C(sp^2)-H FUNCTIONALIZATION OF QUINOLINES, IMIDAZOPYRIDINES, INDOLES AND OTHER C-N BOND FORMING REACTIONS USING ISOCYANIDE AND RONGALITE

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DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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Dedicated
To
My Beloved Family

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CERTIFICATE

This is to certify that the research work presented in this thesis entitled **"C(sp^2)-H Functionalization of Quinolines, Imidazopyridines, Indoles and Other C-N Bond Forming Reactions Using Isocyanide and Rongalite"** submitted by **Mr. Naveenkumar Anugu** for the degree of Doctor of Philosophy in Chemistry, National Institute of Technology, Warangal (Telangana), under my supervision and that the same has not been submitted elsewhere for a degree.

Date:19-12-2022
Place: NIT Warangal

Dr. K. Hari Prasad
Thesis Supervisor

DECLARATION

I hereby declare that the matter embodied in this thesis entitled **"C(sp^2)-H Functionalization of Quinolines, Imidazopyridines, Indoles and Other C-N Bond Forming Reactions Using Isocyanide and Rongalite"** is based entirely on the results of the investigations and research work carried out by me under the supervision of **Dr. K. Hari Prasad**, Department of Chemistry, National Institute of Technology, Warangal. I declare that this work is original and has not been submitted in part or full, for any degree or diploma to this or any other University.

Date:19-12-2022 **(Naveenkumar Anugu)**

Place: NIT Warangal

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(Naveenkumar Anugu)

ABBREVIATIONS

Ac_2O	:	Acetic anhydride
ACN	:	Acetonitrile
AcOH	:	Acetic acid
Ag	:	Silver
Ag_2CO_3	:	Silver carbonate
Ag_2O	:	Silver(I) oxide
AgCN	:	Silver cyanide
AgOTf	:	Silver trifluoromethanesulfonate
$AgSbF_6$	:	Silver hexafluoroantimonate
$AlCl_3$	:	Aluminium chloride
Au	:	Gold
$AuCl_3$	:	Gold trichloride
BF_3. OEt_2	:	Boron trifluoride etherate
$Bi(NO_3)_3.5H_2O$	:	Bismuth(III) nitrate pentahydrate
$Bi(OTf)_3$	:	Bismuth(III) trifluoromethanesulfonate
$BiBr_3$	:	Bismuth (III) bromide
BuLi	:	Butyllithium
$(bmim)PF_6$	:	1-Butyl-3-methylimidazolium hexafluorophosphate
CBr_4	:	Carbon tetrabromide
CCl_4	:	Carbon tetrachloride
$CDCl_3$	:	Deuterated chloroform
CO_2	:	Carbon dioxide
Cs_2CO_3	:	Cesium carbonate
$Cu(OAc)_2.H_2O$	:	Copper(II) acetate monohydrate
$Cu(OTf)_2$	:	Copper(II) trifluoromethanesulfonate
CuBr	:	Copper bromide
CuCl	:	Copper(II) chloride
CuI	:	Copper(I) iodide
$CuSO_4.5H_2O$	:	Copper(II) sulfate pentahydrate
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	:	Dichloroethane
DEAD	:	Diethyl azodicarboxylate
DIAD	:	Diisopropyl azodicarboxylate
		dichloride
DMA	:	Dimethylacetamide
DMF	:	*N*, *N*-Dimethylformamide
DMSO	:	Dimethyl sulfoxide
DMSO-d_6	:	Deuterated dimethyl sulfoxide
DTBP	:	Di-*tert*-butyl peroxide
$Dy(NO_3)_3.6H_2O$	:	Dysprosium(III) nitrate hexahydrate
Dy_2O_3	:	Dysprosiumoxide
EtOAc	:	Ethyl acetate
EtOH	:	Ethanol

Eu_2O_3	:	Europium(III)oxide
$Fe(NO_3)_3.9H_2O$	:	Iron(III) nitrate nonahydrate
$Fe(SO_4)_3$	:	Iron(III) sulfate
$FeCl_3$	:	Iron (III) chloride
FTIR	:	Fourier transform infrared
GABA	:	γ-Amino butyric acid
Gd_2O_3	:	Gadolinium(III) oxide
h	:	Hours
H_2	:	Molecular Hydrogen
H_2O	:	Water
H_2O_2	:	Hydrogen peroxide
H_2Se	:	Hydrogen selenide
H_3PO_4	:	Phosphoric acid
HBTU	:	Hexafluorophosphate Benzotriazole Tetramethyl Uronium
HCl	:	Hydrochloric acid
HIV	:	Human immunodeficiency virus
HOCN	:	Cyanic acid
HRMS	:	High-resolution mass spectrometry
HSCN	:	Thiocyanic acid
H_Z	:	Hertz
I_2	:	Molecular Iodine
$InCl_3$	:	Indium chloride
^{i}PrOH	:	Isopropanol
Ir	:	Iridium
J	:	Coupling constant
K_2CO_3	:	Potassium carbonate
$K_2S_2O_8$	:	Potassium persulfate
KBr	:	Potassium bromide
KI	:	Potassium iodide
KOH	:	Potassium hydroxide
LiBr	:	Lithium bromide
LiCl	:	Lithium Chloride
m	:	Multiplet
m-CPBA	:	*meta*-Chloroperoxybenzoic acid
mg	:	Milligram
min	:	Minutes
mL	:	Millilitre
mmol	:	Milli mole
mp	:	Melting point
MsCl	:	Methanesulfonyl chloride
MW	:	Microwaves
N_2	:	Molecular Nitrogen
Na_2CO_3	:	Sodium carbonate
$Na_2S_2O_3.5H_2O$	:	Sodium thiosulfate pentahydrate

Na_2SO_4	:	Sodium sulfate
$NaBH_4$	:	Sodium borohydride
$NaHCO_3$	:	Sodium bicarbonate
NaI	:	Sodium Iodide
$NaNO_2$	:	Sodium nitrite
NaOAc	:	Sodium acetate
NaOH	:	Sodium hydroxide
NBS	:	*N*-Bromosuccinimide
NCS	:	*N*-Chlorosuccinimide
Nd_2O_3	:	Neodymium(III) oxide
NEt_3	:	Triethylamine
NHC	:	*N*-Heterocyclic Carbene
NHS	:	*N*-Hydroxysuccinimide
NIS	:	*N*-Iodosuccinimide
NMP	:	*N*-Methylpyrrolidone
NMR	:	Nuclear Magnetic Resonance
O_2	:	Molecular oxygen
ORTEP	:	Oak ridge thermal ellipsoid plot
Pd	:	Palladium
$Pd(dppf)_2Cl_2$	:	(1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride
$Pd(OAc)_2$	:	Palladium(II) acetate
$Pd(PPh_3)_4$	:	Tetrakis(triphenylphosphine)palladium
$PdCl_2$	:	Palladium chloride
PEG-400	:	Polyethylene glycol
PIDA	:	Diacetoxyiodobenzene
$POCl_3$	:	Phosphorus Oxychloride
PPA	:	Polyphosphoric acid
PPh_3	:	Triphenylphosphine
Pr_2O_3	:	Praseodymium(III) oxide
PyBroP	:	Bromotripyrrolidinophosphonium hexafluorophosphate
q	:	Quartet
Rh	:	Rhodium
rt	:	Room temperature
Ru	:	Ruthenium
$Ru(acac)_3$	:	Ruthenium(III) acetylacetonate
s	:	Singlet
$Sc(OTf)_3$	:	Scandium trifluoromethanesulfonate
SCXRD	:	Single Crystal X-ray Diffraction
$SOCl_2$	:	Thionyl Chloride
t	:	Triplet
TBAI	:	Tetrabutylammonium iodide
TBHP	:	Tert-butyl hydroperoxide
$^tBuNH_2$	:	Tert-Butylamine
^tBuOH	:	Tert-butyl alcohol

^{t}BuOK	:	Potassium *tert*-butoxide
TEMPO	:	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf_2O	:	Trifluoromethanesulfonic anhydride
TFA	:	Trifluoroacetic acid
TFE	:	Trifluoroethylene
THF	:	Tetrahydrofuran
TLC	:	Thin Layer Chromatography
TMS	:	Tetramethyl silane
TMSOTf	:	Trimethylsilyl trifluoromethanesulfonate
TosMIC	:	*p*-Toluenesulfonylmethyl isocyanide
$TsOH.H_2O$	:	*p*-Toluenesulfonic acid monohydrate
UV-Vis	:	Ultraviolet-visible
$VO(acac)_2$	:	Vanadyl acetylacetonate
$Yb(OTf)_3$	:	Ytterbium(III) trifluoromethanesulfonate hydrate
Yb_2O_3	:	Ytterbium(III) oxide
Zn	:	Zinc
$ZnCl_2$	:	Zinc(II) chloride

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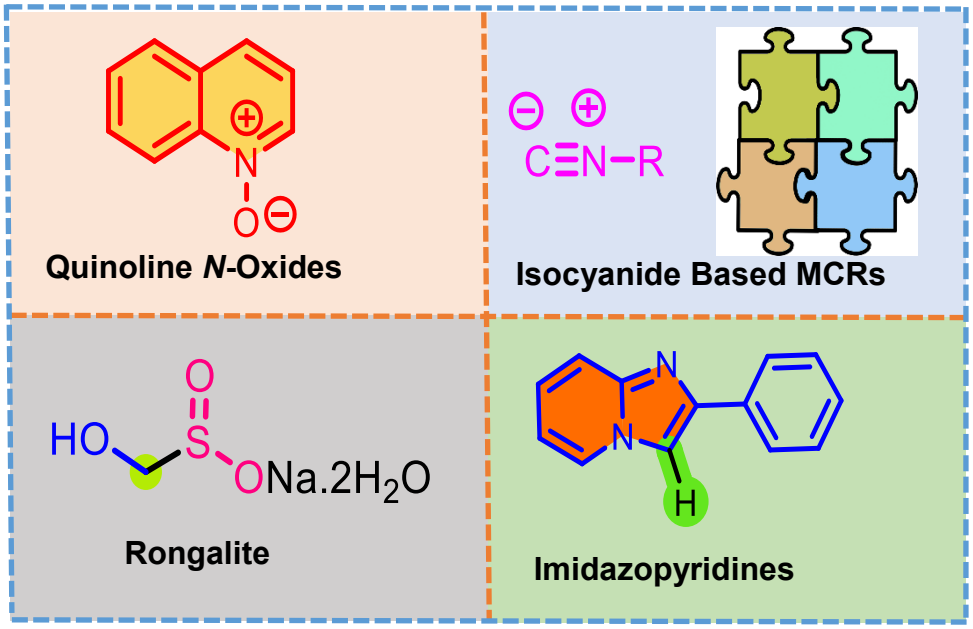
CHAPTER-I

INTRODUCTION



1.1. Introduction

Heterocyclic compounds are ubiquitous in nature and has a rich history with a huge impact on all areas of organic and medicinal chemistry.[1] Development of new methodologies for the synthesis of nitrogen containing heterocycles has become thrust area because of their widespread applications in multi-disciplinary fields ranging from natural products, engineering materials, agrochemicals to pharmaceuticals.[2-11] It is estimated that more than 50% of the published chemical literature contains heterocyclic structures and about 70% of all pharmaceutical products possess heterocyclic structural subunits, because of a favourable combination of drug-like properties. Of those, over 200 are currently marked to be drugs which are undergoing clinical trials (Figure 1.1).[10,12] Thus, the chemistry of heterocycles is still a challenging research area to be explored by researchers across the globe. Among these heterocyclics, the nitrogen containing heterocycles, especially quinolines play an important role in producing the several biological active compounds.[13-15] Hence, there is always high demand for the development of new methodologies for the synthesis of quinoline derivatives. Particularly, *N*-oxide directed C2-selective C-N bond formation has become promising research area due to the importance of the quinolines in medicinal chemistry and pharmaceuticals.[16] These quinoline *N*-oxides are unique substances that has been attracted considerable attention by chemist due to the ability of the *N*-oxide moiety to act as an *ortho*-directing group to control the regioselectivity of the C-H activation.[17] A brief introduction of quinolines, isocyanides and rongalite is given in this chapter.

1.2. Quinolines

Quinoline (1-azanaphthalene) is a heterocyclic aromatic nitrogen compound with the chemical formula C_9H_7N characterized by a double-ring structure that contains a benzene ring fused to pyridine.[18] Friedlieb Ferdinard Runge was the first identify and extract the quinoline from coal tar.[19,20] It is a secondary metabolite under the nitrogen containing natural products. Also, quinoline alkaloids are found in many different plants including berberidaceae, fumariaceae, papaveraceae and rutaceae.[21] A number of these compounds are planar aromatic heterocycles that have shown cytotoxic activity by inhibiting topoisomerase II.[22] Quinoline derivatives are useful in diverse applications including pharmaceuticals, fragrances, dyes and are available as drugs today.

The well-known drugs in the market are the antimalarials (quinine, chloroquine, mefloquine, quinidine, amodiaquine, primaquine etc.), antiviral (saquinavir), antibacterial (ciprofloxacin, sparfloxacin, gatifloxacin etc.), antifungal-antiprotozoal (clioquinol), anthelmintic

(oxamniquine), local anesthetic (dibucaine), antiasthmatic (montelukast), anticancer (camptothecin, irinotecan, topotecan etc.), antipsychotic (aripiprazole, brexpiprazole etc.), antiglaucoma (carteolol) and cardiotonic (vesnarinone). Some of the quinoline based compounds *i.e.*, bosutinib, lenvatinib and cabozantinib are potent protein kinase inhibitors and farnesyltransferase inhibitor (tipifarnib) are currently under clinical trial phase (Figure. 1.1).

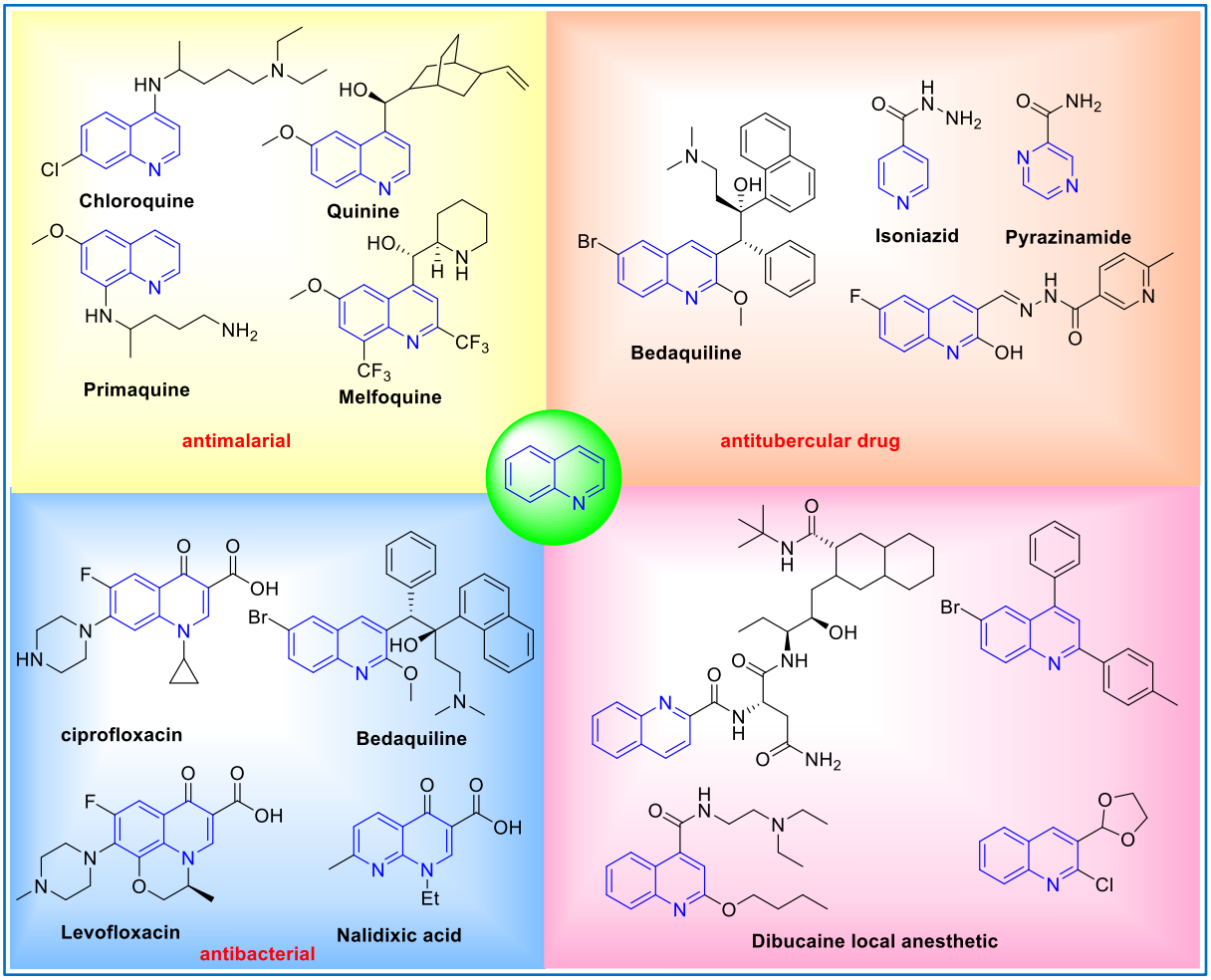


Figure 1.1. Selected quinoline-based marketed drugs.

According to reports, quinoline derivatives play a key role in the creation of anticancer medications that trigger apoptosis. This is successfully accomplished by eliminating cells that endanger animal survival and impair cell migration in addition to acting as angiogenesis inhibitors.[23] In preclinical models of hepatocellular carcinoma, foretinib displays anti-tumor effect and increases overall survival.[24] Cabozantinib, also known as XL184, is a potent inhibitor of the pathways FLT3, AXL, RET, KIT, MET, and VEGFR2, all of which have been implicated in the genesis of tumours (Figure 1.2).[25,26]

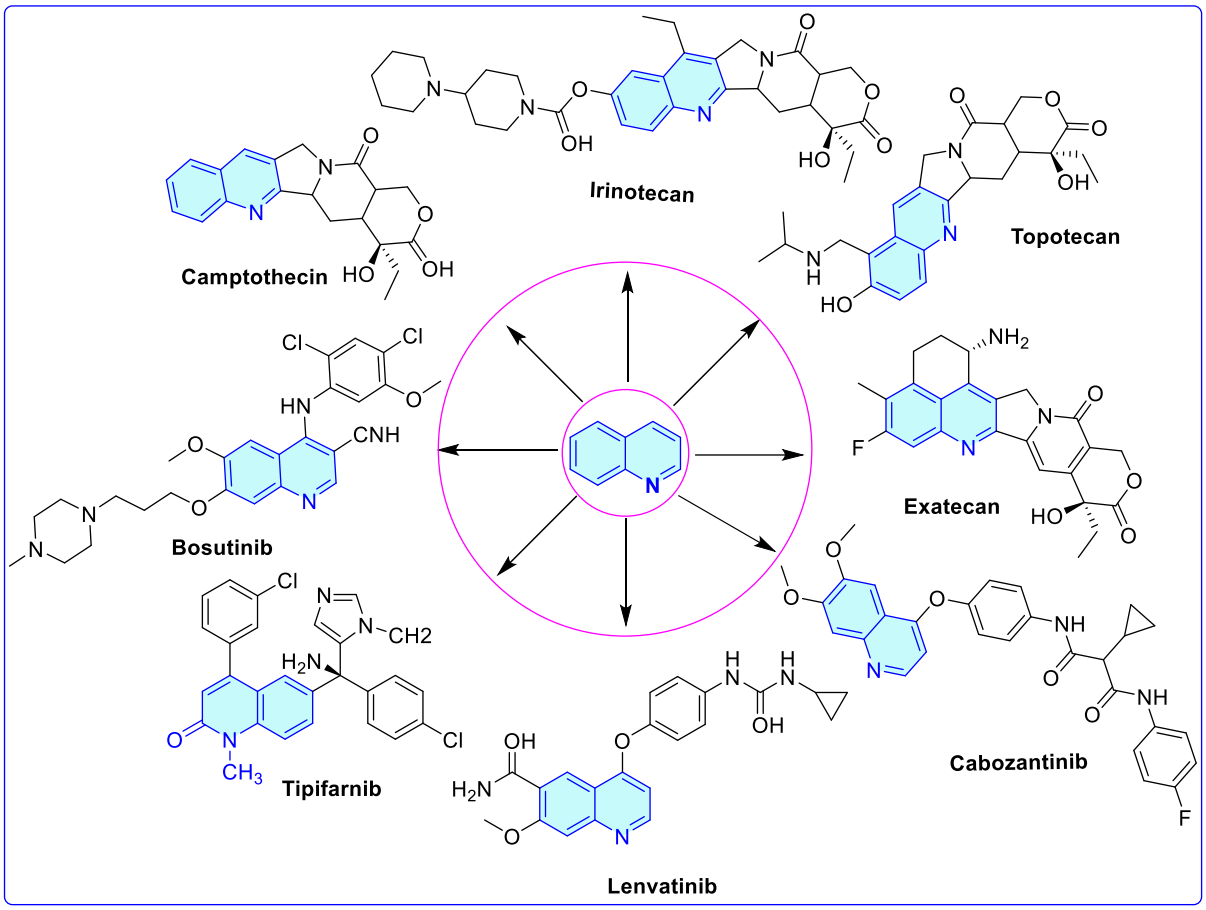
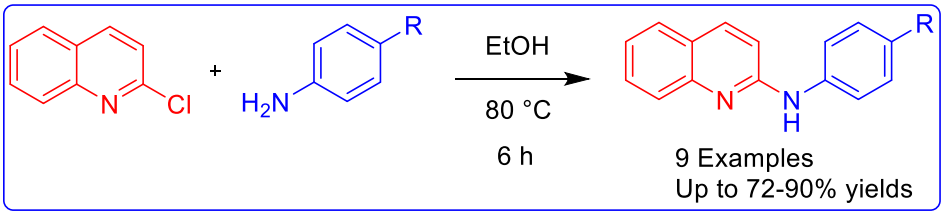


Figure 1.2. The structures of some approved quinoline-containing anticancer drugs

Hisham et al. studied fluorescence properties and applications of *N*-aryl-2-aminoquinolines. The Target molecules *N*-aryl-2-aminoquinolines have been synthesised by 2-chloro quinolines and anilines in ethanol. The fluorescence studies were carried out in ethanol, ethyl acetate, and toluene. According to the results, ethanol had the lowest fluorescence quantum yield of *N*-aryl-2-aminoquinolines, followed by toluene and ethyl acetate (Scheme 1.1).[27]

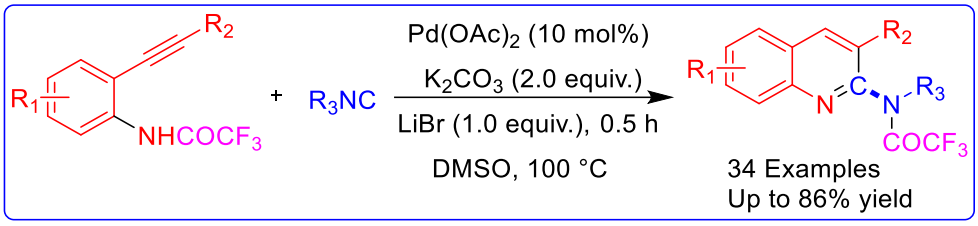


Scheme 1.1

Dhiman et al. synthesized 2-anilinoquinolines from quinoline *N*-oxides and aryldiazonium salts in acetonitrile under microwave irradiation conditions. This method involves three components under metal-free reaction (Scheme 1.2).[28]

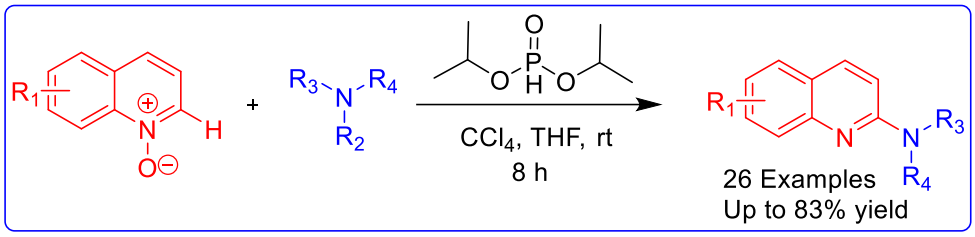
Scheme 1.2

Wu and co-workers introduced an efficient annulation method for synthesis of functionalized 2-aminoquinolines from *N*-acyl-o-alkynylanilines with isocyanides in the presence of palladium catalyst. High atom economy and an unconventional 6-endo-dig cyclization are some of its key features (Scheme 1.3).[29]



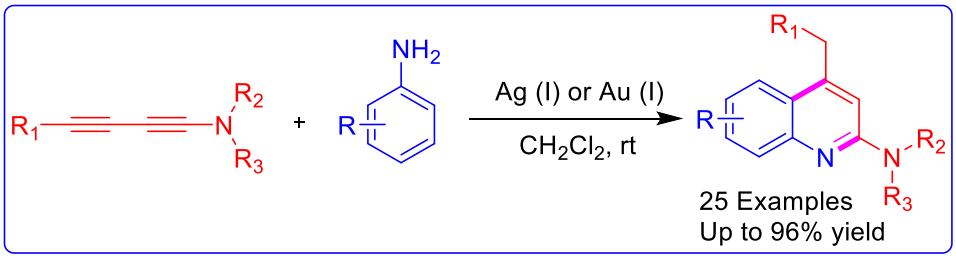
Scheme 1.3

Chen et al. developed a strategy for the synthesis of 2-dialkylaminoquinolines from quinoline *N*-oxides with tertiary amines in the presence of diisopropyl *H*-phosphonate and CCl_4 at room temperature. The benefits of the method were high efficiency, readily available reagents and starting materials, mild and metal free conditions (Scheme 1.4).[30]



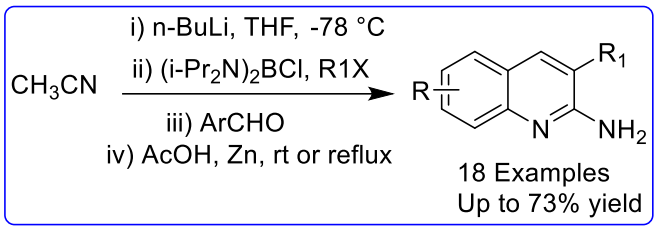
Scheme 1.4

Wang and co-workers synthesized 2-aminoquinoline from 1-aminobutadiynes with anilines in the presence of Ag(I)-catalyzed annulation in dichloromethane at room temperature (Scheme 1.5).[31]



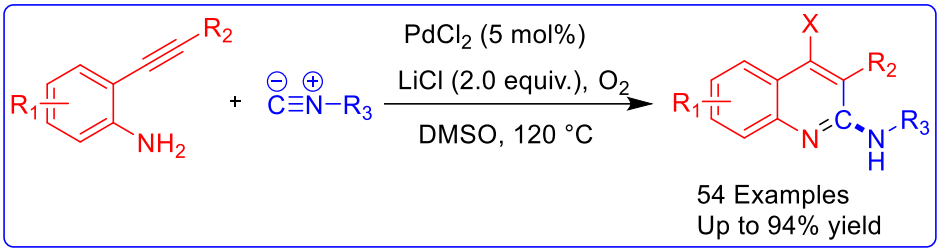
Scheme 1.5

Tomioka and co-workers developed a one-pot synthesis of a variety of substituted 2-aminoquinoline derivatives from α-diaminoboryl carbanions, readily prepared from acetonitrile (Scheme 1.6).[32]



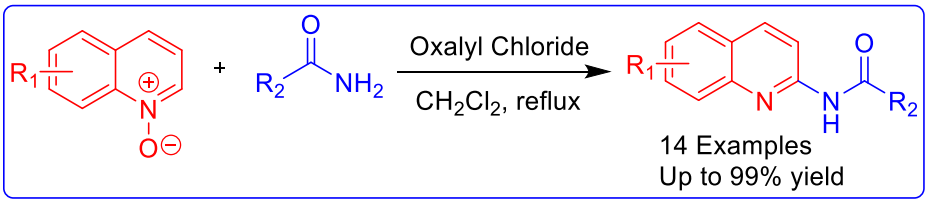
Scheme 1.6

Bifu Liu et al. reported the synthesis of 4-halo-2-aminoquinolines from 2-ethynylanilines with isocyanides in the presence of palladium-catalyzed intermolecular aerobic oxidative cyclization. Additionally, this method can be easily expanded to the two-step, one-pot intramolecular Buchwald-Hartwig cross-coupling to obtain different 6*H*-indolo[2,3 *b*]quinolines (Scheme 1.7).[33]



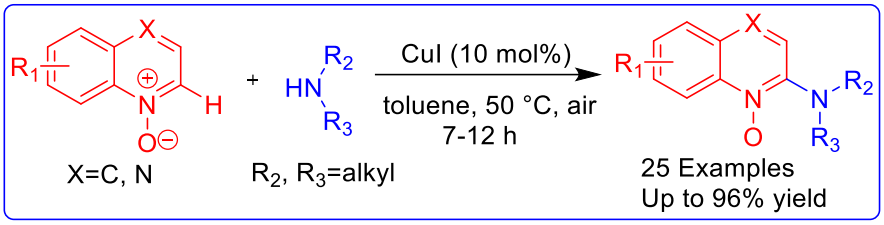
Scheme 1.7

Couturier and co-workers developed a novel procedure for α-amidoquinolines from quinoline *N*-oxides with primary amides, *via* simple, one-pot procedure. This approach is complementary to the Abramovich reaction, which can only introduce secondary amides when imidoyl chlorides are used (Scheme 1.8).[34]



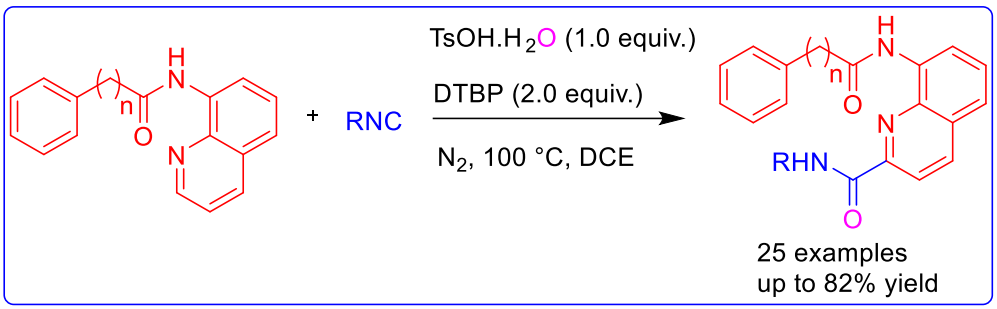
Scheme 1.8

Wu and co-workers introduced a direct amination of quinoline *N*-oxides with aliphatic amines in the presence of copper catalyzed dehydrogenative C-N coupling. This method is simple, high efficiency, low reaction temperature, environmental friendly, base and external oxidant free conditions (Scheme 1.9).[35]



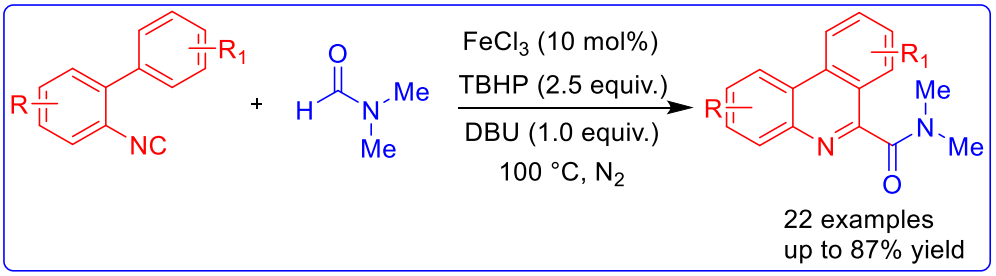
Scheme 1.9

Wenyan Hao et al. have effectively devised a metal-free selective C2-H amidation of 8-amidoquinolines utilizing isocyanide as the source of amide, offering a simple and practical route to C2-amidated 8-amidoquinoline derivatives under the oxidation condition in one-pot procedure (Scheme 1.10).[36]



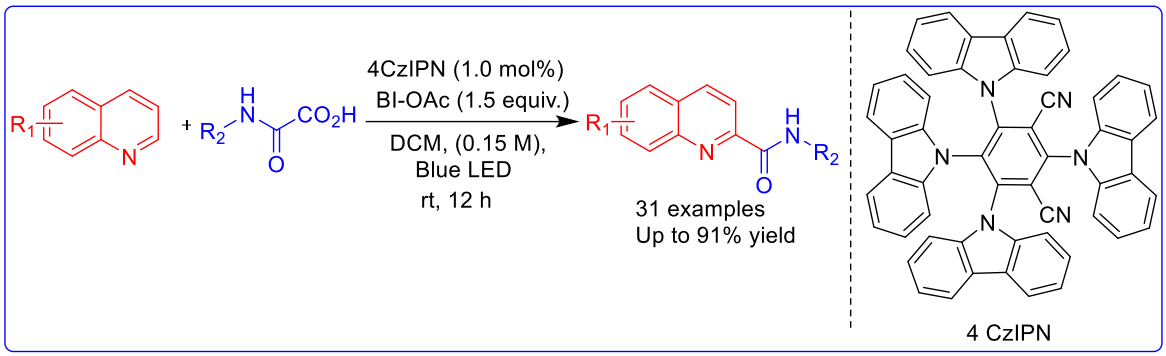
Scheme 1.10

Zhang et al. employed tandem carboxamidation and cyclization reaction by iron-catalysis using aryl isonitrile and formamides. The one-pot method can be used to synthesis phenanthridine-6-carboxamides in a variety of 2-isocyanobiphenyl and formamides with good functional group tolerance (Scheme 1.11).[37]



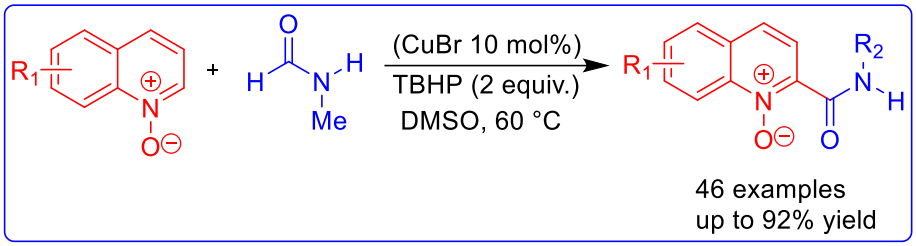
Scheme 1.11

Landais et al. reported a metal-free photo-catalyzed decarboxylation of oxamic acids to form carbamoyl radicals *in situ*, which were then added to heteroarenes under benign reaction conditions. This method has been used to produce the amides without racemization by carbamoylating heteroaromatic bases with a aminoacid-derived oxamic acids (Scheme 1.12).[38]



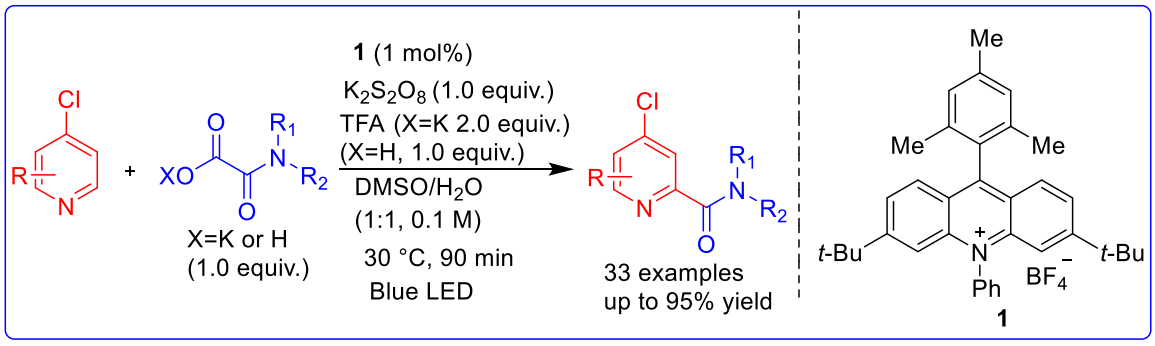
Scheme 1.12

Yan Zhang et al. reported a copper-catalyzed C-C and C-N bond *via* cross-dehydrogenative coupling reactions. This method has been used to create an efficient, direct carbamoylation and amination of quinoline *N*-oxides with formamides to obtain 2-carbamoyl and 2-amino quinolines (Scheme 1.13).[39]



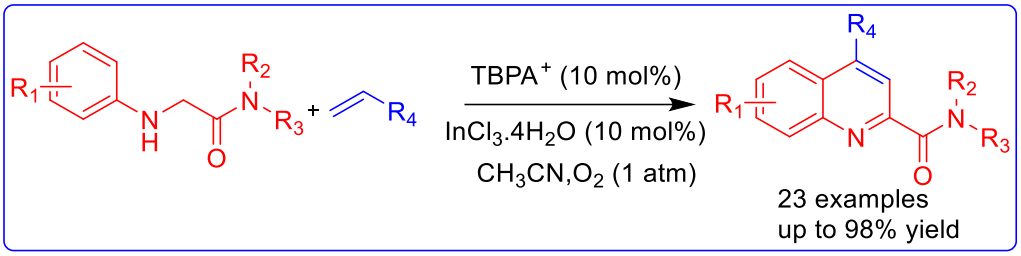
Scheme 1.13

Jouffroy et al. reported a visible light photo redox-mediated reaction, which enables direct C-H carbamoylation of heterocycles by means of a radical addition to a reactive heterocycle to provide nonfunctionalized Csp^2 center (Scheme 1.14).[40]



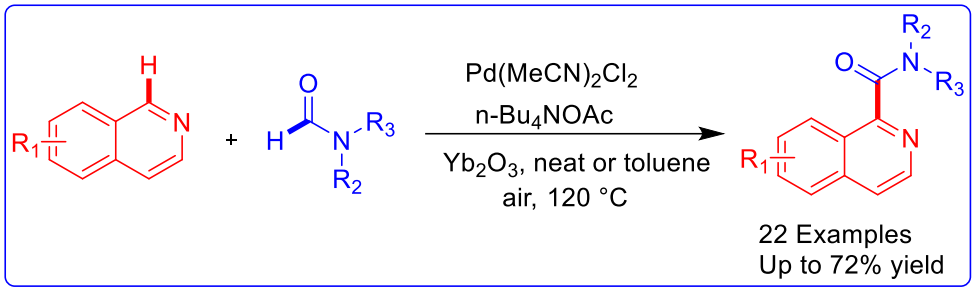
Scheme 1.14

Xiaodong Jia et al. described sp^3 C-H oxidation of peptides and glycine amides by aerial oxidation in presence of TBA to provide library of substituted quinolines (Scheme 1.15).[41]



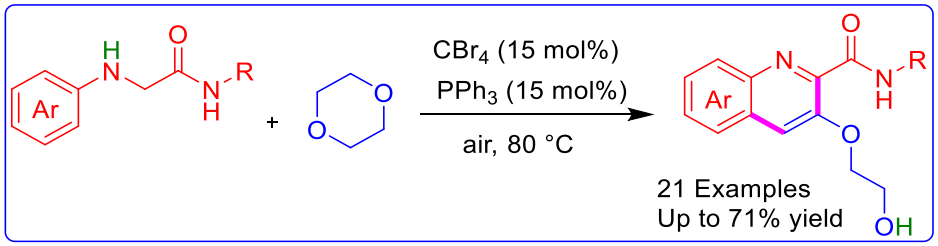
Scheme 1.15

Yao et al. accomplished the synthesis of isoquinoline-1-carboxamides using a novel palladium-catalysed oxidative carbamoylation reaction of isoquinoline *N*-oxides with formylamides. This method involves dual C-H oxidation to form the arylamides (Scheme 1.16).[42]



Scheme 1.16

Huo et al. described tandem carbon tetra bromide-promoted double-oxidative dehydrogenative cyclization/acidic ring opening/aromatization of glycine derivatives with dioxane to produce complex quinoline motifs. This procedure found to be very good for synthetic applications as it uses bench top chemicals under metal-free condition (Scheme 1.17).[43]



Scheme 1.17

Also, some of the recent work on sp^2 C-H functionalization of quinoline at various position are summarized in the figure 1.3.

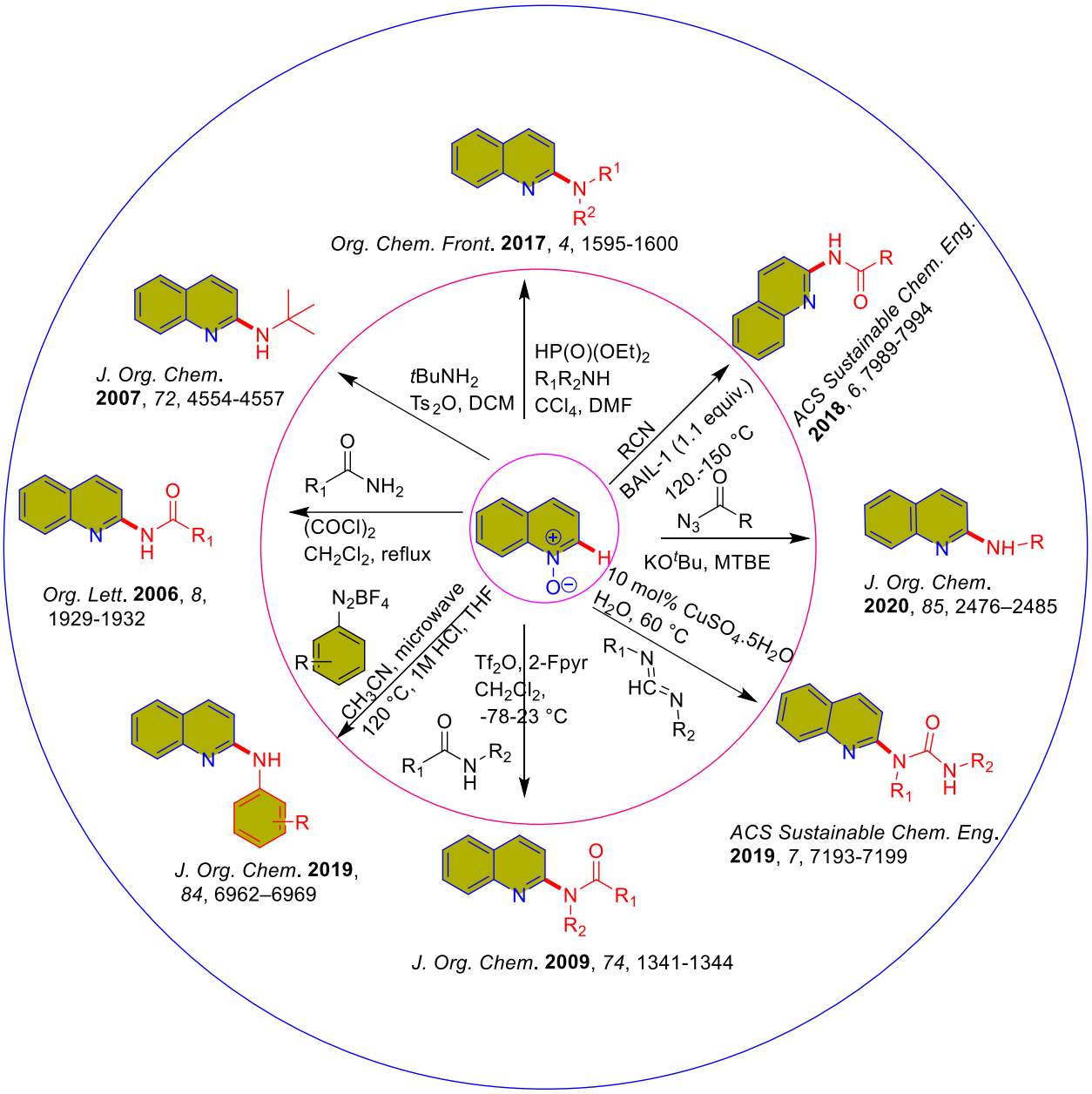


Figure 1.3. Various synthetic methods for the synthesis of C2-H amino quinolines

1.3. Isocyanides

An organic molecule having the functional group -$N^{+}\equiv C^{-}$ is known as isocyanide, commonly called as isonitrile or carbylamine. Its prefix is isocyano because it is an isomer of the closely related compound nitrile (-C≡N). The isocyanide is the unique functional group in organic chemistry. Its chameleonic nature allows for its carbon atom to be virtually the subject of all reactivities in organic chemistry. Indeed, it can act as a nucleophile attacking on activated electrophiles, as an electrophile being intercepted by different nucleophiles, as a carbene involved in formal [4+1] cycloaddition, and as a radical acceptor to form imidoyl radical's reaction intermediates.[44]

Isocyanides shows wide spectrum of biological activities including antibacterial, fungicidal, antineoplastic, and antifouling properties.[45, 46] The most prominent application for them is in isocyanide-based multicomponent reactions (IMCRs),[47,48] which have numerous uses in fields including polymer research,[57-60] drug discovery,[49,50] and chemical synthesis.

Among the isocyanide containing compounds, there are several well-known pharmaceutical agents which contain isocyanide functionalization these compounds are prepared *via* late-stage isocyanide. Amlodipine, an alkaloid used to treat high blood pressure dehydroabietylamine, a widely used pesticide and antifungal agent, tryptophan, an amino acid derivative (Figure 1.4).[51]

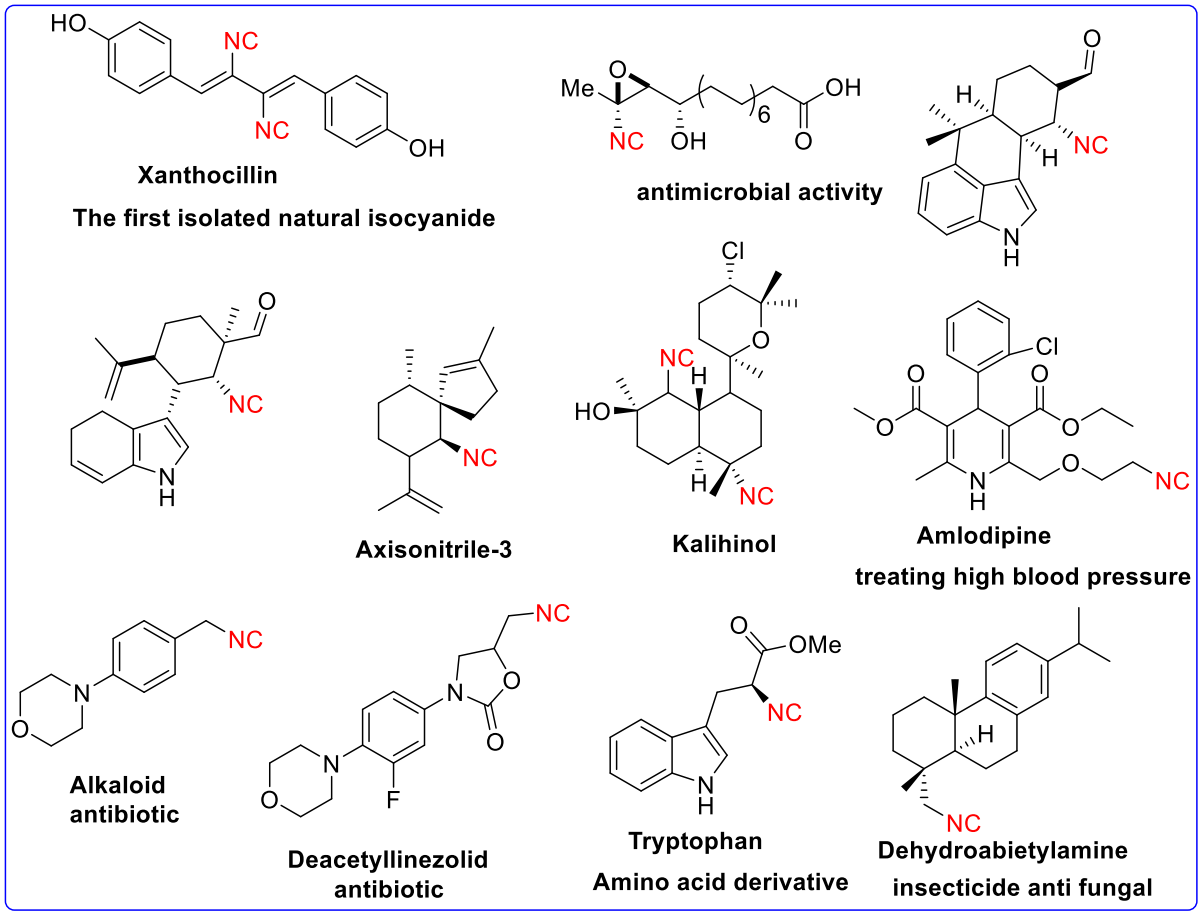


Figure 1.4. Some of the isocyanide containing bioactive compounds

The first isocyanide was synthesized by Lieke in 1859, and showed various synthetic pathways from wide precursors.[52] Lieke and Meyer were also able to produce isocyanides by reacting allyl or sugar halides with silver cyanide.[53] Later Hoffmann produced them by converting amines with *in-situ* generated carbenes of chloroform and potassium hydroxide or by heating isothiocyanates with PPh_3.[54-56] Nowadays *N*-formamides are the most often employed starting materials to create isocyanides with the addition of a reagent for dehydration in a basic environment. Isocyanides are versatile substances that have been used in a variety of

synthetically advantageous processes, such as Passerini or Ugi multicomponent reactions.[57] Various synthetic methods of isocyanides are summarized in the figure 1.5.

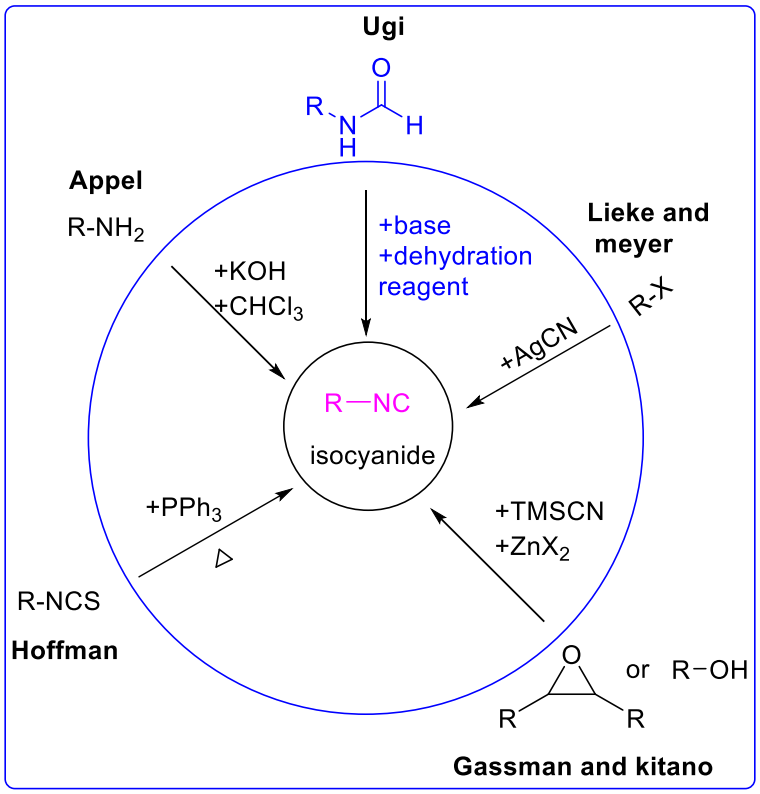
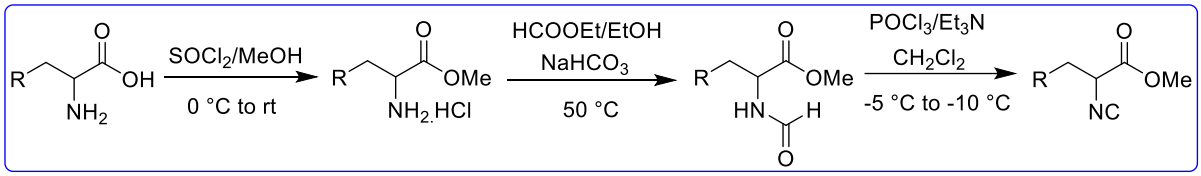


Figure 1.5. Various synthetic methods for the preparation of isocyanides

Halimehjani and co-workers developed a 3 steps one pot method, in which the amino acid is converted into an ester using thionyl chloride in methanol as a reagent and solvent. In the second step, the appropriate amino acid ester salt was formylated with ethyl formate in the presence of $NaHCO_3$. Finally, the formamide group was converted to the corresponding isocyanide by treatment with $POCl_3$ and triethylamine (Scheme 1.18).[58]



Scheme 1.18

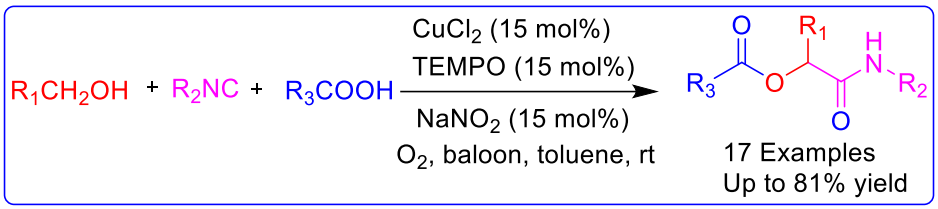
1.4. Multicomponent Reactions

Multi-component reactions are one of the most powerful tools in organic chemistry, in which one pot reactions employing more than two starting materials. Among the multi-component reactions, three component reactants like Strecker (1850), Hantzsch (1882), Biginelli (1891), Mannich (1912), and Passerini (1921) are more popular in organic chemistry.[59] Particularly

isocyanide based multi-component reactions become thrust area in organic chemistry after discovery of the Passerini three component reaction and Ugi four component reactions. The versatile Ugi four component reaction is an example of single reactant replacement (SRR) of Passerini reaction where aldehydes, amines, isocyanides and carboxylic acids are employed to obtain peptomers.[60]

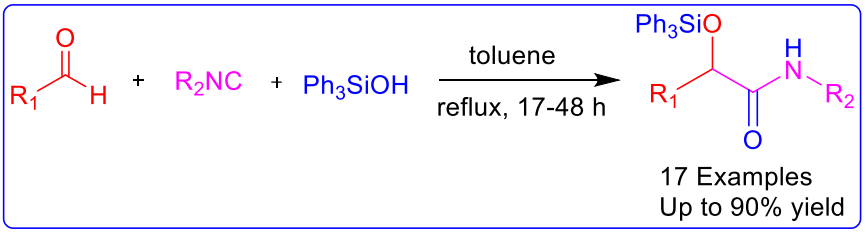
Passerini reactions

Zhu and co-workers developed a Passerini three-component reaction under catalytic aerobic conditions. In this P-3CR, alcohols are used in place of aldehydes to obtain the desired aldehyde component under $NaNO_2$, TEMPO, cupric chloride and, oxygen atmosphere (Scheme 1.19).[61]



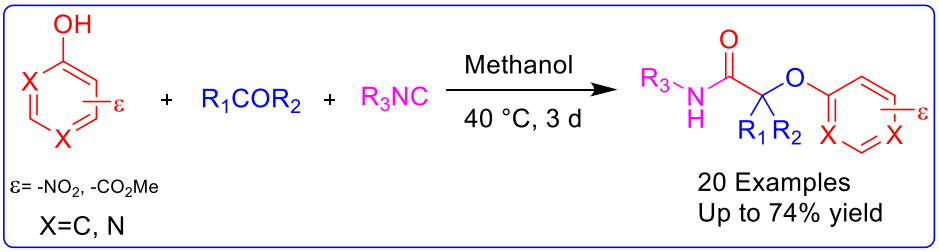
Scheme 1.19

Soeta and co-workers introduced an efficient, novel method for the synthesis of *α*-siloxyamides from aldehyde, isocyanide and silanol in toluene. In this process, a wide variety of aldehydes and isocyanides can be used (Scheme 1.20).[62]



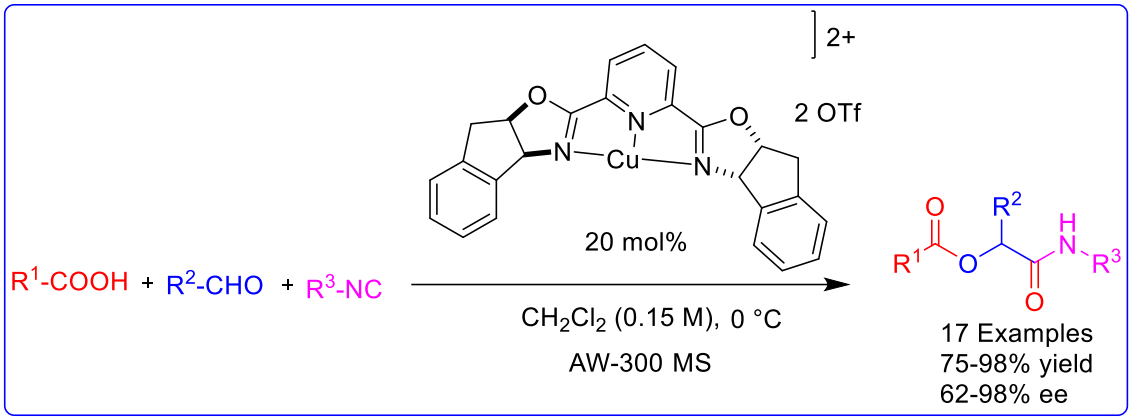
Scheme 1.20

Laurent El Kaïm and co-workers introduced an efficient and novel method of 3-component Passerini-Smiles reaction. In this method phenols are introduced in place of carboxylic acid under standard conditions to obtain *O*-arylated compounds. The key step of the conversion lies in an irreversible Smiles rearrangement of intermediate phenoxyimidate adducts. This methodology represents the first use of a Smiles rearrangement in a Passerini reaction (Scheme 1.21).[63]



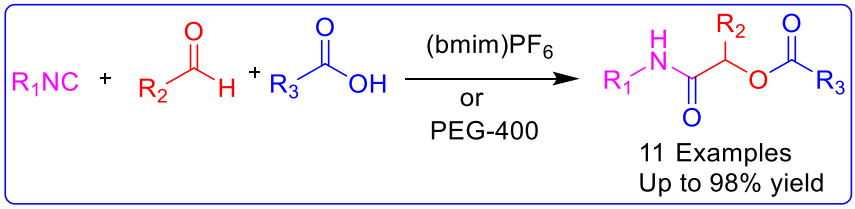
Scheme 1.21

Schreiber and co-workers developed a catalytic asymmetric Passerini reaction using tridentate bis(oxazolinyl)pyridine (pybox)-Cu(II) Lewis acid complex to obtain Passerini adduct in good to excellent yields with help of ligand-accelerated catalysis (Scheme 1.22).[64]



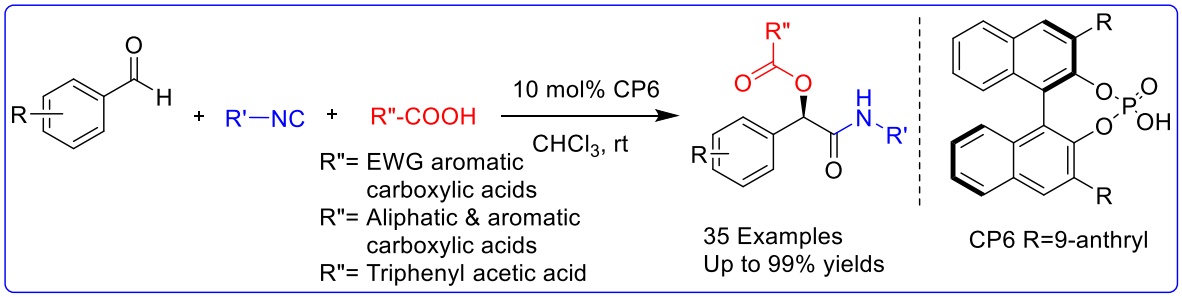
Scheme 1.22

Andrade et al. introduced an efficient green methodology for the synthesis of *α*-acyloxy carboxamides from aldehydes, isocyanides and carboxylic acids using ionic liquids or polyethylene glycol (PEG-400) (Scheme 1.23).[65]



Scheme 1.23

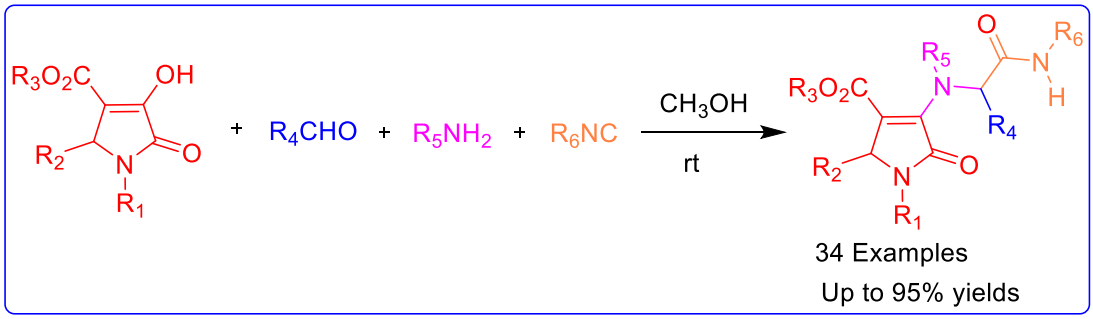
Bin Tan and co-workers developed an efficient enantioselective classic three component Passerini reaction in the presence of a chiral phosphoric acid catalyst. In this method they used a chiral phosphoric acid to activate aldehydes, isocyanides and carboxylic acids to produce target compounds. High enantioselective, mild reaction conditions and broad substrate scope are some of the key features of this method (Scheme 1.24).[66]



Scheme 1.24

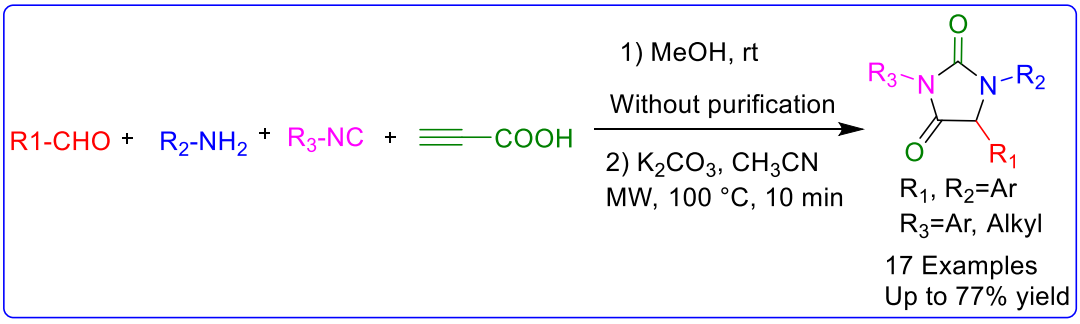
Ugi 4CR reactions

Castellano et al. have developed for the first time Ugi type reactions involving heterocyclic enols, which are used as the acidic partners. They have selected enols with a Michael acceptor for this purpose, in order to achieved an irreversible rearrangement of the Ugi adduct. The reaction proceeds at room temperature without any difficulty and in catalyst free condition (Scheme 1.25).[67]



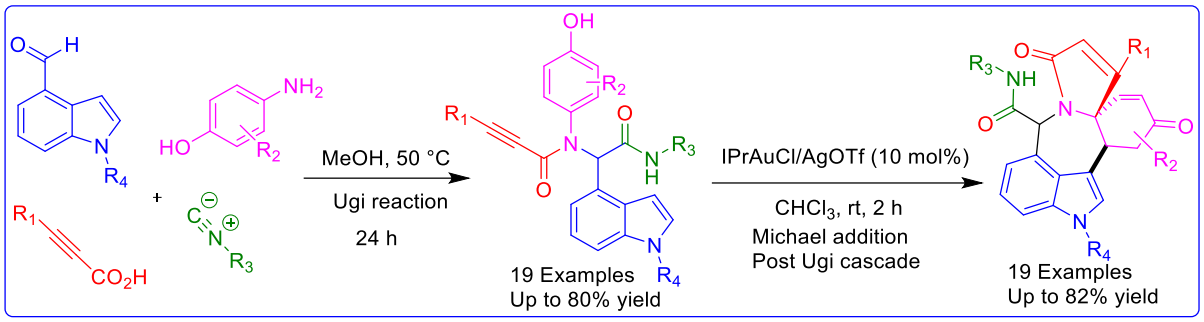
Scheme 1.25

Xu et al. developed a synthesis of hydantoins *via* a two-step Ugi/cyclization reaction sequence using alkyne as a leaving group in the presence of basic medium. For the synthesis of hydantoins with microwave-assisted one-pot cyclization technique may be used in various multicomponent reactions (MCRs). These compounds show wide variety of biological activities (Scheme 1.26).[68]



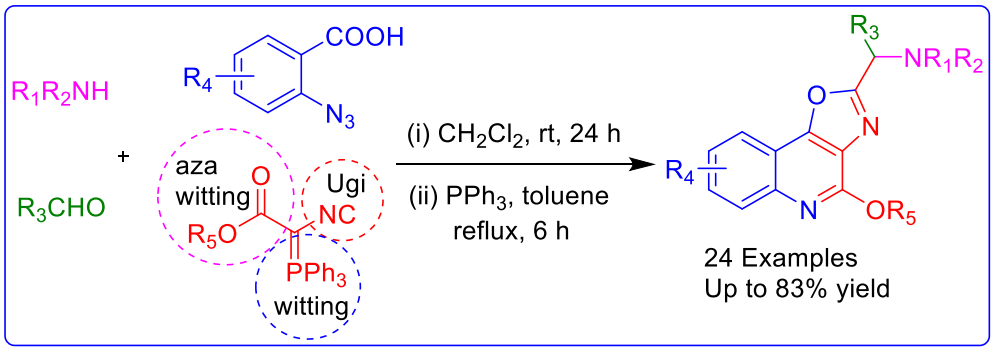
Scheme 1.26

Li and co-workers demonstrated the creation of quick and varied access to complicated natural products like 3,4-fused indole scaffolds. This method affords polycyclic azepino-[5,4,3-*cd*] indole scaffolds in good to excellent yields. This synthetic process involves a gold catalysed domino Ugi-four component and post-Ugi steps *via* dearomatization/Michael addition sequence (Scheme 1.27).[69]



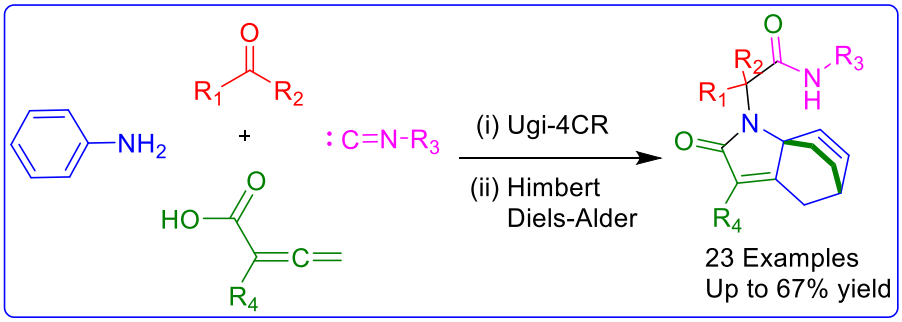
Scheme 1.27

Ding and co-workers introduced a one-pot novel method for the synthesis of various oxazolo[4,5-*c*]quinoline derivatives from amines, aldehydes, 2-azidobenzoic acids and isocyano(triphenylphosphoranylidene)-acetates. In this method synthesis of target products are achieved *via* a sequential Ugi/Wittig/aza-Wittig cyclization process under mild reaction conditions with broad substrate scope (Scheme 1.28).[70]



Scheme 1.28

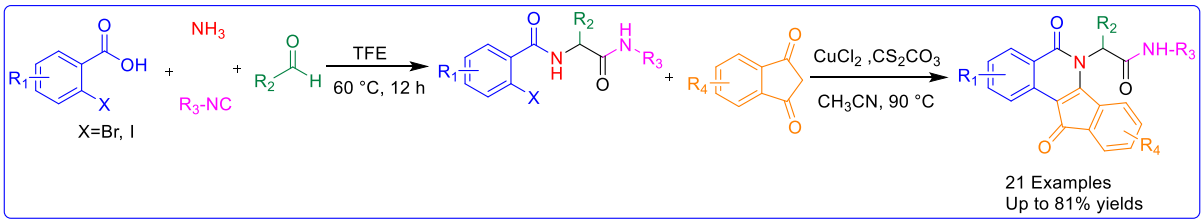
Jia and co-workers developed an efficient multicomponent reaction for the synthesis of strained polycyclic skeletons from isocyanide, allenic acid, aldehyde (ketone), and aniline. This procedure uses Ugi reaction followed by an intramolecular arene/allene Diels−Alder sequence (Scheme 1.29).[71]



Scheme 1.29

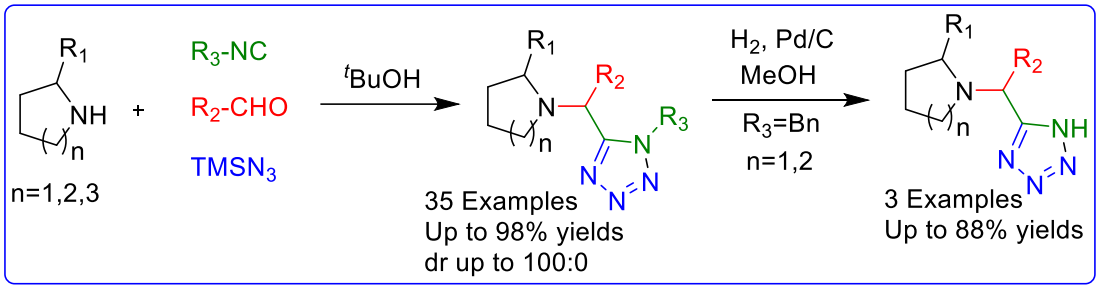
Wang et al. described a novel synthesis of indeno[1,2-*c*]isoquinolinone by using aldehydes, isocyanides, ortho-halobenzoic acids and ammonia, followed by a Cu-catalyzed annulation

reaction with 1,3-indandione. The advantages of this reaction were operation simplicity, broad substrate scope and readily available starting materials (Scheme 1.30).[72]



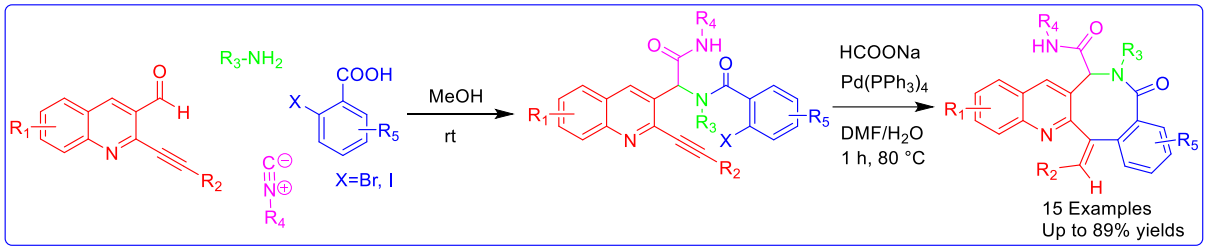
Scheme 1.30

Zarezin et al. developed diastereoselective of azido-Ugi reaction with *α*-substituted five to seven membered cyclic amines in mild reaction conditions using aldehydes, amines and isocyanides (Scheme 1.31).[73]



Scheme 1.31

Ghazvini et al. synthesised quinoline fused eight-membered rings from simple starting materials, base *via* reductive carbopalladation of Ugi-4CR substrates including alkynyl quinolone and *ortho*-halo benzoyl moieties. The bioactivity of medium-sized rings containing fused quinolines used against depressive and anxiety disorders are performed (Scheme 1.32).[74]



Scheme 1.32

1.5. Rongalite

Rongalite is a white crystalline solid with chemical formula $HOCH_2SO_2Na.2H_2O$. It is scientifically called as sodium hydroxymethanesulfinate dihydrate (Figure 1.6) or sodium formaldehyde sulfoxylate.[75] Rongalite has been used as decolourizing agent and also used as bleaching agent in the dyeing and printing industry.[76] It is also used as antidote against heavy metal poisoning caused by Hg, Au, Cu, Ba, Sb, Pb, and Bi.[77] aldehydes,[78] benzils,[79]

nitroaromatics, metal salts.[80] Ronglite act as a green reducing agent.[81] It is also used as veterinary medicines.[82] Rongalite act as an antioxidant in the formulation of anticancer drugs.[83] It is a very less expensive and commercially available. Rongalite acts as a sulfone source, C1 synthon, radical initiator, and reducing agent.

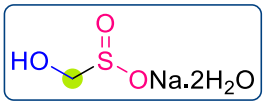
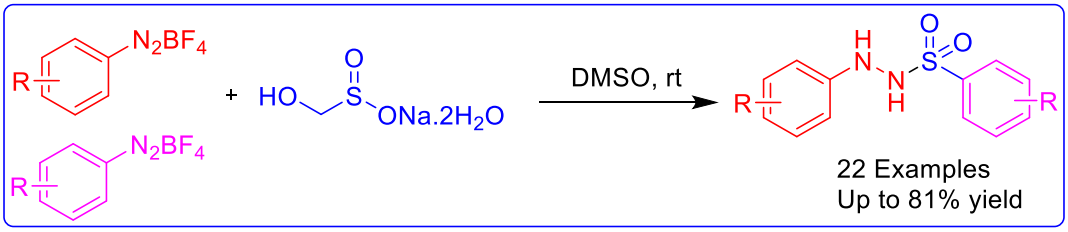


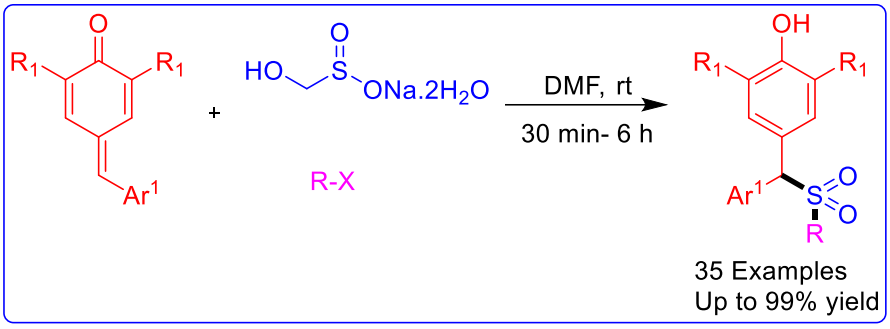
Figure 1.6. Rongalite

Wu and co-workers reported a synthesis of *N*-aminosulphanamide from the cross coupling aryldiazonium tetrafluoroborate and rongalite at room temperature. It is a metal free and oxidant free reaction. In this method aryldiazonium tetrafluoroborate acts as an aryl radical and amine source. Rongalite act as a radical, and sulphur dioxide surrogate and act as a reducing agent simultaneously (Scheme 1.33).[84]



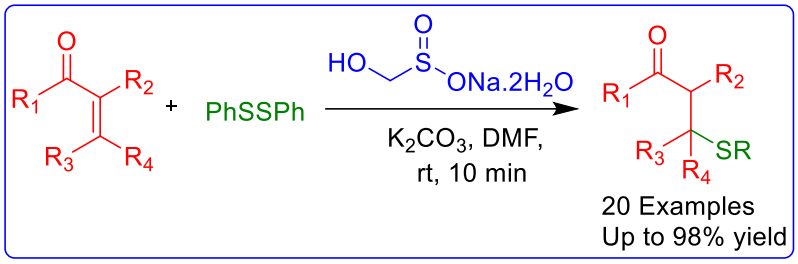
Scheme 1.33

Das and co-workers reported a one-pot multicomponent reaction synthesis of unsymmetrical sulfones from *p*-quinone methides, rongalite and alkyl/allyl halides. It involved a mild reaction conditions in the absence of metal, bases and any other additives (Scheme 1.34).[85]



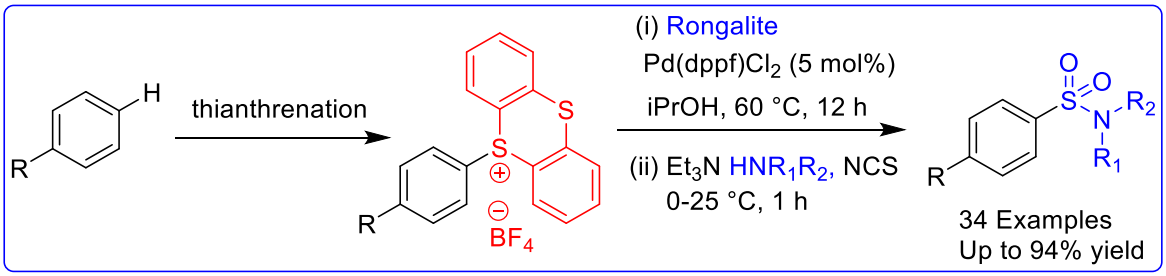
Scheme 1.34

Guo et al. reported an efficient method for the synthesis of *β*-sulfido carbonyl compounds from *α, β*-unsaturated carbonyl ketones or esters and disulfides in the presence of rongalite in *N,N*-dimethylformamide at room temperature. In this method rongalite acts as a promoter for the cleavage of disulfides to generate thiolate anions, which then undergo facile-thia Michael addition (Scheme 1.35).[86]



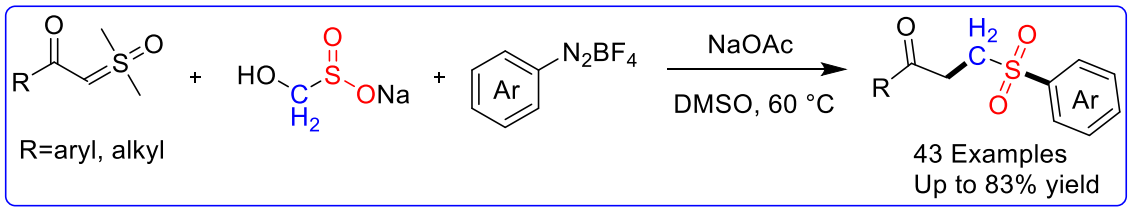
Scheme 1.35

Ritter and co-workers reported a site-selective two-step C-H sulfination sequence *via* aryl sulfonium salts to access aryl sulfonamides. Combined with site-selective aromatic thianthrenation, an operationally simple one-pot palladium-catalyzed protocol introduces the sulfonyl group using sodium hydroxymethylsulfinate (Rongalite) as a source of SO_2^{2-}. The hydroxymethyl sulfone intermediate generated from the catalytic process can be employed as a synthetic handle to deliver a variety of sulfonyl-containing compounds (Scheme 1.36).[87]



Scheme 1.36

Chen et al. reported a synthesis of sulfonylmethylation from sulfoxonium yields, aryldiazonium salts and rongalite in presence of base at 60 °C. In this process rongalite play multiple roles as a sulfone source, C1 synthon, radical initiator, and reducing agent (Scheme 1.37).[88]



Scheme 1.37

1.6. Imidazo[1,2 *a*]pyridines

Imidazole scaffold exhibits numerous therapeutic properties, and involved in the synthesis of novel chemotherapeutic agents like miconazole, ketoconazole, clotrimazole, tioconazol etc. The imidazole and imidazo[1,2 *a*]pyridine have been recognized as a privileged structure

because of its diverse biological and pharmaceutical activity.[89-93] Imidazopyridines are frequently called as imidazo[1,2-*a*]pyridines and imidazo[1,5-*a*]pyridines (Figure 1.7).

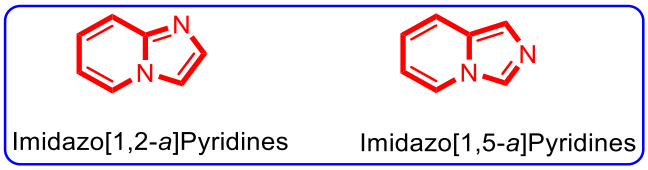


Figure 1.7.

Imidazo[1,2-*a*]pyridines are an important class of fused nitrogen-bridged hetero cyclic compounds and numerous biological and pharmaceutical applications.[94] These derivatives show broad range of biological activities like antibacterial, antiviral, antifungal, anti-inflammatory, antitumor, antiapoptotic, analgesic, antiprotozoal, hypnoselective, and anxioselective activities.[95] There are several drugs such as zolpidem, alpidem, olprinone in the market containing Imidazo[1,2-*a*]pyridine moiety (Figure 1.8).[96-97]

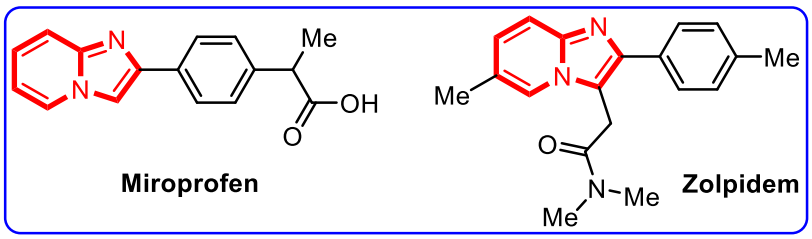


Figure 1.8. Imidazo[1,2-*a*]pyridine drugs

1.7. References

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CHAPTER-IIA

Iodine Catalyzed C2-H Formamidation of Quinoline *N*-oxides Using Isocyanides

2A.1. Introduction

Quinoline-containing compounds exhibit a wide range of intriguing biological activity and physicochemical characteristics among several groups of *N*-hetero-aryl compounds.[1] The quinoline ring serves as the fundamental structural component of a number of naturally occurring products, physiologically active compounds, and a preferred synthon in medicinal chemistry for the identification of novel therapeutic leads.[2] Quinolines and their derivatives are used to treat malaria, and different functional groups have been added to quinolines to enhance their therapeutic properties.[3] However, the quinoline core moiety is prone to detoxification in the body by hydroxylation of its C2 position, which causes a sharp decline in its therapeutic effects.[4] Sulfonylation, amination, and alkylation at the C2 position of quinolines have all been investigated as potential solutions to stop the hydroxylation of these compounds.[5-6] The C2 position in quinolines has been functionalized using a variety of synthetic chemistry techniques because of its biological significance. There are only a few amination methods accessible for the synthesis of 2-aminoquinolines.[7] The conventional techniques used in this category of synthetic synthesis of 2-aminoquinolines require an amination reaction with 2-chloroquinolines, which further necessitates undertaking the laborious process of chlorinating quinoline *N*-oxides with poor 2,4-regioselectivity.[8] Therefore, it is difficult to functionalize quinolines at the C2 position by activating quinoline *N*-oxides with appropriate activators. Although there are several activators available, including sulfonyl chlorides,[9] acyl chlorides,[10] anhydrides,[11] PyBroP,[12] and boron [13] reagents, each has its own drawbacks, such as stoichiometry, cost, and toxicity. To the best of our knowledge, there is no direct procedure for producing *N*-(2-quinolinyl) formamides from isocyanides and quinoline *N*-oxides catalyzed by iodine. We have suggested iodine catalyzed C2-H functionalization of quinoline *N*-oxides with isocyanides to create *N*-(quinolin-2-yl) formamides as part of our continuous interest in green chemistry.[14] In this study, we attempted to develop a method for the deoxygenative 2-amidation of quinoline *N*-oxides with isocyanides without the need of metal catalysts.

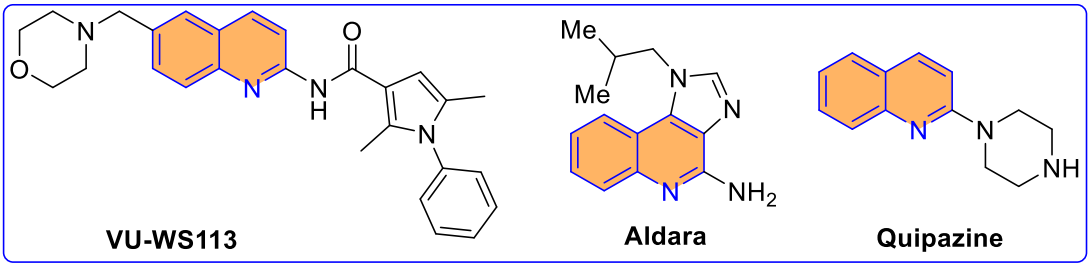
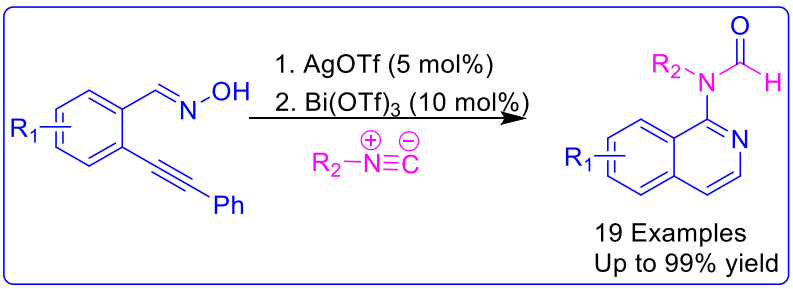


Figure 2A.1. Some examples of functional 2-aminoquinolines

The creation of a mild, effective, and unique approach to the synthesis of *N*-(2-quinolinyl)formamides a substance that is structurally significant in and of itself as well as the availability of a useful way to supplement the C2 aminoquinolines are major benefits of this strategy. For instance, a type of anticancer medication is VU-WS113.[15] Imiquimod (1-isobutyl-1*H*-imidazo[4,5- c]quinolin-4-amine), the brand name of Aldara, has some effects on actinic keratosis and superficial skin malignancies (Fig 2A.1).[16] It was discovered that quipazine can be used to treated with tricyclic antidepressants.[17]

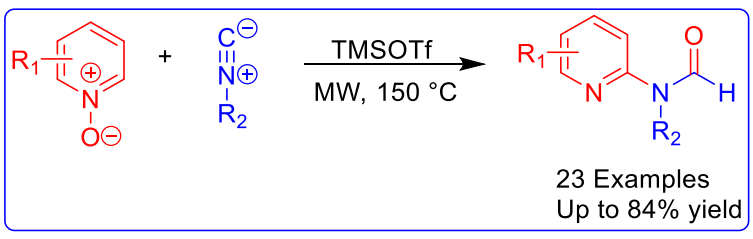
2A.1.1. Reported methods for the synthesis of C2-H formamidation of quinoline *N*-oxides and its derivatives

Wu et al. reported Ag(I) and $Bi(OTf)_3$ mediated tandem reactions on 2-alkynylbenzaldoximes to obtain substituted isoquinolines in good to excellent yields. However, the above mentioned method showed inferior results with quinoline *N*-oxides (Scheme 2A.1).[18]



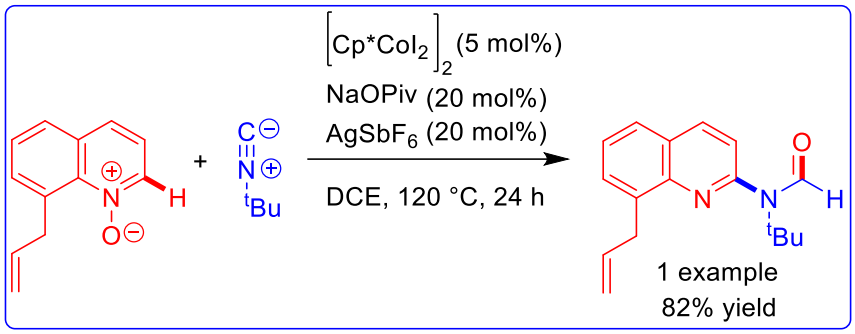
Scheme 2A.1

Vamos et al. introduced a practical and efficient method for the synthesis of substituted 2-aminopyridines from pyridine *N*-oxides with activated isocyanides in presence of TMSOTf under microwave at 150 °C for 15 min, then 1 M HCl and THF, 50 °C. The reaction involves an *in situ* deprotection of an isolable *N*-formylaminopyridine intermediate and facilitates the synthesis of 2-aminopyridines (Scheme 2A.2).[19]



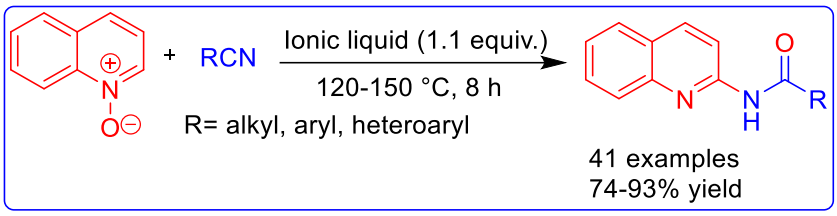
Scheme 2A.2

Sundararaju et al. have reported cobalt-catalyzed an unprecedented C(8)-H bond allylation of quinoline with allyl carbonate and allyl alcohol *via* β-oxygen and β-hydroxy elimination. This site-selective allylation reaction proceeds smoothly with wide functional group tolerance (Scheme 2A.3).[20]



Scheme 2A.3

He et al. developed a simple**,** economic and eco-friendly synthesis of highly diversified *N*-acylated 2-aminoquinolines *via* Bronsted acidic ionic liquid-promoted amidation of quinoline *N*-oxides with nitriles. The easily accessible starting materials, wide group tolerance, 100% atom economy and operational simplicity are some of the key features of this method (Scheme 2A.4).[21]

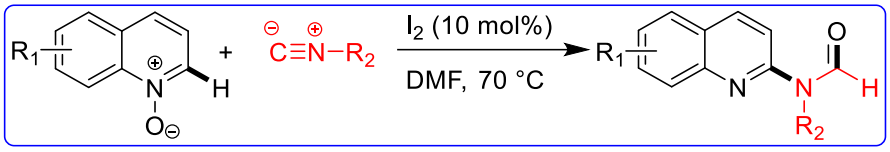


Scheme 2A.4

A considerable attention has been received to the synthesis of quinoline 2-formamides and functionalization of quinolines at C2 position to increase the biological activity of the quinoline core. Much has already been done on alkenylation, arylation, alkynylation, amination, acylation, sulfuration, and alkylation of quinolines. Whereas, formamidation of quinolines are common pharmacophores with wide applications in pharmaceuticals. Nevertheless, the direct formamidation of quinolines has only caught the imagination of only a few chemists. Till now only few reports are available for the direct synthesis of quinoline 2-formamide substituted quinolines. Therefore, introducing formamidation group into the quinoline ring has the potential to attract many researchers in this direction.

2A.2. Present study

Herein we describe metal-free synthesis of quinoline 2-formamides, substituted quinolines *via* C(sp^2)-H functionalization in the presence of molecular iodine and isocyanide. In this chapter, a molecular iodine catalyzed regioselective insertion of isocyanide into C2-H of quinoline *N*-oxides has been described. The reaction proceeds through the nucleophilic addition of isocyanide on quinoline *N*-oxides followed by rearrangement in presence of iodine. This metal-free reaction affords rapid access to quinoline 2-formamides with exceptional functional group tolerance and broad substrate scope (Scheme 2A.5).



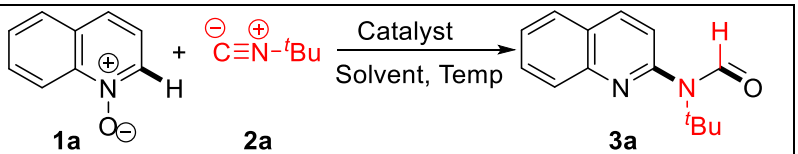
Scheme 2A.5. Synthesis of *N*-(2-quinolinyl)formamides

With this proposed methodology, a library of quinoline 2-formamides could be synthesized under environmentally benign conditions *i.e.*, metal free, less expensive, non-hazardous, and easily available reagents.

2A.2.1. Results and discussion

In our initial screening experiments, the reaction between quinoline *N*-oxide **1a** with *tert*-butyl isocyanide **2a** in the presence of 10 mol% of iodine with suitable solvent and temperatures was investigated to optimize the reaction conditions, and only the key facts are reported in the Table 2A.1. The reaction of quinoline *N*-oxide **1a** with *tert*-butyl isocyanide **2a** in the presence of 10 mol% of iodine in CH_3CN at room temperature did not afford the desired product even after stirring for 24 h (Table 2A.1, entry 1).

Table 2A.1. Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1.	I_2	CH_3CN	rt	0
2.	I_2	CH_3CN	70	50
3.	I_2	CH_2Cl_2	40	n.r
4.	I_2	$ClCH_2CH_2Cl$	60	n.r
5.	I_2	THF	70	10
6.	I_2	CH_3NO_2	70	n.r
7.	I_2	Toluene	70	n.r
8.	**I_2**	**DMF**	**70**	**90**
9.	I_2	DMSO	70	75
10.	I_2	DMF	60	70
11.	I_2	DMF	100	80
12.	NIS	DMF	70	30
13.	NBS	DMF	70	40
14.	NaI	DMF	70	n.r
15.	I_2	DMF	70	65[c]
16.	I_2	DMF	70	30[d]
17.	-	DMF	70	n.r

[a]Reaction conditions: quinoline *N*-oxide **1a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.5 mmol), catalyst (10 mol%), solvent (2 mL), 6 h, [b] Isolated yield, [c] Iodine (5 mol%), [d] Iodine (2 mol%) used, n.r = No reaction.

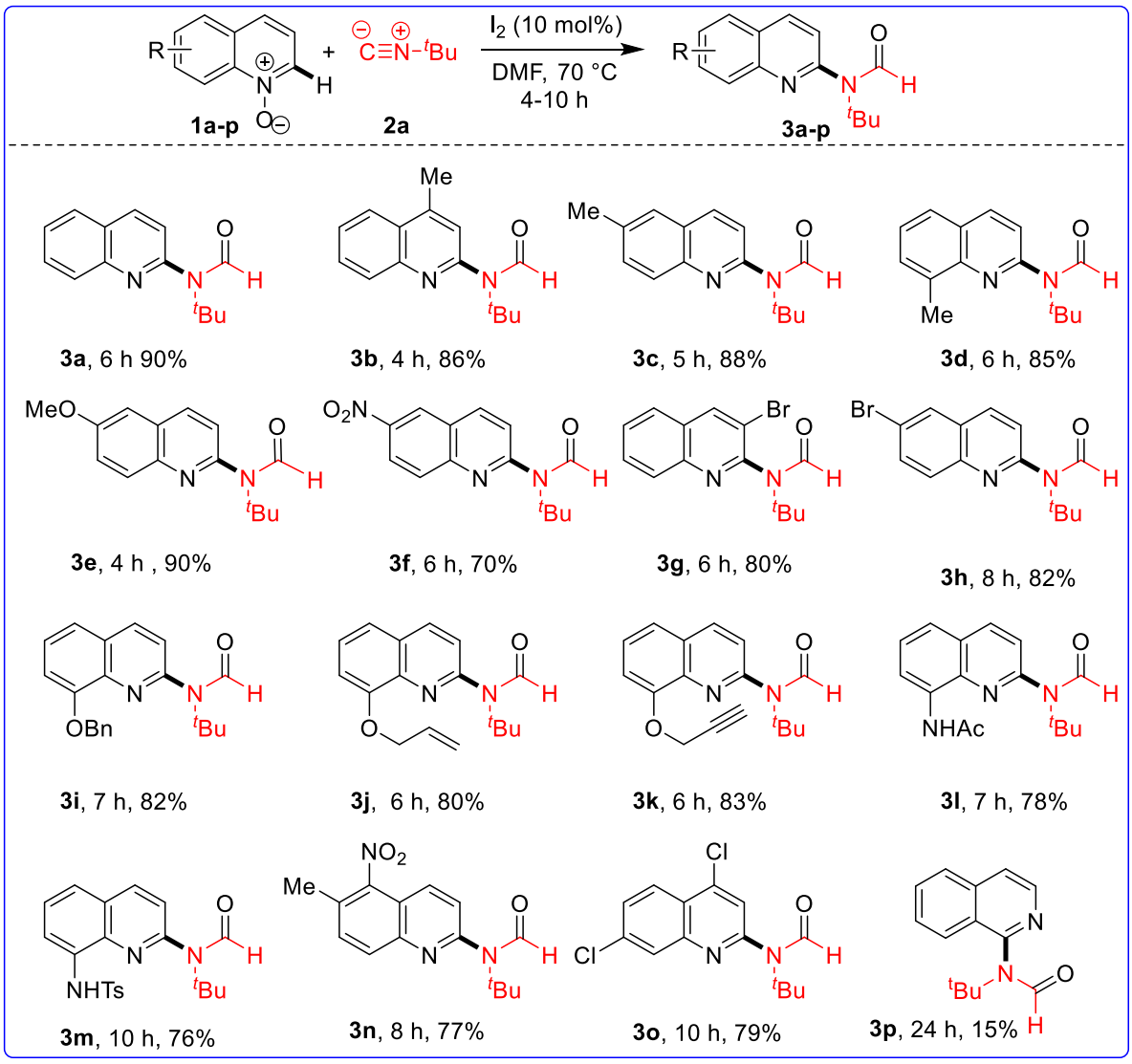
To our delight, the formation of *N*-*tert*-butyl-*N*-(quinolin-2-yl)formamide **3a** was observed with 50% in CH_3CN at elevated temperatures (Table 2A.1, entry 2). These results motivated us to optimize the reaction conditions to improve the product yield. Next, we have carried out the reaction in various solvents to assess their effect on the reaction efficiency. Among all the solvents used, DMF was superior to the tested solvents,such as chlorinated solvents, THF, CH_3NO_2, Toluene and DMSO for this transformation (Table 2A.1, entries 3-9). Further, change in the temperature did not improve the yield. (Table 2A.1, entry 10-11).

Disappointingly, other promoter sources including *N*-iodosuccinimide, *N*-bromosuccinimide and NaI were investigated and found to have negative impact on reaction yields (Table 2A.1, entries 12-14). Additionally, changing the loadings of catalyst had no positive effect on the transformation, only 65% and 30% yields were obtained when 5 mol% and 2 mol% of catalyst were used respectively (Table 2A.1, entries 15-16). It is worth mentioning that our method proceeds with 100% atom-economy. Therefore, the optimized reaction conditions are 0.5 mmol of quinoline *N*-oxide, 0.5 mmol of isocyanide and 10 mol% of I_2 in 2 mL DMF at 70 °C for 6 h as shown in (Table 2A.1, entry 8).

With the optimized conditions in hand, we commenced the evaluation of the scope of the reaction by examining diversely substituted quinoline *N*-oxides with *tert*-butyl isocyanide and results are shown in Table 2A.2. In the beginning we explored the effect of electron donating groups on quinoline *N*- oxides with *tert*-butyl isocyanide to obtain the corresponding quinoline 2-formamides and found to be well tolerated (Table 2A.2, **3b**-**e**). Also, the electron withdrawing group on sixth position of quinoline gave the target product **3f** in 70% yield. Likewise, halogen substituted quinoline *N*-oxides were reacted smoothly with *tert*-butyl isocyanide to give the corresponding 2-formamide quinolines in good yields (Table 2A.2, **3g**-**h**). Notably, substitution at C8 position such as benzyl,allyl, propargyl ethers, *N*-acetyl and *N*-tosyl of the quinoline *N*-oxides are readily converted into the respective C2-formamides in 76-83% yields(Table 2A.2, **3i**-**m**). It is worth noting that the quinoline *N*-oxides having disubstitutions also delivered the product **3n**-**o** in 77–79% yield. Indeed, C2- formami dation of pyridine *N*-oxide was not successful, but isoquinoline *N*-oxide gave poor yield (Table 2A.2, **3p**).

Further, we have turned our attention to the scope of other isocyanides with different quinoline *N*-oxides and results are summarized in Table 2A.3. The 1-pentyl isocyanide **4a** has effortlessly reacted with quinoline*N*-oxide **1a** and produced corresponding product **5a** in 80% yield.

Table 2A.2. Substrate scope for the synthesis of *N*-(2-quinolinyl)formamides[a,b]

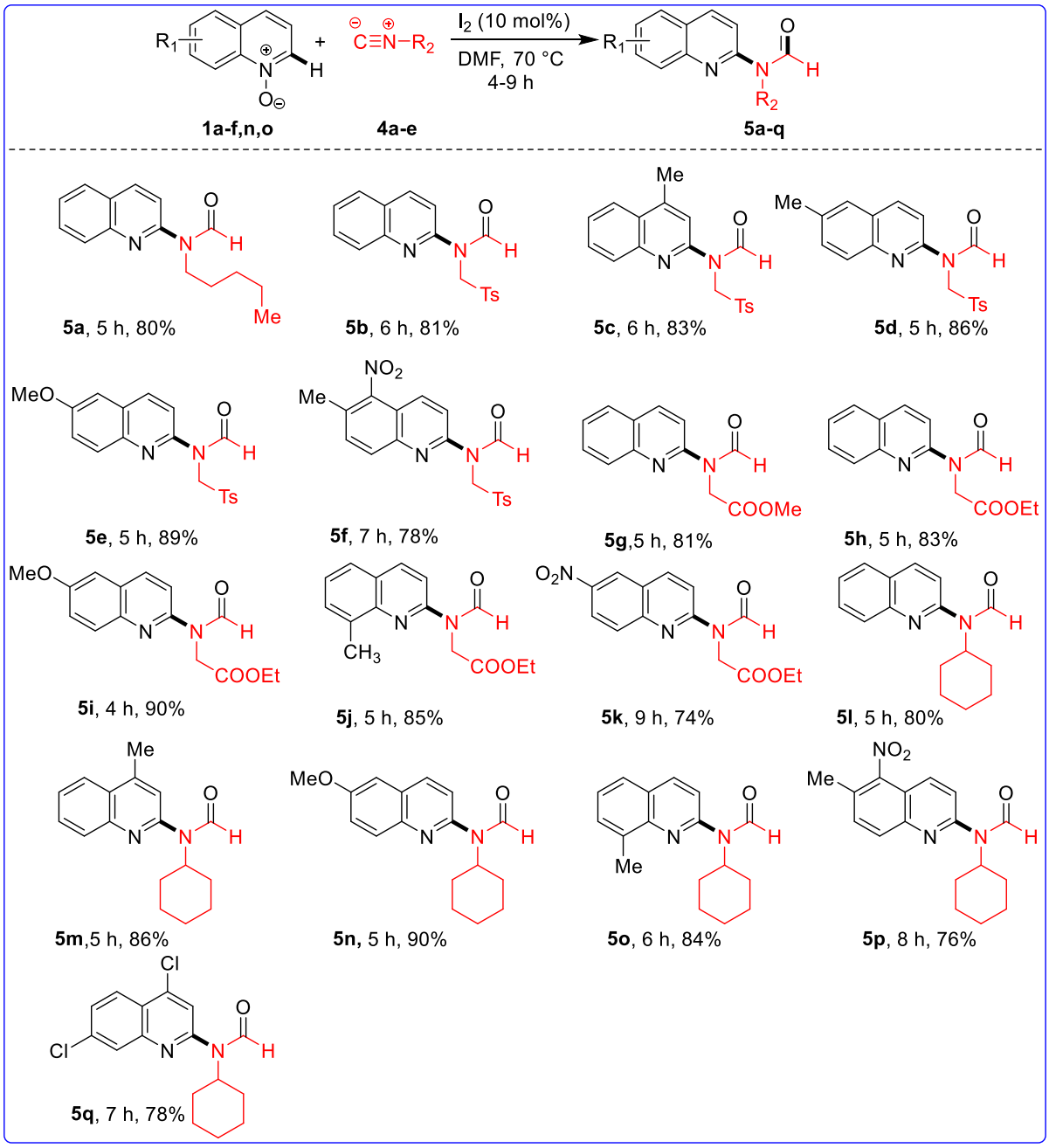


[a]Reaction conditions: quinoline *N*-oxides **1a-p** (0.5 mmol), isocyanide **2a** (0.5 mmol), iodine (10 mol%), DMF (2 mL), 70 °C. [b]Yields are given for isolated products.

Besides, *p*-toluenesulfonylmethyl isocyanide (TosMIC) has been extensively preceded with diverse quinoline *N*-oxides to deliver corresponding formamide derivatives **5b-f** in 78–89% yields. Interestingly, ester attached isocyanides such as methylisocyanoacetate **4c** and ethyl isocyanoacetate **4d** reacted with functional quinoline *N*-oxides to deliver target products **5g-k** in good to excellent yields (74-90%). In addition, the cyclohexyl isocyanide **4e** has been reacted smoothly with several quinoline *N*-oxides to furnish final products **5l-q** in 76-90% of yields.

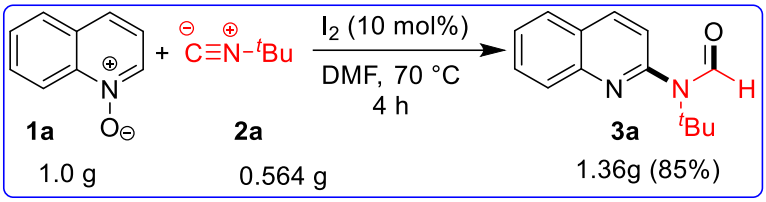
Further, we have investigated the efficiency of this protocol for gram scale reaction using quinoline *N*-oxide **1a** with *tert*-butyl isocyanide **2a** in the presence of 10 mol% of iodine under the standard condition. The reaction afforded the final product **3a** in 85% of yield (Scheme 2A.5).

Table 2A.3. Substrate scope for the synthesis of *N*-(2-quinolinyl)formamides[a, b]

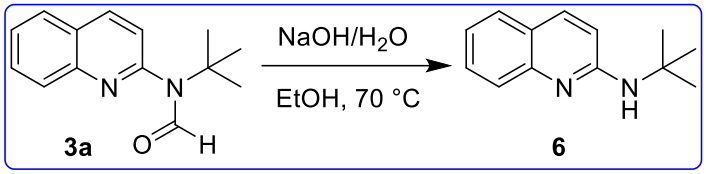


[a]Reaction conditions: quinoline *N*-oxides **1a-f**, **n** and **o** (0.5 mmol), isocyanide **4a-e** (0.5 mmol), I_2 (10 mol%), DMF (2 mL), 70 °C. [b] Yields are given for isolated products.

Formamides are found to be a versatile substrate, and it can act as a hydrogen bonding acceptor.[22] However, it can be further deprotected selectively at later stage keeping the other substituents intact as described in Scheme 2A.6. Selective aldehyde deformylation of **3a** mediated by aqueous NaOH has resulted in the formation of *N*-(*tert*-butyl)quinolin-2-amine **6** with 60% yield (Scheme 2A.6).[23]



Scheme 2A.5. Gram-scale reaction



Scheme 2A.6. Aldehyde deformylation of *N*-*tert*-butyl-*N*-(quinolin-2-yl)formamide

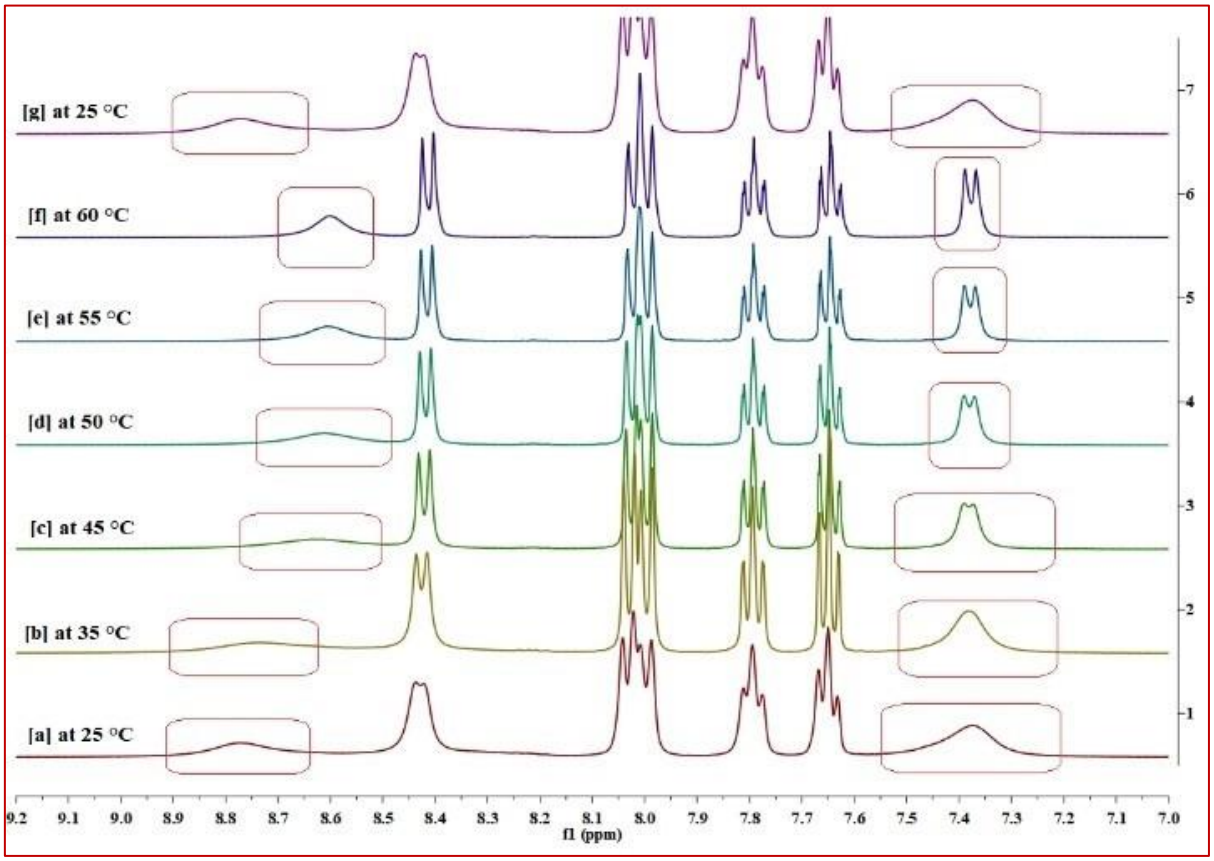


Figure 2A.2. Variable-temperature ^{1}H NMR spectra of **3a** in DMSO-d_6 from 25 °C to 60 °C demonstrating the presence of rotamers

Apart from the traditional FT-IR, ^{1}H & ^{13}C NMR and mass spectral analysis, the formation of *N*-(quinolin-2-yl)formamide was also unambiguously verified by X-ray crystallography of compounds **3f** and **3o** (Figure 2A.2). The crystallographic data and structure refinement parameters are given in the supporting information (Table 2A.4). ^{1}H & ^{13}C NMR of compounds **3a-p** revealed that they exist as a mixture of two rotamers due to the different orientations of the C-N bond. It is well documented that *N*-formyl compounds exist in a

solution as interconverting rotamers.[24] Hence, variable-temperature NMR experiments were performed to confirm the presence of rotamers in solution.

All the variable-temperature NMR experiments were carried out on model compound **3a** in dimethyl sulfoxide (DMSO-d_6), which has a higher boiling point and results are shown in Figure 2A.2. From the variable-temperature ^{1}H NMR experiments in DMSO-d_6, it was observed that three protons showed. A broad singlet at δ 8.61-8.95, 8.52-8.32 and 7.53-7.25 at 25 °C, later the broad singlet at δ 8.61-8.95 was converted to sharp singlet at elevated temperatures. Similarly, the peaks atδ 8.52-8.32 and 7.53-7.25 were started splitting into doublets at high temperature and gave resolved peaks at 60 °C, which is due to the dynamic exchange between the two rotamers (Figure 2A.2. **a-g**).

From the variable-temperature ^{13}C NMR experiments in DMSO-d_6, it was observed that broadening for a subset of ^{13}C NMR peaks at higher temperatures, which is due to the dynamic exchange between the two rotamers (Figure 2A.3. **a-i**). The complete resolved ^{13}CNMR signals were achieved at 60 °C, where the conformation interconversion is fast on the NMR time scale. The reversibility of these changes were verified when the experimental temperature was returned to 25 °C (Figure 2A.3. **a-i**).

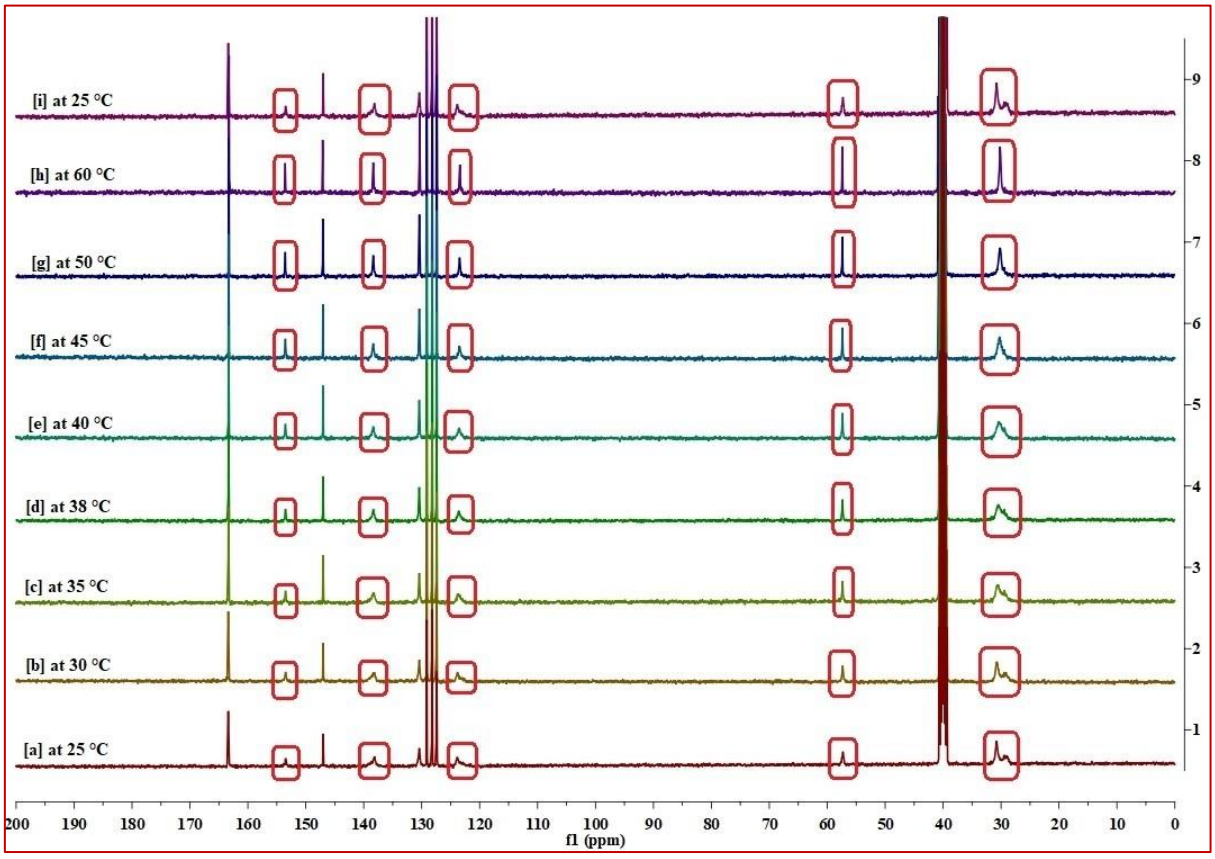
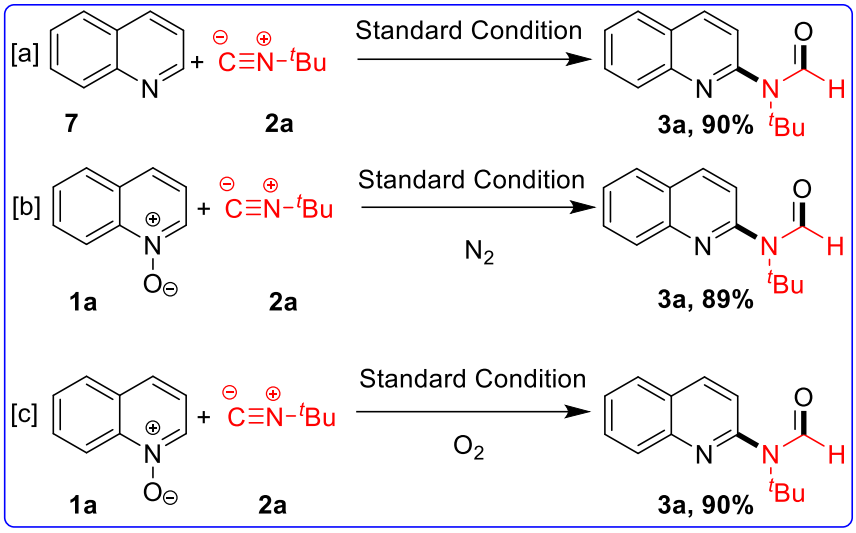


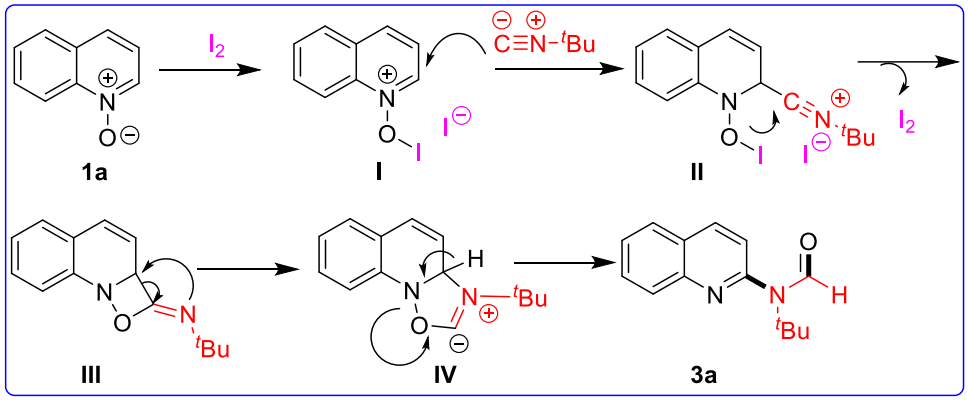
Figure 2A.3. Variable-temperature ^{13}C NMR spectra of **3a** in DMSO-d_6 from 25 ℃ to 60 °C demonstrating the presence of rotamers.

Next, we carried several control experiments to unveil the reaction mechanism (Scheme 2A.7). Initially, quinoline **7** was treated with *tert*-butyl isocyanide **2a** under the standard conditions, no reaction was observed, which indicated the role of *N*-oxide in this transformation (Scheme 2A.7a). Finally, reactions were carried out under nitrogen and oxygen to find out the role of oxygen, the yield of product **3a** was unchanged.



Scheme 2A.7. Control experiments.

On the basis of our control experiments and previous literature,[25] a plausible mechanism of the iodine catalyzed conversion of quinoline *N*-oxides to *N*-(2-quinolinyl)formamides is illustrated in Scheme 2A.8.The catalytic cycle initiates with the reaction of quinoline *N*-oxide **1a** with molecular iodine to produce intermediate **I**, then nucleophilic addition between **I** and isocyanide results in the formation of intermediate **II**. Later, the nucleophilic oxygen of *N*-oxide subsequently attacked on the carbon of isocyanide to form intermediate **III**, which readily undergoes rearrangement to form more stable intermediate **IV**. Finally, the intermediate **IV** undergoes rearomatization to obtain the desired product **3a.**



Scheme 2A.8. Proposed reaction mechanism

2A.3. X-ray diffraction analysis of compound 3f and 3o

The method for crystal growth is slow volatilization using mixture of chloroform, methanol and acetonitrile (4:4:2) as a solvent. The crystallographic data for the single crystal of the compound **3f and 3o** were collected on Xtlab Synergy Rigaku oxford diffraction with HyPix-3000 detector, equipped with graphite monochromated MoKa radiation (λ= 0.71073 Å) at 293K. The data interpretation was processed with CrysAlisPro, Xtlab Synergy Rigaku oxford diffraction, version 171.39.exe and an absorption correction based on multi-scan method. Crystallography data and structure refinement for **3f** (CCDC: 2091561) and **3o** (CCDC: 2091560) (Table 2A.4). Thermal ellipsoids are shown at 50% probability level (Figure 2A.4).

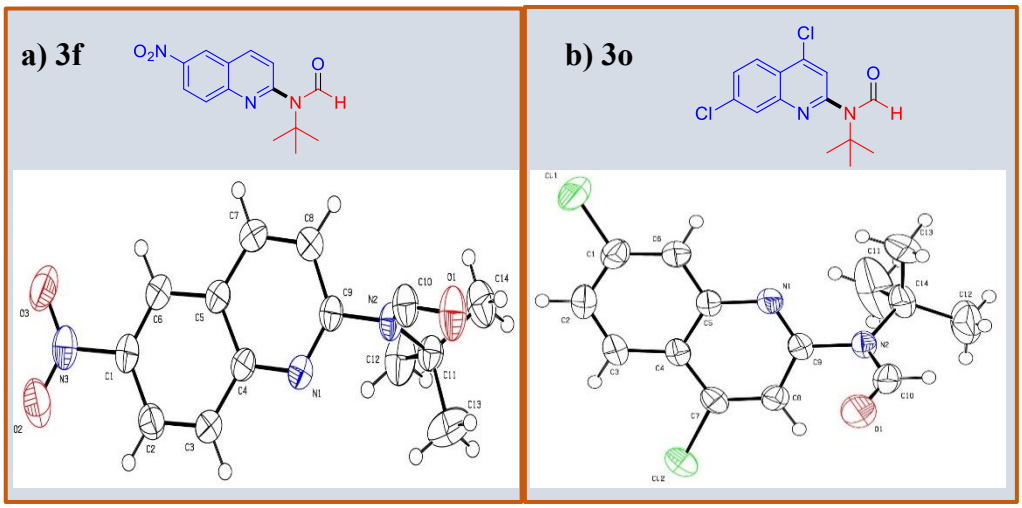


Figure 2A.4. The ORTEP representation of the compounds **3f and 3o**

Table 2A.4. Crystallographic data and structure refinement of compounds **3f** and **3o.**

Identification Code	**Compound 3f**	**Compound 3o**
Empirical formula	$C_{14}H_{14}N_3O_3$	$C_{14}H_{14}Cl_2N_2O$
Formula weight	272.28	297.17
Temperature/K	296(2)	296(2)
Crystal system	Monoclinic	Orthorhombic
Space group	P 21/c	Pbca
a/Å	6.4597(7)	19.327(3)
b/Å	11.7238(18)	7.5531(8)
c/Å	17.672(3)	19.615(2)
α/°	90	90
β/°	90.155(6)	90
γ/°	90	90

Volume/Å^3	1338.3(3)	2863.3(6)
Z	4	8
D_{calc} Mg/m^3	1.351	1.379
μ/mm^{-1}	0.097	0.446
F(000)	572	1232
Crystal size/mm^3	0.6 x 0.3 x 0.2	0.3 x 0.2 x 0.2
2Θ range for data collection/°	2.887 to 28.401	2.077 to 28.492
Index ranges	-8 ≤ h ≤ 5, -14 ≤ k ≤ 15, -23 ≤ l ≤ 23	-20 ≤ h ≤ 25, -10 ≤ k ≤ 8, -26 ≤ l ≤ 26
Reflections collected	10752	21918
Independent reflections	3230	3594
Data/restraints/parameters	3230 / 0 / 184	3594 / 0 / 175
Goodness-of-fit on F^2	0.908	0.962
Final R indexes [I>=2σ (I)]	R1 = 0.0521, wR2 = 0.1444	R1 = 0.0578, wR2 = 0.1553
Final R indexes [all data]	R1 = 0.0882, wR2 = 0.1766	R1 = 0.1160, wR2 = 0.2050
Largest diff. peak/hole / e Å^{-3}	0.617/-0.244	0.361 and -0.311
CCDC	2091561	2091560

2A.4. Conclusion

In summary, we have demonstrated a molecular iodine catalyzed regioselective C2 amino formylation of quinoline *N*-oxides with diversified isocyanides. This metal-free reaction affords rapid access to quinoline 2- formamides with exceptional functional group tolerance, broad substrate scope. This protocol provides 100% atom-economy. A library of 33 *N*-(2-quinolinyl)formamides are synthesized.

2A.5. Experimental Section

2A.5.1. General Information: All chemicals were purchased from Aldrich, Alfa Aesar, TCI, Finar and used as received. All solvents were purchased from commercial sources, then distilled by the standard protocol and stored over molecular sieves under nitrogen atmosphere prior to use. Thin layer chromatography was performed on 200 μm aluminium-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). ^{1}H NMR spectra were recorded on Bruker's AVANCE 400 MHz spectrometer, $CDCl_3$ and

DMSO-d_6 as a solvent and TMS as an internal standard. The following abbreviations were used to explain multiplicities: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *br* = broad, coupling constants, *J* were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker's AVANCE 100 MHz spectrometer, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-d (a multiplet at 39.52 ppm of DMSO-d_6). Melting points were determined with a Stuart SMP30 apparatus and are uncorrected. FT-IR spectra recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230. The X-ray single crystal data of the crystal compounds was collected on an Xtlab Synergy Rigaku oxford diffraction with HyPix-3000 detector, equipped with graphite monochromated MoKα radiation (λ= 0.71073 Å) at 293K.

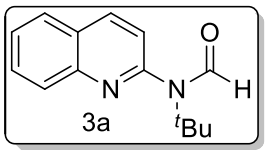
2A.5.2. General procedure for the synthesis of *N*-(2-quinolinyl)formamides (3a-p and 5a-q). An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate quinoline *N*-oxides (0.5 mmol), I_2 (10 mol%), alkyl isocyanides (0.5 mmol) and (*N*, *N*-dimethylformamide) DMF (2 mL). The mixture was stirred at 70 °C for the appropriate time (6-10 h). The progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. After completion, the reaction mixture was cooled to room temperature and treated with saturated $Na_2S_2O_3$, later extracted with ethyl acetate (3 x 10 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent.

2A.5.3. General procedure for hydrolysis of formamides.

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate *N*-2-quinolinyl)formamide (0.5 mmol) in ethanol (2 mL) and aqueous (1.0 mL) sodium hydroxide (20 mg, 0.5 mmol). The reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was monitored by TLC using hexane and ethyl acetate as an eluent. After completion the reaction mixture extracted with ethyl acetate (3 x 10 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated to give a residue purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent.

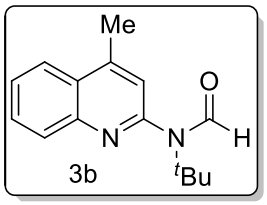
2A.6. Characterization data of products 3a-3p, 5a-5q & 6

***N-tert*-Butyl-*N*-(quinolin-2-yl)formamide (3a).** White crystalline solid (102 mg, 90% yield);



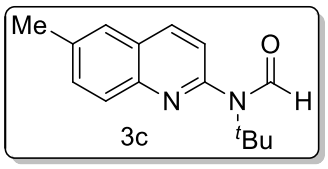
R_f = 0.50 (hexanes/EtOAc = 7:3); mp: 91-92 °C; IR (KBr, cm^{-1}) 3072, 2975, 2925, 1664, 1591, 1502, 1358, 1195, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.82 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.73 (s, 1H), 7.57 (t, *J* = 7.2, 6.8Hz 1H), 7.24 (s, 1H), 1.54 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.9, 152.3, 147.4, 137.7, 129.6, 129.4, 127.5, 127.0, 122.8, 121.8, 57.5, 30.9; ^{13}C NMR {^1H} of major rotamer (100 MHz, DMSO-d_6, 60 °C) δ (ppm): 163.1, 153.6, 147.1, 138.2, 130.3, 129.1, 128.1, 127.4, 127.3, 123.3, 57.4, 30.1; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{16}N_2O$ $[M+H]^+$ 229.1335; found 229.1338.

***N-tert*-Butyl-*N*-(4-methylquinolin-2-yl)formamide (3b**). Brown liquid, (104 mg, 86% yield);

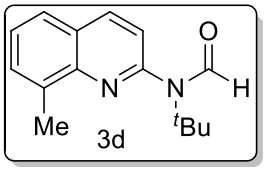


R_f = 0.56 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3042, 2974, 2924, 1681, 1592, 1347, 1200, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (s, 1H), 8.05 (d, *J* = 8.4Hz, 1H), 7.98 (d, *J* = 8.0Hz, 1H), 7.75-7.64 (m, 1H), 7.65-7.52 (m, 1H), 7.09 (s, 1H), 2.70 (s, 3H), 1.53 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.9, 152.0, 147.3, 146.8, 130.0, 129.7, 126.8, 123.7, 123.2, 122.3, 57.4, 30.9, 18.8; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O$ $[M+H]^+$ 243.1492; found 243.1486.

***N-tert*-Butyl-*N*-(6-methylquinolin-2-yl)formamide (3c).** White solid (107 mg, 88% yield); R_f = 0.56 (hexanes/EtOAc = 7:3). mp: 107-108 °C; IR (KBr, cm^{-1}) 3045, 2973, 2922, 2865, 1683, 1586, 1497, 1335, 1296, 1117, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 7.60-7.52 (m, 1H), 7.25-7.15 (m, 1H), 2.55 (s, 3H), 1.53 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.8, 151.4, 146.0, 137.1, 132.0, 129.0, 127.3, 126.3, 123.0, 122.0, 57.4, 31.0, 22.0; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O$ $[M+H]^+$ 243.1492; found 243.1494.



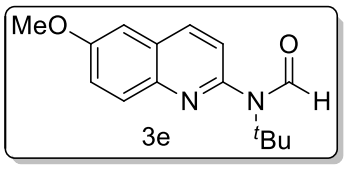
***N-tert*-Butyl-*N*-(8-methylquinilin-2-yl)formamide (3d).** Brown liquid, (103 mg, 85% yield);



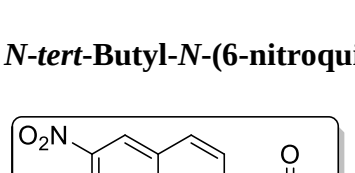
R_f = 0.54 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3032, 2973, 2923, 1682, 1594, 1498, 1345, 1222, 1081, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ δ (ppm): 8.83 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.59-7.51 (m, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.29-7.18 (m, 1H),

2.75 (s, 3H), 1.56 (s, 9H); ^{13}C NMR {^{1}H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.0, 150.0, 145.2, 136.2, 129.0,126.0, 126.0, 124.2, 121.3, 120.0, 56.3, 30.0, 17.0; ^{13}C NMR {^{1}H}of major rotamer (100 MHz, DMSO-d_6, 60 ^{o}C) δ (ppm): 163.2, 152.5, 145.9, 138.4, 136.5, 130.2, 127.2, 126.9, 125.9, 122.9, 57.4, 30.2, 17.6; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O$ $[M+H]^+$ 243.1492; found 243.1491.

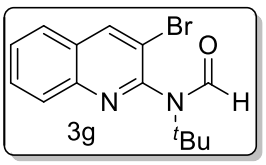
***N*-*tert*-Butyl-*N*-(6-methoxyquinolin-2-yl)formamide (3e).** White crystalline solid, (116 mg, 90% yield); R_f = 0.46 (hexanes/EtOAc = 7:3); mp: 96-97 °C; IR (KBr, cm^{-1}) 3075, 2981, 2964, 1668, 1591, 1496, 1460, 1318, 1232, 1163, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.41-7.35 (m, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 3.94 (s, 3H), 1.52 (s, 9H); ^{13}C NMR {^{1}H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 163.0, 158.2, 149.95, 143.3, 137.0, 131.0, 128.4, 123.0, 122.3, 105.0, 57.3, 56.0, 31.0; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O_2$ $[M+H]^+$ 259.1441; found 259.1440.



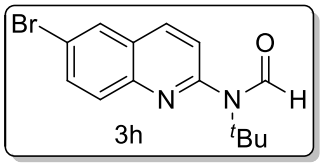
***N*-*tert*-Butyl-*N*-(6-nitroquinilin-2-yl)formamide (3f).** Yellow crystalline solid; (96 mg, 70% yield); R_f = 0.46 (hexanes/EtOAc = 6:4); mp: 130-131 °C; IR (KBr, cm^{-1}) 3032, 2972, 2922, 1682, 1599, 1490, 1393, 1335, 1297, 1188, 1083 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (d, J = 2.4 Hz, 1H), 8.74 (s, 1H), 8.49 (dd, J = 9.2, 2.4 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 9.2 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 1.58 (s, 9H); ^{13}C NMR {^{1}H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 163.0, 156.0, 149.3, 146.0, 139.1, 131.0, 126.0, 124.1, 123.2, 58.3, 30.4; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{15}N_3O_3$ $[M+H]^+$ 274.1186; found 274.1187.



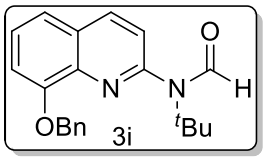
***N*-(3-Bromoquinolin-2-yl)-*N*-(*tert*-butyl)formamide (3g).** Red colour liquid; (123 mg, 80% yield); R_f = 0.58 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3058, 2975, 2924, 1672, 1621, 1578,1488, 1370, 1199, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.77 (s, 1H), 8.40 (s, 1H), 8.05-7.98 (m, 1H), 7.76-7.65 (m, 2H), 7.55 (s, 1H), 1.52 (t, J = 5.2 Hz, 9H); ^{13}C NMR {^{1}H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.7, 150.7, 146.0, 140.7, 130.0, 129.4, 128.6, 128.0, 126.5, 118.2, 58.0, 30.5; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{15}BrN_2O$ $[M+H]^+$ 307.0441; found 307.0442.



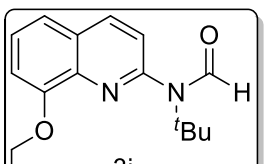
***N*-(6-Bromoquinolin-2-yl)-*N*-(*tert*-butyl)formamide (3h).** White solid; (126 mg, 82% yield); mp: 143-144 °C; R_f = 0.56 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3047, 2976, 2923, 1677, 1584, 1484, 1331, 1298, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 1.56 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 163.0, 146.0, 137.0, 133.3, 131.0, 130.0, 128.3, 122.4, 58.0, 31.0; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{15}BrN_2O$ $[M+H]^+$ 307.0441; found 307.0448.



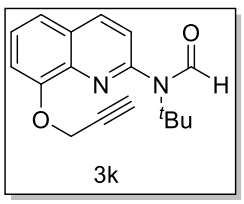
***N*-(8-(benzyloxy)quinolin-2-yl)-*N*-(*tert*-butyl)formamide (3i).** Light yellow liquid (137 mg, 82% yield); R_f = 0.45 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3032, 2974, 2923, 1671, 1594, 1500, 1326, 1206, 1103, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.42 (d, J = 2.8 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 7.17-7.06 (m, 1H), 5.37 (s, 2H), 1.59 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.0, 153.3, 150.1, 138.4, 137.3, 136.2, 127.4, 127.0, 126.0, 122.2, 120.0, 119.0, 118.4, 110.0, 70.0, 57.0, 29.0; HRMS (ESI-TOF) m/z: calculated for $C_{21}H_{22}N_2O_2$ $[M+H]^+$ 335.1754; found 335.1755.



***N*-(8-(allyloxy)quinolin-2-yl)-*N*-(*tert*-butyl)formamide (3j).** Brown liquid (114 mg, 80% yield); R_f = 0.42 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3062, 2954, 2924, 2853, 1653, 1459, 1376, 1263, 1157, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.45-7.40 (m, 2H), 7.34-7.26 (m, 1H), 7.13-7.05 (s, 1H), 6.20-6.11 (m, 1H), 5.54 (d, J = 17.2 Hz, 1H), 5.32 (d, J = 10.4 Hz, 1H), 4.80 (d, J = 4.8 Hz, 2H), 1.57 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.0, 153.3, 150.0, 138.3, 136.3, 132.1, 127.4, 126.0, 122.2, 119.0, 116.3, 110.0, 69.0, 57.0, 29.0; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{20}N_2O_2$ $[M+H]^+$ 285.1598; found 285.1595.

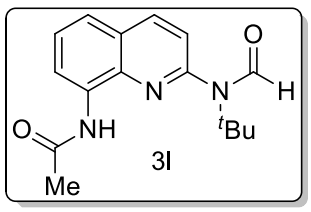


***N*-*tert*-Butyl-*N*-(8-(prop-2-yn-1-yloxy)quinolin-2-yl)formamide (3k).** Brown liquid; (117 mg, 83% yield); R_f = 0.45 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3257, 3058, 2975, 2922, 2116, 1674, 1499, 1459, 1319, 1262, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 2.4 Hz, 2H), 7.30 (s, 2H), 5.01 (s, 2H), 2.52 (t, J = 2.4 Hz, 2.0 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.9,

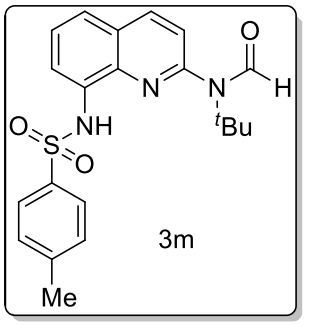


153.1, 139.5, 137.6, 128.5, 126.9, 123.4, 122.1, 120.7, 112.1, 78.5, 76.0, 57.3, 30.8; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{18}N_2O_2$ $[M+H]^+$ 283.1441; found 283.1442.

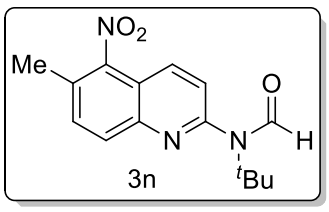
***N*-(2-(*N*-*tert*-Butylformamido)quinolin-8-yl)acetamide (3l).** White solid; (111 mg, 78% yield); mp: 110-111 °C; R_f = 0.42 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3361, 3026, 2967, 2923, 1678, 1593, 1488, 1326, 1271, 1206, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.34 (s, 2H), 8.82-8.55 (m, 2H), 8.12 (d, J = 8.4 Hz, 1H), 7.47-7.41 (m, 2H), 7.20 (d, J = 8.4 Hz, 1H), 2.22 (s, 3H), 1.45 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 168.0, 162.0, 150.0, 137.4, 136.0, 133.2, 127.0, 126.0, 122.0, 120.1, 116.0, 56.3, 30.0, 24.0; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{19}N_3O_2$ $[M+H]^+$ 286.1550; found 286.1546.



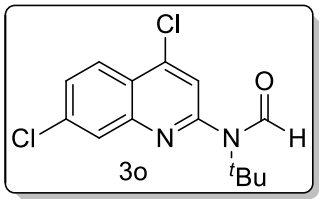
***N*-*tert*-Butyl-*N*-(8-(4-methylphenylsulfonamido)quinolin-2-yl)formamide (3m).** White solid; (151 mg, 76% yield); R_f = 0.46 (hexanes/EtOAc = 7:3); mp: 155-156 °C; IR (KBr, cm^{-1}) 3302, 3065, 2972, 2923, 1668, 1597, 1504, 1470, 1325, 1201, 1164, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.72 (s, 1H), 8.62 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.84-7.73 (m, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.45-7.37 (m, 2H), 7.17 (t, J = 6.2, 1H), 7.06 (d, J = 8.0 Hz, 2H), 2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR {1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 163.0, 151.2, 144.0, 138.0, 136.2, 134.0, 130.0, 128.2, 127.0, 123.0, 122.0, 122.0, 116.1, 58.0, 30.0, 21.4; HRMS (ESI-TOF) m/z: calculated for $C_{21}H_{23}N_3O_3S$ $[M+H]^+$ 398.1533. found 398.1534.



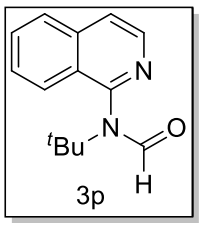
***N*-*tert*-Butyl-*N*-(6-methyl-5-nitroquinolin-2-yl)formamide (3n).** Brown liquid; (111 mg, 77% yield); R_f = 0.42 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3072, 2977, 2929, 1670, 1592, 1527, 1474, 1356, 1199, 1145, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (s, 1H), 8.15 (d, J = 9.2, 1H), 8.12 (d, J = 8.8, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 2.57 (s, 3H), 1.55 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.8, 153.3, 146.5, 145.6, 132.1, 129.5, 124.9, 119.2, 57.9, 30.8, 18.1; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{17}N_3O_3$ $[M+H]^+$ 288.1343; found 288.1339.



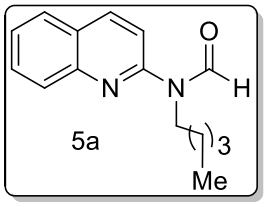
***N-tert*-Butyl-*N*-(4,7-dichloroquinolin-2-yl)formamide (3o).** White solid; (117.4 mg, 79% yield); mp: 107-108 °C; R_f = 0.45 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3032, 2969, 2936, 1660, 1607, 1553, 1490, 1346, 1292, 1213, 1198, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.76 (s, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.10 (s, 1H), 7.61 (dd, J = 8.8, 2.0 Hz, 1H), 7.37 (s, 1H), 1.55 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.0 , 152.1, 147.0, 142.3, 136.0, 128.0, 124.3, 124.0, 122.3, 57.0, 30.0; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{14}Cl_2N_2O$ $[M+H]^+$ 297.0556; found 297.0564.



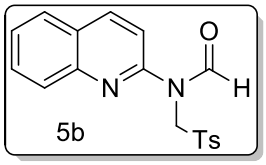
***N-tert*-Butyl-*N*-(isoquinolin-1-yl)formamide (3p).** Brown liquid; (17 mg, 15% yield); R_f = 0.56 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3058, 2924, 2865, 1672, 1459, 1379, 1263, 1197, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.94 (s, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.93-7.84 (m, 2H), 7.78-7.60 (m, 3H), 1.52 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.1, 152.0, 140.2, 137.0, 130.0, 127.3, 127.0, 126.1, 124.4, 121.0, 58.0, 30.0; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{16}N_2O$ $[M+H]^+$ 229.1335; found 229.1342.



***N*-pentyl-*N*-(quinolin-2-yl)formamide (5a).** Colourless liquid; (96.9 mg, 80% yield); R_f = 0.52 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3027, 2955, 2924, 2853, 1684, 1599, 1504, 1467, 1431, 1367, 1260, 1197, 1117, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.42 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.52-7.45 (m, 1H), 7.24 (d, J = 8.8 Hz, 1H), 4.05 (t, J = 7.6 Hz 2H), 1.73-1.63 (m, 2H), 1.40-1.30 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 162.0, 151.1, 146.0, 138.0, 129.3, 127.4, 126.4, 125.0, 125.0, 111.1, 41.0, 28.0, 27.0, 21.3, 13.0; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O$ $[M+H]^+$ 243.1492; found 243.1506.

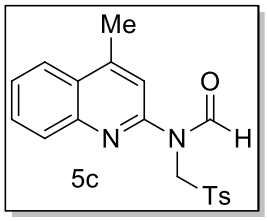


***N*-(quinolin-2-yl)-*N*-(tosylmethyl)formamide (5b).** White solid; (138 mg, 81% yield); R_f = 0.56 (hexanes/EtOAc = 7:3); mp: 128-129 °C; IR (KBr, cm^{-1}) 3067, 2924, 2853, 1693, 1597, 1505, 1476, 1341, 1288, 1143, 1085, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.19 (s, 1H), 8.21 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.70 (t, J = 8.4 Hz, 3H), 7.50 (t, J = 7.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2H), 5.66 (s, 2H), 2.28 (s, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 160.4, 149.0, 145.4, 144.1, 139.0, 134.3, 130.0, 129.0, 128.0,

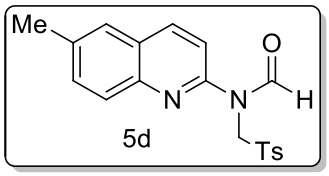


127.3, 126.4, 125.3, 111.4, 61.0, 21.0; HRMS (ESI-TOF) m/z: calculated for $C_{18}H_{16}N_2O_3S$ $[M+H]^+$ 341.0954; found 341.0955.

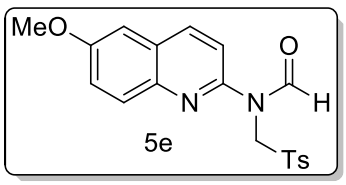
***N*-(4-methylquinolin-2-yl)-*N*-(tosylmethyl)formamide (5c).** White solid; (147 mg, 83% yield); R_f = 0.56 (hexanes/EtOAc = 7:3); mp: 190-191 °C; IR (KBr, cm^{-1}) 3052, 2924, 2851, 1694, 1598, 1350, 1323, 1178, 1147, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.68 (dd, *J* = 16.0, 7.6 Hz, 3H), 7.50 (t, *J* = 6.6, 1H), 7.17 (d, *J* = 8.0 Hz, 3H), 5.65 (s, 2H), 2.72 (s, 3H), 2.28 (s, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 157.0, 145.1, 144.0, 142.0, 140.3, 131.0, 126.0, 125.0, 124.1, 122.0, 121.3, 119.0, 108.2, 57.0, 17.0, 15.0; HRMS (ESI-TOF) m/z: calculated for $C_{19}H_{18}N_2O_3S$ $[M+H]^+$ 355.1111; found 355.1109.



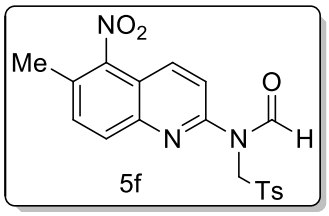
***N*-(6-methylquinolin-2-yl)-*N*-(tosylmethyl)formamide (5d).** White solid; (152 mg, 86% yield); R_f = 0.58 (hexanes/EtOAc = 7:3); mp: 220-221 °C; IR (KBr, cm^{-1}) 3042, 2923, 2831, 1698, 1578, 1476, 1375, 1347, 1288, 1146, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.07 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 3H), 7.47 (t, *J* = 7.4, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.57 (s, 2H), 2.46 (s, 3H), 2.23 (s, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 160.4, 148.3, 144.0, 138.0, 135.3, 134.3, 132.0, 129.0, 128.0, 127.0, 125.3, 112.0, 61.0, 28.6, 20.4; HRMS (ESI-TOF) m/z: calculated for $C_{19}H_{18}N_2O_3S$ $[M+H]^+$ 355.1111; found 355.1117.



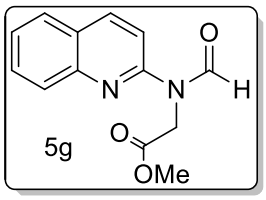
***N*-(6-methoxyquinolin-2-yl)-*N*-(tosylmethyl)formamide (5e).** White solid; (165 mg, 89%), R_f = 0.52 (hexanes/EtOAc = 7:3); mp: 120-121 °C; IR (KBr, cm^{-1}) 3062, 2994, 2929, 2844, 1697, 1598, 1504, 1353, 1290, 1234, 1144, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.09 (s, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.70 (t, *J* = 8.4 Hz, 3H), 7.38-7.32 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 2.4 Hz, 1H), 5.62 (s, 2H), 3.93 (s, 3H), 2.32 (s, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 161.3, 158.0, 148.2, 145.0, 142.3, 135.4, 130.0, 129.0, 127.4, 123.2, 113.0, 105.1, 62.0, 56.0, 22.0; HRMS (ESI-TOF) m/z: calculated for $C_{19}H_{18}N_2O_3S$ $[M+H]^+$ 371.1060; found 371.1059.



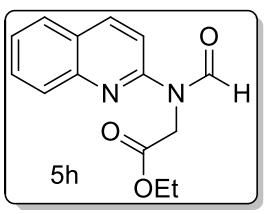
***N*-(6-methyl-5-nitroquinolin-2-yl)-*N*-(tosylmethyl)formamide (5f).** White solid; (156 mg, 78% yield); R_f = 0.48 (hexanes/EtOAc = 7:3); mp: 190-191 °C; IR (KBr, cm^{-1}) 3039, 2993, 2923, 2856, 1696, 1524, 1480, 1382, 1289, 1143, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.23 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 7.6, 2H), 5.62 (s, 2H), 2.55 (s, 3H), 2.35 (s, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 160.0, 150.0, 144.3, 144.0, 134.1, 133.0, 132.0, 130.2, 129.0, 128.0, 117.3, 113.3, 60.3, 29.0, 17.1; HRMS (ESI-TOF) m/z: calculated for $C_{19}H_{17}N_3O_5S$ $[M+H]^+$ 400.0962; found 400.0969.



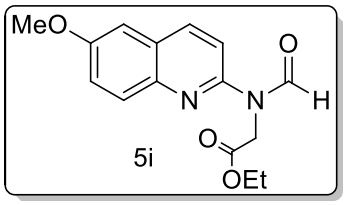
Methyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5g). White solid; (99 mg, 81% yield); R_f = 0.45 (hexanes/EtOAc = 7:3); mp: 90-91 °C; IR (KBr, cm^{-1}) 3068, 2952, 2921, 2850, 1749, 1683, 1596, 1476, 1346, 1286, 1207, 1144, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.39 (s, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 4.91 (s, 2H), 3.76 (s, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 169.1, 162.0, 151.1, 147.0, 139.1, 131.0, 128.4, 128.0, 126.1, 126.0, 111.0, 52.4, 43.0; HRMS (ESI-TOF) m/z: calculated for $C_{13}H_{12}N_2O_3$ $[M+H]^+$ 245.0921: found 245.0932.



Ethyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5h). White solid; (107 mg, 83% yield); R_f = 0.46 (hexanes/EtOAc = 7:3); mp: 84-85 °C; IR (KBr, cm^{-1}) 3061, 2921, 2851, 1747, 1689, 1619, 1599, 1468, 1373, 1351, 1203, 1146, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.30 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 4.79 (s, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 169.0, 162.0, 151.2, 147.0, 139.0, 130.4, 128.4, 128.0, 126.0, 126.0, 111.0, 61.4, 43.2, 14.1; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{14}N_2O_3$ $[M+H]^+$ 259.1077: found 259.1092.

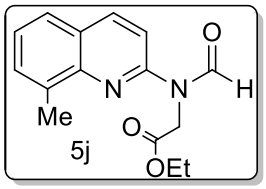


Ethyl 2-(*N*-(6-methoxyquinolin-2-yl)formamido)acetate (5i). White solid; (129 mg, 90% yield); R_f = 0.49 (hexanes/EtOAc = 7:3); mp: 76-77 °C; IR (KBr, cm^{-1}) 3057, 2980, 2938, 1747, 1686, 1600, 1505, 1463, 1358, 1233, 1199, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.30 (s, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.38-7.29 (m, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 4.85 (s, 2H), 4.21 (q, *J* = 6.8 Hz, 2H),

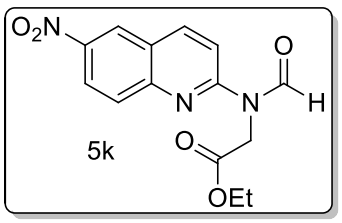


3.89 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 169.0, 162.0, 157.3, 149.4, 142.4, 138.0, 130.0, 127.0, 123.0, 112.0, 105.2, 61.3, 56.0, 43.3, 14.1; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{16}N_2O_4$ $[M+H]^+$ 289.1183; found 289.1183.

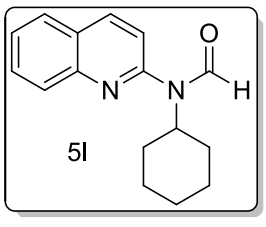
Ethyl 2-(*N*-(8-methylquinolin-2-yl)formamido)acetate (5j). White solid; (116 mg, 85% yield); R_f = 0.46 (hexanes/EtOAc = 7:3); mp: 90-91 °C; IR (KBr, cm^{-1}) 3054, 2966, 2917, 1746, 1687, 1600, 1507, 1402, 1348, 1223, 1199, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.43 (s, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.37 (t, J = 7.6, 1H), 7.33 (d, J = 8.8, 1H), 4.89 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 2.66 (s, 3H), 1.26 (t, J = 6.8.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 169.0, 162.0, 150.0, 146.0, 139.3, 136.3, 131.0, 126.0, 125.0, 110.2, 61.3, 43.2, 18.0, 14.1; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{16}N_2O_3$ $[M+H]^+$ 273.1234; found 273.1241.



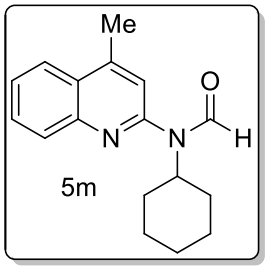
Ethyl 2-(*N*-(6-nitroquinolin-2-yl)formamido)acetate (5k). Yellow solid; (112 mg, 74% yield); R_f = 0.45 (hexanes/EtOAc = 7:3); mp: 190-191 °C; IR (KBr, cm^{-1}) 3062, 2982, 2928, 1740, 1682, 1611, 1498, 1368, 1335, 1215, 1126, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.53 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.46 (dd, J = 9.2, 2.0 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 4.91 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 171.0, 169.0, 163.0, 155.0, 144.4, 141.3, 130.0, 125.2, 125.0, 124.1, 114.0, 61.3, 43.0, 14.4; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{13}N_3O_5$ $[M+H]^+$ 304.0928; found 304.0932.



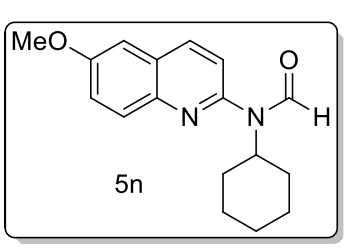
***N*-cyclohexyl-*N*-(quinolin-2-yl)formamide (5l).** White solid; (101 mg, 80% yield); R_f = 0.48 (hexanes/EtOAc = 8:2); mp: 85-86 °C; IR (KBr, cm^{-1}) 3039, 2921, 2866, 2851, 1677, 1599, 1567, 1560, 1445, 1385, 1256, 1210, 1148, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 6.4 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.23 (s, 1H), 4.50-4.39 (m, 1H), 2.08 (s, 2H), 1.94-1.78 (m, 4H), 1.68 (d, J = 11.6 Hz, 1H), 1.40 (q, J = 12.8, 2H), 1.26-1.16 (m, 1H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 163.0, 153.0, 147.0, 138.4, 130.0, 129.0, 129.0, 127.3, 126.3, 117.0, 56.0, 31.0, 26.2, 25.4; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{18}N_2O$ $[M+H]^+$ 255.1492; found 255.1483.



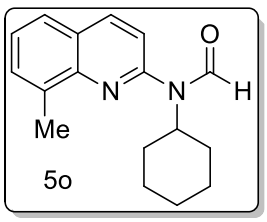
***N*-cyclohexyl-*N*-(4-methylquinolin-2-yl)formamide (5m).** Colourless liquid; (115 mg, 86% yield); R_f = 0.48 (Hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3048, 2926, 2853, 1682, 1597, 1468, 1351, 1210, 1132, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.76 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.65(s, 1H) 7.51 (t, *J* = 6.6 Hz, 1H), 7.06 (s, 1H), 4.50-4.30 (m, 1H), 2.69 (s, 3H), 2.15-2.0 (m, 2H), 1.94–1.73 (m, 4H), 1.70-1.60 (m, 1H), 1.45-1.32 (m, 2H), 1.25-1.14 (m, 1H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 163.0, 147.0, 130.0, 129.3, 127.0, 126.0, 124.0, 117.4, 56.0, 31.0, 26.2, 25.4, 19.0; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{20}N_2O$ $[M+H]^+$ 269.1654; found 269.1656.



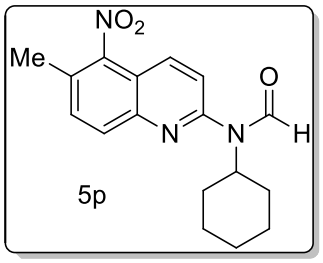
***N*-cyclohexyl-*N*-(6-methoxyquinolin-2-yl)formamide (5n).** White solid; (128 mg, 90% yield); R_f = 0.52 (hexanes/EtOAc = 7:3); mp: 75-76 °C; IR (KBr, cm^{-1}) 3027, 2931, 2915, 2851, 1669, 1599, 1463, 1349, 1259, 1163, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.69 (s, 1H), 8.06 (d, *J* = 6.8 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 6.8 Hz, 1H), 7.19 (d, *J* = 6.0 Hz, 1H), 7.08 (s, 1H), 4.50-4.32 (m, 1H), 3.92 (s, 3H), 1.98-1.79 (m, 5H), 1.70-1.62 (m, 1H), 1.45-1.31 (m, 3H), 1.27-1.12 (m, 1H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 162.0, 157.0, 150.0, 142.0, 136.1, 129.3, 127.0, 122.0, 117.0, 104.0, 55.0, 30.0, 25.1, 24.4; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{20}N_2O_2$ $[M+H]^+$ 285.1598; found 285.1604.



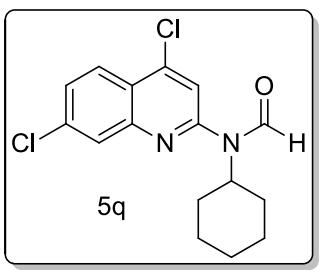
***N*-cyclohexyl-*N*-(8-methylquinolin-2-yl)formamide (5o).** Colourless liquid; (113 mg, 84% yield); R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3032, 2927, 2853, 1682, 1598, 1501, 1450, 1344, 1225, 1142, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.86 (s, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.58-7.51 (m, 1H), 7.38 (t, *J* = 6.8 Hz, 1H), 7.23-7.16 (m, 1H), 4.60-4.41 (m, 1H), 2.74 (m, 3H), 2.35-2.10 (m, 2H), 1.95-1.80(m, 4H), 1.74-1.66 (m, 1H), 1.48-1.35 (m, 2H), 1.27-1.18 (m, 1H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 163.2, 152.0, 146.0, 139.0, 137.0, 130.3, 126.2, 126.0, 116.0, 56.0, 30.4, 26.3, 26.0, 18.0; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{20}N_2O$ $[M+H]^+$ 269.1648; found 269.1657.



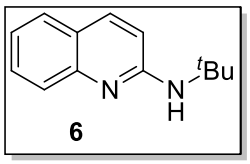
***N*-cyclohexyl-*N*-(6-methyl-5-nitroquinolin-2-yl)formamide (5p).** White solid; (119 mg, 76% yield); R_f = 0.54 (hexanes/EtOAc = 8:2); mp: 110-111 °C; IR (KBr, cm^{-1}) 3072, 2923, 2854, 1687, 1597, 1542, 1480, 1350, 1363, 1217, 1148, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.86 (s, 1H), 8.10 (d, J = 5.2 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.53-7.23 (m, 1H), 4.53-4.37 (m, 1H), 2.53 (s, 3H), 1.95-1.80 (m, 4H), 1.75-1.67 (m, 1H), 1.48-1.36 (m, 2H), 1.27-1.17 (m, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 162.0, 157.0, 150.0, 142.0, 136.1, 129.3, 127.0, 122.0, 117.0, 104.0, 55.0, 30.0, 25.1, 24.4; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{19}N_3O_3$ $[M+H]^+$ 314.1499; found 314.1502.



***N*-cyclohexyl-*N*-(4,7-dichloroquinolin-2-yl)formamide (5q).** White solid; (126 mg, 78% yield); R_f = 0.56 (hexanes/EtOAc = 8:2); mp: 132-133 °C; IR (KBr, cm^{-1}) 3048, 2927, 2853, 1682, 1583, 1491, 1313, 1148, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (s, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.8, 2.0 Hz, 1H), 4.53-4.37 (m, 1H), 2.02-1.82 (m, 5H), 1.75-1.68 (m, 1H), 1.30-1.15 (m, 2H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 163.0, 148.0, 128.0, 125.3, 123.0, 57.0, 26.2, 25.4; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}C_{l2}N_2O$ $[M+H]^+$ 323.0712; found 323.0716.



***N*-(*tert*-Butyl)quinolin-2-amine (6).** Colourless liquid; (60.0 mg, 60% yield); R_f = 0.56 (hexanes/EtOAc = 9:1); IR (KBr, cm^{-1}) 3428, 3034, 2958, 2921, 2851, 1619, 1521, 1400, 1311, 1225, 1120, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 6.59 (d, J = 8.8 Hz, 1H), 4.64 (s, 1H), 1.54 (s, 9H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 156.4, 137.0, 129.2, 127.2, 126.4, 123.0, 122.0, 113.0, 51.4, 29.4; HRMS calculated for $C_{13}H_{16}N_2$ $[M+H]^+$ 201.1386; found 201.1385.



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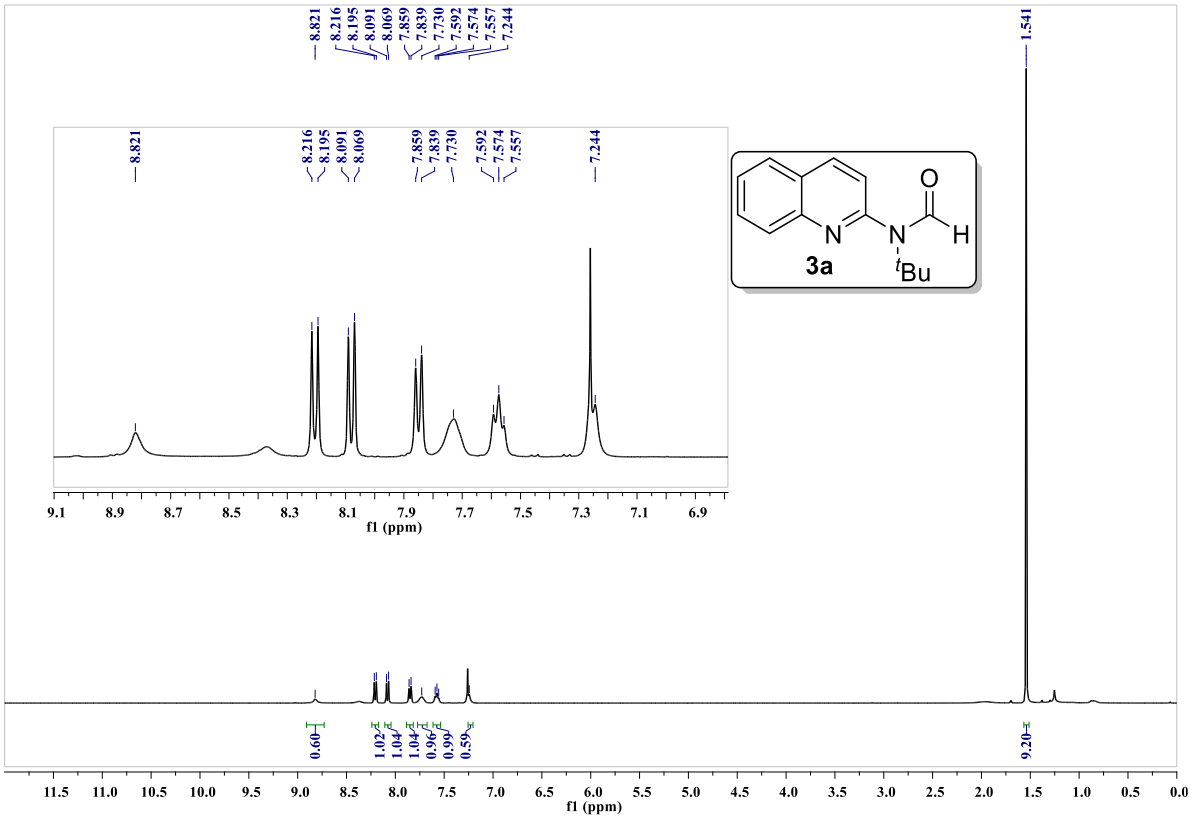
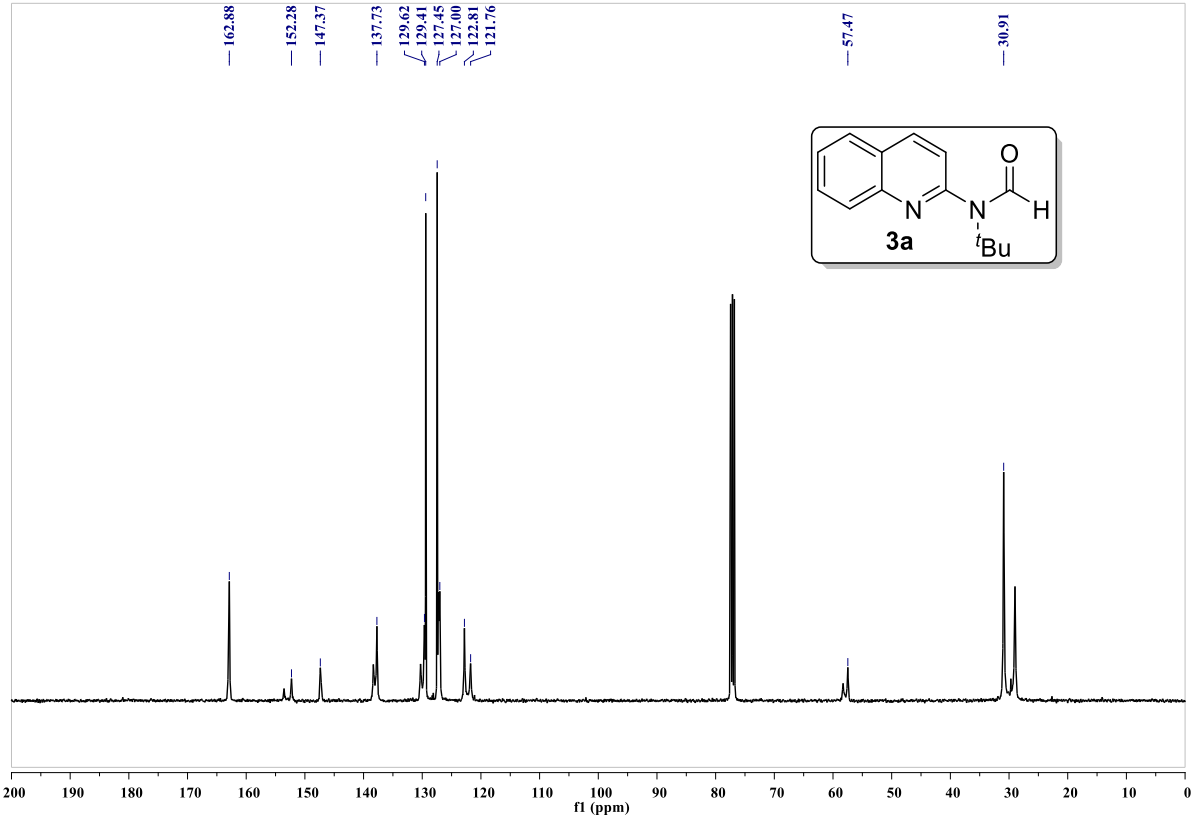
2A.8. Selected NMR (^{1}H and ^{13}C) and HRMS Spectra

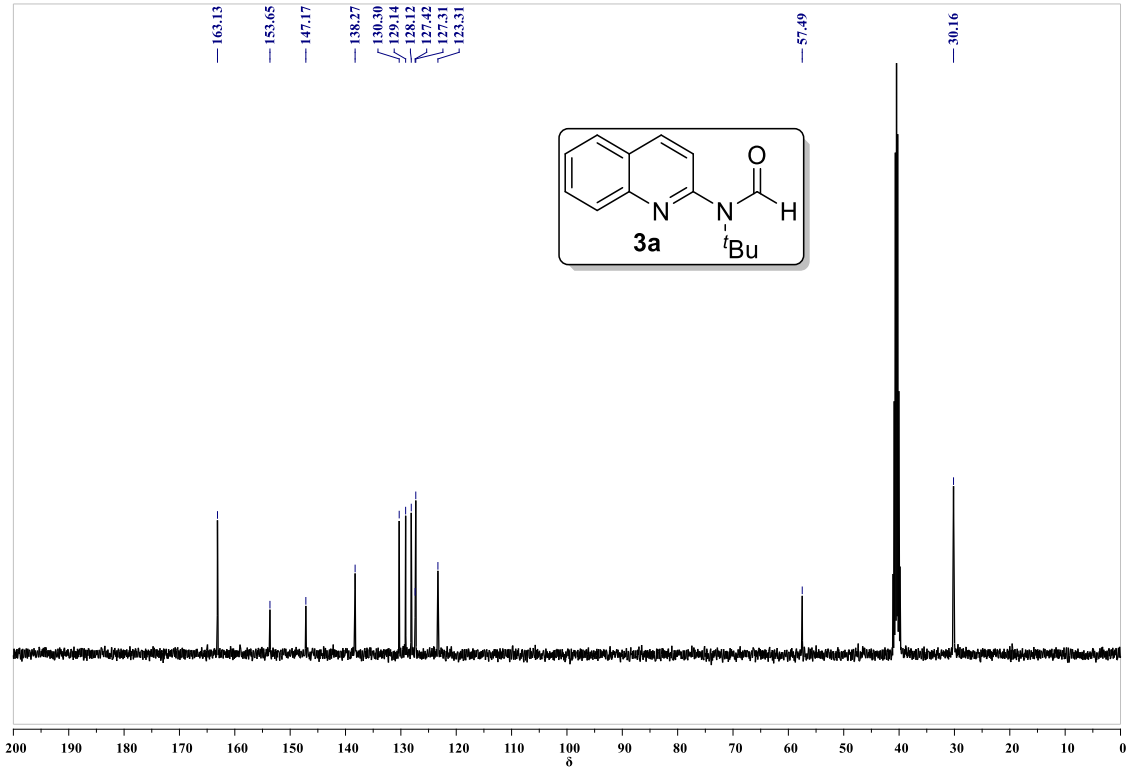
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-*tert*-Butyl-*N*-(quinolin-2-yl) formamide (3a)



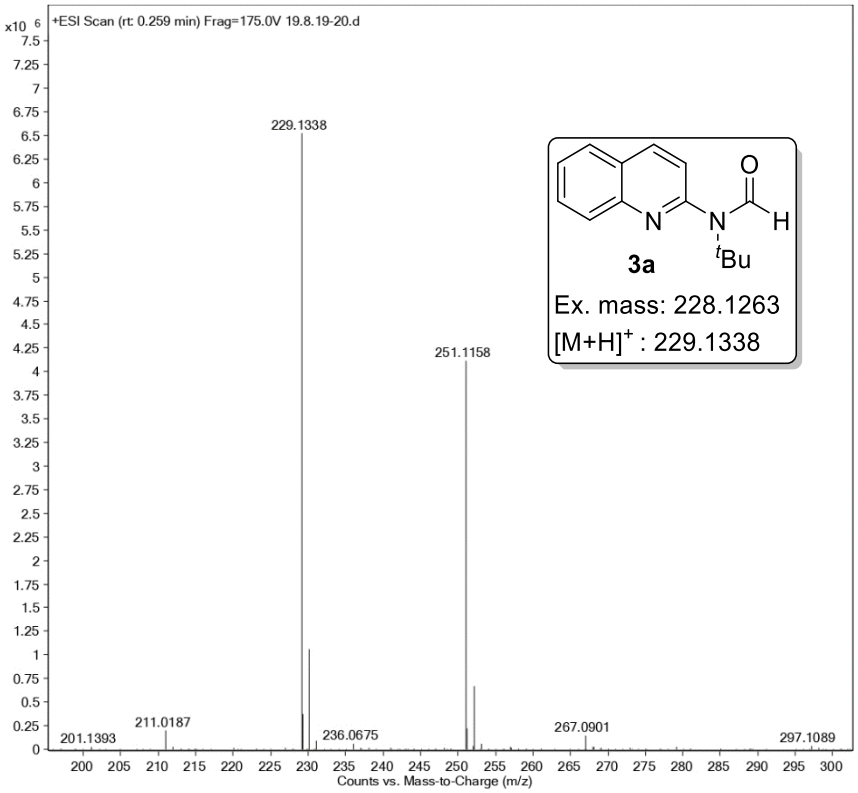
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of *N*-*tert*-Butyl-*N*-(quinolin-2-yl) formamide (3a)



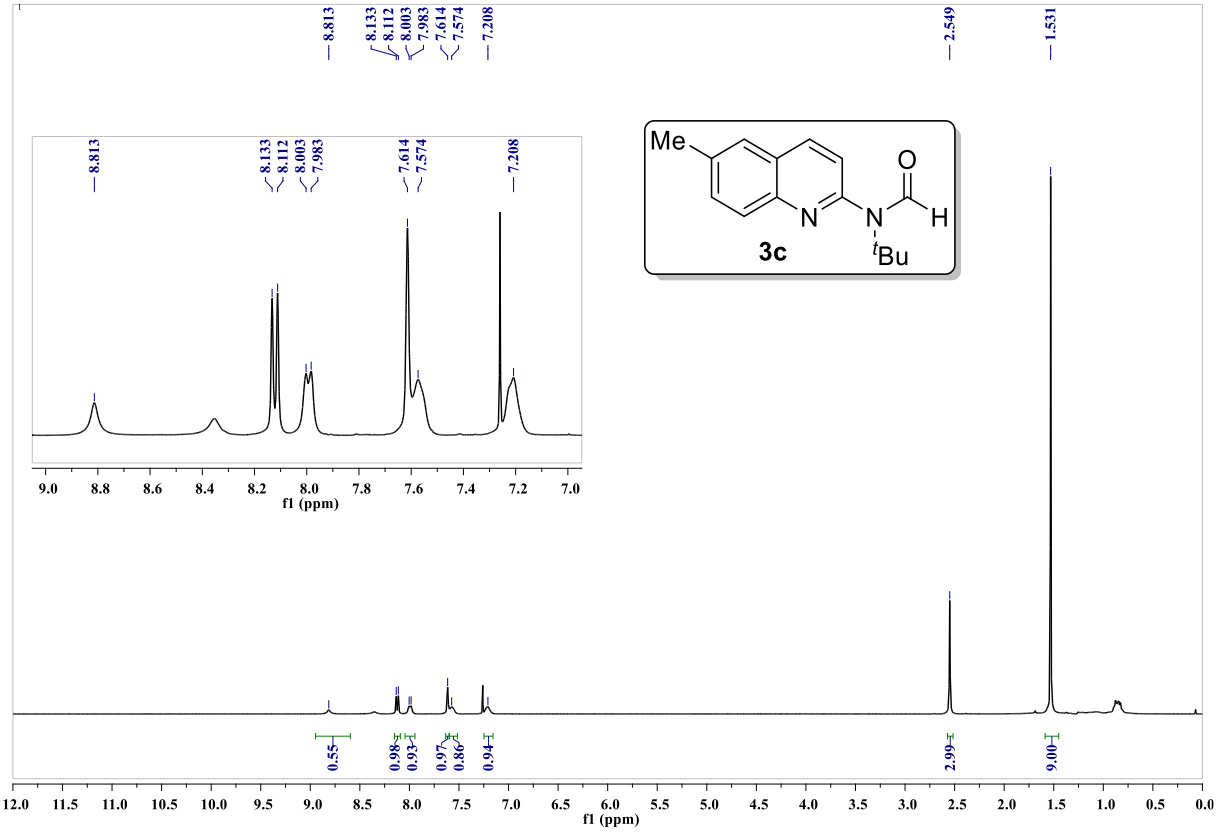
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6, 60 °C) spectrum of *N*-*tert*-Butyl-*N*-(quinolin-2-yl) formamide (3a)



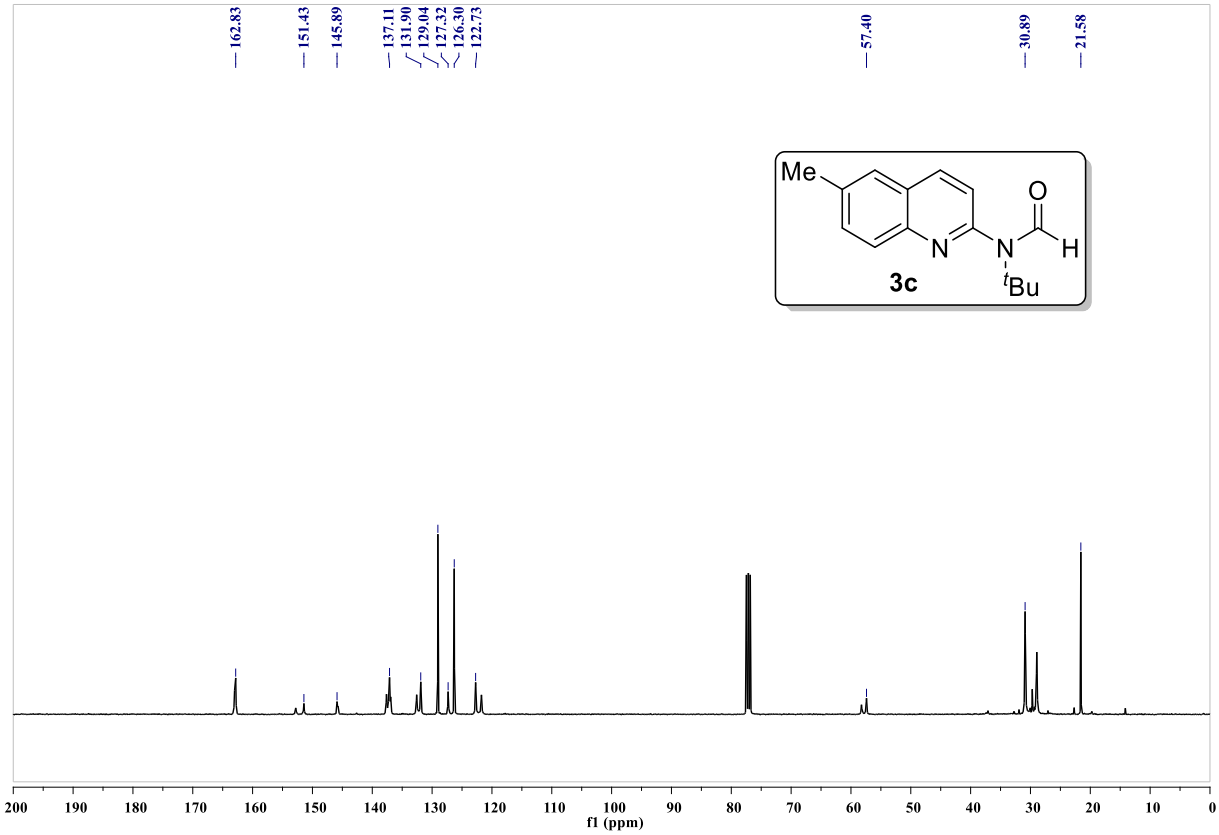
HRMS spectrum of *N*-*tert*-Butyl-*N*-(quinolin-2-yl) formamide (3a)



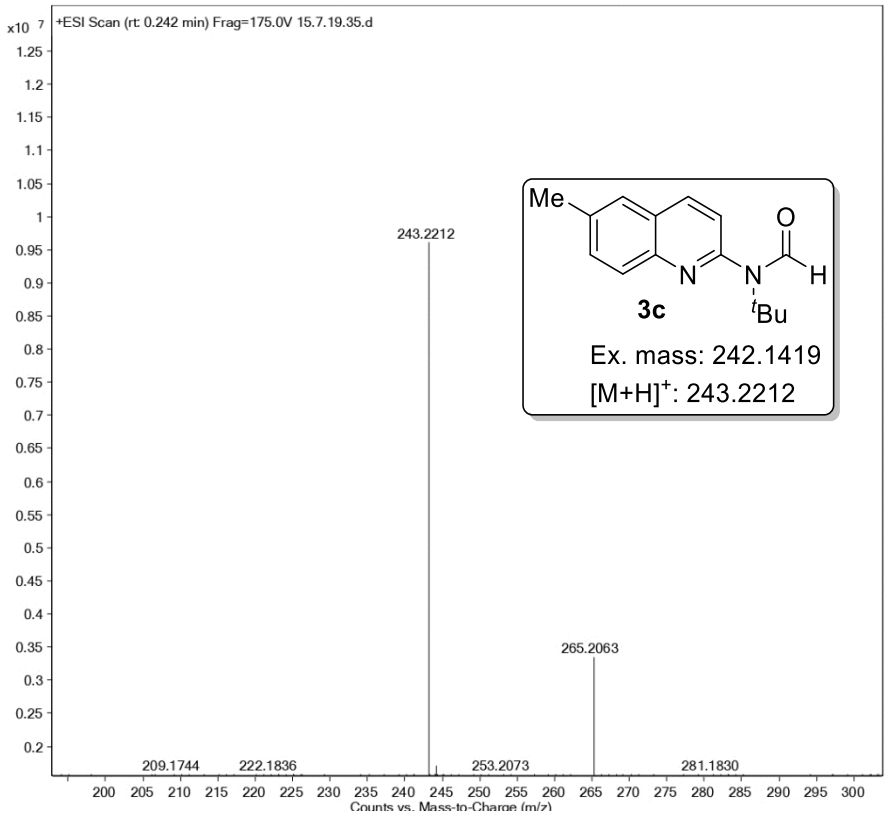
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N-tert*-Butyl-*N*-(6-methylquinolin-2-yl)formamide (3c)



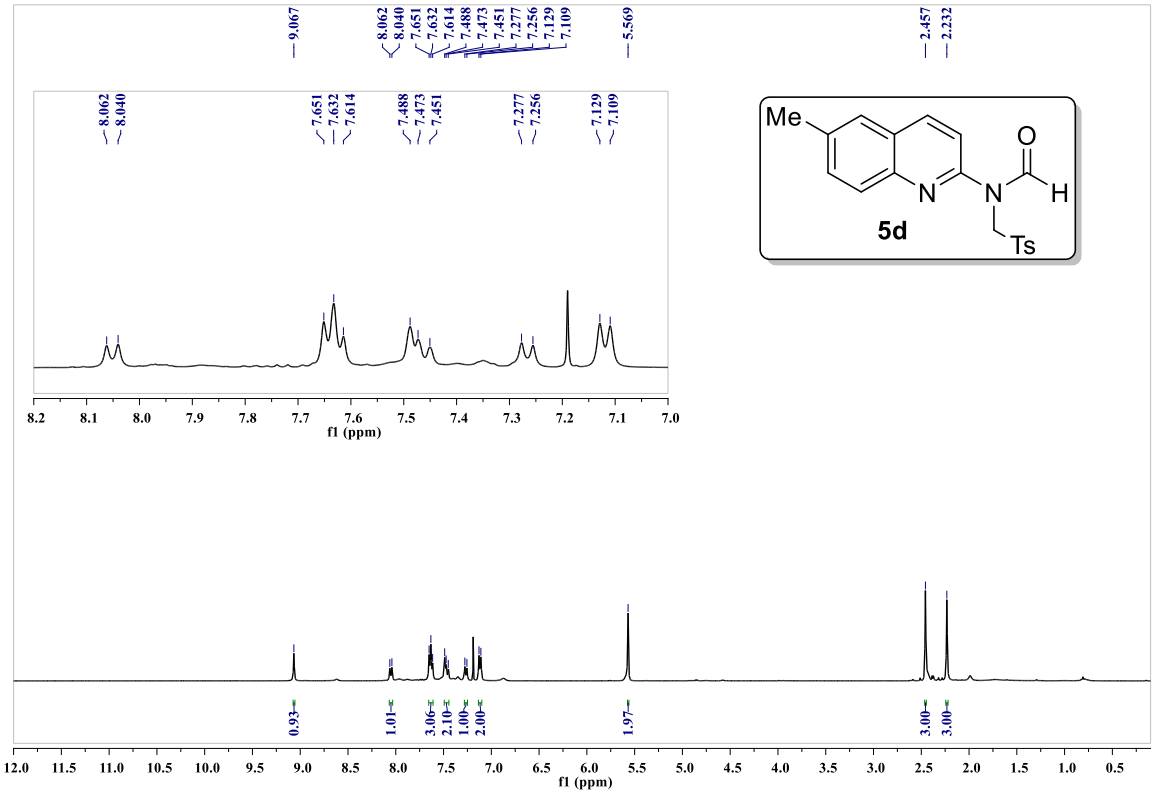
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of *N-tert*-Butyl-*N*-(6-methylquinolin-2-yl)formamide (3c)



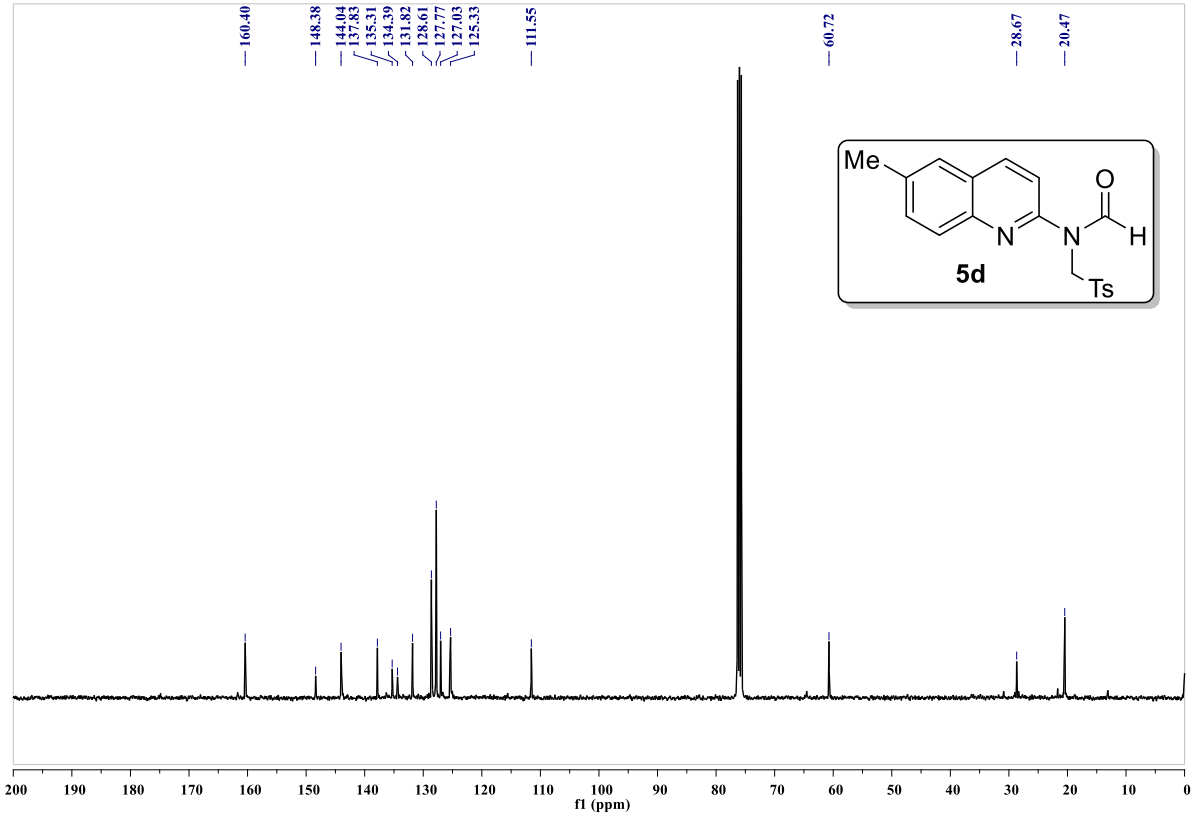
HRMS spectrum of *N*-*tert*-Butyl-*N*-(6-methylquinolin-2-yl)formamide (3c)



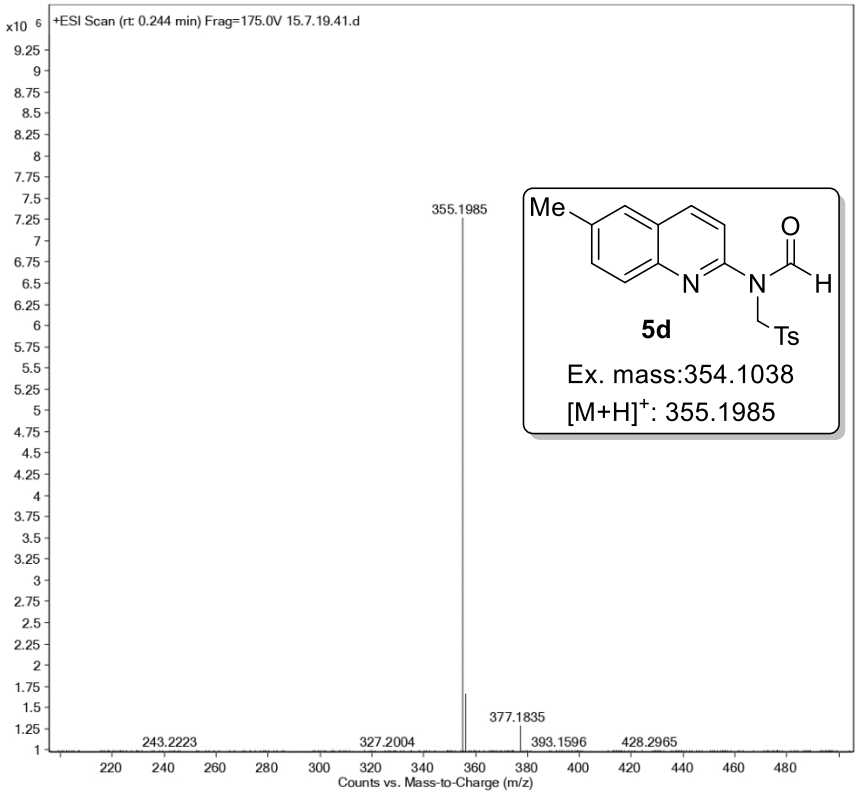
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(6-methylquinolin-2-yl)-*N*-(tosylmethyl)formamide (5d)



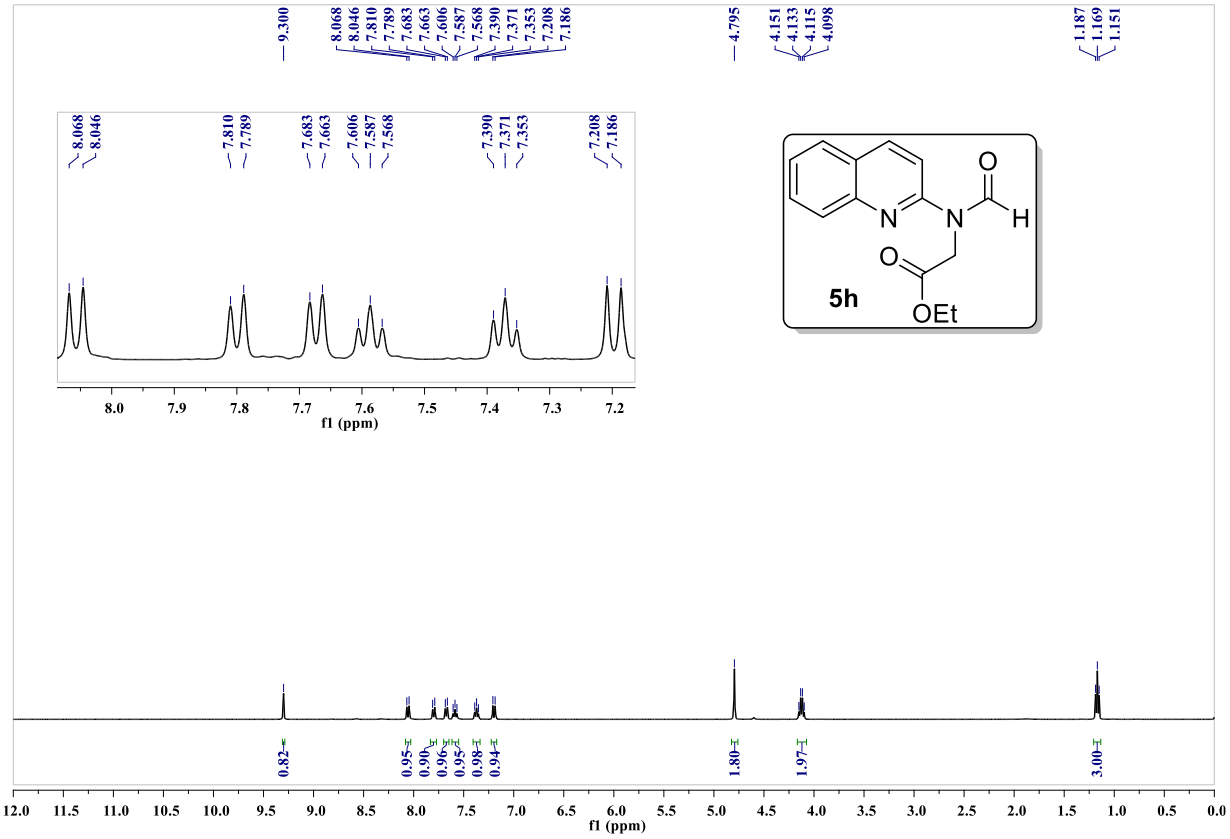
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of *N*-(6-methylquinolin-2-yl)-*N*-(tosylmethyl)formamide (5d)



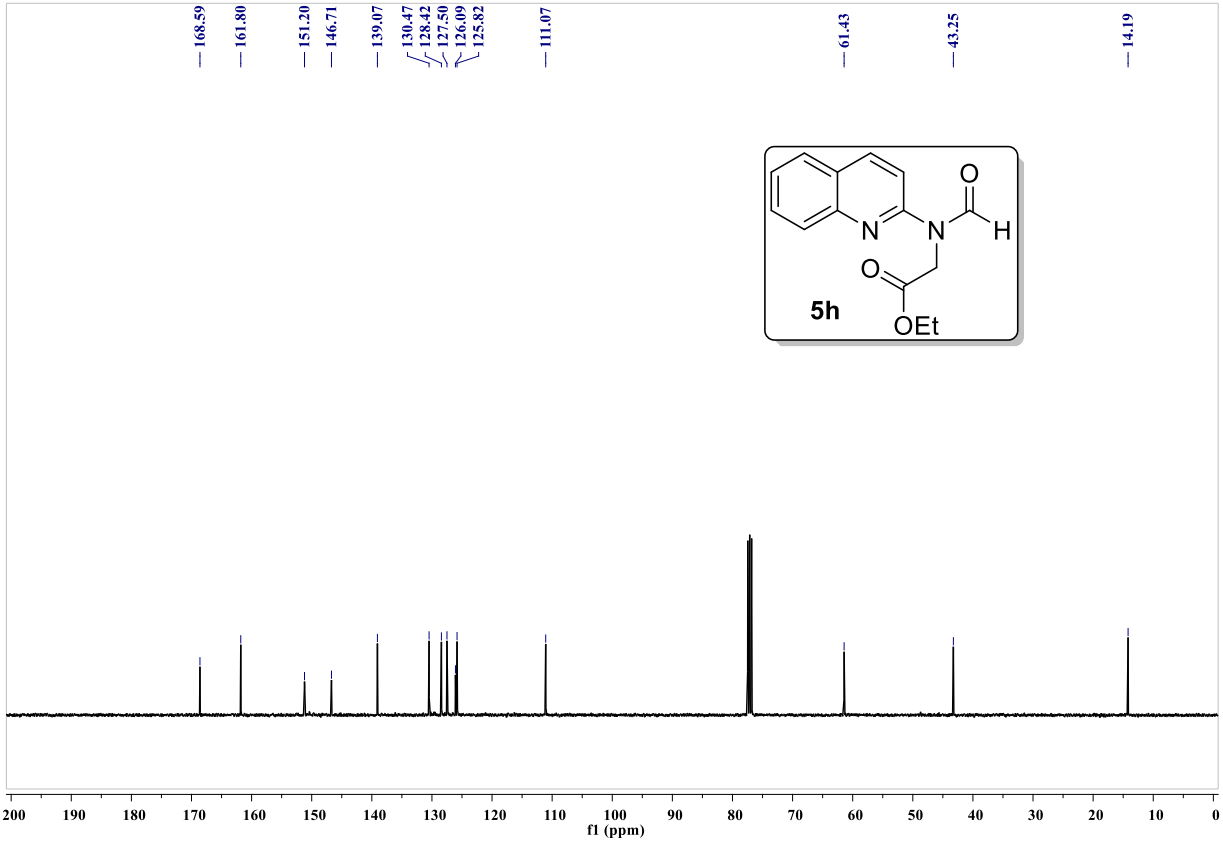
HRMS spectrum of *N*-(6-methylquinolin-2-yl)-*N*-(tosylmethyl)formamide (5d)



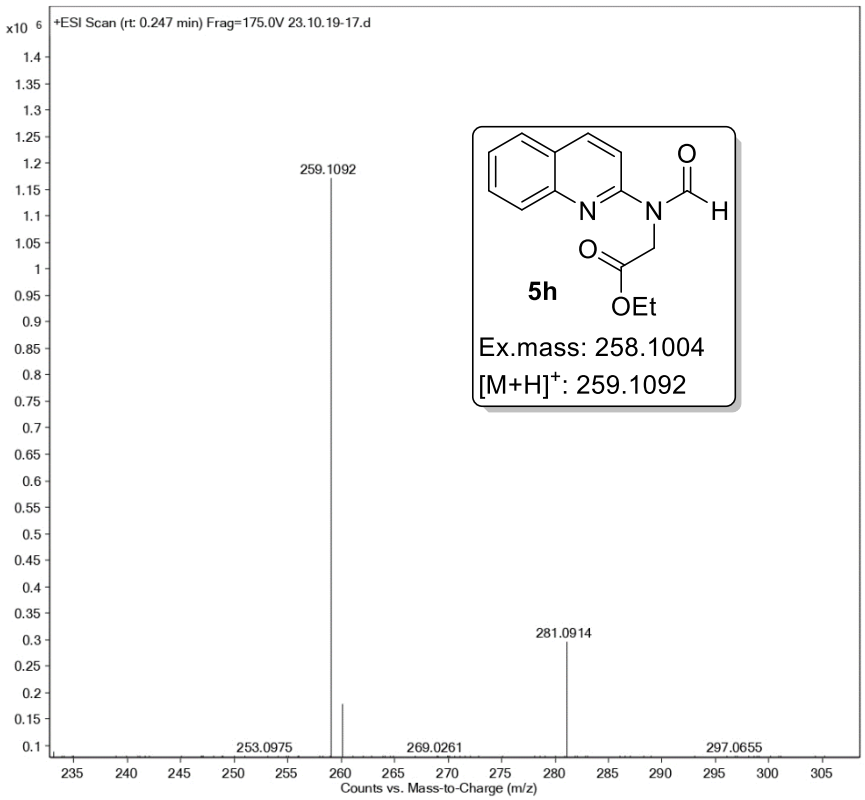
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5h)



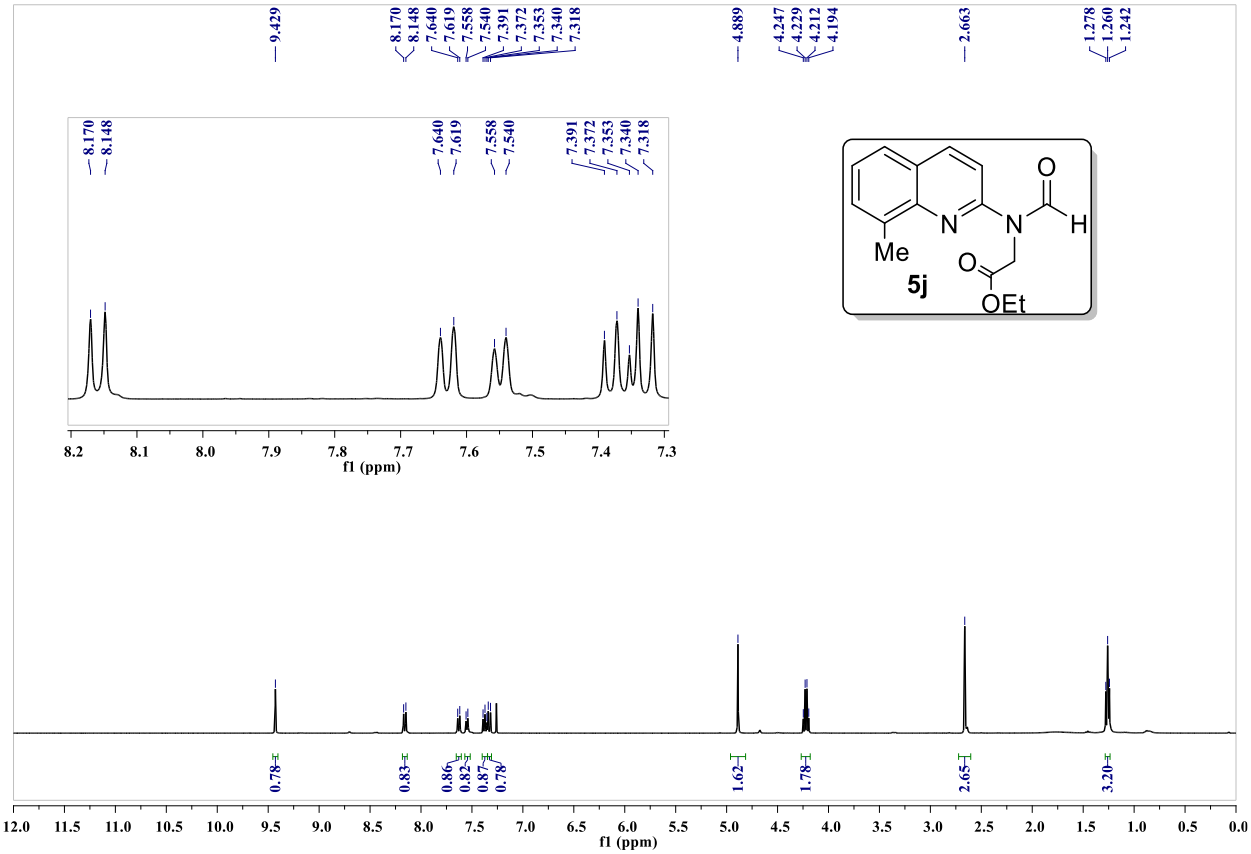
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of ethyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5h)



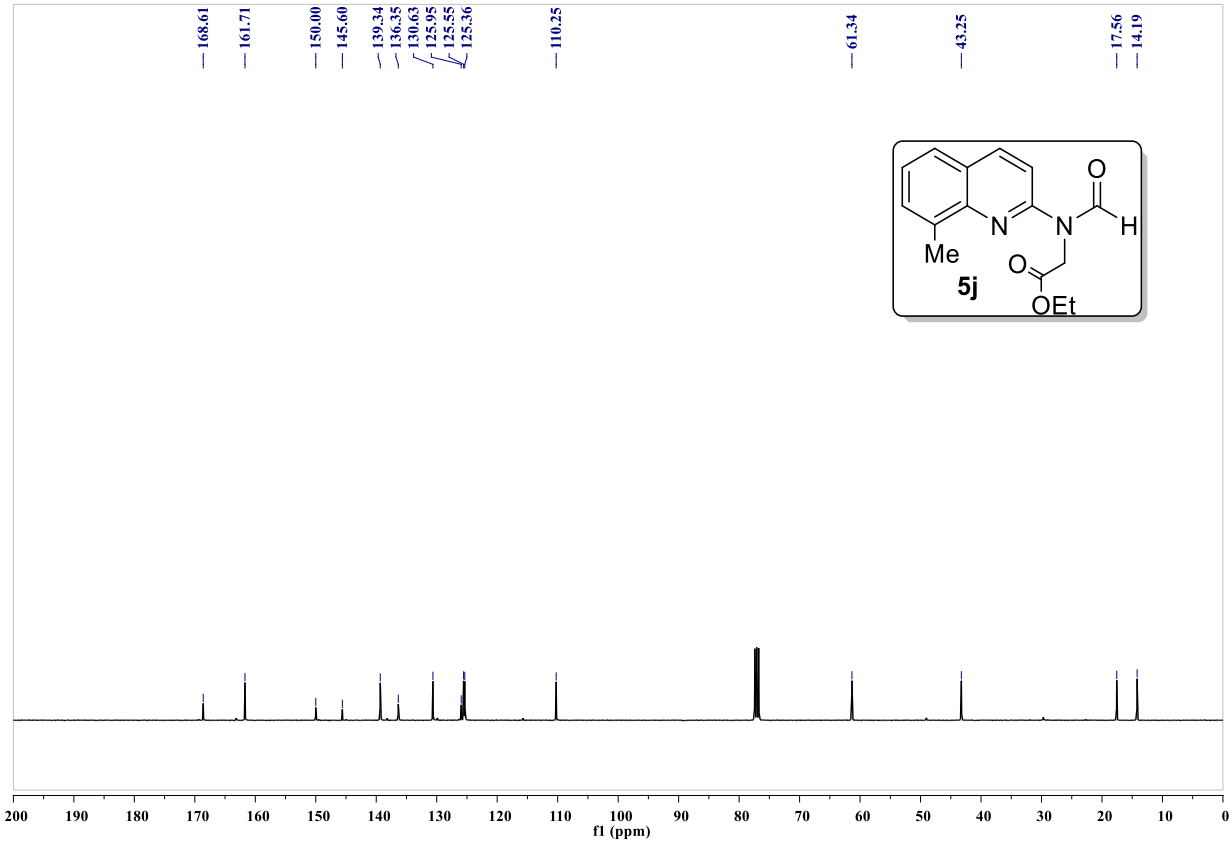
HRMS spectrum of ethyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5h)



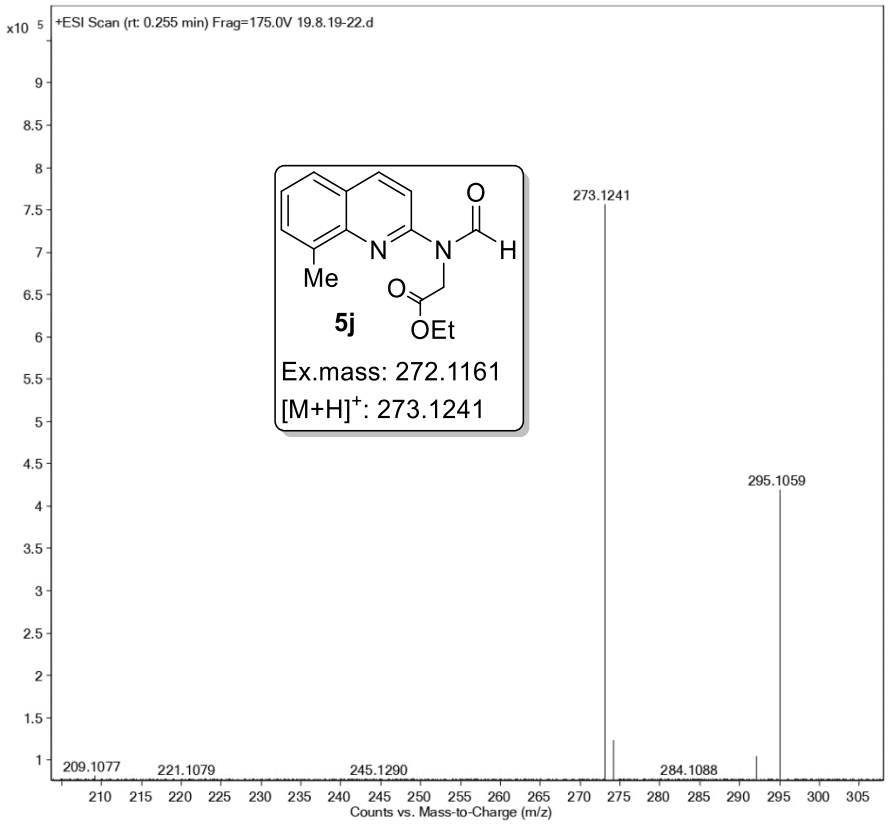
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl 2-(*N*-(8-methylquinolin-2-yl)formamido)acetate (5j)



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of ethyl 2-(*N*-(8-methylquinolin-2-yl)formamido)acetate (5j)

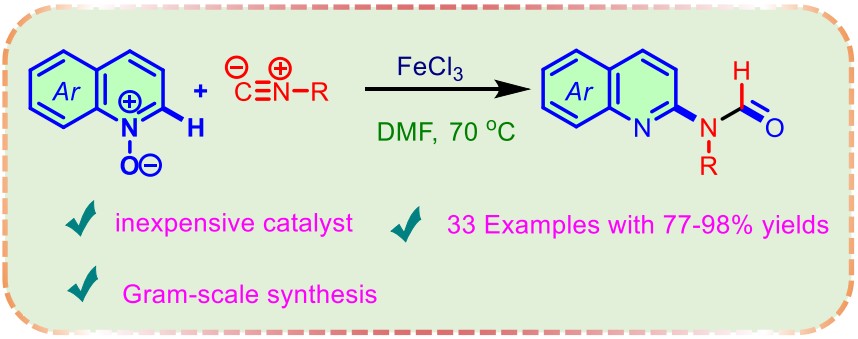


HRMS spectrum of ethyl 2-(*N*-(8-methylquinolin-2-yl)formamido)acetate (5j)



CHAPTER-IIB

Fe-Catalyzed Deoxygenative C2-Formamidation Reaction of Quinoline *N*-oxides with Isocyanides



2B.1. Introduction

The development of sustainable and efficient organic synthesis is one of the fundamental research goals in chemistry.[1-4] In this respect, catalysis plays a key role, since approximately 80% of all fine chemical and pharmaceuticals on an industrial scale are made by catalysts.[5-6] In this context, organometallic compounds have become an established synthetic tool for both fine and bulk chemicals. Among them, transition-metal catalysis is one of the essential tools for organic chemists. A high percentage of catalysts used in organic synthesis comprises of transition metals (TMs) due to their variable oxidation states and coordination numbers (Figure 2B.1).[7-12]

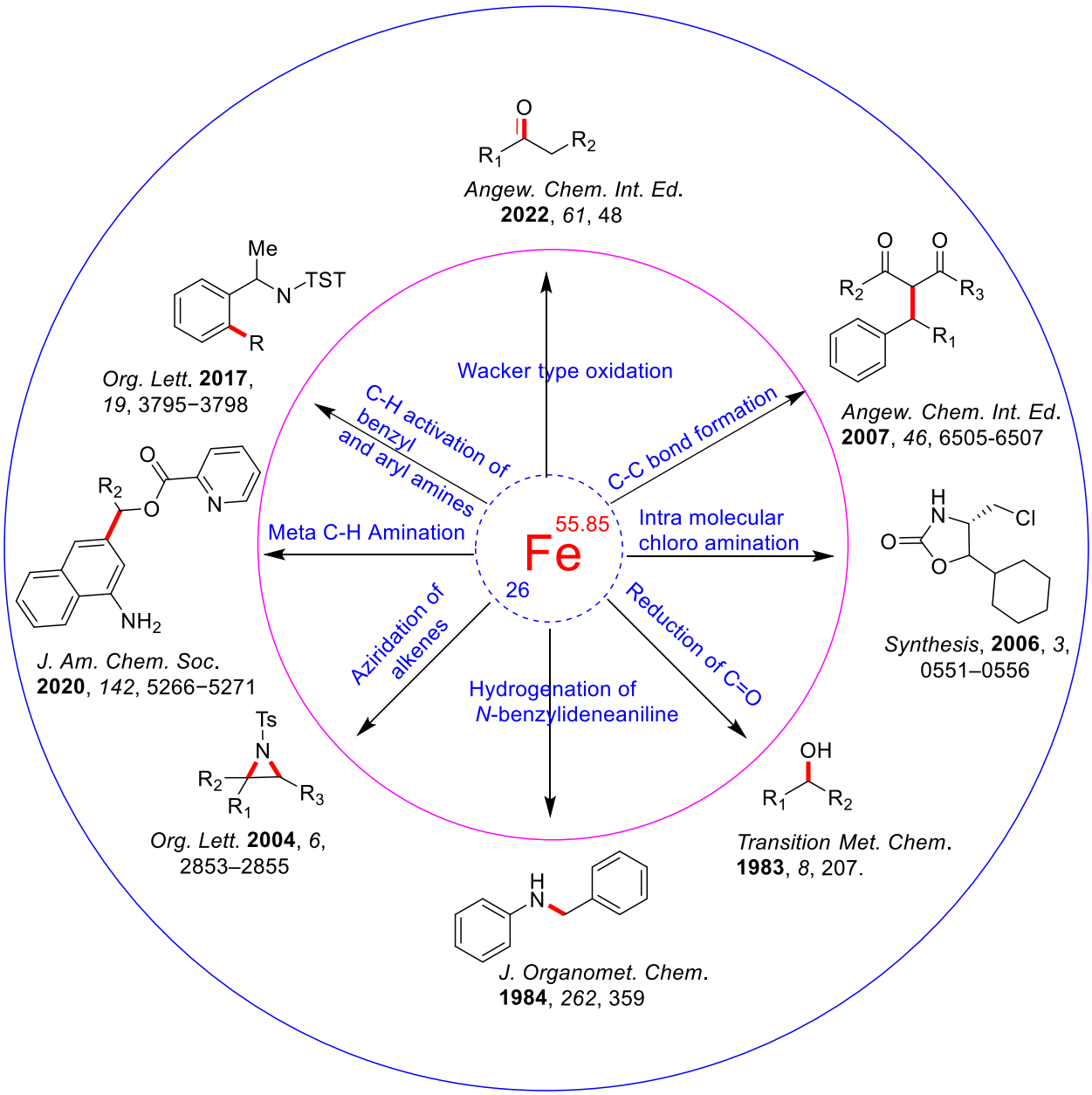


Figure 2B.1. Iron catalysed organic reactions.

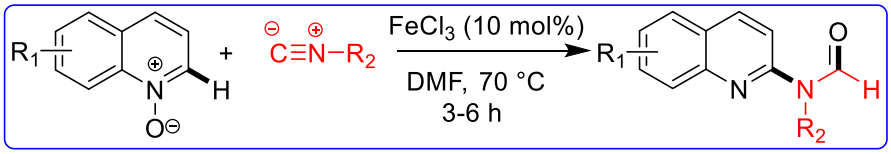
The promising TMs, the late transition metals i.e. Ru,[13-15] Pd,[16-17] Rh,[18] and Ir[19] catalysts have been widely used for the development of synthetic methods since the 1960s. Especially, palladium catalysis has been extensively used in cross-coupling reactions for the formation of carbon-carbon and carbon-heteroatom bonds.[20] Further, many C-H activation reactions, including both directed and non-directed reactions, are being pursued with the late transistion-metal.[21] However, the fundamental problem associated with late TM catalysts is their high price and toxicity to the environment.[22] The metal waste products from late TM catalysis contribute to the pollution in the Earth's crust and oceans. These factors may not be a problem for academic research, but have profound implications for industrial applications. It is for these reasons that attention has shifted towards base transition metals like iron, copper and nickel. Presently, many research groups focus on the development of alternative catalytic methods involving the Earth-abundant and less-toxic 3d metals for organic synthesis considering sustainable chemistry.[23,24] Iron is one of the most abundant metals on Earth, and consequently one of the most inexpensive and environmentally friendly ones.[25] Moreover, many iron salts and complexes are commercially available,[25] or described in the literature.[26]

Contextually, the use of cheap, easily accessible, iron catalysts in organic synthesis can bring a renaissance in the field of catalysis. Notably, iron is the most abundant metal on the Earth's surface among the 3d, 4d and 5d metals. Moreover, if the cost of metallic iron is compared with the other late transition metals, it is found that iron is less expensive by several magnitudes. Thus, the utilization of iron catalysts is certainly a sustainable approach.

A considerable attention has been received to the synthesis of quinoline 2-formamides and functionalization of quinolines at C2 position to increase the biological activity of the quinoline core. Much has already been done on alkenylation, arylation, alkynylation, amination, acylation, sulfuration, and alkylation of quinolines. Whereas, formamidation of quinolines are common pharmacophores with wide applications in pharmaceuticals. Nevertheless, the direct formamidation of quinolines has only caught the imagination of only a few chemists. Till now only few reports are available for the direct synthesis of quinoline 2-formamides substituted quinolines. Therefore, introducing formamidation group into the quinoline ring has the potential to attract many researchers in this direction. The introduction and application of C2-formamides are well discussed in chapter 2A. In this chapter, an efficient iron catalysed C2 formulation is described under mild reaction conditions.

2B.2. Present study

Herein we reported an environmentally benign iron catalysis for the synthesis of quinoline 2-formamides *via* C(sp^2)-H functionalization in the presence of isocyanide. The Fe catalyzed regioselective insertion of isocyanide into C2-H of quinoline *N*-oxides reaction proceeds through the nucleophilic addition of isocyanide on quinoline *N*-oxides followed by rearrangement in presence of iron. This transition-metal reaction affords rapid access to quinoline 2-formamides with exceptional functional group tolerance, broad substrate scope (Scheme 2B.1).

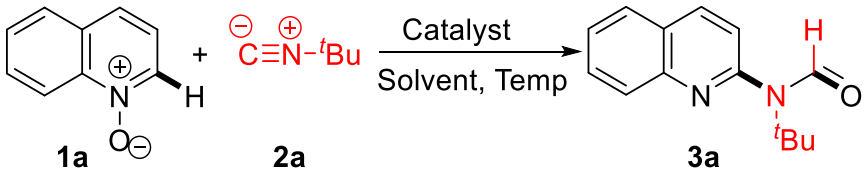


Scheme 2B.1.

2B.2.1. Results and discussion

In our initial screening experiments, the reaction between quinoline *N*-oxide **1a** with *tert*-butyl isocyanide **2a** in the presence of 10 mol% of iron chloride with suitable solvent and temperatures was investigated to optimize the reaction conditions, and only the key facts are reported in the Table 2B.1. The reaction of quinoline *N*-oxide **1a** with *tert*-butyl isocyanide **2a** in the presence of 10 mol% of iron chloride in DMF at room temperature stirring for 24 h the desired product (**3a**) 60% yield (Table 2B.1 entry 1). To our delight, the formation of *N*-*tert*-butyl-*N*-(quinolin-2-yl)formamide **3a** was observed with 75% in DMF at elevated temperatures (Table 2B.1, entry 2). These results motivated us to optimize the reaction conditions to improve the product yield. Next, we have carried out the reaction in various catalysts to assess their effect on the reaction efficiency. Among all the catalysts used, $FeCl_3$ was superior to the tested catalyst, such as different Lewis acids: $Dy(NO_3)_3.6H_2O$, $BF_3.OEt_2$ gave good percentage of yield (Table 2B.1, entry 5-6); $AlCl_3$, $ZnCl_2$, $(FeSO_4)_3$, $Fe(NO_3)_3.9H_2O$, $Bi(NO_3)3.5H_2O$, $Cu(OTf)_2$ gave moderate yields 30-70 % (Table 2B.1, entry 7-13); Pr_2O_3, Yb_2O_3, Eu_2O_3, Gd_2O_3, Nd_2O_3, $Ru(acac)_3$ and Dy_2O_3 gave less yield 20-50 % (Table 2B.1, entry 14-19).

Table 2B.1: Optimization of the catalyst[a]

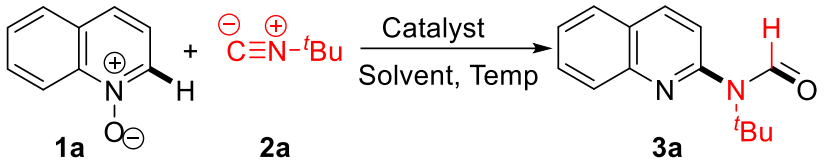


Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1.	$FeCl_3$	DMF	RT	60
2.	$FeCl_3$	DMF	50	75
3.	**$FeCl_3$**	**DMF**	**70**	**98**
4.	$FeCl_3$	DMF	100	80
5.	$Dy(NO_3)_3.\ 6H_2O$	DMF	70	93
6.	BF_3OEt_2	DMF	70	95
7.	$AlCl_3$	DMF	70	70
8.	$ZnCl_2$	DMF	70	40
9.	$Fe_2(SO_4)_3$	DMF	40	40
10.	$Fe(NO_3)_3.\ 9H_2O$	DMF	70	30
11.	$Bi(NO_3)_3.\ 5H_2O$	DMF	70	30
12.	$Cu(OTf)_2$	DMF	70	50
13.	Pr_2O_3	DMF	70	50
14.	Yb_2O_3	DMF	70	42
15.	Eu_2O_3	DMF	70	35
16.	Gd_2O_3	DMF	70	35
17.	Nd_2O_3	DMF	70	30
18.	$Ru(acac)_3$	DMF	70	20
19.	Dy_2O_3	DMF	70	20

[a] Reaction conditions: Quinoline *N*-oxide **1a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.5 mmol), catalyst (10 mol%), solvent (2 mL), 4 h. [b] Isolated yield.

The above results motivated us to screen other solvent and temperatures to know the effect on the product formation and only the key facts are reported in the Table 2B.2.

Table 2B.2. Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1	$FeCl_3$	CH_2Cl_2	RT	0
2	$FeCl_3$	CH_2Cl_2	40	20
3	$FeCl_3$	$CHCl_3$	60	30
4	$FeCl_3$	DCE	70	60
5	$FeCl_3$	CH_3CN	70	75
6	$FeCl_3$	DMF	RT	60
7	$FeCl_3$	DMF	50	75
8	**$FeCl_3$**	**DMF**	**70**	**98**
9	$FeCl_3$	Toluene	70	30
10	$FeCl_3$	THF	40	70
11	$FeCl_3$	DMSO	70	75
12	$FeCl_3$	CH_3NO_2	70	10
13	$FeCl_3$	1,4 dioxane	70	30
14	$FeCl_3$	DMF	70	74[c]
15	$FeCl_3$	DMF	70	35[d]
16	$FeCl_3$	DMF	70	n.r
17	$FeCl_3$	DMF	70	85
18	$FeCl_3$	EtOH	70	40
19	$FeCl_3$	MeOH	70	30

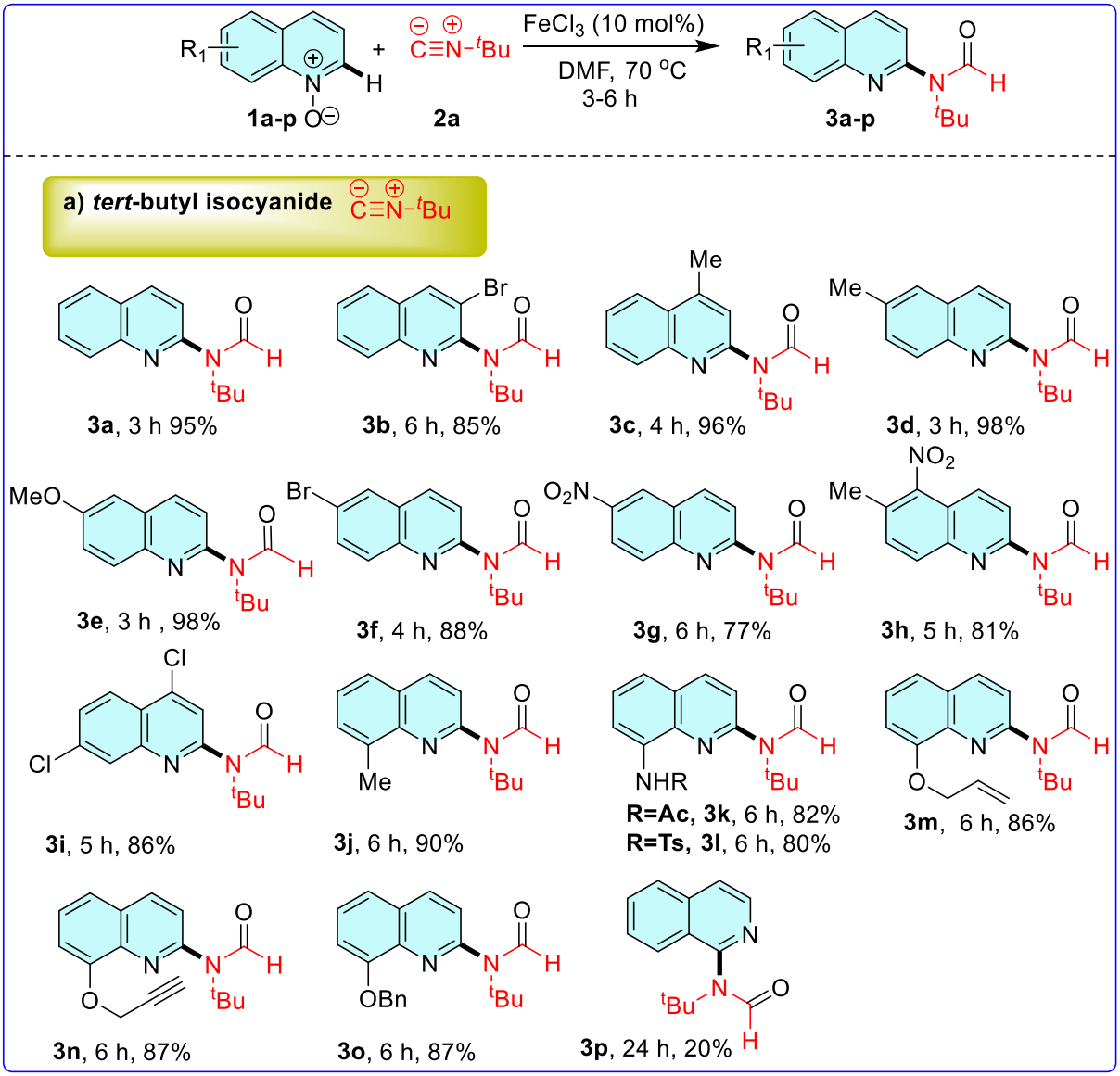
[a] Reaction conditions: quinoline *N*-oxide **1a** (0.5 mmol), *tert*-butyl isocyanide **2a** (0.5 mmol), catalyst (10 mol%), solvent (2 mL), 4 h. [b] Isolated yield. [c] $FeCl_3$ (5 mol%). [d] $FeCl_3$ (2 mol%) used. n.r = No reaction.

Among all the solvents used, DMF was superior to the tested solvents, such as chlorinated solvents, toluene, THF, DMSO, CH_3NO_2 and 1,4 dioxane for this transformation (Table 2B.2, entries 1-4, 9-13). The polar protic solvents such as ethanol and methanol observed less percentage of yield 30-40% (Table 2B.2, entry 18-19).

Further, change in the temperature did not improve the yield (Table 2B.2, entry 20). Additionally, changing the loadings of catalyst had no positive effect on the transformation,

only 74% and 35% yields were obtained when 5 mol% and 2 mol% of catalyst were used respectively (Table 2B.2, entries 14-15). It is worth mentioning that our method proceeds with 100% atom-economy. Therefore, the optimized reaction conditions are 0.5 mmol of quinoline *N*-oxide, 0.5 mmol of isocyanide and 10 mol% of $FeCl_3$ in 2 mL DMF at 70 °C for 4 h as shown in (Table 2B.2, entry 8).

Table 2B.3. Substrate scope for the synthesis of *N*-(2-quinolinyl)formamides[a,b]

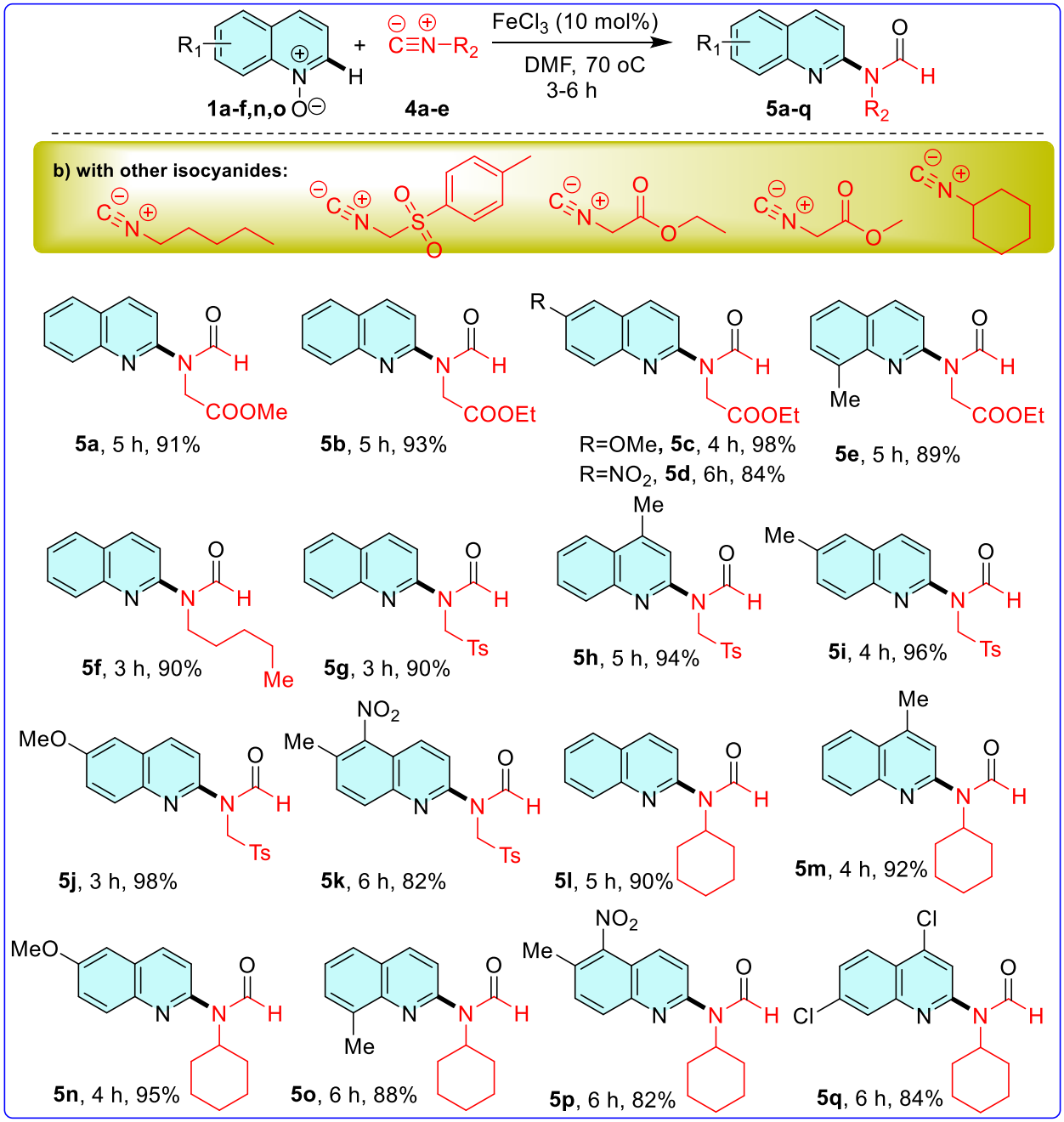


[a]Reaction conditions: quinoline *N*-oxides **1a-p** (0.5 mmol), isocyanide **2a** (0.5 mmol), $FeCl_3$ (10 mol%), DMF (2 mL), 70 °C, [b]Yields are given for isolated products.

With the optimized conditions in hand, we commenced the evaluation of the scope of the reaction by examining diversely substituted quinoline *N*-oxides with *tert*-butyl isocyanide and results are shown in Table 2B.3. In the beginning we explored the effect of electron donating groups on quinoline *N*-oxides with *tert*-butyl isocyanide to obtain the corresponding quinoline

2-formamides and found to be well tolerated (Table 2B.3, **3c-e**). Also, the electron withdrawing group on the sixth position of quinoline gave the target product **3g** in 77% yield.

Table 2B.4. Substrate scope for the synthesis of *N*-(2-quinolinyl)formamides[a,b]



[a]Reaction conditions: quinoline *N*-oxides **1a-f, n, o** (0.5 mmol), isocyanide **4a-f** (0.5 mmol), $FeCl_3$ (10 mol%), DMF (2 mL), 70 °C, [b]Yields are given for isolated products.

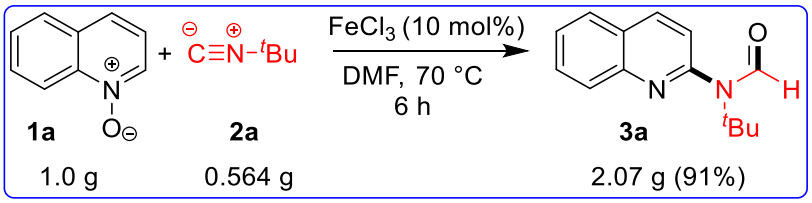
Likewise, halogen substituted quinoline *N*-oxides were reacted smoothly with *tert*-butyl isocyanide to give the corresponding 2-formamide quinolines in good yields (Table 2B.3, **3b, 3f**).

Notably, substitution at C8 position such as benzyl, allyl, propargyl ethers, *N*-acetyl and *N*-tosyl of the quinoline *N*-oxides are readily converted into the respective C2-formamides in 80-87% yields (Table 2B.3, **3k-o**). It is worth noting that the quinoline *N*-oxides having disubstitutions also delivered the product **3h-i** in 81-86% yields. Unfortunately, isoquinoline *N*-oxides gave poor yield (Table 2B.3, **3p**). Indeed, C2 formamidation of pyridine *N*-oxide was not successful, but isoquinoline *N*-oxide gave poor yield (Table 2B.3, **3p**).

Further, we have turned our attention to the scope of other isocyanides with different quinoline *N*-oxides (Table 2B.4). The methyl isocyanoacetate **4a** has effortlessly reacted with quinoline *N*-oxide **1a** and produced corresponding product **5a** in 91% yield. Interestingly, ester attached isocyanides such as methyl isocyanoacetate **4a** and ethyl isocyanoacetate **4b** reacted with functional quinoline *N*-oxides to deliver target products **5g-k** in good to excellent yields (84-98%). The 1-pentyl isocyanide **4c** has effortlessly reacted with quinoline *N*-oxide **1a** and produced corresponding product **5f** in 91% yield. Besides, *p*-toluenesulfonylmethyl isocyanide (TosMIC) has been extensively preceded with diverse quinoline *N*-oxides to deliver corresponding formamide derivatives **5h-k** in 80-98% yields.

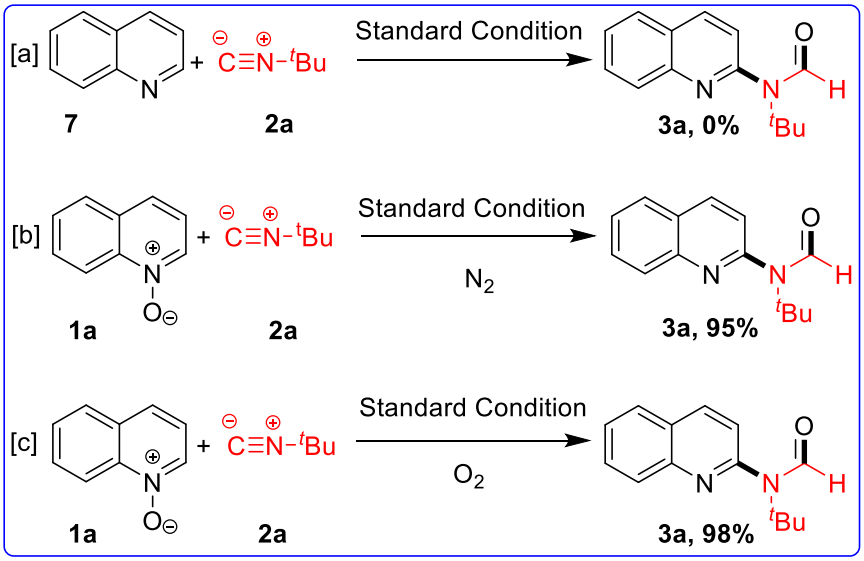
In addition, the cyclohexyl isocyanide **4e** has been reacted smoothly with several quinoline *N*-oxides to furnish final products **5l-q** in 82-95% yields. Apart from the traditional FT-IR, ^{1}H & ^{13}C NMR and mass spectral analysis, the formation of *N*-(quinolin-2- yl)formamide was observed.

Further, we investigated the efficiency of this protocol for gram scale reaction using quinoline *N*-oxide **1a** with *tert*-butyl isocyanide **2a** in the presence of 10 mol% of iron chloride under the standard condition. The reaction afforded the final product **3a** in 91% of yield (Scheme 2B.2).



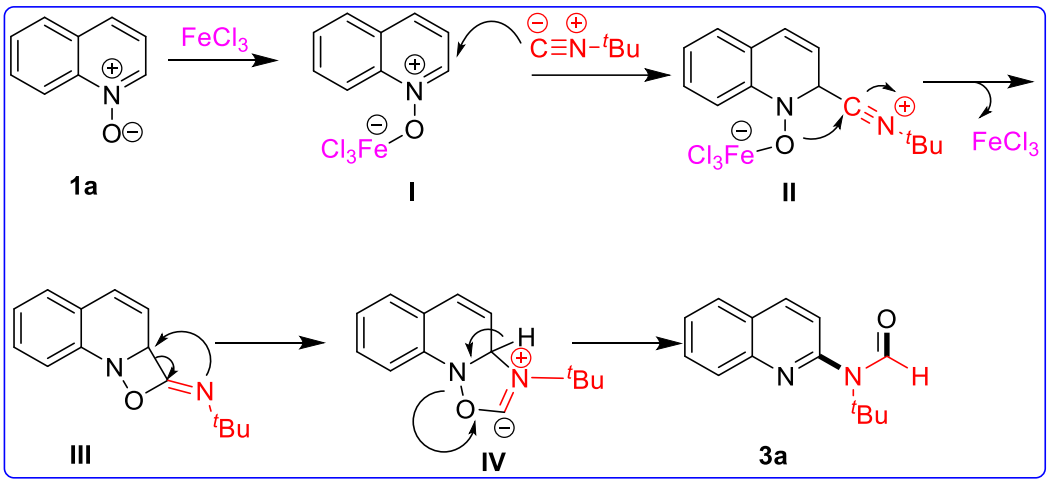
Scheme 2B.2. Gram-scale reaction.

Next, we carried several control experiments to unveil the reaction mechanism (Scheme 2B.3). Initially, quinoline **7** was treated with *tert*-butyl isocyanide **2a** under the standard conditions, no reaction occurred, which indicated the role of *N*-oxide in this transformation (Scheme 2B.**3a**). Finally, reactions were carried out under nitrogen to find out the role of oxygen, the yield of product **3a** was unchanged. On the basis of our control experiments and previous literature, a plausible mechanism of the iron chloride catalysed conversion of quinoline *N*-oxides to *N*-(2-quinolinyl)formamides is illustrated in Scheme 2B.4.



Scheme 2B.3. Control experiments.

The catalytic cycle initiates with the reaction of quinoline *N*-oxides with iron chloride to produce intermediate **I**, then nucleophilic addition between **1a** and isocyanide results in the formation of intermediate **II**. Later, the nucleophilic oxygen of *N*-oxide subsequently attacked on the carbon of isocyanide to form intermediate **III**, which readily undergoes rearrangement to form more stable intermediate **IV**. Finally, the intermediate **IV** undergoes re-aromatization to obtain the desired product **3a.**



Scheme 2B.4. Proposed reaction mechanism

2B.3. Conclusion

In conclusion an efficient iron chloride direct formamidation of quinolines by isocyanides to obtain quinoline 2-formamides products has been described in this chapter. The proposed method delivers end products with high yields (80-98%). This method involves less expensive Fe and bench chemicals. This metal reaction affords rapid access to quinoline 2-formamides

with exceptional functional group tolerance, broad substrate scope. It is also observed that the reaction is also favourable to the synthesis in gram-scale reactions.

2B.4. Experimental section

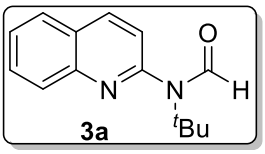
2B.4.1. General Information: All chemicals were purchased from Aldrich, Alfa aesar, TCI, Finar and used as received. All solvents were purchased from commercial sources, then distilled by the standard protocol and stored over molecular sieves under nitrogen atmosphere prior to use. Thin layer chromatography was performed on 200 µm aluminium-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). ^{1}H NMR spectra were recorded on Bruker's AVANCE 400 MHz spectrometer, $CDCl_3$ and DMSO-d_6 as a solvent and TMS as an internal standard. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. Coupling constants, *J* were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker's AVANCE 100 MHz spectrometer, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-d (a multiplet at 39.52 ppm of DMSO-d_6). Melting points were determined with a Stuart SMP30 apparatus and are uncorrected. FT-IR spectra recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230.

2B.4.2. General procedure for the synthesis of *N*-(2-quinolinyl)formamides (3a-p and 5a-q)

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate quinoline *N*-oxides (0.5 mmol), $FeCl_3$ (10 mol%), alkyl isocyanides (0.5 mmol) and (*N*, *N*-dimethylformamide) DMF (2 mL). The mixture was stirred at 70 °C for the appropriate time (3-6 h). The progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. After completion, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 10 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent.

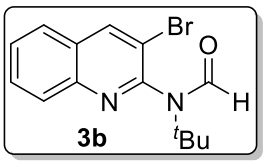
2B.5. Characterization data of products 3a-p, 5a-5q

***N-tert*-butyl-*N*-(quinolin-2-yl) formamide (3a).** White crystalline solid (108 mg, 95% yield);



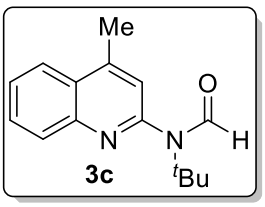
R_f = 0.50 (hexanes/EtOAc = 7:3). mp: 91-92 °C; IR (KBr, cm^{-1}) 3072, 2975, 2925, 1664, 1591, 1502, 1358, 1195, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.82 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.73 (s, 1H), 7.57 (t, J = 7.2, 6.8Hz 1H), 7.24 (s, 1H), 1.54 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.9, 152.3, 147.4, 137.7, 129.6, 129.4, 127.5, 127.0, 122.8, 121.8, 57.5, 30.9; ^{13}C NMR {^1H} of major rotamer (100 MHz, DMSO-d_6, 60 ºC) δ (ppm): 163.1, 153.6, 147.1, 138.2, 130.3, 129.1, 128.1, 127.4, 127.3, 123.3, 57.4, 30.1; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{16}N_2O$ $[M+H]^+$ 229.1335; found 229.1338.

***N*-(3-Bromoquinolin-2-yl)-*N*-(*tert*-butyl)formamide (3b).** Red colour liquid; (131 mg, 85%



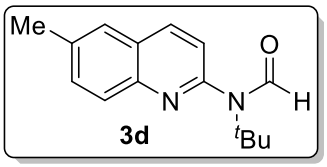
yield); R_f = 0.58 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3058, 2975, 2924, 1672, 1621, 1578,1488, 1370, 1199, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.77 (s, 1H), 8.40 (s, 1H), 8.05-7.98 (m, 1H), 7.76-7.65 (m, 2H), 7.55 (s, 1H), 1.52 (t, J = 5.2 Hz, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.7, 150.7, 146.0, 140.7, 130.0, 129.4, 128.6, 128.0, 126.5, 118.2, 58.0, 30.5; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{15}BrN_2O$ $[M+H]^+$ 307.0441; found 307.0442.

***N-tert*-butyl-*N*-(4-methylquinolin-2-yl)formamide (3c**). Brown liquid, (116 mg, 86% yield);



R_f = 0.56 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3042, 2974, 2924, 1681, 1592, 1347, 1200, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (s, 1H), 8.05 (d, J = 8.4Hz, 1H), 7.98 (d, J = 8.0Hz, 1H), 7.75-7.64 (m, 1H), 7.65-7.52 (m, 1H), 7.09 (s, 1H), 2.70 (s, 3H), 1.53 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.9, 152.0, 147.3, 146.8, 130.0, 129.7, 126.8, 123.7, 123.2, 122.3, 57.4, 30.9, 18.8; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O$ $[M+H]^+$ 243.1492; found 243.1486.

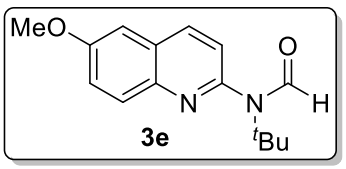
***N-tert*-butyl-*N*-(6-methylquinolin-2-yl)formamide (3d).** White solid (118 mg, 98% yield); R_f



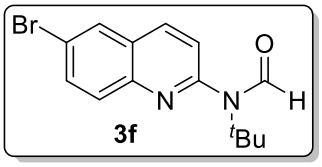
= 0.56 (hexanes/EtOAc = 7:3). mp: 107-108 °C; IR (KBr, cm^{-1}) 3045, 2973, 2922, 2865, 1683, 1586, 1497, 1335, 1296, 1117, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.60-7.52

(m, 1H), 7.25-7.15 (m, 1H), 2.55 (s, 3H), 1.53 (s, 9H); ^{13}C NMR {^{1}H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.8, 151.4, 146.0, 137.1, 132.0, 129.0, 127.3, 126.3, 123.0, 122.0, 57.4, 31.0, 22.0; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O$ $[M+H]^+$ 243.1492; found 243.1494.

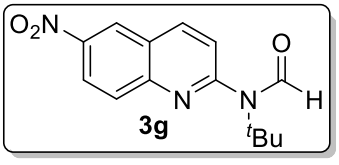
***N*-*tert*-butyl-*N*-(6-methoxyquinolin-2-yl)formamide (3e).** White crystalline solid, (127 mg, 98% yield); R_f = 0.46 (hexanes/EtOAc = 7:3); mp: 96-97 °C; IR (KBr, cm^{-1}) 3075, 2981, 2964, 1668, 1591, 1496, 1460, 1318, 1232, 1163, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.41-7.35 (m, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 3.94 (s, 3H), 1.52 (s, 9H); ^{13}C NMR {^{1}H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 163.0, 158.2, 149.95, 143.3, 137.0, 131.0, 128.4, 123.0, 122.3, 105.0, 57.3, 56.0, 31.0; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O_2$ $[M+H]^+$ 259.1441; found 259.1440.



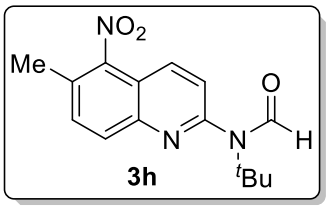
***N*-(6-Bromoquinolin-2-yl)-*N*-(*tert*-butyl)formamide (3f).** White solid; (135 mg, 88% yield); mp: 143-144 °C; R_f = 0.56 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3047, 2976, 2923, 1677, 1584, 1484, 1331, 1298, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 1.56 (s, 9H); ^{13}C NMR {^{1}H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 163.0, 146.0, 137.0, 133.3, 131.0, 130.0, 128.3, 122.4, 58.0, 31.0; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{15}BrN_2O$ $[M+H]^+$ 307.0441; found 307.0448.



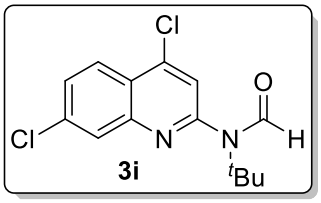
***N*-*tert*-butyl-*N*-(6-nitroquinilin-2-yl)formamide (3g).** Yellow crystalline solid; (105 mg, 77% yield); R_f = 0.46 (hexanes/EtOAc = 6:4); mp: 130-131 °C; IR (KBr, cm^{-1}) 3032, 2972, 2922, 1682, 1599, 1490, 1393, 1335, 1297, 1188, 1083 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (d, J = 2.4 Hz, 1H), 8.74 (s, 1H), 8.49 (dd, J = 9.2, 2.4 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 9.2 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 1.58 (s, 9H); ^{13}C NMR {^{1}H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 163.0, 156.0, 149.3, 146.0, 139.1, 131.0, 126.0, 124.1, 123.2, 58.3, 30.4; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{15}N_3O_3$ $[M+H]^+$ 274.1186; found 274.1187.



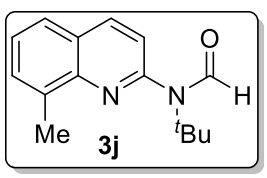
***N-tert*-butyl-*N*-(6-methyl-5-nitroquinolin-2-yl)formamide (3h).** Brown liquid; (116 mg, 81% yield); R_f = 0.42 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3072, 2977, 2929, 1670, 1592, 1527, 1474, 1356, 1199, 1145, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (s, 1H), 8.15 (d, J = 9.2, 1H), 8.12 (d, J = 8.8, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 2.57 (s, 3H), 1.55 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.8, 153.3, 146.5, 145.6, 132.1, 129.5, 124.9, 119.2, 57.9, 30.8, 18.1; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{17}N_3O_3$ $[M+H]^+$ 288.1343; found 288.1339.



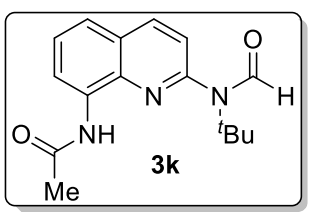
***N-tert*-butyl-*N*-(4,7-dichloroquinolin-2-yl)formamide (3i).** White solid; (128 mg, 86% yield); mp: 107-108 °C; R_f = 0.45 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3032, 2969, 2936, 1660, 1607, 1553, 1490, 1346, 1292, 1213, 1198, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.76 (s, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.10 (s, 1H), 7.61 (dd, J = 8.8, 2.0 Hz, 1H), 7.37 (s, 1H), 1.55 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.0 , 152.1, 147.0, 142.3, 136.0, 128.0, 124.3, 124.0, 122.3, 57.0, 30.0; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{14}Cl_2N_2O$ $[M+H]^+$ 297.0556; found 297.0564.



***N-tert*-butyl-*N*-(8-methylquinilin-2-yl)formamide (3j).** Brown liquid, (109 mg, 90% yield); R_f = 0.54 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3032, 2973, 2923, 1682, 1594, 1498, 1345, 1222, 1081, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ δ (ppm): 8.83 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.59-7.51 (m, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.29-7.18 (m, 1H), 2.75 (s, 3H), 1.56 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.0, 150.0, 145.2, 136.2, 129.0,126.0, 126.0, 124.2, 121.3, 120.0, 56.3, 30.0, 17.0; ^{13}C NMR {^1H}of major rotamer (100 MHz, DMSO-d_6, 60 ºC) δ (ppm): 163.2, 152.5, 145.9, 138.4, 136.5, 130.2, 127.2, 126.9, 125.9, 122.9, 57.4, 30.2, 17.6; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O$ $[M+H]^+$ 243.1492; found 243.1491.

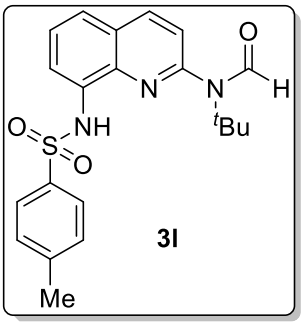


***N*-(2-(*N-tert*-butylformamido)quinolin-8-yl)acetamide (3k).** White solid; (117 mg, 82% yield); mp: 110-111 °C; R_f = 0.42 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3361, 3026, 2967, 2923, 1678, 1593, 1488, 1326, 1271, 1206, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.34 (s, 2H), 8.82-8.55 (m, 2H), 8.12 (d, J = 8.4 Hz, 1H), 7.47-7.41 (m, 2H), 7.20 (d, J = 8.4 Hz, 1H), 2.22 (s, 3H), 1.45 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$)



δ (ppm): 168.0, 162.0, 150.0, 137.4, 136.0, 133.2, 127.0, 126.0, 122.0, 120.1, 116.0, 56.3, 30.0, 24.0; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{19}N_3O_2$ $[M+H]^+$ 286.1550; found 286.1546.

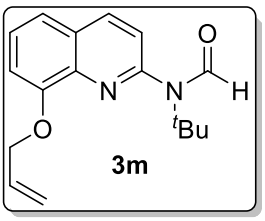
***N*-*tert*-butyl-*N*-(8-(4-methylphenylsulfonamido)quinolin-2-yl)formamide (3l).** White solid;



3l

(159 mg, 80% yield); R_f = 0.46 (hexanes/EtOAc = 7:3); mp: 155-156 ^oC; IR (KBr, cm^{-1}) 3302, 3065, 2972, 2923, 1668, 1597, 1504, 1470, 1325, 1201, 1164, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.72 (s, 1H), 8.62 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.84-7.73 (m, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.45-7.37 (m, 2H), 7.17 (t, J = 6.2, 1H), 7.06 (d, J = 8.0 Hz, 2H), 2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR {1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 163.0, 151.2, 144.0, 138.0, 136.2, 134.0, 130.0, 128.2, 127.0, 123.0, 122.0, 122.0, 116.1, 58.0, 30.0, 21.4; HRMS (ESI-TOF) m/z: calculated for $C_{21}H_{23}N_3O_3S$ $[M+H]^+$ 398.1533. found 398.1534.

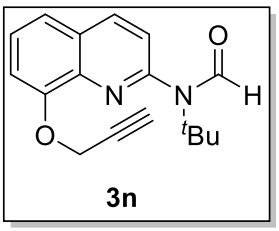
***N*-(8-(allyloxy)quinolin-2-yl)-*N*-(*tert*-butyl)formamide (3m).** Brown liquid (122 mg, 86%



3m

yield); R_f = 0.42 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3062, 2954, 2924, 2853, 1653, 1459, 1376, 1263, 1157, 1098, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.45-7.40 (m, 2H), 7.34-7.26 (m, 1H), 7.13-7.05 (s, 1H), 6.20-6.11 (m, 1H), 5.54 (d, J = 17.2 Hz, 1H), 5.32 (d, J = 10.4 Hz, 1H), 4.80 (d, J = 4.8 Hz, 2H), 1.57 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.0, 153.3, 150.0, 138.3, 136.3, 132.1, 127.4, 126.0, 122.2, 119.0, 116.3, 110.0, 69.0, 57.0, 29.0; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{20}N_2O_2$ $[M+H]^+$ 285.1598; found 285.1595.

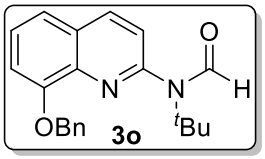
***N*-*tert*-butyl-*N*-(8-(prop-2-yn-1-yloxy)quinolin-2-yl)formamide (3n).** Brown liquid; (123



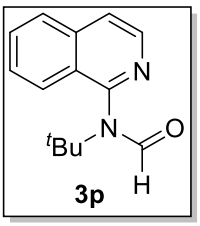
3n

mg, 87% yield); R_f = 0.45 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3257, 3058, 2975, 2922, 2116, 1674, 1499, 1459, 1319, 1262, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 2.4 Hz, 2H), 7.30 (s, 2H), 5.01 (s, 2H), 2.52 (t, J = 2.4 Hz, 2.0 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.9, 153.1, 139.5, 137.6, 128.5, 126.9, 123.4, 122.1, 120.7, 112.1, 78.5, 76.0, 57.3, 30.8; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{18}N_2O_2$ $[M+H]^+$ 283.1441; found 283.1442.

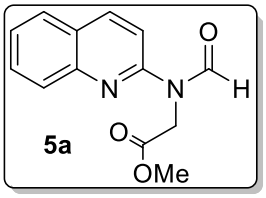
***N*-(8-(benzyloxy)quinolin-2-yl)-*N*-(*tert*-butyl)formamide (3o).** Light yellow liquid (145 mg, 87% yield); R_f = 0.45 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3032, 2974, 2923, 1671, 1594, 1500, 1326, 1206, 1103, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.42 (d, J = 2.8 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 7.17-7.06 (m, 1H), 5.37 (s, 2H), 1.59 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.0, 153.3, 150.1, 138.4, 137.3, 136.2, 127.4, 127.0, 126.0, 122.2, 120.0, 119.0, 118.4, 110.0, 70.0, 57.0, 29.0; HRMS (ESI-TOF) m/z: calculated for $C_{21}H_{22}N_2O_2$ $[M+H]^+$ 335.1754; found 335.1755.



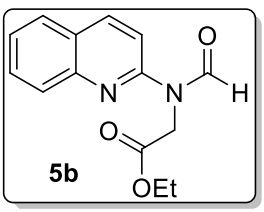
***N*-*tert*-butyl-*N*-(isoquinolin-1-yl)formamide (3p).** Brown liquid; (23 mg, 20% yield); R_f = 0.56 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3058, 2924, 2865, 1672, 1459, 1379, 1263, 1197, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.94 (s, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.93-7.84 (m, 2H), 7.78-7.60 (m, 3H), 1.52 (s, 9H); ^{13}C NMR {^1H} of major rotamer (100 MHz, $CDCl_3$) δ (ppm): 162.1, 152.0, 140.2, 137.0, 130.0, 127.3, 127.0, 126.1, 124.4, 121.0, 58.0, 30.0; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{16}N_2O$ $[M+H]^+$ 229.1335; found 229.1342.



Methyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5a). White solid; (111 mg, 91% yield); R_f = 0.45 (hexanes/EtOAc = 7:3); mp: 90-91 °C; IR (KBr, cm^{-1}) 3068, 2952, 2921, 2850, 1749, 1683, 1596, 1476, 1346, 1286, 1207, 1144, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.39 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 4.91 (s, 2H), 3.76 (s, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 169.1, 162.0, 151.1, 147.0, 139.1, 131.0, 128.4, 128.0, 126.1, 126.0, 111.0, 52.4, 43.0; HRMS (ESI-TOF) m/z: calculated for $C_{13}H_{12}N_2O_3$ $[M+H]^+$ 245.0921: found 245.0932.

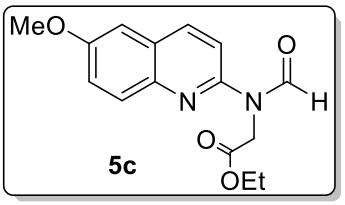


Ethyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5b). White solid; (120 mg, 93% yield); R_f = 0.46 (hexanes/EtOAc = 7:3); mp: 84-85 °C; IR (KBr, cm^{-1}) 3061, 2921, 2851, 1747, 1689, 1619, 1599, 1468, 1373, 1351, 1203, 1146, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.30 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.79 (s, 2H), 4.12 (q, J = 7.0 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ

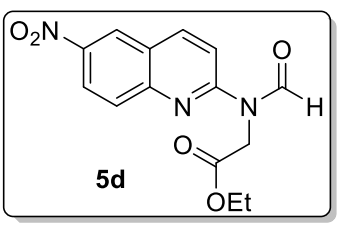


(ppm): 169.0, 162.0, 151.2, 147.0, 139.0, 130.4, 128.4, 128.0, 126.0, 126.0, 111.0, 61.4, 43.2, 14.1; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{14}N_2O_3$ $[M+H]^+$ 259.1077: found 259.1092.

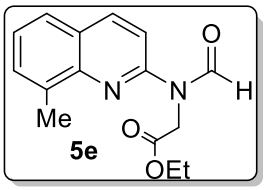
Ethyl 2-(*N*-(6-methoxyquinolin-2-yl)formamido)acetate (5c). White solid; (141 mg, 98% yield); R_f = 0.49 (hexanes/EtOAc = 7:3); mp: 76-77 °C; IR (KBr, cm^{-1}) 3057, 2980, 2938, 1747, 1686, 1600, 1505, 1463, 1358, 1233, 1199, 1028, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.30 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 9.2 Hz, 1H), 7.38-7.29 (m, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.04 (s, 1H), 4.85 (s, 2H), 4.21 (q, J = 6.8 Hz, 2H), 3.89 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR $\{^1H\}$ (100 MHz, $CDCl_3$) δ (ppm): 169.0, 162.0, 157.3, 149.4, 142.4, 138.0, 130.0, 127.0, 123.0, 112.0, 105.2, 61.3, 56.0, 43.3, 14.1; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{16}N_2O_4$ $[M+H]^+$ 289.1183; found 289.1183.



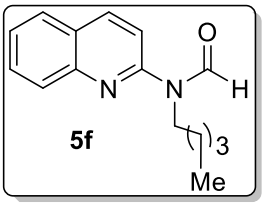
Ethyl 2-(*N*-(6-nitroquinolin-2-yl)formamido)acetate (5d). Yellow solid; (127 mg, 84% yield); R_f = 0.45 (hexanes/EtOAc = 7:3); mp: 190-191 °C; IR (KBr, cm^{-1}) 3062, 2982, 2928, 1740, 1682, 1611, 1498, 1368, 1335, 1215, 1126, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.53 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.46 (dd, J = 9.2, 2.0 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 4.91 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR $\{^1H\}$ (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 171.0, 169.0, 163.0, 155.0, 144.4, 141.3, 130.0, 125.2, 125.0, 124.1, 114.0, 61.3, 43.0, 14.4; HRMS (ESI-TOF) m/z: calculated for $C_{14}H_{13}N_3O_5$ $[M+H]^+$ 304.0928; found 304.0932.



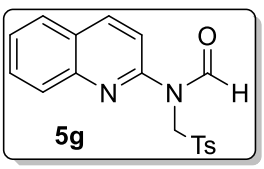
Ethyl 2-(*N*-(8-methylquinolin-2-yl)formamido)acetate (5e). White solid; (121 mg, 89% yield); R_f = 0.46 (hexanes/EtOAc = 7:3); mp: 90-91 °C; IR (KBr, cm^{-1}) 3054, 2966, 2917, 1746, 1687, 1600, 1507, 1402, 1348, 1223, 1199, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.43 (s, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.37 (t, J = 7.6, 1H), 7.33 (d, J = 8.8, 1H), 4.89 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 2.66 (s, 3H), 1.26 (t, J = 6.8.2 Hz, 3H); ^{13}C NMR $\{^1H\}$ (100 MHz, $CDCl_3$) δ (ppm): 169.0, 162.0, 150.0, 146.0, 139.3, 136.3, 131.0, 126.0, 125.0, 110.2, 61.3, 43.2, 18.0, 14.1; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{16}N_2O_3$ $[M+H]^+$ 273.1234; found 273.1241.



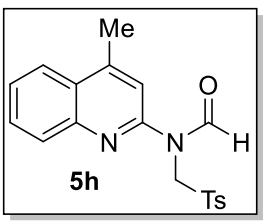
***N*-pentyl-*N*-(quinolin-2-yl)formamide (5f).** Colourless liquid; (109 mg, 90% yield); R_f = 0.52 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3027, 2955, 2924, 2853, 1684, 1599, 1504, 1467, 1431, 1367, 1260, 1197, 1117, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.42 (s, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.52-7.45 (m, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 4.05 (t, *J* = 7.6 Hz 2H), 1.73-1.63 (m, 2H), 1.40-1.30 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 162.0, 151.1, 146.0, 138.0, 129.3, 127.4, 126.4, 125.0, 125.0, 111.1, 41.0, 28.0, 27.0, 21.3, 13.0; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{18}N_2O$ $[M+H]^+$ 243.1492; found 243.1506.



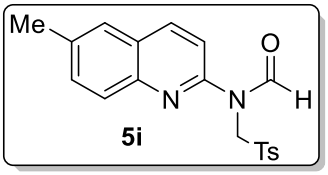
***N*-(quinolin-2-yl)-*N*-(tosylmethyl)formamide (5g).** White solid; (153 mg, 90% yield); R_f = 0.56 (hexanes/EtOAc = 7:3); mp: 128-129 °C; IR (KBr, cm^{-1}) 3067, 2924, 2853, 1693, 1597, 1505, 1476, 1341, 1288, 1143, 1085, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.19 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 8.4 Hz, 3H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 5.66 (s, 2H), 2.28 (s, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 160.4, 149.0, 145.4, 144.1, 139.0, 134.3, 130.0, 129.0, 128.0, 127.3, 126.4, 125.3, 111.4, 61.0, 21.0; HRMS (ESI-TOF) m/z: calculated for $C_{18}H_{16}N_2O_3S$ $[M+H]^+$ 341.0954; found 341.0955.



***N*-(4-methylquinolin-2-yl)-*N*-(tosylmethyl)formamide (5h).** White solid; (167 mg, 94% yield); R_f = 0.56 (hexanes/EtOAc = 7:3); mp: 190-191 °C; IR (KBr, cm^{-1}) 3052, 2924, 2851, 1694, 1598, 1350, 1323, 1178, 1147, 1085, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.68 (dd, *J* = 16.0, 7.6 Hz, 3H), 7.50 (t, *J* = 6.6, 1H), 7.17 (d, *J* = 8.0 Hz, 3H), 5.65 (s, 2H), 2.72 (s, 3H), 2.28 (s, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 157.0, 145.1, 144.0, 142.0, 140.3, 131.0, 126.0, 125.0, 124.1, 122.0, 121.3, 119.0, 108.2, 57.0, 17.0, 15.0; HRMS (ESI-TOF) m/z: calculated for $C_{19}H_{18}N_2O_3S$ $[M+H]^+$ 355.1111; found 355.1109.

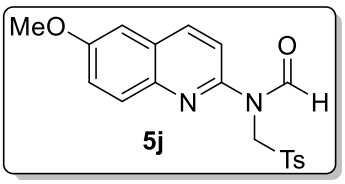


***N*-(6-methylquinolin-2-yl)-*N*-(tosylmethyl)formamide (5i).** White solid; (170 mg, 96% yield); R_f = 0.58 (hexanes/EtOAc = 7:3); mp: 220-221 °C; IR (KBr, cm^{-1}) 3042, 2923, 2831, 1698, 1578, 1476, 1375, 1347, 1288, 1146, 1048, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.07 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 3H), 7.47 (t, *J* = 7.4, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.57 (s, 2H), 2.46 (s, 3H), 2.23 (s, 3H); ^{13}C

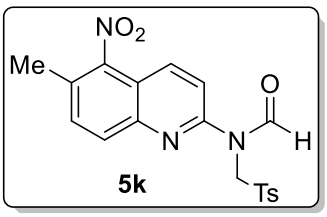


NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 160.4, 148.3, 144.0, 138.0, 135.3, 134.3, 132.0, 129.0, 128.0, 127.0, 125.3, 112.0, 61.0, 20.4; HRMS (ESI-TOF) m/z: calculated for $C_{19}H_{18}N_2O_3S$ $[M+H]^+$ 355.1111; found 355.1117.

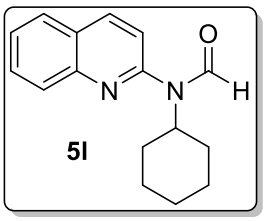
***N*-(6-methoxyquinolin-2-yl)-*N*-(tosylmethyl)formamide (5j).** White solid; (182 mg, 98%), R_f = 0.52 (hexanes/EtOAc = 7:3); mp: 120-121 °C; IR (KBr, cm^{-1}) 3062, 2994, 2929, 2844, 1697, 1598, 1504, 1353, 1290, 1234, 1144, 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.09 (s, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.70 (t, *J* = 8.4 Hz, 3H), 7.38-7.32 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 2.4 Hz, 1H), 5.62 (s, 2H), 3.93 (s, 3H), 2.32 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 161.3, 158.0, 148.2, 145.0, 142.3, 135.4, 130.0, 129.0, 127.4, 123.2, 113.0, 105.1, 62.0, 56.0, 22.0; HRMS (ESI-TOF) m/z: calculated for $C_{19}H_{18}N_2O_3S$ $[M+H]^+$ 371.1060; found 371.1059.



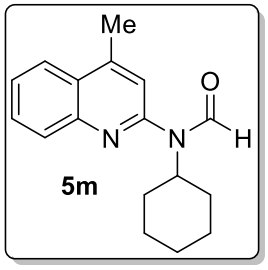
***N*-(6-methyl-5-nitroquinolin-2-yl)-*N*-(tosylmethyl)formamide (5k).** White solid; (164 mg, 82% yield); R_f = 0.48 (hexanes/EtOAc = 7:3); mp: 190-191 °C; IR (KBr, cm^{-1}) 3039, 2993, 2923, 2856, 1696, 1524, 1480, 1382, 1289, 1143, 1086, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.23 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 7.6, 2H), 5.62 (s, 2H), 2.55 (s, 3H), 2.35 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 160.0, 150.0, 144.3, 144.0, 134.1, 133.0, 132.0, 130.2, 129.0, 128.0, 117.3, 113.3, 60.3, 29.0, 17.1; HRMS (ESI-TOF) m/z: calculated for $C_{19}H_{17}N_3O_5S$ $[M+H]^+$ 400.0962; found 400.0969.



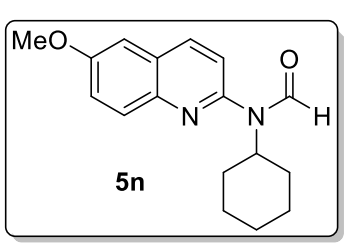
***N*-cyclohexyl-*N*-(quinolin-2-yl)formamide (5l).** White solid; (114 mg, 90% yield); R_f = 0.48 (hexanes/EtOAc = 8:2); mp: 85-86 °C; IR (KBr, cm^{-1}) 3039, 2921, 2866, 2851, 1677, 1599, 1567, 1560, 1445, 1385, 1256, 1210, 1148, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 6.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.23 (s, 1H), 4.50-4.39 (m, 1H), 2.08 (s, 2H), 1.94-1.78 (m, 4H), 1.68 (d, *J* = 11.6 Hz, 1H), 1.40 (q, *J* = 12.8, 2H), 1.26-1.16 (m, 1H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 163.0, 153.0, 147.0, 138.4, 130.0, 129.0, 129.0, 127.3, 126.3, 117.0, 56.0, 31.0, 26.2, 25.4; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{18}N_2O$ $[M+H]^+$ 255.1492; found 255.1483.



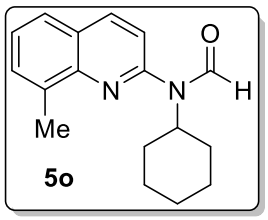
***N*-cyclohexyl-*N*-(4-methylquinolin-2-yl)formamide (5m).** Colourless liquid; (123 mg, 92% yield); R_f = 0.48 (Hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3048, 2926, 2853, 1682, 1597, 1468, 1351, 1210, 1132, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.76 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.65(s, 1H) 7.51 (t, *J* = 6.6 Hz, 1H), 7.06 (s, 1H), 4.50-4.30 (m, 1H), 2.69 (s, 3H), 2.15-2.0 (m, 2H), 1.94–1.73 (m, 4H), 1.70-1.60 (m, 1H), 1.45-1.32 (m, 2H), 1.25-1.14 (m, 1H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 163.0, 147.0, 130.0, 129.3, 127.0, 126.0, 124.0, 117.4, 56.0, 31.0, 26.2, 25.4, 19.0; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{20}N_2O$ $[M+H]^+$ 269.1654; found 269.1656.



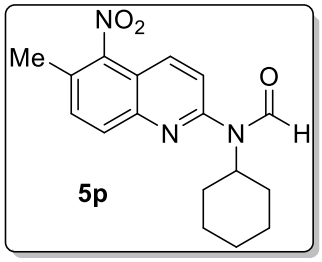
***N*-cyclohexyl-*N*-(6-methoxyquinolin-2-yl)formamide (5n).** White solid; (135 mg, 95% yield); R_f = 0.52 (hexanes/EtOAc = 7:3); mp: 75-76 °C; IR (KBr, cm^{-1}) 3027, 2931, 2915, 2851, 1669, 1599, 1463, 1349, 1259, 1163, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.69 (s, 1H), 8.06 (d, *J* = 6.8 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 6.8 Hz, 1H), 7.19 (d, *J* = 6.0 Hz, 1H), 7.08 (s, 1H), 4.50-4.32 (m, 1H), 3.92 (s, 3H), 1.98-1.79 (m, 5H), 1.70-1.62 (m, 1H), 1.45-1.31 (m, 3H), 1.27-1.12 (m, 1H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 162.0, 157.0, 150.0, 142.0, 136.1, 129.3, 127.0, 122.0, 117.0, 104.0, 55.0, 30.0, 25.1, 24.4; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{20}N_2O_2$ $[M+H]^+$ 285.1598; found 285.1604.



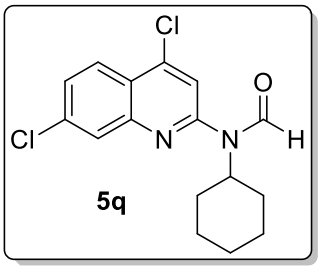
***N*-cyclohexyl-*N*-(8-methylquinolin-2-yl)formamide (5o).** Colourless liquid; (118 mg, 88% yield); R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3032, 2927, 2853, 1682, 1598, 1501, 1450, 1344, 1225, 1142, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.86 (s, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.58-7.51 (m, 1H), 7.38 (t, *J* = 6.8 Hz, 1H), 7.23-7.16 (m, 1H), 4.60-4.41 (m, 1H), 2.74 (m, 3H), 2.35-2.10 (m, 2H), 1.95-1.80(m, 4H), 1.74-1.66 (m, 1H), 1.48-1.35 (m, 2H), 1.27-1.18 (m, 1H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 163.2, 152.0, 146.0, 139.0, 137.0, 130.3, 126.2, 126.0, 116.0, 56.0, 30.4, 26.3, 26.0, 18.0; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{20}N_2O$ $[M+H]^+$ 269.1648; found 269.1657.



***N*-cyclohexyl-*N*-(6-methyl-5-nitroquinolin-2-yl)formamide (5p).** White solid; (128 mg, 82% yield); R_f = 0.54 (hexanes/EtOAc = 8:2); mp: 110-111 °C; IR (KBr, cm^{-1}) 3072, 2923, 2854, 1687, 1597, 1542, 1480, 1350, 1363, 1217, 1148, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.86 (s, 1H), 8.10 (d, J = 5.2 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.53-7.23 (m, 1H), 4.53-4.37 (m, 1H), 2.53 (s, 3H), 1.95-1.80 (m, 4H), 1.75-1.67 (m, 1H), 1.48-1.36 (m, 2H), 1.27-1.17 (m, 3H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 162.0, 157.0, 150.0, 142.0, 136.1, 129.3, 127.0, 122.0, 117.0, 104.0, 55.0, 30.0, 25.1, 24.4; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{19}N_3O_3$ $[M+H]^+$ 314.1499; found 314.1502.



***N*-cyclohexyl-*N*-(4, 7-dichloroquinolin-2-yl)formamide (5q).** White solid; (136 mg, 84% yield); R_f = 0.56 (hexanes/EtOAc = 8:2); mp: 132-133 °C; IR (KBr, cm^{-1}) 3048, 2927, 2853, 1682, 1583, 1491, 1313, 1148, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.80 (s, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.8, 2.0 Hz, 1H), 4.53-4.37 (m, 1H), 2.02-1.82 (m, 5H), 1.75-1.68 (m, 1H), 1.30-1.15 (m, 2H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ (ppm): 163.0, 148.0, 128.0, 125.3, 123.0, 57.0, 26.2, 25.4; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}Cl_2N_2O$ $[M+H]^+$ 323.0712; found 323.0716.



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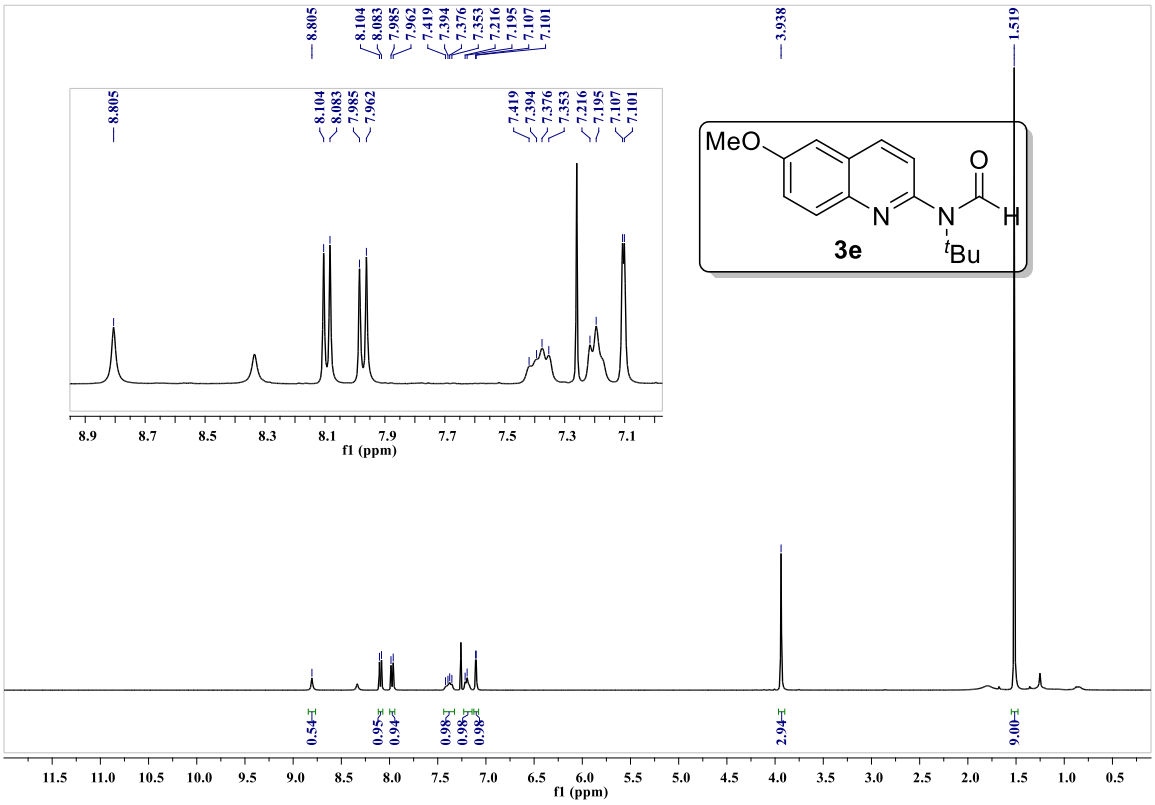
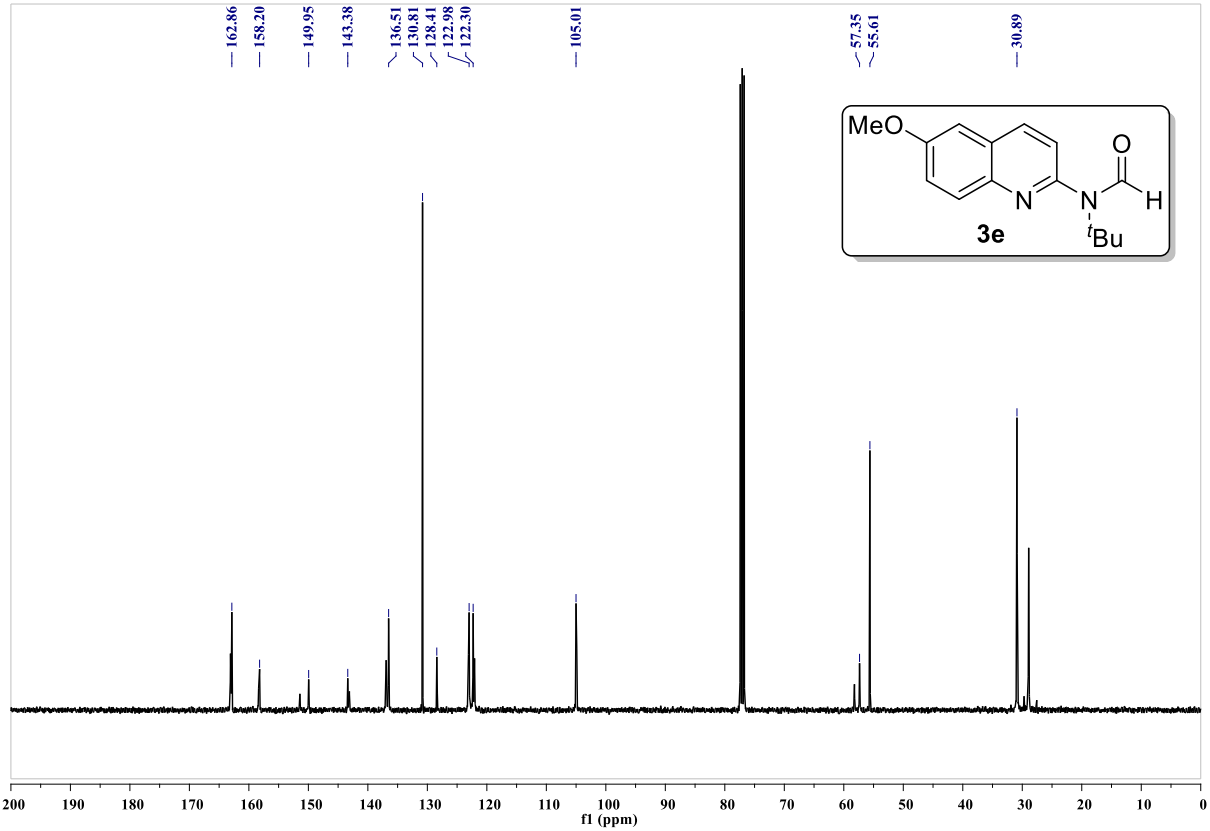
2B.7. Selected NMR (^{1}H and ^{13}C) and HRMS Spectra

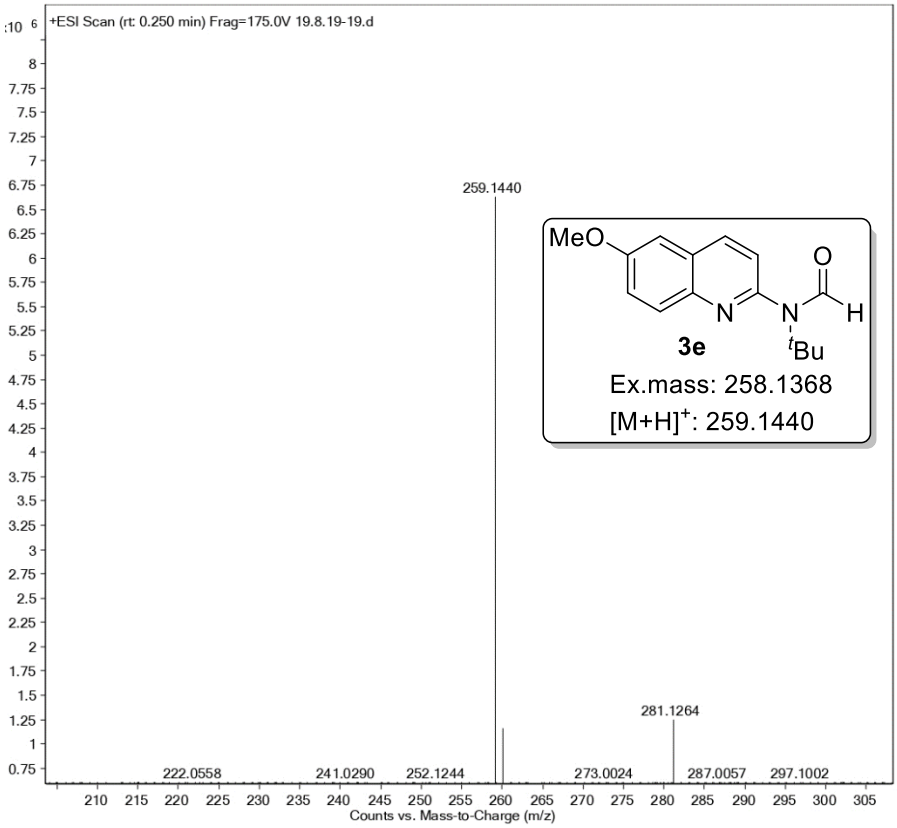
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-*tert*-Butyl-*N*-(6-methoxyquinolin-2-yl)formamide (3e)



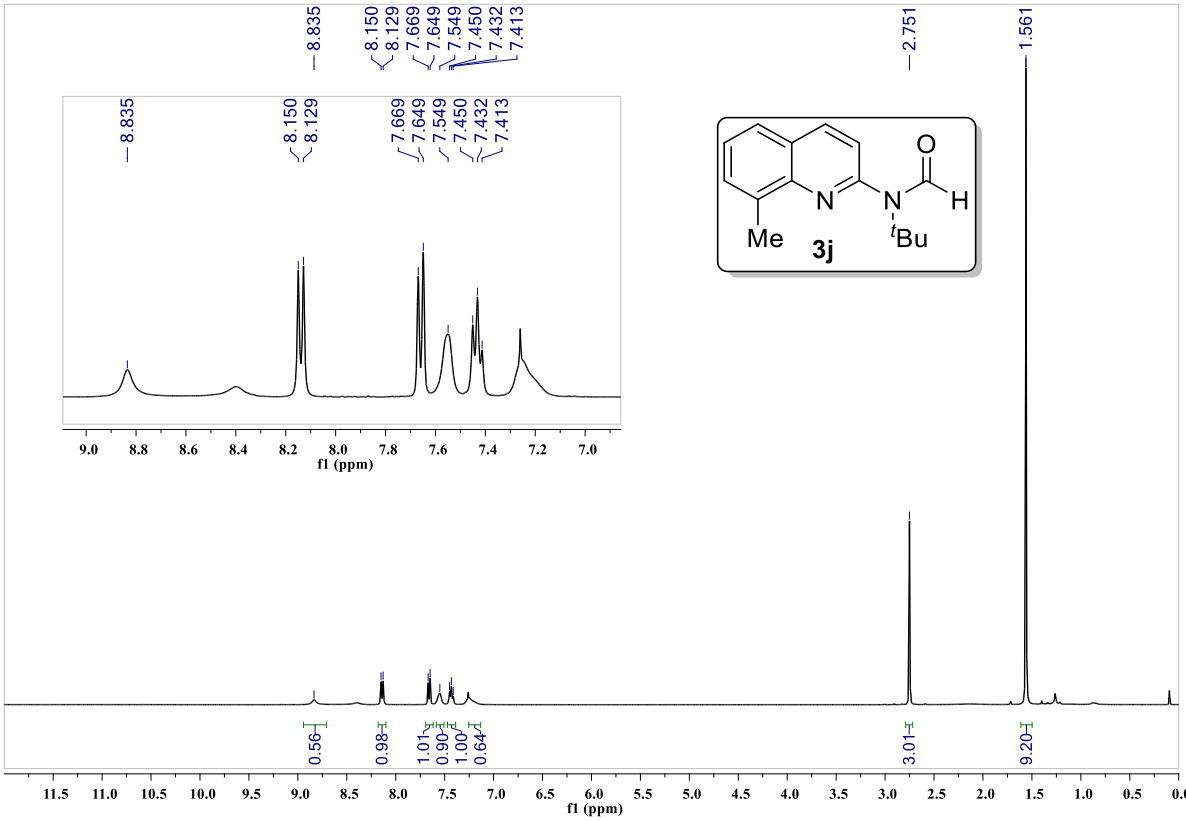
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of *N*-*tert*-Butyl-*N*-(6-methoxyquinolin-2-yl)formamide (3e)



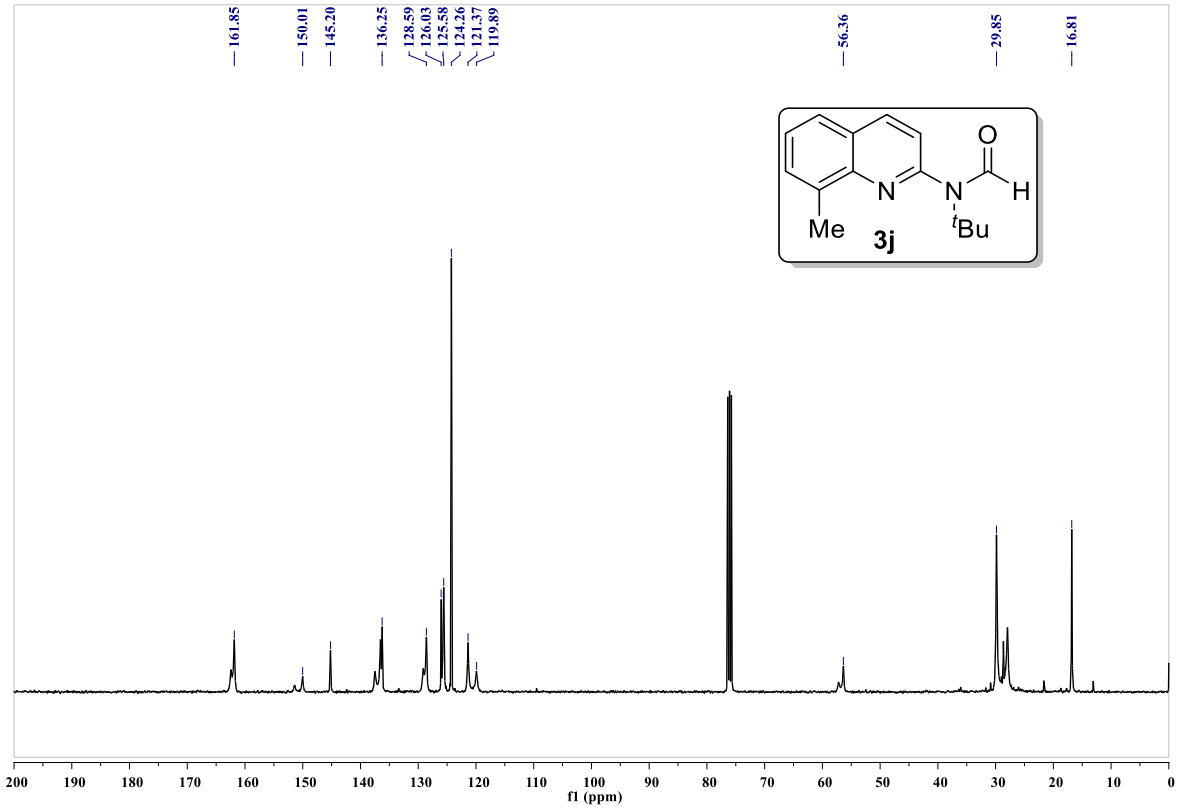
HRMS spectrum of *N*-*tert*-Butyl-*N*-(6-methoxyquinolin-2-yl)formamide (3e)



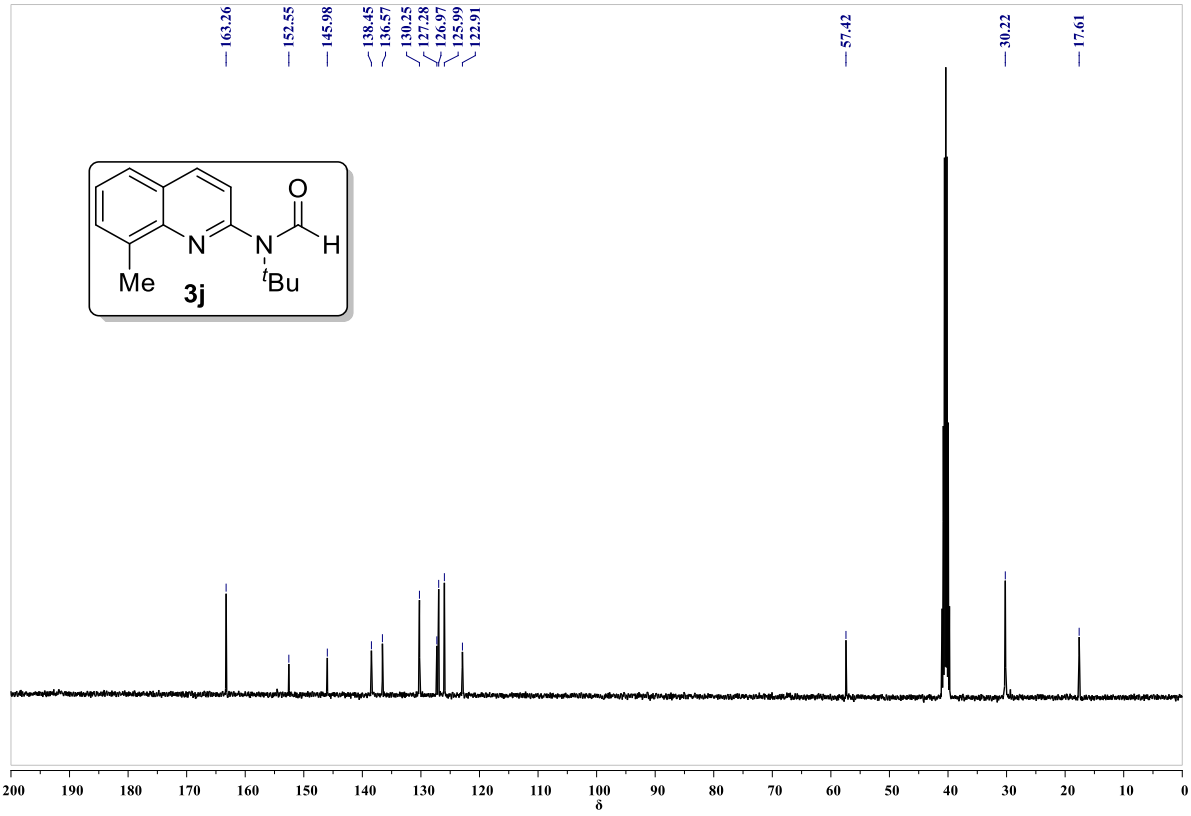
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N-tert*-Butyl-*N*-(8-methylquinilin-2-yl)formamide (3j)



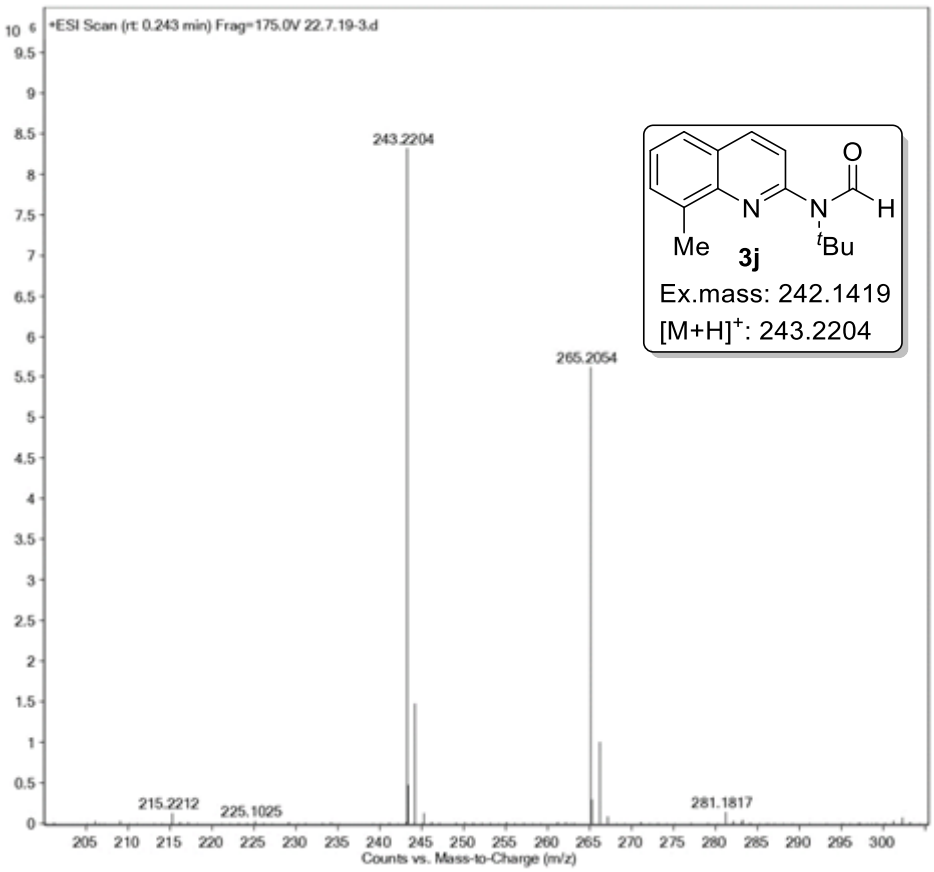
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of *N-tert*-Butyl-*N*-(8-methylquinilin-2-yl)formamide (3j)



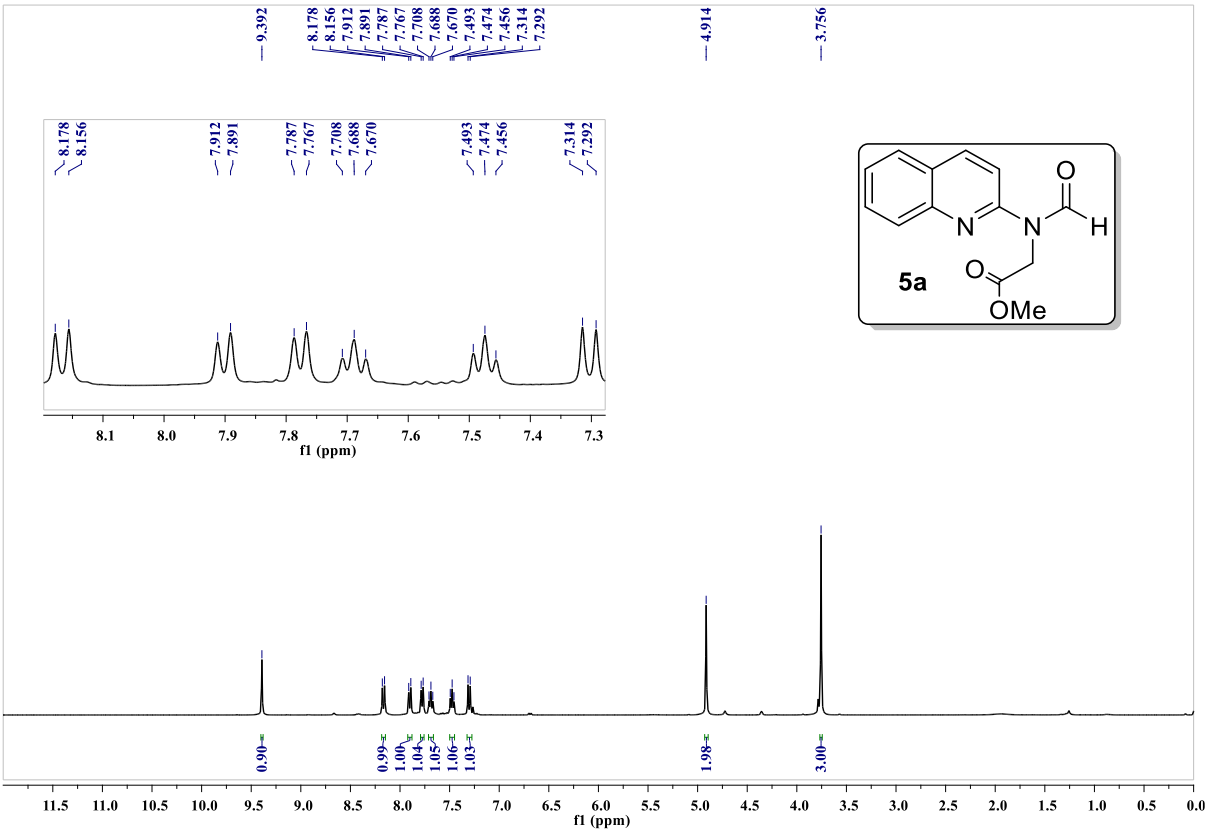
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6, 60 °C) spectrum of *N*-*tert*-Butyl-*N*-(8-methylquinilin-2-yl)formamide (3j)



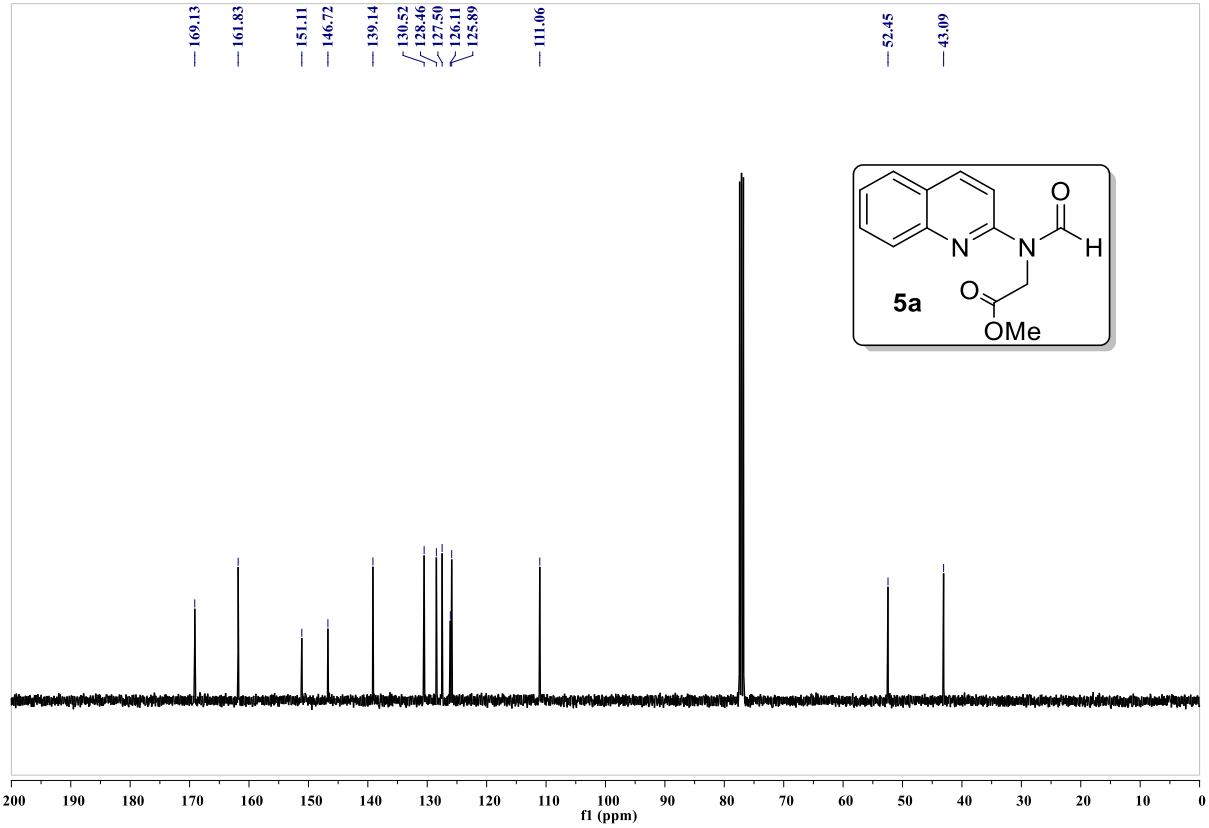
HRMS spectrum of *N*-*tert*-Butyl-*N*-(8-methylquinilin-2-yl)formamide (3j)



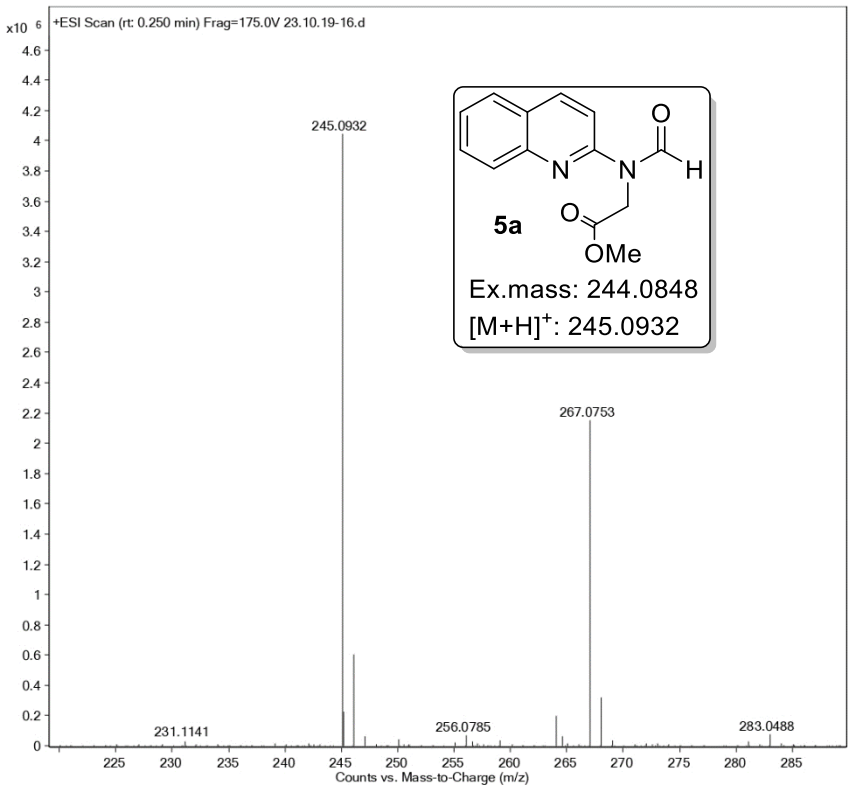
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of methyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5a)



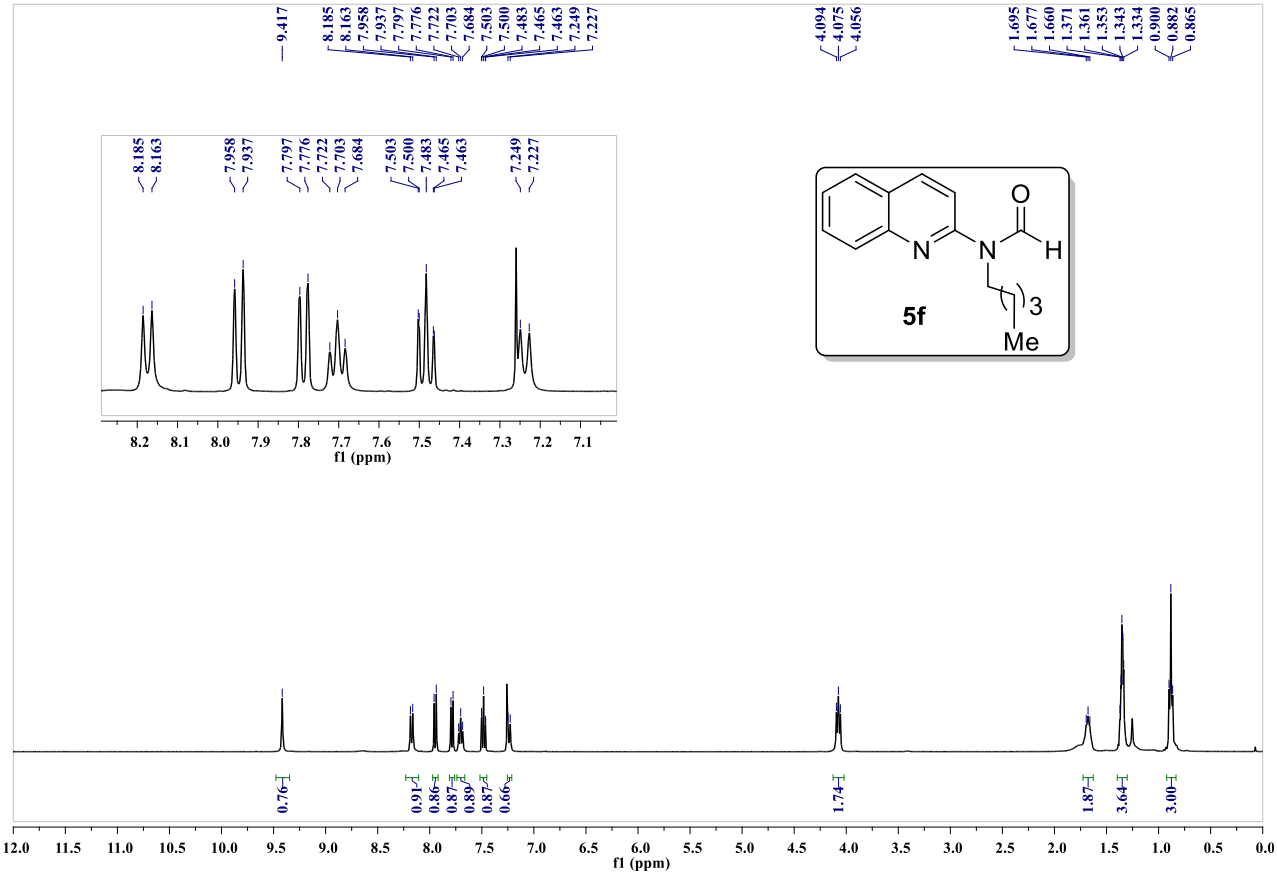
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of methyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5a)



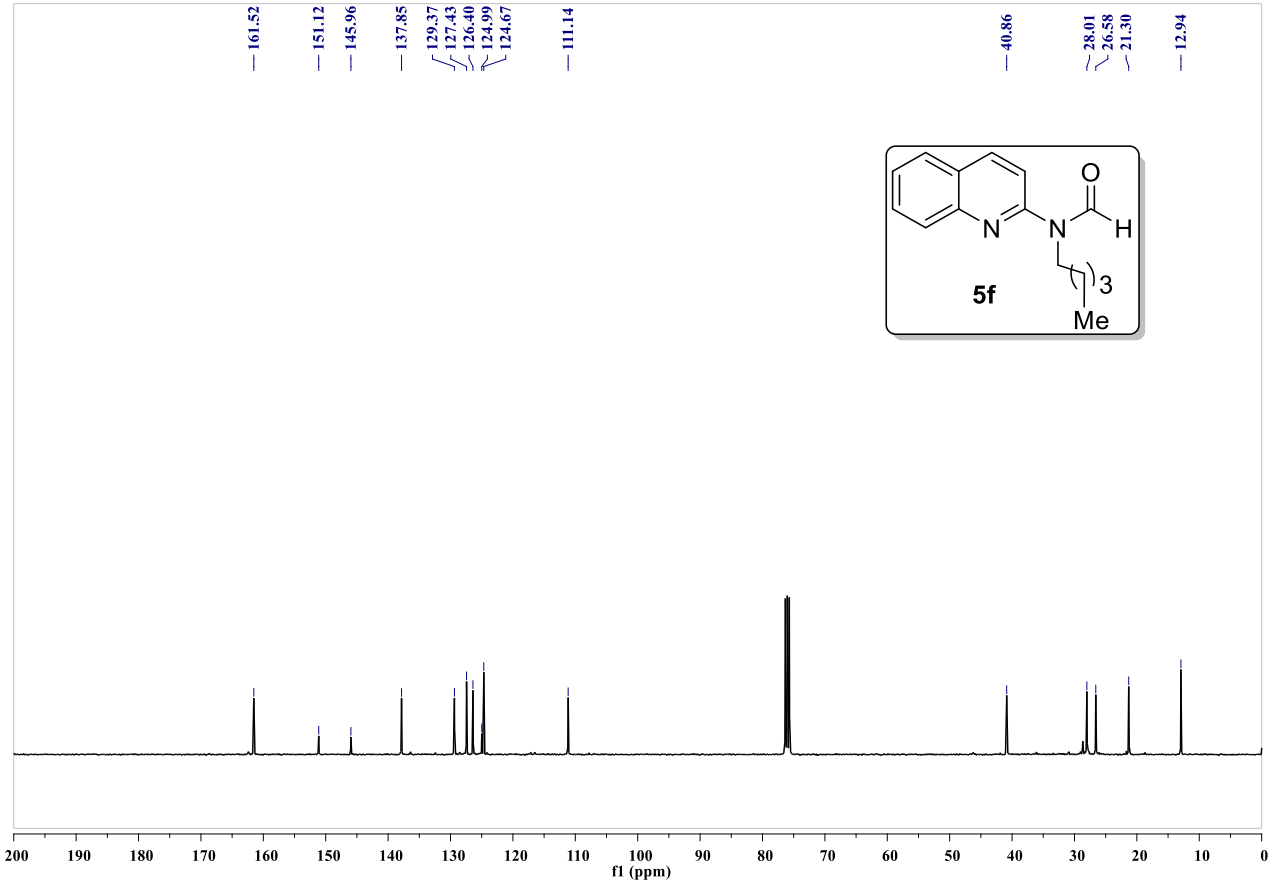
HRMS spectrum of methyl 2-(*N*-(quinolin-2-yl)formamido)acetate (5a)



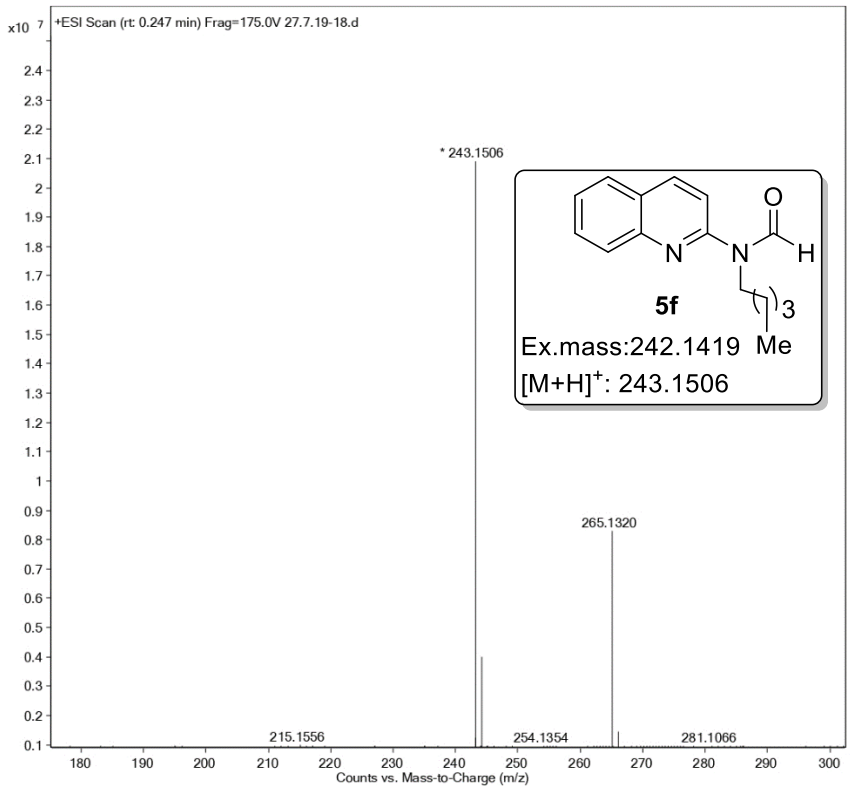
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-pentyl-*N*-(quinolin-2-yl)formamide (5f)



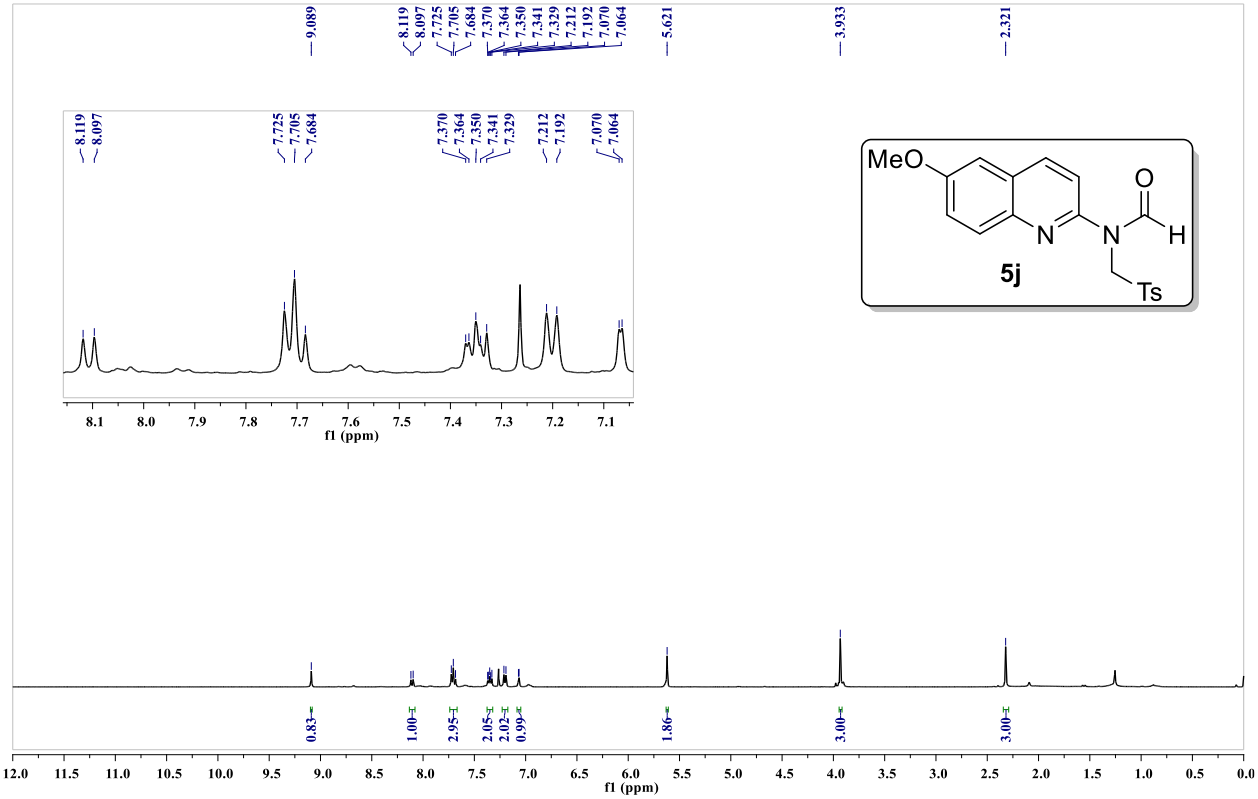
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of *N*-pentyl-*N*-(quinolin-2-yl)formamide (5f)



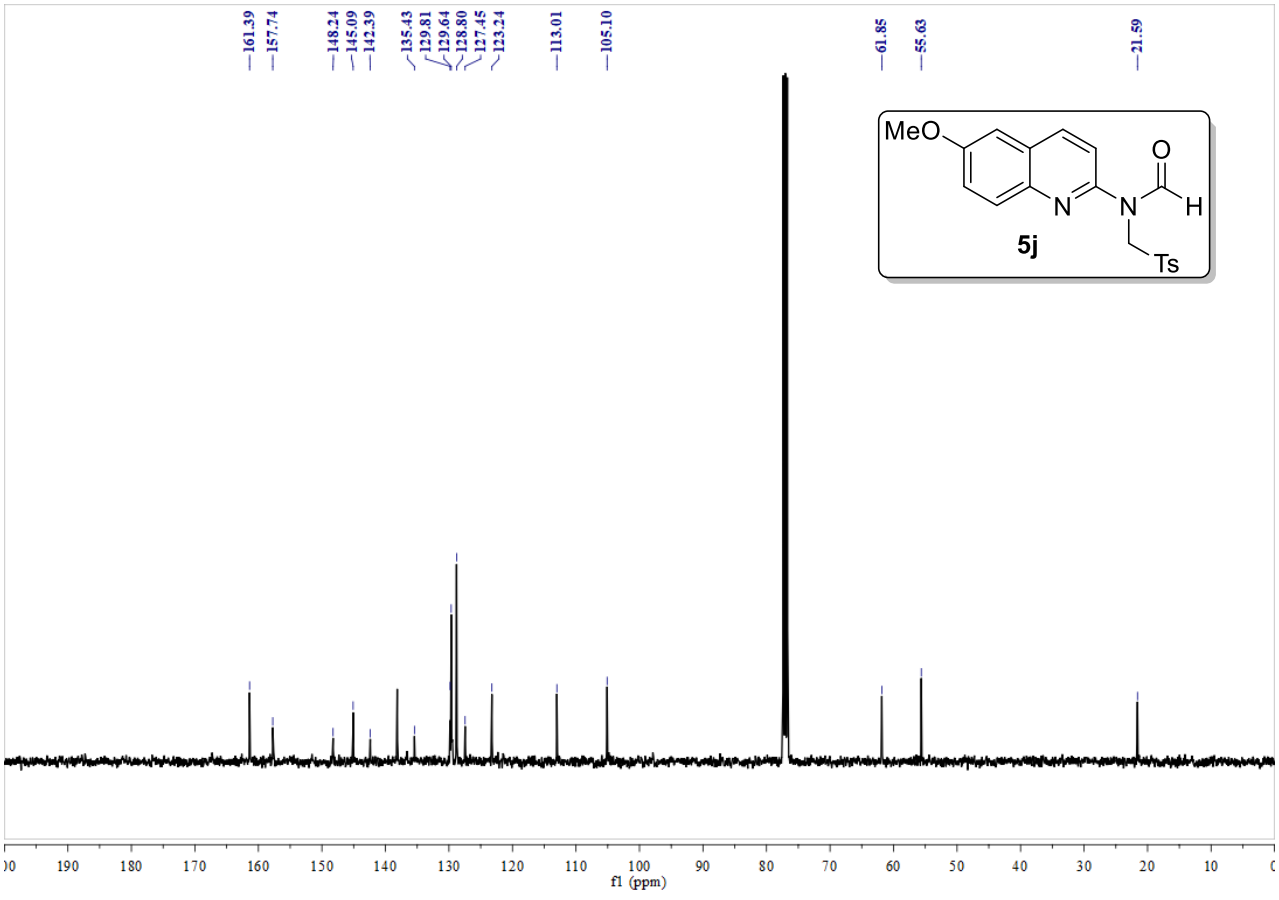
HRMS spectrum of *N*-pentyl-*N*-(quinolin-2-yl)formamide (5f)



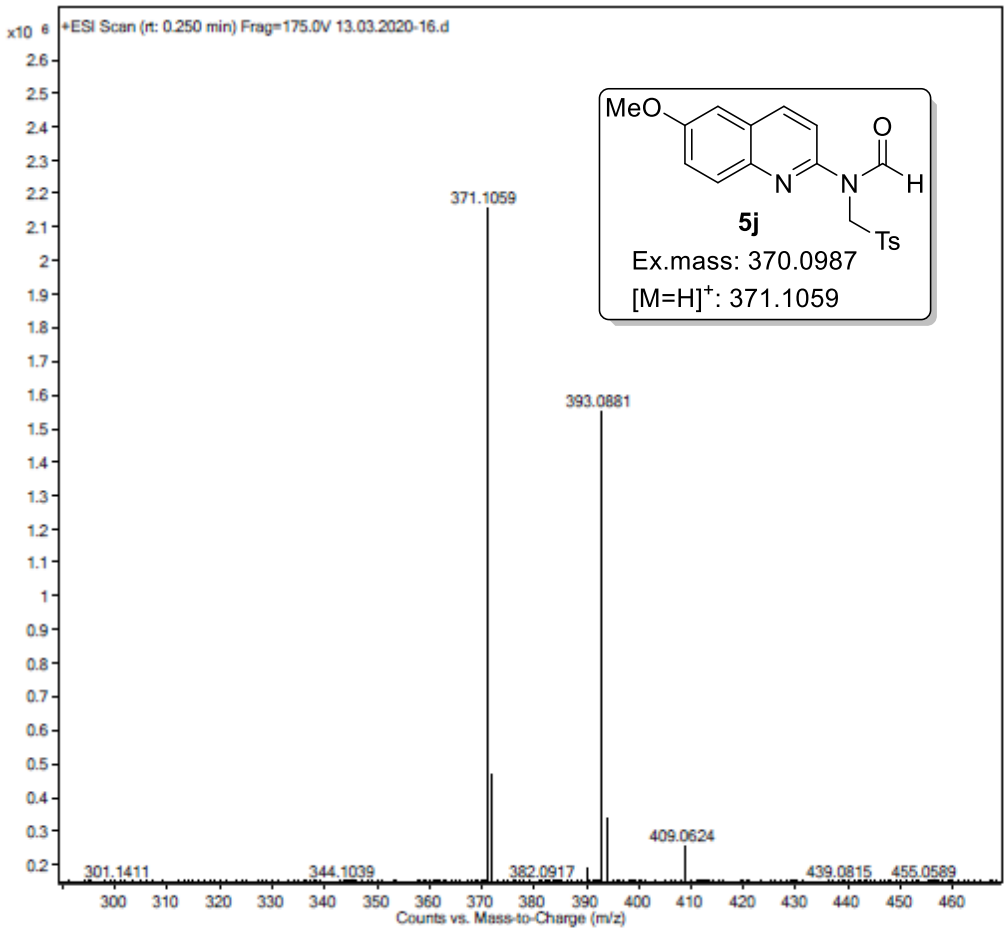
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-(6-methoxyquinolin-2-yl)-*N*-(tosylmethyl)formamide (5j)



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of *N*-(6-methoxyquinolin-2-yl)-*N*-(tosylmethyl)formamide (5j)

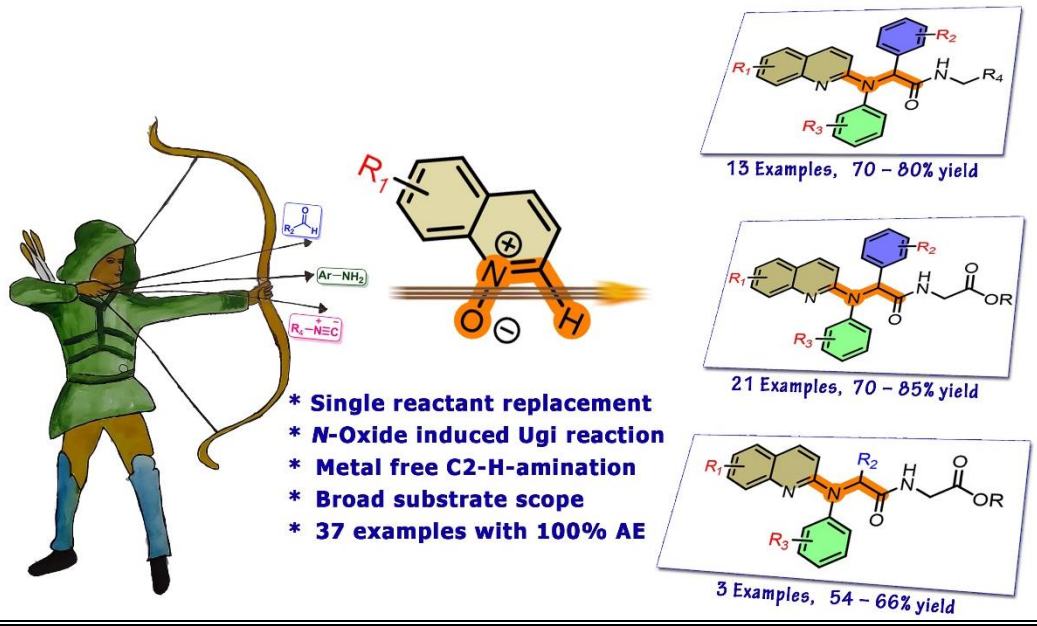


HRMS spectrum of *N*-(6-methoxyquinolin-2-yl)-*N*-(tosylmethyl)formamide (5j)



CHAPTER-IIIA

N-Oxide Induced Ugi Reaction: A Novel Synthesis of Quinoline-C2-Amino Amides *via* Deoxygenative C(sp^2)-H Functionalization



3A.1. Introduction

Multicomponent reactions (MCRs) are efficient synthetic methods, in which more than two components combine with each other to generate multi-functionalized compounds in a single reaction flask (Figure 3A.1).[1] Gerhard and co-workers first described the MCR in 1838 by the formation of cyanohydrin imines from bitter almond oil and ammonia.[2] This type of reaction were later generalised by Strecker in 1850, leading to α-cyano amines, which are important building blocks in the synthesis of α-amino acids.[3] After this pioneering work by Strecker, other MCRs have been described, covering a broad range of structural diversity from linear to complex heterocyclic structures. Nowadays, MCRs are highly effective strategy to synthesize several pharmaceutical and drug-like structure compounds due to their atom economy, high productivity, inexpensive and simple experimental method (Figure 3A.2).[4]

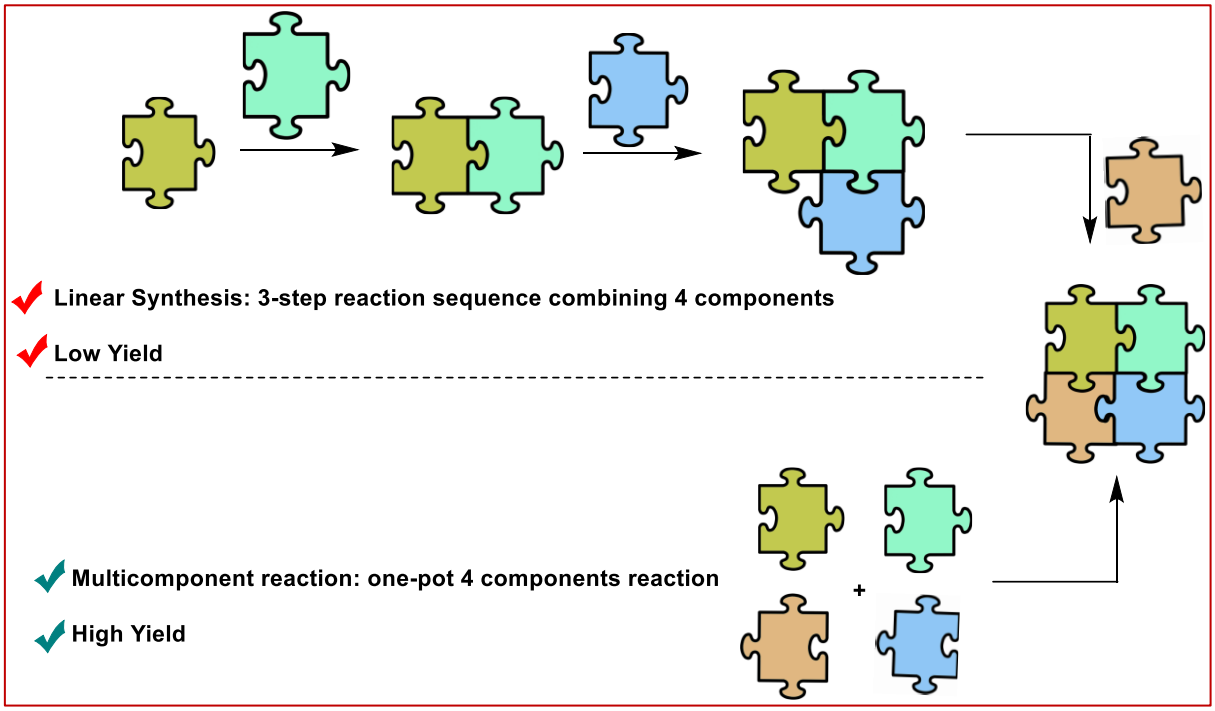


Figure 3A.1. Comparison of stepwise linear synthesis and multicomponent reactions.

Particularly, isocyanide-based multicomponent reactions (IMCRs) have attracted the attention of organic chemists since the discovery of Passerini three component reaction in 1921.[5] This isocyanide-based reaction involves the coupling between aldehyde, carboxylic acid and isonitrile to give α-acyloxycarboxamide (Figure 3A.3a).[6] This Passerini reaction, also known as Passerini 3CR (P-3CR) was ignored synthetic chemists for 4 decades after its discovery. In 1959, Ivar Ugi introduced the concept of single reactant replacement to modify the Passerini reaction (Figure 3A.3b). Most importantly, he was able to recognize the great potential of multicomponent reactions in the fast generation of large collections of similar molecules. His

pioneering work provided the basis for the upsurge of combinatorial chemistry and diversity-oriented synthesis that took place in the 90's. In those years, the Ugi and Passerini reactions

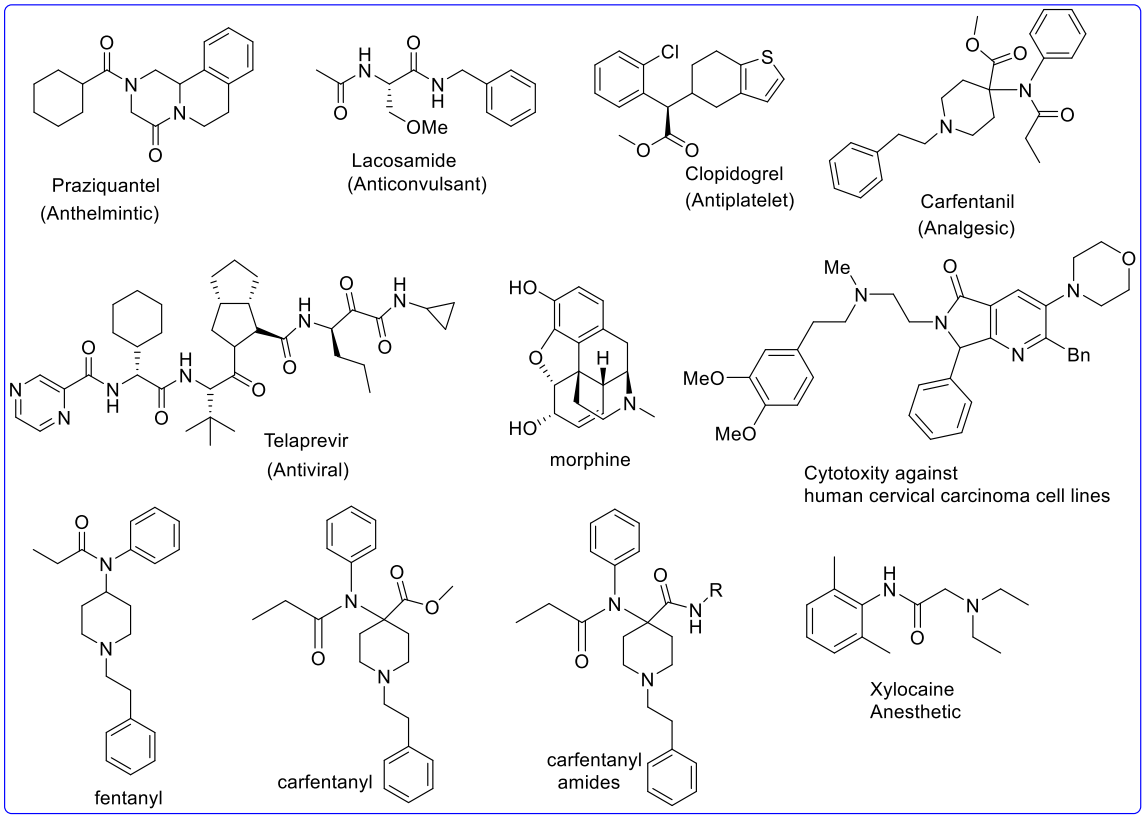


Figure 3A.2. Biologically active compounds synthesized *via* a Ugi reaction

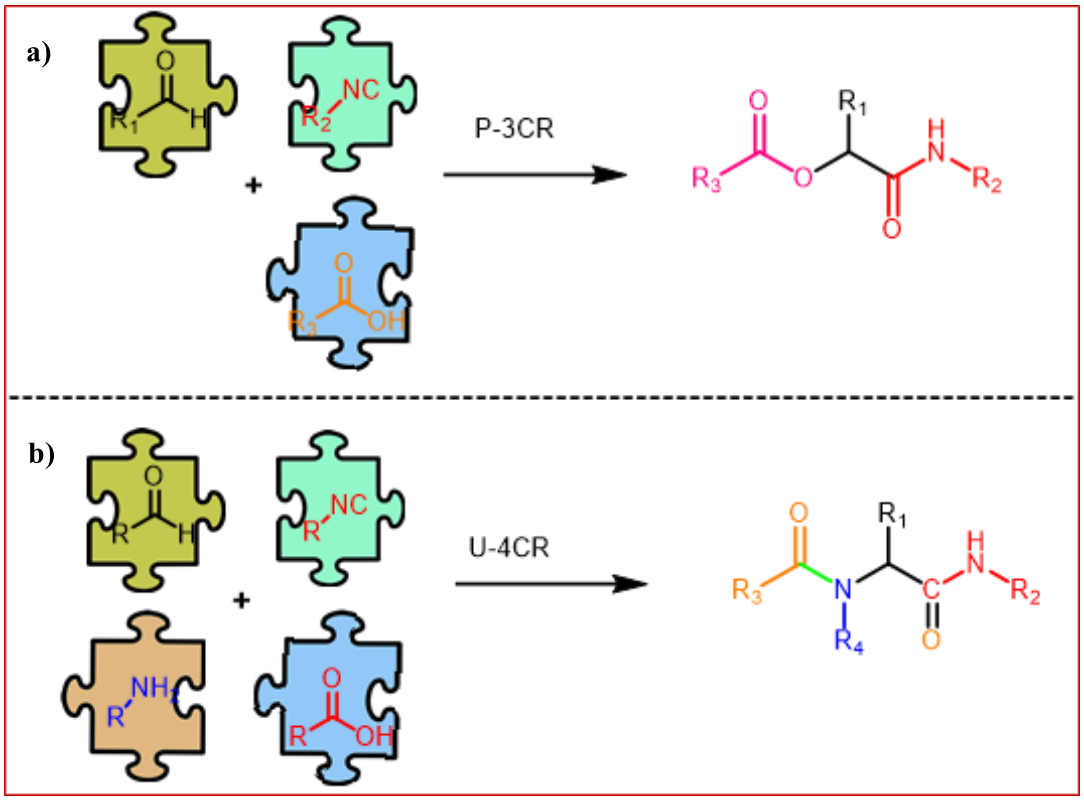


Figure 3A.3. Single reactant replacement (SRR) approach

became well known to most organic chemists, and the publications related to them and to other IMCRs have continued to steadily increase in the new century till nowadays. The Ugi four-component reaction (U-4CR) is one of the most extensively studied multicomponent reactions, which readily give access to the peptide-like structure known as bis-amides or peptomers with potent biological activity and structural diversity (Figure 3A.3b).[7-8] This revolutionary approach by Ugi in 1959 has opened a new platform in isocyanide-based multicomponent reactions (IMCRs) and also, it has been in the limelight recently for obeying the green chemistry principles such as atom-economy, reduced number of steps and use of green solvents.[9]

Due to the emergence of combinatorial chemistry and high throughput screening for efficient preparation of bioactive molecules, medicinal chemists focused more on Ugi reaction in polymer-supported solid-phase synthesis, in combination with post-condensation and modified Ugi conditions.[10] The modifications in Ugi reaction has mainly relied on single reactant replacement (SRR) approach.[11] The single reactant replacement approach involves logic-based alteration of one component by another component with similar mode of reactivity which is required for the known MCR to improve its efficiency and to provide new synthetic routes. For instance, the Ugi is first SRR approach of the Passerini reaction which led to the new MCRs in which imines were introduced in place of carbonyls to synthesize a library of α-acylamino amides, this novel SSR approach triggered the development of new MCRs in the field of drug discovery.

In this connection, replacement of multifaceted carboxylic acids in U-4CR poses challenges because of the key role they play in many equilibrium steps, including formation of imine and nucleophilic addition of moderately reactive isocyanide and final Mumm rearrangement to provide for the target compound.[12] In fact, exchange of the carboxylic acid by other acidic component in Ugi reaction has shown inferior results.[13-19]

Thus, replacement of the carboxylic acid in U-4CR: i) Weak inorganic acids (H_2O, HN_3, HOCN, HSCN, H_2S, H_2Se) (Figure 3A.4), ii) electron deficient nitrophenols, pyridines and pyrimidines has found limited access since the discovery of the reactions.

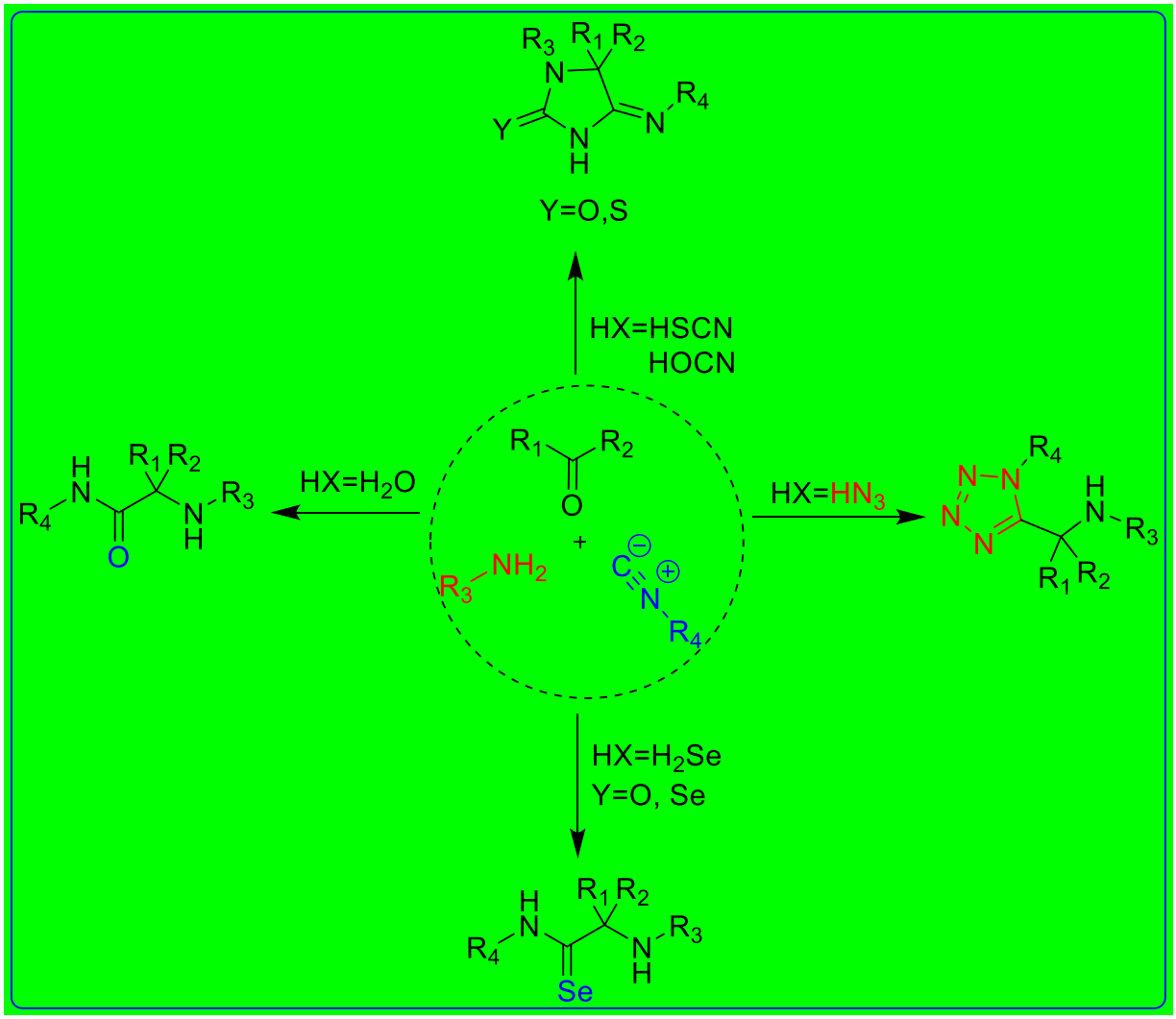
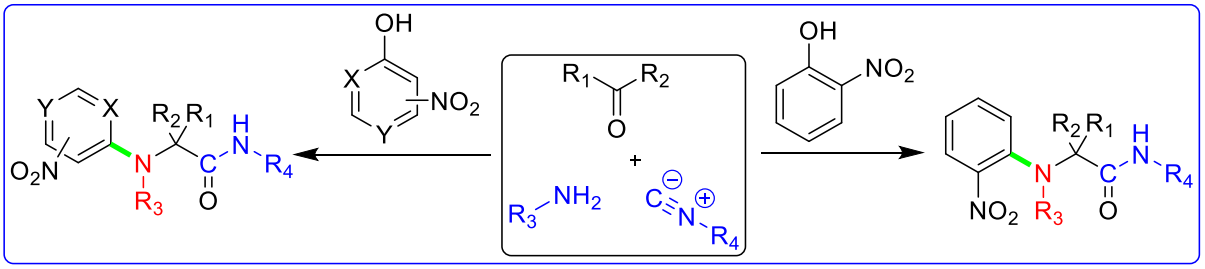


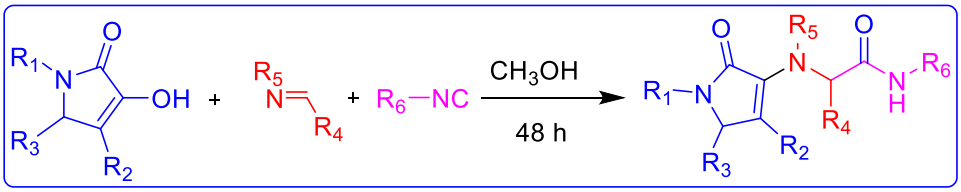
Figure reaction **3A.4.** Other surrogates carboxylic acid of Ugi

El Kaïm *et al*. reported the first use of Smiles rearrangements in Ugi reaction to synthesize *N*-arylated peptides in this phenol Ugi-smile multicomponent reaction, the electron-deficient phenols are used as acidic surrogates to give *O*-aryl- and *N*-arylamides. Although, this sequence opened a rapid access to the *O*-aryl- and *N*-arylamides but has its own limitations such as requirement of strong activation energy, moderate yields and pKa dependency (Scheme 3A.1).[20,21]



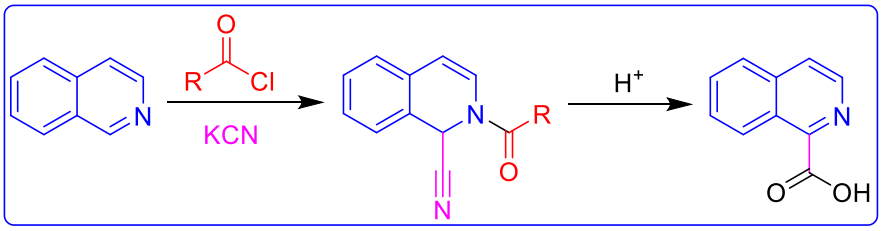
Scheme 3A.1

Later in 2012, Marcos introduced enols for the carboxylic acid surrogated to modify the existing Ugi reaction. Also, enols have pKa values comparable to that of phenols, being sufficiently acidic to protonate imines. Furthermore, enolates are more nucleophilic than carboxylates, and thus able to trap the nitrilium intermediates formed in Ugi-type condensations. This heterocyclic enol derivative would provide a simple approach to the synthesis of libraries of compounds containing biologically privileged heterocyclic structures (Scheme 3A.2).[22]



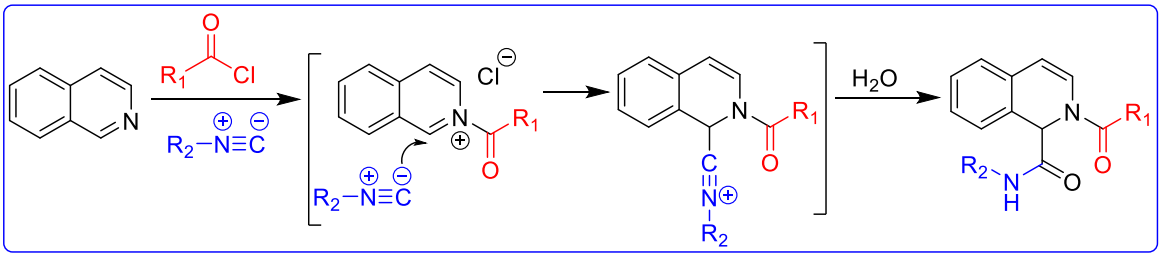
Scheme 3A.2

Saito and co-workers on the other side, the Reissert reaction is a type of 3-CR consisting of the addition of cyanide to the *α*-position of isoquinoline, which was previously activated by an acylating agent. The product of this reaction is known as the Reissert compound which is then hydrolyzed to afford isoquinoline-1-carboxylic acid (Scheme 3A.3).[23]



Scheme 3A.3

In the Ugi–Reissert 3CR variation, the cyanide is replaced by an isocyanide component. Thus, it attacks the electrophilic *α*-position of previously *N*-acylated isoquinoline producing nitrilium intermediate, which is hydrated to afford restricted-peptide backbone, ending the reaction sequence, and thus avoiding the Mumm rearrangement present in the classic U-4CR (Scheme 3A.4).[24]



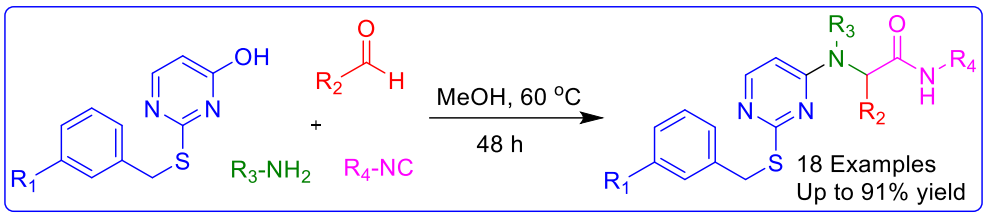
Scheme 3A.4

Recently, aromatic amine *N*-oxides has attracted considerable attention due to the ability of the *N*-oxide moiety to act as an *ortho*-directing group to control the regioselectivity of the C–H activation.[25] In particular, *N*-oxide directed C2-selective C-N bond formation has become

thrust area due to the importance of the 2-amino quinolines in medicinal chemistry and pharmaceuticals.[26] In all the approaches, *N*-oxides are either reacting with the promoters or coordinating with the metals to activate the C2-position of the aromatic *N*-oxides. Thus, the activated C2-position and nucleophilicity of oxygen of *N*-oxide could be a promising candidature for single reactant replacement of Ugi to get the *N*-oxide mediated Ugi four-component reaction.

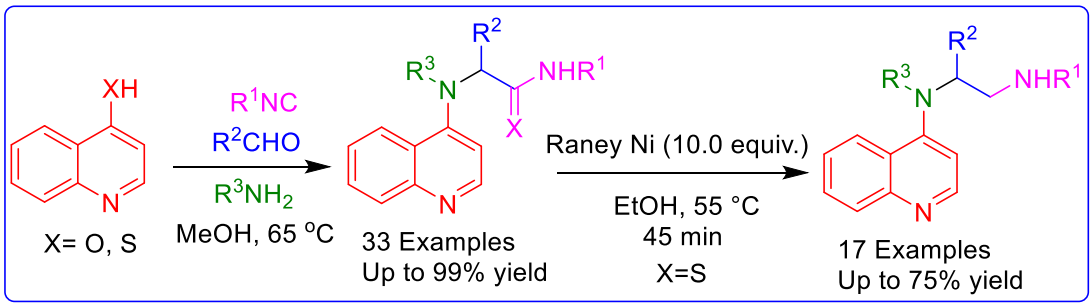
3A.1.1. Reported methods for the synthesis of quinoline-C2-amino amides and its derivatives

Sidhoum et al. developed a Ugi-Smile reaction, synthesis of aminopyrimidine from S-benzyl thiouracil, aldehydes, anilines and isocyanides in methanol at 60 °C (Scheme 3A.5).[27]



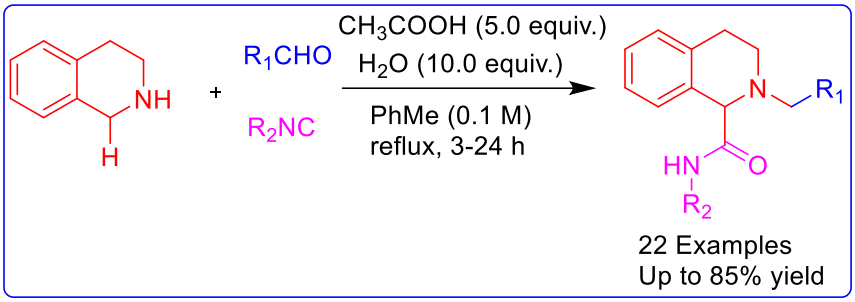
Scheme 3A.5

Laurent and co-workers developed a protocol employing synthesis of antimalarial analogues using Ugi-Smile multicomponent processes. In this method 4-hydroxy and 4-mercapto quinoline derivatives are effective coupling partners in Ugi-Smiles reactions because they are significantly more reactive than their 2-substituted equivalents, which need additional activating groups. They created a simple and effective approach for accessing 4-aminoquinolines, which makes the procedure potentially appealing for the synthesis of novel antimalarial pharmacophores (Scheme 3A.6).[28]



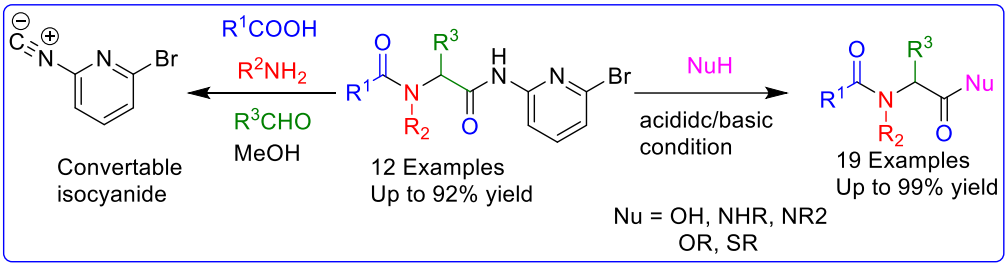
Scheme 3A.6

Zhengbo Zhu et al. introduced the reaction of pyrrolidine and 1,2,3,4-tetrahydroisoquinoline (THIQ) with aromatic aldehydes and isocyanides to result Ugi adducts *via* redox-neutral amidation. They have shown that isocyanides can act as nucleophiles in Ugi-type reactions with an amine C-H bond functionalization (Scheme 3A.7).[29]



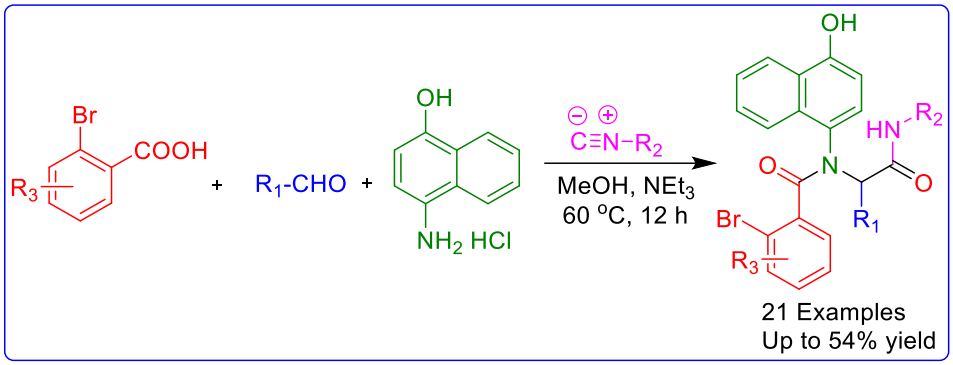
Scheme 3A.7

Heijden et al. developed a 2-isocyanopyridines are becoming innovative convertible isocyanides for multicomponent chemistry. The 2-bromo-6-isocyanopyridine was found to be the best reagent in terms of stability and synthetic effectiveness after comparison of 12 representatives of this class (Scheme 3A.8). Under both basic and acidic circumstances, it successfully combines sufficient nucleophilicity with a good leaving group capacity of the resultant amide moiety. An effective two-step synthesis of the powerful opioid carfentanil is provided to show the reagent's practical utility (Scheme 3A.8).[30]



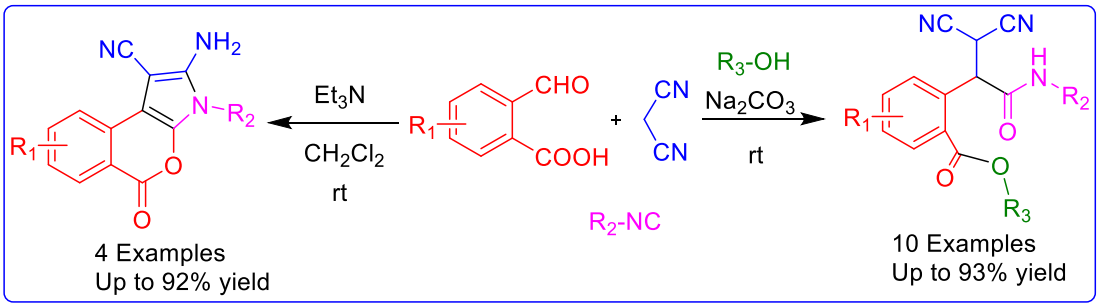
Scheme 3A.8

Song and co-workers have developed a novel palladium-catalyzed arylative dearomatization and subsequent aromatization/dearomatization/aza-Michael process of Ugi adducts, allowing the quick construction of various zephycarinatine and zephygranditine scaffolds containing two adjacent quaternary carbon stereocenters with excellent chemoselectivity and stereoselectivity in a step-economical and highly efficient manner. This method applicable a wide range of aromatic substrates, both electron-deficient and electron-rich, with functional group tolerance. The products can undergo a variety of transformations, which further demonstrates the method's synthetic applicability (Scheme 3A.9).[31]



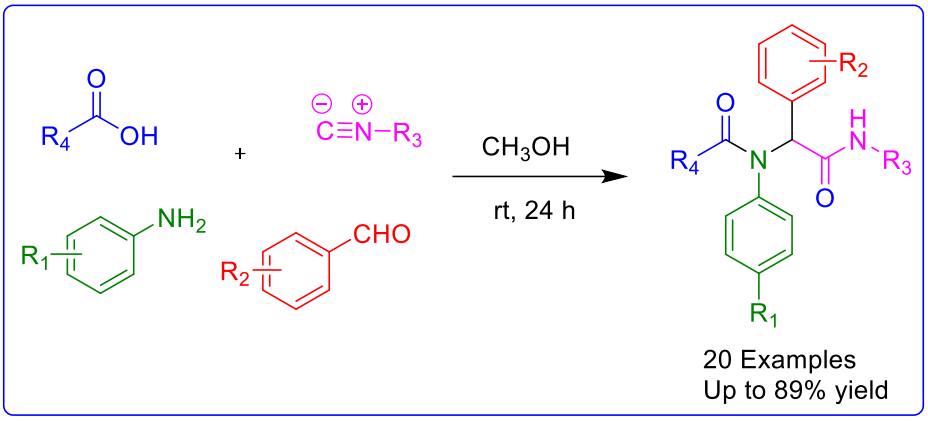
Scheme 3A.9

Zainali et al. was prepared alkyl-2-(1-(alkylcarbamoyl)-2,2-dicyanoethyl)benzoate derivatives with excellent yields using a unique four-component reaction between 2-formylbenzoic acids, malononitrile, isocyanides, and alcohols. This method involves a single synthetic step, high atom economy wide functional group tolerance. Additionally, a three-component synthesis involving malononitrile, isocyanides, and 2-formylbenzoic acids also been reported to produce isochromeno[3,4-*b*]pyrroles (Scheme 3A.10).[32]



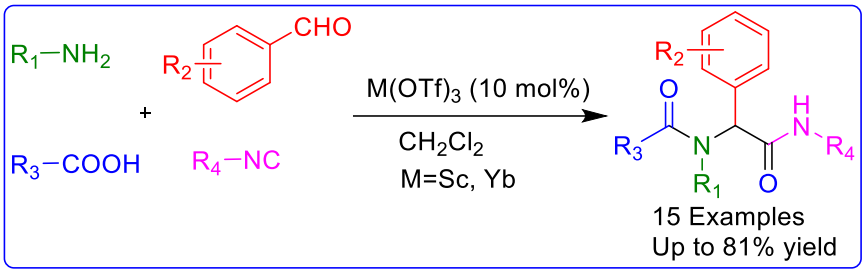
Scheme 3A.10

Wang et al. introduced four-component reaction, using the hydroxyl-substituted benzoic acid, aniline and benzaldehyde to create bisamide. It has been discovered that the structural element derived from isocyanide has a significant impact on the antioxidant efficiency of bis-amide produced by hydroxyl groups. The isocyanide moiety at the opposite tip of the molecule determines whether the phenolic hydroxyl group at one tip of the molecule is an antioxidant, and ferrocenylmethyl isocyanide significantly increases the antioxidant effect (Scheme 3A.11).[33]



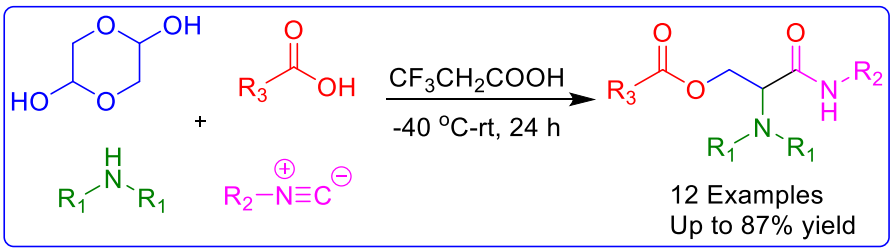
Scheme 3A.11

Okandeji et al. observed that use of transition metals increases the reactivity of the aromatic aldehydes by two to seven times when substoichiometric amounts of scandium and ytterbium triflate are used. These rare earth metal triflates improve the reaction yields in principle by activating the imine intermediate of this multicomponent process (Scheme 3A.12).[34]



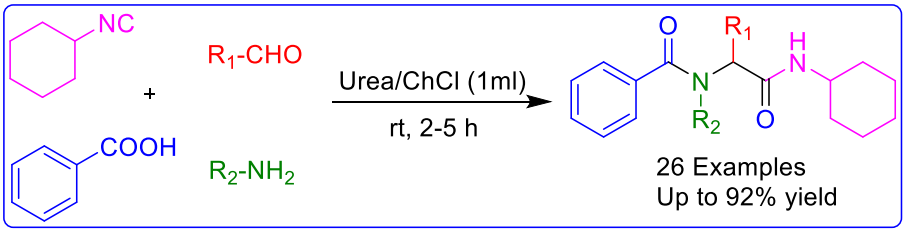
Scheme 3A.12

Mossetti et al. introduced a glycolaldehyde dimer in a four-component synthesis to create Passerini-Ugi hybrid adducts. The utilisation of molecules with the hydroxyl group grafted on isocyanide and secondary amine building blocks is being studied (Scheme 3A.13).[35]



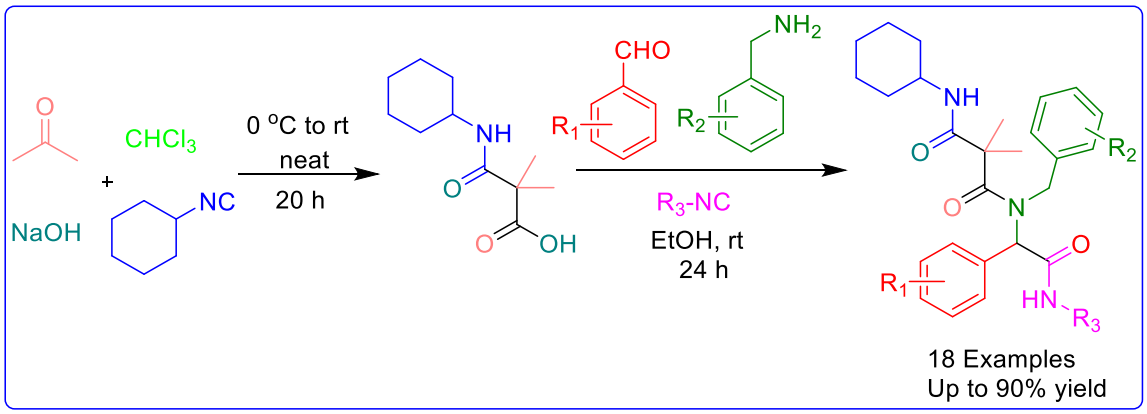
Scheme 3A.13

Azizi and co-workers developed an effective reaction media, the Ugi reaction proceeds quickly and produces high yields in a low melting mixture of choline chloride and urea (DES). The DES is applicable to a wide range of aldehydes, amines, isocyanides, and acids to produce the final products in excellent yields with less time. This solvent (DES) can be used up to four cycles without dropping the yield (Scheme 3A.14).[36]



Scheme 3A.14

Farhid et al. established the procedure for the synthesis of a new family of pseudo-peptides, sequential Bargellini/Ugi multicomponent cascade reactions. Initially 3-carboxamido-isobutyric acids are made utilising the Bargellini reaction by sodium hydroxide, isocyanides, acetone, and chloroform. Then, the crude was subjected to Ugi multicomponent reaction approach, with aldehydes, amines, and isocyanides to produce the final products containing three amide linkages. This method is effective and environmentally safe for producing large quantities of structurally varied, drug-like pseudo-peptides in high yields (Scheme 3A.15).[37]



Scheme 3A.15

Hence C2-H functionalized quinolines are common pharmacophores with wide applications in pharmaceuticals. We observed that considerable attention has been received for C(sp²)-H functionalization of quinolines at C2 position to increase the biological activity of the quinoline core.

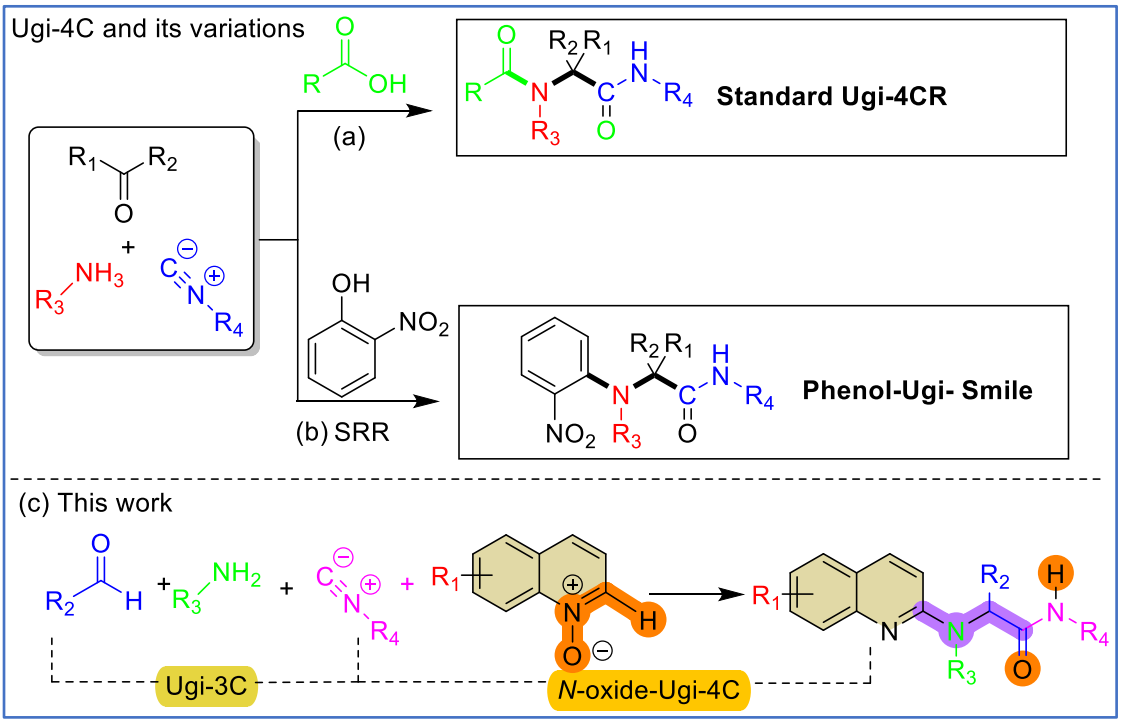
3A.2. Present study

Considering the importance of multicomponent reactions and their hybrid molecules, we have developed a novel *N*-oxide induced Ugi reaction. Here we describe a C(sp²)-H functionalization of quinolines in the presence of aldehydes, anilines and isocyanides. This metal-free reaction affords rapid access to quinoline-C2-amino amides *via* deoxygenative C(sp²)-H functionalization with exceptional functional group tolerance, broad substrate scope.

In continuation of our work on C2-H functionalization of the aromatic amine *N*-oxides using isocyanides,[38] herein we report a *N*-oxide induced Ugi reaction to access library of 2-phenyl-2-

(phenyl(quinolin-2-yl)amino)acetamide derivatives in one-pot reaction *via* C(sp²)-H functionalization.

A logic-based replacement of the carboxylic acid component of the Ugi reaction by quinoline *N*-oxides has been developed. In this approach, the carboxylic isostere, quinoline *N*-oxide, plays a vital role by shifting the equilibria towards the product side with irreversible addition onto the C2-position of the *N*-oxide. Thus, aldehydes react with amines, isocyanides, and quinoline *N*-oxides to furnish quinoline four-component Ugi adducts. The unique reactivity of *N*-oxides with Ugi components opens an efficient synthetic route for the preparation of biologically active compounds (Scheme 3A.16).



Scheme 3A.16

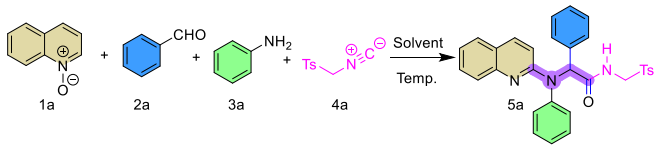
3A.2.1. Results and discussion

To test our hypothesis, initial screening experiments were conducted on quinoline *N*-oxide **1a** with benzaldehyde **2a**, aniline **3a** and *p*-toluenesulfonylmethyl isocyanide (TosMIC) **4a** in the suitable solvent and temperatures to optimize the reaction conditions, and only the key facts are reported in Table 3A.1. The reaction of quinoline *N*-oxide **1a** (0.5 mmol) with benzaldehyde **2a** (0.5 mmol), aniline **3a** (0.5 mmol) and TosMIC **4a** (0.5 mmol) in the CH_2Cl_2 at room temperature failed to give the **5a** but at elevated temperature afforded the desired product **5a** in 10% yield (Table 3A.1, entries 1-2). The standard spectroscopic analysis identified **5a** as *N*-(4-methylbenzyl)-2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamide, in line with the original

design. This result revealed that the quinoline *N*-oxide **1a** indeed acted as a carboxylic acid isostere in the traditional Ugi reaction.

To our delight, the yield of *N*-(4-methylbenzyl)-2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamide **5a** has increased to 60% at elevated temperatures (Table 3A.1, entries 2-4). These results suggested that heating is required to get the better yield of the product. Next, we have carried out the reaction in various solvents to assess their effect on the reaction efficiency. Among other solvents tested, such as toluene, CH_3NO_2, THF, alcohols, DMF and DMSO, CH_3CN turned out to be superior for this transformation (Table 3A.1, entries 5-12). Further change in the temperature and time has no effect on the yields of the reaction (Table 3A.1, entry 13).

Table 3A.1. Optimization of reaction conditions[a]



S. No	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	CH_2Cl_2	rt	24	0
2	CH_2Cl_2	40	12	10
3	$CHCl_3$	60	12	40
4	DCE	60	12	60
5	Toluene	60	12	10
6	**CH_3CN**	**60**	**9**	**80**
7	CH_3NO_2	60	12	40
8	THF	60	12	70
9	CH_3OH	60	8	50
10	EtOH	60	8	45
11	DMF	60	12	trace
12	DMSO	60	2	20
13	CH_3CN	80	24	79

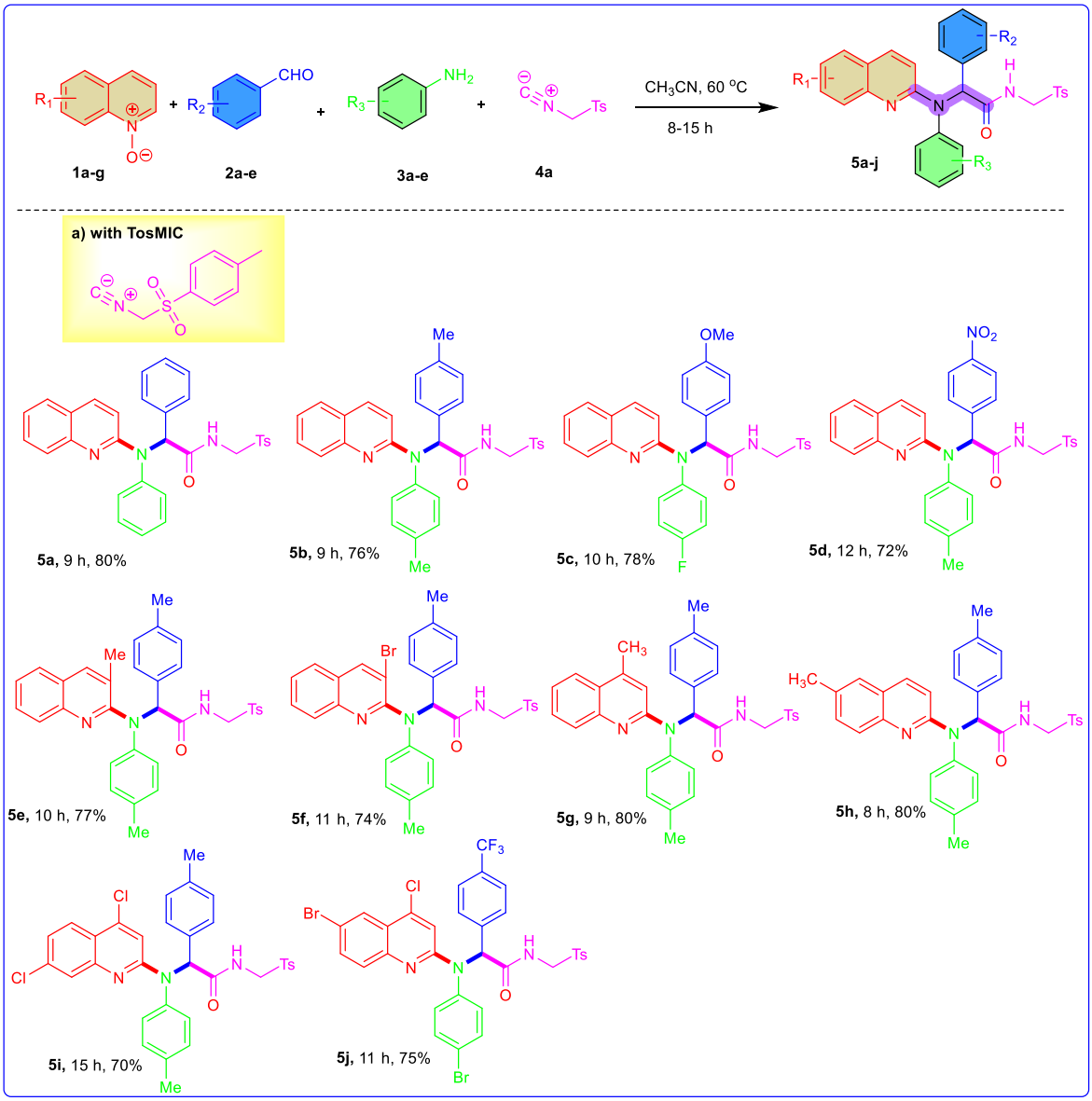
[a]Reaction conditions: quinoline *N*-oxide **1a** (0.5 mmol), benzaldehyde **2a** (0.5 mmol), aniline **3a** (0.5 mmol), isocyanide **4a** (0.5 mmol), and solvent (2.0 mL). [b]isolated yield.

To explore the scope of this new four-component reaction, we examined diversely substituted quinoline *N*-oxides with anilines, aromatic aldehydes and TosMIC (Table 3A.2). The unsubstituted and substituted quinoline *N*-oxide at various positions reacted smoothly to give respective products in excellent yields (Table 3A.2). The substitutions on nitrogenous quinoline ring were also well tolerated to deliver corresponding *N*-(4-methylbenzyl)-2-phenyl-2-

(phenyl(quinolin-2-yl)amino) acetamide **5e-f** in 74-77% yields (Table 3A.2). Presence of a donor group on fourth and sixth position of quinoline gave the target product **5g-h** with 80% yield.

Likewise, 4,7- dichloro and 4-chloro-6-bromo of the quinoline *N*-oxides gave the target product **5i-j** with 70-75% yields respectively. Electron donating and electron withdrawing groups on aldehyde also smoothly reacted under the optimized reaction conditions.

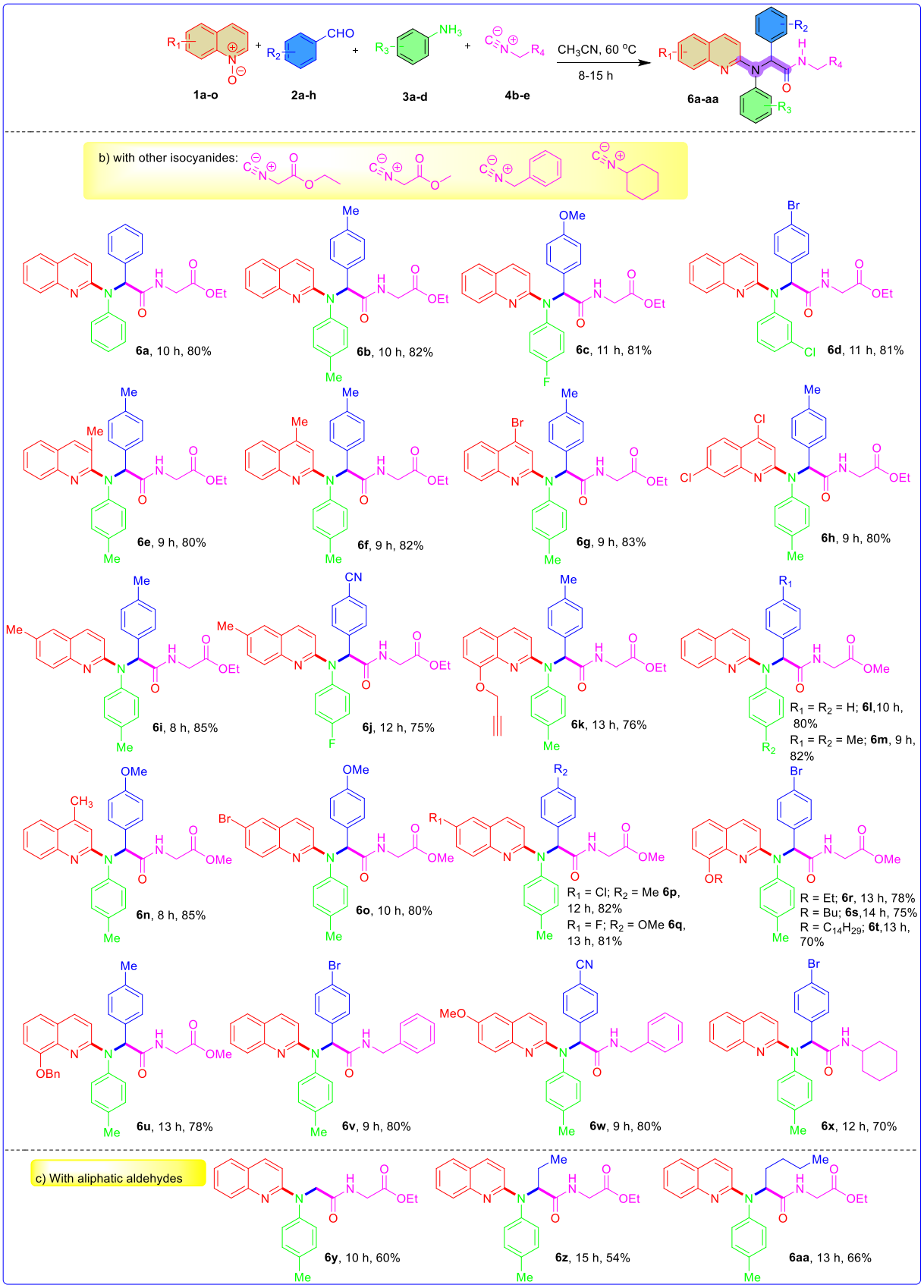
Table 3A.2. Substrate scope for the synthesis of quinoline-C2-amino amides[a,b]



[a]Reaction Conditions: quinoline *N*-oxides **1a-g** (0.5 mmol), aldehydes **2a-e** (0.5 mmol), anilines **3a-e** (0.5 mmol), isocyanide **4a** (0.5 mmol), CH_3CN (2 mL), 60 °C. [b]Isolated yields.

Next, we turned our attention to test the scope of various isocyanides with different quinoline *N*-oxides. The methyl 2-isocyanoacetate and ethyl 2-isocyanoacetate reacted smoothly with various quinoline *N*-oxides to obtain the Ugi products **6a-x** in 70-85% yield (Table 3A.3). The

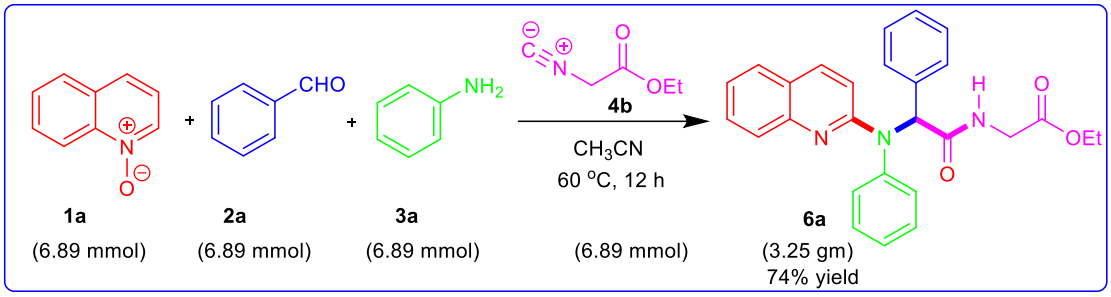
Table 3A.3. Substrate scope for the synthesis of quinoline-C2-amino amides[a,b]



[a]Reaction Conditions: quinoline *N*-oxides **1a-o** (0.5 mmol), aldehydes **2a-h** (0.5 mmol), anilines **3a-d** (0.5 mmol), isocyanides **4b-e** (0.5 mmol), CH_3CN (2 mL), 60 °C. [b]Isolated yields.

substitution on quinoline *N*-oxides with methyl, F, Cl, Br, and alkyl ethers did not alter the product yields (Table 3A.3).

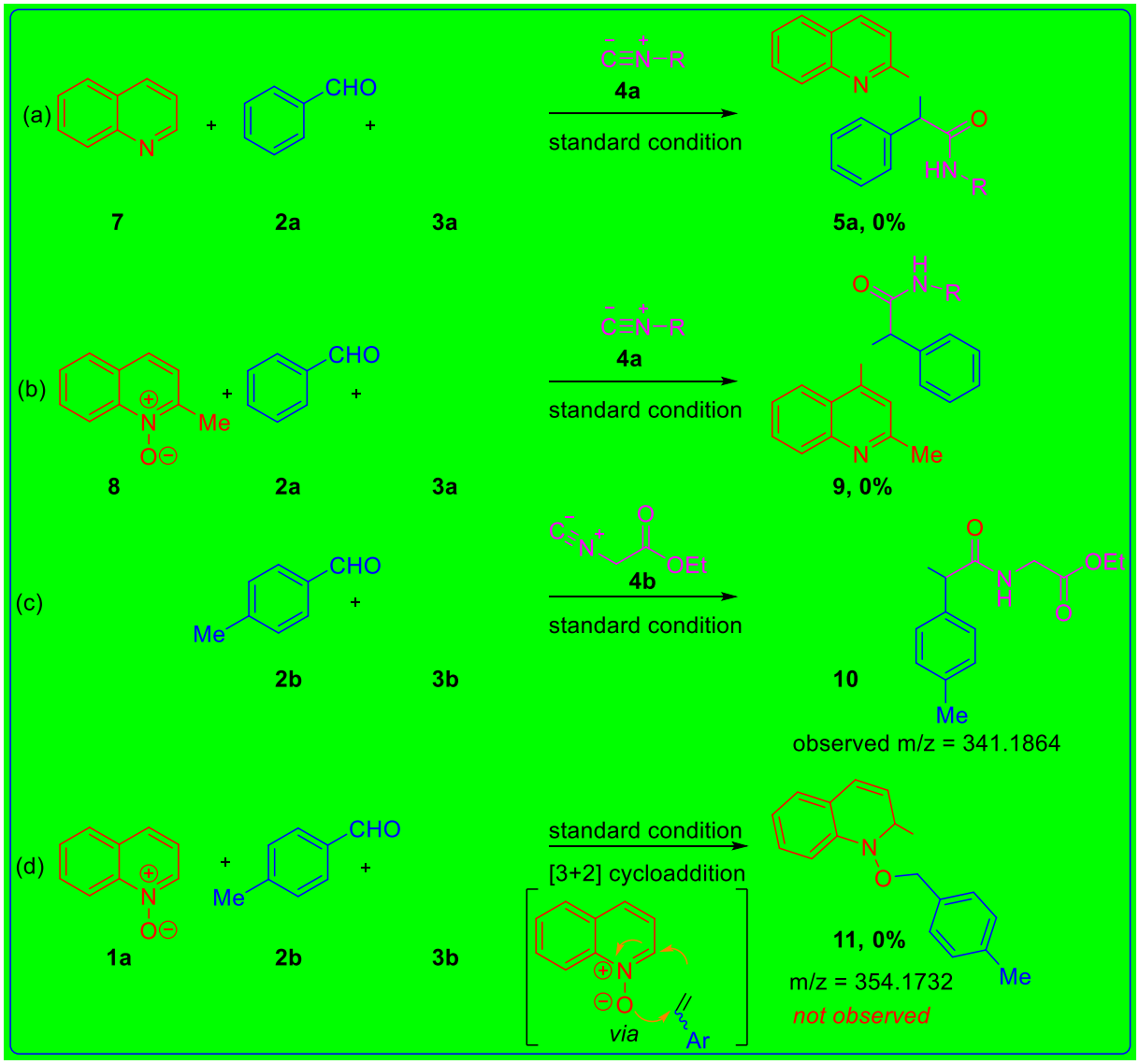
Surprisingly, aliphatic aldehydes such has paraformaldehyde, propionaldehyde and valeraldehyde gave the corresponding adducts **6y**, **6z** and **6aa** with 60%, 54% and 66% yields respectively, which is less in comparison with aromatic aldehydes (Table 3A.3). Simple pyridine *N*-oxides are not reactive under these optimized conditions, which could be on account of their less reactivity.



Scheme 3A.17. Gram-scale synthesis

Further, we investigated the efficiency of this protocol for gram scale reaction using quinoline *N*- oxide **1a** with benzaldehyde **2a,** aniline **3a**, and the isocyanide **4b** The reaction afforded the final product **6a** in 74% of yield (Scheme 3A.17).

Next, we carried several control experiments to unveil the reaction mechanism (Scheme 3A.18). Initially, quinoline **7** was treated with aniline **2a**, aldehyde **3a** and isocyanide **4a**, under the standard conditions, but no reaction was observed, which indicated the important role of *N*-oxide in this transformation (Scheme 3A.18a). Later, 2-substituted quinoline *N*-oxide **8** was used to test the reactive position of the quinoline *N*-oxide and found to be non-reactive under the optimized conditions (Scheme 3A.18b). Then, we have conducted three component reactions by varying isocyanide and quinoline *N*-oxide and recorded the HRMS of reaction aliquots during the course of reaction to know the formation of intermediates (Scheme 3A.18c-d).

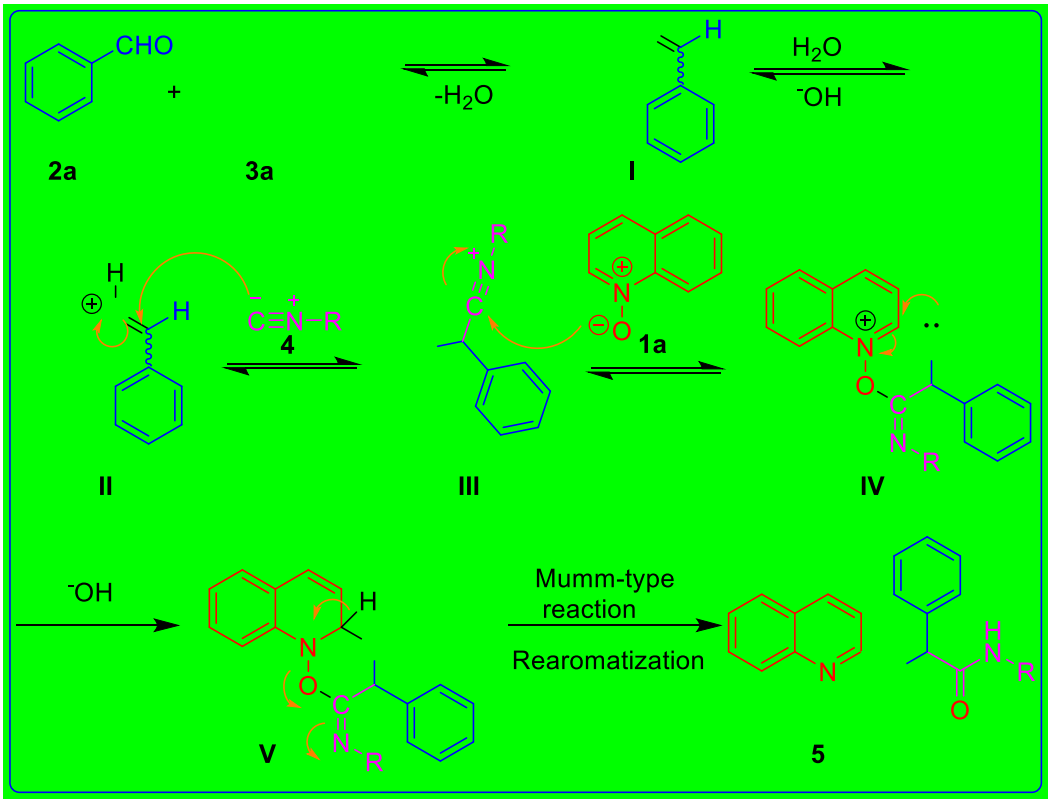


Scheme 3A.18. Control experiments

The HRMS data reveals the following points: i) *p*-toluidine **2b** is initially reacting with aldehyde **3b** to form imine intermediate (observed m/z = 210.1280) which is further undergoing addition by the ethyl 2-isocyanoacetate **4b** followed by hydrolysis to obtain product **10** (observed m/z = 341.1864) in absence of quinoline *N*-oxide (Scheme 3A.18c); ii) quinoline *N*-oxides is not undergoing [3+2] cycloaddition with imine intermediate under standard conditions (Scheme 3A.18d). On the basis of our control experiments and previous literature,[39,40] a plausible mechanism is illustrated in Scheme 3A.19.

Initially, reaction between aniline **2a** and carboxaldehyde **3a** would form imine intermediate **I**. Next, the intermediate **I** would undergo protonation followed by the nucleophilic addition with isocyanide **4** to form intermediate **III**. Later, the nucleophilic oxygen of *N*-oxide subsequently added carbon of nitrilium ion to generate intermediate **IV**. Further, an irreversible nucleophilic addition of nitrogen (aniline) on to the activated C2-carbon of quinoline would furnish bicyclic

intermediate **V** *via* Mumm type reaction. Finally, the intermediate **V** undergoes rearomatization to obtain the desired product **5**.



Scheme 3A.19. Plausible reaction mechanism

3A.3. X-ray diffraction analysis of compound 6p

The method for crystal growth is slow volatilization using the mixture of chloroform, methanol and acetonitrile (4:4:2) as a solvent. The crystallographic data for the single crystal of the compound **6p** was collected on Xtlab Synergy Rigaku oxford diffraction with HyPix-3000 detector, equipped with graphite monochromated MoKa radiation (λ= 0.71073 Å) at 293K. The data interpretation was processed with CrysAlisPro, Xtlab Synergy Rigaku oxford diffraction, version 171.39.exe and an absorption correction based on multi-scan method. Crystallography data and structure refinement for **6p** (CCDC: 2159541) (Table 3A.4). Thermal ellipsoids are shown at 50% probability level (Figure 3A.5).

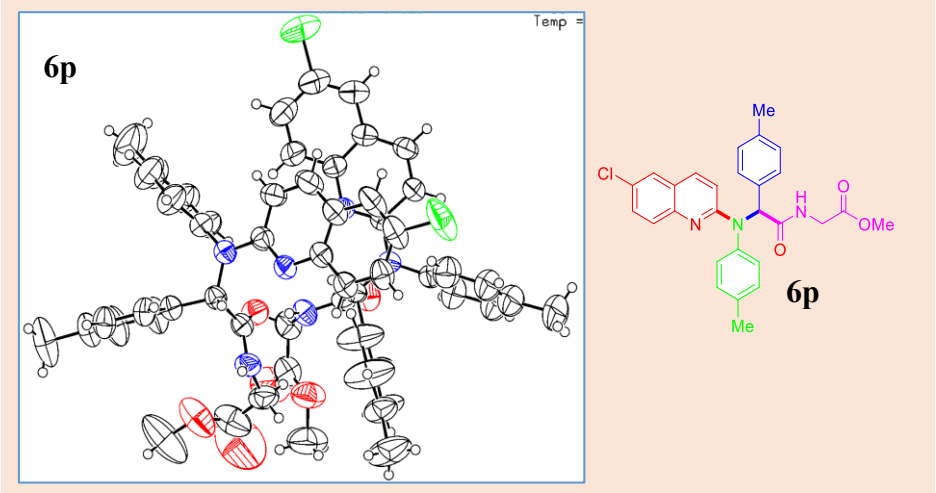


Figure. 3A.5. The ORTEP representation of the compound **6p**

Table 3A.4. Crystallographic data and structure refinement of compound **6p**

Identification Code	**Compound 6p**
Empirical formula	C_{28} $H_{26}Cl$ N_3O_3
Formula weight	487.97
Temperature/K	297K
Crystal system	Monoclinic
Space group	P 121/n1
a/Å	9.3233(2)
b/Å	23.1794(7)
c/Å	24.1963(7)
α/°	90
β/°	91.755(2)
γ/°	90
Volume/Å^3	5226.6(2)
Z	8
D_{calc} Mg/m^3	1.240
μ/mm^{-1}	0.179
F(000)	2048.0
Crystal size/mm^3	0.2 x 0.15x 0.1
2Θ range for data collection/°	1.948 to 25.027
Index ranges	$-11 \leq h \leq 11$, $-27 \leq k \leq 27$, $-28 \leq l \leq 28$
Reflections collected	9219

Independent reflections	5029
Data/restraints/parameters	5029 / 0 / 625
Goodness-of-fit on F^2	1.048
Final R indexes [I>=2σ (I)]	R1 = 0.0685, wR2 = 0.1809
Final R indexes [all data]	R1 = 0.1237, wR2 = 0.2153
Largest diff. peak/hole / e $Å^{-3}$	0.394/ -0.370
CCDC	2159541

3A.4. Conclusion

In summary, aromatic *N*-oxide based single reactant replacement approach of the Ugi reaction has been successfully developed. This approach opens a new era in quinoline *N*-oxides to be a potent acid surrogate in multicomponent reactions. This method provides the one-pot synthesis of *α*-quinoline amino amides while ensuring a wide substrate scope with functional group tolerance.

3A.5. Experimental section

3A.5.1. General Information: All chemicals were purchased from Aldrich, Alfa aesar, TCI, Finar and used as received. All solvents were purchased from commercial sources, then distilled by the standard protocol and stored over molecular sieves under nitrogen atmosphere prior to use. Thin layer chromatography was performed on 200 µm aluminium-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). ^{1}H NMR spectra were recorded on Bruker's AVANCE 400 MHz spectrometer, $CDCl_3$ and DMSO-d_6 as a solvent and TMS as an internal standard. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, coupling constants, *J* were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker's AVANCE 100 MHz spectrometer, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-d (a multiplet at 39.52 ppm of DMSO-d_6). Melting points were determined with a Stuart SMP30 apparatus and are uncorrected. FT-IR spectra recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230. The X-ray single crystal data of the crystal compounds was collected on Xtlab Synergy Rigaku oxford diffraction with HyPix-3000 detector, equipped with graphite monochromated MoKα radiation (λ= 0.71073 Å) at 293K.

3A.5.2. General procedure for the synthesis of 8-*O*-alkylation of quinolines (1k, 1r-u)[41]

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with 8-hydroxy quinoline (1.0 mmol, 1.0 equiv), K_2CO_3 (2.0 mmol, 2.0 equiv) and DMF (2 mL). Allow the mixture to stir at room temperature for 30 min, then corresponding alkyl bromides (1.2 mmol, 1.2 equiv) was added and stirring continued at room temperature for 12 h, The progress of the reaction mixture was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion, the reaction mixture was extracted with ethyl acetate (3 x 10 mL). The organic layer was separated, dried over Na_2SO_4 and evaporated to give a residue that was purified on a silica gel column chromatography using hexanes and ethyl acetate as an eluent to afford the corresponding 8-*O*-alkoxy quinoline.

3A.5.3. General procedure for the synthesis of quinoline *N*-oxides (1a-q)[42]

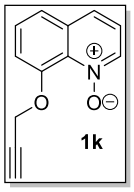
An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate quinoline (1.0 mmol, 1.0 equiv) in $CHCl_3$ (2 mL) and was added 70% *m*-CPBA (1.0 mmol, 1.0 equiv), portion wise at 0 ^oC. The resulting mixture was stirred at room temperature for 12 h. After completion of starting material (monitored by TLC), the reaction mixture was diluted with $CHCl_3$, and solid K_2CO_3 (4 equiv) was added. The resulting mixture was stirred for an additional 10 min. The solid was separated by filtration, and the filtrate was dried over Na_2SO_4 and concentrated under reduced pressure to afford the quinoline *N*-oxide in yields of 82-92%.

3A.5.4. General procedure for the synthesis of quinoline-C2-amino amides (5a-j, and 6a-aa).

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate benzaldehyde (0.5 mmol, 1.0 equiv), aniline (0.5 mmol, 1.0 equiv), quinoline *N*-oxide (0.5 mmol, 1.0 equiv), and the isocyanide (0.5 mmol, 1.0 equiv) in CH_3CN (2 mL). The reaction mixture was stirred at 60 ^oC for 8-15 h. The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion, the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure and extracted with ethyl acetate (3 x 10 mL). The organic layer was separated, dried over Na_2SO_4 and evaporated to give a residue that was purified on a silica gel column chromatography using hexanes and ethyl acetate as an eluent to afford the corresponding quinoline-C2-amino amides in yields of 54-85%.

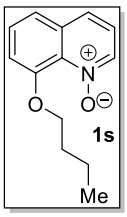
3A.6. Characterization data of products (1k, s & t), 5a-5j, 6a-6aa.

8-(prop-2-yn-1-yloxy)quinoline 1-oxide (1k). White solid; (179 mg, 90% yield); ^{1}H NMR



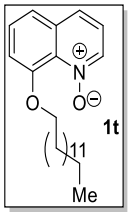
(400 MHz, $CDCl_3$) δ (ppm): 8.39 (dd, J = 6.0, 1.2 Hz, 1H), 7.62 (dd, J = 8.4, 0.8 Hz, 1H), 7.53-7.48 (m, 2H), 7.33 (dd, J = 7.2, 2.0 Hz, 1H), 7.20 (dd, J = 8.4, 6.0 Hz, 1H), 4.95 (d, J = 2.4 Hz, 2H), 2.51 (t, J = 2.4 Hz, 1H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 150.6, 138.1, 135.5, 133.7, 128.4, 125.5, 123.2, 121.2, 118.4, 78.4, 76.3, 60.1; HRMS (ESI-TOF) m/z: calculated for $C_{12}H_{10}NO_2^+$ $[M+H]^+$ 200.0706; found 200.0705.

8-butoxyquinoline 1-oxide (1s). White solid; (195 mg, 90% yield); ^{1}H NMR (400 MHz,



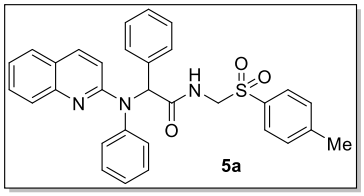
$CDCl_3$) δ (ppm): 8.39 (dd, J = 6.2, 1.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.37 (dd, J = 8.4, 1.2 Hz, 1H), 7.18 (dd, J = 8.4, 6.0 Hz, 1H), 7.08 (dd, J = 7.6, 1.2 Hz, 1H), 4.13 (t, J = 6.6 Hz, 2H), 1.99 – 1.91 (m, 2H), 1.68 – 1.58 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 153.0, 138.0, 134.5, 133.7, 128.6, 125.6, 121.1, 120.6, 113.1, 70.6, 31.2, 19.2, 13.8; HRMS (ESI-TOF) m/z: calculated for $C_{13}H_{16}NO_2^+$ $[M+H]^+$ 218.1176; found 218.1176.

8-(tetradecyloxy)quinoline 1-oxide (1t). White solid; (303 mg, 85% yield); ^{1}H NMR (400



MHz, $CDCl_3$) δ (ppm): 8.38 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.37 (dd, J = 8.2, 1.0 Hz, 1H), 7.17 (dd, J = 8.2, 6.2 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 4.12 (t, J = 6.8 Hz, 2H), 2.01 – 1.93 (m, 2H), 1.62 – 1.53 (m, 2H), 1.26 (s, 20H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 153.2, 138.0, 134.7, 133.7, 128.6, 125.2, 121.1, 120.6, 113.1, 71.0, 31.9, 29.6, 29.5, 29.5, 29.3, 29.2, 26.0, 22.6, 14.1; HRMS (ESI-TOF) m/z: calculated for $C_{23}H_{36}NO_2^+$ $[M+H]^+$ 358.2741; found 358.2740.

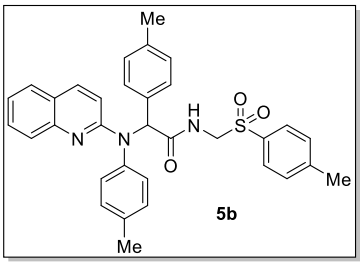
2-phenyl-2-(phenyl(quinolin-2-yl)amino)-*N*-(tosylmethyl)acetamide (5a). White solid; (208



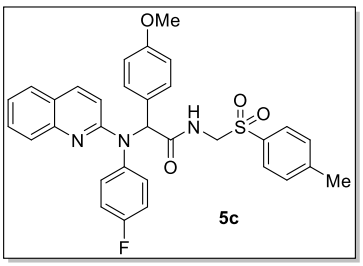
mg, 80% yield); mp 150-151 ^{o}C; R_f = 0.50 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3363, 3065, 2926, 2859, 1694, 1594, 1495, 1453, 1325, 1287, 1142, 1085 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.36 (t, J = 6.2 Hz, 1H), 7.87 (d, J = 9.2 Hz, 1H), 7.72 (t, J = 9.0 Hz, 2H), 7.59 (dd, J = 19.6, 7.8 Hz, 3H), 7.28 (t, J = 7.4 Hz, 1H), 7.25-7.20 (m, 2H), 7.17-7.10 (m, 7H), 7.03 (d, J = 6.0 Hz, 2H), 6.66 (s, 1H), 6.30 (d, J = 9.2 Hz, 1H), 4.93 (dd, J = 14.0, 7.2 Hz, 1H), 4.71 (dd, J = 14.0, 5.6 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR {^{1}H} (100

MHz, DMSO-d_6) δ (ppm): 171.8, 156.6, 147.1, 144.6, 141.3, 137.2, 135.6, 135.3, 131.8, 130.9, 129.9, 129.8, 129.4, 128.8, 128.1, 128.0, 127.8, 127.5, 126.9, 123.6, 122.9, 112.1, 64.7, 61.1, 21.5; HRMS (ESI-TOF) m/z: calculated for $C_{31}H_{28}N_3O_3S^+$ $[M+H]^+$ 522.1846; found 522.1855.

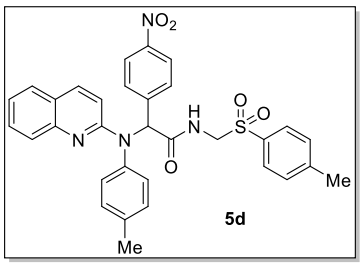
2-(quinolin-2-yl(*p*-tolyl)amino)-2-(*p*-tolyl)-*N*-(tosylmethyl)acetamide (5b). White solid; (208 mg, 76% yield); mp 104-105 °C; R_f = 0.50 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3279, 3061, 2914,2852, 1673, 1616, 1599, 1470, 1323, 1284, 1141, 1085 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.23 (t, *J* = 6.6 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.26 (t, *J* = 7.0 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.99-6.93 (m, 4H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.54 (s, 1H), 6.23 (d, *J* = 9.2 Hz, 1H), 4.86 (dd, *J* = 14.0, 7.2 Hz, 1H), 4.65 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.9, 156.8, 147.1, 144.6, 138.8, 137.0, 136.7, 135.3, 132.7, 131.6, 130.8, 130.0, 129.9, 128.9, 128.8, 127.8, 126.9, 123.5, 122.8, 112.1, 64.3, 61.1, 21.5, 21.2, 21.1; HRMS (ESI-TOF) m/z: calculated for $C_{33}H_{32}N_3O_3S^+$ $[M+H]^+$ 550.2159; found 550.2169.



2-((4-fluorophenyl)(quinolin-2-yl)amino)-2-(4-methoxyphenyl)-*N*(tosylmethyl)acetamide (5c). White solid; (222 mg, 78% yield); mp 187-188 °C; R_f = 0.50 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3320,3052, 2922, 2864, 1687, 1536, 1474, 1328, 1290, 1254, 1136, 1084, 829 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.28 (t, *J* = 6.4 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.17-7.04 (m, 6H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.54 (s, 1H), 6.26 (d, *J* = 9.2 Hz, 1H), 4.88 (dd, *J* = 14.4, 7.2 Hz, 1H), 4.67 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.70 (s, 3H), 2.32 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.1, 162.3, 159.9, 159.1, 156.6, 147.1, 144.6, 137.6 (d, *J* = 2.0 Hz), 137.3, 135.4, 134.1(d, *J* = 8.0 Hz), 132.1, 129.9, (d, *J* = 13.0 Hz), 128.8, 127.9, 127.4, 126.9, 123.5, 122.9, 116.3, 116.1, 113.6, 111.8, 63.8, 61.1, 55.5, 21.5; ^{19}F NMR (376 MHz, DMSO) δ (ppm): -114.65 (s); HRMS (ESI-TOF) m/z: calculated for $C_{32}H_{29}FN_3O_4S^+$ $[M+H]^+$ 570.1857; found 570.1869.

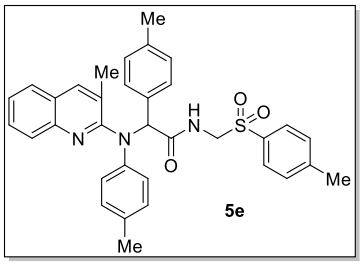


2-(4-nitrophenyl)-2-(quinolin-2-yl(*p*-tolyl)amino)-*N*-(tosylmethyl)acetamide (5d). White



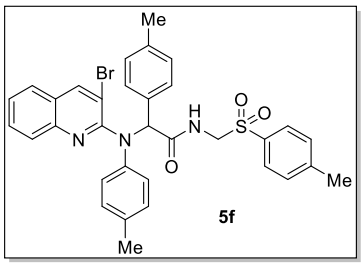
solid; (209 mg, 72% yield); mp 104-105 °C; R_f = 0.50 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3372, 3065, 2922, 2855, 1697, 1599, 1561, 1470, 1346, 1285, 1143, 1086 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.46 (t, J = 6.6 Hz, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 9.2 Hz, 1H), 7.74-7.69 (m, 2H), 7.63-7.59 (m, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.35-7.27 (m, 3H), 7.15 (d, J = 8.0 Hz, 2H), 7.05 (dd, J = 20.0, 8.2 Hz, 4H), 6.72 (s, 1H), 6.31 (d, J = 9.2 Hz, 1H), 4.90 (dd, J = 14.0, 7.2 Hz, 1H), 4.74 (dd, J = 14.0, 6.0 Hz, 1H), 2.31 (s, 3H), 2.23 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm):170.9, 156.5, 147.1, 146.9, 144.8, 143.7, 138.5, 137.4, 137.2, 135.2, 132.1, 131.3, 130.3, 130.0, 129.9, 128.7, 127.9, 126.9, 123.7, 123.2, 123.1, 112.0, 64.0, 60.9, 21.4, 21.0; HRMS (ESI-TOF) m/z: calculated for $C_{32}H_{29}N_4O_5S^+$ $[M+H]^+$ 581.1853; found 581.1867.

2-((3-methylquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)-*N*-(tosylmethyl)acetamide (5e).



White solid; (217 mg, 77% yield); mp 109-110 °C; R_f = 0.50 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3393, 3032, 2920, 2857, 1676, 1512, 1494, 1320, 1256, 1143, 1085 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.54 (t, J = 6.4 Hz, 1H), 7.94 (s, 1H), 7.74 (t, J = 8.8 Hz, 2H), 7.63 – 7.58 (m, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.46-7.42 (m, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6.98 (dd, J = 16.0, 8.0 Hz, 4H), 6.72 (d, J = 8.4 Hz, 2H), 6.03 (s, 1H), 4.93 – 4.88 (m, 2H), 2.33 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H), 1.79 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.9, 156.8, 144.8, 144.8, 143.5, 139.1, 137.1, 135.1, 133.4, 132.9, 130.0, 129.8, 129.6, 129.2, 128.8, 128.7, 128.1, 127.3, 127.0, 126.3, 125.6, 123.9, 69.7, 60.7, 21.5, 21.0, 20.7, 19.2; HRMS (ESI-TOF) m/z: calculated for $C_{34}H_{34}N_3O_3S^+$ $[M+H]^+$ 564.2315; found 564.2328.

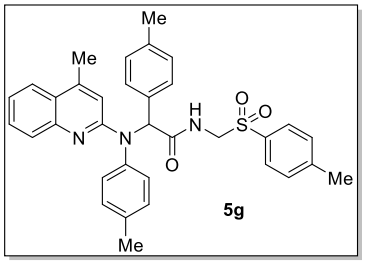
2-((3-bromoquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)-*N*-(tosylmethyl)acetamide (5f). White



solid, (232 mg, 74% yield); mp 95-96 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3359, 3039, 2924, 2853, 1650, 1512, 1408, 1322, 1287, 1144, 1035 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.04 (t, J = 6.6 Hz, 1H), 8.54 (s, 1H), 7.81 (dd, J = 18.0, 8.8 Hz, 2H), 7.74 – 7.63 (m, 2H), 7.52 (dd, J = 12.8, 4.8 Hz, 3H), 7.22 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.98 (dd, J = 8.0, 6.0 Hz, 3H), 6.69 (d, J = 8.4 Hz, 2H), 5.97 (s, 1H), 4.91 (dd, J = 14.2, 7.0 Hz, 1H), 4.84 (dd, J = 14.2, 6.2 Hz, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H); ^{13}C NMR

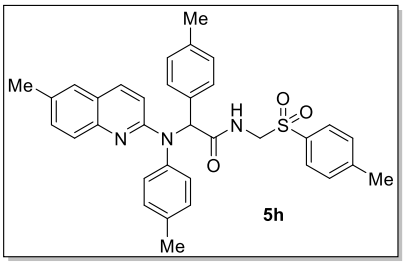
{^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 170.6, 170.1, 168.6, 148.9, 146.9, 137.7, 137.4, 137.0, 136.3, 131.6, 131.3, 131.1, 130.9, 130.3, 129.1, 128.9, 128.7, 127.8, 126.6, 64.6, 61.1, 21.0, 20.7, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{33}H_{31}BrN_3O_3S^+$ $[M+H]^+$ 628.1264; found 628.1275.

2-((4-methylquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)-*N*-(tosylmethyl)acetamide (5g).



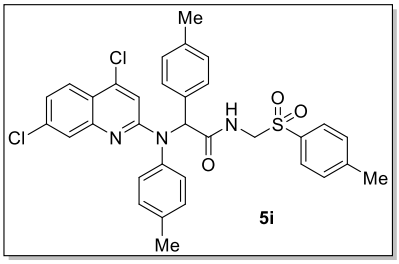
White solid; (225 mg, 80% yield); mp 160-161 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3291, 3061, 2918, 2855, 1677, 1555, 1467, 1394, 1214, 1143, 1087 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.22 (t, J = 6.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.99 – 6.93 (m, 4H), 6.89 (d, J = 7.6 Hz, 2H), 6.56 (s, 1H), 6.12 (s, 1H), 4.86 (dd, J = 14.0, 7.0 Hz, 1H), 4.65 (dd, J = 14.4, 6.0 Hz, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.9, 156.5, 144.6, 138.8, 137.0, 136.6, 135.3, 132.8, 131.5, 130.8, 130.0, 129.9, 128.8, 124.2, 123.7, 122.7, 111.9, 64.3, 61.1, 21.5, 21.2, 21.1, 19.0; HRMS (ESI-TOF) m/z: calculated for $C_{34}H_{34}N_3O_3S^+$ $[M+H]^+$ 564.2315; found 564.2324.

2-((6-methylquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)-*N*-(tosylmethyl)acetamide (5h).



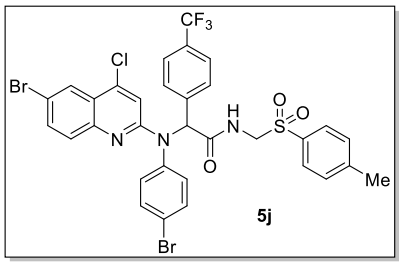
White solid; (225 mg, 80% yield); mp 152-153 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3363, 3031, 2918, 2863, 1693, 1597, 1473, 1312, 1284, 1142, 1086 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.23 (t, J = 6.6 Hz, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.46 (s, 1H), 7.43 (dd, J = 8.4, 1.6 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 4H), 6.90 (d, J = 8.4 Hz, 2H), 6.52 (s, 1H), 6.21 (d, J = 9.2 Hz, 1H), 4.86 (dd, J = 14.4, 7.0 Hz, 1H), 4.65 (dd, J = 14.0, 6.2 Hz, 1H), 2.41 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.0, 156.4, 144.6, 138.9, 137.0, 136.6, 136.5, 135.3, 132.8, 131.8, 131.7, 131.6, 130.8, 130.0, 129.9, 128.8, 128.7, 126.8, 126.7, 123.4, 112.1, 64.3, 61.1, 21.5, 21.5, 21.3, 21.2, 21.1; HRMS (ESI-TOF) m/z: calculated for $C_{34}H_{34}N_3O_3S^+$ $[M+H]^+$ 564.2315; found 564.2321.

2-((4,6-dichloroquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)-*N*-(tosylmethyl)acetamide (5i).

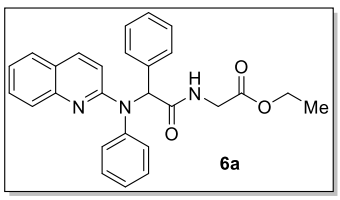


White solid, (216 mg, 70% yield); mp 137-138 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3216, 3040, 2922, 2859, 1700, 1601, 1592, 1490, 1387, 1235, 1144, 1049 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.24 (t, J = 6.6 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.42 (dd, J = 8.8, 2.4 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 7.2 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 6.46 (s, 1H), 6.27 (s, 1H), 4.88 (dd, J = 14.0, 7.0 Hz, 1H), 4.74 (dd, J = 14.0, 6.0 Hz, 1H), 2.35 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.4, 157.1, 148.6, 144.7, 141.3, 137.6, 137.5, 137.4, 136.0, 135.4, 131.9, 131.4, 130.9, 130.3, 129.8, 128.8, 128.7, 126.0, 125.9, 124.2, 119.8, 111.5, 64.5, 61.0, 21.53, 21.2, 21.1; HRMS (ESI-TOF) m/z: calculated for $C_{33}H_{30}Cl_2N_3O_3S^+$ $[M+H]^+$ 618.1379; found 618.1392.

2-((6-bromo-4-chloroquinolin-2-yl)(4-bromophenyl)amino)-*N*-(tosylmethyl)-2-(4-(trifluoromethyl)phenyl)acetamide (5j). white solid (293 mg, 75% yield); mp 132-133 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3336, 3069, 2924, 2852, 1703, 1605, 1592, 1488, 1324, 1287, 1141, 1069 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.45 (t, J = 6.6 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 9.0, 2.2 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.56-7.51 (m, 4H), 7.47 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.62 (s, 1H), 6.44 (s, 1H), 4.90 (dd, J = 14.0, 7.2 Hz, 1H), 4.73 (dd, J = 14.2, 5.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 170.2, 155.6, 146.1, 144.4, 140.4, 139.1, 139.1, 134.7, 134.1, 133.3, 132.4, 131.3, 129.4, 129.3, 128.2, 125.3, 124.7, 124.7, 122.2, 121.0, 116.2, 111.6, 63.7, 60.3, 21.0; HRMS (ESI-TOF) m/z: calculated for $C_{32}H_{24}Br_2ClF_3N_3O_3S^+$ $[M+H]^+$ 779.9540; found 779.9544.

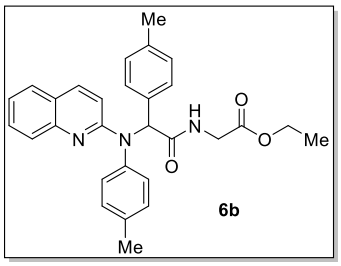


Ethyl 2-(2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamido)acetate (6a). White solid; (175 mg, 80% yield); mp 150-151 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3283, 3061, 2923, 2851, 1741, 1659, 1593, 1495, 1470, 1337, 1204, 1120, 1032 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.68 (t, J = 5.8 Hz, 1H), 7.88 (d, J = 9.2 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.62 – 7.56 (m, 1H), 7.30 – 7.20 (m, 7H), 7.19 – 7.11 (m, 4H), 6.71 (s, 1H), 6.35 (d, J = 9.2 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.91 (d, J = 5.6 Hz, 2H), 1.15 (t, J =

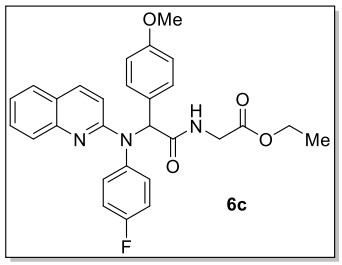


7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.8, 170.2, 156.7, 147.2, 141.7, 137.1, 136.5, 131.7, 131.0, 129.8, 129.4, 128.0, 127.8, 127.4, 126.9, 123.6, 122.8, 112.2, 64.8, 60.7, 41.6, 14.5; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{26}N_3O_3^+$ $[M+H]^+$ 440.1969; found 440.1978.

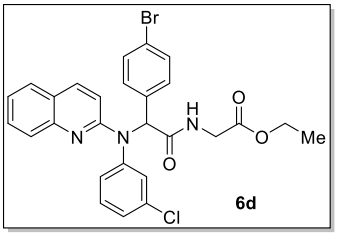
Ethyl 2-(2-(quinolin-2-yl(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6b). White solid; (191 mg, 82% yield); mp 144-145 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3401, 3294, 3094, 2922, 2820, 1733, 1668, 1563, 1471, 1391, 1234, 1107, 1024 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.57 (t, J = 5.8 Hz, 1H), 7.85 (d, J = 9.2 Hz, 1H), 7.68 (dd, J = 8.4, 5.0 Hz, 2H), 7.60 – 7.55 (m, 1H), 7.28 – 7.23 (m, 1H), 7.13 – 7.04 (m, 6H), 6.97 (d, J = 8.0 Hz, 2H), 6.64 (s, 1H), 6.31 (d, J = 9.2 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.88 (d, J = 6.0 Hz, 2H), 2.24 (s, 3H), 2.20 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.0, 170.2, 156.9, 147.2, 139.1, 137.0, 136.9, 136.6, 133.5, 131.5, 130.9, 130.0, 129.8, 128.7, 127.8, 126.8, 123.5, 122.7, 112.2, 64.5, 60.79, 41.6, 21.1, 21.0, 14.4; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{30}N_3O_3^+$ $[M+H]^+$ 468.2282; found 468.2281.



Ethyl 2-(2-((4-fluorophenyl)(quinolin-2-yl)amino)-2-(4-methoxyphenyl)acetamido)acetate (6c). White solid; (197 mg, 81% yield); mp 132-133 °C; R_f = 0.50 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3359, 3042, 2943, 2854, 1728, 1677, 1598, 1428, 1335, 1214, 1191, 1016 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.63 (t, J = 5.8 Hz, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.31-7.23 (m, 3H), 7.14 – 7.06 (m, 4H), 6.73 (d, J = 8.4 Hz, 2H), 6.62 (s, 1H), 6.32 (d, J = 8.8 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.89 (d, J = 5.6 Hz, 2H), 3.68 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.1, 170.2, 159.0, 156.7, 147.2, 138.0, 137.98 (d, J = 3.0 Hz), 137.2, 134.1 (d, J = 8.0 Hz), 134.0, 132.2, 129.9, 128.2, 127.8, 126.9, 123.5, 122.8, 116.3, 116.1, 113.6, 112.0, 64.1, 60.7, 55.4, 41.5, 14.5; ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): -114.82 (s); HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{27}FN_3O_4^+$ $[M+H]^+$ 488.1980; found 488.1985.

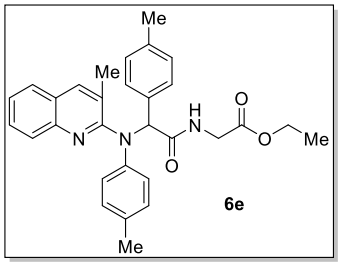


Ethyl (2-(4-bromophenyl)-2-((3-chlorophenyl)(quinolin-2-yl)amino)acetyl)glycinate (6d).



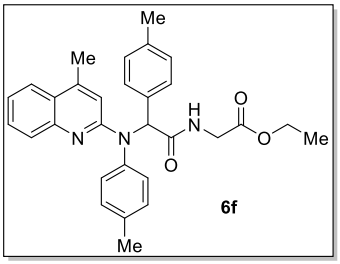
White solid; (223 mg, 81% yield); R_f= 0.50 (hexanes/EtOAc = 7:3); mp 125-126 °C; IR (KBr, cm^{-1}) 3275, 3061, 2982, 2862, 1754, 1663, 1554, 1427, 1323, 1206, 1155, 1013 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.80 (t, J = 5.8 Hz, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.72 (t, J = 7.4 Hz, 2H), 7.61 (m, 1H), 7.45 – 7.37 (m, 3H), 7.33-7.26 (m, 3H), 7.21-7.14 (m, 3H), 6.71 (s, 1H), 6.42 (d, J =8.8 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 3.91 (d, J = 6.0 Hz, 2H), 1.14 (t, J = 3.4 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 171.4, 170.1, 156.2, 147.0, 143.1, 137.5, 135.6, 133.6, 133.0, 131.5, 131.1, 131.0, 130.5, 130.0, 127.9, 127.7, 127.0, 123.8, 123.3, 121.4, 112.1, 64.0, 60.8, 41.5, 14.5; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{24}BrClN_3O_3^+$ $[M+H]^+$ 552.0684; found 552.0687.

Ethyl 2-(2-((3-methylquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6e).



Light yellow solid; (192 mg, 80% yield); mp 129-130 °C; R_f = 0.50 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3435, 3040, 2920, 2850, 1740, 1666, 1508, 1423, 1377, 1253, 1148, 1035 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.89 (t, J = 5.8 Hz, 1H), 7.98 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.51 – 7.45 (m, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.02 (dd, J = 11.2, 8.0 Hz, 4H), 6.82 (d, J = 8.4 Hz, 2H), 6.18 (s, 1H), 4.15 (q, J = 5.8, 2H), 4.10 (dd, J = 16.2, 5.4 Hz, 1H), 3.95 (dd, J = 17.4, 5.0 Hz, 1H), 2.25 (s, 3H), 2.20 (s, 3H), 1.88 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C NMR{^1H} (100 MHz, DMSO-d_6) δ (ppm): 172.2, 170.4, 156.9, 145.0, 143.8, 138.9, 136.9, 134.0, 132.6, 130.0, 129.8, 129.2, 128.7, 128.3, 127.3, 127.0, 126.4, 125.5, 123.6, 69.7, 60.9, 41.5, 21.0, 20.7, 19.2, 14.4; HRMS (ESI-TOF) m/z: calculated for $C_{30}H_{32}N_3O_3^+$ $[M+H]^+$ 482.2438; found 482.2453.

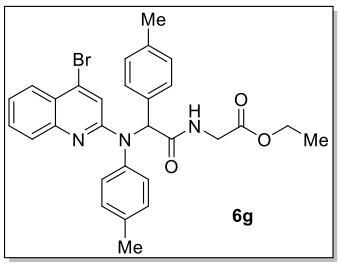
Ethyl 2-(2-((4-methylquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6f).



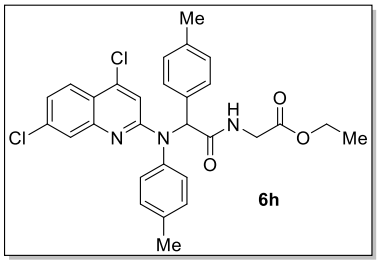
White solid; (197 mg, 82% yield); mp 168-169 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3292, 3045, 2922, 2848, 1734, 1662, 1557, 1468, 1392, 1215, 1028 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.55 (t, J = 5.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.30 – 7.25 (m, 1H), 7.13 – 7.03 (m, 6H), 6.96 (d, J = 8.0 Hz, 2H), 6.65 (s, 1H), 6.19 (s, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.87 (d, J = 5.6 Hz, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 172.0,

170.2, 156.7, 147.2, 144.4, 139.2, 136.8, 136.4, 133.6, 131.4, 130.9, 130.0, 129.6, 128.7, 127.3, 124.2, 123.8, 122.6, 112.1, 64.4, 60.7, 41.6, 21.1, 19.0, 14.5; HRMS (ESI-TOF) m/z: calculated for $C_{30}H_{32}N_3O_3^+$ $[M+H]^+$ 482.2438; found 482.2453.

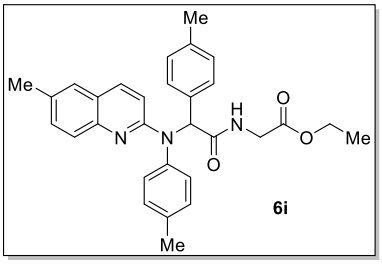
Ethyl (2-((4-bromoquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetyl)glycinate (6g). White solid; (226 mg, 83% yield); mp 155-156 °C; R_f= 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3292, 3068, 2928, 2861, 1752, 1667, 1588, 1410, 1379, 1249, 1188, 1033 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.61 (t, J = 5.8 Hz, 1H), 7.86 (dd, J = 8.2, 1.0 Hz, 1H), 7.72 (dd, J = 8.4, 0.8 Hz, 1H), 7.69-7.65 (m, 1H), 7.41-7.36 (m, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.10-7.06 (m, 4H), 6.96 (d, J = 8.0 Hz, 2H), 6.57 (s, 1H), 6.55 (s, 1H), 4.06 (q, J = 7.2 Hz, 2H), 3.87 (dd, J = 5.6, 1.2 Hz, 2H), 2.24 (s, 3H), 2.18 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.1, 169.7, 156.1, 147.3, 137.8, 136.6, 136.5, 132.6, 132.5, 130.9, 130.7, 130.5, 129.8, 128.3, 127.0, 125.9, 123.6, 121.9, 114.8, 64.2, 60.3, 41.1, 20.6, 14.0; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{29}BrN_3O_3^+$ $[M+H]^+$ 546.1387; found 546.1384.



Ethyl (2-((4,7-dichloroquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetyl)glycinate (6h). white solid; (214 mg, 80% yield); mp 145-146 °C; R_f= 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3304, 3032, 2922, 2853, 1753, 1651, 1593, 1446, 1387, 1185, 1073 $cm^{-1;}$ ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.62 (t, J = 5.8 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.40 (dd, J = 8.8, 2.4 Hz, 1H), 7.13 (d, J = 7.2 Hz, 2H), 7.08 (d, J = 8.4 Hz, 4H), 6.97 (s, 1H), 6.95 (s, 1H), 6.50 (s, 1H), 6.33 (s, 1H), 4.09 (dd, J = 7.2, 1.2 Hz, 1H), 4.05 (dd, J = 7.0, 1.0 Hz, 1H), 3.89 (q, J = 6.0 Hz, 2H), 2.24 (s, 3H), 2.18 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.4, 170.2, 157.2, 148.7, 141.2, 137.9, 137.3, 137.2, 135.9, 132.7, 131.3, 130.9, 130.3, 128.8, 125.9, 125.9, 124.1, 119.8, 111.7, 64.9, 60.8, 41.5, 21.1, 14.5; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{28}Cl_2N_3O_3^+$ $[M+H]^+$ 536.1502; found 536.1504.

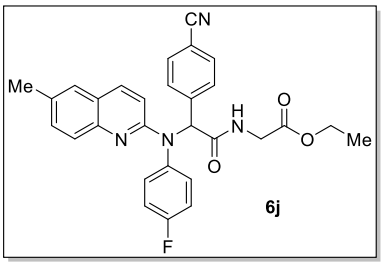


Ethyl 2-(2-((6-methylquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6i).

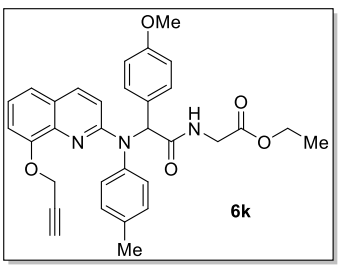


White solid; (204 mg, 85% yield); mp 130-131 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3287, 3054, 2922, 2851, 1731, 1667, 1512, 1479, 1390, 1253, 1148, 1037 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.56 (t, J = 5.8 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.13-7.08 (m, 4H), 7.07-7.02 (m, 2H), 6.96 (d, J= 8.0 Hz, 2H), 6.61 (s, 1H), 6.28 (d, J = 8.8 Hz, 1H), 4.07 (q, J = 7.0 Hz, 2H), 3.88 (d, J = 5.6 Hz, 2H), 2.41 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 172.0, 170.2, 156.5, 145.6, 139.3, 136.8, 136.4, 133.6, 131.7, 131.5, 130.9, 130.0, 128.7, 126.8, 126.7, 123.4, 112.2, 64.5, 60.7, 41.6, 21.2, 21.1, 21.0, 14.5; HRMS (ESI-TOF) m/z: calculated for $C_{30}H_{32}N_3O_3^+$ $[M+H]^+$ 482.2438; found 482.2452.

Ethyl 2-(2-(4-cyanophenyl)-2-((4-fluorophenyl)(6-methylquinolin-2-yl)amino)acetamido)acetate (6j). White solid; (186 mg, 75% yield); mp 161-162 °C; R_f = 0.50 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3281, 3099, 2918, 2855, 2229, 1736, 1663, 1562, 1478, 1391, 1217, 1178, 1031 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.83 (t, J = 5.8 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H), 7.47-7.41 (m, 3H), 7.29 (dd, J = 8.8, 5.4 Hz, 2H), 7.11 (t, J = 8.8 Hz, 2H), 6.75 (s, 1H), 6.34 (d, J = 9.2 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 3.91 (d, J = 5.6 Hz, 2H), 2.42 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 171.0, 170.1,156.1, 145.3, 142.3, 137.8 (d, J = 2.0 Hz), 136.9, 133.8 (d, J = 9.0 Hz), 132.2, 132.0, 131.9, 126.9 (d, J = 12.8 Hz), 123.7, 119.0, 116.5 (d, J = 22 Hz),, 116.3, 111.9, 110.7, 64.2, 60.8, 41.5, 21.2, 14.5; ^{19}F NMR (376 MHz, DMSO-d_6) δ (ppm): -114.36 (s); HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{26}FN_4O_3^+$ $[M+H]^+$ 497.1983; found 497.1992.

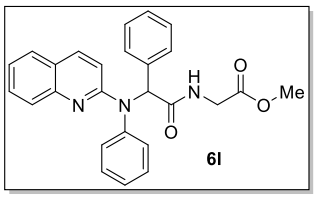


Ethyl (2-(4-methoxyphenyl)-2-((8-(prop-2-yn-1-yloxy)quinolin-2-yl)(*p*-tolyl)amino)acetyl)glycinate (6k). Brown liquid; (198 mg, 76% yield); R_f = 0.50 (hexanes/EtOAc = 7:3); IR (KBr, cm^{-1}) 3422, 3345, 3048, 2924, 2859, 1749, 1617, 1512, 1433, 1383, 1251, 1178, 1094 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.69 (t, J = 5.6 Hz, 1H), 7.86 (d, J = 9.2 Hz, 1H), 7.37 (dd, J = 6.8, 2.4 Hz, 1H), 7.20 (t, J = 8.0 Hz, 4H), 7.11-7.07 (m, 4H), 6.73 (d, J = 8.8 Hz, 2H), 6.54

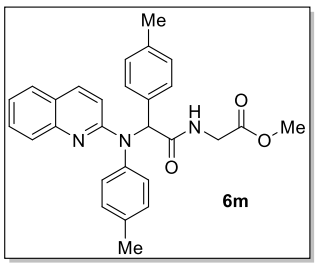


(s, 1H), 6.34 (d, *J* = 9.2 Hz, 1H), 5.04 (d, *J* = 2.0 Hz, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.96 (dd, *J* = 17.6, 5.8 Hz, 1H), 3.82 (dd, *J* = 17.2, 5.6 Hz, 1H), 3.67 (s, 3H), 3.52 (t, *J* = 2.2 Hz, 1H), 2.26 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.7, 170.2, 158.8, 156.0, 151.3, 139.5, 139.4, 137.3, 136.7, 132.2, 131.2, 130.20, 128.4, 124.8, 122.5, 121.9, 115.9, 113.4, 112.7, 80.4, 78.5, 64.7, 60.8, 57.9, 55.4, 41.7, 21.1, 14.4; HRMS (ESI-TOF) m/z: calculated for $C_{32}H_{32}N_3O_5^+$ $[M+H]^+$ 538.2336; found 538.2336.

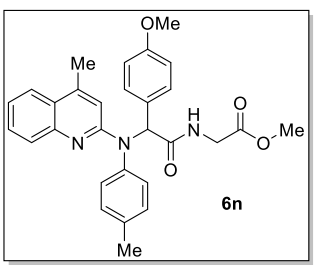
Methyl 2-(2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamido)acetate (6l). White solid; (170 mg, 80% yield); mp 148-149 °C; R_f= 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3260, 3072, 2920, 2854, 1744, 1654, 1593, 1495, 1390, 1222, 1183, 1028 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.69 (t, *J* = 5.8 Hz, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.24-7.19 (m, 6H), 7.18 – 7.11 (m, 4H), 6.68 (s, 1H), 6.34 (d, *J* = 9.2 Hz, 1H), 3.92 (d, *J* = 5.6 Hz, 2H), 3.60 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.9, 170.7, 156.7, 147.2, 141.6, 137.1, 136.4, 131.8, 131.0, 129.9, 129.4, 128.1, 127.9, 127.4, 126.9, 123.6, 122.8, 112.2, 64.9, 52.0, 41.4; HRMS (ESI-TOF) m/z: calculated for $C_{26}H_{24}N_3O_3^+$ $[M+H]^+$ 426.1812; found 426.1811.



Methyl 2-(2-(quinolin-2-yl(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6m). White solid; (185 mg, 82% yield); mp 132-133 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3361, 3021, 2921, 2874, 1739, 1649, 1513, 1470, 1320, 1248, 1140, 1023 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.59 (t, *J* = 5.8 Hz, 1H), 7.85 (d, *J* = 9.2 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.60 – 7.56 (m, 1H), 7.28 – 7.23 (m, 1H), 7.13-7.04 (m, 6H), 6.97 (d, *J* = 7.6 Hz, 2H), 6.62 (s, 1H), 6.30 (d, *J* = 9.2 Hz, 1H), 3.90 (d, *J* = 5.6 Hz, 2H), 3.60 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.0, 170.7, 156.9, 147.2, 139.1, 137.0, 136.6, 133.5, 131.5, 130.9, 130.0, 129.8, 128.7, 127.8, 126.8, 123.5, 122.7, 112.2, 64.6, 52.0, 41.4, 21.1, 21.0; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{28}N_3O_3^+$ $[M+H]^+$ 454.2125; found 454.2124.

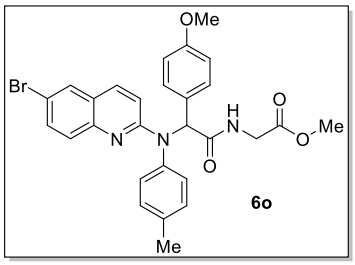


Methyl (2-(4-methoxyphenyl)-2-((4-methylquinolin-2-yl)(*p*-tolyl)amino)acetyl)glycinate (6n). White solid; (205 mg, 85% yield); mp 153-154 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3278, 3069, 2926, 2838, 1752, 1657, 1512, 1468, 1393, 1215, 1179, 1036 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.55 (t, *J* = 5.8 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.61-7.55 (m, 1H), 7.30-7.25 (m,



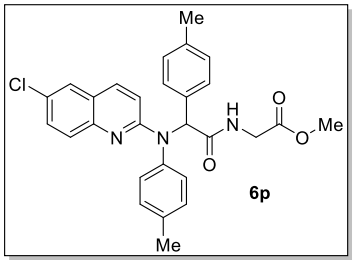
1H), 7.06-7.14 (m, 6H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.60 (s, 1H), 6.18 (s, 1H), 3.89 (d, *J* = 5.6 Hz, 2H), 3.67 (s, 3H), 3.60 (s, 3H), 2.37 (s, 3H), 2.25 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.2, 170.8, 158.8, 156.7, 147.3, 144.4, 139.1, 136.4, 132.2, 131.5, 130.0, 129.6, 128.5, 127.3, 124.2, 123.7, 122.6, 113.5, 112.1, 64.1, 55.4, 52.0, 41.4, 21.1, 19.0; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{30}N_3O_4^+$ $[M+H]^+$ 484.2231; found 484.2228.

Methyl 2-(2-((6-bromoquinolin-2-yl)(*p*-tolyl)amino)-2-(4-methoxyphenyl)acetamido)acetate (6o). White solid; (219 mg, 80% yield); mp 120-121 °C;



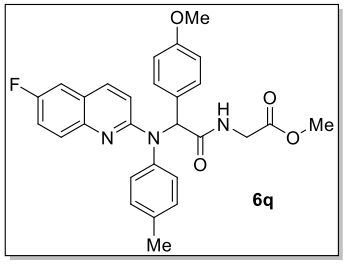
R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3251, 3054, 2923, 2855, 1746, 1650, 1513, 1466, 1390, 1361, 1252, 1181, 1031 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.59 (t, *J* = 5.8 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.83 (d, *J* = 9.2 Hz, 1H), 7.69 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.14 – 7.05 (m, 6H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.54 (s, 1H), 6.32 (d, *J* = 9.2 Hz, 1H), 3.90 (dd, *J* = 8.0, 6.0 Hz, 2H), 3.67 (s, 3H), 3.60 (s, 3H), 2.24 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.1, 170.8, 158.9, 157.1, 146.0, 138.7, 136.8, 136.1, 132.6, 132.2, 131.5, 130.1, 129.6, 128.9, 128.0, 124.9, 114.6, 113.5, 113.0, 64.4, 55.4, 52.0, 41.4, 21.0; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{27}BrN_3O_4^+$ $[M+H]^+$ 548.1179; found 548.1175.

Methyl 2-(2-((6-chloroquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6p).

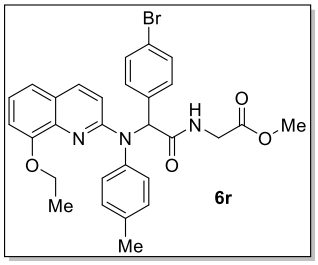


White solid; (200 mg, 82% yield); mp 155-156 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3292, 3094, 2926, 2858, 1732, 1662, 1513, 1488, 1391, 1235, 1074 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.60 (t, *J* = 5.8 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.58 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.12 - 7.04 (m, 6H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.56 (s, 1H), 6.33 (d, *J* = 9.2 Hz, 1H), 3.90 (d, *J*= 5.6 Hz, 2H), 3.60 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.9, 170.7, 157.1, 145.9, 138.7, 137.0, 136.7, 136.2, 133.2, 131.5, 130.9, 130.1, 128.7, 126.5, 124.2, 113.1, 64.6, 52.0, 41.4, 21.1; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{27}ClN_3O_3^+$ $[M+H]^+$ 488.1735; found 488.1735.

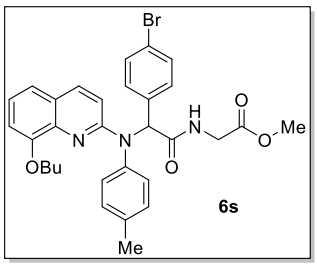
Methyl (2-((6-fluoroquinolin-2-yl)(*p*-tolyl)amino)-2-(4-methoxyphenyl)acetyl)glycinate (6q). White solid; (190 mg, 81% yield); mp 110-111 ºC; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3338, 3054, 2925, 2853, 1755, 1673, 1512, 1390, 1248, 1179, 1027 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.58 (t, J = 5.8 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.75-7.68 (m, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.14-7.04 (m, 6H), 6.71 (d, J = 8.8 Hz, 2H), 6.52 (s, 1H), 6.34 (d, J = 9.2 Hz, 1H), 3.90 (dd, J = 6.0, 3.0 Hz, 2H), 3.66 (s, 3H), 3.60 (s, 3H), 2.24 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.18, 170.8, 158.9, 156.6, 144.3, 139.0, 136.7, 136.5, 136.4 (d, J = 4.0 Hz), 132.2, 131.6, 130.1, 129.0, 128.9 (d, J = 9.0 Hz), 128.3, 123.6 (d, J = 10 Hz), 119.1, 118.94, 113.5, 113.1, 111.3 (d, J = 21 Hz), 64.3, 55.4, 52.0, 41.4, 21.0; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{27}FN_3O_4^+$ $[M+H]^+$ 488.1980; found 488.1981.



Methyl 2-(2-(4-bromophenyl)-2-((8-ethoxyquinolin-2-yl)(*p*-tolyl)amino)acetamido)acetate (6r). Orange liquid; (219 mg, 78% yield); R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3325, 3033, 2923, 2859, 1752, 1673, 1501, 1433, 1343, 1258, 1180, 1094 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.95 (t, J = 5.6 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.27 (dd, J = 8.0, 0.8 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.15-7.12 (m, 4H), 7.10 - 7.06 (m, 1H), 6.55 (s, 1H), 6.38 (d, J = 8.8 Hz, 1H), 4.22 - 4.13 (m, 2H), 4.00 (dd, J = 17.2, 6.0 Hz, 1H), 3.82 (dd, J = 17.2, 5.6 Hz, 1H), 3.60 (s, 3H), 2.28 (s, 3H), 1.43 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.1, 170.70, 155.6, 153.1, 139.8, 138.6, 137.3, 136.9, 136.1, 132.9, 130.9, 130.7, 130.4, 124.6, 123.1, 121.1, 120.0, 112.7, 112.0, 65.2, 64.7, 52.1, 41.5, 21.0, 15.2; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{29}BrN_3O_4^+$ $[M+H]^+$ 562.1336; found 562.1338.

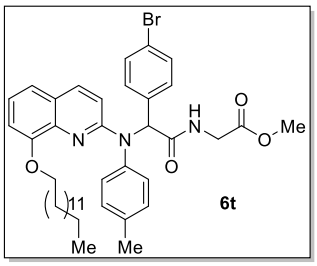


Methyl 2-(2-(4-bromophenyl)-2-((8-butoxyquinolin-2-yl)(*p*-tolyl)amino)acetamido)acetate (6s). Brown liquid; (221 mg, 75% yield); R_f = 0.50 (hexanes/EtOAc = 9:1); IR (KBr, cm^{-1}) 3426, 3027, 2957, 2876, 1754, 1671, 1564, 1434, 1343, 1259, 1180, 1097 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92 (t, J = 5.6 Hz, 1H), 7.92 - 7.90 (m, 1H), 7.85 (d, J = 9.2 Hz, 1H), 7.55 (t, J = 8.2 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.26 (dd, J = 7.6, 1.0 Hz, 1H), 7.15-7.13 (m, 3H), 7.08 (dd, J = 7.6, 0.8 Hz, 1H), 6.65 (s, 1H), 6.41 (d, J = 9.2 Hz, 1H), 4.11

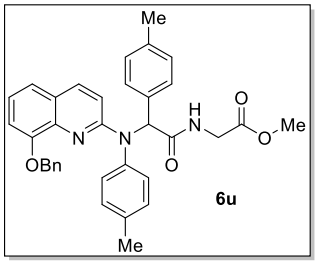


(dd, *J* = 11.2, 6.4 Hz, 2H), 3.98 (dd, *J* = 17.2, 6.0 Hz, 1H), 3.82 (dd, *J* = 17.2, 5.6 Hz, 1H), 3.61 (s, 3H), 2.28 (s, 3H), 1.83 – 1.75 (m, 2H), 1.55 – 1.45 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 170.9, 170.6, 166.5, 155.6, 153.2, 139.9, 138.6, 137.3, 136.9, 136.2, 133.8, 133.1, 132.8, 130.9, 130.4, 129.2, 128.3, 124.6, 123.1, 121.0, 119.9, 112.8, 111.8, 68.7, 65.0, 52.1, 41.5, 31.4, 21.0, 19.3, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{31}H_{33}BrN_3O_4^+$ $[M+H]^+$ 590.1649; found 590.1650.

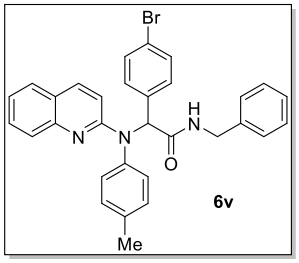
Methyl 2-(2-(4-bromophenyl)-2-((8-(tetradecyloxy)quinolin-2-yl)(p-tolyl)amino)acetamido)acetate (6t). Brown oil liquid; (255 mg, 70% yield); R_f = 0.50 (hexanes/EtOAc = 9:1); IR (KBr, cm^{-1}) 3439, 3034, 2924, 2853, 1755, 1676, 1564, 1434, 1344, 1259, 1180, 1098 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.93 (t, *J* = 5.4 Hz, 1H), 7.85 (d, *J* = 9.2 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.22 – 7.08 (m, 5H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.67 (s, 1H), 6.41 (d, *J*= 9.2 Hz, 1H), 4.16 – 4.03 (m, 2H), 3.97 (dd, *J* = 17.2, 5.8 Hz, 1H), 3.83 (dd, *J* = 17.2, 6.0 Hz, 1H), 3.60 (s, 3H), 2.28 (s, 3H),1.86-1.74 (m, 2H),1.52 – 1.43 (m, 2H), 1.35-1.19 (m, 20H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 170.8, 170.5, 155.6, 153.2, 139.9, 138.5, 137.3, 136.8, 136.2, 132.7, 130.8, 130.5, 130.4, 124.7, 123.1, 121.0, 119.8, 112.8, 111.6, 69.0, 51.9, 41.5, 31.8, 29.6, 29.5, 29.4, 29.2, 26.1, 22.5, 21.0, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{41}H_{53}BrN_3O_4^+$ $[M+H]^+$ 730.3214; found 730.3222.



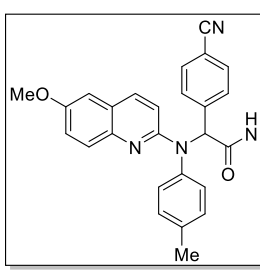
Methyl 2-(2-((8-(benzyloxy)quinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6u). Orange liquid; (218 mg, 78% yield); R_f = 0.50 (hexanes/EtOAc = 9:1); IR (KBr, cm^{-1}) 3424, 3042, 2953, 2853, 1751, 1669, 1512, 1434, 1343, 1259, 1179, 1097 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.84 (s, 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.28 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.16-7.10 (m, 6H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.61 (s, 1H), 6.42 (d, *J*= 9.2 Hz, 1H), 5.30 (q, *J* = 12.6 Hz, 2H), 3.83 (dd, *J* = 17.6, 6.2 Hz, 1H), 3.58 (d, *J* = 5.6 Hz, 1H), 3.55 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 171.8, 170.6, 155.7, 152.4, 140.5, 138.5, 137.8, 137.4, 137.0, 136.8, 133.4, 130.4, 130.0, 128.8, 128.1, 127.7, 124.6, 123.1, 120.4, 113.2, 112.5, 70.5, 52.0, 41.1, 21.0, 20.9; HRMS (ESI-TOF) m/z: calculated for $C_{35}H_{34}N_3O_4^+$ $[M+H]^+$ 560.2544; found 560.2547.



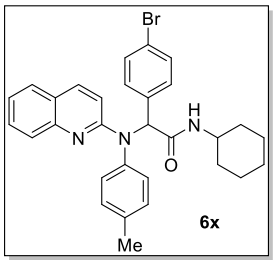
***N*-benzyl-2-(4-bromophenyl)-2-(quinolin-2-yl(*p*-tolyl)amino)acetamide (6v).** White solid; (214 mg, 80% yield); R_f= 0.50 (hexanes/EtOAc = 9:1); mp 190-191 °C; IR (KBr, cm^{-1}) 3267, 3065, 2915, 2874, 1660, 1558, 1469, 1388, 1246, 1069 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.75 (t, J = 6.0 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.58-7.52 (m, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.23 – 7.19 (m, 3H), 7.13 – 7.07 (m, 7H), 7.01 (d, J = 8.0 Hz, 2H), 6.45 (s, 1H), 6.23 (d, J = 8.8 Hz, 1H), 4.43 (dd, J = 15.6, 6.8 Hz, 1H), 4.12 (dd, J = 15.4, 5.4 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 171.2, 156.9, 147.2, 140.0, 138.9, 137.1, 136.9, 136.3, 133.0, 131.8, 131.1, 130.2, 129.8, 128.5, 127.9, 127.4, 126.9, 126.8, 123.6, 122.8, 121.2, 112.2, 64.7, 42.6, 21.1; HRMS (ESI-TOF) m/z: calculated for $C_{31}H_{27}BrN_3O^+$ $[M+H]^+$ 536.1332; found 536.1331.



***N*-benzyl-2-(4-cyanophenyl)-2-((6-methoxyquinolin-2-yl)(*p*-tolyl)amino)acetamide (6w).** Light yellow solid; (205 mg, 80% yield); R_f= 0.50 (hexanes/EtOAc = 9:1); mp 170-171 °C; IR (KBr, cm^{-1}) 3409, 3062, 2922, 2852, 2229, 1659, 1602, 1562, 1499, 1363, 1230, 1162, 1030 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.89 (t, J = 6.0 Hz, 1H), 7.83 (d, J = 9.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 9.2 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.31 – 7.24 (m, 3H), 7.21 – 7.13 (m, 7H), 7.07 (d, J = 8.4 Hz, 2H), 6.54 (s, 1H), 6.34 (d, J = 8.8 Hz, 1H), 4.49 (dd, J = 15.4, 6.6Hz, 1H), 4.19 (dd, J = 15.4, 5.4 Hz, 1H), 3.83 (s, 3H), 2.24 (s, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 170.4, 155.2, 154.7, 142.4, 142.0, 139.5, 138.9, 136.5, 136.0, 131.6, 131.3, 131.2, 129.8, 128.1, 127.7, 127.1, 127.0, 126.6, 123.8, 120.9, 118.7, 113.4, 112.0, 110.1, 106.5, 64.8, 55.3, 42.3, 20.6; HRMS (ESI-TOF) m/z: calculated for $C_{33}H_{29}N_4O_2^+$ $[M+H]^+$ 513.2285; found 513.2284.

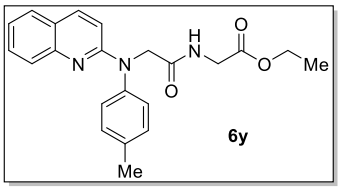


2-(4-bromophenyl)-*N*-cyclohexyl-2-(quinolin-2-yl(*p*-tolyl)amino)acetamide (6x). White solid; (184 mg, 70% yield); R_f = 0.50 (hexanes/EtOAc = 9:1); mp 175-176 °C; IR (KBr, cm^{-1}) 3299, 3069, 2924, 2850, 1655, 1546, 1472, 1391, 1246, 1104, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 8.13 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.64 (t, J = 8.2 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.33 – 7.30 (m, 2H), 7.23 (m, 1H), 7.14 (d, J = 8.4 Hz, 4H), 7.06 (d, J = 8.0 Hz, 2H), 6.37 (s, 1H), 6.31 (d, J = 9.2 Hz, 1H), 3.61 (m, 1H), 2.26 (s, 3H), 1.73 – 1.52 (m, 5H), 1.27 – 1.10 (m, 5H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 170.0, 156.8, 147.2, 139.0, 136.8, 136.7, 136.5, 132.7, 131.6,

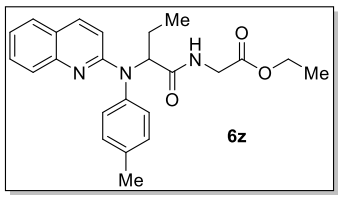


131.0, 130.0, 129.7, 127.8, 126.5, 123.5, 122.6, 121.0, 112.1, 64.7, 48.1, 32.8, 32.7, 25.6, 25.1, 25.0, 21.1; HRMS (ESI-TOF) m/z: calculated for $C_{30}H_{31}BrN_3O^+$ $[M+H]^+$ 528.1645; found 528.1646.

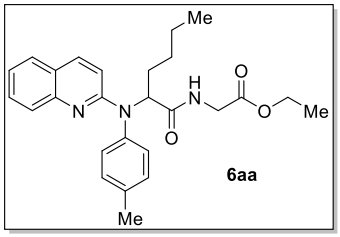
Ethyl *N*-(quinolin-2-yl)-*N*-(*p*-tolyl)glycylglycinate (6y). white solid; (113 mg, 60% yield); R_f = 0.50 (hexanes/EtOAc = 8:2); mp 125-126 °C; IR (KBr, cm^{-1}) 3419, 3051, 2924, 2854, 1746, 1618, 1513, 1428, 1389, 1200, 1121, 1019 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.43 (t, J = 5.8 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.58-7.52 (m, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.29 – 7.22 (m, 3H), 6.69 (d, J = 9.2 Hz, 1H), 4.68 (s, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.87 (d, J = 6.0 Hz, 2H), 2.35 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 170.3, 170.2, 156.3, 147.4, 142.6, 137.2, 136.3, 130.8, 129.9, 127.9, 127.7, 126.7, 123.6, 122.9, 111.6, 60.8, 53.7, 41.2, 21.0, 14.5; HRMS (ESI-TOF) m/z: calculated for $C_{22}H_{24}N_3O_3^+$ $[M+H]^+$ 378.1812; found 378.1818.



Ethyl (2-(quinolin-2-yl(*p*-tolyl)amino)butanoyl)glycinate (6z). white solid; (109 mg, 54% yield); R_f = 0.50 (hexanes/EtOAc = 9:1); mp 138-139 °C; IR (KBr, cm^{-1}) 3426, 3062, 2924, 2852, 1744, 1619, 1512, 1426, 1394, 1232, 1155, 1022 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.46 (t, J = 6.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.60-7.55 (m, 1H), 7.32 (t, J = 8.8 Hz, 3H), 7.29 – 7.23 (m, 2H), 6.39 (d, J = 8.8 Hz, 1H), 5.52 (t, J = 7.4 Hz, 1H), 4.05 (q, J = 7.0 Hz, 2H), 3.88 (dd, J = 6.0, 2.4 Hz, 2H), 2.37 (s, 3H), 1.77-1.69 (m, 1H), 1.57 – 1.49 (m, 1H), 1.13 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 172.5, 170.3, 157.1, 147.1, 138.4, 137.3, 137.2, 130.6, 130.5, 129.9, 127.8, 126.7, 123.5, 122.8, 112.4, 60.8, 60.5, 41.4, 23.0, 21.1, 14.4, 11.6; HRMS (ESI-TOF) m/z: calculated for $C_{24}H_{28}N_3O_3^+$ $[M+H]^+$ 406.2125; found 406.2131.



Ethyl (2-(quinolin-2-yl(*p*-tolyl)amino)hexanoyl)glycinate (6aa). Pale yellow liquid; (143 mg, 66% yield); R_f = 0.50 (hexanes/EtOAc = 9:1); IR (KBr, cm^{-1}) 3394, 3053, 2956, 2857, 1747, 1683, 1511, 1426, 1393, 1245, 1194, 1020 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.44 (t, J = 5.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.69 (dd, J = 15.0, 8.2 Hz, 2H), 7.57 (m, 1H), 7.31 (m, 4H), 7.27 – 7.23 (m, 1H), 6.40 (d, J = 9.2 Hz, 1H), 5.67 (t, J = 7.4 Hz, 1H), 4.05 (q, J = 7.0 Hz, 2H), 3.90 – 3.85 (m, 2H), 2.37 (s, 3H), 1.77 – 1.69 (m, 1H), 1.54 – 1.46 (m, 1H), 1.32 (dd, J = 14.6, 7.0 Hz, 2H), 1.27 – 1.19 (m,



2H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.5, 170.3, 157.1, 147.2, 138.4, 137.3, 137.2, 130.6, 130.4, 129.9, 127.8, 126.7, 123.6, 122.8, 112.4, 60.8, 58.7, 41.5, 29.2, 28.6, 22.5, 21.1, 14.4, 14.2; HRMS (ESI-TOF) m/z: calculated for $C_{26}H_{32}N_3O_3^+$ $[M+H]^+$ 434.2438; found 434.2433.

3A.7. References

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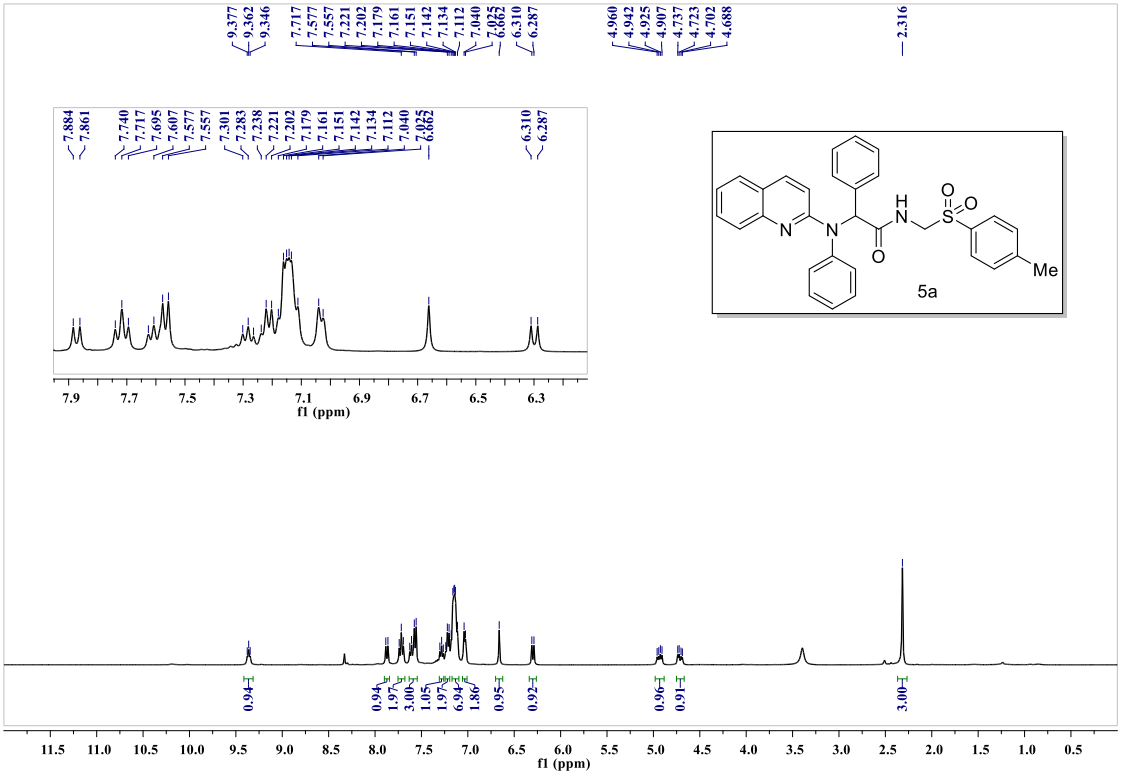
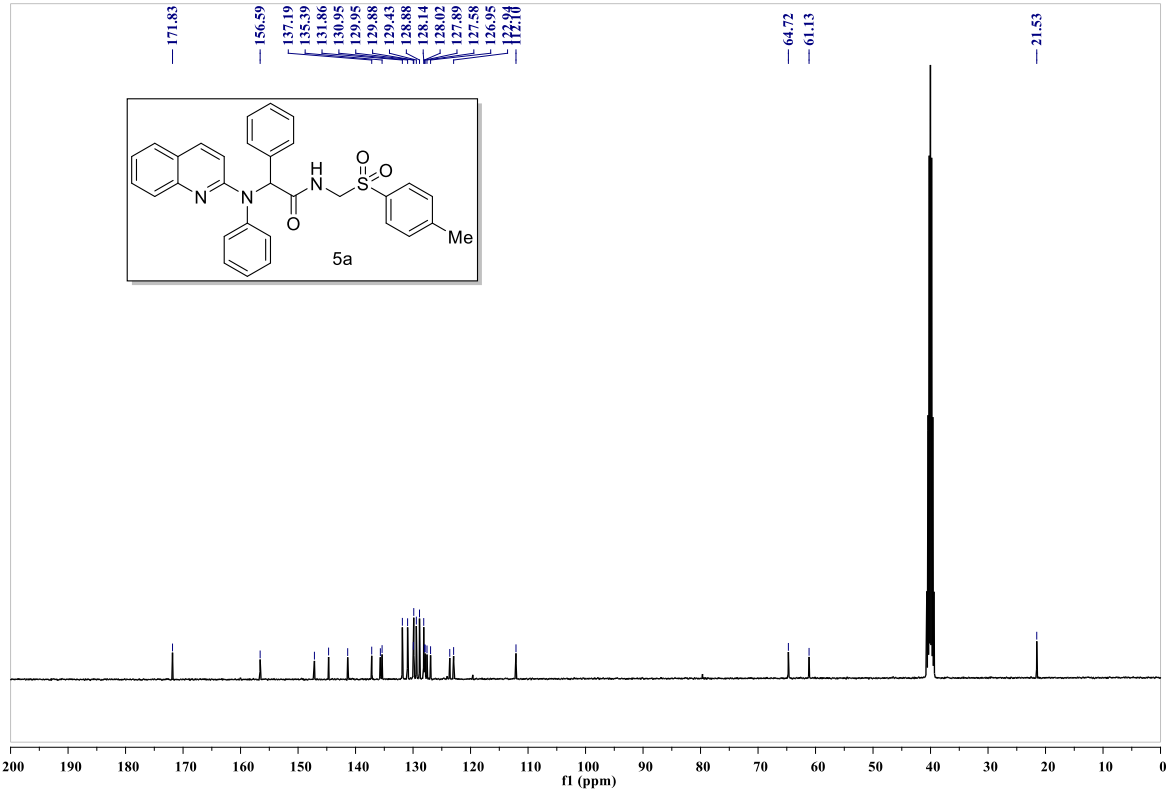
3A.8. Selected NMR (^{1}H and ^{13}C) and HRMS Spectra

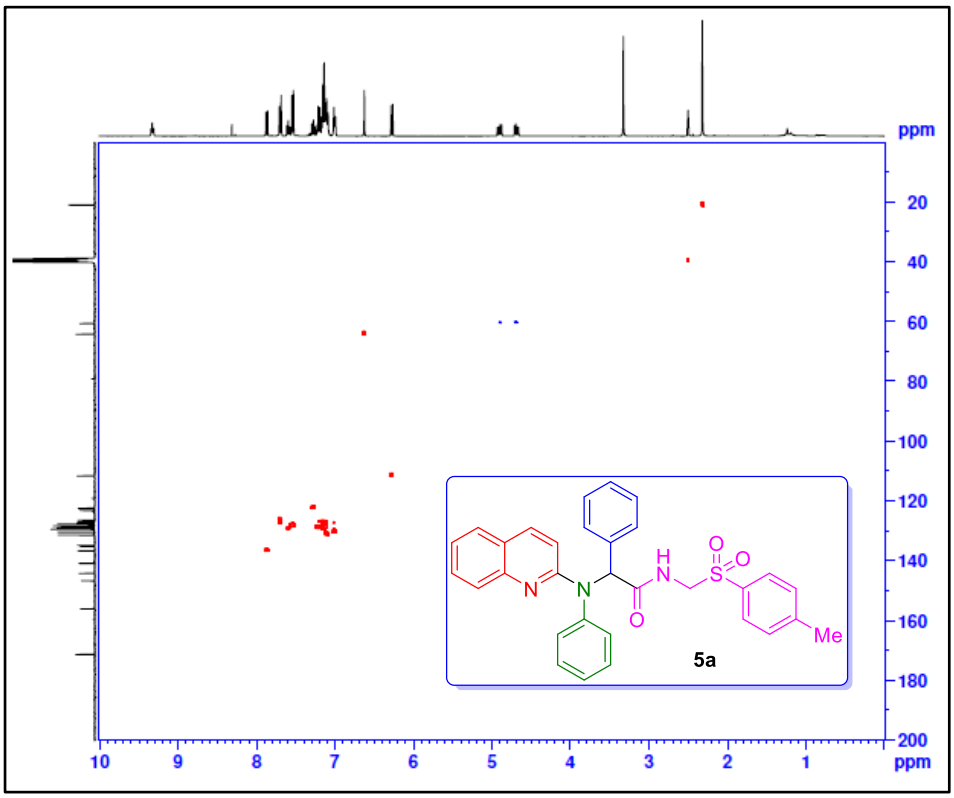
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 2-phenyl-2-(phenyl(quinolin-2-yl)amino)-*N*-(tosylmethyl)acetamide (5a)



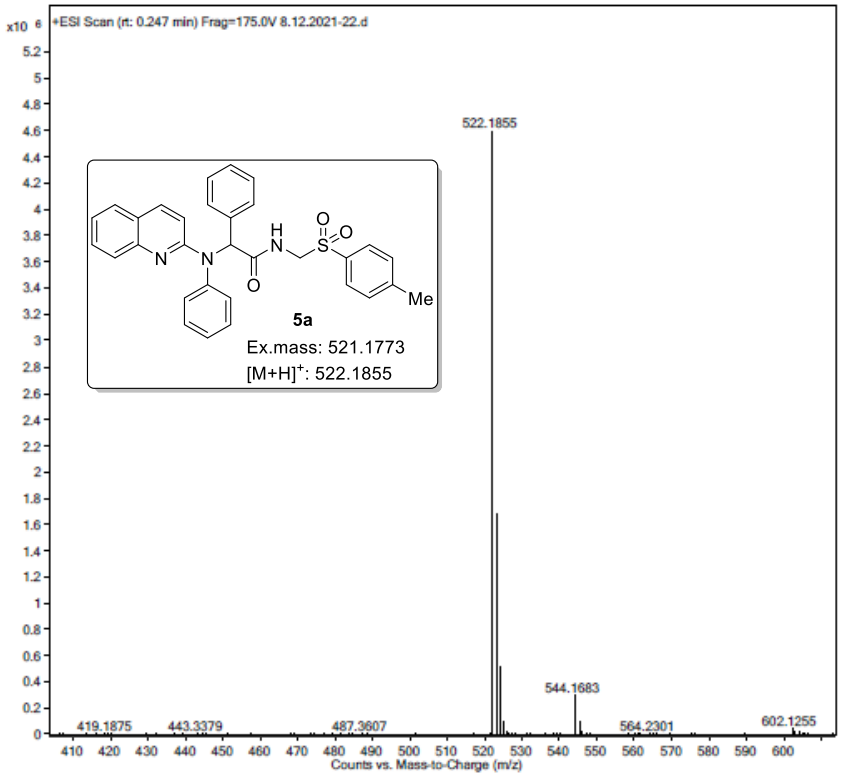
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 2-phenyl-2-(phenyl(quinolin-2-yl)amino)-*N*-(tosylmethyl)acetamide (5a)



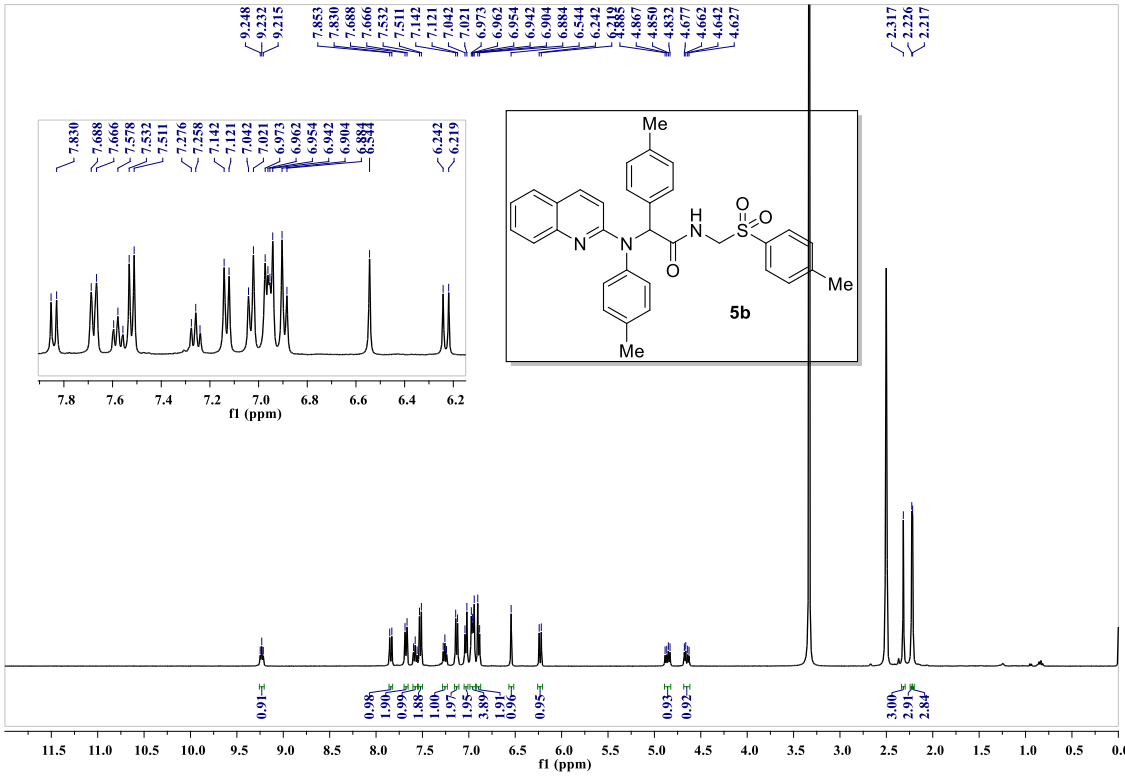
HSQC spectrum of 2-phenyl-2-(phenyl(quinolin-2-yl)amino)-*N*-(tosylmethyl)acetamide (5a)



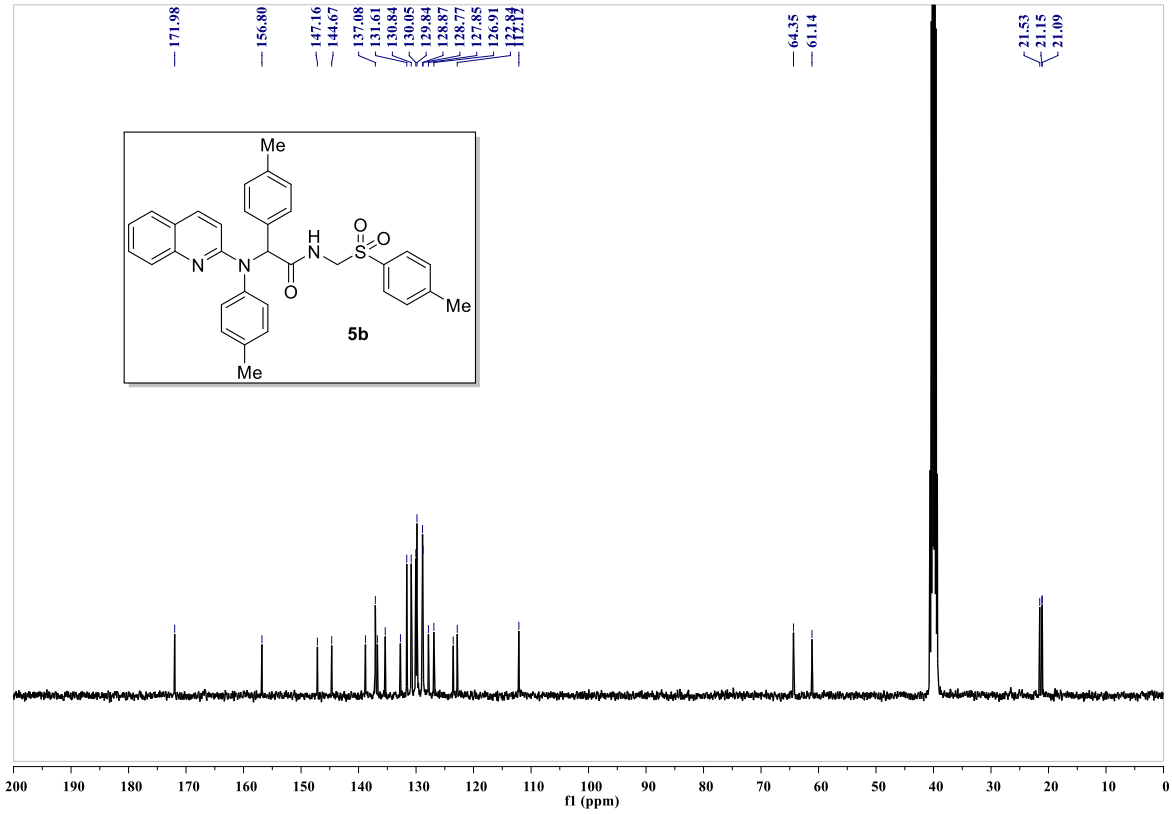
HRMS spectrum of 2-phenyl-2-(phenyl(quinolin-2-yl)amino)-*N*-(tosylmethyl)acetamide (5a)



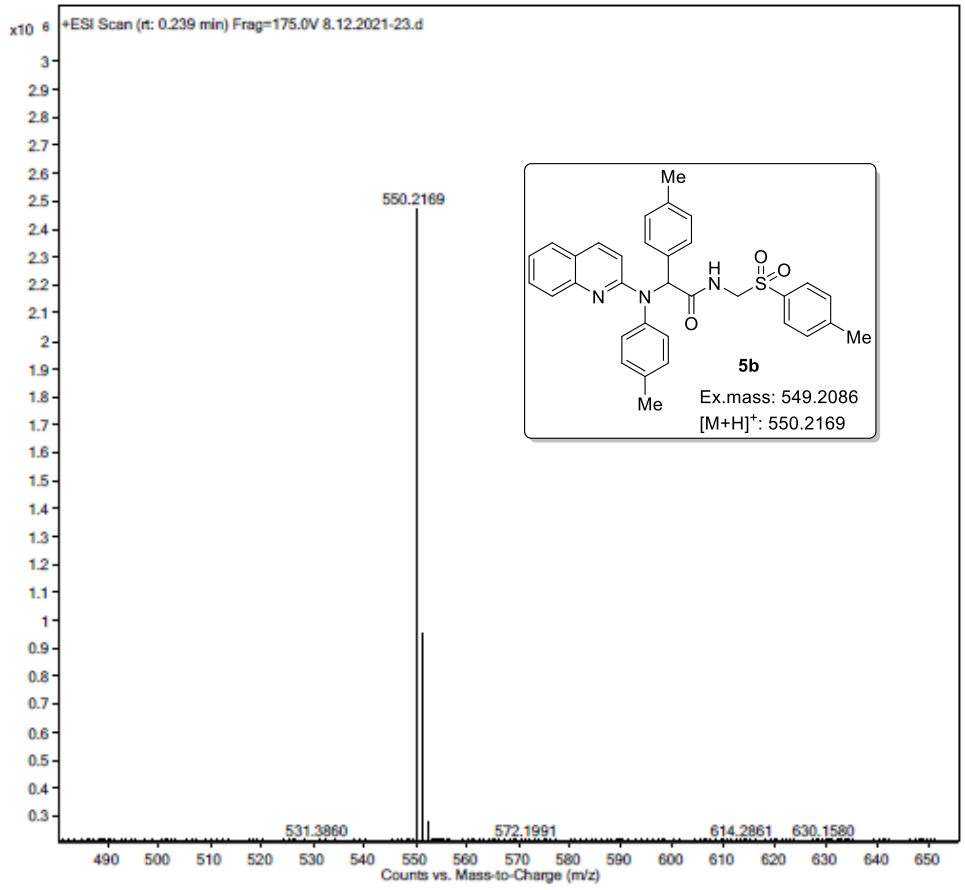
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 2-(quinolin-2-yl(*p*-tolyl)amino)-2-(*p*-tolyl)-*N*-(tosylmethyl)acetamide (5b)



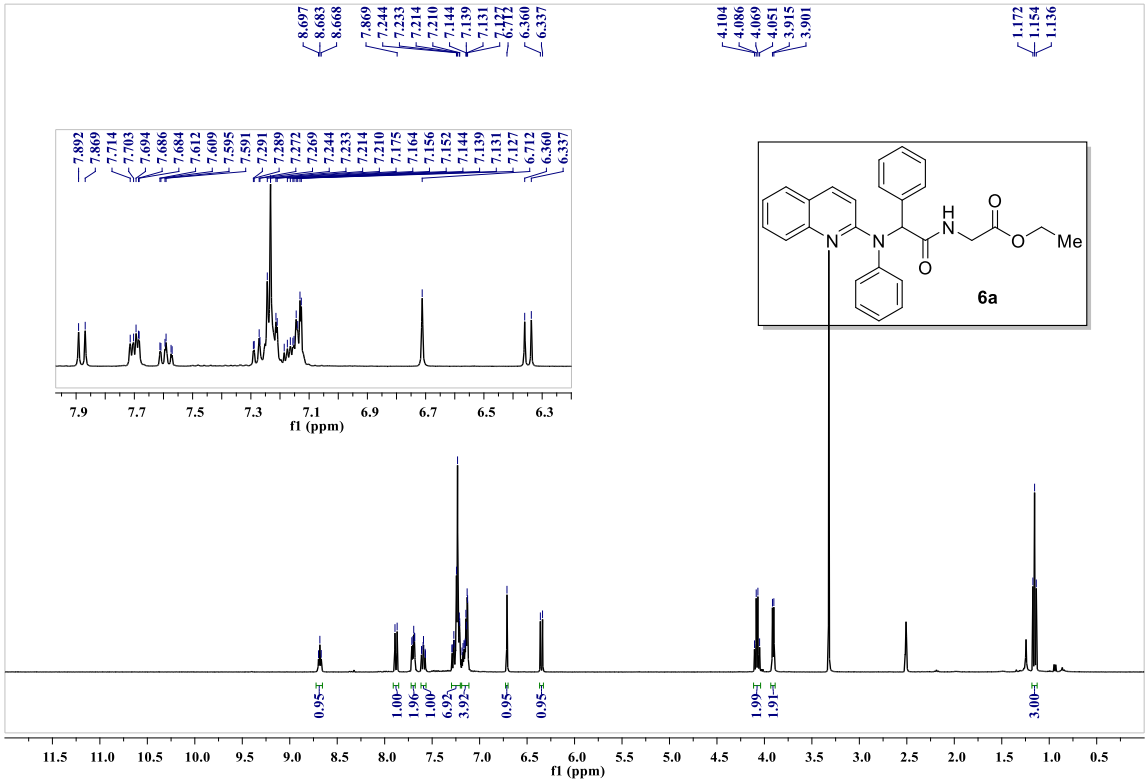
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 2-(quinolin-2-yl(*p*-tolyl)amino)-2-(*p*-tolyl)-*N*-(tosylmethyl)acetamide (5b)



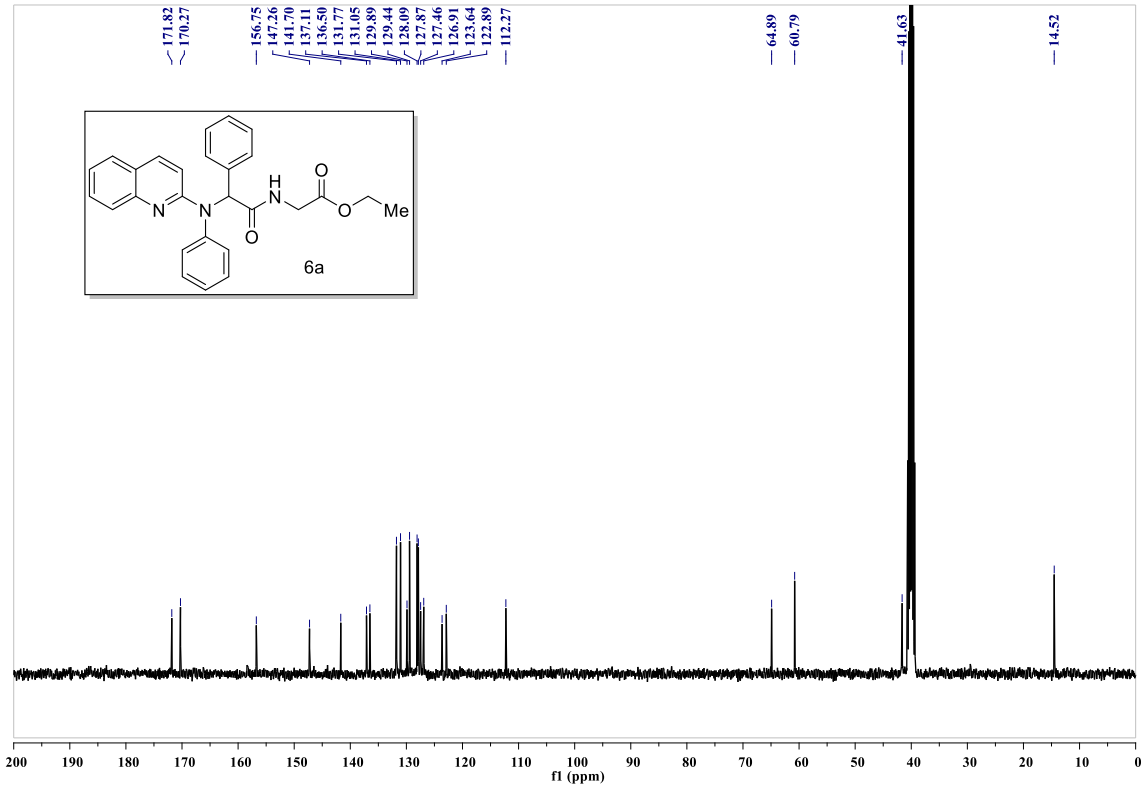
HRMS spectrum of 2-(quinolin-2-yl(*p*-tolyl)amino)-2-(*p*-tolyl)-*N*-(tosylmethyl)acetamide (5b)



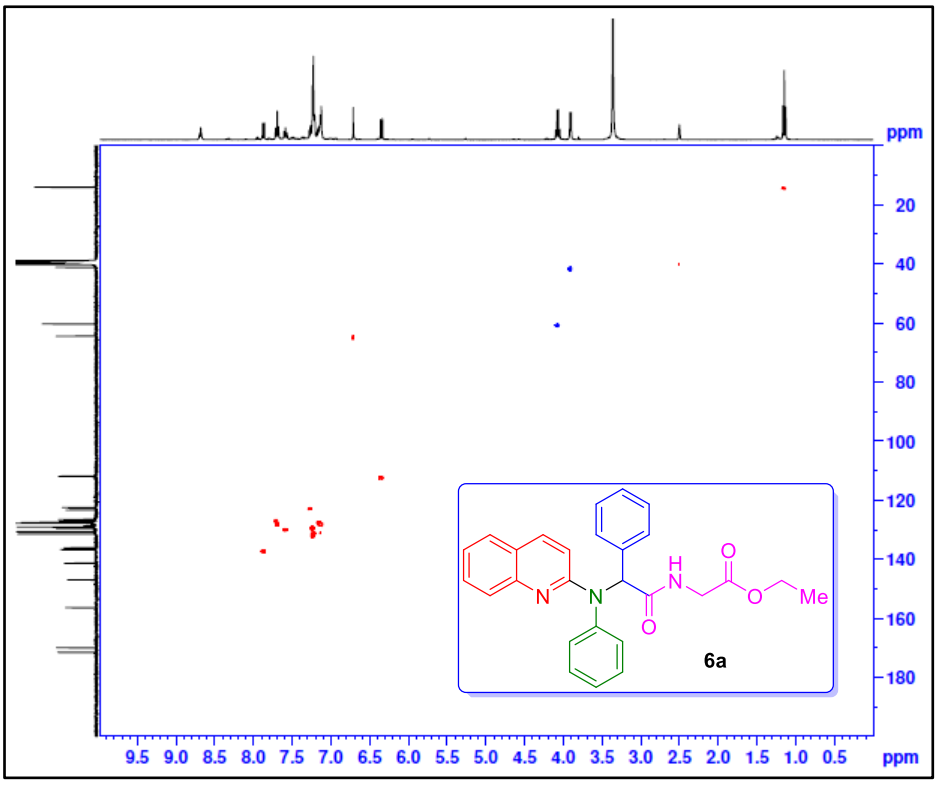
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of ethyl 2-(2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamido)acetate (6a)



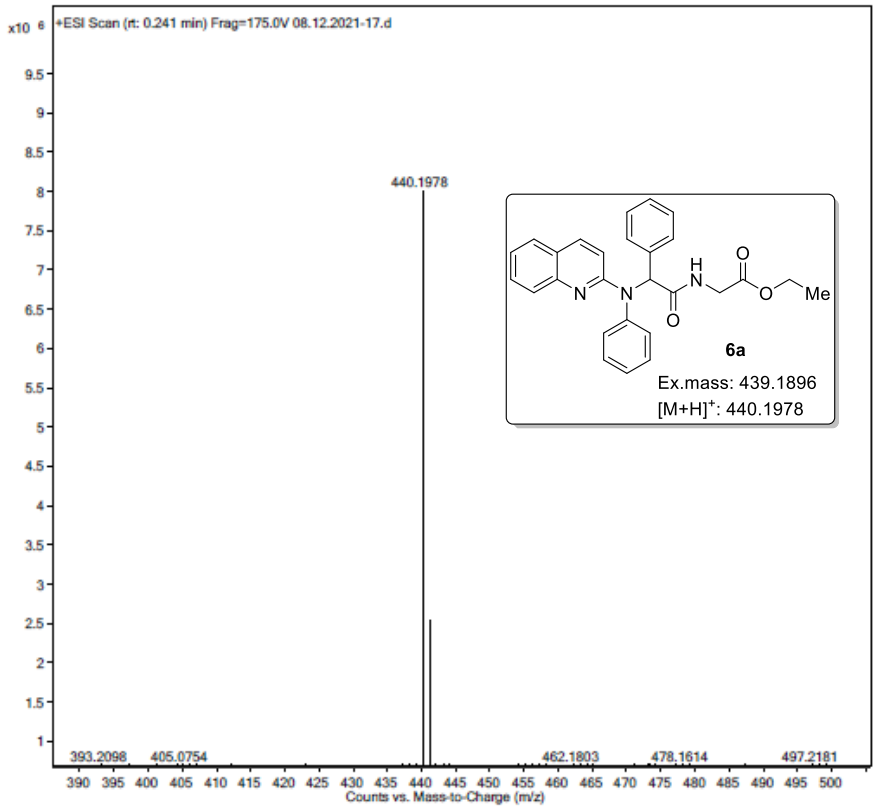
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of ethyl 2-(2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamido)acetate (6a)



HSQC spectrum of ethyl 2-(2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamido)acetate (6a)



HRMS spectrum of ethyl 2-(2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamido)acetate (6a)



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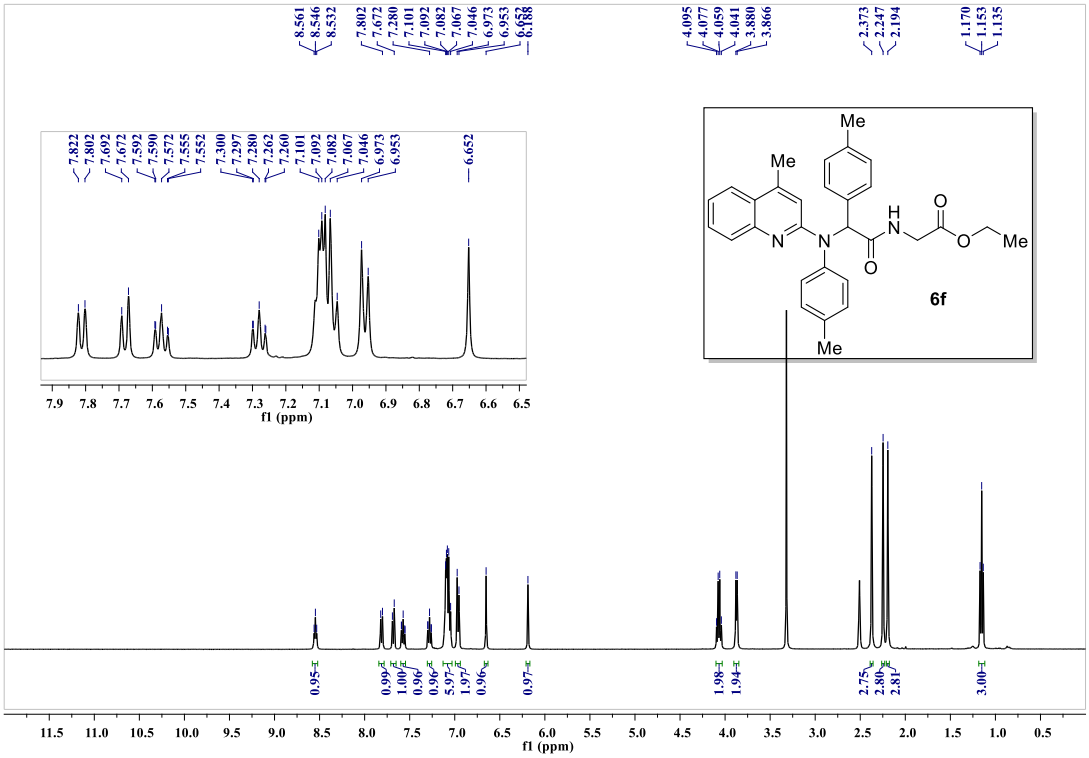
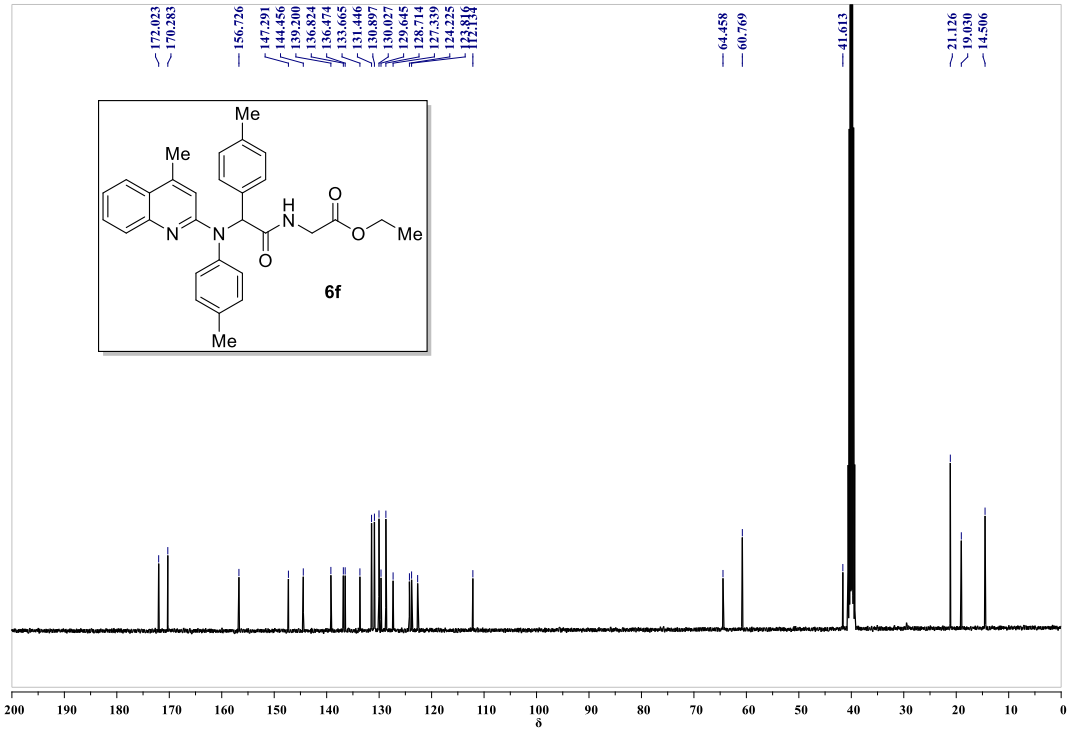
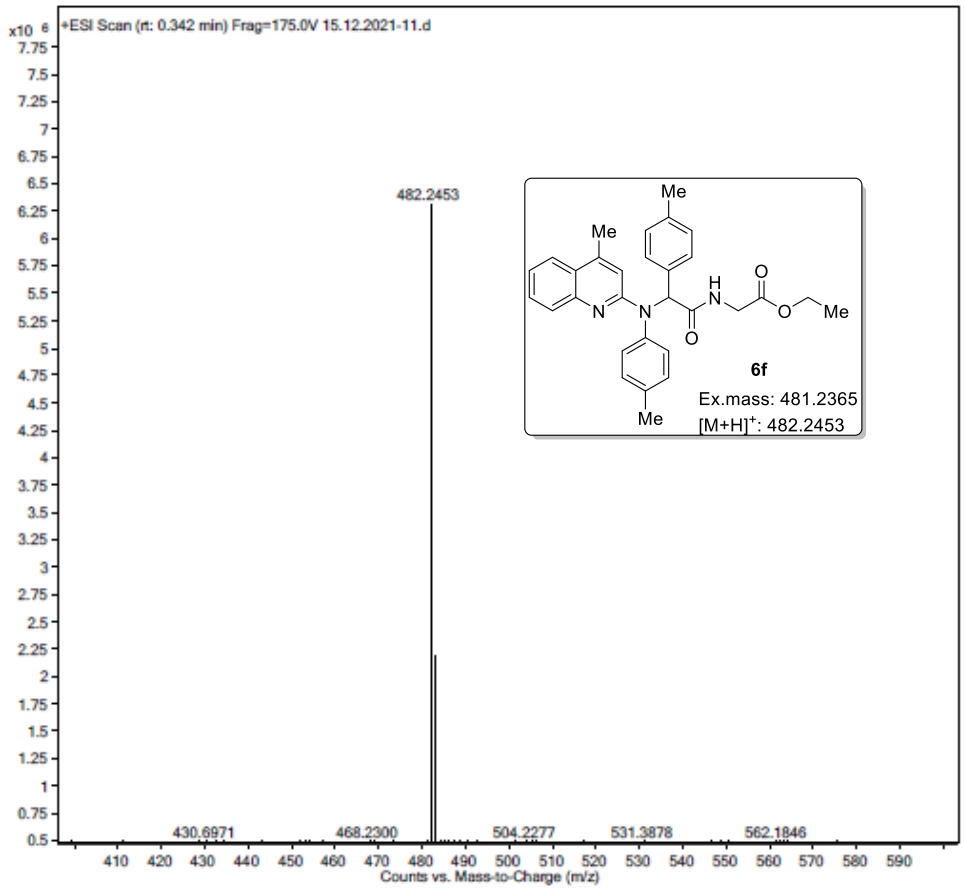


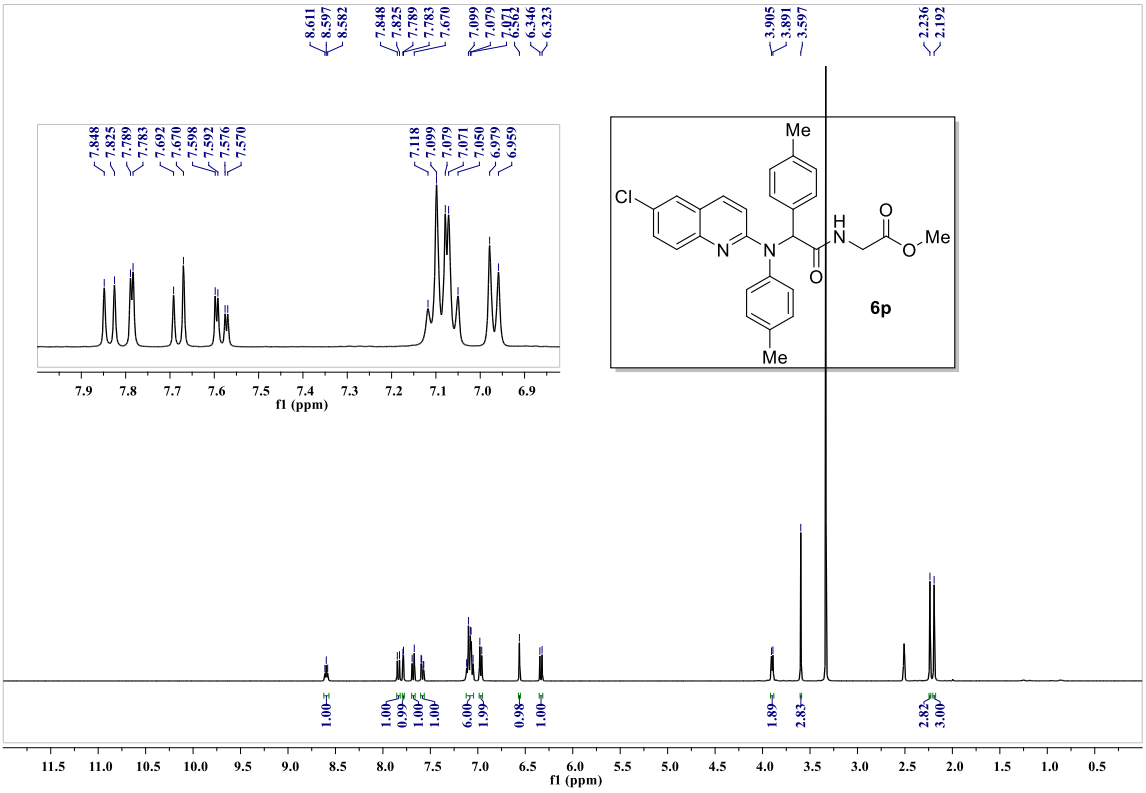
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of ethyl 2-(2-((4-methylquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6f)



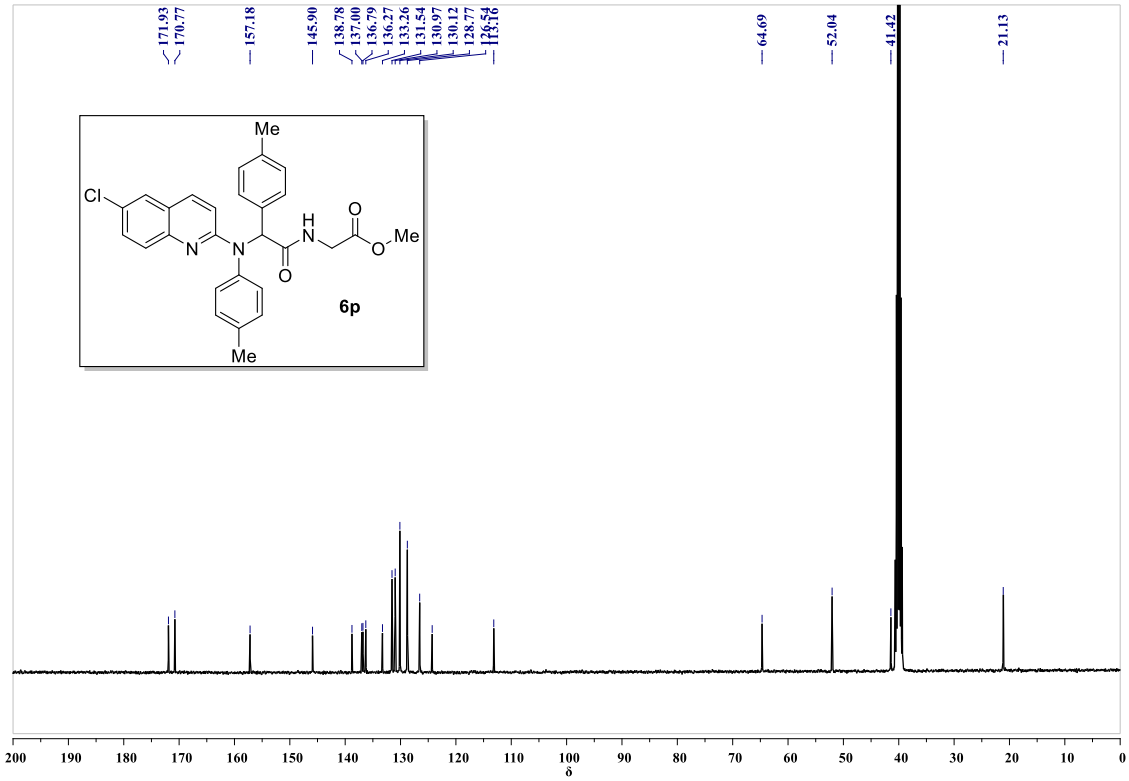
HRMS spectrum of ethyl 2-(2-((4-methylquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6f)



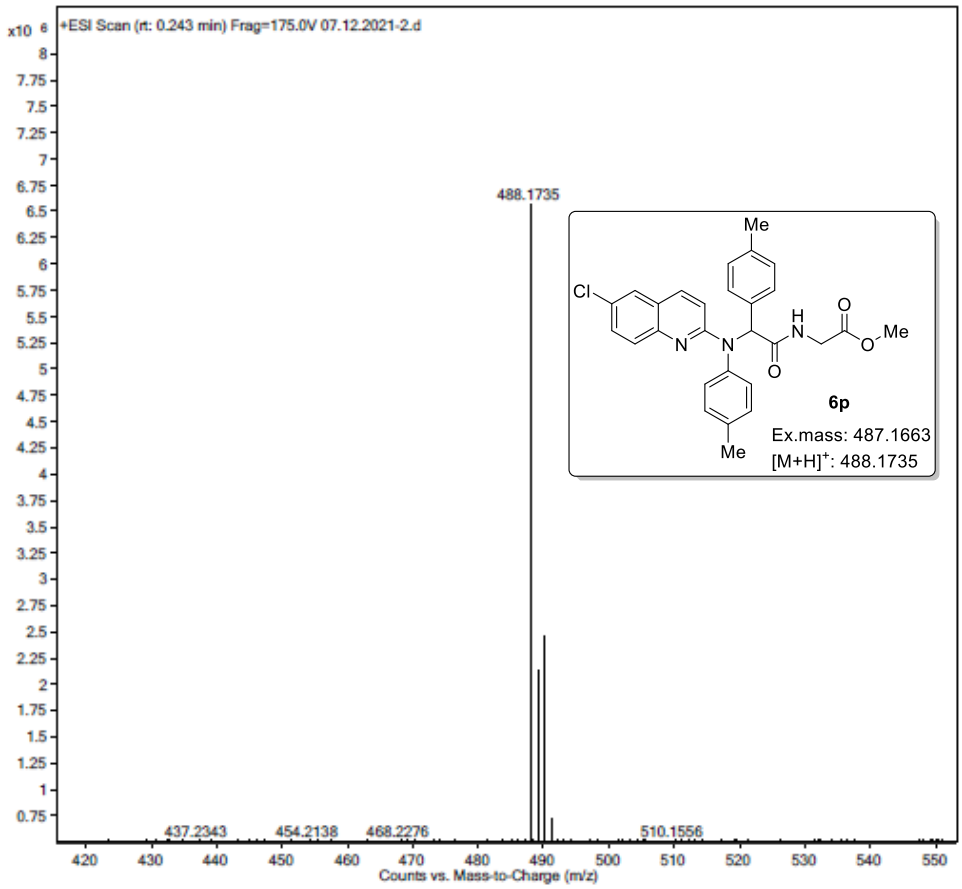
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of methyl 2-(2-((6-chloroquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6p)



^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of methyl 2-(2-((6-chloroquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6p)

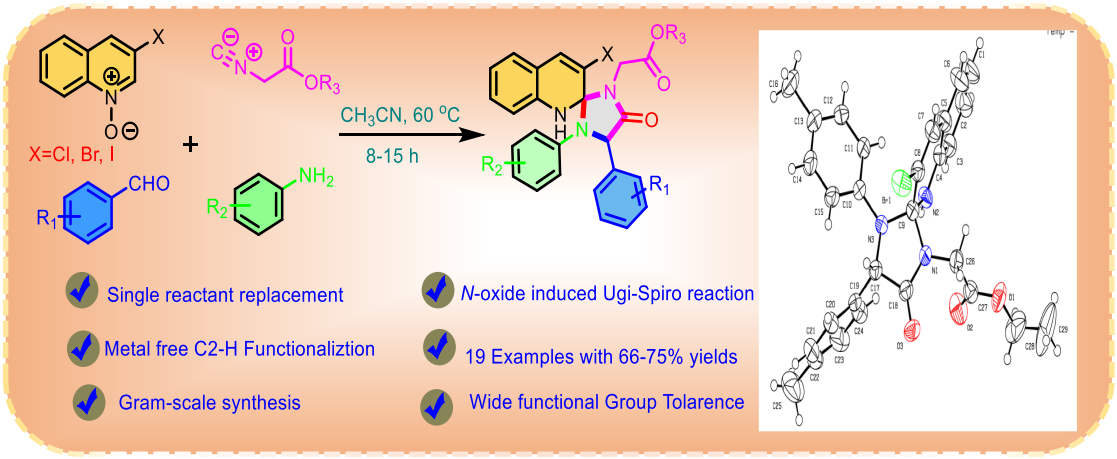


HRMS spectrum of methyl 2-(2-((6-chloroquinolin-2-yl)(*p*-tolyl)amino)-2-(*p*-tolyl)acetamido)acetate (6p)



CHAPTER-IIIB

Effect of 3-Halo Quinoline *N*-oxides in Ugi Reaction: Direct Access to the 1*H*-Spiro[imidazolidine-2,2'-quinolin]-4-ones



3B.1. Introduction

Development of new methodologies that enable the construction of molecular complexity from easily available starting materials in a green manner is a long-standing goal and key challenge in organic synthesis. Organic compounds containing three-dimensional architectures such as spiro compounds have received much attention, as it provides conformational rigidity for tapping into a three-dimensional chemical space and may play an important role in medicinal chemistry and drug discovery. Spiro-compounds are twisted structures in which typically two rings are joined by a single atom, known as a spiroatom.[1] They were isolated from both plant and animal sources.[2] Spirocycles were initially proposed by Von Baeyer in 1900 and they become important class of molecules due to their common occurrence in numerous natural as well as non-natural products.[3]

Generally, heterocyclic spiro-oxindole framework is a crucial structural motif in several biologically relevant natural products and medicines, such as surugatoxin, horsfiline, spirotryprostatin A&B, elacomine, gelsemine, alstonisine, and strychnofoline.[4] Additionally, the chemistry of spiro-indoles, in which an indole ring is connected to heterocycles containing sulphur and nitrogen at the C-3 position via a spiro carbon atom, is quite interesting due to its physiological and biological activities.[5-6] Similarly, a large number of synthetic spiro-isoindolinones and spiro[indole-thiazolidinones] exhibit important biological properties, including the ability to serve as anti-HIV-1, antileukemic, antiviral, anaesthetic, and antihypertensive drugs (Figure 3B.1).[7-8]

In particular, spiro-hydroquinolines containing a quaternary carbon with free N-H group are of much interest, as hydro-quinolines are key structural motifs in many natural products, pharmaceuticals and biologically active molecules.[9-12] This unprotected N-H group may confer high-affinity binding towards proteins and other drug-like molecules.[13,14]

The traditional methods in this category of synthetic preparation of spiro-hydroquinolines involves catalytic dearomative annulation of substituted quinolines which further mandates taking up the cumbersome process of activation of quinolines activators such as acetyl chloride.

However, despite extensive studies and recent advances in the dearomatization of quinolines and related *N*-heteroaromatics,[15] construction of N-H free spiro-hydroquinoline architecture by the dearomatization of a quinoline skeleton has remained a challenge to date.

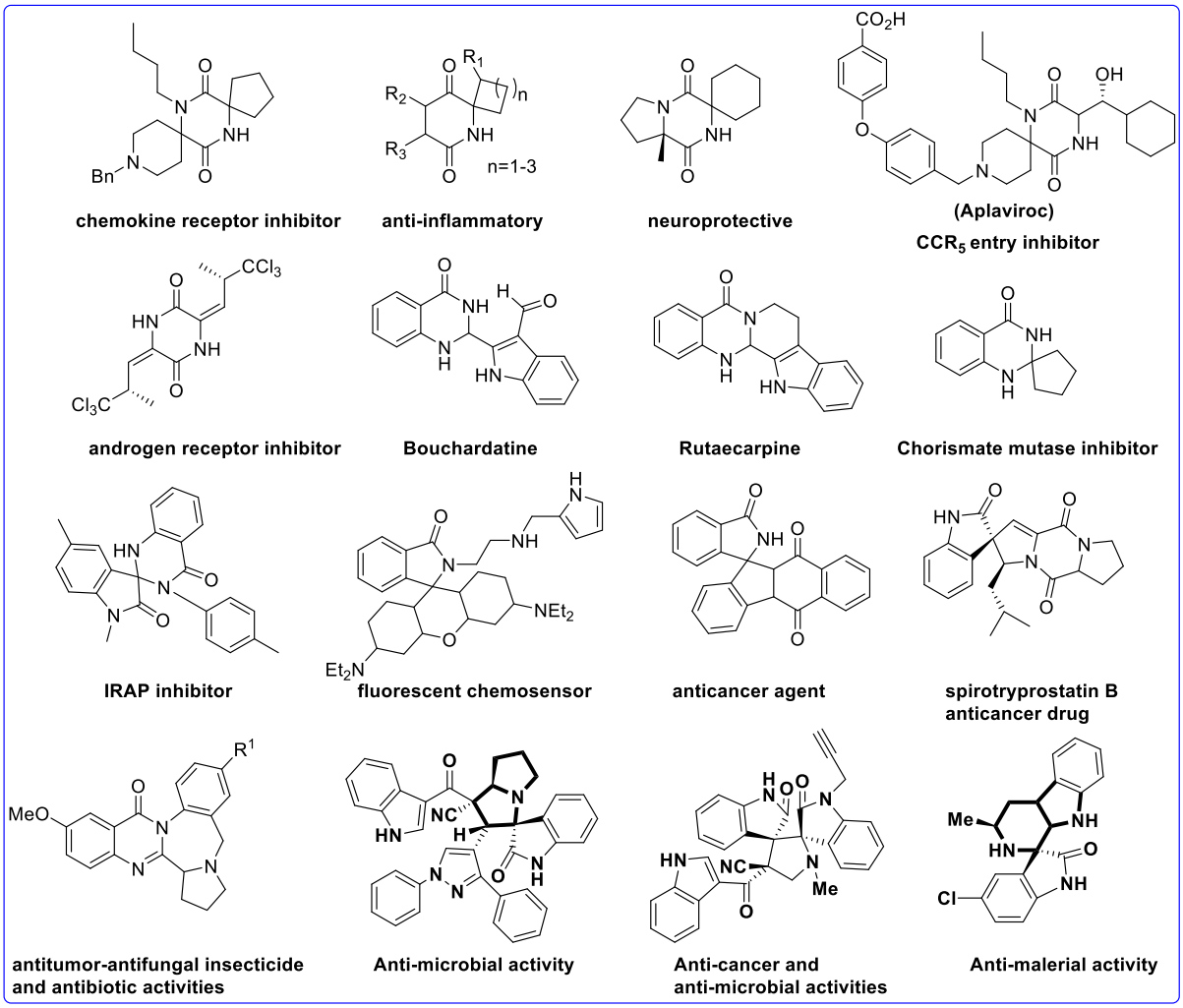
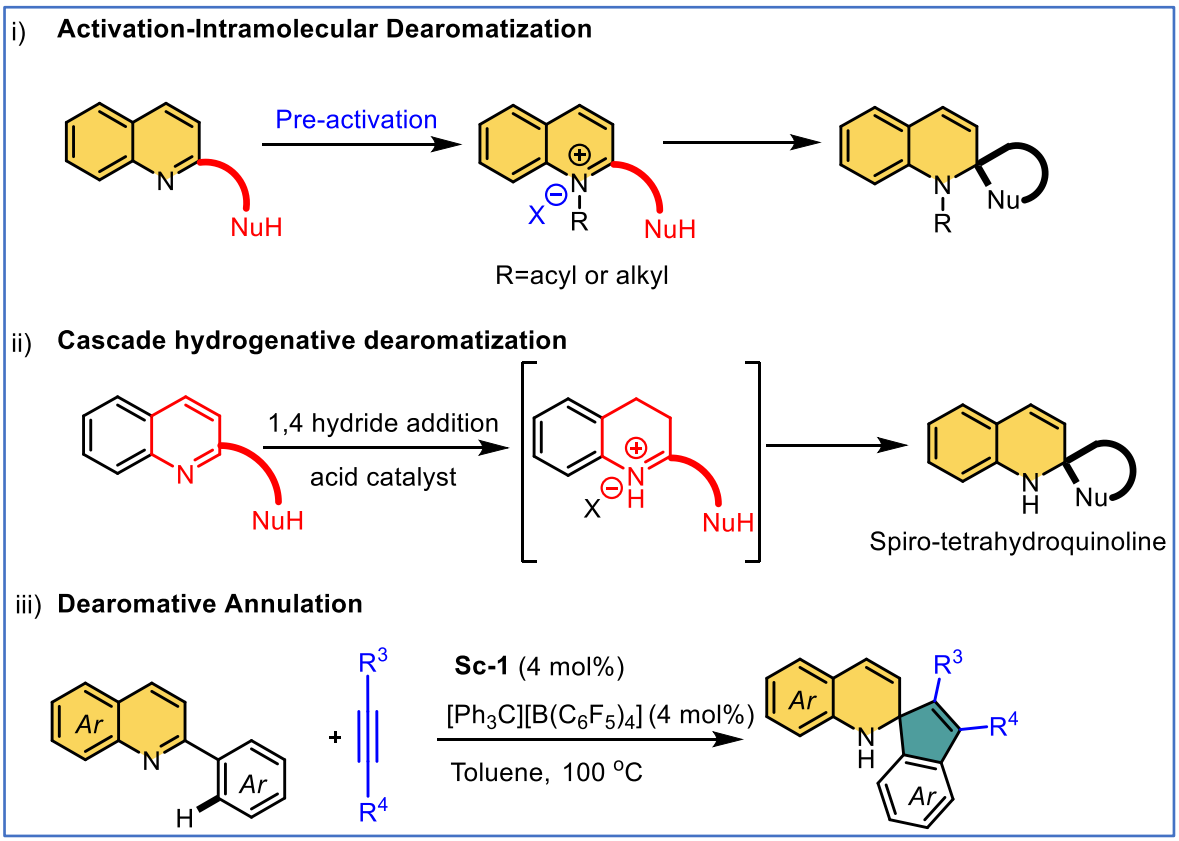


Figure. 3B.1. Some biological activity of spiro compounds.

It has long been known that the dearomative nucleophilic 1,2- addition of organolithium reagents to C2-substituted quinolines could afford the corresponding 2,2-disubstituted N-H free hydroquinoline derivatives containing a quaternary carbon, but this reaction suffers from the low yields and tedious workup procedure. When quinoline was activated by *N*-alkylation, the asymmetric dearomative 1,2-addition of a boronic acid to the quinolinium salt was achieved in the presence of a chiral rhodium catalyst, affording an *N*-protected hydroquinoline product with a chiral quaternary carbon stereocenter albeit in low yield.[16] However, the *N*-protecting group was generally difficult to remove after the reaction (Scheme 3B.1.i).

A cascade hydrogenative dearomatization of a 2,4-disubstituted quinoline and asymmetric intramolecular aza-Friedel-Crafts alkylation of an indole tethered by an iminium species in the presence of a chiral phosphoric acid catalyst could afford N-H free spirotetrahydroquinoline product in an enantioselective fashion, but this transformation suffered from the formation of a mixture of diastereoisomers in low yields (Scheme 2B.1.ii).[17] Recently, transition-metal catalysed dearomative annulation become an efficient method to make

spirotetrahydroquinolines with free N-H group (Scheme 3B.1.iii). Despite the fact that they exhibit the outstanding biological activities, the construction of an N-H free spiro-hydroquinoline architecture by environmentally benign conditions has not been reported in the literature either by direct dearomatization of a quinoline skeleton in either a stoichiometric or catalytic fashion. The lack of chemo- and enantio-selectivity of synthetic products is one of the main challenges in the synthesis of spirocycles. Search for efficient and selective catalysts is therefore of great interest and importance for tackling this challenge.



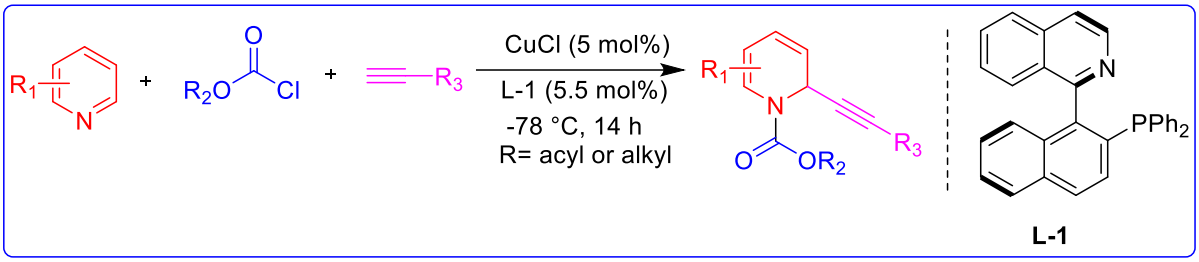
Scheme 3B.1

The capability of the *N*-oxide moiety to function as an ortho directing group to influence the regioselectivity of the C-H activation has recently drawn a lot of attention to aromatic amine *N*-oxides.[18] Due to the significance of 2-amino quinolines in medicinal chemistry and pharmaceuticals, *N*-oxide driven C2-selective C-N bond synthesis in particular has become a focus. In each method, *N*-oxides either interact with the promoters or work in concert with the metals to activate the aromatic *N*-oxides C2 position. As a result, the aromatic *N*-oxide-mediated Ugi four-component reaction could be a good candidate for replacing Ugi with a single reactant due to its activated C2-position and nucleophilicity of oxygen. This cascade *N*-oxide-induced Ugi and dearomatize annulation could be a novel sequence to synthesize 1H-spiro[imidazolidine-2,2'-quinolin]-4-one and its derivatives.

As an extension of our previous work using isocyanides to C2-H functionalize aromatic amine *N*-oxides (Chapter II and Chapter 3A),[19,20] we provide here a tandem *N*-oxide-induced Ugi reaction and dearomatize annulation to access a 1*H*-spiro[imidazolidine-2,2'-quinolin]-4-one derivatives (spiro compounds) in a single pot.

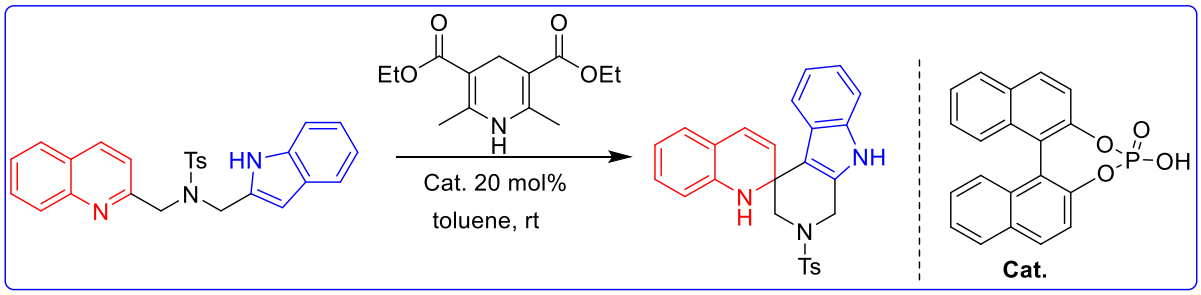
3B.1.1. Reported methods for the synthesis of 1*H*-spiro[imidazolidine-2,2'-quinolin]-4-one and its derivatives

Arndtsen and co-workers employed a copper (I)-catalyzed, asymmetric method to directly functionalized pyridines, quinolines, and isoquinolines with terminal alkynes. The reaction is readily incorporate a range of pyridine based heterocycles and electron-rich or electron-poor alkynes (Scheme 3B.2).[21]



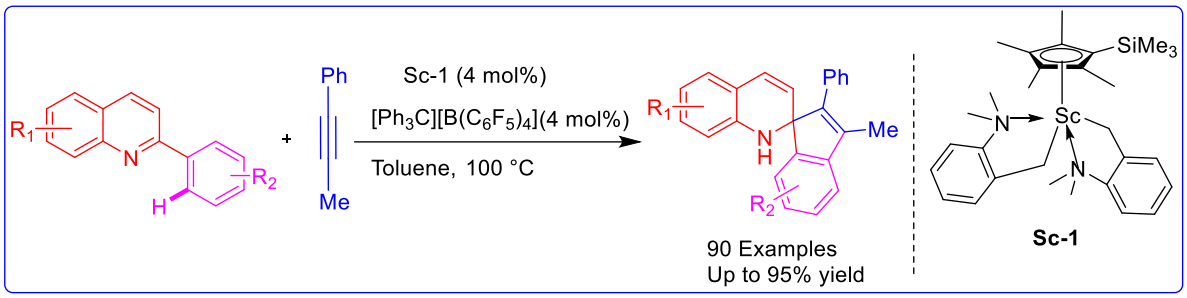
Scheme 3B.2

You and Co-workers developed an efficient synthesis of spiro-tetrahydroquinolines *via* a cascade hydrogenative dearomatization of quinoline and an aza-Friedel-Crafts alkylation reaction. This approach does not require any activation of quinolines and features i.e., inexpensive starting materials, operational simplicity, excellent yields (Scheme 3B.3).[22]



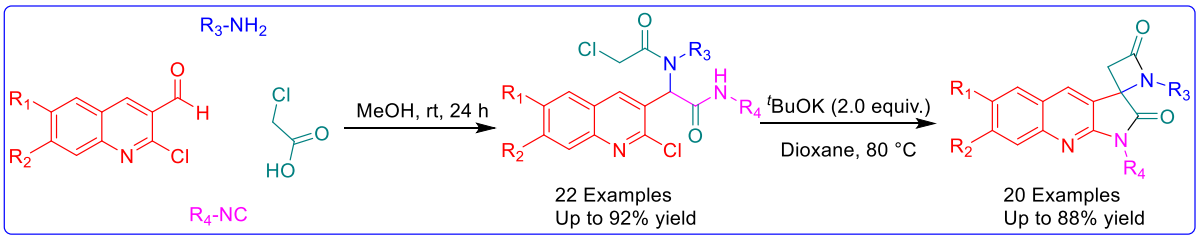
Scheme 3B.3

Lou et al. introduced a half-sandwich scandium catalyst for the dearomative spiro-annulation of 2-arylquinolines with diverse alkynes. The reaction is based on a unique combination of the scandium catalyzed C-H activation, alkyne insertion, and dearomative nucleophilic 1,2-addition of alkenyl species to the C-N unit of a quinoline moiety. This protocol provides 100% atom efficiency, broad substrate scope, high yield, high enantioselectivity (Scheme 3B.4).[23]



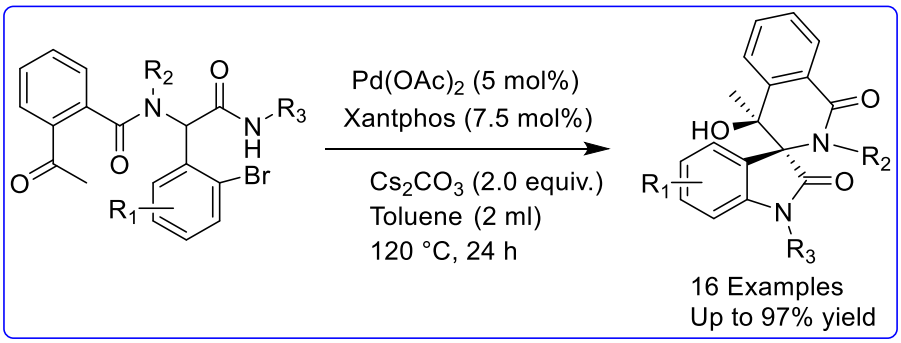
Scheme 3B.4

Golmohammadi et al. synthesized spiro-lactampyrroloquinolines *via* successive post-transformation of the Ugi four-component reaction/nucleophilic substitution. Utilizing the Ugi-4CR of 2-chloro-3-formyl quinolines, amines, 2-chloroacetic acid and isocyanides, a versatile spiro-lactampyrroloquinolines are synthesized. The spiro-lactam-pyrroloquinoline scaffolds were produced by intramolecular cyclization of the Ugi adducts using the sequential nucleophilic aromatic substitution (S_NAr) second-order nucleophilic substitution (S_N^2) reaction under basic conditions. This strategy has a high bond-forming efficiency and is effective for the synthesis of fused bioactive heterocyclic backbones that contain quinoline, pyrrolidone, and -lactam (Scheme 3B.5).[24]



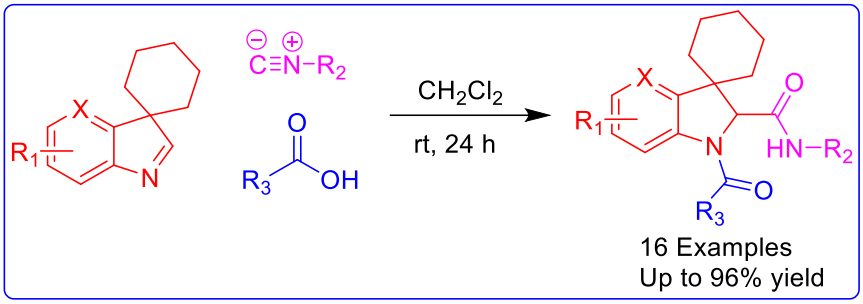
Scheme 3B.5

Sharma and co-workers described a diversity-oriented route to spiro-polyheterocycles with two neighboring quaternary carbon stereocenters. The selectivity of the cyclization is achieved by selecting suitable ligands. Spirooxindoles are produced selectively with xantphos, whereas fused polycyclic cis-dihydrobenzofurans are produced with excellent diastereoselectivity with BINAP under palladium catalysis (Scheme 3B.6).[25]



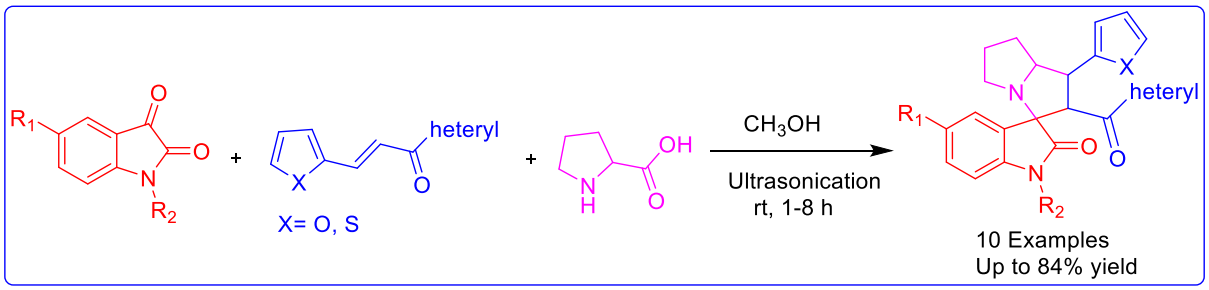
Scheme 3B.6

Ruijter and group synthesized highly substituted spiroindoline derivatives at room temperature under mild conditions. To examine the chemical space surrounding this favoured structure, a fischer indolization is paired with Ugi-type reactions. Additionally, spiropiperidine derivatives may undergo post-modification to create a library of compounds (Scheme 3B.7).[26]



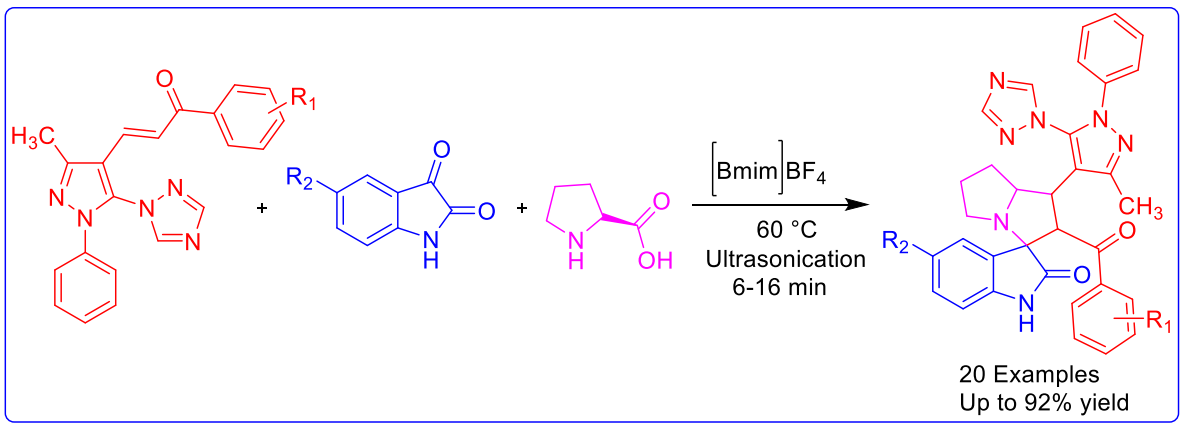
Scheme 3B.7

Basavoju and co-workers developed a one-pot, three-component 1,3-dipolar cycloaddition utilizing ultrasonication for quick and regioselective synthesis novel spirooxindolo and spiroquinoxalinopyrrolizidine derivatives. This ultrasound methodology is unquestionably more advantage over traditional heating and fusion processes because the intended items were produced with a moderate to good yield in a short time (Scheme 3B.8).[27]



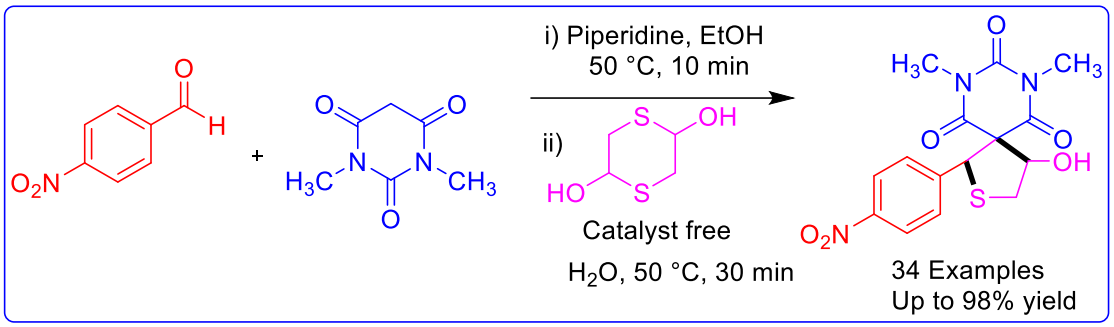
Scheme 3B.8

Pogaku et al. designed and synthesized a novel series of potent antiproliferative and antimycobacterial (anti-TB) benzotriazoloquinolinyl spirooxindolopyrrolizidine derivatives by using ionic liquid under ultrasonication (Scheme 3B.9).[28]



Scheme 3B.9

Dhurke and group synthesized quaternary-centered spirobarbiturate-tetrahydrothiophene hybrids by using "on water" concept *via* domino knoevenagel condensation, 1,4-thia-michael, and intramolecular aldol processes. Use of catalyst free, green solvent, and broad substrate scope are some for the key features of this method (Scheme 3B.10).[29]

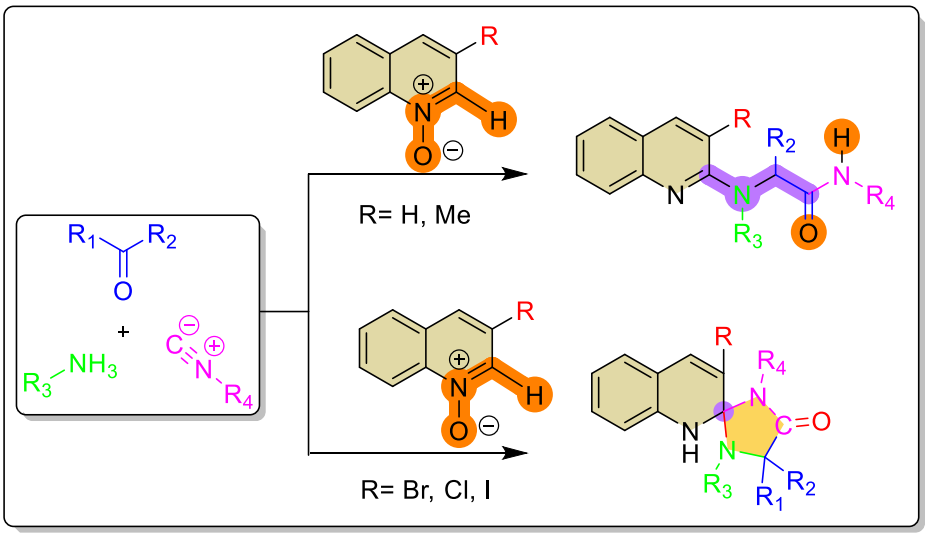


Scheme 3B.10

Based on the previous reports we found that considerable attention has been received for the synthesis of C(sp^2)-H functionalization of quinolines at C2 position to increase the biological activity of the quinoline core. However, the reports C2-spiro quinolines are limited inspite of their wide applications in pharmaceuticals.

3B.2. Present study

Considering the importance of multicomponent reactions and their hybrid molecules, we have developed a novel one-pot synthesis of *N*-oxide induced Ugi-spiro compounds. In chapter **3A**, we found that *N*-oxide is a potential surrogate for the carboxylic acid of Ugi reaction.



Scheme 3B.11. Synthesis of 1*H*-spiro[imidazolidine-2,2'-quinolin]-4-one

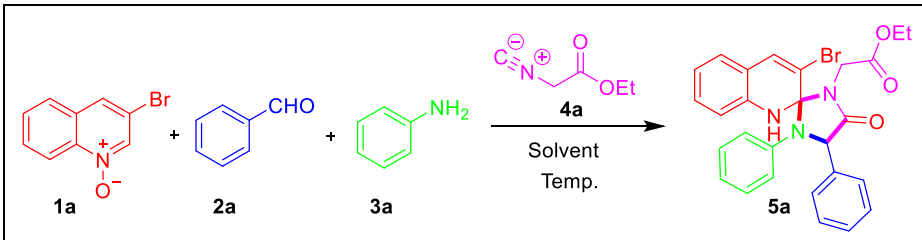
Interestingly, unusual *N*-oxide-induced Ugi products were observed when the 3-halo quinoline *N*-oxides are used under the *N*-oxide-Ugi reaction and the same findings are discussed in this chapter. A transition-metal-free C(sp^2)-H functionalization of quinolines in the presence of aldehydes, anilines and isocyanides are described here. This metal-free reaction affords rapid

access to 1*H*-spiro[imidazolidine-2,2'-quinolin]-4-one with exceptional functional group tolerance, broad substrate scope. (Scheme 3B.11).

3B.2.1. Results and discussion

Initially, screening experiments were conducted on 3-Bromo quinoline-*N*-oxide **1a** with benzaldehyde **2a**, aniline **3a** and ethyl 2-isocyanoacetate **4a** in suitable solvent and temperatures to optimize the reaction conditions, and only the key facts are reported in Table 3B.1.

Table 3B.1. Optimization of reaction conditions[a]

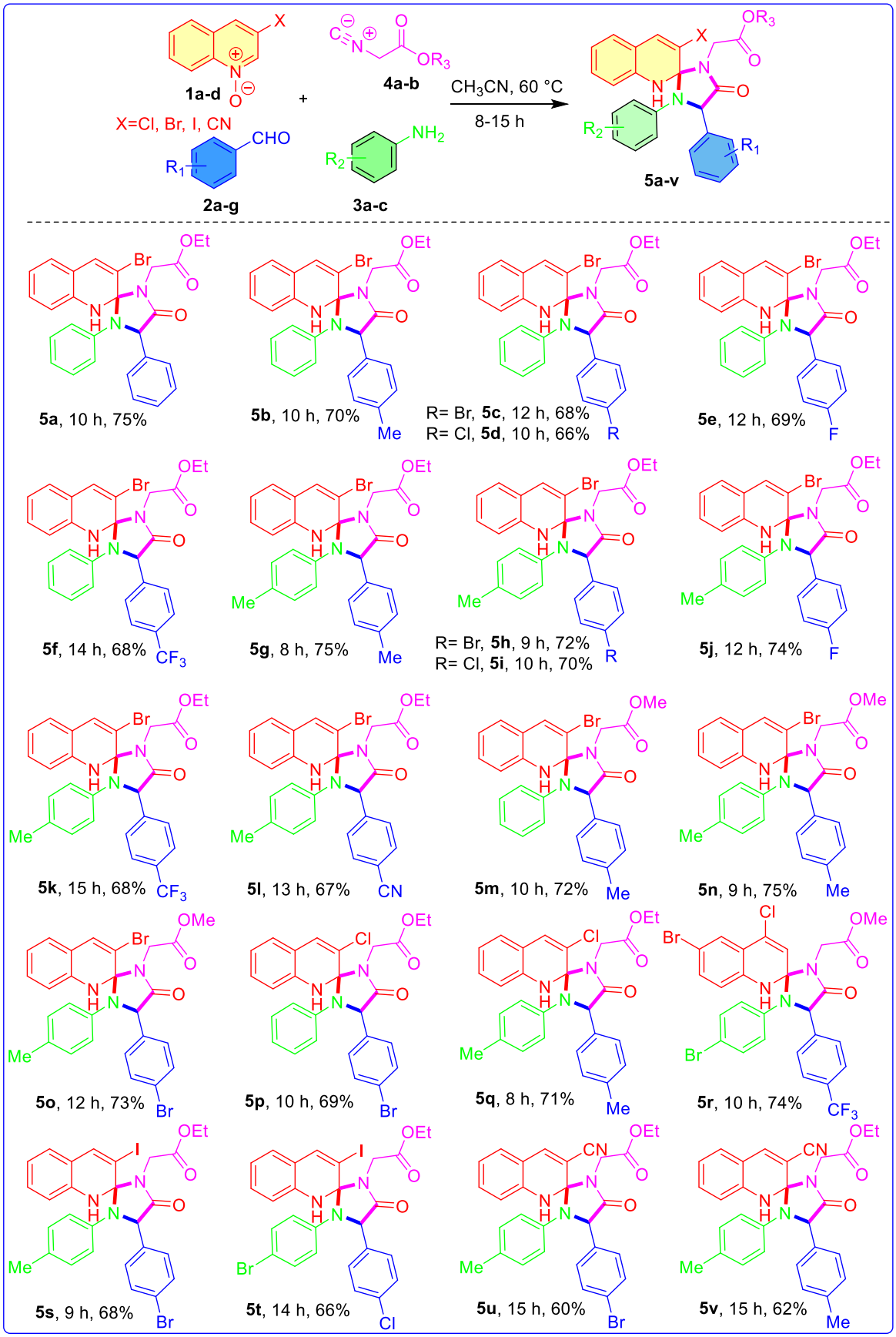


S. No	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1.	CH_2Cl_2	rt	24	0
2.	CH_2Cl_2	40	12	10
3.	$CHCl_3$	60	12	35
4.	DCE	60	12	60
5.	Toluene	60	12	10
6.	**CH_3CN**	**60**	**8**	**75**
7.	CH_3NO_2	60	12	40
8.	THF	60	12	65
9.	CH_3OH	60	10	45
10.	EtOH	60	10	40
11.	DMF	60	12	trace
12.	DMSO	60	12	20
13.	CH_3CN	70	24	70
14.	CH_3CN	80	24	66

[a]Reaction conditions: 3-bromo quinoline *N*-oxide **1a** (0.5 mmol), benzaldehyde **2a** (0.5 mmol), aniline **3a** (0.5 mmol), isocyanide **4a** (0.5 mmol), and solvent (2.0 mL). [b]Isolated yield.

The reaction of 3-bromo quinoline-*N*-oxide **1a** (0.5 mmol) was treated with benzaldehyde **2a** (0.5 mmol), aniline **3a** (0.5 mmol) and ethyl 2-isocyanoaceate **4a** (0.5 mmol) in the CH_2Cl_2 at

Table 3B.2. Substrate scope for the synthesis of 1*H*-spiro[imidazolidine-2,2'-quinolin]-4-one [a,b]

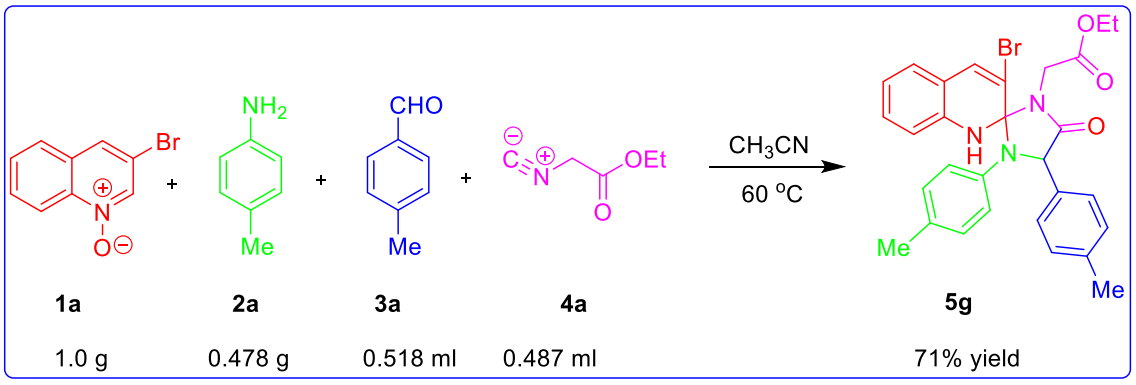


[a]Reaction conditions: 3-halo quinoline *N*-oxide **1a-c** (0.5 mmol), benzaldehyde **2a-g** (0.5 mmol), aniline **3a-c** (0.5 mmol), isocyanide **4a-b** (0.5 mmol), and solvent (2.0 mL). [b]Isolated yield.

room temperature failed to give the **5a** but at elevated temperature afforded the desired product **5a** in 10% yield (Table 3B.1, entries 1-2). The standard spectroscopic analysis identified **5a** as ethyl 2-(3'-bromo-4-oxo-1,5-diphenyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate, in line with the original design. This result revealed that the bromo substitution on quinoline *N*-oxide **1a** indeed acted as a carboxylic acid isostere in the traditional Ugi reaction and activating the C2 carbon of quinoline *N*-oxide to form spiro compound **5a**.

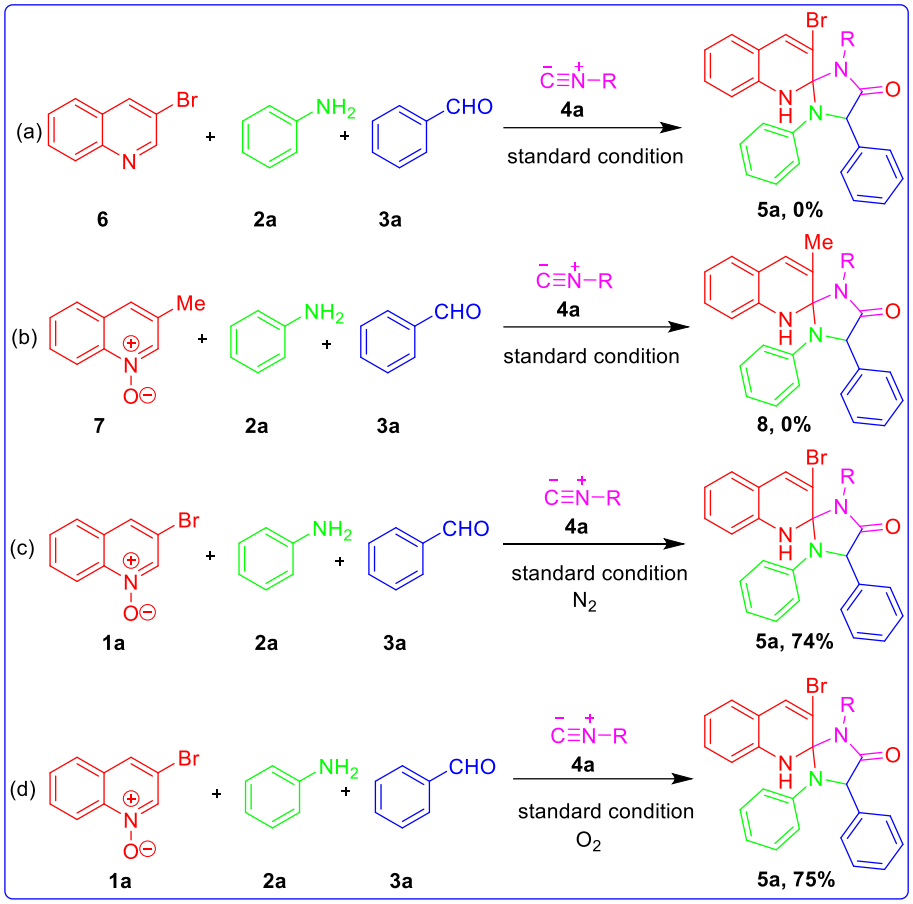
To our delight, the yield of ethyl 2-(3'-bromo-4-oxo-1,5-diphenyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate **5a** has increased to 60% at elevated temperatures (Table 3B.1, entries **2-4**). These results suggested that heating is required to get the better yield of the product. Next, we have carried out the reaction in various solvents to assess their effect on the reaction efficiency. Among other solvents tested, such as toluene, CH_3NO_2, THF, alcohols, DMF and DMSO, CH_3CN turned out to be superior for this transformation (Table 3B.1, entries **5-12**). Further change in the temperature and time has no effect on the yields of the reaction (Table 3B.1, entries **13** and **14**).

To explore the scope of this new four-component reaction, we examined various 3-halo quinoline-N-oxides such as -Br, -Cl, -I with aromatic aldehydes, anilines, and ethyl 2-isocyanoaceate (Table 3B.2). The methyl 2-isocyanoacetate and ethyl 2-isocyanoacetate, which were prepared from the glycine reacted. The 3-halo substituted quinoline N-oxide reacted smoothly to give respective products in excellent yields (Table 3B.2). The 3-bromo quinoline N-oxide reacted smoothly under optimized conditions with various substituted aromatic aldehydes and anilines to give desired products **5m-o** with 72-75%. Likewise, 3-chloro quinoline-N-oxide and 4-chloro-6-bromo quinoline-N-oxide gave the target products **5p-5q** with 69-74% yields respectively. Notably, 3-iodo quinoline-N-oxides also effortlessly participated in the reaction with anilines, aromatic aldehydes and ethyl 2-isocyanoacetate to give corresponding product **5r-s** with 66-68% yield (Table 3B.2).



Scheme 3B.12. Gram-scale reaction

Further, we have investigated the efficiency of this protocol for gram scale reaction using 3-bromo quinoline *N*-oxide **1a** with 4-methyl benzaldehyde **2a**, 4-methyl aniline **3a** and ethyl isocyanoacetate **4a** under the standard condition. The reaction afforded the final product **5g** in 71% of yield (Scheme 3B.12).



Scheme 3B.13. Control experiments.

Next, we carried several control experiments to unveil the reaction mechanism (Scheme 3B.13). Initially, 3-bromo quinoline **6** was treated with aldehyde **2a**, aniline **3a** and isocyanide **4** under the standard conditions, but no reaction was observed, which indicated the important role of *N*-oxide in this transformation (Scheme 3B.13a). Later, 3-substituted quinoline *N*-oxide **7** was used to test the reactive position of the quinoline *N*-oxide and found to be non-reactive under the optimized conditions (Scheme 3B.13). Later 3-bromo quinoline *N*-oxide **1a** was treated with aldehyde **2a**, aniline **3a** and isocyanide **4a** under the standard conditions, at N_2 and O_2 atmosphere we get good yields (Scheme 3B.13c-d).

3B.3. Analysis of simple *N*-oxide-Ugi product with 3-halo *N*-oxide-Ugi product.

3B.3.1. Analysis ^{1}H and ^{13}C NMR data

Proton NMR data revealed the following points: i) The triplet peak at δ 9.89 (t, J = 5.8 Hz, 1H) ppm of the compound **6e** represents -NH proton of amide (uncyclized product), whereas such

peak was not observed in the compound **5g**. However, the down field peak at δ 7.91 (s, 1H) was observed for cyclic -NH proton of compound **5g**. ii) The peak at 6.18 (s, 1H) ppm corresponding to the tertiary CH proton **6e**, whereas, in compound **5g (**spiro**)** the peak at δ 5.20 (s, 1H) ppm is shifted to the upfield (Figure. 3B.2).

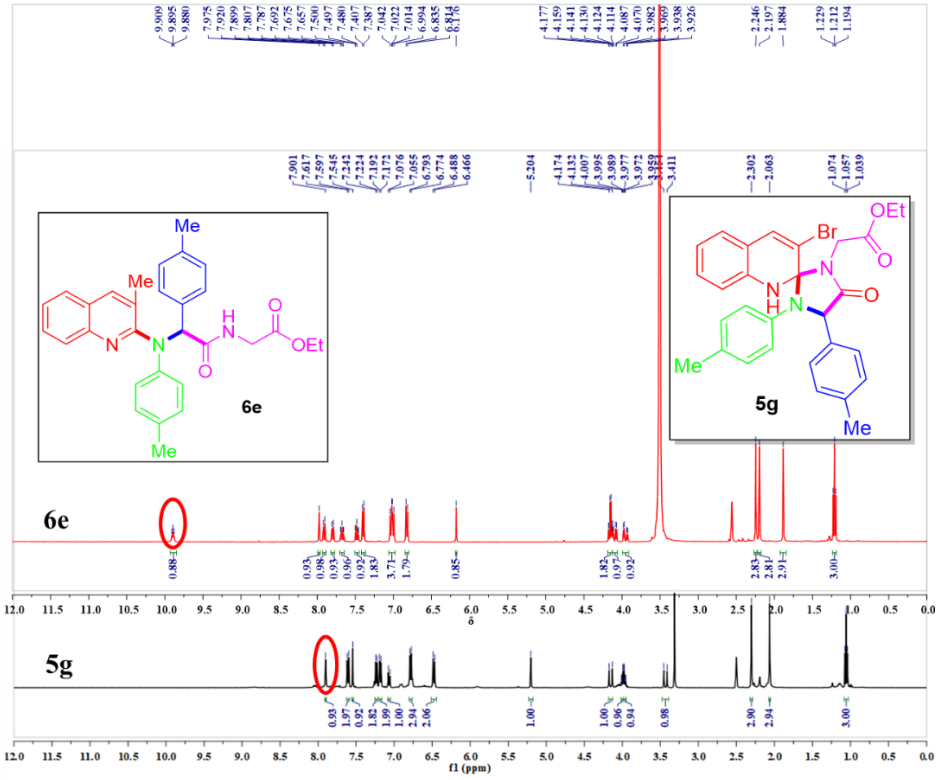


Figure. 3B.2. Comparison of ^{1}H NMR of Ugi product (6e) and Ugi-spiro product (5g) in DMSO-d_6

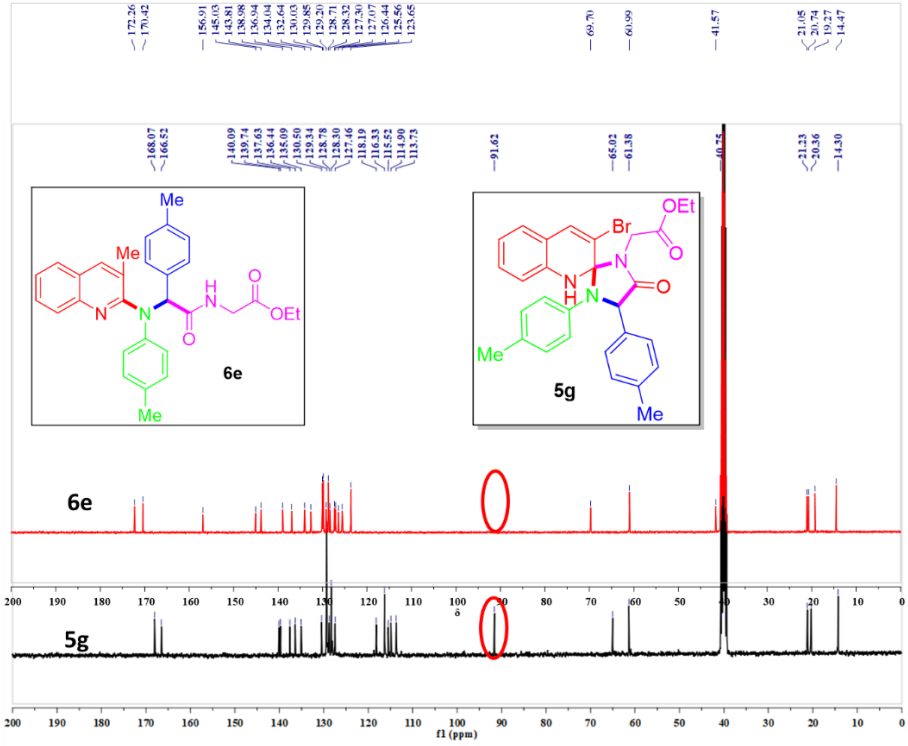


Figure. 3B.3. ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) of compounds **6e** and **5g**.

Similarly, following observations are made on ^{13}C NMR data: i) The peak at δ 172.2 ppm (ester carbonyl carbon) and peak at δ 170.4 ppm (amide carbonyl carbon) represents the compound **6e**. Whereas the same carbons are observed at up filed *i.e.*, δ 168.0 ppm (ester carbonyl carbon) and peak at δ 166.5 ppm (carbonyl carbon of cyclic compound). ii) the peak at δ 91.6 ppm was observed in the **5e** which was missing in the acyclic compound **6e**. Further the formation of the spiro compound confirmed HSQC of compound **5g**.

3B.4. X-ray diffraction analysis of compound 5g

The method for crystal growth is slow volatilization using DMSO-d_6 as a solvent. The crystallographic data for the single crystal of the compound **5g** was collected on an Xtlab Synergy Rigaku oxford diffraction with HyPix-3000 detector, equipped with graphite monochromated MoKa radiation (λ= 0.71073 Å) at 293K. The data interpretation was processed with CrysAlisPro, Xtlab Synergy Rigaku oxford diffraction, version 171.39.exe and an absorption correction based on multi-scan method. Crystallography data and structure refinement for **5g** (CCDC: 2158163) (Table 3B.3). Thermal ellipsoids are shown at 50% probability level (Figure 3B.4).

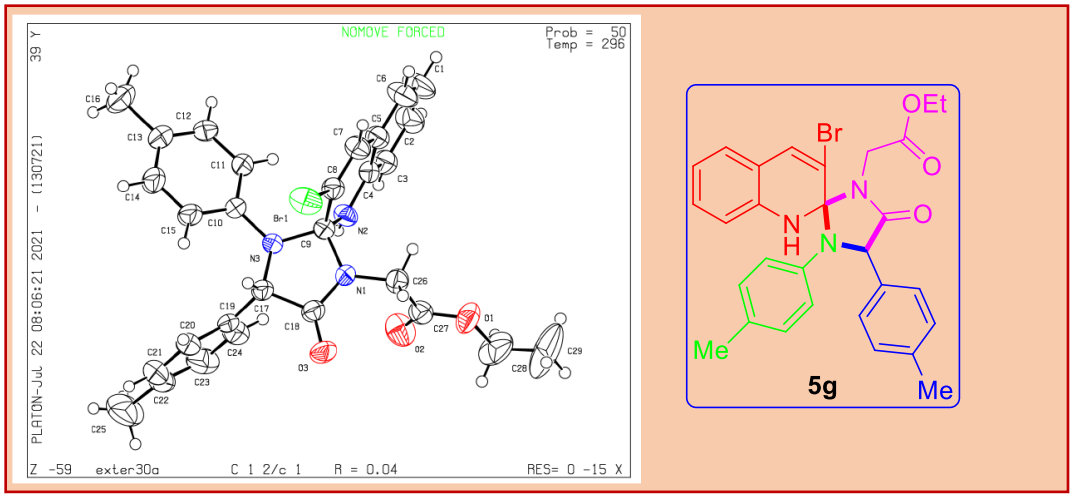


Figure. 3B.4. The ORTEP representation of the compound **5g.**

Table 3B.3. Crystallographic data and structure refinement of compounds **5g**

Identification Code	**Compound 5g**
Empirical formula	$C_{29}H_{28}BrN_3O_3$
Formula weight	546.45
Temperature/K	296K

Crystal system	Monoclinic
Space group	C 12/c1
a/Å	20.5786(6)
b/Å	15.25619(4)
c/Å	17.5941(5)
α/°	90
β/°	109.803(3)
γ/°	90
Volume/Å^3	5197.0(3)
Z	8
D_{calc} Mg/m^3	1.397
μ/mm^{-1}	1.617
F(000)	2256.0
Crystal size/mm^3	0.2 x 0.15x 0.1
2Θ range for data collection/°	1.877 to 25.027
Index ranges	-24 ≤ h ≤ 24, -18 ≤ k ≤ 8, -20 ≤ l ≤ 20
Reflections collected	4588
Independent reflections	3437
Data/restraints/parameters	3437 / 0 / 332
Goodness-of-fit on F^2	1.020
Final R indexes [I>=2σ (I)]	R1 = 0.0421, wR2 = 0.0866
Final R indexes [all data]	R1 = 0.0650, wR2 = 0.0934
Largest diff. peak/hole / e Å^{-3}	0.363 and -0.348
CCDC	2158163

3B.5. Computational studies for Spiro compounds

To investigate the favorability of Ugi-Spiro products over non-spiro products on substitution at *β*-position to N in *N*-oxided Ugi products, Density functional theory (DFT) based calculations were carried out. The structures of the spiro and non-spiro products were modelled and optimized at M062X/def2TZVPlevel of theory without any geometrical and symmetrical constraints.[30,31] The frequency calculations were carried out to confirm the minimum energy structures. All the calculations were performed using ADF software package.[32] The energies of the respective spiro and non-spiro products were systematically compared to check the

favorability. The optimized geometries of various spiro and non-spiro products along with their energies are shown in **Figure 3B.5.**

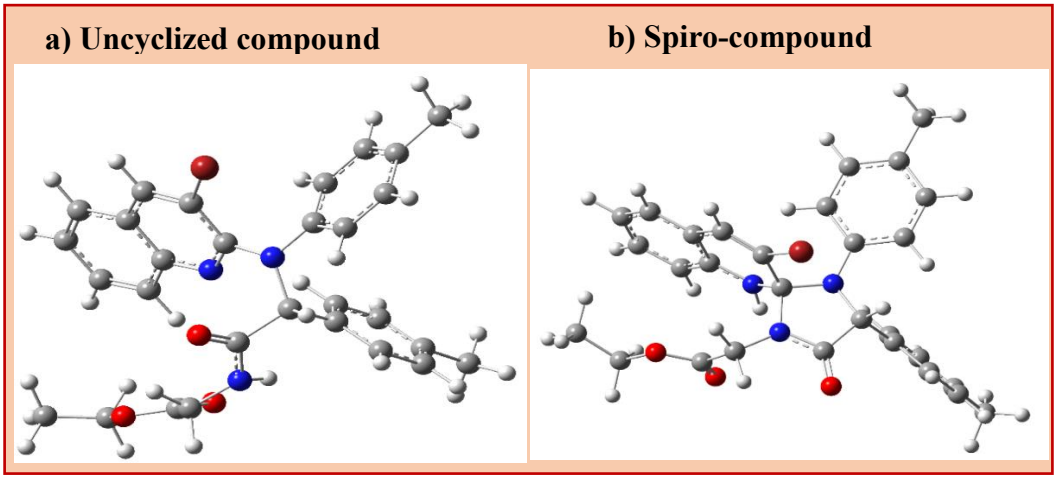


Figure 3B.5.1. Optimized structures of the *N*-oxide induced Ugi products obtained from 3-bromo quinoline.

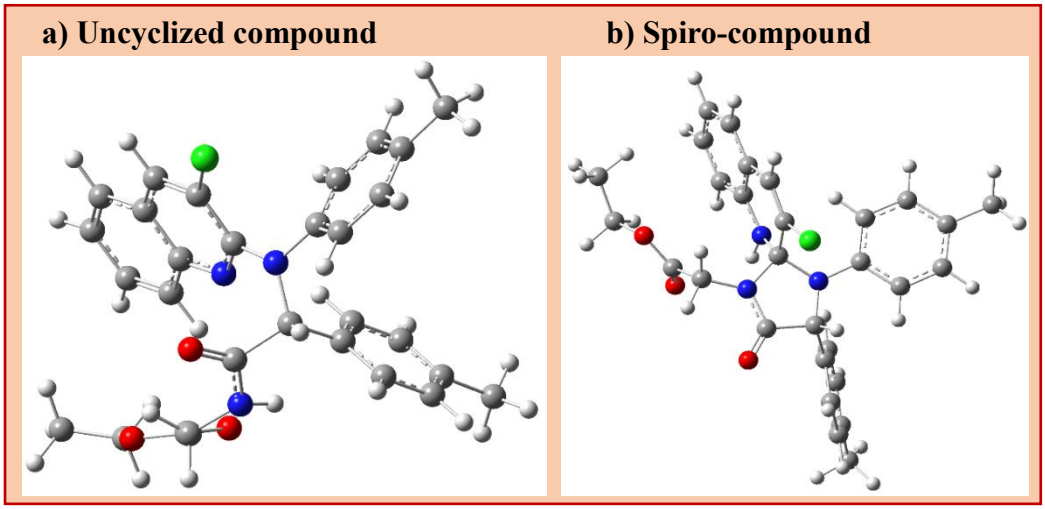


Figure 3B.5.2. Optimized structures of the *N*-oxide induced Ugi products obtained from 3-Chloro quinoline *N*-oxide.

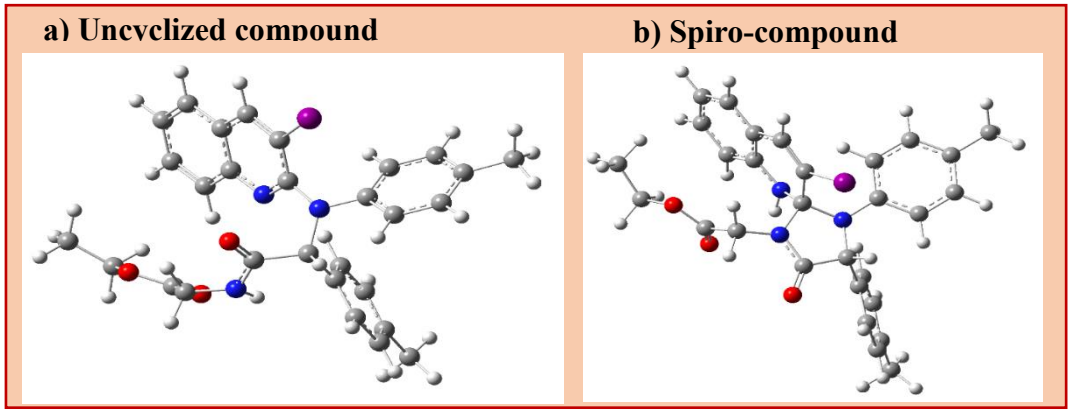


Figure 3B.5.3. Optimized structures of the *N*-oxide induce cyclized and spiro-Ugi products obtained from 3-Iodo quinoline *N*-oxide.

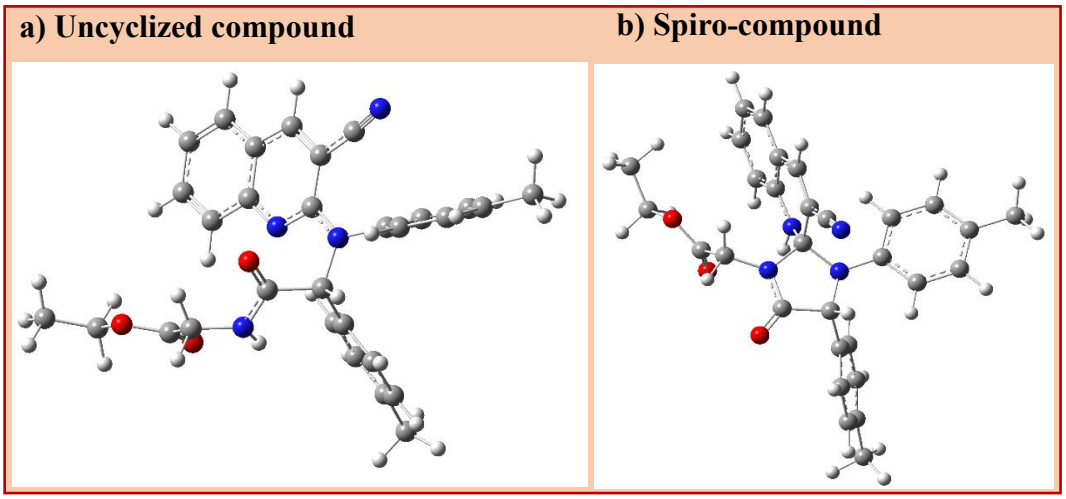
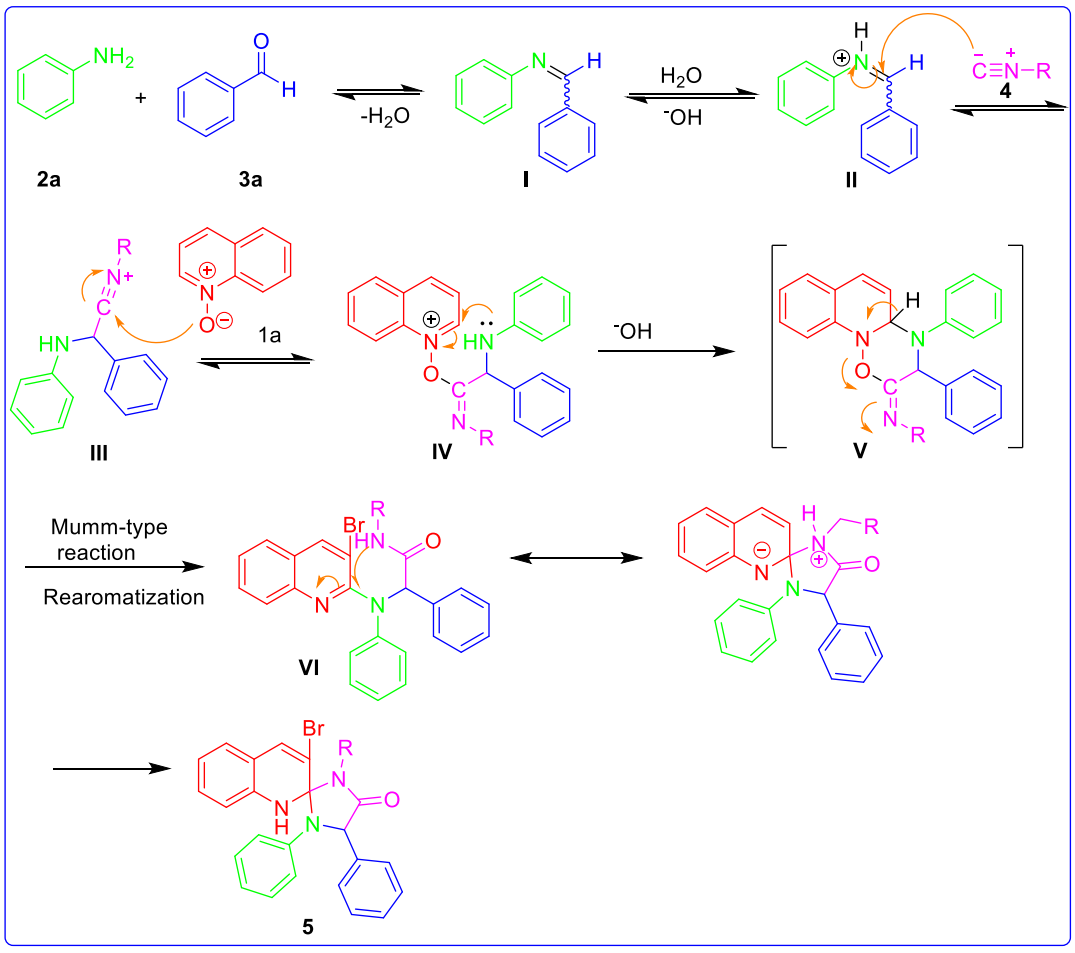


Figure 3B.5.4. Optimized structures of the *N*-oxide induced Ugi products obtained from 3-cyano quinoline *N*-oxide.

From the energy comparisons of the optimized structures, it was found that the spiro products of -Cl, -Br, -I and -CN substituted 1a-b were stable by -3.12, -3.59, -4.52 and -0.55 kcal/mol, respectively than their corresponding non-spiro products. Thus, the spiro products are much favourable than the non-spiro products.



Scheme 3B.14. Proposed reaction mechanism

On the basis of our control experiments, NMR Data, Crystallographic data and computational studies and previous literature,[33,34] a plausible mechanism of the *N*-oxide induced Ugi-spiro reaction is illustrated in (Scheme 3B.14). Initially, reaction between aniline **2a** and carboxaldehyde **3a** would form imine intermediate **I**. Next, the intermediate **I** would undergo protonation followed by the nucleophilic addition with isocyanide **4**, to form intermediate **III**. Later, the nucleophilic oxygen of *N*-oxide subsequently added carbon of nitrilium ion to generate intermediate **IV**. Further, an irreversible nucleophilic addition of nitrogen (aniline) on to the activated C2-carbon of quinoline would furnish bicyclic intermediate **V** *via* Mumm type reaction. Finally, the intermediate **V** undergoes dearomative annulation to obtain the desired Ugi-spiro product **5** which is lower energy that its corresponding Ugi product**.**

3B.6. Conclusion

In summary, halogen substituted *N*-oxide induced Ugi-spiro reaction has been successfully developed. This approach opens a new era in 3-halo quinoline *N*-oxides to be a potent acid surrogate in multicomponent reactions to provide a library of spiro compounds. This new method provides the one-pot synthesis of 1*H*-spiro[imidazolidine-2,2'-quinolin]-4-one while ensuring a wide substrate scope with functional group tolerance.

The formation of spiro compounds were confirmed by comparing the ^{1}H NMR spectra of a simple *N*-oxide induced Ugi product (Chapter IIIA, compound 6e)[19] and dearomative annulated product 5g.

3B.7. Experimental section

3B.7.1. General Information: All chemicals were purchased from Aldrich, Alfa aesar, TCI, Finar and used as received. All solvents were purchased from commercial sources, then distilled by the standard protocol and stored over molecular sieves under nitrogen atmosphere prior to use. Thin layer chromatography was performed on 200 µm aluminium-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). ^{1}H NMR spectra were recorded on Bruker's AVANCE 400 MHz spectrometer, $CDCl_3$ and DMSO-d_6 as a solvent and TMS as an internal standard. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, coupling constants, *J* were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker's AVANCE 100 MHz spectrometer, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-d (a multiplet at 39.52 ppm of DMSO-d_6). Melting points were determined with a Stuart SMP30 apparatus and are uncorrected. FT-IR spectra recorded on a

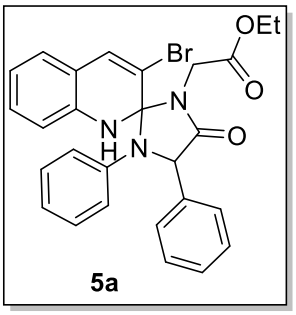
Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230. The X-ray single crystal data of the crystal compounds was collected on Xtlab Synergy Rigaku oxford diffraction with HyPix-3000 detector, equipped with graphite monochromated MoKα radiation (λ= 0.71073 Å) at 293K.

3B.7.2. General procedure for the synthesis of quinoline spiro products (5a-s)

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate benzaldehyde (0.5 mmol), aniline (0.5 mmol), 3-halo quinoline *N*-oxide (0.5 mmol), and the isocyanide (0.5 mmol) in CH_3CN. The reaction mixture was stirred at 60 ^oC for 8-15 h. The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion, the reaction mixture was cooled to room temperature, the solvent removed under reduced pressure and extracted with ethyl acetate (3 x 10 mL). The organic layer was separated, dried over Na_2SO_4 and evaporated to give a residue that was purified on a silica gel column chromatography using hexanes and ethyl acetate as an eluent to afford the corresponding quinoline spiro products in yields of 66-75%.

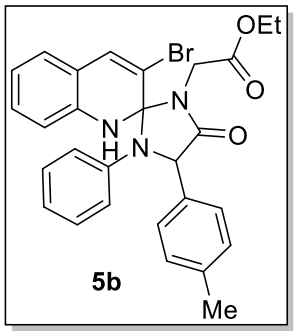
3B.8. Characterization data of products 5a-5s.

Ethyl 2-(3'-bromo-4-oxo-1,5-diphenyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5a). White solid; (194 mg, 75% yield); mp 136-137 ^oC; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3354, 3042, 2925, 2838, 1735, 1636, 1579, 1432, 1316, 1222, 1132, 1028 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.96 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.61 (s, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.00 (t, *J* = 8.0 Hz, 2H), 6.80 (t, *J* = 7.2 Hz, 1H), 6.70 (t, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 2H), 5.29 (s, 1H), 4.18 (d, *J* = 17.2 Hz, 1H), 4.02-3.96 (m, 2H), 3.45 (d, *J* = 17.2 Hz, 1H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 166.1, 142.4, 139.7, 137.9, 136.6, 130.6, 128.9, 128.8, 128.4, 128.3, 127.5, 119.9, 118.3, 115.9, 115.5, 114.6, 113.7, 113.3, 91.6, 65.1, 61.4, 40.6, 14.2; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{25}BrN_3O_3^+$ $[M+H]^+$ 518.1074; found 518.1078.

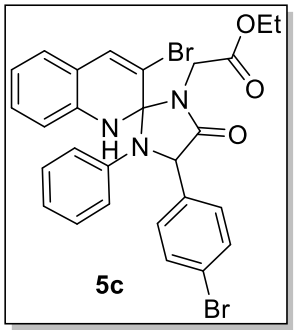


5a

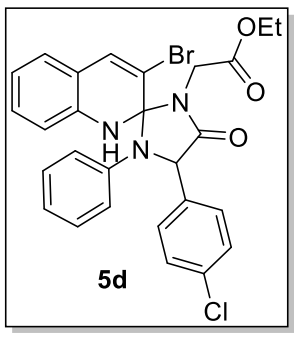
Ethyl 2-((5R)-3'-bromo-4-oxo-1-phenyl-5-(*p*-tolyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5b). White solid; (186 mg, 70% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3357, 3032, 2923, 2858, 1725, 1626, 1599, 1424, 1307, 1214, 1142, 1022 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.31 (s, 1H), 7.93 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.59 (s, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 1H), 7.01-6.96 (m, 2H), 6.79 (t, J = 7.0 Hz, 1H), 6.69 (t, J = 7.2 Hz, 1H), 6.55 (d, J = 8.4 Hz, 2H), 5.22 (s, 1H), 4.17 (d, J = 16.8 Hz, 1H), 3.98 (qd, J = 7.1, 3.0 Hz, 2H), 3.43 (d, J = 17.2 Hz, 1H), 2.31 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 168.05, 166.31, 142.50, 139.72, 137.73, 136.60, 135.02, 130.59, 129.42, 128.89, 128.24, 127.54, 119.89, 118.29, 115.92, 115.49, 114.65, 113.77, 91.59, 65.03, 61.40, 40.6, 21.24, 14.30; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{27}BrN_3O_3^+$ $[M+H]^+$ 532.1230; found 532.1231.



Ethyl 2-(3'-bromo-5-(4-bromophenyl)-4-oxo-1-phenyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5c). White solid; (203 mg, 68% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3353, 3045, 2925, 2833, 1744, 1625, 1504, 1425, 1303, 1224, 1141, 1011 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.03 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 121 Hz, 1H), 7.59 (s, 1H), 7.26 (m, 2H), 7.07 – 6.99 (m, 4H), 6.72 (t, J = 7.4 Hz, 2H), 6.55 (d, J = 8.0 Hz, 2H), 5.34 (s, 1H), 4.18 (d, J = 16.8 Hz, 1H), 3.99 (qd, J = 7.1, 1.8 Hz, 2H), 3.45 (d, J = 17.2 Hz, 1H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 167.9, 165.7, 142.2, 139.6, 137.4, 136.7, 131.7, 130.6, 130.5, 129.0, 127.5, 121.8, 120.1, 118.3, 116.0, 115.4, 114.3, 113.7, 113.4, 91.7, 64.4, 61.4, 40.6, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{24}Br_2N_3O_3^+$ $[M+H]^+$ 596.0179; found 596.0177.

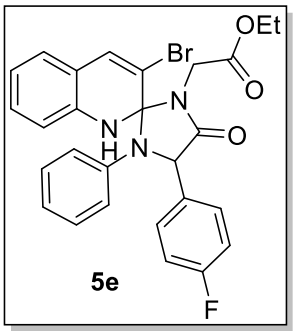


Ethyl 2-(3'-bromo-5-(4-chlorophenyl)-4-oxo-1-phenyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5d). White solid; (182 mg, 66% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3352, 3045, 2924, 2833, 1744, 1625, 1504, 1424, 1304, 1225, 1141, 1016 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.04 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.07-7.00 (m, 3H), 6.80 (t, J = 7.4 Hz, 1H), 6.72 (t, J = 7.4 Hz, 1H), 6.55 (d, J = 8.0 Hz, 2H), 5.36 (s, 1H), 4.18 (d, J = 16.8 Hz, 1H), 3.99 (qd, J = 7.0, 1.5 Hz,

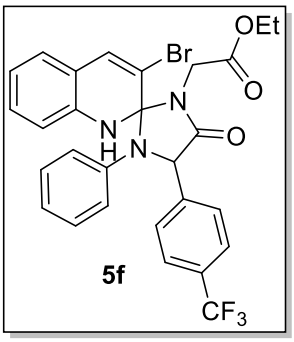


2H), 3.45 (d, *J* = 17.2 Hz, 1H), 1.05 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 165.8, 142.2, 139.6, 136.9, 136.6, 133.1, 132.0, 130.6, 130.1, 129.0, 128.8, 128.1, 127.5, 123.8, 120.2, 118.3, 116.0, 115.4, 114.3, 113.7, 91.7, 64.3, 61.4, 40.6, 14.2; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{24}BrClN_3O_3^+$ $[M+H]^+$ 552.0684; found 552.0688.

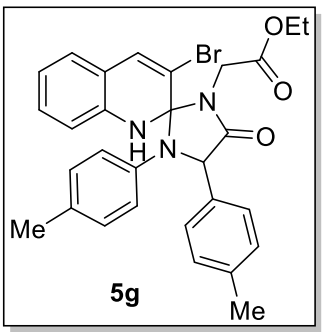
Ethyl 2-(3'-bromo-5-(4-fluorophenyl)-4-oxo-1-phenyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5e). White solid; (185 mg, 69% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3354, 3032, 2925, 2838, 1747, 1625, 1524, 1434, 1314, 1228, 1132, 1026 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.03 (s, 1H), 7.83 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.60 (s, 1H), 7.28 – 7.23 (m, 3H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.00 (t, *J* = 8.0 Hz, 3H), 6.80 (t, *J* = 7.4 Hz, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 2H), 5.35 (s, 1H), 4.19 (d, *J* = 16.8 Hz, 1H), 3.99 (dd, *J* = 13.6, 6.4 Hz, 2H), 3.45 (d, *J* = 17.2 Hz, 1H), 1.05 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 166.1, 142.3, 139.6, 136.6, 134.0, 130.6, 130.3, 130.3, 128.9, 127.5, 120.1, 118.3, 116.0, 115.7, 115.5, 114.5, 113.7, 113.4, 91.7, 64.3, 61.4, 40.6, 14.2;.HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{24}BrFN_3O_3^+$ $[M+H]^+$ 536.0980; found 536.0985.



Ethyl 2-(3'-bromo-4-oxo-1-phenyl-5-(4-(trifluoromethyl)phenyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5f). White solid; (199 mg, 68% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3354, 3045, 2929, 2838, 1742, 1600, 1504, 1427, 1323, 1232, 1159, 1020 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.07 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 1H), 7.30 – 7.24 (m, 2H), 7.06 – 6.99 (m, 3H), 6.81 (t, *J* = 7.0 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 2H), 5.49 (s, 1H), 4.18 (d, *J* = 17.2 Hz, 1H), 3.98 (qd, *J* = 7.1, 1.6 Hz, 2H), 3.46 (d, *J* = 17.2 Hz, 1H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 167.9, 165.4, 142.6, 142.1, 139.5, 136.7, 130.6, 129.0, 127.6, 125.6, 120.3, 118.4, 116.0, 115.5, 114.2, 113.7, 91.8, 64.5, 61.4, 40.7, 14.2; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{24}BrF_3N_3O_3^+$ $[M+H]^+$ 586.0948; found 586.0944.

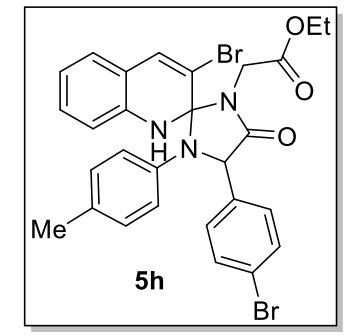


Ethyl 2-(3'-bromo-4-oxo-1,5-di-*p*-tolyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5g). White solid; (204 mg, 75% yield); mp 154-155 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3359, 3062, 2989, 2830, 1745, 1625, 1517, 1423, 1306, 1219, 1140, 1021 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.91 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.55 (s, 1H), 7.24 (d, J = 7.2 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 7.6 Hz, 3H), 6.49 (d, J = 8.8 Hz, 2H), 5.21 (s, 1H), 4.16 (d, J = 16.8 Hz, 1H), 3.99 (dd, J = 7.2, 2.4 Hz, 2H), 3.44 (d, J = 17.2 Hz, 1H), 2.31 (s, 3H), 2.07 (s, 3H), 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 166.5, 140.0, 139.7, 137.6, 136.4, 135.0, 130.5, 129.3, 128.7, 128.3, 127.4, 118.1, 116.3, 115.5, 114.9, 113.7, 91.6, 65.0, 61.3, 40.7, 21.2, 20.3, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{29}BrN_3O_3^+$ $[M+H]^+$ 546.1387; found 546.1386.



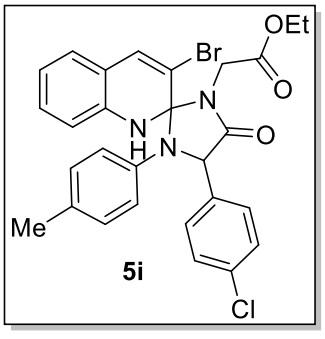
5g

Ethyl 2-(3'-bromo-5-(4-bromophenyl)-4-oxo-1-(*p*-tolyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5h). White solid; (220 mg, 72% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3354, 3044, 2921, 2836, 1742, 1625, 1518, 1423, 1302, 1224, 1139, 1011 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.01 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.60-7.55 (m, 3H), 7.24 (d, J = 7.6 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.81-6.76 (m, 3H), 6.48 (d, J = 8.8 Hz, 2H), 5.32 (s, 1H), 4.16 (d, J = 17.2 Hz, 1H), 3.98 (qd, J = 7.0, 1.1 Hz, 2H), 3.44 (d, J = 16.8 Hz, 1H), 2.07 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 165.9, 139.8, 139.6, 137.5, 136.5, 131.6, 130.5, 129.4, 129.1, 127.5, 121.7, 118.2, 116.4, 115.5, 114.6, 113.6, 91.7, 64.4, 61.4, 40.7, 20.3, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{26}Br_2N_3O_3^+$ $[M+H]^+$ 610.0335; found 610.0331.



5h

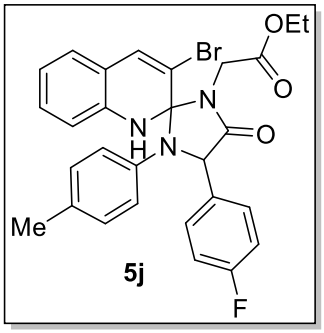
Ethyl 2-(3'-bromo-5-(4-chlorophenyl)-4-oxo-1-(*p*-tolyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5i). White solid; (198 mg, 70% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3345, 3034, 2926, 2838, 1747, 1628, 1528, 1423, 1308, 1234, 1129, 1021 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.02 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.56 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.79 (m, 3H), 6.48 (d, J = 8.8 Hz, 2H), 5.34 (s, 1H), 4.17 (d, J = 17.2 Hz, 1H), 4.02 – 3.96 (m, 2H), 3.45



5i

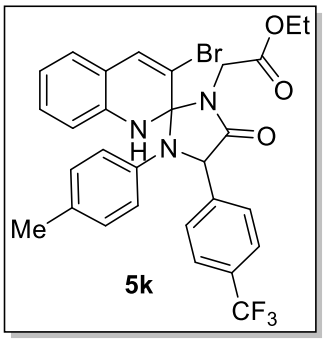
(d, *J* = 17.2 Hz, 1H), 2.08 (s, 3H), 1.05 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 166.0, 139.8, 139.6, 137.0, 136.5, 133.1, 130.5, 130.2, 129.4, 129.1, 128.7, 127.5, 118.2, 116.4, 115.5, 114.6, 113.6, 91.7, 64.3, 61.4, 40.7, 20.3, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{26}BrClN_3O_3^+$ $[M+H]^+$ 566.0841; found 566.0840.

Ethyl 2-(3'-bromo-5-(4-fluorophenyl)-4-oxo-1-(*p*-tolyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5j). White solid; (203 mg, 74% yield); mp 145-146 ^{o}C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3347, 3034, 2925, 2834, 1742, 1635, 1524, 1433, 1318, 1232, 1142, 1028 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.99 (s, 1H), 7.79 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.55 (s, 1H), 7.26-7.18 (m, 4H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.81-6.76 (m, 3H), 6.49 (d, *J* = 8.8 Hz, 2H), 5.32 (s, 1H), 4.16 (d, *J* = 17.2 Hz, 1H), 4.01 – 3.95 (m, 2H), 3.44 (d, *J* = 16.8 Hz, 1H), 2.07 (s, 3H), 1.05 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 166.2, 139.9, 139.6, 136.5, 134.1, 134.1, 130.5, 130.4, 130.3, 129.4, 129.0, 127.4, 118.2, 116.4, 115.6, 115.5, 115.4, 114.7, 113.6, 91.7, 64.3, 61.4, 40.7, 20.3, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{26}BrFN_3O_3^+$ $[M+H]^+$ 550.1136; found 550.1135.



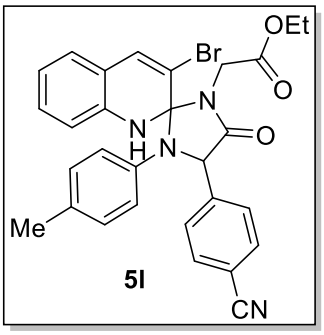
5j

Ethyl 2-(3'-bromo-4-oxo-1-(*p*-tolyl)-5-(4-(trifluoromethyl)phenyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5k). White solid; (204 mg, 68% yield); mp 145-146 ^{o}C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3349, 3044, 2936, 2832, 1739, 1625, 1517, 1422, 1321, 1232, 1133, 1020 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.06 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.57 (s, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.79 (m, 3H), 6.49 (d, *J* = 8.8 Hz, 2H), 5.47 (s, 1H), 4.17 (d, *J* = 16.8 Hz, 1H), 3.98 (dd, *J* = 7.1, 1.0 Hz, 2H), 3.46 (d, *J* = 16.8 Hz, 1H), 2.07 (s, 3H), 1.04 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 167.9, 165.6, 142.7, 139.7, 139.6, 136.6, 130.6, 129.5, 129.2, 129.1, 128.9, 127.5, 126.0, 125.6, 125.5, 123.3, 118.3, 116.4, 115.5, 114.5, 113.6, 91.9, 64.5, 61.4, 40.8, 20.3, 14.2; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{26}BrF_3N_3O_3^+$ $[M+H]^+$ 600.1104; found 600.1103.

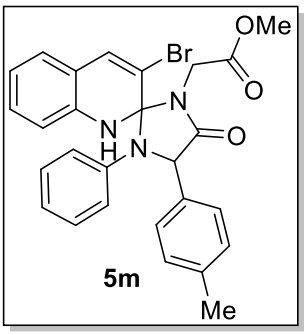


5k

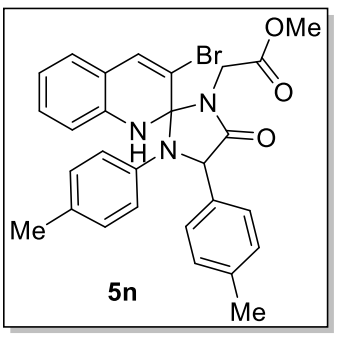
Ethyl 2-(3'-bromo-5-(4-cyanophenyl)-4-oxo-1-(*p*-tolyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5l). White solid; (186 mg, 67% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3347, 3061, 2925, 2858, 2229, 1722, 1609, 1516, 1426, 1213, 1142, 1020 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.09 (s, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.57 (s, 1H), 7.25 (d, J = 7.2 Hz, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 3H), 6.49 (d, J = 8.0 Hz, 2H), 5.49 (s, 1H), 4.18 (d, J = 16.8 Hz, 1H), 3.98 (dd, J = 13.6, 6.4 Hz, 2H), 3.47 (d, J = 17.2 Hz, 1H), 2.06 (s, 3H), 1.04 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 167.9, 165.4, 143.6, 139.6, 139.5, 136.6, 132.7, 130.6, 129.5, 129.3, 127.5, 119.2, 118.3, 116.4, 115.5, 114.4, 113.6, 111.4, 91.9, 64.6, 61.4, 40.8, 20.3, 14.2; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{26}BrN_4O_3^+$ $[M+H]^+$ 557.1183; found 557.1186.



Methyl 2-(3'-bromo-4-oxo-1-phenyl-5-(*p*-tolyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5m). White solid; (186 mg, 72% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3358, 3028, 2925, 2846, 1746, 1600, 1502, 1425, 1224, 1156, 1027 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.98 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.28-7.23 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.98 (t, J = 7.4 Hz, 2H), 6.79 (t, J = 7.4 Hz, 1H), 6.69 (t, J = 7.4 Hz, 1H), 6.55 (d, J = 8.0 Hz, 2H), 5.23 (s, 1H), 4.17 (d, J = 17.2 Hz, 1H), 3.53 (s, 3H), 3.47 (d, J = 7.6 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 168.5, 166.3, 142.4, 139.7, 137.7, 136.5, 134.9, 130.6, 129.4, 128.8, 128.2, 127.5, 119.9, 118.3, 116.0, 115.4, 114.6, 113.7, 113.3, 91.6, 65.0, 52.4, 40.6, 21.2; .HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{25}BrN_3O_3^+$ $[M+H]^+$ 518.1074; found 518.1076.

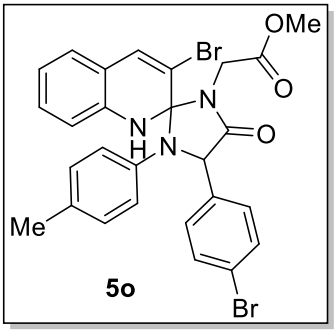


Methyl 2-(3'-bromo-4-oxo-1,5-di-*p*-tolyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5n). White solid; (199 mg, 75% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3367, 3028, 2925, 2858, 1747, 1626, 1519, 1419, 1306, 1223, 1142, 1038 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.96 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.54 (s, 1H), 7.27 – 7.17 (m, 4H), 7.09 (d, J = 7.6 Hz, 1H), 6.81-6.75 (m, 3H), 6.49 (d, J = 8.8 Hz, 2H), 5.23 (s, 1H), 4.16 (d, J = 16.8 Hz, 1H), 3.53 (s, 3H), 3.47 (d, J = 9.6 Hz, 1H), 2.30 (s, 3H), 2.06 (s, 3H);



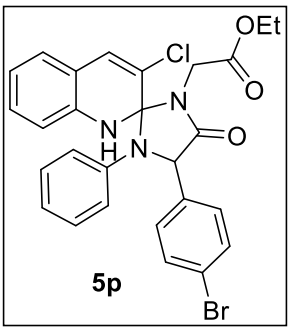
^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.5, 166.5, 140.0, 139.7, 137.6, 136.4, 135.0, 130.5, 129.3, 128.8, 128.2, 127.4, 118.2, 116.3, 115.5, 114.8, 113.6, 91.6, 65.0, 52.4, 40.6, 21.2, 20.3; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{27}BrN_3O_3^+$ $[M+H]^+$ 532.1230; found 532.1237.

Methyl 2-(3'-bromo-5-(4-bromophenyl)-4-oxo-1-(*p*-tolyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5o). White solid; (218 mg, 73% yield); mp 145-146 ^{o}C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3357, 3045, 2916, 2838, 1748, 1625, 1517, 1420, 1303, 1229, 1137, 1013 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.05 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.61-7.55 (m, 3H), 7.30-7.22 (m, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.79 (t, J = 9.0 Hz, 3H), 6.49 (d, J = 8.8 Hz, 2H), 5.34 (s, 1H), 4.17 (d, J = 17.2 Hz, 1H), 3.54 (s, 3H), 3.48 (d, J = 13.6 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.5, 166.0, 139.7, 139.6, 137.4, 136.5, 131.6, 130.6, 130.5, 129.4, 129.2, 127.5, 121.7, 118.3, 116.5, 115.4, 114.5, 113.6, 91.8, 64.4, 52.5, 40.7, 20.3; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{24}Br_2N_3O_3^+$ $[M+H]^+$ 596.0179; found 596.0179.



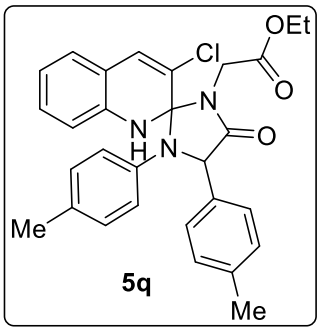
5o

Ethyl 2-(5-(4-bromophenyl)-3'-chloro-4-oxo-1-phenyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5p). White solid; (190 mg, 69% yield); mp 122-123 ^{o}C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3379, 3047, 2928, 2844, 1738, 1648, 1512, 1478, 1338, 1281, 1182, 1014 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.11 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.40 (s, 1H), 7.28-7.23 (m, 2H), 7.06-6.99 (m, 3H), 6.81 (t, J = 8.0 Hz, 1H), 6.73 (t, J = 7.4 Hz, 1H), 6.58 (d, J = 8.0 Hz, 2H), 5.37 (s, 1H), 4.13 (d, J = 17.2 Hz, 1H), 4.03-3.96 (m, 2H), 3.52 (d, J = 17.2 Hz, 1H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 167.9, 165.8, 142.4, 139.3, 137.5, 132.5, 131.7, 130.4, 129.0, 127.6, 122.1, 121.7, 120.4, 118.4, 116.2, 115.0, 113.6, 91.5, 64.2, 61.4, 40.7, 14.3. HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{24}BrClN_3O_3^+$ $[M+H]^+$ 552.0684; found 552.0689.

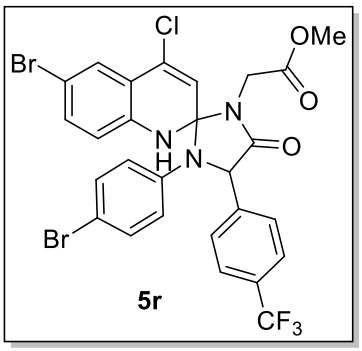


5p

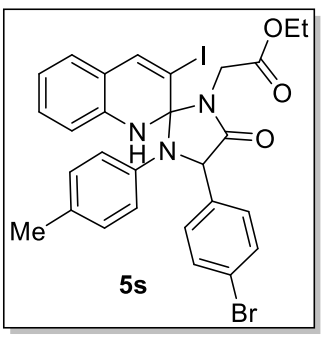
Ethyl 2-(3'-chloro-4-oxo-1,5-di-*p*-tolyl-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5q). White solid; (178 mg, 71% yield); mp 128-129 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3360, 3052, 2983, 2852, 1745, 1631, 1517, 1490, 1373, 1268, 1145, 1017 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.99 (s, 1H), 7.60 (d, J = 6.8 Hz, 2H), 7.33 (s, 1H), 7.25-7.15 (m, 4H), 7.07 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 3.2 Hz, 3H), 6.52 (d, J = 7.6 Hz, 2H), 5.23 (s, 1H), 4.11 (d, J = 17.2 Hz, 1H), 4.02 – 3.96 (m, 2H), 3.50 (d, J = 16.8 Hz, 1H), 2.30 (s, 3H), 2.06 (s, 3H), 1.06 (t, J = 6.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 166.6, 140.2, 139.4, 137.6, 135.1, 132.3, 130.3, 129.3, 129.3, 129.0, 128.2, 127.5, 122.7, 118.2, 116.5, 115.0, 113.6, 91.3, 64.8, 61.3, 40.7, 21.2, 20.3, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{29}ClN_3O_3^+$ $[M+H]^+$ 502.1892; found 502.1893.



Methyl 2-(6'-bromo-1-(4-bromophenyl)-4'-chloro-4-oxo-5-(4-(trifluoromethyl)phenyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5r). White solid; (253 mg, 74% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3355, 3024, 2956, 2851, 1738, 1681, 1584, 1481, 1387, 1287, 1117, 1067 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.29 (d, J = 2.0 Hz, 1H), 8.03 (dd, J = 9.2, 2.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.80 (s, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.58-7.47 (m, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 9.2 Hz, 1H), 6.64 (d, J = 8.4 Hz, 2H), 6.01 (d, J = 9.2 Hz, 1H), 4.75 (d, J = 5.6 Hz, 2H), 3.62 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 172.0, 169.5, 153.6, 146.4, 145.4, 142.5, 135.0, 131.6, 131.3, 129.4, 125.9, 125.7, 125.5, 123.2, 121.5, 119.7, 115.4, 108.3, 79.4, 58.44, 52.5; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{20}Br_2ClF_3N_3O_3^+$ $[M+H]^+$ 683.9507 ; found 683.9511.

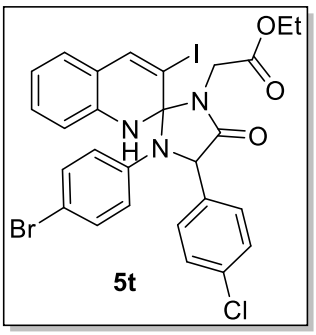


Ethyl 2-(5-(4-bromophenyl)-3'-iodo-4-oxo-1-(*p*-tolyl)-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5s). White solid; (223 mg, 68% yield); mp 145-146 °C; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3375, 3042, 2923, 2858, 1721, 1618, 1518, 1402, 1304, 1213, 1136, 1010 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.77 (s, 1H), 7.73 (d, J = 1.2 Hz, 2H), 7.71 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 8.2 Hz, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 2H), 6.76 (t, J = 7.0 Hz, 1H), 6.42 (d, J = 8.4 Hz, 2H), 5.29 (s, 1H), 4.18 (d, J = 17.2 Hz,



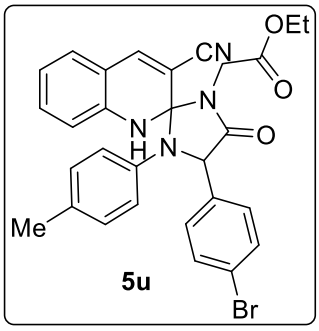
1H), 3.97 (qd, *J* = 7.1, 2.3 Hz, 2H), 3.38 (s, 1H), 2.07 (s, 3H), 1.03 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 165.7, 143.8, 140.0, 139.4, 137.3, 131.6, 130.6, 129.4, 128.6, 127.1, 121.7, 118.0, 116.4, 116.0, 113.7, 92.2, 64.7, 61.4, 40.7, 20.3, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{28}H_{26}BrIN_3O_3^+$ $[M+H]^+$ 658.0197 ; found 658.0196.

Ethyl 2-(1-(4-bromophenyl)-5-(4-chlorophenyl)-3'-iodo-4-oxo-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5t). White solid; (223 mg, 66% yield); mp 145-146 ºC; R_f = 0.50 (hexanes/EtOAc = 8:2); IR (KBr, cm^{-1}) 3389, 3053, 2925, 2854, 1748, 1657, 1506, 1488, 1344, 1272, 1195, 1014 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.84 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.22 (dd, *J* = 15.4, 8.6 Hz, 5H), 6.78 (d, *J* = 7.6 Hz, 2H), 6.46 (d, *J* = 9.2 Hz, 2H), 5.33 (s, 1H), 4.19 (d, *J* = 17.2 Hz, 2H), 3.97 (q, *J* = 2.8 Hz, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 167.9, 165.2, 153.0, 150.1, 144.2, 141.3, 139.8, 136.1, 133.3, 131.6, 130.8, 130.2, 128.8, 127.3, 118.3, 117.8, 116.4, 115.4, 113.8, 111.8, 107.8, 92.2, 64.5, 61.4, 40.6, 14.2. HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{23}BrClIN_3O_3^+$ $[M+H]^+$ 677.9651; found 677.9651.



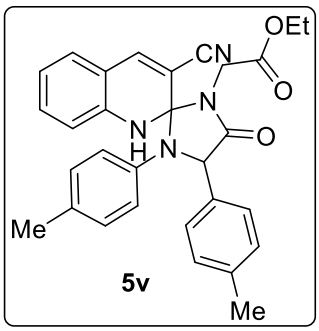
5t

Ethyl 2-(5-(4-bromophenyl)-3'-cyano-4-oxo-1-(*p*-tolyl)-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5u). White solid; (167 mg, 60% yield); mp 164-165 ºC; R_f = 0.50 (hexanes/EtOAc = 6:4); IR (KBr, cm^{-1}) 3362, 2923, 2852, 2229, 1745, 1664, 1514, 1462, 1382, 1295, 1144, 1023 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.74 (t, J = 5.8 Hz, 1H), 8.70 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.81-7.76 (m, 2H), 7.47-7.42 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.02 (s, 3H), 7.00-6.94 (m, 1H), 6.43 (s, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.95-3.81 (m, 2H), 2.24 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 170.7, 170.2, 154.5, 147.9, 147.5, 139.9, 137.2, 135.6, 133.4, 133.2, 131.1, 130.8, 129.8, 128.5, 127.1, 125.1, 122.5, 121.5, 115.6, 98.8, 66.4, 60.8, 41.5, 21.1, 14.4; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{26}BrN_4O_3^+$ $[M+H]^+$ 557.1183; found 557.1185.



5u

Ethyl 2-(3'-cyano-4-oxo-1,5-di-*p*-tolyl-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5v). White solid; (152 mg, 62% yield); mp 175-176 °C; R_f = 0.50 (hexanes/EtOAc = 6:4); IR (KBr, cm^{-1}) 3058, 2923, 2853, 2229, 1743, 1669, 1559, 1463, 1375, 1201, 1115, 1012 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.68 (s, 1H), 8.66 (t, J = 5.8 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 3.6 Hz, 2H), 7.46-7.40 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 6.99-6.93 (m, 4H), 6.38 (s, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.95-3.80 (m, 2H), 2.22 (s, 3H), 2.22 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^1H} (100 MHz, DMSO-d_6) δ (ppm): 168.0, 166.6, 140.2, 139.4, 137.6, 135.1, 132.3, 130.3, 129.3, 129.3, 129.0, 128.2, 127.5, 122.7, 118.2, 116.5, 115.0, 113.6, 91.3, 64.8, 61.3, 40.7, 21.2, 20.3, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{30}H_{29}N_4O_3^+$ $[M+H]^+$ 493.2234; found 493.2236.



5v

3B.9. References

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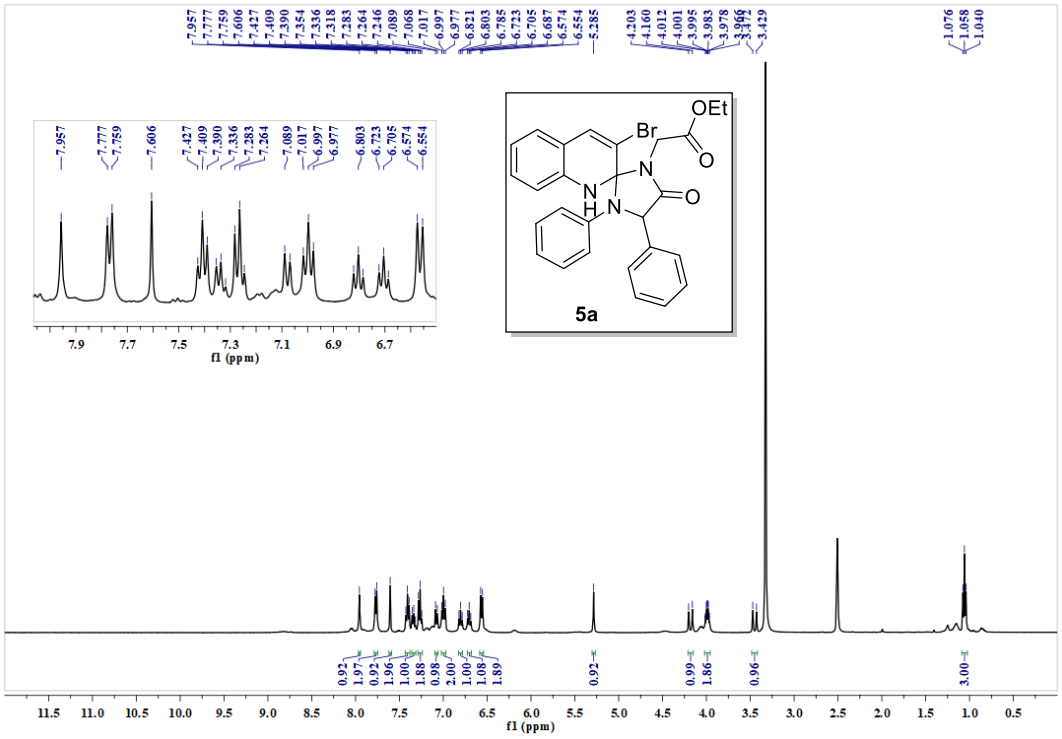
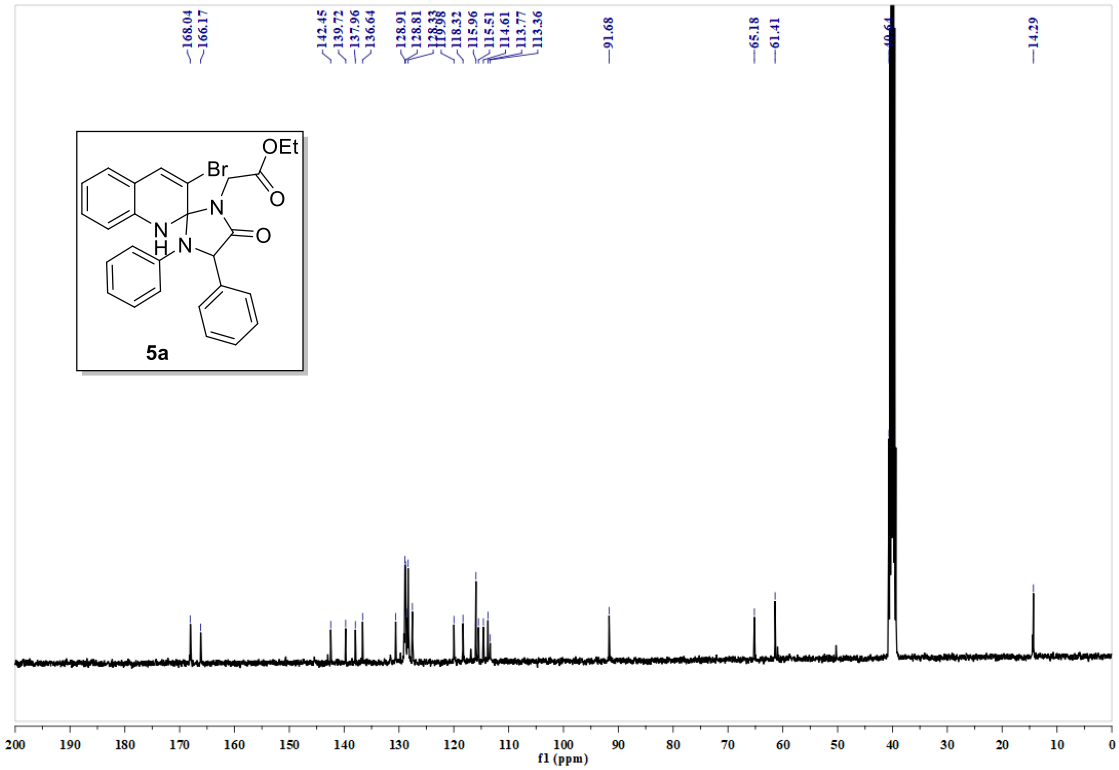
3B.10. Selected NMR (^{1}H and ^{13}C) and HRMS Spectra

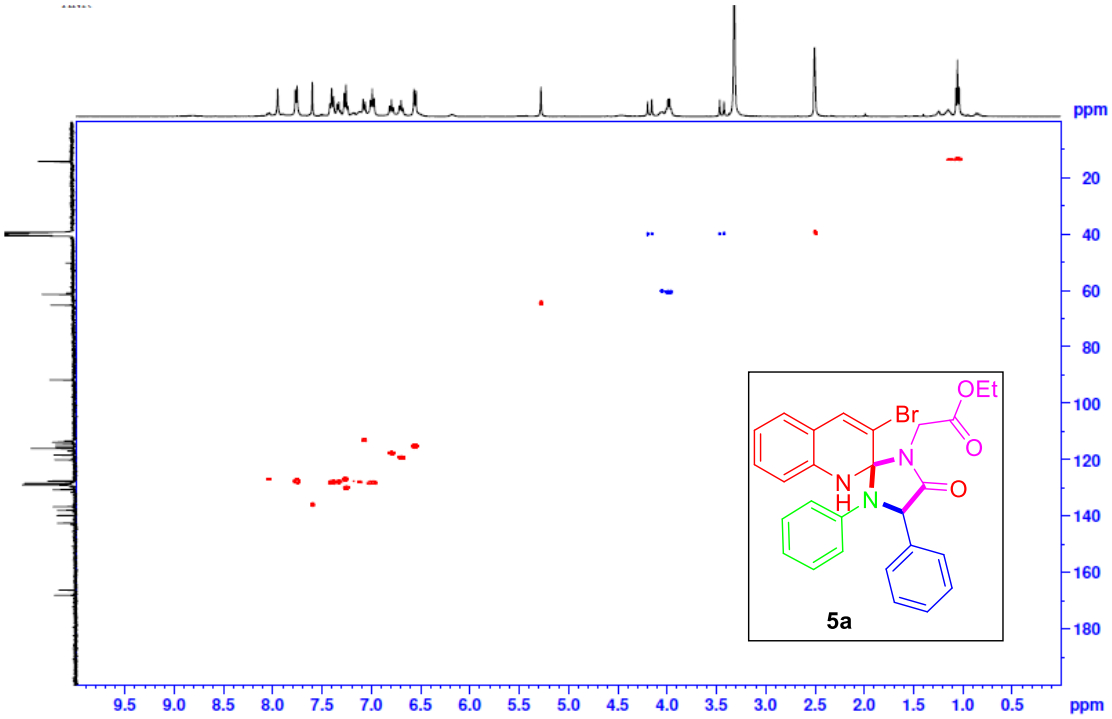
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of ethyl 2-(3'-bromo-4-oxo-1,5-diphenyl-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5a)



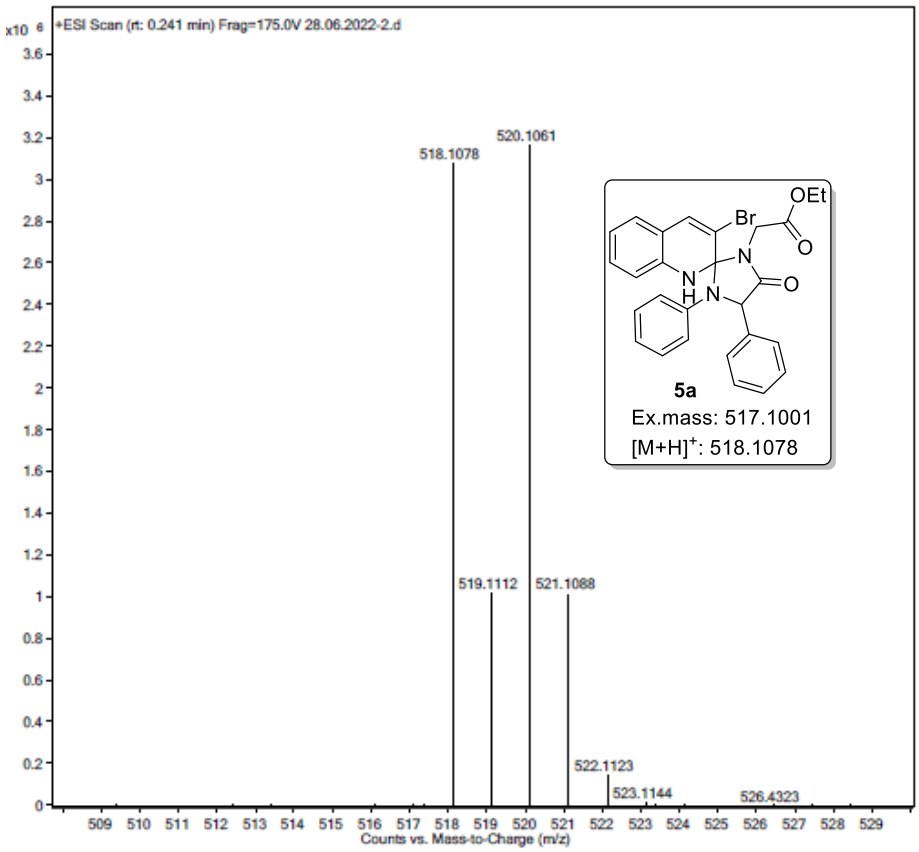
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of ethyl 2-(3'-bromo-4-oxo-1,5-diphenyl-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5a)



HSQC spectrum of ethyl 2-(3'-bromo-4-oxo-1,5-diphenyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5a)



HRMS spectrum of ethyl 2-(3'-bromo-4-oxo-1,5-diphenyl-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5a)



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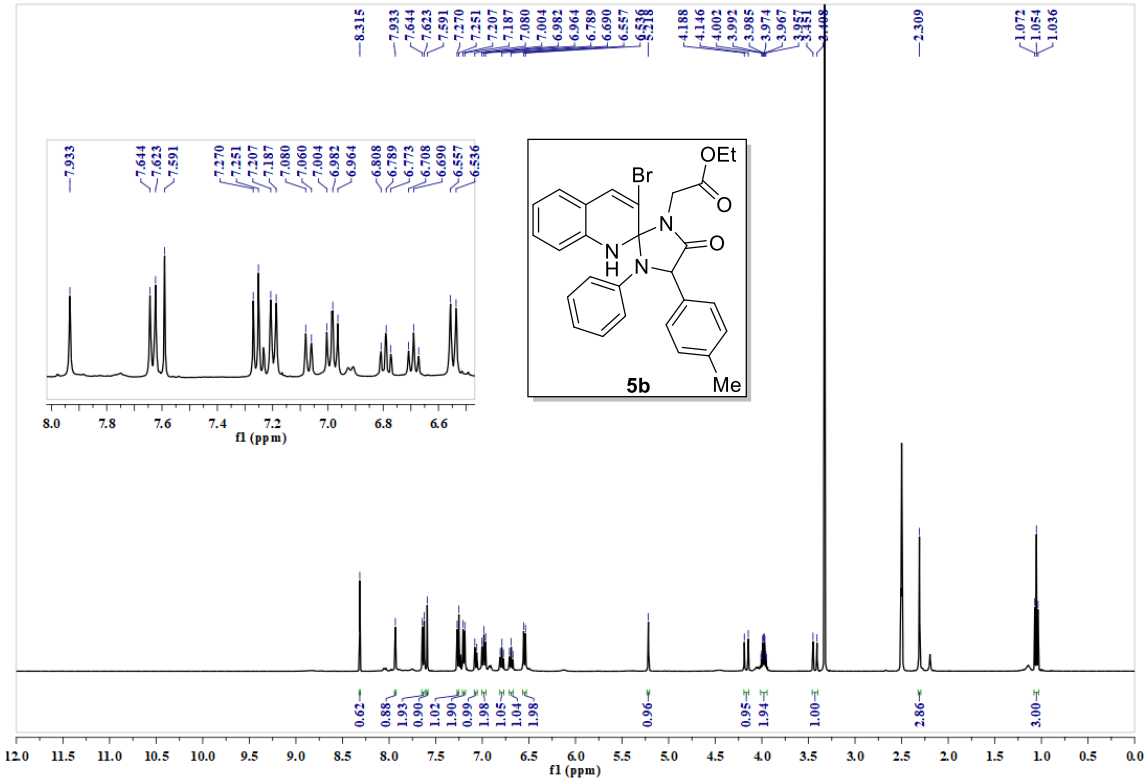

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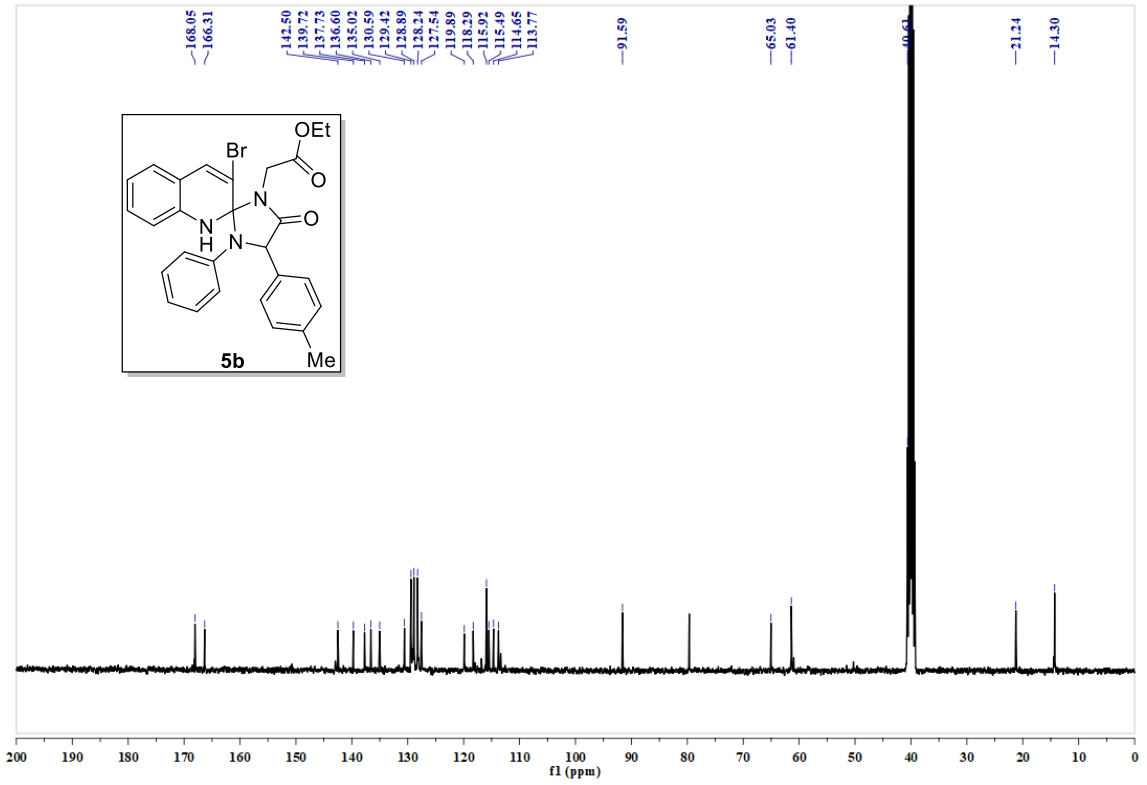

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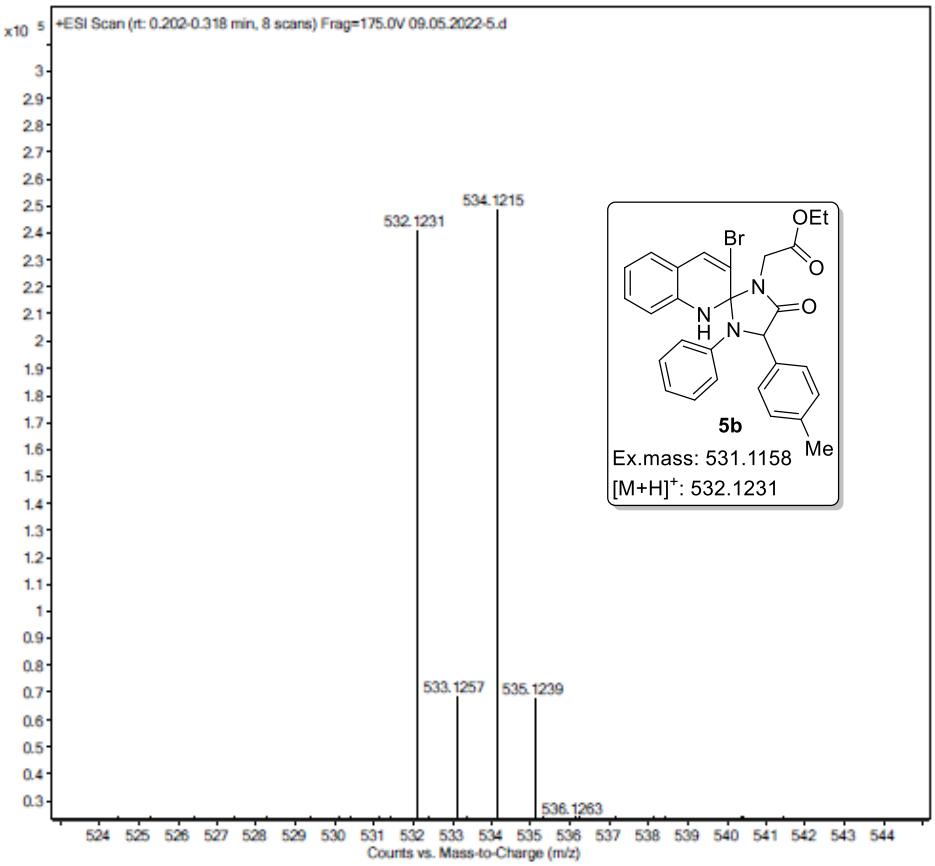
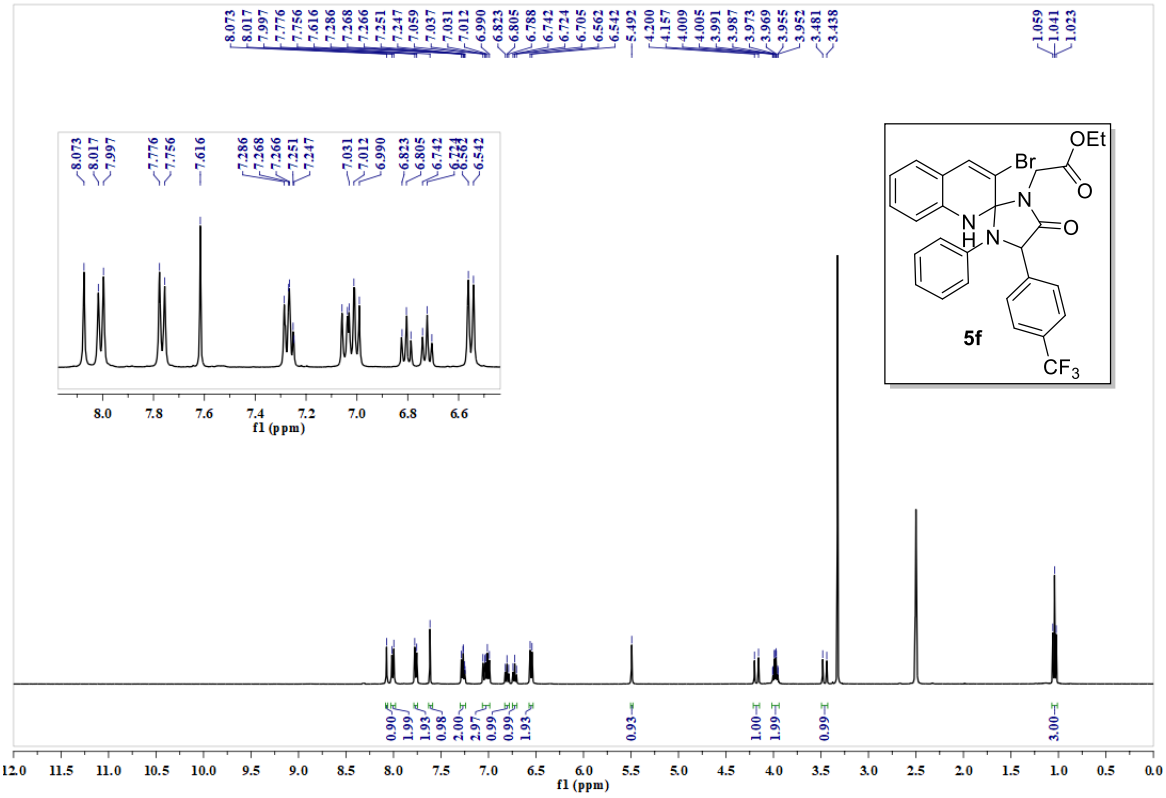


^{1}H NMR (400 MHz, DMSO-d_6) spectrum of ethyl 2-(3'-bromo-4-oxo-1-phenyl-5-(4-(trifluoromethyl)phenyl)-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5f)



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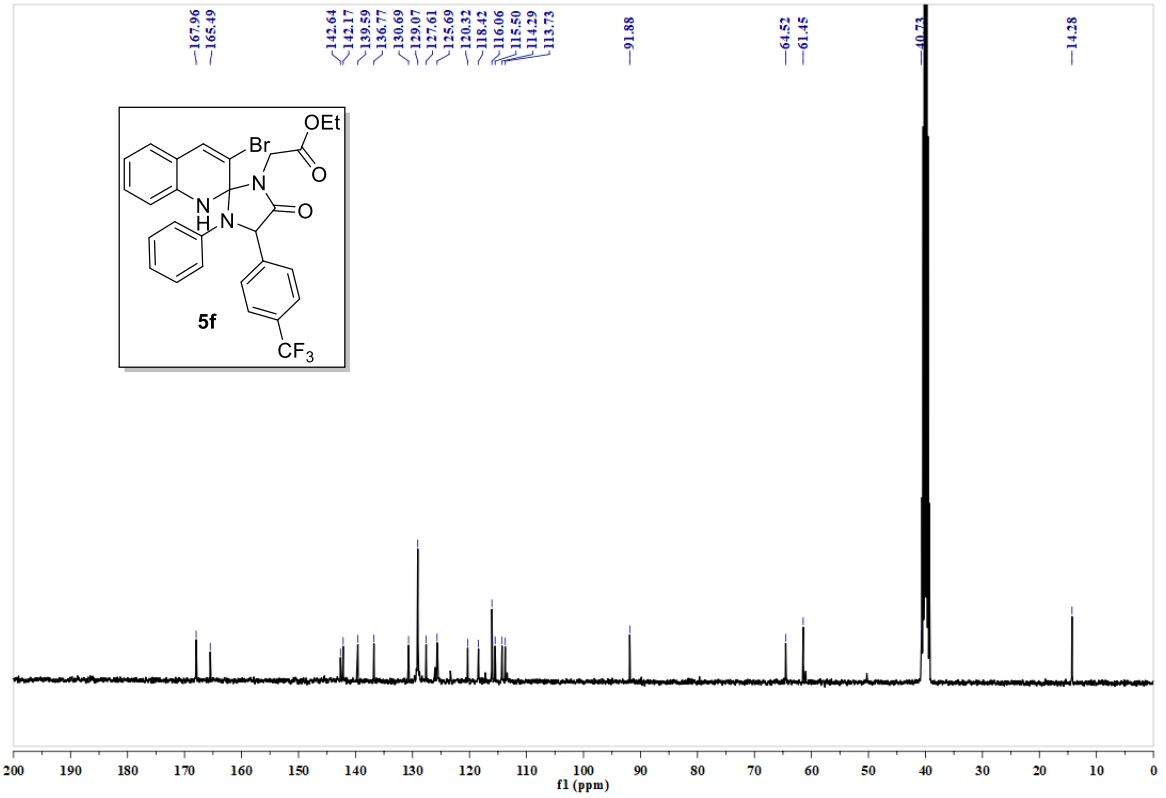
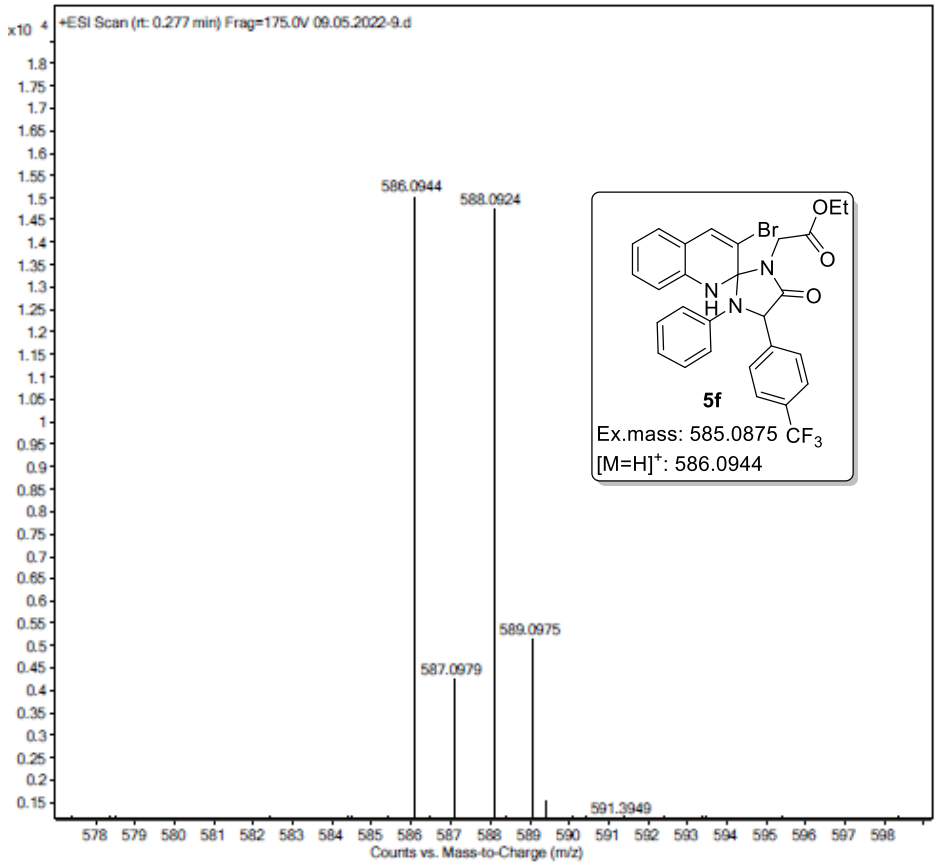
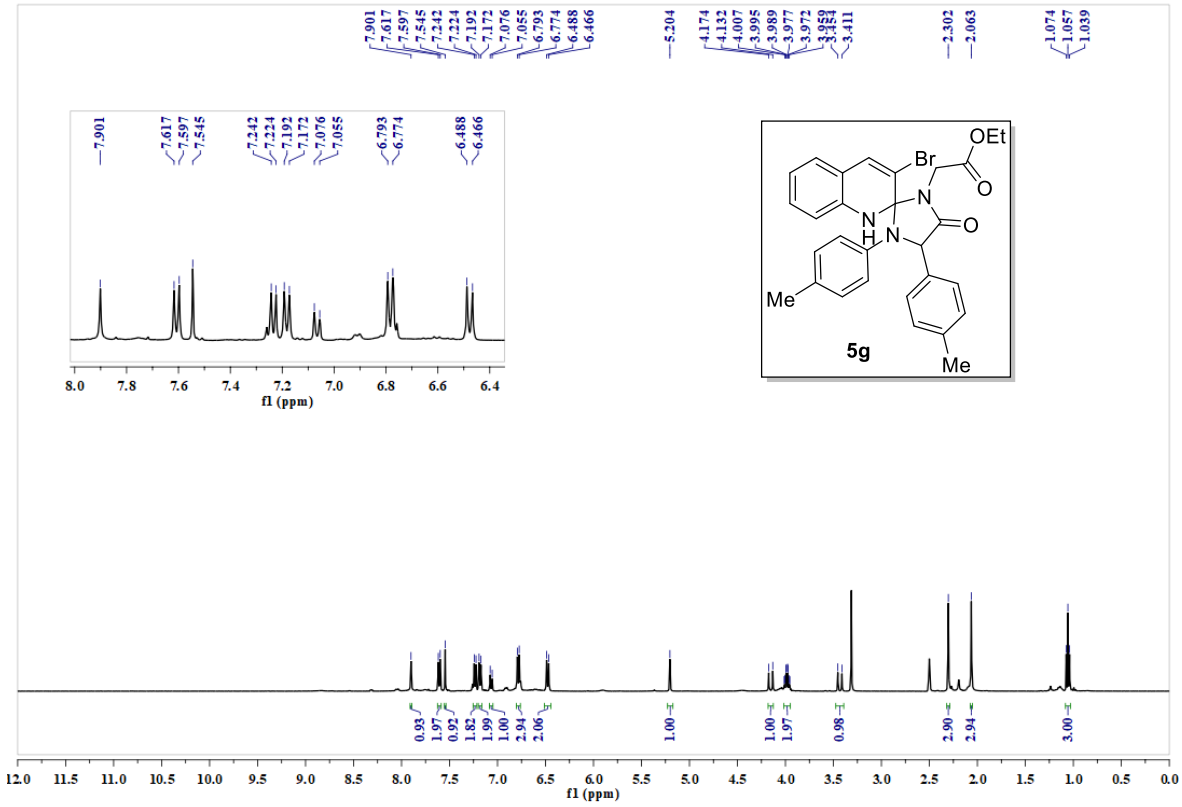


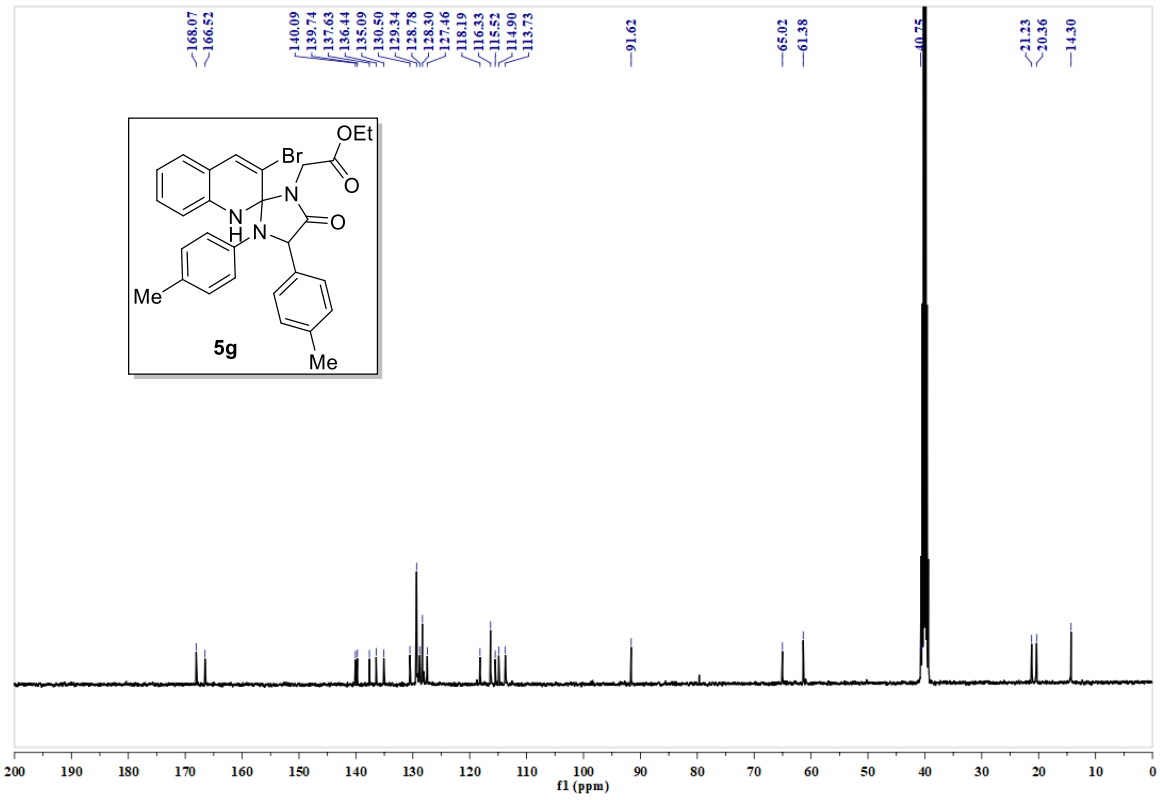
HRMS spectrum of ethyl 2-(3'-bromo-4-oxo-1-phenyl-5-(4-(trifluoromethyl)phenyl)-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5f)



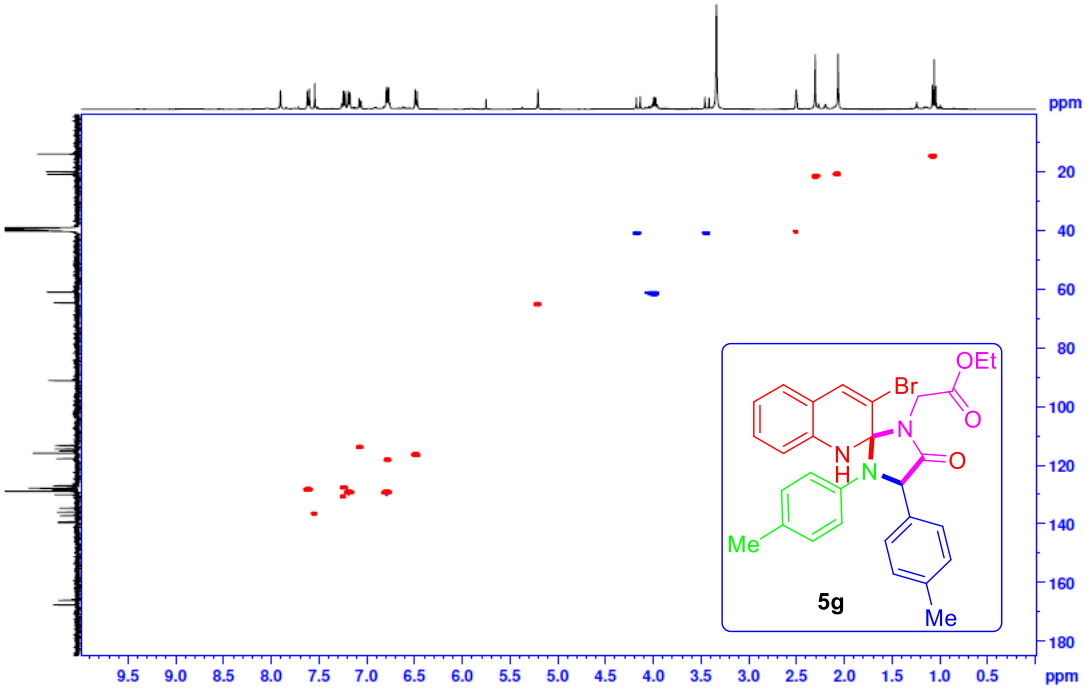
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of ethyl 2-(3'-bromo-4-oxo-1,5-di-*p*-tolyl-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5g)



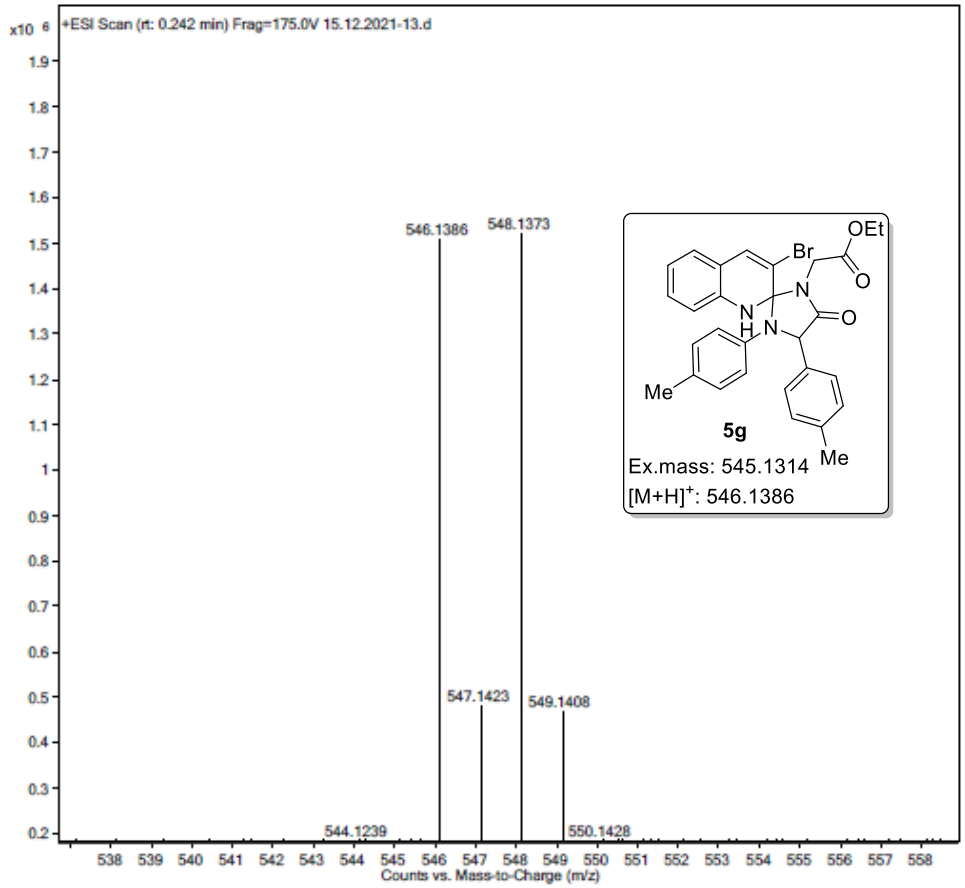
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of ethyl 2-(3'-bromo-4-oxo-1,5-di-*p*-tolyl-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5g)



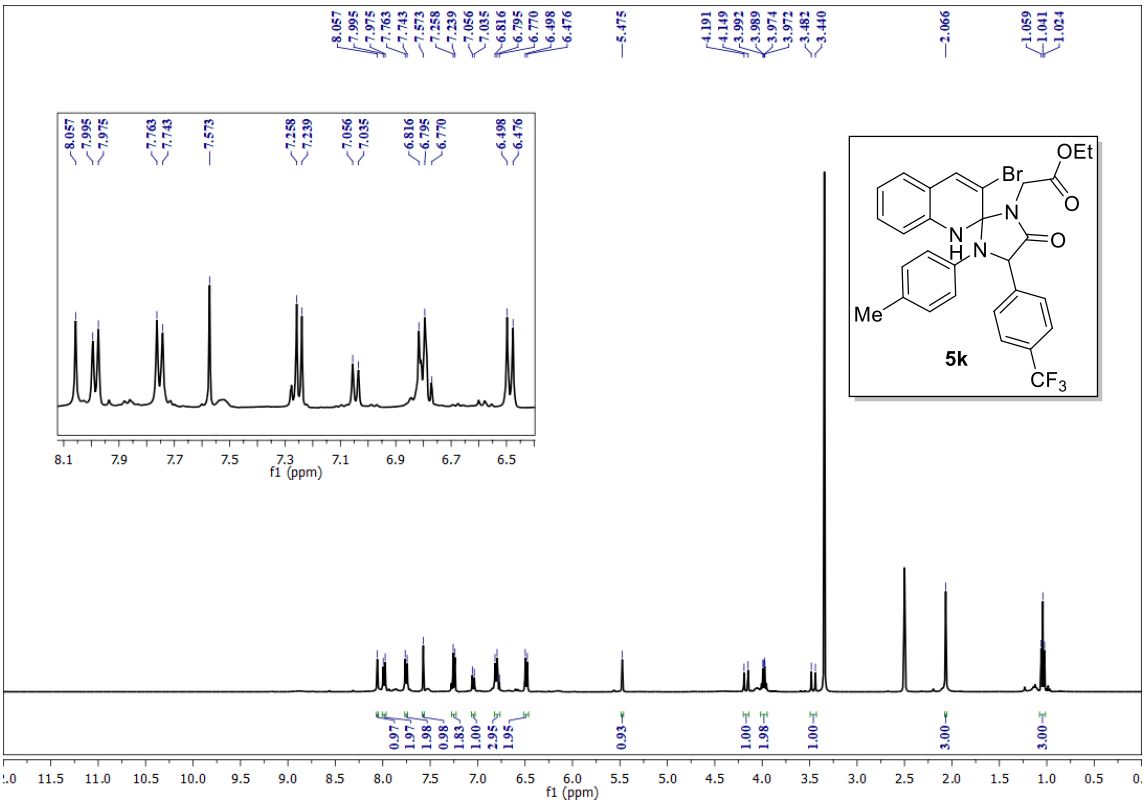
HSQC spectrum of ethyl 2-(3'-bromo-4-oxo-1,5-di-*p*-tolyl-1'*H*-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5g)



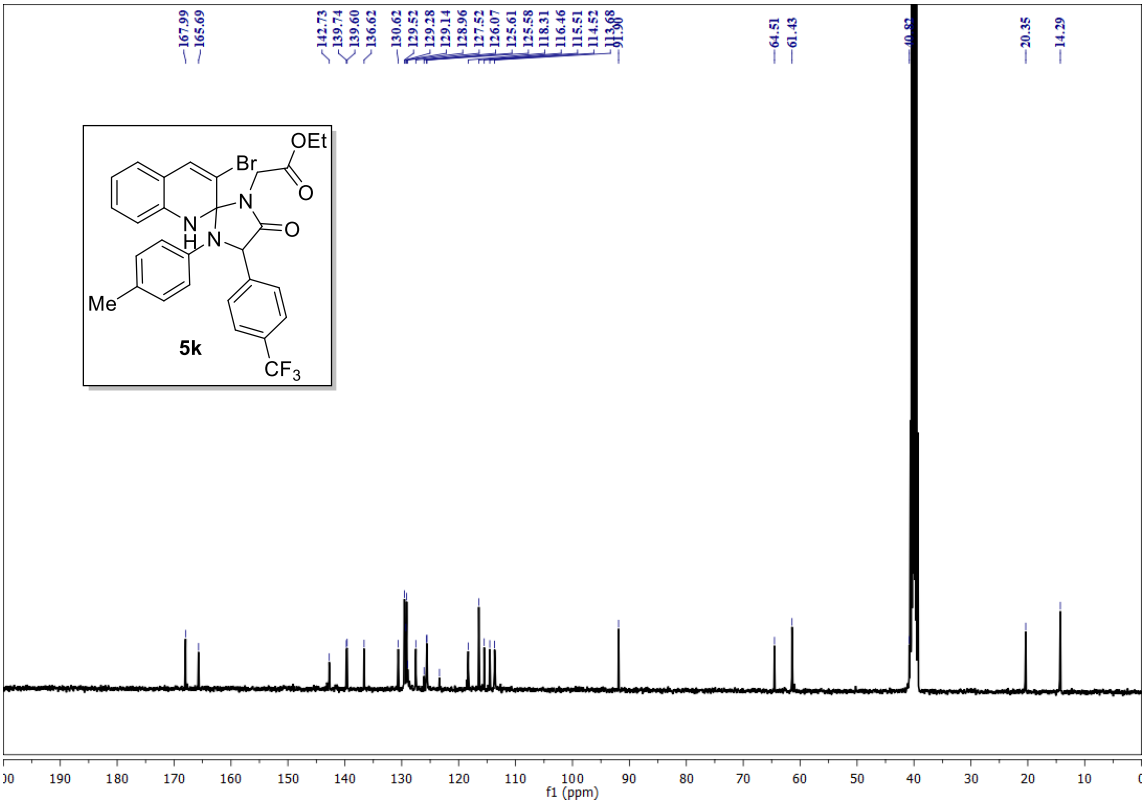
HRMS spectrum of ethyl 2-(3'-bromo-4-oxo-1,5-di-*p*-tolyl-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5g)



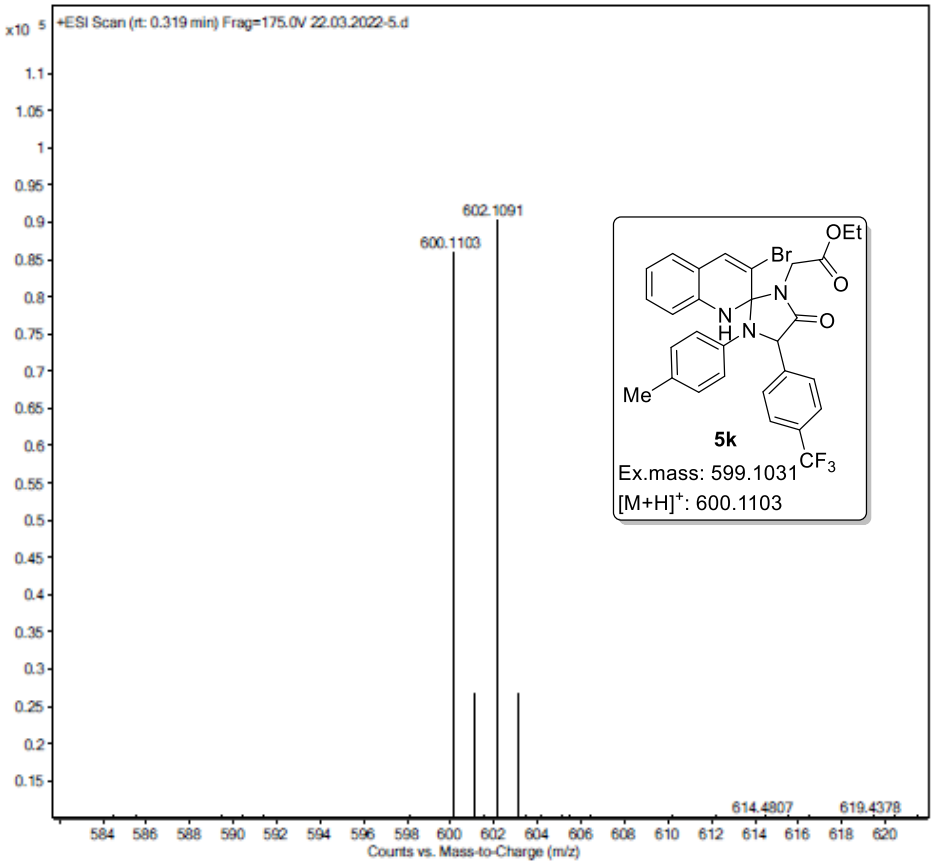
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of ethyl 2-(3'-bromo-4-oxo-1-(*p*-tolyl)-5-(4-(trifluoromethyl)phenyl)-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5k)



^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of ethyl 2-(3'-bromo-4-oxo-1-(*p*-tolyl)-5-(4-(trifluoromethyl)phenyl)-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5k)

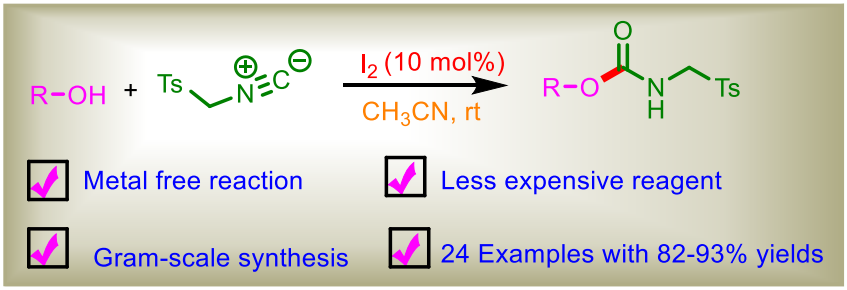


HRMS spectrum of ethyl 2-(3'-bromo-4-oxo-1-(*p*-tolyl)-5-(4-(trifluoromethyl)phenyl)-1'H-spiro[imidazolidine-2,2'-quinolin]-3-yl)acetate (5k)



CHAPTER-IV

Iodide-Catalyzed One-Pot Synthesis of Carbamates Using Alcohols and Isocyanides



4.1 Introduction

Carbamates are derivatives of carbamic acid, which are recognized by the presence of the -O-CO-NH linkage, and whose amino and carboxyl termini are substituted by a wide variety of alkyl, aryl substituents.[1] The US food and drug administration (FDA) and the European Medicines Agency (EMA) have authorised numerous medicines and prodrugs that contain carbamates as an essential component. An illustration of a carbamate substance that has recently received FDA approval "cenobamate",[2] which is used to treat partial-onset seizures in adults.[3] The first studies on carbamates as prospective medications of physostigmine, a methyl carbamate ester discovered in pure form from the seeds of calabar beans (physostigma venenosum), was found in 1864.[4] Physostigmine was initially used to treat glaucoma and excessive eye pressure, but it is now also used to treat delayed stomach emptying and myasthenia gravis. Carbamate chemicals started to be used more widely and when the first carbamate pesticide, carbaryl, was approved for use in the USA in 1959.[4,5] Currently, carbamate compounds are widely utilised as pesticides (fungicides, insecticides, and herbicides), as building blocks for the manufacture of paints and polyurethanes, and as protective groups for amines in the process of organic synthesis.[6] The carbamate group has been proven in investigations to boost the biological activity of active pharmacophores of structurally diverse natural or synthetic drugs.[7] The carbamate group is a desirable component of the structure of many pharmacologically significant compounds and a structural motif of many drugs and prodrugs due to its unique chemical properties, conformational and metabolic stability, ability to cross cell membranes, and ability to cross the blood-brain barrier in some cases. The carbamate group is now included in a wide range of licenced medications and act as chemotherapeutic agents (mitomycin C, irinotecan), neurological diseases are treated with cholinesterase inhibitors (neostigmine, pyridostigmine physostigmine, rivastigmine), human immunodeficiency virus (HIV) protease inhibitors (darunavir, amprenavir, ritonavir, atazanavir), anticonvulsants (cenobamate, retigabine, felbamate), anthelmintics (febantel mebendazole, febendazole, albendazole), and muscle relaxants (metaxalone, methocarbamol). Additionally, they contribute to the production of pharmaceuticals with various medicinal purposes (capecitabine, bambuterol, irinotecan, gabapentin enacarbil).[8,9] In addition, the compounds, such as pyridostigmine and neostigmine, are important as medications for the treatment of myasthenia gravis and alzheimer's disease (Figure. 4.1).[10,11]

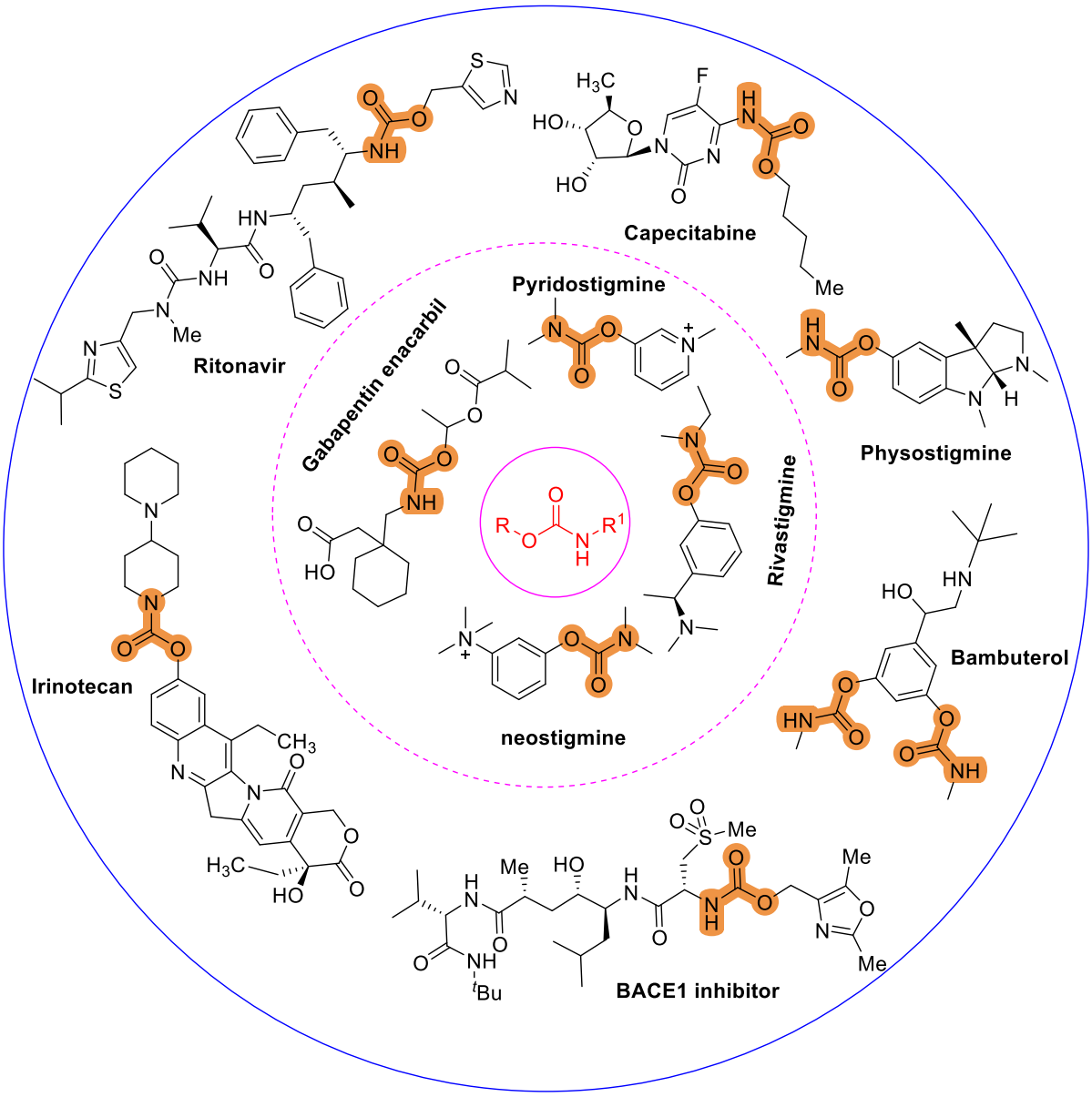


Figure 4.1. Some of the carbamate containing drugs and prodrugs.

The carbamate functionality is a key structural motif in many approved drugs and prodrugs. Pesticides and insecticides are a group of composites that are poisonous to pests and insecticides, respectively. The use of insecticides is beneficial for agriculture and for the eradication of vectors.[12] Pests are controlled by the use of pesticides in the agricultural sector. They are purposefully released into the environment, and this has a negative impact on the biodiversity because they are poisonous and frequently affect organisms that are not the intended targets.[13] Based on their chemical structures, pesticides can be divided into five groups: chlorophenols, carbamates, organochlorines, organophosphorus, and synthetic pyrethroids.[14] Carbamates are a class of insecticides that related to organophosphates in both structurally and mechanistically. Carbamates are *N*-methyl carbamates that create from amino formic acid. The distinction between carbamates and organophosphates is that carbamates have reversible

acetylcholinesterase binding. Organophosphates, on the other hand, can never reverse the phosphorylation of acetylcholinesterase.[15]

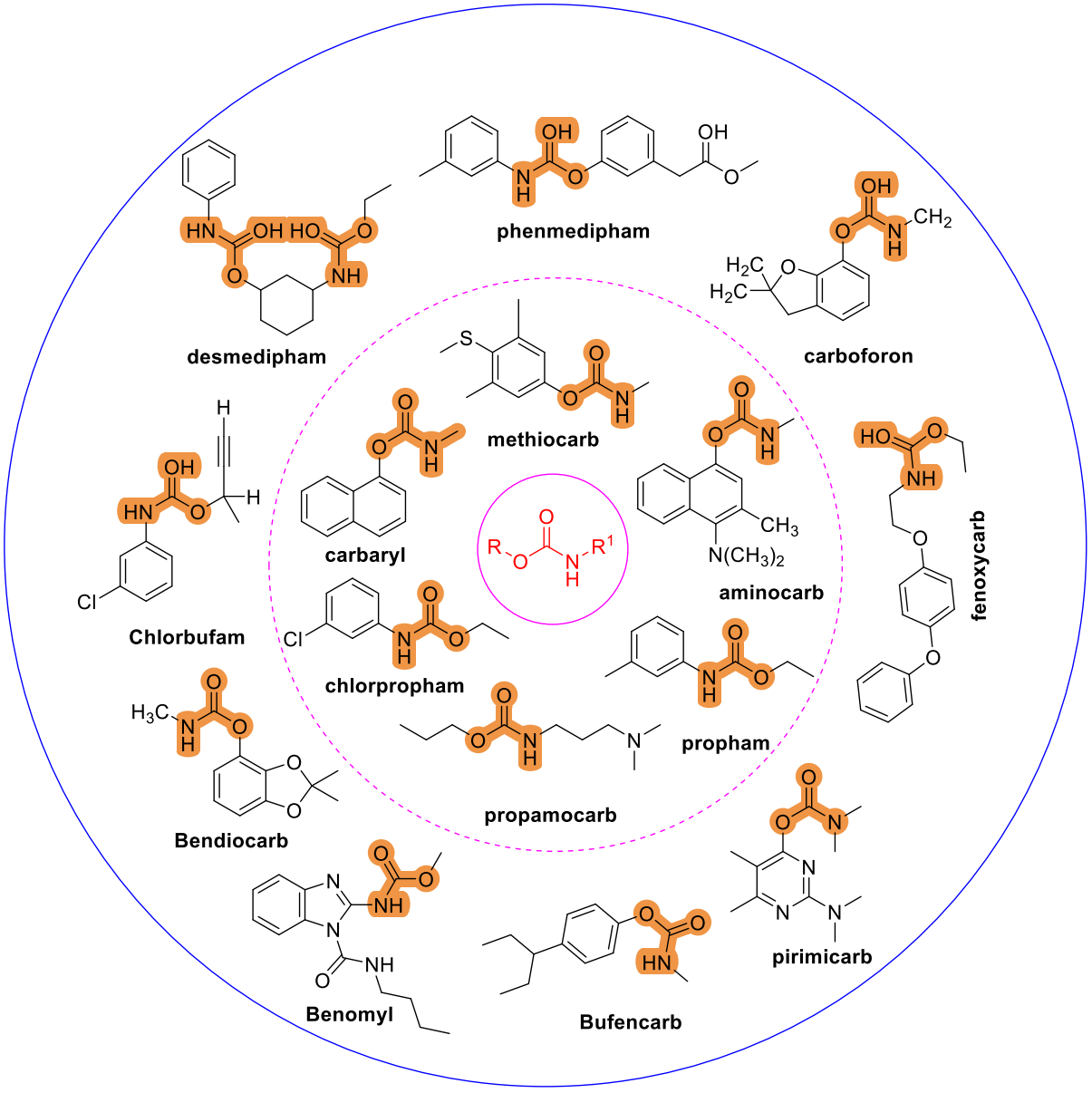


Figure 4.2. Structures of commonly used carbamate pesticides, herbicides, sprout inhibitors and insecticides.

Some commonly used carbamate pesticides include carbofuran, aminocarb and carbaryl.[16] Chlorpropham and propham these are useful for herbicides or sprout inhibitors.[17] Desmedipham is useful for insecticides on beets, strawberries, and spinach. Fenoxycarb is useful as an insecticide for grapes, plum trees, and apple trees. Methiocarb is a solid and it is less soluble in water. It is useful for insecticide, acaricide, repellent (birds) for potatoes, and molluscicide, beet, barley and vegetables (Figure. 4.2).[18]

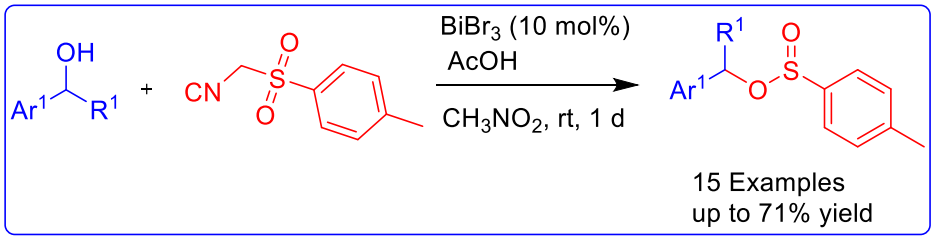
Also, carbamates are a crucial functional group in medicinal chemistry and pharmaceutical industry.[19,20] They demonstrate significant biological functions like HIV-1 protease,[21] anti-tuberculosis, and anti-cancer. Finally, carbamates are used as protecting groups in organic synthesis, particularly peptide chemistry due to their chemical stability toward acids, bases, and hydrogenation.[22] Hence it creates a lot of interest and scope to synthesize carbamates by developing efficient and effective processes.

The two most significant traditional methods to synthesis the carbamates are based on condensation of anilines with phosgene and its derivatives,[23] or interaction of alcohols with isocyanates produced *in situ* through Curtius,[24] Lossen,[25] Hofmann,[26] and Schmidt[27] rearrangement processes. However, these reactions are limited by the highly reactive nature of compounds, toxicity of starting materials and need for metal catalysts. The other widely used techniques to synthesize carbamates are the reaction of amide with lead tetra-acetate,[28] from isonitriles,[29] and reductive carbonylation of aromatic nitro compounds.[30] Another pathway to synthesize the carbamates is using CO_2 as a C1 building block.[31,32] Even though, the substitution of phosgene with CO_2 has been shown to significant improvement, the main problem of harsh reaction conditions because of thermodynamic stability of CO_2 is the main drawback associated with these reports. Therefore, it is highly important to design a universal and useful mechanism for quick access to carbamates. The very few literature reports are known for the direct synthesis of carbamates from isocyanides.[33] The earlier report by Ganem and co-workers for the synthesis of carbamates engaging TosMIC involves a two-step process and low reaction temperature conditions.[34] Tosylmethyl isocyanide (TosMIC) is a versatile reagent and recognised for its variety in organic synthesis.[35]

Inspired by this outcome, we introduce an effective novel method for the synthesis of carbamates from TosMIC reaction with alcohols in the presence of molecular iodine in CH_3CN as the reaction medium.

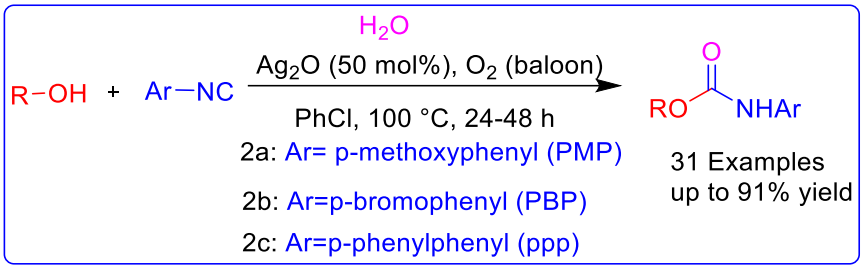
4.1.1. Reported methods for the synthesis of carbamates using alcohols and isocyanides.

Wu et al. reported for the synthesis of sulfinates using bismuth bromide ($BiBr_3$) and acetic acid in nitromethane at room temperature. The results of cytotoxicity studies (*in vitro*) revealed that the sulfinates have antibiotic activity against the human leukaemia cell line HL-60, extending the structural diversity of this antitumor target and supporting the prospects for further research (Scheme 4.1).[36]



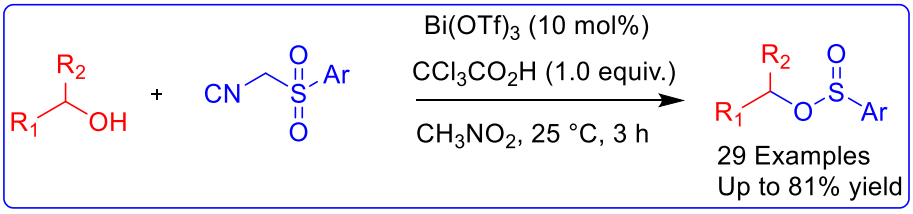
Scheme 4.1

Bi et al. developed a protocol for the synthesis of carbamates from alcohols/phenols and isocyanides promoted a silver oxide in presence of water at 100 °C. This method was found to be the first report which involved a radical coupling reaction with isocyanides and alcohols/phenols. It is a radical mechanism dominates over the traditional 1,1-addition to produce target compounds (Scheme 4.2).[37]



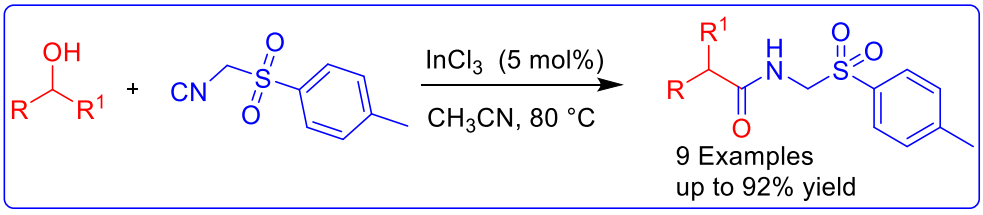
Scheme 4.2

Li and co-workers reported a synthesis of sulfinates instead of the more common sulfones, by using non-activated alcohols and arylsulfonylmethyl isocyanides under mild reaction conditions (10 mol% of $Bi(OTf)_3$, 25 °C) in nitromethane at room temperature for 3 h (Scheme 4.3).[38]



Scheme 4.3

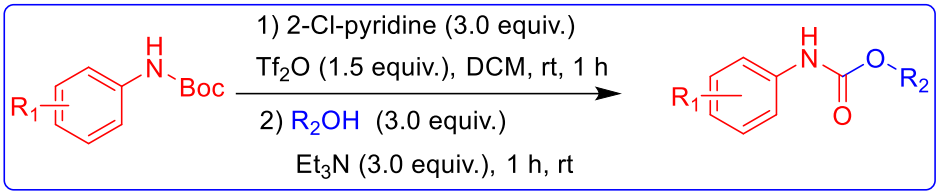
Radha Krishna et al. developed a C-C coupling reaction between aryl alcohols with TosMIC under $InCl_3$ (5 mol%) to produce the corresponding amides in good yields (Scheme 4.4).[39]



Scheme 4.4

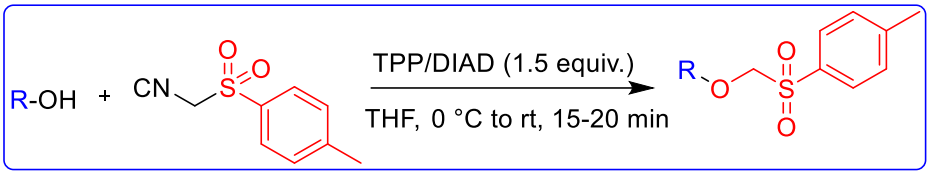
Kim and Anna Lee developed an efficient one-pot procedure for the synthesis of carbamates and thiocarbamates from the corresponding alcohols and thiols respectively. This protocol

utilizes the *in situ* generated isocyanate intermediates convert into carbamates in presence of 2-chloropyridine and trifluoromethanesulfonyl anhydride and alcohols (Scheme 4.5).[40]



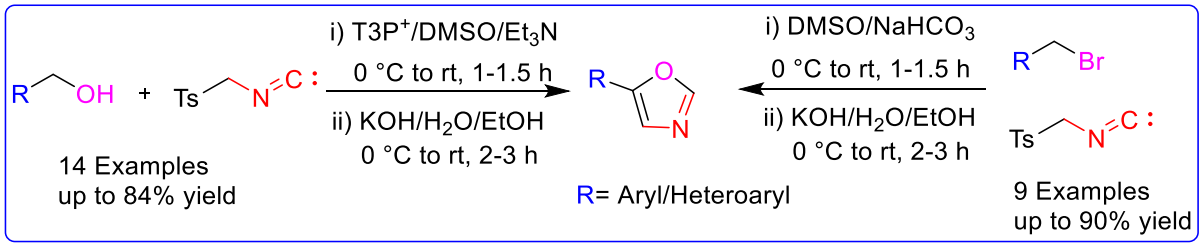
Scheme 4.5

Kadari et al. described a metal-free Mitsunobu approach for the synthesis of sulfinate esters by direct nucleophilic substitution of alcohols. This protocol employs *p*-toluenesulfonylmethyl isocyanide (TosMIC) and the triphenylphosphine (TPP)/diisopropyl azodicarboxylate (DIAD) reagent to synthesis sulfinate esters in good to excellent yields. Mild, and metal-free conditions are some of the salient features of this strategy (Scheme 4.6).[41]



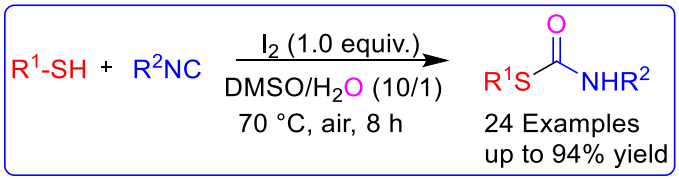
Scheme 4.6

Kumar et al. introduced a modified "Van Leusen" strategy for the synthesis of biologically active 5-substituted oxazoles by using (het)aryl methyl alcohols or benzyl bromides as starting materials with tosylmethyl isocyanide (TosMIC) under basic conditions. This method is mild, efficient, and tolerates wide variety of functional groups (Scheme 4.7).[42]



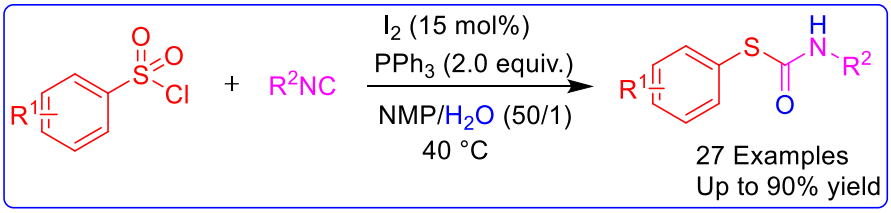
Scheme 4.7

He et al. reported for the synthesis of thiocarbamates from isocyanides, thiols under molecular iodine in DMSO/H_2O at 70 °C for 8 h. This protocol is a completely metal-free green approach. This methodology offers excellent yields with wide substrate scope (Scheme 4.8).[43]



Scheme 4.8

He and co-workers reported a simple and mild iodine-catalysed strategy for construction of thiocarbamates from isocyanides, thiols and water under metal-free conditions. A library of thiocarbamates were synthesized through this procedure, which follow some of the green chemistry principles such as simple reaction conditions, good functional group tolerance, and readily available raw materials (Scheme 4.9).[44]

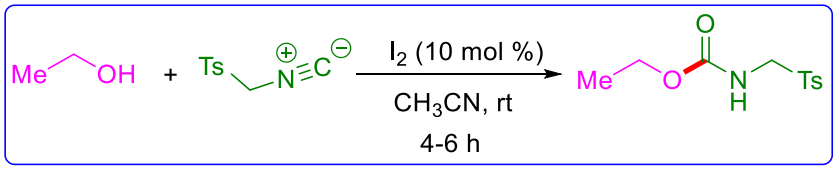


Scheme 4.9

Based on the previous report we found that a considerable attention has been received to the synthesis of carbamates, these are having common pharmacophores with wide applications in pharmaceuticals and agrochemicals. Till now only few reports are available for the direct synthesis of carbamates. Therefore, introducing direct synthesis of carbamates from alcohols with TosMIC in the presence of molecular iodine could be one of the potential methods to synthesize wide variety of carbamates.

4.2. Present study

In this chapter, we describe a transition metal-free synthesis of carbamates using substituted alcohols in the presence of iodine and TosMIC. This metal-free reaction affords rapid access to carbamates with exceptional functional group tolerance, broad substrate scope. With this proposed methodology, we can prepare various alcohols under environmentally benign conditions *i.e.*, metal free, non-hazardous, easily available reagents and less expensive (Scheme 4.10).



Scheme 4.10

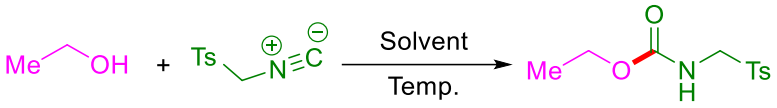
4.2.1. Results and discussion

To validate our hypothesis, a test reaction was conducted between ethanol **1a**, TosMIC **2** and iodine (10 mol%) in dichloromethane solvent. Initially, the reaction mixture was stirred at room temperature for 24 h, change in starting material was observed (monitored by TLC). Then the

formation of desired product **3a** was observed in low yield (Table 4.1, entry 1). The product **3a** was purified and characterized by ^{1}H and ^{13}C and mass spectroscopic techniques.

The above result provoked us to optimize the reaction conditions to improve the product yield by changing the reaction conditions and the results are tabulated in Table 4.1. We have focused on screening of solvents. Initially, reaction was conducted in chlorinated solvents such as chloroform and dichloroethane, but gave low yield (Table 4.1, entries 2-3). It was observed that the same reaction in CH_3CN gave target product in 90% yield (Table 4.1, entry 4).

Table 4.1. Optimization of reaction conditions[a]



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

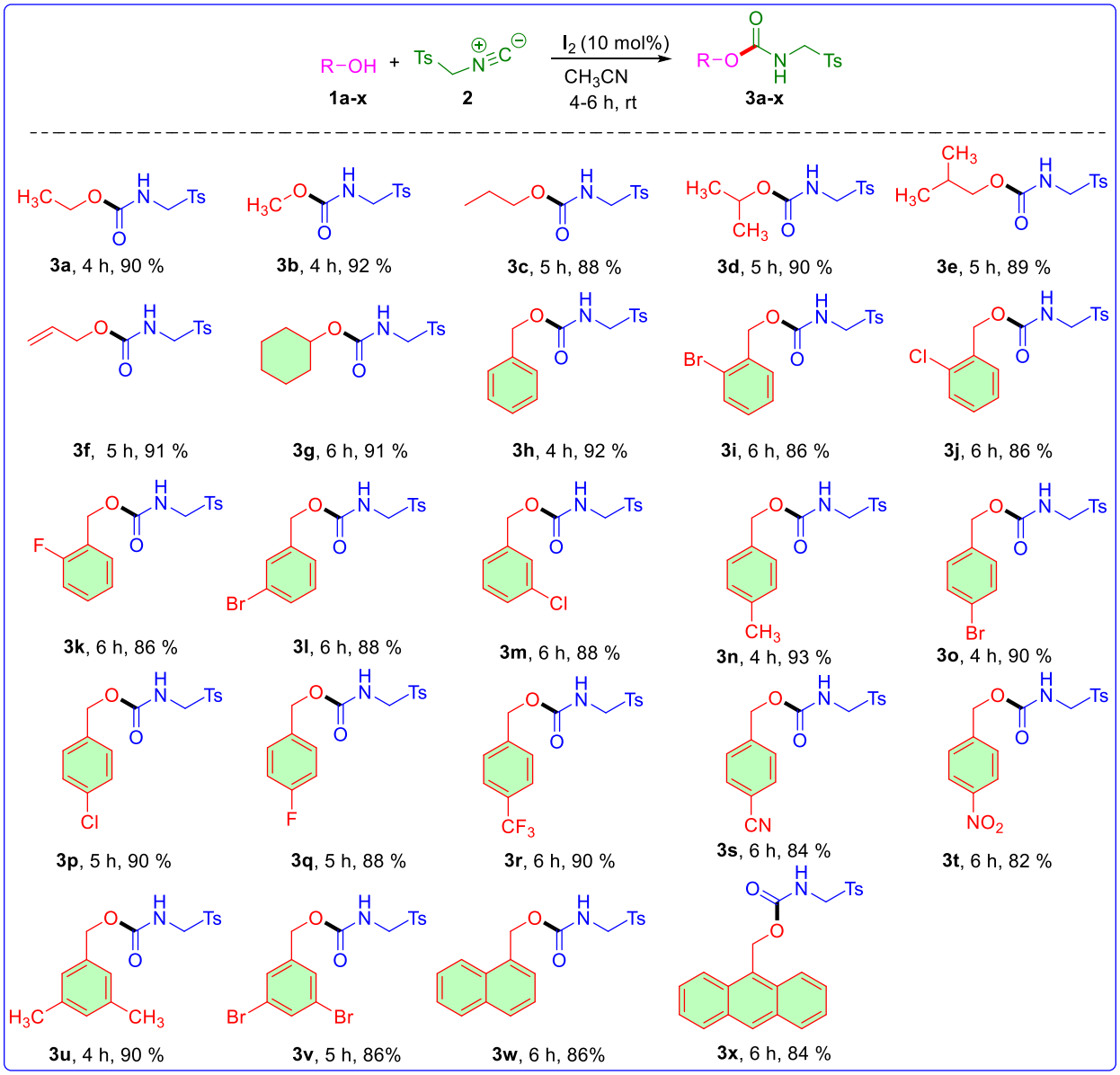
Entry	Catalyst (10 mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1.	I_2	CH_2Cl_2	RT	24	22
2.	I_2	$CHCl_3$	RT	24	31
3.	I_2	DCE	RT	24	35
4.	**I_2**	**CH_3CN**	**RT**	**4**	**90**
5.	I_2	THF	RT	24	24
6.	I_2	DMF	RT	24	26
7.	I_2	DMSO	RT	24	81
8.	I_2	EtOH	RT	24	trace
9.	I_2	CH_3OH	RT	24	trace
10.	I_2	H_2O	RT	24	trace
11.	I_2	CH_3CN	RT	12	72[c]
12.	I_2	CH_3CN	RT	12	45[d]
13.	-	CH_3CN	RT	24	n. r.

[a]Reaction conditions: Ethanol **1a** (0.5 mmol), TosMIC **2a** (0.5 mmol), Iodine (10 mol%), solvent (2 mL), 4 h, [b] Isolated yield, [c] Iodine (5 mol%), [d] Iodine (2 mol%) used, n.r = No reaction.

Later, we have changed the reaction medium to other solvents such as polar aprotic, THF, and DMF, observed formation of final product in poor or less yields (Table 4.1, entries 5-6). Later we used DMSO solvent gave target product in 81% yield (Table 4.1, entry 7). Noteworthy to mention that polar aprotic solvents such as alcohols and water are not suitable for this reaction (Table 4.1, entries 8-10). Additionally, changing the loadings of catalyst had no positive effect

on the transformation, only 72% and 45% yields were obtained when 5 mol% and 2 mol% of catalyst was used respectively (Table 1, entries 11-12). It is worth mentioning that our method proceeds with 100% atom-economy. Therefore, the optimized reaction conditions are 0.5 mmol of ethanol, 0.5 mmol of TosMIC and 10 mol% of I_2 in 2 mL CH_3CN at room temperature for 4 h as shown in (Table 4.1, entry 4).

Table 4.2. Substate scope for the synthesis of carbamates[a,b]

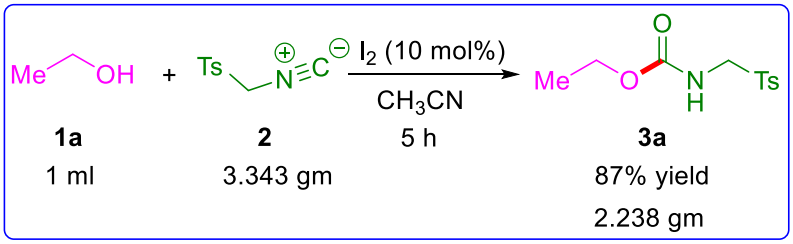


[a]Reaction Conditions: Alcohols **1a-x** (0.5 mmol), TosMIC **2** (0.5 mmol), Iodine (10 mol%) and CH_3CN (2 mL), [b]Isolated yields.

After optimization of the reaction conditions for the synthesis of carbamates from alcohols and TosMIC, then we have focused on the scope of the substrates to examine the applicability of the protocol. The starting materials, alcohols which are used in this method are prepared from reported method using aldehydes and $NaBH_4$ in methanol as solvent and used for next step

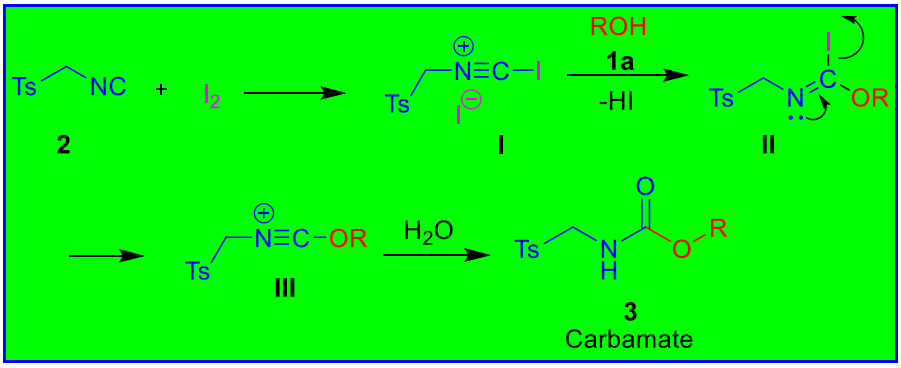
without purification.[45] The aliphatic alcohols such as methanol, ethanol, isopropanol, and isobutanol are reacted smoothly with TosMIC to provide the corresponding carbamates **3a-e** in good to excellent yields (Table 4.2). Similarly, unsaturated alcohols and cyclic alcohols also reacted effortlessly with isocyanide to give respective final products **3f-g** in good yields. Notably, benzyl alcohols are participated well in this optimized reaction conditions. The electron releasing groups such as methyl, methoxide on benzyl alcohols gave the target compounds up to 90% yields. Also, halogens (-Cl, -Br and -F) substituted benzyl alcohols reacted with TosMIC under the optimized condition without undergoing dehalogenation. Notably, electron withdrawing groups (-CF_3, -CN and NO_2) participated in the reaction and gave the target carbamates without affecting the reaction yields. Unfortunately, *tert*-butyl isocyanide, methyl isocyanoacetate, ethyl isocyanoacetate, cyclohexyl isocyanide and benzyl isocyanide are not reactive under the optimised conditions.

All the synthesized compounds (**3a-x**) from this protocol were characterized by ^1H and ^{13}C NMR spectroscopy, HRMS and Single-crystal X-ray Diffraction. The data of all the compounds were compared with the literature.



Scheme 4.11. Gram scale reaction

Finally, we have also tested our protocol in gram scale using ethanol **1a** with TosMIC in the presence of iodine (10 mol%) in CH_3CN (2 mL) at room temperature for 5 h. The reaction afforded the final product **3a** in 87% of yield (Scheme 4.11).



Scheme 4.12. Plausible reaction mechanism.

A plausible reaction mechanism is illustrated in Scheme 4.12. Initially, TosMIC 2 reacts with molecular iodine to form intermediate I, wihich further reaction with alcohol gives intermediate

II. Then, intermediate II coverts into III with the help of a nitrogen lone pair electron. Finally, intermediate III is subjected to hydrolysis with water to produce the relevant carbamate.

4.3. X-ray diffraction analysis of compound 3v

The method for crystal growth is slow volatilization using mixture of chloroform, methanol and acetonitrile (4:4:2) as a solvent. The crystallographic data for the single crystal of the compound **3v** was collected on Xtlab Synergy Rigaku oxford diffraction with HyPix-3000 detector, equipped with graphite monochromated MoKa radiation (λ= 0.71073 Å) at 293K. The data interpretation was processed with CrysAlisPro, Xtlab Synergy Rigaku oxford diffraction, version 171.39.exe and an absorption correction based on multi-scan method. Crystallography data and structure refinement for **3v** (CCDC: 2226564). Thermal ellipsoids are shown at 50% probability level.

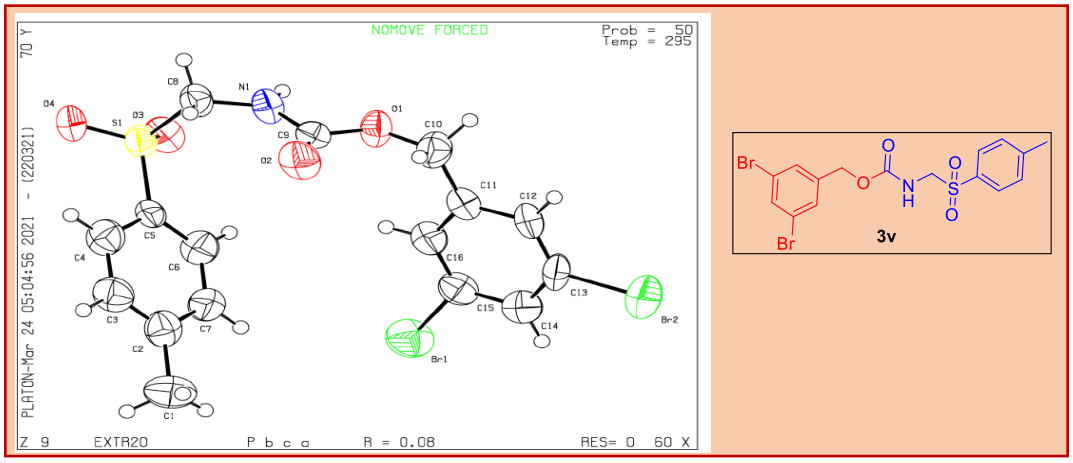


Figure 4.3 The ORTEP representation of the compound **3v**.

Table 4.3 Crystallographic data and structure refinement of compound **3v**

Identification Code	**Compound 5g**
Empirical formula	$C_{16}H_{15}Br_2NO_4S$
Formula weight	954.35
Temperature/K	295K
Crystal system	Orthorhombic
Space group	pbca
a/Å	9.4951(6)
b/Å	10.9827(6)
c/Å	34.514(2)
α/°	90

β/°	90
γ/°	90
Volume/Å^3	3599.2(4)
Z	4
D_{calc} Mg/m^3	1.761
μ/mm^{-1}	4.639
F(000)	1885.5
Crystal size/mm^3	0.2 x 0.15x 0.1
2Θ range for data collection/°	2.36 to 25.68
Index ranges	-11 ≤ h ≤ 11, -13 ≤ k ≤ 13, -43 ≤ l ≤ 43
Reflections collected	3418
Independent reflections	1757
Data/restraints/parameters	1757 / 0 / 218
Goodness-of-fit on F^2	1.0074
Final R indexes [I>=2σ (I)]	R1 = 0.0810, wR2 = 0.1955
Final R indexes [all data]	R1 = 0.1553, wR2 = 0.2332
Largest diff. peak/hole / e Å^{-3}	1.3574 and -1.1161
CCDC	2226564

4.4. Conclusion

In summary, we have demonstrated a molecular iodine catalyzed synthesis of carbamates from alcohols with TosMIC. This metal-free reaction affords rapid access to carbamates with exceptional functional group tolerance, broad substrate scope and operational simplicity. A library of 24 carbamates were synthesized with this protocol.

4.5. Experimental section

4.5.1. General Information: All chemicals were purchased from Aldrich, Alfa aesar, TCI, Finar and used as received. All solvents were purchased from commercial sources, then distilled by the standard protocol and stored over molecular sieves under nitrogen atmosphere prior to use. Thin layer chromatography was performed on 200 μm aluminium-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). ^{1}H NMR spectra were recorded on Bruker's AVANCE 400 MHz spectrometer, $CDCl_3$ and

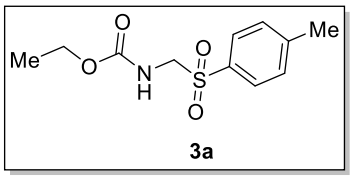
DMSO-d_6 as a solvent and TMS as an internal standard. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, coupling constants, *J* were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker's AVANCE 100 MHz spectrometer, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-d (a multiplet at 39.52 ppm of DMSO-d_6). Melting points were determined with a Stuart SMP30 apparatus and are uncorrected. FT-IR spectra recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230. The X-ray single crystal data of the crystal compounds was collected on Xtlab Synergy Rigaku oxford diffraction with HyPix-3000 detector, equipped with graphite monochromated MoKα radiation (λ= 0.71073 Å) at 293K.

4.5.2. General procedure for the synthesis of carbamates (3a-x).

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate alcohols (0.5 mmol), I_2 (10 mol%), TosMIC (0.5 mmol) and CH_3CN (2 mL). The mixture was stirred at room temperature for the appropriate time (4-6 h). The progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. After completion, the reaction mixture was treated with saturated $Na_2S_2O_3$, later extracted with ethyl acetate (3 x 10 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent.

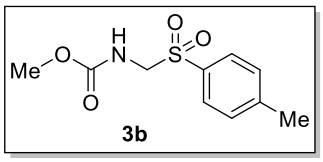
4.6. Characterization data of products 3a-3x.

Ethyl (tosylmethyl)carbamate (3a). White solid; (115 mg, 90% yield); mp 108-109 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (d, *J* = 8.1 Hz, 6H), 7.35 (d, *J* = 7.9 Hz, 6H), 5.51 (s, 2H), 4.54 (d, *J* = 7.0 Hz, 5H), 3.98 (q, *J* = 7.1 Hz, 5H), 2.44 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 8H). ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 155.1, 145.4, 133.8, 129.9, 128.9, 62.3, 61.9, 21.7, 14.3; HRMS (ESI-TOF) m/z: calculated for $C_{11}H_{16}NO_4S^+$ $[M+Na]^+$ 280.0614; found 280.0585.



3a

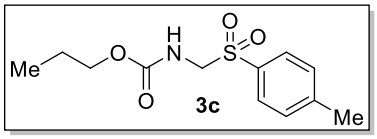
Methyl (tosylmethyl)carbamate (3b). White solid; (111 mg, 92% yield); mp 142-143 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.55 (s, 1H), 4.54 (d, *J* = 7.2 Hz, 2H), 3.56 (s, 3H), 2.45 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm):



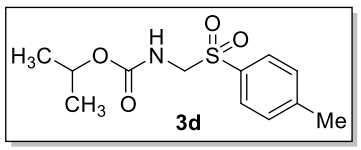
3b

155.7, 145.4, 133.8, 129.9, 128.9, 62.4, 52.9, 21.7. HRMS (ESI-TOF) m/z: calculated for $C_{10}H_{14}NNaO_4S^+$ $[M+Na]^+$ 266.0457; found 266.0465.

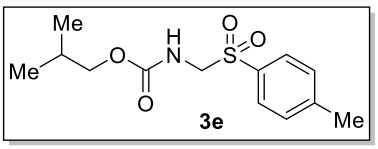
Propyl (tosylmethyl)carbamate (3c). White solid; (119 mg, 88% yield); mp 104-105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 5.50 (s, 1H), 4.55 (d, J = 6.8 Hz, 2H), 3.88 (t, J = 6.6 Hz, 2H), 2.45 (s, 3H), 1.58-1.45 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR $\{^1H\}$ (100 MHz, $CDCl_3$) δ (ppm): 155.2, 145.3, 133.8, 129.9, 128.9, 67.4, 62.3, 22.0, 21.7, 10.1; HRMS (ESI-TOF) m/z: calculated for $C_{12}H_{17}NNaO_4S^+$ $[M+Na]^+$ 294.0770; found 294.0784.



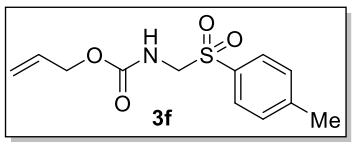
Isopropyl (tosylmethyl)carbamate (3d). White solid; (122 mg, 90% yield); mp 100-101 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 5.41 (s, 1H), 4.70-4.63 (m, 1H), 4.54 (d, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H); ^{13}C NMR $\{^1H\}$ (100 MHz, $CDCl_3$) δ (ppm): 154.7, 145.3, 133.8, 129.8, 129.0, 69.6, 62.3, 21.8, 21.6; HRMS (ESI-TOF) m/z: calculated for $C_{12}H_{17}NNaO_4S^+$ $[M+Na]^+$ 294.0770; found 294.0784.



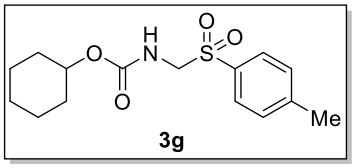
Isobutyl (tosylmethyl)carbamate (3e). White solid; (126 mg, 89% yield); mp 105-106 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.72 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.43 (s, 1H), 4.49 (d, J = 6.8 Hz, 2H), 3.63 (d, J = 6.8 Hz, 2H), 2.38 (s, 3H), 1.75-1.64 (m, 1H), 0.79 (s, 3H), 0.77 (s, 3H); ^{13}C NMR $\{^1H\}$ (100 MHz, $CDCl_3$) δ (ppm): 155.3, 145.3, 133.8, 129.9, 128.9, 71.9, 62.4, 27.7, 21.7, 18.8; HRMS (ESI-TOF) m/z: calculated for $C_{13}H_{19}NNaO_4S^+$ $[M+Na]^+$ 308.0927; found 308.0935.



Allyl (tosylmethyl)carbamate (3f). White solid; (122 mg, 91% yield); mp 83-84 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 5.84-5.70 (m, 1H), 5.60 (s, 1H), 5.21 (t, J = 13.0 Hz, 2H), 4.56 (d, J = 7.2 Hz, 2H), 4.42 (d, J = 5.2 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR $\{^1H\}$ (100 MHz, $CDCl_3$) δ (ppm): 154.8, 145.4, 133.7, 131.9, 129.9, 128.9, 118.2, 66.4, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{12}H_{15}NNaO_4S^+$ $[M+Na]^+$ 292.0614; found 292.0635.

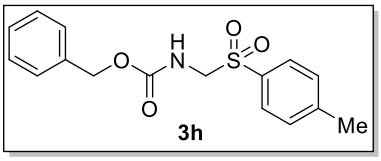


Cyclohexyl (tosylmethyl)carbamate (3g). White solid; (141 mg, 91% yield); mp 98-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 5.44 (s, 1H), 4.55 (d, J = 6.8 Hz, 2H), 4.42 (s, 1H), 2.44 (s, 3H), 1.66 (d, J = 8.0 Hz, 4H), 1.27 (d, J = 9.2 Hz, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.6, 145.3, 133.8, 129.8, 129.0, 74.3, 62.3, 31.5, 25.2, 23.5, 21.6; HRMS (ESI-TOF) m/z: calculated for $C_{15}H_{21}NNaO_4S^+$ $[M+Na]^+$ 334.1083; found 334.1099.



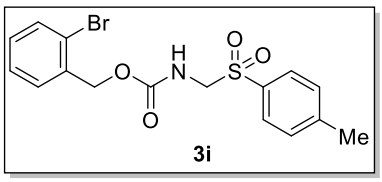
3g

Benzyl (tosylmethyl)carbamate (3h). White solid; (146 mg, 92% yield); mp 114-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (d, J = 8.0 Hz, 2H), 7.37-7.32 (m, 3H), 7.28-7.22 (m, 4H), 5.61 (s, 1H), 4.96 (s, 2H), 4.55 (d, J = 6.8 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 155.0, 145.3, 135.7, 133.7, 129.9, 128.8, 128.5, 128.3, 128.1, 67.5, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{17}NNaO_4S^+$ $[M+Na]^+$ 342.0770; found 342.0779.



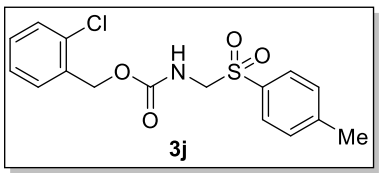
3h

2-bromobenzyl (tosylmethyl)carbamate (3i). White solid; (71 mg, 86% yield); mp 125-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.23-7.18 (m, 4H), 7.15 – 7.10 (m, 1H), 5.75 (t, J = 6.4 Hz, 1H), 4.97 (s, 2H), 4.50 (d, J = 7.2 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.7, 145.4, 134.9, 133.7, 132.8, 129.9, 129.9, 129.8, 128.9, 127.4, 123.3, 67.0, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}BrNNaO_4S^+$ $[M+Na]^+$ 419.9876; found 419.9904.



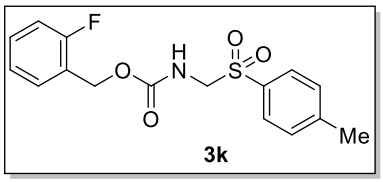
3i

2-chlorobenzyl (tosylmethyl)carbamate (3j). White solid; (152 mg, 86% yield); mp 110-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.33-7.27 (m, 5H), 5.69 (t, J = 6.4 Hz, 1H), 5.09 (s, 2H), 4.59 (d, J = 7.2 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.8, 145.4, 133.7, 133.6, 133.3, 129.9, 129.9, 129.6, 129.5, 128.9, 126.8, 64.8, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}ClNNaO_4S^+$ $[M+Na]^+$ 376.0381; found 376.0412.



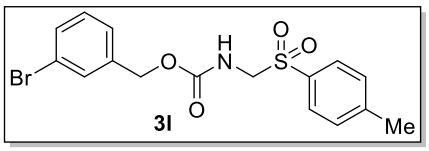
3j

2-fluorobenzyl (tosylmethyl)carbamate (3k). White solid; (145 mg, 86% yield); mp 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 6.8 Hz, 2H), 7.25 -7.19 (m, 2H), 7.03 (t, J = 8.6 Hz, 2H), 5.58 (s, 1H), 4.93 (s, 2H), 4.55 (d, J = 6.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 163.9, 161.4, 154.9, 145.3, 133.7, 131.5, 131.5, 130.2, 130.2, 129.9, 128.8, 115.5, 115.3, 66.7, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}FNNaO_4S^+$ $[M+Na]^+$ 360.0676; found 360.0698.



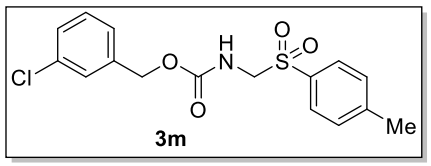
3k

3-bromobenzyl (tosylmethyl)carbamate (3l). White solid; (175 mg, 88% yield); mp 116-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.6 Hz, 1H), 7.25-7.19 (m, 3H), 7.18 – 7.03 (m, 2H), 5.67 (s, 1H), 4.86 (d, J = 2.4 Hz, 2H), 4.48 (d, J = 7.2 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.5, 145.5, 139.6, 133.9, 133.6, 129.9, 129.5, 128.8, 123.0, 65.5, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{10}H_{16}BrNNaO_4S^+$ $[M+Na]^+$ 419.9876; found 419.9901.



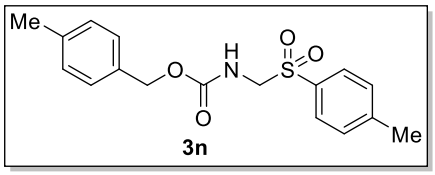
3l

3-chlorobenzyl (tosylmethyl)carbamate (3m). White solid; (155 mg, 88% yield); mp 118-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (d, J = 8.4 Hz, 2H), 7.34-7.27 (m, 4H), 7.24 (s, 1H), 7.12 (d, J = 7.2 Hz, 1H), 5.65 (s, 1H), 4.93 (s, 2H), 4.55 (d, J = 7.2 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.8, 145.4, 137.7, 134.4, 133.6, 129.9, 129.8, 128.8, 128.4, 128.0, 66.5, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}ClNNaO_4S^+$ $[M+Na]^+$ 376.0381; found 376.0411.



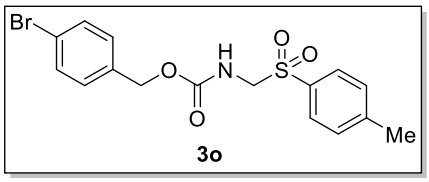
3m

4-methylbenzyl (tosylmethyl)carbamate (3n). White solid; (155 mg, 93% yield); mp 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 6.4 Hz, 2H), 7.20 – 7.10 (m, 4H), 5.54 (s, 1H), 4.91 (s, 2H), 4.54 (d, J = 7.2 Hz, 2H), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 155.0, 145.3, 138.2, 133.7, 132.6, 129.9, 129.2, 128.8, 128.3, 67.5, 62.3, 21.7, 21.2; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{19}NNaO_4S^+$ $[M+Na]^+$ 356.0927; found 356.0960.



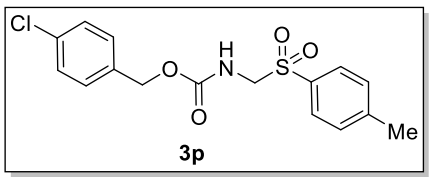
3n

4-bromobenzyl (tosylmethyl)carbamate (3o). White solid; (179 mg, 90% yield); mp 150-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.19-7.14 (m, 2H), 7.04 (d, J = 8.0 Hz, 2H), 5.55 (s, 1H), 4.84 (s, 2H), 4.47 (d, J = 6.8 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.8, 145.4, 134.7, 133.6, 131.6, 129.9, 129.8, 128.8, 122.4, 66.6, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}BrNNaO_4S^+$ $[M+Na]^+$ 419.9876; found 419.9904.



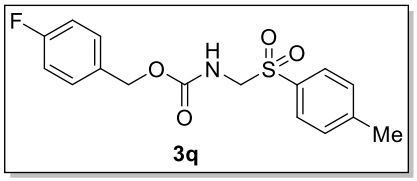
3o

4-chlorobenzyl (tosylmethyl)carbamate (3p). White solid; (148 mg, 88% yield); mp 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.73 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 5.62 (s, 1H), 4.92 (s, 2H), 4.54 (d, J = 6.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.5, 145.5, 139.6, 133.9, 133.6, 129.9, 129.5, 128.8, 123.0, 65.5, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}ClNNaO_4S^+$ $[M+Na]^+$ 376.0381; found 376.0377.



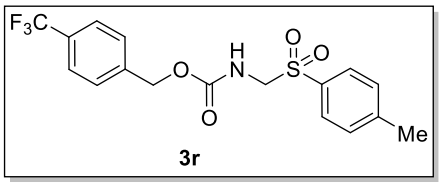
3p

4-fluorobenzyl (tosylmethyl)carbamate (3q). White solid; (148 mg, 88% yield); mp 133-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (d, J = 8.0 Hz, 2H), 7.31-7.26 (m, 2H), 7.25-7.19 (m, 2H), 7.02 (t, J = 8.6 Hz, 2H), 5.58 (s, 1H), 4.93 (s, 2H), 4.54 (d, J = 6.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 163.9, 161.4, 154.8, 145.4, 133.7, 131.5, 130.3, 130.2, 129.9, 128.8, 115.5, 115.3, 66.8, 62.2, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}FNNaO_4S^+$ $[M+Na]^+$ 360.0676; found 360.0679.



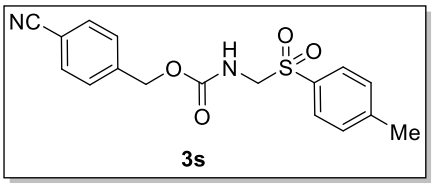
3q

4-(trifluoromethyl)benzyl (tosylmethyl)carbamate (3r). White solid; (174 mg, 90% yield); (115 mg, 90% yield); mp 170-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.28-7.26 (m, 1H), 7.25-7.24 (m, 1H), 5.67 (s, 1H), 5.03 (s, 2H), 4.56 (d, J = 6.8 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCL_3$+DMSO) δ (ppm): 155.6, 144.9, 140.8, 134.4, 129.7, 128.7, 127.8, 125.3, 125.3, 125.2, 125.2, 65.6, 62.9, 21.6; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{16}F_3NNaO_4S^+$ $[M+Na]^+$ 410.0644; found 410.0673.



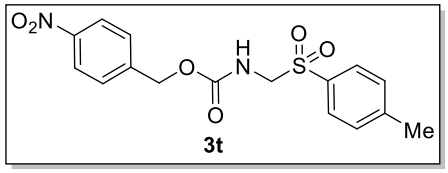
3r

4-cyanobenzyl (tosylmethyl)carbamate (3s). White solid; (144 mg, 84% yield); mp 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 5.64 (s, 1H), 4.96 (s, 2H), 4.49 (d, J = 6.8 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.7, 145.5, 141.0, 133.7, 132.3, 129.9, 128.8, 128.1, 118.4, 112.0, 66.2, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{17}H_{16}N_2NaO_4S^+$ $[M+Na]^+$ 367.0723; found 367.0750.



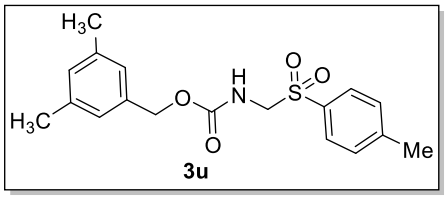
3s

4-nitrobenzyl (tosylmethyl)carbamate (3t). Yellow solid; (149 mg, 82% yield); mp 174-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 8.18 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.43 – 7.37 (m, 2H), 7.30 (d, J = 7.6 Hz, 2H), 5.08 (s, 2H), 4.55 (d, J = 6.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$+ DMSO-d_6) δ (ppm): 155.8, 147.4, 145.1, 144.8, 134.7, 130.2, 128.9, 128.6, 128.4, 125.9, 123.9, 65.2, 62.9, 21.4; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{16}N_2NaO_6S^+$ $[M+Na]^+$ 387.0621; found 280.0620.



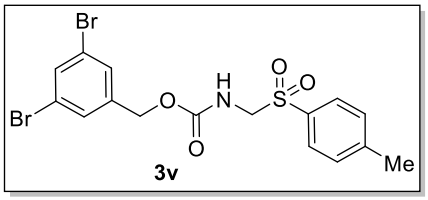
3t

3,5-dimethylbenzyl (4-methylbenzyl)carbamate (3u). White solid; (156 mg, 90% yield); mp 98-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.97 (s, 1H), 6.88 (s, 2H), 5.55 (s, 1H), 4.89 (s, 2H), 4.55 (d, J = 6.8 Hz, 2H), 2.43 (s, 3H), 2.32 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 155.0, 145.3, 138.1, 135.4, 133.8, 130.0, 129.9, 128.8, 125.9, 67.7, 62.4, 21.7, 21.2; HRMS (ESI-TOF) m/z: calculated for $C_{18}H_{21}NNaO_4S^+$ $[M+Na]^+$ 370.1083; found 370.1117.



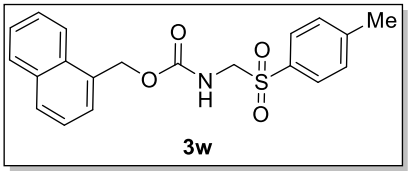
3u

3,5-dibromobenzyl (tosylmethyl)carbamate (3v). White solid; (205 mg, 86% yield); mp 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.35 (s, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.69 (s, 1H), 4.91 (s, 2H), 4.57 (d, J = 6.8 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.5, 145.5, 139.6, 133.9, 133.6, 129.9, 129.5, 128.8, 123.0, 65.5, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{15}Br_2NNaO_4S^+$ $[M+Na]^+$ 497.8981; found 497.8992.



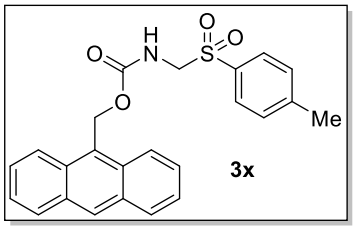
3v

Naphthalen-1-ylmethyl (tosylmethyl)carbamate (3w). White solid; (158 mg, 86% yield); mp 131-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.96-7.85 (m, 3H), 7.70 (d, J = 8.4 Hz, 2H), 7.58-7.52 (m, 2H), 7.44 – 7.40 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 5.57 (s, 1H), 5.42 (s, 2H), 4.54 (d, J = 6.8 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 154.9, 145.3, 133.7, 133.6, 131.5, 131.0, 129.8, 129.4, 128.8, 128.7, 127.6, 126.6, 126.0, 125.2, 123.4, 66.0, 62.3, 21.7; HRMS (ESI-TOF) m/z: calculated for $C_{20}H_{19}NNaO_4S^+$ $[M+Na]^+$ 392.0927; found 392.0952.



3w

Anthracen-9-ylmethyl (tosylmethyl)carbamate (3x). White solid; (176 mg, 84% yield); mp 170-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.52 (s, 2H), 8.10-8.03 (dd, J = 13.0, 8.6 Hz, 4H), 7.62 - 7.54 (m, 4H), 7.35 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 5.88 (s, 1H), 4.51 (s, 2H), 4.49 (s, 2H), 2.38 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 170.3, 144.8, 134.5, 133.7, 131.4, 130.6, 130.0, 129.2, 128.9, 128.0, 127.3, 127.2, 126.8, 126.3, 125.5, 125.2, 60.7, 34.1, 21.4. HRMS (ESI-TOF) m/z: calculated for $C_{24}H_{21}NNaO_4S^+$ $[M+Na]^+$ 442.1083; found 442.0877.



3x

4.7. References

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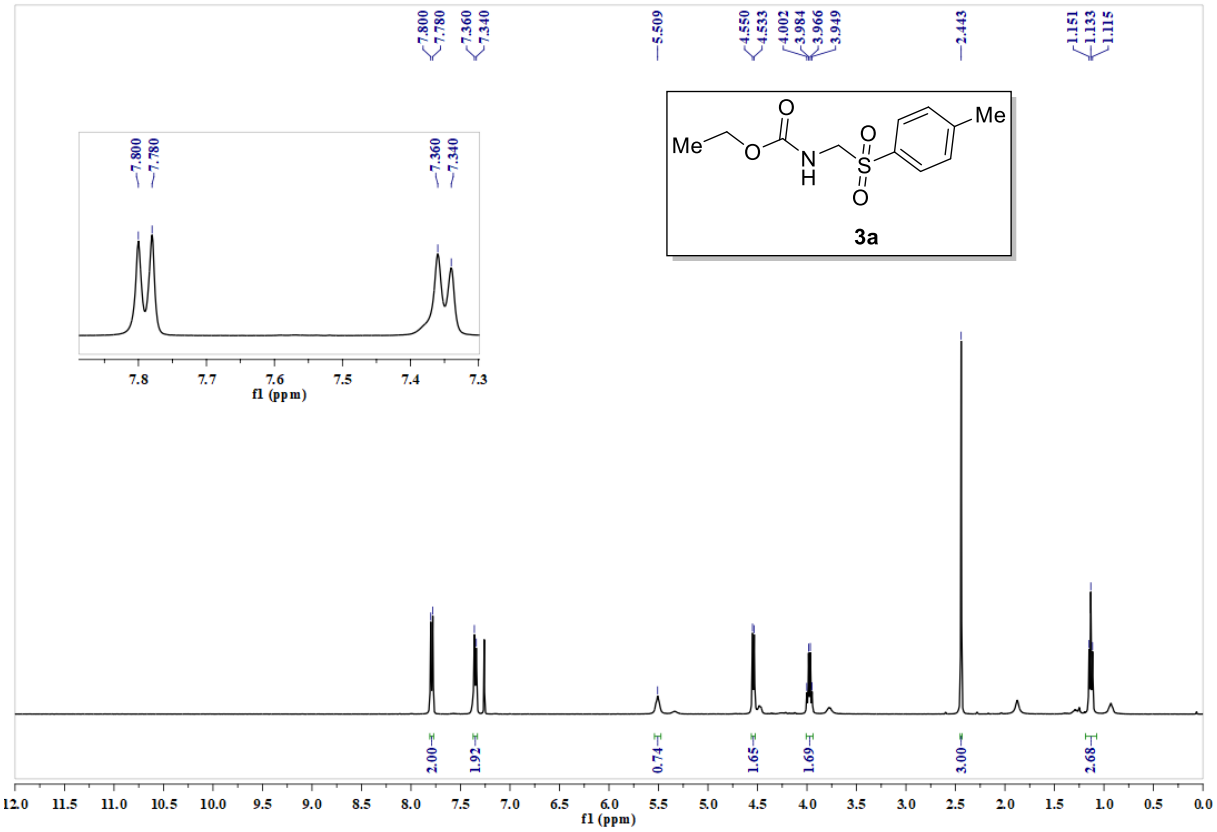
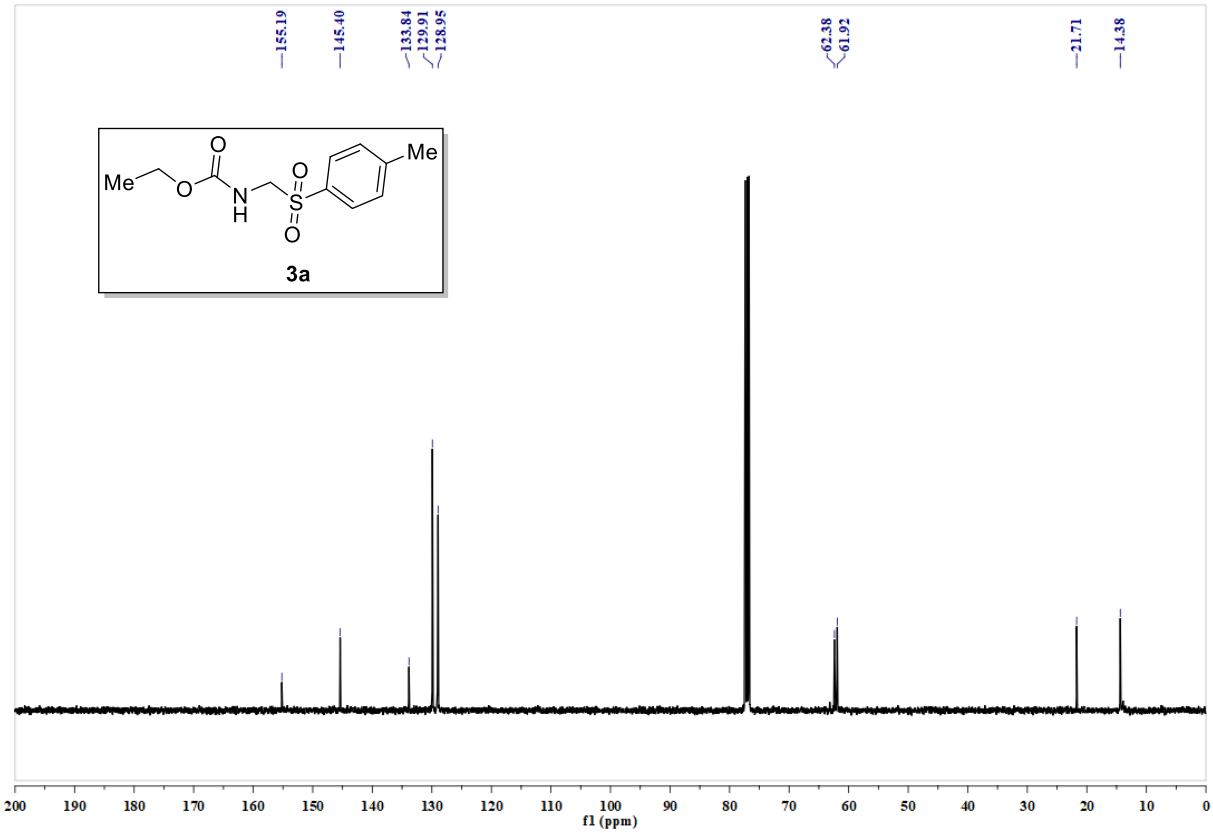
4.8. Selected NMR (^{1}H and ^{13}C) and HRMS Spectra

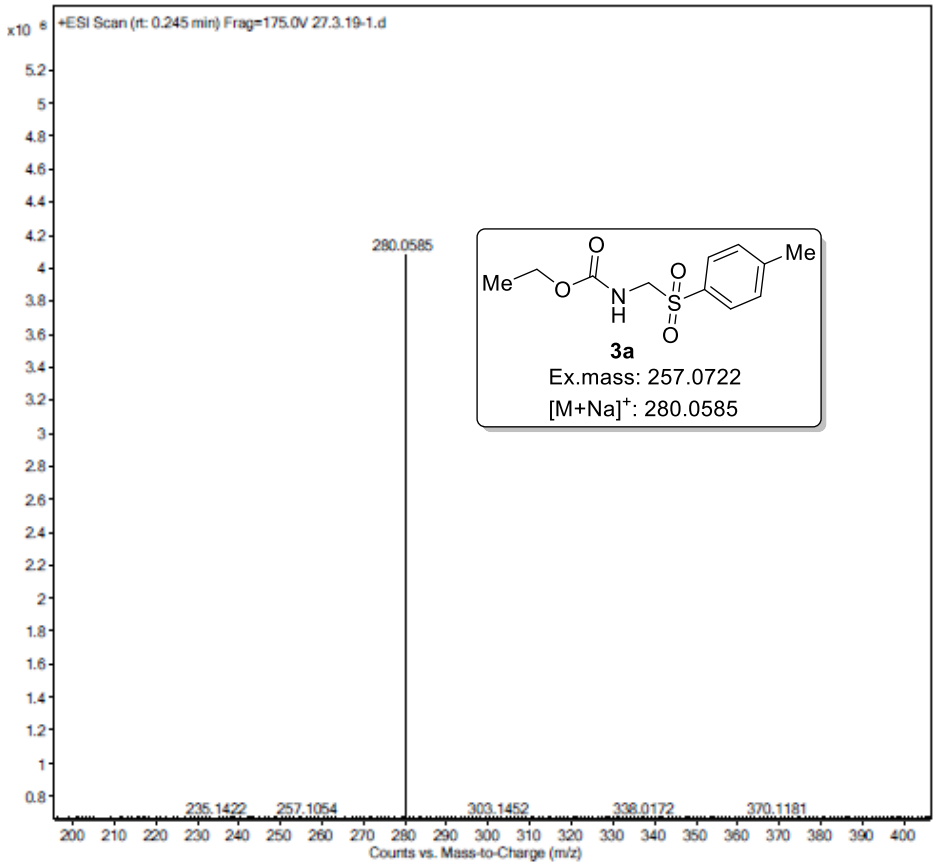
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl (tosylmethyl)carbamate (3a)



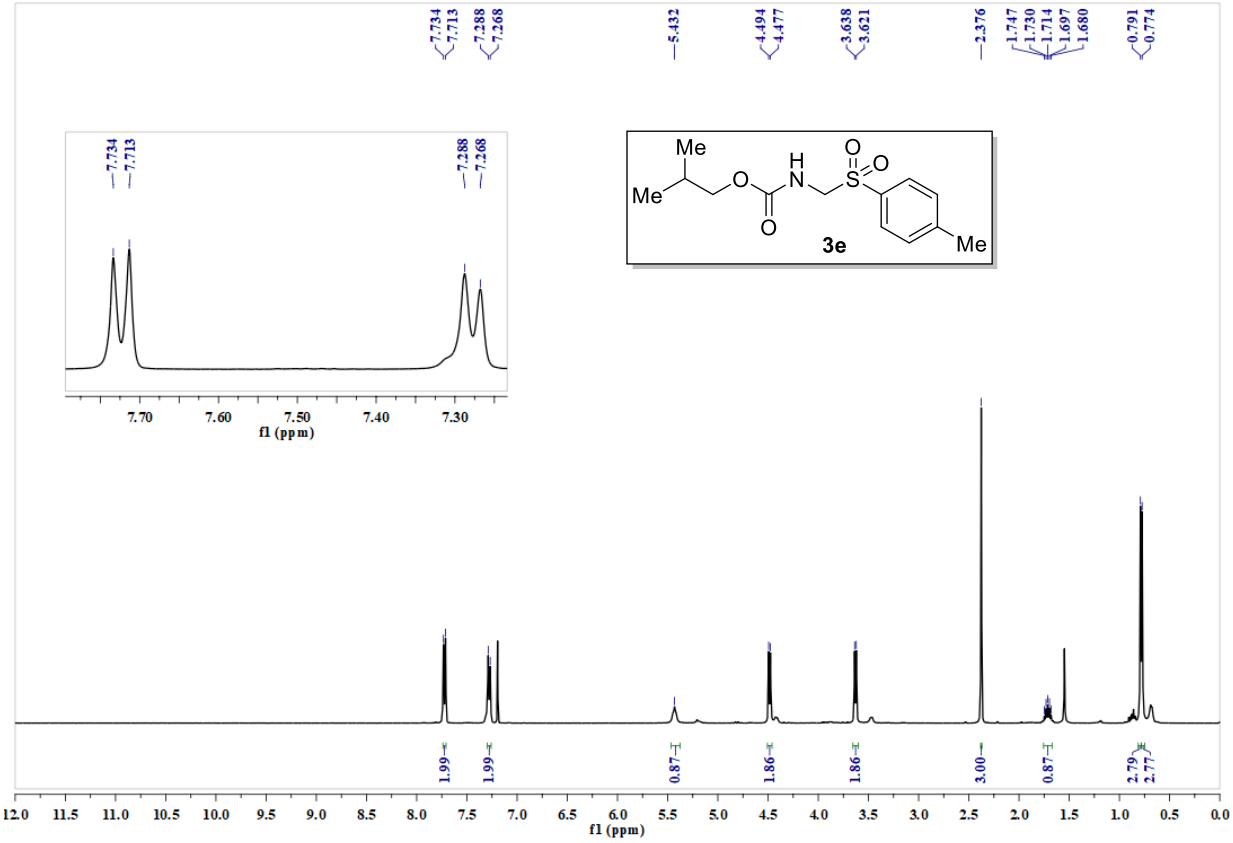
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of ethyl (tosylmethyl)carbamate (3a)



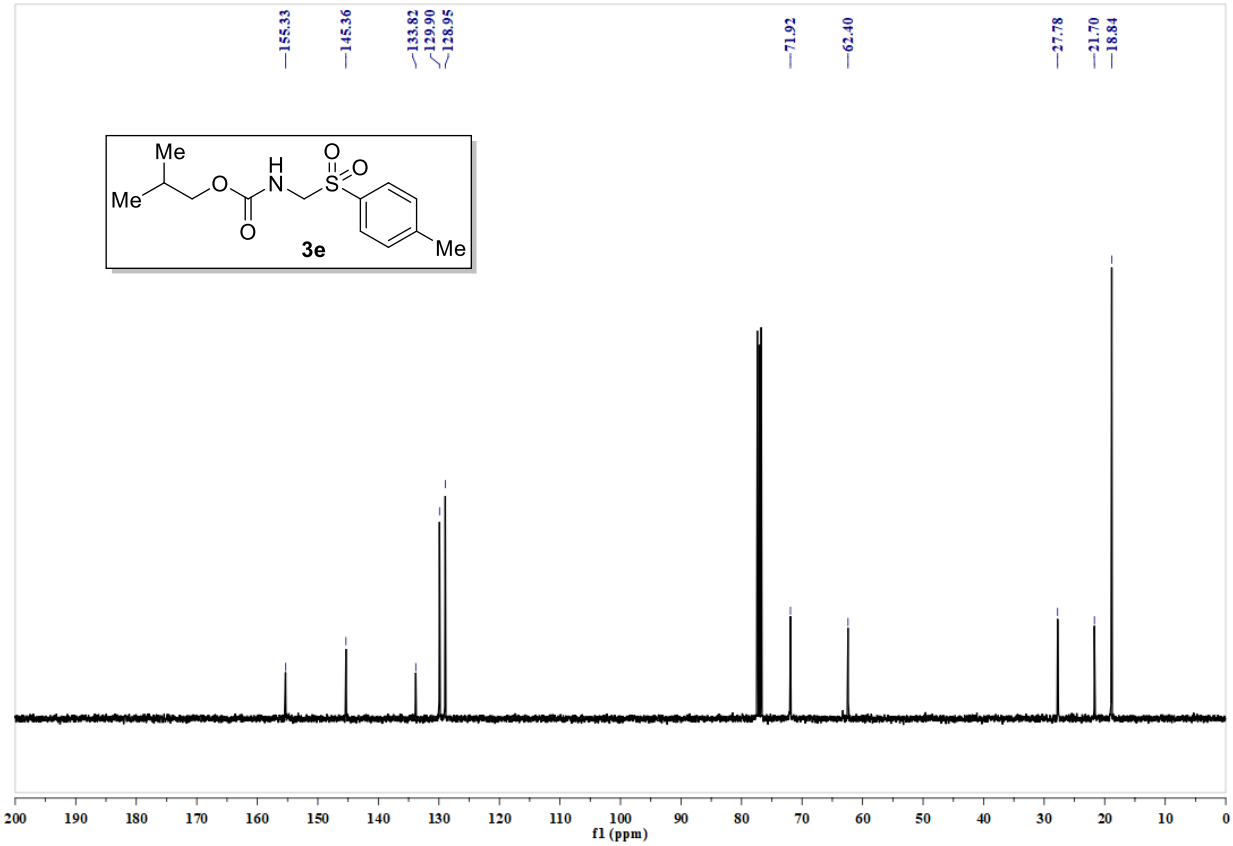
HRMS spectrum of ethyl (tosylmethyl)carbamate (3a)



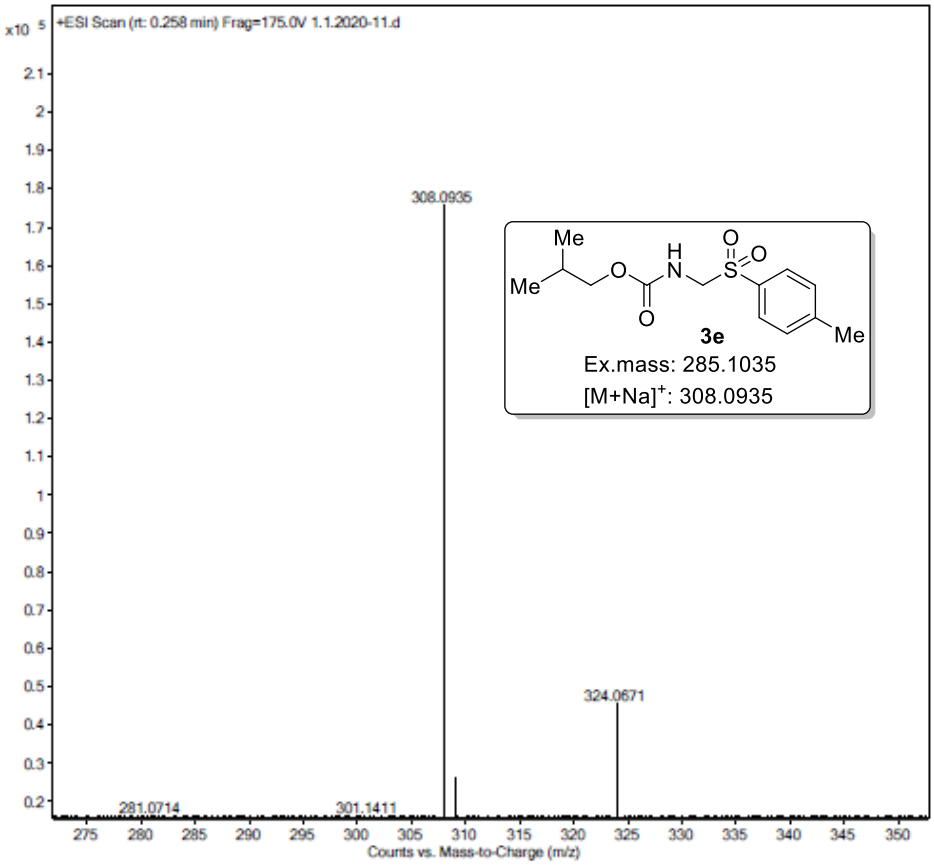
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of isobutyl (tosylmethyl)carbamate (3e)



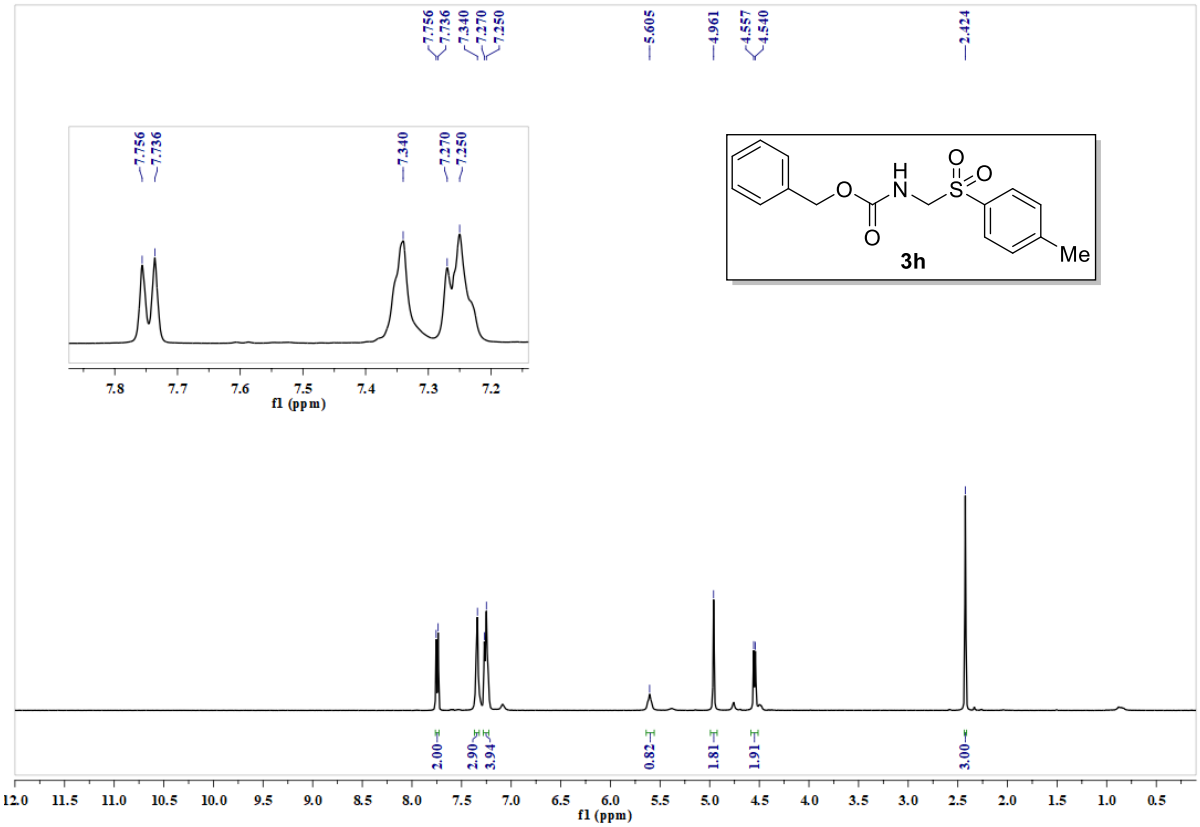
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of isobutyl (tosylmethyl)carbamate (3e)



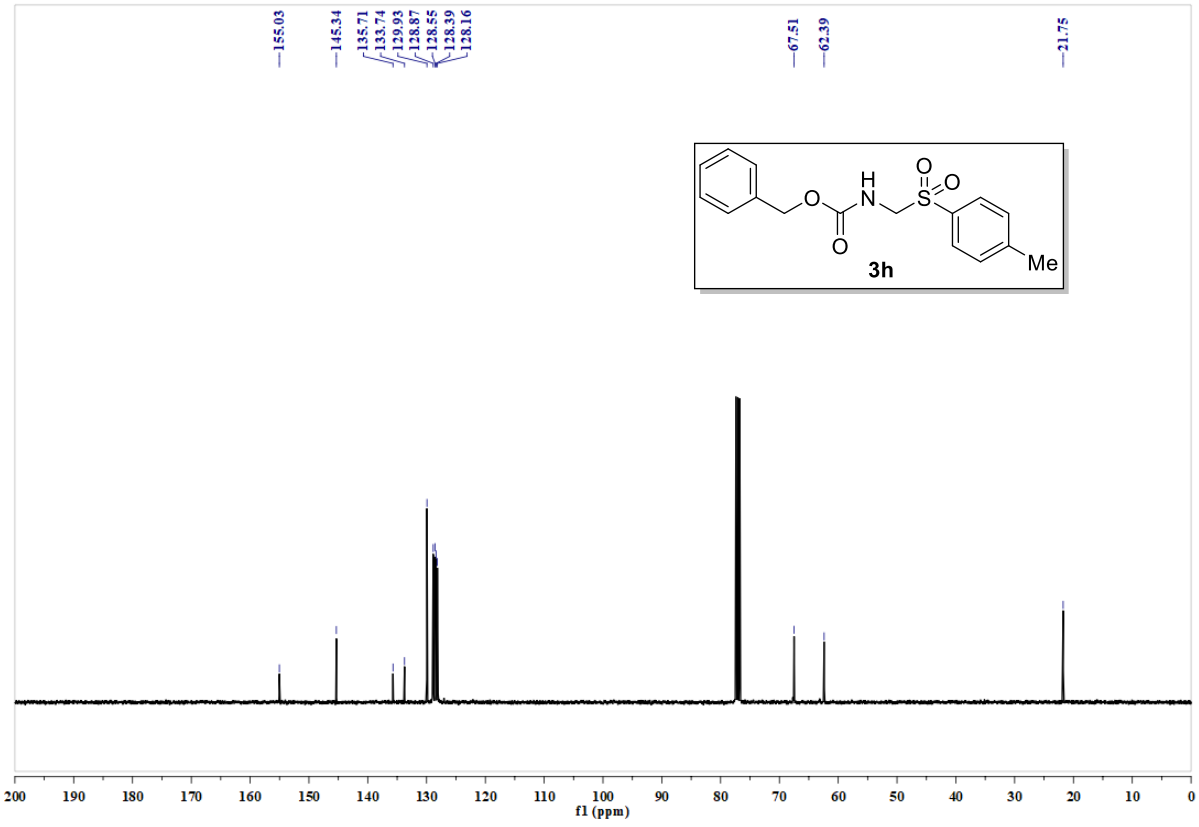
HRMS spectrum of isobutyl (tosylmethyl)carbamate (3e)



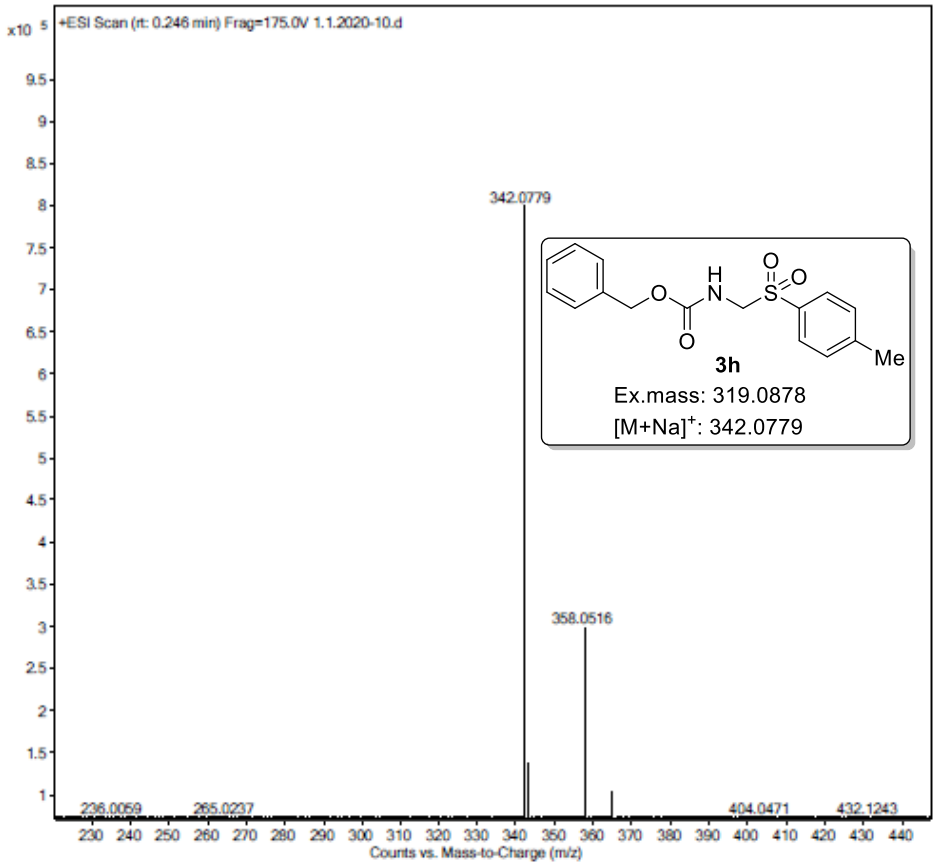
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of benzyl (tosylmethyl)carbamate (3h)



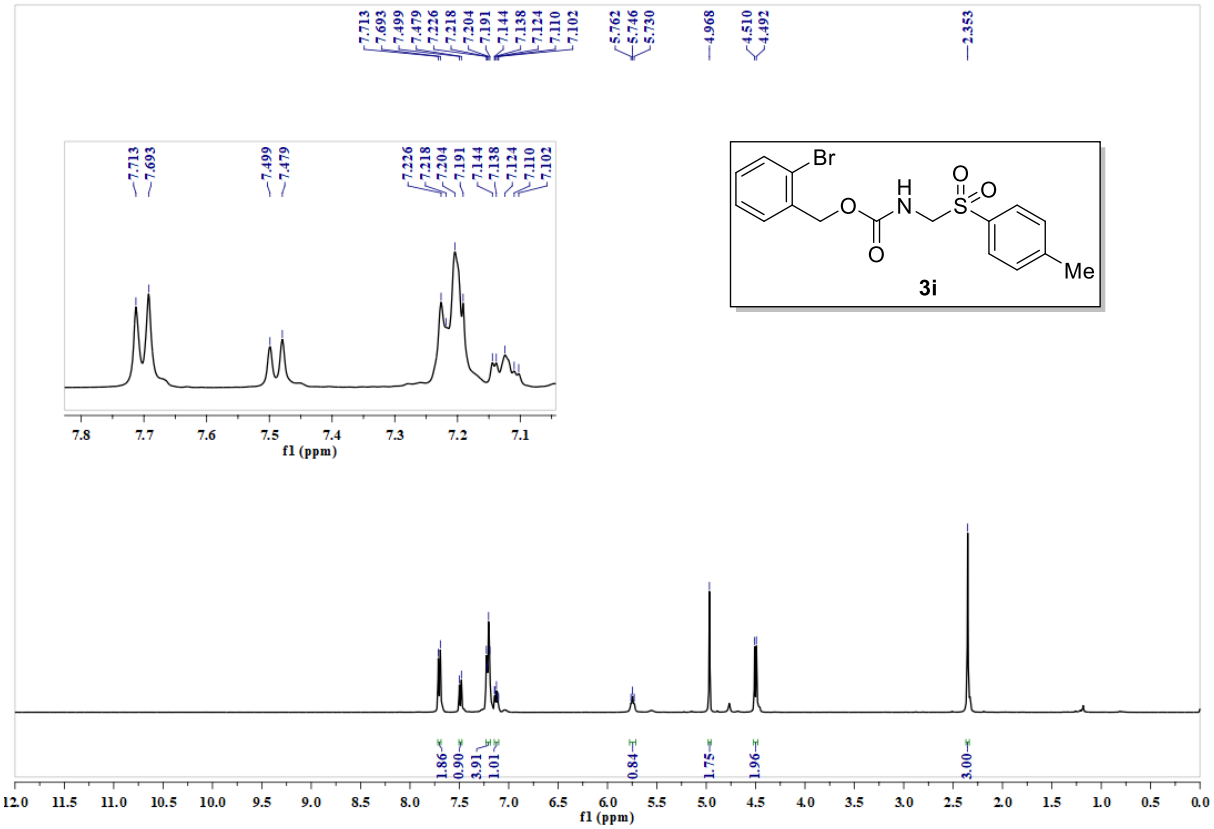
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of benzyl (tosylmethyl)carbamate (3h)



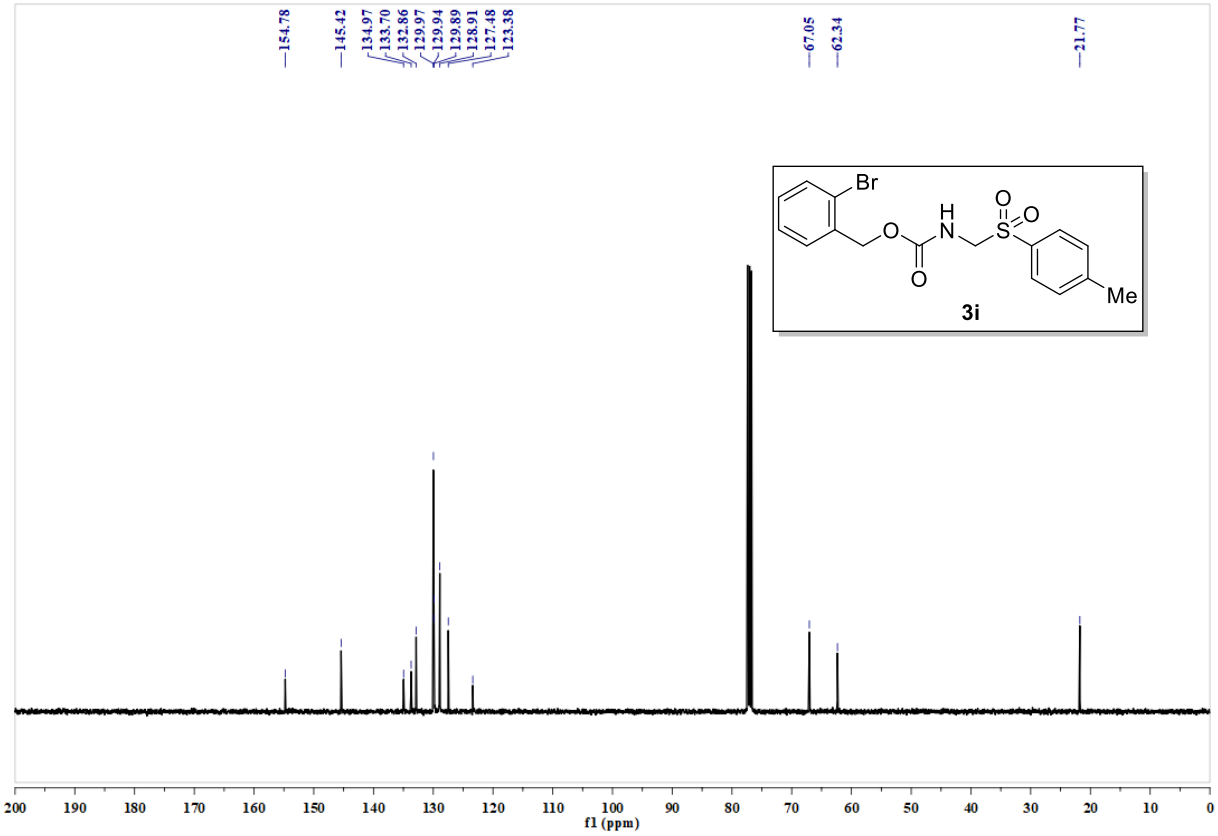
HRMS spectrum of benzyl (tosylmethyl)carbamate (3h)



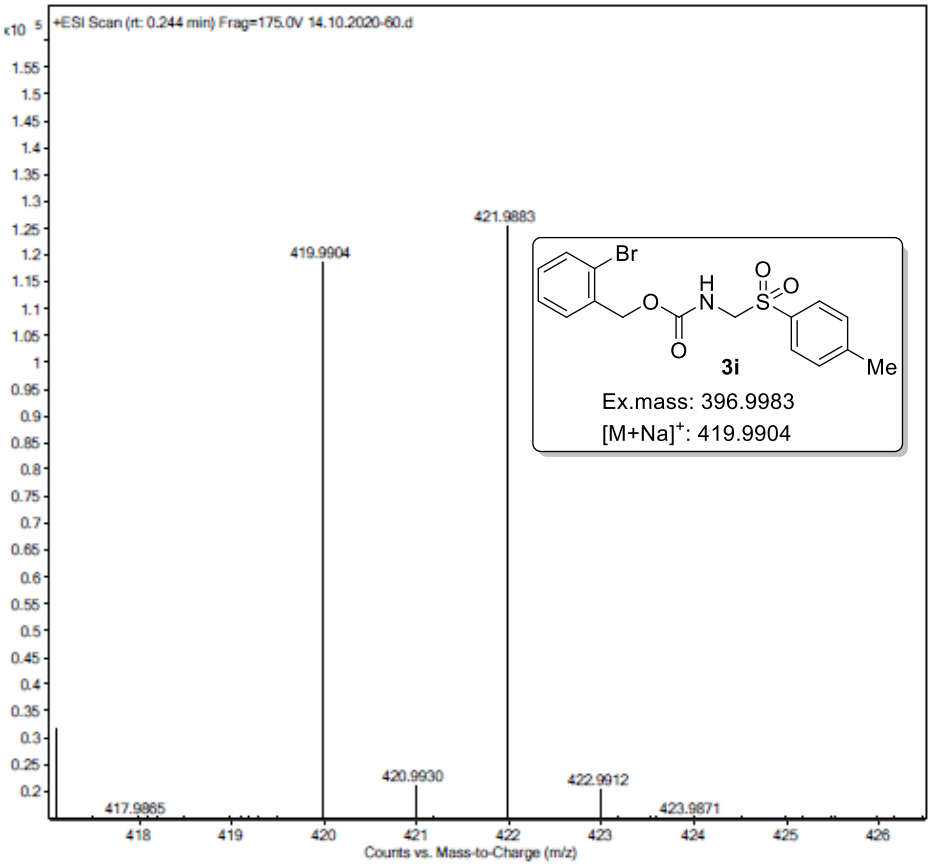
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 2-bromobenzyl (tosylmethyl)carbamate (3i)



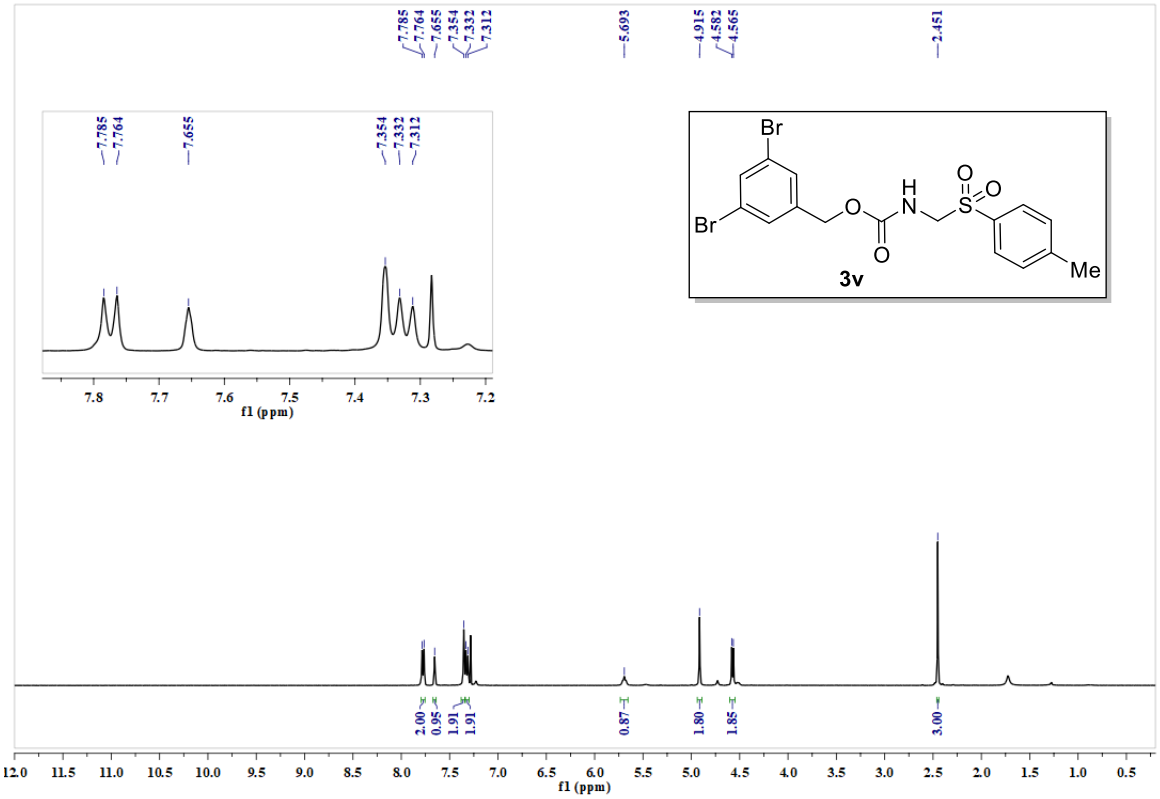
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 2-bromobenzyl (tosylmethyl)carbamate (3i)



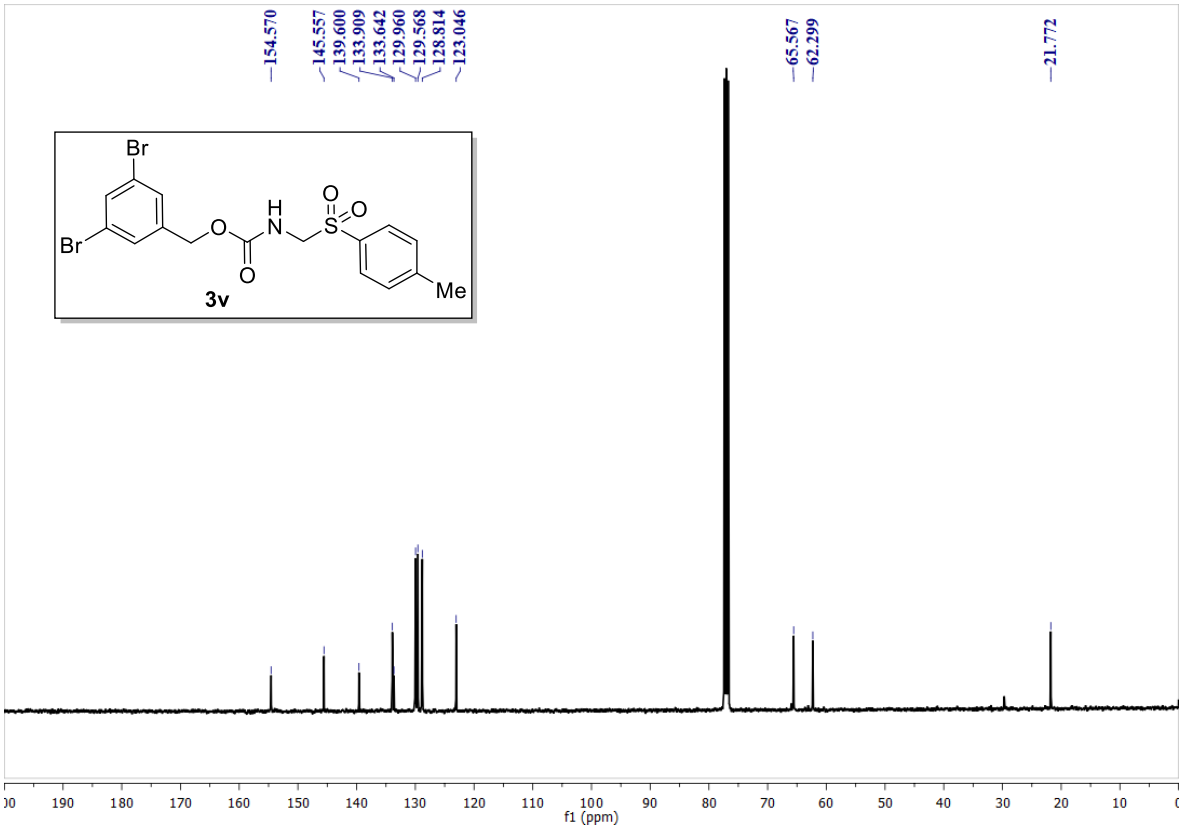
HRMS spectrum of 2-bromobenzyl (tosylmethyl)carbamate (3i)



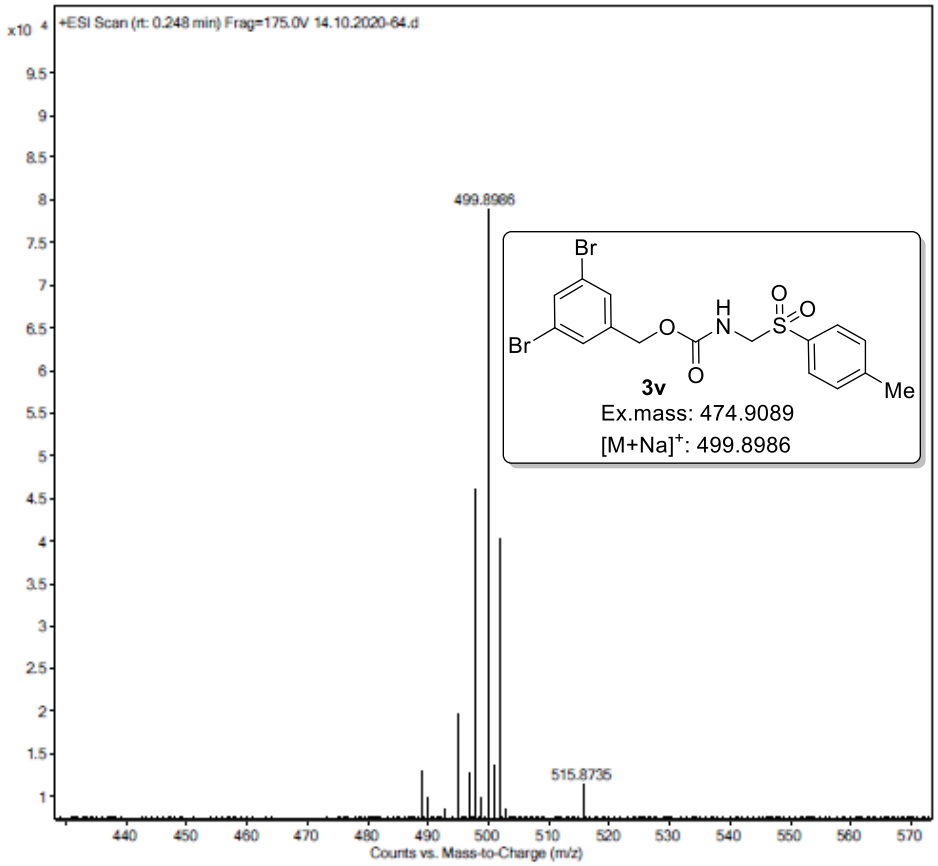
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3,5-dibromobenzyl (tosylmethyl)carbamate (3v)



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 3,5-dibromobenzyl (tosylmethyl)carbamate (3v)

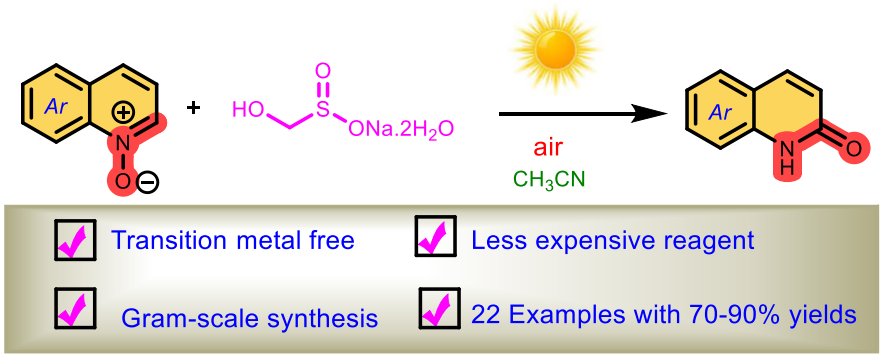


HRMS spectrum of 3,5-dibromobenzyl (tosylmethyl)carbamate (3v)



CHAPTER-V

Efficient Sunlight Mediated Synthesis of Quinoline-2(1*H*)-ones from Quinoline *N*-oxides Using Rongalite



5.1. Introduction

Quinolinones-2(1*H*)-ones and isoquinolin-1(2*H*)-ones are pertained to an important class of heterocycles that are existing in a wide range of natural and biological active compounds.[1] They generally exhibit several biological activities such as antibiotic, antiviral, anticancer, antihypertensive.[2] For instance, the drug indacaterol is using in the treatment of COPD (chronic obstructive pulmonary disease). Dovitinib is another drug, used as a multi-targeted tyrosine kinase inhibitor.[3] Quinolinones-2(1*H*)-ones are also efficient fluorescent biomarkers.[4]

Consequently, various synthetic methods are reported in the literature for the preparation of 2-quinolinone derivatives in recent years.[5-6] Classically, 2-quinolinone derivatives are prepared by the following methods: a) Knorr synthesis, the acid mediated intramolecular cyclization of *β*-keto anilides; b) Friedlander synthesis, a base-mediated intramolecular aldol condensation of 2-aminophenyl substituted carbonyl compounds.[5] Recently, 2-quinolinones were efficiently prepared *via* transition metal catalysis.[6] Fujiwara reported Pd-catalyzed intramolecular electrophilic cyclization of *ortho*-alkynyl anilides for the synthesis of 4-substituted quinolinones.[6c] Larock reported the synthesis of 3,4- disubstituted quinolinones by a Pd-catalyzed carbonylative annulation of 2-iodoanilides with alkynes and CO.[6a] Manley reported a Pd-catalyzed amidation of *ortho*-halo acetophenone with alkyl amides leading to 4-substituted quinolinones.[6b] Alper reported the synthesis of 2-quinolinones *via* the oxidative cyclocarbonylation of 2-vinyl anilines with CO in the presence of a Pd catalyst.[6e] In most of these methods, a preactivated species, such as C-X or C-M having starting material, is required to synthesize the key starting materials. In the meantime, the synthesis of 2- quinolinones are also achieved by the other protocols without a metal catalyst.[7]

Recently, direct C2-hydroxylation of quinoline *N*-oxides has become a versatile synthetic route to prepare 2-quinolinones.[8-15] In this method, a preactivated species such as C-X or C-M having starting material is not required to activate the C2- carbon of the aromatic moiety. By using this method, various heterocyclic compounds were synthesized efficiently in a highly atom economical and environmental friendly manner. However, these methods are efficient, but requires activation of quinoline *N*-oxides with activating agent such as sulfonyl chloride, acyl chloride, boron-based reagents and PyBroP.[16-21]Another advantage regarding the usage of quinoline *N*-oxides is they are widely available and abundant.[22-23]

As an extension of our previous work using isocyanides to C2-H functionalize aromatic amine *N*-oxides,[24] we develop here rongalite-induced transition metal-free approach for the conversion of quinoline *N*-oxides to the corresponding quinolin-2(1*H*)-ones under sunlight.

In this method, rongalite is sensitizing the reactant by absorbing the sunlight a library of quinolin-2(1*H*)-ones were synthesized with this protocol.

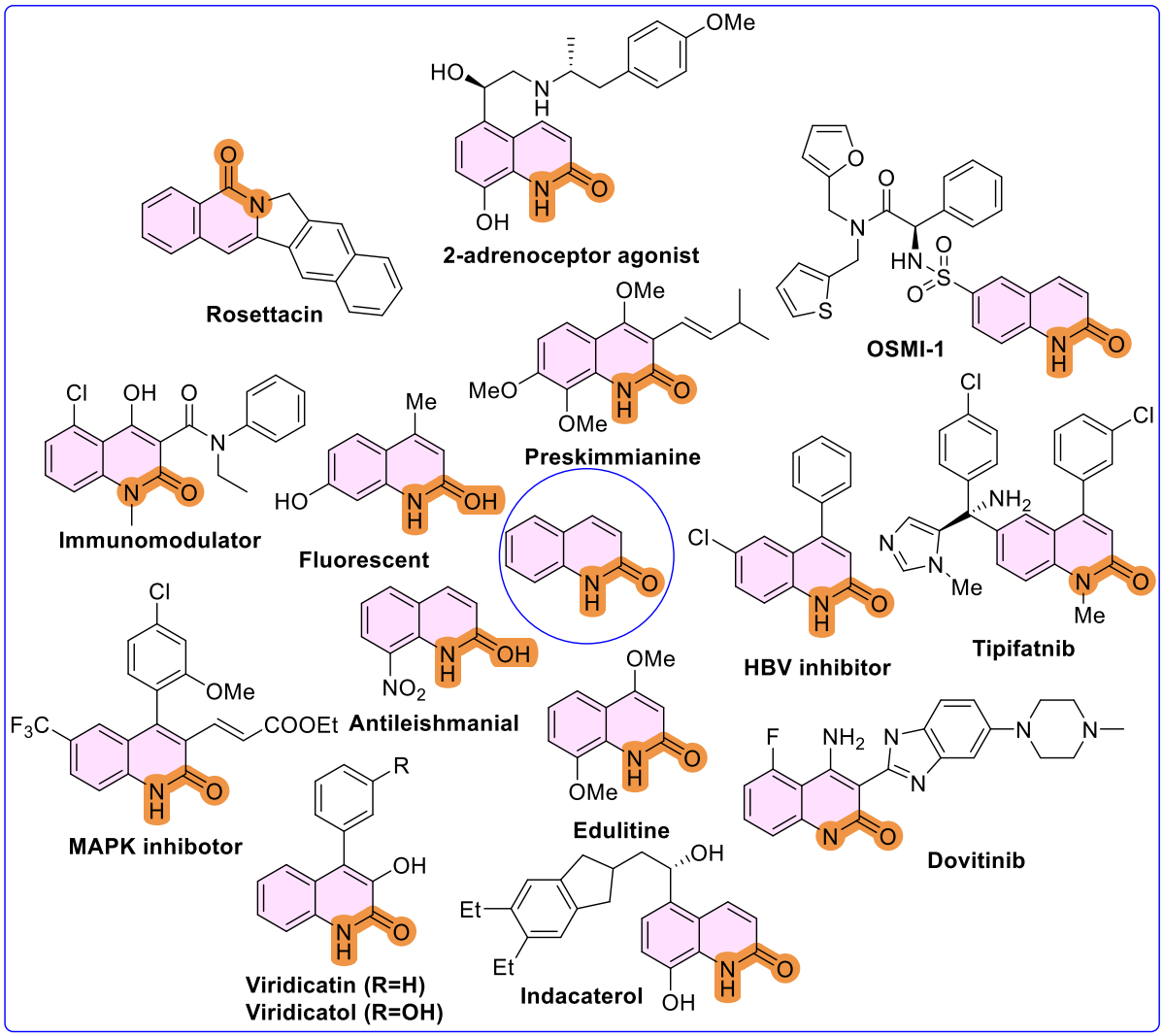
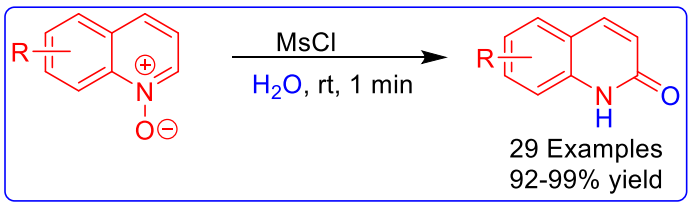


Figure 5.1. Natural products and bioactive drugs containing a quinolin-2(1*H*)-one moiety.

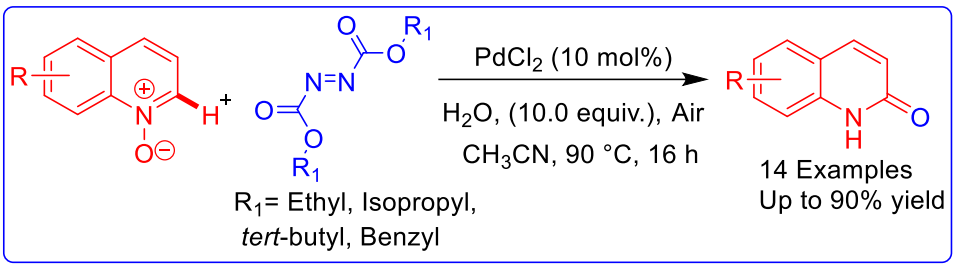
5.1.1. Reported methods for the synthesis of quinolin-2(1*H*)-ones and its derivatives

He and co-workers developed an environmental friendly approach for the aqueous synthesis of several functionalized quinolin-2(1*H*)-ones at room temperature without use of bases or organic solvents. This method is useful to synthesis of wide substrate scope, excellent yield and less time (1-8 min) (Scheme 5.1).[25]



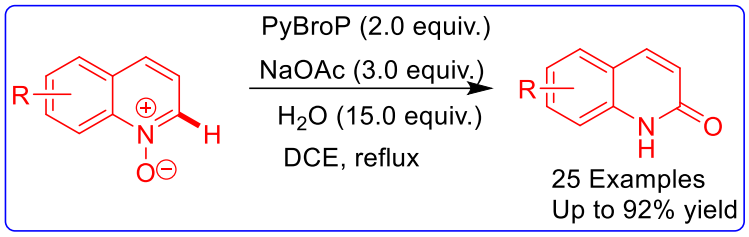
Scheme 5.1

Xiao-Feng et al. introduced a Pd (II) catalyzed synthesis of quinoline 2(1*H*)-one from quinoline *N*-oxides. Azodicarboxylates have a special function in this process and it is act as activating agent and oxidant (Scheme 5.2).[26]



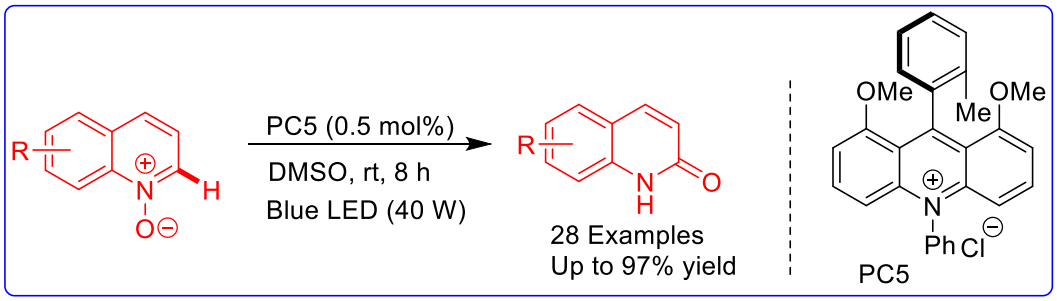
Scheme 5.2

Wang and co-workers developed an efficient protocol for the synthesis of quinolin-2(1*H*)-one employing PyBroP as the activating agent and sodium acetate/water as the base/nucleophile. An isotopic-labeling experiment was carried out to know the reaction's mechanism (Scheme 5.3).[27]



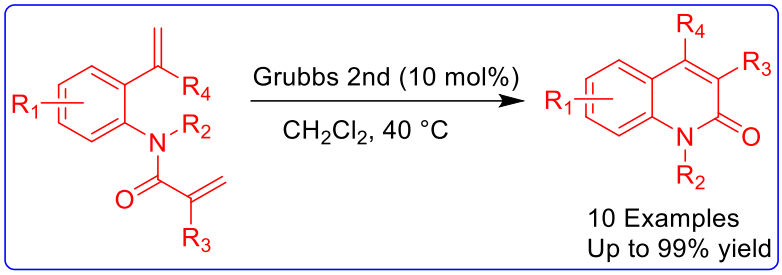
Scheme 5.3

Gopal Roy and co-workers described a novel and unexplored photocatalytic method for producing target compounds from readily available quinoline-*N*-oxides. Reagent-free, cost-effective, photocatalytic process that uses low catalyst loading and high yield are some of the features of this method (Scheme 5.4).[28]



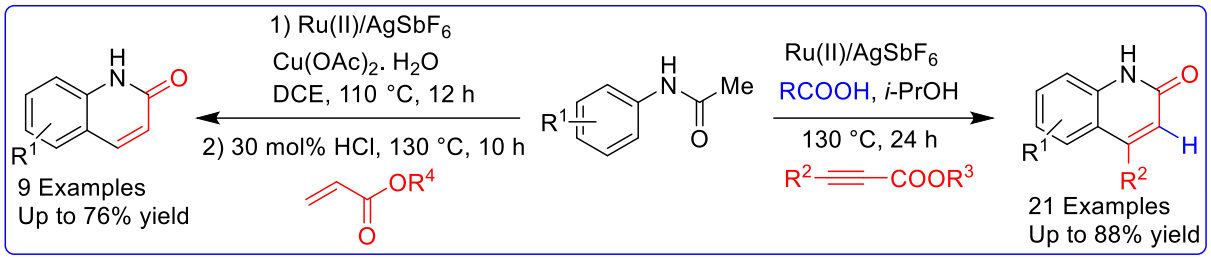
Scheme 5.4

Minville et al. introduced a quinolinones from *N*-phenylacrylamide in the presence of Grubbs catalyst (10 mol%) in dichloromethane at 40 °C. This method undergoes ring closing metathesis to yield the corresponding quinolinones (Scheme 5.5).[29]



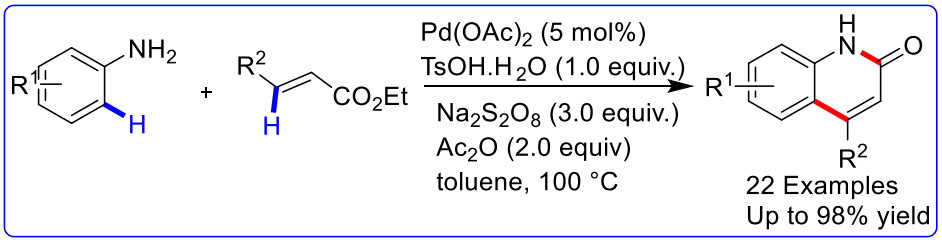
Scheme 5.5

Manikandan et al. introduced a new protocol to produce 2-quinolinones with a variety of functional groups in good to excellent yields by cyclizing anilides with substituted propiolates or acrylates under the influence of Ru catalyst and in the presence of carboxylic acid (Scheme 5.6).[30]



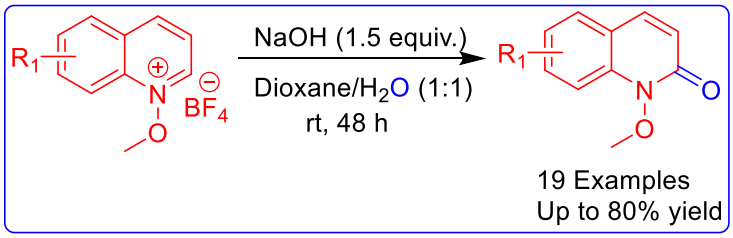
Scheme 5.6

Wu et al. employed Pd-catalyzed C-H bond activation/C-C bond formation/cyclization cascade process to produce quinoline derivatives from simple anilines as the substrates in good to excellent yields. A formal synthesis of tipifarnib achieved from this method (Scheme 5.7).[31]



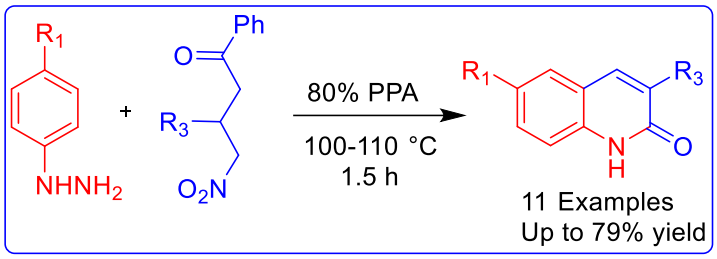
Scheme 5.7

Gao et al developed a *N*-methoxy quinoline-1-ium-tetrafluoroborate, which is stable and widely available reagent, was used as the starting material in a simple and ecologically friendly process for the synthesis of *N*-methoxy quinolin-2(1*H*)-ones. Due to the mild reaction conditions, a wide variety of *N*-methoxy quinolin-2-(1*H*)-ones with various functional groups have been produced in respectable yields (Scheme 5.8).[32]



Scheme 5.8

Aksenov and co-workers developed a cascade annulation pathway to produce 3-substituted 2-quinolones from nitro ketones and hydrazines in polyphosphoric acid (Scheme 5.9).[33]

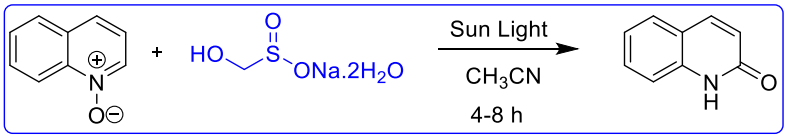


Scheme 5.9

Based on the literature survey we found that a limited number of reports were there on the quinoline *N*-oxides to produce quinolin-2(1*H*)-ones. Also, majority of the literature relay on use of metal catalysts, expensive reagents and long reaction times.

5.2. Present study

In this chapter, we describe a transition metal-free synthesis of quinolin-2(1*H*)-one, substituted quinolines *N*-oxides in the presence of rongalite. This transition metal-free reaction affords rapid access to quinolin-2(1*H*)-one, with exceptional functional group tolerance, broad substrate scope (Scheme 5.10).

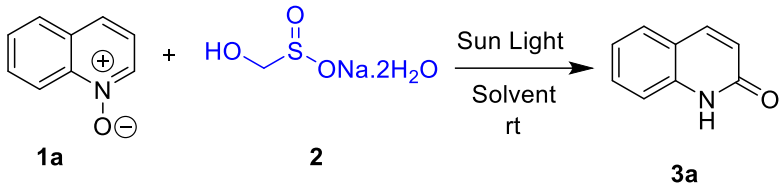


Scheme 5.10

With this proposed methodology we can prepare various quinolin-2(1*H*)-one under environmentally benign conditions *i.e.*, transition metal free, less expensive, non-hazardous, and easily available reagents.

5.2.1. Results and discussion

Table 5.1. Optimization of the reaction conditions[a]



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

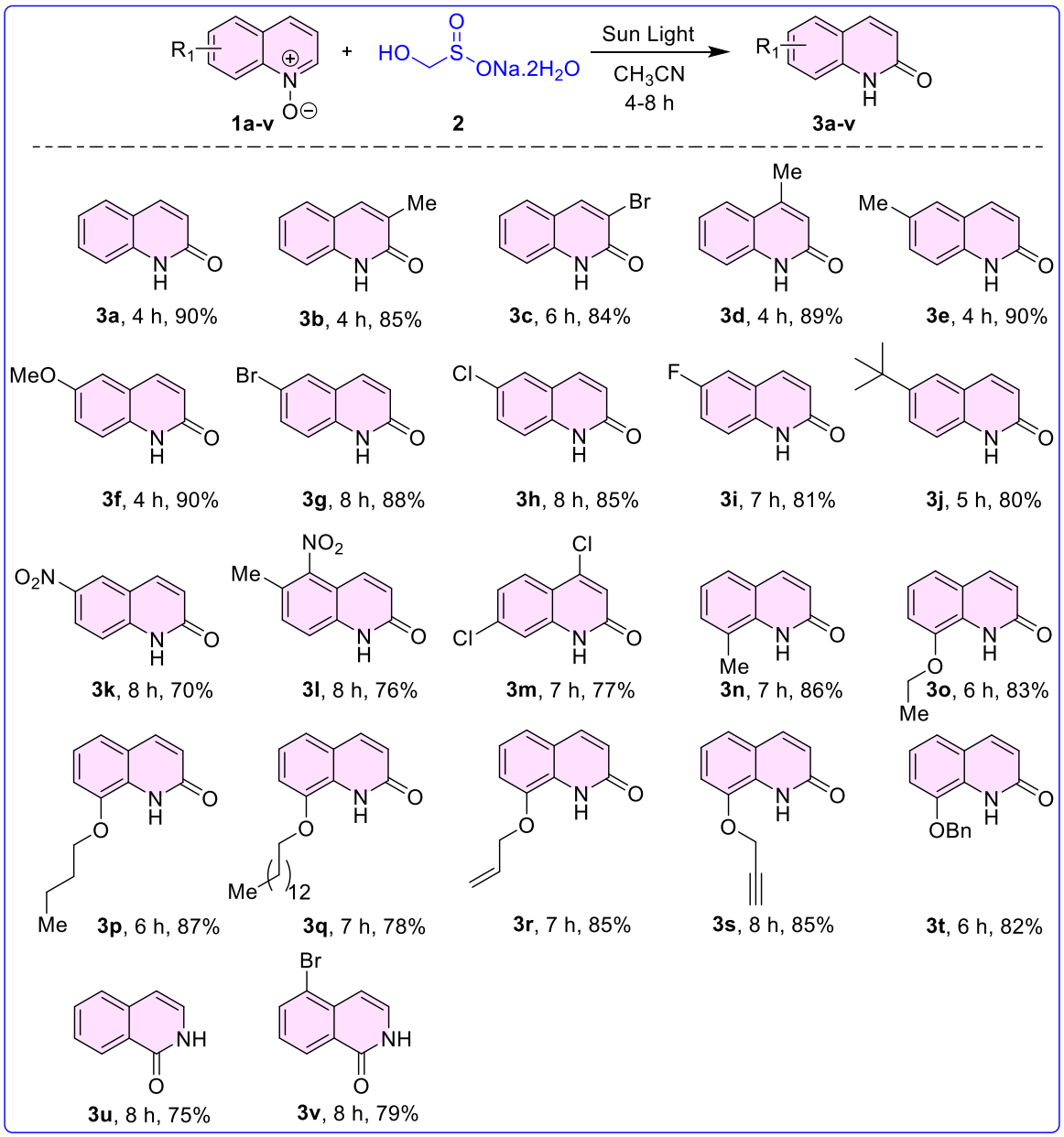
Entry	Solvent	Rongalite (mol%)	Time (h)	Yield (%)[b]
1	CH_2Cl_2	20	8	10
2	$CHCl_3$	20	8	15
3	DCE	20	8	10
4	**CH_3CN**	**20**	**4**	**90**
5	Toluene	20	8	10
6	DMF	20	8	75
7	THF	20	8	70
8	DMSO	20	8	30
9	EtOH	20	8	30
10	MeOH	20	8	40
11	H_2O	20	8	40
12	CH_3CN	-	8	20
13	CH_3CN	10	8	80

[a]Reaction conditions: quinoline-*N*-oxides **1a** (0.5 mmol), rongalite **2** (20 mol%), Solvent (2 mL), 4 h.
[b]Isolated yields.

To validate our hypothesis a test reaction was conducted between quinoline *N*-oxide **1a** and rongalite **2** in dichloromethane solvent. Initially, the reaction mixture was stirred at room temperature, no change in starting material was observed (monitored by TLC) even after 24 h. Then the reaction mixture was stirred at room temperature in presence of sunlight, surprisingly formation of desired product **3a** was observed in low yield (Table 5.1, entry 1).

The above result provoked us to optimize the reaction conditions to improve the product yield by changing the reaction conditions and the results are summarised in Table 5.1. Hence, we have focused on screening of solvents. Firstly, reaction was conducted in chlorinated solvents such as chloroform and dichloroethane, but gave low yield (Table 5.1, entries 2-3). Later, we have changed the reaction medium to other solvents such as, CH_3CN, toluene, DMF, THF, DMSO, polar protic solvents which gave improved yields compared to the chlorinated solvents (Table 5.1, entries 4-11). Among them, CH_3CN solvent in presence of sunlight found to be the best condition to give the desired product in 90% yields (Table 5.1, entries 4).

Table 5.2. Reaction of substituted quinoline-*N*-oxides with rongalite[a,b]

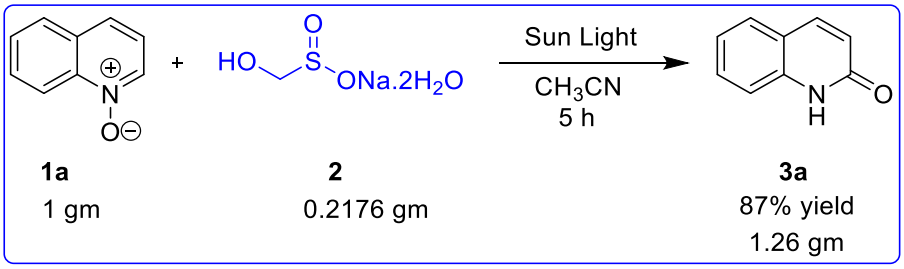


[a]Reaction Conditions: quinoline-*N*-oxide **1a-v** (0.5 mmol), rongalite **2** (20 mol%), CH_3CN (2 mL), sunlight. [b]Isolated yields.

Thus, the optimized conditions for the above reaction is as follows, quinoline *N*-oxide **1a** and rongalite **2** in CH_3CN (2 mL) in the presence of sunlight for 4-8 h (Table 5.1, entry 4). After optimization of the reaction conditions, then we have shifted our focus to explore the scope of the quinoline *N*-oxides with rongalite. Interestingly, electron releasing groups such as methyl, methoxy on quinoline *N*-oxide readily react with rongalite and gave the target quinolin-2(1*H*)-ones up to 90% yields (Table 5.2, **3b-f**). Notably, halogens (Cl, Br, F) on quinoline *N*-oxide smoothly reacted with rongalite to give corresponding quinolin-2(1*H*)-ones in good to excellent yields (Table 5.2, **3g-i).** The electron withdrawing groups, alkyl ethers and di-substitution on

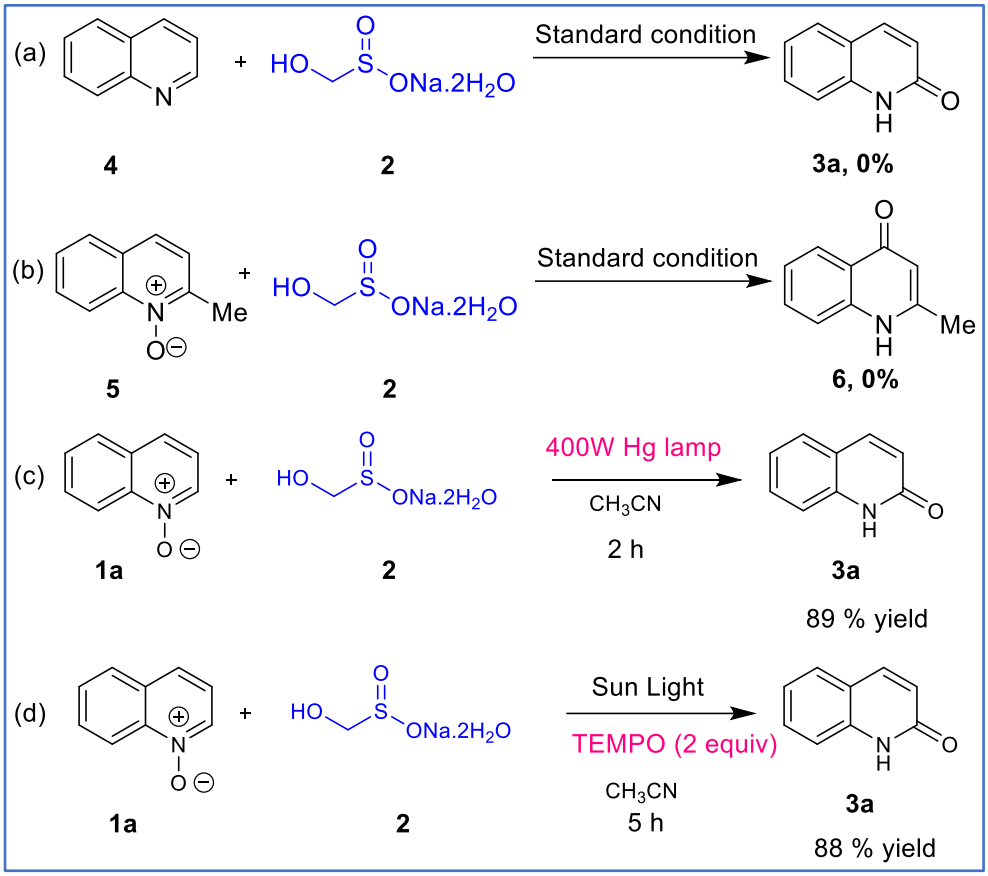
quinoline *N*-oxides did not alter the product yields (Table 5.2). Notably, isoquinoline *N*-oxides also smoothly reacted under optimised conditions to give target compounds **3u-v** in good yields (Table 5.2). The starting materials, quinoline *N*-oxides which are used in this scheme were prepared from reported method using quinoline and *m*-CPBA in $CHCl_3$ as solvent.[34] All the synthesized compounds from this protocol were characterized by ^1H and ^{13}C NMR spectroscopy and mass spectral data. The data of all the compounds were incomparable with the literature reports.

Further, we investigated the efficiency of this protocol for gram scale reaction using quinoline *N*- oxide **1a** with rongalite (20 mol%) **2** under the standard condition. The reaction afforded the final product **3a** in 87% of yield (Scheme 5.11).



Scheme 5.11. Gram-scale reaction.

Next, we carried several control experiments to unveil the reaction mechanism (Scheme 5.12). Initially, quinoline **4** was treated with rongalite **2**, under the standard conditions, but no reaction was observed, which indicated the important role of *N*-oxide in this transformation (Scheme 5.12a). Later, 2-substituted quinoline *N*-oxide **5** was used to test the reactive position of the quinoline *N*-oxide and found to be non-reactive under the optimized conditions (Scheme 5.12b). Then, we conducted another reaction using 400W Hg immersion lamp to know the which region of the light is catalyzing the reaction and observed that the reaction was completed within 2 h (Scheme 5.12c). It clearly indicates that the ultraviolet light is responsible for moving the reaction under sunlight irradiation. Finally, we conducted the same model reaction with radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and observed that there is no effect on reaction outcome (Scheme 5.12b). Also, we have recorded the UV-Visible spectrum of rongalite in water and which was shown absorption at 202 and 227 nm.



Scheme 5.12. Control experiments.

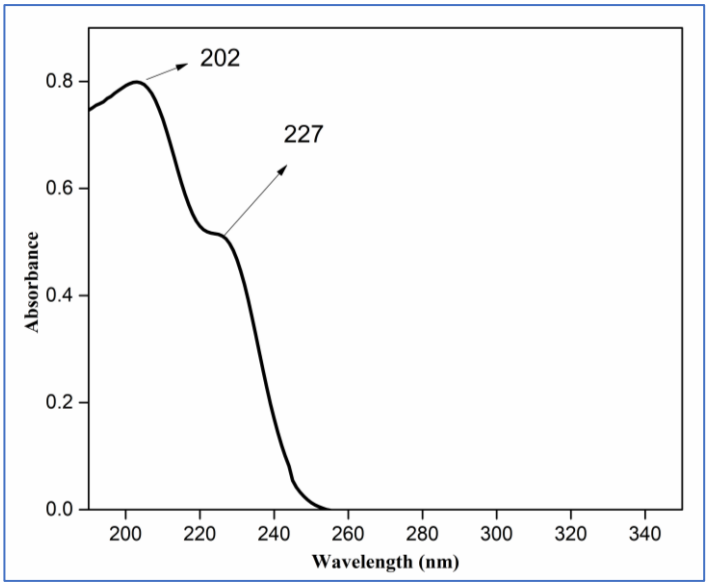
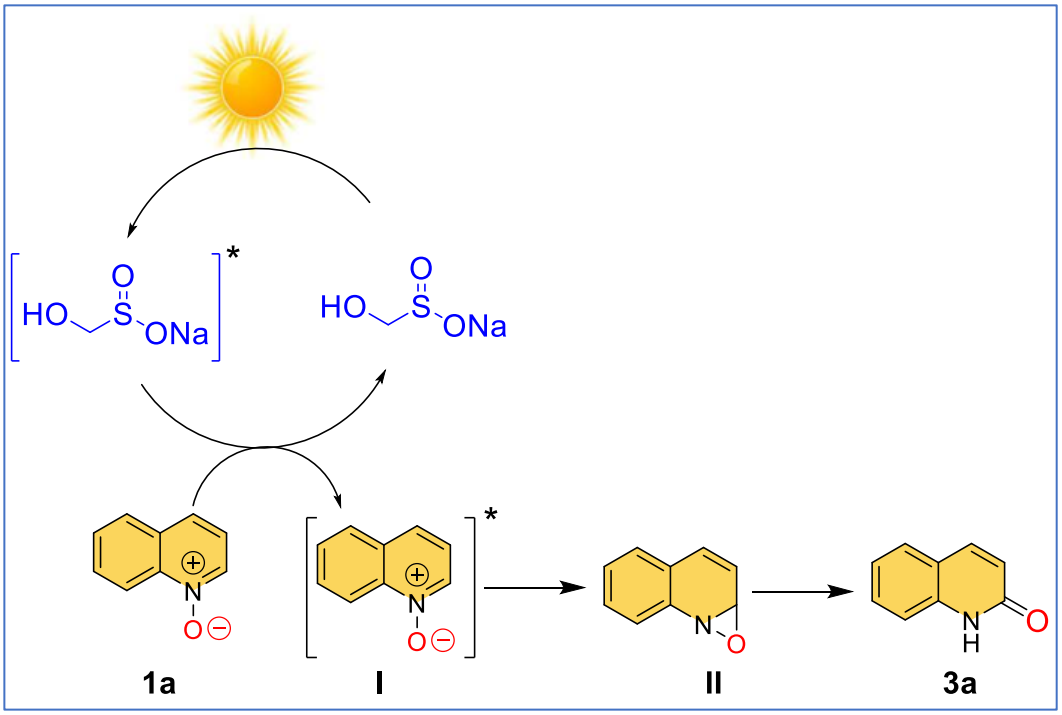


Figure 5.2. UV-VIS spectrum of rongalite in water

On the basis of our control experiments and previous literature,[27,35-37] a plausible single electron transfer mechanism is illustrated in Scheme 5.13. Initially, rongalite absorbing irradiation from sunlight and sensitizing the quinoline *N*-oxide **1a,** which then participates in attacking the vicinal electrophilic C-2 centre to form the kinetically favourable three membered oxaziridine

ring **II**. The weak N-O bond of oxa-ziridine **II** finally isomerizes to form stable carbonyls through simultaneous hydride migration to generate the corresponding quinolin-2(1*H*)-ones **3a** as the final product.



Scheme 5.13. Plausible reaction mechanism

5.3. Conclusion

In summary, we have developed a rongalite-induced transition metal-free approach for the conversion of quinoline *N*-oxides to the corresponding quinolin-2(1*H*)-ones under sunlight. This metal-free reaction affords rapid access to quinolin-2(1*H*)-ones with exceptional functional group tolerance and broad substrate scope. In this method, rongalite is sensitizing the reactant by absorbing the sunlight a library of quinolin-2(1*H*)-ones were synthesized with this protocol.

5.4. Experimental section

5.4.1. General Information: All chemicals were purchased from Aldrich, Alfa, TCI, Finar and used as received. All solvents were purchased from commercial sources, then distilled by the standard protocol and stored over molecular sieves under nitrogen atmosphere prior to use. Thin layer chromatography was performed on 200 µm aluminium-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). ^{1}H NMR spectra were recorded on Bruker's AVANCE 400 MHz spectrometers, DMSO as a solvent and TMS as an internal standard. The following abbreviations were used to explain multiplicities: s

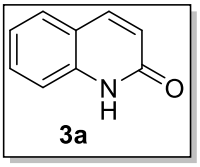
= singlet, d = doublet, t = triplet, q = quartet, br = broad, coupling constants, J, were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker's AVANCE 100 MHz spectrometers, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a multiplet at 39.52 ppm of DMSO-d6). Melting points were determined with a Stuart SMP30 apparatus and are uncorrected. FT-IR spectra recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230.

5.4.2. General procedure for the synthesis of quinolin- 2(1*H*)- ones (3a-v)

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate quinoline *N*-oxides (0.5 mmol), rongalite (20 mol%), acetonitrile (2 mL). The mixture was stirred under sunlight for the appropriate time (4-8 h). The progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. After completion, the reaction mixture was treated with ethyl acetate (3x 10 mL) and water. The organic layer was separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent.

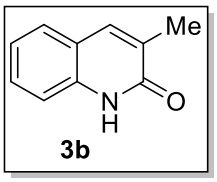
5.5. Characterization data of products 3a-3v.

Quinolin-2(1*H*)-one (3a). White solid; (65 mg, 90% yield);^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.73 (s, 1H), 7.90 (d, J = 9.6 Hz, 1H), 7.65 (dd, J = 7.8, 1.0 Hz, 1H), 7.52-7.47 (m, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.19-7.15 (m, 1H), 6.50 (d, J = 9.6 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 162.8, 141.1, 139.0, 131.0, 128.4, 122.5, 121.9, 119.6, 115.7; HRMS (ESI-TOF) m/z: calculated for C_9H_8NO $[M+H]^+$ 146.0600; found 146.0599.



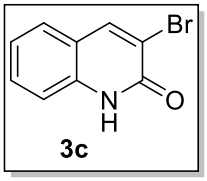
3a

3-methylquinolin-2(1*H*)-one (3b). Pale yellow solid; (67 mg, 85% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 11.73 (s, 1H), 7.76 (s, 1H), 7.57 (d, J = 8.8, Hz, 1H), 7.44-7.40 (m, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.16-7.12 (m, 1H), 2.09 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 162.9, 138.3, 136.8, 130.2, 129.5, 127.3, 122.1, 119.9, 115.2, 16.9; HRMS (ESI-TOF) m/z: calculated for $C_{10}H_{10}NO$ $[M+H]^+$ 160.0757; found 160.0753.



3b

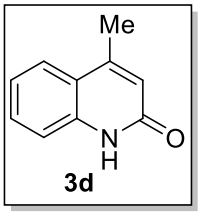
3-bromoquinolin-2(1*H*)-one (3c). White solid; (94 mg, 84% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.31 (s, 1H), 8.56 (s, 1H), 7.73 (dd, J = 7.8, 1.0 Hz, 1H), 7.60 (m, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.30 – 7.25 (m, 1H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 158.1, 142.1, 138.6, 131.2, 127.7,



3c

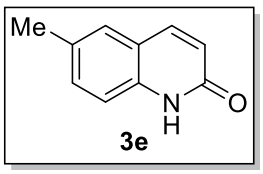
122.8, 119.8, 117.5, 115.7; HRMS (ESI-TOF) m/z: calculated for C_9H_7BrNO $[M+H]^+$ 223.9706; found 223.9707.

4-methylquinolin-2(1*H*)-one (3d). Pale yellow solid; (70 mg, 89% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.60 (s, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.21 – 7.15 (m, 1H), 6.39 (s, 1H), 2.41 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.1, 148.3, 139.1, 130.7, 125.1, 122.1, 121.3, 120.0, 115.8, 18.9; HRMS (ESI-TOF) m/z: calculated for $C_{10}H_{10}NO$ $[M+H]^+$ 160.0757; found 160.0753.



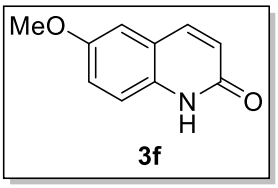
3d

6-methylquinolin-2(1*H*)-one (3e). White solid; (71 mg, 90% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.65 (s, 1H), 7.82 (d, J = 9.6 Hz, 1H), 7.44 (s, 1H), 7.32 (dd, J = 8.4, 1.6 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.46 (d, J = 9.2 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.3, 140.4, 137.3, 132.0, 131.1, 127.8, 122.3, 119.5, 115.5, 20.7; HRMS (ESI-TOF) m/z: calculated for $C_{10}H_{10}NO$ $[M+H]^+$ 160.0757; found 160.0753.



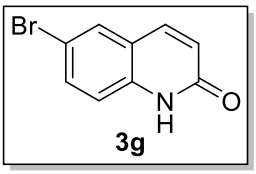
3e

6-methoxyquinolin-2(1*H*)-one (3f). Pale yellow solid; (78 mg, 90% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.62 (s, 1H), 7.85 (d, J = 9.2 Hz, 1H), 7.23 (dd, J = 16.8, 5.6 Hz, 2H), 7.15 (dd, J = 8.8, 2.4 Hz, 1H), 6.49 (d, J = 9.2 Hz, 1H), 3.78 (s, 3H).^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.0, 154.5, 140.2, 133.7, 122.7, 120.1, 119.9, 116.8, 109.7, 55.8; HRMS (ESI-TOF) m/z: calculated for $C_{10}H_{10}NO_2$ $[M+H]^+$ 176.0706; found 176.0702.



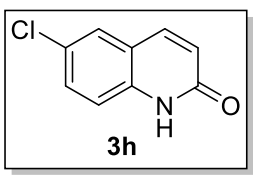
3f

6-bromoquinolin-2(1*H*)-one (3g). Yellow solid; (98 mg, 88% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.86 (s, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.64 (dd, J = 8.6, 2.2 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 9.6 Hz, 1H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.1, 139.6, 138.4, 133.3, 130.3, 123.6, 121.2, 117.7, 113.7; HRMS (ESI-TOF) m/z: calculated for C_9H_7BrNO $[M+H]^+$ 223.9706; found 223.9705.



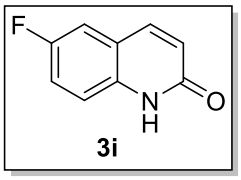
3g

6-chloroquinolin-2(1*H*)-one (3h). White solid; (76 mg, 85% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.86 (s, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 8.8, 2.4 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 6.56 (d, J = 9.6 Hz, 1H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.3, 139.8, 137.8, 130.7, 127.3, 126.2, 123.4, 120.7, 117.5; HRMS (ESI-TOF) m/z: calculated for C_9H_7ClNO $[M+H]^+$ 180.0211; found 180.0207.



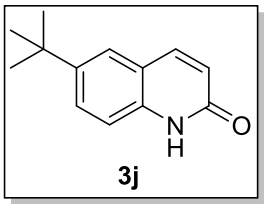
3h

6-fluoroquinolin-2(1*H*)-one (3i). White solid; (66 mg, 81% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.80 (s, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.53 (dd, J = 9.2, 2.8 Hz, 1H), 7.40 (td, J = 8.8, 2.8 Hz, 1H), 7.32 (dd, J = 9.0, 5.0 Hz, 1H), 6.57 (d, J = 9.6 Hz, 1H). ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.10, 158.54, 156.17, 139.87, 136.07, 123.66, 120.25, 118.92, 117.40, 113.19; HRMS (ESI-TOF) m/z: calculated for C_9H_7FNO $[M+H]^+$ 164.0506; found 164.0501.



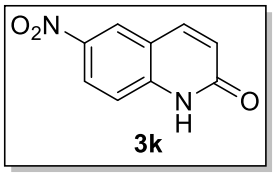
3i

6-(*tert*-butyl)quinolin-2(1*H*)-one (3j). White solid; (80 mg, 80% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.64 (s, 1H), 7.89 (d, J = 9.6 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.26 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 9.2 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.4, 144.6, 140.9, 137.2, 128.6, 124.1, 122.1, 119.1, 115.3, 34.5, 31.6; HRMS (ESI-TOF) m/z: calculated for $C_{13}H_{16}NO$ $[M+H]^+$ 202.1226; found 202.1226.



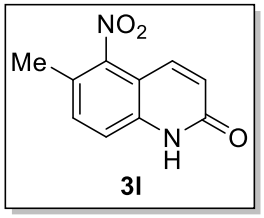
3j

6-nitroquinolin-2(1*H*)-one (3k). Yellow solid; (66 mg, 70% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.28 (s, 1H), 8.68 (d, J = 2.8 Hz, 1H), 8.31 (dd, J = 9.2, 2.4 Hz, 1H), 8.11 (d, J = 9.6 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 6.66 (d, J = 9.6 Hz, 1H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.4, 143.7, 141.9, 140.6, 125.5, 124.7, 124.2, 118.9, 116.5; HRMS (ESI-TOF) m/z: calculated for $C_9H_7N_2O_3$ $[M+H]^+$ 191.0451; found 191.0450.



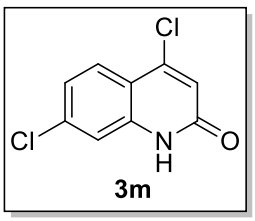
3k

6-methyl-5-nitroquinolin-2(1*H*)-one (3l). Yellow solid; (77 mg, 76% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.16 (s, 1H), 7.65 (d, J = 10.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 10.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 161.3, 147.5, 138.4, 133.5, 133.4, 125.5, 123.0, 118.5, 110.9, 16.9; HRMS (ESI-TOF) m/z: calculated for $C_{10}H_9N_2O3$ $[M+H]^+$ 205.0608; found 205.0616.



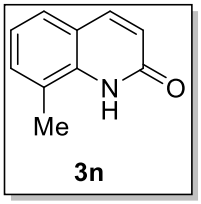
3l

4,7-dichloroquinolin-2(1*H*)-one (3m). White solid; (82 mg, 77%) yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.08 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 1.6 Hz, 1H), 7.34-7.29 (m, 1H), 6.83 (s, 1H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 160.8, 143.9, 139.8, 136.8, 127.0, 123.1, 122.0, 116.6, 115.4; HRMS (ESI-TOF) m/z: calculated for C_9H_6ClNO $[M+H]^+$ 213.9821; found 213.9823.

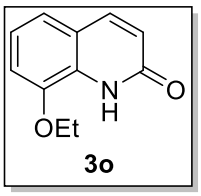


3m

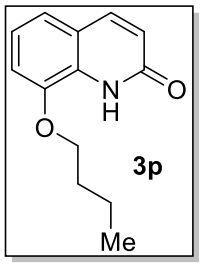
8-methylquinolin-2(1*H*)-one (3n). White solid; (68 mg, 86% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.89 (s, 1H), 7.90 (d, J = 9.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.51 (d, J = 9.6 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.9, 141.3, 137.6, 132.0, 126.4, 123.8, 122.0, 121.9, 119.6, 17.5; HRMS (ESI-TOF) m/z: calculated for $C_{10}H_{10}NO$ $[M+H]^+$ 160.0757; found 160.0752.



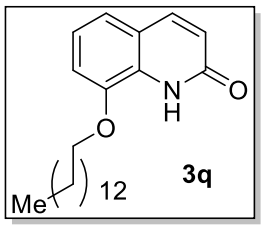
8-Ethoxyquinolin-2(1*H*)-one (3o). White solid; (78 mg, 83% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.72 (s, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.25-7.20 (m, 1H), 7.14 – 7.08 (m, 2H), 6.52 (d, J = 9.6 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 161.9, 145.2, 140.7, 129.3, 122.8, 122.2, 120.0, 119.8, 112.2, 64.7, 14.8; HRMS (ESI-TOF) m/z: calculated for $C_{11}H_{12}NO_2$ $[M+H]^+$ 190.0863; found 190.0858.



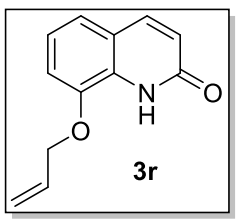
8-butoxyquinolin-2(1*H*)-one (3p). White solid; (94 mg, 87% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.73 (s, 1H), 7.89 (d, J = 9.6 Hz, 1H), 7.25-7.20 (m, 1H), 7.15 – 7.07 (m, 2H), 6.52 (d, J = 9.6 Hz, 1H), 4.09 (t, J = 6.4 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.56 – 1.46 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.0, 145.4, 140.7, 129.2, 122.8, 122.2, 120.0, 119.8, 112.0, 68.8, 30.9, 19.2, 14.2; HRMS (ESI-TOF) m/z: calculated for $C_{13}H_{16}NO_2$ $[M+H]^+$ 218.1176; found 218.1172.



8-(tetradecyloxy)quinolin-2(1*H*)-one (3q). White solid; (139 mg, 78% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.70 (s, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.25-7.20 (m, 1H), 7.14-7.08 (m, 2H), 6.52 (d, J = 9.6 Hz, 1H), 4.08 (t, J = 6.4 Hz, 2H), 1.85 – 1.77 (m, 2H), 1.50 – 1.42 (m, 2H), 1.23 (s, 20H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 161.9, 145.4, 140.7, 129.2, 122.8, 122.2, 120.0, 119.8, 112.0, 69.1, 31.7, 29.4, 29.3, 29.1, 28.8, 26.0, 22.5, 14.4; HRMS (ESI-TOF) m/z: calculated for $C_{23}H_{36}NO_2$ $[M+H]^+$ 358.2741; found 358.2739.

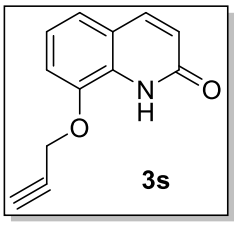


8-(allyloxy)quinolin-2(1*H*)-one (3r). White solid; (85 mg, 85% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.73 (s, 1H), 7.89 (d, J = 9.6 Hz, 1H), 7.27-7.23 (m, 1H), 7.17 – 7.09 (m, 2H), 6.53 (d, J = 9.6 Hz, 1H), 6.20-6.09 (m, 1H), 5.48 (dd, J = 17.2, 1.6 Hz, 1H), 5.28 (dd, J = 10.6, 1.4 Hz, 1H), 4.75-4.70 (m, 2H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 161.9, 144.8, 140.7,

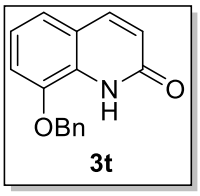


134.0, 129.4, 122.9, 122.2, 120.2, 118.1, 112.9, 69.9; HRMS (ESI-TOF) m/z: calculated for $C_{12}H_{12}NO_2$ $[M+H]^+$ 202.0863; found 202.0857.

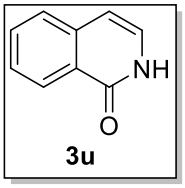
8-(prop-2-yn-1-yloxy)quinolin-2(1*H*)-one (3s). White solid; (84 mg, 85% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.81 (s, 1H), 7.90 (d, J = 9.6 Hz, 1H), 7.32-7.25 (m, 2H), 7.15 (t, J = 7.6 Hz, 1H), 6.53 (d, J = 9.2 Hz, 1H), 4.95 (s, 2H), 3.61 (s, 1H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 161.9, 143.8, 140.6, 129.7, 123.0, 122.0, 121.0, 120.3, 113.7, 79.4, 79.2, 56.9; HRMS (ESI-TOF) m/z: calculated for $C_{12}H_{10}NO_2$ $[M+H]^+$ 200.0706; found 200.0704.



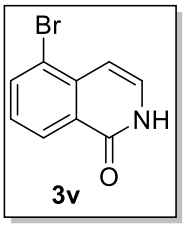
8-(benzyloxy)quinolin-2(1*H*)-one (3t). White solid; (103 mg, 82% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.76 (s, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 7.4 Hz, 2H), 7.08 (t, J = 8.0 Hz, 1H), 6.53 (d, J = 9.6 Hz, 1H), 5.30 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.3, 144.6, 141.0, 137.0, 129.2, 128.8, 128.4, 128.1, 122.6, 122.4, 120.3, 120.2, 113.1, 70.2; HRMS (ESI-TOF) m/z: calculated for $C_{16}H_{14}NO$ $[M+H]^+$ 252.1019; found 252.1015.



Isoquinolin-1(2*H*)-one (3u). White solid; (54 mg, 75% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.24 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.50-7.45 (m, 1H), 7.17 (d, J = 7.2 Hz, 1H), 6.54 (d, J = 6.8 Hz, 1H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 162.3, 138.3, 132.7, 129.3, 127.1, 126.7, 126.6, 126.5, 105.1; HRMS (ESI-TOF) m/z: calculated for C_9H_8NO $[M+H]^+$ 146.0600; found 146.0603.



5-bromoisoquinolin-1(2*H*)-one (3v). White solid; (88 mg, 79% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.52 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.03-7.99 (m, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.36 – 7.31 (m, 1H), 6.66 (d, J = 7.2 Hz, 1H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 161.5, 137.2, 136.5, 131.3, 128.1, 127.7, 127.2, 120.3, 103.1; HRMS (ESI-TOF) m/z: calculated for C_9H_7BrNO $[M+H]^+$ 223.9706; found 223.9703.



5.6. References

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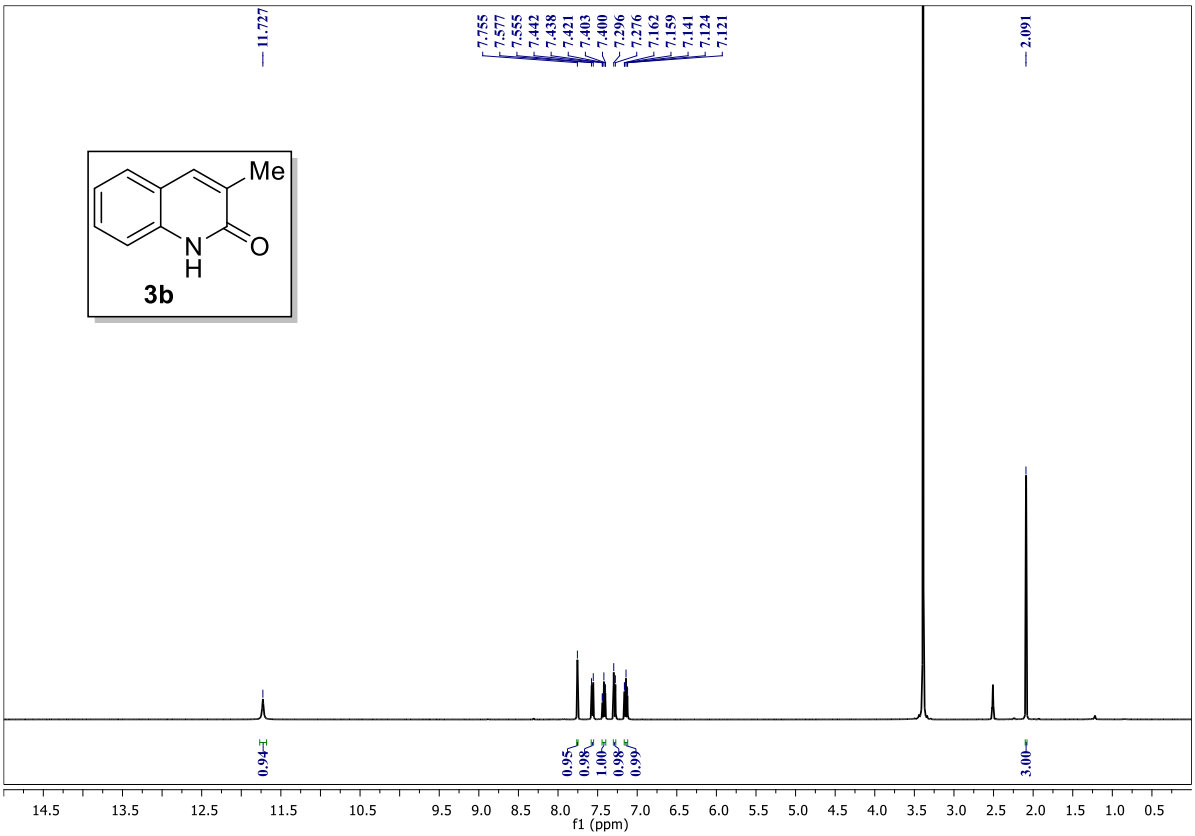
5.7. Selected NMR (^{1}H and ^{13}C) and HRMS Spectra

^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 3-methylquinolin-2(1*H*)-one (3b)



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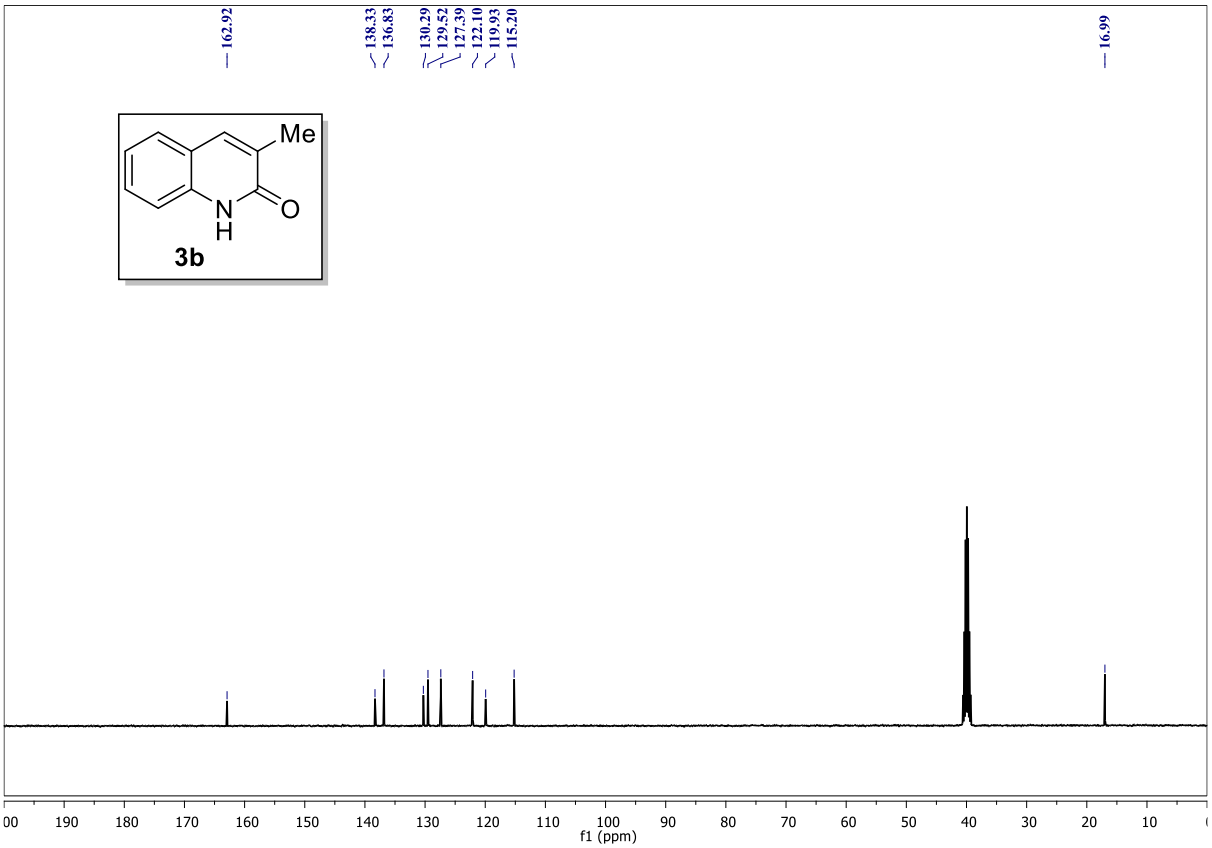
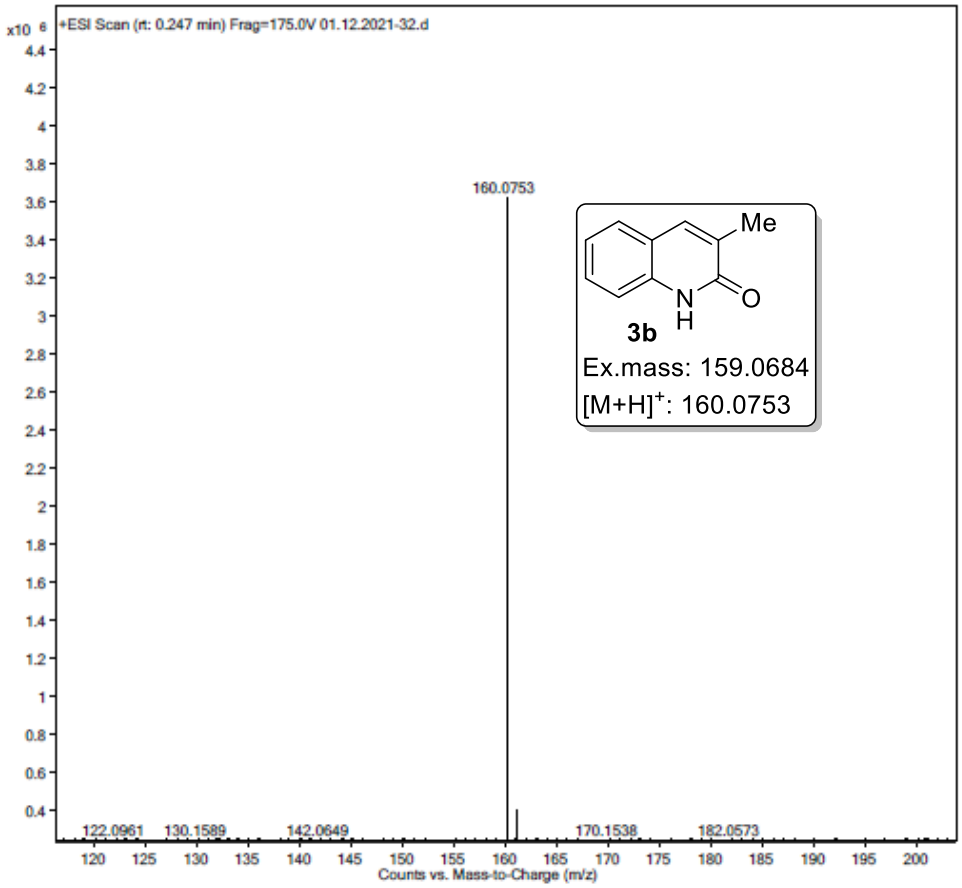
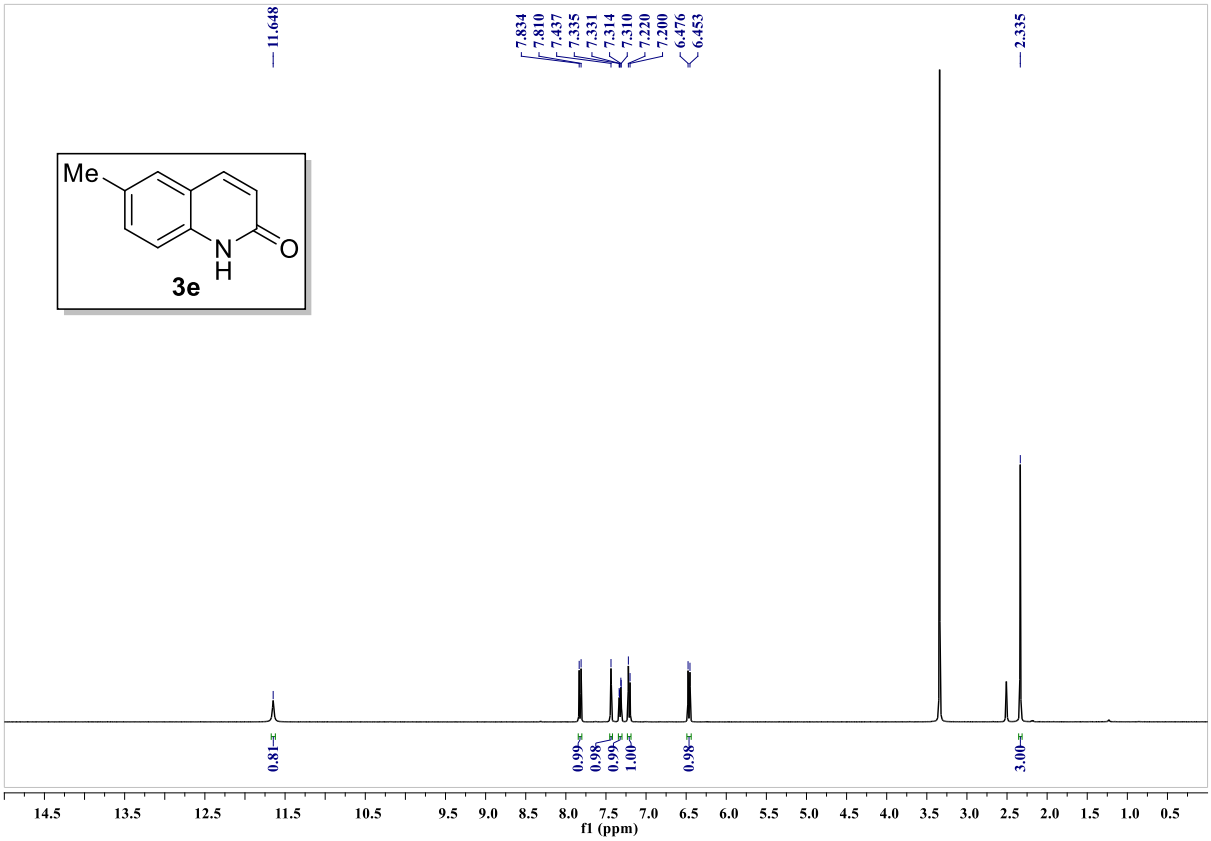


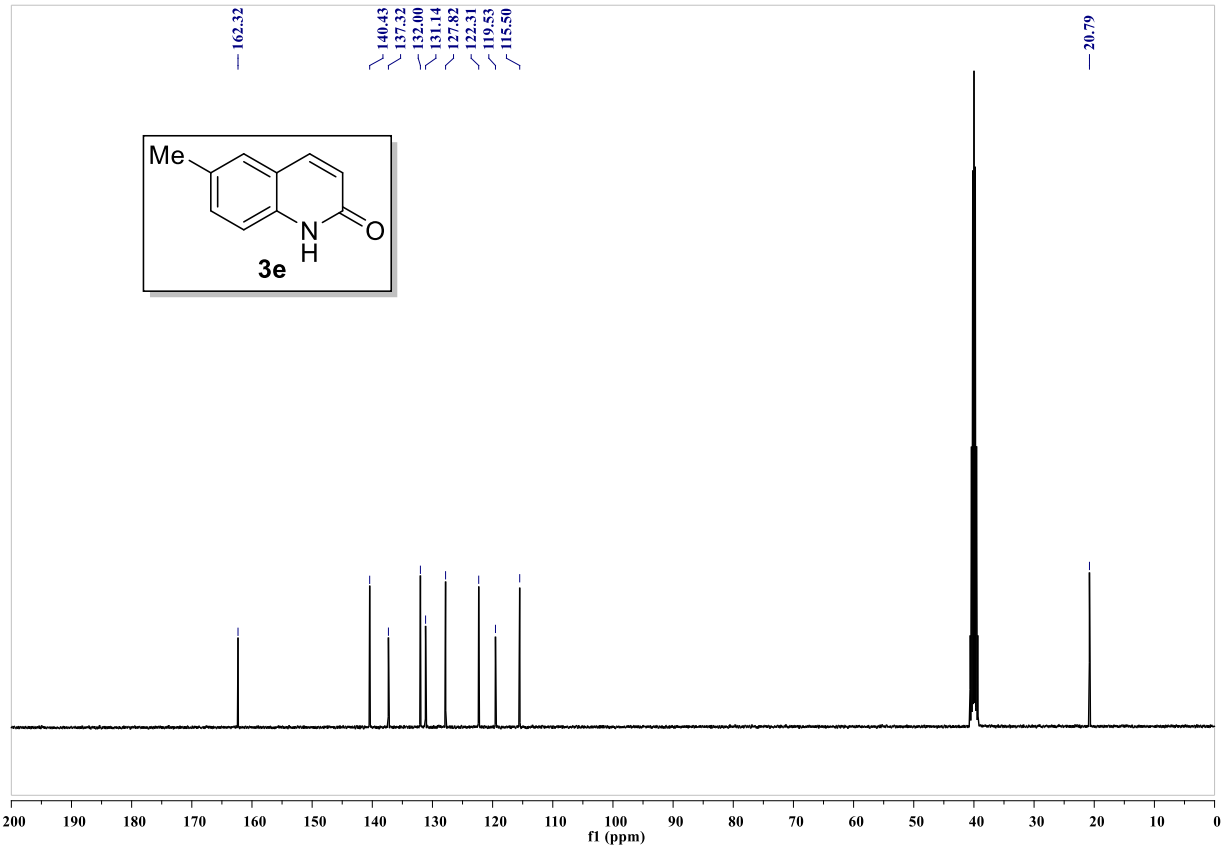
HRMS spectrum of 3-methylquinolin-2(1*H*)-one (3b)



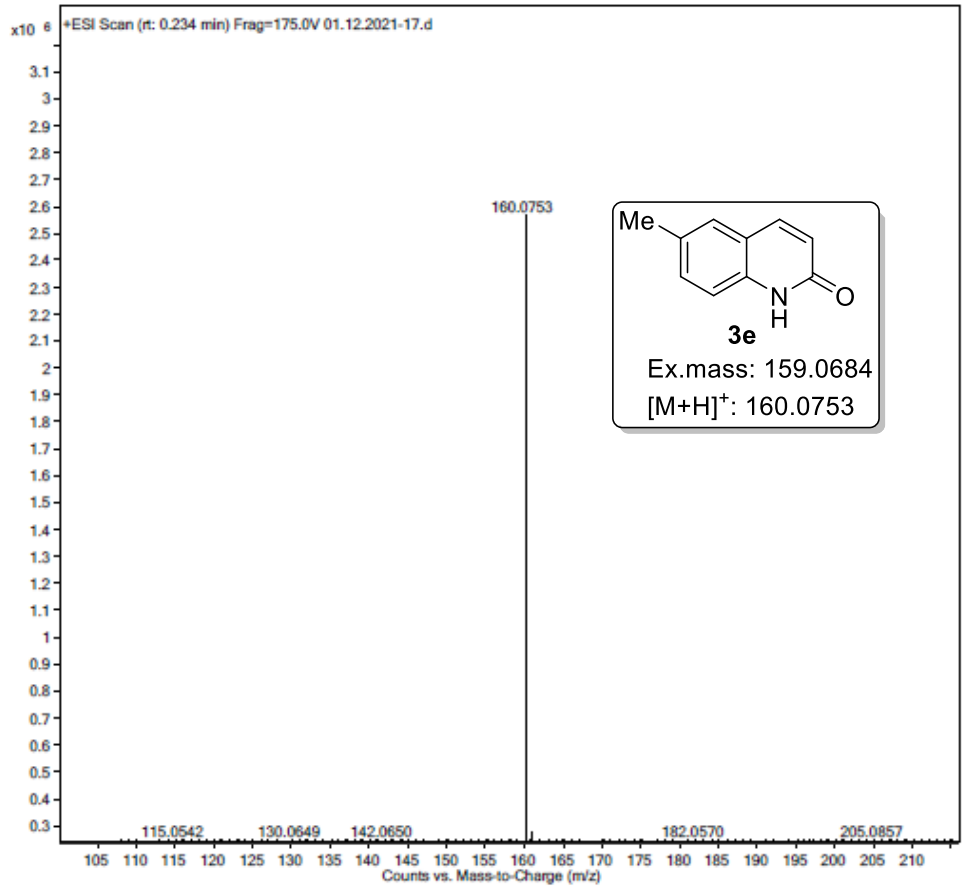
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 6-methylquinolin-2(1*H*)-one (3e)



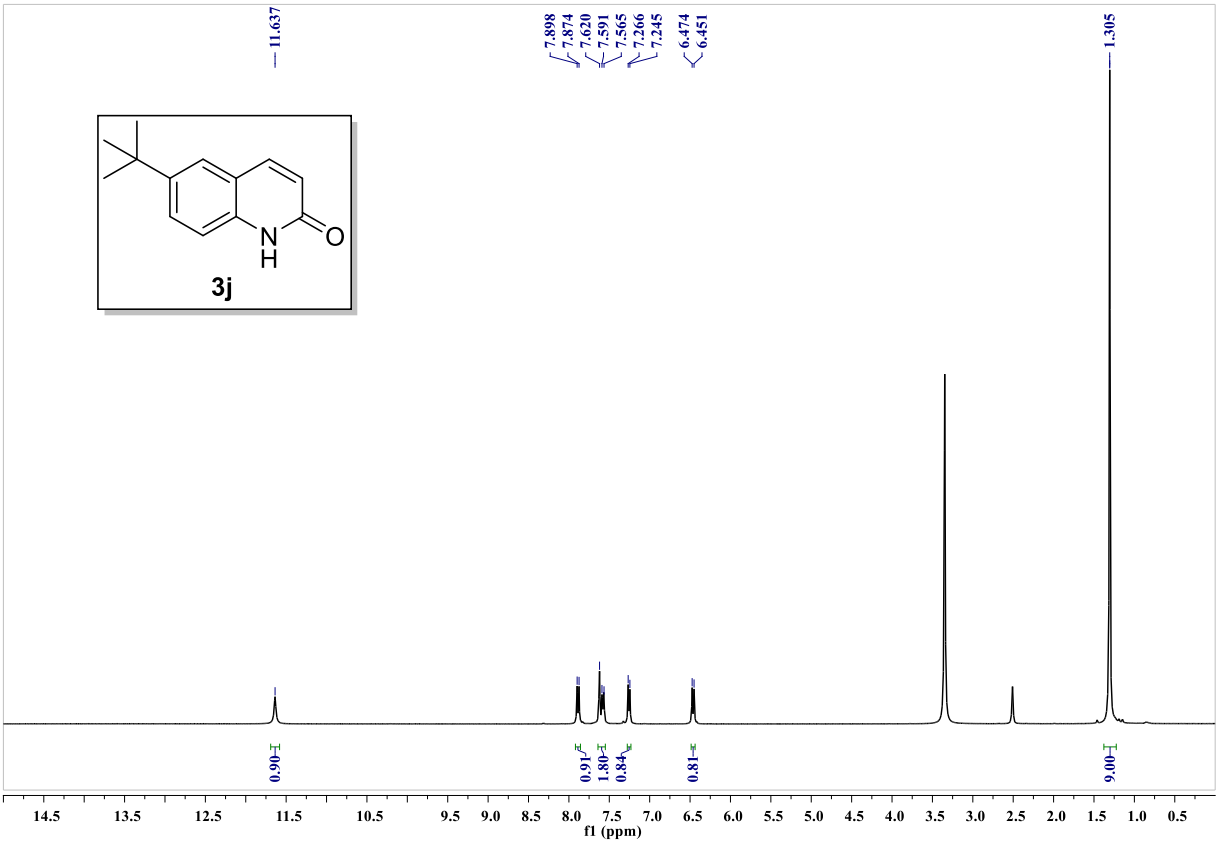
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 6-methylquinolin-2(1*H*)-one (3e)



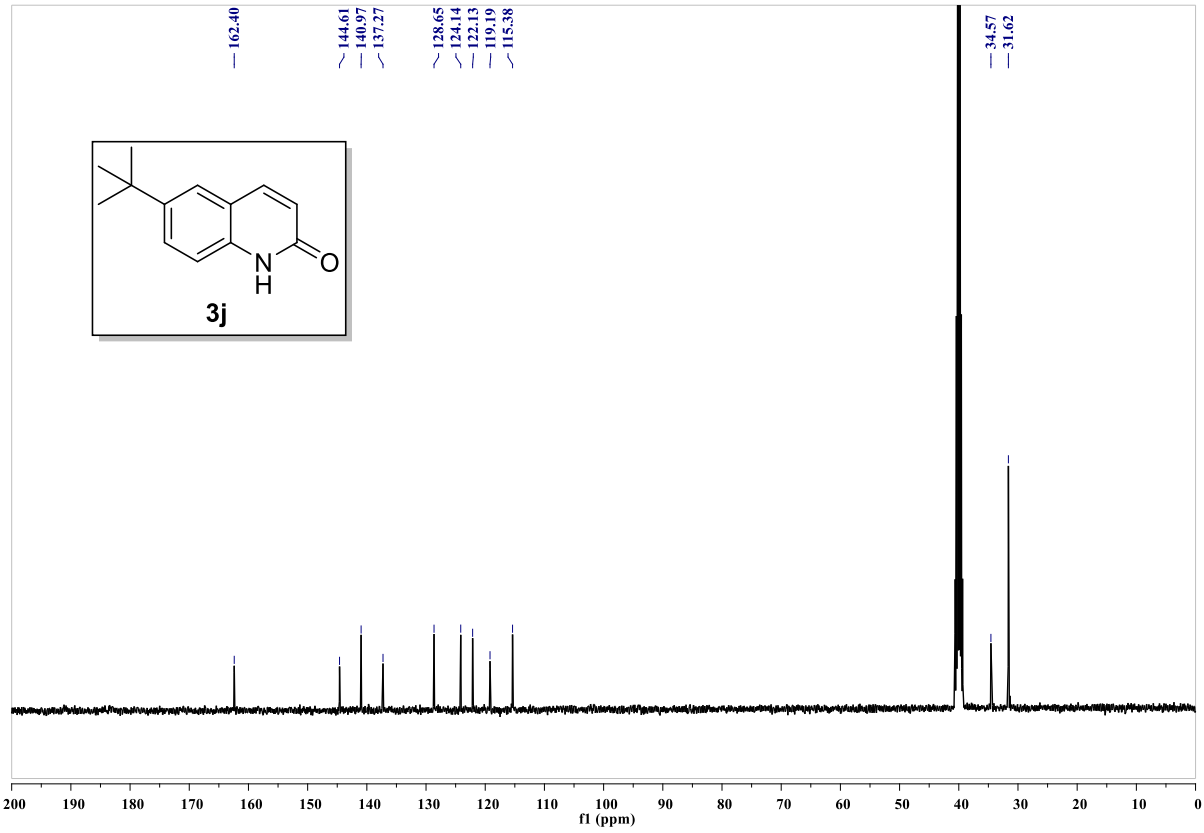
HRMS spectrum of 6-methylquinolin-2(1*H*)-one (3e)



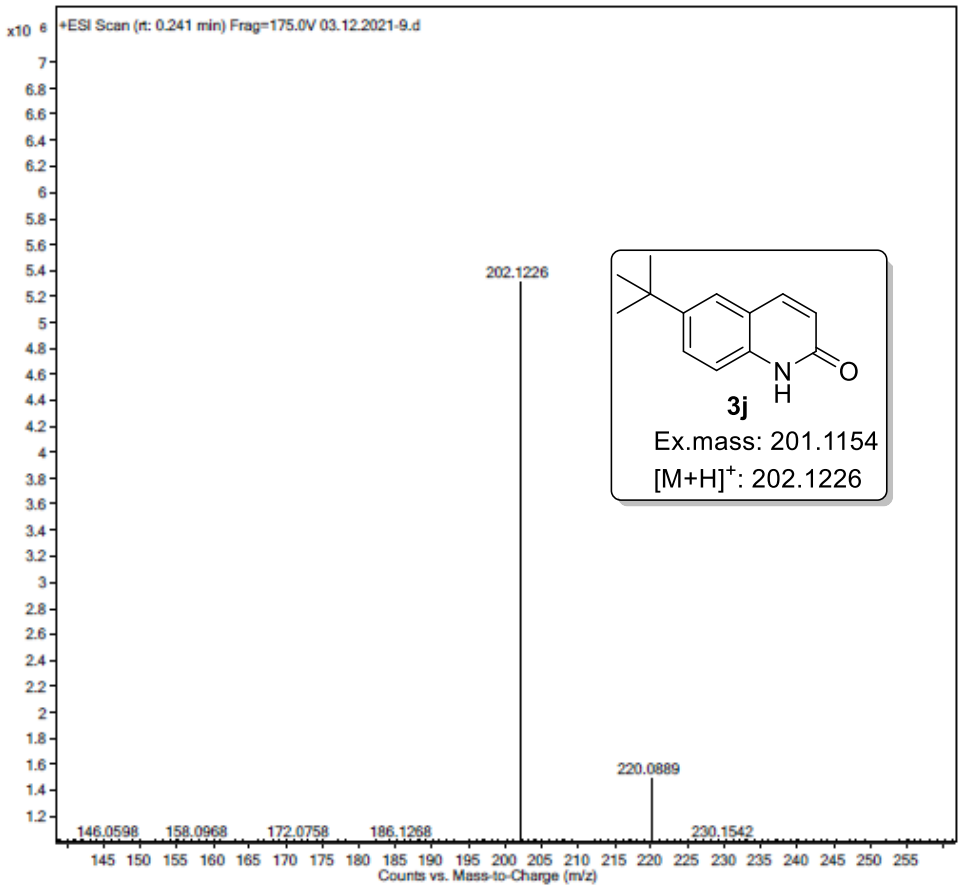
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 6-(*tert*-butyl)quinolin-2(1*H*)-one (3j)



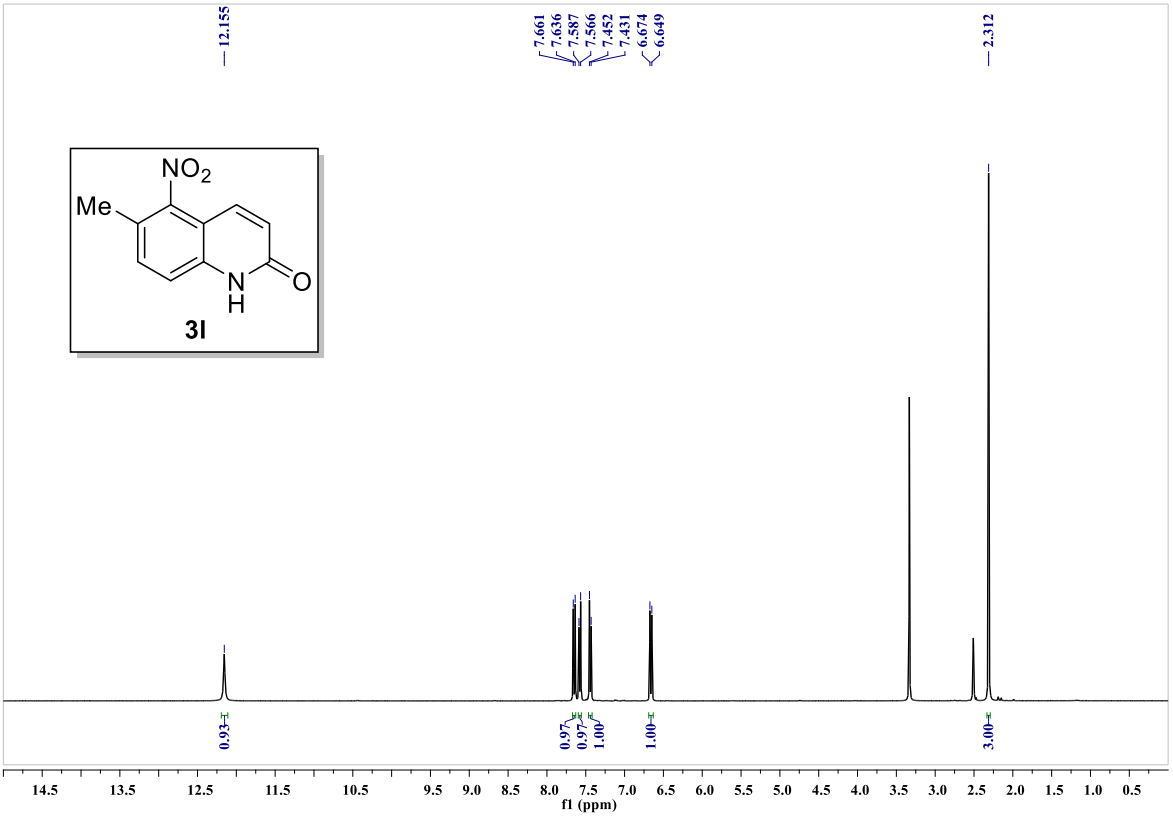
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 6-(*tert*-butyl)quinolin-2(1*H*)-one (3j)



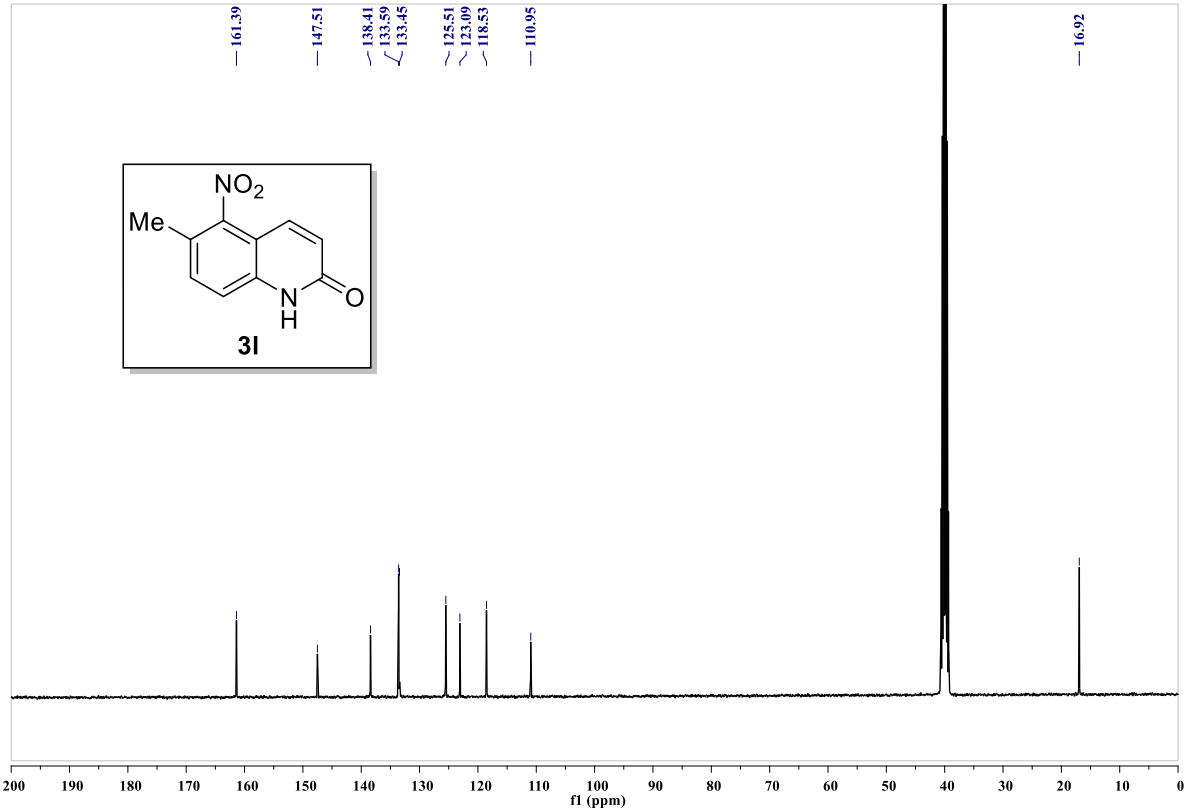
HRMS spectrum of 6-(*tert*-butyl)quinolin-2(1*H*)-one (3j)



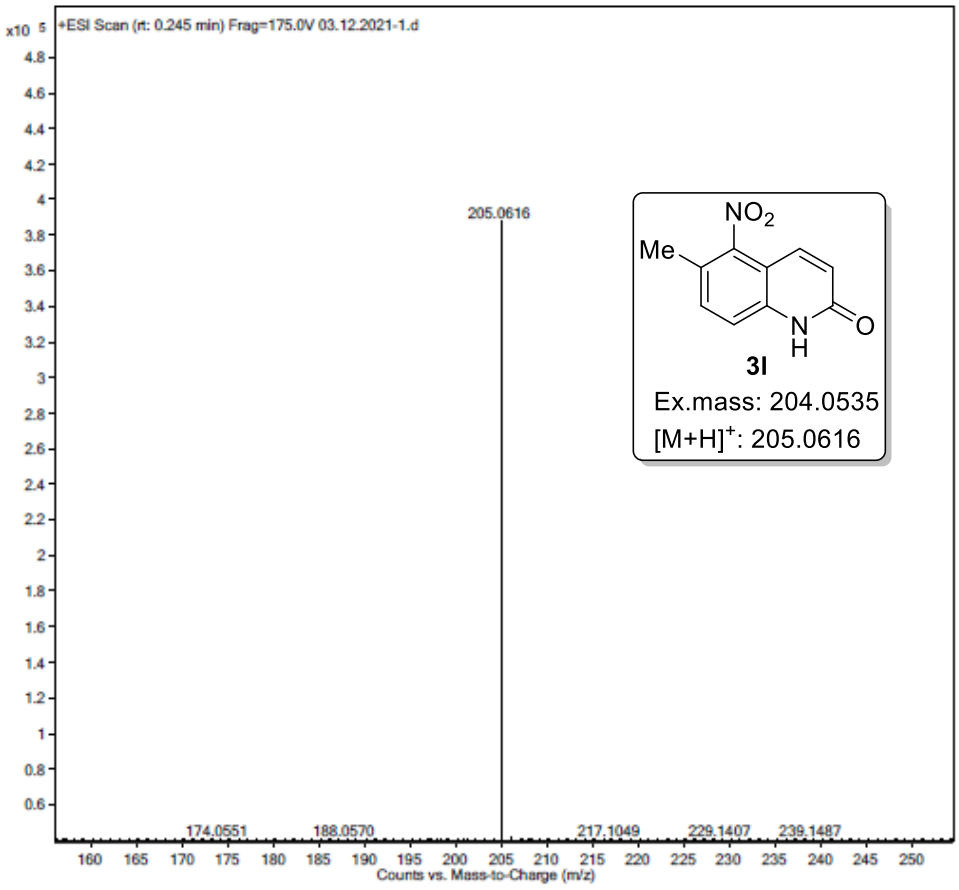
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 6-methyl-5-nitroquinolin-2(1*H*)-one (3l)



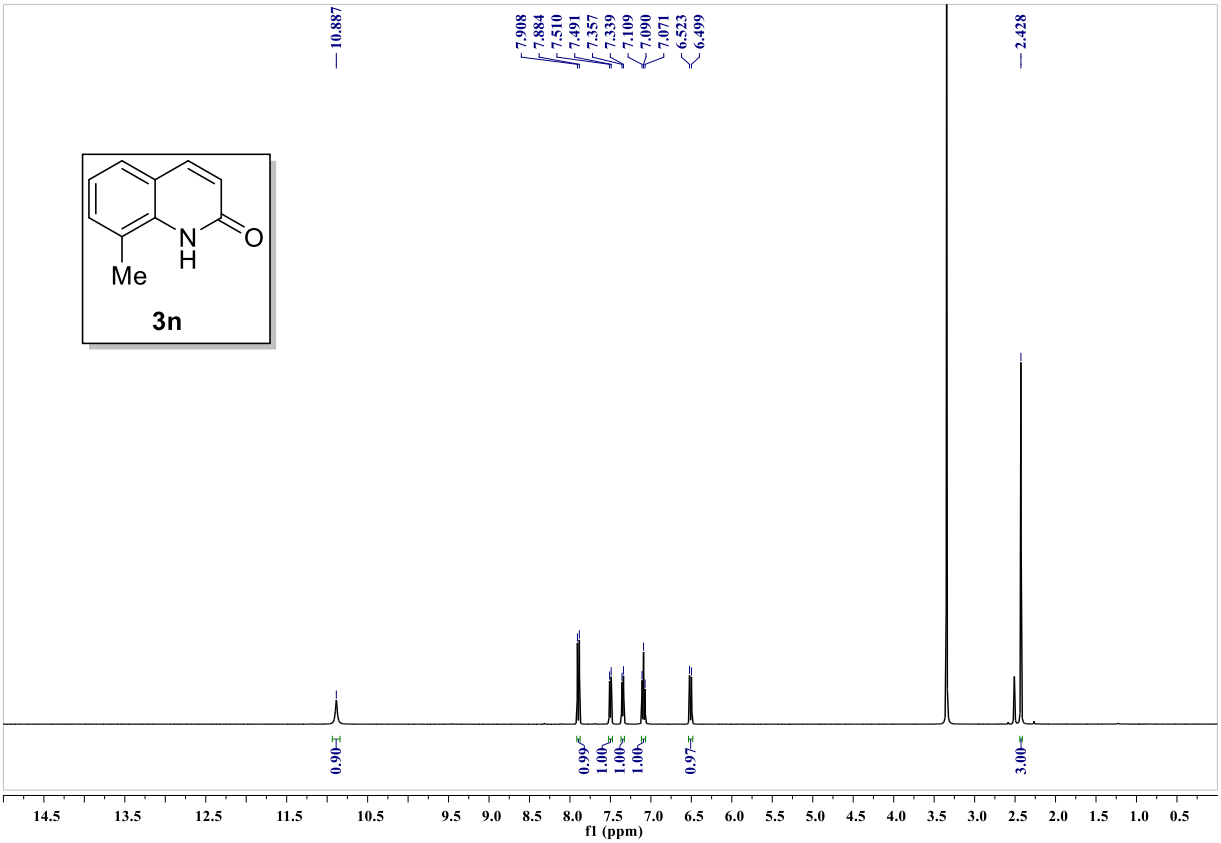
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 6-methyl-5-nitroquinolin-2(1*H*)-one (3l)



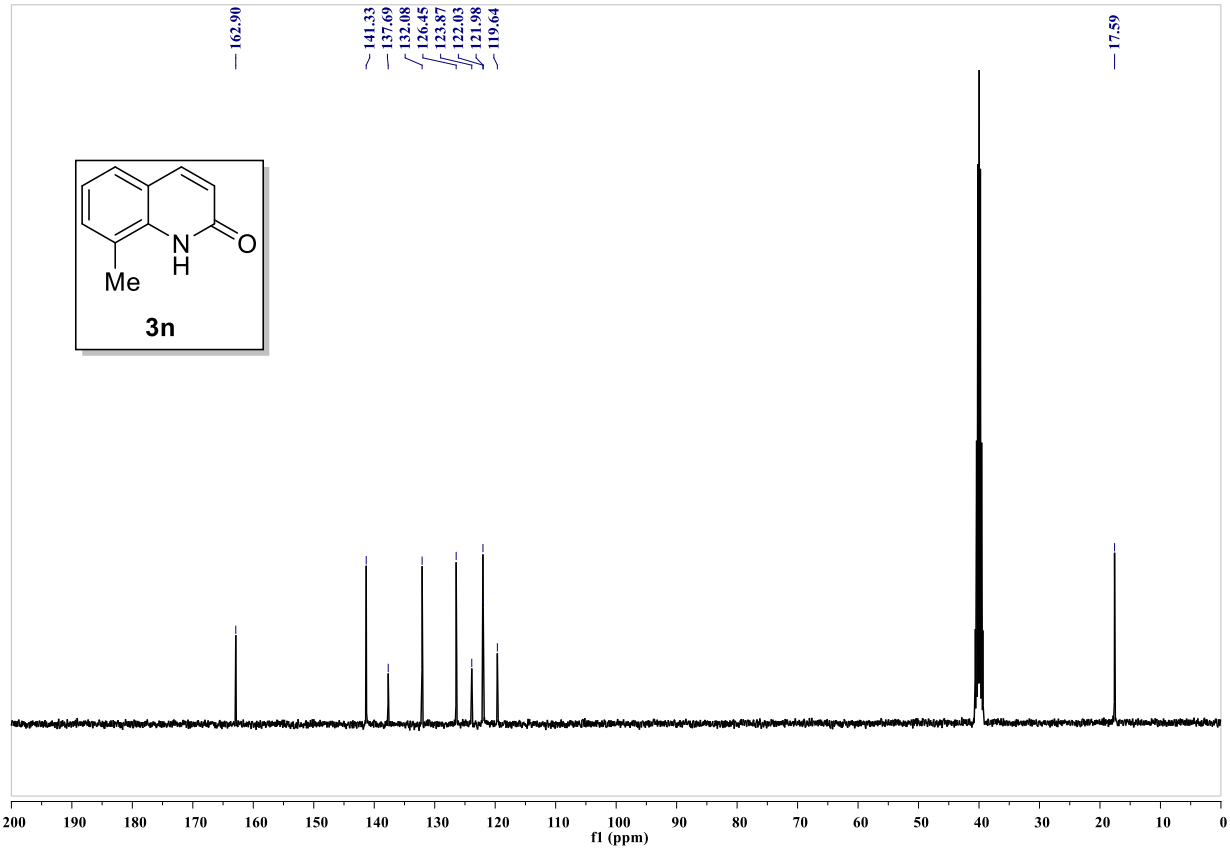
HRMS spectrum of 6-methyl-5-nitroquinolin-2(1*H*)-one (3l)



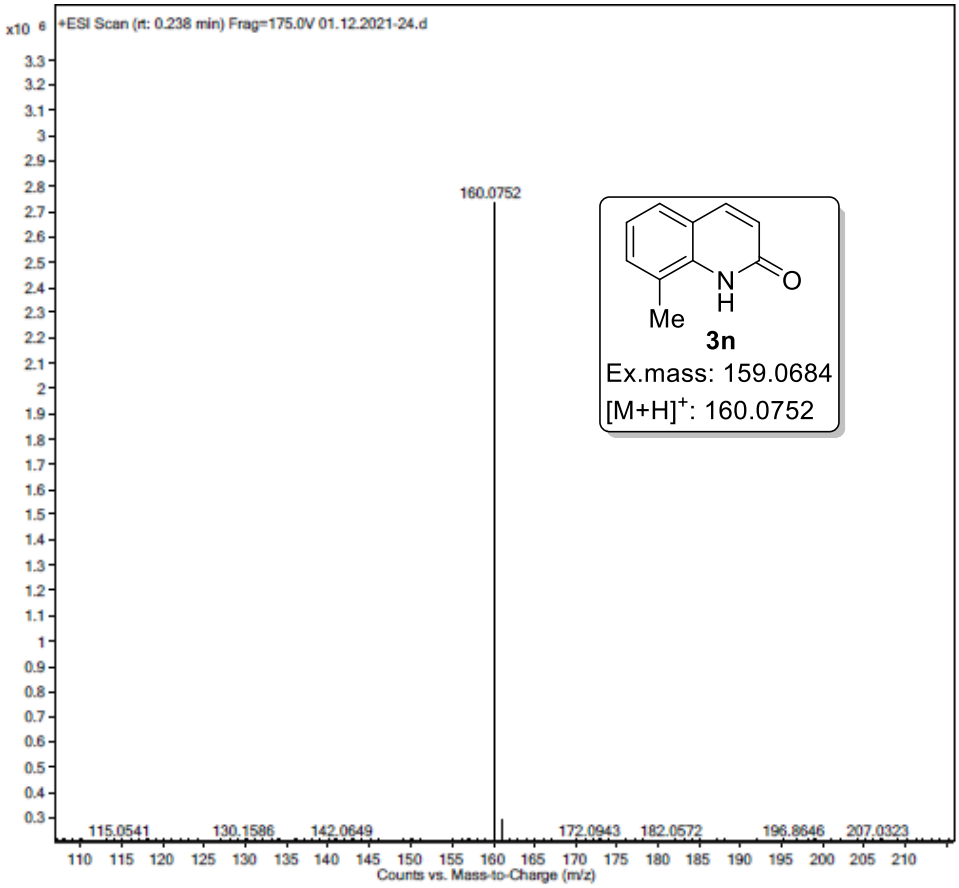
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 8-methylquinolin-2(1*H*)-one (3n)



^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 8-methylquinolin-2(1*H*)-one (3n)



HRMS spectrum of 8-methylquinolin-2(1*H*)-one (3n)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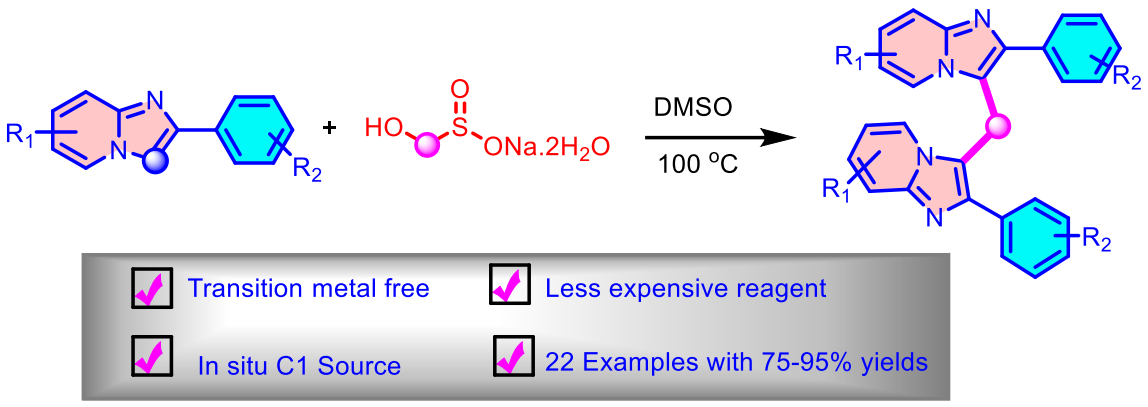
+ESI Scan (rt: 0.238 min) Frag=175.0V 01.12.2021-24.d
160.0752
115.0541
130.1586
142.0649
172.0943
182.0572
196.8646
207.0323
Counts vs. Mass-to-Charge (m/z)
Me
N
H
O
3n
Ex.mass: 159.0684
[M+H]+: 160.0752

CHAPTER-VI

Transition Metal-Free C(sp^2)-H Methylenation of Imidazo[1,2-*a*]pyridines, Indoles by Rongalite: A Rapid Access to Bis(aryl)methanes



6.1. Introduction

N-heterocyclics are important class of compounds which are possessing more pronounced biological activity because they have the ability to bind the biological macromolecules at various places.[1] Among them, imidazo[1,2-*a*]pyridines, fused with and imidazole ring and pyridine, are important nitrogen containing heterocycles have gained much attention of the synthetic organic chemists due to their wide applications in the field of material science, organic synthesis and biological chemistry (Figure 6.1).[2]

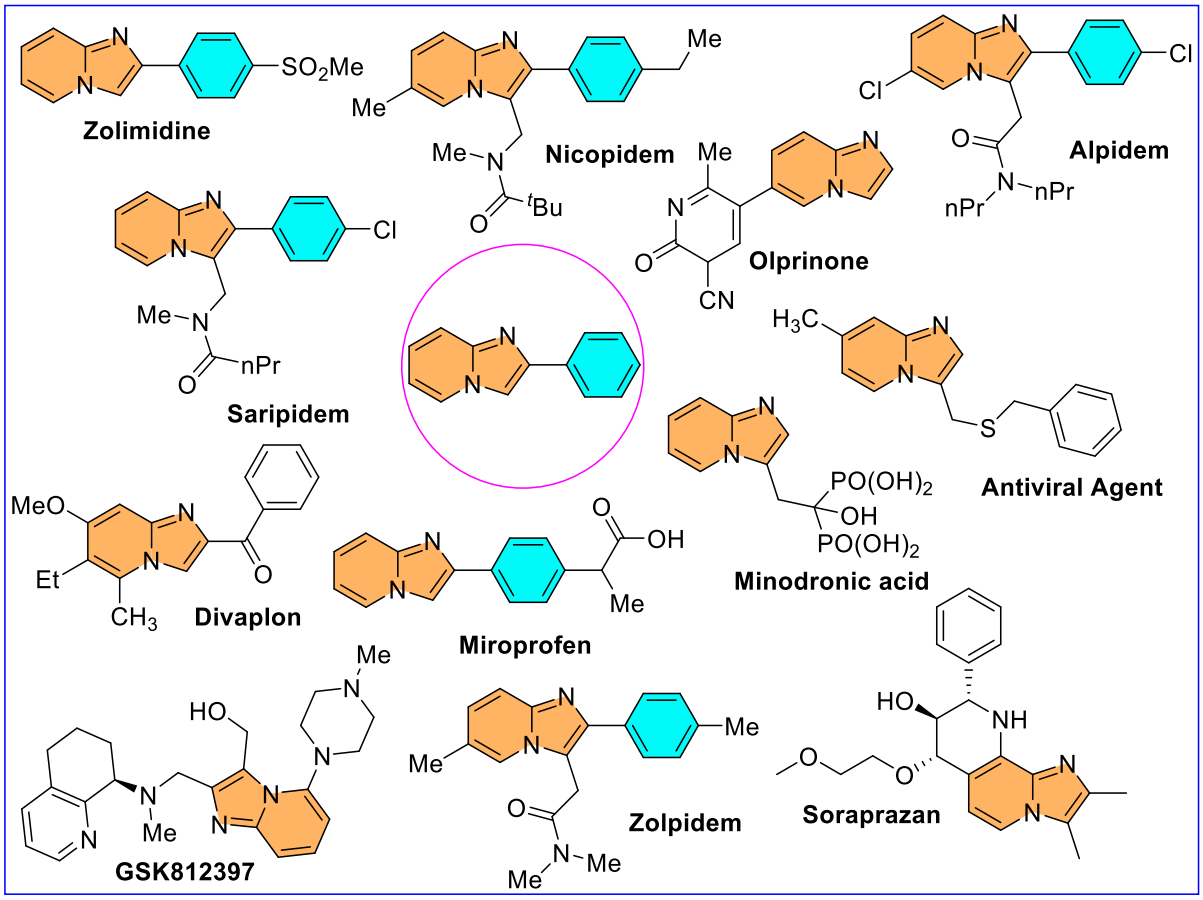


Figure 6.1. Biologically important drugs containing Imidazo[1,2-*a*]pyridine.

These molecules are important structural motifs present in various biologically active compounds such as anticancer,[3] antifungal,[4] antibacterial,[5] anti-inflammatory,[6] and antiviral,[7] many of their derivatives are drugs in the market e.g., zolimidine (treatment of peptic ulcer),[8] zolpidem (treatment of insomnia),[9] alpidem (anxiolytic agent),[10] saripidem & nicopidem (as an anxiolytic agents),[11] olprinone (treatment of acute heart failure),[12] GSK812397 (treatment of HIV infection), analgesic (miroprofen), minodronic acid[13] (used for the treatment of osteoporosis), clinical antiulcer compound Soraprazan[14] (phase II), and the anxiolytic drugs such as divaplon.[15] Some of the drugs containing these compounds in their core structures were

shown. It is prior to notice that these drugs contain methylene linkage at the C-3 position.[16-17] Several methods were reported to synthesize the methylene tethered imidazo[1,2-*a*]pyridines.

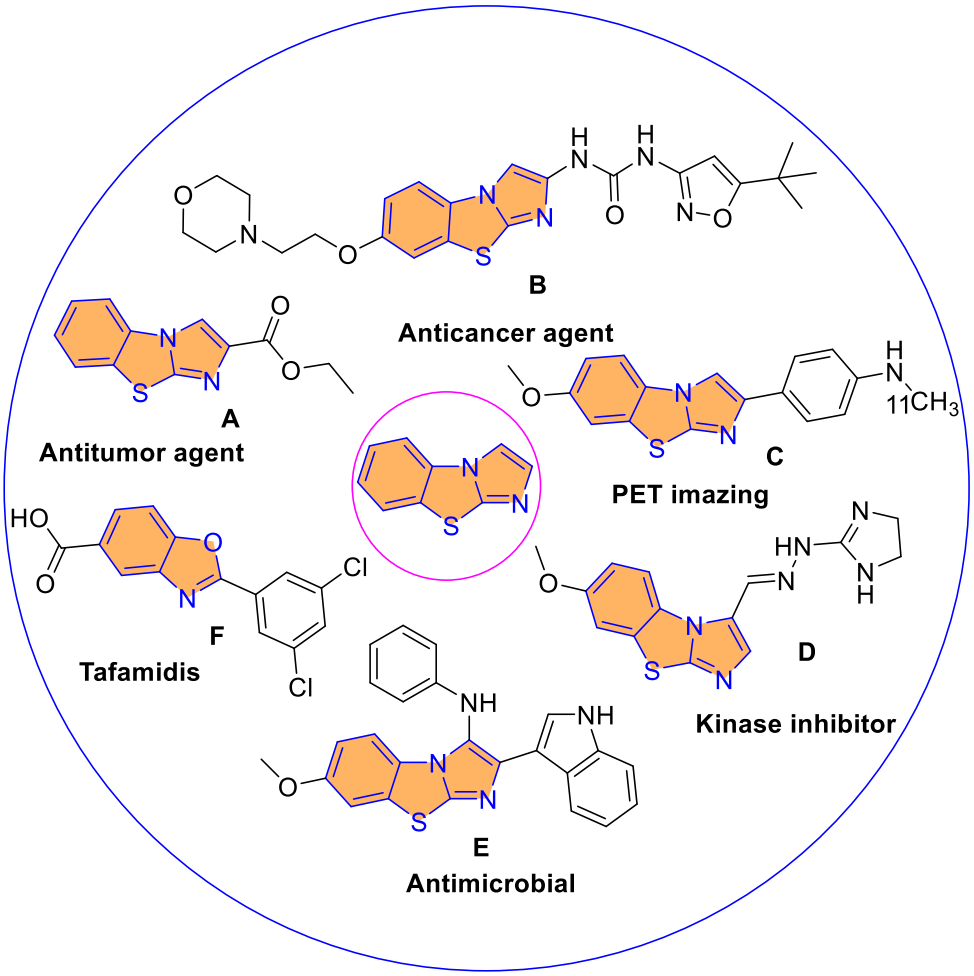


Figure 6.2. Selected biologically active benzo[d]imidazo[2,1-*b*]thiazoles and benzo[*d*]oxazole derivatives.

Also, benzo[*d*]imidazo[2,1-*b*]thiazoles and benzo[*d*]oxazole derivatives are important classes of heterocycles that have attracted significant attention due to their wide range of significant biologically active compounds. Benzo[*d*]imidazo[2,1-*b*]thiazoles have been reported to serve as a potent non-sedative anxiolytic (**A**),[18,19] powerful anticancer agent (**B**)[20-23] PET imaging probe of *β*-amyloid plaques in the brains of alzheimer's patients (**C**),[24-26] kinase inhibitor (**D**),[27-29] and antimicrobially active molecule (**E**),[30] while benzo[*d*]oxazole derivatives have been used to treat interval loss of nerve function (**F**).[31-32]

Therefore, several methodologies have been developed for the preparation and post-transformation of imidazo[1,2-*a*]pyridines and indoles due to the electron-rich nature of the C-3 position. Several synthetic methods have emerged for regioselective oxidative C-H bond functionalization at the C-3 position. However the majority of the synthesis of

bisimidazopyridinylmethanes were achieved by *in situ* generation C1 unit from the different sources: i) Formaldehyde source[33,34] ii) *N*,*N*-dimethylacetamide/metal and oxidant,[35-37] iii) Dimethylsulfoxide[38-39] iv) Tertiary amine/oxidant/metal,[40] v) TosMIC/metal,[41] vi) CH_3NO_2/Au-Cu,[42] and vii) PEG-400/Cu/oxidant.[43]

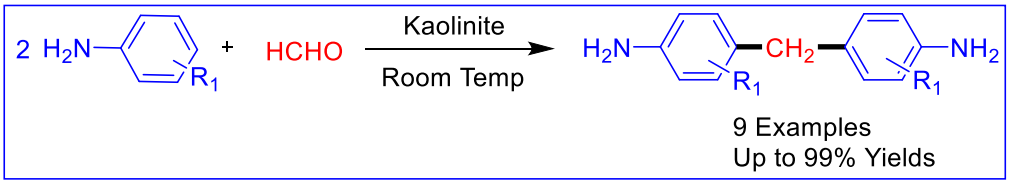
Similarly, diindolylmethanes (DIMs) are dimeric product of indole-3-carbinol (I3C), a natural compound that is abundant in cruciferous vegetables such as broccoli, cabbage, and cauliflower with privileged biological and pharmaceutical properties, such as anti-cancer antihyperlipidemic, antiinflammatory antiproliferative, and GPR84 agonistic activity.[44] The synthesis of DIMs has drawn a lot of attention due to their unusually potent uses in materials and pharmaceuticals.[45]

Diindolylmethane (DIMs) are synthesised from a Lewis or Bronsted acid catalysis, in which the reaction between indoles with C1 unit sources.[46] Methylene sources including alkynes,[47] amino acids,[48] carbonyl compounds,[49] allenes,[50] and alkenes[51] yields the essential skeleton of DIMs. The creation of symmetric diindolylmethane skeletons has also been successfully accomplished *via* electrochemical,[52] transition metal catalysis,[53] and photocatalysis method.[54]

Despite having a few valuable advantages, these reactions suffer from certain limitations such as the use of metal catalysts, inorganic acid, base, inert atmosphere to catalyse the reaction and toxic materials. From the last few decades, eco-friendly methods with obeying green chemistry principles are becoming integral part of the organic synthesis to make fine chemicals and pharmaceuticals. The replacement of such harmful organic reagents and solvents with an eco-friendly compound is one of the major focal points of green chemistry.[55] Moreover, it should be avoiding transition-metal-catalysed reactions, which also generate hazardous waste.[56]

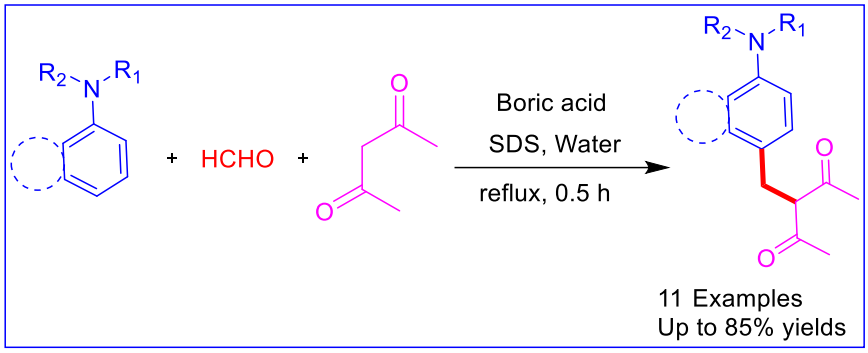
6.1.1. Reported methods for the synthesis of C(sp^2)-H methylenation of imidazo[1,2-*a*]pyridines and indoles

Lalithambika and co-workers developed a cost effective and an eco-friendly catalyst, kaolinitic clay for the synthesis of 4,4-diaminodiphenylmethanes. This naturally abundant catalyst provides 4,4-diaminodiphenylmethanes in high yields in less time with high product selectivity (Scheme 6.1)[33a]



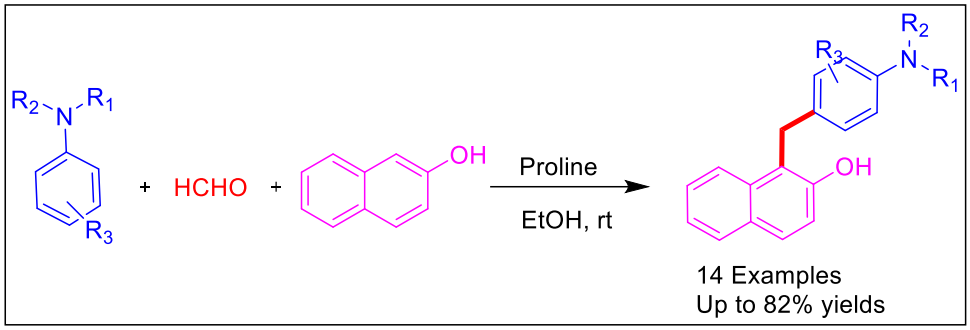
Scheme 6.1

Atul Kumar and group developed an efficient boric acid catalyzed Mannich type reaction of formaldehyde, tertiary aromatic amines, and 1,3-dicarbonyl compounds in aqueous micelles to produce dialkylaminoarylated 1,3-dicarbonyls. In this method, tertiary aromatic amines react with formaldehyde to generate an iminium intermediate, which undergoes nucleophilic addition with enalizable compounds to provide regioselective para functionalized products (Scheme 6.2).[33b]



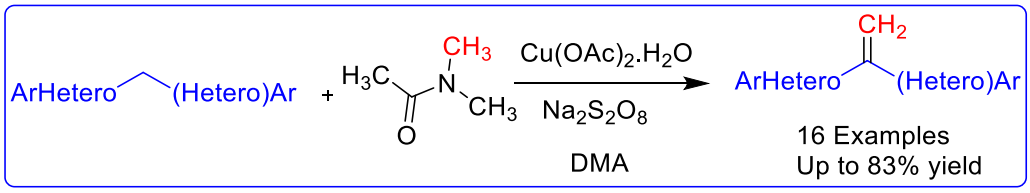
Scheme 6.2

Atul kumar et al. introduced an efficient organocatalyzed domino Mannich and Friedel–Crafts based multicomponent for synthesis of diarylmethane derivatives from tertiary aromatic amines, formaldehyde and 2-naphthols. Among the organocatalysts tested, L-proline found to be a best catalyst to catalyse one-pot Mannich type Friedel–Crafts alkylation obtain substituted diarylmethanes in good to excellent yields (Scheme 6.3).[33c]



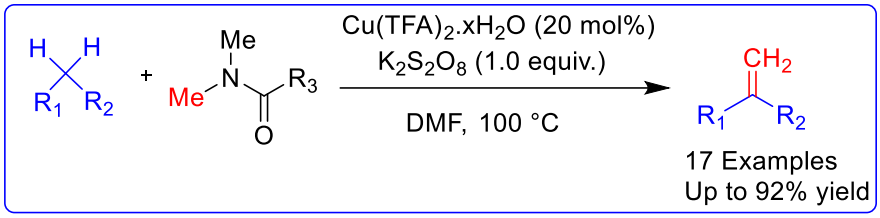
Scheme 6.3

Satoh and co-workers developed a direct *α*-methylenation of benzylpyridines using *N*,*N*-dimethylacetamide (DMA) as a C1 unit source under copper catalyst, *α*-oxygenation and dimerization of benzylpyridines also performed efficiently. A detailed mechanism was proposed by an early stage detection of intermediates (Scheme 6.4).[34]



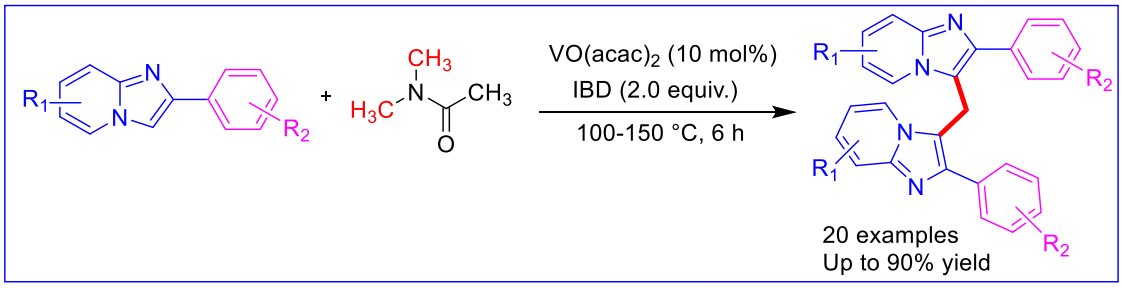
Scheme 6.4

Lei and co-workers demonstrated a copper-catalysed direct oxidative Csp^3-H methylenation of terminal olefins using DMF as one carbon source. In method is compatable with various fuctional gropus and providing a simple way to construct arylvinylketones and arylvinylpyridines (Scheme 6.5).[35]



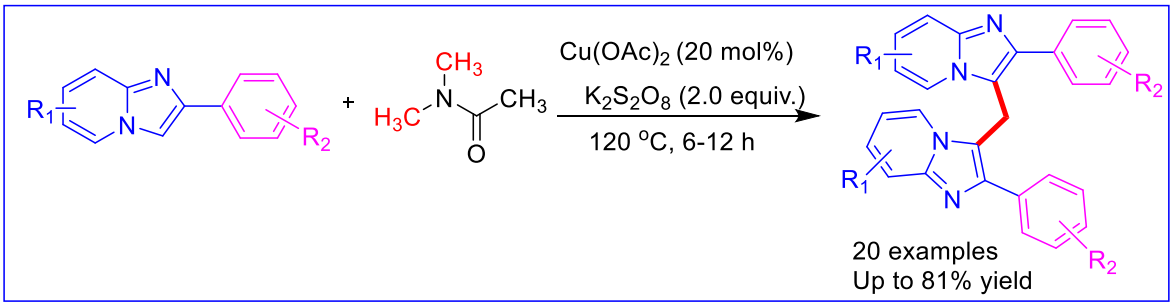
Scheme 6.5

Kaswan et al. employed [$VO(acac)_2$] catalyst to generate *in situ* C1 unit source from dimethylacetamide under iodobenzene diacetate as the oxidant to give imidazo[1,2-*a*]pyridines. The reactive iminium intermediate is enough to undergo coupling of sp^3 and sp^2-hybridized carbons to give bis(imidazo[1,2-*a*]pyridin-3-yl)methanes in good to excellent yields. This method is also applicable to gram-scale synthesis (Scheme 6.6).[36]



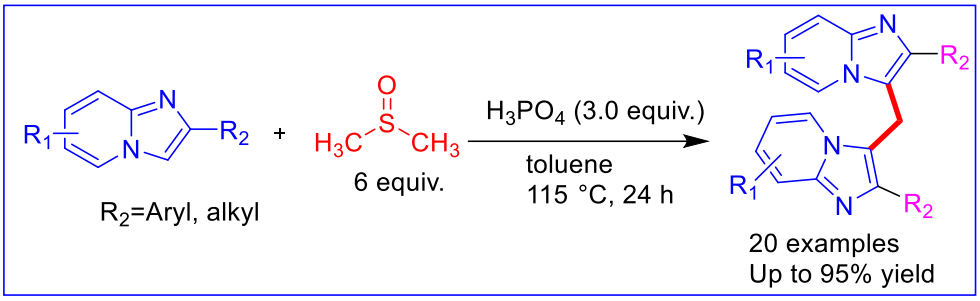
Scheme 6.6

Modi et al. effectively utilized the copper(II) catalyst for *in situ* generation of methylene from *N*,*N*-dimethylacetamide *via* oxidative transformation to obtain methylene-bridged dimerization of two analogous imidazo[1,2-*a*]pyridines. In this protocol, *N*,*N*-dimethylacetamide (DMA) plays dual role as a solvent cum methylene source. This reaction works with a variety of substituted imidazo[1,2-*a*]pyridines giving their products in moderate to good yields (Scheme 6.7).[37]



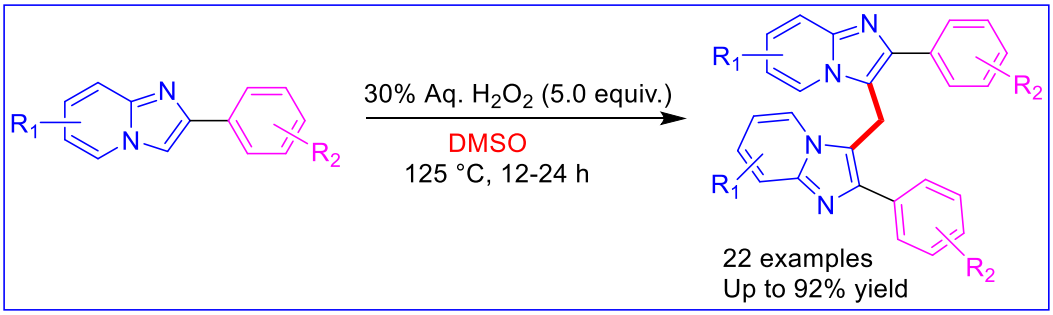
Scheme 6.7

Liu et al. adopted a facile metal-free process for methylenation of imidazopyridines for the synthesis of symmetrical methylene-bridged imidazo heterocycles catalyzed by H_3PO_4 in DMSO solvent. This method provides target compounds in good to excellent yields with high C3-regioselectivity (Scheme 6.8).[38]



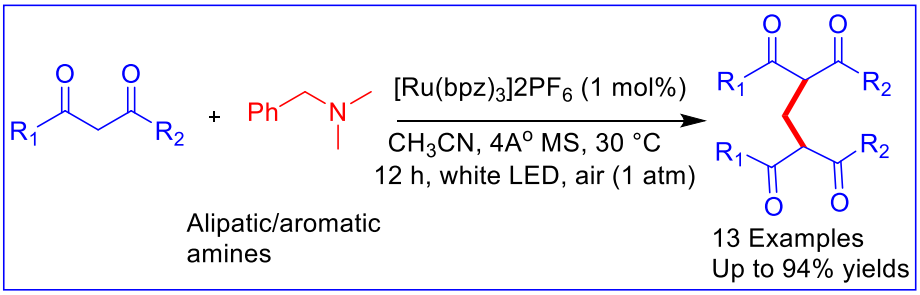
Scheme 6.8

Patel et al. introduces a unique and metal-free method for producing 3,3′-bisimidazopyridinylmethanes using dimethyl sulfoxide (DMSO) as the carbon synthon (CH_2) and H_2O_2 as a mild oxidant in the presence of air (Scheme 6.9).[39]



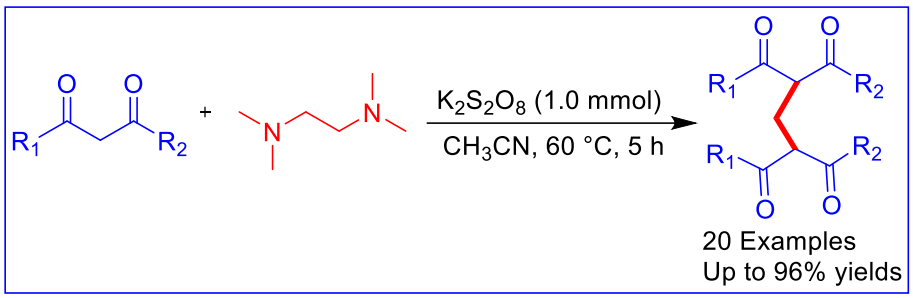
Scheme 6.9

Kobayashi and co-workers developed a synthesis of methylene-bridged 1,3-dicarbonyl compounds from 1,3-dicarbonyl compounds and *N*,*N*-dimethylbenzylamine in the presence of aerobic photocatalytic oxidative coupling reactions. They observed that tertiary aliphatic amines were better methylene source compare to their aromatic counterparts under visible-light photocatalysis (Scheme 6.10).[40b]



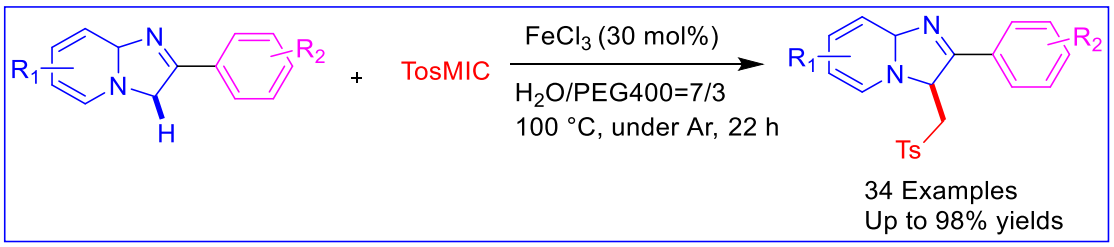
Scheme 6.10

Wang et al. introduced a transition-metal-free oxidative methylenation approach for the synthesis of methylene-bridged bis-1,3-dicarbonyl compounds *via* oxidative C(sp^3)-H activation and C-N cleavage of *N*-methyl amines (Scheme 6.11).[40f]



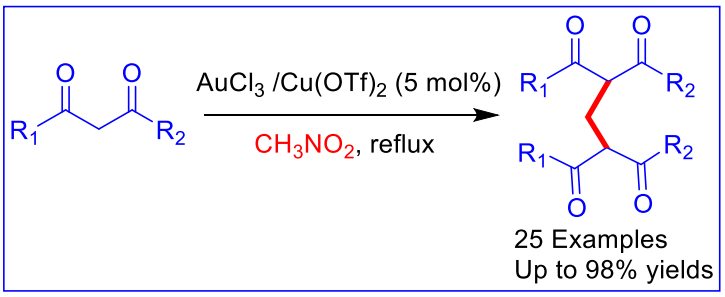
Scheme 6.11

Song and co-workers developed a novel iron catalysis for C-H tosylmethylation of imidazo[1,2-*α*]pyridines with TosMIC. In this method aromatic and heteroaromatic, proceeded smoothly to afford the corresponding products in good yields (Scheme 6.12).[41]



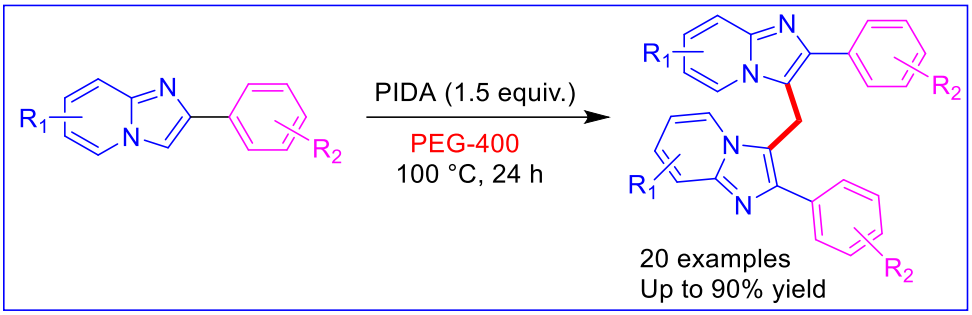
Scheme 6.12

Balamurugan and co-workers described the Lewis acid-activated *aci*-form of nitromethane is a key intermediate in the formation of methylene-bridged bis-1,3-dicarbonyls (Scheme 6.13).[42]



Scheme 6.13

Rahul Kumar et al. developed a green one-pot synthesis of hetero diarylmethanes under metal-free conditions using polyethylene glycol 400 (PEG-400) used as a solvent and methylene source. The reaction was promoted by (diacetoxyiodo)benzene (PIDA) as an oxidant. The procedure can be used with a wide range of heterocycles, including imidazopyridines, imidazothioazoles, imidazobenzothiazoles, indolizines, indole, 1-methyl-1*H*-indole, *N*,*N*-dimethylaniline, and trimethoxybenzene. Both symmetrical and unsymmetrical dimers are dimerized using PEG-400 (Scheme 6.14).[43]

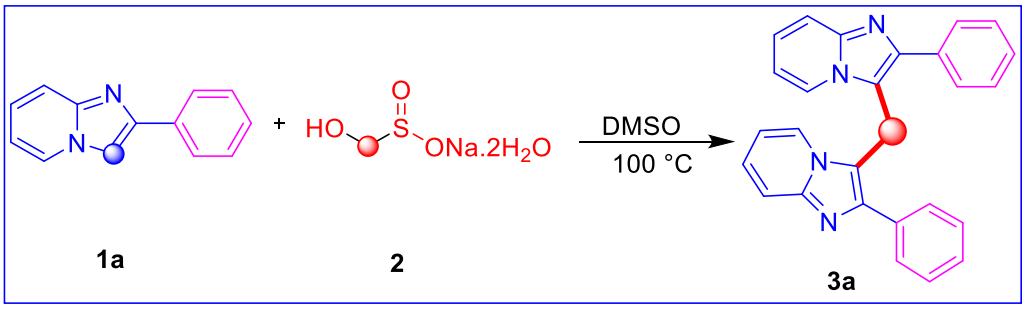


Scheme 6.14

Based on the previous reports, we found that considerable attention has been received to the synthesis of 3,3′-bisimidazopyridinylmethanes. These reported reactions involve the coupling of sp^3 and sp^2-hybridized carbons with the use of a transition metal, base, ligand, or additives. These corresponding products are found to be common pharmacophores with wide applications in biological activity. Hence, development of environmentally benign protocols for the synthesis of methylene-bridged dimerization of imidazo[1,2-*a*]pyridines is still a thrust area in the synthetic chemistry. To the best of our knowledge, synthesis of bis imidazo[1,2-*a*]pyridines by using rongalite is not reported in the literature. The use of transition-metal-free condition, inexpensive reagents and mild conditions are some of the salient features of our methodology.

6.2. Present study

Considering the problems associated with use of toxic formalin solution, toxic metal catalysts and the importance of imidazo[1,2-*a*]pyridine hybrids, we have developed one-pot reaction involving imidazo[1,2-*a*]pyridine, with rongalite in DMSO to produce the desired compounds 3,3′-bisimidazopyridinylmethanes **3a-q** (Table 6.2), **5a-j** (Table 6.3) and **7a-i** (Table 6.4). The key step in this reaction is *in situ* generation of formaldehyde from rongalite (Scheme 6.15).



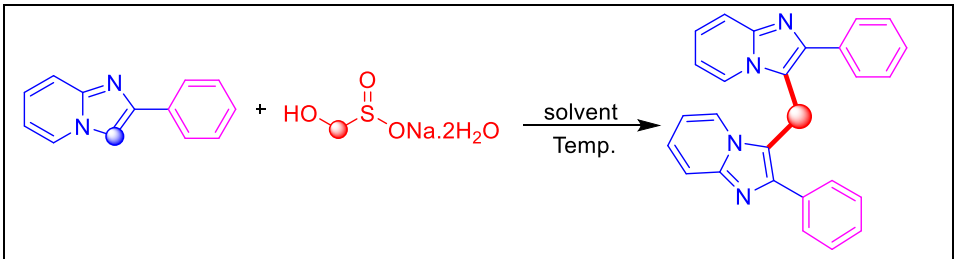
Scheme 6.15

With this proposed methodology we can prepare various methylene bridged imidazo[1,2-*a*]pyridine under environmentally benign conditions *i.e.*, transition metal free, non-hazardous, easily available reagents and less expensive. In the search for green formalin source, we have found that rongalite, a crystalline solid which can generate formaldehyde *in situ* without any

problem. Using this concept, we have developed a green one-pot synthesis of bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane derivatives.

6.2.1. Results and discussion

Table 6.1. Optimization of the reaction conditions[a]



Entry	Solvent	Temp (ºC)	Time (h)	Yield (%)[b]
1	CH_2Cl_2	rt	24	0
2	CH_2Cl_2	40	24	10
3	$CHCl_3$	60	15	40
4	DCE	60	15	60
5	THF	70	12	60
6	CH_3CN	70	15	70
7	DMF	70	10	80
8	DMF	80	10	90
9	**DMSO**	**100**	**5**	**95**
10	CH_3OH	70	15	10
11	EtOH	70	15	10
12	H_2O	100	10	10
13	DMSO	130	10	85

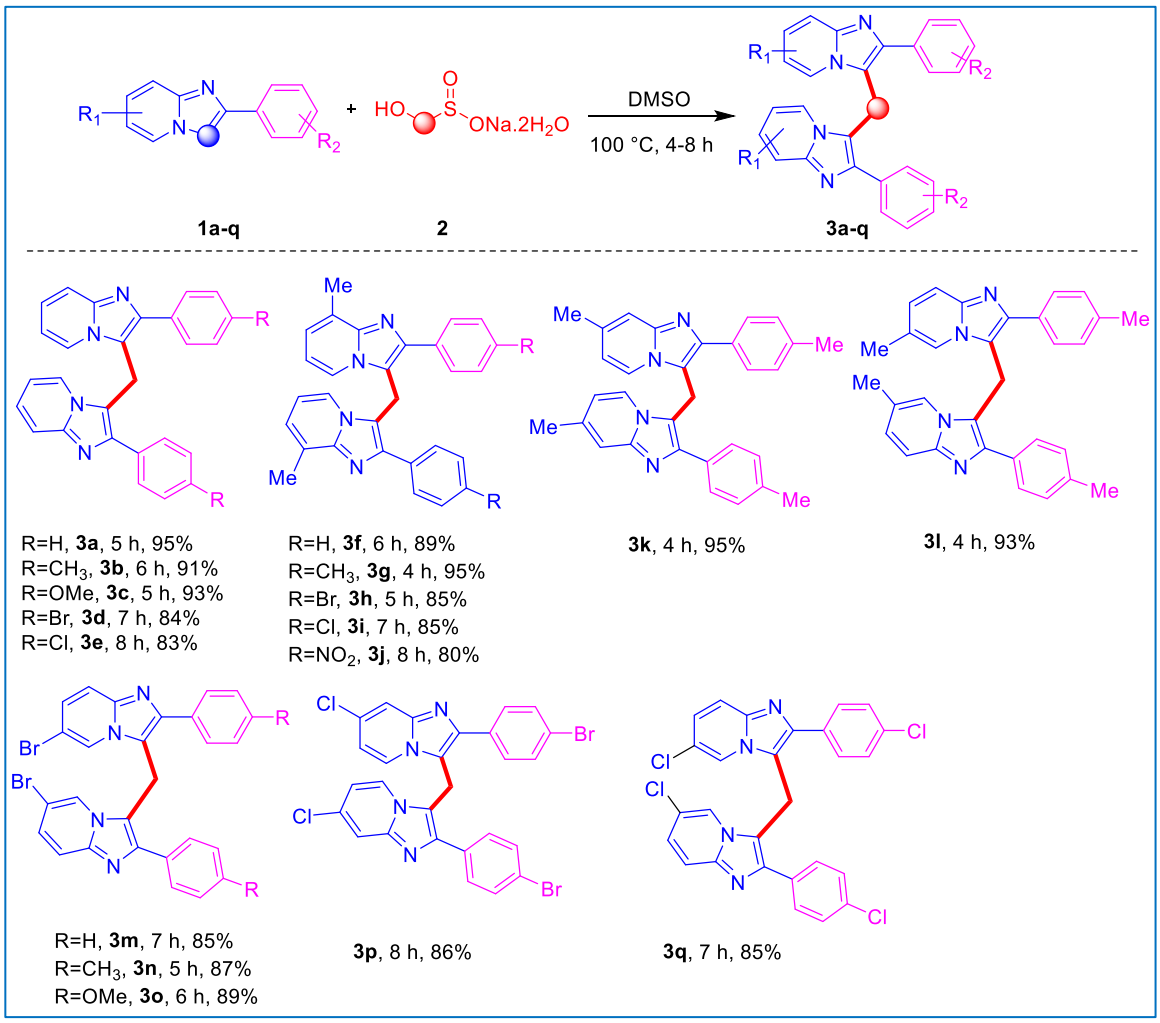
[a]Reaction conditions: 2-phenylimidazo[1,2-*a*]pyridine **1a** (1.0 mmol), rongalite **2** (1.0 mmol) and solvent (2 mL). [b]Isolated yield.

To validate our hypothesis, a test reaction was conducted between imidazo[1, 2-*a*]pyridine **1a** and rongalite **2** in dichloromethane solvent. Initially, the reaction mixture was stirred at room temperature for 24 h, no change in starting material was observed even after 24 h (monitored by TLC). Then the reaction mixture was heated to 40 ºC and surprisingly, formation of desired product **3a** was observed in low yield (Table 6.1, entry 2). The product **3a** was purified and characterized by ^{1}H and ^{13}C and mass spectral data.

The above result provoked us to optimize the reaction conditions to improve the product yield by changing the reaction conditions and the results are presented in Table 6.1. Firstly, we have focused on screening of solvents. Initially, reaction was conducted in chlorinated solvents such as chloroform and dichloroethane, and toluene but gave low yields (Table 6.1, entries 3-5). It was observed from the above results (Table 6.1, entries 3-5) that temperature is playing a role

to furnish product in improvised yield, based on this we have conducted a reaction in CH_3CN, but gave marginal increase in the yield. Later, we have changed the reaction medium to other polar aprotic solvents such as DMF and DMSO and observed the improved yields (Table 6.1, entries 7-9). Finally, the reactions are tested in the polar protic solvents *i.e.*, methanol, ethanol and water but gave the inferior results (Table 6.1, entries 10-12). Finally, we have tested the same reaction in DMSO solvent and surprisingly gave good yields (Table 6.1, entry 9). The optimized conditions for the above reaction is as follows, imidazo[1, 2-*a*]pyridine **1a**, and rongalite **2** in DMSO (2 mL) at 100 °C for 5 h.

Table 6.2. Reaction of substituted imidazo[1,2-*a*]pyridine with rongalite[a,b]

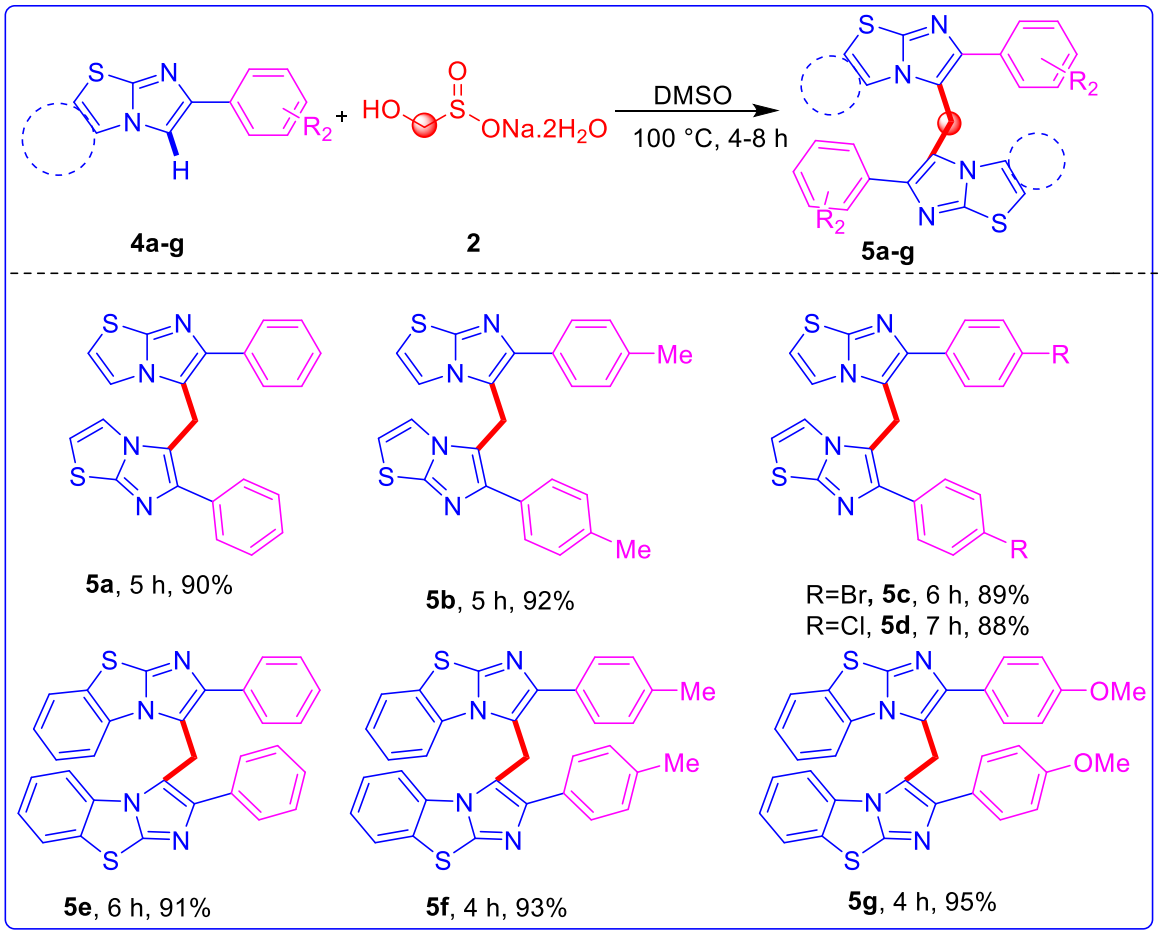


[a]Reaction conditions: 2-phenylimidazo[1,2-*a*]pyridine **1a-q** (1.0 mmol), rongalite **2** (1.0 mmol) and solvent (2 mL). [b]Isolated yield.

After optimized the reaction conditions for one-pot bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane with rongalite, we have explored the scope of the protocol by selecting a wide variety of the substrates. Interestingly substituted imidazo-[1,2-*a*]pyridine reacted smoothly and gave the corresponding bridged bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane **3a-q** in good to excellent yields (Table 6.2).

The starting materials, imidazo-[1,2-*a*]pyridines which are used in this scheme, prepared from reported method using 2-aminiopyridine and phenacyl bromide in EtOH as solvent.[57] Later, we have tested the substrate scope of the imidazopyridines with electron releasing groups such as methyl, methoxy, phenyl and halogens (Cl, Br) on C-2-phenyl gave target compounds up to 95% yields (Table 6.2, **3a-3e**). Substrates which have substitution on the pyridine ring also provided title products in excellent yields (Table 6.2, **3f-3q**). Also, the substitution on both the pyridine ring and C-2-phenyl participated in this reaction and furnished the product in good yields.

Table 6.3. Reaction of simple or benzo[*d*]pyrrolo[2,1-*b*]thiazoles with rongalite[a, b]



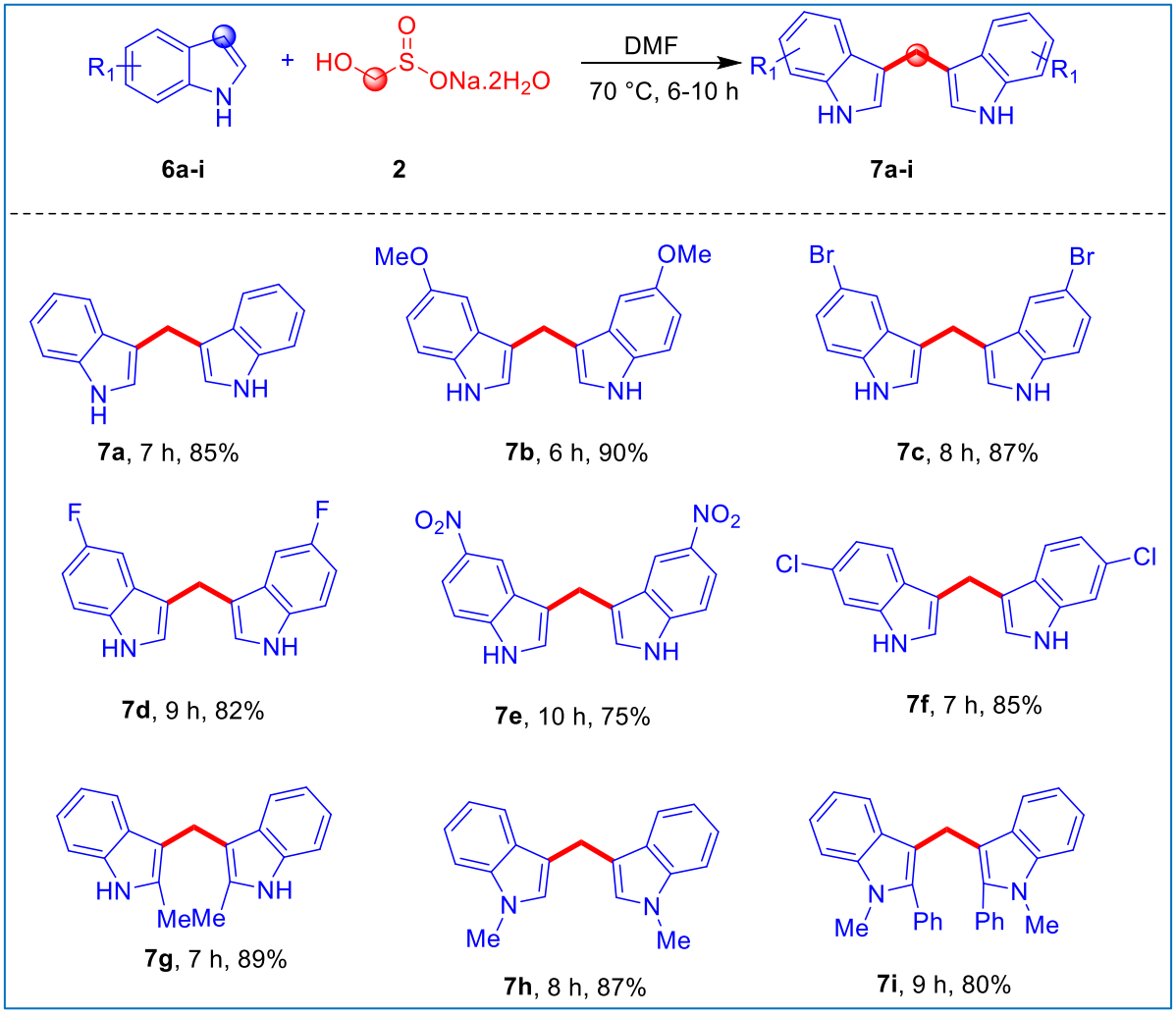
[a]Reaction conditions: Simple or Benzo[*d*]pyrrolo[2,1-*b*]thiazoles **4a-g** (1.0 mmol), rongalite **2** (1.0 mmol) and solvent (2 mL). [b]Isolated yield.

Further, the same reaction conditions were applied to other heteroarenes *i.e.*, imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]-thiazole and the results are shown in Table 6.3. Similar reactivity pattern was observed with imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]-thiazole which gave the end products in moderate to good yields (Table 6.3, **5a-5g**). All the

synthesized compounds (**3a-q** and **5a-g**) from the protocol were characterized by ^{1}H, and ^{13}C NMR spectroscopy and mass spectral data.

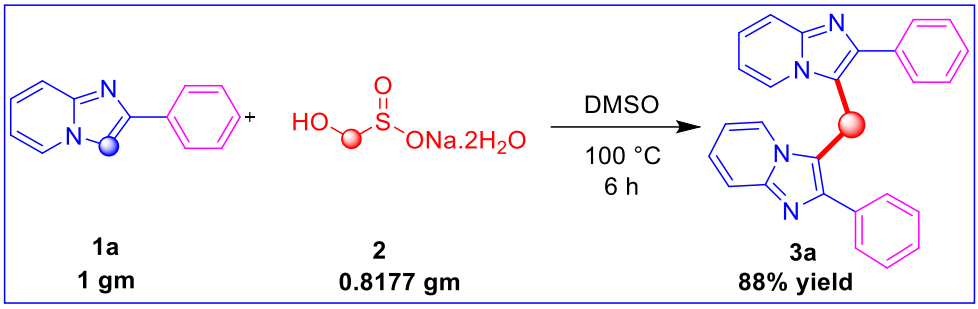
Similarly, indoles are smoothly reacted with rongalite under optimized reaction conditions to give the corresponding bridged di(1*H*-indol-3-yl)methanes. Interestingly both the electron withdrawing and electron donating groups on the indole gave the corresponding bridged di(1*H*-indol-3-yl)methane **7a-i** in good to excellent yields (Table 6.4).

Table 6.4. Reaction of substituted indoles with rongalite[a,b]



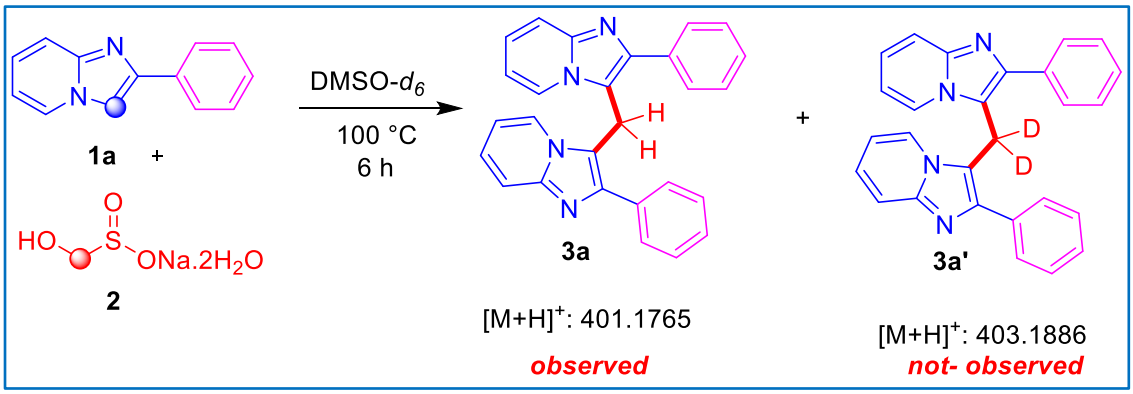
[a]Reaction conditions: indoles **6a-i** (1.0 mmol), rongalite **2** (1.0 mmol) and solvent (2 ml). [b]Isolated yield.

Finally, we have also tested our protocol in gram scale for the industrial applications with 1g scale using imidazo-[1,2-*a*]pyridine **1a** with rongalite **2,** in DMSO (2 mL) at 100 ^{o}C for 6 h. The reaction afforded the final product **3a** in 88% of yield (Scheme 6.16).



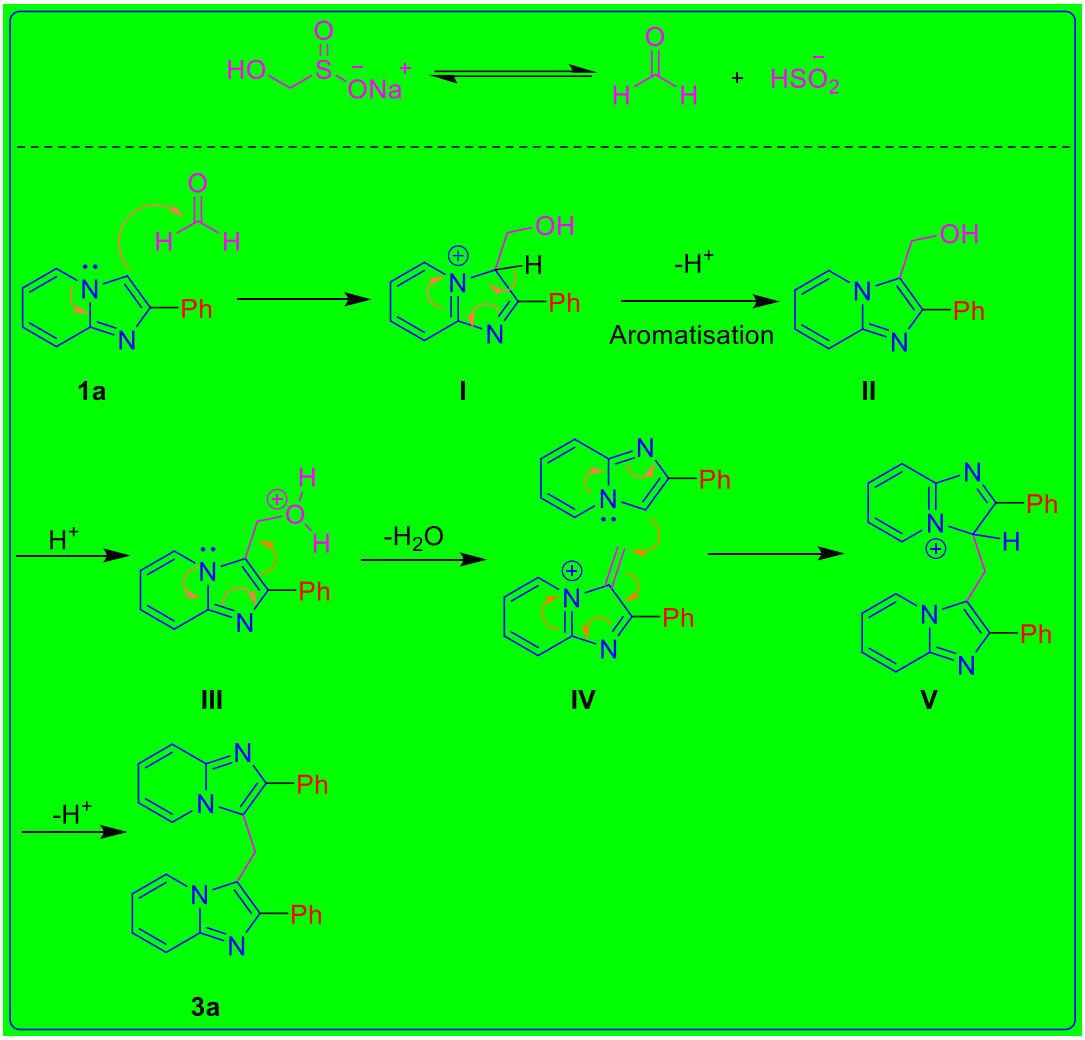
Scheme 6.16. Gram-scale synthesis

Next, we carried a control experiment in DMSO-d_6 to unveil the source of the C1 unit in the reaction (Scheme 6.17). Initially, imidazo-[1,2-*a*]pyridine **1a** was treated with rongalite **2**, in DMSO-d_6 (2 mL) at 100 °C for 6 h under the standard conditions and recorded the proton and HRMS. The ^{1}H NMR data at δ 5.00 (s, 2H) ppm and HRMS (m/z= 400.1688, observed $[M+H]^+$ 401.1765). Data revealed that C1 unit is coming from the rongalite not from the DMSO-d_6.



Scheme 6.17. Control experiments

A plausible mechanism of the reaction is illustrated in Scheme 6.18. In the first step, rongalite dissociates and generate formaldehyde *in situ*, which further reacts with imidazo-[1,2-*a*]pyridine to form an intermediate **I**, which further re-aromatises to form stable (imidazo-[1,2-*a*]pyridyl) methanol compound **II**. Upon dehydration of intermediate **II** yields a Michael acceptor 3-methylene- imidazo-[1,2-*a*]pyridine **IV**. Then another imidazo[1,2-*a*]pyridine π-electrons attack on methylene- imidazo-[1,2-*a*]pyridine **IV** *via* Michael addition to form intermediate **V**, which further undergoes aromatization to furnish desired product **3a** (Scheme 3B.18).



Scheme 6.18. Plausible reaction mechanism

6.3. Conclusion

We have developed a transitional metal-free protocol to synthesize the methylene-bridged homo dimerization of imidazo[1,2-*a*]pyridines, imidazo[2,1-*b*]thiazole, benzo[d]imidazo[2,1-*b*]-thiazole, and indoles in excellent yields. This method tolerates a wide variety of substitutions on the aromatic ring. In this method, rongalite is generating formaldehyde *in situ* which further acts as a methylenating agent. We have synthesized 33 examples up to 80-95% yields.

6.4. Experimental section

6.4.1. General Information: All chemicals were purchased from Aldrich, Alfa aesar, TCI, Finar and used as received. All solvents were purchased from commercial sources, then distilled by the standard protocol and stored over molecular sieves under nitrogen atmosphere prior to use. Thin layer chromatography was performed on 200 µm aluminium-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk).

^{1}H NMR spectra were recorded on Bruker's AVANCE 400 MHz spectrometer, $CDCl_3$ and DMSO-d_6 as a solvent and TMS as an internal standard. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, coupling constants, *J* were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker's AVANCE 100 MHz spectrometer, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-d (a multiplet at 39.52 ppm of DMSO-d_6). Melting points were determined with a Stuart SMP30 apparatus and are uncorrected. FT-IR spectra recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230.

6.4.2. General procedure for the preparation of bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3a-3s)

To a clean and dry round bottom flask equipped with magnetic bead were added imidazo[1, 2-*a*] pyridine **1a** (1.0 mmol), and rongalite **2** (1.0 mmol) in 2 mL of DMSO solvent. The reaction mixture was allowed to stir at 100 ºC for 4-8 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into an ice-cold water and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was separated using column chromatography with silica-gel (100-200 mesh) by eluting with ethyl acetate / hexanes as a mobile phase.

6.4.3. General procedure for the preparation of bis(6-phenylimidazo[2,1-*b*]thiazol-5-yl) and bis(2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)methane derivatives (5a-5g)

To a clean and dry round bottom flask equipped with magnetic bead were added 6-phenylimidazo[2,1-*b*]thiazole or 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole **5a** (1.0 mmol), and rongalite **2** (1.0 mmol) in DMSO solvent (2 mL). The reaction mixture was allowed to stir at 100 ºC for 4-8 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into an ice-cold water and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was separated using column chromatography with silica-gel (100-200 mesh) by eluting with ethyl acetate/ hexanes as a mobile phase.

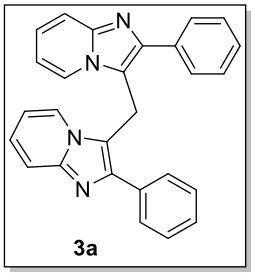
6.4.4. General procedure for the preparation of di(1*H*-indol-3-yl)methane derivatives (7a-7i)

To a clean and dry round bottom flask equipped with magnetic bead were added Indole **6a** (1.0 mmol), and rongalite **2** (1.0 mmol) in DMF solvent (2 mL). The reaction mixture was allowed to stir at 70 ºC for 6-10 h. After completion of the reaction (monitored by TLC), the reaction

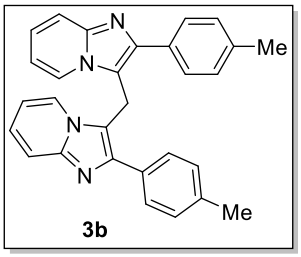
mixture was poured into an ice-cold water and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was separated using column chromatography with silica-gel (100-200 mesh) by eluting with ethyl acetate / hexanes as a mobile phase.

6.5. Characterization data of products 3a-3q, 5a-5g, and 7a-7i.

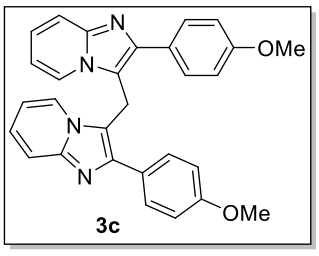
Bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3a). White solid; (190 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79 (d, J = 6.8 Hz, 4H), 7.56 – 7.49 (m, 6H), 7.46 – 7.41 (m, 2H), 7.35 (d, J = 7.2 Hz, 2H), 7.08-7.03 (m, 2H), 6.48 (td, J = 6.8, 1.2 Hz, 2H), 5.00 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 144.9, 144.0, 134.1, 128.9, 128.8, 128.2, 124.4, 123.7, 117.4, 114.2, 112.4, 19.7. HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{21}N_4^+$ $[M+H]^+$ 401.1761; found 401.1765.



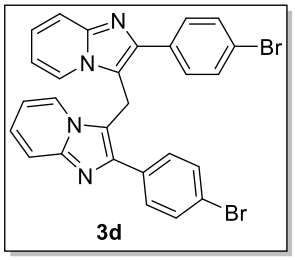
Bis(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3b). Light yellow solid; (195 mg, 91%) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69 (d, J = 8.4 Hz, 4H), 7.53 (d, J = 8.8 Hz, 2H), 7.36 – 7.31 (m, 6H), 7.06-7.01 (m, 2H), 6.46 (td, J= 6.8, 1.2 Hz, 2H), 4.98 (s, 2H), 2.44 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm):144.8, 144.1, 138.0, 131.2, 129.5, 128.8, 124.2, 123.8, 117.2, 114.1, 112.2, 21.3, 19.7; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{25}N_4^+$ $[M+H]^+$ 429.2074; found 429.2090.



Bis(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3c). White solid; (214 mg, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.73 (d, J = 8.8 Hz, 4H), 7.52 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 6.8 Hz, 2H), 7.07-7.02(m, 6H), 6.48 (td, J = 6.8, 0.8 Hz, 2H), 4.95 (s, 2H), 3.89 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 159.6, 144.8, 143.8, 130.1, 126.6, 124.2, 123.7, 117.1, 114.3, 113.8, 112.2, 55.3, 19.7; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{25}N_4O_2^+$ $[M+H]^+$ 461.1972; found 461.2000.

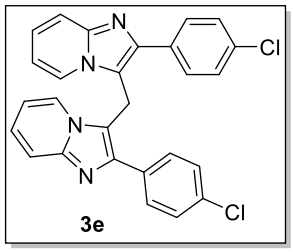


Bis(2-(4-bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3d). Light yellow solid; (234 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.58 (s, 8H), 7.55 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 6.8 Hz, 2H), 7.14 – 7.08 (m, 2H), 6.57 (t, J = 7.0 Hz, 2H), 4.90 (s, 1H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 145.0, 143.1, 133.0, 131.8, 130.1, 124.6, 123.4, 122.5, 117.6, 114.0, 112.7, 20.0; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{19}Br_2N_4^+$ $[M+H]^+$ 556.9971; found 556.9979.



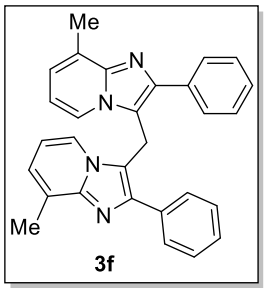
3d

Bis(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3e). Light yellow solid; (194 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65 (d, J = 8.4 Hz, 4H), 7.56 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 4H), 7.38 (d, J = 7.2 Hz, 2H), 7.14-7.09 (m, 2H), 6.57 (td, J = 6.8, 1.2 Hz, 2H), 4.90 (s, 1H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 145.1, 143.3, 133.4, 129.2, 129.0, 128.8, 126.1, 121.9, 120.7, 117.7, 114.6, 19.0; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{19}Cl_2N_4^+$ $[M+H]^+$ 469.0981; found 469.1003.



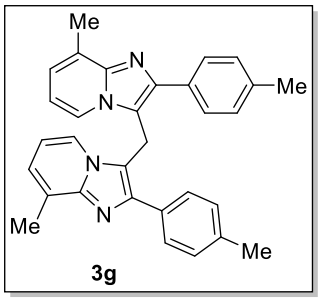
3e

Bis(8-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (5f). White solid; (191 mg, 89%); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.77 (d, J = 7.2 Hz, 4H), 7.50 (t, J = 7.4 Hz, 4H), 7.41 (t, J = 7.2 Hz, 2H), 7.25 (d, J = 6.8 Hz, 2H), 6.86 – 6.83 (m, 2H), 6.40 (t, J = 6.8 Hz, 2H), 4.93 (s, 2H), 2.57 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 145.4, 143.7, 134.7, 129.2, 128.8, 128.1, 127.4, 123.2, 121.8, 114.9, 112.4, 20.0, 17.2; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{25}N_4^+$ $[M+H]^+$ 429.2074; found 429.2090.



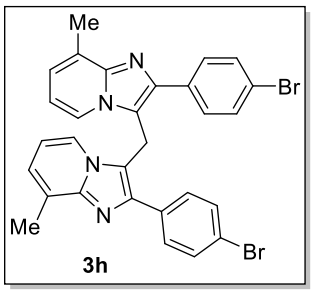
3f

Bis(8-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3g). White solid; (217 mg, 95%);^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67 (d, J = 8.4 Hz, 4H), 7.30 (d, J = 7.6 Hz, 4H), 7.25 (d, J = 7.6 Hz, 2H), 6.82 (d, J = 7.2 Hz, 2H), 6.38 (t, J = 6.8 Hz, 2H), 4.90 (s, 1H), 2.56 (s, 6H), 2.43 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 145.2, 143.6, 137.7, 131.6, 129.4, 129.0, 127.1, 122.9, 121.7, 114.6, 112.1, 21.3, 19.9, 17.0; HRMS (ESI-TOF) m/z: calculated for $C_{31}H_{29}N_4^+$ $[M+H]^+$ 457.2387; found 457.2405.



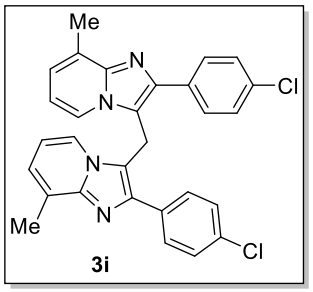
3g

Bis(2-(4-bromophenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3h). White solid; (249 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 8H), 7.30 (d, *J* = 7.2 Hz, 2H), 6.91 (d, *J* = 6.8 Hz, 2H), 6.51 (t, *J* = 6.8 Hz, 2H), 4.80 (s, 2H), 2.57 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) *δ* (ppm): 145.3, 142.5, 133.1, 131.6, 130.3, 127.6, 123.4, 122.2, 121.2, 114.4, 112.7, 20.2, 17.0; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{23}Br_2N_4^+$ $[M+H]^+$ 585.0284; found 585.0311.



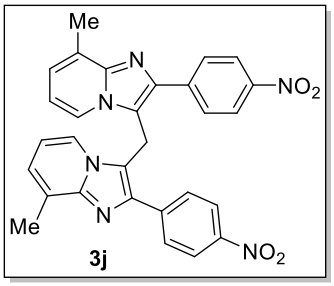
3h

Bis(2-(4-chlorophenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3i). White solid; (21 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm): 7.59 (d, *J* =8.8 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 6.8 Hz, 1H), 6.90 (d, *J* = 6.8 Hz, 1H), 6.50 (t, *J* = 6.8 Hz, 1H), 4.81 (s, 1H), 2.57 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) *δ* (ppm):145.3, 142.5, 133.9, 132.8, 130.0, 128.6, 127.6, 123.3, 121.2, 114.5, 112.6, 20.2, 17.0; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{23}Cl_2N_4^+$ $[M+H]^+$ 497.1294; found 497.1314.



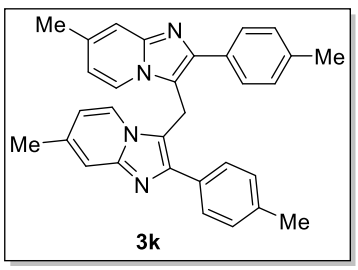
3i

Bis(8-methyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3j). Yellow solid; (207 mg, 80%); ^{1}H NMR (400 MHz, CDCl3+DMSO-d_6) *δ* (ppm): 8.03 (d, *J* = 8.8 Hz, 4H), 7.78 (d, *J* = 6.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 4H), 7.02 (d, *J* = 6.8 Hz, 2H), 6.76 (t, *J* = 6.8 Hz, 2H), 4.97 (s, 2H), 2.49 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCL_3$+DMSO) *δ* (ppm): 146.6, 145.0, 141.0, 140.9, 128.9, 127.1, 123.8, 122.9, 122.0, 116.4, 113.1, 29.5, 16.7; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{23}N_6O_4^+$ $[M+H]^+$ 519.1775; found 519.1799.



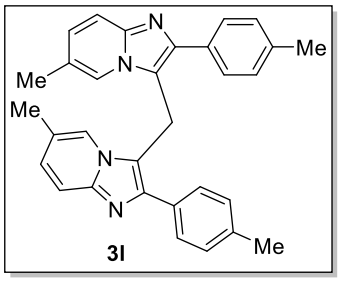
3j

Bis(7-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3k). White solid; (217 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm): 7.62 (d, *J* = 8.4 Hz, 4H), 7.26 (d, *J* = 8.0 Hz, 4H), 7.20 (s, 2H), 7.13 (d, *J* = 7.2 Hz, 2H), 6.21 (dd, *J* = 7.2, 1.6 Hz, 2H), 4.85 (s, 2H), 2.37 (s, 6H), 2.19 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) *δ* (ppm): 145.3, 143.6, 137.8, 135.2, 131.5, 129.5, 128.7, 123.1, 115.6, 114.8, 113.7, 21.3, 21.1, 19.7; HRMS (ESI-TOF) m/z: calculated for $C_{31}H_{29}N_4^+$ $[M+H]^+$ 457.2387; found 457.2387.



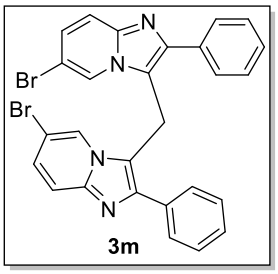
3k

Bis(6-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3l). White solid; (212 mg, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 (d, J = 8.0 Hz, 4H), 7.33 (d, J = 8.0 Hz, 4H), 7.26 (s, 2H), 7.20 (d, J = 7.2 Hz, 2H), 6.28 (dd, J = 7.2, 1.6 Hz, 2H), 4.93 (s, 1H), 2.44 (s, 6H), 2.26 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 145.4, 143.7, 138.0, 135.3, 131.6, 129.7, 128.9, 123.2, 115.7, 114.9, 113.8, 21.5, 21.2, 19.8; HRMS (ESI-TOF) m/z: calculated for $C_{31}H_{29}N_4^+$ $[M+H]^+$ 457.2387; found 457.2409.



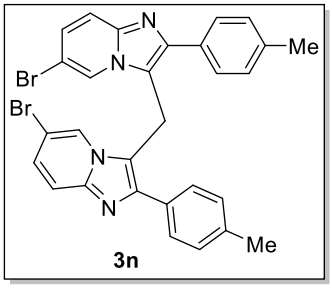
3l

Bis(6-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (3m). White solid; (237 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77 (d, J = 8.0 Hz, 4H), 7.58 (t, J = 7.6 Hz, 4H), 7.50 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 8.8 Hz, 4H), 7.13 (dd, J = 9.8, 1.4 Hz, 2H), 4.93 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 145.0, 143.4, 133.5, 129.2, 129.0, 128.8, 128.0, 124.1, 118.0, 114.5, 107.1, 19.0; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{19}Br_2N_4^+$ $[M+H]^+$ 556.9971; found 556.9992.



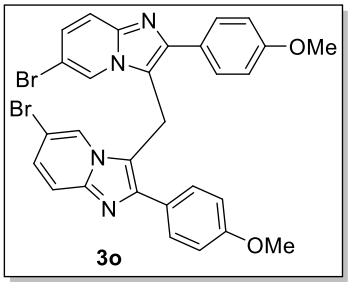
3m

Bis(6-bromo-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3n). White solid; (255 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65 (d, J = 8.0 Hz, 4H), 7.42-7.35 (m, 8H), 7.10 (dd, J = 9.6, 1.6 Hz, 2H), 4.88 (s, 1H), 2.45 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 145.0, 143.3, 138.6, 130.6, 129.9, 128.9, 127.8, 124.2, 117.8, 114.5, 106.9, 21.4, 19.0; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{23}Br_2N_4^+$ $[M+H]^+$ 585.0284; found 585.0308.



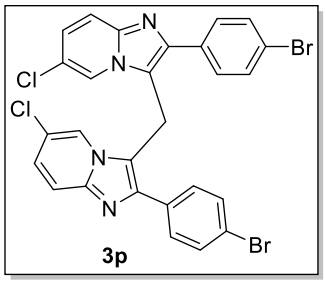
3n

Bis(6-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3o). White solid;(275 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 (d, J = 8.4 Hz, 4H), 7.45 – 7.39 (m, 4H), 7.13 – 7.07 (m, 6H), 4.86 (s, 2H), 3.90 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 160.1, 144.8, 143.3, 130.3, 127.9, 125.8, 124.1, 117.8, 114.7, 114.2, 106.9, 55.4, 19.0; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{23}Br_2N_4O_4^+$ $[M+H]^+$ 617.0182; found 617.0186.



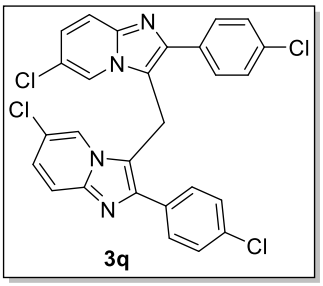
3o

Bis(2-(4-bromophenyl)-6-chloroimidazo[1,2-*a*]pyridin-3-yl)methane (3p). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57 (d, J = 8.4 Hz, 4H), 7.49 (d, J = 8.4 Hz, 4H), 7.41 (d, J = 9.2 Hz, 2H), 7.26 (d, J = 1.2 Hz, 2H), 7.01 (dd, J = 9.6, 2.0 Hz, 2H), 4.74 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 144.1, 143.3, 132.3, 132.2, 130.3, 126.3, 123.1, 121.6, 121.0, 117.8, 114.4, 29.7, 19.3; HRMS (ESI-TOF) m/z: calculated for $C_{29}H_{17}Br_2Cl_2N_4^+$ $[M+H]^+$ 624.9192; found 624.9189.



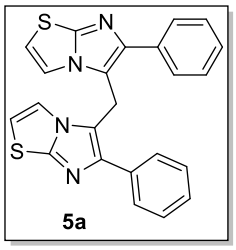
3p

Bis(6-chloro-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3q). White solid; (229 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64 (d, J = 8.4 Hz, 4H), 7.51-7.46 (m, 6H), 7.33 (d, J = 1.2 Hz, 2H), 7.08 (dd, J = 9.6, 2.0 Hz, 2H), 4.82 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 144.1, 143.4, 134.9, 131.9, 130.0, 129.3, 126.2, 121.6, 120.9, 117.8, 114.4, 19.3; HRMS (ESI-TOF) m/z: calculated for $C_{27}H_{17}Cl_4N_4^+$ $[M+H]^+$ 537.0202; found 537.0215.

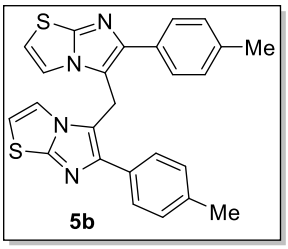


3q

Bis(6-phenylimidazo[2,1-*b*]thiazol-5-yl)methane (5a). White solid; (186 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (d, J = 6.8 Hz, 4H), 7.50 (t, J = 7.6 Hz, 4H), 7.39 (t, J = 7.4 Hz, 2H), 6.56 (q, J = 4.6 Hz, 2H), 4.83 (s, 1H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 149.3, 144.5, 134.2, 128.9, 128.0, 127.8, 117.2, 117.1, 112.8, 21.2; HRMS (ESI-TOF) m/z: calculated for $C_{23}H_{17}N_4S_2^+$ $[M+H]^+$ 413.0889; found 413.0908.

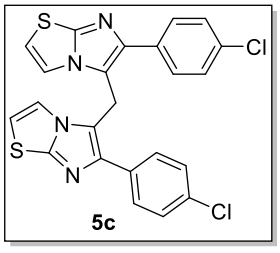

5a

Bis(6-(*p*-tolyl)imidazo[2,1-*b*]thiazol-5-yl)methane (5b). White solid; (203 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 4dH), 7.31 (d, J = 8.0 Hz, 4H), 6.58 – 6.55 (m, 4H), 4.80 (s, 2H), 2.43 (s, 6H). ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 149.2, 144.5, 137.6, 131.3, 129.6, 127.8, 117.2, 116.8, 112.6, 21.3, 21.2. HRMS (ESI-TOF) m/z: calculated for $C_{25}H_{21}N_4S_2^+$ $[M+H]^+$ 441.1202; found 441.1209.



5b

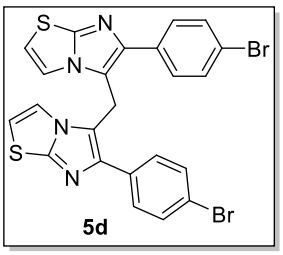
Bis(6-(4-chlorophenyl)imidazo[2,1-*b*]thiazol-5-yl)methane (5c). White solid; (212 mg, 88%);^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67 (d, J = 8.4 Hz, 4H), 7.46 (d, J = 8.4 Hz, 4H), 6.63 (d, J = 4.6 Hz, 2H), 6.58 (d, J = 4.4 Hz, 2H), 4.77 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 149.5,



5c

143.6, 133.7, 132.6, 129.1, 116.9, 113.3, 21.4; HRMS (ESI-TOF) m/z: calculated for $C_{23}H_{15}Cl_2N_4S_2^+$ $[M+H]^+$ 481.0110; found 481.0124.

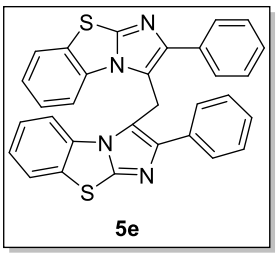
Bis(6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-5-yl)methane (5d). White solid; (254 mg, 89%);



5d

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 8H), 6.63 (d, J = 4.8 Hz, 2H), 6.57 (d, J = 4.4 Hz, 2H), 4.76 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$+DMSO) δ (ppm): 147.9, 142.1, 132.2, 130.5, 128.3, 120.2, 116.3, 116.2, 112.6, 20.4. HRMS (ESI-TOF) m/z: calculated for $C_{23}H_{15}Br_2Cl_2N_4S_2^+$ $[M+H]^+$ 568.9099; found 568.9113.

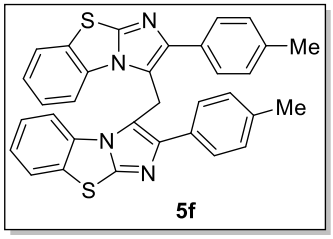
Bis(2-phenylbenzo[d]imidazo[2,1-*b*]thiazol-3-yl)methane (5e). White solid; (233 mg, 91%);



5e

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (d, J = 6.8 Hz, 4H), 7.50 (t, J = 7.6 Hz, 4H), 7.39 (t, J = 7.4 Hz, 2H), 6.56 (q, J = 4.6 Hz, 2H), 4.83 (s, 1H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 147.2, 145.7, 133.4, 133.1, 130.5, 128.0, 127.7, 127.5, 125.9, 124.5, 124.3, 118.8, 112.9, 23.9; HRMS (ESI-TOF) m/z: calculated for $C_{31}H_{21}N_4S_2^+$ $[M+H]^+$ 513.1202; found 513.1220.

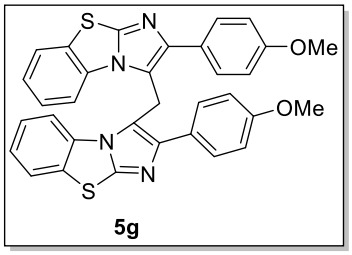
Bis(2-(*p*-tolyl)benzo[d]imidazo[2,1-*b*]thiazol-3-yl)methane (5f). White solid; (251 mg, 93%);



5f

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67 – 7.64 (m, 2H), 7.44 – 7.41 (m, 2H), 7.31-7.28 (m, 4H), 7.13 (d, J = 8.0 Hz, 4H), 6.94 (d, J = 7.6 Hz, 4H), 5.14 (s, 2H), 2.28 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 147.1, 145.7, 137.2, 133.1, 130.5, 130.4, 128.4, 127.9, 125.9, 124.4, 124.1, 118.7, 112.9, 23.9, 21.1; HRMS (ESI-TOF) m/z: calculated for $C_{33}H_{25}N_4S_2^+$ $[M+H]^+$ 541.1515; found 541.1531.

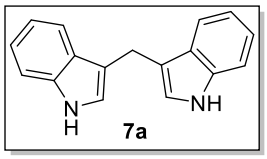
Bis(2-(4-methoxyphenyl)benzo[d]imidazo[2,1-*b*]thiazol-3-yl)methane (5g). White solid; (272 mg, 95%);



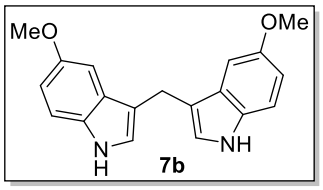
5g

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68-7.65 (m, 2H), 7.46-7.42 (m, 2H), 7.31-7.28 (m, 4H), 7.16 (d, J = 8.4 Hz, 4H), 6.67 (d, J = 8.8 Hz, 4H), 5.12 (s, 2H), 3.76 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ (ppm): 158.9, 147.0, 145.4, 133.1, 130.3, 129.2, 126.0, 125.9, 124.4, 124.2, 118.5, 113.2, 112.9, 55.3, 23.9; HRMS (ESI-TOF) m/z: calculated for $C_{33}H_{25}N_4O_2S_2^+$ $[M+H]^+$ 573.1413; found 573.1418.

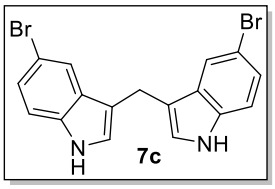
Di(1*H*-indol-3-yl)methane (7a). White solid; (105 mg, 85% yield); ^{1}H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.73 (s, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.35-7.31 (m, 2H), 7.14 (d, J = 2.4 Hz, 2H), 7.07-7.02 (m, 2H), 6.95-6.90 (m, 2H), 4.14 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 136.8, 127.6, 123.2, 121.2, 119.1, 118.5, 114.6, 111.7, 21.3.



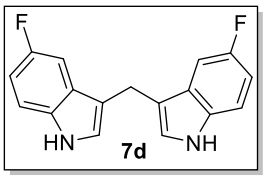
Bis(5-methoxy-1*H*-indol-3-yl)methane (7b). Red solid; (138 mg, 90% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.57 (s, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 2.4 Hz, 2H), 7.04 (d, J = 2.4 Hz, 2H), 6.71 (dd, J = 8.8, 2.4 Hz, 2H), 4.08 (s, 2H), 3.72 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 153.2, 132.0, 127.9, 123.9, 114.4, 112.3, 111.1, 101.1, 55.7, 21.3.



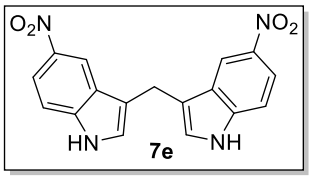
bis(5-bromo-1*H*-indol-3-yl)methane (7c). Yellow solid; (176 mg, 87% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.98 (s, 2H), 7.65 (d, J = 2.0 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 2.4 Hz, 2H), 7.14 (dd, J = 8.6, 1.8 Hz, 2H), 4.10 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 135.5, 129.4, 125.0, 123.7, 121.3, 114.1, 113.8, 111.2, 21.0.



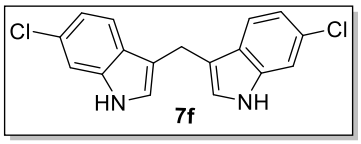
Bis(5-fluoro-1*H*-indol-3-yl)methane (7d). Yellow solid; (116 mg, 82% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.88 (s, 2H), 7.34 (dd, J = 8.8, 4.4 Hz, 2H), 7.30 (d, J = 2.4 Hz, 2H), 7.26 (dd, J = 10.2, 2.6 Hz, 2H), 6.92-6.86 (m, 2H), 4.10 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 158.1, 155.8, 133.5, 127.8, 127.7, 125.4, 114.7, 114.6, 112.7, 112.6, 109.4, 109.1, 103.8, 103.6, 21.2.



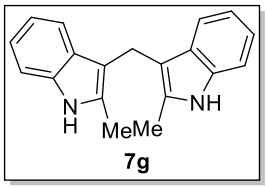
Bis(5-nitro-1*H*-indol-3-yl)methane (7e). Yellow solid; (126 mg, 75% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.60 (s, 2H), 8.51 (d, J = 2.0 Hz, 2H), 7.97 (dd, J = 8.8, 2.4 Hz, 2H), 7.53 – 7.52 (m, 2H), 7.51 (d, J = 2.4 Hz, 2H), 4.33 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 140.5, 140.1, 127.3, 126.7, 117.0, 116.9, 116.3, 112.3, 20.7.



Bis(6-chloro-1*H*-indol-3-yl)methane (7f). Yellowish solid; (139 mg, 85% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.91 (s, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 1.6 Hz, 2H), 7.20 (d, J = 2.0 Hz, 2H), 6.93 (dd, J = 8.4, 1.6 Hz, 2H), 4.11 (s, 2H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 137.2, 126.3, 126.0, 124.4, 120.4, 118.8, 114.7, 111.4, 21.1.

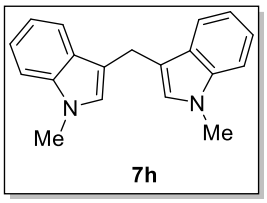


Bis(2-methyl-1*H*-indol-3-yl)methane (7g). Yellow solid (122 mg, 89% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.54 (s, 2H), 7.16 (d, J = 7.6 Hz, 2H), 7.12-7.09 (m, 2H), 6.85-6.80(m, 2H), 6.73-6.69 (m, 2H), 3.90 (s, 2H), 2.29 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 135.5, 131.6, 128.9, 120.1, 118.2, 118.1, 110.6, 110.1, 19.3, 12.0.



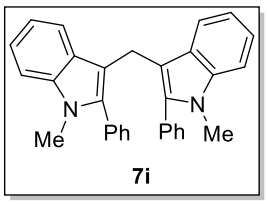
7g

Bis(1-methyl-1*H*-indol-3-yl)methane (7h). Yellowish solid; (119 mg, 87% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.58 – 7.54 (d, J = 7.6, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.15-7.10 (m, 2H), 7.08 (s, 2H), 7.01-6.97 (m, 2H), 4.13 (s, 2H), 3.69 (s, 6H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 137.2, 127.9, 127.6, 121.4, 119.2, 118.6, 113.9, 109.9, 32.6, 20.9.



7h

Bis(1-methyl-2-phenyl-1*H*-indol-3-yl)methane (7i). White solid; (171 mg, 80% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.56 -7.51 (m, 4H), 7.49-7.46 (m, 2H), 7.44 – 7.41 (m, 4H), 7.36 (d, J = 8.0 Hz, 2H), 7.06-7.01 (m, 2H), 6.94 (d, J = 7.6 Hz, 2H), 6.79-6.74 (m, 2H), 4.09 (s, 2H), 3.54 (s, 3H); ^{13}C NMR {^{1}H} (100 MHz, DMSO-d_6) δ (ppm): 137.6, 137.3, 131.9, 131.0, 128.9, 128.5, 127.7, 121.6, 119.5, 119.0, 111.7, 110.0, 31.1, 21.2.



7i

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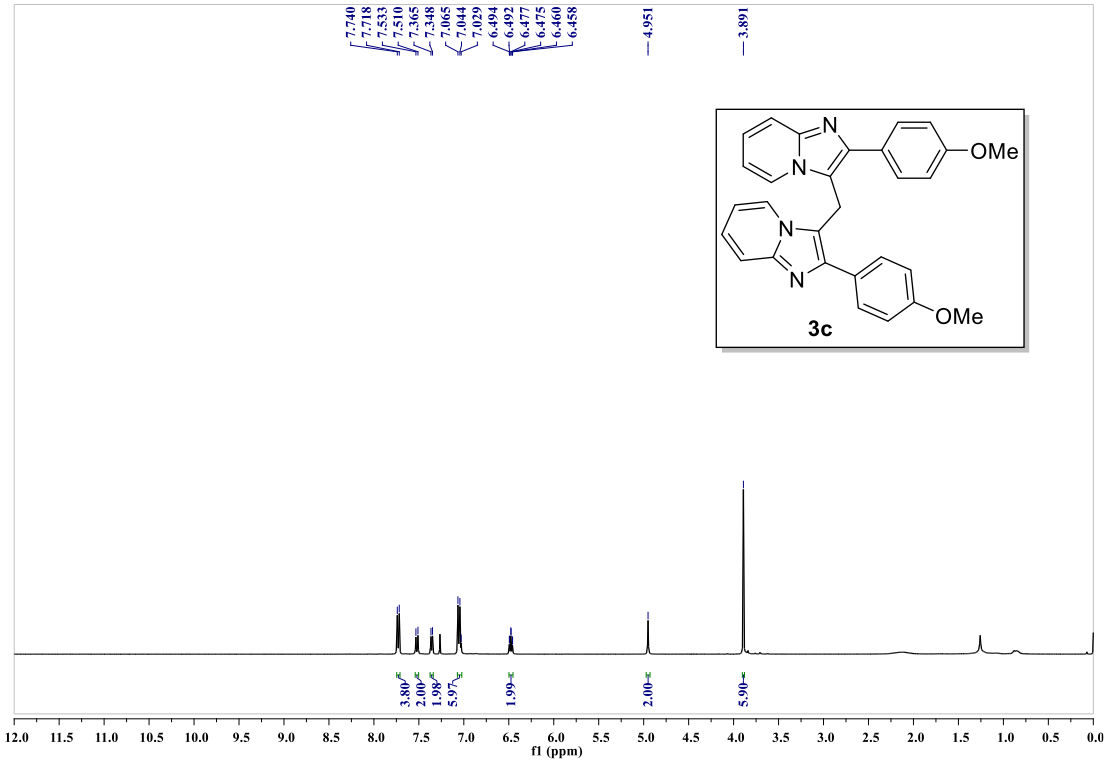
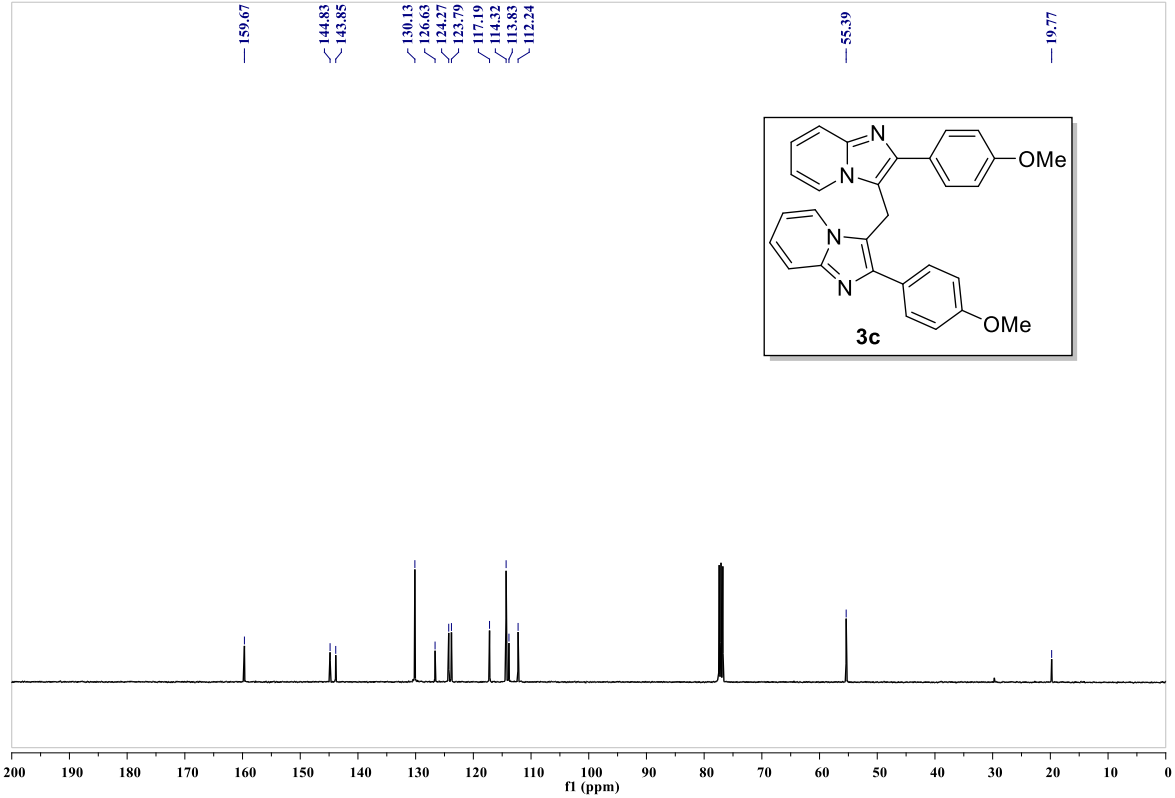
6.7. Selected NMR (^{1}H and ^{13}C) and HRMS Spectra

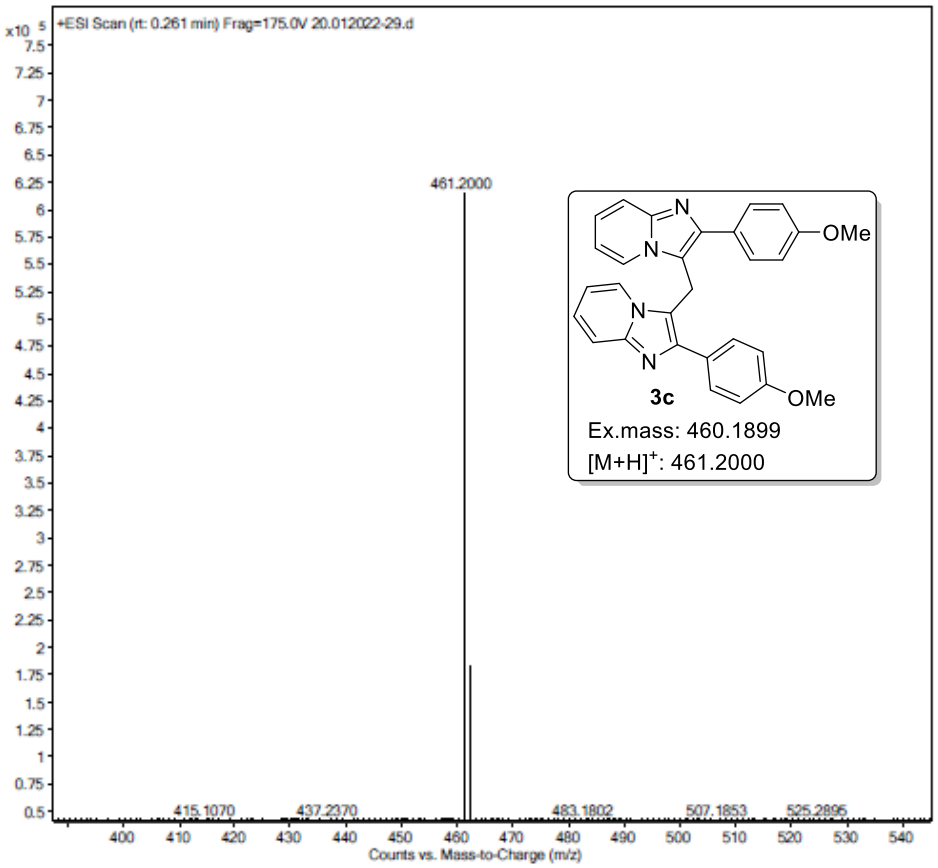
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of bis(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3c)



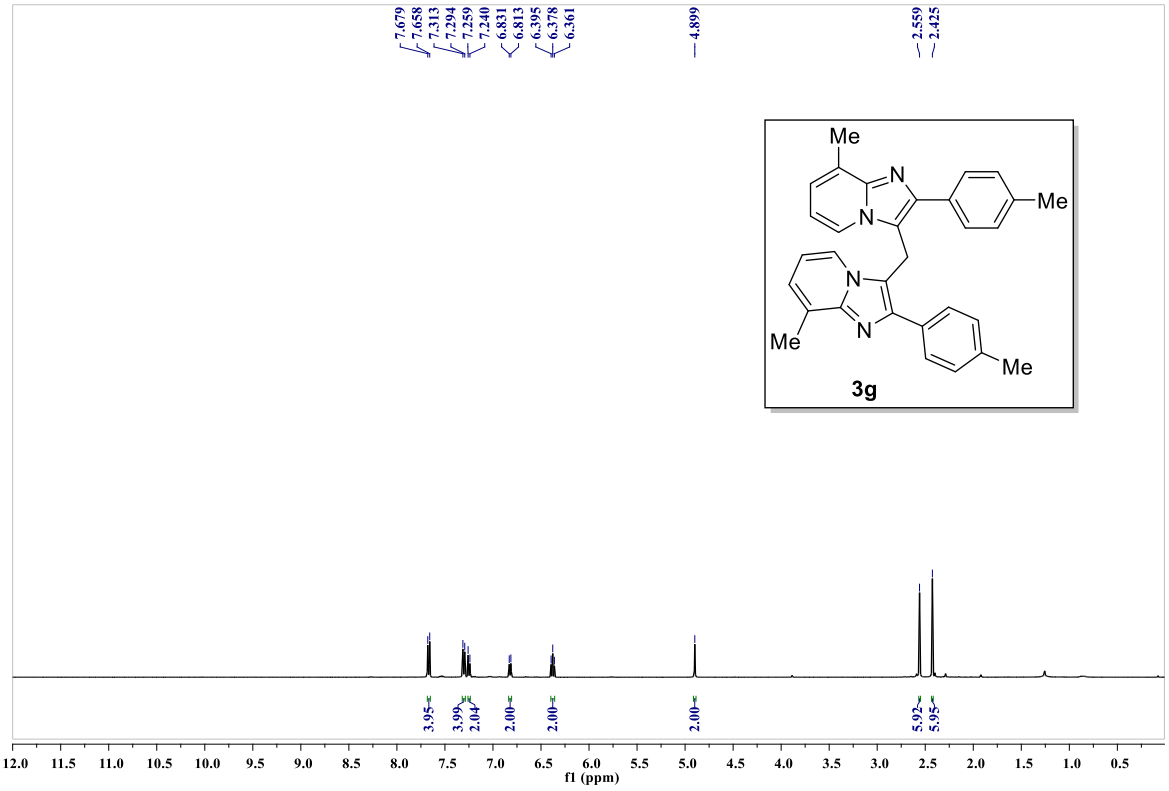
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of bis(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3c)



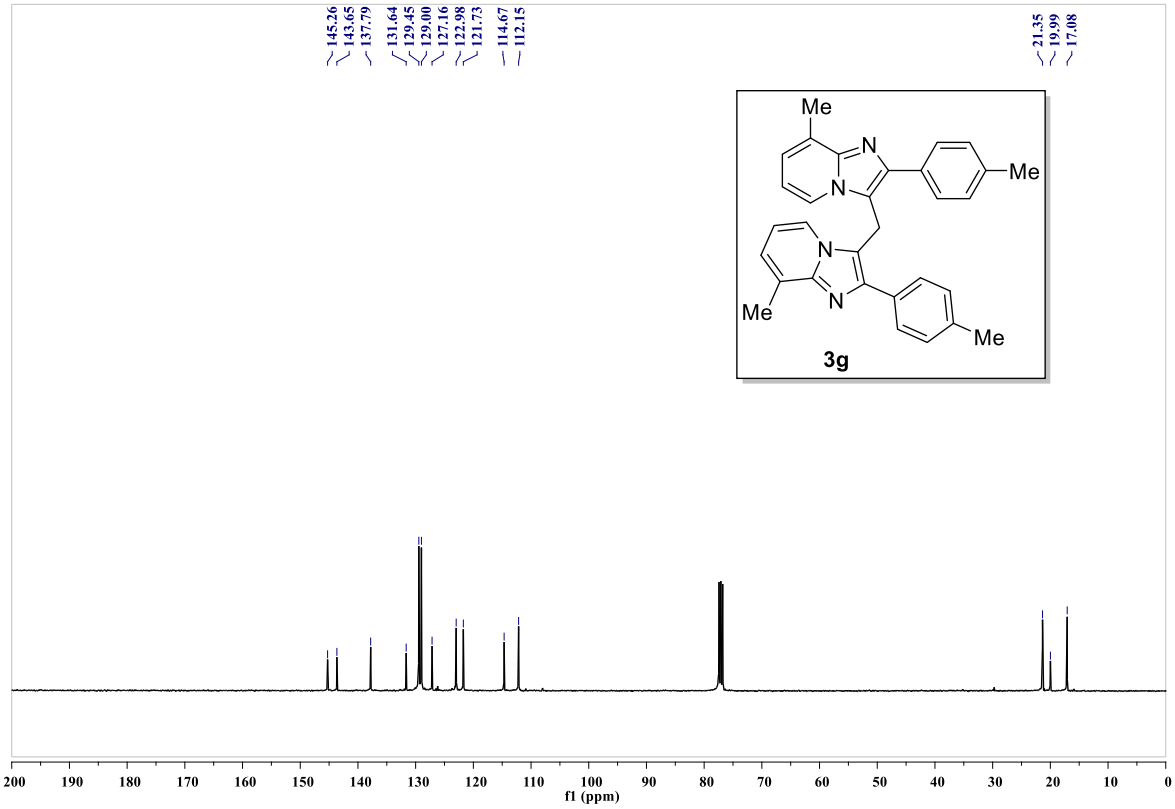
HRMS spectrum of bis(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3c)



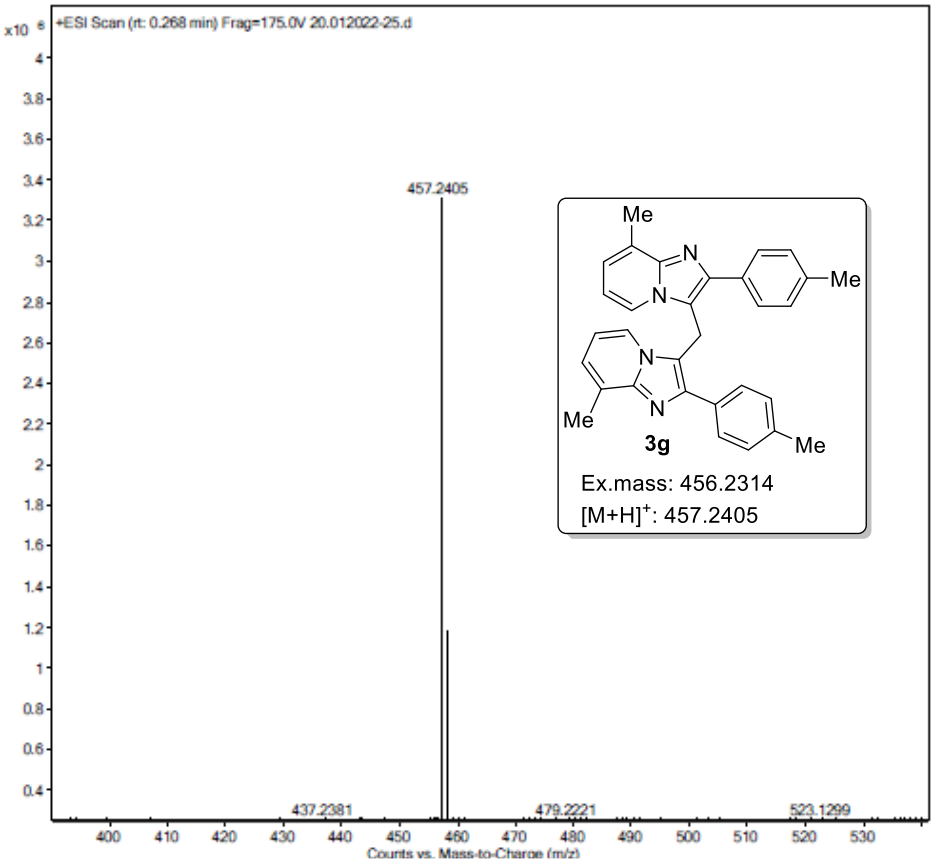
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of bis(8-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3g)



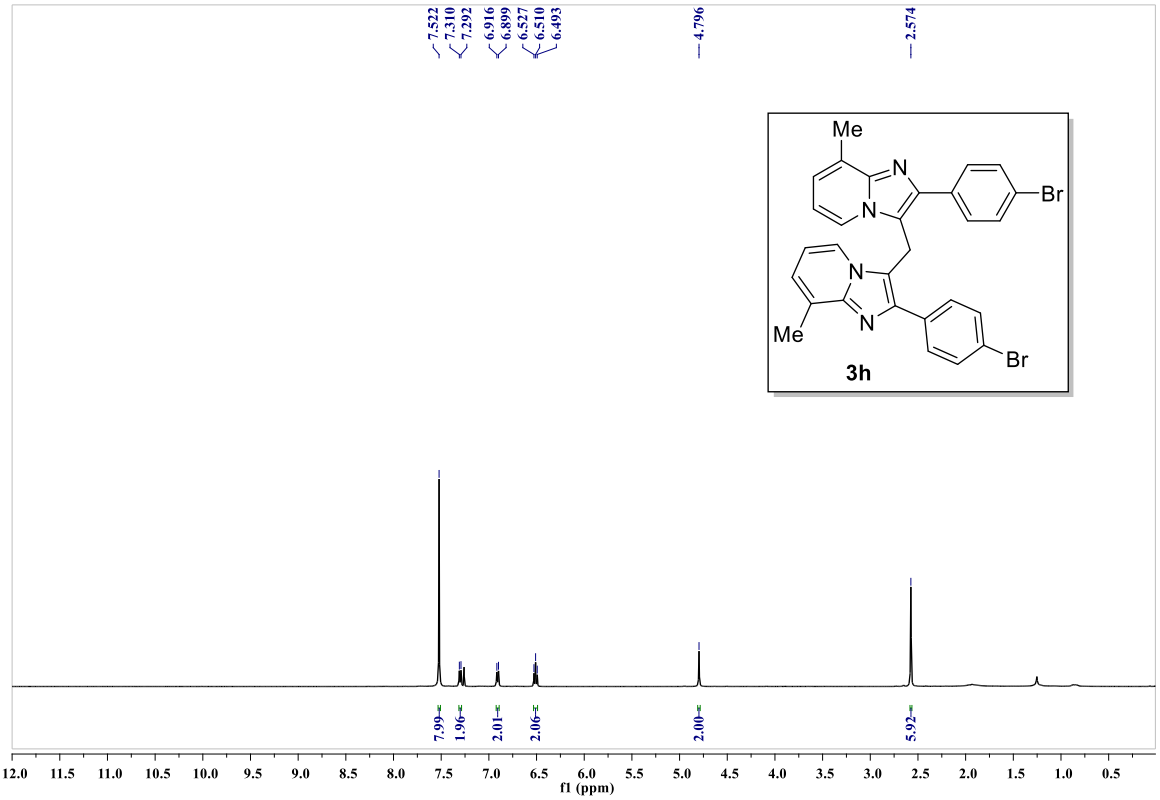
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of bis(8-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3g)



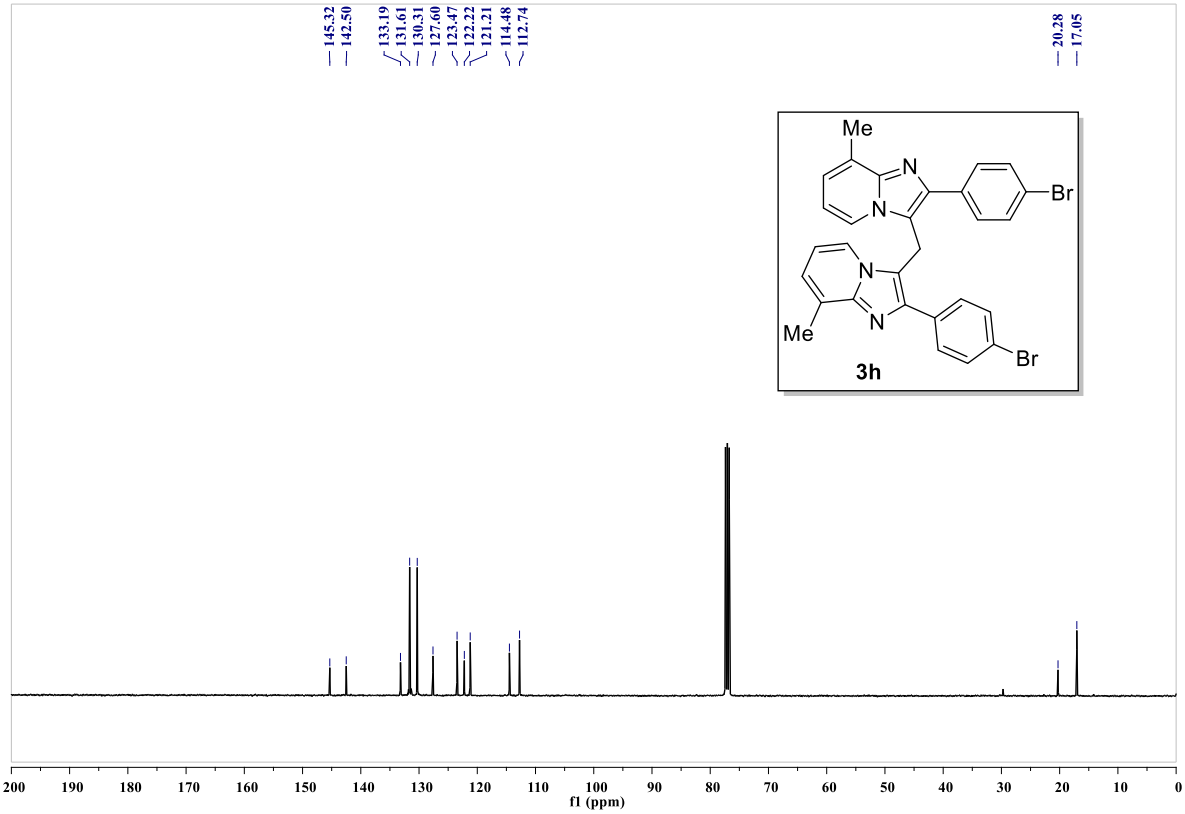
HRMS spectrum of bis(8-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (3g)



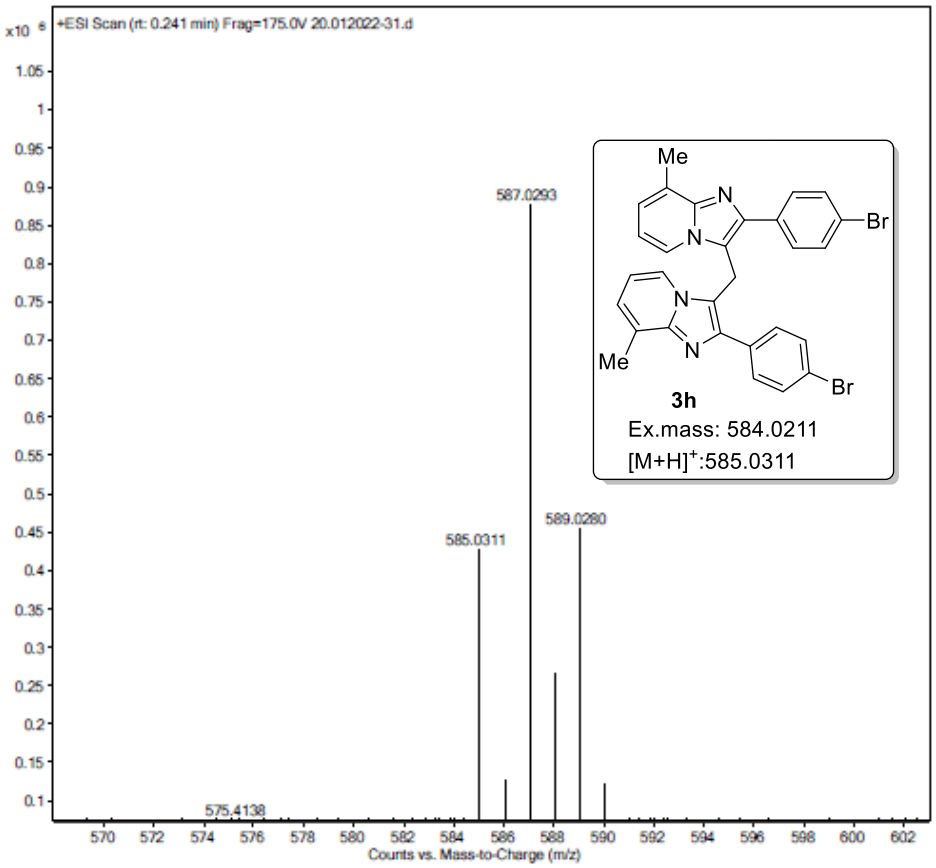
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of bis(2-(4-bromophenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3h)



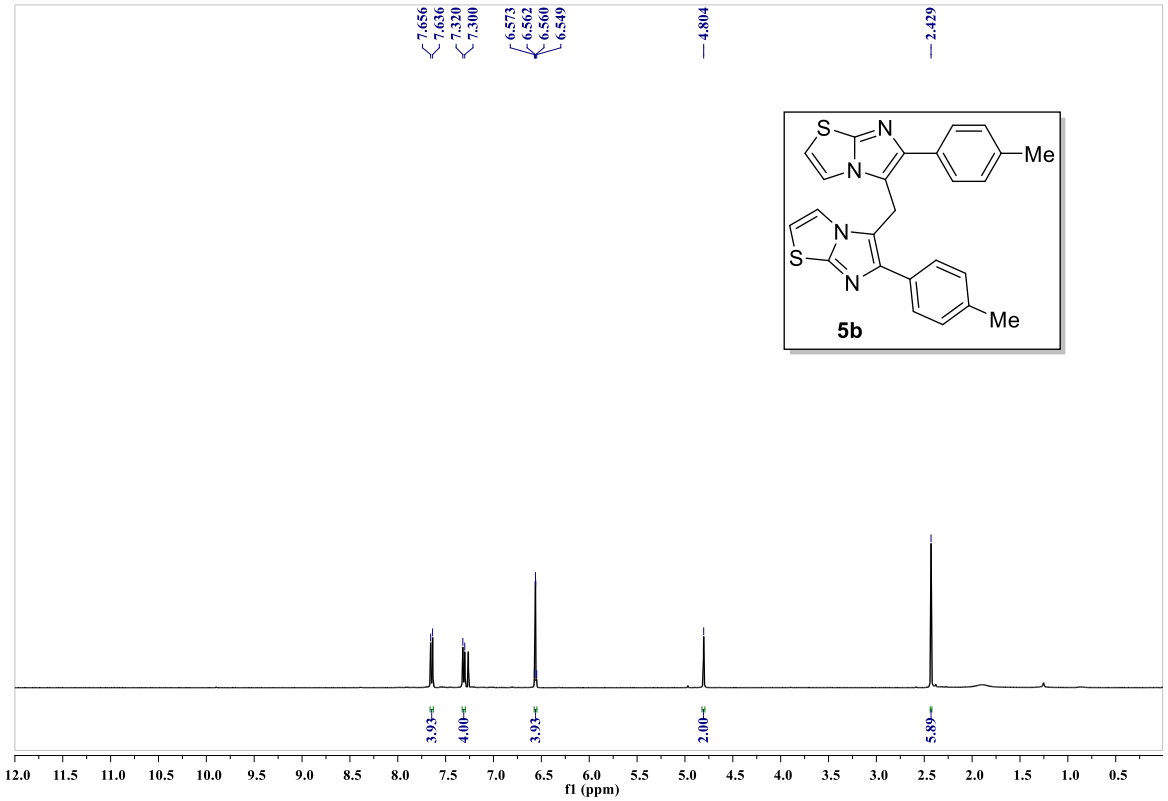
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of bis(2-(4-bromophenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3h)



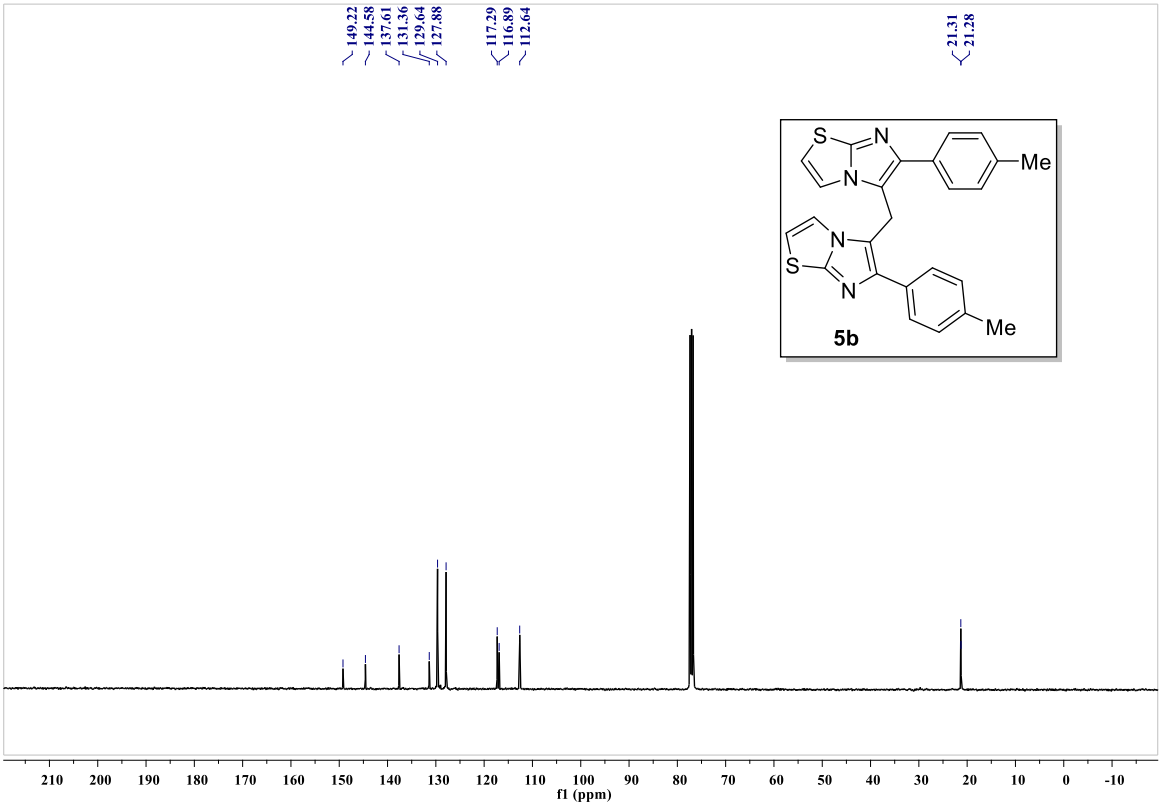
HRMS spectrum of bis(2-(4-bromophenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)methane (3h)



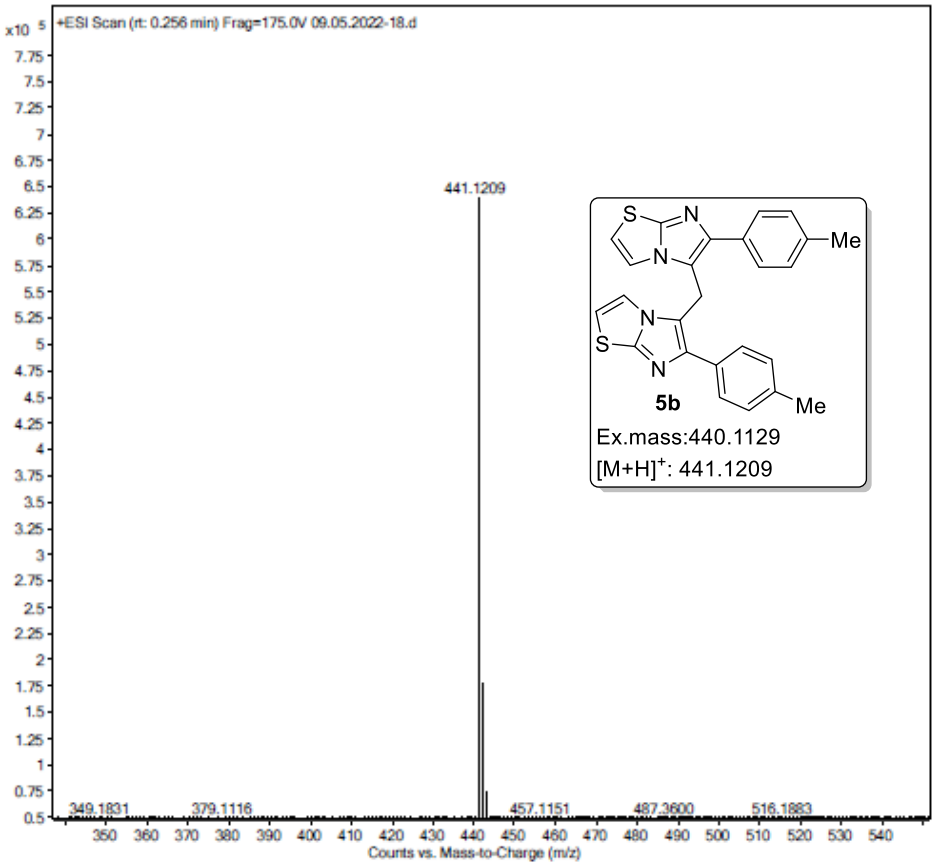
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of bis(6-(*p*-tolyl)imidazo[2,1-*b*]thiazol-5-yl)methane (5b)



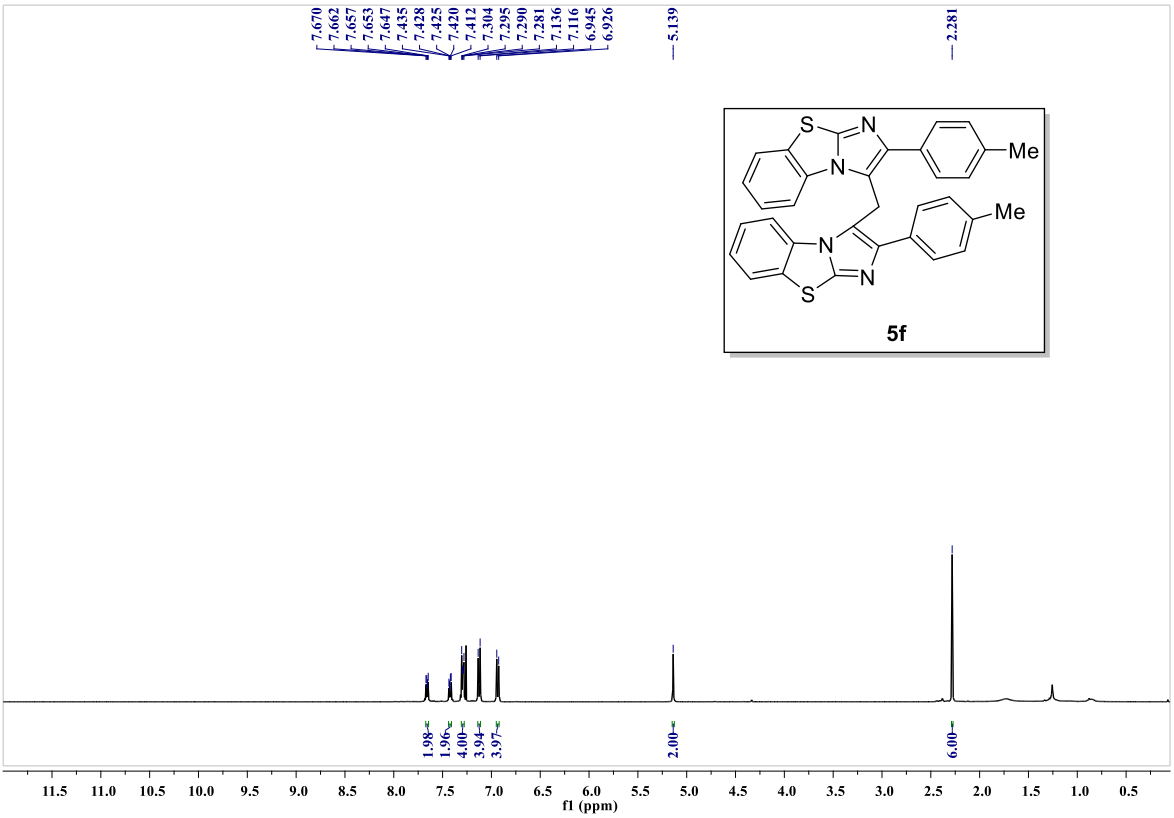
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of bis(6-(*p*-tolyl)imidazo[2,1-*b*]thiazol-5-yl)methane (5b)



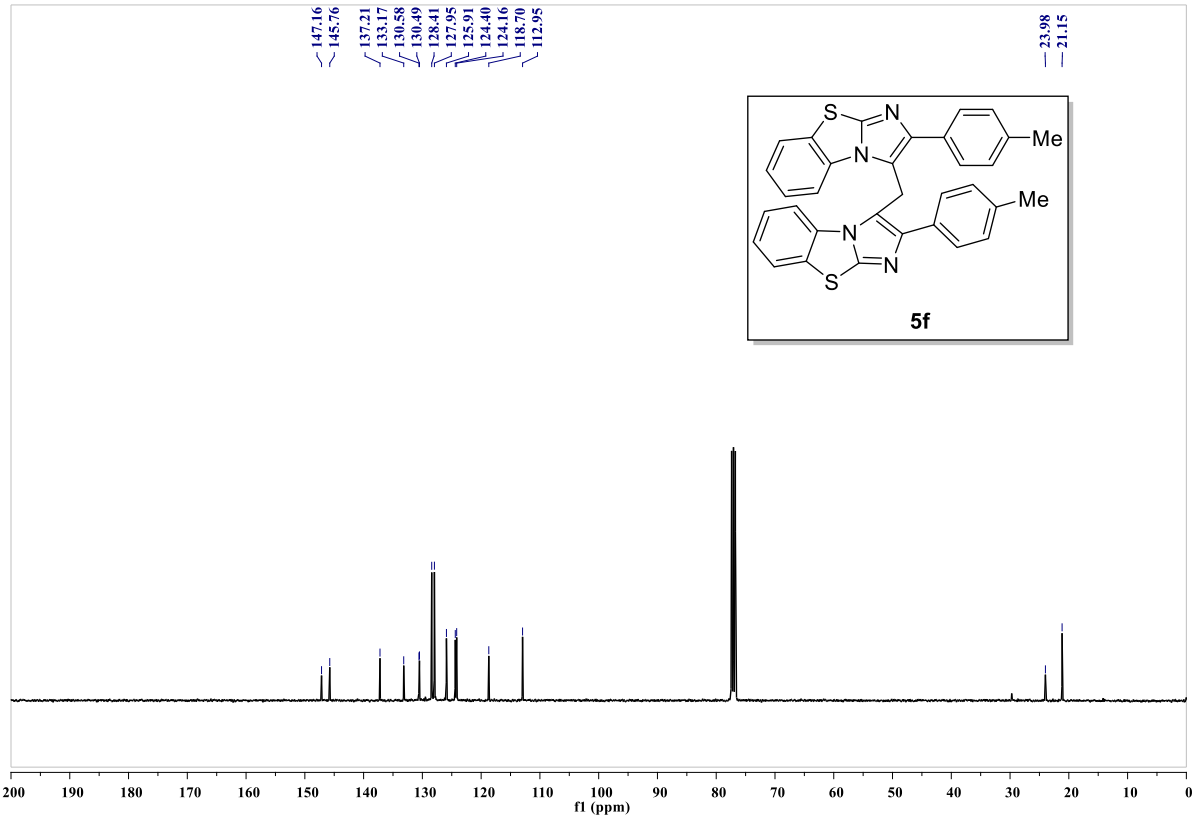
HRMS spectrum of bis(6-(*p*-tolyl)imidazo[2,1-*b*]thiazol-5-yl)methane (5b)



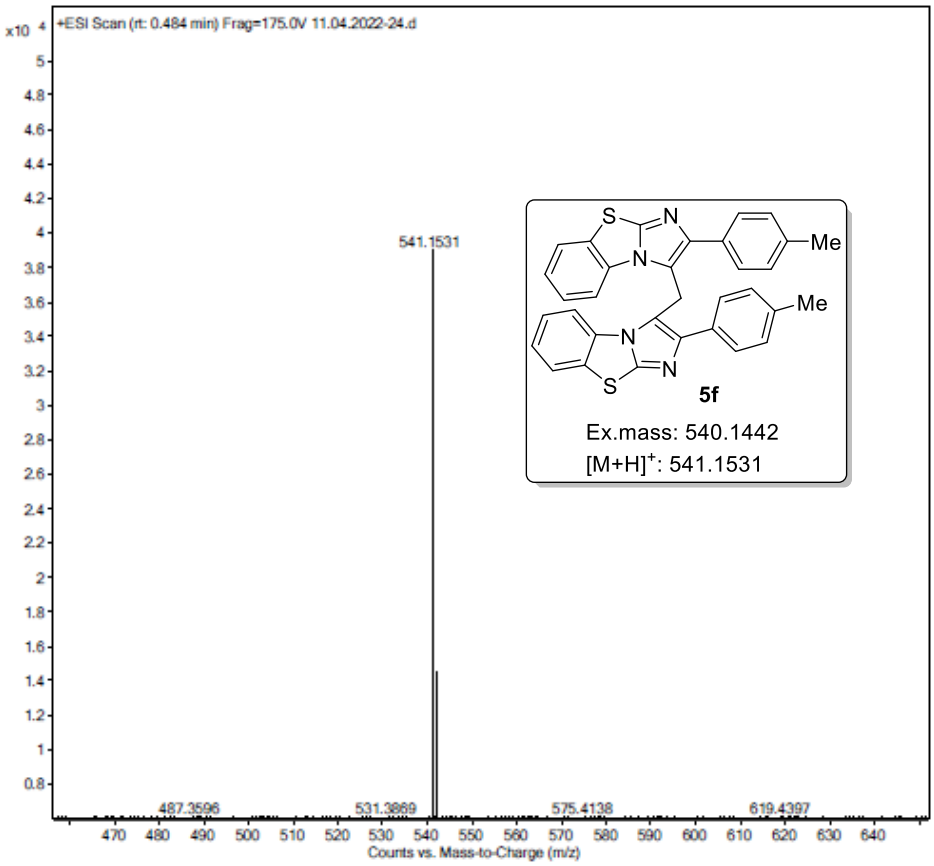
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of bis(2-(*p*-tolyl)benzo[d]imidazo[2,1-*b*]thiazol-3-yl)methane (5f)



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of bis(2-(*p*-tolyl)benzo[d]imidazo[2,1-*b*]thiazol-3-yl)methane (5f)



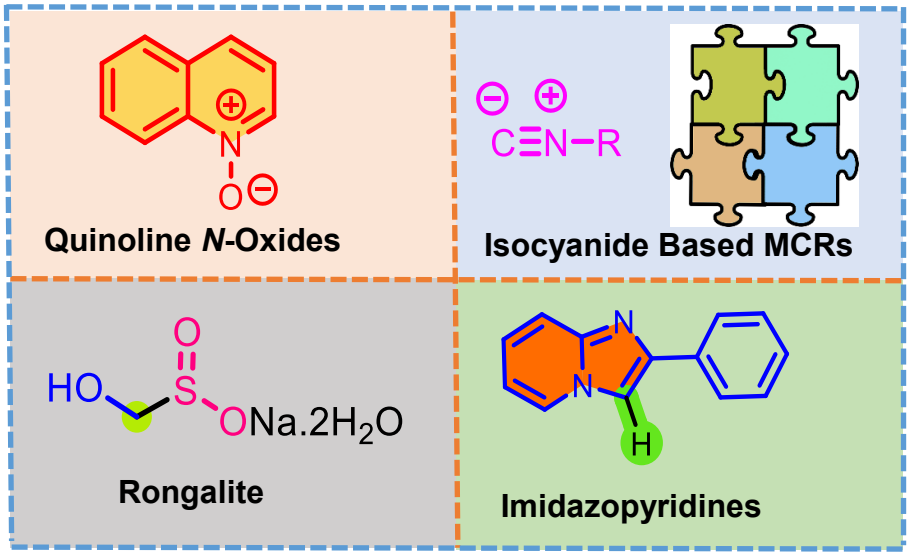
HRMS spectrum of bis(2-(*p*-tolyl)benzo[d]imidazo[2,1-*b*]thiazol-3-yl)methane (5f)



SUMMARY

Chapter-I
Introduction

The literature survey, objectives and prerequisites of the present study are presented in this chapter. Apart from this, a brief introduction of C(sp^2)-H functionalization of *N*-heterocyclic compounds such as quinolines, imidazopyridines and indoles are discussed.[1] Later, applications of isocyanides and rongalite are discussed. Sodium hydroxymethanesulfinate dihydrate (SHM), also called as rongalite is an industrial product that has been used as a bleaching agent in the dye and printing industry, it acts as an antidote against heavy metal poisoning, antioxidant in formulations and green reagent in organic chemistry.[2-4]

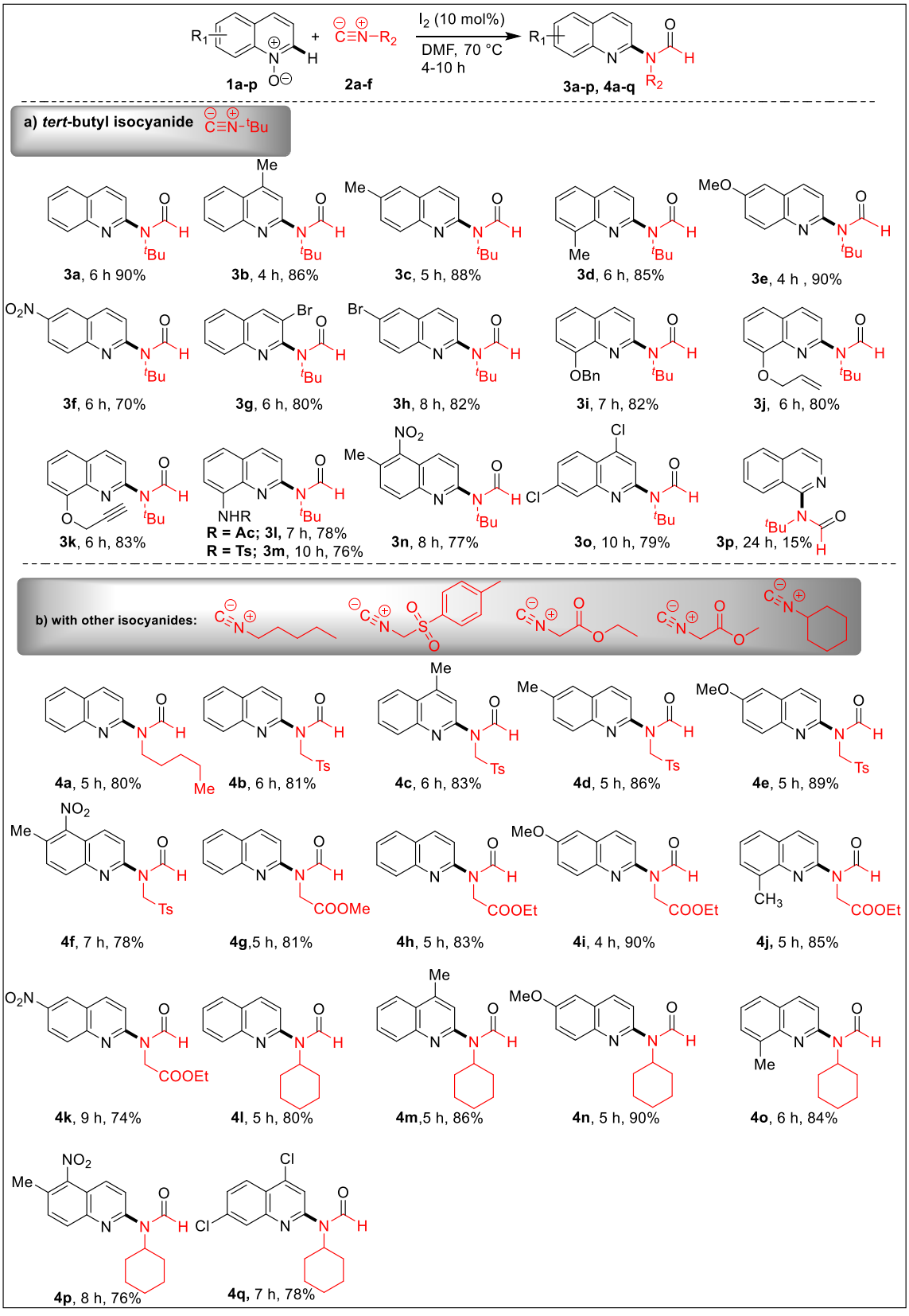


Chapter-IIA and IIB deals with the C2-H formamidation of quinoline *N*-oxides using isocyanides catalysed by molecular iodine and $FeCl_3$ respectively. Chapter IIIA describes the single reactant replacement (SRR) approach to modify the Ugi reactions entitled "*N*-oxide induced Ugi Reaction: A novel synthesis of quinoline-C2-amino amides *via* deoxygenative C(sp^2)-H functionalization" to obtain the library of quinoline containing peptomers. Chapter IIIB comprises the effect of 3-halo quinoline *N*-oxides in Ugi Reaction to obtain the 1*H*-spiro[imidazolidine-2,2'-quinolin]-4-one. Chapter IV describes the iodide-catalyzed one-pot synthesis of carbamates using alcohols and isocyanides. The synthesis of the compounds presented in chapter V and Chapter VI were based on rongalite mediated C(sp^2)-H functionalization of quinolines and methylenation of imidazopyridine derivatives respectively. The structures of the synthesized compounds were characterized by FT-IR, NMR, Mass spectral and single crystal X-ray diffraction methods. All the compounds described in the thesis were synthesized using conventional methods.

Chapter-II

Section-A

Iodine Catalyzed C2-H Formamidation of Quinoline *N*-oxides using Isocyanides



Scheme 2A. C2-H formamidation of quinoline *N*-oxide derivatives using isocyanides

Amides are an important class of *N*-containing compounds in organic chemistry and also potential precursors for the synthesis of numerous natural products.[5] Recently, several modifications have been explored at the C2 position of quinolines including sulfonylation, amination and alkylation to prevent the hydroxylation. Thus, activation of quinoline *N*-oxides with suitable activators remain challenging to functionalize the quinolines at C2 position.

Although, there are various activators available such as sulfonyl chlorides,[6] acyl chlorides,[7] anhydrides,[8] PyBroP,[9] and boron reagents[10] to promote the quinoline C2-H functionalization, but have their own limitations such as stoichiometry, cost and toxicity. Among the C2 functional groups, the biologically important *N*-acylated 2-aminoquinolines are mainly synthesized from *N*-oxides with amide source *via* metal or radical initiators.[11] Thus, we have developed a molecular iodine catalyzed C2-amination of quinolone *N*-oxide under mild conditions.

The optimized reaction conditions are as follows, an oven-dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate quinoline *N*-oxides (0.5 mmol), I_2 (10 mol%), isocyanides (0.5 mmol) and (*N, N*-dimethyl formamide) DMF (2 mL). The mixture was stirred at 70 °C for the appropriate time (4-10 h) to produce the corresponding products **3a-p** and **4a-q** up to 90% yields (Scheme 2A).

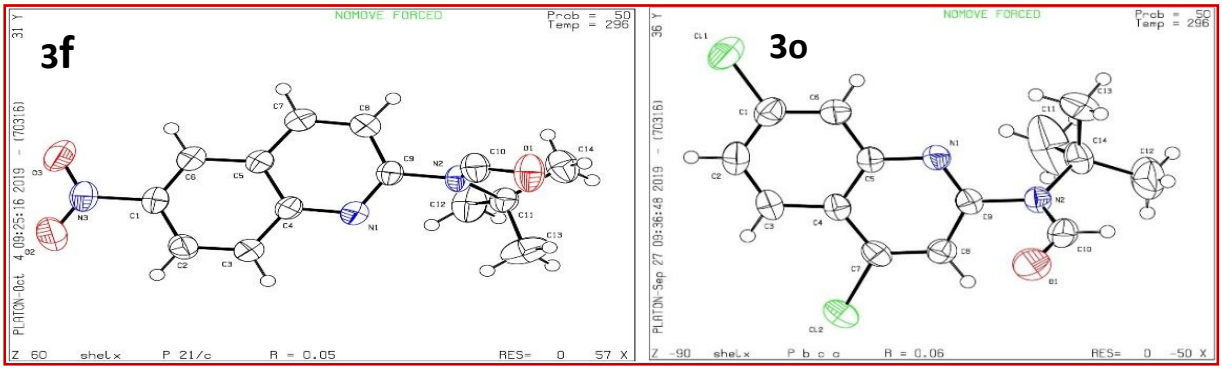


Figure 1: ORTEP diagrams of **3f** and **3o**

Chapter-II

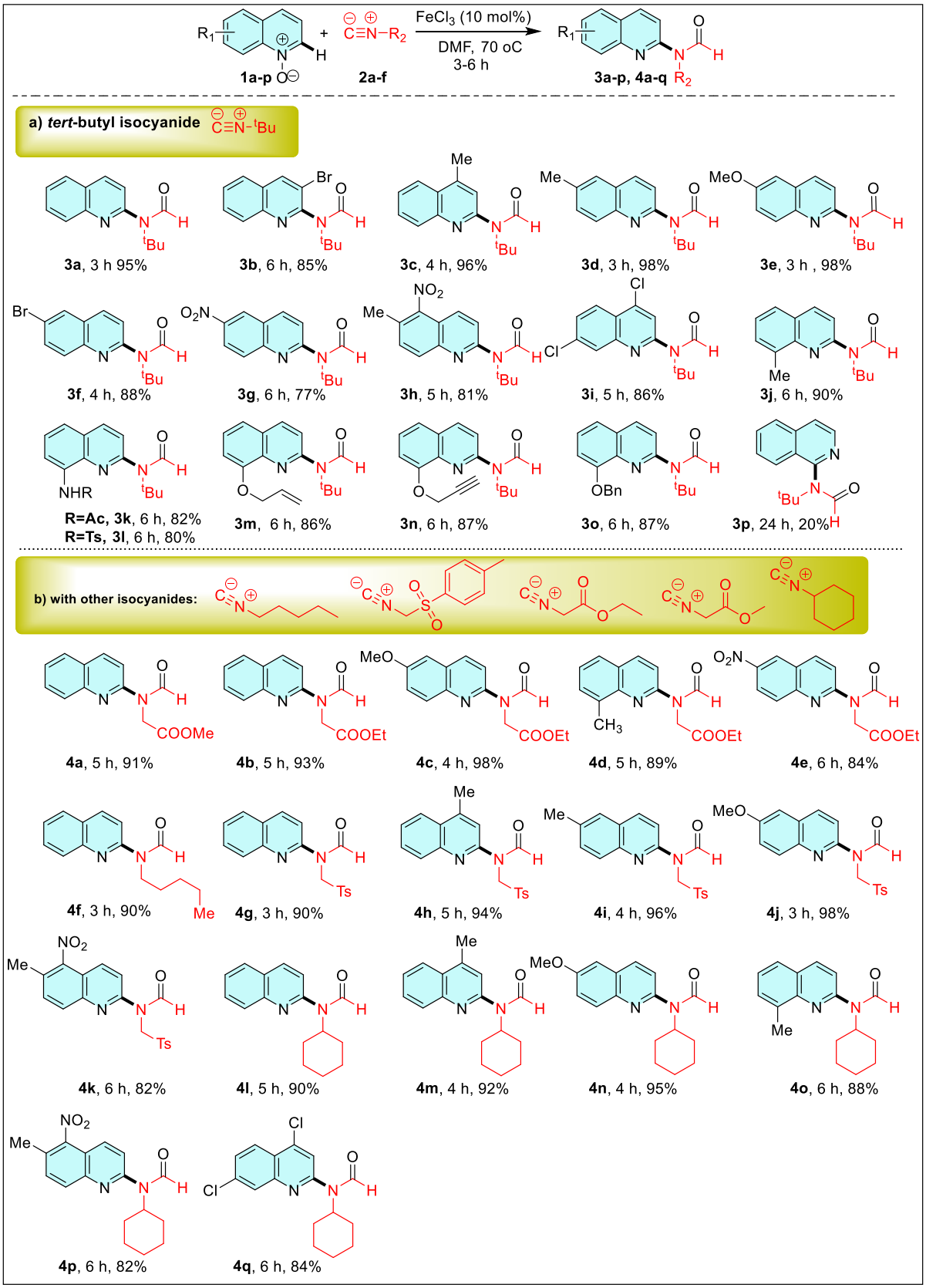
Section-B

Fe-Catalyzed Deoxygenative C2-Formamidation Reaction of Quinoline *N*-oxides with Isocyanides

In this chapter $FeCl_3$ promoted C2-formamidation of quinoline *N*-oxides was developed. This method employs commercially available inexpensive $FeCl_3$ to obtain C-aminoamides in good to excellent yields.

The optimized reaction conditions are as follows, an oven-dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate quinoline *N*-oxides (0.5 mmol), $FeCl_3$

(10 mol%), isocyanides (0.5 mmol) and (*N*, *N*-dimethyl formamide) DMF (2 mL). The mixture was stirred at 70 °C for the appropriate time (3-6 h) to produce the corresponding products **3a-p** and **4a-q** up to 98% yields (Scheme 2B).



Scheme 2B. C2-H formamidation of quinoline *N*-oxide derivatives using isocyanides.

Chapter-III

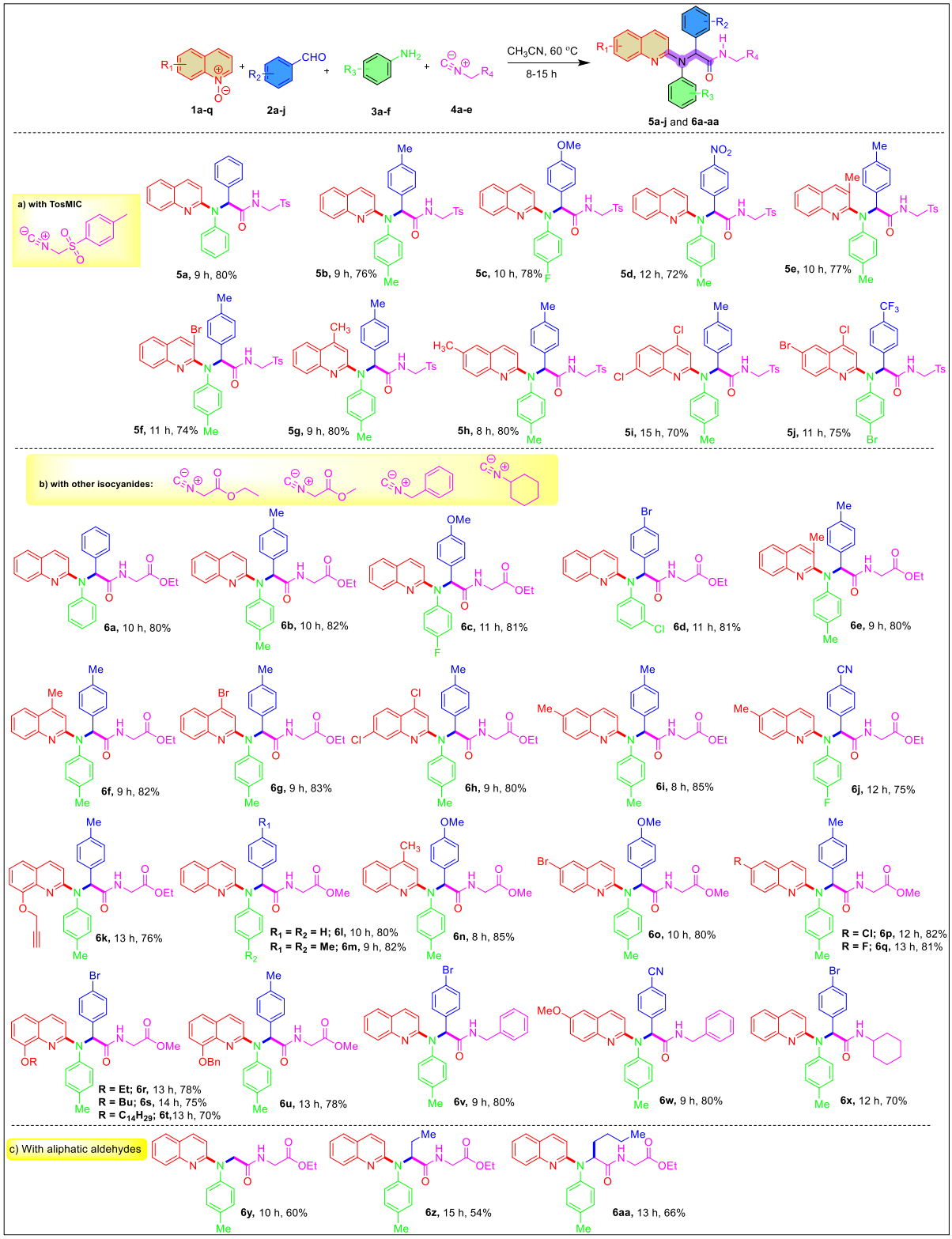
Section-A

N-Oxide Induced Ugi Reaction: A Novel Synthesis of Quinoline-C2-Amino Amides *via* Deoxygenative C(sp^2)-H Functionalization

Recently, aromatic amine *N*-oxides has attracted considerable attention due to the ability of the *N*-oxide moiety to act as an *ortho*-directing group to control the regioselectivity of the C–H activation.[12] In particular, *N*-oxide directed C2-selective C–N bond formation has become thrust area due to the importance of the 2-amino quinolines in medicinal chemistry and pharmaceuticals.[13] In all the approaches, *N*-oxides are either reacting with the promoters or coordinating with the metals to activate the C2-position of the aromatic *N*-oxides. Thus, the activated C2-position and nucleophilicity of oxygen of *N*-oxide could be a promising candidature for single reactant replacement of Ugi to get the *N*-oxide mediated Ugi four-component reaction.

In continuation of our work on C2-H functionalization of the aromatic amine *N*-oxides using isocyanides,[14] herein we report a *N*-oxide induced Ugi reaction to access the library of 2-phenyl-2-(phenyl(quinoline-2-yl)amino)acetamide derivatives in one-pot reaction *via* C(sp^2)-H functionalization.

The optimized reaction conditions are as follows, an oven-dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate benzaldehyde (0.5 mmol, 1.0 equiv), aniline (0.5 mmol, 1.0 equiv), quinoline *N*-oxide (0.5 mmol, 1.0 equiv), and the isocyanide (0.5 mmol, 1.0 equiv) in CH_3CN (2 mL). The reaction mixture was stirred at 60 ^oC for 8-15 h to produce the corresponding products quinoline-C2-amino amides 5**a-j** and **6a-aa** in good to excellent yields (Scheme 3A).



Scheme 3A. Synthesis of quinoline-C2-amino amides

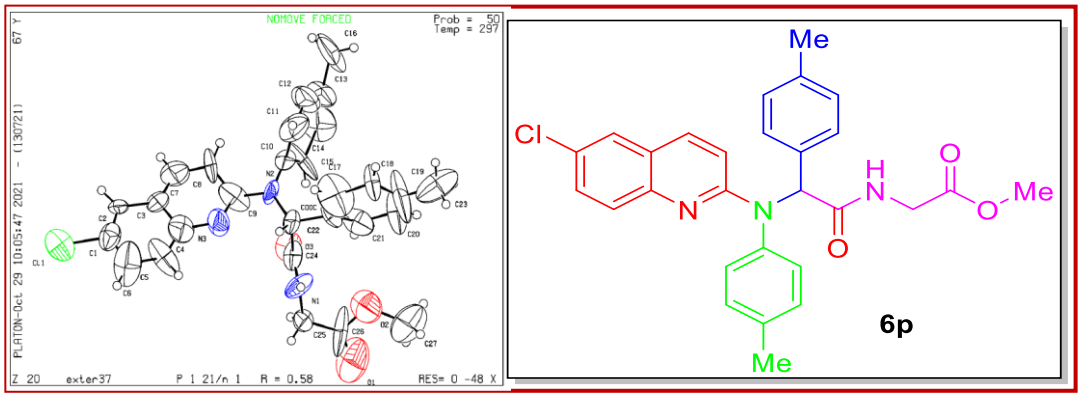


Figure 1: ORTEP diagram of **6p**

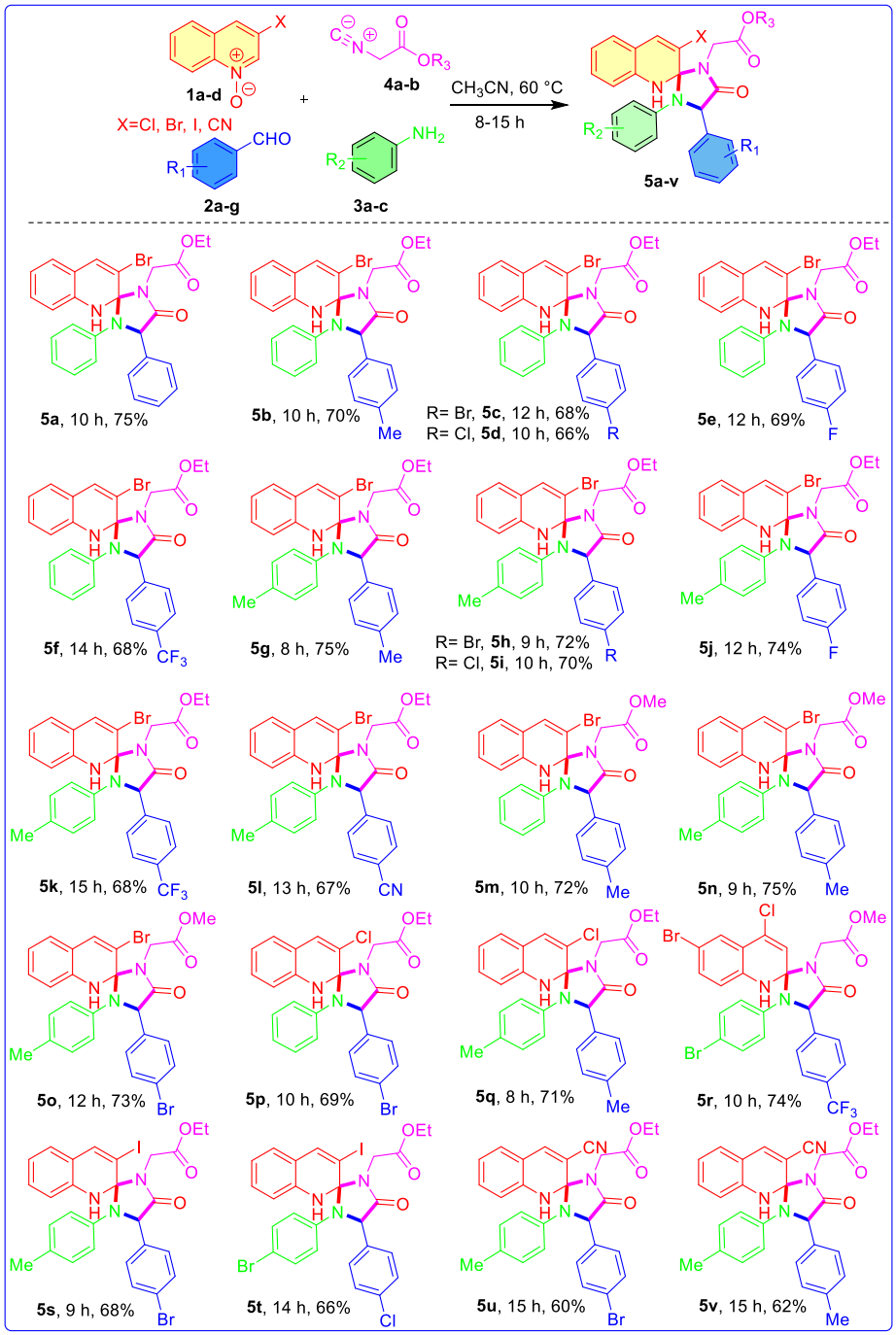
Chapter-III

Section-B

Effect of 3-Halo Quinoline *N*-oxides in Ugi Reaction: Direct Access to the 1*H*-Spiro[imidazolidine-2,2'-quinolin]-4-ones

Spiro[imidazolidine-2,2'-quinolin]-4-ones are privileged class of spirocyclic compounds, that have gained significant attention in medicinal chemistry and drug discovery as well as organic chemistry due to their inherent three dimensional and novel structures.[15] For example, spirocyclopropyloxindoles are known to show interesting biological activity, reflected by their role in natural products and pharmaceutical lead compounds.[16] some of the spiro compounds such as spironolactone[17] and griseofulvin.[18] are FDA approved drugs for anti-hypertensive and anti-fungal agents respectively. Considering the importance of such spiro compounds, we have developed one-pot method for C2-spiro quinolones *via N*-oxide mediated Ugi reaction.

The optimized reaction conditions are as follows, an oven-dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate benzaldehyde (0.5 mmol, 1.0 equiv), aniline (0.5 mmol, 1.0 equiv), 3-halo quinoline *N*-oxide (0.5 mmol, 1.0 equiv), and the isocyanide (0.5 mmol, 1.0 equiv) in CH_3CN (2 mL). The reaction mixture was stirred at 60 °C for 8-15 h to produce the corresponding spiro products **5a-r** with various isocyanides (Scheme 3B).



Scheme 3B. Synthesis of 1*H*-spiro[imidazolidine-2,2'-quinolin]-4-ones

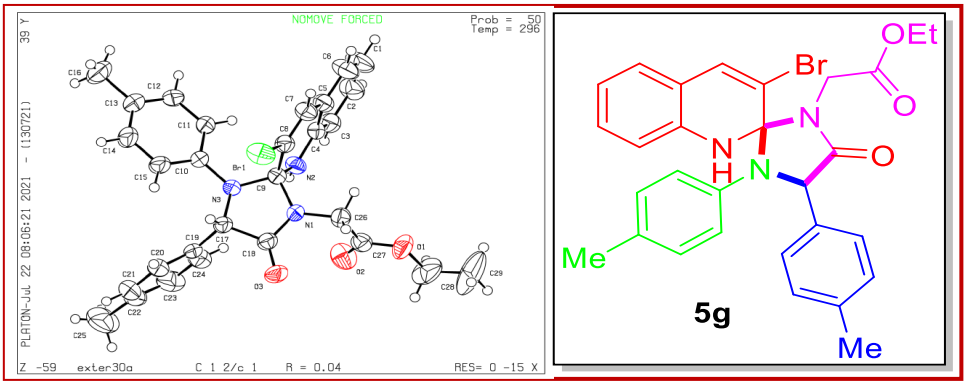


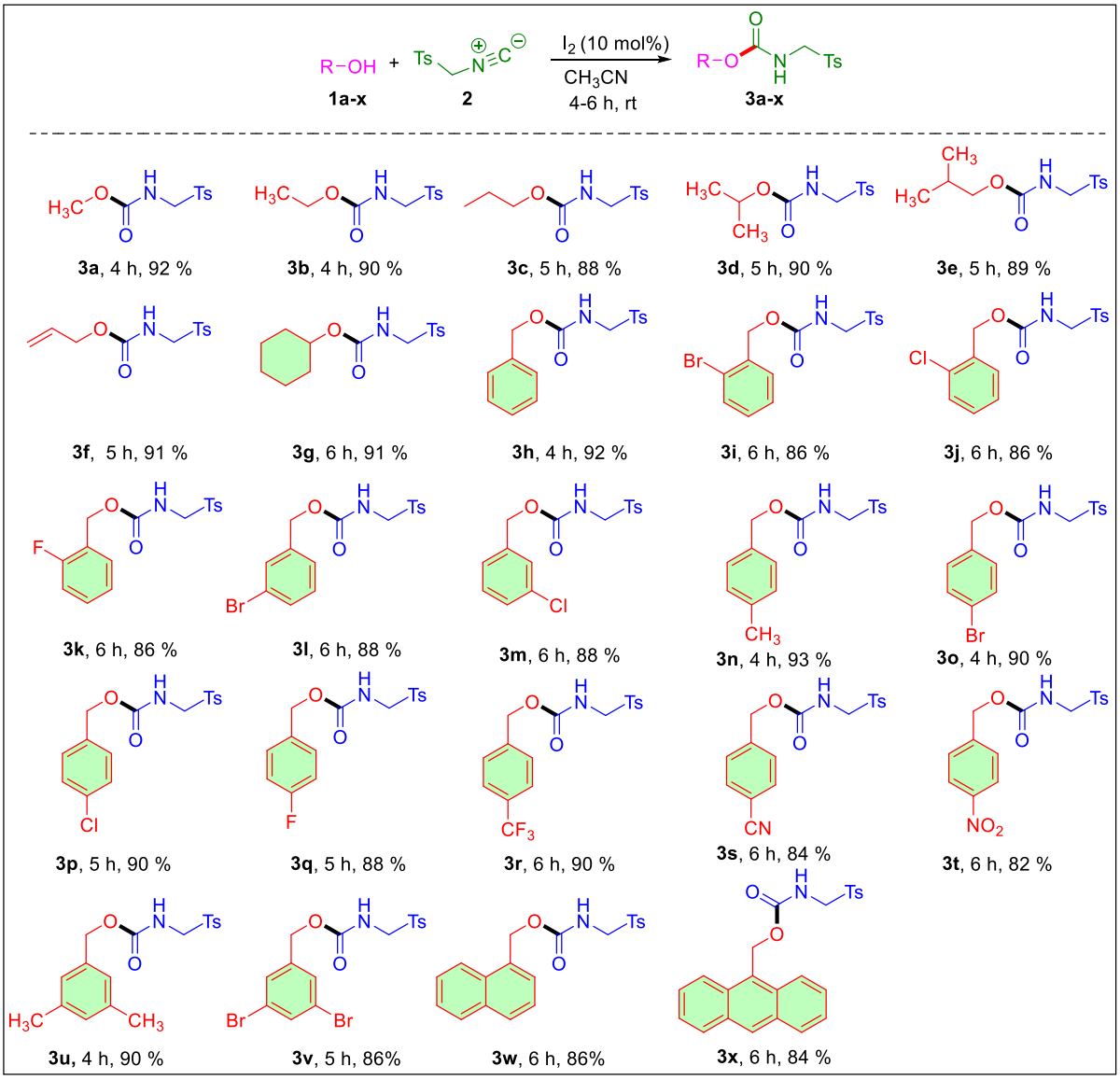
Figure 1: ORTEP diagram of **5g**

Here we have synthesized 18 compounds with moderate to good yields by using present protocol.

Chapter-IV

Iodide-Catalyzed One-Pot Synthesis of Carbamates Using Alcohols and Isocyanides

Carbamates are important synthons with wide applications in organic chemistry, medicinal chemistry, and polymer chemistry.[19] The classical approaches to carbamates includes i) condensation of aniline with phosgene and its derivatives ii) reaction of alcohol with isocyanates generated *in situ via* Hofmann, Curtius, Lossen, and Schmidt rearrangement reactions.[20]



Scheme 4. Synthesis of carbamates from alcohols and TosMIC.

However, these reactions are suffering from the high reactivity, toxicity and use of metal catalysts. Owing to their significance, there is a growing interest in the development of new efficient methods for the synthesis of carbamates. Thus, alternative routes to carbamates employing CO_2 have been established.[21] Even though, the replacement of phosgene with CO_2 has emerged as a significant improvement, the requirement of harsh reaction conditions is the major drawback of this method. Thus, the development of a general and practical method for easy access to carbamates is highly desirable. In continuation to our work on isocyanides, herein we have developed an iodine-catalyzed synthesis of carbamates from the corresponding alcohols and TosMIC.

The optimized reaction conditions are as follows, appropriate alcohols (0.5 mmol), TosMIC (0.5 mmol) in presence of 10 mol% of iodine in CH_3CN was stirred at room temperature for 4-6 h to produce corresponding products of **3a-x** up to 90% yield (Scheme 4).

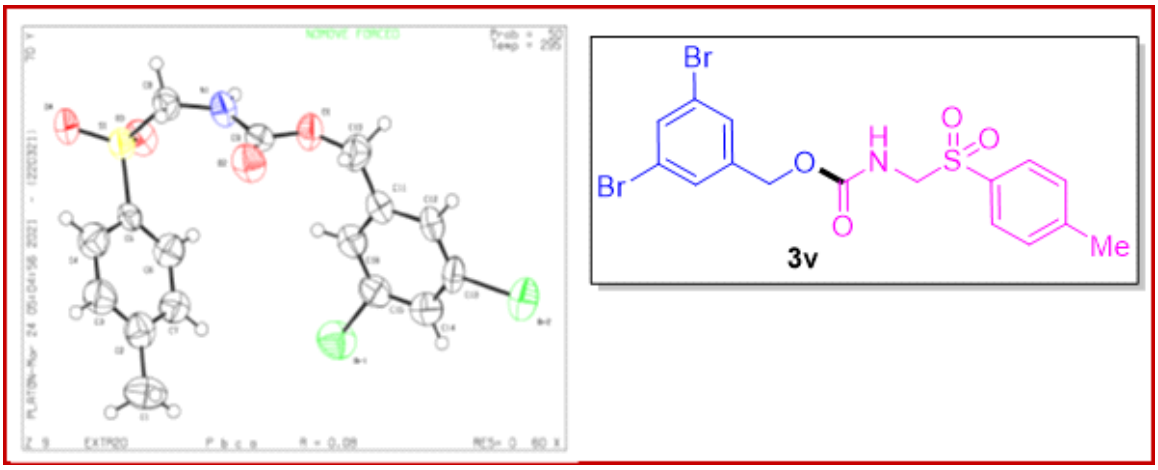
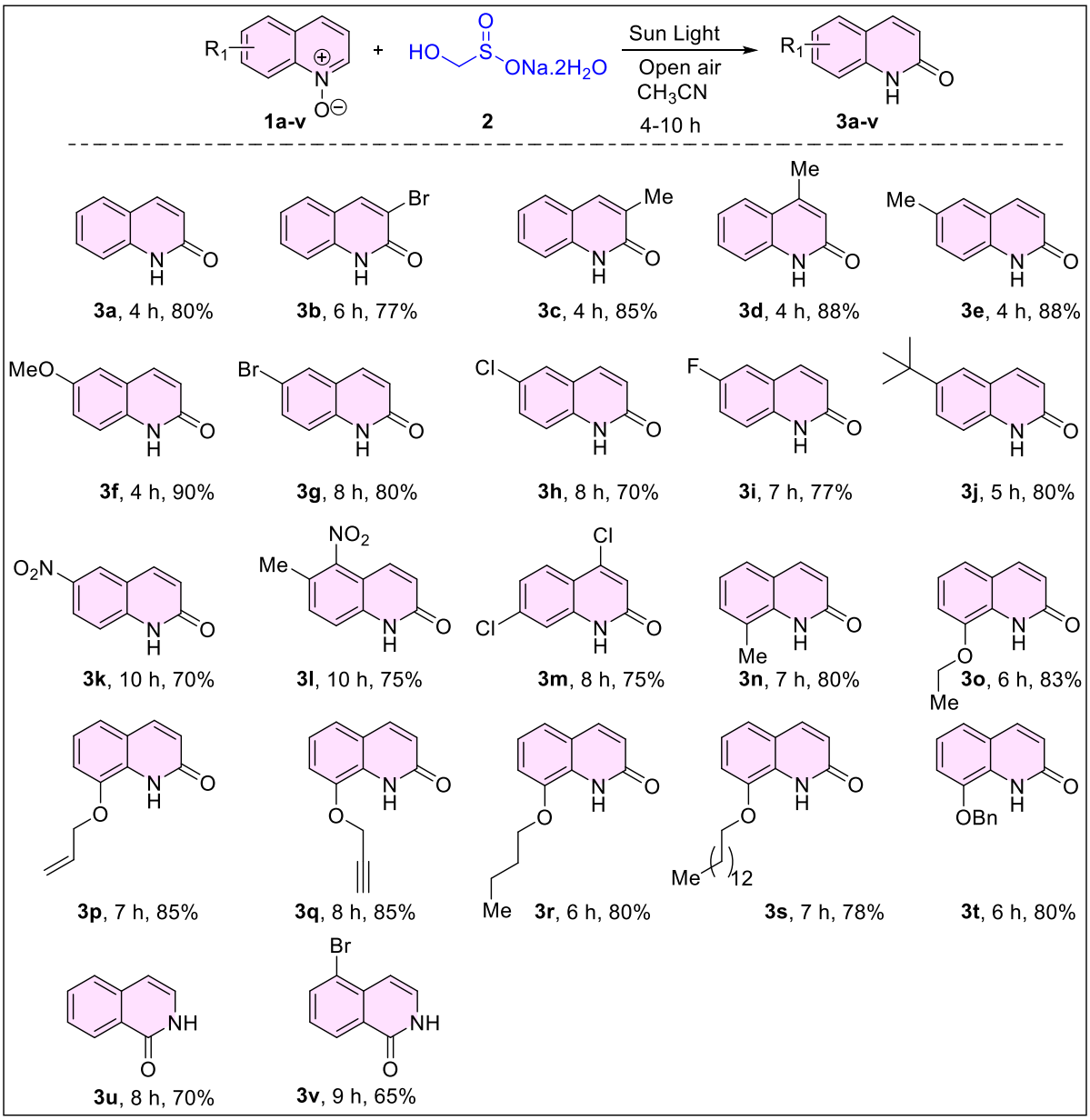


Figure 1: ORTEP diagram of **3v**

Chapter-V

Efficient Sunlight Mediated Synthesis of Quinoline-2(1*H*)-ones from Quinoline *N*-oxides Using Rongalite

Quinolin-2(1*H*)-ones represent an important family of heterocycles that exist in a range of natural products and pharmaceutically active compounds.[22] Due to their important applications in synthetic and pharmaceutical chemistry, several efficient methods have been developed for the construction of this useful structure.[23] Among them, the Reissert-Henze type reactions were the most commonly used method for the synthesis of quinoline-2(1*H*)-ones.[24] Usually, quinoline *N*-oxide is treated with an activating agent such as acyl chloride or sulfonyl chloride in the presence of nucleophiles.



Scheme 5. Quinolin-2(1*H*)-ones by using rongalite.

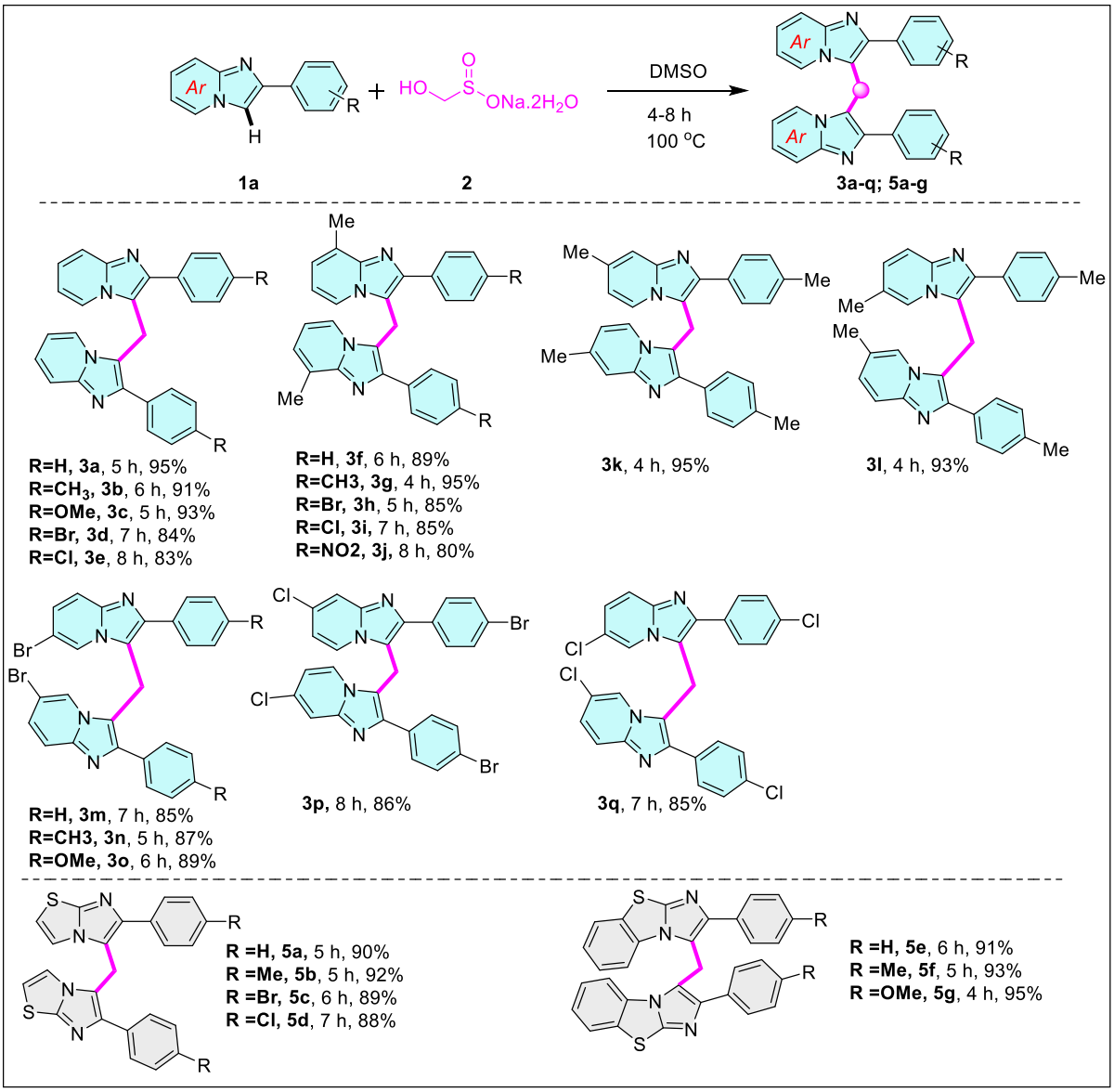
Recently, Wang and Yu developed an efficient procedural employing PyBroP as the activating agent.[25] He and co-workers reported a base-free route to quinoline-2(1*H*)-ones in aqueous media. Thus, we have developed an efficient method for the synthesis of quinoline-2(1*H*)-ones employing rongalite under sunlight.

The optimized reaction conditions are as follows, to a 10 mL round bottom flask, quinoline *N*-oxides (0.5 mmol), rongalite (20 mol%) in CH_3CN (2 mL). The reaction mixture was stirred under sunlight for 4-10 h to produce corresponding quinolin-2(1*H*)-ones **3a-v** up to 65-90% yield (Scheme 5).

Chapter-VI

Transition Metal-Free C(sp^2)-H Methylenation of Imidazo[1,2-*a*]pyridines, Indoles by Rongalite: A Rapid Access to Bis(aryl)methanes

Imidazo[1,2-*a*]pyridines are important heterocyclic compounds and are known for their wide range of biological activities and are building blocks in drugs such as zolpidem , olprinone, zolimidine and show some pharmacological activities like being antibacterial, antiviral, antifungal, anti-inflammatory, analgesic and aromatise-inhibitors.



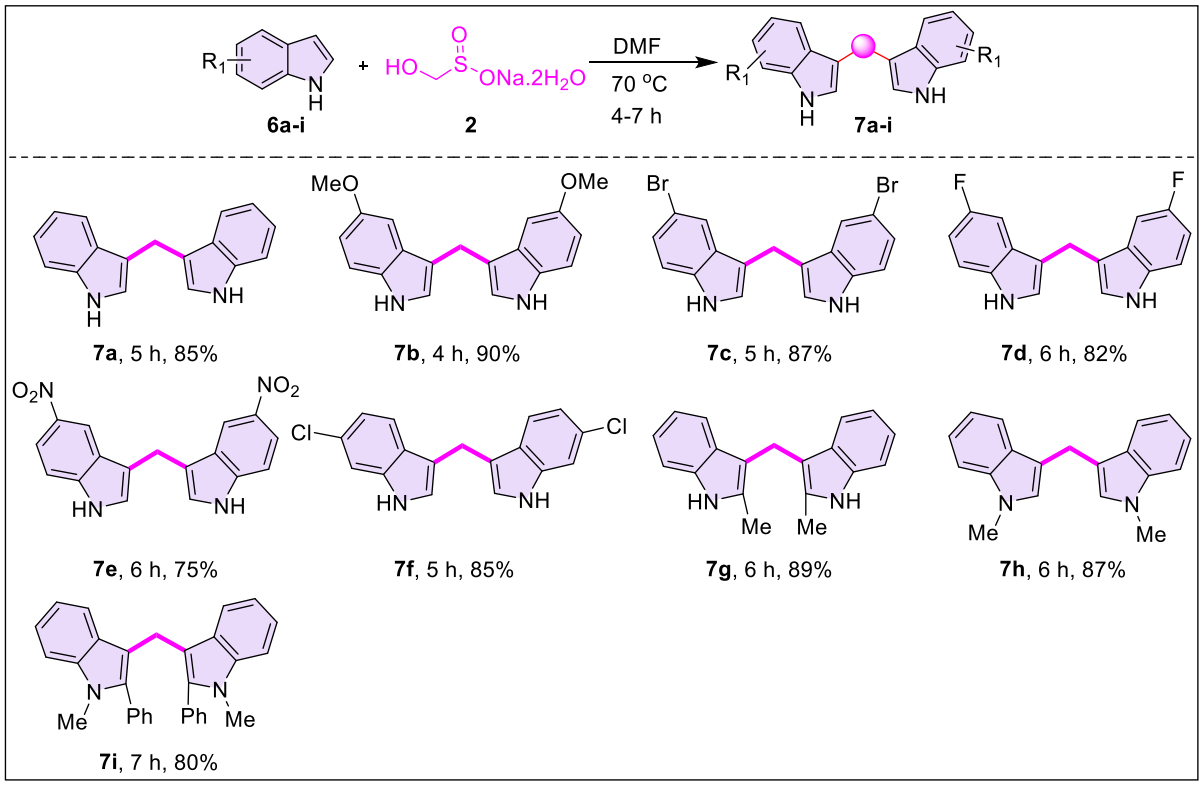
Scheme 6.1. Bis(imidazo[1,2-*a*]pyridin-3-yl)methanes and bis(imidazo[2,1-*b*]thiazole by using rongalite.

Alteration in the structural component leads to change in the activity of the compound. The hybrid molecules of imidazo[1,2-*a*]pyridine and rongalite are key pharmacophores in various drugs and are biologically important molecules because of their significance in the fields of agrochemicals and medicine.

There are few efficient methods that have been reported for the methylene linkage at the C-3 position of fused heterocycles.[26] These methods employ dimethylacetamide (DMA),[27] dimethyl formamide (DMF)[28] or dimethylsulfoxide (DMSO)[29] as methylene source in presence of metal catalysts such as vanadium, copper, palladium. The major concerns about these reagents are carcinogenicity and their associated environmental hazards.

Considering the importance of imidazo[1,2-*a*]pyridine-ronglite hybrids, we have developed one-pot two component reaction using active C(sp^2)-H containing molecules and rongalite in DMSO to produce the desired compounds. The key step in this reaction is *in situ* generation of formaldehyde from rongalite.

The optimized reaction conditions are as follows, to an equimolar solution of imidazopyridines (1 mmol) and rongalite (1 mmol) in DMSO solvent, the reaction mixture was stirred at 100 ^oC for 4-8 h to produce the desired products **3a-q** up to 95% yields (Scheme 6.1). Further, we have extended the optimized protocol of methylenation by rongalite in the presence of the various 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole to obtain 5**a-g** (Scheme 6.1).



Scheme 6.2. Synthesis of 3,3'-bisindolylmethanes by using rongalite

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APPENDICES

List of Publications

Published

1. Iodine Catalyzed C2-H Formamidation of Quinoline *N*-oxides using Isocyanides: A Metal-Free Approach

   Naveeenkumar Anugu, Sanjeeva Thunga, Sivaparwathi Golla and Hari Prasad Kokatla. *Adv. Synth. Catal.* **2022**, *364*, 149-157.

2. *N*-Oxide Induced Ugi Reaction: A Rapid Access to Quinoline-C2-Amino Amides *via* Deoxygenative C(sp^2)-H Functionalization.

   Naveeenkumar Anugu, Sanjeeva Thunga, Soumya Poshala and Hari Prasad Kokatla. *J. Org. Chem.* **2022**, *87*, 10435-10440.

3. Rongalite-induced transition-metal and hydride-free reductive aldol reaction: a rapid access to 3,3′-disubstituted oxindoles and its mechanistic studies.

   Sivaparwathi Golla, **Naveenkumar Anugu**, Swathi Jalagam and Hari Prasad Kokatla. *Org. Biomol. Chem.* **2022**, *20*, 808-816.

4. An efficient Pd(II)-(2-aminonicotinaldehyde) complex as complementary catalyst for the Suzuki-Miyaura coupling in water.

   Sanjeeva Thunga, Soumya Poshala, **Naveenkumar Anugu,** Ramaiah Konakanchi, Satheesh Vanaparthi and Hari Prasad Kokatla, *Tetrahedron Lett*. **2019**, *60*, 2046–2048.

Manuscripts under preparation

5. Fe-Catalyzed Deoxygenative C2-Formamidation Reaction of Quinoline *N*-Oxides with Isocyanides.

   Naveenkumar Anugu, Hari Prasad Kokatla

6. Effect of 3-Halo Quinoline *N*-oxides in Ugi Reaction: Direct Access to the 1*H*-Spiro[imidazolidine-2,2'quinolin]-4-one.

   Naveenkumar Anugu, Hari Prasad Kokatla

7. Iodide-Catalyzed One-Pot Synthesis of Carbamates Using Alcohols and Isocyanides

   Naveenkumar Anugu, Hari Prasad Kokatla

8. Efficient Sunlight Mediated Synthesis of Quinolin-2(1*H*)-ones from Quinoline *N*-oxides Using Rongalite.

Naveenkumar Anugu, Hari Prasad Kokatla

9. Transition Metal-Free C(sp^2)-H Methylenation of Imidazo[1,2-*a*]pyridines, Indoles by Rongalite: Direct Access to Bis(aryl)methanes.
   Naveenkumar Anugu, Hari Prasad Kokatla

PAPERS PRESENTED IN INTERNATIONAL AND NATIONAL CONFERENCES

International

1. **International conference on "Advances in Chemical Sciences and Technologies-2019" (ACST-2019).** During 23-25, September 2019. Organized by Department of Chemistry, National Institute of Technology. Warangal, Telangana.

2. **International conference on "Advanced Functional Materials (ICFAM-2017)**" During 18-20, December 2017. Organized by Department of Chemistry, RGUKT, Basar, Nirmal, Telangana.

National

1. **Online Faculty Development Programme on "Teaching and Learning of NMR Spectroscopy for Structure Determination"** organized by Department of Chemistry in association with Teaching Learning Centre, National Institute of Technology Warangal, during 19-24 February 2021.

2. **National conference on "Emerging Trends in Instrumental Methods of Chemical Analysis"** organized by Department of Chemistry, National Institute of Technology, Warangal, held on 30-31 January, 2019.

3. **Teaching and Learning of "Green Chemistry: Nurturing a New Generation of Chemists"** Organized by Department of Chemistry, National Institute of Technology, Warangal, during 26th Feb-3rd March-2021.

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Mr. Naveenkumar Anugu was born in Baswannapally, Kamareddy district of Telangana State, India. He has completed his secondary school education (Z. P. H. S High School) in Baswannapally and intermediate (Sandeepani Junior College) in Kamareddy. After completion of his B.Sc. (Ramakrishna Degree College, Kamareddy), and M.Sc. (Organic Chemistry) from Osmania University, he has joined the Ph.D., programme under the guidance of Dr. K. Hari Prasad (Associate Professor), Department of Chemistry, National Institute of Technology Warangal with the financial assistance from the DST-INSPIRE (**DST/INSPIRE/04/2014/002550)** in December 2016. He has published four research articles in peer reviewed international journals and presented papers in four national/international conferences. His research interest lies in the synthesis of bio-active molecules by employing efficient and greener methodologies.