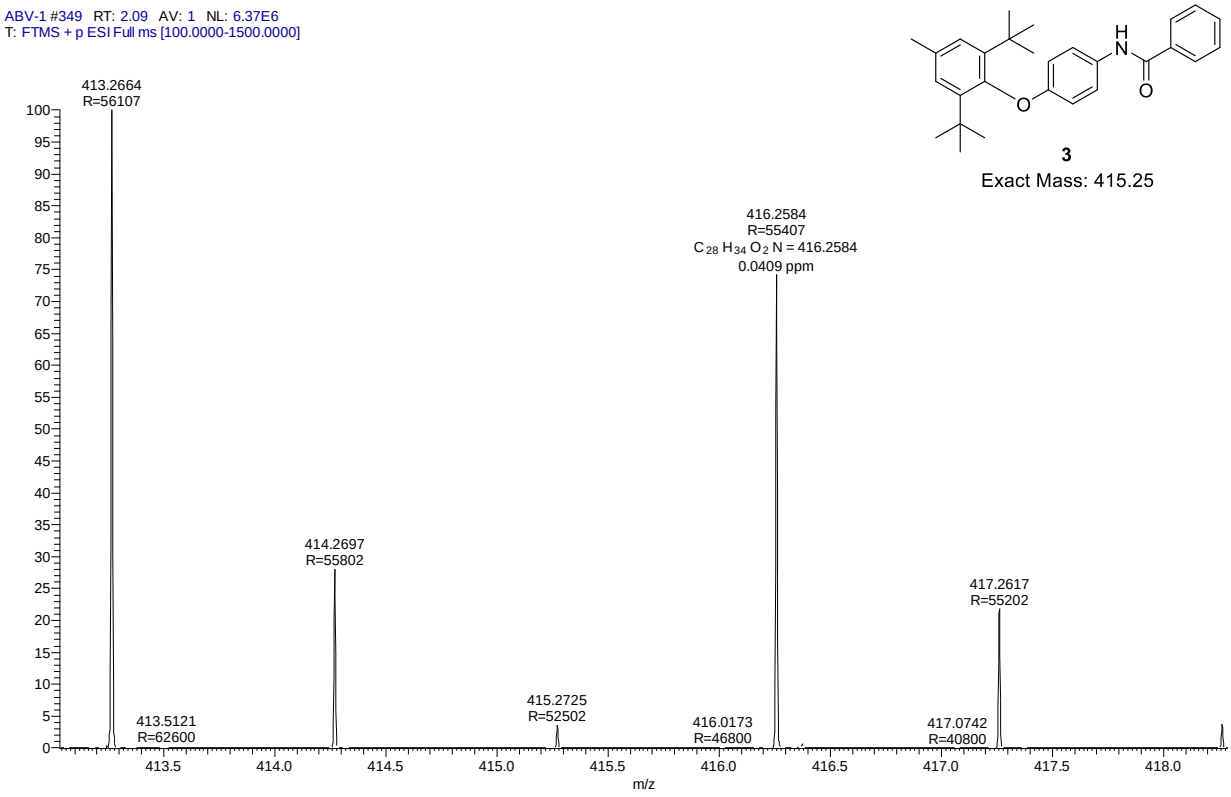


ESI-HRMS Chromatogram



3

Exact Mass: 415.25

Chapter 3

N-Heterocyclic Carbene-Catalyzed Rapid Construction of Biologically Important Scaffolds

Section 1. Studies Towards the Synthesis of (±)-Coniceine Using Intramolecular Stetter Reaction

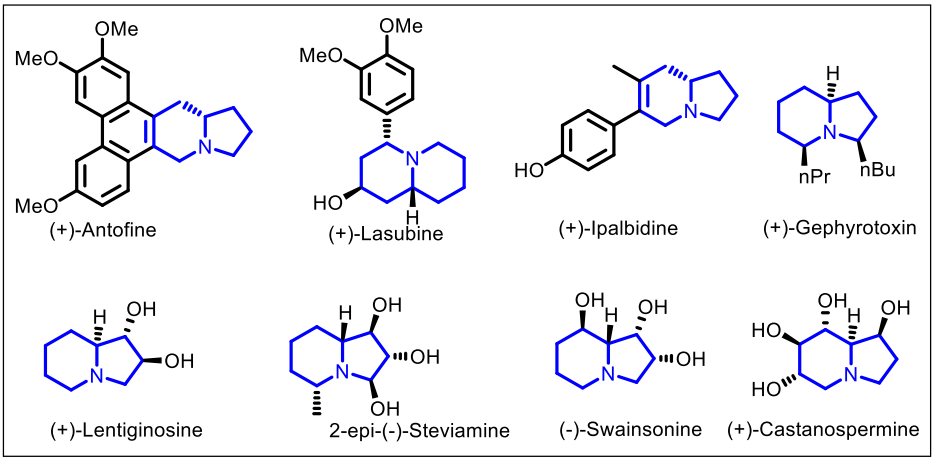
3.1.1. Abstract

This section describes our efforts towards the synthesis of (±)-Coniceine. Different routes were examined to prepare the substrate required for the proposed key-step. The proposed key-step is N-heterocyclic carbene (NHC) catalyzed intramolecular Stetter reaction. That will be followed by usual transformation towards the synthesis of Coniceine.

3.1.2. Introduction

Heterocycles are the privileged scaffolds known for diverse bioactivity. The top ten FDA approved drugs contain at least one heterocyclic atom in their overall structure. Synthesis of such molecules having heterocycles as its part is of contemporary interest to synthetic organic chemists. Alkaloids are a class of naturally occurring organic compounds that mostly contain basic nitrogen atoms and sometimes also includes related compounds having neutral or weakly acidic properties. Indolizidine alkaloids, which are isolated from the skin secretions of certain neotropical frogs, represent a class of pharmacologically important compounds.[1e] For example, polyhydroxylated derivatives such as swainsonine, castanospermine, and entiginosine have also been known to inhibit cardiotonic activity and glycosidase (figure 1).[1] Even the structurally less complex members of this class of natural products such as indolizidine 167B and 209D act as non-competitive blockers of neuromuscular transmission.[2] Coniceine natural product containing the simplest indolizidine skeleton has attracted great attention from synthetic chemists to establish a general route for the preparation of more complex derivatives and this has resulted in several successful approaches to the compound both in racemic and optically active form. The

Figure 1. Selected natural products containing Indolizidine



alkaloids were used since 2000 BC in the home remedy medication, but were not isolated and the structures remained unproven. In 1804, Germen chemist Friedrich Sertürner first isolated Morphine alkaloid from the opium poppy[3] and since then it has attracted the attention of organic chemists. Various routes are established to synthesize such molecule but still there is a scope to develop a better and economic route for their synthesis.

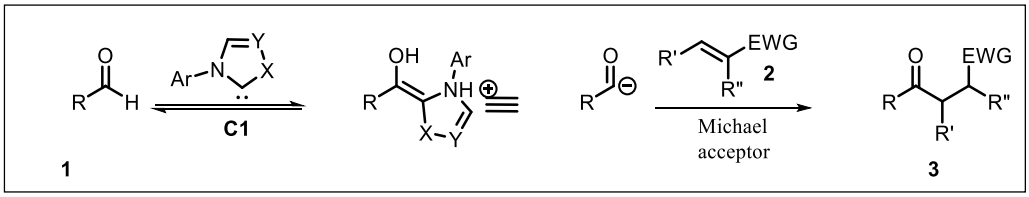
Synthesis of bioactive molecule using simple and economic catalyst is always desired in the field of synthetic chemistry. Organocatalysis is one of the fast growing fields of the organic chemistry because of the readily availability, good selectivity and simple reaction conditions. It was the breakthrough in the field of NHC-organocatalysis, when Breslow in 1958 proposed the involvement of nucleophilic intermediate generated by NHC, which later became popular as 'Breslow intermediate'.[4] NHC has emerged as powerful synthetic tool for the organic chemists, which has witnessed diverse transformations to synthesize complex bioactive scaffolds from simple and readily available starting materials. The property of converting the similar starting materials into different reactive intermediates with slight modifications in the reaction condition improves its importance as a catalyst.[5] NHC is known to catalyze the reaction by different reactive intermediates like acyl anion, homoenolate or enolate pathway. Out of these, the

reaction through acyl anion intermediate is age old discovered pathway and the most studied intermediate since the discovery of benzoin condensation reaction.

3.1.3. Literature review

The umpolung intermediate generated by NHC-catalysis from enal on reaction with different electrophiles leads to the formation of new C–C and C–X (X= N, O, S etc.) bonds. Specifically, acyl anion of aldehydes react with electrophilic alkene substrates by 1,4-conjugate addition to form new carbon-carbon bonds is well known as the Stetter reaction after the discovery by

Scheme 1. General Stetter reaction

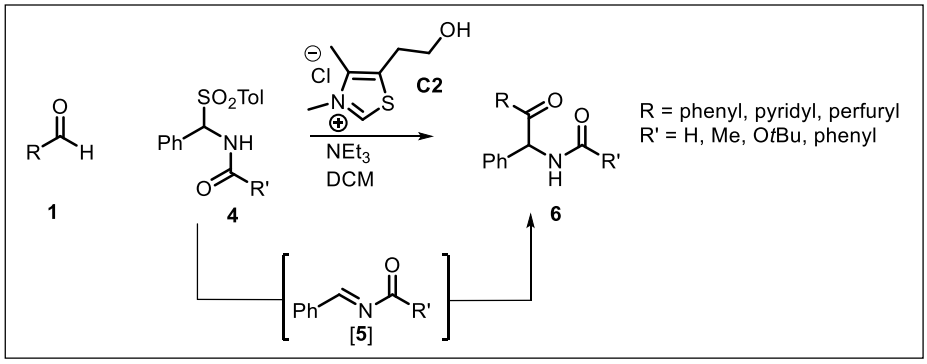


Hermann Stetter (Scheme 1).[6] Stetter reaction is one of the most important and most studied reactions in the area of NHC organocatalysis. The intermolecular Stetter reaction has been demonstrated as a powerful synthetic transformation to access several novel organic scaffolds, which are the building blocks for the construction of various heterocycles, natural products, and bioactive compounds. This transformation was enormously studied with chiral as well as achiral NHC catalysts.

In 2001, Murry and co-workers first time reported practical method for the synthesis of keto-amides **6** using a thiazolium **C2** catalyzed cross coupling of aldehydes **1** with acyl imines **5** (Scheme 2). The acyl imine acceptors were generated in situ from *α*-tosyl amide substrates **4**. It underwent elimination in the presence of base and was attacked by acyl anion generated using NHC. The process has been also demonstrated for a variety of aldehydes in combination with a

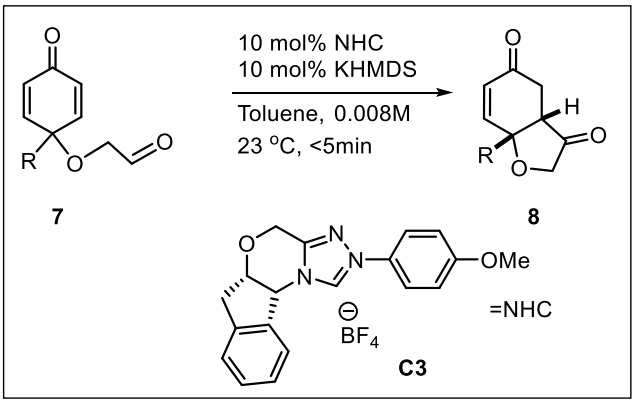
versatile range of sulfonylamides to provide ready access to structurally diverse R-amido ketones.[7]

Scheme 2: Stetter reaction between aldehyde and acyl imines intermediate



The intramolecular Stetter reaction consist of both nucleophilic and electrophilic centre in the same molecule which are tethered through the atoms like carbon, nitrogen oxygen, sulphur, etc. leading to the addition of acyl anion equivalents of aliphatic or aromatic aldehyde to the Michael acceptor. Asymmetric variant of Stetter reaction is also highly desirable conversion, which expands the scope of this reaction and it has been the subject of much research in recent years. This challenge remained unsolved until Rovis group in 2006 first time reported asymmetric synthesis of hydrobenzofuranones **8** via desymmetrization of cyclohexadienones **7** using the intramolecular Stetter reaction (Scheme 3).[8] Different phenol-derived substrates were

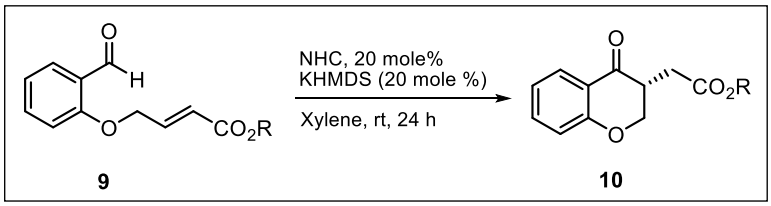
Scheme 3: Intramolecular Stetter reaction



prepared and applied under NHC-catalysed Stetter reaction condition. This was the first report on intramolecular Stetter reaction leading to hydrobenzofuranones involving NHC catalysis.

Enders *et al.* reported intramolecular asymmetric addition to ester by aldehydes using NHC as a catalyst.[9] This method leads to very important building block chroman-4-ones **10** from the corresponding starting material **9** using **C3** triazole NHC catalyst (Scheme 4). They have reported good to excellent enantio-selectivity and very good yields.

Scheme 4: Intramolecular enantioselective Stetter reaction



3.1.4. Origin of the work

Rovis and colleagues in 2006 demonstrated a stereo selective desymmetrization of tethered cyclohexadienone carboxaldehydes **7** through the intramolecular Stetter reaction catalyzed by chiral triazolium salts.[8] Similarly, elegant work by Shu-Li You and group expanded the scope of Michael acceptors in enantioselective desymmetrization of cyclohexadienone via a camphor-derived triazolium salt catalyst.[10] It has been observed from these and others reported example that NHC catalyzed Stetter reaction has emerged as a one of the powerful synthetic transformation in the organic synthesis and has a potential generate important scaffolds. It has been extensively used in the development of methodologies, but its application in the synthesis of natural product is not yet fully explored. In this context we have attempted to synthesize the alkaloid natural product Coniceine.

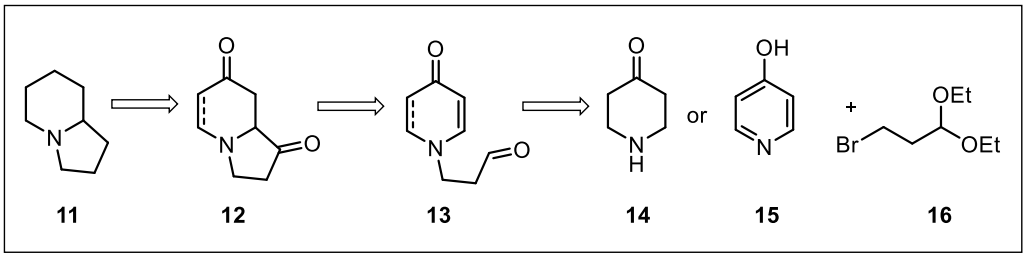
3.1.5. Objective of the work

Utilization of NHC during the course of natural product synthesis is an opportunity as well as challenge for organic chemists. The potential of NHC inspired us to utilize it during the synthesis of natural product. The objective of this work is to develop a novel method for the synthesis of the natural product scaffold and its derivatives.

3.1.6. Result and discussion

We planned to develop a general protocol to synthesize basic core structure of Indolizidine alkaloid, (±)-Coniceine. We hypothesized that (±)-Coniceine (**11**) can be synthesized by complete reduction of diketo **12**. The diketo **12** can be synthesized from intermediate **13** using NHC-catalyzed Stetter reaction. The intermediate **13** can be achieved by coupling between **14** or **15** with **16** or its synthetic equivalent (Scheme 5).

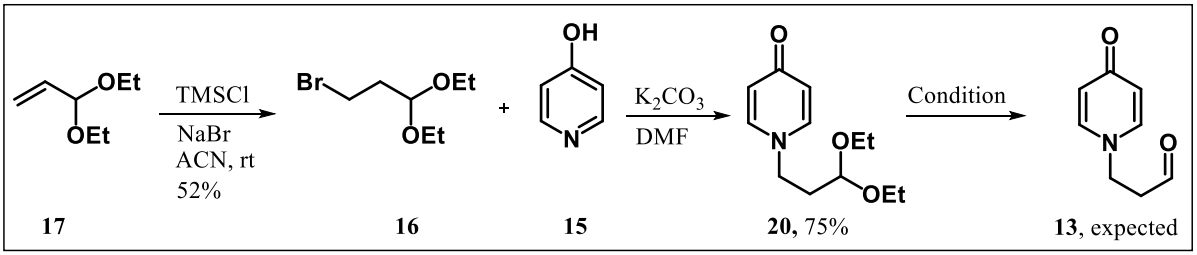
Scheme 5: Retrosynthetic plan for (±) Coniceine



After having a logical retrosynthetic plan ready, we started synthesis of target molecule with bromination of 3,3-diethoxy-1-propene (**17**) in the presence of TMSCl using Sodium bromide as an brominating reagent. We could isolate the pure brominated product **16** in 52% yield after aqueous workup.[11] The isolated product was then used further without column purification.

The bromo compound **16** was then reacted with 4-hydroxy pyridine (**15**) using K_2CO_3 as a base and DMF as a solvent. The *N*-alkylated product **20** was obtained in 75% yield after column purification.[12] Next target was the deprotection of acetal leading to aldehyde **13**, precursor for the NHC catalyzed key reaction.

Scheme 6: Bromination and alkylation



We tried various reaction conditions for deprotection. We did not observe any change in **20** when $In(OTf)_3$, $FeCl_3•6H_2O:SiO_2$ or Iodine was used for the deprotection, whereas, complex NMR was observed when HCl in dioxane, $AlCl_3$ or TFA was used for the deprotection (table 1, entry 1-4, 6-7). Surprisingly, when the reaction was performed in presence of BBr_3 in DCM,[13] we observed the formation of expected product in the reaction mixture, but during the column

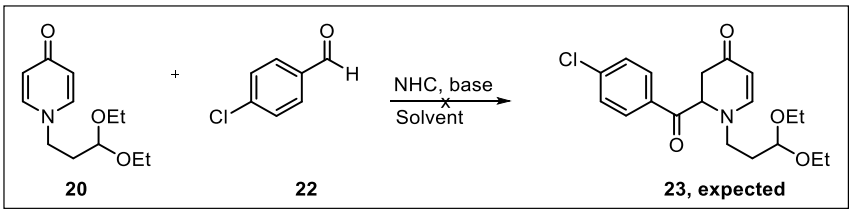
Table 1. Deprotection of acetal

Sr. no	Deprotecting agent	Solvent	Observation
1	$In(OTf)_3$	Acetone	NR
2	I_2	Acetone	NR
3	HCl in Dioxane	Neat	Complex NMR
4	$FeCl_3•6H_2O:SiO_2$	Acetone	NR
5	BBr_3 in DCM	DCM	New spot, crude-Aldehyde After column Dimethyl acetal
6	$AlCl_3$	DCM	Complex NMR
7	TFA	Chloroform	Complex NMR

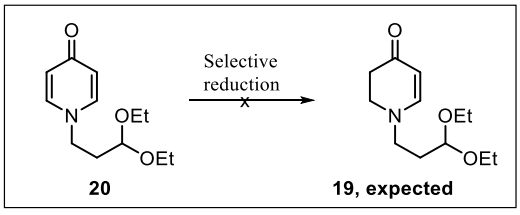
purification using MeOH:DCM, it converted to dimethylacetal **21**. This observation confirms the formation of desired aldehyde but it could not be isolated as aldehyde. We also tried the reaction on the crude aldehyde **13** obtained after the BBr_3 dealkylation. However, a complex reaction mixture was observed.

We tried the model NHC catalyzed Stetter reaction on substrate **20** with aldehyde **22**. We screened different NHC catalysts, bases, solvents at different temperatures, but the reaction failed to give expected product **23**. Here we thought may be due to two double bonds the electrophile is not enough reactive to give expected product and having nitrogen near the electrophilic centre also affect the electrophilicity of double bond. Hence, we targeted to synthesize **19**, by reduction of one double bond selectively using different conditions,[14] but all our efforts did not lead to successful isolation of expected product **19**.

Scheme 7. NHC catalyzed Stetter reaction



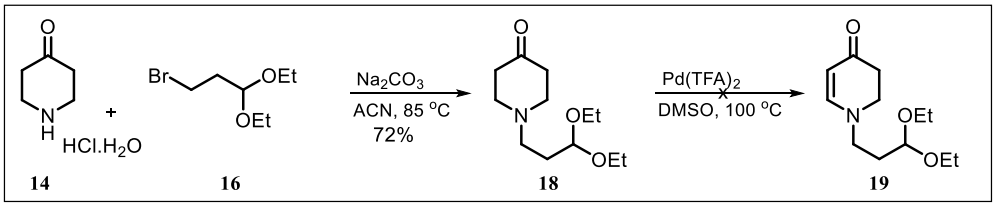
Scheme 8. Reduction



Our next alternative was to synthesize the similar precursor **19** using another pathway. The bromo compound **16** was reacted with commercially available piperidin-4-one hydrochloride (**14**) in presence of Na_2CO_3 in acetonitrile as a solvent at 85 ^oC. The coupled

product **18** was isolated in 72% using column chromatography.[14] Oxidation of the product **18** obtained in pure form was then tried to obtain selectively only one double bond. The oxidized compound **19** can be used further for key NHC catalyzed Stetter reaction after deprotection of acetal group. Here we utilized the condition for oxidation i.e. $Pd(TFA)_2$ in DMSO as a solvent,[16] but we were not able to obtain the expected compound in hand. Then we tried to utilize the modified conditions for similar transformation but multiple trial and errors met with failure.

Scheme 7: Alkylation and oxidation



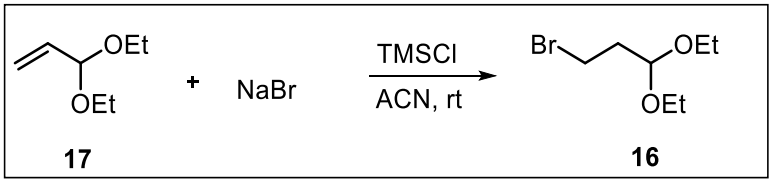
3.1.7. Conclusion

In conclusion we have tried different ways to obtain the desired substrate required for NHC catalyzed Stetter reaction. The formation of the aldehyde was confirmed but could not be isolated. Our next target is to prepare required substrate and to try the key reaction. After having done the NHC catalyzed reaction our next plan will be to perform required transformations to get Coniceine.

3.1.8. Experimental Section

Experimental procedure and data:

3-Bromo-1,1-diethoxypropane (**16**):[11]

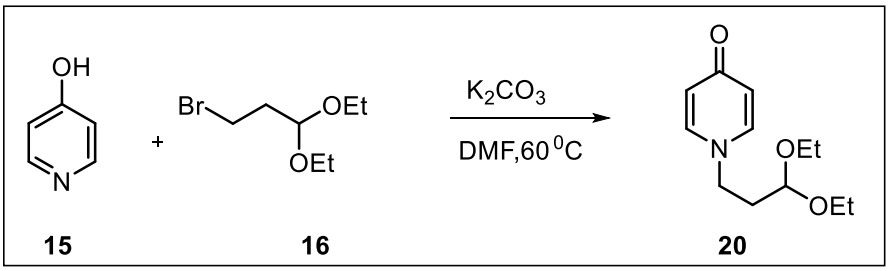


A mixture of 1.566 g of NaBr, 0.974 ml of TMSCl and 0.3 g of 4A^{o} molecular sieves in 20 ml of dry ACN was stirred under nitrogen for 15 minutes. Subsequently, 1.0 g of 3,3-diethoxy-1-propene (**17**) dissolved in 5 ml of ACN was added and the mixture was stirred at 22^{o} C for 90 minutes. After an aqueous workup the 844 mg (52% yield) of 1-bromo-3,3-diethoxy propane (**16**) was obtained using ethyl acetate for extraction of product.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.75 (m, 1H), 3.74-3.42 (m, 6H), 2.18-2.04 (m, 2H), 1.26-1.19 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 101.3, 62.2, 37.0, 28.9, 15.3.

1-(3,3-Diethoxypropyl)pyridin-4(1H)-one (**20**):[12]



In a two necked R.B. equipped with magnetic bar was added potassium carbonate (1.451g, 10.5 mmol), 4-hydroxypyridine (**15**) (500 mg, 5.25 mmol) evacuated with argon and added 20 ml DMF followed by addition of 1-bromo-3,3-diethoxypropane (**16**) (1.662 g, 7.88 mmol). The reaction was stirred at room temperature for overnight. After the complete conversion of all starting material, the expected product (829 mg, 67%) was purified by column chromatography (1:9, MeOH : DCM) without water workup.

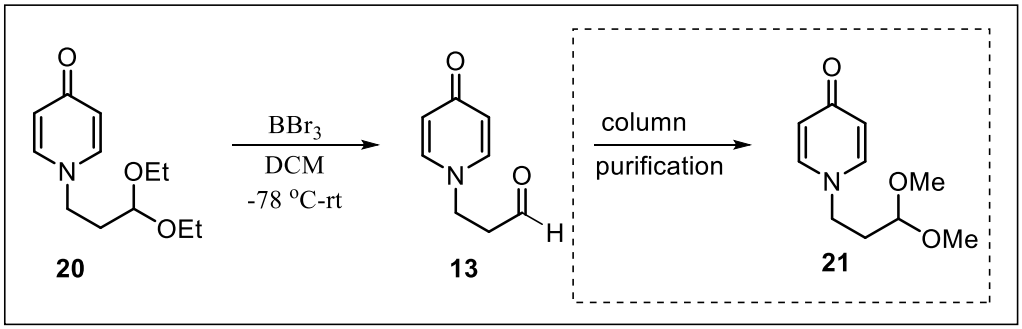
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.3 (d, *J* = 7.30 Hz, 2H), 6.37 (d, *J* =7.33 Hz, 2H), 4.43 (t, *J* = 5.04 Hz, 1H), 3.88 (t, *J* = 6.87 Hz, 2H), 3.66-3.58 (m, 2H), 3.48-3.40 (m, 2H), 2.06-2.01 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 178.7, 139.8, 118.7, 100, 62, 53, 34.6, 15.2.

IR ($CHCl_3$) υ_{max}= 3421, 3022, 2402, 1640, 1574, 1520, 1426, 1216, 927, 772, 671 cm^{-1}.

ESI-Mass $(M+H)^+$ 226

3-(4-Oxopyridin-1(4H)-yl)propanal (13) :[13]



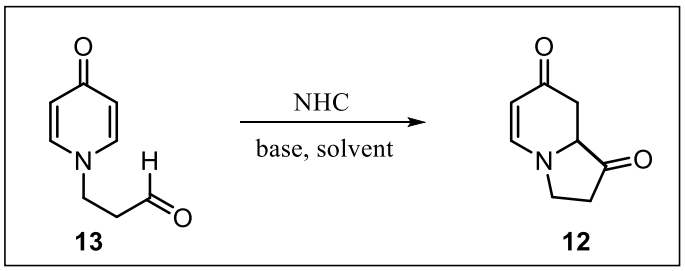
To a solution of acetal **20** (100 mg, 0.444 mmol) in dry CH_2Cl_2 (2 mL) was added BBr_3 solution (0.9 mL, 1 M in CH_2Cl_2, 0.888 mmol) by syringe over 10 min under N_2 at -78 °C. The reaction mixture was stirred from -78 to 25 °C overnight and observed the complete dealkylation. The brown solution was cooled to 0 °C and H_2O (2 mL) was added slowly. The aqueous layer was

saturated with solid NaCl. The two layers were separated and the aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The reaction mixture was then purified by column chromatography (MeOH:DCM, 2:3), and here observed the formation of dimethylacetyl **21**after the purification.

The same reaction was repeated and the crude reaction mixture was used for further reaction without purification.

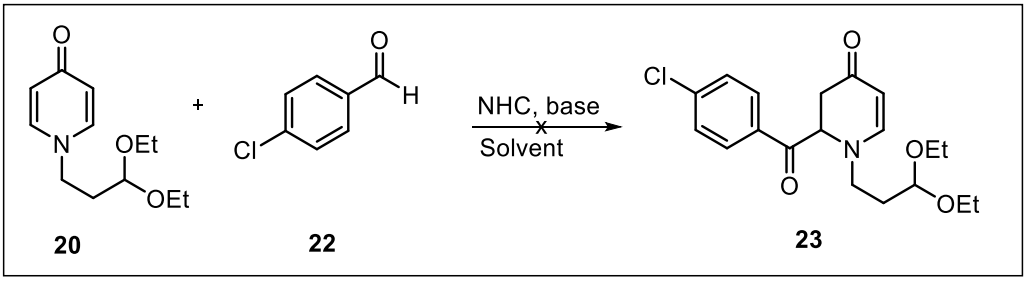
^{1}H NMR (200 MHz, $CDCl_3$) of **21** δ (ppm) 7.4 (2H), 6.45 (2H), 4.33 (t, 1H), 3.89 (t, 2H), 3.34 (s, 6H), 2.05 (m, 2H).

2,3-Dihydroindolizine-1,7-dione (12):



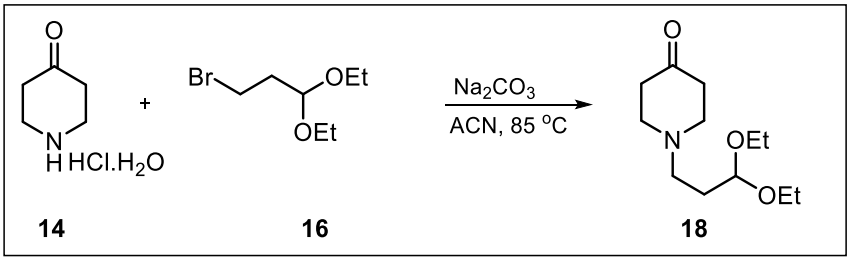
A flame dried Schlenk tube was filled with aldehyde tethered 4-piperidone **20** (30 mg, 0.2 mmol), NHC (0.02 mmol), base (0.04 mmol), solvent (1 mL) and backfilled with argon and stirred at various temperatures. The reaction was monitored with TLC analysis; here we did not observe any new spot formation.

2-(4-Chlorobenzoyl)-1-(3,3-diethoxypropyl)-2,3-dihydropyridin-4(1H)-one (**23**):



A flame dried schlenk tube was filled with alkylated 4-piperidone **20** (22.5 mg, 0.1 mmol), 4-chloro benzaldehyde (**22**) (15 mg, 0.1 mmol), NHC (0.01 mmol), base (0.02 mmol), solvent (1 mL) and backfilled with argon and stirred at various temperatures. The reaction was monitored with TLC analysis; here we did not observe any new spot formation.

1-(3,3-Diethoxypropyl)piperidin-4-one (**18**):[15]



A round bottom flask was charged with piperidin-4-one hydrochloride monohydrate (**14**, 242 mg, 1.58 mmol, 1 equiv), acetonitrile (15ml), 1-bromo-3,3-diethoxypropane (**16**, 500 mg, 2.37 mmol, 1.5 equiv) and sodium carbonate (334 mg, 3.16 mmol, 2 equiv). This mixture was heated overnight at 85^{o} C, then cooled, filtered and filtrate concentrated. The product was purified by flash chromatography (1:1 EtOAc: pet ether) to afford 260 mg (72%) of 1-(3,3-diethoxypropyl) piperidin-4-onein (**18**).

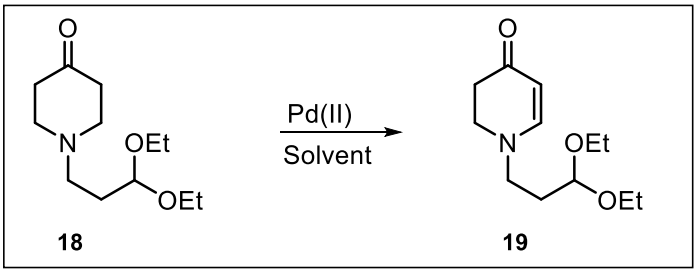
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.62 (t, *J* = 5.50 Hz, 1H), 3.71-3.61 (m, 2H), 3.58-3.49 (m, 2H), 2.75 (t, *J* = 6.18 Hz, 4H), 2.55 (t, *J* = 7.56 Hz, 2H), 2.48 (t, *J* = 6.18 Hz, 4H), 1.89-1.83 (m, 2H), 1.22 (t, *J* = 7.10 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 209.3, 101.3, 61.2, 53.1, 52.8, 41.2, 31.6, 15.3.

IR ($CHCl_3$) υ_{max} = 3021, 2403, 1715, 1521, 1424, 1215, 1124, 1058, 929, 766, 677 cm^{-1}.

ESI-Mass $(M+H)^+$ = 230.

1-(3,3-Diethoxypropyl)-2,3-dihydropyridin-4(1H)-one (**19**):[16]



18 **19**

In a oven dried Teflon screw cap glass tube, 1-(3,3-diethoxypropyl)piperidin-4-one (**18**, 23 mg 0.1 mmol) and Pd(II) (0.01 mmol) catalyst was added followed by 1 mL of solvent. The reaction mixture was then backfilled with oxygen and the stirred in preheated oil bath. The progress of reaction was followed by TLC analysis as well as GC analysis. Here we observed all SM remained as it is without any change.

3.1.9. References:

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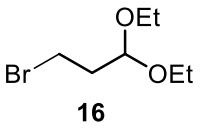
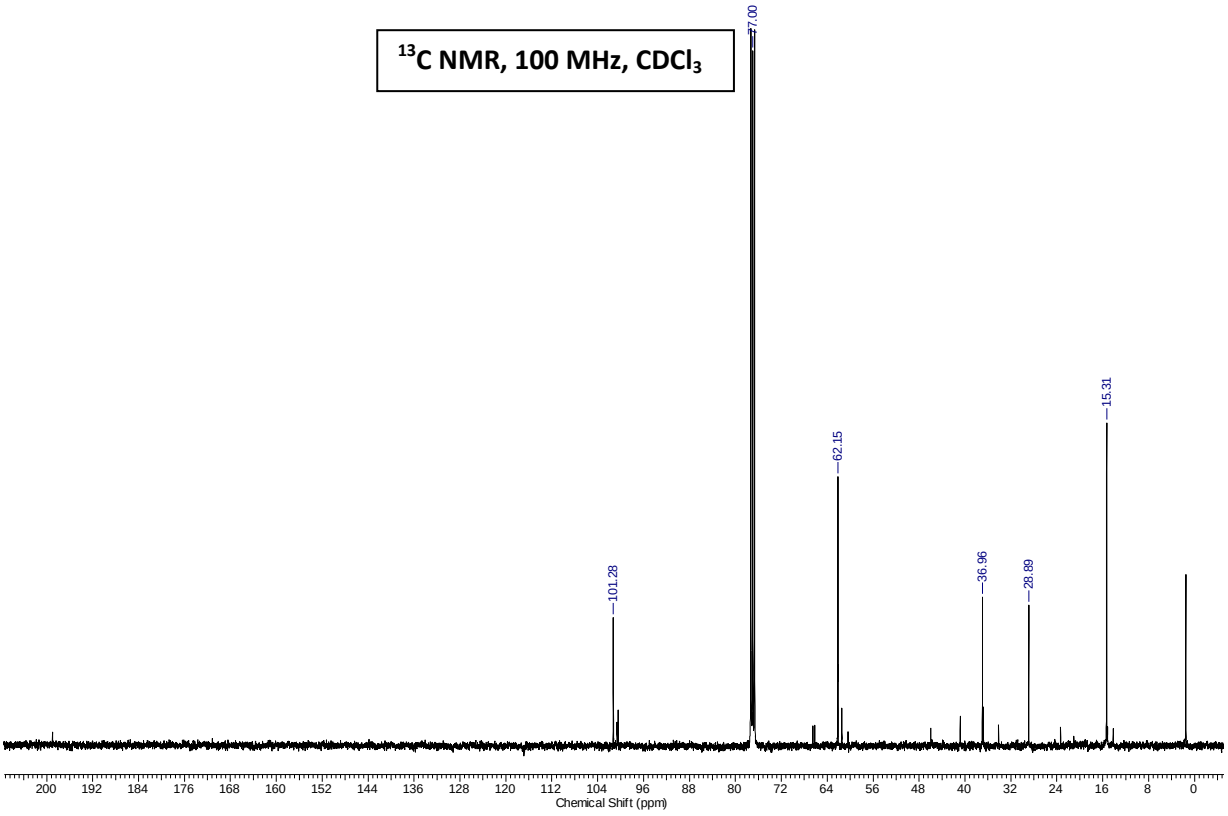
3.1.10. Selected ^{1}H and ^{13}C NMR spectra

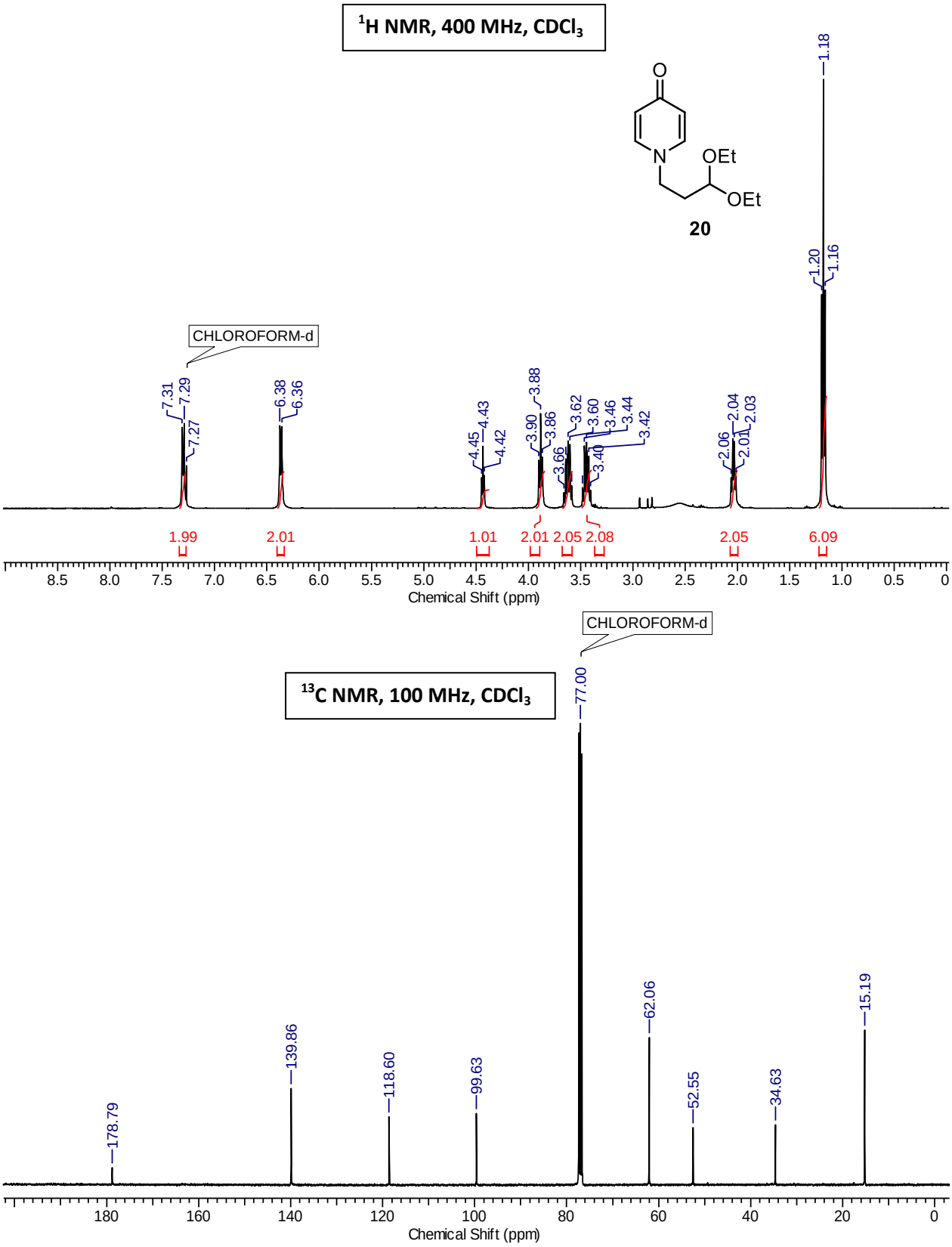
^{1}H NMR, 400 MHz, $CDCl_3$

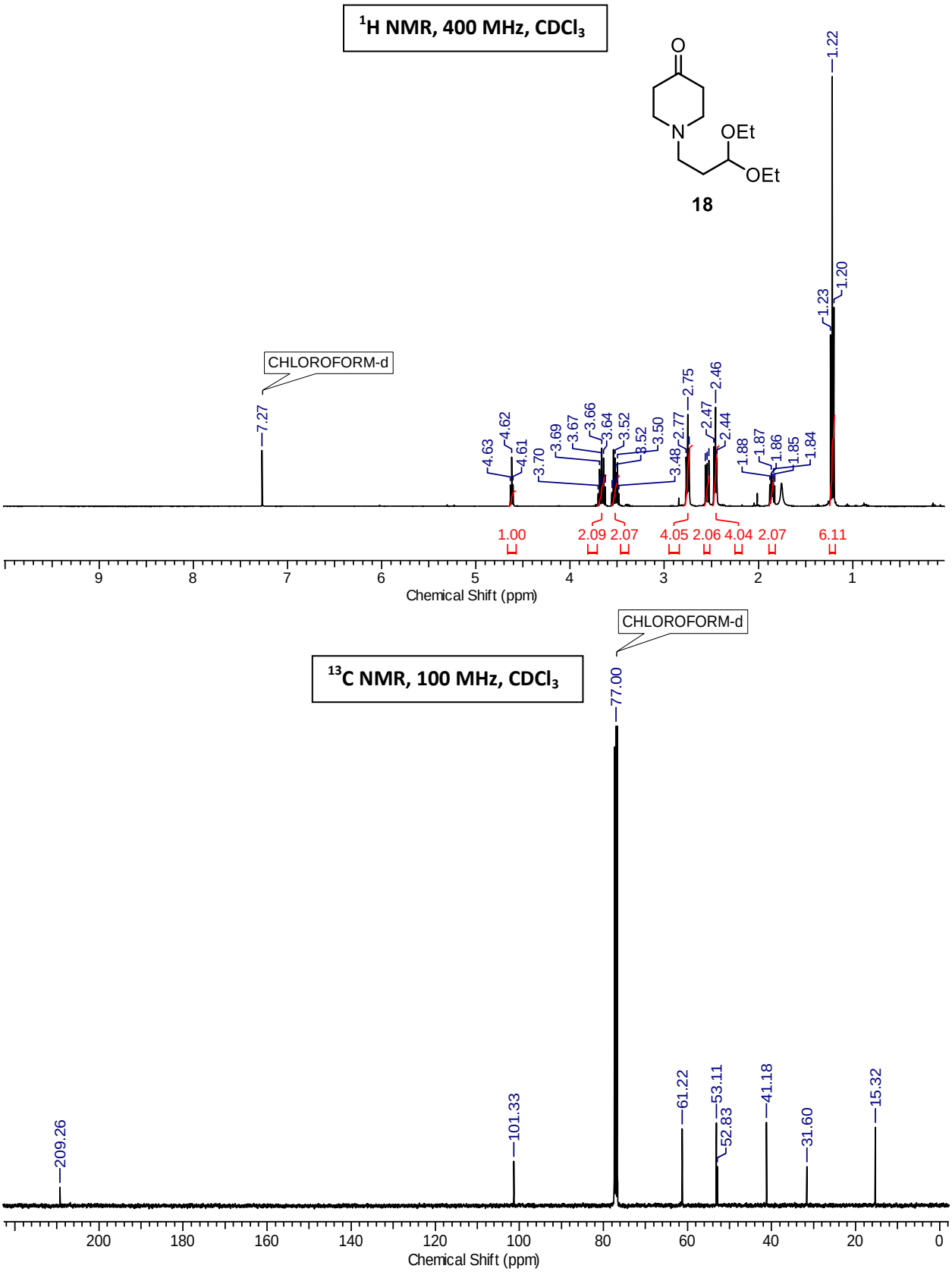


16

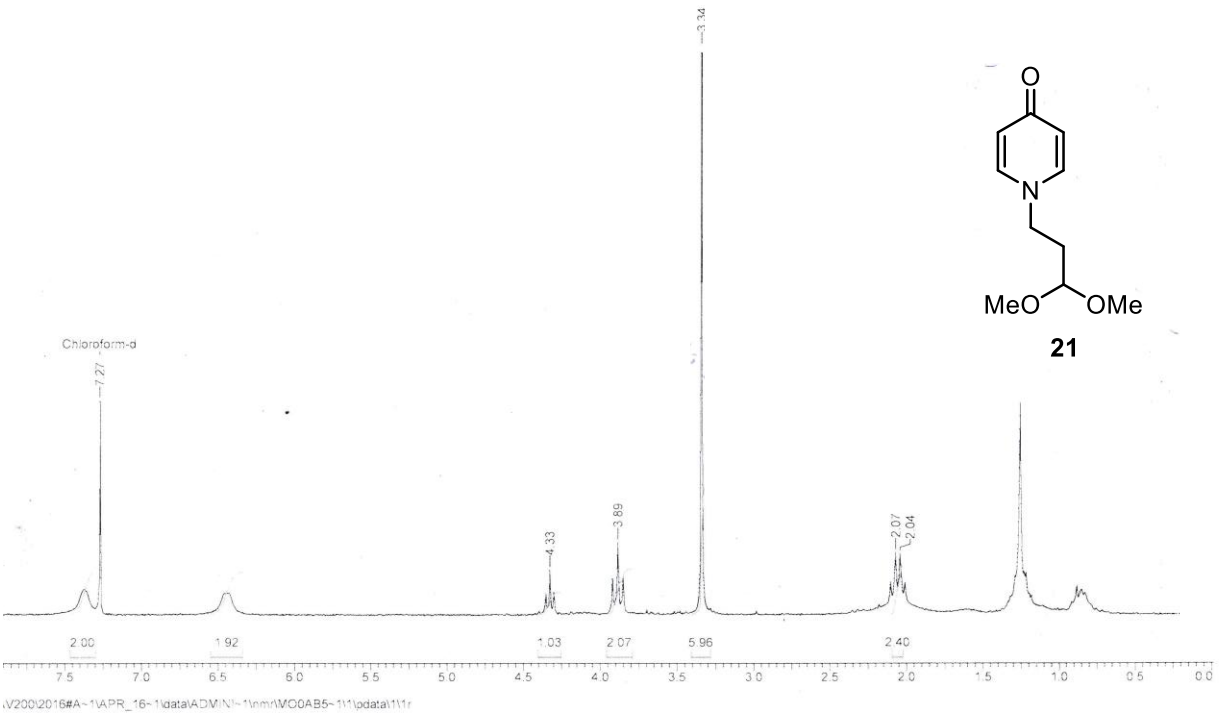
^{13}C NMR, 100 MHz, $CDCl_3$




^{1}H NMR, 400 MHz, CDCl$_3$
O
N
OEt
OEt
20
CHLOROFORM-d
7.31
7.29
7.27
6.38
6.36
4.45
4.43
4.42
3.90
3.88
3.86
3.66
3.62
3.60
3.46
3.44
3.42
3.40
2.06
2.04
2.03
2.01
1.20
1.18
1.16
1.99
2.01
1.01
2.01
2.05
2.08
2.05
6.09
Chemical Shift (ppm)
^{13}C NMR, 100 MHz, CDCl$_3$
CHLOROFORM-d
178.79
139.86
118.60
99.63
77.00
62.06
52.55
34.63
15.19
Chemical Shift (ppm)


^{1}H NMR, 400 MHz, CDCl$_3$
O
N
OEt
OEt
18
CHLOROFORM-d
7.27
4.63
4.62
4.61
3.70
3.69
3.67
3.66
3.64
3.52
3.52
3.50
3.48
2.75
2.77
2.47
2.46
2.44
1.88
1.87
1.86
1.85
1.84
1.23
1.22
1.20
1.00
2.09
2.07
4.05
2.06
4.04
2.07
6.11
Chemical Shift (ppm)
^{13}C NMR, 100 MHz, CDCl$_3$
CHLOROFORM-d
77.00
209.26
101.33
61.22
53.11
52.83
41.18
31.60
15.32
Chemical Shift (ppm)

^{1}H NMR, 200 MHz, $CDCl_3$



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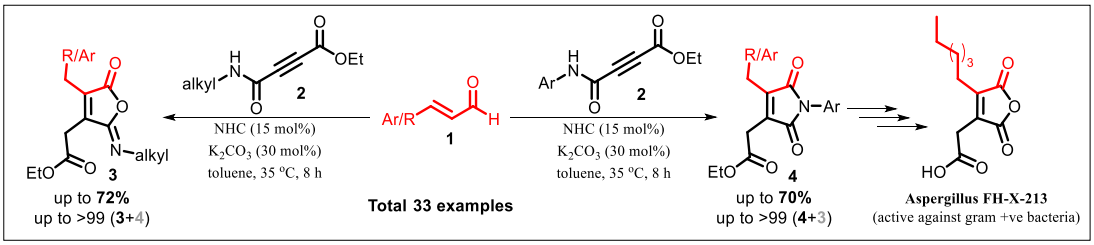
Section 2. Annulation of Enals with Carbamoylpropiolates via NHC-Catalyzed Enolate Pathway: Facile Access to Functionalized Maleimides/Isomaleimides and Synthesis of Aspergillus FH-X-213

3.2.1. Abstract:

We have developed the N-heterocyclic carbene (NHC)-catalyzed [3+2] annulation of *α,β*-unsaturated aldehydes with carbamoylpropiolates via an unusual enolate pathway leading to an elegant construction of the highly functionalized maleimides or isomaleimides. The electronic effect imposed by the alkyl/aryl group present on the amide nitrogen of carbamoylpropiolates plays a crucial role in the selective formation of these important five-membered heterocyclic building blocks. The developed protocol is mild and tolerates a wide range of substituents on both substrates. We have also demonstrated the application of the protocol in the synthesis of the antibacterial natural product Aspergillus FH-X-213.



The manuscript based on this work is under review.

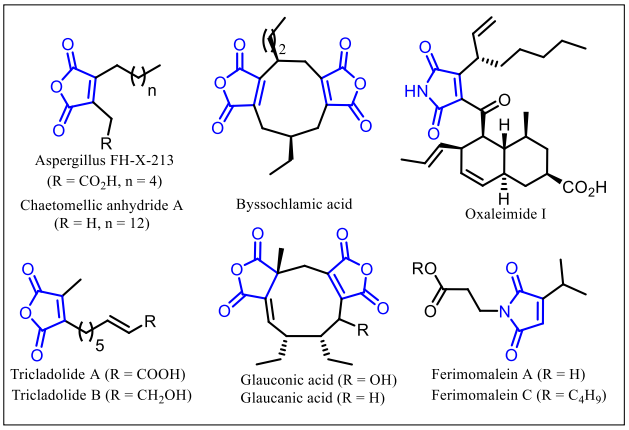
3.2.2. Introduction:

The advancements in the field of organic synthesis has played a pivotal role in the revolutionization of chemical, pharmaceutical and related industrial sectors, which indirectly has improved the quality of human life. This has become possible due to the several synthetic tools that are available in the toolbox of organic chemists to design and synthesize the desired compounds for various applications. Organocatalysis by N-heterocyclic carbenes (NHCs) is one

such synthetic tool of contemporary interest. It has witnessed remarkable growth in the past decade due to its effectiveness in constructing several scaffolds useful in pharmaceutical and material applications under milder and environmentally friendly reaction conditions from simple and readily available starting materials.[1] The exceptional umpolung reactivity of functional groups that is accessible due to NHC catalysis provides an opportunity for chemists to widen their approach during retrosynthetic analysis. It has tremendous potential to access heterocyclic scaffolds.

Nitrogen heterocycles, in particular maleimides (MIs) and isomaleimides (IMIs) are one of the privileged heterocyclic scaffolds abundant in many bioactive molecules, natural products, drugs or advanced materials.[2] They can be easily transformed to the corresponding maleic acid/anhydride, which is also one of the common core in several natural products (figure 1).[3] Moreover, MIs/IMIs are important building blocks of industrial interest and most sought after targets subsequent to the initial synthetic reports by Friedmann et al. in 1949 (MI) and Tsou et al. in 1955 (IMI).[4] Since then several methods for their preparation have been disclosed in the literature, however novel facile methods are always desired.[5]

Figure 1. Selected anhydride and maleimide bioactive natural products

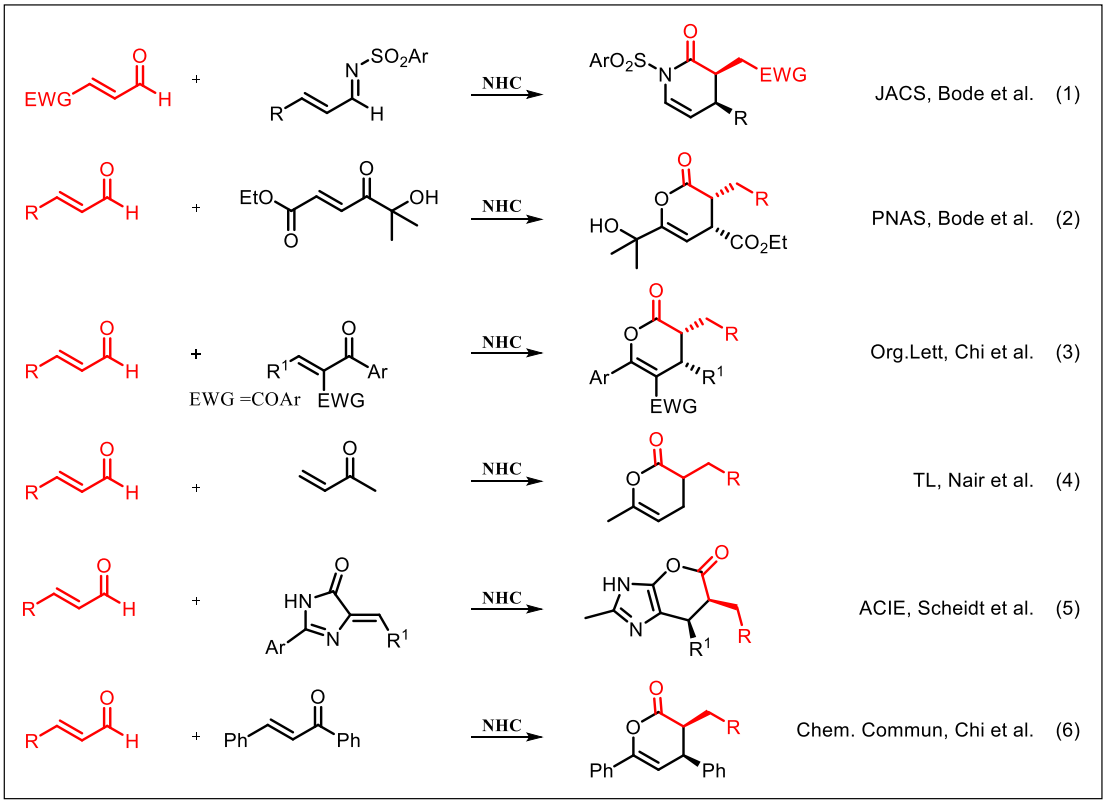


3.2.3. Literature review:

Literature survey revealed that NHC catalysis has been used extensively in the field of synthetic chemistry in the last two decades. The two most common modes of NHC reactivity, wherein the reaction follows either acyl anion or homoenolate pathway are well studied and documented in the literature, however the enolate pathway is relatively less explored.[6] Although, the NHC-catalyzed enolate pathway was indirectly employed utilizing various substrates or with well-designed enals intramolecularly,[7] the use of simple commercially available or easily accessible enals in the intermolecular reactions was not achieved until the pioneering work reported by Bode.[8] Bode and co-workers reported highly enantioselective Diels-Alder reactions between azadiene and enolate catalyzed by chiral NHC (Scheme 1. eq. 1). The same group developed the condition for selective generation of enolate from enal and reported the Diels-Alder reaction between NHC-bound enolate and electron deficient enone (Scheme 1. eq. 2).[9l] They have proved the role of base in dominating the enolate pathway over homoenolate pathway. Chi group reported an interesting observation about the effect of electron-withdrawing group present on the electrophilic partner on the reactivity modes of the NHC-activated enals leading to the selective formation of enolate pathway products (Scheme 1. eq. 3).[9k] Nair and co-workers in 2011 reported the synthesis of dihydropyranone from the corresponding starting materials using NHC catalyzed enolate pathway.[9i] Highly regioselective NHC-catalyzed [4+2] annulation of enal with imidazolidinones has been reported by Scheidt and co-workers in 2013 (Scheme 1. eq. 4).[9h] They observed the necessity of electron-withdrawing substituent at the 2-position of the imidazolidinone to activate the new conjugate acceptor and to achieve high conversion. Furthermore, a Bronsted acid was also an essential additive to obtain highly chemo selective formal [4+2] annulation product. Chi and co-workers reported the NHC-catalyzed reactions of

enals and chalcones and showed substrate-independent selective formation of enolates over homoenolate equivalent (Scheme 1. eq. 5).[9g] Acid co-catalysts play vital roles in control of the reaction pathways, allowing for individual access to diverse products from identical substrates. Such procurement of different outcome from similar kind of starting

Scheme 1. NHC catalyzed annulation reactions via enolate pathway



materials via different reactive intermediate is fascinating, but controlling the reaction pathway in a selective and precise manner is a challenging task. In continuation of our interest in the development of novel methodologies using NHC catalysis and their application in the synthesis of natural product,[10] we were curious to explore such mode of NHC's reactivity in the development of a novel processes to access industrially important heterocyclic scaffolds. Heterocycles are common structural motifs in the bioactive natural products and several marketed drugs.[11] Considering the literature background, the significance of MI/isoMI scaffolds

and scope to employ relatively less exploited NHC reactivity, we endeavored to develop a novel protocol for the construction of MI/IMIs utilizing the rarely explored intermolecular reaction of the NHC-bounded enolates from α,β-unsaturated aldehydes with carbamoylpropiolate as the activated electrophilic coupling partner.

3.2.4. Origin of the work:

It has been observed from the literature reports that, since the isolation of stable NHC in 1991 by Arduengo the chemistry of NHC has grown enormously. The tuning of Breslow intermediate towards particular reactivity has always found to be the challenge with variety of electrophilic partners during the synthesis of heterocyclic moiety. During the course of investigation of NHC catalysis, all possible double bond containing electrophiles were used effectively, but the alkyne based partners have never been utilized. Heterocycles are the synthetic target for chemists because of their wide bioactivity. In this context we have explored the annulation of carbamoylpropiolate with enolate generated by NHC catalysis from enal.

3.2.5. Objective of the work:

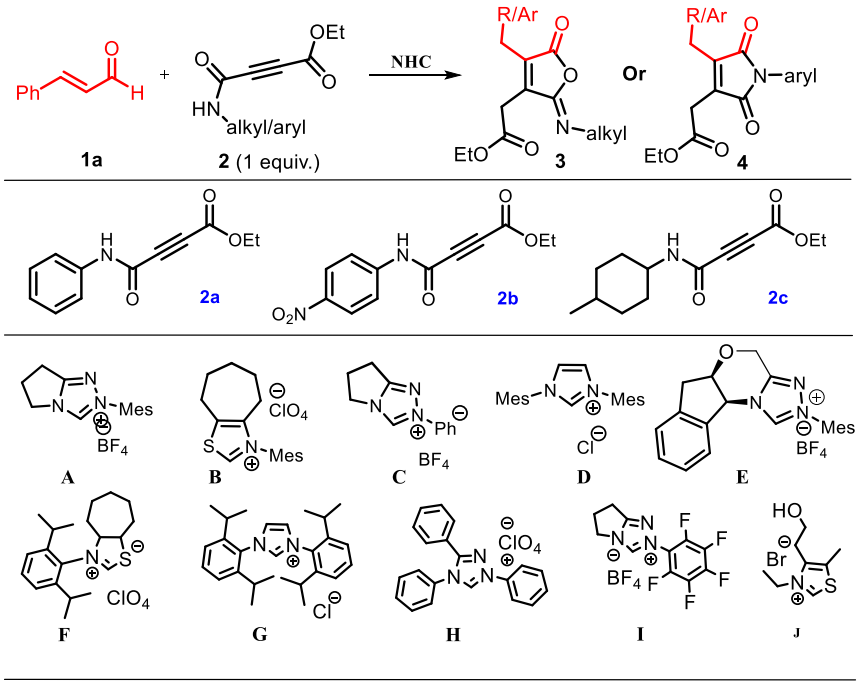
Selective synthesis of heterocycles of biological interest has been always a challenge as well as opportunity for the organic chemists because of multiple reactive centers in the starting materials. NHC's are well known to catalyze diverse organic transformations via different possible intermediates in a selective fashion. The potential of NHC to catalyze various reactions inspired us to utilize it for the proposed reaction. We aimed to utilize alkyne based carbamoylpropiolate as electrophilic coupling partner during annulation. We targeted the selective synthesis of MIs/IMIs of biologically interest. The objective of the present work is to 1) explore and demonstrate the potential of the targeted transformation, 2) extend it for the synthesis of related natural product and 3) study the mechanism of the reaction.

3.2.6. Result and discussion

We commenced our investigation by performing the reaction of cinnamaldehyde (**1a**) with CAP **2a** in the presence of NHC precursors **A-J**. To our delight, the first attempt using NHC-**A** (20 mole%), K_2CO_3 (40 mole%), and one equivalent of the substrates **1a** and **2a** each in THF at room temperature furnished the desired products though in less than 5% yield (Table 1, entry 1). All the NHC precursors as mentioned below were screened under the same reaction condition, and NHC-**E** was found to give better results amongst all (Table 1, entries 1-10). Several polar and non-polar solvents such as THF, dioxane, ACN, benzene, toluene, xylene, acetylene, DMF or DMSO were tried to improve the yield and toluene proved to be a better choice for this transformation (Table 1, entries 11-18). In general non polar solvents found to be better choice for this conversion than polar solvents. The reaction was performed in toluene at various temperatures ranging from rt to 60 ^{o}C, and we observed optimum yield at 35 ^{o}C (Table 1, entries 14, 19 & 20). At higher temperature we observed complex reaction mixture with diminished yield. Further efforts to increase the yield and selectivity by varying the equivalents of the substrates (Table 1, entries 21-23), base, and NHC, as well as the reaction time, provided an optimal reaction condition to obtain IMI **3a** and MI **4a** in 65% combined yield and 1:5.7 ratio (Table 1, entry 24) in 8 h. Our attempts using several inorganic or organic bases and other additives such as sodium benzoate and $Ti(O\textit{i}Pr)_4$ also did not improve the yield further (Table 1, representative entries 25-28). Several permutations and combinations were screened during the optimization studies, and we observed that the variation in the NHC or base doesn't have a substantial effect on the ratio of the products. Hence, to understand the electronic effect of the substituents on the formation of the products, we applied the protocol on two different types of CAP substrates **2b** and **2c,** wherein the substituents can make the nitrogen electron-deficient or

electron-rich, respectively. Interestingly, the CAP substrate **2b** shows enhanced formation of the corresponding MI **4ab** (Table 1, entry 29), whereas the substrate **2c** shows the selective formation of the IMI **3a** (Table 1, entry 30) in good yields. Based on these intriguing results (Table 1, entries 16, 19 & 20), we planned to explore the substrate scope of the NHC-enolate-driven [3+2] annulation protocol developed herein for the selective formation of IMIs and MIs.

Table 1. Optimization of the reaction condition[a]



sr. no.	**1a** equiv.	temp. °C	solvent	NHC, mole%	% yield[b] (**3**:**4**)
01	1.0	rt	THF	**A**, 20	<5
02	1.0	rt	THF	**B**, 20	--
03	1.0	rt	THF	**C**, 20	--
04	1.0	rt	THF	**D**, 20	<9
05	1.0	rt	THF	**E**, 20	<17
06	1.0	rt	THF	**F**, 20	<5
07	1.0	rt	THF	**G**, 20	--
08	1.0	rt	THF	**H**, 20	<10
09	1.0	rt	THF	**I**, 20	--
10	1.0	rt	THF	**J**, 20	--
11	1.0	rt	dioxane	**E**, 20	29 (38:62)
12	1.0	rt	ACN	**E**, 20	--
13	1.0	rt	benzene	**E**, 20	34 (31:69)
14	1.0	rt	toluene	**E**, 20	40 (24:76)
15	1.0	rt	xylene	**E**, 20	25 (28:72)
16	1.0	rt	acetylene	**E**, 20	32 (30:70)
17	1.0	rt	DMF	**E**, 20	trace

18	1.0	rt	DMSO	**E**, 20	trace
19	1.0	35	toluene	**E**, 20	49 (22:78)
20	1.0	50	toluene	**E**, 20	35 (15:85)
21	1.2	35	toluene	**E**, 20	57 (19:81)
22	1.5	35	toluene	**E**, 20	64 (19:81)
23	2.0	35	toluene	**E**, 20	63 (20:80)
24	**1.5**	**35**	**toluene**	**E**, **15**	**65 (15:85)**
25[c]	1.5	35	toluene	**E**, 15	41 (19:81)
26[d]	1.5	35	toluene	**E**, 15	--
27[e]	1.5	35	toluene	**E**, 15	
28[f]	1.5	35	toluene	**E**, 15	
29[g]	**1.5**	**35**	**toluene**	**E**, **15**	**68 (11:89)**
30[h]	**1.5**	**35**	**toluene**	**E**, **15**	**66 (95:05)**

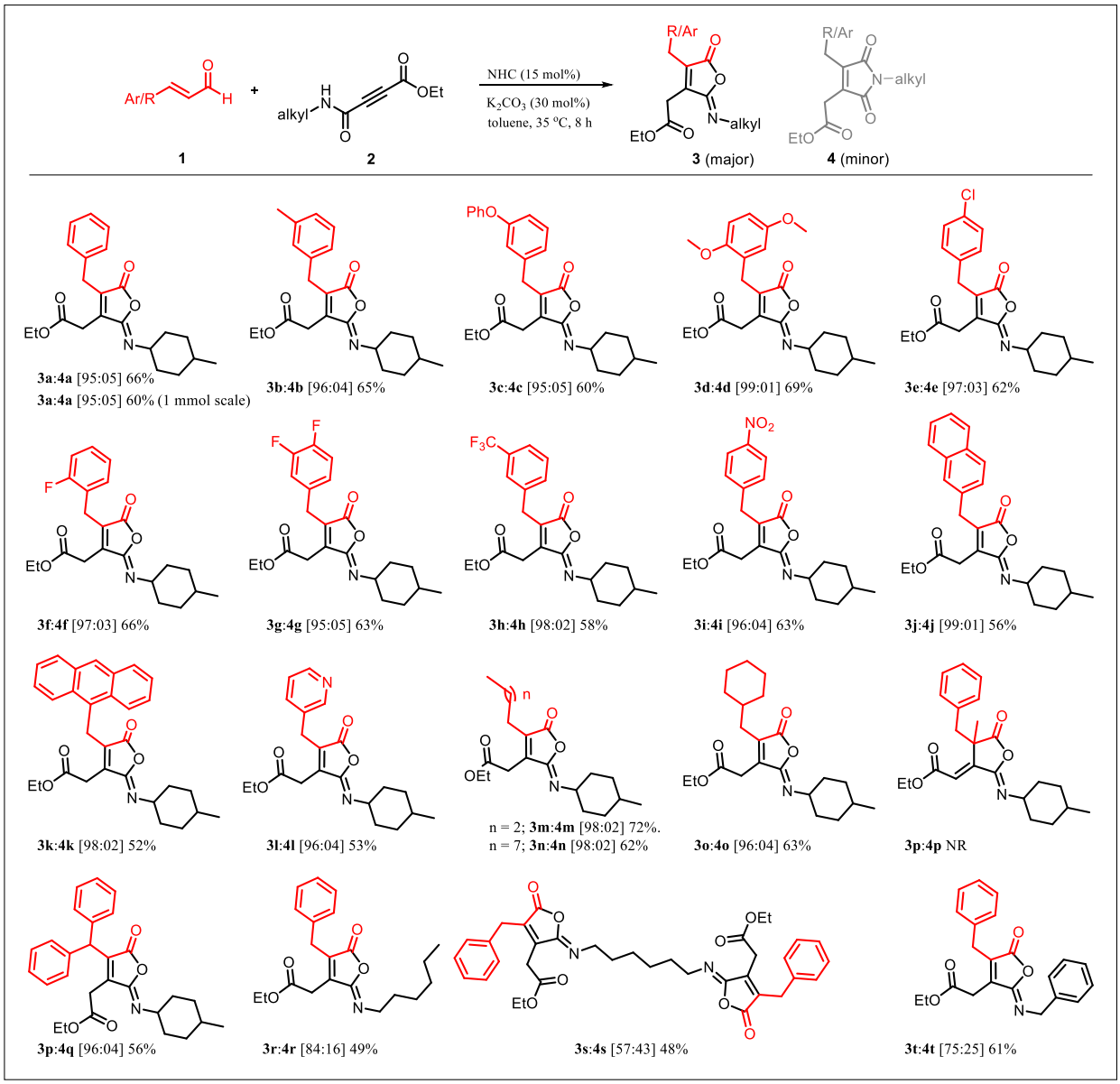
[a]Reaction conditions: **2a-c** (0.1 mmol), **1a**, K_2CO_3 (entries 1-15 = 40 mol%, 16, 19, 20 = 30 mol%), NHC, solvent (1 mL) in Schlenk tube with sidearm, reaction time: 24 h for entries 1-10 and 8 h for entries 11-20. [b]Isolated yield. [c]Cs_2CO_3 as base, [d]NEt_3 as base, [e]$PhCO_2Na$, [f]$Ti(OiPr)_4$ [g]substrate **2b**, [h]substrate **2c**.

First, we tested the substrate scope for IMI synthesis by utilizing alkyl-substituted CAP **2c** (Scheme 2). The reaction with electronically unbiased substrates such as cinnamaldehyde and 3-methyl cinnamaldehyde leads to the formation of IMI products **3a** and **3b,** respectively, in good yield and selectivity as expected. The aldehyde substrates with strong electron-donating groups such as 3-phenoxy and 2,5-dimethoxy also worked well to give the corresponding products **3c** and **3d,** respectively. The chloro- and fluoro-substituted cinnamaldehydes were also found compatible under the optimized reaction condition leading to the related products **3e-g** in good selectivity. The cinnamaldehyde substrates with strong electron-withdrawing groups such as 3-trifluoromethyl and 4-nitro smoothly furnished the products **3h** and **3i,** respectively. Polyaromatic enals worked well to obtain the IMIs **3j** and **3k** in moderate yields but high selectivity. The protocol also tolerated heterocyclic enal to provide the IMI **3l** in moderate yield. The enal substrates with aliphatic β-substituents worked even better with excellent selectivity to furnish IMIs **3m-o** in very good yields. The α-methyl-substituted cinnamaldehyde failed to give the product **3p,** probably because of the steric hindrance at the α-position as the reaction follows the enolate pathway. However, the β-phenyl substituted cinnamaldehyde worked well to provide

the product **3q** in moderate yield.

The variation in the aliphatic substituents on CAP nitrogen was also studied. Long-chain primary alkyl and benzyl substituted CAPs worked well similar to its cyclic substituted analogues leading to the formation of IMIs **3r-t**; however, the selectivity dropped down. This

Scheme 2. Annulation of enals with alkyl substituted carbamoylpropiolate[a]

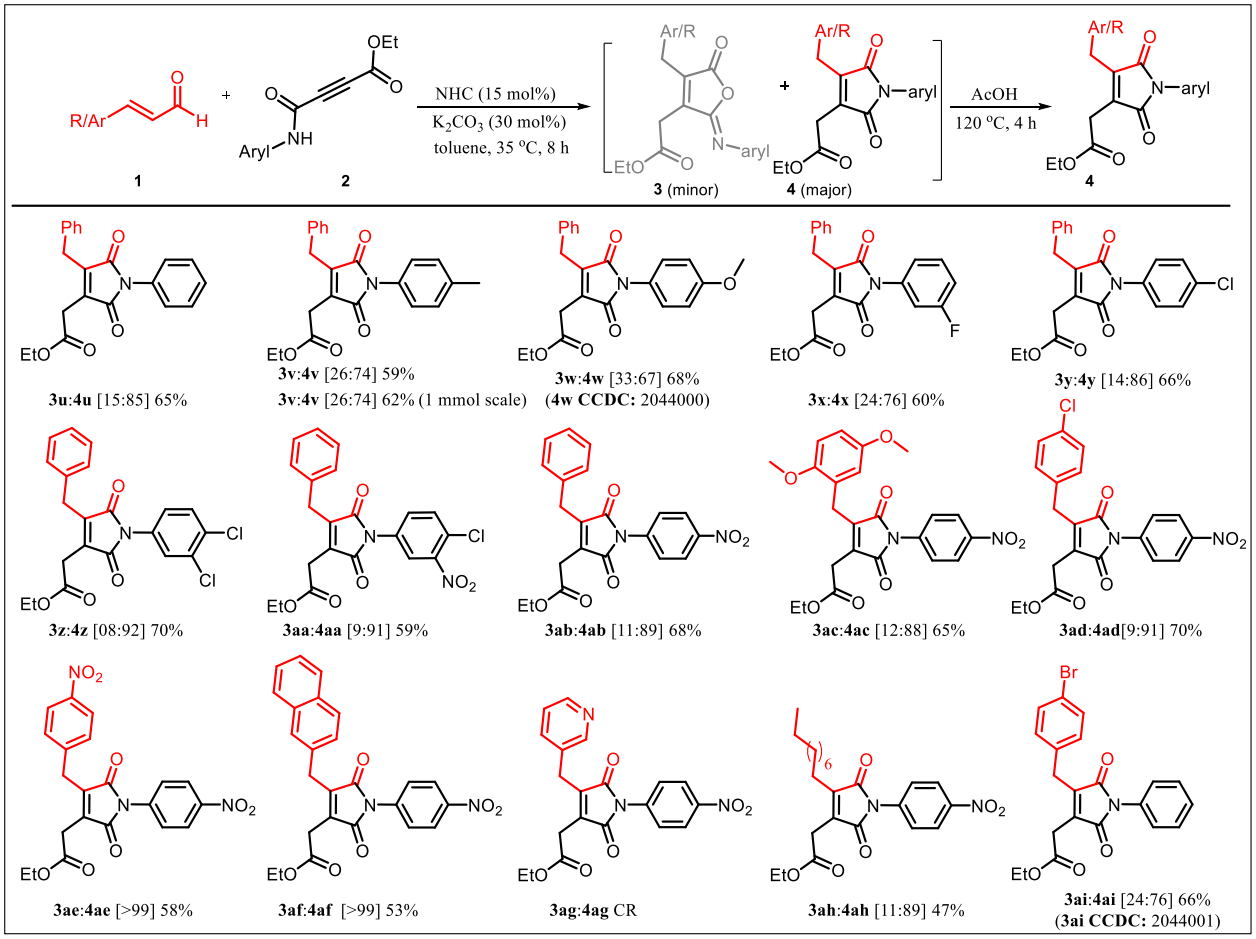


Reaction condition: **1** (0.15 mmol), **2** (0.1 mmol), NHC-**E** (15 mol%), K_2CO_3 (30 mol%), toluene (1 ml), in Schleck tube with sidearm for 8 h. [a]Isolated yield. NR = no reaction

could be due to the change in the bulkiness and electronic nature of the substituent. The bis-IMI **3s**/MI **4s** or its congeners could be interesting monomers for material sciences.

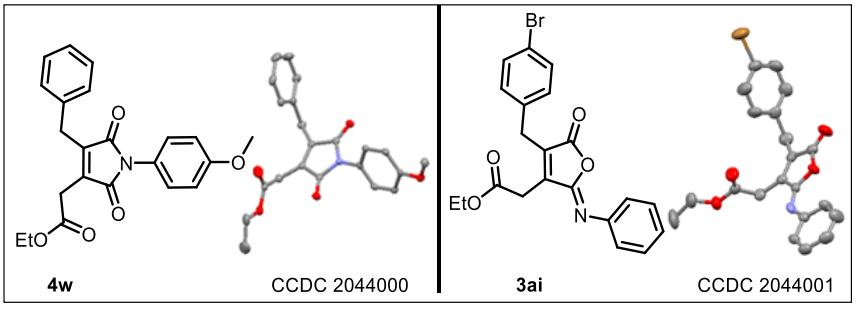
We next aimed to explore the substrate scope of N-aryl substituted CAPs with cinnamaldehyde derivatives to achieve the selective formation of MIs (Scheme 3). To simplify the process, after completion of the reaction, the ratio of IMI vs. MI was determined by ^{1}H NMR of the reaction mixture before converting it to MI completely by heating in acetic acid. First, we varied the substituents on the aromatic ring of CAP. Phenyl and p-tolyl substituted CAP worked well to provide the concerned MIs 4u and 4v in good yield and selectivity. The conversion of the IMI and MI mixture to MI was quantitative. Good yield and selectivity were also observed for the electron-donating and halo-substituted CAPs to obtain MIs **4w-z**. The substrates with a strong electron-withdrawing nitro group interestingly furnished MI products **4aa** and **4ab** with comparatively high selectivity, probably due to higher thermodynamic stability of the MI product. Based on this observation, we planned to vary enal substituents keeping *para*-nitro substituted CAP **2b** as the common electrophilic partner. Various cinnamaldehydes having electron-donating/withdrawing, halide, and polyaromatic substituents underwent a smooth transformation to furnish excellent selectivity (**4ac-af**). Gratifyingly, a complete selectivity to obtain MIs **4ae** and **4af** was observed when both the reacting partners having electron-withdrawing groups were used; hence further heating in acetic acid was not performed in these two cases. However, the heterocyclic substituted MI **4ag** could not be synthesized using our standard protocol. Aliphatic enal with a long alkyl chain also reacted well with CAP **2b** to furnish MI **4ah**; however, the yield was lower as compared to the aromatic enals. Additional support for the structure of the formed products was obtained by single-crystal X-ray analysis (Figure 2) of MI **4w** and bromo-substituted IMI **3ai**, which was prepared especially for this

Scheme 3. Annulation of enal with aryl substituted carbamoylpropiolate[a]



Reaction condition: **1** (0.15 mmol), **2** (0.1 mmol), NHC-**E** (15 mol%), K_2CO_3 (30 mol%), toluene (1 ml), in Schleck tube with sidearm for 8 h. [a]Isolated yield. CR = complex reaction mixture

Figure 2. Single crystal structures

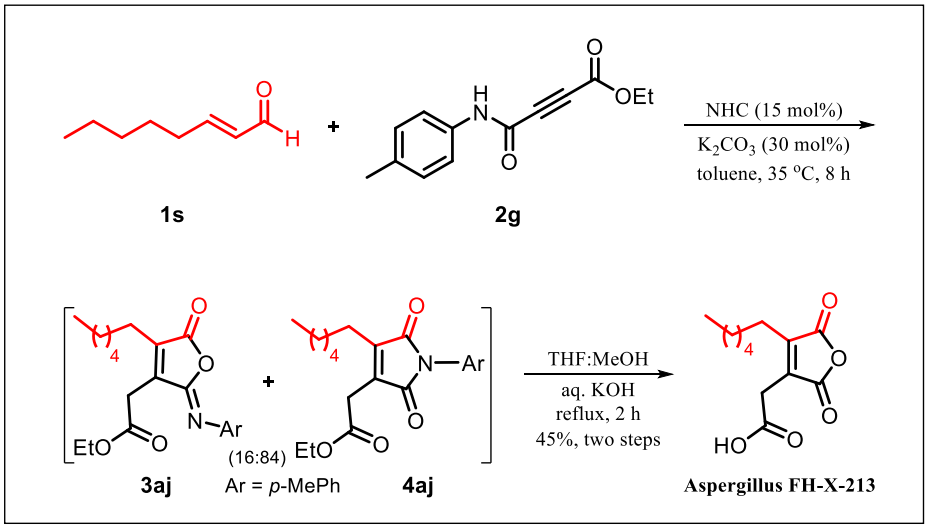


purpose as all the IMIs prepared in scheme 2 are not solids.

The scalability of the developed protocol was demonstrated by performing the reaction of the CAP **2c** on one mmol scale to obtain the IMI **3a** in good yield (Scheme 2). Similarly, the reaction of CAP **2g** followed by heating the reaction mixture in acetic acid worked equally well on one mmol scale to obtain the MI **4v** in good yield (Scheme 3).

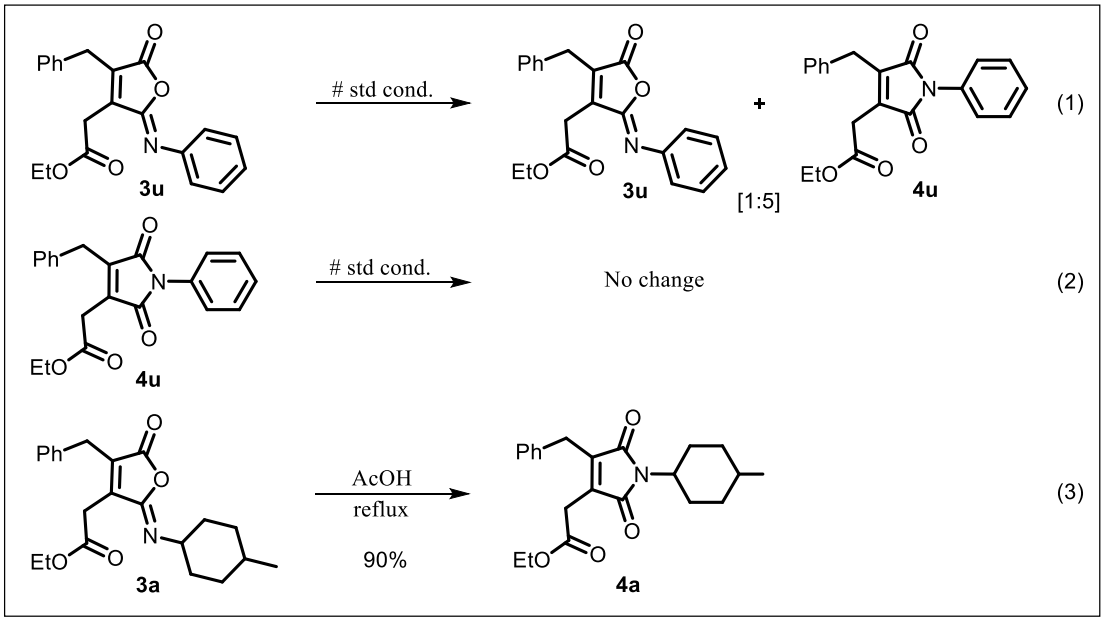
The successful demonstration of the broad substrate scope studies of our NHC-catalyzed protocol prompted us to explore its potential application in the concise synthesis of the natural product Aspergillus FH-X-213 (Scheme 4). It was first isolated in 1972 and displays activity against gram +ve bacteria.[12] To date, four total syntheses of Aspergillus FH-X-213 have been reported in the literature.[13] We subjected *trans*-2-octenal (**1s**) and CAP **2g** to our standard reaction conditions. The resultant reaction mixture containing the desired MI **4aj** and IMI **3aj** was then evaporated in vacuo to remove toluene. The residue was refluxed in THF:methanol (1:2) and aq. KOH.[13b] Usual workup and purification furnished the natural product Aspergillus FH-X-213 in 45% yield over two steps (Scheme 4). It should also be possible to extend the application of the developed protocol in the total synthesis of chaetomellic anhydride A and byssochlamic acid as well as related natural products (figure 1).[3]

Scheme 4. Total synthesis of natural product Aspergillus FH-X-213



We performed few control experiments to understand the reaction pathway. The pure IMI **3u** was subjected to the standard reaction condition, and we observed the mixture of **3u** and **4u** in 1:5 proportion (Scheme 5, eq 1). However, pure MI **4u** did not show any change under the standard reaction condition (Scheme 5, eq 2). Similar to the conversion of *N*-aryl IMIs to MIs (Scheme 3), the *N*-alkyl IMI **3a** could be converted smoothly to MI **4a** in excellent yield (Scheme 5, eq 3). These experiments indicate that IMI could be the actual intermediate during the course of the reaction. These observations also corroborate with the studies indicating the preferred formation of IMIs as products of kinetic control and the formation of the thermodynamically stable MIs via the rearrangement of IMIs depending on the nature of the substituent present on the nitrogen.[14]

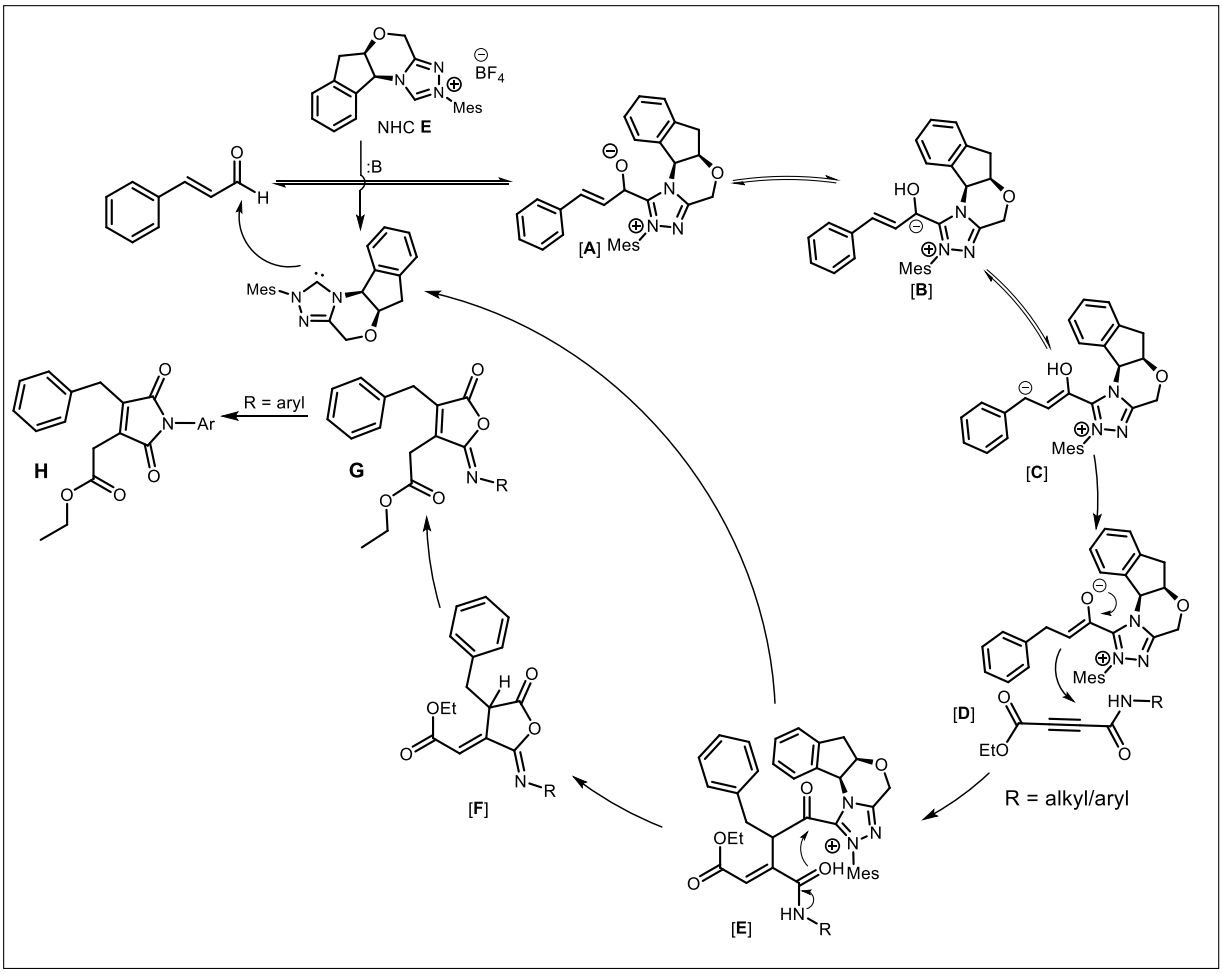
Scheme 5. Control experiments



Based on the experimental observations and literature precedence,[9] a plausible reaction mechanism has been proposed as depicted in Scheme 6. The Breslow intermediate [**B**] formed

from the NHC-**E** and cinnamaldehyde converts to the homoenolate equivalent [**C**] upon the migration of the negative charge. It then leads to the formation of enolate equivalent [**D**] after proton abstraction. The regioselective attack of the active intermediate enolate [**D**] on CAP leads to the generation of intermediate [**E**], which upon the internal attack of oxygen on carbonyl expels NHC for the further catalytic cycle and forms IMI product **G** after proton migration. However, the substrates having an aromatic substituent on the nitrogen transforms to the stable MI product **H**. The more electron-deficient nature of the CAP might be favoring the enolate pathway,[9k] and hence we did not observe the formation of products from the typical homoenolate pathway.

Scheme 6. Plausible reaction mechanism



3.2.7. Conclusion

In summary, we have demonstrated a general and scalable NHC-catalyzed highly selective enolate-driven intermolecular annulation of *α,β*-unsaturated aldehydes with CAPs leading to the synthetically valuable products MIs and IMIs. The choice of CAPs as an optimal electron-deficient reacting partner was critical to the success of the enolate pathway-based protocol. To the best of our knowledge, this report is the first example of alkynes as the electrophilic reacting substrates in the NHC-catalyzed reactions. The protocol has also been extended for the synthesis of natural product Aspergillus FH-X-213. We are now working on the development of the protocol for the asymmetric synthesis of the functionalized succinimides utilizing enal enolates and their application in the construction of related natural products and drugs.

3.2.8. Experimental Section

1. Additional information:

The ^{13}C NMR spectra of compounds **3o**, **4x**, **4aa**, and **4ac** show one carbon less because of peak overlapping. All carbamoylpropiolate starting materials were prepared according to the literature procedure[15] starting from the corresponding isocyanate and ethyl propiolate. All the aldehydes were purchased from commercial source and used without further purification. The NHC precursors were prepared according to the literature procedures.[16]

2. Experimental procedures:

[I] General procedure for the synthesis of carbamoylpropiolates: All the carbamoylpropiolates were prepared according to the reported procedure.[15] Ethyl propiolate (1.0 equiv) was dissolved in THF (5 mL) and the solution was cooled to –78 ^{o}C, followed by the slow addition of n-BuLi (1.2 equiv, 1.5 M in hexane). The mixture was stirred for 30 min and a solution of the corresponding isocyanate (500 mg, 1.0 equiv) in THF (5mL) was added drop-wise. The reaction mixture was then stirred for 3-5 h the at same temperature and acetic acid (1 mL) was added to quench the reaction after completion. The reaction mixture was allowed to warm to room temperature, water was added and the aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined organic extract was dried over anhydrous Na_2SO_4. Removal of the solvent gave a residue, which was subjected to flash column chromatography on silica-gel using ethyl acetate and petroleum ether (1:4) to afford the corresponding compounds.

[II] General procedure for the selective synthesis of isomaleimides 3a-t using *N*-alkyl substituted carbamoylpropiolates: An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate (0.1 mmol, 1 equiv), aldehyde (0.15 mmol, 1.5 equiv), NHC-**E** (6.3 mg, 0.015 mmol, 15 mol%), and K_2CO_3 (4.1 mg, 0.030 mmol, 30 mol%) under argon atmosphere. To this mixture, toluene (1.0 mL) was added and the Schlenk tube was backfilled with argon and heated at 35 ^{o}C in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h and the solvent was evaporated under the reduced pressure. The crude reaction mixture was purified by flash column chromatography using ethyl acetate and petroleum ether as eluents to obtained isomaleimides **3a-t** in good to moderate yields.

[III] General procedure for the selective synthesis of maleimides 4u-ai using *N*-aryl substituted carbamoylpropiolates: An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate (0.1 mmol, 1 equiv), aldehyde (0.15 mmol, 1.5 equiv), NHC-**E** (6.3 mg, 0.015 mmol, 15 mol%), and K_2CO_3 (4.1 mg, 0.030 mmol, 30 mol%) under argon atmosphere. To this mixture, toluene (1.0 mL) was added and the Schlenk tube was backfilled with argon and heated at 35 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h and the solvent was evaporated under the reduced pressure. Acetic acid (1 mL) was added to the crude reaction mixture and heated to 120 ^oC for 4h. Acetic acid was then evaporated and the residue was dissolved in EtOAc, washed with water, aqueous saturated $NaHCO_3$ (10 mL x 2) and brine. The organic layer was dried over Na_2SO_4, concentrated under vacuum, and the crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether as eluents.

[IV] Typical experimental procedure for the preparation of the representative isomaleimide product 3a: An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with ethyl 4-((4-methylcyclohexyl)amino)-4-oxobut-2-ynoate (**2c**, 23.7 mg, 0.1 mmol, 1 equiv), cinnamaldehyde (**1a**, 20 mg, 0.15 mmol, 1.5 equiv), NHC-**E** (6.3 mg, 0.015 mmol, 15 mol%), and K_2CO_3 (4.1 mg, 0.030 mmol, 30 mol%) under argon atmosphere. To this mixture, toluene (1.0 mL) was added and the Schlenk tube was backfilled with argon and heated at 35 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h and the solvent was evaporated under the reduced pressure. The crude reaction mixture was purified by flash column chromatography using ethyl acetate and petroleum ether (1:9) to afford isomaleimide product **3a** (**3a**:**4a** = 95:05) in 66% (24.3 mg) yield.

[V] Typical experimental procedure for the preparation of the representative maleimide product 4u: An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with ethyl 4-oxo-4-(phenylamino)but-2-ynoate (**2a**, 21.7 mg, 0.1 mmol, 1 equiv), cinnamaldehyde (**1a**, 20 mg, 0.15 mmol, 1.5 equiv), NHC-**E** (6.3 mg, 0.015 mmol, 15 mol%), and K_2CO_3 (4.1 mg, 0.030 mmol, 30 mol%) under argon atmosphere. To this mixture, toluene (1.0 mL) was added and the Schlenk tube was backfilled with argon and heated at 35 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h and solvent was evaporated under the reduced pressure (the ^1H NMR analysis shows **3u**:**4u** = 15:85). Acetic acid (1 mL) was added to the crude reaction mixture and heated to 120 ^oC for 4 h. Acetic acid was then evaporated and the residue was dissolved in EtOAc, washed with water, aqueous saturated $NaHCO_3$ (10 mL x 2) and brine. The organic layer was dried over Na_2SO_4, concentrated under vacuum, and the crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether (1:6) to afford pure maleimide product **4u** in 65% (22.6 mg) yield.

[VI] Procedure for 1 mmol scale experiments:

[A] Procedure for the synthesis of 3a: An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate **2c** (237 mg, 1 mmol, 1 equiv), cinnamaldehyde (198 mg, 1.5 mmol, 1.5 equiv), NHC-**E** (63 mg, 0. 15 mmol, 15 mol%), and K_2CO_3 (41 mg, 0. 30 mmol, 30 mol%) under argon atmosphere. To this mixture, toluene (10 mL) was added and the Schlenk tube was backfilled with argon and heated at 35 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h and the solvent was evaporated under the reduced pressure. The crude

reaction mixture was purified by flash column chromatography using ethyl acetate and petroleum ether (1:9) to afford isomaleimide product **3a** (**3a**:**4a =** 95:05) in 60% (221 mg) yield.

[B] Procedure for the synthesis of 4v: An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate **2g** (230 mg, 1 mmol, 1 equiv), cinnamaldehyde (198 mg, 1.5 mmol, 1.5 equiv), NHC-**E** (63 mg, 0. 15 mmol, 15 mol%), and K_2CO_3 (41 mg, 0. 30 mmol, 30 mol%) under argon atmosphere. To this mixture, toluene (10 mL) was added and the Schlenk tube was backfilled with argon and heated at 35 ^oC in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h and solvent was evaporated under the reduced pressure (the ^1H NMR analysis shows **3v**:**4v** = 26:74). Acetic acid (10 mL) was added to the crude reaction mixture and heated to 120 ^oC for 4h. Acetic acid was then evaporated and the residue was dissolved in EtOAc, washed with water, aqueous saturated $NaHCO_3$ (50 mL x 2) and brine. The organic layer was dried over Na_2SO_4, concentrated under vacuum, and the crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether (1:6) to afford pure maleimide product **4v** in 62% (224 mg) yield.

[VII] Control experiments:

[A] **Experimental procedure for the reaction of isomaleimide 3u under the standard conditions**: An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with isomaleimide **3u** (17.5 mg, 0.05 mmol, 1 equiv), NHC-**E** (3 mg, 0. 0075 mmol, 15 mol%), and K_2CO_3 (2 mg, 0. 015 mmol, 30 mol%) under argon atmosphere. To this mixture, toluene (0.5 mL) was added and the Schlenk tube was backfilled with argon and heated at 35 ^oC in a preheated oil bath. The reaction was stopped after 8 h and the solvent was evaporated under the

reduced pressure. The crude product was purified by the flash column chromatography using ethyl acetate and petroleum ether (1:9) to obtain **3u** and **4u** (1:5) in 92% (16 mg) yield.

[B] Experimental procedure for the reaction of maleimide 4u under the standard conditions: An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with maleimide **4u** (17.5 mg, 0.05 mmol, 1 equiv) NHC-**E** (3 mg, 0. 0075 mmol, 15 mol%), and K_2CO_3 (2 mg, 0. 015 mmol, 30 mol%) under argon atmosphere. To this mixture, toluene (0.5 mL) was added and the Schlenk tube was backfilled with argon and heated at 35 ^oC in a preheated oil bath. The reaction was stopped after 8 h and it was found that all the starting material remained unchanged.

[C] Procedure for synthesis of maleimide 4a from the corresponding isomaleimide 3a: A known protocol[17] for the conversion of isomaleimide to maleimides was applied for the preparation of **4a** from **3a**. A solution of isomaleimide **3a** (20 mg) in glacial acetic acid (1 mL) was heated at 120 ^oC for 4 h. Acetic acid was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with water, aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, concentrated under vacuum, and the crude residue was purified by flash column chromatography using ethyl acetate and petroleum ether (1:6) to afford pure maleimide product **4a** in 90% (18 mg) yield.

[VIII] Procedure for the synthesis of natural product Aspergillus FH-X-213:

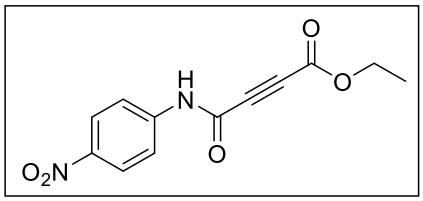
[A] Step-1: An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with carbamoylpropiolate **2g** (46 mg, 0.2 mmol, 1 equiv), *trans*-2-octenal (38 mg, 0.3 mmol, 1.5 equiv), NHC-**E** (12.5 mg, 0.03 mmol, 15 mol%), and K_2CO_3 (8.2 mg, 0.06 mmol, 30 mol%) under argon atmosphere. To this mixture, toluene (2.0 mL) was added and the Schlenk tube was

backfilled with argon and heated at 35 ^{o}C in a preheated oil bath. The progress of the reaction was monitored using TLC analysis. The reaction was stopped after 8 h and the solvent was evaporated under reduced pressure. The crude product was passed through the flash column using ethyl acetate and petroleum ether (1:6) and the obtained mixture of compounds **3aj** and **4aj** (43 mg, **3aj**:**4aj** = 16:84) was utilized for the next step.

[B] Step-2: The reported protocol[13b] for the conversion of maleimide to maleic anhydride was applied on the above obtained mixture of products. To a stirred solution of isomaleimides **3aj** and maleimide **4aj** (43 mg) in a THF-methanol mixture (1:2, 2 mL) was added 20% aqueous KOH solution (1.5 mL) and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated to remove THF-MeOH and the aqueous layer was acidified with 2 N HCl followed by extraction with diethyl ether (3 × 20 mL). The combined organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue with petroleum ether and ethyl acetate furnished 22 mg of the natural product Aspergillus FH-X-213 in 45% yield over two steps.

3. Characterization data of compounds:

Ethyl 4-((4-nitrophenyl)amino)-4-oxobut-2-ynoate (**2b**): The title compound **2b** was prepared according to the general procedure **[I]** as yellow solid in 42% yield (335 mg); R_f 0.5 (ethyl acetate:pet. ether, 1:3); mp: 128-130 ºC.

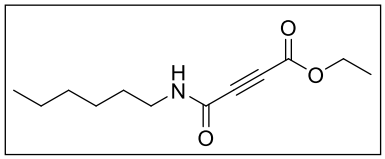


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28-8.26 (m, 1H), 8.26 (d, J = 9.13 Hz, 2H), 7.74 (d, J = 9.13 Hz, 2H), 4.34 (q, J = 7.13 Hz, 2H), 1.37 (t, J = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.0, 148.4, 144.4, 142.1, 125.2, 119.7, 76.2, 75.5, 63.4, 13.9.

HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{12}H_{11}N_2O_5$ 263.0667, found 263.0674.

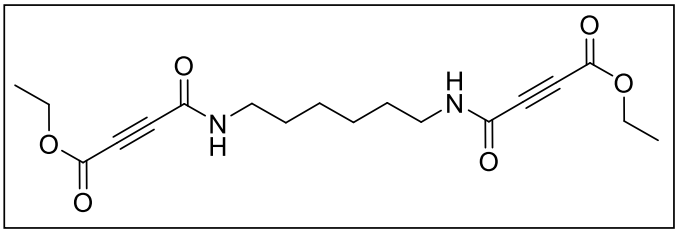
Ethyl 4-(hexylamino)-4-oxobut-2-ynoate (**2d**): The title compound **2d** was prepared according to the general procedure **[I]** as colourless liquid in 62% yield (549 mg); R_f 0.6 (ethyl acetate:pet. ether, 1:3).



^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.00 (brs, 1H), 4.29 (q, J = 7.13 Hz, 2H), 3.36-3.28 (m, 2H), 1.57-1.50 (m, 2H), 1.38-1.29 (m, 9H), 0.92-0.87 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 152.3, 150.7, 76.7, 73.7, 62.9, 40.1, 31.3, 29.1, 26.4, 22.5, 13.96, 13.90.

HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{12}H_{20}NO_3$ 226.1442, found 226.1445.

Diethyl 4,4'-(hexane-1,6-diylbis(azanediyl))bis(4-oxobut-2-ynoate) (**2e**): The title compound



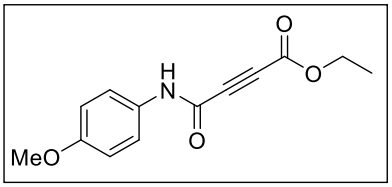
2e was prepared according to the general procedure **[I]** as white solid in 60% yield (649 mg); R_f 0.5 (ethyl acetate:pet. ether, 1:2); mp: 91-93 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.38 (br, 2H), 4.28 (q, J = 7.1 Hz, 4H), 3.32 (q, J = 6.4 Hz, 4H), 1.59-1.52 (m, 4H), 1.37-1.30 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.3, 150.9, 76.7, 73.9, 62.9, 39.7, 28.9, 26.0, 13.9.

HRMS (ESI-TOF) m/z [M+H]$^+$ calcd for $C_{18}H_{25}N_2O_6$ 365.1712, found 365.1711.

Ethyl 4-((4-methoxyphenyl)amino)-4-oxobut-2-ynoate (**2h**): The title compound **2h** was



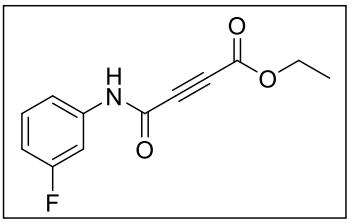
prepared according to the general procedure **[I]** as white solid in 57% yield (472 mg); R_f 0.5 (ethyl acetate:pet. ether, 1:3); mp: 77-79 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80 (brs, 1H), 7.41-7.52 (m, 2H), 6.85-6.92 (m, 2H), 4.31 (q, J = 6.87 Hz, 2H), 3.80 (s, 3H), 1.35 (t, J = 6.87 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.2, 152.3, 148.1, 129.6, 121.8, 114.3, 76.7, 74.4, 63.0, 55.5, 13.9.

HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{14}NO_4$ 248.0922, found 248.0928.

Ethyl 4-((3-fluorophenyl)amino)-4-oxobut-2-ynoate (**2i**): The title compound **2i** was prepared according to the general procedure **[I]** as yellow liquid in 52% yield (446 mg); R_f 0.5 (ethyl acetate:pet. ether, 1:3).

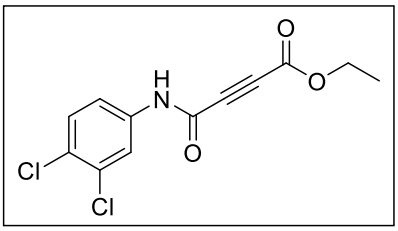


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.91 (brs, 1H), 7.45-7.52 (m, 1H), 7.35-7.28 (m, 1H), 7.20-7.12 (m, 1H), 6.92-6.85 (m, 1H), 4.33 (q, J = 7.13 Hz, 2H), 1.36 (t, J = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.9 (CF, J = 246.3 Hz), 152.2, 148.2, 138.0 (CF, J = 10.9 Hz), 130.4 (CF, J = 9.5 Hz), 115.2 (CF, J = 2.9 Hz), 112.4 (CF, J = 21.8 Hz), 107.7 (CF, J = 26.9 Hz), 76.7, 74.8, 63.2, 13.9.

HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{12}H_{11}FNO_3$ 236.0722, found 236.0727.

Ethyl 4-((3,4-dichlorophenyl)amino)-4-oxobut-2-ynoate (**2k**): The title compound **2k** was prepared according to the general procedure **[I]** as white solid in 51% yield (387 mg); R_f 0.5 (ethyl acetate:pet. ether, 1:3); mp: 69-71 ^{o}C.

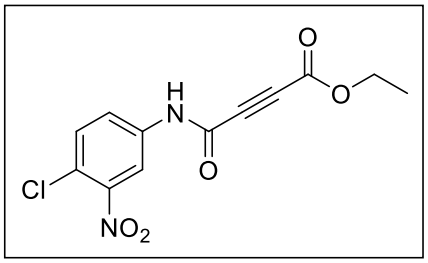


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95 (brs, 1H), 7.77 (d, J = 2.5 Hz, 1H), 7.42 (d, J = 8.63 Hz, 1H), 7.36 (dd, J = 8.76 & 2.5 Hz, 1H), 4.33 (q, J = 7.25 Hz, 2H), 1.36 (t, J = 7.25 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.1, 148.2, 135.9, 133.2, 130.8, 129.1, 121.8, 119.2, 76.5, 75.1, 63.3, 13.9.

HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{12}H_{10}{}^{35}Cl_2NO_3$ 285.9190, found 285.9188.

Ethyl 4-((4-chloro-3-nitrophenyl)amino)-4-oxobut-2-ynoate (2l): The title compound **2l** was prepared according to the general procedure **[I]** as white solid in 44% yield (329 mg); R_f 0.5 (ethyl acetate:pet. ether, 1:3); mp: 99-101 ^oC.

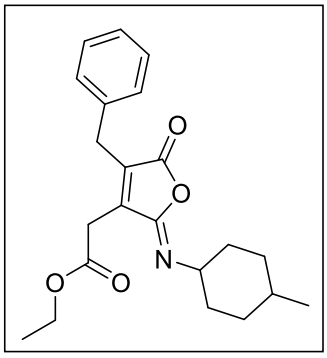


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.53 (brs, 1H), 8.18 (d, J = 2.5 Hz, 1H), 7.77 (dd, J = 8.75 & 2.63 Hz, 1H), 7.54 (d, J = 8.88 Hz, 1H), 4.34 (q, J = 7.13 Hz, 2H), 1.36 (t, J = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.2, 148.5, 147.9, 136.2, 132.5, 124.1, 123.0, 116.8, 76.2, 75.5, 63.6, 13.9.

HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{12}H_{10}{}^{35}ClN_2O_5$ 297.0278, found 297.0280.

Ethyl (Z)-2-(4-benzyl-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3a**): The title compound **3a** was prepared according to the procedure **[IV]** as sticky solid in 66% yield (24.3 mg, **3a**:**4a** = 95:05); Reaction time 8 h/35 ^oC; R_f 0.7 (ethyl acetate:pet. ether, 1:4).

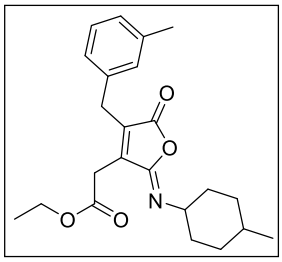


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35-7.18 (m, 5H), 4.11 (q, J = 6.87 Hz, 2H), 3.77 (s, 2H), 3.70-3.76 (m, 1H), 3.44 (s, 2H), 1.76-1.68 (m, 4H), 1.49-1.35 (m, 3H), 1.22 (t, J = 6.87 Hz, 3H), 1.08-0.99 (m, 2H), 0.90 (d, J = 6.10 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.03, 167.96, 149.8, 142.4, 136.8, 136.0, 128.82, 128.78, 127.1, 61.5, 57.9, 33.4, 33.3, 31.8, 30.3, 30.1, 22.3, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{28}NO_4$, 370.2013; found, 370.2017.

Ethyl (Z)-2-(4-(3-methylbenzyl)-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3b**): The title compound **3b** was prepared according to the general procedure **[II]** as sticky solid in 65% yield (25 mg, **3b**:**4b** = 96:04): Reaction time 8 h/35 ^{o}C; R_f 0.7 (ethyl acetate:pet. ether, 1:4).

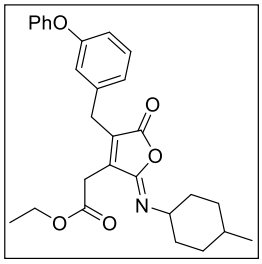


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.19 (t, *J* = 7.44 Hz, 1H), 7.08-6.98 (m, 3H), 4.11 (q, *J* = 7.19 Hz, 2H), 3.81-3.70 (m, 3H), 3.43 (s, 2H), 2.32 (s, 3H), 1.76 (m, 4H), 1.49-1.35 (m, 3H), 1.22 (t, *J* = 7.13 Hz, 3H), 1.08-0.98 (m, 2H), 0.90 (d, *J* = 6.50 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.04, 168.0, 149.9, 142.3, 138.5, 136.9, 135.9, 129.5, 128.7, 127.8, 125.8, 61.4, 57.9, 33.4, 33.3, 31.8, 30.2, 30.1, 22.3, 21.3, 14.0.

HRMS (ESI−TOF) m/z [M + H]+ calcd for $C_{23}H_{30}NO_4$, 384.2169; found, 384.2175.

Ethyl (Z)-2-(2-((4-methylcyclohexyl)imino)-5-oxo-4-(3-phenoxybenzyl)-2,5-dihydrofuran-3-yl)acetate (**3c**): The title compound **3c** was prepared according to the general procedure **[II]** as sticky solid in 60% yield (28 mg, **3c**:**4c** = 95:05); Reaction time 8 h/35 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:4).

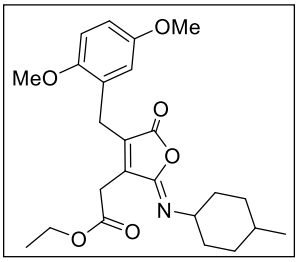


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38-7.32 (m, 2H), 7.27-7.22 (m, 1H), 7.15-7.08 (m, 1H), 7.02-6.94 (m, 3H), 6.93-6.88 (m, 1H), 6.88-6.84 (m, 1H), 4.11 (q, *J* = 6.87 Hz, 2H), 3.83-3.68 (m, 3H), 3.45 (s, 2H), 1.77-1.67 (m. 4H), 1.51-1.36 (m, 3H), 1.22 (t, *J* = 6.87 Hz, 3H), 1.08-1.0 (m, 2H), 0.91 (d, *J* = 6.87 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.8, 157.6, 156.8, 149.9, 142.6, 137.9, 136.4, 130.0, 129.8, 123.5, 123.4, 119.2, 118.9, 117.2, 61.5, 58.0, 33.4, 33.2, 31.7, 30.2, 30.1, 22.3, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{32}NO_5$, 462.2275; found, 462.2281.

Ethyl (Z)-2-(4-(2,5-dimethoxybenzyl)-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3d**): The title compound **3d** was prepared according to the general procedure **[II]** as sticky solid in 69% yield (30 mg, **3d**:**4d** = 99:01); Reaction time 8 h/35 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:4).

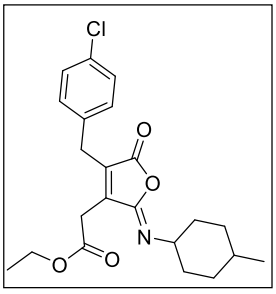


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.88 (d, *J* = 1.53 Hz, 1H), 6.76 (d, *J* = 2.29 Hz, 2H), 4.10 (q, *J* = 7.25 Hz, 2H), 3.76 (s, 3H), 3.76 (s, 3H), 3.73-3.69 (m, 3H), 3.51 (s, 2H), 1.74-1.8 (m, 4H), 1.46-1.37 (m, 3H), 1.22 (t, *J* = 7.25 Hz, 3H), 1.06-0.99 (m, 2H), 0.9 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 168.1, 153.5, 151.2, 150.0, 142.0, 136.5, 125.2, 117.0, 112.7, 111.1, 61.3, 57.8, 55.7, 33.4, 33.3, 31.8, 30.0, 29.7, 25.0, 22.4, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{32}NO_6$, 430.2224; found, 430.2230.

Ethyl (Z)-2-(4-(4-chlorobenzyl)-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3e**): The title compound **3e** was prepared according to the general procedure **[II]** as sticky solid in 62% yield (25 mg, **3e**:**4e** = 97:03); Reaction time 8 h/35 ^{o}C; R_f 0.6 (ethyl acetate:pet. ether, 1:4).

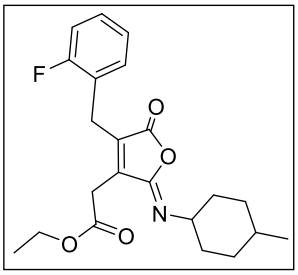


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (d, *J* = 8.25 Hz, 2H), 7.18 (d, *J* = 8.25 Hz, 2H), 4.12 (q, *J* = 7.13 Hz, 2H), 3.80-3.70 (m, 3H), 3.46 (s, 2H), 1.77-1.68 (m, 4H), 1.50-1.35 (m, 3H), 1.23 (t, *J* = 7.13 Hz, 3H), 1.07-1.0 (m, 2H), 0.9 (d, *J* = 6.50 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.8, 149.6, 142.6, 136.3, 134.4, 133.0, 130.1, 128.9, 61.6, 58.0, 33.4, 33.2, 31.8, 30.2, 29.6, 22.3, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}NO_4Cl$, 404.1623; found, 404.1627.

Ethyl (Z)-2-(4-(2-fluorobenzyl)-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3f**): The title compound **3f** was prepared according to the general procedure **[II]** as sticky solid in 66% yield (25.5 mg, **3f**:**4f** = 97:03); Reaction time 8 h/35 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:4).

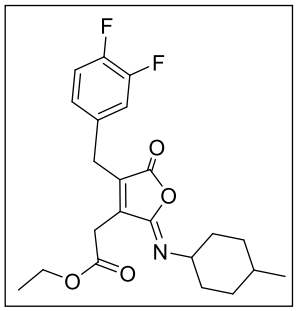


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37-7.32 (m, 1H), 7.27-7.22 (m, 1H), 7.12-7.07 (m, 1H), 7.06-7.00 (m, 1H), 4.12 (q, *J* = 7.13 Hz, 2H), 3.79 (s, 2H), 3.77-3.68 (m, 1H), 3.52 (s, 2H), 1.77-1.63 (m, 4H), 1.50-1.34 (m, 3H), 1.23 (t, *J* = 7.13 Hz, 3H), 1.07-0.97 (m, 2H), 0.9 (d, *J* = 6.50 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 167.7, 160.79 (d, *J* = 245.59 Hz), 149.7, 142.7, 135.6, 131.32 (d, *J* = 3.63 Hz), 129.01 (d, *J* = 7.99 Hz), 124.41 (d, *J* = 3.63 Hz), 122.9 (d, *J* = 15.26 Hz), 115.4 (d, *J* = 21.80 Hz), 61.4, 57.9, 33.4, 33.3, 31.8, 30.0, 23.6, 22.3, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}NO_4F$, 388.1919; found, 388.1921.

Ethyl (Z)-2-(4-(3,4-difluorobenzyl)-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3g**): The title compound **3g** was prepared according to the general procedure **[II]** as sticky solid in 63% yield (25.5 mg, **3g**:**4g** = 95:05); Reaction time 8 h/35 ^{o}C; R_f 0.6 (ethyl acetate:pet. ether, 1:4).

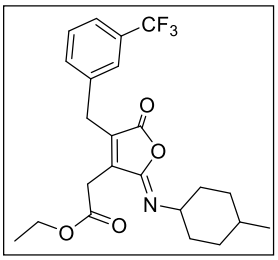


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.15-7.02 (m, 2H), 7.0-6.94 (m, 1H), 4.14 (q, *J* = 7.25 Hz, 2H), 3.80-3.73 (m, 1H), 3.72 (s, 2H), 3.49 (s, 2H), 1.75-1.68 (m, 4H), 1.50-1.36 (m, 3H), 3.87 (t, *J* = 7.25 Hz, 3H), 1.1 (m, 2H), 0.9 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.6, 150.25 (dd, *J* = 249.20, 12.46 Hz), 149.5, 149.48 (dd, *J* = 248.24, 12.46 Hz), 142.8, 135.9, 132.8 (dd, *J* = 8.63, 3.83 Hz), 124.82 (dd, *J* = 5.75, 3.83 Hz), 117.77 (d, *J* = 18.21 Hz), 117.5 (d, *J* = 17.25 Hz), 61.7, 58.1, 33.4, 33.2, 31.7, 30.2, 29.4, 22.3, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{26}NO_4F_2$, 406.1824; found, 406.1829.

Ethyl (Z)-2-(2-((4-methylcyclohexyl)imino)-5-oxo-4-(3-(trifluoromethyl)benzyl)-2,5-dihydrofuran-3-yl)acetate (**3h**): The title compound **3h** was prepared according to the general procedure **[II]** as sticky solid in 58% yield (25.3 mg, **3h**:**4h** = 98:02); Reaction time 8 h/35 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:4).

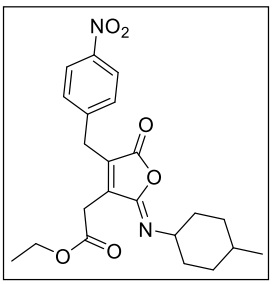


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 (d, *J* = 6.88 Hz, 1H), 7.49 (s, 1H), 7.48-7.40 (m, 2H), 4.12 (q, *J* = 7.13 Hz, 2H), 3.83 (s, 2H), 3.79-3.71 (m, 1H), 3.487 (s, 2H), 1.76-1.69 (m, 4H), 1.50-1.34 (m, 3H), 1.22 (t, *J* = 7.13 Hz, 3H), 1.09-0.98 (m, 2H), 0.90 (d, *J* = 6.50 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8, 167.7, 149.5, 142.9, 136.9, 135.8, 132.26, 132.25, 131.3, 129.3, 125.5 (q, *J* = 7.99 Hz), 124.01 (q, *J* = 7.27 Hz), 61.6, 58.1, 33.4, 33.2, 31.8, 30.2, 30.1, 22.3, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{27}F_3NO_4$, 438.1887; found, 438.1892.

Ethyl *(Z)*-2-(2-((4-methylcyclohexyl)imino)-4-(4-nitrobenzyl)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3i**): The title compound **3i** was prepared according to the general procedure **[II]** as sticky solid in 63% yield (26 mg, **3i**:**4i** = 96:04); Reaction time 8 h/35 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:4).

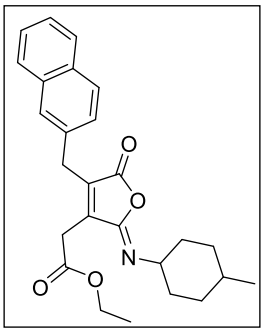


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18 (d, *J* = 8.63 Hz, 2H), 7.44 (d, *J* = 8.63 Hz, 2H), 4.14 (q, *J* = 7.13 Hz, 2H), 3.87 (s, 2H), 3.80-3.70 (m, 1H), 3.53 (s, 2H), 1.78-1.67 (m, 4H), 1.47-1.35 (m, 3H), 1.24 (t, *J* = 7.13 Hz, 3H), 1.09-0.99 (m, 2H), 0.9 (d, *J* = 6.50 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.5, 149.3, 147.1, 143.4, 143.3, 135.3, 129.7, 124.0, 61.8, 58.2, 33.4, 33.2, 31.8, 30.2, 30.1, 22.3, 14.1.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{27}N_2O_6$, 415.1864; found, 415.1867.

Ethyl (Z)-2-(2-((4-methylcyclohexyl)imino)-4-(naphthalen-2-ylmethyl)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3j**): The title compound **3j** was prepared according to the general procedure **[II]** as sticky solid in 56% yield (23.4 mg, **3j**:**4j** = 99:01); Reaction time 8 h/35 ^{o}C; R_f 0.6 (ethyl acetate:pet. ether, 1:4).

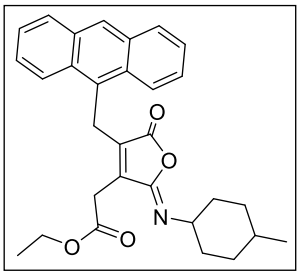


^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.83-7.75 (m, 3H), 7.68 (s, 1H), 7.51-7.43 (m, 2H), 7.35 (d, *J* = 8.38 Hz, 1H), 4.04 (q, *J* = 7.13 Hz, 2H), 3.94 (s, 2H), 3.80-3.72 (m, 1H), 3.47 (s, 2H), 1.78-1.68 (m, 4H), 1.50-1.36 (m, 3H), 1.15 (t, *J* = 7.13 Hz, 3H), 1.08-0.98 (m, 2H), 0.9 (d, *J* = 6.50 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 168.02, 168.01, 149.8, 142.6, 136.7, 133.5, 133.4, 132.4, 128.6, 127.64, 127.55, 127.4, 126.9, 126.3, 125.9, 61.4, 58.0, 33.4, 33.3, 31.8, 30.4, 30.2, 22.3, 14.0.

HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{30}NO_4$, 420.2169; found, 420.2177.

Ethyl (Z)-2-(4-(anthracen-9-ylmethyl)-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3k**): The title compound **3k** was prepared according to the general procedure **[II]** as sticky solid in 52% yield (24.3 mg, **3k**:**4k** = 98:02); Reaction time 8 h/35 ^{o}C; R_f 0.6 (ethyl acetate:pet. ether, 1:4).

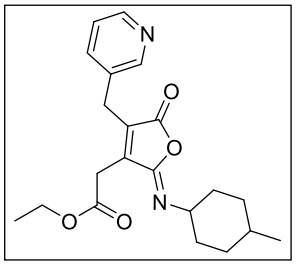


^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.48 (s, 1H), 8.11-8.01 (m, 4H), 7.56-7.45 (m, 4H), 4.78 (s, 2H), 3.80-3.70 (m, 1H), 3.44 (q, *J* = 7.25 Hz, 2H), 2.43 (s, 2H), 1.71-1.63 (m, 4H), 136-1.28 (m, 4H), 1.06-0.99 (m, 2H), 0.89-0.86 (m, 5H).

^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 168.6, 167.2, 150.0, 142.5, 136.1, 131.4, 130.2, 129.4, 127.8, 127.0, 126.6, 125.2, 123.9, 60.7, 57.9, 33.4, 33.3, 31.7, 28.9, 24.0, 22.3, 13.6.

HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{30}H_{32}NO_4$, 470.2326; found, 470.2330.

Ethyl (Z)-2-(2-((4-methylcyclohexyl)imino)-5-oxo-4-(pyridin-3-ylmethyl)-2,5-dihydrofuran-3-yl)acetate (**3l**): The title compound **3l** was prepared according to the general procedure **[II]** as sticky solid in 53% yield (20 mg, **3l**:**4l** = 96:04); Reaction time 8 h/35 ^{o}C; R_f 0.4 (ethyl acetate:pet. ether, 1:2).

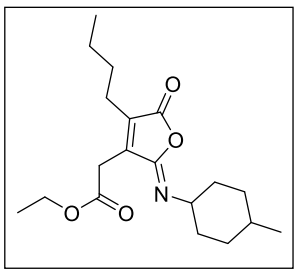


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.57 (m, 2H), 7.64-7.55 (m, 1H), 7.26-7.22 (m, 1H), 4.13 (q, *J* = 7.13 Hz, 2H), 3.77 (s, 2H), 7.76-3.70 (m, 1H), 3.51 (s, 2H), 1.75-1.67 (m, 4H), 1.49-1.34 (m, 3H), 1.23 (t, *J* = 7.25 Hz, 3H), 1.08-0.97 (m, 2H), 0.90 (d, *J* = 6.63 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 167.8, 167.6, 149.9, 149.5, 148.5, 142.9, 136.4, 135.7, 131.8, 123.6, 61.7, 58.1, 33.4, 33.2, 31.8, 30.20, 27.6, 22.3, 14;.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{27}N_2O_4$ 371.1970; found, 371.1966.

Ethyl (Z)-2-(4-butyl-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3m**): The title compound **3m** was prepared according to the general procedure **[II]** as sticky solid in 72% yield (26 mg, **3m**:**4m** = 98:02); Reaction time 8 h/35 ^{o}C; R_f 0.6 (ethyl acetate:pet. ether, 1:4).

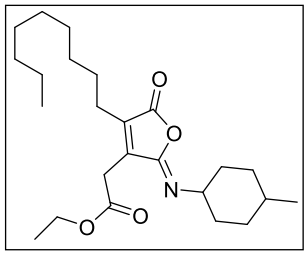


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.16 (q, *J* = 7.13 Hz, 2H), 3.8-3.7 (m, 1H), 3.51 (s, 2H), 2.39 (t, *J* = 7.69 Hz, 2H), 1.77-166 (m, 4H), 1.58-1.50 (m, 2H), 1.46-1.32 (m. 5H), 1.26 (t, *J* = 7.13 Hz, 3H), 1.10-0.98 (m, 2H), 0.95-0.87 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 168.1, 149.9, 141.6, 138.6, 61.4, 57.8, 33.5, 33.3, 31.8, 30.1, 29.7, 24.1, 22.6, 22.3, 14.1, 13.7.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{30}NO_4$, 336.2169; found, 336.2174.

Ethyl (Z)-2-(2-((4-methylcyclohexyl)imino)-4-nonyl-5-oxo-2,5-dihydrofuran-3-yl)acetate



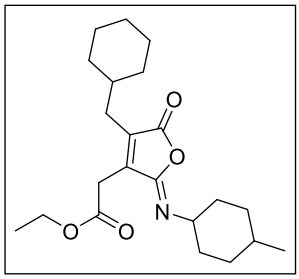
(**3n**): The title compound **3n** was prepared according to the general procedure **[II]** as sticky solid in 62% yield (25 mg, **3n**:**4n** = 98:02); Reaction time 8 h/35 ^{o}C; R_f 0.7 (ethyl acetate:pet. ether, 1:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.16 (q, *J* = 7.13 Hz, 2H), 3.39-3.67 (m, 1H), 3.51 (s, 2H), 2.39 (t, *J* = 7.75 Hz, 2H), 1.78-1.69 (m, 4H), 1.60-1.52 (m, 2H), 1.48-1.40 (m, 2H), 1.33-1.22 (m, 18H), 1.09-0.98 (m, 2H), 0.9-0.88 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 168.1, 149.9, 141.5, 138.6, 61.4, 57.8, 33.5, 33.3, 31.81, 31.79, 30.1, 29.5, 29.4, 29.24, 29.23, 27.6, 24.4, 22.62, 22.4, 14.08, 14.06.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{40}NO_4$, 406.2952; found, 406.2954.

Ethyl (Z)-2-(4-(cyclohexylmethyl)-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3o**): The title compound **3o** was prepared according to the general procedure **[II]** as sticky solid in 63% yield (24 mg, **3o**:**4o** = 96:04); Reaction time 8 h/35 ^{o}C; R_f 0.7 (ethyl acetate:pet. ether, 1:4).

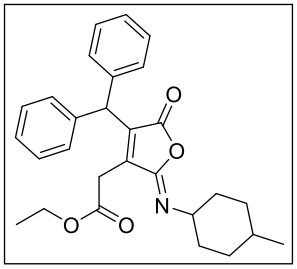


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.16 (q, *J* = 6.87 Hz, 2H), 3.79-3.67 (m, 1H), 3.50 (s, 2H), 2.29 (d, *J* = 6.87 Hz, 2H), 1.81-1.57 (m, 12H), 1.50-1.35 (m, 3H), 1.26-1.23 (m, 4H), 1.21-1.15 (m, 2H), 1.05-0.97 (m. 2H), 0.91 (d. *J* = 6.10 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 149.8, 142.4, 137.5, 61.4, 57.8, 36.8, 33.5, 33.3, 33.2, 31.9, 31.8, 30.4, 26.1, 26.0, 22.4, 14.1.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{34}NO_4$, 376.2482; found, 376.2487.

Ethyl (Z)-2-(4-benzhydryl-2-((4-methylcyclohexyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3q**): The title compound **3q** was prepared according to the general procedure **[II]** as sticky solid in 56% yield (25 mg, **3q**:**4q** = 96:04); Reaction time 8 h/35 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:4).

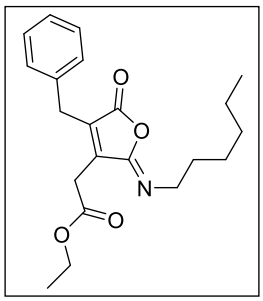


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35-7.28 (m, 6H), 7.20 (d, *J* = 7.25 Hz, 4H), 5.48 (s, 1H), 4.03 (q, *J* = 7.25 Hz, 2H), 3.80-3.70 (m, 1H), 3.09 (s, 2H), 1.77-1.67 (m, 4H), 1.47-1.37 (m, 3H), 1.20 (t, *J* = 7.25 Hz, 3H), 1.08-0.98 (m, 2H), 0.9 (d, *J* = 6.49 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.1, 167.5, 149.9, 143.1, 139.0, 138.7, 128.9, 128.8, 127.4, 61.23, 57.9, 47.7, 33.4, 33.3, 31.8, 30.0, 22.3, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{32}NO_4$, 446.2331; found, 446.2329.

Ethyl (Z)-2-(4-benzyl-2-(hexylimino)-5-oxo-2,5-dihydrofuran-3-yl)acetate (**3r**): The title compound **3r** was prepared according to the general procedure **[II]** as sticky solid in 49% yield (17.4 mg, **3r**:**4r** = 84:16); Reaction time 8 h/35 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:4).

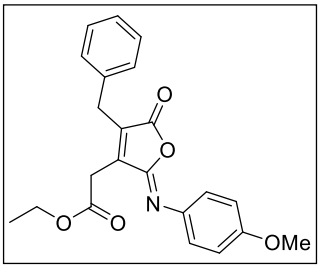


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37-7.27 (m, 2H), 7.27-7.17 (m, 3H), 4.12 (q, *J* = 7.63, 2H), 3.78 (s, 2H). 3.57 (*J* = 7.63 Hz, 2H), 3.44 (s, 2H), 1.65-1.52 (m, 2H), 1.32-1.27 (m, 6H), 1.22 (t, *J* = 6.87 Hz, 3H), 0.88 (t, *J* = 6.87 Hz, 3H);).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 167.8, 151.0, 142.1, 137.0, 135.9, 128.82, 128.75, 127.1, 61.5, 49.3, 31.5, 30.31, 30.27, 30.1, 29.7, 27.0, 22.6, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{28}NO_4$, 358.2018; found, 358.2023.

Ethyl (Z)-2-(4-benzyl-2-((4-methoxyphenyl)imino)-5-oxo-2,5-dihydrofuran-3-yl)acetate



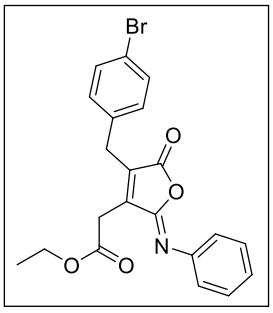
(**3w**): The title compound **3w** was prepared according to the general procedure [**II**]. The obtained mixture of products (**3w**:**4w** = 33:67, 68% yield) was purified to isolate **3w** as white solid in 23% yield (8.7 mg); Reaction time 8 h/35 ^{o}C; R_f 0.6 (ethyl acetate:pet. ether, 1:4); mp: 116-118 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) of pure isomaleimide **3w** δ (ppm) 7.47 (dd, J = 9.13, 2.25 Hz, 2H), 7.34-7.28 (m, 2H), 7.27-7.22 (m, 3H), 6.88 (dd, J = 9.13, 2.25 Hz, 2H), 4.14 (q, J = 7.13 Hz, 2H), 3.82 (s, 5H), 3.56 (2H), 1.23 (t, J = 7.13, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.2, 168.1, 158.9, 148.0, 143.4, 136.5, 136.0, 135.9, 128.9, 128.8, 127.9, 127.1, 114.1, 61.6, 55.4, 30.4, 30.3, 14.1.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}NO_5$, 380.1497; found, 380.1490.

Ethyl (Z)-2-(4-(4-bromobenzyl)-5-oxo-2-(phenylimino)-2,5-dihydrofuran-3-yl)acetate (**3ai**):



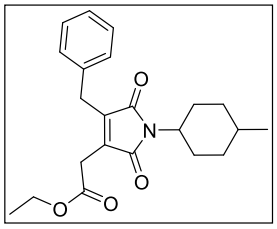
The title compound **3ai** was prepared according to the general procedure [**II**]. The obtained mixture of products (**3ai**:**4ai** = 24:76, 66% yield) was purified to isolate **3ai** as white solid in 17% yield (8 mg); Reaction time 8 h/35 ^{o}C; R_f 0.6 (ethyl acetate:pet. ether, 1:4); mp: 80-82 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) of pure isomaleimide **3ai** δ (ppm) 7.47 (m, 2H), 7.41-7.33 (m, 4H), 7.25-7.21 (1H), 7.17-7.13 (m, 2H), 4.17 (q, J = 7.13 Hz, 2H), 3.79 (s, 2H), 3.61 (s, 2H), 1.26 (J = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 167.7, 149.5, 143.4, 143.3, 136.4, 134.7, 132.0, 130.6, 128.9, 127.0, 124.9, 121.2, 61.8, 30.2, 29.9, 14.1.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}BrNO_4$, 428.0497; found, 428.0493.

Ethyl 2-(4-benzyl-1-(4-methylcyclohexyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate



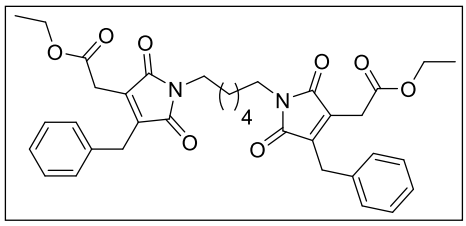
(**4a**): The title compound **4a** was prepared according to the experimental procedure **[VIIC]** as sticky solid in 90% yield (18 mg), Reaction time 4 h/120 ^{o}C; R_f 0.6 (ethyl acetate:pet. ether, 1:4).

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.34-7.27 (m, 2H), 7.27-7.17 (m, 3H), 4.11 (q, *J* = 6.87 Hz, 2H), 3.92-3.82 (m, 1H), 3.76 (s, 2H), 3.28 (s, 2H), 2.15-2.03 (m, 2H), 1.76 (m, 2H), 1.64-1.62 (m, 2H), 1.46-1.37 (m, 1H), 1.22 (t, *J* = 6.87 Hz, 3H), 1.07-0.95 (m, 2H), 0.9 (d, *J* = 6.10 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 171.3, 171.1, 168.5, 141.4, 136.25, 133.3, 128.9, 128.8, 126.9, 61.5, 50.9, 34.4, 31.5, 30.0, 29.6, 28.8, 22.2, 14.0.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{28}NO_4$, 370.2018; found, 370.2010.

Diethyl 2,2'-(hexane-1,6-diylbis(4-benzyl-2,5-dioxo-2,5-dihydro-1H-pyrrole-1,3-diyl))



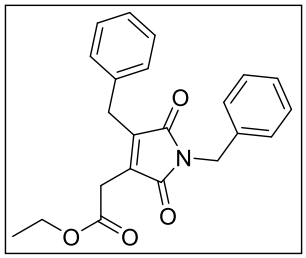
diacetate (**4s**): The general procedure **[II]** provided inseparable mixture of **3s** and **4s** (**3s**:**4s** = 57:43), hence for the characterization purpose the mixture was refluxed in acetic acid to obtain pure maleimide **4s** as sticky solid in 48% yield (30 mg). Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.3

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.33-7.27 (m, 4H), 7.26-7.18 (m, 6H), 4.11 (q, *J* = 6.75 Hz, 4H), 3.78 (s, 4H), 3.48 (t, *J* = 7.0 Hz, 4H), 3.31 (s, 4H), 1.60-1.53 (m, 4H), 1.32-1.27 (m, 4H), 1.24 (t, *J* = 6.75 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 171.3, 171.1, 168.4, 141.7, 136.2, 133.6, 128.9, 128.8, 127.0, 61.5, 38.1, 30.0, 28.9, 28.4, 26.2, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{41}N_2O_8$, 629.2862; found, 629.2863.

Ethyl 2-(1,4-dibenzyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4t**): The general procedure **[II]** provided inseparable mixture of **3t** and **4t** (**3t**:**4t** = 75:25), hence for the characterization purpose the mixture was refluxed in acetic acid to obtain pure maleimide **4t** as sticky solid in 61% yield (22 mg). Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.4 (ethyl acetate:pet. ether, 1:4).

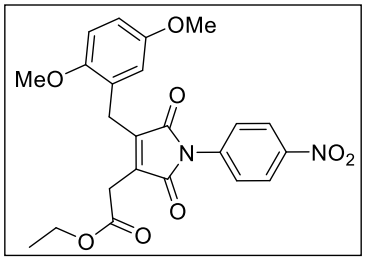


^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.36-7.27 (m, 6H), 7.26-7.28 (m, 4H), 4.66 (s, 2H), 4.09 (q, *J* = 7.25 Hz, 2H), 3.78 (s, 2H), 3.30 (s, 2H), 1.20 (t, *J* = 7.25 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 171.0, 170.8, 168.3, 142.0, 136.3 136.0, 133.9, 128.9, 128.8, 128.6, 128.4, 127.8, 127.0, 61.5, 41.8, 30.1, 28.9, 14.0.

HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{22}NO_4$, 364.1548; found, 364.1542.

Ethyl 2-(4-benzyl-2,5-dioxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4u**): The title compound **4u** was prepared according to the procedure **[V]** as white solid in 65% yield (22.6 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.5 (ethyl acetate:pet. ether, 1:4); mp: 78-80 ^{o}C.

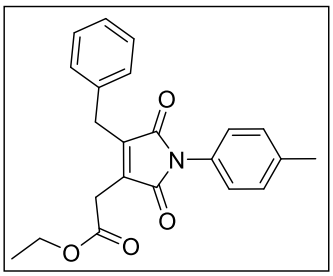


^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.46-7.39 (m, 2H), 7.39-7.28 (m, 5H), 7.28-7.21 (m, 3H), 4.13 (q, *J* = 7.25 Hz, 2H), 3.86 (s, 2H), 3.40 (s, 2H), 1.23 (t, *J* = 7.23 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 170.0, 169.8, 168.2, 142.0, 135.9, 133.8, 131.6, 128.93, 128.92, 128.8, 127.5, 127.1, 125.6, 61.6, 30.1, 29.0, 14.0.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{20}NO_4$, 350.1392; found, 350.1397.

Ethyl 2-(4-benzyl-2,5-dioxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4v**): The title compound **4v** was prepared according to the general procedure **[III]** as white solid in 59% yield (21 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.5 (ethyl acetate:pet. ether, 1:4); mp: 85-87 ^{o}C.

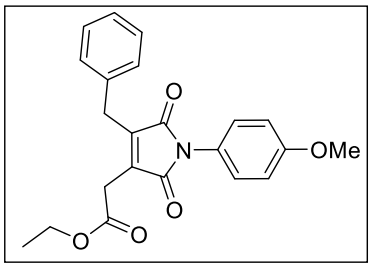


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.5-7.1 (m, 9H), 4.15 (q, J = 7.25 Hz, 2H), 3.88 (s, 2H), 3.41 (s, 2H), 2.38 (s, 3H), 1.25 (t, J = 7.25 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.2, 170.0, 168.3, 142.0, 137.6, 136.0, 133.8, 129.6, 129.0, 128.9, 127.1, 125.6, 61.6, 30.2, 29.0, 21.1, 14.0.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}NO_4$, 364.1549; found, 364.1549.

Ethyl 2-(4-benzyl-1-(4-methoxyphenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4w**): The title compound **4w** was prepared according to the general procedure **[III]** as white solid in 68% yield (25.7 mg); Reaction time 8 h/35 ^{o}C; R_f 0.4 (ethyl acetate:pet. ether, 1:4); mp: 129-131 ^{o}C.

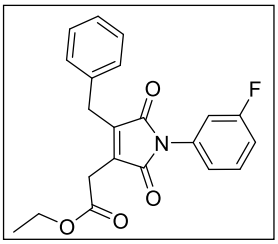


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36-7.30 (m, 2H), 7.30-7.22 (m, 5H), 6.97 (d, J = 6.97 Hz, 2H), 4.15 (q, J = 7.25 Hz, 2H), 3.87 (s, 2H), 3.83 (s, 3H), 3.41 (s, 2H), 1.25 (t, J = 7.25 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.3, 170.1, 168.3, 158.4, 142.0, 135.9, 133.7, 129.0, 128.9, 127.2, 127.1, 124.2, 114.3, 61.6, 55.4, 30.1, 29.0, 14.0.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}NO_5$, 380.1497; found, 380.1497.

Ethyl 2-(4-benzyl-1-(3-fluorophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4x**):



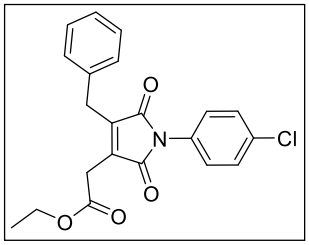
The title compound **4x** was prepared according to the general procedure **[III]** as white solid in 60% yield (22 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.4 (ethyl acetate:pet. ether, 1:4); mp: 75-77 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44-7.37 (m, 1H), 7.35-7.30 (m, 2H), 7.30-7.22 (m, 4H), 7.22-7.17 (m, 1H), 7.07-7.02 (m, 1H), 4.15 (q, *J* = 7.15 Hz, 2H), 3.88 (s, 2H), 3.42 (s, 2H), 1.25 (t, *J* = 7.15 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.6, 169.4, 168.1, 152.6 (d, *J* = 246.32), 142.2, 135.7, 134.0, 133.03 (d, *J* = 10.17 Hz), 130.07 (d, *J* = 9.45 Hz), 128.97, 128.95, 120.87 (d, *J* = 3.63 Hz), 114.41 (d, *J* = 21.07 Hz), 112.85 (d, *J* = 24.70 Hz), 61.7, 30.2, 29.0, 14.0.

HRMS (ESI−TOF) m/z: [M + H]+ calcd for $C_{21}H_{19}FNO_4$, 368.1298; found, 368.1306.

Ethyl 2-(4-benzyl-1-(4-chlorophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4y**):



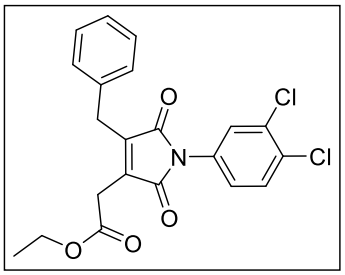
The title compound **4y** was prepared according to the general procedure **[III]** as pale yellow solid in 66% yield (25 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.4 (ethyl acetate:pet. ether, 1:4); mp: 72-74 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45-7.39 (m, 2H), 7.37-7.34 (m, 2H), 7.34-7.23 (m, 5H), 4.16 (q, *J* = 7.25 Hz, 2H), 3.88 (s, 2H), 3.42 (s, 2H), 1.25 (t, *J* = 7.25 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.7, 169.5, 168.2, 142.2, 135.7, 134.0, 133.2, 130.2, 129.2, 129.0, 128.9, 127.2, 126.7, 61.7, 30.2, 29.0, 14.0.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}ClNO_4$, 384.1002; found, 384.0998.

Ethyl 2-(4-benzyl-1-(3,4-dichlorophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4z**):



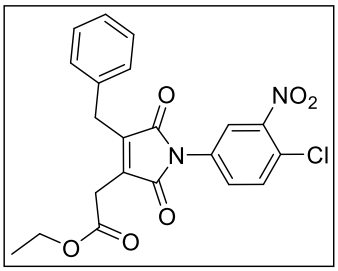
The title compound **4z** was prepared according to the general procedure **[III]** as sticky solid in 70% yield (29 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.5 (ethyl acetate:pet. ether, 1:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (d, J = 2.38 Hz, 1H), 7.52 (d, J = 8.63 Hz, 1H), 7.35-7.30 (m, 3H), 7.30-7.24 (m, 3H), 4.16 (q, J = 7.13 Hz, 2H), 3.87 (s, 2H), 3.42 (s, 2H), 1.26 (t, J = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.4, 169.2, 168.1, 142.4, 135.6, 134.2, 132.9, 131.5, 131.1, 130.6, 129.0, 128.9, 127.3, 127.0, 124.4, 61.8, 30.2, 29.0, 14.1.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}Cl_2NO_4$, 418.0612; found, 418.0620.

Ethyl 2-(4-benzyl-1-(4-chloro-3-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate



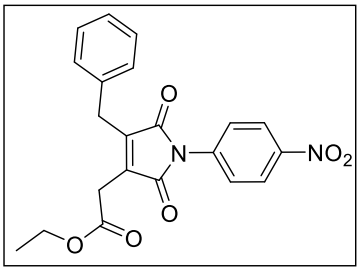
(**4aa**): The title compound **4aa** was prepared according to the general procedure **[III]** as pale yellow solid in 59% yield (25 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.4 (ethyl acetate:pet. ether, 1:4); mp: 79-81 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (d, J = 2.38 Hz, 1H), 7.72 (dd, J = 2.38, 8.76 Hz, 1H), 7.62 (d, J = 8.76 Hz, 1H), 7.37-7.31 (m, 2H), 7.321-7.24 (m, 3H), 4.17 (q, J = 7.13 Hz, 2H), 3.89 (s, 2H), 3.44 (s, 2H), 1.27 (t, J = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.0, 168.8, 167.9, 142.7, 135.4, 134.5, 132.2, 131.3, 129.0, 129.0, 128.9, 127.4, 125.3, 121.7, 61.9, 30.3, 29.1, 14.1.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}ClN_2O_6$, 429.0853; found, 429.0857.

Ethyl 2-(4-benzyl-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (4ab):



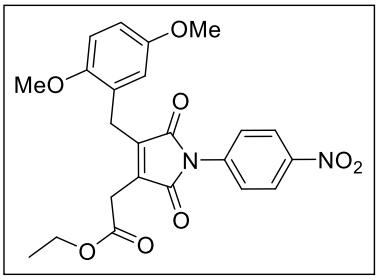
The title compound **4ab** was prepared according to the general procedure **[III]** as pale yellow solid in 68% yield (27 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.4 (ethyl acetate:pet. ether, 1:4); mp: 95-97 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (dd, *J* = 9.2, 2.13 Hz, 2H), 7.72 (dd, *J* = 9.2, 2.13 Hz, 2H), 7.37-7.31 (m, 2H), 7.30-7.23 (m, 3H), 4.17 (q, *J* = 7.13 Hz, 2H), 3.90 (s, 2H), 3.45 (s, 2H), 1.27 (t, *J* = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.2, 169.0, 168.0, 145.9, 142.7, 137.5, 135.4, 134.5, 129.0, 129.0, 127.3, 124.9, 124.4, 61.8, 30.2, 29.1, 14.1.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_6$, 395.1243; found, 395.1235.

Ethyl 2-(4-(2,5-dimethoxybenzyl)-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4ac**): The title compound **4ac** was prepared according to the general procedure **[III]** as pale yellow solid in 65% yield (29.5 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.3 (ethyl acetate:pet. ether, 1:4); mp: 93-95 ^{o}C.

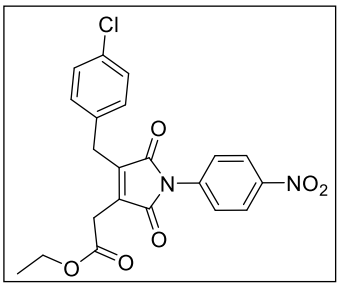


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (d, *J* = 9.26 Hz, 2H), 7.72 (d, *J* = 9.26 Hz, 2H), 6.94-6.90 (m, 1H), 6.80-6.77 (m, 2H), 4.17 (q, *J* = 7.25 Hz, 2H), 3.83 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.53 (s, 2H), 1.27 (t, *J* = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.2, 168.3, 153.6, 151.4, 145.8, 142.4, 137.7, 134.2, 124.9, 124.5, 124.4, 117.4, 112.9, 111.3, 61.6, 55.76, 55.70, 29.0, 25.1, 14.1.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}N_2O_8$, 455.1454; found, 455.1444.

Ethyl 2-(4-(4-chlorobenzyl)-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate



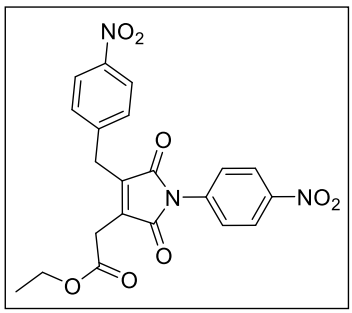
(**4ad**): The title compound **4ad** was prepared according to the general procedure **[III]** as sticky solid in 70% yield (30 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.5 (ethyl acetate:pet. ether, 1:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.32 (dd, *J* = 7.17, 2.20 Hz, 2H), 7.71 (dd, *J* = 7.17, 2.20 Hz, 2H), 7.35-7.27 (m, 2H), 7.26-7.18 (, 2H), 4.18 (q, *J* = 7.17 Hz, 2H), 3.87 (s, 2H), 3.48 (s, 2H), 1.28 (t, *J* = 7.17 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.0, 168.8, 167.9, 145.9, 142.2, 137.4, 134.7, 133.9, 133.3, 130.3, 129.1, 125.0, 124.4, 61.9, 29.6, 29.1, 14.0.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}ClN_2O_6$, 429.0853; found, 429.0873.

Ethyl 2-(4-(4-nitrobenzyl)-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate



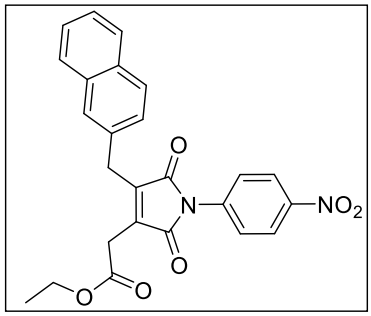
(**4ae**): The title compound **4ae** was prepared according to the general procedure **[II]** as yellow solid in 58% yield (25.5 mg, **3ae**:**4ae** = **4ae** >99); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.4 (ethyl acetate:pet. ether, 1:4); mp: 104-106 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (d, *J* = 9.16 Hz, 2H), 8.19 (d, *J* = 8.39 Hz, 2H), 7.70 (d, *J* = 9.16 Hz, 2H), 7.49 (d, *J* = 8.39 Hz, 2H), 4.20 (d, *J* = 7.25 Hz, 2H), 4.0 (s, 2H), 3.55 (s, 2H), 1.28 (t, *J* = 7.63 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.7, 168.5, 167.8, 147.2, 146.0, 142.9, 141.1, 137.2, 135.5, 129.9, 125.0, 124.4, 124.1, 62.1, 30.0, 29.2, 14.1.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_8$, 440.1093; found, 440.1097.

Ethyl 2-(4-(naphthalen-2-ylmethyl)-1-(4-nitrophenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4af**): The title compound **4af** was prepared according to the general procedure **[II]** as pale yellow solid in 53% yield (23.5 mg, **3af**:**4af** = **4af** >99); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.4 (ethyl acetate:pet. ether, 1:4); mp:112-114 ^{o}C.

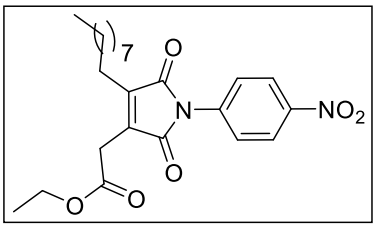


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (dd, J = 9.26, 2.13 Hz, 2H), 7.85-7.77 (m, 3H), 7.76-7.70 (m, 3H), 7.52-7.46 (m, 2H), 7.40-7.35 (m, 1H), 4.10 (q, J = 7.13 Hz, 2H), 4.07 (s, 2H), 3.47 (s, 2H), 1.18 (t, J = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.2, 169.0, 168.0, 145.9, 142.7, 137.5, 134.7, 133.5, 132.8, 132.4, 128.9, 127.72, 127.70, 127.5, 126.9, 126.5, 126.1, 125.0, 124.4, 61.8, 30.4, 29.1, 14.0.

HRMS (ESI−TOF) m/z: $[M]^+$ calcd for $C_{25}H_{20}N_2O_6$, 444.1321; found, 444.1320.

Ethyl 2-(1-(4-nitrophenyl)-4-nonyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4ah**): The title compound **4ah** was prepared according to the general procedure **[III]** as sticky solid in 47% yield (20 mg); Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.5 (ethyl acetate:pet. ether, 1:4).

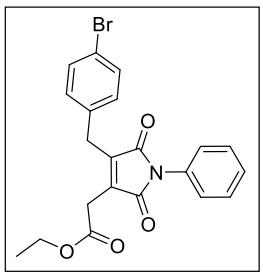


^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.32 (d, J = 9.16 Hz, 2H), 7.74 (d, J = 9.16 Hz, 2H), 4.23 (q, J = 6.87 Hz, 2H), 3.55 (s, 2H), 2.52 (t, J = 7.63 Hz, 2H), 1.65-1.58 (m, 2H), 1.33-1.27 (m, 12H), 0.89 (t, J = 6.48 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 169.3, 169.0, 168.2, 145.9, 145.0, 137.7, 133.9, 125.0, 124.4, 61.8, 31.8, 29.6, 29.4, 29.2, 29.2, 28.1, 24.4, 22.6, 14.11, 14.07.

HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{23}H_{31}N_2O_6$ 431.2182, found 431.2173.

Ethyl 2-(4-(4-bromobenzyl)-2,5-dioxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4ai**):



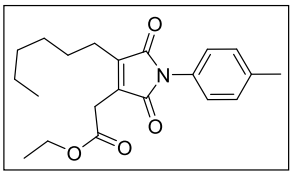
The title compound **4ai** was prepared according to the general procedure **[III]** as white solid in 66% yield (31 mg); Reaction time 8 h/35 ^{o}C; R_f 0.5 (ethyl acetate:pet. ether, 1:4); mp: 98-100 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50-7.41 (m, 4H), 7.40-7.32 (m, 3H), 7.20-7.17 (m, 2H), 4.16 (q, *J* = 7.13 Hz, 2H), 3.83 (s, 2H), 3.45 (s, 2H), 1.27 (t, *J* = 7.13 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.9, 169.6, 168.2, 141.4, 134.9, 134.1, 132.0, 131.5, 130.7, 129.0, 127.7, 125.7, 121.1, 61.8, 29.6, 29.1, 14.1.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}BrNO_4$, 428.0497; found, 428.0498.

Ethyl 2-(4-hexyl-2,5-dioxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrol-3-yl)acetate (**4aj**): The general procedure **[VIIIA]** provided a mixture of **3aj**:**4aj** (16:84, 43 mg). Reaction time 8 h/35 ^{o}C. This mixture was used as such for the next reaction. However, for the characterization purpose pure maleimide **4aj** (yellow oil) was prepared by using procedure **[III]**, Reaction time 8 h/35 ^{o}C (toluene); followed by 4 h/120 ^{o}C (AcOH); R_f 0.7 (ethyl acetate:pet. ether, 1:4).

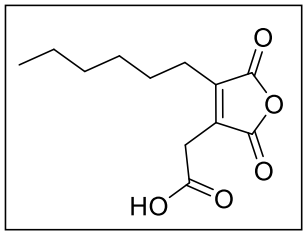


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27-7.20 (m, 4H), 4.21 (q, *J* = 7.13 Hz, 2H), 3.52 (s, 3H), 2.49 (t, *J* = 7.88 Hz, 2H), 2.38 (s, 3H), 1.62-1.57 (m, 2H), 1.37-1.26 (m, 9H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.3, 170.0, 168.6, 144.2, 137.5, 133.0, 129.6, 129.1, 125.7, 61.6, 31.4, 29.3, 29.1, 28.1, 24.3, 22.5, 21.1, 14.1, 14.0.

ESI-MS $(M+H)^+$ 358.1. Known compound.[13b]

2-(4-Hexyl-2,5-dioxo-2,5-dihydrofuran-3-yl)acetic acid (**Aspergillus FH-X-213**): The title compound was prepared according to the general procedure **[VIIIB]** as thick oil starting from the mixture of compounds obtained from procedure **[VIIIA]** in 45% yield (over two steps, 22 mg); R_f 0.4 (ethyl acetate:pet. ether, 1:1).



^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.57 (s, 2H), 2.50 (t, J = 7.88 Hz, 2H), 1.61 (quintet, J = 7.75 Hz, 2H), 1.36-1.28 (m, 6H), 0.89 (t, J = 6.88 Hz, 3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.0, 165.1 (2 carbons), 148.0, 135.5, 31.3, 29.13, 23.05, 27.5, 24.9, 22.4, 14.0.

HRMS (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{17}O_5$, 241.1075; found, 241.1088. Known compound.[13b]

3.2.9. References

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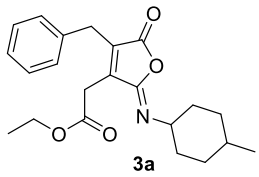
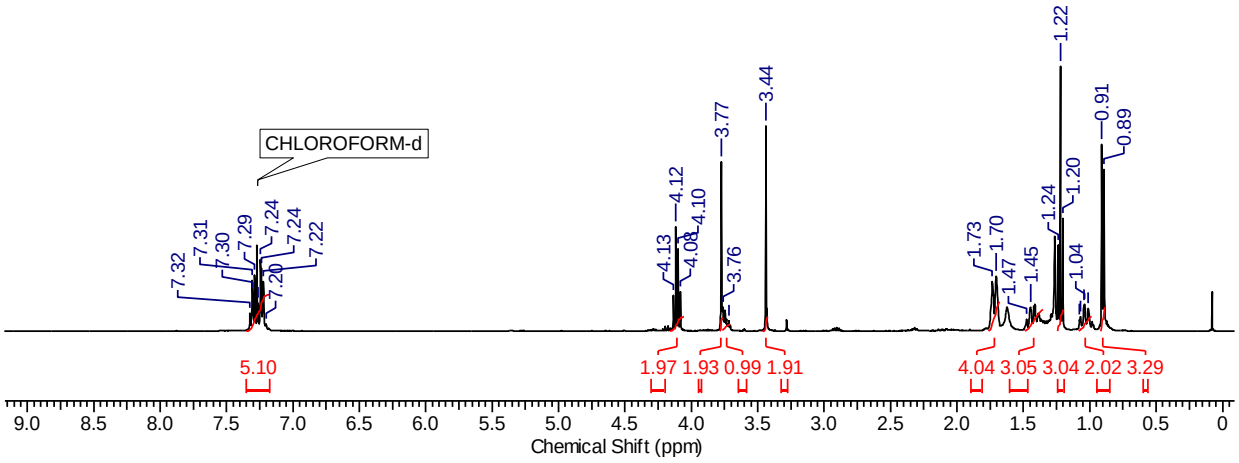
3.2.10. Selected ^{1}H, and ^{13}C spectra

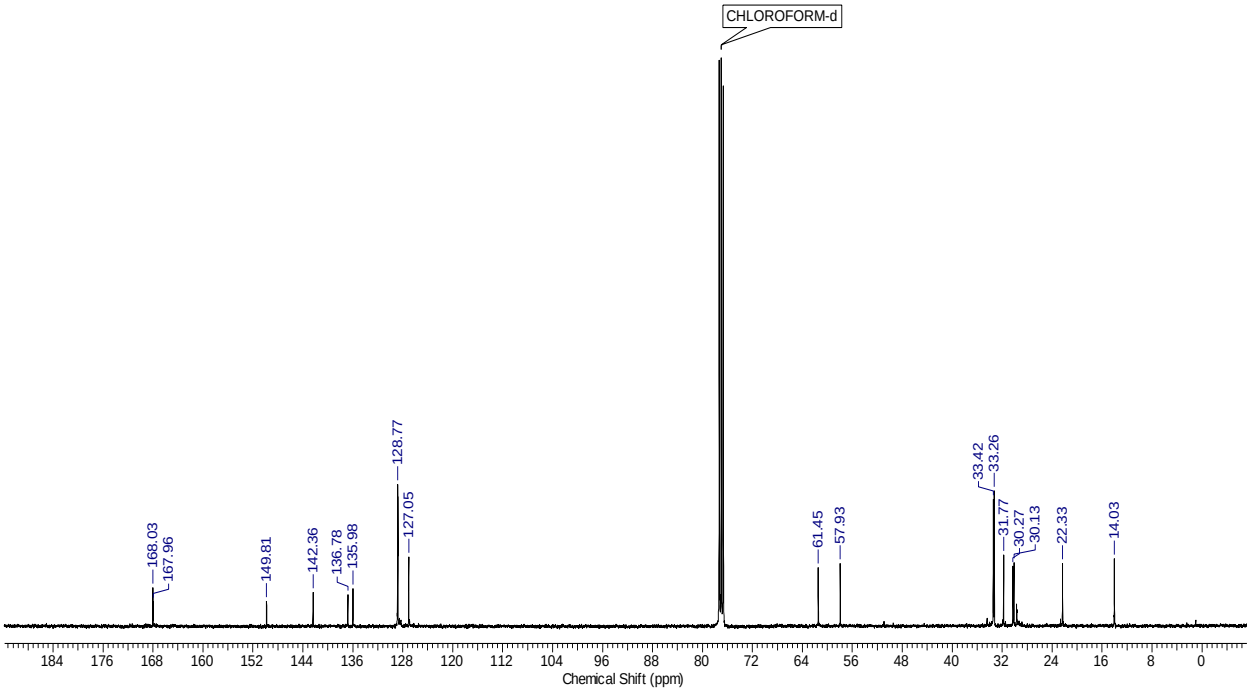
^{1}H, 400 MHz, $CDCl_3$

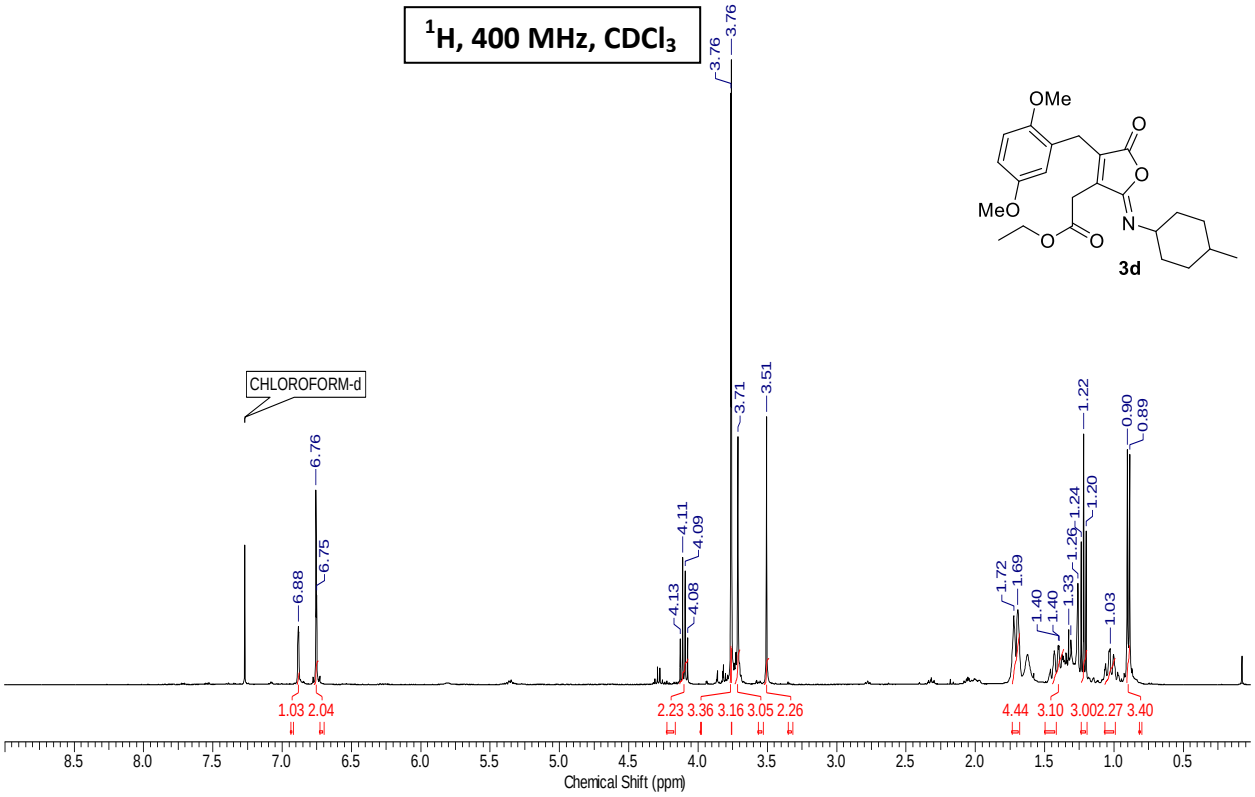


3a



^{13}C, 100 MHz, $CDCl_3$

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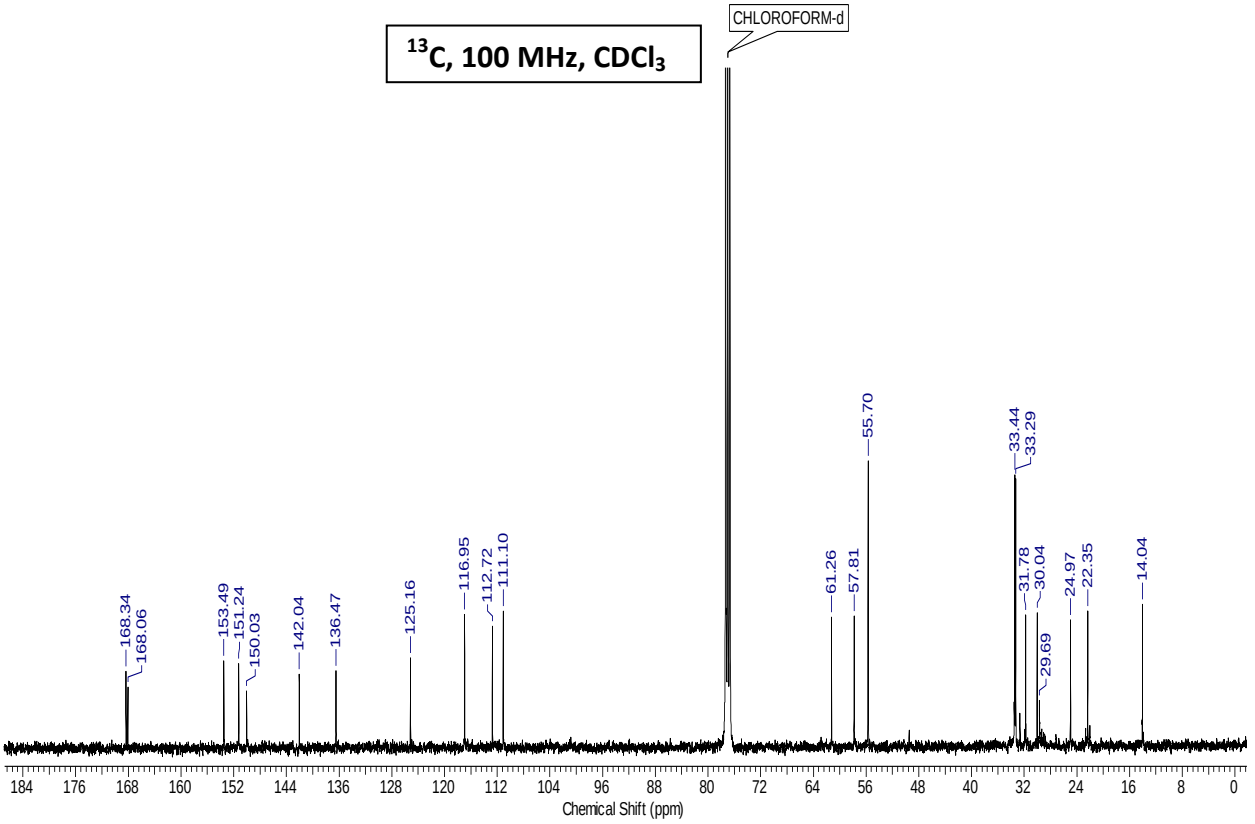
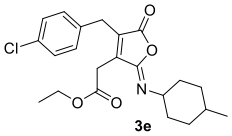
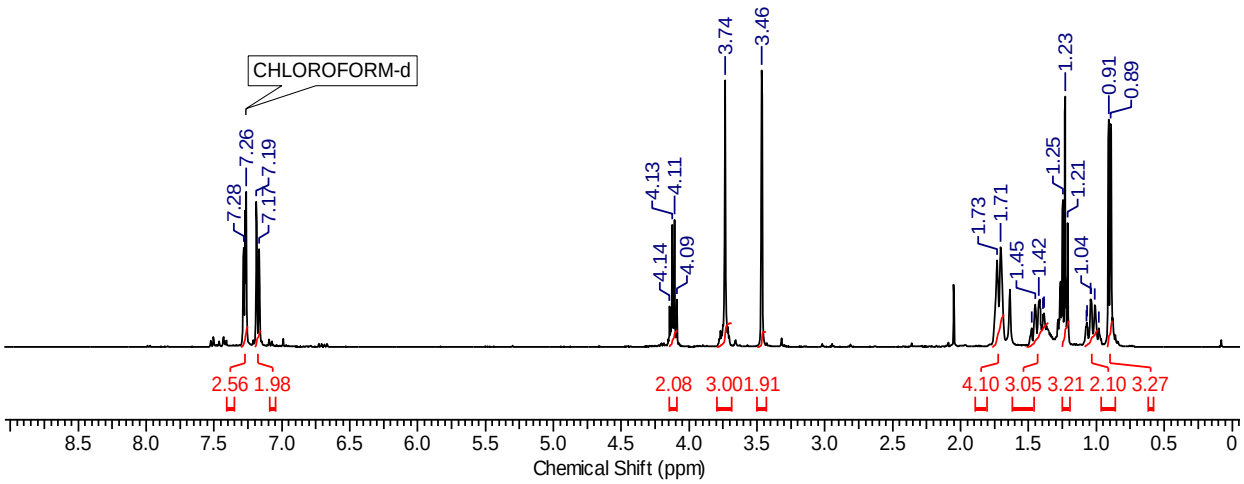
3d
CHLOROFORM-d
Chemical Shift (ppm)

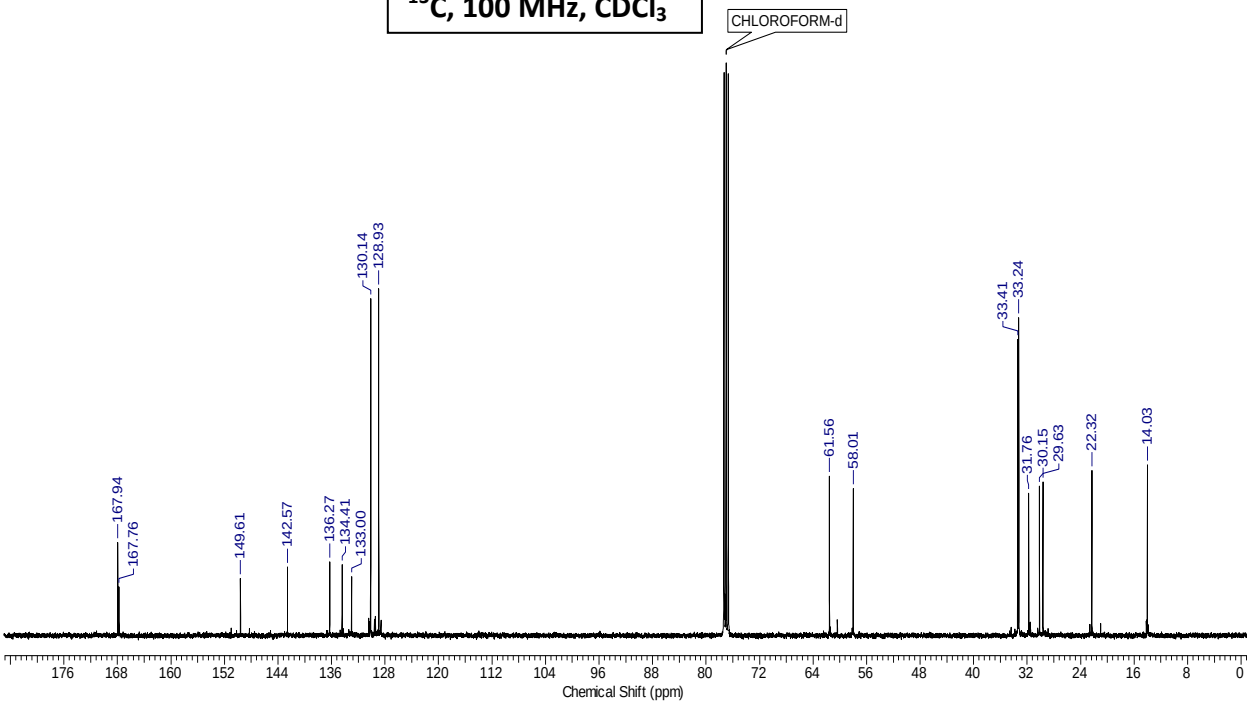

^{13}C, 100 MHz, CDCl$_3$
CHLOROFORM-d
Chemical Shift (ppm)

^{1}H, 400 MHz, $CDCl_3$





^{13}C, 100 MHz, $CDCl_3$



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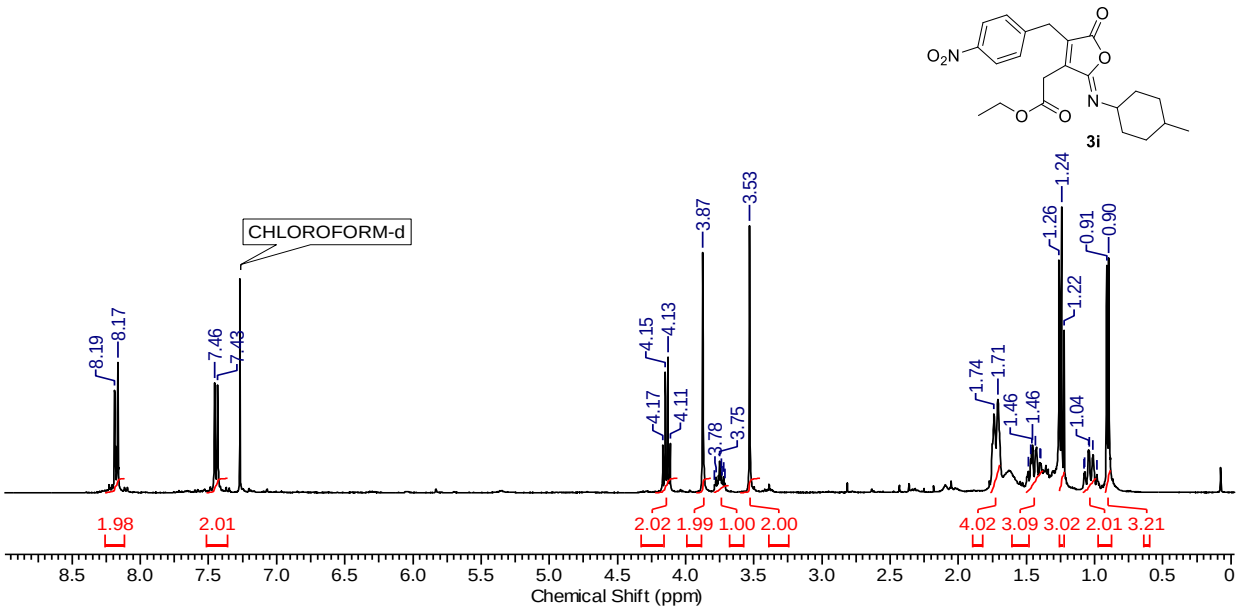

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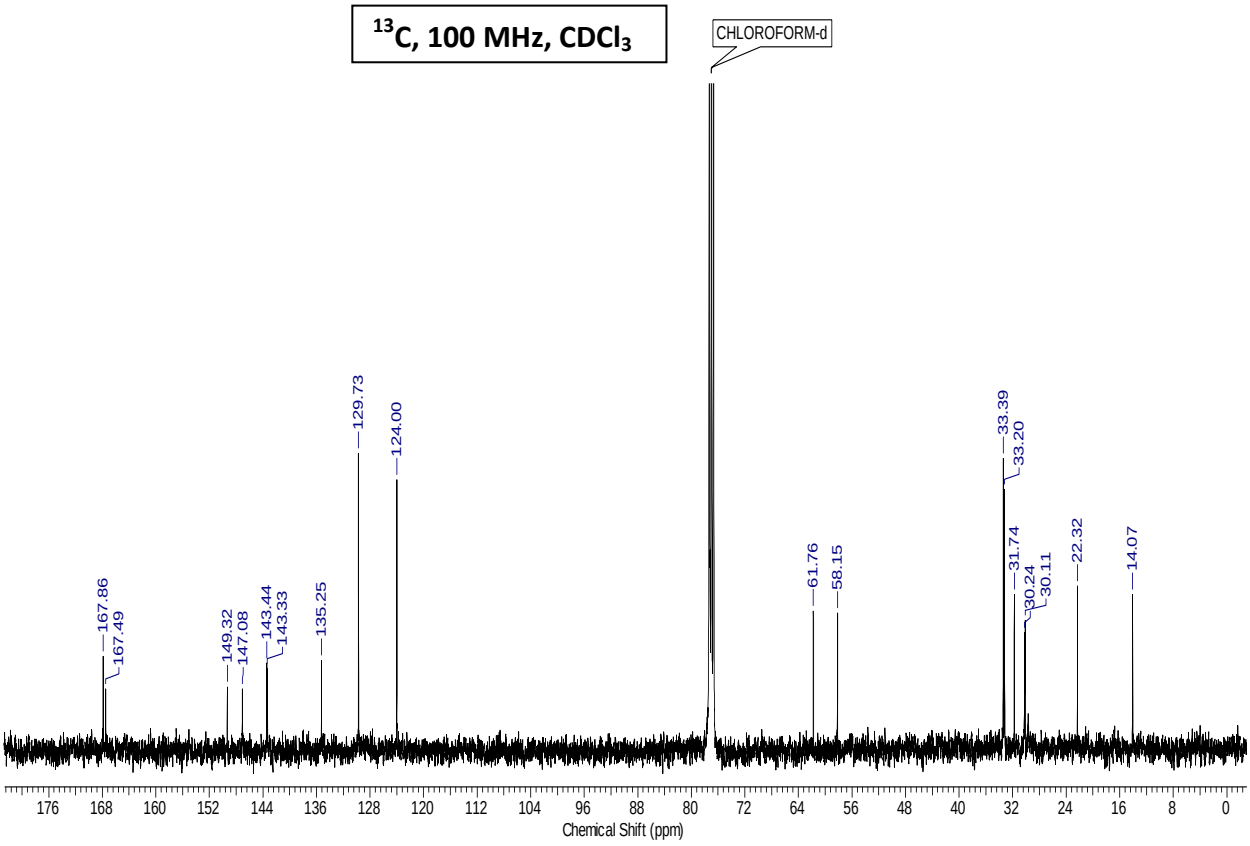

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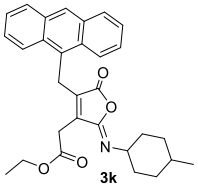

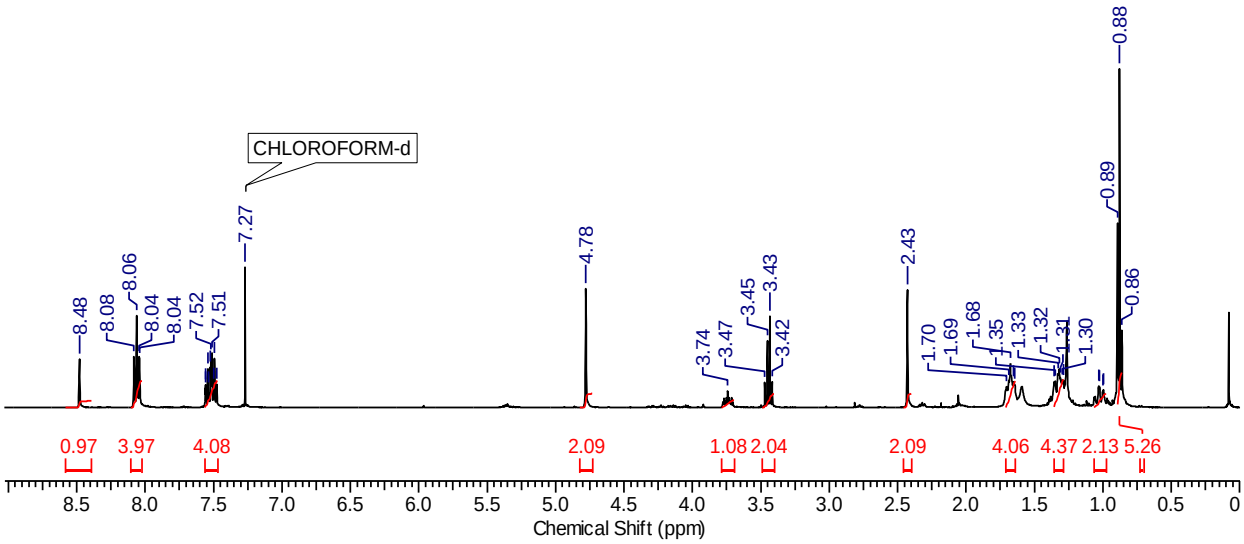

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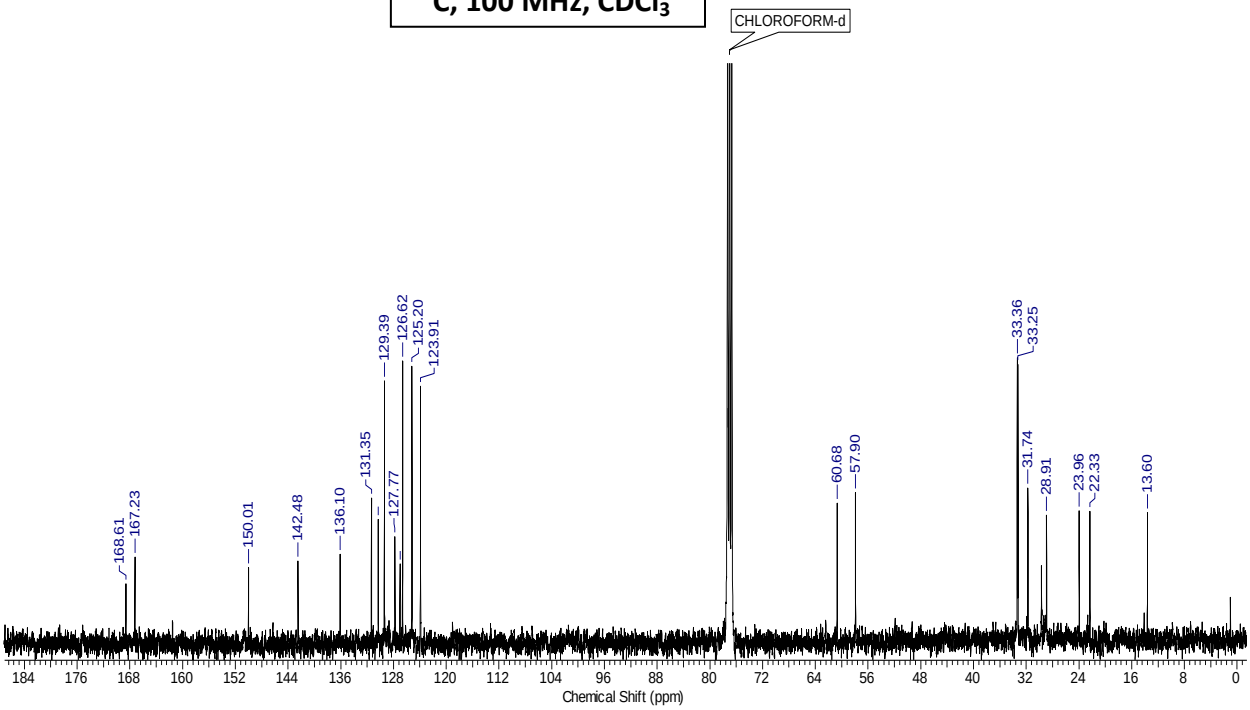
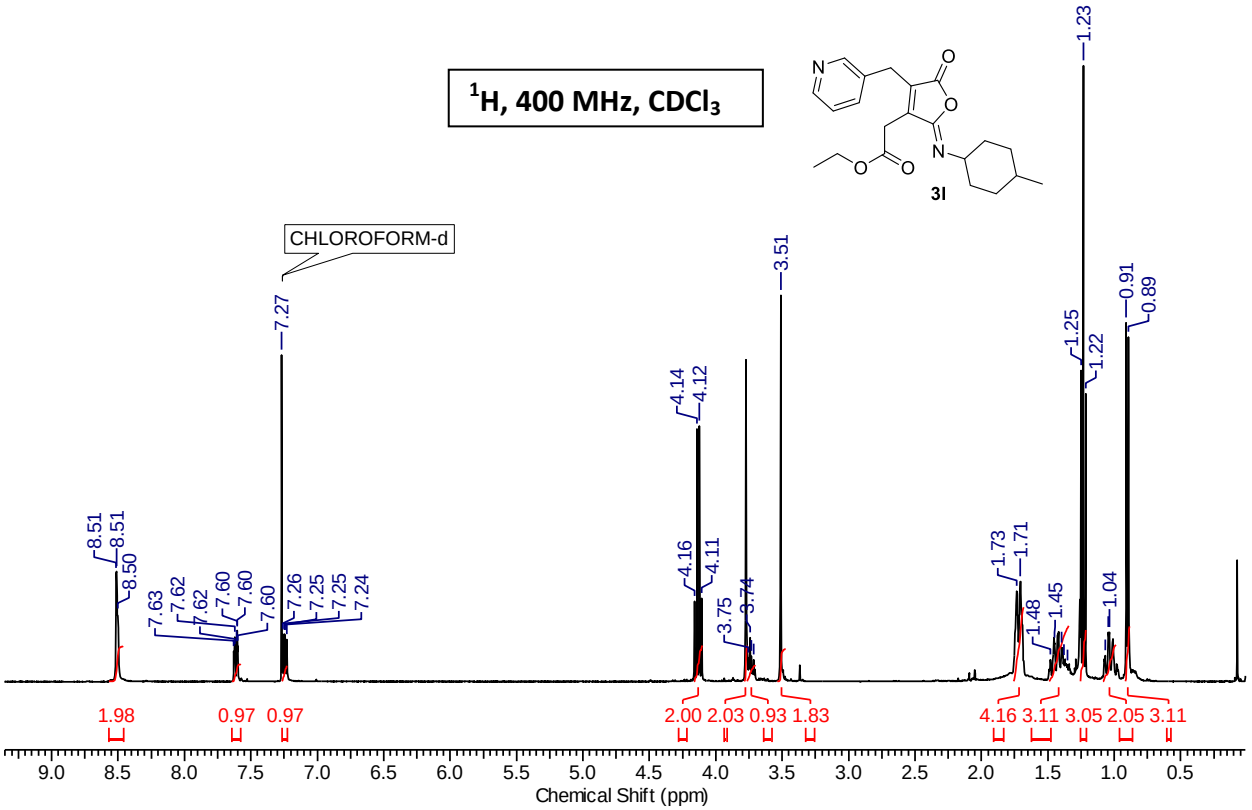
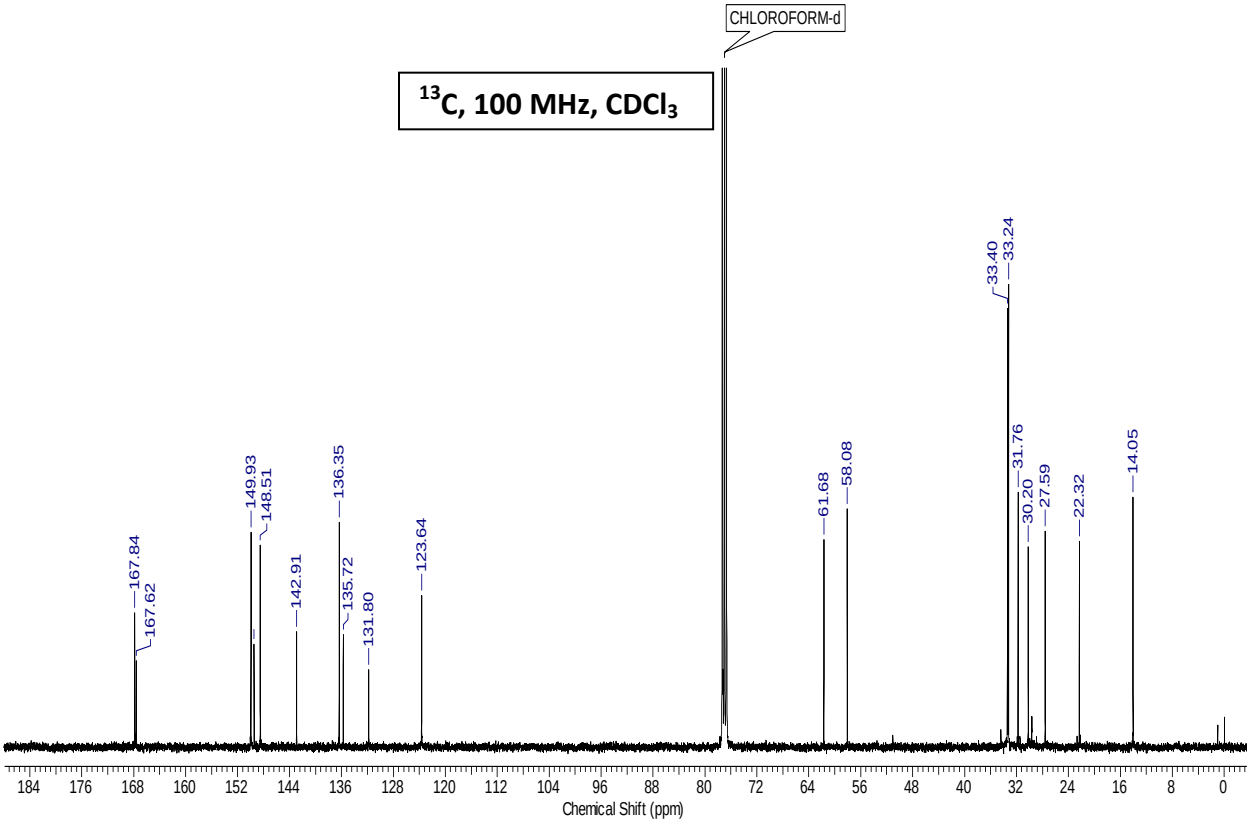
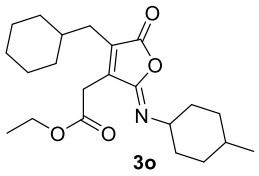



^{1}H, 400 MHz, CDCl$_3$
3l
CHLOROFORM-d
8.51
8.51
8.50
7.63
7.62
7.62
7.60
7.60
7.60
7.27
7.26
7.25
7.25
7.24
4.14
4.12
4.16
4.11
3.75
3.74
3.51
1.73
1.71
1.48
1.45
1.25
1.23
1.22
1.04
0.91
0.89
1.98
0.97
0.97
2.00
2.03
0.93
1.83
4.16
3.11
3.05
2.05
3.11
Chemical Shift (ppm)


^{13}C, 100 MHz, CDCl$_3$
CHLOROFORM-d
167.84
167.62
149.93
148.51
142.91
136.35
135.72
131.80
123.64
61.68
58.08
33.40
33.24
31.76
30.20
27.59
22.32
14.05
Chemical Shift (ppm)

^{1}H, 400 MHz, $CDCl_3$



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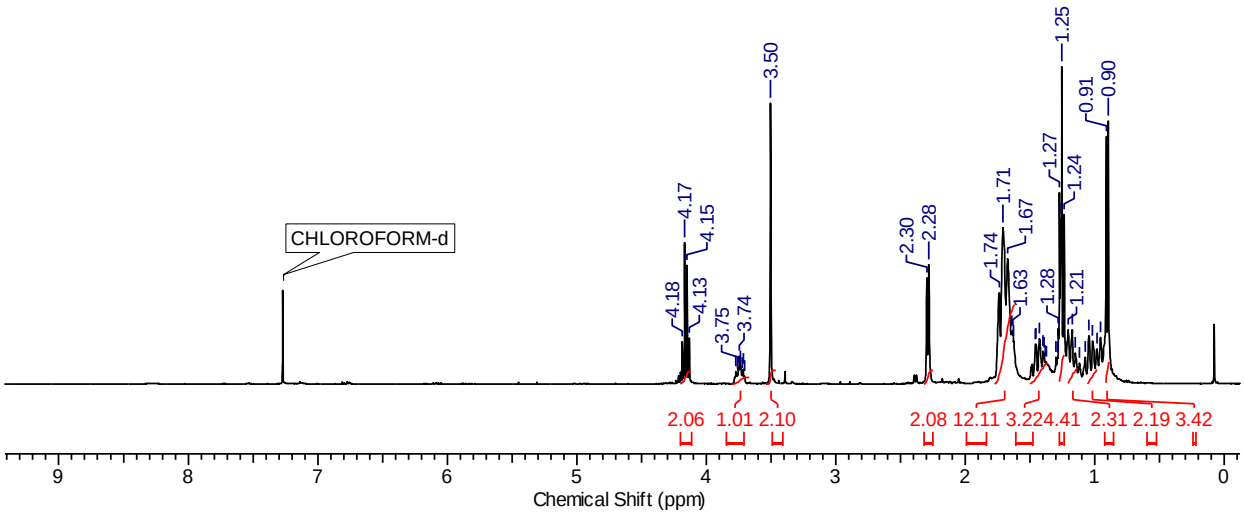

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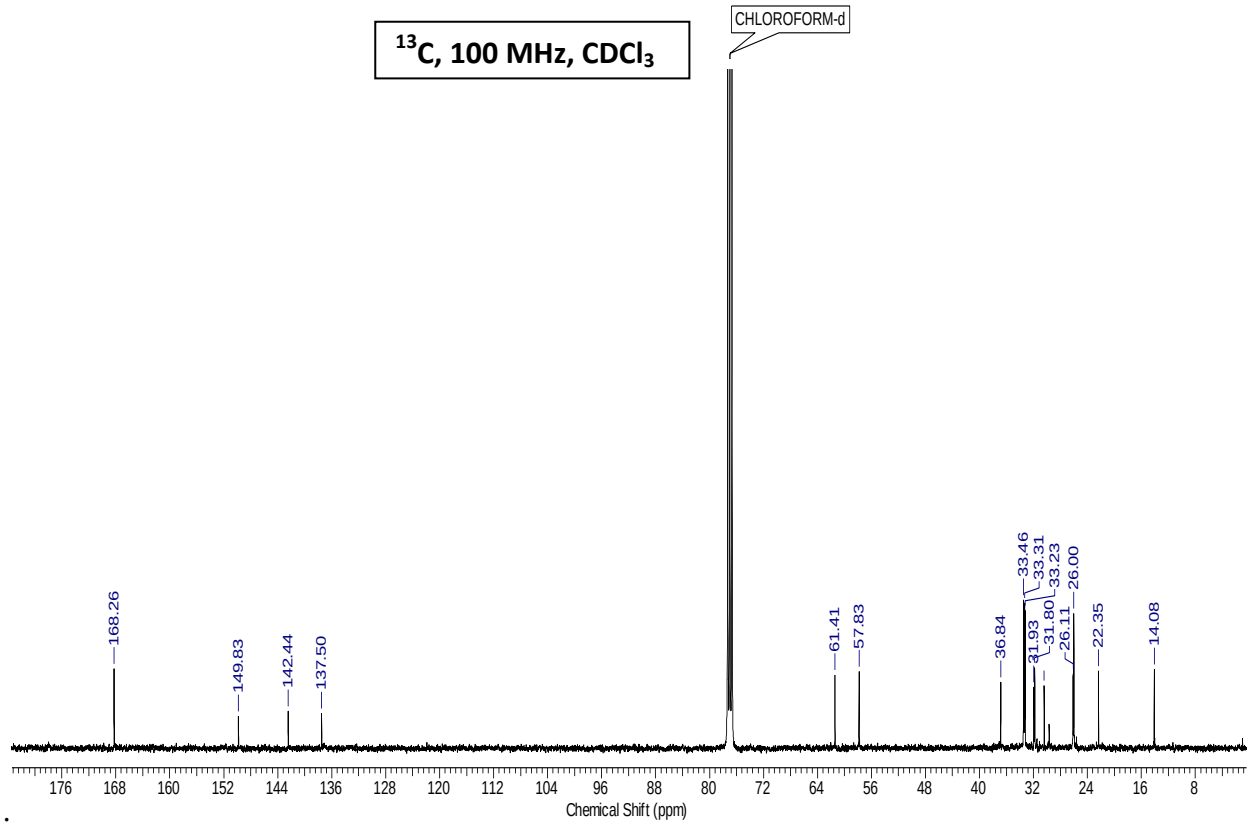

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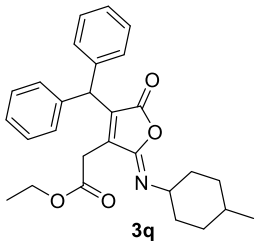
^{1}H, 400 MHz, $CDCl_3$



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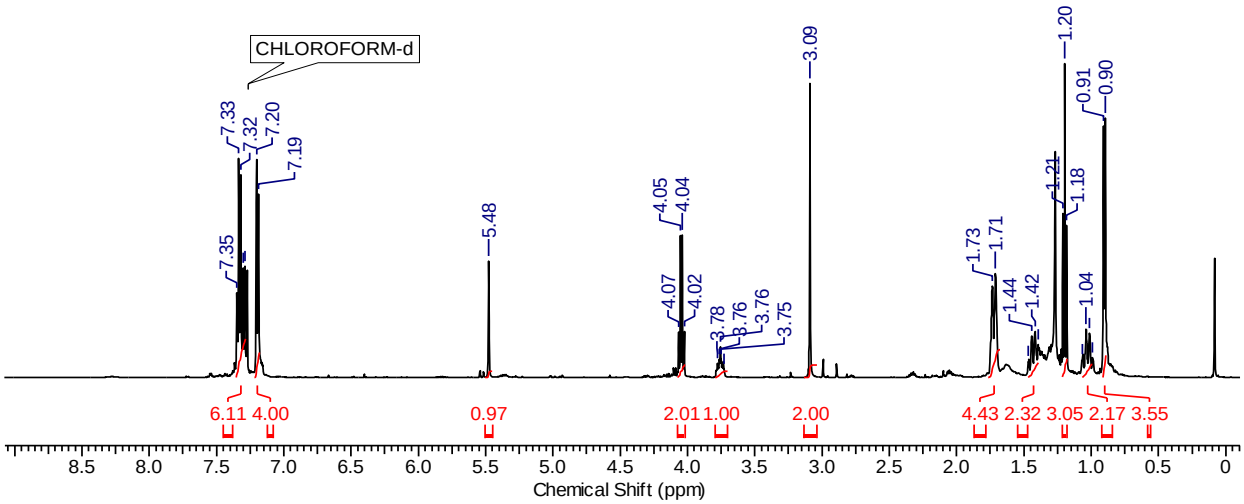
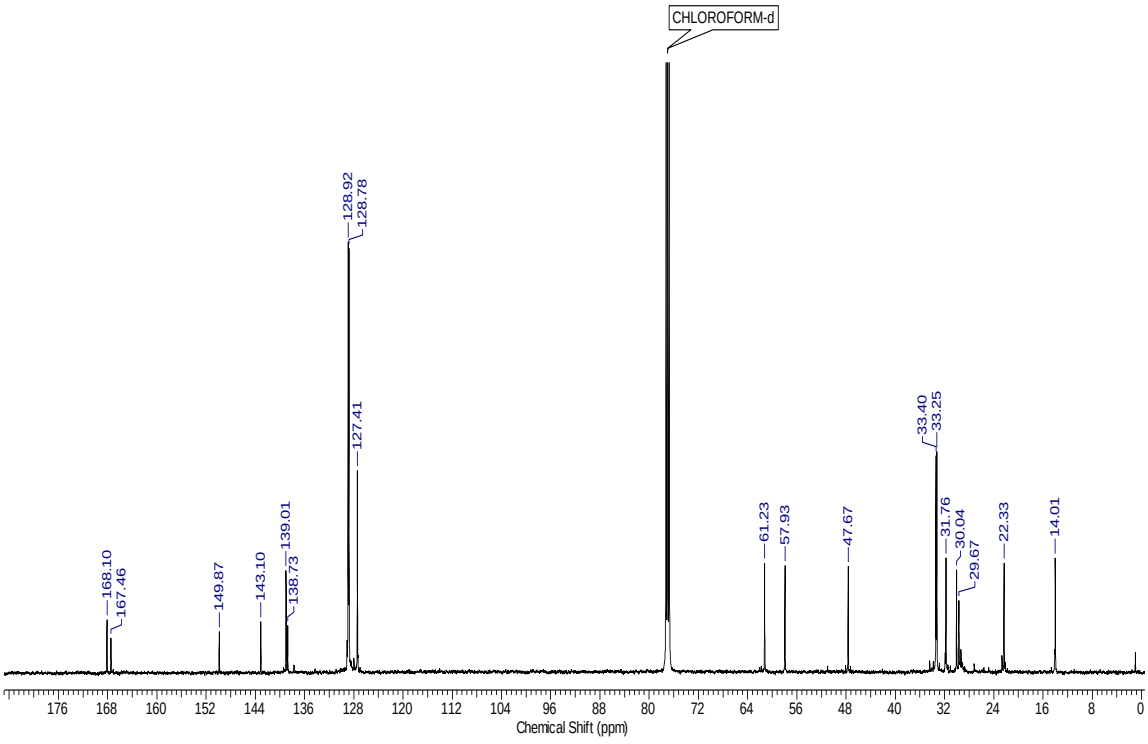
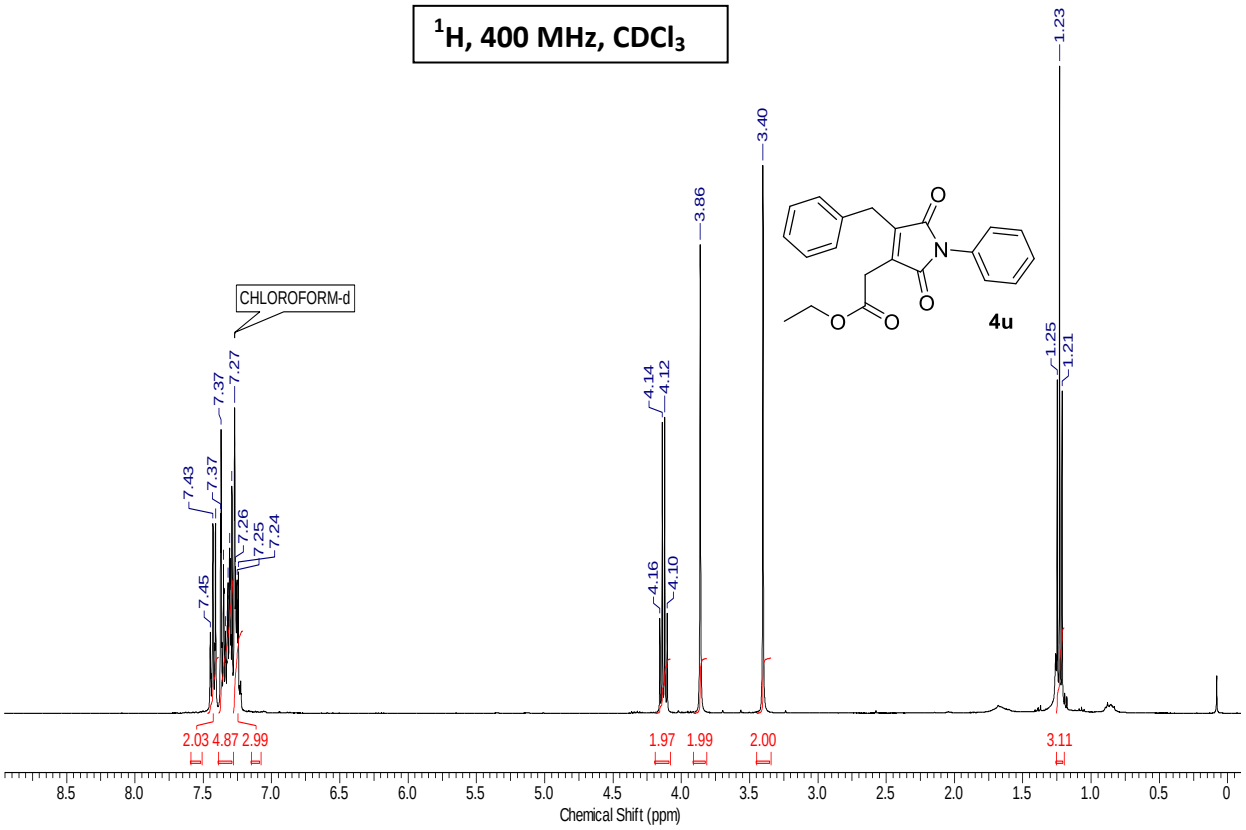
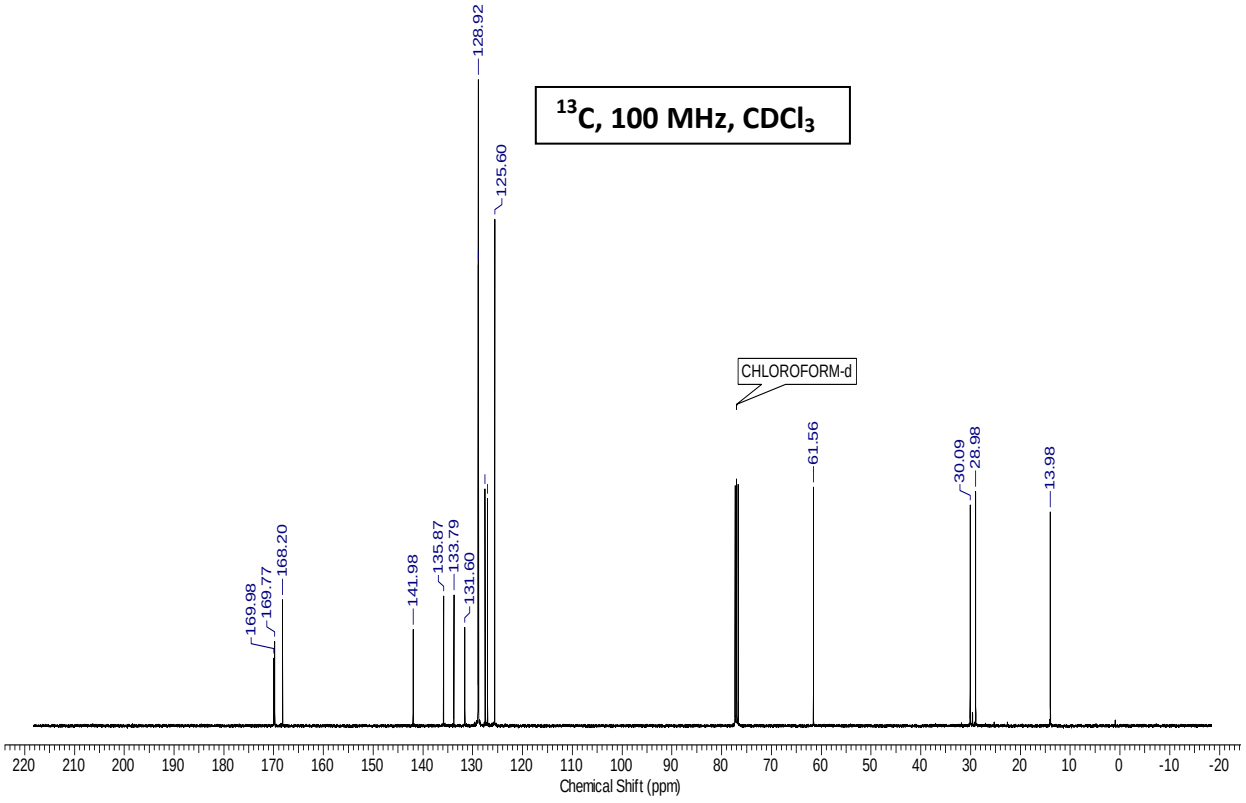


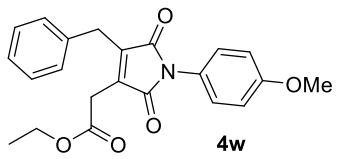
^{13}C, 100 MHz, $CDCl_3$




^{1}H, 400 MHz, CDCl$_3$
CHLOROFORM-d
4u
Chemical Shift (ppm)


^{13}C, 100 MHz, CDCl$_3$
CHLOROFORM-d
Chemical Shift (ppm)

^{1}H, 400 MHz, $CDCl_3$



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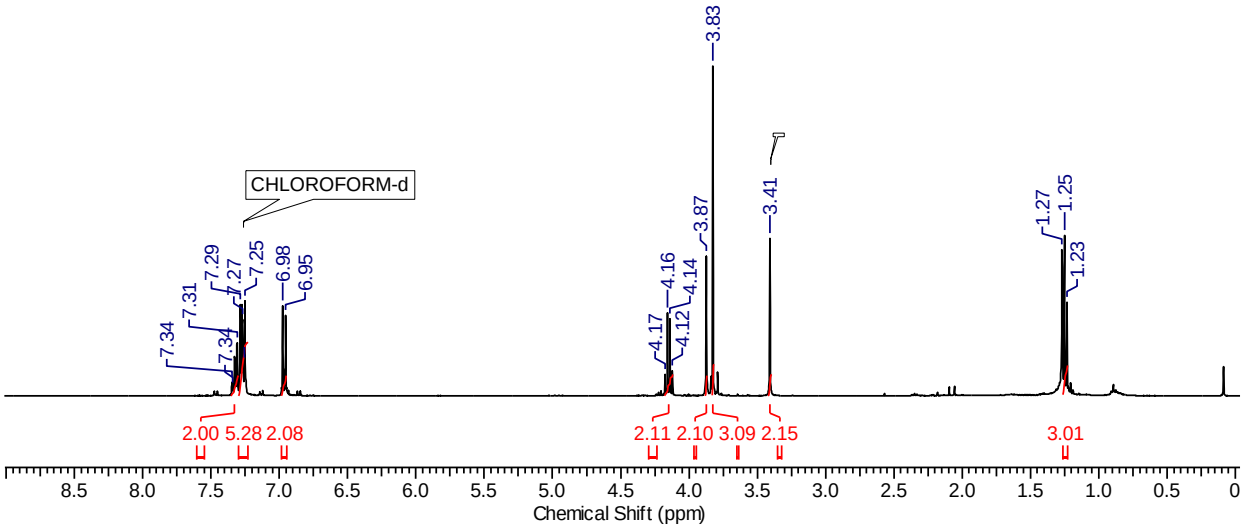

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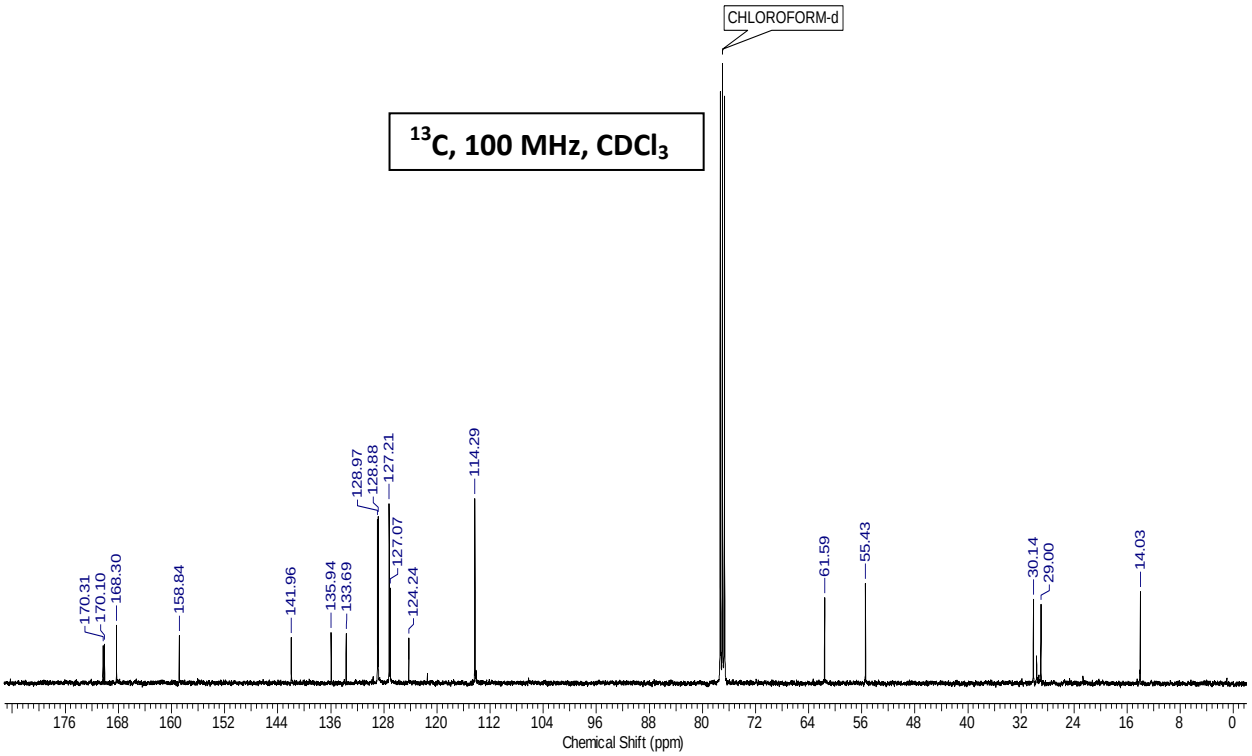

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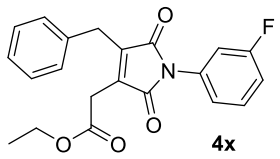

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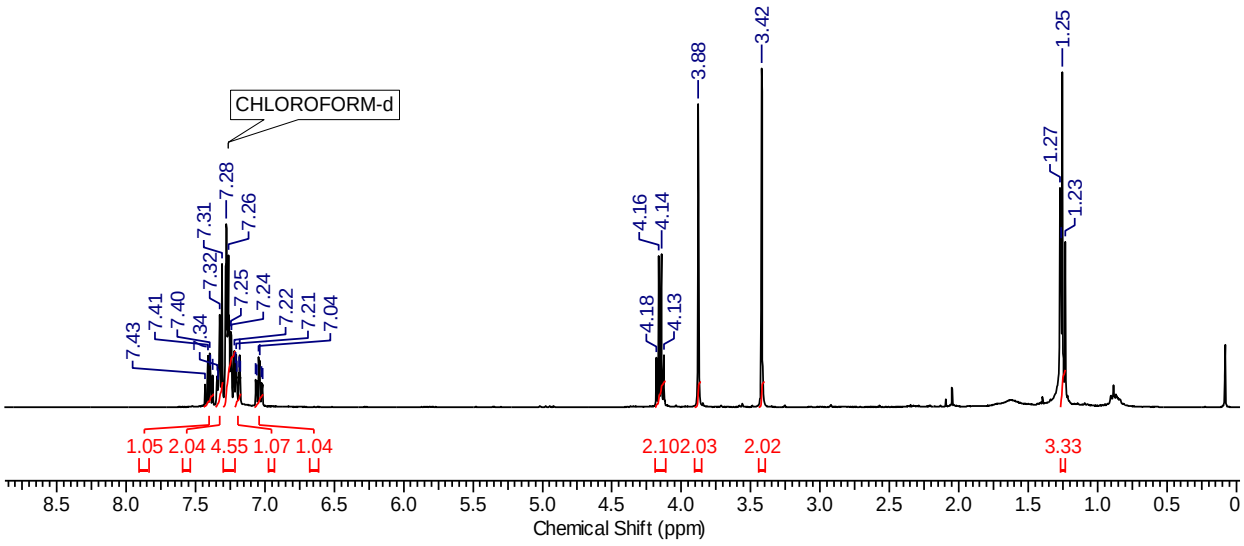
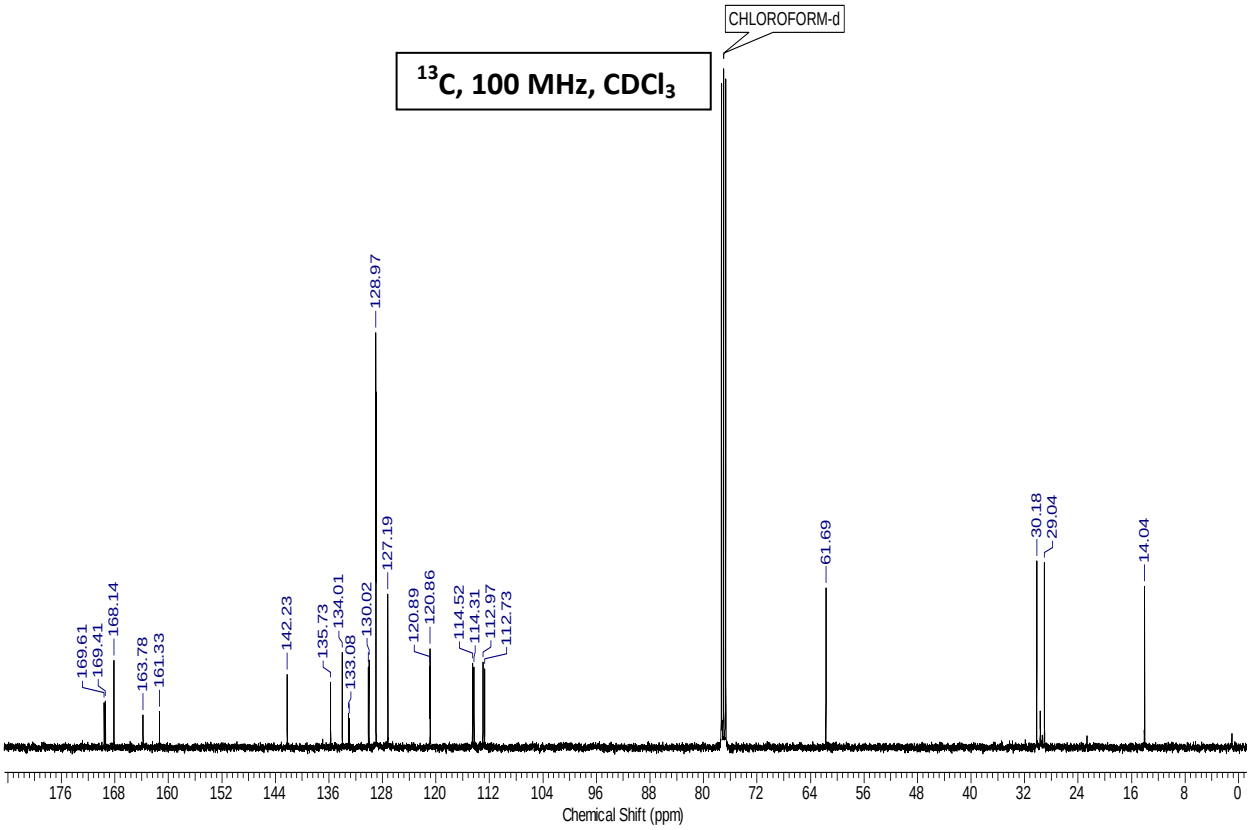
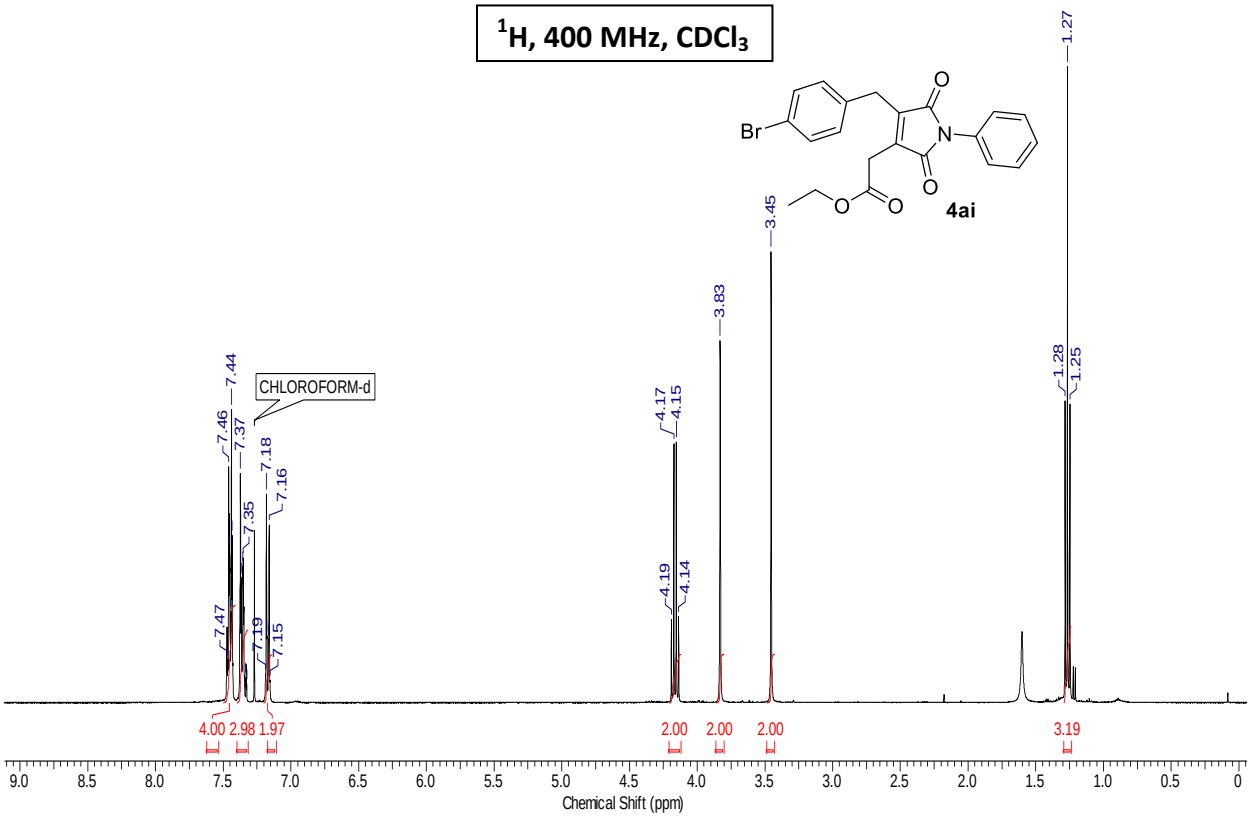
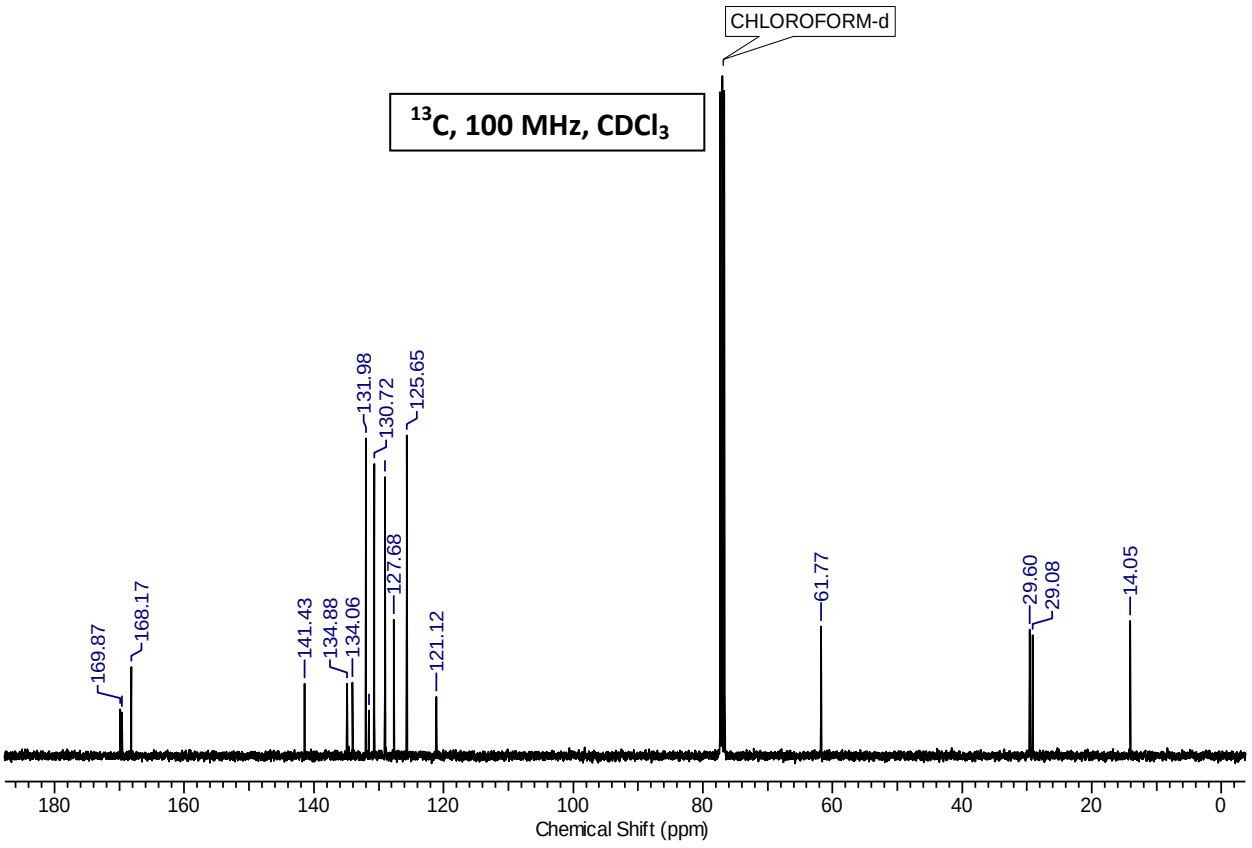


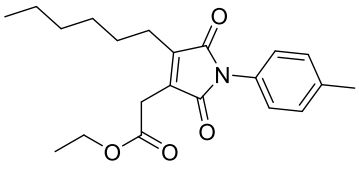
^{13}C, 100 MHz, $CDCl_3$




^{1}H, 400 MHz, CDCl$_3$
Br
O
N
O
O
O
O
4ai
1.27
3.45
3.83
4.17
4.15
4.19
4.14
1.28
1.25
CHLOROFORM-d
7.44
7.46
7.37
7.18
7.16
7.35
7.47
7.19
7.15
4.00
2.98
1.97
2.00
2.00
2.00
3.19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


CHLOROFORM-d
^{13}C, 100 MHz, CDCl$_3$
169.87
168.17
141.43
134.88
134.06
131.98
130.72
127.68
125.65
121.12
61.77
29.60
29.08
14.05
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

^{1}H, 400 MHz, $CDCl_3$



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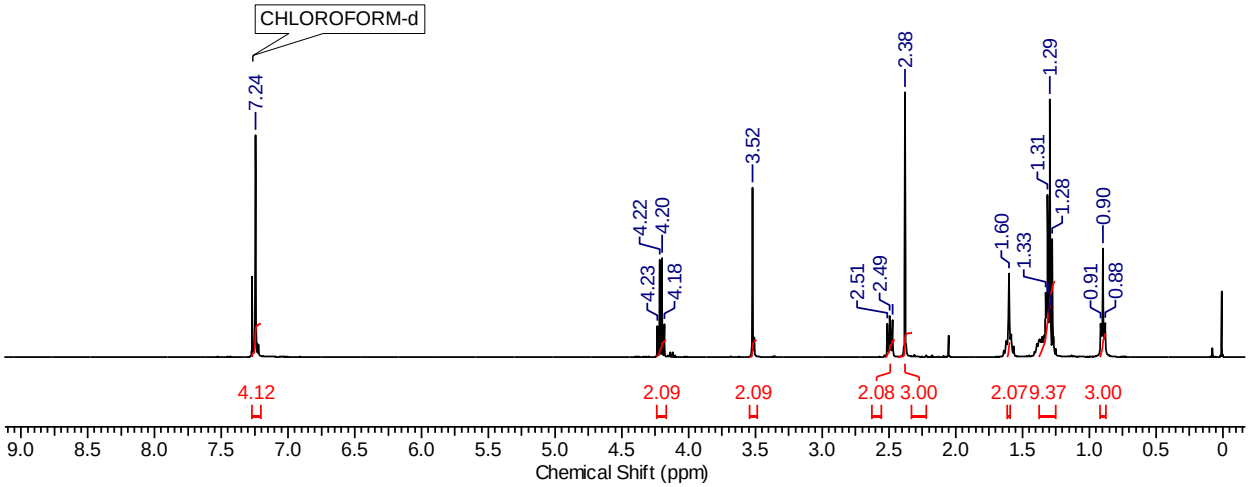

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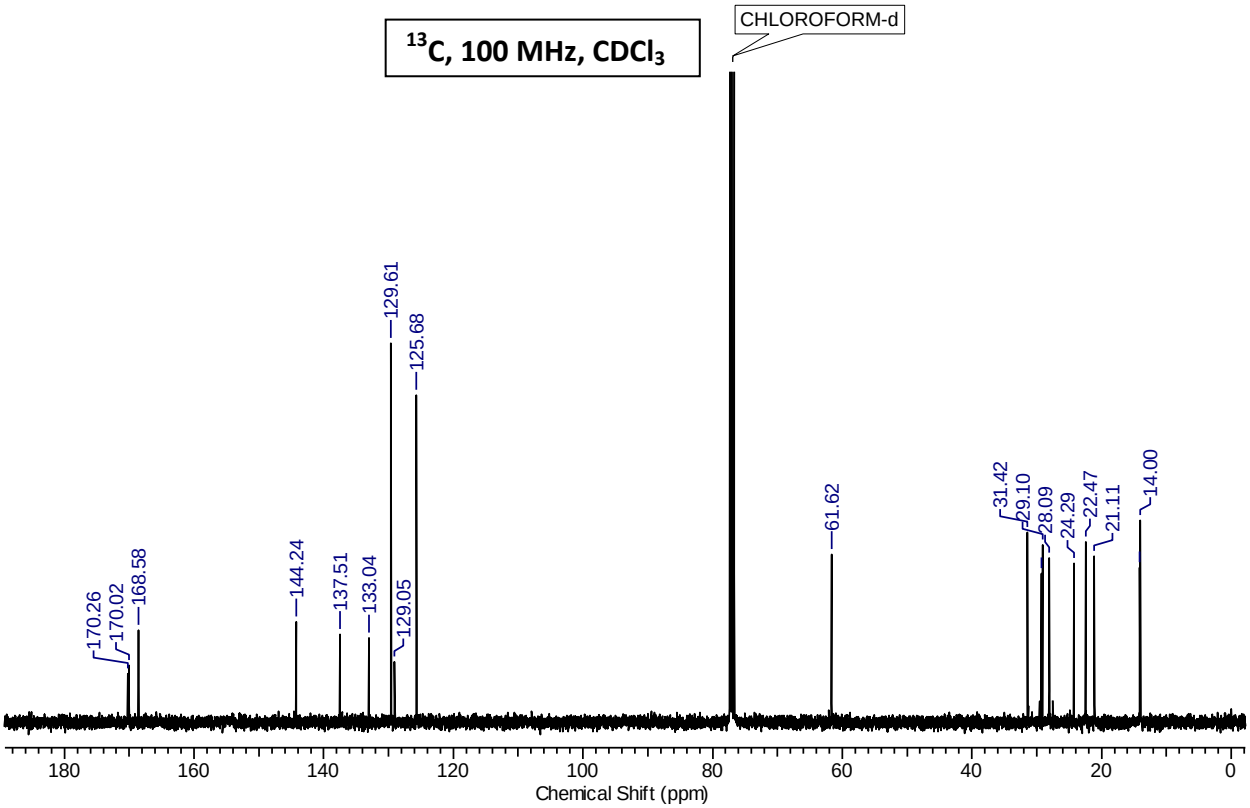
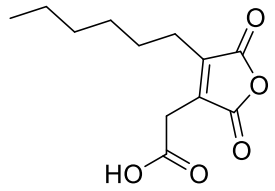
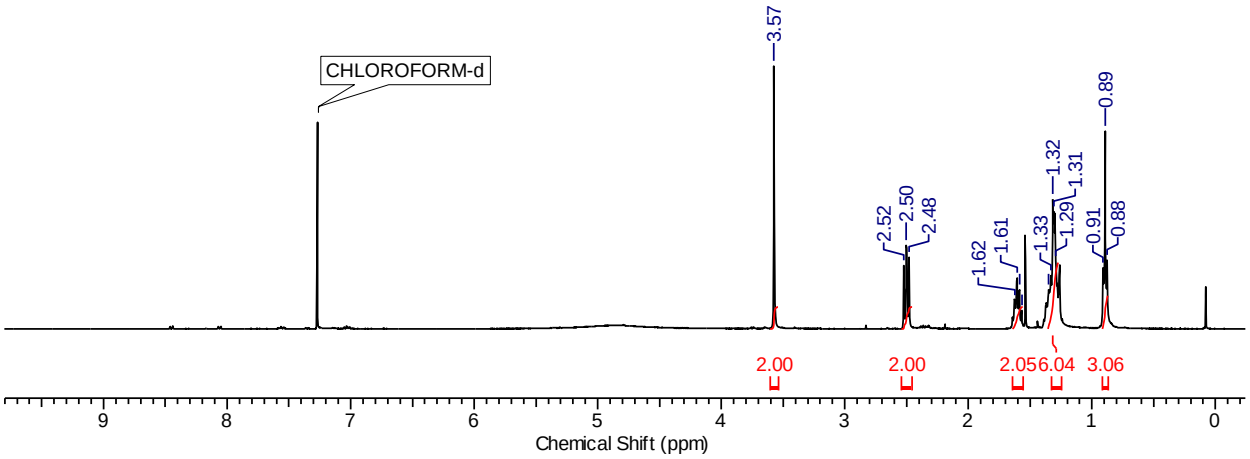


^{1}H, 400 MHz, $CDCl_3$



Aspergillus FH-X-213



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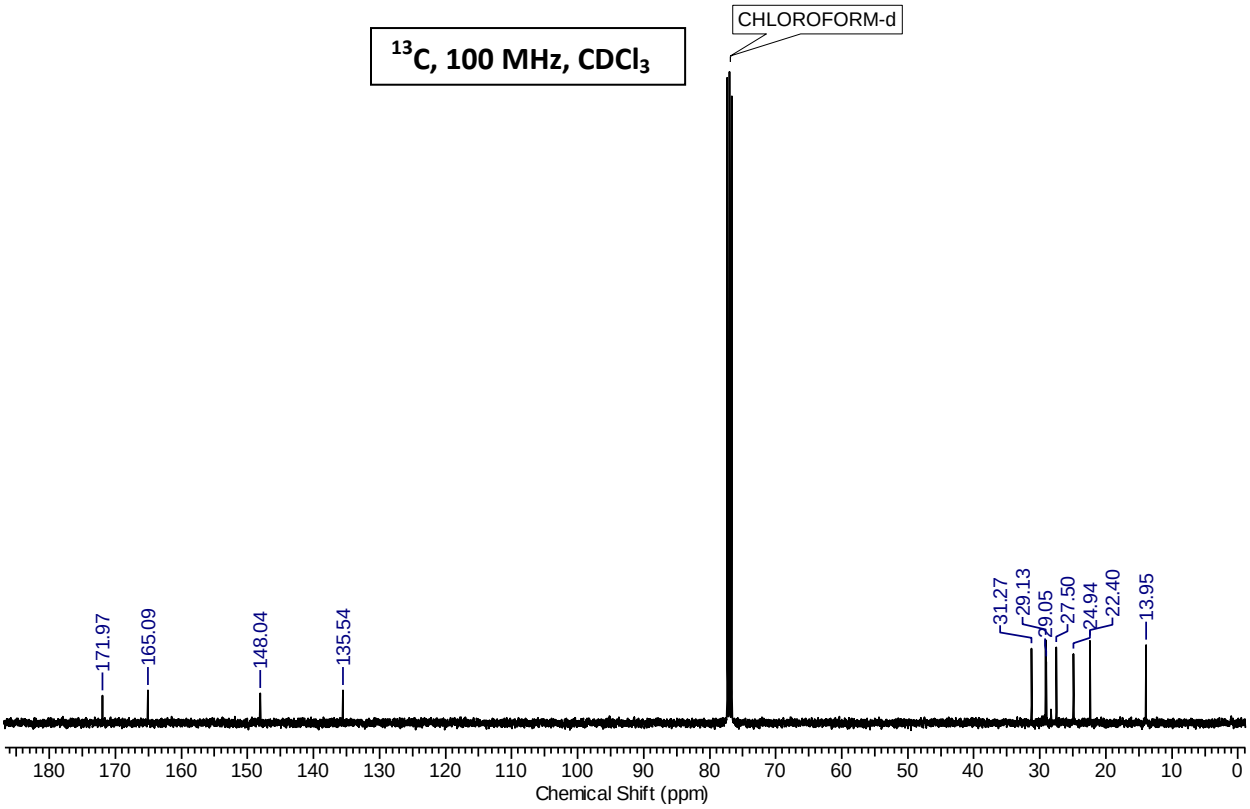

Abstract

Name of the Student: Amol B. Viveki
Registration No. : 10CC15J26016
Faculty of Study: Chemical Science
Year of Submission: 2021
AcSIR academic centre/CSIR Lab: CSIR-NCL
Name of the Supervisor: Dr. Santosh B. Mhaske

Title of the thesis: Development of Synthetic Transformations Comprising C–H Functionalization and NHC Catalysis to Access Vital Scaffolds via C–C and C–N Bond Formation.

Section 1 of first chapter involves our study on highly regeoselective Ruthenium-catalyzed amide directed C_{sp2}─H activation of quinazolinone scaffold. This method leads to the selective mono- or di-alkenylation in moderate to good yields to achieve medicinally important stilbene containing quinazolinones. The terminal alkyne is utilized as a coupling partner, which resulted in the selective *trans*-alkene formation. Electron-deficient phenylacetylenes facilitate alkenylation followed by tandem hydroamidation of the newly generated *trans*-double bond to provide novel quinazolinone alkaloids related to Luotonine class of natural products. A broad substrate scope has been demonstrated for both quinazolinones as well as terminal alkynes.

We described our efforts in section 2 of first chapter towards the synthesis of Crispine and related natural products using C–H functionalization/activation reaction. We hypothesized to utilize Pd-catalyzed tandem aminoalkylation to construct [6+5] heterocyclic rings of Crispine. We have synthesized the required precursor for the key-step and observed either formation of unwanted product or unreacted stating material under various reaction conditions utilized.

Chapter 2 deals with Copper-catalyzed amidation/dimerization of anilides via regioselective $C(sp^2)$─H functionalization. The *para*-selective amidation is accomplished on the anilide aromatic ring via a radical pathway leading to C─N bond formation in the presence of ammonium persulfate (APS) as a radical source/oxidant for the Copper catalyst. The developed protocol tolerates a wide range of anilide substrates. The regioselectivity is confirmed by single-crystal X-ray.

Section 1 of chapter 3 describes our efforts towards the synthesis of (±)-Coniceine. Different routes were examined to prepare the substrate required for the proposed key-step. The proposed key-step is N-heterocyclic carbene (NHC) catalyzed intramolecular Stetter reaction. That will be followed by usual transformation towards the synthesis of Coniceine.

Second section of chapter 3 includes N-heterocyclic carbene (NHC)-catalyzed [3+2] annulation of *α,β*-unsaturated aldehydes with carbamoylpropiolates via an unusual enolate pathway leading to an elegant construction of the highly functionalized maleimides or isomaleimides. The electronic effect imposed by the alkyl/aryl group present on the amide nitrogen of carbamoylpropiolates plays a crucial role in the selective formation of these important five-membered heterocyclic building blocks. The developed protocol is mild and tolerates a wide range of substituents on both substrates. We have also demonstrated the application of the protocol in the synthesis of the antibacterial natural product Aspergillus FH-X-213.

List of Publication

1. Ruthenium-Catalyzed Regioselective Alkenylation/Tandem Hydroamidative Cyclization of Unmasked Quinazolinones Using Terminal Alkynes

   Viveki, A. B.; Mhaske, S. B. *J. Org. Chem.* **2018**, *83*, 8906.

2. *para*-Selective Copper-Catalyzed C(sp2)–H Amidation/Dimerization of Anilides via a Radical Pathway

   Viveki, A. B.; Garad, D. N; Gonnade, R. G.; Mhaske, S. B. *Chem. Commun*. **2020**, *56*, 1565.

3. Annulation of Enals with Carbamoylpropiolates via NHC-Catalyzed Enolate Pathway: Facile Access to Functionalized Maleimides/Isomaleimides and Synthesis of Aspergillus FH-X-213

   Viveki, A. B.; Pol, M. D.; Mhaske, S. B. et al. *Manuscript communicated.*

4. Pd-Catalyzed Regioselective Mono-Arylation: Quinazolinone as the Inherent Directing Group for C(sp2)−H Activation

   Garad, D. N.; **Viveki, A. B**.; Mhaske, S. B. *J. Org. Chem*. **2017**, *82*, 6366.

List of posters, Presentations and Conferences

1. Participated and presented poster on National Science day 2018 held during February 2018, at CSIR-National Chemical Laboratory, Pune India
2. Participated and presented poster on National Science day 2019 held during February 2019, at CSIR-National Chemical Laboratory, Pune India
3. Participated in oral presentation in XIV J-NOST Conference for Research Scholars organized at CSIR-Indian Institute of Chemical Technology, Hyderabad during 28th November to 1st December, 2018.
4. Participated in oral presentation NCL-RF conference-2019 held during November 2019, at CSIR-National Chemical Laboratory, Pune India

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Article
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Ruthenium-Catalyzed Regioselective Alkenylation/Tandem Hydroamidative Cyclization of Unmasked Quinazolinones Using Terminal Alkynes

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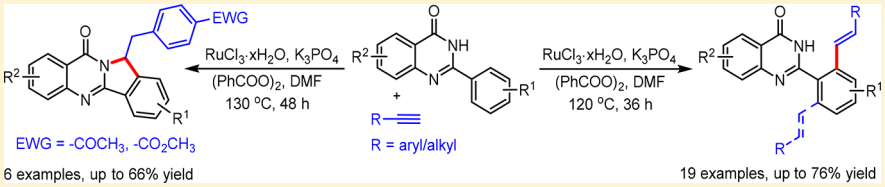
[†]Division of Organic Chemistry and [‡]Academy of Scientific and Innovative Research (AcSIR), CSIR-National Chemical Laboratory, Pune 411008, India

Supporting Information



ABSTRACT: Ruthenium-catalyzed amide directed C_{sp2}−H activation of the quinazolinone scaffold has been demonstrated, leading to the selective mono- or dialkenylation in moderate to good yields to achieve medicinally important stilbene containing quinazolinones. The terminal alkyne is utilized as a coupling partner, which resulted in the selective *trans*-alkene formation. Electron-deficient phenylacetylenes facilitate alkenylation followed by tandem hydroamidation of the newly generated *trans*-double bond to provide novel quinazolinone alkaloids related to the Luotonine class of natural products.

INTRODUCTION

Quinazolinone is one of the most important building blocks found in many biologically active molecules, natural products, as well as drug candidates.[1] Many marketed drugs containing quinazolinone or quinazoline as a basic core with various biological activities are known.[2] This privileged scaffold gained immense attention of synthetic as well as medicinal chemists because of their ubiquitous fascinating structural architecture and wide range of biological properties such as anticancer, antianaphylatic, diuretic, antimalarial, antiinflammatory, antihypertensive, anticonvulsant, and antidiabetic among others.[1,2] Quinazonlinone alkaloids containing a *trans*-stilbene moiety have been found to be 2-fold more potent than the marketed drug Etoposide in the preliminary test against cancer cell lines (Figure 1).[3] Diversity-oriented late-stage functionalization of such biologically active scaffolds broadens the scope of the search for a lead molecule. Incorporating an easily functionalizable moiety, such as an alkene,[4] on an active scaffold improves the chances of larger library generation. Additionally, quinazolinone compounds with extra polar/nonpolar functional groups may enhance their medicinal properties. Hence, the development of efficient and novel methods for their construction is always desired for drug discovery.[1,2]

Metal-catalyzed activation of a neutral C−H bond leading to diverse functionalization is a wide area of chemistry, which can be utilized for this purpose. The functional group directed C−H activation, in particular alkenylation, is often used for the construction of a new C−C bond;[5] nevertheless, C−H bond activation using an intrinsic directing group is more preferred, since it avoids a number of steps to obtain the products with high atom economy.[6] Recent studies revealed that the quinazolinone scaffold could act as a directing group in promoting C−H bond activation. Quinazolinone was previously used as the intrinsic directing group for halogenations, intramolecular amination, acetoxylation, methoxylation, alkenylation/aza-Michael addition, annulation, etc., using Pd, Rh, and Ru catalysts.[7] Peng and coauthors reported the cross-coupling/annulation with internal alkyne leading to fused polycyclic heteroarenes.[7h] Recently, we reported a protocol for C_{sp2}-arylation and C_{sp3}-acetoxylation by taking advantage of quinazolinone as the inherent directing group.[8]

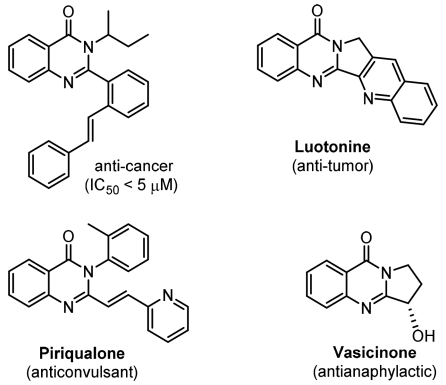


Figure 1. Selected bioactive quinazolinone molecule, drug, and natural products.

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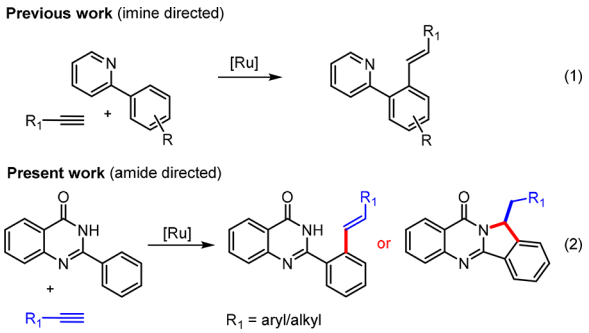
J. Org. Chem. 2018, 83, 8906−8913

Internal alkynes have been exploited more frequently in the nitrogen directed C−H activation to obtain alkenylated products[5b,7h,9] as compared to terminal alkynes.[5c,10] Zhang et al. reported ruthenium catalyzed, pyridine (imine) directed alkenylation of aromatic C−H bonds with terminal alkynes (Scheme 1, eq 1).[10f] However, to the best of our knowledge, alkenylation on quinazolinones by terminal alkynes is still unexplored.

Scheme 1. Ruthenium-Catalyzed Alkenylation



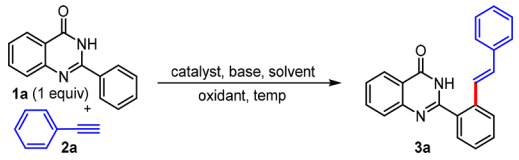
Inspired by the importance of quinazolinone derivatives containing a *trans*-stilbene moiety[3] and Luotonine related quinazolinone compounds[1] as potential bioactive candidates, we planned to develop a protocol for their synthesis using C−H activation.

RESULTS AND DISCUSSION

Our preliminary investigation commenced with the reaction of 2-phenylquinazolin-4(3*H*)-one (**1a**) with phenylacetylene (**2a**) in the presence of ruthenium catalyst ($RuCl_3{\cdot}xH_2O$, 0.05 equiv), base (K_3PO_4, 2 equiv), and oxidant [dibenzoyl peroxide (75% in water), 1.5 equiv] in NMP at 120 °C. To our delight, the desired alkenylated product **3a** was obtained in 15% yield (Table 1, entry 1). When the *N*-methyl protected quinazolinone was treated under the same condition, the reaction failed to give the expected product (Table 1, entry 2). We reasoned that the amide moiety of quinazolinone is acting as the directing group for ruthenium catalyst unlike imine (pyridine) reported by Zhang et al.[10f] Hence, we proceeded further with the unmasked quinazolinone **1a** for the optimization of the protocol. Variation in the reaction time, temperature, and catalyst loading did not show much improvement in the yield (Table 1, entries 3−6). To improve the yield, different solvents were also screened (Table 1, entries 7−9). DMF was found to be better for this transformation (Table 1, entry 9). We were delighted to observe a substantial improvement in the yield on employing 4 equiv of **2a** (Table 1, entry 11). However, the use of 5 equiv resulted in diminished yield and the formation of a trace amount (LC-MS) of dialkenylated product (Table 1, entry 12). Further attempts to improve the yield using various bases and oxidants/additives resulted in either a complex reaction mixture or inferior yields (Table 1, entries 13−20).

After having the optimized condition in hand (Table 1, entry 11), we turned our attention toward the generalization of the developed protocol on varyingly substituted quinazolinones (Scheme 2). Initially, the effect of substituents present on the phenyl ring of the quinazolinone substrate was studied. Electron donating substituents such as methyl and methoxy groups at the *para* position of the phenyl ring provided products **3b** and **3c**, respectively, in good to moderate yields.

Table 1. Optimization of Reaction Conditions[a]



entry	2a (equiv)	solvent	base	temp (°C)	time (h)	yield[b] (%)
1	2	NMP	K_3PO_4	120	24	15
2[c]	2	NMP	K_3PO_4	120	24	NR
3[d]	2	NMP	K_3PO_4	120	36	19
4	2	NMP	K_3PO_4	120	48	12
5	2	NMP	K_3PO_4	100	36	trace
6	2	NMP	K_3PO_4	150	36	*e*
7	2	ACN	K_3PO_4	120	36	10
8	2	DCE	K_3PO_4	120	36	NR
9	2	DMF	K_3PO_4	120	36	24
10	3	DMF	K_3PO_4	120	36	48
11	**4**	**DMF**	**K_3PO_4**	**120**	**36**	**72**
12	5	DMF	K_3PO_4	120	36	60
13	4	DMF	Cs_2CO_3	120	36	*e*
14	4	DMF	K_2CO_3	120	36	45
15	4	DMF	Na_2CO_3	120	36	52
16[f]	4	DMF	K_3PO_4	120	36	35
17[g]	4	DMF	K_3PO_4	120	36	60
18[h]	4	DMF	K_3PO_4	120	36	NR
19[i]	4	DMF		120	36	45
20[j]	4	DMF	K_3PO_4	120	36	NR

[a]Reaction conditions: **1a** (0.2 mmol), **2a**, $RuCl_3{\cdot}xH_2O$ (0.05 equiv), $(PhCOO)_2$ (0.3 mmol), base (0.4 mmol), and solvent (1.4 mL) in glass tube with screw cap. [b]Isolated yield. [c]*N*-CH_3. [d]Catalyst used 2−10 mol %. [e]Multiple products. NR = no reaction. [f]$PhCO_3t$-Bu. [g]$PhCO_2H$. [h]$(t\text{-BuO})_2$. [i]$PhCO_2Na$ as oxidant. [j]$PhCO_2Na$ as additive.

Surprisingly, 4-bromo substituted compound provided dialkenylated product **3d** in good yield under the optimized reaction condition. It may be reasoned that quinazolinone substrate with an electron withdrawing group is more active for such transformations as the reaction proceeds through a deprotonation pathway. With slight modification (2 equiv of **2a**, at 100 °C) in the optimized reaction condition, we could isolate the monoalkenylated product **3e** in very good yield. The carboxylate group substituted quinazolinone also resulted in the dialkenylated product **3f**; however, our attempts to achieve only a monoalkenylated product by modification in the reaction conditions were not successful because of the high reactivity of the substrate. Similar to the carboxylate substituted quinazolinone, the presence of an electron-deficient pyridine ring on quinazolinone substrate provided only dialkenylated product **3g** in moderate yield.

Further, the scope of the alkenylation reaction was studied on substrates with different substituents on the quinazolinone core. A quinazolinone core with the methyl group at the 3- and 6-positions provided the desired products **3h** and **3i**, respectively, in good yields. Substrates with an electron donating methoxy group at the 4- and 5-positions also worked well to provide the corresponding products **3j** and **3k**. A halogen substituent such as chlorine was also tolerated well to furnish the expected product **3l** in good yield. A nitro-substituted electron-deficient substrate provided the expected alkenylated product **3m** in moderate yield. We also invistigated the substrate scope of different terminal alkynes with

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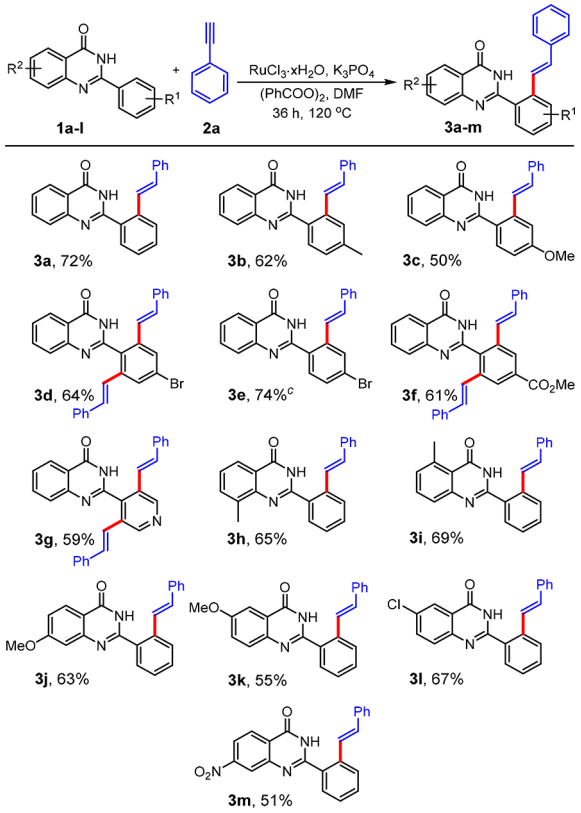
Scheme 2. Ruthenium-Catalyzed Alkenylation of Various Quinazolinones[a,b]

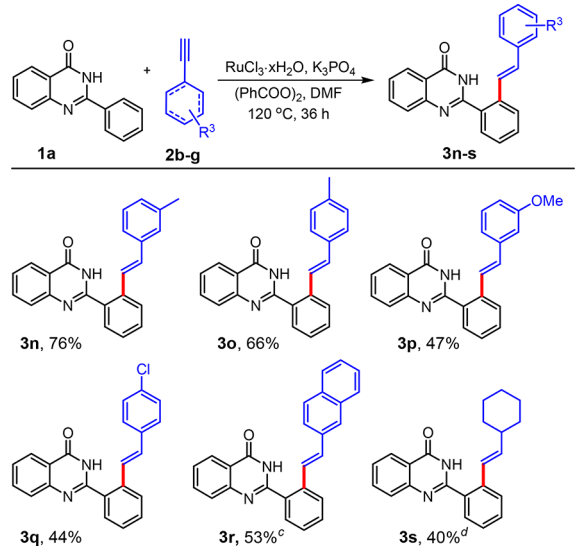


[a]Reaction conditions: **1a–l** (0.2 mmol), **2a** (0.8 mmol), $RuCl_3{\cdot}xH_2O$ (0.05 equiv), $(PhCOO)_2$ (0.3 mmol), K_3PO_4 (0.4 mmol), and DMF (1.4 mL) in glass tube with screw cap for 36 h. [b]Isolated yield. [c]Reaction at 100 °C with **2a** (2 equiv).

quinazolinone **1a** (Scheme 3). 3/4-Methyl-substituted phenylacetylenes furnished the corresponding products **3n** and **3o** in very good yields. In the case of 3-methoxy and 4-chloro phenylacetylene, the expected products **3p** and **3q** were obtained in moderate yields. When the reaction was performed using 2-ethynylnaphthalene, the reaction took a longer time and resulted in the expected product **3r** in moderate yield. It has been observed that aliphatic terminal alkyne was unreactive at 120 °C, but when the temperature was increased to 150 °C, the reaction went to completion and resulted in the corresponding alkenylated product **3s** (*trans*:*cis* = 7:1) though in low yield.

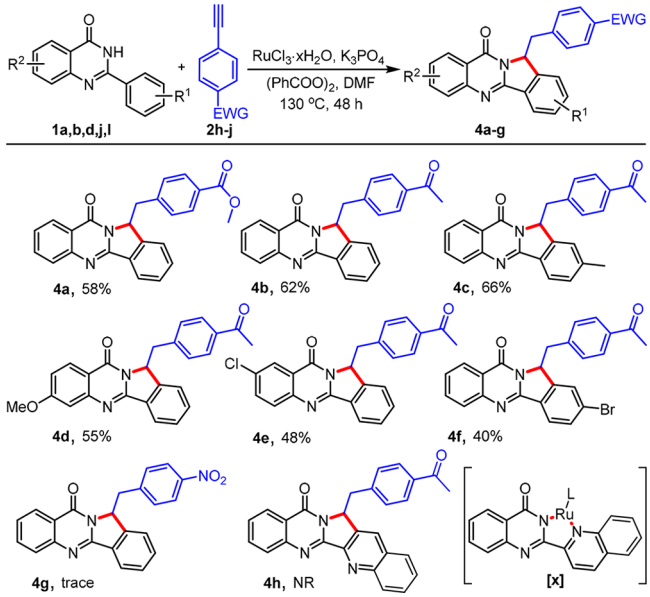
The results obtained during the substrate scope studies (Schemes 2 and 3) prompted us to investigate whether the presence of an electron-withdrawing group on the alkyne partner will induce the envisioned hydroamidative cyclization to obtain interesting compounds related to the Luotonine class of natural products (Scheme 4). To our immense interest, methyl 4-ethynylbenzoate reacted smoothly to provide the cyclized product **4a** in optimum yield at the higher temperature and longer reaction time. Interestingly, keto-substituted phenyl acetylene also worked similarly with various quinazolinone substrates, providing the corresponding cyclized products **4b–f** in good to moderate yields. However, the nitro-substituted phenylacetylene remained unreactive under the optimized reaction conditions, and only a trace amount of product formation was observed (HRMS) at the higher temperature.

Scheme 3. Ruthenium-Catalyzed Alkenylation Using Various Terminal Alkynes[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2b–g** (0.8 mmol), $RuCl_3{\cdot}xH_2O$ (0.05 equiv), $(PhCOO)_2$ (0.3 mmol), K_3PO_4 (0.4 mmol), and DMF (1.4 mL) in glass tube with screw cap for 36 h. [b]Isolated yield. [c]48 h. [d]150 °C, 48 h.

Scheme 4. Ruthenium-Catalyzed Alkenylation–Hydroamidation[a,b]



[a]Reaction conditions: **1a,b,d,j,l** (0.2 mmol), **2h–j** (0.8 mmol), $RuCl_3{\cdot}xH_2O$ (0.05 equiv), $(PhCOO)_2$ (0.3 mmol), K_3PO_4 (0.4 mmol), and DMF (1.4 mL) in glass tube with screw cap for 48 h. [b]Isolated yield.

Most probably, the presence of the strong electron withdrawing nitro group did not facilitate the binding of the electron-deficient alkyne with the in situ generated quinazolinone–ruthenium complex. Hence, the expected product **4g** was not observed. We then attempted the reaction of 2-(2-pyridyl)-substituted quinazolinone under our optimized condition, but the substrate remained unreactive though we tried variations in the reaction conditions. It is interesting to note that the reaction worked well with pyridine substituted quinazolinone,

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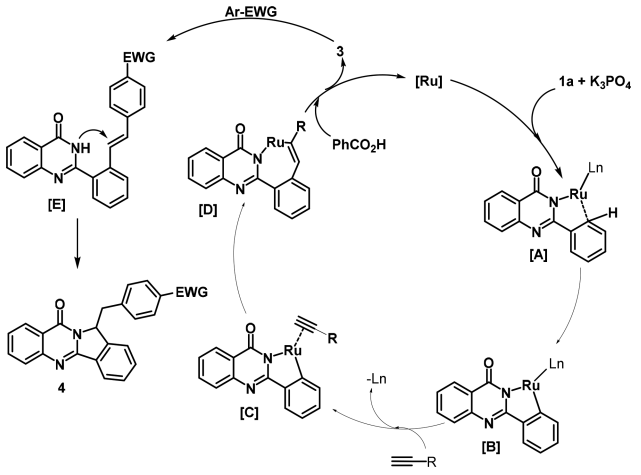
where nitrogen is away from the reacting center (Scheme 1, **3g**). This result suggests that probably the formation of a stable ruthenium complex (Scheme 4, [**x**]) inhibits the reaction; hence, the formation of product **4h** is not observed.

On the basis of the reactivity pattern of various quinazolinone substrates and literature precedence,[7h,10f,11] a plausible reaction mechanism for this transformation is depicted in Scheme 5. Coordination of the ruthenium metal

Scheme 5. Plausible Reaction Pathway



with the amide nitrogen in the presence of a base forms a transition state [**A**]. The abstraction of the acidic proton of the aromatic ring results in the intermediate [**B**]. Exchange of benzoic acid with terminal alkyne produces the complex [**C**]. The consequent migratory insertion of alkyne leads to the intermediate [**D**], which culminates into the expected alkenylated products **3** by protodemetalation. In the case of electron-deficient phenyl acetylenes, further hydroamidative cyclization directly furnishes cyclized products **4**.

In conclusion, we have achieved ruthenium-catalyzed direct C−H bond alkenylation of quinazolinones using terminal alkynes as a coupling alkene partner in good to moderate yields. The developed protocol was successfully extended for the synthesis of Luotonine analogues. Quinazolinone is used as the inherent directing group, which allows late stage diversification and synthesis of a library of medicinally important compounds that could be extended for SAR studies. Screening of the synthesized molecules for anticancer activity and regioselective functionalization of quinazolinone alkaloids using other metals is underway in our laboratory.

EXPERIMENTAL SECTION

1. General Information. All reagents and solvents were used as received from commercial sources unless otherwise noted. All experiments were carried out in a Teflon screw cap glass tube. Precoated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for thin-layer chromatography (TLC). Visualization of the developed TLC plate was performed by irradiation with UV light. Column chromatographic purifications were carried out on flash silica gel (240−400 mesh) using dichloromethane (DCM) and acetone as eluents. The ^{1}H and ^{13}C NMR spectra were recorded on 200/400/500 and 100/125 MHz NMR spectrometers, respectively, in $CDCl_3$ or DMSO-d_6. Chemical shifts were reported as δ values from standard peaks. The melting points were recorded on a Buchi instrument and are uncorrected. High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer. All quinazolinone starting materials were prepared[12] according to literature procedures starting from the corresponding 2-amino benzamide and aldehyde, and the structures were confirmed by literature reports.[12−17] 4-Acetylphenylacetylene (**2i**) was prepared according to the previously reported procedure.[18]

2. Experimental Procedures. *A. General Procedure for Alkenylation/Tandem Hydroamidation of Quinazolinone (**3a−s, 4a−g**).* The oven-dried screw cap glass tube equipped with a magnetic stirring bar was charged with quinazolinone (0.2 mmol, 1 equiv), phenylacetylene (0.8 mmol, 4 equiv), benzoyl peroxide (75% in water, 0.3 mmol, 1.5 equiv), K_3PO_4 (0.4 mmol, 2 equiv), $RuCl_3{\cdot}xH_2O$ (0.05 mmol, 5 mol %), and DMF (1.4 mL). The reaction mixture was backfilled with argon and heated at 100−150 °C in a preheated oil bath. The progress of the reaction was monitored using TLC. After completion of the reaction (36−48 h), the reaction mixture was diluted with ethyl acetate and washed three times with ice cold water. The organic layer was dried over Na_2SO_4 and concentrated under a vacuum, and the crude residue was purified by flash column chromatography using 2% acetone in DCM to afford pure products **3a−s** and **4a−g**.

*B. Typical Experimental Procedure for the Preparation of Representative Product **3a**.* The oven-dried screw cap glass tube equipped with a magnetic stirring bar was charged with quinazolinone **1a** (44.4 mg, 0.2 mmol, 1 equiv), phenylacetylene (**2a**) (87 μL, 0.8 mmol, 4 equiv), benzoyl peroxide (75% in water, 97 mg, 0.3 mmol), K_3PO_4 (85 mg, 0.4 mmol, 2 equiv), $RuCl_3{\cdot}xH_2O$ (2 mg, 0.05 mmol, 5 mol %). and DMF (1.4 mL). The reaction mixture was backfilled with argon and heated at 120 °C in a preheated oil bath. The progress of the reaction was monitored using TLC. After completion of the reaction (36 h), the reaction mixture was diluted with ethyl acetate (25 mL) and washed three times with ice cold water. The organic layer was dried over Na_2SO_4 and concentrated under a vacuum, and the crude residue was purified by flash column chromatography using 2% acetone in DCM to afford pure quinazolinone product **3a** in 72% yield (46 mg).

*C. Typical Experimental Procedure for the Preparation of Representative Product **4c**.* The oven-dried screw cap glass tube equipped with a magnetic stirring bar was charged with quinazolinone **1b** (47.2 mg, 0.2 mmol, 1 equiv), phenylacetylene **2i** (115 mg, 0.8 mmol, 4 equiv), benzoyl peroxide (75% in water, 97 mg, 0.3 mmol, 1.5 equiv), K_3PO_4 (85 mg, 0.4 mmol, 2 equiv), $RuCl_3{\cdot}xH_2O$ (2 mg, 0.05 mmol, 5 mol %), and DMF (1.4 mL). The reaction mixture was backfilled with argon and heated at 130 °C in a preheated oil bath. The progress of the reaction was monitored using TLC. After completion of the reaction (48 h), the reaction mixture was diluted with ethyl acetate (25 mL) and washed three times with ice cold water. The organic layer was dried over Na_2SO_4 and concentrated under a vacuum, and the crude residue was purified by flash column chromatography using 2% acetone in DCM to afford pure quinazolinone product **4c** in 66% yield (50 mg).

3. Characterization Data of Compounds. *(E)-2-(2-Styrylphenyl)quinazolin-4(3H)-one (**3a**).* According to the general procedure, the title compound **3a** was obtained as a colorless solid (46 mg; 72% yield): reaction time 36 h/120 °C; R_f 0.5 (2% acetone in DCM); mp 188−190 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 10.09 (s, 1H), 8.32 (d, J = 7.96 Hz, 1H), 7.84−7.80 (m, 3H), 7.69 (dd, J = 7.39 Hz, 0.95 Hz, 1H), 7.61−7.49 (m, 3H), 7.45−7.38 (m, 3H), 7.34−7.22 (m, 3H), 7.11 (d, J = 16.07 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.8, 152.9, 149.1, 136.9, 136.7, 134.9, 132.3, 132.2, 130.9, 129.5, 128.6, 128.0, 127.9, 127.8, 127.1, 126.9, 126.7, 126.4, 125.6, 120.8; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{17}N_2O$, 325.1335; found, 325.1336.

*(E)-2-(4-Methyl-2-styrylphenyl)quinazolin-4(3H)-one (**3b**).* According to the general procedure, the title compound **3b** was obtained as a colorless solid (42 mg; 62% yield): reaction time 36 h/120 °C; R_f 0.5 (2% acetone in DCM); mp 235−237 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.12 (s, 1H), 8.33 (d, J = 7.93 Hz, 1H), 7.83 (d, J = 3.05 Hz, 2H), 7.60 (apparent d, J = 7.93 Hz, 2H), 7.56−7.52 (m, 1H), 7.46 (d, J = 15.87 Hz, 1H), 7.40 (d, J = 7.32 Hz, 2H), 7.30 (d, J = 7.32 Hz, 2H), 7.26−7.22 (m, 2H) 7.09 (d, J = 15.87 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.5, 152.8, 149.1, 141.2,

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136.9, 136.5, 134.9, 132.1, 129.6, 129.4, 128.8, 128.7, 128.0, 127.9, 127.6, 127.0, 126.7, 126.5, 125.7, 120.7, 21.6; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{19}N_2O$, 339.1492; found, 339.1490.

(E)-2-(4-Methoxy-2-styrylphenyl)quinazolin-4(3H)-one (**3c**). According to the general procedure, the title compound **3c** was obtained as a colorless solid (35 mg; 50% yield): reaction time 36 h/120 °C; R_f 0.4 (2% acetone in DCM); mp 228−230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.19 (s, 1H), 8.31 (d, J = 7.93 Hz, 1H), 7.81 (d, J = 3.66 Hz, 2H), 7.67 (d, J = 8.54 Hz, 1H), 7.54−7.52 (m, 1H), 7.49 (d, J = 15.87 Hz, 1H), 7.41 (d, J = 7.93 Hz, 2H), 7.31−7.21 (m, 4H), 7.08 (d, J = 15.87 Hz, 1H), 6.97 (dd, J = 8.54, 1.83 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.6, 161.5, 152.5, 149.2, 138.5, 136.7, 134.9, 132.5, 131.1, 128.7, 128.1, 127.8, 126.9, 126.8, 126.4, 125.8, 125.1, 120.6, 113.6, 112.1, 55.5; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_2$, 355.1441; found, 355.1442.

2-(4-Bromo-2,6-di((E)-styryl)phenyl)quinazolin-4(3H)-one (**3d**). According to the general procedure, the title compound **3d** was obtained as a colorless solid (64 mg; 64% yield): reaction time 36 h/120 °C; R_f 0.4 (2% acetone in DCM); mp 228−230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.7 (s, 1H), 8.23 (d, J = 7.93 Hz, 1H), 8.07 (s, 2H), 7.86 (t, J = 7.62 Hz, 1H), 7.74 (d, J = 8.54 Hz, 1H), 7.61 (t, J = 7.32 Hz, 1H), 7.42−7.38 (m, 6H), 7.31−7.21 (m, 6H), 6.84 (d, J = 16.48, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.7, 152.3, 148.4, 138.3, 136.3, 134.7, 132.8, 131.3, 128.8, 128.4, 127.4, 127.1, 126.7, 126.6, 126.1, 123.7, 123.2, 121.3; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{30}H_{22}N_2O^{79}Br$, 505.0910; found, 505.0913.

(E)-2-(4-Bromo-2-styrylphenyl)quinazolin-4(3H)-one (**3e**). According to the general procedure, the title compound **3e** was obtained as a colorless solid (59 mg; 74% yield): reaction time 36 h/100 °C; R_f 0.4 (2% acetone in DCM); mp 270−272 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.57 (s, 1H), 8.18 (d, J = 7.93 Hz, 1H), 8.15 (s, 1H), 7.85 (t, J = 7.32 Hz, 1H), 7.70 (d, J = 8.54 Hz, 1H), 7.62 (d, J = 7.93 Hz, 1H), 7.58−7.53 (m, 2H), 7.49 (d, J = 7.93 Hz, 2H), 7.37−7.31 (m, 4H), 7.26 (d, J = 7.32 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.8, 153.0, 148.6, 138.2, 136.6, 134.5, 132.2, 132.1, 131.9, 129.9, 128.8, 128.2, 128.1, 127.4, 126.83, 126.77, 125.8, 124.2, 123.9, 121.2; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{16}N_2O^{79}Br$, 403.0441; found, 403.0444.

Methyl 4-(4-Oxo-3,4-dihydroquinazolin-2-yl)-3,5-di((E)-styryl)-benzoate (**3f**). According to the general procedure, the title compound **3f** was obtained as a colorless solid (59 mg; 61% yield): reaction time 36 h/120 °C; R_f 0.4 (2% acetone in DCM); mp 227−229 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.77 (s, 1H), 8.35 (s, 2H), 8.24 (d, J = 7.93 Hz, 1H), 7.87 (t, J = 7.32 Hz, 1H), 7.75 (d, J = 7.93 Hz, 1H), 7.62 (t, J = 7.62 Hz, 1H), 7.43 (d, J = 7.93 Hz, 4H), 7.37 (d, J = 16.48 Hz, 2H), 7.30 (t, J = 7.82 Hz, 4H), 7.24 (d, J = 7.32 Hz, 2H), 6.95 (d, J = 16.48 Hz, 2H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 165.8, 161.5, 152.2, 148.4, 136.9, 136.3, 135.7, 134.7, 132.5, 131.1, 128.8, 128.3, 127.5, 127.2, 126.7, 126.0, 124.6, 123.8, 121.3, 52.6; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{32}H_{25}N_2O_3$, 485.1860; found, 485.1860.

2-(3,5-Di((E)-styryl)pyridin-4-yl)quinazolin-4(3H)-one (**3g**). According to the general procedure, the title compound **3g** was obtained as a colorless solid (50 mg; 59% yield): reaction time 36 h/120 °C; R_f 0.4 (20% acetone in DCM); mp 281−283 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.77 (s, 1H), 9.06 (s, 2H), 8.23 (d, J = 7.93 Hz, 1H), 7.87 (t, J = 7.32 Hz, 1H), 7.74 (d, J = 8.54 Hz, 1H), 7.62 (t, J = 7.32 Hz, 1H), 7.44−7.39 (m, 6H), 7.33−7.23 (m, 6H), 6.95 (d, J = 16.48 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.5, 150.8, 148.4, 145.8, 137.4, 136.3, 134.7. 133.0, 130.6, 128.8, 128.4, 127.5, 127.3, 126.8, 126.1, 121.9. 121.6; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{29}H_{22}N_3O$, 428.1757; found, 428.1754.

(E)-8-Methyl-2-(2-styrylphenyl)quinazolin-4(3H)-one (**3h**). According to the general procedure, the title compound **3h** was obtained as a colorless solid (44 mg; 65% yield): reaction time 36 h/120 °C; R_f 0.4 (2% acetone in DCM); mp 263−365 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.54 (s, 1H), 8.02 (d, J = 7.93 Hz, 1H), 7.94 (d, J = 7.32 Hz, 1H), 7.69 (d, J = 7.32 Hz, 1H), 7.65 (d, J = 7.32 Hz, 1H), 7.59 (d, J = 7.32 Hz, 1H),7.55 (s, 1H), 7.49−7.41 (m, 4H), 7.34 (t, J = 7.63 Hz, 2H), 7.26−7.21 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 162.3, 152.4, 147.1, 137.0, 136.2, 135.5, 134.8, 133.0, 130.3, 130.1, 130.0, 128.7, 127.8, 127.3, 126.5, 126.4, 126.1, 126.0, 123.4, 120.9, 17.1; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{19}N_2O$, 339.1492; found, 339.1492.

(E)-5-Methyl-2-(2-styrylphenyl)quinazolin-4(3H)-one (**3i**). According to the general procedure, the title compound **3i** was obtained as a colorless solid (47 mg; 69% yield): reaction time 36 h/120 °C; R_f 0.4 (2% acetone in DCM); mp 232−234 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.32 (s, 1H), 7.94 (d, J = 7.93 Hz, 1H), 7.65 (t, J = 7.62 Hz, 1H), 7.56 (t, J = 7.62 Hz, 2H), 7.50−7.39 (m, 5H), 7.34−7.23 (m, 5H); 2.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 162.3, 153.6, 150.3, 140.0, 137.0, 135.7, 133.5, 133.0, 130.4, 130.1, 129.7, 129.0, 128.8, 127.8, 127.3, 126.5, 125.7, 125.6, 125.5, 119.4, 22.5; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{19}N_2O$, 339.1492; found, 339.1494.

(E)-7-Methoxy-2-(2-styrylphenyl)quinazolin-4(3H)-one (**3j**). According to the general procedure, the title compound **3j** was obtained as a colorless solid (45 mg; 63% yield): reaction time 36 h/120 °C; R_f 0.4 (2% acetone in DCM); mp 198−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.40 (s, 1H), 8.08 (d, J = 9.16 Hz, 1H), 7.94 (d, J = 7.93 Hz, 1H), 7.56 (t, J = 7.02 Hz, 2H), 7.48−7.41 (m, 3H), 7.38−7.31 (m, 3H), 7.27 (s, 1H), 7.24 (d, J = 7.32 Hz, 1H), 7.14−7.12 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 164.1, 161.3, 154.6, 150.9, 136.9, 135.6, 133.3, 130.6, 130.2, 129.7, 128.8, 127.9, 127.5, 127.3, 126.6, 125.7, 125.6, 116.2, 114.5, 108.6, 55.7; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_2$, 355.1441; found, 355.1442.

(E)-6-Methoxy-2-(2-styrylphenyl)quinazolin-4(3H)-one (**3k**). According to the general procedure, the title compound **3k** was obtained as a colorless solid (39 mg; 55% yield): reaction time 36 h/120 °C; R_f 0.4 (2% acetone in DCM); mp 219−221 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 12.5 (s, 1H), 7.93 (d, J = 8.01 Hz, 1H), 7.65 (d, J = 8.77 Hz, 1H), 7.58−7.54 (m, 3H), 7.46−7.44 (m, 3H), 7.42 (s, 1H), 7.37 (d, J = 16.4 Hz, 1H), 7.32 (t, J = 7.63 Hz, 2H), 7.25 (s, 1H), 7.23 (d, J = 8.39 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) 161.6, 157.9, 151.6, 143.2, 137.0, 135.7, 133.3, 130.5, 130.1, 129.8, 129.1, 128.8, 127.9, 127.3, 126.5, 125.7, 123.97, 121.86, 105.9, 55.7 (one "C" is merged in one of the above peaks); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_2$, 355.1441; found, 355.1441.

(E)-6-Chloro-2-(2-styrylphenyl)quinazolin-4(3H)-one (**3l**). According to the general procedure, the title compound **3l** was obtained as a colorless solid (48 mg; 67% yield): reaction time 36 h/120 °C; R_f 0.4 (2% acetone in DCM); mp 258−260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.71 (s, 1H), 8.12 (d, J = 1.83 Hz, 1H), 7.95 (d, J = 7.93, 1H), 7.87 (dd, J = 8.55, 2.44 Hz, 1H), 7.72 (d, J = 8.55 Hz, 1H), 7.58 (t, J = 8.24 Hz, 2H), 7.49 (d, J = 7.93, 2H), 7.44 (d, J = 7.32 Hz, 1H), 7.39 (d, J = 16.48. 1H), 7.32 (d, J = 7.32 Hz, 2H), 7.27−7.23 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.9, 154.4, 147.4, 136.9, 135.8, 134.6, 133.0, 130.9, 130.6, 130.3, 129.8, 129.6, 128.7, 127.9, 127.3, 126.6, 125.7, 125.6, 124.8, 122.4; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{16}N_2OCl$, 359.0946; found, 359.0944.

(E)-7-Nitro-2-(2-styrylphenyl)quinazolin-4(3H)-one (**3m**). According to the general procedure, the title compound **3m** was obtained as a colorless solid (38 mg; 51% yield): reaction time 36 h/120 °C; R_f 0.5 (2% acetone in DCM); mp 249−251 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.92 (s, 1H), 8.40 (d, J = 9.16 Hz, 2H), 8.27 (d, J = 9.16 Hz, 1H), 7.97 (d, J = 7.93 Hz, 1H), 7.62−7.58 (m, 2H), 7.52 (d, J = 7.32 Hz, 2H), 7.47−7.41 (m, 2H), 7.33−7.22 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.0, 156.3, 151.2, 149.2, 136.9, 135.9, 132.7, 130.8, 130.5, 129.9, 128.7, 128.2, 127.9, 127.3, 126.7, 125.7, 125.5, 122.3, 120.2 (one "C" is merged in one of the above peaks); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{16}N_3O_3$, 370.1186; found, 370.1187.

(E)-2-(2-(3-Methylstyryl)phenyl)quinazolin-4(3H)-one (**3n**). According to the general procedure, the title compound **3n** was obtained as a colorless solid (51 mg; 76% yield): reaction time 36 h/120 °C; R_f 0.5 (2% acetone in DCM); mp 175−177 °C; ^{1}H NMR (400 MHz,

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DMSO-d_6) δ 12.54 (s, 1H), 8.19 (d, J = 7.93 Hz, 1H), 7.92 (d, J = 7.32 Hz, 1H), 7.84 (t, J = 7.32 Hz, 1H), 7.70 (d, J = 7.93 Hz, 1H), 7.60−7.55 (m, 3H), 7.44 (d, J = 7.93 Hz, 1H), 7.39 (d, J = 16.48 Hz, 1H), 7.26 (d, J = 8.55 Hz, 2H), 7.21−7.17 (m, 2H), 7.06 (d, J = 6.71 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.8, 153.9, 148.7, 137.8, 136.9, 135.8, 134.5, 133.1, 130.7, 130.2, 129.8, 128.61, 128.57, 127.33, 127.25, 126.7, 125.8, 125.7, 125.6, 123.5, 121.1, 20.9 (one "C" is merged in one of the above peaks); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{19}N_2O$, 339.1492; found, 339.1488.

*(E)-2-(2-(4-Methylstyryl)phenyl)quinazolin-4(3H)-one (**3o**).* According to the general procedure, the title compound **3o** was obtained as a colorless solid (45 mg; 66% yield): reaction time 36 h/120 °C; R_f 0.5 (2% acetone in DCM); mp 208−210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.53 (s, 1H), 8.18 (d, J = 7.32 Hz, 1H), 7.92 (d, J = 7.32 Hz, 1H), 7.84 (t, J = 7.63 Hz, 1H), 7.69 (d, J = 7.93 Hz, 1H), 7.58−7.53 (m, 3H), 7.41 (t, J = 7.63 Hz, 1H), 7.36−7.30 (m, 3H), 7.20 (d, J = 16.48 Hz, 1H), 7.12 (d, J = 7.93 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.8, 153.9, 148.7, 137.3, 135.9, 134.5, 134.2, 133.1, 130.5, 130.2, 129.8, 129.3, 127.4, 127.1, 126.7, 126.5, 125.8, 125.6, 124.6, 121.1, 20.82; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{19}N_2O$, 339.1492; found, 339.1488.

*(E)-2-(2-(3-Methoxystyryl)phenyl)quinazolin-4(3H)-one (**3p**).* According to the general procedure, the title compound **3p** was obtained as a colorless solid (33 mg; 47% yield): reaction time 36 h/120 °C; R_f 0.4 (2% acetone in DCM); mp 164−166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.53 (s, 1H), 8.18 (d, J = 7.32 Hz, 1H), 7.92 (d, J = 7.93 Hz, 1H), 7.84 (t, J = 7.63 Hz, 1H), 7.70 (d, J = 7.93 Hz, 1H), 7.61−7.54 (m, 3H), 7.44−7.40 (m, 2H), 7.25−7.19 (m, 2H), 7.07−7.01 (m, 2H), 6.82 (dd, J = 7.93, 1.83 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.9, 159.5, 153.8, 148,7, 138.5, 135.7, 134.5, 133.1, 130.4, 130.2, 129.83, 129.78, 127.38, 127.33, 126.7, 126.2, 125.8, 125.8, 121.1, 118.9, 113.4, 112.1, 55.0; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_2$, 355.1441; found, 355.1439.

*(E)-2-(2-(4-Chlorostyryl)phenyl)quinazolin-4(3H)-one (**3q**).* According to the general procedure, the title compound **3q** was obtained as a colorless solid (32 mg; 45% yield): reaction time 36 h/120 °C; R_f 0.5 (2% acetone in DCM); mp 284−286 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.53 (s, 1H), 8.18 (d, J = 7.93 Hz, 1H), 7.94 (d, J = 7.32 Hz, 1H), 7.84 (t, J = 7.32 Hz, 1H), 7.68 (d, J = 7.93 Hz, 1H), 7.60−7.56 (m, 3H), 7.51 (d, J = 8.54 Hz, 2H), 7.46−7.37 (m, 4H), 7.25 (d, J = 16.48 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.8, 153.8, 148.7, 135.9, 135.6, 134.5, 133.3, 132.2, 130.2, 129.9, 129.2, 128.7, 128.2, 127.5, 127.4, 126.7, 126.6 125.81, 125.76 (one "C" is merged in one of the above peaks); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{16}N_2OCl$, 359.0946; found, 359.0942.

*(E)-2-(2-(2-(Naphthalen-2-yl)vinyl)phenyl)quinazolin-4(3H)-one (**3r**).* According to the general procedure, the title compound **3r** was obtained as a colorless solid (40 mg; 53% yield): reaction time 48 h/120 °C; R_f 0.5 (2% acetone in DCM); mp 265−267 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.58 (s, 1H), 8.2 (d, J = 7.32 Hz, 1H), 8.0 (d, J = 7.93 Hz, 1H), 7.95 (s,1H), 7.87−7.83 (m, 4H), 7.73−7.67 (m, 2H), 7.63−7.55 (m, 4H), 7.51−7.40 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 161.9, 153.9, 148.8, 135.9, 134.6, 134.5, 133.23, 133.19, 132.6, 130.6, 130.3, 130.0, 128.1, 127.9, 127.6, 127.40, 127.39, 126.8, 126.7, 126.5, 126.3, 126.2, 125.9, 125.8, 123.4, 121.2; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{19}N_2O$, 375.1492; found, 375.1489.

*(E)-2-(2-(2-Cyclohexylvinyl)phenyl)quinazolin-4(3H)-one (**3s**).* According to the general procedure, the title compound **3s** was obtained as a colorless solid (26 mg; 40% yield, E:Z 7:1): reaction time 48 h/150 °C; R_f 0.5 (2% acetone in DCM); mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.36 (s, 1H), 8.33 (d, J = 7.96 Hz, 1H), 7.84−7.81 (m, 2H), 7.70 (dd, J = 1.33, 7.53 Hz, 1H), 7.59−7.51 (m, 2H), 7.50−7.44 (m, 1H), 7.40 (dd, J = 1.64, 7.33 Hz, 1H), 6.59 (d, J = 15.66 Hz, 1H), 6.18 (dd, J = 6.82, 15.92 Hz, 1H), 2.21−2.06 (m, 1H), 1.81−1.70 (m, 4H), 1.34−1.29 (m, 2H), 1.22−1.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.8, 153.0, 149.1, 141.9, 137.0, 134.8, 131.6, 130.9, 129.3, 127.9, 127.5, 127.4, 127.1, 126.4, 124.4, 120.8, 41.2, 32.6, 26.0, 25.9; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{23}N_2O$, 331.1805; found, 331.1805.

*Methyl 4-((10-Oxo-10,12-dihydroisoindolo[1,2-b]quinazolin-12-yl)methyl)benzoate (**4a**).* According to the general procedure, the title compound **4a** was obtained as a colorless solid (44 mg; 58% yield); reaction time: 48 h/130 °C; R_f 0.5 (2% acetone in DCM); mp 249−251 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 7.93 Hz, 1H), 8.02 (d, J = 7.32 Hz, 1H), 7.83−7.72 (m, 4H), 7.61−7.52 (m, 3H), 7.31 (d, J = 7.32 Hz, 1H), 6.95 (d. J = 7.93 Hz, 2H), 5.85 (d, J = 6.10 Hz, 1H), 3.92−3.85 (m, 1H), 3.84 (s, 3H), 3.67 (dd, J = 7.32, 13.43 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.8, 161.0, 154.4, 149.2, 142.9, 140.1, 134.4, 132.2, 132.1, 129.7, 129.4, 129.2, 128.8, 127.4, 126.6, 123.5, 123.3, 120.9, 62.4, 52.0, 36.7 (one "C" is merged in one of the above peaks); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{19}N_2O_3$, 383.1390; found, 383.1373.

*12-(4-Acetylbenzyl)isoindolo[1,2-b]quinazolin-10(12H)-one (**4b**).* According to the general procedure, the title compound **4b** was obtained as a colorless solid (45 mg; 62% yield): reaction time 48 h/130 °C; R_f 0.5 (2% acetone in DCM); mp 198−200 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.44 (d, J = 7.71 Hz, 1H), 8.13 (d, J = 7.96 Hz, 1H), 7.88−7.77 (m, 2H), 7.66−7.52 (m, 5H), 7.35 (d, J = 7.07, 1H), 6.96 (d, J = 8.21 Hz, 2H), 5.89−5.84 (m, 1H), 3.90−3.67 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.7, 161.0, 154.4, 149.2, 142.9, 140.3, 135.8, 134.4, 133.5, 132.1, 129.9, 129.3, 128.5, 128.2, 127.4, 126.6, 123.5, 123.3, 120.91, 62.4, 36.6, 26.5; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{19}N_2O_2$, 367.1441; found, 367.1443.

*12-(4-Acetylbenzyl)-2-methylisoindolo[1,2-b]quinazolin-10(12H)-one (**4c**).* According to the general procedure, the title compound **4c** was obtained as a colorless solid (50 mg; 66% yield): reaction time 48 h/130 °C; R_f 0.5 (2% acetone in DCM); mp 215−217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 (d, J = 7.93 Hz, 2H), 8.09 (s, 1H), 7.85−7.79 (m, 1H), 7.65−7.57 (m, 3H), 7.42 (s, 1H), 7.23 (s, 1H), 6.91 (d, J = 7.32 Hz, 2H), 5.86 (s, 1H), 3.79 (s, 2H), 2.53 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.5, 159.8, 155.1, 145.5, 144.0, 142.0, 139.4, 136.1, 135.3, 131.1, 129.7, 128.3, 127.5, 127.4, 126.9, 125.6, 124.9, 123.6, 119.8, 63.32, 36.4, 26.5, 22.4; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{21}N_2O_2$, 381.1598; found, 381.1601.

*12-(4-Acetylbenzyl)-7-methoxyisoindolo[1,2-b]quinazolin-10-(12H)-one (**4d**).* According to the general procedure, the title compound **4d** was obtained as a colorless solid (38 mg; 48% yield): reaction time 48 h/130 °C; R_f 0.5 (2% acetone in DCM); mp 192−194 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23 (d, J = 8.84 Hz, 1H), 8.02 (d, J = 7.45 Hz, 1H), 7.57−7.42 (m, 4H), 7.28 (d, J = 7.33 Hz, 1H), 7.14 (s, 1H), 7.03 (dd, J = 8.84, 2.40 Hz, 1H), 6.86 (d, J = 8.21 Hz, 2H), 5.75 (dd, J = 6.32, 3.54 Hz, 1H), 3.87 (s, 3H), 3.79−3.60 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.6, 165.1, 159.7, 155.3, 143.5, 139.7, 135.9, 133.2, 129.8, 129.6, 128.2, 128.2, 124.8, 123.3, 117.4, 113.6, 106.6, 63.0, 55.9, 36.5, 26.5 (two "C's" are merged in one of the above peaks); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{21}N_2O_3$, 397.1547; found, 397.1548.

*12-(4-Acetylbenzyl)-8-chloroisoindolo[1,2-b]quinazolin-10(12H)-one (**4e**).* According to the general procedure, the title compound **4e** was obtained as a colorless solid (38 mg; 48% yield): reaction time 48 h/130 °C; R_f 0.5 (2% acetone in DCM); mp 171−173 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.40−8.37 (m, 2H), 7.97 (d, J = 8.72 Hz, 1H), 7.78−7.56 (m, 5H), 7.41 (d, J = 7.33 Hz, 1H), 6.91 (d, J = 8.08 Hz, 2H), 5.92−5.88 (m, 1H), 3.86−3.72 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.5, 159.1, 155.0, 143.3, 139.4, 136.0, 135.4, 133.4, 133.1, 130.2, 129.8, 129.7, 128.3, 127.5, 126.2, 125.1, 123.3, 121.4, 63.3, 36.4, 26.5 (one "C" is merged in one of the above peaks); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{18}O_2N_2Cl$, 401.1051; found, 401.1055.

*12-(4-Acetylbenzyl)-2-bromoisoindolo[1,2-b]quinazolin-10(12H)-one (**4f**).* According to the general procedure, the title compound **4f** was obtained as a colorless solid (36 mg; 40% yield): reaction time 48 h/130 °C; R_f 0.5 (2% acetone in DCM); mp 213−215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.41 (d, J = 7.93 Hz, 1H), 8.02 (d, J = 7.93 Hz, 1H), 7.83 (s, 1H), 7.79 (t, J = 7.62 Hz, 1H), 7.72 (d, J = 7.93 Hz, 1H),

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7.62 (t, J = 7.32 Hz, 1H), 7.56 (d, J = 7.93 Hz, 2H), 7.48 (d, J = 7.32 Hz, 1H), 6.80 (d, J = 7.93 Hz, 2H), 5.96 (s, 1H), 4.28 (d, J = 13.43 Hz, 1H), 3.80 (d, J = 13.43 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.4, 159.9, 152.7, 146.2, 138.1, 136.3, 135.7, 134.5, 130.2, 129.8, 128.5, 128.4, 128.3, 127.2, 127.1, 126.2, 124.7, 120.5, 97.2, 43.4, 29.7, 26.5; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{18}N_2O_2Br$, 445.0546; found, 445.0538.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01143.

NMR spectra and HRMS chromatograph of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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para-Selective copper-catalyzed C(sp^2)–H amidation/dimerization of anilides *via* a radical pathway†

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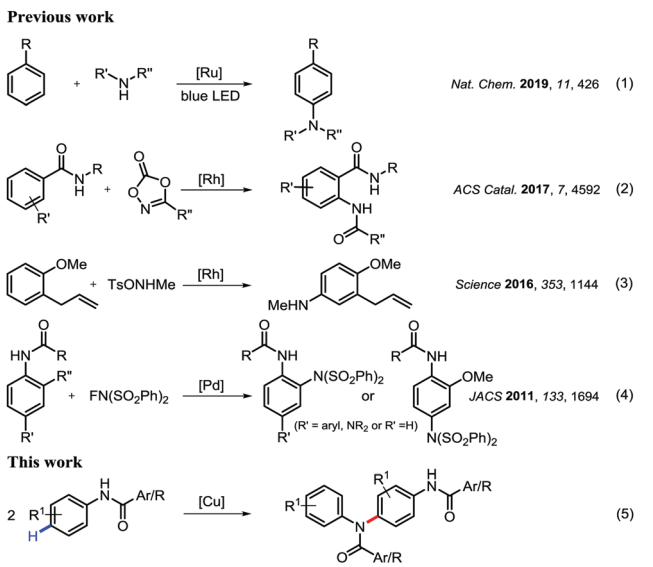
Copper-catalyzed amidation/dimerization of anilides *via* regioselective C(sp^2)–H functionalization is achieved. The *para*-selective amidation is accomplished on the anilide aromatic ring *via* a radical pathway leading to C–N bond formation in the presence of ammonium persulfate as a radical source/oxidant for the copper catalyst. The developed protocol tolerates a wide range of anilide substrates. The regioselectivity is confirmed by single-crystal X-ray studies.

Transition-metal-catalyzed C–H bond functionalization has emerged as a prominent synthetic tool in organic chemistry over the past few decades.[1] It avoids the need for prefunctionalization of substrates and offers straightforward access to the desired scaffold in high atom and step-economy. Regioselective C–H functionalization to furnish C–C and C–X (X = O, N, S, *etc.*) bond formation is generally achieved either by using a directing-group or steric/electronic factors. The functionalization of arenes *ortho* to the directing-groups can be realized easily since the metal can readily reach the desired site. Whereas, selectively reaching the *meta* or *para* position is difficult because of many other factors.[2] The pioneering work in the field of *meta* and *para*-selective C–H functionalization has been reported by the Yu[3] and Maiti[4] groups respectively, employing a molecular template to direct a metal catalyst to a specific position. Despite the many advantages of template-assisted site-selective C–H functionalization over the traditional methods, sometimes the template is larger than the substrate and additional steps are required to install or remove them, which makes the process lengthy, tedious and economically unviable. Hence, the process wherein the functional group of the molecule itself acts as an inherent directing group is preferred over the earlier methods.[5] We have previously utilized amide as an inherent directing group for the functionalization of quinazolinones as well as acrylamides using ruthenium catalysis for alkenylation and cascade annulation respectively.[6]

Amide is one of the potential functional groups as well as directing groups, which has been utilized enormously in chelation controlled functionalization using transition-metal catalysis.[7] In continuation of our interest in developing new methods utilizing amide as an inherent directing group for the C–H activation, we explored the functionalization of anilide derivatives. Interestingly, during the course of our investigation, we observed self-dimerization of anilide under one of our Cu-catalyzed reaction conditions. After careful observation and characterization of the obtained product, we have confirmed the C–N bond formation at the *para*-position to the nitrogen of the electron-rich anilide ring. Interestingly, a literature survey revealed that Masui *et al.* observed dimerization of benzanilides



Scheme 1 Selected metal-catalyzed aminations and our work.

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Table 1 Optimization of the reaction conditions[a]

Obs. no.	Oxidant (equiv.)	$Cu(OAc)_2$ (mol%)	Concen. (in M)	Yield[b] (%)
1	APS (1.5)	5	0.15	27
2	APS (1.0)	—	0.15	Trace
3	—	5	0.15	NR
4	APS (2.0)	5	0.15	16
5	APS (1.0)	5	0.15	41
6	APS (0.75)	5	0.15	32
7	APS (1.0)	5	0.30	21
8	APS (1.0)	5	0.10	49
9	**APS (1.0)**	**10**	**0.10**	**62 (77)[c]**
10	$K_2S_2O_8$ (1.0)	10	0.10	46
11	$Na_2S_2O_8$ (1.0)	10	0.10	42
12	APS (1.0)/O_2	10	0.10	22
13	$(tBuO)_2$ (1.0)	10	0.10	NR
14[d]	APS (1.0)	10	0.10	40
15[e]	APS (1.0)	10	0.10	52

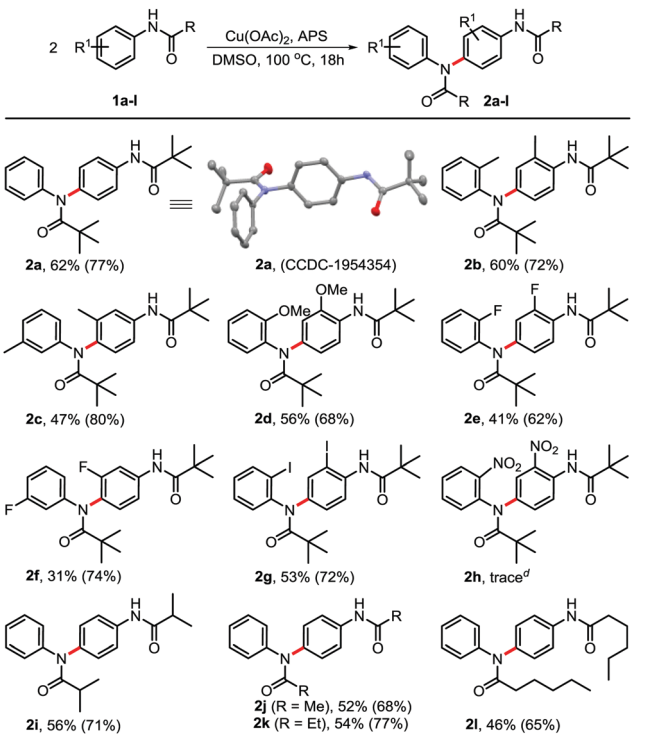
[a] Reaction conditions: **1a** (0.2 mmol), $Cu(OAc)_2$, oxidant-ammonium persulfate (APS) in DMSO at 100 °C for 18 h. [b] Isolated yield. [c] Yield in the parentheses is based on the recovered starting material. [d] Additive: AcOH (1 equiv.). [e] Additive: NaOAc (1 equiv.).

during anodic oxidation,[8] however, metal-catalyzed *para*-selective amidation/dimerization of anilides through C–N bond formation specifically on the aniline aromatic ring as observed here has not been reported until now. Nevertheless, C(sp^2)–H amidation/imidation/sulfonamidation or amination at the *ortho*/*meta*/*para*-position of various functional/directing groups have been reported using transition-metal catalysis (Scheme 1, eqn (1)–(4))[9] or transition metal-free methods.[10] Copper catalysts are the most desired transition-metal catalysts for this purpose as they are robust, cost-effective, and provide a practical alternative over the other expensive transition-metal catalysts such as [Pd], [Ru], [Ir] *etc.*[9b,h,11] Hence, we aimed at optimizing the protocol using a copper catalyst. In this context, reported herein is a protocol for the *para*-selective amidation/dimerization of anilides using a copper catalyst and inexpensive ammonium persulfate (APS) as an oxidant/radical source (Scheme 1, eqn (5)).

The optimization of the protocol commenced with the modifications under the previously perceived conditions. Selected modifications are presented in Table 1. Though several variations in oxidant, catalyst, reaction concentration, time and temperature were tried, the best yield achieved through optimization studies was 62% (Table 1, entry 9). However, 0.037 mmol of the starting material was recovered unchanged, and hence the actual yield based on the recovered starting material (brsm) was 77%. GC/GC-MS analysis of the crude reaction mixture, as well as purified product **2a**, confirms the formation of a single regioisomer. The *para* regioselectivity of **2a** was confirmed by X-ray crystallography (CCDC 1954354†).

After optimizing the reaction conditions, our next target was to generalize the scope of the developed protocol. The study began with the variation of substituents on the aromatic part of the anilide **1a**. The substrates with the methyl substituent *ortho* or *meta* to the anilide nitrogen furnished the corresponding products **2b** and **2c** respectively in good yields. Similarly, anilide with an electron-donating methoxy group at the *ortho* position also worked smoothly to provide the expected compound **2d** in optimum yield. The fluoro substituted anilides resulted into the

Table 2 Amidation/dimerization of *N*-arylalkylamide[a,b,c]



[a] Reaction conditions: **1a–l** (0.2 mmol), $Cu(OAc)_2$ (10 mol%), APS (0.2 mmol), DMSO (0.1 M) in a screw cap glass tube at 100 °C for 18 h. [b] Isolated yields. [c] Yields in parentheses are based on the recovered starting material. [d] Starting material recovered unchanged.

expected products **2e** and **2f** with comparatively lower yields. The *ortho*-substituted anilides (**1b**, **1e**) worked better than the corresponding *meta*-substituted anilides (**1c**, **1f**) probably because of the steric hindrance. Following the same trend, *iodo*-substituted anilide also provided the dimer **2g** in good yield. However, anilide with an electron-withdrawing $-NO_2$ substituent failed to furnish the expected product **2h** under the optimized conditions. We reasoned that the amide group of the electron-deficient anilide fails to bind with the metal during the course of the reaction (Table 2).

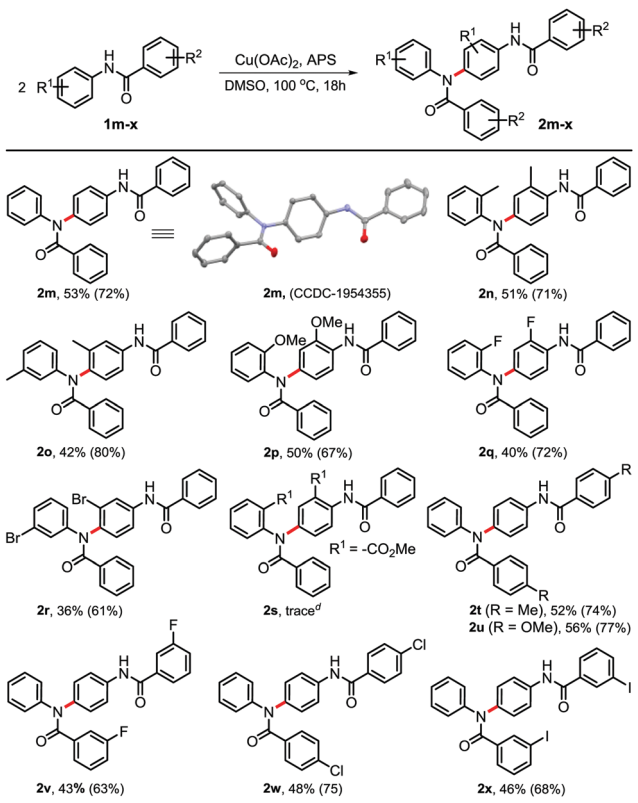
At this point, we decided to study the substrate scope by varying the aliphatic group of anilide **1a**. Accordingly, *N*-phenylisobutyramide was treated under the optimized reaction conditions, which worked well leading to **2i**. *N*-Phenylacetamide also resulted into the corresponding dimerized product **2j** in moderate yield. The reaction worked equally well with *N*-phenylpropionamide to obtain **2k**. However, the substrate *N*-phenylhexanamide having a long alkyl chain provided the corresponding dimer **2l** in relatively lower yield. Overall, the bulkiness of the aliphatic group had minimal effect on the yield. The regioselectivity of **2j** was confirmed by its synthesis from known amine (see the ESI†).

The successful completion of the substrate scope study of *N*-arylalkylamides prompted us to demonstrate the generality of the protocol with varyingly substituted *N*-arylbenzamides. The developed protocol was first applied on *N*-phenylbenzamide, and gratifyingly the product **2m** was obtained in a good yield.

The regioselectivity of the product **2m** was also confirmed by single-crystal X-ray studies (CCDC 1954355†). Initially, we studied the effect of substituents present on the electron-rich anilide aromatic ring. Two anilide substrates with an electronically unbiased methyl substituent at the *ortho* and *meta* positions of the electron-rich aromatic ring worked well to provide **2n** and **2o**, respectively. The anilide substrate with an electron-donating methoxy group furnished **2p** in moderate yield. The *ortho*-fluoro and *meta*-bromo-substituted anilides worked fine to provide the corresponding dimers **2q** and **2r**, respectively. However, as observed before, anilide having a strong electron-withdrawing group failed to give the expected product **2s** under the developed protocol (Table 3).

After the study of variation in the substituents present on the electron-rich aromatic ring of anilide, we targeted to study the effect of variation on the electron-deficient aromatic ring of *N*-arylbenzamides. The substrate with a methyl group at the *para*-position of the amide carbonyl did not affect the yield and **2t** was obtained in comparable yield with **2m**. An electron-donating methoxy group substituted anilide also worked well to furnish dimer **2u**. *meta*-Fluoro, *para*-chloro, and *meta*-iodo substituted anilides also worked fine to provide the corresponding desired products **2v**, **2w** and **2x** respectively in moderate yields.

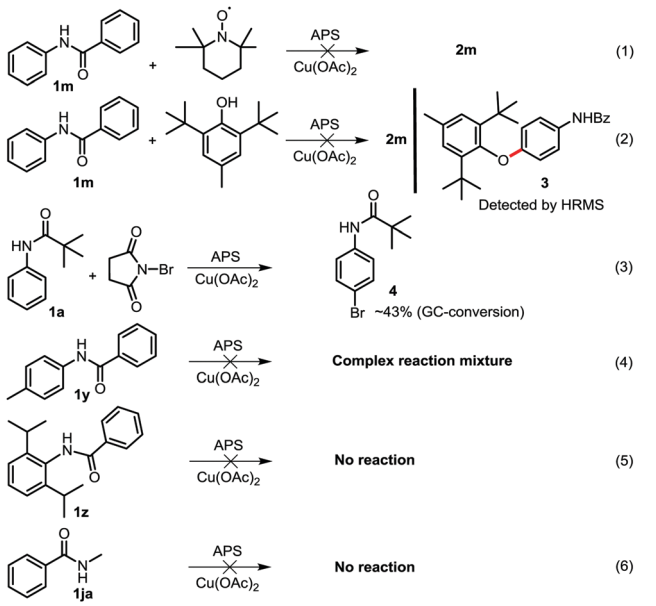
Table 3 Amidation/dimerization of *N*-arylbenzamides[a,b,c]



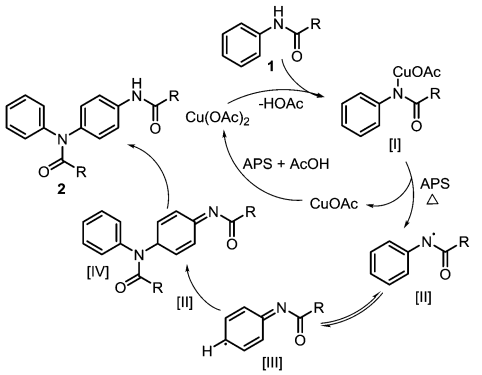
[a] Reaction conditions: **1m–x** (0.2 mmol), $Cu(OAc)_2$ (10 mol%), APS (0.2 mmol), DMSO (0.1 M) in a screw cap glass tube at 100 °C for 18 h. [b] Isolated yields. [c] Yields in parentheses are based on the recovered starting material. [d] Starting material recovered unchanged.

Overall, the developed protocol is quite general and many substituents, except highly electron-withdrawing groups, are well tolerated. The protocol is highly selective for anilides. We neither observed cross-coupling products between anilides and aliphatic/aromatic amides/amines nor dimerization of other amides (see the ESI†). Derivatives of the products **2a–2x** are commonly used in polymer/material chemistry,[12] and they would also be interesting precursors for the synthesis of the corresponding carbazoles or phenanthridinones *via* a regioselective C–H activation strategy.

A few control experiments were performed for preliminary understanding of the mechanism of our protocol. The radical nature of the reaction was determined by performing the reaction of anilide **1m** under the standard reaction conditions in the presence of radical scavengers such as TEMPO and BHT (Scheme 2, eqn (1) and (2)). Complete inhibition of the reactions was observed in both cases. Interestingly, adduct **3** (Scheme 2, eqn (2)) was observed in HRMS of the crude reaction mixture, which confirms the radical pathway of the reaction. The formation of brominated product **4** instead of dimer **2a** in the presence of NBS also confirms the radical pathway (Scheme 2, eqn (3)). The reaction of anilide **1y** showed much less conversion and a complex reaction mixture by TLC (Scheme 2, eqn (4)). The anilide substrate **1z** having a bulky isopropyl substituent on both *ortho*-positions did not react under the standard reaction conditions though the *para*-position was available for the reaction. This observation indicates that probably the approach of the copper catalyst to the amide –NH is blocked due to the steric hindrance of the isopropyl group leading to the failure of the reaction (Scheme 2, eqn (5)). We believe that the developed protocol works *via* a radical mechanism involving the formation of a *para*-quinone type of intermediate on the aniline part of the anilide, which makes it highly regioselective. A tentative proof for our hypothesis of a *para*-quinone type intermediate was



Scheme 2 Control experiments.



Scheme 3 Plausible mechanism.

realized when the substrate **1ja** (a structural isomer of **1j**) lacking the aniline part of the aromatic ring was subjected to our protocol (Scheme 2, eqn (6)). The reaction did not work because a *para*-quinone type intermediate is not possible on a benzamide aromatic ring.

Based on the literature survey,[9b,j,13] and the control experiments (Scheme 2), a plausible mechanism *via* a radical pathway is depicted in Scheme 3. Anilide **1** first chelates with a copper catalyst to form complex [I], which converts to amidyl radical intermediate [II] in the presence of APS. The amidyl radical intermediate transforms to a stable *para*-quinone type imine radical intermediate [III]. A radical coupling between intermediates [II] and [III] provides the intermediate [IV], which on aromatization furnishes the desired products **2**. The copper catalyst is again regenerated in the presence of the oxidant APS. The proposed mechanism provides important starting points for a detailed investigation of the mechanism.

In conclusion, we have developed a unique process for *para*-selective C–H functionalization leading to amidation/dimerization of anilide derivatives. The developed protocol is highly selective as the dimerization through C–N bond formation occurs specifically on the aniline part of the anilide. Preliminary mechanistic investigation demonstrates that the reaction follows a radical pathway. The substrate scope has been demonstrated utilizing an inexpensive copper catalyst. Currently, we are exploring the protocol for C–H functionalization of anilide derivatives with other reacting partners leading to C–C as well as C–X bond formation.

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Conflicts of interest

There are no conflicts to declare.

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

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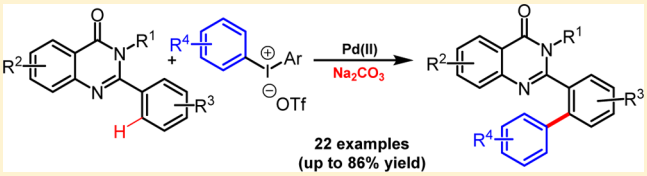
Supporting Information

ABSTRACT: The Pd-catalyzed quinazolinone-directed regioselective monoarylation of aromatic rings by C−H bond activation is developed. A broad substrate scope is demonstrated for both quinazolinone as well as diaryliodonium triflates. The use of a base was found to be crucial for this transformation, unlike for the known nitrogen-directed arylations. All of the novel quinazolinones of biological interest were synthesized by using the operationally simple Pd(II)-catalyzed arylation reaction.



INTRODUCTION

More than 70% of the top branded drugs contain at least one heterocyclic nucleus as a part of its overall skeleton. In particular, for many synthetic drugs, bioactive natural products, and agrochemicals, those encompassing nitrogen-heterocyclic scaffolds are most common.[1] Quinazolinones are one of the important nitrogen-containing heterocyclic motifs; it is found in more than 200 natural products as well as in several drugs (Figure 1).[1b,2] The quinazolinone derivatives possess a wide range of pharmacological activities such as antimalarial, anticancer, antimicrobial, antidiabetic, 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]

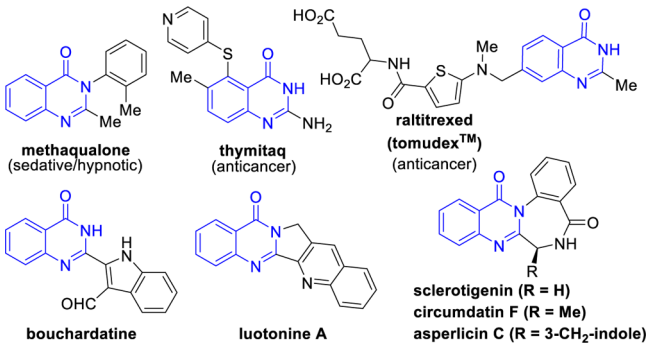


Figure 1. Selected quinazolinone drugs and natural products.[1,2]

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 organic compounds have been developed with or without directing groups.[4] The metal-catalyzed inter- or intramolecular aromatic C−H arylation is one of the most widely used critical steps in the total synthesis of several natural products[4h] and the late-stage derivatization of bioactive molecules.[4g]

Because of 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. In this context, the literature revealed that, although there are several classical methods available for the synthesis of novel quinazolinone derivatives,[2,5] there are only a few instances in which quinazolinone compounds were functionalized by metal catalysis. Pd-catalyzed oxygenations[6] and oxidative C−H aminations[7] were reported by Reddy and Wu et al., respectively. Besson and co-workers reported regioselective arylation of (2*H*)-quinazolin-4-ones.[8] Pd-catalyzed syntheses of phenanthridine/benzoxazine-fused quinazolinones were reported by using three different approaches; intramolecular C−H activation with bromoarenes,[9] intramolecular oxidative C−H amination,[10] and cascade C−H/N−H arylation.[11] A few other metal catalysts were utilized in the quinazolinone/quinazoline functionalization, such as rhodium-catalyzed regioselective direct C−H amidation,[12] copper-catalyzed cascade amination,[13] and Ru/Rh-catalyzed annulation reactions.[14] Nevertheless, to the best of our knowledge, quinazolinone-directed intermolecular arylation of quinazolinone compounds was not known until now.

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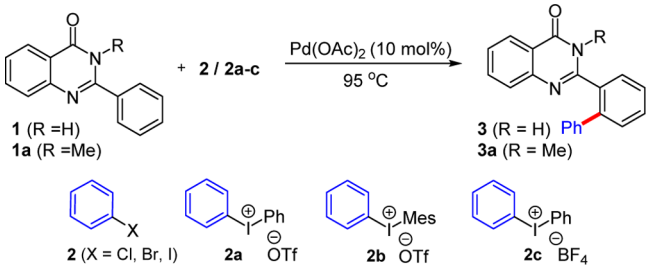
RESULTS AND DISCUSSION

Herein, we report a protocol for the arylation of various quinazolinones. The optimization of the protocol was carried out by screening various reaction parameters. The initial attempts using N−H-free quinazolinone **1** as the substrate with various halobenzenes **2** 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 halobenzenes **2**, using a Pd-catalyst and other additives did not furnish the expected product **3a** under various reaction conditions (Table 1). These

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

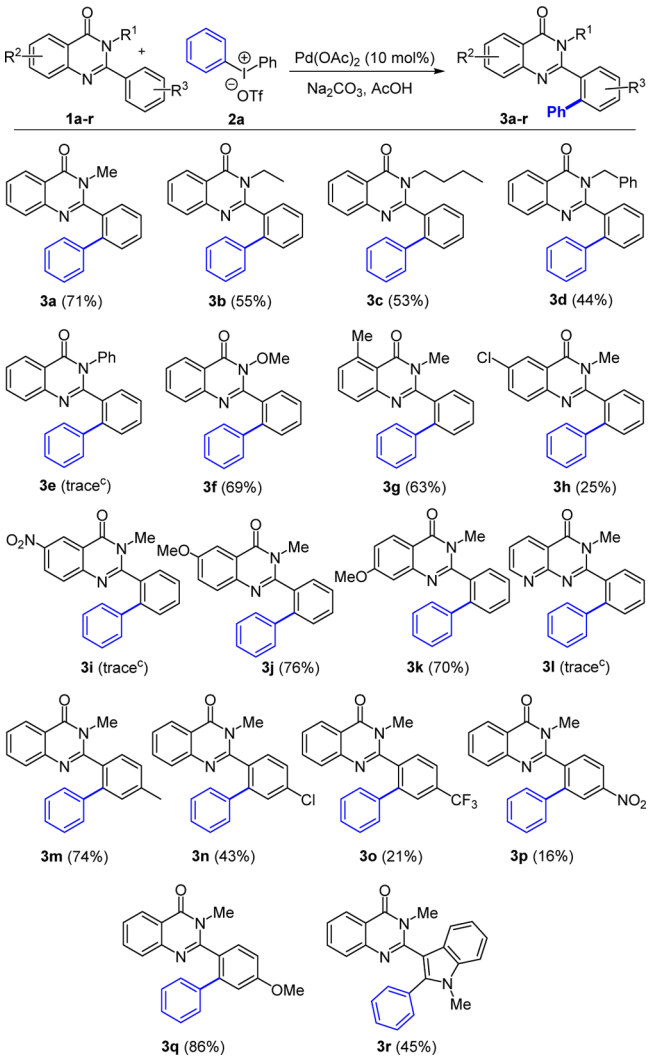
[a]Selected entries. [b]Reaction conditions: **1a** (0.2 mmol), AcOH (1 mL) in a sealed tube for 36 h. [c]Isolated yield. N.R. = No reaction.

observations suggest that more activated arylation reagent was necessary for this transformation. Diaryliodonium salts are well known as an arylation reagent because of 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 halobenzenes to diphenyliodonium triflate **2a**, so expected product **3a** was formed in a 35% yield (entry 2).

The variation in solvents did not show the formation of the expected product (entries 3, 4). Also, the use of the unsymmetrical iodonium salt **2b** or iodonium salt **2c**, which have different counterions, gave lower yields (entries 5, 6). We did not observe the expected product **3a** in the absence of 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-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). Furthermore, variation in the optimized conditions such as a change in the base NaOAc (entry 10), solvent PivOH (entry 11), solvent combinations of AcOH:/PivOH (entry 12), or temperature (among other possibilities), resulted in either low or trace amounts of product formation.

With the optimized conditions established, 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).

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.

Initially, the effect of N-substitution was studied. N-Primary alkyl-substituted quinazolinones furnished the expected products **3a−c** with moderate-to-good yields. We observed that with the increase in the chain length, the yield of the respective product decreases. The quinazolinone substrate with the *N*-benzyl substituent resulted in a moderate yield of **3d**. The N-phenyl-substituted quinazolinone provided only a trace amount of product **3e**. The reason behind this might be the steric hindrance caused by the *N*-phenyl ring, which enforces the

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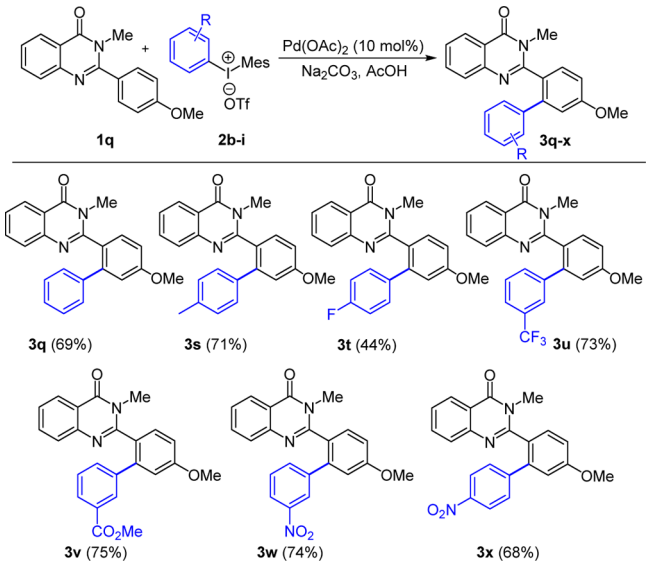
other phenyl ring out of the plane, thus inhibiting the formation of the palladacycle. The quinazolinone substrate with the *N*-methoxy substituent furnished **3f** in good yield. The N-methyl substituted quinazolinone provided a better yield than the substrates with other *N*-substituents. Keeping the N-methyl substitution constant, the further scope of the arylation reaction with varyingly substituted quinazolinone cores 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 yields of products **3h** and **3i**, respectively. Most probably, the electron-withdrawing substituents weaken the coordinating ability of these substrates with the metal catalyst, which results in lower yields. Electron-rich substituents provided the arylated products **3j** and **3k** in very good yields. The heterocyclic substrate could only afford a trace amount of product **3l** because of the 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 an alkyl-substituted aromatic ring resulted in a decent yield of product **3m**; however, as anticipated, chloro and other electron-withdrawing substituents resulted in a moderate-to-low yield of products **3n**−**p**. Electron-rich substituents enhanced the C−H activation process, and the product **3q** was obtained in an excellent yield. 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

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 °C. [b]Isolated yield.

known that the sterically less-hindered aryl group of diaryliodonum triflate undergoes metal-catalyzed coupling;[16d] hence, we kept the sterically hindered mesitylene as one of the substituents in the arylation reagent and varied the other aryl substituents. Various substituents on the arylation reagent 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 a moderate yield. The arylation reagents with electron-withdrawing groups underwent smooth reactions under the developed protocol. The trifluoromethyl and ester groups at the *meta*-position on the arylation reagent were tolerated well, and expected products **3u** and **3v** were synthesized in decent yields, respectively. Nitro groups at the *meta*- and *para*-positions of the arylating reagents provided good yields of products **3w** and **3x**, respectively. Overall, it was observed that having electron-withdrawing groups on arylation reagents facilitates the reaction. It can be reasoned that the palladium insertion takes place promptly on a 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 generation of a library of compounds.

A plausible mechanism for the developed arylation protocol is depicted in Figure 2, which is based on the literature precedence.[4j,7,17]

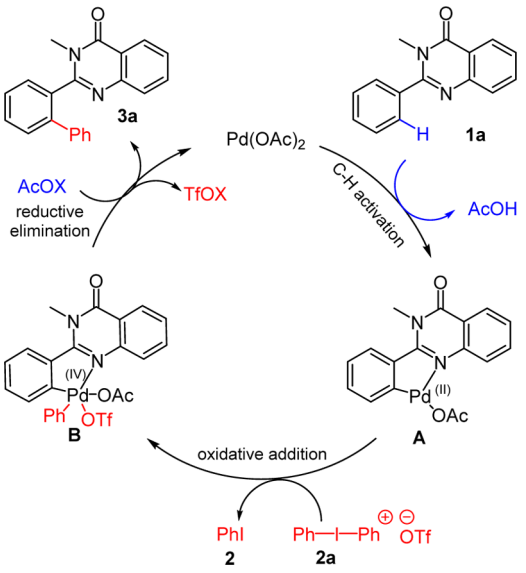


Figure 2. Proposed mechanism.

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**. 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.

CONCLUSION

In summary, a quinazolinone scaffold has been demonstrated as the inherent directing group in the Pd-catalyzed intermolecular, regioselective, monoarylation 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 the late-stage derivatization of bioactive quinazolinones and for the development of natural products for SAR studies. Screening of the anticancer and antimalarial properties of all the new synthesized quinazolinone compounds, and the work toward the development of quinazolinone as a directing group for other C−H activation processes is underway in our laboratory.

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EXPERIMENTAL SECTION

General Information. All reagents and solvents were used as received from commercial sources unless otherwise noted. All experiments were carried out under an argon atmosphere in a sealed tube. Precoated 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 the eluents. The ^{1}H and ^{13}C NMR spectra were recorded on 200/400/500 MHz and 50/100/125 MHz NMR spectrometer, respectively, in $CDCl_3$. Chemical shifts were reported as δ values from standard peaks. The melting points were recorded on a Buchi instrument. The mass spectra were taken on an LC−MS (ESI) mass spectrometer. High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer. All diaryliodonium triflates[15c,d,18] and quinazolinone starting materials[19,20] were prepared according to well-known literature procedures.

EXPERIMENTAL PROCEDURES FOR THE SYNTHESIS OF STARTING MATERIALS

Method A. A known literature 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). The reaction mixture was stirred at 120 °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 petroleum ether/EtOAc (5:1) as an eluent to afford 2,3-disubstituted-4(3*H*)-quinazolinones **1a**−**r**.

Method B. A known literature 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 a portion-wise addition of PIDA (1.5 mmol) over 5 min. After the reaction mixture was stirred for 1 h, it was diluted with EtOAc (20 mL), quenched with 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 petroleum ether/EtOAc (5:1) as an eluent to afford 2,3-disubstituted-4(3*H*)-quinazolinones **1a**−**r**.

*3-Methyl-2-phenylquinazolin-4(3H)-one (**1a**).*[19] Following the **Method A** procedure, **1a** was obtained as a 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 a 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 a 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 a 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 a 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 a 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 a white solid (113 mg; 45% yield): R_f: 0.4 (1:4 EtOAc/ pet. ether); mp 105−107 °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 a white solid (192 mg; 67% yield): R_f: 0.35 (1:4 EtOAc/petroleum ether); mp 126−128 °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 a 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 a 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 a 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 a 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 a 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 a 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 a white solid (131 mg; 43% yield): R_f: 0.35 (1:4 EtOAc/petroleum ether); mp 119−121 °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 a 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 a 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 a white solid (130 mg; 45% yield): R_f: 0.4 (1:1 EtOAc/petroleum ether); mp

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194−196 °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.

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 this mixture, AcOH (1 mL; 0.2M) was added and flushed twice with argon gas. The tube was sealed with a screw cap and placed in a preheated oil bath at 90−120 °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 °C: R_f: 0.4 (1:4 EtOAc/petroleum ether); mp 125−127 °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 °C: R_f: 0.4 (1:4 EtOAc/petroleum ether); mp 137−139 °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 °C: R_f: 0.4 (1:4 EtOAc/petroleum ether); mp 108−110 °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 °C: R_f: 0.4 (1:4 EtOAc/petroleum ether); mp 84−85 °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 a trace amount and was confirmed by TLC analysis and LC−HRMS; reaction time: 36 h at 120 °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 °C: R_f: 0.4 (1:3 EtOAc/petroleum ether); mp 101−103 °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 °C: R_f: 0.4 (1:4 EtOAc/petroleum ether); mp 124−126 °C; ^{1}H 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 °C: R_f: 0.35 (1:3 EtOAc/petroleum ether); mp 129−131 °C; ^{1}H 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 a trace amount and was confirmed by TLC analysis and LC−HRMS; reaction time: 36 h at 120 °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 °C: R_f: 0.35 (1:2 EtOAc/petroleum ether); mp 177−179 °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 °C: R_f: 0.35 (1:2 EtOAc/petroleum ether); mp 197−199 °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 and was confirmed by TLC analysis and LC−HRMS; reaction time: 36 h at 120 °C: 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 °C: R_f: 0.4 (1:4 EtOAc/petroleum ether); mp 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (d, J = 7.9 Hz, 1H), 7.82−7.74 (m,

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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 °C: R_f: 0.5 (1:2 EtOAc/petroleum ether); mp 148−150 °C; ^{1}H 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 °C: R_f: 0.35 (1:2 EtOAc/petroleum ether); mp 140−142 °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 °C: R_f: 0.3 (1:2 EtOAc/petroleum ether); mp 215−217 °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 °C: R_f: 0.5 (1:1 EtOAc/petroleum ether); mp 192−194 °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 °C: R_f: 0.5 (1:4 EtOAc/petroleum ether); mp 198−200 °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 °C: R_f: 0.5 (1:1 EtOAc/petroleum ether); mp 130−132 °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 °C: R_f: 0.5 (1:1 EtOAc/petroleum ether); mp 155−157 °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 °C: R_f: 0.3 (1:2 EtOAc/petroleum ether); mp 142−144 °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 °C: R_f: 0.4 (1:2 EtOAc/petroleum ether); mp 118−120 °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 °C: R_f: 0.5 (1:1 EtOAc/petroleum ether); mp 158−160 °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 °C: R_f: 0.5 (1:1 EtOAc/petroleum ether); mp 205−207 °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.

■ ASSOCIATED CONTENT

Supporting Information

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Spectroscopic data (^{1}H, ^{13}C, and HRMS spectra) of all new compounds (PDF)

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