Development of new carbon-carbon bond forming methodologies for the synthesis of diversely functionalized nitrogen heterocycles

by

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in
SCIENCE

Under the supervision of
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March-2023

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DECLARATION

The research work embodied in this thesis has been carried out at CSIR–National Chemical Laboratory, Pune under the supervision of **Dr. M. Muthukrishnan**, Organic Chemistry Division, CSIR–National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

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Dedicated to

My Beloved Family

With Lots of Love

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Units

°C	Degree centigrade
cm	Centimetre
mg	Milligram
h	Hour
Hz	Hertz
µL	Microlitre
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
ppm	Parts per million

Chemical Notations

AcOH	Acetic acid
Ac_2O	Acetic anhydride
AgSbF6	Silver hexafluoro antimonite
Ag_2O	Silver oxide
AIBN	Azobisisobutyronitrile
$AlCl_3$	Aluminum chloride
AgOTf	Silver trifluoromethanesulfonate
$AgSbF_6$	Silver hexafluoroantimonate
$AgNTf_2$	Silver(I) bis(trifluoromethanesulfonyl)amide
$AuCl_3$	Gold(III) chloride
aq.	Aqueous
$BF_3.OEt_2$	Boron trifluoride diethyl etherate
BHT	Butylated hydroxytoluene
$Bi(OTf)_3$	Bismuth(III) trifluoromethanesulfonate
Boc	*tert*-butyloxycarbonyl
*n*BuLi	*n*-Butyl lithium
^{t}BuNC	*tert*-Butyl isocyanide
Cat.	Catalytic
Conc.	Concentrated
CO	Carbon monoxide
CN	Cyanide
$Cu(OTf)_2$	Copper(II) trifluoromethanesulfonate
$Cu(acac)_2$	Copper(II) acetylacetonate
DCM	Dichloromethane
DCE	Dichloroethane
DMF	*N,N*-Dimethylformamide
DMAP	*N,N′*-Dimethyl aminopyridine

DMSO	Dimethyl sulfoxide
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Et_2AlCl	Diethylaluminium chloride
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
$FeCl_3$	Iron(III) chloride
$Fe(acac)_3$	Tris(acetylacetonato) iron(III)
fac-Ir(ppy)$_3$	*fac*-Tris(2-phenylpyridine)iridium(III)
HBF_4	Fluoroboric acid
H_2	Hydrogen
H_2O	Water
$InCl_3$	Indium(III) chloride
K_2CO_3	Potassium carbonate
$LiAlH_4$	Lithium aluminium hydride
Mg	Magnesium
Me_3SiCN	Trimethylsilyl cyanide
$Mo(CO)_6$	Molybdenum hexacarbonyl
$Mn(acac)_2$	Manganese(II) acetylacetonate
NaOH	Sodium hydroxide
$NaHCO_3$	Sodium bicarbonate
NH_4Cl	Ammonium chloride
Na_2SO_4	Sodium sulfate
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NHC	*N*-Heterocyclic Carbene
NMP	N-Methyl-2-pyrrolidone
$Ni(cod)_2$	Bis(cyclooctadiene)nickel(0)
Pd/C	Palladium on carbon
PPh_3AuCl	Chloro(triphenylphosphine)gold(I)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$P(Cy)_3$	Tricyclohexylphosphine
$PhSiH_3$	Phenylsilane
$PhSO_2Na$	Sodium benzenesulfinate
$Sc(OTf)_3$	Scandium trifluoromethanesulfonate
SPhos	Dicyclohexyl(2′,6′-dimethoxy[1,1′-biphenyl]-2-yl)phosphane
TBACl	Tetrabutylammonium chloride
TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
$TiCl_4$	Titanium tetrachloride

TFA	Trifluoroacetic acid
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
$TMSN_3$	Trimethylsilyl azide
TosMIC	*p*-Toluenesulfonylmethyl isocyanide
XPhos	Dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane
$ZnCl_2$	Zinc chloride
$Zn(CN)_2$	Zinc cyanide

Other Notations

calcd	Calculated
δ	Chemical shift
J	Coupling constant in NMR
DEPT	Distortionless Enhancement by Polarization Transfer
dr	Diastereomeric excess
ee	Enantiomeric excess
equiv.	Equivalents
ESI	Electrospray ionization Mass spectrometry
HPLC	High Pressure Liquid Chromatography
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Homonuclear Correlation Spectroscopy
HRMS	High Resolution Mass Spectrometry
IR	Infra Red
m/*z*	Mass-to-charge ratio
mp	Melting Point
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
rt	Room temperature
TLC	Thin layer chromatography

Abbreviation Used for NMR Spectral Information

br	broad	s	singlet
d	doublet	t	triplet
q	quartet	quint	quintet
sept	septet	m	multiplet
dd	doublet of doublets		
ddd	doublet of doublet of doublets		

- ✓ All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.
- ✓ All the moisture and air sensitive reactions have been carried out in anhydrous solvents under argon atmosphere in oven-dried glassware. Solvents were distilled and dried using standard protocols.
- ✓ Petroleum ether refers to the fraction collected in the boiling range 60-80 °C. Organic layers after every extraction were dried over anhydrous sodium sulfate.
- ✓ Air-sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
- ✓ TLC was performed on E-Merck pre-coated 60 F254 plates and the visualization was accomplished either by exposing to UV light, iodine adsorbed on silica or by immersion in *p*-anisaldehyde (in ethanol), vanillin (in ethanol), KMnO4 (in ethanol) and ninhydrin (in ethanol) followed by heating with a heat gun for ~15 sec.
- ✓ All evaporations were carried out under reduced pressure on the Heidolph rotary evaporator below 50 °C unless otherwise specified.
- ✓ Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- ✓ Deuterated solvents for NMR spectroscopic analyses were used as received. ^{1}H NMR spectra were recorded on AV-200 MHz, AV-400 MHz, JEOL AL-400 (400 MHz) and DRX–500 MHz spectrometer.
- ✓ ^{13}C NMR spectra were recorded on AV-50 MHz, AV-100 MHz, JEOL AL-100 (100 MHz) and DRX-125 MHz spectrometers. ^{19}F NMR spectra were recorded on AV-376 MHz.
- ✓ Chemical shifts (δ) reported are referred to as internal reference tetramethylsilane (TMS). Chemical shifts have been expressed in ppm units relative to TMS, using the residual solvent peak as a reference standard. Coupling constants were measured in Hertz.
- ✓ All the melting points are uncorrected and were recorded using a scientific melting point apparatus (Buchi B-540).

- ✓ High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. EI mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- ✓ Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film.
- ✓ Chemical nomenclature (IUPAC) and structures were generated using Chem Bio Draw Ultra 20.0 software.
- ✓ The compound, scheme, figure and table numbers given in each section of the chapter only refer to the particular section of the chapter.


Synopsis
Report

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	
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Introduction

Nitrogen containing heterocycles occupy an important place in organic chemistry due to their profound applications in the fields of drug discovery, medicinal chemistry, agrochemicals, organic materials, and so on. More than 75% of FDA approved drugs that are currently available in the market are nitrogen-containing heterocycles.[1] Furthermore, these ring systems are also found as a major skeleton in many biological molecules such as hemoglobin, DNA, RNA, vitamins, and hormones. An enormous number of nitrogen-containing heterocycles are known to possess a wide range of pharmacological activities, including anticancer, anti-HIV, anti-malarial, anti-tubercular, anti-microbial, and anti-diabetic activities.[2] Owing to its profound utility in multiple areas, the synthesis of nitrogen-based heterocycle has attracted a great deal of attention from organic chemists worldwide.

Statement of Problem

Despite a great achievements happened over the past several years in the area of synthesis and functionalization of nitrogen-based heterocycles, many challenges and problems remain to be solved. In light of the importance of nitrogen containing heterocycles, as part of the present thesis, we developed a series of novel synthetic strategies for the construction and functionalization of various important nitrogen containing heterocycles such as five & six-membered quinolone fused lactone & lactams, isoquinolin-1(*2H*)-ones, quinoxalin-2(*1H*)-ones.

Objectives

- Exploration of new synthetic transformations employing easily accessible alkyne tethered *N*-aryl glycine derivatives for the synthesis of structurally diverse quinolone-fused lactones and lactams.
- Development of selective alkylation of isoquinolin-1(*2H*)-one moiety under metal-free conditions.
- Development of single-electron oxidant induced radical ring-opening of cyclopropanol and its reaction with quinoxalin-2(*1H*)-ones.

- ❖ Development of visible light-induced C-3 α-aminomethylation of quinoxalin-2(1*H*)-one with tertiary amines under mild Conditions.

Methodology

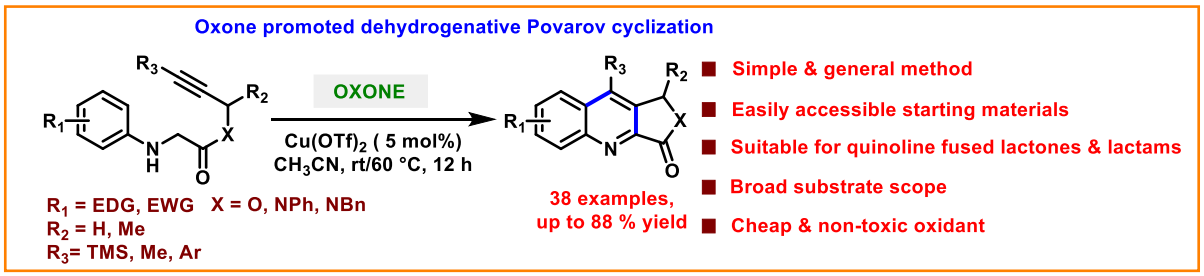
This thesis deals with the development of some new carbon-carbon bond forming methodologies for the synthesis of diversely functionalized nitrogen heterocycles employing Povarov cyclization, direct C-H functionalization strategies, and photoinduced EDA complexes strategy. These aspects have been covered in chapters 1, 2 & 3.

***Chapter 1:* Development of an efficient, greener approach for the synthesis of quinoline fused lactones and lactams**

***Section I:* Oxone promoted dehydrogenative Povarov cyclization of *N*-aryl glycine derivatives: An approach towards quinoline fused lactones and lactams**

Substituted quinolines are a ubiquitous heterocyclic motif present in a plethora of natural products and medicinal agents, among which quinolone-fused lactones and lactams are of great importance due to their presence in complex natural products and pharmaceutically relevant molecules.[3] In addition, they serve as a valuable precursor in the synthesis of biologically active natural products and their analogues such as luotonin-A (cytotoxic alkaloid), uncialamycin (antibiotic), aza podophyllotoxin analogues (antitumor agents), and [^{18}F]-quinoline carboxamide B (radio ligands for molecular imaging). Consequently, there is a great deal of attention on the synthesis of these privileged structures. Conventionally, synthesis of these frameworks is associated with multistep processes and the usage of toxic reagents. Therefore, developing a general, sustainable and efficient synthetic approach to achieve these functionalized quinoline-fused lactones/lactams is of high value.

Scheme:1

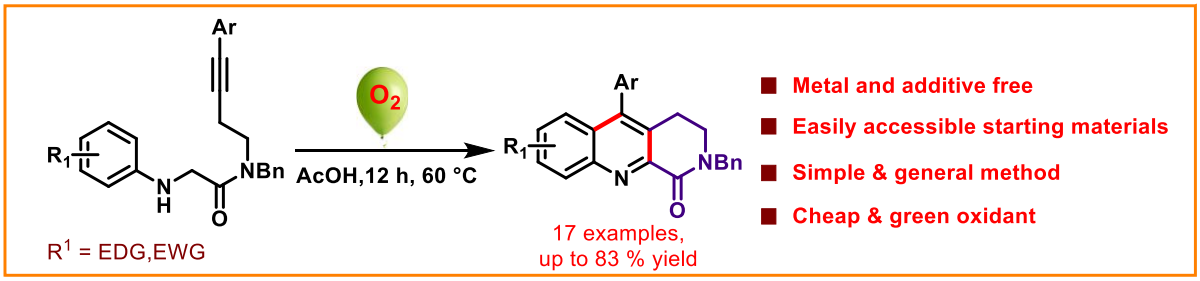


In this section, we developed an oxone promoted intramolecular dehydrogenative Povarov cyclization of various alkyne tethered *N*-aryl glycine derivatives to furnish biologically relevant quinoline fused lactones and lactams. In this reaction, oxone would be a favourable oxidant as it is cheap, non-toxic, and easy to handle. The other salient features of this approach includes readily accessible starting materials, mild reaction conditions, good functional group tolerance, and scalability. The synthetic utility of this methodology was further demonstrated by the construction of a quinoline core of Uncialamycin and Luotonin A analogue.

Section II: **Bronsted acid-catalyzed metal-free synthesis of substituted quinoline fused lactams from *N*-aryl glycine derivatives**

In the previous section, we have shown that alkyne tethered glycine derivatives are potential precursors for the convenient preparation of five-membered quinoline fused lactones and lactams *via* oxone promoted oxidative Povarov cyclization strategy. We were interested in further exploiting this oxidative strategy for more complex heterocyclic synthesis. In this endeavour, we developed a convenient and efficient method for the synthesis of six-membered quinolone fused lactams using simple and readily accessible alkyne tethered *N*-aryl glycine derivatives as a starting material. Six-membered quinoline fused lactams are common subunits in a wide range of natural and synthetic biological compounds.[4] Further, they serve as a key precursors for the synthesis of natural products and bioactive molecules.

Scheme: 2



In this section, we have described a Bronsted acid-mediated, environment-friendly, and economical approach to construct a six-membered quinoline fused lactams from easily accessible alkyne tethered *N*-aryl glycine derivatives for the first time. Employing this protocol six-membered quinoline-fused lactam can be accessed in good yields and with a broad substrate scope, which could be further functionalized to give biologically significant products.

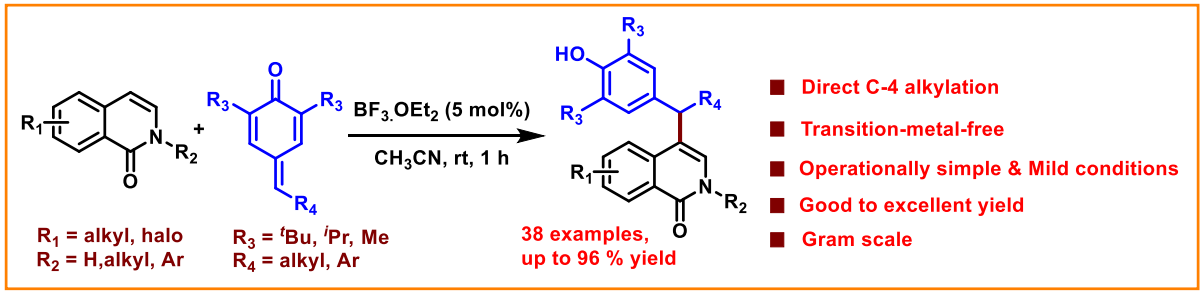
Chapter 2: **Development of metal-free C-H functionalization reactions of isoquinolin-1(2*H*)-ones & quinoxalin-2(1*H*)-ones**

Section I: **$BF_3.Et_2O$ catalyzed selective C-4 diarylmethylation of isoquinolin-1(2*H*)-ones employing *p*-quinone methides**

Isoquinolin-1(2*H*)-ones and their derivatives are an influential class of nitrogen-containing heterocycles and are ubiquitously implicated in a large number of natural products, pharmaceuticals, and biologically active compounds.[5] Among them, C4-substituted isoquinolin-1-(2*H*)-ones are omnipresent in natural alkaloids such as (+)-lycoricidine (antimitotic activity) and narciclasine (cytotoxic activity) etc. Owing to their biological significance, continuous efforts have been made to the synthesis and functionalization of isoquinolin-1-(2*H*)-ones. With the advent of CH-activation strategies, regioselective functionalization at the C-3 and C-8 positions of isoquinolinones has been well studied.[6] In contrast to the C-3 and C-8 positions of isoquinolin-1-(2*H*)-ones, selective functionalization at the C-4 position is comparatively less explored.[7] However, to the best of our knowledge, there is no report on direct C-4

alkylation of isoquinolone reported yet. On the other hand, para-quinone methides (*p*-QMs) have appeared as appealing and multifaceted synthons in organic synthesis due to their unique reactivity. In recent years, *p*-QMs have been successfully used as an alkylating agent for many synthetic transformations.[8] Inspired by the emerging importance of *p*-QMs as an alkylating agent and the biological significance of isoquinolones, we envisioned that *p*-QMs could be efficiently utilized for the selective alkylation of isoquinolin-1(2*H*)-ones. In this section, we describe the successful realization of this new strategy for the direct C-4 alkylation of isoquinolin-1(2*H*)-ones employing *p*-QMs under Lewis acid catalysis.

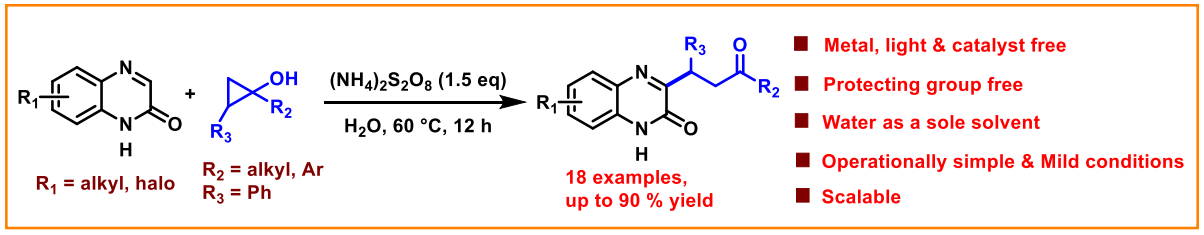
Scheme: 3



Section II: **Metal- and light-free direct C-3 ketoalkylation of quinoxalin-2(1*H*)-ones with cyclopropanols in aqueous medium**

Among various *N*-heterocycles, quinoxalin-2(*1H*)-one has emerged as an important scaffold that is being extensively studied because of its intriguing chemical and biological properties. In particular, C-3 substituted quinoxalin-2(1*H*)-ones are in demand as they possess a wide range of biological activities such as antibacterial, antitumor, antiviral, etc.[9] Hence, there have been continuous efforts devoted toward the functionalization at the C-3 position of quinoxalin-2(*1H*)-ones. Functionalization such as acylation, alkylation, amination, phosphonation, trifluoromethylation, thiolation, silylation etc, has been carried out successfully. However, the study of *β*-carbonyl alkylation on quinoxalin-2(*1H*)-one moiety remains under explored.

Scheme: 4



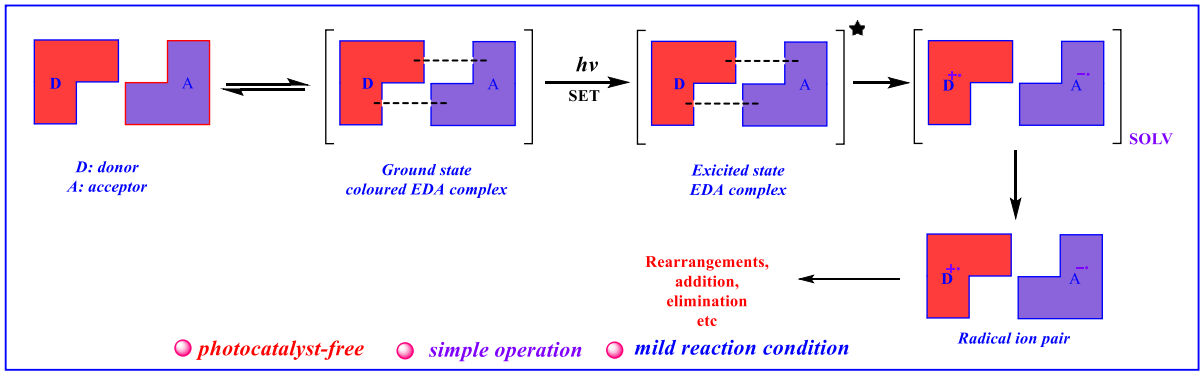
In this section, we report a practical and efficient metal-free approach for the direct C-3 ketoalkylation of quinoxalin-2(*1H*)-ones with readily available cyclopropanols as an alkylating agent in an aqueous medium. The salient features of the methodology are the use of water as a green solvent, good

product yields with high selectivity, and easy of operation. Further, the method does not require any metal catalyst.

Chapter 3: **Catalyst-free organic reactions *via* electron donor-acceptor (EDA) complexes & its applications**

Section I: **A brief introduction to EDA complex in organic synthesis**

Continuous demand for the development of sustainable synthesis has made organic chemists to look for efficient methods to manufacture fine and utility chemicals. In recent years, Visible light-induced organic transformations in the absence of photocatalysts especially using an EDA complex strategy has attracted a great deal of attention due to their economic and synthetic value. EDA complex strategy exploits the association of an electron acceptor substrate A and a donor molecule D to form a new molecular aggregation in the ground state, called an electron donor−acceptor (EDA) complex.[10] This EDA complex harvest the energy of light. Subsequently, photoexcitation of the EDA complex induces a single electron transfer (SET) process to generate the corresponding radical species. The process does not require external photocatalysts and operates under mild conditions. Finally, the generated radical ion pair in the solvent cage undergoes successive radical reactions to yield the desired products. Although significant success has been made in this direction, EDA complex-mediated organic synthesis is still in its infancy and needs further development. This section gives a brief introduction to the EDA complex and its utility in organic synthesis.

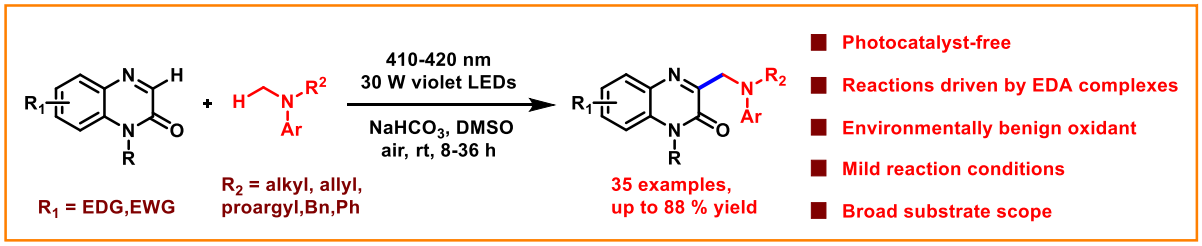


Section II: **Metal- and photocatalyst-free, visible-light-initiated C3 *α*-aminomethylation of quinoxalin-2(1*H*)-ones *via* electron donor-acceptor complexes**

In the previous section of this chapter, it has been described that visible light-induced electron donor-acceptor (EDA) complex photochemistry has become a powerful tool for discovering and improving selective chemical transformations under mild reaction conditions. Consequently, in recent years, the electron donor-acceptor (EDA) complex photochemistry has attracted enormous interest in organic chemistry. However, the EDA complex has been known for many years, but they found only limited applications in organic synthesis. Therefore, developing a new synthetic method employing EDA-

photochemistry is of high value with several advantages. On the other hand, quinoxalin-2(1*H*)-one, particularly the C3-aminoalkylated quinoxalin-2(1*H*)-one are prominent chemical entities commonly featured in several biologically active molecules, natural products, and pharmaceutical compounds.[11] Although various functionalization on quinoxalin-2(1*H*)-one have been made in recent years, however, strategies available for direct aminomethylation reactions on quinoxalin-2(1*H*)-one moiety remains under explored.

Scheme: 6



In this section, we describe an environmentally benign, photocatalyst-free, photoactive EDA-complex-enabled direct C3 α-aminomethylation of quinoxalin-2(1*H*)-ones. The operational simplicity, broad substrate scope, better functional group tolerance, and good yield of the products are some of the salient features of this strategy.

Summary/Conclusion

1. We have demonstrated oxone promoted intramolecular dehydrogenative Povarov cyclization of various alkyne tethered *N*-aryl glycine derivatives to furnish biologically relevant quinoline-fused lactones and lactams.
2. We have developed an efficient, greener approach for the synthesis of biologically relevant six-membered quinoline fused lactones and lactams employing molecular oxygen as an oxidant.
3. We have disclosed 1,6-nucleophilic addition of isoquinolone to *p*-QMs under metal- and additive-free conditions to synthesize C-4 diarylmethylated isoquinolin-1(2*H*)-ones.
4. We have developed a convenient, metal-free protocol for direct C-3 ketoalkylation of quinoxalin-2(1*H*)-ones.
5. We have developed a metal- and photocatalyst-free, visible-light-initiated C3 α-aminomethylation of quinoxalin-2(1*H*)-ones *via* electron donor-acceptor complexes. The reaction protocol is operationally simple and conducted at ambient temperature.

Future directions

In light of the study carried out on the synthesis and functionalization of various nitrogen containing heterocycles, there lies enormous potential on selective and late stage functionalization of biologically important organic molecules as this strategy will save the number of steps, time and energy. Espe-

cially, EDA enabled synthetic transformations to have huge potential in coming years. In addition, strategies developed herein for the synthesis of quinolone-fused lactones and lactam derivatives, C-4 diarylmethylated isoquinolin-1(2*H*)-ones, and C-3 functionalized quinoxalin-2(1*H*)-one would find enormous potential in synthetic and medicinal chemistry. As most of the organic compounds synthesized are hitherto unknown in literature, an appropriate bioassay would be beneficial, and the work is in progress. Furthermore, effective utilization of EDA complex strategy in organic transformations will also be carried out.

Publications

1. **More, D. A.**; Shinde, G. H.; Shaikh, A. C.; Muthukrishnan, M. Oxone promoted dehydrogenative Povarov cyclization of *N*-aryl glycine derivatives: An approach towards quinoline fused lactones and lactams. *RSC Adv.,* **2019**, *9*, 30277–30291.
2. **More, D. A**.; Mujahid M.; Muthukrishnan, M. Metal- and light-free direct C-3 ketoalkylation of quinoxalin-2(1*H*)-ones with cyclopropanols in aqueous medium. *ChemistrySelect* **2022**, *7*, e202203597.
3. **More, D. A.;** Shirsath, S. R.; Muthukrishnan, M. Metal- and photocatalyst-free, visible-light-initiated C3 α-aminomethylation of quinoxalin-2(1*H*)-ones *via* electron donor-acceptor complexes (Manuscript Submitted).
4. **More, D. A.;** Ghotekar, G. S.; Muthukrishnan, M. $BF_3.Et_2O$ catalyzed selective C-4 diaryl methylation of isoquinolin-1(2*H*)-ones employing *p*-quinone methides (Manuscript under Preparation).
5. **More, D. A.;** Shirsath, S. R.; Muthukrishnan. M. Bronsted acid-catalyzed metal-free synthesis of substituted quinoline fused lactams from *N*-aryl glycine derivatives (Manuscript under Preparation).

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CHAPTER-1

Development of an Efficient, Greener Approach for the Synthesis of Quinoline Fused Lactones and Lactams

Section I

Oxone Promoted Dehydrogenative Povarov Cyclization of *N*-Aryl Glycine Derivatives: An Approach towards Quinoline Fused Lactones and Lactams

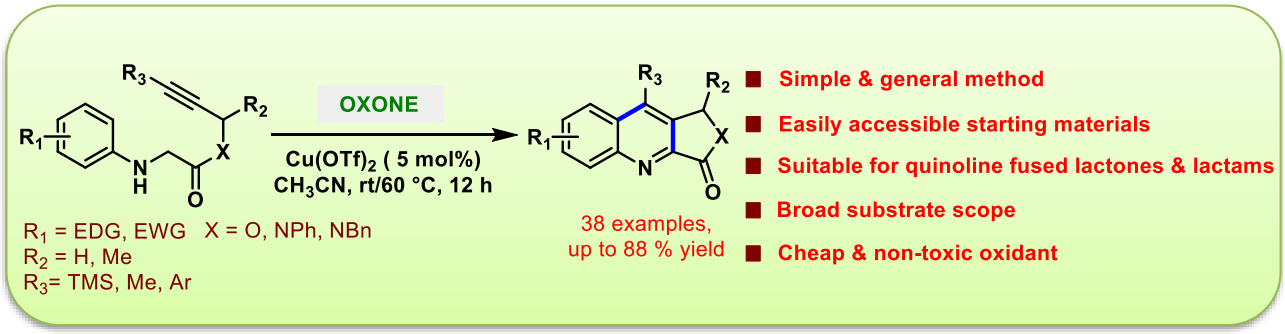
Section II

Bronsted Acid-Catalyzed Metal-Free Synthesis of Substituted Quinoline Fused Lactams from *N*-Aryl Glycine Derivatives

Section-I

Oxone Promoted Dehydrogenative Povarov Cyclization of *N*-Aryl Glycine Derivatives: An Approach towards Quinoline Fused Lactones and Lactams

In this section, Oxone promoted intramolecular dehydrogenative imino Diels-Alder reaction (Povarov cyclization) of alkyne tethered *N*-aryl glycine esters and amides have been explored for the preparation of biologically significant quinoline fused lactones and lactams. The reaction is simple, scalable, and high yielding (up to 88%). The method was further extended to prepare biologically important luotonin-A analogues and quinoline core of uncialamycin.



RSC Adv., **2019,** *9*, 30277–30291

1.1.1 Introduction

Substituted quinolines are ubiquitous heterocyclic motif present in a plethora of natural products, many of them display interesting biological activity,[1] among which quinoline fused lactones and lactams are of great importance due to their presence in complex natural products and pharmaceutically relevant molecules. For example, a natural product Luotonin A **(I)**, isolated from *P. nigelstrum*, exhibits potent antiviral and antiphytopathogenic fungus activity.[2] Camptothecin **(II)**, a quinolone alkaloid isolated from *Camptotheca acuminata* (Camptotheca, happy tree), is used as a chemotherapeutic agent in treating leukemia.[3] [^{18}F]-quinoline carboxamide B (**III**) serves as a radio ligand for molecular imaging.[4] The antibiotic uncialamycin **(IV),** extracted from Streptomyces uncialis, shows plasmid DNA cleavage activity and shows *in vitro* antibacterial activity.[5] Similarly, the 4-aza-podophyllotoxin (**V**) analogues possess antitumor properties[6] (Fig.1.1.1). In addition, they serve as a valuable precursor for the synthesis of natural products, useful drug molecules and other complex molecules. As a result, a great deal of attention

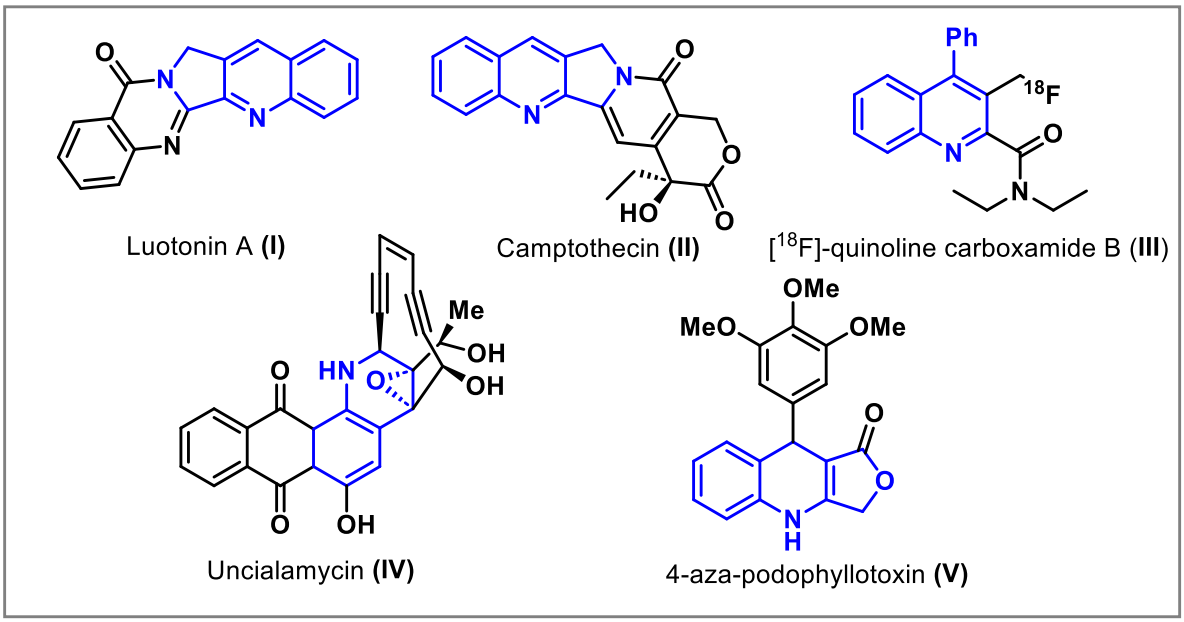


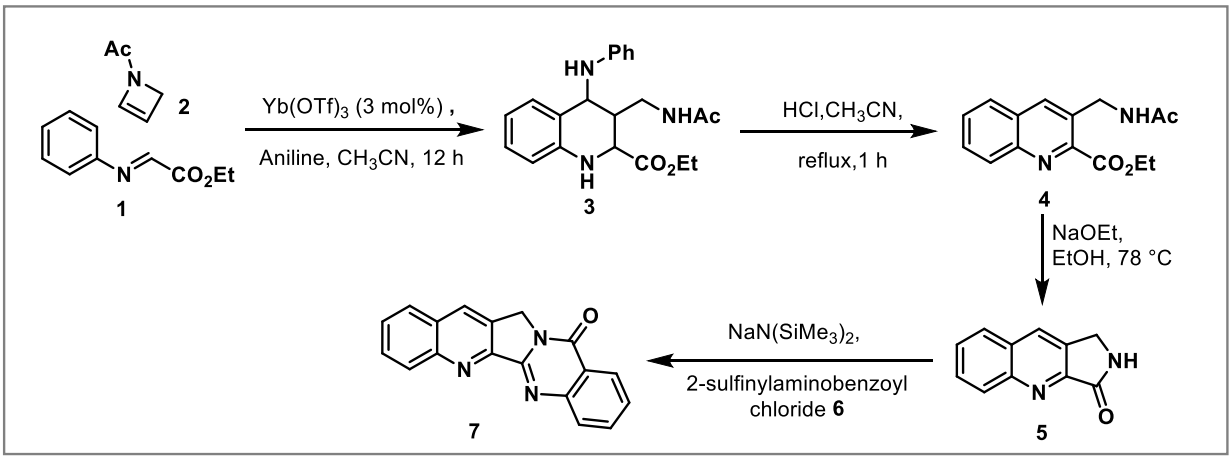
Figure 1.1.1 Representative examples of pharmaceuticals and natural products containing quinoline fused lactone/lactam moiety.

has been paid to the synthesis of these privileged structures. In general, the synthesis of this framework involves multi-step processes and the usage of toxic reagents, which limits the utility of these reactions.[2e,f,7] Therefore, the development of a general, sustainable and efficient syn-

thetic approach to achieve these functionalized quinoline fused lactones/lactams is of high value. Further, it would provide an appropriate platform for the detailed biological investigation of these valuable molecules. Some of the selective approaches toward the synthesis of five-membered quinoline-fused lactones and lactams reported in the literature are described below.

1.1.2 Literature Precedence on the Synthesis of Five-Membered Quinoline fused Lactones and Lactams

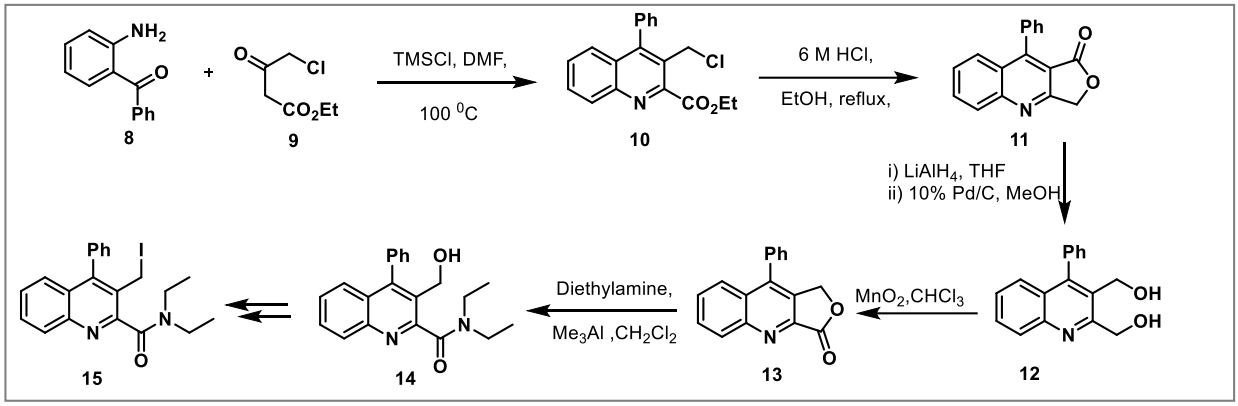
In 2002, Stevenson *et al*. disclosed a stepwise strategy towards the synthesis of Luotonin A. Reaction of ethyl 2-phenyliminoacetate **1**, with 1-(azet-1(2*H*)-yl)ethan-1-one **2**, aniline, and 3 mol % of $Yb(OTf)_3$ at rt afforded tetrahydroquinoline **3**. Further aromatization of this substrate gave 2,3-disubstituted quinolone amide **4**. Finally, amide **4** was treated with sodium ethoxide, which led to cyclization and the subsequent cleavage of the resultant imide to produce lactam **5**. Luotonin A **7** can be generated from lactam **5** in one more step by a reaction with 2-sulfinylaminobenzoyl chloride **6** (Scheme 1.1.1).[7b]



Scheme 1.1.1 Formal total synthesis of Luotonin A.

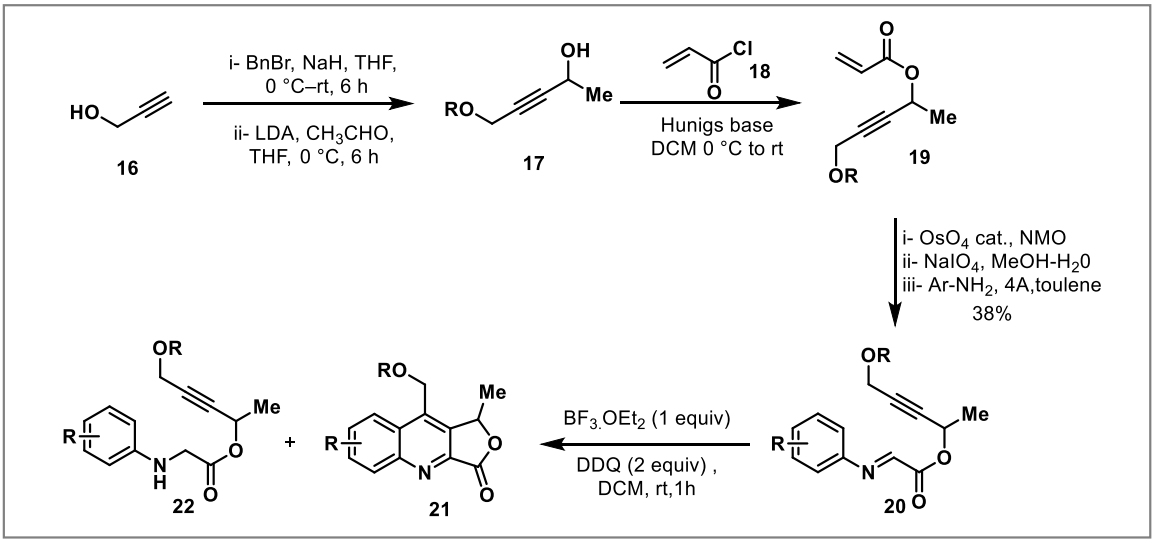
In 2010, Sutherland and colleagues developed a stepwise strategy towards synthesizing quinoline-2-carboxamides. In this approach, a chlorotrimethylsilane-mediated Friedländer condensation of 2-aminobenzophenone **8** with ethyl 4-chloroacetoacetate **9** gave 2,3,4 trisubstituted quinoline **10**. Subsequently, acid-mediated ring closure yielded the lactone product **11**. Further reduction with $LiAlH_4$ afford a diol **12**. Oxidation of this diol **12** with MnO_2 leads to lactone **13**. Further, lactone **13** was reacted with diethylamine and produced 3-

hydroxymethylquinoline-2-carboxamides **14**. An additional chlorination followed by iodide treatment gave 3-iodomethylquinoline-2-carboxamides **15** (Scheme 1.1.2).[7a]



Scheme 1.1.2 Synthesis of quinolinecarboxamide.

In 2009, Weghe and co-workers reported an intramolecular imino Diels-Alder reaction mediated by $BF_3.OEt_2$/DDQ for the construction of quinoline fused lactones **21** employing an alkene or alkyne as a dienophile. However, the preparation of the starting material imine **20** involves a multi-step reaction sequence. This sequence involves the protection of propargyl alcohol followed by the addition of aldehyde, and subsequent coupling with acryloyl chloride

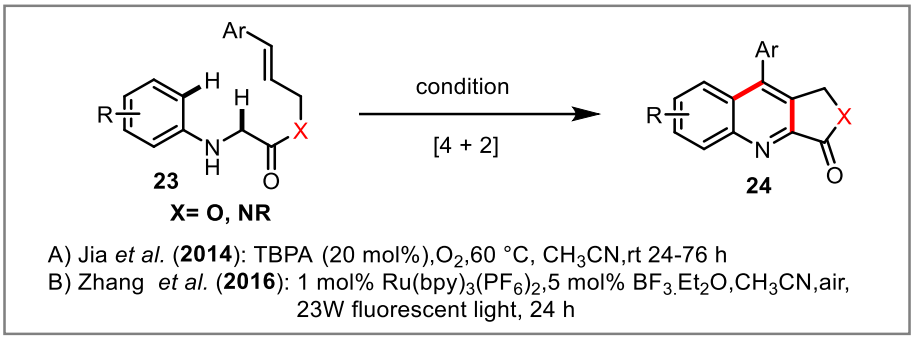


Scheme 1.1.3 Polysubstituted quinolines formation by [4 + 2] intramolecular imino Diels- Alder reaction.

18 to prepare ester **19**. Further, this ester **19** on dihydroxylation with OsO_4 followed by diol cleavage gives aldehyde. The reaction of aldehydes with aryl amine provides the starting material **20** (Scheme 1.1.3)[8]. Notably, this is the first report of intramolecular imino Diels-Alder reaction, which showed to offer rapid access to quinolines fused lactone in moderate yield. This

methodology was also used for the synthesis of chiral quinoline moiety of uncialamycin (enedione natural product).

In 2014, Jia *et al.* described the construction of quinoline-fused lactones and lactams **24** from radical cation salt-promoted, catalytic aerobic sp^3 C-H oxidation of *N*- aryl glycine esters and amides **23**. (Scheme 1.1.4).[9a] TBPA has been used as a catalyst in this reaction.



Scheme 1.1.4 Intramolecular cyclization of *N*-aryl glycine cinnamyl esters/amide promoted by radical cation/ photocatalytic aerobic oxidation.

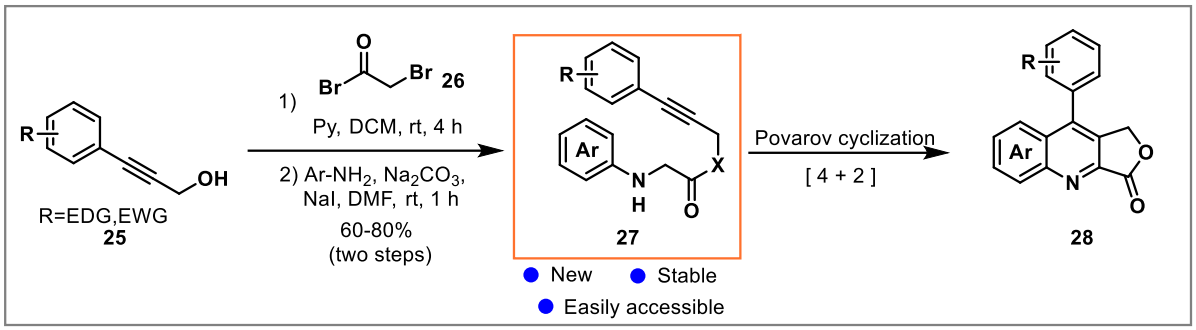
On a similar line, Zhang *et al.* in 2016 reported a visible-light-induced photocatalytic aerobic oxidation reaction of *N*-arylglycine cinnamyl esters **23** to construct quinoline-fused lactones **24**. The reaction was conducted under 23 W fluorescent light in the presence of $Ru(bpy)_3(PF_6)_2$ as a photoredox catalyst. The reaction is amenable to several *N*-arylglycine cinnamyl esters to provide quinoline-fused lactones **24** in satisfactory yield (Scheme 1.1.4).[9b] However, the strategy was not employed for the preparation of quinoline-fused lactams.

1.1.3 Present Work

1.1.3.1 Statement of the Problem

Imino Diels-Alder reaction (Povarov reaction) has received a renewed interest in recent years due to its ability to construct quinoline scaffolds, in which electron-rich alkenes (or alkynes) are added to the electron-deficient aromatic imines followed by oxidation.[10] Importantly, the intramolecular variant of this transformation is less studied compared to the intermolecular reaction.[11] From the above discussion, it is apparent that the intramolecular imino Diels-Alder reaction promoted by $BF_3.OEt_2$/DDQ for the construction of quinoline fused lactones employing an alkene or alkyne as a dienophile developed by Weghe *et al.* is superior in terms of robustness and novelty. Despite the merits, there are certain drawbacks associated with this method such as, non-ready availability of the requisite starting materials, the requirement of multi-

step reaction sequences for their synthesis, hazardous and expensive reagents, limited substrate scope etc. Further, the method have not been explored for the synthesis of quinoline fused lactams. In the context of our ongoing research, we needed an efficient method for the synthesis of quinoline fused lactones and lactams. While studying the suitability of Weghe's method for our library synthesis, we encountered difficulty in the preparation of starting imine compounds as the procedures are lengthy, along with issues pertinent to their stability. With regard to practicality, we envisioned that alkyne tethered *N*-aryl glycine derivatives **27** would be an ideal substrate for our library synthesis as (i) these substrates are stable and can be easily prepared, (ii) In suitable condition, these substrates can undergo oxidative dehydrogenation followed by Povarov cyclization that could lead to the quinoline fused lactones/lactams.



Scheme 1.1.5 This work: Cyclization of alkyne tethered *N*-aryl glycine derivatives.

In this section, we describe the successful realization of this new strategy, which involves Oxone promoted oxidative dehydrogenation, followed by intramolecular Povarov cyclization of alkyne tethered *N*-aryl glycine derivatives for the efficient synthesis of quinoline fused lactones/lactams. Furthermore, to the best of our knowledge, Oxone promoted intramolecular Povarov cyclization of hitherto unknown alkyne tethered *N*-aryl glycine derivatives has not been reported.

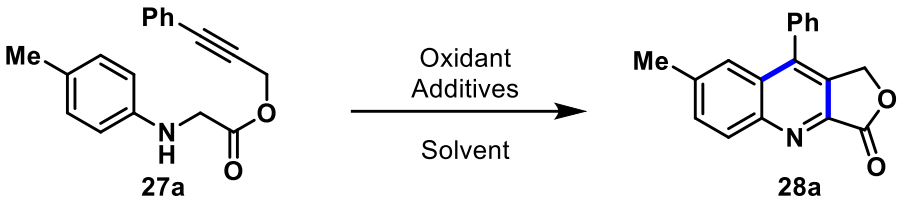
1.1.4 Results and Discussion

1.1.4.1 Optimization of Reaction Conditions

Accordingly, the required starting material alkyne tethered *N*-aryl glycine derivatives were conveniently prepared in two steps from substituted propargyl alcohols (Scheme 1.1.5). Initially, we examined the dehydrogenative Povarov cyclization of *N*- aryl glycine ester **27a** as a model substrate by employing 5 mol% $BF_3.OEt_2$ as a Lewis acid in the presence of IBX as an oxidant at room temperature (Table 1.1.1, entry 1). To our delight, as expected, the reaction

proceeded smoothly to give the desired product **28a** in 58 % yield. The structure of compound **28a** was characterized with the help of spectral and analytical data and completely matched with

Table 1.1.1. Optimization of reaction conditions[a,b]



Entry	Oxidant	Additives	Solvent	Yield (%)
1	IBX	$BF_3.OEt_2$	CH_3CN	58
2	IBX	$Sc(OTf)_3$	CH_3CN	53
3	IBX	$Cu(OTf)_2$	CH_3CN	68
4	IBX	$Cu(OAc)_2$	CH_3CN	51
5	$PhI(OAc)_2$	$Cu(OTf)_2$	CH_3CN	23
6	$PhI(OCOCF_3)_2$	$Cu(OTf)_2$	CH_3CN	21
7	$Na_2S_2O_8$	$Cu(OTf)_2$	CH_3CN	41
8	BPO	$Cu(OTf)_2$	CH_3CN	49
9	**Oxone**	**$Cu(OTf)_2$**	**CH_3CN**	**88**
10	Oxone	$Cu(OTf)_2$	THF	42
11	Oxone	$Cu(OTf)_2$	Toluene	traces
12	Oxone	$Cu(OTf)_2$	$CHCl_3$	<5
13	Oxone	$Cu(OTf)_2$	CH_3CN	89[c]
14	Oxone	-	CH_3CN	60[d]
15	-	$Cu(OTf)_2$	CH_3CN	traces

[a]Reaction conditions: 1) 0.18 mmol **27a**, 0.20 mmol oxidant, additive (5 mol%) solvent (3.0 mL), 12 h; [b]Isolated yields; rt; [c]1.3 equiv. of Oxone was employed; [d]24 h; IBX: 2-iodoxybenzoic acid

the product. In the ^1H NMR spectra of compound **28a**, the appearance of a signal at δ 5.35 (s, 2H) corresponds to methylene proton (-CH_2-) adjacent to the oxygen (cyclic lactone). In addition, the appearance of typical carbon signals at δ 67.8 is due to methylene carbon adjacent oxygen (cyclic lactone), and the disappearance of the alkyne carbon peak justifies the structure.

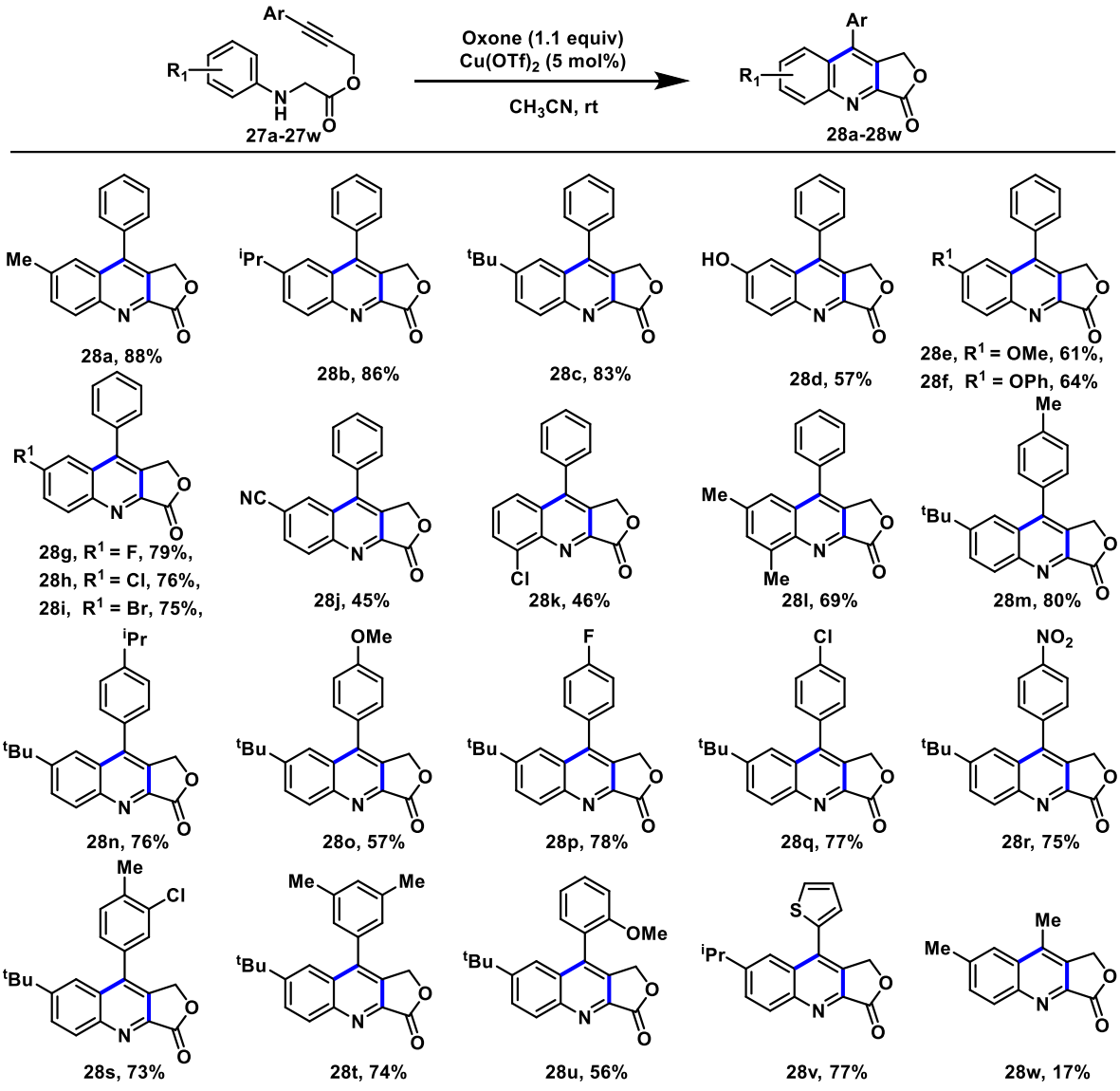
Furthermore, the constitution of **28a** has been confirmed as $C_{18}H_{14}NO_2$ (calculated value 276.1019) by the HRMS $[M+H]^+$ found as 276.1016. With this structure confirmation and inspired by our initial outcome, we screened other Lewis acids and found that $Cu(OTf)_2$ is the best among other Lewis acids tried (Table 1.1.1, entries 1-4). Next, we studied the effect of various oxidants and observed that peroxide-based oxidants were also suitable for this transformation (Table 1.1.1, entries 5-8). Interestingly, the reaction worked well in the presence of Oxone and 5 mol% of $Cu(OTf)_2$ at room temperature, afforded the required product **28a** in 88 % yield (Table 1.1.1, entry 9). Notably, Oxone would be a favourable oxidant as it is cheap, non-toxic, and easy to handle.[12] Screening of other solvents for this transformation reveals that CH_3CN is the best solvent of choice (Table 1.1.1, entry 9 vs 10-12). Further, not significant improvement in the yield has been observed while using more equiv. of Oxone (Table 1.1.1, entry 13). Notably, When we use only Oxone, the desired product formed in a 60 % yield albeit in 24 hours (Table 1.1.1,entry 14), which indicates that the Oxone alone can trigger this transformation presumably due to the slightly acidic nature of Oxone ($2KHSO_5$-$KHSO_4$-K_2SO_4). Finally, in the absence of Oxone, there is only a trace amount of product formation has been observed, which reveals the crucial role of Oxone in this transformation (Table 1.1.1, entry 15).

1.1.4.2 Intramolecular Povarov cyclization of *N*-aryl glycine esters

After the optimal reaction condition was established for the synthesis of quinoline-fused lactones, the scope and generality of this protocol were investigated (Table 1.1.2). Different electron-donating and electron-withdrawing functional groups on the aniline ring as well as the aryl alkyne part, were well tolerated. For example, substrates containing electron-donating groups such as 4-methyl, 4-isopropyl, and 4-*t*butyl on the aniline ring were suitable with the reaction conditions and yielded the desired products **28a**, **28b** and **28c** in 88%, 86% and 83% yields, respectively. However, strong electron-donating such as hydroxy, methoxy, and phenoxy substrates resulted the desired products in moderate yield (**28d-28f**, 57-64%). Additionally, Substrates containing halogen atoms successfully reacted under the optimized condition to give the desired product (**28g-28i**) in good yield (75-79%). However, the electron-withdrawing group at the aniline ring also produced the desired product in moderate quantities (**28j**, 45%). Furthermore, ortho substitution on the aniline ring provided the expected product in moderate yield (**28k**, 46%). Moreover, the di-substituted substrate also underwent smoothly to achieve the desired product **28l** in 69% yield. Next, we study the scope of our protocol by altering the sub-

stitution on aryl alkyne part of *N*-aryl glycine derivatives. EDG and EWG on the aryl alkyne part of *N*-aryl glycine derivatives also underwent the reaction efficiently and afforded the product in good yield (**28m-28r**). Further, the present protocol is suitable for *ortho* substitution,

Table 1.1.2 Intramolecular Povarov cyclization of *N*-aryl glycine esters[a,b]



[a]Reaction conditions: 0.18 mmol **27**, 0.20 mmol oxidant, 5 mol% of $Cu(OTf)_2$, CH_3CN (3.0 mL), rt, 12 h;

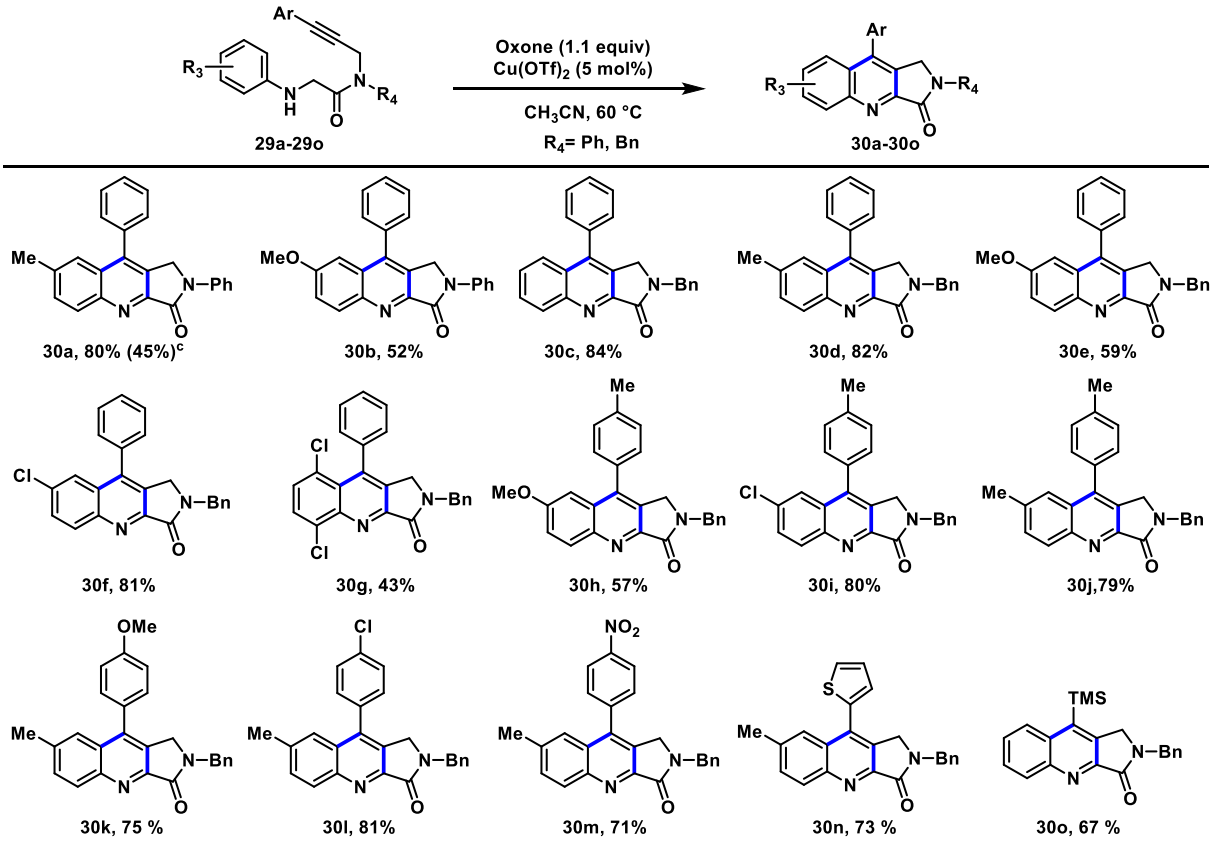
[b]Isolated yields

disubstitution as well as heteroaryl substitution on aryl alkyne part of the glycine derivatives (**28s-28v**). Alkyl substitution on the alkyne moiety under optimal condition provided the required product **28w**, in less yield.

1.1.4.3 Intramolecular Povarov cyclization of *N*-aryl glycine amides

After successfully synthesizing quinoline-fused lactones, we further explored the present protocol's suitability for synthesizing quinoline-fused lactams. Accordingly, we examined the intramolecular dehydrogenative Povarov cyclization of *N*- aryl glycine amide substrates under our optimized reaction condition and were delighted to find that the present protocol is suitable for the construction of quinoline fused lactam as well. However, the reaction requires a higher

Table 1.1.3 Intramolecular Povarov cyclisation of *N*-aryl glycine amides.[a,b]



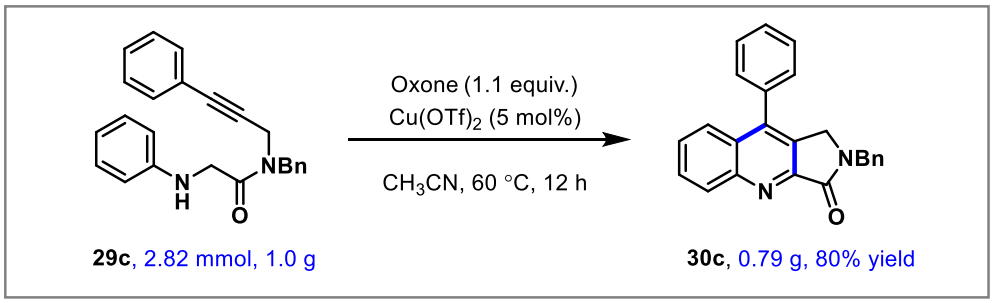
[a]Reaction conditions: 0.14 mmol **29**, 0.15 mmol Oxidant**,** 5 mol% of $Cu(OTf)_2$, CH_3CN (3.0 mL), 60 °C, 12 h; [b]Isolated yields; [c]reaction carried out at room temperature for 12 h.

temperature (60 °C) for completion (Table 1.1.3). Various electron donating as well as electron withdrawing and halo substituents on the aniline ring as well as aryl alkyne part of *N*-protected glycine amide (Ph- and Bn-) such as methyl, methoxy, chloro, dichloro, nitro and underwent cyclization to furnish the corresponding quinoline-fused lactams in moderate to good yields (**30a-30m**, 43-84%). The present protocol is also suitable for heteroaryl substitution (thienyl) on the aryl alkyne part of glycine derivatives and can afford good yields (**30n**, 73%).It is important to mention here that, the substrate bearing a TMS group is also well tolerated (**30o,** 67%) and

the resulted product can conveniently be converted into the natural product Luotonin A in two steps.[7b]

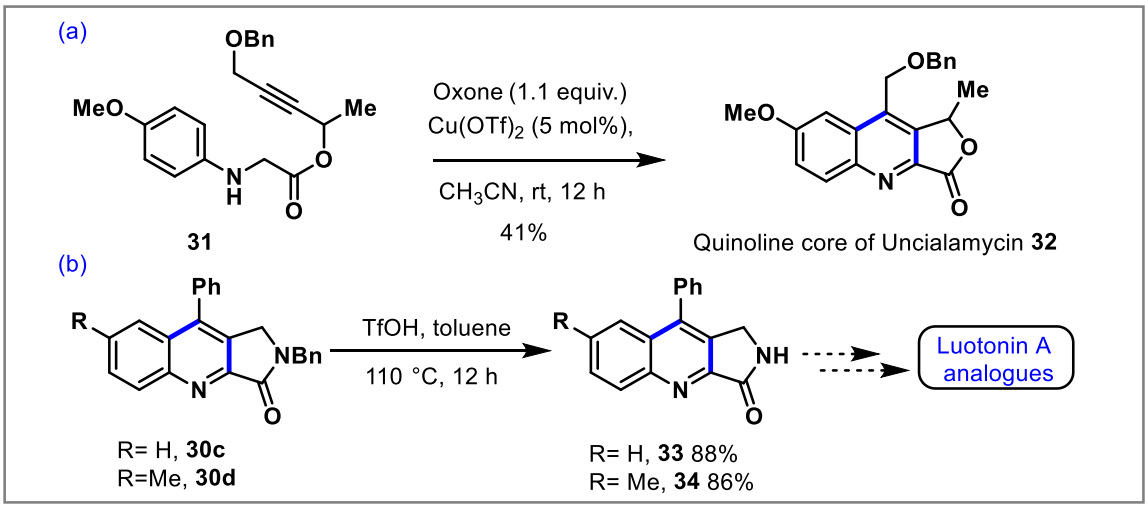
1.1.4.4 Gram-Scale Experiment and Product Transformations:

We performed a gram-scale experiment using **29c** (2.82 mmol, 1.0 g) under the standard reaction conditions to show the synthetic practicability of the current protocol. The desired product **30c** was produced in 80% yield (0.79 g), demonstrating that the current method could be easily modified for large-scale synthesis (Scheme 1.1.6A).



Scheme 1.1.6A Gram scale preparation

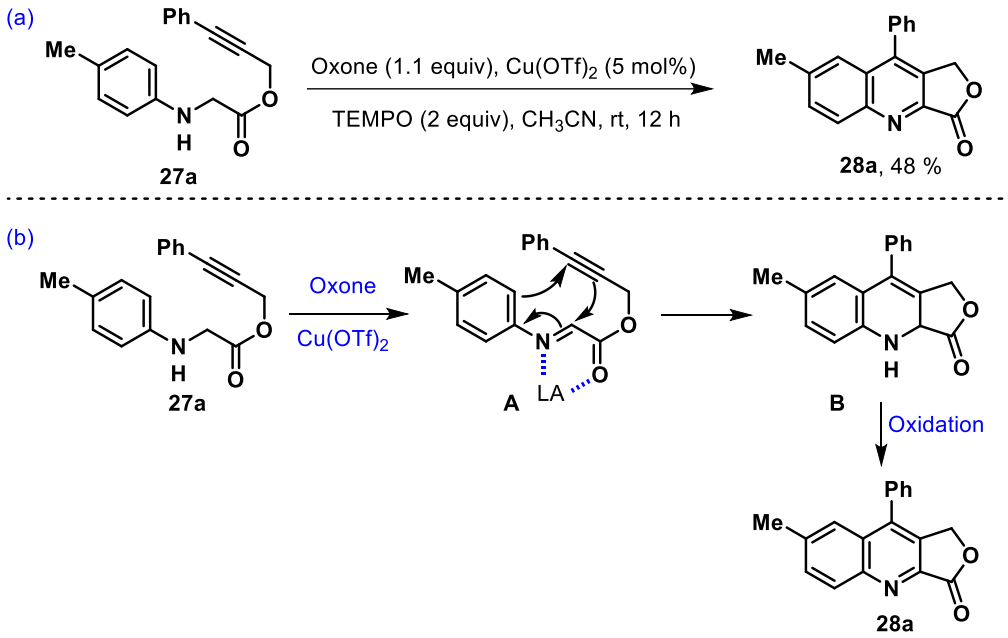
The synthetic applicability of this protocol may find utility in complex molecule synthesis. Some representative examples are shown in (Scheme 1.1.6B). We utilized this method for the preparation of the quinoline core precursor of the antitumor antibiotic uncialamycin.[8] Also, compounds **30c**, **30d** can easily be converted into cytotoxic alkaloid luotonin-A analogues.[7b]



Scheme 1.1.6B Product transformations.

1.1.4.5 Control Experiments and Plausible Reaction Mechanism:

To understand the reaction pathway, a radical trapping experiment was conducted by employing TEMPO as a radical scavenger and obtained **28a** in 48 % yield (Scheme 1.1.7a), which indicates that the reaction proceeds *via* non-radical pathway. Therefore, based on the control experiments and previous literature studies,[13] a tentative reaction mechanism is proposed in Scheme 1.1.7b. The first step involves the *in situ* generation of highly reactive imine intermediate **A**, followed by intramolecular cycloaddition to form an intermediate **B**.[10q-t] Further, intermediate **B** undergoes oxidation to form the corresponding fused quinoline **28a**.



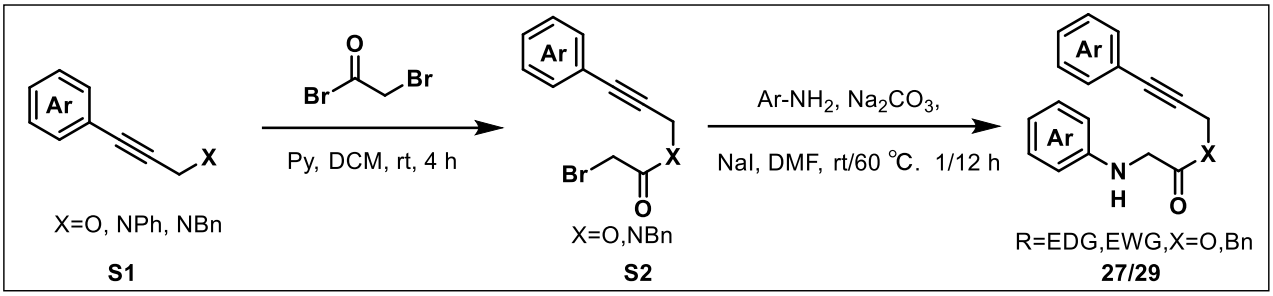
Scheme 1.1.7 Control experiment & a plausible mechanism

1.1.5 Conclusion

In Summary, we have developed Oxone promoted intramolecular dehydrogenative Povarov cyclization of various alkyne tethered *N*-aryl glycine derivatives to prepare biologically relevant quinoline fused lactones and lactams for the first time. This operationally simple, scalable protocol utilizes non-toxic, inexpensive Oxone as an oxidant to furnish the required products in high yield. The method was further utilized for the preparation of cytotoxic alkaloid Luotonin-A analogues and quinoline core of uncialamycin. Efforts are underway in our laboratory to extend the application of this method as well as the detail mechanistic investigation.

1.1.6 Experimental Section

1.1.6.1 General Procedure for the Preparation of *N*-aryl Glycine derivative:



Scheme 1.1.8 Preparation of ***N*-**aryl glycine derivatives.

General procedure for the synthesis of substituted phenyl propargyl bromo acetates/acetamide:

To a solution of substituted propargyl alcohol/amine **S1** (1 equiv) and pyridine (1.2 equiv) in anhydrous DCM was added 2-bromoacetyl bromide (1.2 equiv) in DCM at 0 °C under N_2 atmosphere over 30 min. After the addition was complete, the reaction mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), the crude reaction mixture was then poured into water and extracted with DCM (3 × 20 mL). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo, affording the substituted phenyl propargyl bromoacetate /acetamide **S2** which was used directly without further purification.

General Procedure for the Synthesis of Substituted *N*-aryl Glycine Ester (27a-27w):

A 5 mL Screw Top V vial® was charged with substituted bromoacetate (0.39 mmol), Na_2CO_3 (0.47 mmol), NaI (0.08 mmol), and substituted aniline (0.38 mmol), DMF (2 ml). The solution was stirred at room temperature. After 1 h, the reaction mixture was poured into ice water (10 mL) and extracted with EtOAc (3×20 mL). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography by eluting 5-15 % of ethyl acetate/petroleum ether (silica gel, 100-200 mesh), to afford substituted *N*-aryl glycine esters (**27a-27w**).

General Procedure for the Synthesis of Substituted *N*-aryl Glycine Amide (29a-29o):

A 5 mL glass vial® was charged with substituted Bromo acetamide (0.3 mmol), Na_2CO_3 (0.36 mmol), NaI (0.061 mmol), Substituted aniline (0.29 mmol), DMF (3ml). The mixture was stirred for 12 h at 60 °C. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, then poured into ice water, extracted with ethyl acetate

(20 mL × 3). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography by eluting 10-20 % of ethyl acetate/petroleum ether (silica gel, 100-200 mesh), to afford the substituted *N*-aryl glycine amides (**29a-29o**).

1.1.6.2 General Procedure for the Synthesis of Quinoline Fused Lactones (28a-28w):

To a 5 ml Screw Top V vial® containing a stirring mixture of substituted *N*- aryl glycine ester (0.18 mmol), Oxone® (122 mg, 0.20 mmol) in CH_3CN (3 ml) was added $Cu(OTf)_2$ (3.25 mg, 0.009 mmol) and the vial cap was wrapped tightly with a Teflon. The solution was then stirred at room temperature. After 12 h (Colourless to dark Brown colour was observed), the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography by eluting 20-30 % of ethyl acetate/petroleum ether (silica gel, 100-200 mesh), to afford the pure substituted quinoline fused lactones (**28a-28w**).

1.1.6.3 General Procedure for the Synthesis of Quinoline Fused Lactams (30a-30o):

To a 5 ml Screw Top V vial® containing a stirring mixture of substituted *N*- aryl glycine amide (0.14 mmol), oxone® (92 mg, 0.15 mmol) in CH_3CN (3 ml) was added $Cu(OTf)_2$ (2.64 mg, 0.0073 mmol) and the vial cap was wrapped tightly with a Teflon. The solution was stirred at 60 °C . After 12 h (colourless to dark Brown colour was observed), the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography by eluting 25-40 % of ethyl acetate/petroleum ether (silica gel, 100-200 mesh), to afford the pure substituted quinoline fused lactams (**30a-30o**).

1.1.6.4 Control Experiments Procedure:

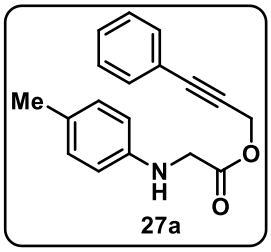
To a 5 ml Screw Top V vial® containing a stirring mixture of substituted *N*- aryl glycine ester **27a** (0.18 mmol), Oxone® (122 mg, 0.20 mmol) and TEMPO (2 equiv) in CH_3CN (3 ml) was added $Cu(OTf)_2$ (3.25 mg, 0.009 mmol) and the vial cap was wrapped tightly with a Teflon. The solution was then stirred at room temperature. After 12 hours the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography by eluting 20-30 % of ethyl acetate/petroleum ether (silica gel, 100-200 mesh), to afford the quinoline fused lactones.

1.1.6.5 Procedure for Product Transformations:

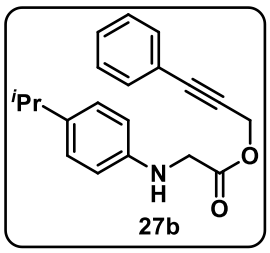
Procedure for Synthesis of 33/34: To a solution of **30c/30d** (0.137 mmol) in dry toluene (3 mL) was added TfOH (1.2 equiv) under an argon atmosphere, and the resulting mixture was stirred reflux for 12 h. The reaction mixture was then quenched with aqueous NaOH and extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography by eluting 3-5 % of DCM/MeOH (silica gel, 100-200 mesh), to afford **33/34**.

1.1.6.6 Characterization of 27a-w, 28a-w, 29a-o, 30a-o, 31, 32, 33 & 34:

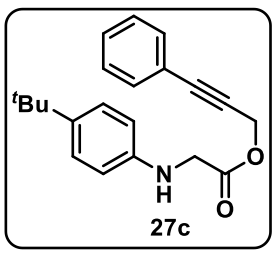
3-Phenylprop-2-yn-1-yl *p*-tolylglycinate (27a): Compound **27a** was isolated in 84% yield (93 mg, Yellow solid); **mp** = 88-90 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.48 (d, *J* = 7.3 Hz, 2H), 7.38– 7.33 (m, 3H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.58 (d, *J* = 8.1 Hz, 2H), 5.02 (s, 2H), 4.18 (bs, 1H), 3.99 (s, 2H), 2.26 (s, 3H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 170.7, 144.6, 131.9, 129.8, 128.8, 128.3, 127.6, 121.9, 113.2, 86.9, 82.3, 53.4, 46.1, 20.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}NO_2$ 280.1332; found 280.1325.



3-Phenylprop-2-yn-1-yl (4-*iso*-propylphenyl) glycinate (27b): Compound **27b** was isolated in 81% yield (98 mg, Viscous liquid); R_f = 0.55 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.48 (d, *J* = 6.3 Hz, 2H), 7.34 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 8.0 Hz, 2H), 5.03 (s, 2H), 4.07 (bs, 1H), 4.00 (s, 2H), 2.83 (sept, *J* = 6.8 Hz, 1H), 1.23 (d, *J* = 6.8 Hz, 6H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 170.7, 144.7, 138.9, 131.8, 128.8, 128.3, 127.1, 121.9, 113.2, 86.9, 82.3, 53.4, 46.1, 33.1, 24.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{20}H_{22}NO_2$ 308.1645; found 308.1646.

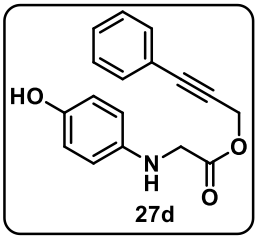


3-Phenylprop-2-yn-1-yl (4-(*tert*-butyl)phenyl) glycinate (27c): Compound **27c** was isolated in 80% yield (102 mg, Yellow solid); **mp** = 89-91 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.43 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.29 (m, 3H), 7.20 (d, *J* = 8.7 Hz, 2H) 6.55 (d, *J* = 8.7 Hz, 2H), 4.96 (s, 2H), 4.20 (bs, 1H), 3.93 (s, 2H), 1.26 (s, 9H); **^{13}C {^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 170.7, 144.4, 140.9, 131.8, 128.8, 128.2, 125.9, 121.8, 112.7, 86.9, 82.4, 53.3, 45.9, 33.7, 31.39; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for



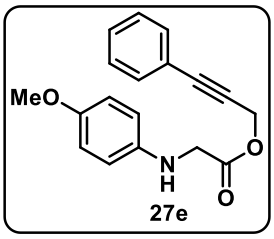
$C_{21}H_{24}NO_2$ 322.1802; found 322.1801.

3-Phenylprop-2-yn-1-yl (4-hydroxyphenyl) glycinate (27d): Compound **27d** was isolated in



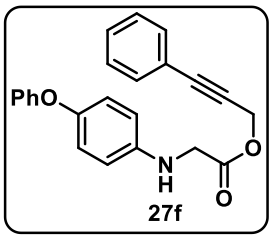
70% yield (78 mg, Viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.46 – 7.42 (m, 2H), 7.36 – 7.30 (m, 3H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 8.7 Hz, 2H), 4.99 (s, 2H), 3.92 (s, 2H); **^{13}C {^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 171.2, 148.7, 140.6, 131.8, 128.8, 128.3, 121.8, 116.2, 114.9, 86.9, 82.3, 53.5, 46.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3$ 282.1125; found 282.1126.

3-Phenylprop-2-yn-1-yl (4-methoxyphenyl) glycinate (27e): Compound **27e** was isolated in



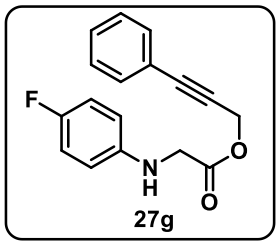
60 % yield (Note: Decomposition was observed after keeping prolong time in column (Brown liquid); R_f = 0.40 (V_{PE}/V_{EA} = 80/20); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.47 – 7.44 (m, 2H), 7.37 – 7.31 (m, 3H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 5.00 (s, 2H), 3.96 (s, 2H), 3.74 (s, 3H); **^{13}C {^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 170.8, 152.7, 141.0, 131.8, 128.8, 128.3, 121.9, 114.9, 114.4, 86.9, 82.4, 55.6, 53.4, 46.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}NO_3$ 296.1281; found 296.1280.

3-Phenylprop-2-yn-1-yl (4-phenoxyphenyl) glycinate (27f): Compound **27f** was isolated in



75% yield (106 mg, Off white solid); **mp** = 109-111 °C; R_f = 0.40 (V_{PE}/V_{EA} = 80/20); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.48 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.39 – 7.27 (m, 5H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.95 (dt, *J* = 7.7, 3.4 Hz, 4H), 6.66 – 6.61 (m, 2H), 5.04 (s, 2H), 4.26 (bs, 1H), 4.00 (s, 2H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 170.6, 158.7, 148.4, 143.3, 131.8, 129.4, 128.9, 128.3, 122.0, 121.8, 121.1, 117.2, 114.1, 87.0, 82.3, 53.5, 46.2; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{23}H_{20}NO_3$ 358.1438; found 358.1429.

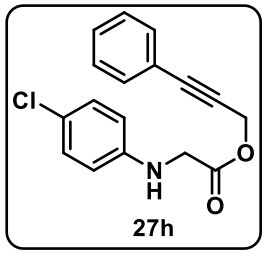
3-Phenylprop-2-yn-1-yl (4-fluorophenyl) glycinate (27g): Compound **27g** was isolated in



78% yield (87 mg, Off white solid); **mp** = 86-88 °C; R_f = 0.40 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.48 (d, *J* = 7.3 Hz, 2H), 7.38-7.34 (m, 3H), 6.92 (t, *J* = 8.6 Hz, 2H), 6.56 (dd, *J* = 8.7 Hz, 4.2 Hz, 2H), 5.02 (s, 2H), 4.15 (bs, 1H), 3.95 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 170.5, 156.2 (d, *J* =235.9 Hz) 143.2, 131.8, 128.8, 128.3, 121.8, 115.7 (d, *J* = 22.5 Hz), 113.9 (d, *J* = 7.5 Hz), 86.9, 82.3, 53.4, 46.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -126.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}FNO_2$ 284.1081;

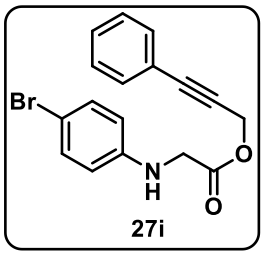
found 284.1075.

3-Phenylprop-2-yn-1-yl (4-chlorophenyl) glycinate (27h): Compound **27h** was isolated in



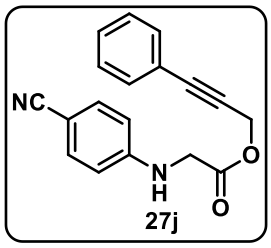
79% yield (93 mg, Off white solid); **mp** = 83-85 °C; R_f = 0.40 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.45 (d, *J* = 7.3 Hz, 2H), 7.37-7.31 (m, 3H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.55 (d, *J* = 8.6 Hz, 2H), 5.02 (s, 2H), 4.31 (bs, 1H), 3.97 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 170.3, 145.4, 131.9, 129.2, 128.9, 128.3, 123.1, 121.8, 114.1, 87.1, 82.2, 53.6, 45.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}ClNO_2$ 300.0786; found 300.0780.

3-Phenylprop-2-yn-1-yl (4-bromophenyl) glycinate (27i): Compound **27i** was isolated in 78%



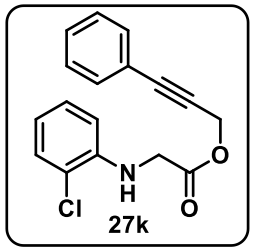
yield (107 mg, Brown solid); **mp** = 86-88 °C; R_f = 0.40 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.44 (d, *J* = 6.8 Hz, 2H), 7.37 – 7.29 (m, 3H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.48 (d, *J* = 8.5 Hz, 2H), 5.00 (s, 2H), 4.31 (bs, 1H), 3.94 (s, 2H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 170.2, 145.8, 132.0, 131.9, 128.9, 128.3, 121.8, 114.6, 110.1, 87.1, 82.2, 53.6, 45.6; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}BrNO_2$ 344.0281; found 344.0284.

3-Phenylprop-2-yn-1-yl (4-cyanophenyl)glycinate (27j): Compound **27j** crude (90 mg, Vis-



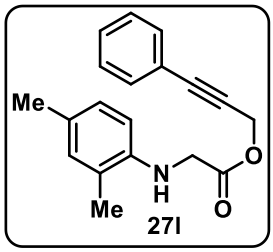
cous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 80/20)R_f = 0.40 (V_{PE}/V_{EA} = 80/20); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.44 (d, *J* = 7.2 Hz, 4H), 7.34 (t, *J* = 8.1 Hz, 3H), 6.58 (d, *J* = 8.2 Hz, 2H), 5.03 (s, 2H), 4.87 (s, 1H), 4.01 (d, *J* = 4.9 Hz, 2H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 169.5, 149.9, 133.7, 131.8, 129.0, 128.3, 121.6, 120.0, 112.5, 100.0, 87.2, 81.9, 53.9, 44.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_2$ 291.1178; found 291.1140.

3-Phenylprop-2-yn-1-yl (2-chlorophenyl)glycinate (27k): Compound **27k** was isolated in



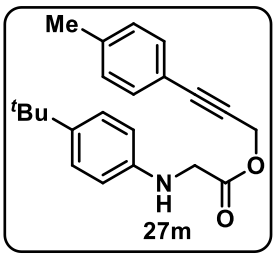
68% yield (80 mg, off white solid); **mp** = 69-71°C; R_f = 0.40 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.54 – 7.44 (m, 2H), 7.43 – 7.27 (m, 4H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.71 (t, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.04 (s, 2H), 4.98 (bs, 1H), 4.05 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 169.9, 142.7, 131.8, 129.3, 128.9, 128.3, 127.8, 121.8, 119.5, 118.2, 111.2, 87.0, 82.2, 53.6, 45.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}ClNO_2$ 300.0778; found 300.0796.

3-Phenylprop-2-yn-1-yl (2,4-dimethylphenyl)glycinate (27l): Compound **27l** was isolated in



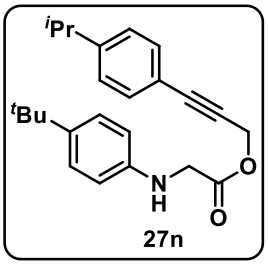
72% yield (83 mg, Viscous liquid); R_f = 0.50 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.47 (d, *J* = 7.7 Hz, 2H), 7.38 – 7.31 (m, 3H), 6.94 (s, 1H), 6.92 (s, 1H), 6.43 (d, *J* = 7.9 Hz, 1H), 5.02 (s, 2H), 4.03 (s, 2H) 2.24 (s, 3H), 2.21 (s, 3H); **^{13}C {^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 170.9, 142.6, 131.9, 131.2, 128.9, 128.3, 127.3, 127.2, 122.8, 121.9, 110.2, 86.9, 82.3, 53.5, 46.1, 20.3, 17.3**; HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{19}H_{20}NO_2$ 294.1489, found 294.1476.

3-(*p*-tolyl)prop-2-yn-1-yl (4-(*tert*-butyl)phenyl) glycinate (27m): Compound **27m** was isolat-



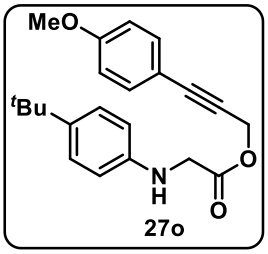
ed in 77% yield (97 mg, Off white solid); **mp** = 85-87 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.34 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 6.57 (d, *J* = 8.3 Hz, 2H), 4.99 (s, 2H), 3.96 (s, 2H), 2.34 (s, 3H), 1.27 (s, 9H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 170.8, 144.4, 141.1, 139.1, 131.8, 129.0, 126.1, 118.8, 112.8, 87.2, 81.7, 53.6, 46.0, 33.8, 31.5, 21.4; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{22}H_{26}NO_2$ 336.1958; found 336.1969.

3-(4-*iso*-Propylphenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (27n): Compound **27n**



was isolated in 76% yield (93 mg, Off white solid); **mp** = 86.5-88.5 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.38 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.58 (d, *J* = 8.6 Hz, 2H), 4.99 (s, 2H), 3.96 (s, 2H), 3.86 (bs, 1H), 2.89 (sept, *J* = 6.9 Hz, 1H), 1.26 (s, 9H), 1.23 (d, *J* = 6.9 Hz, 6H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 170.8, 149.9, 144.4, 141.1, 131.9, 126.4, 126.1, 119.2, 112.8, 87.2, 81.6, 53.6, 46.0, 34.0, 33.8, 31.4, 23.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{30}NO_2$ 364.2271;found 364.2272.

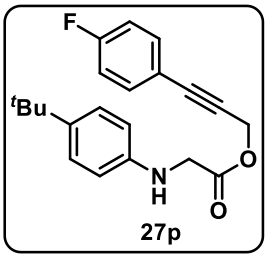
3-(4-Methoxyphenyl)prop-2-yn-1-yl (4-(*tert*-butyl)phenyl)glycinate (27o): Compound **27o**



was isolated in 75% yield (93 mg, Viscous liquid); R_f = 0.45 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.49 (d, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.67 (d, *J* = 8.1 Hz, 2H), 5.08 (s, 2H), 4.31 (bs, 1H), 4.05 (s, 2H), 3.86 (s, 3H), 1.38 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 170.7, 159.9, 144.4, 140.9, 133.3, 125.9, 114.7, 113.8, 112.7, 86.9, 81.0, 55.1, 53.5, 45.8, 33.7, 31.4; **HRMS (ESI-TOF)** *m/z*: [M

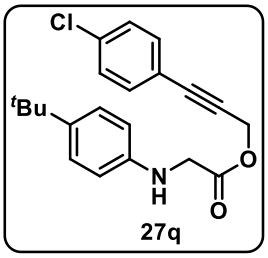
+ H]$^+$ calcd for $C_{22}H_{26}NO_3$ 352.1907; found 352.1906.

3-(4-Fluorophenyl)prop-2-yn-1-yl (4-(*tert*-butyl)phenyl)glycinate (27p): Compound **27p** was



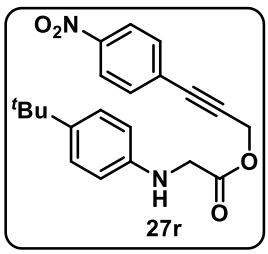
isolated in 72% yield (90 mg, Off white solid); **mp** = 78.5-80.5 °C; R_f = 0.50 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.42 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 8.6 Hz, 2H), 4.98 (s, 2H), 3.97 (s, 2H), 1.27 (s, 9H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 170.8, 162.8 (d, *J* = 250.2 Hz), 144.4, 141.2, 133.9 (d, *J* = 8.5 Hz), 126.1, 117.9 (d, *J* = 3.4 Hz), 115.6 (d, *J* = 22.2 Hz), 112.8, 85.9, 82.1, 53.3, 45.9, 33.8, 31.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -109.8; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{21}H_{23}FNO_2$ 340.1707; found 340.1709.

3-(4-Chlorophenyl)prop-2-yn-1-yl (4-(*tert*-butyl)phenyl)glycinate (27q): Compound **27q**



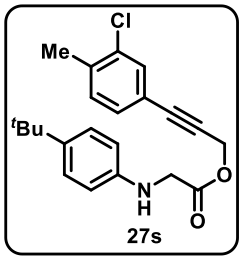
was isolated in 72% yield (89 mg, Off white solid); **mp** = 76-78 °C; R_f = 0.52 (V_{PE}/V_{EA} = 90/10) ; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.39 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 8.7 Hz, 2H), 5.00 (s, 2H), 4.00 (s, 2H), 1.28 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 170.8, 144.4, 141.2, 135.0, 133.1, 128.7, 126.1, 120.4, 112.8, 85.8, 83.3, 53.3, 46.0, 33.9, 31.5; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{21}H_{23}ClNO_2$ 356.1412;found 356.1405.

3-(4-Nitrophenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (27r): Compound **27r** was



isolated in 70% yield (86 mg, Yellow solid); **mp** = 76.5-78.5 °C; R_f = 0.45 (V_{PE}/V_{EA} = 90/10) ; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.17 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 5.02 (s, 2H), 4.00 (s, 2H), 1.27 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 170.7, 147.4, 144.3, 141.2, 132.5, 128.7, 126.1, 123.5, 112.8, 87.6, 84.8, 52.9, 45.9, 33.8, 31.4; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{21}H_{23}N_2O_4$ 367.1652; found 367.1658.

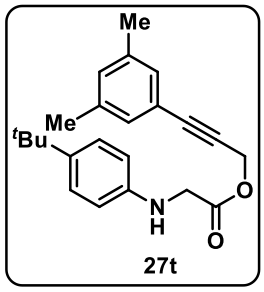
3-(3-Chloro-4-methylphenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (27s): Com-



pound **27s** was isolated in 68% yield (83 mg, Off white solid); **mp** = 66.5-68.5 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.47 (d, *J* = 1.0 Hz, 1 H), 7.29 – 7.24 (m, 3 H), 7.20 (d, *J* = 7.8 Hz, 1 H), 6.62 (d, *J* = 8.6 Hz, 2 H), 5.02 (s, 2 H), 4.01 (s, 2 H), 3.46 (bs, 1 H), 2.40

(s, 3 H), 1.30 (s, 9 H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 170.8, 144.4, 141.2, 137.3, 134.2, 132.2, 130.8, 130.0, 126.1, 120.9, 112.8, 85.7, 82.8, 53.4, 46.0, 33.9, 31.5, 20.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{22}H_{25}ClNO_2$ 370.1568;found 370.1570.

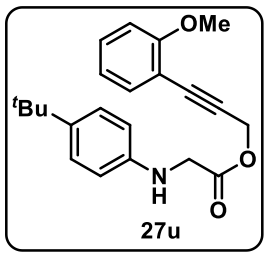
3-(3,5-Dimethylphenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (27t): Compound **27t**



27t

was isolated in 69% yield (86 mg, Off white solid); **mp** = 89-91 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.21 (d, *J* = 8.2 Hz, 2H), 7.08 (s, 2H), 6.96 (s, 1H), 6.57 (d, *J* = 8.1 Hz, 2H), 4.97 (s, 2H), 3.95 (s, 2H), 2.27 (s, 6H), 1.26 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 170.7, 144.4, 141.0, 137.8, 130.7, 129.5, 126.0, 121.5, 112.8, 87.3, 81.6, 53.5, 45.9, 33.8, 31.4, 20.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{23}H_{28}NO_2$ 350.2115;found 350.2109.

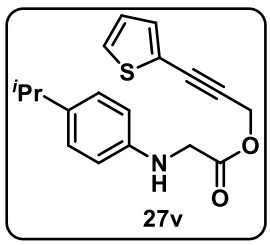
3-(2-Methoxyphenyl)prop-2-yn-1-yl (4-(*tert*-butyl)phenyl)glycinate (27u): Compound **27u**



27u

was isolated in 69% yield (86 mg, Yellow solid); **mp** = 96-98 °C; R_f = 0.45 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.42 (d, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.88 (dd, *J* = 7.5Hz, 8.5 Hz, 2H), 6.57 (d, *J* = 8.3 Hz, 2H), 5.05 (s, 2H), 4.18 (bs, 1H), 3.96 (s, 2H), 3.86 (s, 3H), 1.27 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 170.7, 160.2, 144.4, 140.9, 133.9, 130.4, 126.0, 120.4, 112.7, 110.9, 110.6, 86.2, 83.4, 55.7, 53.7, 45.9, 33.8, 31.4; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{22}H_{26}NO_3$ 352.1907; found 352.1899.

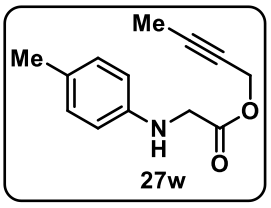
3-(Thiophen-2-yl)prop-2-yn-1-yl (4-*iso*-propylphenyl)glycinate (27v): Compound **27v** was



27v

isolated in 69% yield (84 mg, Viscous liquid); R_f = 0.50 (V_{PE}/V_{EA} = 95/5); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.28 (d, *J* = 5.1 Hz, 1H), 7.25 (d, *J* = 3.8 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.97 (dd, *J* = 4.9, 3.9 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 5.01 (s, 2H), 3.97 (s, 2H), 3.54 (bs, 1H), 2.80 (sept, *J* = 6.9 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 6H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 170.7, 144.8, 138.9, 133.1, 128.0, 127.2, 126.9, 121.8, 113.2, 86.4, 80.4, 53.5, 46.1, 33.1, 24.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}NO_2S$ 314.1209; found 314.1210.

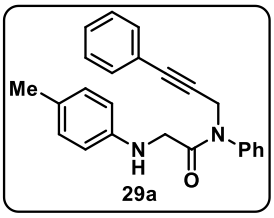
But-2-yn-1-yl p-tolylglycinate (27w): Compound **27w** was isolated in 60% yield (94 mg, Viscous liquid); R_f = 0.5 (V_{PE}/V_{EA} = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 6.99 (d, *J* = 8.1 Hz, 2H), 6.52 (d, *J* = 8.3 Hz, 2H), 4.72 (s, 2H), 4.09 (bs, 1H), 3.91 (s, 2H), 2.23 (s, 3H), 1.85 (s,



27w

3H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 170.7, 144.5, 129.7, 127.4, 113.1, 83.7, 72.6, 53.4, 45.9, 20.3, 3.5; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{13}H_{16}NO_2$ 218.1178.; found 218.1176.

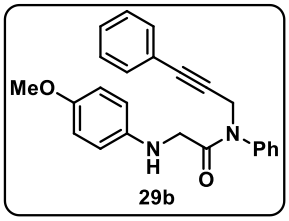
N-Phenyl-*N*-(3-phenylprop-2-yn-1-yl)-2-(*p*-tolylamino)acetamide (29a): Compound **29a** was



29a

isolated in 73% yield (79 mg, Off white solid); **mp** = 94.2-96.2 °C; R_f = 0.40 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.55 – 7.47 (m, 3H), 7.38 (d, *J* = 7.0 Hz, 2H), 7.35 (d, *J* = 7.3 Hz, 2H), 7.32 – 7.26 (m, 3H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.39 (d, *J* = 8.0 Hz, 2H), 4.77 (s, 2H), 4.59 (bs, 1H), 3.58 (s, 2H), 2.21 (s, 3H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 169.3, 145.1, 140.0, 131.6, 129.9, 129.6, 129.1, 128.4, 128.3, 128.2, 126.9, 122.6, 113.1, 84.5, 83.9, 46.6, 39.4, 20.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_2O$ 355.1805; found 355.1807.

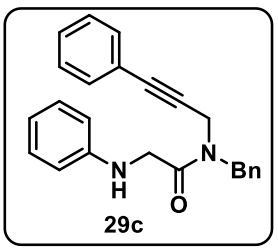
2-((4-Methoxyphenyl)amino)-*N*-phenyl-N-(3-phenylprop-2-yn-1-yl)acetamide (29b): Com-



29b

pound **29b** was isolated in 41% yield (46 mg, Brown liquid); R_f = 0.35 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (400 MHz, $CDCl_3$, Starting material was not stable) δ** = 7.49 (d, *J* = 7.3 Hz, 2H), 7.39 – 7.33 (m, 5H), 7.32-7.25 (m, 3H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 2H), 3.69 (s, 3H), 3.55 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 169.4, 152.3, 141.6, 139.9, 131.7, 131.6, 129.9, 129.1, 128.8, 128.4, 128.3, 128.2, 114.7, 114.3, 84.4, 83.9, 55.7, 47.1, 39.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_2$ 371.1754; found 371.1755.

***N*-Benzyl-2-(phenylamino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (29c):** Compound **29c** was

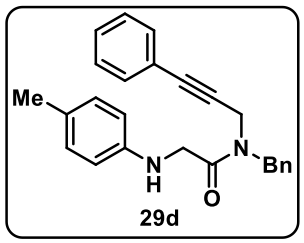


29c

isolated in 76% yield (79 mg, Off white solid); **mp** = 95.5-97.5 °C; R_f = 0.40 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (500 MHz, $CDCl_3$, Rotameric mixture found in 1:0.98 ratio) δ** = 7.44 – 7.39 (Rotameric m, 6H, Aromatic) 7.34 (Rotameric m, 14 H, Aromatic), 7.21 (Rotameric quin, 4H, Aromatic), 6.79 – 6.73 (Rotameric m, 2H, Aromatic), 6.71 (d, *J* = 8.0 Hz, 2H, Aromatic) and 6.61 (d, *J* = 7.9 Hz, 2H, Aromatic) (Rotameric), 4.93 (Rotameric bs, 2H, **NH**), 4.84 (s, 2H, C**H$_2$**) and 4.76 (s, 2H, C**H$_2$**) (Rotameric), 4.56 (s, 2H, C**H$_2$**) and 4.00 (s, 2H, C**H$_2$**) (Rotameric), 4.21 (s, 2H, C**H$_2$**) and 4.16 (s, 2H, C**H$_2$**) (Rotameric); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 169.5 and 162.4 (Rotameric **C=O**), 147.4 and 147.3 (Rotameric), 136.5 and 135.6 (Rotameric), 131.9 (Rotameric), 129.4 and 129.4 (Rotameric), 129.2 and 128.9 (Rota-

meric), 128.8 and 128.6 (Rotameric), 128.5 and 128.4 (Rotameric), 128.2 and 127.9 (Rotameric), 126.8 (Rotameric), 122.6 and 122.0 (Rotameric), 117.8 (Rotameric), 113.2 and 113.1 (Rotameric), 85.2 and 84.5 (Rotameric **C** alkyne), 83.7 and 82.7 (Rotameric **C** alkyne**)**, 49.4 and 49.3 (Rotameric **C**H_2), 45.6 and 45.5 (Rotameric **C**H_2), 36.4 and 35.7 (Rotameric **C**H_2); **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_2O$; 355.1805 found 355.1798.

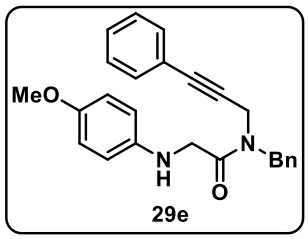
***N*-Benzyl-*N*-(3-phenylprop-2-yn-1-yl)-2-(*p*-tolylamino)acetamide (29d):** Compound **29d** was



29d

isolated in 74% yield (80 mg, Off white solid); **mp** = 93-95 °C; R_f = 0.40 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (500 MHz, $CDCl_3$, Rotameric mixture found in 1:0.98 ratio) δ** = 7.43 (Rotameric m, 6H, Aromatic), 7.35 (Rotameric m, 14H, Aromatic), 7.06 (d, *J* = 8.0 Hz, 2H, Aromatic) and 7.02 (d, *J* = 8.0 Hz, 2H, Aromatic) (Rotameric), 6.66 (d, *J* = 8.1 Hz, 2H, Aromatic) and 6.56 (d, *J* = 8.1 Hz, 2H, Aromatic) (Rotameric), 4.85 (s, 2H, C**H**$_2$) and 4.76 (s, 2H, C**H**$_2$) (Rotameric), 4.57 (s, 2H, C**H**$_2$) and 4.00 (s, 2H, C**H**$_2$) (Rotameric) 4.21 (s, 2H, C**H**$_2$) and 4.15 (s, 2H, C**H**$_2$) (Rotameric), 2.29 (s, 3H, 4-**C**H_3 aniline) and 2.27 (s, 3H, 4-**C**H_3 aniline) (Rotameric); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$ Rotamers) δ** = 169.5 and 169.4 (Rotameric **C=O**), 145.1 and 145.0 (Rotameric) 136.4 and 135.5 (Rotameric), 131.7, 129.7 and 129.6 (Rotameric), 129.0 and 128.7 (Rotameric), 128.6 and 128.4 (Rotameric), 128.3 and 128.2 (Rotameric), 127.9 and 127.7 (Rotameric), 126.8 and 128.6 (Rotameric), 122.4 and 121.9 (Rotameric), 113.1, 84.9 and 84.2 (Rotameric **C** alkyne), 83.6 and 82.6 (Rotameric **C** alkyne**)**, 49.2 and 49.1 (Rotameric **C**H_2), 45.8 and 45.7 (Rotameric **C**H_2), 36.2 and 35.5 (Rotameric **C**H_2), 20.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{25}N_2O$ 369.1961; found 369.1958.

***N*-Benzyl-2-((4-methoxyphenyl)amino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (29e):** Com-

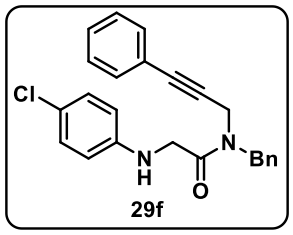


29e

pound **29e** crude (Note: Crude was Recrystallize in n- Hexane) **mp** = 79-81 °C; R_f = 0.35 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (400 MHz, $CDCl_3$, Rotameric mixture found in 1:0.97 ratio) δ** = 7.45 – 7.26 (m, 20H, Aromatic) (Rotameric), 6.85 – 6.72 (m, 4H, Aromatic) (Rotameric), 6.66 (d, *J* = 8.6 Hz, 2H, Aromatic) and 6.56 (d, *J* =8.5 Hz 2H, Aromatic) (Rotameric), 4.80 (s, 2H, C**H**$_2$) and 4.74 (s, 2H, C**H**$_2$) (Rotameric), 4.53 (s, 2H, C**H**$_2$) and 3.95 (s, 2H, C**H**$_2$), (Rotameric), 4.19 (s, 2H, C**H**$_2$) and 4.11 (s, 2H, C**H**$_2$) (Rotameric), 3.75 (s, 3H, O**Me**) and 3.73 (s, 3H, O**Me**) (Rotameric); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, Rotamers) δ** = 169.7 and 169.6 (Rotameric **C=O**), 152.3 and 152.2 (Rotameric), 141.7 and 141.6

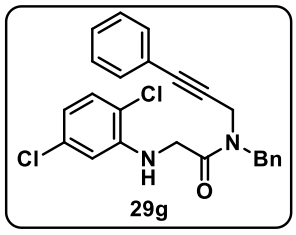
(Rotameric), 136.4 and 135.5 (Rotameric), 131.7 (Rotameric), 129.1 and 128.3 (Rotameric), 128.8 and 128.7 (Rotameric), 128.5 and 128.4 (Rotameric), 128.0 and 127.8 (Rotameric), 126.7 (Rotameric), 122.5 and 121.9 (Rotameric), 114.9 and 114.9 (Rotameric), 114.4 (Rotameric), 84.9 and 84.3 (Rotameric **C** alkyne), 83.6 and 82.6 (Rotameric **C** alkyne), 55.8 (O**Me**) 49.2 and 49.1 (Rotameric **C**H_2), 46.5 and 46.4 (Rotameric **C**H_2), 36.3 and 35.5 (Rotameric **C**H_2); **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_2$ 385.1911; found 385.1911.

***N*-Benzyl-2-((4-chlorophenyl)amino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (29f):** Compound **29f** was isolated in 74% yield (42 mg, Brown solid); **mp** = 91-93 °C; R_f = 0.40 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (400 MHz, $CDCl_3$, Rotameric mixture found in 1:0.98 ratio) δ** = 7.40 – 7.26 (m, 20H, Aromatic) (Rotameric), 7.11 (dd, *J* = 11.5, 8.6 Hz, 4H, Aromatic) (Rotameric), 6.59 (d, *J* = 8.3 Hz, 2H) and 6.48 (d, *J* = 8.4 Hz, 2H, Aromatic) (Rotameric), 4.80 (s, 2H, C**H**$_2$) and 4.73 (s, 2H, C**H**$_2$) (Rotameric), 4.53 (s, 2H, C**H**$_2$) and 3.93 (s, 2H, C**H**$_2$) (Rotameric), 4.17 (s, 2H, C**H**$_2$) and 4.09 (s, 2H, C**H**$_2$) (Rotameric); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, Rotamers) δ** = 169.0 and 168.8 (Rotameric **C=O**), 145.8 and 145.7 (Rotameric), 136.2 and 135.3 (Rotameric), 131.7 (Rotameric), 129.1 (Rotameric) 129.1 and 129.0 (Rotameric), 128.8 and 128.7 (Rotameric), 128.5 and 128.3 (Rotameric), 128.4 and 128.3 (Rotameric), 128.1 and 127.8 (Rotameric), 126.6 (Rotameric), 122.4 and 122.2 (Rotameric), 114.0 and 114.0 (Rotameric), 85.1 and 84.5 (Rotameric **C** alkyne), 83.4 and 82.4 (Rotameric **C** alkyne), 49.2 (Rotameric **C**H_2), 45.4 (Rotameric **C**H_2), 36.3 and 35.6 (Rotameric **C**H_2); **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{22}ClN_2O$ 389.1415; found 389.1422.



29f

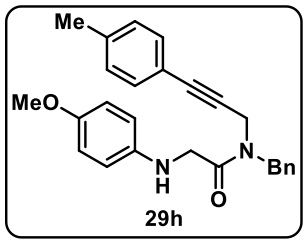
***N*-Benzyl-2-((2,5-dichlorophenyl)amino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (29g):** Compound **29g** was isolated in 61% yield (76 mg, Viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (400 MHz, $CDCl_3$, Rotameric mixture found in 1:0.97 ratio) δ** = 7.49 – 7.28 (m, 20H, Aromatic) (Rotameric), 7.18 (t, *J* = 7.9 Hz, 2H, Aromatic), (Rotameric), 6.62 (t, *J* = 8.1 Hz, 2H, Aromatic) (Rotameric), 6.58 (s, 1H, Aromatic) and 6.41 (s, 1H, Aromatic) (Rotameric), 5.72 (bs, 2H, **NH**) (Rotameric), 4.83 (s, 2H, C**H**$_2$) and 4.76 (s, 2H, C**H**$_2$) (Rotameric), 4.56 (s, 2H, C**H**$_2$) and 4.20 (s, 2H, C**H**$_2$) (Rotameric), 4.13 (s, 2H, C**H**$_2$) and 3.98 (s, 2H, C**H**$_2$) (Rotameric); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, Rotamers) δ** = 168.4 and 168.3 (Rotameric **C=O**), 144.0, 136.3 and 135.3 (Rotameric), 133.6 and 133.5 (Rotameric), 131.9, 130.1 and 129.4 (Rotameric), 129.0, 128.9 and 128.7 (Rotameric), 128.6 and 128.4 (Ro-



29g

tameric), 128.3 and 128.1 (Rotameric), 126.8, 122.5 and 121.9 (Rotameric), 118.0, 117.3, 111.3 and 111.2 (Rotameric), 85.5 and 84.6 (Rotameric **C** alkyne), 83.4 and 82.4 (Rotameric **C** alkyne**)**, 49.5 and 49.4 (Rotameric **C**H_2), 45.0, 36.5 and 35.9 (Rotameric **C**H_2); **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{21}Cl_2N_2O$ $(M + H)^+$ 423.1025; found 423.1016.

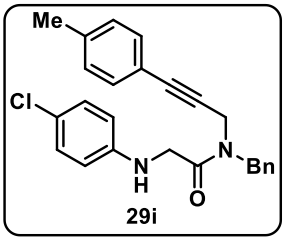
***N*-Benzyl-2-((4-methoxyphenyl)amino)-*N*-(3-(p-tolyl)prop-2-yn-1-yl)acetamide (29h):**



29h

Compound **29h** was isolated in 68% yield (76 mg, Off white solid); **mp** = 115.5-117.5 °C; R_f = 0.35 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (500 MHz, $CDCl_3$, Rotameric mixture found in 1:0.98 ratio) δ** = 7.41 – 7.31 (m, 14H Aromatic) (Rotameric), 7.15 (d, *J* = 7.9 Hz, 4H, Aromatic) (Rotameric), 6.81 (dd, *J* = 9.0, 8.1 Hz, 4H, Aromatic) (Rotameric), 6.69 (d, *J* = 7.8 Hz, 2H, Aromatic) and 6.58 (d, *J* = 7.8 Hz, 2H, Aromatic) (Rotameric), 4.83 (s, 2H, C**H$_2$**) and 4.75 (s, 2H, C**H$_2$**) (Rotameric), 4.63 (bs, 2H, **NH**) (Rotameric), 4.55 (s, 2H, C**H$_2$**) and 3.96 (s, 2H, C**H$_2$**) (Rotameric), 4.19 (s, 2H, C**H$_2$**) and 4.12 (s, 2H, C**H$_2$**) (Rotameric), 3.76 (s, 3H, O**CH$_3$**) and 3.75 (s, 3H, O**CH$_3$**) (Rotameric), 2.37 (s, 3H, 4-**Me**Ph) and 2.36, (s, 3H, 4-**Me**Ph) (Rotameric); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$ Rotamers) δ** = 169.6 and 169.5 (Rotameric **C=O**), 152.2, 141.7 and 141.6 (Rotameric), 138.9 and 138.5 (Rotameric), 136.4 and 135.5 (Rotameric), 131.5, 129.0 and 128.9 (Rotameric), 128.6 and 128.3 (Rotameric), 127.8 and 127.6 (Rotameric), 126.6, 119.3 and 118.8 (Rotameric), 114.8 and 114.8 (Rotameric), 114.2, 85.0 and 84.3 (Rotameric **C** alkyne), 82.8 and 81.9 (Rotameric **C** alkyne), 55.6, 49.1 and 49.0 (Rotameric **C**H_2), 46.4 and 46.3 (Rotameric **C**H_2), 36.3 and 35.5 (Rotameric **C**H_2), 21.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_2$ 399.2067; found 399.2065.

***N*-Benzyl-2-((4-chlorophenyl)amino)-*N*-(3-(p-tolyl)prop-2-yn-1-yl)acetamide (29i):** Com-

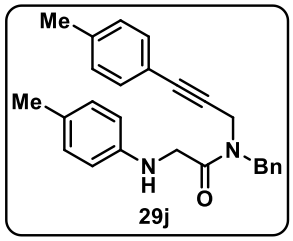


29i

pound **29i** was isolated in 71% yield (80 mg, Off white solid); **mp** = 96-98 °C; R_f = 0.35 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (400 MHz, $CDCl_3$, Rotameric mixture found in 1:0.9 ratio) δ** = ^{1}H NMR (400 MHz, DMSO) δ 7.44 – 7.28 (m, 14H, Aromatic) (Rotameric), 7.13 (t, *J* = 8.5 Hz, 8H, Aromatic) (Rotameric), 6.61 (d, *J* = 8.5 Hz, 2H, Aromatic) and 6.50 (d, *J* = 8.5 Hz, 2H, Aromatic) (Rotameric), 4.96 (bs, 2H, **NH**) (Rotameric), 4.82 (s, 2H, C**H$_2$**) and 4.74 (s, 2H, C**H$_2$**) (Rotameric), 4.54 (s, 2H, C**H$_2$**) and 3.93 (s, 2H, C**H$_2$**) (Rotameric), 4.18 (s, 2H, C**H$_2$**) and 4.10 (s, 2H, C**H$_2$**) (Rotameric), 2.36 (s, 6H, NHCH_2 4-**Me**Ph) (Rotameric); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, Rotamers) δ** = 169.0 and 168.9 (Rotameric **C=O**),

145.8 and 145.7 (Rotameric), 139.0 and 138.6 (Rotameric), 136.3 and 135.4 (Rotameric), 131.6, 129.1 and 129.0 (Rotameric), 128.7 and 128.4 (Rotameric), 128.0 and 127.8 (Rotameric), 126.6, 122.2, 119.3 and 118.7 (Rotameric), 114.0, 85.3 and 84.5 (Rotameric **C** alkyne), 82.6 and 81.7 (Rotameric **C** alkyne), 49.2, 45.4 and 45.3 (Rotameric **C**H_2), 36.3 and 35.7 (Rotameric **C**H_2), 21.4; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{24}ClN_2O$ 403.1572; found 403.1570.

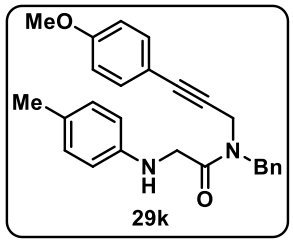
***N*-Benzyl-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)-2-(*p*-tolylamino)acetamide (29j):** Compound 29j was



29j

isolated in 77% yield (83 mg, Off white solid); **mp** = 106-108 °C; R_f = 0.35 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (400 MHz, $CDCl_3$, Rotameric mixture found in 1:0.97 ratio) δ** = 7.42 – 7.29 (m, 14H, Aromatic) (Rotameric), 7.14 (t, *J* = 7.1 Hz, 4H, Aromatic) (Rotameric), 7.03 (dd, *J* = 12.4, 8.1 Hz, 4H, Aromatic) (Rotameric), 6.65 (d, *J* = 7.9 Hz, 2H, Aromatic) and 6.54 (d, *J* = 7.9 Hz, 2H, Aromatic) (Rotameric), 4.83 (s, 2H, **C**H_2) and 4.76 (s, 2H, **C**H_2) (Rotameric), 4.55 (s, 2H, **C**H_2) and 3.98 (s, 2H, **C**H_2) (Rotameric), 4.20 (s, 2H, **C**H_2) and 4.14 (s, 2H, **C**H_2) (Rotameric), 2.38 (s, 3H, NHCH_2 4-**Me**Ph) and 2.37 (s, 3H, NHCH_2 4-**Me**Ph) (Rotameric), 2.28 (s, 3H, 4-**Me** aniline) and 2.26 (s, 3H, 4-**Me** aniline) (Rotameric); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$ Rotamers) δ** = 169.5 and 169.4 (Rotameric C=O), 145.1 and 145.0 (Rotameric), 138.9 and 138.5 (Rotameric), 136.4 and 135.5 (Rotameric), 131.6, 129.7 and 129.7 (Rotameric), 129.1 and 129.0 (Rotameric), 128.9, 128.6 and 128.4 (Rotameric), 127.9 and 128.4 (Rotameric), 126.8 and 126.7 (Rotameric), 119.3 and 118.8 (Rotameric), 113.2, 85.1 and 84.4 (Rotameric **C** alkyne), 82.8 and 81.9 (Rotameric **C** alkyne), 49.1 and 49.0 (Rotameric **C**H_2), 45.8 and 45.8 (Rotameric **C**H_2), 36.3 and 35.5 (Rotameric **C**H_2), 21.4 and 20.3 (Rotameric, N-CH_2,4-PhCH_3); **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{27}N_2O$ 383.2118; found 383.2115.

***N*-Benzyl-*N*-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-2-(p-tolylamino) acetamide (29k):** Com-

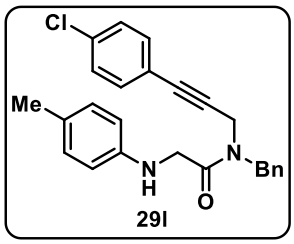


29k

pound **29k** was isolated in 71% yield (76 mg, Viscous liquid); R_f= 0.35 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$, Rotameric mixture found in 1: 0.96 ratio) δ** = 7.39 – 7.24 (m, 14H, Aromatic) (Rotameric), 6.98 (dd, *J* = 13.3, 8.1 Hz, 4H, Aromatic) (Rotameric), 6.80 (dd, *J* = 7.9, 6.0 Hz, 4H, Aromatic) (Rotameric), 6.60 (d, *J* = 8.0 Hz, 2H, Aromatic) and 6.49 (d, *J* = 8.0 Hz, 2H, Aromatic) (Rotameric), 4.78 (s, 2H, C**H$_2$**) and 4.70 (s, 2H, C**H$_2$**) (Rotameric), 4.50 (s, 2H, C**H$_2$**) and 3.93 (s, 2H, C**H$_2$**) (Rotameric), 4.13 (s, 2H, C**H$_2$**) and

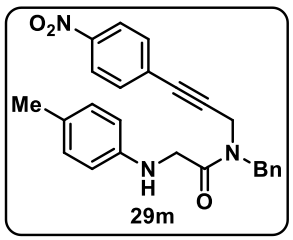
4.09 (s, 2H, C**H₂**) (Rotameric), 3.76 (s, 6H, O**CH₃**) (Rotameric), 2.23 (s, 3H, Ph**CH₃**) and 2.21 (s, 3H, Ph**CH₃**) (Rotameric); **^{13}C {^{1}H} NMR (100 MHz, CDCl₃, Rotamers) δ** = 169.5 and 169.3 (Rotameric), 159.8 and 159.6 (Rotameric), 145.0 and 144.9 (Rotameric), 136.4 and 135.5 (Rotameric), 133.1, 129.7 and 129.6 (Rotameric), 128.9 and 128.7 (Rotameric), 128.6 and 128.3 (Rotameric), 127.8 and 127.6 (Rotameric), 126.7 and 126.6 (Rotameric), 114.4 and 114.3 (Rotameric), 113.9 and 113.8 (Rotameric), 113.2 and 113.1 (Rotameric), 84.8 and 84.1 (Rotameric **C** alkyne), 82.0 and 81.2 (Rotameric **C** alkyne), 55.14 (Rotameric O**C**H₃), 49.1 and 49.0 (Rotameric **C**H₂), 45.8 and 45.7 (Rotameric **C**H₂), 36.3 and 35.5 (Rotameric **C**H₂), 20.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_2$ $(M + H)^+$ 399.2067; found 399.2075.

***N*-Benzyl-*N*-(3-(4-chlorophenyl)prop-2-yn-1-yl)-2-(p-tolylamino) acetamide (29l):** Compound 29l was isolated in 73% yield (81 mg, Viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (400 MHz, CDCl₃, Rotameric mixture found in 1: 0.88 ratio) δ** = 7.42 – 7.21 (m, 18H, Aromatic) (Rotameric), 6.99 (dd, *J* = 12.0, 8.2 Hz, 4H, Aromatic) (Rotameric), 6.60 (d, *J* = 8.1 Hz, 2H, Aromatic) and 6.51 (d, *J* = 8.1 Hz, 2H, Aromatic) (Rotameric), 4.78 (s, 2H, **CH₂**) and 4.71 (s, 2H, **CH₂**) (Rotameric), 4.50 (s, 2H, **CH₂**) and 3.96 (s, 2H, **CH₂**) (Rotameric), 4.16 (s, 2H, **CH₂**) and 4.09 (s, 2H, **CH₂**) (Rotameric), 2.24 (s, 3H, NHPh**CH₃**) and 2.22 (s, 3H, NHPh**CH₃**) (Rotameric); **^{13}C {^{1}H} NMR (100 MHz, CDCl₃, Rotamers) δ** = 169.5, 145.0 and 144.9 (Rotameric), 136.3 and 135.4 (Rotameric), 134.8 and 134.4 (Rotameric), 132.9, 129.7 and 129.6 (Rotameric), 129.0, 128.7, 128.6 and 128.4 (Rotameric), 128.0 and 127.7 (Rotameric), 126.9 and 126.6 (Rotameric), 120.9 and 120.3 (Rotameric), 113.16, 84.7 and 83.0 (Rotameric **C** alkyne), 83.8 and 83.7 (Rotameric **C** alkyne), 49.3 and 49.2 (Rotameric **C**H₂), 45.81, 36.2 and 35.5 (Rotameric **C**H₂), 20.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{24}ClN_2O$ $(M + H)^+$ 403.1572; found 403.1584.



29l

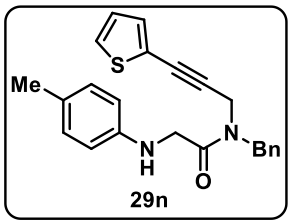
***N*-Benzyl-*N*-(3-(4-nitrophenyl)prop-2-yn-1-yl)-2-(p-tolylamino) acetamide (29m):** Compound **29m** was isolated in 65% yield (69 mg, Viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (500 MHz, CDCl₃, Rotameric mixture found in 1:0.86 ratio) δ** = 8.20 (m, 4H, Aromatic) (Rotameric), 7.52 (d, *J* = 7.5 Hz, 4H, Aromatic) (Rotameric), 7.46 – 7.29 (m, 10H, Aromatic) (Rotameric), 7.08 – 6.99 (m, 4H, Aromatic) (Rotameric), 6.65 (d, *J* = 6.8 Hz, 2H, Aromatic) and 6.56 (d, *J* = 7.4 Hz, 2H, Aromatic) (Rotameric), 4.84 (s, 2H, C**H₂**) and 4.77 (s, 2H, C**H₂**) (Rotameric), 4.58 (s, 2H, C**H₂**) and 4.28 (s, 2H, C**H₂**), (Rota-



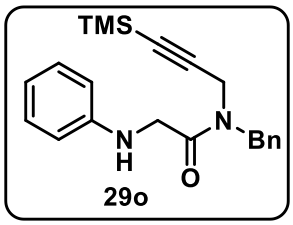
29m

meric), 4.15 (s, 2H, C**H**$_2$) and 4.03 (s, 2H, C**H**$_2$) (Rotameric), 2.27 (s, 6H, NHPh**CH**$_3$) (Rotameric). **^{13}C {^{1}H} NMR (100 MHz, CDCl$_3$, Rotamers) δ** = 169.7 and 169.5 (Rotameric **C=O**), 147.4 and 147.2 (Rotameric), 145.0 and 144.9 (Rotameric), 136.1 and 135.2 (Rotameric), 132.5 and 132.4 (Rotameric), 129.8 and 129.7 (Rotameric), 129.3 and 129.1 (Rotameric), 128.8 and 128.4 (Rotameric), 128.2 and 127.9 (Rotameric), 127.2 and 127.1 (Rotameric), 126.8 and 126.7 (Rotameric), 123.6 and 123.5 (Rotameric), 113.2 (Rotameric), 89.3 and 88.1 (Rotameric **C** alkyne), 83.1 and 82.3 (Rotameric **C** alkyne), 49.7 and 49.1 (Rotameric **C**H$_2$), 45.9 and 45.8 (Rotameric **C**H$_2$), 36.3 and 35.7 (Rotameric **C**H$_2$), 20.3; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{25}H_{24}N_3O_3$ (M + H)$^+$ 414.1812; found 414.1817.

***N*-Benzyl-N-(3-(thiophen-2-yl)prop-2-yn-1-yl)-2-(p-tolylamino) acetamide (29n):** Compound **29n** was isolated in 74% yield (79 mg, Viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 70/30); **^{1}H NMR (500 MHz, CDCl$_3$, Rotameric mixture found in 1:0.98 ratio) δ** = 7.36 – 7.26 (m, 8H) (Rotameric), 7.20 (dd, *J* = 13.2, 6.2 Hz, 3H, Aromatic) (Rotameric), 7.15 (dd, *J* = 9.0, 4.6 Hz, 3H, Aromatic) (Rotameric), 6.98 (d, *J* = 7.9 Hz, 2H, Aromatic) and 6.94 (d, *J* = 7.9 Hz, 2H, Aromatic) (Rotameric), 6.92 – 6.88 (m, 2H, Aromatic) (Rotameric), 6.58 (d, *J* = 8.0 Hz, 2H, Aromatic) and 6.47 (d, *J* = 8.0 Hz, 2H, Aromatic) (Rotameric), 4.74 (s, 2H, **CH**$_2$) and 4.61 (s, 2H, **CH**$_2$) (Rotameric), 4.47 (s, 2H, **CH**$_2$) and 3.89 (s, 2H, **CH**$_2$) (Rotameric), 4.11 (s, 2H, **CH**$_2$) and 4.03 (s, 2H, **CH**$_2$) (Rotameric), 2.22 (s, 3H, NHPh**CH**$_3$) and 2.20 (s, 3H, NHPh**CH**$_3$) (Rotameric); **^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$, Rotamers) δ** = 169.7 and 169.6 (Rotameric **C=O**), 145.3 and 145.2 (Rotameric), 136.5 and 135.6 (Rotameric), 132.9 and 132.6 (Rotameric), 129.9 and 129.9 (Rotameric), 129.2 and 129.0 (Rotameric), 128.9 and 128.6 (Rotameric), 128.2 and 127.5 (Rotameric), 127.92 and 127.84 (Rotameric), 127.2 and 127.1 (Rotameric), 126.9 and 126.9 (Rotameric), 122.6 and 121.9 (Rotameric), 113.4 and 113.3 (Rotameric), 88.0 and 86.9 (Rotameric **C** alkyne), 78.5 and 77.7 (Rotameric **C** alkyne), 49.5 and 49.4 (Rotameric **C**H$_2$), 45.9, 36.6 and 35.8 (Rotameric **C**H$_2$), 20.6; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{23}H_{23}N_2OS$ (M + H)$^+$ 375.1526; found 375.1533

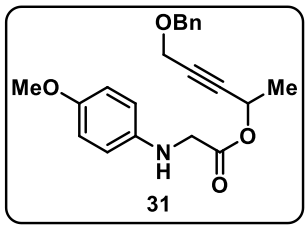


29n

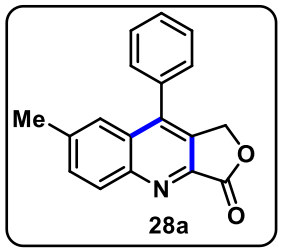


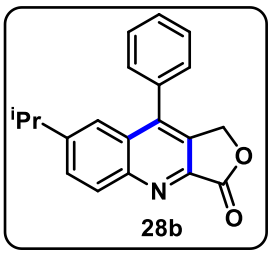
***N*-Benzyl-2-(phenylamino)-*N*-(3-(trimethylsilyl)prop-2-yn-1-yl) acetamide (29o):** Compound **29o** was isolated in 65% yield (64 mg, Viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 80/20); **^{1}H NMR (400 MHz, $CDCl_3$, Rotameric mixture found in 1:0.96 ratio) δ** = ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 6.96 (m, 14H) (Rotameric), 6.59 – 6.54 (m, 2H) (Rotameric), 6.50 (d, *J* = 7.8 Hz, 2H) and 6.39 (d, *J* = 7.6 Hz, 2H) (Rotameric), 4.71 (bs, 2H, **NH**) (Rotameric), 4.57 (s, 2H, C**H$_2$**) and 4.50 (s, 2H, C**H$_2$**) (Rotameric), 4.17 (s, 2H, C**H$_2$**) and 3.88 (s, 2H, C**H$_2$**) (Rotameric), 3.79 (s, 2H, C**H$_2$**) and 3.75 (s, 2H, C**H$_2$**) (Rotameric), 0.00 (s, 9H, **TMS**) and 0.00 (s, 9H, **TMS**) (Rotameric); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, Rotamers) δ** = 169.3 and 169.1 (Rotameric **C=O**), 147.3 and 147.2 (Rotameric), 136.3 and 135.4 (Rotameric), 129.2 and 129.1 (Rotameric), 128.9 and 126.6 (Rotameric), 128.6 and 128.4 (Rotameric), 127.9 and 127.7 (Rotameric), 117.6 (Rotameric), 112.9 (Rotameric), 99.7 and 98.8 (Rotameric), 90.5 and 89.6 (Rotameric), 49.1 and 49.0 (Rotameric), 45.4 and 45.3 (Rotameric), 36.4 and 35.7 (Rotameric), -0.2 and 0.3 (Rotameric **TMS**); **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{21}H_{27}N_2OSi$ 351.1878; found 351.1895.

5-(Benzyloxy)pent-3-yn-2-yl (4-methoxyphenyl)glycinate (31): Compound **31** was isolated in 62% yield (70 mg, Viscous liquid); R_f = 0.35 (V_{PE}/V_{EA}= 70/30); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.33-7.27 (m, 5H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 8.9 Hz, 2H), 5.56 (q, *J* = 6.7 Hz, 1H), 4.73 (bs, 1H), 4.54 (s, 2H), 4.16 (d, *J* = 1.6 Hz, 2H), 3.87 (s, 2H), 3.68 (s, 3H), 1.50 (d, *J* = 6.7 Hz, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 169.9 , 152.9, 139.9, 137.0, 128.2, 127.9, 127.7, 114.9, 114.6, 84.2, 81.1, 71.4, 61.1, 56.9, 55.4, 46.9, 21.0; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{21}H_{24}NO_4$ 354.1700; found 354.1692.



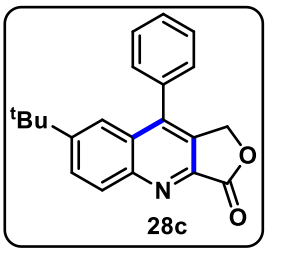
7-Methyl-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28a): Compound **28a** was isolated in 88% yield (43.5 mg, Off white solid); **mp** = 198-200 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.30 (d, *J* = 8.7 Hz, 1H), 7.67 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.64 – 7.57 (m, 4H), 7.46 – 7.42 (m, 2H), 5.35 (s, 2H), 2.50 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 168.9, 149.3, 143.2, 142.8, 139.9, 133.7, 133.1, 132.5, 130.9, 129.4, 129.3, 128.8, 127.9, 124.2, 67.8, 22.1; **HRMS (ESI-TOF)** *m/z*: [M + H]+ calcd for $C_{18}H_{14}NO_2$ 276.1019; found 276.1016.



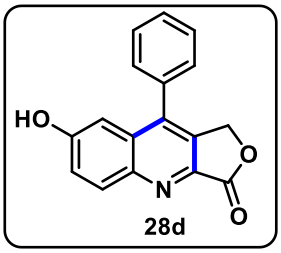


7-*iso*-Propyl-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28b):Compound **28b** was isolated in 86% yield (42.5 mg, Off white solid); **mp** = 197-199 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.37 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.67 – 7.58 (m, 4H), 7.45 (d, *J* = 6.7 Hz, 2H), 5.37 (s, 2H), 3.05 (Sept, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 6H); **^{13}C {^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 168.9, 150.5, 149.7, 143.4, 143.1, 133.8, 132.4, 131.3, 130.5, 129.4, 129.3, 128.8, 127.9, 121.7, 67.8, 34.5, 23.6; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{20}H_{18}NO_2$ 304.1332; found 304.1328.

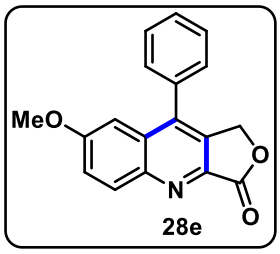
7-(*tert*-Butyl)-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28c): Compound **28c** was isolated in 83% yield (41 mg, Off white solid); **mp** = 236-238 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.33 (d, *J* = 8.9 Hz, 1H), 7.93 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.82 (d, *J* = 1.9 Hz, 1H), 7.64 – 7.57 (m, 3H), 7.46 (dd, *J* = 5.0, 2.8 Hz, 2H), 5.37 (s, 2H), 1.32 (s, 9H); **^{13}C {^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 168.9, 152.6, 149.2, 143.4, 133.6, 132.4, 130.7, 129.8, 129.4, 129.2, 128.8, 127.5, 120.3, 67.8, 35.3, 30.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_2$ 318.1489;found 318.1483.



7-Hydroxy-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28d): Compound **28d** was isolated in 57% yield (28 mg, Off white solid); **mp** = 259-261 °C; R_f = 0.30 (V_{PE}/V_{EA} = 50/50); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 9.73 (s, 1H), 8.16 (d, *J* = 9.2 Hz, 1H), 7.64 (m, 2H), 7.61 – 7.57 (m, 3H), 7.54 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.17 (d, *J* = 2.7 Hz, 1H), 5.43 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 169.1, 158.9, 146.6, 142.4, 141.4, 134.8, 134.3, 133.3, 130.3, 129.8, 129.7, 129.6, 124.0, 106.8, 68.0; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{12}NO_3$ 278.0812; found 278.0809.

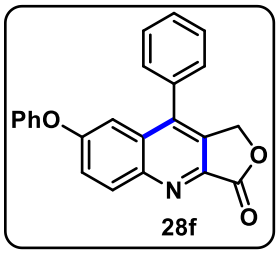


7-Methoxy-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28e): Compound **28e** was isolated in 61% yield (30 mg, Off white solid); **mp** = 242.5-244.5 °C; R_f = 0.35 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR 500 MHz, $CDCl_3$) δ** = 8.31 (d, *J* = 9.3 Hz, 1H), 7.61 (m, 3H), 7.49 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.45 (d, *J* = 7.1 Hz, 2H), 7.10 (d, *J* = 2.6 Hz, 1H), 5.34 (s, 2H), 3.80 (s, 3H); **^{13}C {^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 168.9, 160.1, 147.0, 141.8, 141.7, 133.9, 133.1, 132.8, 129.5, 129.4(two ^{13}C), 128.6, 123.9, 102.9, 67.7, 55.6; **HRMS (ESI-TOF)** *m/z*:

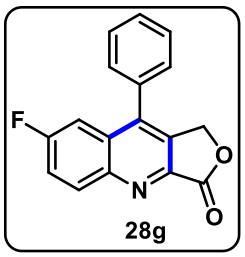


$[M + H]^+$ calcd for $C_{18}H_{14}NO_3$ 292.0968; found 292.0965.

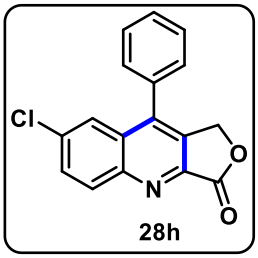
7-Phenoxy-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28f): Compound **28f** was isolated in 64% yield (32 mg, Off white solid); **mp** = 232-234 °C; R_f = 0.35 (V_{PE}/V_{EA} = 50/50); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.39 (d, *J* = 9.3 Hz, 1H), 7.55 (m, 4H), 7.43 – 7.33 (m, 5H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 2H), 5.38 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 168.7, 158.0, 155.7, 147.5, 143.0, 142.4, 133.3, 133.3, 132.9, 130.0, 129.5, 129.3 (two ^{13}C), 128.7, 124.5, 123.9, 119.6, 110.9, 67.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{23}H_{16}NO_3$ 354.1125; found 354.1121.



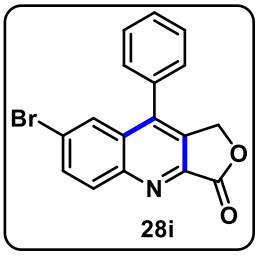
7-Fluoro-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28g): Compound **28g** was isolated in 79% yield (39 mg, Off white solid); **mp** = 218-220 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.40 (dd, *J* = 9.4, 5.6 Hz, 1H), 7.65 – 7.58 (m, 4H), 7.49 (dd, *J* = 9.8, 2.8 Hz, 1H), 7.46 – 7.42 (m, 2H), 5.39 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 168.4, 162.2 (d, J=253.1 Hz), 147.7, 143.8 (d, J=2.8 Hz), 143.3 (d, *J* = 6.4 Hz), 133.9 (d, *J* = 9.6 Hz), 132.9 (d, *J* = 5.9 Hz), 129.8, 129.5, 129.0 (d, *J* = 9.9 Hz), 128.6, 121.4 (d, *J* = 26.5 Hz), 109.1 (d, *J* = 23.6 Hz), 67.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -107.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{11}FNO_2$ 280.0768; found 280.0765.



7-Chloro-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28h): Compound **28h** was isolated in 76% yield (38 mg, Off white solid); **mp** = 216-218 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.23 (d, *J* = 9.1 Hz, 1H), 7.80 (s, 1H), 7.72 – 7.65 (m, 1H), 7.65 – 7.55 (m, 3H), 7.47 – 7.42 (m, 2H), 5.36 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 168.2, 148.7, 144.3, 143.0, 135.6, 133.1, 132.7, 132.5, 131.6, 129.7, 129.4, 128.7, 128.3, 124.4, 67.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{11}ClNO_2$ 296.0473; found 296.0469.

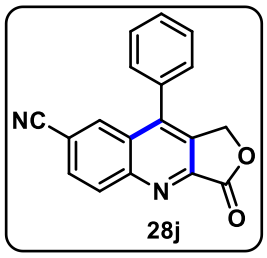


7-Bromo-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28i): Compound **28i** was isolated in 75% yield (37 mg, Yellow solid); **mp** = 219-221 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.26 (d, *J* = 9.1 Hz, 1H), 8.03 (d, *J* = 1.2 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.65 – 7.59 (m, 3H), 7.44 (d, *J* = 7.4 Hz, 2H), 5.39 (s, 2H); **^{13}C {^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 168.2, 149.2, 144.6, 143.1, 134.3, 133.1, 132.8, 129.9, 129.5, 128.9, 128.7,

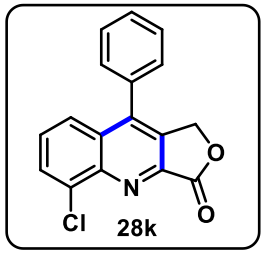


127.9, 124.2, 67.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{11}BrNO_2$ 339.9968; found 339.9963.

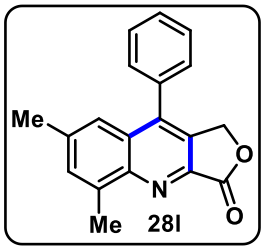
3-Oxo-9-phenyl-1,3-dihydrofuro[3,4-b]quinoline-7-carbonitrile (28j): Compound **28j** was isolated in 45% yield (23 mg, Viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 50/50); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.51 (d, *J* = 8.8 Hz, 1H), 8.30 (d, *J* = 1.5 Hz, 1H), 7.97 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.71 – 7.62 (m, 3H), 7.47 – 7.42 (m, 2H), 5.45 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 167.7, 151.2, 146.9, 145.1, 133.5, 132.8, 132.4, 131.9, 130.9, 130.4, 129.7, 128.7, 127.2, 117.9, 112.9, 67.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{11}N_2O_2$ 287.0778.; found 287.0824.



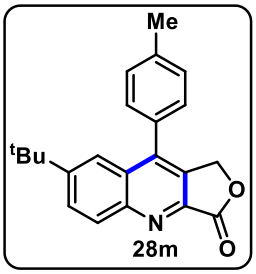
5-Chloro-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28k): Compound **28k** was isolated in 46% yield (23 mg, Off white solid); **mp** = 246-248 °C; R_f = 0.40 (V_{PE}/V_{EA} = 50/50); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.96 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.64 – 7.55 (m, 4H), 7.45 (dd, *J* = 7.7, 1.6 Hz, 2H), 5.39 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 167.9, 147.1, 144.7, 135.8, 133.2, 130.8, 129.8, 129.4, 129.3, 128.9, 128.8 (two ^{13}C), 124.9, 67.5; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{11}ClNO_2$ 296.0478.; found 296.0480.



5,7-Dimethyl-9-phenylfuro[3,4-b]quinolin-3(1H)-one (28l): Compound **28l** was isolated in 69% yield (34 mg, Off white solid); **mp** = 177-179 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.63 – 7.54 (m, 3H), 7.52 (s, 1H), 7.45 (s, 1H), 7.43 – 7.41 (m, 2H), 5.33 (s, 2H), 2.90 (s, 3H), 2.45 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 169.3, 148.6, 142.7, 142.0, 139.5, 139.1, 134.1, 133.1, 132.4, 129.2, 129.1, 128.8, 128.0, 122.2, 67.7, 22.1, 18.5; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{19}H_{16}NO_2$ 290.1176; found 290.1173.

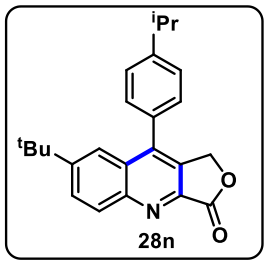


7-(*tert*-Butyl)-9-(p-tolyl)furo[3,4-b]quinolin-3(1H)-one (28m): Compound **28m** was isolated in 80% yield (39 mg, Pale yellow solid); **mp** = 205-207 °C; R_f = 0.40(V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.33 (d, *J* = 8.8 Hz, 1H), 7.93 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.37 (s, 2H), 2.49 (s, 3H), 1.33 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 169.0, 152.4, 149.3,



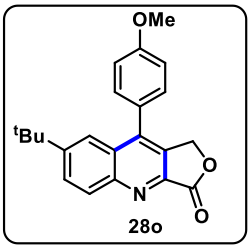
143.6, 143.4, 139.5, 132.4, 130.7, 130.6, 129.9, 129.7, 128.7, 127.6, 120.4, 67.9, 35.4, 30.9, 21.4; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{22}H_{22}NO_2$ 332.1645; found 332.1642.

7-(*tert*-Butyl)-9-(4-isopropylphenyl)furo[3,4-b]quinolin-3(1H)-one (28n): Compound **28n**



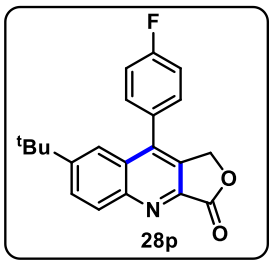
was isolated in 76% yield (38 mg, Off white solid); **mp** = 239-241 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.35 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 9.1 Hz, 1H), 7.89 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 5.40 (s, 2H), 3.05 (sept, *J* = 6.8 Hz, 1H), 1.36 (d, *J* = 7.1 Hz, 6H), 1.35 (s, 9H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 169.1, 152.4, 150.3, 149.4, 143.6, 143.5, 132.5, 131.0, 130.8, 129.7, 128.9, 127.7, 127.3, 120.5, 68.0, 35.4, 34.0, 30.9, 23.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{26}NO_2$ 360.1958;found 360.1953.

7-(*tert*-Butyl)-9-(4-methoxyphenyl)furo[3,4-b]quinolin-3(1H)-one (28o): Compound **28o** was



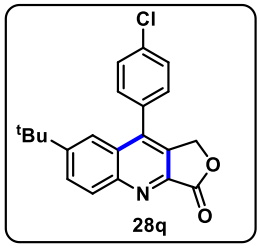
isolated in 57% yield (28 mg, Off white solid); **mp** = 262-264 °C; R_f = 0.35 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.34 (d, *J* = 9.0 Hz, 1H), 7.93 (dd, *J* = 9.0, 1.7 Hz, 1H), 7.88 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 5.39 (s, 2H), 3.94 (s, 3H), 1.35 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 169.1, 160.4, 152.4, 149.3, 143.5, 143.3, 132.5, 130.8, 130.3, 129.7, 127.8, 125.7, 120.4, 114.7, 67.9, 55.4, 35.4, 30.9; **HRMS (ESI-TOF)** *m/z*: [M + H]+ calcd for $C_{22}H_{22}NO_3$ 348.1594; found 348.1589.

7-(*tert*-Butyl)-9-(4-fluorophenyl)furo[3,4-b]quinolin-3(1H)-one (28p): Compound **28p** was



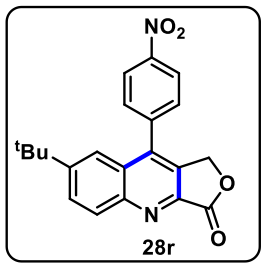
isolated in 78% yield (39 mg, Yellow solid); **mp** = 299-301°C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.31 (d, *J* = 9.0 Hz, 1H), 7.93 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.33 (m, 2H), 5.34 (s, 2H), 1.33 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 168.7, 163.2 (d, *J*= 250.2 Hz), 152.8, 149.2, 143.4, 142.3, 132.5, 130.8, 130.7, 129.9, 129.6 (d, *J* = 3.6 Hz), 127.6, 120.0, 116.5 (d, *J*=21.8 Hz), 67.7, 35.4, 30.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -110.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{21}H_{18}FNO_2Na$ 358.1214; found 358.1208.

7-(*tert*-Butyl)-9-(4-chlorophenyl)furo[3,4-b]quinolin-3(1H)-one (28q): Compound **28q** was isolated in 77% yield (38 mg, Pale yellow solid); **mp** = 265-267 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.33 (d, *J* = 9.0 Hz, 1H), 7.94 (dd, *J* = 8.9, 1.9 Hz,

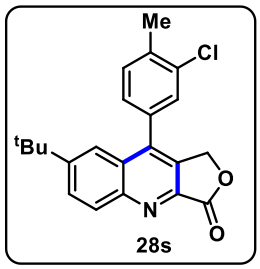


1H), 7.76 (d, *J* = 2.1 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 5.35 (s, 2H), 1.34 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, CDCl$_3$) δ** = 168.7, 152.9, 149.2, 143.5, 142.1, 135.7, 132.4, 132.1, 130.8, 130.2, 130.0, 129.6, 127.3, 119.9, 67.6, 35.4, 30.8; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{21}H_{19}ClNO_2$ 352.1099; found 352.1096.

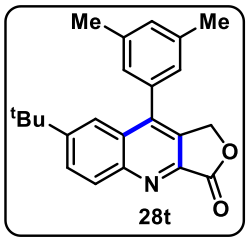
7-(*tert*-Butyl)-9-(4-nitrophenyl)furo[3,4-b]quinolin-3(1H)-one (28r):Compound **28r** was isolated in 75% yield (37 mg, Yellow solid); **mp** = 310-312 °C; R_f = 0.35 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (500 MHz, CDCl$_3$) δ** = 8.50 (d, *J* = 8.6 Hz, 2H), 8.37 (d, *J* = 9.0 Hz, 1H), 7.99 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 1.9 Hz, 1H), 5.35 (s, 2H), 1.34 (s, 9H); **^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$) δ** = 168.2, 153.7, 149.3, 148.5, 143.6, 140.7, 140.5, 132.2, 131.1, 130.4, 130.1, 126.9 124.5, 119.5, 67.3, 35.5, 30.8; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{21}H_{19}N_2O_4$ 363.1339; found 363.1333.



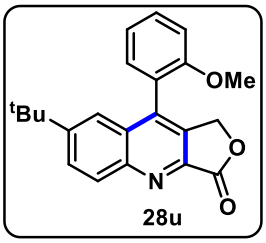
7-(*tert*-Butyl)-9-(3-chloro-4-methylphenyl)furo[3,4-b]quinolin-3(1H)-one (28s): Compound **28s** was isolated in 73% yield (36 mg, Off white solid); **mp** = 241-243 °C; R_f = 0.35 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.36 (d, *J* = 9.0 Hz, 1H), 7.96 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 1.7 Hz, 1H), 7.27 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.38 (s, 2H), 2.52 (s, 3H), 1.35 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, CDCl$_3$) δ** = 168.7, 152.9, 149.3, 143.5, 141.9, 137.7, 135.4, 132.7, 132.4, 131.8, 130.9, 129.9, 129.2, 127.4, 127.1, 120.0, 67.7, 35.4, 30.9, 20.1; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{22}H_{21}ClNO_2$ 366.1255; found 366.1251.



7-(*tert*-Butyl)-9-(3,5-dimethylphenyl)furo[3,4-b]quinolin-3(1H)-one (28t): Compound **28t** was isolated in 74% yield (37 mg, Yellow solid); **mp** = 214.5-216.5 °C; R_f = 0.45 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (500 MHz, CDCl$_3$) δ** = 8.34 (d, *J* = 9.0 Hz, 1H), 7.93 (dd, *J* = 9.0, 1.0 Hz, 1H), 7.86 (s, 1H), 7.19 (s, 1H), 7.05 (s, 2H), 5.38 (s, 2H), 2.43 (s, 6H), 1.34 (s, 9H); **^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$) δ** = 169.0, 152.3, 149.3, 143.8, 143.5, 138.9, 133.6, 132.3, 130.9, 130.7, 129.7, 127.7, 126.5, 120.6, 67.9, 35.3, 30.9, 21.3; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{23}H_{24}NO_2$ 346.1802; found 346.1797.

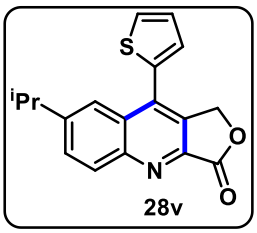


7-(*tert*-Butyl)-9-(2-methoxyphenyl)furo[3,4-b]quinolin-3(1H)-one (28u):



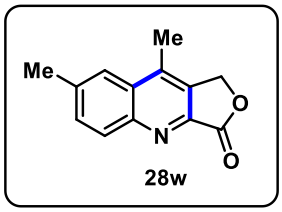
Compound **28u** was isolated in 56% yield (28 mg, Off white solid); **mp** = 257-259 °C; R_f = 0.30 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.35 (d, *J* = 9.0 Hz, 1H), 7.92 (dd, *J* = 9.0, 1.9 Hz, 1H), 7.68 (d, *J* = 1.6 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.30 – 7.27 (m, 1H), 7.20 – 7.13 (m, 2H), 5.35 (d, *J* = 15.0 Hz, 1H), 5.25 (d, *J* = 15.0 Hz, 1H), 3.78 (s, 3H), 1.32 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 169.2, 156.4, 152.1, 149.2, 143.3, 140.5, 133.7, 131.2, 130.9, 130.7, 129.6, 128.2, 121.9, 120.9, 120.6, 111.6, 68.3, 55.4, 35.3, 30.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{22}H_{22}NO_3$ 348.1594;found 348.1590.

7-*iso*-Propyl-9-(thiophen-2-yl)furo[3,4-b]quinolin-3(1H)-one (28v):



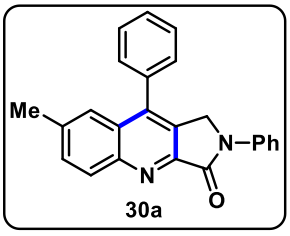
Compound **28v** was isolated in 77% yield (38 mg, Brown solid); **mp** = 157-159 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.33 (d, *J* = 8.8 Hz, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.77 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.67 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.38 (dd, *J* = 3.5, 1.2 Hz, 1H), 7.33 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.50 (s, 2H), 3.11 (sept, *J* = 6.9 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 6H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 168.7, 150.9, 149.7, 143.3, 136.1, 133.6, 132.6, 131.3, 130.7, 129.9, 128.7, 128.3, 127.8, 121.7, 68.2, 34.5, 23.6; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}NO_2S$ 310.0896; found 310.0891.

7,9-Dimethylfuro[3,4-b]quinolin-3(1H)-one (28w):



Compound **28w** was isolated in 17% yield (11 mg, Brown solid); **mp** = 213-215 °C; R_f = 0.40 (V_{PE}/V_{EA} = 50/50); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.25 (d, *J* = 8.8 Hz, 1H), 7.85 (s, 1H), 7.67 (dd, *J* = 8.7, 1.6 Hz, 1H), 5.49 (s, 2H), 2.69 (s, 3H), 2.63 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 169.2, 148.5, 143.0, 139.7, 138.7, 133.0, 131.5, 129.1, 122.4, 67.7, 22.3, 14.6; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{13}H_{12}NO_2$ 214.0878.; found 214.0869.

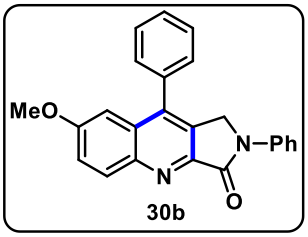
7-Methyl-2,9-diphenyl-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (30a):



Compound **30a** was isolated in 80% yield (39 mg, Brown solid); **mp** = 247-249 °C; R_f = 0.40 (V_{PE}/V_{EA} = 40/60); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.32 (d, *J* = 8.7 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 2H), 7.66 – 7.58 (m, 4H), 7.54 (s, 1H), 7.51 – 7.47 (m, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 4.79 (s, 2H), 2.48 (s, 3H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 165.6, 150.0, 148.7, 142.8, 139.4, 138.7, 134.6, 132.5, 130.9, 129.3

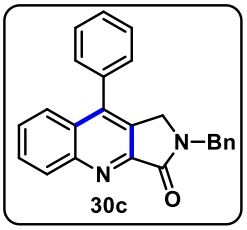
(two ^{13}C), 129.2, 129.1, 127.9, 127.7, 125.3, 124.5, 119.7, 48.3, 22.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{19}N_2O$ 351.1492; found 351.1494.

7-Methoxy-2,9-diphenyl-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (30b):



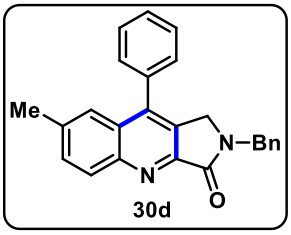
Compound **30b** was isolated in 52% yield (26 mg, Yellow solid); **mp** = 236-238 °C; R_f = 0.30 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.33 (d, *J* = 9.3 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.61 (m, 3H), 7.50 (d, *J* = 6.8 Hz, 2H), 7.45 – 7.38 (m, 3H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 4.78 (s, 2H), 3.78 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 165.5, 159.2, 148.4, 146.1, 141.7, 139.2, 134.6, 132.5, 129.3, 129.2, 129.1, 129.1, 128.8, 128.1, 125.1, 122.7, 119.5, 103.3, 55.5, 48.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{19}N_2O_2$ 367.1441 found 367.1435.

2-Benzyl-9-phenyl-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (30c):



Compound **30c** was isolated in 84% yield (41 mg, Yellow solid); **mp** = 192-194 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.45 (d, *J* = 8.4 Hz, 1H), 7.78 (t, *J* = 8.5 Hz, 2H), 7.58 – 7.50 (m, 4H), 7.38 (m, 2H), 7.34 – 7.27 (m, 5H), 4.89 (s, 2H), 4.24 (s, 2H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 166.4, 150.7, 149.6, 143.5, 136.2, 134.3, 131.1, 129.8, 128.9, 128.8, 128.3 (two ^{13}C), 128.0, 127.9, 127.5, 125.6, 47.2, 46.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{19}N_2O$ 351.1492; found 351.1487.

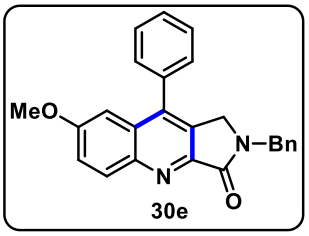
2-Benzyl-7-methyl-9-phenyl-1,2-dihydro-3H-pyrrolo[3,4-b] quinolin-3-one (30d):



Compound **30d** was isolated in 82% yield (40 mg, Yellow solid); **mp** = 204-206 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.29 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.36 – 7.33 (m, 2H), 7.29 – 7.23 (m, 5H), 4.85 (s, 2H), 4.19 (s, 2H), 2.43 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 166.5, 149.7, 148.1, 142.6, 138.2, 136.3, 134.4, 132.1, 130.6, 128.9 (two ^{13}C), 128.8, 128.8, 128.4, 128.2, 127.8, 127.4, 124.3, 47.0, 46.7, 21.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{21}N_2O$ 365.1648; found 365.1653.

2-Benzyl-7-methoxy-9-phenyl-1,2-dihydro-3H-pyrrolo[3,4-b] quinolin-3-one (30e):

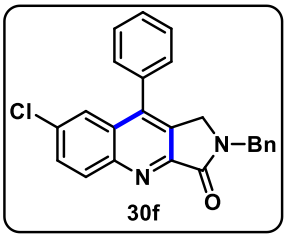
Compound **30e** was isolated in 59% yield (29 mg, Brown solid); **mp** = 179-181 °C; R_f = 0.35 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.31 (d, *J* = 9.2 Hz, 1H), 7.57-7.51 (m, 3H), 7.43 – 7.39 (m, 3H), 7.31 – 7.27 (m, 5H), 6.98 (d, *J* = 2.6 Hz, 1H), 4.87 (s, 2H), 4.21 (s,



30e

2H), 3.75 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 166.6, 158.9, 148.3, 145.6, 141.7, 136.3, 134.5, 132.4, 129.0, 128.9, 128.8, 128.7 (two ^{13}C), 128.2, 127.8, 122.4, 103.3, 55.4, 46.9, 46.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_2$; 381.1598 found 381.1597.

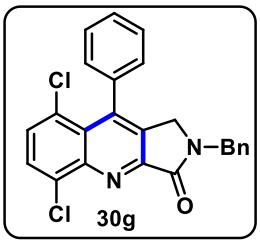
2-Benzyl-7-chloro-9-phenyl-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (30f):



30f

Compound **30f** was isolated in 81% yield (40 mg, Brown solid); **mp** = 224-226 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.33 (d, *J* = 8.6 Hz, 1H), 7.70 (s, 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.59 – 7.51 (m, 3H), 7.37 (m, 2H), 7.33 – 7.27 (m, 5H), 4.88 (s, 2H), 4.24 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 165.9, 150.9, 147.8, 142.7, 136.0, 134.1, 133.5, 132.5, 130.8, 129.3, 129.2, 129.1, 128.9 (two ^{13}C), 128.3, 128.1, 127.9, 124.4, 47.1, 46.7; **HRMS (ESI-TOF)** m/z: $[M + H]^+$ calcd for $C_{24}H_{18}ClN_2O$ 385.1102; found 385.1100.

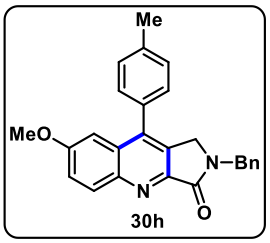
2-Benzyl-5,8-dichloro-9-phenyl-1,2-dihydro-3H-pyrrolo[3,4-b] quinolin-3-one (30g): Com-



30g

pound **30g** was isolated in 43% yield (21 mg, Yellow solid); **mp** = 231-233 °C; R_f = 0.45 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.80 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.47 – 7.44 (m, 3H), 7.34 – 7.26 (m, 7H), 4.85 (s, 2H), 4.10 (s, 2H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 165.3, 151.0, 147.1, 144.2, 136.3, 136.0, 135.1, 132.3, 130.4, 129.7, 129.5, 128.8, 128.6, 128.4, 128.2, 128.1, 127.9, 125.8, 47.2, 46.9; **HRMS (ESI-TOF)** m/z: $[M + H]^+$ calcd for $C_{24}H_{17}Cl_2N_2O$ $(M + H)^+$ 419.0712; found 419.0703.

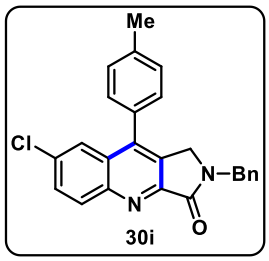
2-Benzyl-9-(4-methoxyphenyl)-7-methyl-1,2-dihydro-3H-pyrrolo [3,4-b]quinolin-3-one



30h

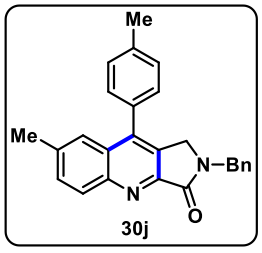
(30h): Compound **30h** was isolated in 57% yield (28 mg, Yellow solid); **mp** = 197-199 °C; R_f = 0.35 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.31 (d, *J* = 9.3 Hz, 1H), 7.41 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.34(d, *J* = 7.6 Hz, 2H), 7.31 – 7.27 (m, 7H), 7.03 (d, *J* = 1.7 Hz, 1H), 4.87 (s, 2H), 4.20 (s, 2H), 3.76 (s, 3H), 2.46 (s, 3H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 166.7, 158.9, 148.4, 145.7, 141.9, 138.8, 136.4, 132.4, 131.5, 129.7, 128.9, 128.9, 128.8, 128.7, 128.2, 127.7, 122.4, 103.4, 55.4, 47.0, 46.8, 21.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_2$ 395.1754; found 395.1750.

2-Benzyl-7-chloro-9-(p-tolyl)-1,2-dihydro-3H-pyrrolo[3,4-b] quinoline-3-one (30i):

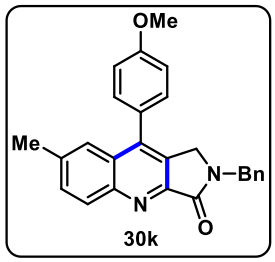


Compound **30i** was isolated in 80% yield (39 mg, Yellow solid); **mp** = 187-189 °C; R_f = 0.45 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.28 (d, *J* = 9.0 Hz, 1H), 7.71 (s, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.37 – 7.27 (m, 9H), 4.87 (s, 2H), 4.24 (s, 2H), 2.46 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 165.9, 150.8, 147.8, 142.8, 139.3, 136.0, 133.9, 132.3, 130.7, 130.5, 129.8, 129.2, 128.8, 128.2, 128.1, 127.8, 124.5, 113.9, 47.1, 46.8, 21.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}ClN_2O$ 399.1259; found 399.1261.

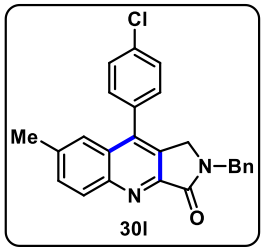
2-Benzyl-7-methyl-9-(*p*-tolyl)-1,2-dihydro-3H-pyrrolo[3,4-b] quinolin-3-one (30j): Compound **30j** was isolated in 79% yield (39 mg, Yellow solid); **mp** = 203-205 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.33 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.54 (s, 1H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.33 – 7.25 (m, 7H), 4.89 (s, 2H), 4.23 (s, 2H), 2.47 (s, 6H); **^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 166.6, 149.8, 148.2, 142.8, 138.8, 138.1, 136.4, 132.1, 131.5, 130.7, 129.6, 128.9, 128.8, 128.5, 128.3, 127.8, 127.6, 124.4, 47.1, 46.8, 21.9, 21.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O$ 379.1805; found 379.1801.



2-Benzyl-9-(4-methoxyphenyl)-7-methyl-1,2-dihydro-3H-pyrrolo [3,4-b]quinolin-3-one (30k): Compound **30**k was isolated in 75% yield (37 mg, Yellow solid); **mp** = 190-192 °C; R_f = 0.35 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.29 (d, *J* = 8.6 Hz, 1H), 7.58 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.54 (s, 1H), 7.34 – 7.27 (m, 7H), 7.07 (d, *J* = 8.7 Hz, 2H), 4.86 (s, 2H), 4.22 (s, 2H), 3.90 (s, 3H), 2.46 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 166.54, 159.91, 149.66, 148.11, 142.47, 138.03, 136.29, 131.98, 130.57, 130.30, 128.75, 128.53, 128.23, 127.74, 127.67, 126.41, 124.34, 114.36, 55.31, 47.00, 46.82, 21.90; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_2$ 395.1754; found 395.1762.

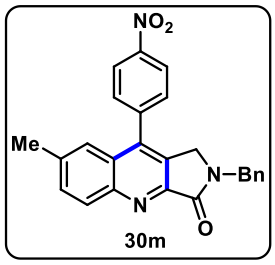


2-Benzyl-9-(4-chlorophenyl)-7-methyl-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (30l): Compound **30l** was isolated in 81% yield (40 mg, Yellow solid); **mp** = 193-195 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.27 (d, *J* = 8.6 Hz, 1H), 7.59 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.43 (s, 1H), 7.36 – 7.26 (m, 7H), 4.85 (s, 2H), 4.19 (s, 2H),



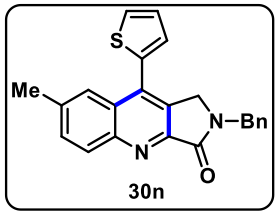
2.46 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 166.3, 149.6, 147.9, 141.3, 138.5, 136.1, 135.1, 132.8, 132.2, 130.7, 130.4, 129.3, 128.8, 128.4, 128.3, 127.9, 127.2, 123.9, 47.0, 46.6, 21.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}ClN_2O$ 399.1259; found 399.1271.

2-Benzyl-7-methyl-9-(4-nitrophenyl)-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (30m):



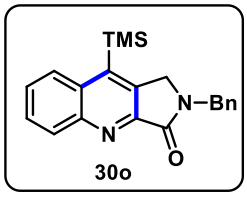
Compound **30m** was isolated in 71% yield (35 mg, Yellow solid); **mp** = 200-202 °C; R_f = 0.30 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.43 (d, *J* = 8.8 Hz, 2H), 8.34 (d, *J* = 8.7 Hz, 1H), 7.65 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.36 – 7.29 (m, 6H), 4.86 (s, 2H), 4.18 (s, 2H), 2.48 (s, 3H). **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 166.10, 149.92, 148.32, 148.19, 141.38, 140.16, 139.33, 136.10, 132.75, 131.06, 130.30, 129.03, 128.49, 128.31, 128.12, 126.74, 124.40, 123.63, 47.26, 46.55, 22.11; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}N_3O_3$ 410.1499; found 410.1505.

2-Benzyl-7-methyl-9-(thiophen-2-yl)-1,2-dihydro-3H-pyrrolo[3,4-b] quinolin-3-one (30n):



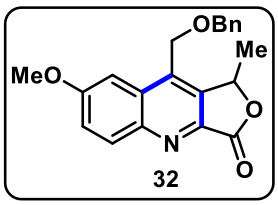
Compound **30n** was isolated in 73% yield (36 mg, Yellow solid); **mp** = 221-223 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.31 (d, *J* = 8.7 Hz, 1H), 7.84 (s, 1H), 7.61 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.59 – 7.56 (m, 1H), 7.36 – 7.31 (m, 4H), 7.31 – 7.23 (m, 4H), 4.90 (s, 2H), 4.36 (s, 2H), 2.51 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 166.42, 149.87, 148.32, 138.82, 136.35, 135.73, 134.26, 132.42, 130.88, 129.55, 129.27, 128.96, 128.41, 128.01, 127.97, 127.95, 127.72, 124.34, 47.41, 47.20, 22.16; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{23}H_{19}N_2OS$ 371.1213; found 371.1221.

2-Benzyl-9-(trimethylsilyl)-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (30o): Compound

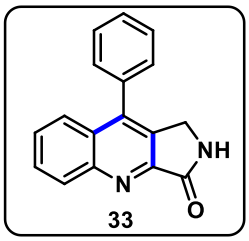


30o was isolated in 67% yield (33 mg, Off white solid); **mp** = 202-204 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.42 (d, *J* = 8.2 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.75 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.62 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.41 – 7.27 (m, 5H), 4.94 (s, 2H), 4.46 (s, 2H), 0.51 (s, 9H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 166.0, 149.3, 148.1, 142.9, 136.2, 135.7, 132.3, 132.1, 129.1, 128.9, 128.3, 127.9, 127.8, 127.4, 49.3, 47.1, 1.5; **HRMS (ESI-TOF)** m/z: $[M + H]^+$ calcd for $C_{21}H_{23}N_2OSi$ $(M + H)^+$ 347.1578; found 347.1581.

9-((Benzyloxy)methyl)-7-methoxy-1-methylfuro[3,4-b]quinolin-3(1H)-one (32): Compound **32** was isolated in 41% yield (21 mg, Yellow solid); **mp** = 174-176 °C; R_f = 0.35 (V_{PE}/V_{EA} = 30/70); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.26 (d, *J* = 9.3 Hz, 1H), 7.47 (dd, *J* = 9.3, 2.7 Hz,

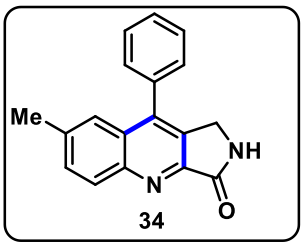


1H), 7.41 – 7.36 (m, 5H), 7.18 (d, *J* = 2.7 Hz, 1H), 5.88 (q, *J* = 6.5 Hz, 1H), 5.06 (q, *J* = 13.20 Hz, 2H), 4.71 (q, *J* = 11.74 Hz, 2H), 3.92 (s, 3H), 1.68 (d, *J* = 6.5 Hz, 3H); **^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 168.2, 160.1, 146.3, 142.3, 137.8, 136.7, 136.3, 133.2, 129.0, 128.7, 128.4, 128.1, 123.7, 101.2, 76.8, 73.7, 65.9, 55.7, 21.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_4$ 350.1387; found 350.1380.

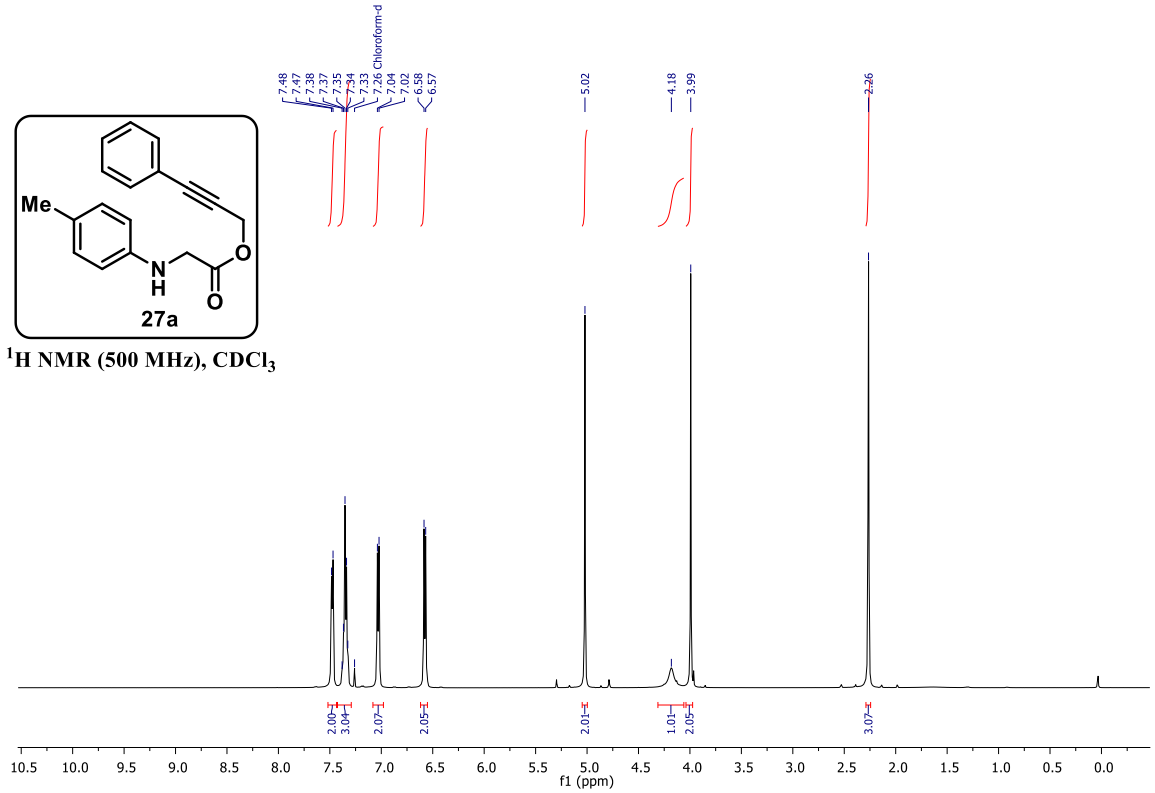


9-Phenyl-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (33): Compound **33** was isolated in 88% yield (65 mg, Grey solid); **mp** = 279-281°C (Decomposed); R_f = 0.40 (V_{DCM}/V_{MeOH} = 90/10); **^{1}H NMR (400 MHz DMSO d_6) δ** = 9.26 (bs, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.87 (t, *J* = 7.4 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.58-7.62 (m, 5H), 4.38 (s, 2H); **^{13}C {^{1}H} NMR (100 MHz, DMSO d_6) δ** = 167.6, 151.4, 148.7, 142.9, 133.9, 131.0, 130.3, 129.7, 129.2, 128.9 (two ^{13}C), 128.1, 126.6, 125.4, 42.0; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O$ 261.1022; found 261.1019.

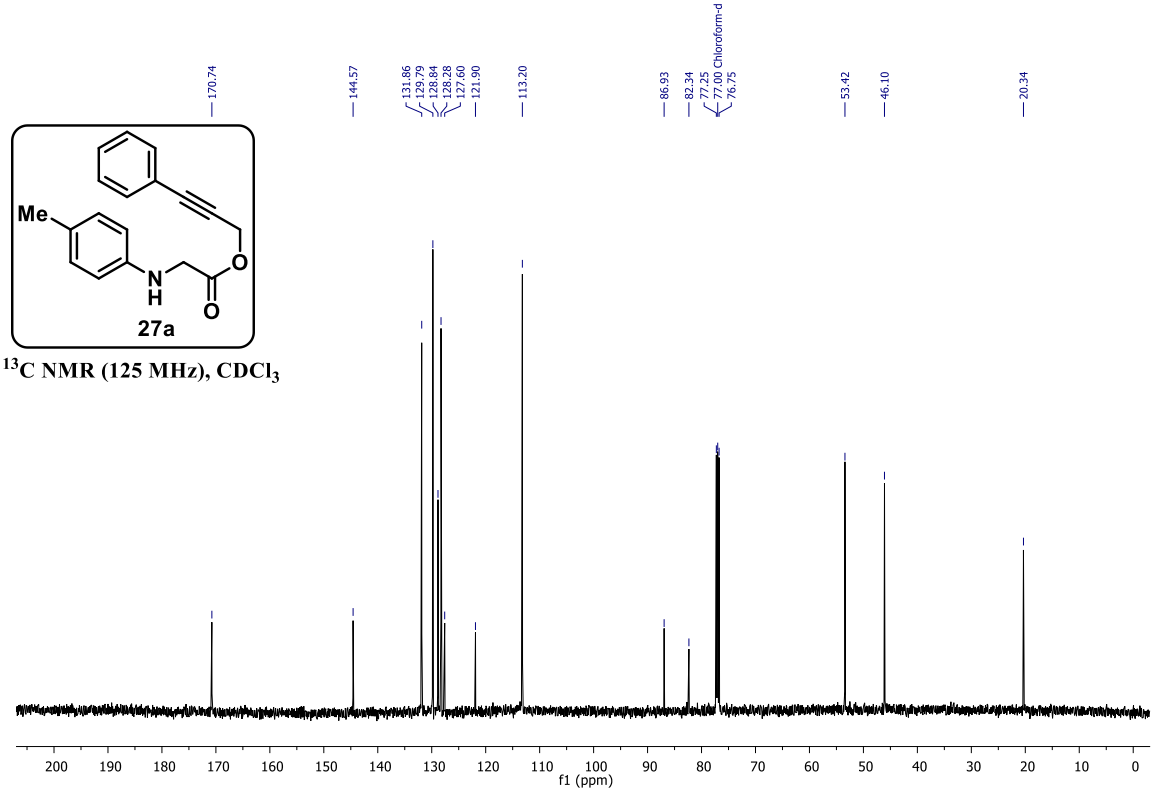
7-Methyl-9-phenyl-1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (34): Compound **34** was isolated in 86% yield (65 mg, Grey solid); **mp** = 317-319 °C (Decomposed); R_f = 0.40 (V_{DCM}/V_{MeOH} = 90/10); **^{1}H NMR (400 MHz, DMSO d_6) δ** = 9.19 (bs, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.62-7.52 (m, 6H), 4.34 (s, 2H), 2.45 (s, 3H); **^{13}C {^{1}H} NMR (100 MHz, DMSO d_6) δ** = 168.2, 151.0, 147.9, 142.7, 138.3, 134.5, 132.4, 131.7, 130.6, 129.7, 129.4, 129.3, 127.0, 124.3, 42.5, 22.0; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$ 275.1179; found 275.1176.



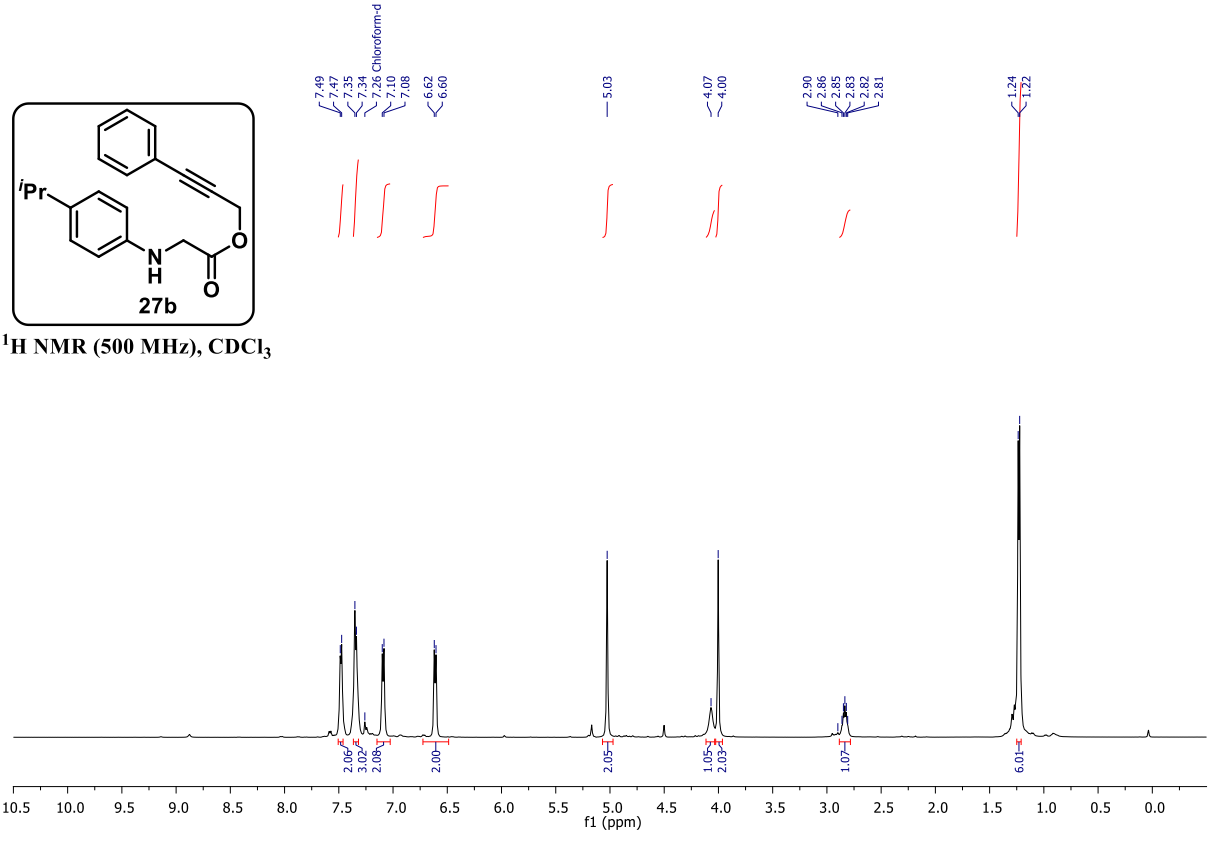
1.1.7 Spectral data for the representative compounds:

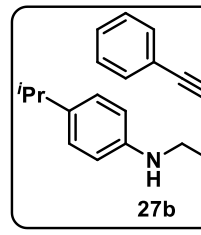


^{1}H NMR (500 MHz), $CDCl_3$



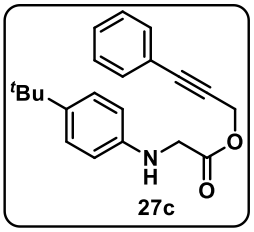
^{13}C NMR (125 MHz), $CDCl_3$



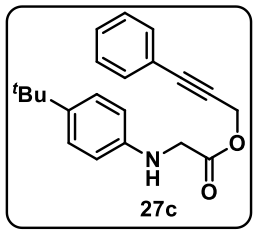


^{1}H NMR (500 MHz), $CDCl_3$

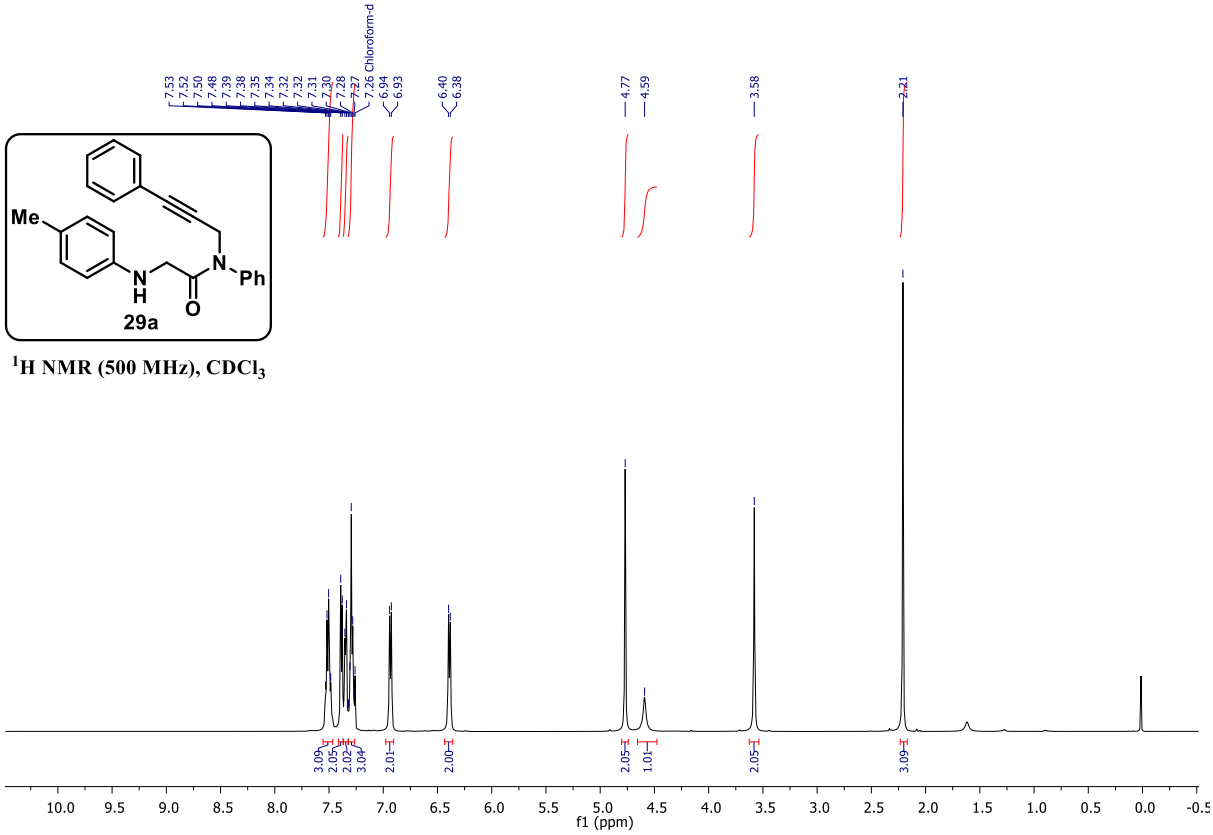
^{13}C NMR (125 MHz), $CDCl_3$



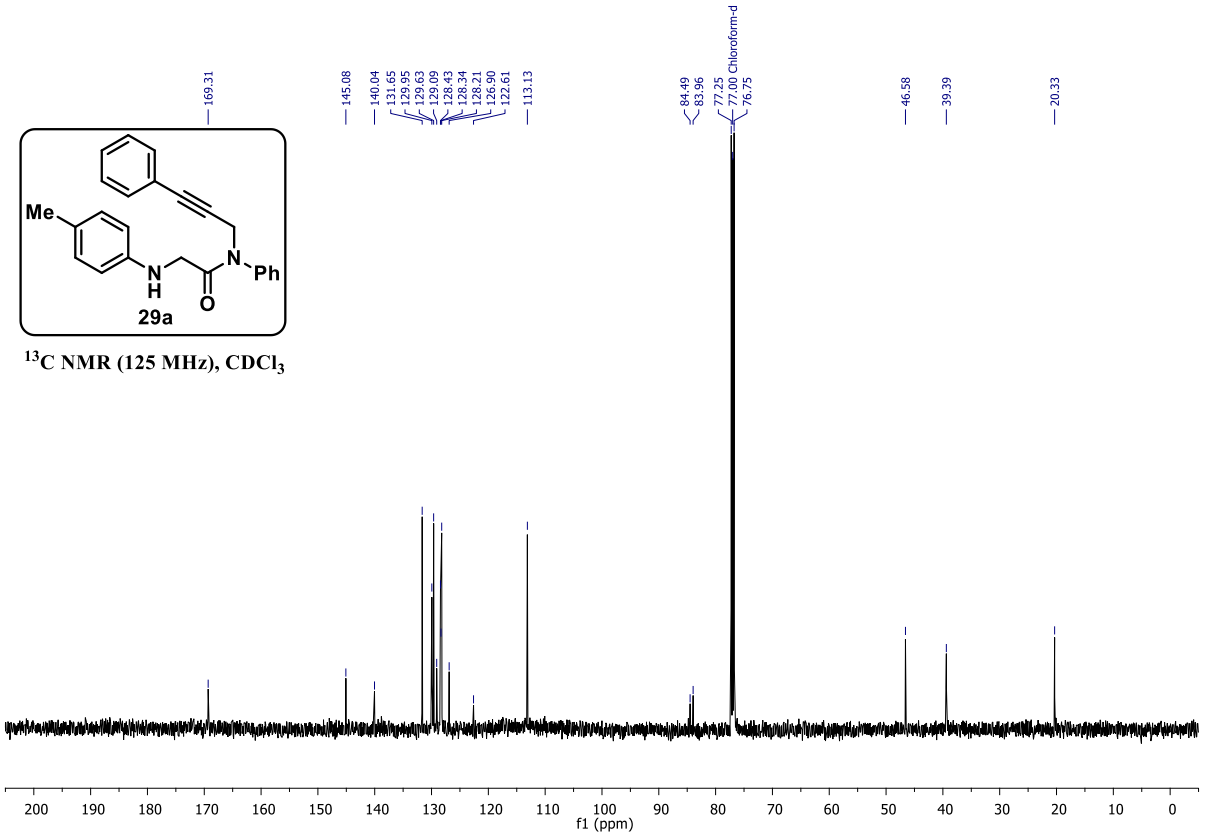
^{1}H NMR (500 MHz), $CDCl_3$



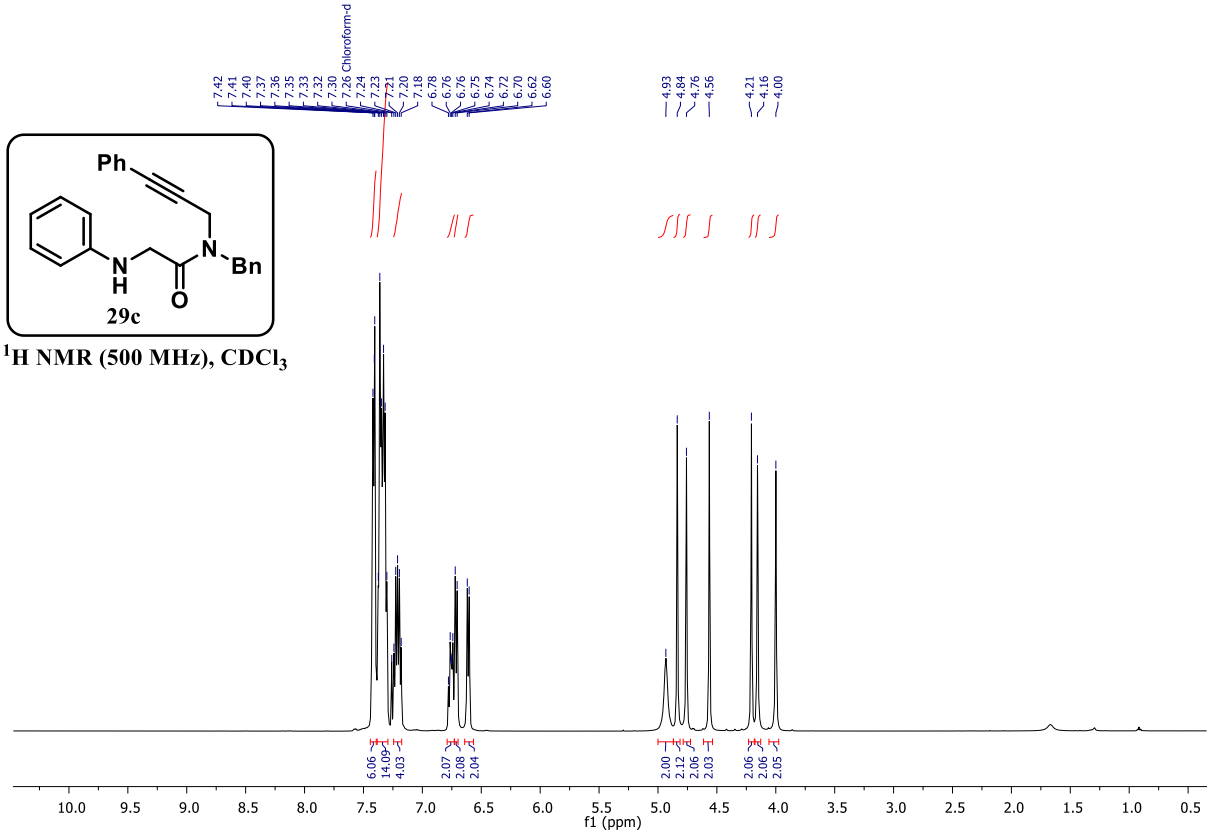
^{13}C NMR (125 MHz), $CDCl_3$



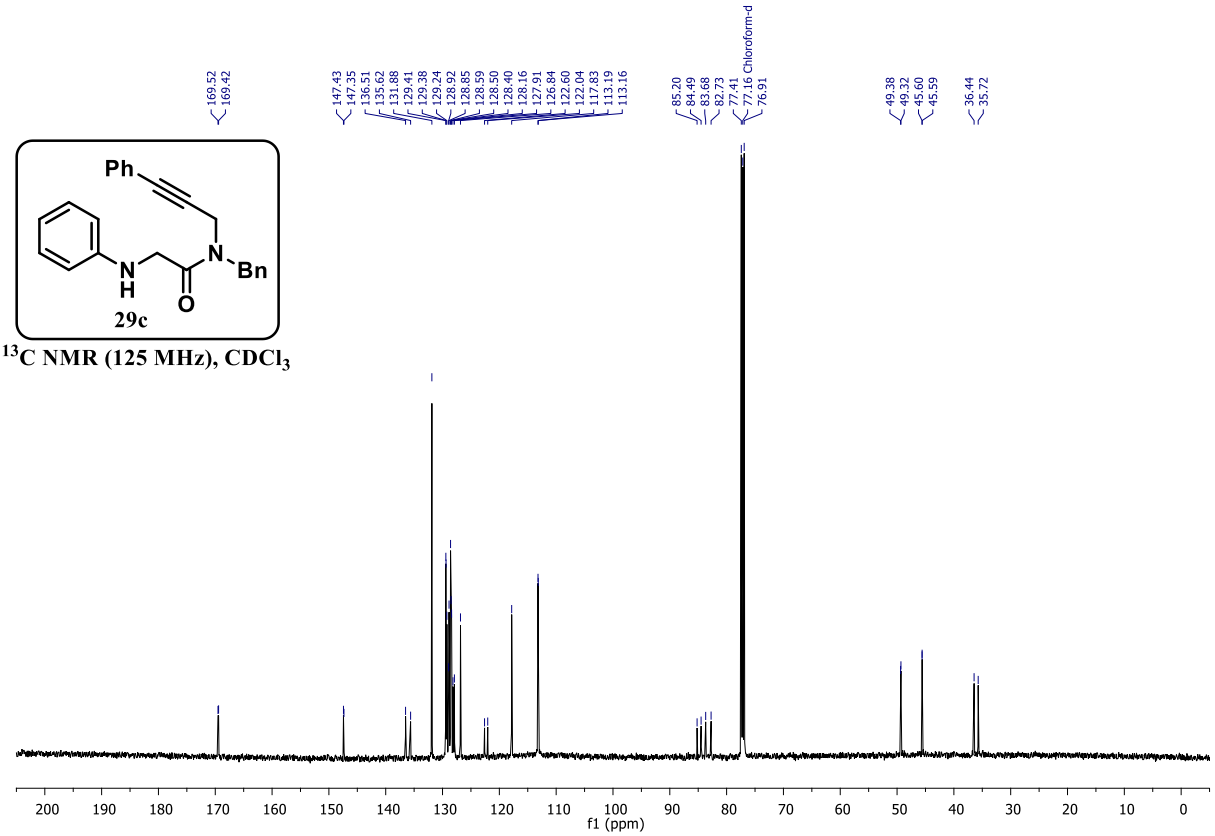
^{1}H NMR (500 MHz), $CDCl_3$



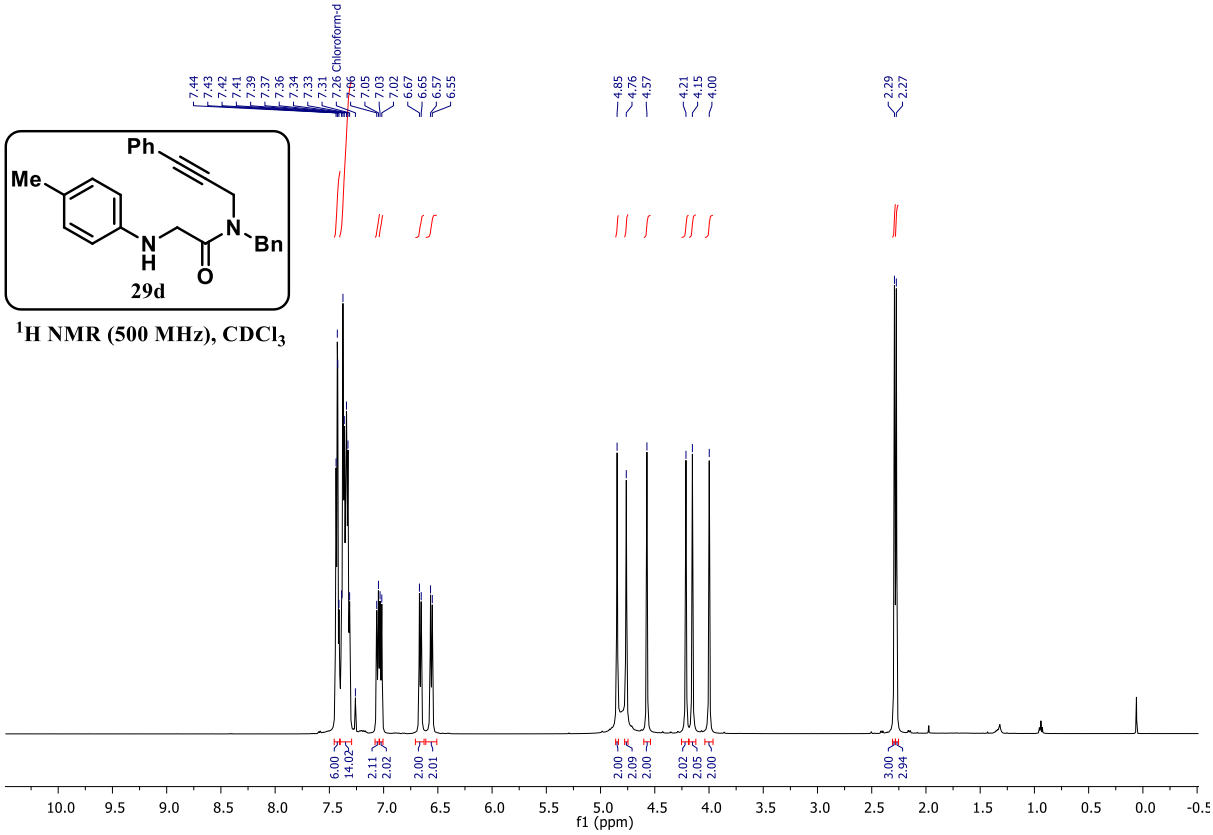
^{13}C NMR (125 MHz), $CDCl_3$



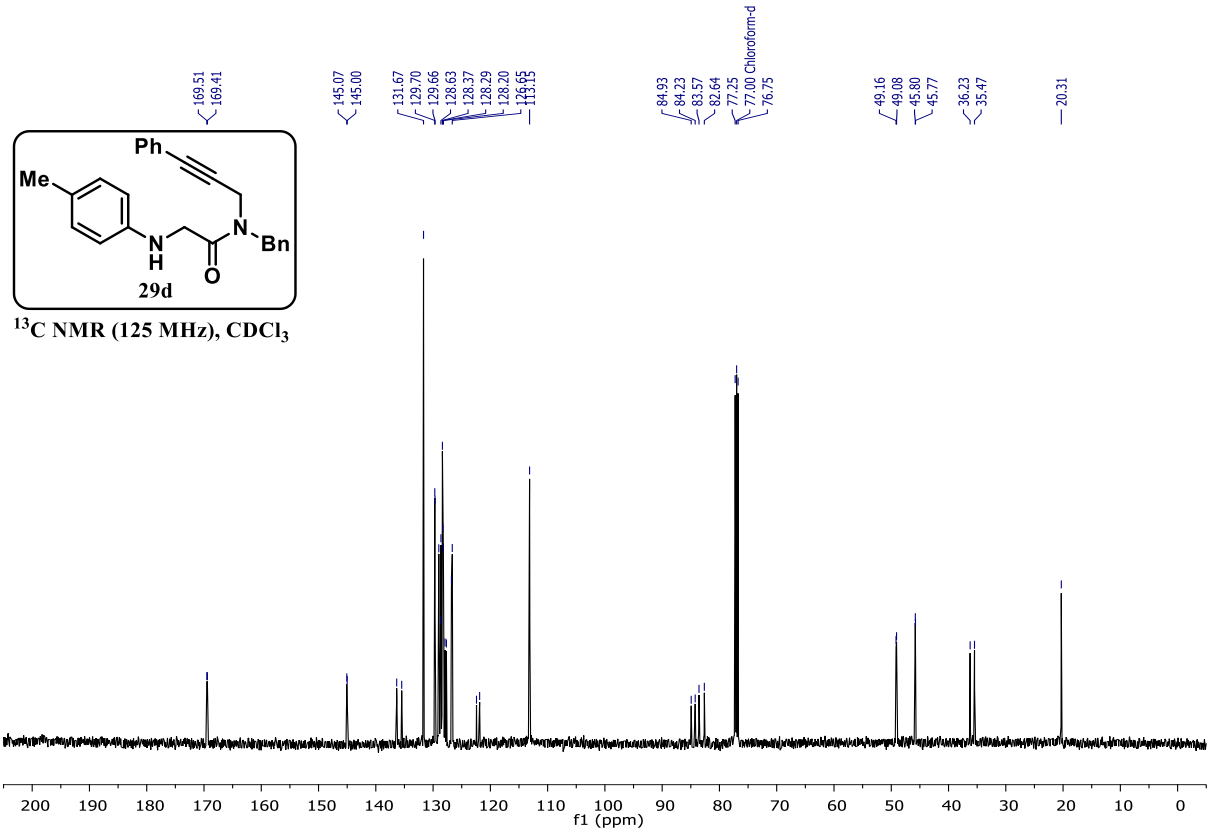
^{1}H NMR (500 MHz), $CDCl_3$



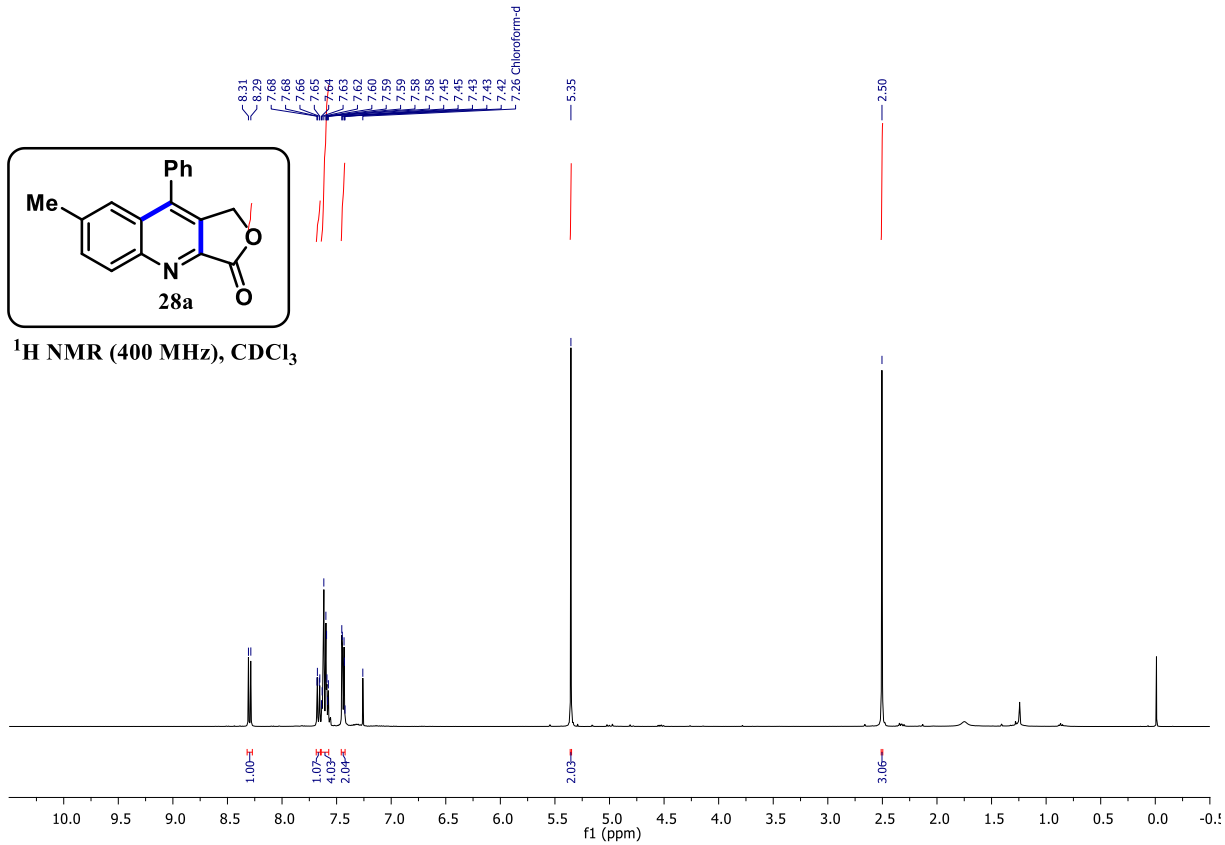
^{13}C NMR (125 MHz), $CDCl_3$



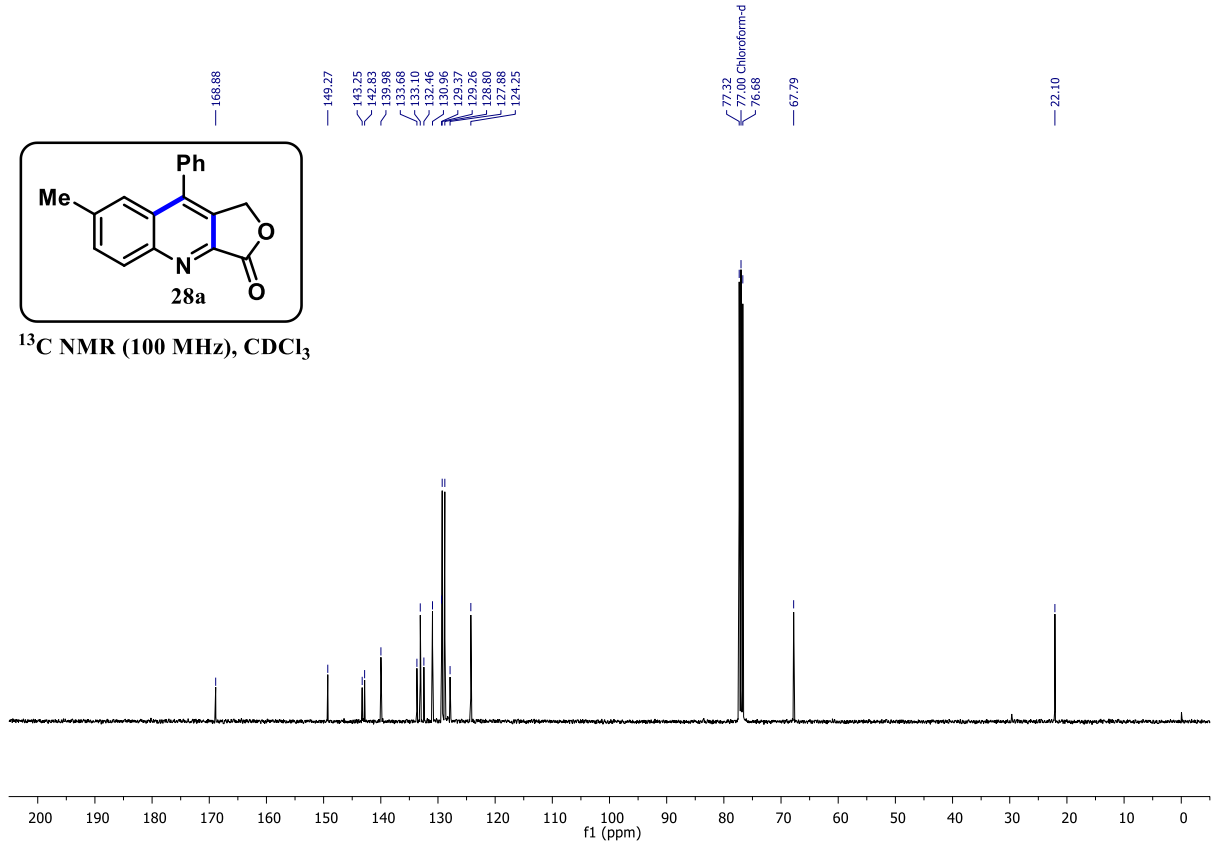
^{1}H NMR (500 MHz), $CDCl_3$



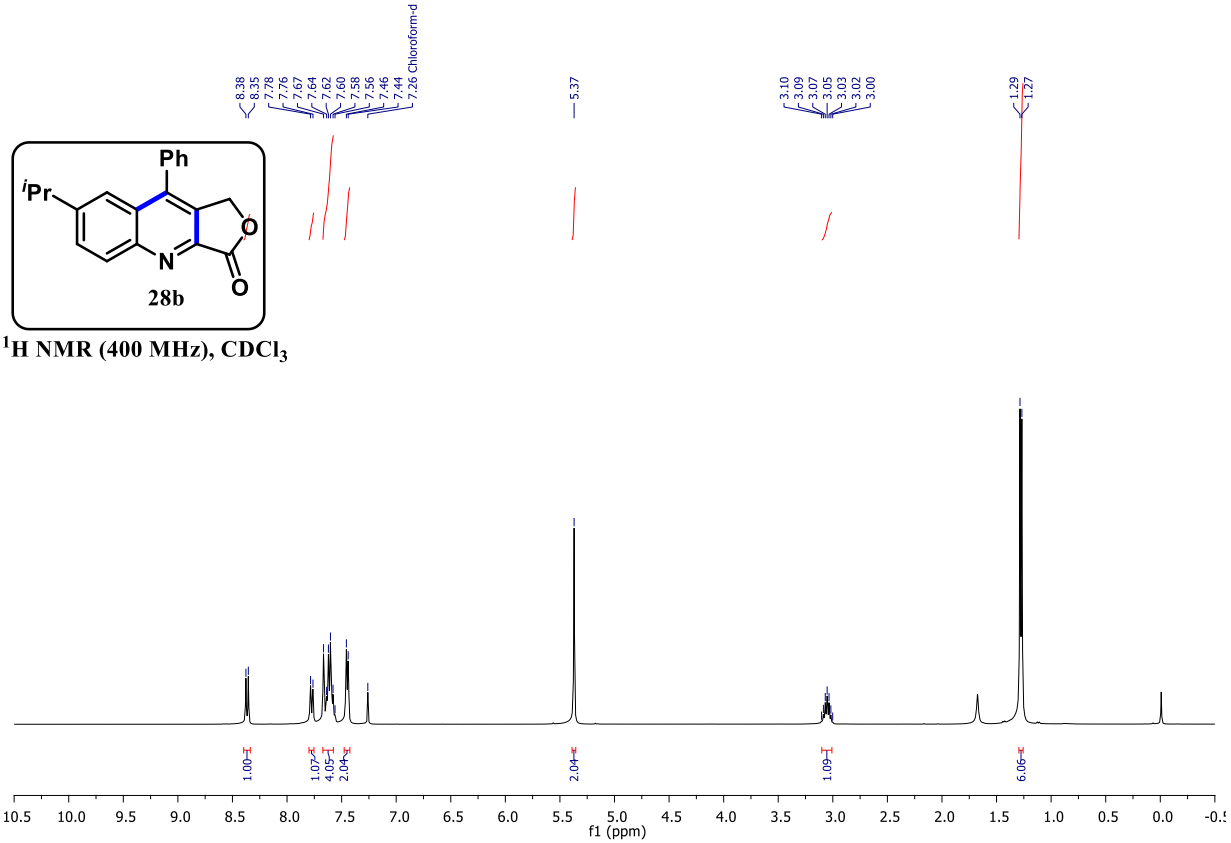
^{13}C NMR (125 MHz), $CDCl_3$



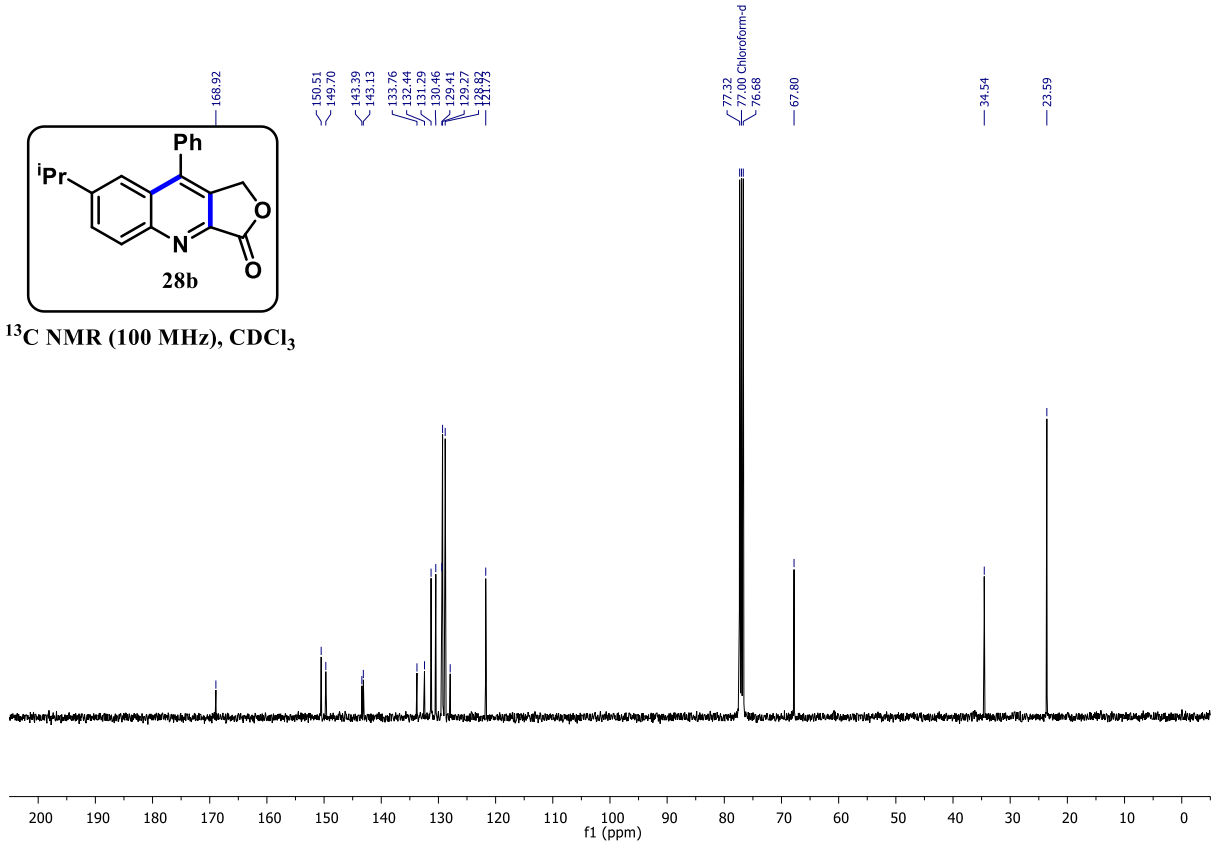
^{1}H NMR (400 MHz), $CDCl_3$



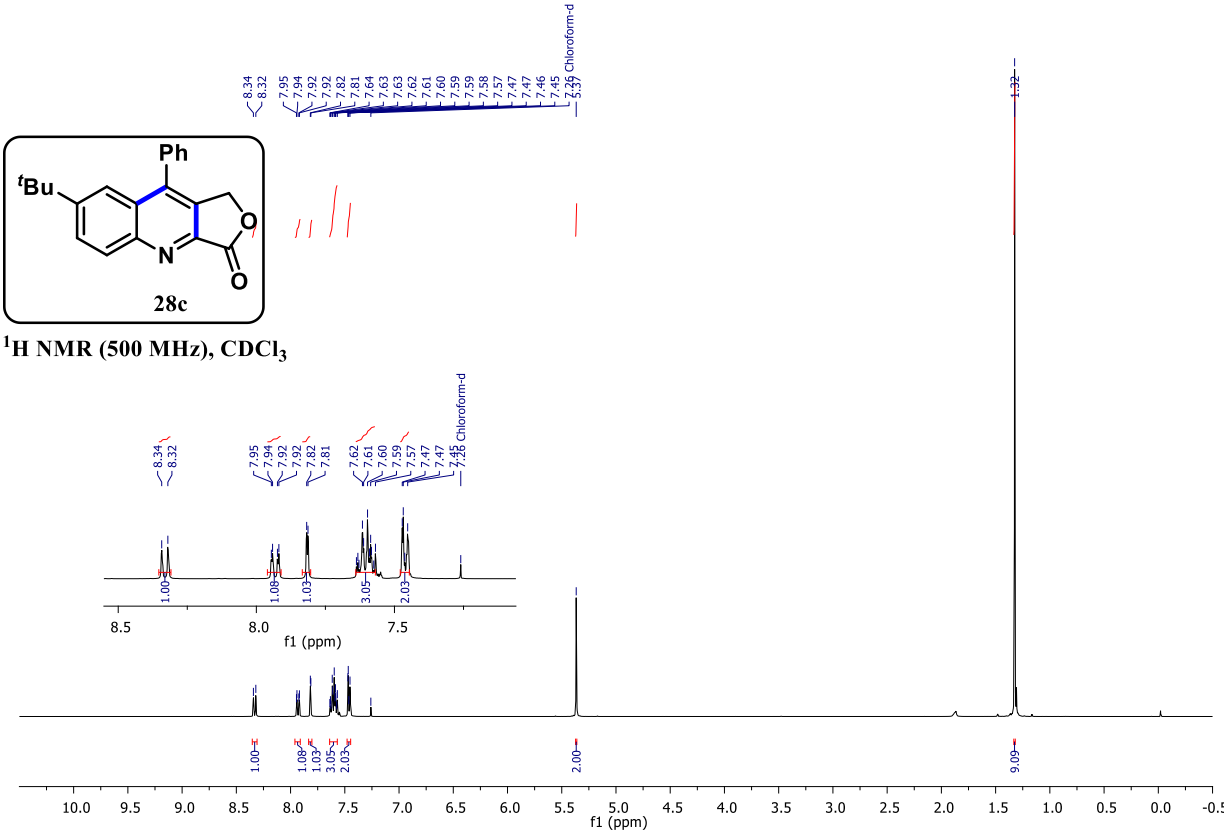
^{13}C NMR (100 MHz), $CDCl_3$



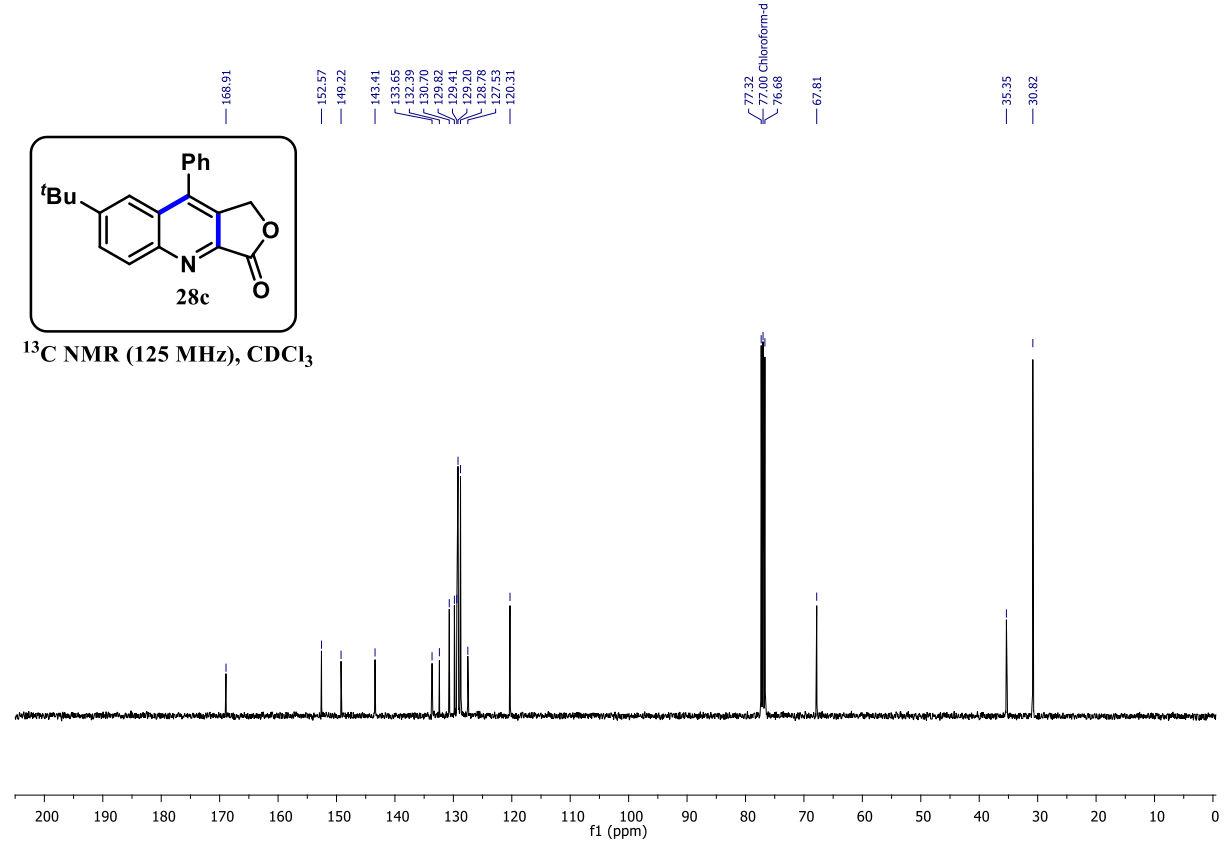
^{1}H NMR (400 MHz), $CDCl_3$



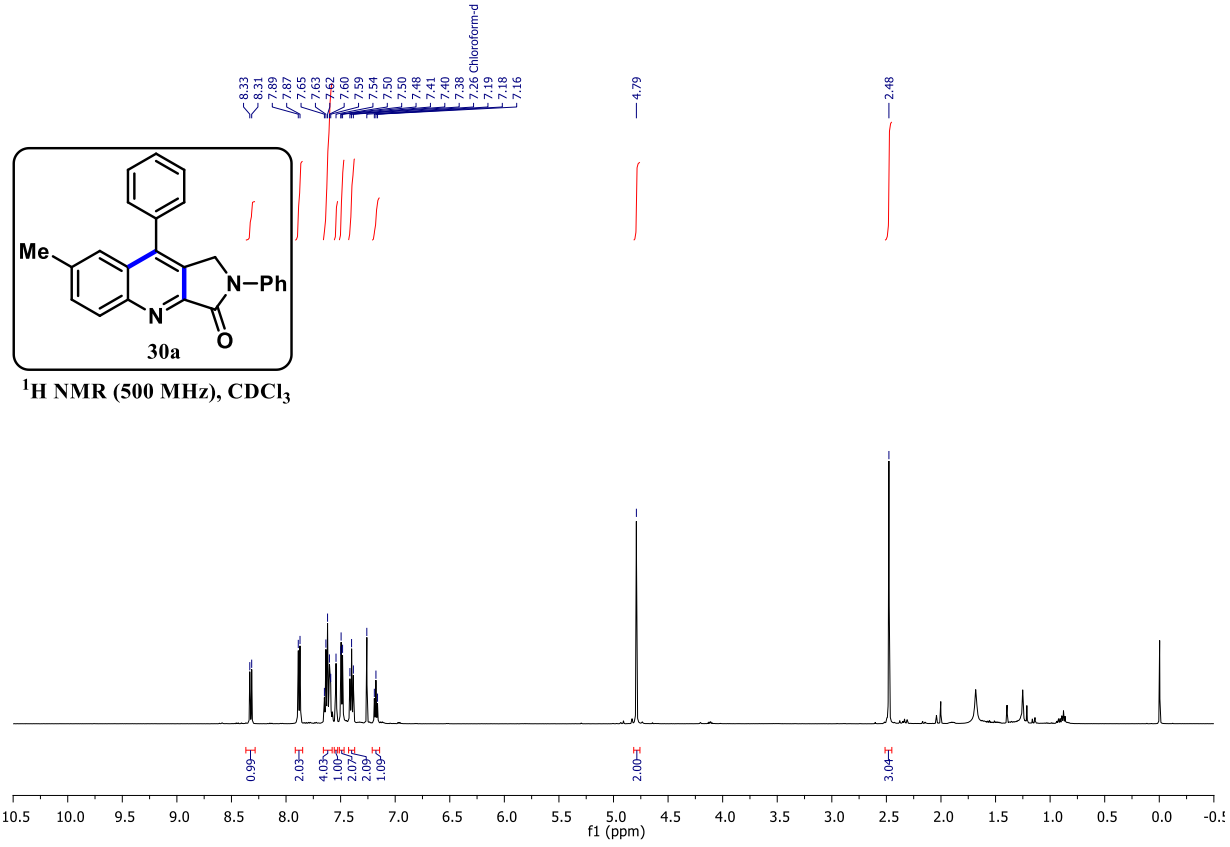
^{13}C NMR (100 MHz), $CDCl_3$



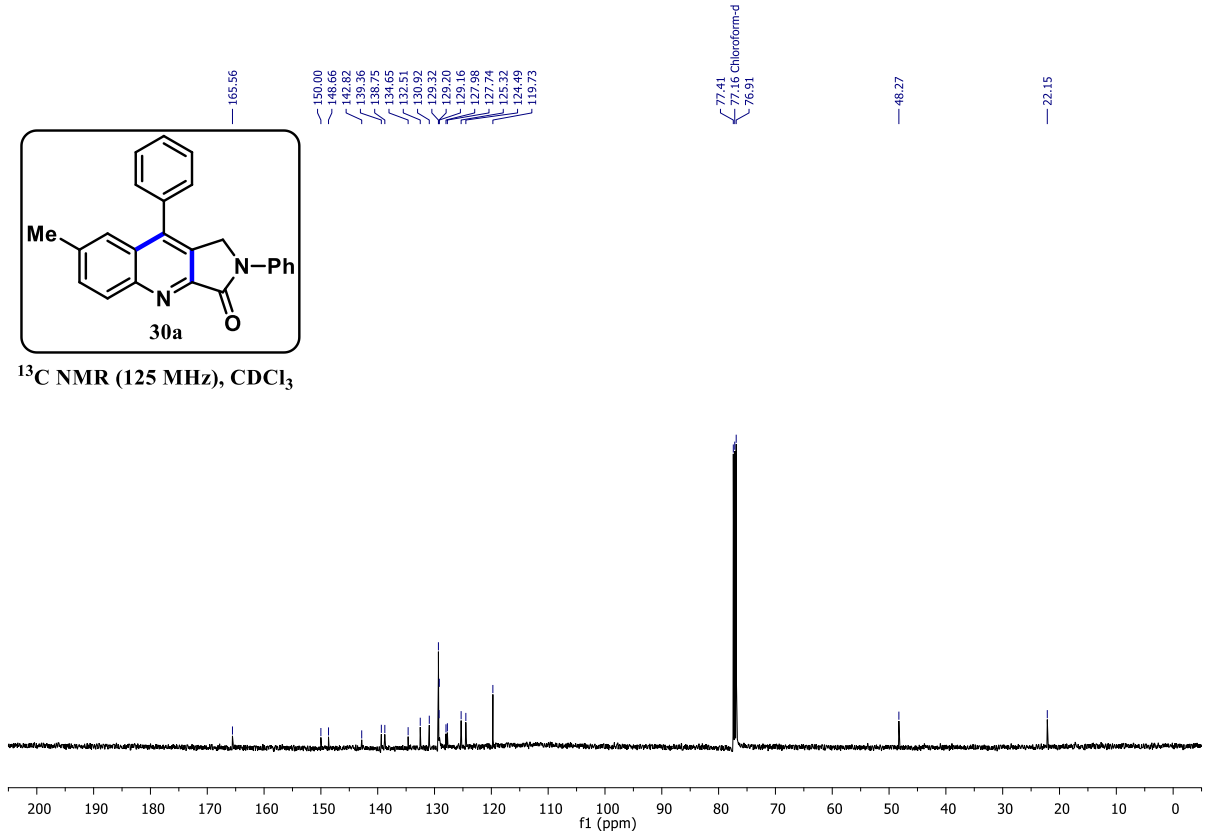
^{1}H NMR (500 MHz), $CDCl_3$



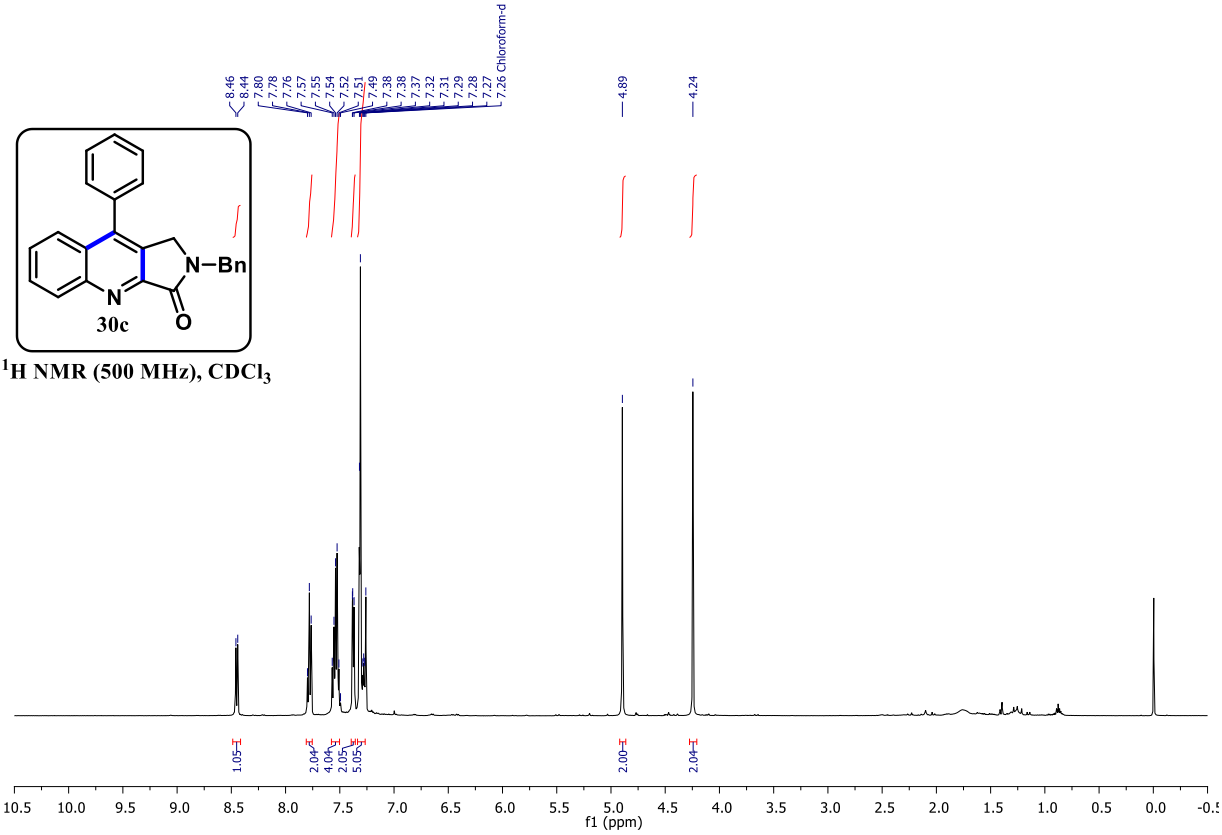
^{13}C NMR (125 MHz), $CDCl_3$



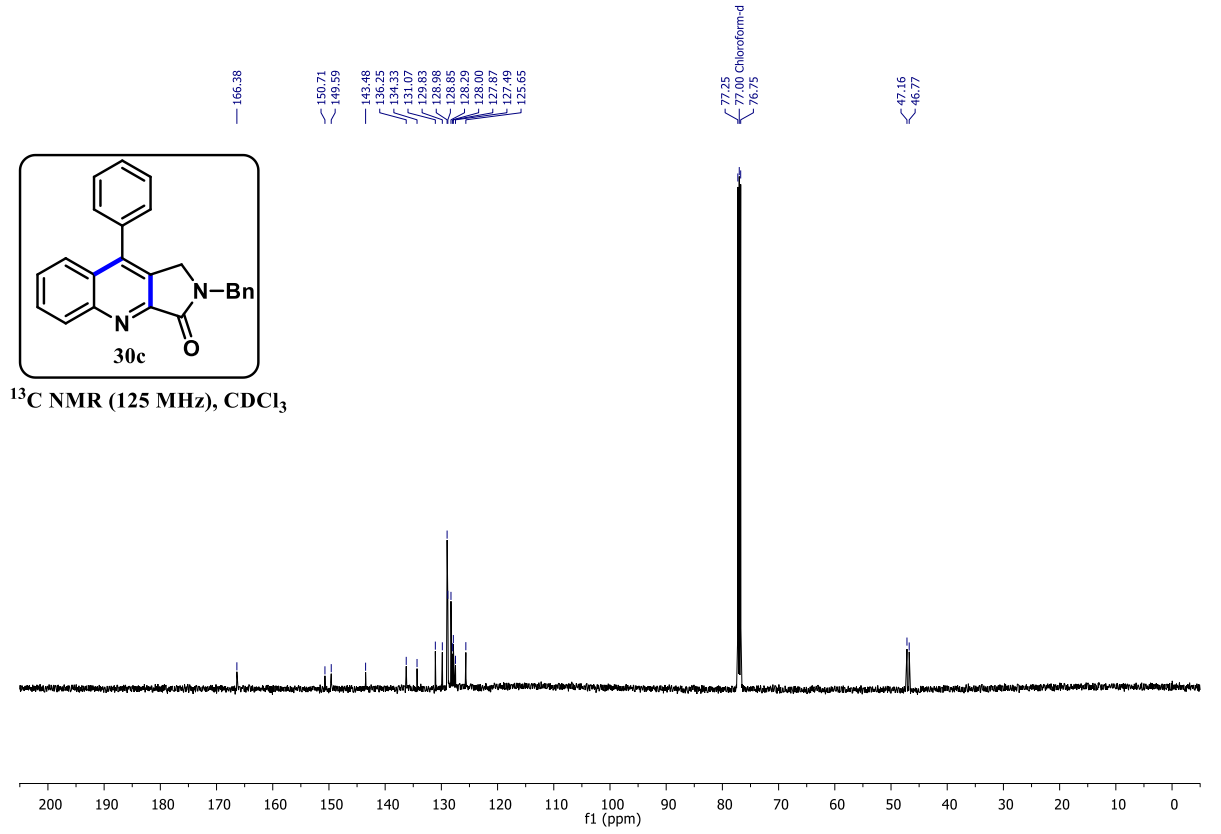
^{1}H NMR (500 MHz), $CDCl_3$



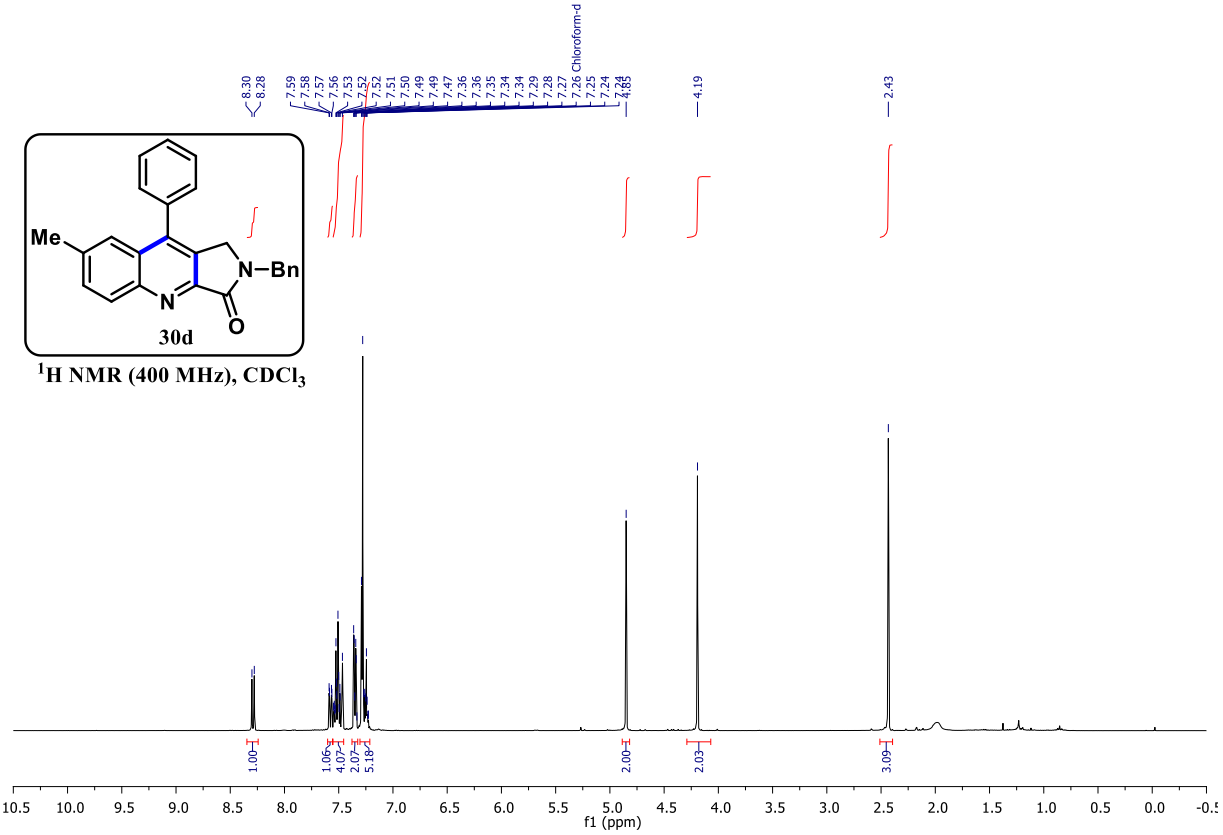
^{13}C NMR (125 MHz), $CDCl_3$



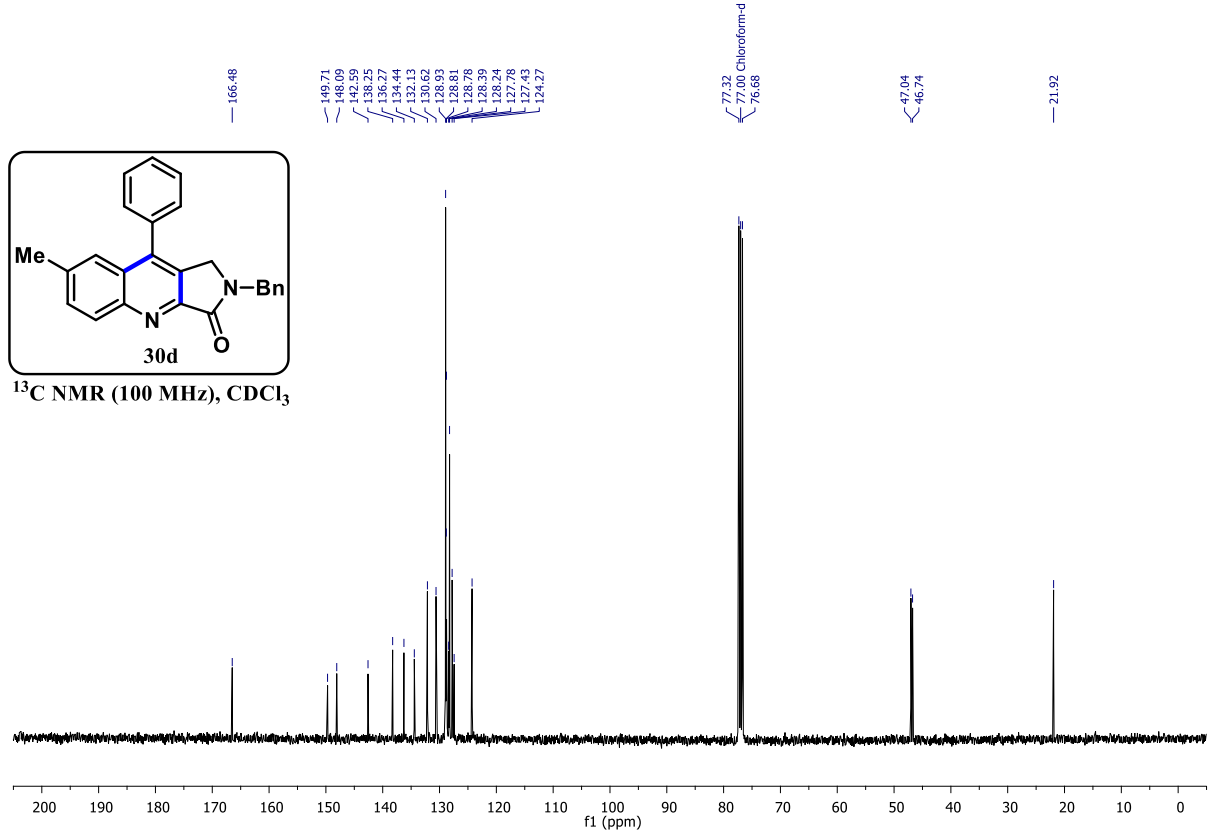
^{1}H NMR (500 MHz), $CDCl_3$



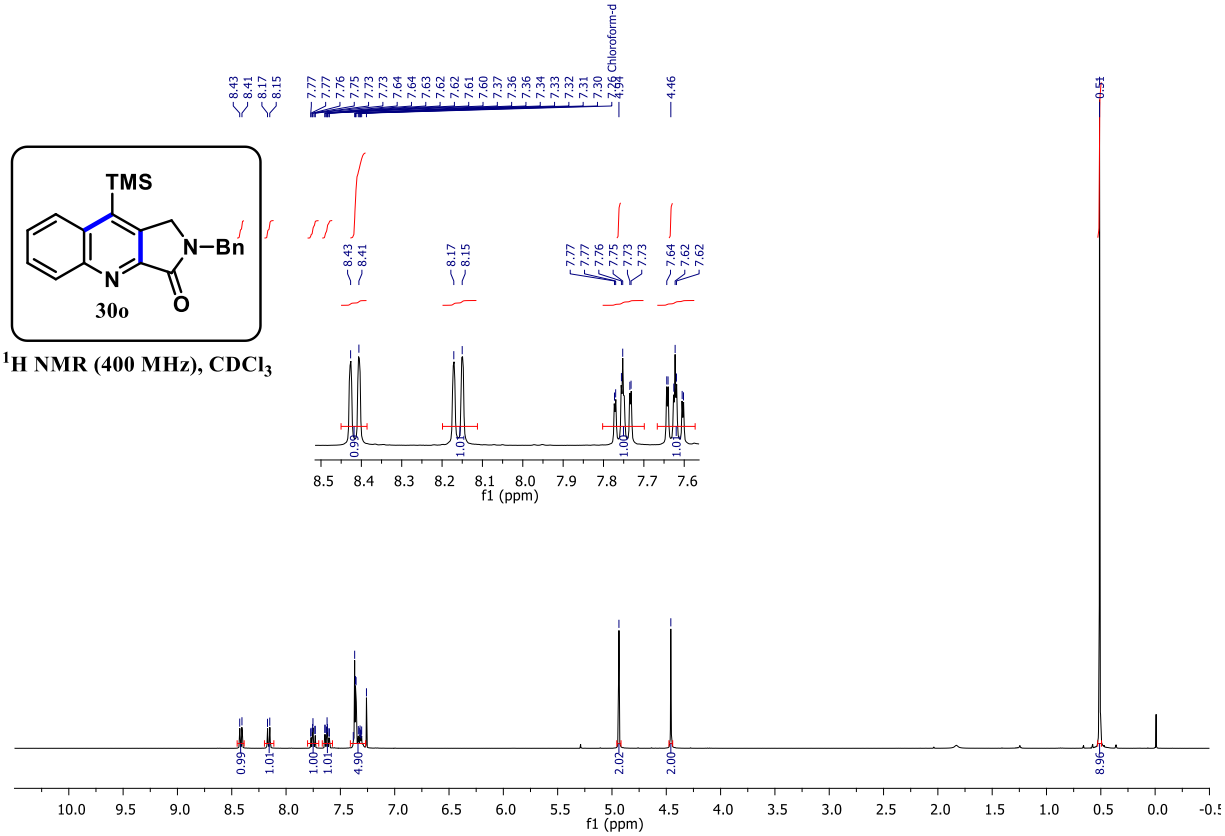
^{13}C NMR (125 MHz), $CDCl_3$



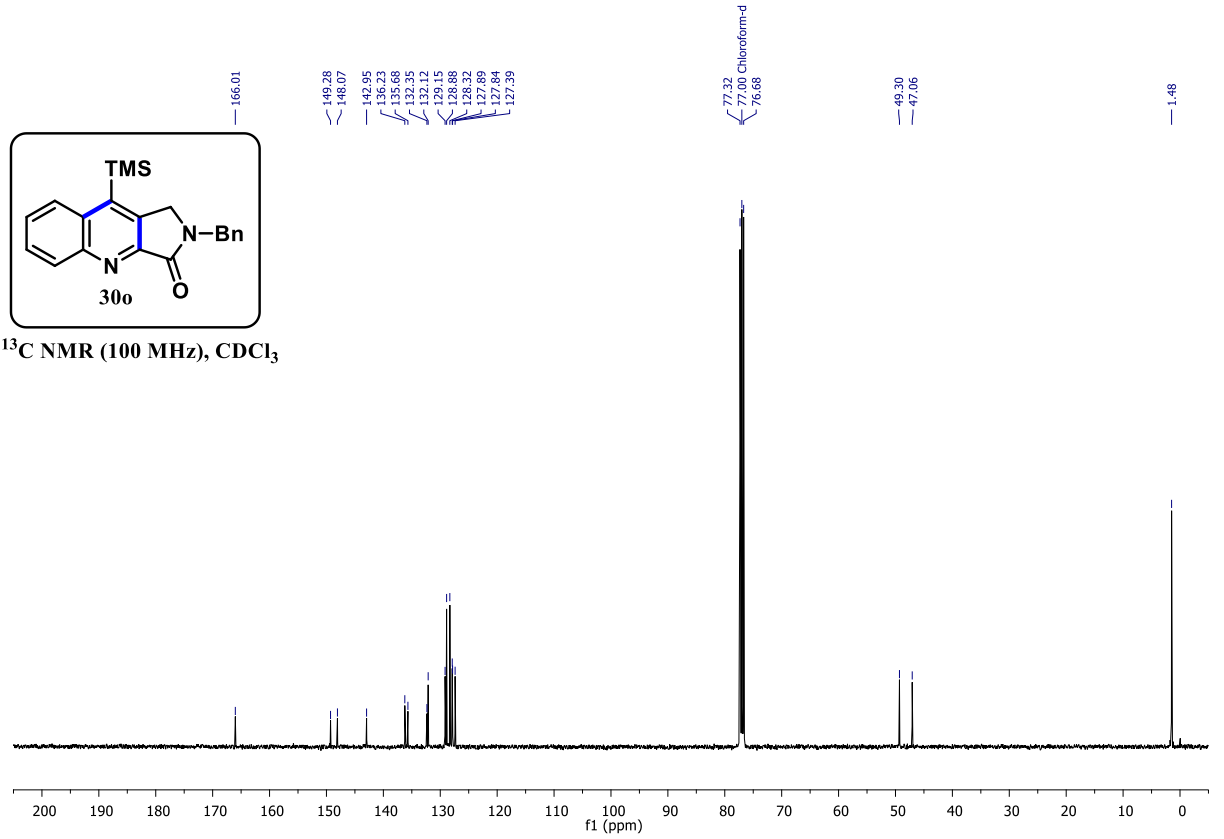
^{1}H NMR (400 MHz), $CDCl_3$



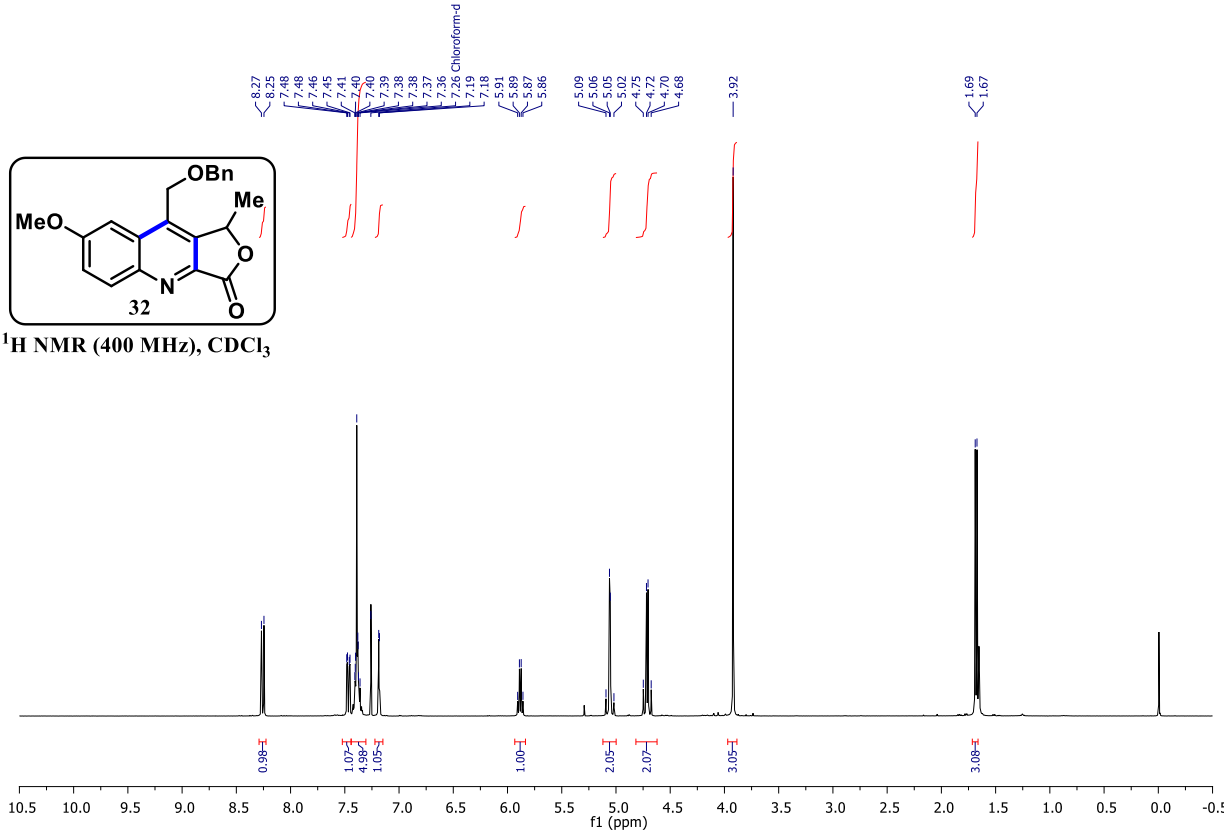
^{13}C NMR (100 MHz), $CDCl_3$



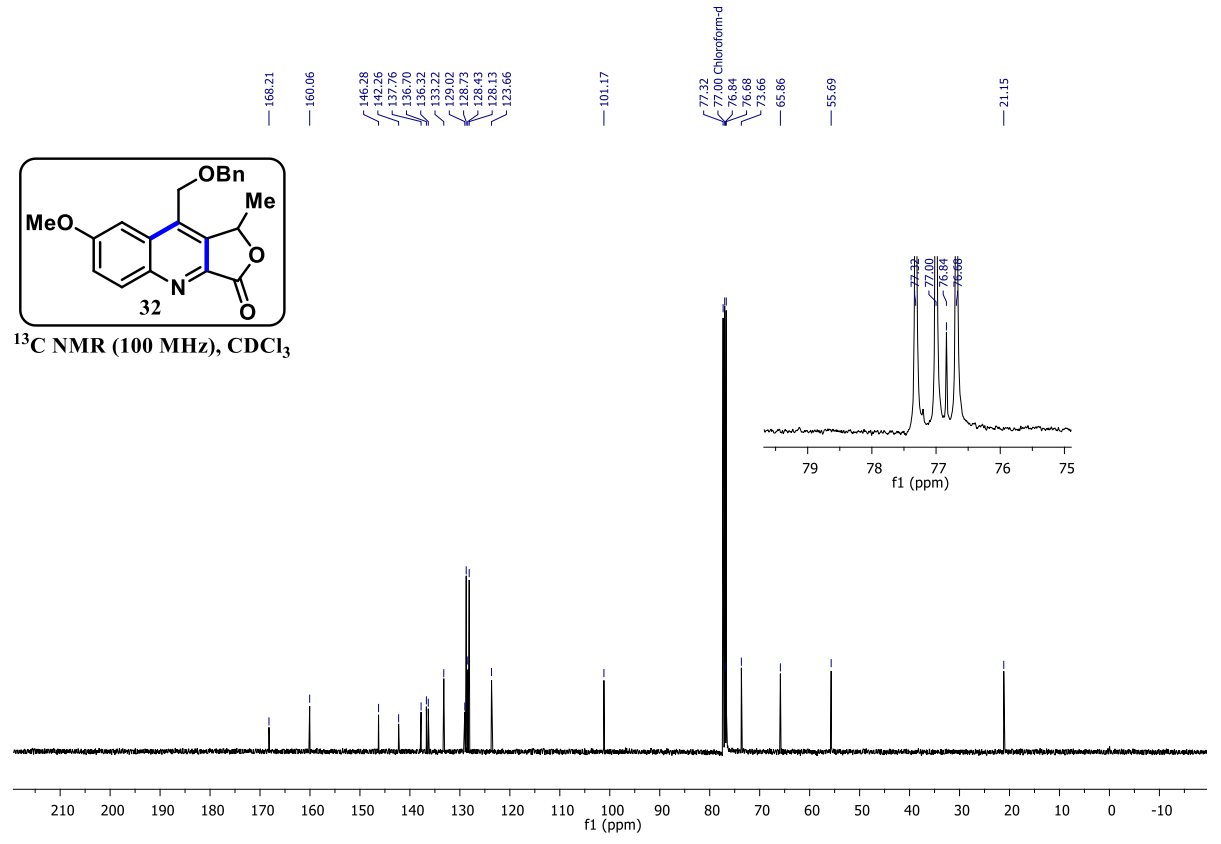
^{1}H NMR (400 MHz), $CDCl_3$



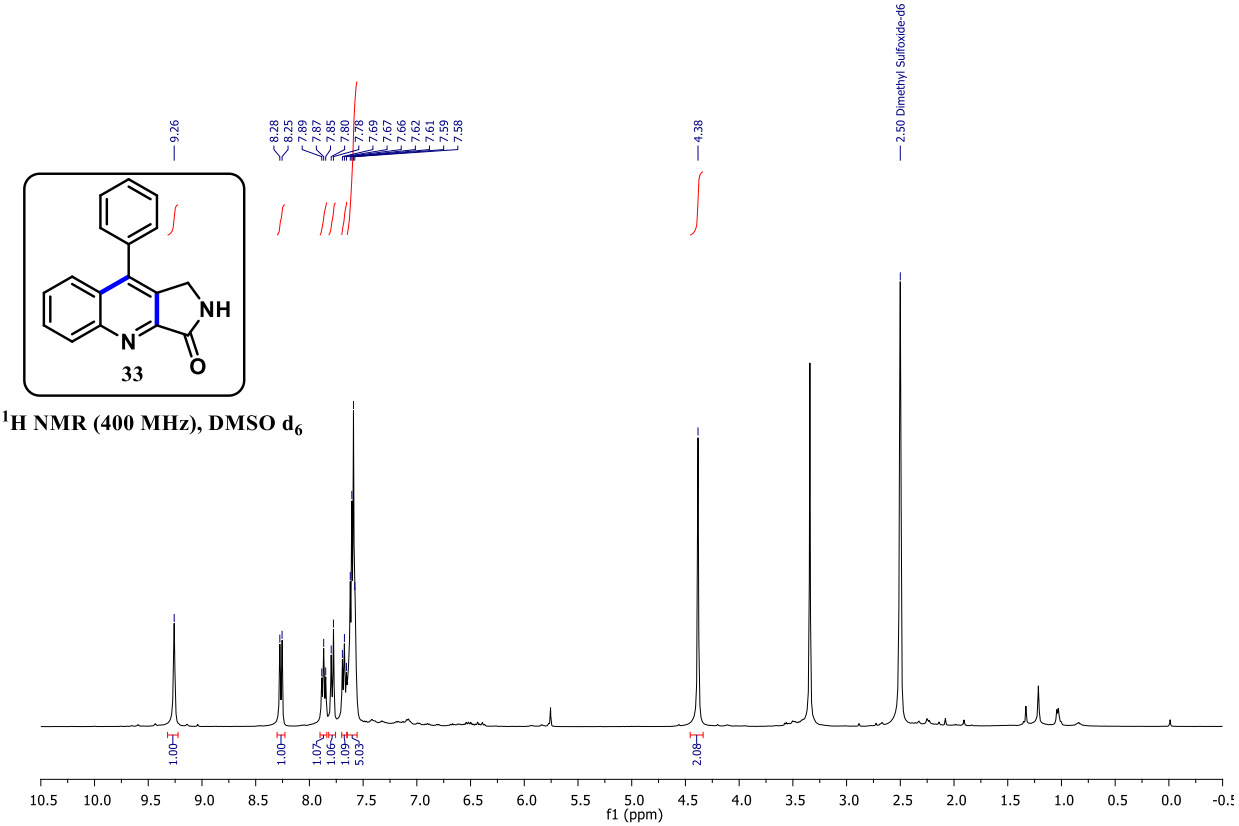
^{13}C NMR (100 MHz), $CDCl_3$



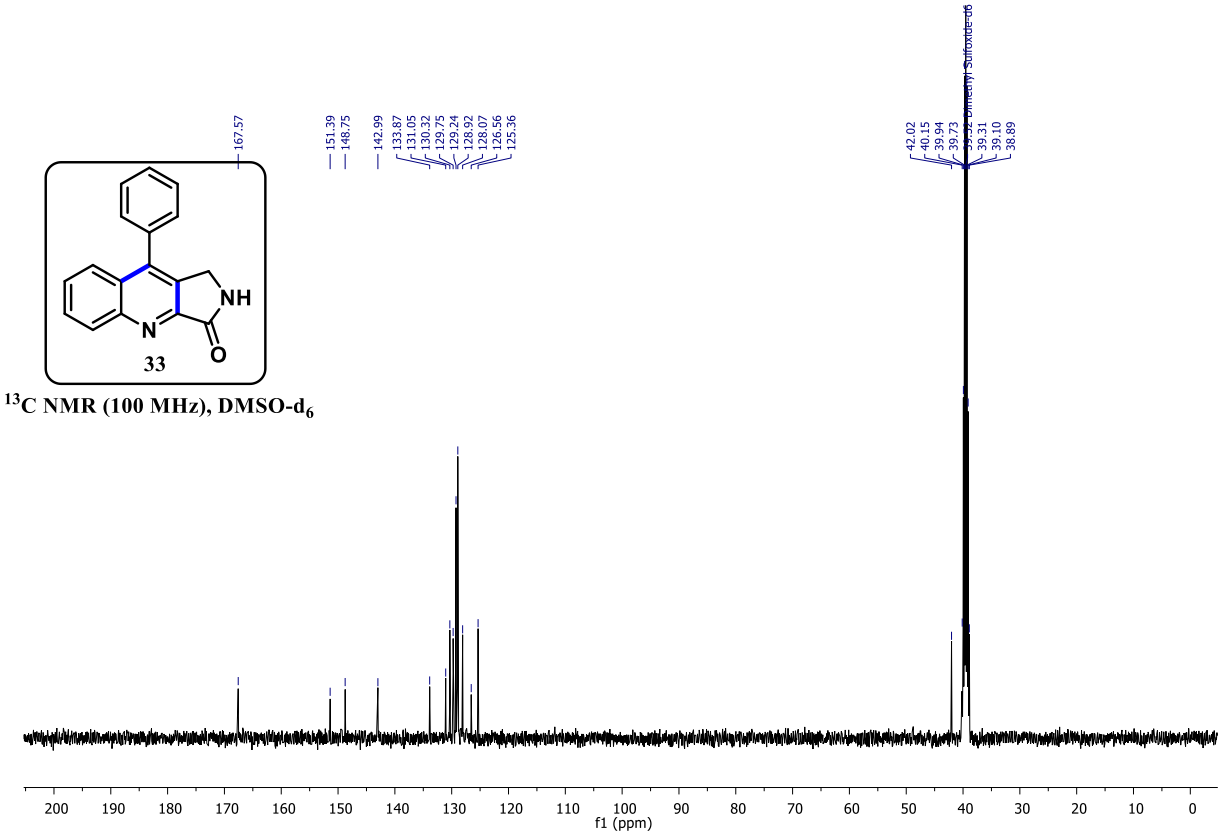
^{1}H NMR (400 MHz), $CDCl_3$



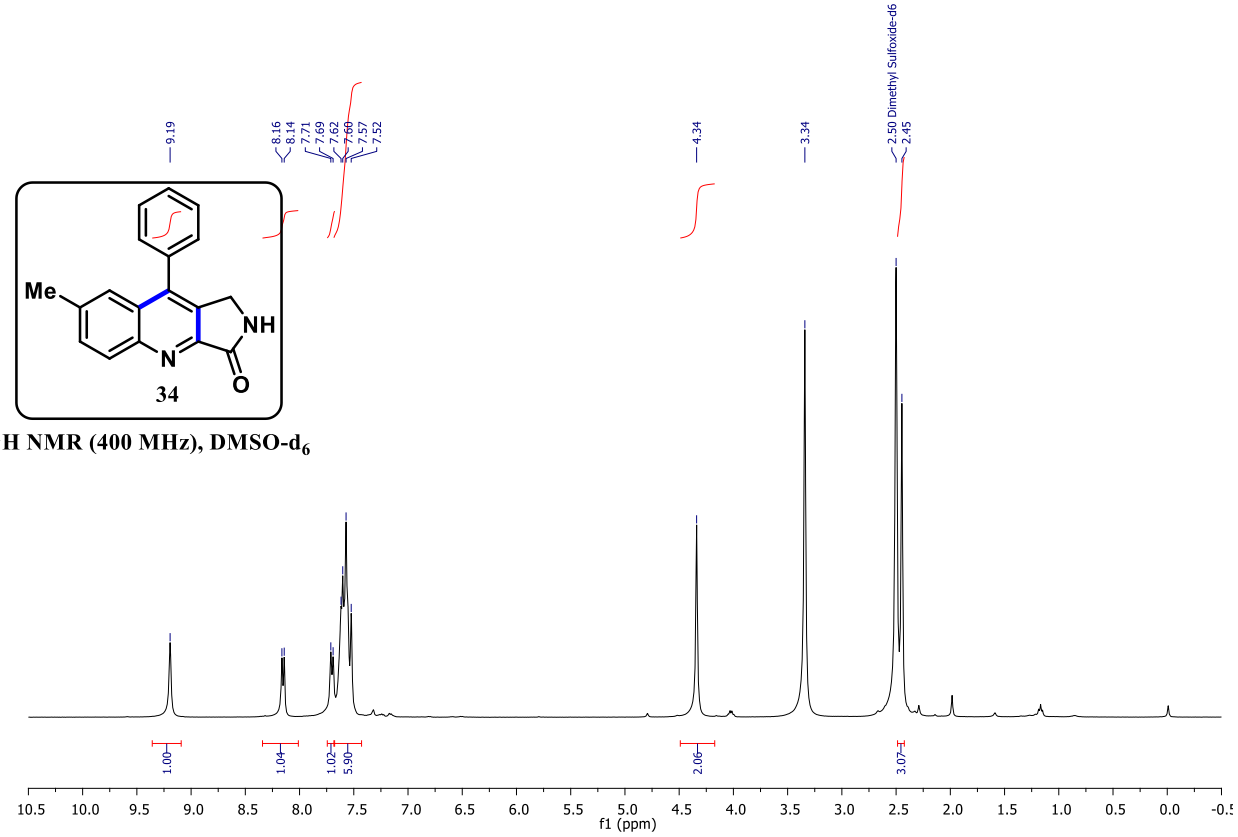
^{13}C NMR (100 MHz), $CDCl_3$



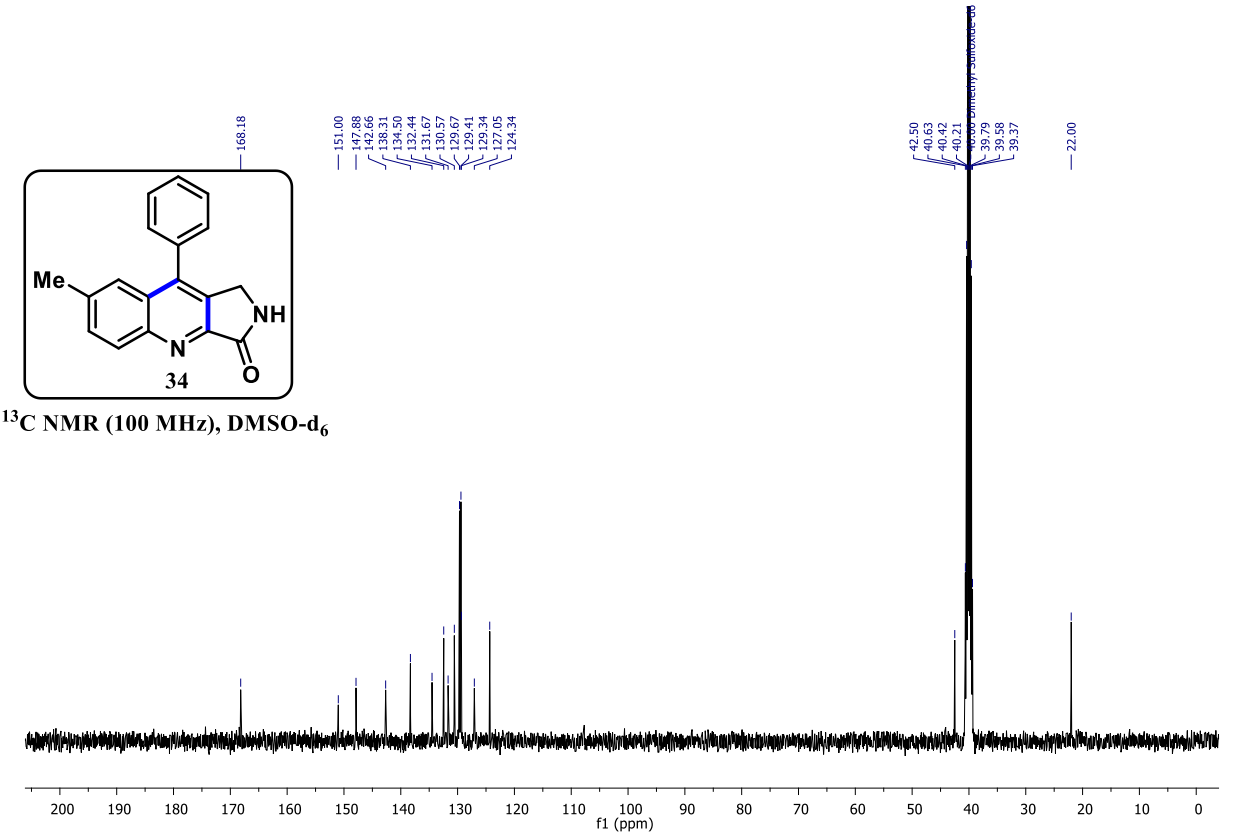
^{1}H NMR (400 MHz), DMSO d$_6$



^{13}C NMR (100 MHz), DMSO-d$_6$



^{1}H NMR (400 MHz), DMSO-d$_6$



^{13}C NMR (100 MHz), DMSO-d$_6$

1.1.8 References

1. (a) Solomon, V. R.; Lee, H. *Curr. Med. Chem.,* **2011***, 18*, 1488–1508. (b) Musiol, R.; Serda, M.; Hensel-Bielowka, S.; Polanski, J. *Curr. Med. Chem.,* **2010***, 17*, 1960–1973. (c) Musiol, R.; Jampilek, J.; Kralova, K.; Richardson, D. R.; Kalinowski, D.; Podeszwa, B.; Finster, J.; Niedbala, H.; Palka, A.; Polanski, J. *Bioorg. Med. Chem.,* **2007**, *15*, 1280–1288. (d) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223–246. (e) Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.,* **2005***, 9*, 141–161.
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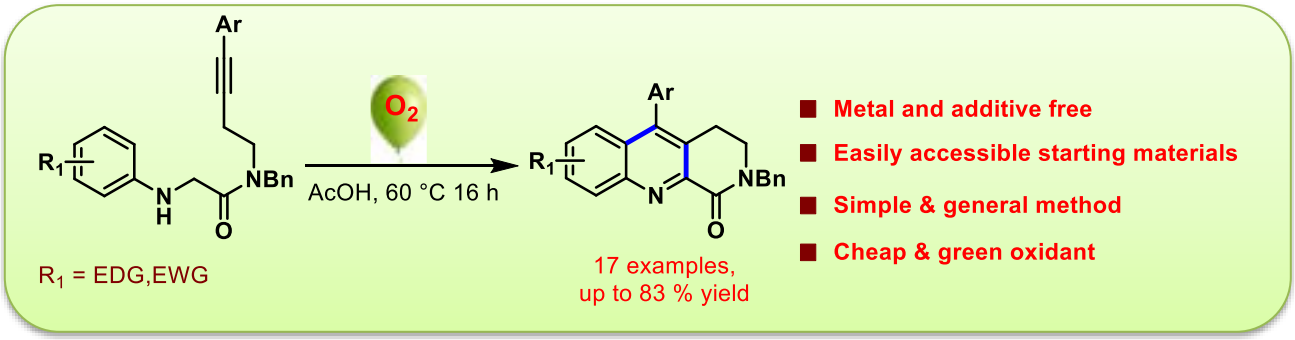
Section-II

Bronsted Acid-Catalyzed, Metal-Free Synthesis of Substituted Quinoline-Fused Lactams from *N*-Aryl Glycine Derivatives

The development of Brønsted acid-catalyzed cyclization reactions of alkyne tethered *N*-aryl glycine amide in the presence of molecular oxygen under metal-free conditions have been described in this section. Various six-membered quinoline fused lactam derivatives were obtained in moderate to good yields. This environment friendly protocol tolerates wide functional groups and could be useful in the drug discovery program for the rapid generation of biologically important quinolone fused lactams



1.2.1 Introduction

From the previous section, it is evident that glycine derivatives are potential building blocks for the preparation of complex organic molecules and biologically active compounds.[1] On the other hand, the six-membered quinoline-fused lactones/lactams are an important sub-class of quinolines and are frequently found in numerous biologically active compounds, natural products and pharmaceuticals.[2] Besides, compounds possessing six-membered lactones/lactams motif are known antimalarial agents, HIV reverse transcriptase inhibitors and bone morphogenetic protein active agents. Further, they possess antibacterial and fungicidal properties and also serve as a precursor for the Luotonin A analogue (more active analogue) (Fig 1.2.1).[3] Despite the importance, in contrast to their structural analogues such as five-membered quinoline-fused lactones/lactams, which could be easily synthesized by many methods[4] surprisingly, synthetic methods to access six-membered quinoline-fused lactones/lactams are rare and considered to be challenging.[5] Very few approaches reported recently for the synthesis of six-membered quinoline-fused lactones/lactams are described below.

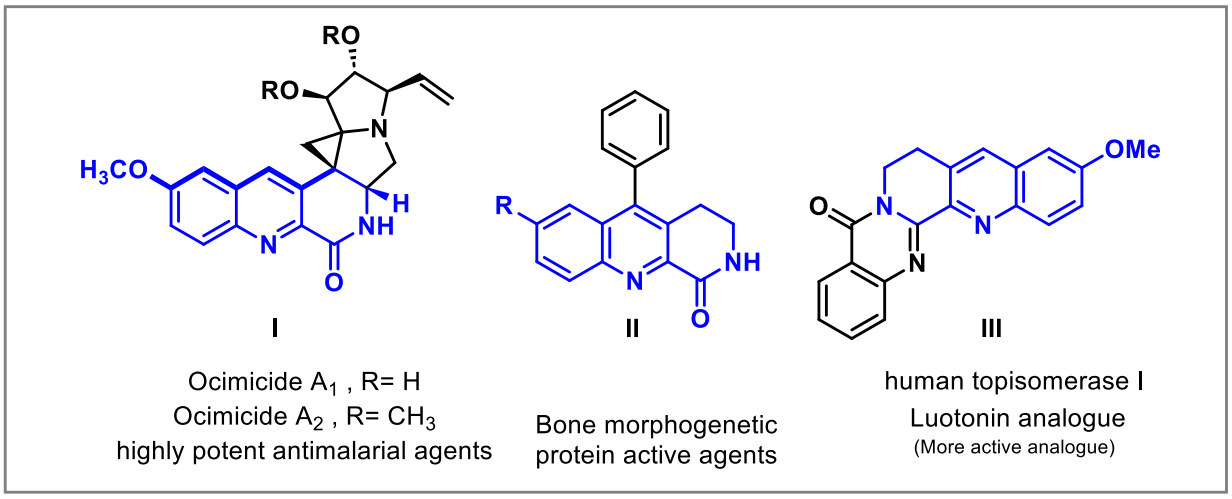
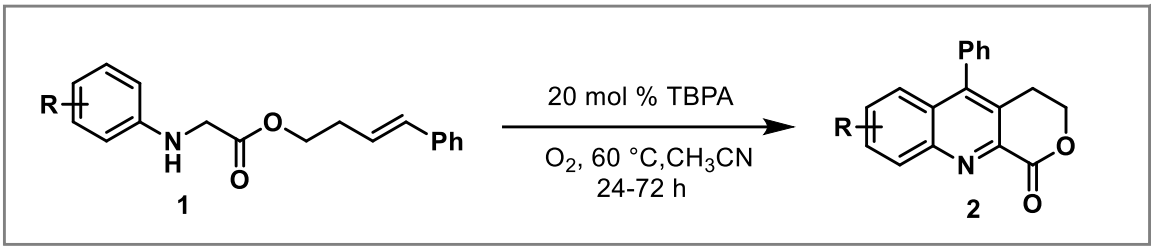


Figure 1.2.1 Representative examples of bioactive molecules, natural products containing six-membered quinoline-fused lactone/lactam moiety.

1.2.2 Literature Precedence on the Synthesis of Six membered Quinoline-fused Lactones and Lactams

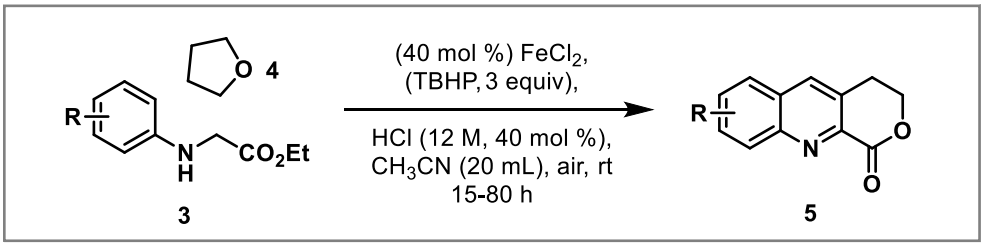
In 2014, Jia and co-workers described the synthesis of six-membered quinoline-fused lactones **2** from radical cation salt (TBPA) promoted catalytic aerobic sp^3 C-H oxidation of *N*-

aryl glycine esters **1**. This reaction gives easy access to six-membered quinoline-fused lactones in good yields under mild conditions and with good functional group tolerance (Scheme 1.2.1).[6]



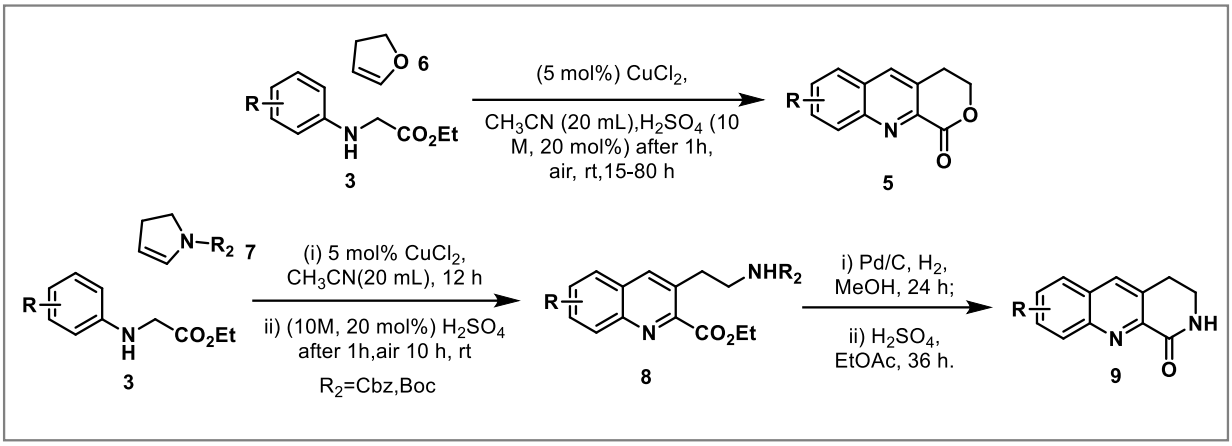
Scheme 1.2.1 Intramolecular cyclization of *N*-aryl glycine cinnamyl esters.

In 2016, Wang and colleague developed a Fe(II)-catalyzed synthesis of complex quinoline fused lactone derivatives **5** using glycine derivatives **3** and tetrahydrofuran **4**. The reaction proceeds through dual-oxidative dehydrogenative tandem annulation sequences. This reaction provides access to a broad range of quinoline-fused lactones in moderate to good yields (Scheme 1.2.2).[7]



Scheme 1.2.2 Dual-oxidative dehydrogenative annulation reaction of glycine esters with THF.

In 2015, Wang *et al.* developed a sequential Copper/Brønsted acid-catalyzed aerobic oxidative protocol to synthesize six-membered quinoline-fused lactones **5** and lactams **9** using glycine derivatives with 2,3-dihydrofurans **6**/2,3-dihydropyrroles **7**. Using this method, six-membered quinoline-fused lactones can be synthesized sequentially in one pot with moderate to good yields. However, the synthesis of six-membered quinoline-fused lactams requires multi-step sequences, and the yields are moderate. (Scheme 1.2.3).[5]



Scheme 1.2.3 Cu(II)-H_2SO_4-air-catalyzed reaction of glycine esters with 2,3-dihydropyrrole & 2,3-dihydrofurans.

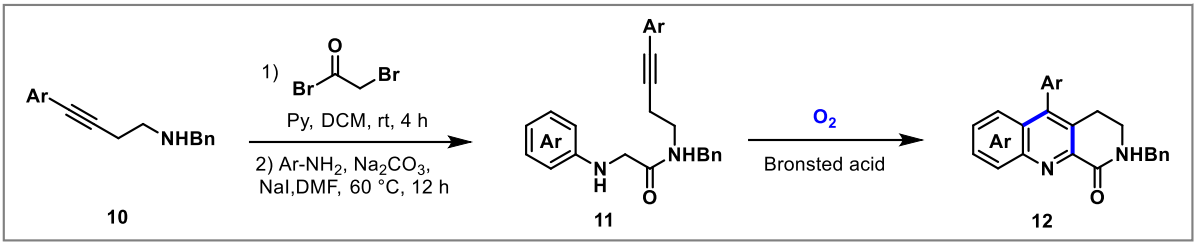
On a similar line, Li *et al.* in 2018 reported a visible-light-induced aerobic oxidative dehydrogenative coupling /tandem cyclization reaction of *N*-aryl glycine cinnamyl esters **3** with 2,3-dihydrofurans **6** to construct the quinoline-fused lactones (Scheme 1.2.4).[8] The synthetic applicability of this methodology has been demonstrated for the construction of quinoline-fused lactams using a multistep protocol.

Scheme 1.2.4 Photocatalyzed aerobic oxidative dehydrogenative coupling/annulation.

1.2.3 Present Work

1.2.3.1 Statement of the Problem

As described above, there are only a few methods available for the synthesis of six-membered quinoline-fused lactams. Still, these methods suffer from certain disadvantages, such as the requirement of metal catalysts, involving multistep processes, harsh reaction conditions, prolonged reaction time, and limited substrate scope, which hamper the superiority of these methods. Therefore, the development of a simple, efficient and metal-free approach to access these six-membered quinoline-fused lactams from easily accessible starting materials is highly favourable.



Scheme 1.2.5 Hypothesis on cyclization of alkyne tethered *N*-aryl glycine derivatives.

In the previous section, we have shown that alkyne-tethered glycine derivatives are the potential precursor for the convenient preparation of five-membered quinoline-fused lactones and lactams *via* oxone-promoted oxidative Povarov cyclization strategy. We were interested in pursuing this oxidative strategy for more complex heterocyclic synthesis. Inspired by the biological importance of six-membered quinoline-fused lactams, we surmised that intramolecular cyclization of appropriately substituted *N*-aryl glycine amide derivatives **11** in the presence of Bronsted acid/O_2 could provide straightforward access to six-membered quinoline-fused lactams **12** in one pot (Scheme 1.2.5) and herein we describe the successful realization of this strategy Further, as far as we know, Bronsted acid-catalyzed, metal-free synthesis of six-membered quinoline-fused lactams from *N*-aryl glycine amide derivatives has not been reported yet.

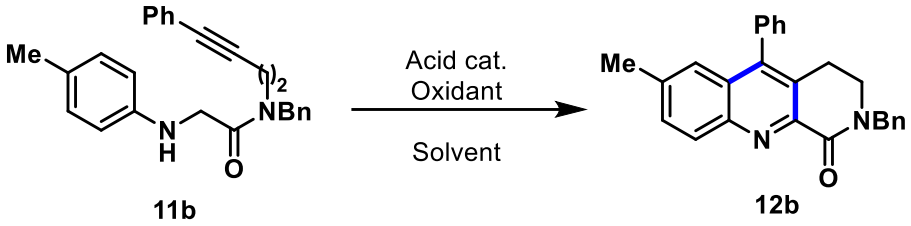
1.2.4 Results and Discussion

1.2.4.1 Optimization of Reaction Conditions

In light of Bao's work,[9] we envisaged that the presence of acid and air could promote the oxidation and intramolecular cyclization of alkyne tethered *N*-aryl glycine amide. Before this new strategy was brought under trial, we prepared *N*-benzyl-*N*-(4-phenylbut-3-yn-1-yl)-2-(*p*-tolylamino)acetamide **11b**, according to our previous method. Initially, we examined the cyclization of *N*-aryl glycine amide **11b** as a model substrate by employing Bronsted acids, such as sulfuric acid (H_2SO_4), trifluoromethanesulfonic acid (TfOH) and acetic acid (AcOH) in acetonitrile solvent under open air condition at room temperature (Table 1.2.1, entries 1-3). Interestingly, in the presence of AcOH, we obtained quinoline fused lactam **12b** in 22% yield (Table 1.2.1, entries 2). The formation of the desired product **12b** was ascertained by its ^{1}H, ^{13}C NMR and HRMS analysis. The appearance of a typical ^{1}H signal at δ 3.37 (t, 2H) corresponds to methylene protons (-CH_2-**CH_2**-N-) *α* to nitrogen (cyclic lactam), and δ 2.77 (t, 2H) corresponds to the methylene protons (-**CH_2**-CH_2-N-) *β* to nitrogen (cyclic lactam). In addition, the appearance of typical carbon signals at δ 163.3 is due to the carbonyl carbon of cyclic lactam and the

disappearance of the alkyne carbon peak justifies the structure. Furthermore, the constitution of **12b** has been confirmed as $C_{26}H_{23}N_2O$ (calculated value 379.1805) by the HRMS $[M+H]^+$ found as 379.1810. With this structure confirmation of product **12b**, we turned

Table 1.2.1 Optimization of the reaction conditions[a,b]



Entry	Acid cat.	Solvent	O_2	Yield (%)
1	H_2SO_4	CH_3CN	O_2 in air	trace
2	AcOH	CH_3CN	O_2 in air	22
3	TfOH	CH_3CN	O_2 in air	Trace
4	AcOH	DCE	O_2 in air	11
5	AcOH	MeOH	O_2 in air	Trace
6	AcOH	DMF	O_2 in air	Trace
7	AcOH	H_2O	O_2 in air	Trace
8[c]	AcOH	CH_3CN	O_2 in air	34
9[c]	AcOH	CH_3CN	O_2 balloon	51
10[d]	**AcOH**	**-**	**O_2 balloon**	**82**
11[e]	AcOH	-	O_2 balloon	83
12[f]	AcOH	-	O_2 balloon	84
13[g]	-	-	O_2 balloon	NR
14[h]	AcOH	-	N_2	NR

[a]Reaction conditions: 1) 0.13 mmol **11b**, 0.20 mmol, Acid cat.(2 equiv.) , solvent (2.0 mL), 16 h; [b]Isolated yields; rt; [c]The reaction occurred at 60 °C. [d]The reaction was performed in the presence of 0.5 ml AcOH at 60 °C. [e]The reaction was performed in the presence of 1 ml AcOH at 60 °C. [f]The reaction was performed in the presence of 0.5 ml AcOH at 80 °C. [g]The reaction was performed in the absence of AcOH. [h]The reaction was performed in the presence of 0.5 ml AcOH in an inert (N_2) atmosphere.

our focus on improving the yield of product. Subsequently, the screening of various solvents (DCE, MeOH, DMF and H_2O) were investigated and they are not helping in improving the

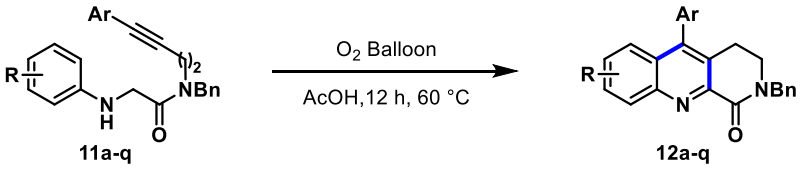
yield of the product **12b** (Table 1.2.1, entries 4–7). Notably, conducting the reaction at a temperature of 60 °C enhances the yield of product **12b** (Table 1.2.1, entries 8). It is also observed that the reaction proceeds well under a pure oxygen atmosphere (O_2 balloon) (Table 1.2.1, entries 9). Interestingly, the reaction proceeds well without solvents (Table 1.2.1, entries 10, 82%). Further, no significant improvement has been observed while changing the quantity of acetic acid as well conducting the reaction at high temperature (Table 1.2.1, entries 11 and 12). No reaction was observed in the absence of an acid catalyst and in an inert atmosphere (Table 1.2.1, entries 13 and 14). On the basis of these results, carrying out the reaction of *N*-aryl glycine amide **11b** (1 equiv.) in acetic acid (0.5 mL) at 60 °C in the O_2 atmosphere were selected as the optimized conditions.

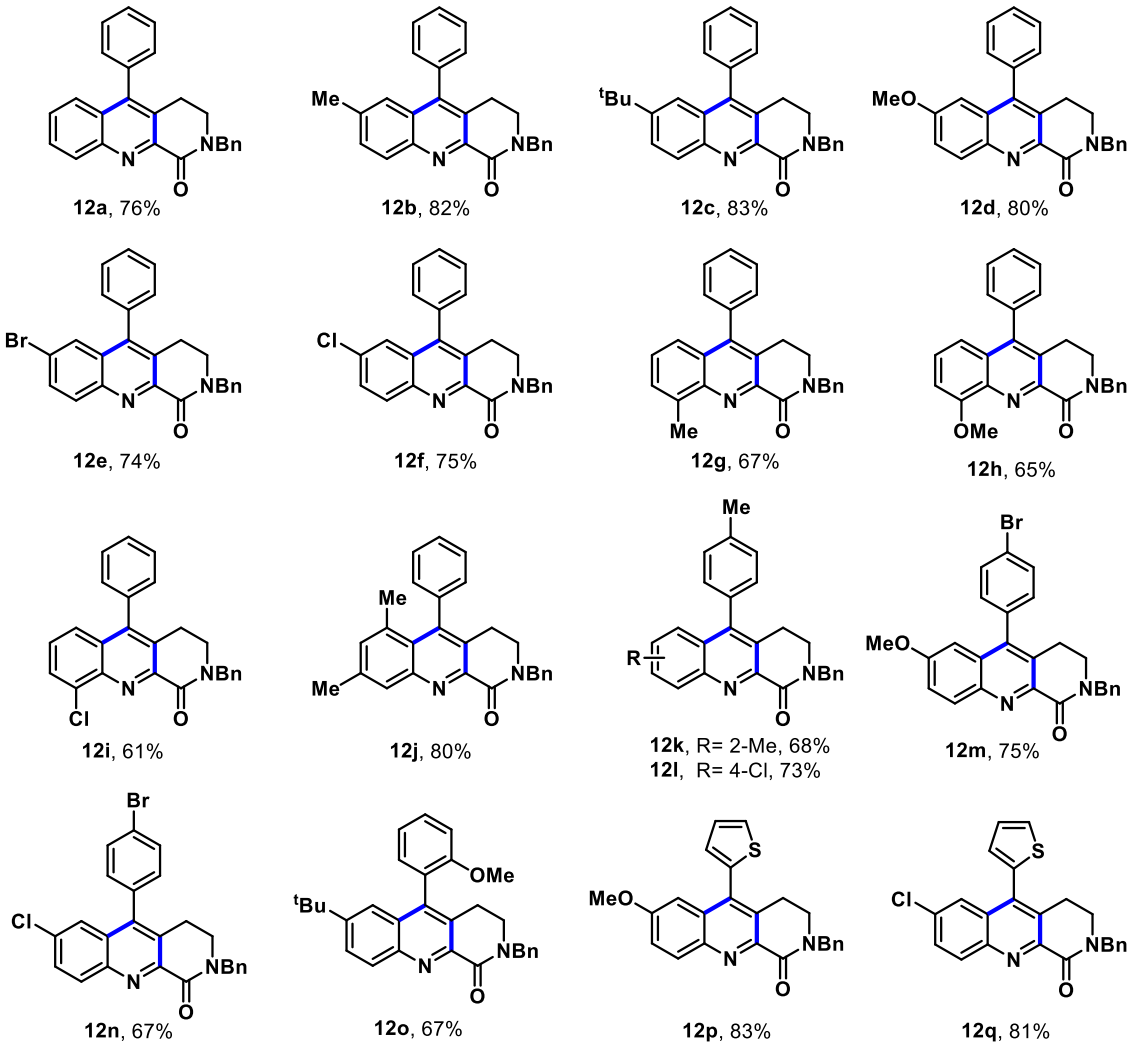
1.2.4.2 Intramolecular cyclization of various *N*-aryl glycine amides

With the optimal reaction conditions in hand, the substrate scope of various alkyne tethered *N*-aryl glycine amides (**11**) was then explored (Table 1.2.2.). Different electron-donating and halo substituents on the aniline ring as well as the aryl alkyne part were well tolerated. For example, substrates containing electron-donating groups such as 4-methyl and 4-*t*butyl on an aniline ring were suitable with the reaction conditions and produced the desired products **12b** and **12c** in 82%, and 83% yields, respectively. However, electron-donating group such as methoxy bearing substrate gave the expected product in good yield (**12d**, 80%). Additionally, substrates containing halogen atoms like Br and Cl successfully reacted under the optimized condition to produce the desired products (**12e-12f**) in good yield (74-75%). Furthermore, electron-donating and electron-withdrawing such as methyl, methoxy and chloro substitution on the ortho position of the aniline ring provided the desired products **12g**, **12h** and **12i** in 67%, 65% and 61% yields, respectively. Moreover, the di-substituted substrate also underwent smoothly to achieve the desired product **12j** in 80% yield. Next, we study the scope of our method by altering the substitution on the aryl alkyne part of *N*-aryl glycine amide derivatives. Electron donating and halo substituents on the aryl alkyne part of *N*-aryl glycine amide derivatives also took part in this transformation and afforded the products good yield. For example, substrates bearing electron-donating and halo groups such as 4-methyl and 4-bromo on the aryl alkyne part of *N*-aryl glycine were suitable with the reaction conditions and yielded the desired products **12k**, **12l, 12m** and **12n** in 68%, 73%, 75% and 67% yields, respectively. Further, the present protocol is suitable for ortho substitution on aryl alkyne part of the glycine derivatives (**11o**). Interestingly, het-

eroaryl substitution on the alkyne moiety, also a suitable substrate for this transformation, demonstrates the generality of this protocol (**12p-12q,** 83-81%).

Table 1.2.2 Intramolecular cyclization of *N*-aryl glycine amide[a,b]

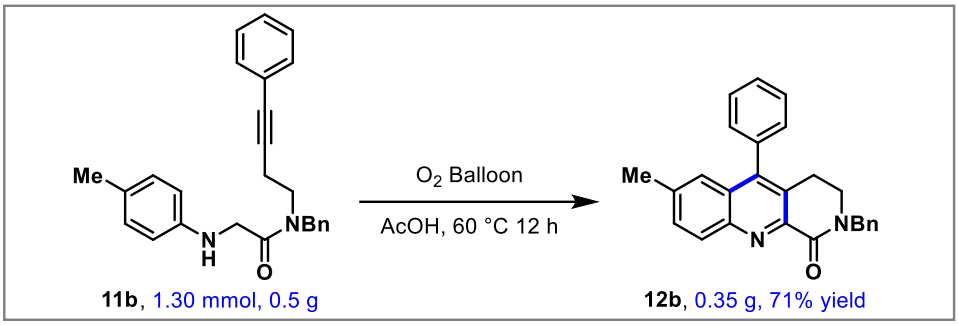




[a]Reaction conditions: 0.13 mmol **11**, AcOH (0.5 mL), 60 °C, 16 h; [b]Isolated yields

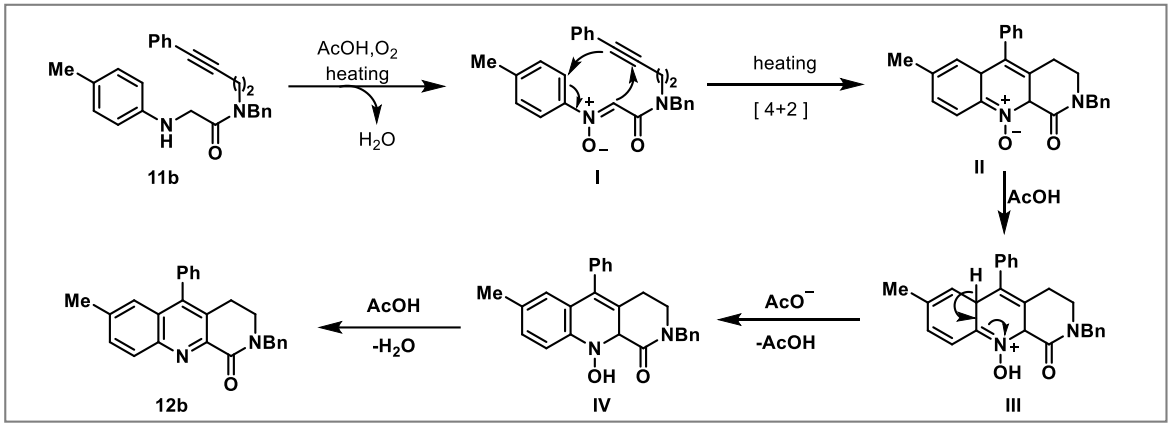
1.2.4.3 Gram-Scale Experiment

To further demonstrate the efficiency and practicality of the methodology, gram-scale synthesis was performed to obtain the desired product (**12b**) in 71% yield (0.35 g).



Scheme 1.2.6 Gram scale experiment

1.2.4.4 Plausible Reaction Mechanism



Scheme 1.2.7 A plausible mechanism

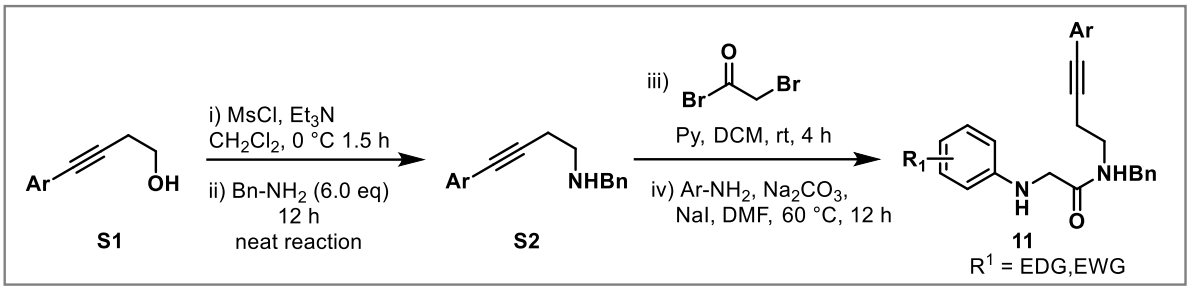
A plausible mechanism is proposed in Scheme 1.2.7.[9,10] As indicated, initially, alkyne tethered *N*-aryl glycine amide substrate **11b** was oxidized in the presence of O_2 and AcOH to *in situ* generate highly reactive imine-*N*-oxide intermediate I, followed by intramolecular Diels–Alder-type cyclization under heating conditions give tricyclic imine-*N*-oxide intermediate **II**. Next, intermediate **II** abstract a proton from AcOH to give intermediate **III**, which on rearomatization, gives intermediate **IV**. Finally, protonation of N-OH, followed by dehydration and aromatization of intermediate **IV,** deliver the quinoline fused lactam **12b**.

1.2.5 Conclusion

We have developed a straightforward and efficient strategy for the construction of six-membered quinoline fused lactams employing simple and easily accessible starting materials. This brønsted acid-catalyzed metal-free cyclization method works well under an O_2 atmosphere, providing six-membered quinoline fused lactams in moderate to good yields. The salient features of this reaction include mild reaction conditions, cheap and environment-friendly oxidants, experimental simplicity, and scalability.

1.2.6 Experimental Section

1.2.6.1 General Procedure for the Preparation of *N*-aryl glycine amide derivatives:



Scheme 1.2.8 Preparation of *N*-aryl glycine amide derivatives

*N-benzyl-4-phenylbut-3-yn-1-amine (**S2**)*:

To a solution of 4-phenylbut-3-yn-1-ol (1 equiv), triethylamine (1.5 equiv) in dichloromethane was added methane sulfonyl chloride (1.25 equiv) in dichloromethane dropwise for a period of 30 minutes at 0 °C. The mixture was stirred for 1.5 h at room temperature. Then water was added, and the organic layer separated. The organic layer was washed with 1 M HCl, sat. $NaHCO_3$ sol., brine and dried (Na_2SO_4). After the evaporation of the solvent, the crude mesylate was used in the next step without further purification.

The mesylate was added dropwise to neat benzyl amine, and the reaction was stirred at room temperature overnight. Then 2 M NaOH and Et_2O were added. The organic layer was separated, and the aqueous layer was extracted 2× with Et_2O. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo and purified *via* column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the desired product **S2**.

General procedure for the synthesis of substituted phenyl propargyl bromo acetamide:

To a solution of substituted *N-benzyl-4-phenylbut-3-yn-1-amine* **S2** (1 equiv) and pyridine (1.1 equiv) in anhydrous DCM was added 2-bromoacetyl bromide (1.1 equiv) in DCM at 0 °C under N_2 atmosphere over 30 min. After the addition was complete, the reaction mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), the crude reaction mixture was then poured into water and extracted with DCM (3 × 20 mL). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo, affording the substituted phenyl propargyl bromo acetamide, which was used directly without further purification.

General Procedure for the Synthesis of Substituted *N*-aryl Glycine Amide (11a-11q):

A 5 mL glass vial® was charged with substituted bromo acetamide (0.3 mmol), Na_2CO_3 (0.36 mmol), NaI (0.061 mmol), Substituted aniline (0.29 mmol), DMF (3ml). The mixture was

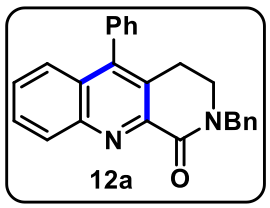
stirred for 12 h at 60 °C . After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, then poured into ice water and extracted with ethyl acetate (20 mL × 3). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography by eluting 10-20 % of ethyl acetate/petroleum ether (silica gel, 100-200 mesh), to afford the substituted *N*-aryl glycine amides (**11a-11q**).

1.2.6.2 General Procedure for the Synthesis of Six-membered Quinoline Fused Lactams (12a-12q):

Substituted *N*-aryl glycine amides **11** (0.13 mmol) and acetic acid (0.5 mL) were added to a clean, oven-dried glass round bottom flask equipped with a stir bar. Oxygen was purged directly from the oxygen balloon such that the environment was completely saturated with it for 16 h at 60 °C. After completion of the reaction (monitored with TLC), the reaction mixture was evaporated. The crude reaction mixture was washed with aqueous $NaHCO_3$, and the mixture was extracted with ethyl acetate (20 mL X 3). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography by eluting 30-40 % of ethyl acetate/petroleum ether (silica gel, 100-200 mesh), to afford the substituted quinoline fused lactams (**12a-12q**).

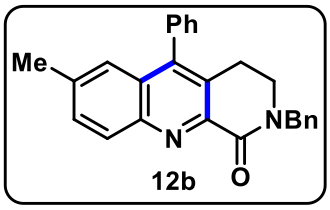
1.2.6.3 Characterization of 12:

2-benzyl-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12a):



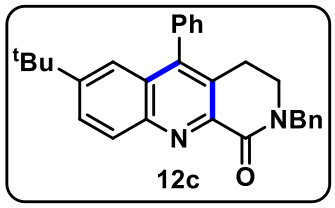
The product **12a** was obtained in 76% yield (37.5 mg, brown solid); **mp** = 154-156 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.34 (d, *J* = 8.5 Hz, 1H), 7.64 (m, *J* = 8.3, 4.1 Hz, 1H), 7.52 – 7.36 (m, 5H), 7.31 (d, *J* = 7.1 Hz, 2H), 7.25 – 7.16 (m, 5H), 4.82 (s, 2H), 3.38 (t, *J* = 6.3 Hz, 2H), 2.79 (t, *J* = 6.3 Hz, 2H).;**^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 163.1, 147.3, 146.7, 146.2, 136.8, 135.4, 131.5, 131.0, 129.3,129.2, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 127.6, 125.7, 50.9, 44.7, 26.1.; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{21}N_2O$ 365.1648; found 365.1653.

2-benzyl-7-methyl-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12b):The product **12b** was obtained in 82% yield (40.5 mg, brown solid); **mp** = 216-218 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.25 (d, J = 8.5 Hz, 1H), 7.52 – 7.41 (m, 4H), 7.32 (d, J = 7.1 Hz, 2H), 7.26 – 7.13 (m, 6H), 4.82 (s, 2H), 3.37 (t, J =



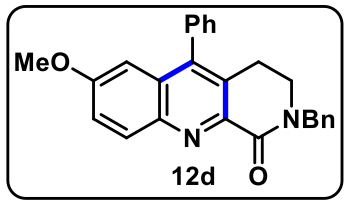
5.9 Hz, 2H), 2.77 (t, J = 6.2 Hz, 2H), 2.35 (s, 3H).;**^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 163.3, 146.1, 146.0, 145.2, 138.4, 137.0, 135.7, 131.5, 130.9, 129.3, 128.7,128.6, 128.3,128.2,128.1,128.0, 127.5, 124.3, 50.9, 44.7, 26.2, 21.9.; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O$ 379.1805; found 379.1810.

2-benzyl-7-(tert-butyl)-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12c):



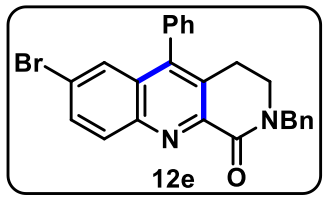
The product **12c** was obtained in 83% yield (41 mg, white solid); **mp** = 205-207 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.27 (d, *J* = 9.0 Hz, 1H), 7.74 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.33 – 7.29 (m, 3H), 7.25 – 7.18 (m, 5H), 4.82 (s, 2H), 3.36 (t, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 6.4 Hz, 2H), 1.20 (s, 9H).; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 163.4, 151.2, 146.1, 146.0, 145.9. 136.9, 135.6, 131.5, 130.5, 129.3, 128.6(2C), 128.3, 128.2, 128.0, 127.8, 127.5, 120.5, 50.9, 44.8, 35.1, 30.9, 26.2.; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{29}H_{29}N_2O$ 421.2274; found 421.2282.

2-benzyl-7-methoxy-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12d):



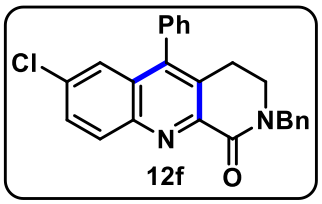
The product **12d** was obtained in 80% yield (39.5 mg, brown solid); **mp** = 228-230 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 4:6); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.33 (d, *J* = 9.3 Hz, 1H), 7.58 – 7.46 (m, 3H), 7.41 – 7.34 (m, 3H), 7.34 – 7.24 (m, 5H), 6.70 (d, *J* = 2.7 Hz, 1H), 4.89 (s, 2H), 3.71 (s, 3H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.83 (t, *J* = 6.4 Hz, 2H).; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 163.4, 151.2, 146.1, 146.0, 145.9. 136.9, 135.6, 131.5, 130.5, 129.3, 128.6(2C), 128.3, 128.2, 128.0, 127.8, 127.5, 120.5, 50.9, 44.8, 35.1, 30.9, 26.2.; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_2$ 395.1754; found 395.1759.

2-benzyl-7-bromo-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12e):



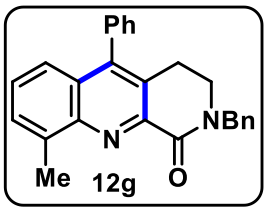
The product **12e** was obtained in 74% yield (37 mg, brown solid); **mp** = 168-170 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.22 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.50 (s, 1H), 7.40 (m, *J* = 14.0, 7.1 Hz, 3H), 7.17 (m, 7H), 4.76 (s, 2H), 3.34 (br s, 2H), 2.74 (br s, 2H).; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.5, 146.9, 145.9, 145.5, 136.7, 134.6, 133.2, 132.5, 129.3, 129.2, 129.1, 129.0, 128.8, 128.7, 128.4, 127.9, 127.7, 123.0, 51.1, 44.6, 26.7.; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}BrN_2O$ 443.0754; found 443.0747.

2-benzyl-7-chloro-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12f):



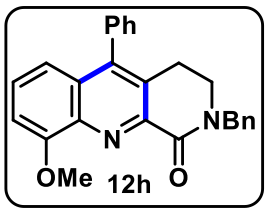
The product **12f** was obtained in 75% yield (37 mg, brown solid); **mp** = 176-178 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.36 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.52 – 7.41 (m, 3H), 7.37 (d, J = 2.2 Hz, 1H), 7.30 (d, J = 6.7 Hz, 2H), 7.21 (m, 5H), 4.82 (s, 2H), 3.40 (t, J = 6.3 Hz, 2H), 2.79 (t, J = 6.4 Hz, 2H).; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.9,146.0,145.3, 145.2, 136.3, 134.5,134.4, 132.4, 130.6, 129.0,128.9(2C),128.8,128.6,128.4, 128.3, 127.7, 124.5, 51.1, 44.5, 25.9.; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}ClN_2O$ 399.1259; found 399.1267.

2-benzyl-9-methyl-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12g):

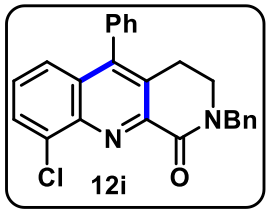


The product **12g** was obtained in 67% yield (33 mg, white solid); **mp** = 179-181 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.66 – 7.50 (m, 4H), 7.44 (m, *J* = 12.7, 7.1 Hz, 3H), 7.34 (m, *J* = 13.6, 11.9, 6.7 Hz, 6H), 4.94 (s, 2H), 3.54 (br s, 2H), 3.06 (s, 3H), 2.89 (br s, 2H).;**^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 163.2, 146.4, 146.3, 145.4, 139.0, 137.1, 135.9, 129.5, 129.4, 128.6(2C), 128.4, 128.3, 128.2, 128.0, 127.9, 127.6, 123.8, 50.9, 44.8, 26.3, 18.5.;**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O$ 379.1805; found 379.1796.

2-benzyl-9-methoxy-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12h):



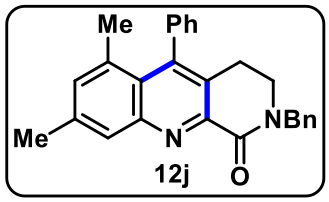
The product **12h** was obtained in 65% yield (32 mg, brown solid); **mp** = 163-165 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 4:6); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.45 – 7.36 (m, 3H), 7.30 (dd, *J* = 14.1, 5.5 Hz, 2H), 7.23 – 7.12 (m, 6H), 6.93 (dd, *J* = 8.0, 3.3 Hz, 2H), 4.77 (s, 2H), 3.99 (s, 3H), 3.36 (t, *J* = 6.3 Hz, 2H), 2.74 (t, *J* = 6.3 Hz, 2H).; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 163.1, 156.0, 146.0, 145.1, 139.3, 139.1, 136.7, 135.5, 129.2, 129.1, 128.7, 128.6, 128.5, 128.4, 128.2, 127.5, 117.4, 107.2, 55.8, 50.8, 44.6, 26.0.;**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_2$ 395.1754; found 395.1745.



2-benzyl-9-chloro-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12i): The product **12i** was obtained in 61% yield (30 mg, white solid); **mp** = 178-180 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.75 (d, *J* = 6.1 Hz, 1H), 7.51 – 7.39 (m, 3H), 7.38 – 7.28 (m, 4H), 7.22 (m, *J* = 17.5, 8.8, 3.2 Hz, 5H), 4.80 (s, 2H), 3.41 (br s,

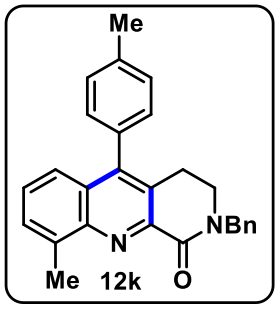
2H), 2.78 (br s, 2H).;**$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 162.4, 147.1, 147.0, 143.6, 136.9, 136.2, 136.1, 129.5, 129.4, 129.2, 128.8, 128.6(2C), 128.5, 128.4, 127.8, 127.6, 124.9, 50.8, 44.5, 26.3.;**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}ClN_2O$ 399.1259; found 399.1255.

2-benzyl-6,8-dimethyl-5-phenyl-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12j):



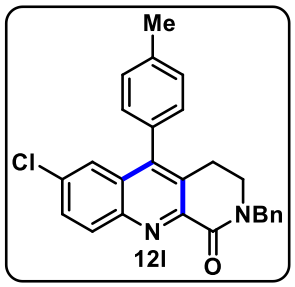
The product **12j** was obtained in 80% yield (39.5 mg, white solid); **mp** = 216-218 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^1H NMR (400 MHz, $CDCl_3$) δ** = 8.20 (s, 1H), 7.46 (s, 3H), 7.41 – 7.27 (m, 5H), 7.19 (d, *J* = 19.8 Hz, 3H), 4.89 (s, 2H), 3.42 (br s, 2H), 2.68 (br s, 2H), 2.52 (s, 3H), 1.91 (s, 3H).; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 162.8, 148.4, 146.8, 145.2, 139.5, 139.3, 136.9, 134.7, 134.3, 128.8, 128.6, 128.5, 128.4(2C), 128.3, 128.1, 127.6, 125.1, 50.8, 44.6, 26.0, 24.0, 21.3.;**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{27}H_{25}N_2O$ 393.1961; found 393.1950.

2-benzyl-9-methyl-5-(p-tolyl)-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12k):



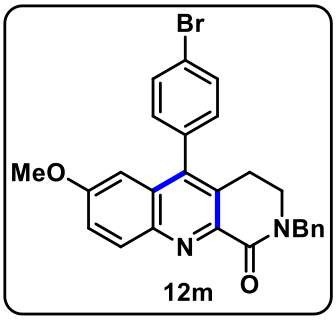
The product **12k** was obtained in 68% yield (33.5 mg, white solid); **mp** = 270-272 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:6); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.58 – 7.51 (m, 1H), 7.39 (d, J = 6.9 Hz, 2H), 7.37 – 7.23 (m, 7H), 7.12 (d, J = 8.0 Hz, 2H), 4.87 (s, 2H), 3.45 (t, J = 6.4 Hz, 2H), 2.98 (s, 3H), 2.83 (t, J = 6.4 Hz, 2H), 2.44 (s, 3H).; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 163.4, 146.6, 146.3, 145.5, 139.01, 138.0, 137.1, 132.9, 129.3(2C),129.2, 128.6, 128.3, 128.2, 127.9, 127.8, 127.5, 123.8, 50.8, 44.6, 26.3, 21.2, 18.3.; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{27}H_{25}N_2O$ 393.1961; found 393.1952.

2-benzyl-7-chloro-5-(p-tolyl)-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12l):The

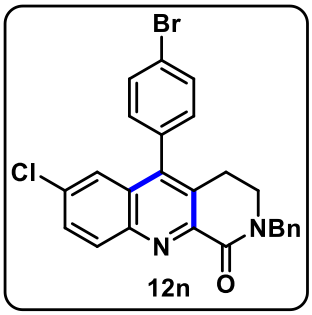


product **12l** was obtained in 73% yield (36 mg, white solid); **mp** = 182-184 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^1H NMR (400 MHz, $CDCl_3$) δ** = 8.32 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 6.0 Hz, 1H), 7.41 (s, 1H), 7.36 – 7.14 (m, 7H), 7.05 (d, *J* = 7.0 Hz, 2H), 4.82 (s, 2H), 3.38 (br s, 2H), 2.81 (br s, 2H), 2.39 (s, 3H).; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 162.7, 146.9, 145.9, 145.5, 138.7, 136.7, 134.3, 132.6, 131.6, 130.4, 129.6, 129.2, 129.1, 128.7, 128.6, 128.3, 127.7, 124.6, 51.0, 44.6, 26.3, 21.3.;**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{22}ClN_2O$ 413.1415; found 413.1418.

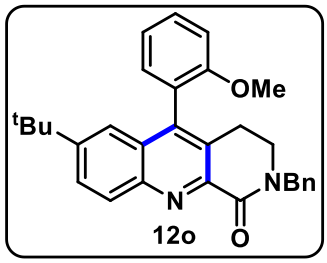
2-benzyl-5-(4-bromophenyl)-7-methoxy-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12m): The product **12m** was obtained in 75% yield (37 mg, brown solid); **mp** = 270-272 °C; ***R*$_f$** = 0.40 (petroleum ether:ethyl acetate = 4:6); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.40 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.39 (d, *J* = 7.0 Hz, 3H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.66 (d, *J* = 2.2 Hz, 1H), 4.88 (s, 2H), 3.75 (s, 3H), 3.46 (t, *J* = 5.7 Hz, 2H), 2.84 (t, *J* = 5.8 Hz, 2H).; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.8, 159.4, 144.0, 143.7, 143.1, 136.8, 134.5, 132.5, 132.4, 132.2, 130.9, 129.3, 128.6, 128.3, 127.6, 122.8, 122.4, 103.1, 55.5, 50.9, 44.6, 26.2.;**HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{26}H_{22}BrN_2O_2$ 473.0859; found 473.0862.



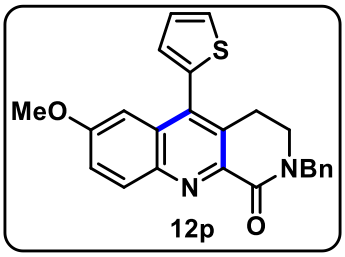
2-benzyl-5-(4-bromophenyl)-7-chloro-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2H)-one (12n): The product **12n** was obtained in 67% yield (33 mg, brown solid); **mp** = 172-174 °C; ***R*$_f$** = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.36 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.57 (m, 3H), 7.32 (m, *J* = 19.2, 12.6, 3.0 Hz, 6H), 7.13 (d, *J* = 7.3 Hz, 2H), 4.87 (s, 2H), 3.46 (br s, 2H), 2.85 (br s, 2H).;**^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.6, 147.0, 145.6, 144.2, 136.6, 134.7, 133.6, 132.8, 132.3, 130.9, 130.6, 129.1, 128.7, 128.5, 128.3, 127.7, 124.1, 123.2, 51.0, 44.5, 26.2.;**HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{25}H_{19}BrClN_2O$ 479.0343; found 479.0340.



2-benzyl-7-(tert-butyl)-5-(2-methoxyphenyl)-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one (12o): The product **12o** was obtained in 67% yield (33 mg, brown solid); **mp** = 207-209 °C; ***R*$_f$** = 0.50 (petroleum ether:ethyl acetate = 4:6); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.36 (d, J = 9.0 Hz, 1H), 7.80 (dd, J = 9.0, 2.1 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.41 (d, J = 7.3 Hz, 2H), 7.38 – 7.24 (m, 5H), 7.17 – 7.06 (m, 3H), 4.96 – 4.85 (m, 2H), 3.69 (s, 3H), 3.45 (t, J = 6.4 Hz, 2H), 2.91 – 2.75 (m, 2H), 1.29 (s, 9H).; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 163.5, 156.7, 150.7, 146.1, 142.8, 137.1, 131.0, 130.6, 130.1, 129.0, 128.6(2C), 128.4, 128.0, 127.9., 127.5, 124.1, 120.6, 120.4, 111.1, 55.4, 50.9, 44.8, 35.0, 30.9, 26.0.;**HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{30}H_{31}N_2O_2$ 451.2380; found 451.2382.

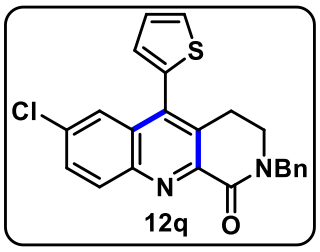


2-benzyl-7-methoxy-5-(thiophen-2-yl)-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one



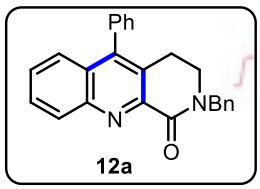
(12p): The product **12p** was obtained in 83% yield (41 mg, brown solid); **mp** = 189-191 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 4:6); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.36 (d, *J* = 9.6 Hz, 1H), 7.58 (d, *J* = 4.3 Hz, 1H), 7.45 – 7.24 (m, 7H), 7.03 (d, *J* = 47.7 Hz, 2H), 4.92 (s, 2H), 3.80 (s, 3H), 3.50 (br s, 2H), 2.99 (br s, 2H).**^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.6, 159.5, 144.1, 143.3, 137.5, 136.9, 135.2, 132.6, 130.5, 128.7, 128.6, 128.3, 127.6, 127.5, 127.4,127.3, 122.4, 103.2, 55.4, 51.0, 44.7, 26.5.;**HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{21}N_2O_2S$ 401.1318; found 401.1317.

2-benzyl-7-chloro-5-(thiophen-2-yl)-3,4-dihydrobenzo[b][1,7]naphthyridin-1(2*H*)-one



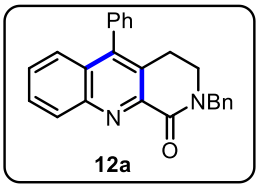
(12q): The product **12q** was obtained in 81% yield (40 mg, white solid); **mp** = 201-203 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.27 (d, *J* = 9.6 Hz, 1H), 7.58 (d, *J* = 1.7 Hz, 2H), 7.50 (d, *J* = 5.0 Hz, 1H), 7.30 (d, *J* = 7.1 Hz, 2H), 7.19 (m, *J* = 13.7, 10.8, 6.0 Hz, 4H), 6.98 (d, *J* = 3.2 Hz, 1H), 4.81 (s, 2H), 3.40 (t, *J* = 6.2 Hz, 2H), 2.91 (t, *J* = 6.3 Hz, 2H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.6, 146.9, 145.7, 138.4, 136.7, 134.8, 134.1, 132.7, 131.1, 130.6, 129.7, 129.1, 128.8, 128.8, 128.3, 127.8, 127.7, 124.3, 51.0, 44.5, 26.4.; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{23}H_{18}ClN_2OS$ 405.0823; found 405.0824.

1.2.7 Spectral data for the representative compounds:



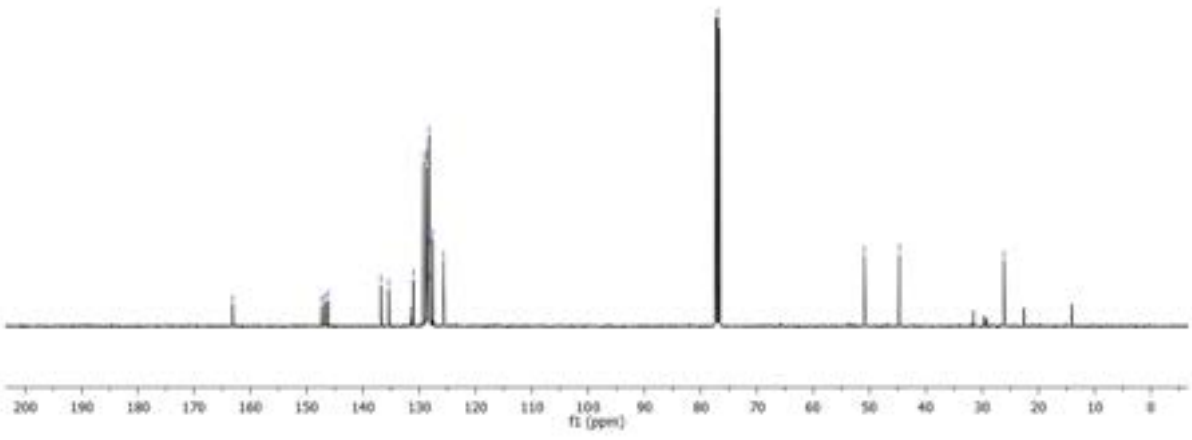
12a

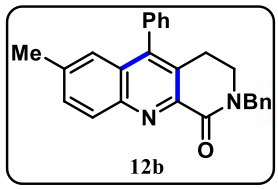
^{1}H NMR (400 MHz), $CDCl_3$



12a

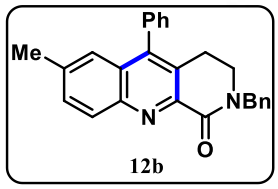
^{13}C NMR (125 MHz), $CDCl_3$





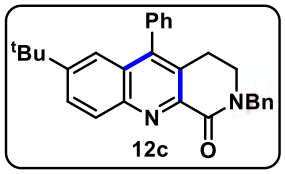
12b

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

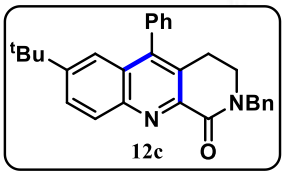


12b

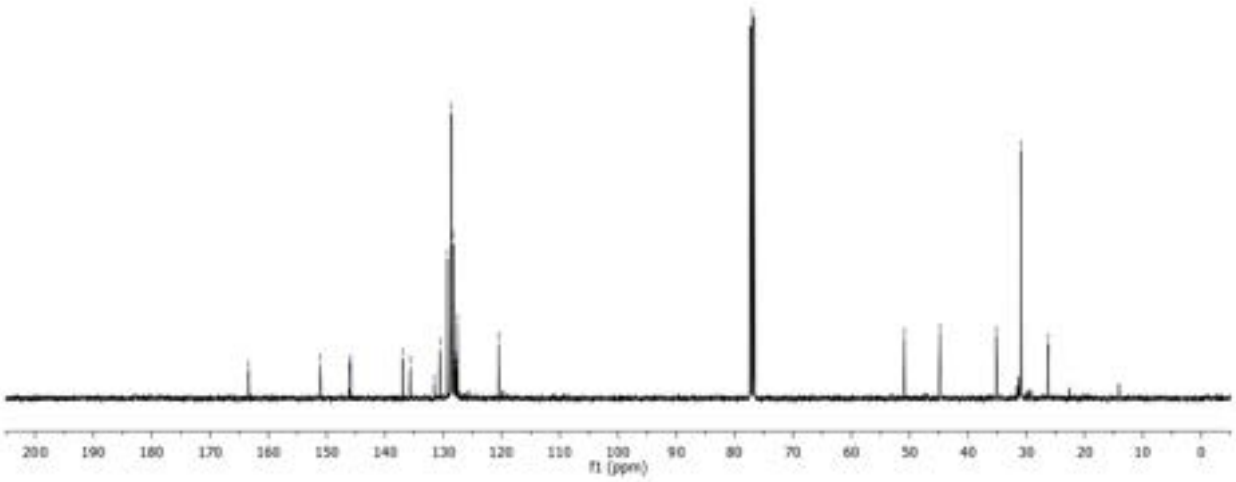
^{13}C NMR (125 MHz), $CDCl_3$

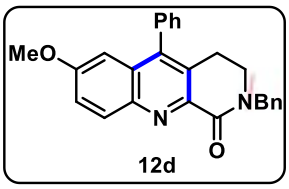


^{1}H NMR (400 MHz), $CDCl_3$

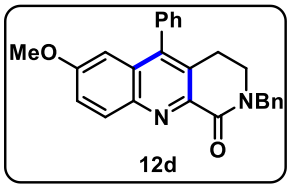


^{13}C NMR (125 MHz), $CDCl_3$

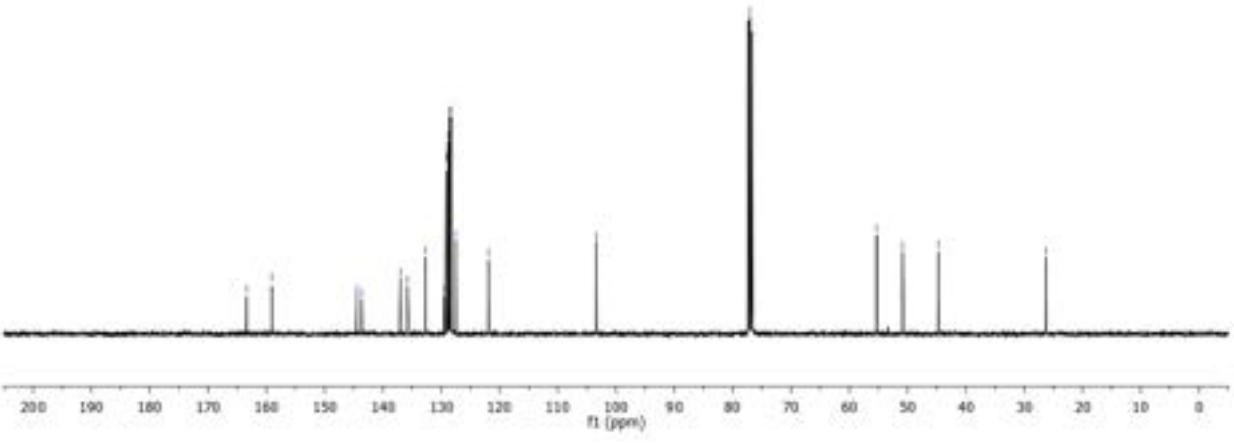


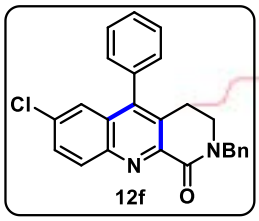


^{1}H NMR (400 MHz), $CDCl_3$

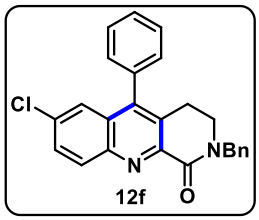


^{13}C NMR (125 MHz), $CDCl_3$

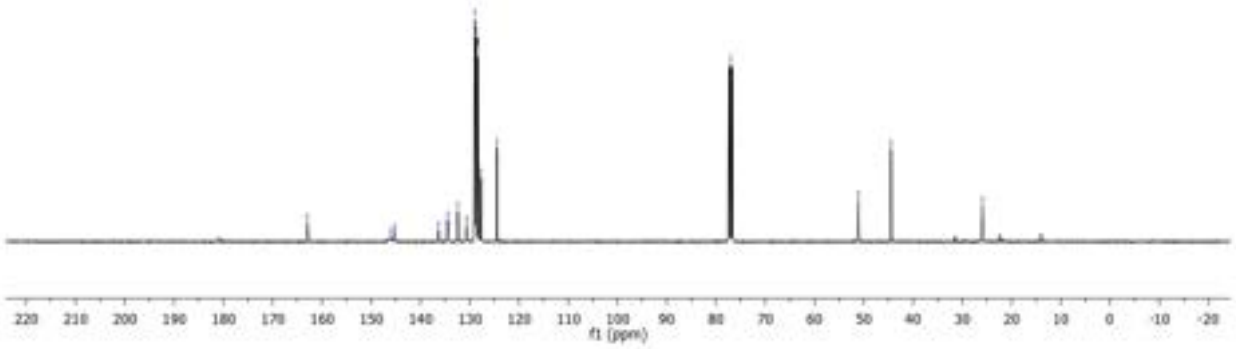


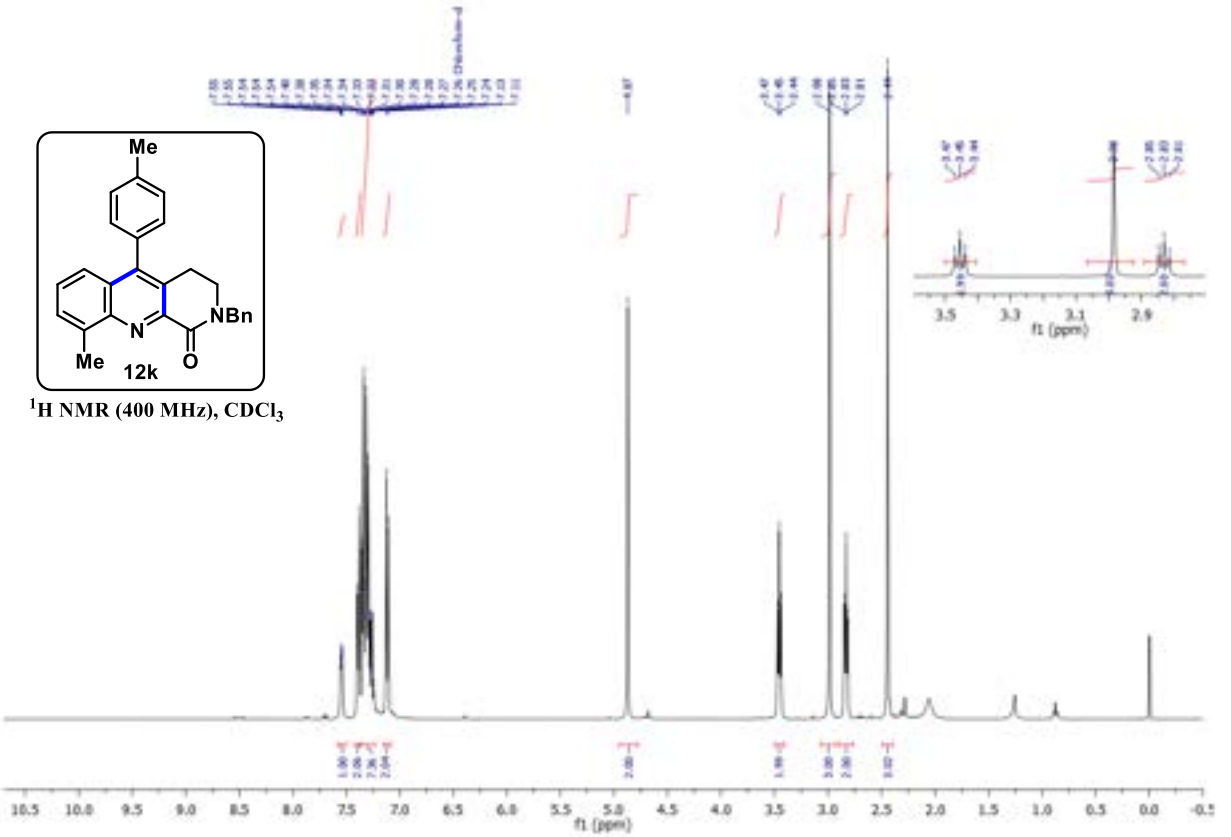


^{1}H NMR (400 MHz), $CDCl_3$

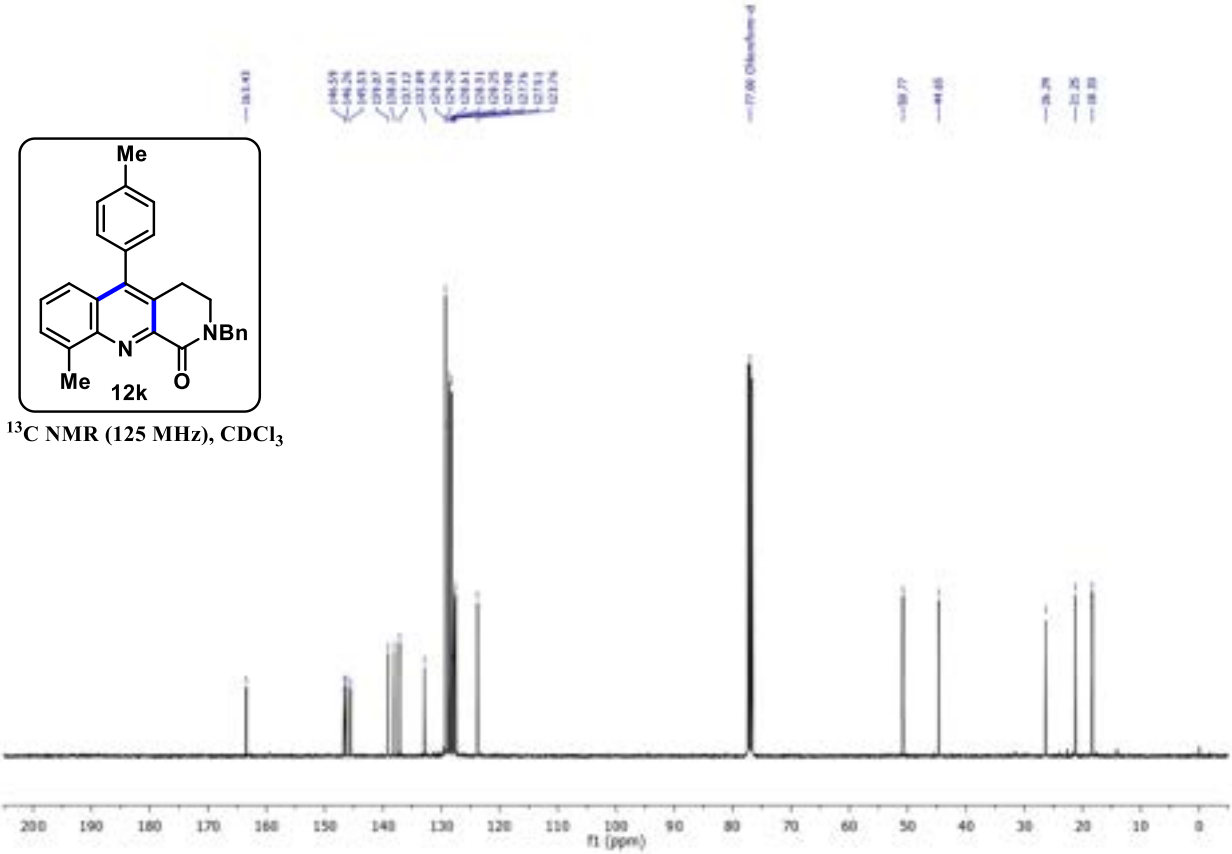


^{13}C NMR (125 MHz), $CDCl_3$

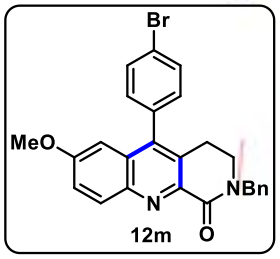




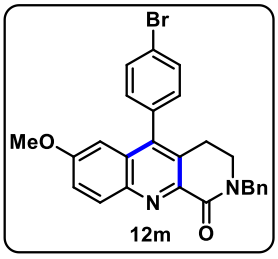
^{1}H NMR (400 MHz), $CDCl_3$



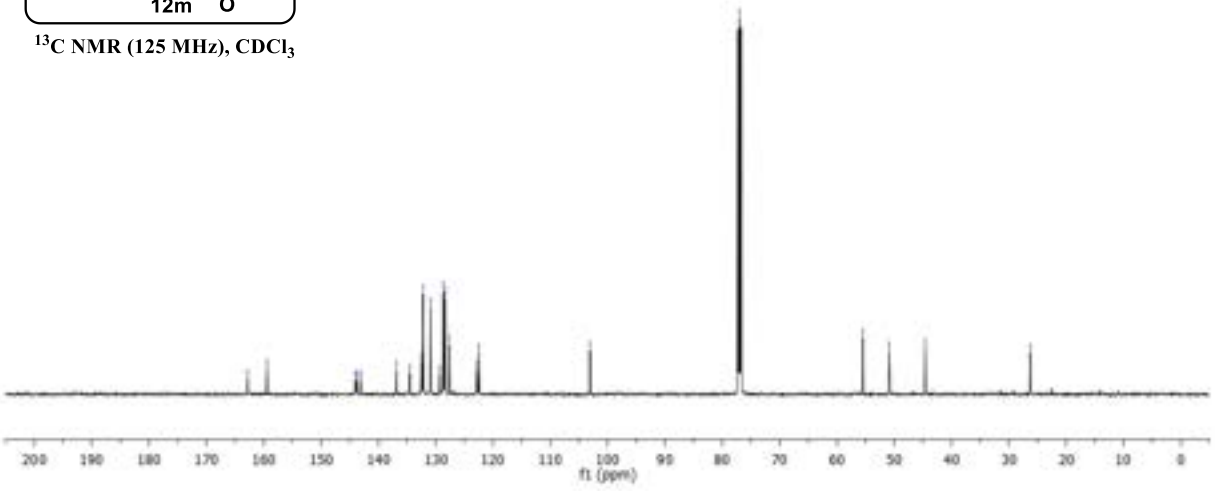
^{13}C NMR (125 MHz), $CDCl_3$

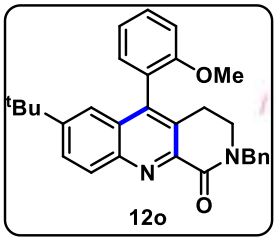


^{1}H NMR (400 MHz), $CDCl_3$

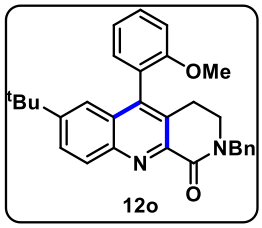


^{13}C NMR (125 MHz), $CDCl_3$

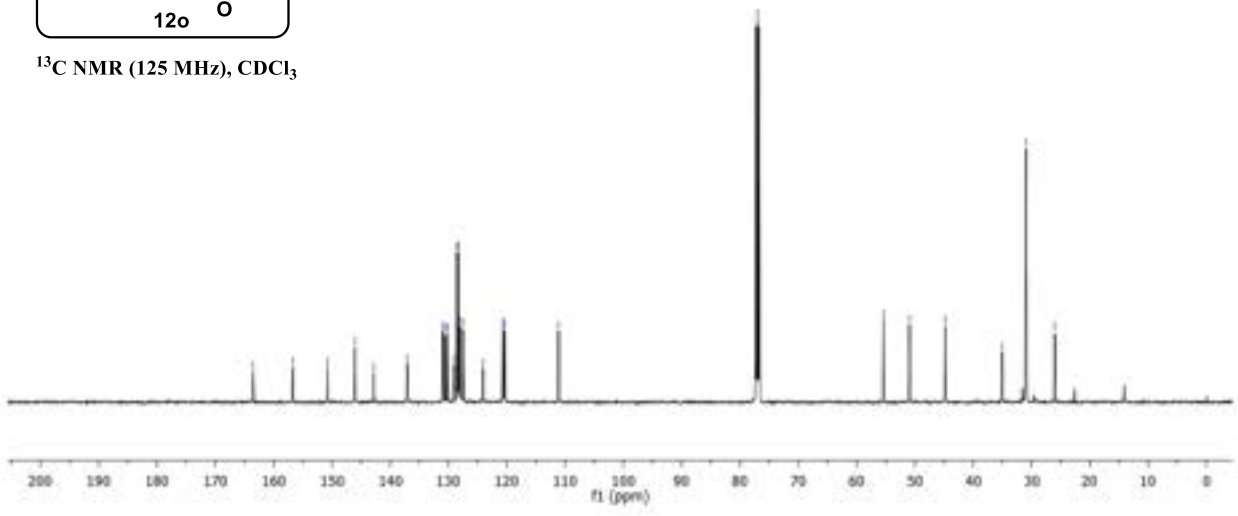


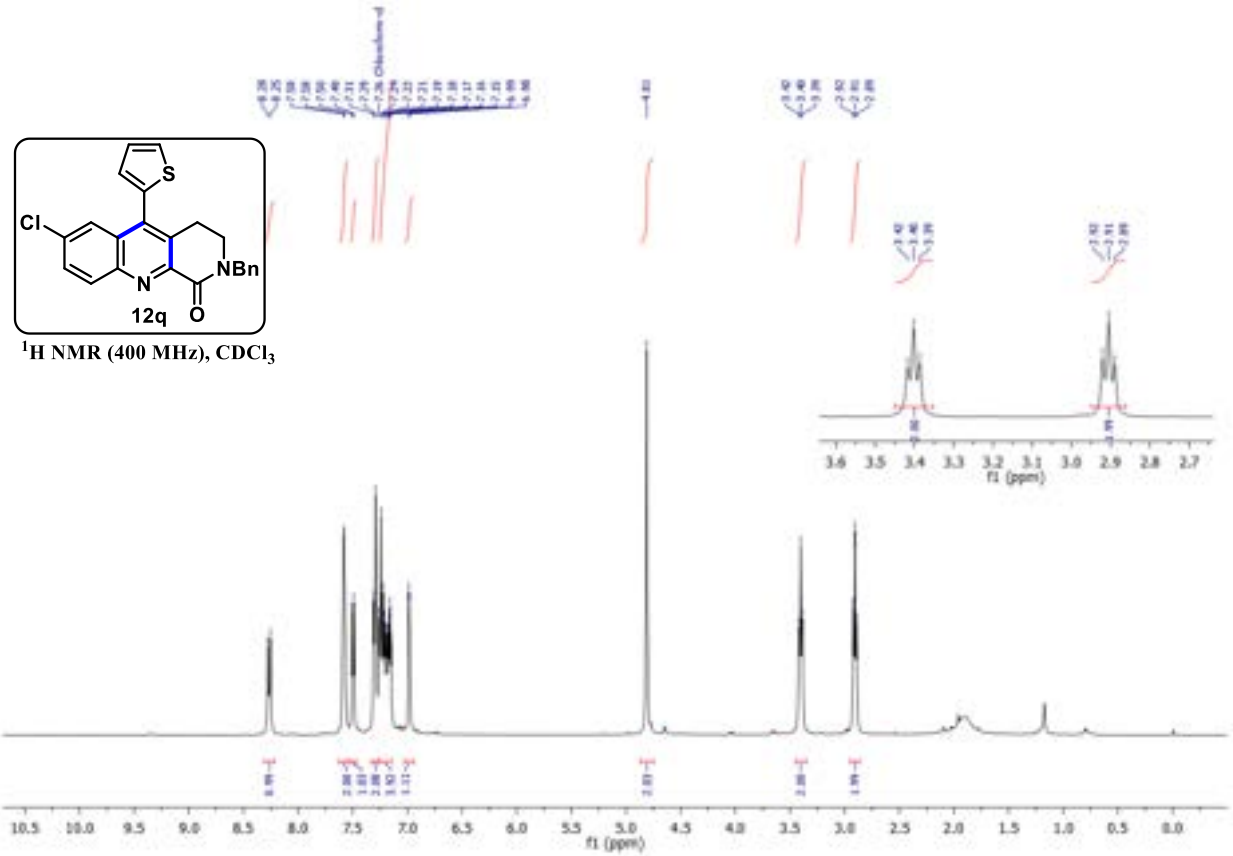


^{1}H NMR (400 MHz), $CDCl_3$

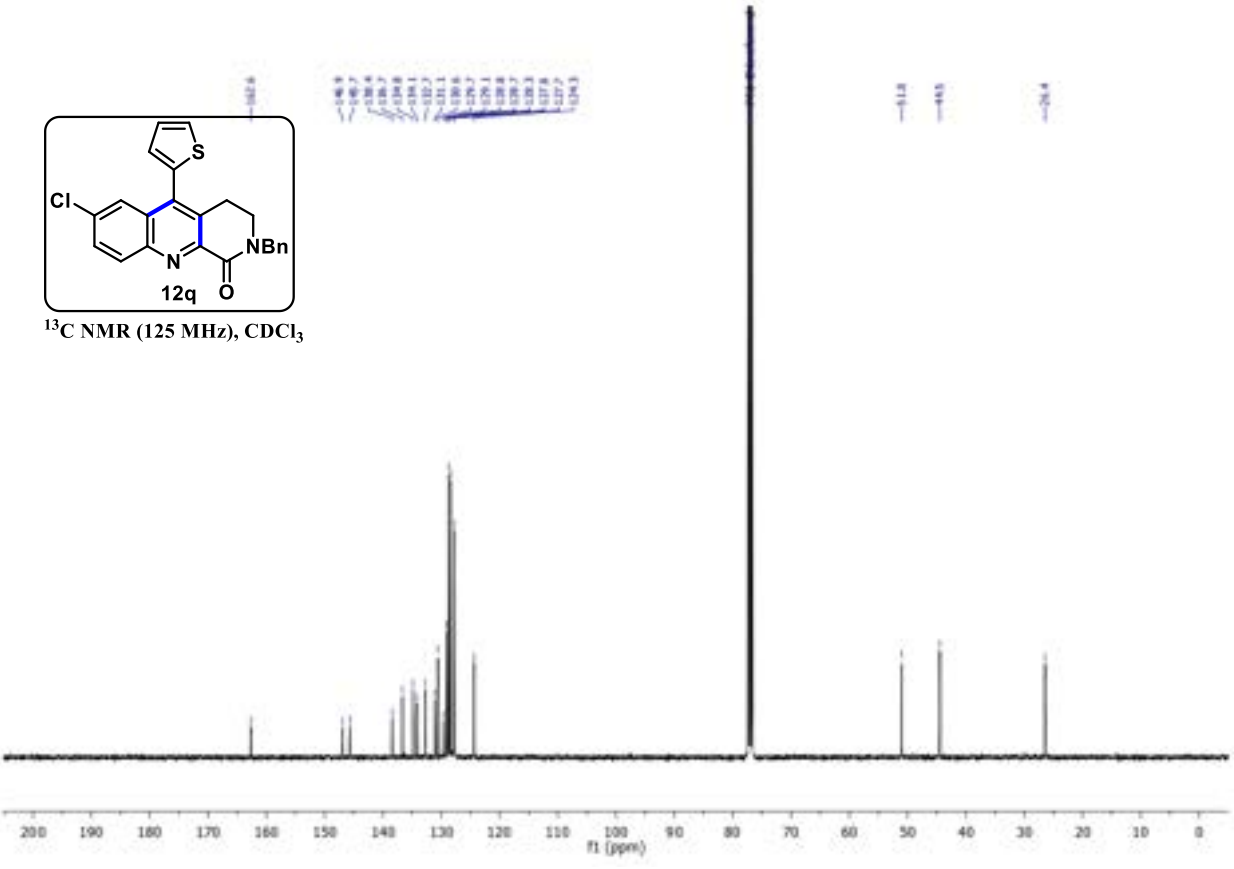


^{13}C NMR (125 MHz), $CDCl_3$





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



^{13}C NMR (125 MHz), $CDCl_3$

1.2.8 References

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CHAPTER-2

Development of Metal-free CH-Functionalization Reactions of Isoquinolin-1(2*H*)-ones & Quinoxalin-2(1*H*)-ones

Section I

$BF_3.Et_2O$ Catalyzed Selective C-4 Diarylmethylation of Isoquinolin-1(2*H*)-ones Employing *p*-Quinone Methides

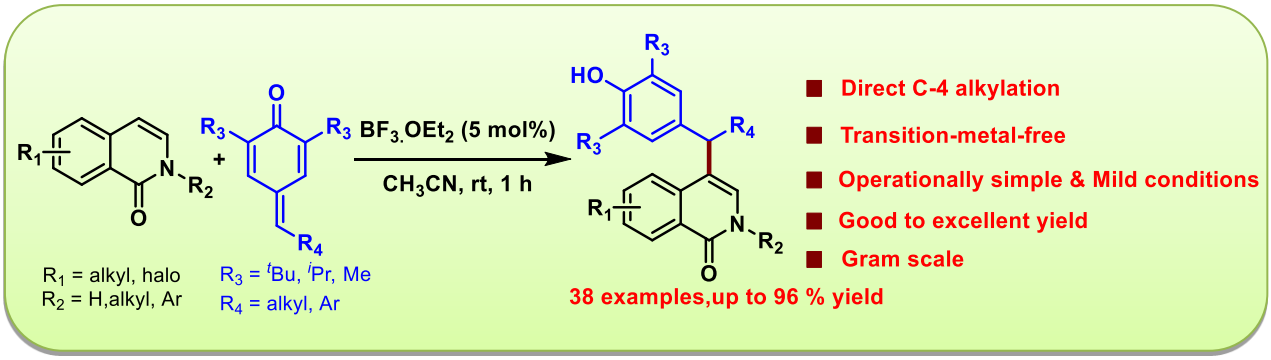
Section II

Metal- and Light-Free Direct C-3 Ketoalkylation of Quinoxalin-2(1*H*)-ones with Cyclopropanols in Aqueous Medium

Section-I

$BF_3.Et_2O$ Catalyzed Selective C-4 Diarylmethylation of Isoquinolin-1(2*H*)-ones Employing *p*-Quinone Methides

The direct C4 alkylation of isoquinolin-1(2*H*)-ones & their derivatives is a challenging transformation in organic synthesis, and there are only few direct methods are known. In this section, we have developed a metal-free, catalytic approach for the direct C4 alkylation of a wide range of isoquinolin-1(2*H*)-ones using *p*-QMs as an alkylating agent. The current method employs $BF_3.OEt_2$ as a catalyst; the reaction proceeds smoothly at ambient temperature and shows a broad substrate scope (38 examples) with low catalyst loading.



2.1.1 Introduction

Isoquinolin-1(2*H*)-ones and their derivatives are an influential class of nitrogen-containing heterocycles and are ubiquitously implicated in a large number of natural products, pharmaceuticals and biologically active compounds.[1] Among them, C4-substituted isoquinolin-1-(2*H*)-ones are omnipresent in natural alkaloids such as (+)-lycoricidine[2a,b] **Ia** (antimitotic activity) and narciclasine[2b] **Ib** (cytotoxic activity). In addition, molecule **II** (CRA-680) having substituted isoquinolin-1(2*H*)-one moiety, has been identified as a promising candidate for treating allergic and inflammatory diseases.[3] Additionally, isoquinolin-1(2*H*)-ones **III** (BI-7271) significantly suppresses the proliferation of mouse and human AML cells.[4] Trotabresib[5] **IV** is a reversible, potent bromodomain and extraterminal inhibitor used in high-grade gliomas. Furthermore, substituted isoquinolin-1-(2*H*)-ones are important precursors for the preparation of isoquinolines and 1,2,3,4-tetrahydroisoquinoline derivatives.[6,7]

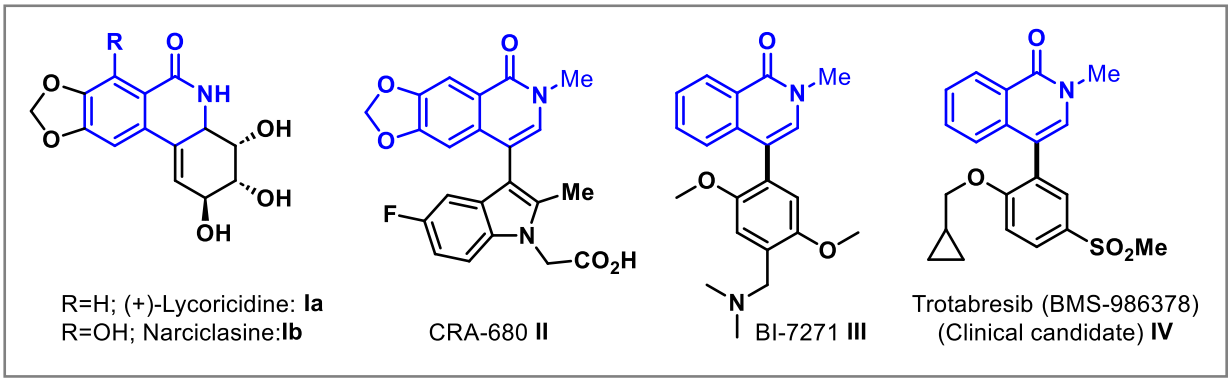


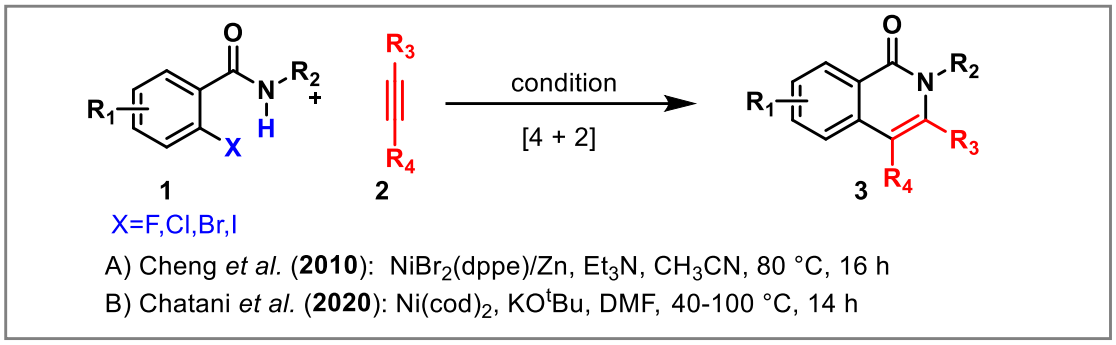
Figure 2.1.1 Representative biologically active C-4 isoquinolones, and their derivatives.

Owing to their biological significance, continuous efforts have been made to the synthesis and functionalization of isoquinolin-1-(2*H*)-ones. With the advent of CH-activation strategies, regioselective functionalization at the C-3 and C-8 positions of isoquinolinones has been well studied.[8] In contrast to the C-3 and C-8 positions of isoquinolin-1-(2*H*)-ones, selective functionalization at the C-4 position is comparatively less explored.[9a,b] Typical functionalization such as halogenation, arylation, alkynylation, borylation, and sulfenylation have been successfully carried out into the C-4 position of isoquinolin-1-(2*H*)-ones.[9a,b] Most of these methods rely on transition metal catalysis and employ harsh reaction conditions. However, to the best of our knowledge, there is no report on direct C-4 alkylation of isoquinolone reported yet. Few of the significant synthetic strategies employed for the preparation of C-4 substituted isoquinolin-1-(2*H*)-ones are described below.

2.1.2 Literature Precedence on the Synthesis of C-4 substituted Isoquinolin-1-(2*H*)-ones

a) Intermolecular annulations *via* aryl C–X/N–H activation

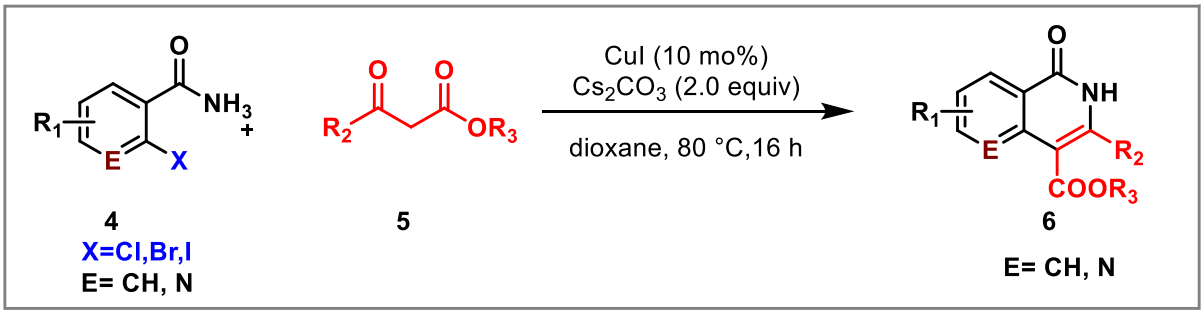
In 2010, Cheng and co-workers reported a nickel-catalyzed heteroannulation reaction of *ortho*-iodobenzamides **1** with alkynes **2** to synthesize *N*-substituted isoquinolin-1-(2*H*)-ones derivatives **3** (Scheme 2.1.1A).[10] Using this protocol, a total synthesis of oxyavicine was successfully synthesized with excellent yield.



Scheme 2.1.1 [4 + 2] intermolecular annulation of *ortho*- halobenzamides with alkynes.

Similarly, Chatani *et al.* also reported $Ni(cod)_2$ catalyzed synthesis of isoquinolones **3** *via* annulation of *o*-fluorobenzamides **1** with alkynes **2**. Use of bases, such as Cs_2CO_3 or KO^tBu, is crucial to the reaction's success. The reaction works well in the absence of a ligand and under mild reaction conditions (Scheme 2.1.1B).[11]

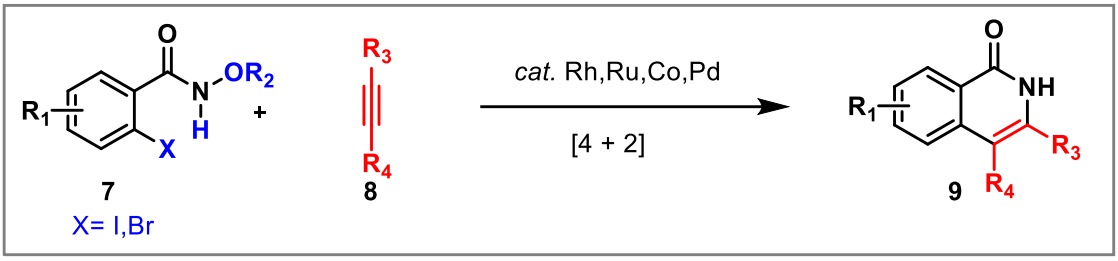
In 2009, Zhao *et al.* developed a copper (I)-catalyzed approach toward substituted isoquinolones **6** *via* annulation of *ortho*-halobenzamides **4** with *β*-keto esters **5**. Without the use of ligands or additives, the reaction proceeds well under mild conditions (Scheme 2.1.2).[12]



Scheme 2.1.2 CuI-catalyzed synthesis of 3,4-disubstituted isoquinolones.

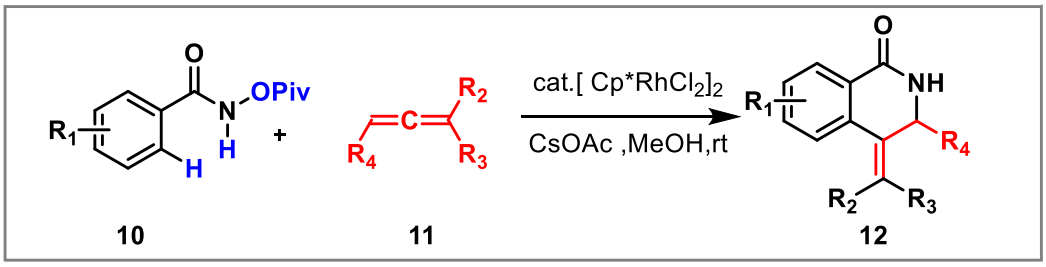
b) Intermolecular [4 + 2] annulations *via* aryl C–H/N–O activation

A detailed study has been conducted regarding the synthesis of 3,4-disubstituted isoquinolones using transition-metal catalysts such as Rh, Ru, Co, and Pd *via* C-H/N-O bond cleavages with dealkoxylation reactions (Scheme 2.1.3).[13a-g]



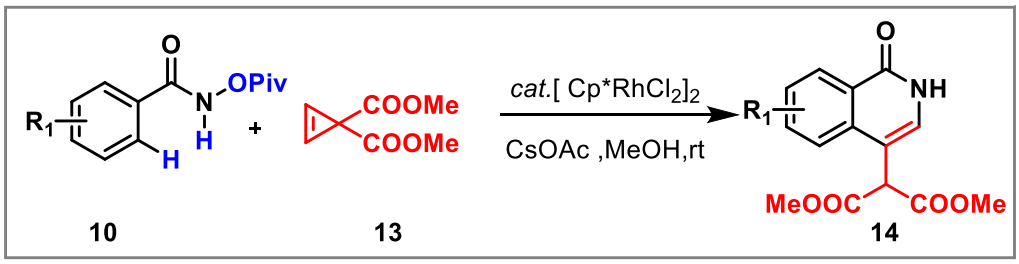
Scheme 2.1.3 [4 + 2] intermolecular annulation of *N*-alkoxybenzamides with alkynes.

In 2012, Glorius *et al.* reported a Rhodium (III)-catalyzed intermolecular cyclization of *N*-pivaloyloxybenzamides **10** with allenes **11** for the construction of 3,4-dihydroisoquinolin-1(2*H*)-ones **12** (Scheme 2.1.4).[14] The reaction displays high stereo and regioselectivity for both the coupling partners, and this strategy allows several functional groups.



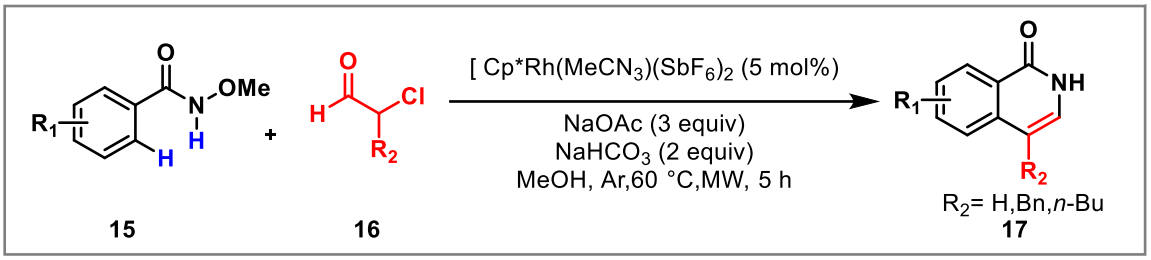
Scheme 2.1.4 Annulation of *N*-OPiv benzamides with substituted allenes.

Similar conditions were later applied by Rovis and co-workers for the synthesis of 4-substituted *N*–H isoquinolones *via* [4 + 2] intermolecular annulation of *N*-pivaloyloxy bezamides **10** with cyclopropanes **13**. The reaction proceeds *via* [4.1.0] bicyclic system, which can open under acidic conditions to produce the isoquinolone (Scheme 2.1.5).[15]



Scheme 2.1.5 Annulation of *N*-OPiv benzamides with cyclopropenes.

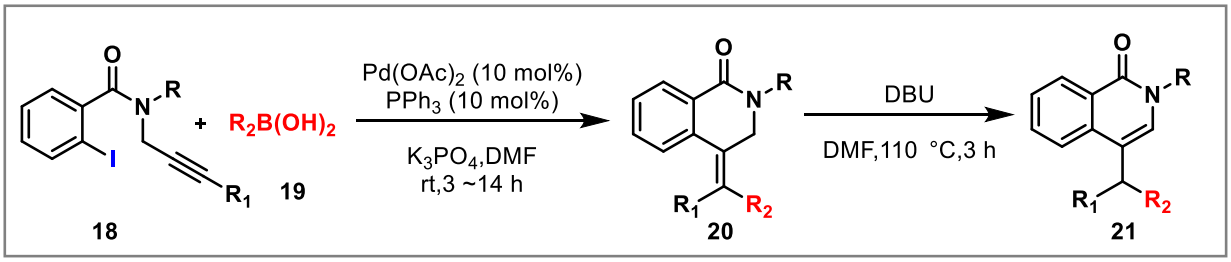
Bolm and co-workers developed a microwave-assisted Rh (III)-catalyzed [4 + 2] annulation of *N*-methoxybenzamides **15** with α-chloroaldehydes **16** to afford various 4-substituted isoquinolones **17** in satisfactory yields. In this strategy, α-chloroaldehyde is used as the terminal alkyne equivalent (Scheme 2.1.6).[16]



Scheme 2.1.6 Annulation of *N*- methoxybenzamides with α-chloroaldehydes.

c) Isoquinolone synthesis *via* intramolecular annulation reactions

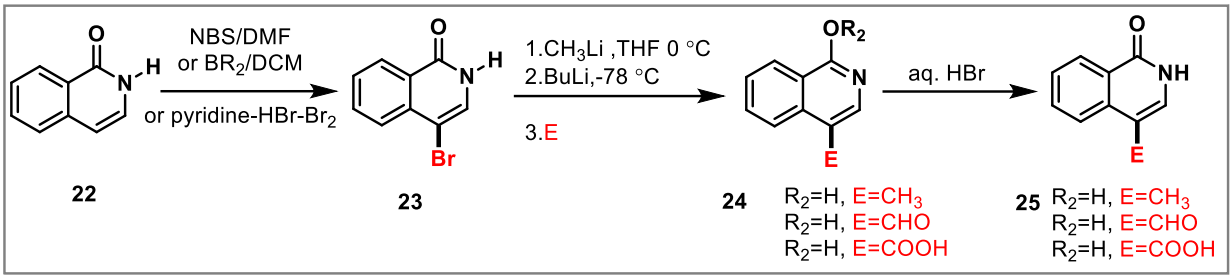
In 2016, Chowdhury and co-workers developed a palladium-catalyzed tandem Heck-Suzuki coupling reaction between *ortho*-iodo-*N*-(prop-2-ynyl)-benzamides **18** and arylboronic acids **19** to synthesize 4-(diarylmethylidene)-3,4-dihydroisoquinolin-1(2*H*)-ones **20**. The exocyclic double bond of these compounds were converted to their endo-isomers by reaction with DBU to provide isoquinolin-1(2*H*)-ones derivatives **21** (Scheme 2.1.7).[17]



Scheme 2.1.7 Stereoselective synthesis of 4-(diarylmethylidene)-3,4-dihydroisoquinolin-1(2*H*)-ones

d) Methods for direct substitution of the isoquinolone moiety

In 2007, Sercel and colleagues reported a synthetic route toward C-4 alkyl substituted isoquinolin-1(2*H*)-ones **25** through electrophilic trapping of di- and monolithium anions derived from alkyllithium exchange of 4-bromoisoquinolin-1(2*H*)-one **23** and corresponding 4-bromo-1-methoxyisoquinolines respectively (Scheme 2.1.8).[18] The method can be applied to access C-4 substituted isoquinolinones with substituents such as CHO, COOH and SCH_3.

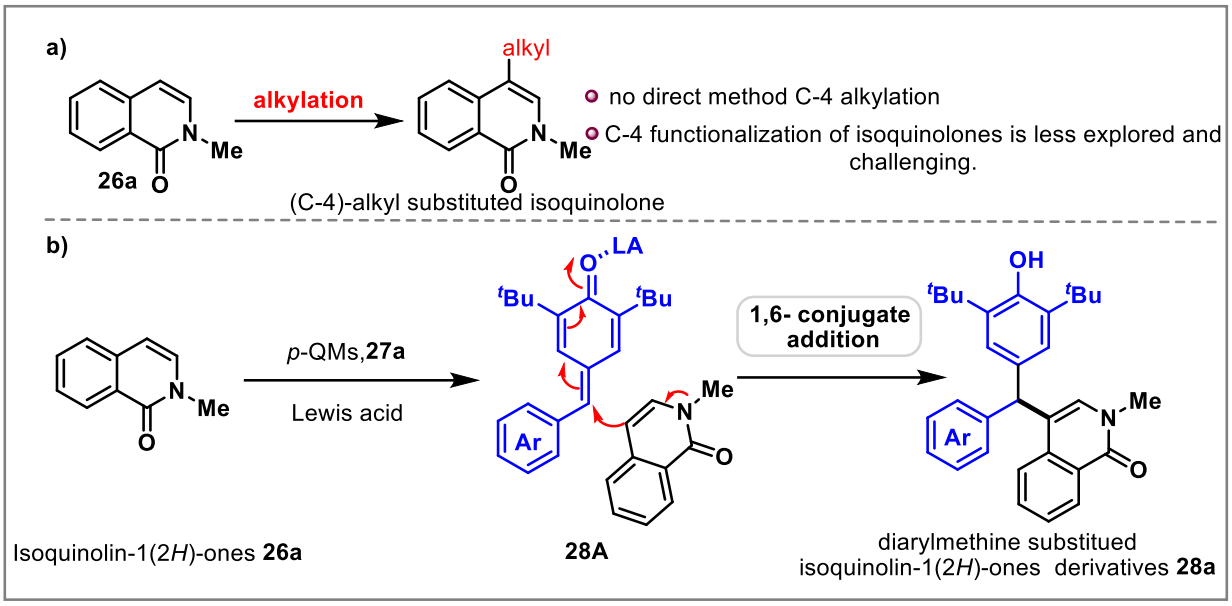


Scheme 2.1.8 Synthesis of 4-substituted isoquinolin-1(2*H*)-ones *via* electrophilic trapping of lithiated mono- and dianion precursors.

2.1.3 Present Work

2.1.3.1 Statement of the Problem

In general, most of the approaches discussed above for direct or indirect C-4 substitution, especially alkylation of isoquinolones are suffered from certain drawbacks, such as the requirement of an expensive transition-metal catalyst for substrate activation, multiple steps, relatively harsh reaction conditions, limited substrate scope etc. Further, the direct C–H functionalization strategy also encounters a problem, such as prolonged heating as well as unwanted isomeric side products. Therefore, the development of robust and practical methods for C4 alkylation of isoquinolin-1(2*H*)-ones is highly desirable. On the other hand, para-quinone methides have appeared as appealing and multifaceted synthons in organic synthesis due to their unique reactivity.[19] In recent years, *p*-quinone methides have been successfully used as an alkylating agent for many synthetic transformations.[20] Inspired by the emerging importance of *p*-QMs as an alkylating agent and the biological significance of isoquinolones, we envisioned that *p*-QMs can be efficiently utilized for the selective alkylation of isoquinolin-1(2*H*)-ones. Here, we demonstrate the successful realization of a new strategy for the direct C-4 alkylation of isoquinolin-1(2*H*)-ones employing *p*-QMs under Lewis acid catalysis (Scheme 2.1.9). As far as we know, Lewis acid-catalyzed 1,6-Conjugate addition of isoquinolin-1(2*H*)-ones to *p*-quinone methides (*p*-QMs) to access diarylmethine substituted isoquinolinones has not been reported yet.



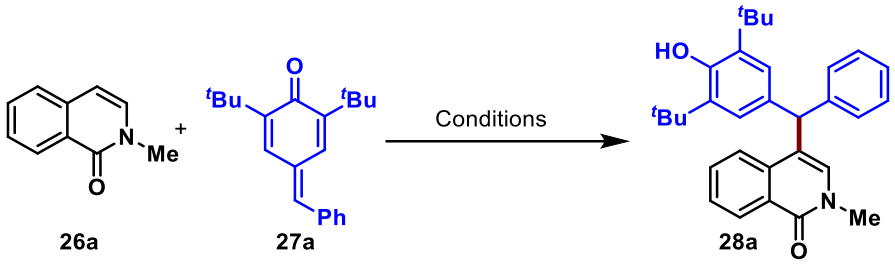
Scheme 2.1.9 Lewis acid-catalyzed 1,6-conjugate addition of isoquinolin-1(2*H*)-ones to *p*-QMs

2.1.4 Results and Discussion

2.1.4.1 Optimization of Reaction Conditions

Initially, optimization of the reaction condition was investigated using isoquinolone **26a** and *p*-quinone methide **27a** as model substrates in the presence of $Sc(OTf)_3$ in DCM. To our delight, the expected product **28a** was isolated in 57 % yield after 6 h (Table 2.1.1, entry 1). The structure of compound **28a** was characterized with the help of spectral and analytical data and completely matched with the product. In the ^1H NMR spectra of compound **28a**, signal at δ 5.16 (s, 1H) is due to methine proton (-CH), and a signal at δ 5.66 (s, 1H) corresponds to the phenolic (-OH). In addition, the appearance of typical carbon signals at δ 162.2 is due to amide carbonyl carbon, and the signal at δ 50.6 is attributed to the methine carbon. Further, the HRMS (ESI-TOF) m/z: $[M–H]^+$ the peak of **28a** at 454.2749 corresponds to formula $C_{31}H_{36}O_2N$ (calculated value 454.2741), confirms the structure of **28a**. With this structure confirmation and encouraged by this initial result, efforts were made to further improve the yield of **28a**. The reaction was carried out with several Lewis acids such as $Cu(OTf)_2$, $Yb(OTf)_3$, $Bi(OTf)_3$, $In(OTf)_3$, $BF_3{\cdot}(OEt)_2$, and Brønsted acid such as PTSA, TFA (Table 2.1.1, entries 2−8). Among all, $BF_3{\cdot}(OEt)_2$ was found to be the efficient catalyst for providing product **28a** in 90 % yield (Table 2.1.1, entry 6). Subsequently, the effect of solvents such as DCE, $CHCl_3$, Toulene, CH_3CN, THF, and DMF were screened (Table 2.1.1, entries 9−14). It was observed that

Table 2.1.1 Optimization of the reaction conditions[a,b]



26a 27a 28a

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	$Sc(OTf)_3$	DCM	06 h	57
2	$Cu(OTf)_2$	DCM	06 h	40
3	$Yb(OTf)_3$	DCM	06 h	NR
4	$Bi(OTf)_3$	DCM	06 h	86
5	$In(OTf)_3$	DCM	06 h	50
6	$BF_3{\cdot}OEt_2$	DCM	06 h	90
7	PTSA	DCM	06 h	82
8	TFA	DCM	06 h	09
9	$BF_3{\cdot}OEt_2$	DCE	06 h	81
10	$BF_3{\cdot}OEt_2$	$CHCl_3$	06 h	69
11	$BF_3{\cdot}OEt_2$	Toluene	06 h	27
12	$BF_3{\cdot}OEt_2$	CH_3CN	06 h	94
13	$BF_3{\cdot}OEt_2$	THF	06 h	36
14	$BF_3{\cdot}OEt_2$	DMF	06 h	trace
15	**$BF_3{\cdot}OEt_2$**	**CH_3CN**	**01 h**	**95**
16	$BF_3{\cdot}OEt_2$	CH_3CN	0.5 h	84
17	-	CH_3CN	24 h	NR

[a]Reaction conditions: All reactions were carried out with **26a** (0.19 mmol), **27a** (1.1 equiv.), 5 mol % of catalyst, in a solvent (2.0 mL) at room temperature. [b]The yields refer to the isolated yields.

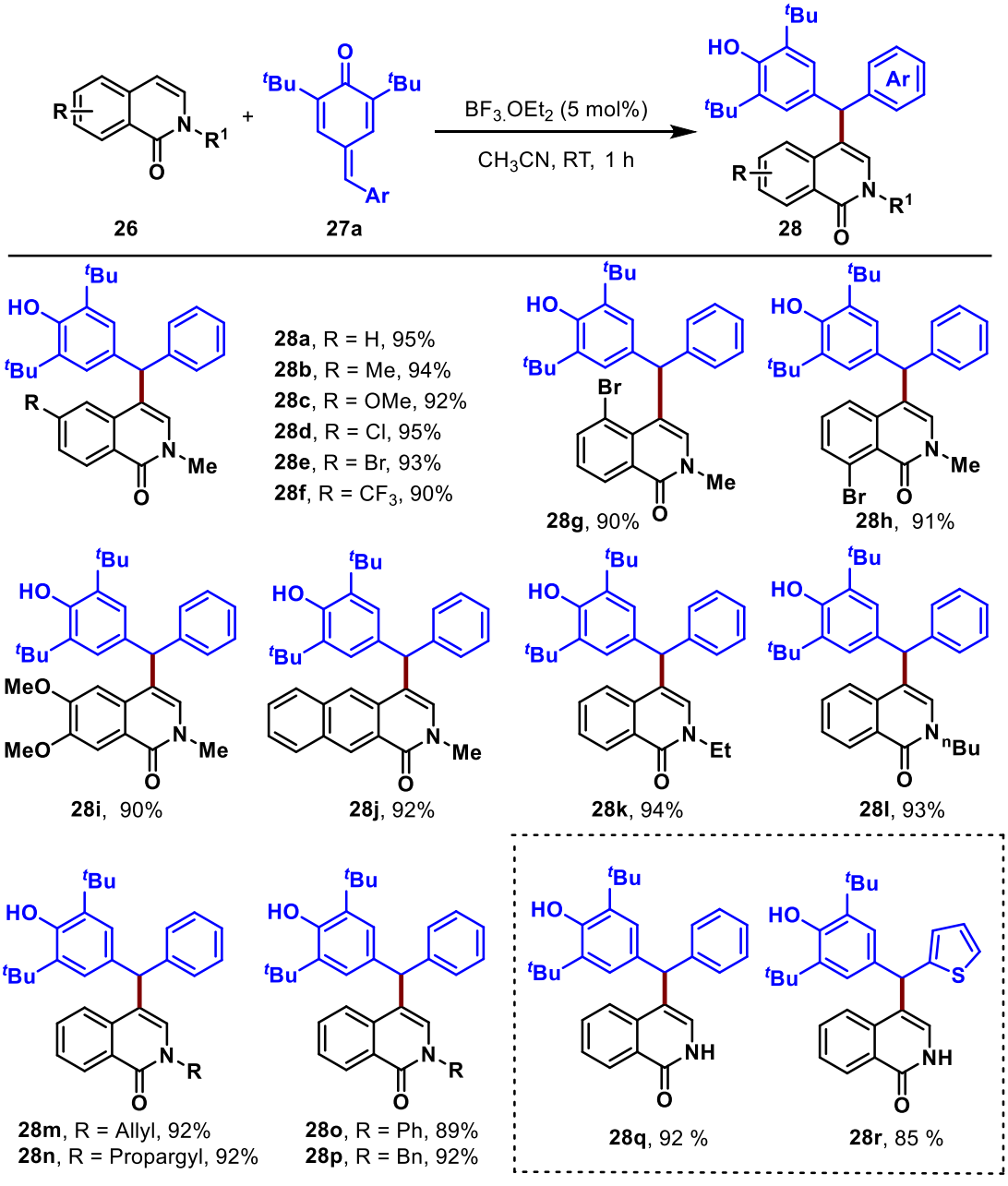
acetonitrile was the most suitable solvent for this transformation. Afterwards, we examined the duration of the reaction and found that 1 h is sufficient to effect this transformation (Table 2.1.1, entries 15&16). Furthermore, product **28a** was not observed when the reaction was carried out under catalyst-free condition (Table 2.1.1, entry 17). Finally, the optimal conditions comprising

the treatment of isoquinolone **26a** and *p*-quinone methide **27a** with 5 mol% $BF_3{\cdot}OEt_2$ at room temperature in acetonitrile for 1 h to afford **28a** in 95 % yield.

2.1.4.2 Scope of the Reaction: Substituents on the Isoquinoline-1(2*H*)-ones

With the optimized condition in hand, we explored the scope of this direct C-4 alkylation reaction with respect to isoquinolone **26** (Table 2.1.2). To our delight, a wide range

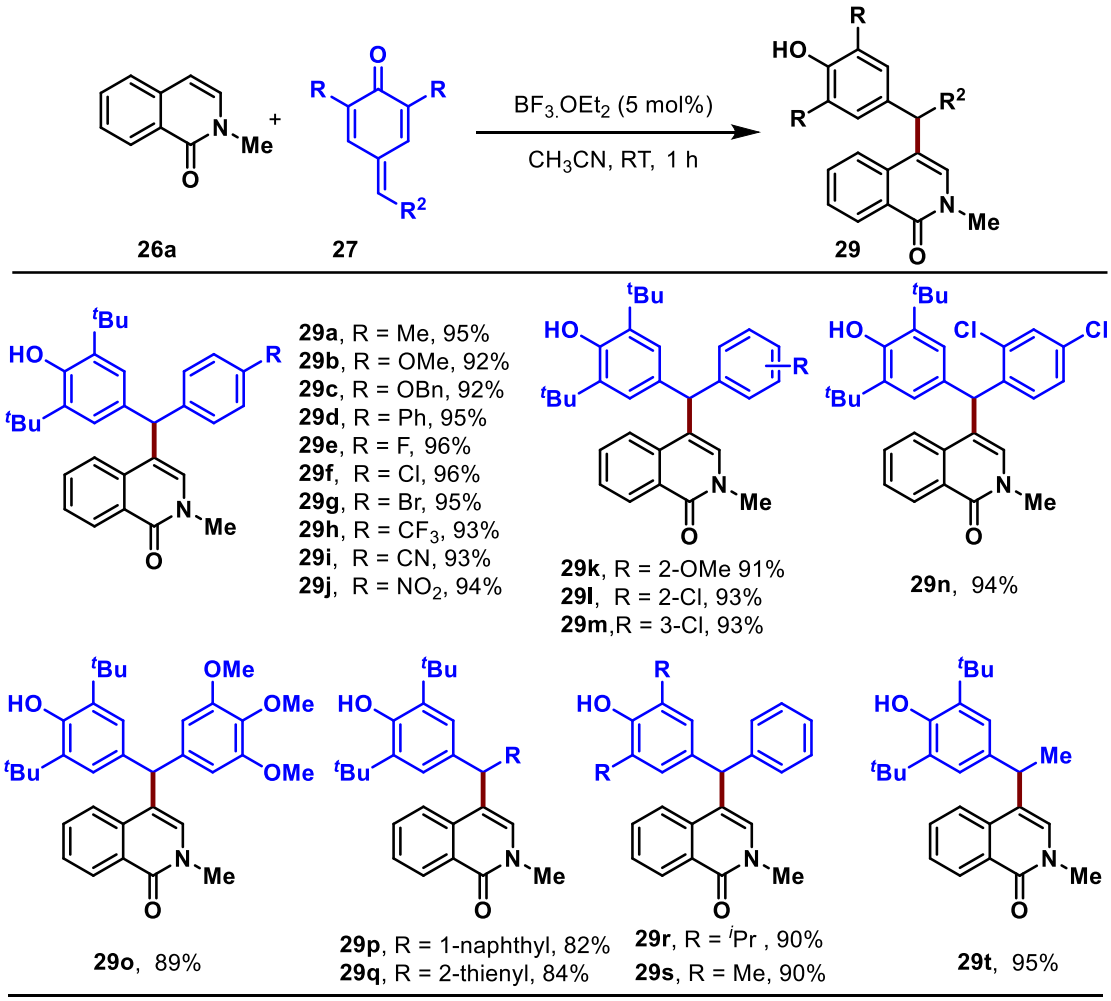
Table 2.1.2 Scope of the Reaction: Substituents on the Isoquinolin-1(2*H*)-ones[a,b]



[a]All reactions were performed with 0.19 mmol **26a-q**, 1.1 equiv. **27a & 27q**, 5 mol% $BF_3{\cdot}OEt_2$, dry CH_3CN (2.0 mL). [b]Isolated yields.

of isoquinolones were suitable for this reaction with good to excellent yields. Isoquinolones bearing C-6 substituted electron donating, halo, and electron-withdrawing groups reacted with *p*-QMs **27a** to provide the corresponding products (**28a-28f**) in excellent yields (90-95%).

Table 2.1.3 Scope of the Reaction: Substituents on the *p*-QMs[a,b]



[a]All reactions were performed with 0.19 mmol **26a**, 1.1 equiv. **27b-t**, 5 mol% $BF_3{\cdot}OEt_2$, dry CH_3CN (2.0 mL). [b]Isolated yields.

Further, C-5 and C-8 bromo-substituted isoquinolones also deliver the desired products in excellent yields (**28g-28h**, 90-91%). In addition, 6, 7 dimethoxy substituted isoquinolone is well tolerated, resulting desired product **28i** in 90% yield. Moreover, when the benzoisoquinolone substrate was submitted to the standard reaction conditions, product **28j** was isolated in 92% yield. It is important to noting here that various *N*-substitutions on isoquinolone, such as ethyl, butyl, allyl and propargyl, underwent a smooth transformation to give their corresponding products (**28k**−**28n**) in good to excellent yields. Similarly, *N*-phenyl and benzyl-substituted isoquinolones

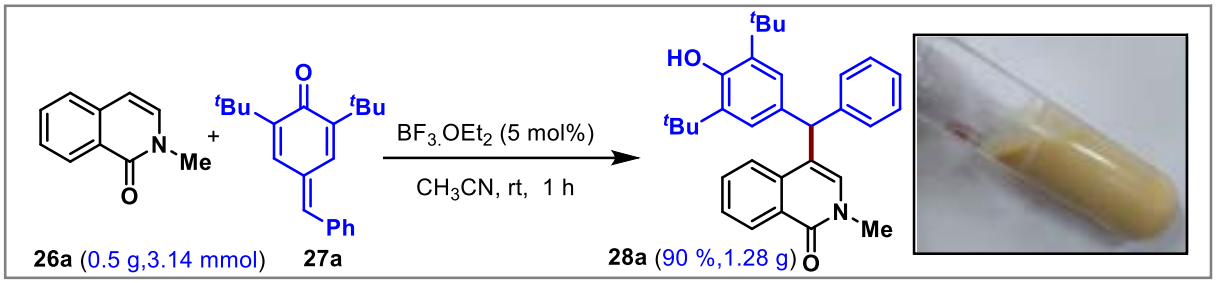
are also applicable in this process to furnish the required product in excellent yield (**28o-28p**, 89-92%). Interestingly, unprotected isoquinolones with **27a** & **27q** also gave desired product in excellent yields (**28q-28r**, 92% & 85%) under optimal reaction condition.

2.1.4.3 Scope of the Reaction: Substituents on the *p*-QMs

Next, the scope of *para*-quinone methides (*p*-QMs) **27** was tested under optimal reaction conditions. As shown in Table 2.1.3, *p*-QMs **27** with electron-donating, electron-withdrawing substituents at the *para*-, ortho-*, or meta*-positions of the phenyl ring were well tolerated, and the desired products **29a**−**29m** were obtained in excellent yields (91–96%). Furthermore, the di- and tri-substituted aromatic rings proceeded efficiently and resulted in good to excellent yields of the corresponding products (**29n-29o**, 89−94%). Additionally, *p*-QMs with bulky naphthyl groups are also compatible and produce **29p** in 82% yield. Moreover, *p*-QMs derived from heterocyclic rings such as 2-thienyl reacted efficiently with **26a** to produce the corresponding products **29q** in 84% yield. Moreover, this approach can work with the C2 and C6 positions of *p*-QMs with isopropyl and methyl substitutions (**29r-29s**). Notably, the alkyl-derived *p*-QMs were also amenable in this strategy to provide product **29t** in 95% yield.

2.1.4.4 Gram-Scale Experiment and Product Transformations

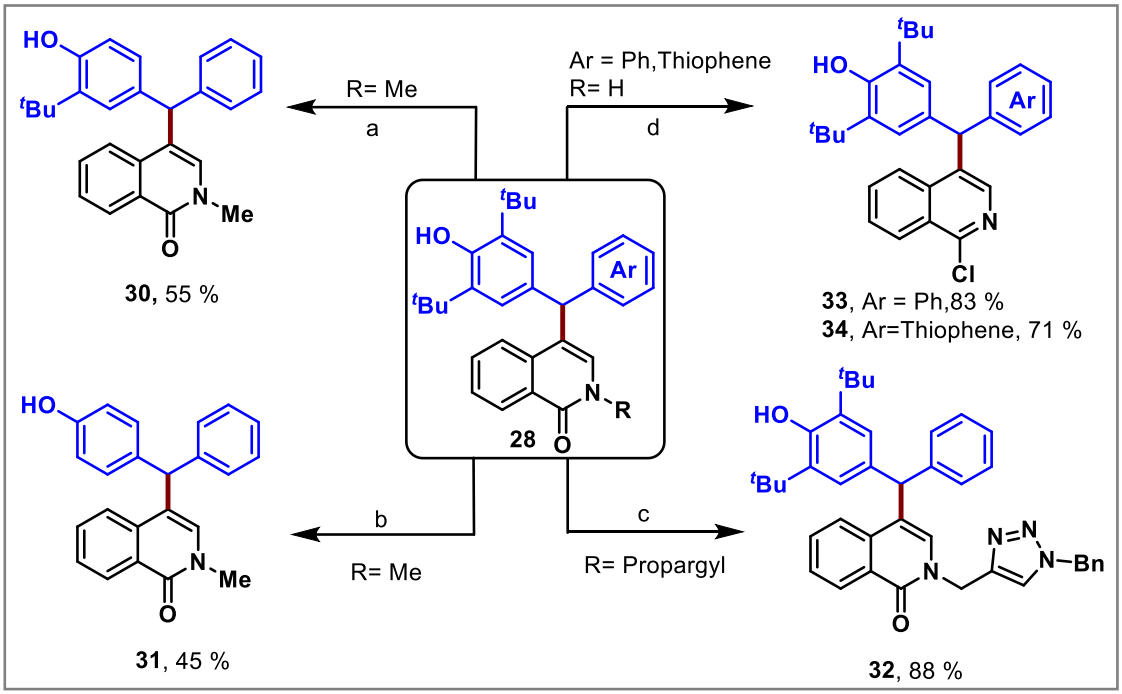
To show the synthetic utility of this reaction, a gram scale experiment was performed under optimal conditions and obtained **28a** in 90 % yield, which indicates the method is suitable for scale-up. (Scheme 2.1.10).



Scheme 2.1.10 Gram scale preparation

Further, the synthetic relevance of this protocol was also demonstrated by performing a few interesting organic transformations of compound **28** (Scheme 2.1.13). The bulk *tert*-butyl group was removed using $AlCl_3$ (retro-Friedel−Crafts reaction) to afford the deprotected product **30** (monoalkylated, 1.5 equiv. of $AlCl_3$)/**31** (di dealkylation, 3 equiv. of $AlCl_3$). Further, compound **28** has been converted into medicinally relevant tricyclic 1, 2, 3-triazoles **32** *via* intermolecular cycloaddition of alkyne and benzyl azide. The unprotected isoquinolones products **28q/28r**

were successfully converted to the corresponding 1-chloro isoquinoline derivative **33/34** in 83/71% yield upon reaction with phosphorus oxychloride.

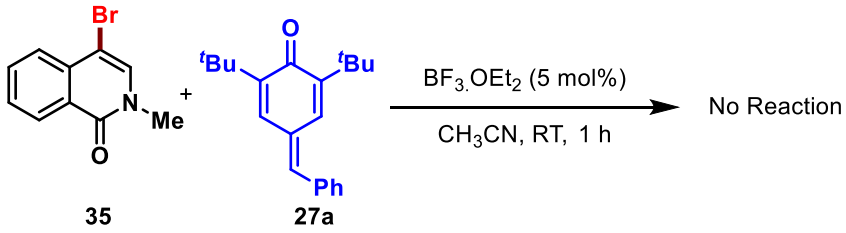


Reaction conditions: a) $AlCl_3$ (1.5 equiv), dry toluene, rt, 2 h; b) $AlCl_3$ (3 equiv), dry toluene, rt, 2 h; c) BnN_3,$CuSO_4$, sodium ascorbate, $^tBuOH/H_2O$ rt, 6 h; d) $POCl_3$ (3 mL), reflux, 12 h.

Scheme 2.1.11 Product transformations

2.1.4.5 Control Experiment and Plausible Reaction Mechanism

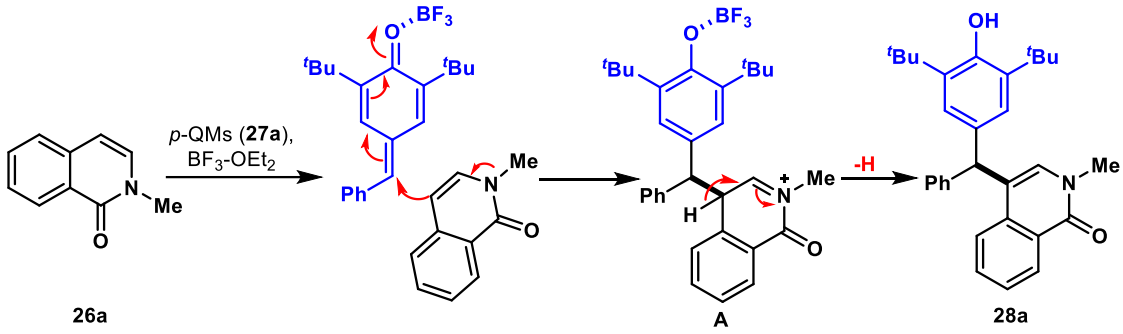
To ascertain the regioselectivity of this transformation, we carried out the alkylation of isoquinolone, wherein the C-4 position is blocked by bromide. In that case, we did not observe the product formation indicating the reaction is highly regioselective (Scheme 2.1.12).



Scheme 2.1.12 Control experiment

A plausible mechanism for this transformation is depicts in Scheme 2.1.13. First, *p*-QMs **27a** was activated by $BF_3.Et_2O$, leading to the formation of highly electrophilic methylenic carbon. Afterwards, conjugated nucleophilic attack by C-4 position from

isoquinolone **26a**, forming intermediate **A**. Further, aromatization result the formation of a desired product **28a**



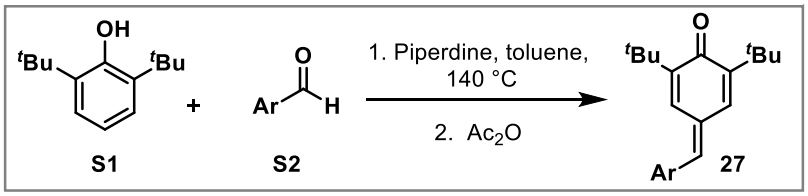
Scheme 2.1.13 A plausible mechanism

2.1.5 Conclusion

In summary, we developed a simple and straightforward strategy for the direct C-4 alkylation isoquinolin-2-(1*H*)-ones employing *p*-QMs as an alkylating agent for the first time. The current method employs $BF_3.OEt_2$ as a catalyst; the reaction proceeds smoothly at ambient temperature and shows a broad substrate scope and good functional group tolerance. We believe this simple strategy provides a rapid and convenient way to synthesize substituted isoquinolin-2-(1*H*)-one derivatives.

2.1.6 Experimental Section

2.1.6.1 General Procedure for the Preparation of *p*-Quinone Methides (*p*-QMs)[21]:



Scheme 2.1.14 Preparation of *p*-quinone methides.

2,6-di-*tert*-butylphenol (1.0 equiv) and 1.0 equiv of aldehyde were dissolved in toluene and the mixture was heated to 140 °C in a Dean−Stark apparatus (oil bath). Piperidine (2.0 equiv) was added dropwise over 1 h, and the reaction mixture was refluxed for 6-12 h. After cooling just below the boiling point of the mixture, acetic anhydride (2.0 equiv) was added and stirring was continued for 15 min. Then the reaction mixture was poured into an ice-water, extracted with DCM (3 x 200 mL), and dried over Na_2SO_4, the solvent was evaporated, and the

residue was dried in vacuo. The crude products were purified by flash column chromatography using petroleum ether as eluent, affording the desired *p*-QMs **27**.

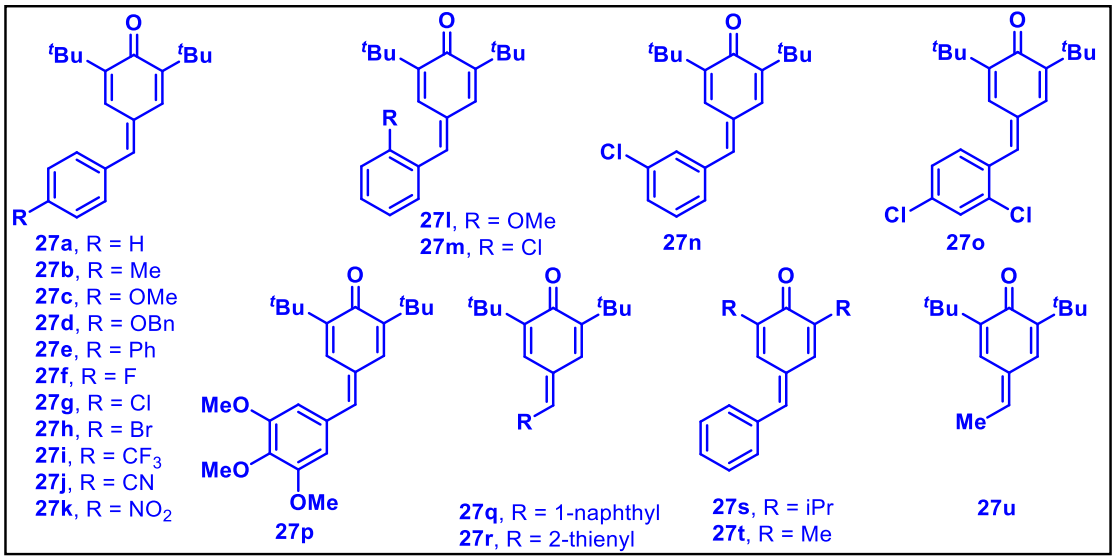
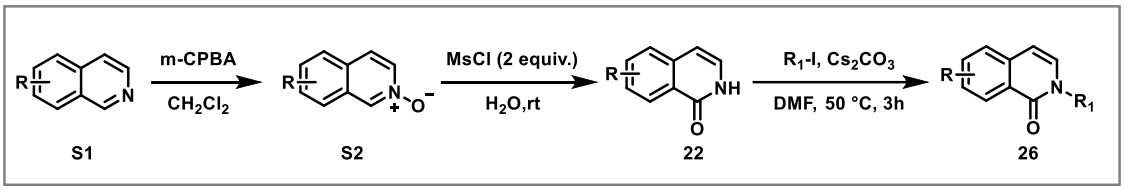


Fig. 2.1.2 Structures of *p*-Quinone Methides used in this study.

2.1.6.2 General Procedure for the Preparation of Isoquinolin-2(1*H*)-one[22]:



Scheme 2.1.15 Preparation of Substituted Isoquinolin-2(1*H*)-one

General procedure for the synthesis of substituted isoquinoline N-oxides (S2):

To a solution of the corresponding quinolines substrate (1 equiv) in CH_2Cl_2, *m*-chloroperbenzoic acid (1.5 equiv) was added at 0 °C. The reaction mixture was allowed to stir at room temperature for 24 h. Next, saturated aq. $NaHCO_3$ solution was added to the reaction mixture. Then it was extracted with CH_2Cl_2 (50mL x 3) and the organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain the pure isoquinoline *N*-oxides **S2**.

General procedure for the synthesis of isoquinolin-2(1H)-one (22):

In a round-bottom flask isoquinoline *N*-oxide (1 equiv.), H_2O and MsCl (2 equiv) was added. The reaction mixture was stirred at room temperature for 10 min. After completion of

the reaction (detected by TLC), the reaction mixture was subjected to filtration and vacuum drying to obtain an isoquinolin-2(1*H*)-one **22**.

General Procedure for Preparation of Various *N*-substituted Isoquinolone (26):

In a 10 mL round-bottom flask isoquinolin-1(2*H*)-ones (1.0 equiv), alkyl or aryl halide (1.5 equiv), and cesium carbonate (1.5 equiv) in DMF was added. The reaction was heated to 50

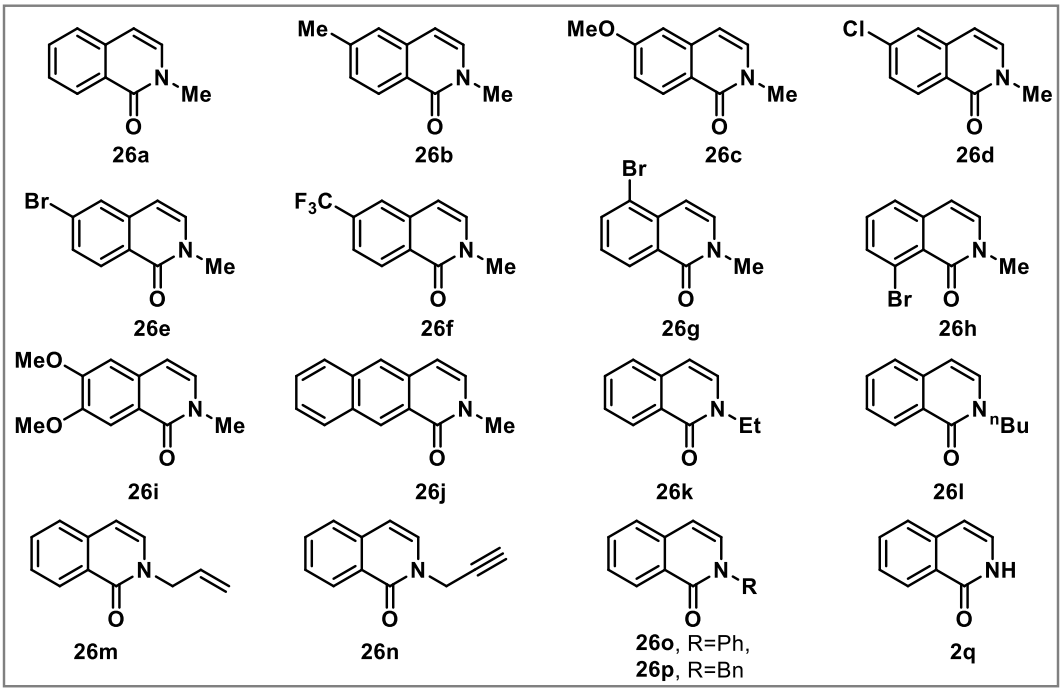


Fig. 2.1.3 Structures of isoquinolin-2(1*H*)-one used in this study.

°C in an oil bath for 3 h. After completion of the reaction (detected by TLC), reaction mixture was diluted with EtOAc and organic layer was washed with water (3 x 20 mL). Organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to obtain the pure *N*-substituted isoquinolones **26**.

2.1.6.3 General Procedure for the Synthesis of C-4 diarylmethylated isoquinolin-1(2*H*)-one derivatives:

The isoquinolin-1(2*H*)-one **26** (1 equiv., 0.19 mmol), *p*-QM's **27** (1.1 equiv) in CH_3CN (2 mL) were taken into an oven dried 5 mL screw-cap reaction vial equipped with a magnetic stir bar. Then, $BF_3{\cdot}OEt_2$ (5 mol %) dissolved in CH_3CN (0.2 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 1h. After completion of the reaction (detected by TLC), the solvent was removed under reduced pressure, and the residue was directly

loaded over a silica gel column and eluted using an petroleum ether/ethyl acetate mixture to obtain a pure C-4 diarylmethylated isoquinolin-1(2*H*)-one derivatives **28/29**.

2.1.6.4 Control Experiments Procedure:

The 4-bromo isoquinolin-1(2*H*)-one **35** (0.12 mmol), *p*-QM's **27a** (1.1 equiv) in CH_3CN (2 mL) were taken into an oven dried 5 mL screw-cap reaction vial equipped with a magnetic stir bar. Then, $BF_3{\cdot}OEt_2$ (5 mol %) dissolved in CH_3CN (0.2 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 1h, and the reaction was monitored by TLC.

2.1.6.5 Procedure for Product Transformations:

(a) Procedure for Synthesis of 30: To a solution of **28a** (50 mg, 0.11 mmol) in dry toluene (3 mL) was added $AlCl_3$ (22 mg, 0.16 mmol) under an argon atmosphere, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with 10 mL of ice-cold water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using a petroleum ether/ethyl acetate mixture as an eluent to afford **30** (24 mg, 55%).

(b) Procedure for Synthesis of 31: To a solution of **28a** (50 mg, 0.11 mmol) in dry toluene (3 mL) was added $AlCl_3$ (44 mg, 0.33 mmol) under an argon atmosphere, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with 10 mL of ice-cold water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using a petroleum ether/ethyl acetate mixture as an eluent to afford **31** (17 mg, 45%).

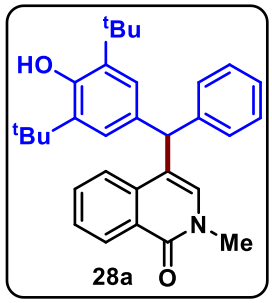
(a) Procedure for the Synthesis of 32: To a solution of $CuSO_4.\ 5H_2O$ (3.4 mg, 0.02 mmol), sodium ascorbate (8.3 mg, 0.04 mmol), in ^{t}BuOH/H_2O (1:2 v/v, 2.0 mL) was added a compound **27n** (50 mg, 0.10 mmol) and benzyl azide (14 mg, 0.10 mmol) at room temperature. The resultant mixture was stirred for 8 h. After completion of the reaction (detected by TLC), then CH_2Cl_2 (5 mL) was added to dissolve the crude product. The organic layer was washed with H_2O followed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was

subjected to column chromatography on silica gel using a petroleum ether/ethyl acetate mixture as an eluent to afford **32** (56 mg, 88%).

(b) Procedure for the Synthesis of 33/34: In a 10 mL round-bottom flask, compound (**28q**/**28r**, 50 mg, 1 equiv.) and phosphorus oxychloride (3 mL) was added. The resulting reaction mixture was then heated under reflux for 12 h until completion of the reaction (detected by TLC). Then phosphorus oxychloride was removed by vacuum distillation, and the crude residue was dissolved in ethyl acetate (8 mL). This solution was successively washed with saturated $NaHCO_3$ solution, water, and brine and then dried over anhydrous sodium sulfate. The solvent was then evaporated under reduced pressure to obtain a crude residue was subjected to column chromatography on silica gel using a petroleum ether/ethyl acetate mixture as an eluent to afford **33**/**34** (43 mg, 83% / 37.5 mg, 71%).

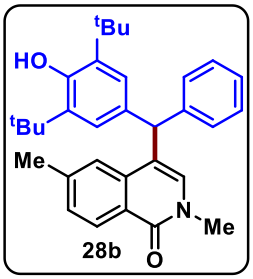
2.1.6.6 Characterization of 28a-r, 29a-t, 30, 31, 32, 33, 34 and 35:

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-methylisoquinolin-1(2*H*)-one



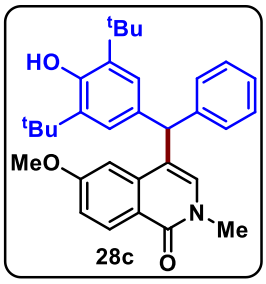
(28a): The product **28a** was obtained in 95% yield (80 mg, Off-white solid); **mp** = 237-239 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = δ 8.48 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.44 (ddd, *J* = 8.2, 6.7, 1.6 Hz, 1H), 7.30 (ddd, *J* = 7.5, 4.4, 1.2 Hz, 2H), 7.25 – 7.19 (m, 1H), 7.17 (dd, *J* = 5.2, 3.3 Hz, 2H), 6.89 (s, 2H), 6.36 (d, *J* = 0.9 Hz, 1H), 5.66 (s, 1H), 5.16 (s, 1H), 3.49 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.2, 152.4, 142.4, 136.4, 135.4, 133.4, 132.4, 131.7, 129.1, 128., 127.9, 126.5, 126.4, 125.9, 125.8, 123.8, 119.5, 50.6, 37.3, 34.3, 30.2; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{36}O_2N$ 454.2741; found 454.2749.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2,6-dimethylisoquinolin-1(2*H*)-one



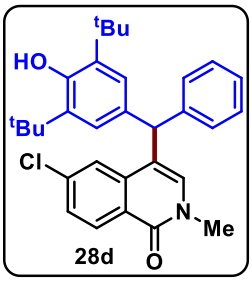
(28b): The product **28b** was obtained in 94% yield (76 mg, Off-white solid); **mp** = 263-265 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.35 (d, *J* = 8.2 Hz, 1H), 7.33 – 7.19 (m, 5H), 7.16 (d, *J* = 7.1 Hz, 2H), 6.88 (s, 2H), 6.33 (s, 1H), 5.63 (s, 1H), 5.12 (s, 1H), 3.46 (s, 3H), 2.33 (s, 3H), 1.34 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.2, 152.3, 142.9, 142.1, 136.8, 135.7, 133.3, 132.5, 129.1, 128.4, 128.1, 127.9, 126.4, 125.9, 123.7, 123.6 119.4, 50.6, 37.2, 34.3, 30.3, 22.1; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{38}O_2N$ 468.2897; found 468.2903.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-6-methoxy-2-methylisoquinolin-



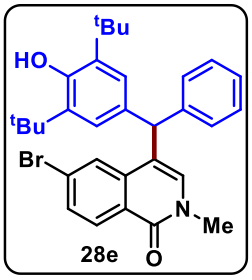
1(2*H*)-one (28c):The product **28c** was obtained in 92% yield (70.5 mg, Off-white solid); **mp** = 175-177 °C; R_f = 0.40 (petroleum ether:ethyl acetate =5:5); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.37 (d, *J* = 8.8 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.25 – 7.17 (m, 3H), 6.99 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.92 (s, 2H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.35 (s, 1H), 5.55 (s, 1H), 5.14 (s, 1H), 3.63 (s, 3H), 3.46 (s, 3H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.0, 161.9, 152.4, 142.7, 138.6, 135.9, 133.8, 132.2, 129.9, 129.1, 128.5, 126.5, 125.9, 119.8, 119.2, 115.8, 105.5, 55.1, 51.2, 37.1, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{38}O_3N$ 484.2846; found 484.2859.

6-Chloro-4-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-methylisoquinolin-



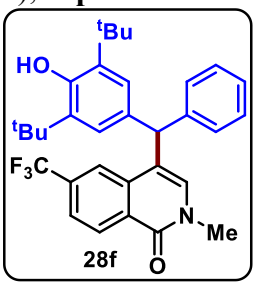
1(2*H*)-one (28d):The product **28d** was obtained in 95% yield (72 mg, Off-white solid); **mp** = 253-255 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.39 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.37 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.31 (dd, *J* = 7.9, 6.6 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.19 – 7.14 (m, 2H), 6.88 (s, 2H), 6.40 (s, 1H), 5.57 (s, 1H), 5.16 (s, 1H), 3.47 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 161.6, 152.5, 142.3, 138.4, 138.0, 135.9, 134.4, 131.9, 129.8, 129.0, 128.6, 126.9, 126.7, 125.9, 124.3, 123.5, 118.7, 50.6, 37.3, 34.3, 30.2; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{35}O_2NCl$ 488.2351; found 488.2357.

6-Bromo-4-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-methylisoquinolin-

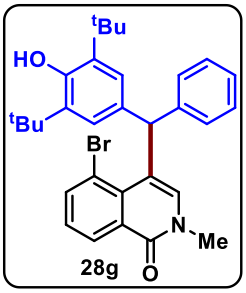


1(2H)-one (28e): The product **28e** was obtained in 93% yield (62.5 mg, Off-white solid); **mp** = 242-244 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.31 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.26 – 7.21 (m, 1H), 7.20 – 7.14 (m, 2H), 6.89 (s, 2H), 6.40 (d, *J* = 0.8 Hz, 1H), 5.56 (s, 1H), 5.16 (s, 1H), 3.47 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 161.7, 152.5, 142.2, 138.2, 135.9, 134.3, 131.9, 129.8, 129.7, 129.0, 128.6, 127.2, 126.7, 126.6, 125.9, 124.6, 118.7, 50.6, 37.3, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{35}O_2NBr$ 532.1846; found 532.1857.

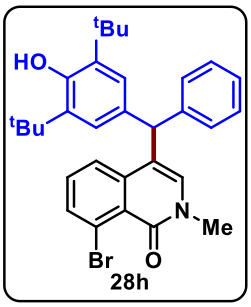
4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-methyl 6(trifluoromethyl) isoquinolin -1(2*H*)-one (28f):The product **28f** was obtained in 90% yield (62 mg, Off-white solid); **mp** = 245-247 °C; R_f = 0.40 (petroleum ether:ethyl acetate =5:5); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.57 (d, *J* = 8.4 Hz, 1H), 7.80 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27 – 7.23 (m, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 6.92 (s, 2H), 6.46 (s, 1H), 5.62 (s, 1H), 5.15 (s, 1H), 3.51 (s, 3H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 161.4, 152.6, 142.0, 136.7, 136.1, 134.3, 133.3, 133.0, 131.7, 129.1, 129.0 128.6, 128.1, 126.8, 125.8, 122.4, 121.5, 119.6, 50.9, 37.4, 34.3, 30.2;**^{19}F NMR (376 MHz, CDCl$_3$) δ** = -106.09 **HRMS (ESI$^+$)** *m/z*: [M]$^+$ calcd for $C_{32}H_{34}O_2NF_3$ 521.2536; found 521.2560.

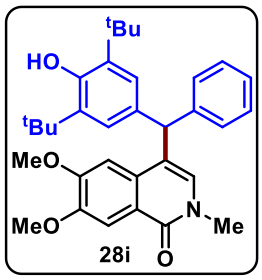


5-Bromo-4-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (28g):The product **28g** was obtained in 90% yield (60.5 mg, Off-white solid); **mp** = 122-124°C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.69 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.24 – 7.18 (m, 2), 7.12 (d, *J* = 7.2 Hz, 2H), 6.84 (s, 2H), 6.37 (s, 1H), 5.56 (s, 1H), 5.14 (s, 1H), 3.43 (s, 3H), 1.34 (s, 18H).; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 160.4, 152.4, 142.6, 139.6, 135.8, 134.3, 133.7, 132.1, 131.7, 129.1, 128.5, 126.6, 126.0, 123.7, 123.1, 123.0, 118.4, 51.0, 37.9, 34.3, 30.2.;**HRMS (ESI$^+$)** *m/z*: [M +H]$^+$ calcd for $C_{31}H_{35}O_2NBr$ 532.1846; found 532.1857.



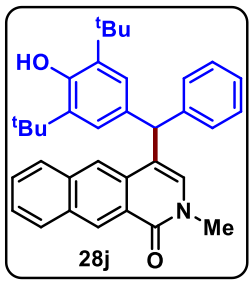
8-Bromo-4-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (28h):The product **28h** was obtained in 91% yield (61 mg, Off-white solid); **mp** = 192-194 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.71 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.32 – 7.20 (m, 4H), 7.13 (d, *J* = 7.4 Hz, 2H), 6.85 (s, 2H), 6.38 (s, 1H), 5.57 (s, 1H), 5.14 (s, 1H), 3.44 (s, 3H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 160.5, 152.5, 142.7, 139.6, 135.9, 134.4, 133.8, 132.2, 131.7, 129.1, 128.5, 126.6, 125.9, 123.7, 123.2, 118.4, 51.0, 37.9, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{31}H_{35}O_2NBr$ 532.1846; found 532.1864.

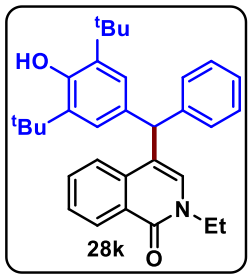


4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-6,7-dimethoxy-2-methylisoquinolin-1(2*H*)-one (28i): 

The product **28i** was obtained in 90% yield (63 mg, Off-white solid); **mp** = 246-248 °C; R_f = 0.40 (petroleum ether:ethyl acetate =5:5); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.82 (s, 1H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.25 – 7.18 (m, 3H), 6.94 (s, 2H), 6.81 (s, 1H), 6.28 (s, 1H), 5.52 (s, 1H), 5.14 (s, 1H), 3.97 (s, 3H), 3.62 (s, 3H), 3.48 (s, 3H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 161.5, 152.4, 152.3, 148.6, 142.7, 135.9, 132.2, 131.9, 131.8, 129.1, 128.5, 126.5, 125.8, 120.1, 119.2, 107.7, 105.1, 56.1, 55.5, 51.6, 37.3, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{33}H_{40}O_4N$ 514.2952; found 514.2958.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-methylbenzo[g]isoquinolin-1(2*H*)-one (28j): The product **28j** was obtained in 92% yield (66.5 mg, Off-white solid); **mp** = 200-202 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 9.08 (s, 1H), 8.01 (d, *J* = 4.5 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.35 – 7.19 (m, 5H), 6.99 (s, 2H), 6.33 (s, 1H), 5.81 (s, 1H), 5.17 (s, 1H), 3.50 (s, 3H), 1.38 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.7, 152.4, 142.9, 135.8, 134.7, 132.7, 132.5, 131.3, 129.1, 129.0, 128.4, 127.9, 127.74, 126.5, 125.9, 125.8, 124.4, 122.8, 119.5, 50.9, 36.9, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{35}H_{38}O_2N$ 504.2897; found 504.2906.

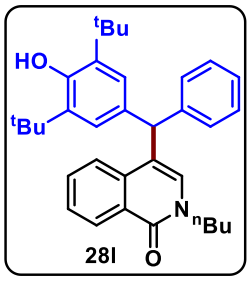


4-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-ethylisoquinolin-1(2*H*)-one (28k): 

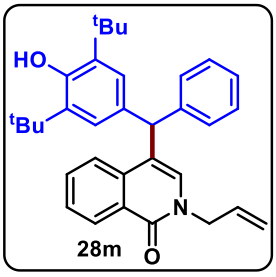
The product **28k** was obtained in 94% yield (76 mg, Yellow solid); **mp** = 193-195 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.48 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.53 (dtd, *J* = 9.6, 8.2, 1.3 Hz, 2H), 7.44 (ddd, *J* = 8.1, 6.8, 1.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.19 (m, 1H), 7.19 – 7.13 (m, 2H), 6.88 (s, 2H), 6.34 (d, *J* = 0.9 Hz, 1H), 5.67 (s, 1H), 5.15 (s, 1H), 4.13 – 4.00 (m, 1H), 3.88 – 3.77 (m, 1H), 1.35 (s, 18H), 1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 161.5, 152.3, 142.9, 136.5, 135.7, 132.4, 131.9, 131.8, 129.1, 128.4, 128.1, 126.5, 126.4, 126.1, 125.9, 123.70, 119.91, 50.6, 44.0, 34.3, 30.3, 14.5; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{32}H_{38}O_2N$ 468.2897; found 468.2906.

2-Butyl-4-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)isoquinolin-1(2*H*)-one (28l): The product **28l** was obtained in 93% yield (69 mg, Off-white solid); **mp** = 184-186 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.49 (d, *J* = 7.9 Hz,

1H), 7.54 (m, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.22 (dd, *J* = 12.7, 5.3 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 2H), 6.89 (s, 2H), 6.31 (s, 1H), 5.67 (s, 1H), 5.15 (s, 1H), 4.05 (m, *J* = 13.4, 6.8 Hz, 1H), 3.78 – 3.67 (m, 1H), 1.70 – 1.59 (m, 2H), 1.36 (s, 18H), 1.30 – 1.24 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 161.6, 152.3, 142.9, 136.5, 135.8, 132.9, 132.5, 131.8, 129.1, 128.4, 128.1, 126.5, 126.3, 126.1, 125.9, 123.7, 119.3, 50.6, 48.9, 34.3, 31.1, 30.2, 19.7, 13.6; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{34}H_{42}O_2N$ 496.3210; found 496.3217.

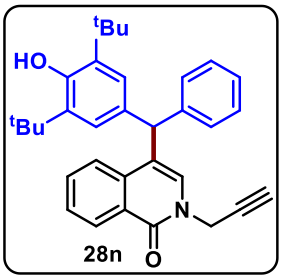


2-Allyl-4-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)isoquinolin-1(2*H*)-one



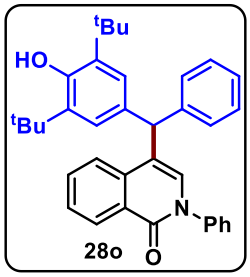
(28m): The product **28m** was obtained in 92% yield (71.5 mg, Off-white solid); **mp** = 170-172 °C; ***R$_f$*** = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.50 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.1 Hz, 2H), 6.88 (s, 2H), 6.33 (s, 1H), 5.87 (dq, *J* = 10.9, 5.7 Hz, 1H), 5.66 (s, 1H), 5.15 (d, *J* = 4.7 Hz, 2H), 5.03 (d, *J* = 16.6 Hz, 1H), 4.65 (dd, *J* = 15.3, 5.7 Hz, 1H), 4.41 (dd, *J* = 15.3, 5.9 Hz, 1H), 1.35 (s, 18H).; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 161.5, 152.3, 142.8, 136.5, 135.7, 132.8, 132.4, 132.0, 131.9, 129.0, 128.4, 128.3, 126.5, 126.4, 126.0 125.9, 123.8, 119.7, 117.6, 50.6, 50.4, 34.3, 30.2; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{33}H_{38}O_2N$ 480.2897; found 480.2904.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-(prop-2-yn-1-yl)isoquinolin-



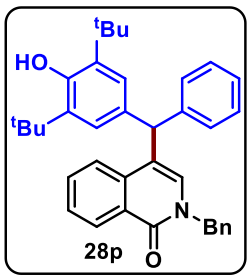
1(2*H*)-one (28n):The product **28n** was obtained in 92% yield (72 mg, Off-white solid); **mp** = 98-100 °C; ***R$_f$*** = 0.40 (petroleum ether:ethyl acetate =7:3); **^{1}H NMR (500 MHz, CDCl$_3$) δ** = 8.49 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.48 – 7.42 (m, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 8.8 Hz, 3H), 6.93 (s, 2H), 6.71 (s, 1H), 5.69 (s, 1H), 5.19 (s, 1H), 4.83 (dd, *J* = 17.6, 2.6 Hz, 1H), 4.69 (dd, *J* = 17.6, 2.6 Hz, 1H), 2.25 (t, *J* = 2.5 Hz, 1H), 1.38 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,CDCl$_3$) δ** = 161.2, 152.4, 142.7, 136.5, 135.8, 132.2, 132.2, 130.7, 129.0, 128.4, 128.2, 126.6, 126.5, 125.9, 125.6, 123.9, 120.2, 77.4, 73.9, 50.7, 37.2, 34.3, 30.2; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{33}H_{36}O_2N$ 478.2741; found 478.2753.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-phenylisoquinolin-1(2*H*)-one (28o): The product **28o** was obtained in 89% yield (62 mg, Off-white solid); **mp** = 164-166 °C;



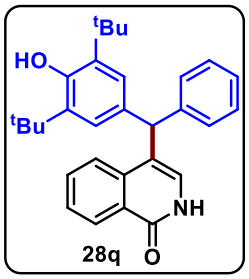
***R*$_f$** = 0.40 (petroleum ether:ethyl acetate =7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.52 (d, *J* = 7.9 Hz, 1H), 7.63 – 7.52 (m, 2H), 7.49 – 7.38 (m, 3H), 7.36 – 7.25 (m, 5H), 7.20 (d, *J* = 7.1 Hz, 3H), 6.91 (s, 2H), 6.57 (s, 1H), 5.69 (s, 1H), 5.09 (s, 1H), 1.32 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 161.5, 152.4, 142.7, 141.5, 136.7, 135.8, 132.9, 132.4, 132.2, 129.1, 129.0, 128.6, 128.5, 127.7, 126.8, 126.6, 126.5, 126.4, 125.9, 123.9, 119.8, 50.6, 34.3, 30.2; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{36}H_{38}O_2N$ 516.2897; found 516.2905.

2-Benzyl-4-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)isoquinolin-1(2*H*)-one (28p):



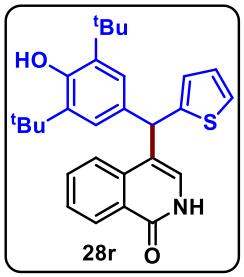
The product **28p** was obtained in 92% yield (62 mg, Off-white solid); **mp** = 204-206 °C; ***R*$_f$** = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.50 (d, *J* = 7.8 Hz, 1H), 7.51 (dt, *J* = 8.2, 4.9 Hz, 2H), 7.46 – 7.40 (m, 1H), 7.29 – 7.22 (m, 5H), 7.21 – 7.15 (m, 3H), 7.11 (d, *J* = 7.1 Hz, 2H), 6.82 (s, 2H), 6.40 (s, 1H), 5.62 (s, 1H), 5.23 (d, *J* = 14.5 Hz, 1H), 5.11 (s, 1H), 4.92 (d, *J* = 14.5 Hz, 1H), 1.31 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 161.7, 152.3, 142.8, 136.9, 136.5, 135.7, 132.3, 132.2, 132.0, 129.0, 128.7, 128.4, 128.3, 127.8, 127.7, 126.5, 126.4, 126.1, 125.9, 123.8, 119.8, 51.8, 50.7, 34.3, 30.2; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{37}H_{40}O_2N$ 530.3054; found 530.3063.

4-((3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)isoquinolin-1(2*H*)-one) (28q):



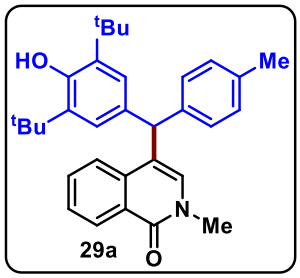
The product **28q** was obtained in 92 % yield (84 mg, Off-white solid); **mp** = 204-206 °C; ***R*$_f$** = 0.40 (petroleum ether:ethyl acetate =3:7); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 10.25 (s, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.49 – 7.43 (m, 1H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.24 – 7.15 (m, 3H), 6.87 (s, 2H), 6.47 (d, *J* = 5.4 Hz, 1H), 5.66 (s, 1H), 5.13 (s, 1H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 163.4, 152.4, 142.8, 137.6, 135.8, 132.6, 132.4, 129.2, 128.5, 128.2, 127.7, 126.6, 126.5, 126.1, 125.8, 124.2, 120.7, 50.7, 34.4, 30.3.;**HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{30}H_{33}O_2N$ 440.2584; found 440.2586.

4-((3,5-di-tert-butyl-4-hydroxyphenyl)(thiophen-2-yl)methyl)isoquinolin-1(2*H*)-one (28r):



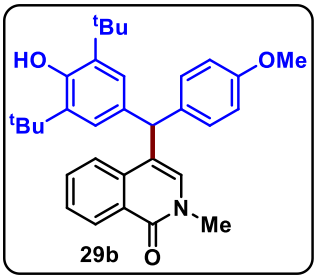
The product **28r** was obtained in 85 % yield (78 mg, Off-white solid); **mp** = 206-208 °C; R_f = 0.40 (petroleum ether:ethyl acetate =4:6); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.06 (s, 1H), 8.45 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.20 (dd, *J* = 5.1, 0.8 Hz, 1H), 6.99 (s, 2H), 6.93 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.79 – 6.62 (m, 2H), 5.88 (s, 1H), 5.16 (s, 1H), 1.38 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 152.9, 147.3, 137.5, 136.1, 134.7, 132.9, 132.5, 129.9 127.9, 127.8, 126.9 ,126.8, 126.6, 125.5, 124.7, 123.9, 120.9, 45.7, 34.5, 30.5.; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{28}H_{32}O_2NS$ 446.2148; found 446.2148.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(p-tolyl)methyl)-2-methylisoquinolin-1(2*H*)-one



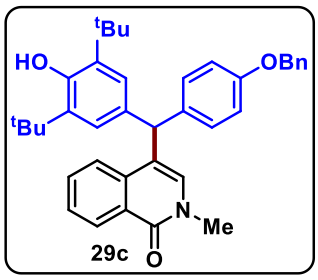
(29a): The product **29a** was obtained in 95% yield (84 mg, Off-white solid); **mp** = 236-238 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.48 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.52 (ddd, *J* = 10.5, 9.6, 4.4 Hz, 2H), 7.46 – 7.39 (m, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.89 (s, 2H), 6.36 (s, 1H), 5.61 (s, 1H), 5.14 (s, 1H), 3.49 (s, 3H), 2.32 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.2, 152.3, 139.9, 136.7, 135.9, 135.7, 133.1, 132.6, 131.8, 129.1, 128.9, 127.9, 126.4, 125.9, 123.9, 119.7, 50.3, 37.2, 34.3, 30.3, 21.0; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{32}H_{38}O_2N$ 468.2897; found 468.2906.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)-2-methylisoquinolin-



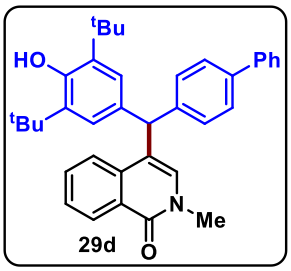
1(2*H*)-one (29b):The product **29b** was obtained in 92% yield (84 mg, Off-white solid); **mp** = 189-191 °C; R_f = 0.30 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.48 (d, *J* = 7.6 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.43 (dd, *J* = 11.1, 4.1 Hz, 1H), 7.07 (d, *J* = 5.7 Hz, 2H), 6.89 (s, 2H), 6.83 (dd, *J* = 8.9, 2.2 Hz, 2H), 6.35 (s, 1H), 5.61 (s, 1H), 5.16 (s, 1H), 3.78 (s, 3H), 3.49 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.2, 158.0, 152.3, 136.6, 135.7, 135.0, 133.1, 132.7, 131.7, 130.0, 127.9, 126.4, 125.8, 123.9, 119.8, 113.7, 55.1, 49.8, 37.2, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{32}H_{38}O_3N$ 484.2846; found 484.2854.

4-((4-(Benzyloxy)phenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-2-methylisoquinolin-



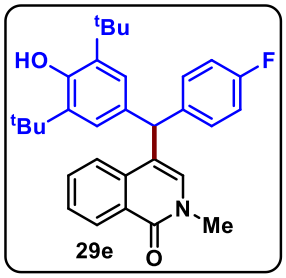
1(2*H*)-one (29c):The product **29c** was obtained in 92% yield (97 mg, Off-white solid); **mp** = 174-176 °C; R_f = 0.30 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.47 (d, *J* = 7.6 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.47 – 7.40 (m, 3H), 7.40 – 7.35 (m, 2H), 7.35 – 7.29 (m, 1H), 7.06 (d, *J* = 5.7 Hz, 2H), 6.95 – 6.85 (m, 4H), 6.34 (s, *J* = 0.6 Hz, 1H), 5.60 (s, 1H), 5.13 (s, 1H), 5.04 (s, 2H), 3.49 (s, 3H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.4, 157.5, 152.5, 137.2, 136.8, 135.9, 135.5, 133.3, 132.9, 131.9, 130.3, 128.7, 128.1, 128.1, 127.7, 126.6, 126.1, 126.0, 124.1, 119.9, 114.9, 70.1, 50.0, 37.3, 34.5, 30.5; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{42}O_3N$ 560.3159; found 560.3169.

4-([1,1'-Biphenyl]-4-yl(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-2-methylisoquinolin-

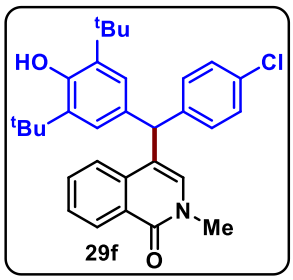


1(2*H*)-one (29d): The product **29d** was obtained in 95% yield (95 mg, Yellow solid); **mp** = 222-224 °C; R_f = 0.50 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.46 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.56 (dd, *J* = 10.4, 3.3 Hz, 3H), 7.49 (ddd, *J* = 9.6, 6.6, 2.4 Hz, 3H), 7.44 – 7.35 (m, 3H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.23 – 7.18 (m, 2H), 6.90 (s, 2H), 6.38 (s, 1H), 5.66 (s, 1H), 5.14 (s, 1H), 3.47 (s, 3H), 1.33 (s, 18H).; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.2, 152.4, 142.1, 140.6, 139.1, 136.6, 135.8, 133.2, 132.3 131.8, 129.5, 128.7, 127.9, 127.1, 127.0, 126.9, 126.5, 125.9, 123.9, 119.4, 50.3, 37.3, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{37}H_{40}O_2N$ 530.3054; found 530.3062.

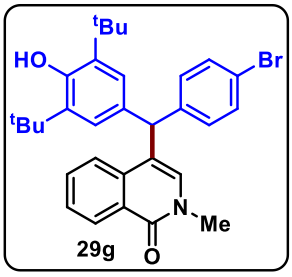
4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-fluorophenyl)methyl)-2-methylisoquinolin-



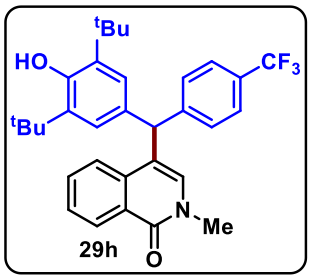
1(2*H*)-one (29e): The product **29e** was obtained in 96% yield (85 mg, Off-white solid); **mp** = 228-230 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (500 MHz, CDCl$_3$) δ** = 8.48 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.12 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.98 (t, *J* = 8.6 Hz, 2H), 6.85 (s, 2H), 6.33 (s, 1H), 5.63 (s, 1H), 5.16 (s, 1H), 3.49 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,CDCl$_3$) δ** = 162.4, 162.2, 160.5, 152.5, 138.7, 136.5, 135.9, 133.3, 132.2, 131.8, 130.6, 130.5, 128.0, 126.5, 125.9, 125.8, 123.7, 119.3, 115.4, 115.2, 49.9, 37.3, 34.3, 30.3; **^{19}F NMR (376 MHz, CDCl$_3$) δ = -**116.37 **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{35}O_2NF$ 472.2646; found 472.2655.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-chlorophenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (29f): 

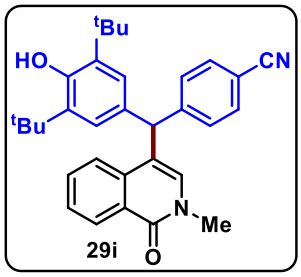
The product **29f** was obtained in 96% yield (88 mg, Off-white solid); **mp** = 222-224 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (500 MHz, CDCl$_3$) δ** = 8.49 (d, *J* = 7.8 Hz, 1H), 7.58 – 7.42 (m, 3H), 7.32 – 7.23 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.87 (s, 2H), 6.34 (s, 1H), 5.63 (s, 1H), 5.19 (s, 1H), 3.50 (s, 3H), 1.37 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,CDCl$_3$) δ** = 162.3, 152.7, 141.8, 136.6 136.1, 133.5, 132.4, 132.0, 130.6, 128.8, 128.2, 126.7, 126.1, 126.0, 123.8, 119.1, 50.2, 37.4, 34.5, 30.4; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{31}H_{35}O_2NCl$ 488.2351; found 488.2359.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-bromophenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (29g): 

The product **29g** was obtained in 95% yield (95 mg, Off-white solid); **mp** = 219-221 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (500 MHz, CDCl$_3$) δ** = 8.48 (d, *J* = 7.9 Hz, 1H), 7.52 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.45 (dd, *J* = 13.3, 7.1 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.86 (s, 2H), 6.33 (s, 1H), 5.60 (s, 1H), 5.18 (s, 1H), 3.49 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,CDCl$_3$) δ** = 162.3, 152.7, 142.3, 136.5, 136.1, 133.5, 132.0, 131.9, 131.7, 131.0, 128.2, 126.7, 126.1, 126.0, 123.8, 120.5, 119.0, 50.3, 37.4, 34.5, 30.4; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{31}H_{35}O_2NBr$ 532.1846; found 532.1858.

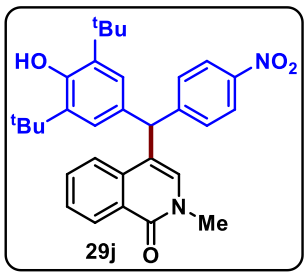
4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-(trifluoromethyl)phenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (29h): 

The product **29h** was obtained in 93% yield (91 mg, Off-white solid); **mp** = 165-167 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.60 – 8.44 (m, 1H), 7.59 – 7.50 (m, 3H), 7.46 (t, *J* = 7.0 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.85 (s, 2H), 6.35 (s, 1H), 5.70 (s, 1H), 5.19 (s, 1H), 3.50 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.2, 152.7, 147.3, 136.3, 136.1, 133.4, 131.9, 131.4, 129.4, 128.9, 128.6, 128.1, 126.7, 125.9, 125.4, 125.4, 123.6, 122.8, 118.5, 50.5, 37.4, 34.3, 30.2; **^{19}F NMR (376 MHz, CDCl$_3$) δ** = -62.31 **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{32}H_{35}O_2NF_3$ 522.2614; found 522.2623.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)methyl)ben- zonitrile (29i): 

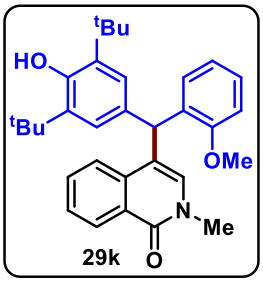
29i

The product **29i** was obtained in 93% yield (84 mg, off-white solid); **mp** = 241-243 °C; R_f = 0.40 (petroleum ether:ethyl acetate =5:5); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.48 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.49 (m, 1H), 7.48 – 7.43 (m, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.82 (s, 2H), 6.33 (d, *J* = 0.6 Hz, 1H), 5.69 (s, 1H), 5.28 (s, 1H), 5.23 (s, 1H), 3.49 (s, 3H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.0, 152.8, 148.8, 136.1, 133.5, 132.3, 131.9, 130.9, 129.8, 128.2, 126.7, 125.9, 125.8, 123.4, 118.8, 117.9, 110.4, 50.7, 37.3, 34.3, 30.1; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{35}O_2N_2$ 479.2693; found 479.2703.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (29j): 

29j

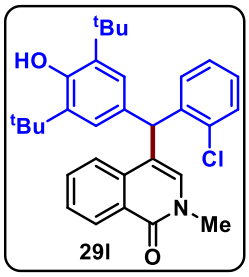
The product **29j** was obtained in 94% yield (88 mg, Yellow solid); **mp** = 228-230 °C; R_f = 0.40 (petroleum ether:ethyl acetate =5:5); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.49 (dd, *J* = 7.9, 1.3 Hz, 1H), 8.20 – 8.12 (m, 2H), 7.55 – 7.44 (m, 2H), 7.37 (ddd, *J* = 11.0, 8.8, 1.5 Hz, 3H), 6.84 (s, 2H), 6.35 (s, 1H), 5.73 (s, 1H), 5.22 (s, 1H), 3.50 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.1, 152.9, 150.9, 146.6, 136.3, 136.0, 133.6, 132.0, 130.8, 129.9, 128.2, 126.8, 125.9, 123.8, 123.4, 117.9, 50.6, 37.4, 34.4, 30.2; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{35}O_4N_2$ 499.2591; found 499.2597.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (29k): 

29k

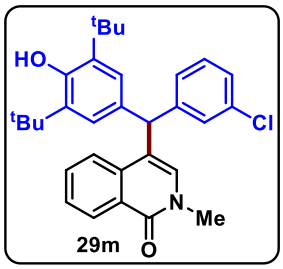
The product **29k** was obtained in 91% yield (83 mg, Off-white solid); **mp** = 212-214 °C; R_f = 0.40 (petroleum ether:ethyl acetate =5:5); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.46 (d, *J* = 7.7 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.42 (ddd, *J* = 8.1, 6.6, 1.6 Hz, 1H), 7.22 (td, *J* = 8.3, 1.8 Hz, 1H), 6.94 – 6.88 (m, 4H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.36 (s, 1H), 6.03 (s, 1H), 5.11 (s, 1H), 3.78 (s, 3H), 3.48 (s, 3H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.3, 156.6, 152.2, 136.8, 135.5, 132.3, 131.8, 131.7, 131.4, 129.7, 127.8, 127.7, 126.3, 125.9, 125.8, 123.7, 120.2, 119.7, 110.6, 55.6, 43.0, 37.2, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{38}O_3N$ 484.2846; found 484.2850.

4-((2-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-2-methylisoquinolin-



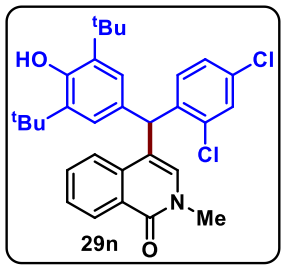
1(2*H*)-one (29l):The product **29l** was obtained in 93% yield (86 mg, Off-white solid); **mp** = 194-196 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.48 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.48 – 7.39 (m, 3H), 7.22 – 7.11 (m, 2H), 6.99 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.89 (s, 2H), 6.35 (s, 1H), 6.00 (s, 1H), 5.16 (s, 1H), 3.49 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.2, 152.5, 140.7, 136.4, 135.8, 134.2, 132.9, 131.9, 130.3, 130.2, 129.8, 127.98, 127.93, 126.6, 126.5, 126.0, 125.8, 123.5, 118.6, 47.3, 37.3, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{35}O_2NCl$ 488.2351; found 488.2362.

4-((3-Chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-2-methylisoquinolin-

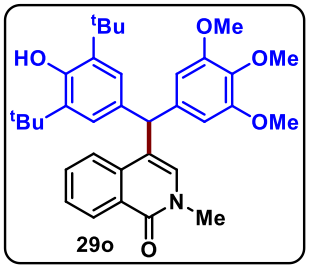


1(2*H*)-one (29m):The product **29m** was obtained in 93% yield (86 mg, Off-white solid); **mp** = 226-228 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.49 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 7.1 Hz, 1H), 7.46 (dd, *J* = 14.0, 7.1 Hz, 2H), 7.21 (t, *J* = 8.1 Hz, 3H), 7.04 (d, *J* = 6.0 Hz, 1H), 6.85 (s, 2H), 6.34 (s, 1H), 5.61 (s, 1H), 5.17 (s, 1H), 3.50 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.2, 152.6, 145.2, 136.4, 136.0, 134.4, 133.4, 131.9, 131.6, 129.7, 129.2, 128.1, 127.3, 126.8, 126.6, 125.98, 125.91, 123.6, 118.7, 50.4, 37.3, 34.4, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{35}O_2NCl$ 488.2351; found 488.2363.

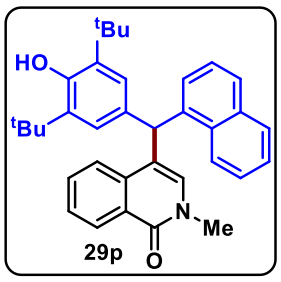
4-((3,5-di-tert-butyl-4-hydroxyphenyl)(2,4-dichlorophenyl)methyl)-2-methylisoquinolin-



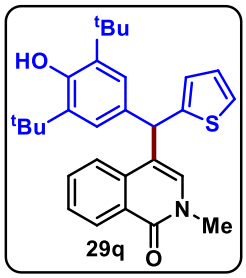
1(2*H*)-one (29n): The product **29n** was obtained in 94% yield (93 mg, Off-white solid); **mp** = 245-247 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.48 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 9.3, 4.8 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.13 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 2H), 6.34 (s, 1H), 5.92 (s, 1H), 5.18 (s, 1H), 3.49 (s, 3H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.2, 152.7, 139.5, 136.2, 136.1, 134.9, 132.9, 132.1, 131.0, 129.7, 129.6, 128.1, 126.9, 126.7, 125.9, 123.3, 118.1, 47.0, 37.3, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{34}O_2NCl_2$ 422.1961; found 422.1978.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(3,4,5-trimethoxyphenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (29o): 

The product **29o** was obtained in 89% yield (91 mg, Off-white solid); **mp** = 155-157 °C; R_f = 0.40 (petroleum ether:ethyl acetate =4:6); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.47 (d, *J* = 7.7 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.47 – 7.42 (m, 1H), 6.91 (s, 2H), 6.34 (s, 3H), 5.55 (s, 1H), 5.14 (s, 1H), 3.83 (s, 3H), 3.72 (s, 6H), 3.49 (s, 3H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.2, 153.1, 152.5, 138.7, 136.7, 136.5, 135.8, 133.1, 132.0, 131.9, 127.9, 126.5, 125.8, 125.7, 123.8, 119.6, 106.4, 60.9, 56.1, 50.9, 37.3, 34.4, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{34}H_{42}O_5N$ 544.3057; found 544.3071.

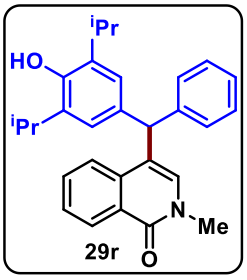
4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(naphthalen-1-yl)methyl)-2-methylisoquinolin-1(2*H*)-one (29p): 

The product **29p** was obtained in 82% yield (78 mg, Off-white solid); **mp** = 192-194 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.53 – 8.49 (m, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.41 (m, 5H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 7.1 Hz, 1H), 6.97 (s, 2H), 6.35 (d, *J* = 7.6 Hz, 2H), 5.14 (s, 1H), 3.43 (s, 3H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.2, 152.5, 138.9, 136.6, 135.9, 134.0, 133.3, 132.0, 131.7, 131.6, 128.8, 128.0, 127.5, 127.0, 126.5, 126.3, 125.9, 125.5, 125.3, 123.9, 123.5, 119.3, 46.7, 37.2, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{35}H_{38}O_2N$ 504.2897; found 504.2901.

4-((3,5-Di-tert-butyl-4-hydroxyphenyl)(thiophen-2-yl)methyl)-2-methylisoquinolin-1(2*H*)-one (29q): 

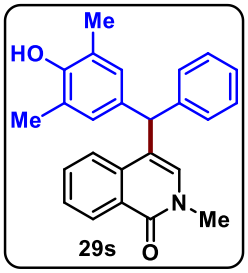
The product **29q** was obtained in 84% yield (73 mg, Off-white solid); **mp** = 196-198 °C; R_f = 0.40 (petroleum ether:ethyl acetate =5:5); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.49 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.57 (dd, *J* = 11.1, 4.0 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.20 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.01 (s, 2H), 6.93 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.74 (d, *J* = 3.4 Hz, 1H), 6.55 (s, 1H), 5.86 (s, 1H), 5.19 (s, 1H), 3.52 (s, 3H), 1.38 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 162.2, 152.7, 147.3, 136.4, 135.9, 132.7, 132.3, 131.9, 128.0, 126.7, 126.5, 126.3, 125.8, 125.3, 124.5, 123.4, 119.6, 45.6, 37.3, 34.3, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{29}H_{34}O_2NS$ 460.2305; found 460.2314.

4-((4-Hydroxy-3,5-diisopropylphenyl)(phenyl)methyl)-2-methylisoquinolin-1(2*H*)-one



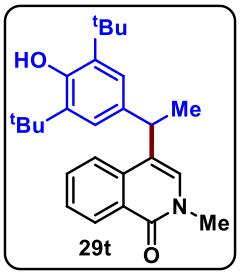
(29r): The product **29r** was obtained in 90% yield (72 mg, Off-white solid); **mp** = 237-239 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.47 (d, *J* = 7.7 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.43 (ddd, *J* = 8.2, 5.7, 2.6 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 1H), 7.18 – 7.12 (m, 2H), 6.77 (s, 2H), 6.34 (s, 1H), 5.66 (s, 1H), 4.86 (s, 1H), 3.48 (s, 3H), 3.17 – 3.05 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 12H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.3, 148.7, 142.9, 136.7, 133.8, 133.7, 133.3, 131.8, 129.2, 128.5, 127.9, 126.5, 126.4, 125.9, 124.5, 123.8, 119.4, 50.6, 37.3, 27.3, 22.7; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{29}H_{32}O_2N$ 426.2428; found 426.2433.

4-((4-hydroxy-3,5-dimethylphenyl)(phenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (29s):



The product **29s** was obtained in 90% yield (62.5 mg, Off-white solid); **mp** = 124-126 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.47 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.43 (ddd, *J* = 8.0, 5.4, 2.8 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.24 (dd, *J* = 12.5, 5.4 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 2H), 6.72 (s, 2H), 6.36 (s, 1H), 5.62 (s, 1H), 5.06 (bs, 1H), 3.49 (s, 3H), 2.19 (s, 6H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.3, 151.1, 142.7, 136.6, 133.4, 133.3, 131.9, 129.3, 129.2, 128.5, 127.9, 126.6, 125.8, 123.8, 123.3, 119.4, 50.0, 37.3, 16.1; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{24}O_2N$ 370.1802; found 370.1810.

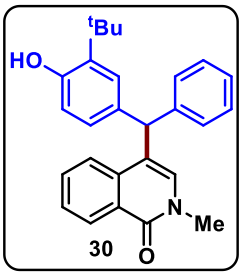
4-(1-(3,5-Di-tert-butyl-4-hydroxyphenyl)ethyl)-2-methylisoquinolin-1(2*H*)-one (29t):



The product **29t** was obtained in 95% yield (70 mg, Off-white solid); **mp** = 185-187 °C; R_f = 0.40 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.49 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.56 (t, 1H), 7.49 – 7.42 (t, 1H), 7.03 (s, 2H), 6.84 (s, 1H), 5.10 (s, 1H), 4.36 (q, *J* = 7.0 Hz, 1H), 3.61 (s, 3H), 1.62 (d, *J* = 7.1 Hz, 3H), 1.39 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.2, 152.1, 136.6, 135.8, 135.2, 131.7, 130.1, 128.0, 126.3, 126.0, 123.9, 123.3, 120.7, 38.1, 37.2, 34.3, 30.3, 22.1; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{34}O_2N$ 392.2584; found 392.2589.

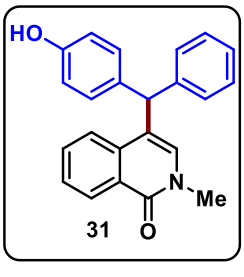
4-((3-(Tert-butyl)-4-hydroxyphenyl)(phenyl)methyl)-2-methylisoquinolin-1(2*H*)-one (30):

The product **30** was obtained in 55 % yield (24 mg, Off-white solid); **mp** = 253-255 °C; R_f = 0.40 (petroleum ether:ethyl acetate =5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 9.27 (s, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 7.60 (dt, *J* = 8.2, 4.8 Hz, 2H), 7.50 – 7.43 (m, 1H), 7.33 – 7.26 (m, 2H), 7.19 (dd, *J* = 9.9, 4.1 Hz, 3H), 7.03 (d, *J* = 1.8 Hz, 1H), 6.74 (dt, *J* = 18.6, 5.1 Hz, 2H), 6.54 (s, 1H), 5.76 (s, 1H), 3.39 (s, 3H), 1.27 (s, 9H); **^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ** = 160.7, 154.3, 143.3, 136.2, 135.1, 133.3, 131.9, 128.9, 128.4, 127.3, 127.3 , 126.5, 126.4, 125.4, 123.9, 118.2, 116.0, 49.1, 36.7, 34.3, 29.4; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{27}H_{28}O_2N$ 398.2115; found 398.2121.

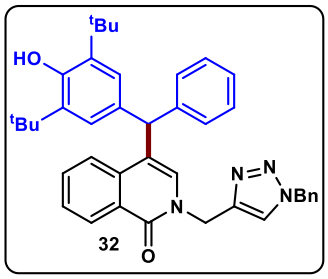


4-((4-Hydroxyphenyl)(phenyl)methyl)-2-methylisoquinolin-1(2H)-one (31):

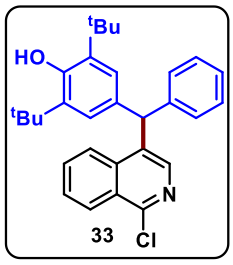
The product **31** was obtained in 45% yield (17 mg, Off-white solid); **mp** = 265-267 °C; R_f = 0.40 (petroleum ether:ethyl acetate =4:6); **^{1}H NMR (500 MHz, DMSO-d$_6$) δ** = 9.33 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 5.4 Hz, 2H), 7.46 (ddd, *J* = 8.0, 5.7, 2.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.20 (dd, *J* = 15.3, 7.4 Hz, 3H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.52 (s, 1H), 5.77 (s, 1H), 3.39 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d$_6$) δ** = 160.8, 155.9, 142.9, 136.2, 133.4, 132.4, 131.9, 130.1, 129.0, 128.4, 127.3, 126.5, 126.4 125.4, 123.9, 118.0, 115.3 48.8, 36.6; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{23}H_{20}O_2N$ 342.1489; found 342.1493.



2-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-4-((3,5-di-tert-butyl-4 hydroxy-phenyl)(phenyl)methyl)isoquinolin-1(2*H*)-one (32) : The product **32** was obtained in 88 % yield (56 mg, yellow solid); **mp** = 111-113 °C; R_f = 0.35 (petroleum ether:ethyl acetate =6:4); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.43 (d, *J* = 7.1 Hz, 1H), 7.62 (s, 1H), 7.58 – 7.48 (m, 2H), 7.45 – 7.40 (m, 1H), 7.38 – 7.30 (m, 4H), 7.30 – 7.18 (m, 6H), 7.15 – 7.10 (m, 2H), 6.84 (s, 2H), 6.70 (d, *J* = 0.8 Hz, 1H), 5.63 (s, 1H), 5.45 (d, *J* = 2.8 Hz, 2H), 5.14 (s, 2H), 1.34 (s, 18H).**^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 161.6, 152.4, 142.7, 136.8, 135.8, 134.4, 132.4, 132.1, 132.1, 129.1, 129.1, 129.1, 128.7, 128.5, 128.5, 128.1, 128.0, 126.5, 126.5, 126.0, 125.9, 123.9, 120.1, 54.1, 50.6, 44.6, 34.3, 30.2.**HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{28}H_{32}O_2NS$ 446.2148; found 446.2148.

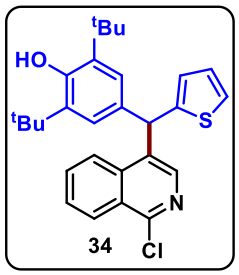


2,6-di-tert-butyl-4-((1-chloroisoquinolin-4-yl)(phenyl)methyl)phenol (33) :



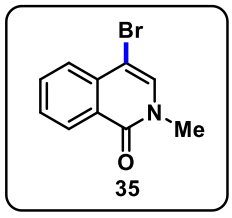
The product **33** was obtained in 83 % yield (43 mg, white solid); **mp** = 207-209 °C; R_f = 0.40 (petroleum ether:ethyl acetate =9:1); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.30 (dd, *J* = 6.8, 2.6 Hz, 1H), 7.93 – 7.85 (m, 1H), 7.64 (s, 1H), 7.61 – 7.53 (m, 2H), 7.23 – 7.17 (m, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 2H), 6.82 (s, 2H), 5.93 (s, 1H), 5.06 (s, 1H), 1.26 (s, 18H);**^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 152.5, 150.6, 142.9, 142.8, 136.7, 135.9, 134.1, 132.2, 131.1, 129.2, 128.5, 127.9, 126.9, 126.6, 126.4, 126.06, 124.3, 51.2, 34.3, 30.2.; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{30}H_{33}ONCl$ 458.2245; found 458.2250.

2,6-di-tert-butyl-4-((1-chloroisoquinolin-4-yl)(thiophen-2-yl)methyl)phenol (34) :



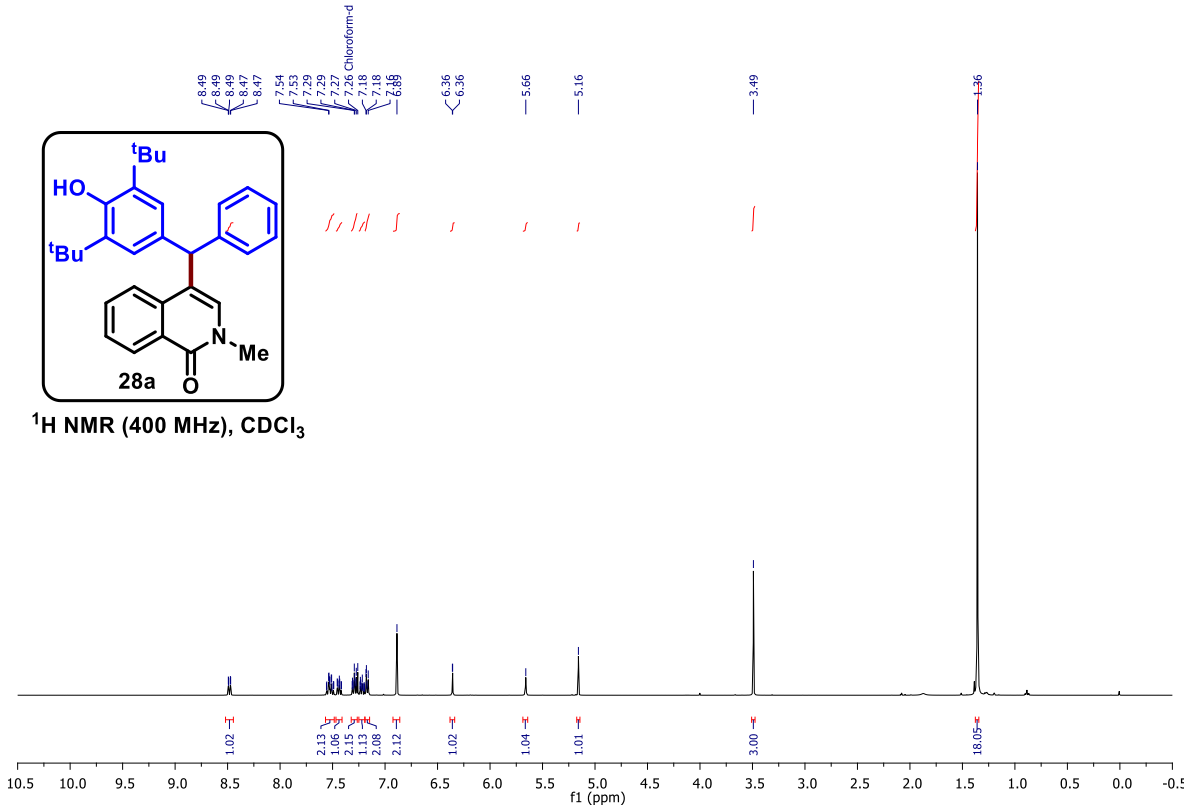
The product **7** was obtained in 71 % yield (37.5 mg, white solid); **mp** = 160-162 °C; R_f = 0.40 (petroleum ether:ethyl acetate =9:1); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.39 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.86 (s, 1H), 7.69 (ddd, *J* = 21.0, 14.2, 7.0 Hz, 2H), 7.21 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.01 (s, 2H), 6.91 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.66 (d, *J* = 3.4 Hz, 1H), 6.20 (s, 1H), 5.16 (s, 1H), 1.36 (s, 18H).;**^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 152.8, 150.9, 146.9, 142.2, 136.4, 136.0, 134.0, 132.1, 131.2, 127.9, 127.0, 126.7, 126.6, 126.4, 125.4, 124.7, 123.9, 46.2, 34.3, 30.2; **HRMS (ESI$^+$)** *m/z*: [M+H]$^+$ calcd for $C_{28}H_{31}ONClS$ 464.1809; found 464.1814.

4-bromo-2-methylisoquinolin-1(2*H*)-one (35):

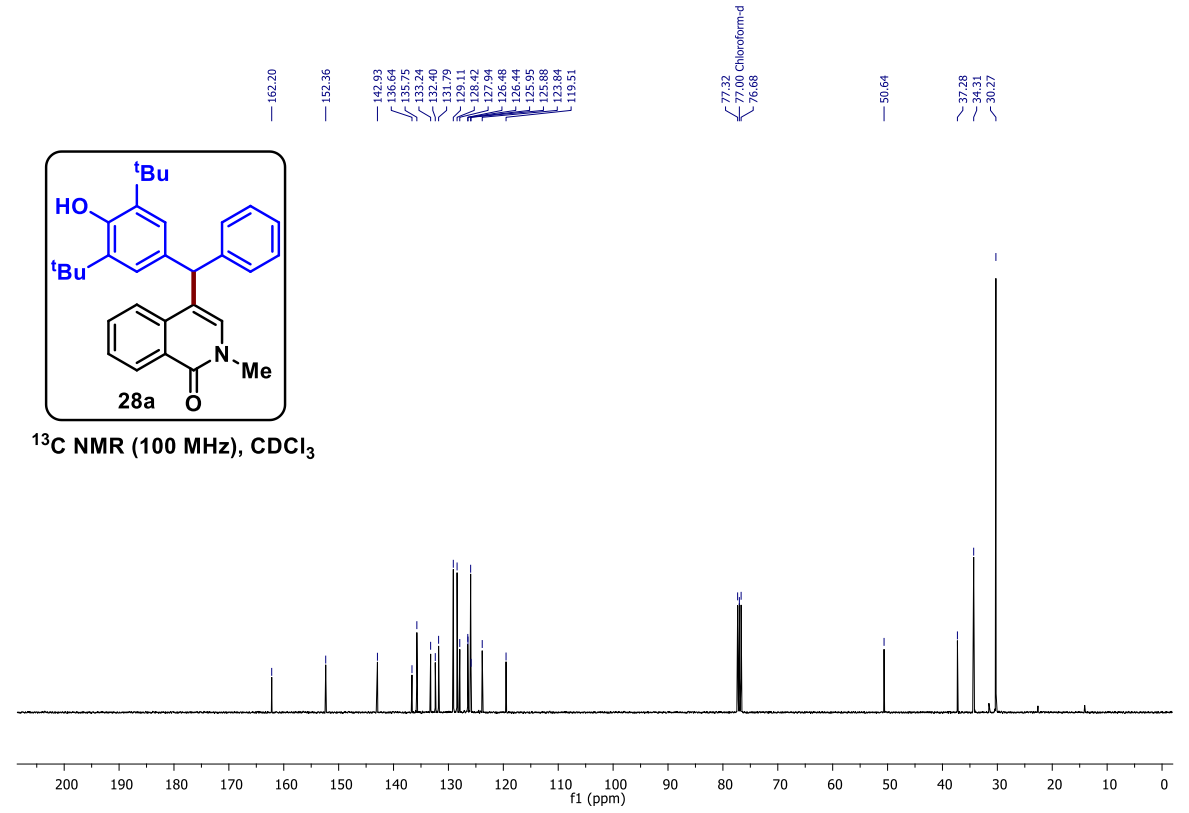


White solid; **mp** = 128-130 °C, **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.45 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.59 – 7.52 (m, 1H), 7.37 (s, 1H), 3.61 (s, 3H).**^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ** = 161.9, 135.7, 133.1, 133.0, 128.3, 127.9, 126.5, 125.9, 99.7, 37.1.

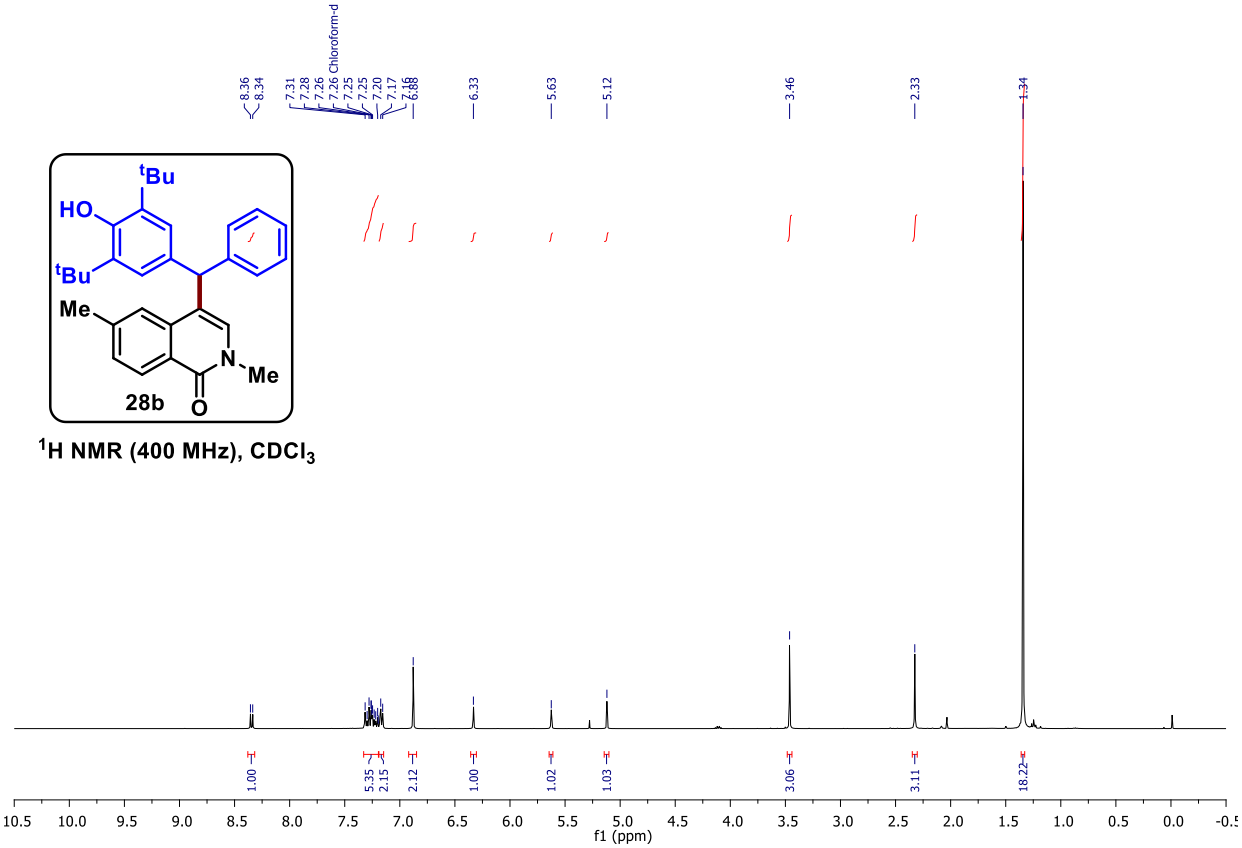
2.1.7 Spectral data for the representative compounds:



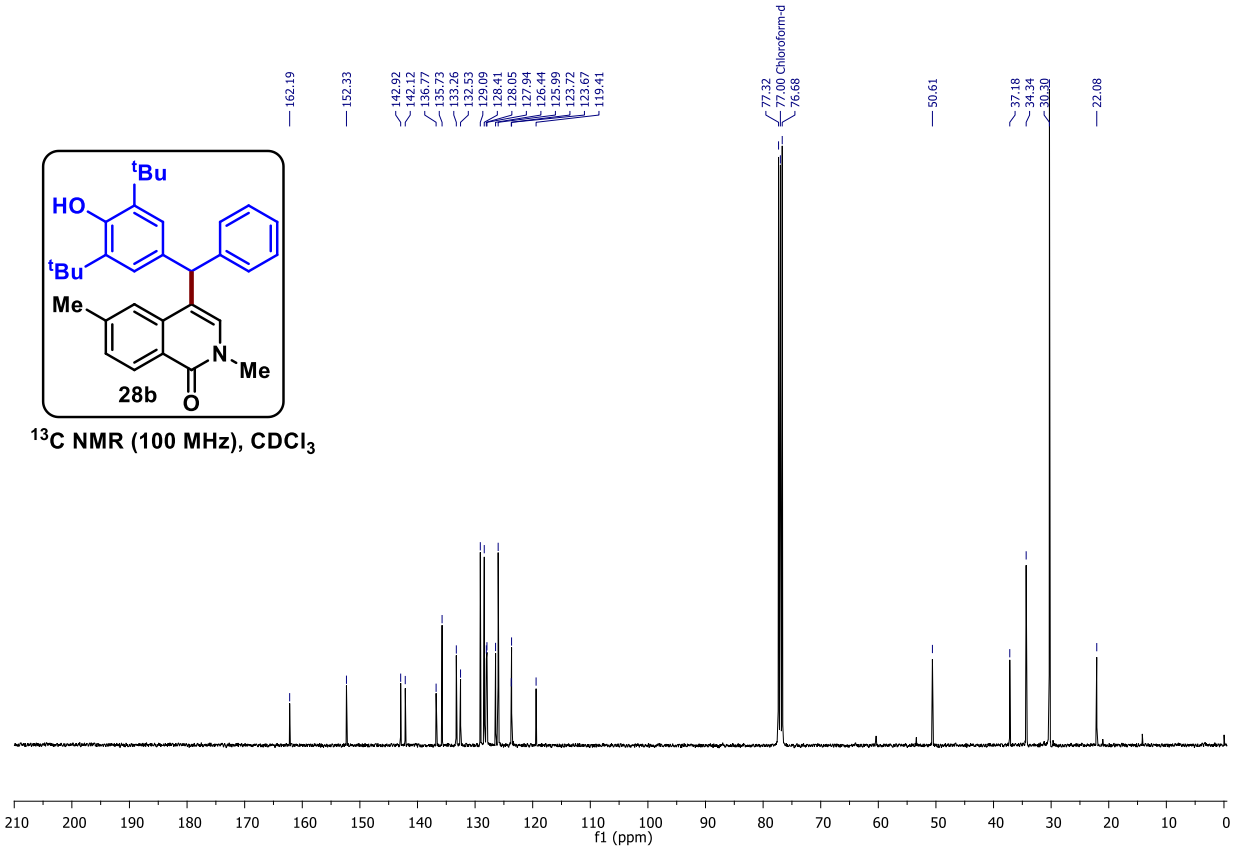
^{1}H NMR (400 MHz), $CDCl_3$



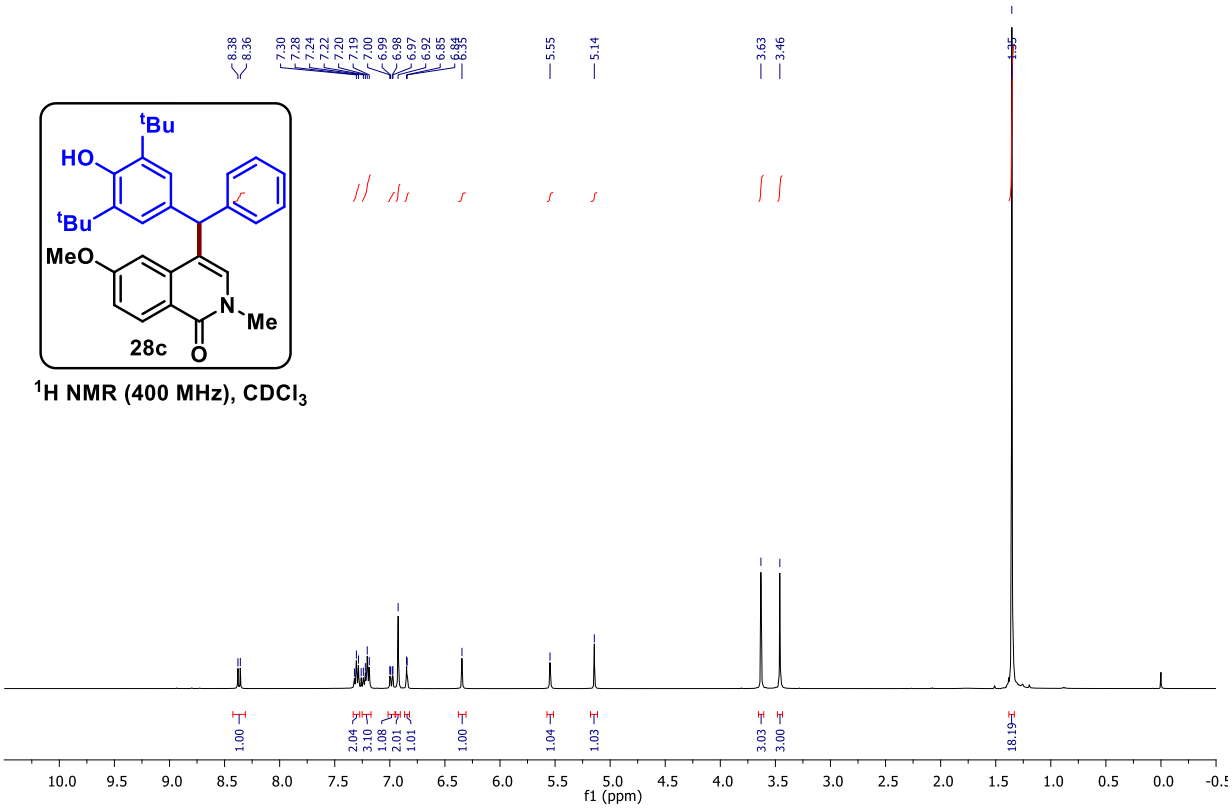
^{13}C NMR (100 MHz), $CDCl_3$



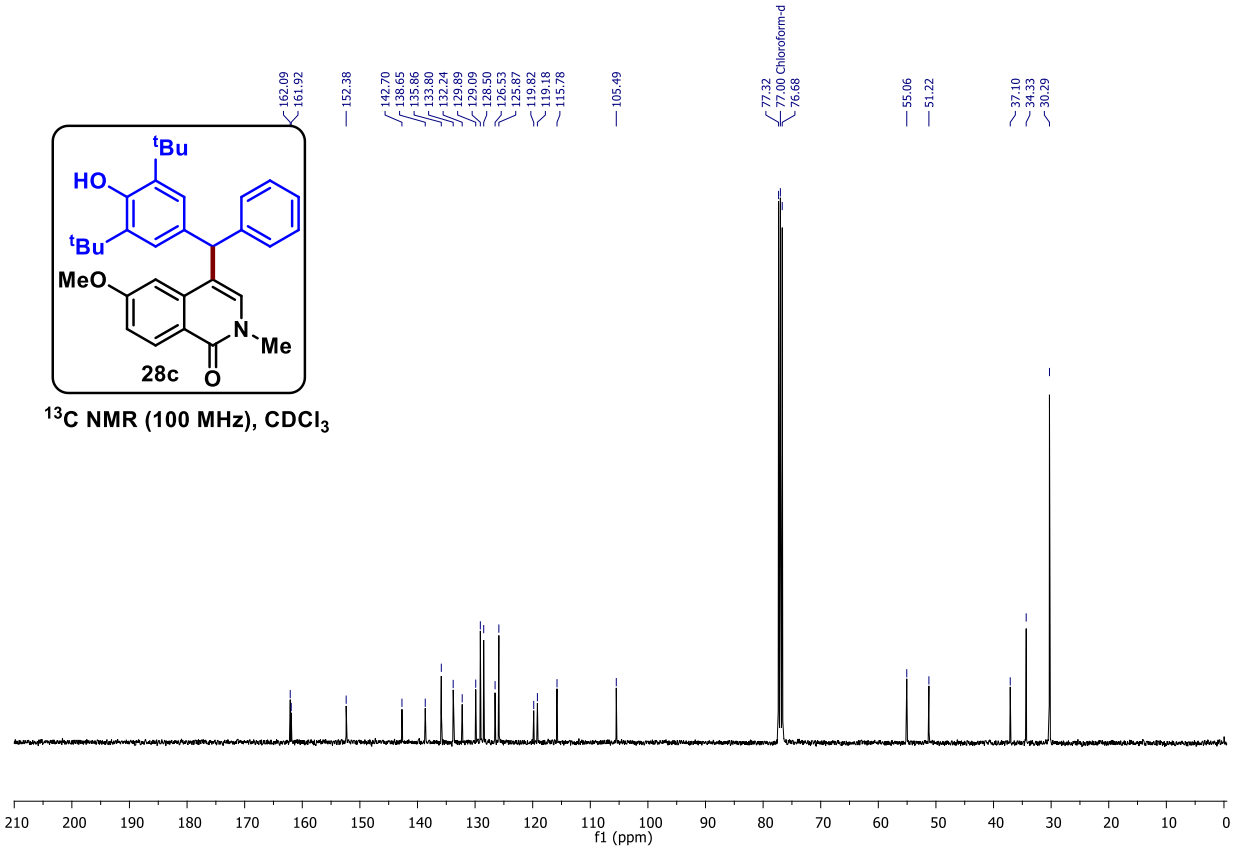
^{1}H NMR (400 MHz), $CDCl_3$



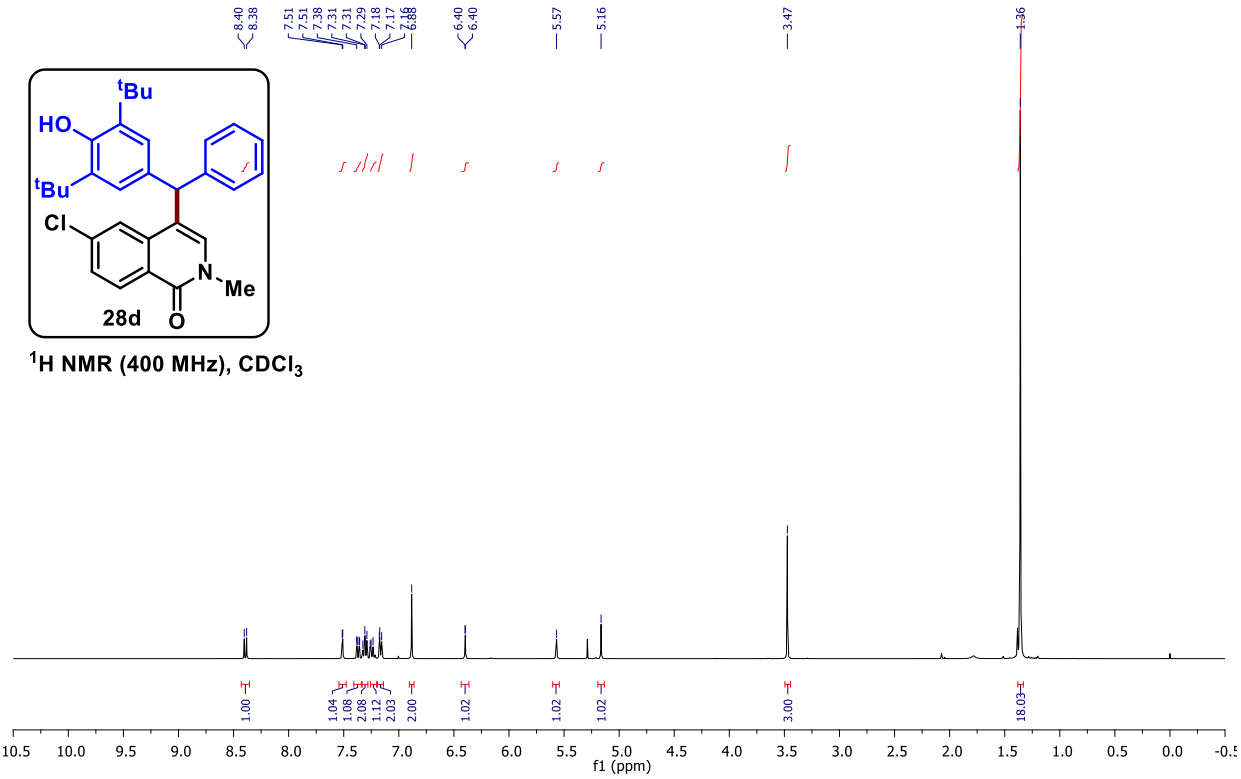
^{13}C NMR (100 MHz), $CDCl_3$



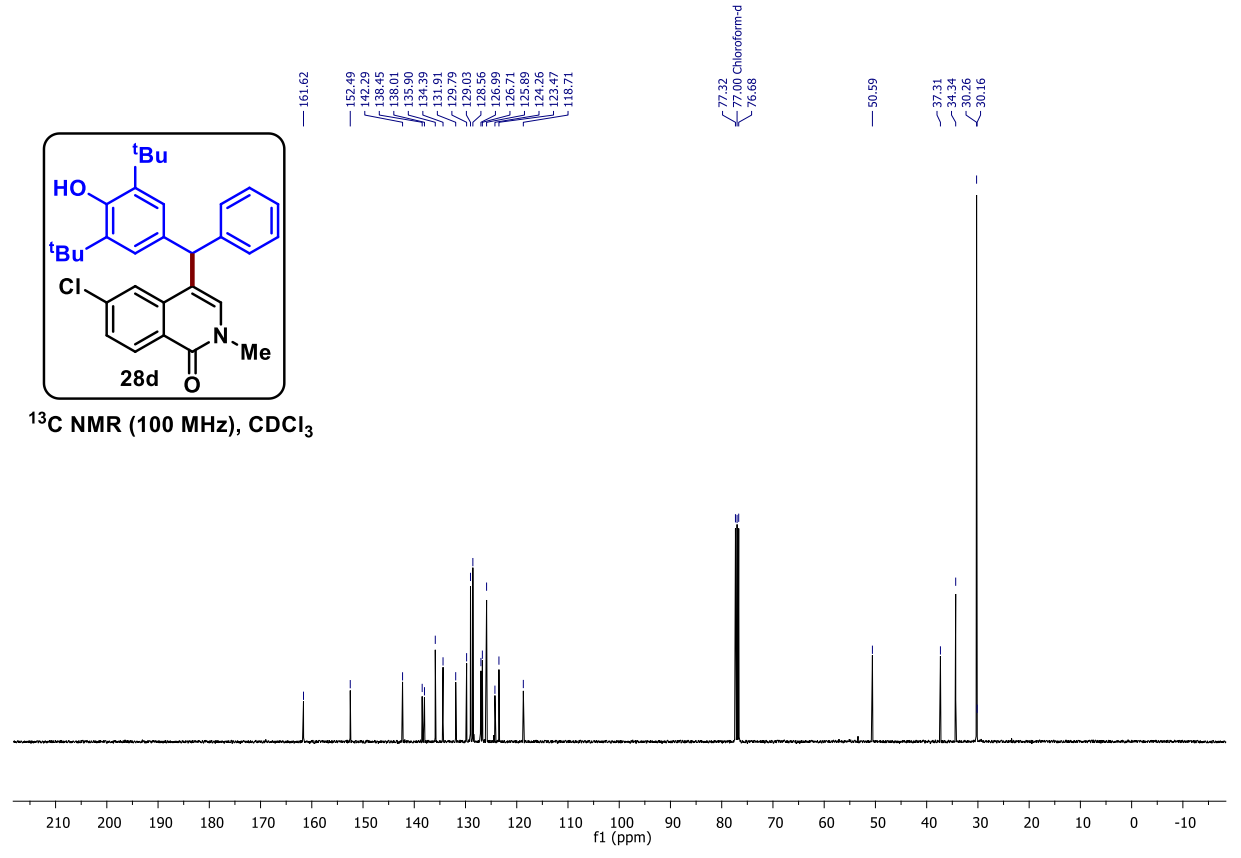
^{1}H NMR (400 MHz), $CDCl_3$



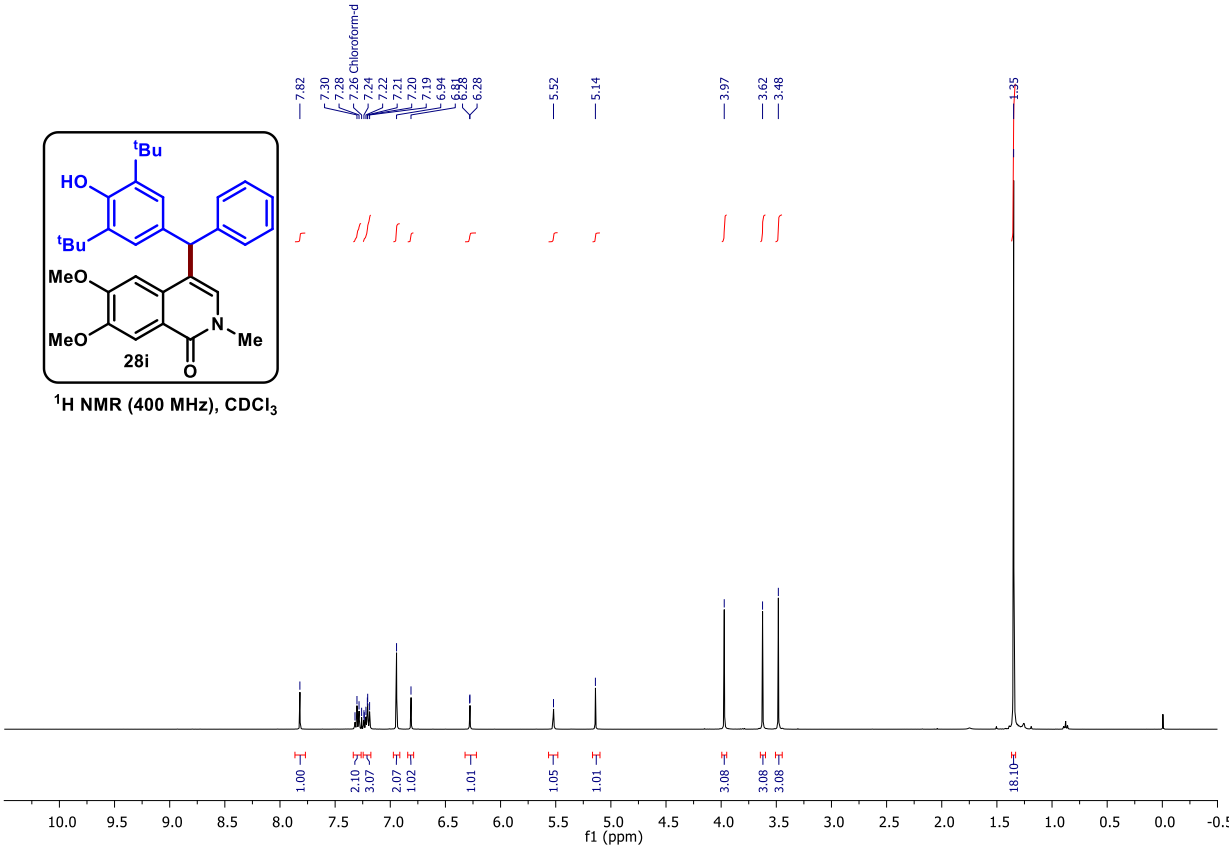
^{13}C NMR (100 MHz), $CDCl_3$



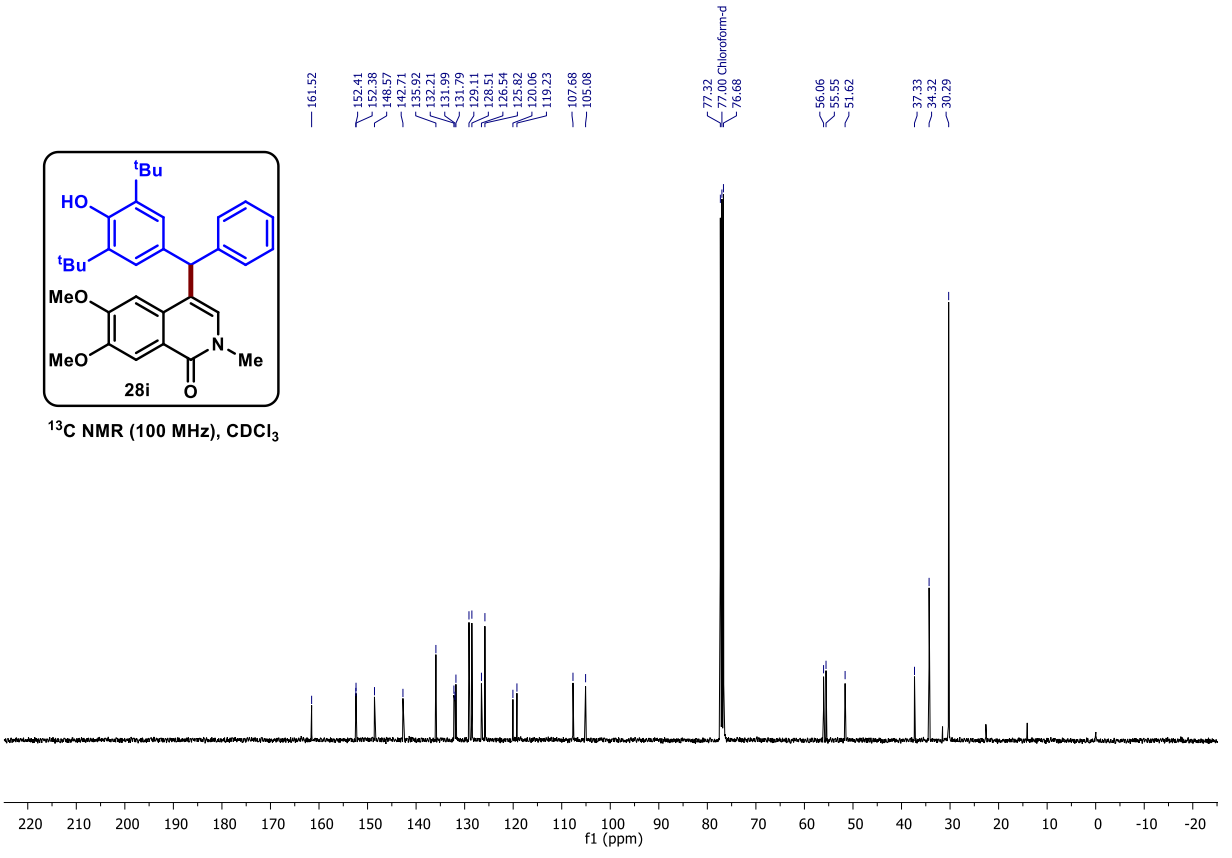
^{1}H NMR (400 MHz), $CDCl_3$



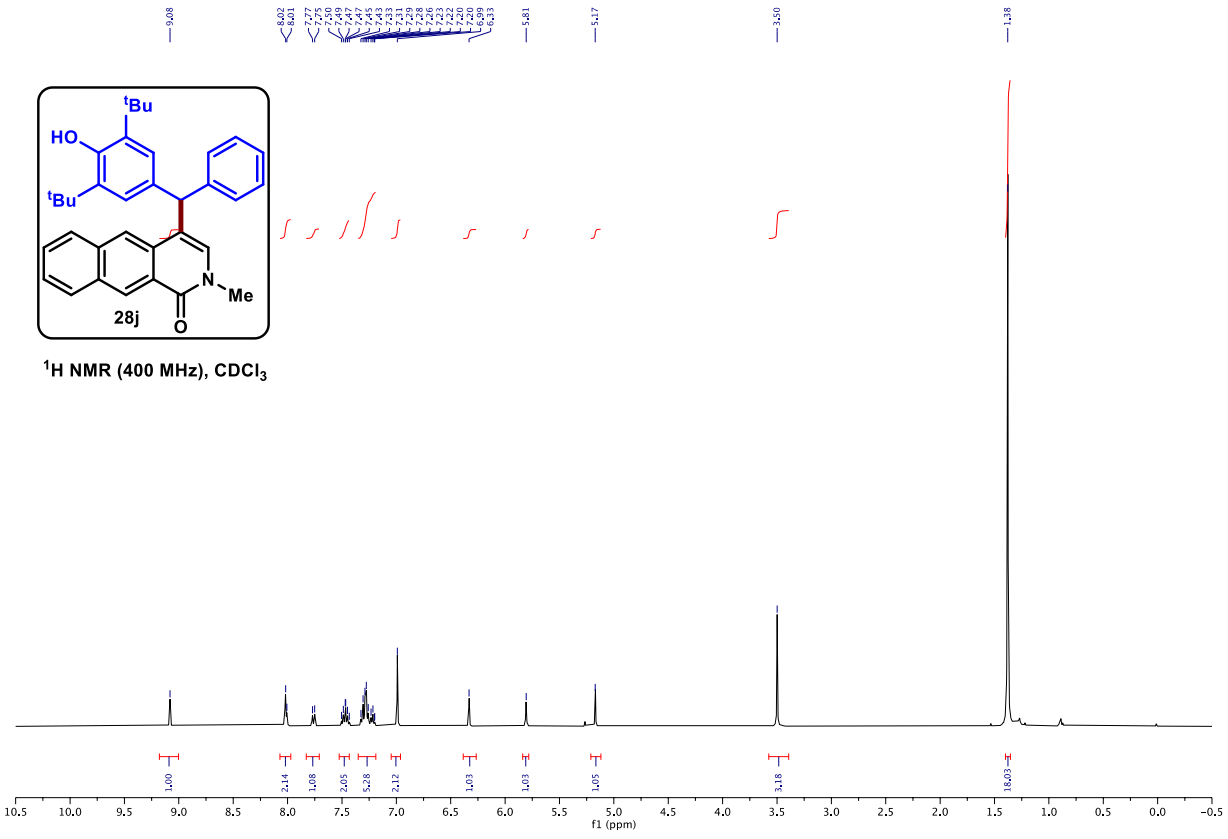
^{13}C NMR (100 MHz), $CDCl_3$



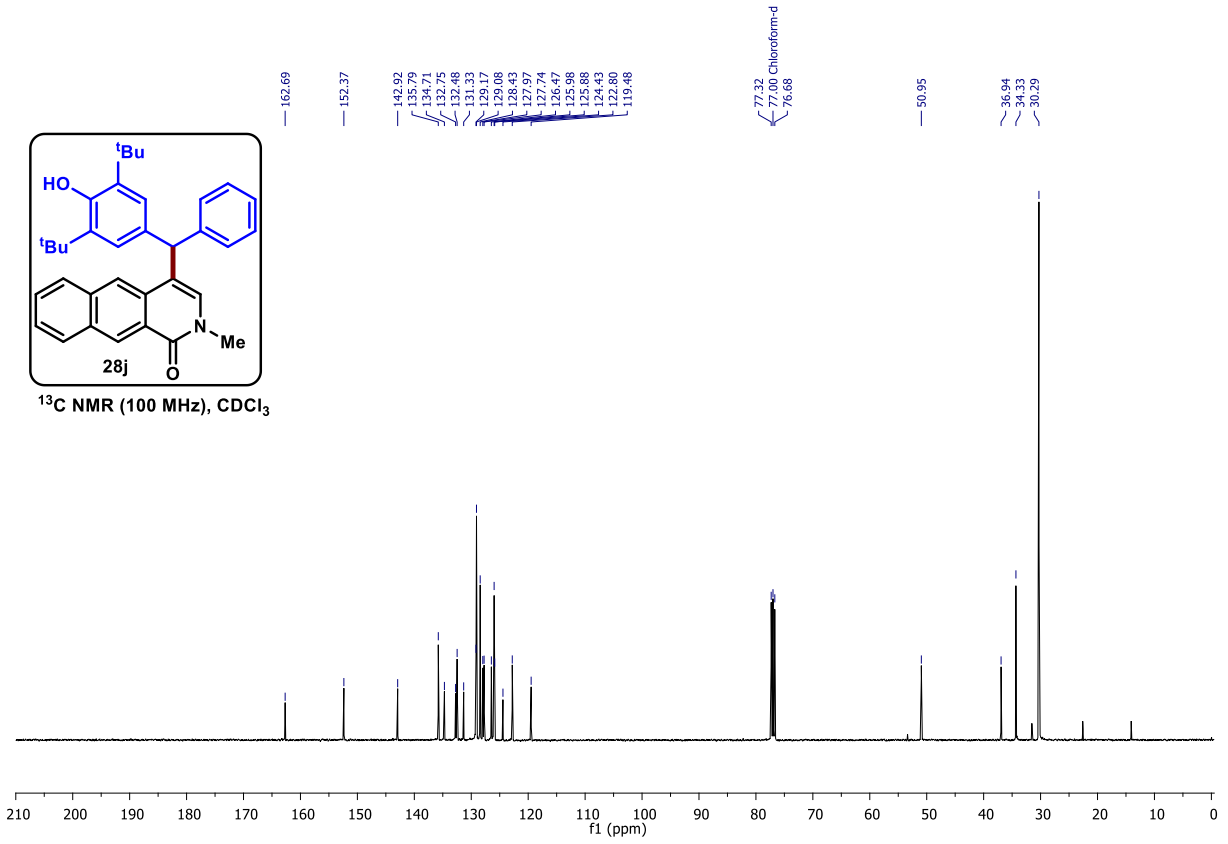
^{1}H NMR (400 MHz), $CDCl_3$



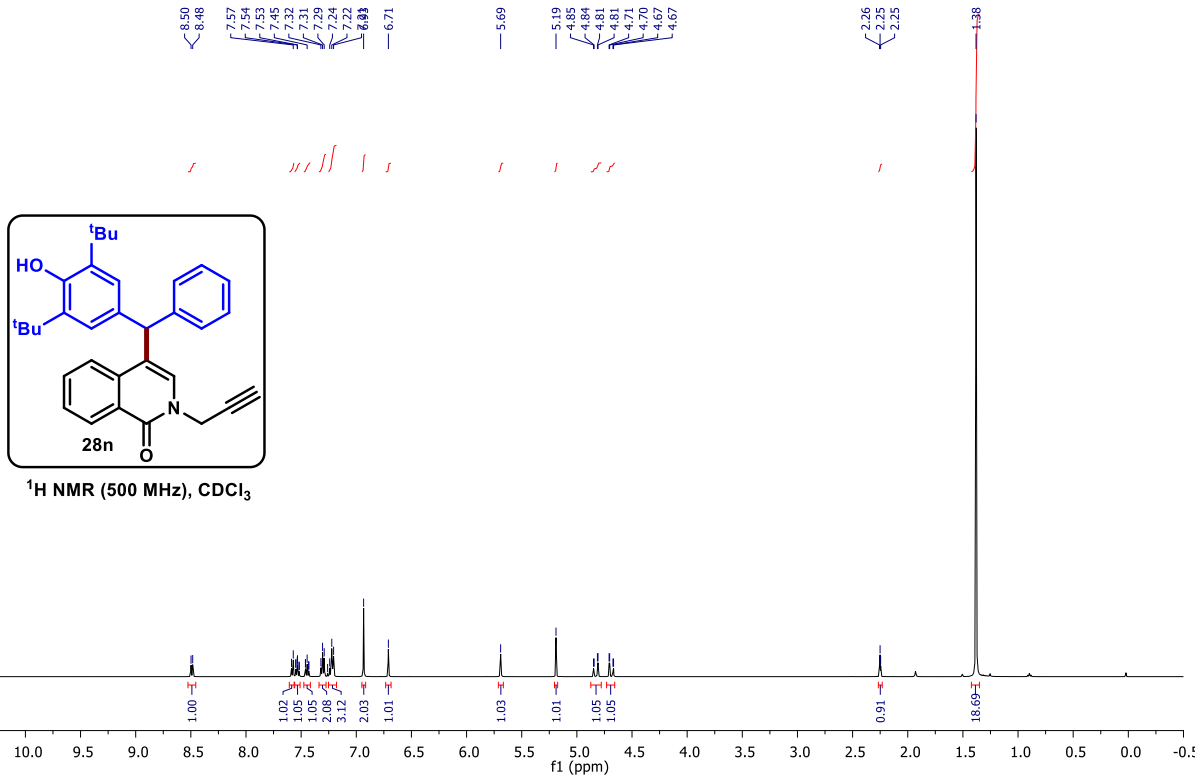
^{13}C NMR (100 MHz), $CDCl_3$



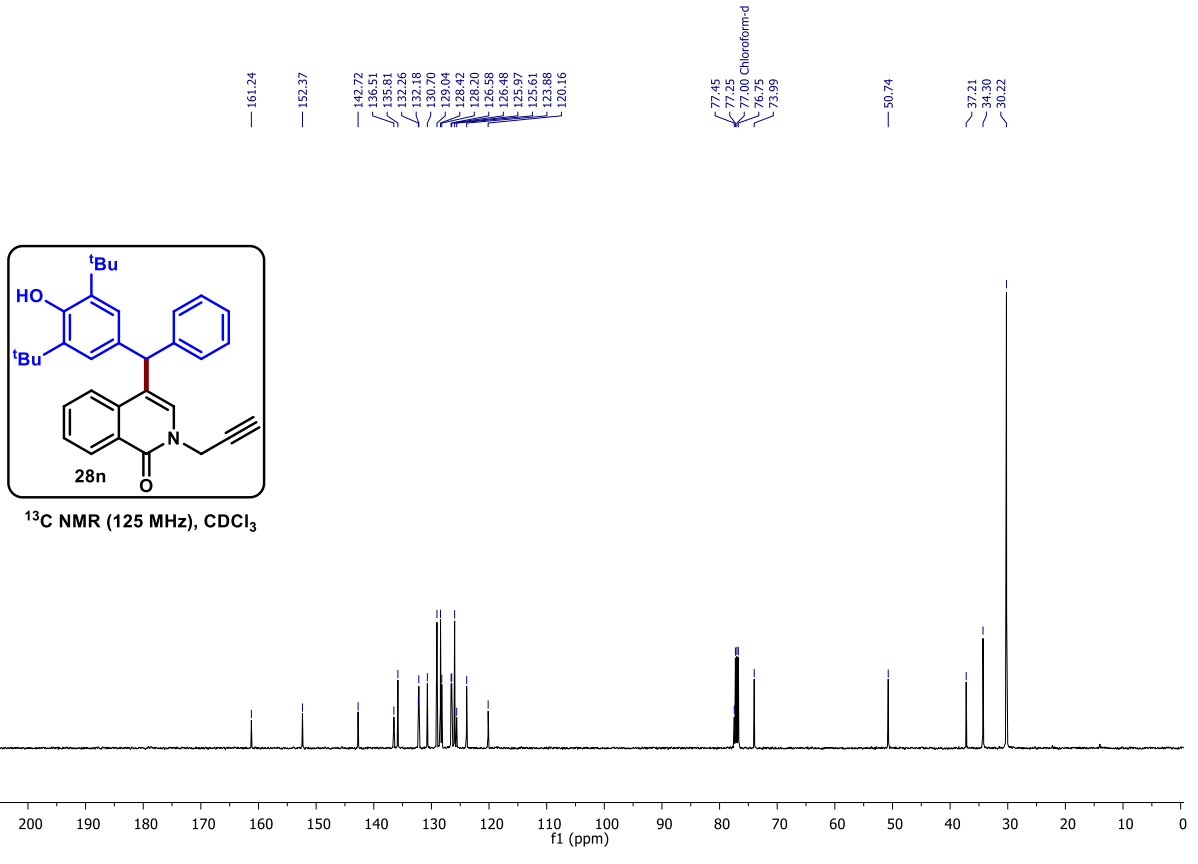
^{1}H NMR (400 MHz), $CDCl_3$



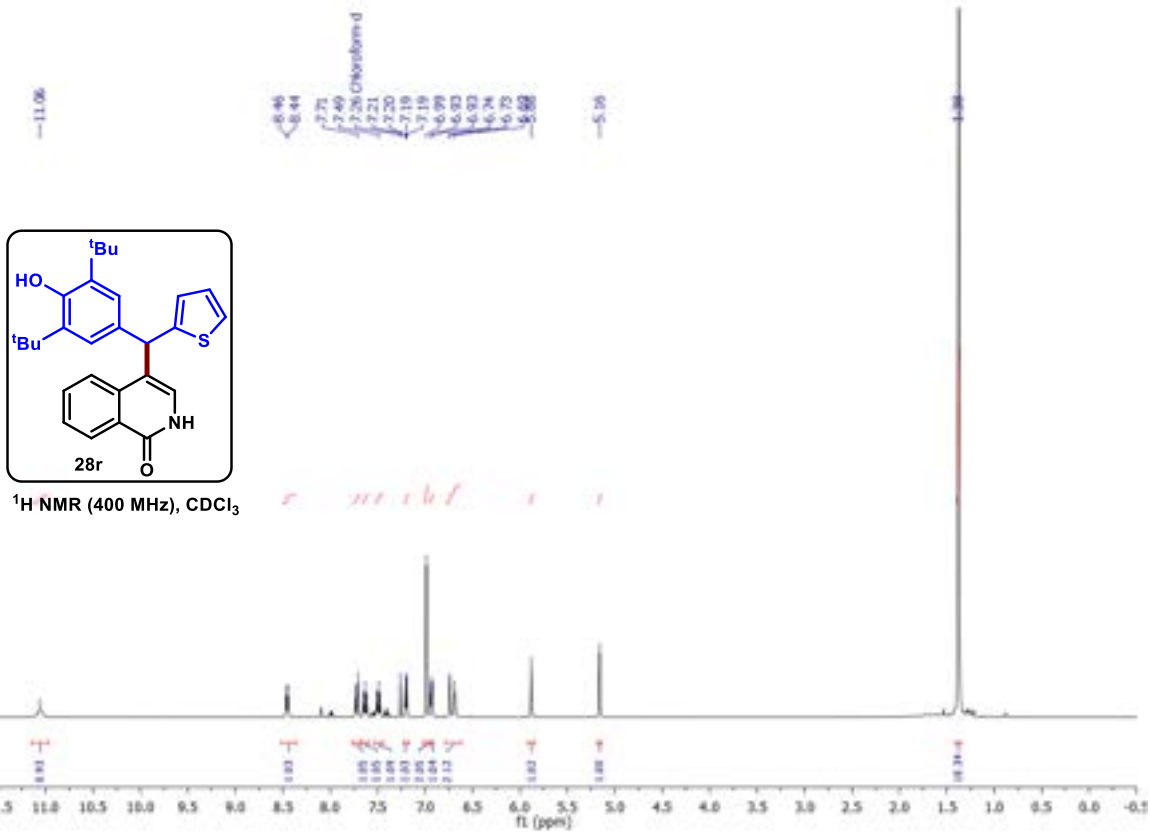
^{13}C NMR (100 MHz), $CDCl_3$



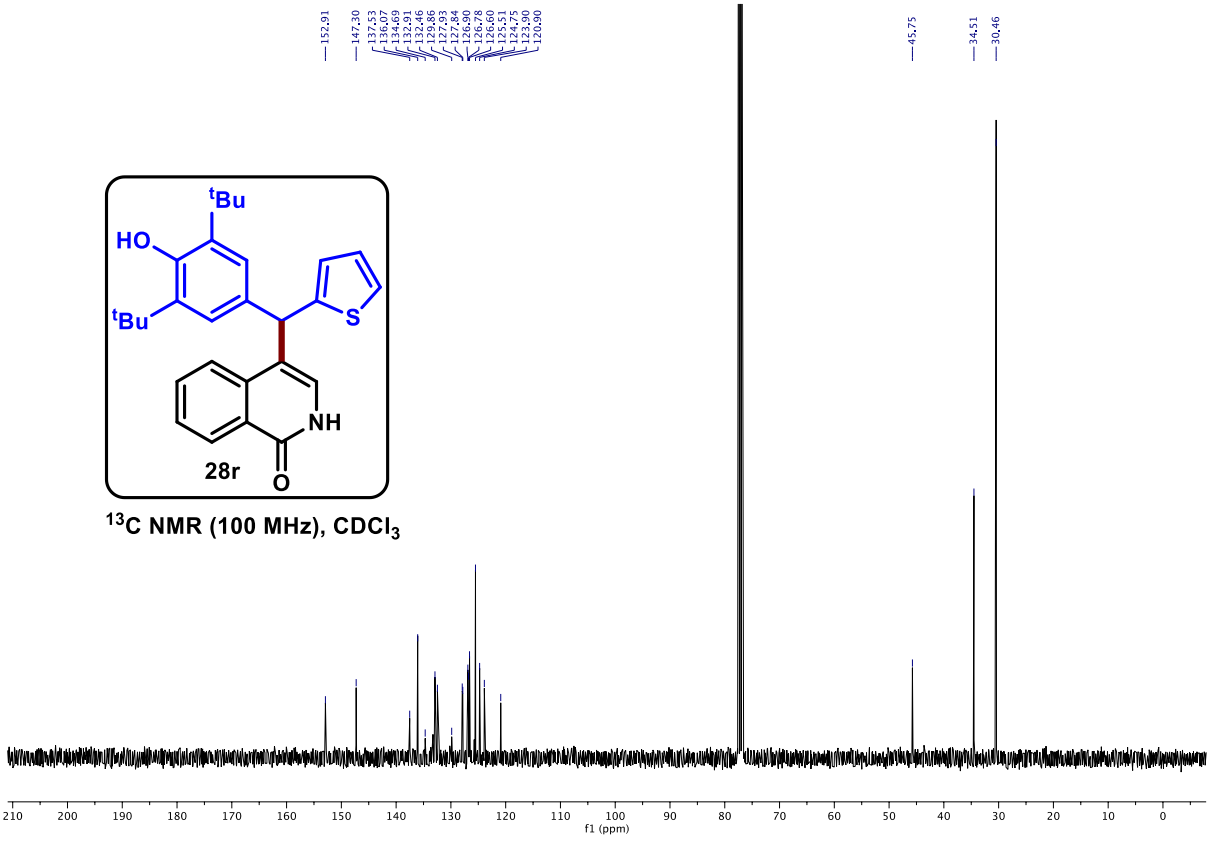
^{1}H NMR (500 MHz), $CDCl_3$



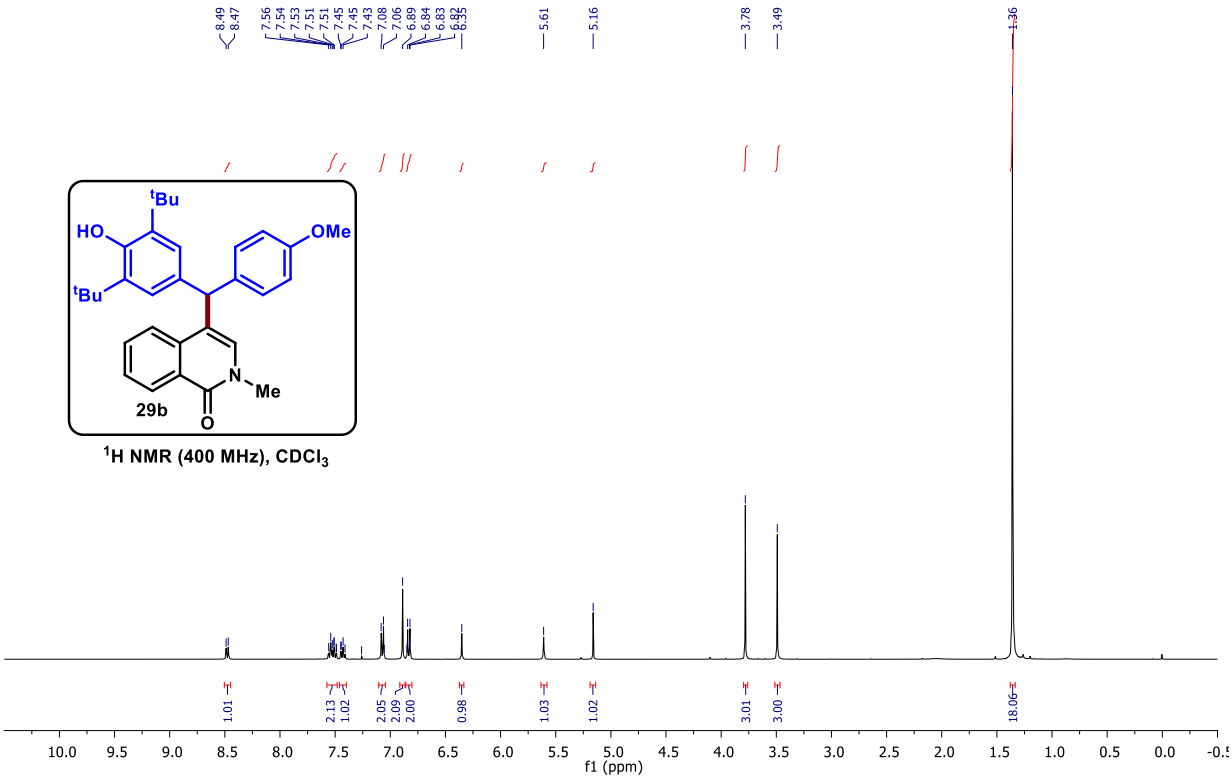
^{13}C NMR (125 MHz), $CDCl_3$



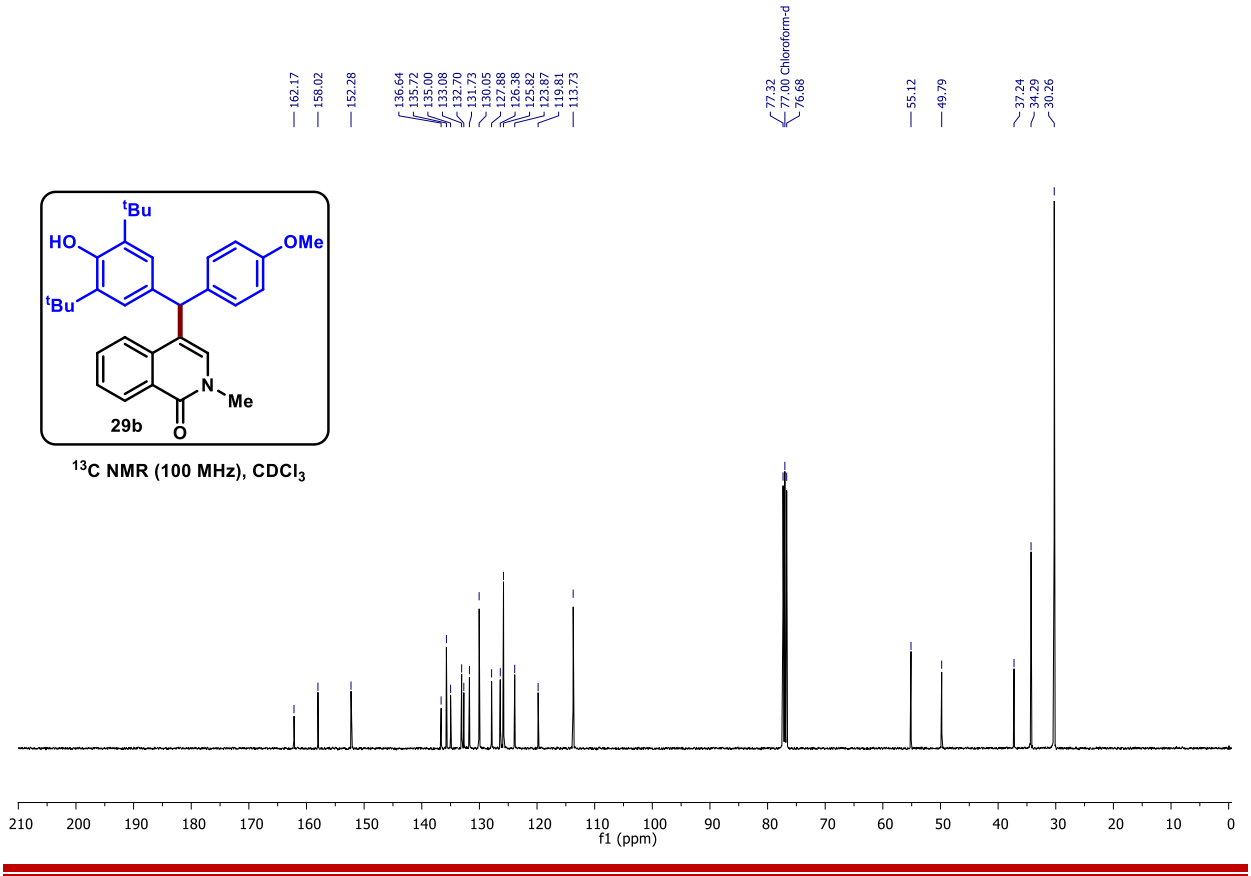
^{1}H NMR (400 MHz), $CDCl_3$



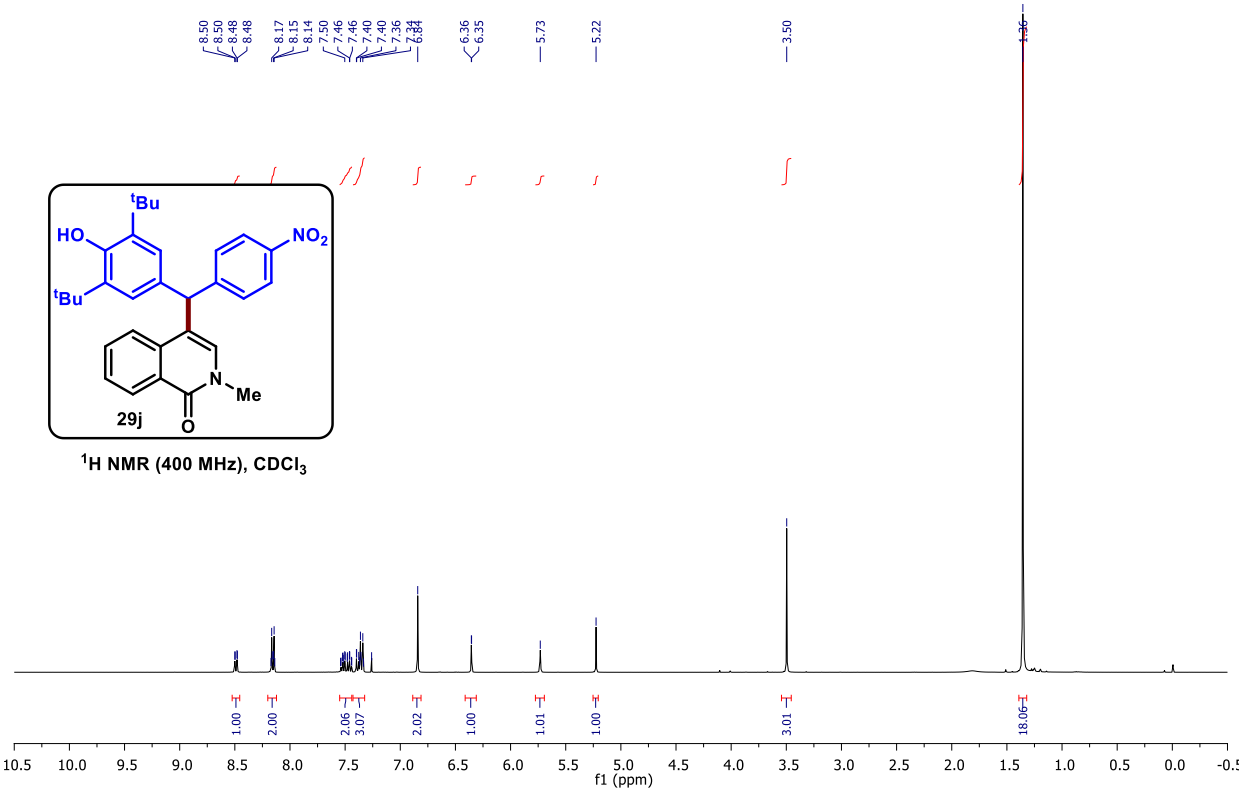
^{13}C NMR (100 MHz), $CDCl_3$



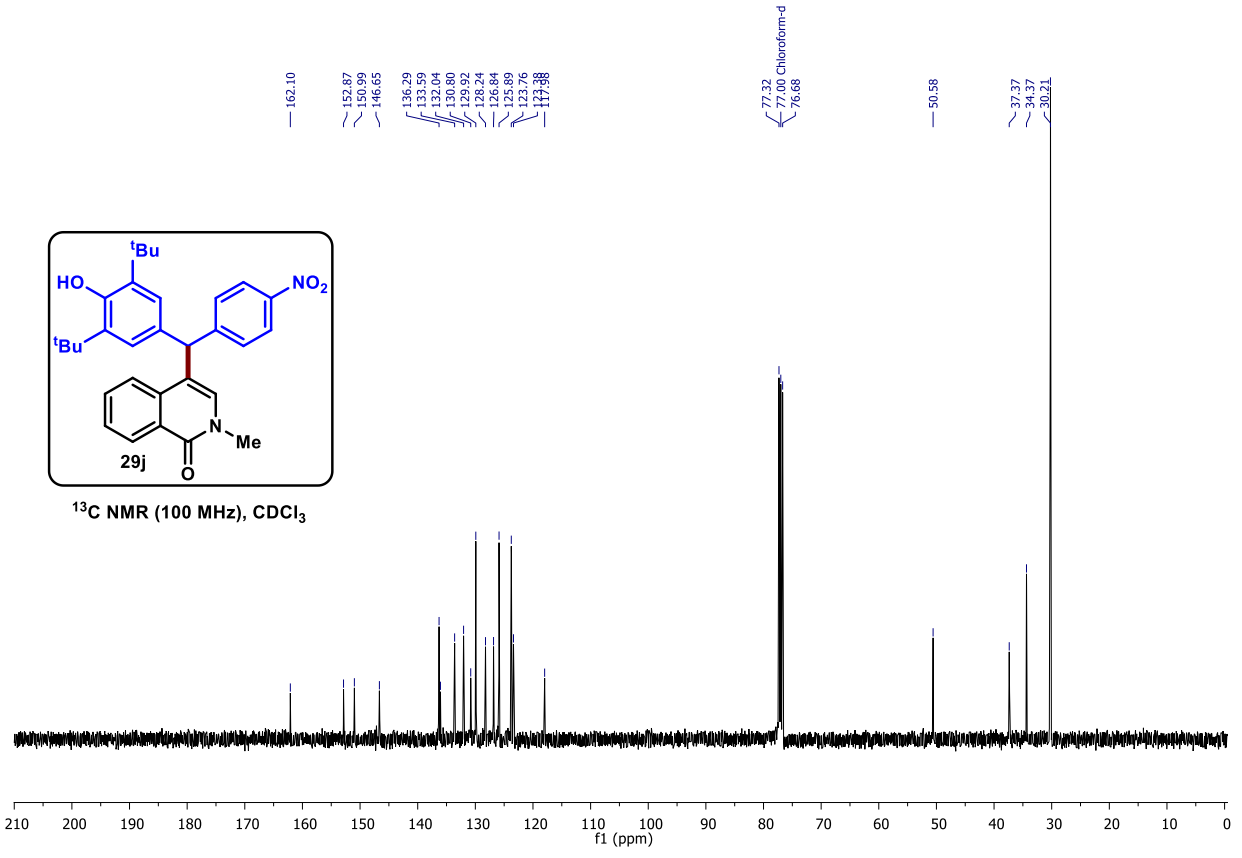
^{1}H NMR (400 MHz), $CDCl_3$



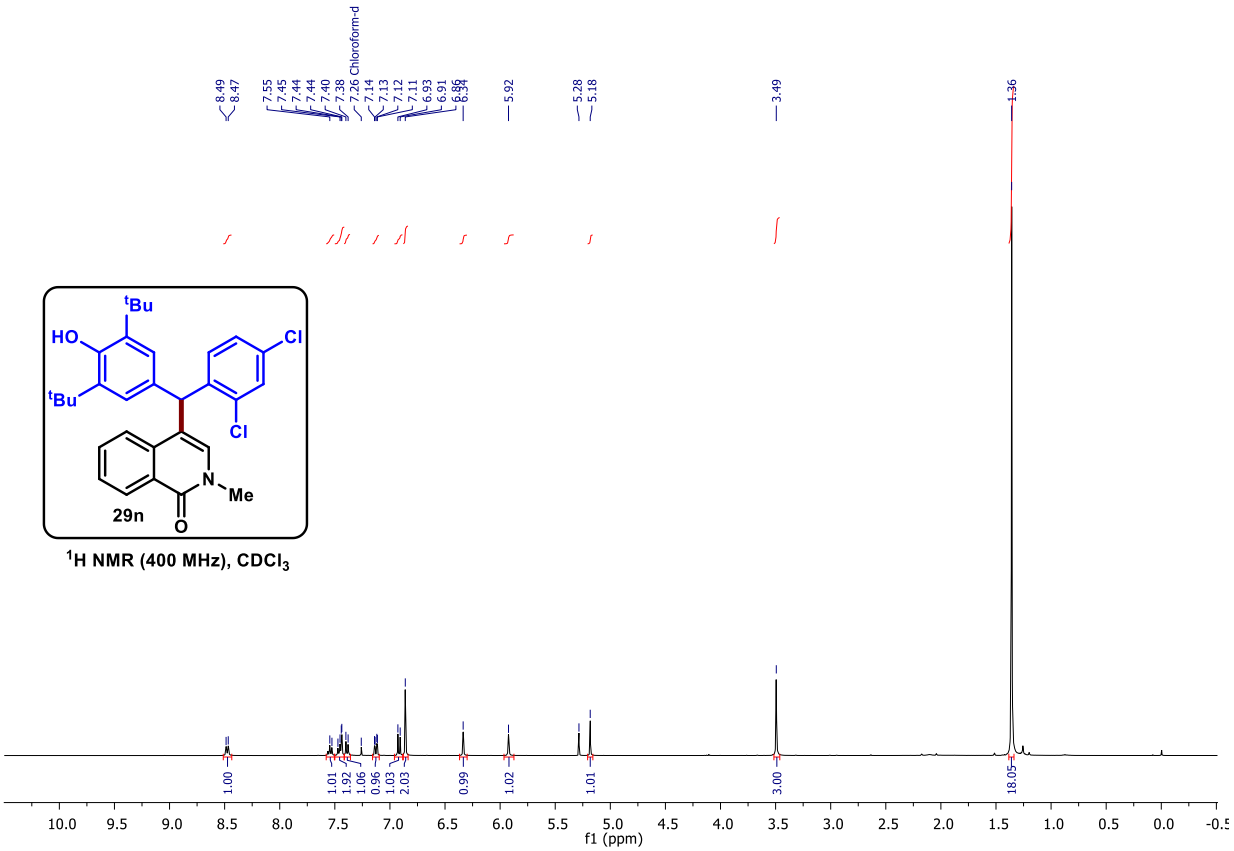
^{13}C NMR (100 MHz), $CDCl_3$



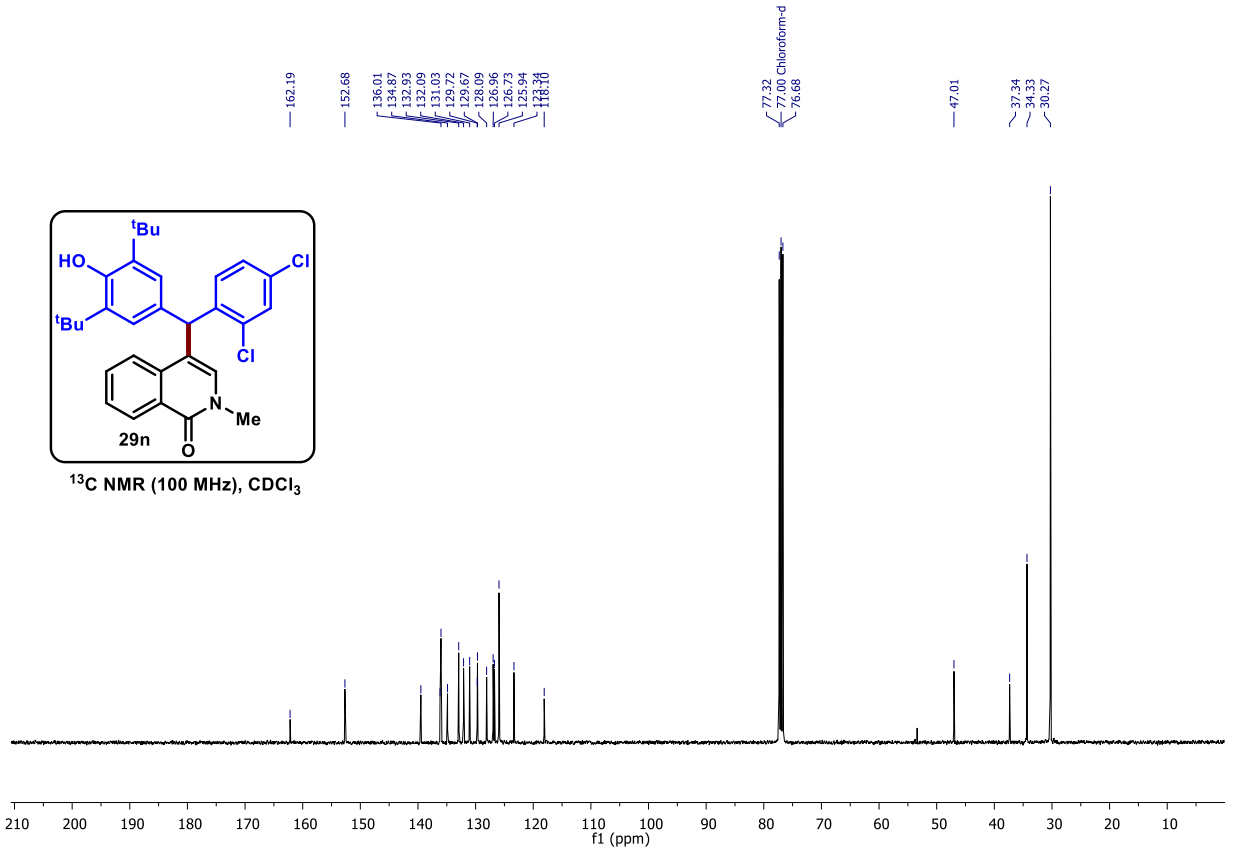
^{1}H NMR (400 MHz), $CDCl_3$



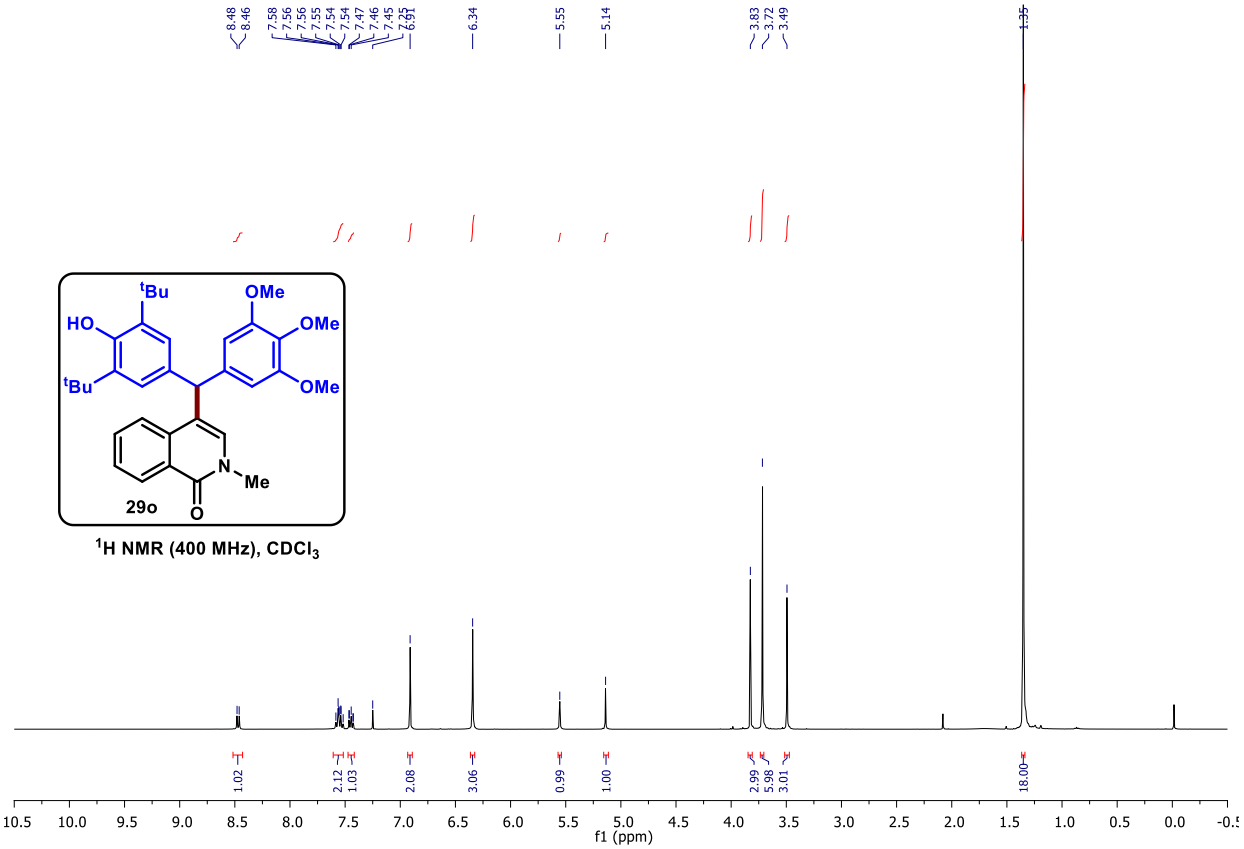
^{13}C NMR (100 MHz), $CDCl_3$



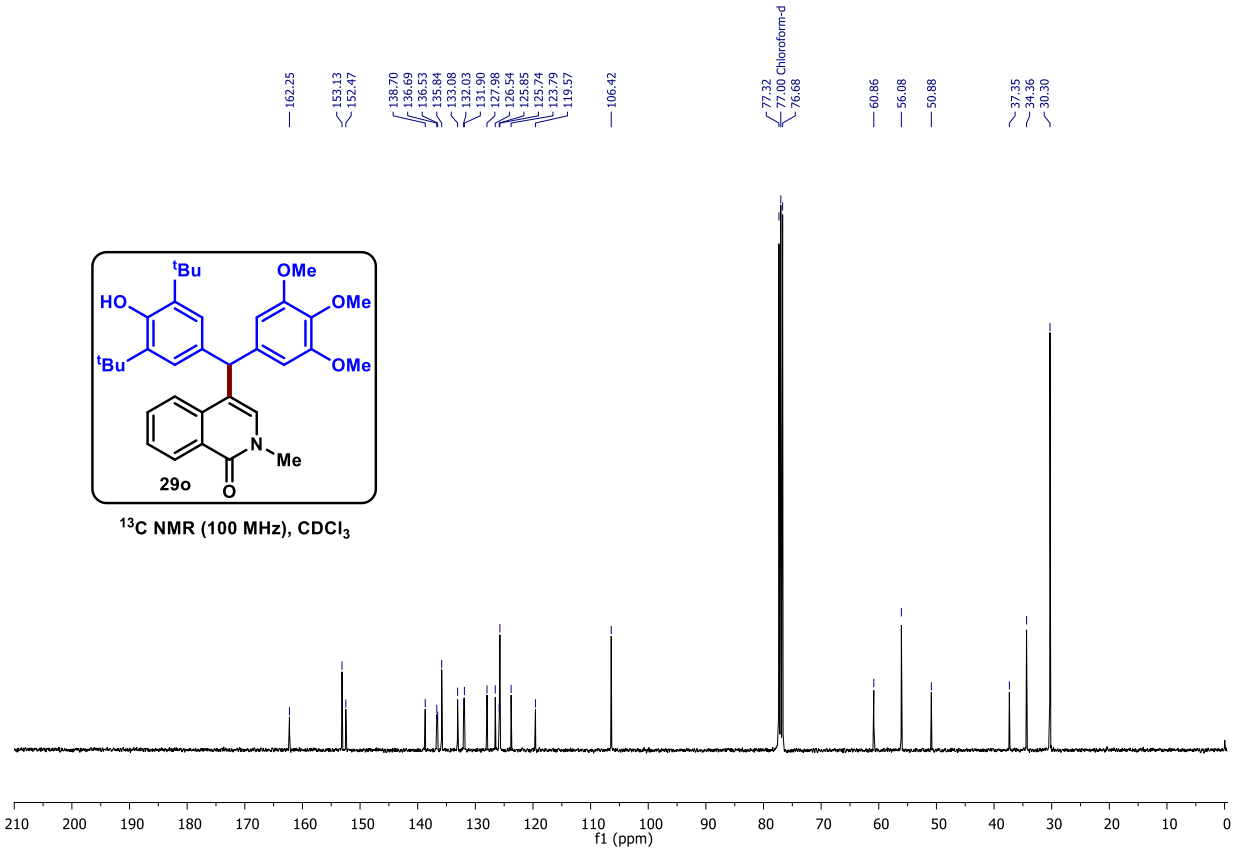
^{1}H NMR (400 MHz), $CDCl_3$



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



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



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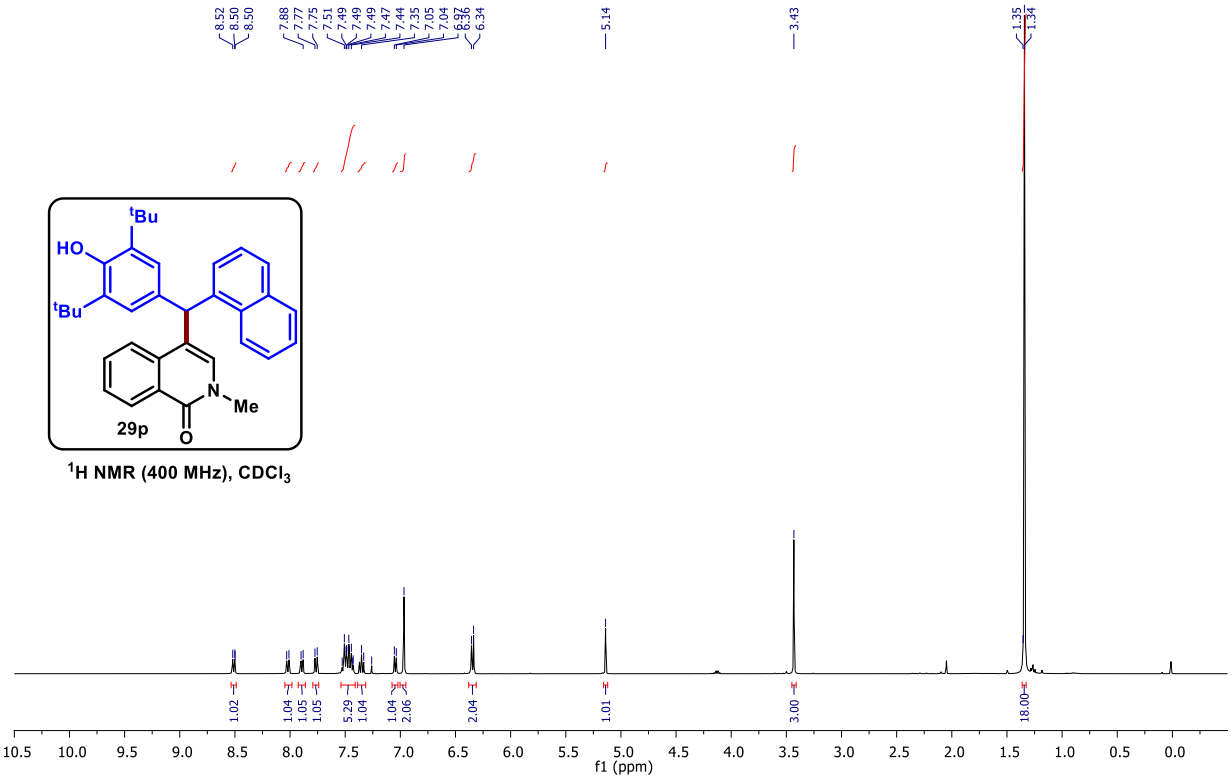

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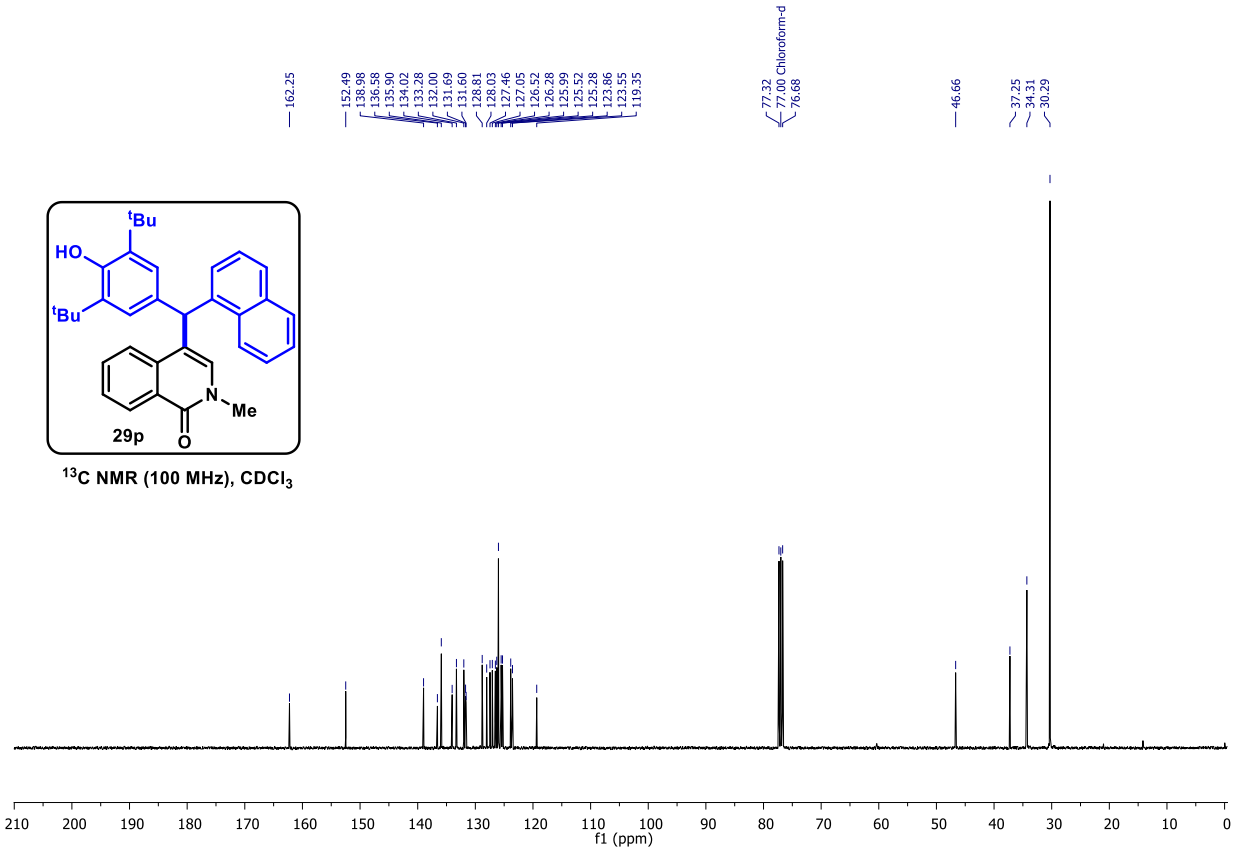

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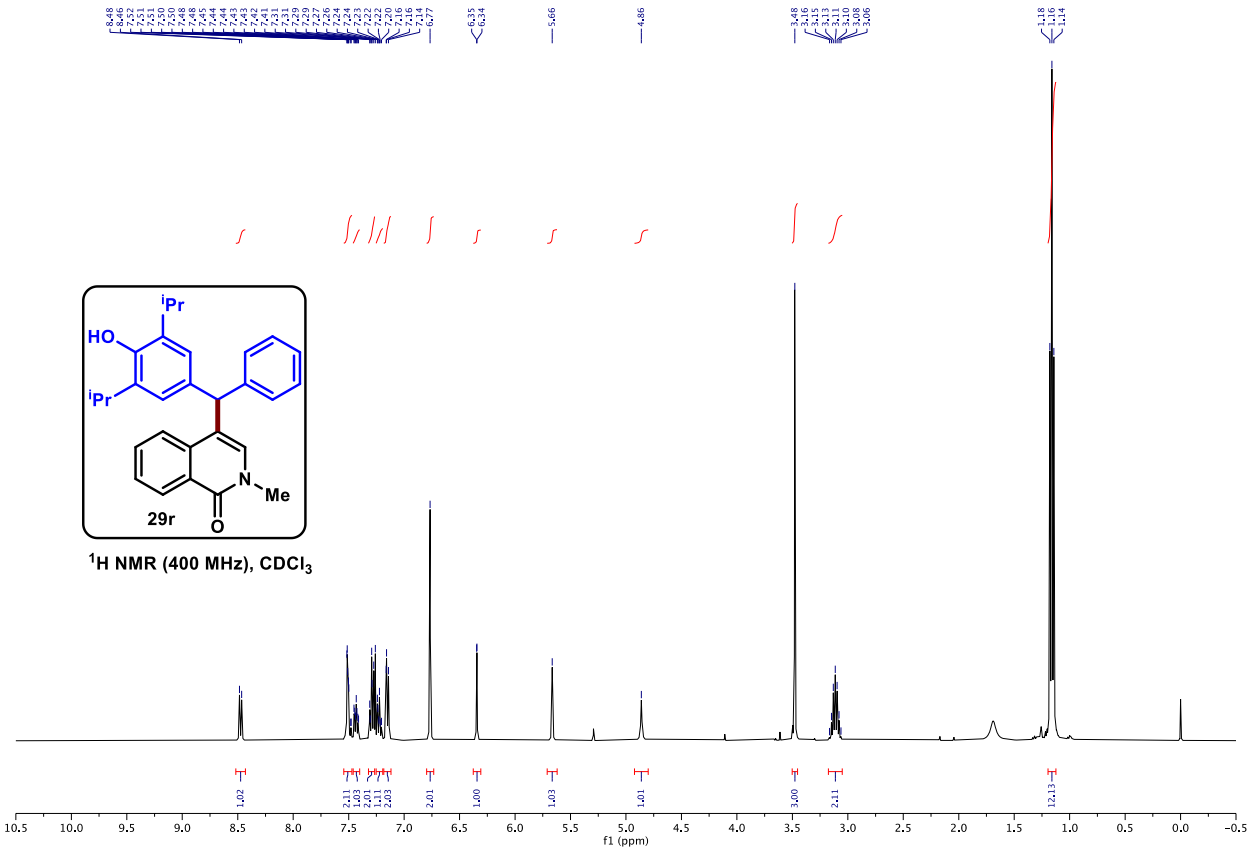

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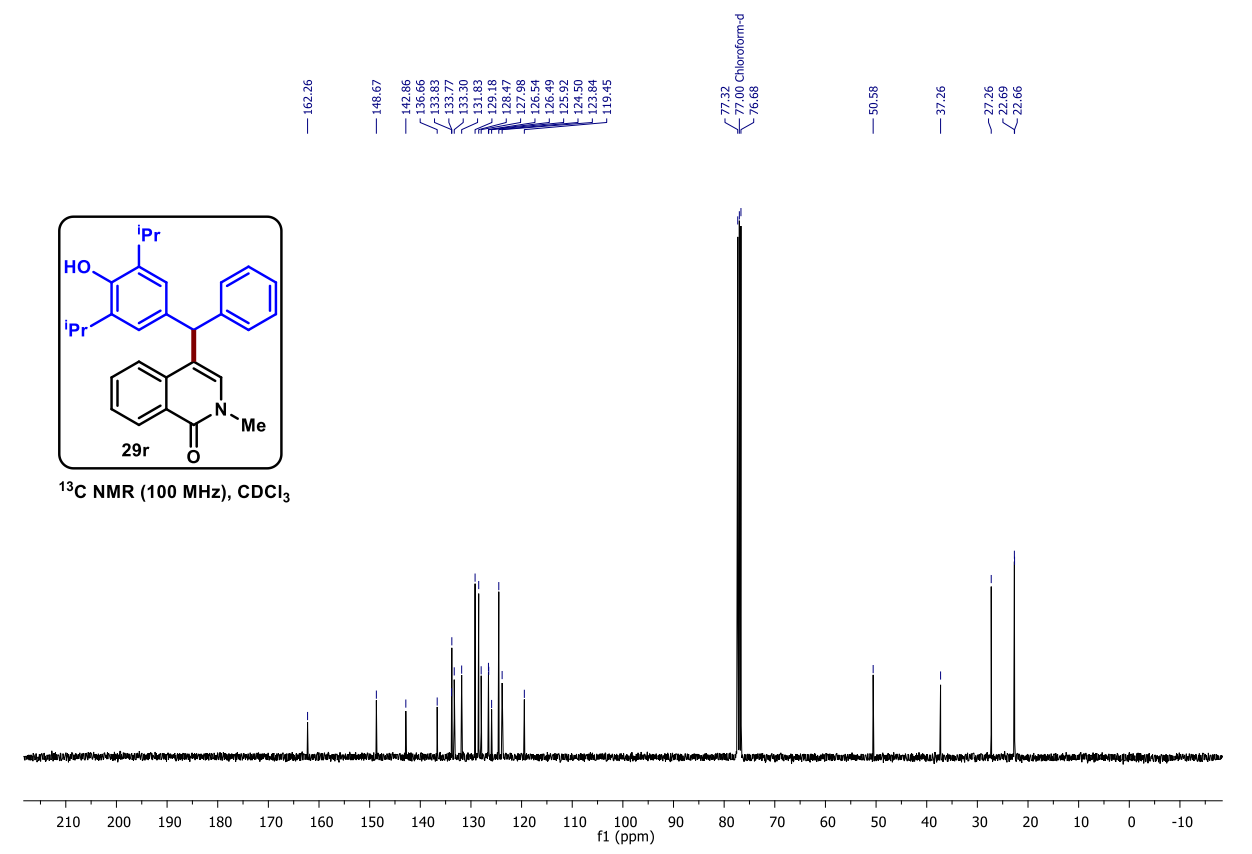

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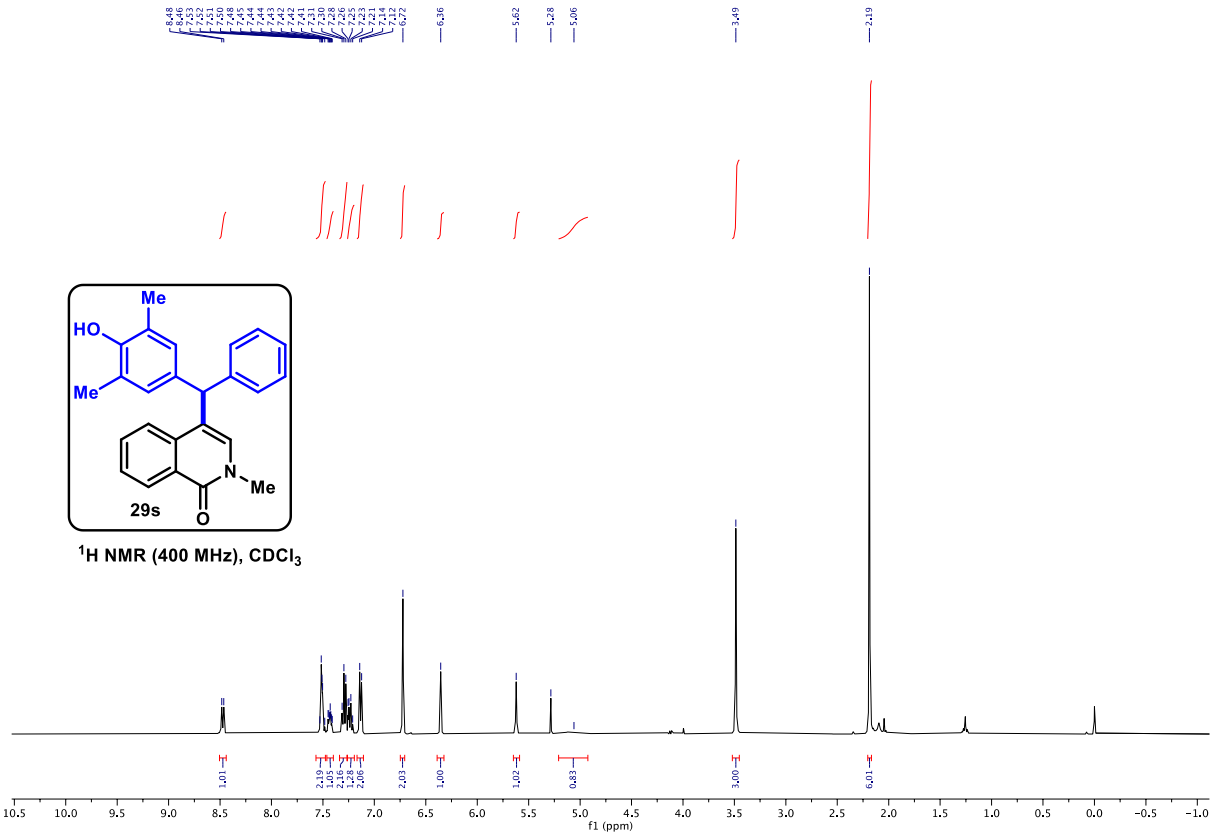
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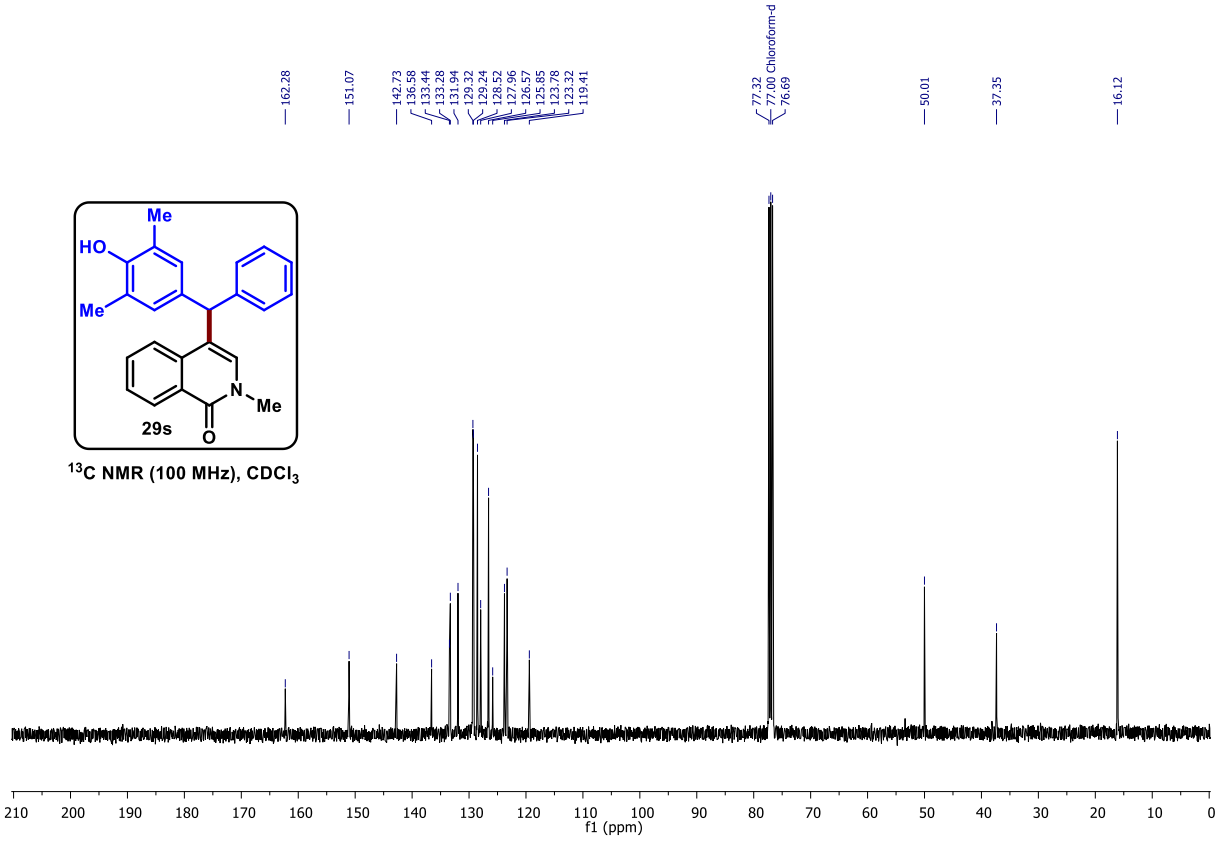
HO
Me
N
Me
O
29s
1H NMR (400 MHz), CDCl3
f1 (ppm)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N
Me
O
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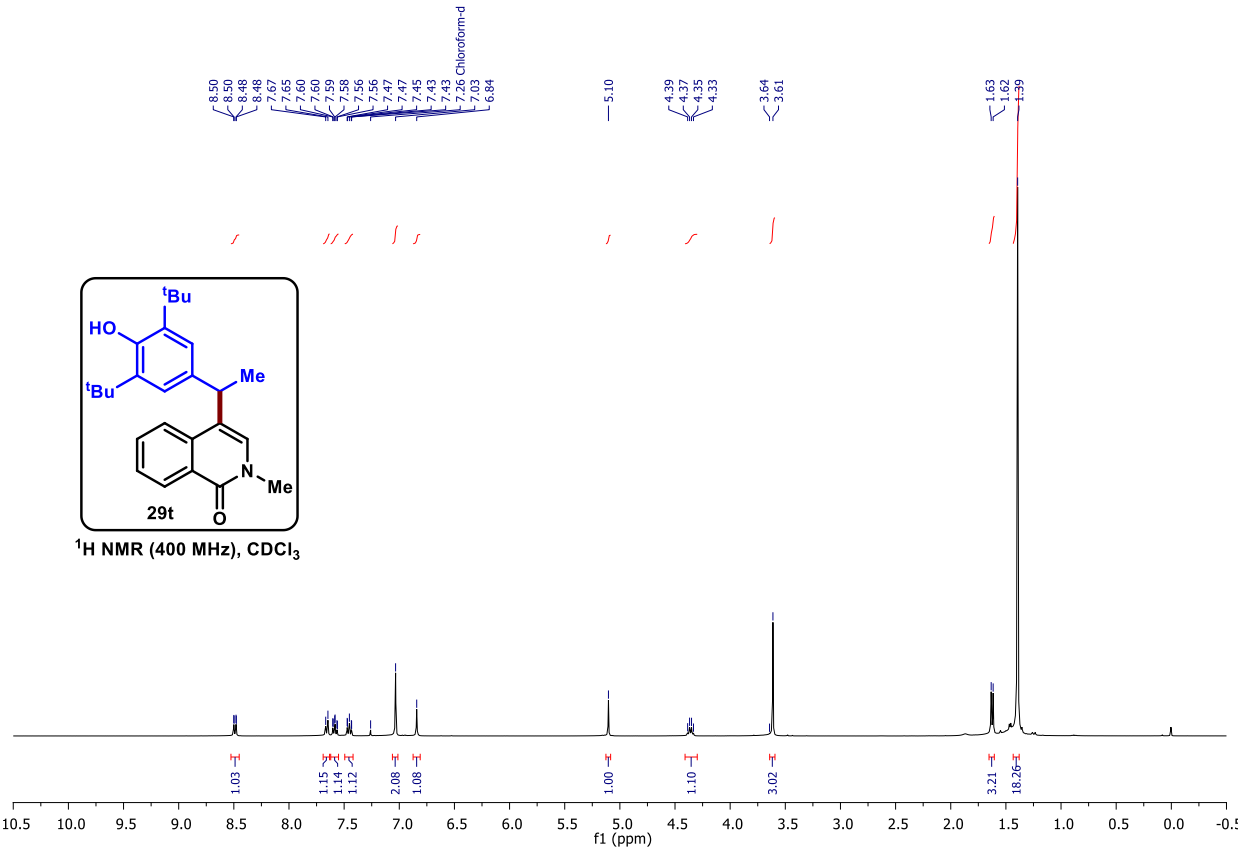
f1 (ppm)



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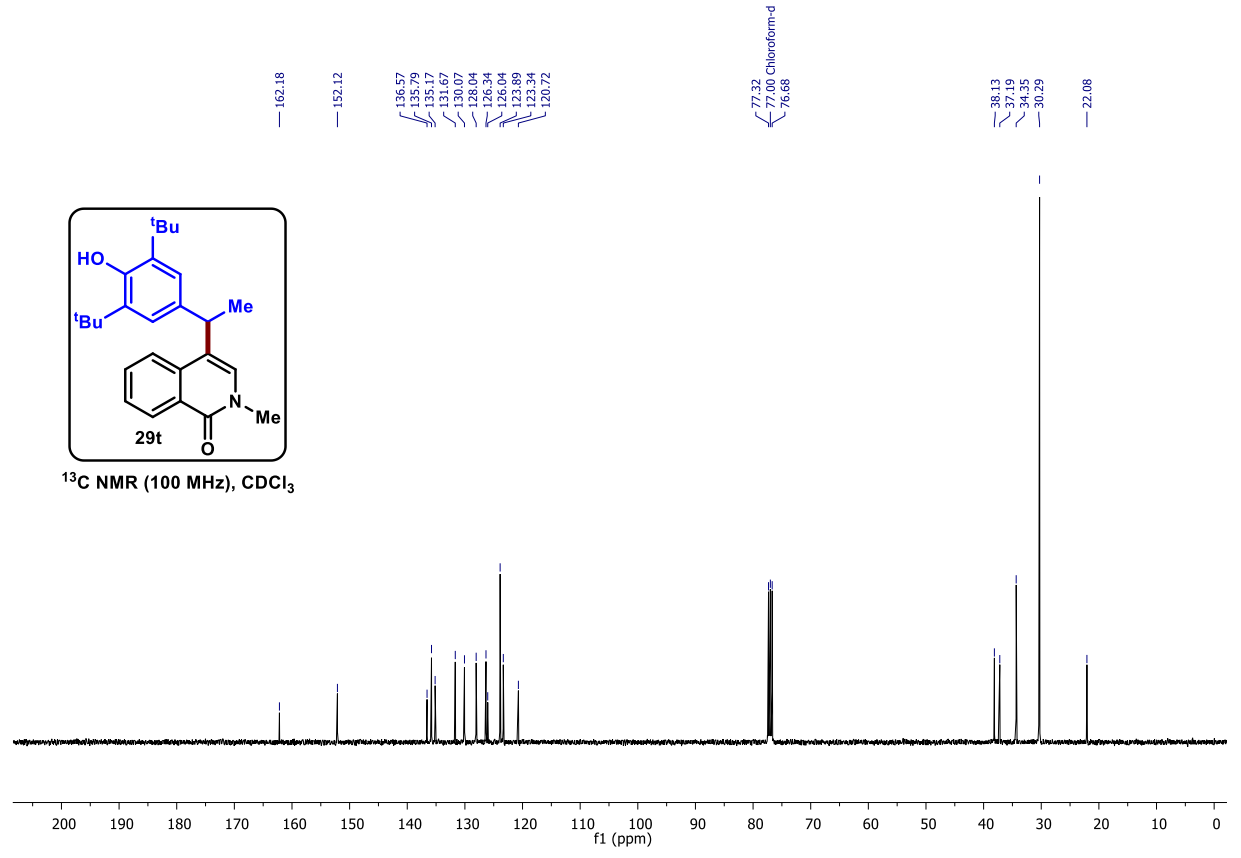

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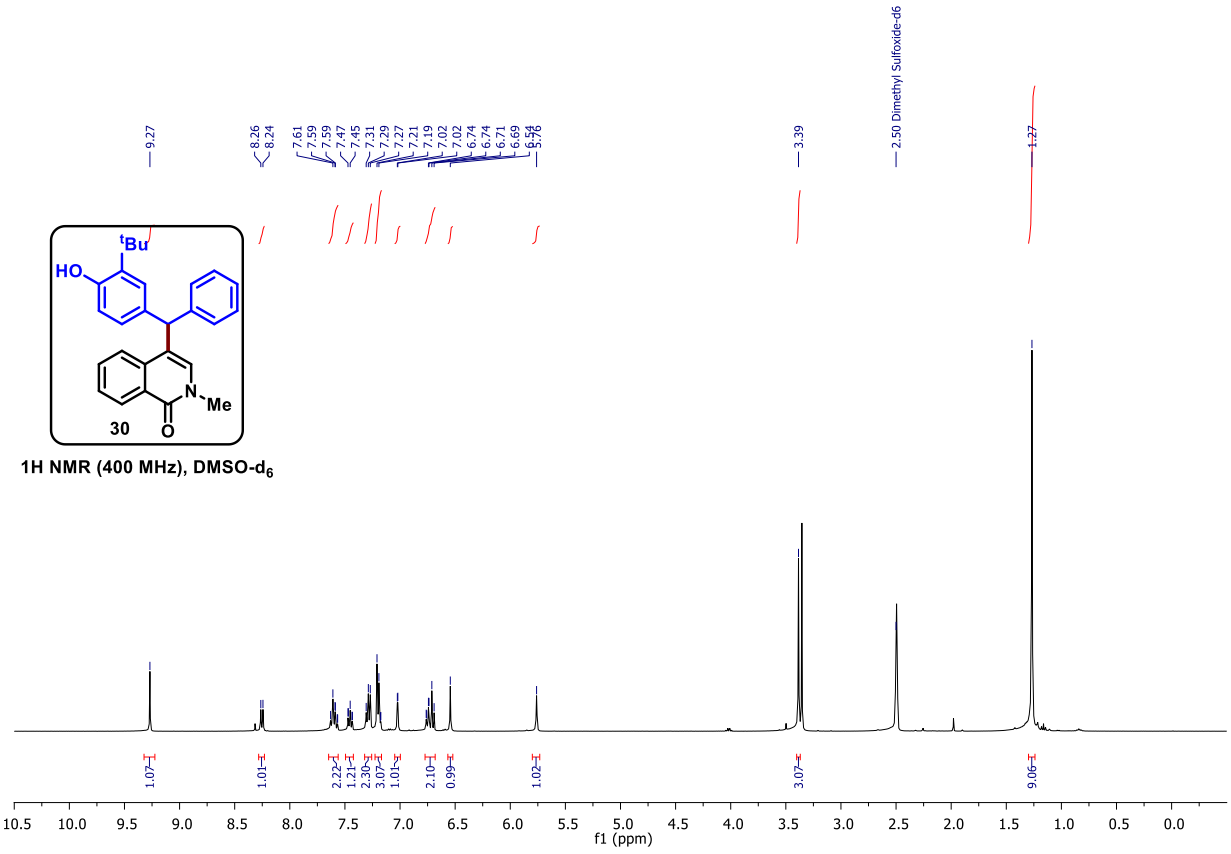
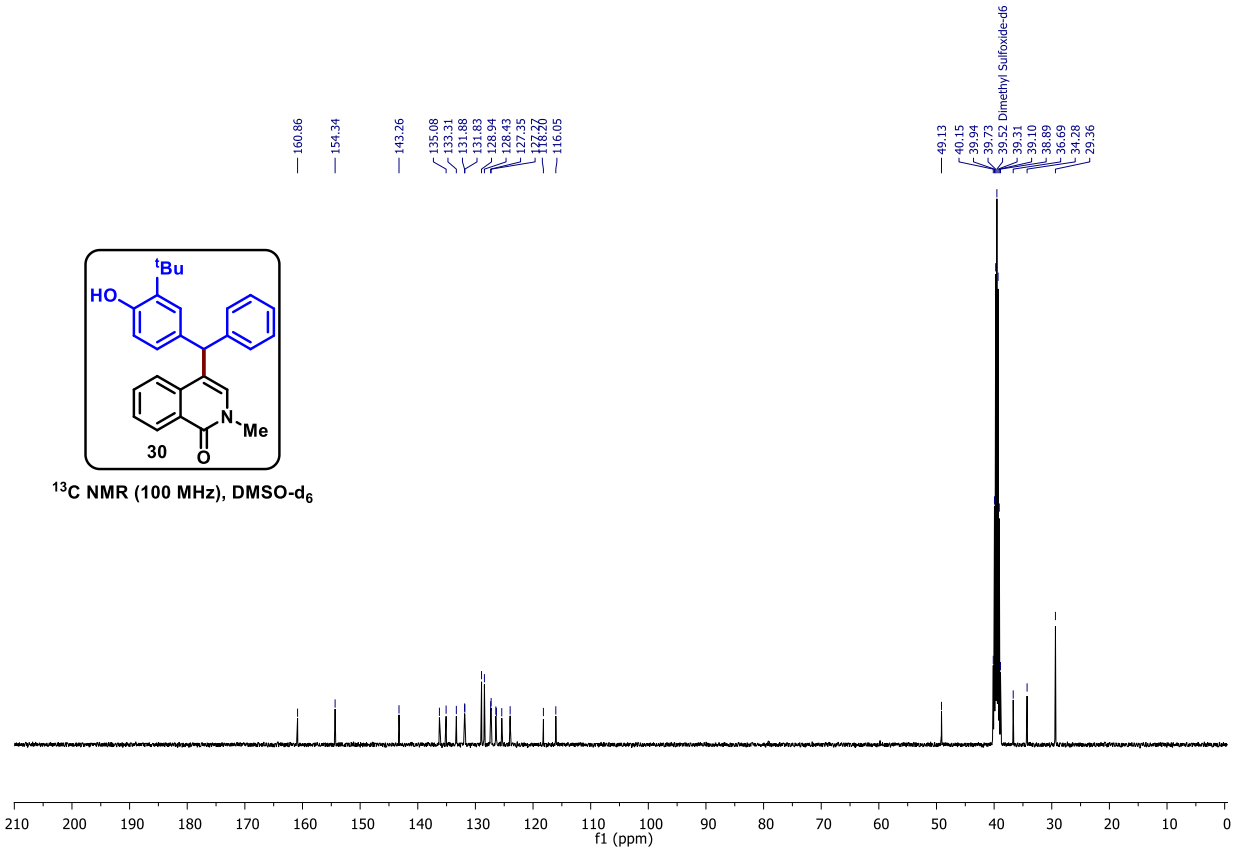


1H NMR (400 MHz), DMSO-d_6



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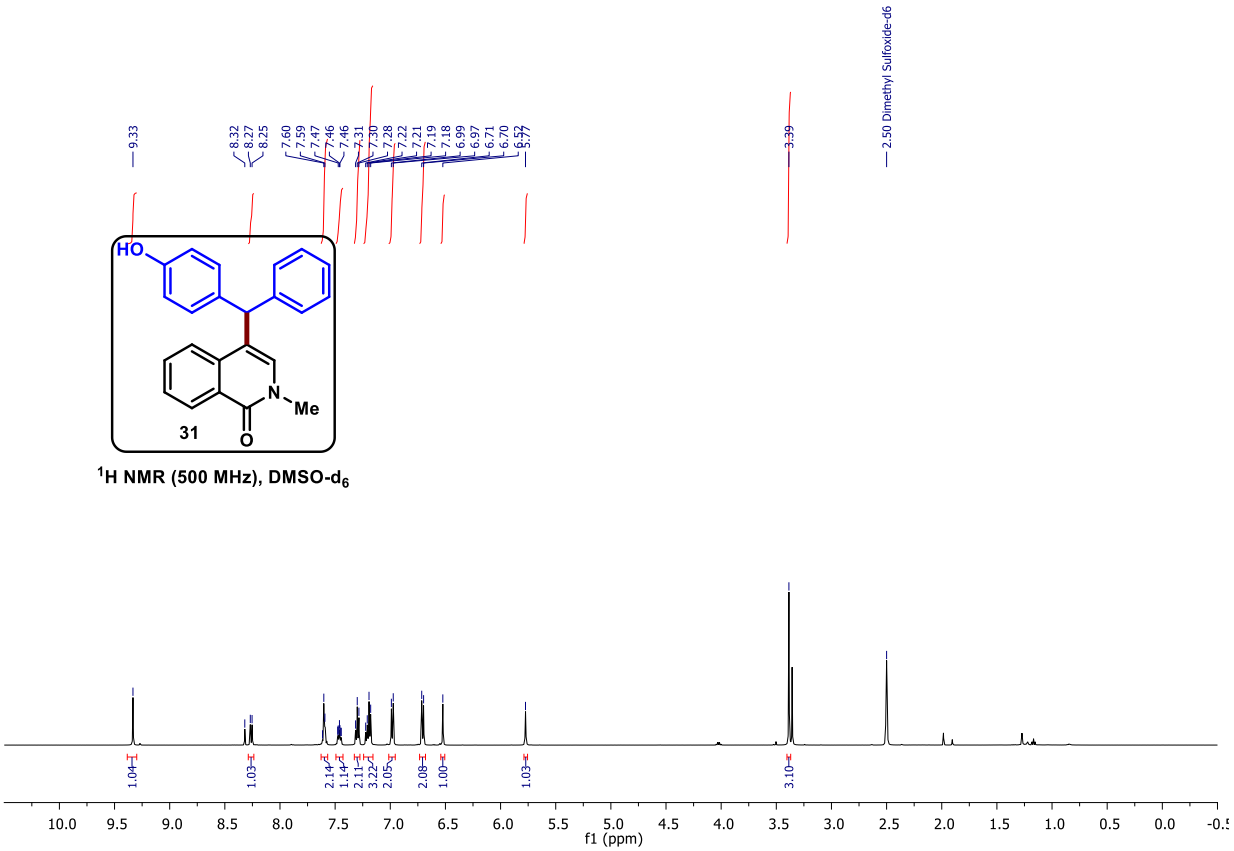

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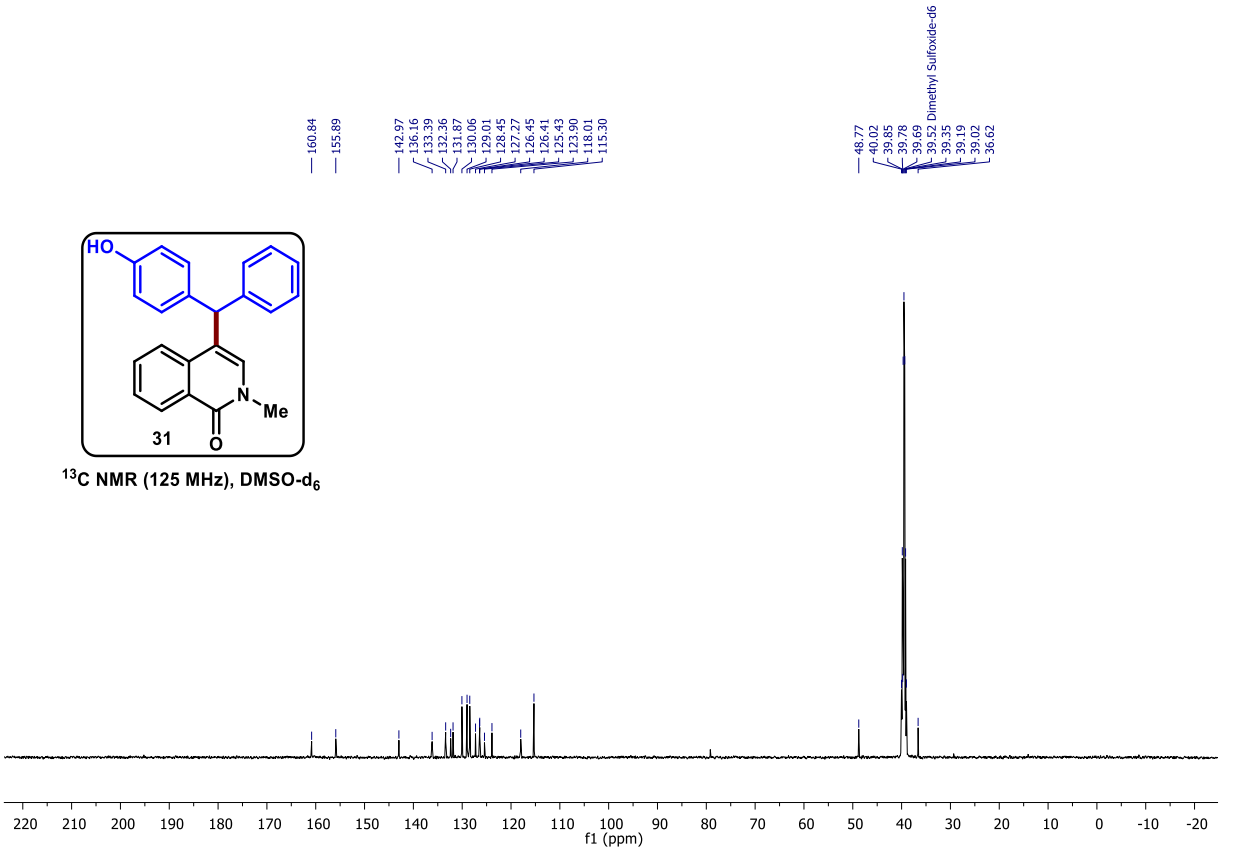

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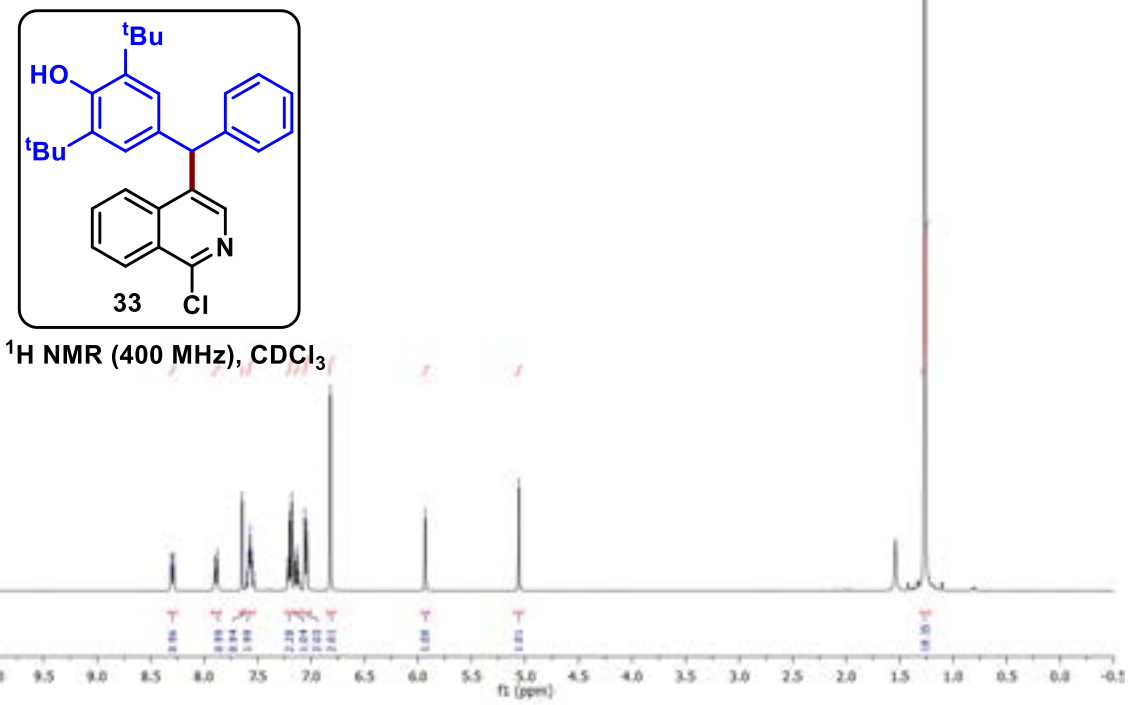
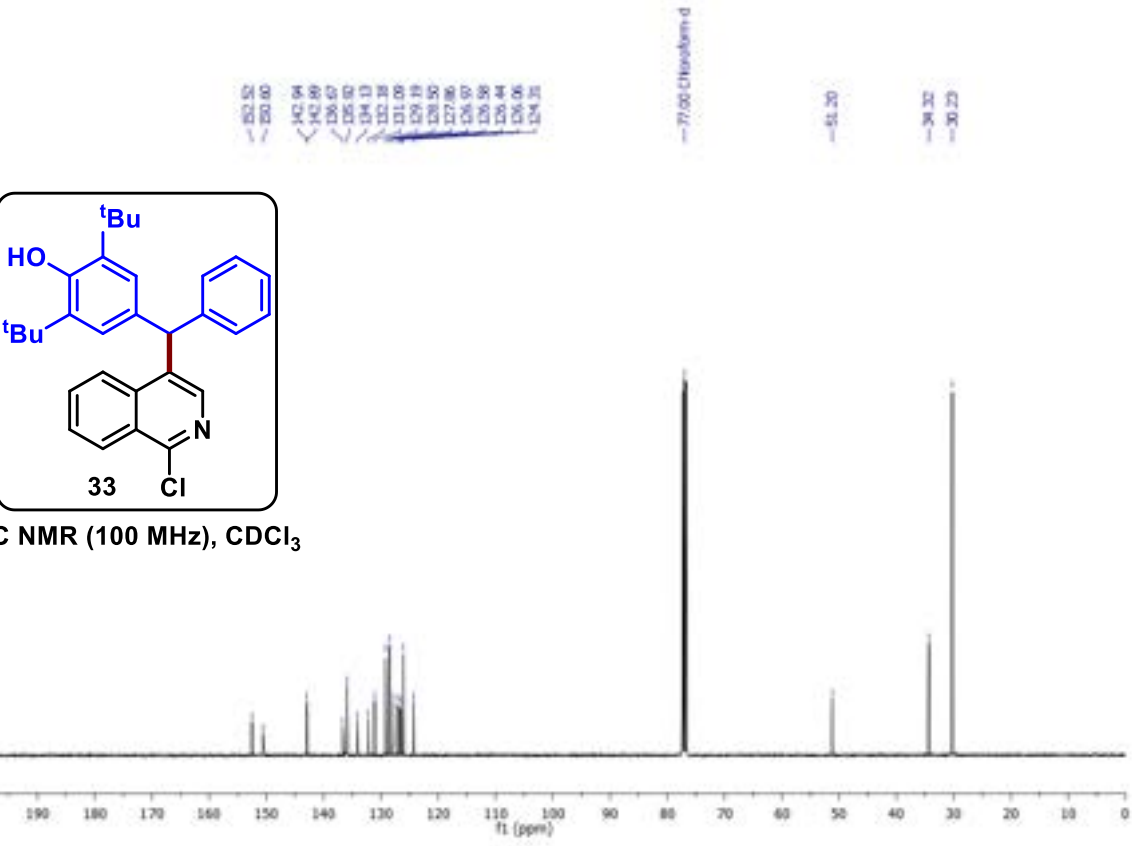


^{1}H NMR (400 MHz), $CDCl_3$



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

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Souza, A. S.; Forezi, L. S. M.; Ferreira, V. F.; de Carvalho da Silva, F. *Eur. J. Org. Chem.* **2020**, *2020*, 2650−2692. (c) Singh, G.; Pandey, R.; Pankhade, Y. A.; Fatma, S.; Anand, R. V. *Chem. Rec.* **2021**, *21*, 4150−4173. (d) Ali, K.; Mishra, P.; Kumar, A.; Reddy, D. N.; Chowdhury, S.; Panda, G. *Chem. Commun.* **2022,** *58*, 6160-6175.

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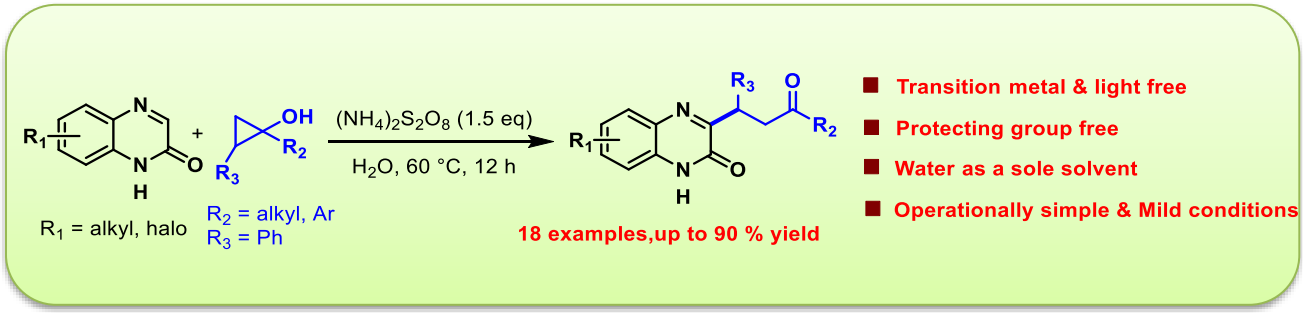
Section-II

Metal- and Light-Free Direct C-3 Ketoalkylation of Quinoxalin-2(1*H*)-ones with Cyclopropanols in Aqueous Medium

Direct oxidative C-3 ketoalkylation of quinoxalin-2(1*H*)-ones with cyclopropanols using ammonium persulfate as an oxidant in an aqueous medium has been achieved in a moderate to good yield. The reaction does not require metals, light source, or catalysts to facilitate the reaction and could be efficiently utilized to construct a wide range of biologically relevant 3-ketoalkylated quinoxalin-2(*1H*)-ones.



Chemistryselect **2022**, *7*, e2022035971

2.2.1 Introduction

Among various *N*-heterocycles, quinoxalin-2(1*H*)-ones has emerged as an essential scaffold in organic and medicinal chemistry as they possess many biological and pharmaceutical activities.[1] In particular, C-3 functionalized quinoxalin-2(1*H*)-ones proved to be critical constituents of several therapeutic agents, and they possess a myriad of biological activities such as antibacterial,[2a] aldose reductase & antioxidant,[2b] antitumor,[2c,d] (Fig. 2.2.1).[3] Given their immense medicinal importance, convenient synthesis to access C-3 functionalized quinoxalin-2(1*H*)-ones are of great interest. In the last decade, remarkable advances have been achieved in CH-functionalization strategies, especially the late stage functionalization (LSF), as it provides enormous opportunities in achieving atom & step economy, reaction efficiency, selectivity, and allowing a rapid way to generate a diverse set of compounds etc., that are critical in the area of drug discovery, material research and molecular imaging.[4,5] Conceivably, this strategy have been aptly applied to functionalize quinoxalin-2(1*H*)-one moiety, and notable examples include acylation,[6] arylation,[7] alkylation,[8] alkoxylation,[9] amination,[10] phosphonation,[11] di/trifluoromethylation,[12] thiolation,[13] and other[14] have been carried out efficiently.

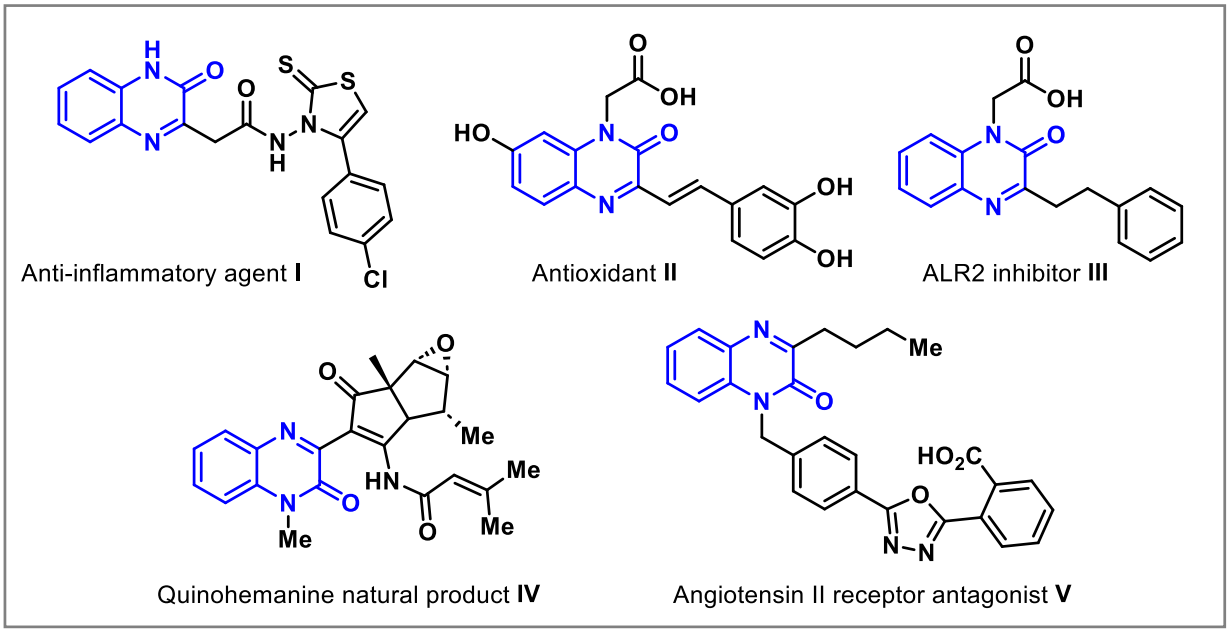


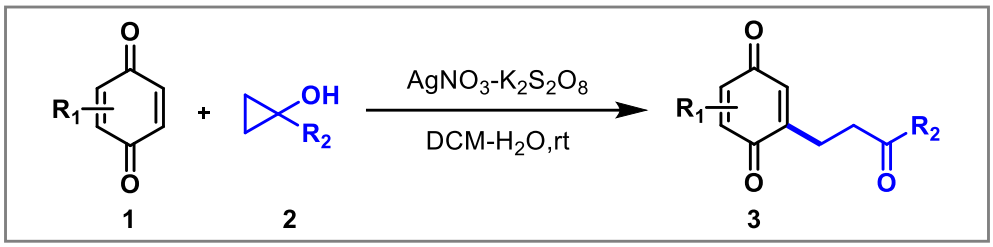
Figure 2.2.1. Representative biologically active C3-substituted quinoxalin-2(1*H*)-ones.

Indeed, *β*-carbonyl alkylation of various *N*-heterocycles is also considered significant because the resultant *β*-heteroarylated ketone moiety is found in many natural products and biologically active molecules. Furthermore, they serve as an important functional building blocks for further useful synthetic elaborations.[15] Surprisingly, the study of *β*-carbonyl alkylation on

quinoxalin-2(1*H*)-one moiety remains under explored.[16] In recent years, the chemistry of cycloalkanols and its derivatives has received a considerable attention owing to its capacity to produce highly reactive alkoxy radicals *via* *β*-scission and subsequent powerful synthetic transformations.[17,18] Apparently, this ring-opening, functionalization has become a prudent strategy for preparing a variety of molecules of interest, and few interesting examples are delineated below.

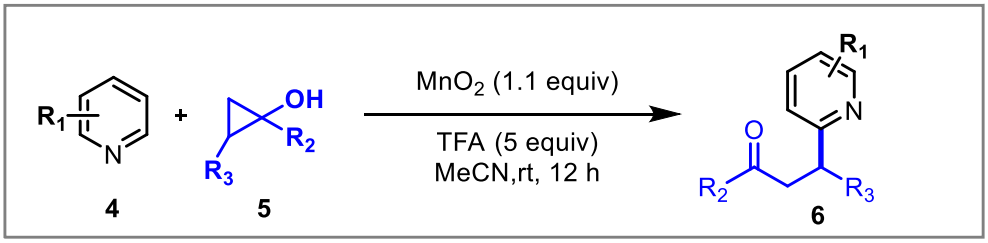
2.2.2 Literature Precedence on Ketoalkylation employing Cycloalkanols

In 2013, Malayappasamy *et al.* developed a radical strategy for synthesizing γ-carbonyl quinones *via* C–H activation of quinones **1** with cyclopropanols **2** (Scheme 2.2.1).[19] $AgNO_3$ acts as an effective catalyst for ring-opening and functionalization reactions. A natural cytotoxic product, evelynin and 4,6-dimethoxy-2,5-quinodihydrochalcone, were successfully prepared using this strategy.



Scheme 2.2.1 Ag(I)-catalyzed oxidative ring-opening of cyclopropanols with quinones.

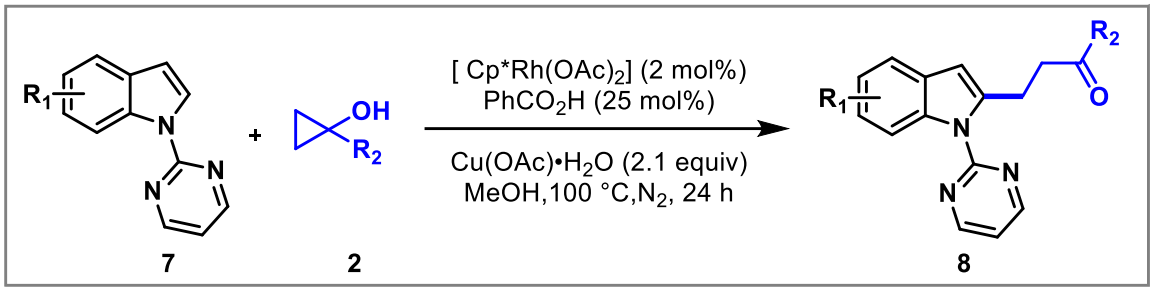
Lectka *et al.* in 2016, developed a direct C–H to C–C bond functionalization of electron-deficient heteroarenes (pyridines) **4** facilitated by mild C–C bond cleavage of cyclopropanols **5** to produce *β*-aryl carbonyl-containing products **6**. Manganese dioxide is used as an oxidant for the ring-opening of cyclopropanols and to regenerate aromaticity (after C−C bond formation) (Scheme 2.2.2).[20]



Scheme 2.2.2 Manganese(IV) oxide-mediated coupling of cyclopropanols with heteroarenes.

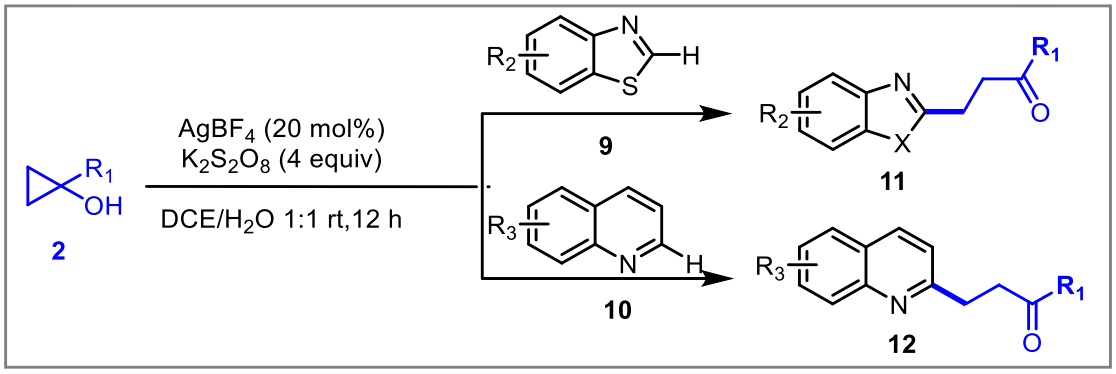
In 2016, Li and colleagues disclosed the synthetic method for *β*-heteroaryl ketones **8** *via* Rh(III)-catalyzed C−H activation of arenes **7**. In this study, cyclopropanol ring opening and CH bond activation were combined under Rh(III)-catalysis for the first time. Mild reaction condi-

tions, good functional group tolerance and high regioselectivity, are the salient features of this method (Scheme 2.2.3).[21]



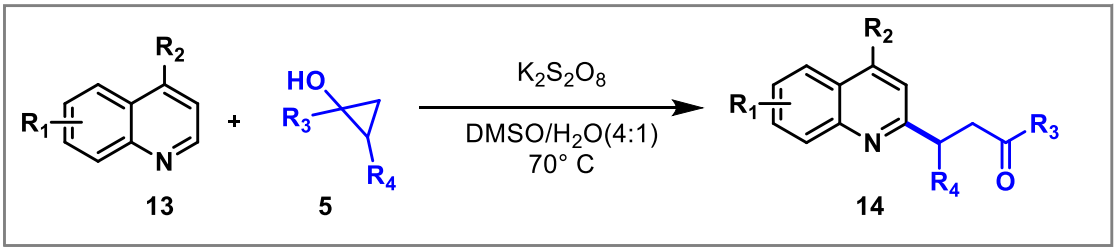
Scheme 2.2.3 Rhodium(III)-catalyzed coupling of arenes with cyclopropanols.

In 2017, Duan *et al.* reported an efficient silver (I)-catalyzed oxidative ring-opening of cyclopropanols **2** with azoles **9** & quinolines **10** for the synthesis of *β*−carbonyl alkylated azoles **11** & quinolines **12** (Scheme 2.2.4).[22] This method allows the synthesis of diverse *β*−carbonyl alkylated heteroarenes derivatives in satisfactory yields under mild conditions from easily accessible starting materials.



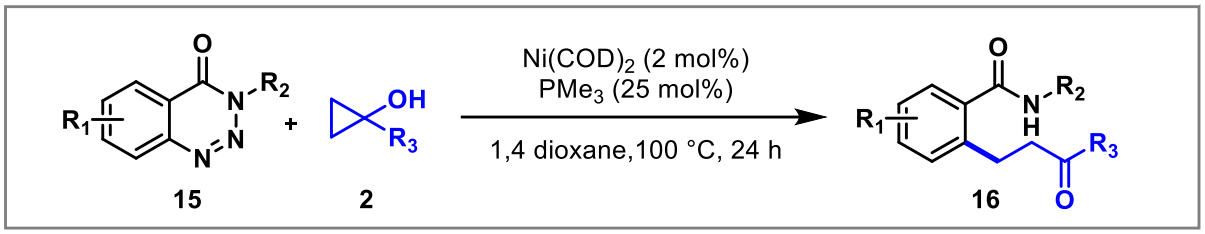
Scheme 2.2.4 Ag (I)-catalyzed oxidative ring-opening of cyclopropanols with heteroarenes.

In 2020, Wang and colleagues developed the synthesis of *β*−carbonyl alkylated quinolines **14** *via* $K_2S_2O_8$-mediated ring-opening of cyclopropanols **5**. This method obviates the use of metal and photocatalyst and gives moderate to excellent yields of the product (Scheme 2.2.5).[23]



Scheme 2.2.5 Catalyst-free oxidative ring-opening of cyclopropanols with quinolines.

Li *et al.* in 2020 reported the Ni-catalyzed reaction of benzotriazinones **15** and cyclopropanols **2** for the synthesis of *β*-(*o*-amido)aryl ketones **16**. This reaction gives easy access to functionalized *β*-aryl ketones from readily available starting materials with moderate to good yields (Scheme 2.2.6).[24]

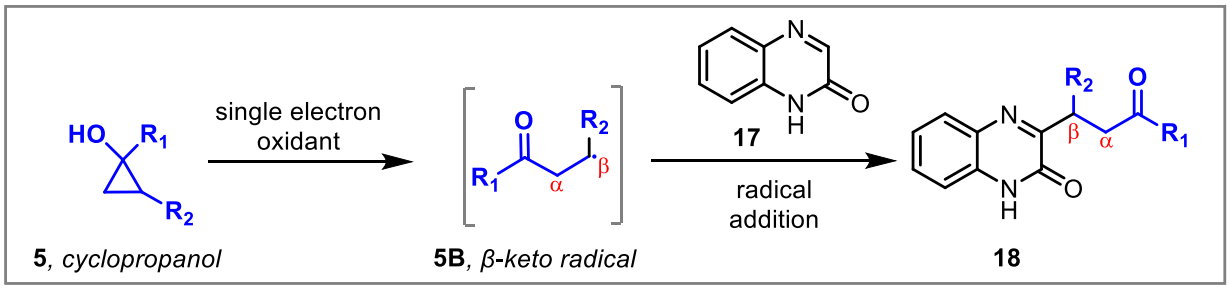


Scheme 2.2.6 Cross-coupling of benzotriazinones with cyclopropanols.

2.2.3 Present Work

2.2.3.1 Statement of the Problem

From the above discussion, it is worth noting that the C-C bond cleavage of cycloalkanols and their derivatives offers an enormous opportunity for the generation of complex molecular synthesis. Intrigued by the biological significance associated with the quinoxalin-2(1*H*)-one moiety and the remarkable progress achieved so far in cyclopropanol chemistry, we sought to examine the possibility of utilizing cyclopropanol chemistry for the functionalization of quinoxalin-2(1*H*)-one. We envisioned that the radical ring-opening of cyclopropanol **5** in the presence of a single electron oxidant would generate *β*-keto radical **5B,** and its subsequent addition to quinoxalin-2(1*H*)-one **17** might provide a new opportunity to access structurally diverse C-3 ketoalkylated quinoxalin-2(1*H*)-ones **18** (Scheme 2.2.7). In this section, we describe the development of metal- and light-free direct C-3 ketoalkylation of quinoxalin-2(1*H*)-ones with cyclopropanols in an aqueous medium.



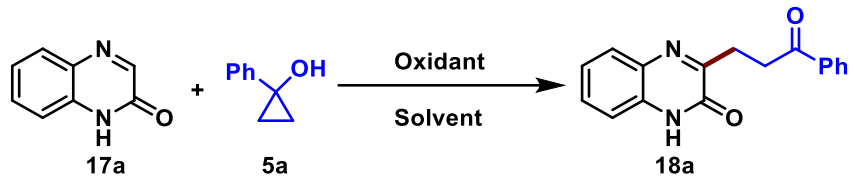
Scheme 2.2.7 Hypothesis on *β*-carbonyl alkylation on quinoxalin-2(1*H*)-one.

2.2.4 Results and Discussion

2.2.4.1 Optimization of Reaction Conditions

Most of the C-3 functionalization strategy of quinoxalin-2(1*H*)-ones reported in the literature employs only *N*-protected quinoxalin-2(1*H*)-ones.[25] So we thought of testing the

Table 2.2.1 Optimization of the reaction conditions[a,b]



entry	Oxidant (equiv.)	solvent	temp (°C)	time (h)	yield (%)
1	$K_2S_2O_8$ (3)	H_2O	60	24 h	71
2	None	H_2O	60	24 h	NR
3	$K_2S_2O_8$ (3)	DCE /H_2O (1:1)	60	24 h	59
4	$K_2S_2O_8$ (3)	DMSO /H_2O (1:1)	60	12 h	56
5	$Na_2S_2O_8$ (3)	H_2O	80	12 h	74
6	$(NH_4)_2S_2O_8$ (3)	H_2O	60	12 h	79
7	CHP (3)	H_2O	60	12 h	21
8	H_2O_2 (3)	H_2O	60	12 h	10
9	TBHP (3)	H_2O	60	12 h	06
10	BPO(3)	H_2O	60	12 h	trace
11	$(NH_4)_2S_2O_8$ (2)	H_2O	60	12 h	85
12	$(NH_4)_2S_2O_8$ (1.5)	H_2O	60	12 h	89
13	$(NH_4)_2S_2O_8$ (1)	H_2O	60	12 h	75
14	$(NH_4)_2S_2O_8$ (1.5)	H_2O	70	12 h	87
15	$(NH_4)_2S_2O_8$ (1.5)	H_2O	50	12 h	59

[a]Reaction conditions: **17a** (0.34 mmol), **5a** (0.51 mmol), oxidant, solvent (3.0 mL), 60 °C, 12h. [b]The yields refer to the isolated yields.CHP= Cumene Hydroperoxide. NR = No reaction.

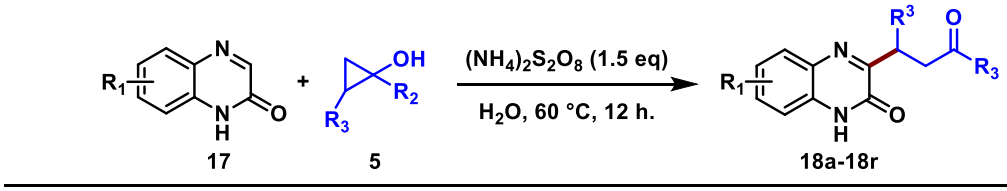
ketoalkylation of unprotected quinoxalin-2(1*H*)-one first. In a prototype experiment, quinoxalin-2(1*H*)-one **17a** was treated with phenyl cyclopropanol **5a** using $K_2S_2O_8$ in pure water at 60 °C. Delightfully, the reaction went smoothly, and the expected product **18a** was afforded with 71% yield (Table 2.2.1, entry 1). The formation of the desired product **18a** was ascertained by its ^1H, ^{13}C NMR and HRMS analysis. The appearance of a typical ^1H signal at δ 3.51 (t, 2H) corresponds to methylene protons (-*CH*$_2$-CO-) *α* to ketone, and δ 3.17 (t, 2H) corresponds to the methylene protons (-*CH*$_2$-CH$_2$-CO-) *β* to the ketone. In addition, the appearance of typical carbon signals at δ 199.1 is due to the carbonyl carbon of ketone. Furthermore, the constitution of **18a** has been confirmed as $C_{17}H_{15}O_2N_2$ (calculated value 279.1128) by the HRMS $[M+H]^+$ found as 279.1123. With this structure confirmation of product **18a**, we turned our focus on improving the yield of product **18a.** The control experiment suggests that $K_2S_2O_8$ is necessary for the reaction to proceed (Table 1, entry 2). Subsequently, solvent combinations (DCE/H_2O, DMSO/H_2O) were investigated to test the effect of the solvents, which did not improve the yield of **18a** (Table 2.2.1, entries 3–4). In order to further optimize the reaction conditions, different oxidizing agents such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, CHP, H_2O_2, TBHP, and BPO were tested in this reaction (Table 2.2.1, entries 5–10), and among them $(NH_4)_2S_2O_8$ was found to be more suitable for this transformation generating **18a** in 79 % yield (Table 2.2.1, entry 6). Further screening of oxidant loading reveals that 1.5 equiv. of $(NH_4)_2S_2O_8$ is optimum, and the yield of **18a** was improved to 89 % (Table 2.2.1, entries 6, 11–13). Finally, after studying the effect of reaction temperature (Table 2.2.1, entries 14, 15), we reached the ideal condition to perform the reaction being 1 equiv. of **17a**, 1.5 equiv. of **5a** & 1.5 equiv. of $(NH_4)_2S_2O_8$ in pure water at 60 °C.

2.2.4.2 Scope of the reaction: Substituents on the Quinoxalin-2(1*H*)ones and Cycloalkanols

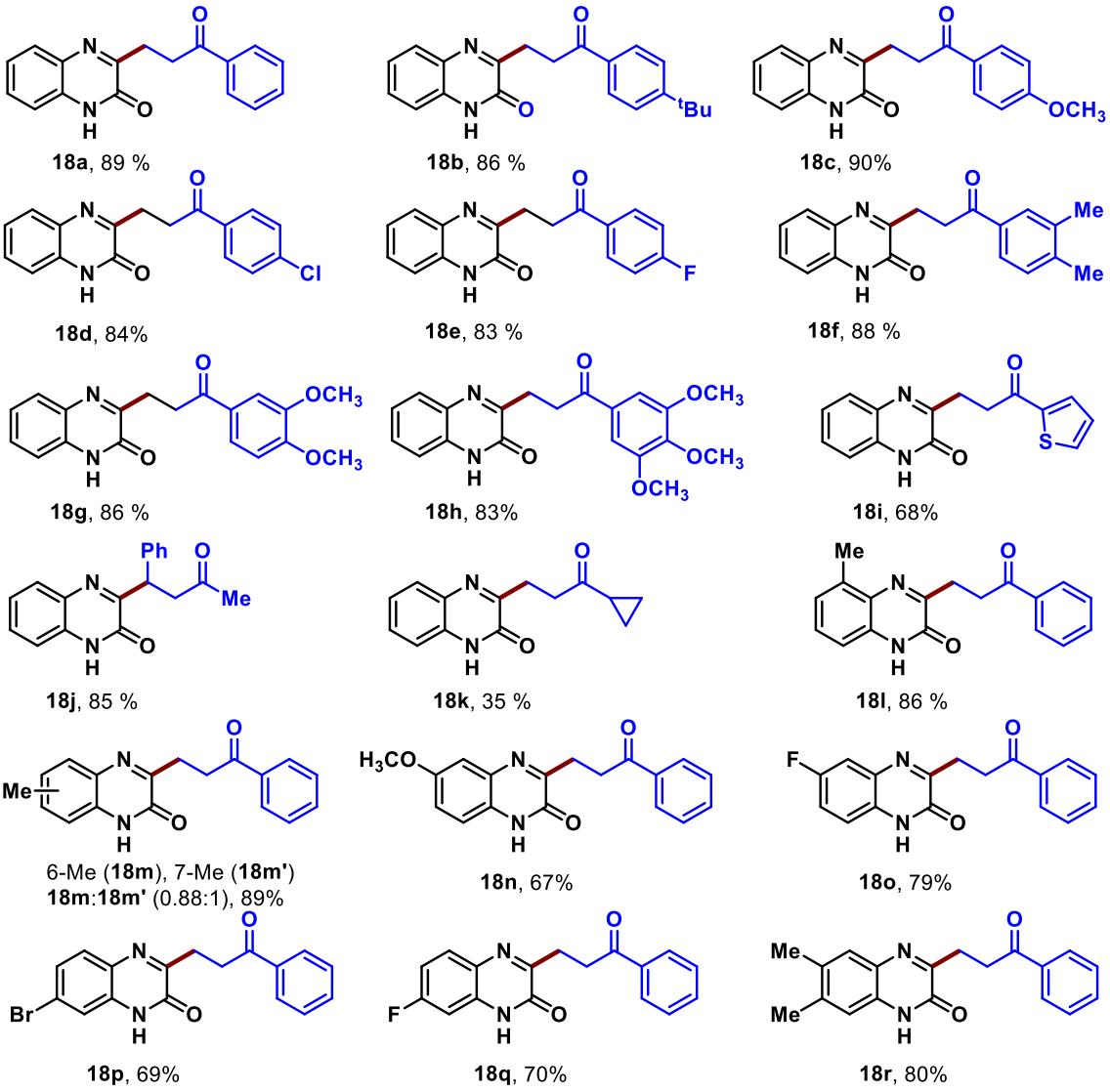
With the optimal reaction conditions in hand, the scope of the reaction was investigated (Table 2.2.2). Various substituted cyclopropanols and quinoxalin-2(1*H*)-ones were allowed to react in the presence of $(NH_4)_2S_2O_8$ in pure water. Most of the substituted cyclopropanols participated in the reaction efficiently, yielding the desired products **18** in moderate to good yields. Substituted cyclopropanols containing an electron-donating & halo substitution at the *para* position of the benzene ring, such as alkyl, alkoxy, chloro & fluro functionalities, were found to react smoothly to afford the corresponding products in good yields (**18a–18e**). Next, di and tri substitutions on the benzene ring of cyclopropanols worked well, and the corresponding products (**18f–18h**) were isolated in good yields. It is worth mentioning that heteroaryl-

substituted cyclopropanol (**5i**) also underwent the reaction despite in moderate yield (68%). Furthermore, 1,2-disubstituted cyclopropanol was also involved in this reaction, yielding **18j** in

Table 2.2.2 Substrate scope of quinoxalin-2(1*H*)-ones and cycloalkanols.[a,b]



17 5 18a-18r



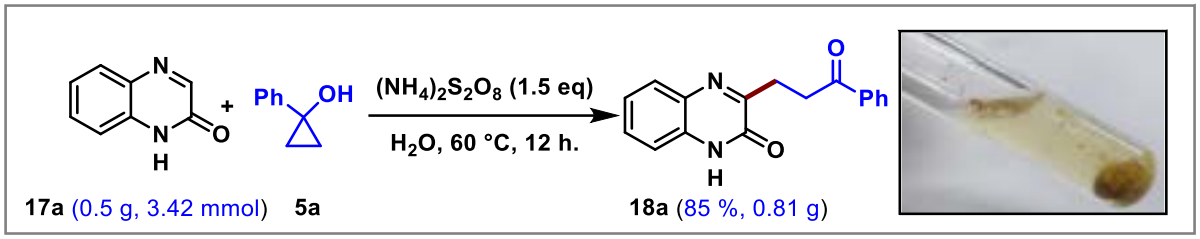
[a]All reactions were performed with **17** (0.34 mmol, 1 equiv.), **5** (1.5 equiv.), $(NH_4)_2S_2O_8$ (1.5 equiv.), water (3 mL), 60 °C, 12h. [b]Isolated yields.

85% yield. However, cycloalkyl-substituted cyclopropanol also participated in this reaction, albeit in less yield (**18k**). Subsequently, the effect of various substitutions on the quinoxalin-

2(1*H*)-ones **17** were also investigated. Quinoxalin-2(1*H*)-ones bearing electron-donating groups such as alkyl and alkoxy on the aryl ring also yielded the corresponding products in good yields (**18l-18n**, 67-89 %). Notably, halo-substituted quinoxalin-2(*1H*)-ones were well tolerated to give the corresponding products in moderate to good yields (**18o-18q**, 69-79 %). In addition, quinoxalin-2(1*H*)-one bearing disubstitution on the phenyl ring has proved to be compatible and provided the target product **18r** in good yield (80%).

2.2.4.3 Gram-Scale Experiment

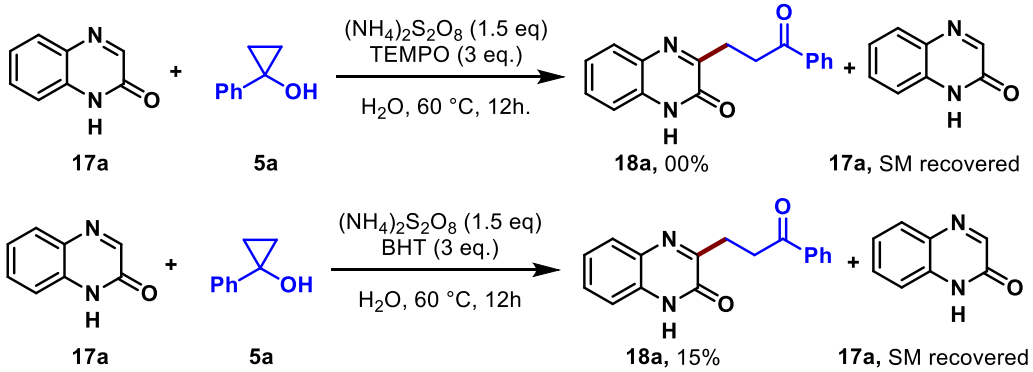
A gram-scale experiment was carried out to show the utility of this protocol. The scale-up experiment using **17a** (3.42 mmol, 0.5 g) and **5a** (5.13 mmol, 0.68 g) gave product **18a** (0.81 g) in 85% yield (Scheme 2.2.8). It is important to mention here that as the reaction medium is pure water, the product isolation is quite simple. After completion of the reaction, the solid product **18a** precipitated out from the reaction mixture as shown in Scheme 2.2.8, which can be simply filtered and washed with water followed by *n*-hexane to provide sufficiently pure **18a**.



Scheme 2.2.8 Gram scale preparation

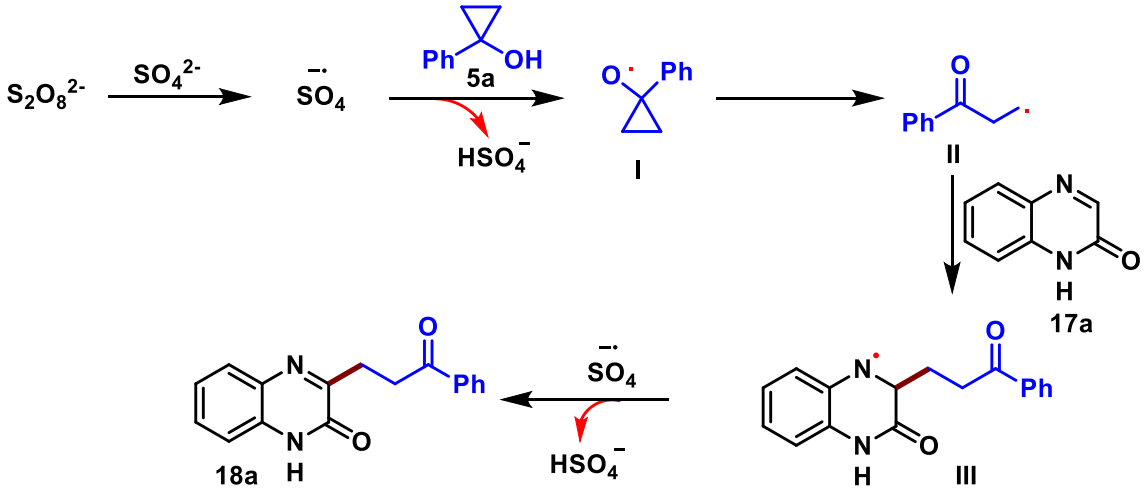
2.2.4.4 Control Experiments and Plausible Reaction Mechanism

To understand the reaction mechanism of the present protocol, a few control experiments were carried out. TEMPO & BHT were selected as radical scavengers and employed under optimal reaction conditions. As a result, the product formation was suppressed, which indicates that the reaction should proceed through a radical pathway (Scheme 2.2.9).



Scheme 2.2.9 Control experiments

On the basis of the control experiments and precedent studies, [24,26] a plausible reaction mechanism is proposed as shown in Scheme 2.2.10. First, the single-electron oxidation of cyclopropanol **5a** by $(NH_4)_2S_2O_8$ generates an oxygen-centred alkoxy radical **I**, which undergoes rearrangement to form *β*-keto radical **II** that can react with quinoxalin-2(*1H*)-one (**17a**) leads to radical intermediate **III**. Subsequently, intermediate **III** undergoes one-electron oxidation and loses H^+ to form the final product **18a**.



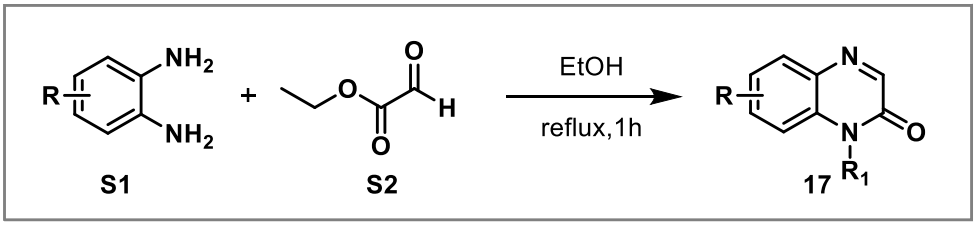
Scheme 2.2.10 A plausible mechanism

2.2.5 Conclusion

In summary, we have developed a simple and economical method for *β*-keto alkylation of quinoxalin-2(1*H*)-ones with cyclopropanol in a water medium. Various quinoxalin-2(1*H*)-ones and cyclopropanols were successfully participated in this reaction. This operationally simple process does not require a transition metal catalyst, usual *NH* protection, and external light source, thus provide a greener pathway which we believe will find application in drug discovery program.

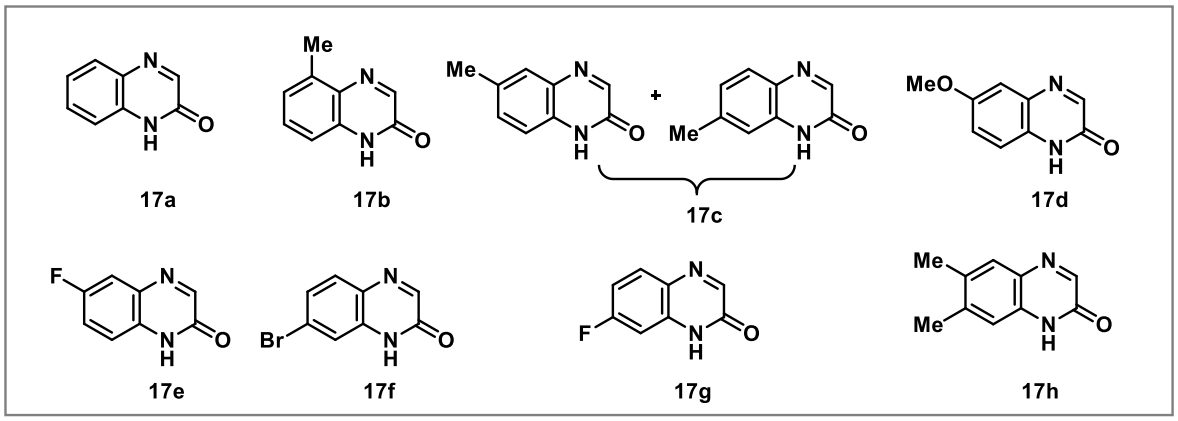
2.2.6 Experimental Section

2.2.6.1 General Procedure for the Preparation of Quinoxalin-2(1*H*)-ones[27]:



Scheme 2.2.11 Preparation of quinoxalin-2(1*H*)-ones

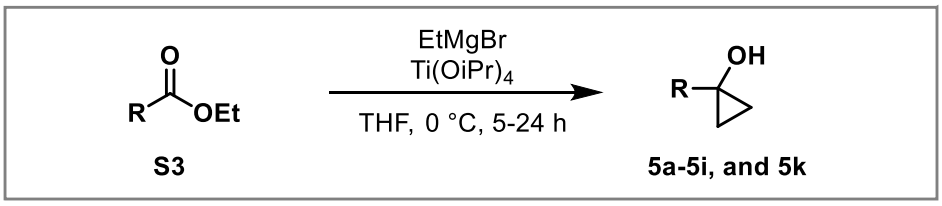
To a suspension of *o*-arylenediamine **S1** (1 equiv.) in ethanol was added ethyl 2-oxoacetate **S2** (1.1 equiv.). The mixture was stirred at reflux for 1h, then at room temperature overnight. The precipitated solid was filtered and washed with ethanol, then dried to give quinoxalinone **17**.



The quinoxalin-2(1*H*)-ones (**17a-17h**) were prepared by following the above general procedure**.**

2.2.6.2 General Procedure for the Preparation of Cyclopropanols[28]:

Procedure A: Kulinkovich reaction: Cyclopropanols **2a-2i** and **2k** were prepared according to procedure A.

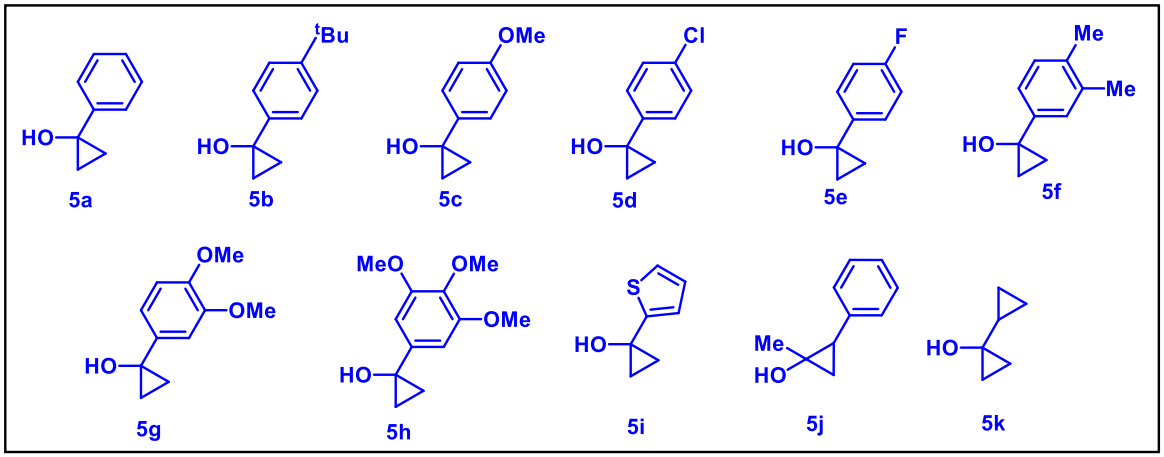


Scheme 2.2.12 Preparation of cyclopropanols *via* Kulinkovich reaction

Ethylmagnesium bromide (2.8 equiv, 2M in THF) in THF was added dropwise over 30 min at 0 °C to a solution of ester **S3** (1.0 equiv) and titanium isopropoxide (1.4 equiv) in THF under argon. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water, and the precipitated solid was removed by filtration. The filtrate was extracted with ethyl acetate (3 × 30 mL), washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the cyclopropanols **5a-5i** and **5k**.

Procedure for the synthesis of 5j: Titanium isopropoxide (1.36 g, 1.45 mL, 4.8 mmol, 1.0 equiv) was added to a flame-dried flask at room temperature under argon. Anhydrous THF (20 mL) was added to the flask, followed by styrene (0.5 g, 4.8 mmol, 1.0 equiv) and EtOAc (0.69

mL, 7.2 mmol, 1.5 eq). Then freshly prepared cyclohexyl magnesium bromide (19 mL, 19.2 mmol, 4 equiv, ~1M in THF) was added dropwise over the period of 1 h at 25 ºC. The reaction was stirred overnight at room temperature, diluted with EtOAc (50 mL) and poured into NH_4Cl (50 mL). The mixture was stirred vigorously for 0.5 h to break up the emulsion and then filtered through celite. The layers were separated, and the aqueous layer was extracted twice with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography to yield the desired cyclopropanols **5j**



2.2.6.3 General procedure for ketoalkylation of quinoxalin-2(1*H*)-ones:

To an oven-dried 5 mL reaction vial equipped with a magnetic stir bar was added quinoxalin-2(*1H*)-ones **17** (0.34 mmol), $(NH_4)_2S_2O_8$ (1.5 equiv., 0.51 mmol), water (3 mL) and the mixture was stirred at 60 °C for 5 min. Then, cyclopropanol **5** (1.5 equiv., 0.51 mmol) was added slowly, and the reaction mixture was stirred at 60 °C for 12 h. After completion of the reaction (detected by TLC), extracted with DCM/MeOH (9:1) (20 mL ×3). The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to obtain a crude product which was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent to afford the pure product **18**.

2.2.6.4 Procedure for Gram Scale experiment:

To an oven-dried 15 mL reaction vial equipped with a magnetic stir bar was added quinoxalin-2(*1H*)-ones **17a** (0.5 g, 3.42 mmol) $(NH_4)_2S_2O_8$ (1.5 equiv., 5.1 mmol), water (7 mL) and the mixture was stirred at 60 °C for 5 min. Then, cyclopropanol **5a** (1.5 equiv., 5.1 mmol) was added slowly, and the reaction mixture was stirred at 60 °C for 12 h. After comple-

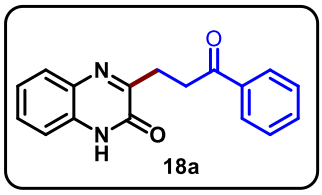
tion of the reaction (detected by TLC), the solid product **18a** precipitated out from the reaction mixture, which can be simply filtered and washed with water followed by *n*-hexane to provide sufficiently pure **18a**.

2.2.6.5 Procedure for the Control Reaction:

To an oven-dried 5 mL reaction vial equipped with a magnetic stir bar was added quinoxalin-2(*1H*)-ones **17a** (0.34 mmol), $(NH_4)_2S_2O_8$ (1.5 equiv., 0.51 mmol), 2,2,6,6-tetramethylpiperidinooxy (TEMPO) or butylated hydroxytoluene (BHT) (3 equiv), water (3 mL) Then, cyclopropanol **5a** (1.5 equiv., 0.51 mmol) was added slowly, and the reaction mixture was stirred at 60 °C for 12 h. and the reaction was monitored by TLC.

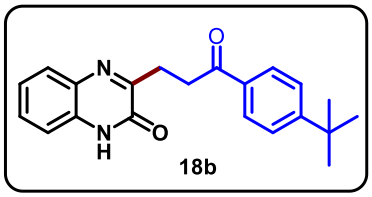
2.2.6.6 Characterization Data of Compounds:

3-(3-oxo-3-phenylpropyl)quinoxalin-2(1*H*)-one (18a):



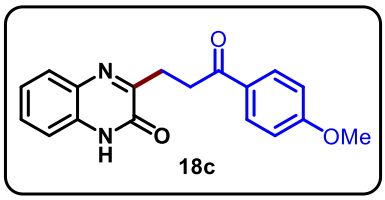
The product **18a** was obtained in 89% yield (85 mg, pale brown solid); **mp** = 178-180 °C; R_f = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (500 MHz, DMSO-d$_6$) δ** = 12.35 (s, 1H), 8.02 (d, *J* = 7.3 Hz, 2H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 8.3 Hz, 3H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 3.51 (t, *J* = 6.6 Hz, 2H), 3.17 (t, *J* = 6.6 Hz, 2H); **^{13}C NMR (125 MHz, DMSO-d$_6$) δ** = 199.1, 160.5, 154.6, 136.9, 133.0, 131.7, 131.4, 129.4, 128.7, 127.9, 127.8, 123.0, 115.2, 33.9, 27.0; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{17}H_{15}O_2N_2$ 279.1128; found 279.1123.

3-(3-(4-(tert-butyl)phenyl)-3-oxopropyl)quinoxalin-2(1*H*)-one (18b):



The product **18b** was obtained in 86% yield (98 mg, pale brown solid); **mp** = 176-178 °C; R_f = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (500 MHz, DMSO- d$_6$) δ** = 12.37 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 3H), 7.45 (dd, *J* = 11.7, 4.7 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.25-7.18 (m, 1H), 3.49 (t, *J* = 6.6 Hz, 2H), 3.15 (t, *J* = 6.7 Hz, 2H), 1.31 (s, 9H); **^{13}C NMR (125 MHz, DMSO-d$_6$) δ** = 198.5, 160.6, 156.1, 154.7, 134.3, 131.7, 131.4, 129.4, 128.0, 127.9,125.5, 123.0, 115.2, 34.8, 33.9, 30.9, 27.0; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{21}H_{23}O_2N_2$ 335.1756; found 335.1754.

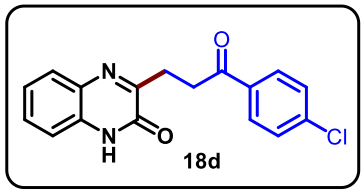
3-(3-(4-methoxyphenyl)-3-oxopropyl)quinoxalin-2(1*H*)-one (18c):



18c

The product **18c** was obtained in 90% yield (95 mg, pale brown solid); **mp** = 185-187 °C; R_f = 0.40 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 12.34 (s, 1H), 8.04 – 7.97 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.31 – 7.27 (m, 1H), 7.25–7.19 (m, 1H), 7.07 (t, *J* = 5.8 Hz, 2H), 3.85 (s, 3H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.14 (t, *J* = 6.7 Hz, 2H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 197.3, 163.0, 160.7, 154.6, 131.7, 131.4, 130.2, 129.7, 129.4, 127.9, 123.0, 115.2, 113.9, 55.5, 33.6, 27.1; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{18}H_{17}O_3N_2$ 309.1234; found 309.1233.

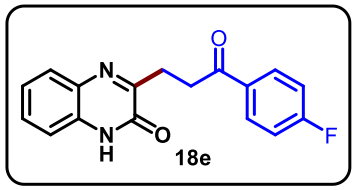
3-(3-(4-chlorophenyl)-3-oxopropyl)quinoxalin-2(1*H*)-one (18d):



18d

The product **18d** was obtained in 84% yield (90 mg, pale brown solid); **mp** = 201-203 °C; R_f = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 12.38 (s, 1H), 8.09-7.96 (m, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 5.8 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 3.49 (t, *J* = 6.5 Hz, 2H), 3.17 (t, *J* = 6.5 Hz, 2H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 198.2, 160.4, 154.7, 138.0, 135.6, 131.7, 131.4, 129.9, 129.4, 128.9, 128.0, 123.1, 115.3, 33.9, 27.0; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{17}H_{14}O_2N_2Cl$ 313.0738; found 313.0739.

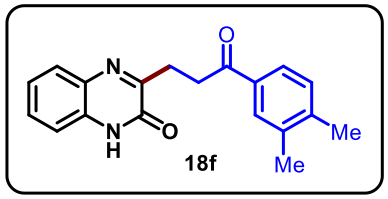
3-(3-(4-fluorophenyl)-3-oxopropyl)quinoxalin-2(1*H*)-one (18e):



18e

The product **18e** was obtained in 83% yield (84 mg, pale brown solid; **mp** = 218-220 °C; R_f = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (500 MHz, DMSO-d$_6$) δ** = 12.35 (s, 1H), 8.15-8.06 (m, 2H), 7.53 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.49-7.42 (m, 1H), 7.41-7.33 (m, 2H), 7.28 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.25-7.18 (m, 1H), 3.50 (t, *J* = 6.6 Hz, 2H), 3.17 (t, *J* = 6.6 Hz, 2H); **^{13}C NMR (125 MHz, DMSO-d$_6$) δ** = 197.7, 164.9 (d, J_{C-F} = 251.01 Hz) 160.4, 154.6, 133.6, 133.6, 131.5 (d, J_{C-F} = 29.76 Hz), 130.9, 130.8 128.6(d, J_{C-F} = 149.54 Hz), 123.0, 115.7 (d, J_{C-F} = 22.12 Hz), 115.2, 33.8, 27.0; **^{19}F NMR (376 MHz, DMSO-d$_6$) δ** = -106.38; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{17}H_{14}FN_2O_2$ 297.1034; found 297.1031.

3-(3-(3,4-dimethylphenyl)-3-oxopropyl)quinoxalin-2(1*H*)-one (18f):

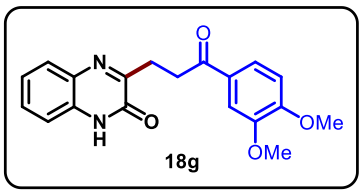


18f

The product **18f** was obtained in 88% yield (92 mg, pale brown solid); **mp** = 185-187 °C; R_f = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (500 MHz, DMSO-d$_6$) δ** = 12.34 (s, 1H), 7.79

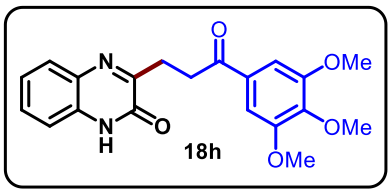
(s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.46 (dd, *J* = 11.2, 4.1 Hz, 1H), 7.28 (dd, *J* = 7.6, 3.2 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.14 (t, *J* = 6.7 Hz, 2H), 2.29 (s, 6H); **^{13}C NMR (125 MHz, DMSO-d$_6$) δ** = 198.6, 160.6, 154.6, 142.1, 136.6, 134.7, 131.6, 131.4, 129.7, 129.3, 128.8, 127.9, 125.6, 123.0, 115.2, 33.9, 27.1, 19.6, 19.3; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{19}H_{19}O_2N_2$ 307.1441; found 307.1441.

3-(3-(3,4-dimethoxyphenyl)-3-oxopropyl)quinoxalin-2(1*H*)-one (18g):



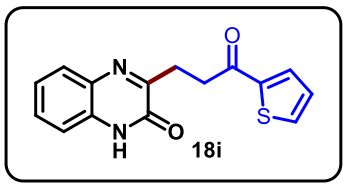
The product **18g** was obtained in 86% yield (100 mg, pale brown solid); **mp** = 183-185 °C; ***R$_f$*** = 0.35 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 12.34 (s, 1H), 7.71 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.59-7.55 (m, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.45 (ddd, *J* = 8.4, 5.9, 1.4 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.22 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.46 (t, *J* = 6.8 Hz, 2H), 3.14 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 197.4, 160.7, 154.7, 153.0, 148.5, 131.7, 131.4, 129.7, 129.4, 128.0, 123.0, 122.5, 115.2, 110.9, 110.2, 55.7, 55.5, 33.7, 27.3; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{19}H_{19}O_4N_2$ 339.1339; found 339.1339.

3-(3-oxo-3-(3,4,5-trimethoxyphenyl)propyl)quinoxalin-2(1*H*)-one (18h):



The product **18h** was obtained in 83% yield (105 mg, pale brown solid); **mp** = 226-228 °C; ***R$_f$*** = 0.30 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (500 MHz, DMSO-d$_6$) δ** = 7.59 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.32 (s, 2H), 7.30 – 7.21 (m, 2H), 3.85 (s, 6H), 3.75 (s, 3H), 3.51 (t, *J* = 6.7 Hz, 2H), 3.15 (t, *J* = 6.7 Hz, 2H); **^{13}C NMR (125 MHz, DMSO-d$_6$) δ** = 197.9, 160.7, 154.7, 152.8, 141.8, 132.1, 131.7, 131.4, 129.4, 128.0, 123.1, 115.2, 105.5, 60.1, 56.0, 34.1, 27.3; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{20}H_{21}O_5N_2$ 369.1445; found 369.1443.

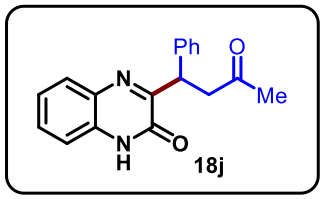
3-(3-oxo-3-(thiophen-2-yl)propyl)quinoxalin-2(1*H*)-one (18i):



The product **18i** was obtained in 68% yield (66 mg, pale brown solid); **mp** = 183-185 °C; ***R$_f$*** = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (500 MHz, DMSO-d$_6$) δ** = 12.35 (s, 1H), 8.04 (d, *J* = 2.9 Hz, 1H), 8.00 (d, *J* = 4.9 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.29-7.21 (m, 3H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.16 (t, *J* = 6.7 Hz, 2H); **^{13}C NMR (125 MHz, DMSO-d$_6$) δ** = 192.1, 160.3, 154.6, 143.8, 134.4, 133.0, 131.7, 131.4, 129.4,128.7, 127.9, 123.0, 115.2, 34.4, 27.1; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$calcd for

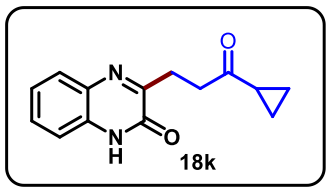
$C_{15}H_{13}O_2N_2S$ 285.0692; found 285.0688.

3-(3-oxo-1-phenylbutyl)quinoxalin-2(1*H*)-one (18j):



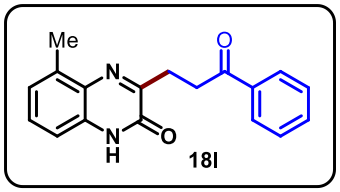
The product **18j** was obtained in 85% yield (85 mg, pale brown solid); **mp** = 209-211 °C; R_f = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 12.33 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.53 – 7.44 (m, 1H), 7.32 – 7.24 (m, 6H), 7.21 – 7.15 (m, 1H), 4.97 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.63 (dd, *J* = 17.7, 10.3 Hz, 1H), 3.00 (dd, *J* = 17.7, 4.9 Hz, 1H), 2.12 (s, 3H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 206.6, 161.4, 154.0, 140.6, 131.6, 131.2, 129.8, 128.4, 128.3, 128.1, 126.6, 123.2, 115.2, 47.5, 41.4, 30.0; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$calcd for $C_{18}H_{17}O_2N_2$ 293.1285; found 293.1284.

3-(3-cyclopropyl-3-oxopropyl)quinoxalin-2(1*H*)-one (18k):



The product **18k** was obtained in 35% yield (29 mg, pale brown solid); **mp** = 174-176 °C; R_f = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 12.32 (s, 1H), 7.69-7.62 (m, 1H), 7.51-7.43 (m, 1H), 7.30-7.23 (m, 2H), 3.08-2.95 (m, 4H), 2.13 (tt, *J* = 7.6, 4.8 Hz, 1H), 0.92-0.82 (m, 4H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 209.1, 160.4, 154.6, 131.6, 131.4, 129.4, 127.9, 123.1, 115.2, 37.8, 26.7, 20.4, 9.9; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{14}H_{15}O_2N_2$ 243.1128; found 243.1123.

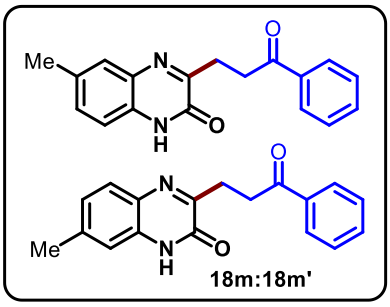
5-methyl-3-(3-oxo-3-phenylpropyl)quinoxalin-2(1*H*)-one (18l):



The product **18l** was obtained in 86% yield (78 mg, pale brown solid); **mp** = 216-218 °C; R_f = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 8.03 (dd, *J* = 6.8, 5.6 Hz, 2H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 3.51 (t, *J* = 6.2 Hz, 2H), 3.21 (t, *J* = 6.3 Hz, 2H), 2.20 (s, 3H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 199.0, 158.5, 154.6, 137.0, 136.1, 133.0, 131.6, 129.8, 129.1, 128.7, 127.8, 123.9, 113.1, 33.3, 27.1, 16.5; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{18}H_{17}O_2N_2$ 293.1285; found 293.1278.

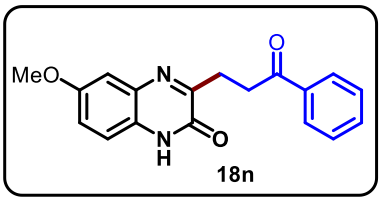
6-methyl-3-(3-oxo-3-phenylpropyl)quinoxalin-2(1*H*)-one (18m):
7-methyl-3-(3-oxo-3-phenylpropyl)quinoxalin-2(1*H*)-one (18m′):

The product **18m: 18m′** was obtained in 89% yield in a ratio (0.88:1) (81 mg, pale brown solid); **mp** = 173-175°C; R_f = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 12.28 (s, 1.78H), 8.02 (d, *J* = 8.2 Hz, 3.52H), 7.65 (dd, *J* = 7.8, 5.9 Hz, 1.82H), 7.55 (dd, *J* =



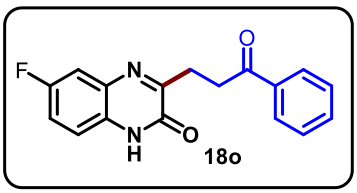
10.5, 4.7 Hz, 3.98H), 7.42 – 7.26 (m, 3.15H), 7.17 (d, *J* = 8.2 Hz, 1.02H), 7.05 – 7.02 (m, 1.96H), 3.50 (q, 3.52H), 3.15 (q, 3.49H), 2.36 (s, 2.32H), 2.31 (s, 3H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 199.1, 199.0, 160.3, 159.1, 154.8, 154.6, 139.4, 136.8, 133.0, 132.2, 130.5, 129.6, 129.4, 128.7, 127.9, 127.7, 127.6, 127.3, 124.3, 114.9, 114.9, 33.9, 33.8, 26.9, 21.2, 20.3; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$calcd for $C_{18}H_{17}O_2N_2$ 293.1285; found 293.1285.

6-methoxy-3-(3-oxo-3-phenylpropyl)quinoxalin-2(1*H*)-one (18n):



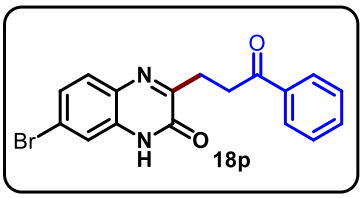
The product **18n** was obtained in 67% yield (59 mg, pale brown solid); **mp** = 193-195 °C; ***R$_f$*** = 0.35 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 12.25 (s, 1H), 8.06 – 7.99 (m, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.21 (d, J = 8.9 Hz, 1H), 7.10 (dd, J = 8.9, 2.8 Hz, 1H), 7.04 (d, J = 2.7 Hz, 1H), 3.74 (s, 3H), 3.51 (t, J = 6.7 Hz, 2H), 3.16 (t, J = 6.7 Hz, 2H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 199.0, 160.9, 155.2, 154.3, 136.9, 133.1, 132.0, 128.7, 127.9, 125.7, 118.4, 116.1, 109.7, 55.5, 34.0, 27.1; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$calcd for $C_{18}H_{17}O_3N_2$ 309.1234; found 309.1233.

6-fluoro-3-(3-oxo-3-phenylpropyl)quinoxalin-2(1*H*)-one (18o):



The product **18o** was obtained in 79 % yield (71 mg, pale brown solid); ***R$_f$*** = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 12.41 (s, 1H), 8.01 (d, *J* = 7.3 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.40 – 7.26 (m, 3H), 3.51 (t, *J* = 6.6 Hz, 2H), 3.17 (t, *J* = 6.6 Hz, 2H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 199.0, 162.2, 157.7 (d, J_{C-F} = 239.56 Hz), 154.4, 136.8, 133.1, 131.7 (d, J_{C-F} = 11.44 Hz), 128.9(d, J_{C-F} = 74.77 Hz), 128.7, 127.9,117.3(d, J_{C-F} = 24.41 Hz), 116.6 (d, J_{C-F} = 9.16 Hz), 113.1(d, J_{C-F} = 22.12 Hz), 33.9, 27.1; **^{19}F NMR (376 MHz, DMSO-d$_6$) δ** = -119.60; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{17}H_{14}FN_2O_2$ 297.1034; found 297.1032.

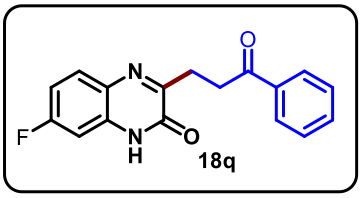
7-bromo-3-(3-oxo-3-phenylpropyl)quinoxalin-2(1*H*)-one (18p):



The product **18p** was obtained in 69% yield (55 mg, pale brown solid); ***R$_f$*** = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (400 MHz, DMSO-d$_6$) δ** = 12.41 (s, 1H), 8.04-7.99 (m, 2H), 7.67-

7.62 (m, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.44 (dd, *J* = 16.3, 5.3 Hz, 2H), 7.36 (dd, *J* = 8.6, 2.1 Hz, 1H), 3.50 (t, *J* = 6.6 Hz, 2H), 3.15 (t, *J* = 6.6 Hz, 2H); **^{13}C NMR (100 MHz, DMSO-d$_6$) δ** = 198.9, 161.2, 154.3, 136.8, 133.1, 132.9, 130.4, 129.7, 128.7, 127.8, 125.9, 121.8, 117.5, 33.8, 27.0; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{17}H_{14}O_2N_2Br$ 357.0233; found 357.0237.

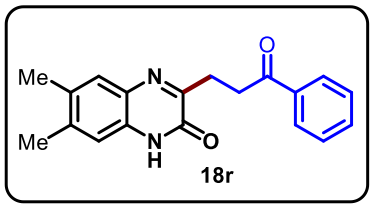
7-fluoro-3-(3-oxo-3-phenylpropyl)quinoxalin-2(1*H*)-one (18q):



18q

The product **18q** was obtained in 70% yield (63 mg, pale brown solid); ***R$_f$*** = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (500 MHz, DMSO-d$_6$) δ** = 12.43 (s, 1H), 8.05-7.98 (m, 2H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.56 (dt, *J* = 11.0, 6.6 Hz, 3H), 7.12 – 6.98 (m, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 3.15 (t, *J* = 6.6 Hz, 2H); **^{13}C NMR (125 MHz, DMSO-d$_6$) δ** = 199.0, 161.8 (d, J_{C-F} = 246.43 Hz), 159.6, 154.5, 136.8, 133.1 (d, J_{C-F} = 12.21 Hz), 133.1 130.1 (d, J_{C-F} = 10.68 Hz), 128.7, 128.4 (d, J_{C-F} = 1.53 Hz), 127.9, 110.8 (d, J_{C-F} = 23.65 Hz), 101.1(d, J_{C-F} = 26.70 Hz), 33.9, 26.9; **^{19}F NMR (376 MHz, DMSO-d$_6$) δ** = -110.39; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{17}H_{14}FN_2O_2$ 297.1034; found 297.1031.

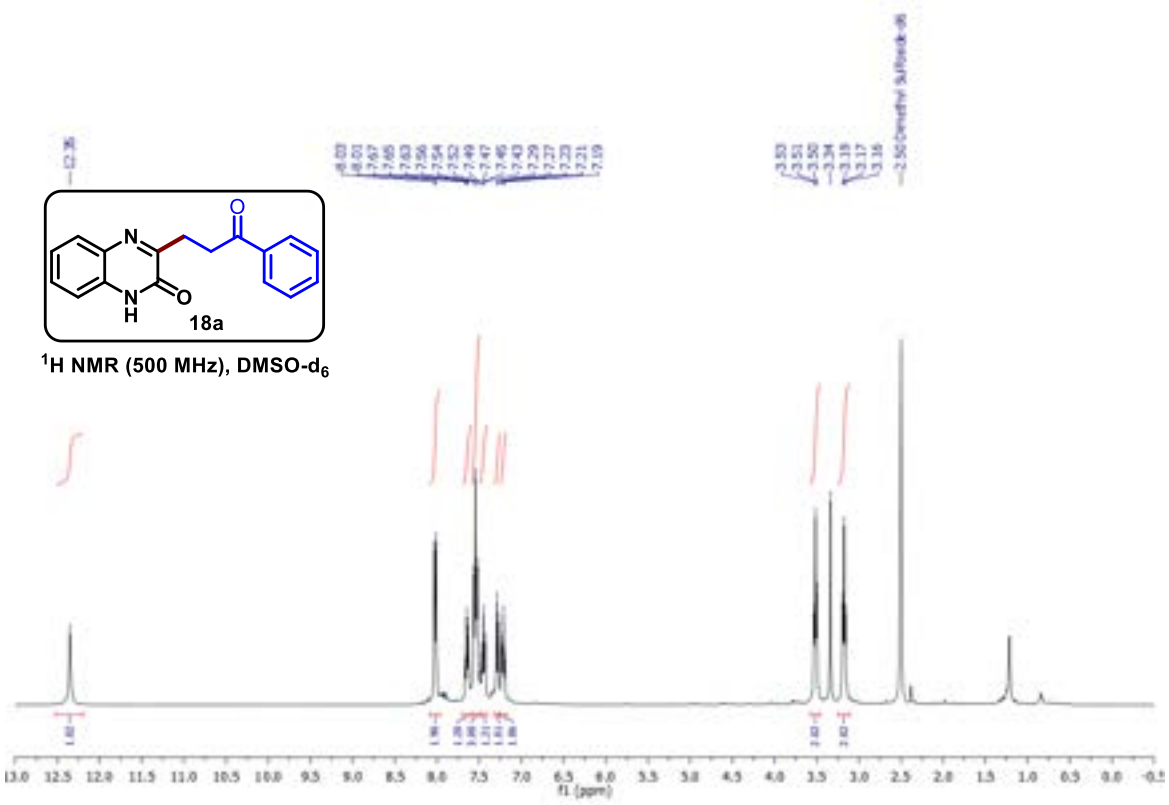
6,7-dimethyl-3-(3-oxo-3-phenylpropyl)quinoxalin-2(1*H*)-one (18r):

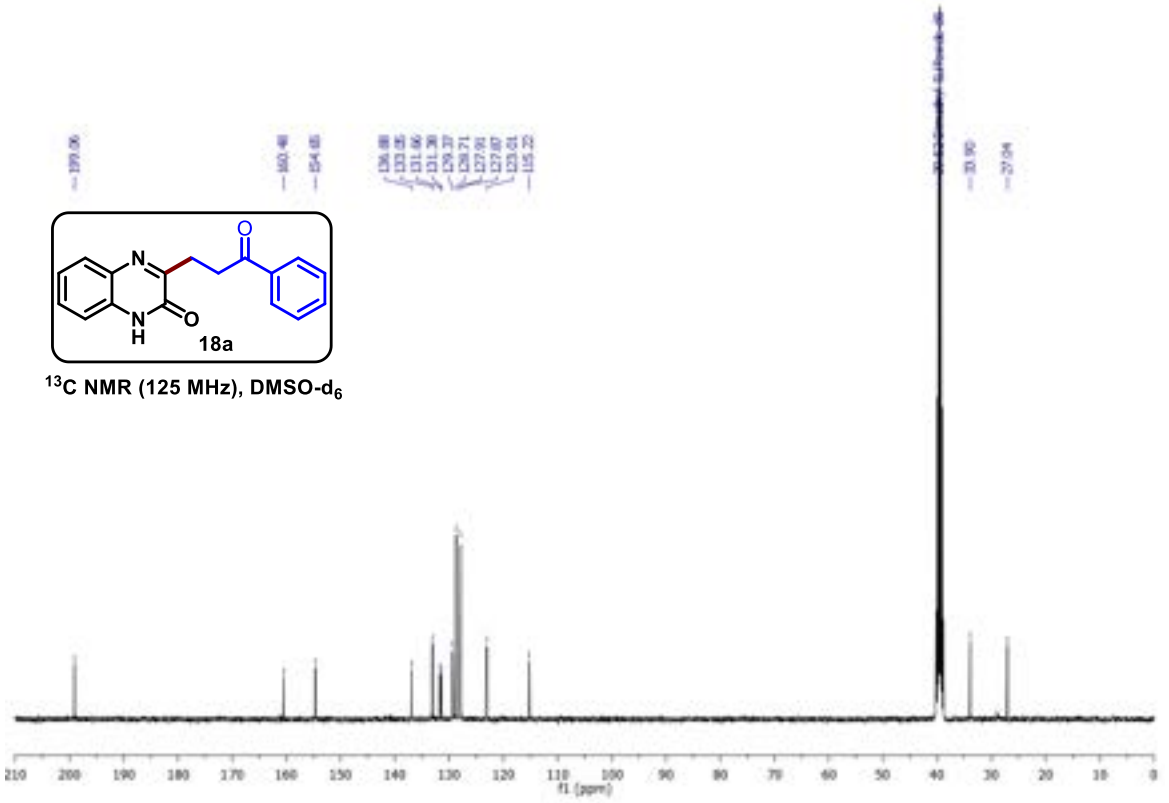


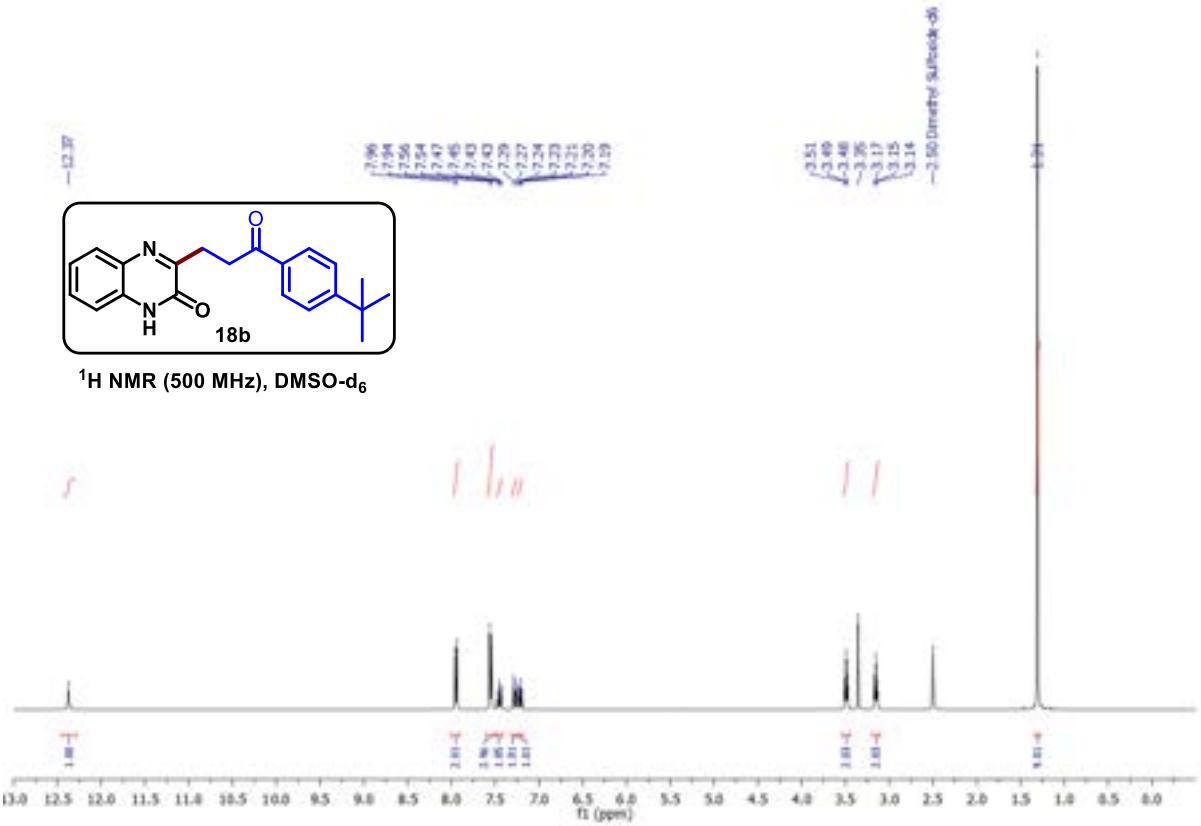
18r

The product **18r** was obtained in 80% yield (70 mg, pale brown solid); **mp** = 165-167 °C; ***R$_f$*** = 0.50 (Petroleum ether: EtOAc = 5:5); **^{1}H NMR (500 MHz, DMSO-d$_6$) δ** = 12.22 (s, 1H), 8.02 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.32 (s, 1H), 7.03 (s, 1H), 3.50 (t, *J* = 6.6 Hz, 2H), 3.13 (t, *J* = 6.6 Hz, 2H), 2.27 (s, 3H), 2.22 (s, 3H); **^{13}C NMR (125 MHz, DMSO-d$_6$) δ** = 199.0, 159.0, 154.7, 138.7, 136.9, 133.0, 131.6, 129.9, 129.6, 128.7, 127.9, 127.8, 115.3, 33.9, 26.9, 19.7, 18.8; **HRMS (ESI-TOF)** *m:z*: $[M+H]^+$ calcd for $C_{19}H_{19}N_2O_2$ 307.1441; found 307.1439.

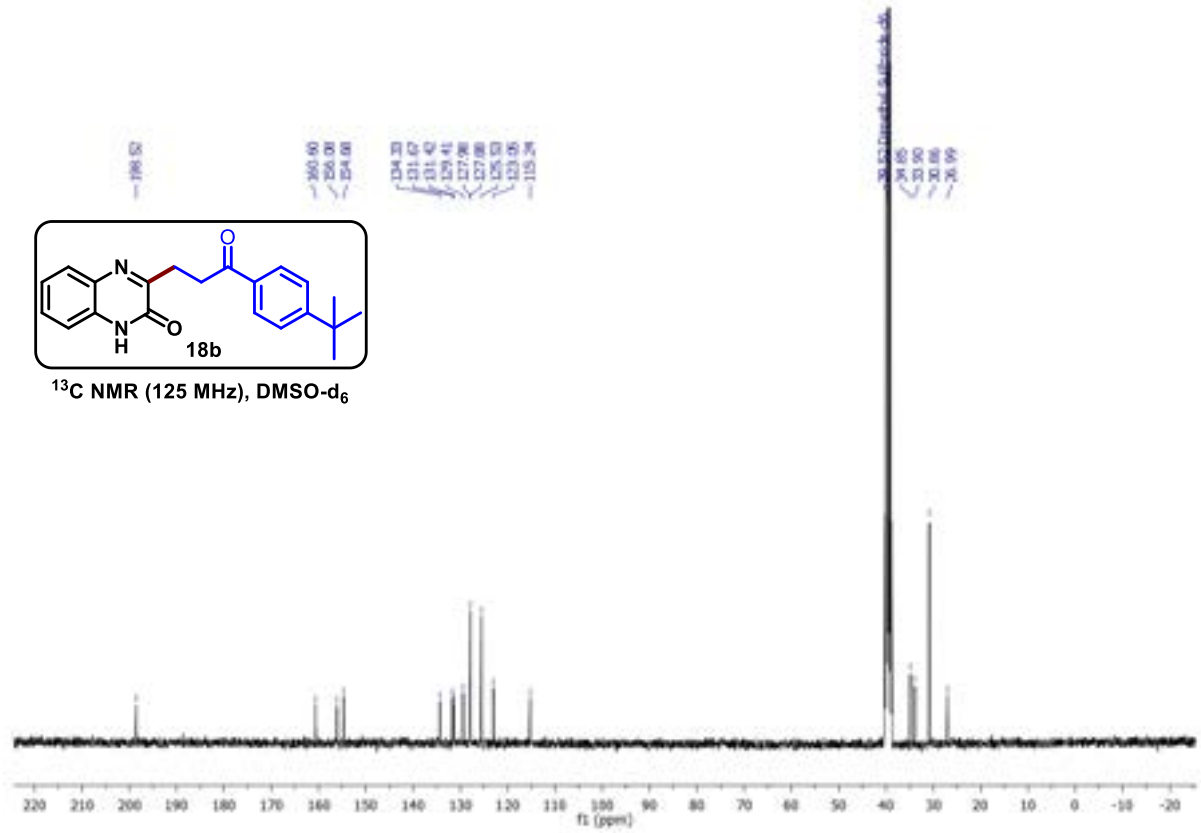
2.2.7 Spectral data for the representative compounds:



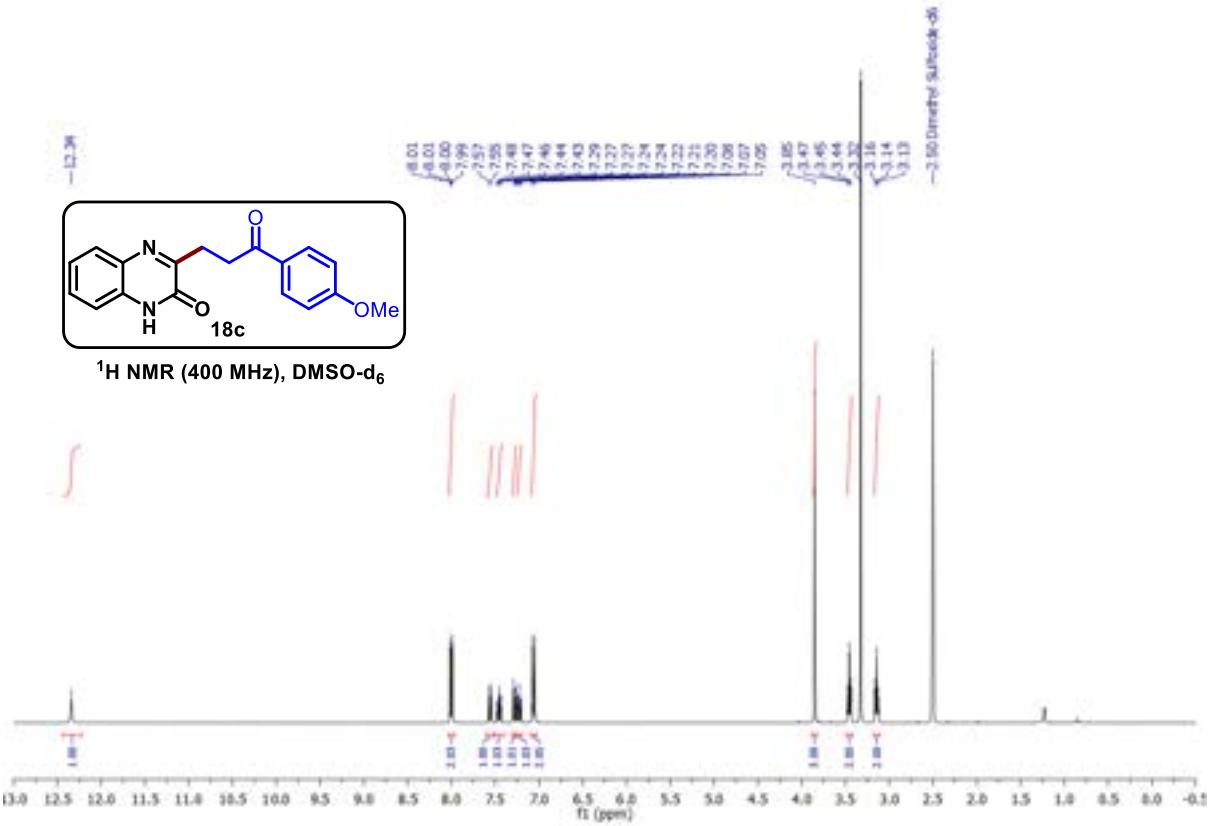




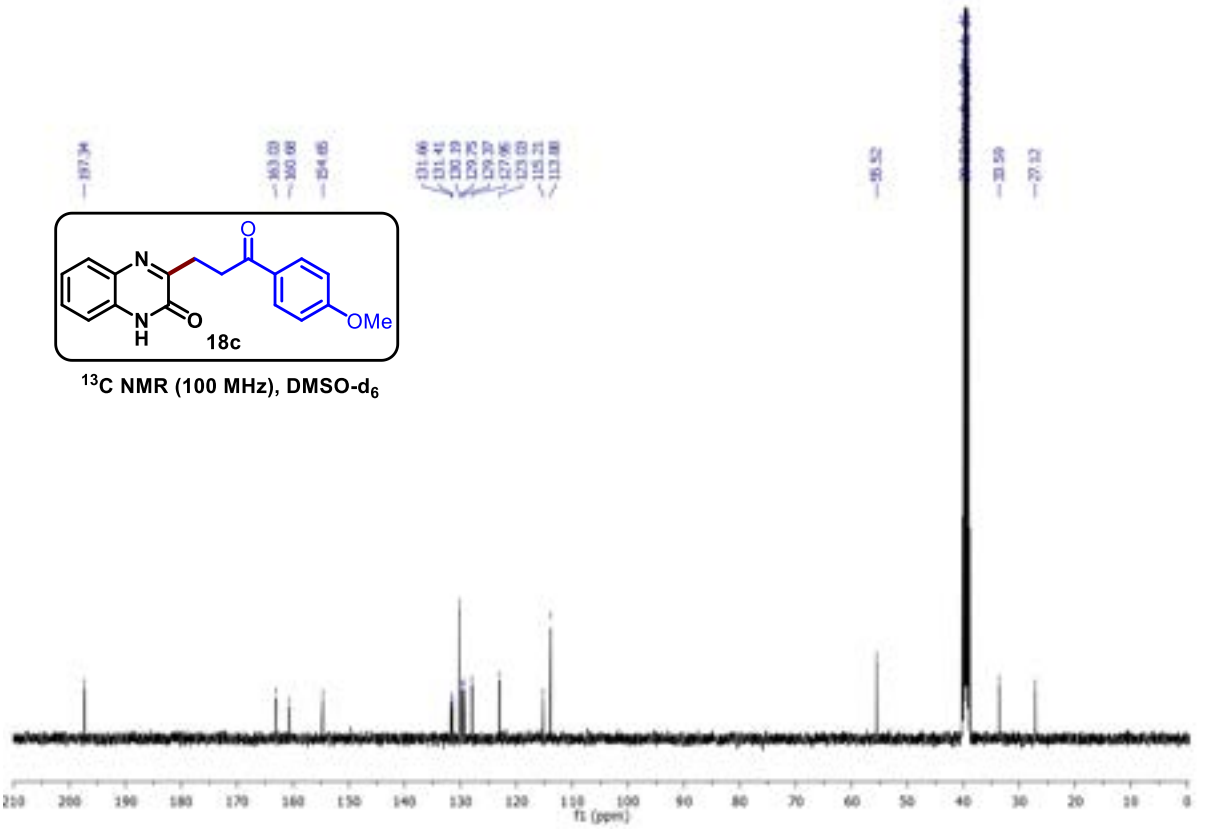
^{1}H NMR (500 MHz), DMSO-d_6



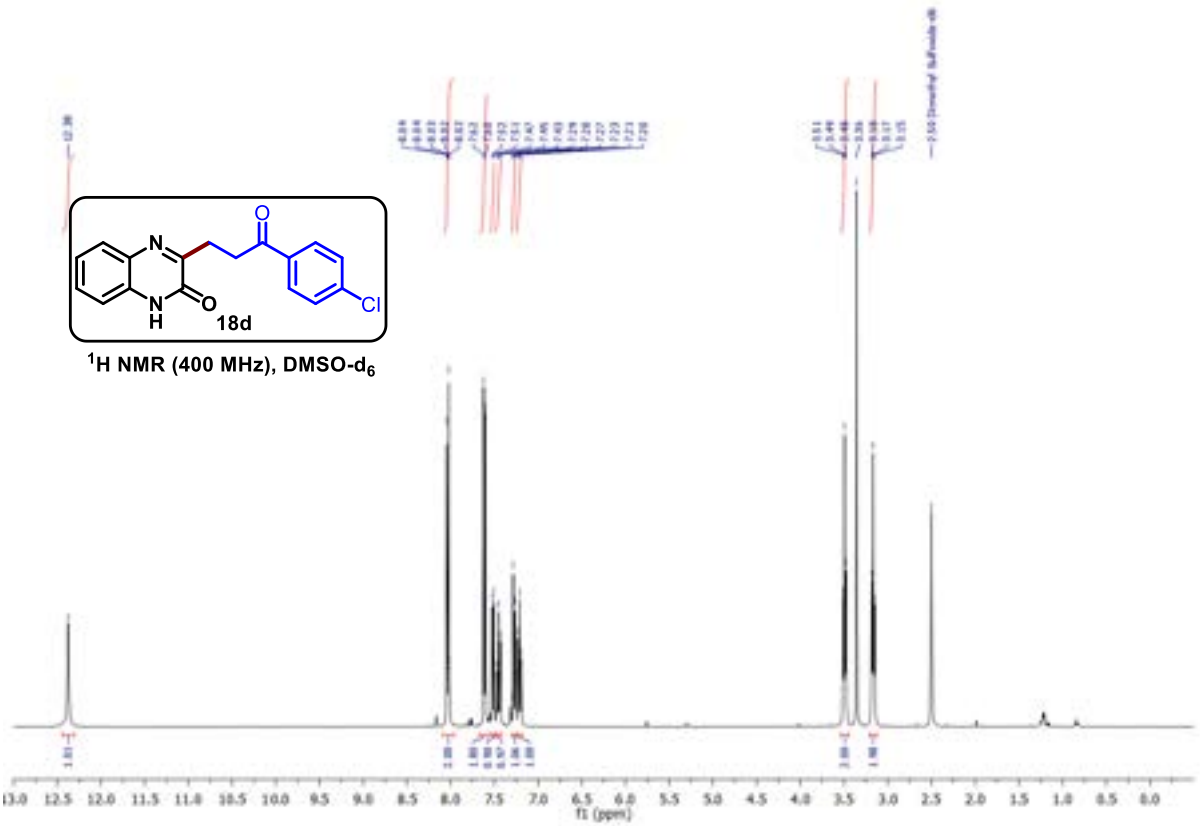
^{13}C NMR (125 MHz), DMSO-d_6

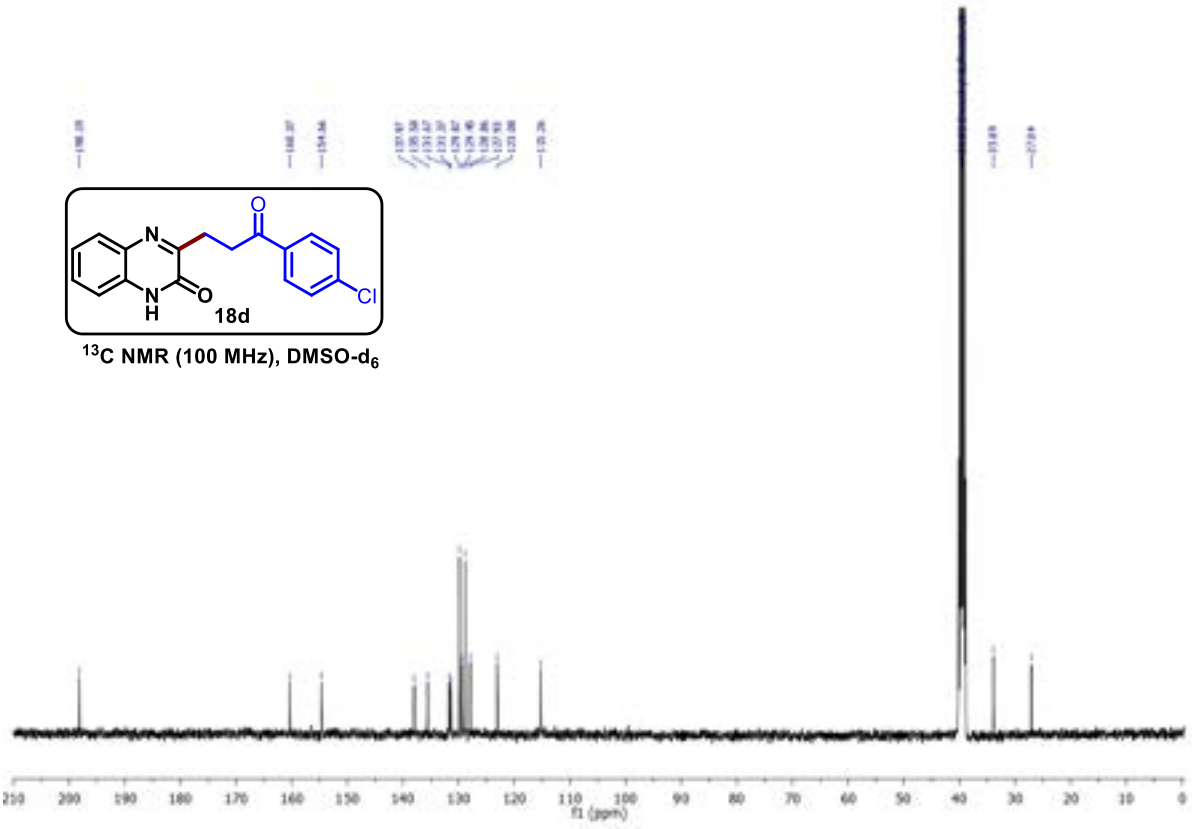


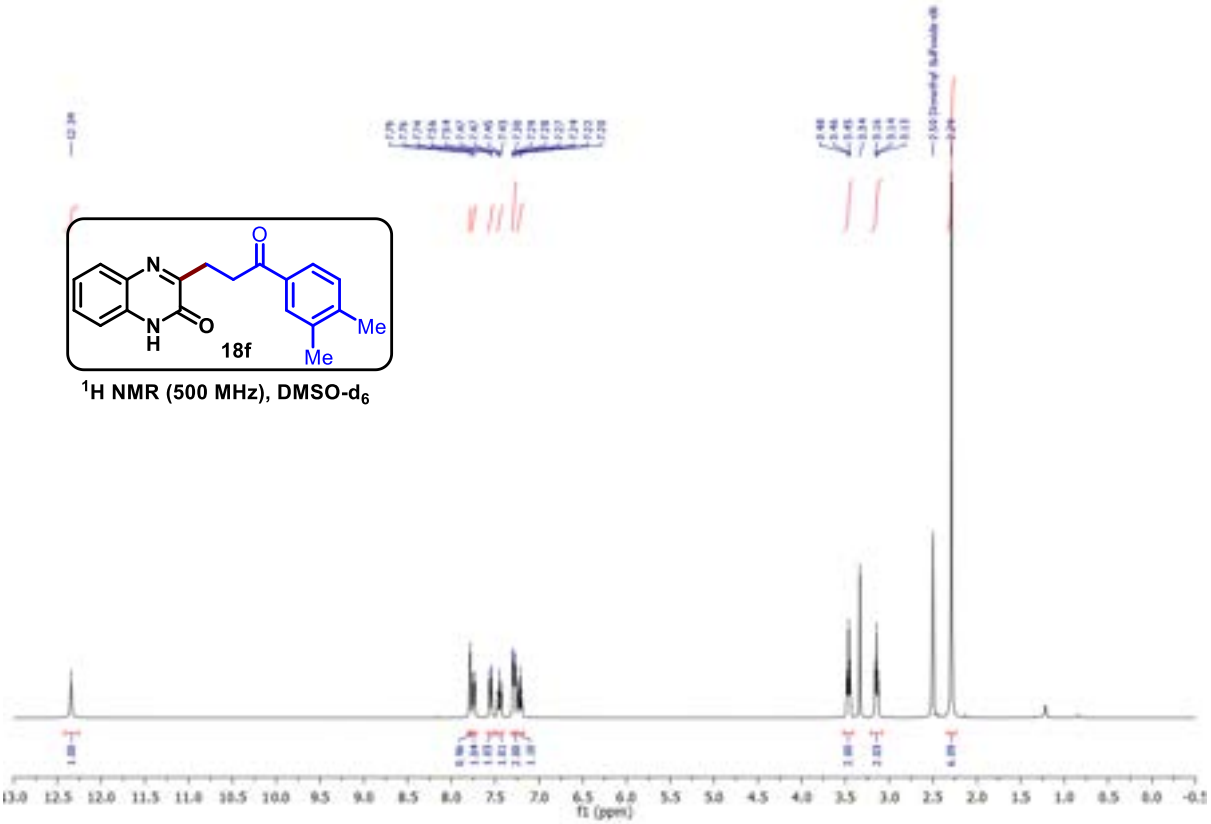
^{1}H NMR (400 MHz), DMSO-d_6



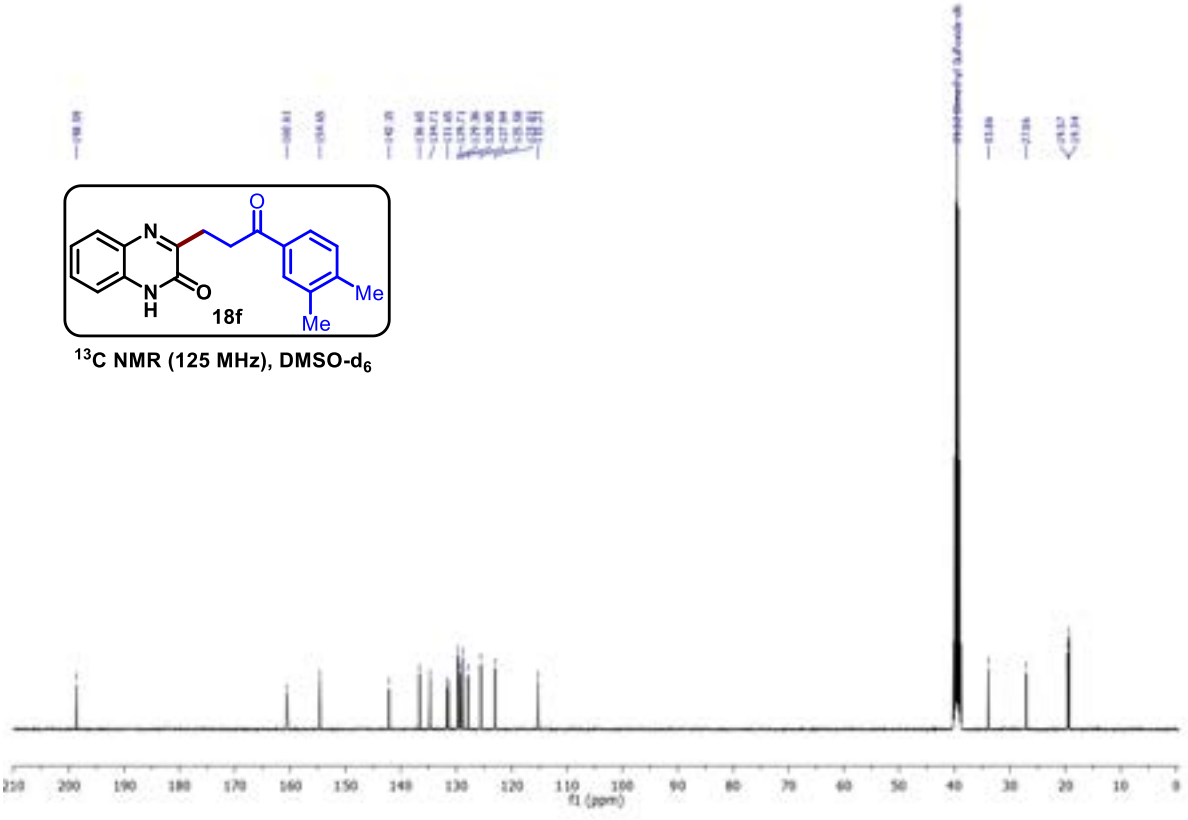
^{13}C NMR (100 MHz), DMSO-d_6


18d
^{1}H NMR (400 MHz), DMSO-d$_6$

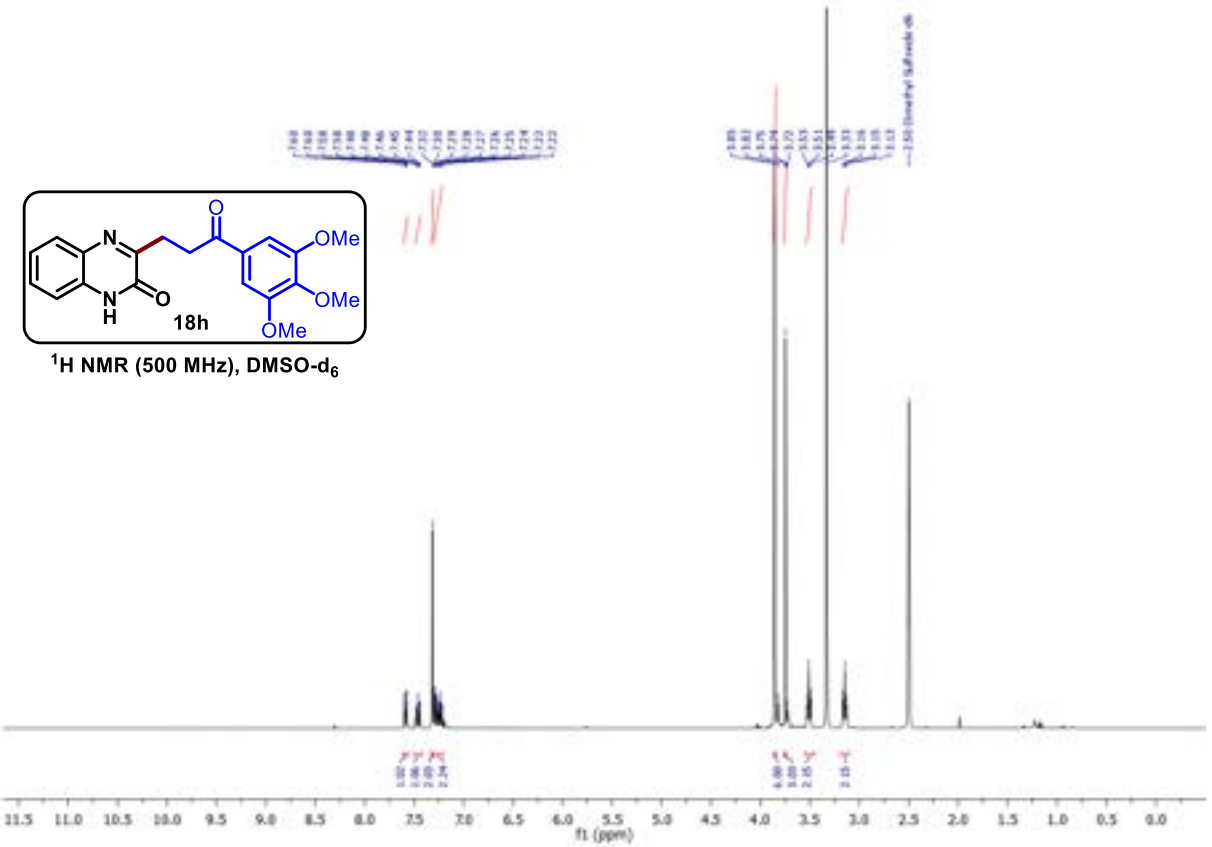

18d
^{13}C NMR (100 MHz), DMSO-d$_6$



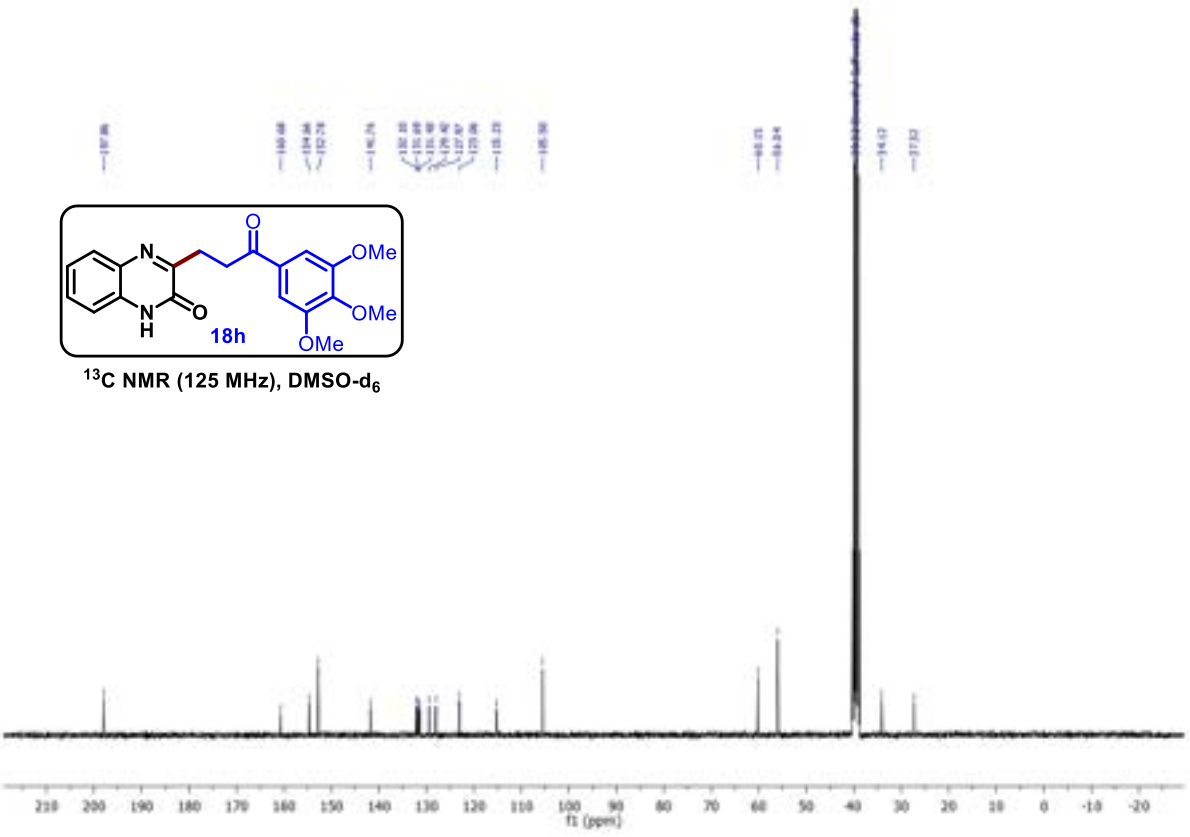
^{1}H NMR (500 MHz), DMSO-d_6



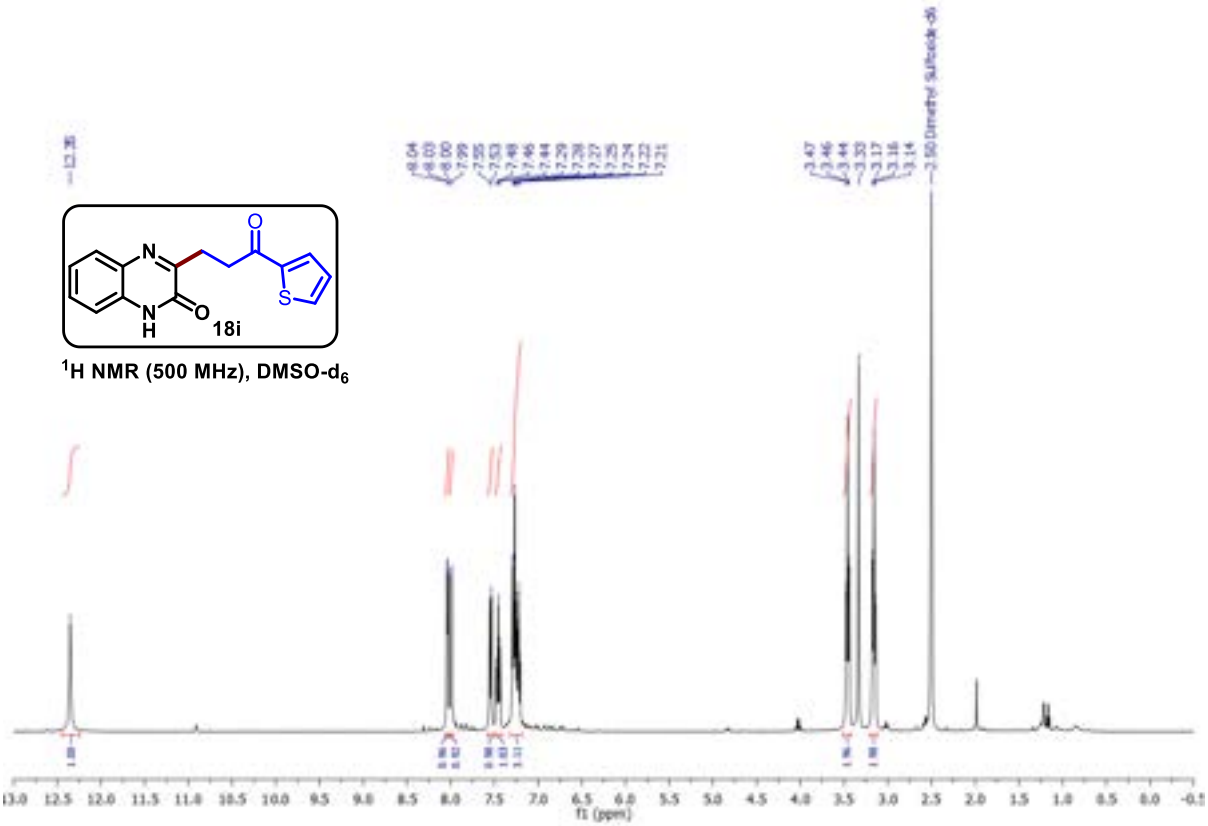
^{13}C NMR (125 MHz), DMSO-d_6



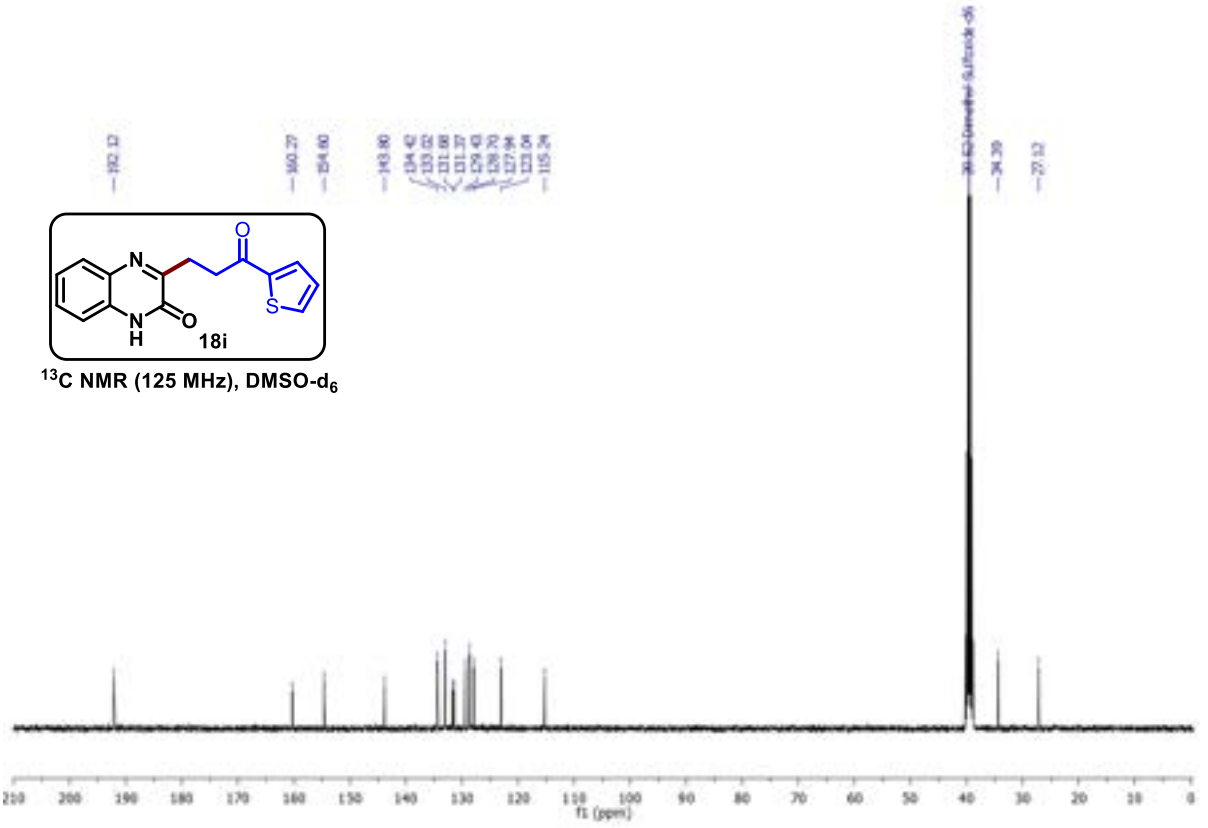
^{1}H NMR (500 MHz), DMSO-d_6



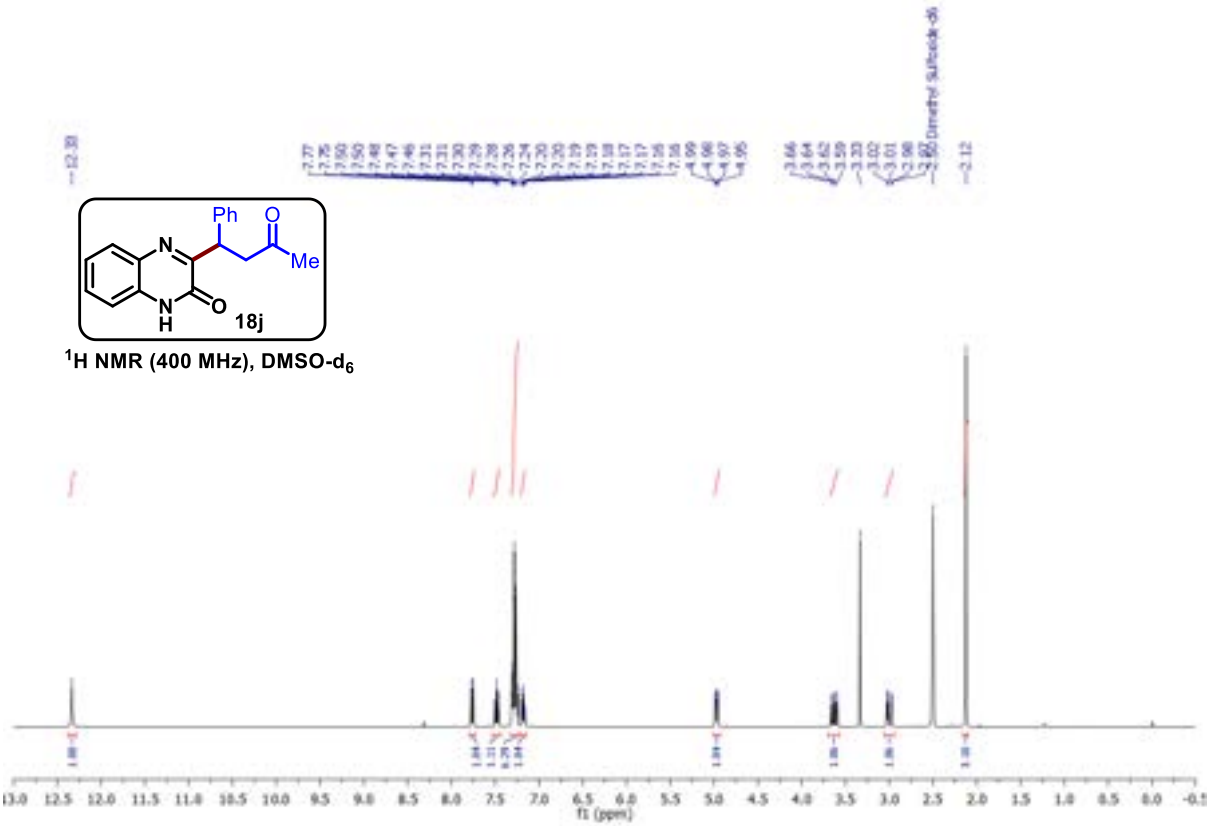
^{13}C NMR (125 MHz), DMSO-d_6



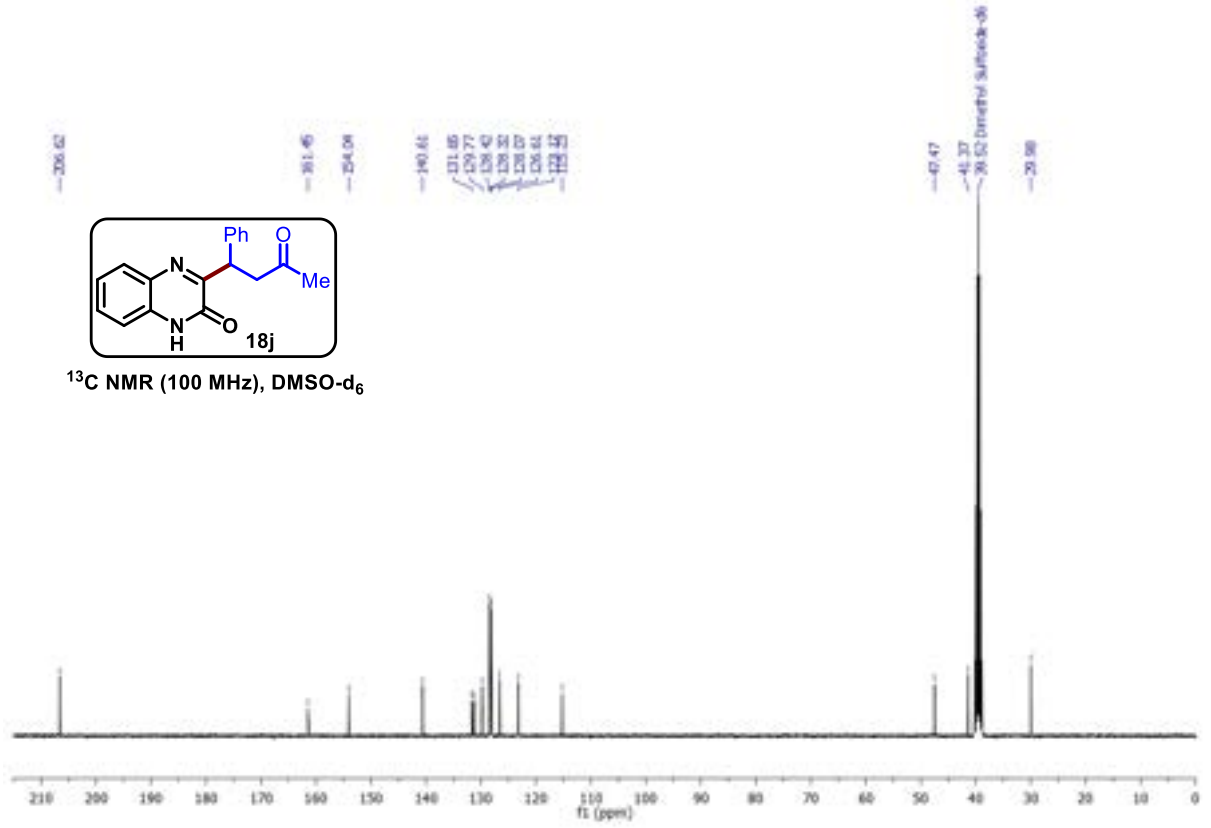
^{1}H NMR (500 MHz), DMSO-d_6



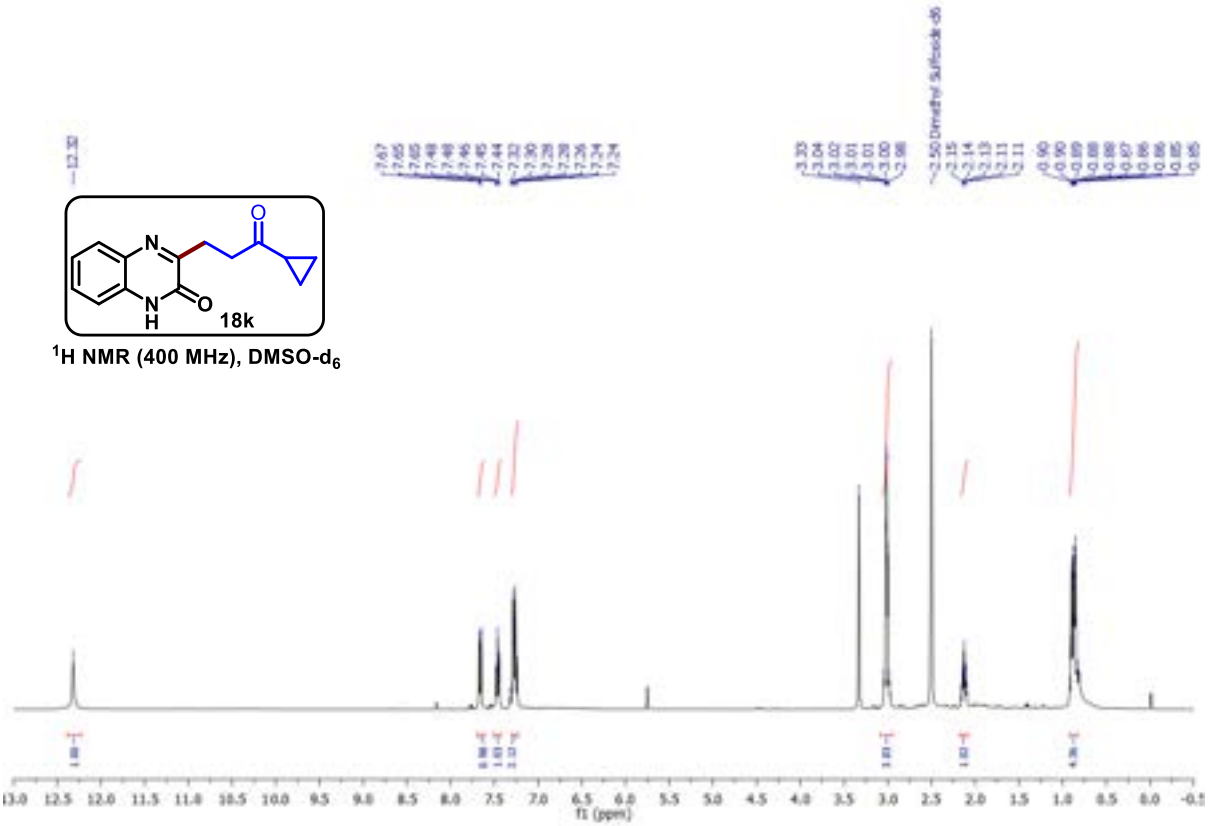
^{13}C NMR (125 MHz), DMSO-d_6



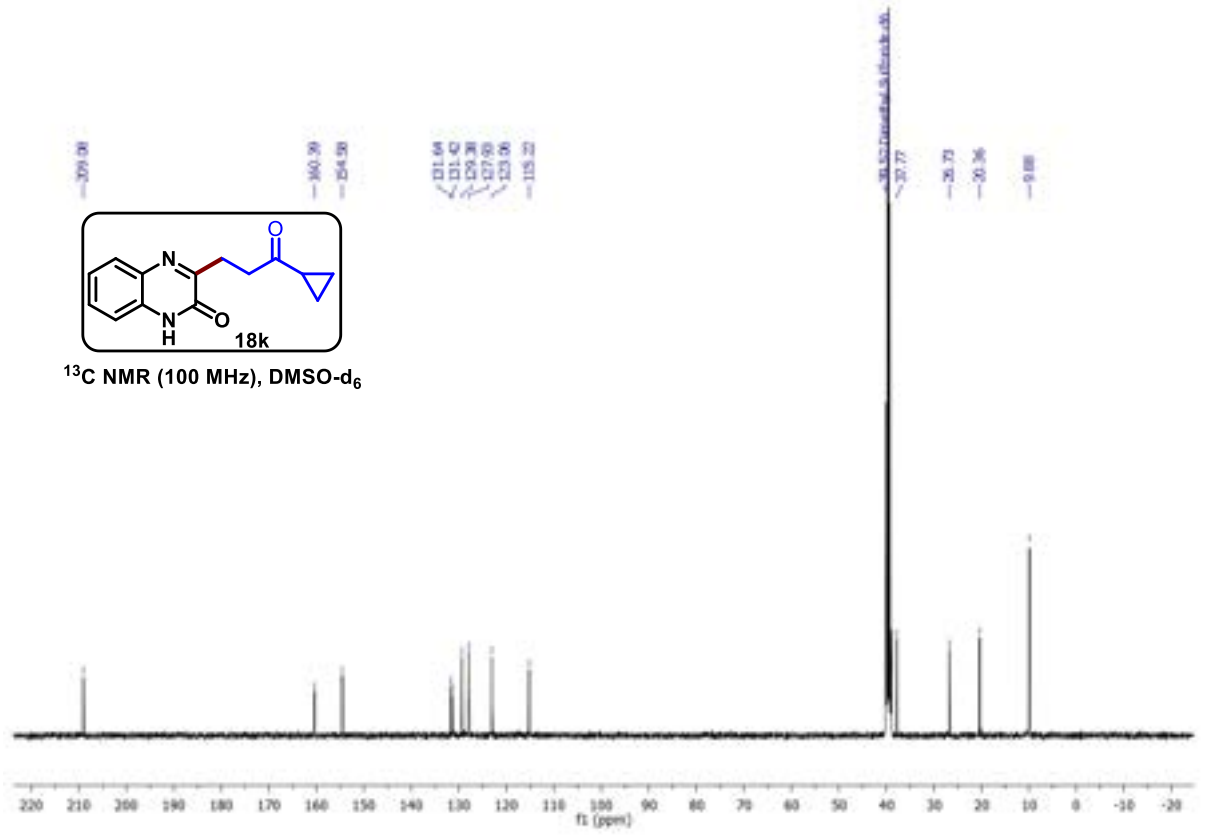
^{1}H NMR (400 MHz), DMSO-d_6



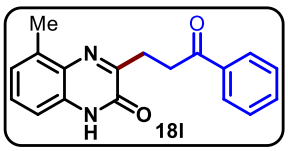
^{13}C NMR (100 MHz), DMSO-d_6



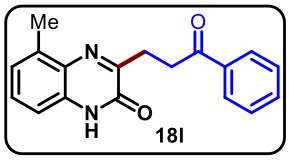
^{1}H NMR (400 MHz), DMSO-d_6



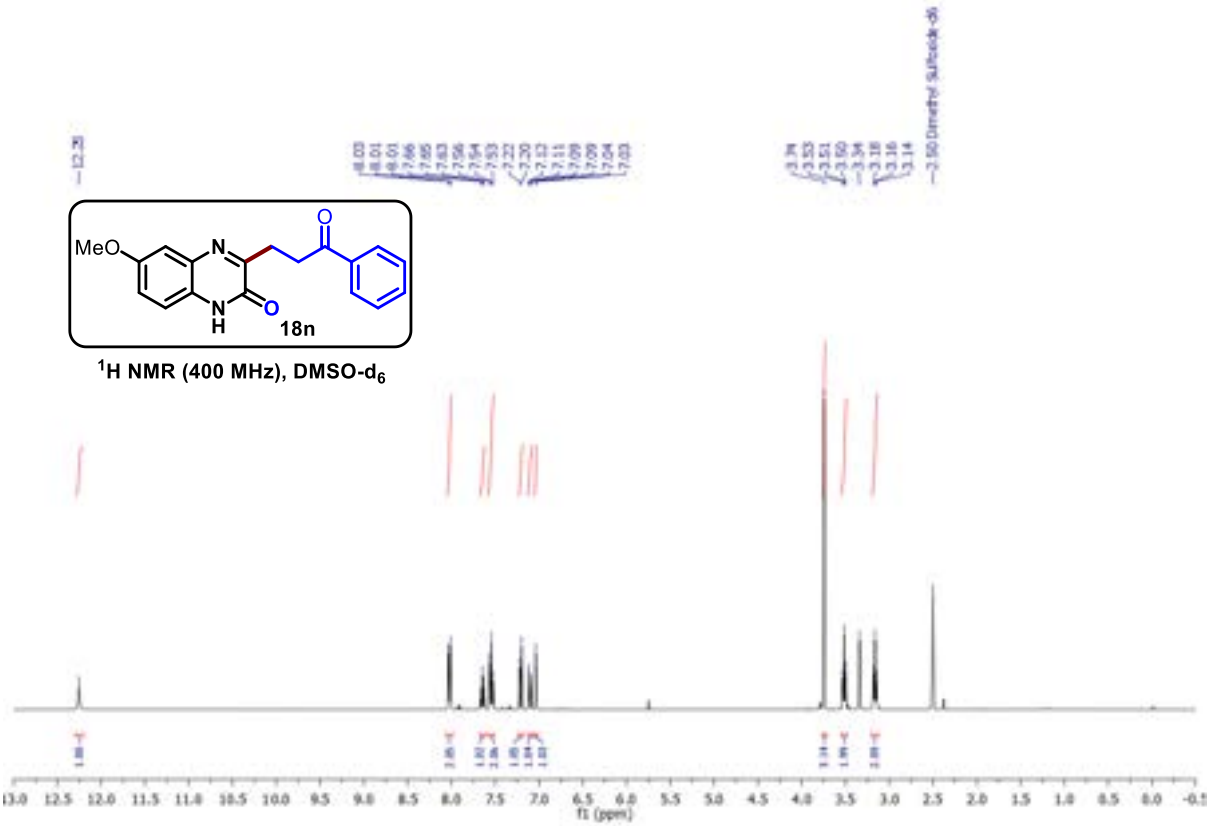
^{13}C NMR (100 MHz), DMSO-d_6



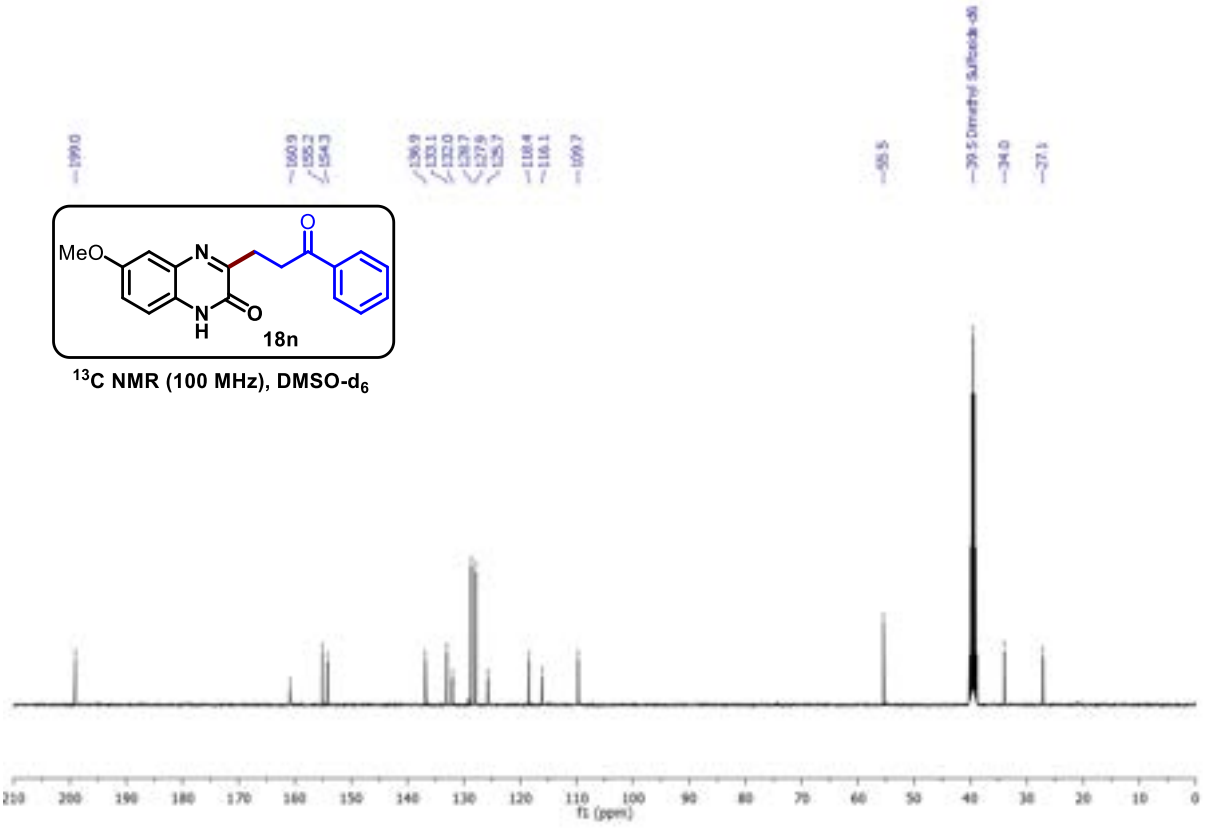
^{1}H NMR (400 MHz), DMSO-d_6



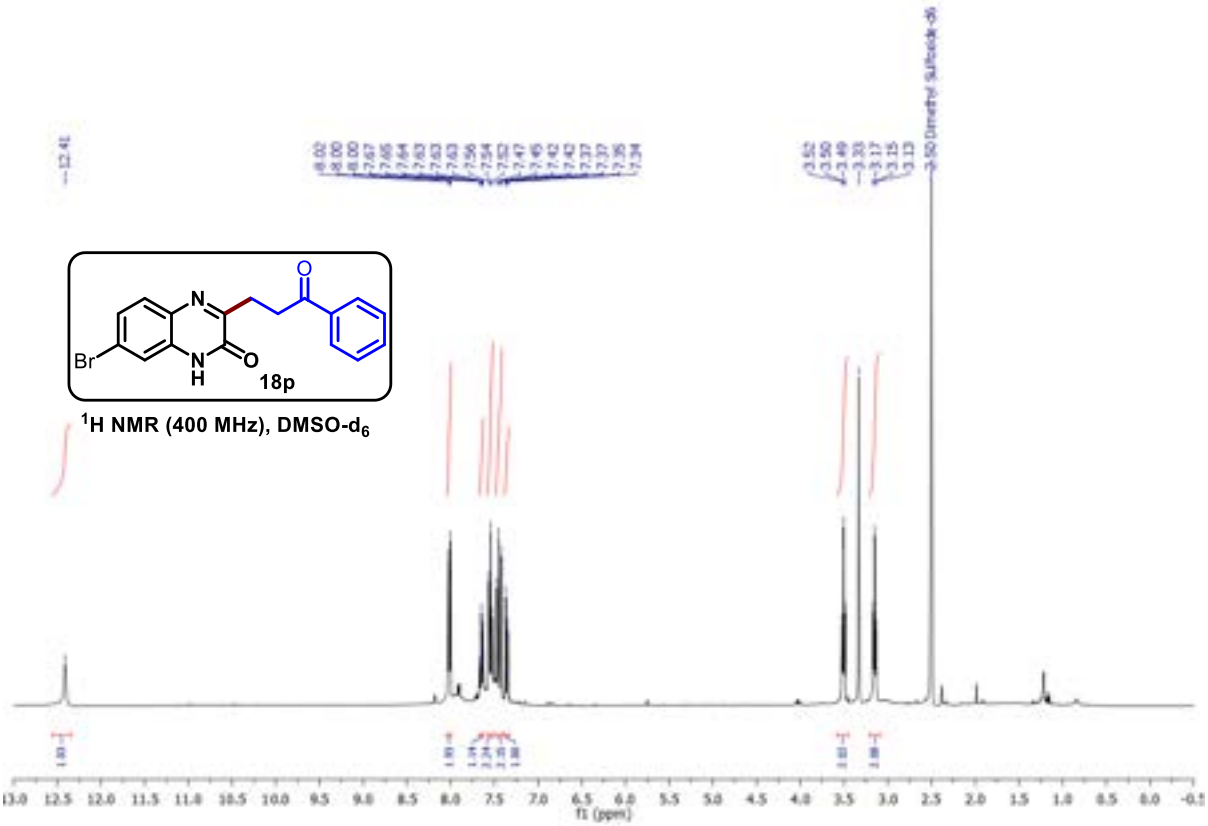
^{13}C NMR (100 MHz),DMSO-d_6



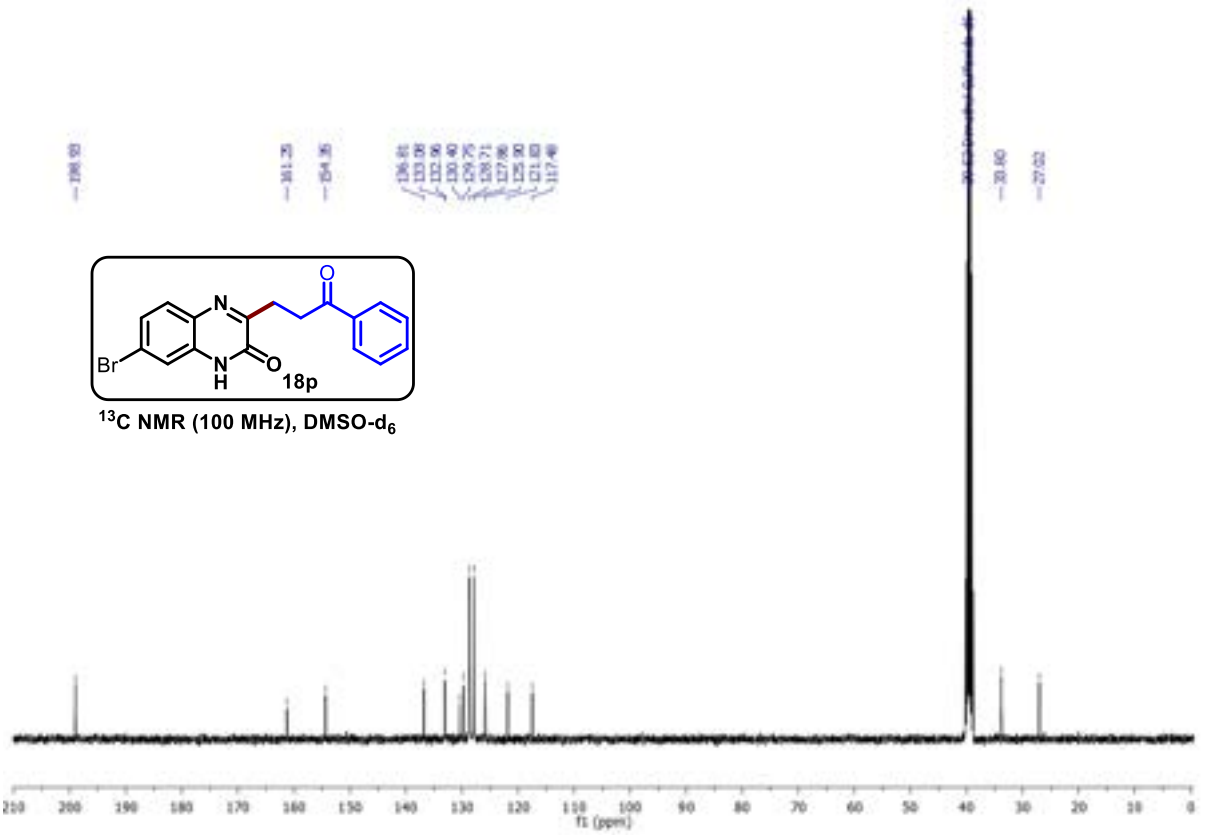
^{1}H NMR (400 MHz), DMSO-d_6



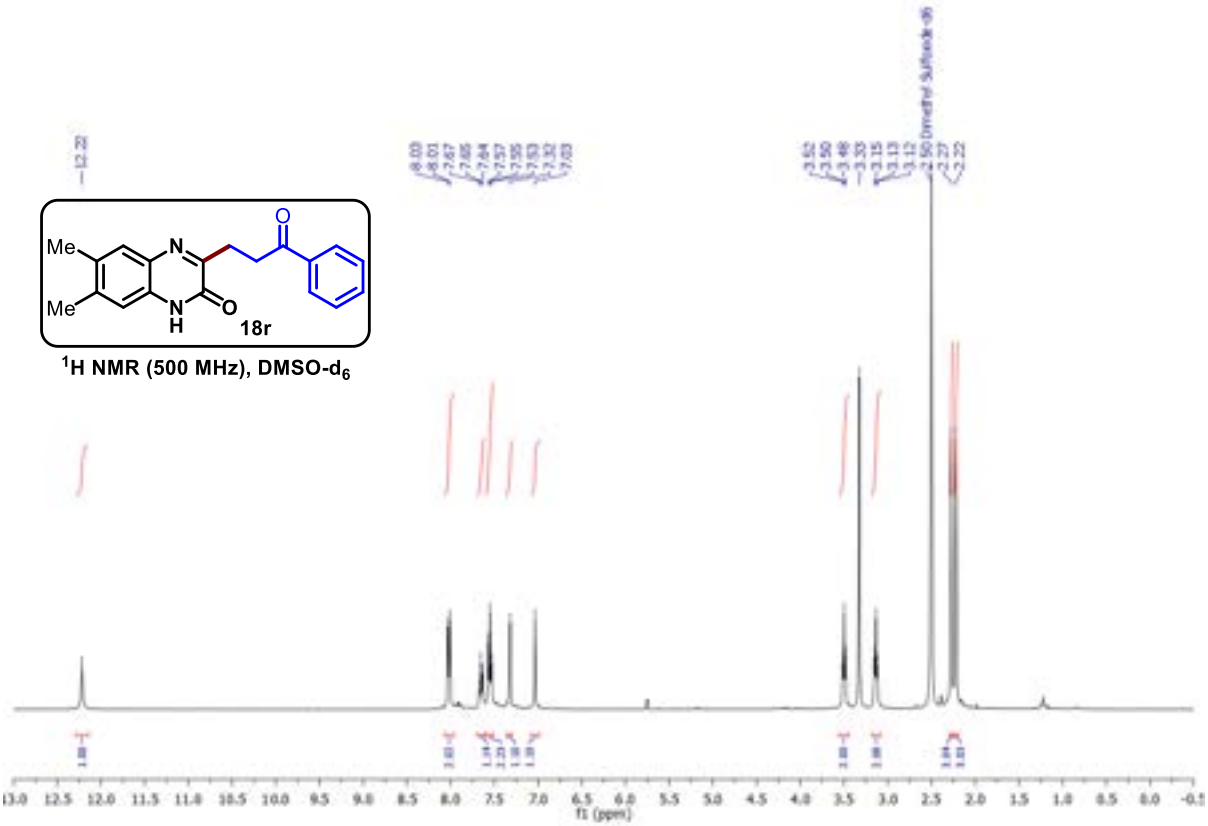
^{13}C NMR (100 MHz), DMSO-d_6



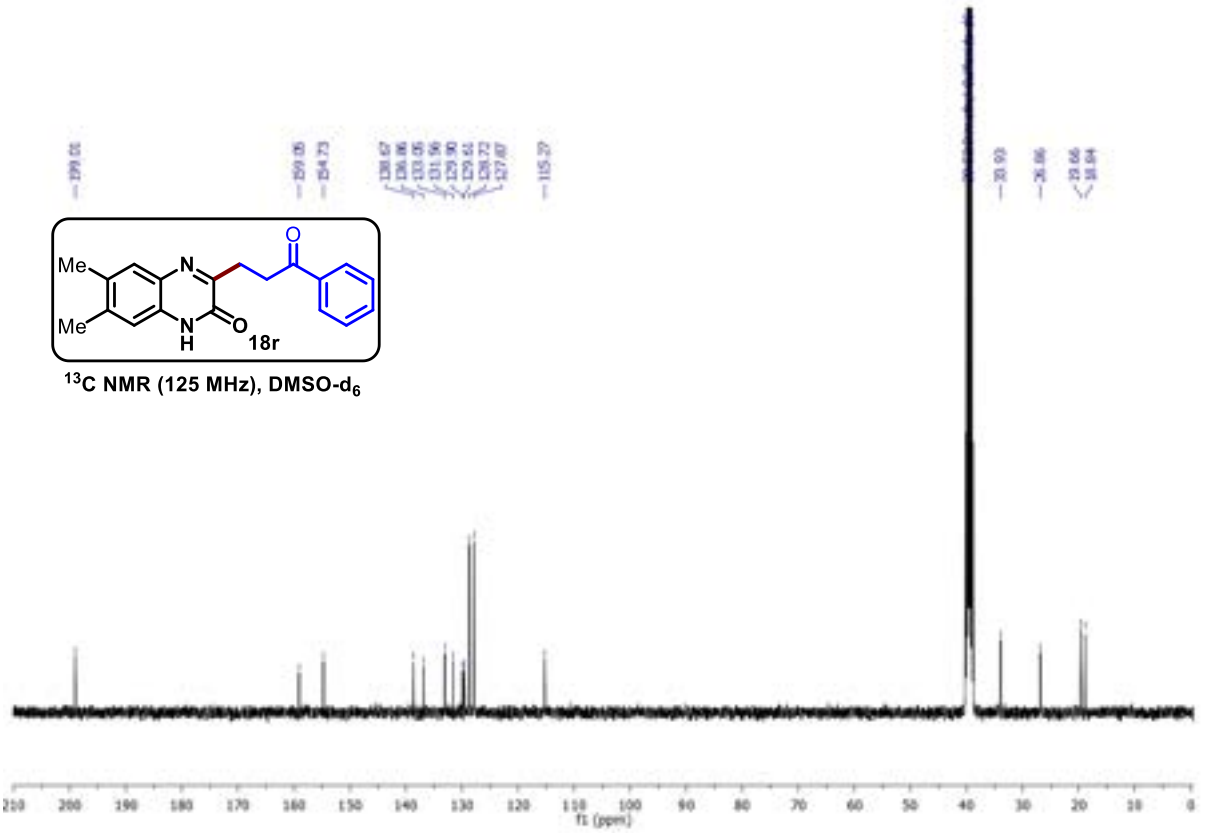
^{1}H NMR (400 MHz), DMSO-d_6



^{13}C NMR (100 MHz), DMSO-d_6



^{1}H NMR (500 MHz), DMSO-d_6



^{13}C NMR (125 MHz), DMSO-d_6

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CHAPTER-3
Catalyst-Free Organic Reactions *via* Electron Donor-Acceptor (EDA) Complexes & its Applications

Section I

A Brief Introduction to EDA Complex in Organic Synthesis

Section II

Metal- And Photocatalyst-Free, Visible-Light-Initiated C3 *α*-Aminomethylation of Quinoxalin-2(1*H*)-ones *via* Electron Donor-Acceptor Complexes

Section-I:

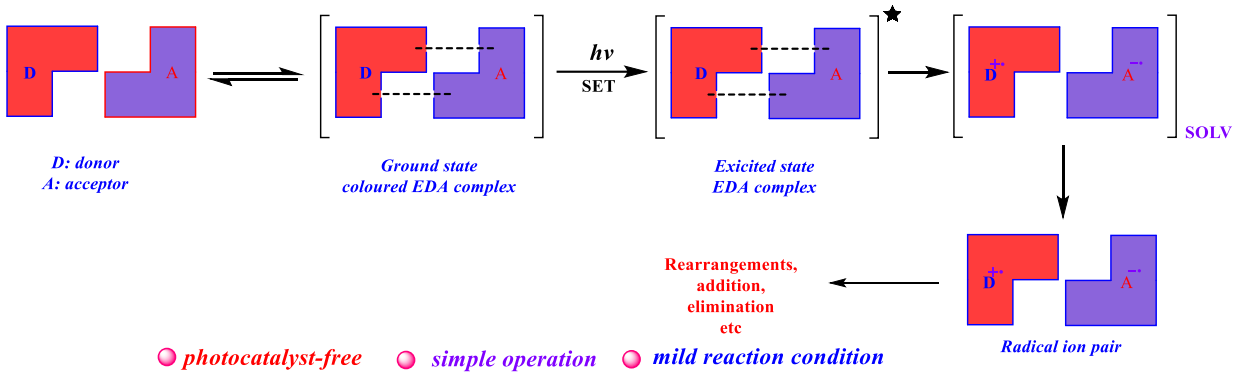
A Brief Introduction to EDA Complex in Organic Synthesis

3.1.1 Introduction

With rising waste and pollutants from chemical operations in industries and academic laboratories, the significance of green chemistry has become more apparent to all chemists. So they are now looking for eco-friendly alternatives to traditional methods, such as the use of green solvents, green catalysts and carryout the reactions under solvent-free conditions.[1-3] The majority of chemical reactions necessitate appropriate catalysts to generate the desired products. There are some drawbacks associated with using catalysts in chemical processes, but catalyst-free conditions remain more appealing, especially for industrial and pharmaceutical applications. A catalyst plays a critical role in the success of a reaction, so removing it from the reaction requires effective and cheaper alternatives. Photosynthesis, in which nature uses sunlight as a renewable energy source to transform simple compounds to complex structures.[4] For centuries, photosynthesis has driven researchers to develop efficient ways to harvest light to promote chemical reactions. The application of visible light in organic photochemistry is increasing as this strategy is a safer and more practical source of photons. To achieve this desired transformation, an external photocatalysts such as metal complexes, ligands or organic dyes[5] are required because most of the organic compounds do not absorb light in the visible region. Performing the reactions in visible light without a photocatalyst has been rarely studied.

In recent years, a visible light-induced organic transformation in the absence of photocatalysts especially using the EDA complex strategy has garnered considerable interest due to their economic and synthetic value.[6] EDA complex strategy takes advantage of the association of an electron acceptor molecule **A,** and a donor molecule **D** to create a new molecular aggregation in the ground state called an electron donor-acceptor (EDA) complex.[7] This EDA complex harvests the energy of light. Subsequently, photoexcitation of the EDA complex initiates a single electron transfer (SET) process, which produces the respective radical species. The process does not require external photocatalysts and operates under mild conditions. The created radical ion pair then undergoes additional radical reactions within the solvent cage to produce the required chemicals. EDA complexes are capable of absorbing visible light even when the two components (**A** and **D**) themselves cannot. The characterization of EDA complexes shows the

appearance of a weak absorption band, which corresponds to an electron transfer from donor to acceptor which could be proved by the UV–vis spectroscopy (new absorption band) and NMR titration experiments. The radical clock experiment and the electron paramagnetic resonance (EPR) also can reveal the radical nature of EDA complexes.



Scheme 3.1.1 General representation of photoinduced electron transfer mediated by electron donor–acceptor complex.

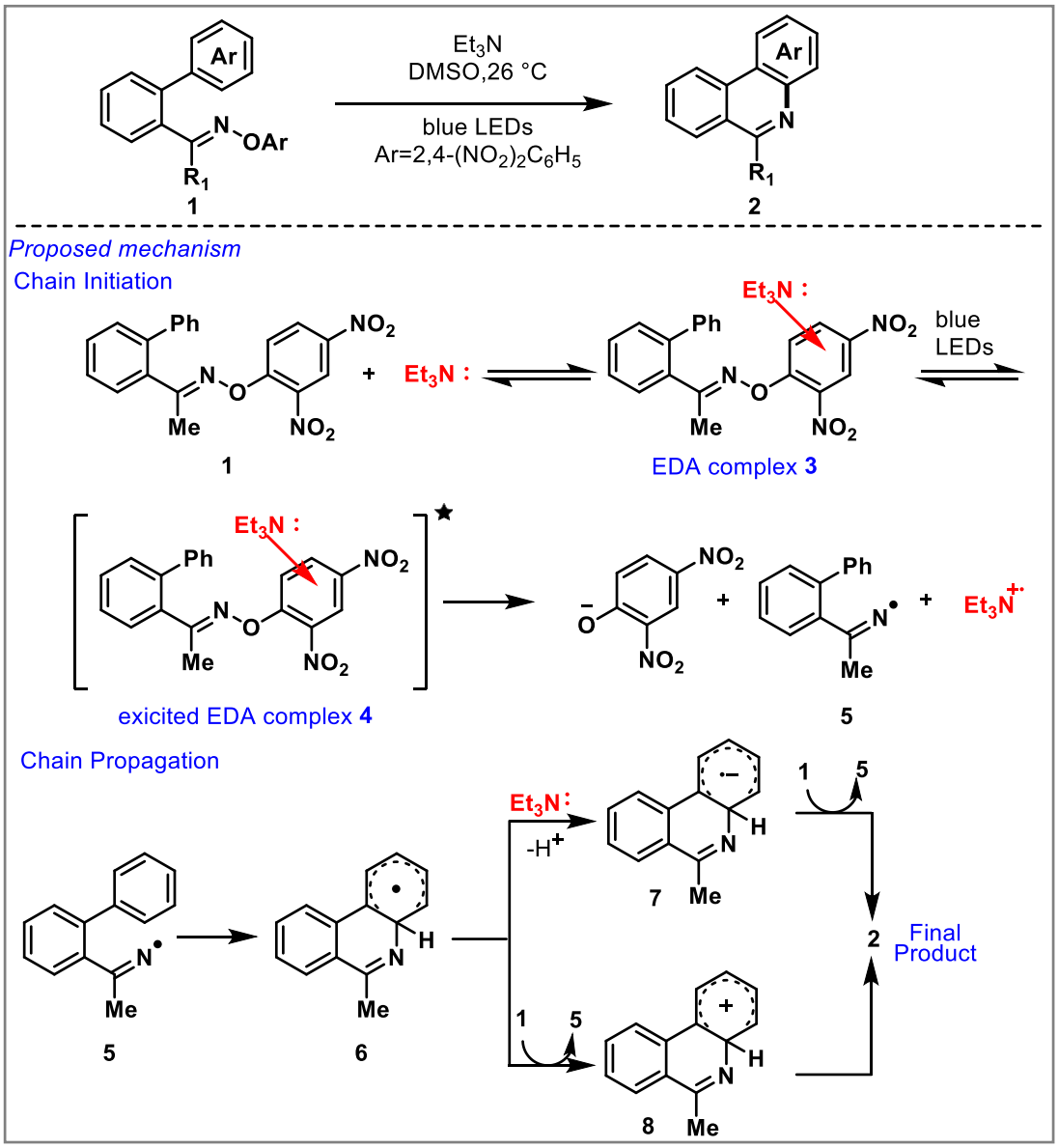
In 1952, Mulliken provided proof related to the characterization and comprehension of EDA complexes.[8] Subsequently, Marcus,[9] Kochi[10] and others[11] reported their studies, laying a solid theoretical foundation on which many synthetic transformations of today are based. According to Melchiorre and Chatani in 2013, EDA complex photochemistry could be initiated under visible light irradiation for synthetically useful transformations.[12,13] Inspired by these reports, the synthetic community became more interested in this photochemical approach. As a result of their ability to obviate photoredox catalysts or transition metal catalysts in the vast majority of reactions, EDA complexes have shown to be an enormous success.[14] This section highlights the selected recent advancements on the metal-/photocatalyst-free photoinduced organic reactions, which involves ring annulation, intermolecular charge transfer and photochemical asymmetric catalysis radical reactions and their mechanistic aspects.

3.1.2 Application of EDA Complex in Organic Transformations

3.1.2.1 Ring Annulation Reactions *via* EDA complex process

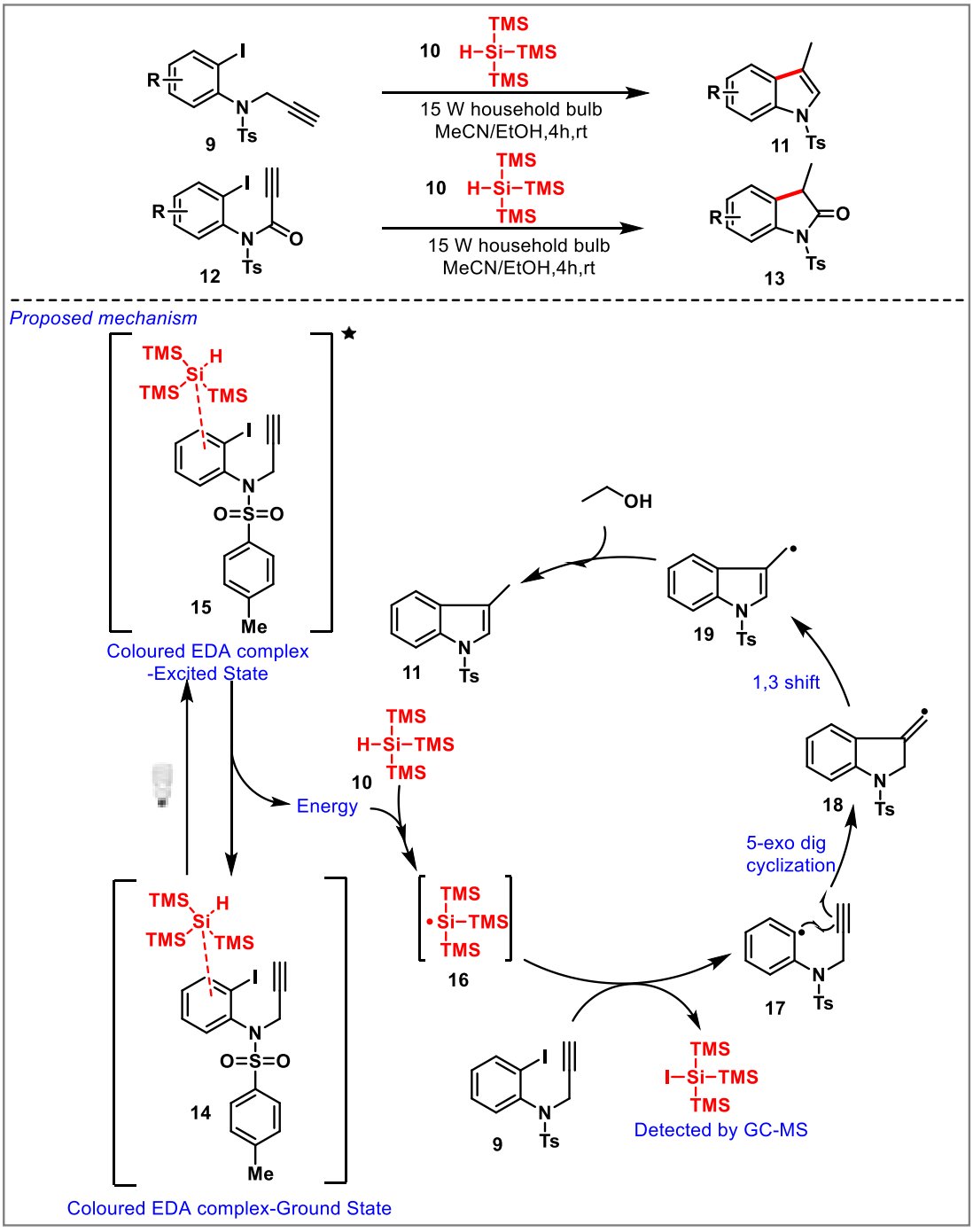
a) Intramolecular cyclization *via* EDA complex process

In 2018, Yu *et al.* reported a visible light-induced metal-/photocatalyst-free synthesis of phenanthridines **2** from *o*-2,4-dinitrophenyl oximes **1** (Scheme 3.1.2).[15] Under mild conditions, several substituted oximes were converted to the corresponding phenanthridines in good yield. UV/vis absorption spectra reveal the formation of an EDA complex.



Scheme 3.1.2 EDA complex mediated synthesis of phenanthridines

The mechanism of this transformation is outlined in Scheme 3.1.2. Initially, the formation of EDA aggregates when *O*-aryl oxime **1** interacts with Et_3N reversibly. After visible light irradiation, complex **3** is excited to its excited state **4** using the SET process, and then the excited EDA complex **4** collapses to afford the iminyl radical **5**. Radical anion **7** is formed by intramolecular HAS of iminyl radical **5** followed by deprotonation. The radical anion **7** can be used to reduce the aryl oxime **1** to afford the final product **2** and regenerate the iminyl radical **5**, which propagates the chain. Alternatively, the oxidation of **5** by **1** followed by deprotonation of **8** gives the final product **2**.

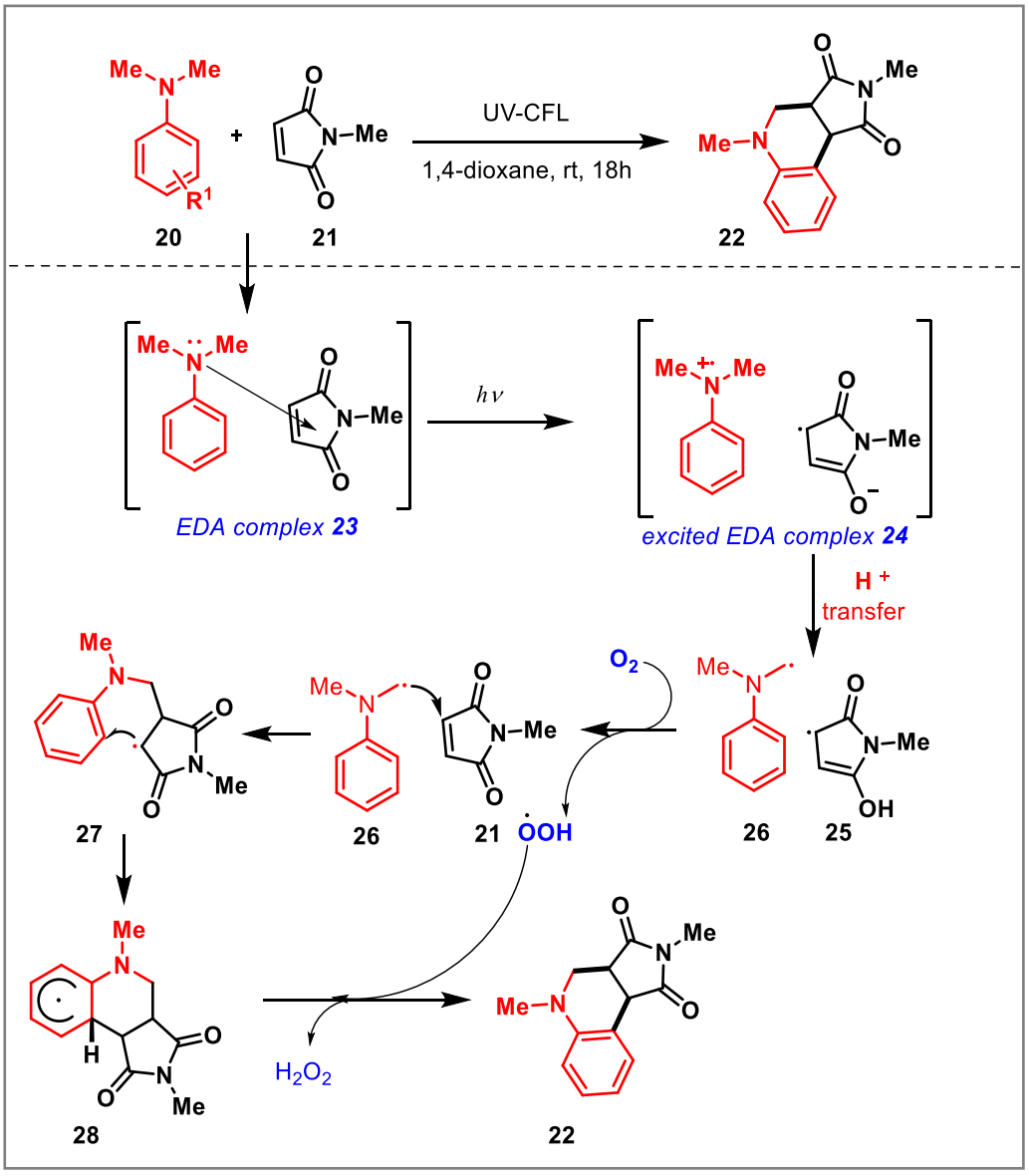


Scheme 3.1.3 Visible-light-mediated indole/oxindoles synthesis.

In 2015, Paixão *et al.* reported the synthesis of indoles **11** or oxindoles **13** through visible-light-mediated dehalogenation and intramolecular cyclization of halobenzene-sulfonamides **9/12** bearing terminal alkynes under a mild reaction condition (Scheme 3.1.3).[16] The wide variety of substrates bearing both EWG or EDG provided the desired indole **11**/oxindoles **13** in good yields. The electron donor-acceptor complex **14** was formed by the association of the aryl sub-

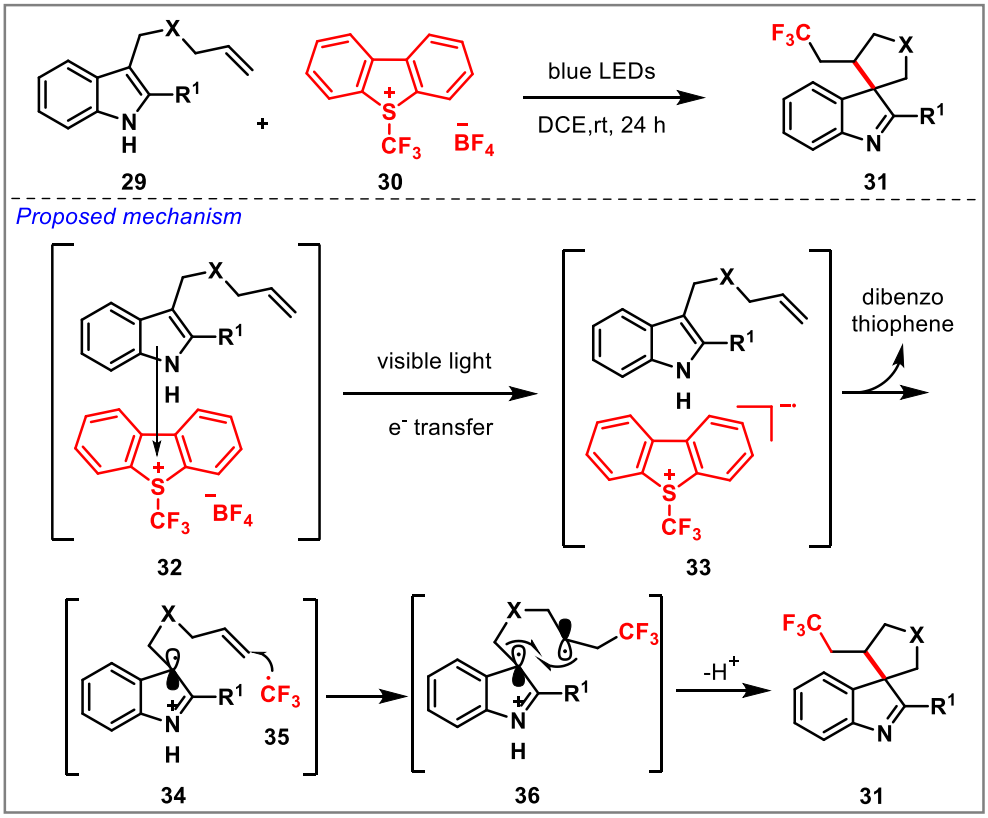
strate **9** with tris(trimethylsilyl)silane (TTMSS) **10**. Visible light irradiation promoted the excitation of EDA complex **14**, giving the species **15**. After an energy transfer, the silicon radical **16** is formed and subsequently promotes the single-electron reduction of the halobenzenesulfonamides **9**, generating the aryl radical **17**. A kinetically favoured 5-exo-dig cyclization leads to the formation of a vinyl radical **18**. Further, 1,3 H-shift produces allylic radical **19**. Finally, the proton abstraction of EtOH gives to the corresponding heterocyclic product **11** (Scheme 3.1.3).

b) Intermolecular cyclization *via* EDA complex process



Scheme 3.1.4 α– aminoalkyl radical addition to maleimides *via* EDA complex.

In 2018, Sunden *et al.* reported an EDA complex mediated direct synthesis of tetrahydroquinolines **22** from *N,N*-dimethylanilines **20** and maleimides **21** using molecular oxygen as an oxidant and without any catalyst (Scheme 3.1.4).[17] The Mechanistic rationale of this transformation is the formation of an electron donor-acceptor (EDA) complex **23** between the *N,N*-dimethylanilines **20** and maleimide **21.** Photon-induced electron transfer from *N,N*-dimethylanilines **20** to maleimide **21** occurs *via* irradiation, followed by a proton transfer to generate the maleimide radical **25** and α-aminoalkyl radical **26**. Maleimide radical **25** accepts one electron from oxygen and forms hydroperoxyl radical. Subsequently, α-aminoalkyl radical **26** attacked the maleimide, forming intermediate **27**, which rapidly cyclizes to an intermediate **28**. Finally, abstracting hydrogen of compound **28** by hydroperoxyl radical to give the product.

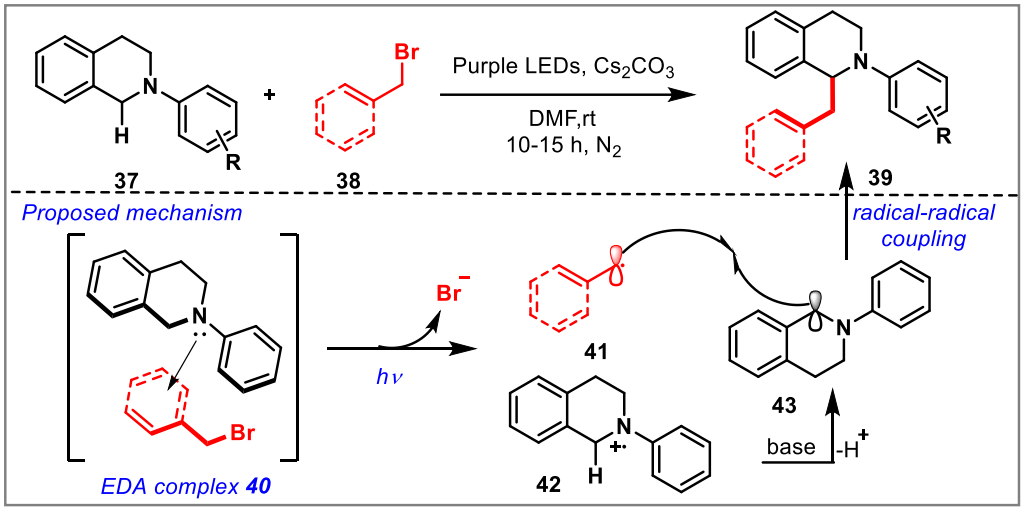


Scheme 3.1.5 Trifluoromethylation and dearomatization of indole *via* EDA complex.

In 2018, You and co-workers described a reaction between indoles **29** with trifluoromethylating reagent **30**, wherein the trifluoromethyl group was introduced into the spiroindolenine moiety (Scheme 3.1.5).[18] In this method, a large array of spiroindolenines **31** bearing trifluoromethyl (CF_3) groups can be easily obtained with very mild and simple reaction conditions.

The mechanism of this radical cross-coupling reaction is illustrated in Scheme 3.1.5. Initially, the aggregation between two starting materials, indoles **29** and Umemoto's reagent **30**, delivers the EDA complex **32**. This complex **32,** under visible-light irradiation, undergoes single-electron transfer, and CF_3 radical **35** is formed through S-CF_3 bond cleavage. Further, CF_3 radical **35** added to the terminal alkene **34** gives the intermediate **36**. Finally, radical coupling and deprotonation to produce the desired product **31**.

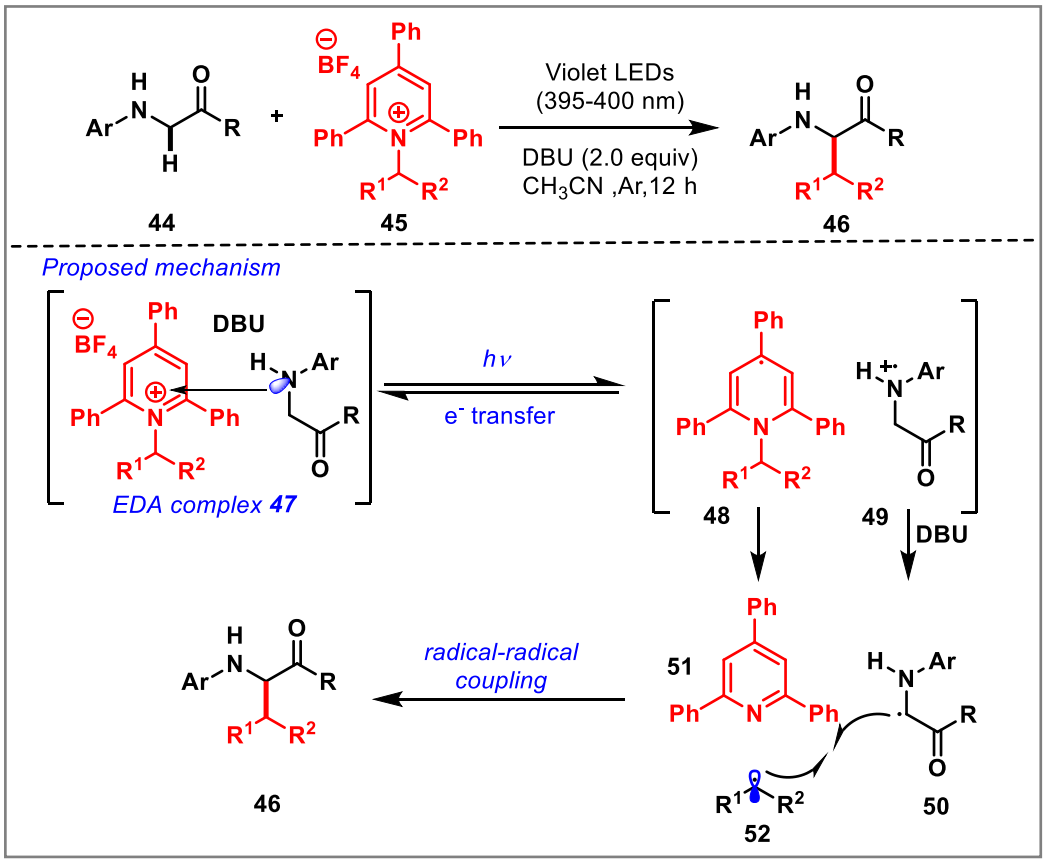
3.1.2.2 Intermolecular charge transfer coupling *via* EDA complex process



Scheme 3.1.6 Visible-light promoted α-allylation/benzylation of *N*-aryl tetrahydroisoquinolines.

Li and co-workers in 2020 demonstrated a visible light promoted α-allylation and benzylation of *N*-aryltetrahydroisoquinolines **37** *via* the formation of an EDA complex. (Scheme 3.1.6).[19] The reaction can tolerate several allyl and benzyl bromides. The mechanism of this reaction comprises the formation of EDA complex **40** between tetrahydroisoquinolines **37** and benzyl bromide **38**. This complex **40,** under visible-light irradiation produces benzyl radical **41** & radical cation **42**. Further, the deprotonation of tetrahydroisoquinolines radical cation **42** gave α-amino radical of *N*-aryl tetrahydroisoquinolines **43,** which undergoes coupling with benzyl or allylic radical **41** to provide the products **39** (Scheme 3.1.6).

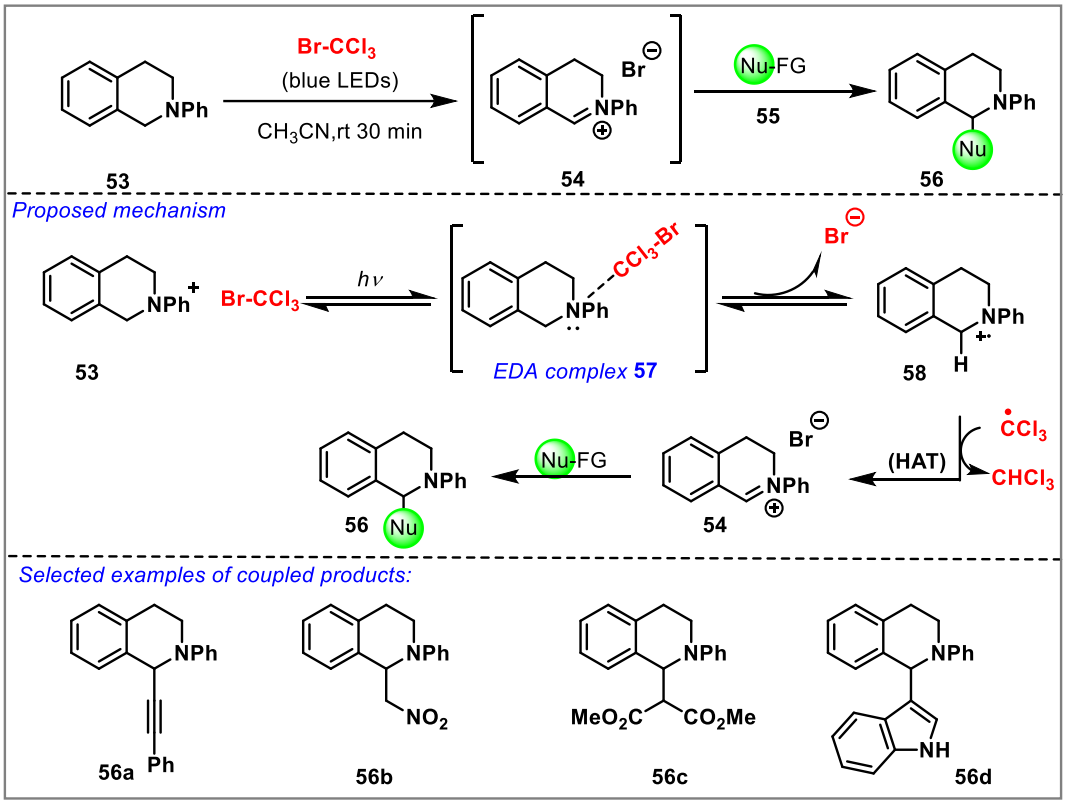
In 2020, Xu and colleague disclosed the EDA complex mediated deaminative C(sp^3)−H alkylation of glycine derivatives **44** by using Katritzky salts **45**. This protocol displays excellent functional group tolerance and high efficiency. Additionally, this method is employed for the synthesis of unnatural α-amino acid derivatives (Scheme 3.1.7).[20]



Scheme 3.1.7 Site-specific modification of peptides under visible light.

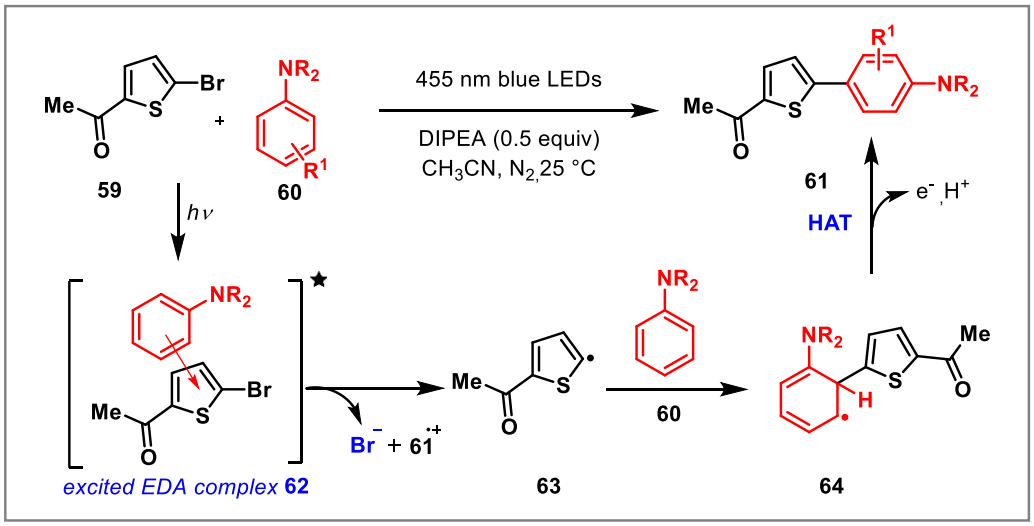
A plausible mechanism for this reaction is illustrated in Scheme 3.1.7. Firstly, a coloured EDA complex **47** was formed in the presence of Katritzky salt **45** and *N*-aryl glycine derivative **44** and DBU. Under visible light irradiation, SET occurred between **44** and **45**, followed by the formation of the radical **48** and radical cation **49**. **48** was fragmented to form the alkyl radical **52** and 2,4,6-triphenylpyridine. The radical cation **49** was deprotonated by DBU to provide an α-carbon radical **50**. Ultimately, the radical coupling between **50** and **52** gave the alkylation product **46** (Scheme 3.1.7).

Zeitler *et al.* in 2015, discovered a catalyst-free visible-light-induced approach for the oxidative α-CH functionalization of *N*-aryl tetrahydroisoquinolines **53** (Scheme 3.1.8).[21] The reaction occurred *via* in situ-generated EDA complex **57** between $BrCCl_3$ and *N*-aryl tetrahydroisoquinoline **53**, under visible light irradiation, complex **57** breaks into a radical cation **58**, which undergoes hydrogen atom transfer to provide the iminium ion intermediate **54**. The formation of $CHCl_3$ as a byproduct in this transformation indicates that the hydrogen atom transfer (HAT) must be operative. Subsequently, nucleophilic attack by various nucleophiles afforded the products **56 (a-d)** (Scheme 3.1.8).



Scheme 3.1.8 Photocatalyst-free protocol for the photochemical α-functionalization of tetrahydroisoquinolines.

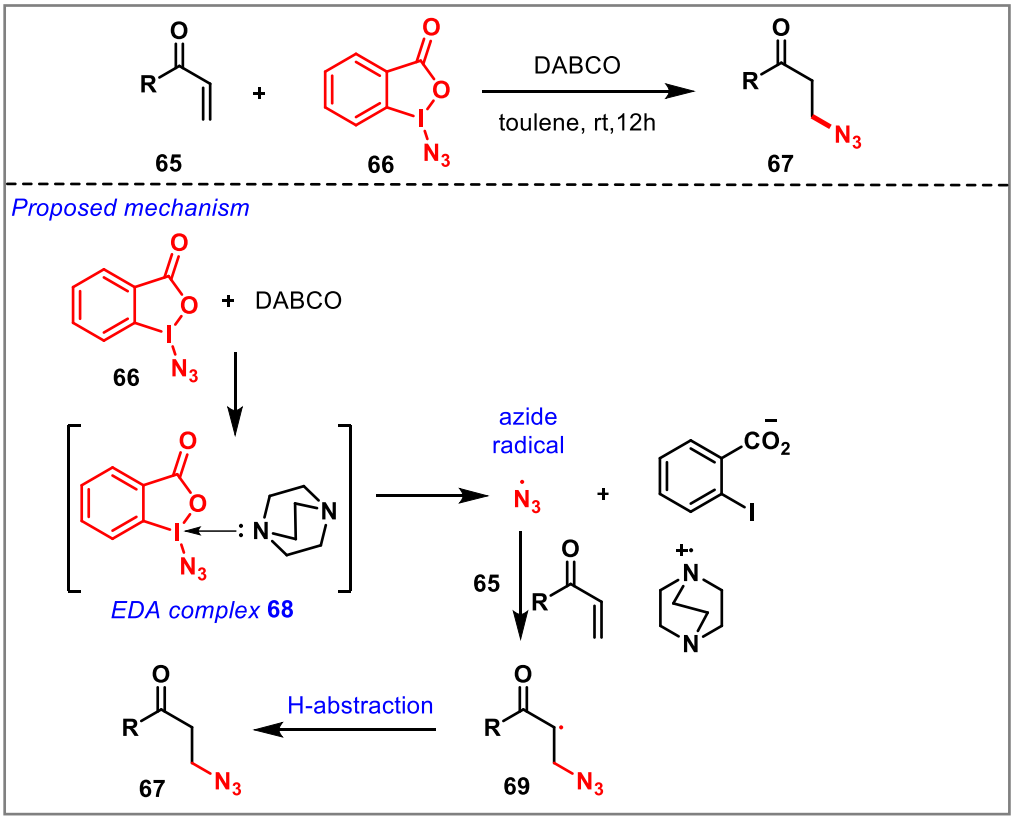
In 2017, König *et al*. reported a visible light induced (hetero)arylation of anilines **60** using (hetero)aryl halides **59** sans the use of photocatalyst and transition metals (Scheme 3.1.9).[22]



Scheme 3.1.9 Arylation of(hetero)aryl halides.

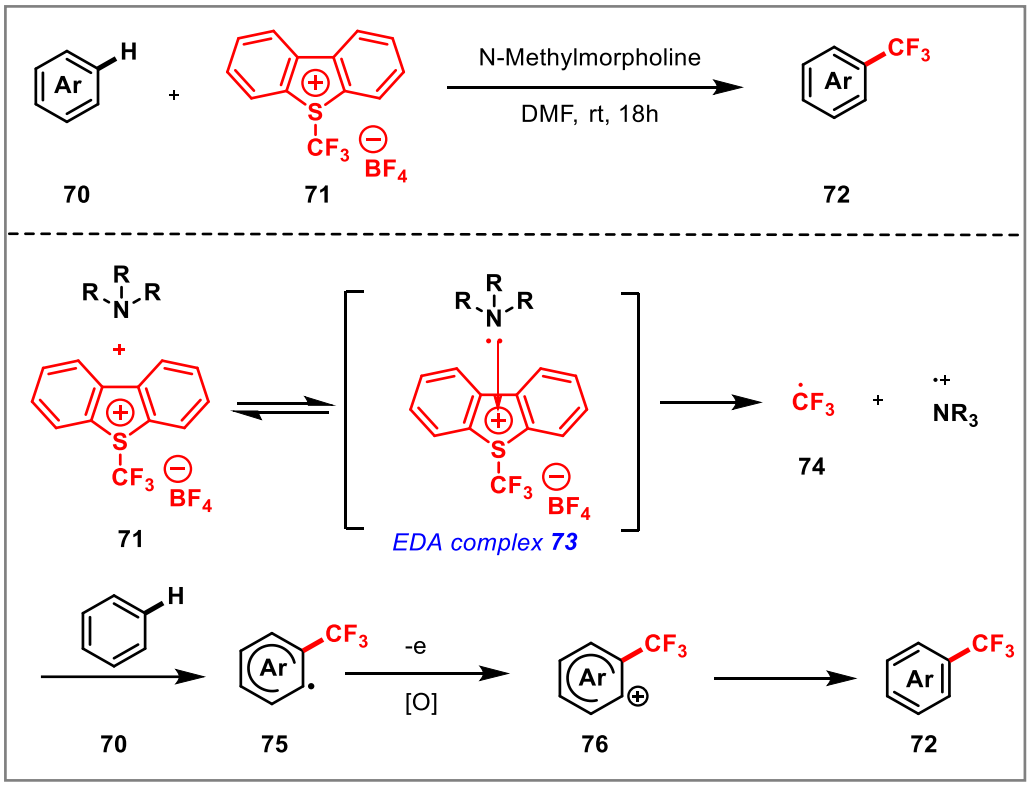
Variety of anilines with an EWG or EDG could produce the corresponding products in good yields. UV-Vis absorption experiments supported the formation of the EDA complex **62**. The

mechanism of this reaction comprises the formation of electron donor-acceptor (EDA) complex **62** between bromothiophene **59** and aniline **60**. Under visible light irradiation, single electron transfer, followed by C−Br bond cleavage, provided radical intermediate **63**. Further, this intermediate **63,** coupled with **60**, affords the radical intermediate **64**. Finally, the HAT process restores aromaticity and provides compound **61**.



Scheme 3.1.10 *β*-azidation of *α,β*-unsaturated ketones.

In 2017, Ramasastry and co-workers developed an organocatalytic *β*-azidation of α,β-unsaturated ketones **65** with Zhdankin's reagent **66** in the presence of DABCO (Scheme 3.1.10).[23] Under mild reaction condition, this method provides valuable *β*-azido ketones **67** in high yields. Further, the authors exhibited the utility of product **67** to synthesize the tricyclic 1,2,3-triazoles *via* an intramolecular cycloaddition of azide and alkyne. The reaction's mechanism begins with forming an EDA complex **68**, which generates an azide radical. Subsequently, azide radical coupled with an olefin to form the α-alkyl radical intermediate **69**. Finally, H-abstraction, either from the solvent or from the water (present in the medium), provide the product **67**. The role of 1,4-Diazabicyclo[2.2.2]octane is a key factor in this transformation (one promotes the formation of the EDA complex, and the other acts as a base).

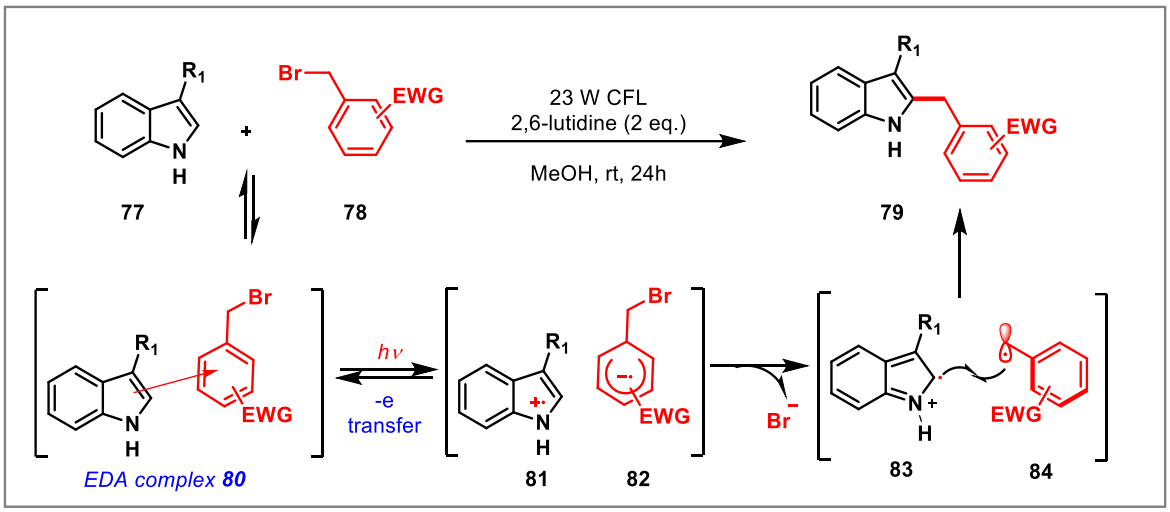


Scheme 3.1.11 Direct aromatic C-H trifluoromethylation *via* an EDA complex.

In 2015, Yu and colleagues reported an easy and effective method for the C-H trifluoromethylation of arenes **70** with trifluromethylating reagent **71** (Umemoto's reagent). This reaction gives easy access to trifluoromethylation of arenes **72** in moderate to good yields under mild conditions and with good functional group tolerance (Scheme 3.1.11).[24] The proposed mechanism comprises the initial EDA complex formation **73** between the tertiary amine and trifluromethylating reagent **71**. The reversible electron transfer (ET) in the EDA complex **73** is activated thermally and subsequently collapsed into the CF_3 radical **74**. This CF_3 radical was added to the arenes **70** to give a radical intermediate **75**. Lastly, this radical intermediate **75** was oxidized into a cation **76**. Further, deprotonation gives trifluoromethylated arenes **72**.

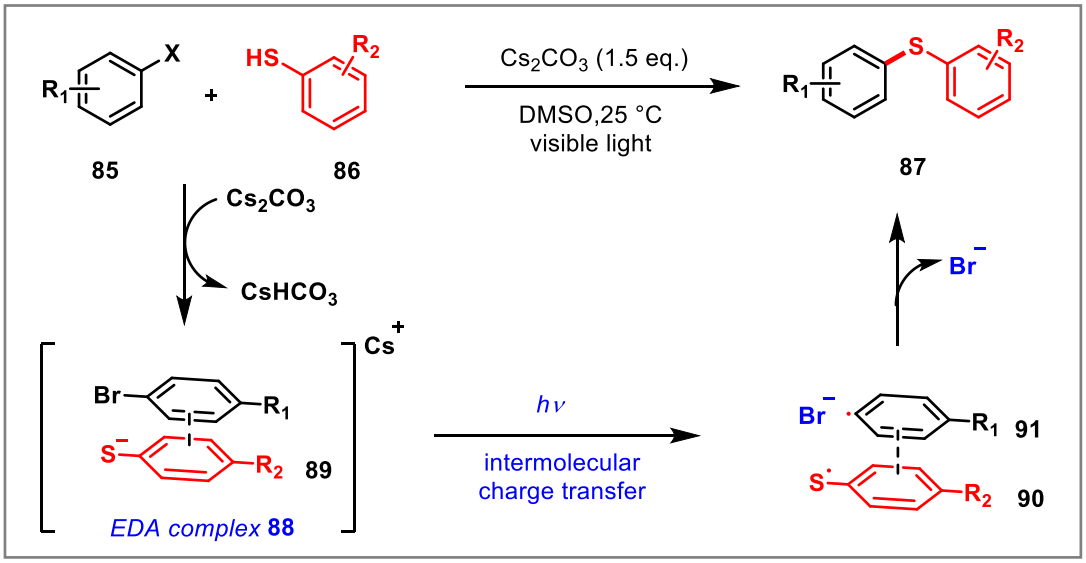
Melchiorre *et al.* in 2019 described a straightforward method for direct phenacylation and benzylation of indoles **77** under mild and photocatalyst-free condition (Scheme 3.1.12).[25] In addition to providing the mechanistic insights of this transformation, an EDA complex were isolated and characterized by X-ray single-crystal analysis. The reaction mechanism begins with the formation of the coloured EDA complex **80**. The photoexcited EDA complex provides a contact radical pair **81** and **82**. Subsequently, radical anion **82**, loose bromide anion, affording the benzylic radical **84** and positively charged intermediate **83**. Finally, radical coupling gave

the product **79**.



Scheme 3.1.12 photochemical alkylation of indoles.

In 2017, Miyake *et al.* disclosed the formation of the C-S bond through a mild, visible-light induced cross-coupling reaction between aryl halides **85** and thiols **86** without the aid of any photoredox catalyst or metal catalyst. (Scheme 3.1.13).[26] The mechanistic rationale of this

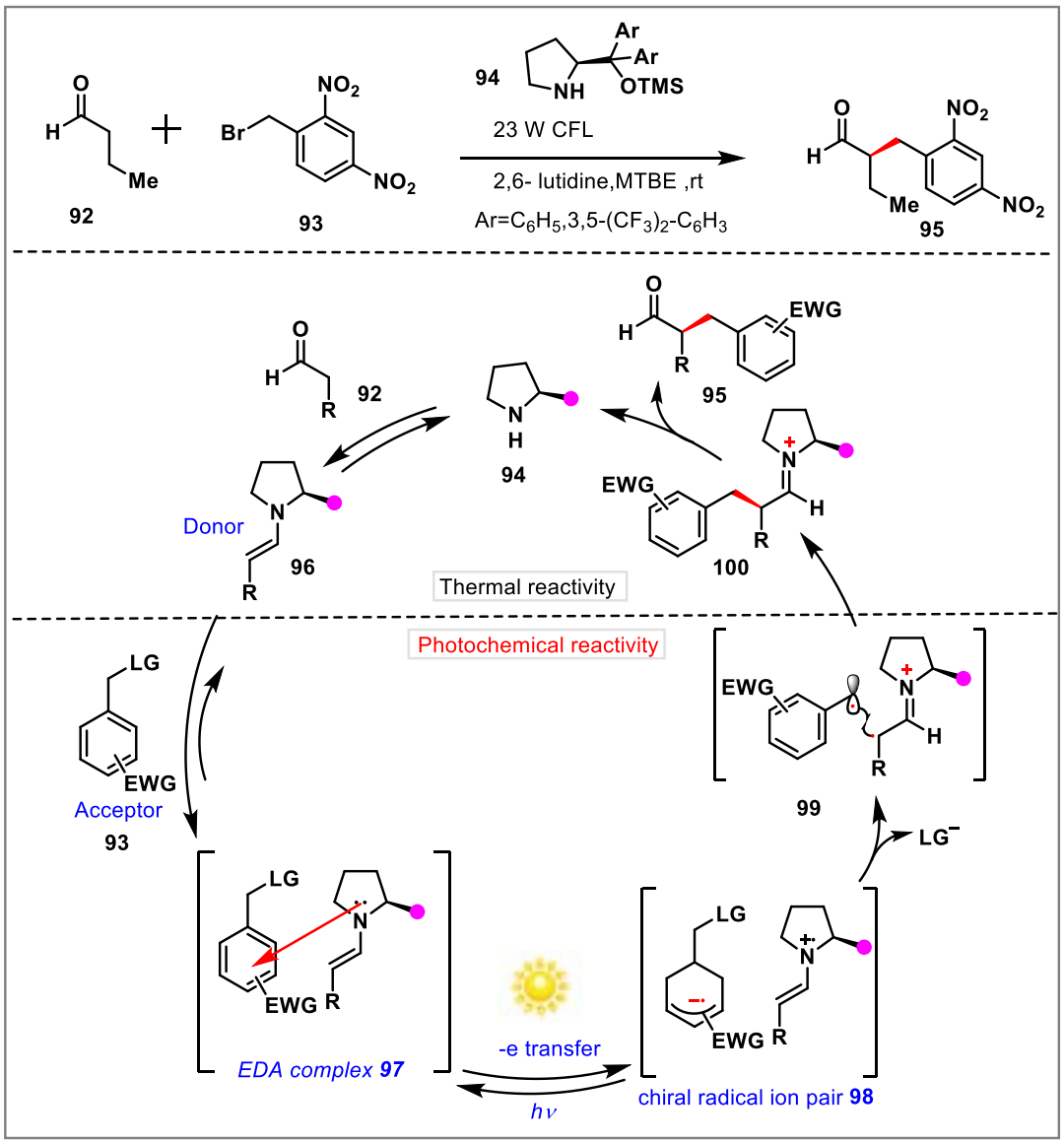


Scheme 3.1.13 visible-light-induced C–S cross-coupling.

transformation is outlined in Scheme 3.1.13. Initially, a base abstracts a proton from thiophenol, giving a thiolate anion **89,** and this thiolate anion forms an EDA complex with aryl halide **85**. Photoinduced electron transfer (ET) of this thiolate anion **89** to the aryl halide **85** gives rise to the intermediate thiyl radical **90**, aryl radical **91** and halide anion. The desired C-S cross-coupled product **87** is produced by coupling of these two radicals (Scheme 3.1.13).

3.1.2.3 Photochemical asymmetric catalysis *via* EDA complexes

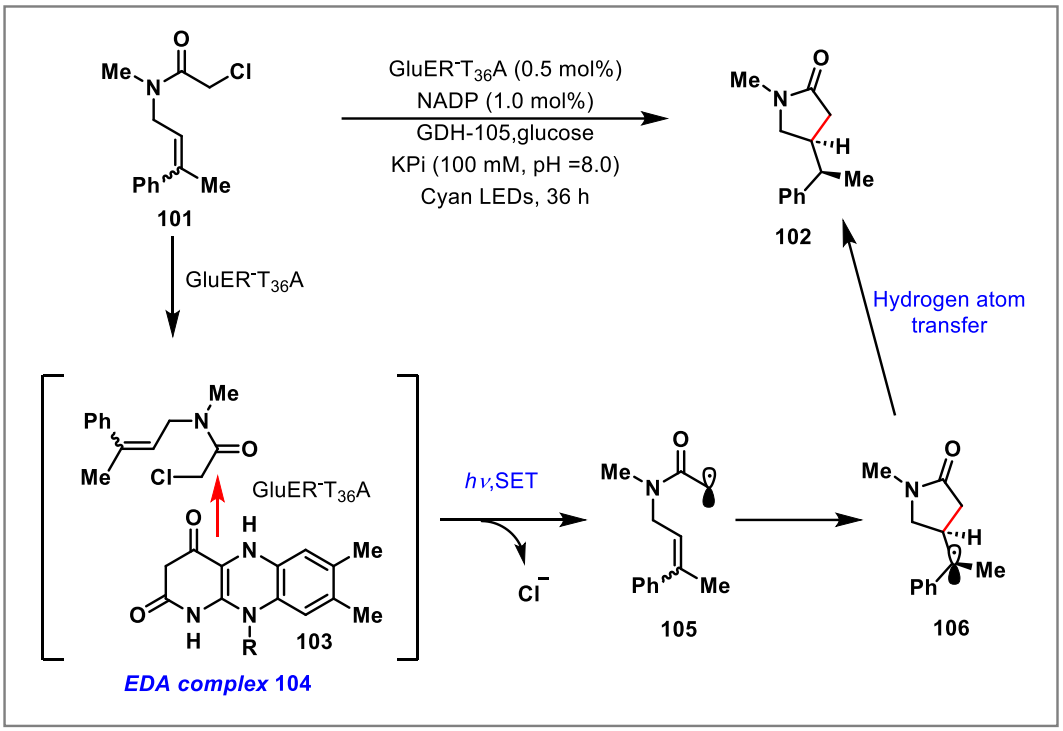
In 2013, Melchiorre*et al.* disclosed an asymmetric catalytic variant of sunlight-driven photochemical α-alkylation of aldehydes (Scheme 3.1.14).[27] The desired α-alkylated product **95** was obtained with a promising level of optical purity using sodium acetate/2,6-lutidine as a



Scheme 3.1.14 Stereoselective catalytic *α*-alkylation of aldehydes.

base. In this photochemical asymmetric catalysis, the authors connect two important fields of molecular activation *i.e.* photochemistry and asymmetric organocatalysis, without the need of an external photosensitizer. Chiral secondary amine **94** readily react with aldehydes **92** to produce reactive nucleophilic enamine intermediates **96**. EDA complex **97** is formed between tertiary amine **96** and substituted benzyl bromide **93** (electron-acceptor). Under visible light irradi-

ation, EDA complex **97** electron transfer produces the chiral radical ion pair **98** due to the presence of bromide as leaving group. Subsequently, it gives the positively charged intermediate pair **99**. Further, radical-radical coupling followed by hydrolysis to produce the product **95**.



Scheme 3.1.15 Stereoselective synthesis of lactams

In 2019, Biegasiewicz *et al.* developed a stereoselective radical cyclization strategy for synthesizing lactams **102** (Scheme 3.1.15).[28] The mechanism of this stereoselective radical cyclization process is illustrated in Scheme 3.1.15. Initially, electron donor-acceptor (EDA) complexes **104** forms between substrate **101** and the reduced Flavin **103**. Under visible light irradiation, EDA complex **104** loses chloride anion to afford the radical intermediate **105**. Further, intramolecular cyclization of intermediate **105** gives intermediate **106**. Finally, hydrogen atom transfer (HAT) through a stereo-defined fashion provides the final lactam product **102**.

3.1.3 Conclusion

The present section highlights the recent advancement in the investigation of photocatalyzed synthetic methods facilitated by EDA complexes without using metals or photocatalysts. These methods outline the advancement of a new and environmentally friendly strategy for the photoinduced ring annulation reaction, intermolecular charge transfer, and photochemical asymmetric catalysis employing EDA complexes. Further, these strategies provide a straight-

forward pathway to deliver the structurally diverse target products under mild reaction conditions. Yet, the significance of EDA complexes has just recently come to light, even though they were previously thought of as a distinct chemical reaction rather than a subfield of photochemistry. There are still many problems to be overcome in the early stages of the study of EDA complexes. Without a doubt, though, this strategy will have a highly promising future in the field of green chemical synthesis.

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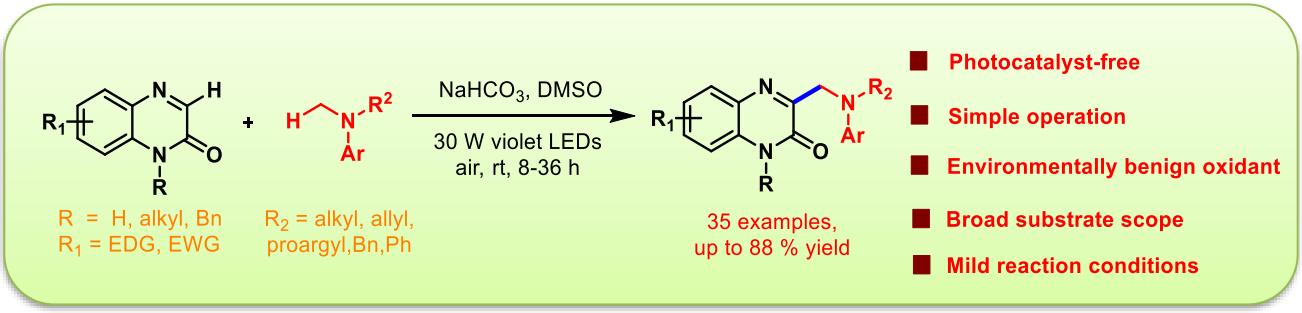
Section-II

Metal- And Photocatalyst-Free, Visible-Light-Initiated C3 *α*-Aminomethylation of Quinoxalin-2(1*H*)-ones *via* Electron Donor-Acceptor Complexes

We report, for the first time, a metal and photocatalyst-free, C3 *α*-aminomethylation of quinoxaline-2(1*H*)-ones with *N*-alkyl-*N*-methylanilines. The reaction proceeds through the formation of an electron donor-acceptor complex between quinoxaline-2(1*H*)-ones with *N*-alkyl-*N*-methylanilines. The present methodology offers a mild, environmentally friendly, exhibits good atomic economy and excellent functional group tolerance to obtain a library of C3 *α*-aminomethylated quinoxaline-2(1*H*)-ones products in good yields.



3.2.1 Introduction

The aminomethyl moiety plays a significant role in organic synthesis and this subunit is found in a wide range of compounds of interest. In addition, it creates an important link between fragments of complex molecules.[1] In addition of serving as an useful synthon, this moiety is often installed within the structure of bioactive compounds, alkaloids derived from several plant species or in promising pharmaceuticals (Figure 3.2.1).[2] For example, Trimetazidine **I** possessing an aminomethyl unit, is used clinically for the treatment of angina pectoris

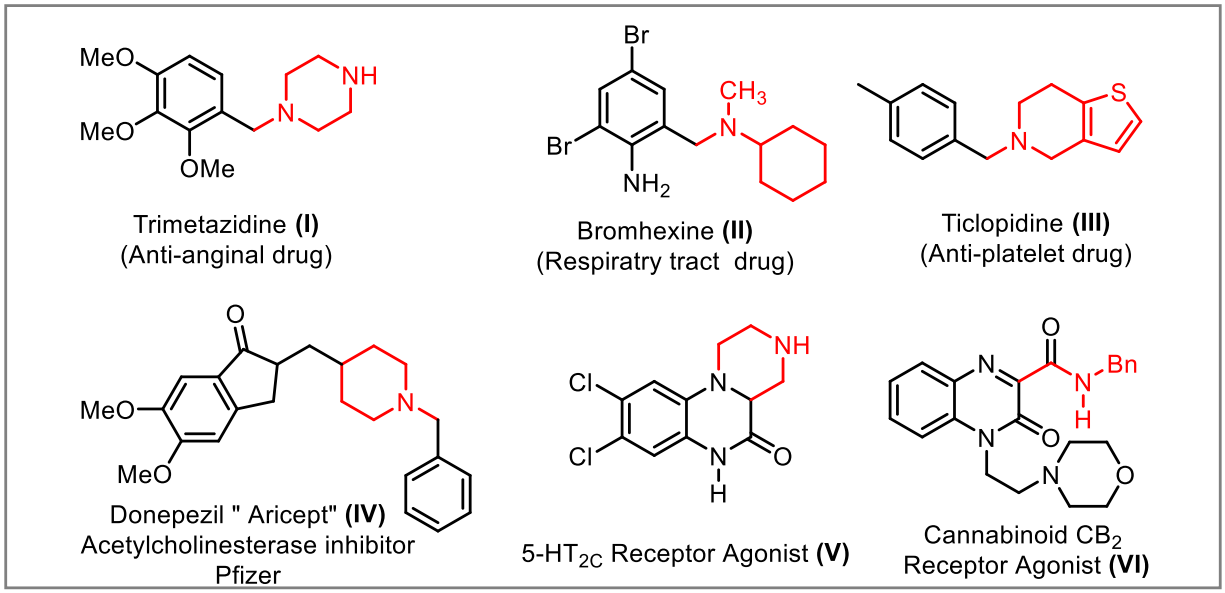
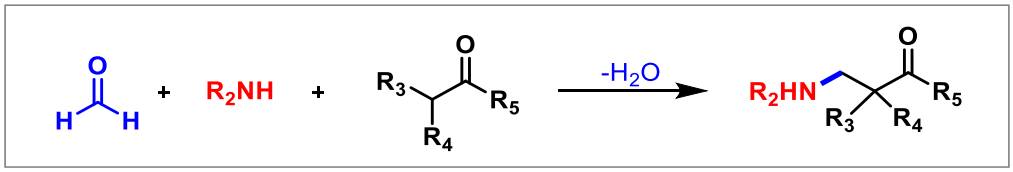


Figure 3.2.1 Representative natural or man-made molecules containing the aminomethyl motif.

(anti-anginal drug), Bromhexine **II** has been approved for the treatment of respiratory disorders associated with viscid, Ticlopidine **III** has been identified as an antiplatelet drug for reducing the risk of thrombotic strokes. Donepezil **IV** is used to treat Alzheimer's disease-related dementia. α-aminoalkyl derivative **V** displays a cannabinoid CB_2 receptor agonist activity, and compound **VI** possesses 5-HT_{2C} receptor agonist activity. Owing to its biological significance, the development of a novel strategy for the incorporation of α-aminoalkylation have attracted a great deal of attention. Conventionally, aminomethylation of CH acidic compounds, known as

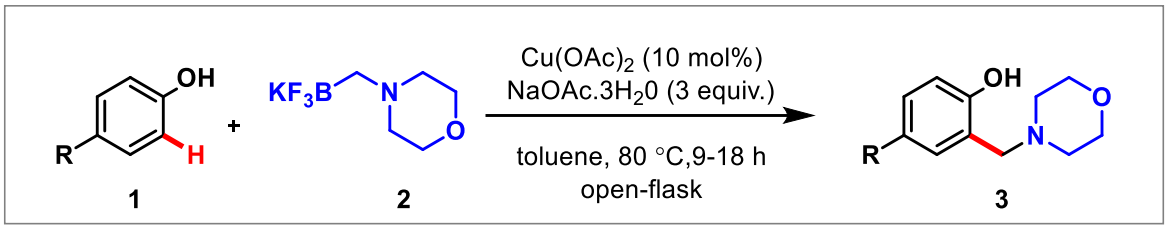


Scheme 3.2.1 Mannich reaction

Mannich reaction is the most important aminoalkylation reaction (Scheme 3.2.1).[3] A limitation of the classical Mannich reaction is that its products (Mannich bases) undergo various secondary Mannich-like reactions and other side reactions that are difficult to avoid and is limited to aminomethylation of carbon nucleophiles. Given the increasing importance of α-aminoalkylation, several methods have long been developed and sought after. Some of the significant approaches developed recently toward the α-aminoalkylation of arenes/heteroarenes have been discussed below.

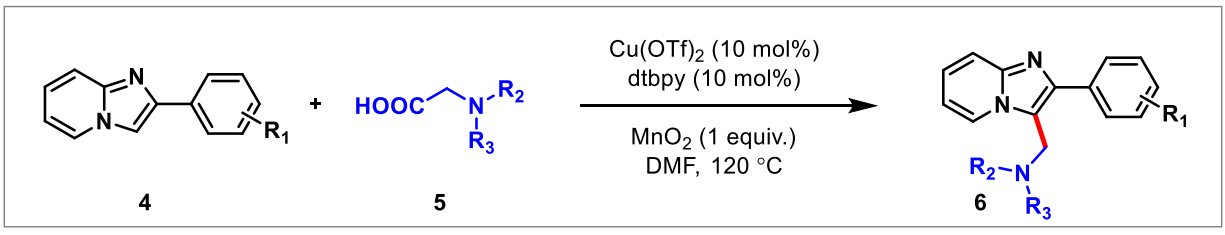
3.2.2 Literature Precedence on α-aminoalkylation of Arenes/Heteroarenes:

Wang *et al*. in 2017 documented the Cu(II)catalyzed *ortho*-selective aminoalkyation of phenol **1** with trifluoroborates **2**. This reaction gives easy access to *o*-aminomethylated phenols **3** in satisfactory yields under mild conditions and with excellent functional group compatibility (Scheme 3.2.2).[4] Additionally, this reaction delivers biologically important serine hydrolase inhibitors with high efficiency.



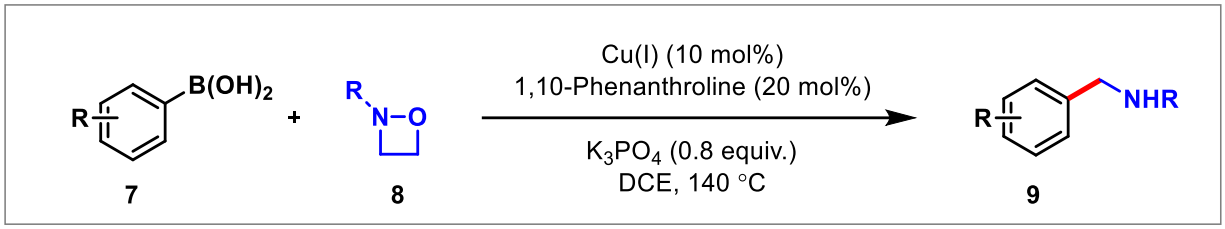
Scheme 3.2.2 Cu(II)-catalyzed *ortho*-selective aminomethylation of phenols.

In 2021, Yang and colleague developed Cu(II)-catalyzed decarboxylative C–H aminoalkyation of heteroarenes **4** with alkyl carboxylic acids **5**. This reaction allows several alkyl carboxylic acids **5** to be converted to alkyl radicals, which are then added to imidazo[1,2-a]-pyridines **4** to produce various aminoalkyl group substituted imidazo[1,2-a]-pyridine **6** units (Scheme 3.2.3).[5]



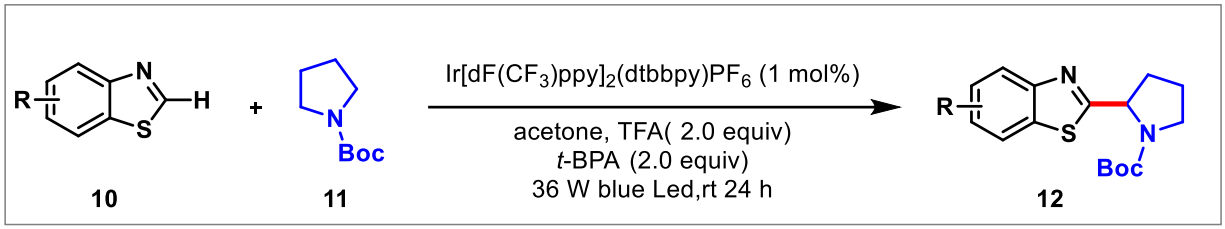
Scheme 3.2.3 Decarboxylative C–H aminomethylation of heteroarenes.

Recently, Hu *et al.* demonstrated a Cu(I)-catalyzed cross-coupling reaction of aryl-boronic acids **7** with 1,2-oxazetidines **8** to access aminomethylated products **9**. In this reaction, the highly strained 1,2-oxazetidine was employed as a precursor of formaldimine (Scheme 3.2.4).[6]



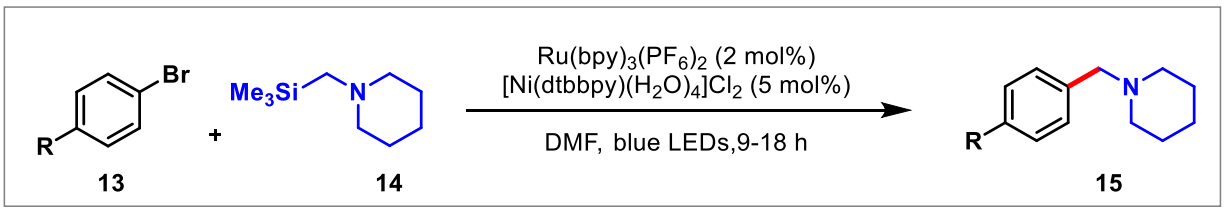
Scheme 3.2.4 Copper–catalyzed cross-coupling of 1,2-oxazetidines with boronic acid.

In 2018, Liu and colleagues reported a visible light-mediated cross-dehydrogenative coupling reaction of benzothiazole **10** with *N*-Boc-pyrrolidine **11** for the efficient synthesis of α-aminoalkylated benzothiazole **12**. The features of this reaction are that the reaction is scalable to a gram level and does not require substrate prefunctionalization (Scheme 3.2.5).[7]



Scheme 3.2.5 Photoredox-mediated direct CDC of heteroarenes and amines.

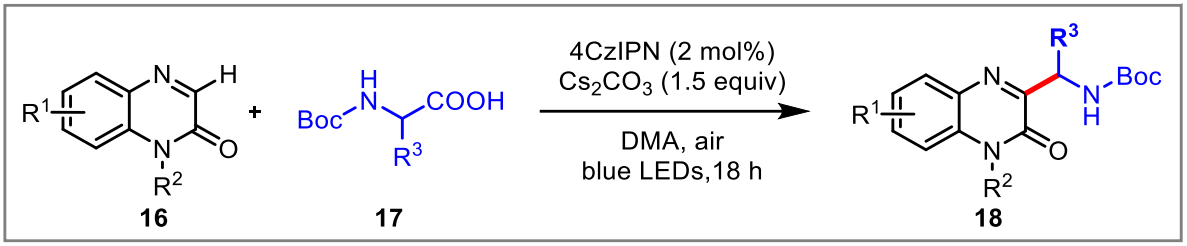
In 2018, Molander and co-workers demonstrated a dual Ni/photoredox catalyzed reaction of aryl halides **13** with α-silylamines **14** to synthesize aminomethylated heteroarenes **15**. In this reaction, various aromatic bromides and various cyclic or acyclic α-silylamines are well tolerated (Scheme 3.2.6).[8]



Scheme 3.2.6 Aminomethylation of aryl halides using α-silyl amines enabled by Ni/photoredox dual catalysis.

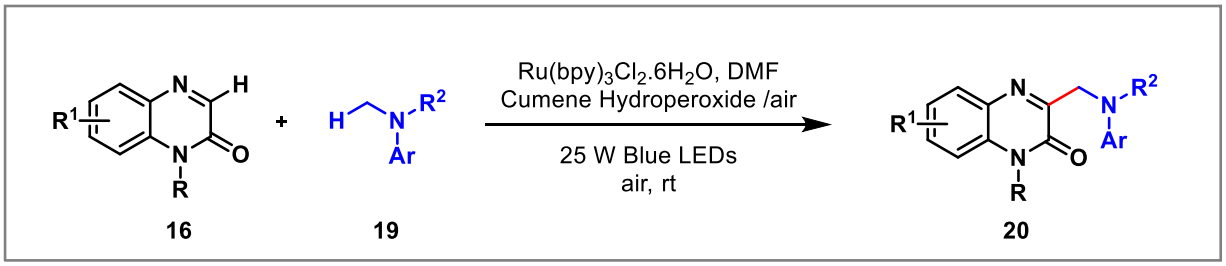
Sun and colleagues, in 2021, reported a photoinduced aminoalkylation of quinoxalin-2(1*H*)-ones **16** *via* decarboxylation of *N*-protecting amino acids **17**. This protocol attempts to develop a new method that allows the coupling of two pharmaceutically important structure mo-

tifs. This reaction delivers various biologically important complex derivatives with high efficiency under mild reaction conditions (Scheme 3.2.7).[9]



Scheme 3.2.7 Aminoalkylation of heterocycles by the decarboxylation coupling of amino acid.

Very recently, Zhang *et al.* disclosed the photoinduced cross-dehydrogenative-coupling reaction of quinoxaline-2(1*H*)-ones **16** with *N*-methylanilines **19** for the synthesis of α-aminoalkylated quinoxaline-2(1*H*)-ones **20**. In this reaction, $Ru(bpy)_3Cl_2·6H_2O$ serves as the photocatalyst and cumene hydroperoxide (CHP)/air acts as an oxidant (Scheme 3.2.8).[10]

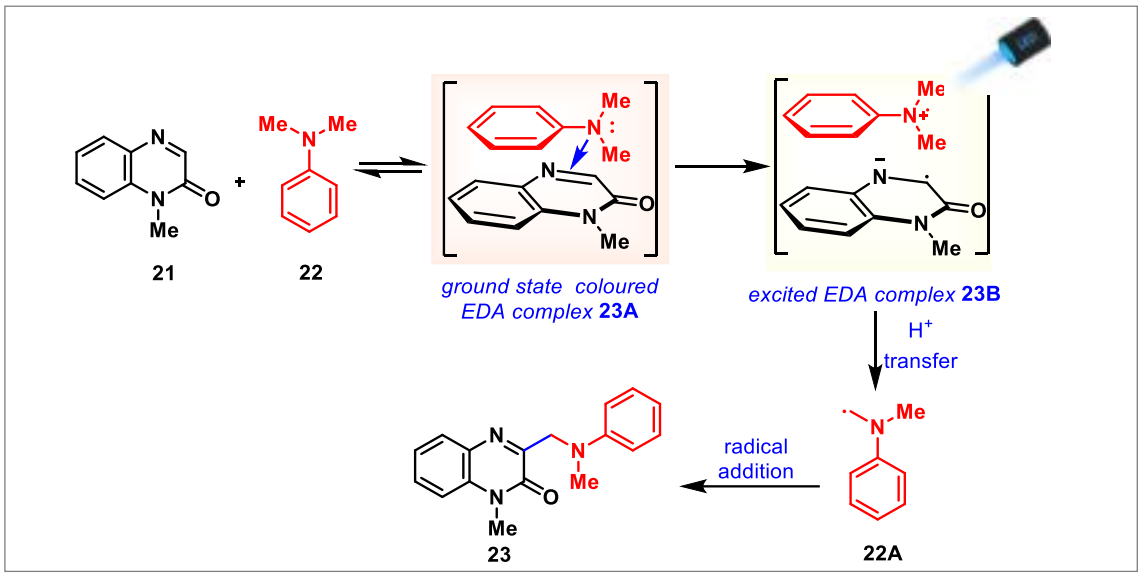


Scheme 3.2.8 CDC reaction of *N*-heterocycles with *N*-alkyl-*N*-methylanilines.

3.2.3 Present Work

3.2.3.1 Statement of the Problem

From the above discussion, it is clear that α-aminoalkylation of aryl/heteroaryl moiety is very important in organic reactions, as the end products of this reaction are often medicinally important. On the other hand, quinoxalin-2(1*H*)-one is a privileged chemical entity commonly encountered in several biologically active molecules, natural products, and pharmaceutical compounds[11] (detailed illustration of quinoxalin-2(1*H*)-one is already present in chapter-2, section-II). Considering the prevalence of α-aminoalkyl[12] and heteroarenes moieties in biologically active molecules, the development of an eco-friendly, photocatalyst-free method for direct *α*-aminomethylation of quinoxaline-2(1*H*)-ones without pre-functionalization of starting material would be highly desirable.



Scheme 3.2.9 Hypothesis on α-aminomethylation of quinoxalin-2(1*H*)-one.

As discussed in the previous section, the chemistry of the electron donor-acceptor complex (EDA) has enormous potential in organic synthesis. From the viewpoint of green chemistry, a mild, environmentally friendly, atomic economical, and photocatalyst-free process under visible-light photochemistry is immensely important. Understanding the paramount importance of EDA complex in organic synthesis, we presumed that the reaction between quinoxalin-2(*1H*)-ones **21** and *N,N*-dimethylaniline **22** could undergo EDA complex formation at the ground state **23A**. Under visible irradiation, a single electron transfer might occur in the excited state of EDA complex **23B**, and subsequent proton transfer could result the α-amino alkyl radical **22A**. Further, its addition with quinoxalin-2(*1H*)-ones could result the formation of α-amino alkylated product **23** (Scheme 3.2.9). Herein, we represent the successful realization of this approach of accessing biologically relevant C-3 amino alkylated quinoxalin-2(*1H*)-ones *via* simple, eco-friendly EDA-complex formation under visible light conditions without additives and photocatalyst.

3.2.4 Results and Discussion

3.2.4.1 Optimization of reaction conditions

At the outset, the interaction between 1-methylquinoxalin-2(1*H*)-one (**21a**) and *N,N*-dimethyl aniline/*N,N*-Dimethyl-*p*-toluidine (**22a/22b**) was studied first (Figure 3.2.2). Upon mixing, a colour change from colourless to light yellow was observed (Figure 3.2.2A), and UV–Vis studies of **21a**, **22a** or **22b**, and a mixture of the two compounds were performed. Appear

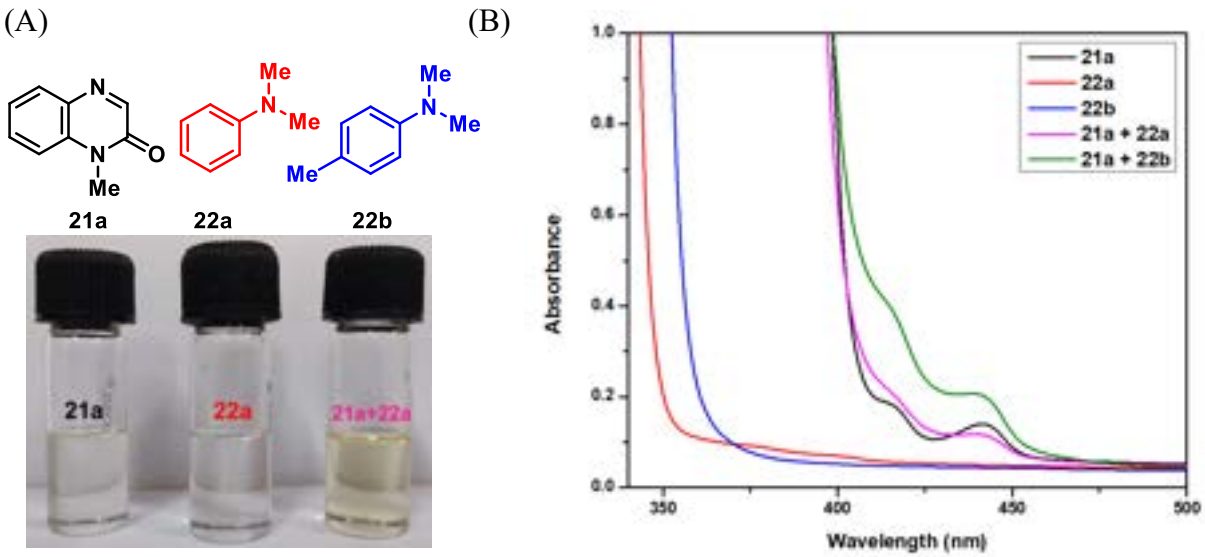
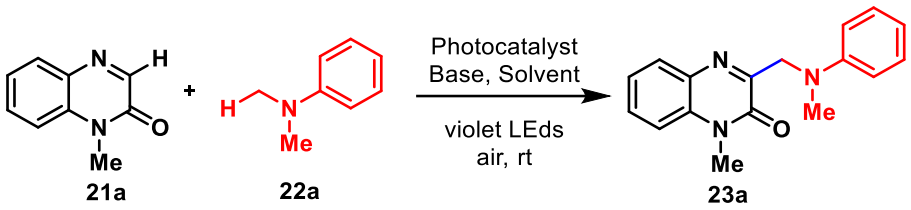


Figure 3.2.2 (A) Photos of **21a**, **22a**, and **21a + 22a** in DMSO. **(B)** UV/vis absorption spectra of **21a** (quinoxalin-2(1*H*)-ones,0.1 M in DMSO, black band), **22a** or **22b** (*N,N*-dimethylaniline or, *N,N*-dimethyl-*p*-toluidine 0.3 M in DMSO, red and blue band), their mixtures in DMSO **21a** + **22a** (pink band) and in **21a + 22b** (green band).

ance of a new absorption band in the visible region (Figure 3.2.2B) indicates EDA interaction. Intrigued by this interesting observation, subsequently, we carried out the feasibility studies of utilizing this EDA complex for the C3 α-aminomethylation of 1-methylquinoxalin-2(1*H*)-one (**21a**). At first, the reaction mixture of **21a** and **22a** was irradiated with 30 W violet LEDs (410–420 nm) in the presence of K_2HPO_4 in DMSO solvent at room temperature under an open-air atmosphere. To our delight, the expected C3 α-aminomethylated product **23a** was obtained with 69 % yield (Table 3.2.1, entry 1). The structure of product **23a** was confirmed by its ^{1}H and ^{13}C NMR spectral analysis. In the ^{1}H NMR spectrum of compound 23a, the characteristic methylene (-**CH$_2$**-N) proton resonates as a singlet at δ 4.74 (s, 2H) and disappearance of the C3-H proton signal of quinoxalin-2(1*H*)-ones (**21a**) at δ 8.31(s, 1H) was observed. In the ^{13}C NMR, the appearance of the characteristic signal of methylene carbon resonates at δ 55.2 ppm, supports product **23a**. Furthermore, the constitution of **23a** has been confirmed as $C_{17}H_{18}N_3O$ (calculated value 280.1444) by the HRMS $[M+H]^+$ found as 280.1449. With the confirmation of this structure and motivated by these initial findings, our efforts towards improving the reaction yield shifted to investigate the effect of solvents, visible light sources and bases. Subsequently, we evaluated the effect of several solvents, such as DMF, CH_3CN, DCE, 1,4-dioxane, toluene, EtOH, H_2O and observed that DMSO was the most effective solvent (Table 3.2.1, entries 2-8).

Table 3.2.1 Optimization of the reaction conditions[a,b]



entry	Base	Light source	Solvent	Yield[b] (%)
1	K_2HPO_4	410-420 nm	DMSO	69
2	K_2HPO_4	410-420 nm	DMF	45
3	K_2HPO_4	410-420 nm	CH_3CN	trace
4	K_2HPO_4	410-420 nm	DCE	trace
5	K_2HPO_4	410-420 nm	1,4-dioxane	trace
6	K_2HPO_4	410-420 nm	Toluene	NR
7	K_2HPO_4	410-420 nm	EtOH	trace
8	K_2HPO_4	410-420 nm	H_2O	NR
9[c]	K_2HPO_4	410-420 nm	DMSO	46
10	K_2HPO_4	440-450 nm	DMSO	47
11	K_2HPO_4	490-505 nm	DMSO	trace
12[d]	K_2HPO_4	410-420 nm	DMSO	71
13[d]	K_3PO_4	410-420 nm	DMSO	86
14[d]	K_2CO_3	410-420 nm	DMSO	63
15[d]	**$NaHCO_3$**	**410-420 nm**	**DMSO**	**88**
16[d]	Na_2CO_3	410-420 nm	DMSO	70
17[d]	KOH	410-420 nm	DMSO	NR
18[d]	DABCO	410-420 nm	DMSO	70%
19[d]	NaOAc	410-420 nm	DMSO	69%
20[d,e]	$NaHCO_3$	410-420 nm	DMSO	75%

[a]Reaction conditions: **21a** (0.19 mmol,1 equiv), **22a** (1.5 equiv), base (1.5 equiv), solvent (2.0 mL) and 30W violet LEDs, under an open-air atmosphere at room temperature and 24 h. [b]Isolated yields. [c]In presence of O_2 atmosphere. [d]Stirred for 16 h. [e]Base(1.0 equiv).

Next, in the case of the reaction, which was performed under O_2 atmosphere instead of open air, **23a** was obtained in decreased yield (Table 3.2.1, entry 9). Further, screening of different visible-light sources revealed that the wavelength of LEDs significantly affects the performance of the reaction (Table 3.2.1, entries 10-11). Afterwards, we examined the duration of the reaction and found that 16 h is sufficient to effect this transformation (Table 3.2.1, entry 12). Additionally, a series of bases were also examined, and $NaHCO_3$ was proved to be the effective base delivering the product **23a** in 88% yield (Table 3.2.1, entry 15). It was also observed that decreasing the equivalent of the base to 1.0 equivalent lowers the yield of product **23a**. Finally, the reaction conditions comprising **21a** (1 equiv), **22a** (1.5 equiv), 410-420 nm violet LEDs (30W) and 1.5 equiv of $NaHCO_3$ as abase in 1.5 mL of DMSO under an open-air atmosphere at ambient temperature was found optimal.

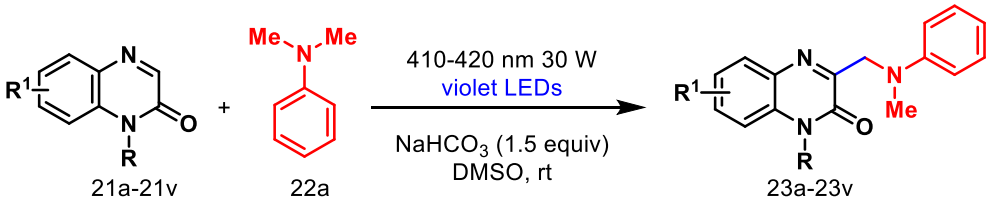
3.2.4.2 Substrate scope of various quinoxalin-2(1*H*)-ones

With the optimized conditions in hand, we next explored the substrate scope of this reaction using different quinoxalin-2(1*H*)-ones **21a-v** with *N*,*N*-dimethylaniline **22a**. As illustrated in Table 3.2.2, initially quinoxalin-2(1*H*)-ones with various *N*-protecting groups such as methyl, ethyl, allyl, propargyl, ethyl ester and benzyl were tested, and all of them gave products **23a-23f** in good yields. In addition, *N*-methyl quinoxalin-2(1*H*)-one of various EDG or EWG at C5/C6/C7-positions of the phenyl ring efficiently participated in the reaction and produced the corresponding C-3 aminoalkylated products **23g-23n** in good yields. The quinoxalin-2(1*H*)-one carrying electron-withdrawing cyano substituents at C6 provided the desired product **23l** in a 30 % yield. Furthermore, disubstitution on the quinoxalin-2(1*H*)-one moiety was well tolerated and produced the desired products with satisfactory yields (**23o-23p**). Notably, the reaction of various *N*-unsubstituted quinoxalin-2(1*H*)-one derivative were well tolerated in the present transformation, giving the desired product **23q-23u** in 48-65% yields. However, the reaction of 2H-benzo[b][1,4]oxazin-2-one 21v with 22a under the optimized conditions failed to give the product.

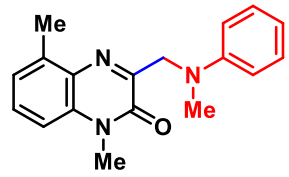
3.2.4.3 Substrate scope of various *N,N*-dimethylaniline

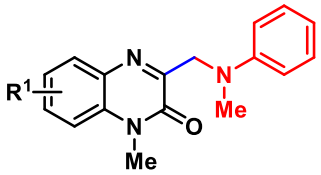
Next, the substituent effects on the *N,N*-dimethylaniline were also investigated. As shown in (Table 3.2.3), *N,N*-dimethylanilines with electron-donating or halo-substituents at the *ortho*, *meta* or *para* position of phenyl ring were compatible with this reaction affording the products **24a-24h** in moderate to good yields. Furthermore, disubstituted *N*,*N*-dimethylaniline **22g-22h** were good candidates, yielding the corresponding products **24i-24j** in good yields (77-85%).

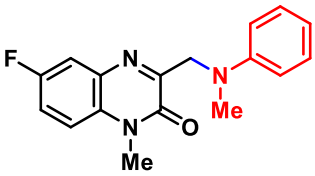
Table 3.2.2 Substrate scope of various quinoxalin-2(1*H*)-ones 23[a,b]

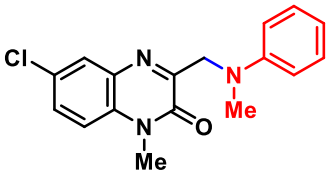


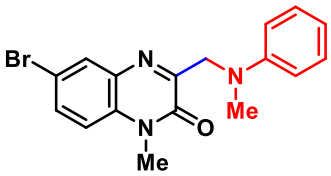
23a, R = Me, 16 h, 88%
23b, R = Et, 16 h, 83%
23c, R = allyl, 16 h, 79%
23d, R = propargyl, 16 h, 77%
23e, R = CH_2CO_2Et, 16 h, 83%
23f, R = Bn, 16 h, 77%

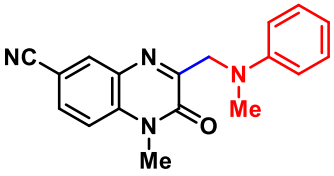

23g,16 h, 81%

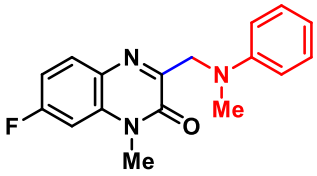

23h/23h' (6/7-Me), 16 h, 86%

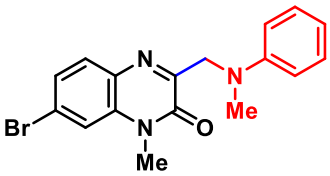

23i,10 h, 88%

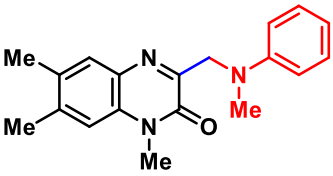

23j,10 h, 83%

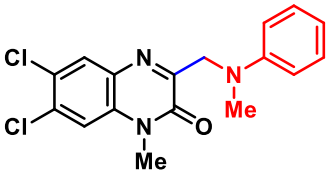

23k,8 h, 85%

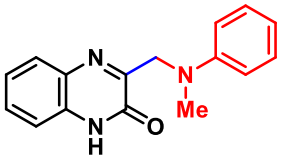

23l, 24 h, 30%

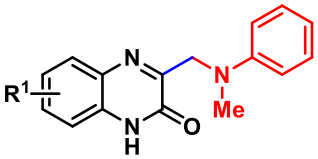

23m,10 h, 72%

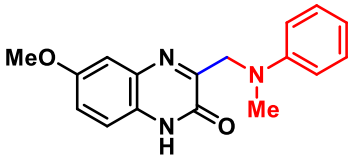

23n, 8 h, 75%

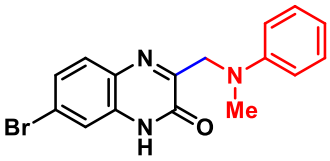

23o,16 h, 84%

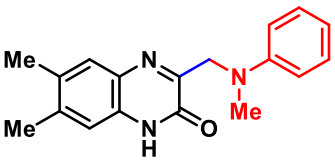

23p,16 h, 83%

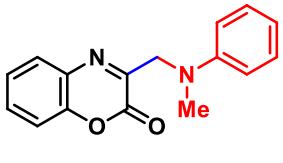

23q, 36 h, 65%


23r/23r' (6/7-Me), 36 h, 65%


23s, 36 h, 52%


23t, 24 h, 48%


23u, 36 h, 64%

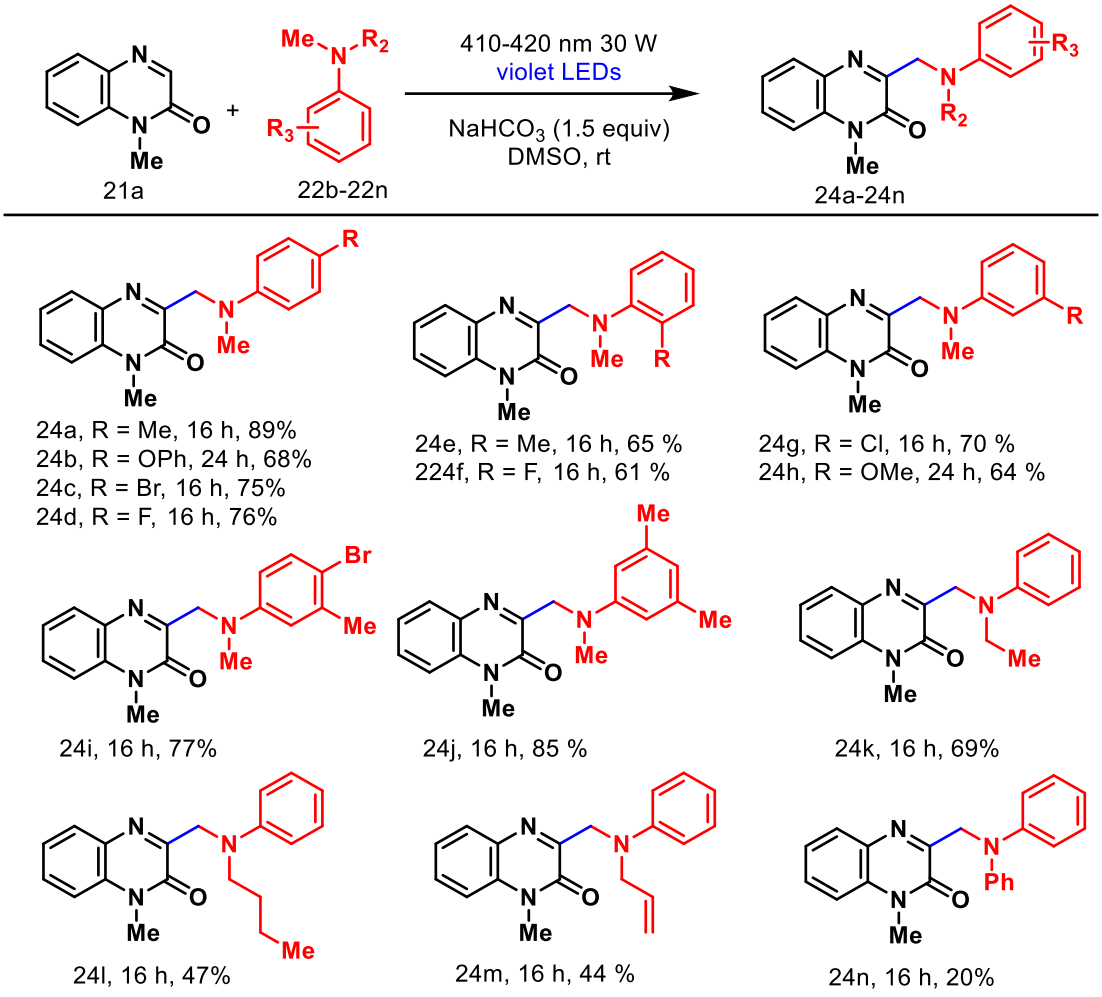

23v, 24 h, 00%

[a]All reactions were performed with **21a-21v** (1 equiv), **22a** (1.5 equiv), base (1.5 equiv), solvent (1.5 mL) and 30W violet LEDs and ambient air at room temperature 16-36h. [b]Isolated yields.

Gratifyingly, changing the *N*-methyl substitution to *N*-ethyl, *N*-butyl, *N*-allyl and *N*-phenyl were

proven to be good substrates in this protocol and provided the corresponding C-3 aminomethylated products in moderate yields (**24k-24n**).

Table 3.2.3 Substrate scope of various *N,N*-dimethylaniline 22[a,b]

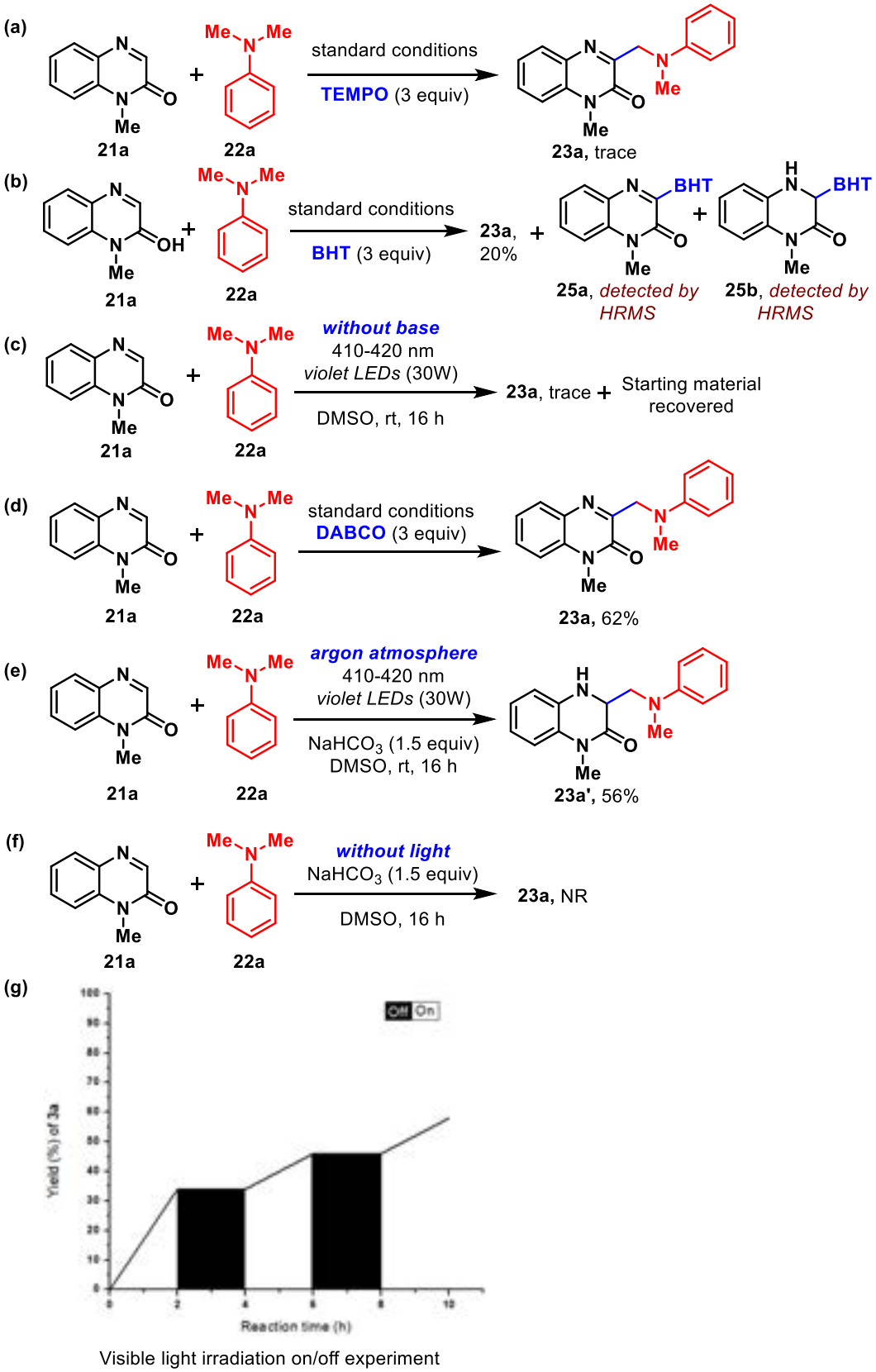


[a]All reactions were performed with **21a** (1 equiv), **22b-n** (1.5 equiv), base (1.5 equiv), solvent (1.5 mL) and 30W violet LEDs and ambient air at room temperature 16-24 h. [b]Isolated yields.

3.2.4.4 Control Experiments and Plausible Reaction Mechanism

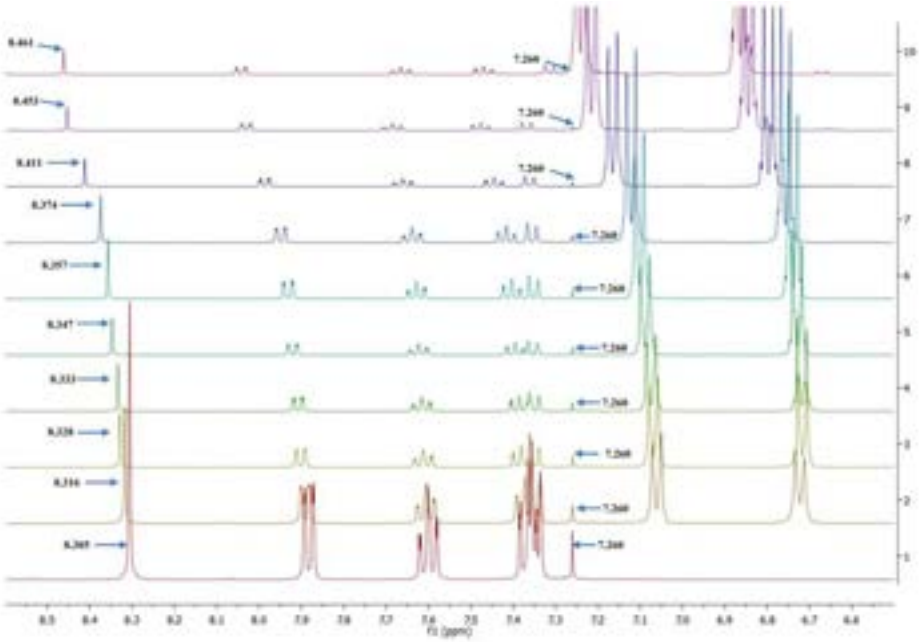
In order to gain some insights into the reaction mechanism, several control experiments were carried out. The addition of 3 equiv of TEMPO under the standard reaction conditions significantly suppressed product **23a** (Scheme 3.2.10a). Interestingly, in the case of BHT, product **23a** was obtained in 20% yield, and BHT-linked adducts **25a** and **25b** were also detected by the HRMS analysis (Scheme 3.2.10b). The result indicates that a single electron transfer might be involved in this transformation. Further, when the reaction was carried out in the absence of a base, the formation of the desired product **23a** was found in trace amount, indicating the crucial

Scheme 3.2.10 Control experiments[a]



Visible light irradiation on/off experiment

(h)



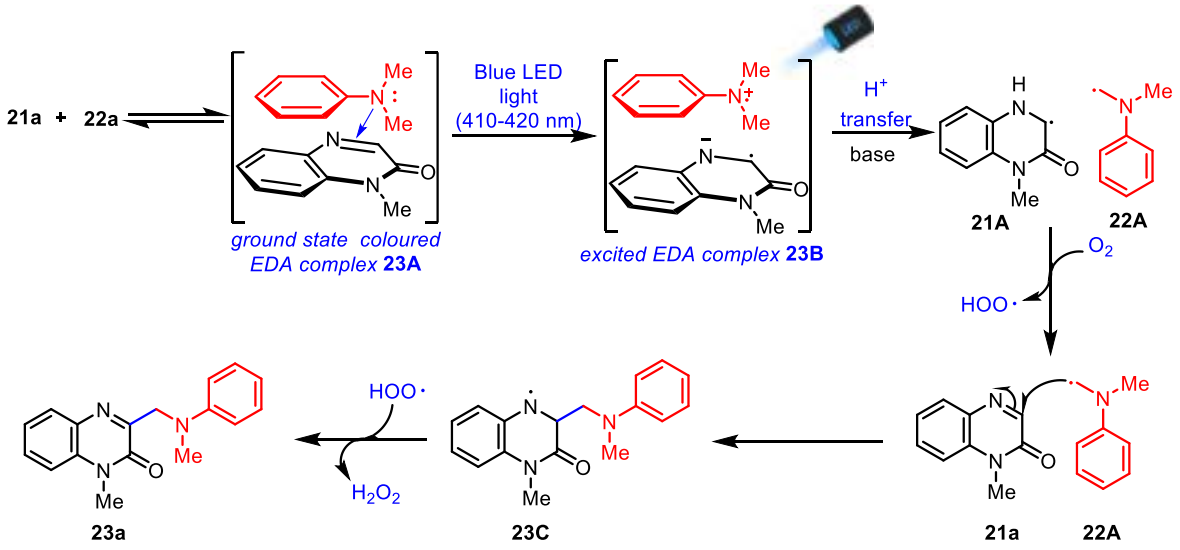
1H NMR shift of quinoxalin-2(1*H*)-one (**21a**) with *N,N*-dimethyl-p-toluidine (**22b**).

[a]Control experiments: (a) and (b) Radical trapping experiment. (c) Reaction without base (d) Singlet oxygen trapping experiment. (e) Reaction under argon atmosphere. (f) Reaction without light. (g) ON/OFF experiment. (h) NMR titration experiment of **21a** and **22b**.

role of the base in this transformation (Scheme 3.2.10c). When singlet oxygen scavenger DABCO (3 equiv) was added under optimized reaction conditions, product **23a** was obtained in 62% yield, which excluded the possible involvement of the singlet oxygen as a reactive intermediate in this reaction (Scheme 3.2.10d). Moreover, when the reaction was carried out under an argon atmosphere *(freeze-pump-thaw cycles)*, only addition product **23a'** in 56% yield was observed, indicating the important role of air in this reaction (Scheme 3.2.10e). Finally, carrying out the reaction in the absence of light did not deliver the target product **23a.** This shows the importance of light in this transformation (Scheme 3.2.10f). Additionally, the on/off visible-light irradiation experiments also confirmed the significant effect of continuous illumination in this reaction (Scheme 3.2.10g). In addition, we performed an NMR titration experiment using **21a** and varied **22b** in different ratios (Scheme 3.2.10h). The chemical shift of ArH in quinoxalin-2(1*H*)-ones **21a** shifted downfield along with increasing the amount of **22b**, indicating the formation of EDA complex between quinoxalin-2(1*H*)-ones **21a** with ***N,N***-dimethyl-*p*-toluidine **22b**.

Based on the above control experiments and previous reports,[13] a plausible reaction mechanism for this aminomethylation reaction between quinoxalin-2(1*H*)-ones (**21a**) and *N,N*-dimethylaniline (**22a**) is depicted in Scheme 3.2.11. The reaction begins with forming an EDA

complex **23A** between quinoxalin-2(1*H*)-ones **21a** and *N,N*-dimethylaniline **22a**. Under visible irradiation, an single electron transfer occurs (excited EDA complex **II**). Subsequent proton transfer with the help of base produces quinoxaline-2(1*H*)-ones **21A** radical and α-aminomethyl radical **22A**. The radical intermediate **21A** reacts with oxygen, regenerates **21a** and forms a hydroperoxyl radical. Further, *α*-amino alkyl radical **22A** reacts with **21a** to form coupling intermediate **23C** which on oxidation will generate the desired product **23a** with formation of H_2O_2 as a byproduct .



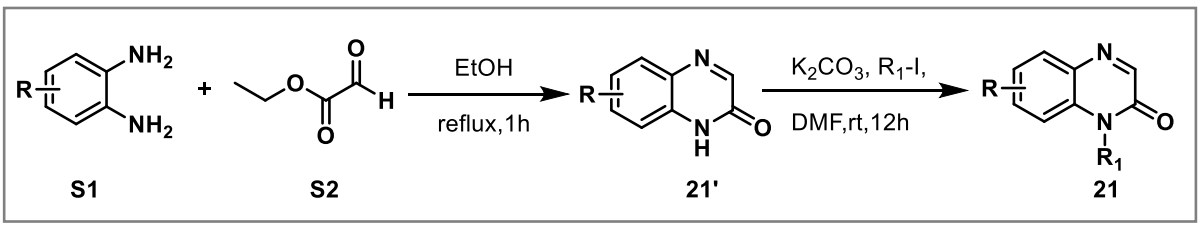
Scheme 3.2.11 Plausible reaction mechanism

3.2.5 Conclusion

In conclusion, we have developed an EDA-complex enabled C3-aminomethylation of quinoxalin-2(1*H*)-ones with *N*-Alkyl-*N*-methylanilines for the first time. The reaction features metal-free, atom economical, environmentally benign chemical processes and does not require a photocatalyst, where atmospheric air serves as a terminal oxidant. Notably, this aminomethylation also works well with *N*-unsubstituted quinoxalin-2(1*H*)-ones derivatives to deliver corresponding products in good yields.

3.2.6 Experimental Section

3.2.6.1 General Procedure for the Preparation of Quinoxalin-2(1*H*)-ones[14]:



Scheme 3.2.12 Preparation of quinoxalin-2(1*H*)-ones.

To a suspension of *o*-arylenediamine **S1** in ethanol was added ethyl 2-oxoacetate **S2** (1.1 equiv.). The mixture was stirred at reflux for 1h, then at room temperature overnight. The precipitated solid was filtered and washed with ethanol, then dried to give quinoxalin-2(1*H*)-ones **21'**. To a suspension of quinoxalin-2(1*H*)-ones **21'** (1 equiv.) in DMF was added potassium carbonate (1.2 equiv.) and the corresponding halo alkane (1.6 equiv). The mixture was stirred at room temperature overnight. Ethyl acetate and water were added. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue is purified by flash chromatography over silica gel to afford the desired product **21**.

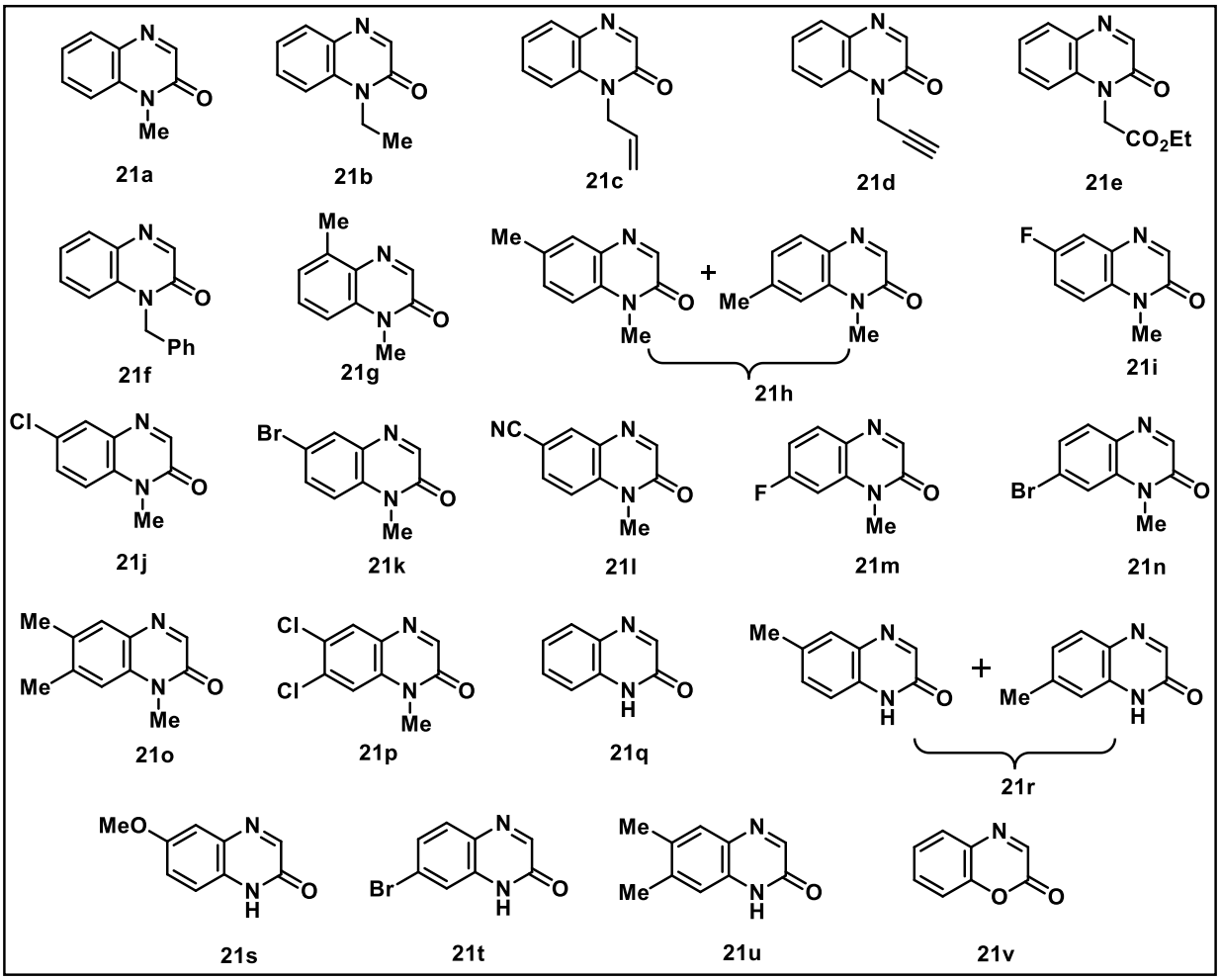
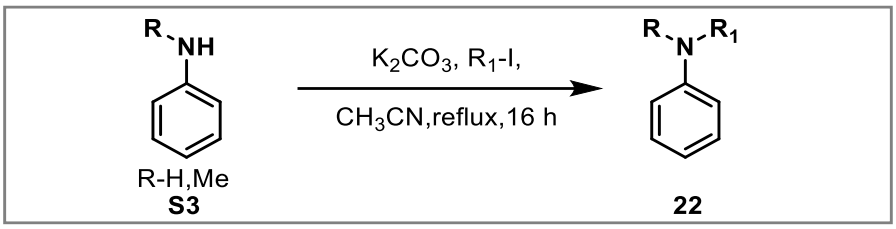


Fig. 3.2.3 Structures of Quinoxalin-2(1*H*)-ones **21a-21v** used in this study.

3.2.6.2 General Procedure for the Preparation of Various *N,N*-dialkylanilines[15]:



Scheme 3.2.13 Preparation of *N,N*-dialkylanilines

To a stirred solution of Aniline or *N*-methylaniline **S3** and Et_3N in MeCN, various halogenoalkanes (R-I) were added, and the mixture was heated to reflux for 16 h. Then, the solution was added with brine and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to obtain a crude product, which was purified by column chromatography on silica gel to afford the *N,N*-dialkylanilines or alkylated *N*-methylanilines **22**.

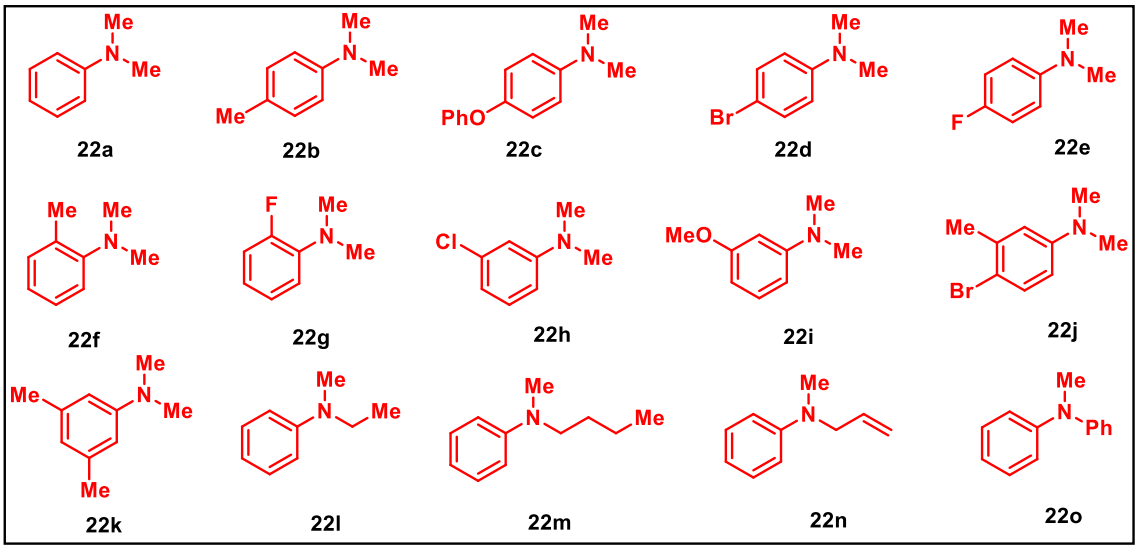


Fig. 3.2.4 Structures of *N,N*-dialkylanilines or alkylated *N*-methylanilines **22a-22o** used in this study.

3.2.6.3 Reaction Setup

Irradiation of photochemical reactions was carried out using a 30W violet LEDs spotlight lamp. The floodlight lamp was manually converted to a spotlight using a plastic box wrapped with aluminium foil from the outer and inner sides. The fan was used according to the external temperature to maintain 20 ~ 30 °C in the reactor. The pictures of reaction setup utilized are shown below:

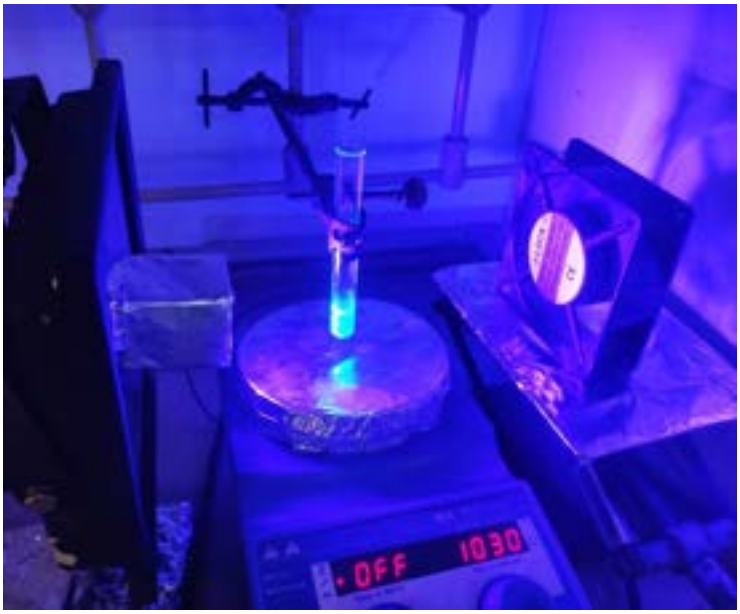


Fig. 3.2.5 Reaction setup (front view)

3.2.6.4 General Procedure of α-aminomethylation of Quinoxalin-2(1*H*)-ones:

Quinoxalin-2(1*H*)-one derivatives (**21**) (0.187 mmol) and $NaHCO_3$ (1.5 equiv., 0.280 mmol) were added to an oven-dried reaction test tube equipped with a magnetic stir bar. Subsequently, anhydrous DMSO (1.5 mL), *N*-methylaniline derivatives (**22**) (1.5 equiv., 0.280 mmol) were added successively through respective syringes. The mixture was stirred at room temperature under an air atmosphere and irradiated with 30W violet LEDs (410-420 nm) until the substrate was consumed completely (checked by TLC). Then, the reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (20 mL × 3). The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to obtain a crude product, which was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent to afford the pure product **23**/**24**.

3.2.6.5 Control Experiments:

a) Procedure for radical scavenging reactions: Quinoxalin- 2(1*H*)-one (**21a**) (0.030 g, 0.187 mmol), $NaHCO_3$ (0.024 g, 1.5 equiv., 0.280 mmol) and 2,2,6,6-tetramethylpiperidinooxy (TEMPO) (3 equiv, 0.562 mmol) or BHT (3 equiv, 0.562 mmol)were added to an oven-dried reaction test tube equipped with a magnetic stir bar. Subsequently, anhydrous DMSO (1.5 mL) and *N*, *N*-dimethylaniline (**22a**) (0.034 g, 35 µL, 1.5 equiv., 0.280 mmol) were added. The mixture was then allowed to stir under the irradiation of the 30 W violet LEDs (410-420 nm), and the reaction was monitored by TLC. No adduct of TEMPO corresponding to **21a** or **22a** was

detected by either ^{1}H NMR ($CDCl_3$) or HRMS analysis of the residue. In the case of BHT, BHT-adducts **25a/25a'**were detected by the HRMS analysis of the reaction mixture.

b) Procedure for without base: Quinoxalin-2(1*H*)-one (**21a**) (0.030 g, 0.187 mmol) was taken-in an oven-dried reaction test tube equipped with a magnetic stir bar. Subsequently, anhydrous DMSO (1.5 mL) and *N*, *N*-dimethylaniline (**22a**) (0.034 g, 35 µL, 1.5 equiv., 0.280 mmol) were added. The mixture was then allowed to stir under the irradiation of the 30 W violet LEDs (410-420 nm), and the reaction was monitored by TLC. No product formation was observed, instead starting material was recovered.

c) Procedure for the addition of DABCO: Quinoxalin-2(1*H*)-one (**21a**) (0.030 g, 0.187 mmol), $NaHCO_3$ (0.024 g, 1.5 equiv., 0.280 mmol) and DABCO (0.063 g, 3 equiv, 0.562 mmol) were takenin an oven-dried reaction test tube equipped with a magnetic stir bar. Subsequently, anhydrous DMSO (1.5 mL) and *N*, *N*-dimethylaniline (**22a**) (0.034 g, 35 µL, 1.5 equiv., 0.280 mmol) were added. The mixture was then allowed to stir under the irradiation of the 30 W violet LEDs (410-420 nm) and the reaction was monitored by TLC. After completion, the reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (20 mL × 3). The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to obtain a crude product, which was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent to afford the pure product**23a** in 62%.

c) Procedure for the reaction under inert atmosphere: Quinoxalin-2(1*H*)-one (**21a**) (0.030 g, 0.187 mmol) and $NaHCO_3$ (0.024 g, 1.5 equiv., 0.280 mmol) were takenin an oven-dried schlenk tube equipped with a magnetic stir bar. Subsequently, anhydrous DMSO (1.5 mL) and *N*, *N*-dimethylaniline (**22a**) (0.034 g, 35 µL, 1.5 equiv, 0.280 mmol) were added. After three freeze-pump-thaw cycles, the reaction mixture was sealed and allowed to stir for 16h under the irradiation of the 30 W violet LEDs (410-420 nm). After completion, the reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (20 mL × 3). The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to obtain a crude product, which was purified by column chromatography on silica gel using petroleum ether/ethyl acetate delivered the **23a'** in 56%.

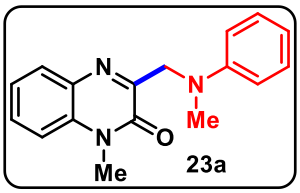
3.2.6.6 Titration Experiments

^{1}H NMR spectra of mixtures of quinoxalin-2(1*H*)-ones **21a** and ***N,N*-dimethyl-*p*-toluidine **22b** in $CDCl_3$ were recorded at 298 K. In an NMR tube, the total volume of the mix-

ture was 0.6 mL, the concentration of quinoxalin-2(1*H*)-ones **21a** (0.0625 mmol) was kept constant at 0.1 M, and that of *N,N*-dimethyl-*p*-toluidine **22b** was varied from 0 to 2.08 M. The molar ratios of quinoxalin-2(1*H*)-ones **21a**: *N,N*-dimethyl-*p*-toluidine **22b** were 1:0, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:10, 1:15, 1:20. $CDCl_3$(δ = 7.260) was used as an internal standard. The ^1H NMR signal of ArH in quinoxalin-2(1*H*)-ones **21a** shifted downfield along with increasing the amount of **22b**, indicating the formation of EDA complex of quinoxalin-2(1*H*)-ones **21a** with *N,N*-dimethyl-*p*-toluidine **22b.**

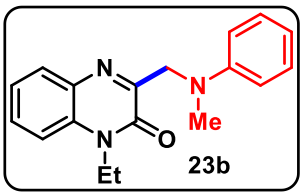
3.2.6.7 Characterization of 23a-v and 24a-n:

1-methyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23a):



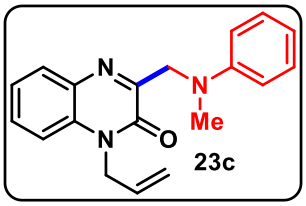
The product **23a** was obtained in 88% yield (46 mg, Yellow solid); **mp** = 86-88 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.81 (dd, J = 8.0, 1.4 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.34 – 7.24 (m, 2H), 7.23 – 7.17 (m, 2H), 6.90 (d, J = 8.1 Hz, 2H), 6.68 (t, J = 7.2 Hz, 1H), 4.74 (s, 2H), 3.69 (s, 3H), 3.20 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 156.5, 154.7, 149.6, 133.2, 132.6, 130.3, 130.1, 128.9, 123.5, 116.5, 113.5, 112.5, 55.2, 39.6, 28.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{18}N_3O$ 280.1444; found 280.1449.

1-ethyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23b):



The product **23b** was obtained in 83 % yield (42 mg, Yellow liquid); **mp** = 106-108 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.83 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.52 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.30 (ddd, *J* = 9.1, 6.3, 2.1 Hz, 2H), 7.25 – 7.18 (m, 2H), 6.94 – 6.88 (m, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 4.75 (s, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.20 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 156.5, 154.2, 149.7, 132.9, 132.1, 130.6, 130.1, 128.9, 123.4, 116.5, 113.4, 112.6, 55.1, 39.5, 37.2, 12.4; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_3O$ 294.1601; found 294.1594.

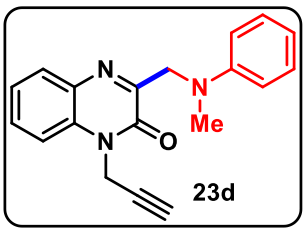
1-allyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23c):



The product **23c** was obtained in 79 % yield (39 mg, Yellow solid); **mp** = 112-114 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.82 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.53 – 7.44 (m, 1H), 7.28 (ddd, *J* = 7.0, 5.0, 1.2 Hz, 2H), 7.24 – 7.18 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.69 (t, *J* = 7.2 Hz, 1H), 5.94 (ddt, *J* = 17.2, 10.4, 5.1 Hz, 1H),

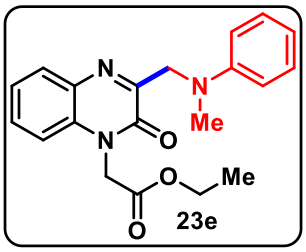
5.32 – 5.25 (m, 1H), 5.18 (dd, *J* = 17.2, 0.6 Hz, 1H), 4.91 (dt, *J* = 5.0, 1.6 Hz, 2H), 4.76 (s, 2H), 3.21 (s, 3H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 156.6, 154.3, 149.6, 132.7, 132.4, 130.6, 130.4, 130.0, 129.0, 123.6, 118.2, 116.5, 114.1, 112.6, 55.1, 44.4, 39.5; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{19}H_{20}N_3O$ 306.1601; found 306.1595.

3-((methyl(phenyl)amino)methyl)-1-(prop-2-yn-1-yl)quinoxalin-2(1*H*)-one (23d):



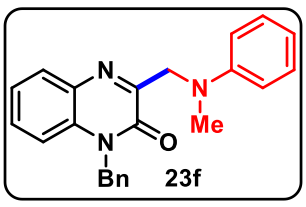
The product **23d** was obtained in 77 % yield (38 mg, Yellow liquid); **mp** = 110-112 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 7:3); **^1H NMR (500 MHz, $CDCl_3$) δ** = 7.84 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 8.5, 7.5 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.70 (t, *J* = 7.2 Hz, 1H), 5.05 (d, *J* = 2.4 Hz, 2H), 4.76 (s, 2H), 3.20 (s, 3H), 2.30 (t, *J* = 2.4 Hz, 1H); **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 156.4, 153.7, 149.6, 132.8, 131.6, 130.5, 130.2, 129.0, 123.9, 116.6, 114.0, 112.5, 76.7, 73.3, 55.1, 39.5, 31.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{19}H_{17}N_3O$ 304.1444; found 304.1443.

ethyl 2-(3-((methyl(phenyl)amino)methyl)-2-oxoquinoxalin-1(2*H*)-yl)acetate (23e):



The product **23e** was obtained in 83 % yield (37.5 mg, Yellow solid) ; **mp** = 112-114 °C; R_f = 0.30 (petroleum ether: ethyl acetate = 7:3); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.84 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.6, 7.4, 1.5 Hz, 1H), 7.31 (ddd, *J* = 8.4, 7.4, 1.2 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.06 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.90 (dt, *J* = 9.3, 1.8 Hz, 2H), 6.73 – 6.66 (m, 1H), 5.03 (s, 2H), 4.76 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.20 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 167.0, 156.3, 154.3, 149.6, 132.7, 132.3, 130.7, 130.3, 129.0, 123.9, 116.6, 113.0, 112.6, 62.1, 55.1, 43.4, 39.5, 14.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{20}H_{21}N_3O_3$ 352.1656; found 352.1651.

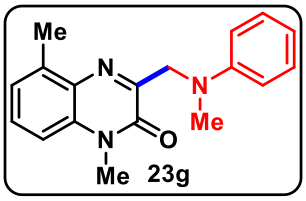
1-benzyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23f):



The product **23f** was obtained in 77% yield (35 mg, Yellow solid); **mp** = 142-144 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.83 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.35 – 7.27 (m, 4H), 7.26 – 7.20 (m, 5H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.71 (t, *J* = 7.2 Hz, 1H), 5.50 (s, 2H), 4.82 (s, 2H), 3.24 (s, 3H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 156.7, 154.8, 149.6, 135.1, 132.9, 132.5, 130.5, 130.1, 129.0, 128.9, 127.7, 126.8, 123.6, 116.5, 114.3, 112.6, 55.2, 45.8, 39.6; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$

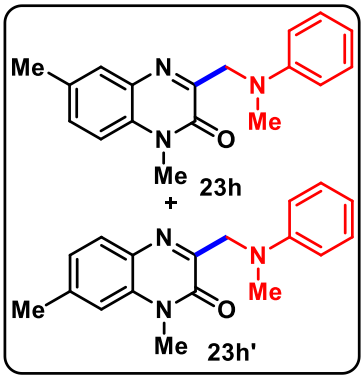
calcd for $C_{23}H_{22}N_3O$ 356.1757; found 356.1762.

5-methyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23g):



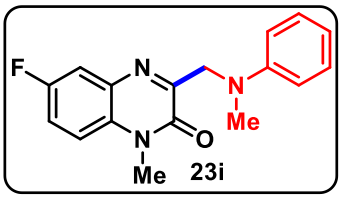
The product **23g** was obtained in 81 % yield (41 mg, Yellow liquid); R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.38 (t, *J* = 7.9 Hz, 1H), 7.20 (dd, *J* = 8.7, 7.4 Hz, 2H), 7.13 (dd, *J* = 12.4, 7.9 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.68 (t, *J* = 7.2 Hz, 1H), 4.82 (s, 2H), 3.68 (s, 3H), 3.23 (s, 3H), 2.50 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 154.6, 153.8, 149.4, 139.0, 133.2, 131.1, 129.8, 128.9, 124.8, 116.5, 112.6, 111.4, 54.5, 39.8, 29.0, 17.5; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_3O$ 294.1601; found 294.1615.

Isomer-1,6-dimethyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one&1,7-dimethyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23h/23h'):



The product **23h/23h'** was obtained in 86% yield (43.5 mg, Yellow liquid); R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.48 (s, 0.64H), 7.69 (d, *J* = 8.1 Hz, 0.68H), 7.62 (d, *J* = 0.7 Hz, 0.98H), 7.46 – 7.37 (m, 1.66H), 7.35 – 7.27 (m, 1.67H), 7.24 – 7.10 (m, 7.11H), 7.07 (s, 0.77H), 6.90 (dd, *J* = 7.9, 5.1 Hz, 3.53H), 6.69 (t, *J* = 7.2 Hz, 1.96H), 4.74 (s, 2H), 4.72 (s, 1.37H), 3.67 (s, 5H), 3.33 (s, 2.09H), 3.20 (s, 3H), 3.20 (s, 1.98H), 2.50 (s, 2.04H), 2.41 (s, 3.04H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 162.3, 156.3, 155.1, 154.8, 154.6, 149.6, 149.6, 140.9, 133.4, 132.4, 131.2, 130.1, 130.0, 129.6, 128.9, 126.3, 124.8, 122.3, 116.4, 116.4, 113.6, 113.2, 112.5, 112.5, 55.2, 55.1, 39.5, 39.5, 28.8, 28.7, 22.0, 20.5; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_3O$ 294.1601; found 294.1599.

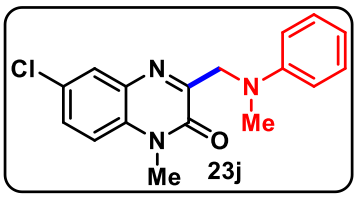
6-fluoro-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23i):



The product **23i** was obtained in 88 % yield (44 mg, Yellow liquid); R_f = 0.30 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.51 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.28 – 7.19 (m, 4H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 4.75 (s, 2H), 3.69 (s, 3H), 3.20 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 158.6 (d, $J_{C\text{-}F}$ = 243.19 Hz), 158.1, 154.3, 149.4, 133.1 (d, $J_{C\text{-}F}$ = 11.44 Hz), 129.8, 129.0, 117.8 (d, $J_{C\text{-}F}$ = 23.84 Hz), 116.6, 115.7 (d, $J_{C\text{-}F}$ = 21.94 Hz), 114.6 (d, $J_{C\text{-}F}$ = 8.58 Hz), 112.4, 55.0, 39.6, 29.1; **^{19}F NMR**

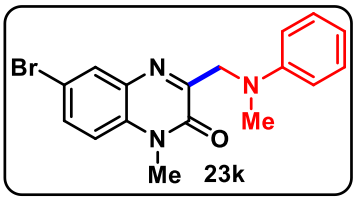
(376 MHz, $CDCl_3$) δ = -118.97; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}FN_3O$ 298.1350; found 298.1349.

6-chloro-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23j):



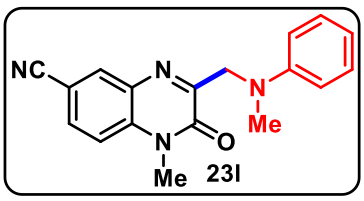
The product **23j** was obtained in 83% yield (40 mg, Yellow solid) ; **mp** = 125-127 °C; R_f = 0.30 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** =7.80 (d, *J* = 2.4 Hz, 1H), 7.47 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.25 – 7.16 (m, 3H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 4.75 (s, 2H), 3.68 (s, 3H), 3.20 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 158.0, 154.3, 149.4, 133.0, 131.8, 130.1, 129.6, 129.0, 128.9, 116.6, 114.7, 112.4, 55.0, 39.6, 29.0; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}ClN_3O$ 314.1055; found 314.1057.

6-bromo-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23k):



The product **23k** was obtained in 85 % yield (38 mg, Yellow solid) ; **mp** = 97-99 °C; R_f = 0.30 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** =7.95 (d, *J* = 2.2 Hz, 1H), 7.60 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.21 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.15 (d, *J* = 8.9 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 2H), 6.70 (t, *J* = 7.2 Hz, 1H), 4.75 (s, 2H), 3.67 (s, 3H), 3.19 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 157.9, 154.3, 149.4, 133.4, 132.8, 132.7, 132.3, 129.0 , 116.6, 116.2, 115.0, 112.4, 55.0, 39.6, 29.00; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}BrN_3O$ 358.0550; found 358.0562.

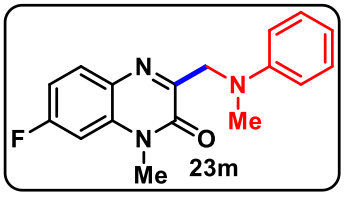
3-((methyl(phenyl)amino)methyl)-2-oxo-1,2-dihydroquinoxaline-6-carbonitrile (23l):



The product **23l** was obtained in 30 % yield (15 mg, Yellow solid); R_f = 0.40 (petroleum ether:ethyl acetate = 6:4); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.12 (d, *J* = 1.8 Hz, 1H), 7.75 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.21 (dd, *J* = 8.7, 7.3 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 4.76 (s, 2H), 3.71 (s, 3H), 3.19 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 159.0, 154.3, 149.2, 136.4, 134.6, 132.7, 132.1, 129.1, 117.8, 116.8, 114.7, 112.4, 107.2, 54.9, 39.7, 29.2; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}N_4O$ 305.1397; found 305.1401.

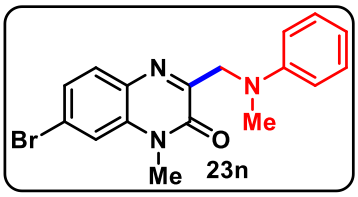
7-fluoro-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23m):

The product **23m** was obtained in 72 % yield (36 mg, Yellow solid) ; **mp** = 73-75 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.79 (dd, *J* = 8.9, 6.0



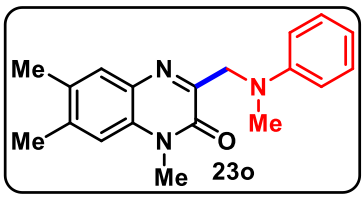
Hz, 1H), 7.24 – 7.18 (m, 2H), 7.02 (ddd, J = 8.8, 8.1, 2.6 Hz, 1H), 6.97 (dd, J = 10.0, 2.6 Hz, 1H), 6.91 – 6.86 (m, 2H), 6.69 (tt, J = 7.3, 1.0 Hz, 1H), 4.72 (s, 2H), 3.65 (s, 3H), 3.19 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 163.2 (d, $J_{C\text{-}F}$ = 251.01 Hz), 155.4, 154.6, 149.5, 134.6 (d, $J_{C\text{-}F}$ = 12.21 Hz), 132.2 (d, $J_{C\text{-}F}$ = 10.68 Hz), 129.3 (d, $J_{C\text{-}F}$ = 2.29 Hz), 129.0, 116.5, 112.5, 111.4 (d, $J_{C\text{-}F}$ = 23.65 Hz), 100.5 (d, $J_{C\text{-}F}$ = 27.47 Hz), 55.0, 39.6, 29.1; **^{19}F NMR (376 MHz, CDCl$_3$) δ** = -107.23; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{17}H_{17}FN_3O$ 298.1350; found 298.1348.

7-bromo-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23n):



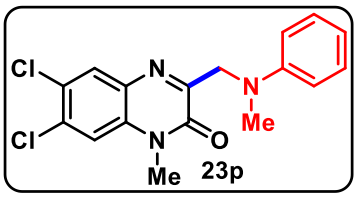
The product **23n** was obtained in 75% yield (34 mg, Yellow solid) ; **mp** = 62-64 °C; ***R$_f$*** = 0.40 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** =7.65 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.40 (dd, J = 8.5, 1.9 Hz, 1H), 7.20 (dd, J = 8.7, 7.3 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 6.69 (t, J = 7.2 Hz, 1H), 4.72 (s, 2H), 3.66 (s, 3H), 3.19 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 156.9, 154.4, 149.4, 134.2, 131.5, 131.4, 129.0 (2C), 126.8, 124.2, 116.6, 112.5, 55.1, 39.6, 29.0; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{17}H_{17}BrN_3O$ 358.0550; found 358.0558.

6,7-dimethyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23o):



The product **23o** was obtained in 84 % yield (41 mg, Yellow solid) ; **mp** = 122-124 °C; ***R$_f$*** = 0.40 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.57 (s, 1H), 7.20 (dt, J = 12.5, 6.4 Hz, 2H), 7.05 (s, 1H), 6.90 (d, J = 8.4 Hz, 2H), 6.69 (dd, J = 12.8, 5.5 Hz, 1H), 4.72 (s, 2H), 3.67 (s, 3H), 3.19 (s, 3H), 2.40 (s, 3H), 2.31 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 155.1, 154.8, 149.7, 139.9, 132.5, 131.0, 130.4, 128.9, 122.4, 116.4, 114.1, 112.5, 55.2, 39.5, 28.8, 20.5, 19.0; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{19}H_{22}N_3O$ 308.1757; found 308.1751.

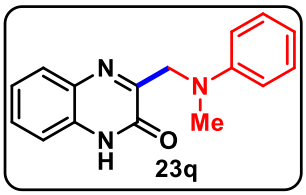
6,7-dichloro-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23p):



The product **23p** was obtained in 83% yield (38 mg,Yellow solid) ; **mp** = 95-97 °C; ***R$_f$*** = 0.50 (petroleum ether:ethyl acetate = 7:3);**^{1}H NMR (400 MHz, CDCl$_3$) δ** =7.88 (s, 1H), 7.37 (s, 1H), 7.21 (t, J = 7.4 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 6.70 (t, J = 7.2 Hz, 1H), 4.73 (s, 2H), 3.65 (s, 3H), 3.18 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 158.2,

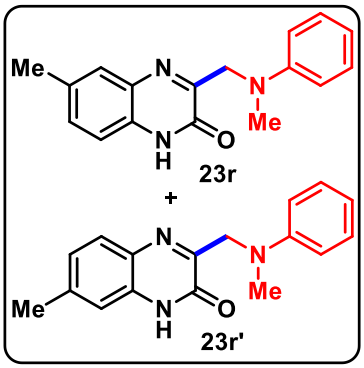
154.1, 149.3, 134.2, 132.5, 131.6, 131.1, 129.0, 127.4, 116.7, 115.1, 112.4, 54.9, 39.6, 29.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}Cl_2N_3O$ 348.0665; found 348.0664.

3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23q):



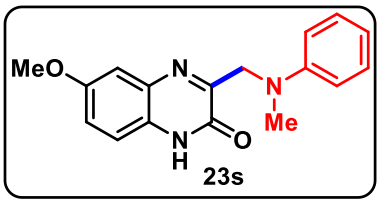
The product **23q** was obtained in 65% yield (35.5 mg, Yellow solid); **mp** = 224-226 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 1:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 12.64 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.30 – 7.26 (m, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.76 (t, *J* = 7.2 Hz, 1H), 4.82 (s, 2H), 3.25 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 157.0, 156.6, 149.6, 132.7, 131.1, 130.3, 129.4, 129.0, 124.2, 116.7, 115.7, 112.7, 54.6, 39.3; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{16}H_{16}N_3O$ 266.1288; found 266.1288.

Isomer-6/7-methyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23r/23r'):



The product **23r/23r'** (isomer ratio = 3:2) was obtained in 65% yield (34 mg, Yellow solid); **mp** = 244-246 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 1:1); **^{1}H NMR (500 MHz, DMSO-d6) δ** = 12.36 (s, 1.63 H), 7.51 (d, *J* = 8.1 Hz, 0.64H), 7.43 (s, 0.98H), 7.29 (d, *J* = 8.3 Hz, 1.10H), 7.18 (d, *J* = 8.3 Hz, 1.09H), 7.11 (t, *J* = 7.9 Hz, 3.39H), 7.05 (d, *J* = 10.5 Hz, 1.31H), 6.74 (dd, *J* = 7.9, 4.3 Hz, 3.41H), 6.57 (t, *J* = 7.2 Hz, 1.72H), 4.66 (s, 2H), 4.64 (s, 1.27H), 3.11 (s, 2.86H), 3.10 (s, 1.90H), 2.36 (s, 1.96H), 2.31 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d6) δ** = 158.0, 156.9, 154.7, 154.5, 149.3, 140.0, 132.5, 131.8, 131.4, 130.9, 129.7, 129.5, 129.0, 128.8, 128.2, 128.1, 124.5, 115.7, 115.6, 115.0, 114.9, 113.5, 111.9, 111.8, 53.2, 21.2, 20.2; **DEPT NMR (125 MHz, DMSO-d6) δ** = 130.7, 128.6, 128.0, 127.9, 124.2, 115.4, 115.4, 114.8, 114.7, 111.6, 111.6, 52.9, 38.9, 20.9, 20.0; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{18}N_3O$ 280.1444; found 280.1431.

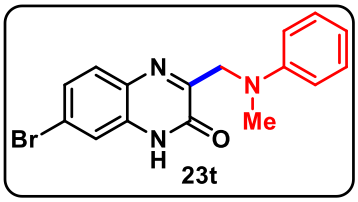
6-methoxy-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23s):



The product **23s** was obtained in 52% yield (26 mg, Yellow solid); **mp** = 182-184 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 1:1); **^{1}H NMR (500 MHz, DMSO-d6) δ** = 12.35 (s, 1H), 7.24 – 7.20 (m, 1H), 7.15 – 7.09 (m, 4H), 6.73 (d, *J* = 8.2 Hz, 2H), 6.57 (t, *J* = 7.2 Hz, 1H), 4.66 (s, 2H), 3.77 (s, 3H), 3.12 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d6) δ** = 158.6, 155.3, 154.1, 149.3, 132.1, 128.9, 125.9, 119.2, 116.2, 115.6, 111.8,

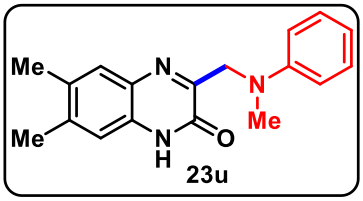
109.9, 55.6, 53.2, 39.0; **DEPT NMR (125 MHz, DMSO-d6) δ** = 128.6, 119.0, 116.0, 115.4, 111.5, 109.7, 55.3, 53.0, 38.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{18}N_3O_2$ 296.1394; found 296.1404.

7-bromo-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23t):



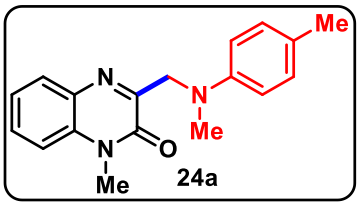
The product **23t** was obtained in 48% yield (22 mg, Yellow solid); **mp** = 144-146 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 1:1); **^{1}H NMR (500 MHz, DMSO-d6) δ** = 12.49 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 25.6, 8.7 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 2H), 6.73 (d, *J* = 8.1 Hz, 2H), 6.57 (t, *J* = 7.0 Hz, 1H), 4.64 (s, 2H), 3.09 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz, DMSO-d6) δ** = 158.9, 154.2, 149.2, 133.1, 130.4, 130.3, 128.8, 126.0, 122.3, 117.6, 115.8, 111.9, 53.3, 39.0; **DEPT NMR (125 MHz, DMSO-d6) δ** = 158.9, 154.2, 149.2, 133.1, 130.4, 130.3, 128.8, 126.0, 122.3, 117.6, 115.8, 111.9, 53.3, 39.0; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{16}H_{15}BrN_3O$ 344.0393; found 344.0390.

6,7-dimethyl-3-((methyl(phenyl)amino)methyl)quinoxalin-2(1*H*)-one (23u):



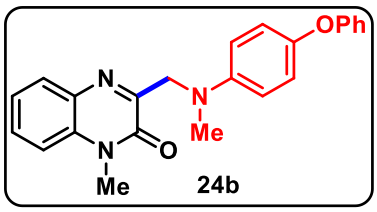
The product **23u** was obtained in 64% yield (32.5 mg, Yellow oily liquid); **mp** = 200-202 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 1:1); **^{1}H NMR (400 MHz, DMSO-d6) δ** = 12.32 (s, 1H), 7.41 (s, 1H), 7.10 (t, *J* = 7.3 Hz, 2H), 7.03 (s, 1H), 6.72 (d, *J* = 7.9 Hz, 2H), 6.56 (t, *J* = 7.0 Hz, 1H), 4.63 (s, 2H), 3.11 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz, DMSO-d6) δ** = 156.8, 154.7, 149.3, 139.3, 131.9, 130.0, 129.8, 128.9, 128.4, 115.6, 115.3, 111.8, 53.2, 39.2, 19.7, 18.8; **DEPT NMR (100 MHz, DMSO-d6) δ** = 128.5, 128.1, 115.3, 115.1, 111.5, 52.9, 38.9, 19.4, 18.5; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_3O$ 294.1601; found 294.1598.

1-methyl-3-((methyl(p-tolyl)amino)methyl)quinoxalin-2(1*H*)-one (24a):



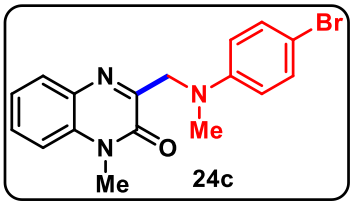
The product **24a** was obtained in 89% yield (49 mg, Yellow oily liquid); R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.76 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.51 – 7.39 (m, 1H), 7.27 – 7.19 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.64 (s, 2H), 3.63 (s, 3H), 3.10 (s, 3H), 2.16 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** =156.6, 154.7, 147.5, 133.2, 132.6, 130.3, 130.1, 129.5 (2C), 123.5, 113.5, 113.0, 55.5, 39.7, 28.8, 20.2; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_3O$ 294.1601; found 294.1603.

1-methyl-3-((methyl(4-phenoxyphenyl)amino)methyl)quinoxalin-2(1*H*)-one (24b):



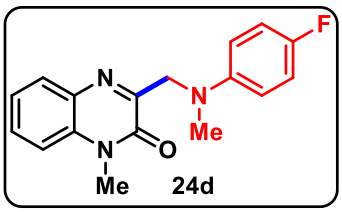
The product **24b** was obtained in 68 % yield (47 mg, Yellow solid); **mp** = 74-76 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.84 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.32 (dd, *J* = 14.4, 7.7 Hz, 2H), 7.28 – 7.22 (m, 2H), 7.06 – 6.94 (m, 2H), 6.92 (t, *J* = 4.9 Hz, 5H), 4.72 (s, 2H), 3.71 (s, 3H), 3.18 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 159.2, 156.6, 154.9, 147.3, 146.8, 133.4, 132.72, 130.4, 130.0, 129.6, 124.5, 123.8, 121.9, 121.0, 119.7, 119.2, 117.2, 114.0, 113.7, 56.0, 39.9, 29.1; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{23}H_{22}N_3O_2$ 372.1707; found 372.1708.

3-(((4-bromophenyl)(methyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24c):



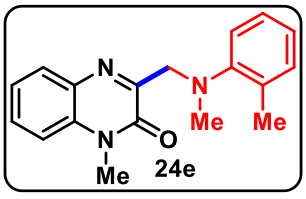
The product **24c** was obtained in 75% yield (50.5 mg, yellow oily liquid); R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.79 (dd, J = 7.9, 1.4 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.35 – 7.22 (m, 4H), 6.78 – 6.71 (m, 2H), 4.71 (s, 2H), 3.70 (s, 3H), 3.17 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 155.9, 154.7, 148.6, 133.2, 132.5, 131.6, 130.4, 129.5, 123.7, 114.2, 113.6, 108.4, 55.1, 39.7, 28; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}BrN_3O$ 358.0550; found 358.0554.

3-(((4-fluorophenyl)(methyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24d):



The product **24d** was obtained in 76% yield (42 mg, Yellow liquid); R_f = 0.50 (petroleum ether:ethyl acetate = 8:2); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.82 (dd, J = 8.0, 1.4 Hz, 1H), 7.54 (ddd, J = 8.7, 7.4, 1.5 Hz, 1H), 7.37 – 7.27 (m, 2H), 6.99 – 6.77 (m, 4H), 4.69 (s, 2H), 3.71 (s, 3H), 3.14 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 155.7 (d, $J_{C\text{-}F}$ = 234.99 Hz), 156.3, 154.7, 146.4, 133.2, 132.5, 130.2 (d, $J_{C\text{-}F}$ = 8.39 Hz), 123.6, 115.4, 115.1, 113.8 (d, $J_{C\text{-}F}$ = 6.87 Hz), 113.6, 55.9, 39.8, 28.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}FN_3O$ 298.1350; found 298.1350.

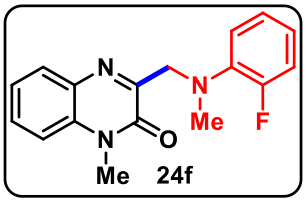
1-methyl-3-((methyl(o-tolyl)amino)methyl)quinoxalin-2(1*H*)-one (24e):



The product **24e** was obtained in 65% yield (36 mg, yellow oily liquid); R_f = 0.50 (petroleum ether: ethyl acetate = 7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.94 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 1H), 4.41 (s, 2H), 3.69 (s, 3H), 2.93 (s, 3H), 2.36 (s, 3H); **^{13}C{^{1}H} NMR**

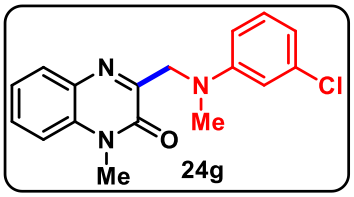
(100 MHz,$CDCl_3$) δ = 156.9, 154.5, 152.0, 133.0, 132.7, 132.5, 131.1, 130.2, 129.9, 126.2, 123.5, 122.7, 120.0, 113.5, 57.7, 41.7, 28.8, 18.4; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_3O$ 294.1601; found 294.1602.

3-(((2-fluorophenyl)(methyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24f):



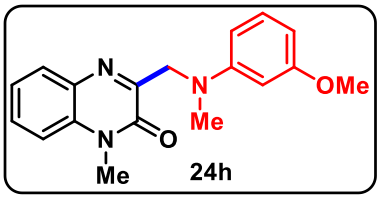
The product **24f** was obtained in 61 % yield (34 mg, yellow oily liquid); ***R**f* = 0.50 (petroleum ether:ethyl acetate = 8:2); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.84 (dd, J = 8.0, 1.4 Hz, 1H), 7.52 (ddd, J = 8.6, 7.4, 1.5 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.08 – 6.92 (m, 3H), 6.80 (dddd, J = 8.1, 6.5, 4.5, 2.1 Hz, 1H), 4.70 (s, 2H), 3.69 (s, 3H), 3.11 (d, J = 0.9 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** =156.5, 154.8 (d, $J_{C\text{-}F}$ = 244.14 Hz), 154.4, 139.6 (d, $J_{C\text{-}F}$ = 8.39 Hz), 133.0, 132.6, 130.1 (d, $J_{C\text{-}F}$ = 34.33 Hz), 124.1, 124.0, 123.5, 120.5 (d, $J_{C\text{-}F}$ = 8.39 Hz), 119.3 (d, $J_{C\text{-}F}$ = 3.82 Hz), 116.1 (d, $J_{C\text{-}F}$ = 21.36 Hz), 113.5, 56.3, 56.2, 40.6, 40.5, 28.8; **^{19}F NMR (376 MHz, CDCl3) δ** = -123.05; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}FN_3O$ 298.1350; found 298.1347.

3-(((3-chlorophenyl)(methyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24g):



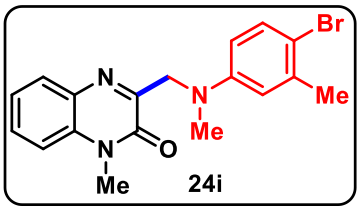
The product **24g** was obtained in 70 % yield (41 mg, yellow solid); **mp** = 96-98 °C; ***R**f* = 0.50 (petroleum ether:ethyl acetate =7:3); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.34 – 7.28 (m, 2H), 7.08 (t, *J* = 8.1 Hz, 1H), 6.85 (t, *J* = 2.1 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.64 (dd, *J* = 7.8, 1.2 Hz, 1H), 4.73 (s, 2H), 3.70 (s, 3H), 3.19 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 155.8, 154.6, 150.7, 134.8, 133.1, 132.5, 130.4, 130.3, 129.8, 123.7, 116.2, 113.6, 112.3, 110.6, 54.9, 39.6, 28.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{17}ClN_3O$ 314.1055; found 314.1047.

3-(((3-methoxyphenyl)(methyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24h):



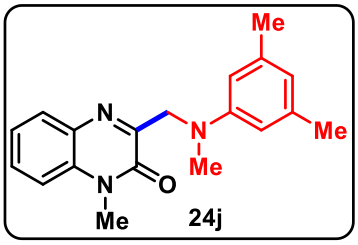
The product **24h** was obtained in 64 % yield (37 mg, Yellow liquid); ***R**f* = 0.40 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.80 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.3 Hz, 1H), 7.35 – 7.23 (m, 2H), 7.10 (t, J = 8.5 Hz, 1H), 6.49 (d, J = 6.6 Hz, 2H), 6.32 – 6.20 (m, 1H), 4.73 (s, 2H), 3.78 (s, 3H), 3.69 (d, J = 4.1 Hz, 3H), 3.20 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 160.6, 156.4, 154.7, 151.0, 133.2, 132.5, 130.3, 130.1, 129.6, 123.5, 113.5, 105.5, 101.7, 98.8, 55.3, 55.1, 39.8, 28.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_3O_2$ 310.1550; found 310.1548.

3-(((4-bromo-3-methylphenyl)(methyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24i):



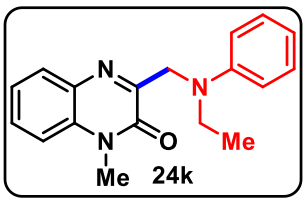
The product **24i** was obtained in 77% yield (54 mg, Yellow liquid); R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.80 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.30 (dd, *J* = 16.0, 8.1 Hz, 3H), 6.76 (s, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.71 (s, 2H), 3.69 (s, 3H), 3.16 (s, 3H), 2.31 (s, 3H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 156.0, 154.6, 148.8, 137.7, 133.1, 132.5, 132.2, 130.3, 130.2, 123.6, 114.8, 113.5, 111.8, 111.2, 55.0, 39.7, 28.8, 23.3 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}BrN_3O$ 372.0706; found 372.0717.

3-(((4-bromo-3-methylphenyl)(methyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24j):



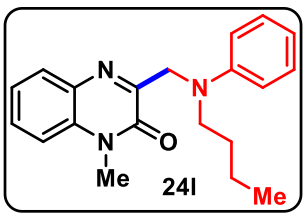
The product **24j** was obtained in 85 % yield (49 mg, Yellow oily liquid); R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.83 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.34 – 7.27 (m, 2H), 6.54 (s, 2H), 6.36 (s, 1H), 4.72 (s, 2H), 3.70 (s, 3H), 3.17 (s, 3H), 2.25 (s, 6H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 156.6, 154.7, 149.7, 138.4, 133.2, 132.6, 130.3, 130.1, 123.5, 118.6, 113.5, 110.5, 55.3, 39.6, 28.8, 21.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{19}H_{22}N_3O$ 308.1757; found 308.1750.

3-((ethyl(phenyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24k):



The product **24k** was obtained in 69 % yield (38 mg, Yellow oily liquid); R_f = 0.50 (petroleum ether:ethyl acetate =7:3); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.82 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.33 – 7.28 (m, 2H), 7.18 (dd, *J* = 8.7, 7.3 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 6.65 (t, *J* = 7.2 Hz, 1H), 4.73 (s, 2H), 3.71 (s, 3H), 3.67 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 156.6, 154.7, 148.3, 133.1, 132.6, 130.3, 130.1, 129.0, 123.6, 115.9, 113.5, 112.3, 52.5, 45.7, 28.8, 12.0; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_3O$ 294.1601; found 294.1608.

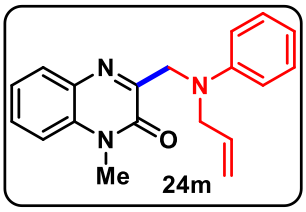
3-((ethyl(phenyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24l):



The product **24l** was obtained in 47 % yield (28.5 mg, Yellow oily liquid R_f = 0.50 (petroleum ether:ethyl acetate =7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.81 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.33 – 7.27 (m, 2H), 7.18 (dd, *J* = 8.8, 7.3 Hz, 2H), 6.81 (d, *J* = 8.1

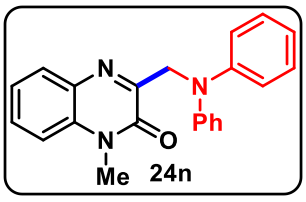
Hz, 2H), 6.64 (t, *J* = 7.2 Hz, 1H), 4.75 (s, 2H), 3.71 (s, 3H), 3.62 – 3.57 (m, 2H), 1.69 (dt, *J* = 15.3, 7.6 Hz, 2H), 1.46 – 1.36 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 156.5, 154.7, 148.5, 133.1, 132.6, 130.3, 130.0, 129.0, 123.5, 115.8, 113.5, 112.2, 53.0, 51.5, 29.2, 28.8, 20.4, 14.0; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{20}H_{24}N_3O$ 322.1914; found 322.1917.

3-((allyl(phenyl)amino)methyl)-1-methylquinoxalin-2(1*H*)-one (24m):



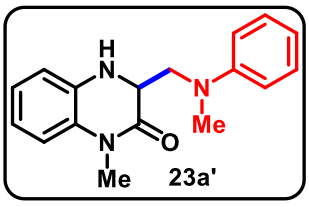
The product **24m** was obtained in 44% yield (25 mg, Yellow oily liquid); ***R*$_f$** = 0.50 (petroleum ether:ethyl acetate = 7:3); **^1H NMR (500 MHz, $CDCl_3$) δ** = 7.83 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.57 – 7.50 (m, 1H), 7.31 (ddd, *J* = 8.4, 6.4, 2.1 Hz, 2H), 7.18 (dd, *J* = 8.7, 7.3 Hz, 2H), 6.83 (d, *J* = 8.1 Hz, 2H), 6.67 (t, *J* = 7.2 Hz, 1H), 5.96 (ddt, *J* = 17.2, 10.0, 4.9 Hz, 1H), 5.26 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dd, *J* = 10.3, 1.6 Hz, 1H), 4.76 (s, 2H), 4.25 (dd, *J* = 3.1, 1.7 Hz, 2H), 3.71 (s, 3H); **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 156.5, 154.7, 148.8, 134.2, 133.1, 132.6, 130.3, 130.1, 128.9, 123.6, 116.4, 116.1, 113.5, 112.5, 53.9, 52.6, 28.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{19}H_{20}N_3O$ 306.1601; found 342.1599.

3-((diphenylamino)methyl)-1-methylquinoxalin-2(1*H*)-one (24n):



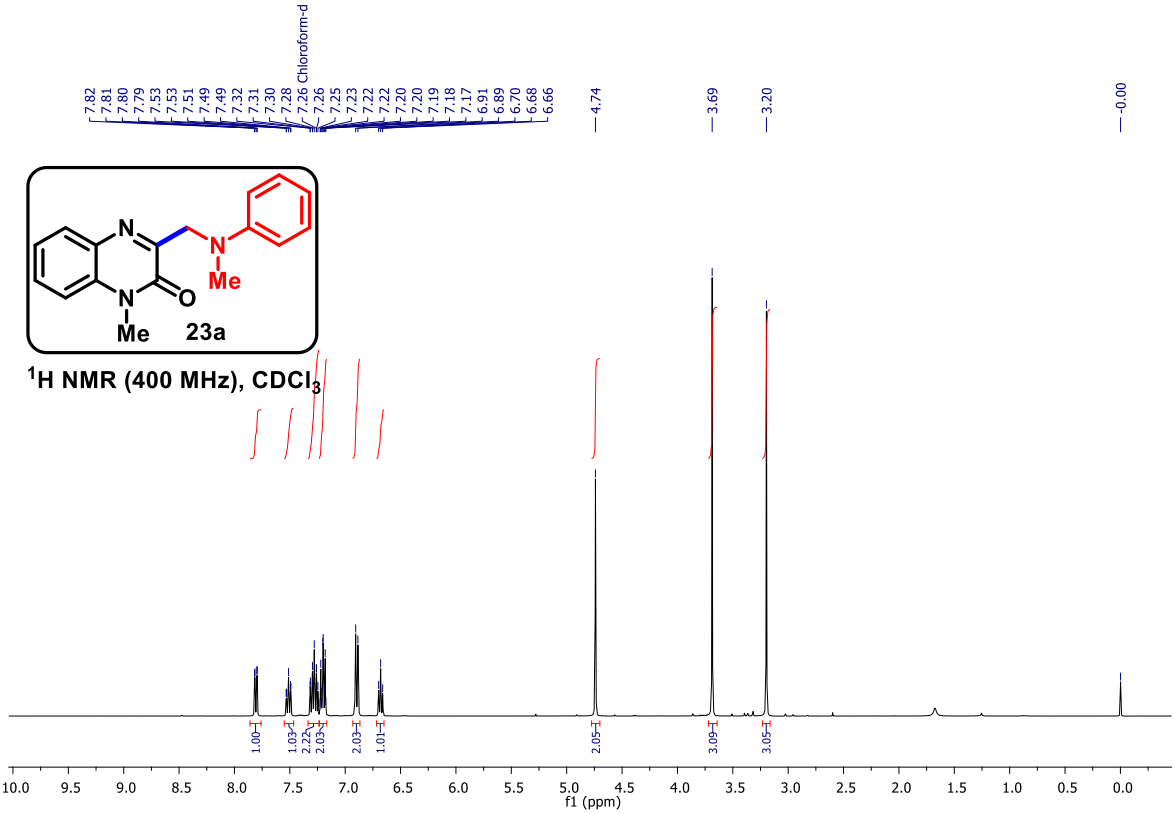
The product **24n** was obtained in 20 % yield (13 mg, Yellow oily liquid); ***R*$_f$** = 0.50 (petroleum ether:ethyl acetate =7:3); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.79 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.26 (dt, *J* = 18.4, 7.8 Hz, 6H), 7.16 (d, *J* = 7.8 Hz, 4H), 6.92 (t, *J* = 7.2 Hz, 2H), 5.23 (s, 2H), 3.69 (s, 3H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 155.8, 154.4, 148.1, 133.0, 132.7, 130.4, 130.0, 129.0, 123.6, 121.2, 121.1, 113.5, 54.0, 28.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{22}H_{20}N_3O$ 342.1601; found 342.1587.

1-methyl-3-((methyl(phenyl)amino)methyl)-3,4-dihydroquinoxalin-2(1H)-one (23a'):

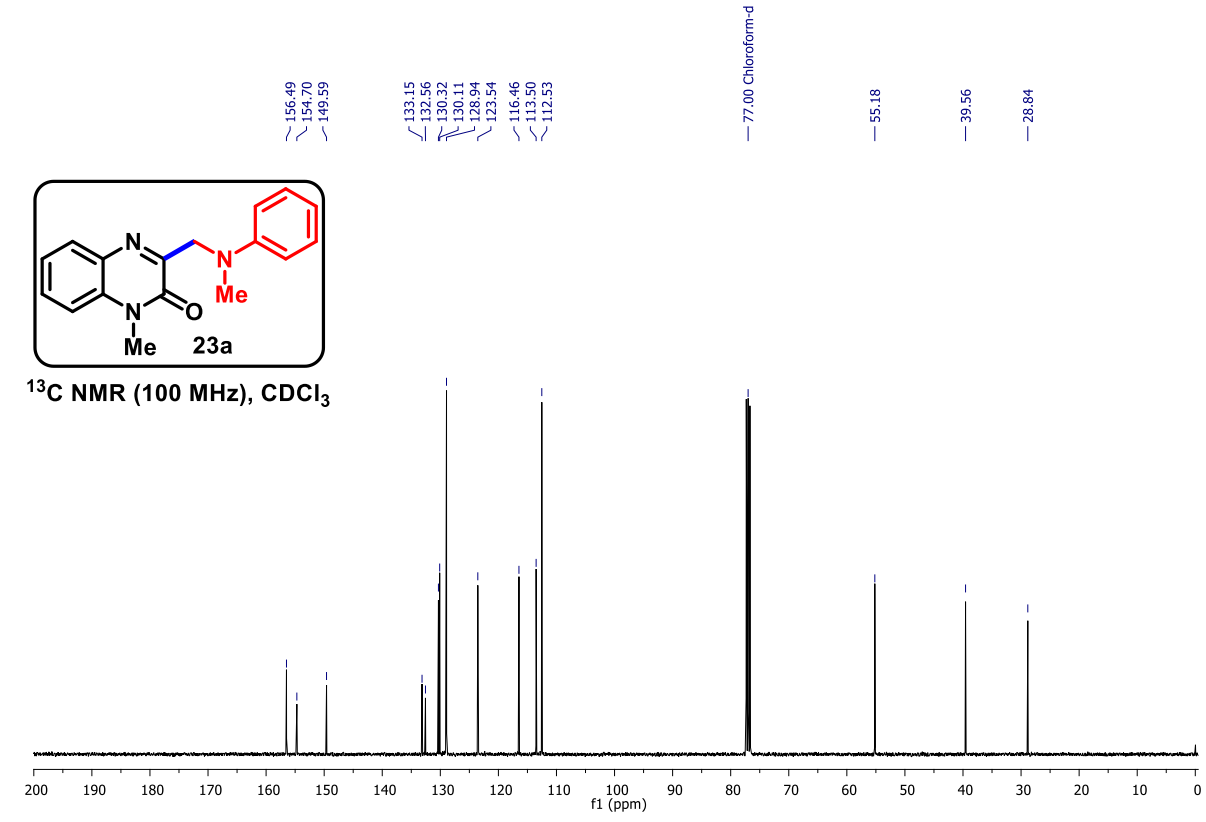


The product **23a'** was obtained in 56% yield (36 mg, Yellow sticky liquid); ***R*$_f$** = 0.50 (petroleum ether:ethyl acetate =7:3); **^1H NMR (500 MHz, $CDCl_3$) δ** = 7.24 (dd, *J* = 8.7, 7.3 Hz, 2H), 6.95 – 6.91 (m, 2H), 6.89 – 6.85 (m, 1H), 6.80 – 6.75 (m, 3H), 6.61 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.26 (dd, *J* = 10.4, 2.2 Hz, 1H), 4.17 (s, 1H), 3.74 – 3.69 (m, 1H), 3.57 (dd, *J* = 14.7, 10.4 Hz, 1H), 3.38 (s, 3H), 2.97 (s, 3H); **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 166.5, 149.5, 134.1, 129.3, 128.7, 123.8, 119.7, 117.6, 114.7, 114.7, 113.0, 55.0, 54.7, 39.0, 28.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{20}N_3O$ 282.1601; found 282.1612.

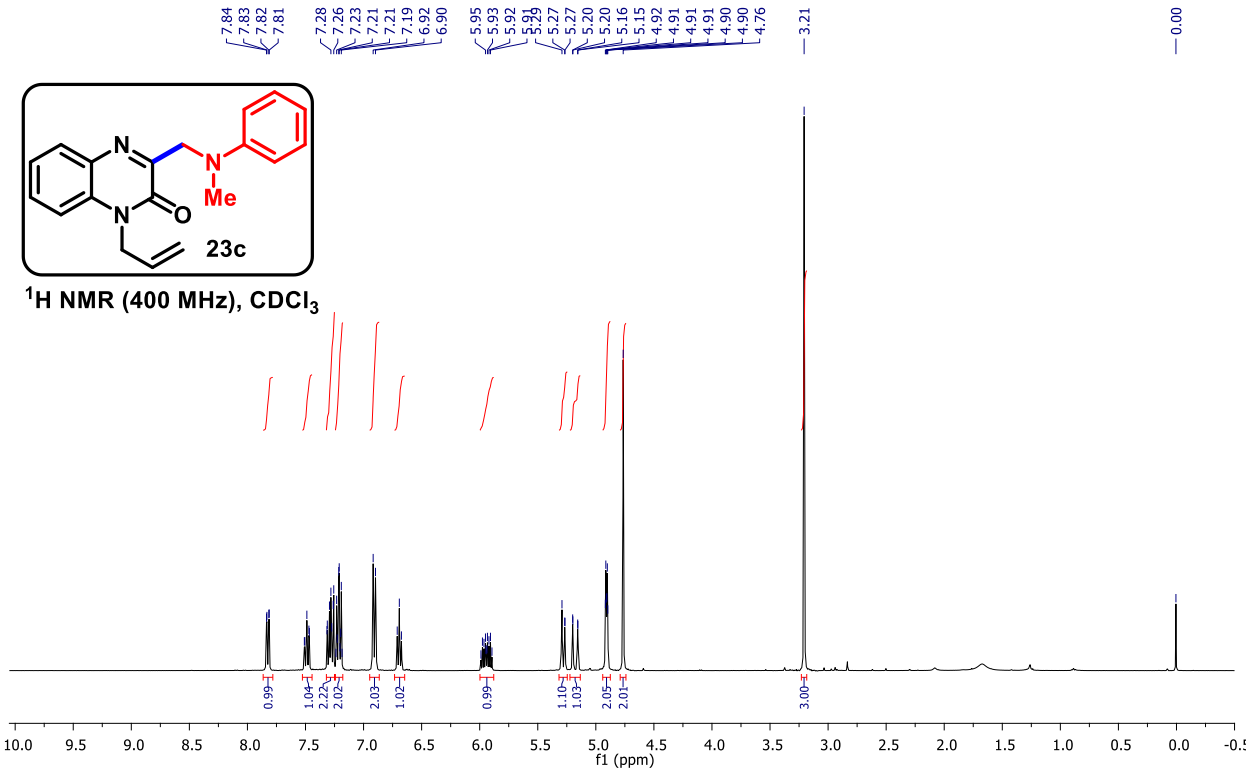
3.2.7 Spectral data for the representative compounds:



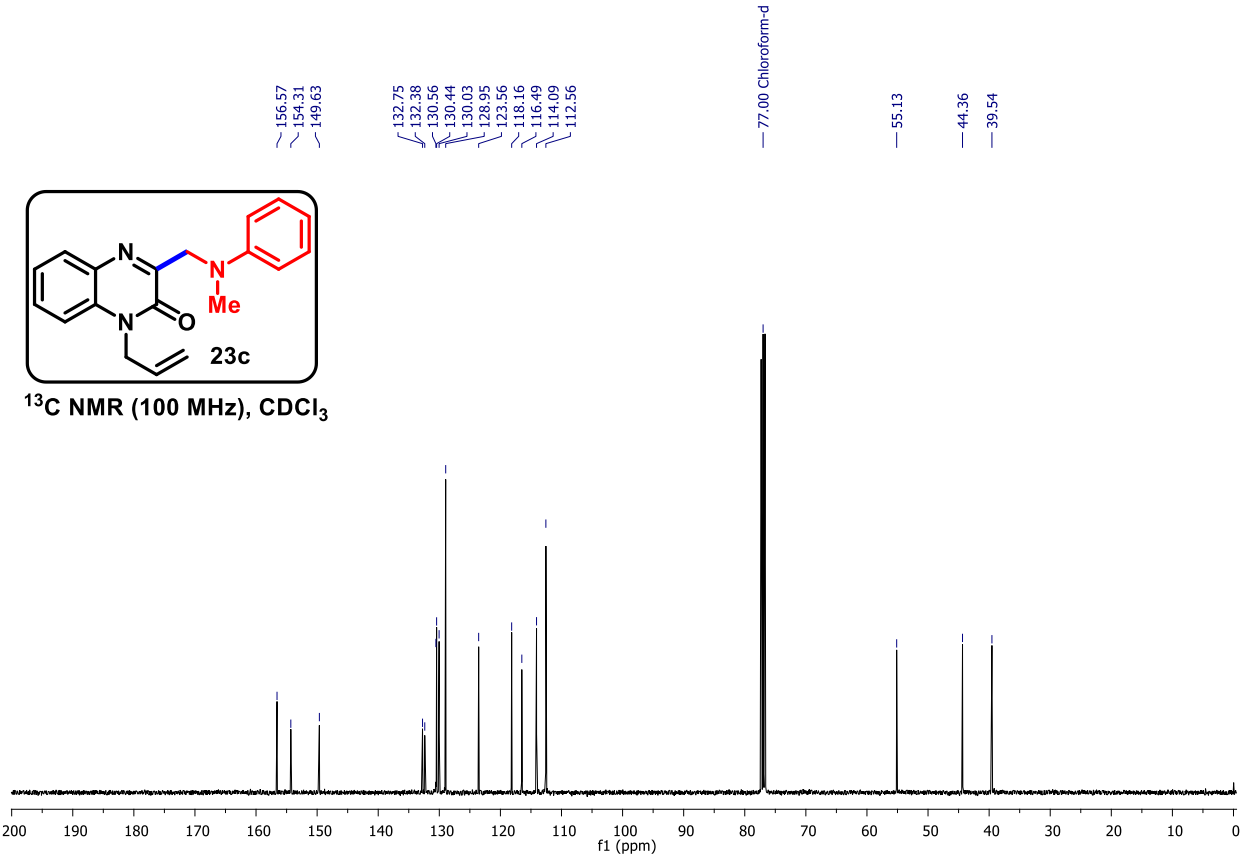
^{1}H NMR (400 MHz), $CDCl_3$



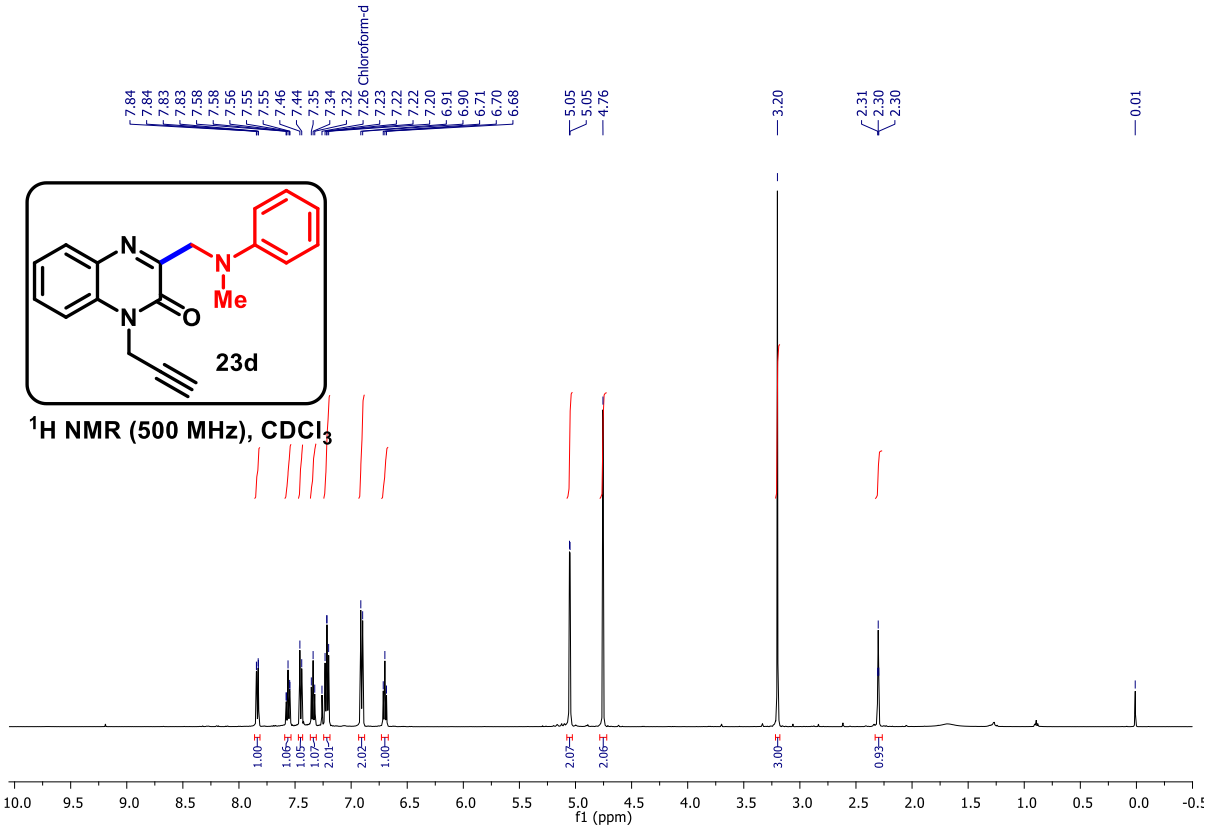
^{13}C NMR (100 MHz), $CDCl_3$



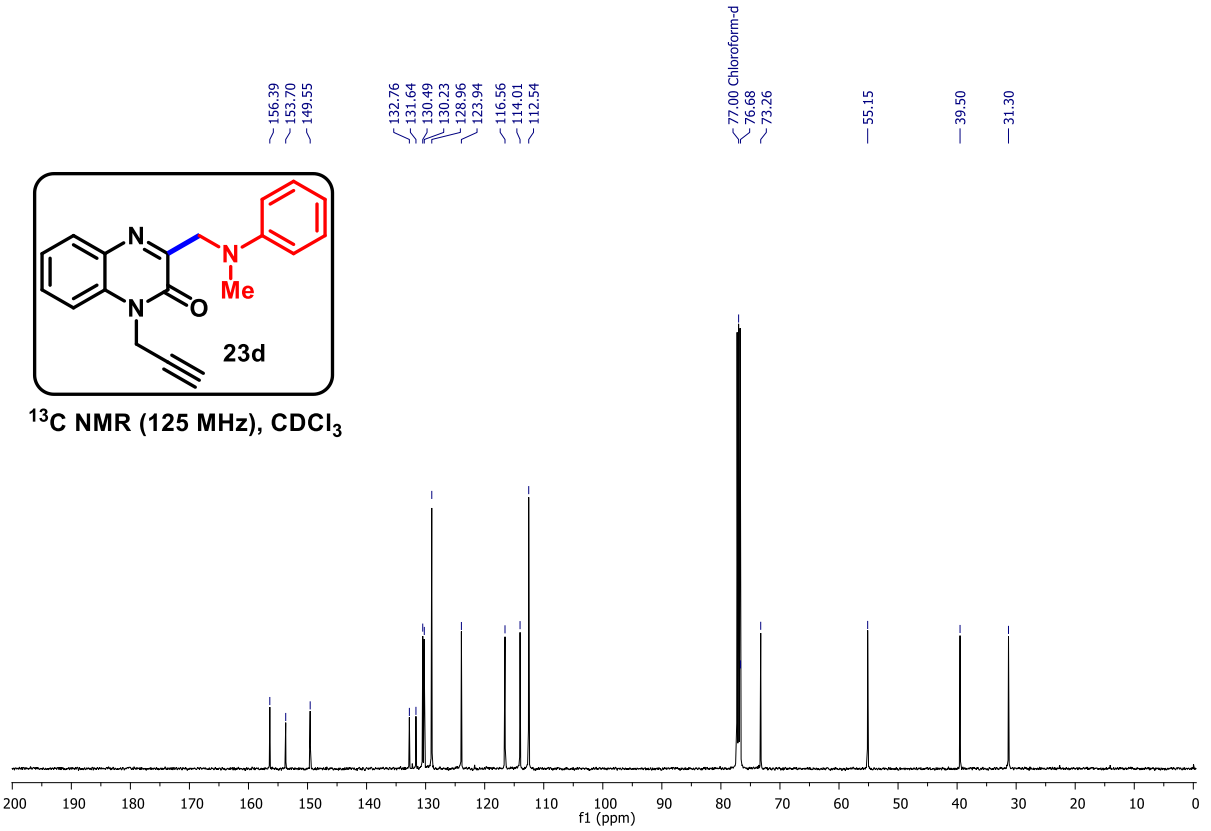
^{1}H NMR (400 MHz), $CDCl_3$



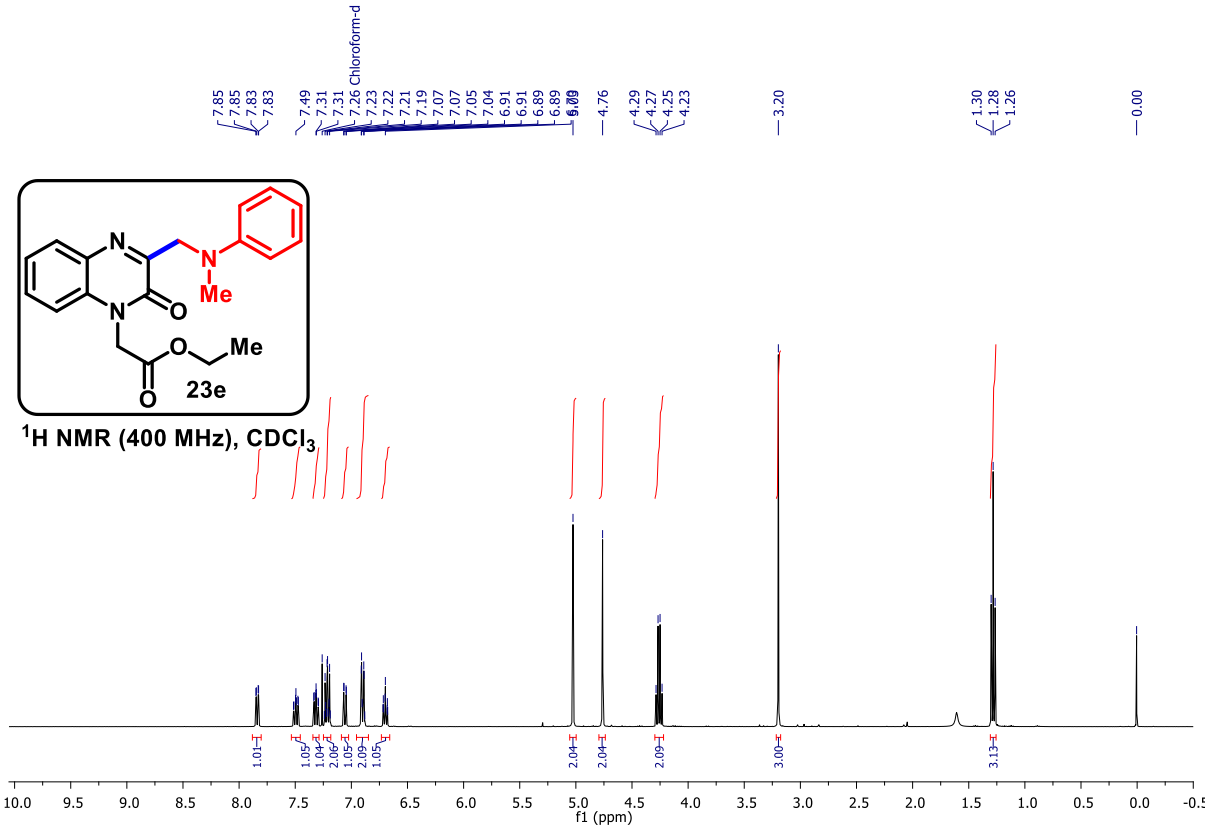
^{13}C NMR (100 MHz), $CDCl_3$

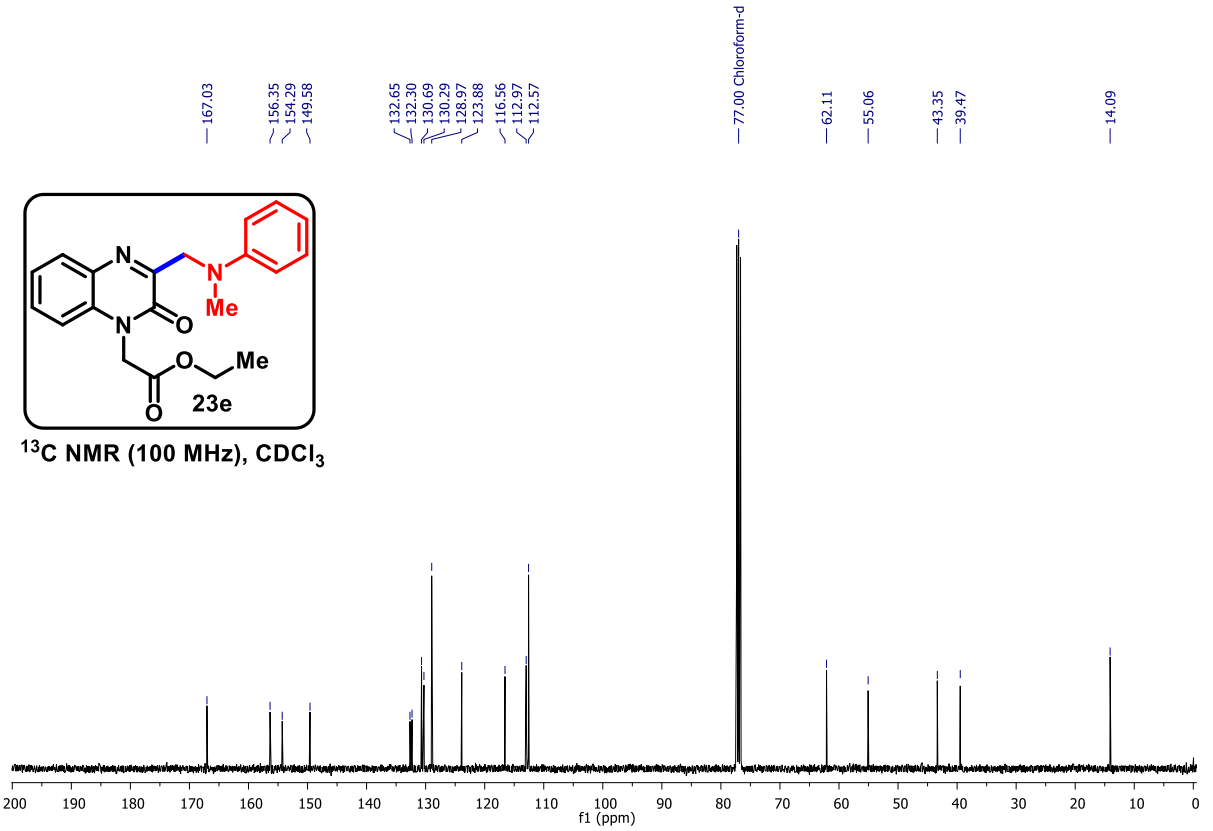


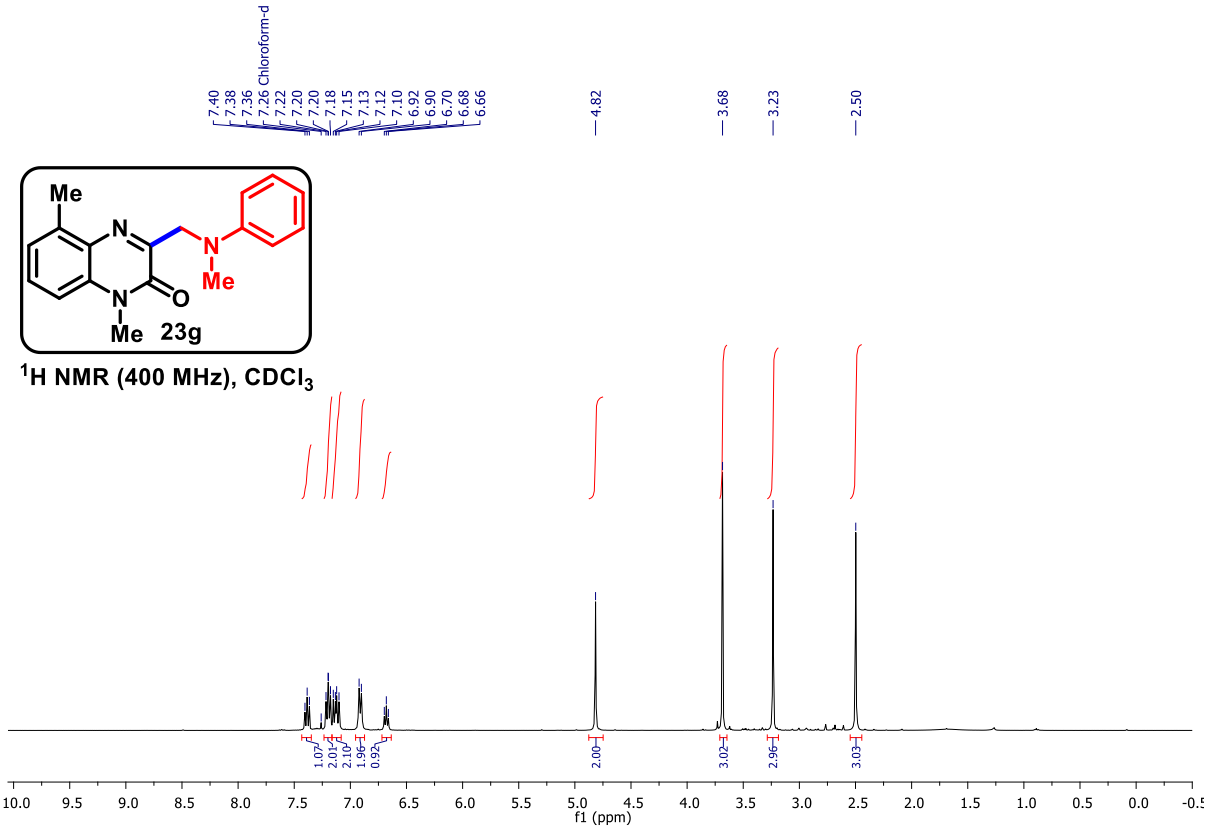
^{1}H NMR (500 MHz), $CDCl_3$



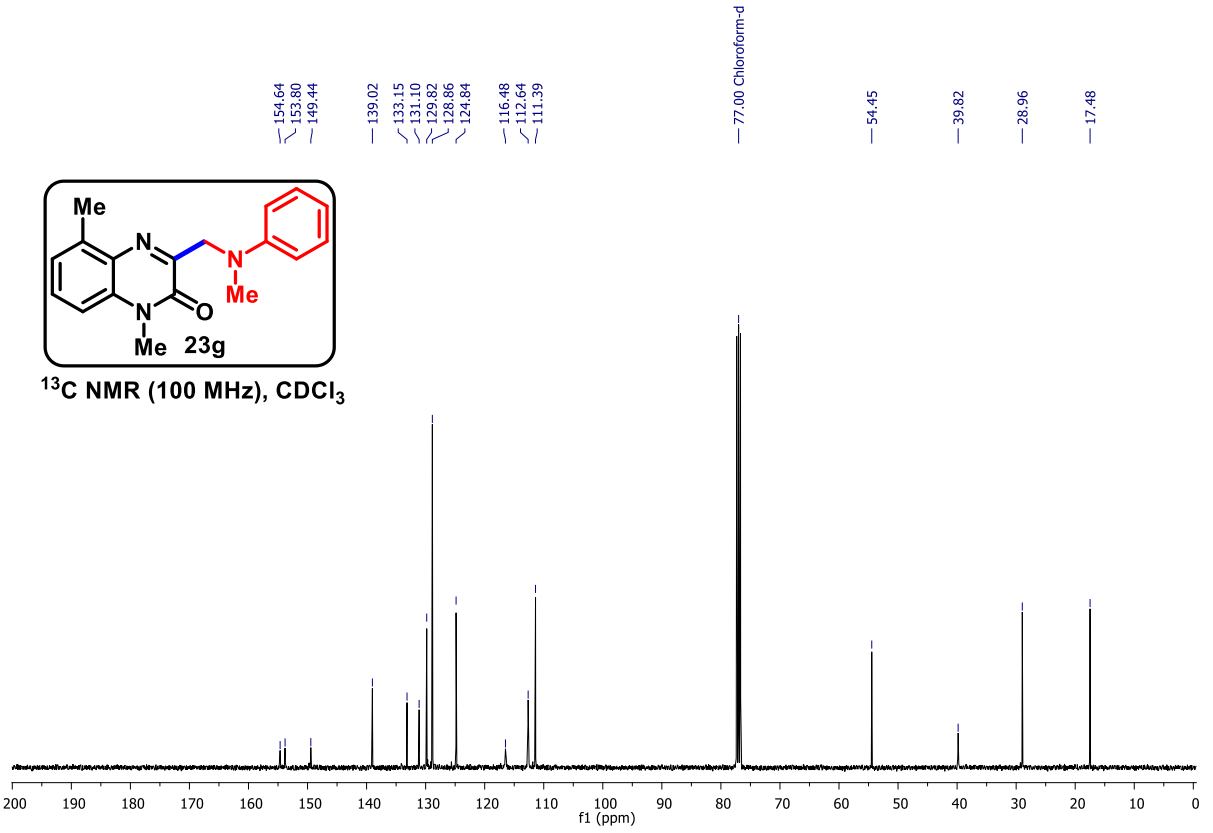
^{13}C NMR (125 MHz), $CDCl_3$


7.85
7.85
7.83
7.83
7.49
7.31
7.31
7.26 Chloroform-d
7.23
7.22
7.21
7.19
7.07
7.07
7.05
7.04
6.91
6.91
6.89
6.89
4.76
4.29
4.27
4.25
4.23
3.20
1.30
1.28
1.26
0.00
N
N
Me
N
O
O
Me
O
23e
1H NMR (400 MHz), CDCl3
1.01
1.05
1.04
2.06
1.05
2.09
1.05
2.04
2.04
2.09
3.00
3.13
10.0
9.5
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
0.0
f1 (ppm)

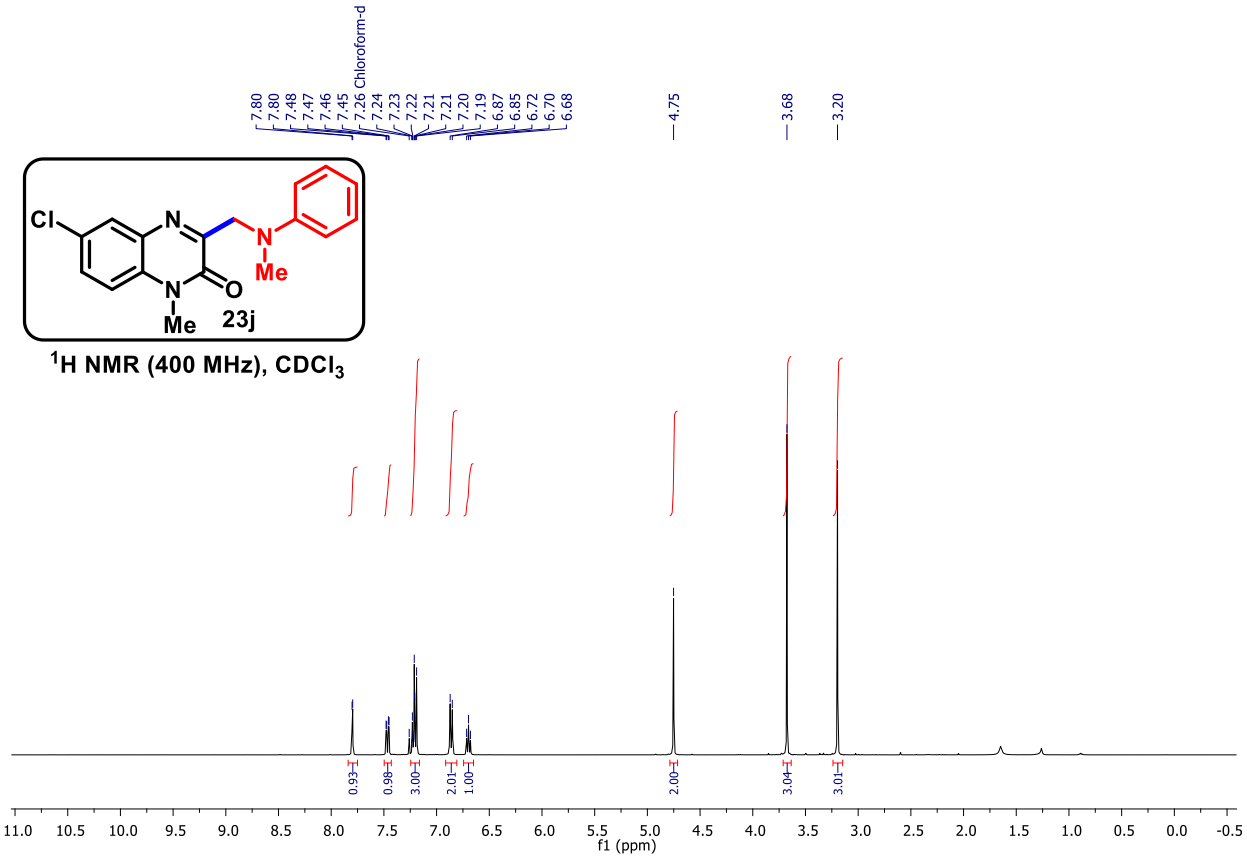

167.03
156.35
154.29
149.58
132.65
132.30
130.69
130.29
128.97
123.88
116.56
112.97
112.57
77.00 Chloroform-d
62.11
55.06
43.35
39.47
14.09
N
N
Me
N
O
O
Me
O
23e
13C NMR (100 MHz), CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



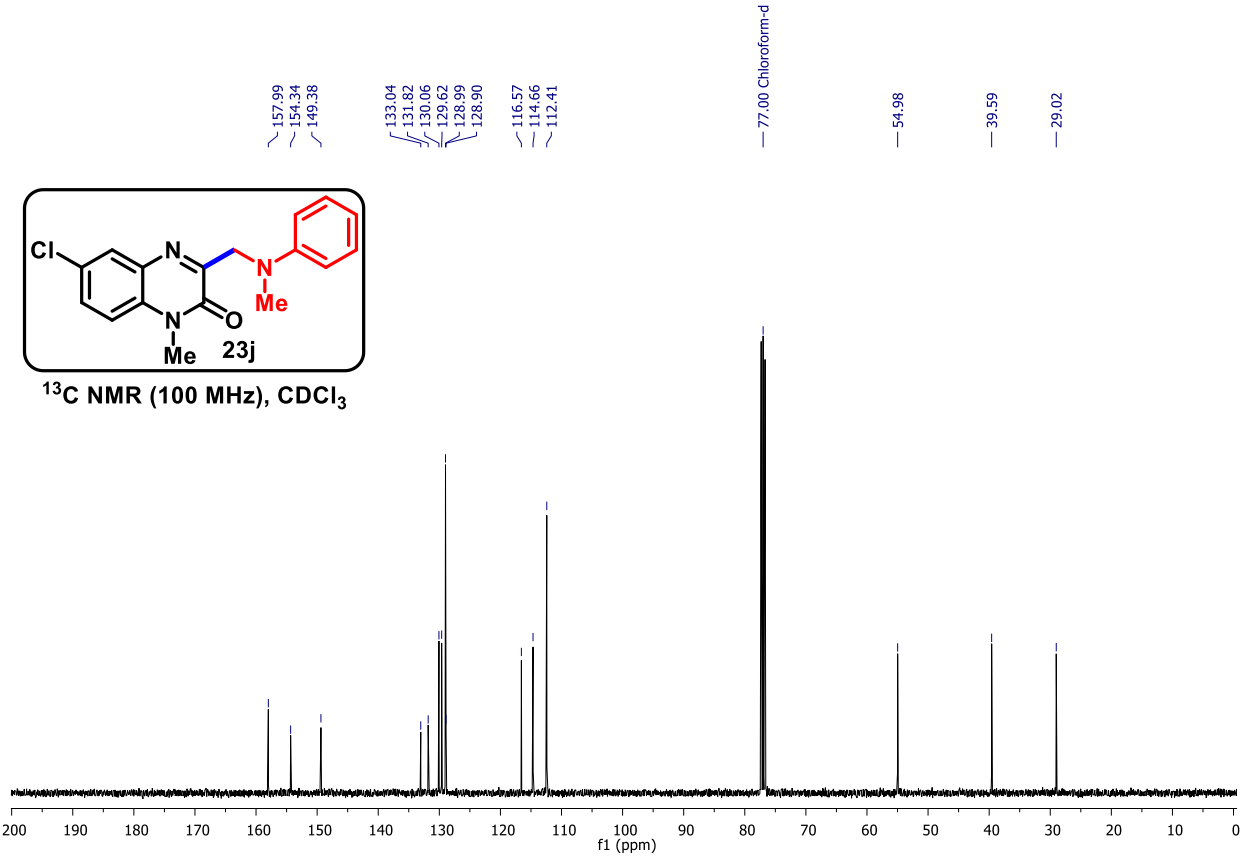
^{1}H NMR (400 MHz), $CDCl_3$



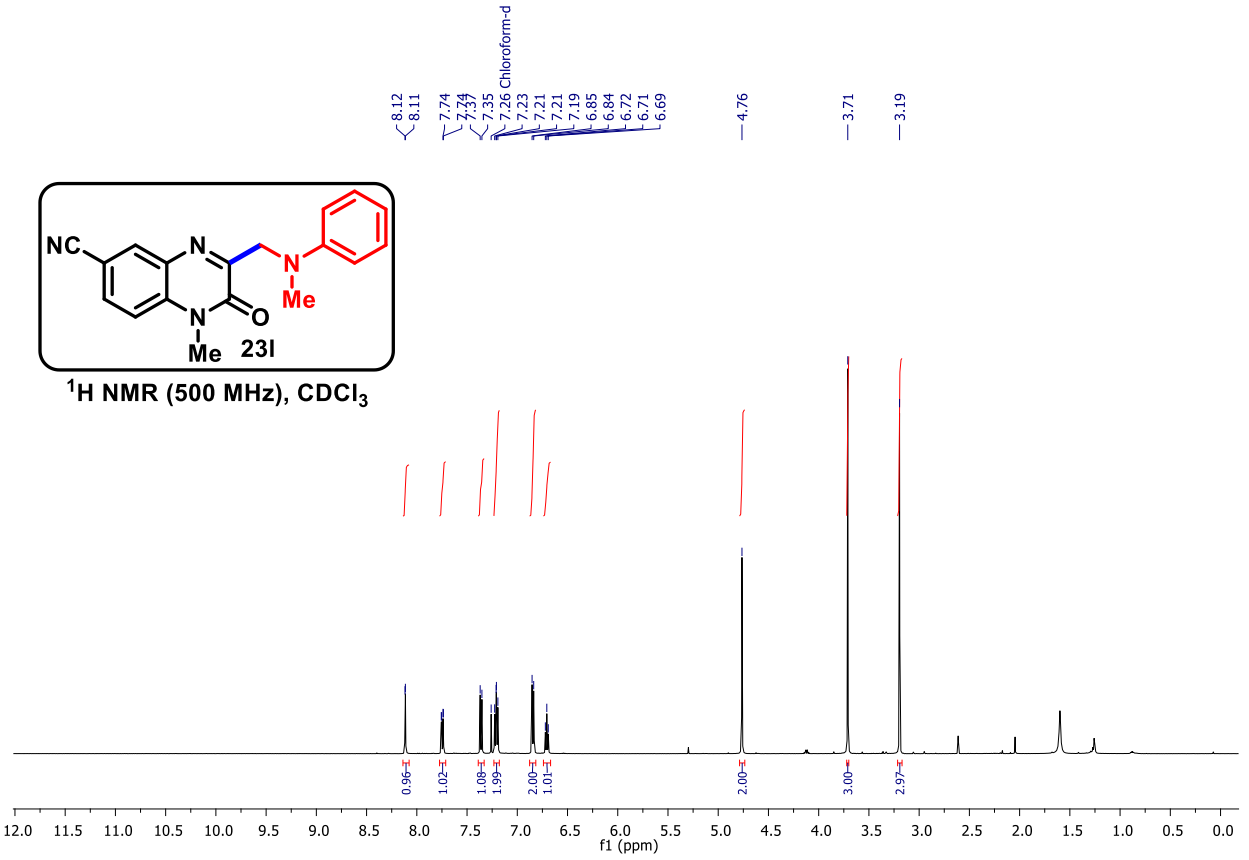
^{13}C NMR (100 MHz), $CDCl_3$



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



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



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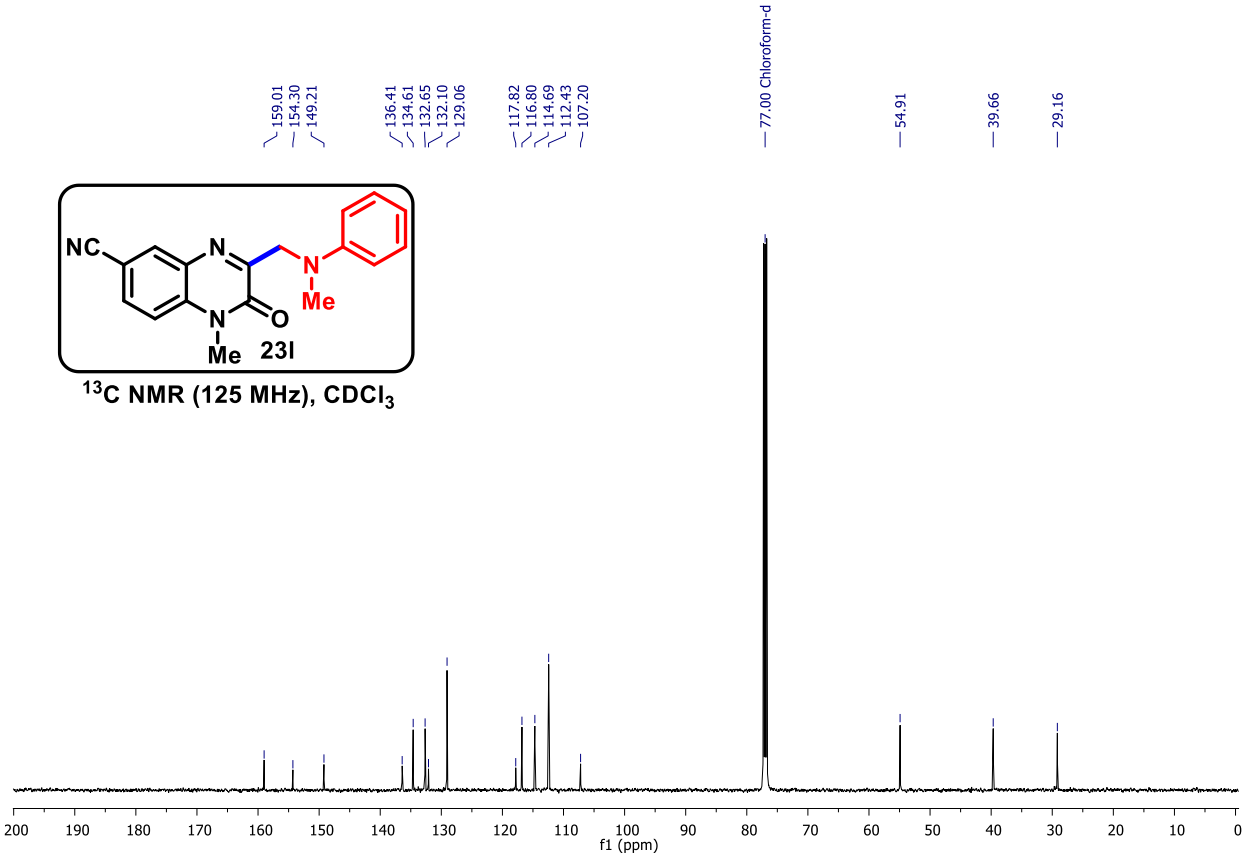

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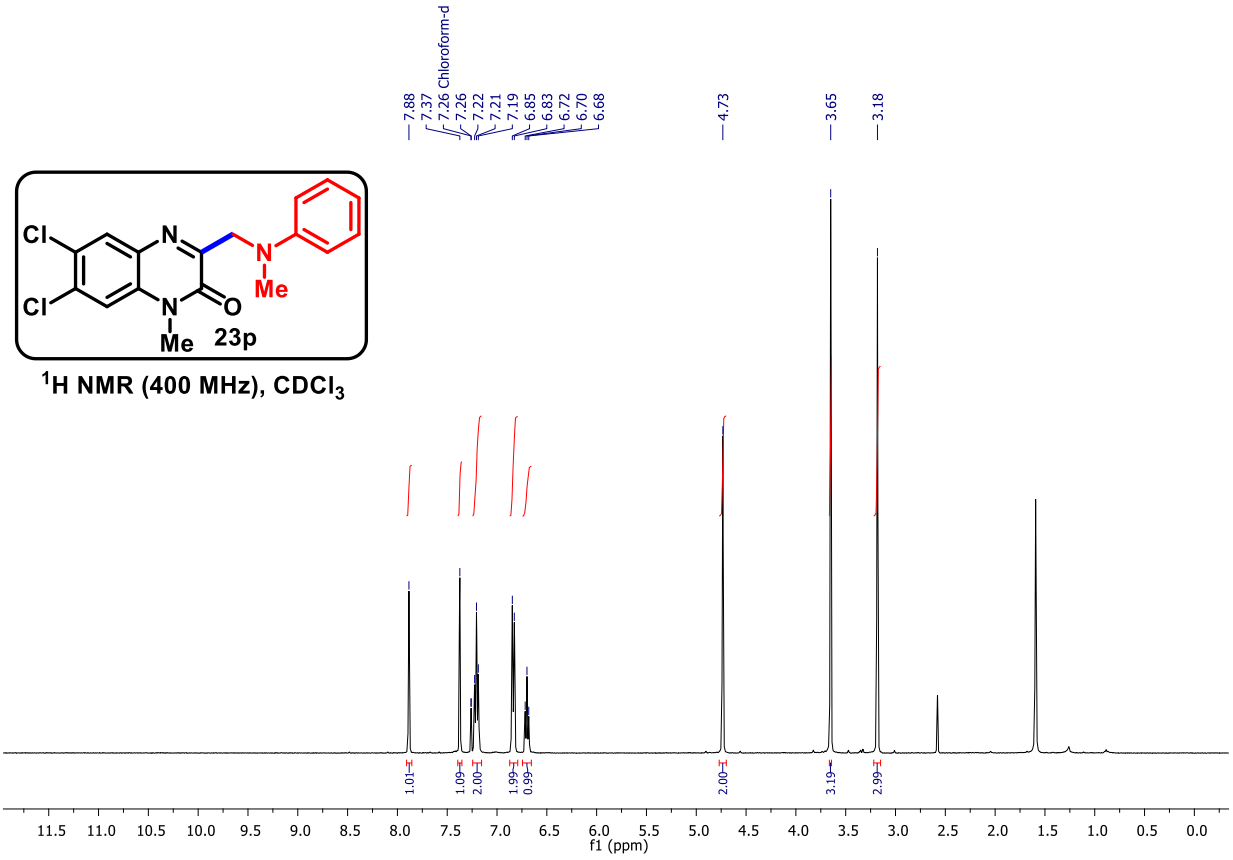

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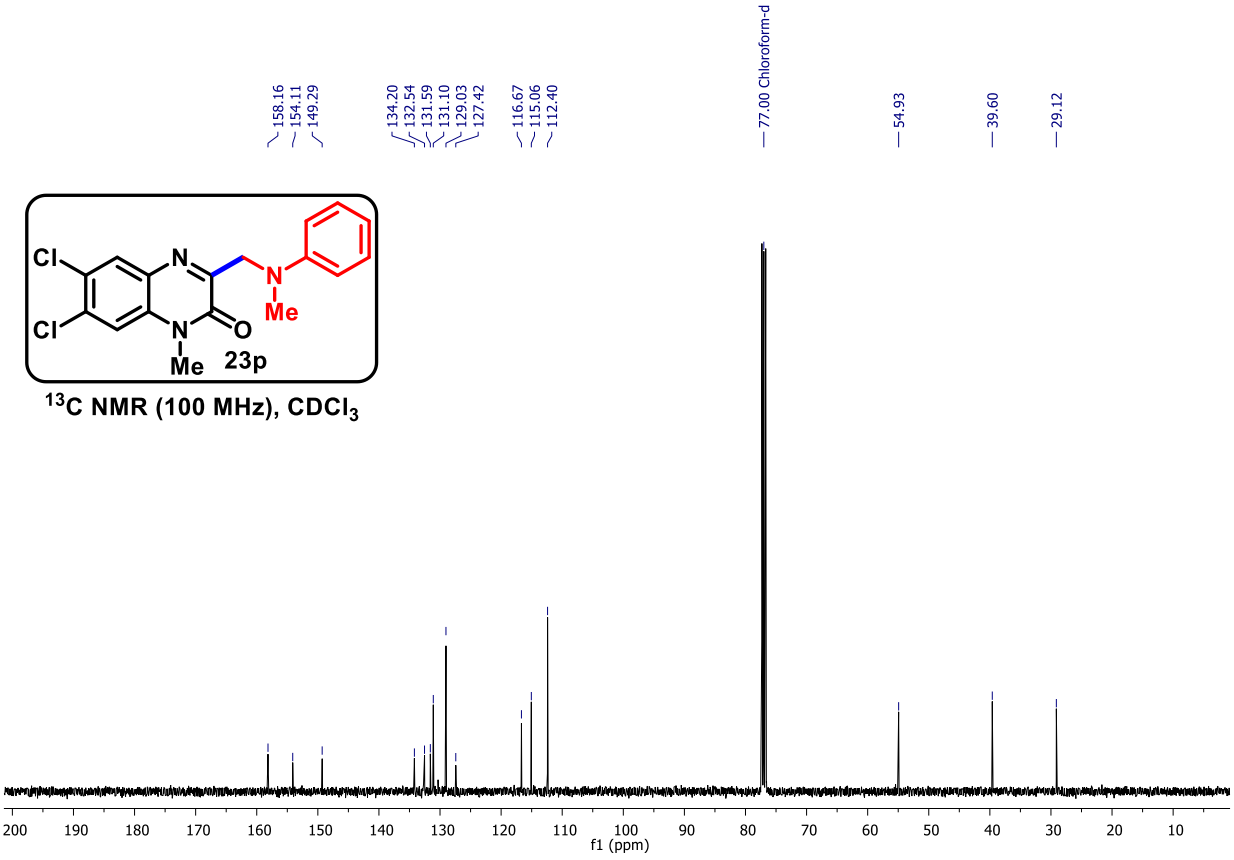

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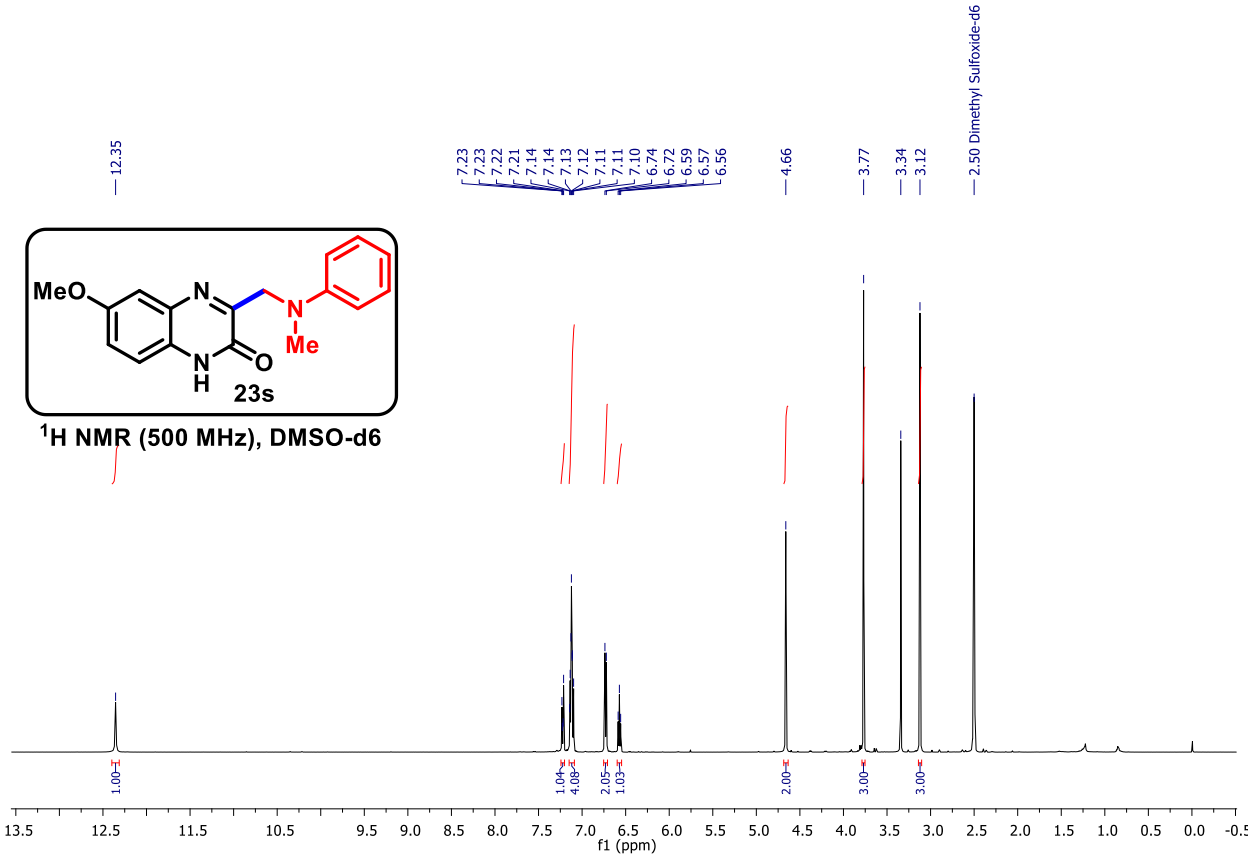
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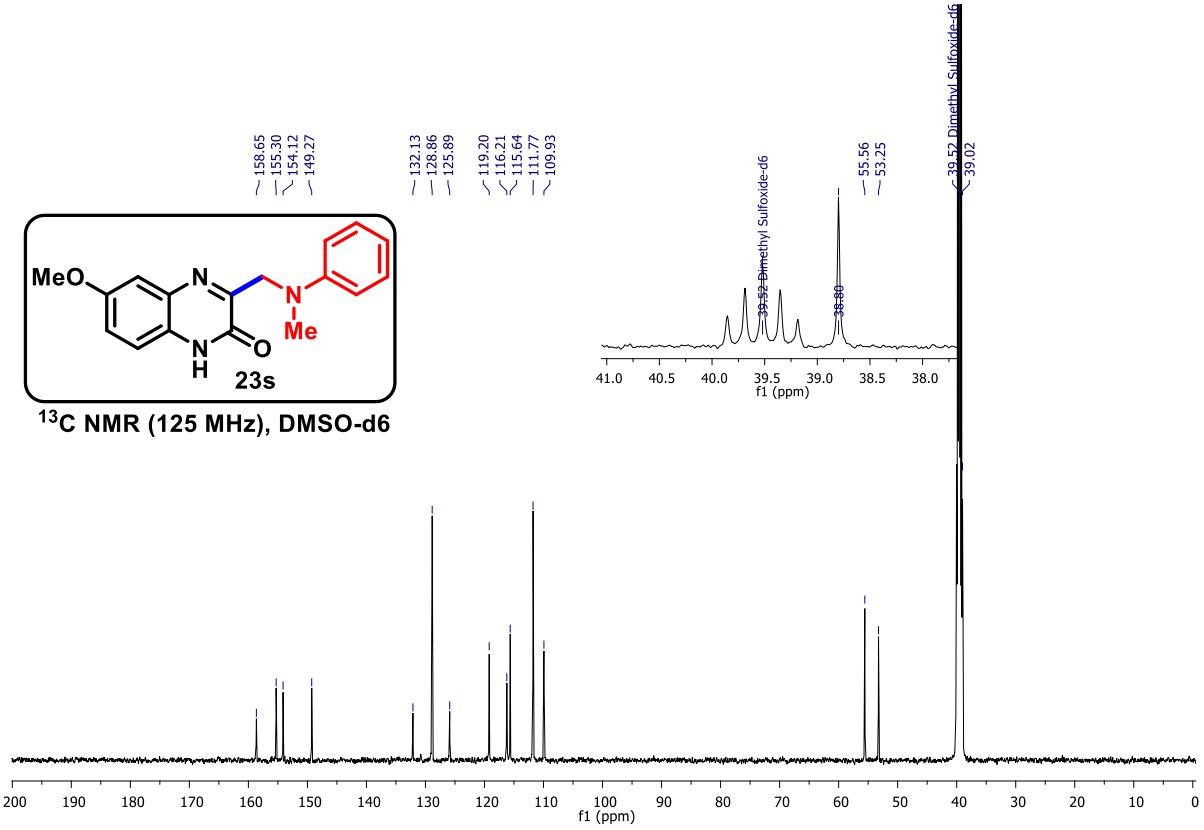
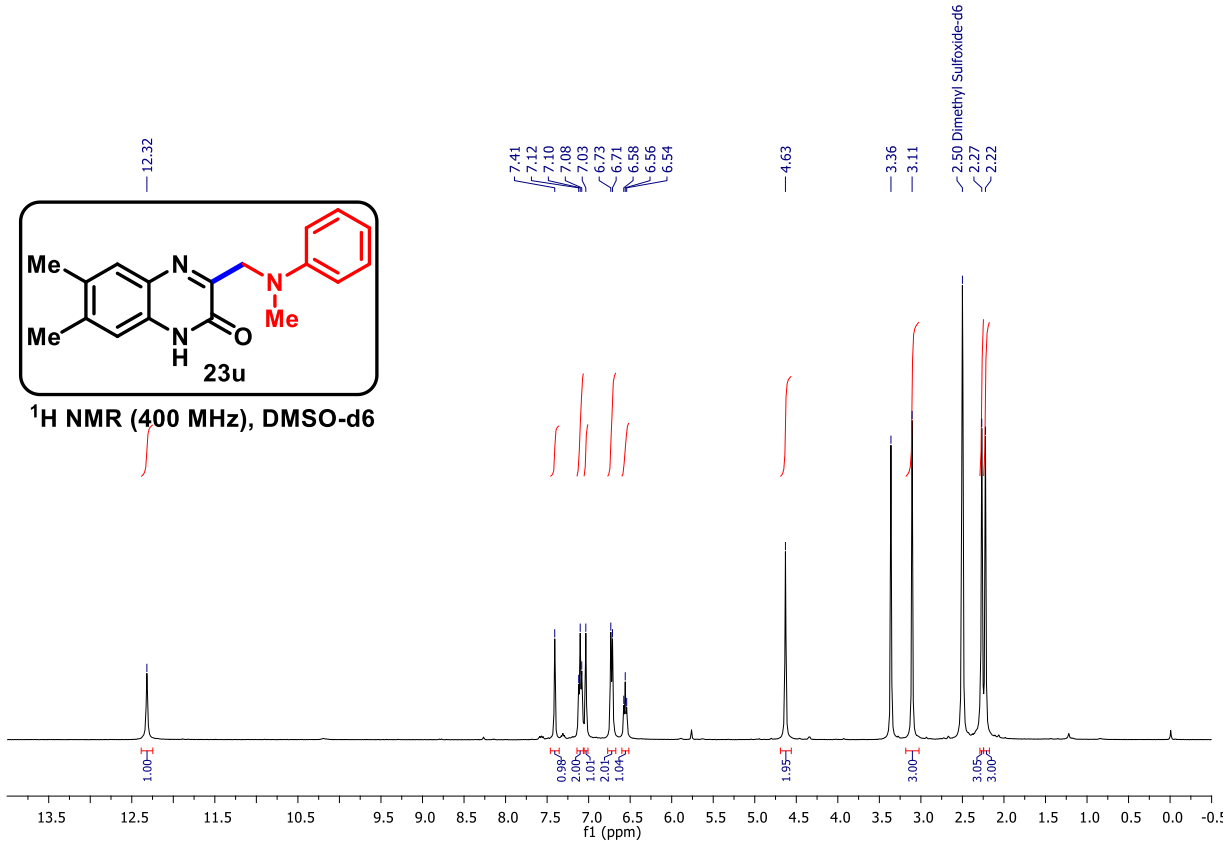
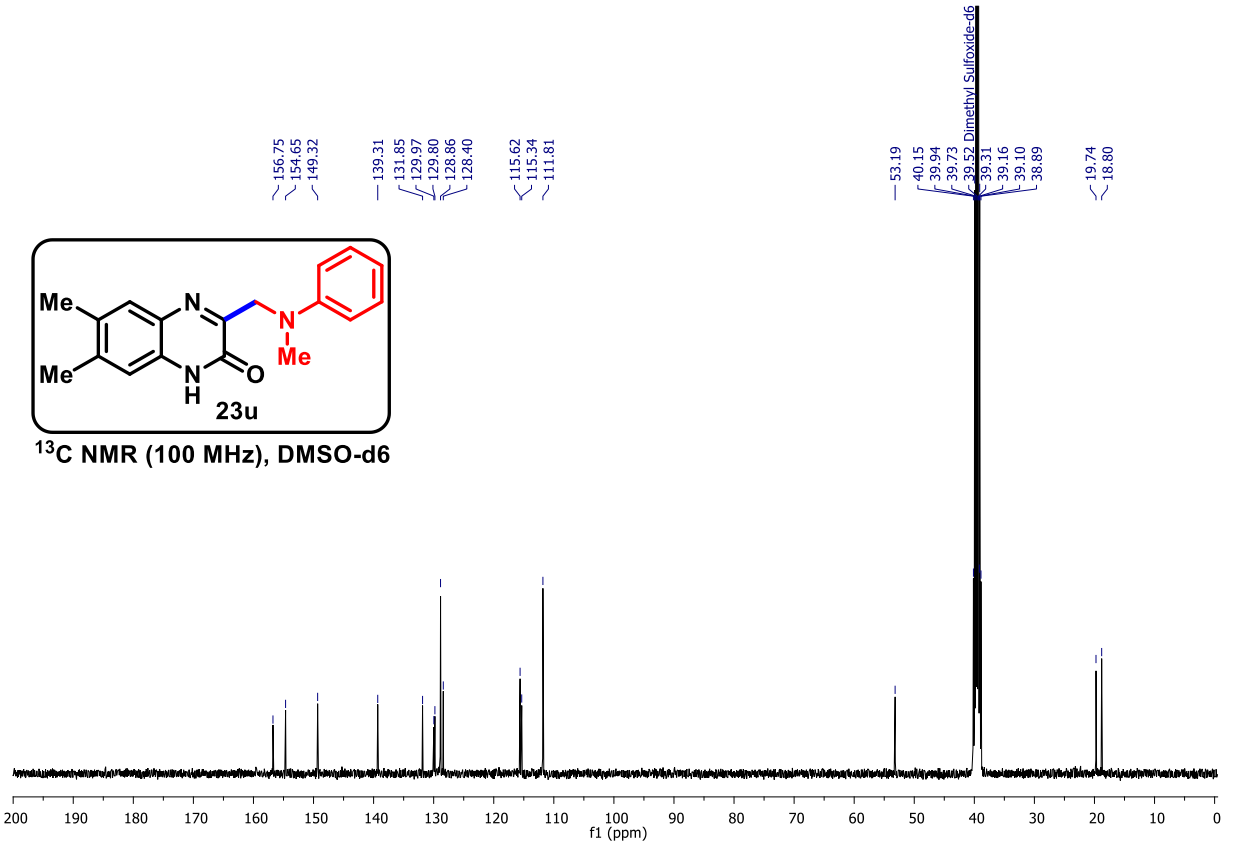
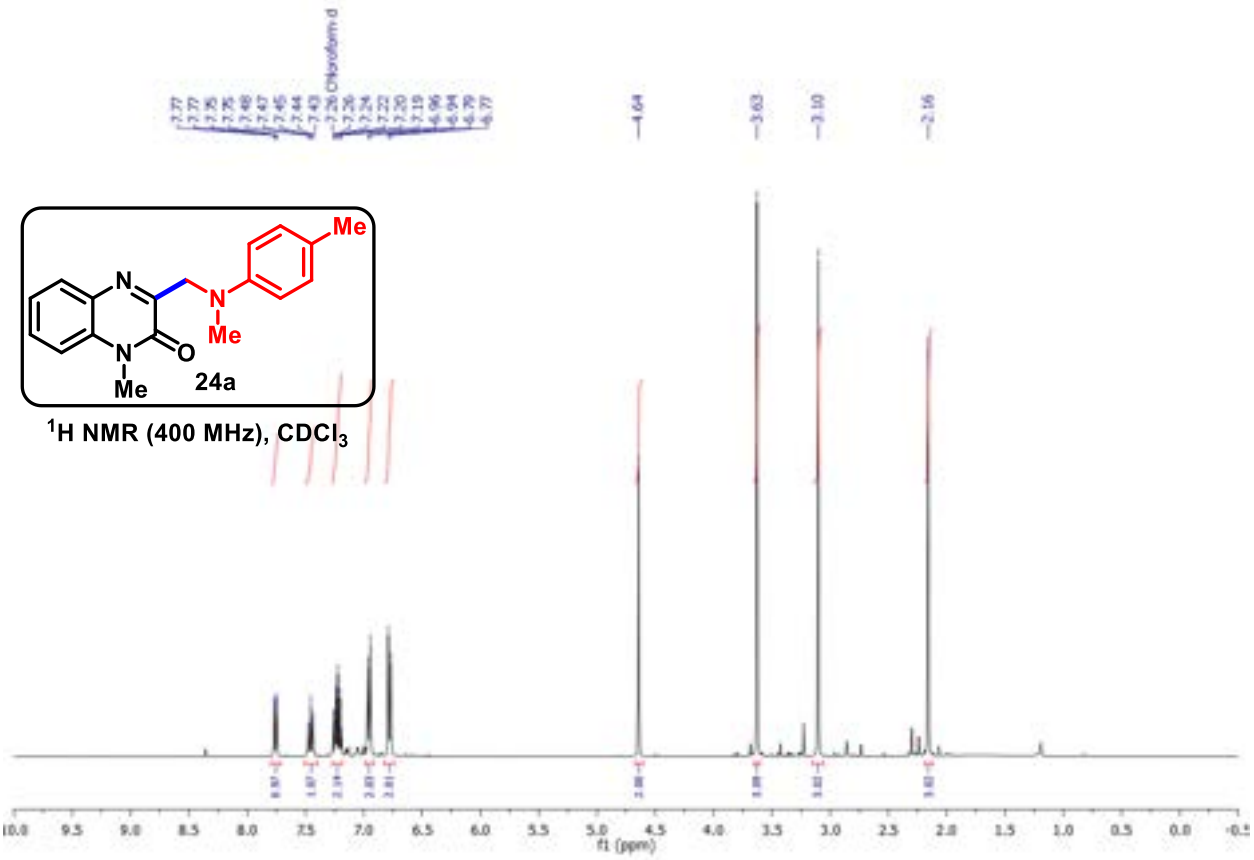
7.23
7.23
7.22
7.21
7.14
7.14
7.13
7.12
7.11
7.11
7.10
6.74
6.72
6.59
6.57
6.56
4.66
3.77
3.34
3.12
2.50 Dimethyl Sulfoxide-d6
MeO
N
N
Me
N
H
O
23s
1H NMR (500 MHz), DMSO-d6
1.00
1.04
4.08
2.05
1.03
2.00
3.00
3.00
f1 (ppm)


158.65
155.30
154.12
149.27
132.13
128.86
125.89
119.20
116.21
115.64
111.77
109.93
55.56
53.25
39.52 Dimethyl Sulfoxide-d6
39.02
MeO
N
N
Me
N
H
O
23s
13C NMR (125 MHz), DMSO-d6
f1 (ppm)


12.32
7.41
7.12
7.10
7.08
7.03
6.73
6.71
6.58
6.56
6.54
4.63
3.36
3.11
2.50 Dimethyl Sulfoxide-d6
2.27
2.22
Me
Me
N
N
H
O
N
Me
23u
1H NMR (400 MHz), DMSO-d6
1.00
0.98
2.00
1.01
2.01
1.04
1.95
3.00
3.05
3.00
f1 (ppm)


156.75
154.65
149.32
139.31
131.85
129.97
129.80
128.86
128.40
115.62
115.34
111.81
53.19
40.15
39.94
39.73
39.52 Dimethyl Sulfoxide-d6
39.31
39.16
39.10
38.89
19.74
18.80
Me
Me
N
N
H
O
N
Me
23u
13C NMR (100 MHz), DMSO-d6
f1 (ppm)



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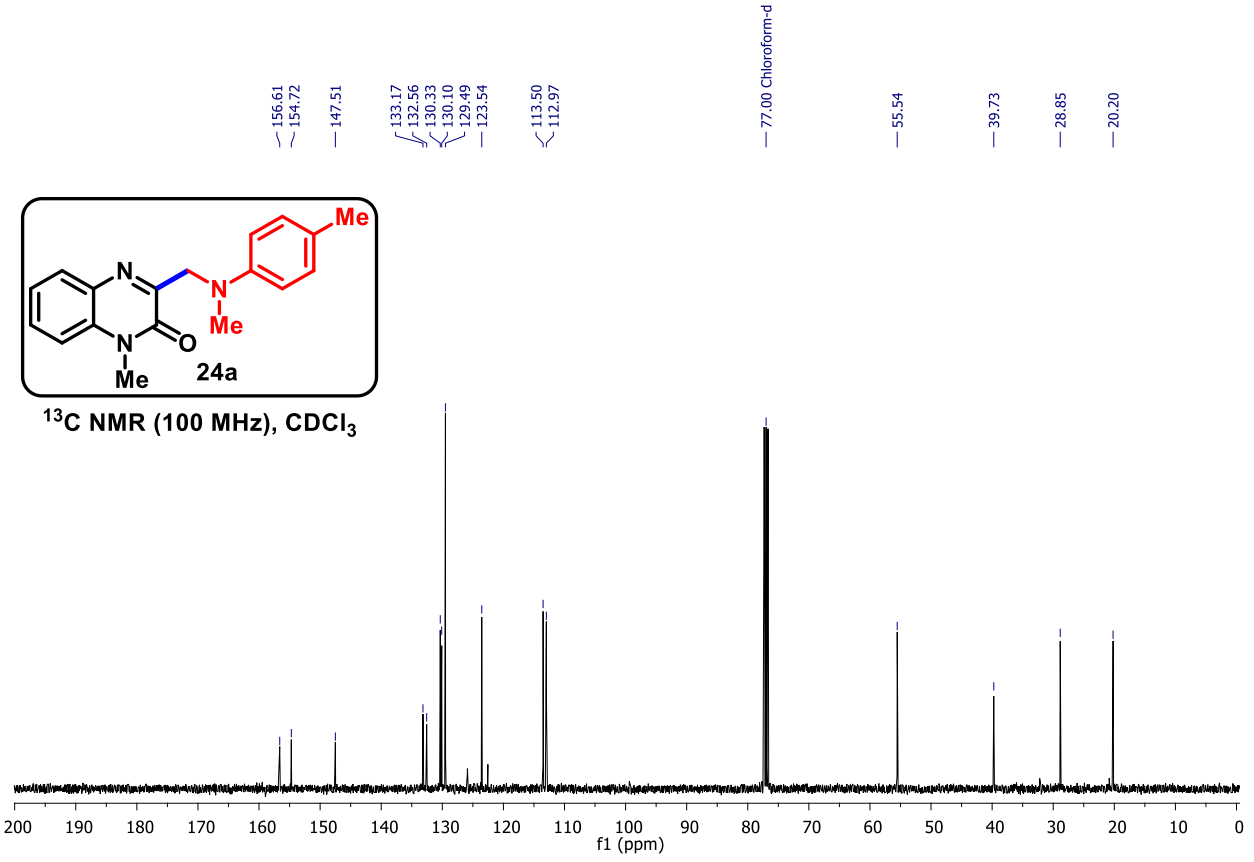
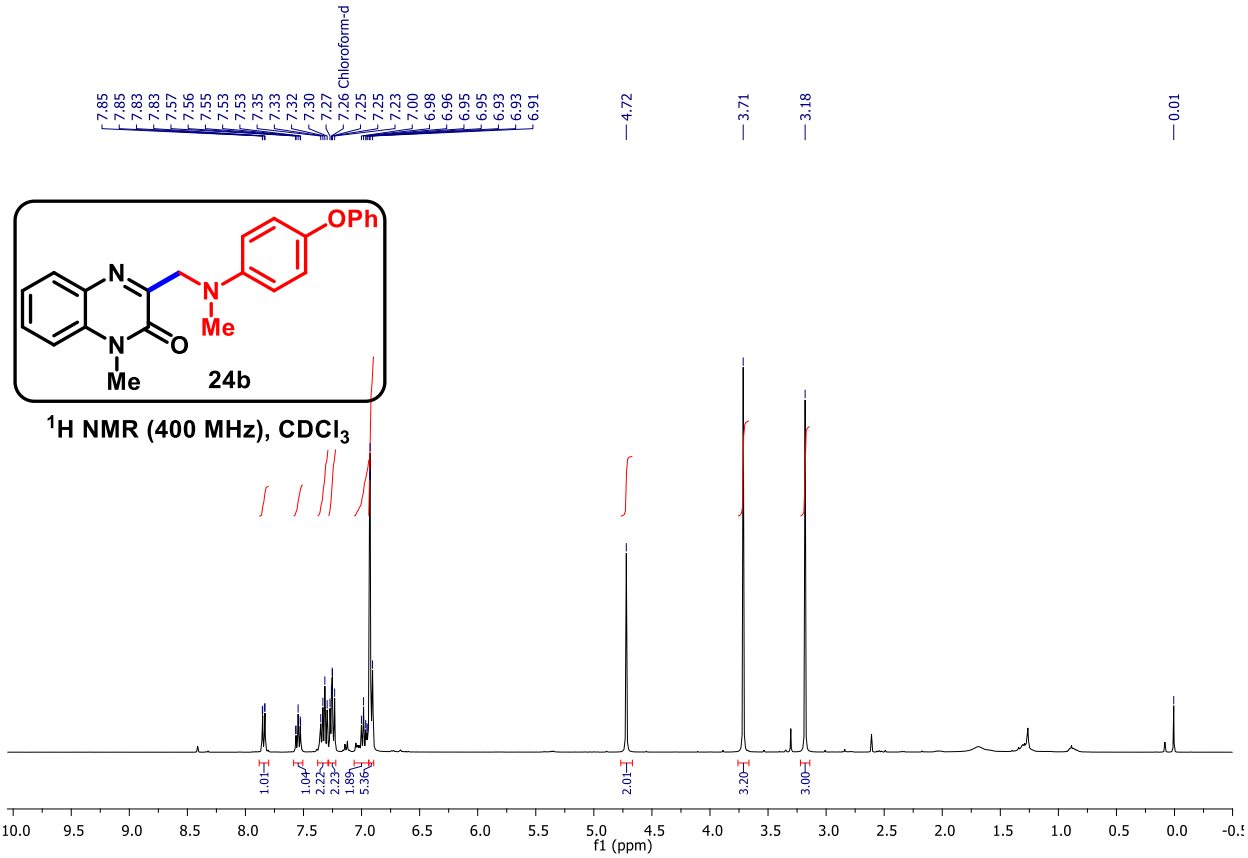


^{13}C NMR (100 MHz), $CDCl_3$



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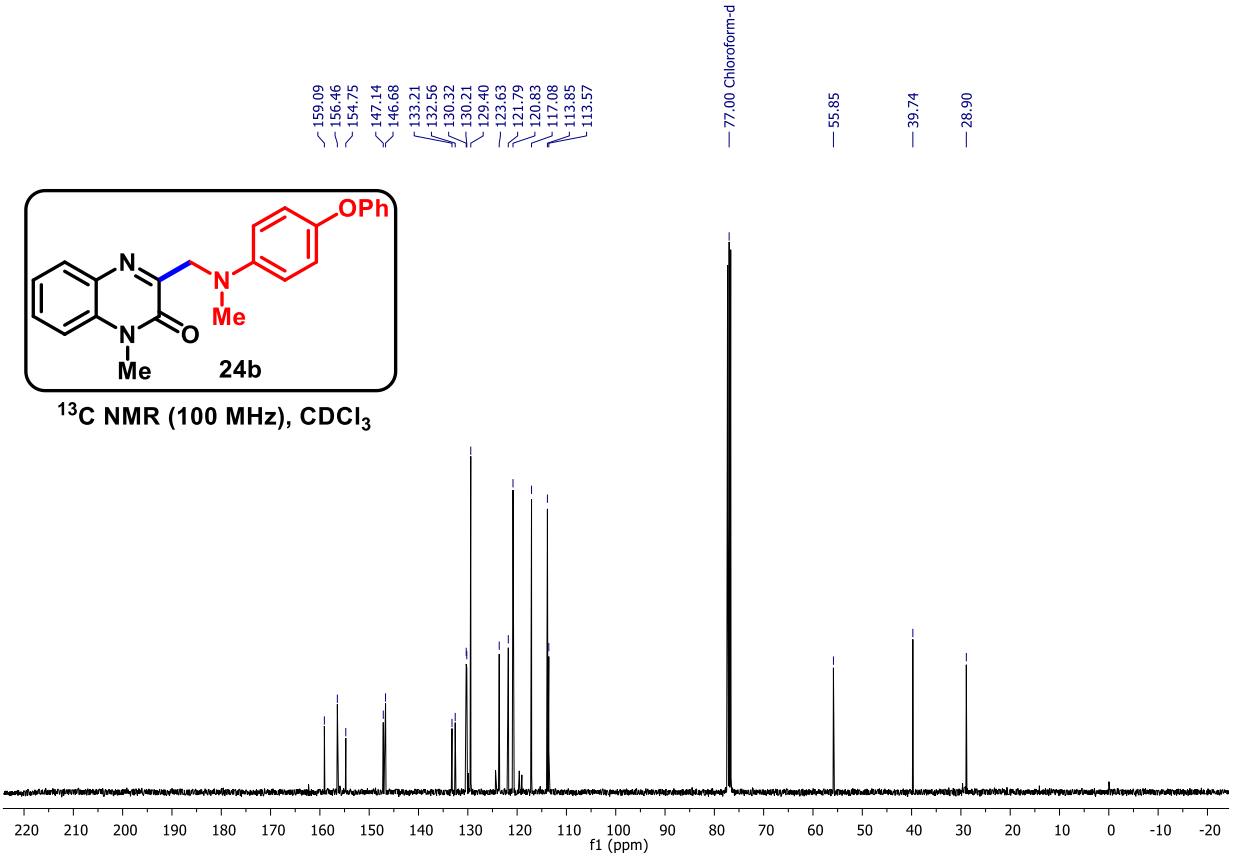

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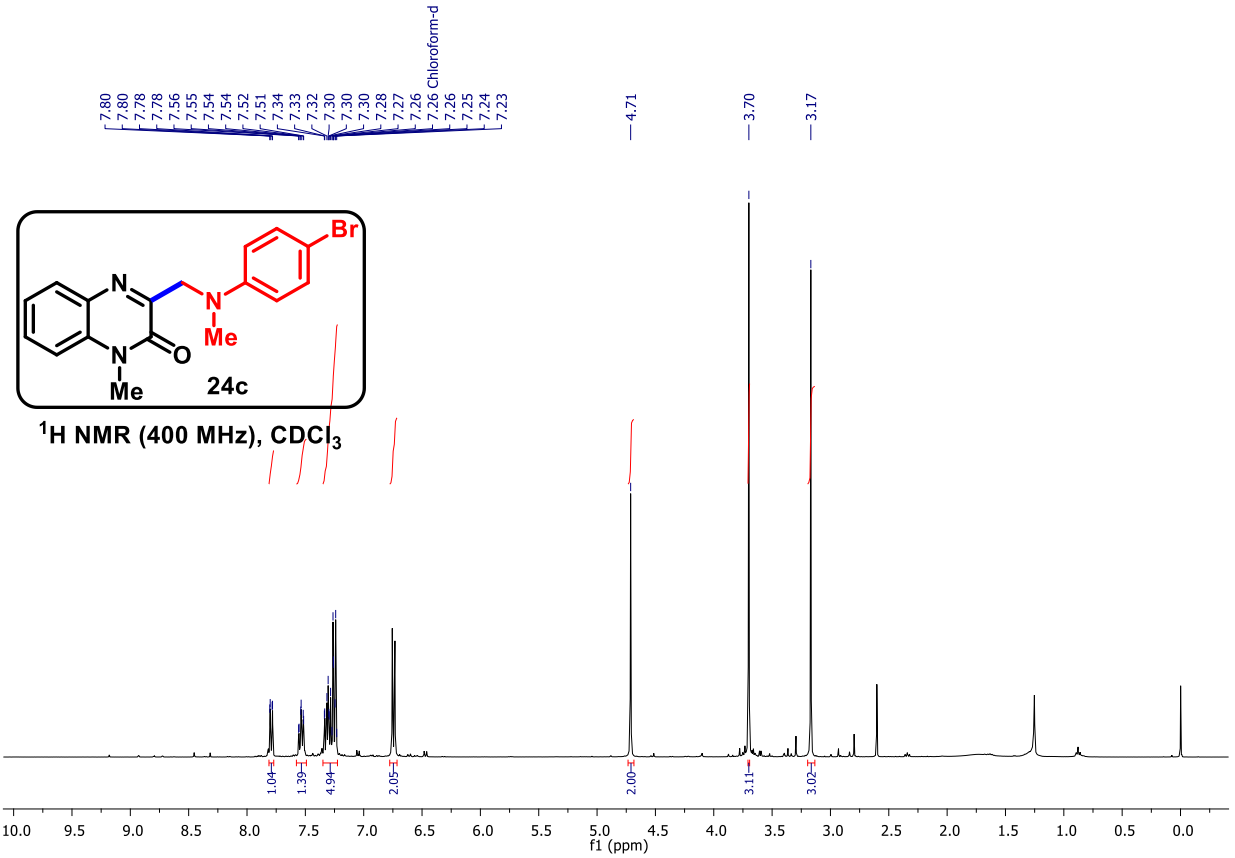

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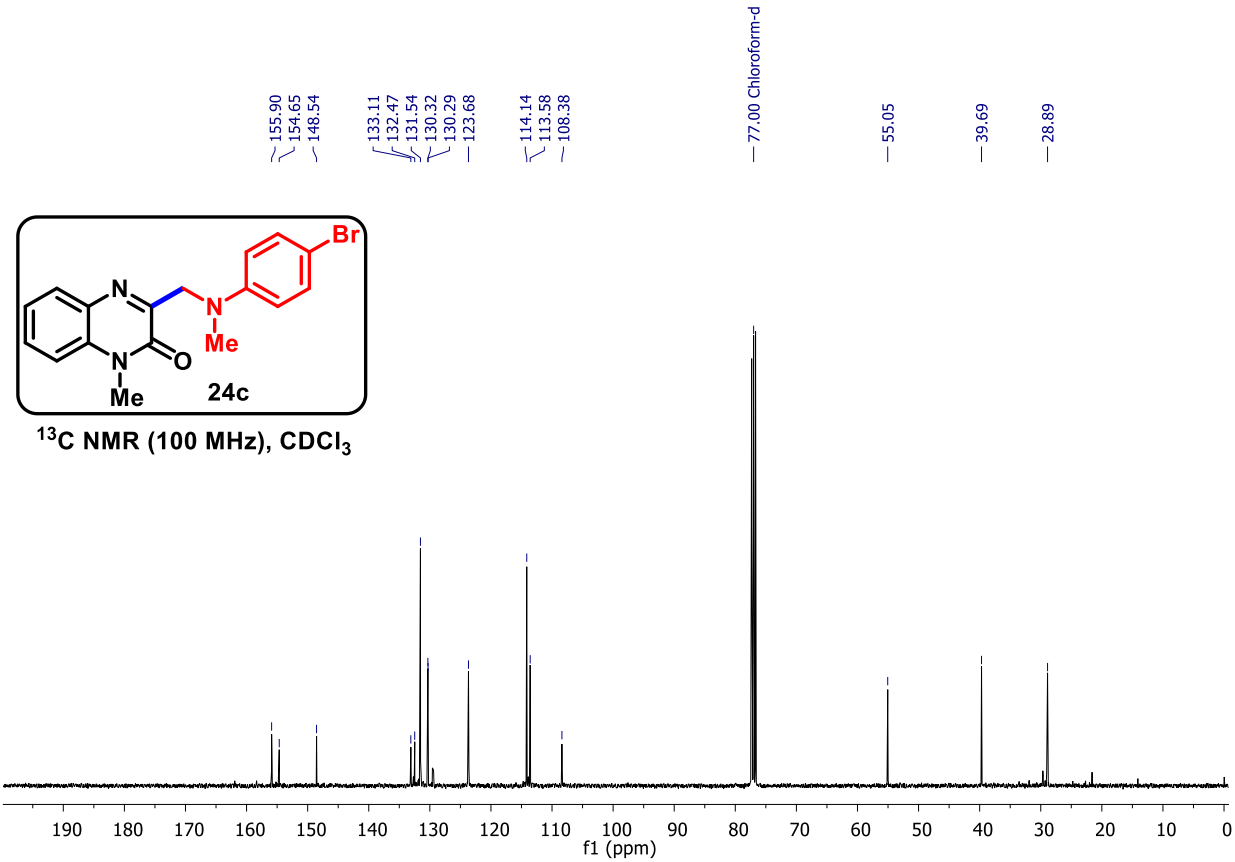

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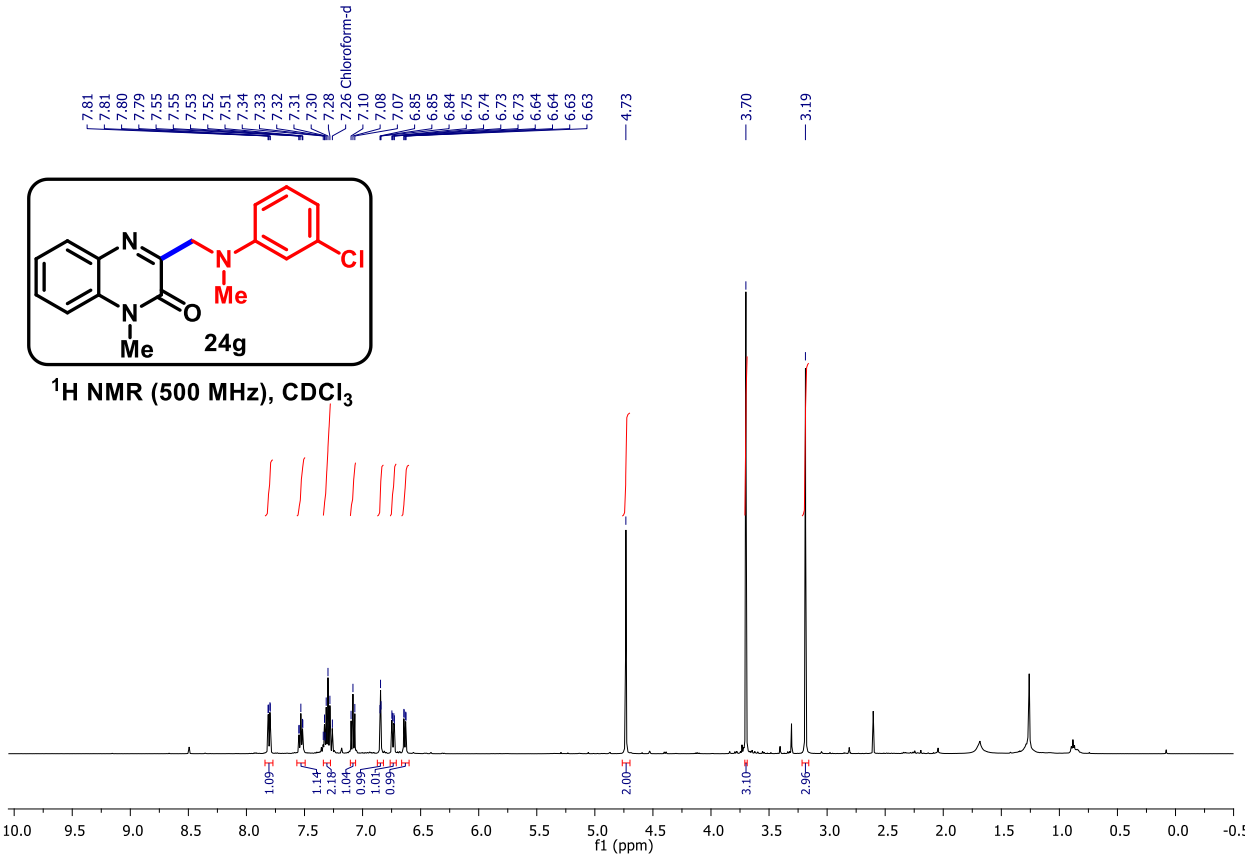

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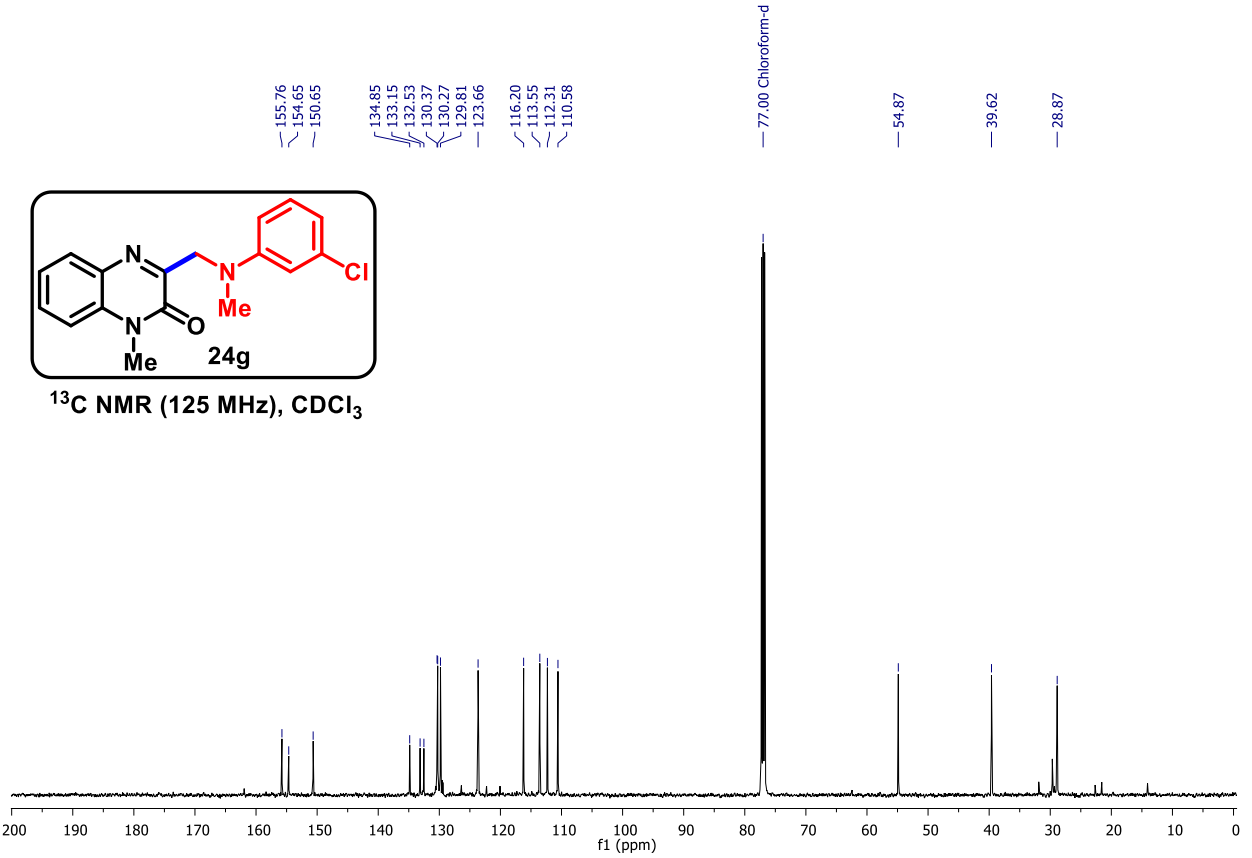

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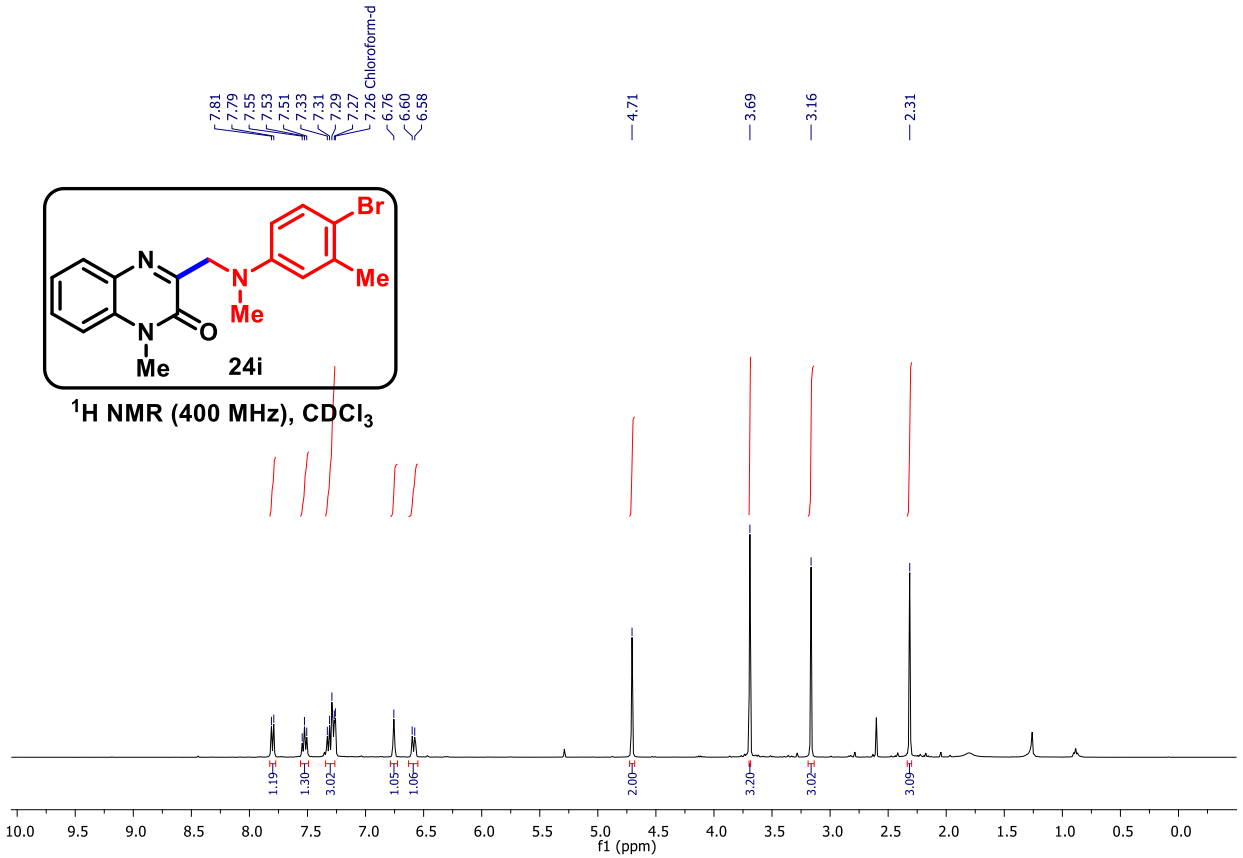
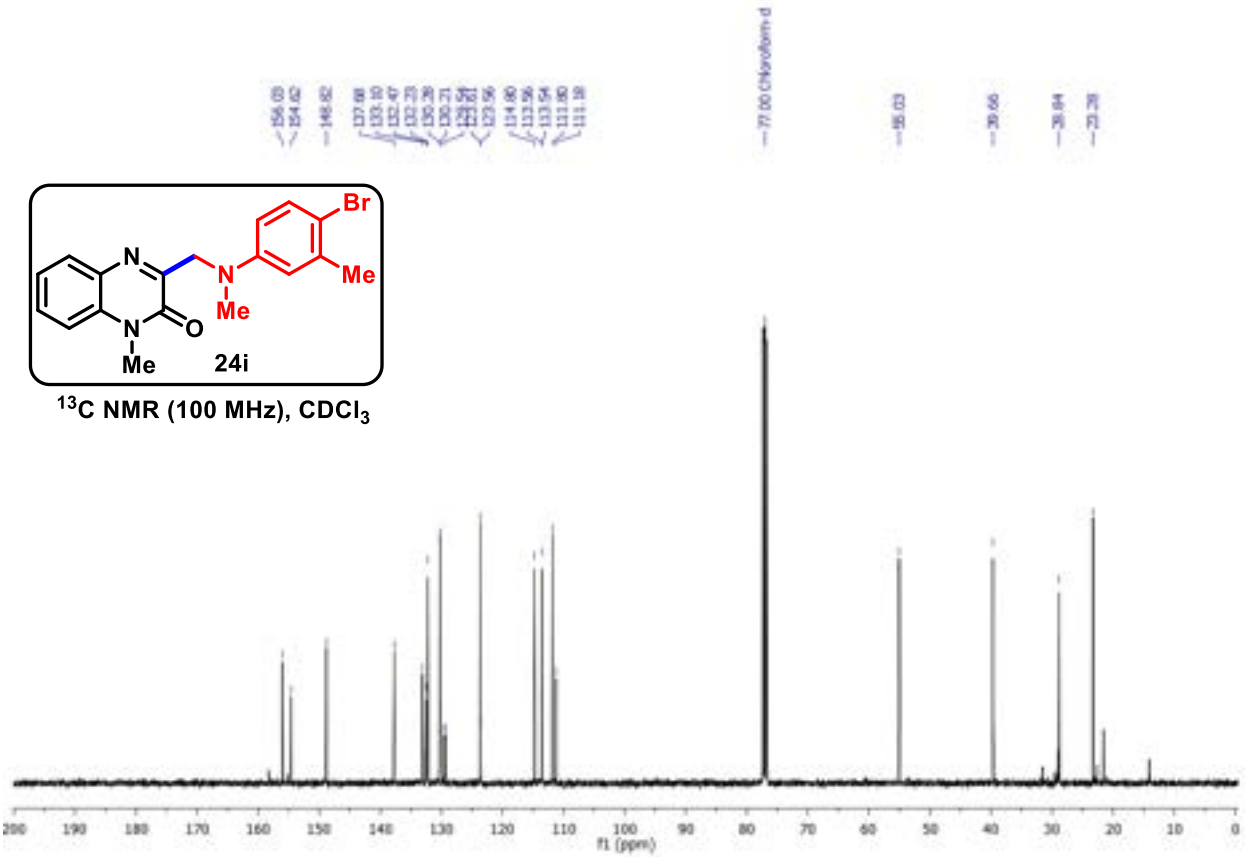


^{1}H NMR (400 MHz), $CDCl_3$



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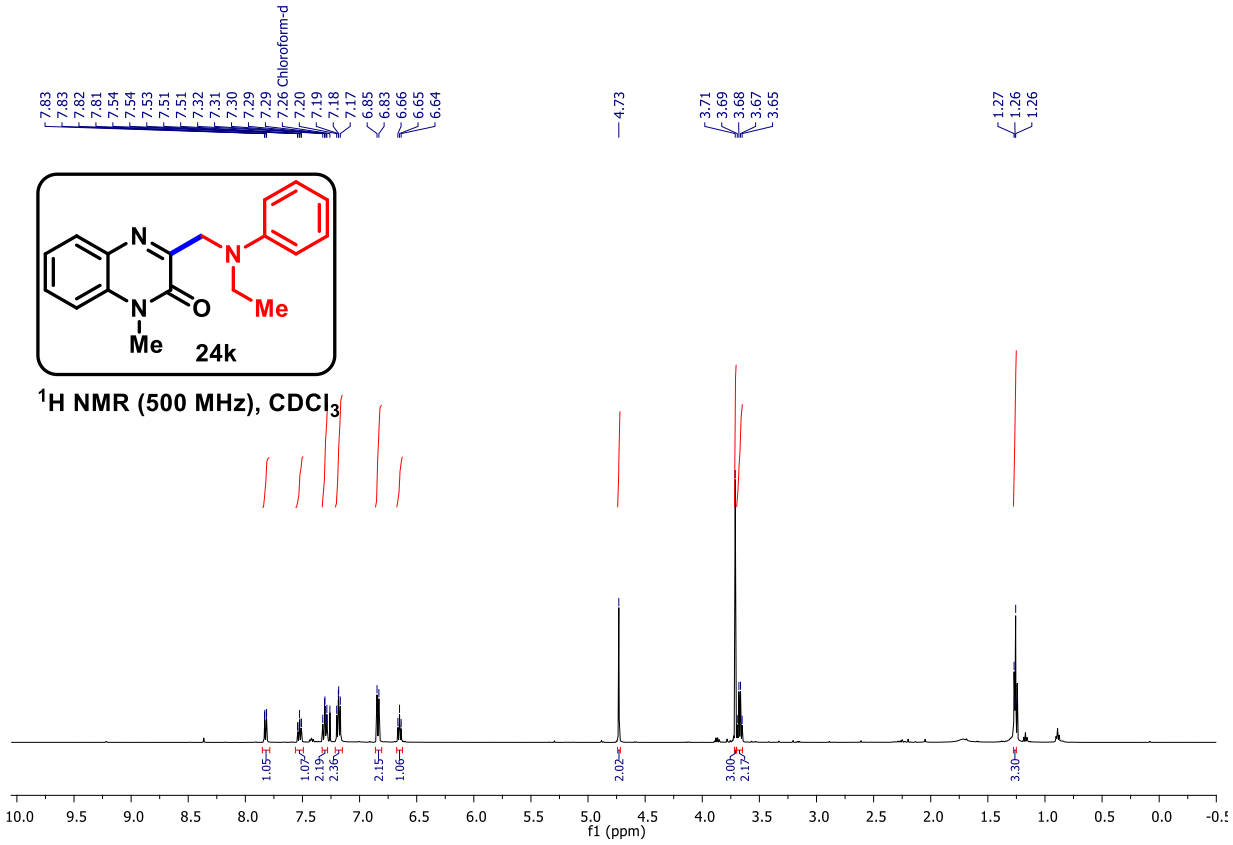

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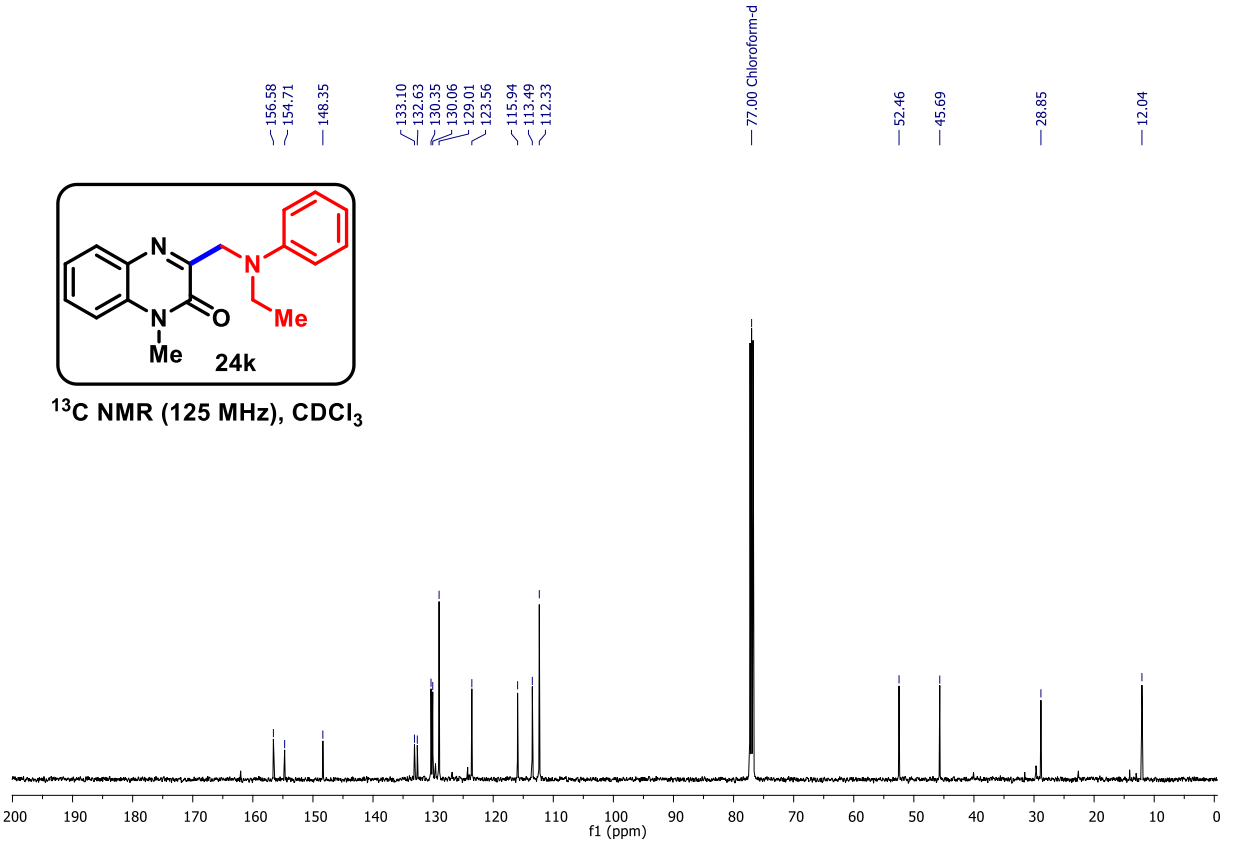

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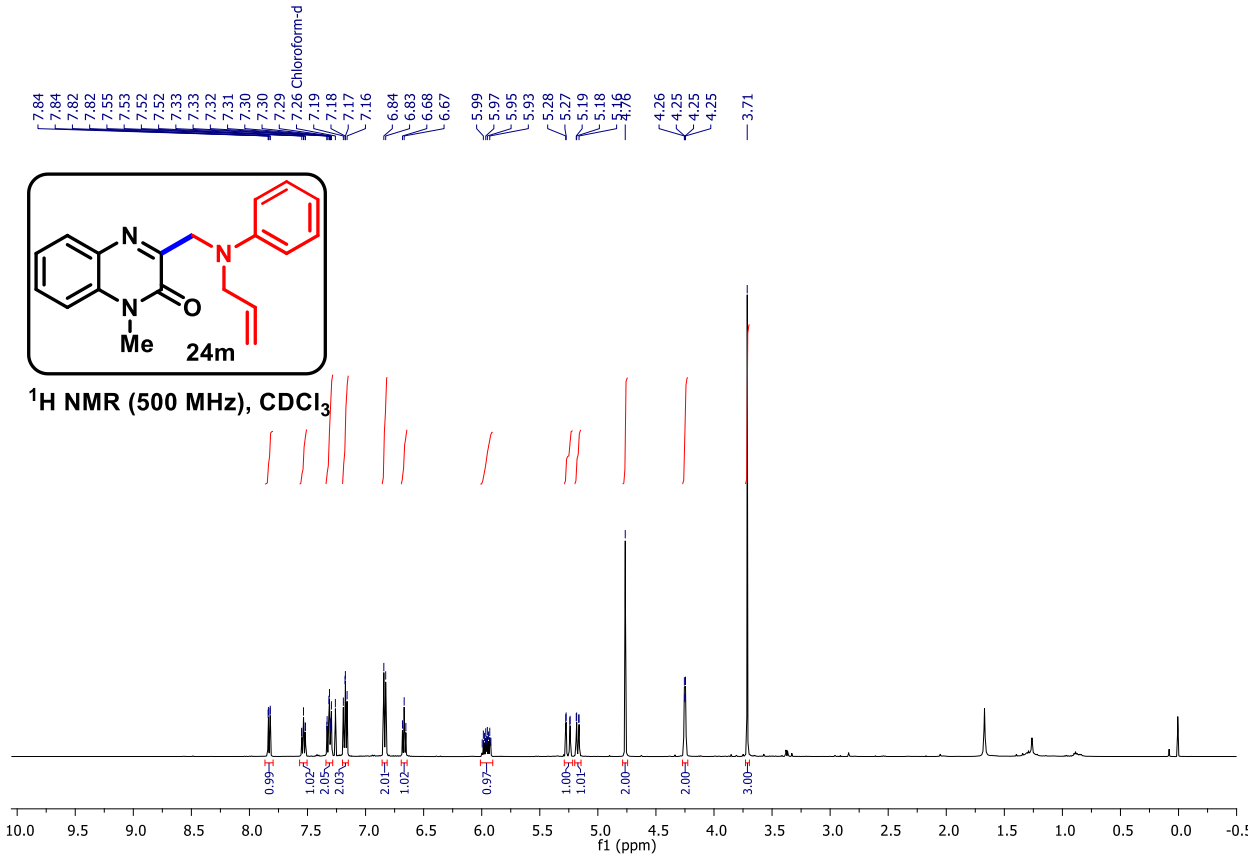

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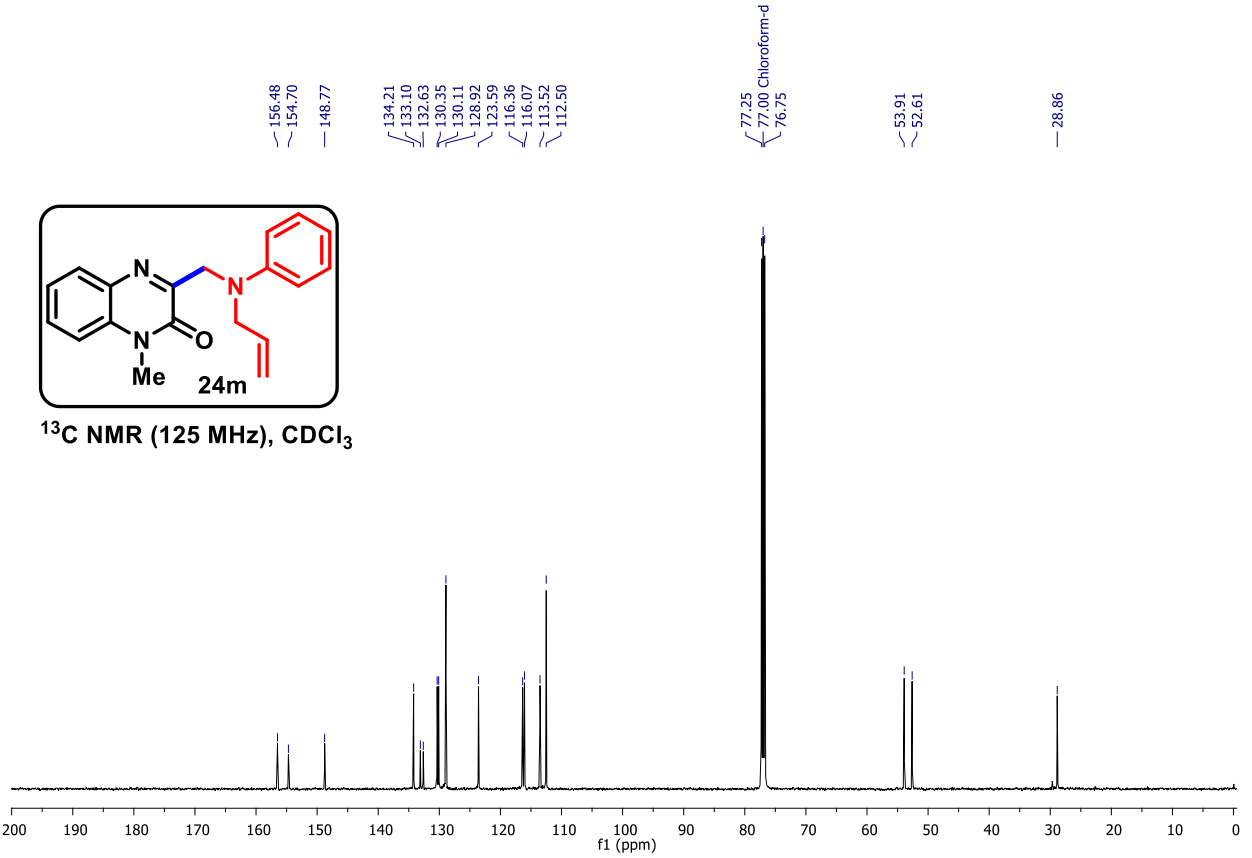

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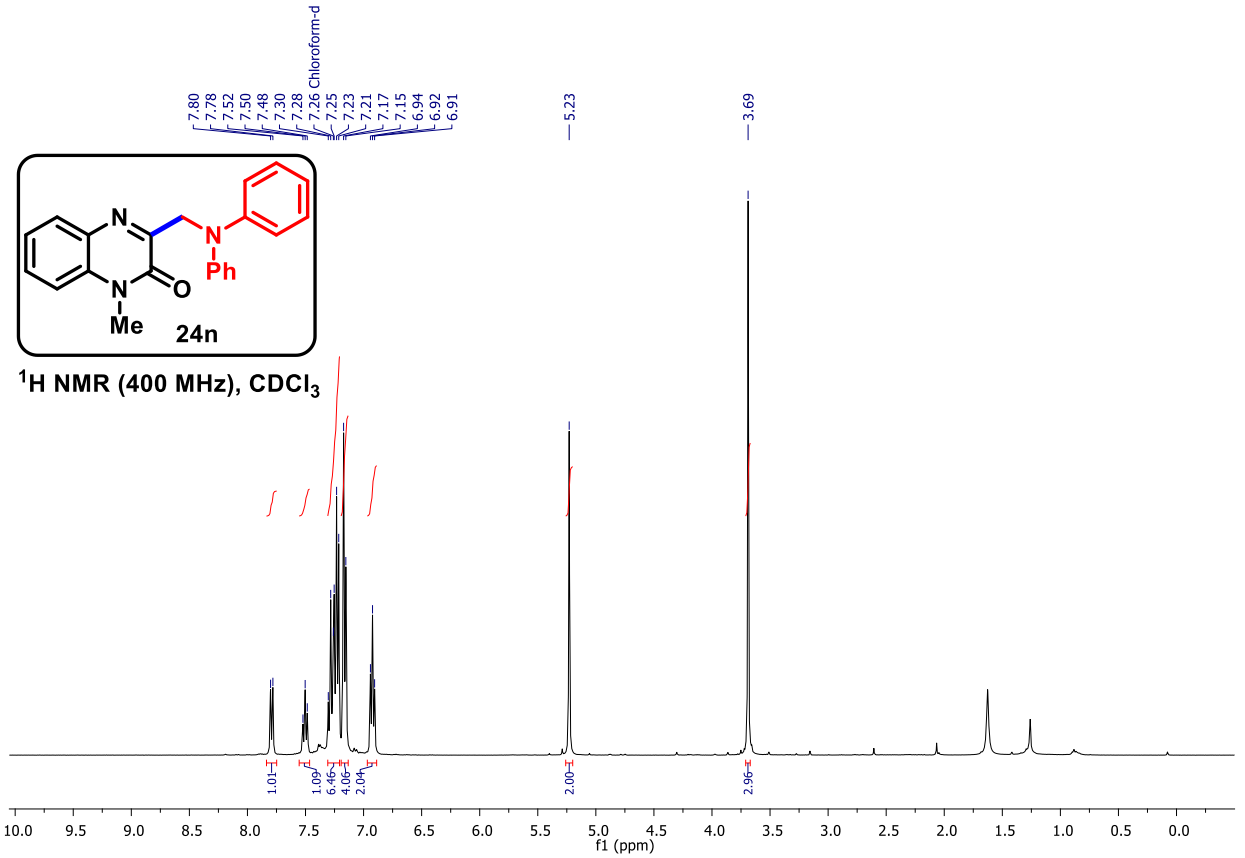

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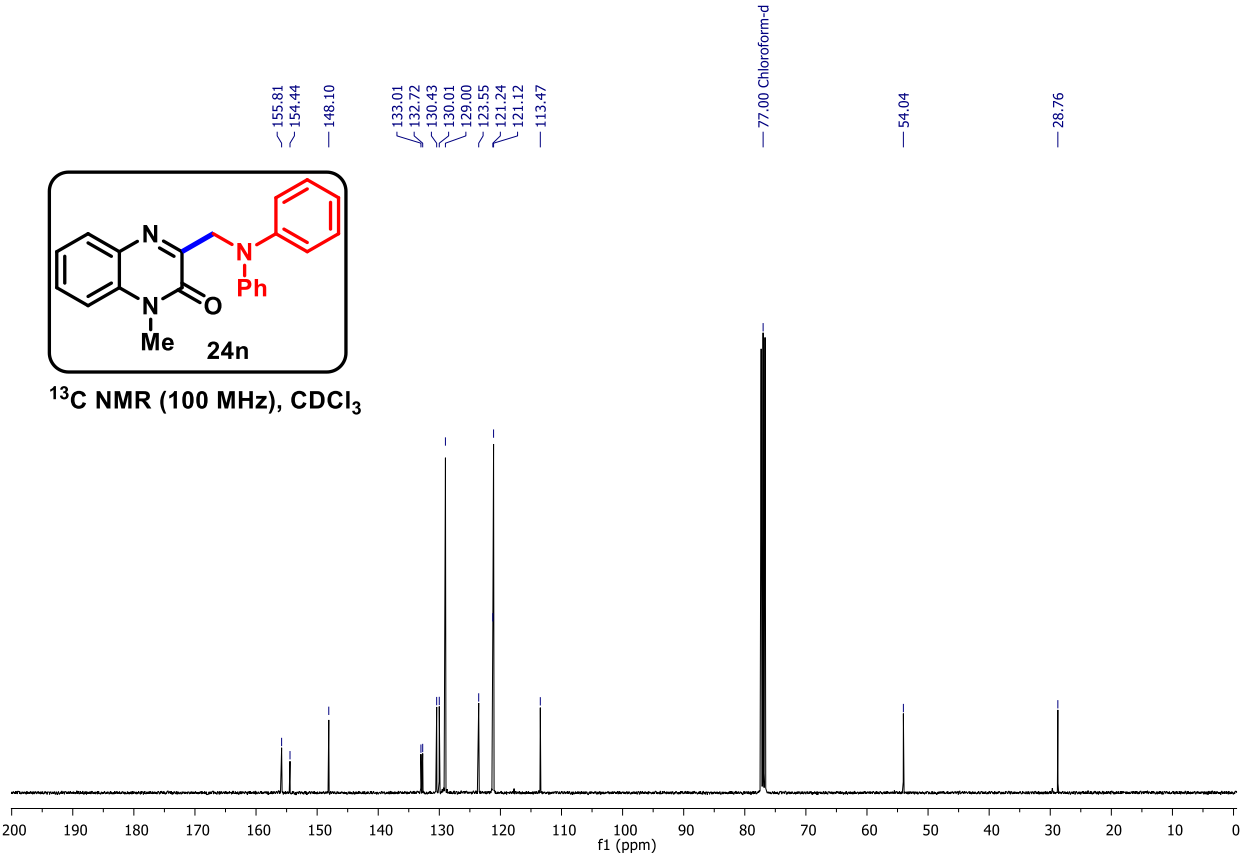

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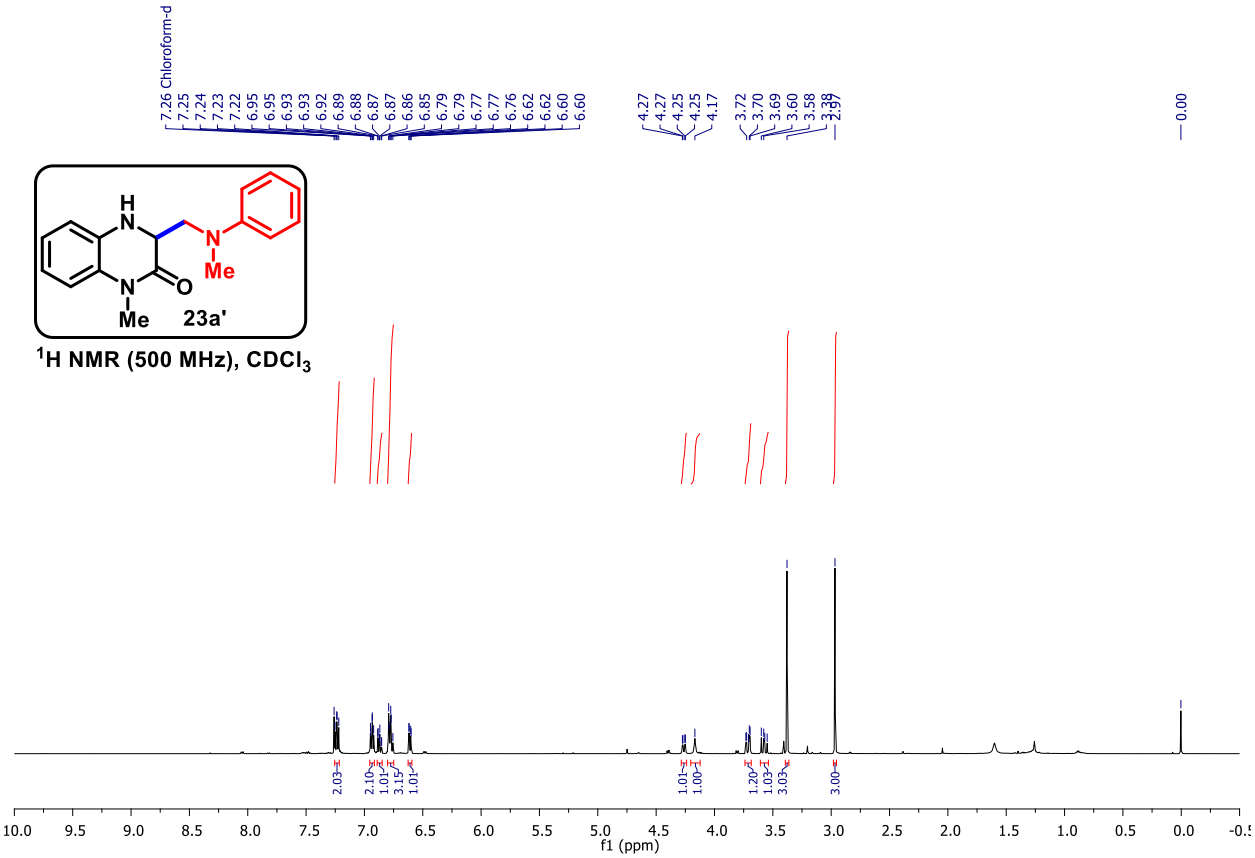

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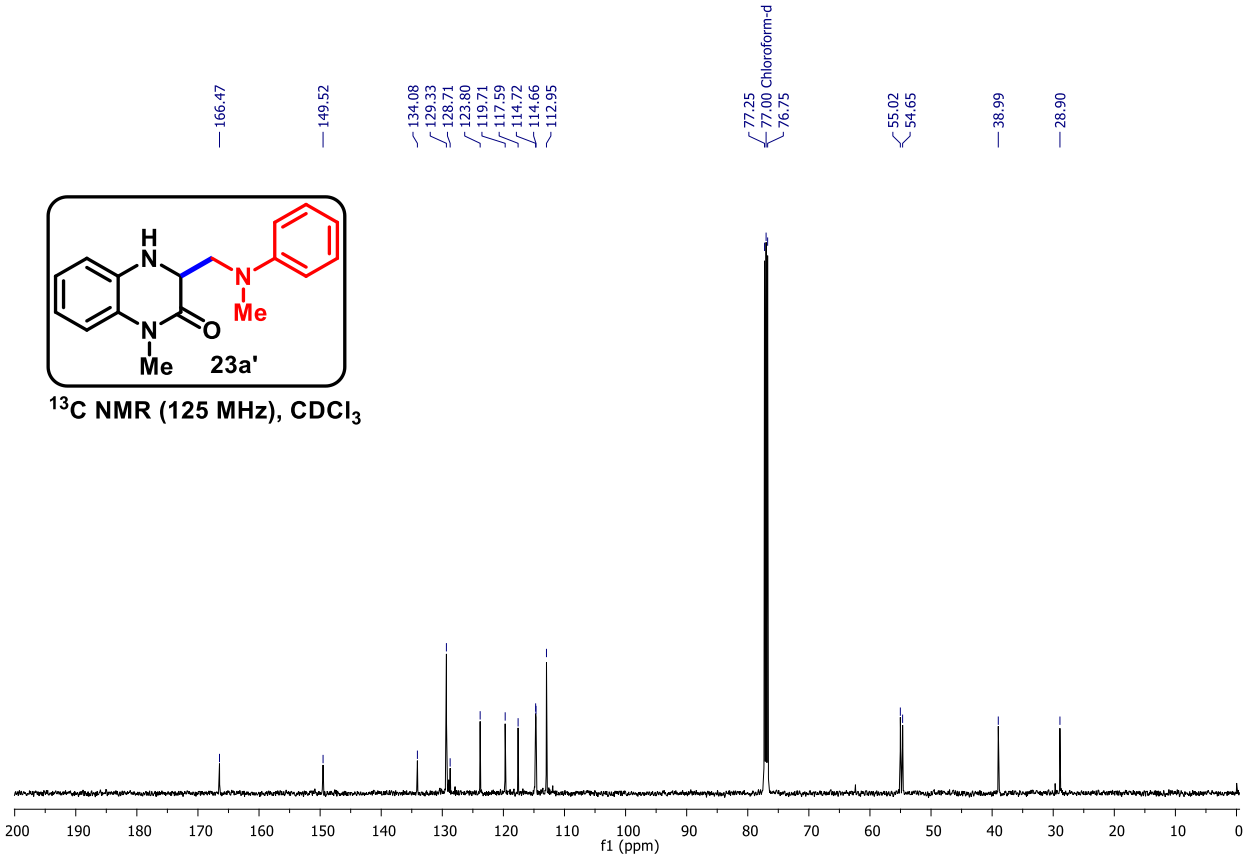

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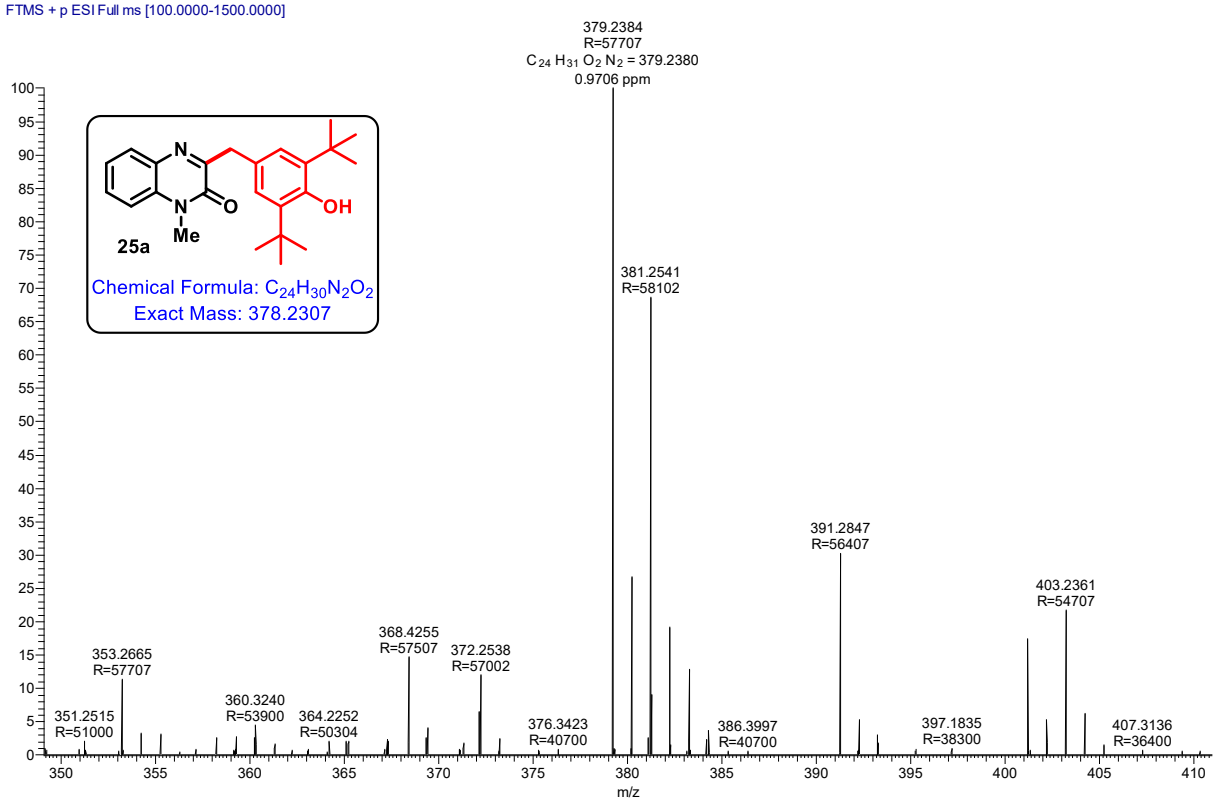

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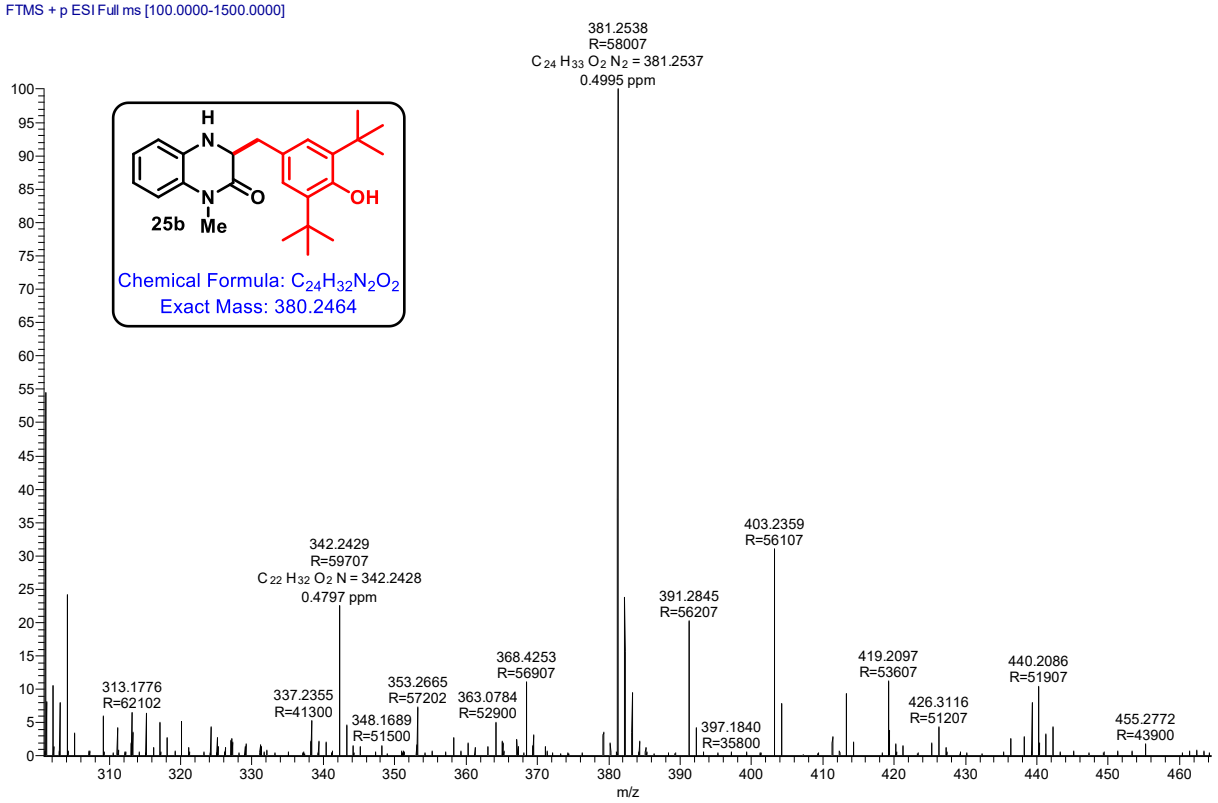

3.2.8 References

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ABSTRACT

Name of the Student: Mr. Devidas Abasaheb More **Registration No.:** 10CC17J26008

Faculty of Study: Chemical Science **Year of Submission:** 2023

AcSIR academic centre/CSIR Lab: **Name of the Supervisor:** Dr. M. Muthukrishnan

CSIR-National Chemical Laboratory, Pune.

Title of the thesis: Development of new carbon-carbon bond forming methodologies for the synthesis of diversely functionalized nitrogen heterocycles

Nitrogen containing heterocycles occupy an important place in organic chemistry due to their profound applications in the fields of drug discovery, medicinal chemistry, agrochemicals, organic materials, and so on. Due to its wide applicability, the synthesis and functionalization of nitrogen-based heterocycles has been a major research area in organic chemistry. Although substantial advances have been made in the area of the synthesis and functionalization of nitrogen-based heterocycles, many challenges and problems remain to be solved. Given the importance of nitrogen containing heterocycles, as part of the present thesis, we developed several novel synthetic strategies for the construction and functionalization of various important nitrogen containing heterocycles such as five & six-membered quinolone fused lactones & lactams, isoquinolin-1(2*H*)-ones and quinoxalin-2(1*H*)-ones using green protocols.

Chapter 1 describes the development of an efficient, greener approach for the synthesis of quinoline fused lactones and lactams. This chapter includes two sections, **Section-I** deals with the synthesis of five-membered quinoline fused lactones and lactams through Oxone promoted dehydrogenative Povarov cyclization of *N*-aryl glycine derivatives, and **Section-II** focus on the synthesis of diverse six-membered quinoline fused lactams that comprises Brønsted acid-catalyzed cyclization reactions of alkyne tethered *N*-aryl glycine amide in the presence of molecular oxygen.

Chapter 2 covers, the development of metal-free CH-functionalization reactions of isoquinolin-1(2*H*)-ones & quinoxalin-2(1*H*)-ones. This chapter includes two sections, **Section-I** deals with the synthesis of C-4 diarylmethylated isoquinolin-1(2*H*)-ones *via* $BF_3 \cdot OEt_2$ catalyzed alkylation of isoquinolin-1(2*H*)-ones with *p*-quinone methides. **Section-II** of this chapter describes the synthesis of C-3 ketoalkylated quinoxalin-2(1*H*)-ones that comprise *β*-ketoalkylation of quinoxalin-2(1*H*)-ones with cyclopropanols under metal-free conditions.

Chapter 3 describes catalyst-free organic reactions *via* electron donor-acceptor (EDA) complexes & its applications. This chapter includes two sections, **Section-I** describe a brief introduction to EDA complexes in organic synthesis, and **Section-II** focus on the metal- and photocatalyst free, visible-light-initiated C3 α-aminomethylation reaction of quinoxalin-2(1*H*)-ones *via* EDA complexes.

List of Publications Emanating from the Thesis work

1. **More, D. A.**; Shinde, G. H.; Shaikh, A. C.; Muthukrishnan, M. Oxone promoted dehydrogenative Povarov cyclization of *N*-aryl glycine derivatives: An approach towards quinoline fused lactones and lactams. *RSC Adv.,* **2019**, *9*, 30277–30291.
2. **More, D. A**.; Mujahid M.; Muthukrishnan, M. Metal- and light-free direct C-3 ketoalkylation of quinoxalin-2(1*H*)-ones with cyclopropanols in aqueous medium. *ChemistrySelect* **2022**, *7*, e202203597.
3. **More, D. A.;** Shirsath, S. R.; Muthukrishnan, M. Metal- and photocatalyst-free, visible-light-initiated C3 α-aminomethylation of quinoxalin-2(1*H*)-ones *via* electron donor-acceptor complexes (*Manuscript Submitted*).
4. **More, D. A.;** Ghotekar, G. S.; Muthukrishnan, M. $BF_3.Et_2O$ catalyzed selective C-4 diaryl methylation of isoquinolin-1(2*H*)-ones employing *p*-quinone methides (*Manuscript under Preparation*).
5. **More, D. A.;** Shirsath, S. R.; Muthukrishnan. M. Bronsted acid-catalyzed metal-free synthesis of substituted quinoline fused lactams from *N*-aryl glycine derivatives (*Manuscript under Preparation*).

List of Publications Non-Emanating from the Thesis Work

1. Ghotekar, G. S.; **More, D. A**.; Muthukrishnan, M. A new enantioselective synthesis of antiobesity drug lorcaserin. *New J. Chem.,* **2019**, *43*, 16876-16880.
2. Shirsath, S. R.; **More, D. A.**; Muthukrishnan, M. Metal-free aminocarbonylation of *p*-quinone methides with isocyanides: Synthesis of sterically hindered α-arylated acetamides. *Chem. Asian. J.* **2022**, *17*, e2022006.

Patents- Nil

List of Posters Presented with Details

1. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, 2019)

Title: Oxone Promoted Dehydrogenative Povarov Cyclization of *N*-Aryl Glycine Derivatives: An Approach Towards Quinoline Fused Lactones and Lactams.

Abstract: Oxone promoted dehydrogenative Povarov cyclization of various glycine derivatives tethered with alkynes to furnish quinoline-fused lactones and lactams. This mild reaction has an excellent functional group tolerance and exhibits a broad substrate scope, allowing a new strategic opportunities for the facile synthesis of a diverse range of quinoline-fused lactones and lactams

2. First Virtual JNOST Conference organized by IISC-Bangalore on 31st Oct-1st Nov 2020.

Title: Oxone Promoted Dehydrogenative Povarov Cyclization of *N*-Aryl Glycine Derivatives: An Approach Towards Quinoline Fused Lactones and Lactams.

Abstract: Oxone promoted intramolecular dehydrogenative imino Diels–Alder reaction (Povarov cyclization) of alkyne tethered *N*-aryl glycine esters and amide has been explored, thus affording biologically significant quinoline fused lactones and lactams. The reaction is simple, scalable, and high yielding (up to 88%). The method was further extended to prepare biologically important luotonin-A analogues and the quinoline core of uncialamycin.

List of Conference Attended with Details

1. Nov 2019- NCL-Research Foundation Annual Students Conference-NCL Pune.
2. January 2020- Advances Organic Synthesis (AOS)- IISER/NCL Pune.
3. First Virtual JNOST Conference organized by IISC-Bangalore on 31st Oct-1st Nov 2020.

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Oxone promoted dehydrogenative Povarov cyclization of *N*-aryl glycine derivatives: an approach towards quinoline fused lactones and lactams†

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Oxone promoted intramolecular dehydrogenative imino Diels–Alder reaction (Povarov cyclization) of alkyne tethered *N*-aryl glycine esters and amides has been explored, thus affording biologically significant quinoline fused lactones and lactams. The reaction is simple, scalable, and high yielding (up to 88%). The method was further extended to prepare biologically important luotonin-A analogues and the quinoline core of uncialamycin.

Introduction

Substituted quinolines are a ubiquitous heterocyclic motif present in a plethora of natural products and medicinal agents,[1] among which quinoline fused lactones and lactams are of great importance due to their presence in complex natural products and pharmaceutically relevant molecules. In addition, they serve as a valuable precursor in the synthesis of biologically active natural products and their analogues such as luotonin-A (cytotoxic alkaloid),[2] uncialamycin (antibiotic),[3] aza podophyllotoxin[4] analogues (antitumor agents) and quinoline carboxamides (radio ligands for molecular imaging).[5] (Fig. 1). Consequently, there is a great deal of attention on the synthesis of these privileged structures. In general, the synthesis of these frameworks is associated with multistep processes as well as usage of toxic reagents.[2e,g,6] Therefore, the development of a general, sustainable and efficient synthetic approach to achieve these functionalized quinoline-fused lactones/lactams is of high value, and it would provide an appropriate platform for the detail biological investigation of these valuable molecules.

In recent years, imino Diels–Alder reaction (Povarov reaction) has received a renewed interest to construct quinoline scaffolds, in which electron-rich alkenes (or alkynes) were added to the electron-deficient aromatic imines followed by oxidation.[7] However, an intramolecular variant of this transformation is less explored compared to intermolecular.[8] In 2009, Weghe *et al.* elegantly utilized intramolecular imino Diels–Alder reaction promoted by $BF_3 \cdot OEt_2$/DDQ for the construction of quinoline fused lactones employing an alkene or alkyne as a dienophile.[9] Despite the merits, there are certain drawbacks associated with this method such as, non-ready availability of the requisite starting materials, requiring a multistep reaction sequences for their synthesis, hazardous and expensive reagents, limited substrate scope, and the method have not been explored for the synthesis of quinoline fused lactams. Later, Jia and Zhang group also explored the concept of cross dehydrogenative coupling (CDC) for the construction quinoline fused lactone/lactam in the presence of TBPA radical cation salt and visible-light photoredox

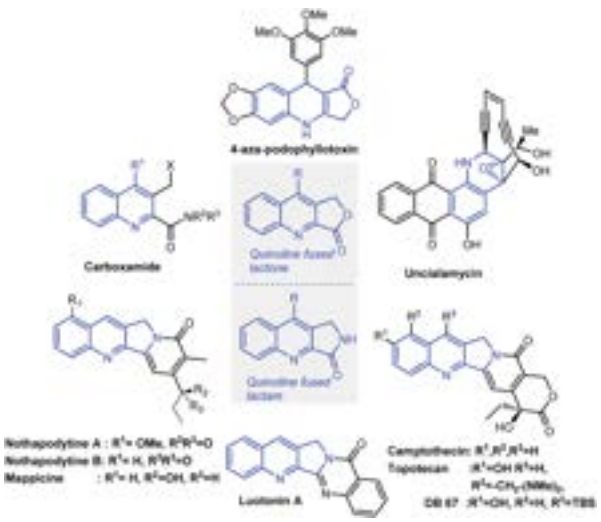

Fig. 1 Examples of pharmaceuticals and natural products containing quinoline-fused lactone/lactam moiety.

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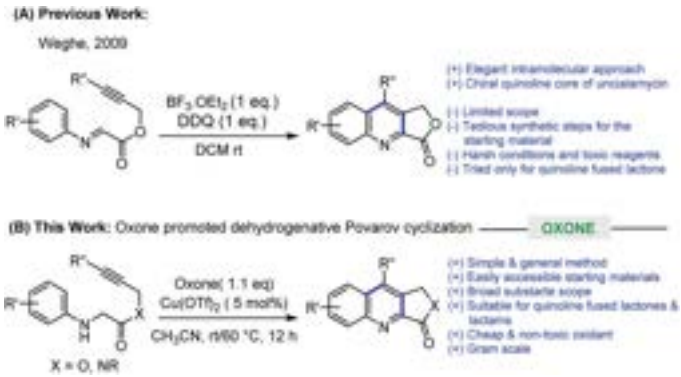


Scheme 1 Intramolecular Povarov cyclization for the synthesis of quinoline fused lactones and lactams.

conditions, respectively.[10] In the context of our ongoing research program dealing with drug discovery, we were encountered with a need for an efficient methodology for the synthesis of quinoline fused lactones and lactams for our internal screening program. While studying the suitability of Weghe's method for our library synthesis, we encountered a difficulty in the preparation of starting imine compounds as the procedures are lengthy along with issues pertinent to their stability. With regard to practicality, we envisioned that alkyne tethered *N*-aryl glycine derivatives would be an ideal substrate for our library synthesis as (i) these substrates are stable and can be easily prepared (ii) in suitable condition, these substrates can undergo oxidative dehydrogenation[11] followed by Povarov cyclization could lead to quinoline fused lactones/lactams.

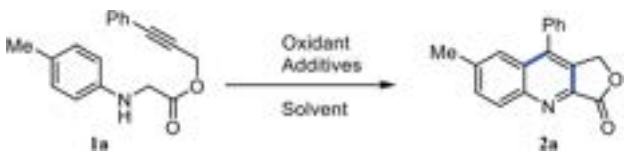
In this manuscript, we wish to disclose the successful realization of this new strategy, which involves Oxone promoted oxidative dehydrogenation followed by intramolecular Povarov cyclization of alkyne tethered *N*-aryl glycine derivatives for the efficient synthesis of quinoline fused lactones/lactams (Scheme 1). Furthermore, to the best of our knowledge, Oxone promoted intramolecular Povarov cyclization of hitherto unknown alkyne tethered *N*-aryl glycine derivatives has not been reported.

Results and discussion

Accordingly, the required starting material alkyne tethered *N*-aryl glycine derivatives were conveniently prepared in two steps from substituted propargyl alcohols (Scheme 2). Initially, we examined the dehydrogenative Povarov cyclization of *N*-aryl glycine ester **1a** as a model substrate by employing 5 mol% $BF_3 \cdot OEt_2$ as a Lewis acid in the presence of IBX as an oxidant at room temperature (Table 1, entry 1).[12] To our delight, as expected, the reaction proceeded smoothly to give the desired product **3a** in 58% yield. Inspired by this initial result, we screened other Lewis acids and found that $Cu(OTf)_2$ is the best among other Lewis acids tried (Table 1, entries 1–4). Next, we studied the effect of various oxidants and observed that peroxide-based oxidants also suitable for this transformation (Table 1, entries 5–8). Interestingly, the reaction proceeded well in the presence of Oxone and 5 mol% of $Cu(OTf)_2$ at room temperature afforded the required product **3a** in 88% yield (Table 1, entry 9). Notably, Oxone would be a favourable oxidant as it is cheap, non-toxic, and

Scheme 2 Synthesis of alkyne tethered *N*-aryl glycine derivatives.

Table 1 Optimization studies[a,b]

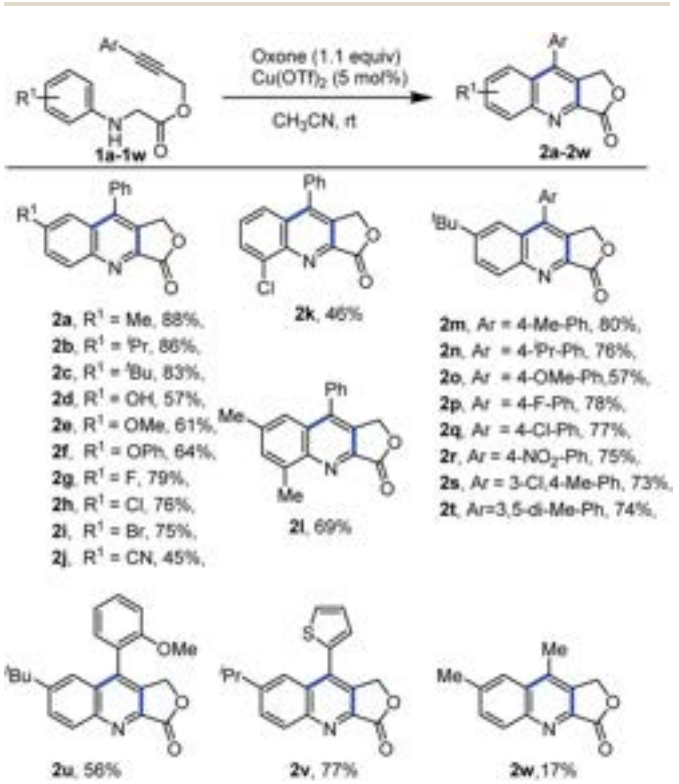


Entry	Oxidant	Additives	Solvent	Yield (%) **3a**
1	IBX	$BF_3 \cdot OEt_2$	CH_3CN	58
2	IBX	$Sc(OTf)_3$	CH_3CN	53
3	IBX	$Cu(OTf)_2$	CH_3CN	68
4	IBX	$Cu(OAc)_2$	CH_3CN	51
5	$PhI(OAc)_2$	$Cu(OTf)_2$	CH_3CN	23
6	$PhI(OCOCF_3)_2$	$Cu(OTf)_2$	CH_3CN	21
7	$Na_2S_2O_8$	$Cu(OTf)_2$	CH_3CN	41
8	BPO	$Cu(OTf)_2$	CH_3CN	49
9	Oxone	$Cu(OTf)_2$	CH_3CN	88
10	Oxone	$Cu(OTf)_2$	THF	42
11	Oxone	$Cu(OTf)_2$	Toluene	Traces
12	Oxone	$Cu(OTf)_2$	$CHCl_3$	<5
13	Oxone	$Cu(OTf)_2$	CH_3CN	89[c]
14	Oxone	—	CH_3CN	60[d]
15	—	$Cu(OTf)_2$	CH_3CN	Traces

[a] Reaction conditions: (1) 0.18 mmol **1a**, 0.20 mmol oxidant, additive (5 mol%) solvent (3.0 mL), 12 h. [b] Isolated yields; rt. [c] 1.3 equiv. of Oxone was employed. [d] 24 h; IBX: 2-iodoxybenzoic acid.

easy to handle.[13] Screening of other solvents for this transformation reveals that CH_3CN is the best solvent of choice (Table 1, entry 9 *vs.* 10–12). Further, not significant improvement in the yield has been observed while using more equiv. of Oxone (Table 1, entry 13). Notably, when we use only Oxone, the desired product formed in a 60% yield albeit in 24 hours (entry 14), which indicates that the Oxone alone can trigger this transformation presumably due to the slightly acidic nature of Oxone ($2KHSO_5$-**$KHSO_4$**-K_2SO_4). Finally, in the absence of Oxone there is only a trace amount of product formation has been observed, which reveals the crucial role of Oxone in this transformation (Table 1, entry 15).

After the optimal reaction condition was established for the construction of quinoline-fused lactones, the scope and generality of this protocol were investigated (Scheme 3). Different electron-donating and electron-withdrawing functional groups on the aniline ring as well as the aryl alkyne part were well tolerated. For example, substrates bearing electron-donating groups such as 4-methyl, 4-isopropyl, and 4-^{t}butyl on aniline ring were compatible with the reaction conditions and provided the desired products **2a**, **2b** and **2c** in 88%, 86% and 83% yields, respectively. However, strong electron-donating such as hydroxy, methoxy, and phenoxy substrates resulted the desired products in moderate yield (**2d–2f**, 57–64%). Additionally, substrates bearing halogen atoms such as F, Cl, and Br successfully reacted under the optimized condition to give the desired product (**2g–2i**) in good yield (75–79%). However, the electron-withdrawing group at the aniline ring also gave the desired product in moderate yield (**2j**, 45%). Furthermore, substitution on the *ortho* position of the aniline ring provided the desired product in moderate yield (**2k**, 46%). Moreover, the di-substituted substrate also underwent smoothly, to achieve the desired product **2l** in 69% yield. Next, we examined the scope of our protocol by altering the substitution on aryl alkyne part of *N*-aryl glycine derivatives. Electron donating and withdrawing substituents on the aryl alkyne part of *N*-aryl glycine derivatives also underwent the reaction smoothly and afforded the product in good yield (**2m–2r**). Further, the present protocol is suitable for *ortho* substitution, disubstitution as well as heteroaryl substitution on aryl alkyne part of the glycine derivatives (**2s–2v**). Alkyl substitution on the alkyne moiety under optimal condition provided the required product **2w**, in less yield.

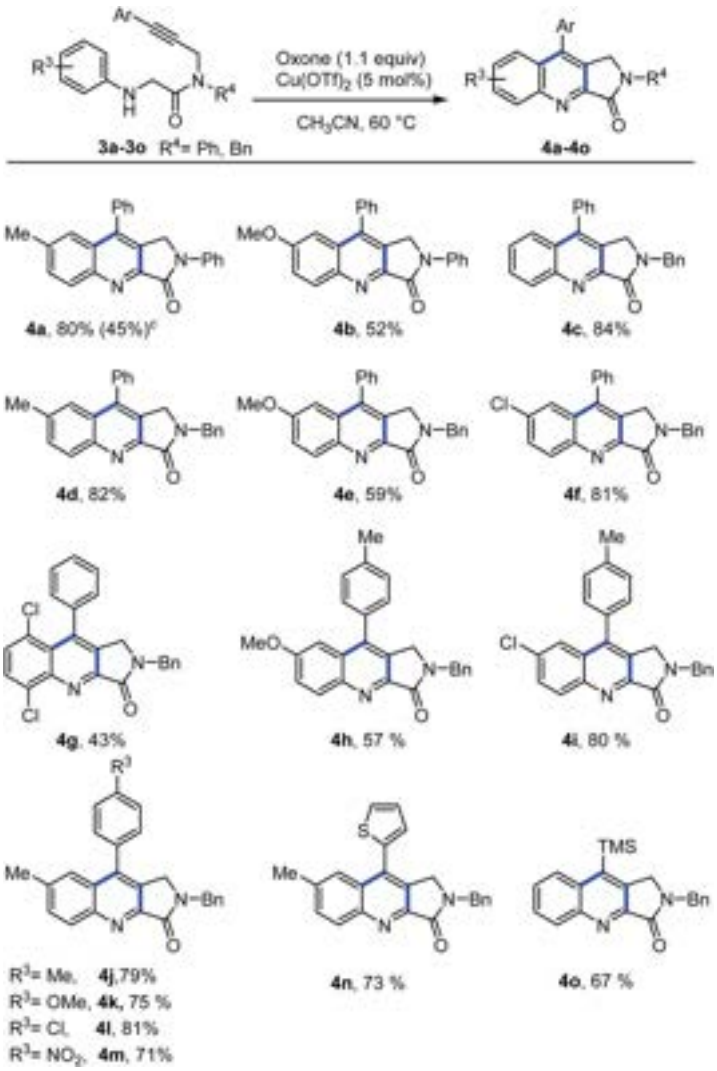


Scheme 3 Intramolecular Povarov cyclization of *N*-aryl glycine esters[a,b]. [a]Reaction conditions: 0.18 mmol **1a**, 0.20 mmol oxidant, 5 mol% of $Cu(OTf)_2$, CH_3CN (3.0 mL), rt, 12 h; [b]isolated yields.

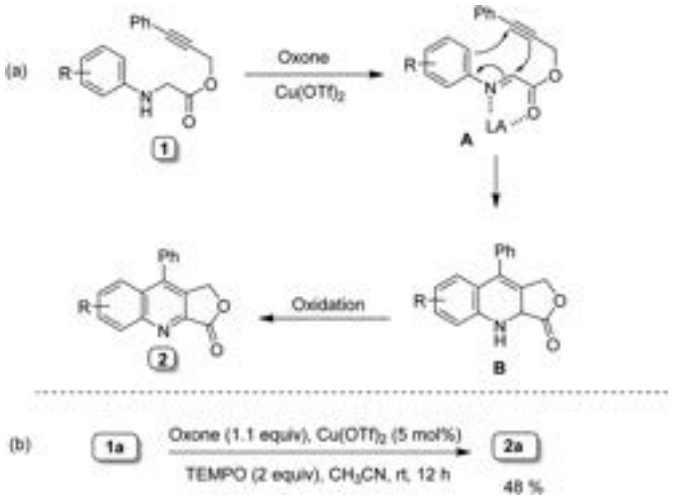
Although the mechanism of this transformation is not fully understood, however, based on the above experiments (Table 1. Entry 14 and 15) and previous literature reports,[14] a tentative reaction mechanism is proposed in Scheme 5a. The first step involves the *in situ* generation of highly reactive imine intermediate **A**, followed by intramolecular cycloaddition to form an intermediate **B**.[7q–t] Further, intermediate **B** undergoes oxidation to form the corresponding fused quinoline **2**. A radical trapping experiment was conducted by employing TEMPO as a radical scavenger and obtained **2a** in 48% yield (Scheme 5b), which indicates that the reaction proceeds *via* non-radical pathway.

The quinoline fused lactone/lactam produced from the method described here may find utility in complex molecule synthesis. Some representative examples are shown in Scheme 6. We utilized this method for the preparation of quinoline core precursor of antitumor antibiotic uncialamycin **6**.[9] Also, compounds **4c**, **4d** can easily be converted into cytotoxic alkaloid luotonin-A analogues.[2f]

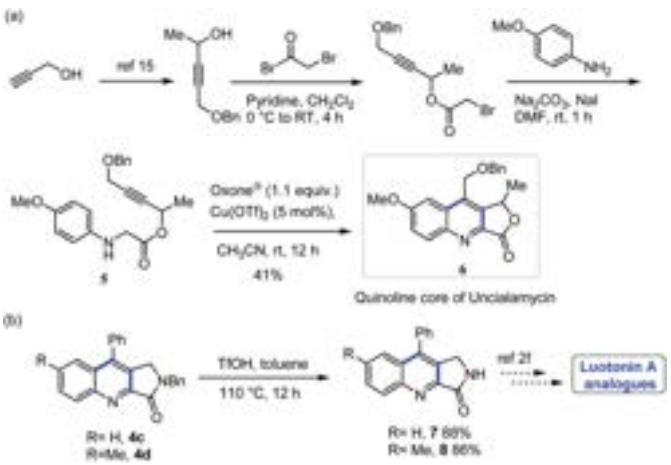
After successful synthesis of quinoline-fused lactones, we further explored the suitability of the present protocol for the synthesis of quinoline-fused lactams. Accordingly, we examined the intramolecular dehydrogenative Povarov cyclization of *N*-aryl glycine amide substrates under our optimized reaction condition and delighted to find that the present protocol is suitable for the construction of quinoline fused lactam as well. However, the reaction requires higher temperature (60 °C) for completion. Various electron donating as well as electron withdrawing substituents on the aniline ring as well as aryl alkyne part of N-protected glycine amide (Ph- and Bn-) such as methyl, methoxy, chloro, di chloro, nitro and thienyl underwent cyclization to furnish the corresponding quinoline-fused lactams in moderate to good yields (Scheme 4). It is noteworthy to mention here that, the substrate bearing a TMS group is also well tolerated (Scheme 4, **4o**) and the resulted product can conveniently be converted into the natural product luotonin A in two steps.[2] To demonstrate the synthetic practicality of the present protocol, we conducted a gram-scale experiment by employing **3c** (2.82 mmol, 1.0 g) under the optimal reaction conditions in which the desired product **4c** was obtained in 80% yield (0.79 g) showing that the present method could be easily adapted for the large-scale synthesis with high efficiency.



Scheme 4 Intramolecular Povarov cyclisation of *N*-aryl glycine amides.[a,b]. [a]Reaction conditions: 0.14 mmol **3a**, 0.15 mmol Oxidant, 5 mol% of $Cu(OTf)_2$, CH_3CN (3.0 mL), 60 °C, 12 h; [b]isolated yields; [c]reaction carried out at room temperature for 12 h.



Scheme 5 A plausible mechanism and control experiment.



Scheme 6 Utility of the reaction.

Conclusions

In conclusion, we have demonstrated Oxone promoted intramolecular dehydrogenative Povarov cyclization of various alkyne tethered *N*-aryl glycine derivatives to furnish biologically relevant quinoline-fused lactones and lactams. This operationally simple, scalable protocol utilizes non-toxic, inexpensive Oxone as an oxidant to furnish the required products in high yield. The method was further utilized for the preparation of cytotoxic alkaloid luotonin-A analogues and quinoline core of uncialamycin. Efforts are underway in our laboratory to extend the application of this method as well as the detail mechanistic investigation.

Experimental section

General information

Where stated, all reagents were purchased from commercial sources and used without further purification. All the substituted propargyl alcohols were prepared using a known literature procedure.[15,16] ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on Bruker AV, 200/400/500, JEOL 400 MHz spectrometers in appropriate solvents using TMS as an internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, ^{1}H NMR δ_H 7.26 and ^{13}C $\{^1$H$\}$ NMR δ_C 77.0 for $CDCl_3$ were used as a reference. Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.1 Hz. Multiplicities of ^{1}H NMR signals are designated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), quin (quintet), sept (septet) bs (broad singlet), m (multiplet), *etc.* Melting points were determined using digital Buchi Melting Point Apparatus B-540 and are uncorrected. Thin layer chromatography was carried out on Merck silica gel 60F254 pre-coated aluminum foil sheets and was visualized using UV light (254 nm) and stained with Ninhydrin. Flash column chromatography was carried out through silica gel (100–200 mesh) using ethyl acetate/hexane as eluent. Structures of the products were identified by ^{1}H NMR, ^{13}C $\{^1$H$\}$ NMR, ^{19}F NMR, HRMS.

General procedure for the synthesis of substituted phenyl propargyl bromo acetate

To a solution of substituted propargyl alcohol (7.56 mmol) and pyridine (9.0 mmol) in anhydrous DCM (15 mL) was added 2-bromoacetyl bromide (8.31 mmol) in DCM (5 mL) at 0 °C under N_2 atmosphere over 30 min. After the addition was complete, the reaction mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), the crude reaction mixture was then poured into water (30 mL) and extracted with DCM (3 × 20 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*, affording the substituted phenyl propargyl bromoacetate which was used directly without further purification.

General procedure for the synthesis of substituted *N*-aryl glycine ester (1a–1w)

A 5 mL Screw Top V vial® was charged with substituted bromoacetate (0.39 mmol), Na_2CO_3 (0.47 mmol), NaI (0.08 mmol), and substituted aniline (0.38 mmol), DMF (2 mL). The solution was stirred at room temperature. After 1 h, the reaction mixture was poured into ice water (10 mL) and extracted with EtOAc (2 × 20 mL). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography by eluting 5–15% of ethyl acetate/petroleum ether (silica gel, 100–200 mesh), to afford substituted *N*-aryl glycine esters (**1a–1w**).

General procedure for the synthesis of substituted *N*-aryl glycine amide (3a–3o)

A 5 mL glass vial® was charged with substituted bromo acetamide (0.3 mmol), Na_2CO_3 (0.36 mmol), NaI (0.061 mmol), substituted aniline (0.29 mmol), DMF (3 mL). The mixture was stirred for 12 h at 60 °C. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, then poured into ice water, extracted with ethyl acetate (20 mL × 2). The organic extracts were combined, washed with brine (15 mL), dried over Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography by eluting 10–20% of ethyl acetate/petroleum ether (silica gel, 100–200 mesh), to afford the substituted *N*-aryl glycine amides (**3a–3o**).

General procedure for the synthesis of quinoline fused lactones (2a–2w)

To a 5 mL Screw Top V vial® containing a stirring mixture of substituted *N*-aryl glycine ester (0.18 mmol), Oxone® (122 mg, 0.20 mmol) in CH_3CN (3 mL) was added $Cu(OTf)_2$ (3.25 mg, 0.009 mmol) and the vial cap was wrapped tightly with a Teflon. The solution was then stirred at room temperature. After 12 h (colorless to dark brown color was observed), the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography by eluting 20–30% of ethyl acetate/petroleum ether (silica gel, 100–200 mesh), to afford the pure substituted quinoline fused lactones (**2a–2w**).

General procedure for the synthesis of quinoline fused lactams (4a–4o)

To a 5 mL Screw Top V vial® containing a stirring mixture of substituted *N*-aryl glycine amide (0.14 mmol), oxone® (92 mg, 0.15 mmol) in CH_3CN (3 mL) was added $Cu(OTf)_2$ (2.64 mg, 0.0073 mmol) and the vial cap was wrapped tightly with a Teflon. The solution was stirred at 60 °C. After 12 h (colorless to dark brown color was observed), the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography by eluting 25–40% of ethyl acetate/petroleum ether (silica gel, 100–200 mesh), to afford the pure substituted quinoline fused lactams (**4a–4o**).

3-Phenylprop-2-yn-1-yl *p*-tolylglycinate (1a). Compound **1a** was isolated in 84% yield (93 mg, yellow solid); mp = 88–90 °C; $R_f = 0.55$ ($V_{PE}/V_{EA} = 90/10$); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 7.48$

(d, J = 7.3 Hz, 2H), 7.38–7.33 (m, 3H), 7.03 (d, J = 7.8 Hz, 2H), 6.58 (d, J = 8.1 Hz, 2H), 5.02 (s, 2H), 4.18 (bs, 1H), 3.99 (s, 2H), 2.26 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.7, 144.6, 131.9, 129.8, 128.8, 128.3, 127.6, 121.9, 113.2, 86.9, 82.3, 53.4, 46.1, 20.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}NO_2$ 280.1332; found 280.1325.

3-Phenylprop-2-yn-1-yl(4-*iso*-propylphenyl)glycinate (1b). Compound **1b** was isolated in 81% yield (98 mg, viscous liquid); R_f = 0.55 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.48 (d, J = 6.3 Hz, 2H), 7.34 (m, 3H), 7.09 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 8.0 Hz, 2H), 5.03 (s, 2H), 4.07 (bs, 1H), 4.00 (s, 2H), 2.83 (sept, J = 6.8 Hz, 1H), 1.23 (d, J = 6.8 Hz, 6H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.7, 144.7, 138.9, 131.8, 128.8, 128.3, 127.1, 121.9, 113.2, 86.9, 82.3, 53.4, 46.1, 33.1, 24.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}NO_2$ 308.1645; found 308.1646.

3-Phenylprop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1c). Compound **1c** was isolated in 80% yield (102 mg, yellow solid); mp = 89–91 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43 (dd, J = 7.7, 1.7 Hz, 2H), 7.29 (m, 3H), 7.20 (d, J = 8.7 Hz, 2H) 6.55 (d, J = 8.7 Hz, 2H), 4.96 (s, 2H), 4.20 (bs, 1H), 3.93 (s, 2H), 1.26 (s, 9H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.7, 144.4, 140.9, 131.8, 128.8, 128.2, 125.9, 121.8, 112.7, 86.9, 82.4, 53.3, 45.9, 33.7, 31.39; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}NO_2$ 322.1802; found 322.1801.

3-Phenylprop-2-yn-1-yl(4-hydroxyphenyl)glycinate (1d). Compound **1d** was isolated in 70% yield (78 mg, viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46–7.42 (m, 2H), 7.36–7.30 (m, 3H), 6.68 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 8.7 Hz, 2H), 4.99 (s, 2H), 3.92 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 171.2, 148.7, 140.6, 131.8, 128.8, 128.3, 121.8, 116.2, 114.9, 86.9, 82.3, 53.5, 46.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3$ 282.1125; found 282.1126.

3-Phenylprop-2-yn-1-yl(4-methoxyphenyl)glycinate (1e). Compound **1e** was isolated in 60% yield (note: decomposition was observed after keeping prolong time in column; brown liquid); R_f = 0.40 (V_{PE}/V_{EA} = 80/20); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47–7.44 (m, 2H), 7.37–7.31 (m, 3H), 6.80 (d, J = 8.8 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 5.00 (s, 2H), 3.96 (s, 2H), 3.74 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.8, 152.7, 141.0, 131.8, 128.8, 128.3, 121.9, 114.9, 114.4, 86.9, 82.4, 55.6, 53.4, 46.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}NO_3$ 296.1281; found 296.1280.

3-Phenylprop-2-yn-1-yl(4-phenoxyphenyl)glycinate (1f). Compound **1f** was isolated in 75% yield (106 mg, off white solid); mp = 109–111 °C; R_f = 0.40 (V_{PE}/V_{EA} = 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (dd, J = 7.6, 1.7 Hz, 2H), 7.39–7.27 (m, 5H), 7.04 (t, J = 7.4 Hz, 1H), 6.95 (dt, J = 7.7, 3.4 Hz, 4H), 6.66–6.61 (m, 2H), 5.04 (s, 2H), 4.26 (bs, 1H), 4.00 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.6, 158.7, 148.4, 143.3, 131.8, 129.4, 128.9, 128.3, 122.0, 121.8, 121.1, 117.2, 114.1, 87.0, 82.3, 53.5, 46.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{20}NO_3$ 358.1438; found 358.1429.

3-Phenylprop-2-yn-1-yl(4-fluorophenyl)glycinate (1g). Compound **1g** was isolated in 78% yield (87 mg, off white solid); mp = 86–88 °C; R_f = 0.40 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, J = 7.3 Hz, 2H), 7.38–7.34 (m, 3H), 6.92 (t, J = 8.6 Hz, 2H), 6.56 (dd, J = 8.7 Hz, 4.2 Hz, 2H), 5.02 (s, 2H), 4.15 (bs, 1H), 3.95 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.5, 156.2 (d, J = 235.9 Hz) 143.2, 131.8, 128.8, 128.3, 121.8, 115.7 (d, J = 22.5 Hz), 113.9 (d, J = 7.5 Hz), 86.9, 82.3, 53.4, 46.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −126.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}FNO_2$ 284.1081; found 284.1075.

3-Phenylprop-2-yn-1-yl(4-chlorophenyl)glycinate (1h). Compound **1h** was isolated in 79% yield (93 mg, off white solid); mp = 83–85 °C; R_f = 0.40 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (d, J = 7.3 Hz, 2H), 7.37–7.31 (m, 3H), 7.14 (d, J = 8.6 Hz, 2H), 6.55 (d, J = 8.6 Hz, 2H), 5.02 (s, 2H), 4.31 (bs, 1H), 3.97 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.3, 145.4, 131.9, 129.2, 128.9, 128.3, 123.1, 121.8, 114.1, 87.1, 82.2, 53.6, 45.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}ClNO_2$ 300.0786; found 300.0780.

3-Phenylprop-2-yn-1-yl(4-bromophenyl)glycinate (1i). Compound **1i** was isolated in 78% yield (107 mg, brown solid); mp = 86–88 °C; R_f = 0.40 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44 (d, J = 6.8 Hz, 2H), 7.37–7.29 (m, 3H), 7.27 (d, J = 8.5 Hz, 2H), 6.48 (d, J = 8.5 Hz, 2H), 5.00 (s, 2H), 4.31 (bs, 1H), 3.94 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.2, 145.8, 132.0, 131.9, 128.9, 128.3, 121.8, 114.6, 110.1, 87.1, 82.2, 53.6, 45.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}BrNO_2$ 344.0281; found 344.0284.

3-Phenylprop-2-yn-1-yl(4-cyanophenyl)glycinate (1j). Compound **1j** crude (90 mg, viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 80/20) R_f = 0.40 (V_{PE}/V_{EA} = 80/20); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44 (d, J = 7.2 Hz, 4H), 7.34 (t, J = 8.1 Hz, 3H), 6.58 (d, J = 8.2 Hz, 2H), 5.03 (s, 2H), 4.87 (s, 1H), 4.01 (d, J = 4.9 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 169.5, 149.9, 133.7, 131.8, 129.0, 128.3, 121.6, 120.0, 112.5, 100.0, 87.2, 81.9, 53.9, 44.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_2$ 291.1178; found 291.1140.

3-Phenylprop-2-yn-1-yl(2-chlorophenyl)glycinate (1k). Compound **1k** was isolated in 68% yield (80 mg, off white solid); mp = 69–71 °C; R_f = 0.40 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54–7.44 (m, 2H), 7.43–7.27 (m, 4H), 7.15 (t, J = 7.7 Hz, 1H), 6.71 (t, J = 7.6 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 5.04 (s, 2H), 4.98 (bs, 1H), 4.05 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.9, 142.7, 131.8, 129.3, 128.9, 128.3, 127.8, 121.8, 119.5, 118.2, 111.2, 87.0, 82.2, 53.6, 45.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}ClNO_2$ 300.0778; found 300.0796.

3-Phenylprop-2-yn-1-yl(2,4-dimethylphenyl)glycinate (1l). Compound **1l** was isolated in 72% yield (83 mg, viscous liquid); R_f = 0.50 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47 (d, J = 7.7 Hz, 2H), 7.38–7.31 (m, 3H), 6.94 (s, 1H), 6.92 (s, 1H), 6.43 (d, J = 7.9 Hz, 1H), 5.02 (s, 2H), 4.03 (s, 2H) 2.24 (s, 3H), 2.21 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.9, 142.6, 131.9, 131.2, 128.9, 128.3, 127.3, 127.2, 122.8, 121.9, 110.2, 86.9, 82.3, 53.5, 46.1, 20.3, 17.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}NO_2$ 294.1489, found 294.1476.

3-(*p*-Tolyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1m). Compound **1m** was isolated in 77% yield (97 mg, off white solid); mp = 85–87 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.34 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 7.7 Hz, 2H), 6.57 (d, J = 8.3 Hz, 2H), 4.99 (s, 2H), 3.96 (s, 2H), 2.34 (s, 3H), 1.27 (s, 9H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.8, 144.4, 141.1, 139.1, 131.8, 129.0, 126.1, 118.8, 112.8, 87.2, 81.7, 53.6, 46.0, 33.8, 31.5, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}NO_2$ 336.1958; found 336.1969.

3-(4-*iso*-Propylphenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1n). Compound **1n** was isolated in 76% yield (93 mg, off white solid); mp = 86.5–88.5 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.58 (d, J = 8.6 Hz, 2H), 4.99 (s, 2H), 3.96 (s, 2H), 3.86 (bs, 1H), 2.89 (sept, J = 6.9 Hz, 1H), 1.26 (s, 9H), 1.23 (d, J = 6.9 Hz, 6H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.8, 149.9, 144.4, 141.1, 131.9, 126.4, 126.1, 119.2, 112.8, 87.2, 81.6, 53.6, 46.0, 34.0, 33.8, 31.4, 23.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{30}NO_2$ 364.2271; found 364.2272.

3-(4-Methoxyphenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1o). Compound **1o** was isolated in 75% yield (93 mg, viscous liquid); R_f = 0.45 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, J = 7.7 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 6.93 (d, J = 7.9 Hz, 2H), 6.67 (d, J = 8.1 Hz, 2H), 5.08 (s, 2H), 4.31 (bs, 1H), 4.05 (s, 2H), 3.86 (s, 3H), 1.38 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.7, 159.9, 144.4, 140.9, 133.3, 125.9, 114.7, 113.8, 112.7, 86.9, 81.0, 55.1, 53.5, 45.8, 33.7, 31.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}NO_3$ 352.1907; found 352.1906.

3-(4-Fluorophenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1p). Compound **1p** was isolated in 72% yield (90 mg, off white solid); mp = 78.5–80.5 °C; R_f = 0.50 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42 (dd, J = 8.7, 5.4 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 7.00 (t, J = 8.7 Hz, 2H), 6.58 (d, J = 8.6 Hz, 2H), 4.98 (s, 2H), 3.97 (s, 2H), 1.27 (s, 9H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.8, 162.8 (d, J = 250.2 Hz), 144.4, 141.2, 133.9 (d, J = 8.5 Hz), 126.1, 117.9 (d, J = 3.4 Hz), 115.6 (d, J = 22.2 Hz), 112.8, 85.9, 82.1, 53.3, 45.9, 33.8, 31.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −109.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{23}FNO_2$ 340.1707; found 340.1709.

3-(4-Chlorophenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1q). Compound **1q** was isolated in 72% yield (89 mg, off white solid); mp = 76–78 °C; R_f = 0.52 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 6.59 (d, J = 8.7 Hz, 2H), 5.00 (s, 2H), 4.00 (s, 2H), 1.28 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.8, 144.4, 141.2, 135.0, 133.1, 128.7, 126.1, 120.4, 112.8, 85.8, 83.3, 53.3, 46.0, 33.9, 31.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{23}ClNO_2$ 356.1412; found 356.1405.

3-(4-Nitrophenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1r). Compound **1r** was isolated in 70% yield (86 mg, yellow solid); mp = 76.5–78.5 °C; R_f = 0.45 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 5.02 (s, 2H), 4.00 (s, 2H), 1.27 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.7, 147.4, 144.3, 141.2, 132.5, 128.7, 126.1, 123.5, 112.8, 87.6, 84.8, 52.9, 45.9, 33.8, 31.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_4$ 367.1652; found 367.1658.

3-(3-Chloro-4-methylphenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1s). Compound **1s** was isolated in 68% yield (83 mg, off white solid); mp = 66.5–68.5 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47 (d, J = 1.0 Hz, 1H), 7.29–7.24 (m, 3H), 7.20 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 8.6 Hz, 2H), 5.02 (s, 2H), 4.01 (s, 2H), 3.46 (bs, 1H), 2.40 (s, 3H), 1.30 (s, 9H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.8, 144.4, 141.2, 137.3, 134.2, 132.2, 130.8, 130.0, 126.1, 120.9, 112.8, 85.7, 82.8, 53.4, 46.0, 33.9, 31.5, 20.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{25}ClNO_2$ 370.1568; found 370.1570.

3-(3,5-Dimethylphenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1t). Compound **1t** was isolated in 69% yield (86 mg, off white solid); mp = 89–91 °C; R_f = 0.55 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 (d, J = 8.2 Hz, 2H), 7.08 (s, 2H), 6.96 (s, 1H), 6.57 (d, J = 8.1 Hz, 2H), 4.97 (s, 2H), 3.95 (s, 2H), 2.27 (s, 6H), 1.26 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.7, 144.4, 141.0, 137.8, 130.7, 129.5, 126.0, 121.5, 112.8, 87.3, 81.6, 53.5, 45.9, 33.8, 31.4, 20.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}NO_2$ 350.2115; found 350.2109.

3-(2-Methoxyphenyl)prop-2-yn-1-yl(4-(*tert*-butyl)phenyl)glycinate (1u). Compound **1u** was isolated in 69% yield (86 mg, yellow solid); mp = 96–98 °C; R_f = 0.45 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 6.88 (dd, J = 7.5 Hz, 8.5 Hz, 2H), 6.57 (d, J = 8.3 Hz, 2H), 5.05 (s, 2H), 4.18 (bs, 1H), 3.96 (s, 2H), 3.86 (s, 3H), 1.27 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 170.7, 160.2, 144.4, 140.9, 133.9, 130.4, 126.0, 120.4, 112.7, 110.9, 110.6, 86.2, 83.4, 55.7, 53.7, 45.9, 33.8, 31.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}NO_3$ 352.1907; found 352.1899.

3-(Thiophen-2-yl)prop-2-yn-1-yl(4-*iso*-propylphenyl)glycinate (1v). Compound **1v** was isolated in 69% yield (84 mg, viscous liquid); R_f = 0.50 (V_{PE}/V_{EA} = 95/5); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28 (d, J = 5.1 Hz, 1H), 7.25 (d, J = 3.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.97 (dd, J = 4.9, 3.9 Hz, 1H), 6.57 (d, J = 8.4 Hz, 2H), 5.01 (s, 2H), 3.97 (s, 2H), 3.54 (bs, 1H), 2.80 (sept, J = 6.9 Hz, 1H), 1.20 (d, J = 6.9 Hz, 6H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.7, 144.8, 138.9, 133.1, 128.0, 127.2, 126.9, 121.8, 113.2, 86.4, 80.4, 53.5, 46.1, 33.1, 24.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}NO_2S$ 314.1209; found 314.1210.

But-2-yn-1-yl *p*-tolylglycinate (1w). Compound **1w** was isolated in 60% yield (94 mg, viscous liquid); R_f = 0.5 (V_{PE}/V_{EA} = 90/10); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.99 (d, J = 8.1 Hz, 2H), 6.52 (d, J = 8.3 Hz, 2H), 4.72 (s, 2H), 4.09 (bs, 1H), 3.91 (s, 2H), 2.23 (s, 3H), 1.85 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 170.7, 144.5, 129.7, 127.4, 113.1, 83.7, 72.6, 53.4, 45.9, 20.3, 3.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}NO_2$ 218.1178.; found 218.1176.

***N*-Phenyl-*N*-(3-phenylprop-2-yn-1-yl)-2-(*p*-tolylamino)acetamide (3a).** Compound **3a** was isolated in 73% yield (79 mg, off white solid); mp = 94.2–96.2 °C; R_f = 0.40 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55–7.47 (m, 3H), 7.38 (d, J = 7.0 Hz, 2H), 7.35 (d, J = 7.3 Hz, 2H), 7.32–7.26 (m, 3H), 6.93 (d, J = 8.0 Hz, 2H),

6.39 (d, J = 8.0 Hz, 2H), 4.77 (s, 2H), 4.59 (bs, 1H), 3.58 (s, 2H), 2.21 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 169.3, 145.1, 140.0, 131.6, 129.9, 129.6, 129.1, 128.4, 128.3, 128.2, 126.9, 122.6, 113.1, 84.5, 83.9, 46.6, 39.4, 20.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}N_2O$ 355.1805; found 355.1807.

2-((4-Methoxyphenyl)amino)-*N*-phenyl-*N*-(3-phenylprop-2-yn-1-yl)acetamide (3b). Compound **3b** was isolated in 41% yield (46 mg, brown liquid); R_f = 0.35 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$, starting material was not stable) δ = 7.49 (d, J = 7.3 Hz, 2H), 7.39–7.33 (m, 5H), 7.32–7.25 (m, 3H), 6.71 (d, J = 8.8 Hz, 2H), 6.43 (d, J = 8.8 Hz, 2H), 4.75 (s, 2H), 3.69 (s, 3H), 3.55 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.4, 152.3, 141.6, 139.9, 131.7, 131.6, 129.9, 129.1, 128.8, 128.4, 128.3, 128.2, 114.7, 114.3, 84.4, 83.9, 55.7, 47.1, 39.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_2$ 371.1754; found 371.1755.

***N*-Benzyl-2-(phenylamino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (3c).**[17,18] Compound **3c** was isolated in 76% yield (79 mg, off white solid); mp = 95.5–97.5 °C; R_f = 0.40 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.98 ratio) δ = 7.44–7.39 (rotameric m, 6H, aromatic) 7.34 (rotameric m, 14H, aromatic), 7.21 (rotameric quin, 4H, aromatic), 6.79–6.73 (rotameric m, 2H, aromatic), 6.71 (d, J = 8.0 Hz, 2H, aromatic) and 6.61 (d, J = 7.9 Hz, 2H, aromatic) (rotameric), 4.93 (rotameric bs, 2H, **NH**), 4.84 (s, 2H, C**H$_2$**) and 4.76 (s, 2H, C**H$_2$**) (rotameric), 4.56 (s, 2H, C**H$_2$**) and 4.00 (s, 2H, C**H$_2$**) (rotameric), 4.21 (s, 2H, C**H$_2$**) and 4.16 (s, 2H, C**H$_2$**) (rotameric); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 169.5 and 162.4 (rotameric **C=O**), 147.4 and 147.3 (rotameric), 136.5 and 135.6 (rotameric), 131.9 (rotameric), 129.4 and 129.4 (rotameric), 129.2 and 128.9 (rotameric), 128.8 and 128.6 (rotameric), 128.5 and 128.4 (rotameric), 128.2 and 127.9 (rotameric), 126.8 (rotameric), 122.6 and 122.0 (rotameric), 117.8 (rotameric), 113.2 and 113.1 (rotameric), 85.2 and 84.5 (rotameric **C**alkyne), 83.7 and 82.7 (rotameric **C**alkyne), 49.4 and 49.3 (rotameric **C**H$_2$), 45.6 and 45.5 (rotameric **C**H$_2$), 36.4 and 35.7 (rotameric **C**H$_2$); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}N_2O$; 355.1805 found 355.1798.

***N*-Benzyl-*N*-(3-phenylprop-2-yn-1-yl)-2-(*p*-tolylamino)acetamide (3d).** Compound **3d** was isolated in 74% yield (80 mg, off white solid); mp = 93–95 °C; R_f = 0.40 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.98 ratio) δ = 7.43 (rotameric m, 6H, aromatic), 7.35 (rotameric m, 14H, aromatic), 7.06 (d, J = 8.0 Hz, 2H, aromatic) and 7.02 (d, J = 8.0 Hz, 2H, aromatic) (rotameric), 6.66 (d, J = 8.1 Hz, 2H, aromatic) and 6.56 (d, J = 8.1 Hz, 2H, aromatic) (rotameric), 4.85 (s, 2H, C**H$_2$**) and 4.76 (s, 2H, C**H$_2$**) (rotameric), 4.57 (s, 2H, C**H$_2$**) and 4.00 (s, 2H, C**H$_2$**) (rotameric) 4.21 (s, 2H, C**H$_2$**) and 4.15 (s, 2H, C**H$_2$**) (rotameric), 2.29 (s, 3H, 4-**CH$_3$** aniline) and 2.27 (s, 3H, 4-**CH$_3$** aniline) (rotameric); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$ rotamers) δ = 169.5 and 169.4 (rotameric **C=O**), 145.1 and 145.0 (rotameric) 136.4 and 135.5 (rotameric), 131.7, 129.7 and 129.6 (rotameric), 129.0 and 128.7 (rotameric), 128.6 and 128.4 (rotameric), 128.3 and 128.2 (rotameric), 127.9 and 127.7 (rotameric), 126.8 and 128.6 (rotameric), 122.4 and 121.9 (rotameric), 113.1, 84.9 and 84.2 (rotameric **C**alkyne), 83.6 and 82.6 (rotameric **C**alkyne), 49.2 and 49.1 (rotameric **C**H$_2$), 45.8 and 45.7 (rotameric **C**H$_2$), 36.2 and 35.5 (rotameric **C**H$_2$), 20.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{25}N_2O$ 369.1961; found 369.1958.

***N*-Benzyl-2-((4-methoxyphenyl)amino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (3e).** Compound **3e** crude (note: crude was recrystallize in *n*-hexane) mp = 79–81 °C; R_f = 0.35 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.97 ratio) δ = 7.45–7.26 (m, 20H, aromatic) (rotameric), 6.85–6.72 (m, 4H, aromatic) (rotameric), 6.66 (d, J = 8.6 Hz, 2H, aromatic) and 6.56 (d, J = 8.5 Hz 2H, aromatic) (rotameric), 4.80 (s, 2H, C**H$_2$**) and 4.74 (s, 2H, C**H$_2$**) (rotameric), 4.53 (s, 2H, C**H$_2$**) and 3.95 (s, 2H, C**H$_2$**), (rotameric), 4.19 (s, 2H, C**H$_2$**) and 4.11 (s, 2H, C**H$_2$**) (rotameric), 3.75 (s, 3H, O**Me**) and 3.73 (s, 3H, O**Me**) (rotameric); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ = 169.7 and 169.6 (rotameric **C=O**), 152.3 and 152.2 (rotameric), 141.7 and 141.6 (rotameric), 136.4 and 135.5 (rotameric), 131.7 (rotameric), 129.1 and 128.3 (rotameric), 128.8 and 128.7 (rotameric), 128.5 and 128.4 (rotameric), 128.0 and 127.8 (rotameric), 126.7 (rotameric), 122.5 and 121.9 (rotameric), 114.9 and 114.9 (rotameric), 114.4 (rotameric), 84.9 and 84.3 (rotameric **C**alkyne), 83.6 and 82.6 (rotameric **C**alkyne), 55.8 (O**Me**) 49.2 and 49.1 (rotameric **C**H$_2$), 46.5 and 46.4 (rotameric **C**H$_2$), 36.3 and 35.5 (rotameric **C**H$_2$); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_2$ 385.1911; found 385.1911.

***N*-Benzyl-2-((4-chlorophenyl)amino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (3f).** Compound **3f** was isolated in 74% yield (42 mg, brown solid); mp = 91–93 °C; R_f = 0.40 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.98 ratio) δ = 7.40–7.26 (m, 20H, aromatic) (rotameric), 7.11 (dd, J = 11.5, 8.6 Hz, 4H, aromatic) (rotameric), 6.59 (d, J = 8.3 Hz, 2H) and 6.48 (d, J = 8.4 Hz, 2H, aromatic) (rotameric), 4.80 (s, 2H, C**H$_2$**) and 4.73 (s, 2H, C**H$_2$**) (rotameric), 4.53 (s, 2H, C**H$_2$**) and 3.93 (s, 2H, C**H$_2$**) (rotameric), 4.17 (s, 2H, C**H$_2$**) and 4.09 (s, 2H, C**H$_2$**) (rotameric); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ = 169.0 and 168.8 (rotameric **C=O**), 145.8 and 145.7 (rotameric), 136.2 and 135.3 (rotameric), 131.7 (rotameric), 129.1 (rotameric) 129.1 and 129.0 (rotameric), 128.8 and 128.7 (rotameric), 128.5 and 128.3 (rotameric), 128.4 and 128.3 (rotameric), 128.1 and 127.8 (rotameric), 126.6 (rotameric), 122.4 and 122.2 (rotameric), 114.0 and 114.0 (rotameric), 85.1 and 84.5 (rotameric **C**alkyne), 83.4 and 82.4 (rotameric **C**alkyne), 49.2 (rotameric **C**H$_2$), 45.4 (rotameric **C**H$_2$), 36.3 and 35.6 (rotameric **C**H$_2$); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{22}ClN_2O$ 389.1415; found 389.1422.

***N*-Benzyl-2-((2,5-dichlorophenyl)amino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (3g).** Compound **3g** was isolated in 61% yield (76 mg, viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.97 ratio) δ = 7.49–7.28 (m, 20H, aromatic) (rotameric), 7.18 (t, J = 7.9 Hz, 2H, aromatic), (rotameric), 6.62 (t, J = 8.1 Hz, 2H, aromatic) (rotameric), 6.58 (s, 1H, aromatic) and 6.41 (s, 1H, aromatic) (rotameric), 5.72 (bs, 2H, **NH**) (rotameric), 4.83 (s, 2H, C**H$_2$**) and 4.76 (s, 2H, C**H$_2$**) (rotameric), 4.56 (s, 2H, C**H$_2$**) and 4.20 (s, 2H, C**H$_2$**) (rotameric), 4.13 (s, 2H, C**H$_2$**) and 3.98 (s, 2H, C**H$_2$**) (rotameric); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ = 168.4 and 168.3 (rotameric **C=O**), 144.0, 136.3 and 135.3 (rotameric), 133.6 and 133.5 (rotameric), 131.9, 130.1 and 129.4 (rotameric), 129.0, 128.9 and 128.7 (rotameric), 128.6 and 128.4 (rotameric), 128.3 and 128.1 (rotameric), 126.8, 122.5 and 121.9 (rotameric), 118.0,

117.3, 111.3 and 111.2 (rotameric), 85.5 and 84.6 (rotameric **C**alkyne), 83.4 and 82.4 (rotameric **C**alkyne), 49.5 and 49.4 (rotameric **C**H_2), 45.0, 36.5 and 35.9 (rotameric **C**H_2); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{21}Cl_2N_2O$ $(M + H)^+$ 423.1025; found 423.1016.

***N*-Benzyl-2-((4-methoxyphenyl)amino)-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)acetamide (3h).** Compound **3i** was isolated in 68% yield (76 mg, off white solid); mp = 115.5–117.5 °C; R_f = 0.35 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.98 ratio) δ = 7.41–7.31 (m, 14H aromatic) (rotameric), 7.15 (d, J = 7.9 Hz, 4H, aromatic) (rotameric), 6.81 (dd, J = 9.0, 8.1 Hz, 4H, aromatic) (rotameric), 6.69 (d, J = 7.8 Hz, 2H, aromatic) and 6.58 (d, J = 7.8 Hz, 2H, aromatic) (rotameric), 4.83 (s, 2H, C**H**$_2$) and 4.75 (s, 2H, C**H**$_2$) (rotameric), 4.63 (bs, 2H, **NH**) (rotameric), 4.55 (s, 2H, C**H**$_2$) and 3.96 (s, 2H, C**H**$_2$) (rotameric), 4.19 (s, 2H, C**H**$_2$) and 4.12 (s, 2H, C**H**$_2$) (rotameric), 3.76 (s, 3H, O**CH**$_3$) and 3.75 (s, 3H, O**CH**$_3$) (rotameric), 2.37 (s, 3H, 4-**Me**Ph) and 2.36, (s, 3H, 4-**Me**Ph), (rotameric); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$ rotamers) δ = 169.6 and 169.5 (rotameric **C**=**O**), 152.2, 141.7 and 141.6 (rotameric), 138.9 and 138.5 (rotameric), 136.4 and 135.5 (rotameric), 131.5, 129.0 and 128.9 (rotameric), 128.6 and 128.3 (rotameric), 127.8 and 127.6 (rotameric), 126.6, 119.3 and 118.8 (rotameric), 114.8 and 114.8 (rotameric), 114.2, 85.0 and 84.3 (rotameric **C**alkyne), 82.8 and 81.9 (rotameric **C**alkyne), 55.6, 49.1 and 49.0 (rotameric **C**H_2), 46.4 and 46.3 (rotameric **C**H_2), 36.3 and 35.5 (rotameric **C**H_2), 21.3; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_2$ 399.2067; found 399.2065.

***N*-Benzyl-2-((4-chlorophenyl)amino)-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl) acetamide (3i).** Compound **3j** was isolated in 71% yield (80 mg, off white solid); mp = 96–98 °C; R_f = 0.35 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.9 ratio) δ = ^{1}H NMR (400 MHz, DMSO) δ 7.44–7.28 (m, 14H, aromatic) (rotameric), 7.13 (t, J = 8.5 Hz, 8H, aromatic) (rotameric), 6.61 (d, J = 8.5 Hz, 2H, aromatic) and 6.50 (d, J = 8.5 Hz, 2H, aromatic) (rotameric), 4.96 (bs, 2H, **NH**) (rotameric), 4.82 (s, 2H, C**H**$_2$) and 4.74 (s, 2H, C**H**$_2$) (rotameric), 4.54 (s, 2H, C**H**$_2$) and 3.93 (s, 2H, C**H**$_2$) (rotameric), 4.18 (s, 2H, C**H**$_2$) and 4.10 (s, 2H, C**H**$_2$) (rotameric), 2.36 (s, 6H, $NHCH_2$ 4-**Me**Ph) (rotameric); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ = 169.0 and 168.9 (rotameric **C**=**O**), 145.8 and 145.7 (rotameric), 139.0 and 138.6 (rotameric), 136.3 and 135.4 (rotameric), 131.6, 129.1 and 129.0 (rotameric), 128.7 and 128.4 (rotameric), 128.0 and 127.8 (rotameric), 126.6, 122.2, 119.3 and 118.7 (rotameric), 114.0, 85.3 and 84.5 (rotameric **C**alkyne), 82.6 and 81.7 (rotameric **C**alkyne), 49.2, 45.4 and 45.3 (rotameric **C**H_2), 36.3 and 35.7 (rotameric **C**H_2), 21.4; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{24}ClN_2O$ 403.1572; found 403.1570.

***N*-Benzyl-*N*-(3-(*p*-tolyl)prop-2-yn-1-yl)-2-(*p*-tolylamino)acetamide (3j).** Compound **3h** was isolated in 77% yield (83 mg, off white solid); mp = 106–108 °C; R_f = 0.35 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.97 ratio) δ = 7.42–7.29 (m, 14H, aromatic) (rotameric), 7.14 (t, J = 7.1 Hz, 4H, aromatic) (rotameric), 7.03 (dd, J = 12.4, 8.1 Hz, 4H, aromatic) (rotameric), 6.65 (d, J = 7.9 Hz, 2H, aromatic) and 6.54 (d, J = 7.9 Hz, 2H, aromatic) (rotameric), 4.83 (s, 2H, C**H**$_2$) and 4.76 (s, 2H, C**H**$_2$) (rotameric), 4.55 (s, 2H, C**H**$_2$) and 3.98 (s, 2H, C**H**$_2$) (rotameric), 4.20 (s, 2H, C**H**$_2$) and 4.14 (s, 2H, C**H**$_2$) (rotameric), 2.38 (s, 3H, $NHCH_2$ 4-**Me**Ph) and 2.37 (s, 3H, $NHCH_2$ 4-**Me**Ph) (rotameric), 2.28 (s, 3H, 4-**Me** aniline) and 2.26 (s, 3H, 4-**Me** aniline) (rotameric); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$ rotamers) δ = 169.5 and 169.4 (rotameric C=O), 145.1 and 145.0 (rotameric), 138.9 and 138.5 (rotameric), 136.4 and 135.5 (rotameric), 131.6, 129.7 and 129.7 (rotameric), 129.1 and 129.0 (rotameric), 128.9, 128.6 and 128.4 (rotameric), 127.9 and 128.4 (rotameric), 126.8 and 126.7 (rotameric), 119.3 and 118.8 (rotameric), 113.2, 85.1 and 84.4 (rotameric **C**alkyne), 82.8 and 81.9 (rotameric **C**alkyne), 49.1 and 49.0 (rotameric **C**H_2), 45.8 and 45.8 (rotameric **C**H_2), 36.3 and 35.5 (rotameric **C**H_2), 21.4 and 20.3 (rotameric, N–CH_2, 4-Ph**C**H_3); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{27}N_2O$ 383.2118; found 383.2115.

***N*-Benzyl-*N*-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-2-(*p*-tolylamino) acetamide (3k).** Compound **3k** was isolated in 71% yield (76 mg, viscous liquid); R_f = 0.35 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.96 ratio) δ = 7.39–7.24 (m, 14H, aromatic) (rotameric), 6.98 (dd, J = 13.3, 8.1 Hz, 4H, aromatic) (rotameric), 6.80 (dd, J = 7.9, 6.0 Hz, 4H, aromatic) (rotameric), 6.60 (d, J = 8.0 Hz, 2H, aromatic) and 6.49 (d, J = 8.0 Hz, 2H, aromatic) (rotameric), 4.78 (s, 2H, C**H**$_2$) and 4.70 (s, 2H, C**H**$_2$) (rotameric), 4.50 (s, 2H, C**H**$_2$) and 3.93 (s, 2H, C**H**$_2$) (rotameric), 4.13 (s, 2H, C**H**$_2$) and 4.09 (s, 2H, C**H**$_2$) (rotameric), 3.76 (s, 6H, O**CH**$_3$) (rotameric), 2.23 (s, 3H, Ph**CH**$_3$) and 2.21 (s, 3H, Ph**CH**$_3$) (rotameric); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ = 169.5 and 169.3 (rotameric), 159.8 and 159.6 (rotameric), 145.0 and 144.9 (rotameric), 136.4 and 135.5 (rotameric), 133.1, 129.7 and 129.6 (rotameric), 128.9 and 128.7 (rotameric), 128.6 and 128.3 (rotameric), 127.8 and 127.6 (rotameric), 126.7 and 126.6 (rotameric), 114.4 and 114.3 (rotameric), 113.9 and 113.8 (rotameric), 113.2 and 113.1 (rotameric), 84.8 and 84.1 (rotameric **C**alkyne), 82.0 and 81.2 (rotameric **C**alkyne), 55.14 (rotameric O**CH**$_3$), 49.1 and 49.0 (rotameric **CH**$_2$), 45.8 and 45.7 (rotameric **C**H_2), 36.3 and 35.5 (rotameric **C**H_2), 20.3; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_2$ $(M + H)^+$ 399.2067; found 399.2075.

***N*-Benzyl-*N*-(3-(4-chlorophenyl)prop-2-yn-1-yl)-2-(*p*-tolylamino) acetamide (3l).** Compound **3l** was isolated in 73% yield (81 mg, viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.88 ratio) δ = 7.42–7.21 (m, 18H, aromatic) (rotameric), 6.99 (dd, J = 12.0, 8.2 Hz, 4H, aromatic) (rotameric), 6.60 (d, J = 8.1 Hz, 2H, aromatic) and 6.51 (d, J = 8.1 Hz, 2H, aromatic) (rotameric), 4.78 (s, 2H, C**H**$_2$) and 4.71 (s, 2H, C**H**$_2$) (rotameric), 4.50 (s, 2H, C**H**$_2$) and 3.96 (s, 2H, C**H**$_2$) (rotameric), 4.16 (s, 2H, C**H**$_2$) and 4.09 (s, 2H, C**H**$_2$) (rotameric), 2.24 (s, 3H, NHPh**CH**$_3$) and 2.22 (s, 3H, NHPh**CH**$_3$) (rotameric); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ = 169.5, 145.0 and 144.9 (rotameric), 136.3 and 135.4 (rotameric), 134.8 and 134.4 (rotameric), 132.9, 129.7 and 129.6 (rotameric), 129.0, 128.7, 128.6 and 128.4 (rotameric), 128.0 and 127.7 (rotameric), 126.9 and 126.6 (rotameric), 120.9 and 120.3 (rotameric), 113.16, 84.7 and 83.0 (rotameric **C**alkyne), 83.8 and 83.7 (rotameric **C**alkyne), 49.3 and 49.2 (rotameric **C**H_2), 45.81, 36.2 and 35.5 (rotameric **C**H_2), 20.3; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{24}ClN_2O$ $(M + H)^+$ 403.1572; found 403.1584.

***N*-Benzyl-*N*-(3-(4-nitrophenyl)prop-2-yn-1-yl)-2-(*p*-tolylamino) acetamide (3m).** Compound **3m** was isolated in 65% yield (69 mg, viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.86 ratio) δ = 8.20 (m, 4H,

aromatic) (rotameric), 7.52 (d, J = 7.5 Hz, 4H, aromatic) (rotameric), 7.46–7.29 (m, 10H, aromatic) (rotameric), 7.08–6.99 (m, 4H, aromatic) (rotameric), 6.65 (d, J = 6.8 Hz, 2H, aromatic) and 6.56 (d, J = 7.4 Hz, 2H, aromatic) (rotameric), 4.84 (s, 2H, C**H**$_2$) and 4.77 (s, 2H, C**H**$_2$) (rotameric), 4.58 (s, 2H, C**H**$_2$) and 4.28 (s, 2H, C**H**$_2$), (rotameric), 4.15 (s, 2H, C**H**$_2$) and 4.03 (s, 2H, C**H**$_2$) (rotameric), 2.27 (s, 6H, NHPhC**H**$_3$) (rotameric). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ = 169.7 and 169.5 (rotameric **C**=**O**), 147.4 and 147.2 (rotameric), 145.0 and 144.9 (rotameric), 136.1 and 135.2 (rotameric), 132.5 and 132.4 (rotameric), 129.8 and 129.7 (rotameric), 129.3 and 129.1 (rotameric), 128.8 and 128.4 (rotameric), 128.2 and 127.9 (rotameric), 127.2 and 127.1 (rotameric), 126.8 and 126.7 (rotameric), 123.6 and 123.5 (rotameric), 113.2 (rotameric), 89.3 and 88.1 (rotameric **C**alkyne), 83.1 and 82.3 (rotameric **C**alkyne), 49.7 and 49.1 (rotameric **C**H$_2$), 45.9 and 45.8 (rotameric **C**H$_2$), 36.3 and 35.7 (rotameric **C**H$_2$), 20.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{24}N_3O_3$ $(M + H)^+$ 414.1812; found 414.1817.

***N*-Benzyl-*N*-(3-(thiophen-2-yl)prop-2-yn-1-yl)-2-(*p*-tolylamino) acetamide (3n).** Compound **3n** was isolated in 74% yield (79 mg, viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (500 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.98 ratio) δ = 7.36–7.26 (m, 8H) (rotameric), 7.20 (dd, J = 13.2, 6.2 Hz, 3H, aromatic) (rotameric), 7.15 (dd, J = 9.0, 4.6 Hz, 3H, aromatic) (rotameric), 6.98 (d, J = 7.9 Hz, 2H, aromatic) and 6.94 (d, J = 7.9 Hz, 2H, aromatic) (rotameric), 6.92–6.88 (m, 2H, aromatic) (rotameric), 6.58 (d, J = 8.0 Hz, 2H, aromatic) and 6.47 (d, J = 8.0 Hz, 2H, aromatic) (rotameric), 4.74 (s, 2H, **CH$_2$**) and 4.61 (s, 2H, **CH$_2$**) (rotameric), 4.47 (s, 2H, **CH$_2$**) and 3.89 (s, 2H, **CH$_2$**) (rotameric), 4.11 (s, 2H, **CH$_2$**) and 4.03 (s, 2H, **CH$_2$**) (rotameric), 2.22 (s, 3H, NHPh**CH$_3$**) and 2.20 (s, 3H, NHPh**CH$_3$**) (rotameric); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, rotamers) δ = 169.7 and 169.6 (rotameric **C**=**O**), 145.3 and 145.2 (rotameric), 136.5 and 135.6 (rotameric), 132.9 and 132.6 (rotameric), 129.9 and 129.9 (rotameric), 129.2 and 129.0 (rotameric), 128.9 and 128.6 (rotameric), 128.2 and 127.5 (rotameric), 127.92 and 127.84 (rotameric), 127.2 and 127.1 (rotameric), 126.9 and 126.9 (rotameric), 122.6 and 121.9 (rotameric), 113.4 and 113.3 (rotameric), 88.0 and 86.9 (rotameric **C**alkyne), 78.5 and 77.7 (rotameric **C**alkyne), 49.5 and 49.4 (rotameric **C**H$_2$), 45.9, 36.6 and 35.8 (rotameric **C**H$_2$), 20.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}N_2OS$ $(M + H)^+$ 375.1526; found 375.1533.

***N*-Benzyl-2-(phenylamino)-*N*-(3-(trimethylsilyl)prop-2-yn-1-yl) acetamide (3o).** Compound **3k** was isolated in 65% yield (64 mg, viscous liquid); R_f = 0.40 (V_{PE}/V_{EA} = 80/20); ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture found in 1 : 0.96 ratio) δ = ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–6.96 (m, 14H) (rotameric), 6.59–6.54 (m, 2H) (rotameric), 6.50 (d, J = 7.8 Hz, 2H) and 6.39 (d, J = 7.6 Hz, 2H) (rotameric), 4.71 (bs, 2H, **NH**) (rotameric), 4.57 (s, 2H, C**H$_2$**) and 4.50 (s, 2H, C**H$_2$**) (rotameric), 4.17 (s, 2H, C**H$_2$**) and 3.88 (s, 2H, C**H$_2$**) (rotameric), 3.79 (s, 2H, C**H$_2$**) and 3.75 (s, 2H, C**H$_2$**) (rotameric), 0.00 (s, 9H, **TMS**) and 0.00 (s, 9H, **TMS**) (rotameric); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, rotamers) δ = 169.3 and 169.1 (rotameric **C**=**O**), 147.3 and 147.2 (rotameric), 136.3 and 135.4 (rotameric), 129.2 and 129.1 (rotameric), 128.9 and 126.6 (rotameric), 128.6 and 128.4 (rotameric), 127.9 and 127.7 (rotameric), 117.6 (rotameric), 112.9 (rotameric), 99.7 and 98.8 (rotameric), 90.5 and 89.6 (rotameric), 49.1 and 49.0 (rotameric), 45.4 and 45.3 (rotameric), 36.4 and 35.7 (rotameric), −0.2 and 0.3 (rotameric **TMS**); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{27}N_2OSi$ 351.1878; found 351.1895.

5-(Benzyloxy)pent-3-yn-2-yl(4-methoxyphenyl)glycinate (5). Compound **5** was isolated in 62% yield (70 mg, viscous liquid); R_f = 0.35 (V_{PE}/V_{EA} = 70/30); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.27 (m, 5H), 6.76 (d, J = 8.9 Hz, 2H), 6.62 (d, J = 8.9 Hz, 2H), 5.56 (q, J = 6.7 Hz, 1H), 4.73 (bs, 1H), 4.54 (s, 2H), 4.16 (d, J = 1.6 Hz, 2H), 3.87 (s, 2H), 3.68 (s, 3H), 1.50 (d, J = 6.7 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.9, 152.9, 139.9, 137.0, 128.2, 127.9, 127.7, 114.9, 114.6, 84.2, 81.1, 71.4, 61.1, 56.9, 55.4, 46.9, 21.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}NO_4$ 354.1700; found 354.1692.

7-Methyl-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2a). Compound **2a** was isolated in 88% yield (43 mg, off white solid); mp = 198–200 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 8.7 Hz, 1H), 7.67 (dd, J = 8.7, 1.7 Hz, 1H), 7.64–7.57 (m, 4H), 7.46–7.42 (m, 2H), 5.35 (s, 2H), 2.50 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.9, 149.3, 143.2, 142.8, 139.9, 133.7, 133.1, 132.5, 130.9, 129.4, 129.3, 128.8, 127.9, 124.2, 67.8, 22.1; HRMS (ESI-TOF) m/z: [M + H]+ calcd for $C_{18}H_{14}NO_2$ 276.1019; found 276.1016.

7-*iso*-Propyl-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2b). Compound **2b** was isolated in 86% yield (43 mg, off white solid); mp = 197–199 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.67–7.58 (m, 4H), 7.45 (d, J = 6.7 Hz, 2H), 5.37 (s, 2H), 3.05 (Sept, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.9, 150.5, 149.7, 143.4, 143.1, 133.8, 132.4, 131.3, 130.5, 129.4, 129.3, 128.8, 127.9, 121.7, 67.8, 34.5, 23.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}NO_2$ 304.1332; found 304.1328.

7-(*tert*-Butyl)-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2c). Compound **2c** was isolated in 83% yield (41 mg, off white solid); mp = 236–238 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.33 (d, J = 8.9 Hz, 1H), 7.93 (dd, J = 8.9, 1.9 Hz, 1H), 7.82 (d, J = 1.9 Hz, 1H), 7.64–7.57 (m, 3H), 7.46 (dd, J = 5.0, 2.8 Hz, 2H), 5.37 (s, 2H), 1.32 (s, 9H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 168.9, 152.6, 149.2, 143.4, 133.6, 132.4, 130.7, 129.8, 129.4, 129.2, 128.8, 127.5, 120.3, 67.8, 35.3, 30.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{20}NO_2$ 318.1489; found 318.1483.

7-Hydroxy-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2d). Compound **2d** was isolated in 57% yield (28 mg, off white solid); mp = 259–261 °C; R_f = 0.30 (V_{PE}/V_{EA} = 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.73 (s, 1H), 8.16 (d, J = 9.2 Hz, 1H), 7.64 (m, 2H), 7.61–7.57 (m, 3H), 7.54 (dd, J = 9.2, 2.7 Hz, 1H), 7.17 (d, J = 2.7 Hz, 1H), 5.43 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.1, 158.9, 146.6, 142.4, 141.4, 134.8, 134.3, 133.3, 130.3, 129.8, 129.7, 129.6, 124.0, 106.8, 68.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}NO_3$ 278.0812; found 278.0809.

7-Methoxy-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2e). Compound **2e** was isolated in 61% yield (30 mg, off white solid); mp = 242.5–244.5 °C; R_f = 0.35 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.31 (d, J = 9.3 Hz, 1H), 7.61 (m,

3H), 7.49 (dd, J = 9.3, 2.6 Hz, 1H), 7.45 (d, J = 7.1 Hz, 2H), 7.10 (d, J = 2.6 Hz, 1H), 5.34 (s, 2H), 3.80 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 168.9, 160.1, 147.0, 141.8, 141.7, 133.9, 133.1, 132.8, 129.5, 129.4 (two ^{13}C), 128.6, 123.9, 102.9, 67.7, 55.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{14}NO_3$ 292.0968; found 292.0965.

7-Phenoxy-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2f). Compound **2f** was isolated in 64% yield (32 mg, off white solid); mp = 232–234 °C; R_f = 0.35 (V_{PE}/V_{EA} = 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (d, J = 9.3 Hz, 1H), 7.55 (m, 4H), 7.43–7.33 (m, 5H), 7.16 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 7.9 Hz, 2H), 5.38 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.7, 158.0, 155.7, 147.5, 143.0, 142.4, 133.3, 133.3, 132.9, 130.0, 129.5, 129.3 (two ^{13}C), 128.7, 124.5, 123.9, 119.6, 110.9, 67.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{16}NO_3$ 354.1125; found 354.1121.

7-Fluoro-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2g). Compound **2g** was isolated in 79% yield (39 mg, off white solid); mp = 218–220 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (dd, J = 9.4, 5.6 Hz, 1H), 7.65–7.58 (m, 4H), 7.49 (dd, J = 9.8, 2.8 Hz, 1H), 7.46–7.42 (m, 2H), 5.39 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.4, 162.2 (d, J = 253.1 Hz), 147.7, 143.8 (d, J = 2.8 Hz), 143.3 (d, J = 6.4 Hz), 133.9 (d, J = 9.6 Hz), 132.9 (d, J = 5.9 Hz), 129.8, 129.5, 129.0 (d, J = 9.9 Hz), 128.6, 121.4 (d, J = 26.5 Hz), 109.1 (d, J = 23.6 Hz), 67.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −107.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}FNO_2$ 280.0768; found 280.0765.

7-Chloro-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2h). Compound **2h** was isolated in 76% yield (38 mg, off white solid); mp = 216–218 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, J = 9.1 Hz, 1H), 7.80 (s, 1H), 7.72–7.65 (m, 1H), 7.65–7.55 (m, 3H), 7.47–7.42 (m, 2H), 5.36 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.2, 148.7, 144.3, 143.0, 135.6, 133.1, 132.7, 132.5, 131.6, 129.7, 129.4, 128.7, 128.3, 124.4, 67.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}ClNO_2$ 296.0473; found 296.0469.

7-Bromo-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2i). Compound **2i** was isolated in 75% yield (37 mg, yellow solid); mp = 219–221 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.26 (d, J = 9.1 Hz, 1H), 8.03 (d, J = 1.2 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.65–7.59 (m, 3H), 7.44 (d, J = 7.4 Hz, 2H), 5.39 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 168.2, 149.2, 144.6, 143.1, 134.3, 133.1, 132.8, 129.9, 129.5, 128.9, 128.7, 127.9, 124.2, 67.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}BrNO_2$ 339.9968; found 339.9963.

3-Oxo-9-phenyl-1,3-dihydrofuro[3,4-*b*]quinoline-7-carbonitrile (2j). Compound **2j** was isolated in 45% yield (23 mg, viscous liquid); $\boldsymbol{R_f}$ = 0.40 (V_{PE}/V_{EA} = 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51 (d, J = 8.8 Hz, 1H), 8.30 (d, J = 1.5 Hz, 1H), 7.97 (dd, J = 8.7, 1.7 Hz, 1H), 7.71–7.62 (m, 3H), 7.47–7.42 (m, 2H), 5.45 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 167.7, 151.2, 146.9, 145.1, 133.5, 132.8, 132.4, 131.9, 130.9, 130.4, 129.7, 128.7, 127.2, 117.9, 112.9, 67.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{11}N_2O_2$ 287.0778.; found 287.0824.

5-Chloro-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2k). Compound **2k** was isolated in 51% yield (25 mg, off white solid); mp = 246–248 °C; R_f = 0.40 (V_{PE}/V_{EA} = 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (dd, J = 7.4, 0.8 Hz, 1H), 7.86–7.80 (m, 1H), 7.64–7.55 (m, 4H), 7.45 (dd, J = 7.7, 1.6 Hz, 2H), 5.39 (s, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 167.9, 147.1, 144.7, 135.8, 133.2, 130.8, 129.8, 129.4, 129.3, 128.9, 128.8 (two ^{13}C), 124.9, 67.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}ClNO_2$ 296.0478.; found 296.0480.

5,7-Dimethyl-9-phenylfuro[3,4-*b*]quinolin-3(1*H*)-one (2l). Compound **2l** was isolated in 69% yield (34 mg, off white solid); mp = 177–179 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63–7.54 (m, 3H), 7.52 (s, 1H), 7.45 (s, 1H), 7.43–7.41 (m, 2H), 5.33 (s, 2H), 2.90 (s, 3H), 2.45 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.3, 148.6, 142.7, 142.0, 139.5, 139.1, 134.1, 133.1, 132.4, 129.2, 129.1, 128.8, 128.0, 122.2, 67.7, 22.1, 18.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{16}NO_2$ 290.1176; found 290.1173.

7-(*tert*-Butyl)-9-(*p*-tolyl)furo[3,4-*b*]quinolin-3(1*H*)-one (2m). Compound **2m** was isolated in 80% yield (39 mg, pale yellow solid); mp = 205–207 °C; R_f = 0.40(V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (d, J = 8.8 Hz, 1H), 7.93 (dd, J = 9.0, 2.1 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 5.37 (s, 2H), 2.49 (s, 3H), 1.33 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.0, 152.4, 149.3, 143.6, 143.4, 139.5, 132.4, 130.7, 130.6, 129.9, 129.7, 128.7, 127.6, 120.4, 67.9, 35.4, 30.9, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}NO_2$ 332.1645; found 332.1642.

7-(*tert*-Butyl)-9-(4-isopropylphenyl)furo[3,4-*b*]quinolin-3(1*H*)-one (2n). Compound **2n** was isolated in 76% yield (38 mg, off white solid); mp = 239–241 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.89 (s, 1H), 7.46 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 5.40 (s, 2H), 3.05 (sept, J = 6.8 Hz, 1H), 1.36 (d, J = 7.1 Hz, 6H), 1.35 (s, 9H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 169.1, 152.4, 150.3, 149.4, 143.6, 143.5, 132.5, 131.0, 130.8, 129.7, 128.9, 127.7, 127.3, 120.5, 68.0, 35.4, 34.0, 30.9, 23.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{26}NO_2$ 360.1958; found 360.1953.

7-(*tert*-Butyl)-9-(4-methoxyphenyl)furo[3,4-*b*]quinolin-3(1*H*)-one (2o). Compound **2o** was isolated in 57% yield (28 mg, off white solid); mp = 262–264 °C; R_f = 0.35 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.34 (d, J = 9.0 Hz, 1H), 7.93 (dd, J = 9.0, 1.7 Hz, 1H), 7.88 (s, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 5.39 (s, 2H), 3.94 (s, 3H), 1.35 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.1, 160.4, 152.4, 149.3, 143.5, 143.3, 132.5, 130.8, 130.3, 129.7, 127.8, 125.7, 120.4, 114.7, 67.9, 55.4, 35.4, 30.9; HRMS (ESI-TOF) m/z: [M + H]+ calcd for $C_{22}H_{22}NO_3$ 348.1594; found 348.1589.

7-(*tert*-Butyl)-9-(4-fluorophenyl)furo[3,4-*b*]quinolin-3(1*H*)-one (2p). Compound **2p** was isolated in 78% yield (39 mg, yellow solid); mp = 299–301 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, J = 9.0 Hz, 1H), 7.93 (dd, J = 9.0, 2.1 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.50–7.44 (m, 2H), 7.33 (m, 2H), 5.34 (s, 2H), 1.33 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.7, 163.2 (d, J = 250.2 Hz), 152.8, 149.2, 143.4, 142.3, 132.5, 130.8, 130.7, 129.9, 129.6 (d, J = 3.6 Hz), 127.6, 120.0, 116.5 (d, J = 21.8 Hz), 67.7, 35.4, 30.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −110.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}FNO_2Na$ 358.1214; found 358.1208.

7-(*tert*-Butyl)-9-(4-chlorophenyl)furo[3,4-*b*]quinolin-3(1*H*)-one (2q). Compound **2q** was isolated in 77% yield (38 mg, pale yellow

solid); mp = 265–267 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (d, J = 9.0 Hz, 1H), 7.94 (dd, J = 8.9, 1.9 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 5.35 (s, 2H), 1.34 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.7, 152.9, 149.2, 143.5, 142.1, 135.7, 132.4, 132.1, 130.8, 130.2, 130.0, 129.6, 127.3, 119.9, 67.6, 35.4, 30.8; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}ClNO_2$ 352.1099; found 352.1096.

7-(*tert*-Butyl)-9-(4-nitrophenyl)furo[3,4-*b*]quinolin-3(1*H*)-one (2r). Compound **2r** was isolated in 75% yield (37 mg, yellow solid); mp = 310–312 °C; R_f = 0.35 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.50 (d, J = 8.6 Hz, 2H), 8.37 (d, J = 9.0 Hz, 1H), 7.99 (dd, J = 9.0, 2.0 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 1.9 Hz, 1H), 5.35 (s, 2H), 1.34 (s, 9H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 168.2, 153.7, 149.3, 148.5, 143.6, 140.7, 140.5, 132.2, 131.1, 130.4, 130.1, 126.9, 124.5, 119.5, 67.3, 35.5, 30.8; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{19}N_2O_4$ 363.1339; found 363.1333.

7-(*tert*-Butyl)-9-(3-chloro-4-methylphenyl)furo[3,4-*b*]quinolin-3(1*H*)-one (2s). Compound **2s** was isolated in 73% yield (36 mg, off white solid); mp = 241–243 °C; R_f = 0.35 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (d, J = 9.0 Hz, 1H), 7.96 (dd, J = 9.0, 2.1 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 1.7 Hz, 1H), 7.27 (dd, J = 7.8, 1.8 Hz, 1H), 5.38 (s, 2H), 2.52 (s, 3H), 1.35 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.7, 152.9, 149.3, 143.5, 141.9, 137.7, 135.4, 132.7, 132.4, 131.8, 130.9, 129.9, 129.2, 127.4, 127.1, 120.0, 67.7, 35.4, 30.9, 20.1; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{21}ClNO_2$ 366.1255; found 366.1251.

7-(*tert*-Butyl)-9-(3,5-dimethylphenyl)furo[3,4-*b*]quinolin-3(1*H*)-one (2t). Compound **2t** was isolated in 74% yield (37 mg, yellow solid); mp = 214.5–216.5 °C; R_f = 0.45 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.34 (d, J = 9.0 Hz, 1H), 7.93 (dd, J = 9.0, 1.0 Hz, 1H), 7.86 (s, 1H), 7.19 (s, 1H), 7.05 (s, 2H), 5.38 (s, 2H), 2.43 (s, 6H), 1.34 (s, 9H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 169.0, 152.3, 149.3, 143.8, 143.5, 138.9, 133.6, 132.3, 130.9, 130.7, 129.7, 127.7, 126.5, 120.6, 67.9, 35.3, 30.9, 21.3; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{23}H_{24}NO_2$ 346.1802; found 346.1797.

7-(*tert*-Butyl)-9-(2-methoxyphenyl)furo[3,4-*b*]quinolin-3(1*H*)-one (2u). Compound **2u** was isolated in 56% yield (28 mg, off white solid); mp = 257–259 °C; R_f = 0.30 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (d, J = 9.0 Hz, 1H), 7.92 (dd, J = 9.0, 1.9 Hz, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.57–7.53 (m, 1H), 7.30–7.27 (m, 1H), 7.20–7.13 (m, 2H), 5.35 (d, J = 15.0 Hz, 1H), 5.25 (d, J = 15.0 Hz, 1H), 3.78 (s, 3H), 1.32 (s, 9H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.2, 156.4, 152.1, 149.2, 143.3, 140.5, 133.7, 131.2, 130.9, 130.7, 129.6, 128.2, 121.9, 120.9, 120.6, 111.6, 68.3, 55.4, 35.3, 30.9; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{22}NO_3$ 348.1594; found 348.1590.

7-*iso*-Propyl-9-(thiophen-2-yl)furo[3,4-*b*]quinolin-3(1*H*)-one (2v). Compound **2v** was isolated in 77% yield (38 mg, brown solid); mp = 157–159 °C; R_f = 0.40 (V_{PE}/V_{EA} = 60/40); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.77 (dd, J = 8.8, 1.9 Hz, 1H), 7.67 (dd, J = 5.1, 1.1 Hz, 1H), 7.38 (dd, J = 3.5, 1.2 Hz, 1H), 7.33 (dd, J = 5.1, 3.5 Hz, 1H), 5.50 (s, 2H), 3.11 (sept, J = 6.9 Hz, 1H), 1.32 (d, J = 6.9 Hz, 6H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.7, 150.9, 149.7, 143.3, 136.1, 133.6, 132.6, 131.3, 130.7, 129.9, 128.7, 128.3, 127.8, 121.7, 68.2, 34.5, 23.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{16}NO_2S$ 310.0896; found 310.0891.

7,9-Dimethylfuro[3,4-*b*]quinolin-3(1*H*)-one (2w). Compound **2w** was isolated in 17% yield (11 mg, brown solid); mp = 213–215 °C; R_f = 0.40 (V_{PE}/V_{EA} = 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 (d, J = 8.8 Hz, 1H), 7.85 (s, 1H), 7.67 (dd, J = 8.7, 1.6 Hz, 1H), 5.49 (s, 2H), 2.69 (s, 3H), 2.63 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.2, 148.5, 143.0, 139.7, 138.7, 133.0, 131.5, 129.1, 122.4, 67.7, 22.3, 14.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{12}NO_2$ 214.0878; found 214.0869.

7-Methyl-2,9-diphenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (4a). Compound **4a** was isolated in 80% yield (39 mg, brown solid); mp = 247–249 °C; R_f = 0.40 (V_{PE}/V_{EA} = 40/60); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.32 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 7.9 Hz, 2H), 7.66–7.58 (m, 4H), 7.54 (s, 1H), 7.51–7.47 (m, 2H), 7.40 (t, J = 8.0 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 4.79 (s, 2H), 2.48 (s, 3H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 165.6, 150.0, 148.7, 142.8, 139.4, 138.7, 134.6, 132.5, 130.9, 129.3 (two ^{13}C), 129.2, 129.1, 127.9, 127.7, 125.3, 124.5, 119.7, 48.3, 22.1; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{19}N_2O$ 351.1492; found 351.1494.

7-Methoxy-2,9-diphenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (4b). Compound **4b** was isolated in 52% yield (26 mg, yellow solid); mp = 236–238 °C; R_f = 0.30 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (d, J = 9.3 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.61 (m, 3H), 7.50 (d, J = 6.8 Hz, 2H), 7.45–7.38 (m, 3H), 7.17 (t, J = 7.3 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 4.78 (s, 2H), 3.78 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 165.5, 159.2, 148.4, 146.1, 141.7, 139.2, 134.6, 132.5, 129.3, 129.2, 129.1, 129.1, 128.8, 128.1, 125.1, 122.7, 119.5, 103.3, 55.5, 48.1; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{19}N_2O_2$ 367.1441 found 367.1435.

2-Benzyl-9-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (4c). Compound **4c** was isolated in 84% yield (41 mg, yellow solid); mp = 192–194 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.45 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 8.5 Hz, 2H), 7.58–7.50 (m, 4H), 7.38 (m, 2H), 7.34–7.27 (m, 5H), 4.89 (s, 2H), 4.24 (s, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ = 166.4, 150.7, 149.6, 143.5, 136.2, 134.3, 131.1, 129.8, 128.9, 128.8, 128.3 (two ^{13}C), 128.0, 127.9, 127.5, 125.6, 47.2, 46.8; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{19}N_2O$ 351.1492; found 351.1487.

2-Benzyl-7-methyl-9-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (4d). Compound **4d** was isolated in 82% yield (40 mg, yellow solid); mp = 204–206 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 (d, J = 8.7 Hz, 1H), 7.58 (dd, J = 8.7, 1.5 Hz, 1H), 7.55–7.46 (m, 4H), 7.36–7.33 (m, 2H), 7.29–7.23 (m, 5H), 4.85 (s, 2H), 4.19 (s, 2H), 2.43 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 166.5, 149.7, 148.1, 142.6, 138.2, 136.3, 134.4, 132.1, 130.6, 128.9 (two ^{13}C), 128.8, 128.8, 128.4, 128.2, 127.8, 127.4, 124.3, 47.0, 46.7, 21.9; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{21}N_2O$ 365.1648; found 365.1653.

2-Benzyl-7-methoxy-9-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (4e). Compound **4e** was isolated in 59% yield (29 mg, brown solid); mp = 179–181 °C; R_f = 0.35 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, J = 9.2 Hz, 1H), 7.57–7.51 (m, 3H), 7.43–7.39 (m, 3H), 7.31–7.27 (m, 5H), 6.98 (d, J = 2.6 Hz, 1H), 4.87 (s, 2H), 4.21 (s, 2H), 3.75 (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 166.6,

158.9, 148.3, 145.6, 141.7, 136.3, 134.5, 132.4, 129.0, 128.9, 128.8, 128.7 (two ^{13}C), 128.2, 127.8, 122.4, 103.3, 55.4, 46.9, 46.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_2$; 381.1598 found 381.1597.

2-Benzyl-7-chloro-9-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*] quinolin-3-one (4f). Compound **4f** was isolated in 81% yield (40 mg, brown solid); mp = 224–226 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (d, J = 8.6 Hz, 1H), 7.70 (s, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.59–7.51 (m, 3H), 7.37 (m, 2H), 7.33–7.27 (m, 5H), 4.88 (s, 2H), 4.24 (s, 2H); ^{13}C $\{^1$H$\}$ NMR (100 MHz, $CDCl_3$) δ = 165.9, 150.9, 147.8, 142.7, 136.0, 134.1, 133.5, 132.5, 130.8, 129.3, 129.2, 129.1, 128.9 (two ^{13}C), 128.3, 128.1, 127.9, 124.4, 47.1, 46.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{18}ClN_2O$ 385.1102; found 385.1100.

2-Benzyl-5,8-dichloro-9-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*] quinolin-3-one (4g). Compound **4g** was isolated in 43% yield (21 mg, yellow solid); mp = 231–233 °C; R_f = 0.45 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.80 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.47–7.44 (m, 3H), 7.34–7.26 (m, 7H), 4.85 (s, 2H), 4.10 (s, 2H); ^{13}C $\{^1$H$\}$ NMR (125 MHz, $CDCl_3$) δ = 165.3, 151.0, 147.1, 144.2, 136.3, 136.0, 135.1, 132.3, 130.4, 129.7, 129.5, 128.8, 128.6, 128.4, 128.2, 128.1, 127.9, 125.8, 47.2, 46.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{17}Cl_2N_2O$ $(M + H)^+$ 419.0712; found 419.0703.

2-Benzyl-9-(4-methoxyphenyl)-7-methyl-1,2-dihydro-3*H*-pyrrolo [3,4-*b*]quinolin-3-one (4h). Compound **4h** was isolated in 57% yield (28 mg, yellow solid); mp = 197–199 °C; R_f = 0.35 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.31 (d, J = 9.3 Hz, 1H), 7.41 (dd, J = 9.2, 2.0 Hz, 1H), 7.34 (d, J = 7.6 Hz, 2H), 7.31–7.27 (m, 7H), 7.03 (d, J = 1.7 Hz, 1H), 4.87 (s, 2H), 4.20 (s, 2H), 3.76 (s, 3H), 2.46 (s, 3H); ^{13}C $\{^1$H$\}$ NMR (125 MHz, $CDCl_3$) δ = 166.7, 158.9, 148.4, 145.7, 141.9, 138.8, 136.4, 132.4, 131.5, 129.7, 128.9, 128.9, 128.8, 128.7, 128.2, 127.7, 122.4, 103.4, 55.4, 47.0, 46.8, 21.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_2$ 395.1754; found 395.1750.

2-Benzyl-7-chloro-9-(*p*-tolyl)-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinoline-3-one (4i). Compound **4i** was isolated in 80% yield (39 mg, yellow solid); mp = 187–189 °C; R_f = 0.45 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 (d, J = 9.0 Hz, 1H), 7.71 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.37–7.27 (m, 9H), 4.87 (s, 2H), 4.24 (s, 2H), 2.46 (s, 3H); ^{13}C $\{^1$H$\}$ NMR (100 MHz, $CDCl_3$) δ = 165.9, 150.8, 147.8, 142.8, 139.3, 136.0, 133.9, 132.3, 130.7, 130.5, 129.8, 129.2, 128.8, 128.2, 128.1, 127.8, 124.5, 113.9, 47.1, 46.8, 21.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{20}ClN_2O$ 399.1259; found 399.1261.

2-Benzyl-7-methyl-9-(*p*-tolyl)-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (4j). Compound **4j** was isolated in 79% yield (39 mg, yellow solid); mp = 203–205 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.33 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.54 (s, 1H), 7.35 (d, J = 7.7 Hz, 2H), 7.33–7.25 (m, 7H), 4.89 (s, 2H), 4.23 (s, 2H), 2.47 (s, 6H); ^{13}C $\{^1$H$\}$ NMR (125 MHz, $CDCl_3$) δ = 166.6, 149.8, 148.2, 142.8, 138.8, 138.1, 136.4, 132.1, 131.5, 130.7, 129.6, 128.9, 128.8, 128.5, 128.3, 127.8, 127.6, 124.4, 47.1, 46.8, 21.9, 21.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O$ 379.1805; found 379.1801.

2-Benzyl-9-(4-methoxyphenyl)-7-methyl-1,2-dihydro-3*H*-pyrrolo [3,4-*b*]quinolin-3-one (4k). Compound **4k** was isolated in 75% yield (37 mg, yellow solid); mp = 190–192 °C; R_f = 0.35 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 (d, J = 8.6 Hz, 1H), 7.58 (dd, J = 8.7, 1.8 Hz, 1H), 7.54 (s, 1H), 7.34–7.27 (m, 7H), 7.07 (d, J = 8.7 Hz, 2H), 4.86 (s, 2H), 4.22 (s, 2H), 3.90 (s, 3H), 2.46 (s, 3H); ^{13}C $\{^1$H$\}$ NMR (100 MHz, $CDCl_3$) δ = 166.54, 159.91, 149.66, 148.11, 142.47, 138.03, 136.29, 131.98, 130.57, 130.30, 128.75, 128.53, 128.23, 127.74, 127.67, 126.41, 124.34, 114.36, 55.31, 47.00, 46.82, 21.90; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_2$ 395.1754; found 395.1762.

2-Benzyl-9-(4-chlorophenyl)-7-methyl-1,2-dihydro-3*H*-pyrrolo [3,4-*b*]quinolin-3-one (4l). Compound **4l** was isolated in 81% yield (40 mg, yellow solid); mp = 193–195 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (d, J = 8.6 Hz, 1H), 7.59 (dd, J = 8.5, 1.3 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.43 (s, 1H), 7.36–7.26 (m, 7H), 4.85 (s, 2H), 4.19 (s, 2H), 2.46 (s, 3H); ^{13}C $\{^1$H$\}$ NMR (100 MHz, $CDCl_3$) δ = 166.3, 149.6, 147.9, 141.3, 138.5, 136.1, 135.1, 132.8, 132.2, 130.7, 130.4, 129.3, 128.8, 128.4, 128.3, 127.9, 127.2, 123.9, 47.0, 46.6, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{20}ClN_2O$ 399.1259; found 399.1271.

2-Benzyl-7-methyl-9-(4-nitrophenyl)-1,2-dihydro-3*H*-pyrrolo [3,4-*b*]quinolin-3-one (4m). Compound **4m** was isolated in 71% yield (35 mg, yellow solid); mp = 200–202 °C; R_f = 0.30 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (d, J = 8.8 Hz, 2H), 8.34 (d, J = 8.7 Hz, 1H), 7.65 (dd, J = 8.7, 1.8 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.36–7.29 (m, 6H), 4.86 (s, 2H), 4.18 (s, 2H), 2.48 (s, 3H). ^{13}C $\{^1$H$\}$ NMR (100 MHz, $CDCl_3$) δ = 166.10, 149.92, 148.32, 148.19, 141.38, 140.16, 139.33, 136.10, 132.75, 131.06, 130.30, 129.03, 128.49, 128.31, 128.12, 126.74, 124.40, 123.63, 47.26, 46.55, 22.11; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{20}N_3O_3$ 410.1499; found 410.1505.

2-Benzyl-7-methyl-9-(thiophen-2-yl)-1,2-dihydro-3*H*-pyrrolo [3,4-*b*]quinolin-3-one (4n). Compound **4n** was isolated in 73% yield (36 mg, yellow solid); mp = 221–223 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, J = 8.7 Hz, 1H), 7.84 (s, 1H), 7.61 (dd, J = 8.7, 1.9 Hz, 1H), 7.59–7.56 (m, 1H), 7.36–7.31 (m, 4H), 7.31–7.23 (m, 4H), 4.90 (s, 2H), 4.36 (s, 2H), 2.51 (s, 3H); ^{13}C $\{^1$H$\}$ NMR (100 MHz, $CDCl_3$) δ = 166.42, 149.87, 148.32, 138.82, 136.35, 135.73, 134.26, 132.42, 130.88, 129.55, 129.27, 128.96, 128.41, 128.01, 127.97, 127.95, 127.72, 124.34, 47.41, 47.20, 22.16; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{19}N_2OS$ 371.1213; found 371.1221.

2-Benzyl-9-(trimethylsilyl)-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (4o). Compound **4o** was isolated in 67% yield (33 mg, off white solid); mp = 202–204 °C; R_f = 0.40 (V_{PE}/V_{EA} = 30/70); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.42 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.75 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 7.62 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 7.41–7.27 (m, 5H), 4.94 (s, 2H), 4.46 (s, 2H), 0.51 (s, 9H); ^{13}C $\{^1$H$\}$ NMR (100 MHz, $CDCl_3$) δ = 166.0, 149.3, 148.1, 142.9, 136.2, 135.7, 132.3, 132.1, 129.1, 128.9, 128.3, 127.9, 127.8, 127.4, 49.3, 47.1, 1.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{23}N_2OSi$ $(M + H)^+$ 347.1578; found 347.1581.

9-((Benzyloxy)methyl)-7-methoxy-1-methylfuro[3,4-*b*]quinolin-3(1*H*)-one (6). Compound **7** was isolated in 41% yield (21 mg, yellow solid); mp = 174–176 °C; $R_f = 0.35$ ($V_{PE}/V_{EA} = 30/70$); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.26$ (d, $J = 9.3$ Hz, 1H), 7.47 (dd, $J = 9.3$, 2.7 Hz, 1H), 7.41–7.36 (m, 5H), 7.18 (d, $J = 2.7$ Hz, 1H), 5.88 (q, $J = 6.5$ Hz, 1H), 5.06 (ABq, $J = 13.20$ Hz, 2H), 4.71 (ABq, $J = 11.74$ Hz, 2H), 3.92 (s, 3H), 1.68 (d, $J = 6.5$ Hz, 3H); ^{13}C $\{^1$H$\}$ NMR (100 MHz, $CDCl_3$) δ = 168.2, 160.1, 146.3, 142.3, 137.8, 136.7, 136.3, 133.2, 129.0, 128.7, 128.4, 128.1, 123.7, 101.2, 76.8, 73.7, 65.9, 55.7, 21.1; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_4$ 350.1387; found 350.1380.

9-Phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (7). Compound **7** was isolated in 88% yield (65 mg, grey solid); mp = 279–281 °C (decomposed); $R_f = 0.40$ ($V_{DCM}/V_{MeOH} = 90/10$); ^{1}H NMR (400 MHz DMSO d_6) $\delta = 9.26$ (bs, 1H), 8.26 (d, $J =$ 8.4 Hz, 1H), 7.87 (t, $J = 7.4$ Hz, 1H), 7.79 (d, $J = 8.3$ Hz, 1H), 7.67 (t, $J = 7.4$ Hz, 1H), 7.58–7.62 (m, 5H), 4.38 (s, 2H); ^{13}C $\{^1$H$\}$ NMR (100 MHz, DMSO d_6) $\delta = 167.6$, 151.4, 148.7, 142.9, 133.9, 131.0, 130.3, 129.7, 129.2, 128.9 (two ^{13}C), 128.1, 126.6, 125.4, 42.0; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O$ 261.1022; found 261.1019.

7-Methyl-9-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one (8). Compound **8** was isolated in 86% yield (65 mg, grey solid); mp = 317–319 °C (decomposed); $R_f = 0.40$ ($V_{DCM}/V_{MeOH} = 90/10$); ^{1}H NMR (400 MHz, DMSO d_6) $\delta = 9.19$ (bs, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.62–7.52 (m, 6H), 4.34 (s, 2H), 2.45 (s, 3H); ^{13}C $\{^1$H$\}$ NMR (100 MHz, DMSO d_6) $\delta =$ 168.2, 151.0, 147.9, 142.7, 138.3, 134.5, 132.4, 131.7, 130.6, 129.7, 129.4, 129.3, 127.0, 124.3, 42.5, 22.0; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$ 275.1179; found 275.1176.

Conflicts of interest

There are no conflicts to declare.

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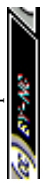

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Metal- And Light-Free Direct C-3 Ketoalkylation of Quinoxalin-2(1*H*)-Ones with Cyclopropanols in Aqueous Medium

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Direct oxidative C-3 ketoalkylation of quinoxalin-2(1*H*)-ones with cyclopropanols using ammonium persulfate in an aqueous medium has been achieved in a moderate to good yield. The reaction does not require metals, light-source, or catalysts to facilitate the reaction and could be efficiently utilized to construct a wide range of biologically relevant 3-ketoalkylated quinoxalin-2(*1H*)-ones.

Introduction

Among various *N*-heterocycles, quinoxalin-2(1*H*)-ones has emerged as an essential scaffold as they possess a diverse range of biological and pharmaceutical activities.[1] In particular, C-3 functionalized quinoxalin-2(1*H*)-ones proved to be critical constituents of several therapeutic agents, and they possess a wide range of biological activities such as antibacterial,[2a] aldose reductase & antioxidant,[2b] antitumor,[2c,d] etc.[3] (Figure 1) Given their immense medicinal importance, convenient synthesis to access C-3 functionalized quinoxalin-2(1*H*)-ones are of great interest. In the last decade, remarkable advances have been achieved in CH-functionalization strategies, especially the late stage functionalization (LSF), as it provides enormous opportunities in achieving atom & step economy, reaction efficiency, selectivity, and allowing a rapid way to generate a diverse set of compounds, etc.that are critical in the area of drug discovery, material research and molecular imaging.[4,5]

Conceivably, this strategy have been aptly applied to functionalize quinoxalin-2(1*H*)-one moiety, and notable examples include acylation,[6] arylation,[7] alkylation,[8] alkoxylation,[9] amination,[10] phosphonation,[11] di/trifluoromethylation,[12] thiolation,[13] and other[14] have been carried out efficiently. There are excellent reviews detailing various CH-functionalization strategies and the medicinal importance of quinoxalin-2(1*H*)-ones have appeared recently.[3,15]

Indeed, β-carbonyl alkylation of various *N*-heterocycles is also considered significant because the resultant β-heteroarylated ketone motifs exist in many natural products and bioactive molecules. Furthermore, they serve as functional building blocks for further useful synthetic elaborations.[16]

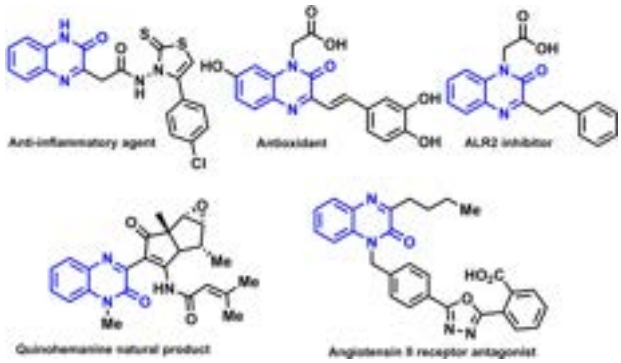

Figure 1. Representative biologically active 3-substituted quinoxalin-2(1*H*)-one derivatives.

Surprisingly, the study of β-carbonyl alkylation on quinoxalin-2(1*H*)-one moiety remains under explored. In recent years, the chemistry of cyclopropanols has received a considerable attention owing to its capacity to produce highly reactive alkoxy radicals *via* β-scission and subsequent powerful synthetic transformations.[17,18] Apparently, this ring-opening functionalization has become a prudent strategy for preparing β-functionalized carbonyl compounds. In this context, it is noteworthy that Guo *et al.* elegantly utilized visible light enabled C-3 ketoalkylation of quinoxalin-2(1*H*)-ones *via* oxidative ring-opening of cycloalkanols.[19] Although this method appears impressive, the requirement of *N*-protected quinoxalin-2(1*H*)-ones and the need of light source to facilitate the reaction limits its synthetic superiority. Owing to the biological significance of quinoxalin-2(1*H*)-one core, the development of an alternative, sustainable and greener protocol of β-keto alkylation of quinoxalin-2(1*H*)-one is still desirable. So, we herein describe a simple and straightforward protocol for C-3 ketoalkylation of quinoxalin-2(1*H*)-ones *via* oxidative ring-opening of cyclopropanols. The present protocol does not require *N*-protection, light source and employs only aqueous solution as a reaction medium (Scheme 1).

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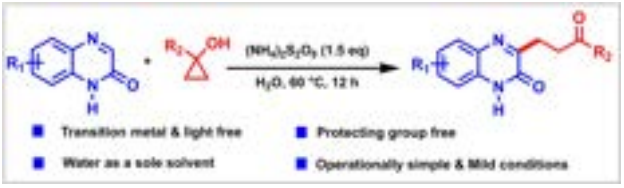


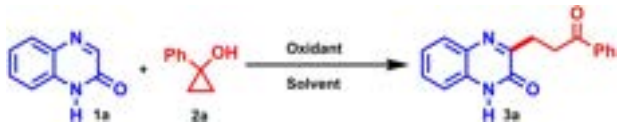
Scheme 1. C-3 ketoalkylation of quinoxalin-2(1*H*)-ones.

Results and Discussion

Most of the C-3 functionalization of quinoxalin-2(1*H*)-ones has been carried out using *N*-protected quinoxalin-2(1*H*)-ones.[15,19] It was decided to test the ketoalkylation of unprotected quinoxalin-2(1*H*)-ones first. In a prototype experiment, quinoxalin-2(1*H*)-one **1a** was treated with phenyl cyclopropanol **2a** using $K_2S_2O_8$ in pure water at 60 °C. Delightfully, the reaction went smoothly, and the desired product **3a** was obtained in 71% yield (Table 1, entry 1). The control experiment suggests that $K_2S_2O_8$ is necessary for the reaction to proceed (Table 1, entry 2). Subsequently, solvent combinations (DCE/H_2O, DMSO/H_2O) were investigated to test the effect of solvent, which did not improve the yield of **3a** (Table 1, entries 3–4). In order to further optimize the reaction condition, different oxidizing agents such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, CHP, H_2O_2, TBHP, and BPO were tested in this reaction (Table 1, entries 5–10), and among them $(NH_4)_2S_2O_8$ was found to be more suitable for this transformation generating **3a** in 79% yield (Table 1, entry 6). Further screening of oxidant loading reveals that 1.5 equiv. of $(NH_4)_2S_2O_8$ is optimum, and the yield of **3a** was improved to 89% (Table 1, entries 6, 11–13). Finally, after studying the effect of reaction temperature (Table 1, entries 14, 15), we reached the ideal condition to perform the reactions being 1 equiv. of **1a**, 1.5 equiv. of **2a** & 1.5 equiv. of $(NH_4)_2S_2O_8$ in pure water at 60 °C.

With the optimal reaction conditions in hand, the scope of the reaction was investigated (Table 2). Various substituted cyclopropanols and quinoxalin-2(1*H*)-ones were allowed to react in the presence of $(NH_4)_2S_2O_8$ in pure water. Most of the substituted cyclopropanols participated in the reaction efficiently, yielding the desired products **3** in moderate to good yields. Substituted cyclopropanols containing an electron-donating & electron-withdrawing substitution at the *para* position of the benzene ring, such as alkyl, alkoxy, chloro & fluro functionalities, were found to react smoothly to afford the corresponding products in good yields (Table 2, **3b**–**3e**). Furthermore, di and tri substitutions on the benzene ring of cyclopropanols were also well tolerated, and the corresponding products (Table 2, **3f**–**3h**) were isolated in good yields under optimal conditions. It is worth mentioning that, heteroaryl substituted cyclopropanol (**2i**) also underwent the reaction despite in moderate yield (68%). Notably, 1,2-disubstituted cyclopropanol also participated in this transformation to provide **3j** in 85% yield. However, cycloalkyl substituted cyclopropanol also participated in this reaction albeit in less yield (**3k**). Subsequently, the effect of various substitutions on the quinoxalin-2(1*H*)-ones **1** were also investigated. Quinoxalin-2(1*H*)-ones bearing electron-donating groups such as alkyl and alkoxy on the aryl ring also yielded the corresponding products in good yields (**3l**–**3n**, 67–89%). It is noteworthy that halo-

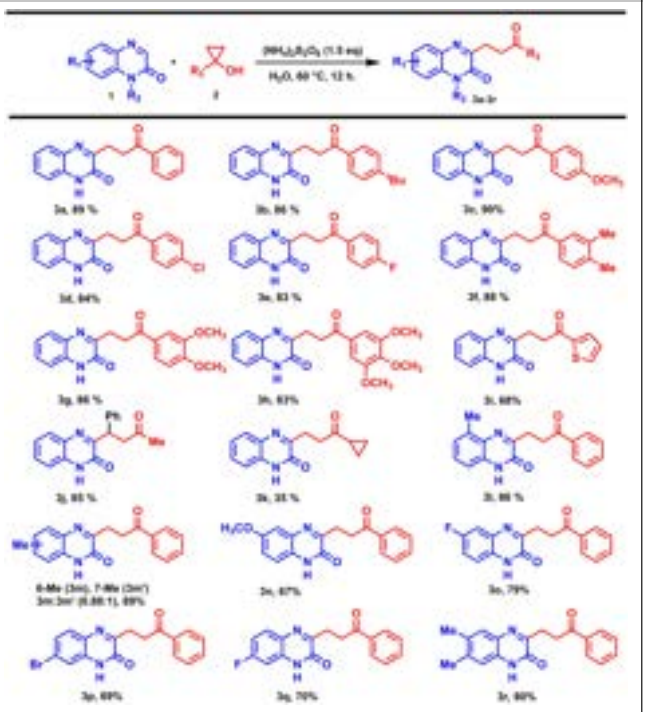
Table 1. Optimization of the reaction conditions.[a,b]



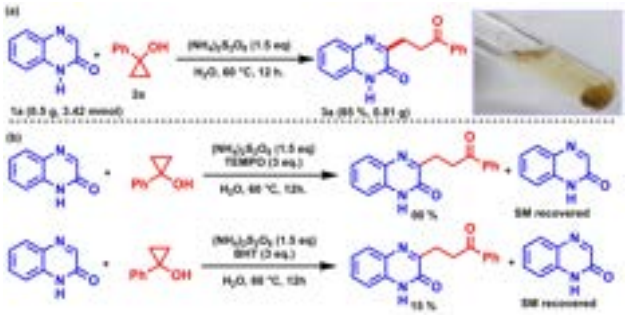
Entry	Oxidant (equiv.)	Solvent	Yields
1	$K_2S_2O_8$ (3)	H_2O	71
2	None	H_2O	NR
3	$K_2S_2O_8$ (3)	DCE /H_2O (1:1)	59
4	$K_2S_2O_8$ (3)	DMSO /H_2O (1:1)	56
5	$Na_2S_2O_8$ (3)	H_2O	74
6	$(NH_4)_2S_2O_8$ (3)	H_2O	79
7	CHP (3)	H_2O	21
8	H_2O_2 (3)	H_2O	10
9	TBHP (3)	H_2O	06
10	BPO(3)	H_2O	trace
11	$(NH_4)_2S_2O_8$ (2)	H_2O	85
12	$(NH_4)_2S_2O_8$ (1.5)	H_2O	89
13	$(NH_4)_2S_2O_8$ (1)	H_2O	75
14[c]	$(NH_4)_2S_2O_8$ (1.5)	H_2O	87
15[d]	$(NH_4)_2S_2O_8$ (1.5)	H_2O	59

[a] Reaction conditions: **1a** (0.34 mmol), **2a** (0.51 mmol), oxidant, solvent (3.0 mL), 60 °C, 12 h. [b] The yields refer to the isolated yields.[c] Reaction was carried out at 70 °C. [d] Reaction was carried out at 50 °C. CHP = Cumene Hydroperoxide. NR = No reaction.

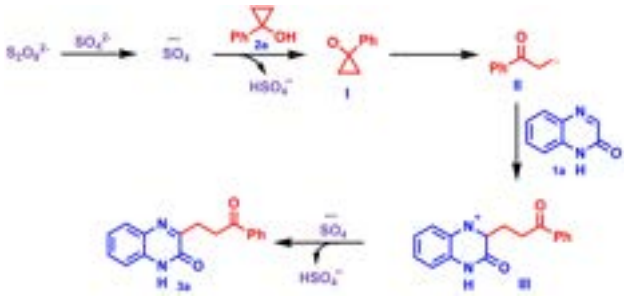
Table 2. Scope of quinoxalin-2(1*H*)-ones and cycloalkanols.[a,b]



[a] All reactions were performed with **1** (0.34 mmol, 1 equiv.), **2** (1.5 equiv.), $(NH_4)_2S_2O_8$ (1.5 equiv.), water (3 mL), 60 °C, 12 h. [b] Isolated yields.



Scheme 2. Gram-scale experiment and control experiments.



Scheme 3. Plausible mechanism.

substituted quinoxalin-2(*1H*)-ones were also well tolerated with moderate to good yields (**3 o**–**3 q**, 69–79 %) opening the door for further functionalization. In addition, quinoxalin-2 (1*H*)-one bearing disubstitution on the phenyl ring have proved to be compatible and afforded the target product **3 r** in good yield (80 %).

To show the synthetic potential of this protocol, a gram-scale experiment was carried out. The reaction of **1 a** (3.42 mmol, 0.5 g) with **2 a** (5.13 mmol, 0.68 g) under the optimal conditions afforded **3 a** (0.81 g) in 85 % yield (Scheme 2a). It is important to mention here that as the reaction medium is pure water, the product isolation is quite simple. After completion of the reaction, the solid product **3 a** precipitated out from the reaction mixture as shown in Scheme 2a, which can be simply filtered, washed with water followed by *n*-hexane to provide sufficiently pure **3 a**.

To explore the reaction mechanism of the present protocol, few control experiments were carried out. 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) & 2,6-di-tert-butyl-4-methylphenol (BHT) were selected as a radical scavangers and employed under standard reaction condition. As a result, the product formation was suppressed, which indicates the reaction should proceed through a radical pathway (Scheme 2b). On the basis of the control experiments and previous reports,[16a,f,20] a plausible reaction mechanism is proposed as shown in Scheme 3. First, the single-electron oxidation of cyclopropanol **2 a** by $(NH_4)_2S_2O_8$ generates an oxygen-centered alkoxy radical **I**, which undergoes rearrangement to form β-keto radical **II** that can react with quinoxalin-2(*1H*)-one (**1 a**) leads to radical intermediate **III**. Subsequently, intermediate **III** undergoes one-electron oxidation and loses H^+ to form the final product **3 a**.

Conclusion

In conclusion, we have developed a simple and efficient C-3 β-keto alkylation of quinoxalin-2(1*H*)-ones with cyclopropanol in a water medium. Various quinoxalin-2(1*H*)-ones and cyclopropanols were successfully participated in this reaction. This operationally simple process does not require a transition metal catalyst, usual *NH* protection, and external light source, thus provide a greener pathway which we believe will find application in drug discovery program.

Experimental Section

General information

Most of the reagents and starting materials used were purchased from commercial sources. Melting points are uncorrected and recorded using digital Buchi Melting Point Apparatus B-540. ^{1}H, ^{13}C, and ^{19}FNMR spectra were recorded on Bruker AV 400/500, AV 100/125, and AV 376 MHz spectrometers, respectively, in DMSO-D_6 using TMS as the internal standard, and the chemical shifts are shown in δ scale. Multiplicities of ^{1}HNMR signals are designated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), quin (quintet), spt (septet), bs (broad signal), m (multiplet), etc. Thin layer chromatography was performed on Merck silica gel 60 F254 TLC plates using petroleum ether/ethyl acetate as an eluent. Column chromatography was carried out through silica gel (100-200 mesh) using petroleum ether/ethyl acetate as an eluent. High-resolution mass spectra (HRMS) were recorded on a Q Exactive Hybrid Quadrupole Orbitrap Mass Spectrometer, where the mass analyzer used for analysis is orbitrap.

General procedure for ketoalkylation of quinoxalin-2(1H)-ones:

To an oven-dried 5 mL reaction vial equipped with a magnetic stir bar was added quinoxalin-2(*1H*)-ones **1** (0.34 mmol), $(NH_4)_2S_2O_8$ (1.5 equiv.0.51 mmol), water (3 mL) and the mixture was stirred at 60 °C for 5 min. Then, cyclopropanol **2** (1.5 equiv.0.51 mmol) was added slowly, and the reaction mixture was stirred at 60 °C for 12 h. After completion of the reaction (detected by TLC), extracted with DCM/MeOH (9 : 1) (20 mL × 3). The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure to obtain a crude product which was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent to afford the pure product **3**.

Supporting Information Summary

The supporting information includes characterization data, copies of ^{1}H, ^{13}C & ^{19}FNMR spectra for all isolated compounds **3**.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: aqueous medium · cyclopropanols · ketoalkylation · metal-free · quinoxalin-2(*1H*)-ones

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