Selective C-H and C-C Bond Functionalization of Benzo-Fused N-Heteroaromatic Compounds

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Doctor of Philosophy

Submitted by

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Dedicated to

My family

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STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Selective C-H and C-C Bond Functionalization of Benzo-Fused N-Heteroaromatic Compounds***" is the outcome of the research work carried out by me under the supervision of **Dr. Animesh Das, Department of Chemistry, Indian Institute of Technology Guwahati, India**, for the award of the degree of Doctor of Philosophy.

In harmony with the general practice of reporting scientific observations, due acknowledgements have been made if the work is established on the findings of other investigators.

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Selective C-H and C-C Bond Functionalization of Benzo-Fused N-Heteroaromatic Compounds***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by **Mr. Bikash Kumar Sarmah** (Roll No: 166122031) was carried out by him under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati ***Dr. Animesh Das***
April, 2022

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Bikash Kumar Sarmah

List of abbreviations

Ac	Acetyl
α	Alpha
Å	Angstrom
Ar	Argon
ACN	Acetonitrile
br.	Broad
bi pyridine	2,2′-bipyridine
β	Beta
Bn	Benzyl
Bu	Butyl
CCDC	Cambridge crystallographic data centre
$CDCl_3$	Chloroform-*d*
COSY	Correlated spectroscopy
Cy	Cyclohexyl
Cat	Catalyst
ºC	Degree Celsius
d	Doublet or day
dd	Doublet of doublet
δ	Chemical shift or delta
DA	Donor-acceptor
DCE	Dichloroethane
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarisation transfer
DFT	Density functional theory
DMSO	Dimethylsulfoxide
DMF	Dimethylformamide
EtOAc	Ethyl acetate
equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group

EDG	Electron donating group
g	Grams
GC-MS	Gas chromatography mass spectrometry
γ	Gamma
h	Hours
HRMS	High resolution mass spectrometry
Hz	Hertz
MHz	Mega Hertz
i	Iso
FT-IR	Fourier transform infrared spectroscopy
J	Coupling constant
m	Multiplet
m	Meta
Me	Methyl
min	Minute
mg	Milligram
mL	Millilitre
mmol	Millimole
Mp	Melting point
MS	Molecular seive
NMR	Nuclear magnetic resonance
Ts	Tosylate
o	Ortho
ω	Omega
ORTEP	Oak ridge thermal ellipsoid plot program
p	Para
Ph	Phenyl
Py	Pyridine
Pr	propyl
ppm	Parts per million
q	Quartet
rt	Room temperature
s	Singlet

THF	Tetrahydrofuran
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
t	Tert
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TS	Transition state
XRD	X-ray diffraction

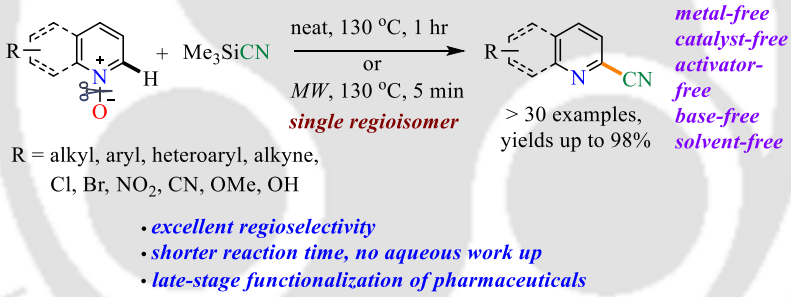
Abstract

The present thesis, entitled "***Selective C-H and C-C Bond Functionalization of Benzo-Fused N-Heteroaromatic Compounds***" is divided into five chapters based on the results obtained from the experimental works during the course of PhD research period.

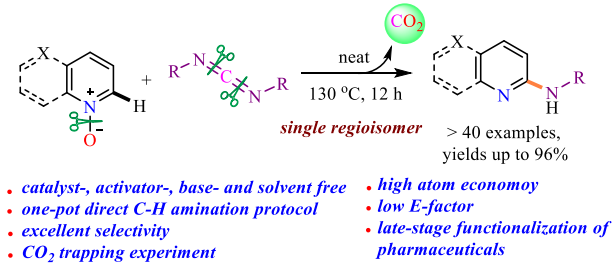
Chapter-1 includes a brief introduction about the importance of C-H activation process for *N*-heterocyclic compounds, the problems associated with the classical processes and a short account of the literature reports for C-H activation involving *N*-oxide chemistry to solve the above shortcomings by both conventional and green chemistry protocols.

Each of the following chapters contains an introduction, previous literature reports, present results and discussion, experimental section and references. The spectral data for the newly synthesized molecules are provided in the **Annexure I-IV**.

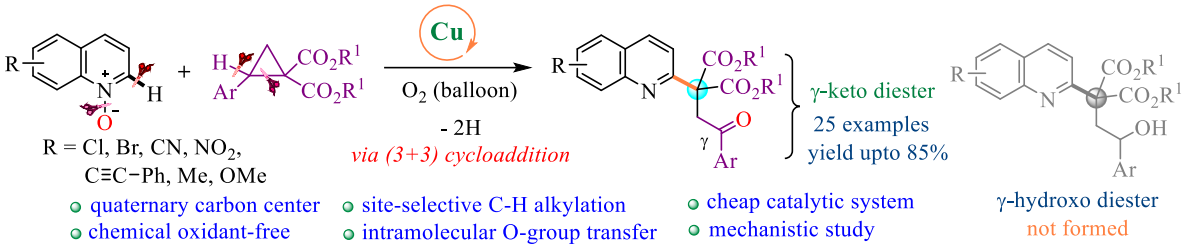
Chapter 2 reports the regioselective deoxygenative C2-cyanation of quinoline *N*-oxides with trimethylsilyl cyanide (TMSCN) under a completely metal-, activator-, catalyst- and solvent-free condition using both conventional heating and microwave irradiation methods. The reaction is both regio- and chemoselective and the mechanistic investigations revealed the dual role of TMSCN as the cyanation agent as well as an activator. Late-stage cyanation of bio-active molecules quinine and (±)-*α*-tocopherol modified quinoline derivative is also demonstrated. Notably, the product gets sublimated during the reaction and thus, can be easily isolated, avoiding any aqueous work-up.



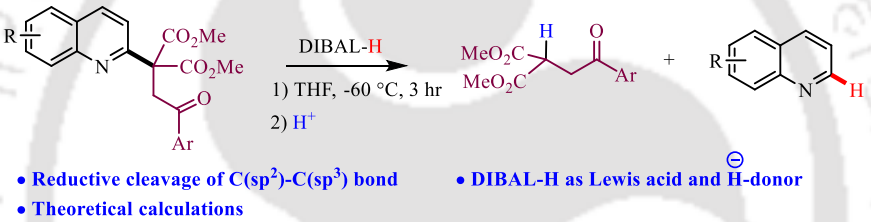
Chapter 3 describes the regioselective deoxygenative C2-amination of quinoline *N*-oxides with carbodiimides under completely metal-, activator- and catalyst-free conditions to give both aryl- and alkylaminated quinolines. The protocol supports a wide range of functional groups and bulky arylamino groups also can be introduced under the reaction conditions. The protocol can be extended to late-stage amination of bio-active molecules like anti-malarial drug quinine, tryptamine, and (±)-α-tocopherol modified quinolines effectively. It also includes the possible mechanistic pathway derived from both experimental works and theoretical calculations. The present protocol displays impressive figures for different green matrix parameters and produces only CO_2 as a co-product, which could be trapped easily.



Chapter 4 reports the copper-catalysed deoxygenative alkylation of quinoline *N*-oxides with donor-acceptor cyclopropanes to introduce a tertiary alkyl motif at the C2-position of quinoline. This work uses molecular oxygen as a benign oxidant and supports a range of functional groups. The mechanistic pathway has been investigated using both experimental and theoretical calculations which shows the involvement of a possible radical pathway.



Chapter 5 demonstrates DIBAL-H mediated reductive cleavage of $C(sp^3)$-$C(sp^2)$ bond in *N*-heteroaryl *γ*-ketodiester compounds to give biologically relevant *β*-ketodiester motifs. DIBAL-H works both as a Lewis acid and a hydride donor. Theoretical calculations have been performed to investigate the possible mechanistic pathway which shows that 2 equivalents of DIBAL-H are required for one equivalent of the *N*-heteroarene compound.



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Chapter 1

General Introduction

1.1. Six-membered *N*-Heteroaromatic compounds

Six membered heteroaromatic compounds are of paramount importance in synthetic organic chemistry, forming a family with the largest and most varied members. The word 'hetero' has come from the Greek word 'heteros', meaning 'different'. Heteroaromatic compounds refer to those aromatic compounds where one of the methine (-CH=) groups is replaced with a different atom like nitrogen, oxygen, sulfur etc. Among these compounds, nitrogen containing heteroaryl compounds have been the most explored ones, given its widespread presence in biological and material sciences.[1] These heteroaryl compounds could be standalone ones or remain fused with other aromatic rings. Pyridine and quinoline are the basic and most studied six-membered molecules from the above two classes of *N*-heteroaromatic compounds. These molecules with a six-membered heteroaromatic ring containing nitrogen are also known as azines. Quinoline consists of a benzene ring fused to the α- and β- positions of a pyridine ring. In 1834, a German chemist Friedlieb Ferdinand Runge isolated quinoline for the first time from coal tar which still remains the chief source of commercial quinoline.[2a] Then in 1842, Gerhardt described the formation of quinoline by vigorous distillation under alkaline condition from the natural alkaloids chinconine and quinine.[2b] Author also named this species as quinoleine as a derivative to the word quinine, to be renamed as quinoline by Berzelius later. Quinoline occurs in coal-tar, bone oil, and in angosturabark.

1.2. Biological importance of six-membered *N*-heteroarenes

Quinoline and its derivatives form a highly privileged class of organic compounds in terms of medicinal and biological importance. Quinoline nucleus forms the core of a large number of anti-malarial and anti-microbial drugs (figure 1.1). In fact, Quinine and its diastereomer quinidine were some of the oldest drugs which have been used for treatment of malaria since more than 200 years.[3a] Chloroquine and Mefloquine are two other examples of anti-malarial drugs possessing the quinoline core. To remove the blood flukes (*Schistosoma mansoni*), Oxamniquine is a common drug used in the tropical regions.[3b] The alkaloids Cusparine, Galipine and various other quinoline alkaloids isolated from the bark of *Galipea longiflora* trees are found to treat leishmaniasis, a South American tropical disease.[3c] PBT2 has been found to be effective against Alzheimer's disease and also as an antibacterial agent[3d], while Topotecan has found application in lung cancer treatment[3e]. Chlorquinaldol is commonly used as antimicrobial agent and an internal antiseptic.[3f] Likewise, the 2-aminoquinoline derivative quipazine is employed as a potential antidepressing agent[3g]. In fact, 2-aminoquinoline, found in the mushroom *Leucopaxillus albissimus*, itself possesses an array of biological properties like antibacterial, antitumor, protease inhibitory and mutagenic activities etc. In addition, these 2-aminoquinoline derivatives also exhibit anticancer, antihypertensive and anthelmintic activities.[3h] 2-methylpyridyl based drug etoricoxib is an anti-arthritis drug which is also used to relieve post-surgical dental pain.[3i] Pentoprazole is another very common pyridine-based drug used for treatment of stomach ulcers.[3j] Likewise, isoquinoline, quinoxaline and other fused-azines based compounds also possess diverse bio-activities like anti-malarial, pigmentation etc.[1] Apart from the biological applications, these moieties also find usefulness in industrial applications as dyes, luminescent materials etc.[4]

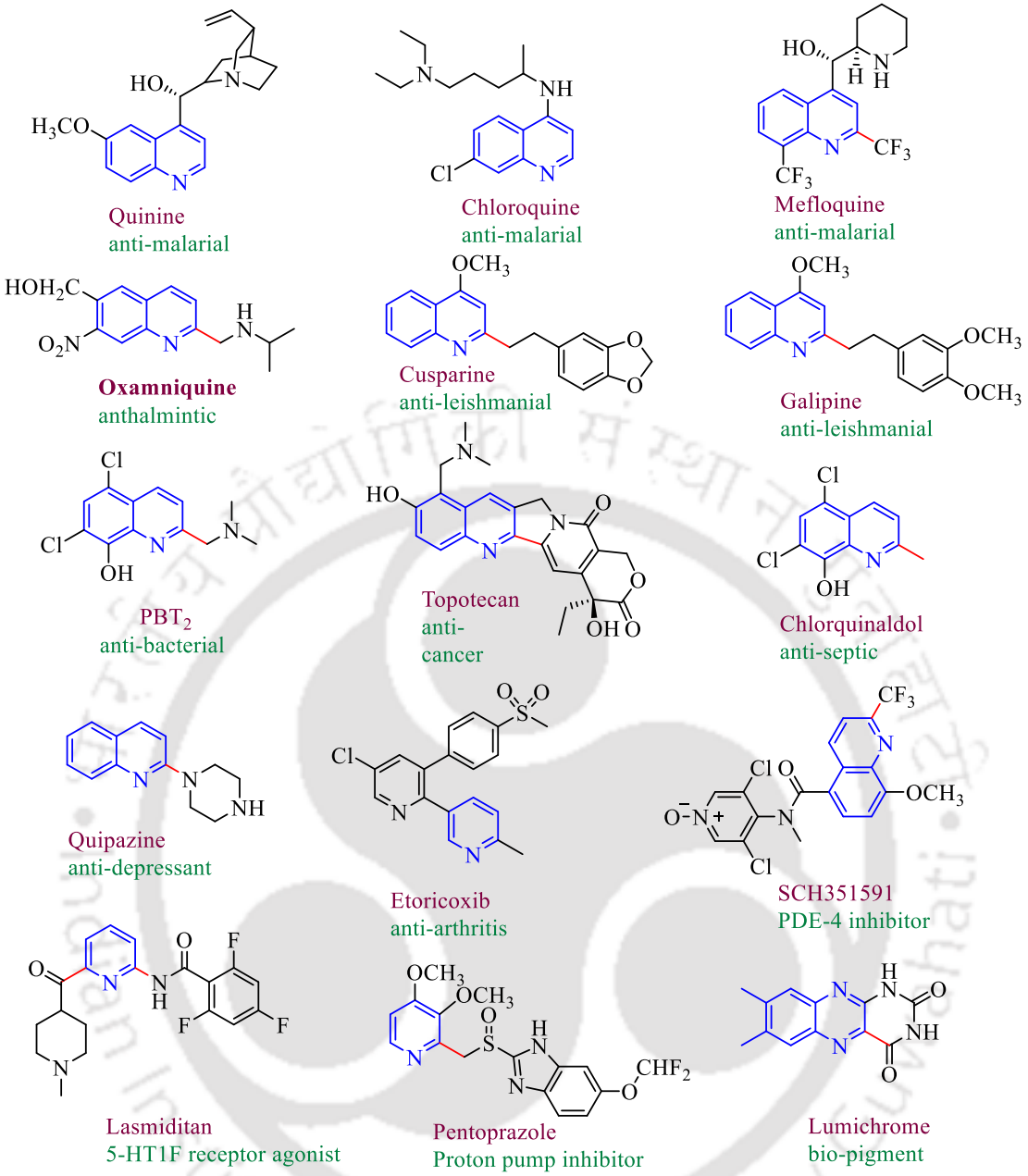


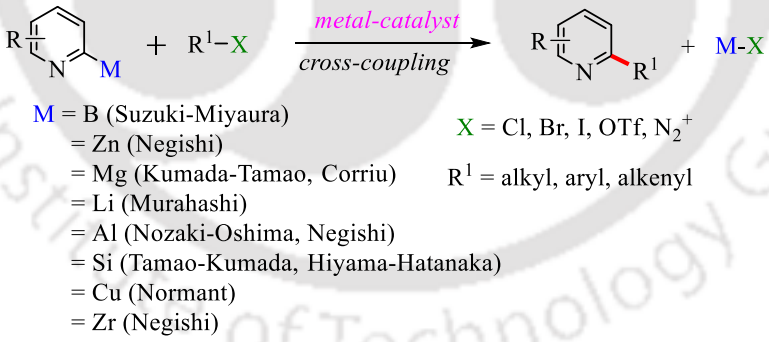
Figure 1.1: bio-active molecules containing *N*-heteroarenes

From the above representative examples, it is evident that a significant volume among this large pool of bioactive *N*-heteroaromatics consists of C2-functionalised derivatives of quinoline. Moreover, it has been found that the therapeutic effect of the quinoline moiety often gets detoxified in the body by hydroxylation at the C2-position.[5] Blocking the C2-position by introducing different functional groups has been found to be the suitable alternative to prevent this detoxification and thus, various synthetic strategies have been explored in recent literature. However, the conventional cyclocondensation reaction, or cyclisation reactions for azine synthesis, such as Skraup synthesis, Doebner-Miller synthesis, Knorr synthesis, Friedlender synthesis etc. have several drawbacks.[6] They often required harsh reaction conditions, long reaction times, and displayed limited substrate scope as well as poor functional group tolerance. Use of hazardous solvents and low yields of the products were some other notable drawbacks of these protocols. Therefore, the search for an efficient and operationally simple protocol for

synthesis of C2-functionalised azines is always in demand. In this context, the discovery of direct C-H functionalization has been a major advancement in recent literature.

1.2.1. Cross-coupling reactions

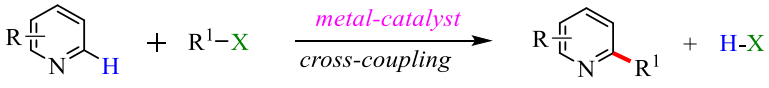
Instead of introducing the desired functional groups during the synthesizing step, functionalization at a later stage was found to be more effective for substrate diversification from a parent scaffold.[7] These molecular transformations primarily involve modifications of pre-existing functional groups on the *N*-heteroaromatic scaffolds. Among such transformations, palladium-catalysed cross-coupling reactions between organometallic nucleophiles such as Grignard reagents and organohalides/pseudo halide electrophiles have been used extensively in both academic and industrial scales.[8] Different varieties of such reactions were discovered and developed further by Suzuki, Sonogashira, Heck, Negishi, Stille etc. to instill better selectivity (scheme 1.1).[9] These protocols were successful in efficiently constructing C-C bonds as well as C-X (X = N, O) bonds, e.g., Buchwald-Hartwig amination reaction[10]. In addition, ease of product isolation, functional group compatibility and applicability in industrial scale for natural product synthesis have been other notable advantages of palladium-catalysed cross-coupling reactions. Despite of such achievements, these cross-coupling reactions still suffer from some serious limitations. In general, these cross-coupling reactions occur between two coupling partners, where, one component is organohalide (or analogous compound such as organotriflate or diazo compound) and another is a transmetallic agent (such as HetAr-M (M = B, Si, Al, Mg, Li etc.). These precursors are primarily synthesized through multiple steps under harsh reaction conditions and often the inherent instability of the 2-pyridylorganometallics further makes them inappropriate to use in cross-coupling reactions.[11,12] Moreover, functionalization of C(sp^3)-X often resulted in undesired *β*-hydride elimination products. Generation of stoichiometric amount of halogenated waste is another aspect of such reactions which makes a negative impact on the environment.



Scheme 1.1: cross-coupling reactions with pre-functionalised *N*-heteroarene systems

1.2.2. Direct C-H functionalization reactions

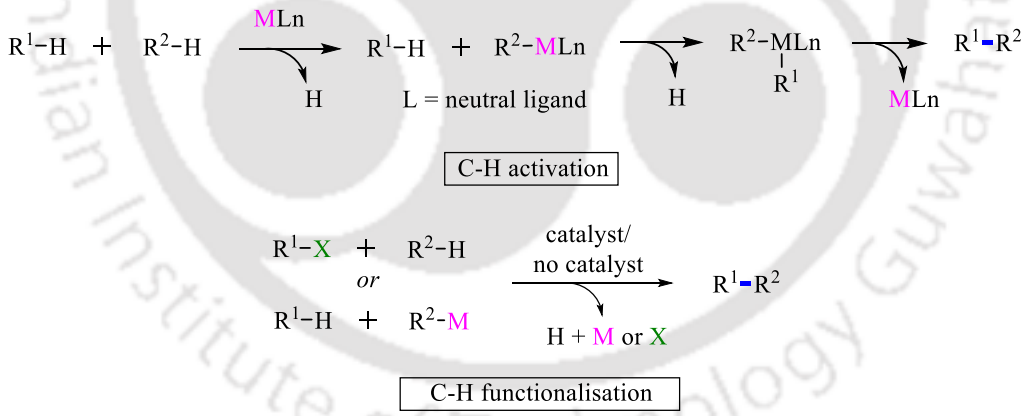
Cross-coupling reaction involving C-H bond (instead of organometallic nucleophiles) is an efficient and powerful approach which eliminates the need of pre-functionalization and avoids the generation of undesired synthetic waste (scheme 1.2). The process is becoming a promising



Scheme 1.2: direct C-H functionalization reactions

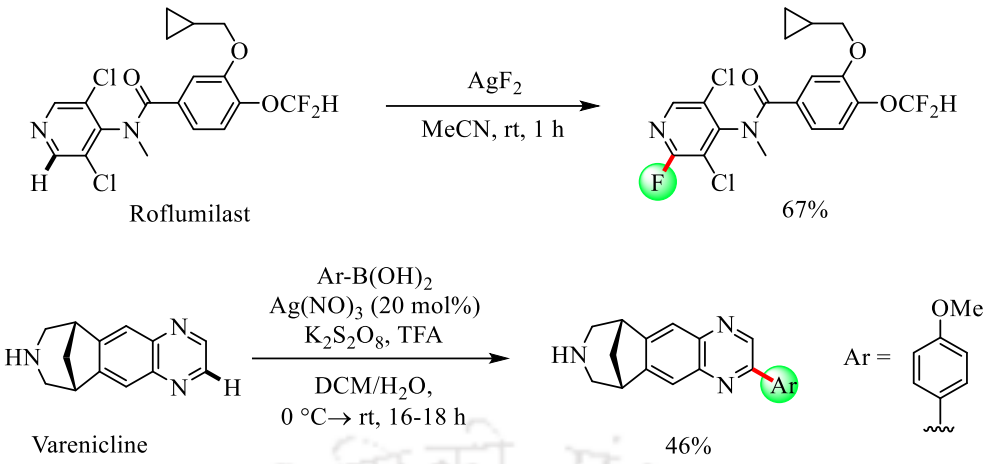
Synthetic tool towards synthesis of natural products, pharmaceutical drugs, other synthetics like optical materials and their late-stage modifications.[7b]

Carbon–hydrogen bond functionalization (C–H functionalization) is a type of reaction in which a carbon–hydrogen bond is cleaved and replaced with a carbon–X bond (where X is usually carbon, oxygen, or nitrogen).[13] The term usually implies that a transition metal is involved in the C-H cleavage process (scheme 1.3). Reactions classified by the term typically involve the formation of an organometallic complex in which the hydrocarbon is coordinated to the inner-sphere of a metal, either *via* an intermediate "alkane or arene complex" or a transition state leading to a "M−C" intermediate. This intermediate from the first step (known as C–H activation and sometimes used interchangeably with C-H functionalization) can then undergo subsequent reactions to produce the functionalized product.[14] Although scientists originally observed such direct C-H activation processes in 1960s and 1970s in saturated hydrocarbons, but the real breakthrough was obtained when R. G. Bergman and W.A.G. Graham reported independently in 1982 that Cp*Ir complex could activate the C-H bond of simple and saturated hydrocarbons under photochemical conditions.[15] The reaction was reported to proceed *via* the insertion of a 16-electron iridium(I) intermediate to C-H bond of an alkane – the first direct observation of an oxidative addition. Then, C-H functionalization was widely explored in the aromatic compounds. Nature also offered C-H activation processes in various enzymatic reactions, such as, cytochrome P-450 and methane monooxygenase etc. Cytochrome P-450 converts C-H bonds to C-O bonds for preparation of steroids, cholesterol etc. whereas methane monooxygenase converts methane to methanol.[16] Additionally, C-H functionalization can also proceed in the absence of transition metal ions, where C-M bond is not involved, and proceeds *via* hydrogen atom transfers or radical processes.[13]



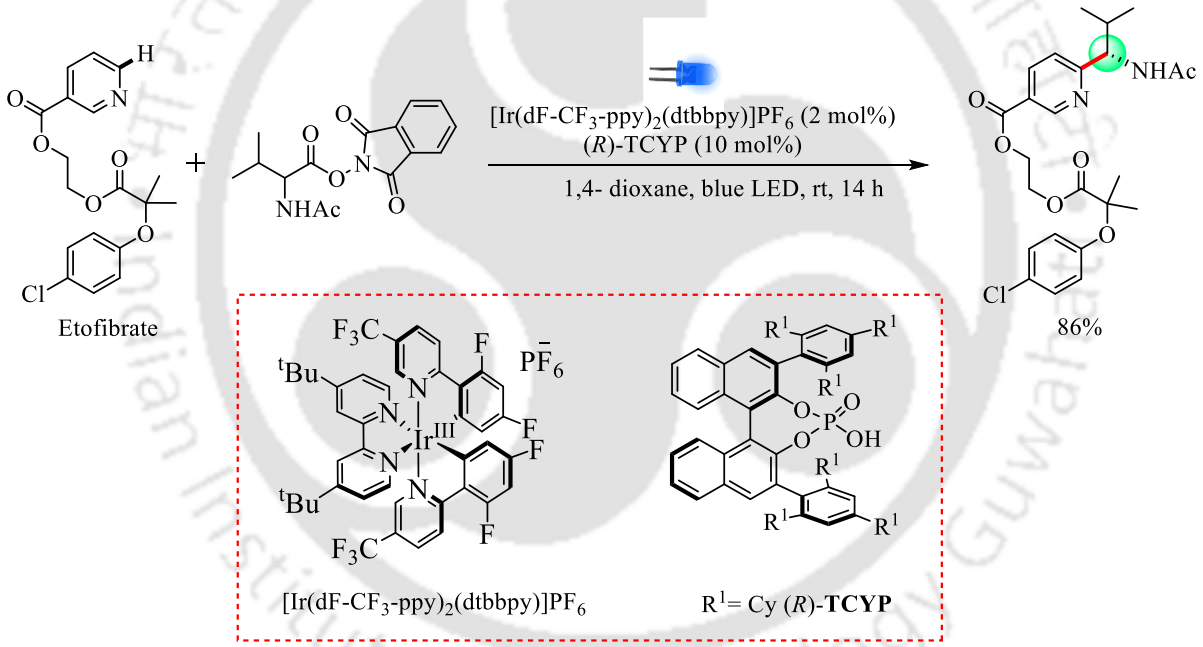
Scheme 1.3: C-H activation and C-H functionalization

Direct C-H functionalization reactions can allow access to variety of functional groups, such as halogen, hydroxyl, methyl, cyano, amino, aryl groups etc. effectively.[7a] These functionalities are not only useful in the synthetic perspective but also beneficial in the drug modifications. For instance, silver fluoride can act as an efficient fluorinating agent for the C2-fluorination of electron deficient pyridine containing drug roflumilast in a very regioselective way (scheme 1.4).[17] Similarly, arylboronic acids are very good radical precursors for direct C-H arylation of *N*-heterocycles and thus, was successfully employed for C2-arylation of the drug varenicline.[18]



Scheme 1.4: direct C-H functionalization reactions of rofluminast and varenicline

Another representative example reported by Phipps and co-workers involved the incorporation of *α*-aminoalkyl moiety to the drug etofibrate in a photoredox Minisci-type reaction catalyzed by Iridium with remarkable enatioselectivity and regioselectivity (scheme 1.5).[19]



Scheme 1.5: Ir-catalysed direct C-H alkylation of etofibrate

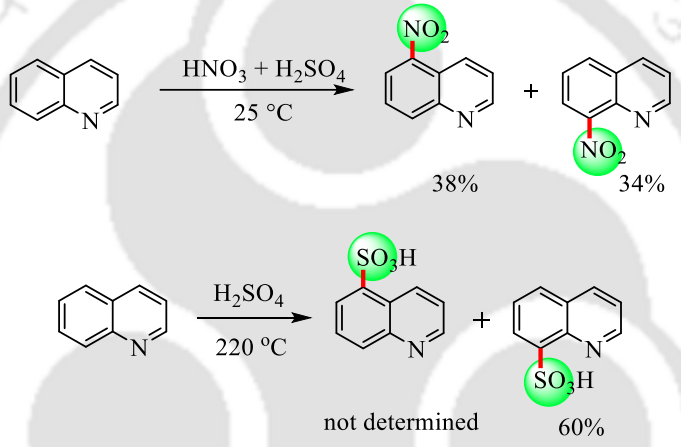
1.2.3. Synthetic challenges

Despite the widespread applications of C–H functionalization, it has one major challenge to overcome, i.e., to control the selectivity of the reaction due to the presence of multiple C-H bonds in a complex organic molecule with similar steric and electronic properties. Transition-metal-catalyzed directing groups (DGs) assisted C-H functionalization is one of the well-studied approaches to counter this problem, where the metal centers coordinate to a chelating side arm of the substrates and activate the proximal C-H bonds *via* cyclometallated intermediates, thereby, improving the regioselectivity of the transformations. But these DGs are not necessarily part of the final product with genuine application, and often require an additional step for disconnection. Alternatively, a transient directing group (TDG) strategy,

also known as traceless DG and temporary DG, has also been recently studied for a range of selective transition metal-catalyzed C─H bond functionalizations, where additional steps for installation and removal of covalently attached DGs can be avoided.[20]

1.3. Classical approach for C-H functionalization of quinolines

The chemistry of the quinoline ring can be considered as a combination of benzene and pyridine. Owing to the presence of the electronegative nitrogen atom in the core, it shows extremely low reactivity in aromatic electrophilic substitution (S_EAr) reactions such as nitration or sulfonation. These reactions often occur only under vigorous conditions and substitution happens in the benzene ring rather than the pyridyl ring.[21] Quinoline undergoes nitration with fuming nitric acid in the presence of fuming sulphuric acid to give a mixture of 8-nitroquinoline and 5-nitroquinoline. Similarly, quinoline may be sulphonated with fuming sulphuric acid at 220°C to yield a mixture of quinoline-8-sulphonic acid and quinoline-5-sulphonic acid (scheme 1.6). In addition, Friedel-Crafts reactions are also troublesome as the Lewis base quinoline can inactivate the Lewis acid, consequently suppressing the reactivity.



Scheme 1.6: electrophilic substitution reactions on quinoline

On the other hand, nucleophilic aromatic substitution (S_NAr) of quinolines takes place relatively easily.[21] This is again attributed to the electron deficiency incurred to the ring by the electron withdrawing N-atom. Various nucleophiles like sodamide, cyanide etc. can react to pyridyl ring, although strong nucleophilicity and drastic conditions were often required while starting from quinoline. Also, since both the C2- and C4-positions were affected similarly by the mesomeric effect of the N-atom, so often mixture of regioisomers were obtained during this reaction (figure 1.2).

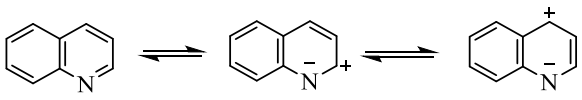
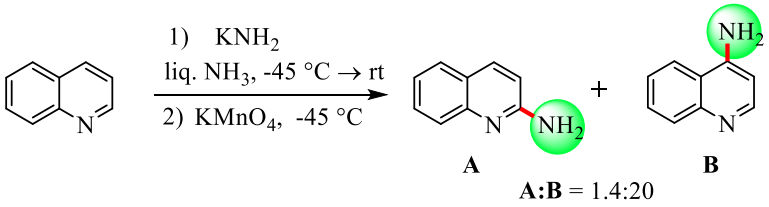


Figure 1.2: resonance structures for quinoline

For example, amination of quinoline with potassium amide, known as the Chichibabin reaction, gave both 2-amino- and 4-aminoquinolines (scheme 1.7).

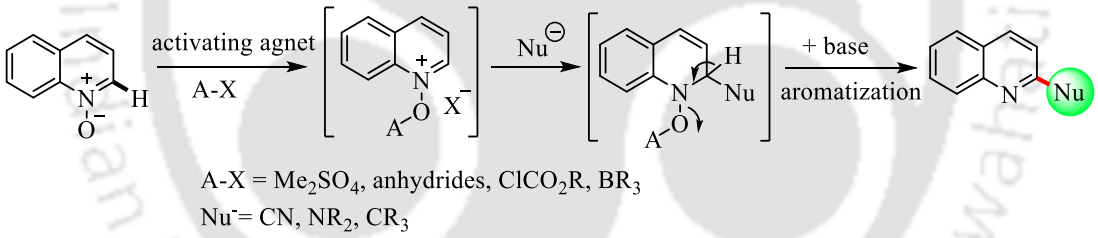


Scheme 1.7: nucleophilic Chichibabin reaction on quinoline

A second approach for improving the regioselectivity in such reactions required *o*-haloquinolines as the starting material instead of quinolines to achieve satisfactory C2-selectivity. However, the preparation of such 2-haloquinolines is troublesome as it often led to mixture of regioisomers and excessive halogenation which renders the purification process a tedious one.[22]

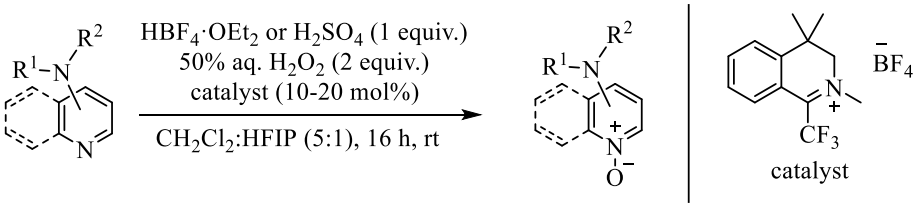
1.4. Reactivity of *N*-oxide: An approach towards solving the selectivity issue

To improve the issue of selectivity, a more practical approach is the activation of the ring by oxidation to give corresponding *N*-oxide which can enhance the electrophilicity at the C2 position and thereby, reactivity of the respective center towards nucleophilic substitution would seemingly be more facile compared to the C4-position. In addition, activating agent can further activate the *N*-oxides by the simple coordination, followed by nucleophilic substitution with concomitant aromatization to give the desired C2-functionalized products (scheme 1.8). Later, the N-O moiety gets reduced during the final aromatization step or it can be reduced by an additional reagent like PCl_3.[23]



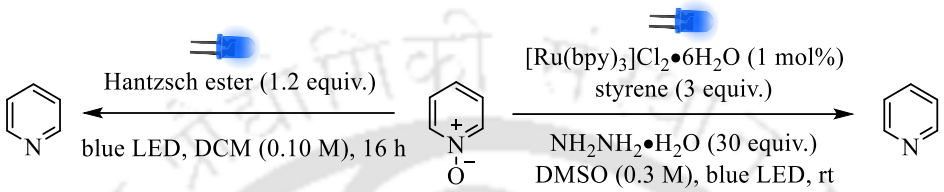
Scheme 1.8: activating agent assisted nucleophilic substitution on quinoline *N*-oxide

N-oxide is prepared in laboratory scale using the inexpensive reagent *m*-chloroperbenzoic acid (*m*-CPBA) under mild condition using halogenated solvents.[24] One problem associated with this simple protocol is the requirement of column chromatography to remove the *m*-chlorobenzoic acid byproduct from the reaction mixture. In industrial scale, hence, hydrogen peroxide is used to prepare *N*-oxides which is a very efficient protocol, although, the recovery of the product from the aqueous phase is difficult due to good solubility of the *N*-oxides in water.[25] In 2018, Hilinski and coworkers reported the first example of selective *N*-heteroarene oxidation in presence of reactive aliphatic amines. They achieved this by using H_2O_2 as oxidant in presence of Bronsted acid and a trifluoromethyl iminium salt as catalyst (scheme 1.9).[26]



Scheme 1.9: preparation of quinoline *N*-oxide in presence of aliphatic amine substituent

If the deoxygenation of the product does not occur during the reaction itself, then, a separate step is needed to reduce the *N*-oxide to the corresponding *N*-heteroarene. Different reducing agents are employed for this step, such as Pd/C, trifluoroacetic acid (TFAA) etc., the most efficient reagent is found to be phosphorus trichloride (PCl_3).[23] Recently, two different photo-catalysed reduction of *N*-heteroarene oxides are also reported (scheme 1.10).[27] The first one used hanztsch ester as a reducing agent whereas the second approach used Ru-photocatalyst with hydrazine hydrate as a proton source and a reductive quencher. Although these reactions could be performed under mild conditions, sometimes, they suffer from use of excess reagents.



Scheme 1.10: photocatalyzed reduction of *N*-oxide

There are 4 different types of C-H functionalization reactions that are displayed by the *N*-oxides-

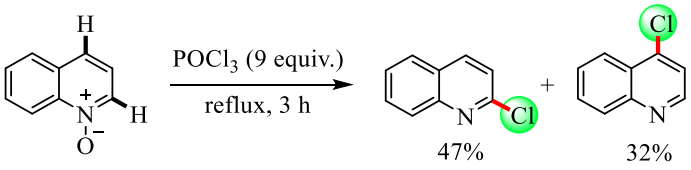
1. Nucleophilic addition to activated *N*-oxides (Reissert type),
2. Minisci type reactions,
3. Metal-catalysed C-H functionalisation and
4. 1,3-dipolar cycloaddition reactions

With few selected examples, each type of reaction is discussed in below.

1.4.1. Nucleophilic addition to activated *N*-oxides (Reissert type):

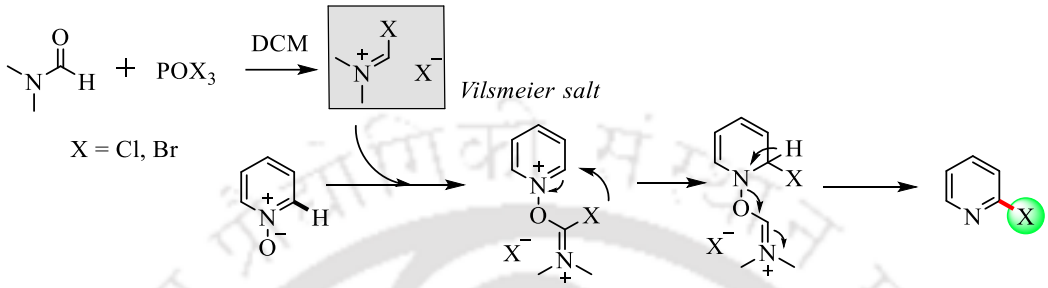
As mentioned, *N*-oxide moiety can further be activated by the activators or electrophiles through coordination to the oxygen atom, making the ring more electron deficient and more reactive towards nucleophilic reaction. Occasionally, both the electrophilic and nucleophilic centers are parts of the same reagent (e.g., $POCl_3$, Ac_2O), thereby, eliminating the need of an additional activating agent for the transformation. This kind of reactivity was first reported by Reissert in 1905 and hence, known as Reissert type reactions.[28]

The most common protocol for preparation of 2-haloheterocycles is the treatment of corresponding *N*-oxides with phosphorus oxyhalides under harsh reaction conditions (high temperature, excess use of nucleophile). $POCl_3$ works both as activating agent and halide source in this reaction (scheme 1.11). But this protocol displayed poor selectivity (C2 *vs* C4) as well as low yields for azines, entailing a tedious separation of the regioisomers. The substrate scope was also limited and often different side reaction occurred including reduction of the parent *N*-oxide.[29]



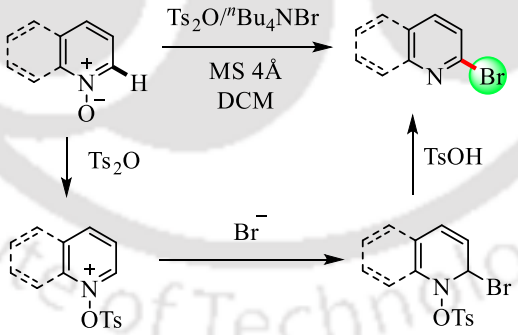
Scheme 1.11: halogenation of quinoline *N*-oxide with phosphorus oxychloride

To improve this regioselectivity issue, Wang and Yu reported the combination of POX_3/DMF (X= Cl, Br) system for deoxygenative halogenation of *N*-oxides under mild conditions. The reaction produced excellent selectivity at the C2-position. Besides this, the use of stoichiometric use of POX_3 was another advantage of this protocol. The authors proposed the *in-situ* formation of Vilsmeier salt which would activate the *N*-oxide followed by subsequent nucleophilic attack at the C2-position to give the final product (scheme 1.12).[30]



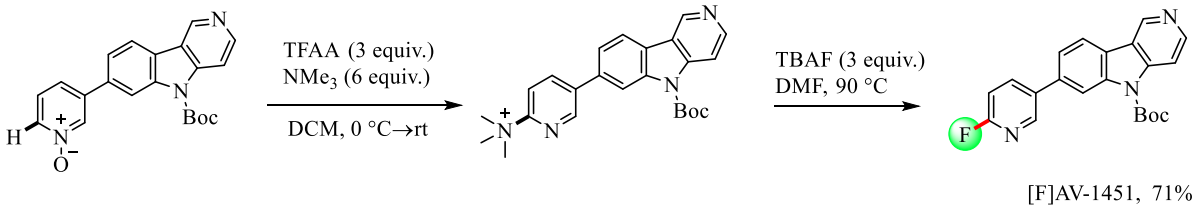
Scheme 1.12: mechanism for halogenation of quinoline *N*-oxide with phosphorus oxychloride and DMF

Baran and coworkers in 2013 reported an elegant nucleophilic bromination of azine *N*-oxides with *p*-toluenesulphonyl anhydride (Ts_2O) as an activator and *n*-butylammonium bromide as bromide source under mild conditions (scheme 1.13).[31] This protocol was further improvised by Lucas using triflic anhydride (Tf_2O) instead of Ts_2O as the activating agent to broaden the substrate scope. Although this protocol was highly regioselective for both quinoline and isoquinoline systems, but it was failure for pyridyl systems.[32] Chen and coworkers have taken an alternative route to solve this problem where they had used oxalyl halide as an activator as well as halide source in the presence of triethylamine as a base to prepare 2-halopyridines.[33]



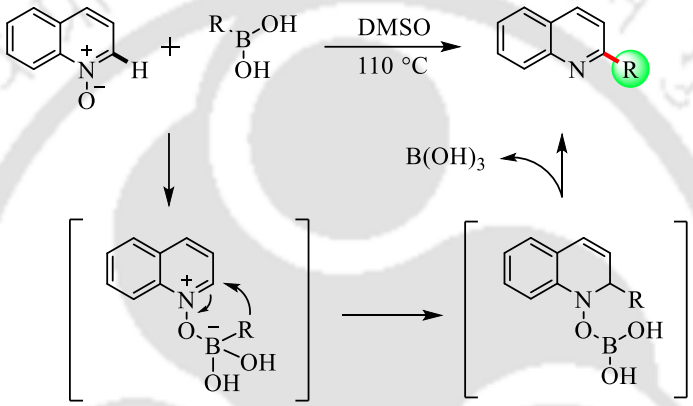
Scheme 1.13: C2-bromination of azine *N*-oxide with Ts_2O as activating agent

Unlike, chlorination or bromination, direct functionalization of fluorine atom into the heteroaromatic compound is challenging due to its low reactivity as a nucleophile. In this regard, Attardo and co-workers have developed a method for the synthesis of 2-fluoroazines from the *in-situ* generated reactive 2-azinetrialkylammonium salt and TBAF. Scope of the reaction was further expanded into late-stage manipulation of some drug molecules (scheme 1.14).[34]



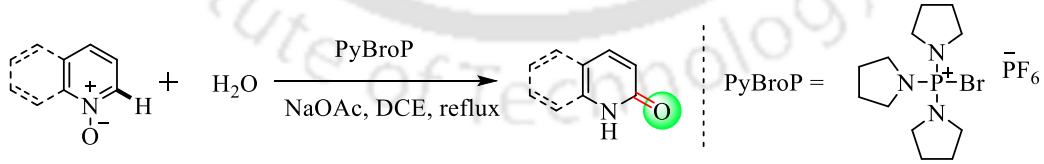
Scheme 1.14: C2-fluorination of azine *N*-oxide

Similar to a Petasis-type reaction, Antonchick and group have achieved the arylation and alkenylation of quinoline *N*-oxide using boronic acid in DMSO. First, boronic acid coordinated to the *N*-oxide moiety under the reaction conditions which brought the reactants into close proximity and then aryl/alkenyl group migrated from the boronic acid to the C2-position of quinoline. This is the first example of metal- and oxidant-free cross-coupling of quinoline *N*-oxide with boronic acid (scheme 1.15).[24]



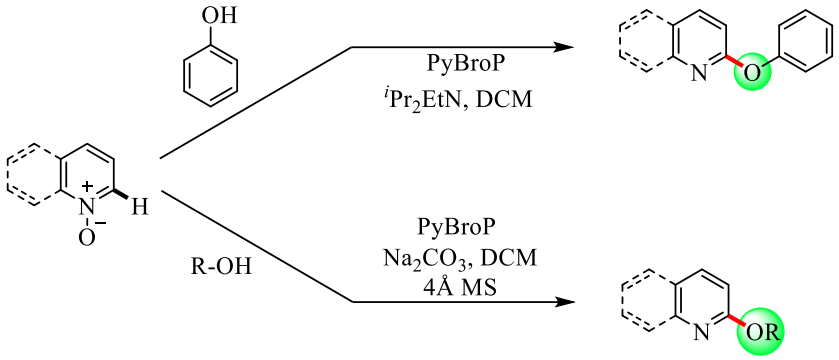
Scheme 1.15: metal- and oxidant-free cross-coupling of quinoline *N*-oxide with boronic acid

Phosphorus-based activating agents are attractive candidates for activation of azine *N*-oxides for their tendency to form strong P=O bonds with the oxide center. Among them, PyBroP is a widely investigated activating agent for C2-functionalisation reactions. Yu and co-workers have developed the synthesis of 2-hydroxyquinolines from *N*-oxides using PyBroP and sodium acetate as base with water as the hydroxyl-source. The reaction worked quite well with other *N*-heteroarenes, *viz.* isoquinoline and pyridine derivatives (scheme 1.16).[35]



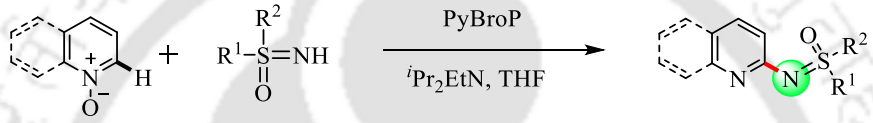
Scheme 1.16: preparation of 2-hydroxyquinoline from quinoline *N*-oxide

The synthesis of 2-aryloxypyridines and 2-alkoxypyridines were also realized by using PyBroP as activating agent with aryl and alkyl alcohols respectively in two separate reports by Londragan *et. al* (scheme 1.17). DIPEA was found as an effective base for the reaction of hyroxybenzenes and *N*-oxide, whereas Na_2CO_3 was appropriate for the reaction involving aliphatic alcohols.[36]



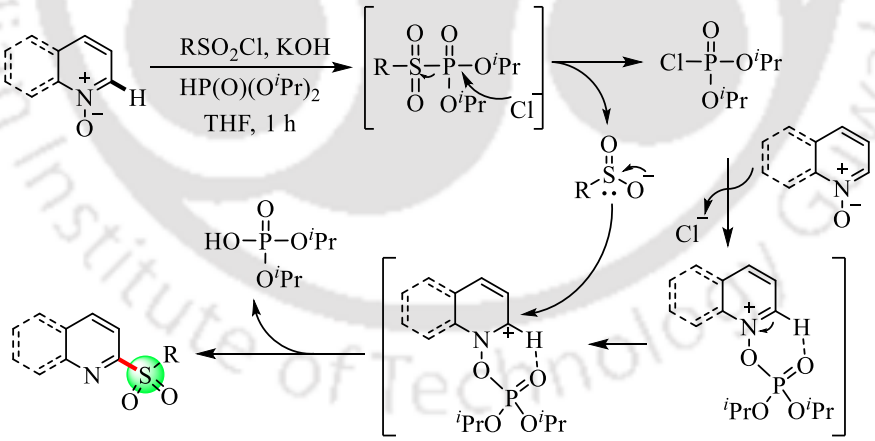
Scheme 1.17: C2-aryloxylation and C2-alkoxylation of quinoline *N*-oxide

Using PyBroP, Singh and co-workers have developed a transition-metal-free sulphoximination of heteroaromatic *N*-oxides in a straightforward manner under mild reaction conditions. Interestingly, enantiopure substrates were also applicable under the reaction conditions and gave the corresponding products without any racemization (scheme 1.18).[37]



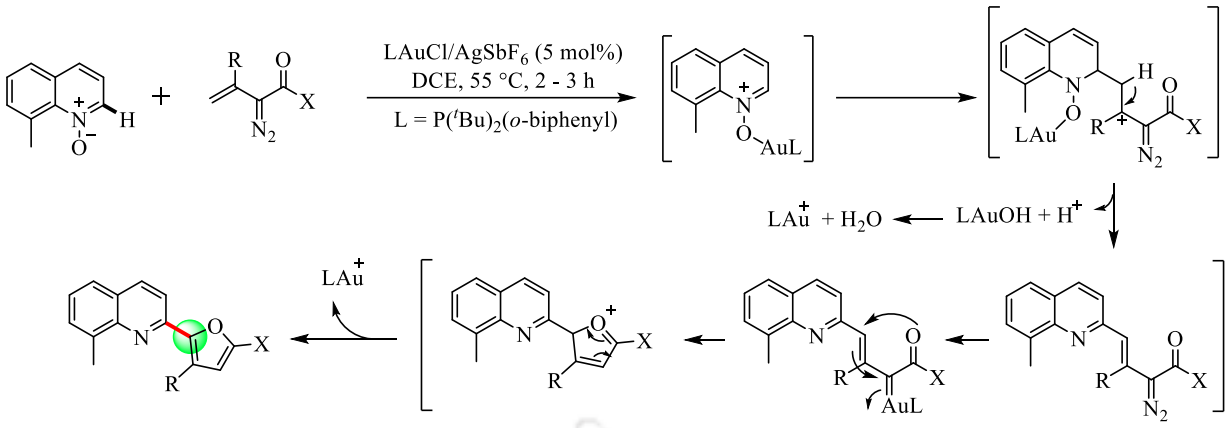
Scheme 1.18: C2- sulphoximination of quinoline *N*-oxide

H-phosphonate, another class of phosphorus-based activating agent, was explored by Li and co-workers for C2-sulphonylation of quinoline *N*-oxides. Interestingly, *H*-phosphonate not only served as an activating agent but also helped to generate the sulphonyl nucleophile in the reaction (scheme 1.19).[38]



Scheme 1.19: C2- sulphonylation of quinoline *N*-oxide using *H*-phosphonate

Liu developed a gold-catalysed C2-furanylation of 8-alkylquinoline *N*-oxides using vinyl-diazo-carbonyl compounds, where the gold-catalyst acted as the activating agent for both the *N*-oxide and diazo-compound. The reaction proceeded *via* a proposed gold-carbene intermediate. The reaction was found to be suitable for only fused *N*-oxides (scheme 1.20).[39]



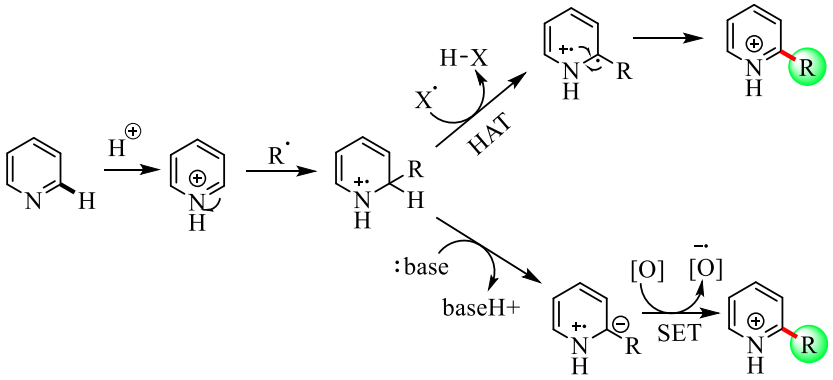
Scheme 1.20: C2- furanylation of 8-methylquinoline *N*-oxide

Although a lot of advancements have been made in the nucleophilic Reissart-type reactions for azine C-H functionalisations, still, some shortcomings are always there. These reactions often used halogenated solvents, super stoichiometric amounts of activating agents and bases. All of these necessitated generation of lots of chemical wastes which contributed to problems in large-scale adaptation of such protocols.

1.4.2. The Minisci reaction

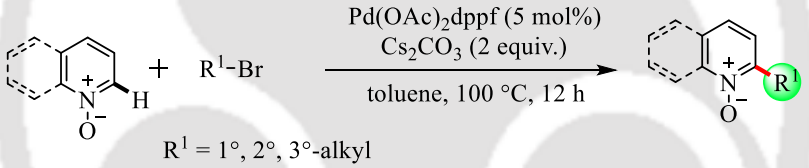
Free radical based alkylation of *N*-heteroarenes, popularly known as Minisci reaction, is one of the well-known methods for C2-alkylated heteroaromatic compounds. The reaction is often carried out in acidic medium, which not only helps to achieve the selectivity at the C2-position but also accelerates the reaction rate by generating a more electron-deficient pyridium salt as the intermediate. This commonly used protocol was first described by Minisci in 1971, when he reported homolytic alkylation of *N*-heteroarenes, wherein, alkyl radical was generated *in-situ via* silver catalysed oxidative decarboxylation of carboxylic acid.[40] Interestingly, the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) for a radical lie in the same orbital, called singly occupied molecular orbital (SOMO). So, they can show both nucleophilic and electrophilic behaviors. Although it certainly depends on the substituents, alkyl radicals are often found to be nucleophilic given their preference towards pyridinium ions compared to pyridines.[41]

The Minisci reaction follows the following general mechanism. First the *N*-heteroarene gets protonated at the *N*-center in an acidic environment, rendering the ring more electron-deficient. Then, the radical partner attacks to the C2-carbon center, leading to the formation of a nitrogen-radical cation species. This reactive radical cation now can undergo two pathways- 1) hydrogen atom transfer (HAT) to give the C2-functionalised heteroaromatic compounds, or 2) base-promoted deprotonation followed by a single electron transfer (SET) step to give the final product (scheme 1.21).[42]



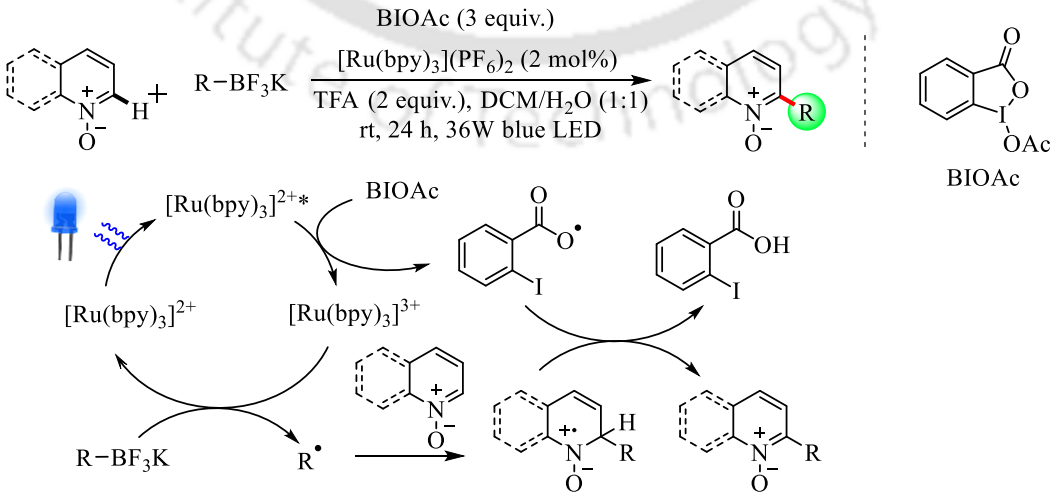
Scheme 1.21: general mechanism for Minisci reaction

Alongside quinoline, quinoline *N*-oxides has also been subjected to the Minisci type alkylation reactions. The usage of *N*-oxides has manifold advantages- they work as transient redox auxiliary for radical generation, in addition to being an activated substrate, thereby, eliminating the need of an external oxidant and strong acidic conditions otherwise required.[42] In 2013, Fu *et al.* developed an elegant C-C cross-coupling reaction between *N*-oxides and non-activated secondary and even tertiary alkyl bromides to produce C2-alkylated *N*-oxides. Pd-catalysed activation of such secondary or tertiary alkyl bromides was rather less known. The experimental evidences suggested the involvement of a possible hybrid organometallic-radical mechanism (scheme 1.22). [43]



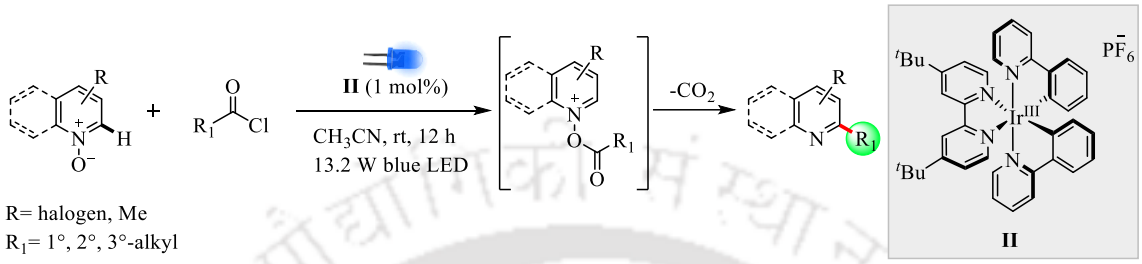
Scheme 1.22: Pd-catalysed C2-alkylation of azine *N*-oxides

A Ru-photoredox catalysed direct C2-alkylation of pyridyl *N*-oxides was reported by Xu *et al.* in 2017, where they used alkyl trifluoroborate as the radical alkylating agent. The radical generation was aided by visible light under mild conditions and hypervalent iodine-based oxidant BIOAc was used to obtain the final product (scheme 1.23).[44]



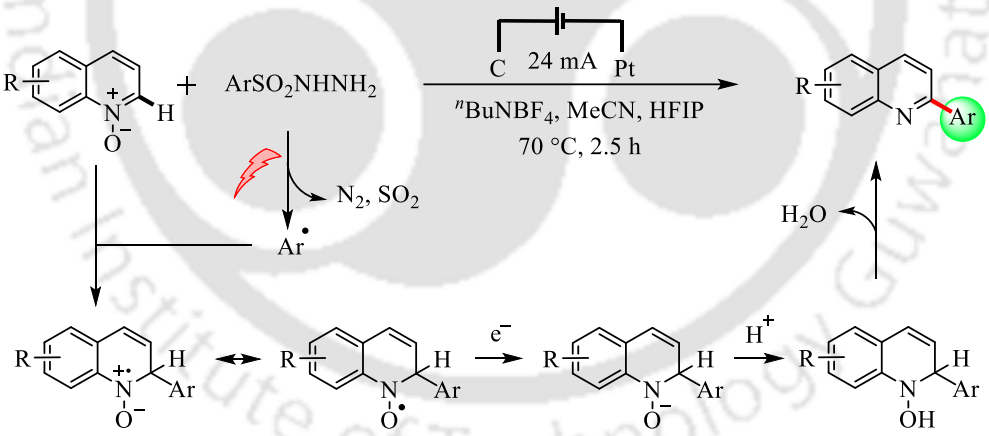
Scheme 1.23: Ru-catalysed C2-alkylation of azine *N*-oxides

Later in 2018, Stephenson reported the reductive decarboxylative alkylation of heteroarene *N*-oxides in the presence of an Ir-photocatalyst without the need of any added oxidant or harsh reagents. The acyl chloride first activated the *N*-oxide to give *N*-acyloxypyridinium salt which then underwent reductive decarboxylation through a single electron transfer step from a photoredox catalyst to give the alkyl radical. As such they worked as both redox auxiliaries and coupling partners, which was very encouraging as most redox auxiliaries generally went out as chemical wastes (scheme 1.24).[45]



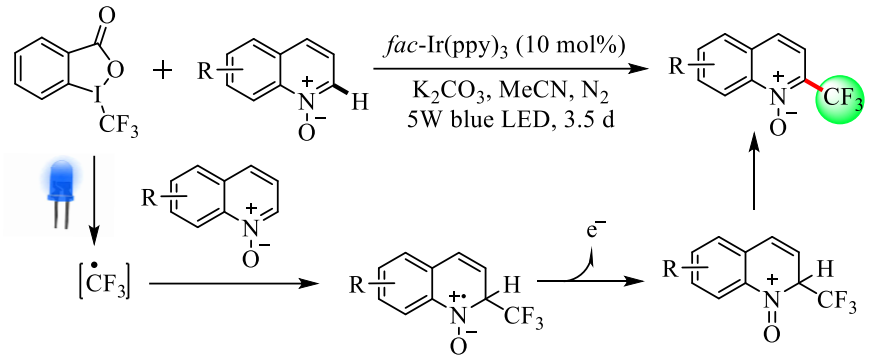
Scheme 1.24: Ir-catalysed decarboxylative C2-alkylation of azine *N*-oxides

Apart from alkylation reactions, Minisci-type reactions are also explored towards selective incorporation of aryl group into the C-H bond of quinoline moiety using electrochemical approach. A deoxygenative C2-arylation of quinoline *N*-oxides with sulphonyl hydrazines has been reported without the requirement of any transition metal catalyst and exogenous oxidant- or reductant. Reactive aryl radical species was generated *in-situ* from aryl sulphonyl hydrazines with concomitant loss of 3 electrons and protons. Surprisingly, the reaction failed to give the alkylated product under the reaction conditions (scheme 1.25).[46]



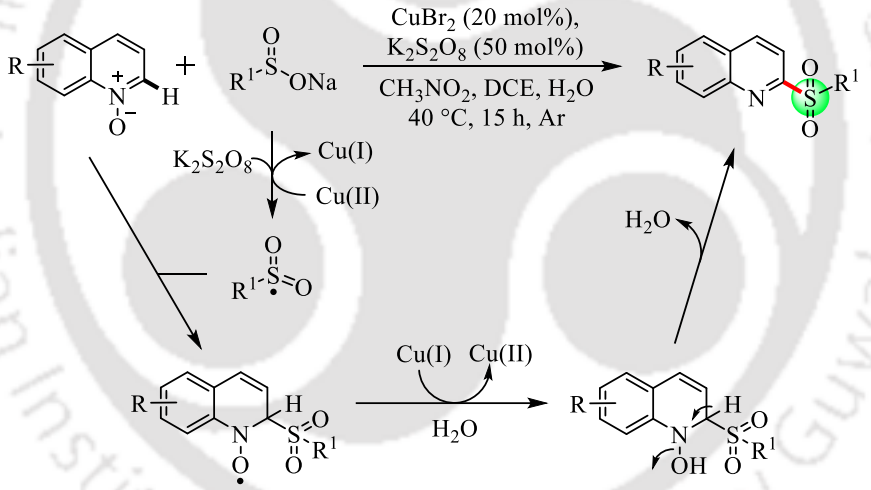
Scheme 1.25: metal-free electrochemical C2-arylation of azine *N*-oxides

Recently, Gao and co-workers reported an operationally simple, visible light promoted C2-trifluoromethylation of quinoline *N*-oxides using Ir-photocatalyst. The reaction showed good to moderate yields for the products with broad substrate scope, although long time was required to complete the reaction (scheme 1.26).[47]



Scheme 1.26: Ir-photocatalysed C2-trifluoromethylation of azine *N*-oxides

Next, Pan and co-workers reported a unique Cu(II)-catalysed deoxygenative C2-sulphonylation of *N*-oxides. In the process, sodium sulphinate was employed as the coupling partner while $K_2S_2O_8$, along with the catalyst $CuBr_2$, acted as the radical initiator. This happened through a single electron transfer step, during which Cu(II) got converted to Cu(I). The oxo-radical intermediate formed was then converted to a hydroxylamine intermediate and Cu(II) was also regenerated for the next cycle. The deoxygenation product was unexpected owing to the fact that no added reductant was present in the reaction mixture. The reaction did not work with parent quinoline (scheme 1.27).[48]

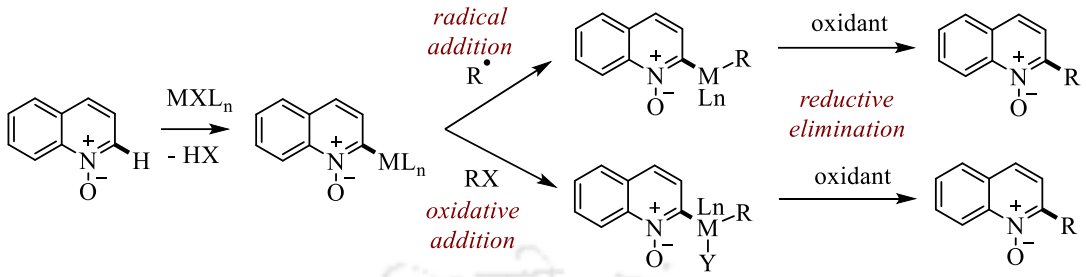


Scheme 1.27: Cu-catalysed C2- sulphonylation of *N*-oxides with sodium sulphinate

Though the use of *N*-oxides in Minisci reactions is well studied, selectivity (C2 vs. C4) remains one of the unresolved challenges in this chemistry, often giving a mixture of regioisomers if one position is not blocked. The ability of *N*-oxides to work as oxidants give them an upper hand compared to their reduced congeners in case of substrate scope broadening and sustainability as the need for external oxidant and acidic conditions is reduced. Alternative photoredox catalysis or electrochemical pathway also usually eliminate the need of an external oxidant and may overcome the issue of selectivity in some cases. However, photocatalysts are generally expensive and sophisticated set-up is required in the latter case, which bring limitations to their scale-up reactions and/or practical applications.

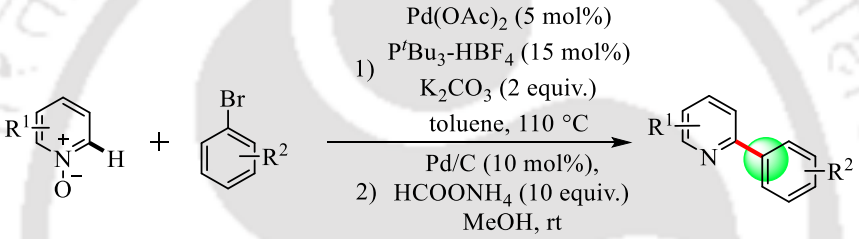
1.4.3. Metal-catalysed C-H functionalization of *N*-oxides

In this kind of reactions, the metal center under consideration first coordinates to the *N*-oxide substrate at the C2-position. Then the nucleophile attacks the metal center either by oxidative addition or in the form of a radical addition (scheme 1.28). Consequently, the reductive elimination process gives the desired product and regenerates the catalyst.



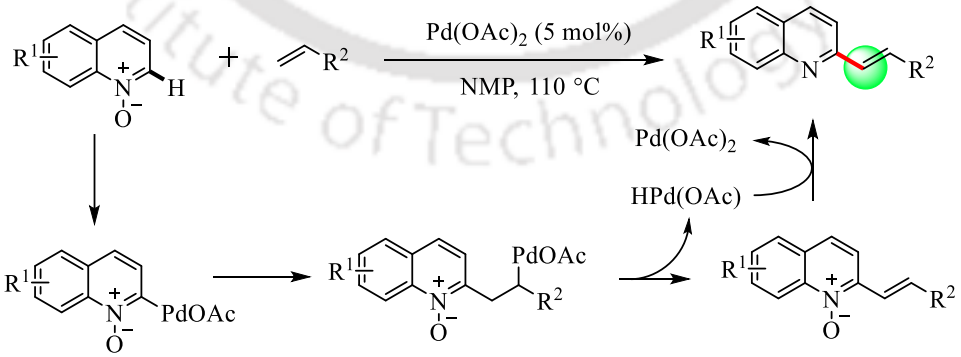
Scheme 1.28: general mechanism for metal-catalysed C-H functionalization of *N*-oxides

In 2005, Fagnou and coworkers have demonstrated the usefulness of *N*-oxides in cross-coupling reactions by using aryl halides in the presence of palladium catalyst. After completion of the reaction C2-arylated *N*-oxide was formed which was subsequently reduced to the corresponding 2-arylated pyridine derivatives using Pd/C and HCO_2NH_4 (scheme 1.29).[12]



Scheme 1.29: Pd-catalysed C2-arylation of *N*-oxides

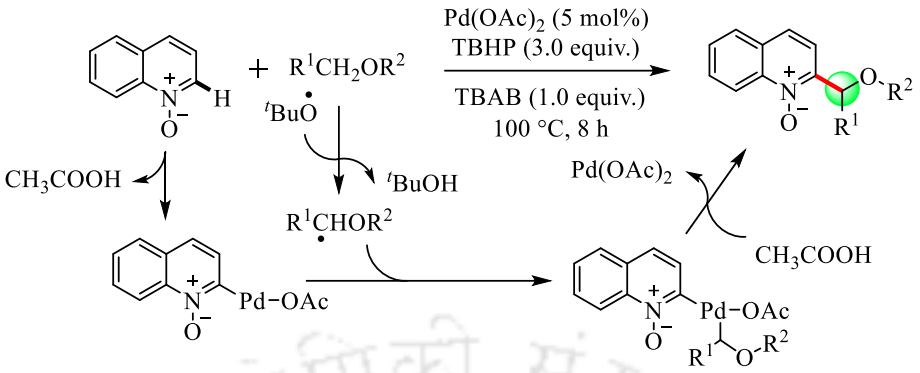
Poli and coworkers reported direct C2-alkenylation and allylation of *N*-oxides under similar catalytic conditions using KF (instead of K_2CO_3) in association with P^{t}Bu$_3$-HBF$_4$.[49] Interestingly, in their report of direct C2-alkenylation reaction of *N*-oxides with olefins using $Pd(OAc)_2$ catalyst, Wu group have described that the *N*-oxide itself worked as an oxidant to regenerate the catalyst. Thus, the process eliminated the need of an external oxidant and also avoided an extra step to reduce the *N*-oxide product (scheme 1.30).[50]



Scheme 1.30: Pd-catalysed C2-alkenylation of *N*-oxides

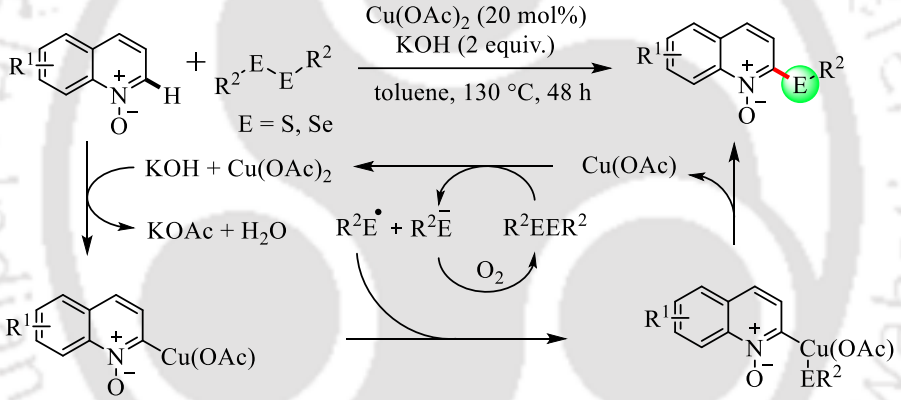
The same group also developed an efficient protocol for direct C2-alkylation of quinoline *N*-oxides using both ethers and thioethers as alkylating agents in the presence of catalytic amount of $Pd(OAc)_2$ under a base-free condition. The alkylating agents also acted as the solvent

medium. This dehydrogenative cross-coupling reaction was performed in presence of TBHP as oxidant and TBAB as an additive (scheme 1.31).[51]



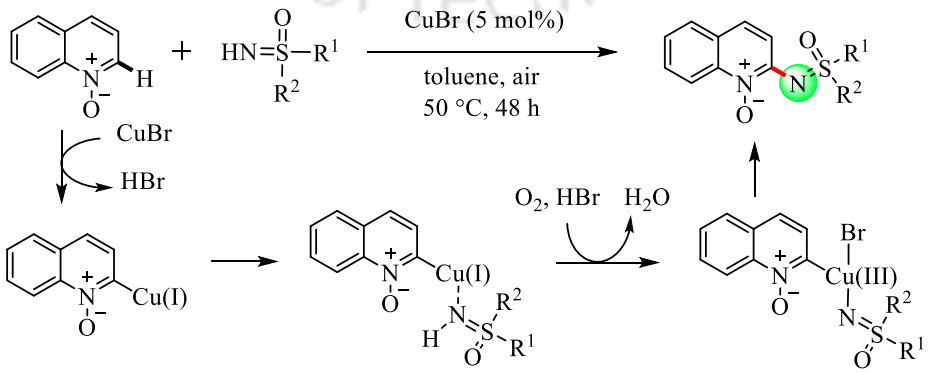
Scheme 1.31: Pd-catalysed C2-alkylation of *N*-oxides with ether

In 2018, a Cu(II)-catalysed non-deoxygenative C2-thiolation and selenation of *N*-oxides was reported by Zhao and co-workers. The reaction was carried out under air which helped to regenerate the Cu-catalyst, hence, eliminating the need of an external chemical oxidant (scheme 1.32).[52]



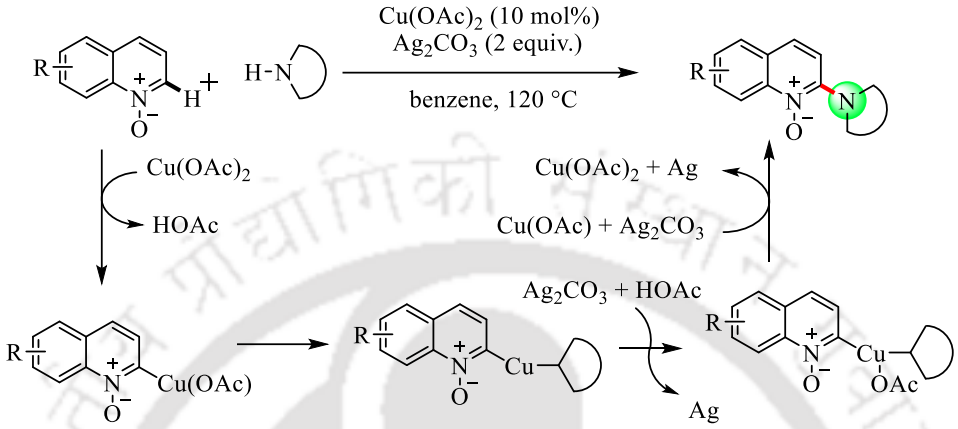
Scheme 1.32: Pd-catalysed C2-thiolation/selenation of *N*-oxides

Bolm groups reported copper(I) bromide catalyzed synthesis of sulphoximines of *N*-oxides under air. The reaction involved dual C-H and N-H activation by copper metal ions without any additional base or additive, and air served as the oxidant. The reaction was not suitable for pyridine *N*-oxides (scheme 1.33).[53]



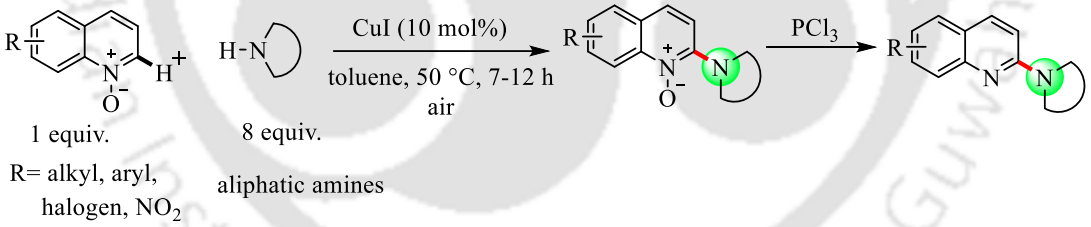
Scheme 1.33: Cu-catalysed C2-sulphoximination of *N*-oxides

In 2013, Li and co-workers have demonstrated copper-catalysed intermolecular dehydrogenative amidation/amination of quinoline *N*-oxides with lactams/cyclamines in good yields in the presence of Ag_2CO_3 as an oxidant (scheme 1.34).[54] Using a similar approach, later Wu and co-workers reported copper acetate-catalyzed electrophilic amination of quinoline *N*-oxides with *O*-benzoyl hydroxylamines.[55]



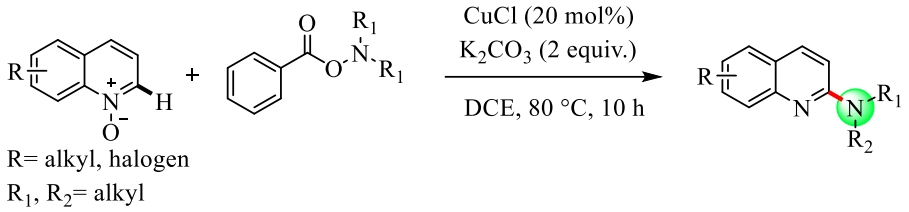
Scheme 1.34: Cu-catalysed C2-amination of *N*-oxides with cyclamines

In 2014, Wu and Cui have developed an efficient method for the amination of quinoline *N*-oxides by using secondary aliphatic amines in presence of CuI catalyst. The reaction proceeded smoothly under mild conditions in air and gave excellent to good yields of C2 aminated product (scheme 1.35).[56] In general, these copper catalyzed C-H bond aminations of *N*-oxides were discussed *via* Cu(I)/Cu(III)-redox system.



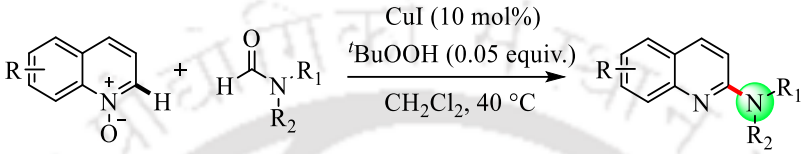
Scheme 1.35: Cu-catalysed C2-amination of *N*-oxides with 2º aliphatic amines

Besides the metal-catalysed pathways involving oxidative addition/reductive elimination to generate the product, transition-metal centers also worked as radical initiator in presence of an oxidant. Wang *et al.* in 2018, reported deoxygenative C2-amination of quinoline *N*-oxides with *O*-benzoylhydroxyamines using CuCl as the catalyst, wherein aminyl radical was generated from *O*-benzoyl hydroxylamine with the assistance of Cu(I) while either oxygen or quinoline *N*-oxide itself might act as the oxidant. Interestingly, the solvent dichloroethane (DCE) also worked as the reductant, breaking the N-O bond (scheme 1.36) .[57]



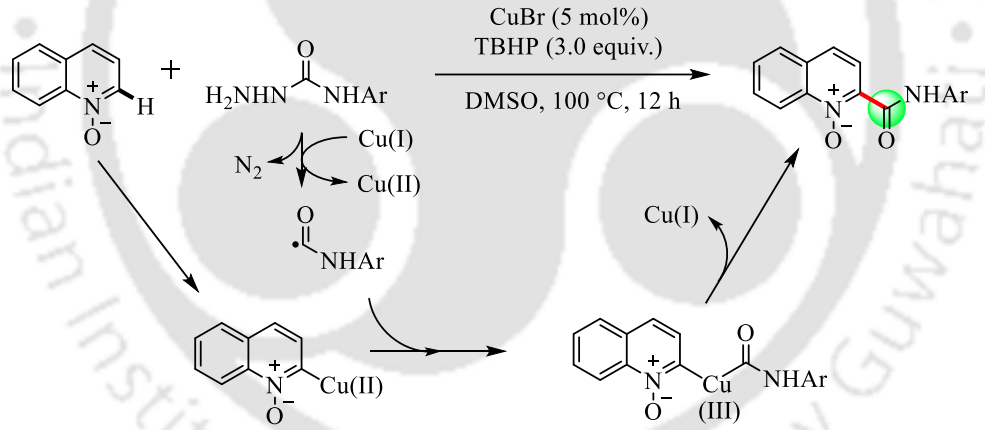
Scheme 1.36: Cu-catalysed C2-amination of *N*-oxides with *O*-benzoylhydroxyamines

Fan and co-workers in 2019, reported the synthesis of 2-aminoquinolines from quinoline *N*-oxides and *N,N*-dialkylformamide using CuI with *tert*-butylhydroperoxide as oxidant in a one-step process (scheme 1.37).[58]



Scheme 1.37: Cu-catalysed C2-amination of *N*-oxides with *N,N*-dialkylformamide

Later Wang *et al.* reported the C2-carbamoylation of quinoline *N*-oxides using hydrazinecarboxamides as carbamoyling agent in presence of CuBr as catalyst and TBHP as oxidant. They postulated that the reaction had proceeded through the generation of a carbamoyl radical species (scheme 1.38).[59]



Scheme 1.38: Cu-catalysed C2- carbamoylation of *N*-oxides

As evident from the reports, these processes, while successfully generating C2-functionalised quinolines, often need an additional reduction step from the CH functionalized *N*-oxide moiety to the corresponding quinoline derivatives. This reduces the step-economy of the process and also often requires the use of harsh reagents like PCl_3. So, there are still plenty of rooms for scientific advancements in these fields.

1.4.4. 1,3-dipolar behavior of *N*-oxides

One of the interesting features of quinoline *N*-oxide is its ability to work as 1,3-dipoles.[60] These dipoles were defined by Huisgen as a species "*that is represented by zwitterionic structures with a positive and negative charge distributed over three atoms and has 4π electrons*".[61] There are two ways one can represent this schematically- the octet structure where the central atom

contains the positive charge and the negative charge is distributed about the two terminal atoms, and the sextet structure which depicts one of the two π-electron pairs located on the central atom (figure 1.3). Although the sextet structure has not much contribution towards the overall electronic distribution of the molecule, it does give a good insight into the ambivalence and reactivity of such molecules towards 1,3-dipolar cycloaddition reactions.[62]

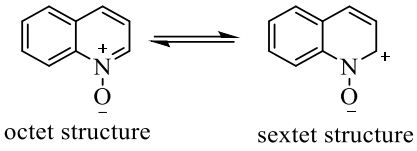
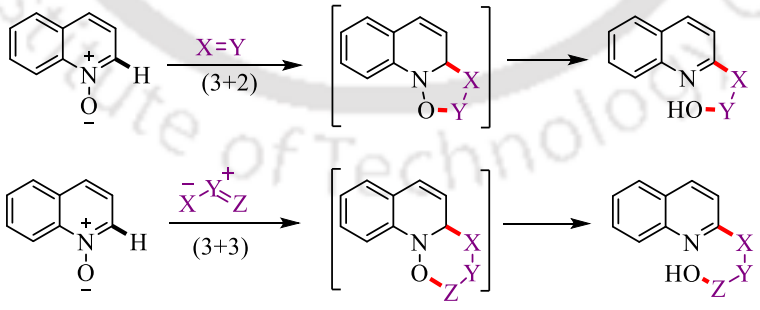


Figure 1.3: resonance structures for quinoline *N*-oxide

Owing to the 1,3-dipolar nature of *N*-oxides, it can undergo (3 + *n*)-cycloaddition reactions (*n* = 2, 3) with suitable dipolarophiles to give the C2-functionalised products. Initially, *N*-oxide forms a 5- or 6-membered cycloadduct (depending on n = 2 or 3, respectively) by the reaction with dipolarophile, which results in loss of aromaticity in the heteroaromatic ring. This kind of cycloaddition may follow either concerted or stepwise pathway depending on the structure and electronic nature of the substrates. Huisgen explained this from molecular orbital theory.[63] Accordingly, the two new σ-bonds are formed from two π HOMO-LUMO interactions of the coupling partners. When both interactions are equally contributing to the transition state, a concerted pathway occurs. However, if one interaction predominates compared to the other, the second HOMO-LUMO interaction cannot contribute much to the transition state energy and thereby, cannot compensate the entropy requirement for the concerted pathway. This leads to a stepwise mechanism. Then the cycloadduct can undergo aromatization under appropriate conditions to give the final product (scheme 1.39). The reaction possibly occurs *via* the abstraction of C2-proton from the vicinal carbon to the nitrogen center, followed by heterolytic cleavage of the N-O bond. Similar type of reactions has also been observed in case of the non-aromatic analogue nitrones, but unlike nitrones, heteroaromatic *N*-oxides lose their aromaticity during the cycloaddition reactions, which might limit their reactivity. That might be one of the reasons why C2-functionalisation of heteroaromatic *N*-oxides *via* (3+n)-cycloaddition reactions have not been explored much till date.[60]

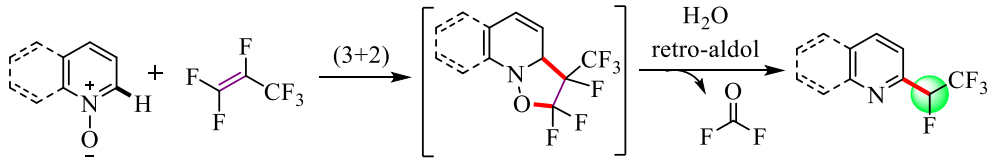


Scheme 1.39: (3+n)-cycloaddition of *N*-oxides

a) (3+2)-cycloaddition reactions

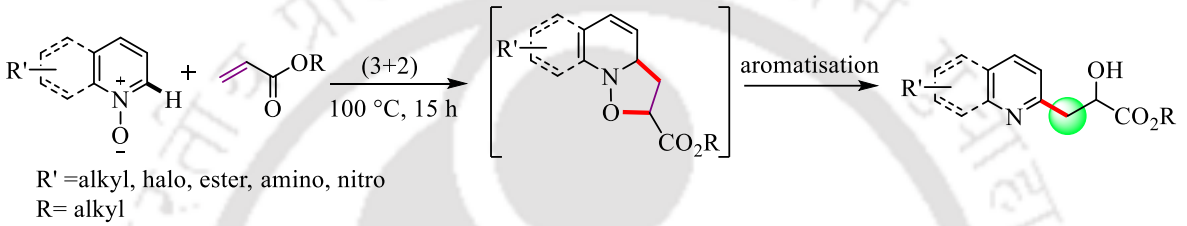
Pioneering work on site-selective C-H functionalization of *N*-oxides *via* 1,3-diploar cycloaddition pathway was demonstrated almost 50 years ago by the group of Mailey and Ocone.[64] They have described the synthesis of C2-alkylated quinolines by a (3+2)-cycloaddition of pyridine *N*-oxides with highly electron deficient hexafluoropropene followed

by retro-aldol fragmentation (scheme 1.40). A similar C2-alkylation of both pyridine- and quinoline *N*-oxides was also investigated by Loska and Makosza later in 2008, where they have shown the reaction mechanism in details.[65]



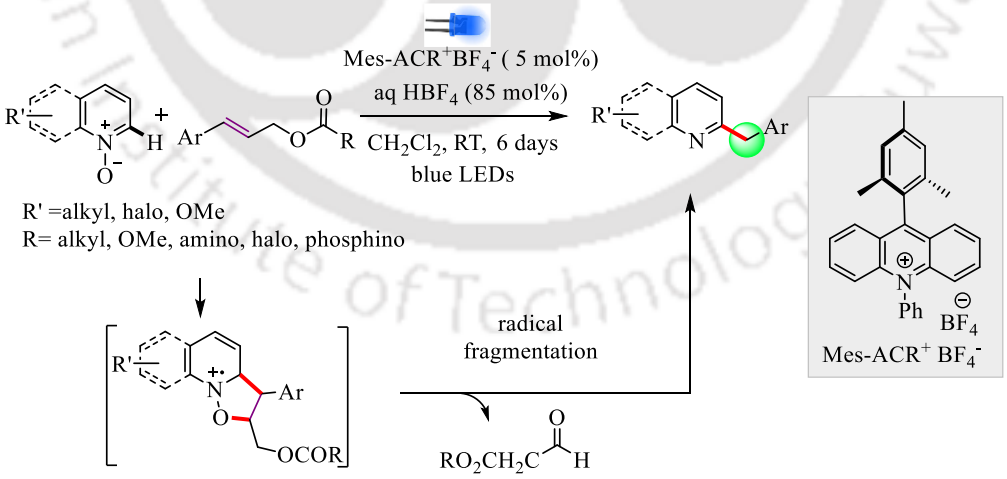
Scheme 1.40: (3+2)-cycloaddition of *N*-oxides with electron-deficient alkenes

Later, Sharma and coworkers, in 2016, demonstrated the (3+2)-cycloaddition of quinoline *N*-oxides with acrylates to get C2-alkylated quinolines. Interestingly, the reaction proceeded smoothly under solvent-free conditions without any catalyst or base and gave the desired products in moderate to good yields (scheme 1.41).[66]



Scheme 1.41: (3+2)-cycloaddition of *N*-oxides with acrylates

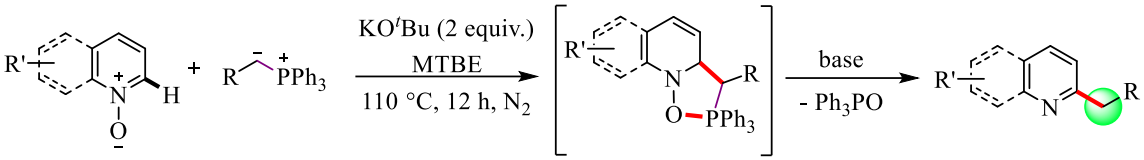
Recently, Murakami and co-workers have disclosed another fascinating approach for C2-alkylation of *N*-oxides with esters of cinnamyl alcohols under photocatalytic reaction conditions. They postulated that the cation radical species, formed by photoirradiation of an alkene in the presence of a photocatalyst, was electrophilic enough to couple with the *N*-oxide, giving the desired product. The process eliminated the need of electron-deficient alkenes as a coupling partner for such reactions (scheme 1.42).[67]



Scheme 1.42: (3+2)-cycloaddition of *N*-oxides with cinnamyl esters

Although Wittig reagents are considered as well-known carbon nucleophiles in organic synthesis, however, it was only recently that they were explored as an alkylating agent in synthesis of alkylated heteroaromatic compounds. In 2018, Kim *et al.* described transition-metal-free reductive (3+2)-cycloaddition reaction of pyridine and quinoline *N*-oxides with

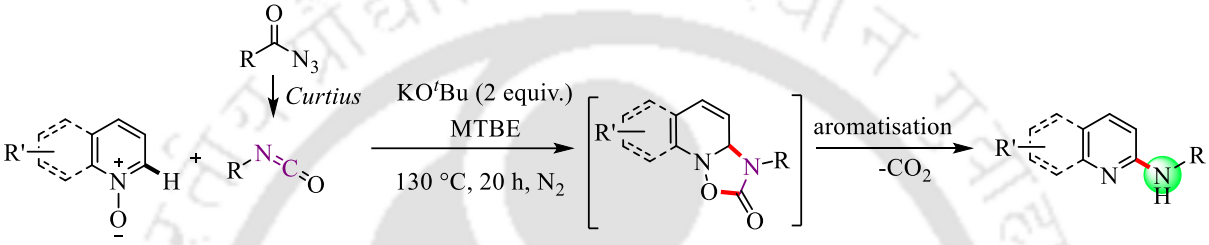
Wittig reagents. The reaction provides a variety of C2-alkylated pyridines and quinolines with excellent site selectivity and functional-group compatibility (scheme 1.43).[68]



R' =Me,Cl, OMe; R= alkyl

Scheme 1.43: (3+2)-cycloaddition of *N*-oxides with Wittig reagents

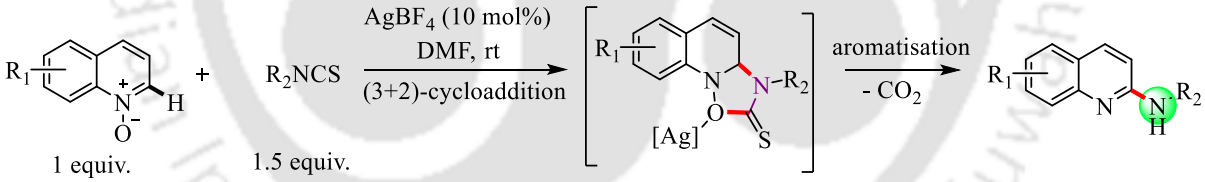
Very recently, the same group also disclosed C2-amination of azine *N*-oxides with isocyanates, derived from acyl azides *via* Curtius rearrangement and subsequently undergoing (3+2)-cycloaddition reaction to give the aminated product (scheme 1.44).[69]



R' = alkyl, halo, OMe; R= Ar, adamantyl

Scheme 1.44: (3+2)-cycloaddition of *N*-oxides with acyl azides

By applying similar (3+2)-cycloaddition concept, He *et al.* reported a silver catalysed amination reaction of quinoline *N*-oxides with isothiocyanates to obtain 2-aminoquinoline derivatives in good yields (scheme 1.45).[70]



1 equiv.

R_1= alkyl, aryl, halogen, CN, ester, CH=CHPh, C≡CPh

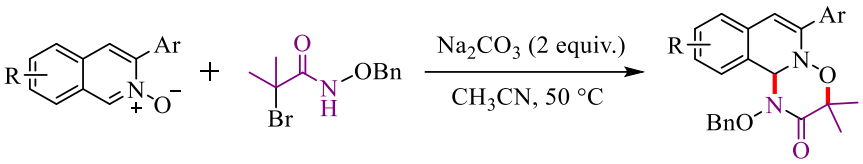
1.5 equiv.

R_2= alkyl, aryl, py

Scheme 1.45: (3+2)-cycloaddition of *N*-oxides with isothiocyanates

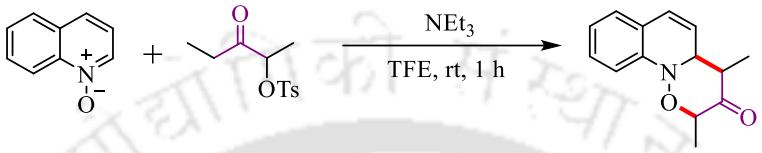
b) (3+3)-cycloaddition reactions

In comparison to (3+2)-cycloaddition, reports on (3+3)-cycloaddition reactions of *N*-oxides are very limited. In 2016, Wu and group reported (3+3)-cycloaddition reaction of isoquinoline *N*-oxide with *in-situ* generated azaoxyallyl cations. The reaction was found to be base-dependent, as with different bases, different products were formed. *α*-bromohydroxamates were used as precursor to the azaoxyallyl cations and C3-substituted *N*-oxides were used for the study (scheme 1.46).[71]



Scheme 1.46: (3+3)-cycloaddition of *N*-oxides with *α*-bromohydroxamates

Next, Archambaeu and coworkers developed another method for (3+3)-cycloaddition reactions of *N*-oxides with *in-situ* generated oxyallyl cations. They have shown only two examples with aromatic *N*-oxides, one is with quinoline *N*-oxide and another is with isoquinoline *N*-oxide (scheme 1.47).[72]



Scheme 1.47: (3+3)-cycloaddition of *N*-oxides with oxyallyl cations

The above reports suggest that C-H functionalization of *N*-oxides *via* 1,3-dipolar cycloaddition is very significant. The approach offers high selectivity at the C2 position, and good atom economy. However, only a handful of literatures are there exploring this 1,3-dipolar behavior of quinoline *N*-oxides. Hence, there are a lot to be investigated in this regard.

1.5. Sustainable approaches towards heteroaromatic C-H functionalization

As the threats of man-made pollutions are becoming more imminent in day-to-day lives of modern society, 'sustainable development' has been marked as a major way to regenerate the natural world. According to the 1987 Bruntland Commission Report, the concept of sustainable development can be described as "development that meets the needs of the present without compromising the ability of future generations to meet their own needs".[73] In recent times, this concept has also paved its way into the synthetic organic chemistry with the aim of developing newer methodologies for industrial application. Such developments for sustainable methodologies have been guided by the "12 principles of green chemistry", put forward by Anastas and Warner in 1998.[74] This inspires the development of new catalytic systems with milder reaction conditions, reduction of reaction-steps, elimination of scarce and/or hazardous materials etc. which make the processes eco-friendly.[20] As discussed above, one of the important developments in this direction is the direct C-H activation/functionalization process. The current study is more focused towards sustainable C-H functionalization of arene/heteroarene systems by the use of earth abundant 3d-base metal catalysts, heterogenous catalytic condition, environmentally benign oxidants, greener solvents, or alternative energy sources (e.g., microwave irradiation, ultrasound etc.) (figure 1.4). These will be briefly discussed in below with a few representative examples.

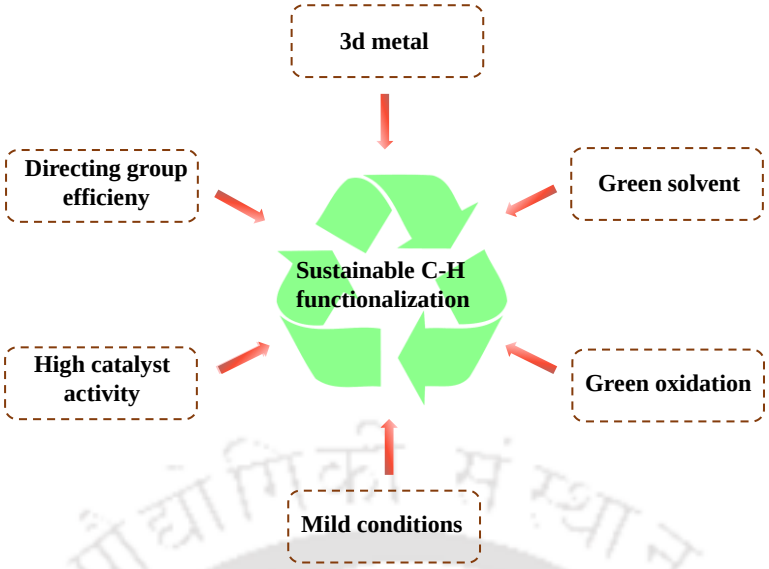


Figure 1.4: sustainable C-H functionalisation

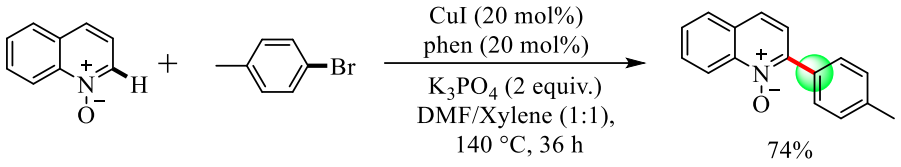
1.5.1. Use of 3d-metal catalysis

Although precious metal catalysts (such as Pd, Rh, Ru) are highly successful in C-H functionalization chemistry, their high cost and scarcity stand in the way of the large-scale applications of such protocols.[20] Compared to this, the 3d-transition metals are more abundant and less costly (for comparison, see table 1.1) due to their ease of extraction and purification. Moreover, these elements are also present as nutrients in plants and animals and also in enzymatic processes. Transition metals like Fe and Mn-based systems are used in redox reactions to remediate contaminated water or soil and also to protect them. Their post-reaction treatment is also less costly compared to the heavy transition metals. So, these 3d-metal atoms are considered as environmentally benign compared to the heavier 4d- and 5d-transition metals. As such, current research is more inclined towards the use of inexpensive, earth-abundant, and environmentally benign 3d-base metals for these reactions in terms of sustainability and scalability.[75] In below selected examples, the use of 3d-base metal catalysts has been discussed for C-H functionalization of *N*-oxides (or related fused *N*-heteroarenes).

Table 1.1: cost comparison of different transition metals

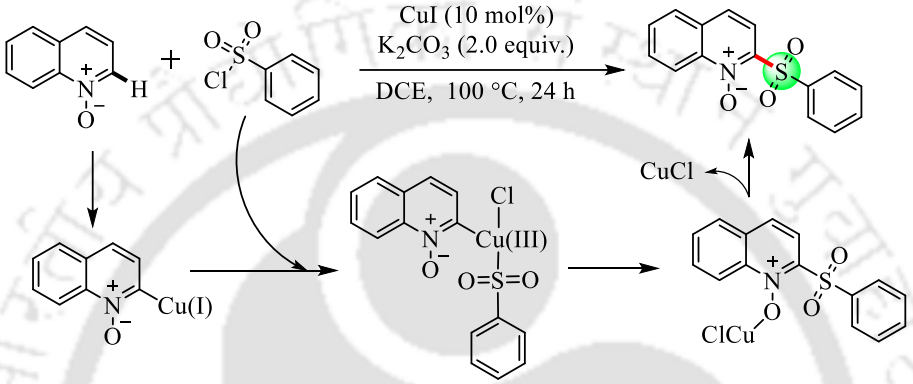
Metal	Price (€/g)
Iron	0.10
Palladium	73.2
Ruthenium	241.0
Iridium	315.22
Platinum	395.45
Rhodium	642.78

In 2009, You group reported copper-catalysed arylation of *N*-oxides with aryl bromides under mild basic conditions with very good functional group compatibility. They have also shown a library of fluorophores with intense emission properties (scheme 1.48).[76]



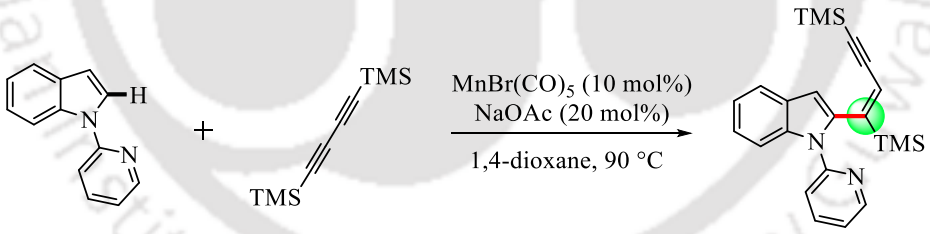
Scheme 1.48: Cu-catalysed C2-arylation of quinoline *N*-oxides

Later, Wu and co-workers reported copper catalyzed direct C2-sulphonylation of quinoline *N*-oxides by using inexpensive arylsulphonyl chlorides as sulphonylation reagents. The protocol was tested with both electron donating and withdrawing substituent containing sulphonyl chlorides and showed good regioselectivity (scheme 1.49).[77]



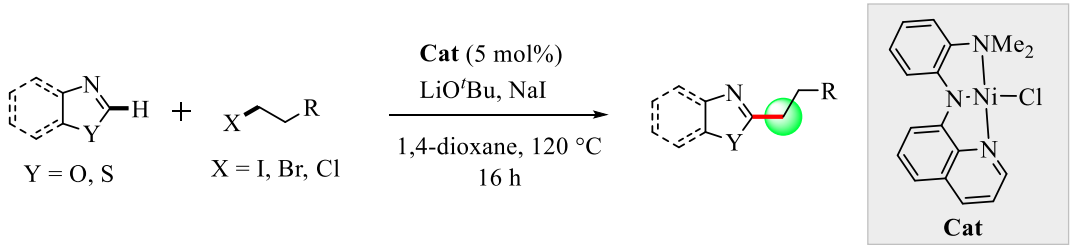
Scheme 1.49: Cu-catalysed C2-sulphonylation of quinoline *N*-oxides

In 2020, Glorius and co-workers have reported the synthesis of 1,3-enynes, pyrrols and furans using $MnBr(CO)_5$ as catalyst in a chemo-, regio- and stereoselective way. Interestingly, same transformation did not proceed with Ru- and Rh-based catalysts (scheme 1.50).[78]



Scheme 1.50: Mn-catalysed C-H functionalization of indole with 1,3-enynes

Transition –metal catalyzed C-H alkylation with *β*-hydrogen containing alkyl halides is always a challenge due to the possible competitive *β*-H elimination product. Punji prepared the quinolinyl based Ni(II)-pincer catalyst **Cat** using which they were able to perform alkylation of azoles with alkyl halides. Both experimental and DFT studies indicated the involvement of Ni(II)/Ni(III)-redox system in the catalytic cycle (scheme 1.51).[79]

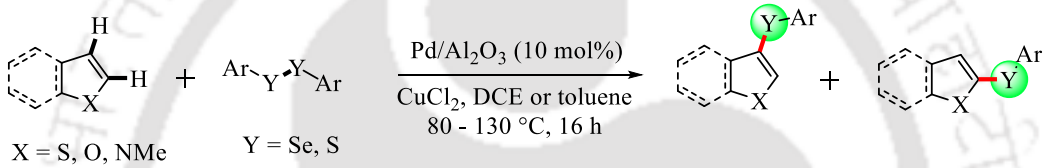


Scheme 1.51: Ni-catalysed C-H functionalization of azoles with alkyl halides

1.5.2. Heterogeneous catalysis

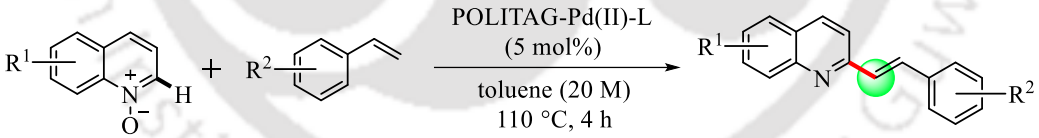
Although 3d-metal catalysts have provided a cheaper and less-toxic alternative to the heavier counterparts, they still suffer from low recyclability and the fact that the removal of such trace metal impurities from pharmaceutical products in industrial scale demands special treatments. In this regard, heterogeneous catalysts provide a promising alternative, as they allow the easy recovery of the catalyst. If the catalytic activity loss is very low during recovering, the process can be very sustainable even with the precious heavier transition metals. Such heterogeneous catalytic systems can provide specific site-selectivity over their homogeneous counterparts. Further, their catalytic activity can be increased by judicious design of hybrid metal catalysts which can lead to innovative transformations.[20] A few selected examples are shown in below for C-H functionalization of *N*-oxides (or related fused *N*-hetroarenes) under heterogenous catalytic condition.

In 2015, Glorius and co-workers reported the use of Pd/Al_2O_3 catalytic system with $CuCl_2$ for the direct C-H thiolation and selenation of fused heteroarenes (scheme 1.52).[80]



Scheme 1.52: Pd-catalysed C-H thiolation/selenation of fused heteroarenes

Vaccaro and his group in 2020 reported the first regioselective C2-alkenylation of quinoline *N*-oxides using recoverable Pd(II)-catalyst supported on polystyrene. The recovered catalyst did not lose its morphology during reaction and was reusable for several times without hampering the percentage of yield (scheme 1.53).[81]

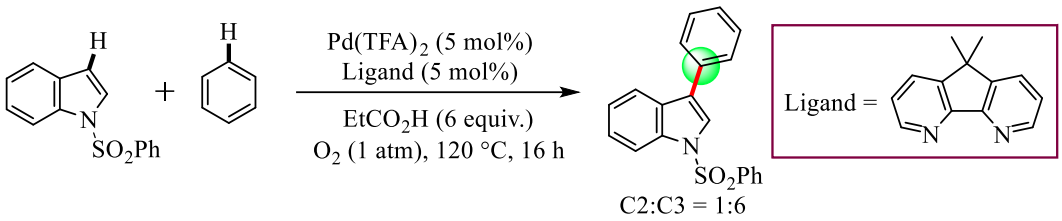


Scheme 1.53: C-H alkenylation of quinoline *N*-oxides using heterogeneous Pd-catalyst

1.5.3. Benign oxidants

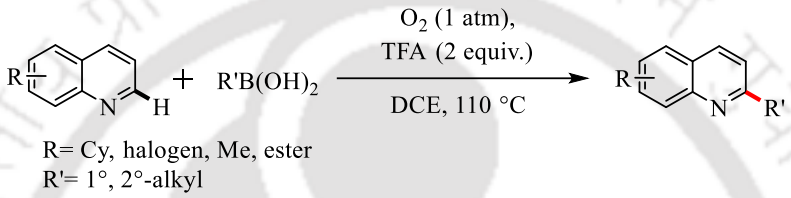
The classical transition-metal-catalyzed C-H functionalization involves the following steps- i) C-H activation, ii) functionalization of the carbametallic intermediate, iii) reductive elimination and iv) reoxidation of the metal center. To regenerate the catalyst in the catalytic cycle, often oxidants are used. They are either metal-based oxidants (such as, Ag(I) or Cu(II) salts), or organic (e.g., benzoquinone) /inorganic-based oxidants (e.g., persulfate). However, they have their own limitations. In this context, molecular oxygen was found as the alternative benign oxidant as it produces water as the only byproduct. But the use of oxygen is limited to metal systems with competent redox potential.[20] In their pioneering work, Stahl and co-workers reported the Pd-catalysed aerobic oxidative cross-coupling between indoles and benzene using diazafluorene based ligands. They have mentioned that C2:C3 selectivity was governed by the

choice of ancilliary ligand as well as the Pd(II)-salt. The role of molecular oxygen in the catalytic process was also demonstrated (scheme 1.54).[82]



Scheme 1.54: C-H arylation of indoles using Pd-catalyst and molecular O_2

Liu and co-workers reported the C2-alkylation of quinolines with arylboronic acid with the help of molecular oxygen as an oxidant. This was one of the first reports to use molecular oxygen in a Minisci type alkylation reaction (scheme 1.55).[83]



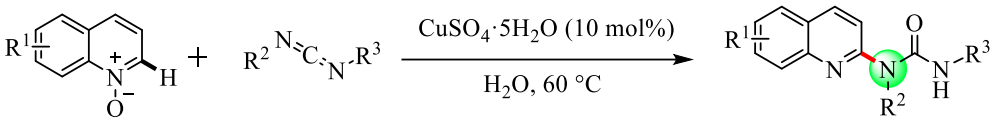
Scheme 1.55: C-H alkylation of quinolines using arylboronic acids and molecular O_2

Photoredox and metalloelectro-catalysis are another two alternative approaches for benign oxidation reactions. I have shown some of the photoredox catalytic reactions in section X. The metallaelectrocatalysis has the advantage that it does not depend upon expensive catalysis and the redox potentials could be tuned according to the requirement using a potentiostat.[20] This generally gives a broader functional group tolerance and eliminates the need of multistep ligand synthesis. Also, the byproduct is generally hydrogen which could be further used as fuel in the energy sector.

1.5.4. Greener solvents

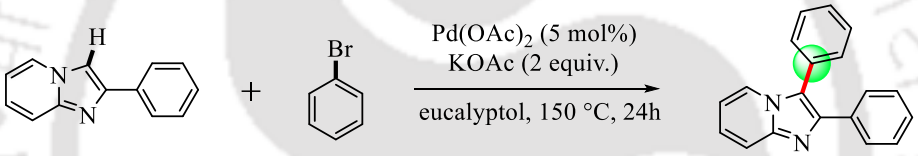
In general, a large amount of organic solvent is required in organic transformations, either during synthesis steps or in purifications steps and later, these are not often reusable with appropriate technique. Most of the organic solvents commonly used in laboratory like dichloromethane, tetrahydrofuran etc. are volatile, flammable and toxic and certified unwanted in a medicinal environment. These volatile organic solvents contribute to acid rain, ozone depletion and various health hazards. Compared to them, water is the most abundant solvent in nature and non-corrosive, non-toxic and non-flammable. Hence scientific community seeks to develop reactions with green-directed solvents (e.g., H_2O) or under solvent-free conditions.[84] Different pharmaceutical companies have published their own guidelines for determining green solvents, where environmental factors like biodegradability and environmental toxicity, Industrial constraints like costliness, very low or very high boiling points, freezing point above 0 ºC etc., health hazards like allergic to carcinogenic etc. are some of the points where the solvents are ranked and graded. Some of the selected reports are given in below for C-H functionalization of *N*-oxides or *N*-heteroarenes.

Recently, He and coworkers have reported copper catalyzed synthesis of quinoline-2-yl substituted ureas in water from the reaction of quinoline *N*-oxide and carbodiimide under mild reaction conditions. The protocol also benefitted from the fact that there were no other additive or base used and the products were easily obtained *via* simple filtration and washing with ethanol (scheme 1.56).[85]



Scheme 1.56: synthesis of quinoline-2-yl substituted ureas in water

Alcohol based solvents like ethanol, PEG-400, ethyl acetate, 2-methyltetrahydrofuran etc. are also utilized as green solvents in industrial purposes. In this regard, biomass derived solvents, or bio-solvents are gaining popularity among academia as well as industries. Eucalyptol, the main component of eucalyptus essential oil and considered as a byproduct in the paper industry, is being explored as a rival to THF, 1,4-dioxane and DCE etc. Raboin and co-workers reported the use of eucalyptol as a green solvent for the first time for C-H arylation of *N*-heteroarenes in 2019 (scheme 1.57).[86] Other such biomass derived solvents are limonene, γ-valerolactone, cyrene etc. are also useful.[20]

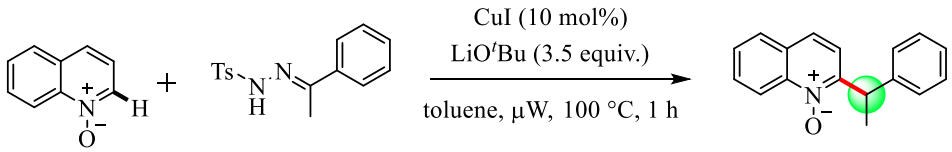


Scheme 1.57: C-H arylation of *N*-heteroarenes using eucalyptol as solvent

1.5.5. Alternative energy sources

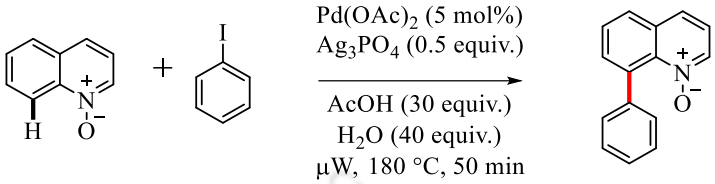
a) Microwave irradiation

Generally, C-H activation requires high temperature and long reaction times. In this regard, microwave irradiation has emerged as non-conventional energy source which can provide the advantage of instantaneous and rapid heating which would lead to very short reaction times. This rapid heating can be attributed to the fact that microwave frequencies directly interact with the dipoles or ionic molecules in the reaction medium and energy transfer happens within a nanosecond (10^{-9} sec). Since the interaction happens at molecular level, the entire medium is exposed to the applied electromagnetic field at the same time with little wall effects, thus, resulting in homogeneous heating. Microwave processes are also shown to be effective alternative to many organic solvents, thus, inspiring different solvent-less processes.[87] Recently, Jain *et. al.* reported the microwave-assisted cross-coupling reaction between *N*-oxides and *N*-tosylhydrazones using cuprous iodide as the catalyst, producing C2-alkylated *N*-ozides in a highly chemo- and regioselective manner. Both primary and secondary alkylated *N*-oxides could be achieved by this protocol (scheme 1.58).[88]



Scheme 1.58: microwave-assisted C-H arylation of *N*-oxides

In another example, C8-arylation of quinoline *N*-oxides was described by Larionov using $Pd(OAc)_2$ as catalyst with Ag_3PO_4 as an additive under MW irradiation. Complete conversion was achieved under 1 h using MW, whereas the same outcome required 16 h while carried out under conventional heating (scheme 1.59).[89]

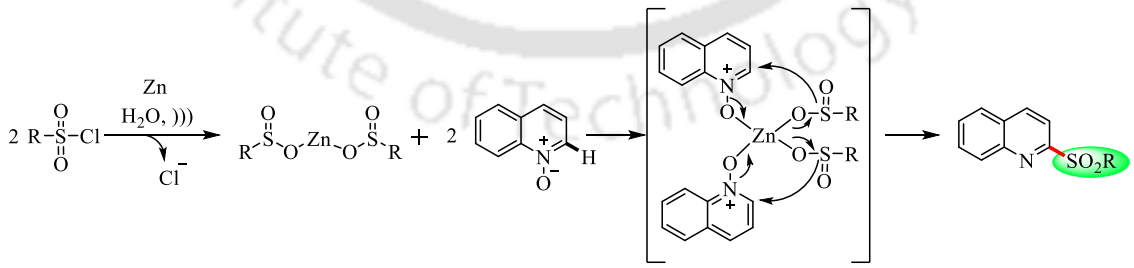


Scheme 1.59: microwave-assisted C8-arylation of quinoline *N*-oxides

b) Ultrasound

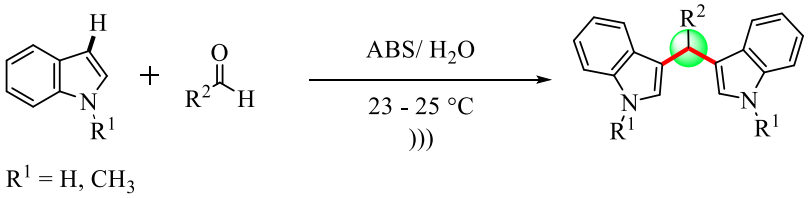
Besides MW irradiation, another emerging greener energy source for organic synthesis is ultrasound technique. This works *via* a phenomenon called acoustic cavitation (formation, growth and implosion of microbubbles inside a liquid) which starts with the pre-existing bubbles in the system. The very fast implosion process means almost adiabatic heating process in a small intra-bubble 'hot-spot' that can reach temperature and pressure of about 5000 K and 1000 bar respectively. The sonochemistry has been used to carry out different kinds of chemical reactions in a greener way.[90] Two selected examples are given in below.

In 2017, He *et.al* reported ultrasound-assisted C2-sulfonylation of quinoline *N*-oxides under open-air conditions in a base- and organic solvent-free manner. Surprisingly, the reaction proceeds efficiently in aqueous medium. With the assistance of ultrasound irradiation, sulfonyl chloride is reduced with zinc dust to form a zinc bis-sulphinate compound. Then, quinoline *N*-oxide coordinated with zinc complex to produce the reactive intermediate, which underwent an intramolecular nucleophilic addition reaction to form the sulphonylated product with the release of zinc hydroxide. The use of ultrasound not only helped to increase the efficiency and reaction rate of the reaction but also minimized the side reactions while comparing to conventional heating conditions. The reaction exhibited impressive green matrix parameter values (scheme 1.60).[91]



Scheme 1.60: ultrasound-assisted C2-sulphonylation of quinoline *N*-oxides

Later, Li group reported another ultrasound assisted synthesis of bis(indolyl)methanes using dodecyl benzenesulphonic acid (ABS) as catalyst under aqueous medium. The reaction occurred at room temperature and use of water as solvent made the whole process very interesting and useful from sustainability point of view (scheme 1.61).[92]

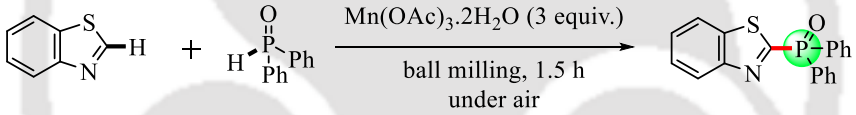


Scheme 1.61: ultrasound-assisted C-H functionalisation of indoles

c) Mechanochemical synthesis

Mechanochemical synthesis processes constitute another aspect of sustainable energy sources used in organic synthesis. Solid-state materials have some inherent properties like highly ordered molecular arrangement and highly reduced molecular motions. These properties give them some distinctive chemical behaviors from the liquid state counterparts. Under mechanochemical processes, which are carried out in solvent-less conditions, the manual grinding or high-energy ball-mills allow the solid-state materials to have intimate contacts between them. These processes serve various sustainability aspects, such as energy conservation and waste minimization as no solvent is involved.[93] A representative example is given below.

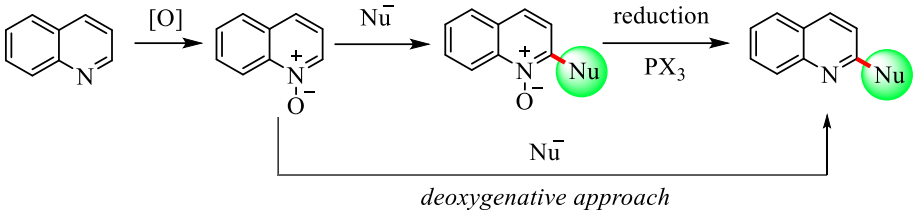
A direct phosphonylation reaction of benzothiazole with organophosphorus compounds has been reported under ball-milling conditions. $Mn(OAc)_3 \cdot 2H_2O$ was used as a promoter and the reaction proceeded smoothly under air in an efficient manner (scheme 1.62).[94]



Scheme 1.62: C-H functionalisation of thiazoles under ball-milling conditions

1.6. Scope and objective of the thesis:

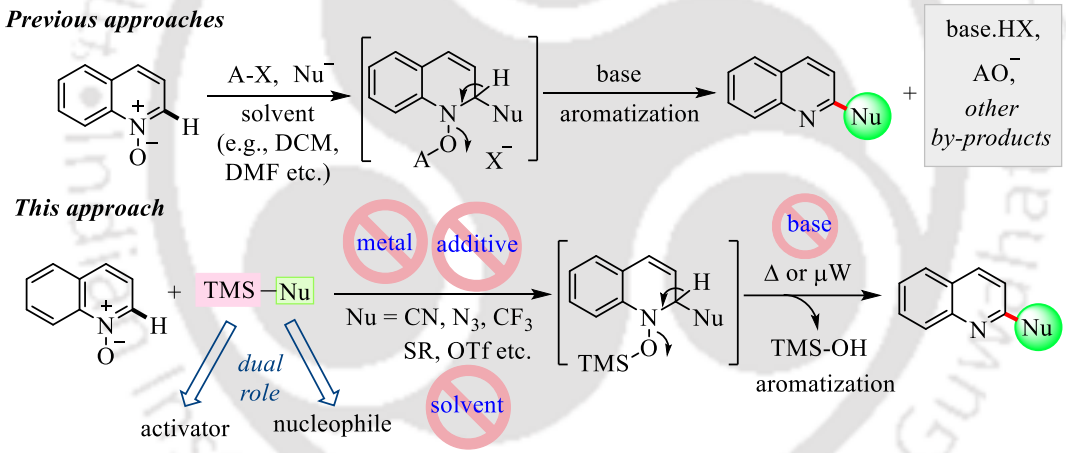
After a detailed investigation of the literature, it can be said that though several methods have been reported for site-selective C2-functionalization of quinoline, still there is sufficient room for further improvements, especially towards construction of C-C and C-N bonds in a sustainable manner. It has also been found that quinoline *N*-oxide is the most appropriate choice (instead of quinolines) for C2-selective functionalization (See section 1.4). In the literature, three principal approaches have been demonstrated for C2-functionalization of *N*-oxides: firstly, activation of the substrate followed by nucleophilic aromatic substitution, secondly, radical Minisci addition to the substrate and lastly, transition-metal catalyzed cross-coupling reactions. Often these methods lead to products with *N*-oxide moiety being intact, which necessitate one additional reduction step to obtain the more desired quinoline product, thereby, reducing the step-economy of the process (scheme 1.63). To address this limitation, my research interest is towards the development of deoxygenative nucleophilic functionalization of *N*-oxide in one-pot with low-waste and eco-friendly manner (a). In addition, another research interest is direct C-H functionalization of *N*-oxides *via* 1,3-dipolar cycloaddition reaction (b).



Scheme 1.63: direct deoxygenative C-H functionalisation of quinoline *N*-oxides

(a) C2-functionalization of *N*-oxides *via* a nucleophilic aromatic substitution

Conventionally, superstoichiometric amount of activating agents, and bases are required and halogenated solvents are used as the reaction medium for the deoxygenative nucleophilic functionalization of *N*-oxides. Hence, the process is not economically viable and possesses also an environmental issue. Herein, I am planning to explore the substrate/reagent which would show dual behavior of a nucleophile and an activating agent, by which the process can avoid any external promoters, or additives. Simple heating, or microwave irradiation (μw) may be enough to facilitate aromatization in the final step, by which conventional bases can be avoided. Besides this, it would be definitely beneficial if the protocol could be carried out in a solvent-free manner and avoiding any aqueous work-up (which is often required to remove the promoters, additives, bases, and side products in the traditional C-H functionalization of *N*-heteroarenes) (scheme 1.64).



Scheme 1.64: metal-free deoxygenative C-H functionalisation of quinoline *N*-oxides

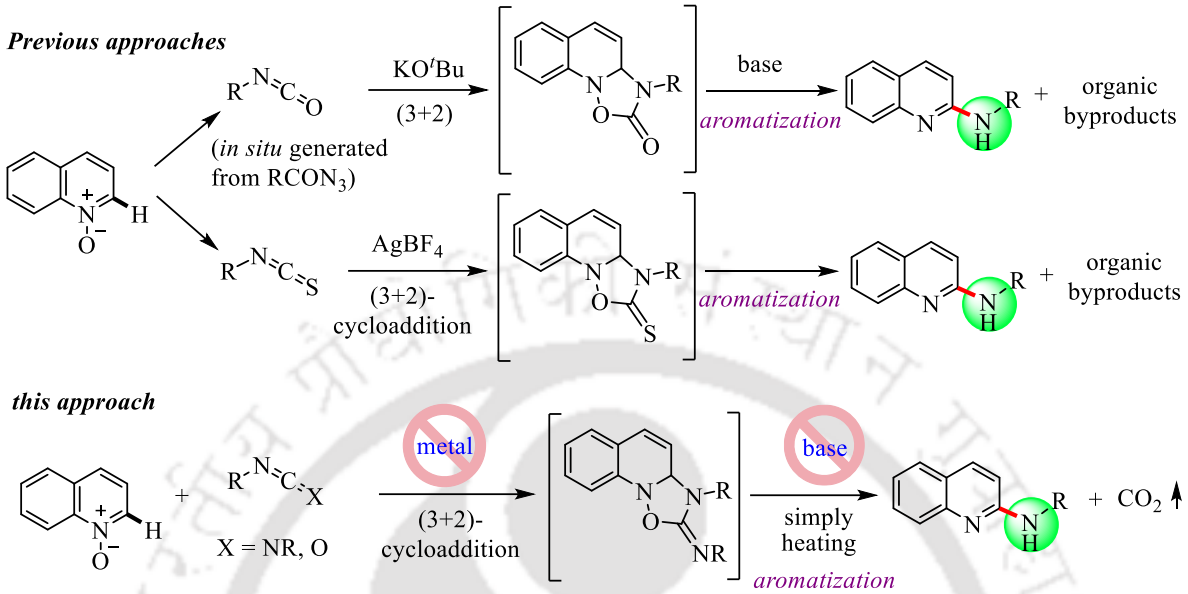
(b) C2-functionalization of *N*-oxides *via* 1,3-dipolar cycloaddition reaction

As mentioned, since C-H functionalization of *N*-oxide *via* the 1,3-dipolar cycloaddition pathway is less explored (see Section X), present study focuses on the construction of C-N and C-C bonds at the C2 position *via* a (3 + *n*)-type cycloadduct (n = 2, 3) by using carbodiimide as 1,2-dipole or D–A cyclopropane as an *in-situ* generated 1,3-dipole species.

C2-amination of heteroaromatic *N*-oxides:

It has been discussed that *in-situ* formed isocyanate with base and isothiocyanates with $AgBF_4$ catalyst would undergo deoxygenative C2-amination with *N*-oxides to afford C2-aminated products *via* [3+2]-cycloaddition reactions. However, their congeners, the carbodiimide remains underexplored for C2 amination. Herein I thought that carbodiimides may take part in cycloaddition reaction with azine *N*-oxides to provide (3+2)-cycloadduct, which can subsequently get aromatized by simply conventional heating (in absence of any catalyst, base

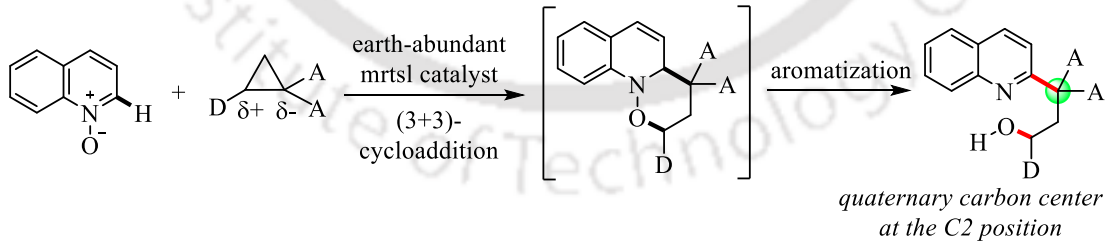
or additives etc.) to produce the desired aminated product and isocyanate. The corresponding isocyanate can further react with another molecule of *N*-oxide to give the aminated compound via (3+2)-cycloaddition pathway, and liberate CO_2 as the sole byproduct in the overall reaction (scheme 1.65). As a whole, the proposed strategy could be superior to the known methods in the context of atom economy, step economy and the reduction of undesired chemical waste.



Scheme 1.65: metal-free deoxygenative C-H amination of quinoline *N*-oxides

C2-alkylation of heteroaromatic *N*-oxides:

From the above literature survey, it was found that there is no report on tertiary alkylation of *N*-oxides *via* cycloaddition pathway, thereby I intend to explore the reactivity of *N*-oxides in this direction. Owing to the 1,3-zwitterion equivalent nature of donor–acceptor (D–A) cyclopropanes and the presence of ring strain (27.5 kcal mol^{-1}) and vicinal substitution of D–A groups, I anticipate that D–A cyclopropane might take part in (3+3)-dipolar cycloaddition reaction with *N*-oxides and subsequent aromatization would provide desired alkylated product with quaternary carbon at the C2 centre (scheme 1.66). Obviously, the proposed strategy would be beneficial in terms of atom- and step-economy.



Scheme 1.66: deoxygenative C-H alkylation of quinoline *N*-oxides

References:

1. (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257 – 10274, (b) Jain, S.; Chandra, V.; Jain, P. K.; Pathak, K.; Pathak, D.; Vaidya, A. Comprehensive Review on Current Developments of Quinoline-based Anticancer Agents. *Arab. J. Chem.* **2016**, *12*, 4920 – 4946.

2. (a) Runge, F. F. On Some Products of Coal Distillation. *Ann. Phy. Chem.* **1834**, *31*, 65–78, (b) Chisholm, H. Quinoline . In *Encyclopaedia Britannica, 11th Edition*; Chisholm, H. ed.; Cambridge University Press, 1911, pp 759.

3. (a) Levy, S.; Azoulay, S. J. Stories About the Origin of Quinquina and Quinidine. *Cardiovas. Electrophysiol.* **1994**, *5*, 635 – 636, (b) Claret, P. A. In *Comprehensive organic chemistry*; Sammes P. G. Ed.; Pergamon Press, Oxford, 1979; Vol 4, pp 55, (c) Calla-Magariños, J.; Quispe, T.; Giménez, A.; Freysdottir, J.; Troye-Blomberg, M.; Fernández, C. Quinolinic Alkaloids from *Galipea longiflora Krause* Suppress Production of Proinflammatory Cytokines *in vitro* and Control Inflammation *in vivo* upon *Leishmania* Infection in Mice. *Scand J Immunol.* **2013**, 77, 30–38, (d) Faux, N. G.; Ritchie, C. W.; Gunn, A.; Rembach, A.; Tsatsanis, A.; Bedo, J.; Harrison, J.; Lannfelt, L.; Blennow, K.; Zetterberg, H.; Ingelsson, M.; Masters, C. L.; Tanzi, R. E.; Cummings, J. L.; Herd, C. M.; Bush, A. I. PBT2 Rapidly Improves Cognition in Alzheimer's Disease: Additional Phase II Analyses. *J. Alzheimer's Dis.* **2010**, *20*, 509 – 516, (e) Haglof, K. J.; Popa, E.; Hochster, H. S. Recent Developments in the Clinical Activity of Topoisomerase-I Inhibitors. *Update Cancer Ther.* **2006**, *1*, 117– 145, (f) Mett, H.; Gyr, K.; Zak, O.; Vosbeck, K. Duodeno-pancreatic Secretions Enhance Bactericidal Activity of Antimicrobial Rugs. *Antimicrob Agents Chemother* **1984**, *26*, 35–38, (g) de la Fuente Revenga, M.; Shah, U. H.; Nassehi, N.; Jaster, A. M.; Hemanth, P.; Sierra, S.; Dukat, M.; González-Maeso, J. Psychedelic-like Properties of Quipazine and Its Structural Analogues in Mice. *ACS Chem. Neurosci.* **2021**, *12*, 831– 844, (h) Pfister, J. R. Isolation and Bioactivity of 2-Aminoquinoline from *Leucopaxillus albissimus*. *J. Nat. Prod.* **1988**, *51*, 969−970, (i) Huang, W. N.; Tso, T. K. Etoricoxib Improves Osteoarthritis Pain Relief, Joint Function, and Quality of Life in the Extreme Elderly. *Bosn. J. Basic Med. Sci*. **2018**, *18*, 87–94, (j) Chioukh, R.; Noel-Hudson, M.S.; Ribes, S.; Fournier, N.; Becquemont, L.; Verstuyft, C. Proton Pump Inhibitors Inhibit Methotrexate Transport by Renal Basolateral Organic Anion Transporter hOAT3. *Drug Metab. Dispos. Biol. Fate Chem.* **2014**, *42*, 2041–2048.

4. Yamamoto, K.; Asano, Y. Efficient production of lumichrome by *Microbacterium* sp. strain TPU 3598. *Appl. Environ. Microbiol.* **2015**, *81*, 7360 –7367.

5. (a) Kelsey, F. E.; Oldham, F. K.; Cantrell, W.; Geiling, E. M. K. Antimalarial Activity and Toxicity of a Metabolic Derivative of Quinine. *Nature* **1946**, *157*, 440 – 440, (b) Marshall, P. B. Loss of Antimalarial Properties in Quinine Degradation Products. *Nature* **1945**, *156*, 505 – 506.

6. Corio, A.; Gravier-Pelletier, C.; Busca, P. Regioselective Functionalization of Quinolines through C-H Activation: A Comprehensive Review. *Molecules*, **2021**, *26*, 5467.

7. (a) Guillemard, L.; Kaplaneris, N.; Ackermann, L.; Johansson, M. J. Late-stage C–H functionalization offers new opportunities in drug discovery. *Nat. Rev. Chem.* **2021**, *5*, 522 – 545, (b) Wencel-Delord, J.; Glorius, F. C–H bond activation enables the rapid construction and late-stage diversification of functional molecules. *Nat. Chem.* **2013**, *5*, 369 – 375.

8. (a) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062 – 5085, (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442– 4489.

9. Mphahlele, M. J.; Lesenyeho, L. G. Halogenated Quinolines as Substrates for the Palladium-Catalyzed Cross-Coupling Reactions to Afford Substituted Quinolines. *J. Heterocyclic Chem.* **2013**, *50*, 1 – 16.

10. Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M.; Malmir, M. Buchwald-Hartwig Reaction: An Overview. *J. Organomet. Chem.* **2018**, *861*, 17– 104.

11. (a) Campeau, L.-C.; Fagnou, K. Applications of and Alternatives to π-Electron-Deficient Azine Organometallics in Metal Catalyzed Cross-Coupling Reactions. *Chem. Soc. Rev.* **2007**, *36*, 1058 – 1068, (b) Rewcastle, G. W.; Katritzky, A. R. Generation and Reactions of sp^2-Carbanionic Centers in the Vicinity of Heterocyclic Nitrogen Atoms. *Adv. Heterocycl. Chem.* **1993**, *56*, 155 – 302.

12. Campeau, L.-C.; Rousseaux, S.; Fagnou, K. A Solution to the 2-Pyridyl Organometallic Cross-Coupling Problem: Regioselective Catalytic Direct Arylation of Pyridine *N*-Oxides. *J. Am. Chem. Soc.* **2005**, *127*, 18020 – 18021.

13. Rogge, T.; Kaplaneris, N.; Chatani, N.; Kim, J.; Chang, S.; Punji, B.; Schafer, L. L.; Musaev, D. G.; Wencel-Delord, J.; Roberts, C. A.; Sarpong, R.; Wilson, Z. E.; Brimble, M. A.; Johansson, M. J.; Ackermann, L. C – H Activation *Nat. Rev. Methods Prim.* **2021**, *1*, 43.

14. Roudesly, F.; Oble, J.; Poli, G. Metal-catalyzed C – H Activation/functionalization: The Fundamentals. *J. Mol. Catal. A: Chem.* **2017**, *426*, 275– 296.

15. (a) Janowicz, A. H.; Bergman, R. G. C–H Activation in Completely Saturated Hydrocarbons: Direct Observation of M(R)(H). *J. Am. Chem. Soc.* **1982**, *104*, 352– 354, (b) Hoyano, J. K.; Graham, W. A. G. Oxidative Addition of the Carbon–Hydrogen Bonds of Neopentane and Cyclohexane to a Photochemically Generated Iridium(I) Complex. *J. Am. Chem. Soc.* **1982**, *104*, 3723– 3725.

16. Bergman, R. G. C – H Activation. *Nature* **2007**, *446*, 391 – 393.

17. Fier, P. S.; Hartwig, J. F. Selective C-H Fluorination of Pyridines and Diazines Inspired by a Classic Amination Reaction. *Science* **2013**, *342*, 956 – 960.

18. Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. Innate C – H Trifluoromethylation of Heterocycles. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 14411– 14415.

19. Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. Catalytic enantioselective Minisci-type addition to heteroarenes. *Science* **2018**, *360*, 419– 422.

20. Dalton, T.; Faber, T.; Glorius, F. C-H Activation: Toward Sustainability and Applications. *ACS Cent. Sci.* **2021**, *7*, 245– 261.

21. Ji Ram, V.; Sethi, A.; Nath, M.; Pratap, R. Chapter 2 - Six-Membered Heterocycles. In *The Chemistry of Heterocycles*, Ji Ram, V.; Sethi, A.; Nath, M.; Pratap, R. Eds. Elsevier: 2019; pp 3-391.

22. Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. C–H Functionalization of Azines. *Chem. Rev.* **2017**, *117*, 9302– 9332.

23. Wang, D.; Désaubry, L.; Li, G.; Huang, M.; Zheng, S. Recent Advances in the Synthesis of C2-Functionalized Pyridines and Quinolines Using *N*-Oxide Chemistry. *Adv. Synth. Catal.* **2015**, *363*, 2– 39.

24. Bering, L.; Antonchick, A. P. Regioselective Metal-Free Cross-Coupling of Quinoline N-Oxides with Boronic Acids. *Org. Lett.* **2015**, *17*, 3134– 3137.

25. Yuan, Y.; Jiang, M.; Wang, T.; Xiong, Y.; Li, J.; Guo, H.; Lei, A. Synergy of Anodic Oxidation and Cathodic Reduction Leads to Electrochemical Deoxygenative C2 Arylation of Quinoline *N*-Oxides. *Chem. Commun*. **2019**, *55*, 11091– 11094.

26. Dyer, R. M. B.; Hahn, P. L.; Hilinski, M. K. Selective Heteroaryl *N*-Oxidation of Amine-Containing Molecules. *Org. Lett.* **2018**, *20*, 2011−2014.

27. (a) Konev, M. O.; Cardinale, L.; von Wangelin, A. J. Catalyst-Free *N*-Deoxygenation by Photoexcitation of Hantzsch Ester. *Org. Lett.* **2020**, *22*, 1316−1320, (b) Kim, K. D.; Lee, J. H. Visible-Light Photocatalyzed Deoxygenation of *N*-Heterocyclic *N*-Oxides. *Org. Lett.* **2018**, *20*, 7712−7716.

28. Reissert, A. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 3415-3435.

29. Malykhin, R. S.; Sukhorukov, A. Y. Nucleophilic Halogenation of Heterocyclic *N*-Oxides: Recent Progress and a Practical Guide. *Adv. Synth. Catal.* **2021**, *363*, 3170– 3188.

30. (a) Wang, D.; Wang, Y.; Zhao, J.; Li, L.; Miao, L.; Wang, D.; Sun, H.; Yu, P. A Highly Practical and Convenient Halogenation of Fused Heterocyclic *N*-oxides. *Tetrahedron*, **2016**, *72*, 5762 – 5768, (b) Wang, D.; Jia, H.; Wangb, W.; Wanga, Z. A Practical and Mild Chlorination of Fused Heterocyclic *N*-oxides. *Tetrahedron Lett.*, **2014**, *55*, 7130 – 7132.

31. Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. Regioselective Bromination of Fused Heterocyclic *N*-Oxides. *Org. Lett.* **2013**, *15*, 792– 795.

32. Lucas, S. C. C.; Moore, J. E.; Donald, C. S.; Hawkins, J. L. Synthesis of 4-arylthieno[2,3-*b*]pyridines and 4-aminothieno[2,3-*b*]pyridines via a regioselective bromination of thieno[2,3-*b*]pyridine. *J. Org. Chem.* **2015**, *80*, 12594 – 12598.

33. Hwang, T.; Bartberger, M. D.; Chen, Y. Application of 1,1-ADEQUATE, HMBC, and Density Functional Theory to Determine Regioselectivity in the Halogenation of Pyridine *N*-Oxides. *Org. Lett.* **2016**, *18*, 1956– 1959.

34. Xiong, H.; Hoye, A. T.; Fan, K.-H.; Li, X.; Clemens, J.; Horchler, C. L.; Lim, N. C.; Attardo, G. Facile Route to 2-fluoropyridines *via* 2-pyridyltrialkylammonium Salts Prepared from Pyridine *N*-oxides and Application to ^{18}F-labeling. *Org. Lett.* **2015**, *17*, 3726–3729.

35. Wang, D.; Zhao, J.; Wang, Y.; Hu, J.; Li, L.; Miao, L.; Feng, H.; Désaubry, L.; Yu, P. A General and Efficient Synthesis of 2-Pyridones, 2-Quinolinones, and 1-Isoquinolinones from Azine *N*-Oxides. *Asian J. Org. Chem.* **2016**, *5*, 1442 – 1446.

36. (a) Londregan, A. T.; Jennings, S.; Wei, L. Mild Addition of Nucleophiles to Pyridine-*N*-Oxides. *Org. Lett.* **2011**, *13*, 1840– 1843, (b) Lian, Y.; Coffey, S. B.; Li, Q.; Londregan, A. T. Preparation of Heteroaryl Ethers from Azine *N*-Oxides and Alcohols. *Org. Lett.* **2016**, *18*, 1362– 1365.

37. Aithagani, S. K.; Kumar, M.; Yadav, M.; Vishwakarma, R. A.; Singh, P. P. Metal-Free, Phosphonium Salt-Mediated Sulfoximination of Azine *N*-Oxides: Approach for the Synthesis of *N*-Azine Sulfoximines. *J. Org. Chem.* **2016**, *81*, 5886 – 5894.

38. Sun, K.; Chen, X.-L.; Li, X.; Qu, L.-B.; Bi, W.-Z.; Chen, X.; Ma, H.-L.; Zhang, S.-T.; Han, B.-W.; Zhao, Y.-F.; Li, C.-J. *H*-phosphonate-Mediated Sulfonylation of Heteroaromatic *N*-Oxides: A Mild and Metal-free One-pot Synthesis of 2-Sulfonyl Quinolines/pyridines. *Chem. Commun.* **2015**, *51*, 12111– 12114.

39. Pagar, V. V.; Liu, R. –S. Gold-catalyzed *α*-Furanylations of Quinoline *N*-Oxides with Alkenyldiazo Carbonyl Species. *Org. Biomol. Chem.* **2015**, *13*, 6166–6169.

40. Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. Nucleophilic Character of Alkyl Radicals-VI: A New Convenient Selective Alkylation of Heteroaromatic Bases. *Tetrahedron* **1971**, *27*, 3575– 2579.

41. Tauber, J.; Imbri, D.; Opatz, T. Radical Addition to Iminium Ions and Cationic Heterocycles. *Molecules* **2014**, *19*, 16190 – 16222.

42. Proctor, R. S. J.; Phipps, R. J. Recent Advances in Minisci-Type Reactions. *Angew. Chem. Int. Ed.* **2019**, *58*, 13666 – 13699.

43. Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. Palladium-Catalyzed C-H Activation/Cross-Coupling of Pyridine *N*-Oxides with Nonactivated Secondary Alkyl Bromides. *J. Am. Chem. Soc.* **2013**, *135*, 616– 619.

44. Zhang, W.-M.; Dai, J.-J.; Xu, J.; Xu, H.-J. Visible-Light-Induced C2 Alkylation of Pyridine N-Oxides. *J. Org. Chem.* **2017**, *82*, 2059– 2066.

45. Sun, A. C.; McClain, E. J.; Beatty, J. W.; Stephenson, C. R. J. Visible Light-mediated Decarboxylative Alkylation of Pharmaceutically Relevant Heterocycles. *Org. Lett.* **2018**, *20*, 3487– 3490.

46. Yuan, Y.; Jiang, M.; Wang, T.; Xiong, Y.; Li, J.; Guo, H.; Lei, A. Synergy of Anodic Oxidation and Cathodic Reduction Leads to Electrochemical Deoxygenative C2 Arylation of Quinoline *N*-Oxides. *Chem. Commun.* **2019**, *55*, 11091– 11094.

47. Liang, C.; Zhuo, W.-T.; Niu, Y.-N.; Gao, G.-L. Visible-Light-Promoted C2 Trifluoromethylation of Quinoline *N*-Oxides. *Synthesis* **2020**, 52, 219-226.

48. Du, B.; Qian, P.; Wang, Y.; Mei, H.; Han, J.; Pan, Y. Cu-Catalyzed Deoxygenative C2-Sulfonylation Reaction of Quinoline *N*-Oxides with Sodium Sulfinate. *Org. Lett.* **2016**, *18*, 4144– 4147.

49. Roudesly, F.; Veiros, L. F.; Oble, J.; Poli, G. Pd-Catalyzed Direct C–H Alkenylation and Allylation of Azine *N*-Oxides. *Org. Lett.* **2018**, *20*, 2346– 2350.

50. Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. Palladium-Catalyzed Alkenylation of Quinoline *N*-oxides *via* C–H Activation under External-Oxidant-Free Conditions. *J. Am. Chem. Soc.* **2009**, *131*, 13888– 13889.

51. Wu, Z.; Pi, C.; Cui, X.; Bai, J.; Wu, Y. Direct C-2 Alkylation of Quinoline *N*-Oxides with Ethers *via* Palladium-Catalyzed Dehydrogenative Cross-Coupling Reaction. *Adv. Synth. Catal.* **2013**, *355*, 1971– 1976.

52. Lai, M.; Zhai, K.; Cheng, C.; Wu, Z.; Zhao, M. Direct Thiolation of Aza-heteroaromatic *N*-oxides with Disulfides *via* Copper-catalyzed Regioselective C-H Bond Activation. *Org. Chem. Front.* **2018**, *5*, 2986– 2991.

53. Yu, H.; Dannenberg, C. A.; Li, Z.; Bolm, C. Copper-Catalyzed Direct Sulfoximination of Heteroaromatic *N*-Oxides by Dual C–H/N–H Dehydrogenative Cross-Coupling. *Chem.—Asian J.* **2016**, *11*, 54– 57.

54. Li, G.; Jia, C.; Sun, K. Copper-Catalyzed Intermolecular Dehydrogenative Amidation/Amination of Quinoline *N*-Oxides with Lactams/Cyclamines. *Org. Lett.* **2013**, *15*, 5198– 5201.

55. Li, G.; Jia, C.; Sun, K.; Lv, Y.; Zhao, F.; Zhou, K.; Wu, H. Copper (II)-Catalyzed Electrophilic Amination of Quinoline *N*-oxides with *O*-benzoyl Hydroxylamines. *Org. Biomol. Chem.* **2015**, *13*, 3207– 3210.

56. Zhu, C.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. Copper-Catalyzed Direct Amination of Quinoline *N*-Oxides *via* C-H Bond Activation under Mild Conditions. *Org. Lett.* **2014**, *16*, 1840– 1843.

57. Wang, Z.; Han, M.-Y.; Li, P.; Wang, L. Copper-Catalyzed Deoxygenative C-2 Amination of Quinoline *N*-Oxides. *Eur. J. Org. Chem.* **2018**, *2018*, 5954– 5960.

58. Zhang, Y.; Zhang, S.; Xu, G.; Li, M.; Tang, C.; Fan, W. Cu-Catalyzed Carbamoylation *versus* Amination of Quinoline *N*-Oxide with Formamides. *Org. Biomol. Chem.* **2019**, *17*, 309– 314.

59. Wang, Z.-L.; Li, G.; Dong, D.-Q.; Yang, Y.; Yu, X.-Y. Direct Carbamoylation of Quinoline N-oxides with Hydrazinecarboxamides *via* C–H Bond Activation Catalyzed by Copper Catalyst. *Adv. Synth. Catal.* **2019**, *361*, 832– 835.

60. Loska, R. Recent Advances in Cycloaddition Reactions of Heterocyclic *N*-Oxides. In *Heterocyclic N-Oxides*, Larionov, O. V. Ed.; Springer International Publishing: Cham, 2017; pp 85-110.

61. Huisgen, R. 1,3-Dipolar Cycloadditions-Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A. Ed.; Wiley Interscience: New York, 1984; Vol.1, pp 3.

62. Huisgen, R. 1,3-Dipolar Cycloadditions: Past and Future. *Angew. Chem., Int. Ed.* **1963**, *2*, 565 – 632.

63. Huisgen, R.; Mloston, G.; Langhals, E. The First Two-step 1,3-Dipolar Cycloadditions: Interception of Intermediate. *J. Org. Chem.* **1986**, *51*, 4085– 4087.

64. Mailey, E. A.; Ocone, L. R. Fluoroalkylpyridines. A Novel Rearrangement. *J. Org. Chem.* **1968**, *33*, 3343– 3344.

65. Loska, R.; Mąkosza, M. New Synthesis of 2-Heteroarylperfluoropropionic Acids Derivatives by Reaction of Azine *N*-Oxides with Hexafluoropropene. *Chem. – Eur. J.* **2008**, *14*, 2577– 2589.

66. Kumar, R.; Kumar, I.; Sharma, R.; Sharma, U. Catalyst and Solvent-Free Alkylation of Quinoline *N*-oxides with Olefins: A Direct Access to Quinoline-Substituted α-Hydroxy Carboxylic Derivatives. *Org. Biomol. Chem.* **2016**, *14*, 2613– 2617.

67. Zhou, W.; Miura, T.; Murakami, M. Photocatalyzed Ortho-Alkylation of Pyridine *N*-Oxides through Alkene Cleavage. *Angew. Chem. Int. Ed.* **2018**, *57*, 5139– 5142.

68. Han, S.; Chakrasali, P.; Park, J.; Oh, H.; Kim, S.; Kim, K.; Pandey, A. K.; Han, S. H.; Han, S. B.; Kim, I. S. Reductive C2-Alkylation of Pyridine and Quinoline *N*-Oxides Using Wittig Reagents. *Angew. Chem. Int. Ed.* **2018**, *57*, 12737– 12740.

69. Kim, D.; Ghosh, P.; Kwon, N. Y.; Han, S. H.; Han, S.; Mishra, N. K.; Kim, S.; Kim, I. S. Deoxygenative Amination of Azine *N*-oxides with Acyl Azides *via* [3 + 2] Cycloaddition. *J. Org. Chem.* **2020**, *85*, 2476– 2485.

70. Xie, L.-Y.; Peng, S.; Jiang, L.-L.; Peng, X.; Xia, W.; Yu, X.; Wang, X.-X.; Cao, Z.; He, W.-M. $AgBF_4$-Catalyzed Deoxygenative C2-amination of Quinoline *N*-Oxides with Isothiocyanates. *Org. Chem. Front.* **2019**, *6*, 167– 171.

71. An, Y.; Xia, H.; Wu, J. Base-controlled [3+3] Cycloaddition of Isoquinoline *N*-oxides with Azaoxyallyl Cations. *Chem. Commun.* **2016**, *52*, 10415– 10418.

72. Cordier, M.; Archambeau, A. (3 + 3) Cycloaddition of Oxyallyl Cations with Nitrones: Diastereoselective Access to 1,2-oxazinanes. *Org. Lett.* **2018**, *20*, 2265 – 2268.

73. Brundtland, G. Report of the World Commission on Environment and Development: Our Common Future. *United Nations General Assembly document A/42/427* 1987.

74. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*. Oxford University Press: 1998.

75. Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C-H Activation. *Chem. Rev.* **2019**, *119*, 2192– 2452.

76. Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. Copper-Catalyzed Direct C Arylation of Heterocycles with Aryl Bromides: Discovery of Fluorescent Core Frameworks. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296– 3300.

77. Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y. Sulfonylation of Quinoline *N*-Oxides with Aryl Sulfonyl Chlorides via Copper-Catalyzed C–H Bonds Activation. *Org. Lett.* **2013**, *15*, 1270– 1273.

78. Cembellín, S.; Dalton, T.; Pinkert, T.; Schäfers, F.; Glorius, F. Highly Selective Synthesis of 1,3-Enynes, Pyrroles, and Furans by Manganese(I)-Catalyzed C–H Activation. *ACS Catal.* **2020**, *10*, 197– 202.

79. Patel, U. N.; Jain, S.; Pandey, D. K.; Gonnade, R. G.; Vanka, K.; Punji, B. Mechanistic Aspects of Pincer Nickel(II)-Catalyzed C–H Bond Alkylation of Azoles with Alkyl Halides. *Organometallics* **2018**, *37*, 1017– 1025.

80. Vásquez-Céspedes, S.; Ferry, A.; Candish, L.; Glorius, F. Heterogeneously Catalyzed Direct C–H Thiolation of Heteroarenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 5772– 5776.

81. Ferlin, F.; Lanari, D.; Vaccaro, L. Sustainable Flow Approaches to Active Pharmaceutical Ingredients. *Green Chem.* **2020**, *22*, 5937– 5955.

82. Campbell, A. N.; Meyer, E. B.; Stahl, S. S. Regiocontrolled Aerobic Oxidative Coupling of Indoles and Benzene using Pd Catalysts with 4,5-Diazafluorene Ligands. *Chem. Commun.* **2011**, *47*, 10257 – 10259.

83. Zhang, L.; Liu, Z.-Q. Molecular Oxygen-Mediated Minisci-Type Radical Alkylation of Heteroarenes with Boronic Acids. *Org. Lett.* **2017**, *19*, 6594 – 6597.

84. Gandeepan, P.; Kaplaneris, N.; Santoro, S.; Vaccaro, L.; Ackermann, L. Biomass-Derived Solvents for Sustainable Transition Metal-Catalyzed C–H Activation. *ACS Sustainable Chem. Eng.* **2019**, *7*, 8023– 8040.

85. Xie, L.-Y.; Peng, S.; Liu, F.; Liu, Y.-F.; Sun, M.; Tang, Z.-L.; Jiang, S.; Cao, Z.; He, W.-M. Clean Preparation of Quinolin-2-yl Substituted Ureas in Water. *ACS Sustainable Chem. Eng.* **2019**, *7*, 7193– 7199.

86. Campos, J. F.; Scherrmann, M. C.; Berteina-Raboin, S. Eucalyptol: A New Solvent for the Synthesis of Heterocycles Containing Oxygen, Sulfur and Nitrogen. *Green Chem.* **2019**, *21*, 1531– 1539.

87. Sharma, N.; Sharma, U. K.; Van der Eycken, E. V. Microwave-Assisted Organic Synthesis: Overview of Recent Applications. In *Green Techniques for Organic Synthesis*

and Medicinal Chemistry, Second Edition; Zhang, W., Cue, B. W. Eds.; John Wiley & Sons, 2018; pp 441– 468.

88. Jha, A. K.; Jain, N. The Microwave-Assisted *ortho*-Alkylation of Azine *N*-oxides with *N*-tosylhydrazones Catalyzed by Copper(I) Iodide. *Chem. Commun.* **2016**, *52*, 1831 – 1834.

89. Stephens, D. E.; Lakey-Beitia, J.; Atesin, A. C.; Ateşin, T. A.; Chavez, G.; Arman, H. D.; Larionov, O. V. Palladium-Catalyzed C8-Selective C-H Arylation of Quinoline *N*-Oxides: Insights into the Electronic, Steric, and Solvation Effects on the Site Selectivity by Mechanistic and DFT Computational Studies. *ACS Catal.* **2015**, *5*, 167– 175.

90. Wood, R. J.; Lee, J.; Bussemaker, M. J. A Parametric Review of Sonochemistry: Control and Augmentation of Sonochemical Activity in Aqueous Solutions. *Ultrason. Sonochem.* **2017**, *38*, 351– 370.

91. Xie, L.-Y.; Li, Y.-J.; Qu, J.; Duan, Y.; Hu, J.; Liu, K.-J.; Cao, Z.; He, W.-M. A Base-Free, Ultrasound Accelerated One-pot Synthesis of 2-Sulfonylquinolines in Water. *Green Chem.* **2017**, *19*, 5642– 5646.

92. Li, J. T.; Sun, M. X.; He, G. Y.; Xu, X. Y. Efficient and Green Synthesis of Bis(indolyl)methanes Catalyzed by ABS in Aqueous Media under Ultrasound Irradiation. *Ultrason. Sonochem.* **2011**, *18*, 412– 414.

93. Zhao, S.; Li, Y.; Liu, C.; Zhao, Y. Recent Advances in Mechanochemical C–H Functionalization Reactions. *Tetrahedron Lett.* **2018**, *59*, 317–324.

94. Li, L.; Wang, J.-J.; Wang, G.-W. Manganese(III) Acetate-Promoted Cross-Coupling Reaction of Benzothiazole/Thiazole Derivatives with Organophosphorus Compounds under Ball-Milling Conditions. *J. Org. Chem.* **2016**, *81*, 5433– 5439.

Regioselective Cyanation of Six-Membered *N*-Heteroaromatic Compounds Under Metal-, Activator-, Base- and Solvent-Free Conditions

2.1. Introduction

Heterocyclic compounds, especially *N*-containing heterocycles, represent a highly important class of compounds that exhibit diverse pharmacological and therapeutic effects.[1] However, the therapeutic effect of the *N*-heterocyclic scaffolds (such as the quinoline moiety) is often detoxified in the body due to the hydroxylation at the C-2 position, thereby resulting in the decline of the aforementioned therapeutic effect.[2] To block this detoxification, a vast majority of research is aimed towards functionalization at the C-2 position in fused azine systems for the construction of new C-C bonds.[3] Among them, functionalization with a nitrile group is an important methodology as it plays a key role in chemistry, biology, and medicine.[4] The nitrile group itself acts as a good hydrogen bond acceptor promoting binding to the protein backbone. It can also serve as an isostere to the carboxyl or hydroxyl moiety because of its strong dipole nature.[4a] In addition, the nitrile can easily be converted to various other functional groups such as amide, amine, ketone, carboxylic acid, etc. as well as other pharmaceutically relevant heterocyclic compounds.[5] The nitrile containing derivatives of *N*- heteroarenes are widely used in pharmaceutical and agrochemical industries and for the total synthesis of natural products. These include the anti-HIV and anti-AIDS drug saquinavir (I),[6] anti-HIV drug MIV-150 (II),[7] agrochemical fungicides (III),[8] cannabinoid CB2 receptor (IV),[9] neuroactive agent acridinic acid (V),[10] and TB inhibitor (VI)[11] (figure 2.1). As a result, a considerable effort has been devoted to developing an efficient synthetic protocol that gives facile access to the 2-cyano heterocyclic scaffolds.

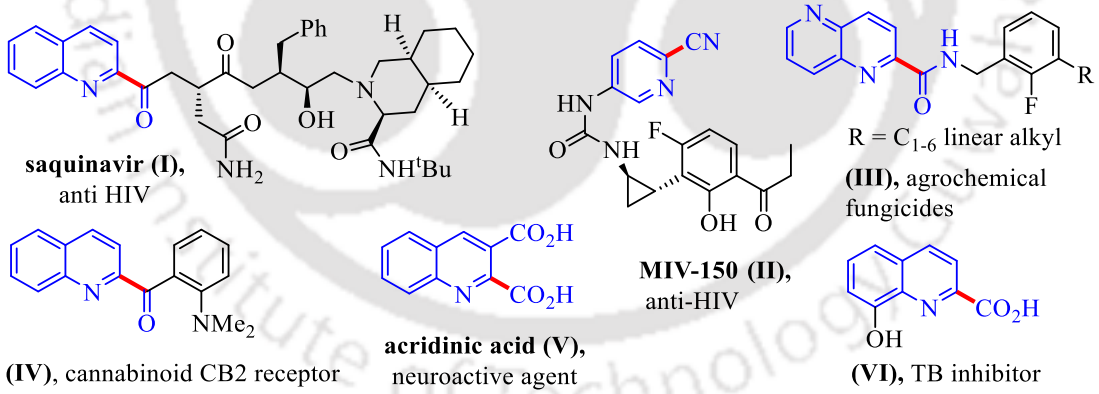
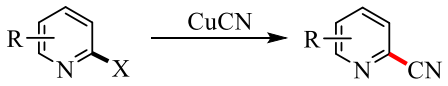


Figure 2.1. Selected bio-active compounds with 2-cyano *N*-heteroaromatic derivatives.

Earlier research to incorporate the nitrile group into the *N*-heteroaromatic system included transition-metal mediated pathways- either through the Pd-catalyzed cyanation approach [12] or *via* the Sandmeyer and Rosenmund-von Braun reaction[13]. The latter requires the prefunctionalization of the heterocyclic ring and the use of copper cyanide as a cyanide source. To avoid the prefunctionalization approach, Hartwig and Fier[14] introduced direct functionalization of pyridines at the C-2 position *via* silver fluoride mediated sequential C-H fluorination and subsequent nucleophilic displacement of the fluoride in the presence of a base (scheme 2.1). Though it provided a diverse range of nucleophiles, there are still some disadvantages. These include (a) the use of expensive and super stoichiometric metals and (b)

late-stage removal of the trace metal contamination in the final product, which can be difficult. Because of this, the applications of this methodology have been limited from the pharmaceutical point of view, therefore a transition metal-free cyanation approach is highly desirable.

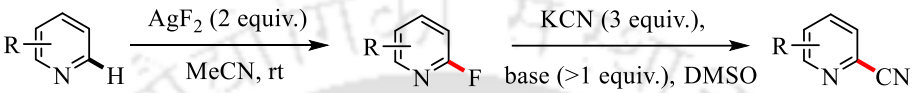
prefunctionalization approach



X = halide, Rosenmund-von Braun reaction

N_2^+, Sandmeyer reaction

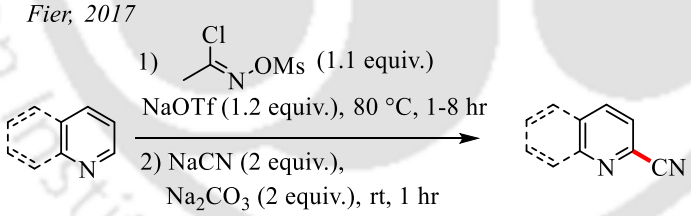
via C-H fluorination (Hartwig, 2014)



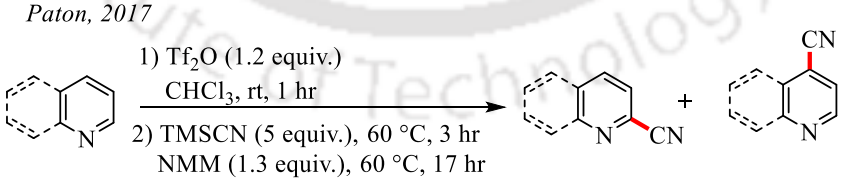
Scheme 2.1: transition metal-mediated cyanation of *N*-heteroarenes

In general, the transition metal-free approach for the cyanation of *N*-heteroarenes (or *N*-oxides) often involves two steps: (1) activation of the heteroaromatic ring by a suitable electrophilic activator and (2) the nucleophilic addition of the cyanide ion immediately followed by the associated base mediated elimination and rearomatization to generate the cyanated heteroaromatic compounds. Two encouraging reports appeared in the recent literature, one each by the groups of Fier[15] and Paton[16] describing the transition metal-free direct cyanation approach. However, both methodologies have limitations. For instance, the Fier group used toxic NaCN as a cyano group source and the super stoichiometric base was employed to facilitate complete conversion. And although the Paton group used triflic anhydride (Tf_2O) as an activating agent with NMM as a base and Me_3SiCN as the cyanide source, ultimately it suffered from poor regioselectivity (scheme 2.2).

Fier, 2017

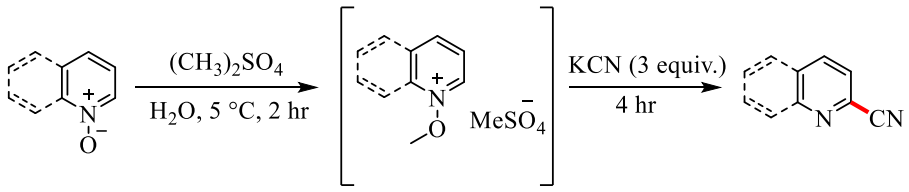


Paton, 2017



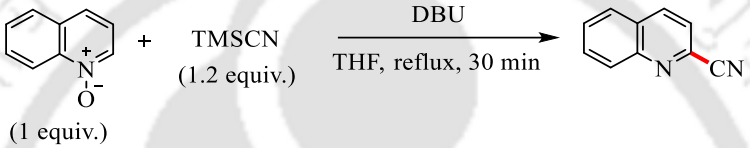
Scheme 2.2: transition metal-free cyanation of *N*-heteroarenes

The *N*-heteroaromatic *N*-oxides as the starting precursor was the better option to obtain good regioselectivity compared to the non-oxidised one. Additional activating agents were often used to enhance the regioselectivity which would coordinate to the oxygen atom of the N-O moiety. In 1959, Feely and Beavers reported dimethyl sulphate as an effective activating agent for cyanation of azine *N*-oxides with potassium cyanide.[17] They obtained exclusively C2-functionalised product with quinoline *N*-oxide whereas, with pyridine *N*-oxide, excessive tar formation created difficulty for product separation (scheme 2.3).



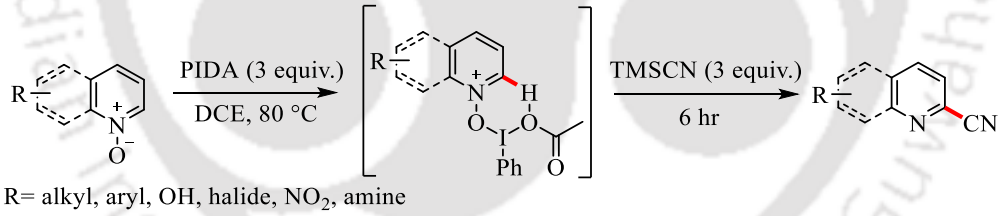
Scheme 2.3: cyanation of *N*-heteroarene *N*-oxide activated by dimethyl sulphate

In 1983, Fife investigated *N*,*N*-dimethylcarbamoyl chloride as activating agent for pyridine *N*-oxides with TMSCN as the nitrile source.[18] The reaction proceeded at room temperature itself for 2 days. Although they obtained excellent yields for the products, the need for a harsh and sensitive activating agent limits its applicability. Various other activating agents were also explored, *viz.* ethyl chloroformate,[19a] benzoyl halide,[19b] acetic anhydride[19c] and MsCl[19d] for this purpose. In 1992, Miyashita and his group reported the cyanation of *N*-heteroaryl *N*-oxides with TMSCN in presence of DBU as the base, where TMSCN also acted as an activating agent (scheme 2.4).[20]



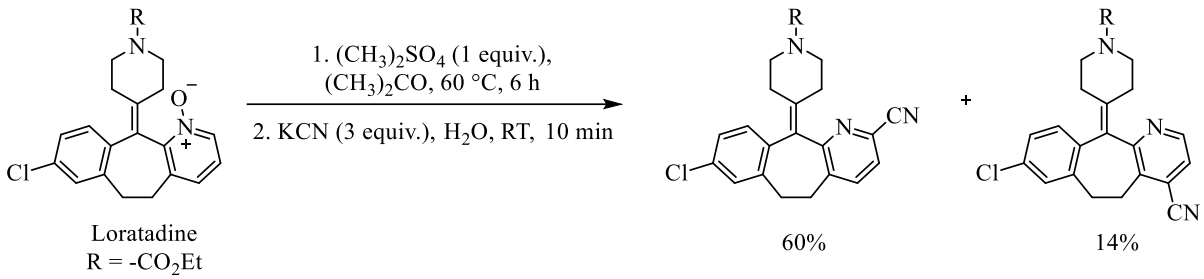
Scheme 2.4: cyanation of *N*-heteroarene *N*-oxide in presence of DBU

More recently, in 2019, Sun and co-workers described the use of hypervalent iodine compound, phenyl iododiacetate (PIDA) as the activating agent, to achieve 2-cyanoquinolines from quinoline *N*-oxide and TMSCN. The appearance of quinoline-2-acetate as a by-product was a drawback with this protocol (scheme 2.5).[21]



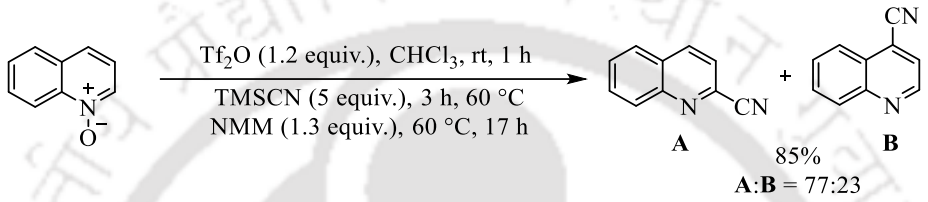
Scheme 2.5: cyanation of *N*-heteroarene *N*-oxide activated by PIDA

In spite of making considerable progress, still these protocols suffer from several limitations like longer reaction times, excess use of reagents or activators and thus generation of stoichiometric chemical waste etc. Besides this, often the reagents are hazardous and sensitive towards air and moisture which constrain easy handling. Additionally, in many cases, competing additions of the activator counter-ion are also problematic.[21,22] Bases are also very much important[19c,20] and generally required in super-stoichiometric amounts to facilitate full conversion at the final rearomatization step.[15,16,20] Therefore, the above issues not only necessitate high cost but also exhibit environmental issues. Apart from this, lack of regioselectivity[15,16,19c,23a,24] is found to be another major drawback in most of the cases whereas the regioselectivity always plays an important role in designing such protocol as different regioisomers showed opposing effects in pharmacology.[25] In 2005, Alvarez-Builla and co-workers performed cyanation of the antihistamine drug loratadine to obtain a mixture of C2- and C4-cyanated products where the C2-substituted product predominated.



Scheme 2.6: Cyanation of loratadine

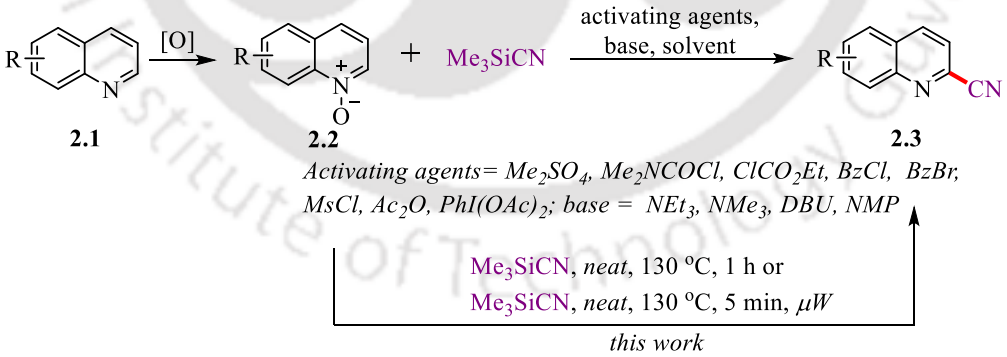
Similarly, Paton and co-workers described the C2-cyanation of azine *N*-oxides in presence of triflic anhydride as an activator, where they reported mixture of regioisomers being formed during the reaction.



Scheme 2.7: Cyanation of azine N-oxide with triflic anhydride as activator

In addition to the above cited facts, the common organic solvents like halogenated solvents were used in this particular transformation which brings some level of toxicity and bio-hazards to the table.[26] In today's pursuit of greener synthetic methodologies, eliminating the solvent with somewhat excess reagent makes the process simpler, industrial friendly and lowers the solvent waste.[27] As Sheldon pointed out, the "best catalyst is no catalyst" and "best solvent is no solvent".[28] So designing a methodology which is devoid of any solvent is always attractive considering the sustainability and also industrial applicability points of view.

2.2. Present work



Scheme 2.8: cyanation of *N*-heteroarene *N*-oxide with TMSCN

Based on the literature reports and understanding the role of quinoline *N*-oxides for regioselective C2-functionalization, herein, I report the first example of an operationally simple, one-pot heteroaromatic C-H cyanation protocol of quinoline *N*-oxide with trimethylsilyl cyanide (TMSCN) that proceeds without the need for metals, catalysts, activators, base, and solvent with excellent regioselectivity at the C-2 position (scheme 2.6).

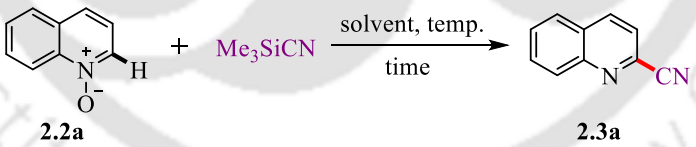
Another notable aspect of the protocol is the successful application of microwave irradiation as an alternate energy source in addition with conventional heating.

2.3. Results and discussion

2.3.1. Optimization of reaction conditions

As a preliminary study towards cyanation of *N*-heteroaromatic compounds under metal-, activator-, and base-free condition, 1 equiv. of quinoline *N*-oxide was taken with 3 equiv. of trimethylsilyl cyanide in dichloroethane (DCE) as a model reaction. The reaction was stirred at room temperature for 15 hours followed by stirring at reflux condition for another 15 hours, during which period, no conversion was obtained (table 2.1, entries 1 and 2), which was compatible with recent reported data.[21] However, when dimethylformamide (DMF) was employed as the solvent rather than DCE, the conversion was slightly improved and the desired product was obtained with a modest 12% yield (entry 3). But when the reaction was performed under solvent-free conditions with the same stoichiometry of Me_3SiCN (3 equiv.) at 80 °C, substrate **2.2a** was completely consumed and quinoline-2-carbonitrile **2.3a** was obtained with a 90% yield within 6 hours. In addition, it was found that increasing the reaction temperature more than 80 ºC resulted in even shorter reaction times. This suggested that the reaction temperature played a significant role in the reaction outcome. To investigate the influence of the concentration of Me_3SiCN, different equivalents of trimethylsilyl cyanide were employed and the results revealed that 2.2 equiv. of Me_3SiCN gave the same conversion as that in the case with 3 equiv. However, lowering the equivalents below 2.2 led to a decrease in conversion (entries 10 and 11). Then the reaction was tried under microwave irradiation (μw) as this method is emerging as an alternative to conventional heating practice and leads to accelerated reaction rates.[29] Gratifyingly, it was found that the reaction under the optimized conditions using microwave irradiation completed within five minutes and gave quantitative yields at 130 °C (entry 15).

Table 2.1. Optimization of C-H cyanation of heterocyclic *N*-oxides[a,b]



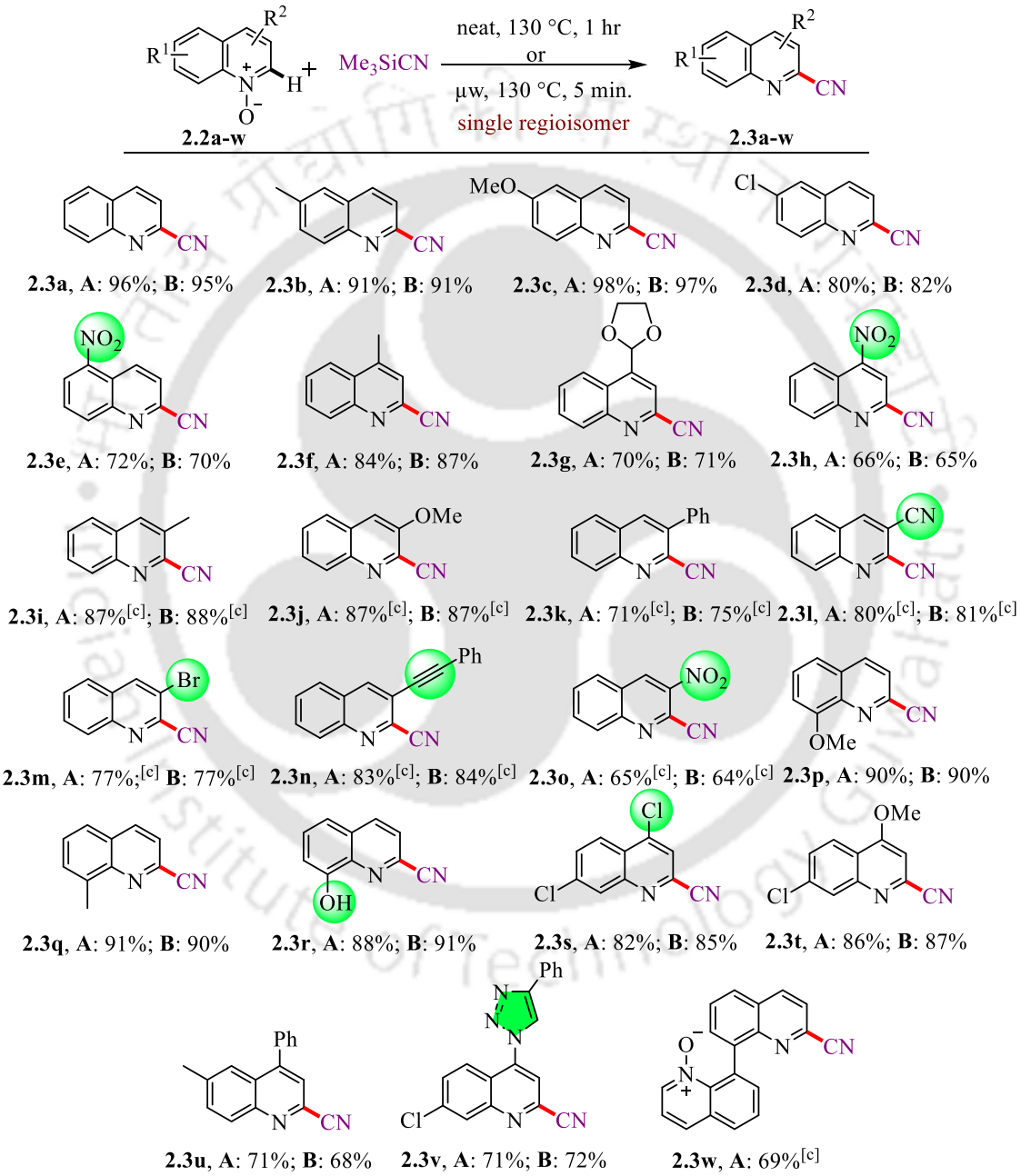
2.2a **2.3a**

Entry	Cyanide source (equiv.)	Temperature	Solvent	Time	Yield (%)
1	Me_3SiCN (3)	rt	DCE	15 h	n.d.
2	Me_3SiCN (3)	90 ºC	DCE	15 h	n.d.
3	Me_3SiCN (3)	130 ºC	DMF	15 h	12
4	Me_3SiCN (3)	rt	neat	15 h	n.d.
5	Me_3SiCN (3)	60 ºC	neat	15 h	10
6	Me_3SiCN (3)	80 ºC	neat	6 h	90
7	Me_3SiCN (3)	100 ºC	neat	2 h	92
8	Me_3SiCN (3)	130 ºC	neat	1 h	96
9	Me_3SiCN (2.2)	130 ºC	neat	1 h	96
10	Me_3SiCN (1.5)	130 ºC	Neat	15 h	60
11	Me_3SiCN (1)	130 ºC	Neat	15 h	45

12	PhCOCN (3)	130 °C	neat	15 h	19
13	$K_4Fe(CN)_6$ (3)	130 °C	neat	15 h	n.d.
14	Me_3SiCN (3)	80 °C, µw	neat	1 h	76
15	Me_3SiCN (2.2)	130 °C, µw	neat	5 m	95

[a]Reaction was carried out using 0.6 mmol of quinoline *N*-oxide under argon atmosphere. [b]Isolated yield after column chromatography. n.d. = not detected.

Scheme 2.9: substrate scope for cyanation of quinoline *N*-oxides



[a]Reaction conditions: substrate **2.2a-w** (0.6 mmol), TMSCN (1.32 mmol), neat, under argon atmosphere, at 130 °C. [b]Isolated yield; recovered substrates are given in parentheses. Method-**A**. The reaction was performed under conventional heating method at 130 °C for 1 h. Method-

B. The reaction was performed under Microwave (power-50 Watt) at 130 °C for 5 to 15 min. [c]4.2 equiv. Me_3SiCN was used.

2.3.2. Scope of cyanation of quinoline *N*-oxides

With the optimized conditions in hand, the scope of the cyanation reaction was explored between various quinoline *N*-oxide derivatives (**2.2a-w**) and the trimethylsilyl cyanide nucleophile. The reaction seems to be fairly effective for a wide pool of substrates with high to good yields of the cyanation products at the C-2 position. This was observed for both electron-donating as well as electron-withdrawing substituents (such as −Me, −Ph, −OH, −OMe, −Cl, −Br, −CN, −C≡C–Ph and $–NO_2$) at the quinoline scaffold. Notably, the electron-donating substituents (table 2, products **2.3b**, **2.3c**) led to the desired products with higher yields compared to electron-withdrawing substituents (product **2.3d**). Retaining halogen functional groups can be beneficial as it allows for further functionalization. In our study, the halogen substituents remained intact giving desired nitrile compounds in excellent yields.

In the case of 4,7-dichloroquinoline *N*-oxide, the C4-substituted chloro group is susceptible to nucleophilic attack. Despite this, I was able to obtain only C2-cyanated single regioisomer **2.3s** with 85% yield. It should be noted that aliphatic substituted *N*-oxides at various positions were explored (products **2.3b**, **2.3f**, **2.3I** and **2.3q**) and very good yields were obtained in all of the cases. Next it was decided to explore various polysubstituted quinoline *N*-oxide derivatives and found that the desired products were obtained in modest to good yields (products **2.3s**-**v**). C3- and C8- functionalized quinoline *N*-oxides were also employed for cyanation, providing the products **2.3i**-**o** and **2.3p**-**r** with good yields. To our delight, the current protocol is not sensitive to the steric effect and shows excellent regioselectivity for all of the cases. However, complete conversion for the substrates with C3-substituents required an additional two equivalents of the nucleophile. Interestingly, the hydroxy functional group survived under the current protocol (product **2.3r**). It was also found that the cyano- group can be installed selectively at one C2-position in 8,8′-biquinolyl *N*,*N*′- dioxide (**2.1w**) moiety with a 69% yield. The entity of the quinoline moiety and substitution of the nitrile unit at the C2-position was confirmed by X-ray crystallography (**2.3n** in figure 2.2).

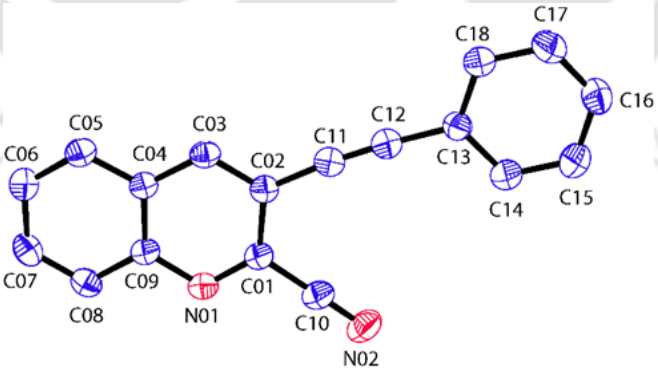
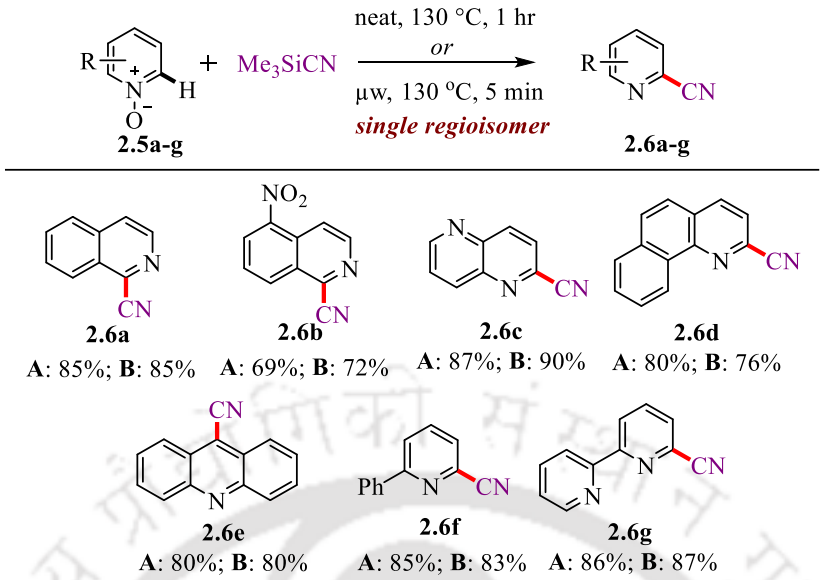


Figure 2.2: Molecular structure of compound **2.3n** (thermal ellipsoid 25% probability level).

2.3.3. Scope of cyanation of other *N*-heteroarene *N*-oxides

After successfully obtaining quinoline *N*-oxide derivatives using this protocol, I then turned my attention to the isoquinoline systems as it is an important scaffold in medicinal chemistry which makes them attractive substrates for investigation. The protocol was successfully applied to different isoquinoline *N*-oxide derivatives, leading to the isoquinoline-1-carbonitrile products with good yields up to 85% (table 2.3, products **2.6a-b**).

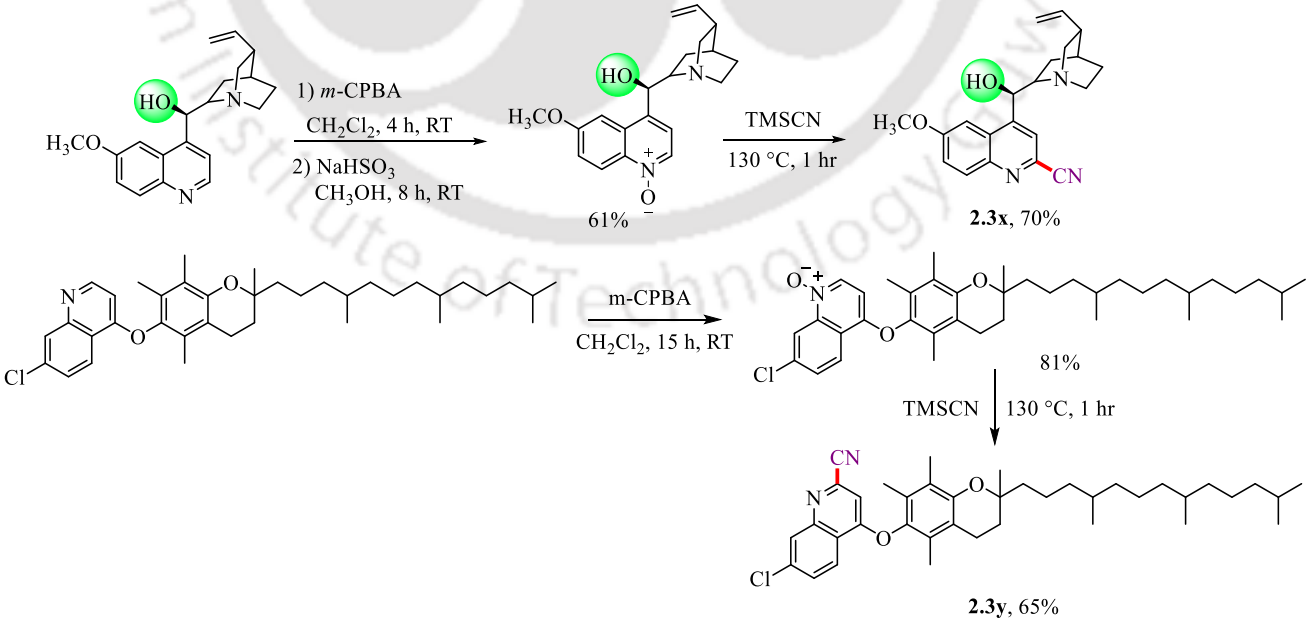
Scheme 2.10: substrate scope for cyanation of other azine *N*-oxides



[a]Reaction conditions: **2.5a-g** (0.6 mmol), Me_3SiCN (1.32 mmol), neat, under argon atmosphere. [b]Isolated yield; recovered substrates are given in parentheses. Method-**A**. The reaction was performed under conventional heating method at 130 °C for 1 h. Method-**B**. The reaction was performed under Microwave (power-50 Watt) at 130 °C for 5 to 15 min. [c]4.2 equiv. Me_3SiCN was used.

However, the scope of the present synthetic protocol is not just limited to quinoline and isoquinoline scaffolds, but expands readily to other *N*-heteroarenes such as 1,5- naphthyridine, benzo[*h*]quinoline and acridine, giving very good yields for the corresponding products (**2.6c-e**). 2-phenylpyridine *N*-oxide and 2,2'-bipyridine-*N*-oxide were also examined and the corresponding cyanated pyridine derivatives (**2.6f-g**) were obtained in very good yields.

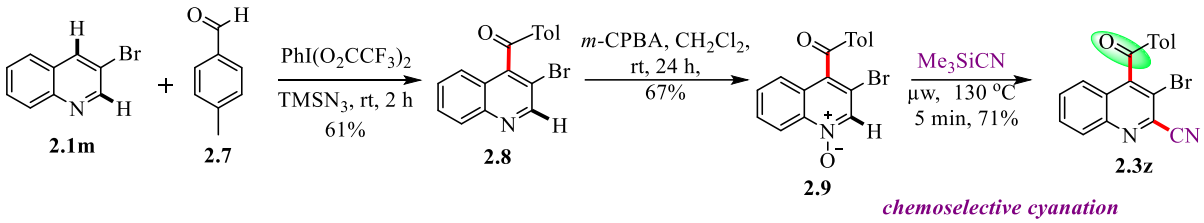
2.3.4. Late-stage functionalization of bio-active molecules



Scheme 2.11: late-stage modification of bio-active molecules

The current methodology was also used for the late-stage functionalization of the anti-malarial drug quinine (**2.3x**) and (±)-α-tocopherol modified quinoline derivative (**2.3y**). Both were obtained in good yields.

2.3.5. Sequential C-H functionalization of *N*-heteroarene

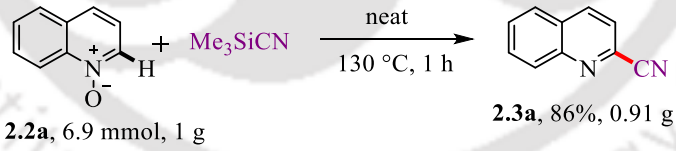


Scheme 2.12: sequential C-H functionalisation of 3-bromoquinoline

Our methodology was further applied to the selective substitution of nitrogenous heterocycles.[30] First, metal-free C-H bond functionalization of 3-bromoquinoline was carried out using cross-dehydrogenative coupling with *p*-tolualdehyde **2.7** to obtain **2.8** in 61% yield. **2.8** was then subjected to *N*-oxidation and concomitant cyanation. This resulted in the formation of **2.3z** in 71% yield (scheme 2.7), thus demonstrating that the sequential C-C bond formation at C2- and C4-positions with different substituents could be obtained without the need for metal-containing reagents. Interestingly, the carbonyl group remained intact during the cyanation process, suggesting the chemoselective nature of the developed protocol.[31]

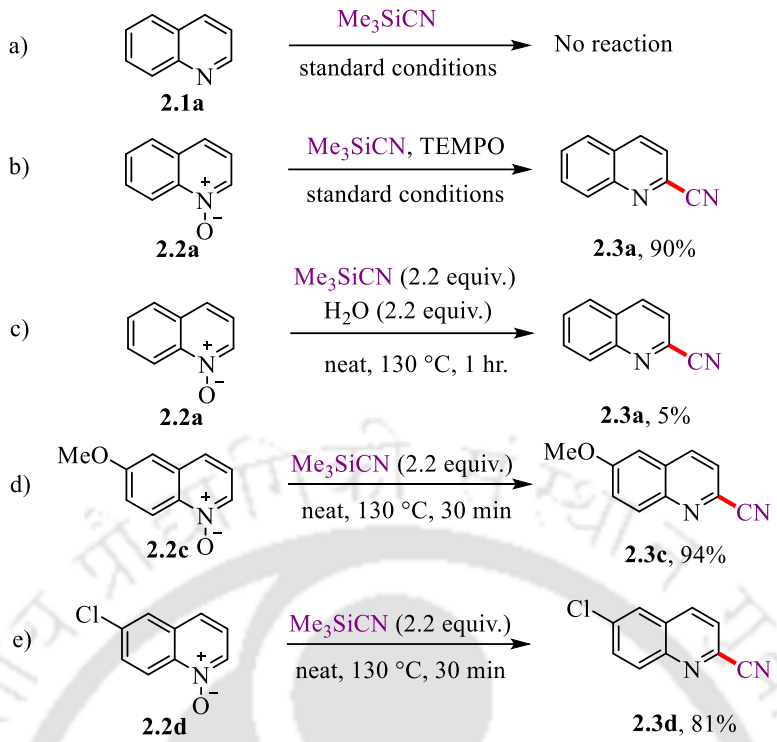
2.3.6. Gram-scale synthesis

The efficiency of this process was studied by scaling up the reaction in a gram scale for bulk utilization. First, synthesis of 2-cyanoquinoline (**2.3a**) was attempted from 1 g of quinoline *N*-oxide using standard conditions when **2.3a** was obtained in 86% yield (Scheme 3a). It was also observed that the final compound was easily isolable through sublimation (sublimated yield for **2.3a**, 76%), thereby evading any aqueous workup (which is often required to remove the promoters, additives, bases, and side products in the traditional cyanation of *N*-heteroarenes). Hence, the process is overall very efficient from a practical perspective.



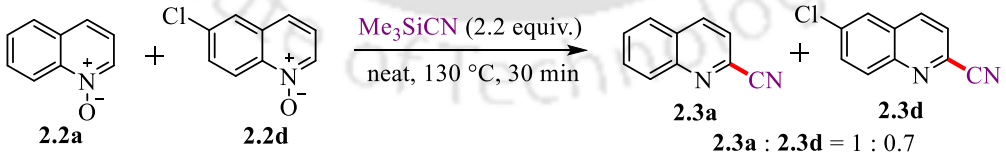
Scheme 2.13: gram-scale synthesis of **2.3a**

2.3.7. Mechanistic investigation



Scheme 2.14: control experiments

To gain insight into the reaction pathway, a series of control experiments were performed. At first, when quinoline **2.1a** was treated with trimethylsilyl cyanide, the desired 2-cyanoquinoline product was not observed, suggesting the important role of the *N*-O group in this transformation (Scheme 5a). Further, by using radical scavenger TEMPO in the reaction mixture, the expected product **2.3a** was formed without any change in the reaction conditions which suggested exclusion of any radical mechanistic pathway. In addition, the cyanation of quinoline *N*-oxide was ineffective with water, which implied that the present transformation may not occur *via* the hydrogen cyanide pathway. To check for the electronic effect on the reaction outcome, the reaction was performed independently with 6-methoxyquinoline *N*-oxide and 6-chloroquinoline *N*-oxide with trimethylsilyl cyanide at 130 °C for half an hour. While 94% desired product **2.3c** was observed for the former, 81% product was obtained in the latter case (scheme 2.9d and 2.9e). It suggested the favourable effect of electron donating substituents on the reaction outcome.



Scheme 2.15: competitive reaction between **2.2a** and **2.2d** with TMSCN

Further, the intermolecular competition reaction between quinoline *N*-oxide and 6-chloroquinoline *N*-oxide with trimethylsilyl cyanide yielded the desired products **2.3a** and **2.3d** in a 10:7 ratio, as can be observed from the crude NMR spectrum. This implied that the electron withdrawing substituents had a negative impact on the reaction outcome.

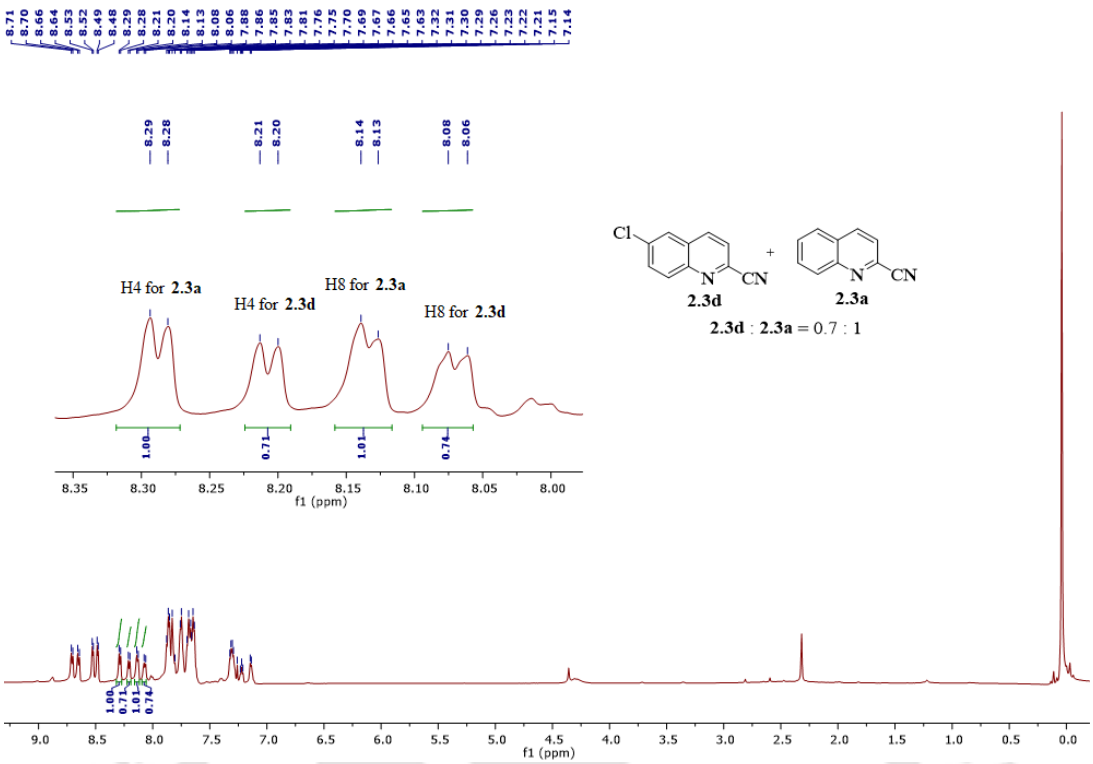
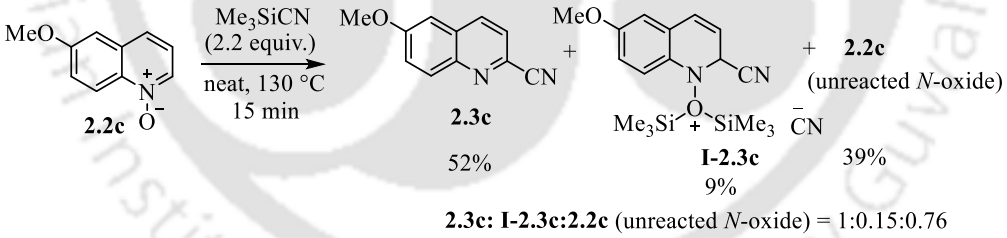


Figure 2.4: ^{1}H NMR spectrum for the competitive cyanation reaction between **2.2a** and **2.2d**

In an attempt to look for the intermediate of the cyanation reaction, the reaction of 6-methoxyquinoline *N*-oxide was performed with trimethylsilyl cyanide under conventional heating condition. After 15 minutes, the reaction was monitored through ^{1}H NMR spectroscopy which showed the presence of dearomatized cyanated intermediate **I-2.3c** along with **2.3c** and the unreacted *N*-oxide **2.2c** in the ratio **2.3c**:**I-2.3c**:**2.2c** = 1:0.15:0.76.



Scheme 2.16. Cyanation reaction of 6-methoxyquinoline *N*-oxide after 15 min.

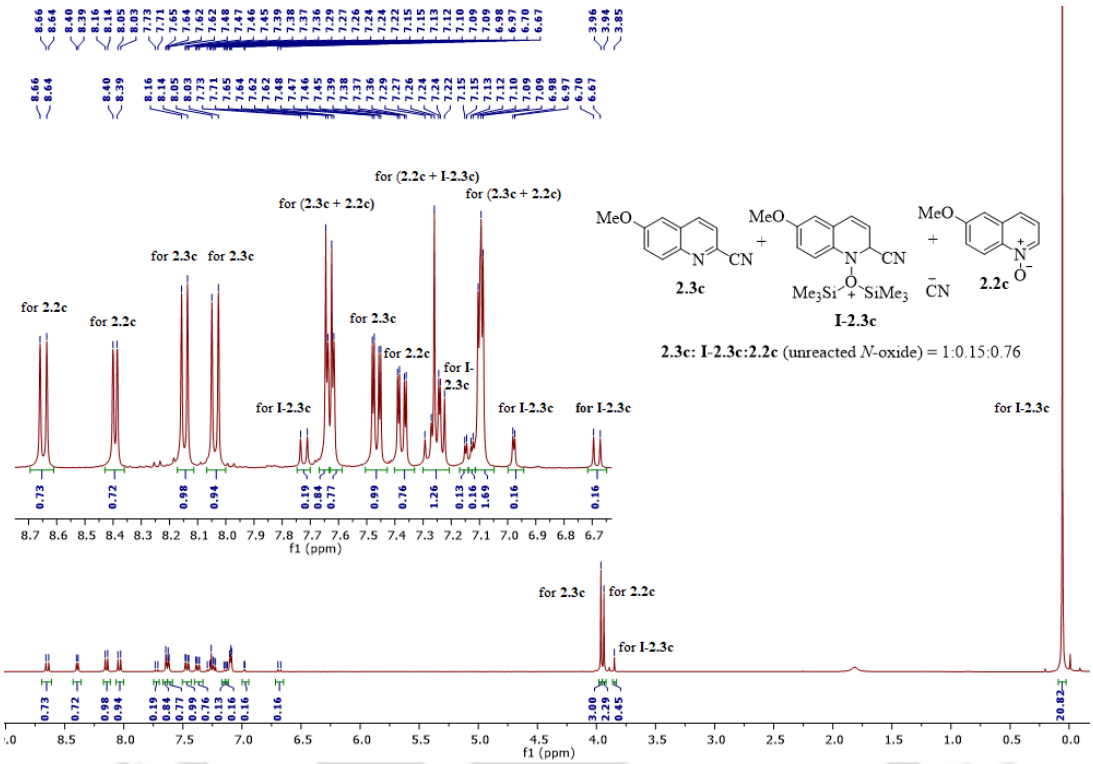
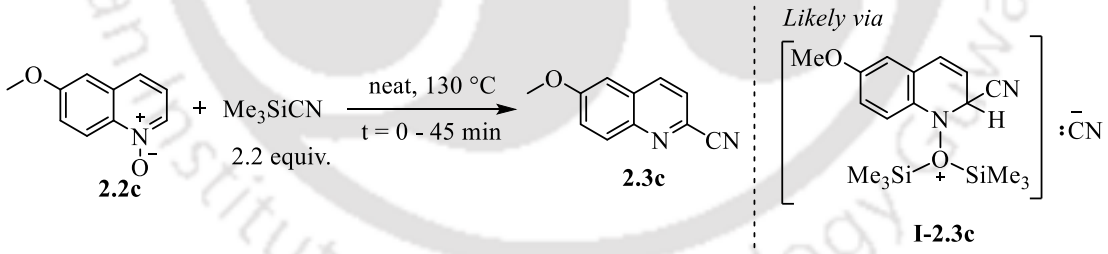


Figure 2.5: ^{1}H NMR spectrum for the cyanation reaction of **2.2c** at 15 minutes

Further, when the crude reaction mixture was subjected to GC-MS analysis, a peak was observed at *m/z* = 147.06 which corresponded to $(Me_3Si)_2O$ which was the by-product in the reaction. This was also confirmed by the appearance of the peak at δ = 7.31 ppm in ^{29}Si NMR spectroscopy. The formation of proposed intermediate **I-2.3c** (for the product **2.3c**) was also supported by the appearance of the respective peaks in the crude ^{1}H NMR at different interval of times (see figure 2.6).



Scheme 2.17. Study of the cyanation reaction of 6-methoxy quinoline *N*-oxide with trimethylsilyl cyanide at different time interval.

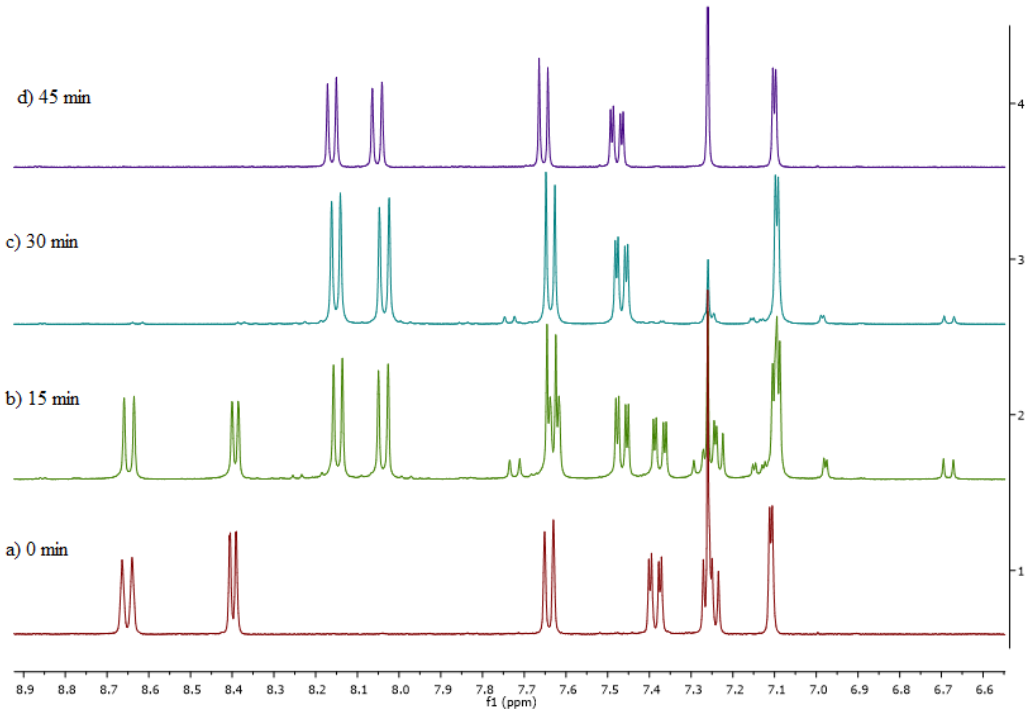
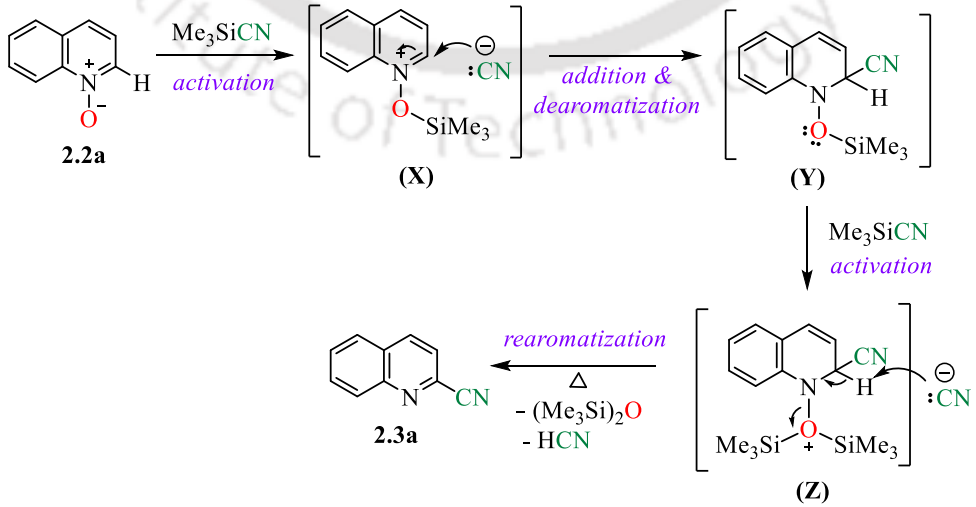


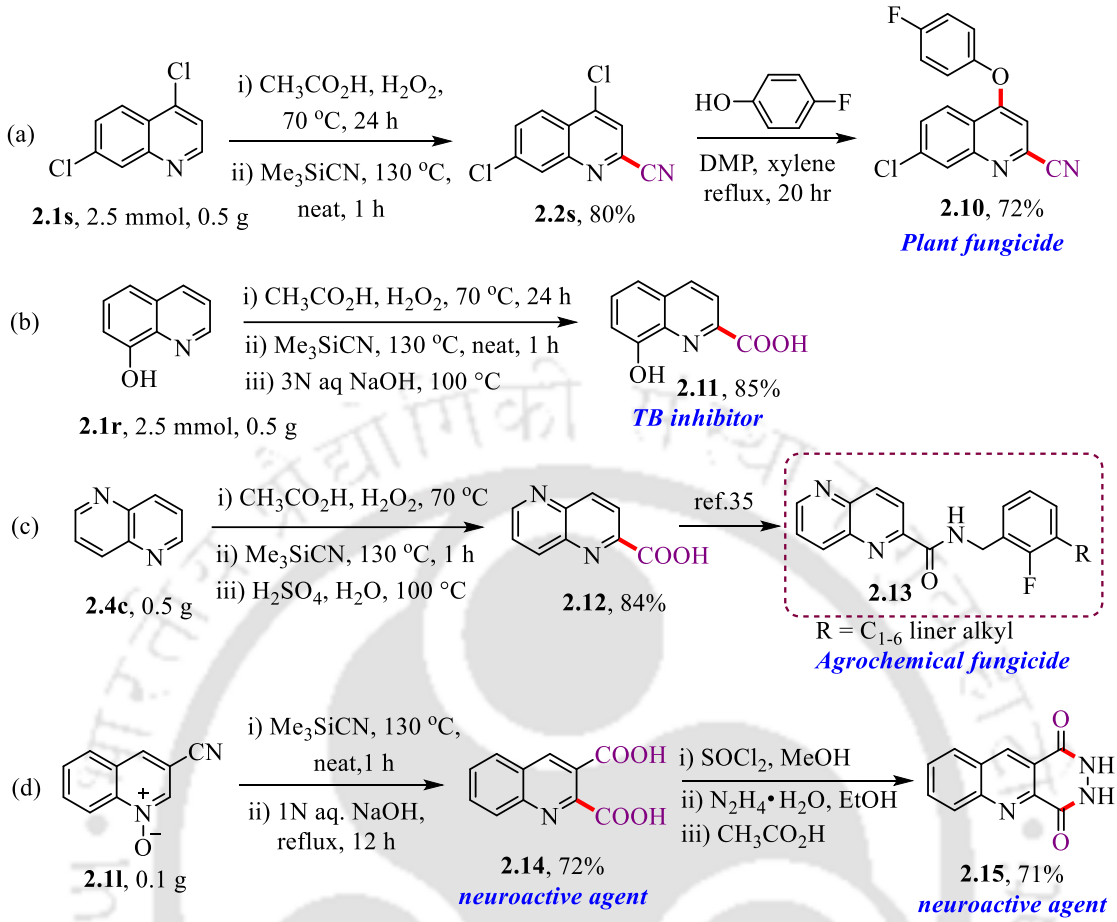
Figure 2.6. NMR spectra of the reaction mixture at different interval of time, a) 0 minute, b) 15 minute, c) 30 minute, d) 45 minute. All the spectra were recorded in $CDCl_3$ in 400 MHz NMR spectrometer at 298 K.

Based on earlier reports[20] and our experimental findings a plausible reaction mechanism has been proposed in scheme 2.13. At first, quinoline *N*-oxide **2.2a** is activated by trimethylsilyl cyanide releasing the cyanide anion. In the next step, the nucleophilic addition of cyanide at the C-2 position of the activated ring takes place, resulting in the dearomatized intermediate **Y**. The latter is further activated by an additional equivalent of trimethylsilyl cyanide generating the ionic species **Z**. Subsequent rearomatization gives the final compound **2.3a** with concomitant release of hexamethyldisiloxane [$(Me_3Si)_2O$] as the byproduct (see section 2.6.8) This plausible pathway explains the dual role of trimethylsilyl cyanide as a cyanide source for the cyanation reaction as well as an activating agent for the *N*-oxides to produce the target heterocycles.



Scheme 2.18: proposed mechanism

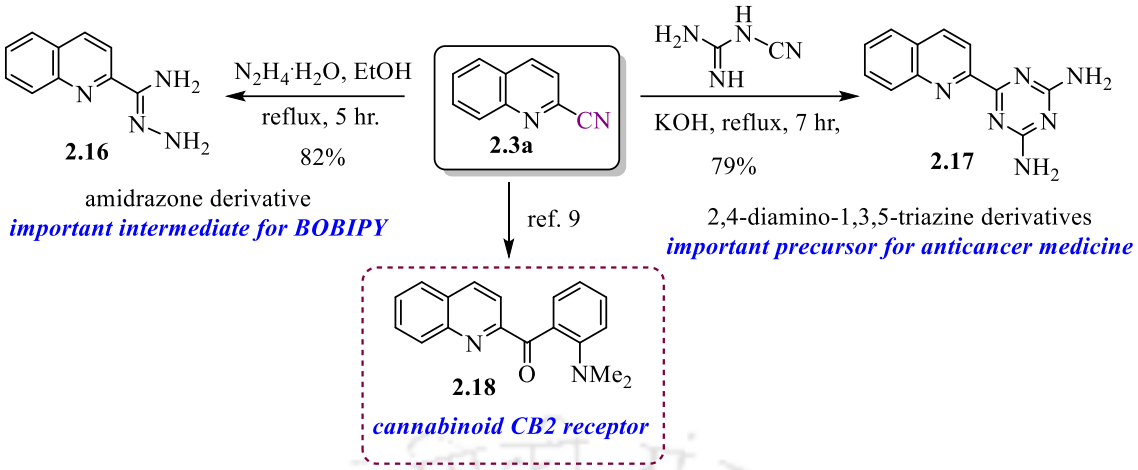
2.4. Downstream transformations



Scheme 2.19: useful post-synthetic transformations

Compound **2.2s,** which represents an important reaction intermediate for MRK-8-29,[32] a specific *in vivo* agent for mGlu2 negative allosteric modulator, was efficiently prepared by one-pot oxidation and cyanation reaction on 4,7-dichloroquinoline. **2.2s** could then be transformed into the potent plant fungicide derivative **2.10** in 72% yield (Scheme 2.14a).[33] This protocol was also extended to the synthesis of the TB inhibitor **2.11**[11] and a plant fungicide precursor **2.12**[34], obtaining both in high yields (Scheme 2.14b and 2.14c). It was also observed that different neuroactive agents could also easily be accessed by simple hydrolysis of **2.2l**, leading to acridinic acid (**2.14**)[35] and it's derivative 2,3-dihydropyridazino [4,5-*b*] quinoline-1,4-dione (**2.15**)[36] in 72% and 71% yield, respectively (Scheme 2.14d).

The application of 2-cyanoquinoline (**2.3a**) as a substrate were further explored in the synthesis of amidrazone derivative **2.16**, which is an important building block for biological imaging studies.[37] **2.3a** could be easily converted to the 2,4-diamino- 1,3,5-triazine derivative **2.17**, an important precursor for anticancer medicine.[38] In addition, carbonitrile **2.3a** can be easily transformed into the quinolinyl aryl ketone **2.18**, which is used as a novel agonist for the cannabinoid CB2 receptor (Scheme 2.15).[39]



Scheme 2.20: useful post-synthetic transformations

2.5. Summary

In summary, I have demonstrated the cyanation of heteroaromatic *N*-oxides with trimethylsilyl cyanide in the absence of metals, external activators, base and solvent with excellent regioselectivity at the C-2 position. To the best of our knowledge, this is the first example of an efficient incorporation of a nitrile moiety into the C-H bond of *N*-heteroaromatic compounds in the absence of any external activator and base. The present protocol proceeds smoothly in conventional heating as well as under microwave irradiation with shorter reaction times. The synthetic utility of the C2-substituted heteroaromatic nitriles is further demonstrated by the synthesis of several bioactive molecules, including late-stage functionalization of antimalarial drug quinine and the (±)-α-tocopherol modified quinoline derivative. Preliminary mechanistic data highlight the dual role of trimethylsilyl cyanide, which can act as a cyanide source as well as an activating agent. From an industrial perspective, this method is promising as it is (a) operationally simple, (b) highly efficient, (c) economically viable, and (d) easy to scale-up. Further utilization of this simple trimethylsilyl cyanide in other cyanation reactions under solvent-free conditions is underway.

2.6. Experimental section:

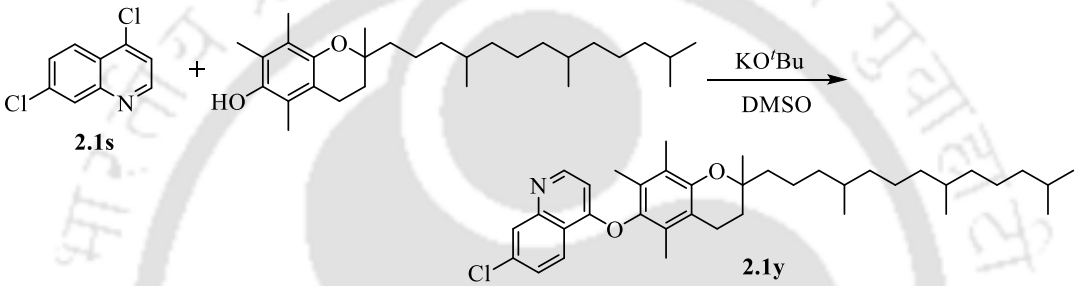
2.6.1. General information

All the reagents and chemicals were purchased from common commercial suppliers like Sigma-Aldrich, Alfa Aesar, Merck, Spectrochem, Avra Synthesis Pvt. Ltd. and directly used as received without any further purification unless otherwise mentioned. 3-methoxyquinoline,[40] 3-phenylquinoline,[41] 3-cyanoquinoline,[42] 3-phenylacetylquinoline,[43] 4-(1,3-dioxolan-2-yl)quinoline,[44] 7-chloro-4-(4-phenyl-1H-1,2,3-triazol-1-yl)quinoline,[45] 4-phenyl-6-methylquinoline,[46] 8-methyl quinoline,[47] 8-methoxyquinoline,[48] (3-bromoquinolin-4-yl)(*p*-tolyl)methanone[49] were prepared according to reported procedures. All reactions were either carried out under air (for oxidation of azines) or in flame-dried glassware under an atmosphere of argon (for cyanation of azine *N*-oxides). Microwave reactions were carried out using a CEM discovery microwave reactor. Completion of reactions was examined by thin layer chromatography carried out on pre-coated Merck silica gel 60 F_{254} aluminium plates with ultraviolet light (UV) or iodine as visualizing agents. Purification of compounds was performed by column chromatography using Merck silica gel 60-120 mesh. All starting azine *N*-oxides and their cyanation products were characterized by spectroscopic methods and compared to literature wherever applicable, otherwise stated. ^{1}H and ^{13}C NMR spectra of all the compounds

were measured using Bruker Avance III 600 and 400 spectrometers in $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts (δ in ppm) are reported relative to the external reference TMS [δ (^{1}H) 0.0 ppm and δ (^{13}C) 0.0 ppm]. Otherwise, residual undeuterated solvent's proton resonance and carbon resonance [$CHCl_3$, δ 7.26 ppm (^{1}H), δ 77.16 ppm (^{13}C); DMSO, δ 2.50 ppm (^{1}H), δ 39.52 ppm (^{13}C)] were used for calibration. The abbreviations used to report the multiplicities: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quartet, sext = sextet, br = broad, and brs = broad singlet. IR spectra were recorded using Perkin Elmer Instrument at normal temperature on KBr pellet by grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak). X-ray crystallographic data were collected using a 'Bruker SMART APEX CCD' diffractometer. Melting points were recorded using Buchi Melting Point B-540 Instrument and are uncorrected.

2.6.2. Preparation of starting materials

Preparation of (±)-α-tocopherol-modified quinoline substrate (2.1y)

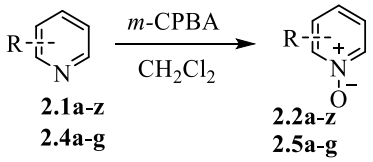


Scheme 2.21: Synthesis of (±)-α-tocopherol modified quinoline.

In an oven-dried schlenk tube, potassium *tert*-butoxide (272 mg, 2.42 mmol, 1.2 equiv.) was taken and dried under vacuum. Then, (±)-α-tocopherol (864 mg, 2.0 mmol, 1 equiv) in dry DMSO (3 mL) was added and stirred at 120 °C for 1 hour. Then 4,7-dichloroquinoline (200 mg, 1.0 mmol, 0.5 equiv.) was added to the mixture and stirred at 120 °C for overnight. After completion of the reaction as confirmed by TLC, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 15 mL). The excess tocopherol was recovered by silica gel column chromatography (CH_2Cl_2 : *n*-hexane, 1 : 5) followed by the pure product **2.1y** (CH_2Cl_2 : *n*-hexane; 2 : 5) as brown viscous liquid (615 mg, yield 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 5.2 Hz, 1H), 8.41 (d, J = 8.9 Hz, 1H), 8.09 (d, J = 1.9 Hz, 1H), 7.53 (dd, J = 8.9, 2.0 Hz, 1H), 6.26 (d, J = 5.1 Hz, 1H), 2.64 (t, J = 6.6 Hz, 2H), 2.15 (s, 3H), 1.99 (s, 3H), 1.95 (s, 3H), 1.88 – 1.83 (m, 2H), 1.66 – 1.48 (m, 4H), 1.45 – 1.35 (m, 4H), 1.32 – 1.27 (m, 10H), 1.17 – 1.08 (m, 6H), 0.88 – 0.85 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.71, 152.73, 150.32, 149.68, 142.60, 136.10, 128.19, 127.53, 126.96, 125.70, 124.0, 123.54, 119.49, 118.42, 103.07, 75.44, 39.53, 37.62, 37.58, 37.55, 37.45, 32.94, 32.82, 28.13, 24.96, 24.60, 24.40, 23.59, 22.86, 22.77, 21.16, 20.80, 19.90, 19.84, 19.79, 12.82, 12.01, 11.96. HRMS (ESI) *m/z*: calcd. for $C_{38}H_{55}ClNO_2^+$ [M+H$^+$] 592.3916, found 592.3932.

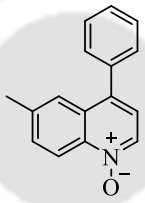
General procedure for synthesis of heterocyclic *N*-oxides (GP-I):



Scheme 2.22: Synthesis of heterocyclic *N*-oxides.

Representative procedure: In a round-bottom flask, quinoline (1 g, 7.74 mmol, 1 equiv.) was dissolved in dichloromethane (5mL). Then, at 0 °C, *m*-chloroperbenzoic acid (*m*-CPBA) (2.7 g, 15.5 mmol, 2 equiv.) in dichloromethane (10 mL) was added portion wise. After addition, the reaction mixture was allowed to come to room temperature and stirred for 15 hours. The mixture was diluted with dichloromethane (10 mL) after completion and combined organic part was washed with 6 N aqueous KOH solution followed by brine solution. The organic part was dried over Na_2SO_4 and solvent was removed under reduced pressure. The crude product was purified through silica-gel flush column chromatography (methanol: ethyl acetate; 1:10) to get brown solid as pure product (1 g, yield 90%). Other heterocyclic *N*-oxides **2.2a-z**, **2.5a-g** were prepared according to above procedure.[50] All compounds spectral data were in accordance with literature.

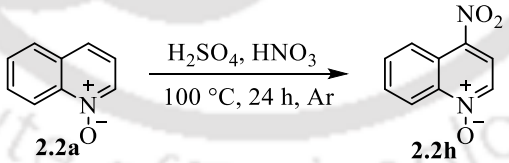
Procedure for synthesis of 6-methyl-4-phenylquinoline 1-oxide (2.2u)



Using 6-methyl-4-phenylquinoline in accordance with GP-I, the above compound was obtained through SiO_2-gel column chromatography (MeOH : EtOAc, 1:10) as a brown solid. Isolated yield = 815 mg (76%).

M.p. 75-77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 8.9 Hz, 1H), 8.47 (d, J = 6.1 Hz, 1H), 7.61 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.48 – 7.39 (m, 5H), 7.13 (d, J = 6.1 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.86, 138.95, 138.66, 137.04, 134.39, 132.40, 129.46, 128.72, 128.69, 128.49, 125.42, 121.30, 119.77, 21.58. HRMS (ESI) *m/z*: calcd. for $C_{16}H_{14}NO^+$ [M+H$^+$] 236.1070, found 236.1099.

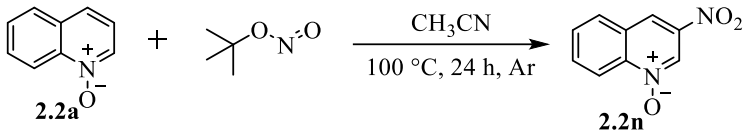
Procedure for Synthesis of 4-nitroquinoline-*N*-oxide (2.2h)[51]



Scheme 2.23: Synthesis of 4-nitroquinoline-*N*-oxide.

Quinoline *N*-oxide (500 mg, 3.4 mmol, 1 equiv.) was taken in a one-neck round-bottom flask and 5 mL concentrated H_2SO_4 was added. To this solution, at 70 °C, concentrated HNO_3 (369 mg, 5.9 mmol, 1.7 equiv.) was added dropwise under fumehood. The mixture was stirred for another 3 hours at 70 °C, cooled and poured onto ice. Orange precipitate came out which was filtered, washed with water, dilute sodium carbonate, water and a small amount of alcohol (in given order). The product was purified by crystallization from acetone to get orange solid (151 mg, 23% yield). The spectroscopic characterization data matches with literature reported procedure.[12i]

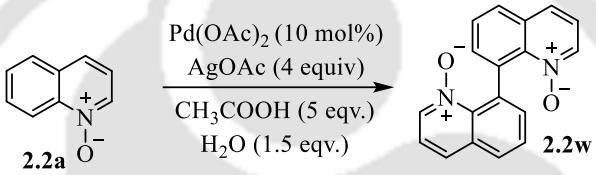
Procedure for Synthesis of 3-nitroquinoline-*N*-oxide (2.2n)[52]



Scheme 2.24: Synthesis of 3-nitroquinoline-*N*-oxide.

In a 15-mL reaction tube, quinoline N-oxide (200 mg, 1.38 mmol, 1 equiv.) was taken in dry acetonitrile (3 mL) and followed by addition of *tert*-butyl nitrite (498 mg, 4.83 mmol, 3.5 equiv.). the reaction mixture was stirred at 100 °C for 24 hours under argon. After completion of the reaction as observed from TLC, brine solution (5 mL) was added and extracted with EtOAc (2×10 mL). The organic part was dried over Na_2SO_4 and solvent was removed under reduced pressure. The crude product was purified through silica-gel column chromatography (EtOAc: Petroleum ether; 0.6: 1) to get the pure product as yellow solid (210 mg, 80% yield).

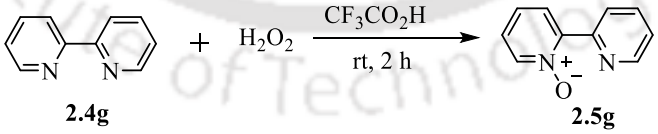
Procedure for synthesis of 8, 8′-biquinoline-*N, N′*-dioxide (2.2w) [53]



Scheme 2.25: Synthesis of 8, 8′-biquinoline-*N, N′*-dioxide.

In a 10 mL-vial, quinoline *N*-oxide (110 mg, 0.75 mmol, 1 equiv.), silver acetate (525 mg, 3.14 mmol, 4 equiv.), palladium acetate (17 mg, 0.08 mmol, 0.10 equiv.), glacial acetic acid (0.3 mL, 5 equiv.) and deionized water (1.5 equiv.) were taken, flushed with argon and sealed the vial with cap. Then the mixture was heated at 120 °C for 48 hours till TLC showed complete consumption of starting material. Then the reaction mixture was diluted with dichloromethane (10 mL) and filtered through celite. The solvent is removed under reduced pressure. The product was purified through SiO_2 column chromatography (MeOH: EtOAc, 1:1) to get yellow solid as pure product (64 mg, yield 30%).

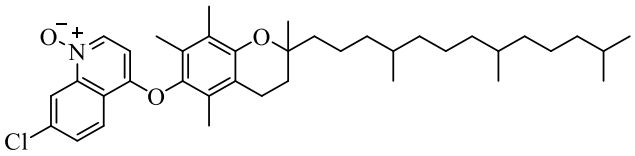
Procedure for synthesis of 2, 2′-bipyridine-*N*-oxide (2.5g)[54]



Scheme 2.26: Synthesis of 2, 2′-bipyridine-*N*-oxide.

2,2′-Bipyridine (500 mg, 3.2 mmol, 1 equiv.) was taken in an oven dried round-bottom flask and trifluoroacetic acid (2.4 mL) was added, followed by slow addition of 30% H_2O_2 (163 mg, 4.8 mmol, 1.5 equiv.) through a septum. The mixture was stirred for 2 hours at room temperature. The reaction mixture was diluted with dichloromethane (20 mL) and washed with 6M aqueous NaOH solution under fume hood. The combined organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure to give the product as beige solid (hygroscopic) (468 mg, yield 85%).

Procedure for the synthesis of 7-chloro-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyl tridecyl) chroman-6-yl)oxy)quinoline 1-oxide (2.2y)



Using 7-chloro-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy) quinoline **2.1y** (600 mg, 1 mmol) in accordance with GP-I, the above compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 1:2) as a light yellow viscous oil. Isolated yield = 81% (493 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, J = 1.9 Hz, 1H), 8.42 (d, J = 8.9 Hz, 1H), 8.31 (d, J = 6.9 Hz, 1H), 7.67 (dd, J = 8.9, 2.0 Hz, 1H), 6.17 (d, J = 6.9 Hz, 1H), 2.63 (t, J = 6.7 Hz, 2H), 2.13 (s, 3H), 1.98 (s, 3H), 1.94 (s, 3H), 1.90 – 1.72 (m, 2H), 1.63 – 1.47 (m, 4H), 1.45 – 1.35 (m, 4H), 1.33 – 1.25 (m, 10H), 1.20 – 1.05 (m, 6H), 0.87 – 0.84 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.75, 149.95, 142.34, 141.97, 138.27, 137.52, 129.49, 127.35, 125.59, 124.35, 124.29, 120.62, 119.90, 118.60, 102.71, 75.56, 39.51, 37.60, 37.55, 37.53, 37.43, 32.93, 32.84, 28.11, 24.94, 24.57, 24.33, 23.60, 22.84, 22.75, 21.16, 20.76, 19.88, 19.82, 19.76, 12.81, 12.01, 11.96. HRMS (ESI) *m/z*: calcd. for $C_{38}H_{55}ClNO_3^+$ [M+H$^+$] 608.3865, found 608.3904.

2.6.3. Cyanation of heteroaromatic *N*-oxides with trimethylsilyl cyanide

General procedure for cyanation of heterocyclic *N*-oxides (GP-II)

Heterocyclic *N*-oxides (0.6 mmol, 1 equiv.) and trimethylsilyl cyanide (1.32 mmol, 2.2 equiv.) were added successively to an oven dried 15 mL-vial containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 1 hour. After the reaction was completed as determined from TLC, the reaction mixture was dried under reduced pressure. The crude product was purified through SiO_2-gel column chromatography to afford analytically pure cyanoheterocyclic compounds.

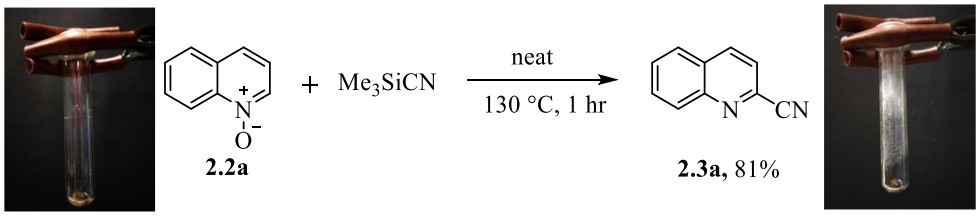
General procedure for cyanation of heterocyclic *N*-oxides (GP-III)

Heterocyclic *N*-oxides (0.6 mmol, 1 equiv.) and trimethylsilyl cyanide (131 mg, 1.32 mmol, 2.2 equiv.) were added successively to an oven dried microwave reaction tube containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 5 min under microwave irradiation (50 watt). Then the reaction mixture was cooled to room temperature. After the reaction is completed as determined from TLC, the reaction mixture was dried under reduced pressure. The crude product was purified through SiO_2-gel column chromatography to afford analytically pure cyanoheterocyclic compounds.

Synthetic protocol for cyanation of quinoline *N*-oxides using sublimation approach (GP-IV)

Representative procedure: Quinoline *N*-oxide (0.3 mmol, 1 equiv.) and trimethylsilyl cyanide (1.32 mmol, 2.2 equiv.) were loaded to an oven dried reaction tube containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was

heated at 130 °C for 1 hour. The sublimated product was isolated to afford analytically pure quinoline-2-carbonitrile compound (81% yield).



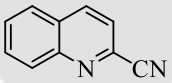
Scheme 2.27: Isolation of carbonitrile compound using sublimation approach, before reaction (in left), after reaction (in right).

Procedure for gram-scale cyantion reaction (scheme 2.8)

Quinoline *N*-oxide (1 g, 6.9 mmol) and trimethylsilyl cyanide (1.5 g, 15 mmol) were taken in a 50 mL pyrex tube, and the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 1 hour. After the reaction was completed as determined from TLC, the reaction mixture was dried under reduced pressure. The crude product was purified through SiO_2-gel column chromatography to afford analytically pure 2-cyanoquinoline **2.3a** with 86% yield. Using the above scale-up protocol, sublimated **2.3a** was obtained with 76% yield.

2.6.4. Analytical data for 2-cyanoheterocycles

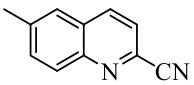
Quinoline-2-carbonitrile (2.3a)



Using quinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petroleum ether, 2 : 10) as a white solid. Isolated yield = 96% (89 mg) from GP-II; 95% (88 mg) from GP-III.

M.p. 93-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.87 – 7.82 (m, 1H), 7.73 – 7.69 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.34, 137.63, 133.75, 131.40, 130.12, 129.6, 128.8, 127.91, 123.46, 117.78. HRMS (ESI) *m/z*: calcd. for $C_{10}H_7N_2^+$ [M+H$^+$]: 155.0604, found 155.0616. FT-IR (KBr, selected band): 2233 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported literature.[21]

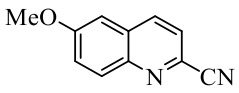
6-methylquinoline-2-carbonitrile (2.3b)



Using 6-methylquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2 : 10) as an yellow solid. Isolated yield = 91% (92 mg) from GP-II; 91% (92 mg) from GP-III.

M.p. 103-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.72 – 7.61 (m, 3H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.08, 140.16, 136.73, 133.80, 132.79, 129.77, 128.93, 126.63, 123.54, 117.86, 22.00. HRMS (ESI) *m/z*: calcd. for $C_{11}H_9N_2^+$ 169.0760, found 169.0773. FT-IR (KBr, selected band): 2230 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported literature.[21]

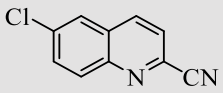
6-Methoxyquinoline-2-carbonitrile (2.3c)



Using 6-methoxyquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2 : 10) as an yellow solid (108 mg, 98% yield from GP-II; 107 mg, 97% yield from GP-III).

M.p. 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 9.3 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 9.3, 2.7 Hz, 1H), 7.10 (d, J = 2.7 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.12, 144.72, 135.81, 131.67, 130.88, 130.46, 124.76, 123.97, 118.01, 104.80, 55.92. HRMS (ESI TOF) [M+H$^+$] calcd. for [$C_{11}H_9N_2O$] 185.0709, found 185.0709. FT-IR (KBr, selected band): 2228 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported literature.[21]

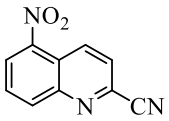
6-Chloroquinoline-2-carbonitrile (2.3d)



Using 6-chloroquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2 : 10) as an white solid (90 mg, 80% yield from GP-II; 93 mg, 82% yield from GP-III).

M.p. 198-200 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.23 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 9.0, 2.2 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 146.73, 136.68, 135.80, 133.96, 132.53, 131.74, 129.31, 126.56, 124.33, 117.38. HRMS (ESI) *m/z*: calcd. for $C_{10}H_6N_2Cl^+$ 189.0214, found 189.0221. FT-IR (KBr, selected band): 2232 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported literature.[21]

5-Nitroquinoline-2-carbonitrile (2.3e)

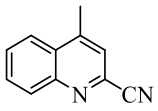


Using 5-nitroquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2.5 : 10) as an off-white solid (86 mg, 72% yield from GP-II, 84 mg, 70% yield from GP-III).

M.p. 164-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (d, J = 9.0 Hz, 1H), 8.59 – 8.54 (m, 1H), 8.51 (d, J = 8.5 Hz, 1H), 8.00 – 7.92 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 148.18, 145.34, 137.18, 135.43, 134.29, 129.49, 127.50, 126.12, 121.79, 116.73. HRMS (ESI) *m/z*: calcd. for

$C_{10}H_6N_3O_2^+$ [M+H$^+$] 200.0455, found 200.0490. FT-IR (KBr, selected band): 2242 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported literature.[21]

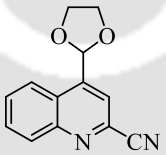
4-Methylquinoline-2-carbonitrile (2.3f)



Using 4-methylquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 1.5 : 10) as an off-white solid (85 mg, 84% yield from GP-II, 88 mg, 87% yield from GP-III).

M.p. 97-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.74 – 7.70 (m, 1H), 7.54 (s, 1H), 2.77 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 148.03, 146.74, 133.57, 130.96, 130.77, 129.31, 128.92, 124.04, 124.01, 117.82, 18.89. HRMS (ESI) *m/z*: calcd. for $C_{11}H_9N_2^+$ [M+H$^+$] 169.0760, found 169.0772. FT-IR (KBr, selected band): 2235 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported literature.[21]

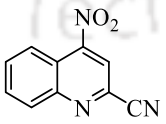
4-(1,3-dioxolan-2-yl)quinoline-2-carbonitrile (2.3g)



Using 4-(1,3-dioxolan-2-yl)quinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2.5 : 10) as an off-white solid (95 mg, 70% yield from GP-II, 96 mg, 71% yield from GP-III).

M.p. 156-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (d, J = 8.5 Hz, 1H), 8.26 – 8.24 (m, 2H), 7.94 – 7.88 (m, 1H), 7.86 – 7.80 (m, 1H), 4.61 – 4.64 (m, 2H), 4.10 – 4.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.89, 149.46, 136.33, 133.38, 131.64, 131.43, 130.81, 125.92, 125.84, 124.62, 117.10, 67.82, 61.01. HRMS (ESI) *m/z*: calcd. for $C_{13}H_{10}N_2O_2K^+$ 265.0374, found 265.0601. FT-IR (KBr, selected band): 2233 cm^{-1} (CN).

4-Nitroquinoline-2-carbonitrile (2.3h)

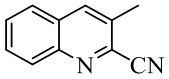


Using 4-nitroquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2 : 10) as an yellow solid (79 mg, 66% yield from GP-II, 78 mg, 65% yield from GP-III).

M.p. 126-128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.25 (s, 1H), 8.07 – 8.01 (m, 1H), 7.97 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.90, 150.70, 133.39, 133.10, 132.82, 131.05, 123.12, 119.51, 117.88, 116.12. HRMS (ESI) *m/z*: calcd. for $C_{10}H_6N_3O_2^+$ [M+H$^+$] 200.0455, found 200.0472. FT-IR

(KBr, selected band): 2239 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported literature.[21]

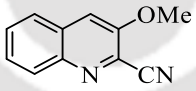
3-methylquinoline-2-carbonitrile (2.3i)



Using 3-methylquinoline *N*-oxide in accordance with 4 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petroleum ether, 2 : 10) as an white solid (88 mg, 87% yield from GP-II; 89 mg, 88% yield from GP-II).

M.p. 126-127 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 – 8.11 (m, 2H), 7.81 (d, J = 8.2 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 2.72 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 146.83, 136.86, 135.26, 132.74, 130.36, 129.82, 129.57, 129.03, 127.21, 116.69, 18.94. HRMS (ESI) *m/z*: calcd. for $C_{11}H_9N_2^+$ [M+H$^+$] 169.0760, found 169.0784. FT-IR (KBr, selected band): 2232 cm^{-1} (CN).

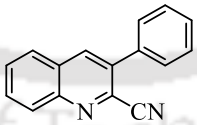
3-Methoxyquinoline-2-carbonitrile (2.3j)



Using 3-methoxyquinoline *N*-oxide in accordance with GP-II, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 1.2 : 10) as a light yellow solid (96 mg, 87% yield from GP-II; 96 mg, 87% from GP-III).

M.p. 151-153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.04 (m, 1H), 7.81 – 7.75 (m, 1H), 7.68 – 7.61 (m, 2H), 7.56 (s, 1H), 4.06 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 153.85, 143.42, 130.12, 130.05, 129.93, 128.40, 127.26, 126.78, 115.21, 114.11, 56.37. HRMS (ESI) *m/z*: calcd for $C_{11}H_9N_2O^+$ [M+H$^+$] 185.0709, found 185.0724. FT-IR (KBr, selected band): 2236 cm^{-1} (CN).

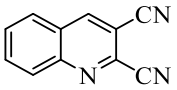
3-Phenylquinoline-2-carbonitrile (2.3k)



Using 3-phenylquinoline *N*-oxide with 4 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 1.2 : 10) as an off-white solid (98 mg, 71% yield from GP-II, 103 mg, 75% yield from GP-III).

M.p. 140-142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.87 – 7.82 (m, 1H), 7.74 – 7.71 (m, 1H), 7.65 (dd, J = 8.0, 1.4 Hz, 2H), 7.59-7.50 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.36, 137.23, 137.03, 135.88, 133.24, 131.14, 129.95, 129.93, 129.33, 129.17, 128.77, 127.92, 117.24. HRMS (ESI) *m/z*: calcd. for $C_{16}H_{11}N_2^+$ [M+H$^+$] 231.0917, found 231.0930. FT-IR (KBr, selected band): 2232 cm^{-1} (CN).

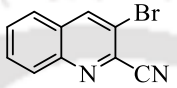
3-Cyanoquinoline-2-carbonitrile (2.3l)



Using 3-cyanoquinoline *N*-oxide with 4 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2 : 10) as an yellow solid. Isolated yield = 86 mg, 80% from GP-II; 87 mg, 81% from GP-III.

M.p. 201-203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.07 – 8.00 (m, 2H), 7.92 – 7.84 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.49, 142.98, 134.55, 133.43, 131.51, 130.62, 128.42, 126.72, 114.68, 114.40, 109.04. HRMS (ESI) *m/z*: calcd. for $C_{11}H_6N_3^+$ [M+ H^+] 180.0556, found 180.0581. FT-IR (KBr, selected band): 2235 cm^{-1} (CN).

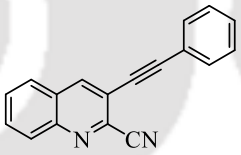
3-Bromoquinoline-2-carbonitrile (2.3m)



Using 3-bromoquinoline *N*-oxide with 4 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 1.5 : 10) as an white solid. Isolated yield = 107 mg, 77% from GP-II; 107 mg, 77% from GP-III.

M.p. 139-141 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.87 – 7.82 (m, 2H), 7.74 (t, J = 7.5 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): 146.59, 139.65, 134.72, 131.58, 130.67, 130.17, 129.69, 126.99, 117.57, 116.03. HRMS (ESI) *m/z*: calcd. for $C_{10}H_6BrN_2^+$ [M+H^+] 232.9709, found 232.9706. FT-IR (KBr, selected band): 2235 cm^{-1} (CN).

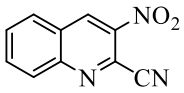
3-Phenylethynylquinoline-2-carbonitrile (2.3n)



Using 3-phenylethynylquinoline *N*-oxide with 4 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 1.2 : 10) as an off-white solid. Isolated yield = 126 mg, 83% from GP-II; 128 mg, 84% from GP-III.

M.p. 153-155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.72 – 7.65 (m, 3H), 7.41 – 7.38 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 146.56, 139.11, 135.47, 132.09, 131.63, 130.12, 130.02, 129.63, 128.63, 127.89, 127.63, 121.75, 119.71, 116.26, 97.59, 83.63. HRMS (ESI) *m/z*: calcd. for $C_{18}H_{11}N_2^+$ [M+H^+] 255.0917, found 255.0912. FT-IR (KBr, selected band): 2231 cm^{-1} (CN).

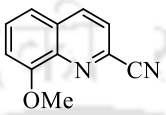
3-Nitroquinoline-2-carbonitrile (2.3o)



Using 3-nitroquinoline *N*-oxide with 4 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2 : 10) as an yellow solid (78 mg, 65% yield from GP-II; 76 mg, 64% yield from GP-II).

M.p. 140-142 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.34 (d, J = 8.5 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.10 (t, J = 7.7 Hz, 1H), 7.93 (t, J = 7.5 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 149.17, 135.07, 134.58, 131.90, 130.56, 129.69, 126.90, 114.52. HRMS (ESI) *m/z*: calcd. for $C_{10}H_6N_3O_2^+$ [M+H$^+$] 200.0455, found 200.0466. FT-IR (KBr, selected band): 2238 cm^{-1} (CN).

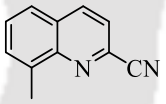
8-Methoxyquinoline-2-carbonitrile (2.3p)



Using 8-methoxyquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2 : 10) as an white solid (99 mg, 90% yield from GP-II; 99 mg, 90% yield from GP-III).

M.p. 106-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 4.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.62, 140.50, 137.43, 132.43, 130.18, 130.03, 124.30, 119.47, 117.66, 109.32, 56.46. HRMS (ESI) *m/z*: calcd. for $C_{11}H_9N_2O^+$ 185.0709, found 185.0735. FT-IR (KBr, selected band): 2234 cm^{-1} (CN). Spectroscopic characterization data are in accordance with literature.[21]

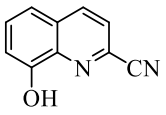
8-Methylquinoline-2-carbonitrile (2.3q)



Using 8-methylquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 1 : 10) as an yellow solid (92 mg, 91% yield from GP-II; 91 mg, 90% from GP-III yield).

M.p. 126-128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.4 Hz, 1H), 7.70 (m, 3H), 7.60 – 7.56 (m, 1H), 2.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.59, 138.59, 137.63, 132.52, 131.24, 129.41, 128.93, 125.75, 123.20, 118.04, 17.89. HRMS (ESI) *m/z*: calcd. for $C_{11}H_9N_2^+$ [M+ H$^+$] 169.0760, found 169.0770. FT-IR (KBr, selected band): 2237 cm^{-1} (CN).

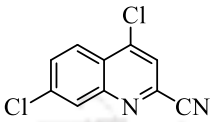
8-Hydroxyquinoline-2-carbonitrile (2.3r)



Using 8-hydroxyquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2.0 : 10) as an yellow solid (90 mg, 88% yield from GP-II; 93 mg, 91% yield from GP-III).

M.p. 130-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.5 Hz, 1H), 7.89 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.51, 138.59, 137.77, 131.40, 131.03, 129.26, 124.09, 118.14, 117.44, 112.21. HRMS (ESI) *m/z*: calcd. for $C_{10}H_7N_2O^+$ [M+ H^+] 171.0553, found 171.0567. FT-IR (KBr, selected band): 2242 cm^{-1} (CN). Spectroscopic characterization data are in accordance with literature.[21]

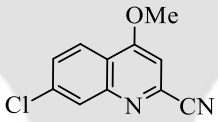
4, 7-Dichloroquinoline-2-carbonitrile (2.3s)



Using 4,7-Dichloroquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 –gel column chromatography (EtOAc : Petrolium ether, 1 : 10) as an white solid (110 mg, 82% yield from GP-II; 114 mg, 85% yield from GP-III).

M.p. 175-177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 9.0 Hz, 1H), 8.18 (d, J = 1.3 Hz, 1H), 7.77 (s, 1H), 7.74 (dd, J = 9.0, 1.5 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$): δ 149.18, 144.46, 138.74, 134.51, 131.71, 129.42, 125.82, 125.77, 123.65, 116.43. HRMS (ESI) *m/z*: calcd. for $C_{10}H_5Cl_2N_2^+$ [M+H^+] 222.9824, found 222.9857. FT-IR (KBr, selected band): 2241 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported literature.[32]

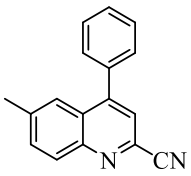
7-Chloro-4-methoxyquinoline-2-carbonitrile (2.3t)



Using 7-chloro-4-methoxyquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 1.5 : 10) as an yellow solid (113 mg, 86% yield from GP-II; 114 mg, 87% yield from GP-III).

M.p. 221-223 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 9.0 Hz, 1H), 8.07 (d, J = 1.9 Hz, 1H), 7.58 (dd, J = 9.0, 2.0 Hz, 1H), 7.04 (s, 1H), 4.11 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 163.39, 149.53, 137.77, 135.80, 129.42, 128.56, 123.59, 120.36, 117.52, 103.41, 56.67. HRMS (ESI) *m/z*: calcd. for $C_{11}H_8N_2OCl^+$ [M+H^+] 219.0320, found 219.0335. FT-IR (KBr, selected band): 2257 cm^{-1} (CN).

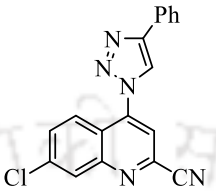
4-Phenyl-6-methylquinoline-2-carbonitrile (2.3u)



Using 4-phenyl-6-methylquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 1.5 : 10) as white solid (104 mg, 71% yield from GP-II; 100 mg, 68% yield from GP-III).

M.p. 123-125 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.11 (d, J = 8.6 Hz, 1H), 7.71 (brs, 1H), 7.67 (dd, J = 8.7 Hz, 1.7 Hz, 1H), 7.59 (brs, 1H), 7.58 – 7.54 (m, 2H), 7.50 – 7.48 (m, 2H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.60, 147.61, 140.22, 136.68, 133.46, 132.48, 130.24, 129.55, 129.29, 129.04, 127.56, 124.74, 123.74, 117.92, 22.25. HRMS (ESI) *m/z*: calcd. for $C_{17}H_{13}N_2^+$ [M+ H^+] 245.1073, found 245.1099. FT-IR (KBr, selected band): 2231 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported data.[55]

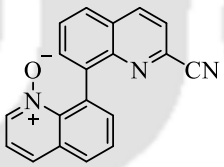
7-chloro-4-(4-phenyl-1H-1,2,3-triazol-1-yl)quinoline-2-carbonitrile (2.3v)



Using 7-chloro-4-(4-phenyl-1H-1,2,3-triazol-1-yl)quinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 2 : 10) as an yellow solid (141 mg, 71% yield from GP-II; 143 mg, 72% yield from GP-III).

M.p. 228-230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 2.0 Hz, 1H), 8.28 (m, 2H), 7.96 (d, J = 7.3 Hz, 2H), 7.87 (s, 1H), 7.79 (dd, J = 9.1, 1.9 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 7.4 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$): δ 150.35, 149.14, 142.12, 139.04, 134.75, 132.31, 129.50, 129.29, 129.22, 129.04, 126.11, 125.20, 121.07, 120.84, 117.78, 116.25. HRMS (ESI) *m/z*: calcd. for $C_{18}H_{11}N_5Cl^+$ [M+H^+] 332.0697, found 332.0707. FT-IR (KBr, selected band): 2239 cm^{-1} (CN).

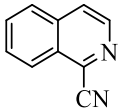
2'-cyano-[8,8'-biquinoline] 1-oxide (2.3w)



Using [8,8'-biquinoline] 1,1'-dioxide with 4.2 equivalents of trimethylsilyl cyanide in accordance with GP-III, the title compound was obtained through activated SiO_2 column chromatography as yellow solid (123 mg, 69% yield). Activated SiO_2-gel was made by running the column two times with 5% NEt_3/hexane.

M.p. 157-160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.4 Hz, 1H), 8.27 (brs, 1H), 8.05 (dd, J = 7.8, 1.9 Hz, 1H), 7.88-7.89 (m, 3H), 7.77 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 7.8, 1.1 Hz, 1H), 7.47 (dd, J = 7.4, 1.3 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 6.64 (d, J = 9.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.52, 146.48, 141.30, 138.22, 136.42, 136.24, 134.35, 133.66, 132.97, 129.68, 129.44, 129.35, 128.4, 125.2, 124.36, 122.38, 121.91, 120.15, 117.33. HRMS (ESI) *m/z*: calcd. for $C_{19}H_{12}N_3O^+$ [M+H^+] 298.0975, found 298.0981. FT-IR (KBr, selected band): 2171 cm^{-1} (CN).

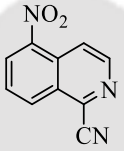
Isoquinoline-1-carbonitrile (2.6a)



Using isoquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 2.0 : 10) as white solid (79 mg, 85% yield from GP-II; 79 mg, 85% yield from GP-III).

M.p. 88-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 5.6 Hz, 1H), 8.37 – 8.35 (m, 1H), 7.95 (dd, J = 6.7, 2.3 Hz,1H), 7.91 (d, J = 5.5 Hz, 1H), 7.87 – 7.78 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.45, 136.07, 135.00, 131.88, 130.02, 129.54, 127.46, 125.52, 124.57, 115.97. HRMS (ESI) *m/z*: calcd. for $C_{10}H_7N_2^+$ [M+H$^+$] 155.0604, found 155.0621. FT-IR (KBr, selected band): 2228 cm^{-1} (CN). Spectroscopic characterization data are in accordance with literature.[16]

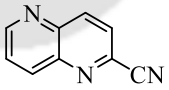
5-Nitroisoquinoline-2-carbonitrile (2.6b)



Using 5-Nitroisoquinoline *N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 1.2 : 10) as yellow solid (82 mg, 69% yield from GP-II; 86 mg, 72% yield from GP-III).

M.p. 215 - 217 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, J = 6.1 Hz, 1H), 8.77 (d, J = 6.2 Hz, 1H), 8.74 (d, J = 8.4 Hz, 1H), 8.68 (d, J = 7.7 Hz, 1H), 7.96 (t, J = 8.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.61, 145.28, 135.94, 132.43, 129.75, 129.63, 128.74, 128.56, 120.00, 115.28. HRMS (ESI) *m/z*: calcd. for $C_{10}H_5N_3O_2^+$ [M+H$^+$] 200.0455, found 200.0488. FT-IR (KBr, selected band): 2223 cm^{-1} (CN).

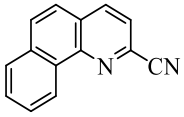
1,5-naphthyridine-2-carbonitrile (2.6c)



Using 1,5-naphthyridine 1-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 3.0 : 10) as white solid (81 mg, 87% yield from GP-II; 84 mg, 90% yield from GP-III).

M.p. 195-198 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.12 (dd, J = 4.1, 1.6 Hz, 1H), 8.57 (dd, J = 8.6 Hz, 0.5 Hz, 1H), 8.53 – 8.46 (m, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.78 (dd, J = 8.6, 4.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 154.15, 144.48, 143.70, 139.25, 137.90, 134.49, 126.92, 126.17, 117.14. HRMS (ESI) *m/z*: calcd. for $C_9H_6N_3^+$ [M+H$^+$] 156.0556, found 156.0570.
FT-IR (KBr, selected band): 2236 cm^{-1} (CN). Spectroscopic characterization data are in accordance with literature.[34]

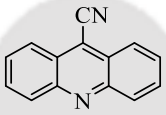
Benzo[*h*]quinoline-2-carbonitrile (2.6d)



Using Benzo[*h*]quinoline-*N*-oxide in accordance with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 1.0 : 10) as an white solid (98 mg, 80% from GP-II; 93 mg, 76% from GP-III yield).

M.p. 165-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 – 9.25 (m, 1H), 8.27 (d, J = 8.2 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.83 (d, J = 8.2 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.70 (d, J = 8.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.25, 136.67, 133.86, 131.83, 131.11, 130.73, 129.51, 128.12, 128.00, 127.84, 124.92, 124.77, 124.43, 118.02. HRMS (ESI) *m/z*: calcd. for $C_{14}H_9N_2^+$ [M+H$^+$] 205.0760, found 205.0767. FT-IR (KBr disc): 2235 cm^{-1} (CN). Spectroscopic characterization data are in accordance with literature.[56]

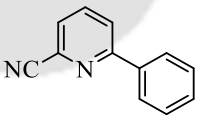
Acridine-9-carbonitrile (2.6e)



Using acridine-*N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : Petrolium ether, 2.0 : 10) as white solid (98 mg, 80% from GP-II; 98 mg, 80% from GP-III yield).

M.p. 184-187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 8.5 Hz, 2H), 8.31 (d, J = 8.8 Hz, 2H), 7.93 – 7.87 (m, 2H), 7.79 – 7.75 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.48, 131.15, 130.56, 129.25, 126.27, 125.33, 115.49, 115.21. HRMS (ESI) *m/z*: calcd. for $C_{14}H_9N_2^+$ [M+H$^+$] 205.0760, found 205.0778. FT-IR (KBr, selected band): 2227 cm^{-1} (CN). Spectroscopic characterization data are in accordance with reported data.[57]

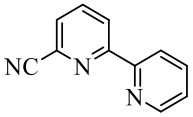
6-Phenylpyridine-2-carbonitrile (2.6f)



Using 2-phenylpyridine-*N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 1.2 : 10) as off white solid (92 mg, 85% yield from GP-II; 90 mg, 83% yield from GP-III).

M.p. 65-68 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 – 8.02 (m, 2H), 7.95 (dd, J = 8.1, 0.8 Hz, 1H), 7.89 (t, J = 7.8 Hz, 1H), 7.62 (dd, J = 7.5, 0.8 Hz, 1H), 7.53 – 7.44 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.10, 137.86, 137.31, 133.94, 130.31, 129.13, 127.19, 126.72, 123.62, 117.55. HRMS (ESI) *m/z*: calcd. for $C_{12}H_9N_2^+$ [M+H$^+$] 181.0760, found 181.0773. Spectroscopic characterization data are in accordance with literature.[16]

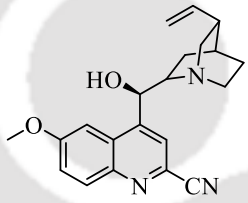
2, 2′-Bipyridyl-6-Carbonitrile (2.6g)



Using 2, 2′-bipyridine-*N*-oxide with 2.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 3.0 : 10) as off white solid (93 mg, 86% yield from GP-II; 94 mg, 87% yield from GP-III).

M.p. 130-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 – 8.65 (m, 2H), 8.45 (d, J = 8.0 Hz, 1H), 7.94 (t, J = 7.9 Hz, 1H), 7.85 (td, J = 7.8, 1.7 Hz, 1H), 7.69 (dd, J = 7.6, 0.9 Hz, 1H), 7.37 (ddd, J = 7.5, 4.8, 1.0 Hz 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.82, 154.11, 149.42, 138.02, 137.34, 133.30, 128.25, 124.90, 124.34, 121.69, 117.51. HRMS (ESI) *m/z*: calcd. for $C_{11}H_8N_3^+$ [M+H$^+$] 182.0713, found 182.0748. FT-IR (KBr, selected band): 2234 cm^{-1} (CN). Spectroscopic characterization data are in accordance with literature reported procedure.[16]

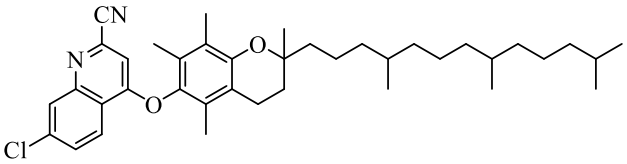
4-((1R)-hydroxy((1S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-6-methoxyquinoline-2-carbonitrile (2.3x)



Using 4-((1R)-hydroxy((1S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-6-methoxyquinoline 1-oxide (0.2 mmol, 1 equiv.) with 3.5 equivalent of trimethylsilyl cyanide in accordance with GP-II or GP-III, after completion of the reaction, the crude reaction mixture was dissolved in dry methanol (5 mL) and potassium fluoride (116 mg, 2 mmol, 5 equiv.) was added to it. The mixture was stirred at room temperature for overnight. The reaction was monitored by TLC, then solvent was removed under reduced pressure. The mixture was washed with water and extracted with chloroform (2×5 mL). The crude product was purified through SiO_2 column chromatography (methanol : chloroform, 1 : 10) as light yellow solid (147 mg, 70% from GP-II; 147 mg, 70% from GP-III yield).

M.p. 228-230 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.38 (brs, 1H), 7.95 (s, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.07 (dd, J = 9.2, 2.4 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 6.49 (d, J = 4.5 Hz, 1H), 5.89 (d, J = 4.6 Hz, 1H), 5.52 (ddd, J = 17.1, 10.5, 6.7 Hz, 1H), 5.01 (dd, J = 13.7, 5.8 Hz, 2H), 4.56 (t, J = 10.8 Hz, 1H), 3.74 (s, 3H), 3.45 – 3.41 (m, 1H), 3.28 – 3.25 (m, 1H), 3.15 (td, J = 12.0, 5.1 Hz, 1H), 3.07 (d, J = 12.9 Hz, 1H), 2.71 (s, 1H), 2.25 (t, J = 11.4 Hz, 1H), 2.11 (s, 1H), 2.05 (dd, J = 13.3, 7.8 Hz, 2H), 1.88 (t, J = 9.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.60, 145.62, 143.95, 137.02, 132.28, 130.26, 126.32, 124.32, 121.53, 117.98, 117.67, 99.79, 65.71, 60.02, 57.98, 55.06, 44.63, 37.09, 26.86, 24.31, 18.45. HRMS (ESI) *m/z*: calcd. for $C_{21}H_{24}N_3O_2^+$ [M+H$^+$] 350.1863, found 350.1870. FT-IR (KBr, selected band): 2232 cm^{-1} (CN).

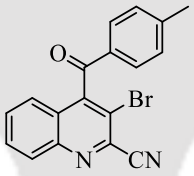
7-chloro-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy) quinoline -2-carbonitrile (2.3y)



Using 7-chloro-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy) quinoline 1-oxide in accordance with GP-III with 4.2 equivalents of trimethylsilyl cyanide, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 1.0 : 10) as colourless liquid (241 mg, 65% yield). Here it was observed that starting material of *N*-oxide was not completely consumed, after column chromatography, 28% of *N*-oxide was recovered.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, J = 8.9 Hz, 1H), 8.14 (d, J = 1.9 Hz, 1H), 7.67 (dd, J = 8.9, 2.0 Hz, 1H), 6.56 (d, J = 4.6 Hz, 1H), 2.65 (t, J = 6.8 Hz, 2H), 2.16 (s, 3H), 1.97 (s, 3H), 1.93 (s, 3H), 1.89 – 1.77 (m, 2H), 1.56 – 1.49 (m, 4H), 1.39 – 1.34 (m, 4H), 1.30 – 1.21 (m, 10H), 1.16 – 1.08 (m, 6H), 0.90 – 0.84 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.89, 150.26, 150.10, 142.06, 138.01, 135.82, 129.68, 128.74, 127.01, 125.26, 124.53, 123.53, 119.90, 118.77, 117.50, 105.93, 75.69, 39.53, 37.73, 37.64, 37.56, 37.45, 32.95, 32.84, 28.13, 24.97, 24.61, 24.32, 23.74, 22.86, 22.77, 21.22, 20.80, 19.91, 19.84, 19.79, 12.81, 12.08, 11.98. HRMS (ESI) *m/z*: calcd. for $C_{39}H_{54}ClN_2O_2^+$ [M+H$^+$] 617.3868, found 617.3867.

3-bromo-4-(4-methylbenzoyl)quinoline-2-carbonitrile (2.3z)

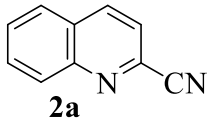
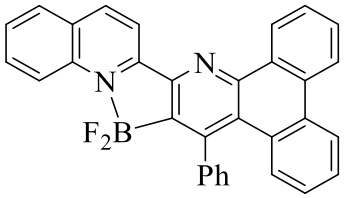
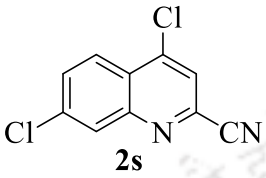
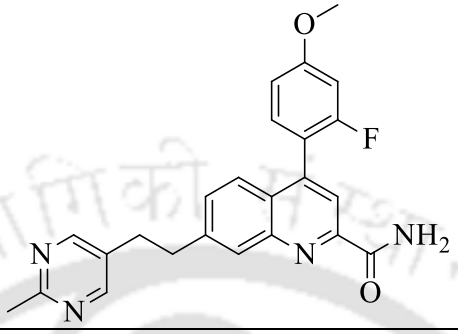
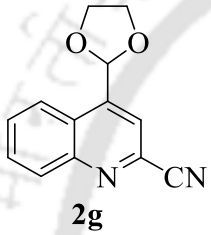
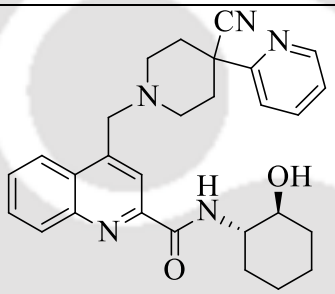


Using 3-bromo-4-(4-methylbenzoyl)quinoline-*N*-oxide with 4.2 equivalents of trimethylsilyl cyanide in accordance with GP-III, the title compound was obtained through SiO_2 column chromatography (EtOAc : Petrolium ether, 2.0 : 10) as off white solid (149 mg, 71% yield).

M.p. 214-216 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.23 (d, J = 8.6 Hz, 1H), 7.88 (dd, J = 11.4, 4.0 Hz, 1H), 7.69 – 7.67 (m, 2H), 7.65 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.54, 147.96, 146.95, 146.67, 135.11, 132.40, 131.84, 131.34, 130.63, 130.28, 130.18, 126.90, 125.10, 115.75, 114.20, 22.11. HRMS (ESI) *m/z*: calcd. for $C_{18}H_{11}BrN_2O^+$ [M+H$^+$] 351.0128, found 351.0133. FT-IR (KBr, selected band): 2238 cm^{-1} (CN), 1661 cm^{-1} (CO).

2.6.5. Synthesized building blocks for bioactive molecules

Table 2.4: Various 2-cyanoheterocyclic derivative as an active intermediate for the synthesis of bioactive molecules.

Entry	2-cyanoheterocyclic derivative	bioactive compound	application	ref.
1	 **2a**		*Broadly use in bio-imaging purpose*	58
2	 **2s**		*negative allosteric modulator for mGlu3*	32
3	 **2g**		*potent Alzheimer's drug*	59

2.6.6. Mechanistic studies

Cyanation reaction of quinoline *N*-oxide in presence of TEMPO (scheme 2.9b)

Quinoline *N*-oxide **2.2a** (0.02 g, 0.14 mmol, 1 equiv.), TEMPO (0.044 g, 0.28 mmol, 2 equiv.) and trimethylsilyl cyanide (0.042 g, 0.31 mmol, 2.2 equiv.) were added successively to an oven dried 15 mL-vial containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 1 hour. After the reaction was completed as determined from TLC, the reaction mixture was dried under reduced pressure. The product was purified through SiO_2-gel column chromatography (EtOAc : Petroleum ether; 0.1 : 1) to afford pure quinoline-2-carbonitrile (0.019 g, 90% yield).

Cyanation reaction of quinoline *N*-oxide in presence of water (scheme 2.9c)

Trimethylsilyl cyanide (0.045 g, 0.45 mmol, 2.2 equiv.) and water (0.008 g, 0.31 mmol, 2.2 equiv.) were stirred in a vial for 2 minutes. Then quinoline *N*-oxide **2.2a** (0.03 g, 0.21 mmol, 1 equiv.) was added to it and the vial was sealed with screw-cap. The resulting solution was heated at 130 °C for 1 hour. The reaction mixture was extracted with dichloromethane (2×2 mL) and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified through silica-gel column chromatography (EtOAc : Petroleum ether; 0.1 : 1) to afford trace amount of pure quinoline-2-carbonitrile (5% yield).

Cyanation reaction of 6-methoxyquinoline *N*-oxide after 30 minutes (scheme 2.9d).

6-Methoxyquinoline *N*-oxide **2.2c** (0.11 mmol, 1 equiv.) and trimethylsilyl cyanide (0.24 mmol, 2.2 equiv.) were added successively to an oven dried 15 mL-vial containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 30 minutes. Then $CDCl_3$ was added to this reaction mixture and checked the NMR.

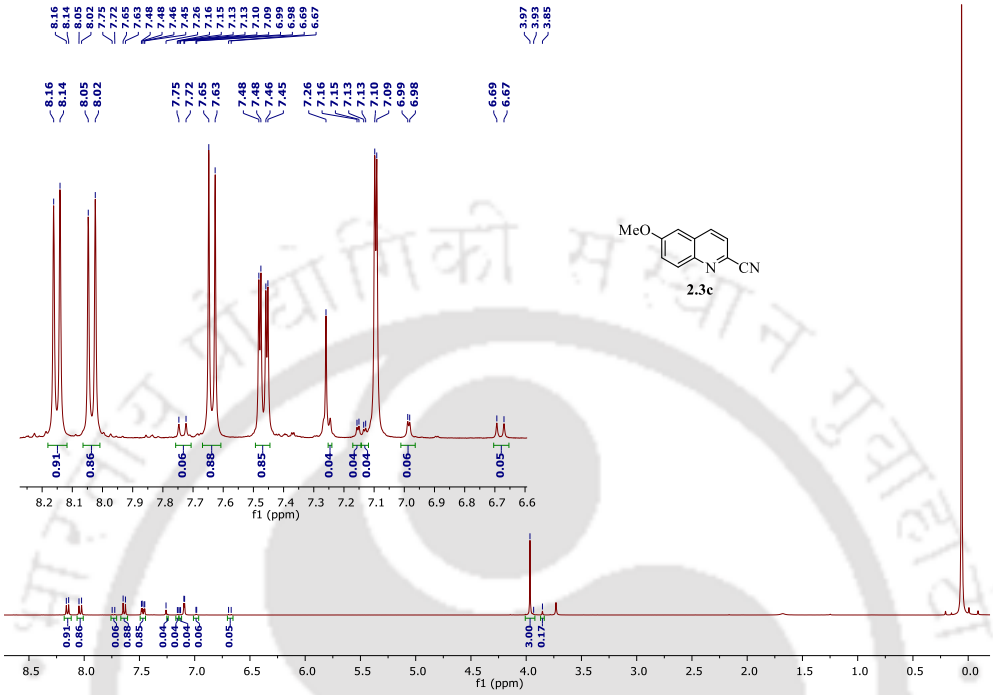


Figure 2.7. ^{1}H NMR spectrum of cyanation reaction of **2.2c** after 30 min.

Cyanation reaction of 6-chloroquinoline *N*-oxide after 30 minutes (scheme 2.9e)

6-Chloroquinoline *N*-oxide **2.2d** (0.11 mmol, 1 equiv.) and trimethylsilyl cyanide (0.24 mmol, 2.2 eqv.) were added successively to an oven dried 15 mL-vial containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 30 minutes. Then $CDCl_3$ was added to this reaction mixture and checked the ^{1}H NMR with internal standard CH_3CN (0.134 mmol).

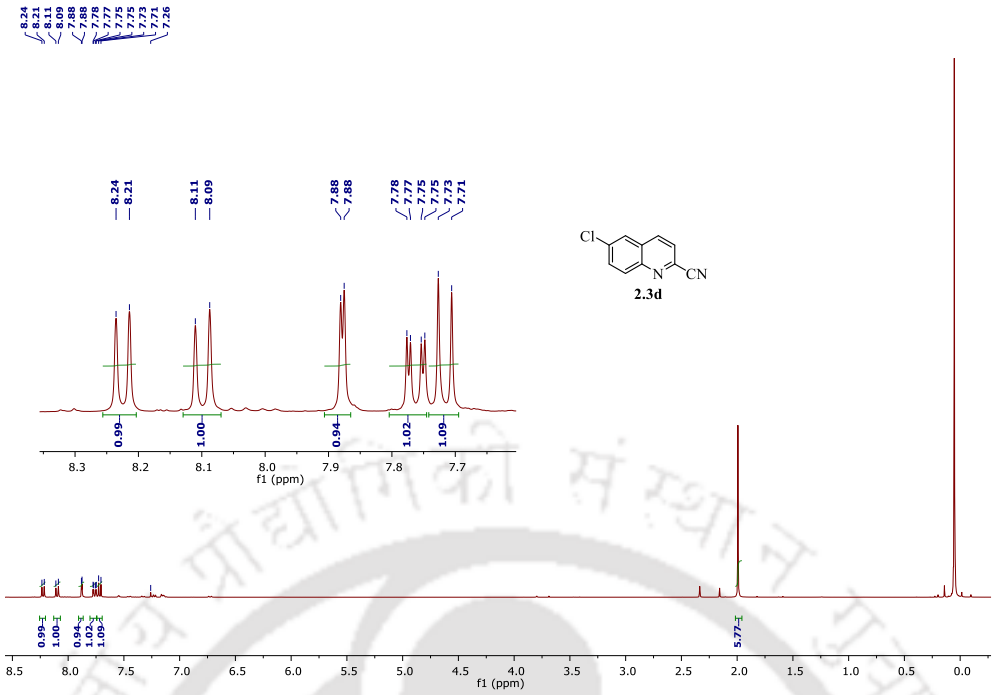


Figure 2.8. ^{1}H NMR spectrum of cyanation reaction of **2.2d** after 30 min.

Competition experiments between electronically differentiated quinoline *N*-oxide (scheme 2.10)

Quinoline *N*-oxide **2.2a** (0.1 mmol, 1 equiv.), 6-chloroquinoline *N*-oxide (0.1 mmol, 1 equiv.) and trimethylsilyl cyanide (0.22 mmol, 2.2 equiv.) were taken in an oven dried vial containing a stirring bar. The tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 1 hour. The crude compound was dissolved in $CDCl_3$ and checked the NMR.

Cyanation reaction of 6-methoxyquinoline *N*-oxide after 15 minutes (scheme 2.11)

6-Methoxyquinoline *N*-oxide **2.2c** (0.11 mmol, 1 equiv.) and trimethylsilyl cyanide (0.24 mmol, 2.2 equiv.) were added successively to an oven dried vial containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 15 minutes. Then $CDCl_3$ was added to this reaction mixture and checked the NMR.

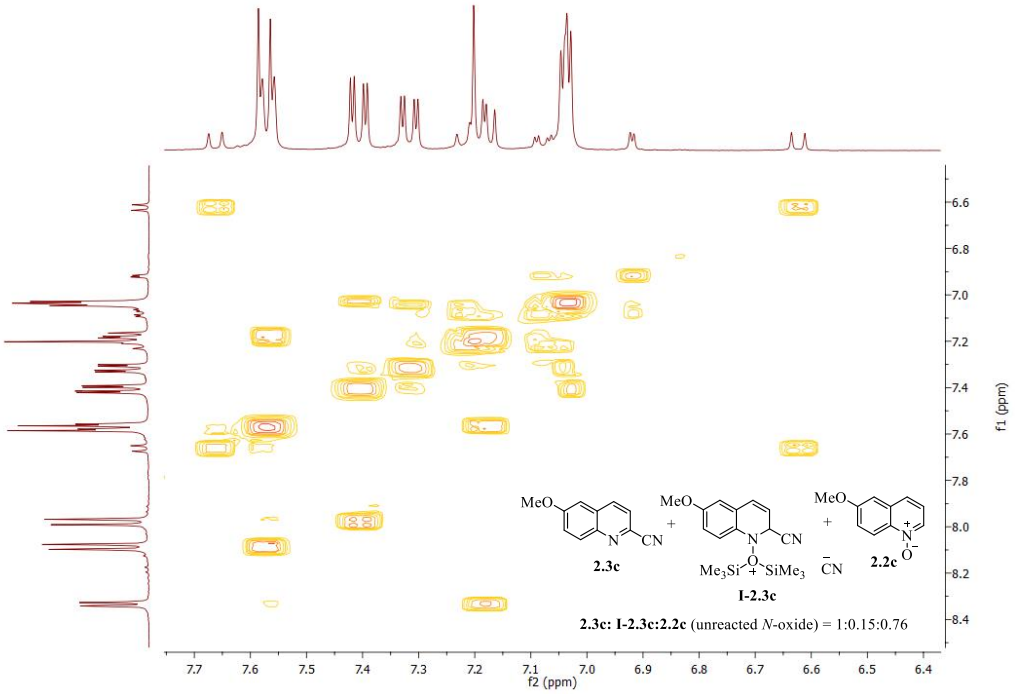


Figure 2.9. ^{1}H COSY spectrum for the cyanation reaction of **2.2c** at 15 min.

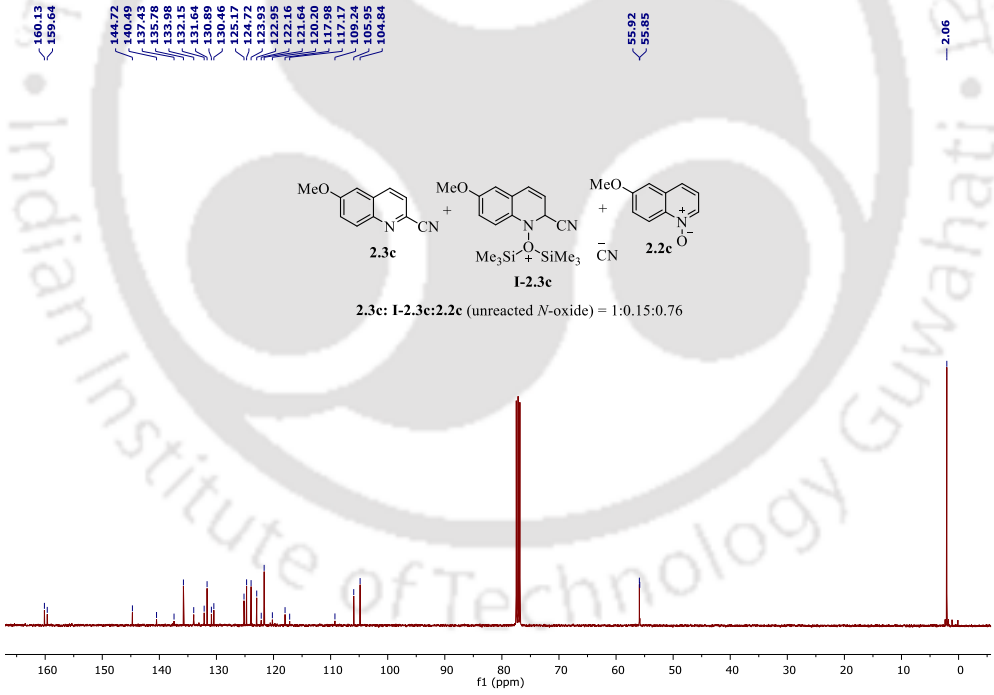


Figure 2.10. ^{13}C NMR spectrum for the cyanation reaction of **2.2c** at 15 min.

NMR study of cyanation reaction of 6-methoxyquinoline *N*-oxide at different intervals of time (scheme 2.12)

6-Methoxyquinoline *N*-oxide **2.3c** (0.11 mmol, 1 equiv.) and trimethylsilyl cyanide (0.24 mmol, 2.2 equiv.) were added successively to an oven dried vial containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated

at 130 °C and checked the ^{1}H NMR in $CDCl_3$ at different time iterval, after 15 minutes, 30 minutes and 45 minutes respectively.

^{29}Si NMR study of cyanation reaction of quinoline *N*-oxide

Quinoline *N*-oxide **2.2a** (0.11 mmol, 1 equiv.) and trimethylsilyl cyanide (0.24 mmol, 2.2 equiv.) were added successively to an oven dried vial containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 1 h. Then $CDCl_3$ was added to this reaction mixture and checked the ^{29}Si NMR.

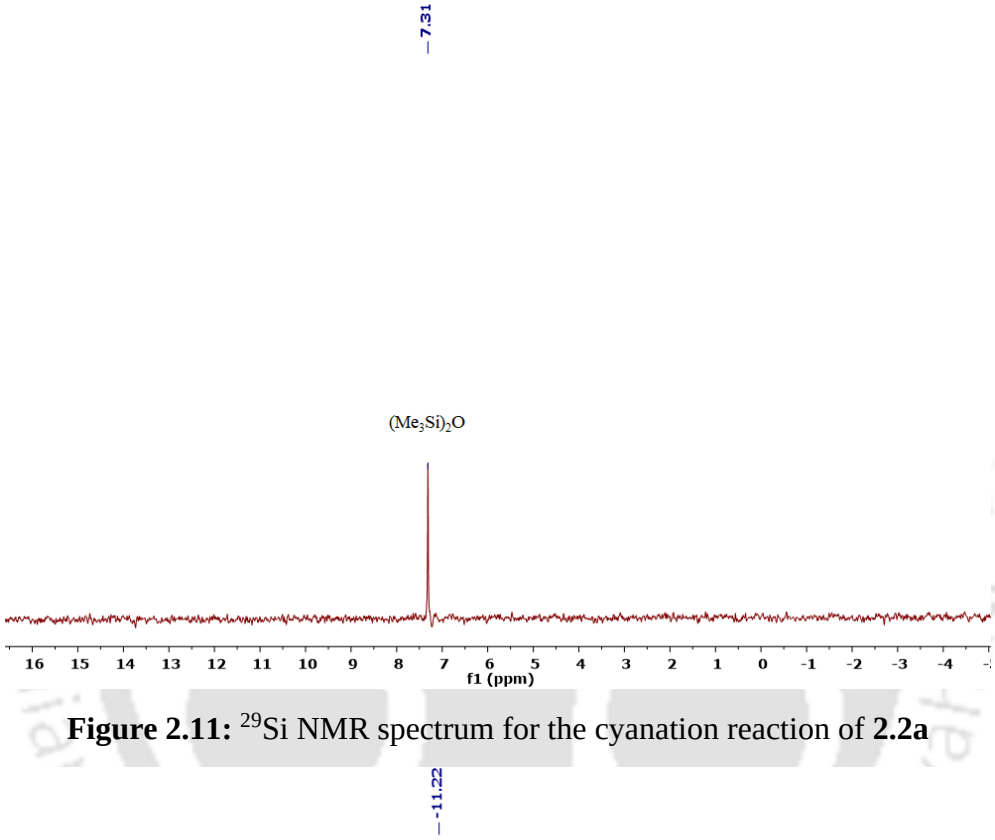


Figure 2.11: ^{29}Si NMR spectrum for the cyanation reaction of **2.2a**

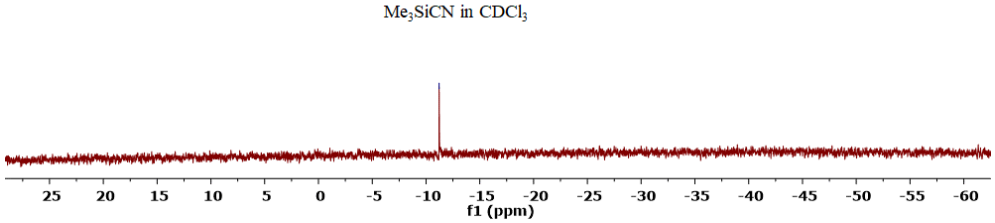


Figure 2.12: ^{29}Si NMR spectrum for the TMSCN

2.6.7. Synthetic utility of *N*-containing 2-cyano heteroaromatic derivatives

One-pot, two-step synthesis of 4,7-dichloroquinoline-2-carbonitrile (2.3s) and 7-chloro-4-(4-fluorophenoxy)quinoline-2-carbonitrile (2.10) (scheme 2.13a)

In a reaction vial, 4,7-dichloroquinoline (0.5 g, 2.5 mmol, 1 equiv.) was dissolved in acetic acid (3 mL) and H_2O_2 (30% in water, 425 mg, 3.75 mmol, 1.5 equiv.) was added to it. The reaction mixture was stirred at 70 °C for 24 hours. After completion of the reaction as confirmed by TLC, acetic acid was removed in vacuo at 60 °C and the reaction mixture was allowed to come to room temperature. Trimethylsilyl cyanide (0.546 g, 5.5 mmol, 2.2 equiv.) was added to the yellowish solid residue and the mixture was stirred at 130 °C for 1 hour. The reaction completion was examined by TLC and the reaction mixture was dried under reduced pressure. The crude product was purified through silica-gel column chromatography (EtOAc : petroleum ether; 1 : 10) to get the pure 4,7-dichloroquinoline-2-carbonitrile **2.3s** in 80% yield (446 mg) based on 4,7-dichloroquinoline.

In an oven-dried round-bottom flask, **2.3s** (20 mg, 0.09 mmol, 1 equiv.), 4-fluorophenol (22 mg, 0.2 mmol, 2.2 equiv.) and *N*, *N*′-dimethylaminopyridine (3 mg, 0.02 mmol, 0.2 equiv.) were taken in 4 mL of dry xylene and the mixture was refluxed at 140 °C for 20 hours. After complete conversion of starting material as confirmed by TLC, the solid was filtered and washed with ethyl acetate. The solid was again suspended in 5 mL of 5N NaOH solution and filtered and dried under reduced pressure to get the product **2.10** as yellow solid (20 mg, yield 72%).

M.p. 133-135 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (d, J = 8.9 Hz, 1H), 8.14 (s, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.28 – 7.26 (m, 2H), 7.22 – 7.15 (m, 2H), 6.77 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.11, 162.10, 159.65, 150.02, 148.95 (d, J = 3.03 Hz), 138.30, 135.45, 130.02, 128.68, 123.45, 122.83 (d, J = 9.1 Hz), 120.14, 117.85, 117.62, 117.10, 106.52. HRMS (ESI) *m/z*: calcd. for $C_{16}H_9N_2ClFO^+$ [M+H$^+$] 299.0382, found 299.0396. FT-IR (KBr, selected band): 2238 cm^{-1} (CN).

One-pot, three-step synthesis of 8-hydroxyquinoline-2-carboxylic acid (2.11) (scheme 2.13b)

In a 15-mL reaction vial, 8-hydroxyquinoline (500 mg, 3.4 mmol, 1 equiv.) was dissolved in acetic acid (3 mL) and H_2O_2 (30% in water, 587 mg, 5.2 mmol, 1.5 equiv.) was added to it. The reaction mixture was stirred at 70 °C for 24 hours. After completion of the reaction as confirmed by TLC, acetic acid was removed in vacuo at 60 °C and the reaction mixture was allowed to come to room temperature. Trimethylsilyl cyanide (742 mg, 7.5 mmol, 2.2 equiv.) was added to the solid residue and the mixture was stirred at 130 °C for 1 hour. The reaction completion was examined by TLC and the reaction mixture was dried under reduced pressure. Then, 3N aqueous NaOH solution (3 mL) was added to the mixture and stirred at 100 °C for 15 hours. After complete conversion as suggested by TLC, the pH of the solution was adjusted to 4 with aqueous HCl solution and the reaction mixture was extracted with dichloromethane (3×20 mL). The organic phase was separated and solvent was evaporated under reduced pressure to get the product **2.11** as yellow solid with 85% (546 mg) yield based on 8-hydroxyquinoline.

M.p. 217-219 °C. ^{1}H NMR (400 MHz, DMSO-d^6): δ 10.24 (brs, 1H), 8.56 (d, J = 8.5 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d^6): δ 165.17, 153.83, 144.34, 138.38, 136.51, 130.48, 129.95, 120.00, 117.63, 112.05. HRMS (ESI) *m/z*: calcd. for $C_{10}H_8NO_3^+$ [M+H$^+$] 190.0499, found 190.0513. The spectroscopic characterization data are matched with the literature reported data.[21]

One-pot, three-step synthesis of 1,5-nephthyridine-2-carboxylic acid (2.12) (scheme 2.13c)

In a 15-mL reaction vial, 1,5-nephthyridine (500 mg, 3.8 mmol, 1 equiv.) was dissolved in acetic acid (3 mL) and H_2O_2 (30% in water, 653 mg, 5.8 mmol, 1.5 equiv.) was added to it. The reaction mixture was stirred at 70 °C for 24 hours. After completion of the reaction as confirmed by TLC, acetic acid was removed in vacuo at 60 °C and the reaction mixture was allowed to come to room temperature. Trimethylsilyl cyanide (829 mg, 8.4 mmol, 2.2 equiv.) was added to the solid residue and the mixture was stirred at 130 °C for 1 hour. The reaction completion was examined by TLC and the reaction mixture was dried under reduced pressure. Then, 40% aqueous H_2SO_4 solution (3 mL) was added to the mixture and stirred at 100 °C for 15 hours. After complete conversion as suggested by TLC, the pH of the solution was adjusted to 2-3 with aqueous KOH solution when white precipitate started to come. The precipitate was filtered, washed with water and diethyl ether to get the product **2.12** as white solid with 84% (555 mg) yield based on 1,5-nephthyridine.

M.p. 247-249 °C. ^{1}H NMR (400 MHz, DMSO-d^6): δ 9.15 – 9.10 (m, 1H), 8.59 (t, J = 8.5 Hz, 2H), 8.35 (d, J = 8.7 Hz, 1H), 7.90 (dd, J = 8.6, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d^6): δ 165.86, 153.41, 149.32, 143.74, 142.54, 138.39, 137.76, 125.76, 124.28. HRMS (ESI) *m/z*: calcd. for $C_9H_7N_2O_2^+$ [M+ H$^+$] 175.0502, found 175.0526. FT-IR (KBr, selected band): 3071, 1703 (for CO_2H) cm^{-1}.

Preparation of quinoline-2,3-dicarboxylic acid (2.14) and 2,3-dihydropyridazino[4,5-*b*]quinoline-1,4-dione (2.15) (scheme 2.13d)

3-cyano quinoline *N*-oxide **2.2l** (0.1 g, 1 eqv.) and trimethylsilyl cyanide (4.2 eqv.) were taken in an oven dried 15 mL-reaction tube containing a stirring bar. Then the tube was flushed with argon and sealed with screw-cap. The resulting solution was heated at 130 °C for 1 hour. After the reaction was completed as determined from TLC, the reaction mixture was dried under reduced pressure. To the crude product, 1N aqueous NaOH solution was added and refluxed overnight. After completion of the reaction as confirmed by TLC, the reaction mixture is neutralized by 1N HCl solution. Then the organic phase is extracted with dichloromethane (3 × 5 mL). The organic layer was dried over Na_2SO_4 and removed under reduced pressure to obtain quinoline-2,3-carboxylic acid **2.14** as yellow solid (92 mg, 72% yield).

M.p. 277-280 °C. ^{1}H NMR (400 MHz, DMSO-d^6): δ 9.31 (d, J = 1.8 Hz, 1H), 8.97 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.91 (t, J = 7.4 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d^6): δ 166.31, 149.82, 149.10, 138.45, 131.92, 129.55, 128.77, 127.47, 126.59. HRMS (ESI) *m/z*: calcd. for $C_{11}H_8NO_4^+$ [M+ H$^+$] 218.0448, found 218.0459. FT-IR (KBr, selected band): 3053, 1711, 1627 (for CO_2H) cm^{-1}.

Quinoline-2,3-carboxylic acid (50 mg, 1 equiv.) was dissolved in dry methanol (5 mL), transfer in an oven-dried two-neck round-bottom flask fitted with a reflux condenser and flushed with

argon. Then, under argon flow at 0 °C, $SOCl_2$ (109 mg, 0.92 mmol, 4 equiv.) was added slowly. The reaction was refluxed at 70 °C overnight. After reaction was completed as indicated by TLC, then the volatiles were removed under reduced pressure. The residue was dissolved in dichloromethane and washed with aqueous $NaHCO_3$ solution. The organic layer was collected and dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude dimethyl quinoline-2,3-dicarboxylate (53 mg, 0.22 mmol, 1 equiv.) was dissolved in ethanol (5 mL) and hydrazine hydrate (70 mg, 2.2 mmol, 10 equiv.) was added and the solution was refluxed overnight at 82 °C. Then the precipitate was filtered, washed with ethanol and diethyl ether. This hydrazinium salt was treated with acetic acid (5 mL) and the mixture was stirred at 100 °C for 3 hours. The precipitate was washed with ethanol and diethyl ether to get 2,3-dihydropyridazino[4,5-*b*]quinoline-1,4-dione **2.15** as reddish solid (33 mg, 71% yield).

M.p. 374-376 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.35 (d, J = 7.9 Hz, 1H), 8.29 (d, J = 8.1 Hz, 1H), 8.10 – 7.99 (m, 1H), 7.86 – 7.79 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d^6 + $CDCl_3$): δ 149.90, 137.04, 133.4, 129.82, 129.79, 129.05, 128.53. HRMS (ESI) *m/z*: calculated for $C_{11}H_8N_3O_2$ ($M+H^+$): 214.0612; found: 214.0586. The spectroscopic characterization data were matched with the literature reported data.[36]

Preparation of quinoline-2-carboximidhydrazide (2.16) and 6-(quinolin-2-yl)-1,3,5-triazine-2,4-diamine (2.17) (scheme 2.14)

Quinoline-2-carbonitrile (31 mg, 0.2 mmol, 1 equiv.) was dissolved in ethanol (3 mL) in a round-bottom flask and hydrazine hydrate (64 mg, 2 mmol, 10 equiv.) was added to it. The solution was stirred at room temperature for 5 hours and then solvents were removed under reduced pressure and the residue was washed with ether to obtain the pure product quinoline-2-carboximidhydrazide **2.16** (30 mg, yield 82%).

M.p. 191-193 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 5.43 (brs, 2H), 3.68 (brs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.59, 148.75, 146.80, 136.17, 129.55, 129.31, 128.34, 127.58, 126.75, 117.54. FT-IR (KBr, selected band): 3437, 3291, 3183, 3064, 1635, 1597, 1558, 1503 cm^{-1}. The spectroscopic characterization data matched with the literature reported data.[60]

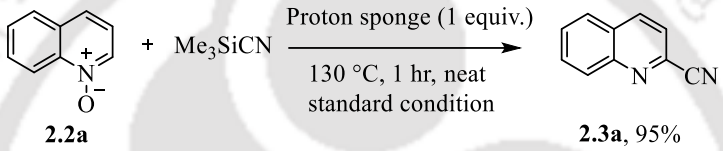
Quinoline-2-carbonitrile (31 mg, 0.2 mmol, 1 equiv.), dicyandiamide (15 mg, 0.18 mmol, 0.9 equiv.), potassium hydroxide (2 mg, 0.03 mmol, 0.2 equiv.) and 2-methoxyethanol (5 mL) were taken in a round-bottom flask under air and refluxed for 7 hours. Then the mixture was cooled to room temperature and the white solid was collected, washed with diethyl ether and dried under vacuum to get the analytically pure product **2.17** (37 mg, yield 79%).

M.p. 311-313 °C. ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.48 (d, J = 8.6 Hz, 1H), 8.33 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.81 (dd, J = 11.3, 4.0 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 7.08 (br, 2H), 6.86 (br, 2H). ^{13}C NMR (101 MHz, DMSO-d^6): δ 170.36, 167.7, 155.05, 147.24, 136.51, 129.92, 129.56, 128.26, 127.86, 127.48, 120.54. HRMS (ESI) *m/z*: calcd. for $C_{12}H_{11}N_6^+$ [$M+H^+$] 239.1040, found 239.1060. The spectroscopic characterization data matched with the literature reported data.[61]

2.6.8. Trapping of evolved HCN gas

Since experimental evidences suggest that one of the by-products of this protocol is HCN, which is a toxic waste, it is required to remove the same from the reaction system. It can be neutralized by either *in situ* trapping or by external processing. I have carried out two different experiments- one each for trapping and processing the HCN to OCN^- so that it could be disposed.

1) 1,8-bis(dimethylamino)naphthalene, also known as Proton sponge is well-known in literature for its affinity towards proton through strong hydrogen-bonding interaction and it can also act as a non-nucleophilic base.[62,63] I envisioned that due to its bulky and strained nature, 1,8-bis(dimethylamino)naphthalene would not affect the current reaction protocol but could be an ideal non-nucleophilic base to extract the proton from HCN. When I performed the reaction of quinoline *N*-oxide with trimethylsilyl cyanide in presence of the diamine, indeed the IR spectrum displayed two bands at 2234 cm^{-1} (belongs to quinoline-2-carbonitrile) and 2207 cm^{-1}, indicating presence of trapped HCN in the reaction medium. I was happy to observe that use of Proton sponge did not really hamper the yield of the desired cyanoquinoline product which was obtained in 95% yield.



2.2a **2.3a**, 95%

Scheme 2.28: cyanation reaction of quinoline *N*-oxide with proton sponge for HCN trapping

2) The evolved HCN gas can be oxidized using an aqueous solution of H_2O_2 in presence of catalytic $CuSO_4 \cdot 5H_2O$ having a pH=9.7 according to literature reported procedure.[64,65] I have designed the following set-up for this purpose which effectively trapped the HCN generated in the reaction.

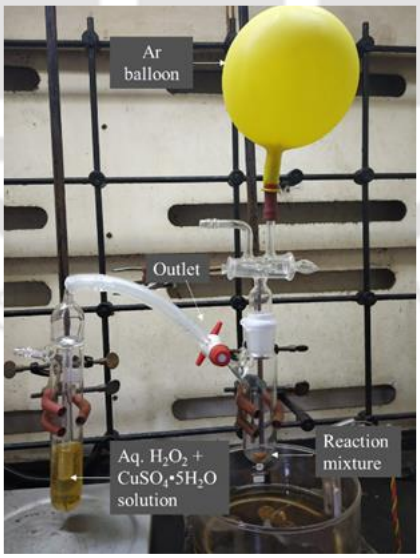


Figure 2.13: set-up for oxidation of evolved HCN

To prepare the oxidizing solution, 3 mL 30% aqueous H_2O_2 solution was taken in 100 mL distilled water to which 0.1 mol% $CuSO_4 \cdot 5H_2O$ was added. The pH of the solution was adjusted to 9.8 by adding NaOH. The HCN evolved during the reaction went to the bubbler to

this oxidizing solution through the outlet where it was oxidized to OCN^-, which is about 1000 times less toxic compared to HCN gas and is disposable.

2.6.9. Crystallographic study of compound 2.3n

The crystal was obtained by crystallization of compound **2.3n** in the presence of ethyl acetate as solvent at room temperature using slow evaporation technique. The crystallographic data were recorded at room temperature using a 'Bruker SMART APEX CCD' diffractometer equipped with a fine focus 1.75 kW sealed tube Mo-Kα (λ = 0.71073 Å) X-ray source, a graphite monochromator and Apex CCD camera. The SMART software was used for data acquisition and the 'Bruker SAINT' software for data refinement and reduction. All crystallographic data were refined using the software SHELXL-2014/7 and WinGX. The ORTEP diagram was obtained with the help of ORTEP software with 25% thermal ellipsoid (Figure S1). The crystallographic parameters and refinement data were listed in Table S2. All H-atoms are omitted from the ORTEP diagram for clarity.

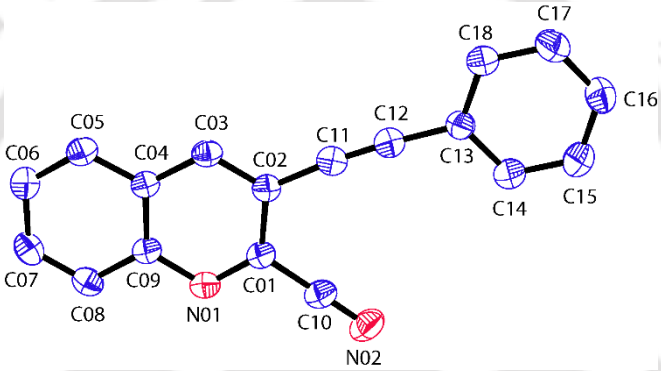


Figure 2.14: Molecular structure of compound **2.3n** (thermal ellipsoid 25% probability level). Selected Bond lengths (in Å): C(10)-N(02) 1.138(4), C(11)-C(12) 1.193(5), C(12)-C(13) 1.436(5), C(13)-C(14) 1.382(5), N(01)-C(01) 1.317(4), N(01)-C(09) 1.370(4), C(01)-C(10) 1.446(5).

Table 2.5. Crystal data and structure refinement for **2.3n**.

Identification code	shelx	
CCDC	1947601	
Empirical formula	$C_{36}\ H_{20}\ N_4$	
Formula weight	508.56	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*Pbca*	
Unit cell dimensions	a = 12.830(2) Å	α = 90°.
	b = 9.6136(16) Å	β = 90°.
	c = 21.402(4) Å	γ = 90°.
Volume	2639.8(8) $Å^3$	

Z	4
Density (calculated)	1.280 Mg/m^3
Absorption coefficient	0.077 mm^{-1}
F(000)	1056
Crystal size	0.35 x 0.32 x 0.30 mm^3
Theta range for data collection	1.903 to 24.996°.
Index ranges	-15<=h<=15, -11<=k<=11, -25<=l<=25
Reflections collected	87113
Independent reflections	2330 [R(int) = 0.2929]
Completeness to theta = 24.996°	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2330 / 0 / 182
Goodness-of-fit on F^2	1.011
Final R indices [I>2sigma(I)]	R1 = 0.0627, wR2 = 0.1420
R indices (all data)	R1 = 0.1498, wR2 = 0.1960
Extinction coefficient	0.0045(15)
Largest diff. peak and hole	0.193 and -0.174 $e.Å^{-3}$

Author's comment on IUCR check.cif alert:

RINTA01_ALERT_3_A The value of Rint is greater than 0.25

Author Response: The crystal quality under experiment was not good. The crystal was moderately diffracting. So many diffractions could not be included during data integration and refinement process. After several attempts of data collection, the best result obtained is reported here.

2.7. References:

1. (a) Hughes, R. A.; Moody, C. J. From Amino Acids to Heteroaromatics-Thiopeptide Antibiotics, Nature's Heterocyclic Peptides. *Angew. Chem., Int. Ed.* **2007**, *46*, 7930– 7954, (b)Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, andFrequency of Nitrogen Heterocycles among U.S. FDA ApprovedPharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257 – 10274.

2. (a) Marshall, P. B. Loss of Antimalarial Properties in Quinine Degradation Products. *Nature* **1945,**156, 505–506, (b) Kelsey, F. E.; Oldham, F. K.; Cantrell, W.; Geiling, E. M. K. Antimalarial Activity and Toxicity of a Metabolic Derivative of Quinine. *Nature* **1946**, *157*, 440-440.

3. (a) Han, S.; Chakrasali, P.; Park, J.; Oh, H.; Kim, S.; Kim, K.; Pandey, A. K.; Han, S. H.; Han, S. B.; Kim, I. S. Reductive C2-Alkylation of Pyridine and Quinoline *N*-Oxides Using Wittig Reagents. *Angew. Chem., Int. Ed.* **2018**, *57*, 12737– 12740, (b) Puthanveedu, M.; Polychronidou, V.; Antonchick, A. P. Catalytic Selective Metal-Free Cross-Coupling of

Heteroaromatic *N*-Oxides with Organosilanes. *Org. Lett.* **2019**, *21*, 3407– 3411, (c) Bering, L.; Antonchick, A. P. Regioselective Metal-Free Cross-Coupling of Quinoline *N*-Oxides with Boronic Acids. *Org. Lett.* **2015**, *17*, 3134– 3137, (d) Kumar, R.; Kumar, I.; Sharma, R.; Sharma, U. Catalyst and Solvent-Free Alkylation of Quinoline *N*-oxides with Olefins: A Direct Access to Quinoline-Substituted α-Hydroxy Carboxylic Derivatives. *Org. Biomol. Chem.* **2016**, *14*, 2613– 2617, (e) Chen, X.; Cui, X.; Yang, F.; Wu, Y. Base-Promoted Cross-Dehydrogenative Coupling of Quinoline *N*-Oxides with 1,3-Azoles. *Org. Lett.* **2015**, *17*, 1445 – 1448, (f) Crisenza, G. E. M.; Dauncey, E. M.; Bower, J. F. C2-Alkenylation of *N*-Heteroaromatic Compounds *via* Brønsted Acid Catalysis. *Org. Biomol. Chem.* **2016**, *14*, 5820–5825.

4. (a) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902– 7917, (b) Murphy, S. T.; Case, H. L.; Ellsworth, E.; Hagen, S.; Huband, M.; Joannides, T.; Limberakis, C.; Marotti, K. R.; Ottolini, A. M.; Rauckhorst, M.; Starr, J.; Stier, M.; Taylor, C.; Zhu, T.; Blaser, A.; Denny, W. A.; Lu, G. L.; Smaill, J. B.; Rivault, F. The Synthesis and Biological Evaluation of Novel Series of Nitrile-Containing Fluoroquinolones as Antibacterial Agents. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2150– 2155, (c) Markus, B.; Kwon, C.-H. *In vitro* Metabolism of Aromatic Nitriles. *J. Pharm. Sci.* **1994**, *83*, 1729– 1734.

5. (a) Patai, S.; Rappoport, Z. *The Chemistry of the Cyano Group*; Vol. 2, John Wiley & Sons, Chichester, 1983, (b) Soffer, L. M.; Katz, M. Direct and Reverse Addition Reactions of Nitriles with Lithium Aluminum Hydride in Ether and in Tetrahydrofuran. *J. Am. Chem. Soc*. **1956**, *78*, 1705– 1709, (c) Yu, C.; Ma, X.; Song, Q. Palladium-catalyzed Cyanation of Aryl Halides with *in situ* Generated CN^- from $ClCF_2H$ and $NaNH_2$. *Org. Chem. Front.* **2020**, *7*, 2950– 2954,

6. Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A. Studies toward the Large-Scale Synthesis of the HIV Proteinase Inhibitor Ro 31-8959. *J. Org. Chem.* **1994**, *59*, 3656– 3664.

7. (a) Villegas, G.: Calenda, G.; Zhang, S.; Mizenina, O.; Kleinbeck, K.; Cooney, M.L.; Hoesley, C.J.; Creasy, G.W.; Friedland, B., Fernández-Romero, J.A.; Zydowsky, T.M. In vitro exposure to PC-1005 and cervicovaginal lavage fluid from women vaginally administered PC-1005 inhibits HIV-1 and HSV-2 infection in human cervical mucosa. *Antimicrob. Agents Chemother.* **2016**, *60*, 5459-5466, (b) Cai, S.: Dimitroff, M.; McKennon, T.; Reider, M.; Robarge, L.; Ryckman, D.; Shang, X.; Therrien, J. Process development on an efficient new convergent formal synthesis of MIV-150. *Org. Process Res. Dev*. **2004**, *8*, 353-359.

11. (a) Xu, H.; Chen, W.; Zhan, P.; Liu, X. 8-Hydroxyquinoline: A privileged structure with a broad-ranging pharmacological potential. *Med. Chem. Comm.* **2015**, *6*, 61-74, (b) Capodagli, G.C.; Sedhom, W.G.; Jackson, M.; Ahrendt, K.A.; Pegan, S. D. A noncompetitive inhibitor for Mycobacterium tuberculosis's class IIa fructose 1, 6-bisphosphate aldolase. *Biochemistry* **2014**, *53*, 202-213.

12. Tagawa, Y.; Higuchi, Y.; Yamagata, K. Palladium (II)-mediated nucleophilic cyanation of 4-substituted quinoline 1-oxide in the presence of trimethylsilyl cyanide and an oxidant. *Heterocycles* **2004**, *63*, 2859-2862.

13. (c) Almaliti, J.; Al-Hamashi, A.A.; Negmeldin, A.T.; Hanigan, C.L.; Perera, L.; Pflum, M.K.H.; Casero Jr, R.A.; Tillekeratne, L.V. Largazole analogues embodying radical changes in the depsipeptide ring: development of a more selective and highly potent analogue. *J. Med. Chem.* **2016**, *59*, 10642-10660.

14. Fier, P.S.: Hartwig, J.F. Synthesis and late-stage functionalization of complex molecules through C–H fluorination and nucleophilic aromatic substitution. *J. Am. Chem. Soc.* **2014**, *136*, 10139-10147.

15. Fier, P. S. A Bifunctional Reagent Designed for the Mild, Nucleophilic Functionalization of Pyridines. *J. Am. Chem. Soc.* **2017**, *139*, 9499-9502.

16. Elbert, B.L.; Farley, A.J.; Gorman, T.W.; Johnson, T.C.; Genicot, C.; Lallemand, B.; Pasau, P.; Flasz, J.; Castro, J.L.; MacCoss, M.; Paton, R.S. C-H cyanation of 6-ring N-containing heteroaromatics. *Chem. Eur. J.* **2017**, *23*, 14733-14737.

17. Feely, W.E.; Beavers, E.M. Cyanation of amine oxide salts. A new synthesis of cyanopyridines. *J. Am. Chem. Soc.* **1959**, *81*, 4004-4007.

18. Fife, W.K. Regioselective cyanation of pyridine 1-oxides with trimethylsilanecarbonitrile: a modified Reissert-Henze reaction. *J. Org. Chem.* **1983**, *48*, 1375-1377.

19. (a) Veerareddy, A.; Surendrareddy, G.; Dubey, P.K. A simple procedure for the preparation of 2-cyano-4-chloropyridines. *J. Heterocycl. Chem.* **2011**, *48*, 961-964, (b) van der Vlugt, J.I.; Demeshko, S.; Dechert, S.; Meyer, F. Tetranuclear Co^{II}, Mn^{II}, and Cu^{II} complexes of a novel binucleating pyrazolate ligand preorganized for the self-assembly of compact [2× 2]-Grid Structures. *Inorg. Chem.* **2008**, *47*, 1576-1585, (c) Ashimori, A.; Ono, T.; Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoyama, K. Novel 1, 4-Dihydropyridine Calcium Antagonists. I.: Synthesis and Hypotensive Activity of 4-(Substituted Pyridyl)-1, 4-Dihydropyridine Derivatives. *Chem. Pharm. Bull.* **1990**, *38*, 2446-2458, (d) Bernard, H.; Bülow, G.; Lange, U. E. W.; Mack, H.; Pfeiffer, T.; Schäfer, B.; Seitz, W.; Zierke, T. Technical Scale Synthesis of a New and Highly Potent Thrombin Inhibitor. *Synthesis* **2004**, *14*, 2367–2375.

20. Miyashita, A.; Kawashima, T.; Iijima, C.; Higashino, T. Preparation of Heteroarenecarbonitriles by Reaction of Heteroarene *N*-Oxides with Trimethylsilyl Cyanide in the Presence of DBU. *Heterocycles*, **1992**, *33*, 211 – 218.

21. Xu, F.; Li, Y.; Huang, X.; Fang, X.; Li, Z.; Jiang, H.; Qiao, J.; Chu, W.; Sun, Z. Hypervalent Iodine (III)-Mediated Regioselective Cyanation of Quinoline *N*-Oxides with Trimethylsilyl Cyanide. *Adv. Synth. Catal*. **2019**, *361*, 520-525.

22. Wengryniuk, S.E.; Weickgenannt, A.; Reiher, C.; Strotman, N.A.; Chen, K.; Eastgate, M.D.; Baran, P.S. Regioselective bromination of fused heterocyclic *N*-oxides. *Org. Lett*. **2013**, *15*, 792-795.

23. (a) Sakamoto, T.; Kaneda, S.; Nishimura, S.; Yamanaka, H. Site-selectivity in the cyanation of 3-substituted pyridine 1-oxides with trimethylsilanecarbonitrile. *Chem. Pharm. Bull*. **1985**, *33*, 565-571.

24. Cerrada, V.; Matía-Martín, M.P.; Novella, J.L.; Alvarez-Builla, J. Synthesis of 2-and 4-hydroxymethyl Loratadine, usual impurities in Loratadine syrup formulations. *Arkivoc* **2005**, *9*, 200-206.

25. Chhabra, N.; Aseri, M. L.; Padmanabhan, D. A Review of Drug Isomerism and Its Significance. *Int. J. Appl. Basic Med. Res.* **2013**, *3*, 16– 18.

26. Prat, D.; Pardigon, O.; Flemming, H.-W.; Letestu, S.; Ducandas, V.; Isnard, P.; Guntrum, E.; Senac, T.; Ruisseau, S.; Cruciani, P.; Hosek, P. Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes. *Org. Process Res. Dev*. **2013**, *17*, 1517– 1525.

27. (a) Sarkar, A.; Santra, S.; Kundu, S. K.; Hajra, A.; Zyryanov, G. V.; Chupakhin, O. N.; Charushin, V. N.; Majee, A. A Decade Update on Solvent and Catalyst-Free Neat Organic Reactions: A Step Forward Towards Sustainability. *Green Chem*. **2016**, *18*, 4475– 4525, (b) Gawande, M. B.; Bonifácio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. Solvent-Free and Catalysts-Free Chemistry: A Benign Pathway to Sustainability. *ChemSusChem* **2014**, *7*, 24–44.

28. Sheldon, R. A. E Factors, Green Chemistry and Catalysis: An Odyssey. *Chem. Commun*. **2008**, 3352-3365.

29. (a) Polshettiwar, V.; Varma, R. S. Microwave-Assisted Organic Synthesis and Transformations Using Benign Reaction Media. *Acc. Chem. Res*. **2008**, *41*, 629– 639, (b) Strauss, C. R.; Varma, R. S. In *Microwave Methods in Organic Synthesis*, Larhed, M.; Olofsson, K. Eds.; Springer, Heidelberg, 2006, pp. 199–231, (c) Varma, R. S. Solvent-free synthesis of heterocyclic compounds using microwaves. *J. Heterocycl. Chem*. **1999**, *36*, 1565–1571, (d) Varma, R. S. Solvent-Free Accelerated Organic Syntheses Using Microwaves. *Pure Appl. Chem*. **2001**, *73*, 193-198.

30. Bering, L.; Antonchick, A. P. Regioselective Metal-Free Cross-Coupling of Quinoline *N*-Oxides with Boronic Acids. *Org. Lett.* **2015**, *17*, 3134– 3137.

31. Iida, H.; Hamana, H.; Matsumoto, K. Highly Efficient Cyanosilylation of Aldehydes and Ketones under Microwave, Solvent-Free, and Lewis Acid–Free Conditions. *Synth. Commun*. **2007**, *37*, 1801–1805.

32. Walker, A. G.; Wenthur, C. J.; Xiang, Z.; Rook, J. M.; Emmitte, K. A.; Niswender, C. M.; Lindsley, C. W.; Conn, P. J. Metabotropic Glutamate Receptor 3 Activation is Required for Long-term Depression in Medial Prefrontal Cortex and Fear Extinction. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 1196–1201.

33. Coghlan, M. J.; Krumkalns, E. V.; Caley, B. A.; Hall, H. R.; Arnold, W. R. In *Synthesis and Chemistry of Agrochemicals II* Moberg, W. K. Eds.; ACS Symposium Series, American Chemical Society, Washington DC, **1991**, *443*, pp. 538–552.

34. Kubota, M.; Sakaguchi, H.; Kandoh, Y. Amide Compound and Use Thereof. Patent WO2009093640 (A1), 2009.

35. Curry, K.; Magnuson, D. S.; McLennan, H.; Peet, M. J. Acridinic Acid: A New Antagonist of Amino Acid-Induced Excitations of Central Neurons. *Neurosci. Lett*. **1986**, *66*, 101– 105.

36. Rozhkov, E.; Piskunova, I.; Gol'd, M.; Kalvin'sh, I. Cyclic Hydrazides 1. Synthesis of 4-Hydroxy-1-oxo-1,2-dihydropyridazino[4,5-b]quinolones. *Chem. Heterocycl. Compd*. **1998**, *34*, 77– 91.

37. Bachollet, S. P. J. T.; Volz, D.; Fiser, B.; Münch, S.; Rönicke, F.; Carrillo, J.; Adams, H.; Schepers, U.; Gómez-Bengoa, E.; Bräse, S.; Harrity, J. P. A. A Modular Class of Fluorescent Difluoroboranes: Synthesis, Structure, Optical Properties, Theoretical Calculations and Applications for Biological Imaging. *Chem. - Eur. J*. **2016**, *22*, 12430 – 12438.

38. (a) Brzozowski, Z.; Saczewski, F.; Gdaniec, M. Synthesis, Structural Characterization and Antitumor Activity of Novel 2,4-Diamino-1,3,5-Triazine Derivatives. *Eur. J. Med. Chem*. **2000**, *35*, 1053 – 1064, (b) Chen, X.; Zhan, P.; Liu, X.; Cheng, Z.; Meng, C.; Shao, S.; Pannecouque, C.; Clercq, E. D.; Liu, X. Design, Synthesis, Anti-HIV Evaluation and Molecular Modeling of Piperidine-linked Amino-triazine Derivatives as Potent Non-nucleoside Reverse Transcriptase Inhibitors. *Bioorg. Med. Chem*. **2012**, *20*, 3856– 3864.

39. Reux, B.; Nevalainen, T.; Raitio, K. H.; Koskinen, A. M. P. Synthesis of Quinolinyl and Isoquinolinyl Phenyl Ketones as Novel Agonists for the Cannabinoid CB2 Receptor. *Bioorg. Med. Chem*. **2009**, *17*, 4441 – 4447.

40. Anand, N.; Koley, S.; Ramulu, B. J.; Singh, M. S. Metal-Free Aerobic One-Pot Synthesis of Substituted/Annulated Quinolines from Alcohols *via* Indirect Friedländer Annulation. *Org. Biomol. Chem*. **2015**, *13*, 9570-9574.

41. Saunthwal, R. K.; Patel, M.; Verma, A. K. Regioselective Synthesis of C-3-Functionalized Quinolines via Hetero-Diels-Alder Cycloaddition of Azadienes with Terminal Alkynes. *J. Org. Chem.* **2016**, *81*, 6563– 6572.

42. Shen, G.-B.; Xia, K.; Li, X.-T.; Li, J.-L.; Fu, Y.-H.; Yuan, L.; Zhu, X.-Q. Prediction of Kinetic Isotope Effects for Various Hydride Transfer Reactions Using a New Kinetic Model. *J. Phys. Chem. A* **2016**, *120*, 1779– 1799.

43. Dubovtsev, A. Y.; Dar'in, D. V.; Krasavin, M.; Kukushkin, V. Y. Gold-Catalyzed Oxidation of Internal Alkynes into Benzils and Its Application for One-Pot Synthesis of Five-, Six-, and Seven-Membered Azaheterocycles. *Eur. J. Org. Chem*. **2019**, *2019*, 1856– 1864.

44. Nanjappa, C.; Hanumanthappa, S. K. T.; Nagendrappa, G.; Ganapathy, P. S. S.; Shruthi, S. D.; More, S. S.; Jose, G.; Sowmya, H. B. V.; Kulkarni, R. S. Synthesis, ABTS-Radical Scavenging Activity, and Antiproliferative and Molecular Docking Studies of Novel Pyrrolo[1,2-a]quinoline Derivatives. *Synth. Commun*. **2015**, *45*, 2529– 2545.

45. Pereira, G. R.; Brandao, G. C.; Arantes, L. M.; de-Oliveira Jr, H. A.; de-Paula, R. C.; do-Nascimento, M. F. A.; dos-Santos, F. M.; da-Rocha, R. K.; Lopes, J. C. D.; de-Oliveira, A. B. 7-chloroquinolinotriazoles: synthesis by the azide-alkyne cycloaddition click chemistry, antimalarial activity, cytotoxicity and SAR studies. *Eur. J. Med. Chem*. **2014**, *73*, 295– 309.

46. Phanindrudu, M.; Wakade, S. B.; Tiwari, K. D.; Likhar, P. R.; Tiwari, D. K. Transition-Metal-Free Approach for the Synthesis of 4-Aryl-quinolines from Alkynes and Anilines. *J. Org. Chem.* **2018**, *83*, 9137– 9143.

47. Tang, C.; Zou, M.; Liu, J.; Wen, X.; Sun, X.; Zhang, Y.; Jiao, N. Rh-Catalyzed Direct Amination of Unactivated C(sp^3)–H bond with Anthranils Under Mild Conditions. *Chem. - Eur. J.* **2016**, *22*, 11165– 11169.

48. Maji, A.; Guin, S.; Feng, S.; Dahiya, A.; Singh, V. K.; Liu, P.; Maiti, D. Experimental and Computational Exploration of *para*-Selective Silylation with a Hydrogen-Bonded Template. *Angew. Chem., Int. Ed.* **2017**, *56*, 14903– 14907.

49. Matcha, K.; Antonchick, A. P. Metal-Free Cross-Dehydrogenative Coupling of Heterocycles with Aldehydes. *Angew. Chem., Int. Ed.* **2013**, *52*, 2082– 2086.

50. (a) Bering, L.; Antonchick, A. P. Regioselective Metal-Free Cross-Coupling of Quinoline *N*-Oxides with Boronic Acids. *Org. Lett.* **2015**, *17*, 3134– 3137. (b) Frei, P.; Jones, D.

H.; Kay, S. T.; McLellan, J. A.; Johnston, B. F.; Kennedy, A. R.; Tomkinson, N. C. O. Regioselective Reaction of Heterocyclic *N*-Oxides, an Acyl Chloride, and Cyclic Thioethers. *J. Org. Chem.* **2018**, *83*, 1510– 1517. (c) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. Regioselective Bromination of Fused Heterocyclic *N*-Oxides. *Org. Lett.* **2013**, *15*, 792– 795. (d) Bjørsvik, H.-R.; Gambarotti, C.; Jensen, V. R.; Gonźalez, R. R. A Novel Efficient Deoxygenation Process for *N*-Heteroarene *N*-Oxides. *J. Org. Che*m. **2005**, *70*, 3218– 3224. (e) Singh, A. N.; Thumme, R. P. 1,5-Naphthyridine as a New Linker for the Construction of Bridging Ligands and Their Corresponding Ru(II) Complexes. *Inorg. Chem.* **2009**, *48*, 6459–6470. (f) Dyer, R. M. B.; Hahn, P. L.; Hilinski, M. K. Selective Heteroaryl *N*-Oxidation of Amine-Containing Molecules. *Org. Lett.* **2018**, *20*, 2011−2014.

51. Ochiai, E. Recent Japanese Work on the Chemistry of Pyridine 1-Oxide and Related Compounds. *J. Org. Chem*. **1953**, *18*, 534– 551.

52. Zhao, J.; Li, P.; Xia, C.; Li, F. Metal-free Regioselective C-3 Nitration of Quinoline *N*-Oxides with *tert*-Butyl Nitrite. *RSC Adv*. **2015**, *5*, 32835 – 32838.

53. Stephens, D. E.; Lakey-Beitia, J.; Chavez, G.; Ilie, C.; Arman, H. D.; Larionov, O. V. Experimental and Mechanistic Analysis of the Palladium-Catalyzed Oxidative C8-Selective C–H Homocoupling of Quinoline *N*-Oxides. *Chem. Commun*. **2015**, *51*, 9507– 9510.

54. Homberg, L.; Roller, A.; Hultzsch, K. C. A Highly Active PN^3 Manganese Pincer Complex Performing N-Alkylation of Amines under Mild Conditions. *Org. Lett.* **2019**, *21*, 3142– 3147.

55. Rohlmann, R.; Stopka, T.; Richter, H.; García Mancheño, O. Iron-Catalyzed Oxidative Tandem Reactions with TEMPO Oxoammonium Salts: Synthesis of Dihydroquinazolines and Quinolines. *J. Org. Chem*. **2013**, *78*, 6050– 6064.

56. Kopchuk, D. S.; Khasanov, A. F.; Kovalev, I. S.; Kim, G. A.; Nikonov, I. L.; Zyryanov, G. V.; Rusinov V. L.; Chupakhin, O. N. (Benzo[*h*])Quinolinyl-Substituted Monoazatriphenylenes: Synthesis and Photophysical Properties. *Chem. Heterocycl. Compd*. **2014**, *50*, 864-870.

57. Bobin, M.; Kwast, A.; Wróbel, Z. Efficient formation of σ^H-adducts as a key step in the synthesis of acridines via Lewis acid-promoted transformations of the nitro group. *Tetrahedron* **2007**, *63*, 11048-11054.

58. Bachollet, S. P. J. T.; Volz, D.; Fiser, B.; Münch, S.; Rönicke, F.; Carrillo, J.; Adams, H.; Schepers, U.; Gómez-Bengoa, E.; Bräse, S.; Harrity, J. P. A. A Modular Class of Fluorescent Difluoroboranes: Synthesis, Structure, Optical Properties, Theoretical Calculations and Applications for Biological Imaging. *Chem. - Eur. J.* **2016**, *22*, 12430 – 12438.

59. Kuduk, S. D.; DiMarco, C. N.; Yang, Z.-Q. N-linked Quinolineamide M1 Receptor Positive Allosteric Modulators. US 8,940,765 B2, 2015.

60. Cheng, H.; Zhu, D.; Lu, W.; Xu, R.; Shen, X. Synthesis and Crystal Structure Characterization of 3,5-bis(2-quinolyl)-1,2,4-triazole. *J. Heterocyclic Chem*. **2009**, *47*, 210-213.

61. Chen, Y.; Xu, W.; Kou, J.; Wei, X.; Yu, B.; Chao, H.; Ji, L. Synthesis, Crystal Structures, Electrochemical and Spectroscopic Properties of Ruthenium(II) Complexes Containing Diamino-1,3,5-triazine Derivatives. *Sci. China Chem*. **2010**, *53*, 2099-2105.

62. Perrin, C. L.; Ohta, B. K. Symmetry of N–H–N Hydrogen Bonds in 1,8-Bis (dimethylamino)naphthalene·H^+ and 2,7-Dimethoxy-1,8-bis(dimethylamino)naphthalene·H^+. *J. Am. Chem. Soc*. **2001**, *123*, 6520– 6526.

63. Pozharskii, A. F.; Ozeryanskii, V. A. Proton Sponges and Hydrogen Transfer Phenomena. *Mendeleev Commun*. **2012**, *22*, 117– 124.

64. Kitis, M.; Akcil, A.; Karakaya, E.; Yigit, N. O. Destruction of Cyanide by Hydrogen Peroxide in Tailings Slurries from Low Bearing Sulphidic Gold Ores. *Miner. Eng*. **2005**, *18*, 353– 362.

65. Khodadadi, A.; Abdollahi, M.; Teimoury, P. Detoxification of Cyanide in Gold Processing Wastewater by Hydrogen Peroxide. *Iran. J. Environ. Health. Sci. Eng*. **2005**, *2*, 177–182.

Chapter-3

Site-Selective Deoxygenative Amination of Azine *N*-oxides with Carbodiimides under Catalyst-, Activator-, Base- and Solvent-Free Conditions

3.1. Introduction

Introducing new functionalities to already established drug candidates often lead to improved physicochemical properties which is very encouraging for medicinal chemistry.[1] Azines, being an important class of molecules with huge pharmacological applications,[2] are thus constantly subjected to different site-selective functionalizations for furthering the development of their biological properties.[3] Among them, C2 aminated azines are of utmost interest in drug discovery due to their significance as therapeutics.[4] They are used as proton-pump inhibitor, anti-tumor, anti-malarial, anti-inflammatory drugs etc., among others. Some representative examples of C2-aminated azines used for medicinal applications are listed in figure 3.1.

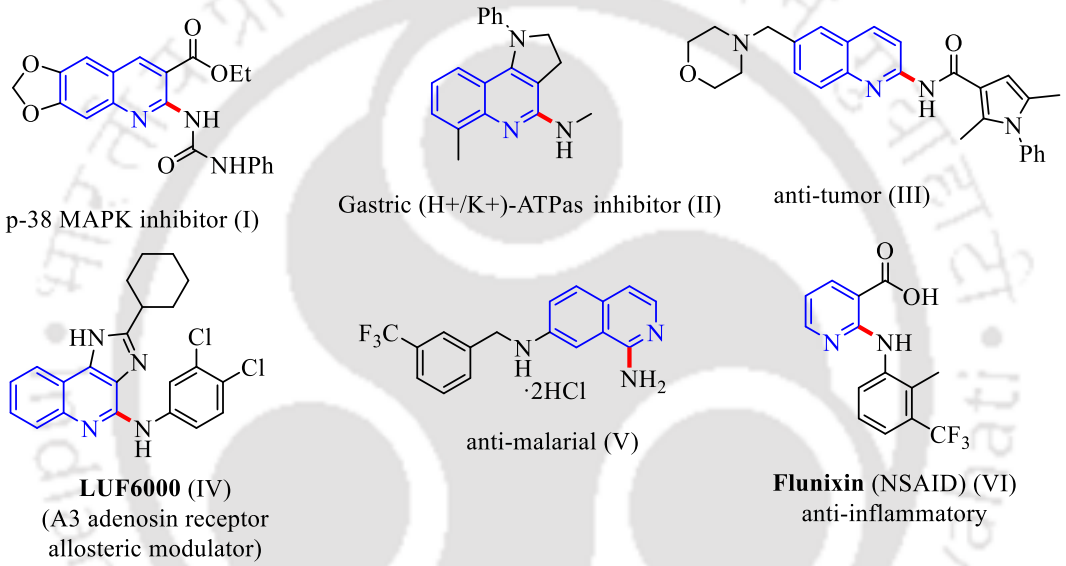
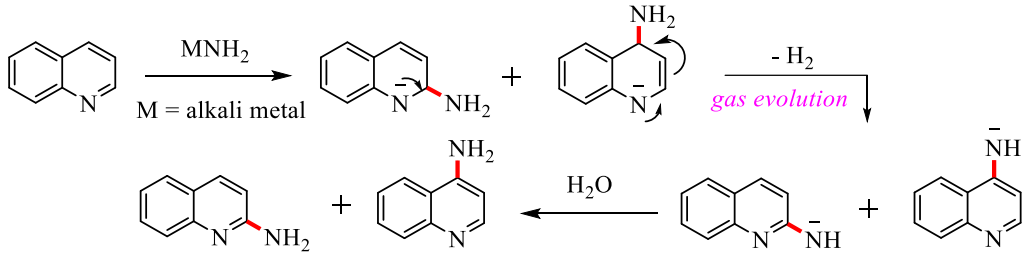


Figure 3.1: biologically important C2-aminated azines

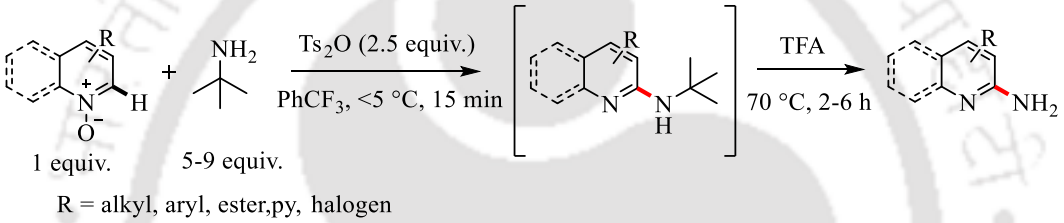
Classically amination of quinolines was carried out through nucleophilic aromatic substitution using either non-functionalized or pre-functionalized quinolines.[5,3b] Chichibabin reaction was first reported in the early 1900's where amination of quinolines using alkali amides were described.[5a] This is the most well-known nucleophilic amination reaction for *N*-heteroaromatic systems. But this protocol often used harsh reaction conditions and the alkali amides are very sensitive towards air and moisture, forming explosive chemical mixtures. Their strong basic nature also affected the substrate scope compatibility for the reaction (scheme 3.1).[5b]



Scheme 3.1: nucleophilic aromatic substitution of alkali amides on quinoline

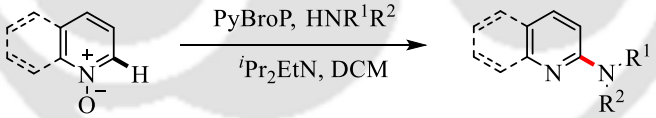
The generation of hydrogen gas during the reaction implied requirement of special care and equipment. Additionally, the reaction often displayed poor regioselectivity.

Due to these drawbacks in nucleophilic substitution on quinolines, scientists turned to the corresponding *N*-oxides in search of solutions. Transition-metal catalysed cross-coupling reactions for C2-amination of *N*-heteroarene *N*-oxides have been explored well in the past years.[6] The metal centre activates the C2-H bond of the *N*-oxide, followed by oxidative addition of the aminating agent and concomitant reductive elimination to give the desired product. These processes, while successfully generating 2-aminoquinolines, need an additional step for reduction of the *N*-oxide moiety to the corresponding quinolines. This reduces the step-economy of the process and necessitates the use of harsh reagents like PCl_3. This kind of reactions are discussed in chapter 1. A second approach towards metal-free step-economic deoxygenative azine C2-amination involves use of superstoichiometric amount of organic reagents as activators or bases.[7] Activation of the ring enhances the tendency of nucleophilic attack on the C2-position of the ring, which, upon aromatization, gives the final product. In this regard, in 2007, Davies *et. al*. published C2-amination of azine *N*-oxides with $^tBuNH_2$ using tosyl anhydride and TFA to obtain 2-aminoazines. In addition to being the source of amino moiety, $^tBuNH_2$ also acted as the base (scheme 3.2).[7a]



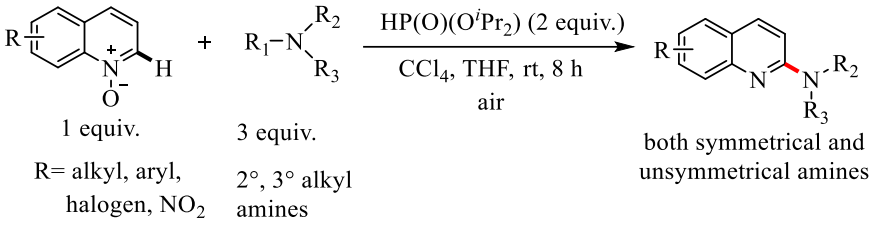
Scheme 3.2: C2-amination of azine *N*-oxide activated by tosyl anhydride

In 2010, Wei *et. al.* explored C2-amination of primarily pyridine *N*-oxides with both alkyl- and aryl-amines using costly phosphorus-based reagent PyBroP to further activate the *N*-oxide and $^iPr_2EtN$ as base (scheme 3.3).[7c]



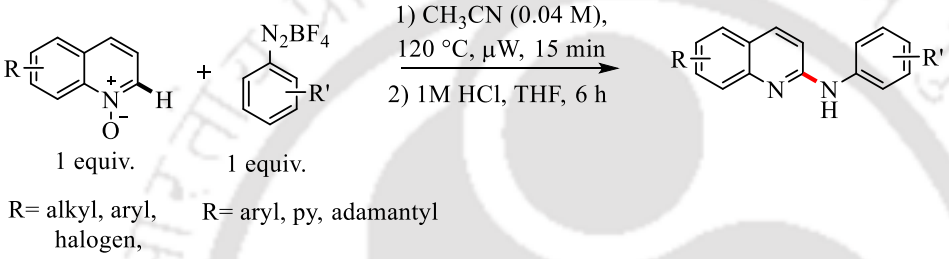
Scheme 3.3: C2-amination of azine *N*-oxide activated by PyBroP

In both of these works, researchers were mostly interested in introducing mono-alkyl or mono-arylamino groups to the *N*-heteroaryl core. To overcome the difficulties in developing an efficient protocol for 2-(dialkylamino)quinolines, Zhao and his co-workers reported the use of dialkyl *H*-phosphonates with CCl_4 as activator whereby they successfully prepared 2-(dialkylamino)quinolines from quinoline *N*-oxides under mild reaction conditions without using any base. Though both secondary and tertiary amines were successful in this report, primary amines were not reported. Later in 2017, they came up with another report of C2-amination of quinolines using dialkyl *H*-phosphonates as activator and K_2CO_3 as a base, where they could successfully use primary amines as the amino source (scheme 3.4).[7d,7e]



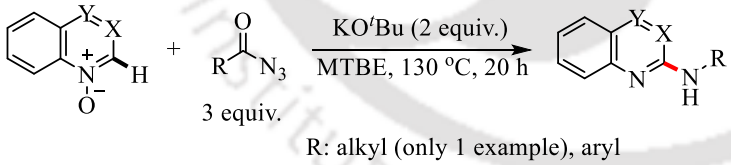
Scheme 3.4: C2-amination of azine *N*-oxide activated by H-phosphonate

These methodologies although provided the desired C2-functionalised quinolines in a regioselective way without any transition metal catalysts, however, they suffered from excess use of external activators with the implication of excess chemical waste generation. In this regard, an encouraging report by Sharma and group in 2019 demonstrated three-component reaction involving *N*-oxide, aryl diazonium salt and acetonitrile under microwave irradiation to obtain 2-aminoquinolines (scheme 3.5).[7g]



Scheme 3.5: 3-component C2-amination reaction of azine *N*-oxide with diazonium salt

In the same year, He and co-workers reported an Ag(I)-catalysed C2-amination reaction of quinoline *N*-oxides with isothiocyanates *via* a (3+2)-cycloaddition reaction (chapter 1).[6i] Recently, Kim *et al.* showed that acyl azides could work as a precursor to isocyanate which could take part in (3+2)-cycloaddition reaction with azine *N*-oxides to give the corresponding C2-aminated azines (chapter 1). The protocol has dealt with mainly aryl aminated products, whereas, only one alkylaminated product being reported, thus, limiting the substrate scope for the reaction (scheme 3.6).[7h]



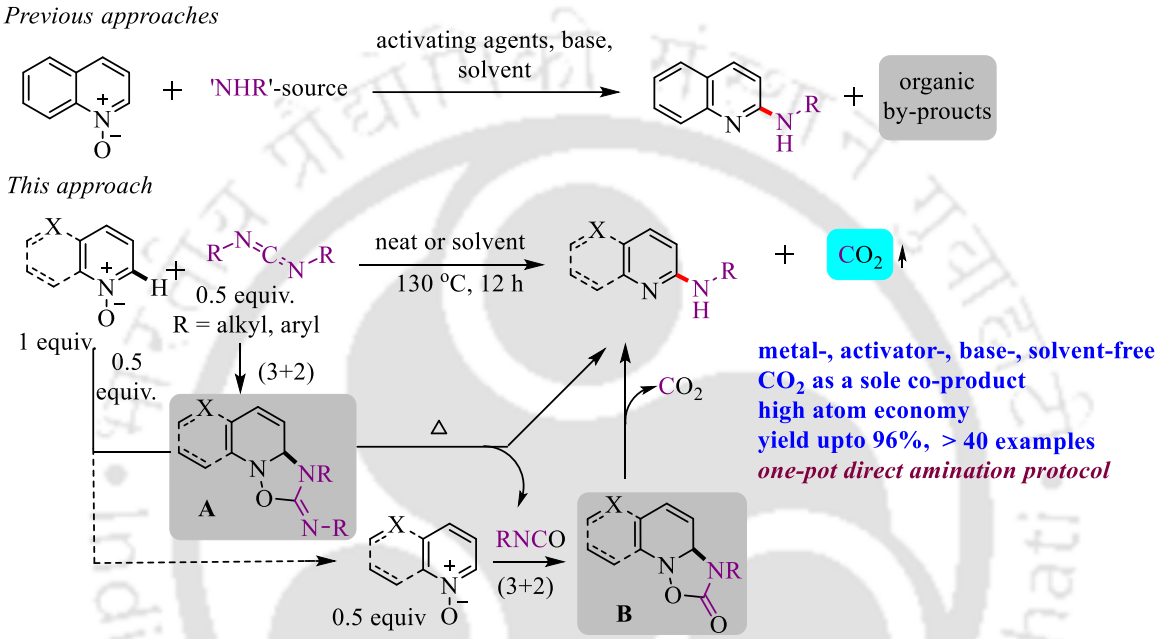
Scheme 3.6: C2-amination of azine *N*-oxide with acyl azide

From the above discussion, it could be concluded that the need of an efficient amination protocol encompassing both alkyl- and arylaminated product generation is still in demand. Along with that, one major problem of the literature reported protocols is the generation of an excess amount of chemical waste, originating from phosphorus-based activating agents, bases as well as solvents used, which reduces the industrial applicability of these strategies. Therefore, the development of an operationally simple, easy, and straightforward method with minimal chemical waste and good green-metrics is highly desired.[8]

3.2. Present work

Owing to the 1,2-dipolar nature of N-O bond and the presence of electrophilic C2 site in the azine *N*-oxide,[6i,9] it was anticipated that *N*-oxide might involve in the (3+2)-cycloaddition

reaction with carbodiimide[10] to give desired aminated azine along with isocyanate. The corresponding isocyanate can further react with another molecule of *N*-oxide in a (3+2)-type cycloaddition reaction to give the product and eliminate CO_2 as the only co-product in the overall reaction (scheme 3.7). The use of two amino group in the carbodiimide is likely to be beneficial compared to the previously reported amino precursors such as acyl azides,[7h] diazonium salts[7g] and aryl thiocyanates[6i]. Herein, I report the first example of a one-step heteroaromatic C-H amination process without the aid of any additional metal-catalyst, base, additives or solvents. The reaction exhibited an excellent selectivity at the C2 position and impressively low E-factor.



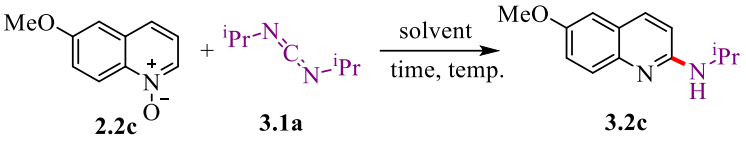
Scheme 3.7: previous approaches vs current approach for C2-amination of quinoline

3.3. Results and Discussion

3.3.1. Optimization of the reaction conditions

To put the plan into practice, optimization studies were commenced by reacting 6-methoxyquinoline *N*-oxide **2.2c** with diisopropyl carbodiimide **3.1a** (0.5 equiv.) as a model substrate in neat condition. However, the desired aminated product **3.2c** was not obtained at room temperature (table 3.1, entry 1). Interestingly, when the reaction was carried out at 90 °C, the compound **3.2c** was isolated in 41% yield after 12 h (table 3.1, entry 3). Upon further increasing the temperature, an increase of yield upto 96% was observed at 130 °C (table 3.1, entry 5). Decreasing the reaction duration below 12 h resulted in reduced yield of the product (table 3.1, entry 7 – 8). As a part of further optimization, the reaction was performed in various solvents. A dramatic drop in yield has been observed in polar protic solvents, whereas, in the polar aprotic solvents, the reaction proceeds equally well as in solvent-free conditions (table 3.1, entries 10-16). Interestingly, cyclopentyl methyl ether (CPME) was also found to be a suitable eco-friendly ethereal solvent[11] for this transformation (Table 3.1, entry 12).

Table 3.1. Optimization of reaction conditions[a]



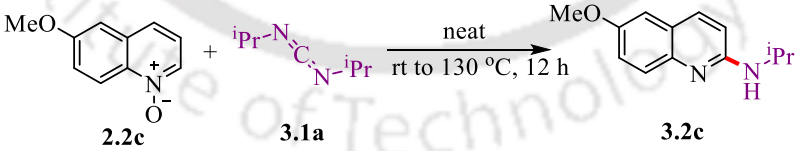
2.2c 3.1a 3.2c

Entry	Amount of **2a** (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	0.5	neat	27	12	n.d.
2	0.5	neat	60	12	10
3	0.5	neat	90	12	41
4	0.5	neat	110	12	72
5	0.5	neat	130	12	96
6[b]	0.5	neat	130	12	86
7	0.5	neat	130	10	82
8	0.5	neat	130	6	65
9	1	neat	130	12	96
10	0.5	DMSO	130	12	96
11	0.5	DMF	130	12	92
12	0.5	CPME	130	12	95
13	0.5	toluene	130	12	42
14	0.5	MeOH	130	12	80
15	0.5	*i*PrOH	130	12	67
16	0.5	EtOAc	130	12	89

[a]Reaction conditions: **1b** (1 mmol), **2a** (x equiv.), solvent (1 mL) under Ar atmosphere in the sealed reaction tube under preheated oil-bath. Isolated yield. [b]Under air.

3.3.2. Effect of temperature on the reaction

The study of the reaction at various temperatures led us to understand the influence of the temperature on the outcome of the reaction. This effect is represented in the figure 3.2. To confirm the accuracy of the observations, each experiment was performed 3 times and the results are compared in the figure.



2.2c 3.1a 3.2c

1 equiv. 0.5 equiv.

Scheme 3.8: C2-amination of 6-methoxyquinoline *N*-oxide at different temperatures

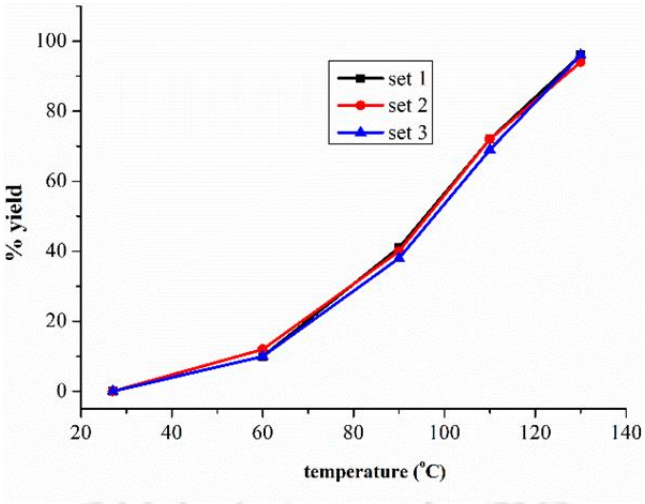
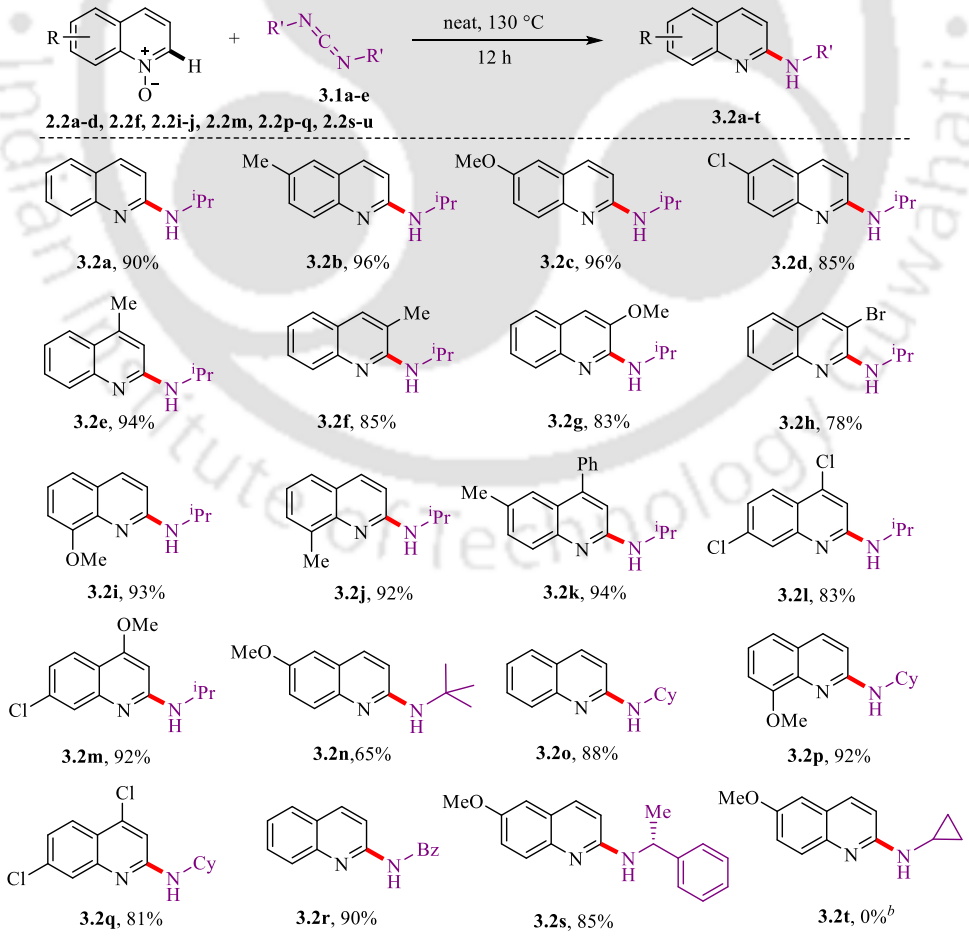


Figure 3.2. Effect of temperature on the amination of 6-methoxyquinoline *N*-oxide (**1b**) with 1,3-diisopropylcarbodiimide (**2a**).

3.3.3. Scope of amination of quinoline *N*-oxides with dialkyl carbodiimides

With the optimized conditions in hand, the scope of the reaction was investigated with a variety of substituted quinoline *N*-oxides using **3.1a** as the standard substrate (table 3.2).

Table 3.2. substrate scope for dialkyl carbodiimide[a]



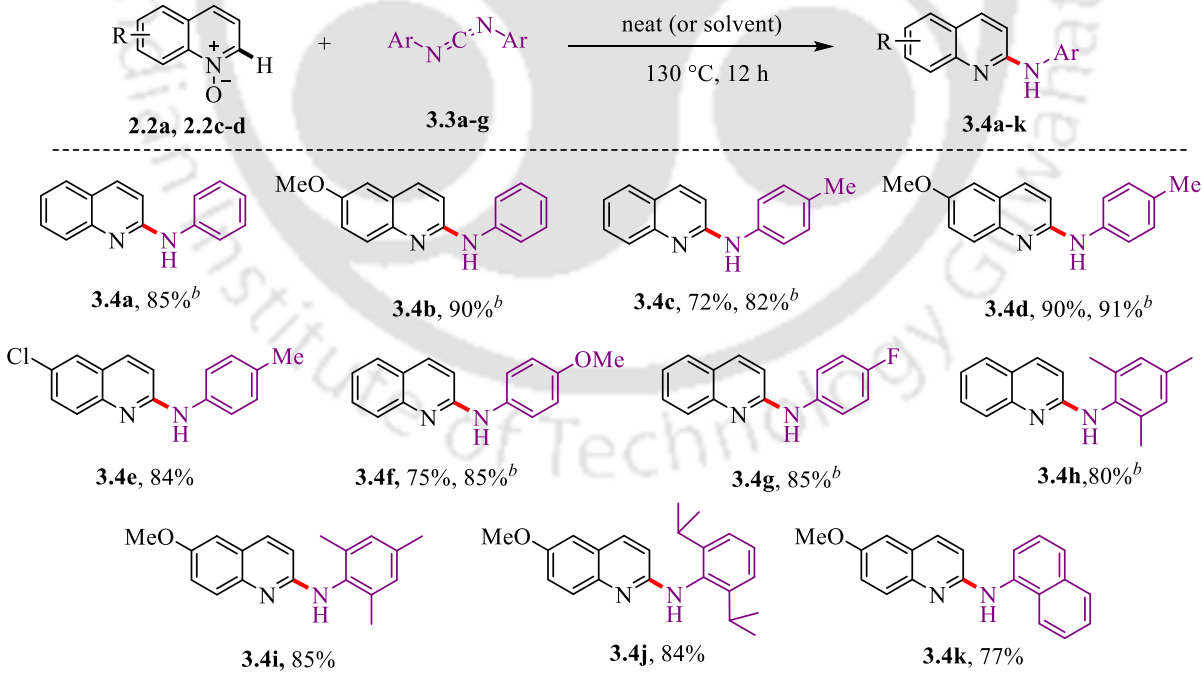
[a]Reaction conditions: quinoline *N*-oxide (1 mmol, 1 equiv.), alkyl carbodiimide (0.5 mmol, 0.5 equiv.), neat, 130 °C, 12 h. Isolated yield. [b]Cyclopropyl isothiocyanate was used.

The substrates bearing methyl (**2.2b, 2.2f, 2.2i** and **2.2q**), methoxy (**2.2c, 2.2j, 2.2p**), chloro (**2.2d**) and bromo (**2.2m**) substituents led to the aminated products **3.2a-j** in 78-96% yields. Interestingly, halogen groups were retained during these transformations, which can be beneficial for further functionalization. Multi-substituted quinoline *N*-oxides also proceeded smoothly to deliver **3.2k-m** efficiently. Furthermore, the protocol was checked with other alkyl carbodiimides such as di-*tert*-butyl, di-cyclohexyl and di-benzyl carbodiimide derivatives (**3.1b-d**), which also afforded the corresponding aminated products in good to excellent yields. Interestingly, the chiral carbodiimide **3.1e** gave the desired product **3.2s** in 85% yield. However, method has failed to achieve cyclopropane ring bearing aminated compound **3.2t**.

3.3.4. Scope of amination with diaryl carbodiimides

After inspecting the reactivities of different dialkyl carbodiimides, various diaryl carbodiimides were also examined to assess the diversity of our protocol (table 3.3). The substrates containing both electron-donating (e.g., -CH_3, -OCH_3) and electron- withdrawing (e.g., -F) groups on the aryl ring of the carbodiimide were efficiently reacted to obtain the desired aminated products **3.4a-3.4g** in 72-90% yields. Fortunately, in case of the products **3.4a-c** and **3.4f-h**, the use of CPME solvent helped to increase the yield compared to that in neat conditions. Notably, the aminated compound **3.4h-k** could be obtained easily in 77-85% yields from the reaction of sterically demanding carbodiimides **3.3e-g**, indicating that bulky functionality is well tolerated in our reaction conditions.

Table 3.3. substrate scope for diaryl carbodiimide[a]

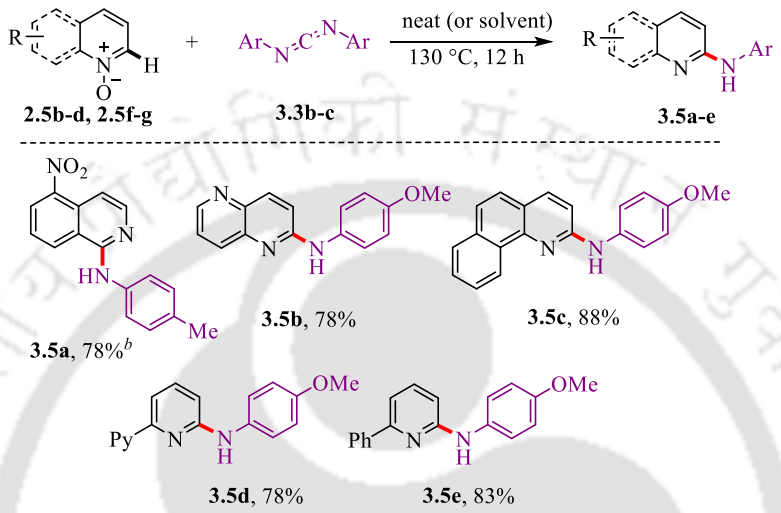


[a]Reaction conditions: quinioline *N*-oxide (1 mmol, 1 equiv.), aryl carbodiimide (0.5 mmol, 0.5 equiv.), neat, 130 °C, 12 h. Isolated yield. [b]CPME (1 mL) was used.

3.3.5. Scope of amination with different *N*-heteroarene *N*-oxides

Additionally, the reaction was found to be effective to other heteroaromatic *N*-oxides as well, such as 5-nitroisoquinoline *N*-oxide (**2.5b**), 1,5-naphthyridine *N*-oxide (**2.5c**), benzo[*h*]quinoline *N*-oxide (**2.5d**), pyridine *N*-oxide derivative (**2.5f**) and 2,2′-bipyridine *N*-oxide (**2.5g**), proving the generality of the present protocol (table 3.4). The successful amination of bipyridine scaffold is encouraging as they are useful building blocks and bidentate ligand motif in bifunctional metal catalysis.[12]

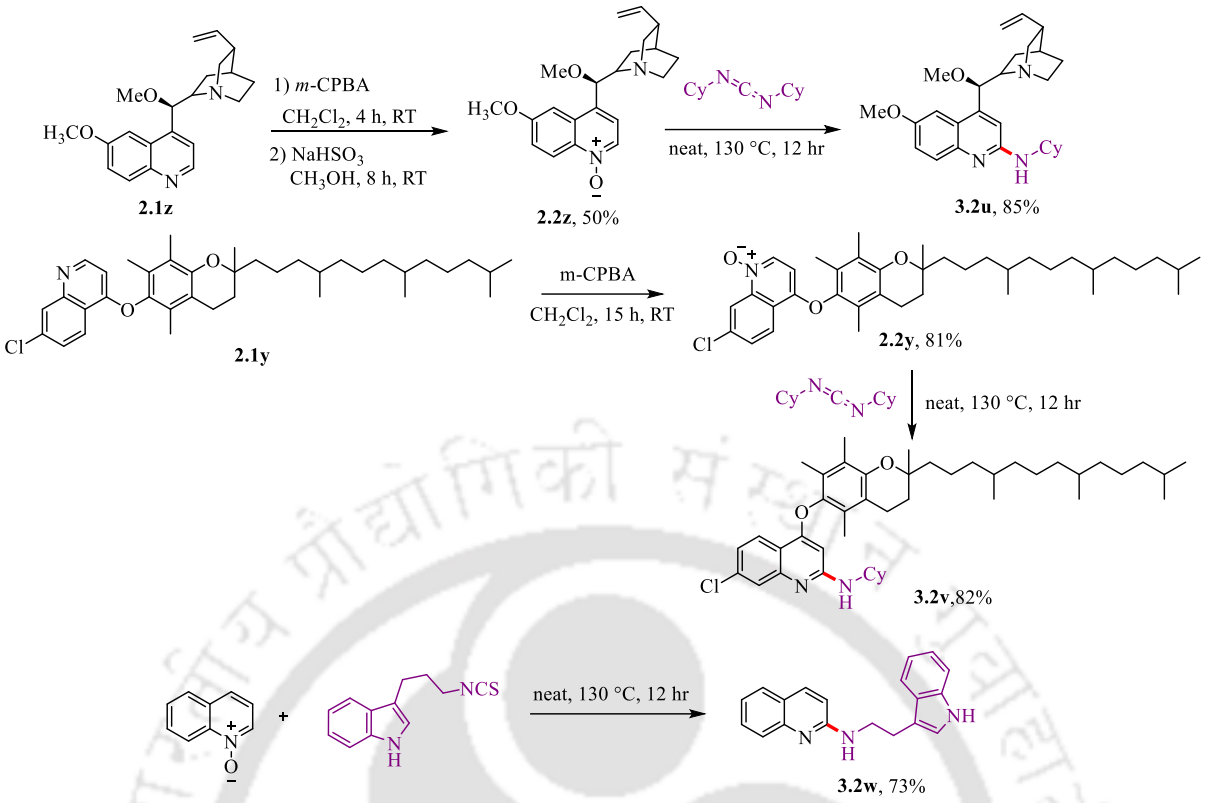
Table 3.4. substrate scope for other *N*-heteroarene *N*-oxides[a]



[a]Reaction conditions: azine *N*-oxide (1 mmol, 1 equiv.), aryl carbodiimide (0.5 mmol, 0.5 equiv.), neat, 130 °C, 12 h. Isolated yield. [b]CPME (1 mL) was used.

3.3.6. Late-stage drug modifications

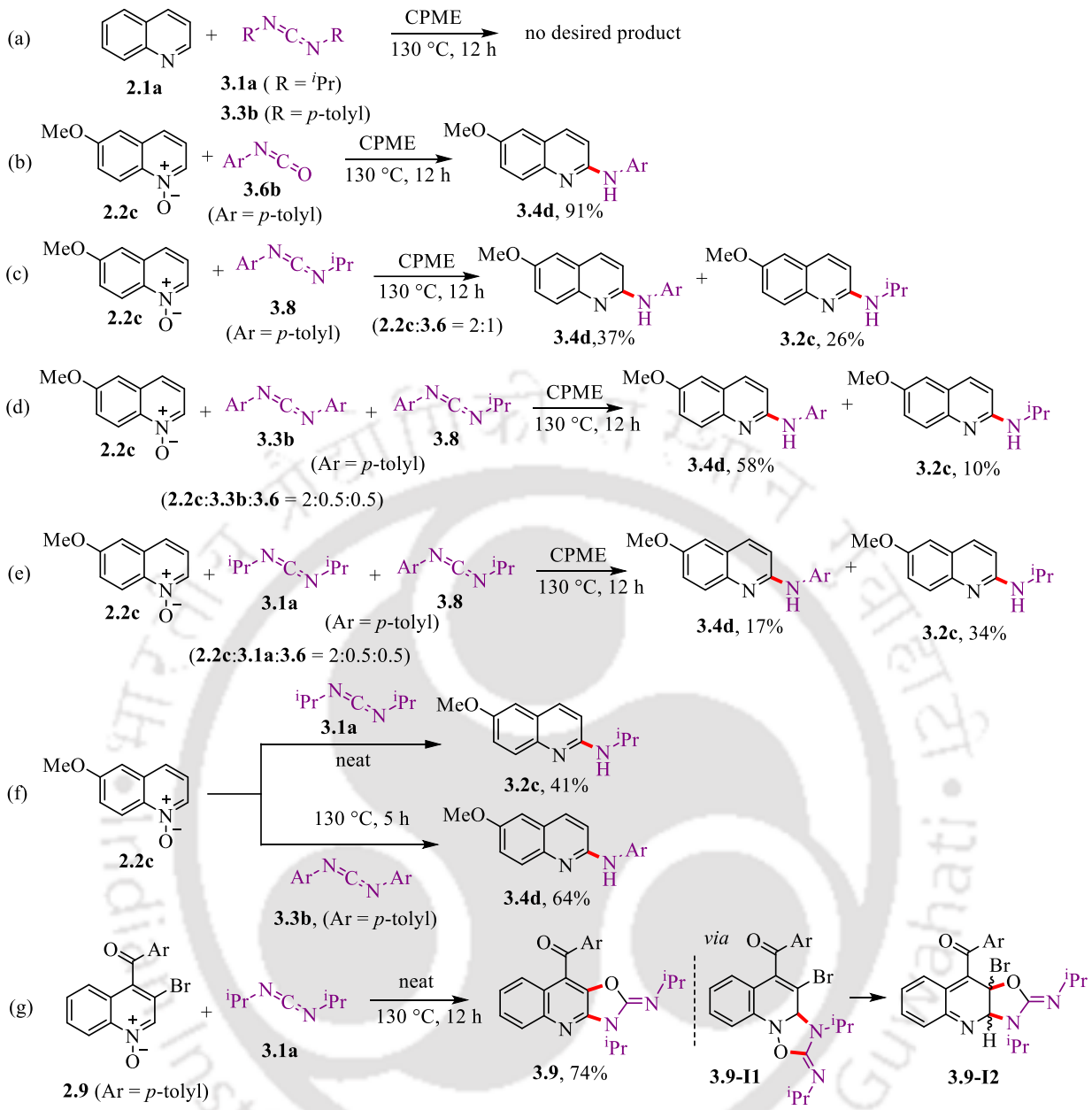
This method allows late-stage C-H amination of biologically important *N*-heteroaromatic compounds (scheme 3.9). For example, the anti-malarial drug quinine, (±)-α-tocopherol and tryptamine modified quinoline **3.2u**, **3.2v** and **3.2w** respectively, were functionalized with good to excellent yields.



Scheme 3.9: late-stage C2-amination of biologically active azines

3.3.7. Mechanistic investigations

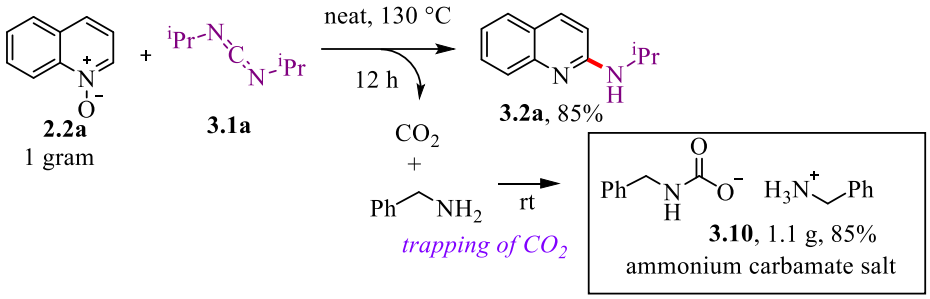
To gain insight into the reaction pathway, a series of control experiments was performed (scheme 3.10). For example, the reaction has not proceeded by reacting quinoline **2.1a** with carbodiimide **3.1a** (or **3.3b**) under the optimal reaction conditions. This suggests the role of N-O group in this transformation. When *N*-oxide **2.2c** was treated with *p*-tolyl isocyanate **3.6b**, the desired aminated product **3.4d** was isolated in 91% yield, suggesting the isocyanate as the potential intermediate in this transformation (scheme 3.10b). To understand the reactivity of aryl *vs.* alkyl carbodiimide in the present reaction conditions, I have performed the experiment using *N*-oxide **2.2c** (2 equiv.) and isopropyl(4-methylphenyl)carbodiimide **3.8** (1 equiv.) in CPME. Gratifyingly, analytically pure **3.4d** and **3.2c** were isolated in 37% and 26% yields respectively (Scheme 3.10c). The reaction between **2.2c** and carbodiimides **3.8** (0.5 equiv.) and **3.3b** (0.5 equiv.) led to the arylaminated product **3.4d** and alkylaminated product **3.2c** in 58% and 10% yields, respectively (Scheme 3.10d). On the other hand, upon using 1,3-diisopropylcarbodiimide **3.1a** (0.5 equiv.) in place of arylcarbodiimide **3.3b** (0.5 equiv.), the yields of **3.4d** and **3.2c** were reduced to 17% and 34% respectively (Scheme 3.10e). The higher yield of **3.4d** (58%) with respect to **3.2c** (34%) suggests that the reactivity of carbodiimide containing aromatic backbone is likely to be higher than that with aliphatic substituent under the current reaction conditions.



Scheme 3.10: control experiments

To understand the rate of amination of aliphatic *vs.* aromatic carbodiimides, *N*-oxide **2.2c** was reacted with **3.1a** and **3.3b** individually under the standard conditions for 5 h. A higher yield of **3.4d** (64%) was obtained with respect to **3.2c** (41%), which revealed that the amination with aromatic carbodiimide was faster than that with alkyl carbodiimide under the reaction conditions (Scheme 3.10f). Surprisingly, the oxazolo derivative **3.9** was isolated in 74% yield when the reaction was carried out with *N*-oxide **2.9** and carbodiimide **3.1a** under the standard conditions (Scheme 3.10g). This observation suggests that initially formed 1,2-dihydro-cycloadduct **3.9-I1** possibly rearranged to the 2,3-dihydro-cycloadduct **3.9-I2**, followed by hydrogen bromide elimination to give the oxazolo derivative **3.9**.

3.3.8. Gram-scale amination of quinoline *N*-oxide and CO_2 trapping experiment



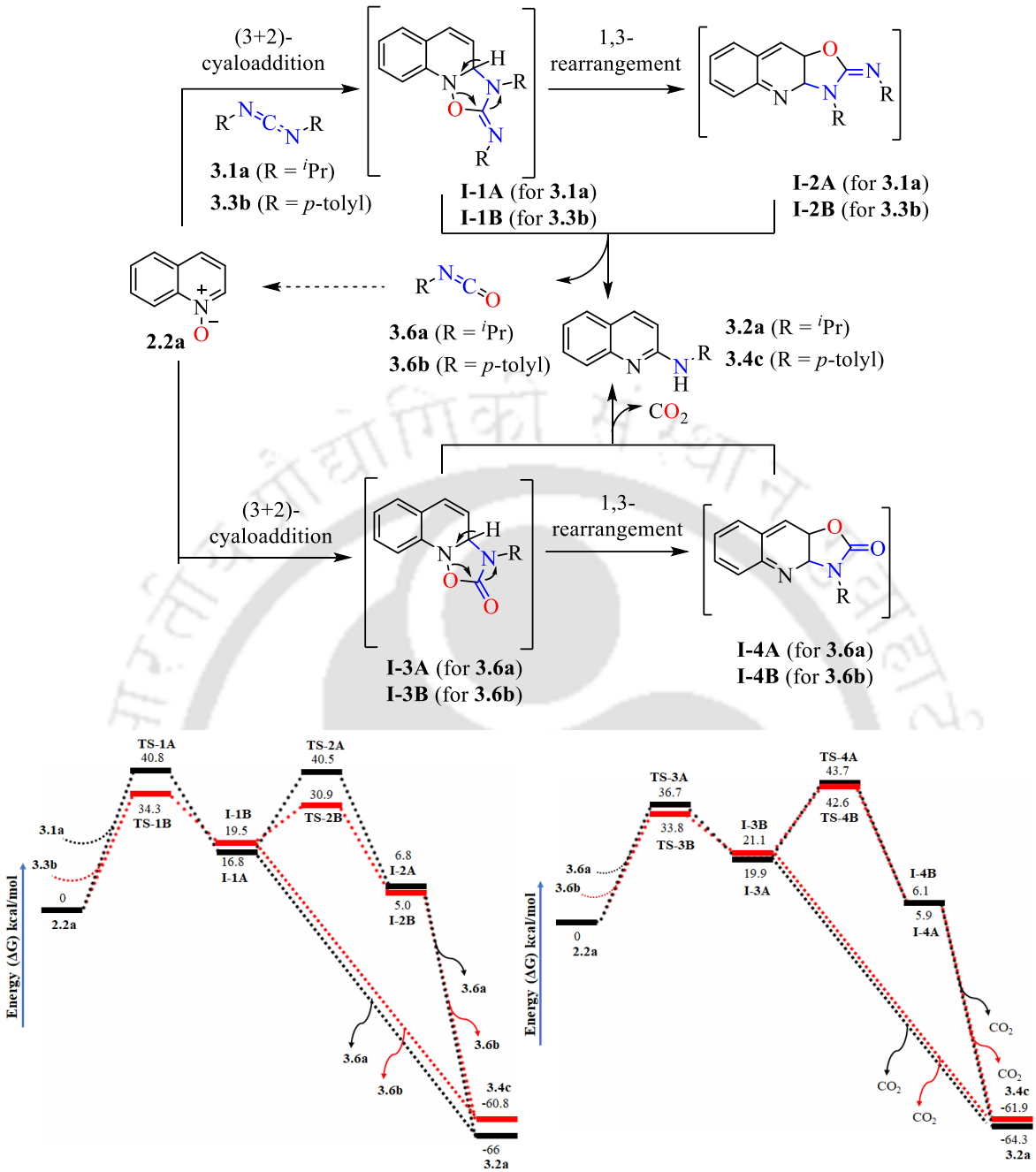
Scheme 3.11: gram-scale reaction and CO_2-trapping experiment

For practical utility, the reaction was also performed in gram-scale, and analytically pure compound **3.2a** was obtained in 85% yield using this method. In the hope of trapping the CO_2 formed as by-product, the reaction set-up was connected to another reaction tube containing benzylamine in precooled condition through cannula. Gratifyingly, the formation of the solid ammonium carbamate salt **3.10** was observed during the process. Hence, the evolved CO_2 was trapped efficiently as the bench-stable salt **3.10**, and this can be utilized as a reagent and catalyst for different organic transformations.[13]

3.3.9. Computational studies

For further understanding of the mechanistic pathway, DFT calculations have been performed using B3LYP level of theory (scheme 3.12). The calculated free energy result and some key optimized structures are depicted in table 3.6. Initially, *N*-oxide **1a** was reacted with **2a** (or **4b**) to form 1,2 dihydroquinoline intermediate **I-1A** (or **I-1B**) *via* (3+2)-dipolar cycloaddition reaction. The process is uphill (ΔG = 16.8 kcal/ mol for **1a** → **I-1A** and ΔG = 19.5 kcal/ mol for **1a** → **I-1B**). The energy barrier for the formation of **I-1B** ($\Delta G^{\ddagger}$ = 34.3 kcal/mol) is slightly lowered compared to **I-1A** ($\Delta G^{\ddagger}$ = 40.8 kcal/mol). Subsequent aromatization afforded the desired product **3aa** (or **5ab**) in a downhill process of ΔG = -49.2 kcal/ mol (**I-1A** → **3aa**), or ΔG = -41.3 kcal/ mol (**I-1B** → **5ab**) and releases the corresponding isocyanates **2a'** (or **4b'**). On the other hand, the intermediate **I-1A** (or **I-1B**) can also easily rearrange to the 2,3-dihydroquinoline cycloadduct **I-2A** (or **I-2B**) with a low energy barrier (**TS-2A**, $\Delta G^{\ddagger}$ = 23.7 kcal/mol; **TS-2B**, $\Delta G^{\ddagger}$ = 11.4 kcal/mol). It proceeds in a downhill process (**I-2A**, ΔG = 6.8 kcal/mol; **I-2B**, ΔG = 5.0 kcal/mol). Then, **I-2A** (or **I-2B**) undergoes aromatization to form the product **3aa** (or **5ab**) with the liberation of isocyanate **2a'** (or **4b'**). This is also a downhill process (ΔG = -59.2 kcal/ mol, **I-2A** → **3aa**; ΔG = -55.8 kcal/ mol, **I-2B** → **5ab**).

The produced isocyanate **2a'** (or **4b'**) can further take part in dipolar cycloaddition with *N*-oxide **1a** to form cycloadduct **I-3A** (or **I-3B**) which is uphill process (ΔG = 19.9 kcal/ mol, **1a** → **I-3A**; ΔG = 21.1 kcal/ mol, **1a** → **I-3B**), and has a barrier (**TS-3A**, $\Delta G^{\ddagger}$ = 36.7 kcal/mol; **TS-3B**, $\Delta G^{\ddagger}$ = 33.8 kcal/mol). The subsequent aromatization gives the aminated product **3aa** (or **5ab**) either derived from direct **I-3A** (or **I-3B**) (ΔG = -44.4 kcal/ mol for **I-3A** → **3aa**), and ΔG = -40.8 kcal/ mol for **I-3B** → **5ab**) or *via* intermediate **I-4A** (or **I-4B**). Carbon dioxide is released as the co-product in the overall process.

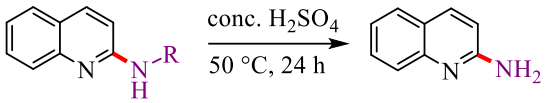


Scheme 3.12: probable mechanism and energy profile diagram

On the basis of the previous reports,[6i,7h,14] our observations, and with the help of calculations, the plausible pathway has been presented and is depicted in Scheme 6. At first, quinoline *N*-oxide and carbodiimide take part in (3+2)-dipolar cycloaddition to give the 1,2-dihydroquinoline intermediate, followed by aromatization (or *via* rearrangement to 2,3-dihydroquinoline intermediate and then aromatization) to form C2-aminated quinoline and generating isocyanate. The produced isocyanate is further reacted with another molecule of *N*-oxide to provide (3+2)-type cycloadduct intermediate and subsequently decarboxylate to give the desired product.

3.4. Downstream transformations

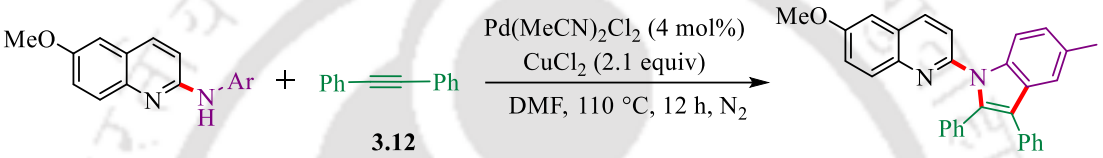
The synthetic utility of the C2-aminated quinolines is illustrated through the preparation of 2-aminoquinoline **7** by simple acid-mediated hydrolysis of *N*-isopropylquinolin-2-amine (**3aa**) or *N*-benzylquinolin-2-amine (**3ad**) affording the product in very good yield (> 82%). It is noteworthy that 2-aminoquinoline motif containing compounds are an important class of compounds, widely utilized in the pharmaceutical industry and the total synthesis of natural products.[4g]



3.2a (R = ^{i}Pr), **3.2s** (CH_2Ph) — **3.11** (82% yield from **3.2a**), **3.11** (90% yield from **3.2s**)

Scheme 3.13: preparation of 2-aminoquinoline **7**

Additionally, readily obtained C2-aminated quinoline **5bb** can be easily transformed into the 2-(1*H*-indol-1-yl)quinoline derivative **8** *via* a Pd-catalysed oxidative coupling reaction.[15]



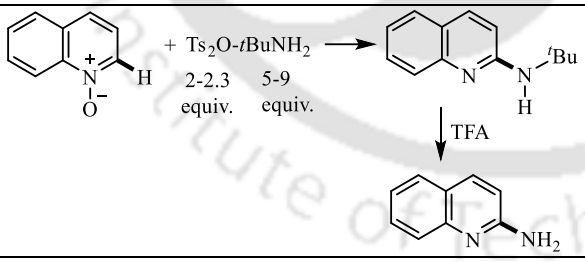
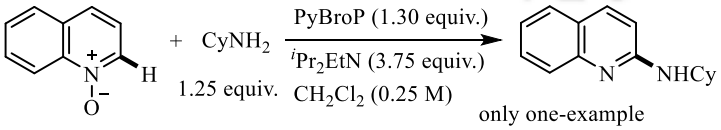
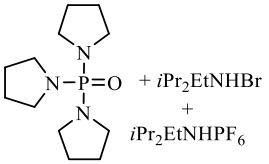
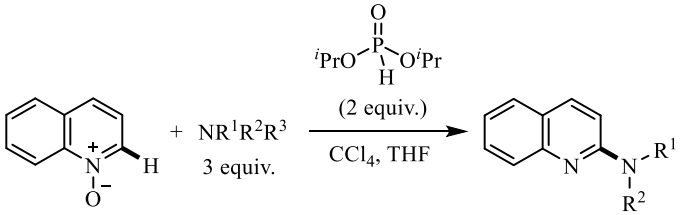
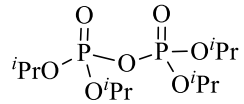
3.4d (Ar = *p*-tolyl) — **3.12** — **3.13**, 68%

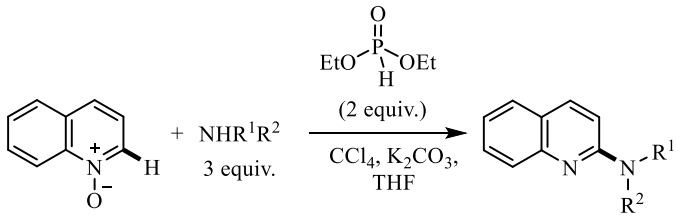
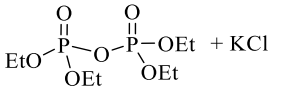
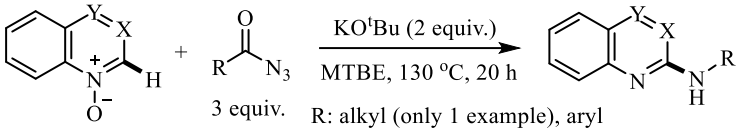
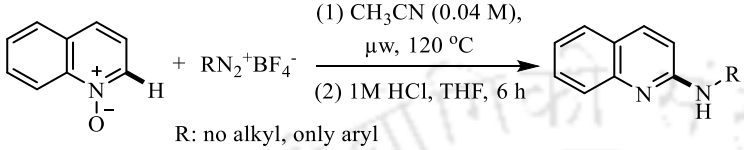
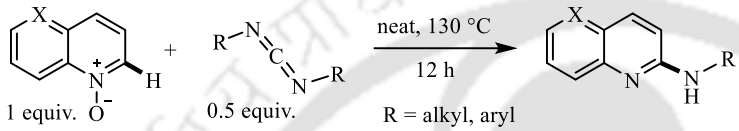
Scheme 3.14: Pd-catalysed coupling reaction of 2-arylaminoquinoline with diphenylacetylene

3.5. Comparison of present protocol with the previous protocols for byproduct generation

Further to show the advantages of the present protocol over the previous protocols with respect to the generation of by-products and hence, overall eco-friendly nature of the system, I have tabulated these protocols and the corresponding by-products and compared them with ours.

Table 3.5: comparison of present protocol with the previous protocols for byproduct generation

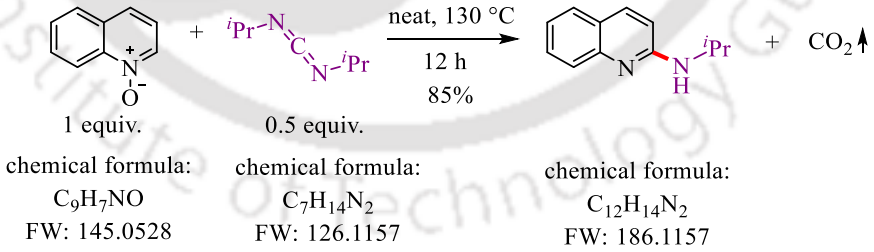
Reported reaction condition	By-products	Ref.
	^{t}BuNHTs + unidentified byproducts (originated from excess Ts_2O and $^{t}BuNH_2$)	7a
		7c
	 + R^3Cl and/or alkene derivetive + $CH_3NEt_3CCl_3$	7d

	 + $CHCl_3$ + HCl + CO_2 + H_2O	7e
	CO_2 + unidentified byproducts (originated from excess acyl azide)	7h
	CH_3CO_2H + N_2 + HBF_4 + acetanilide derivative + unidentified byproducts (originated from the unreacted diazonium salt)	7g
	CO_2 formed as a co-product	***this work***

3.6. Green metrics calculations for sustainability measurements

The green metrics parameters, *viz.* atom economy, atom efficiency, carbon efficiency and E-factor are the most viable tools to quantify the efficiency of chemical processes.[8,16] Herein, these parameters were calculated by using our protocol and comparing with recent reported procedures which are shown in the table 3.5.[17] The atom economy and atom efficiency values for our protocol are very satisfying owing to the fact that only CO_2 was liberating, and no any other organic byproduct was formed. Because of this, the value of E-factor is reasonably low, i.e., only 0.30. E-factor is a practical tool to assess the sustainability of a process as the more the value of E-factor for a reaction, the more will be the generation of waste in the reaction. In addition, the other green metrics parameter is also impressive.

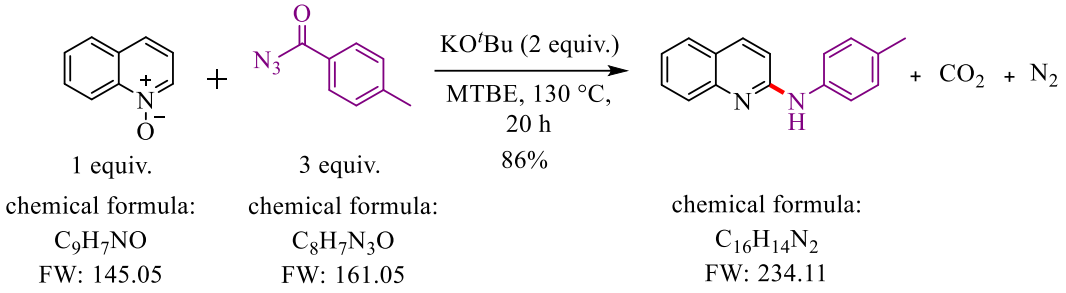
3.6.1. Method A (this work):



Entry	Weight taken	FW
Quinoline *N*-oxide	1 g	145.05
Diisopropyl carbodiimide	0.434 g	126.11
N-isopropylquinoline-2-amine	1.1 g	186.11

E-factor = [{(1 g + 0.434 g) - 1.1 g}/1.1 g] = 0.334 g/1.1 g = **0.30** kg waste/1 kg of product
Atom economy = {186.11 / (145.05 + 0.5 × 126.11)} × 100% = **89.4%**
Atom efficiency = 85 × (89.4/100) = **76%**
Carbon efficiency = {(12 × 2) / (9 × 2 + 7)} × 100% = **96%**

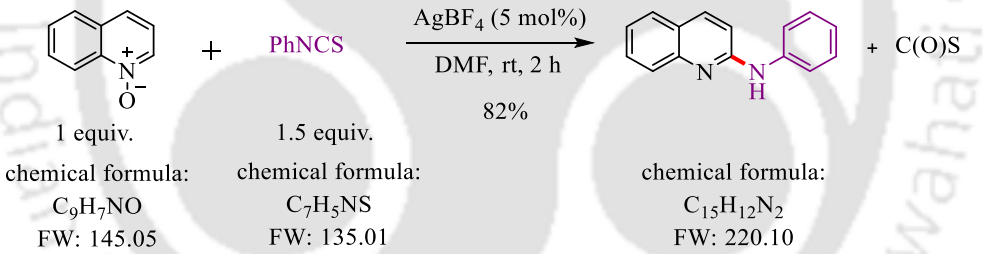
3.6.2. Method B:[7h]



Entry	Weight taken	FW
Quinoline *N*-oxide	1.0 g	145.05
4-methylbenzoyl azide	3.33 g	161.05
KO^{t}Bu	1.54 g	112.02
MTBE	3.7 g (5 mL)	88.08
N-(*p*-tolyl)quinolin-2-amine	1.39 g	234.11

E-factor = [{(1.0 g + 3.33 g + 1.54 g + 3.7 g) - 1.39 g}/1.39 g] = 8.18 g /1.39 g = **5.88** kg waste /1 kg of product
Atom economy = {234.11/ (145.05 + 161.05 × 3)} × 100% = **37.3%**
Atom efficiency = 86 × (37.3/100) = **57.9%**
Carbon efficiency = {(16 / (9 + 8 × 3)} × 100% = **48.5%**

3.6.3. Method C:[6i]



Entry	Weight taken	FW
Quinoline *N*-oxide	0.870 g	145.15
Phenyl thiocyanate	1.22 g	135.19
Silver tetrafluoroborate	0.058 g	194.67
DMF	22.6 g (24 mL)	73.09
N-phenylquinolin-2-amine	1.08 g	220.27

E-factor = [{(0.870 g + 1.22 g + 0.058 g + 22.6 g) - 1.08 g}/1.08 g] = 23.66 g / 1.08 g = **21.90** kg waste/1 kg of product
Atom economy = {220.27 / (145.15 + 135.19)} × 100% = **78.5**%
Atom efficiency = 82 × (78.5/100) = **64.4%**
Carbon efficiency = {15 / (9 + 1.5 × 7)} × 100% = **76.9%**

Table 3.6. Summary of green chemistry metrics

Metrics parameters	Method A (this work)	Method B[4]	Method C[6]
E-factor (kg of waste / 1 kg of product)	0.30	5.88	21.9
Atom economy (%)	89.4	37.3	78.5
Atom efficiency (%)	76	57.9	64.4
Carbon efficiency (%)	96	48.5	76.9

3.7. Summary

In summary the C-H amination of azine *N*-oxides with carbodiimides in the absence of metals, external activators, base, and solvent is developed with excellent site-selectivity at the C2 position. The origin of selectivity is derived from the (3+2)-diploar cycloaddition reaction of polar *N*-oxide with carbodiimide. Contrary to previously reported procedures, this method enables not only the synthesis of bulky aryl bearing aminated azines but also showcases bioactive molecules like the anti-malarial drug quinine, tryptamine, and (±)-α-tocopherol modified aminated quinolines efficiently. This reaction is highly atom economical with CO_2 gas as the only co-product. I believe that this convenient method will find wide range of applications to synthesize a library of therapeutically potent aminated azine derivatives in a waste minimized way.

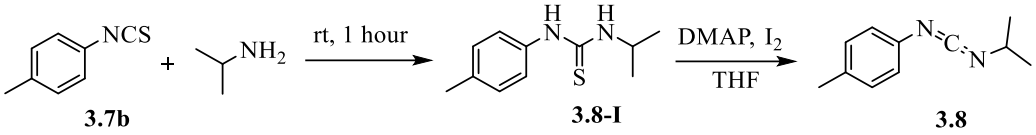
3.8. Experimental section

3.8.1. General Information

All the reagents and chemicals were purchased from common commercial suppliers like Sigma-Aldrich, Alfa Aesar, Merck, Spectrochem, Avra Synthesis Pvt. Ltd. and directly used as received without any further purification unless otherwise mentioned. Azine *N*-oxides,[18] *N,N'*-(*R*)-(+)-α-methylbenzylcarbodiimide,[19a] dibenzyl carbodiimide,[19b] diphenyl carbodiimide,[19b] di-(*p*-tolyl) carbodiimide,[19b] di-(4-methoxyphenyl) carbodiimide,[19b] di-(4-fluorophenyl) carbodiimide,[19b] dimesityl carbodiimide,[19c] di-(2,6-diisopropylphenyl) carbodiimide,[19c] dinaphthyl carbodiimide,[19c] tryptamine isothiocyanate[20] and *p*-tolyl isocyanate[21] were prepared according to the literature reported procedures. CPME was freshly distilled over CaH_2 and stored in 4 Å molecular sieves before use. ^1H, ^{13}C, and ^{19}F NMR spectra of the compounds were measured in $CDCl_3$ as a solvent by using TMS as an internal standard. Chemical shifts, δ (in ppm), are reported relative to TMS δ (^1H) 0.0 ppm, δ (^{13}C) 0.0 ppm, which was used as the internal reference. Otherwise, the solvents residual proton resonance and carbon resonance $CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.16 ppm was used for calibration. Bruker Avance III 600 and 400 spectrometers were used to record the NMR spectra. Chemical shifts (δ) values were reported in ppm and spin-spin coupling constant (J) were expressed in Hz, and other data were reported as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quartet, sext = sextet, br = broad, and brs = broad singlet. IR spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520. Merck silica gel 60-120 and Merck neutral aluminium oxide were used for column chromatography. Melting points were recorded using Buchi Melting Point B-540 Instrument and are uncorrected. All starting azine *N*-oxides and their amination products were characterized by spectroscopic methods and compared to literature wherever applicable, otherwise stated. All the amination reaction was

carried out in oven-dried glassware under argon atmosphere. Completion of reactions was examined by thin layer chromatography carried out on pre-coated Merck silica gel 60 F_{254} aluminium plates with ultraviolet light (UV) or iodine as visualizing agents.

3.8.2. Preparation of isopropyl(4-methylphenyl)carbodiimide (3.8):



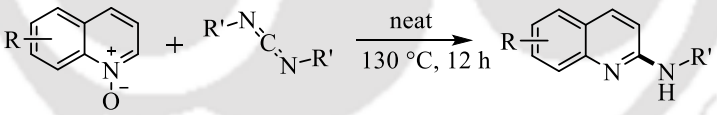
3.7b 3.8-I 3.8

Scheme 3.15: synthesis of unsymmetric carbodiimide 10

In a round-bottom flask, *p*-tolyl isothiocyanate **3.7b** (200 mg, 1.2 mmol, 1 equiv.) and isopropyl amine (88 mg, 1.4 mmol, 1.1 equiv.) were added and flushed with nitrogen before closing with a glass stopper. White precipitate started to come almost instantly. The reaction mixture was stirred at that condition for about 1 hour. After confirming the completion of the reaction by TLC, the resultant 1-isopropyl-3-(*p*-tolyl)thiourea **3.8-I** (200 mg, 0.96 mmol, 1 equiv.) was dissolved in THF (5 mL) in a round-bottom flask. DMAP (236 mg, 1.9 mmol, 2 equiv.) was added to it. Then at 0 °C, iodine (268 mg, 1.04 mmol, 1.1 equiv.) was added portionwise to this mixture. The mixture was stirred at room temperature for overnight. After completion of the reaction as indicated by TLC, the reaction mixture was filtered and washed with *n*-hexane. The filtrate was dried by removing the solvent under reduced pressure. The crude mixture was purified through silica-gel column chromatography (*n*-hexane) to get the pure compound as yellow oil (90% yield, 150 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, J = 8.0 Hz, 2H), 7.03 – 6.94 (m, 2H), 3.82 – 3.71 (m, 1H), 2.31 (s, 3H), 1.33 (d, J = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 138.0, 137.2, 134.5, 130.1, 123.2, 50.3, 25.0, 21.0. FT-IR (KBr, selected band): 2111 cm^{-1} (N=C=N). HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{11}H_{15}N_2$: 175.1230; found: 175.1231.

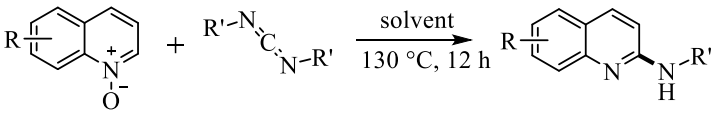
3.8.3. General procedure for C2-amination of azine *N*-oxides with carbodiimides (GP-I):



Scheme 3.16: C2-amination of quinoline *N*-oxides with carbodiimides under neat condition

A mixture of azine *N*-oxide (1 mmol, 2 equiv) and carbodiimide (0.5 mmol, 1 equiv) was loaded in an oven-dried 25 mL reaction tube equipped with stirring bar. The tube was flushed with argon and properly closed with a screw-cap. Then the reaction tube was placed in a preheated oil bath at 130 ºC with continuous stirring for 12 hours. After completion of the reaction, the crude reaction mixture was purified by column chromatography over silica-gel to obtain the analytically pure compound.

3.8.4. General procedure for C2-amination of azine *N*-oxides with carbodiimides (GP-II):



Scheme 3.17: C2-amination of quinoline *N*-oxides with carbodiimides with solvent

A mixture of azine *N*-oxide (1 mmol, 2 equiv.), carbodiimide (0.5 mmol, 1 equiv.), and CPME (1 mL) was loaded in an oven-dried 25 mL reaction tube equipped with stirring bar. The tube was flushed with argon and properly closed with a screw-cap. Then the reaction tube was placed in a preheated oil bath at 130 ^{o}C with continuous stirring for 12 hours. After completion of the reaction, all the volatiles were removed. The crude reaction mixture was purified by column chromatography over silica-gel to obtain the analytically pure compound.

3.8.5. Controlled experiments for reaction mechanism

Amination reaction of 6-methoxyquinoline with carbodiimide (scheme 3.10a)

6-Methoxyquinoline **2.1c** (159 mg, 1 mmol), 1,3-diisopropylcarbodiimide **3.1a** (63 mg, 0.50 mmol) or 1,3-di-*p*-tolylcarbodiimide **3.3b** (111 mg, 0.50 mmol) and CPME (1 mL) were taken in a 25 mL reaction tube. The tube was flushed with argon and properly closed with a screw-cap. Then the reaction tube was placed in a preheated oil bath at 130 ^{o}C with continuous stirring for 12 hours. TLC showed no formation of desired C2-aminated product.

Amination reaction of 6-methoxyquinoline *N*-oxide with isocyanate (scheme 3.10b)

6-Methoxyquinoline *N*-oxide **2.2c** (175 mg, 1 mmol), *p*-tolyl isocyanate **3.6b** (133 mg, 1 mmol), and CPME (1 mL) were taken in a 25 mL reaction tube. The tube was flushed with argon and properly closed with a screw-cap. Then the reaction tube was placed in a preheated oil bath at 130 ^{o}C with continuous stirring for 12 hours. All the volatile was removed and crude mixture was purified by silica-gel column chromatography (EtOAc: petroleum ether 1:4) to get the pure product **5bb** (91% yield, 240 mg).

Amination reaction of 6-methoxyquinoline *N*-oxide with unsymmetrical carbodiimide 10 (scheme 3.10c)

6-Methoxyquinoline *N*-oxide **2.2c** (175 mg, 1 mmol), isopropyl(4-methylphenyl)carbodiimide **3.8** (87 mg, 0.5 mmol), and CPME (1 mL) were taken in a 25 mL reaction tube. The tube was flushed with argon and properly closed with a screw-cap. Then the reaction tube was placed in a preheated oil bath at 130 ^{o}C with continuous stirring for 12 hours. All the volatile was removed and the crude mixture was purified by silica-gel column chromatography to obtain the aminated product **3.4d**, 98 mg, 37% and **3.2c**, 56 mg, 26% yield respectively.

Amination reaction of 6-methoxyquinoline *N*-oxide with ditolyl carbodiimide and unsymmetrical carbodiimide 10 (scheme 3.10d)

6-Methoxyquinoline *N*-oxide **2.2c** (175 mg, 1 mmol), isopropyl(4-methylphenyl)carbodiimide **3.8** (43 mg, 0.25 mmol), 1,3-di-*p*-tolylcarbodiimide **3.3b** (55 mg, 0.25 mmol) and CPME (1 mL) were taken in a 25 mL reaction tube. The tube was flushed with argon and properly closed with a screw-cap. Then the reaction tube was placed in a preheated oil bath at 130 ^{o}C with continuous stirring for 12 hours. All the volatile was removed and the crude mixture was purified by silica-gel column chromatography to obtain the aminated product **3.4d**, 153 mg, 58% and **3.2c**, 22 mg, 10% yield respectively.

Amination reaction of 6-methoxyquinoline *N*-oxide with diisopropyl carbodiimide and unsymmetrical carbodiimide 10 (scheme 3.10d)

6-Methoxyquinoline *N*-oxide **2.2c** (175 mg, 1 mmol), isopropyl(4-methylphenyl)carbodiimide **3.8** (43 mg, 0.25 mmol), 1,3-diisopropylcarbodiimide **3.1a** (31 mg, 0.25 mmol) and CPME (1 mL) were taken in a 25 mL reaction tube. The tube was flushed with argon and properly closed with a screw-cap. Then the reaction tube was placed in a preheated oil bath at 130 ^{o}C with

continuous stirring for 12 hours. All the volatile solvent was removed and the crude mixture was purified by silica-gel column chromatography to obtain the aminated product **3.4d**, 45 mg, 17% and **3.2c**, 73 mg, 34% yield respectively.

Amination reaction of 6-methoxyquinoline *N*-oxide after 5 hours (scheme 3.10e)

6-Methoxyquinoline *N*-oxide **2.2c** (175 mg, 1 mmol), and 1,3-diisopropylcarbodiimide **3.1a** (63 mg, 0.50 mmol) or 1,3-di-*p*-tolylcarbodiimide **3.3b** (111 mg, 0.50 mmol) were taken in a 25 mL reaction tube. The tube was flushed with argon and properly closed with a screw-cap. Then the reaction tube was placed in a preheated oil bath at 130 ^{o}C with continuous stirring for 5 hours. The crude reaction mixture was purified by silica-gel column chromatography to obtain the aminated product. Isolated yield **3.2c**, 88 mg, 41%. Isolated yield **3.4d**, 169 mg, 64%.

Amination reaction of 3-bromo-4-(4-methylbenzoyl)quinoline *N*-oxide (scheme 3.10f)

3-bromo-4-(4-methylbenzoyl)quinoline *N*-oxide **2.9** (342 mg, 1 mmol) was taken in a 25-mL reaction tube and diisopropyl carbodiimide **3.1a** (63 mg, 0.5 mmol) was added to it. The tube was flushed with argon and closed with screw cap. The reaction mixture was stirred at 130 °C for 12 hours. After completion of the reaction, the crude product was purified by silica-gel column chromatography (EtOAc: petroleum ether 1:10) to get **3.9** (brown viscous oil) with 74% yield (286 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.61 – 7.50 (m, 2H), 7.30 (d, J = 8.0 Hz, 3H), 4.78 – 4.71 (m, 1H), 3.83 – 3.69 (m, 1H), 2.44 (s, 3H), 1.62 (d, J = 6.8 Hz, 6H), 1.05 (d, J = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 192.2, 148.4, 145.8, 144.6, 144.3, 135.6, 134.4, 130.3, 129.8, 128.0, 127.9, 125.4, 124.7, 122.5, 119.5, 47.1, 46.5, 24.5, 22.0, 19.1. FT-IR (KBr, selected band): 1671 (C=O), 1604 (C=N) cm^{-1}. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{26}N_3O_2$: 388.2020; found: 388.2019.

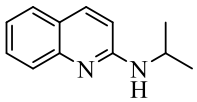
3.8.6. Procedure for gram-scale amination of quinoline *N*-oxide and CO_2 trapping (scheme 3.11)

A mixture of quinoline *N*-oxide **2.2a** (1 g, 6.9 mmol, 2 equiv.), and 1,3-diisopropylcarbodiimide **3.1a** (0.435 g, 3.4 mmol, 1 equiv.) was loaded in an oven-dried 50 mL round bottom flask equipped with stirring bar. The flask was flushed with argon and properly closed with a septum. Then one end of a cannula was connected through septum and another end of cannula was dipped to precooled benzylamine containing flask. The reaction mixture was kept into the preheated oil bath at 130 ^{o}C with continuous stirring for 12 hours. The evolved carbon dioxide was allowed to pass through cannula and reacted with benzyl amine to form benzylammonium benzylcarbamate as a white solid **3.10** (0.749 g, 85% yield). the crude reaction mixture was purified by column chromatography over silica-gel to obtain the analytically pure compound **3.2a** in 85% yield (1.1 g).

Benzylammonium benzylcarbamate (3.10): ^{1}H NMR (600 MHz, D_2O): δ 7.47 – 7.27 (m, 10H), 4.21 (s, 1H), 4.04 (s, 4H). ^{13}C{^{1}H} NMR (151 MHz, D_2O): δ 164.7, 161.0, 140.7, 135.2, 129.0, 128.6, 128.4, 126.8, 126.6, 44.7, 43.5. Spectral data is in accordance with the literature.[13d]

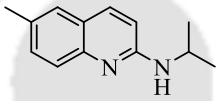
3.8.7. Analytical data of the products

***N*-isopropylquinolin-2-amine (3.2a)**[6i]:



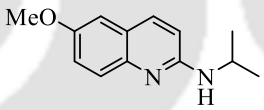
Using quinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether 3 : 17) as a light yellow solid (168 mg, 90%). M. p. 66 – 68 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 6.62 (d, J = 9.0 Hz, 1H), 4.65 (s, 1H), 4.22-4.17 (m, 1H), 1.29 (d, J = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 156.5, 148.3, 137.5, 129.7, 127.5, 126.1, 123.4, 122.0, 111.3, 43.1, 23.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{12}H_{15}N_2$: 187.1235; found: 187.1235.

***N*-isopropyl-6-methylquinolin-2-amine (3.2b):**



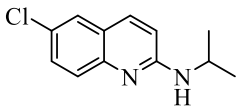
Using 6-methylquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) as an yellow oil (192 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.38 – 7.32 (m, 2H), 6.59 (d, J = 8.8 Hz, 1H), 4.60 (br, 1H), 4.20 – 4.12 (m, 1H), 2.43 (s, 3H), 1.28 (d, J = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.2, 146.5, 137.0, 131.6, 131.4, 126.7, 125.8, 123.3, 111.1, 43.1, 23.3, 21.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{13}H_{17}N_2$: 201.1392; found: 201.1392.

***N*-isopropyl-6-methoxyquinolin-2-amine (3.2c):**



Using 6-methoxyquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) as a light yellow oil (207 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 9.2 Hz, 1H), 7.20 (dd, J = 8.8, 2.8 Hz, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 4.53 (d, J = 6.4 Hz, 1H), 4.17 – 4.09 (m, 1H), 3.86 (s, 3H), 1.26 (d, J = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.5, 154.7, 143.7, 136.6, 127.5, 123.6, 121.0, 111.5, 106.6, 55.6, 43.1, 23.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{13}H_{16}N_2O$: 217.1336; found 217.1337.

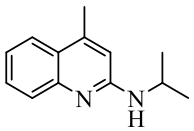
6-chloro-*N*-isopropyl quinolin-2-amine (3.2d):



Using 6-chloroquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as an yellow oil (187 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (d,

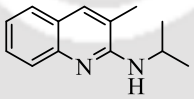
J = 9.0 Hz, 1H), 7.57 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.44 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.94 (br, 1H), 4.20 – 4.14 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): *δ* 156.5, 146.5, 136.6, 130.2, 127.3, 127.0, 126.3, 123.8, 112.2, 43.1, 23.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{12}H_{14}ClN_2$: 221.0846; found: 221.0844.

_N_-isopropyl-4-methylquinolin-2-amine (3.2e):[22]



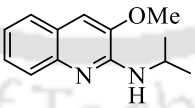
Using 4-methylquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as an off white solid (188 mg, 94%). M. p. 107 – 108 °C. ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.75 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.50 (m, 1H), 7.23 – 7.20 (m, 1H), 6.48 (s, 1H), 4.56 (br, 1H), 4.21 – 4.15 (m, 1H), 2.56 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): *δ* 156.4, 150.3, 148.2, 145.2, 129.4, 126.4, 123.7, 121.7, 111.2, 42.9, 23.4, 19.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{13}H_{17}N_2$: 201.1392; found: 201.1413.

_N_-isopropyl-3-methylquinolin-2-amine (3.2f):



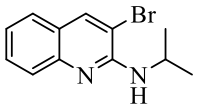
Using 3-methylquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as an yellow oil (170 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.72 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 7.53 (dd, *J* = 8, 1.2 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.22 – 7.16 (m, 1H), 4.60 – 4.52 (m, 1H), 4.31 (d, *J* = 6.6 Hz, 1H), 2.22 (s, 3H), 1.33 (d, *J* = 6.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): *δ* 155.3, 147.3, 135.5, 128.4, 126.7, 126.2, 123.6, 121.8, 119.6, 42.4, 23.3, 17.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{13}H_{17}N_2$: 201.1392; found: 201.1400.

_N_-isopropyl-3-methoxyquinolin-2-amine (3.2g):



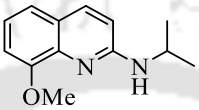
Using 3-methoxyquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) as an yellow oil (179 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.68 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.22 – 7.15 (m, 1H), 7.01 (s, 1H), 5.20 (d, *J* = 7.6 Hz, 1H), 4.54 – 4.45 (m, 1H), 3.93 (s, 3H), 1.31 (d, *J* = 6.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 149.4, 143.2, 126.6, 126.1, 125.8, 123.9, 122.0, 109.3, 55.4, 42.0, 23.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{13}H_{17}N_2O$: 217.1341; found: 217.1341.

3-bromo-_N_-isopropylquinolin-2-amine (3.2h):



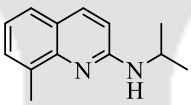
Using 3-bromoquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as a light yellow oil (206 mg, 78%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.54 – 7.52 (m, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 5.18 (d, J = 6.6 Hz, 1H), 4.48 – 4.43 (m, 1H), 1.32 (d, J = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 151.7, 147.1, 138.7, 129.8, 126.6, 126.5, 124.1, 122.5, 108.6, 43.1, 23.0. HRMS (ESI) *m/z*: $[M+H]^+$calculated for $C_{12}H_{13}BrN_2$: 265.0340; found: 265.0371.

_N_-isopropyl-8-methoxyquinolin-2-amine (3.2i):



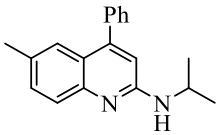
Using 8-methoxyquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a light yellow solid (201 mg, 93%). M. p. 79 – 81 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, J = 9 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 9.0 Hz, 1H), 5.00 (d, J = 7.2 Hz, 1H), 3.99 (s, 3H), 3.97 – 3.92 (m, 1H), 1.25 (d, J = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.3, 153.1, 139.7, 137.9, 124.1, 121.5, 119.7, 109.6, 108.4, 56.0, 43.4, 23.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{13}H_{17}N_2O$: 217.1341; found: 217.1347.

_N_-isopropyl-8-methylquinolin-2-amine (3.2j):



Using 8-methylquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a light yellow oil (184 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 6.8 Hz, 1H), 7.12 – 7.08 (m, 1H), 6.58 (d, J = 8.8 Hz, 1H), 4.54 (d, J = 6 Hz, 1H), 4.33 – 4.24 (m, 1H), 2.66 (s, 3H), 1.32 (d, J = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 155.6, 147.1, 137.5, 134.1, 129.7, 125.4, 123.0, 121.5, 111.2, 43.0, 23.0, 18.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{13}H_{17}N_2$: 201.1392; found: 201.1396.

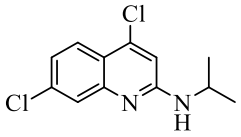
_N_-isopropyl-6-methyl-4-phenylquinolin-2-amine (3.2k):[23]



Using 4-phenyl-6-methylquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as an off white solid (259 mg, 94%). M. p. 109 – 111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 9.2 Hz, 1H), 7.53 – 7.46 (m, 5H), 7.38 – 7.36 (m, 2H), 6.54 (s, 1H), 4.61 (d, J = 7.6 Hz, 1H), 4.23 – 4.15 (m, 1H), 2.36 (s, 3H), 1.30 (d, J = 6.4 Hz, 6H).

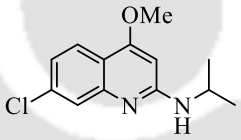
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 155.8, 149.3, 147.1, 139.0, 131.5, 131.4, 129.4, 128.5, 128.2, 126.3, 124.9, 122.3, 111.1, 43.1, 23.4, 21.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{21}N_2$: 277.1705; found: 277.1706.

4,7-dichloro-*N*-isopropylquinolin-2-amine (3.2l):



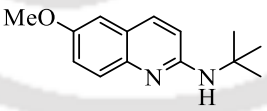
Using 4, 7-dichloroquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as an yellow oil (212 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.19 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.67 (s, 1H), 4.66 (d, *J* = 7.2 Hz, 1H), 4.22 – 4.14 (m, 1H), 1.27 (d, *J* = 6.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 156.6, 149.7, 142.6, 136.5, 125.6, 125.4, 123.3, 120.1, 111.2, 43.1, 23.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{12}H_{13}Cl_2N_2$: 255.0456; found: 255.0456.

7-chloro-*N*-isopropyl-4-methoxyquinolin-2-amine (3.2m):



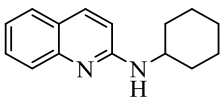
Using 7-chloro-4-methoxyquinoline *N*-oxide with 1,3-diisopropylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as an white solid (231 mg, 92%). M. p. 119 – 121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.87 (s, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.22 – 4.13 (m, 1H), 3.93 (s, 3H), 1.27 (d, *J* = 6.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 162.8, 158.5, 149.9, 135.8, 124.8, 123.2, 121.8, 116.1, 89.0, 55.5, 43.1, 23.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{13}H_{16}ClN_2O$: 251.0951; found: 251.0968.

***N*-(*tert*-butyl)-6-methoxyquinolin-2-amine (3.2n):**



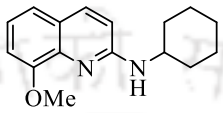
Using 6-methoxyquinoline *N*-oxide with di-*tert*-butylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as an yellow solid (150 mg, 65%). M. p. 82 – 84 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 9.0 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.19 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.93 (d, *J* = 3.0 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 1.51 (s, 9H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 154.9, 131.3, 130.0, 127.2, 125.0, 123.2, 120.9, 113.1, 106.6, 55.7, 51.5, 29.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{14}H_{19}N_2O$: 231.1497; found: 231.1498.

***N*-cyclohexylquinolin-2-amine (3.2o):**[24]



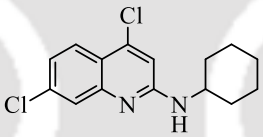
Using quinoline *N*-oxide with 1,3-dicyclohexylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as an yellowish solid (200 mg, 88%). M. p. 125 – 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.50 (m, 1H), 7.21 – 7.15 (m, 1H), 6.62 (d, J = 8.8 Hz, 1H), 4.72 (d, J = 5.6 Hz, 1H), 3.88 – 3.77 (m, 1H), 2.16 – 2.03 (m, 2H), 1.84 – 1.70 (m, 2H), 1.70 – 1.61 (m, 1H), 1.47 – 1.40 (m, 2H), 1.28 – 1.19 (m, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 156.5, 148.3, 137.5, 129.6, 127.5, 126.0, 123.4, 121.9, 111.1, 50.0, 33.6, 25.9, 25.6, 25.0, 24.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{19}N_2$: 227.1543; found: 227.1543.

_N_-cyclohexyl-8-methoxyquinolin-2-amine (3.2p):



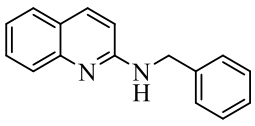
Using 8-methoxyquinoline *N*-oxide with 1,3-dicyclohexylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as an white solid (235 mg, 92%). M. p. 169 – 171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 9.2 Hz, 1H), 7.19 (dd, J = 8.0, 0.8 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 5.14 (brs, 1H), 4.01 (s, 3H), 3.58 – 3.54 (m, 1H), 2.08 – 2.04 (m, 1H), 1.93 – 1.91 (m, 1H), 1.83 – 1.76 (m, 2H), 1.42 – 1.30 (m, 3H), 1.29 – 1.20 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.9, 156.3, 153.1, 138.0, 124.1, 121.5, 119.8, 109.6, 108.4, 56.0, 50.7, 34.1, 33.7, 25.8, 25.1, 25.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{21}N_2O$: 257.1654; found: 257.1655.

4,7-dichloro-_N_-cyclohexylquinolin-2-amine (3.2q):



Using 4, 7-dichloroquinoline *N*-oxide with 1,3-dicyclohexylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as an yellow oil (239 mg, 81%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.18 (dd, J = 9.0, 1.8 Hz, 1H), 6.68 (s, 1H), 4.77 (brs, 1H), 3.81 (brs, 1H), 2.08 – 2.06 (m, 2H), 1.79 – 1.75 (m, 2H), 1.68 – 1.65 (m, 1H), 1.45 – 1.40 (m, 2H), 1.28 – 1.18 (m, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 156.5, 149.7, 142.7, 136.5, 125.5, 125.4, 123.2, 120.0, 111.0, 50.1, 33.4, 25.8, 25.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{17}Cl_2N_2$: 295.0769; found: 295.0769.

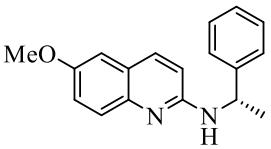
_N_-benzylquinolin-2-amine (3.2r):[6i]



Using quinoline *N*-oxide with dibenzylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as an white solid (211 mg, 90%). M. p. 100 – 102 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.42 – 7.41 (m, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.32 – 7.27 (m, 1H), 7.24 – 7.22 (m, 1H),

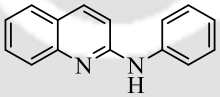
6.63 (d, *J* = 9.0 Hz, 1H), 5.21 (s, 1H), 4.73 (d, *J* = 5.4 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 156.8, 147.8, 139.3, 137.8, 129.8, 128.8, 127.9, 127.6, 127.5, 126.1, 123.6, 122.4, 111.4, 46.0.

6-methoxy-*N*-[(*S*)-1-phenylethyl]quinolin-2-amine (3.2s):



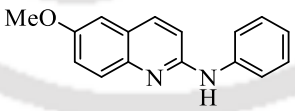
Using 6-methoxyquinoline *N*-oxide with bis[(*S*)-1-phenylethyl]carbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as an yellow oil (236 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 8 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.25 – 7.18 (m, 2H), 6.91 (d, *J* = 2.8 Hz, 1H), 6.53 (d, *J* = 9.2 Hz, 1H), 5.56 (s, 1H), 5.07 – 4.91 (m, 1H), 3.85 (s, 3H), 1.61 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 155.1, 155.1, 144.9, 137.3, 137.2, 128.8, 127.2, 126.9, 126.1, 123.7, 121.5, 110.9, 106.6, 55.7, 51.9, 24.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{19}N_2O$: 279.1492; found: 279.1493. $[\alpha]_D^{24.3}$ = -65.00 (c = 0.02 M, $CHCl_3$).

***N*-phenylquinolin-2-amine (3.4a):**[6i]



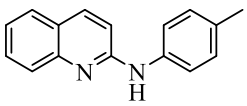
Using quinoline *N*-oxide, diphenylcarbodiimide, and CPME (1 mL) in accordance with GP-II, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as an off white solid (187 mg, 85%). M. p. 98 – 99 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.28 (m, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 154.5, 147.2, 140.1, 138.2, 130.1, 129.4, 127.6, 126.2, 124.1, 123.5, 123.3, 120.9, 111.7.

6-methoxy-*N*-phenylquinolin-2-amine (3.4b):[7h]



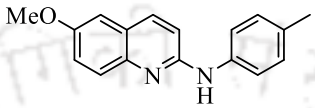
Using 6-methoxyquinoline *N*-oxide, diphenylcarbodiimide, and CPME (1 mL) in accordance with GP-II, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as an off white solid (225 mg, 90%). M. p. 144 – 146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.55 – 7.52 (m, 2H), 7.38 – 7.33 (m, 2H), 7.27 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.00 (s, 1H), 6.98 (d, *J* = 5.6 Hz, 1H), 6.81 (br, 1H), 3.89 (s, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 155.7, 153.0, 143.2, 140.7, 136.9, 129.3, 128.2, 124.7, 122.8, 121.6, 120.1, 112.1, 106.3, 55.6.

***N*-(*p*-tolyl)quinolin-2-amine (3.4c):**[6i]



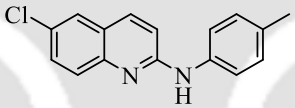
Using quinoline *N*-oxide, di-*p*-tolylcarbodiimide, and CPME (1 mL) in accordance with GP-II, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as an white solid (192 mg, 82% yield from GP-II; 169 mg, 72% yield from GP-I). M. p. 103 – 105 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.59 – 7.56 (m, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 9.0 Hz, 1H), 6.80 (br, 1H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.9, 147.9, 137.9, 137.5, 133.3, 130.0, 129.9, 127.6, 126.7, 124.2, 123.1, 121.5, 111.4, 21.0. HRMS (ESI) *m/z*: calculated for $C_{16}H_{15}N_2^+$ $(M+H)^+$: 235.1235; found: 235.1246.

6-methoxy-*N*-(*p*-tolyl)quinolin-2-amine (3.4d):[7h]



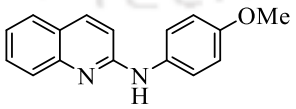
Using 6-methoxyquinoline *N*-oxide, di-*p*-tolylcarbodiimide, and CPME (1 mL) in accordance with GP-II, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a white solid (240 mg, 91% yield from GP-II; 237 mg, 90% yield from GP-I). M. p. 113 – 114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.38 (d, J = 8 Hz, 2H), 7.27 – 7.24 (m, 1H), 7.16 (d, J = 8 Hz, 2H), 6.99 – 6.96 (m, 2H), 6.72 (brs, 1H), 3.89 (s, 3H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.6, 153.5, 143.1, 137.8, 137.0, 132.9, 129.95, 127.9, 124.6, 121.6, 121.1, 111.7, 106.4, 55.7, 21.0.

6-chloro-*N*-(*p*-tolyl)quinolin-2-amine (3.4e):[7h]



Using 6-chloroquinoline *N*-oxide with di(*p*-tolyl)carbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a white solid (225 mg, 84%). M. p. 109 – 111 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.50 (dd, J = 8.8, 2.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.75 (brs, 1H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.0, 146.3, 137.2, 136.9, 133.6, 130.5, 130.0, 128.2, 128.2, 126.3, 124.7, 121.5, 112.4, 21.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{14}ClN_2$: 269.0846; found: 269.0856.

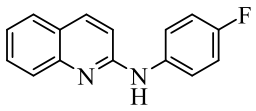
***N*-(4-methoxyphenyl)quinolin-2-amine (3.4f):**[7e]



Using quinoline *N*-oxide, di-(4-methoxyphenyl)carbodiimide, and CPME (1 mL) in accordance with GP-II, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a light yellow solid (212 mg, 85% yield from GP-II; 187 mg, 75% yield from GP-I). M. p. 125 – 127 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.58 – 7.56 (m, 1H), 7.42 – 7.40 (m, 2H), 7.28 – 7.26 (m, 1H), 6.94 – 6.92 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H),

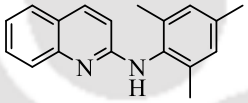
3.83 (s, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 156.6, 155.5, 147.7, 138.0, 132.9, 130.0, 127.6, 126.3, 124.2, 124.0, 122.9, 114.7, 111.0, 55.7.

_N_-(4-fluorophenyl)quinolin-2-amine (3.4g):[6i]



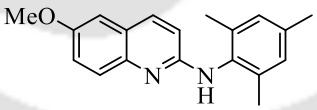
Using quinoline *N*-oxide, di(4-fluorophenyl)carbodiimide, and CPME (1 mL) in accordance with GP-II, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a light yellow solid (202 mg, 85%). M. p. 101 – 103 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.53 (dd, J = 8.8, 4.8 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.06 (t, J = 9.0 Hz, 2H), 6.97 (brs, 1H), 6.87 (d, J = 9.0 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 159.1 (d, J = 242.3 Hz), 154.7, 147.6, 138.0, 136.3 (d, J = 2.6 Hz), 130.0, 127.6, 126.7, 124.2, 123.3, 122.8 (d, J = 7.8 Hz), 115.9 (d, J = 22.5 Hz), 111.6. ^{19}F NMR (565 MHz, $CDCl_3$): δ -119.5.

_N_-mesitylquinolin-2-amine (3.4h):



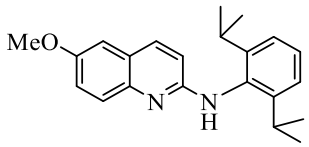
Using quinoline *N*-oxide, dimesitylcarbodiimide, and CPME (1 mL) in accordance with GP-II, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a white solid (210 mg, 80%). M. p. 127 – 129 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (d, J = 9.0 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.57 – 7.54 (m, 1H), 7.24 (t, J = 7.2 Hz, 1H), 6.80 (br, 1H), 6.99 (s, 2H), 6.33 (d, J = 9 Hz, 1H), 2.34 (s, 3H), 2.21 (s, 6H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 156.9, 147.9, 138.4, 137.1, 137.0, 133.4, 130.0, 129.4, 127.6, 125.7, 123.8, 122.4, 109.0, 21.1, 18.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{19}N_2$: 263.1543; found: 263.1550.

_N_-mesityl-6-methoxyquinolin-2-amine (3.4i):



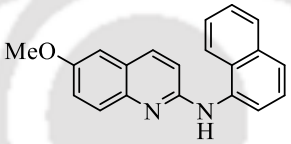
Using 6-methoxyquinoline *N*-oxide with dimesitylcarbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a white solid (248 mg, 85%). M. p. 162 – 164 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.24 (dd, J = 9.0, 2.4 Hz, 1H), 7.02 – 6.91 (m, 3H), 6.43 (brs, 1H), 6.31 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 2.33 (s, 3H), 2.21 (s, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 155.7, 155.0, 143.7, 137.3, 137.1, 136.8, 133.8, 129.4, 127.3, 124.1, 121.6, 109.2, 106.4, 55.7, 21.1, 18.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{21}N_2O$: 293.1654; found: 293.1654.

_N_-(2,6-diisopropylphenyl)-6-methoxyquinolin-2-amine (3.4j):



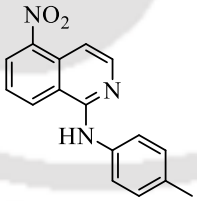
Using 6-methoxyquinoline *N*-oxide with bis(2,6-diisopropylphenyl)carbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a white solid (281 mg, 84%). M. p. 192 – 194 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 9.1 Hz, 1H), 7.37 – 7.35 (m, 1H), 7.29 – 7.21 (m, 3H), 6.96 (d, J = 2.8 Hz, 1H), 6.60 (brs, 1H), 6.29 (d, J = 8.9 Hz, 1H), 3.87 (s, 3H), 3.27 (sept, J = 6.8 Hz, 2H), 1.13 (d, J = 6.2 Hz, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.7, 155.0, 148.3, 143.6, 137.2, 133.4, 128.3, 127.3, 124.2, 124.1, 121.7, 109.2, 106.5, 55.7, 28.7, 28.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{22}H_{27}N_2O$: 335.2123; found: 335.2143.

6-methoxy-*N*-(naphthalen-1-yl)quinolin-2-amine (3.4k):



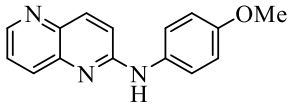
Using 6-methoxyquinoline *N*-oxide (1 mmol) with dinaphthylcarbodiimide (0.5 mmol) in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a light yellow solid (231 mg, 77%). M. p. 182 – 184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.07 (m, 1H), 7.93 – 7.88 (m, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.72 (t, J = 9.4 Hz, 2H), 7.67 (dd, J = 7.2, 1.2 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.29 (dd, J = 9.2, 3.2 Hz, 1H), 7.00 (d, J = 2.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.7, 154.9, 143.4, 137.1, 136.1, 134.8, 129.3, 128.7, 127.8, 126.5, 126.4, 126.0, 125.5, 124.8, 122.3, 121.8, 120.4, 111.3, 106.4, 55.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{17}N_2O$: 301.1336; found 301.1349.

5-nitro-*N*-(*p*-tolyl)isoquinolin-1-amine (3.5a):



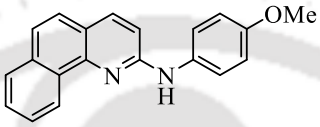
Using 5-nitroisoquinoline *N*-oxide with di(*p*-tolyl)carbodiimide and CPME (1 mL) in accordance with GP-II, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a brown solid (218 mg, 78%). M. p. 157 – 158 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.40 (d, J = 7.8 Hz, 1H), 8.26 (dd, J = 12, 8.4 Hz, 2H), 7.78 (d, J = 6.0 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 153.2, 145.9, 145.4, 137.0, 133.8, 130.5, 129.8, 128.2, 127.6, 124.7, 121.7, 119.8, 107.5, 21.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{14}N_3O_2$: 280.1081; found: 280.1110.

***N*-(4-methoxyphenyl)-1,5-naphthyridin-2-amine (3.5b):**



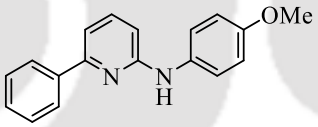
Using 1,5-naphthyridine 1-oxide with di(4-methoxyphenyl) carbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a yellow solid (196 mg, 78%). M. p. 174 – 176 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.66 (d, J = 4.2, 1H), 8.08 (d, J = 9.2 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.49 – 7.45 (m, 3H), 7.07 (d, J = 9.2 Hz, 1H), 6.94 (m, J = 9.0 Hz, 2H), 6.81 (brs, 1H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 156.8, 155.5, 146.8, 143.6, 141.1, 138.9, 134.2, 132.5, 124.6, 124.2, 114.7, 55.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{14}N_3O$: 252.1132; found: 252.1133.

_N_-(4-methoxyphenyl)benzo[*h*]quinolin-2-amine (3.5c):



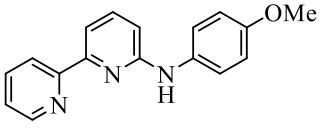
Using benzo[*h*]quinoline *N*-oxide with di(4-methoxyphenyl)carbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a light yellow liquid (264 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 – 9.11 (m, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.70 – 7.62 (m, 2H), 7.61 – 7.52 (m, 4H), 7.00 – 6.90 (m, 2H), 6.91 (d, J = 8.8 Hz, 1H), 6.75 (brs, 1H), 3.85 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 156.0, 155.0, 145.8, 137.8, 134.3, 133.4, 130.6, 127.8, 127.7, 126.2, 125.3, 124.5, 123.5, 123.2, 120.7, 114.6, 110.1, 55.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{17}N_2O$: 301.1336; found: 301.1336.

_N_-(4-methoxyphenyl)-6-phenylpyridin-2-amine (3.5d):[25]



Using 2-phenylpyridine *N*-oxide with di(4-methoxyphenyl)carbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a colorless oil (230 mg, 83%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 1H), 7.31 (d, J = 9.0 Hz, 2H), 7.14 (d, J = 7.2 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.56 (brs, 1H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 157.0, 156.3, 156.2, 139.7, 138.5, 133.6, 128.8, 128.7, 126.9, 123.9, 114.7, 111.3, 105.9, 55.7.

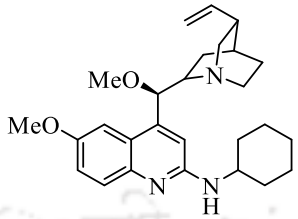
_N_-(4-methoxyphenyl)-[2,2'-bipyridin]-6-amine (3.5e):[12c]



Using 2,2′-bipyridine *N*-oxide with di(4-methoxyphenyl) carbodiimide in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a light yellow liquid (216 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 – 8.66 (m, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.59 (t, J = 8.0 Hz, 1H),

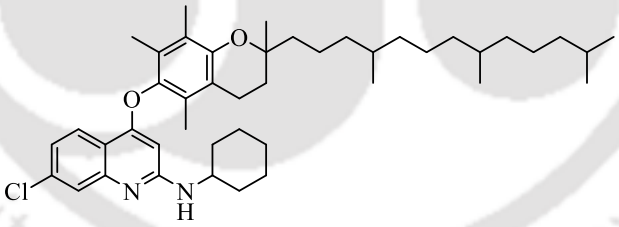
7.34-7.26 (m, 3H), 6.94 – 6.90 (m, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.54 (brs, 1H), 3.83 (s, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 156.7, 156.5, 156.2, 154.7, 149.2, 138.7, 136.9, 133.5, 123.8, 123.6, 121.1, 114.7, 112.0, 107.9, 55.7.

_N_-cyclohexyl-6-methoxy-4-((1*R*)-methoxy((1*S*,4*S*)-5-vinylquinuclidin-2-yl)methyl) quinolin-2-amine (3.2u):



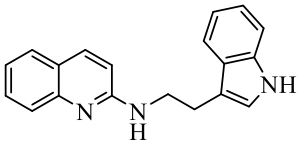
Using 6-methoxy-4-((1*R*)-methoxy((1*S*,4*S*)-5-vinylquinuclidin-2-yl)methyl)quinoline 1-oxide (0.5 mmol) with dicyclohexylcarbodiimide (0.25 mmol) in accordance with GP-I, the title compound was obtained by using SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as a light yellow oil (185 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 9.2 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.22 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.75 (s, 1H), 5.70 (brs, 1H), 5.67 – 5.59 (m, 1H), 5.05 – 5.04 (m, 1H), 5.01 (brs, 1H), 3.98 (s, 3H), 3.93 – 3.80 (m, 1H), 3.43 (s, 3H), 3.39 – 3.36 (m, 1H), 3.28 – 3.23 (m, 1H), 3.09 – 3.05 (m, 1H), 2.99 – 2.96 (m, 1H), 2.59 (br, 1H), 2.07 – 2.05 (m, 3H), 2.0 – 1.98 (m, 3H), 1.81 –1.77 (m, 3H), 1.67 – 1.64 (m, 1H), 1.53 – 1.49 (m, 1H), 1.46 –1.39 (m, 2H), 1.36 – 1.29 (m, 2H), 1.27 – 1.24 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 178.2, 155.9, 154.2, 142.1, 138.6, 126.6, 122.3, 120.9, 116.8, 107.7, 102.5, 59.5, 57.3, 56.9, 55.0, 50.5, 43.5, 38.0, 34.1, 33.5, 33.4, 27.4, 25.8, 25.4, 25.0, 24.9, 23.4, 19.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{38}N_3O_2$: 436.2964; found: 436.2964.

7-chloro-_N_-cyclohexyl-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy) quinolin-2-amine (3.2v):



Using 7-chloro-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy) quinoline 1-oxide (0.5 mmol) with dicyclohexylcarbodiimide (0.25 mmol) in accordance with GP-I, the title compound was obtained by using SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) as a yellow oil (282 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 1.8 Hz, 1H), 7.17 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.35 (d, *J* = 9.4 Hz, 1H), 3.74 (s, 1H), 2.63 (m, 2H), 2.14 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.87 – 1.82 (m, 2H), 1.71 – 1.67 (m, 3H), 1.64 – 1.60 (m, 7H), 1.53 – 1.51 (m, 2H), 1.31 (brs, 3H), 1.25 (brs, 10H), 1.15 – 1.12 (m, 5H), 1.08 – 1.06 (m, 4H), 0.88 – 0.84 (m, 12H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 161.8, 158.3, 149.4, 142.6, 136.0, 129.9, 127.8, 125.9, 123.8, 123.7, 123.2, 122.0, 118.2, 115.7, 91.8, 75.4, 49.8, 40.8, 39.5, 37.6, 37.5, 37.4, 33.4, 32.9, 32.1, 29.9, 29.5, 28.1, 25.9, 25.0, 24.9, 24.6, 23.4, 22.9, 22.8, 21.2, 20.8, 20.8, 19.9, 19.8, 19.8, 14.3, 12.9, 12.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{44}H_{65}ClN_2O_2$: 689.4808; found: 689.4837.

_N_-(2-(1H-indol-3-yl)ethyl)quinolin-2-amine (3.2w):



Using quinoline *N*-oxide with tryptamine isothiocyanate in accordance with GP-I, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a brown oil (210 mg, 73%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.72-7.67 (m, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.54-7.52 (m, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.21 (t, J = 7.8 Hz, 2H), 7.16-7.13 (m, 1H), 7.05 (s, 1H), 6.56 (d, J = 8.4 Hz, 1H), 4.95 (s, 1H), 3.85 (m, 2H), 3.15 (t, J = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 157.0, 148.1, 137.4, 136.6, 129.7, 127.6, 127.6, 126.1, 123.5, 122.3, 122.3, 122.1, 119.5, 119.0, 113.4, 111.6, 111.4, 42.0, 25.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{18}N_3$: 288.1496; found: 288.1531.

3.8.8. Experimental procedure for synthesis of 3.11 (scheme 3.13):

Conc. sulphuric acid (0.3 mL) was added to the 2-alkylamino quinoline (1 mmol, 1 equiv) containing 50 mL round-bottom flask equipped with a magnetic bar. The reaction mixture was stirred under air at 50 °C for 24 hours. After the starting material was completely consumed as confirmed by TLC, the mixture was neutralized using aq. NaOH solution, the desired product has precipitated out from the reaction mixture. The collected residue was dissolved in CH_2Cl_2 and the organic layer was separated in separating funnel and dried over anhydrous Na_2SO_4. All the volatile was removed under reduced pressure and the crude compound was purified through column chromatography (neutral alumina) using ethyl acetate: petroleum ether (1:1) as eluent to obtain the pure product as white solid **3.11** (118 mg, 82% isolated yield from **3.2a**; 130 mg, 90% isolated yield from **3.2s**).

2-Aminoquinoline (3.11):[7a] ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.29 – 7.26 (m, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.33 (br, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 157.0, 146.5, 138.8, 130.3, 127.7, 125.1, 123.4, 123.1, 112.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_9H_9N_2$: 145.0761; found: 145.0761.

3.8.9. Experimental procedure for synthesis of 3.13 (scheme 3.14):[15]

In an oven-dried sealed tube, **3.4d** (80 mg, 0.3 mmol, 1 equiv), diphenyl acetylene (81 mg, 0.45 mmol, 1.5 equiv), $Pd(MeCN)_2Cl_2$ (4 mg, 0.015 mmol, 4 mol%) and anhydrous $CuCl_2$ (85 mg, 0.63 mmol, 2.1 equiv) were added followed by dry DMF (2 mL). The reaction mixture was stirred at 110 °C for 12 hours under N_2 environment. After completion of the reaction as confirmed by TLC, the reaction was quenched with ice-water and extracted with ethyl acetate (10 mL × 2). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The reaction mixture was purified by silica-gel column chromatography (EtOAc: petroleum ether = 1:4) to get the pure product **3.13** as yellow solid (68% yield, 90 mg).

6-methoxy-2-(5-methyl-2,3-diphenyl-1*H*-indol-1-yl)quinoline (3.13):[7h] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 9.2 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.52 (brs, 1H), 7.43 (dd, J = 9.2, 2.4 Hz, 1H), 7.37 – 7.32 (m, 4H), 7.28 – 7.24 (m, 1H), 7.19 – 7.09 (m, 6H), 7.06 (d, J = 2.8 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.1, 149.4, 143.2, 136.3, 136.1, 135.8, 135.0, 132.1, 131.1, 130.5, 130.5, 128.8, 128.4, 128.2, 127.5, 126.3, 125.1, 122.7, 120.9, 119.3, 118.2, 111.8,

105.4, 55.8, 21.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{31}H_{25}N_2O$: 441.1962; found: 441.1973.

3.8.10. Computational studies

All calculations were performed using the Gaussian-16 program package[26] in the gas phase. Full geometry optimizations were carried out using Kohn-Sham hybrid-DFT B3LYP[27] level of theory and 6-311++G (d,p) basis set. Frequency calculations at the same method and basis set were performed to distinguish transition state structures (one imaginary frequency) and minima structures (no imaginary frequency) on the potential energy surface. The transition states were verified by the intrinsic reaction coordinate (IRC) calculations, wherever necessary.[28] Free energies were calculated by using frequency calculations at 130 °C to match the experimental conditions.

Table 3.7. Free Energies (G) and Total Energies (E) given in Hartree along with the number of imaginary frequencies[a]

Species	Free energy (G)	Total energy (E)	# Imaginary Frequency (NImag)
1st step: **1a** + **2a** → **3aa** + **2a'**			
1a+2a	-861.744421	-862.0004653	0
TS1A	-861.679478	-861.9474819	1
I-1A	-861.717711	-861.9897954	0
TS2A	-861.679845	-861.9490000	1
I-2A	-861.733587	-862.0074531	0
3aa+2a′	-861.849591	-862.1019336	0
1st step: **1a** + **4b** → **5ab** + **4b'**			
1a + 4b	-1166.637745	-1166.9241288	0
TS1B	-1166.583098	-1166.8843556	1
I-1B	-1166.606604	-1166.9102129	0
TS2B	-1166.588550	-1166.8900125	1
I-2B	-1166.629753	-1166.9324441	0
5ab + 4b'	-1166.734711	-1167.0208551	0
2nd step: **1a** + **2a'** → **3aa** + **CO_2**			
1a + 2a'	-763.766744	-763.9383098	0
TS3A	-763.708300	-763.8924805	1
I-3A	-763.735042	-763.9232523	0
TS4A	-763.697022	-763.8811722	1
I-4A	-763.757324	-763.9455762	0
3aa + CO_2	-763.869308	-764.0373900	0
2nd step: **1a** + **4b'** → **5ab** + **CO_2**			
1a + 4b'	-916.211660	-916.3983910	0
TS3B	-916.157748	-916.3585894	1
I-3B	-916.178027	-916.3814688	0
TS4B	-916.143789	-916.3423302	1
I-4B	-916.201999	-916.4060290	0
5ab + CO_2	-916.310262	-916.4968452	0

[a](G) is calculated at 130 °C to meet the experimental conditions. All the figures were generated using (G) values. All the transition states have one NImag and all the reactants, intermediates and products have zero NImag. All the calculations were performed at B3LYP level of DFT.

3.9. References:

1. (a) Wencel-Delord, J.; Glorius, F. C–H Bond Activation Enables the Rapid Construction and Late-Stage Diversification of Functional Molecules. *Nat. Chem.* **2013**, *5*, 369–375, (b) Guillemard, L.; Kaplaneris, N.; Ackermann, L.; Johansson, M. J. Late-Stage C–H Functionalization Offers New Opportunities in Drug Discovery. *Nat. Rev. Chem.* **2021**, *5*, 522–545, (c) Wu, G.; Zhao, T.; Kang, D.; Zhang, J.; Song, Y.; Namasivayam, V.; Kongsted, J.; Pannecouque, C.; De Clercq, E.; Poongavanam, V.; Liu, X.; Zhan, P. Overview of Recent Strategic Advances in Medicinal Chemistry. *J. Med. Chem.* **2019**, *62*, 9375– 9414, (d) Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M. Expanding the Medicinal Chemistry Synthetic Toolbox. *Nat. Rev. Drug Discovery* **2018**, *17*, 709– 727.

2. (a) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*; 5th Ed.; Wiley-Blackwell: New York, 2010; pp 249−288., (b) Afzal, O.; Kumar, S.; Haider, M. R.; Ali, M. R.; Kumar, R.; Jaggi, M.; Bawa, S. A Review on Anticancer Potential of Bioactive Heterocycle Quinoline. *Eur. J. Med. Chem.* **2015**, *97*, 871– 910, (c) Hu, Y. Q.; Gao, C.; Zhang, S.; Xu, L.; Xu, Z.; Feng, L. S.; Wu, X.; Zhao, F. Quinoline hybrids and their antiplasmodial and antimalarial activities. *Eur. J. Med. Chem.* **2017**, *139*, 22– 47, (d) Asif, M. Recent Efforts for the Development of Antitubercular Drug Containing Diazine Ring. *Med. Chem.* **2012**, *2*, 151−167, (e) Nikishkin, N. I.; Huskens, J.; Verboom, W. Transition Metal-Catalyzed Functionalization of Pyrazines. *Org. Biomol. Chem.* **2013**, *11*, 3583−3602, (f) Baumann, M.; Baxendale, I. R. An Overview of the Synthetic Routes to the Best Selling Drugs Containing 6-Membered Heterocycles. *Beilstein J. Org. Chem*. **2013**, *9*, 2265−2319, (g) Dolezal, M.; Zitko, J. Pyrazine Derivatives: A Patent Review (June 2012−present). *Expert Opin. Ther. Pat* **2014**, *25*, 33−47.

3. (a) Iwai, T.; Sawamura, M. Transition-Metal-Catalyzed Site- Selective C−H Functionalization of Quinolines beyond C2 Selectivity. *ACS Catalysis* **2015**, *5*, 5031−5040, (b) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. C−H Functionalization of Azines. *Chem. Rev.* **2017**, *117*, 9302−9332.

4. (a) Fourie, T.; Cromarty, D.; Duncan, N.; Wolter, K.; Naidoo, The Safety and Pharmacokinetics of Carprofen, Flunixin and Phenylbutazone in the Cape Vulture (Gyps coprotheres) Following Oral Exposure. *PLoS One* **2015**, *10*, e0141419, (b) Gao, Z.-G.; Verzijl, D.; Zweemer, A.; Ye, K.; Göblyös, A.; Ijzerman, A. P.; Jacobson, K. A. Functionally Biased Modulation of A3 Adenosine Receptor Agonist Efficacy and Potency by Imidazoquinolinamine Allosteric Enhancers. *Biochem. Pharmacol.* **2011**, *82*, 658−668, (c) Contreras, J.-M.; Rival, Y. M.; Chayer, S.; Bourguignon, J.-J.; Wermuth, C. G. Aminopyridazines as Acetylcholinesterase Inhibitors. *J. Med. Chem.* **1999**, *42*, 730– 741, (d) Manley, P. W.; Cowan-Jacob, S. W.; Buchdunger, E.; Fabbro, D.; Fendrich, G.; Furet, P.; Meyer, T.; Zimmermann, J. Imatinib: A Selective Tyrosine Kinase Inhibitor. *Eur. J. Cancer* **2002**, *38*, S19– S27, (e) Holden, J. K.; Lewis, M. C.; Cinelli, M. A.; Abdullatif, Z.; Pensa, A. V.; Silverman, R. B.; Poulos, T. L. Targeting Bacterial Nitric Oxide Synthase with Aminoquinoline-Based Inhibitors. *Biochemistry* **2016**, *55*, 5587- 5594, (f) Cinelli, M. A.; Li, H.; Pensa, A. V.; Kang, S.; Roman, L. J.; Martasek, P.; Poulos, T. L.; Silverman, R. B. Phenyl ether- and aniline-containing 2-aminoquinolines as potent and selective inhibitors of neuronal nitric oxide synthase. *J. Med. Chem.* **2015**, *58*, 8694– 8712, (g) Pfister, J. R. Isolation and Bioactivity of 2-Aminoquinoline from *Leucopaxillus albissimus*. *J. Nat. Prod.* **1988**, *51*, 969–970.

5. (a) Chichibabin, A. E.; Zeide, O. A. New Reaction for Compounds Containing the Pyridine Nucleus. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 1216−1236, (b) Bergstrom, F. W.; Fernelius, W. C. The Chemistry of the Alkali Amides. *Chem. Rev.* **1933**, *12*, 43– 179.

6. (a) Wang, D.; Désaubry, L.; Li, G.; Huang, M.; Zheng, S. Recent Advances in the Synthesis of C2-Functionalized Pyridines and Quinolines Using *N*-Oxide Chemistry. *Adv. Synth. Catal.* **2021**, *363*, 2 – 39, (b) Li, G.; Jia, C.; Sun, K. Copper-Catalyzed Intermolecular Dehydrogenative Amidation/Amination of Quinoline *N*-Oxides with Lactams/Cyclamines. *Org. Lett.* **2013**, *15*, 5198–5201, (c) Zhu, C.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. Copper-Catalyzed Direct Amination of Quinoline *N*-Oxides *via* C-H Bond Activation under Mild Conditions. *Org. Lett.* **2014**, *16*, 1840– 1843, (d) Li, G.; Jia, C.; Sun, K.; Lv, Y.; Zhao, F.; Zhou, K.; Wu, H. Copper (II)-Catalyzed Electrophilic Amination of Quinoline *N*-oxides with *O*-benzoyl Hydroxylamines. *Org. Biomol. Chem.* **2015**, *13*, 3207– 3210, (e) Yu, H.; Dannenberg, C. A.; Li, Z.; Bolm, C. Copper-Catalyzed Direct Sulfoximination of Heteroaromatic *N*-Oxides by Dual C– H/N– H Dehydrogenative Cross-Coupling. *Chem. - Asian J.* **2016**, *11*, 54– 57, (f) Biswas, A.; Karmakar, U.; Nandi, S.; Samanta, R. Copper-Catalyzed Direct, Regioselective Arylamination of *N*-Oxides: Studies to Access Conjugated π-Systems. *J. Org. Chem.* **2017**, *82*, 8933– 8942, (g) Wang, Z.; Han, M.-Y.; Li, P.; Wang, L. Copper-Catalyzed Deoxygenative C-2 Amination of Quinoline *N*-Oxides. *Eur. J. Org. Chem.* **2018**, *2018*, 5954– 5960, (h) Behera, A.; Sau, P.; Sahoo, A. K.; Patel, B. K. Cyano-Sacrificial (Arylthio)arylamination of Quinoline and Isoquinoline *N*-Oxides Using *N*-(2-(Arylthio)aryl)cyanamides. *J. Org. Chem.* **2018**, *83*, 11218– 11231, (i) Xie, L.-Y.; Peng, S.; Jiang, L.-L.; Peng, X.; Xia, W.; Yu, X.; Wang, X.-X.; Cao, Z.; He, W.-M. $AgBF_4$-Catalyzed Deoxygenative C2-amination of Quinoline *N*-Oxides with Isothiocyanates. *Org. Chem. Front.* **2019**, *6*, 167– 171.

7. (a) Yin, J. J.; Xiang, B. P.; Huffman, M. A.; Raab, C. E.; Davies, I. W. A General and Efficient 2-Amination of Pyridines and Quinolines. *J. Org. Chem.* **2007**, *72*, 4554– 4557, (b) Farrell, R. P.; Elipe, M. V. S.; Bartberger, M. D.; Tedrow, J. S.; Vounatsos, F. An Efficient, Regioselective Amination of 3,5-Disubstituted Pyridine *N*-Oxides Using Saccharin as an Ammonium Surrogate. *Org. Lett.* **2013**, *15*, 168– 171, (c) Londregan, A. T.; Jennings, S.; Wei, L. General and Mild Preparation of 2-Aminopyridines. *Org. Lett.* **2010**, *12*, 5254– 5257, (d) Chen, X.; Li, X.; Qu, Z.; Ke, D.; Qu, L.; Duan, L.; Mai, W.; Yuan, J.; Chen, J.; Zhao, Y. H-Phosphonate-Mediated Amination of Quinoline *N*-Oxides with Tertiary Amines: A Mild and Metal-Free Synthesis of 2-Dialkylaminoquinolines. *Adv. Synth. Catal.* **2014**, *356*, 1979– 1985, (e) Bi, W.-Z.; Sun, K.; Qu, C.; Chen, X.-L.; Qu, L.-B.; Zhu, S.-H.; Li, X.; Wu, H.-T.; Duan, L.-K.; Zhao, Y.-F. A direct metal-free C2-H functionalization of quinoline *N*-oxides: a highly selective amination and alkylation strategy towards 2-substituted quinolines. *Org. Chem. Front.* **2017**, *4*, 1595– 1600, (f) Bugaenko, D. I.; Yurovskaya, M. A.; Karchava, A. V. Quaternary *N*-(2-Pyridyl)-DABCO Salts: One-Pot in Situ Formation from Pyridine-*N*-oxides and Reactions with Nucleophiles: A Mild and Selective Route to Substituted *N*-(2-Pyridyl)-*N*′-ethylpiperazines. *J. Org. Chem.* **2017**, *82*, 2136– 2149, (g) Dhiman, A. K.; Chandra, D.; Kumar, R.; Sharma, U. Catalyst-Free Synthesis of 2-Anilinoquinolines and 3-Hydroxyquinolines via Three-Component Reaction of Quinoline *N*-Oxides, Aryldiazonium Salts, and Acetonitrile. *J. Org. Chem.* **2019**, *84*, 6962– 6969, (h) Kim, D.; Ghosh, P.; Kwon, N. Y.; Han, S. H.; Han, S.; Mishra, N. K.; Kim, S.; Kim, I. S. Deoxygenative Amination of Azine-*N*-oxides with Acyl Azides via [3 + 2] Cycloaddition**.** *J. Org. Chem.* **2020**, *85*, 2476–2485, (i) Nanaji, Y.; Kirar, S.; Pawar, S. V.; Yadav, A. K. A mild and metal-free synthesis of 2- and 1-alkyl/aryl/dialkyl-aminoquinolines and isoquinolines. *RSC Adv*. **2020**, *10*, 7628–7634.

8. (a) Sheldon, R. A. E factors, green chemistry and catalysis: an odyssey. *Chem. Commun.* **2008**, 3352–3365, (b) Sheldon, R. A. The *E* factor 25 years on: the rise of green chemistry and sustainability. *Green Chem.* **2017**, *19*, 18– 43, (c) Horvath, I. Introduction: Sustainable Chemistry. *Chem. Rev.* **2018**, *118*, 369–371, (d) Li, C. –J. Exploration of New Chemical Reactivities for Sustainable Molecular Transformations. *Chem.* **2016**, *1*, 423–437.

9. Loska, R. Recent Advances in Cycloaddition Reactions of Heterocyclic *N*-Oxides. In *Heterocyclic N-Oxides*, Larionov, O. V. Ed.; Springer International Publishing: Cham, 2017; pp 85-110.

10. Wang, Y.; Zhang, W. –X.; Xi, Z. Carbodiimide-based Synthesis of *N*-heterocycles: Moving from Two Classical Reactive Sites to Chemical Bond Breaking/Forming Reaction. *Chem. Soc. Rev.* **2020**, *49*, 5810 –5849.

11. (a) Azzena, U.; Carraro, M.; Pisano, L.; Monticelli, S.; Bartolotta, R.; Pace, V. Cyclopentyl Methyl Ether: An Elective Ecofriendly Etheral Solvent in Classical and Modern Organic Chemistry. *ChemSusChem.* **2019**, *12*, 40– 70, (b) Watanabe, K.; Yamagiwa, N.; Torisawa, Y. Cyclopentyl Methyl Ether as a New and Alternative Process Solvent. *Org. Process Res. Dev.* **2007**, *11*, 251–258, (c) Antonucci, V.; Coleman, J.; Ferry, J. B.; Johnson, N.; Mathe, M.; Scott, J. P.; Xu, J. Toxicological Assessment of 2-Methyltetrahydrofuran and Cyclopentyl Methyl Ether in Support of Their Use in Pharmaceutical Chemical Process Development. *Org. Process Res. Dev.* **2011**, *15*, 939–941, (d) Prat, D.; Hayler, J.; Wells, A. A survey of solvent selection guides. *Green Chem.* **2014**, *16*, 4546–4551.

12. (a) Roy, B. C.; Debnath, S.; Chakrabarti, K.; Paul, B.; Maji, M.; Kundu, S. *ortho*-Amino Group Functionalized 2,2′-Bipyridine Based Ru(II) Complex Catalysed Alkylation of Secondary Alcohols, Nitriles and Amines using Alcohols. *Org. Chem. Front.* **2018**, *5*, 1008– 1018, (b) Roy, B. C.; Samim, S. A.; Panja, D.; Kundu, S. Tandem Synthesis of Quinazolinone Scaffolds from 2-Aminobenzonitriles using Aliphatic Alcohol–Water System. *Catal. Sci. Technol.* **2019**, *9*, 6002–6006, (c) Carroll, J.; Woolard, H. G.; Mroz, R.; Nason, C. A.; Huo, S. Regiospecific Acylation of Cycloplatinated Complexes: Scope, Limitations, and Mechanistic Implications. *Organometallics* **2016**, *35*, 1313–1322.

13. (a) Yo, B.; Cheng, B. –B.; Liu, W. –Q.; Li, W.; Wang, S. –S.; Cao, J.; Hu, C. –W. Atmospheric Pressure of CO_2 as Protecting Reagent and Reactant: Efficient Synthesis of Oxazolidin-2-ones with Carbamate Salts, Aldehydes and Alkynes. *Adv. Synth. Catal.* **2016**, *358*, 90–97; (b) Yang, T.; Lu, H.; Qiu, R.; Hong, L.; Yin, S. F.; Kambe, N. Photocatalyst-free Synthesis of Indazolones under CO_2 Atmosphere. *Chem. –Asian J.* **2019**, *14*, 1436–1442; (c) Mase, N.; Horibe, T. Organocatalytic Knoevenagel Condensations by Means of Carbamic Acid Ammonium Salts. *Org. Lett.* **2013**, *15*, 1854–1857; (d) Ghosh, S.; Purkait, A.; Jana, C. K. Environmentally benign decarboxylative *N*-, *O*-, and *S*-acetylations and acylations. *Green Chem.* **2020**, *22*, 8721–8727.

14. (a) Hisano, T.; Matsuoka, T.; Tsutsumi, K.; Muraoka, K.; Ichikawa, M. Reaction of Aromatic *N*-Oxides with Dipolarophiles. IV. Factors Affecting the 1, 3-Cycloaddition of Pyridine 1-Oxide with Phenyl Isocyanates. *Chem. Pharm. Bull.* **1981**, *29*, 3706–3712; (b) Du, S.; Pi, C.; Wan, T.; Wu, Y.; Cui, X. I_2-Mediated Iodization / [3+2] Cycloaddition / Nucleophilic Addition Tandem Reaction: Synthesis of Polyheterocycles Bearing Furoquinoline and Maleimide. *Adv. Synth. Catal.* **2019**, *361*, 1766 – 1770.

15. Chen, J.; Pang, Q.; Sun, Y.; Li, X. Synthesis of *N*-(2-Pyridyl)indoles *via* Pd(II)-Catalyzed Oxidative Coupling. *J. Org. Chem.* **2011**, *76*, 3523–3526.

16. Sheldon, R. A. Metrics of Green Chemistry and Sustainability: Past, Present, and Future. *ACS Sustainable Chem. Eng.* **2018**, *6*, 32-48.

17. Paul, B.; Maji, M.; Panja, D.; Kundu, S. Tandem Transformation of Aldoximes to N-Methylated Amides using Methanol. *Adv. Synth. Catal.* **2019**, *361*, 5357 – 5362.

18. (a) Bering, L.; Antonchick, A. P. Regioselective Metal-Free Cross-Coupling of Quinoline *N*-Oxides with Boronic Acids. *Org. Lett.* **2015**, *17*, 3134– 3137. (b) Frei, P.; Jones, D. H.; Kay, S. T.; McLellan, J. A.; Johnston, B. F.; Kennedy, A. R.; Tomkinson, N. C. O. Regioselective Reaction of Heterocyclic *N* -Oxides, an Acyl Chloride, and Cyclic Thioethers. *J. Org. Chem.* **2018**, *83*, 1510– 1517. (c) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. Regioselective Bromination of Fused Heterocyclic *N*-Oxides. *Org. Lett.* **2013**, *15*, 792– 795. (d) Bjørsvik, H.-R.; Gambarotti, C.; Jensen, V. R.; Gonźalez, R. R. A Novel Efficient Deoxygenation Process for *N*-Heteroarene *N*-Oxides. *J. Org. Che*m. **2005**, *70*, 3218– 3224. (e) Singh, A. N.; Thumme, R. P. 1,5-Naphthyridine as a New Linker for the Construction of Bridging Ligands and Their Corresponding Ru(II) Complexes. *Inorg. Chem.* **2009**, *48*, 6459–6470. (f) Dyer, R. M. B.; Hahn, P. L.; Hilinski, M. K. Selective Heteroaryl *N*-Oxidation of Amine-Containing Molecules. *Org. Lett.* **2018**, *20*, 2011−2014.

19. (a) Busacca, C. A.; Milligan, J. A.; Rattanangkool, E.; Ramavarapu, C.; Chen, A.; Saha, A. K.; Li, Z.; Lee, H.; Geib, S. J.; Wang, G.; Senanayake, C. H.; Wipf, P. Synthesis of phosphaguanidines by hydrophosphination of carbodiimides with phosphine boranes. *J. Org. Chem.* **2014**, *79*, 9878−9887. (b) Ali, A. R.; Ghosh, H.; Patel, B. K. A greener synthetic protocol for the preparation of carbodiimide. *Tetrahedron Lett*. **2010**, *51*, 1019-1021. (c) Peddarao, T.; Baishya, A.; Barman, M. K.; Kumar, A.; Nembenna, S. Metal-free access of bulky *N*, *N*′-diarylcarbodiimides and their reduction: bulky *N*,*N*′-diarylformamidines. *New J. Chem.* **2016**, *40*, 7627– 7636.

20. Kim, T.; Kim, Y.-J.; Han, I.-H.; Lee, D.; Ham, J.; Kang, K. S.; Lee, J. W. The Synthesis of Sulforaphane Analogues and Their Protection Effect Against Cisplatin Induced Cytotoxicity in Kidney Cells. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 62-66.

21. Chen, Y.; Fuyue, L.; Wang, G.; Wang, H.; Lu, C.; Guo, H.; Amant, C. St.; Sun, S.; Xing, Y. Synthesis of 1,2,4-Oxadiazolidines *via* [3+2] Cycloaddition of Nitrones with Carbodiimides. *New J. Chem.*, **2019,** *43*, 4329-4332.

22. Wiggall, K. J.; Richardson, S. K. A Versatile Synthesis of Functionalised 2-Aminoquinolines by Mercury Controlled Cyclisation of 2-Vinylphenylthioureas. *J. Heterocycl. Chem*. **1995,** *32*, 867–870.

23. Zhang, X.; Wang, T.-L.; Huo, C.-D.; Wang, X.-C.; Quan, Z.-J. Base-Controlled Chemoselectivity Reaction of Vinylanilines with Isothiocyanates for Synthesis of Quinolino-2-thione and 2-Aminoquinoline Derivatives. *Chem. Commun.* **2018**, *54*, 3114-3117.

24. Liang, Y.; Jiang, H.; Tan, Z.; Zhang, M. Direct *α*-C–H Amination using Various Amino Agents by Selective Oxidative Copper Catalysis: A Divergent Access to Functional Quinolines. *Chem. Commun*. **2018**, *54*, 10096−10099.

25. Koley, M.; Schnürch, M.; Mihovilovic, M. D. Metal assisted synthesis of mono and diamino substituted pyridines. *Tetrahedron*. **2011**, *67*, 4169−4178.

26. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich,

A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, Revision C.01, Gaussian, Inc., Wallingford CT, 2016.

27. (a) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys*, **1993**, *98*, 5648-5652. (b) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B.* **1988**, *37*, 785-789.

28. Fukui, K. The path of chemical reactions - the IRC approach. *Acc. Chem. Res.* **1981**, *14*, 363-368.

Chapter-4

Copper-Catalyzed Oxidative Dehydrogenative Reaction of Quinoline-*N*-Oxides with Donor–Acceptor Cyclopropanes: Facile Installation of Tertiary Alkyl Motif at C2 Position

4.1. Introduction

Among different functionalised quinoline-based compounds, C2-alkylated quinolines are of utmost interest in medicinal chemistry due to their excellent therapeutic potential.[1] For example, pitavastatin (I) is a new generation statin drug used for prevention of cardiovascular disease by lowering cholesterol level in blood.[1f] Primaquine analogue drug II is used for its improved anti-malarial property.[1g] Similarly, C2-alkylated quinoline-based drugs are also used for their antileishmanial, antidiabetic, antioxidant and antibacterial properties, among others.[1] Besides these, other C2-alkylated *N*-heteroarene based drugs such as rosuvastatin (VI), another statin drug used for treatment of high-risk cardiovascular disease, are also in high demand for their medicinal applications (figure 4.1).[2] Therefore, considerable efforts have been made for the efficient synthesis of such C2-alkylated azine derivatives.

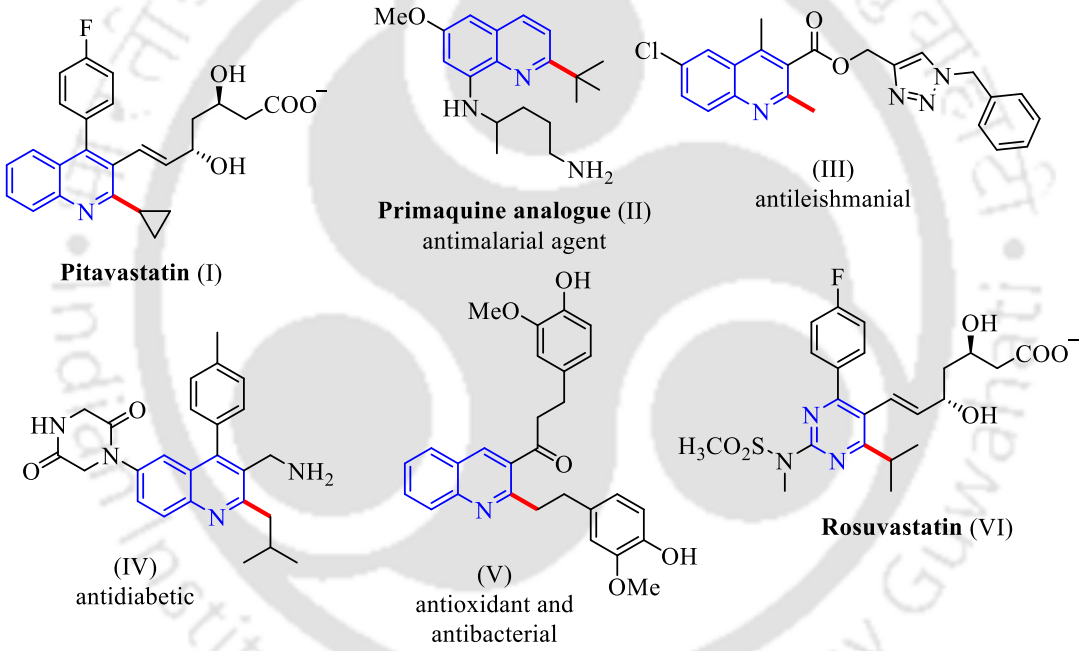
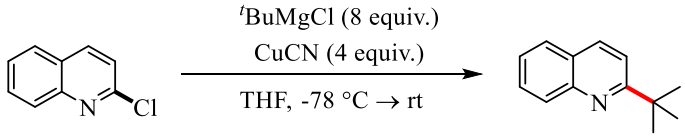


Figure 4.1: representative examples of C2-alkylated N-heteroarene compounds

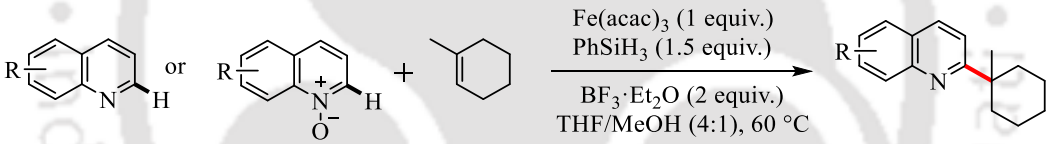
Over the past few decades, several methods have been developed for the synthesis of C2-alkylated quinolines using either prefunctionalised or non-functionalised precursors.[3] Martin and Taylor in 1974 described the C2-alkylation of 2-chloroquinoline with Wittig reagent.[3c] Similarly, alkyl lithium, Grignard reagents etc. were also explored with 2-haloheteroarene for C2-alkylation. Thorsett and Stermitz observed that when Grignard reagent containing *β*-hydrogen was used, corresponding alkene product due to *β*-hydride elimination was formed along with reduction of 2-chloroquinoline to quinoline.[3d] In addition, most approaches focus primarily on the introduction of primary alkyl groups[4] and secondary alkyl groups.[5] In contrast, the scope and diversity of the tertiary alkyl motif are limited, whereas, tertiary alkyl-substituted quinoline derivatives are of important physicochemical values.[6] Patel and co-workers reported in 1987 the introduction of *tert*-butyl group to 2-haloquinoline using a 2:1 mixture of Grignard

reagent and Cu(I) salt where they found that the common occurrence of *β*-hydride elimination in such reactions was dormant in their protocol.[6a]



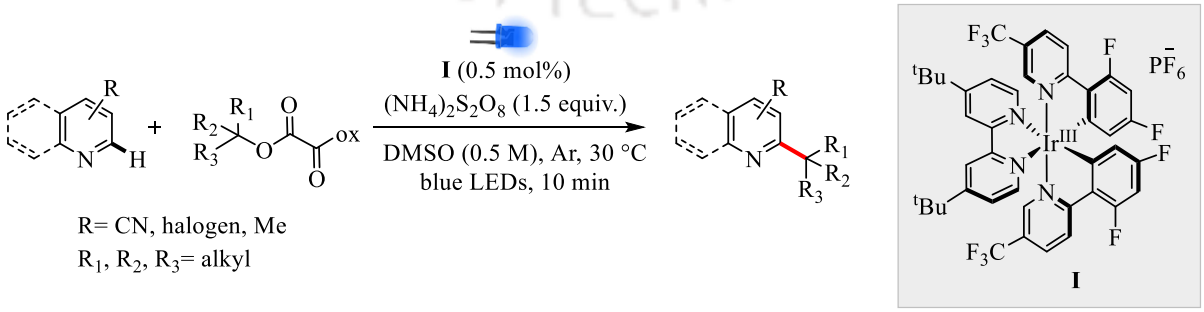
Scheme 4.1: C2-alkylation of 2-haloquinolines using Grignard reagent/Cu(I) salt

Along with the conventional nucleophilic reactions, photoredox- or Minisci-type C-H alkylation of *N*-heteroarenes (or *N*-oxides) have also been documented.[7] These reactions are believed to proceed *via* the *in-situ* formation of carbon-based radical species. A wide variety of radical precursors have been employed for this transformation, such as a simple alkane,[7a] alkene,[7b] alkyl-halides,[7c] alkyltrifloroborate,[7d] xanthate,[7e] oxalate,[7f] alcohol,[7g] carboxylic acid,[7h] and acid chloride.[7i] However, most of these studies are limited to the insertion of adamantyl or *tert*-butyl groups as tertiary alkyl motifs into *N*-heteroarenes. Baran *et al.*, in 2017, demonstrated the reductive Minisci alkylation of quinolines using 1-methylcyclohexene as the donor olefin, resulting in the generation of 3º-alkyl group at C2-position of quinolines.[7b] The presence of Lewis acidic $BF_3{\cdot}Et_2O$ was necessary to activate the heteroaromatic substrate. As discussed in the chapter 1, the reductive radical generation pathway eliminates the need of an external oxidant. Although the protocol was very elegant, but the yields were low, which was attributed to the reduction of the heteroarenes as well as the alkenes. They also faced the problem of regioisomeric mixtures, which could be approached by performing the reaction with the corresponding *N*-oxides.



Scheme 4.2: reductive Minisci alkylation of quinolines/quinoline *N*-oxides

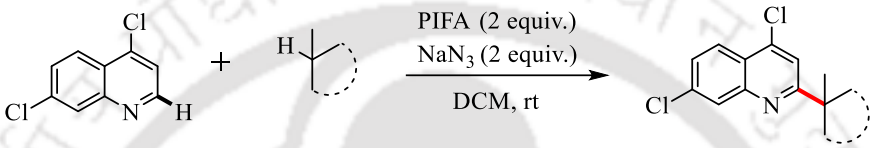
In 2019, Overmann and group demonstrated the use of *tert*-alkyl oxalate as precursor for 3°-alkyl radicals under photoredox conditions. Interestingly, this reaction also worked under thermal condition without the catalyst as the oxidant $(NH_4)_2S_2O_8$ was sufficient to generate the radicals under those conditions. They found computationally that the addition of *tert*-alkyl radical to protonated lepidine was an endothermic reversible process which, according to them, might be the reason these radicals were left unexplored. When quinoline was subjected to the reaction conditions, it gave mixture of C2/C4-substituted isomers referring to the lack of regioselectivity.[7f]



Scheme 4.3: photoredox Minisci alkylation of quinolines using *tert*-alkyl oxalate

Though this radical-based approach is promising, developing more practical methods without the use of expensive photocatalyst, special-light sources, or chemical oxidant-free conditions is highly desirable. Moreover, selectivity (C2 vs. C4 position) remains one of the difficult challenges in the Minisci chemistry,[7] where mixture of regioisomers is often obtained if either of the positions is not blocked.

In addition to these approaches, one more protocol is the cross-dehydrogenative coupling of azines or azine *N*-oxides involving direct cleavage of C-H bonds and concomitant functionalization to form C-C bonds rendering a step- and atom-economical process. In 2013, Wu *et al.* reported Pd-catalysed C2 alkylation of quinoline *N*-oxide by cross-dehydrogenative coupling with saturated heterocycles although it included only one example of tertiary carbon substitution.[5d] In the same year, Antonchick *et al.* described oxidative coupling of quinoline with alkanes which involved broader substrate scope considering generation of quaternary carbon center.[7a]

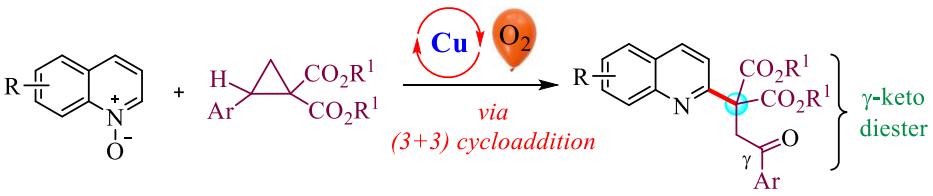


Scheme 4.4: hypervalent iodine-mediated cross-coupling reaction of quinoline with alkane

But along with being a waste-effective way, this approach has inherent challenges to overcome. Although reported as dehydrogentaive coupling, hydrogen gas is not usually the by-product in such reactions which is difficult from thermodynamic point of view. So, these processes require stoichiometric amount of an oxidant as an external driving force.[8] Again, in reactions involving azine *N*-oxides, sometimes, the product retains the N-O moiety which require additional steps to give the desired azine derivative.[9] Therefore, it is deemed desirable to develop selective alkylated heteroaromatic compounds in an environmentally benign manner by using an inexpensive and easily accessible catalyst.

4.2. Present work

Owing to the 1,3-zwitterion equivalent[10] nature of the donor–acceptor (D–A) cyclopropanes, and the presence of ring strain (27.5 kcal mol^{-1}) and vicinal substitution of D–A groups,[11] I envisaged that D–A cyclopropanes might react with heteroaromatic *N*-oxides *via* (3+3)-cycloaddition to form the corresponding cycloadducts.[12,13] Subsequent aromatization could lead to selective C-alkylated heteroaromatic compounds. In the course of our studies on selective C-H functionalization of heteroaromatic *N*-oxides, herein, I report copper-catalyzed C2-selective tertiary alkylation of fused heteroaromatic *N*-oxides with donor–acceptor cyclopropanes (D-A cyclopropanes) under aerobic conditions (scheme 4.5). The catalytic protocol provides a quaternary carbon center at the C2 position of the heteroaromatic moiety and forms an unprecedented biologically important motif called γ-keto diester,[14] which further shows the usefulness of the present method. Notably, the reaction offers an efficient construction of C_{sp}^3(cyclopropane)-C_{sp}^2(heteroarene) bonds *via* oxidative dehydrogenative reaction without the need of any external chemical oxidant or additives.



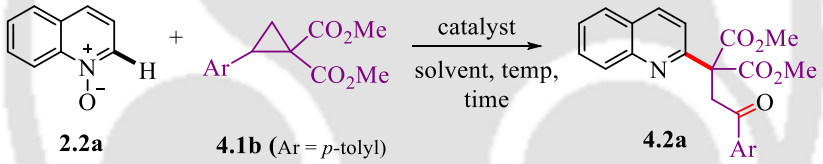
Scheme 4.5: $Cu(OTf)_2$-catalysed C2-alkylation of quinoline *N*-oxide with D-A cyclopropanes

4.3. Results and discussion

4.3.1. Optimisation of reaction conditions

The above hypothesis was initially executed by the reaction of quinoline *N*-oxide (**2.2a**, 1 equiv) and dimethyl 2-(*p*-tolyl) cyclopropane-1,1-dicarboxylate (**4.1b**, 1 equiv) in dry acetonitrile with 10 mol% of $Cu(OTf)_2$ for 48 h under argon atmosphere at 90 °C. Surprisingly, unusual oxidized γ-keto diester product **4.2a** was obtained, albeit in only an 18% yield (table 1, entry 1). Compound **4.2a** was unambiguously confirmed by X-ray diffraction analysis (figure 4.2). Under the same reaction condition with the 2 equiv of *N*-oxide **2.2a**, the yield of the desired product **4.2a** slightly improved to 31% (entry 3). Interestingly, when the reaction was carried out under air, product **4.2a** was obtained in 51% yield (entry 4). The yield of **4.2a** substantially enhanced to 81% when the reaction was carried out under oxygen atmosphere (entry 5). Decreasing the catalyst loading or the reaction time only resulted in the incomplete conversion of **4.1b,** thereby, producing lower yields of **4.2a** (entry 6-7). For further optimization, the reaction has been analyzed by utilizing a series of other Lewis acid catalysts (entry 8-14), where it was found that $Cu(OTf)_2$ gave the best results. Next, various solvents were investigated where acetonitrile was found to be the appropriate solvent for the present protocol (entry 15-18). Therefore, I fixed the optimized reaction conditions as **2.2a** (2 equiv), **4.1b** (1 equiv), $Cu(OTf)_2$ (10 mol%), 90 °C for 48 h under oxygen atmosphere in acetonitrile (2 mL).

Table 4.1. Optimisation of reaction conditions[a]



2.2a **4.1b** (Ar = *p*-tolyl) **4.2a**

Entry	**1a** (equiv)	catalyst (10 mol%)	environment	solvent	yield (%)
1	1	$Cu(OTf)_2$	Ar	CH_3CN	18
2	1.5	$Cu(OTf)_2$	Ar	CH_3CN	25
3	2	$Cu(OTf)_2$	Ar	CH_3CN	31
4	2	$Cu(OTf)_2$	air	CH_3CN	51
5	2	$Cu(OTf)_2$	O_2	CH_3CN	81
6[b]	2	$Cu(OTf)_2$	O_2	CH_3CN	55
7[c]	2	$Cu(OTf)_2$	O_2	CH_3CN	49
8	2	$Cu(OAc)_2$	O_2	CH_3CN	n.d.
9	2	CuI	O_2	CH_3CN	n.d.
10	2	$MgBr_2$	O_2	CH_3CN	n.d.
11	2	$FeCl_3$	O_2	CH_3CN	trace
12	2	$Ca(OTf)_2$	O_2	CH_3CN	n.d.
13	2	$Bi(OTf)_3$	O_2	CH_3CN	n.d.
14	2	$BF_3•OEt_2$	O_2	CH_3CN	n.d.

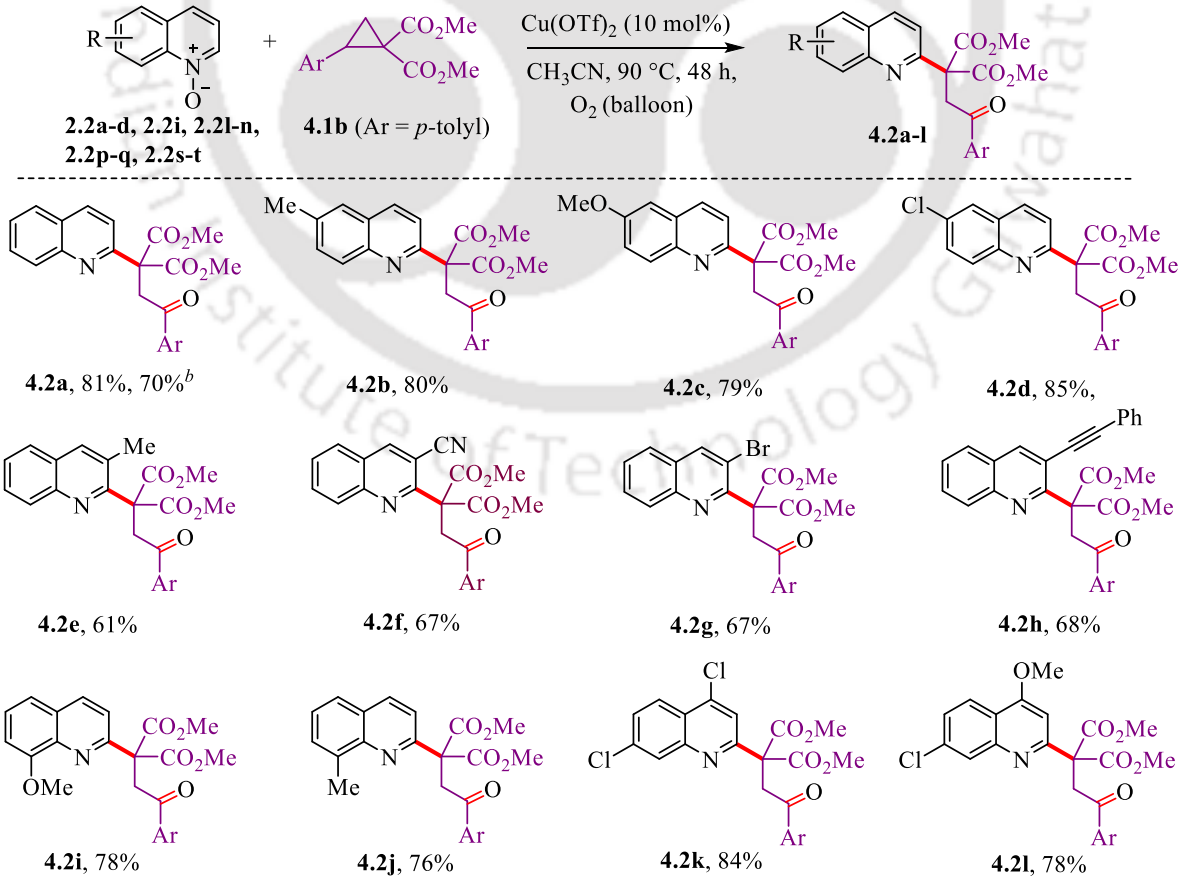
15	2	$Cu(OTf)_2$	O_2	THF	47
16	2	$Cu(OTf)_2$	O_2	DCE	58
17	2	$Cu(OTf)_2$	O_2	DMSO	40
18	2	$Cu(OTf)_2$	O_2	Toluene	32

[a]Reaction conditions: **2.2a** (x mmol), **4.2b** (0.4 mmol), catalyst (10 mol%) in solvent (2 mL) at 90 °C for 48 h (under Ar, air, O_2), isolated yield. [b]catalyst (5 mol%) was used. [c]The reaction was examined after 24 h.

4.3.2. Substrate scope with different quinoline *N*-oxides

With the optimized conditions in hand, the substrate scope of this reaction was investigated by employing a variety of substituted quinoline *N*-oxides with cyclopropane **4.1b** as the standard substrate (table 4.2). Quinoline *N*-oxides with a wide range of functional groups having both electron-donating (*e.g.* −Me, −OMe) and electron-withdrawing (*e.g.* −Cl, −Br, −CN, and −C≡CPh) groups as substituents were efficiently reacted to obtain the desired products with moderate to good yields (61-85%). The *N*-oxides containing electron-withdrawing substituents such as **2.2d** and **2.2s** gave slightly higher yields of the corresponding products than the electron-donating substituent containing *N*-oxides **2.2b-c**, **2.2t**. Interestingly, substrates having substituents near the cycloaddition site of *N*-oxide such as C3 substituted *N*-oxides **2.2i-n** and C8 substituted *N*-oxides **2.2p-q** reacted efficiently with **4.1b** leading to the desired C2-alkylated products in 61-78% yield. The present reaction condition tolerated the halogen functional groups, which can be beneficial for further functionalization. It is worth noting that

Table 4.2. substrate scope for C2-alkylation of different quinoline *N*-oxides[a]

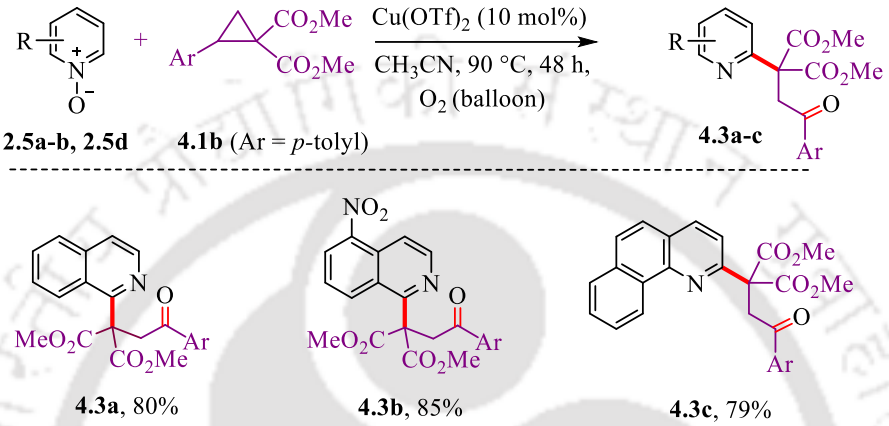


[a]Reaction conditions: **2.2** (0.8 mmol), **4.1b** (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol) in CH_3CN (2 mL) at 90 °C for 48 h under 1 atm. of oxygen (oxygen balloon), isolated yield. [b]Gram-scale reaction.

in the case of the substrate 4,7-dichloroquinoline *N*-oxide **2.2s**, though C4 substituent chloro group is susceptible to nucleophilic attack, the C2-alkylated product **4.2k** was obtained solely in 84% yield, indicating impressive selectivity of our present protocol.

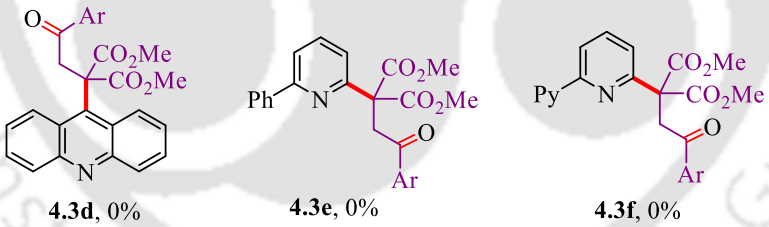
4.3.3. Substrate scope with other *N*-heterocyclic *N*-oxides

Table 4.3. substrate scope for C2-alkylation of different other *N*-heteroarene *N*-oxides[a]



[a]Reaction conditions: **2.5** (0.8 mmol), **4.1b** (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol) in CH_3CN (2 mL) at 90 °C for 48 h under 1 atm. of oxygen (oxygen balloon), isolated yield. [b]Gram-scale reaction.

Table 4.4. failed substrates for C2-alkylation of different other *N*-heteroarene *N*-oxides[a]

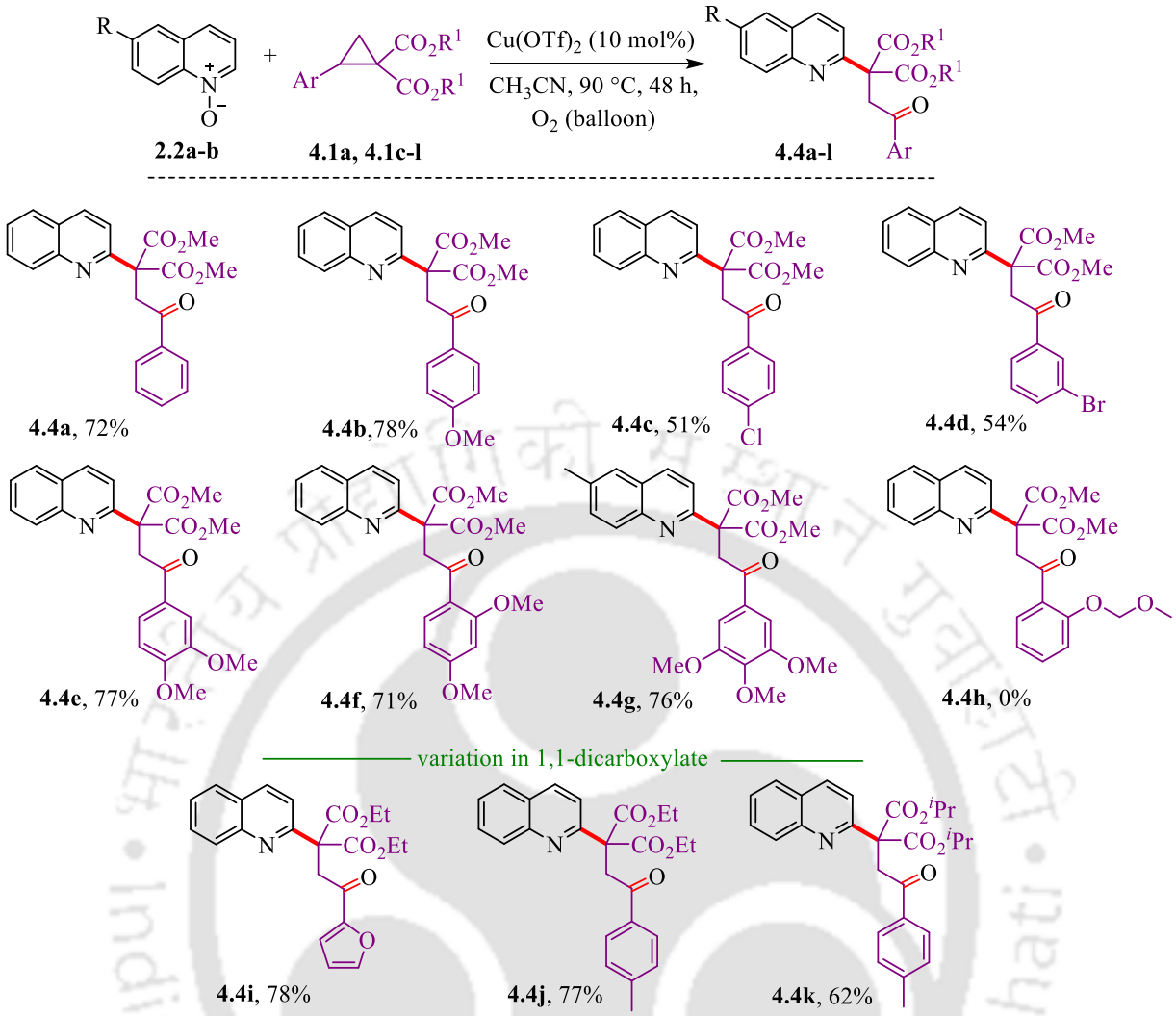


To our delight, the method was successfully extended to other *N*-heteroaromatic scaffolds such as isoquinoline *N*-oxides **2.4a-b** and benzo[*h*]quinoline- *N*-oxides (**2.4d**), giving the corresponding products **4.3a-c** in good yields (table 4.3). However, I failed to obtain the alkylated product **4.3d** by the reaction of acridine *N*-oxide and **4.1b**. This example indirectly suggests that 1,3-dipolar cycloaddition site of *N*-oxide is necessary for the success of such transformation. Moreover, pyridine *N*-oxides derivatives also did not give desired C2-alkylated products (**4.3e**, **4.3f**) (table 4.4).

4.3.4. Substrate scope with different D-A cyclopropanes

Next, the scope of the reaction was expanded for the synthesis of C2-alkylated quinoline derivatives by using a series of cyclopropanes **4.1a, 4.1c-k** with quinoline *N*-oxide **2.2a** as the standard substrate (table 4.5).

Table 4.5. substrate scope for C2-alkylation with different D-A cyclopropanes[a]



[a]Reaction conditions: **2.2a-b** (0.8 mmol), **4.1** (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol) in CH_3CN (2 mL) at 90 °C for 48 h under 1 atm. of oxygen (oxygen balloon), isolated yield.

Cyclopropanes bearing 4-methoxy (**4.1c**), and 4-chloro (**4.1d**) substituents at the aryl ring afforded the target product **4.4b** and **4.4c** in 78% and 51% yields, respectively. Similarly, cyclopropane (**4.1e**) having a 3-bromo congener gave **4.4d** in 54% yield. This suggests that electron-donating group substituted aryl moiety on the cyclopropane affords a better outcome for the reaction compared to electron-withdrawing group substituted aryl moiety. Substrates containing polysubstituted aromatic ring in the cyclopropane derivative such as 3,4-dimethoxy (**4.1f**)-, 2,4-dimethoxy (**4.1g**)-, and 3,4,5-trimethoxy (**4.1h**) afforded the products **4.4e-g** in 71-77% yields. In contrast, the 2-(methoxymethyl)phenyl cyclopropane derivative **4.1i** was incompatible with this method, probably due to the bulkiness of the methoxymethyl group. Interestingly, furan-bearing cyclopropane **4.1j** successfully participated in the reaction to provide the desired product **4.4i** in 78% yield. Besides this, other 1,1-diester variants of D−A cyclopropanes, such as **4.1k** and **4.1l**, reacted smoothly to produce the desired product **4.4j** and **4.4k** in good yields.

4.3.5. Crystal structures of compounds 4.2a and 4.2d

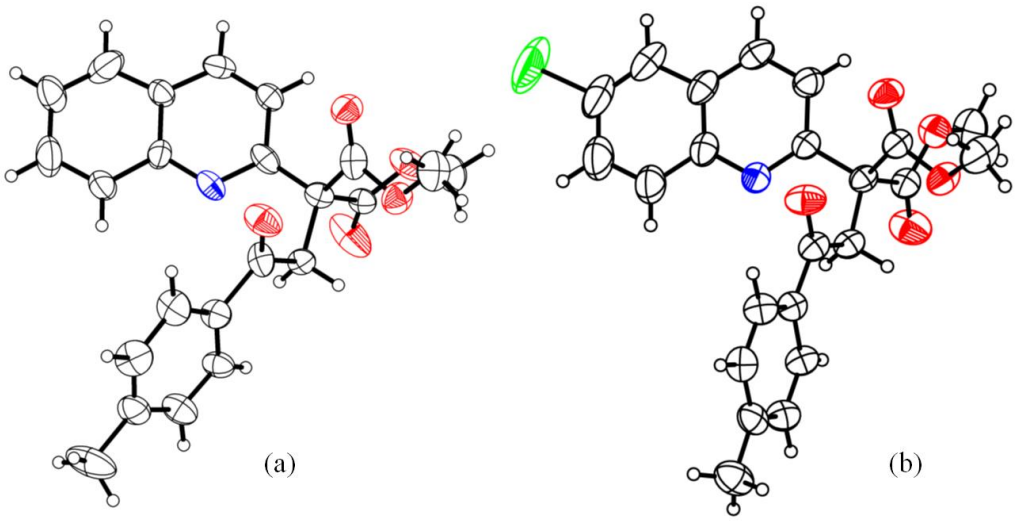
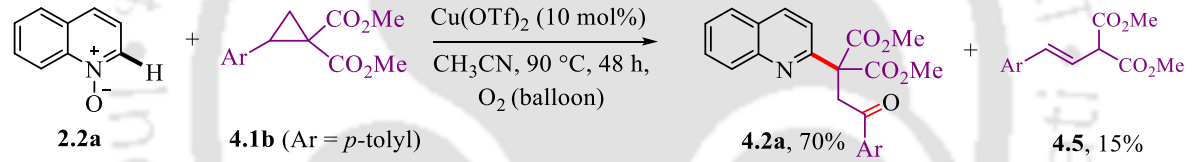


Figure 4.2. ORTEP Structure of **4.2a** (a) and **4.2d** (b) (thermal ellipsoids are drawn with 50% probability level).

4.3.6. Gram scale synthesis

To check the applicability of the protocol in large-scale, I have carried out the C2-alkylation of *N*-oxide **2.2a** with **4.1b** in gram scale, when the desired product **4.2a** was formed in 70% yield (scheme 4.6). Along with **4.2a**, small amount of styrylmalonate **4.5** was also formed.

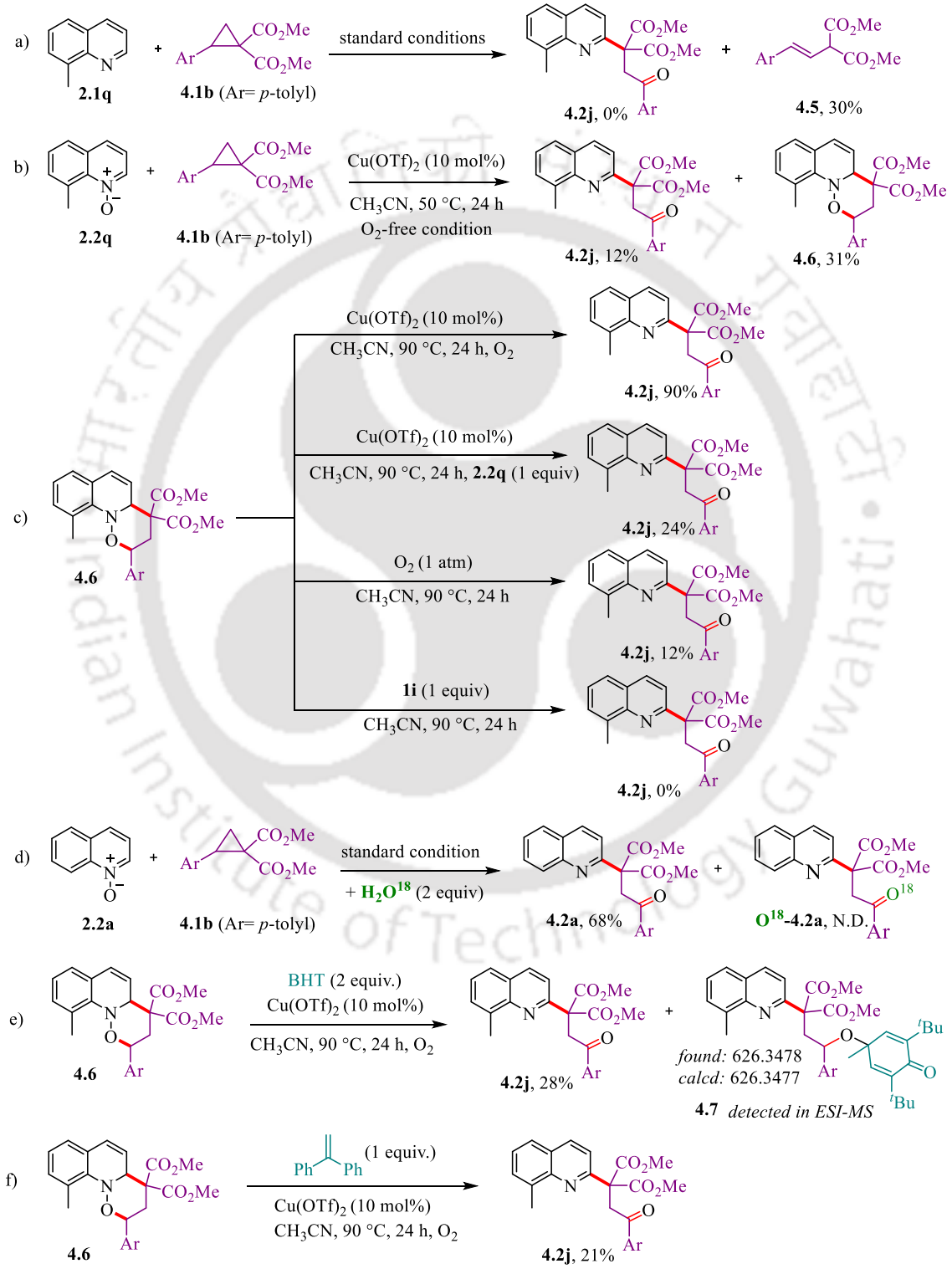


Scheme 4.6: $Cu(OTf)_2$-catalysed C2-alkylation of quinoline *N*-oxide with **4.1b** in gram-scale

4.3.7. Mechanistic investigations

To get insight into the reaction pathway, a few control experiments were performed. The reaction of quinoline **2.1q** and cyclopropane **4.1b** under standard conditions gave no desired product, suggesting the important role of *N*-O group in this transformation (scheme 4.7a). When *N*-oxide **2.2q** was treated with **4.1b** at 50 °C for 24 hours under oxygen-free conditions, intermediate **4.6** was isolated in 31% yield along with product **4.2j** (12%) (scheme 4.7b). The NMR and ESI-MS spectroscopic data suggested that the species **4.6** is a (3+3)-cycloadduct. Compound **4.6** could be converted entirely into product **4.2j** under the optimal reaction conditions, further supporting cycloadduct **4.6** as the reaction intermediate in this transformation. To understand the role of molecular oxygen in the oxidation process, I have performed control experiments using cycloadduct **4.6** (scheme 4.7c). Experimental data revealed that the combination of $Cu(OTf)_2$ (10 mol%) and molecular O_2 could oxidize **4.6** to the final product **4.2j** in 90% yield whereas, $Cu(OTf)_2$ (10 mol%) and *N*-oxide **2.2q** together lead to the desired product in only 24% yield. Meanwhile, when **4.6** was treated with only molecular oxygen, the desired product **3i** was obtained in 12% yield, and no conversion was achieved in the presence of *N*-oxide **2.2q** or copper (II) triflate individually. These 4 experiments suggested that molecular oxygen is superior to *N*-oxide in this oxidation process. When the reaction was performed in the presence of $H_2{}^{18}O$, no ^{18}O incorporation product **O^{18}-4.2a** was detected by HRMS, which suggests that the present transformation may occur *via* the intramolecular oxygen atom transfer pathway (scheme 4.7d). Interestingly, when **4.6** was

subjected to the reaction with the radical trapping agent BHT, product **4.2j** was obtained with only 28% yield (scheme 4.7e). ESI-MS analysis of the crude reaction mixture indicated the likely formation of BHT-adduct **4.7**, implying a possible radical pathway involved in the reaction (figure 4.3). Further, by using a different radical quencher 1,1-diphenylethylene in the reaction mixture, the yield of the product was again found to be decreased to 21% (scheme 4.7f). Though these experiments do not provide concluding evidence for the radical pathway, the involvement of such species in the current transformation cannot be ruled out.



Scheme 4.7: control experiments

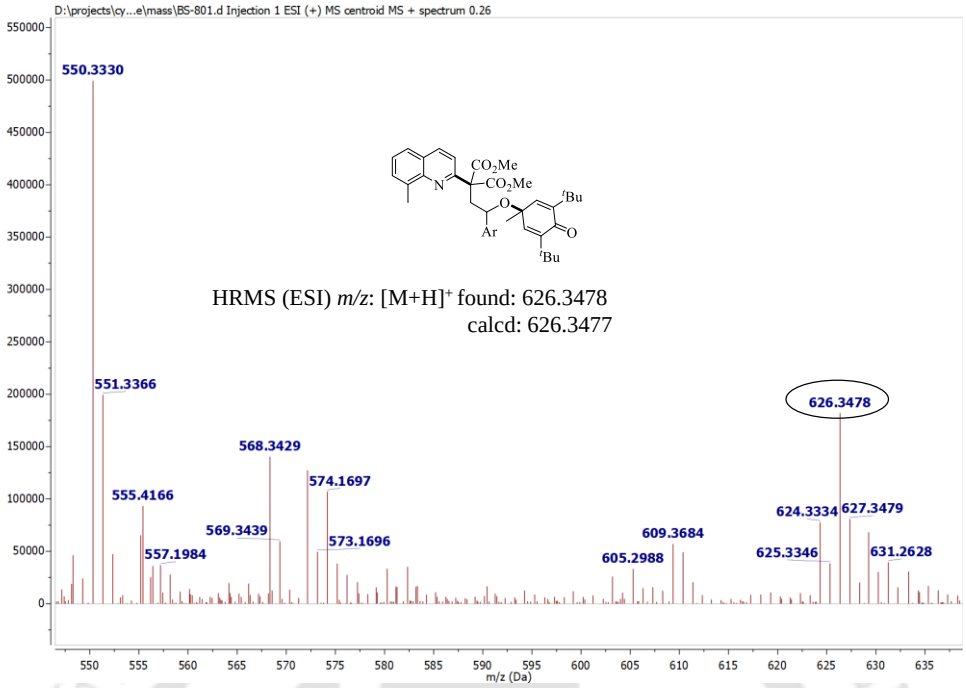
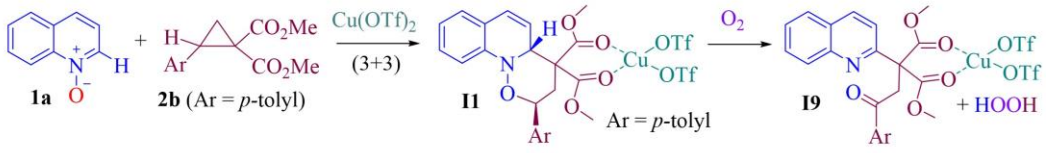


Figure 4.3: ESI-MS spectrum showing the presence of BHT-adduct **4.7**

4.3.8. DFT calculations

For further understanding of the mechanistic pathway, DFT calculations have been performed using B3LYP level of theory. Initially, copper triflate mediated (3+3)-dipolar cycloaddition reaction of cyclopropane **4.1b** with *N*-oxide **2.2a** gives intermediate **I1**.[12,13] The subsequent single-electron transfer (SET) occurs from the electron-rich nitrogen atom to the copper (II) center, forming a nitrogen radical cation **I2**.[15] The process is energetically uphill (ΔG = 10.9 kcal/mol; **I1**→ **I2**). **I2** is then transformed to α-amino radical **I3** in an exothermic manner (ΔG = 6.6 kcal/mol). The intermediate **I3** undergoes the N-O bond cleavage and the concomitant aromatization *via* **TS-1** to give alkoxy radical **I4** with an energy barrier of 10.8 kcal/mol. The process (**I3** → **I4**) is thermodynamically downhill with 5.5 kcal/mol. The copper (I) center of **I4** reacts with molecular oxygen to form the superoxide **I5** (ΔG = 3.6 kcal/mol) and hydroperoxide species **I6** (ΔG = 5 kcal/mol), respectively. The intermediate **I6** leads to the product **I9** (ΔG = -61.7 kcal/mol) and releases hydrogen peroxide in an exothermic fashion *via* the intermediates **I7** (ΔG = -53.6 kcal/mol) and **I8** (ΔG = -61.8 kcal/mol).



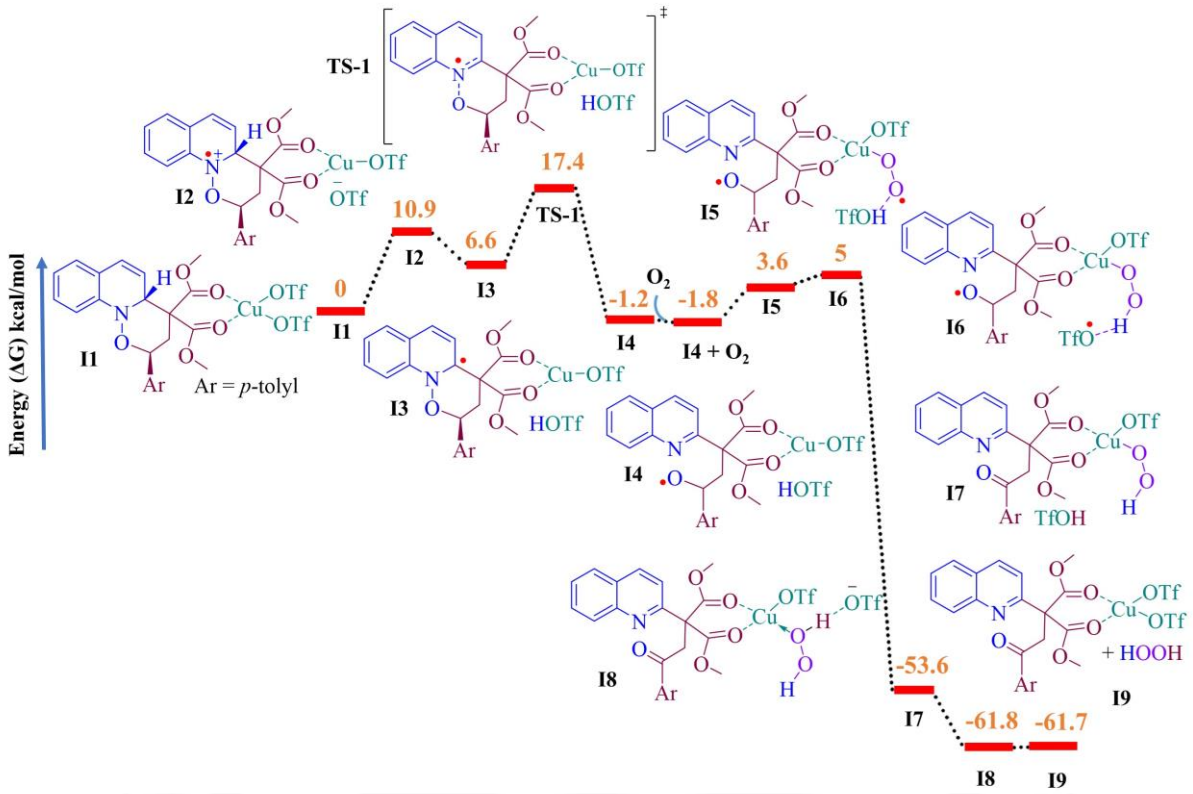
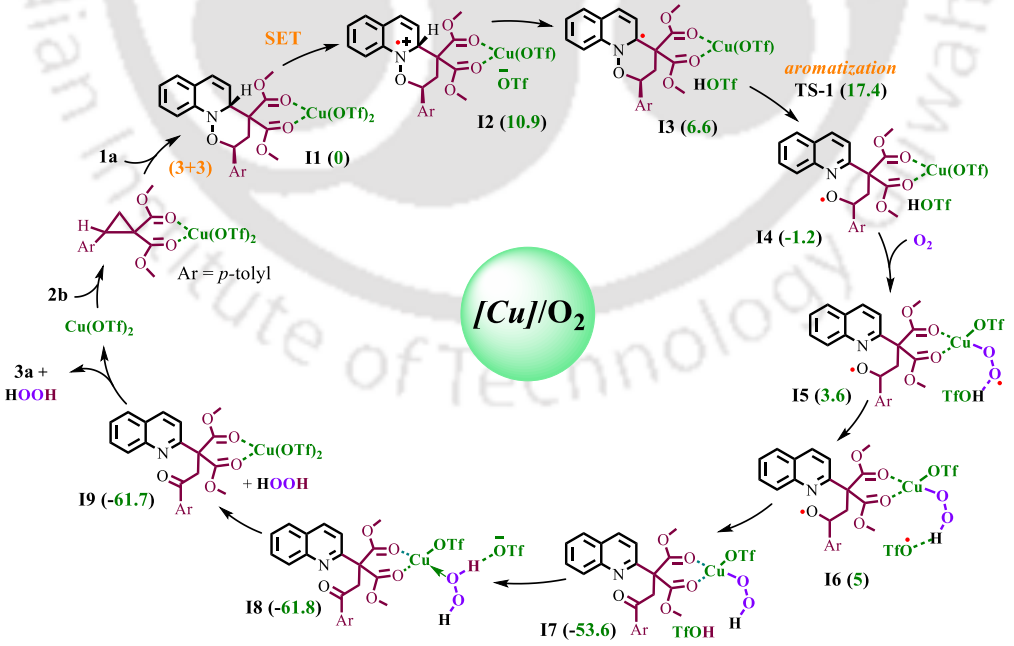


Figure 4.4: reaction profile diagram based on DFT calculations

4.3.9. Proposed mechanism

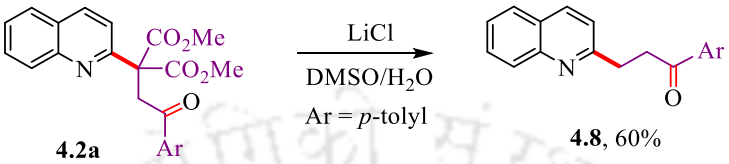
Based on the experimental evidences and theoretical calculations, a plausible mechanism can be proposed as shown.



Scheme 4.8: proposed mechanism

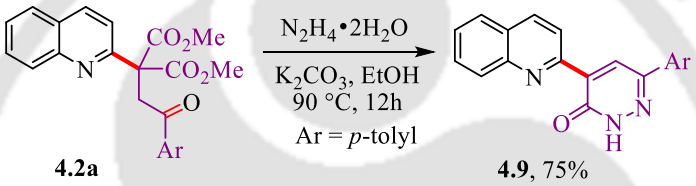
4.4. Synthetic Modifications

Aside from the substrate scope and functional group tolerance, it is worthy to note that the resulting compounds contain γ-keto diester motif, which is of biological significance.[14] When the product **4.2a** was treated with lithium chloride in dimethyl sulfoxide-water (3:1) mixture, the corresponding γ-ketoquinoline compound **4.8** was obtained in 60% yield *via* dealkoxycarbonylation[16] of malonate ester (scheme 4.9). The resulting compound, **4.8** could then further be transformed into varieties of important nitrogen-containing heterocyclic scaffolds.[17]



Scheme 4.9: dealkoxycarboxylation of **4.2a** in presence of LiCl

Additionally, upon reaction with hydrazine hydrate under the alkaline conditions, **4.2a** was efficiently converted to AIDS therapeutic agent[18] derivative **4.9**, in 75% yield (scheme 4.10).



Scheme 4.10: reaction of **4.2a** with hydrazine hydrate

4.5. Summary

In summary, a copper-catalyzed aerobic alkylation of fused heteroaromatic *N*-oxides with cyclopropane *via* (3+3)-cycloaddition is developed for the construction of a quaternary carbon center at the C2-position of the heteroaromatic moiety. The important practical features are (a) the use of a cheap catalytic system, (b) aerobic reaction conditions, (c) functional group diversity, and (d) high selectivity in the C−C bond formation. The present study provides the precise role of catalyst in both cycloaddition and the oxidative dehydrogenative segment.

4.6. Experimental section

General experimental

All the reagents and chemicals were purchased from common commercial suppliers like Sigma-Aldrich, Alfa Aesar, Merck, Spectrochem, Avra Synthesis Pvt. Ltd. and directly used as received without any further purification unless otherwise mentioned. Azine *N*-oxides[19] and donor-acceptor cyclopropanes[20] were prepared according to the literature reported procedures. CH_3CN was freshly distilled over CaH_2 and stored in 4 Å molecular sieves before use. ^1H and ^{13}C NMR spectra of the compounds were measured in $CDCl_3$ as a solvent by using TMS as an internal standard. Chemical shifts, δ (in ppm), were reported relative to TMS δ (^1H) 0.0 ppm, δ (^{13}C) 0.0 ppm, which was used as the internal reference. Otherwise, the solvent's residual proton resonance and carbon resonance $CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.16 ppm were used for calibration. Bruker Avance III 600, 500 and 400 spectrometers were used to record the NMR spectra. Chemical shift (δ) values were reported in ppm and spin-spin coupling constant (J) was expressed in Hz and other data were reported as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quartet, sext = sextet,

br = broad, and brs = broad singlet. IR spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520. Merck silica gel 60-120 was used for column chromatography. Melting points were recorded using Buchi Melting Point B-540 Instrument and are uncorrected. All starting azine *N*-oxides, donor acceptor cyclopropanes and their cycloaddition products were characterized by spectroscopic methods and compared to literature wherever applicable, otherwise stated. All the cycloaddition reactions were carried out in oven-dried glassware under oxygen-atmosphere. Completion of reactions was examined by thin layer chromatography carried out on pre-coated Merck silica gel-60 F_{254} aluminium plates with ultraviolet light (UV) or iodine as visualizing agents.

4.6.1. Donor-acceptor cyclopropanes and azine *N*-oxides used in the reaction

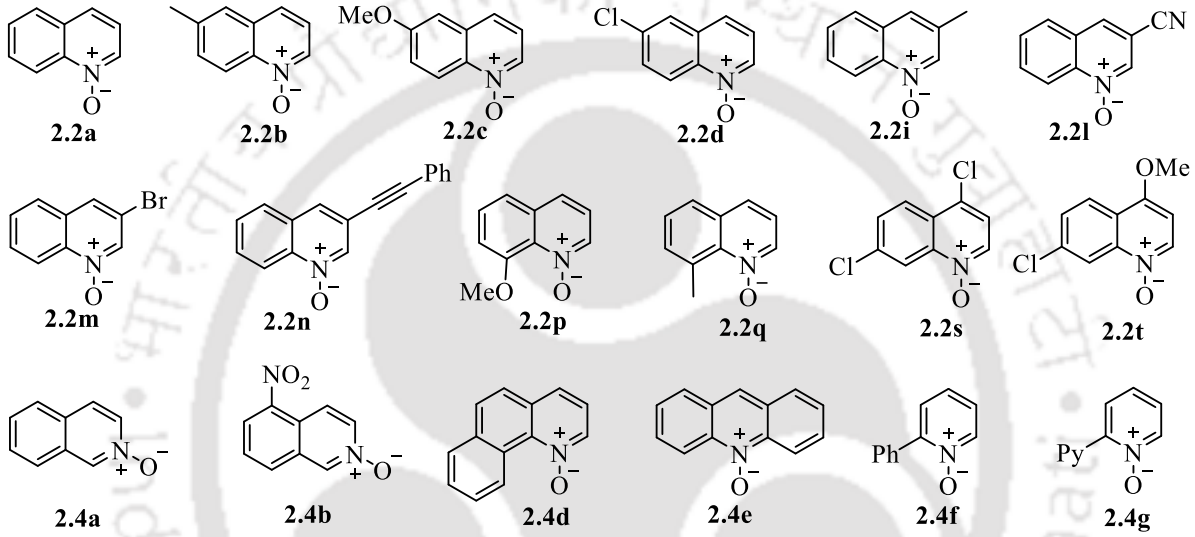


Figure 4.5. azine *N*-oxides used in the reaction

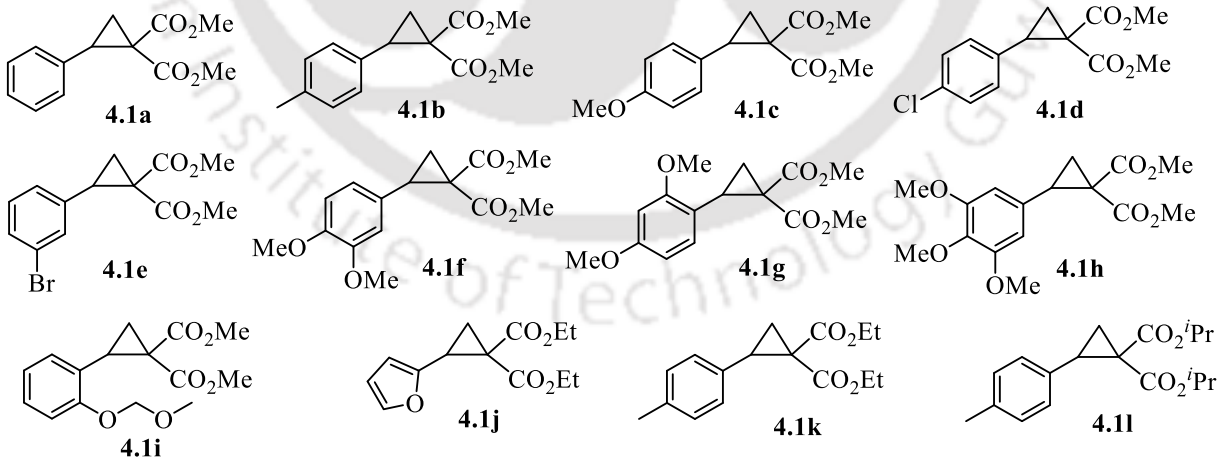
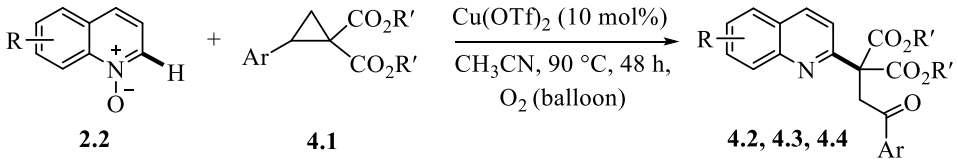


Figure 4.6. donor-acceptor cyclopropanes used in the reaction

4.6.2. General procedure for oxidative dehydrogenative reaction of heteroaromatic *N*-oxide and donor-acceptor cyclopropane:



Scheme 4.10: synthesis of C2-alkylated quinoline with γ-keto diesters motif

A mixture of heteroaromatic *N*-oxide (0.8 mmol), cyclopropane (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol, 10 mol%), and acetonitrile (2 mL) was loaded in an oven-dried Schleck tube equipped with stirring bar. The reaction mixture was degassed three times using freeze-pump technique, flushed with oxygen-balloon and then properly closed with a teflon cap. The reaction tube was placed in an oil bath, gradually increase the bath temperature to 90 ^oC and stirred for 48 hours. After completion of the reaction, all the volatiles were removed under reduced pressure and the crude reaction mixture was purified by column chromatography using ethyl acetate and petroleum ether as eluents.

4.6.3 Gram-scale synthesis (scheme 4.6):

A mixture of quinoline *N*-oxide **2.2a** (1.16 g, 8 mmol), cyclopropane **4.1b** (1.0 g, 4 mmol), $Cu(OTf)_2$ (0.144 g, 0.4 mmol, 10 mol%), and acetonitrile (10 mL) was loaded in an oven-dried schlenk tube equipped with stirring bar. The reaction mixture was degassed three times using freeze-pump technique, flushed with oxygen-balloon and then properly closed with a teflon cap. The reaction tube was placed in an oil bath, gradually increase the bath temperature to 90 ^oC and stirred for 48 hours. After completion of the reaction, all the volatiles were removed under reduced pressure and the crude reaction mixture was subjected to silica gel column chromatography (EtOAc : petroleum ether; 3 : 17) to get the pure product as a white solid (yield = 70%, 1.1 g). Additionally, quinoline *N*-oxide **2.2a** (0.420 g, 72%), and styrylmalonate (**4.5**, 0.150 g, 15%) were recovered after column chromatography.

4.6.4. Mechanistic studies:

a) Control experiments

The reaction of 8-methylquinoline and cyclopropane 4.2b (scheme 4.7a)

A mixture of 8-methylquinoline **2.1q** (58 mg, 0.4 mmol, 2 equiv), cyclopropane **4.1b** (50 mg, 0.2 mmol, 1 equiv), $Cu(OTf)_2$ (7 mg, 0.02 mmol, 10 mol%) and acetonitrile (1 mL) was loaded in an oven-dried schlenk tube equipped with stirring bar. The mixture was degassed three times using freeze-pump technique, flushed with oxygen and then properly closed with a teflon cap. The reaction tube was placed in an oil bath, gradually increase the bath temperature to 90 ^oC and stirred for 48 hours. Then, the volatile organics were removed under reduced pressure and the crude reaction mixture was subjected to silica gel column chromatography. Compounds **2.1q** (55 mg, 96%), and **4.1b** (31 mg, 62%) were recovered after column chromatography, along with styrylmalonate (**4.5**, 15 mg, 30%). There was no any oxidized product **4.2j**.

Isolation of (3+3) cycloadduct (scheme 4.7b)

A mixture of 8-methylquinoline *N*-oxide **2.2q** (318 mg, 2 mmol, 1 equiv), cyclopropane **4.1b** (500 mg, 2 mmol, 1 equiv), $Cu(OTf)_2$ (72 mg, 0.2 mmol, 10 mol%) and acetonitrile (5 mL) was loaded in an oven-dried schlenk tube equipped with stirring bar. The mixture was degassed three times using freeze-pump technique, flushed with argon and then properly closed with a

teflon cap. The reaction tube was placed in an oil bath, gradually increase the bath temperature to 50 °C and stirred for 24 hours. Then, the volatile organics were removed under reduced pressure and the crude reaction mixture was purified by column chromatography over silica gel (EtOAc : petroleum ether 3 : 22) to get the intermediate **4.6** as yellow oil (yield = 31%, 253 mg). Additionally, the oxidized product **4.2j** was isolated in 12% yield (97 mg).

The formation of oxidized product from cycloadduct under standard condition (scheme 4.7c)

A mixture of intermediate **4.6** (50 mg, 0.12 mmol, 1 equiv), $Cu(OTf)_2$ (4 mg, 0.01 mmol, 10 mol%) and acetonitrile (2 mL) was loaded in an oven-dried schlenk tube equipped with stirring bar. The reaction mixture was degassed three times using freeze-pump technique, flushed with oxygen-balloon and properly closed with a teflon cap. The reaction tube was placed in an oil bath, heated at 90 °C with continuous stirring for 24 hours. Then, the volatile organics were removed under reduced pressure and the crude reaction mixture was subjected to silica gel column chromatography (EtOAc : petroleum ether; 3 : 17) to get the analytically pure product **4.2j** as yellow oil (yield = 90%, 43 mg).

Oxidation of cycloadduct 4.6 in the presence of 2.2q (scheme 4.7c)

A mixture of intermediate **4.6** (50 mg, 0.12 mmol, 1 equiv), $Cu(OTf)_2$ (4 mg, 0.01 mmol, 10 mol%), 8-methylquinoline *N*-oxide **2.2q** (19 mg, 0.12 mmol, 1 equiv), and acetonitrile (2 mL) was loaded in an oven-dried schlenk tube equipped with stirring bar. The mixture was degassed three times using freeze-pump technique, flushed with argon and then properly closed with a teflon cap. The reaction tube was placed in an oil bath, heated at 90 °C with continuous stirring for 24 hours. Then all the volatiles were removed under reduced pressure and the crude reaction mixture was subjected to silica gel column chromatography (EtOAc : petroleum ether; 3 : 17) to get the pure product **4.2j** as yellow oil (yield = 24%, 11 mg).

Molecular oxygen promoted oxidation of cycloadduct 4.6 (scheme 4.7c)

A mixture of intermediate **4.6** (50 mg, 0.12 mmol), and acetonitrile (2 mL) was taken in an oven-dried schlenk tube equipped with stirring bar. The mixture was degassed three times using freeze-pump technique, flushed with oxygen-balloon and then properly closed with a teflon cap. The reaction tube was placed in an oil bath at 90 °C with continuous stirring for 24 hours. Then all the volatiles were removed and the crude reaction mixture was subjected to silica gel column chromatography (EtOAc : petroleum ether; 3 : 17) to get the pure product **4.2j** as yellow oil (yield = 12%, 5 mg).

***N*-oxide mediated oxidation of cycloadduct 4.6 (scheme 4.7c)**

A mixture of intermediate **4.6** (50 mg, 0.12 mmol, 1 equiv), 8-methylquinoline *N*-oxide **2.2q** (19 mg, 0.12 mmol, 1 equiv) and acetonitrile (2 mL) was loaded in an oven-dried schlenk tube equipped with stirring bar. This mixture was degassed three times using freeze-pump technique, flushed with argon and then properly closed with a teflon cap. The reaction tube was placed in an oil bath at 90 °C with continuous stirring for 24 hours. No conversion of **4.6** was observed under the reaction conditions.

b) Isotope labeling experiment (scheme 4.7d)

A mixture of **2.2a** (46 mg, 0.32 mmol, 2 equiv), **4.1b** (40 mg, 0.16 mmol, 1 equiv), $Cu(OTf)_2$ (6 mg, 0.016 mmol, 0.1 equiv), $H_2{}^{18}O$ (6.4 mg, 0.32 mmol, 2 equiv), and acetonitrile (2 mL) was loaded in an oven-dried Schlenk tube equipped with stirring bar. The mixture was degassed three times using freeze-pump technique, flushed with oxygen-balloon and then properly

closed with a teflon cap. This mixture was progressively heated to 90 °C in an oil bath and stirred for 48 hours. After completion of the reaction, all the volatiles were removed under reduced pressure. The crude reaction mixture was purified by column chromatography using ethyl acetate and petroleum ether as eluent. The oxidized product **4.2a** was isolated as white solid (yield = 68%, 42 mg). No ^{18}O incorporation product **^{18}O-4.2a** was detected by HRMS analysis.

c) Radical trapping experiments

Radical scavenger experiment using BHT (scheme 4.7e)

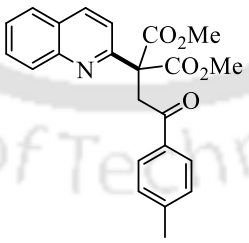
A mixture of intermediate **4.6** (50 mg, 0.12 mmol, 1 equiv), butylated hydroxytoluene (BHT, 53 mg, 0.24 mmol, 2 equiv), $Cu(OTf)_2$ (4 mg, 0.012 mmol, 0.1 equiv.) and acetonitrile (2 mL) was loaded in an oven-dried Schlenk tube equipped with stirring bar. The mixture was degassed three times using freeze-pump technique, flushed with oxygen-balloon and then properly closed with a teflon cap. This mixture was stirred at 90 °C in an oil bath for 24 hours. After completion of the reaction, all the volatiles were removed under reduced pressure. The crude reaction mixture was subjected to silica gel column chromatography (EtOAc : petroleum ether; 3 : 17) to get the pure product **4.2j** as yellow oil (yield = 28%, 12 mg). Additionally, ESI-MS analysis of the crude reaction mixture suggested the possible formation of BHT-adduct **4.7**. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{39}H_{48}NO_6$: 626.3477; found: 626.3478.

Radical scavenger experiment using 1,1-diphenylethylene (scheme 4.7f)

A mixture of intermediate **4.6** (50 mg, 0.12 mmol, 1 equiv), 1,1-diphenylethylene (22 mg, 0.12 mmol, 1 equiv), $Cu(OTf)_2$ (4 mg, 0.012 mmol, 0.1 equiv) and acetonitrile (2 mL) was loaded in an oven-dried schlenk tube equipped with stirring bar. The mixture was degassed three times using freeze-pump technique, flushed with oxygen-balloon and then properly closed with a teflon cap. This mixture was stirred at 90 °C in an oil bath for 24 hours. After completion of the reaction, all the volatiles were removed under reduced pressure. The crude reaction mixture was subjected to silica gel column chromatography (EtOAc : petroleum ether; 3 : 17) to get the pure product **4.2j** as yellow oil (yield = 21%, 9 mg).

4.6.5. Analytical data of the products

Dimethyl 2-(2-oxo-2-(*p*-tolyl)ethyl)-2-(quinolin-2-yl)malonate (4.2a)

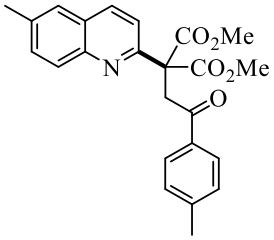


Using quinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as a white solid (0.127 g, 81%).

M.p. 131 – 133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.50 – 7.44 (m, 1H), 7.30 (d, J = 8.1 Hz, 2H), 4.28 (s, 2H), 3.83 (s, 6H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 196.9, 170.2, 155.0, 147.0, 143.8, 136.1, 134.9, 129.6, 129.3, 129.3, 128.6, 127.5, 127.4, 126.9, 122.0, 64.2, 53.3, 43.2, 21.8. HRMS (ESI) *m/z*:

$[M+H]^+$ calculated for $C_{23}H_{22}NO_5$: 392.1493; found: 392.1498. FT-IR (KBr, selected band): 1750, 1726, 1678, 1609, 1430 cm^{-1}.

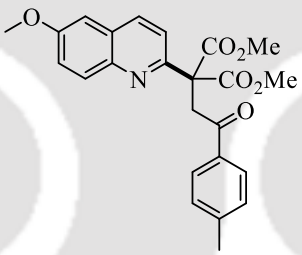
Dimethyl 2-(6-methylquinolin-2-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (4.2b)



Using 6-methylquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as yellow viscous oil (yield = 80%, 0.130 g).

^1H NMR (600 MHz, $CDCl_3$): δ 8.03 – 7.99 (m, 3H), 7.80 (d, J = 8.6 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.38 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 4.26 (s, 2H), 3.82 (s, 6H), 2.48 (s, 3H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 197.0, 170.3, 154.0, 145.5, 143.8, 136.8, 135.4, 134.9, 131.6, 129.3, 129.2, 128.6, 127.5, 126.2, 121.9, 64.1, 53.3, 43.2, 21.8, 21.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{24}NO_5$: 406.1649; found: 406.1643. FT-IR (KBr, selected band): 1756, 1668, 1596, 1430 cm^{-1}.

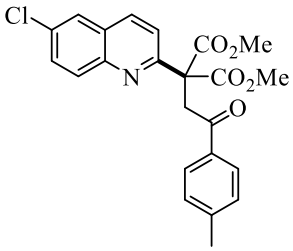
Dimethyl 2-(6-methoxyquinolin-2-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (4.2c)



Using 6-methoxyquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 11 : 39) as brown oil (yield = 79%, 0.133 g).

^1H NMR (400 MHz, $CDCl_3$): δ 8.02 – 7.99 (m, 3H), 7.80 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 9.2 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.20 (dd, J = 9.2, 2.8 Hz, 1H), 7.01 (d, J = 3.4 Hz, 1H), 4.26 (s, 2H), 3.88 (s, 3H), 3.82 (s, 6H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.0, 170.3, 158.2, 152.4, 143.8, 143.0, 134.9, 134.9, 130.9, 129.3, 128.5, 128.5, 122.2, 122.0, 104.8, 63.9, 55.6, 53.3, 43.2, 21.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{24}NO_6$: 422.1599; found: 422.1611. FT-IR (KBr, selected band): 1750, 1678, 1600, 1429 cm^{-1}.

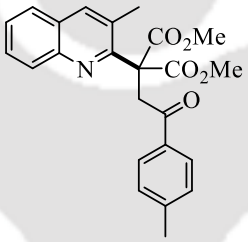
Dimethyl 2-(6-chloroquinolin-2-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (**4.2d**)



Using 6-chloroquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as yellow solid (yield = 85%, 0.144 g).

M. p. 140 – 142 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.48 (dd, J = 9.0, 2.2 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 4.26 (s, 2H), 3.83 (s, 6H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 196.8, 170, 155.2, 145.2, 144, 135.1, 134.7, 132.6, 131.1, 130.3, 129.4, 128.5, 128.0, 126.0, 123.1, 64, 53.4, 43, 21.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{21}ClNO_5$: 426.1103; found: 426.1118. FT-IR (KBr, selected band): 1748, 1728, 1672, 1605, 1432 cm^{-1}.

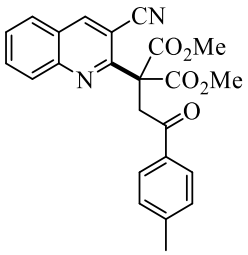
Dimethyl 2-(3-methylquinolin-2-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (**4.2e**)



Using 3-methylquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) as yellow oil (yield = 61%, 0.099 g).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 8.1 Hz, 2H), 7.87 (s, 1H), 7.68 – 7.63 (m, 1H), 7.42 – 7.37 (m, 2H), 7.33 (d, J = 8 Hz, 2H), 7.27 – 7.26 (m, 1H), 4.08 (s, 2H), 3.83 (s, 6H), 2.47 (s, 3H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 196.1, 170.4, 153.8, 144.8, 143.5, 137.7, 135.4, 131.2, 129.4, 128.8, 128.6, 128.4, 127.9, 126.9, 126.4, 64.9, 53.2, 44.1, 21.9, 19.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{24}NO_5$: 406.1649; found: 406.1663. FT-IR (KBr, selected band): 1750, 1678, 1600, 1429 cm^{-1}.

Dimethyl 2-(3-cyanoquinolin-2-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (4.2f)

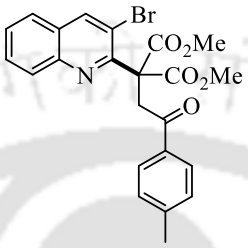


Using 3-cyanoquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column

chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as light yellow oil (yield = 67%, 0.111 g).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.4 Hz, 1H), 7.68 (m, 1H), 7.60 (m, 1H), 7.51 (d, J = 8 Hz, 1H), 7.33 (d, J = 8 Hz, 2H), 4.18 (s, 2H), 3.91 (s, 6H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 195.7, 169.2, 153.8, 146.6, 144.0, 143.5, 134.9, 132.5, 129.7, 129.5, 128.7, 128.5, 127.6, 125.4, 117.0, 108.6, 64.9, 53.7, 43.3, 21.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{21}N_2O_5$: 417.1445; found: 417.1452. FT-IR (KBr, selected band): 2230, 1740, 1721, 1681, 1610 cm^{-1}.

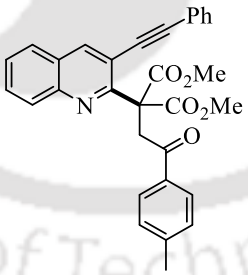
Dimethyl 2-(3-bromoquinolin-2-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (4.2g)



Using 3-bromoquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) to get the pure product as white solid (yield = 67%, 0.126 g).

M. p. 135 – 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.41 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 8 Hz, 2H), 4.11 (s, 2H), 3.85 (s, 6H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 195.7, 169.3, 153.3, 144.7, 143.7, 140.2, 135.1, 129.8, 129.4, 129.3, 128.5, 128.4, 128.0, 126.3, 118.5, 65.5, 53.4, 43.7, 21.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{21}BrNO_5$: 470.0598; found: 470.0603. FT-IR (KBr, selected band): 1740, 1687, 1608, 1433 cm^{-1}.

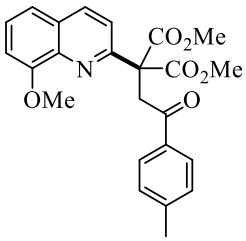
Dimethyl 2-(2-oxo-2-(*p*-tolyl)ethyl)-2-(3-(phenylethynyl)quinolin-2-yl)malonate (4.2h)



Using 3-(phenylethynyl)quinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) to get the pure product as white solid (yield = 68%, 0.133 g).

M.p. 181 – 183 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.97 (d, J = 7.8 Hz, 2H), 7.76 (d, J = 8 Hz, 1H), 7.62 – 7.48 (m, 5H), 7.38 – 7.33 (m, 3H), 7.30 – 7.23 (m, 2H), 4.19 (s, 2H), 3.82 (s, 6H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 195.9, 169.8, 155.9, 145.3, 143.6, 140.4, 135.2, 131.6, 130.1, 129.6, 129.3, 129.0, 128.6, 128.5, 127.6, 127.0, 126.6, 122.6, 117.5, 96.2, 86.1, 65.5, 53.3, 43.0, 21.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{31}H_{26}NO_5$: 492.1806; found: 492.1791. FT-IR (KBr, selected band): 2210, 1744, 1687, 1606, 1490 cm^{-1}.

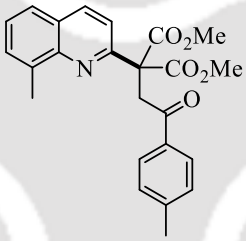
Dimethyl 2-(8-methoxyquinolin-2-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (4.2i)



Using 8-methoxyquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) to get the pure product as brown oil (yield = 78%, 0.131 g).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 8.7 Hz, 1H), 8.04 (d, J = 8 Hz, 2H), 7.89 (d, J = 8.7 Hz, 1H), 7.41 (t, J = 8 Hz, 1H), 7.33 – 7.31 (m, 3H), 6.91 (d, J = 7.6 Hz, 1H), 4.34 (s, 2H), 3.85 (s, 6H), 3.61 (s, 3H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 197.0, 170.3, 155.7, 153.3, 143.5, 135.9, 135.0, 129.1, 128.8, 128.6, 127.2, 122.7, 119.1, 108.4, 64.2, 55.8, 53.3, 43.0, 21.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{24}NO_6$: 422.1599; found: 422.1585. FT-IR (KBr, selected band): 1742, 1719, 1682, 1605 cm^{-1}.

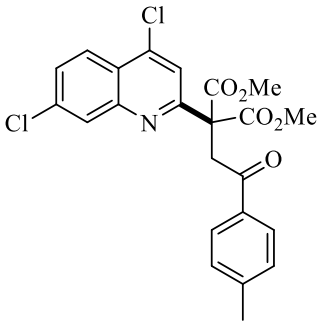
Dimethyl-2-(8-methylquinoline-2-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)melonate (4.2j)



Using 8-methylquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as yellow oil (yield = 76%, 0.123 g). Additionally, the compound styrylmalonate (**9**, 16%) was isolated after column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.7 Hz, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.29 (d, J = 8.2 Hz, 2H) 4.35 (s, 2H), 3.83 (s, 5H), 2.44 (s, 3H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 196.4, 170.3, 153.6, 146.0, 144.1, 137.5, 136.3, 134.5, 129.5, 129.4, 128.5, 127.4, 126.7, 125.3, 121.9, 63.9, 53.3, 43.4, 21.8, 17.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{24}NO_5$: 406.1649; found: 406.1653. FT-IR (KBr, selected band): 1745, 1732, 1674, 1609 cm^{-1}.

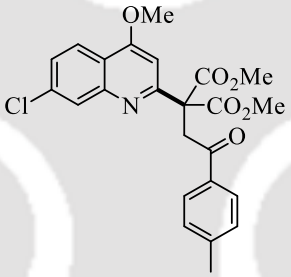
Dimethyl 2-(4,7-dichloroquinolin-2-yl)-2-(2-oxo-2-(p-tolyl)ethyl)malonate (4.2k)



Using 4,7-dichloroquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as light yellow oil (yield = 84%, 0.155 g).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 9.0 Hz, 1H), 8.05 (s, 1H), 7.97 (d, J = 8 Hz, 2H), 7.65 (d, J = 1.7 Hz, 1H), 7.52 (dd, J = 9.0, 2.4 Hz, 1H), 7.32 (d, J = 8 Hz, 2H), 4.28 (s, 2H), 3.84 (s, 6H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 196.5, 169.5, 156.3, 147.8, 144.2, 142.5, 136.4, 134.5, 129.5, 128.9, 128.8, 128.5, 125.4, 124.3, 122.7, 63.7, 53.6, 43.2, 21.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{20}Cl_2NO_5$: 460.0714; found: 460.0708. FT-IR (KBr, selected band): 1753, 1673, 1598, 1433 cm^{-1}.

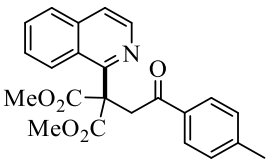
Dimethyl 2-(7-chloro-4-methoxyquinolin-2-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (4.2l)



Using 7-chloro-4-methoxyquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) to get the pure product as brownish solid (yield = 78%, 0.142 g).

M. p. 155 – 157 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 8.9 Hz, 1H), 7.96 (d, J = 8 Hz, 2H), 7.60 (d, J = 1.7 Hz, 1H), 7.36 (dd, J = 8.9, 2.1 Hz, 1H), 7.29 (m, 3H), 4.26 (s, 2H), 4.05 (s, 3H), 3.82 (s, 6H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.8, 170.0, 162.2, 157.6, 148.2, 144.0, 135.5, 134.6, 129.4, 128.5, 128.0, 126.8, 123.2, 119.2, 101.4, 64.0, 56.0, 53.3, 43.5, 21.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{23}ClNO_6$: 456.1209; found: 456.1214. FT-IR (KBr, selected band): 1750, 1678, 1602, 1431 cm^{-1}.

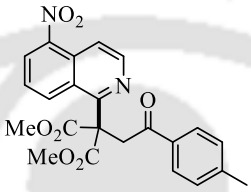
Dimethyl 2-(isoquinolin-1-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (4.3a)



Using isoquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) to get the pure product as yellow solid (yield = 80%, 0.125 g).

M.p. 150 – 152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.59 – 7.53 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.19 (s, 2H), 3.78 (s, 6H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 196.0, 170.7, 154.3, 143.6, 140.6, 137.1, 135.0, 129.7, 129.3, 128.5, 127.8, 127.8, 127.4, 125.5, 121.6, 64.7, 53.3, 44.5, 21.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{22}NO_5$: 392.1493; found: 392.1486. FT-IR (KBr, selected band): 1752, 1722, 1691, 1608, 1453 cm^{-1}.

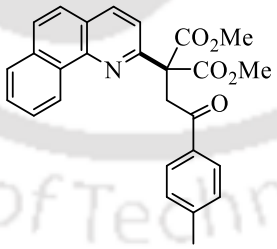
Dimethyl 2-(5-nitroisoquinolin-1-yl)-2-(2-oxo-2-(*p*-tolyl)ethyl)malonate (4.3b)



Using 5-nitroisoquinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as brown oil (yield = 85%, 0.148 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 – 8.39 (m, 3H), 8.30 (d, J = 6.1 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.68 – 7.64 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 4.22 (s, 2H), 3.78 (s, 6H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 195.7, 170.5, 154.7, 146.1, 144.0, 143.5, 134.6, 132.7, 129.5, 129.4, 128.5, 128.4, 127.3, 125.5, 116.1, 64.8, 53.6, 44.6, 21.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{20}N_2O_5$: 437.1344; found: 437.1350. FT-IR (KBr, selected band): 1735, 1687, 1606, 1526, 1434 cm^{-1}.

Dimethyl 2-(benzo[*h*]quinolin-2-yl)-2-(2-oxo-2-(p-tolyl)ethyl)malonate (4.3c)

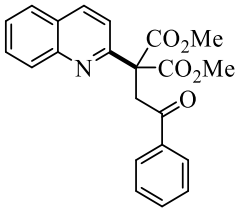


Using benzo[*h*]quinoline *N*-oxide and dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) to get the pure product as brownish solid (yield = 79%, 0.139 g).

M. p. 155 – 157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 8.2 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 8.05 – 8.02 (m, 3H), 7.81 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.27 – 7.24 (m, 1H), 4.44 (s, 2H), 3.85 (s, 6H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 196.6, 170.3, 153.4, 145.0, 144.2, 136.1, 134.5, 133.7, 131.4, 129.5, 128.7, 128.2, 128.0, 127.7, 126.7, 125.5, 124.9, 124.5,

122.9, 63.9, 53.4, 43.6, 21.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{24}NO_5$: 442.1649; found: 442.1653. FT-IR (KBr, selected band): 1734, 1678, 1590, 1453 cm^{-1}.

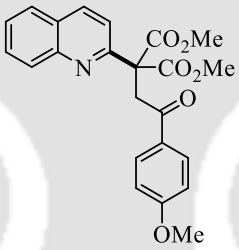
Dimethyl 2-(2-oxo-2-phenylethyl)-2-(quinolin-2-yl)malonate (4.4a)



Using quinoline *N*-oxide and dimethyl 2-(phenyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as colorless oil (yield = 72%, 0.109 g).

^1H NMR (600 MHz, $CDCl_3$) δ 8.14 – 8.09 (m, 3H), 7.86 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.60 (m, 2H), 7.57 – 7.46 (m, 4H), 4.30 (s, 2H), 3.84 (s, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 197.4, 170.1, 154.7, 146.9, 137.4, 136.1, 133.1, 129.5, 129.4, 128.7, 128.4, 127.5, 127.4, 127.0, 122.0, 64.2, 53.4, 43.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{22}H_{20}NO_5$: 378.1336; found: 378.1342. FT-IR (KBr, selected band): 1730, 1678, 1593, 1440 cm^{-1}.

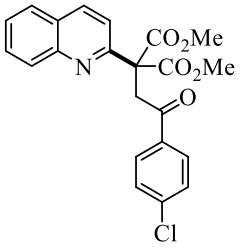
Dimethyl 2-(2-(4-methoxyphenyl)-2-oxoethyl)-2-(quinolin-2-yl)malonate (4.4b)



Using quinoline *N*-oxide and dimethyl 2-(*p*-methoxyphenyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as colorless oil (yield = 78%, 0.127 g).

^1H NMR (600 MHz, $CDCl_3$): δ 8.13 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.76 (t, J = 8.8 Hz, 2H), 7.65 – 7.53 (m, 3H), 7.51 – 7.40 (m, 2H), 7.16 (dd, J = 8.0, 2.4 Hz, 1H), 4.29 (s, 2H), 3.86 (s, 3H), 3.84 (s, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 197.2, 170.1, 159.9, 154.6, 146.9, 138.7, 136.1, 129.6, 129.5, 129.4, 127.4, 127.3, 127.0, 121.9, 121.2, 119.9, 112.3, 64.2, 55.6, 53.4, 43.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{22}NO_6$: 408.1442; found: 408.1445. FT-IR (KBr, selected band): 1743, 1729, 1683, 1600, 1433 cm^{-1}.

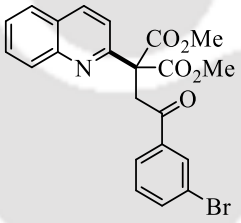
Dimethyl 2-(2-(4-chlorophenyl)-2-oxoethyl)-2-(quinolin-2-yl)malonate (4.4c)



Using quinoline *N*-oxide and dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as white solid (yield = 51%, 0.084 g).

M. p. 134 – 136 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8 Hz, 1H), 7.56 – 7.55 (m, 2H), 7.51 – 7.48 (m, 3H), 4.25 (s, 2H), 3.84 (s, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 196.3, 170.0, 154.2, 146.8, 139.5, 136.2, 135.8, 129.9, 129.5, 129.3, 129.0, 127.5, 127.4, 127.1, 122.0, 64.3, 53.5, 42.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{22}H_{19}ClNO_5$: 412.0947; found: 412.0952. FT-IR (KBr, selected band): 1748, 1722, 1680, 1604, 1430 cm^{-1}.

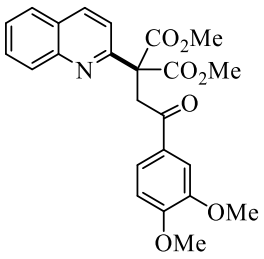
Dimethyl 2-(2-(3-bromophenyl)-2-oxoethyl)-2-(quinolin-2-yl)malonate (4.4d)



Using quinoline *N*-oxide and dimethyl 2-(3-bromophenyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as yellow oil (yield = 54%, 0.098 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (bs, 1H), 8.13 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 7.4 Hz, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.59 – 7.55 (m, 2H), 7.50 – 7.47 (m, 1H), 7.41 (t, J = 7.6 Hz, 1H), 4.24 (s, 2H), 3.84 (s, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 196.1, 170.0, 154.2, 146.8, 139.3, 136.2, 135.9, 131.6, 130.3, 129.5, 129.3, 127.5, 127.4, 127.1, 127.0, 123.0, 122.0, 64.3, 53.5, 42.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{22}H_{19}BrNO_5$: 456.0442; found: 456.0447. FT-IR (KBr, selected band): 1751, 1721, 1678, 1698 cm^{-1}.

Dimethyl 2-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)-2-(quinolin-2-yl)malonate (4.4e)

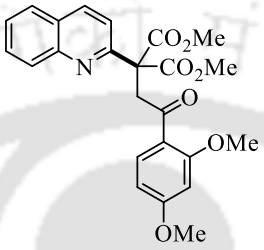


Using quinoline *N*-oxide and dimethyl dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through

SiO_2-gel column chromatography (EtOAc : petroleum ether, 1 : 4) to get the pure product as white solid (yield = 77%, 0.135 g).

M. p. 145 – 147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.81 (dd, J = 8.4, 2.0 Hz, 1H), 7.79 – 7.74 (m, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.50 – 7.46 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.27 (s, 2H), 3.98 (s, 3H), 3.92 (s, 3H), 3.84 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 195.9, 170.2, 155.1, 153.4, 149.1, 146.9, 136.1, 130.6, 129.5, 129.3, 127.5, 127.4, 126.9, 123.0, 122.0, 110.6, 110.2, 64.2, 56.2, 56.1, 53.3, 43.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{24}NO_7$: 438.1548; found: 438.1546. FT-IR (KBr, selected band): 1755, 1674, 1604, 1432 cm^{-1}.

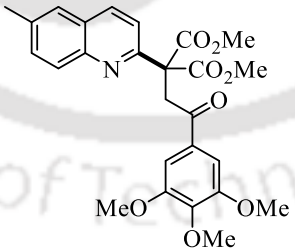
Dimethyl 2-(2-(2,4-dimethoxyphenyl)-2-oxoethyl)-2-(quinolin-2-yl)malonate (4.4f)



Using quinoline *N*-oxide and dimethyl 2-(2,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as yellow oil (yield = 71%, 0.124 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.7 Hz, 1H), 7.83 (m, 2H), 7.78– 7.74 (m, 2H), 7.62 – 7.56 (m, 1H), 7.51 – 7.45 (m, 1H), 6.56 (dd, J = 8.8, 2.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 4.26 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.82 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 196.9, 170.5, 164.6, 161.0, 155.9, 147.0, 135.9, 133.1, 129.7, 129.2, 127.4, 127.4, 126.8, 122.0, 121.3, 105.3, 98.3, 64.3, 55.7, 53.2, 48.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{24}NO_7$: 438.1548; found: 438.1556. FT-IR (KBr, selected band): 1747, 1680, 1602, 1433 cm^{-1}.

Dimethyl 2-(2-oxo-2-(3,4,5-trimethoxyphenyl)ethyl)-2-(quinolin-2-yl)malonate (4.4g)

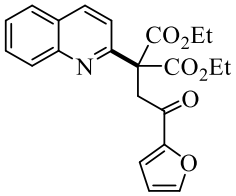


Using 6-methylquinoline *N*-oxide and dimethyl 2-(3,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as yellow oil (yield = 76%, 0.146 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.40 (dd, J = 8.7, 2.0 Hz, 1H), 7.35 (s, 2H), 4.25 (s, 2H), 3.95 (s, 3H), 3.92 (s, 6H), 3.84 (s, 6H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.2, 170.2, 153.9, 153.2, 145.6, 142.7, 136.9, 135.5, 132.7, 131.7, 129.1, 127.5, 126.2, 121.9, 106.0, 64.2, 61.1, 56.5,

53.3, 43.2, 21.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{26}H_{28}NO_8$: 482.1810; found: 482.1817. FT-IR (KBr, selected band): 1747, 1726, 1681, 1602 cm^{-1}.

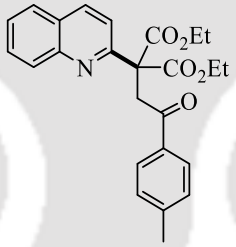
Dimethyl 2-(2-(furan-2-yl)-2-oxoethyl)-2-(quinolin-2-yl)malonate (4.4i)



Using quinoline *N*-oxide and diethyl 2-(furan)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 4 : 21) to get the pure product as dark brown oil (yield = 78%, 0.123 g).

^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 1.0 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.50 – 7.47 (m, 1H), 7.30 (d, J = 3.5 Hz, 1H), 6.60 (dd, J = 3.5, 1.6 Hz, 1H), 4.31 (q, J = 7.1 Hz, 4H), 4.14 (s, 2H), 1.28 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 186.3, 169.4, 154.8, 153.1, 146.8, 146.1, 135.9, 129.5, 129.3, 127.4, 127.4, 126.9, 122.1, 116.8, 112.4, 64.2, 62.3, 42.4, 14.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{22}H_{22}NO_6$: 396.1442; found: 396.1444. FT-IR (KBr, selected band): 1743, 1731, 1679, 1597, 1431 cm^{-1}.

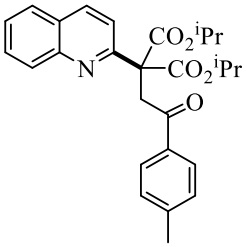
Diethyl 2-(2-oxo-2-(p-tolyl)ethyl)-2-(quinolin-2-yl)malonate (4.4j)



Using quinoline *N*-oxide and diethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) to get the pure product as brownish oil (yield = 77%, 0.129 g).

^1H NMR (600 MHz, $CDCl_3$): δ 8.12 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.48 – 7.45 (m, 1H), 7.31 (d, J = 8.1 Hz, 2H), 4.31 (q, J = 7.1 Hz, 4H), 4.28 (s, 2H), 2.45 (s, 3H), 1.28 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 196.9, 169.6, 155.0, 146.8, 143.7, 135.8, 134.9, 129.4, 129.3, 129.2, 128.5, 127.4, 127.3, 126.8, 122.2, 64.1, 62.2, 43.0, 21.8, 14.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{25}H_{26}NO_5$: 420.1806; found: 420.1800. FT-IR (KBr, selected band): 1731, 1685, 1603 cm^{-1}.

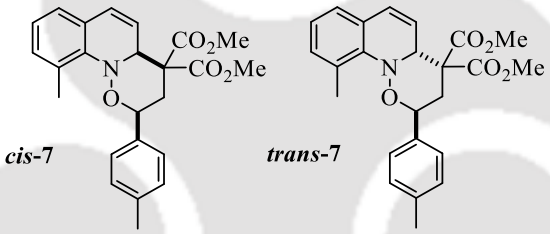
Diisopropyl 2-(2-oxo-2-(*p*-tolyl)ethyl)-2-(quinolin-2-yl)malonate (4.4k)



Using quinoline *N*-oxide and diisopropyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate in accordance with general procedure, the title compound was obtained through SiO_2-gel column chromatography (EtOAc : petroleum ether, 3 : 17) to get the pure product as brown oil (yield = 62%, 0.111 g).

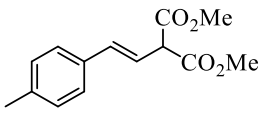
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.48 – 7.43 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 5.21 – 5.17 (m, 2H), 4.25 (s, 2H), 2.45 (s, 3H), 1.26 (t, J = 6.0 Hz, 12H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 196.9, 169.0, 155.2, 146.9, 143.6, 135.6, 135.1, 129.5, 129.3, 129.1, 128.5, 127.4, 127.3, 126.7, 122.5, 69.7, 64.2, 43.0, 21.8, 21.6, 21.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{30}NO_5$: 448.2119; found: 448.2113. FT-IR (KBr, selected band): 1741, 1680, 1606, 1431 cm^{-1}.

Dimethyl 10-methyl-2- (*p*-tolyl)-2,3- dihydro- [1,2]oxazino[2,3-*a*]quinoline- 4, 4(4a*H*)-dicarboxylate (4.6)



^{1}H NMR analysis of the crude reaction mixture showed *cis*/*trans* ratio of 1:1. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (d, J = 8.4 Hz, 2H), 7.67 – 7.60 (m, 2H), 7.55 – 7.54 (m, 2H), 7.43 – 7.40 (m, 2H), 7.39 – 7.34 (m, 2H), 7.27 – 7.26 (m, 2H), 7.23 (d, J = 7.8 Hz, 2H), 7.17 – 7.13 (m, 4H), 5.61 (t, J = 7.1 Hz, 1H), 5.48 (dd, J = 9.4, 4.6 Hz, 1H), 4.20 (dd, J = 8.6, 6.0 Hz, 1H), 4.08 (t, J = 7.4 Hz, 1H), 3.68 – 3.66 (m, 12H), 2.84 – 2.80 (m, 2H), 2.78 (s, 3H), 2.77 (s, 3H), 2.75 – 2.71 (m, 2H), 2.34 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 173.0, 172.9, 156.5, 156.0, 155.1, 155.1, 146.9, 146.9, 138.3, 138.2, 137.6, 137.6, 137.1, 137.0, 136.6, 129.8, 129.4, 127.2, 127.2, 126.7, 126.4, 126.4, 125.5, 125.5, 120.9, 120.4, 78.4, 78.1, 54.8, 52.4, 51.0, 50.8, 38.3, 37.9, 21.3, 21.3, 18.0, 17.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{26}NO_5$: 408.1806; found: 408.1812. FT-IR (KBr, selected band): 1745, 1599, 1441, 1260 cm^{-1}.

Dimethyl 2-(4-methylstyryl)malonate (4.5)



^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (d, J = 8 Hz, 2H), 7.13 (d, J = 8 Hz, 2H), 6.55 (d, J = 15.9 Hz, 1H), 6.34 (dd, J = 15.9, 9.1 Hz, 1H), 4.20 (d, J = 9.1 Hz, 1H), 3.77 (s, 6H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 168.7, 138.3, 135.3, 133.4, 129.4, 126.7, 119.7, 55.8, 53.0, 21.4. Spectroscopic data matched with literature reported data.[21]

4.6.6. Crystallographic study

For compound 4.2a

The crystal was obtained by crystallization of compound **4.2a** from ethyl acetate as solvent at room temperature using slow evaporation technique. The crystallographic data were recorded at room temperature using a 'Bruker SMART APEX CCD' diffractometer equipped with a fine focus 1.75 kW sealed tube Mo-Kα (λ = 0.71073 Å) X-ray source, a graphite monochromator and Apex CCD camera. The SMART software was used for data acquisition and the 'Bruker SAINT' software for data refinement and reduction. All crystallographic data were refined using the software SHELXL-2014/7 and WinGX. The ORTEP diagram was obtained with the help of Diamond software with 50% thermal ellipsoid (figure 4.2a). The crystallographic parameters and refinement data were listed in table 4.6.

Table 4.6. Crystal data and structure refinement for **4.2a**.

Identification code	BS-19	
CCDC	2091973	
Empirical formula	C23 H21 N O5	
Formula weight	391.41	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P*c	
Unit cell dimensions	a = 16.305(2) Å	a= 90°.
	b = 6.4911(8) Å	b= 90°.
	c = 19.257(3) Å	g = 90°.
Volume	2038.1(5) $Å^3$	
Z	4	
Density (calculated)	1.276 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	824	
Crystal size	0.28 x 0.23 x 0.18 mm^3	
Theta range for data collection	3.138 to 25.000°.	
Index ranges	-19<=h<=19, -5<=k<=7, -16<=l<=22	
Reflections collected	7209	
Independent reflections	4278 [R(int) = 0.0569]	
Completeness to theta = 25.000°	99.4 %	

Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4278 / 2 / 530
Goodness-of-fit on F^2	1.543
Final R indices [I>2sigma(I)]	R1 = 0.1224, wR2 = 0.3185
R indices (all data)	R1 = 0.1512, wR2 = 0.3404
Absolute structure parameter	-2.3(10)
Extinction coefficient	0.020(5)
Largest diff. peak and hole	0.598 and -0.405 e.Å^{-3}

Author's comment on IUCR check.cif alert:

SYMMS02 ALERT 1 B All angles should not be 90 for a monoclinic cell.

Author Response: The crystal quality was not good. The crystal was moderately diffracting. So some diffractions could not be included during data integration and refinement process. After several attempts of data collection, the best result obtained is reported herein.

For compound 4.2d

The crystal was obtained by crystallization of compound **4.2d** from ethyl acetate as solvent at room temperature using slow evaporation technique. The X-ray crystallographic intensity data were collected using a Supernova, single source at offset, Eos diffractometer using Mo-Kα radiation (λ = 0.71073 Å) equipped with a CCD area detector, and the corresponding data refinement and cell reduction were performed using CrysAlisPro. The data integration and reduction were carried out with SAINT and XPREP. All crystallographic data were refined using the software SHELXL-2014/7 and WinGX. The ORTEP diagram was obtained with the help of Diamond software with 50% thermal ellipsoid (Figure 4.2b). The crystallographic parameters and refinement data were listed in table 4.7.

Table 4.7. Crystal data and structure refinement for **4.2d**.

Identification code	BS-571	
CCDC	2081283	
Empirical formula	C_{23} H_{20} Cl N O_5	
Formula weight	425.85	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C2/c*	
Unit cell dimensions	a = 19.9065(13) Å	α = 90°.
	b = 9.7167(6) Å	β = 103.503(7)°.

	c = 22.6697(17) Å γ = 90°.
Volume	4263.7(5) $Å^3$
Z	8
Density (calculated)	1.327 Mg/m^3
Absorption coefficient	0.213 mm^{-1}
F(000)	1776
Crystal size	0.36 x 0.20 x 0.10 mm^3
Theta range for data collection	2.35 to 25.00°.
Index ranges	-22<=h<=23, -11<=k<=9, -16<=l<=26
Reflections collected	6680
Independent reflections	3707 [R(int) = 0.0377]
Completeness to theta = 25.00°	98.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.01322
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3707 / 0 / 274
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0601, wR2 = 0.1381
R indices (all data)	R1 = 0.1170, wR2 = 0.1749
Largest diff. peak and hole	0.451 and -0.324 $e.Å^{-3}$

4.6.7. Synthetic transformation

Dealkoxycarbonylation of malonate ester 4.2a (scheme 4.9)

To a solution of compound **4.2a** (0.05 g, 0.12 mmol, 1 equiv.) in dry DMSO (0.3 mL), LiCl (0.016 g, 0.36 mmol, 3 equiv.) and water (0.1 mL) were added in a reaction tube. The mixture was stirred under air at 110 °C for 48 hours. On reaction completion, ice-water was added to the reaction mixture and extracted with CH_2Cl_2 (10 mL). The combined organics was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified through silica-gel column chromatography (EtOAc : petroleum ether, 3 : 17) to get the pure product **4.8** as brown oil (yield = 60%, 20 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.64 – 7.68 (m, 1H), 7.53 – 7.46 (m, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.26 – 7.24 (m, 2H), 3.60 (t, J = 7.2 Hz, 2H), 3.43 (t, J = 7.2 Hz, 2H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 199.2, 161.5, 148.0, 143.9, 136.4, 134.7, 129.5, 129.4, 128.9, 128.4, 127.7, 127.0, 125.9, 122.1, 37.7, 33.0, 21.8. Spectroscopic data matched with literature reported data.[22]

Condensation of malonate ester 4.2a with hydrazine (scheme 4.10)

Compound **4.2a** (0.03 g, 0.08 mmol, 1 equiv.) was dissolved in ethanol (2 mL) in a round-bottom flask under air. Hydrazine hydrate (0.006 g, 0.11 mmol, 1.5 equiv.) and K_2CO_3 (0.015 g, 0.11 mmol, 1.5 equiv.) were added to the solution. The reaction mixture was stirred at 90 °C for 15 hours. After complete consumption of the starting materials as notified by TLC, the mixture was concentrated under reduced pressure, extracted with CH_2Cl_2. The combined organics was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified through silica gel column chromatography (EtOAc : petroleum ether 1 :4) to get the pure product **4.9** as brown oil (yield = 75%, 19 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.99 (s, 1H), 8.87 (s, 1H), 8.73 (d, J = 8.6 Hz, 1H), 8.29 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.77 (m, 1H), 7.60 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 160.8, 151.4, 148.3, 146.9, 139.9, 137.8, 136.5, 132.2, 130.4, 130.0, 129.9, 129.8, 128.6, 127.8, 127.5, 126.2, 122.4, 21.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{16}N_3O$: 314.1288; found: 314.1306. FT-IR (KBr, selected band): 2918, 1649, 1597, 1500 cm^{-1}.

4.6.8. Computational studies

All calculations were performed using the Gaussian-16 program package.[23] Full geometry optimizations were carried out using Kohn-Sham hybrid-DFT B3LYP[24] level of theory and the standard double-ζ quality def2SVP basis set.[25] To take into account of the use of solvent in the experimental setup, the Polarizable Continuum Model (PCM)[26] was used for the calculations. Frequency calculations at the same method and basis set were performed to distinguish transition state structures (one imaginary frequency) and minima structures (no imaginary frequency) on the potential energy surface. The transition states were verified by the intrinsic reaction coordinate (IRC) calculations, wherever necessary.[27] Free energies were calculated by using frequency calculations at 90 °C to match the experimental conditions.

Table 4.8. Free Energies (G) and Total Energies (E) given in Hartree along with the number of imaginary frequencies

Species	Free energy (G)	Total energy (E)	# Imaginary Frequency (NImag)
I1	-4881.989188	-4882.3506451	0
I1′	-4881.974586	-4882.3316533	0
I2	-4881.971798	-4882.3206065	0
I3	-4881.978724	-4882.3272900	0
TS-1	-4881.961388	-4882.3070653	1
I4	-4881.991054	-4882.3353576	0
I4 + O_2	-5032.218244	-5032.5359685	0
I5	-5032.209734	-5032.5602658	0
I6	-5032.207459	-5032.5618511	0

I7	-5032.300761	-5032.6334679	0
I8	-5032.313953	-5032.6666414	0
I9	-5032.313737	-5032.6670776	0

[a](G) is calculated at 90 °C to meet the experimental conditions. All the figures were generated using (G) values. The transition state has one NImag and all the reactants, intermediates and products have zero NImag. All the calculations were performed at B3LYP level of DFT.

4.7. References:

1. (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. Analysis of the Reactions used for the Preparation of Drug Candidate Molecules. *Org. Biomol. Chem.* **2006**, *4*, 2337-2347. (b) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451– 3479. (c) Matada, B. S.; Pattanashettar, R.; Yernale, N. G. A Comprehensive Review on the Biological Interest of Quinoline and Its Derivatives. *Bioorg. Med. Chem.* **2021**, *32*, 115973. (d) Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. Recent Advances in the Synthesis of Quinolines: A Review. *RSC Adv.* **2014**, *4*, 24463– 24476. (e) Weyesa, A.; Mulugeta, E. Recent Advances in the Synthesis of Biologically and Pharmaceutically Active Quinoline and Its Analogues: A Review. *RSC Adv.* **2020**, *10*, 20784– 20793, (f) Kajinami, K.; Takekoshi, N.; Saito, Y. Pitavastatin: Efficacy and Safety Profiles of a Novel Synthetic HMG-CoA Reductase Inhibitor. *Cardiovasc. Drug Rev.* **2003**, *21*, 199– 215, (g) Kaur, K.; Jain, M.; Khan, S. I.; Jacob, M. R.; Tekwani, B. L.; Singh, S.; Singh, P. P.; Jain, R. Amino Acid, Dipeptide and Pseudodipeptide Conjugates of Ring-Substituted 8-Aminoquinolines: Synthesis and Evaluation of Anti-infective, β-Haematin Inhibition and Cytotoxic Activities. *Eur. J. Med. Chem.* **2012**, *52*, 230– 241.

2. Aggarwal, R. K. Showkathali, R. Rosuvastatin Calcium in Acute Coronary Syndromes. *Expert Opin. Pharmacother*. **2013**, *14*, 1215 – 1227.

3. (a) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. C–H Functionalization of Azines. *Chem. Rev.* **2017**, *117*, 9302–9332, (b) Aynetdinova, D.; Callens, M. C.; Hicks, H. B.; Poh, C. Y. X.; Shennan, B. D. A.; Boyd, A. M.; Lim, Z. H.; Leitch, J. A.; Dixon, D. J. Installing the "magic methyl"– C–H Methylation in Synthesis. *Chem. Soc. Rev.* **2021**, *50*, 5517– 5563, (c) Taylor, E. C.; Martin, S. F. A General Method for Alkylation and Alkenylation of Heterocycles. *J. Am. Chem. Soc.* **1974**, *96*, 8095–8102, (d) Thorsett, E. D.; Stermitz, F. R. Alkylation of Haloquinolines by Grignard Reagents with Nickel-Phosphine Complex Catalysts. *J. Heterocycl. Chem.* **1973**, *10*, 243 – 244, (e) Ishikura, M.; Oda, I.; Kamada, M.; Terashima, M. Reactions of Trialkyl(2- or 4-Quinolyl)-Borates. *Synth. Commun*. **1987**, *17*, 959 – 967, (f) Gómez, I.; Alonso, E.; Ramón, D. J.; Yus, M. Naphthalene-catalysed Lithiation of Chlorinated Nitrogenated Aromatic Heterocycles and Reaction with Electrophiles. *Tetrahedron* **2000**, *56*, 4043 – 4052.

4. Selected examples for the introduction of primary alkyl group into *N*-heteroarenes, see: (a) Han, S.; Chakrasali, P.; Park, J.; Oh, H.; Kim, S.; Kim, K.; Pandey, A. K.; Han, S. H.; Han, S. B.; Kim, I. S. Reductive C2-Alkylation of Pyridine and Quinoline *N*-Oxides Using Wittig Reagents. *Angew. Chem., Int. Ed.* **2018**, *57*, 12737– 12740. (b) An, W.; Choi, S. B.; Kim, N.; Kwon, N. Y.; Ghosh, P.; Han, S. H.; Mishra, N. K.; Han, S.; Hong, S.; Kim, I. S. C2-Selective C–H Methylation of Heterocyclic *N*-Oxides with Sulfonium Ylides. *Org. Lett.* **2020**, *22*, 9004– 9009. (c) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. Rh(I)-Catalyzed Alkylation of Quinolines and Pyridines via C-H Bond Activation. *J. Am. Chem. Soc.* **2007**,

129, 5332– 5333. (d) Liu, D.-Y.; Liu, X.; Gao, Y.; Wang, C.-Q.; Tian, J.-S.; Loh, T.-P. Decarboxylative C–H Alkylation of Heteroarene *N*-Oxides by Visible Light/Copper Catalysis. *Org. Lett.* **2020**, *22*, 8978– 8983. (e) Puthanveedu, M.; Polychronidou, V.; Antonchick, A. P. Catalytic Selective Metal-Free Cross-Coupling of Heteroaromatic *N*-Oxides with Organosilanes. *Org. Lett.* **2019**, *21*, 3407– 3411.

5. Selected examples for the introduction of secondary alkyl group into *N*-heteroarenes, see: (a) Larionov, O. V.; Stephens, D.; Mfuh, A.; Chavez, G. Direct, Catalytic, and Regioselective Synthesis of 2-Alkyl-, Aryl-, and Alkenyl-Substituted *N*-Heterocycles from *N*-Oxides. *Org. Lett.* **2014**, *16*, 864– 867. (b) Jha, A. K.; Jain, N. The Microwave-assisted *ortho*-Alkylation of Azine *N*-Oxides with *N*-tosylhydrazones Catalyzed by Copper(I) Iodide. *Chem. Commun.* **2016**, *52*, 1831– 1834. (c) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. Palladium-Catalyzed C-H Activation/Cross-Coupling of Pyridine *N*-Oxides with Nonactivated Secondary Alkyl Bromides. *J. Am. Chem. Soc.* **2013**, *135*, 616– 619. (d) Wu, Z.; Pi, C.; Cui, X.; Bai, J.; Wu, Y. Direct C-2 Alkylation of Quinoline N-Oxides with Ethers *via* Palladium-Catalyzed Dehydrogenative Cross-Coupling Reaction. *Adv. Synth. Catal.* **2013**, *355*, 1971– 1976. (e) Bi, W.-Z.; Sun, K.; Qu, C.; Chen, X.-L.; Qu, L.-B.; Zhu, S.-H.; Li, X.; Wu, H.-T.; Duan, L.-K.; Zhao, Y.-F. A Direct Metal-free C2-H Functionalization of Quinoline *N*-Oxides: A Highly Selective Amination and Alkylation Strategy Towards 2-Substituted Quinolines. O*rg. Chem. Front.* **2017**, *4*, 1595– 1600. (f) Liu, Q.; Wang, Q.; Xie, G.; Fang, Z.; Ding, S.; Wang, X. Metal-Free Direct C-H β-Carbonyl Alkylation of Heteroarenes with Cyclopropanols Mediated by $K_2S_2O_8$. *Eur. J. Org. Chem.* **2020**, *2020*, 2600– 2604. (g) Tang, N.; Wu, X.; Zhu, C. Practical, Metal-free Remote Heteroarylation of Amides *via* Unactivated C(sp^3)-H Bond Functionalization. *Chem. Sci.* **2019**, *10*, 6915– 6919.

6. For tertiary C-H alkylation of fused *N*-heteroarenes, see: (a) Bell, T. W.; Hu, L.–Y.; Patel, S. V. Alkylation of heteroaryl halides by 2:1 Grignard reagent/copper(I) mixtures. Synthesis of alkylated octahydrodibenzo[b,j][1,10]phenan throlines. *J. Org. Chem.* **1987**, *52*, 3847–3850, (b) Russell, G. A.; Rajaratnan, R.; Wang, L.; Shi, B. Z.; Kim, B. H.; Yao, C. F. *tert*-Butylation of pyridines, quinolines, and isoquinolines by *tert*-butylmercury halides. *J. Am. Chem. Soc.***1993**, *115*, 10596– 10604, (c) Jeong, H. J.; Chae, S.; Jeong, K.; Namgoong, S. K. The Diverse One-Pot Reactions of 2-Quinolylzincates: Homologation, Electrophilic Trapping, Hydroxylation, and Arylation Reactions. *Eur. J. Org. Chem.* **2018**, 6343– 6349.

7. (a) Antonchick, A. P.; Burgmann, L. Direct Selective Oxidative Cross-Coupling of Simple Alkanes with Heteroarenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3267– 3271, (b) Lo, J. C.; Kim, D.; Pan, C.-M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutierrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S. Fe-catalyzed C-C bond construction from olefins *via* radicals. *J. Am. Chem. Soc.* **2017**, *139*, 2484– 2503, (c) Dong, J.; Lyu, X.; Wang, Z.; Wang, X.; Song, H.; Liu, Y.; Wang, Q. Visible-Light-Mediated Minisci C–H Alkylation of Heteroarenes with Unactivated Alkyl Halides Using O_2 as an Oxidant. *Chem. Sci.* **2019**, *10*, 976– 982, (d) Matsui, J. K.; Primer, D. N.; Molander, G. A. Metal-free C-H alkylation of heteroarenes with alkyltrifluoroborates: a general protocol for 1°, 2° and 3° alkylation. *Chem. Sci.* **2017**, *8*, 3512– 3522, (e) Revil-Baudard, V. L.; Vors, J.-P.; Zard, S. Z. Xanthate-Mediated Incorporation of Quaternary Centers into Heteroarenes. *Org. Lett.* **2018**, *20*, 3531– 3535, (f) Pitre, S. P.; Muuronen, M.; Fishman, D. A.; Overman, L. E. Tertiary Alcohols as Radical Precursors for the Introduction of Tertiary Substituents into Heteroarenes. *ACS Catal.* **2019**, *9*, 3413– 3418, (g) Wang, Y.; Yang, L.; Liu, S.; Huang, L.; Liu, Z. Q. Surgical Cleavage of Unstrained C(sp^3)−C(sp^3) Bonds in General Alcohols for Heteroaryl C−H Alkylation and Acylation. *Adv. Synth. Catal.* **2019**, *361*, 4568– 4574, (h) Garza-Sanchez, R. A.; Tlahuext-Aca, A.; Tavakoli, G.; Glorius, F. Visible light-mediated direct decarboxylative C–H

functionalization of heteroarenes. *ACS Catal.* **2017**, *7*, 4057– 4061, (i) Sun, A. C.; McClain, E. J.; Beatty, J. W.; Stephenson, C. R. J. Visible light-mediated decarboxylative alkylation of pharmaceutically relevant heterocycles. *Org. Lett.* **2018**, *20*, 3487– 3490.

8. Tang, S.; Liu, Y.; Lei, A. Electrochemical Oxidative Cross-coupling with Hydrogen Evolution: A Green and Sustainable Way for Bond Formation. *Chem.* **2018**, *4*, 27 – 45.

9. For some representative examples, see: (a) Lantaño, B.; Barata-Vallejo, S.; Postigo, A. Organic Dye-Photocatalyzed Fluoroalkylation of Heteroarene *N*-Oxide Derivatives. *Org. Biomol. Chem.* **2018**, *16*, 6718-6727, (b) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. Palladium-Catalyzed C-H Activation/Cross-Coupling of Pyridine *N*-Oxides with Nonactivated Secondary Alkyl Bromides. *J. Am. Chem. Soc.* **2013**, *135*, 616– 619, (c) Zhang, W.-M.; Dai, J.-J.; Xu, J.; Xu, H.-J. Visible-Light-Induced C2 Alkylation of Pyridine N-Oxides. *J. Org. Chem.* **2017**, *82*, 2059– 2066, (d) Liang, C.; Zhuo, W.-T.; Niu, Y.-N.; Gao, G.-L. Visible-Light-Promoted C2 Trifluoromethylation of Quinoline *N*-Oxides. *Synthesis* **2020**, 52, 219-226.

10. For some recent reviews, see: (a) Reissig, H.-U.; Zimmer, R. Donor-Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1151– 1196. (b) Cavitt, M. A.; Phun, L. H.; France, S. Intramolecular Donor–Acceptor Cyclopropane Ring-Opening Cyclizations. *Chem. Soc. Rev.* **2014**, *43*, 804– 818. (c) Schneider, T. F.; Kaschel, J.; Werz, D. B. A New Golden Age for Donor–Acceptor Cyclopropanes. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504– 5523. (d) Grover, H. K.; Emmett, M. R.; Kerr, M. A. Carbocycles from Donor–Acceptor Cyclopropanes. *Org. Biomol. Chem.* **2015**, *13*, 655– 671. (e) Werz, D. B.; Biju, A. T. Uncovering the Neglected Similarities of Arynes and Donor-Acceptor Cyclopropanes. *Angew. Chem. Int. Ed.* **2020**, *59*, 3385– 3398.

11. (a) Kreft, A.; Lücht, A.; Grunenberg, J.; Jones, P. G.; Werz, D. B. Kinetic Studies of Donor–Acceptor Cyclopropanes: The Influence of Structural and Electronic Properties on the Reactivity. *Angew. Chem., Int. Ed.* **2019**, *58*, 1955– 1959. (b) Vartanova, A. E.; Plodukhin, A. Yu.; Ratmanova, N. K.; Andreev, I. A.; Anisimov, M. N.; Gudimchuk, N. B.; Rybakov, V. B.; Levina, I. I.; Ivanova, O. A.; Trushkov, I. V.; Alabugin, I. V. Expanding Stereoelectronic Limits of endo-tet Cyclizations: Synthesis of Benz[*b*]azepines from Donor–Acceptor Cyclopropanes. *J. Am. Chem. Soc.* **2021**, *143*, 13952– 13961. (c) Chakrabarty, S.; Chatterjee, I.; Wibbeling, B.; Daniliuc, C. G.; Studer, A. Stereospecific Formal [3+2] Dipolar Cycloaddition of Cyclopropanes with Nitrosoarenes: an Approach to Isoxazolidines. *Angew. Chem., Int. Ed.* **2014**, *53*, 5964– 5968.

12. For (3+3)-cycloaddition of D-A cyclopropanes with nitrones, see: (a) Kerr, M. A. The Annulation of Nitrones and Donor-Acceptor Cyclopropanes: A Personal Account of our Adventures to Date. *Isr. J. Chem.* **2016**, *56*, 476– 487. (b) Braun, C. M.; Congdon, E. A.; Nolin, K. A. Diastereoselective 1,3-Dipolar Cycloaddition of Nitrones to Donor–Acceptor Cyclopropanes Catalyzed by a Calcium(II) Complex. *J. Org. Chem.* **2015**, *80*, 1979–1984. (c) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. Multicomponent Synthesis of Pyrroles from Cyclopropanes: A One-Pot Palladium(0)-Catalyzed Dehydrocarbonylation/Dehydration. *Angew. Chem. Int. Ed.* **2012**, *51*, 11088– 11091. (d) Dias, D. A.; Kerr, M. A. Domino Synthesis of Bridged Bicyclic Tetrahydro-1,2-oxazines: Access to Stereodefined 4-Aminocyclohexanois. *Org. Lett.* **2009**, *11*, 3694– 3697. (e) Young, I. S.; Kerr, M. A. Total Synthesis of (+)-Nakadomarin A. *J. Am. Chem. Soc.* **2007**, *129*, 1465– 1469.

13. For (3+3)-cycloaddition of D-A cyclopropanes with other 1,3-dipoles and their equivalents, see: (a) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. Cycloadditions of Aromatic Azomethine Imines with 1,1-Cyclopropane Diesters. *Org. Lett.* **2008**, *10*, 689– 692.

(b) Garve, L. K. B.; Petzold, M.; Jones, P. G.; Werz, D. B. [3 + 3]-Cycloaddition of Donor-Acceptor Cyclopropanes with Nitrile Imines Generated in Situ: Access to Tetrahydropyridazines *Org. Lett.* **2016**, *18*, 564– 567. (c) Gorbacheva, E. O.; Tabolin, A. A.; Novikov, R. A.; Khomutova, Y. A.; Nelyubina, Y. V.; Tomilov, Y. V.; Ioffe, S. L. Six-Membered Cyclic Nitronates as 1,3-Dipoles in Formal [3 + 3]-Cycloaddition with Donor–Acceptor Cyclopropanes. Synthesis of New Type of Bicyclic Nitrosoacetals. *Org. Lett.* **2013**, *15*, 350– 353. (d) Zhang, H.-H.; Luo, Y.-C.; Wang, H.-P.; Chen, W.; Xu, P.-F. $TiCl_4$ Promoted Formal [3 + 3] Cycloaddition of Cyclopropane 1,1-Diesters with Azides: Synthesis of Highly Functionalized Triazinines and Azetidines. *Org. Lett.* **2014**, *16*, 4896– 4899. (e) Liu, H.; Yuan, C.; Wu, Y.; Xiao, Y.; Guo, H. $Sc(OTf)_3$-Catalyzed [3+3] Cycloaddition of Cyclopropane 1,1-Diesters with Phthalazinium Dicyanomethanides. *Org. Lett.* **2015**, *17*, 4220– 4223. (f) Chagarovskiy, A. O.; Vasin, V. S.; Kuznetsov, V. V.; Ivanova, O. A.; Rybakov, V. B.; Shumsky, A. N.; Makhova, N. N.; Trushkov, I. V. (3 + 3)-Annulation of Donor–Acceptor Cyclopropanes with Diaziridines. *Angew. Chem., Int. Ed.* **2018**, *57*, 10338– 10342. (g) Petzold, M.; Jones, P. G.; Werz, D. B. (3 + 3)-Annulation of Carbonyl Ylides with Donor-Acceptor Cyclopropanes: Synergistic Dirhodium(II) and Lewis Acid Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 6225– 6229.

14. (a) Bera, S.; Samanta, R. C.; Daniliuc, C. G.; Studer, A. Asymmetric Synthesis of Highly Substituted β-Lactones through Oxidative Carbene Catalysis with LiCl as Cooperative Lewis Acid. *Angew. Chem., Int. Ed.* **2014**, *53*, 9622– 9626. (b) Van der Mey, M.; Hatzelmann, A.; Van der Laan, I. J.; Sterk, G. J.; Thibaut, U.; Timmerman, H. Novel Selective PDE4 Inhibitors. 1. Synthesis, Structure−Activity Relationships, and Molecular Modeling of 4-(3,4-Dimethoxyphenyl)-2H-phthalazin-1-ones and Analogues. *J. Med. Chem.* **2001**, *44*, 2511–2522. (c) Matsumoto, T.; Imai, S.; Yamaguchi, T.; Morihira, M. The Total Synthesis of (±)-Megaphyllone Acetate, A Cytotoxic Neolignan. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 346– 351.

15. (a) Jia, Y.-X.; Kündig, E. P. Oxindole Synthesis by Direct Coupling of C-H and C-H Centers. *Angew. Chem. Int. Ed.* **2009**, *48*, 1636– 1639. (b) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidative C–H Functionalizations: Trends and Mechanistic Insights. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062– 11087.

16. For an excellent review on dealkoxycarbonylation of malonate esters, see: Krapcho, A. P. Synthetic Applications of Dealkoxycarbonyl ations of Malonate Esters, *β*-Keto Esters, *α*-Cyano Esters and Related Compounds in Dipolar Aprotic Media- Part I. *Synthesis* **1982**, 805–822.

17. Zhang, M.; Xie, J.; Zhu. C. A General Deoxygenation Approach for Synthesis of Ketones from Aromatic Carboxylic Acids and Alkenes. *Nat. Commun.* **2018**, *9*, 3517 and the reference therein.

18. Mori, M.; Manetti, F.; Botta, M. Predicting the Binding Mode of Known NCp7 Inhibitors to Facilitate the Design of Novel Modulators. *J. Chem. Inf. Model.* **2011**, *51*, 446– 454.

19. a) Bering, L.; Antonchick, A. P. Regioselective Metal-Free Cross-Coupling of Quinoline *N*-Oxides with Boronic Acids. *Org. Lett.* **2015**, *17*, 3134– 3137. (b) Li, P.; Zhao, J.; Xia, C.; Li, F. The development of carbene-stabilized N–O radical coupling strategy in metal-free regioselective C–H azidation of quinoline *N*-oxides. *Org. Chem. Front.* **2015**, *2*, 1313-1317. (c) Larionov, O. V.; Stephens, D.; Mfuh, A.; Chavez, G. Direct, catalytic, and regioselective synthesis of 2-alkyl-, aryl-, and alkenyl substituted *N*-heterocycles from *N*-oxides. *Org. Lett.* **2014**, *16*, 864− 867. (d) Frei, P.; Jones, D. H.; Kay, S. T.; McLellan, J. A.; Johnston, B. F.; Kennedy, A. R.; Tomkinson, N. C. O. Regioselective Reaction of Heterocyclic *N* -Oxides,

an Acyl Chloride, and Cyclic Thioethers. *J. Org. Chem.* **2018**, *83*, 1510– 1517. (e) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. Regioselective Bromination of Fused Heterocyclic *N*-Oxides. *Org.Lett.* **2013**, *15*, 792– 795. (f) Sharma, R.; Kumar, R.; Sharma, U. Rh/O_2-Catalyzed C8 Olefination of Quinoline *N*-oxides with Activated and Unactivated Olefins. *J. Org. Chem.* **2019**, *84*, 2786– 2797. (g) Biswas, A.; Karmakar, U.; Pal, A.; Samanta, R. Copper-Catalyzed Regioselective Cascade Alkylation and Cyclocondensation of Quinoline *N*-Oxides with Diazo Esters: Direct Access to Conjugated π-Systems. *Chem. - Eur. J.* **2016**, *22*, 13826−13830. (h) Bertuzzi, G.; Pecorari, D.; Bernardi, L.; Fochi, M. An Organocatalytic Enantioselective Direct α-Heteroarylation of Aldehydes with Isoquinoline *N*-Oxides. *Chem. Commun.* **2018**, *54*, 3977− 3980. (i) Bjørsvik, H.-R.; Gambarotti, C.; Jensen, V. R.; Gonźalez, R. R. A Novel Efficient Deoxygenation Process for *N*-Heteroarene *N*-Oxides. *J. Org. Che*m. **2005**, *70*, 3218– 3224. (j) Schießl, J.; Stein, P. M.; Stirn, J.; Emler, K.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Strategic Approach on *N*-Oxides in Gold Catalysis - A Case Study. *Adv. Synth. Catal.* **2019**, *361*, 725− 738. (k) Singh, A. N.; Thumme, R. P. 1,5-Naphthyridine as a New Linker for the Construction of Bridging Ligands and Their Corresponding Ru(II) Complexes. *Inorg. Chem.* **2009**, *48*, 6459–6470. (l) Dyer, R. M. B.; Hahn, P. L.; Hilinski, M. K. Selective Heteroaryl *N*-Oxidation of Amine-Containing Molecules. *Org. Lett.* **2018**, *20*, 2011−2014.

20. (a) Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. A New Type of Donor–Acceptor Cyclopropane Reactivity: The Generation of Formal 1,2- and 1,4-Dipoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 3187– 3191; (b) Andreev, I. A.; Ratmanova, N. K.; Augustin, A. U.; Ivanova, O. A.; Levina, I. I.; Khrustalev, V. N.; Werz, D. B.; Trushkov, I. V. Protic Ionic Liquid as Reagent, Catalyst, and Solvent: 1-Methylimidazolium Thiocyanate. *Angew. Chem., Int. Ed.* **2021**, *60*, 7927– 7934; (c) Varshnaya, R. K.; Banerjee, P. Lewis Acid-Catalyzed [3+3] Annulation of Donor–Acceptor Cyclopropanes and Indonyl Alcohols: One Step Synthesis of Substituted Carbazoles with Promising Photophysical Properties. *J. Org. Chem.* **2019**, *84*, 1614 – 1623.

21. Chagarovskiy, A. O.; Ivanova, O. A.; Rakhmankulov, E. R.; Budynina, E. M.; Trushkov, I. V.; Melnikov, M. Y. Lewis Acid-Catalyzed Isomerization of 2-Arylcyclopropane-1,1-dicarboxylates: A New Efficient Route to 2-Styrylmalonates. *Adv. Synth. Catal.* **2010**, *352*, 3179– 3184.

22. Chen, Y.; He, Y.-M.; Zhang, S.; Miao, T.; Fan, Q.-H. Rapid Construction of Structurally Diverse Quinolizidines, Indolizidines, and Their Analogues via Ruthenium-Catalyzed Asymmetric Cascade Hydrogenation/Reductive Amination. *Angew. Chem., Int. Ed.* **2019**, *58*, 3809– 3813.

23. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, Revision C.01, Gaussian, Inc., Wallingford CT, 2016.

24. (a) Becke, A. D. Density-Functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys*, **1993**, *98*, 5648-5652. (b) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev. B.* **1988**, *37*, 785-789.

25. Weigend, F.; Alhrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys*. **2005**, *7*, 3297 – 3305.

26. (a) Miertuš, S.; Scrocco, E.; Tomasi, J. Electrostatic Interaction of a Solute with a Continuum. A Direct Utilizaion of AB Initio Molecular Potentials for the Prevision of Solvent Effects. *Chem. Phys*. **1981**, *55*, 117 – 129; (b) Pascual-Ahuir, J. L.; Silla, E.; Tuñón, I. GEPOL: An Improved Description of Molecular-Surfaces. 3. A New Algorithm for the Computation of a Solvent-Excluding Surface. *J. Comput. Chem.* **1994**, *15*, 1127– 1138; (c) Barone, V.; Cossi, M. Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model. *J. Phys. Chem. A* **1998**, *102*, 1995– 2001.

27. Fukui, K. The Path of Chemical Reactions - the IRC Approach. *Acc. Chem. Res.* **1981**, *14*, 363 – 368.

Chapter-5

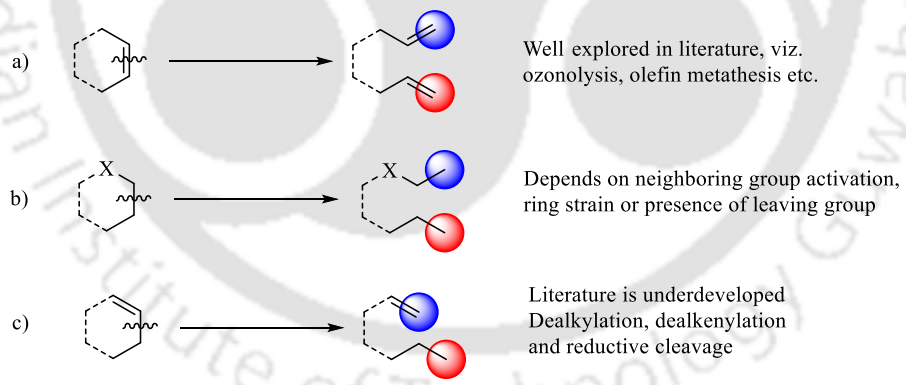
DIBAL-H mediated reductive cleavage of C(sp^2)-C(sp^3) bonds in *N*-heteroaryl γ-keto diester derivatives

5.1. Introduction

The chemistry of bond-breaking and bond-making is the main cornerstone of the synthetic methodologies towards realization of complex organic molecules. In general, transition-metal-catalysed cross-coupling strategies have enabled the selective formation of C–C bonds in an efficient manner; however, the selective cleavage of these inherently inert bonds is still a remaining challenge.[1]

The cleavage of C–C bonds is commonly encountered in the steam cracking process of crude oil at high temperatures and pressures in the petroleum industry.[2] Also, many classical reactions (for instance, sigmatropic rearrangements, Beckmann rearrangement, Bayer–Villiger oxidation, retro-aldol, and others) allow for C–C bond cleavage.[3] However, there is still a lack of mild methods to activate unbiased C–C bonds in a general and efficient manner.

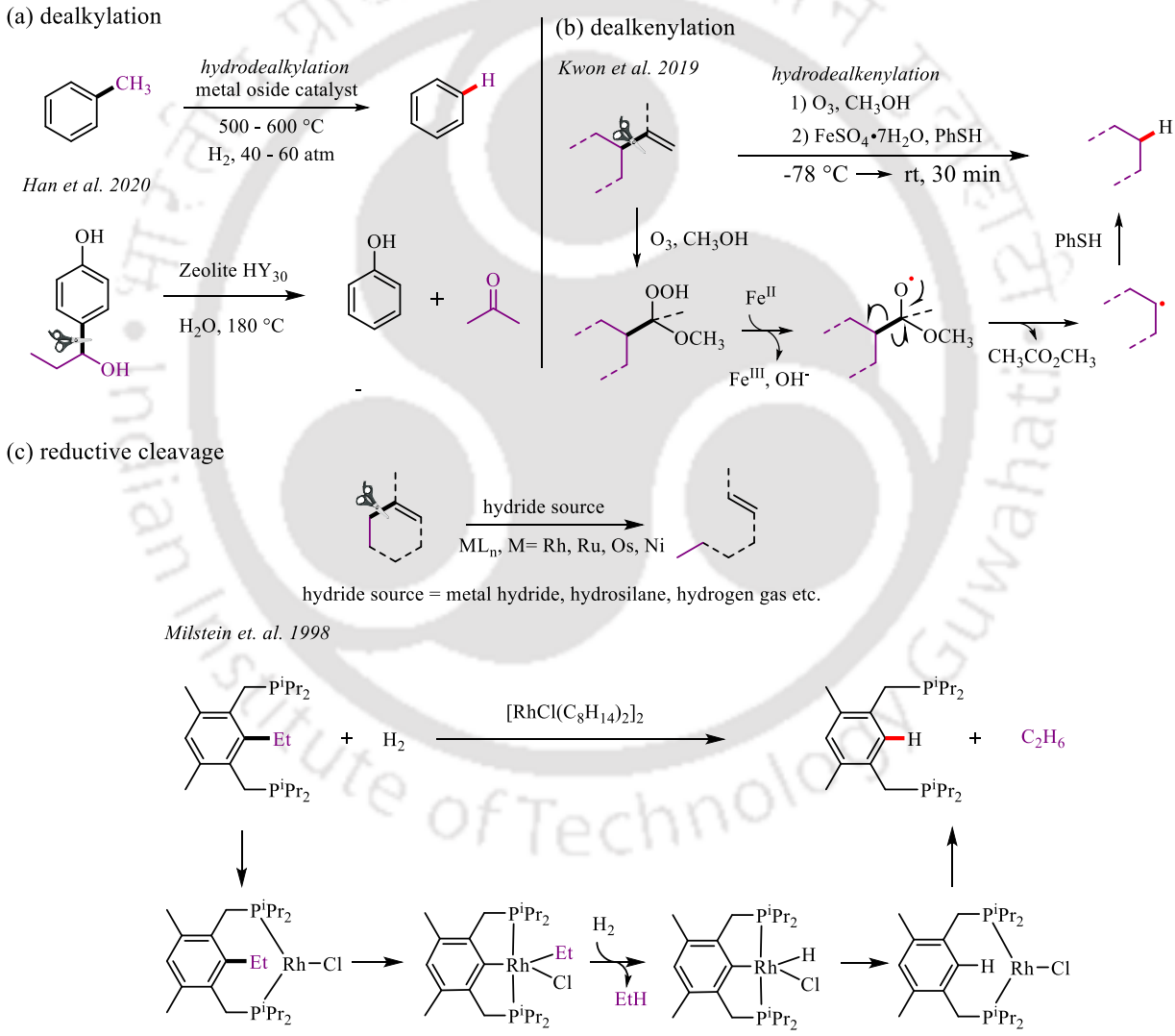
Among different types of C-C bond fission processes, the most well-established method is C(sp^2)-C(sp^2) bond-breaking.[4] Generally, it was achieved *via* olefin metathesis, ozonolysis etc. (scheme 5.1a). Another route is C(sp^3)-C(sp^3) bond-scission process which is relatively less explored and typically requires C-C bond activation *via* ring strain, neighboring group participation or effect of leaving groups (scheme 5.1b).[5] In contrast, reports on the C(sp^2)-C(sp^3) bond fragmentation are limited, as they are less polar and hence kinetically inert, although, this can be beneficial given the library of compounds found in petrochemical products containing such linkages and their potential as precursor in organic synthesis.



Scheme 5.1: Approaches for C-C bond fission processes

In general, C(sp^2)-C(sp^3) bond fragmentation are realized through three different pathways: dealkylation,[6] dealkenylation[7] and reductive cleavage[8]. The toluene hydrodealkylation process is commonly performed in industry where toluene and hydrogen are converted in a reactor packed with suitable metal oxide catalyst to produce benzene and methane.[6a] Typically, the reaction reaches a conversion of 90%. The reaction is highly exothermic and the typical operating conditions are 500 to 600 ºC, and 40 to 60 atm. Another dealkylation process is the cumene-phenol process (Hock process) for synthesizing phenol and acetone from benzene and propylene.[6b] During the process, cumene (isopropyl benzene) is formed as the intermediate in the gas phase by the Friedel–Crafts alkylation of benzene and propene. Benzene and propene

are compressed together to a pressure of 30 standard atmospheres at 250 °C in presence of a catalytic Lewis acid. Formed cumene is oxidized in air to generate cumene hydroperoxide species, followed by hydrolysis under acidic medium to give phenol and acetone. This is one of the successful methods and about 95% of world's phenol production occurs in this way. To reduce the complexity of these processes, scientists are trying to explore milder reaction conditions for the production of such valuable products. In 2020, Han and co-workers reported zeolite catalyzed direct deconstruction of C(sp^2)-C(sp^3) bond to produce phenol from lignin, a lignocellulose biomass-derived precursor.[6c] They have demonstrated that the reaction involved dihydroxylation, γ-methyl shift, followed by C-C bond breaking. Very recently, the same research group have developed sustainable production of benzene from lignin by using a RuW/zeolite HY_{30} multifunctional alloy catalyst where RuW component helped to reduce the competitive hydrogenolysis and reductive catalytic fractionation process. However, the reaction proceeded under autoclave at high temperature (240 °C).[6d]



Scheme 5.2: Approaches for C(sp3)-C(sp2) bond fission processes

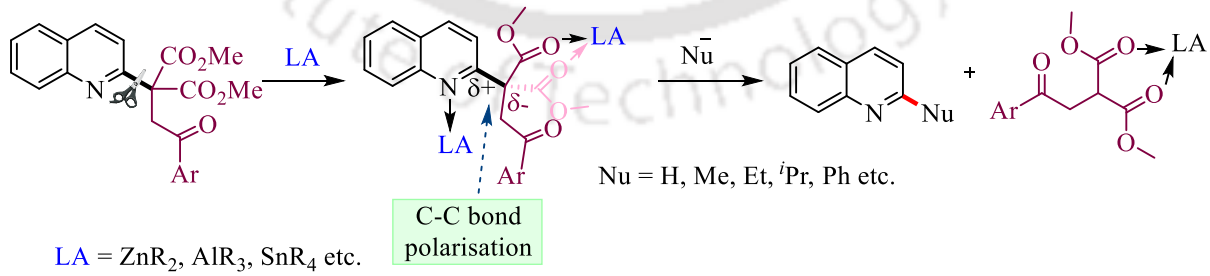
To achieve milder conditions, researchers usually coupled the fragmentation process with spontaneous bond construction by suitable other coupling partners like alkene, thio-ether etc. Kwon and her group in their elegant works reported the hydrodealkenylation process involving

ozonolysis followed by electron transfer mediated with Fe(II)-salt which led to the C(sp^2)-C(sp^3) bond fission process. The bond fission process was further combined with subsequent bond-forming process which would increase the applicability of the process.[7]

The process on reductive cleavage of C-C bonds was also explored by reducing agent (H_2 gas, hydrosilane) and transition metals catalysts.[8] In general, the insertion of metals into inert C-C bond is kinetically unfavorable due to lack of proper orbital overlapping compared to the competing C-H insertion process. To allow the kinetically unfavorable cleavage, commonly employed strategies are to raise the energy of the starting material by either introducing ring strain or chelation assisted activation, followed by reductive condition.

Milstein and group, in their pioneering work, reported for the first time Rh- mediated C(sp^2)-C(sp^3) bond activation in presence of hydrogen pressure (~80 psi) which did not use aromatization or ring strain removal as a driving force.[8a] They have judiciously chosen phosphine-based donor ligand as a substrate to serve this purpose. The phosphine arms could coordinate to the metal center, and then close proximal C(sp^2)-alkyl bond was activated by the metal site. The formation of strong metal-organic linkage and corresponding gaseous products more than compensated the kinetic activation barrier of C(sp^2)-C(sp^3) bond cleavage. The excess hydrogen pressure was required to overcome the competing C-H activation process. They later also upgraded this protocol to a catalytic one.[8b] The selectivity between C-C activation and C-H activation can also be affected by tuning the ligand system. Other transition metal ions such as Ru, Pt, Os, Ir and Ni were also explored towards C(sp^2)-C(sp^3) bond fission process using similar ligand systems and the hydrogenation step was also carried out under H_2-gas pressure.[8c-f] In pursuit of a milder approach, Shi and coworkers in 2012 reported the H_2 gas as hydride source by using H_2 balloon.[8g] Transition metal complexes with monodentate *N*-heterocyclic carbene ligands have also been explored for ligand assisted C(aryl)-C(sp^3) bond activation reactions, without the need of hydrogen gas pressure.[8h] In spite of these achievements, still, the literature on C(sp^2)-C(sp^3) bond cleavage is limited and leaves room for further explorations. Further, to the best of my knowledge, there is no report on C(hetaryl)-C(sp^3) bond cleavage and subsequent incorporation of new functionalities in the *N*-heteroarene moiety.

5.2. Present approach



Scheme 5.3: Lewis acid-mediated C(sp2)-C(sp3) bond fission

In the previous chapter (chapter-4), it has been shown the synthesis of C2-alkylated quinoline derivatives. Herein I thought that Lewis acid can activate the *N*-atom containing heteroaromatic ring and enhance the electrophilicity at the C2-position.[9] Likewise, diester moiety can

coordinate to the oxophilic Lewis acidic metal ions.[10] As a result, C(hetaryl)-C(sp^3) bond is more polarized, and hence, subsequent fission may take place.

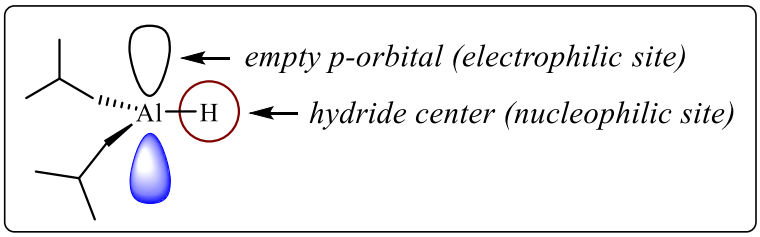


Figure 5.1: electrophilic and nucleophilic sites of DIBAL-H

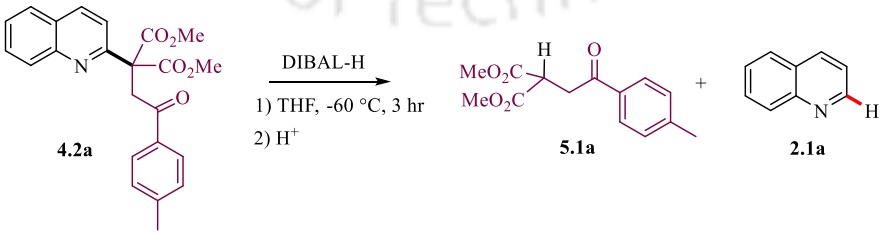
Because of low-lying vacant 3p orbital of aluminum and hydride center of DIBAL-H, it has been considered as a unique reducing agent in the reduction chemistry.[11] Lewis acidic Al-center can form the adduct with the Lewis basic *N*-center of quinoline, which would polarize the C(sp^2)-C(sp^3) bond at the C2-position of quinoline moiety. Then, hydride transfer can happen from N-coordinated DIBAL-H to the electrophilic C2-carbon center, rendering a dearomatized product which may undergo C-C bond cleavage to attain aromatization. Thus, DIBAL-H can function in two ways- 1) as a Lewis acid, and 2) as a hydride source. Such reductive fragmentation of C-C bond in the presence of DIBAL-H is unprecedented.

5.3. Results and discussion

5.3.1. Optimization of reaction conditions

The above hypothesis was initially executed for the reaction of dimethyl 2-(2-oxo-2-(phenyl)ethyl)-2-(quinolin-2-yl)malonate **4.2a** and 2 equivalents of DIBAL-H in dry tetrahydrofuran at -60 °C under inert atmosphere. Surprisingly, after 12 hours, unusual fragmentation products, *viz.* dimethyl 2-(2-oxo-2-(phenyl)malonate **5.1a** and quinoline **2.1a** were obtained in 56% and 52% yields, respectively (table 5.1, entry 1). Under the same reaction conditions with the 6 equiv. of DIBAL-H, the yields of the products **5.1a** and **2.1a** were substantially enhanced to 82% (table 5.1, entry 3). Interestingly, the similar yields were observed while decreasing the reaction time from 12 h to 3 h. However, upon further reducing the reaction time from 3 h to 2 h, incomplete conversion of **4.2a** was observed, resulting in the lower yield of **5.1a** (68%) (table 5.1, entry 5). Performing the reaction at room temperature resulted in very poor yields for the products.

Table 5.1: optimization studies for reductive cleavage of C(sp2)-C(sp3) bond with DIBAL-H[a]

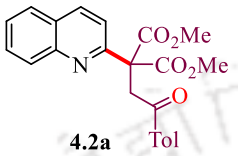
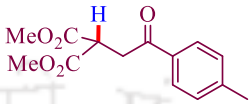
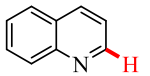
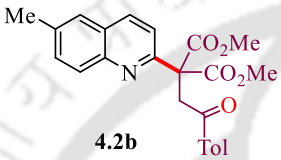
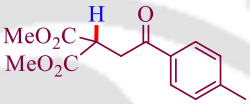
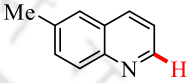
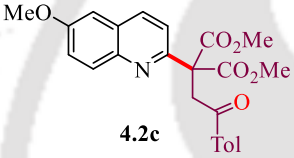
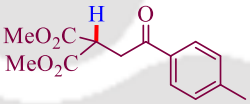
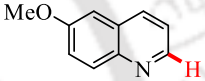
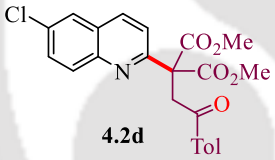
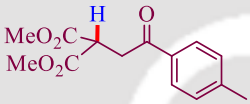
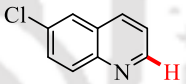
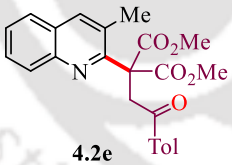
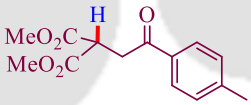
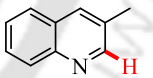
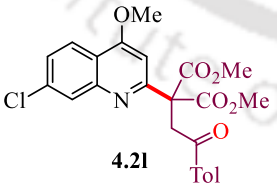
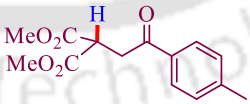
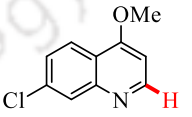
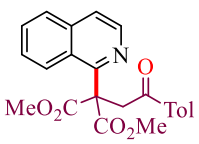
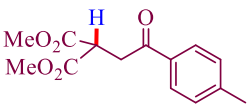
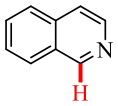


Entry	Equivalent of DIBAL-H	Time (in hour)	Yield of **5.1a** (%)	Yield of **2.1a** (%)
1	2	12	56	52
2	4	12	70	71

3	6	12	82	82
4	6	3	84	83
5	6	2	68	67
6[b]	6	3	12	8

Reaction conditions:[a] **4.2a** (0.2 mmol, 1 equiv.), DIBAL-H (x equiv.), THF (5 mL), -60 ºC, under Ar atmosphere. [b]Performed at room temperature.

Table 5.2: substrate scope with different substituted quinolines

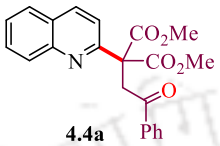
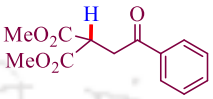
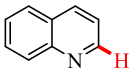
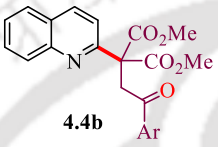
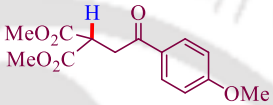
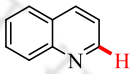
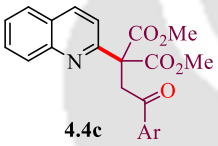
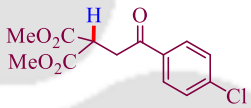
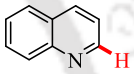
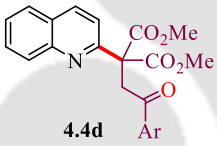
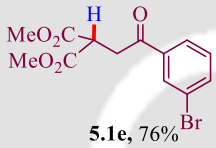
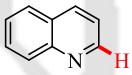
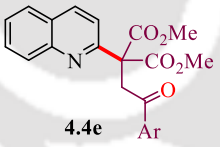
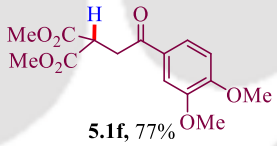
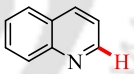
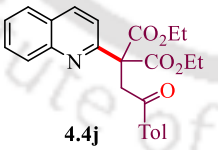
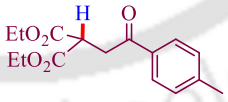
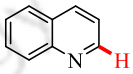
Entry	Substrate	Product 5.1, yield	Product 2.1, yield
1	 **4.2a**	 **5.1a**, 84%	 **2.1a**, 83%
2	 **4.2b**	 **5.1a**, 86%	 **2.1b**, 83%
3	 **4.2c**	 **5.1a**, 86%	 **2.1c**, 82%
4	 **4.2d**	 **5.1a**, 84%	 **2.1d**, 81%
5	 **4.2e**	 **5.1a**, 75%	 **2.1i**, 70%
6	 **4.2l**	 **5.1a**, 85%	 **2.2t**, 83%
Other *N*-heteroarene systems			
7	 **4.3a**	 **5.1a**, 80%	 **2.4a**, 84%

Reaction conditions: 4.2, **4.3** (0.2 mmol, 1 equiv.), DIBAL-H (1.2 mmol, 6 equiv), THF (5 mL), -60 ºC, 3 hr, under Ar atmosphere.

5.3.2. Substrate scope investigation

With optimization condition in hand, scope of the reaction was examined by employing a variety of substituted quinoline containing C2-alkylated γ-keto diester compounds **4.2a-l**. Substituents at the 6-position of the quinoline moiety (**4.2b-d**) gave the corresponding dissociated

Table 5.3: substrate scope with different γ-ketodiester moieties

Entry	Substrate	Product 5.1, yield	Product 2.1a, 2.4a, yield
1	 **4.4a**	 **5.1b,** 88%	 **2.1a**, 86%
2	 **4.4b**	 **5.1c,** 86%	 **2.1a**, 81%
3	 **4.4c**	 **5.1d,** 87%	 **2.1a**, 82%
4	 **4.4d**	 **5.1e,** 76%	 **2.1a**, 76%
5	 **4.4e**	 **5.1f,** 77%	 **2.1a**, 77%
6	 **4.4j**	 **5.1g,** 81%	 **2.1a**, 77%

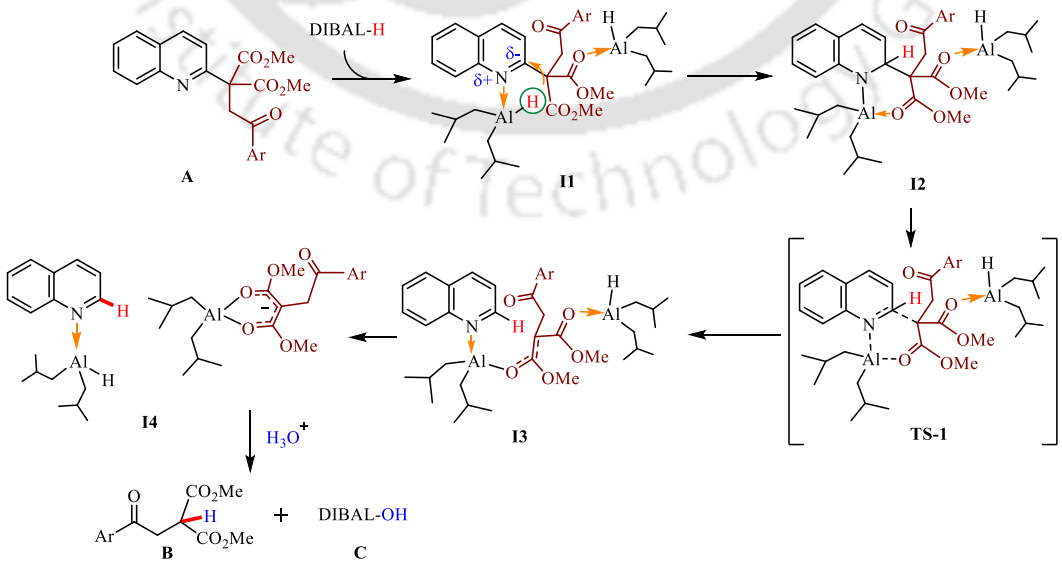
Reaction conditions: 4.4 (0.2 mmol, 1 equiv.), DIBAL-H (1.2 mmol, 6 equiv), THF (5 mL), -60 ºC, 3 hr, under Ar atmosphere.

products **5.1a** and **2.1b-d** in good yields (81-86%) (table 5.2). Interestingly, 3-methyl quinoline containing substrate **4.2e** also provided the corresponding products **5.1a** and **2.1i**, with slightly lower yield (75 and 70%, respectively) which might be due to steric influence (table 5.2, entry 5). Polysubstituted quinoline containing substrate **4.2l** can also provide the desired fission product quinoline **2.2t** and diester **5.1a** (table 5.2, entry 6). Furthermore, the substrate scope could also be expanded to other *N*-heteroarene such as isoquinoline derivative **4.3a** (table 5.2, entry 7). Then scope of the reaction was further explored with different aromatic substituent

containing γ-ketodiester derivatives **4.4a-e**, **4.4j**. Both electron-donating (-OMe) and electron-withdrawing (-Cl) functional group at the *para*-position are proceeded smoothly gave the desired product **5.1c-d** (86% and 87%, respectively) and **2.1a** (table 5.3, entry 2-3). When *meta*-substituted aryl group containing γ-ketodiester compound **4.4d** was subjected to the reaction conditions, corresponding product **5.1e** was obtained in slightly lower yield of 76% (table 5.3, entry 4). Further, 3,4-dimethoxy substituted aryl group containing substrate **4.4e** gave the fission product **5.1f** (in 77% yield) (table 5.3, entry 5). Besides this, different ester group containing substrate **4.4j** also yielded the corresponding fragmented products in good yields (table 5.3, entry 6).

5.3.3. Mechanistic investigation

To understand the role of DIBAL-H in the reductive cleavage of C(sp^2)-C(sp^3) bonds, I have performed DFT calculations using B3LYP level of theory with def2SVP functional. Based on the theoretical calculations, experimental observation and literature reports, the plausible reaction pathway has been depicted in scheme 5.4. Since > 2 equivalents of DIBAL-H are required for the complete conversion of the substrate, it is believed that same DIBAL-H may not activate both quinoline and diester moiety *via* chelation. One DIBAL-H first formed a Lewis acid-base adduct with the nitrogen-center of the quinoline and other DIBAL-H unit may activate the ketodiester moiety in the **A**, to give intermediate **I1** in an endothermic process (ΔG = 4.1 kcal/mol) (figure 5.2). On the other hand, conventional Lewis acid-base adduct formation with simple quinoline and DIBAL-H is a spontaneous process (ΔG = -18.3 kcal/mol) (figure 5.2). Hence, the possible involvement of sterically congested γ-ketodiester moiety at the C2 position may destabilize the species **I1**. Then, hydride transfer occurs from *N*-coordinated DIBAL-H to the electrophilic C2-carbon center of the quinoline moiety, producing a dearomatized product **I2** in an energetically downhill process (ΔG = -19.2 kcal/mol). Notably, C2-C(sp^3) bond at the C2-center of quinoline is elongated from 1.55 Å to 1.60 Å in **I1** → **I2**. It may undergo subsequent C-C bond cleavage to give aromatized product **I3** (**I2** → **I3**; ΔG = -34.5 kcal/mol) *via* barrier of 24.1 kcal/mol (**TS-1**). Then, **I3** converted to **I4** in a further energetically downhill process (**I3** → **I4**; ΔG = -14 kcal/mol), subsequent aqueous work up leads to dissociated product **B** and **C** respectively.



Scheme 5.4: proposed mechanism

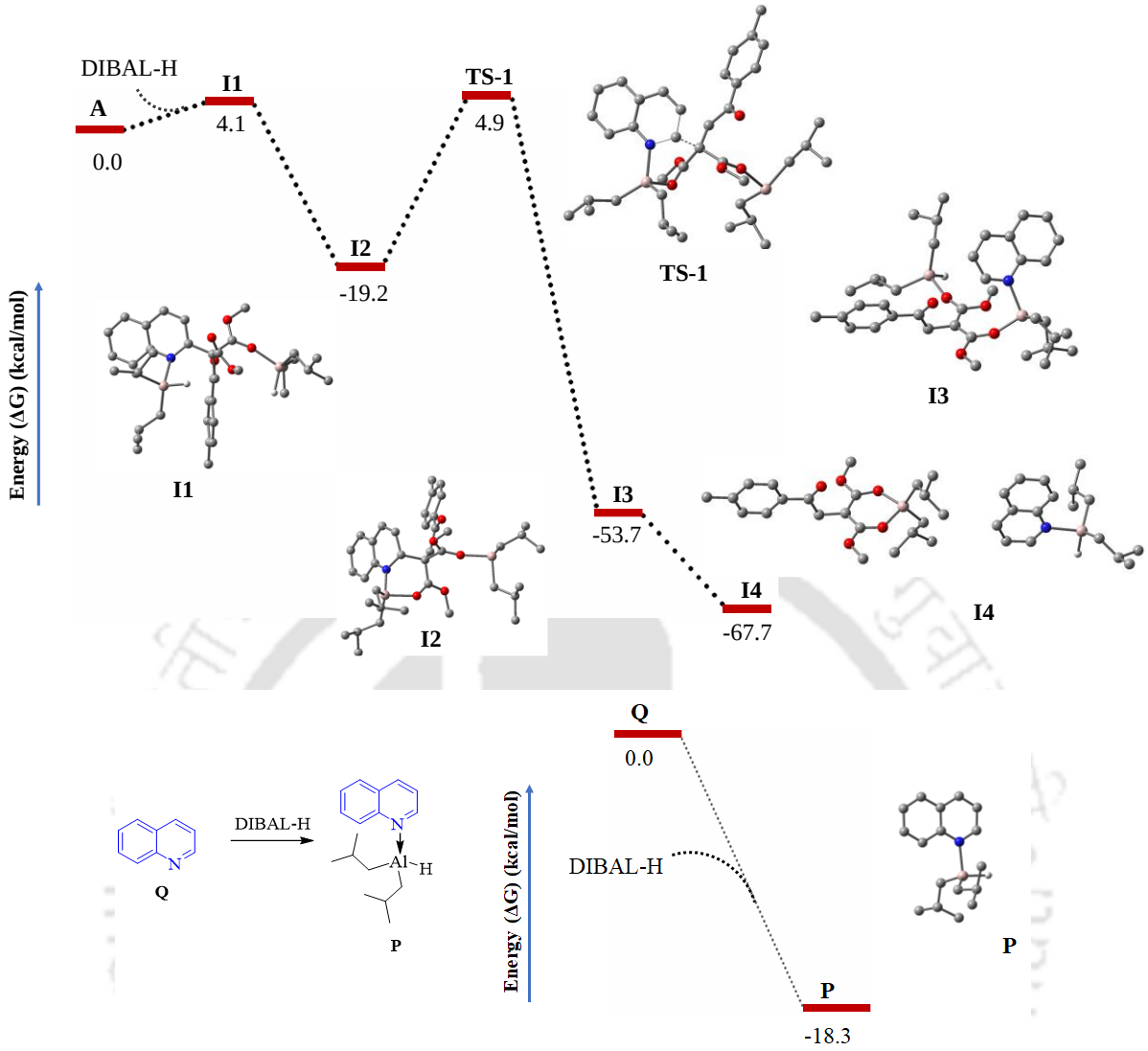


Figure 5.2: energy profile diagram from DFT analysis

5.4. Summary

Herein, an unpresented DIBAL-H mediated reductive cleavage of unstrained C(sp^2)-C(sp^3) bond have been demonstrated in the quinoline containing C2-alkylated γ-keto diester derivatives. Surprisingly, ester and keto moiety is intact under the reaction condition. The process gives two fragments parent quinoline and β-ketodiester compound where two new CH bonds are formed. DIBAL-H plays a dual role as a Lewis acid and as a hydride source. The mechanism of the reaction is studied through DFT calculations to put forward a plausible reaction pathway.

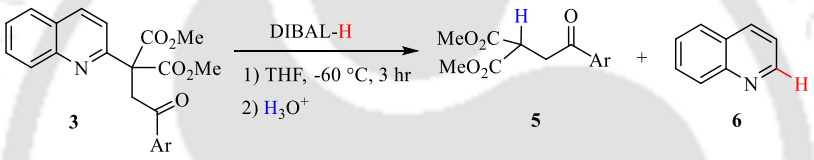
5.5. Experimental section

5.5.1. General information

All the reagents and chemicals were purchased from common commercial suppliers like Sigma-Aldrich, Alfa Aesar, Merck, Spectrochem, Avra Synthesis Pvt. Ltd. and directly used as received without any further purification unless otherwise mentioned. THF was freshly dried using Na/benzophenone. ^{1}H and ^{13}C NMR spectra of the compounds were measured in $CDCl_3$

as a solvent by using TMS as an internal standard. Chemical shifts, δ (in ppm), are reported relative to TMS δ (^{1}H) 0.0 ppm, δ (^{13}C) 0.0 ppm, which was used as the internal reference. Otherwise the solvents residual proton resonance and carbon resonance $CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.16 ppm was used for calibration. Bruker Avance III 600, 500 and 400 spectrometers were used to record the NMR spectra. Chemical shifts (δ) values were reported in ppm and spin-spin coupling constant (J) were expressed in Hz, and other data were reported as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quartet, sext = sextet, br = broad, and brs = broad singlet. IR spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520. Merck silica gel 60-120 was used for column chromatography. All the prepared compounds were characterized by spectroscopic methods and compared to literature wherever applicable, otherwise stated. All the dissociation reactions were carried out in oven-dried glassware under inert atmosphere. Completion of reactions was examined by thin layer chromatography carried out on pre-coated Merck silica gel 60 F_{254} aluminium plates with ultraviolet light (UV) or iodine as visualizing agents.

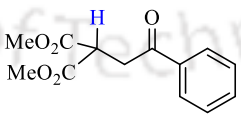
5.5.2. General procedure for C-C bond breaking procedure (G-1):



A 50-mL schlenk flask was properly evacuated and flushed with argon. To this, compound **3** (0.12 mmol, 1 equiv.) in dry THF (3 mL) was added. Then at -60 C, DIBAL-H (102 mg, 0.72 mmol, 6 equiv.) was added dropwise. After complete addition, the reaction mixture was stirred at that temperature for 3 hours when TLC showed complete consumption of starting materials. Then the reaction was quenched by adding 5 mL aq. HCl solution (1 M) and extracted with EtOAc and the organic layer was dried over anhydrous Na_2SO_4. The volatiles were evaporated under reduced pressure and the crude products were purified by silica gel column chromatography.

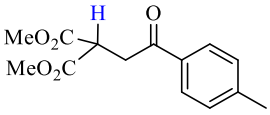
5.5.3. Spectroscopic data

Dimethyl 2-(2-oxo-2-phenylethyl)malonate (5.1b)



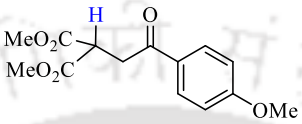
The title compound was obtained by silica gel column chromatography (EtOAc:petroleum ether 1:5) as yellow oil (26 mg, 88%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, J = 7.0 Hz, 1H), 7.56 (t, J = 7.4 Hz, 0H), 7.45 (t, J = 7.8 Hz, 1H), 4.07 (t, J = 7.1 Hz, 1H), 3.76 (s, 4H), 3.63 (d, J = 7.0 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 196.5, 169.5, 136.0, 133.7, 128.8, 128.2, 52.9, 46.9, 38.0.[12]

Dimethyl 2-(2-oxo-2-(p-tolyl)ethyl)malonate (5.1a)



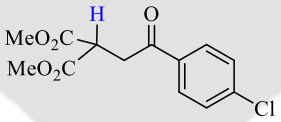
The title compound was obtained by silica gel column chromatography (EtOAc:petroleum ether 1:5) as yellow oil (27 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.01 (t, J = 7.0 Hz, 1H), 3.70 (s, 6H), 3.54 (d, J = 7.0 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 169.6, 144.6, 133.6, 129.5, 128.4, 52.9, 47.0, 37.9, 21.8. [12]

Dimethyl 2-(2-(4-methoxyphenyl)-2-oxoethyl)malonate (5.1c)



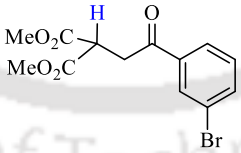
The title compound was obtained by silica gel column chromatography (EtOAc:petroleum ether 1:5) as yellow oil (29 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, J = 7.2 Hz, 2H), 6.94 (d, J = 7.8 Hz, 2H), 4.08 (t, J = 4.2 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 6H), 3.60 (d, J = 4.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.0, 169.7, 164.0, 130.6, 129.2, 114.0, 55.7, 53.0, 47.0, 37.7. [13]

Dimethyl 2-(2-(4-chlorophenyl)-2-oxoethyl)malonate (5.1d)



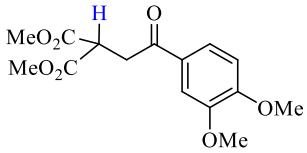
The title compound was obtained by silica gel column chromatography (EtOAc:petroleum ether 1:5) as yellow oil (30 mg, 87%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 4.07 (t, J = 7.0 Hz, 1H), 3.78 (s, 6H), 3.60 (d, J = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 169.4, 140.2, 134.4, 129.7, 129.2, 53.0, 46.9, 38.0. [12]

Dimethyl 2-(2-(3-bromophenyl)-2-oxoethyl)malonate (5.1e)



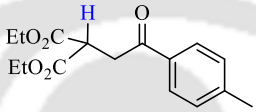
The title compound was obtained by silica gel column chromatography (EtOAc:petroleum ether 1:5) as yellow oil (30 mg, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.70 (dd, J = 8.0, 2.0 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 4.07 (t, J = 7.0 Hz, 1H), 3.78 (s, 6H), 3.60 (d, J = 7.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.3, 169.3, 137.8, 136.6, 131.3, 130.4, 126.8, 123.2, 53.1, 46.8, 38.1. [12]

Dimethyl 2-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)malonate (5.1f)



The title compound was obtained by silica gel column chromatography (EtOAc:petroleum ether 1:5) as yellow oil (27 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, J = 8.4, 2.0 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.08 (t, J = 7.0 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.78 (s, 6H), 3.61 (d, J = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.1, 169.7, 153.9, 149.3, 129.4, 123.1, 56.3, 56.2, 53.0, 47.1, 37.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{19}O_7$: 311.1126; found: 311.1112. FT-IR (KBr, selected band): 1747, 1726, 1681 cm^{-1}.

Diethyl 2-(2-oxo-2-(p-tolyl)ethyl)malonate (5.1g)



The title compound was obtained by silica gel column chromatography (EtOAc:petroleum ether 1:5) as yellow oil (28 mg, 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 7.8 Hz, 2H), 4.26 – 4.20 (m, 4H), 4.05 (t, J = 7.2 Hz, 1H), 3.60 (d, J = 7.2 Hz, 2H), 2.41 (s, 2H), 1.29 (t, J = 7.2 Hz, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.2, 169.2, 144.5, 133.7, 129.4, 128.4, 61.8, 47.4, 37.8, 21.8, 14.1. [12]

5.5.4. Computational studies

All calculations were performed using the Gaussian-16 program package.[14] Full geometry optimizations were carried out using Kohn-Sham hybrid-DFT B3LYP[15] level of theory and the standard double-ζ quality def2SVP basis set.[16] Frequency calculations at the same method and basis set were performed to distinguish transition state structures (one imaginary frequency) and minima structures (no imaginary frequency) on the potential energy surface. The transition states were verified by the intrinsic reaction coordinate (IRC) calculations, wherever necessary.[17] Free energies were calculated by using frequency calculations at -60 °C to match the experimental conditions.

Table 5.4. Free Energies (G) and Total Energies (E) given in Hartree along with the number of imaginary frequencies

Species	Free energy (G)	Total energy (E)	# Imaginary Frequency (NImag)
A	-2435.142499	-2435.9691924	0
I1	-2435.135975	-2435.9696543	0
I2	-2435.173100	-2436.0111397	0
TS-1	-2435.165318	-2436.0030941	1

I3	-2435.228016	-2436.0637713	0
I4	-2435.250428	-2436.0817515	0
Q	-959.743255	-960.0884202	0
P	-959.772424	-960.1242329	0

[a](G) is calculated at -60 °C to meet the experimental conditions. All the figures were generated using (G) values. The transition state has one NImag and all the reactants, intermediates and products have zero NImag. All the calculations were performed at B3LYP level of DFT.

5.6. References:

1. For some selected reviews, see: (a) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417– 1492, (b) Magano, J.; Dunetz, J. R. Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of Pharmaceuticals. *Chem. Rev.* **2011**, *111*, 2177– 2250, (c) Kwiatkowski, M. R.; Alexanian, E. J. Transition-Metal (Pd, Ni, Mn)-Catalyzed C-C Bond Constructions Involving Unactivated Alkyl Halides and Fundamental Synthetic Building Blocks. *Acc. Chem. Res.* **2019**, *52*, 1134– 1144, (d) Kaga, A.; Chiba, S. Engaging Radicals in Transition Metal-Catalyzed Cross-Coupling with Alkyl Electrophiles: Recent Advances. *ACS Catal.* **2017**, *7*, 4697– 4706, (e) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C–H Bonds. *Chem. Rev.* **2017**, *117*, 8754– 8786.

2. Squires, A. M. Chemicals from Coal. *Science* **1976**, *191*, 689–700.

3. For some related reviews, see: (a) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. [3,3]-Sigmatropic Rearrangements: Recent Applications in the Total Synthesis of Natural Products. *Chem. Soc. Rev*. **2009**, *38*, 3133– 3148, (b) Tomiczek, B. M.; Grenning, A. J. Aromatic Cope Rearrangements. *Org. Biomol. Chem*. **2021**, *19*, 2385-2398, (c) Kaur, K.; Srivastava, S. Beckmann Rearrangement Catalysis: A Review of Recent Advances. *New J. Chem*. **2020**, *44*, 18530– 18572, (d) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. The Baeyer–Villiger Reaction: New Developments toward Greener Procedures. *Chem. Rev*. **2004**, *104*, 4105– 4123, (e) Zhang, S.-L.; Yu, Z.-L. C–C Activation by Retro-Aldol Reaction of Two β-Hydroxy Carbonyl Compounds: Synergy with Pd-Catalyzed Cross-Coupling to Access Mono-α-Arylated Ketones and Esters. *J. Org. Chem*. **2016**, *81*, 57– 65.

4. (a) Vougioukalakis, G. C.; Grubbs, R. H. Ruthenium-Based Heterocyclic Carbene-Coordinated Olefin Metathesis Catalysts. *Chem. Rev*. **2010**, *110*, 1746– 1787, (b) Murray, R. W. Mechanism of Ozonolysis. *Acc. Chem. Res*. **1968**, *1*, 313 – 320, (c) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. Ozonolysis Applications in Drug Synthesis. *Chem. Rev.* **2006**, *106*, 2990– 3001.

5. (a) Marek, I.; Masarwa, A.; Delaye, P.-O.; Leibeling, M. Selective Carbon–Carbon Bond Cleavage for the Stereoselective Synthesis of Acyclic Systems. *Angew. Chem., Int. Ed*. **2015**, *54*, 414– 429, (b) Nairoukh, Z.; Cormier, M.; Marek, I. Merging C–H and C–C Bond Cleavage in Organic Synthesis. *Nat. Rev. Chem*. **2017**, *1*, 0035, (c) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies That Exploit C–C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev*. **2017**, *117*, 9404– 9432.

6. (a) Grenoble, D. C. The Chemistry and Catalysis of the Toluene Hydrodealkylation Reaction. *J. Catal*. **1979**, *56*, 32 – 39, (b) Zhu, F.; Johnson, J. A.; Ablin, D. W.; Ernst, G. A. Market and Technology Overview, in *Efficient Petrochemical Processes: Technology, Design and Operation*, John Wiley and Sons: 2020; pp. 21–22, (c) J. Yan, J.; Meng, Q.; Shen, X.; Chen, B.; Sun, J.; Xiang, Y.; Liu, H.; Han, B. Selective Valorization of Lignin to Phenol by Direct Transformation of Csp^2–Csp^3 and C–O bonds. *Sci. Adv*. **2020**, *6*, eabd1951, (d) Meng, Q.; Yan, J.; Wu, R.; Liu, H.; Sun, Y.; Wu, N.; Xiang, J.; Zheng, L.; Zhang, J.; Han, B. Sustainable Production of Benzene from Lignin. *Nat. Commun*. **2021**, *12*, 4534.

7. (a) Smaligo, A. J.; Swain, M.; Wu, J.; Quintana, J. C.; Tan, M. F.; Kim, D. A.; Kwon, O. Hydrodealkenylative $C(sp^3)$–$C(sp^2)$ Bond Fragmentation. *Science* **2019**, *364*, 681–685, (b) Smaligo, A. J.; Kwon, O. Dealkenylative Thiylation of $C(sp^3)$−$C(sp^2)$ Bonds. *Org. Lett.* **2019**, *21*, 8592−8597, (c) Smaligo, A. J.; Wu, J.; Burton, N. R.; Hacker, A. S.; Shaikh, A. C.; Quintana, J. C.; Wang, R.; Xie, C.; Kwon, O. Oxodealkenylative Cleavage of Alkene $C(sp^3)$−$C(sp^2)$ Bonds: A Practical Method for Introducing Carbonyls into Chiral Pool Materials. *Angew. Chem. Int, Ed*. **2020**, *59*, 1211-1215.

8. (a) Gozin, M.; Weisman, A.; Ben-David, Y.; Milstein, D. Activation of a Carbon-Carbon Bond in Solution by Transition-Metal Insertion. *Nature* **1993**, *364*, 699 – 701, (b) Liou, S.-Y.; van der Boom, M. E.; Milstein, D. Catalytic Selective Cleavage of a Strong C–C Single Bond by Rhodium in Solution. *Chem. Commun*. **1998**, *1996*, 687 – 688, (c) van der Boom, M. E.; Kraatz, H.-B.; Hassner, L.; Ben-David, Y.; Milstein, D. *Organometallics* **1999**, *18*, 3873 – 3884, (d) Gauvin, R. M.; Rozenberg, H.; Shimon, L. J. W.; Milstein, D. Synthesis and Structure of New Osmium-PCP Complexes. Osmium-Mediated C-C Bond Activation. *Organometallics* **2001**, *20*, 1719 – 1724, (e) (f) van der Boom, M. E.; Liou, S.-Y.; Shimon, L. J. W.; Ben-David, Y.; Milstein, D. Nickel Promoted C–H, C–C and C–O Bond Activation in Solution. *Inorg. Chim. Acta* **2004**, *357*, 4015 – 4023, (g) Chen, K.; Li, H.; Lei, Z.-Q.; Li, Y.; Ye, W.-H.; Zhang, L.-S.; Sun, J.; Shi, Z.-J. Reductive Cleavage of the Csp^2-Csp^3 Bond of Secondary Benzyl Alcohols: Rhodium Catalysis Directed by N-Containing Groups. *Angew. Chem. Int. Ed.* **2012**, *51*, 9851 –9855, (h) Sakurai, S.; Tobisu, M. Iridium-Mediated Arylation of Quinoline via the Cleavage of Carbon−Carbon and Carbon−Nitrogen Bonds of 1,3- Dimesitylimidazol-2-ylidene. *Organometallics* **2019**, *38*, 2834−2838.

9. (a) Lokhov, R. E.; Gigolaeva, N. D.; Gusalova, É. G.; Avezov, M. Bromination of Quinoline in the Presence of Some Lewis Acids. *Chem. Heterocycl. Compd*. **1985**, *21*, 458 – 460, (b) Elbert, B. L.; Farley, A. J. M.; Gorman, T. W.; Johnson, T. C.; Genicot, C.; Lallemand, B.; Pasau, P.; Flasz, J.; Castro, J. L.; MacCoss, M.; Paton, R. S.; Schofield, C. J.; Smith, M. D.; Willis, M. C.; Dixon, D. J. C–H Cyanation of 6-Ring N-Containing Heteroaromatics. *Chem. - Eur. J.* **2017**, *23*, 14733– 14737, (c) Fier, P. S.; Hartwig, J. F. Selective C-H Fluorination of Pyridines and Diazines Inspired by a Classic Amination Reaction. *Science* **2013**, *342*, 956 – 960.

10. Pandey, A. K.; Ghosh, A.; Banerjee, P. Reactivity of Donor-Acceptor Cyclopropanes with Saturated and Unsaturated Heterocyclic Compounds. *Isr. J. Chem*. **2016**, *56*, 512– 521.

11. (a) Xiao, S.; Yang, M.; Sinaÿ, P.; Blériot, Y.; Sollogoub, M.; Zhang, Y. Diisobutylaluminium Hydride (DIBAL-H) Promoted Secondary Rim Regioselective Demethylations of Permethylated β-Cyclodextrin: A Mechanistic Proposal. *Eur. J. Org. Chem.*

2010, *2010*, 1510 – 1516, (b) Lecourt, T.; Herault, A.; Pearce, A. J.; Sollogoub, M.; Pierre Sinaÿ, P. Triisobutylaluminium and Diisobutylaluminium Hydride as Molecular Scalpels: The Regioselective Stripping of Perbenzylated Sugars and Cyclodextrins. *Chem. - Eur. J.* **2004**, *10*, 2960– 2971, (c) Forster, F.; Metsänen, T. T.; Irran, E.; Hrobárik, P.; Oestreich, M. Cooperative Al–H Bond Activation in DIBAL-H: Catalytic Generation of an Alumenium-Ion-Like Lewis Acid for Hydrodefluorinative Friedel–Crafts Alkylation. *J. Am. Chem. Soc*. **2017**, *139*, 16334–16342.

12. Chowdhury, S. R.; Hoque, I. U.; Maity, S. TBAI/TBHP-Promoted Generation of Malonyl Radicals: Oxidative Coupling with Styrenes Leads to γ-Keto Diesters. *Chem.—Asian J*. **2018**, *13*, 2824– 2828.

13. Di Bussolo, V.; Princiotto, S.; Martinelli, E.; Bordoni, V.; Crotti, P. Dimethyl Malonate/LHMDS System as a New Protocol for Generating Methyl Formate Anion (−COOMe) in the Condensed-phase. *Tetrahedron Lett*. **2016**, *57*, 1644 – 1647.

14. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, Revision C.01, Gaussian, Inc., Wallingford CT, 2016.

15. (a) Becke, A. D. Density-Functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys*, **1993**, *98*, 5648-5652. (b) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev. B.* **1988**, *37*, 785-789.

16. Weigend, F.; Alhrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys*. **2005**, *7*, 3297 – 3305.

17. Fukui, K. The Path of Chemical Reactions - the IRC Approach. *Acc. Chem. Res.* **1981**, *14*, 363 – 368.

Annexure I

^{1}H and ^{13}C NMR spectra of compounds (*Chapter 2*)

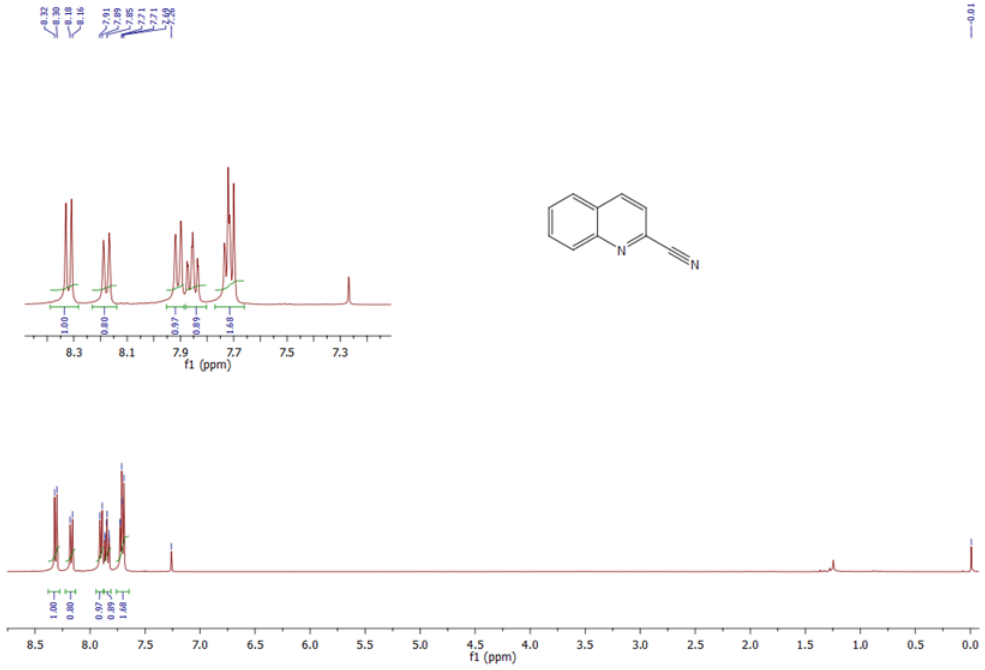


Figure S1: ^{1}H NMR spectrum of **2.3a** (400 MHz, $CDCl_3$, 298 K)

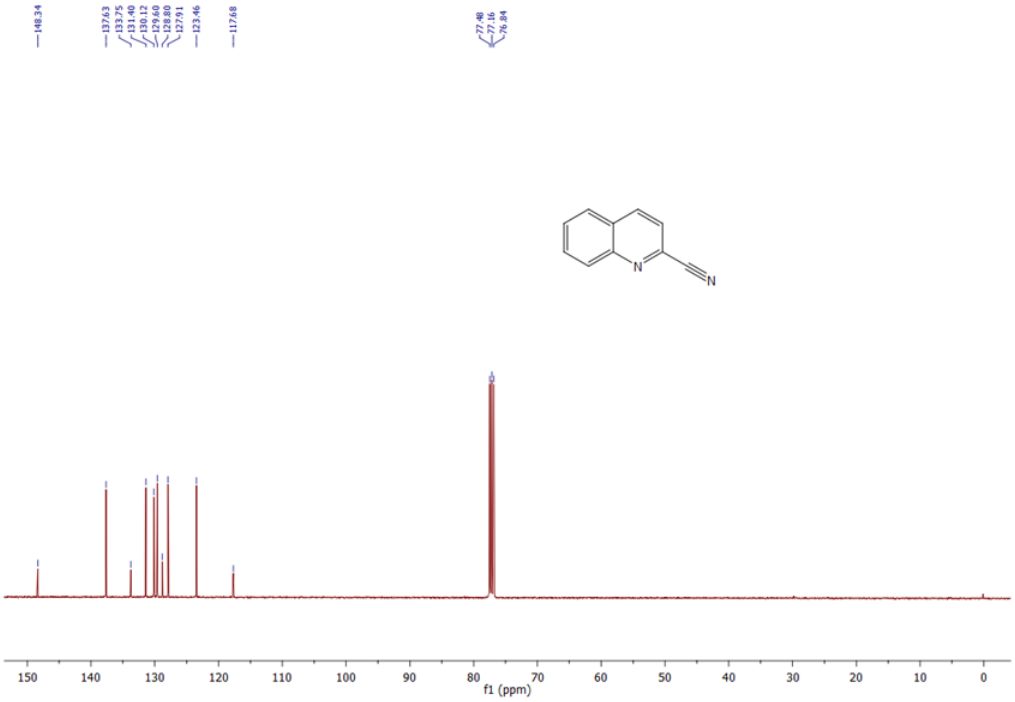


Figure S2: ^{13}C NMR spectrum of **2.3a** (101 MHz, $CDCl_3$, 298 K)

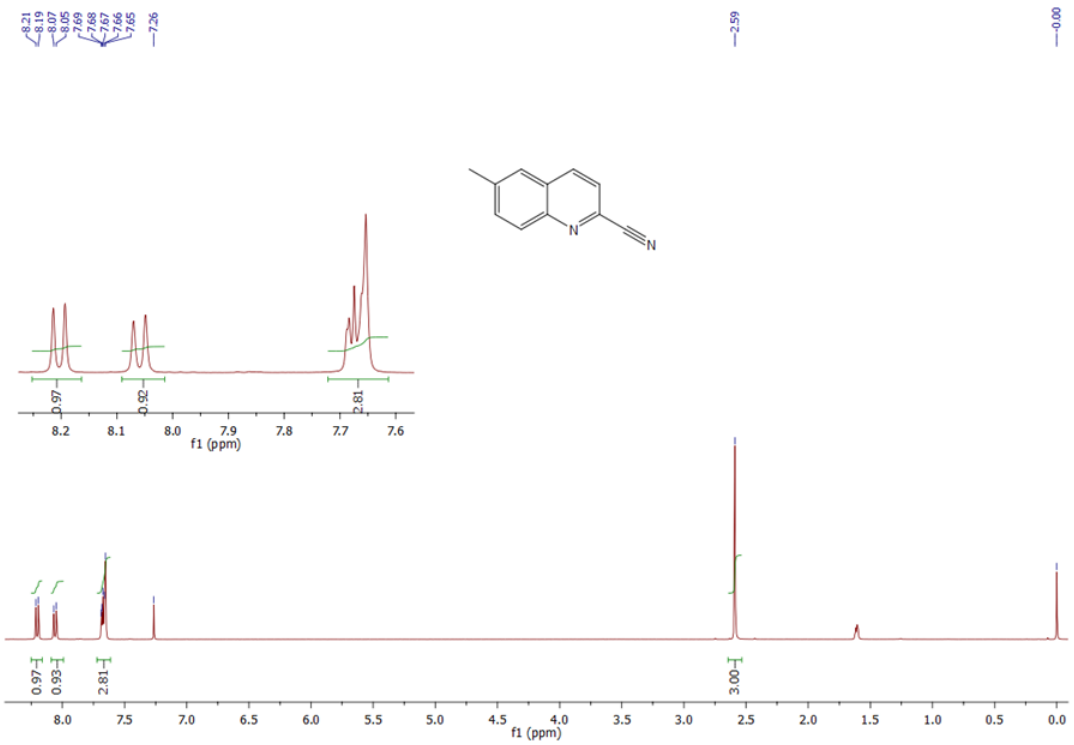


Figure S3: ^{1}H NMR spectrum of **2.3b** (400 MHz, $CDCl_3$, 298 K)

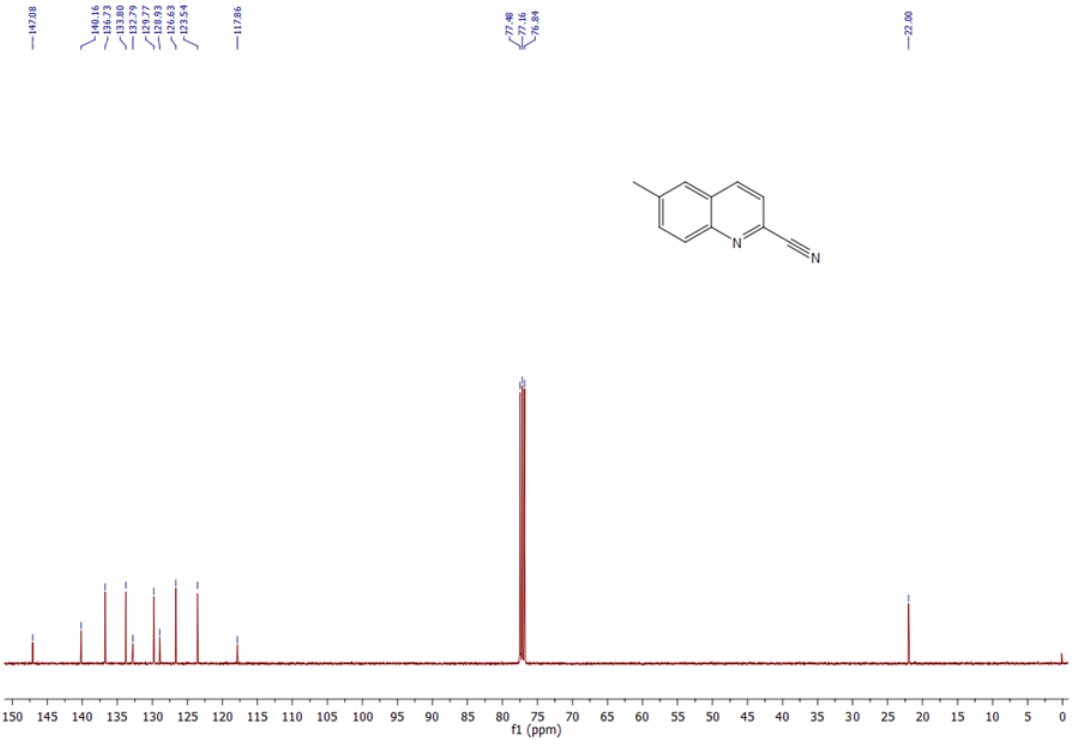


Figure S4: ^{13}C NMR spectrum of **2.3b** (101 MHz, $CDCl_3$, 298 K)

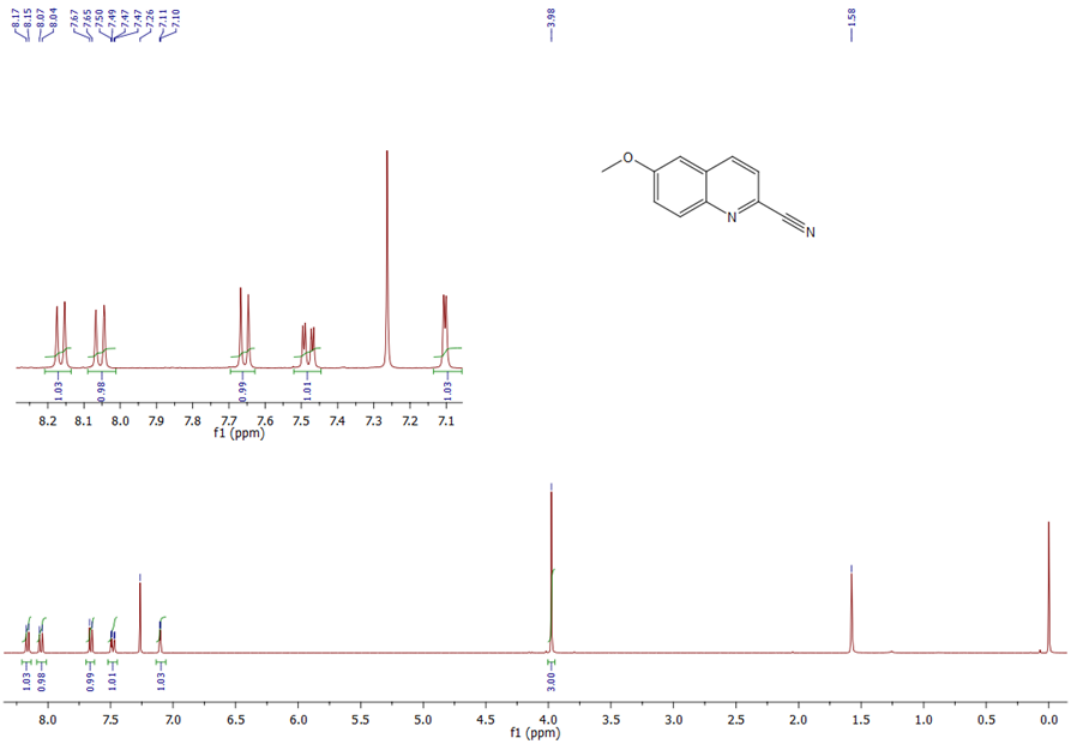


Figure S5: ^{1}H NMR spectrum of **2.3c** (400 MHz, $CDCl_3$, 298 K)

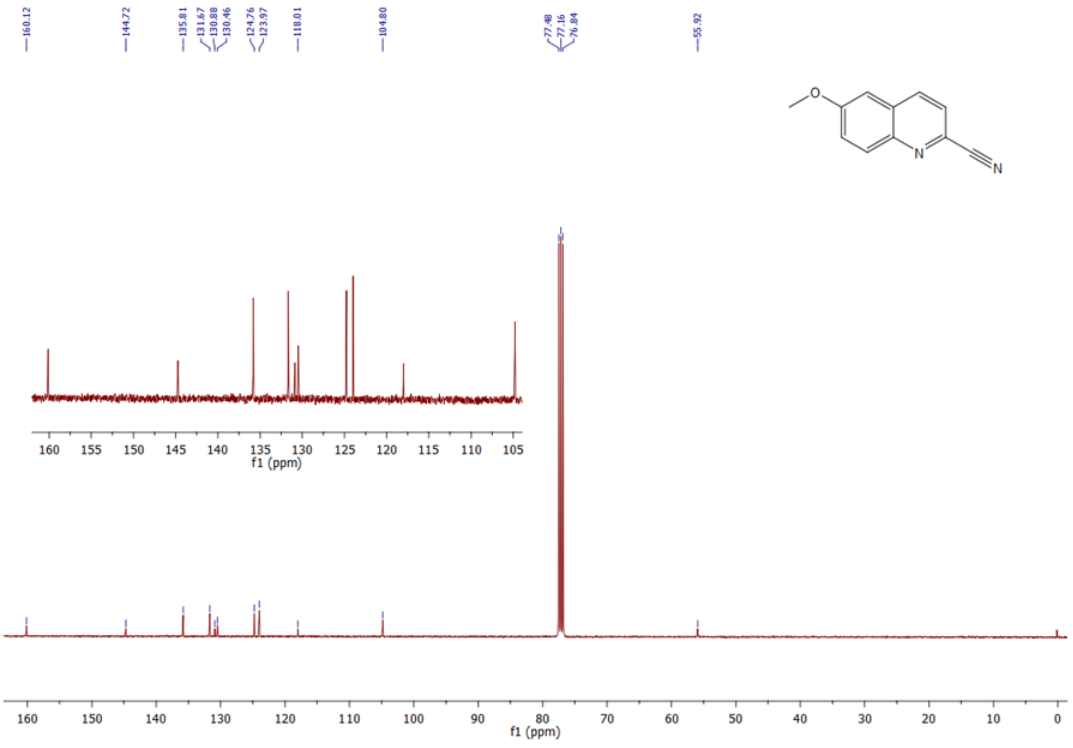


Figure S6: ^{13}C NMR spectrum of **2.3c** (101 MHz, $CDCl_3$, 298 K)

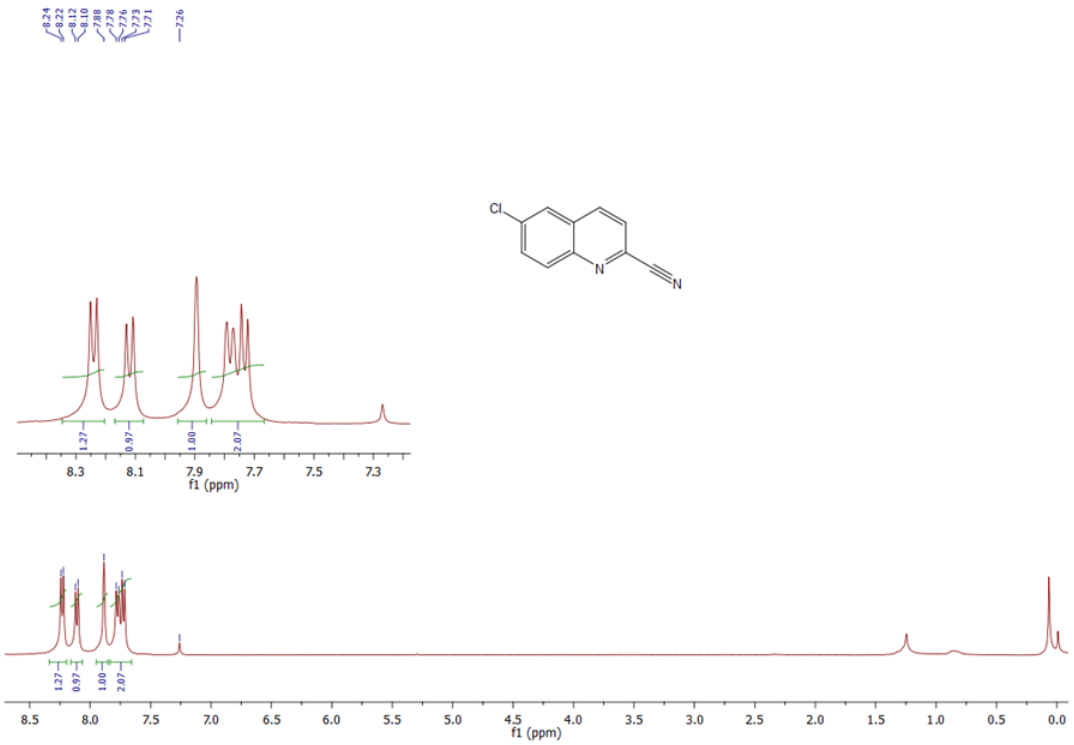


Figure S7: ^{1}H NMR spectrum of **2.3d** (600 MHz, $CDCl_3$, 298 K)

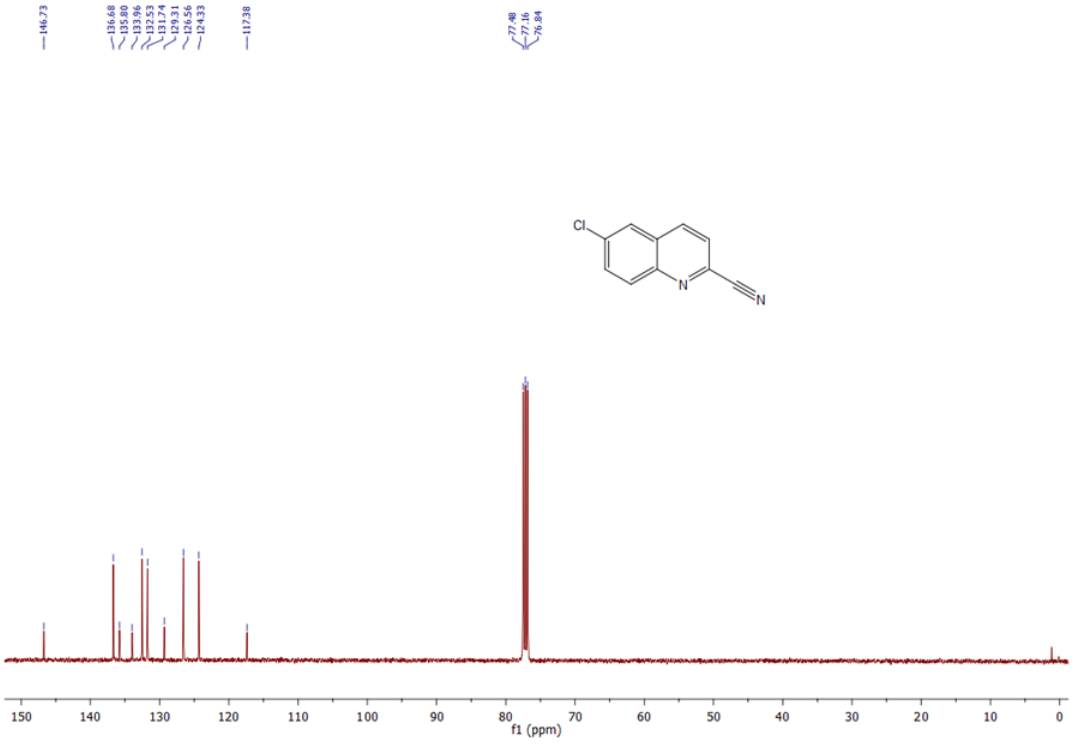


Figure S8: ^{13}C NMR spectrum of **2.3d** (151 MHz, $CDCl_3$, 298 K)

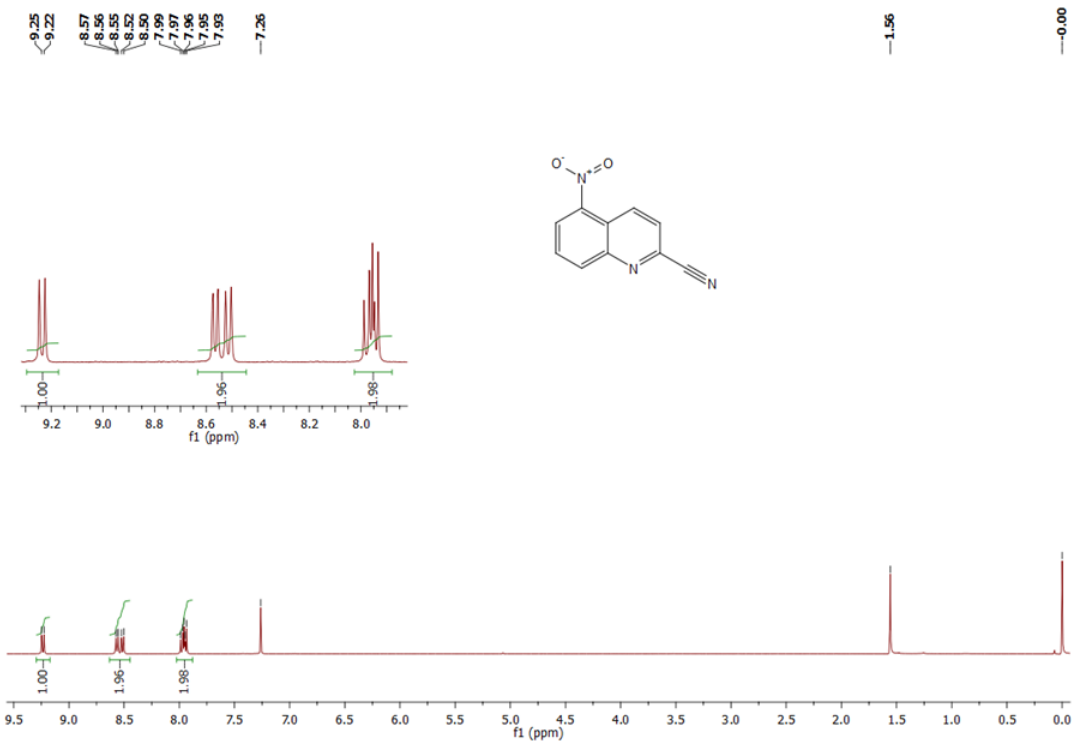


Figure S9: ^{1}H NMR spectrum of **2.3e** (400 MHz, $CDCl_3$, 298 K)

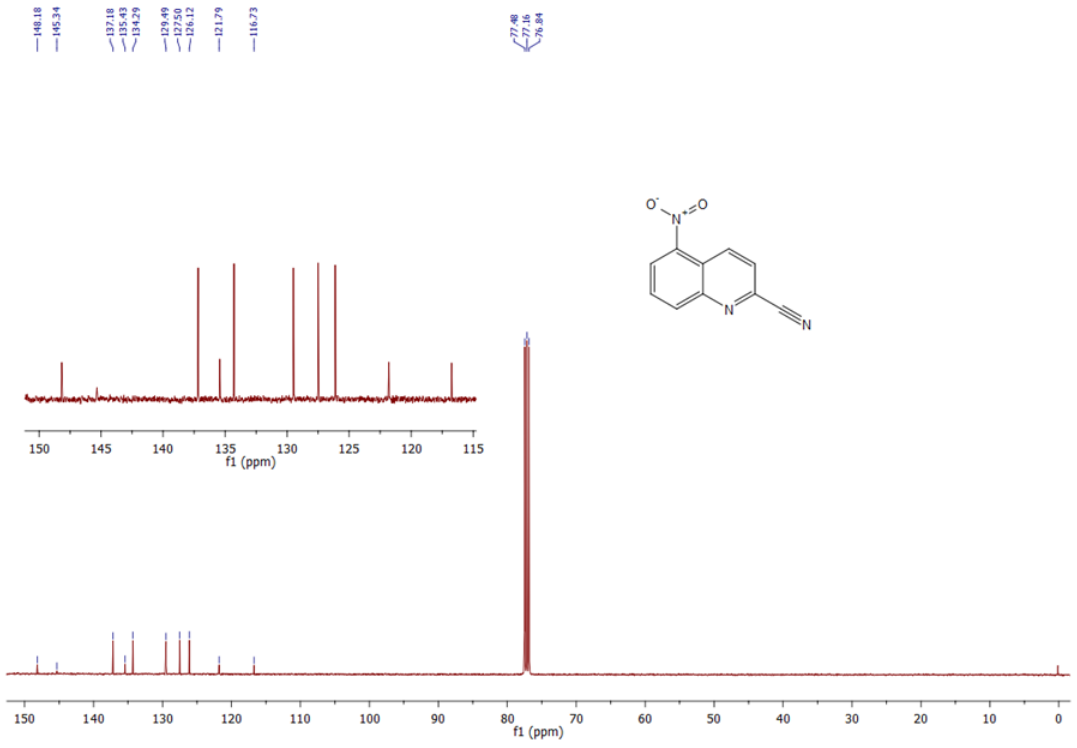


Figure S10: ^{13}C NMR spectrum of **2.3e** (101 MHz, $CDCl_3$, 298 K)

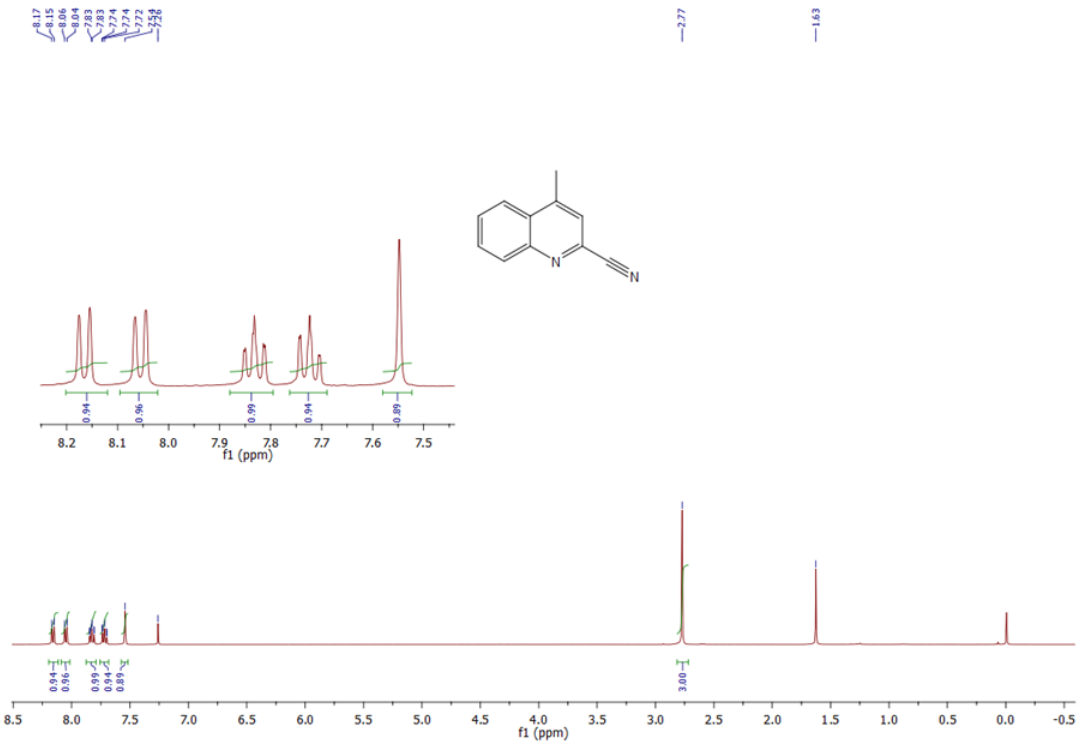


Figure S11: ^{1}H NMR spectrum of **2.3f** (400 MHz, $CDCl_3$, 298 K)

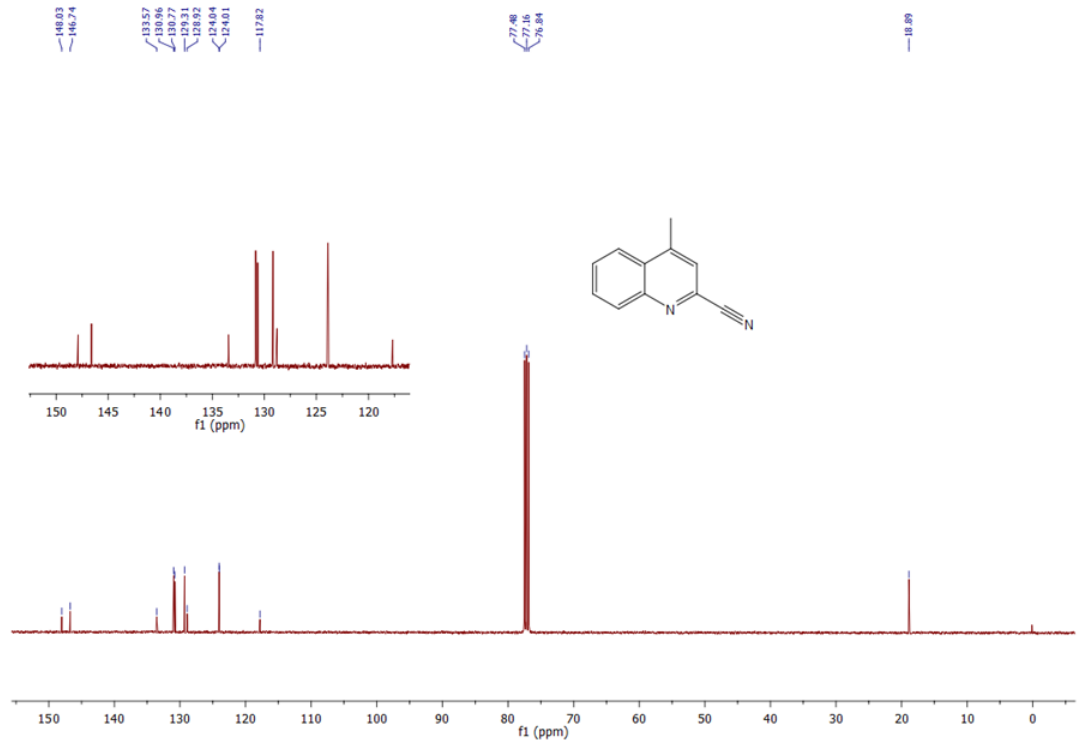


Figure S12: ^{13}C NMR spectrum of **2.3f** (101 MHz, $CDCl_3$, 298 K)

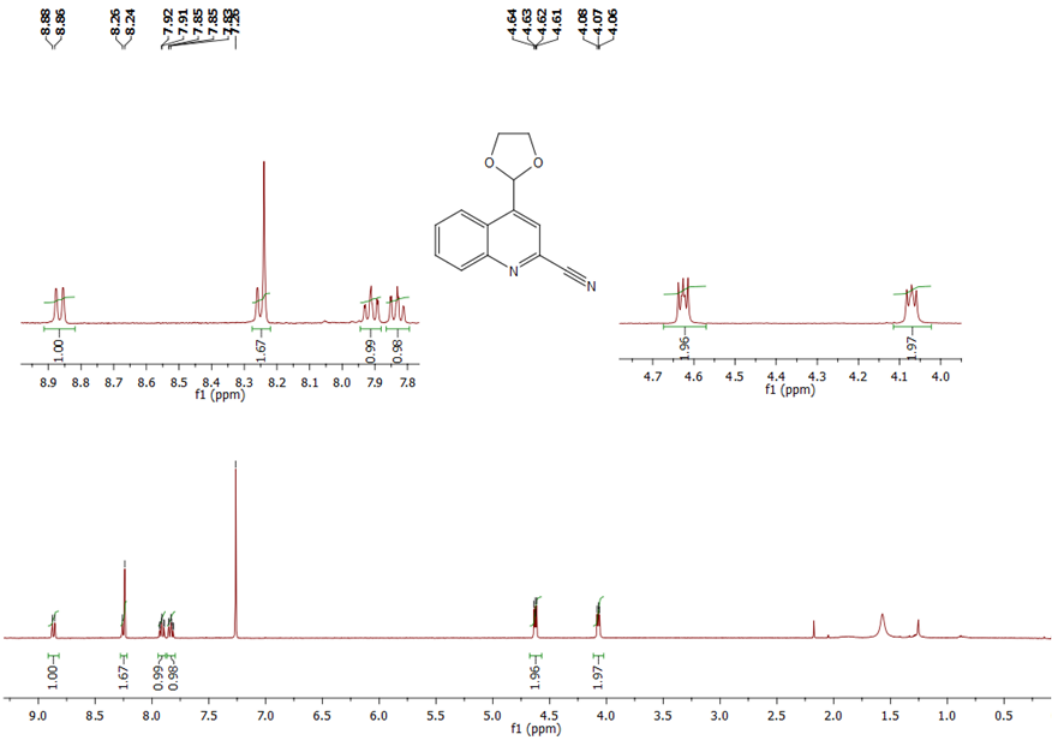


Figure S13: ^{1}H NMR spectrum of **2.3g** (400 MHz, $CDCl_3$, 298 K)

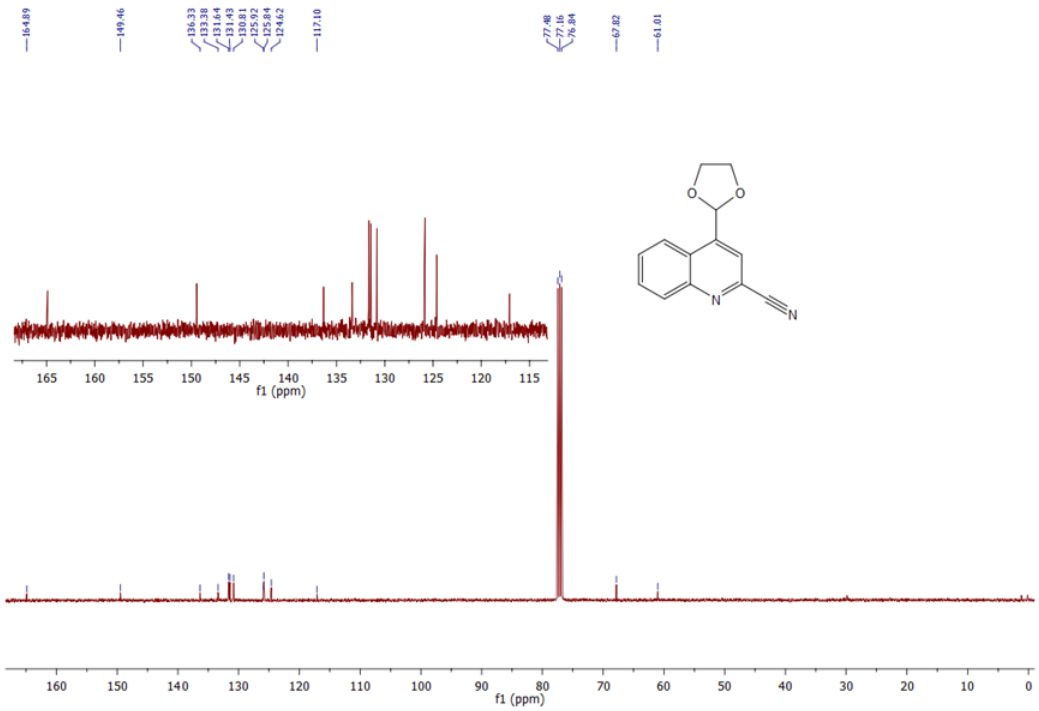


Figure S14: ^{13}C NMR spectrum of **2.3g** (101 MHz, $CDCl_3$, 298 K)

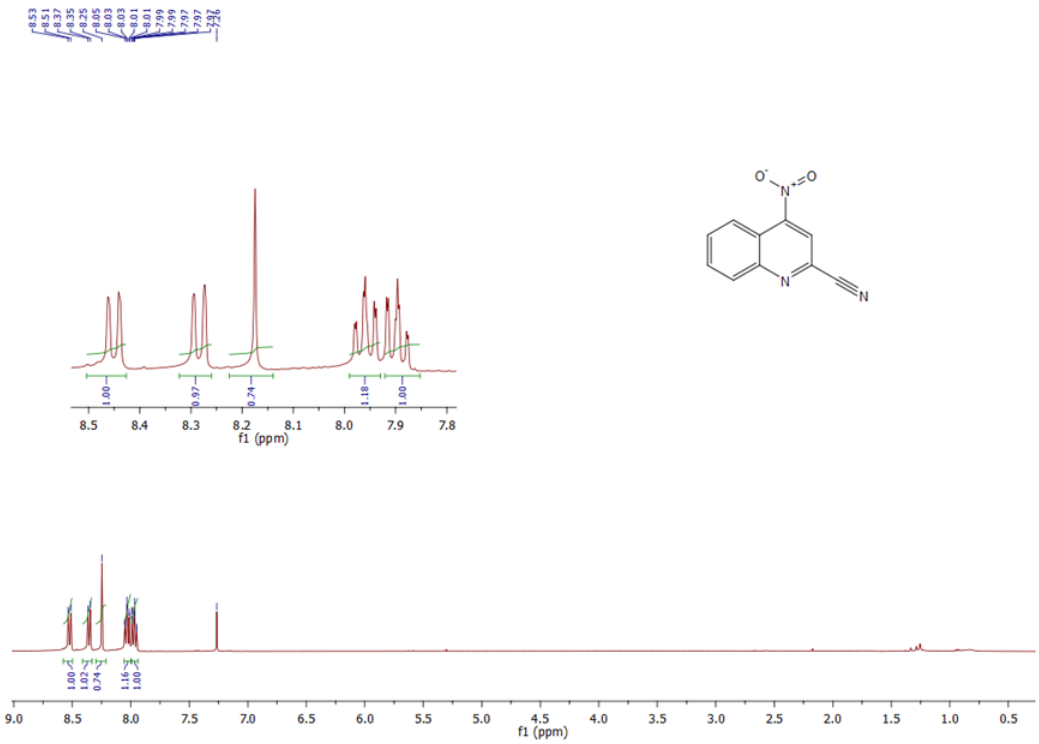


Figure S15: ^{1}H NMR spectrum of **2.3h** (400 MHz, $CDCl_3$, 298 K)

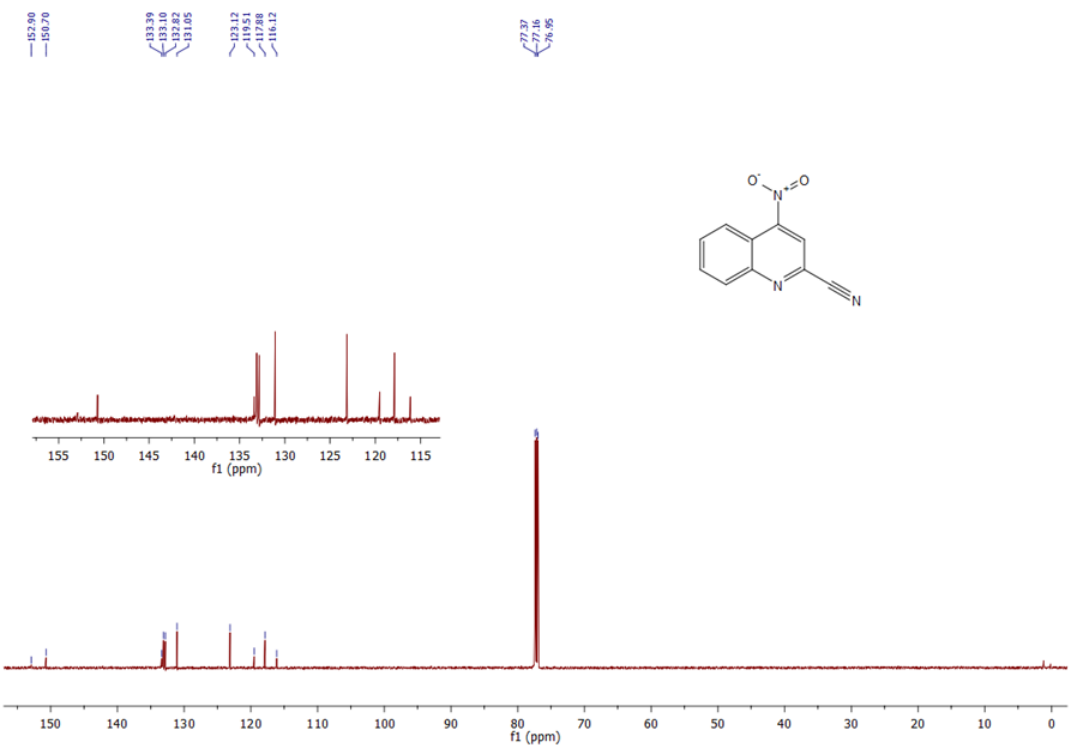


Figure S16: ^{13}C NMR spectrum of **2.3h** (101 MHz, $CDCl_3$, 298 K)

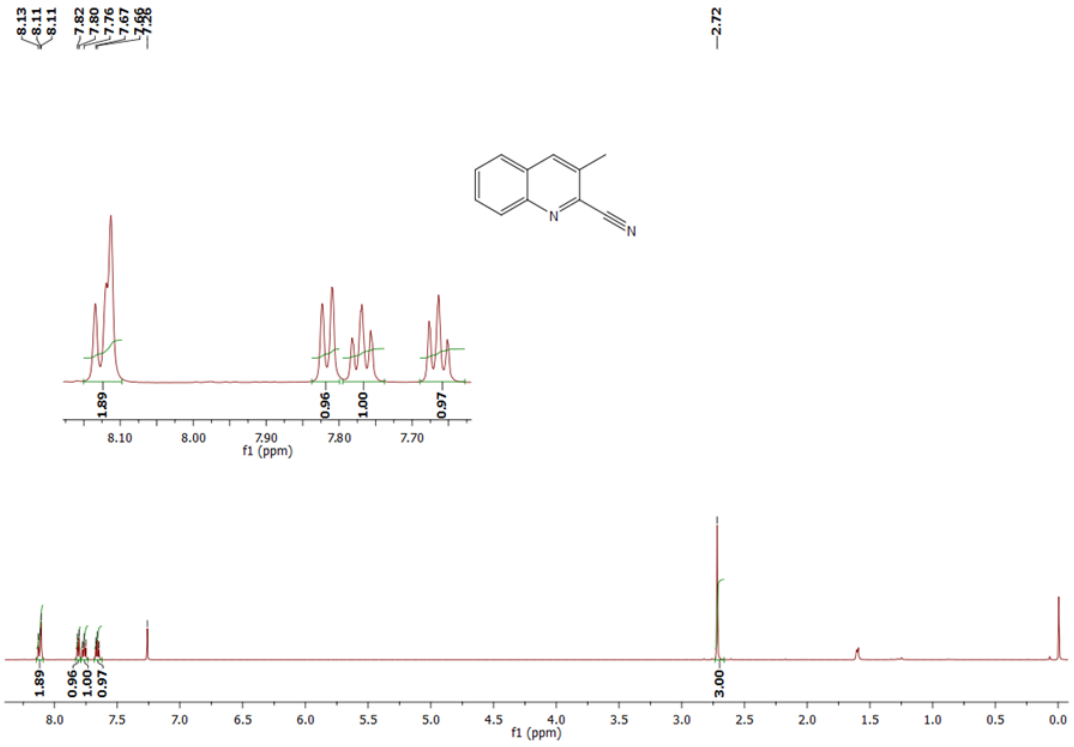


Figure S17: ^{1}H NMR spectrum of **2.3i** (600 MHz, $CDCl_3$, 298 K)

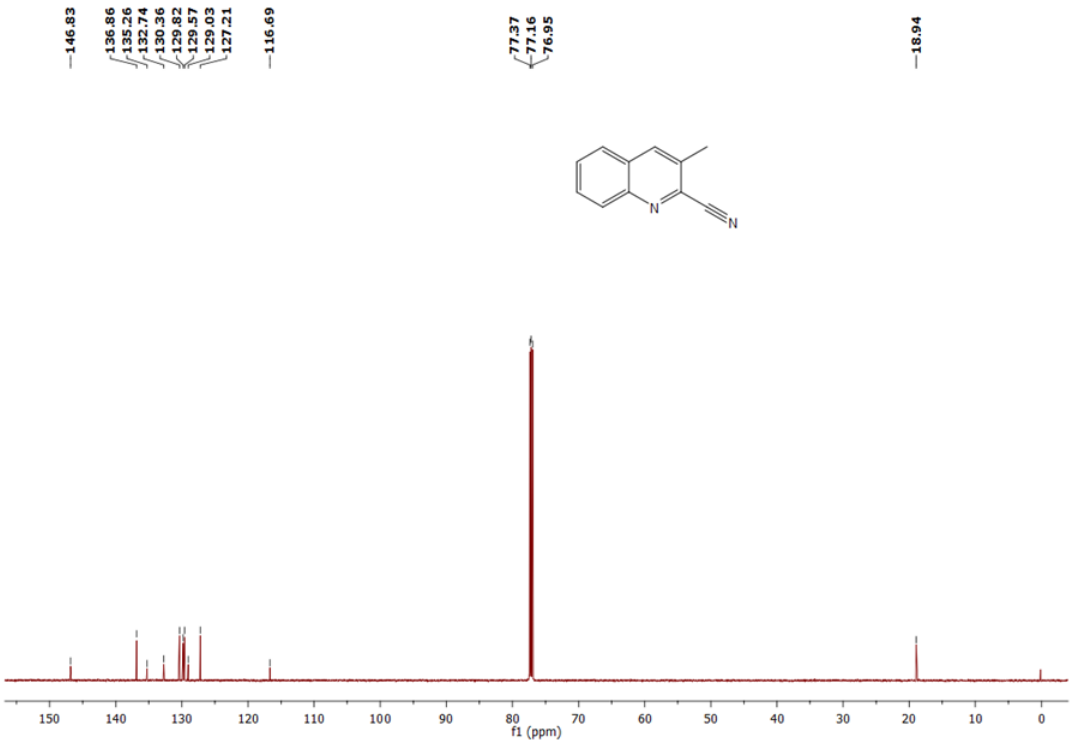


Figure S18: ^{13}C NMR spectrum of **2.3i** (151 MHz, $CDCl_3$, 298 K)

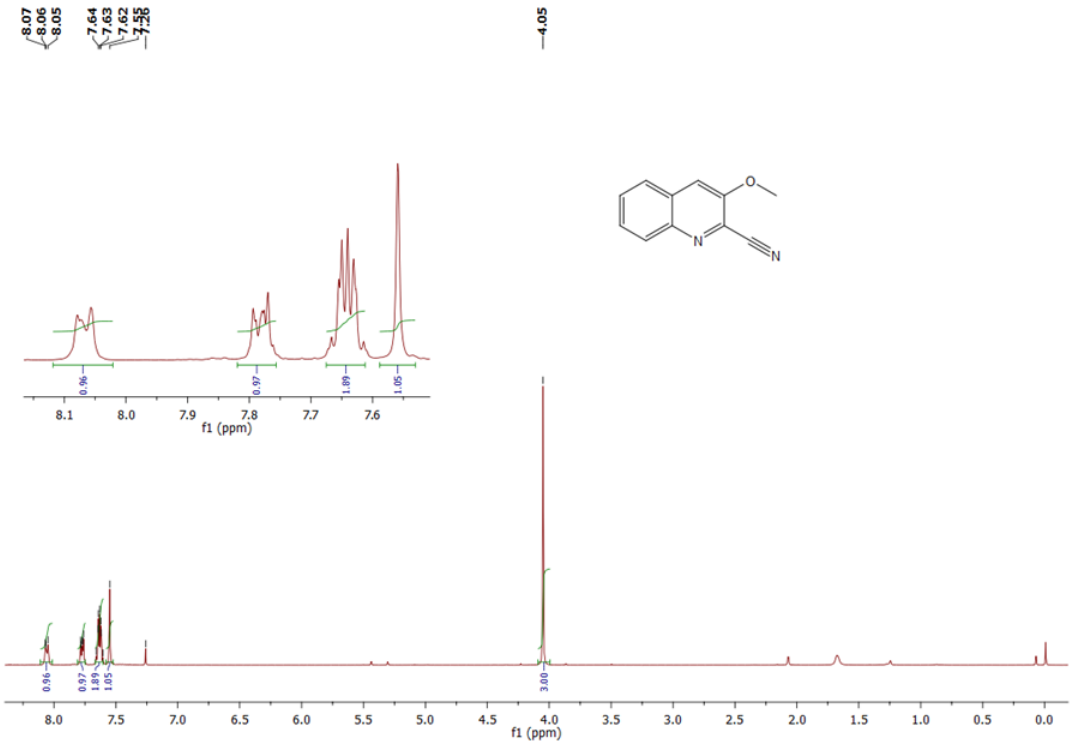


Figure S19: ^{1}H NMR spectrum of **2.3j** (400 MHz, $CDCl_3$, 298 K)

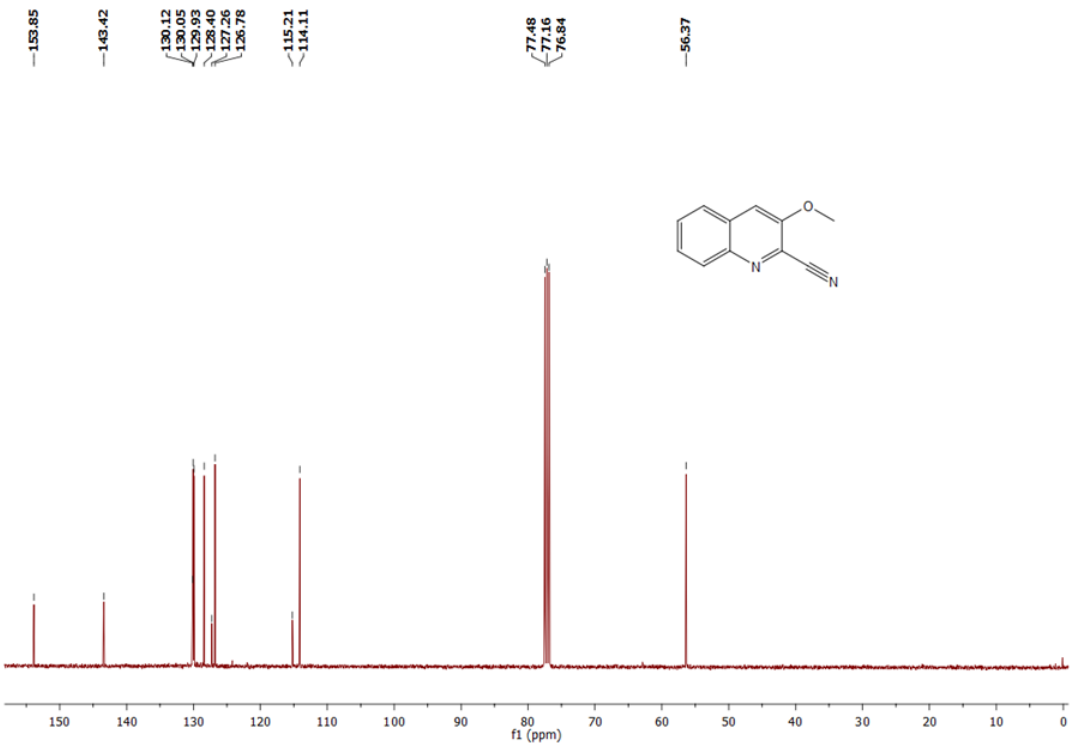


Figure S20: ^{13}C NMR spectrum of **2.3j** (101 MHz, $CDCl_3$, 298 K)

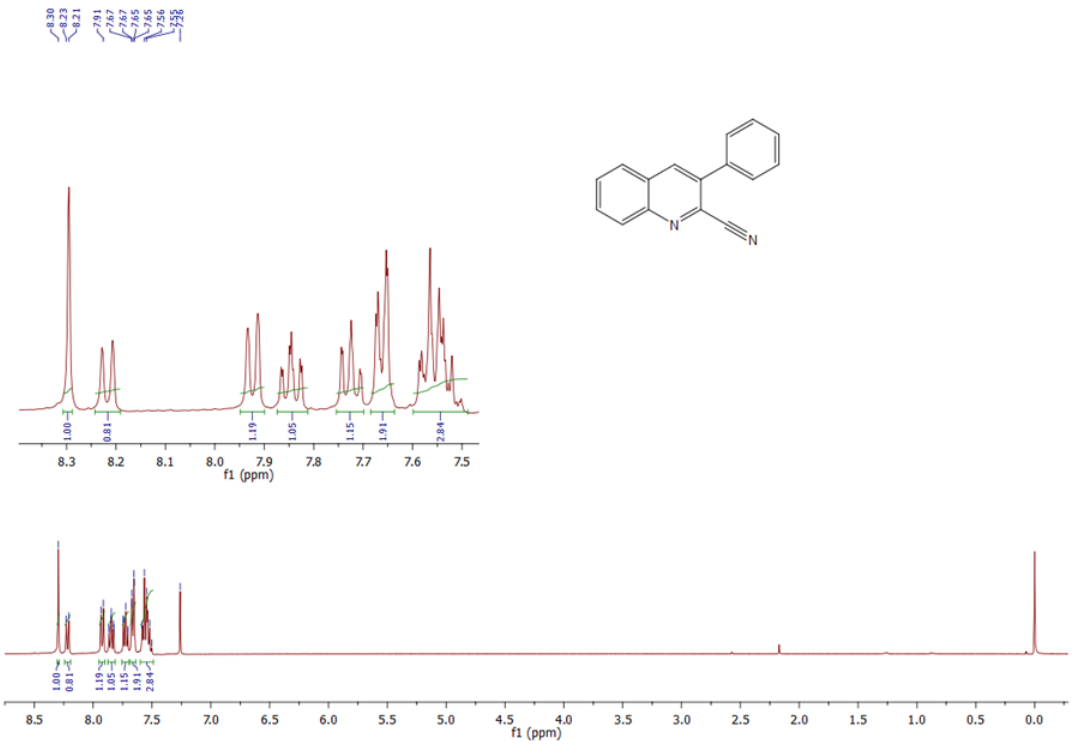


Figure S21: ^{1}H NMR spectrum of **2.3k** (400 MHz, $CDCl_3$, 298 K)

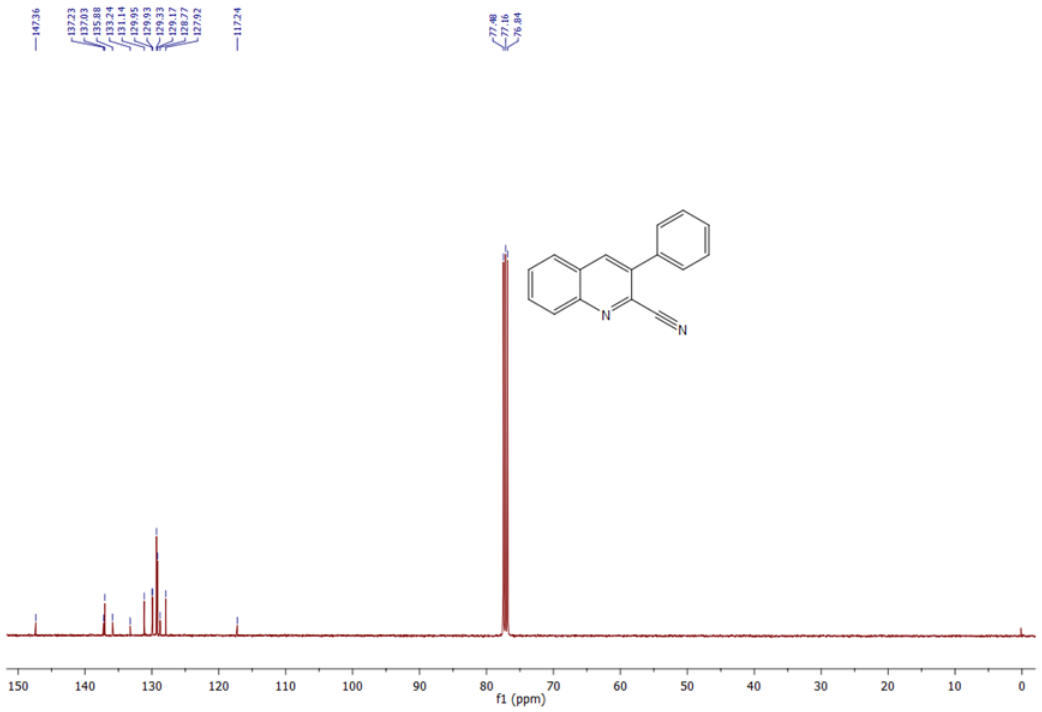


Figure S22: ^{13}C NMR spectrum of **2.3k** (101 MHz, $CDCl_3$, 298 K)

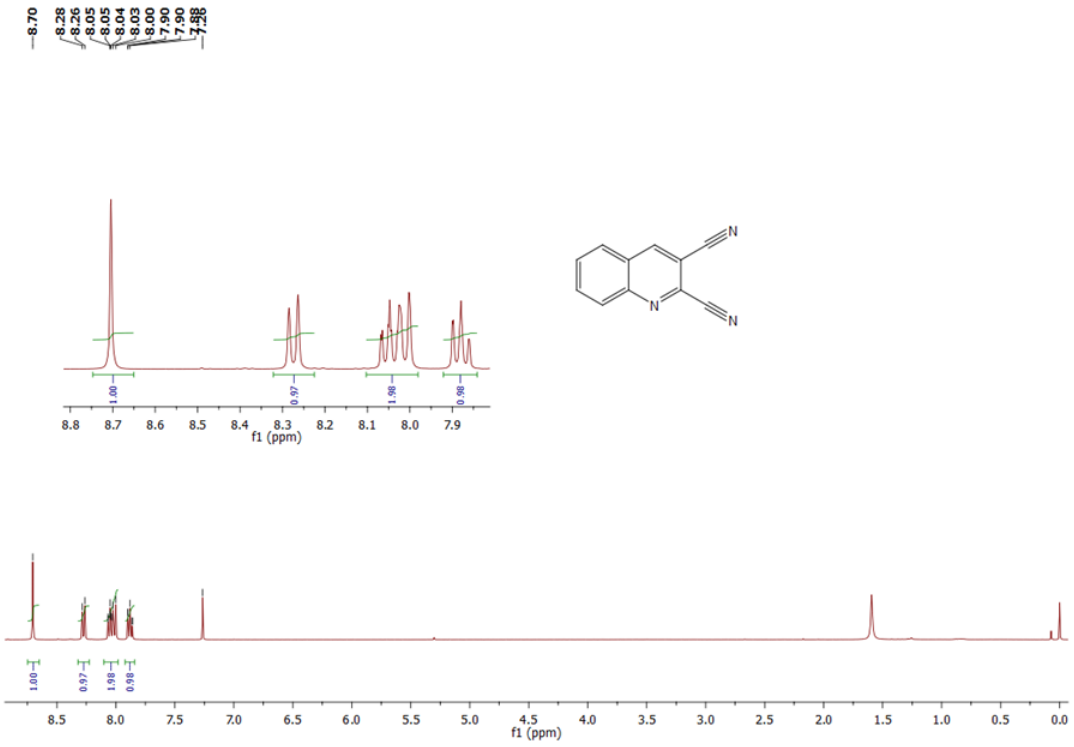


Figure S23: ^{1}H NMR spectrum of **2.3l** (400 MHz, $CDCl_3$, 298 K)

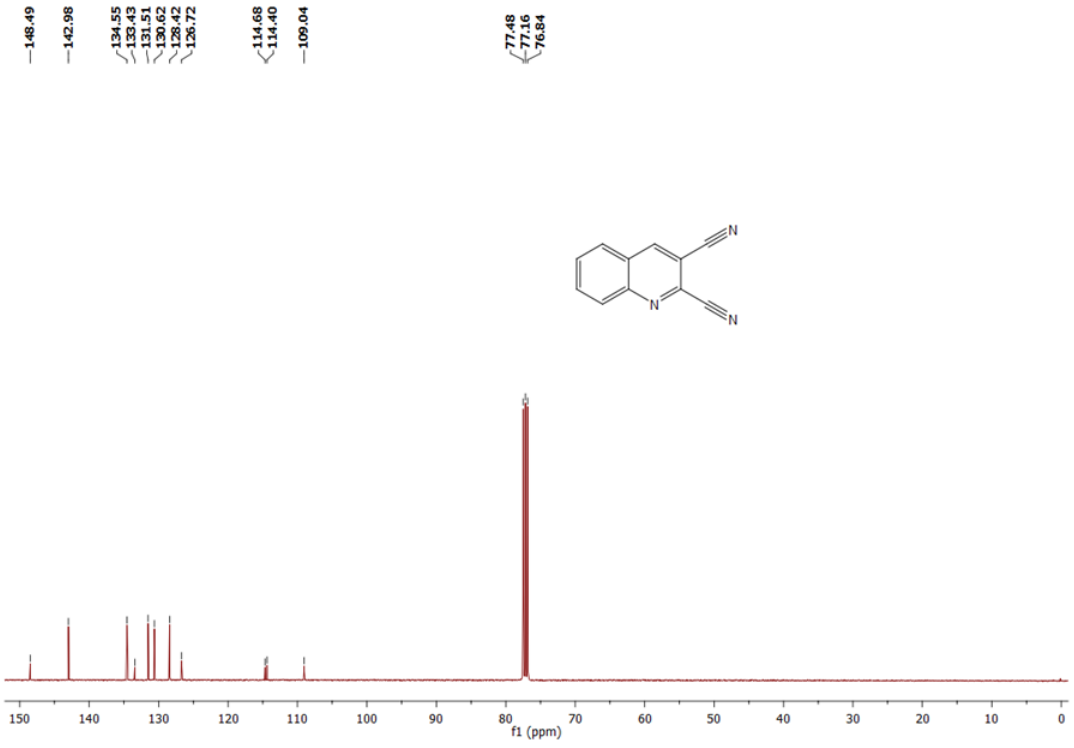


Figure S24: ^{13}C NMR spectrum of **2.3l** (101 MHz, $CDCl_3$, 298 K)

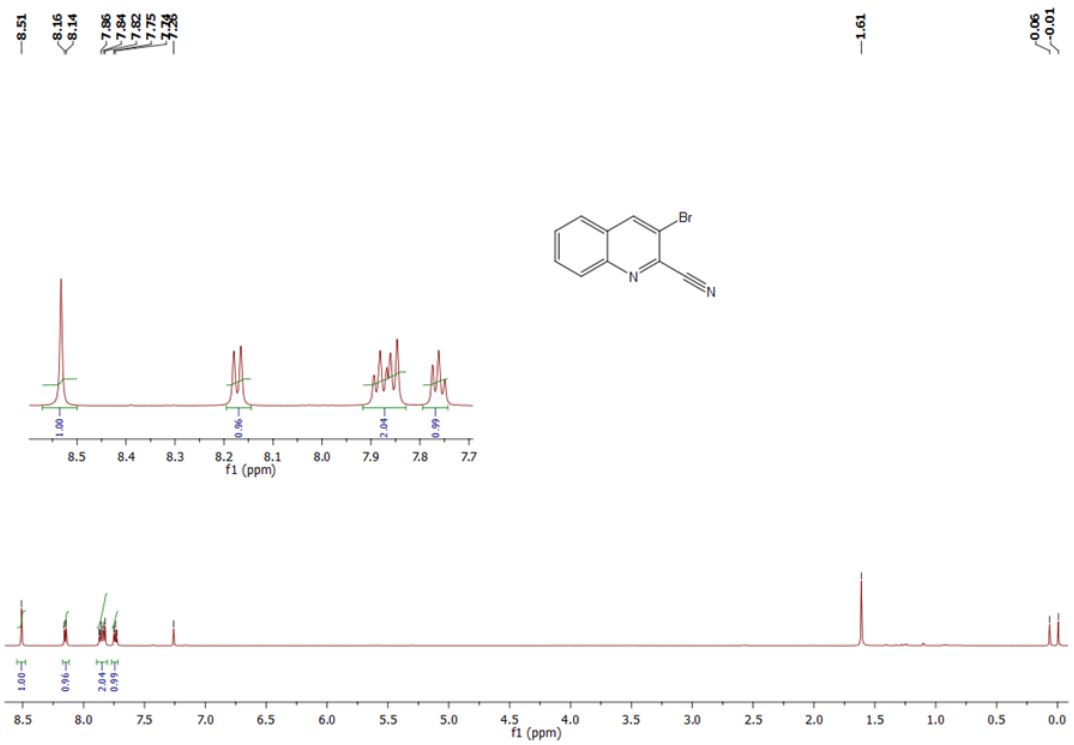


Figure S25: ^{1}H NMR spectrum of **2.3m** (600 MHz, $CDCl_3$, 298 K)

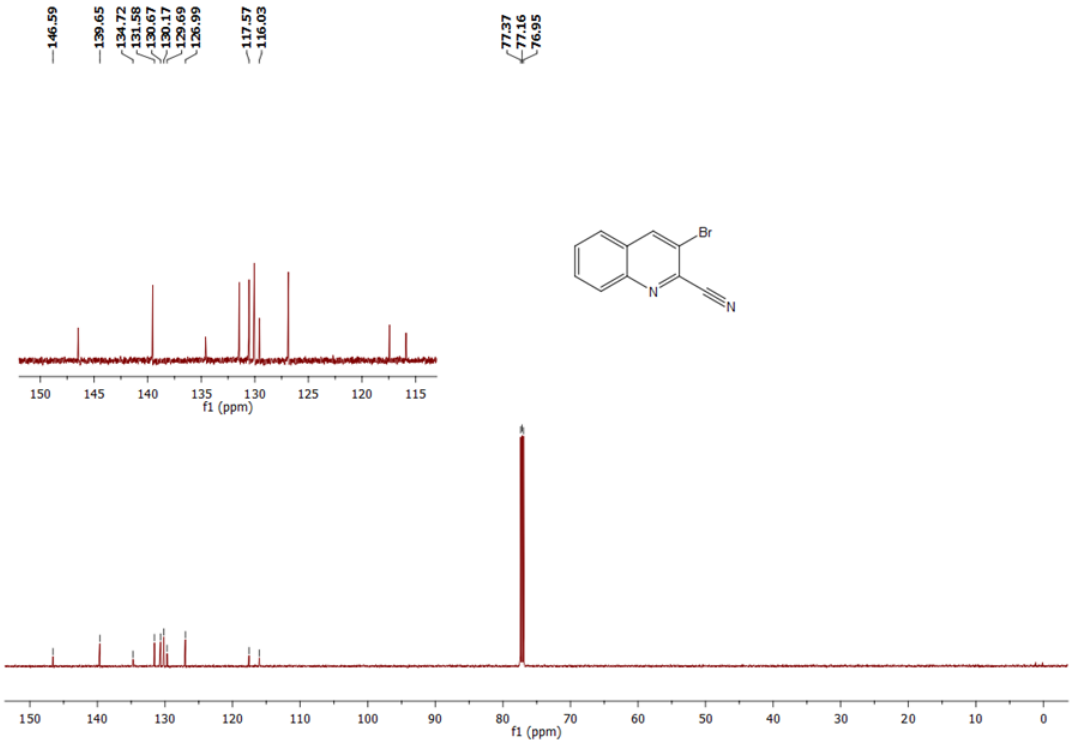


Figure S26: ^{13}C NMR spectrum of **2.3m** (151 MHz, $CDCl_3$, 298 K)

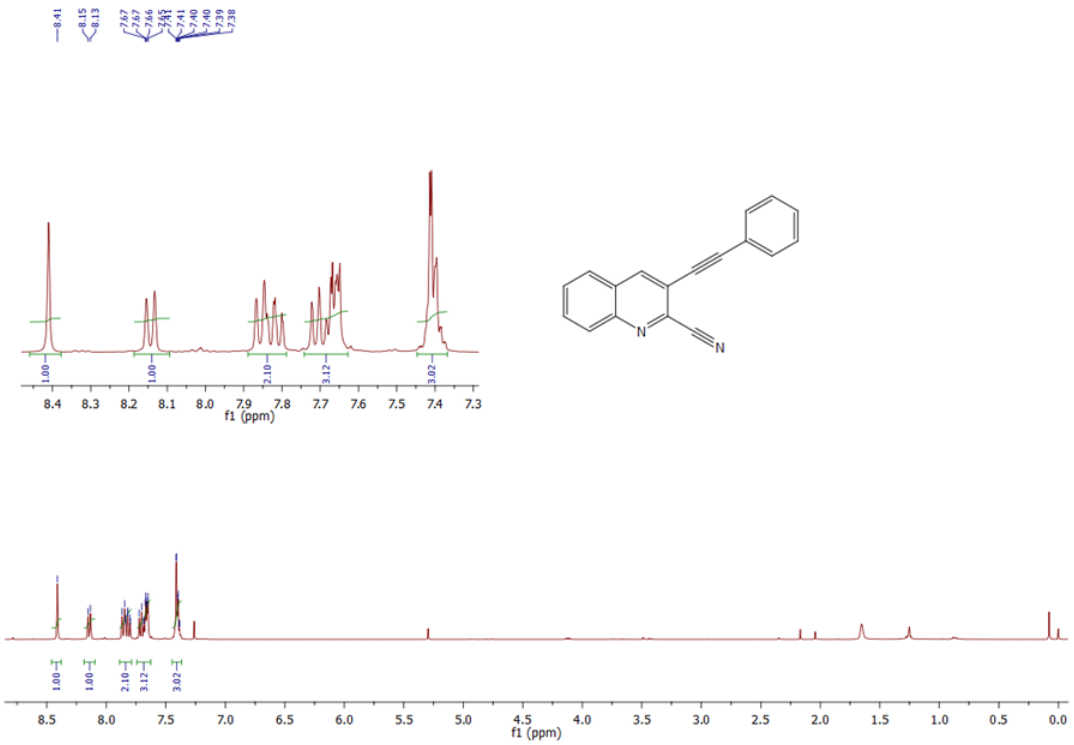


Figure S27: ^{1}H NMR spectrum of **2.3n** (400 MHz, $CDCl_3$, 298 K)

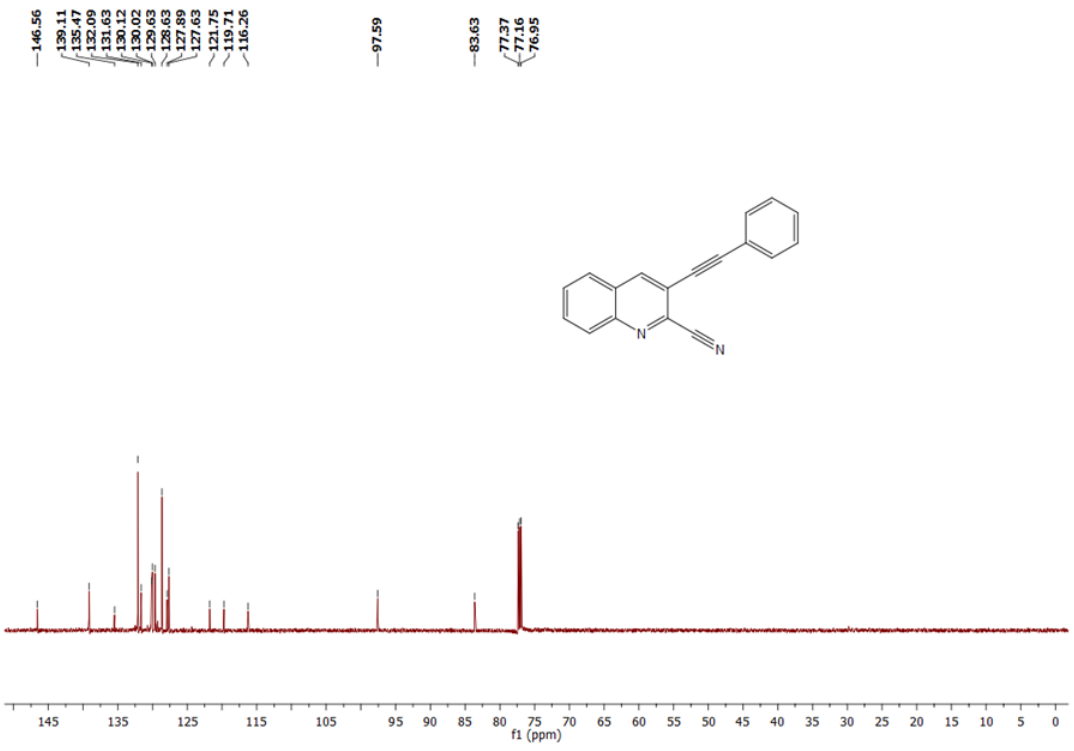


Figure S28: ^{13}C NMR spectrum of **2.3n** (101 MHz, $CDCl_3$, 298 K)

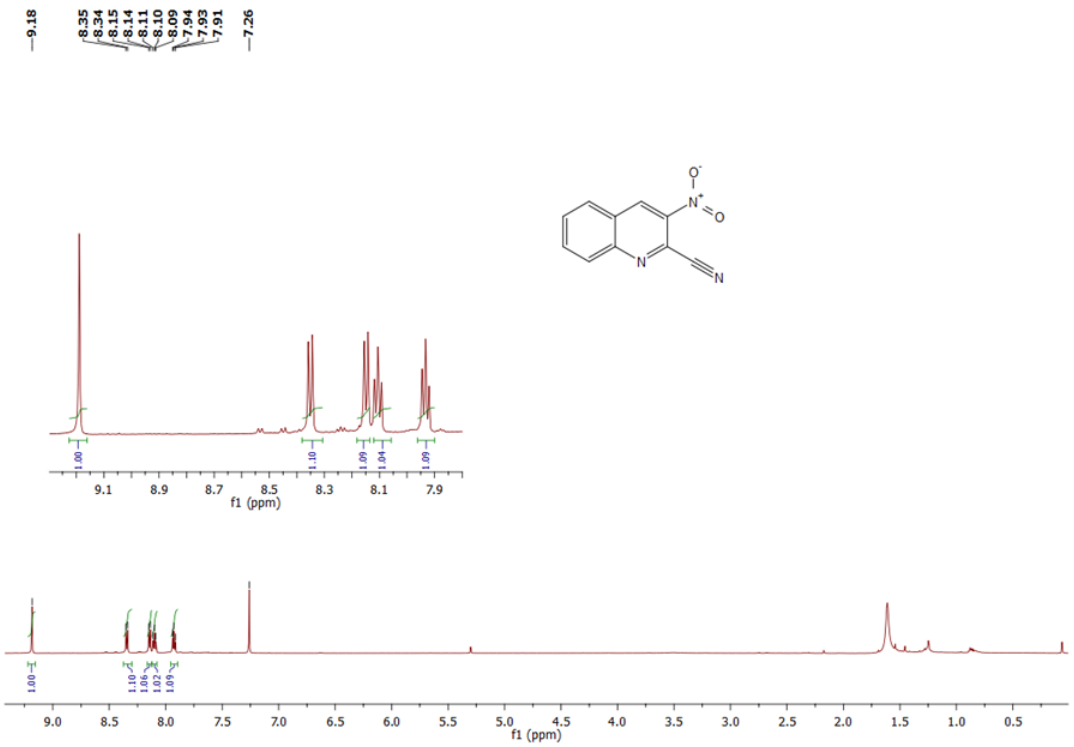


Figure S29: ^{1}H NMR spectrum of **2.3o** (600 MHz, $CDCl_3$, 298 K)

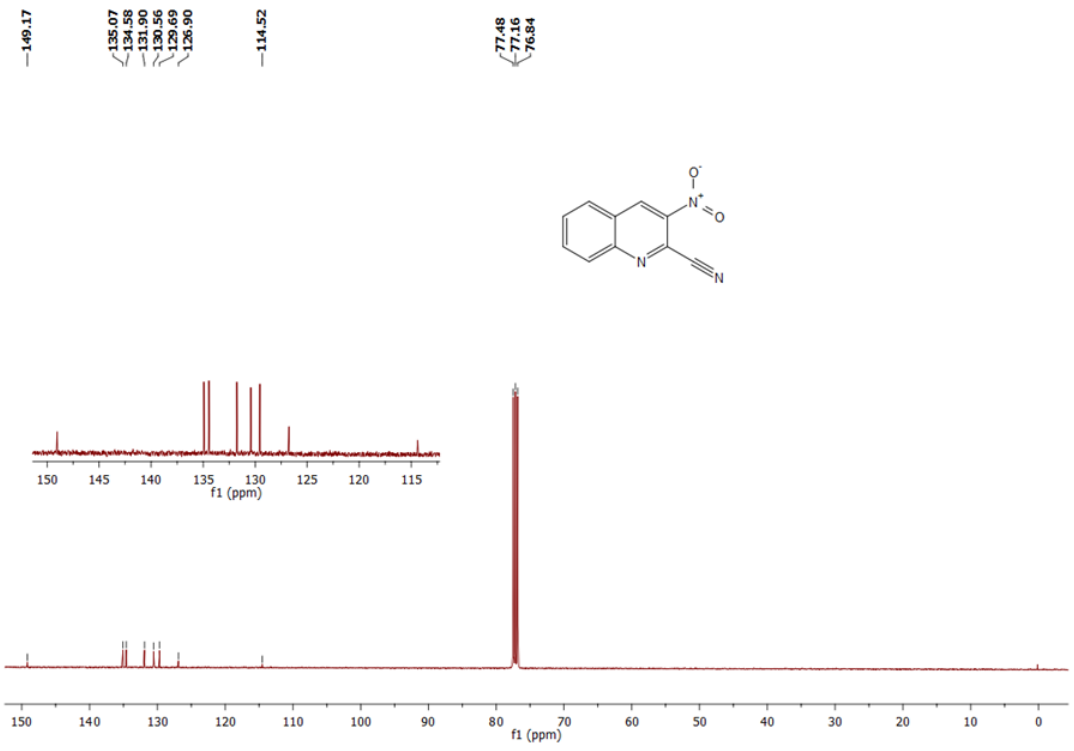


Figure S30: ^{13}C NMR spectrum of **2.3o** (151 MHz, $CDCl_3$, 298 K)

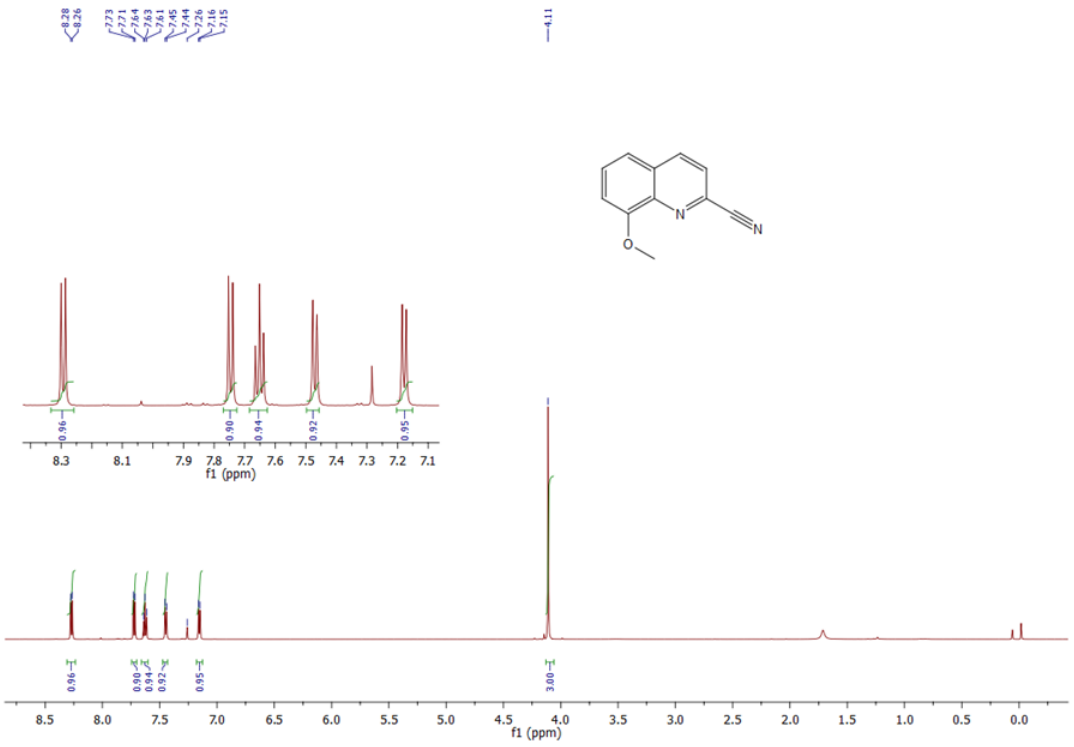


Figure S31: ^{1}H NMR spectrum of **2.3p** (400 MHz, $CDCl_3$, 298 K)

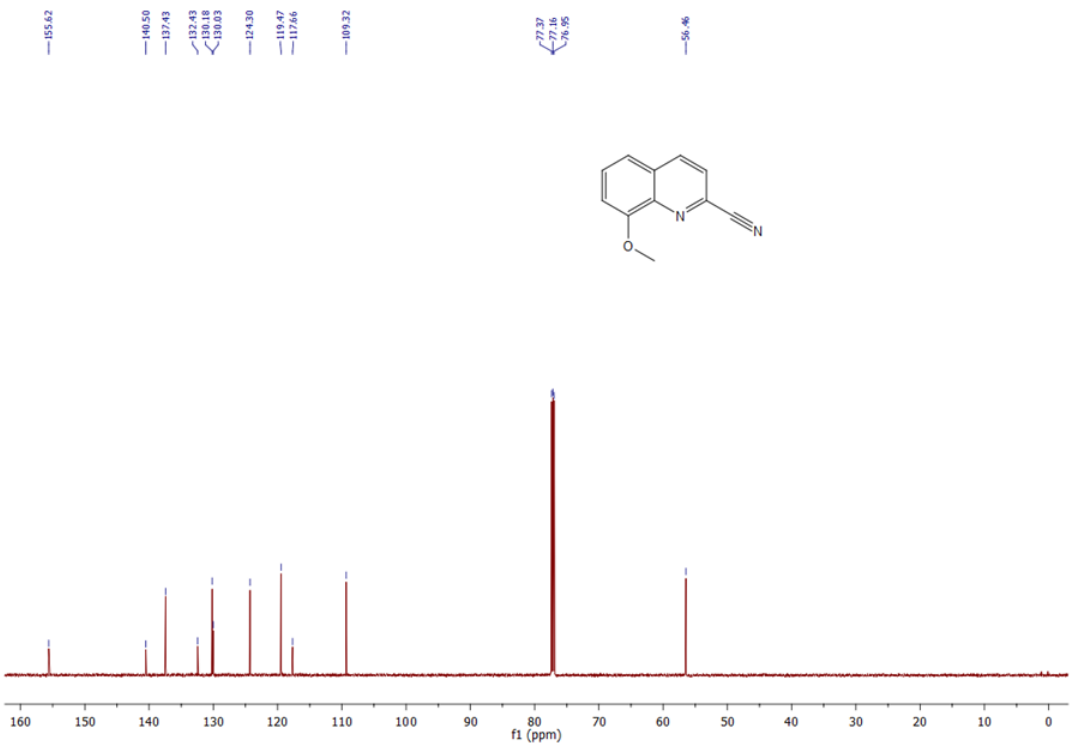


Figure S32: ^{13}C NMR spectrum of **2.3p** (101 MHz, $CDCl_3$, 298 K)

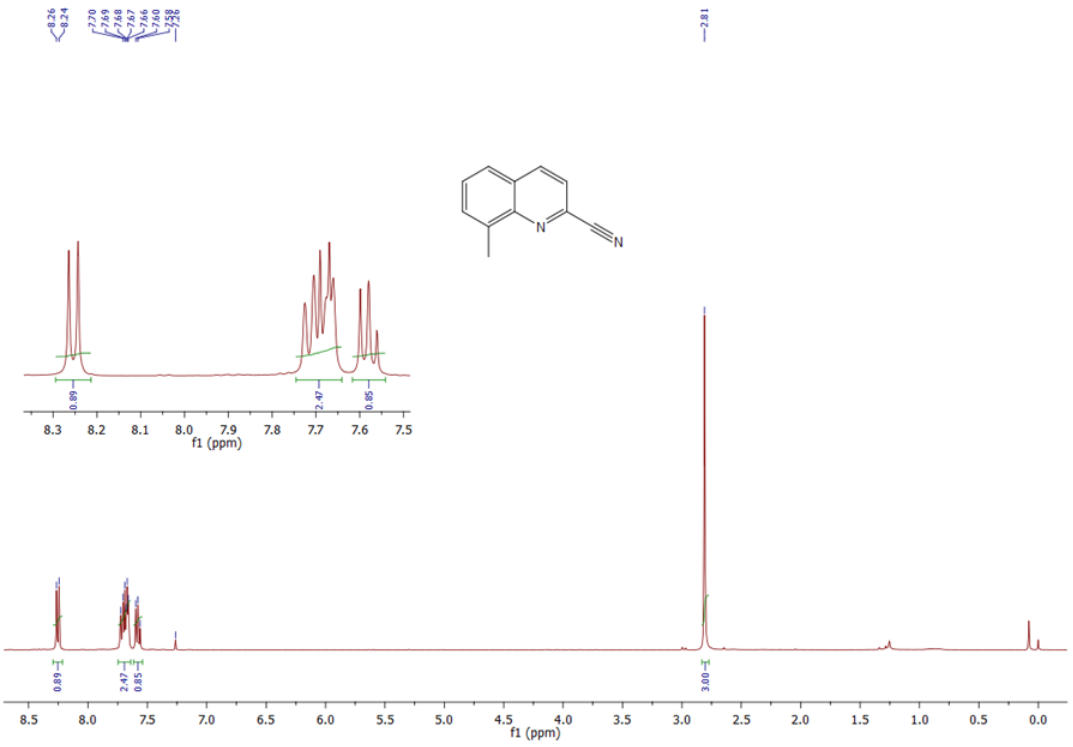


Figure S33: ^{1}H NMR spectrum of **2.3q** (400 MHz, $CDCl_3$, 298 K)

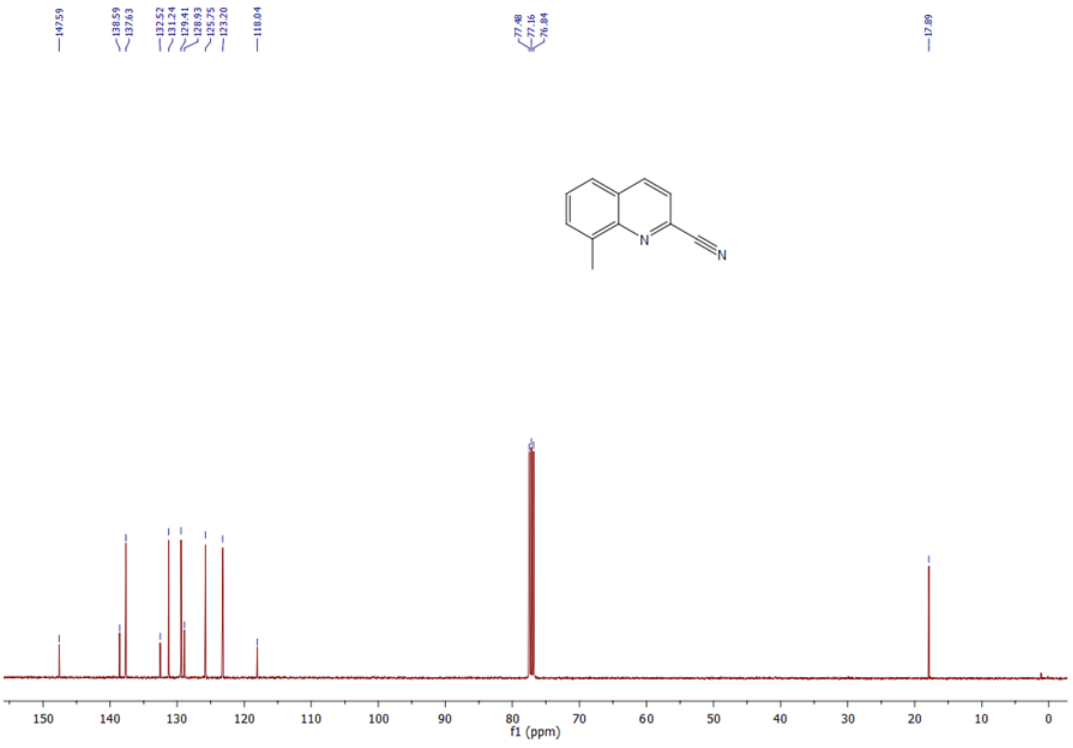


Figure S34: ^{13}C NMR spectrum of **2.3q** (101 MHz, $CDCl_3$, 298 K)

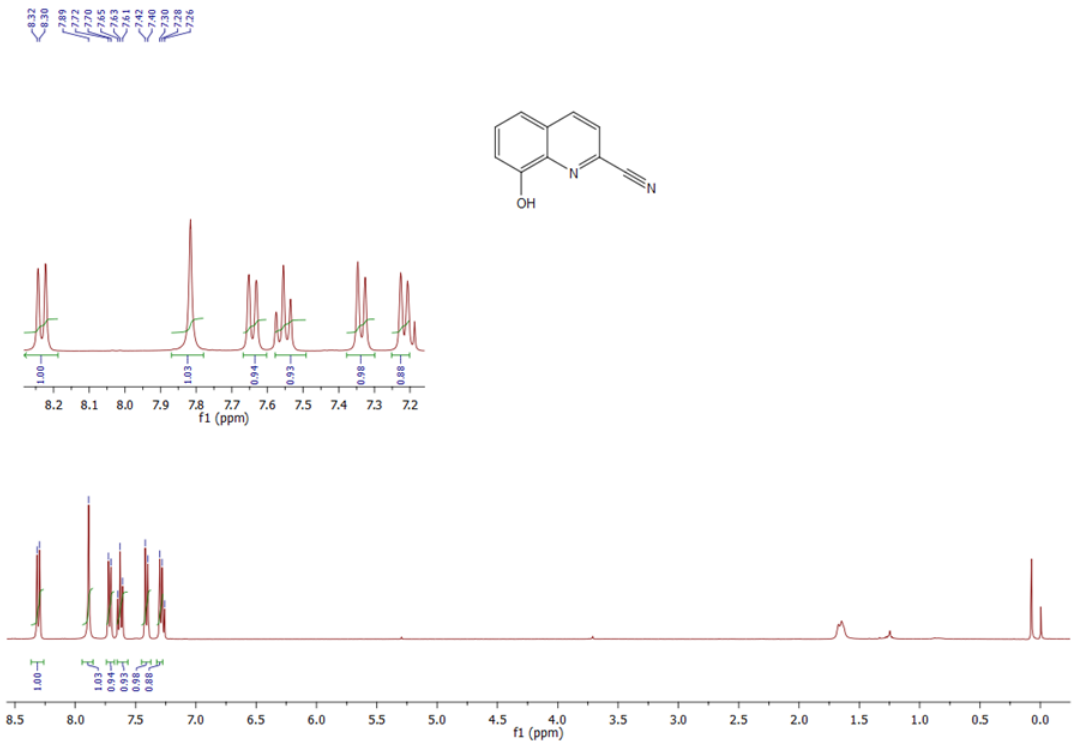


Figure S35: ^{1}H NMR spectrum of **2.3r** (400 MHz, $CDCl_3$, 298 K)

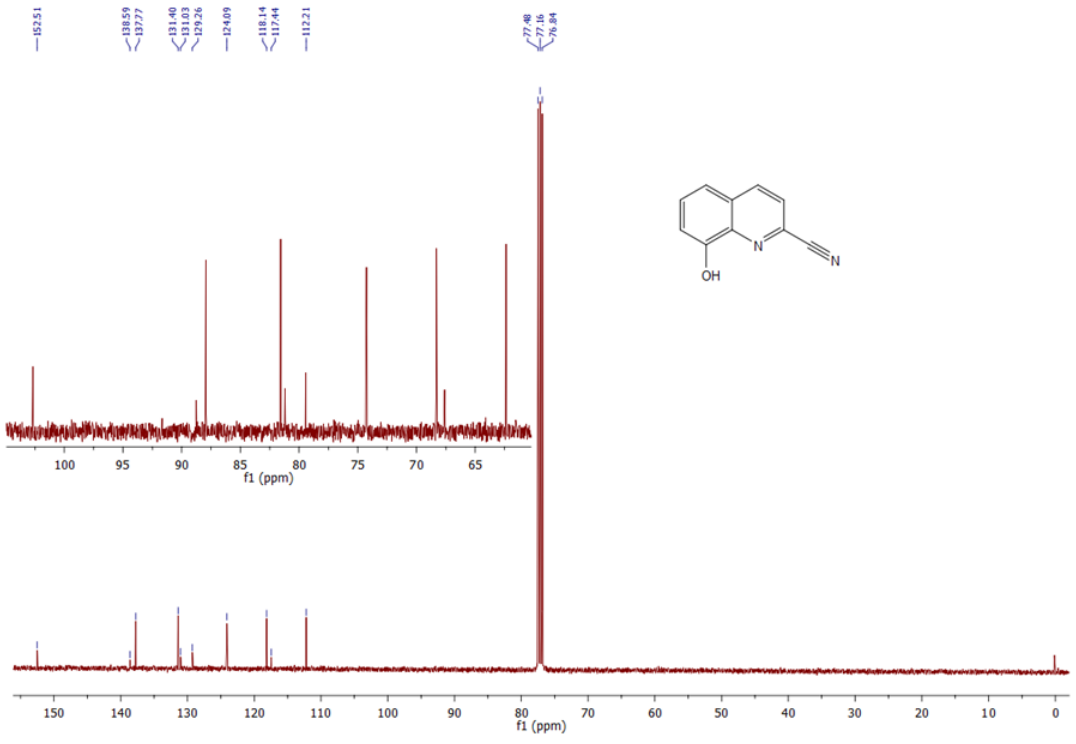


Figure S36: ^{13}C NMR spectrum of **2.3r** (101 MHz, $CDCl_3$, 298 K)

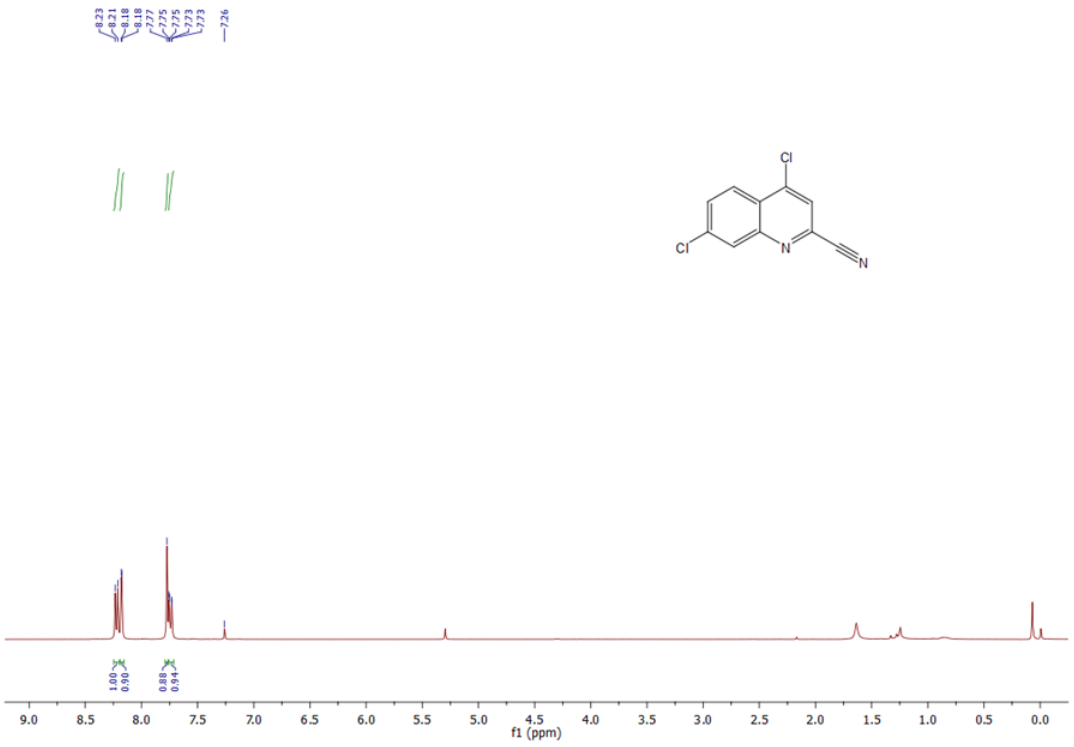


Figure S37: ^{1}H NMR spectrum of **2.3s** (400 MHz, $CDCl_3$, 298 K)

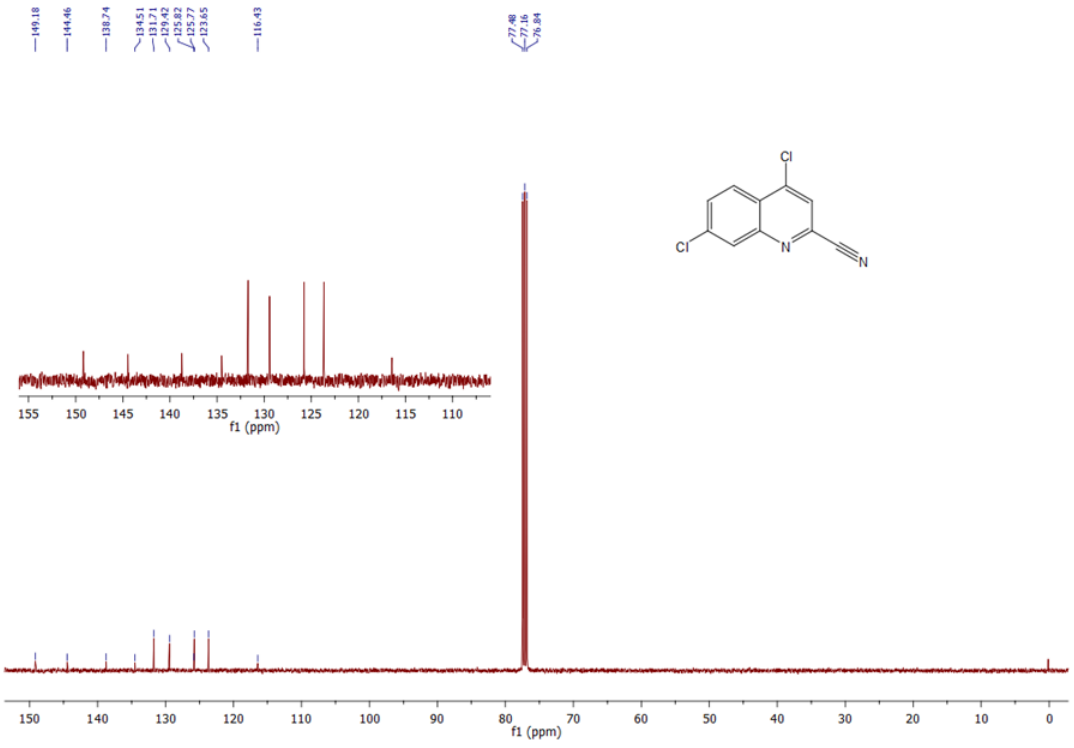


Figure S38: ^{13}C NMR spectrum of **2.3s** (101 MHz, $CDCl_3$, 298 K)

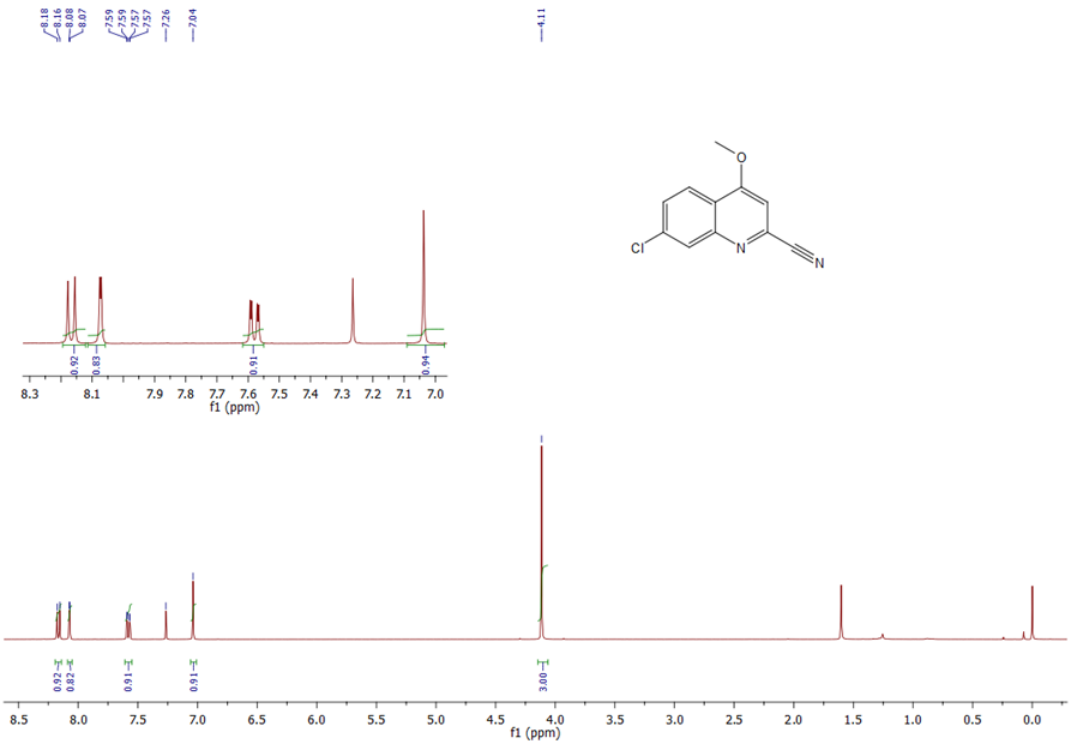


Figure S39: ^{1}H NMR spectrum of **2.3t** (400 MHz, $CDCl_3$, 298 K)

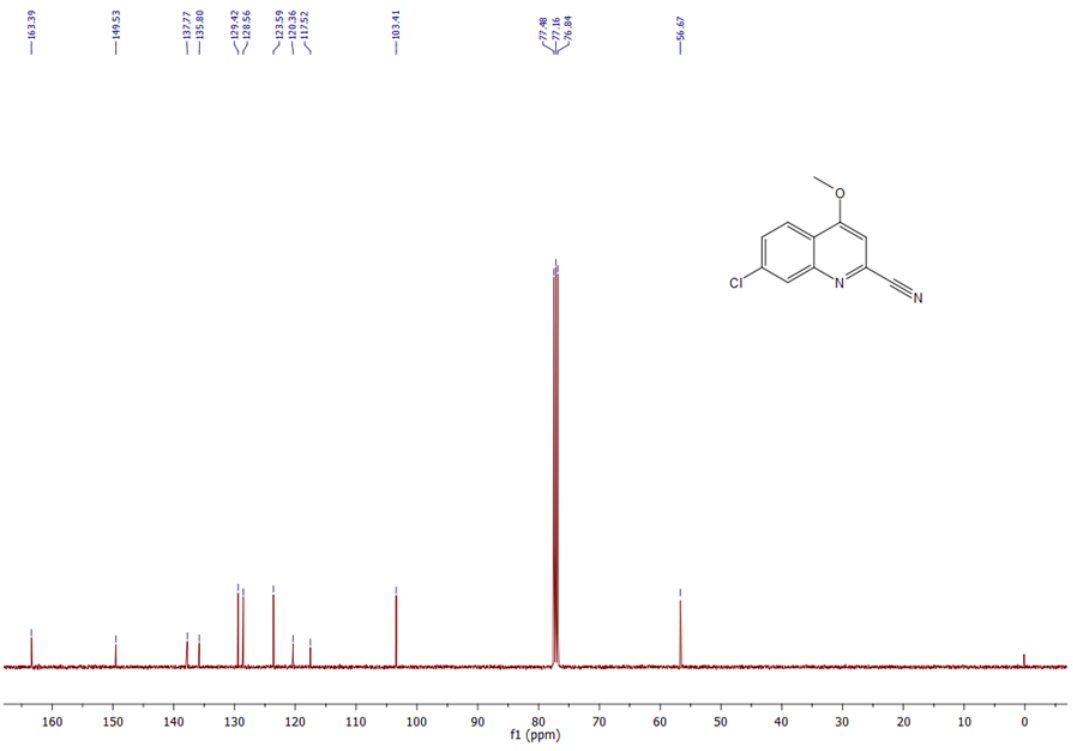


Figure S40: ^{13}C NMR spectrum of **2.3t** (101 MHz, $CDCl_3$, 298 K)

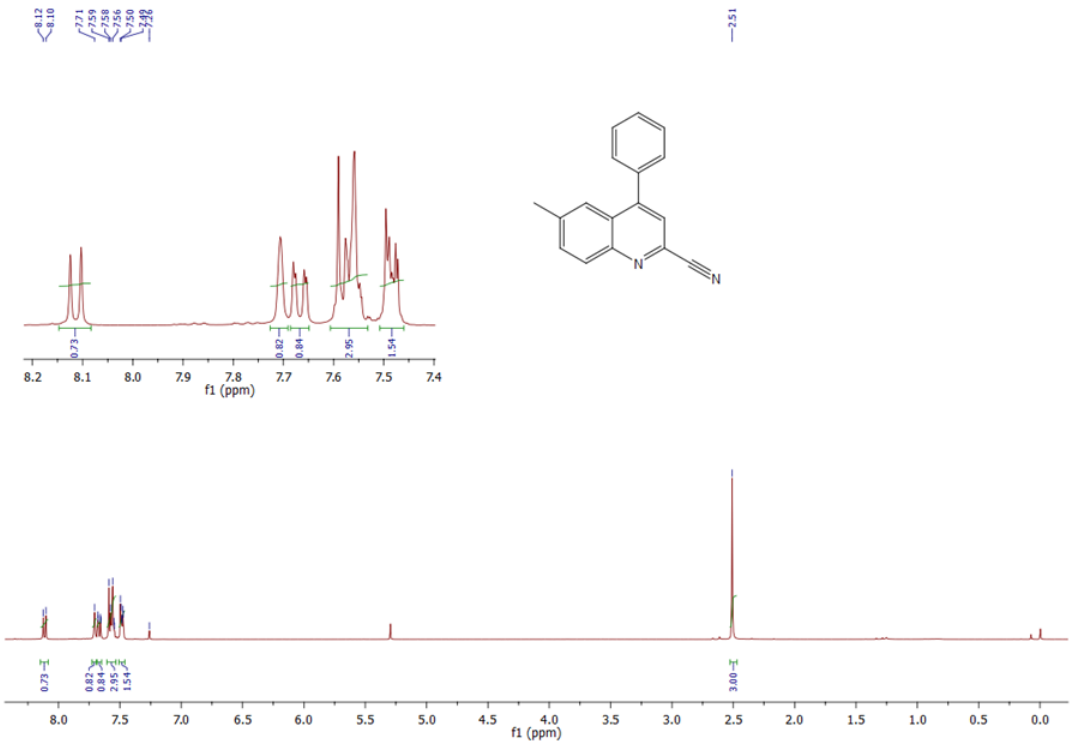


Figure S41: ^{1}H NMR spectrum of **2.3u** (600 MHz, $CDCl_3$, 298 K)

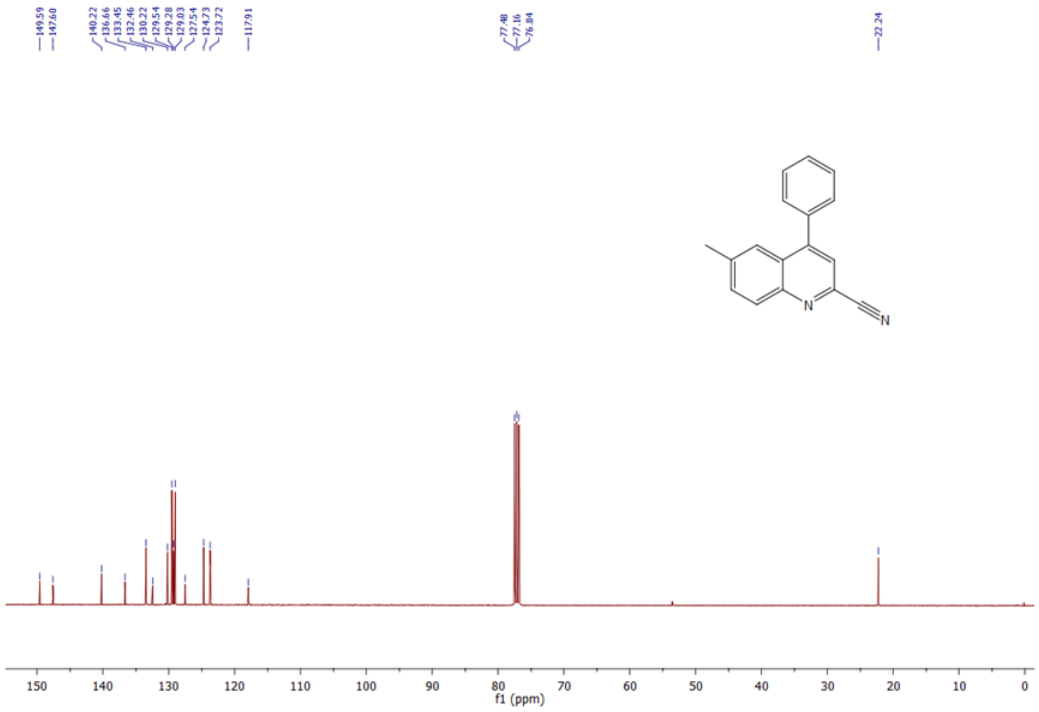


Figure S42: ^{13}C NMR spectrum of **2.3u** (101 MHz, $CDCl_3$, 298 K)

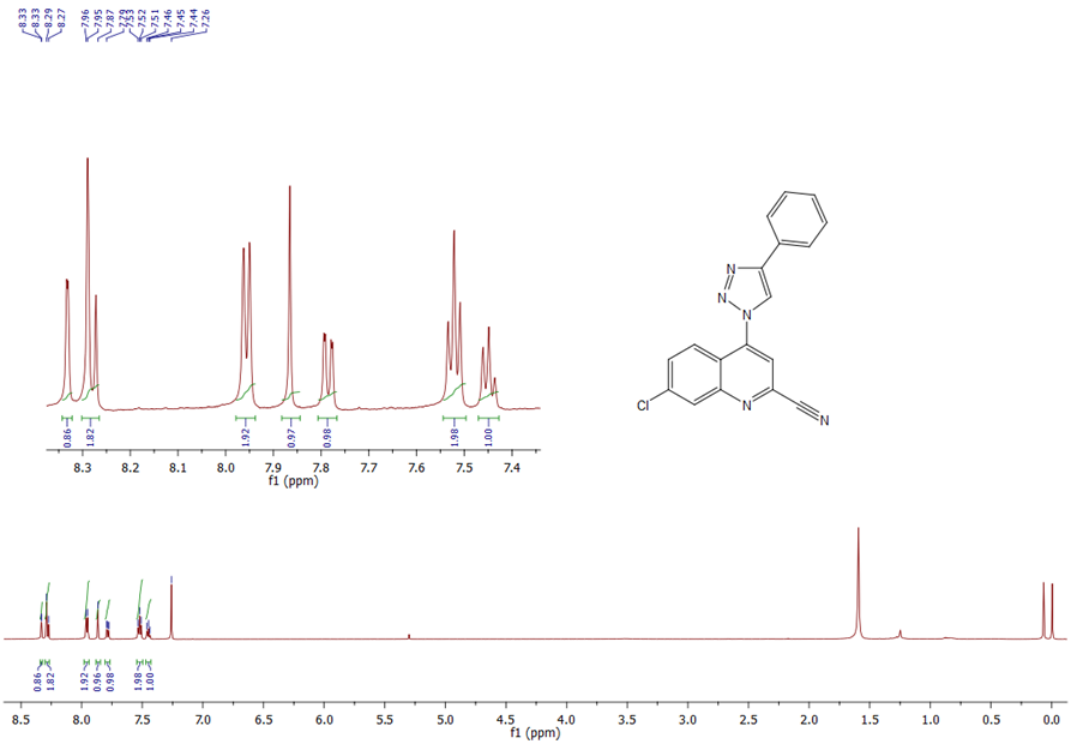


Figure S43: ^{1}H NMR spectrum of **2.3v** (400 MHz, $CDCl_3$, 298 K)

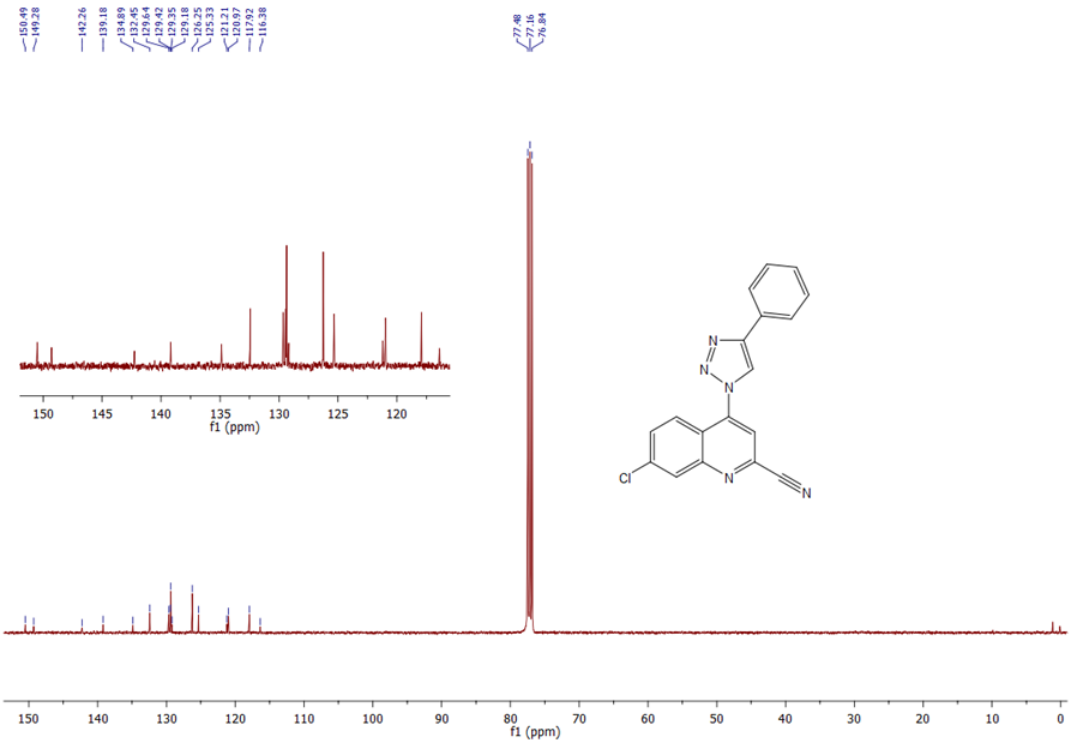


Figure S44: ^{13}C NMR spectrum of **2.3v** (101 MHz, $CDCl_3$, 298 K)

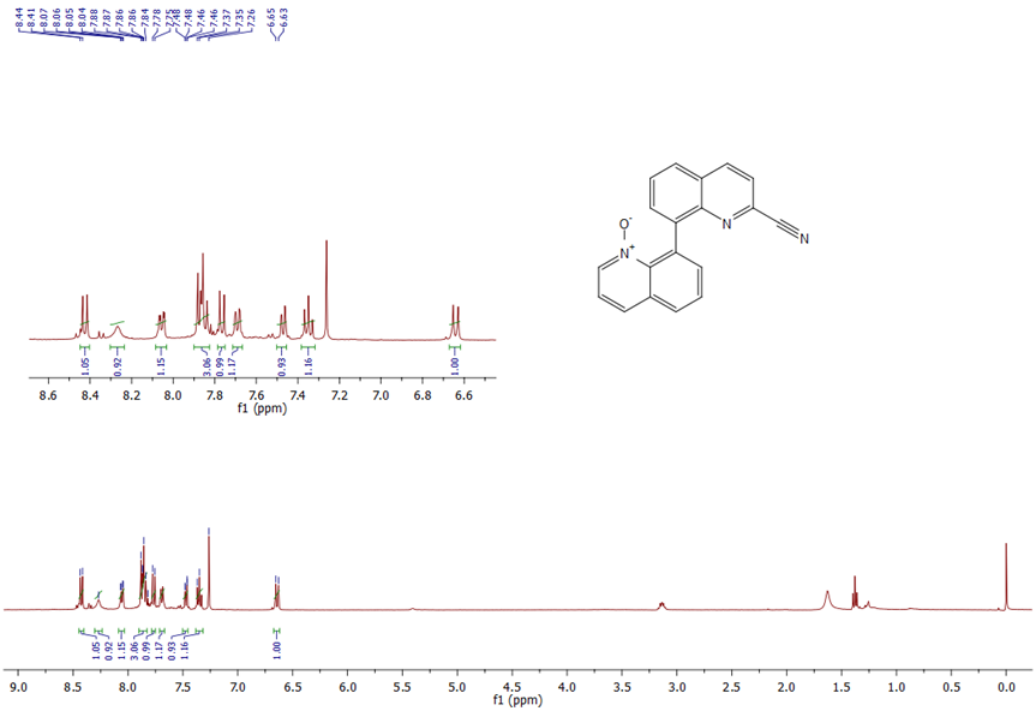


Figure S45: ^{1}H NMR spectrum of **2.3w** (400 MHz, $CDCl_3$, 298 K)

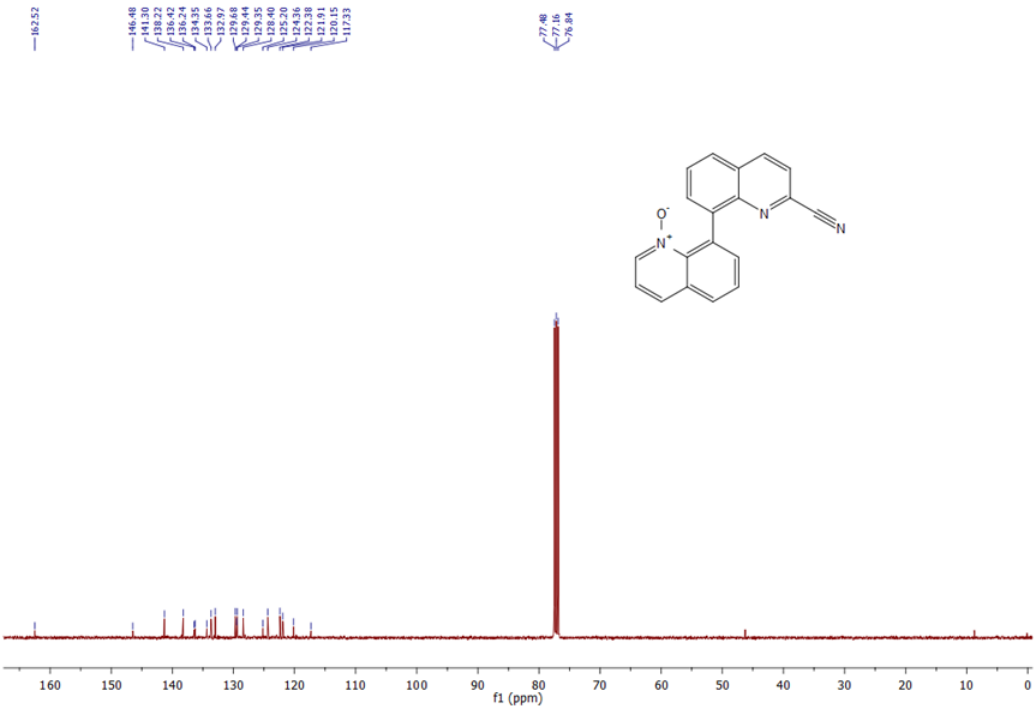


Figure S46: ^{13}C NMR spectrum of **2.3w** (101 MHz, $CDCl_3$, 298 K)

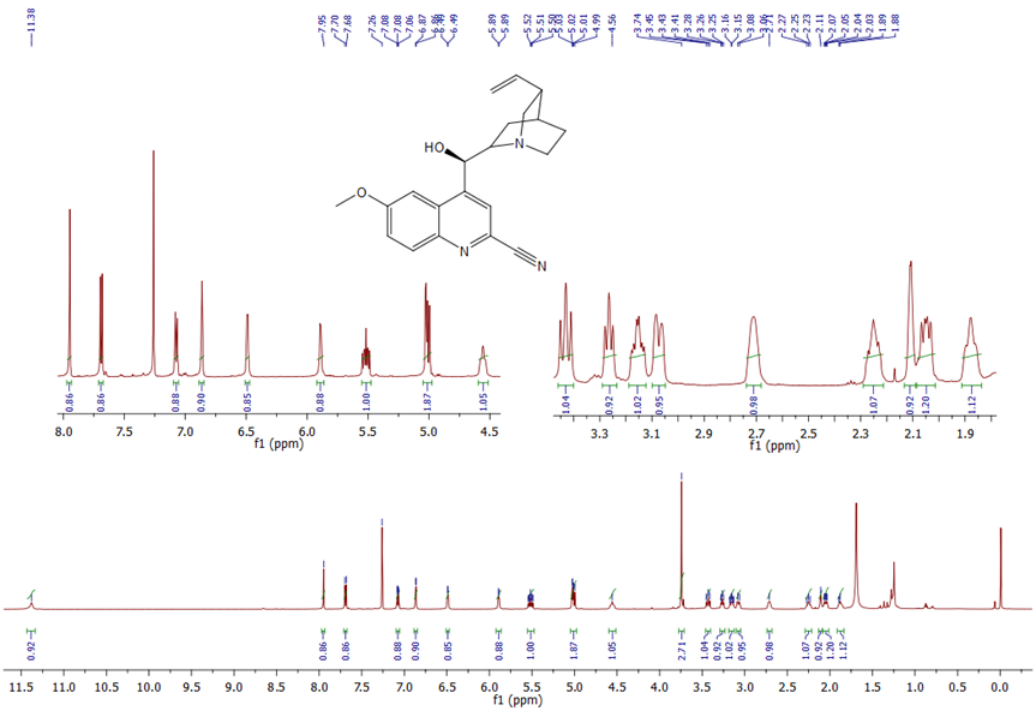


Figure S47: ^{1}H NMR spectrum of **2.3x** (600 MHz, $CDCl_3$, 298 K)

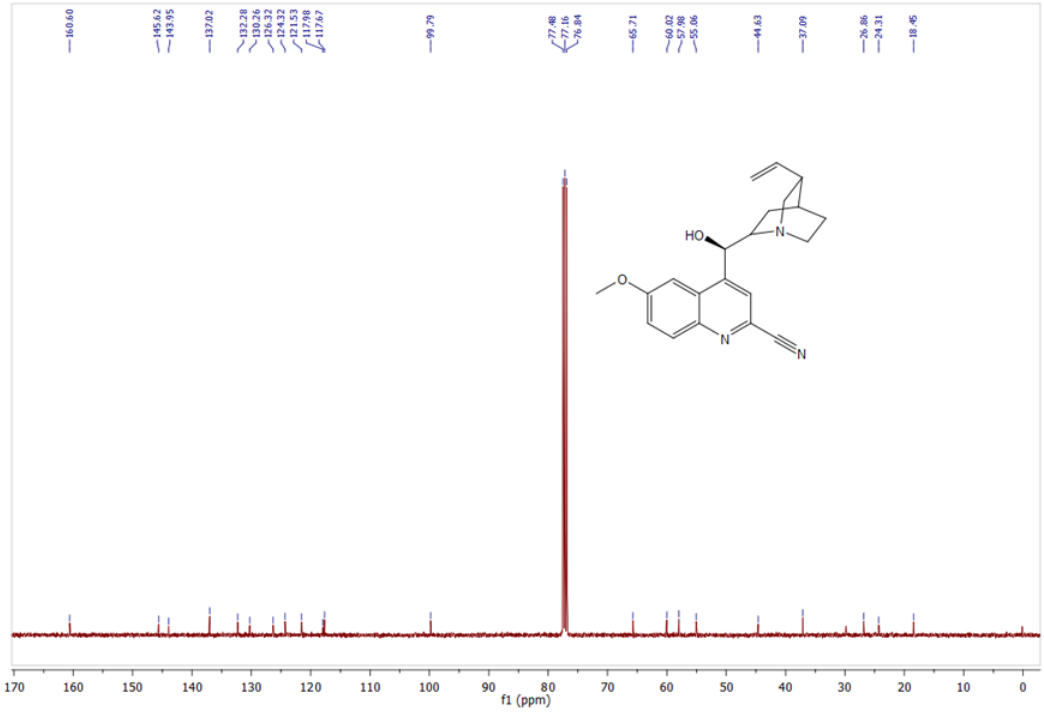


Figure S48: ^{13}C NMR spectrum of **2.3x** (101 MHz, $CDCl_3$, 298 K)

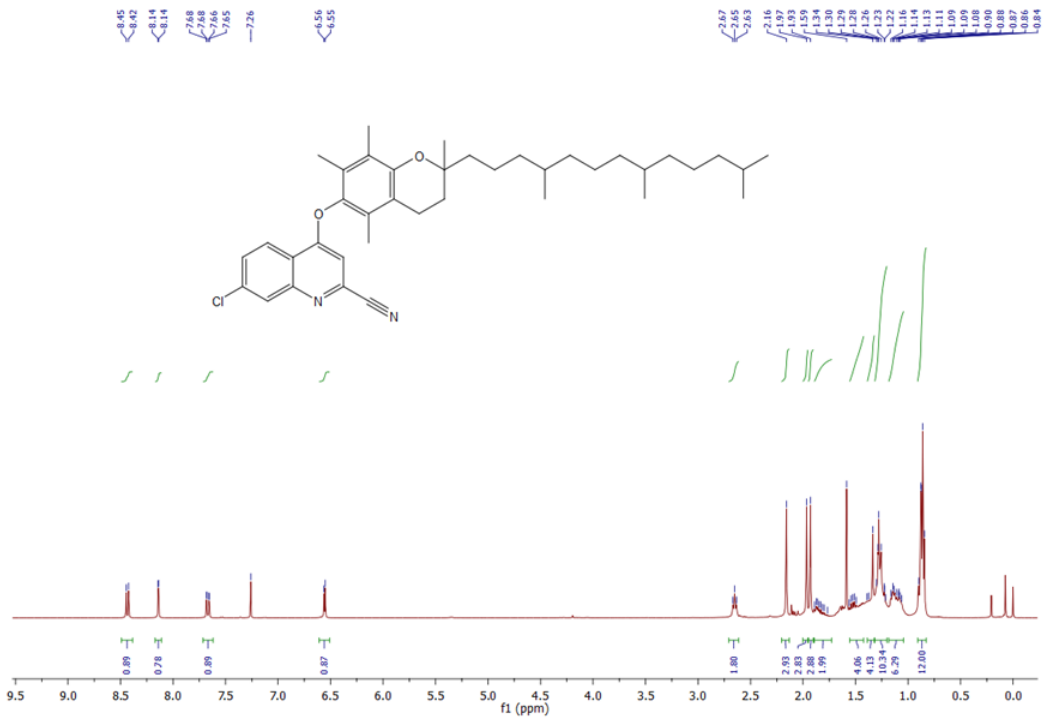


Figure S49: ^{1}H NMR spectrum of **2.3y** (400 MHz, $CDCl_3$, 298 K)

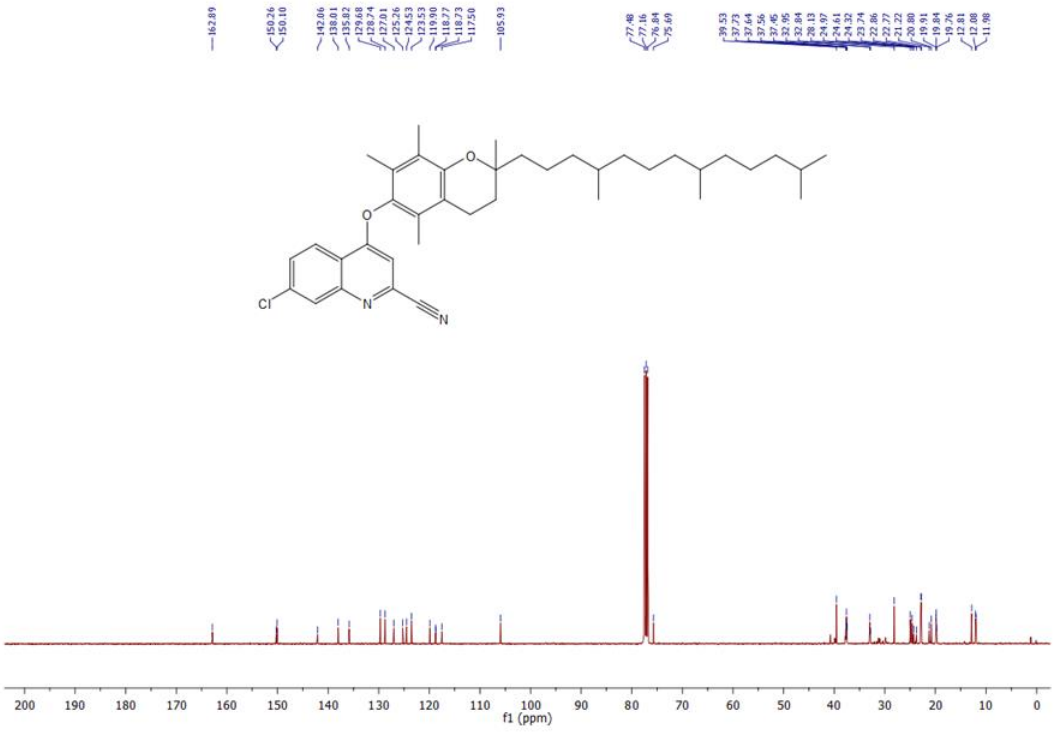


Figure S50: ^{13}C NMR spectrum of **2.3y** (101 MHz, $CDCl_3$, 298 K)

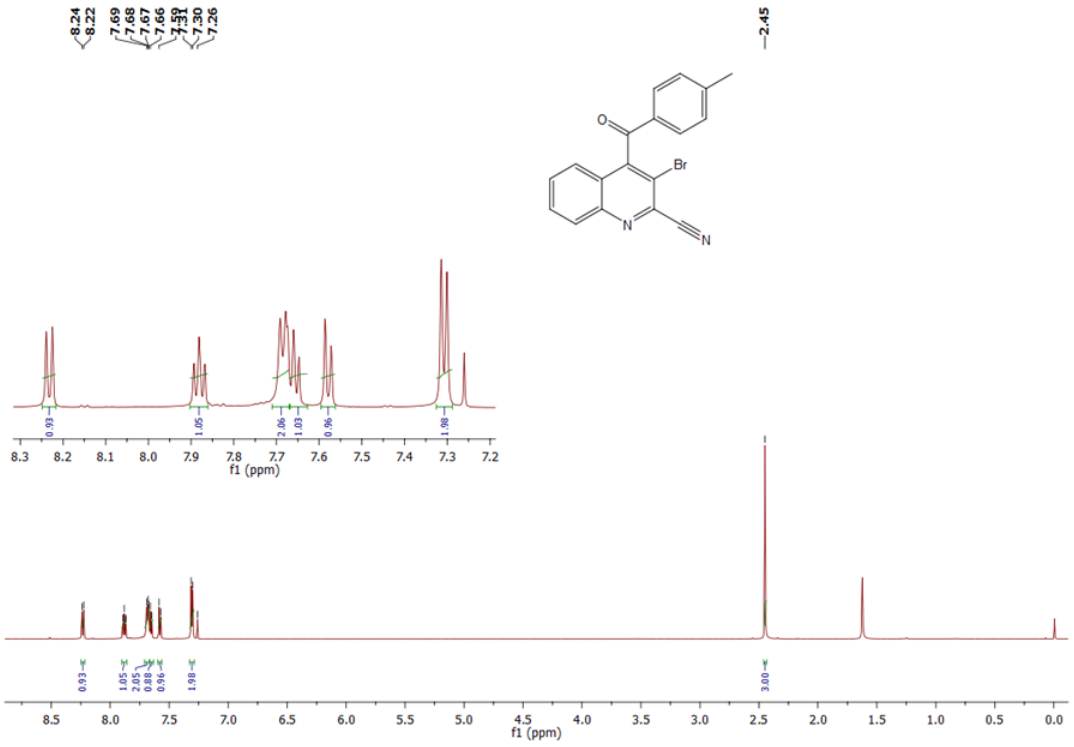


Figure S51: ^{1}H NMR spectrum of **2.3z** (600 MHz, $CDCl_3$, 298 K)

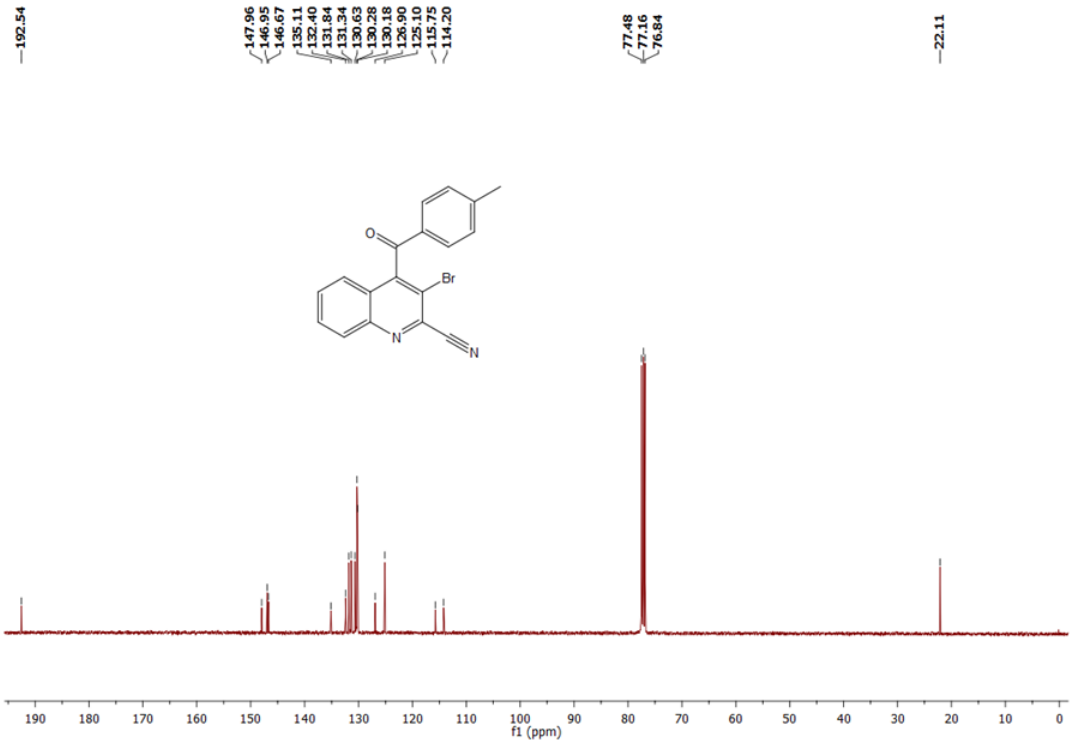


Figure S52: ^{13}C NMR spectrum of **2.3z** (101 MHz, $CDCl_3$, 298 K)

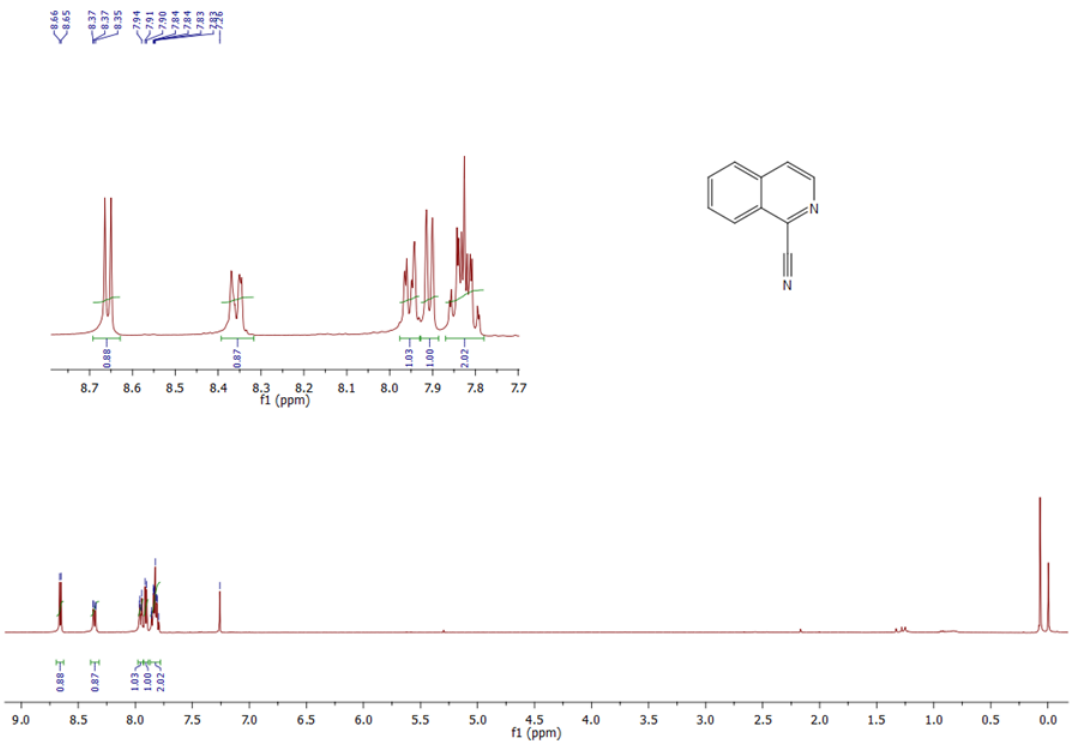


Figure S53: ^{1}H NMR spectrum of **2.6a** (400 MHz, $CDCl_3$, 298 K)

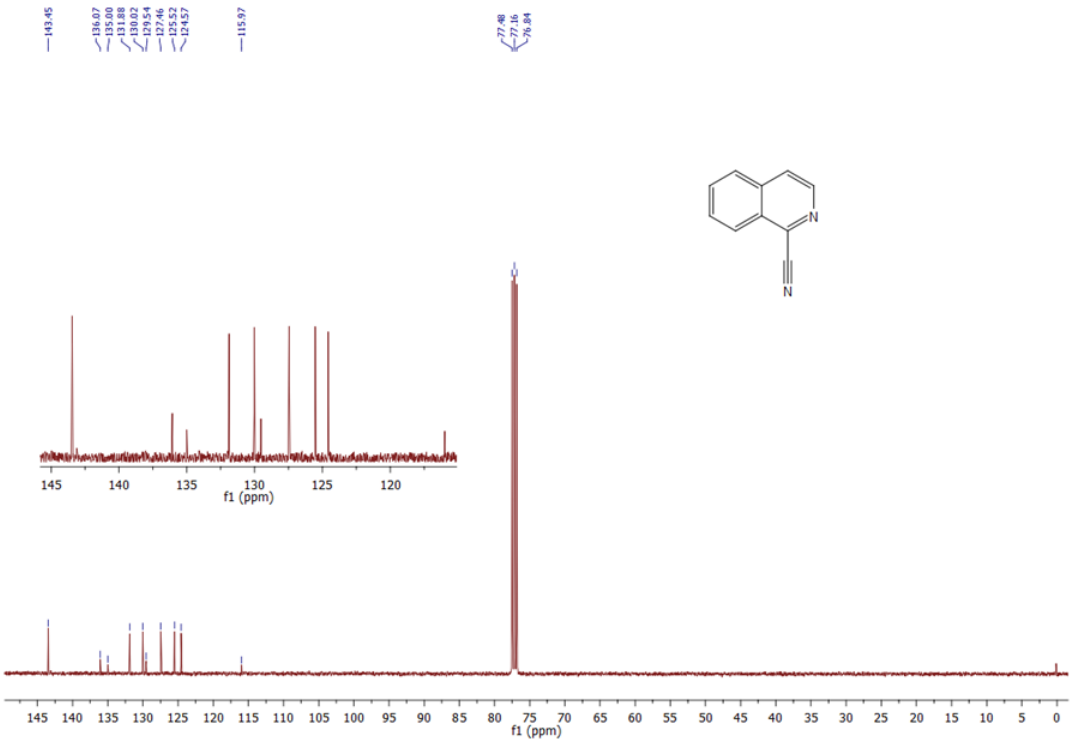


Figure S54: ^{13}C NMR spectrum of **2.6a** (101 MHz, $CDCl_3$, 298 K)

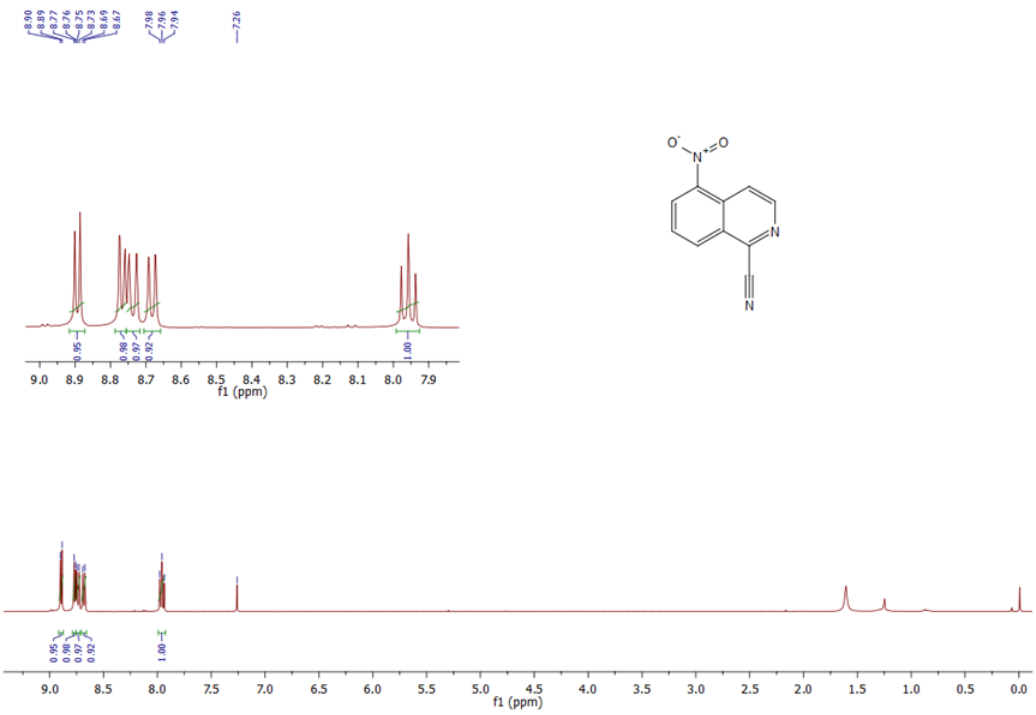


Figure S55: ^{1}H NMR spectrum of **2.6b** (400 MHz, $CDCl_3$, 298 K)

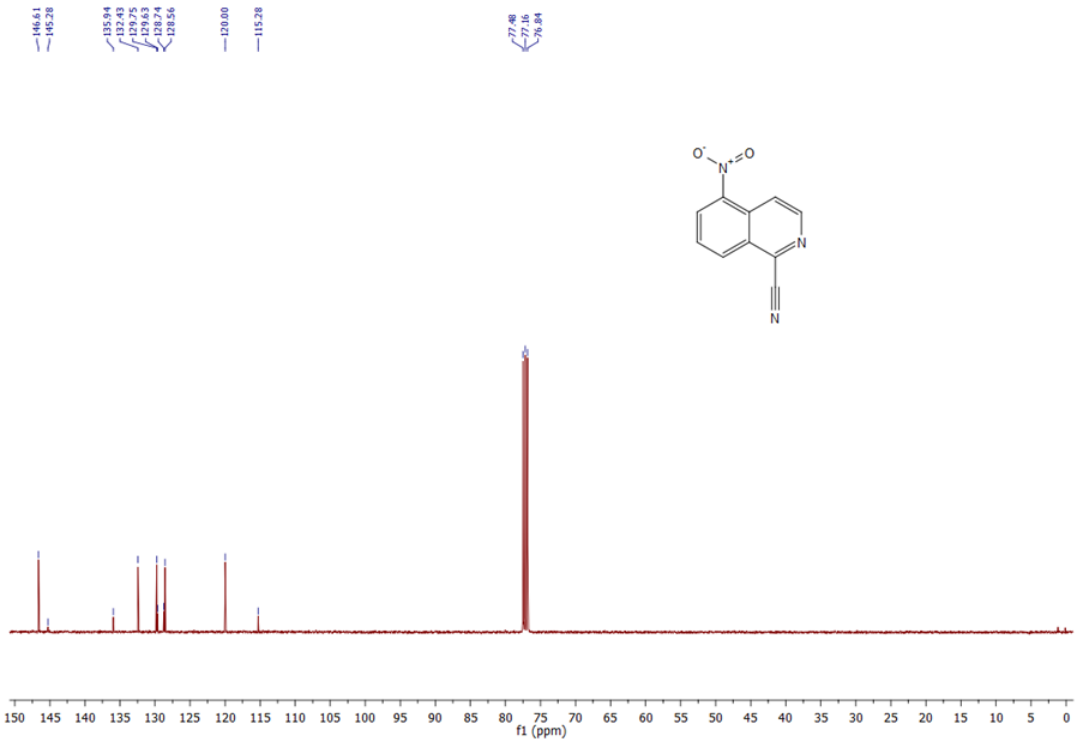


Figure S56: ^{13}C NMR spectrum of **2.6b** (101 MHz, $CDCl_3$, 298 K)

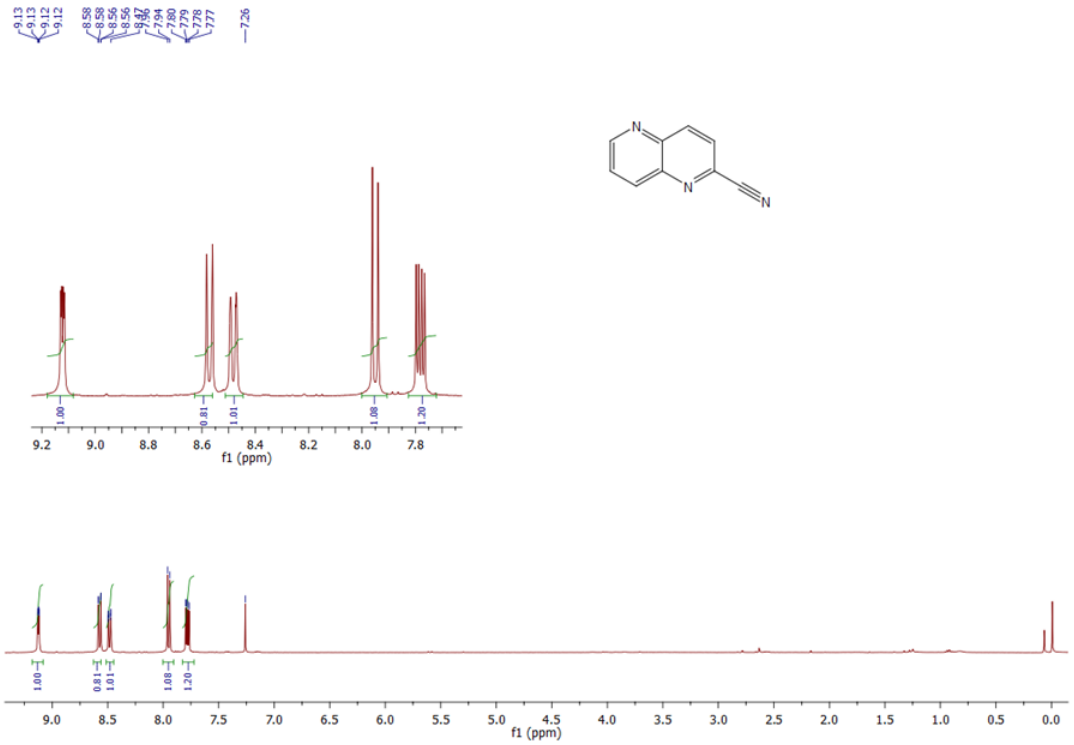


Figure S57: ^{1}H NMR spectrum of **2.6c** (600 MHz, $CDCl_3$, 298 K)

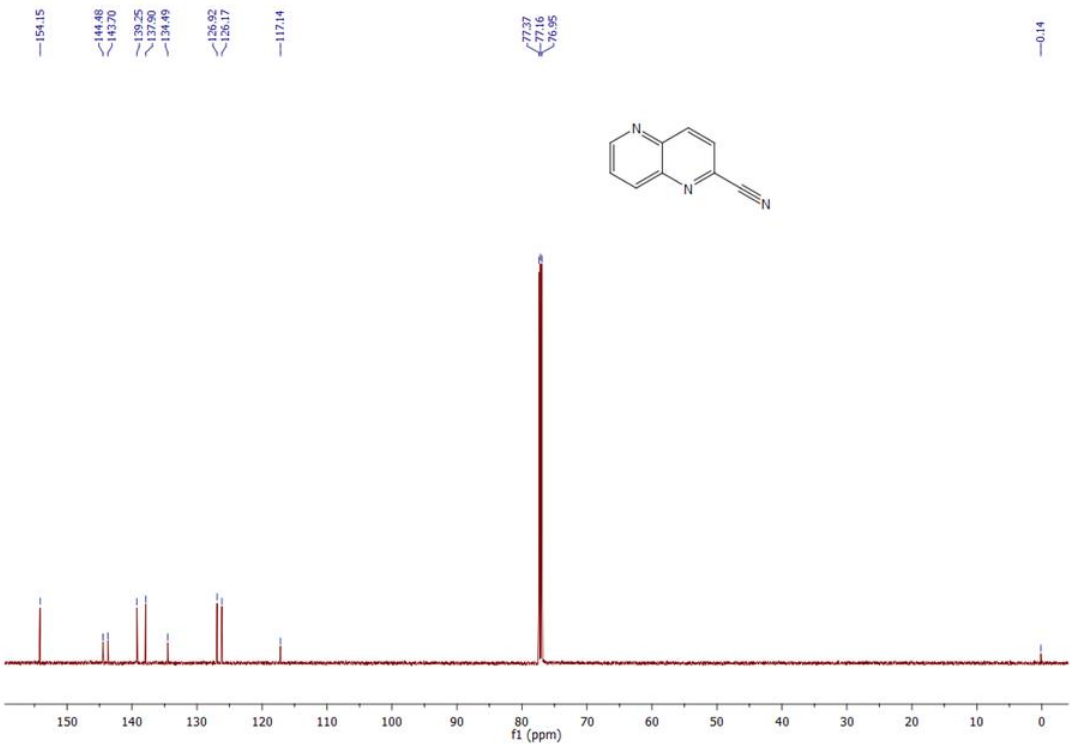


Figure S58: ^{13}C NMR spectrum of **2.6c** (151 MHz, $CDCl_3$, 298 K)

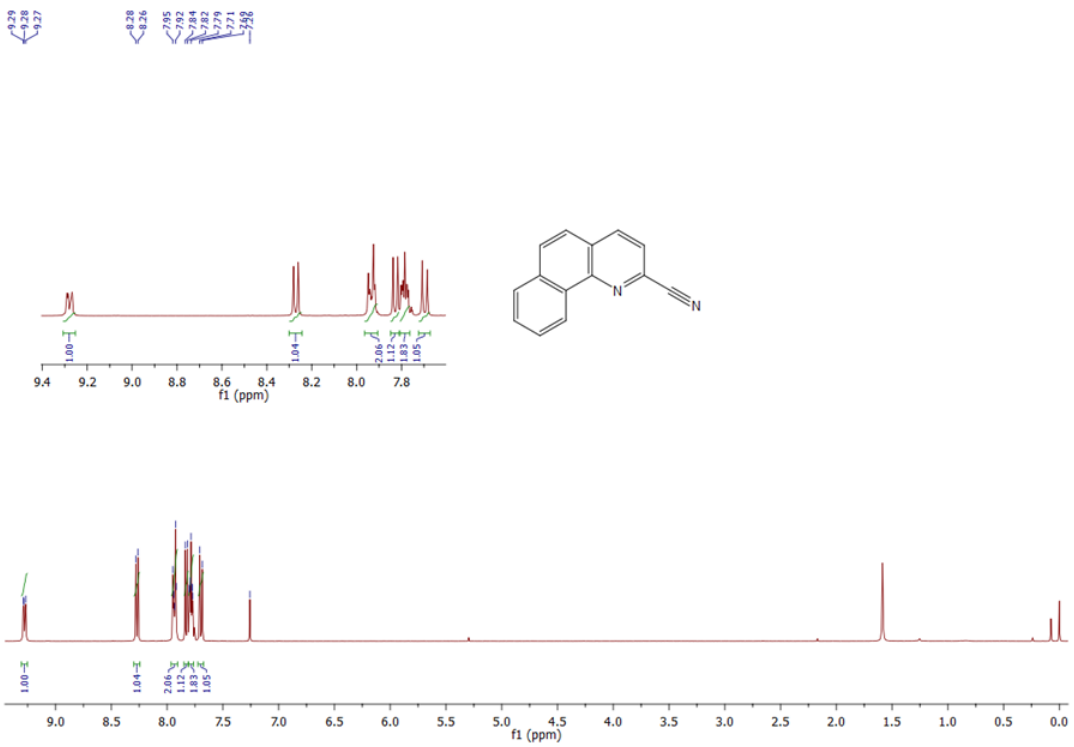


Figure S59: ^{1}H NMR spectrum of **2.6d** (400 MHz, $CDCl_3$, 298 K)

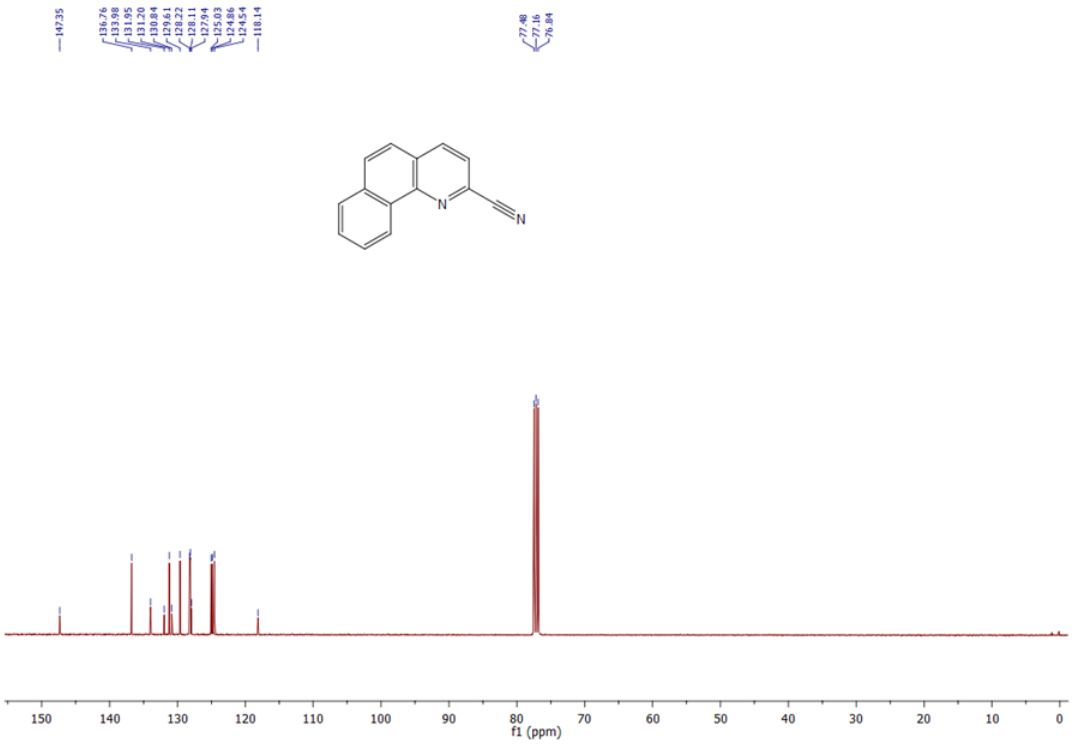


Figure S60: ^{13}C NMR spectrum of **2.6d** (101 MHz, $CDCl_3$, 298 K)

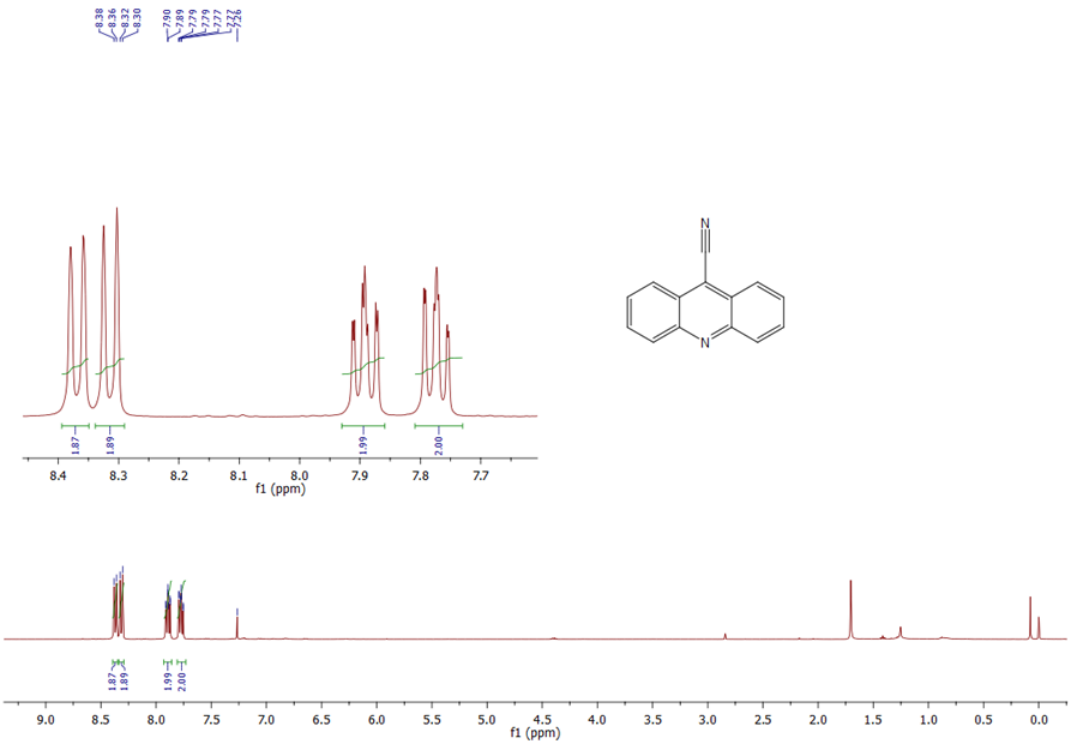


Figure S61: ^{1}H NMR spectrum of **2.6e** (400 MHz, $CDCl_3$, 298 K)

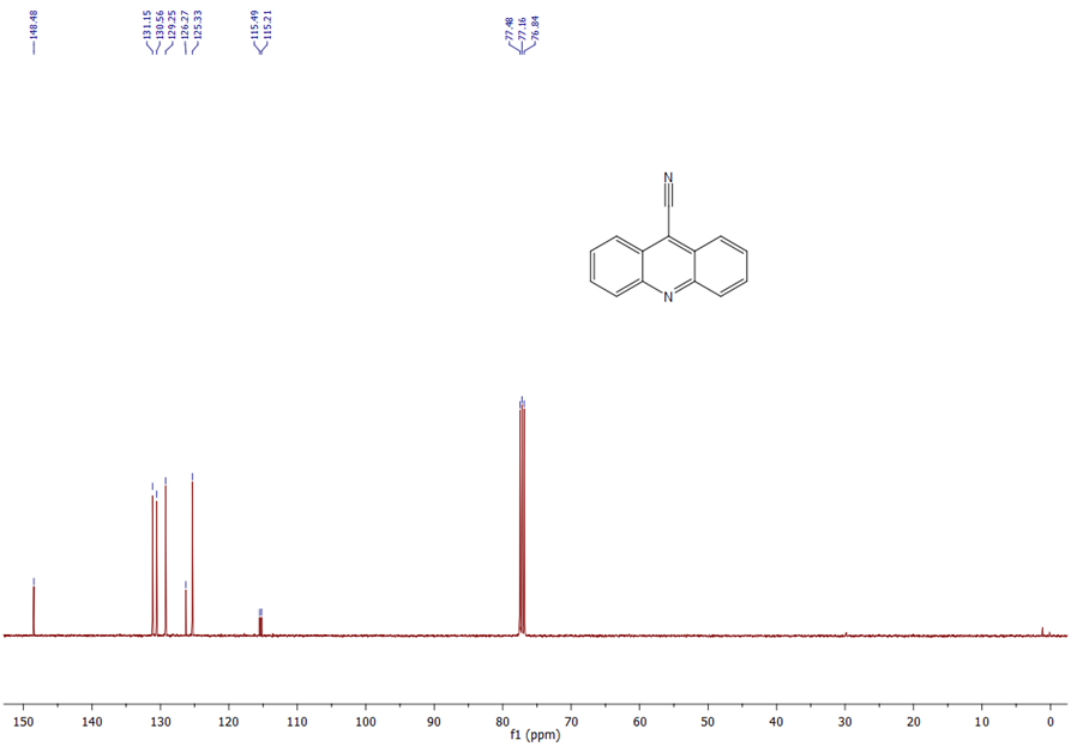


Figure S62: ^{13}C NMR spectrum of **2.6e** (101 MHz, $CDCl_3$, 298 K)

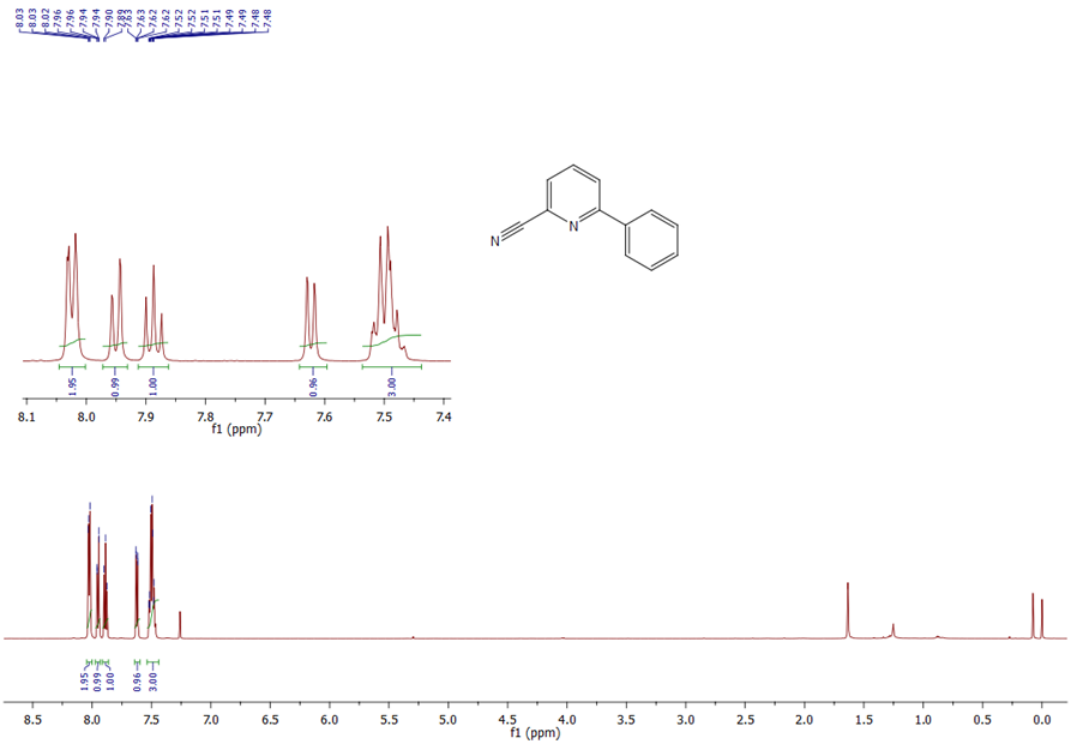


Figure S63: ^{1}H NMR spectrum of **2.6f** (600 MHz, $CDCl_3$, 298 K)

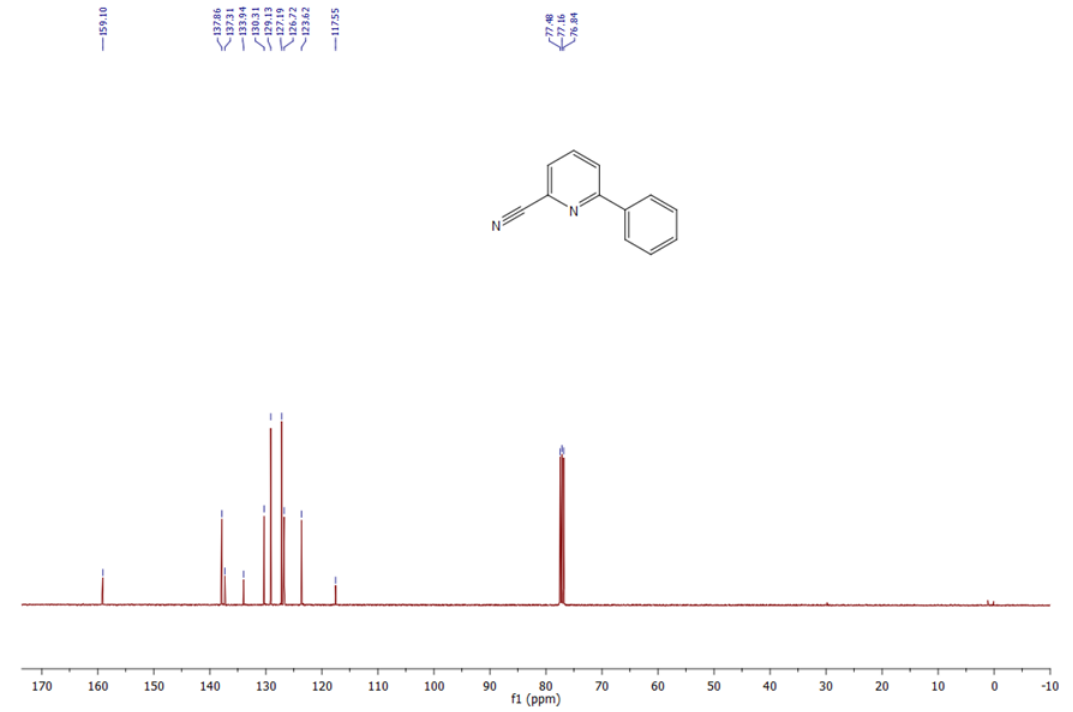


Figure S64: ^{13}C NMR spectrum of **2.6f** (101 MHz, $CDCl_3$, 298 K)

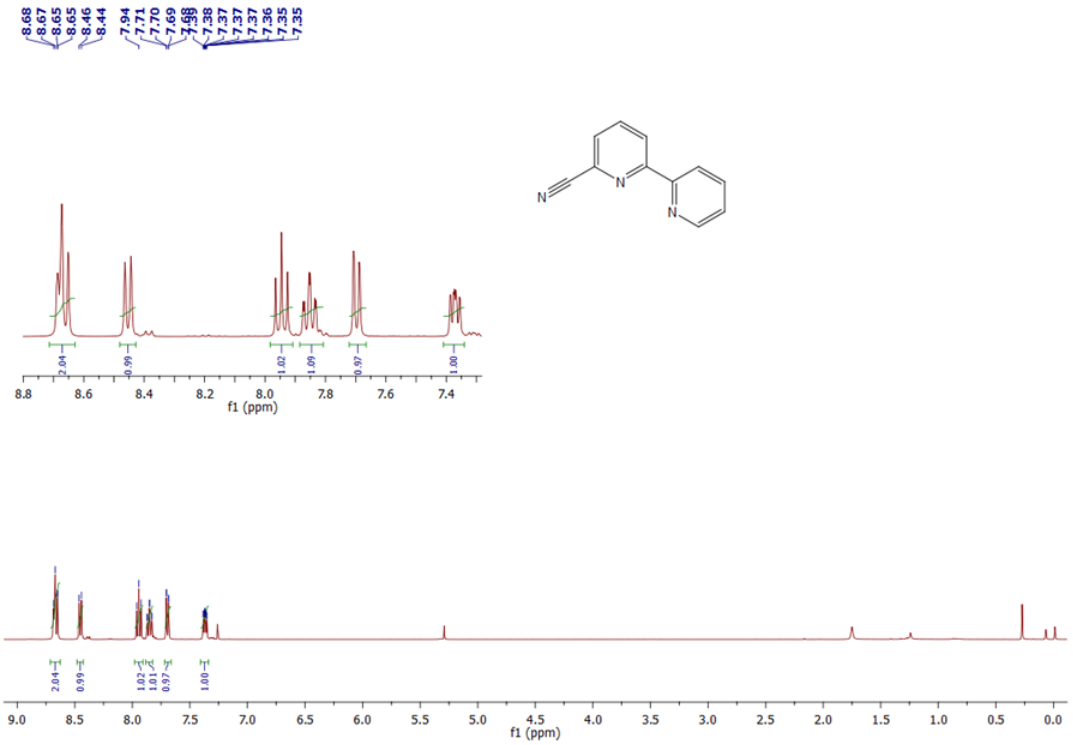


Figure S65: ^{1}H NMR spectrum of **2.6g** (400 MHz, $CDCl_3$, 298 K)

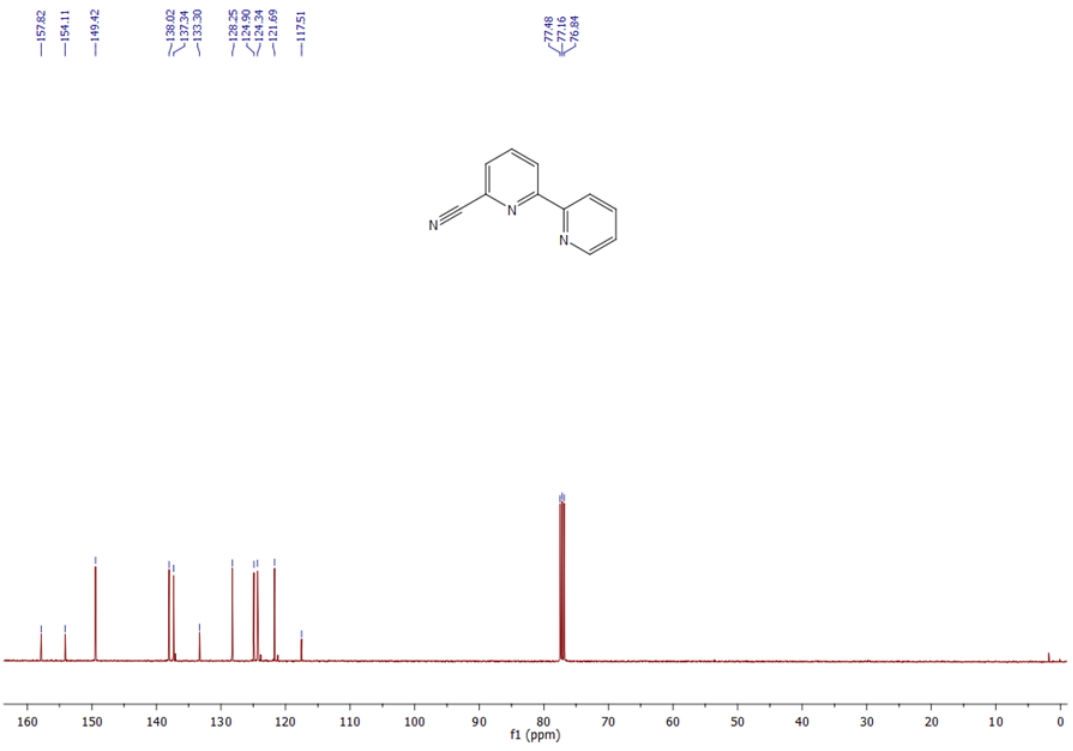


Figure S66: ^{13}C NMR spectrum of **2.6g** (101 MHz, $CDCl_3$, 298 K)

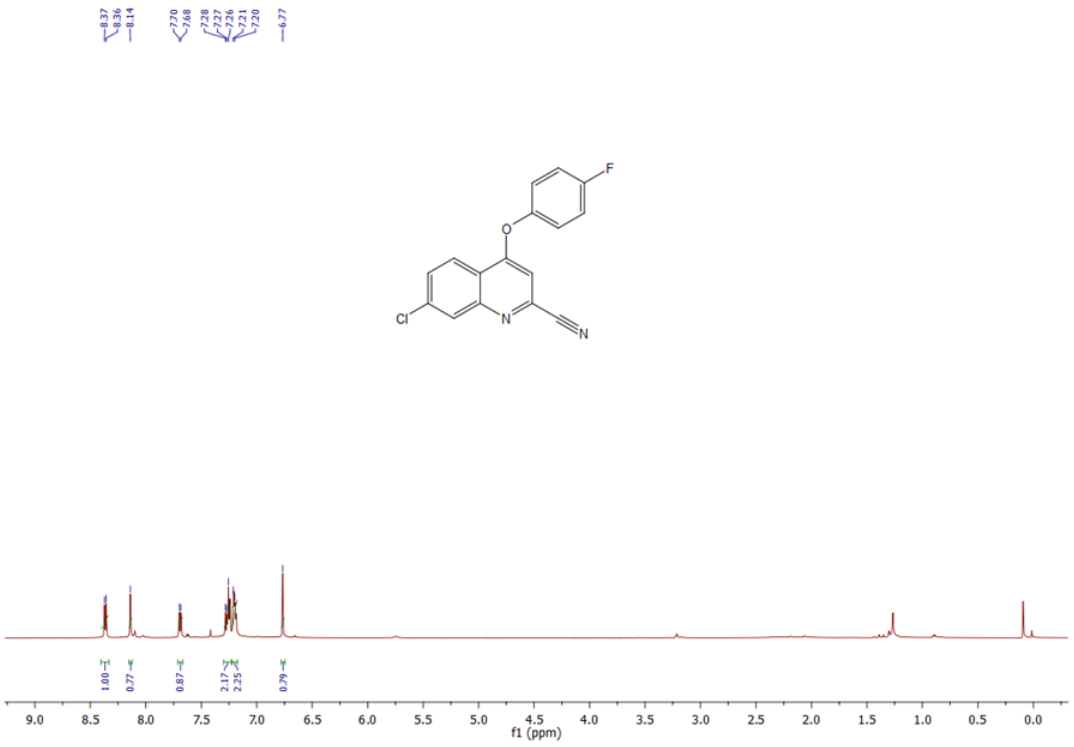


Figure S67: ^{1}H NMR spectrum of **2.10** (600 MHz, $CDCl_3$, 298 K)

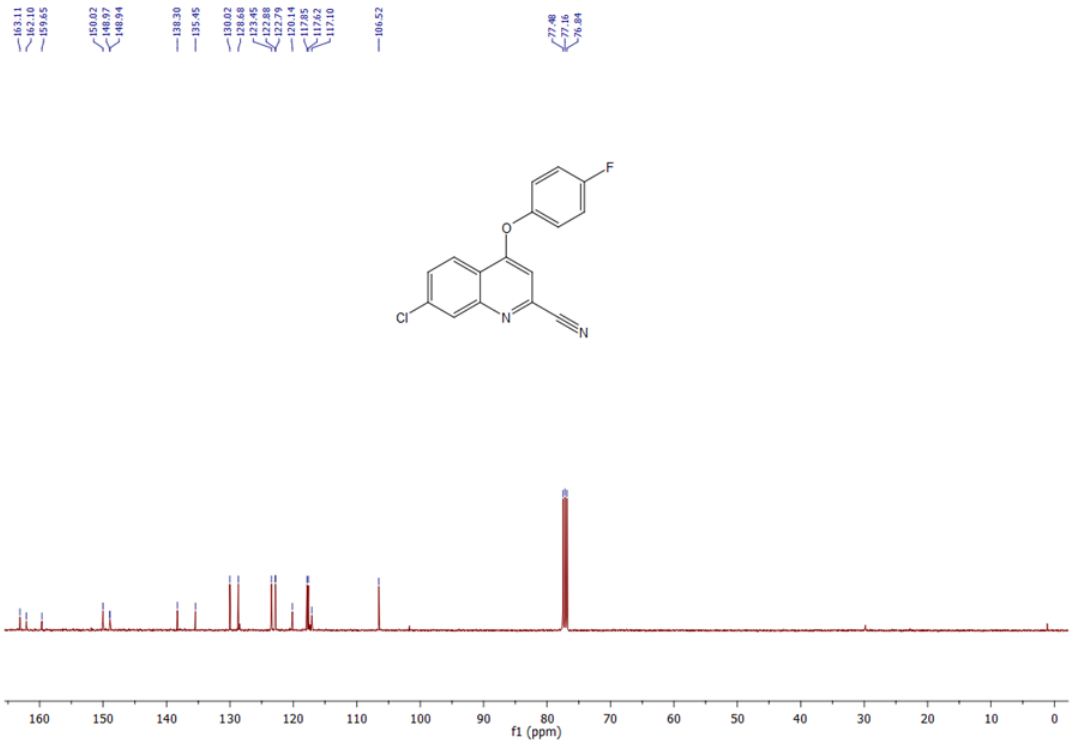


Figure S68: ^{13}C NMR spectrum of **2.10** (101 MHz, $CDCl_3$, 298 K)

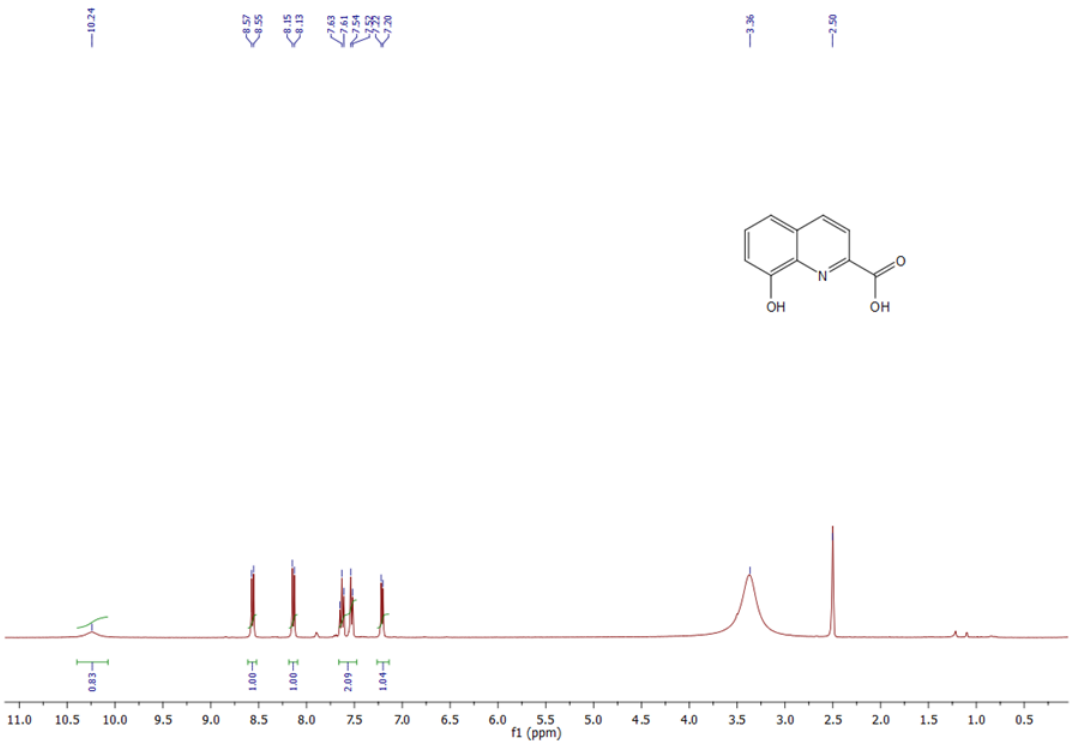


Figure S69: ^{1}H NMR spectrum of **2.11** (400 MHz, DMSO-d^6, 298 K)

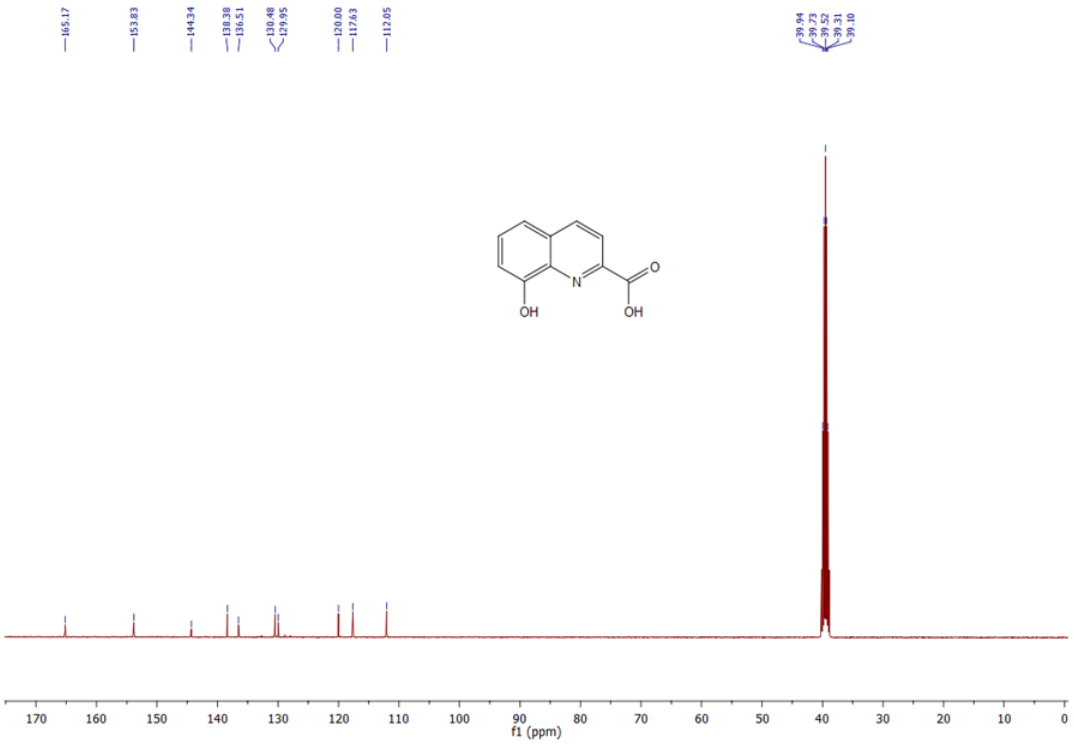


Figure S70: ^{13}C NMR spectrum of **2.11** (101 MHz, DMSO-d^6, 298 K)

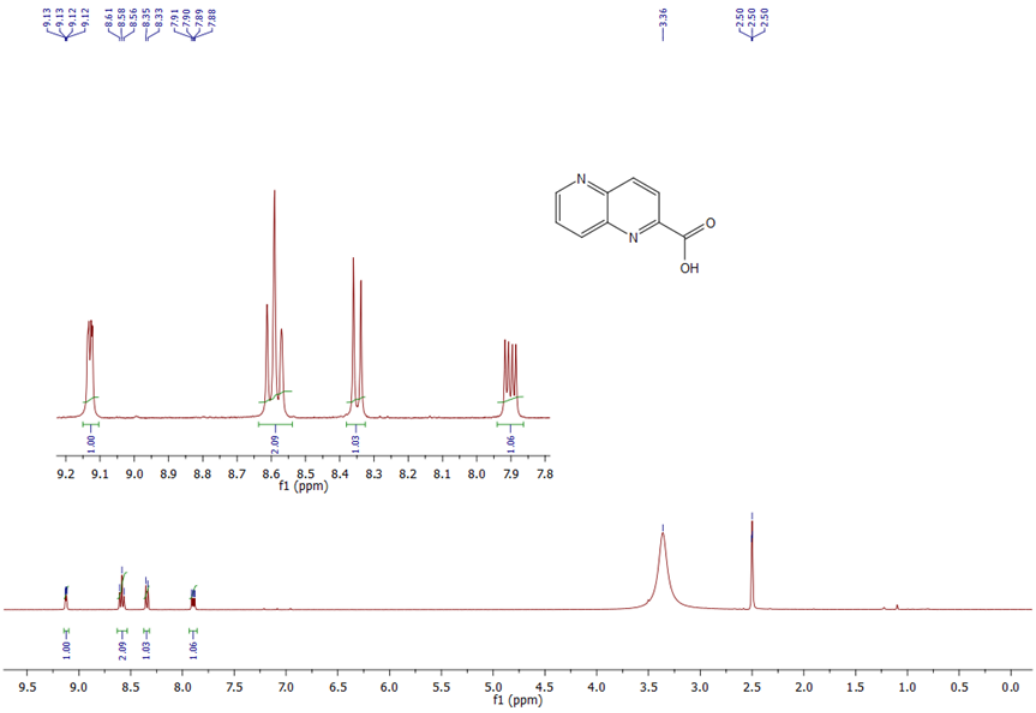


Figure S71: ^{1}H NMR spectrum of **2.12** (400 MHz, DMSO-d^6, 298 K)

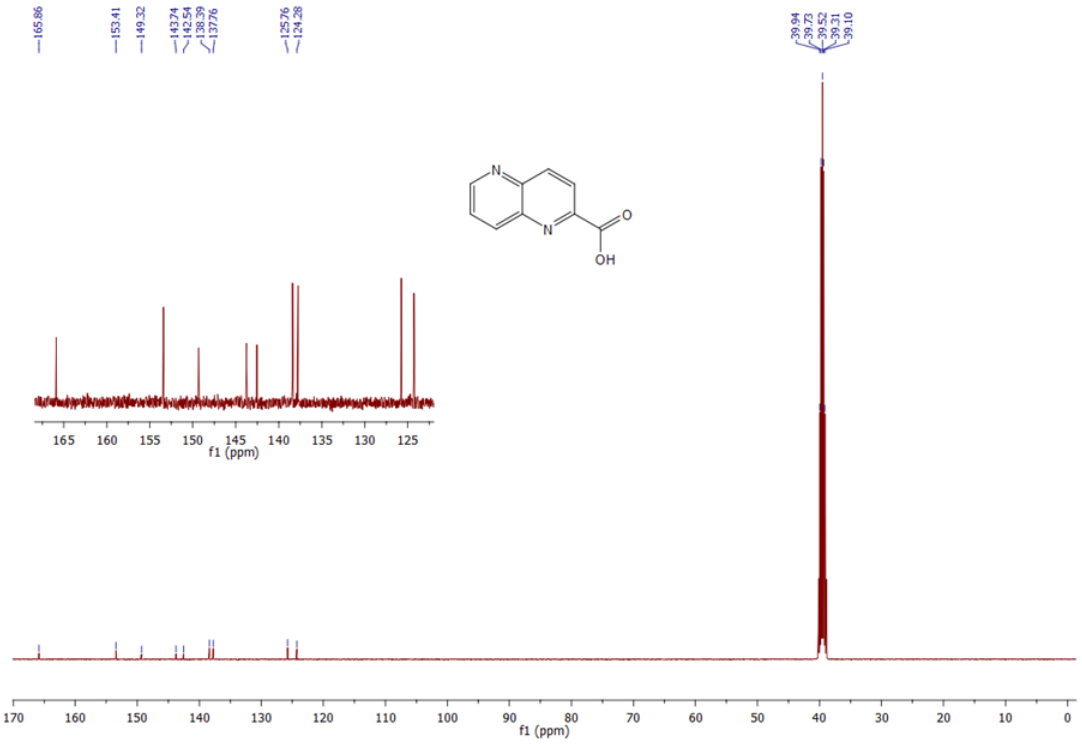


Figure S72: ^{13}C NMR spectrum of **2.12** (101 MHz, DMSO-d^6, 298 K)

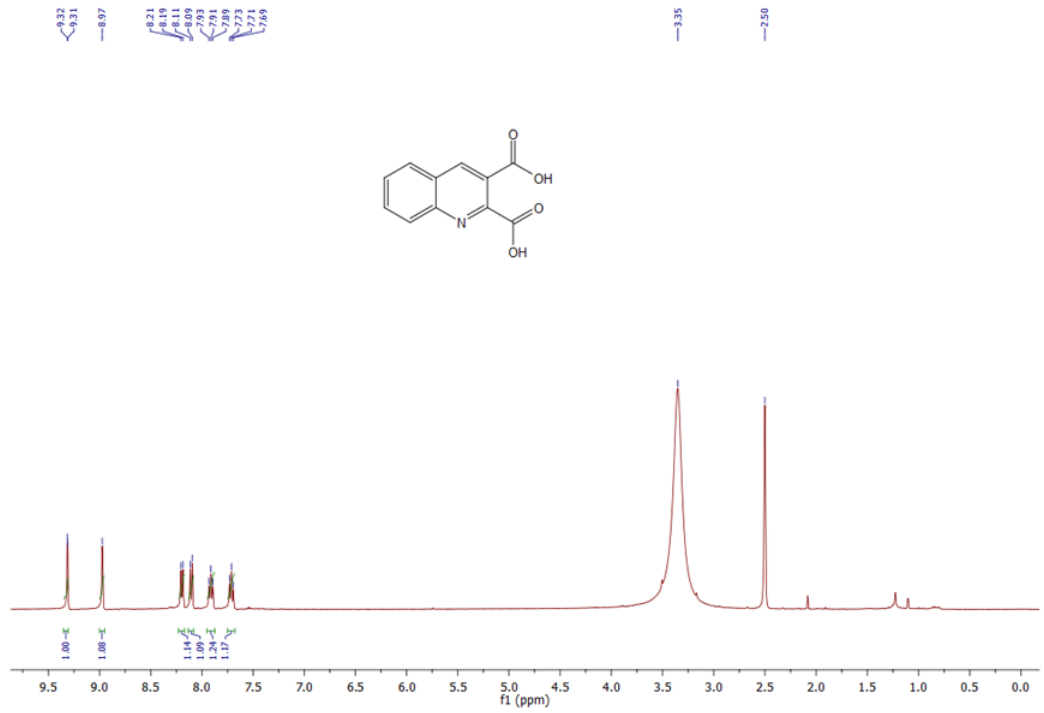


Figure S73: ^{1}H NMR spectrum of **2.14** (400 MHz, DMSO-d^6, 298 K)

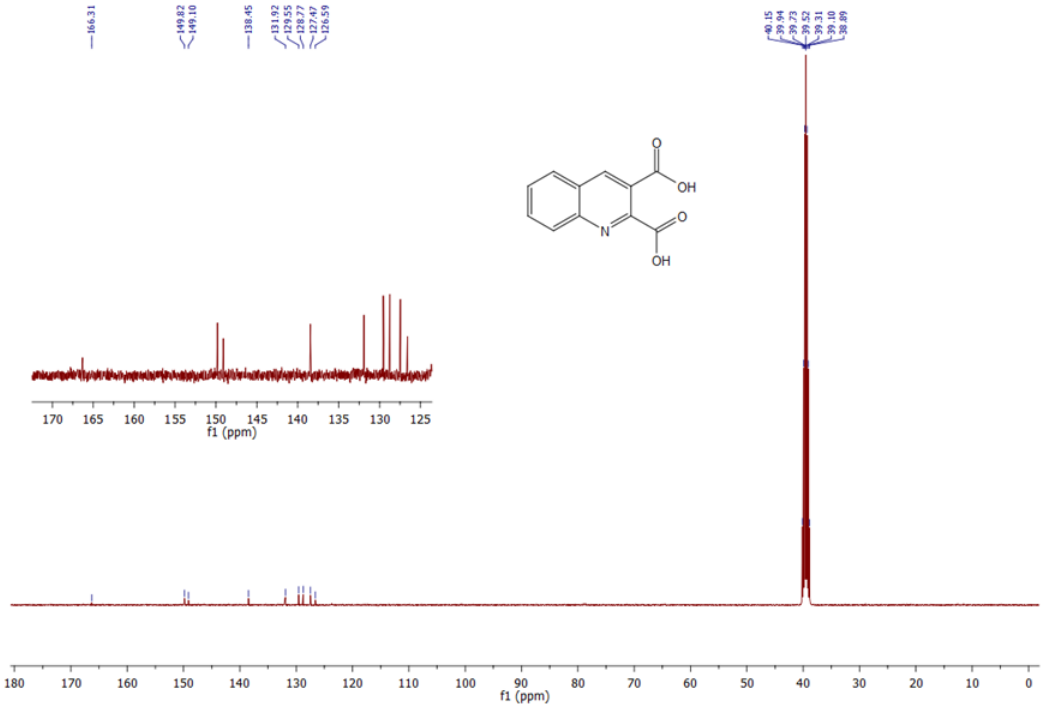


Figure S74: ^{13}C NMR spectrum of **2.14** (101 MHz, DMSO-d^6, 298 K)

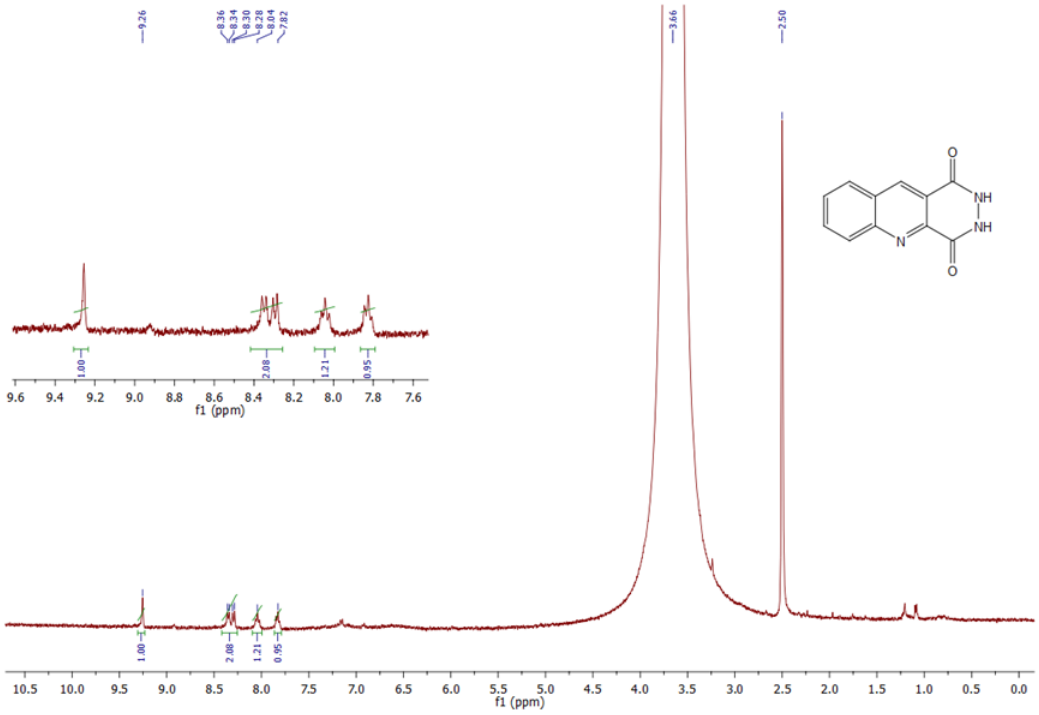


Figure S75: ^{1}H NMR spectrum of **2.15** (400 MHz, DMSO-d^6, 298 K)

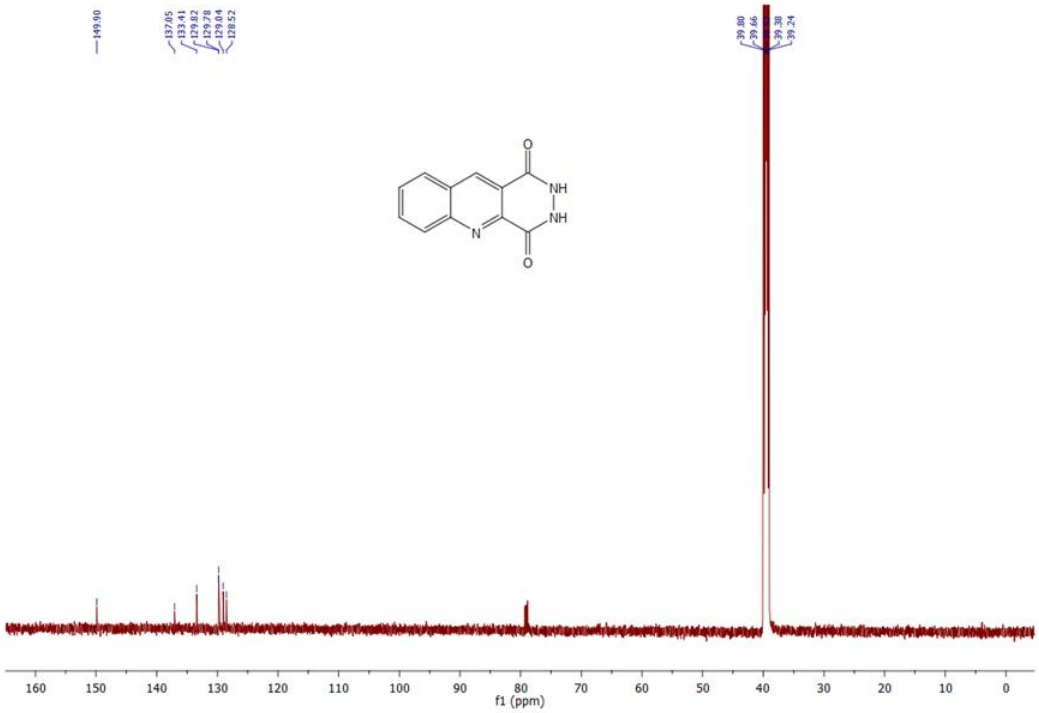


Figure S76: ^{13}C NMR spectrum of **2.15** (151 MHz, DMSO-d^6, 298 K)

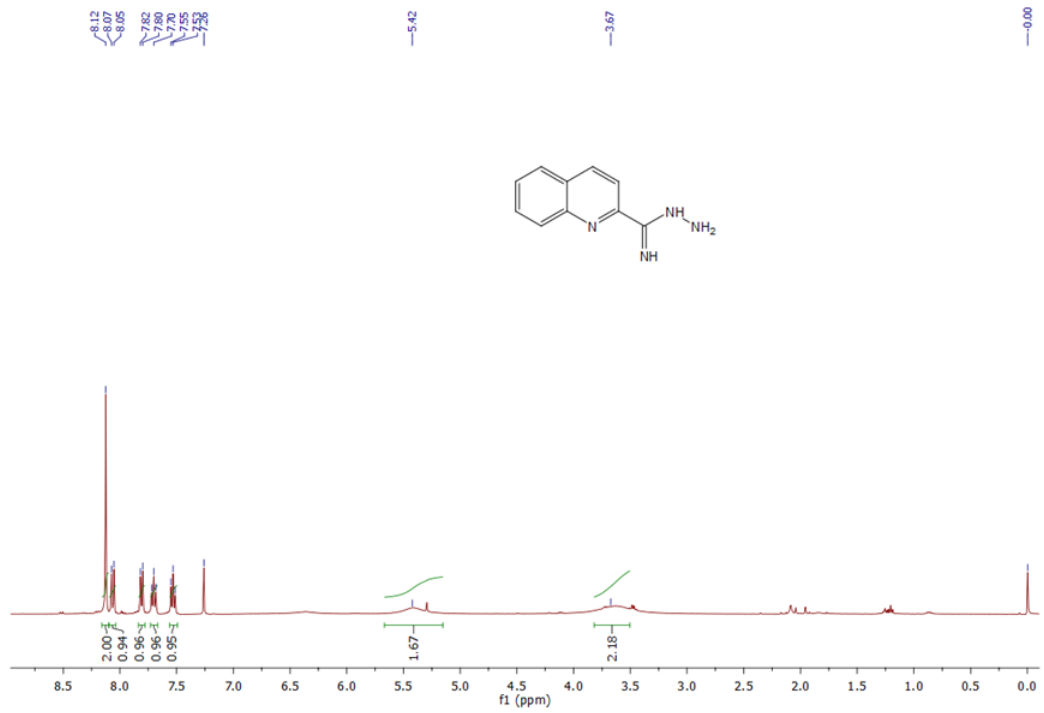


Figure S77: ^{1}H NMR spectrum of **2.16** (400 MHz, $CDCl_3$, 298 K)

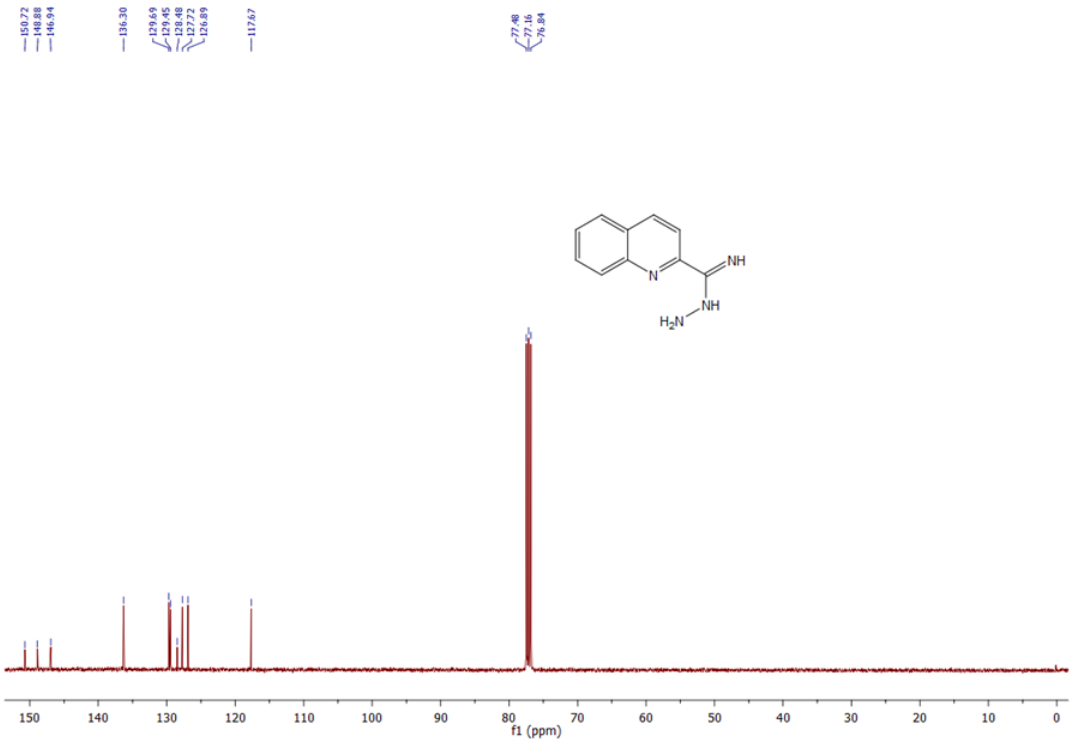


Figure S78: ^{13}C NMR spectrum of **2.16** (101 MHz, $CDCl_3$, 298 K)

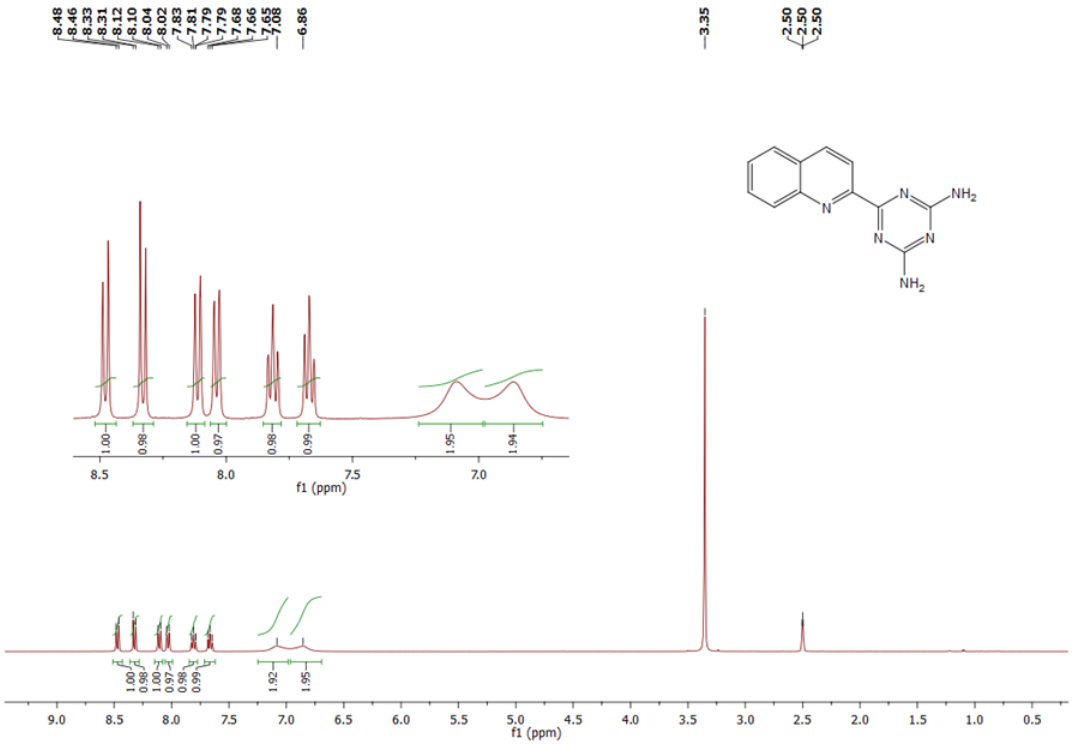


Figure S79: ^{1}H NMR spectrum of **2.17** (400 MHz, DMSO-d^6, 298 K)

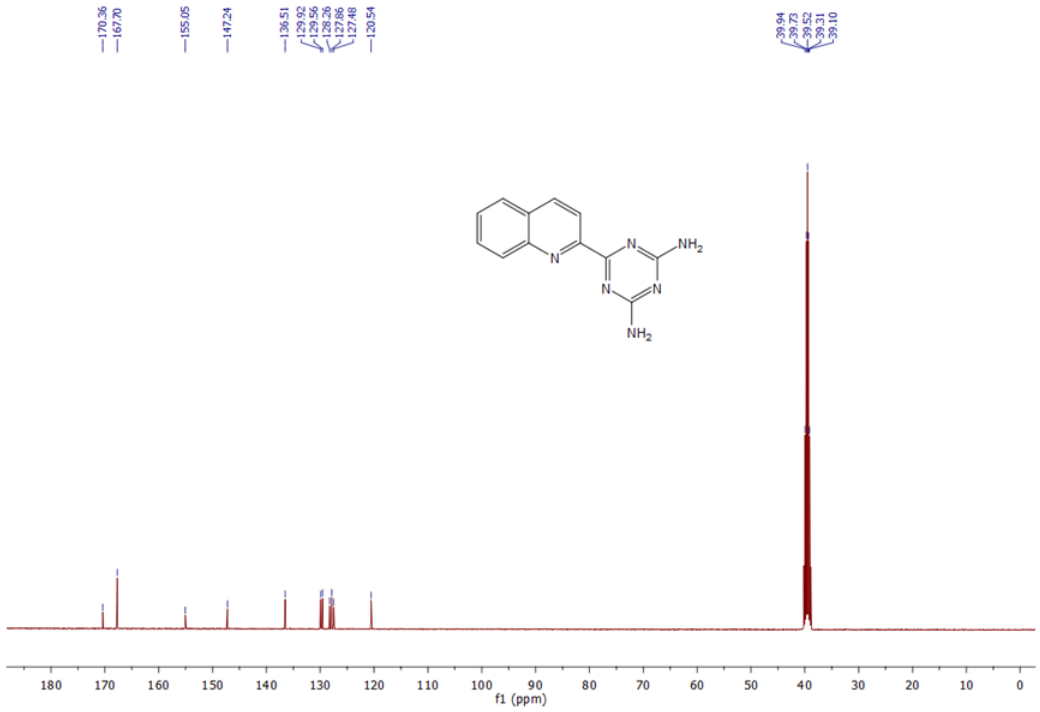


Figure S80: ^{13}C NMR spectrum of **2.17** (101 MHz, DMSO-d^6, 298 K)

Annexure II

^{1}H, ^{13}C and ^{19}F NMR spectra of compounds (*Chapter 3*)

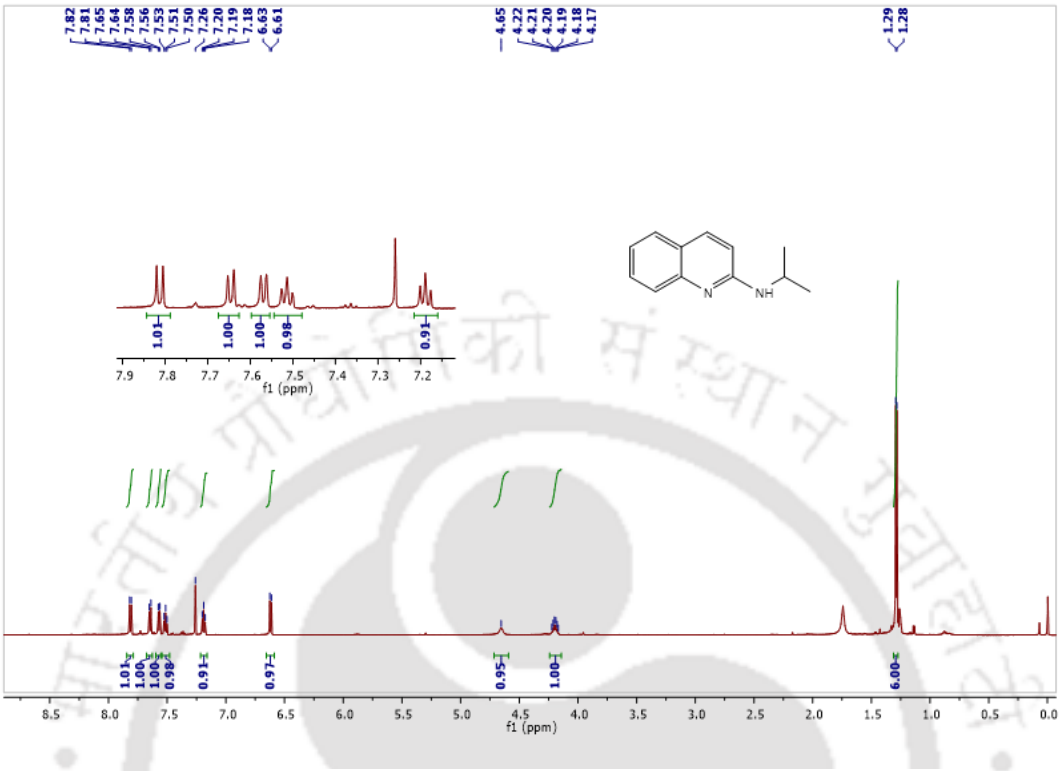


Figure S81. ^{1}H NMR Spectrum of **3.2a** ($CDCl_3$, 600 MHz, 298 K)

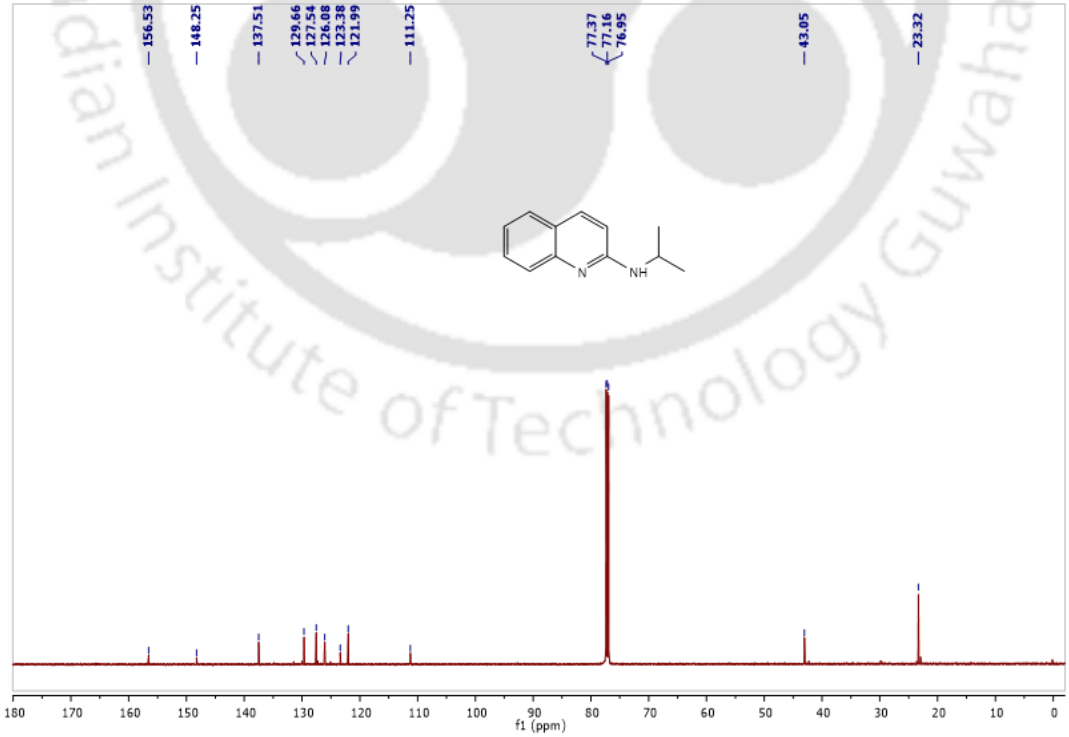


Figure S82. ^{13}C NMR Spectrum of **3.2a** ($CDCl_3$, 151 MHz, 298 K)

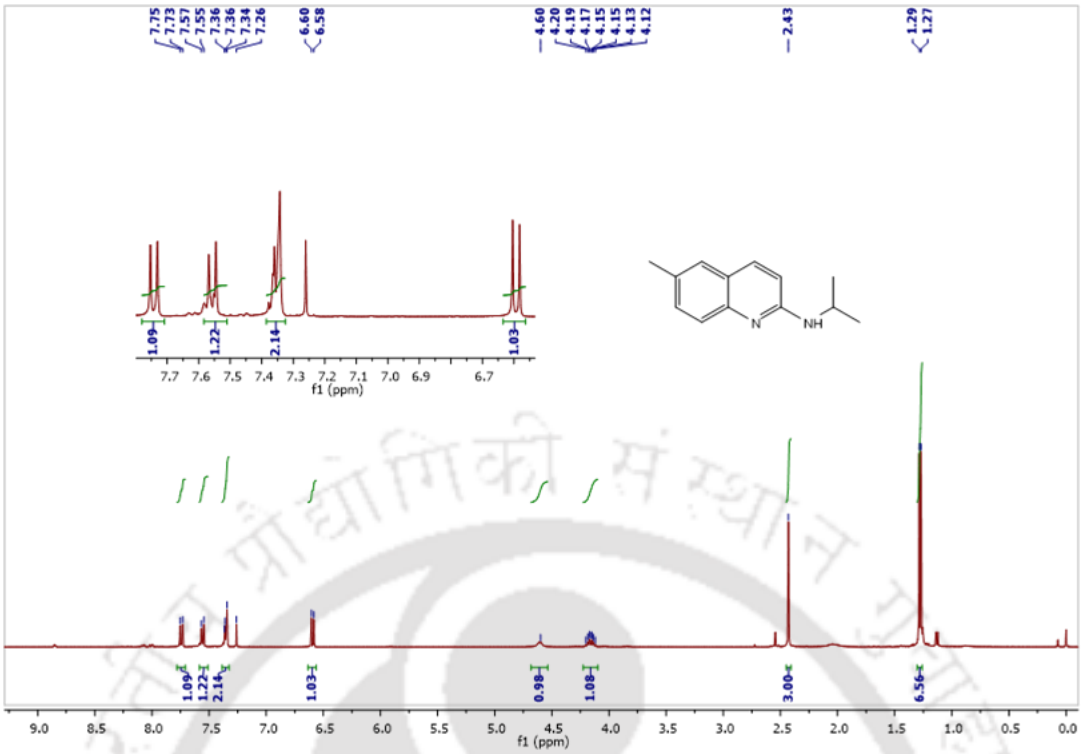


Figure S83. ^{1}H NMR Spectrum of **3.2b** ($CDCl_3$, 400 MHz, 298 K)

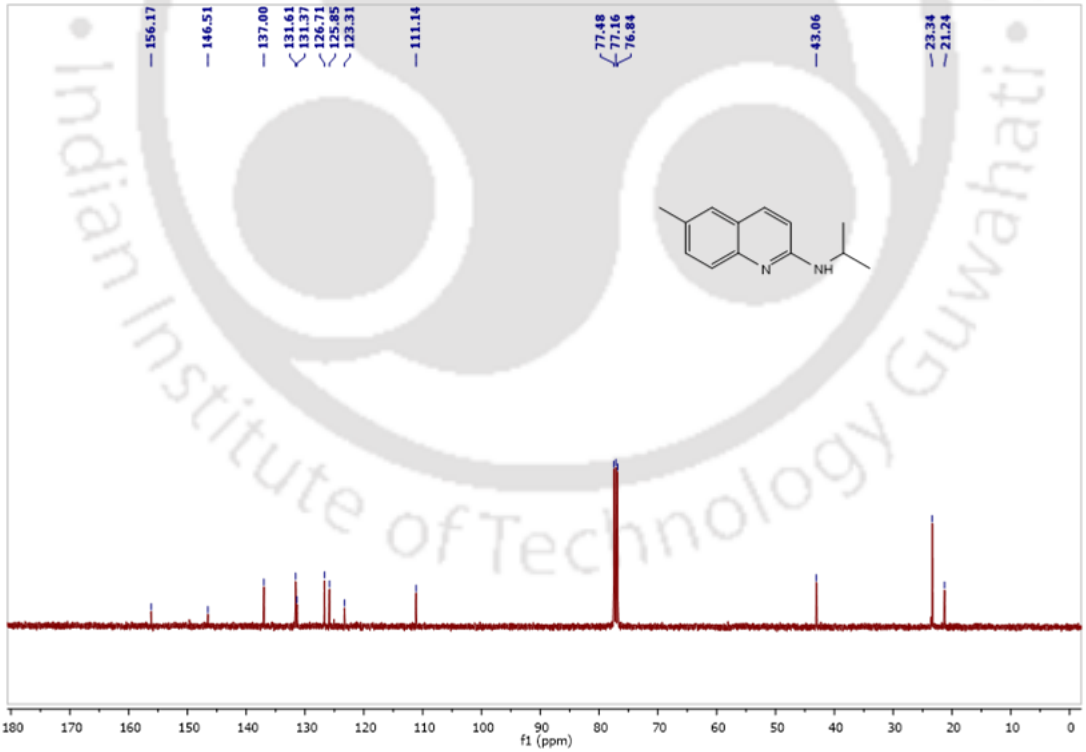


Figure S84. ^{13}C NMR Spectrum of **3.2b** ($CDCl_3$, 101 MHz, 298 K)

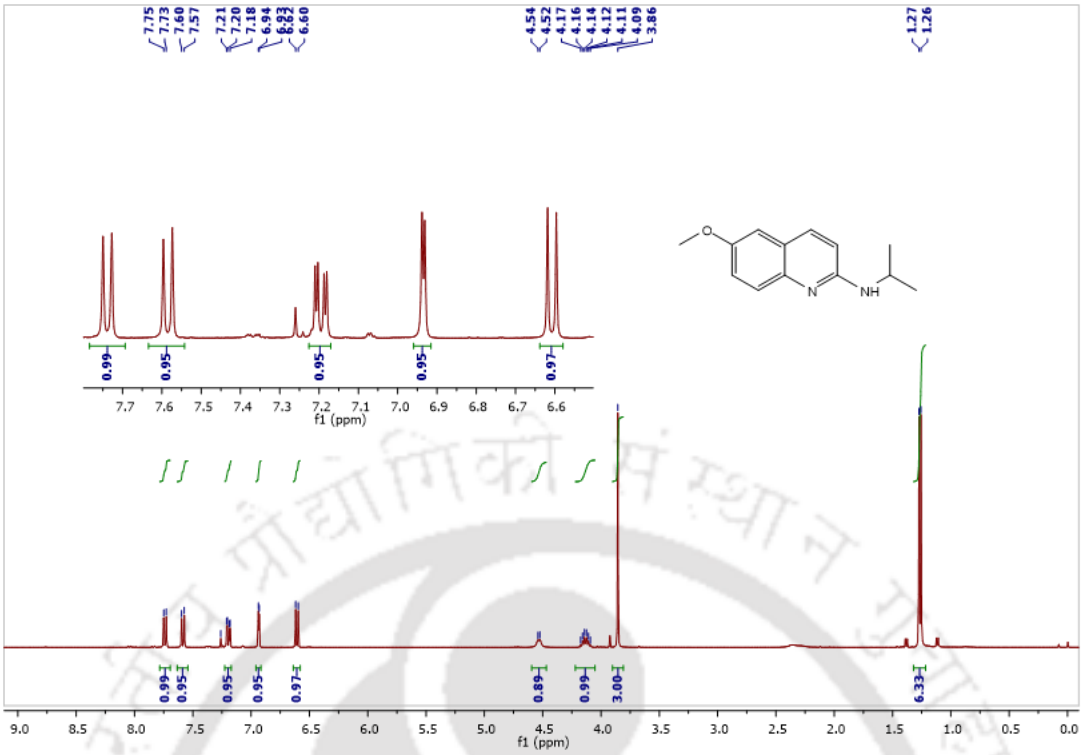


Figure S85. ^{1}H NMR Spectrum of **3.2c** ($CDCl_3$, 400 MHz, 298 K)

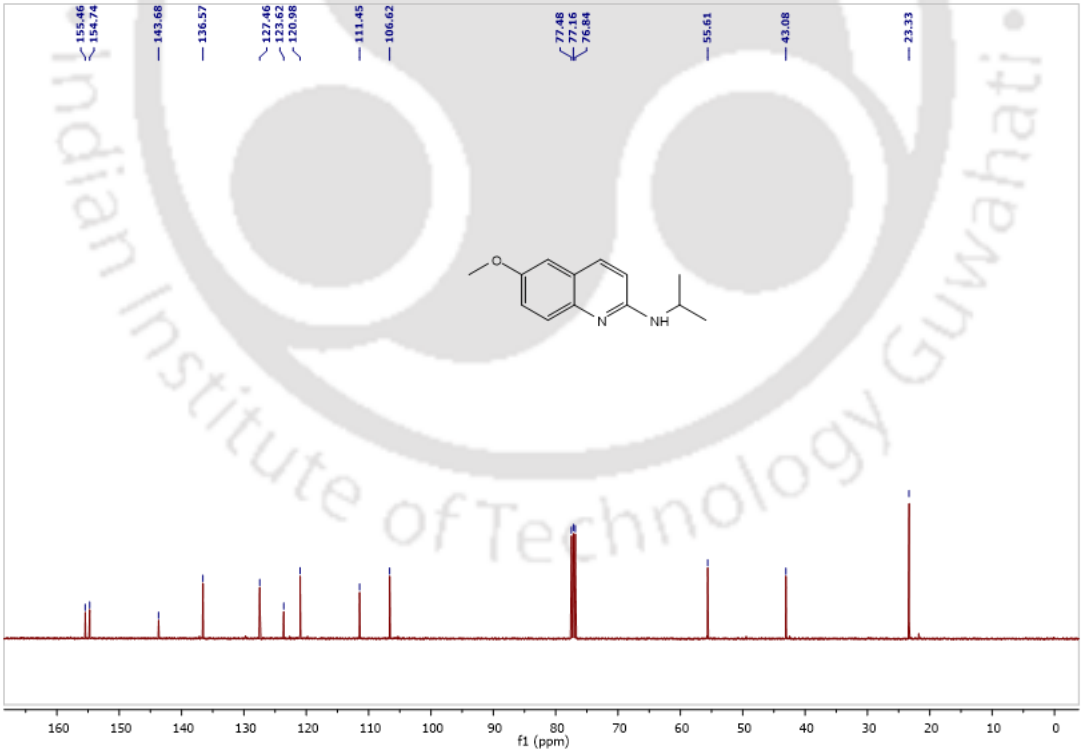


Figure S86. ^{13}C NMR Spectrum of **3.2c** ($CDCl_3$, 101 MHz, 298 K)

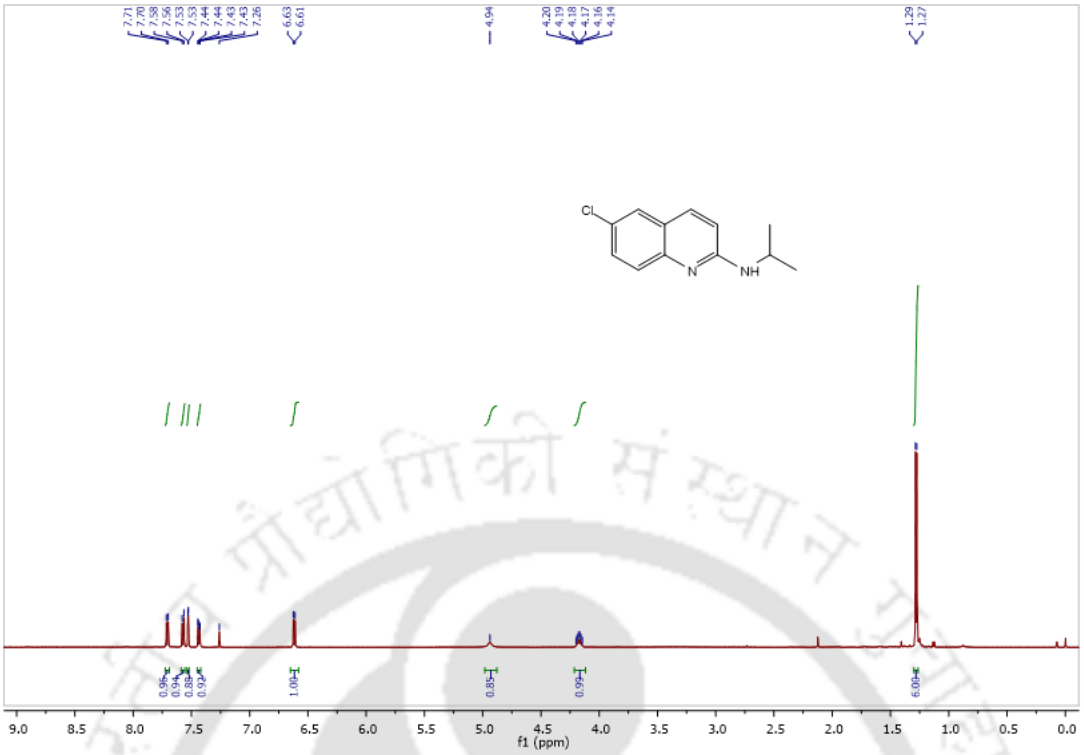


Figure S87. ^{1}H NMR Spectrum of **3.2d** ($CDCl_3$, 600 MHz, 298 K)

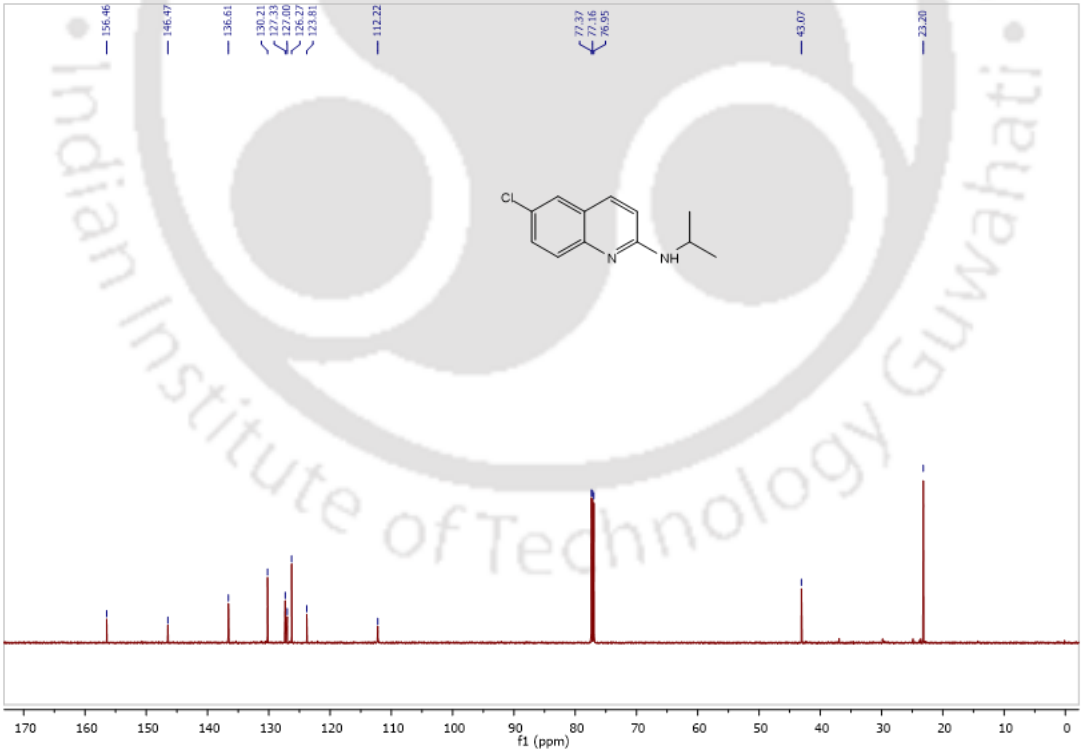


Figure S88. ^{13}C NMR Spectrum of **3.2d** ($CDCl_3$, 151 MHz, 298 K)

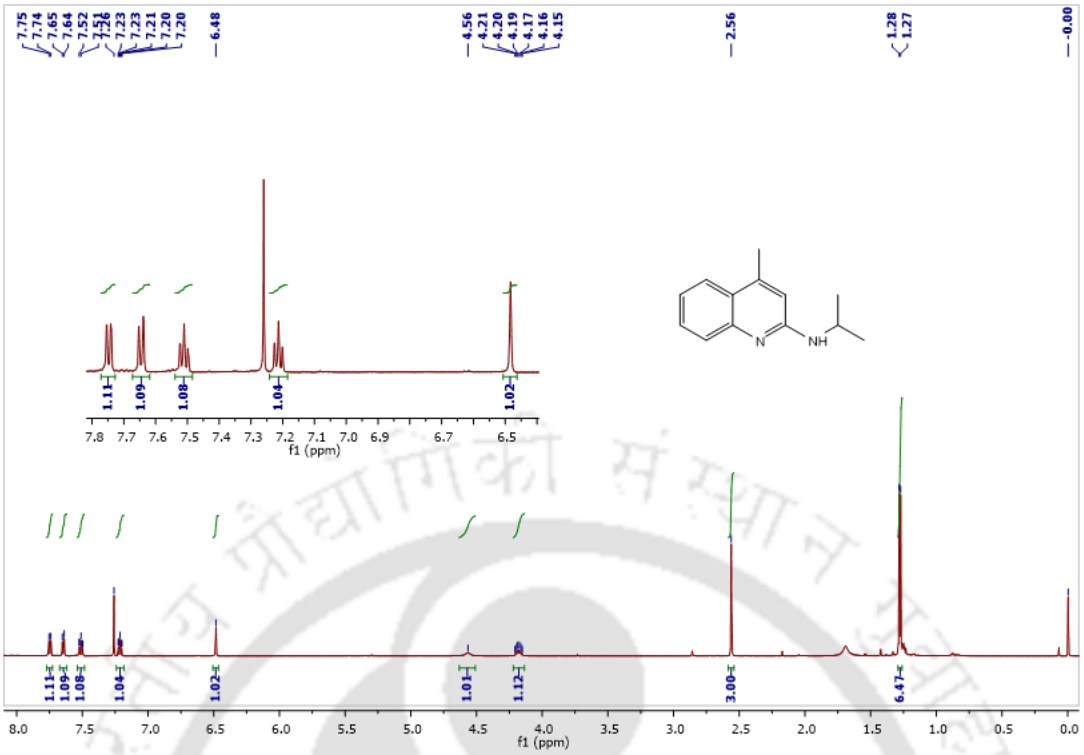


Figure S89. ^{1}H NMR Spectrum of **3.2e** ($CDCl_3$, 600 MHz, 298 K)

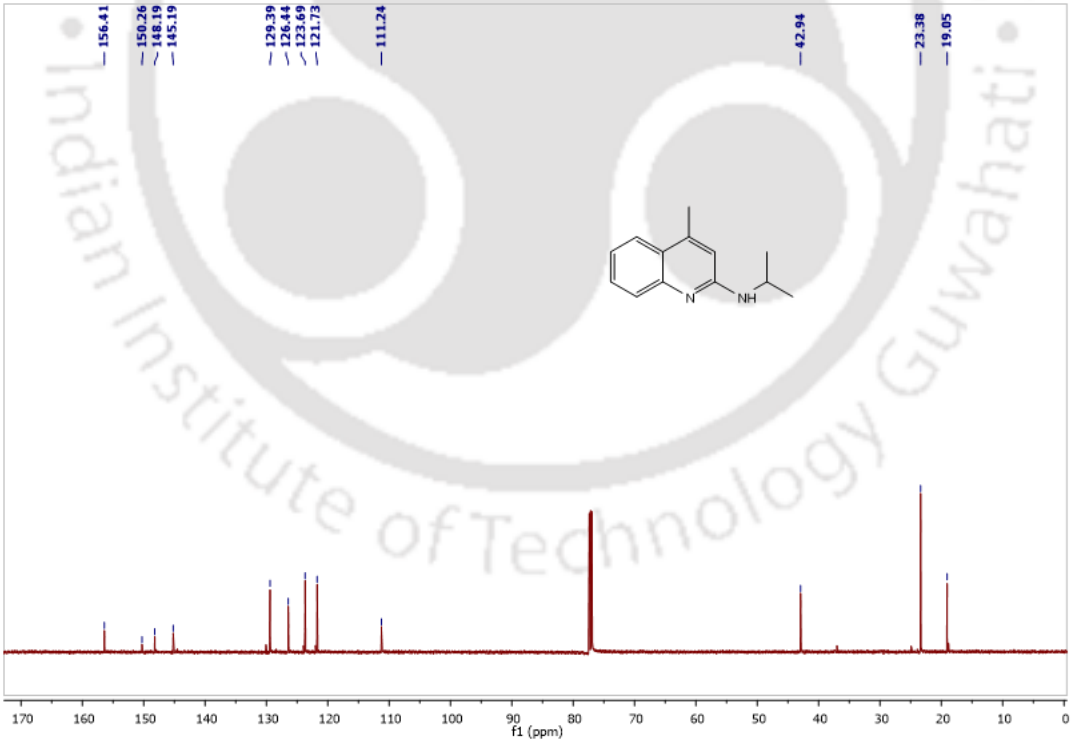


Figure S90. ^{13}C NMR Spectrum of **3.2e** ($CDCl_3$, 151 MHz, 298 K)

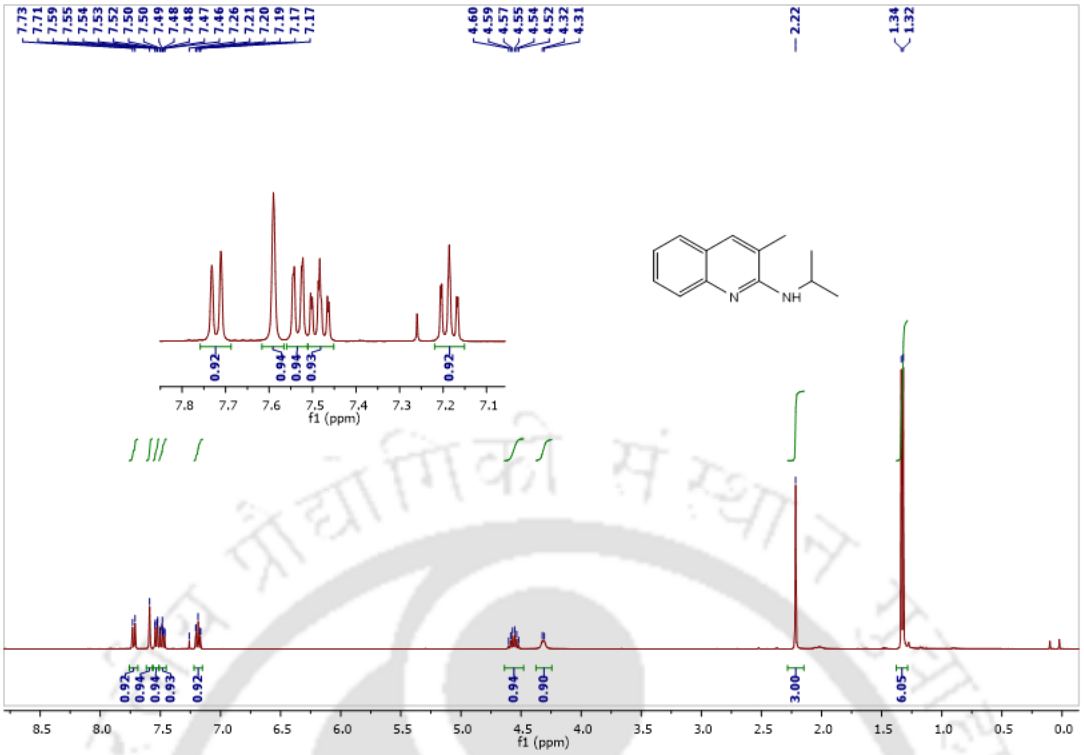


Figure S91. ^{1}H NMR Spectrum of **3.2f** ($CDCl_3$, 400 MHz, 298 K)

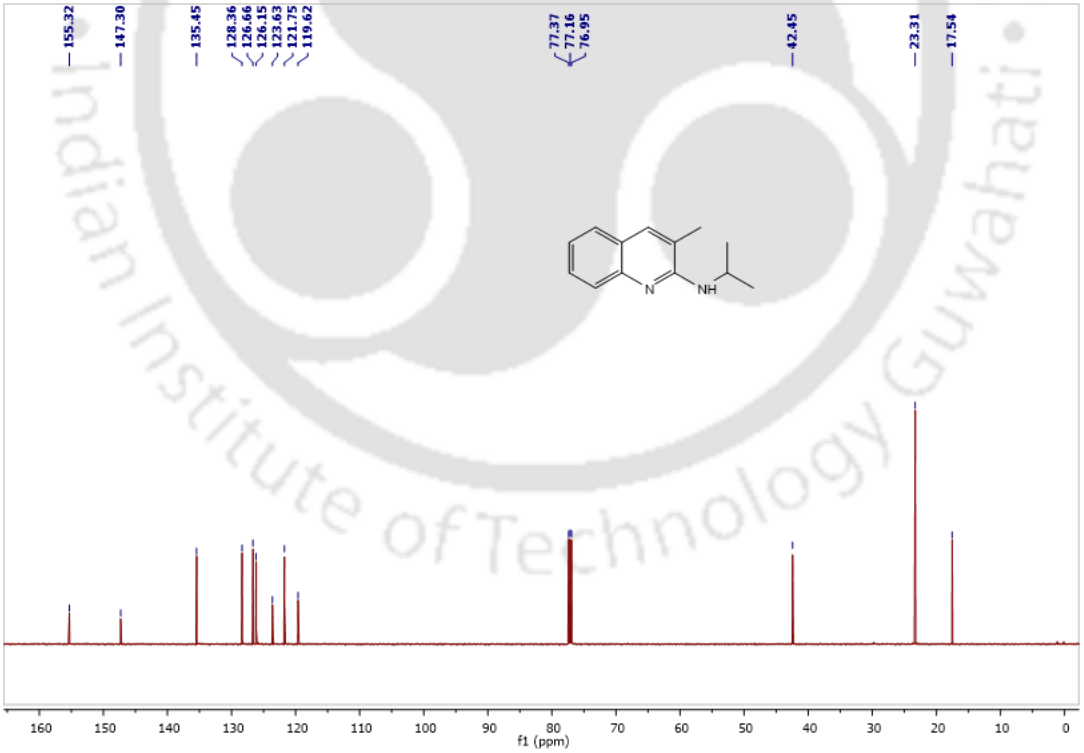


Figure S92. ^{13}C NMR Spectrum of **3.2f** ($CDCl_3$, 151 MHz, 298 K)

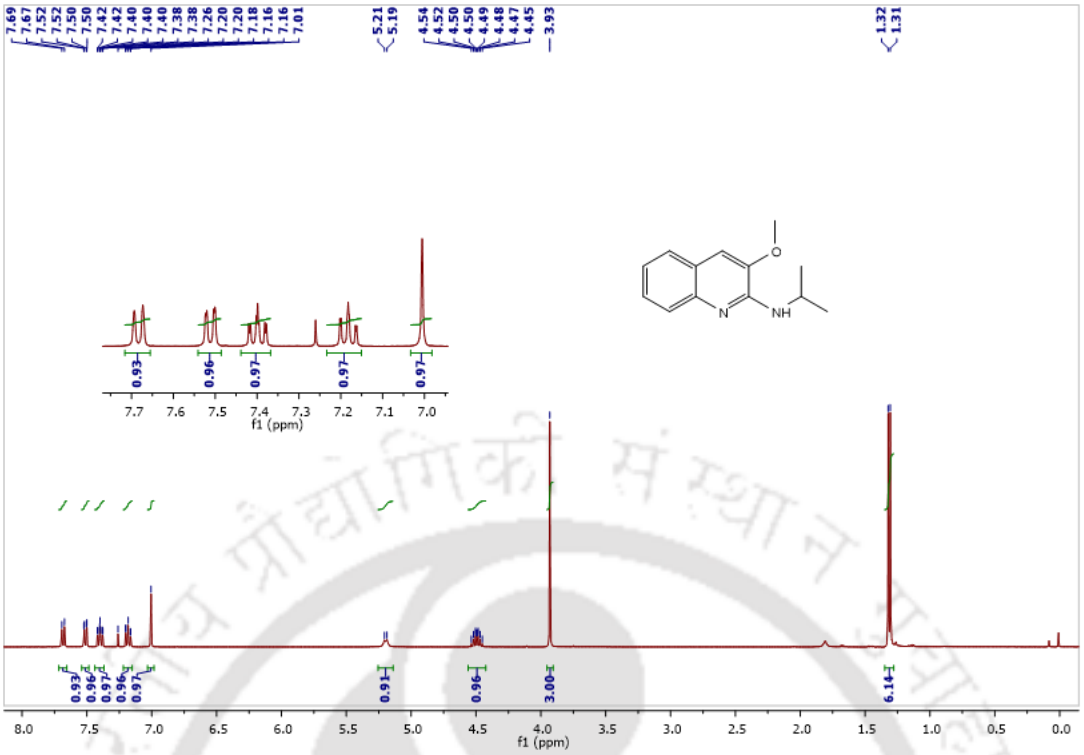


Figure S93. ^{1}H NMR Spectrum of **3.2g** ($CDCl_3$, 400 MHz, 298 K)

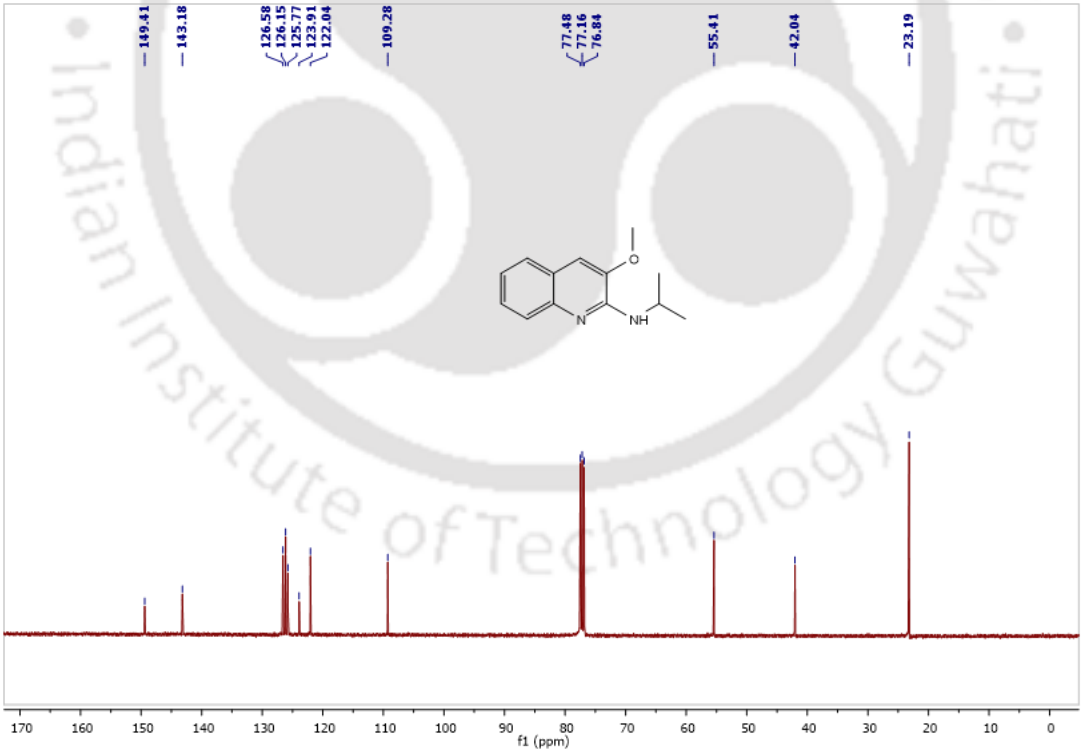


Figure S94. ^{13}C NMR Spectrum of **3.2g** ($CDCl_3$, 101 MHz, 298 K)

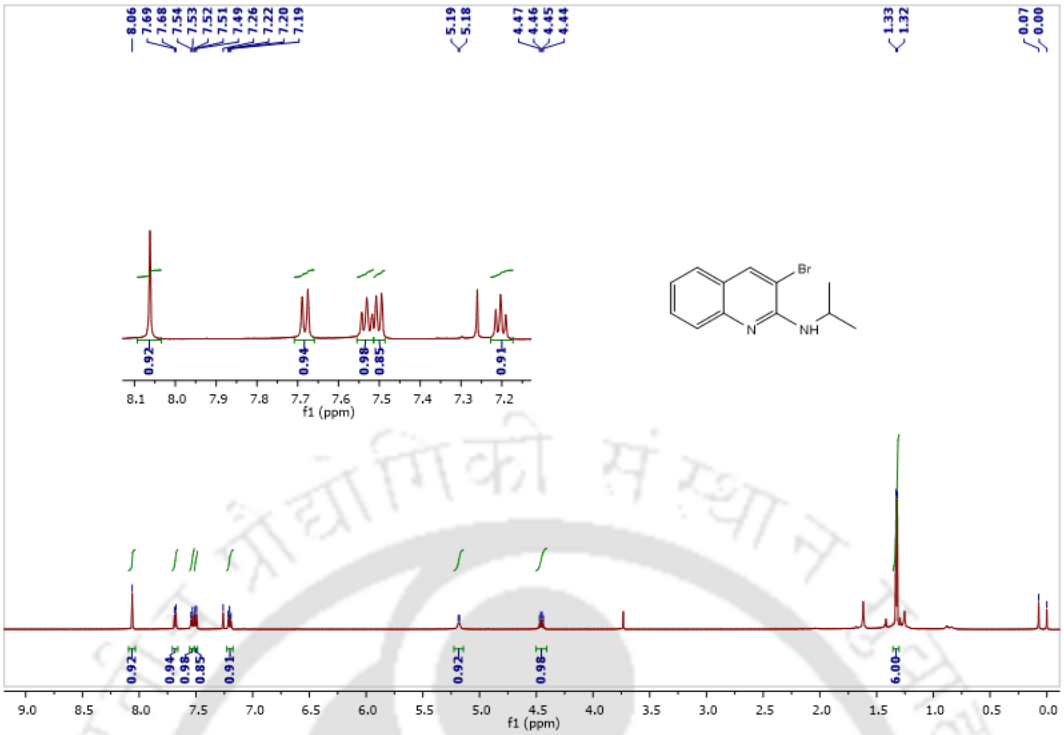


Figure S95. ^{1}H NMR Spectrum of **3.2h** ($CDCl_3$, 600 MHz, 298 K)

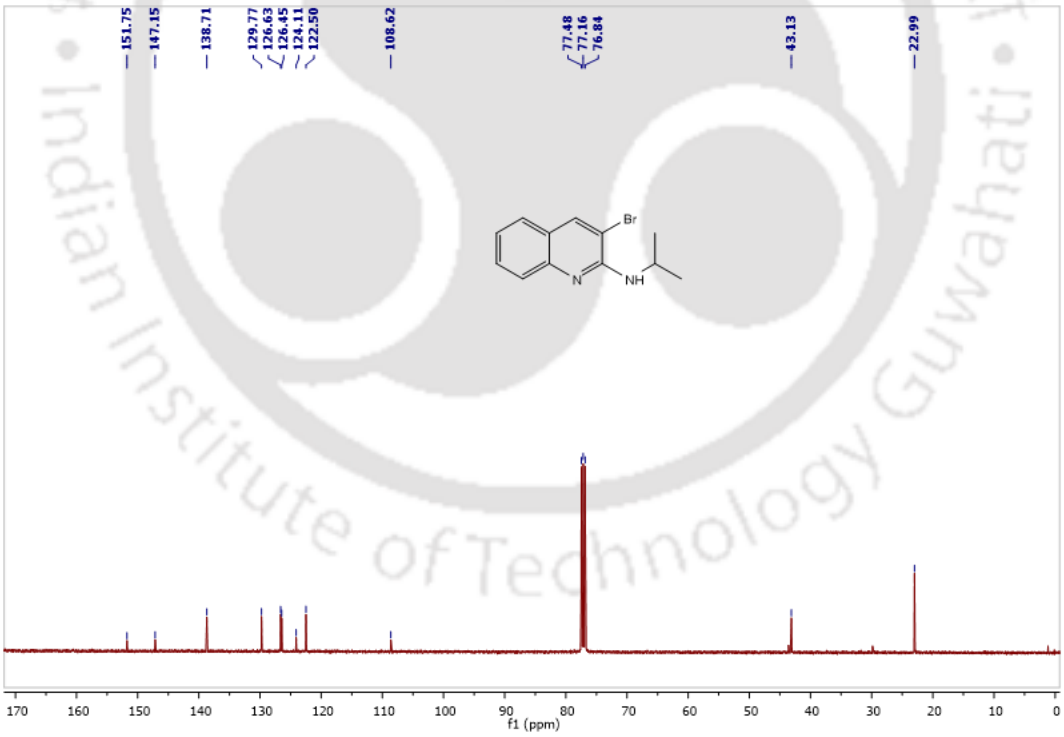


Figure S96. ^{13}C NMR Spectrum of **3.2h** ($CDCl_3$, 101 MHz, 298 K)

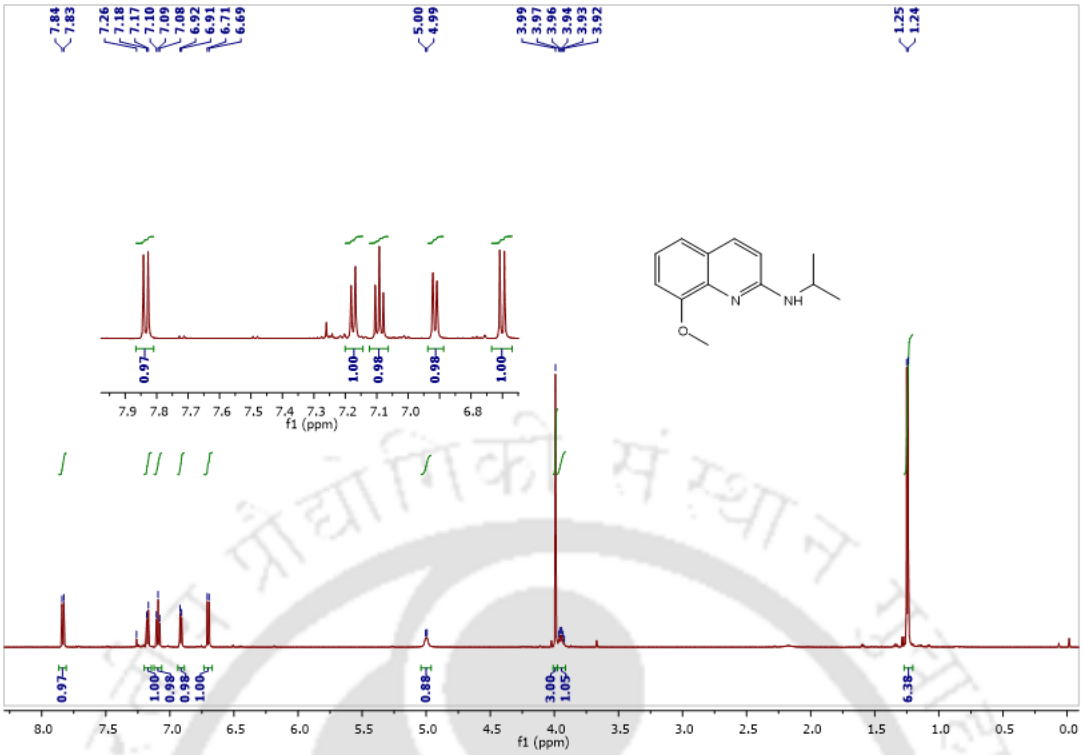


Figure S97. ^{1}H NMR Spectrum of **3.2i** ($CDCl_3$, 600 MHz, 298 K)

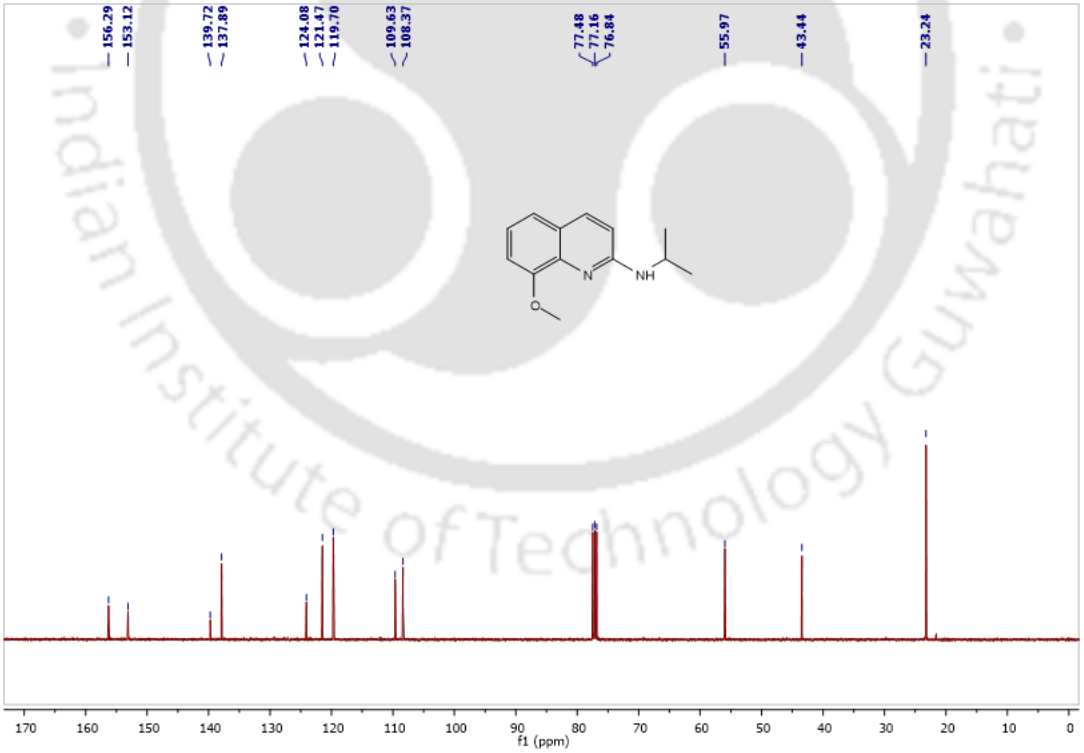


Figure S98. ^{13}C NMR Spectrum of **3.2i** ($CDCl_3$, 101 MHz, 298 K)

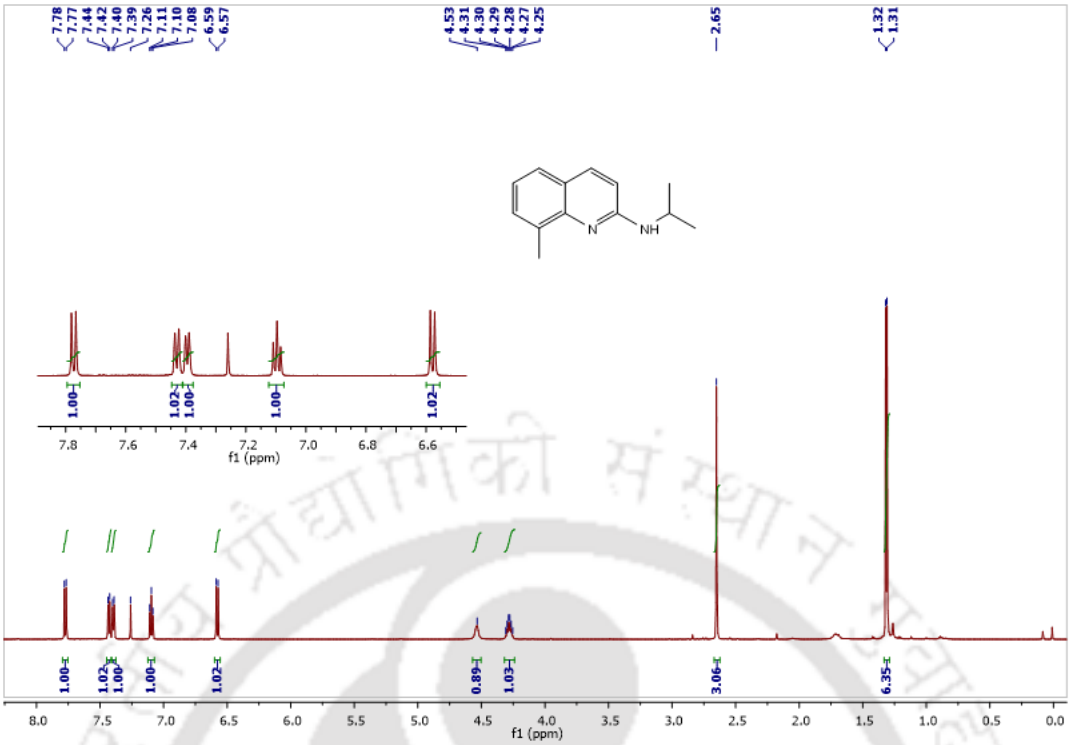


Figure S99. ^{1}H NMR Spectrum of **3.2j** ($CDCl_3$, 600 MHz, 298 K)

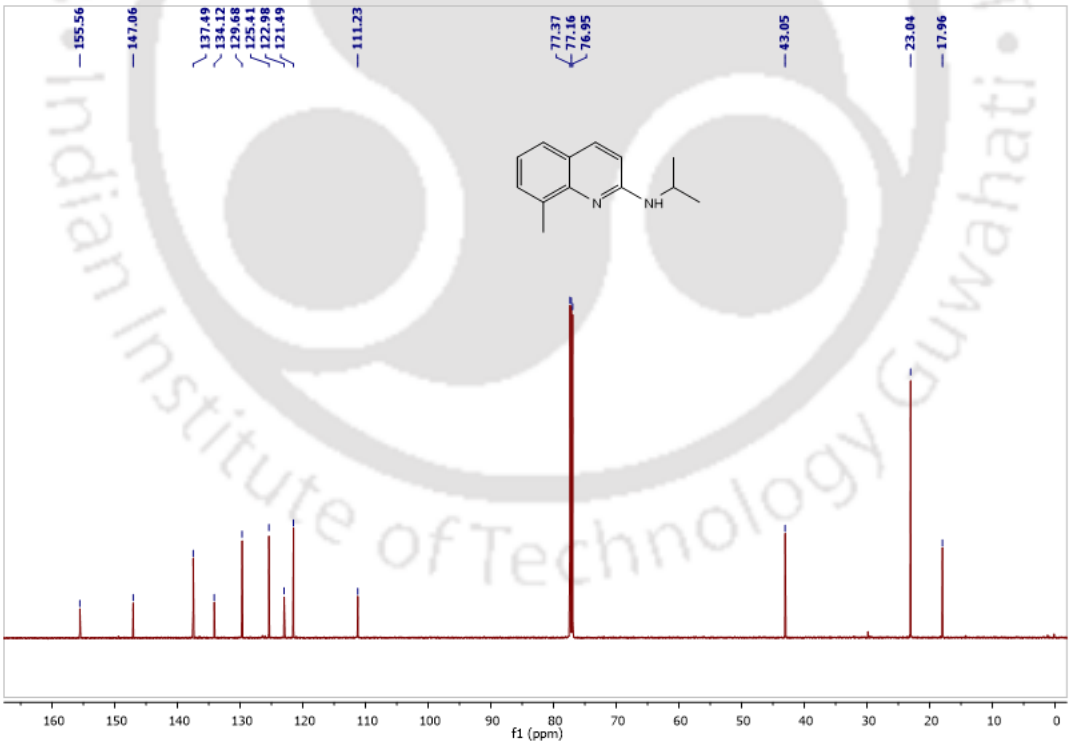


Figure S100. ^{13}C NMR Spectrum of **3.2j** ($CDCl_3$, 151 MHz, 298 K)

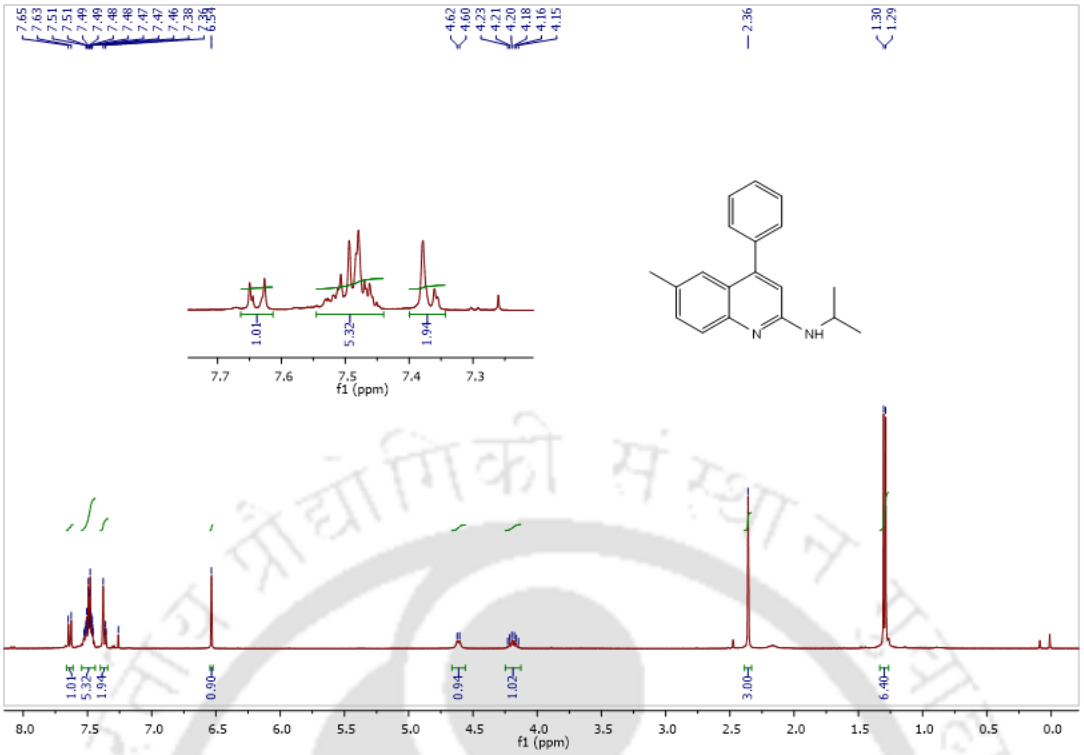


Figure S101. ^{1}H NMR Spectrum of **3.2k** ($CDCl_3$, 400 MHz, 298 K)

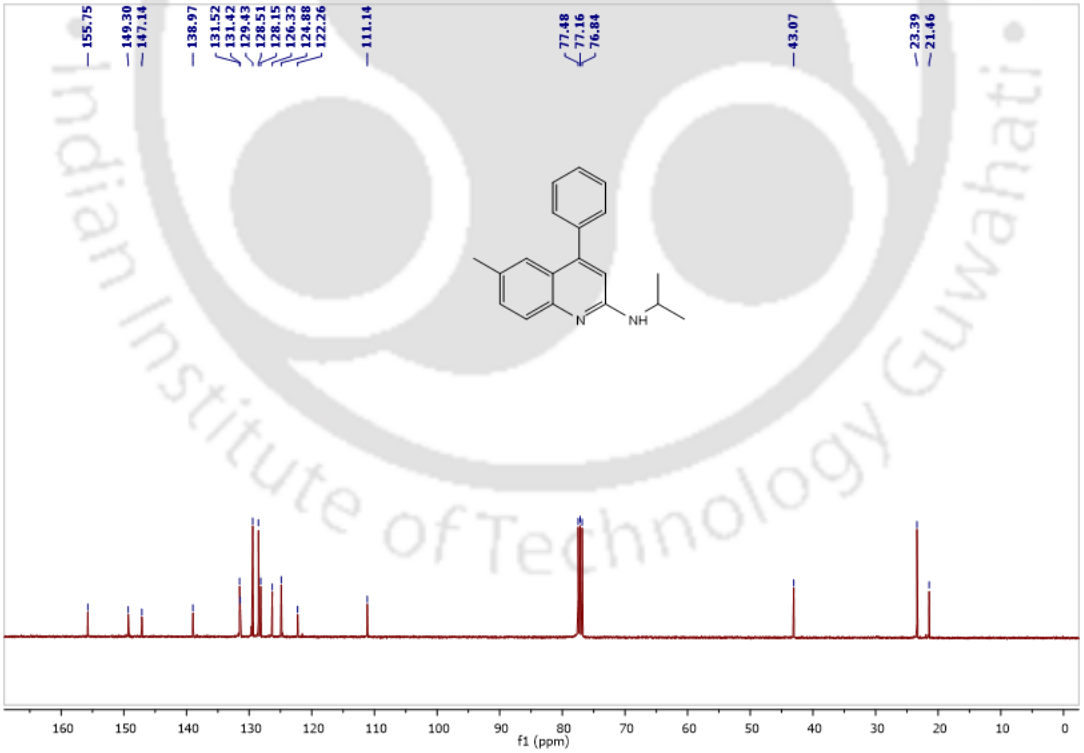


Figure S102. ^{13}C NMR Spectrum of **3.2k** ($CDCl_3$, 101 MHz, 298 K)

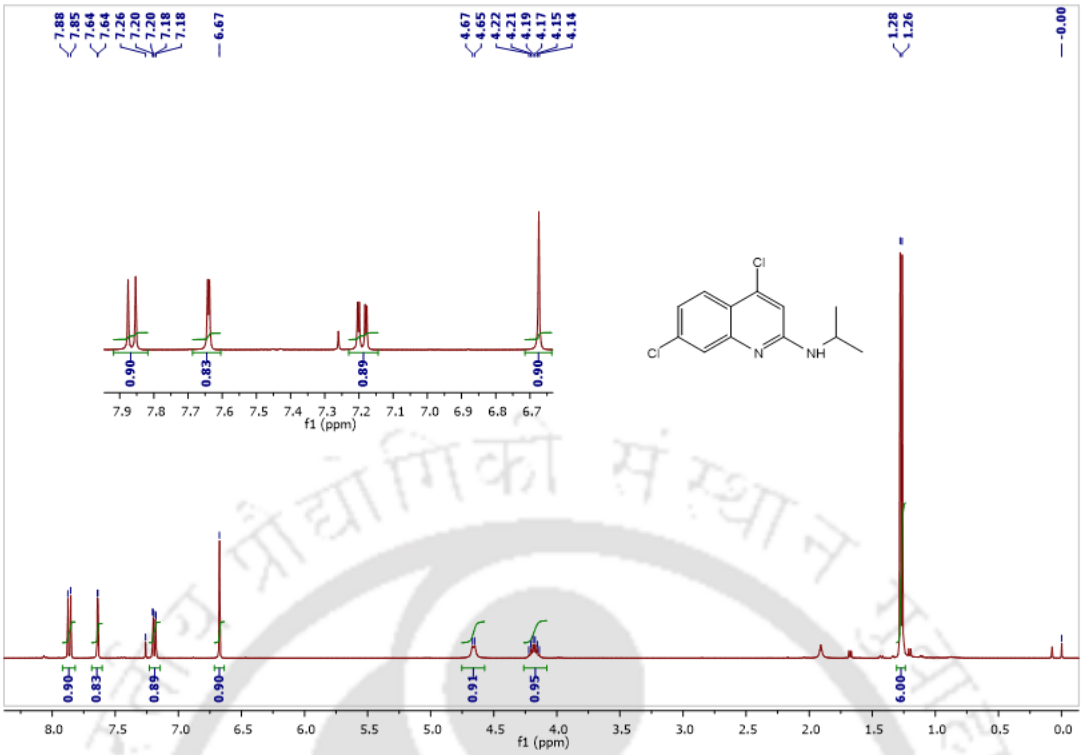


Figure S103. ^{1}H NMR Spectrum of **3.2l** ($CDCl_3$, 400 MHz, 298 K)

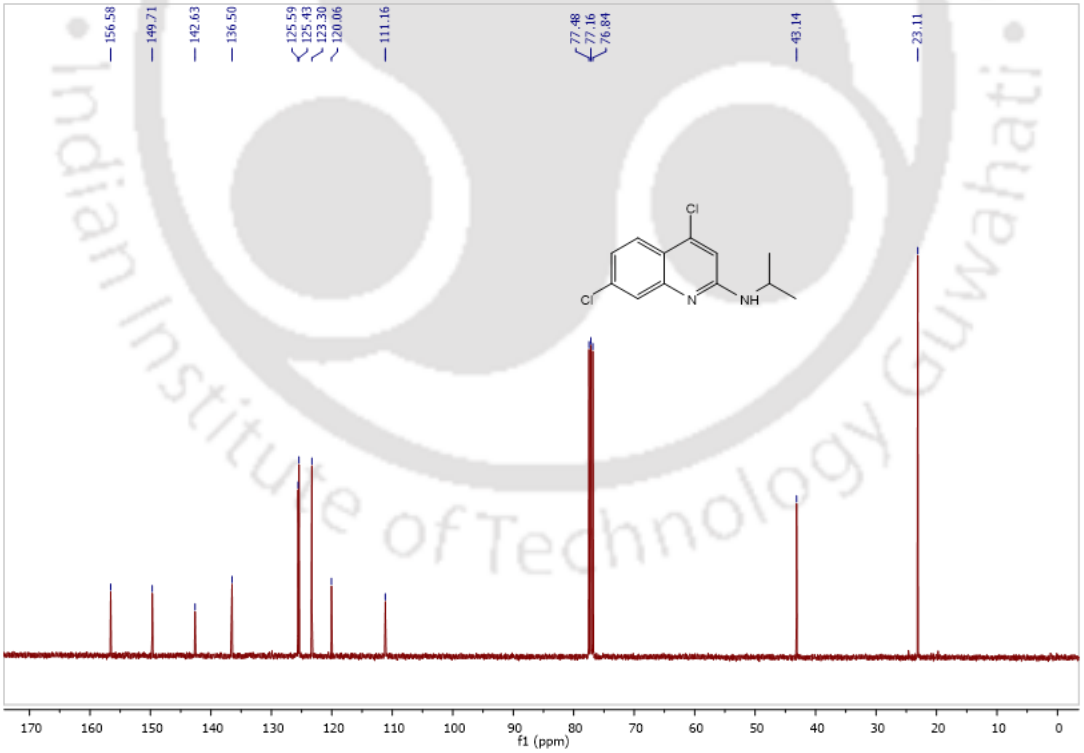


Figure S104. ^{13}C NMR Spectrum of **3.2l** ($CDCl_3$, 101 MHz, 298 K)

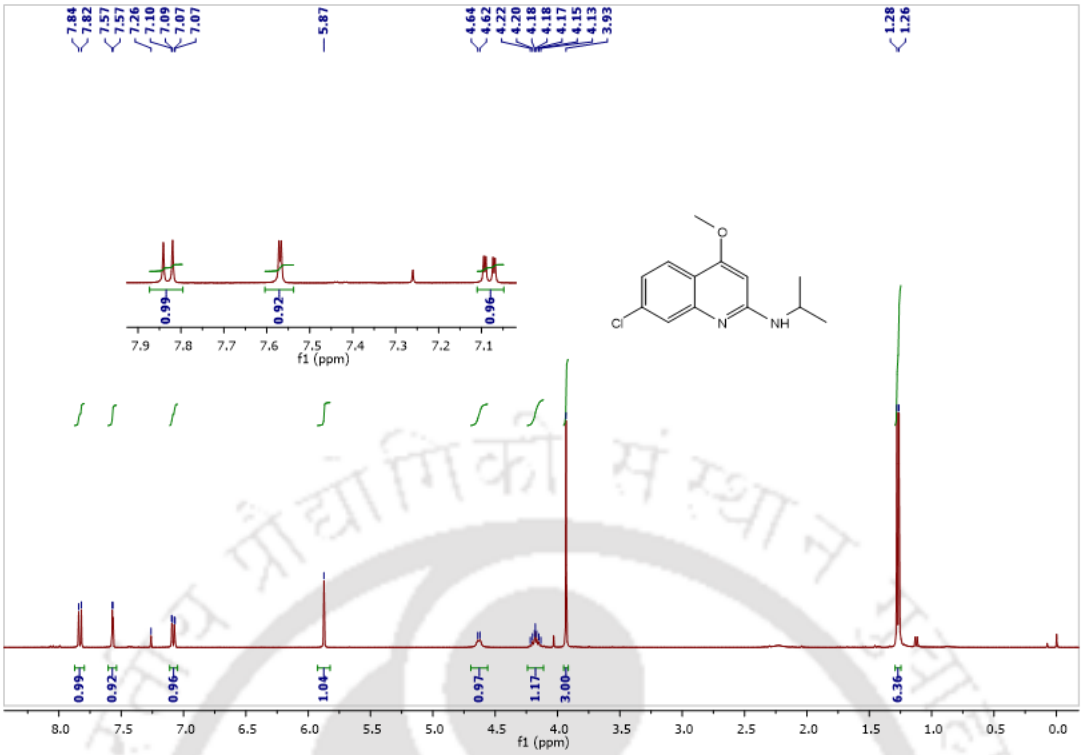


Figure S105. ^{1}H NMR Spectrum of **3.2m** ($CDCl_3$, 400 MHz, 298 K)

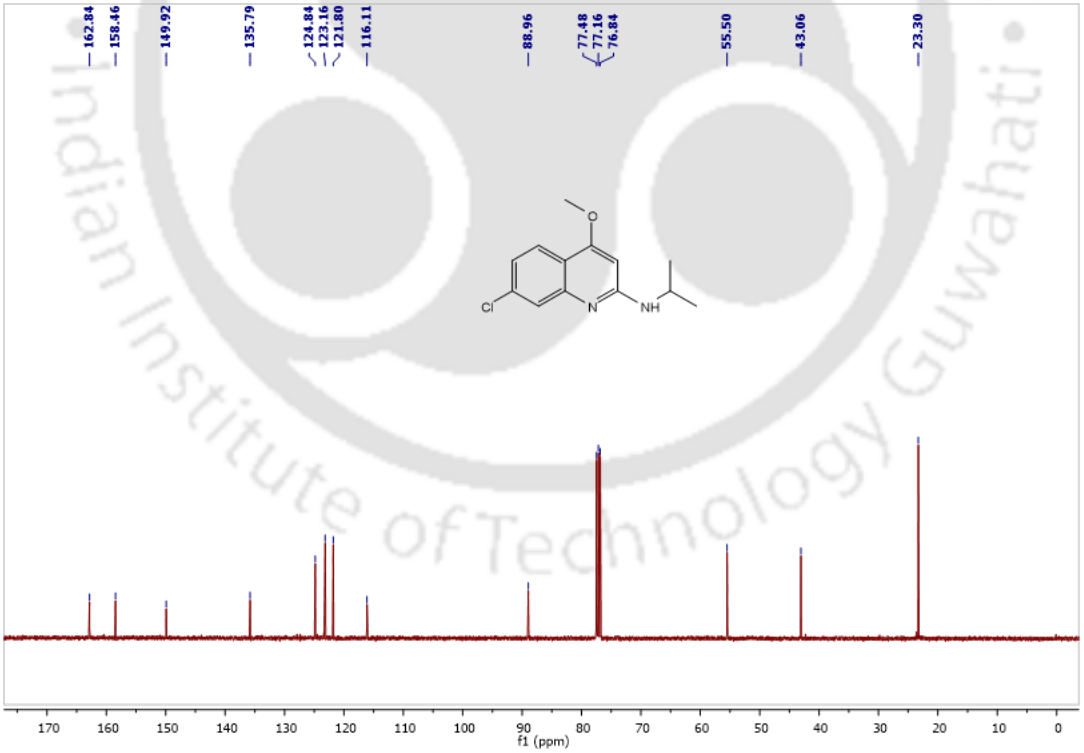


Figure S106. ^{13}C NMR Spectrum of **3.2m** ($CDCl_3$, 101 MHz, 298 K)

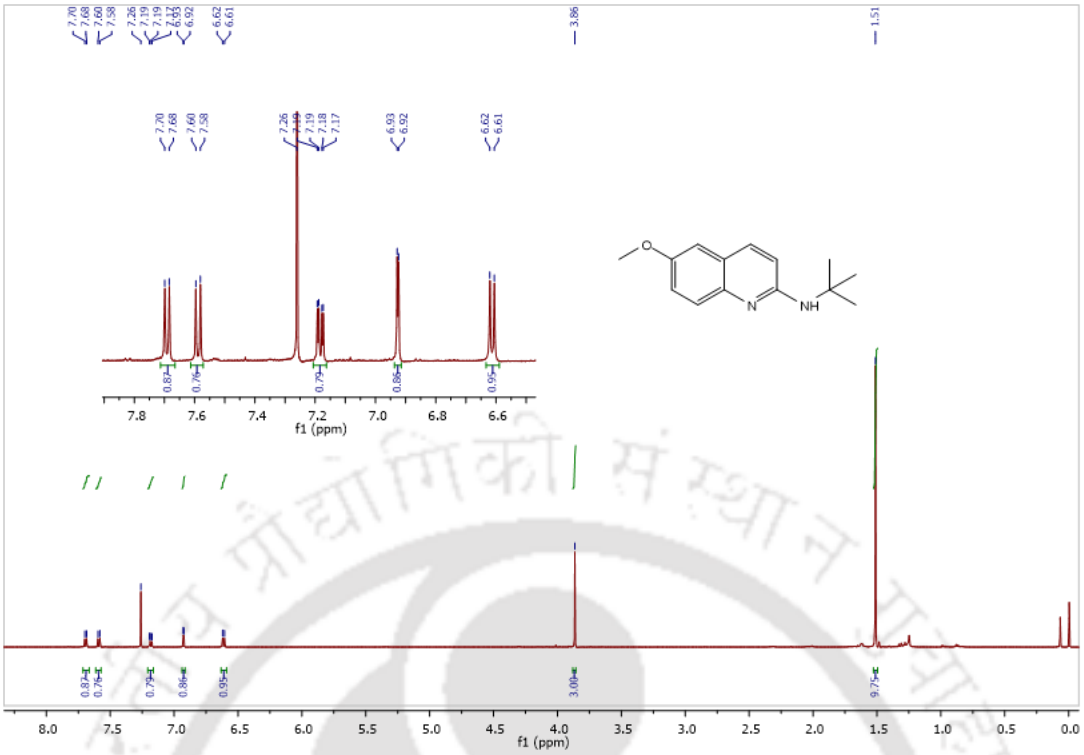


Figure S107. ^{1}H NMR Spectrum of **3.2n** ($CDCl_3$, 600 MHz, 298 K)

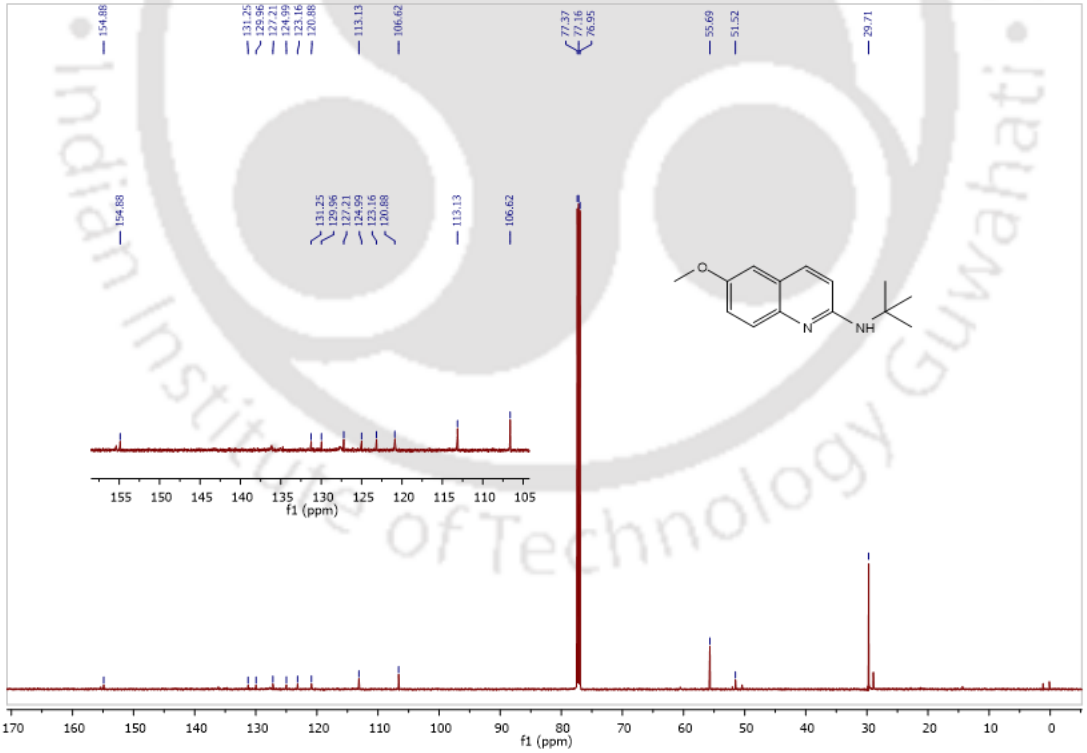


Figure S108. ^{13}C NMR Spectrum of **3.2n** ($CDCl_3$, 151 MHz, 298 K)

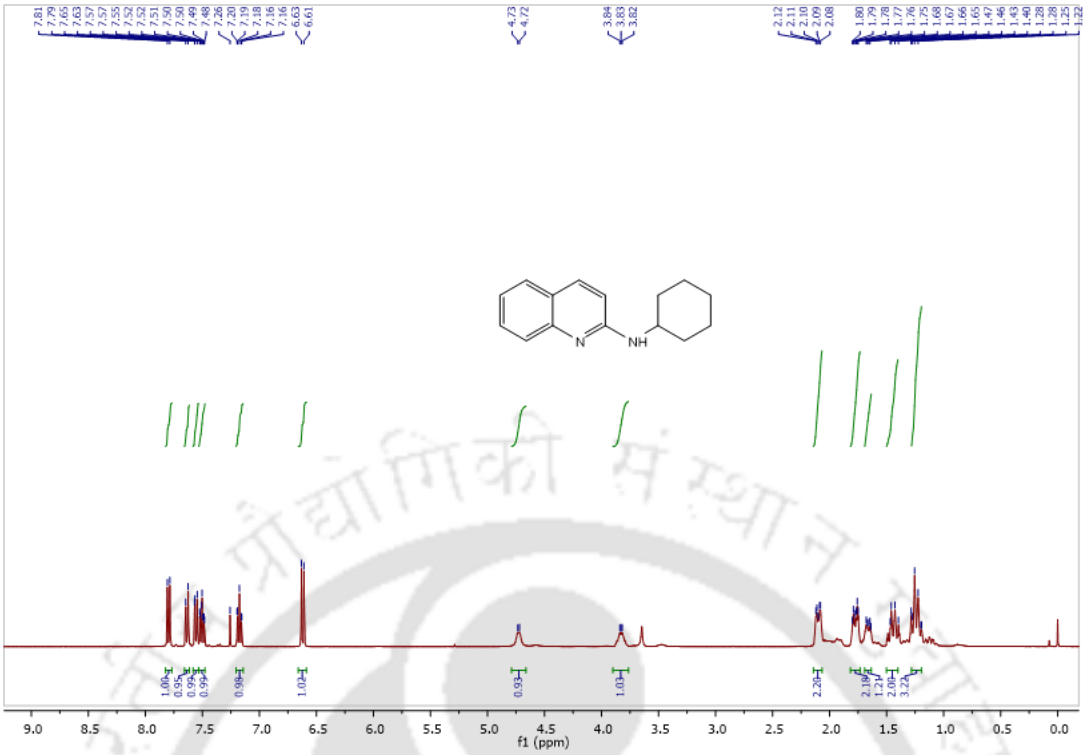


Figure S109. ^{1}H NMR Spectrum of **3.2o** ($CDCl_3$, 600 MHz, 298 K)

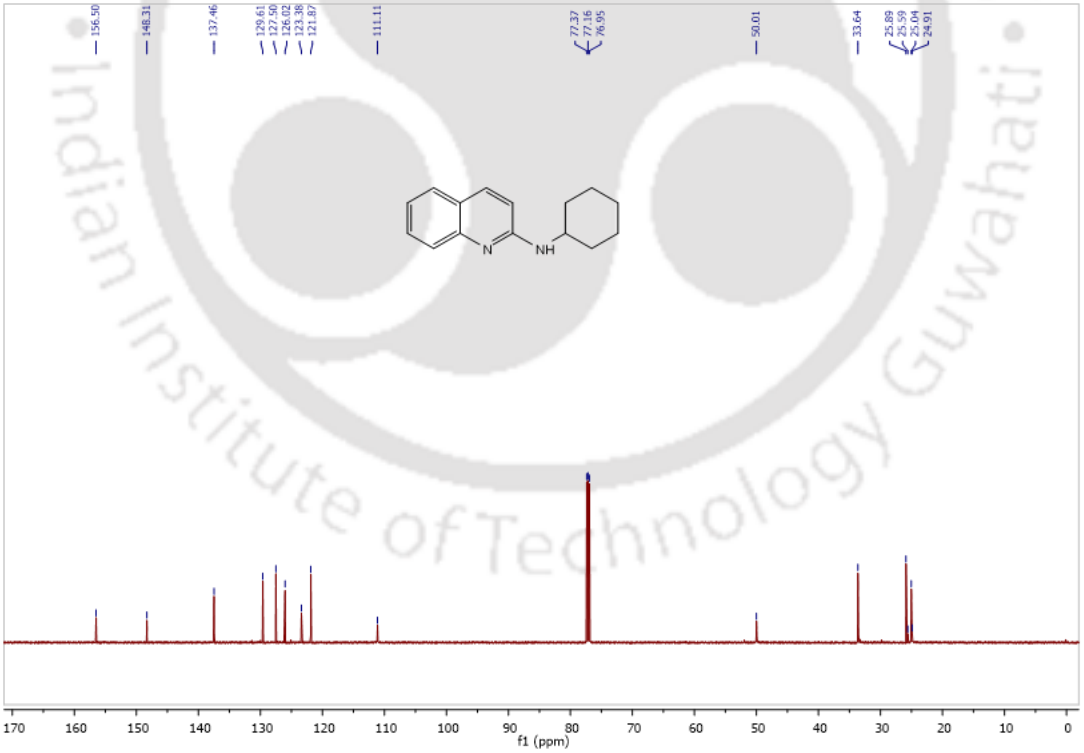


Figure S110. ^{13}C NMR Spectrum of **3.2o** ($CDCl_3$, 151 MHz, 298 K)

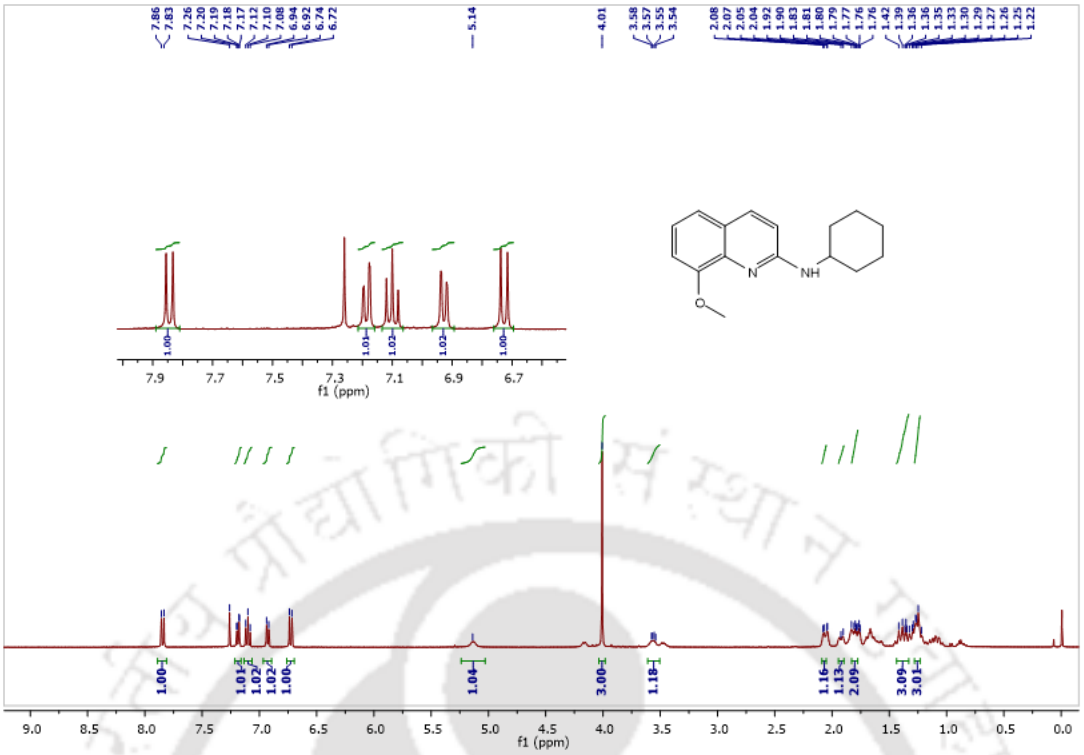


Figure S111. ^{1}H NMR Spectrum of **3.2p** ($CDCl_3$, 400 MHz, 298 K)

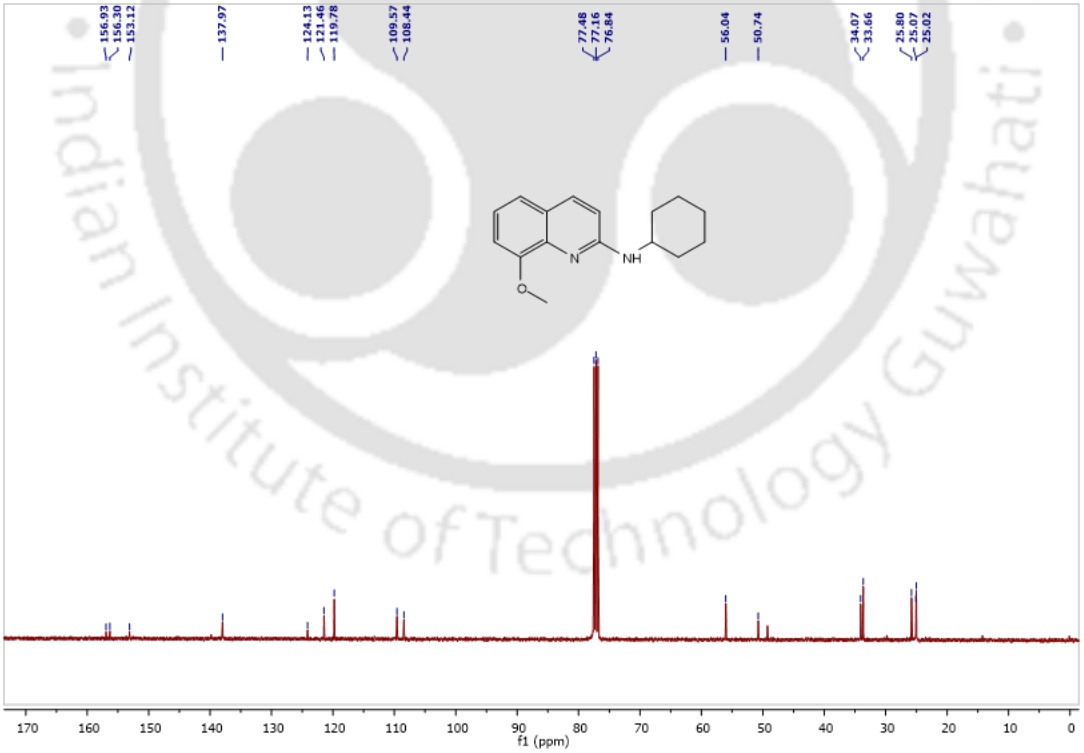


Figure S112. ^{13}C NMR Spectrum of **3.2p** ($CDCl_3$, 101 MHz, 298 K)

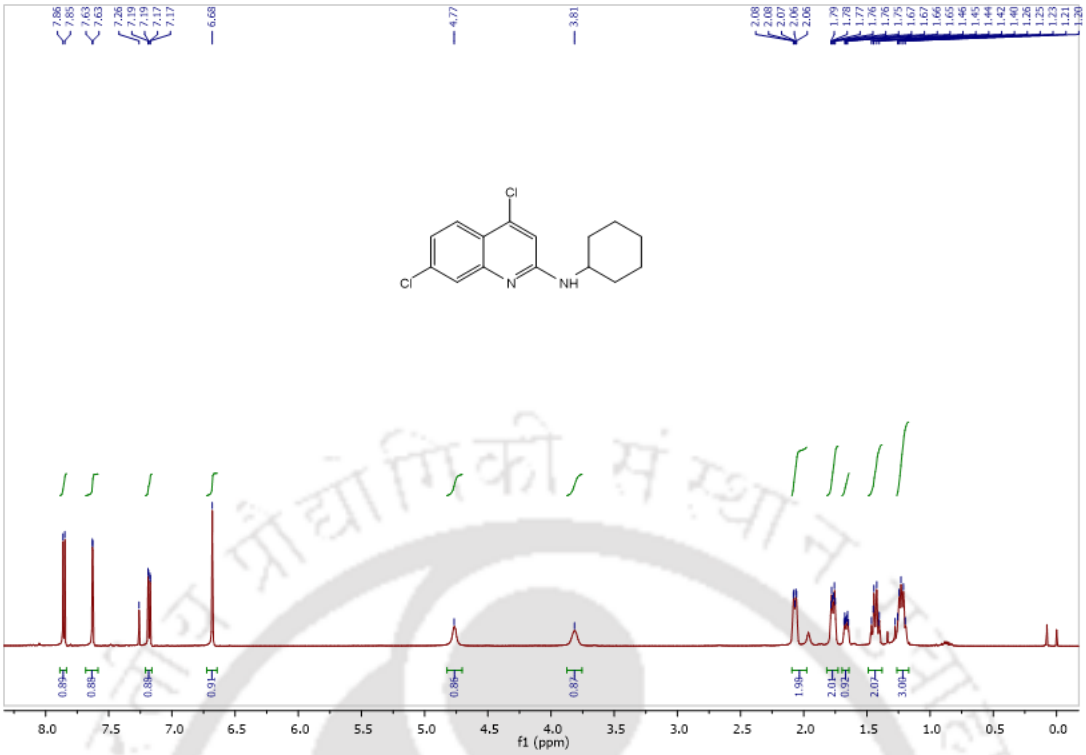


Figure S113. ^{1}H NMR Spectrum of **3.2q** ($CDCl_3$, 600 MHz, 298 K)

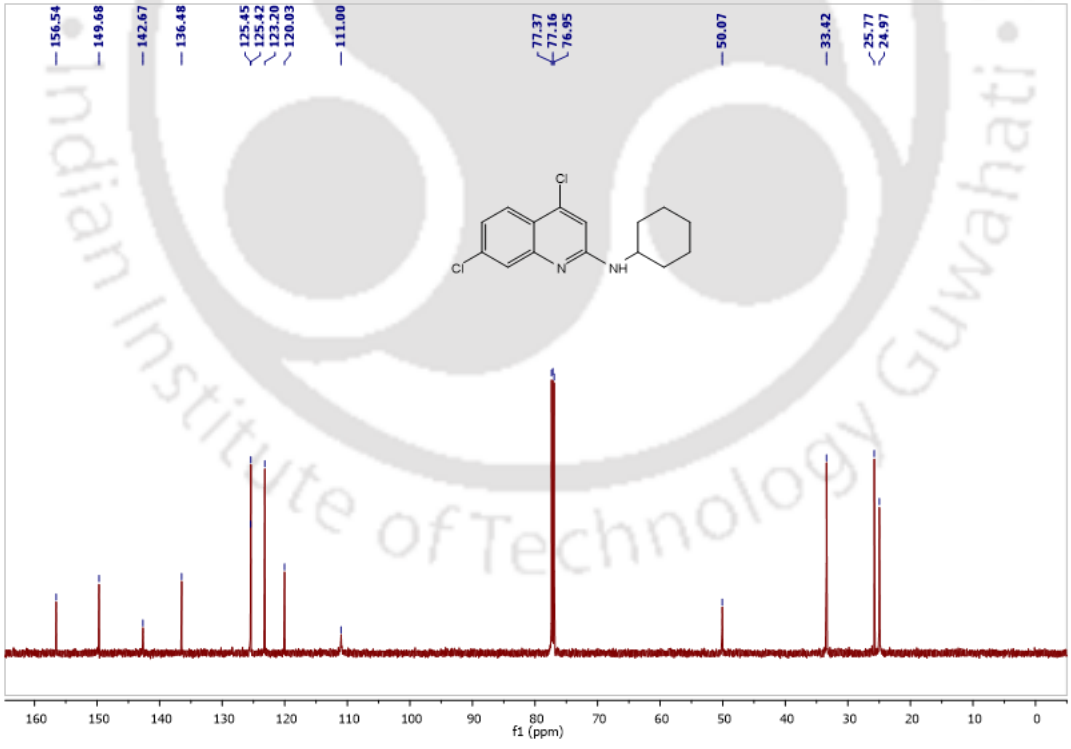


Figure S114. ^{13}C NMR Spectrum of **3.2q** ($CDCl_3$, 151 MHz, 298 K)

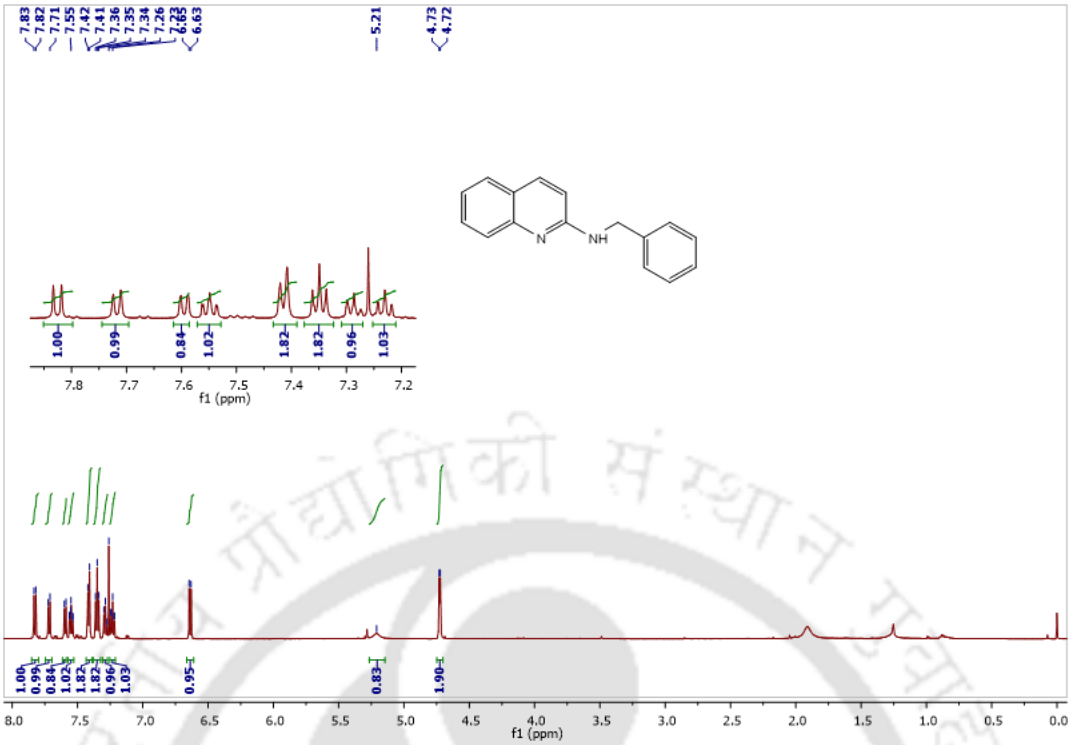


Figure S115. ^{1}H NMR Spectrum of **3.2r** ($CDCl_3$, 600 MHz, 298 K)

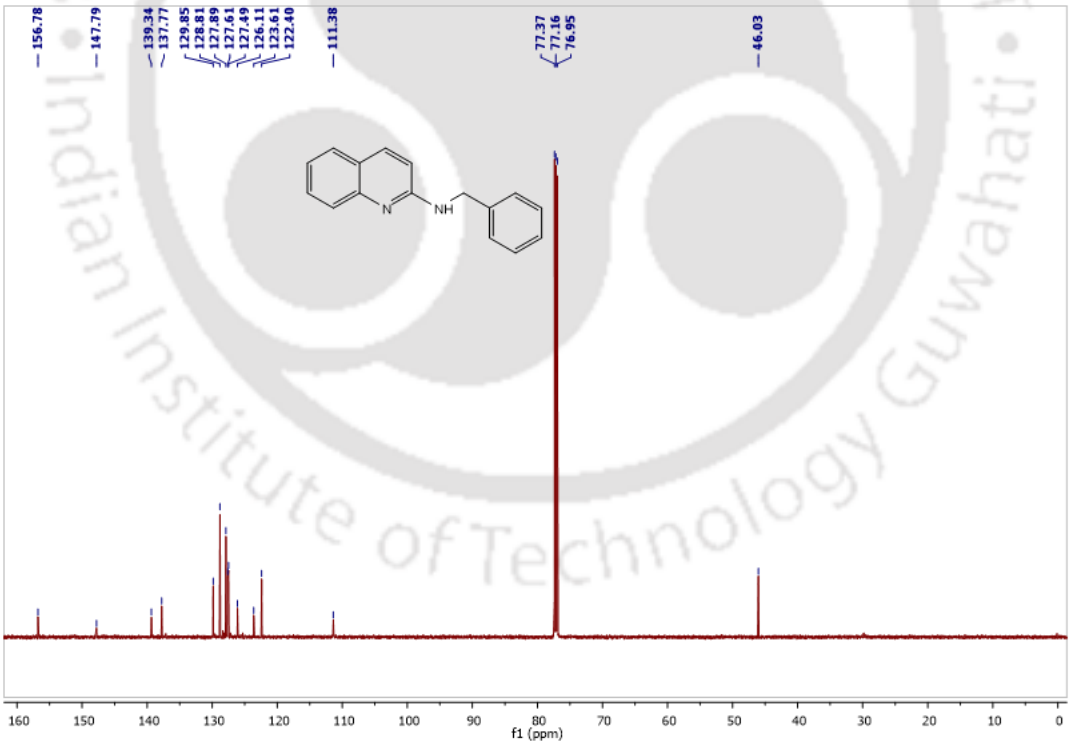


Figure S116. ^{13}C NMR Spectrum of **3.2r** ($CDCl_3$, 151 MHz, 298 K)

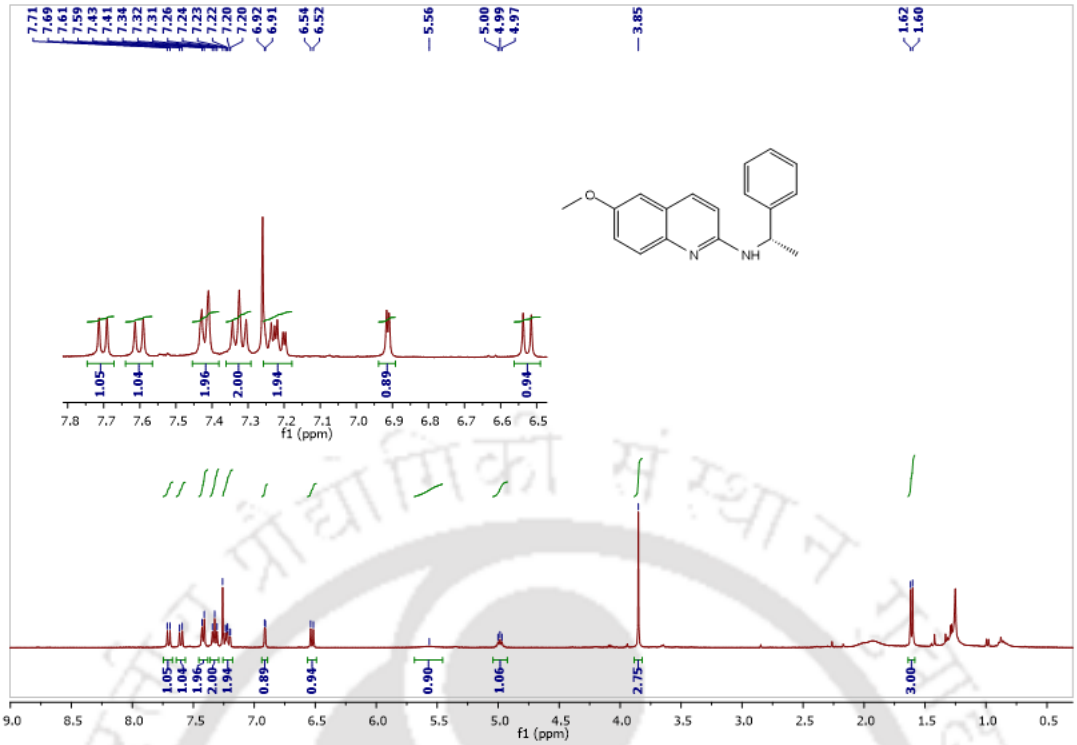


Figure S117. ^{1}H NMR Spectrum of **3.2s** ($CDCl_3$, 400 MHz, 298 K)

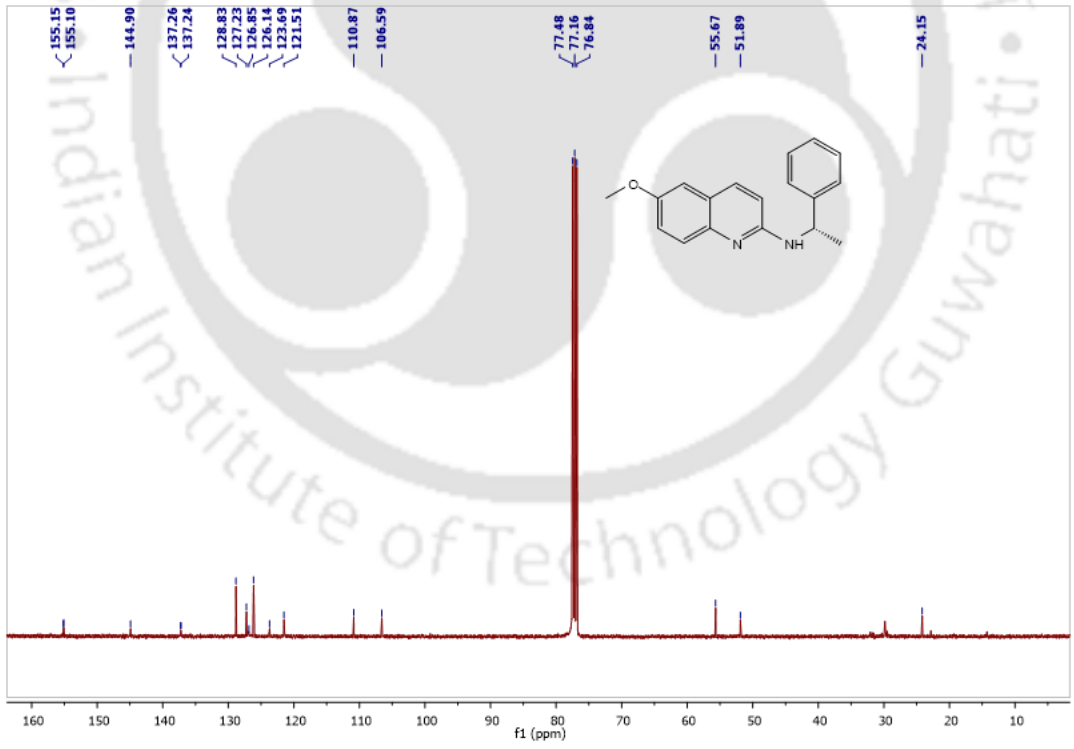


Figure S118. ^{13}C NMR Spectrum of **3.2s** ($CDCl_3$, 101 MHz, 298 K)

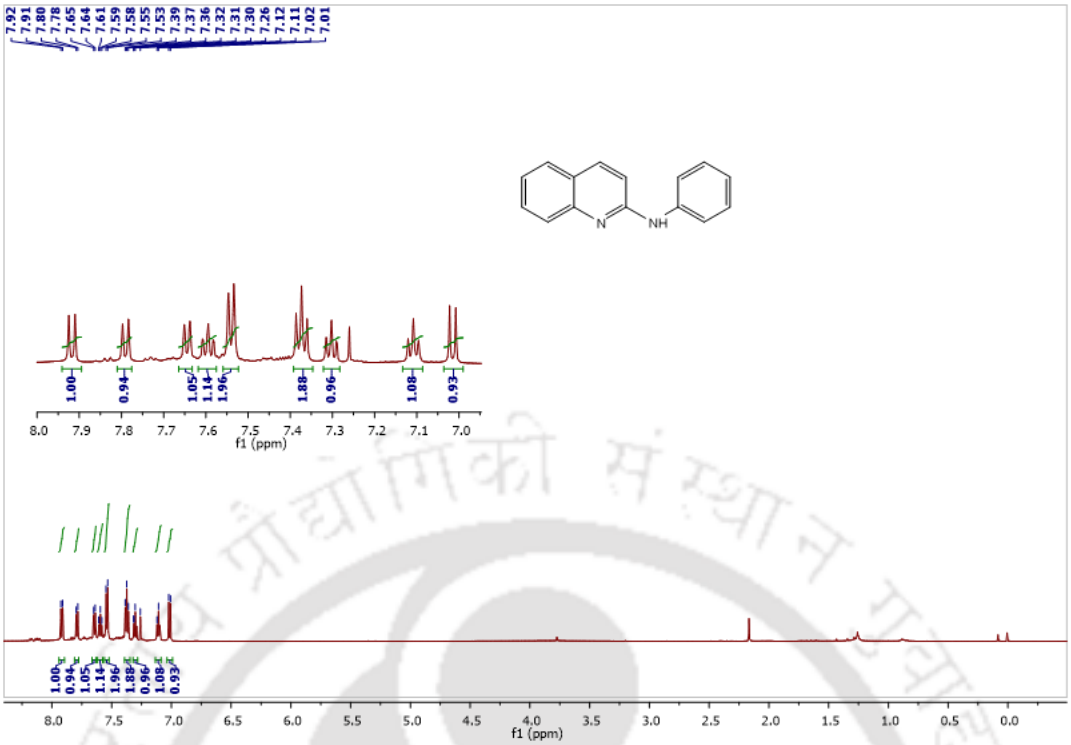


Figure S119. ^{1}H NMR Spectrum of **3.4a** ($CDCl_3$, 600 MHz, 298 K)

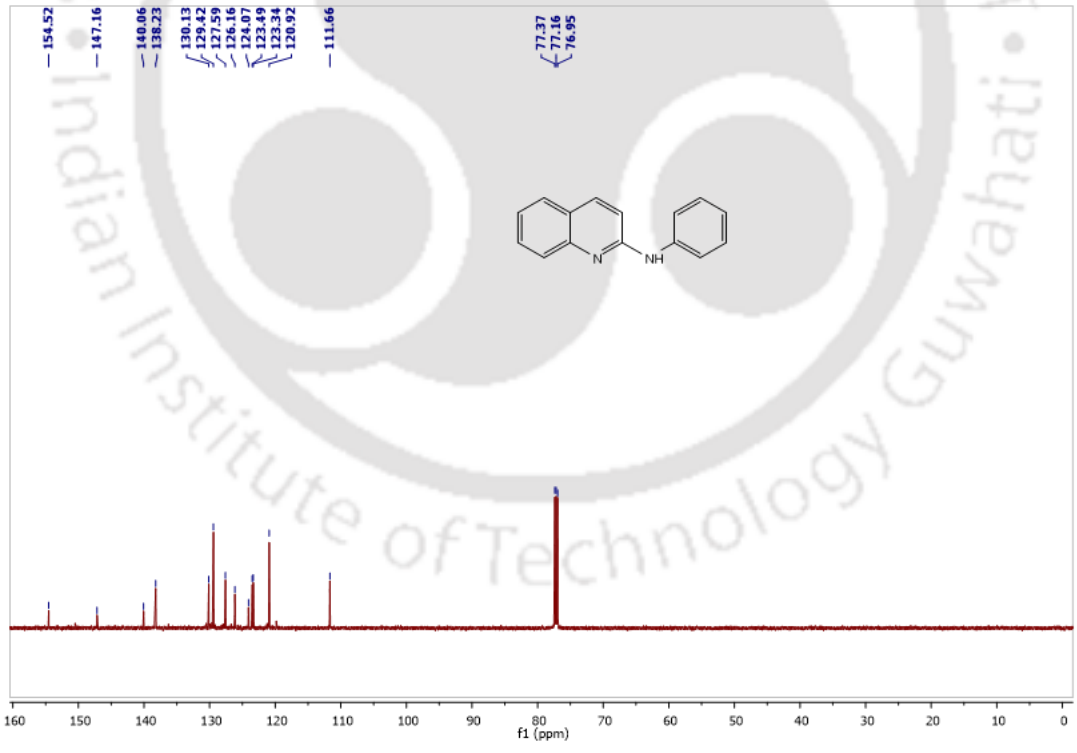


Figure S120. ^{13}C NMR Spectrum of **3.4a** ($CDCl_3$, 151 MHz, 298 K)

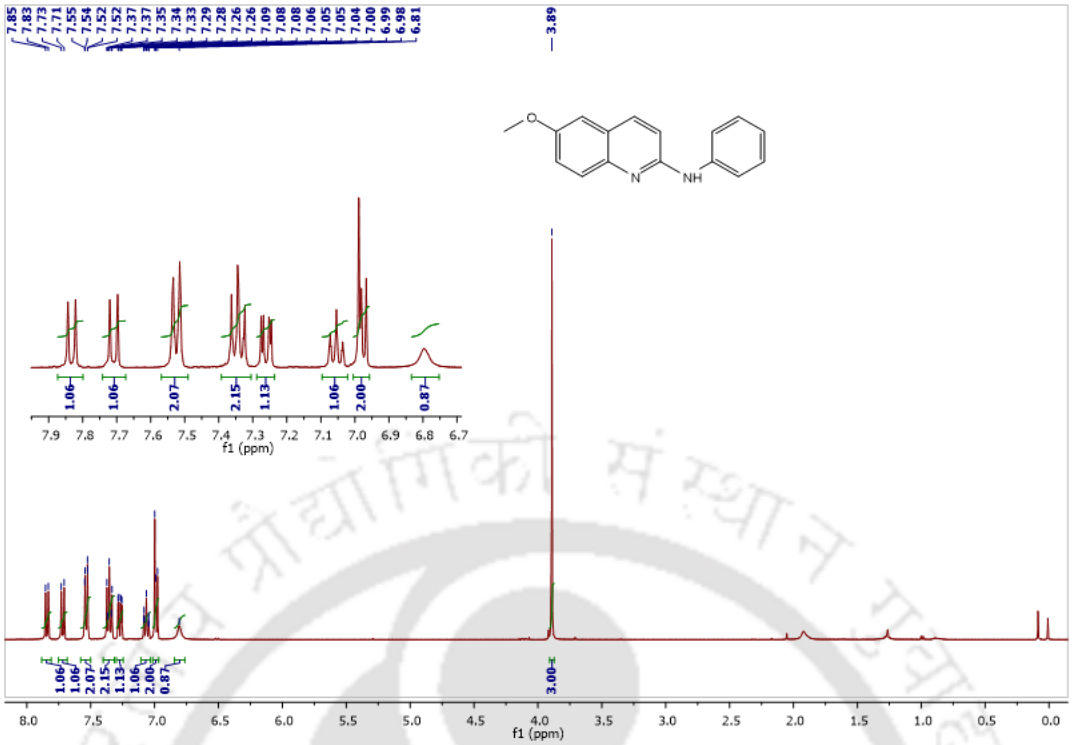


Figure S121. ^{1}H NMR Spectrum of **3.4b** ($CDCl_3$, 400 MHz, 298 K)

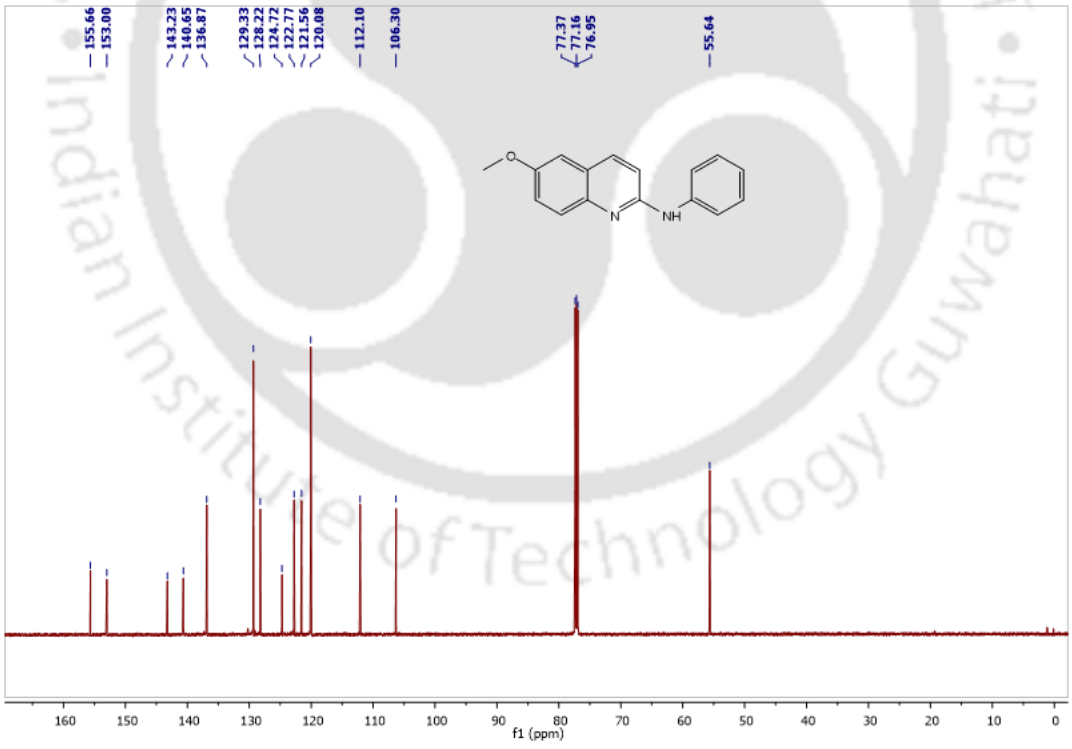


Figure S122. ^{13}C NMR Spectrum of **3.4b** ($CDCl_3$, 151 MHz, 298 K)

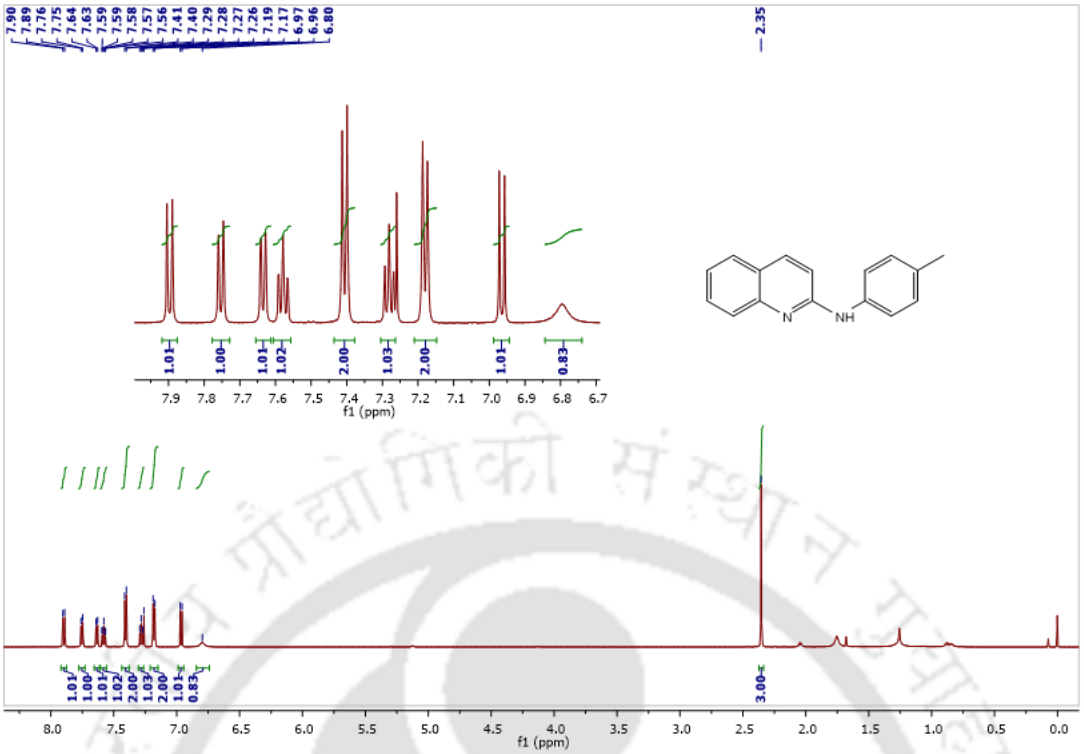


Figure S123. ^{1}H NMR Spectrum of **3.4c** ($CDCl_3$, 600 MHz, 298 K)

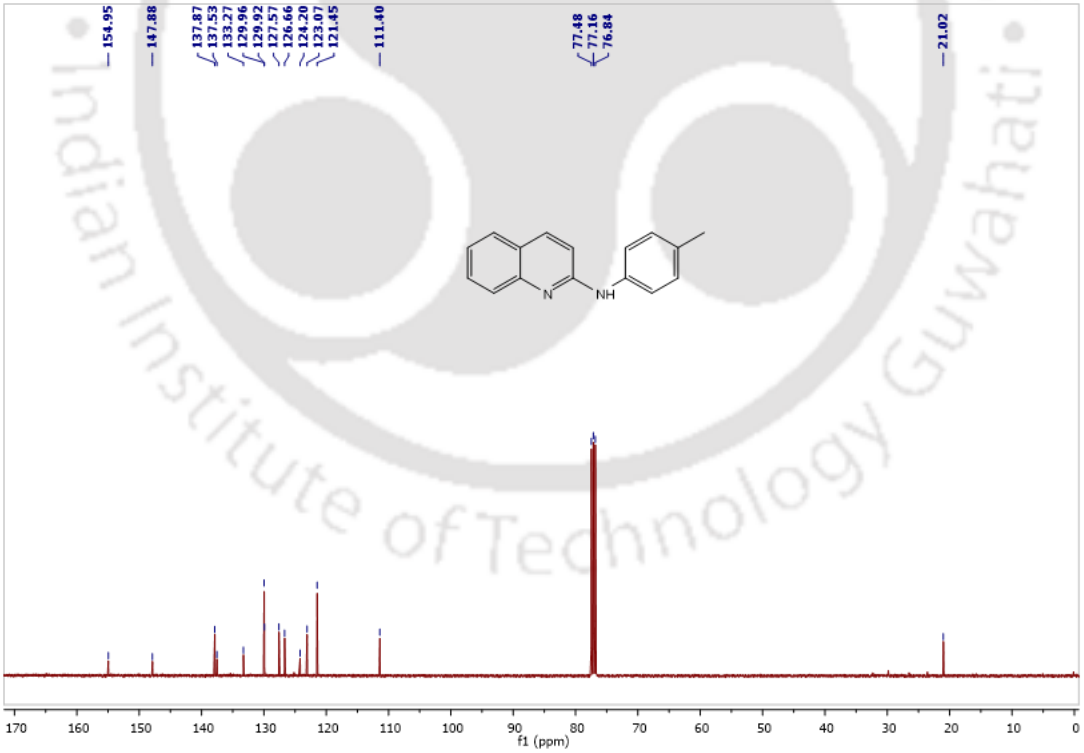


Figure S124. ^{13}C NMR Spectrum of **3.4c** ($CDCl_3$, 101 MHz, 298 K)

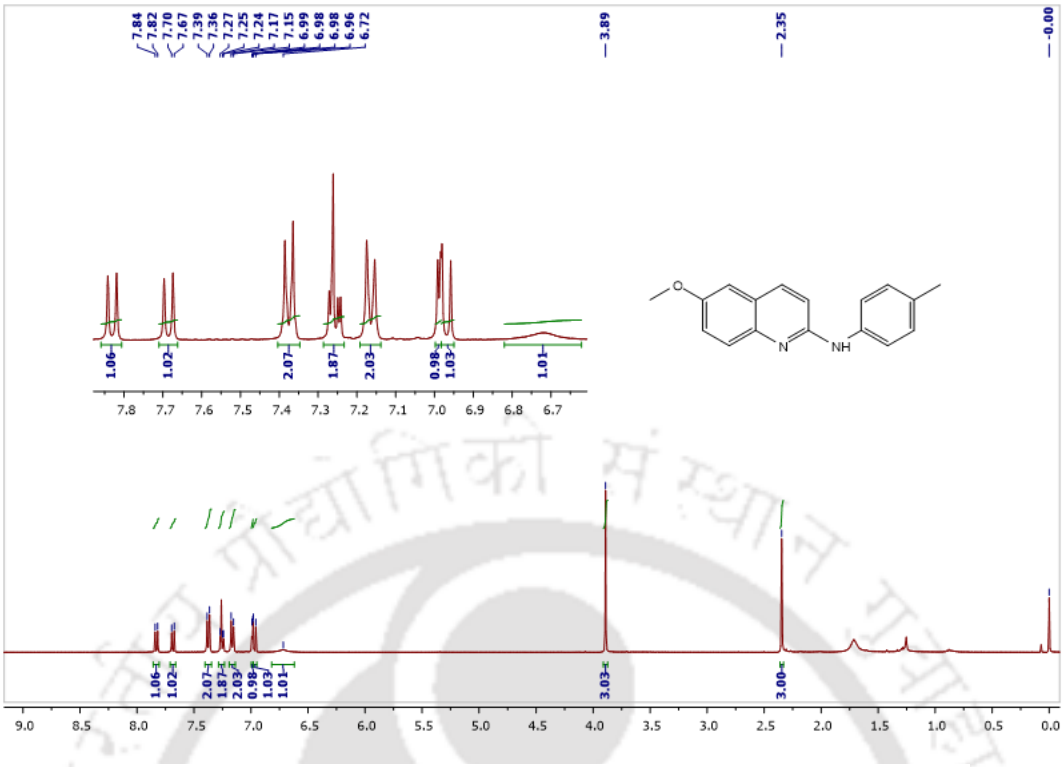


Figure S125. ^{1}H NMR Spectrum of **3.4d** ($CDCl_3$, 400 MHz, 298 K)

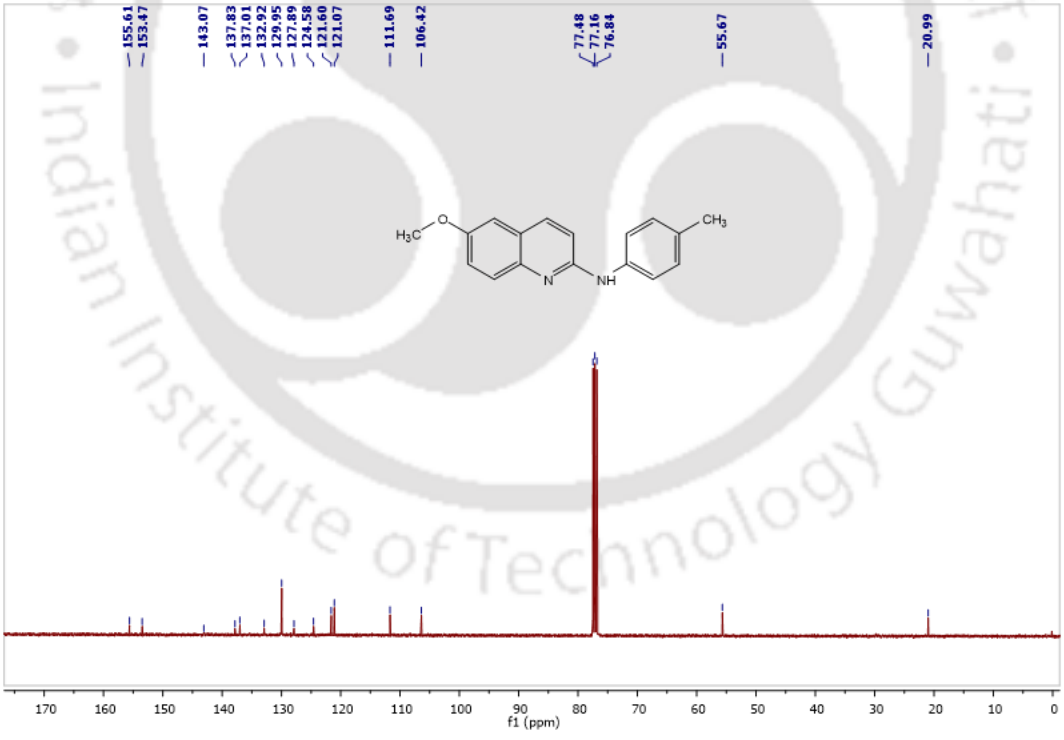


Figure S126. ^{13}C NMR Spectrum of **3.4d** ($CDCl_3$, 101 MHz, 298 K)

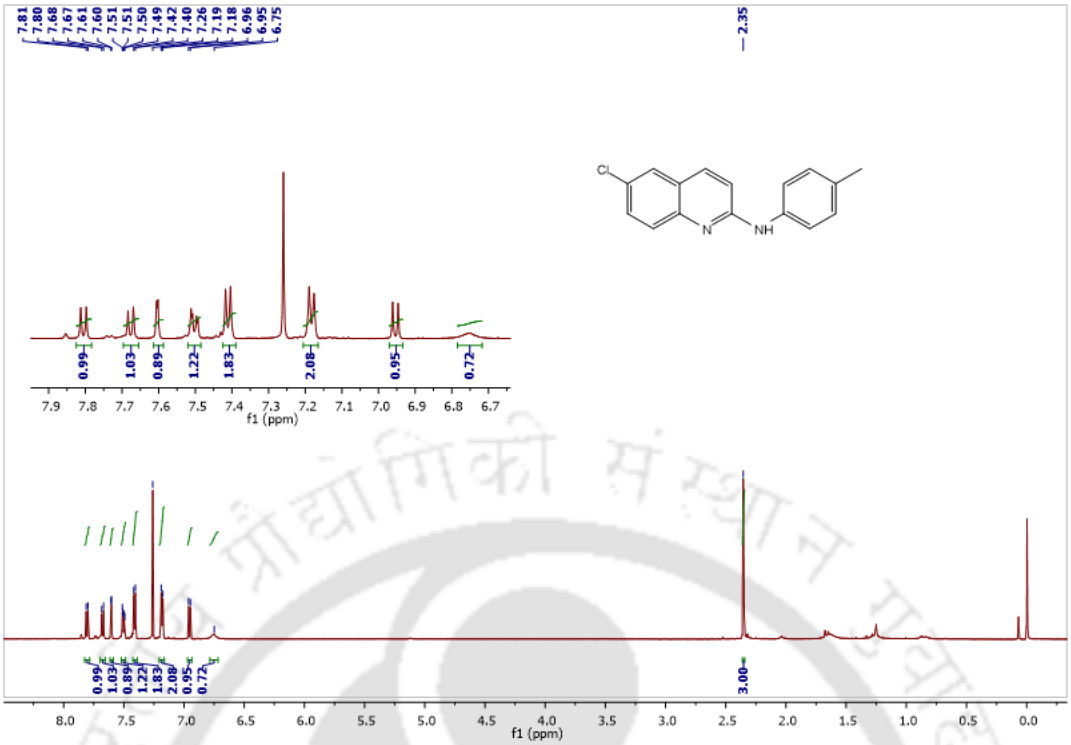


Figure S127. ^{1}H NMR Spectrum of **3.4e** ($CDCl_3$, 400 MHz, 298 K)

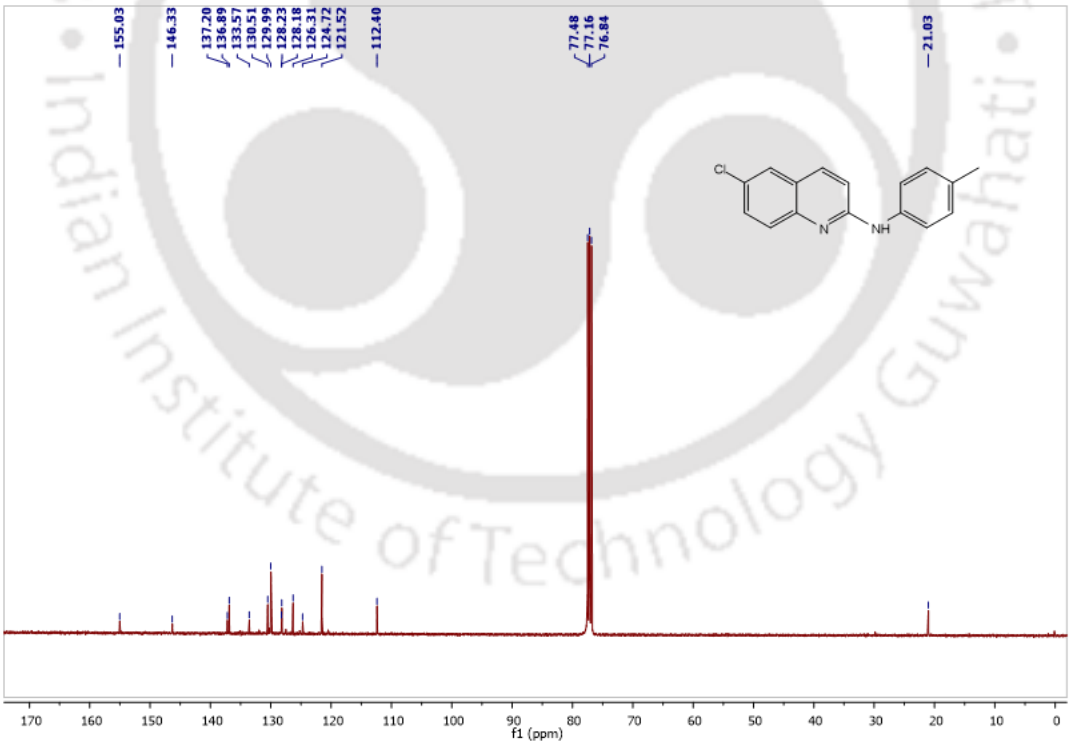


Figure S128. ^{13}C NMR Spectrum of **3.4e** ($CDCl_3$, 101 MHz, 298 K)

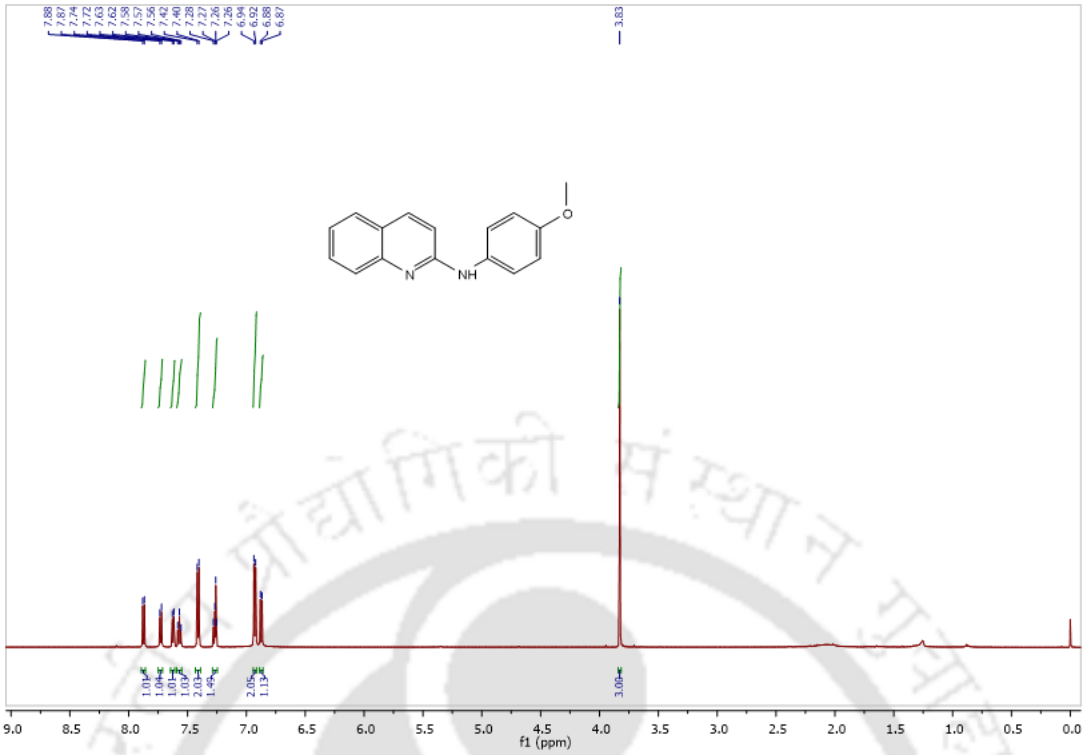


Figure S129. ^{1}H NMR Spectrum of **3.4f** ($CDCl_3$, 600 MHz, 298 K)

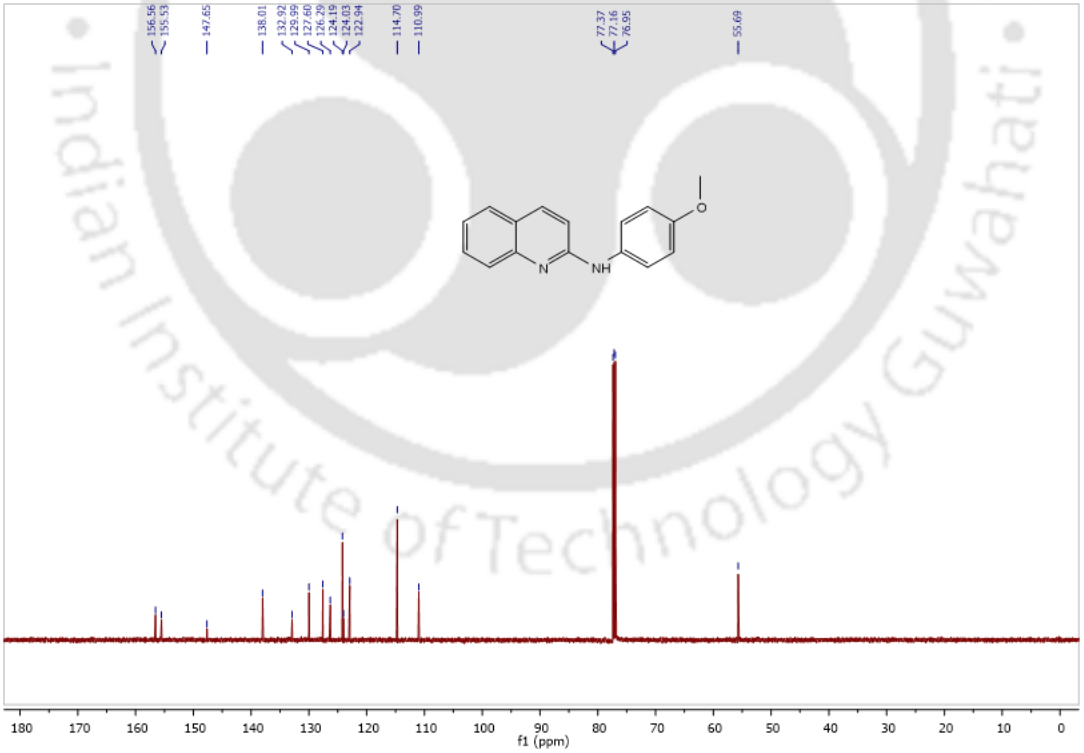


Figure S130. ^{13}C NMR Spectrum of **3.4f** ($CDCl_3$, 151 MHz, 298 K)

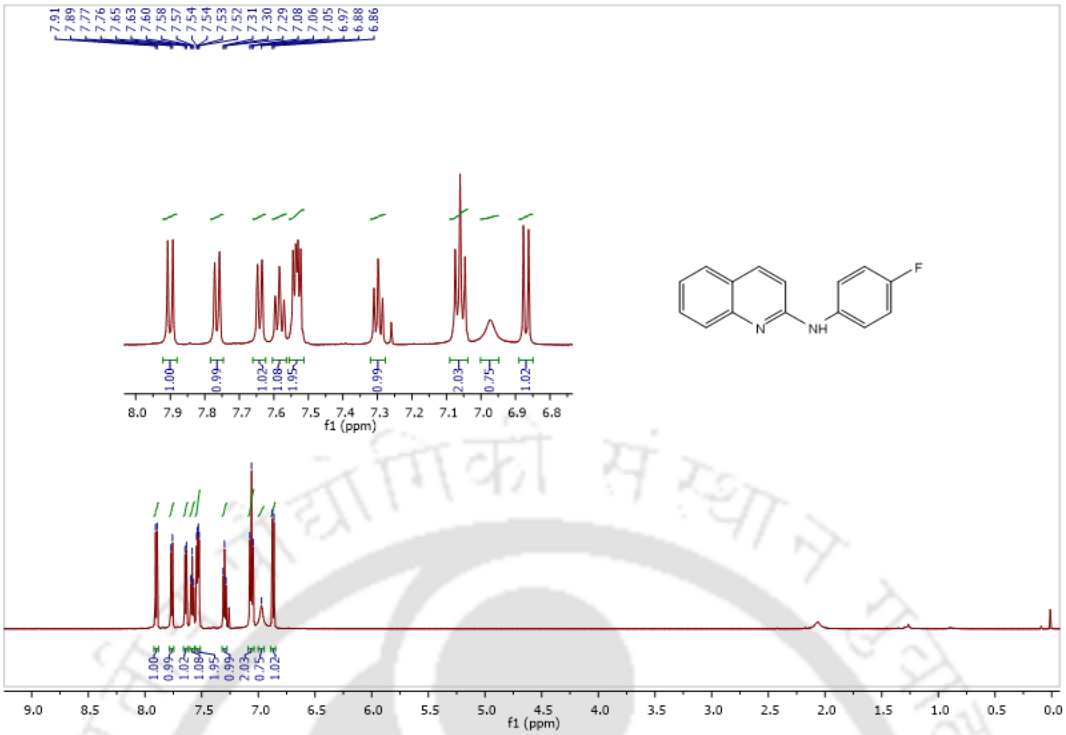


Figure S131. ^{1}H NMR Spectrum of **3.4g** ($CDCl_3$, 600 MHz, 298 K)

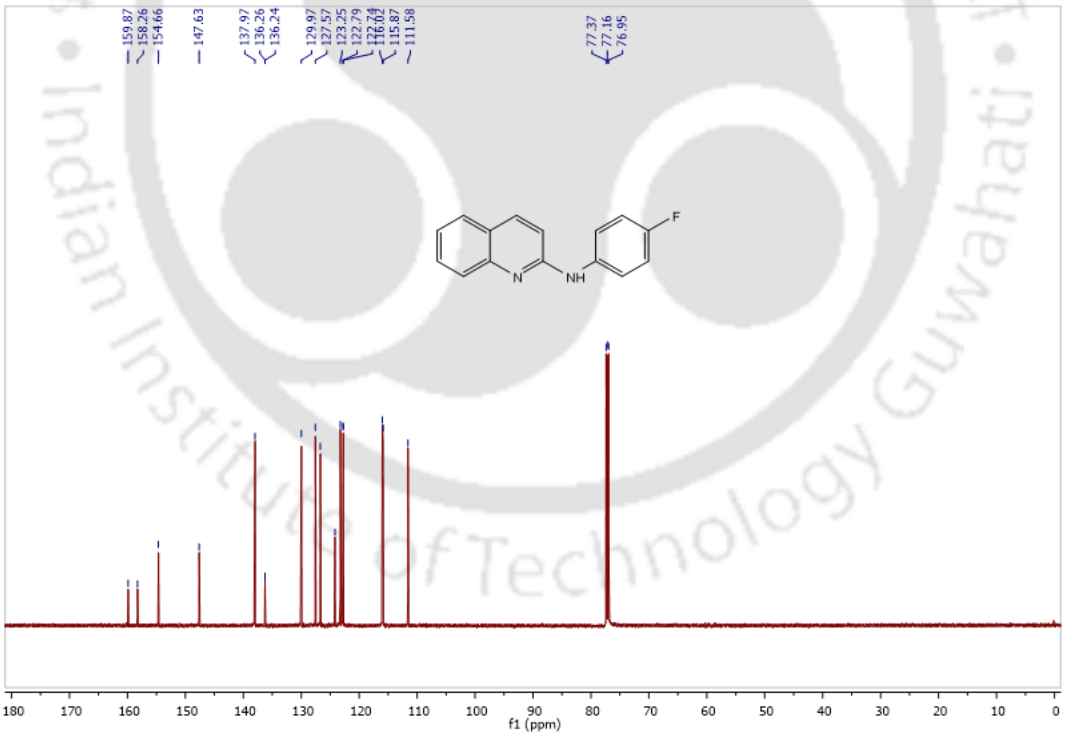


Figure S132. ^{13}C NMR Spectrum of **3.4g** ($CDCl_3$, 151 MHz, 298 K)

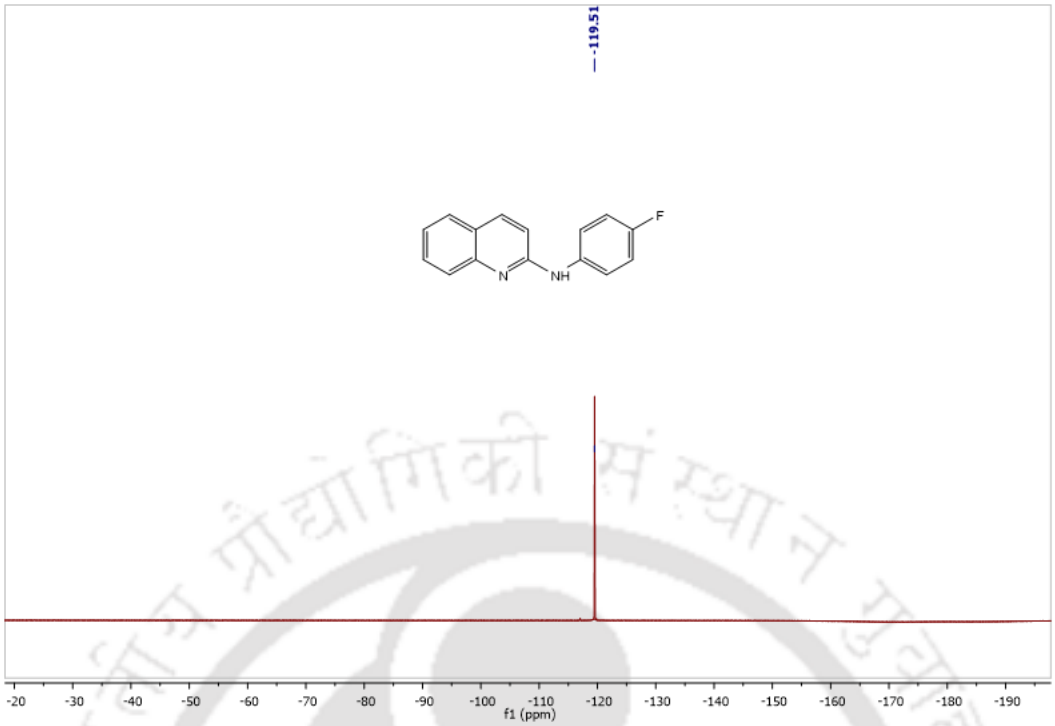


Figure S133. ^{19}F NMR Spectrum of **3.4g** ($CDCl_3$, 565 MHz, 298 K)

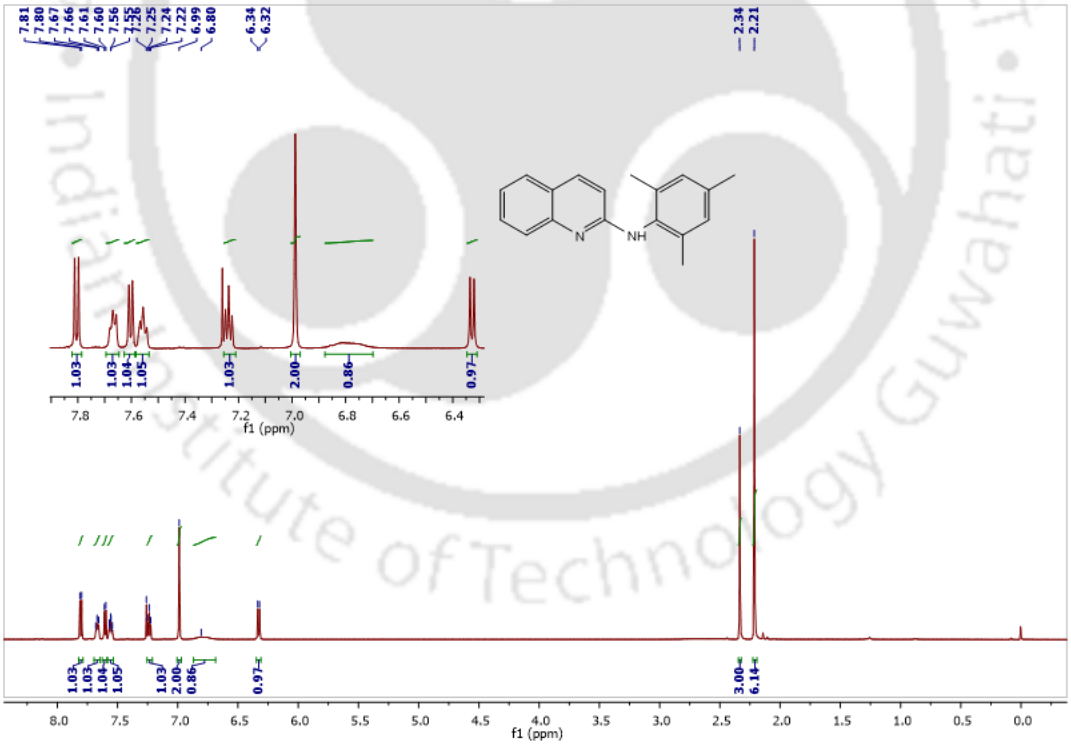


Figure S134. ^{1}H NMR Spectrum of **3.4h** ($CDCl_3$, 600 MHz, 298 K)

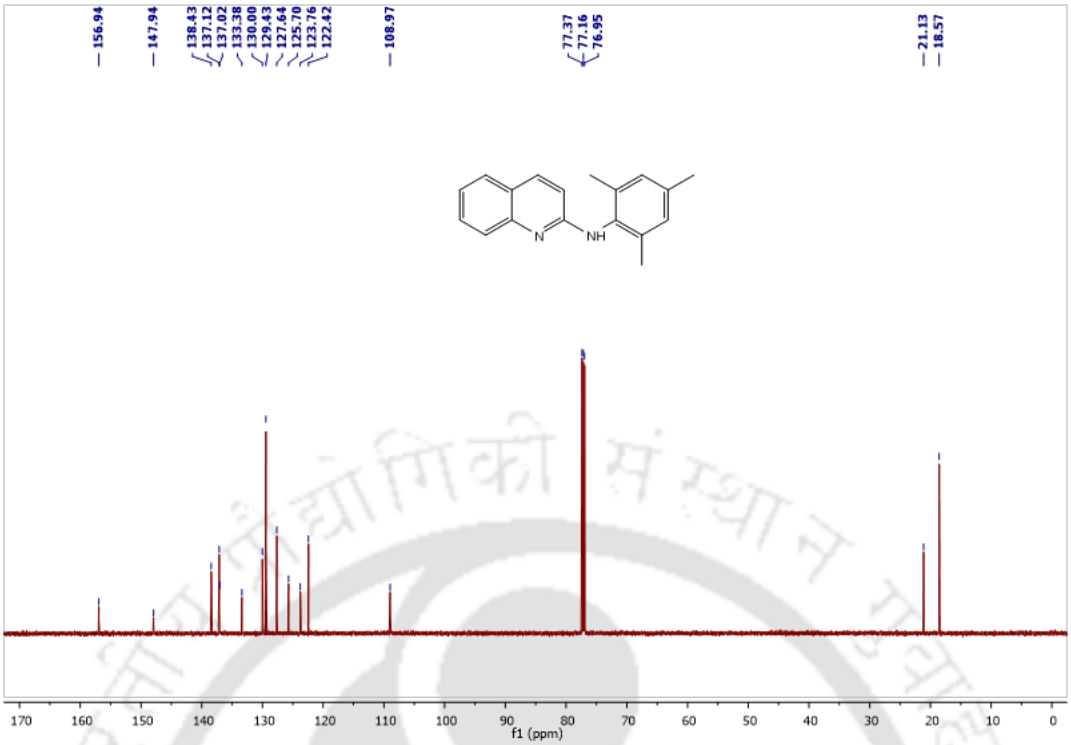


Figure S135. ^{13}C NMR Spectrum of **3.4h** ($CDCl_3$, 151 MHz, 298 K)

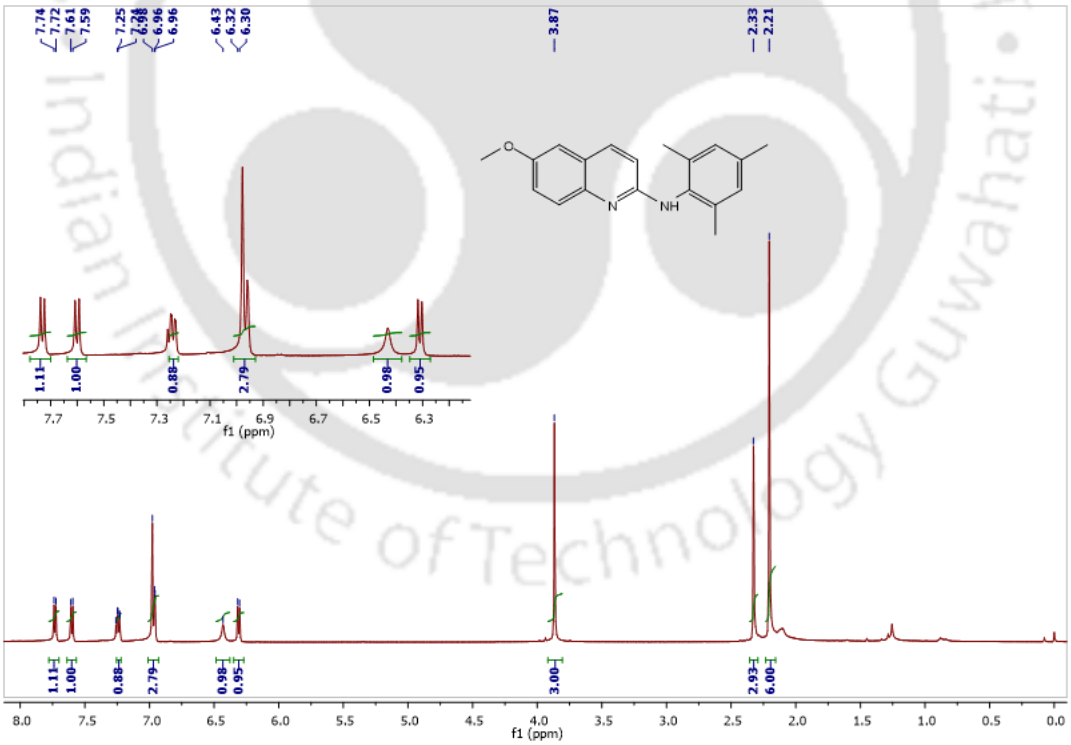


Figure S136. ^{1}H NMR Spectrum of **3.4i** ($CDCl_3$, 600 MHz, 298 K)

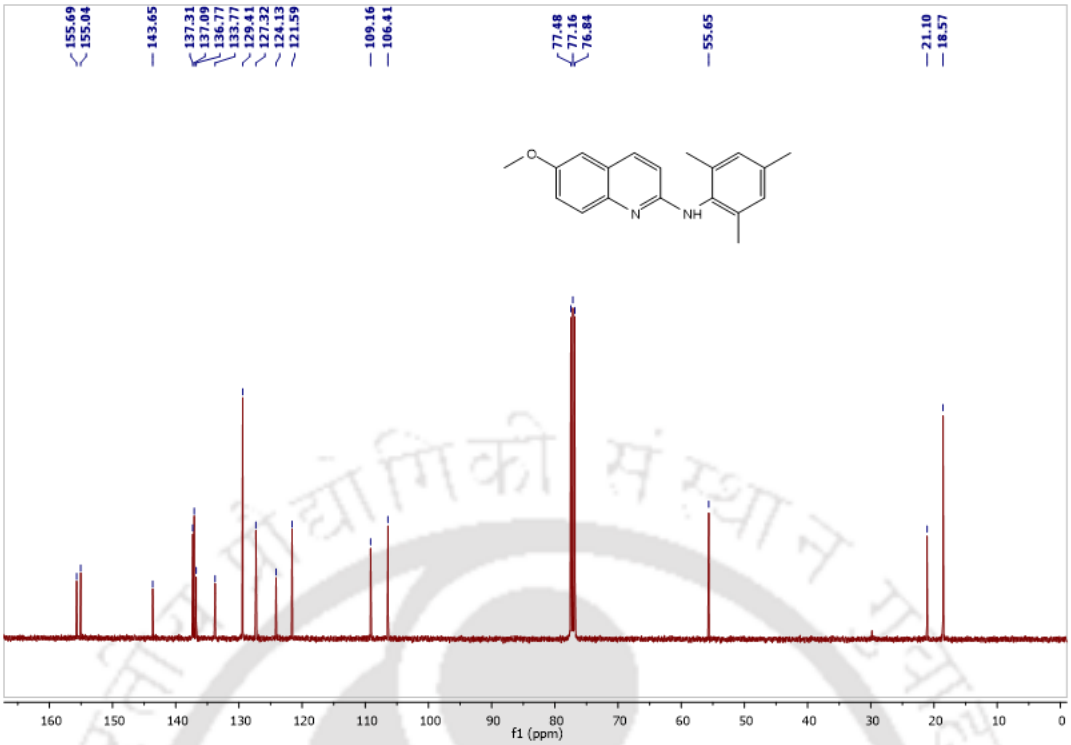


Figure S137. ^{13}C NMR Spectrum of **3.4i** ($CDCl_3$, 101 MHz, 298 K)

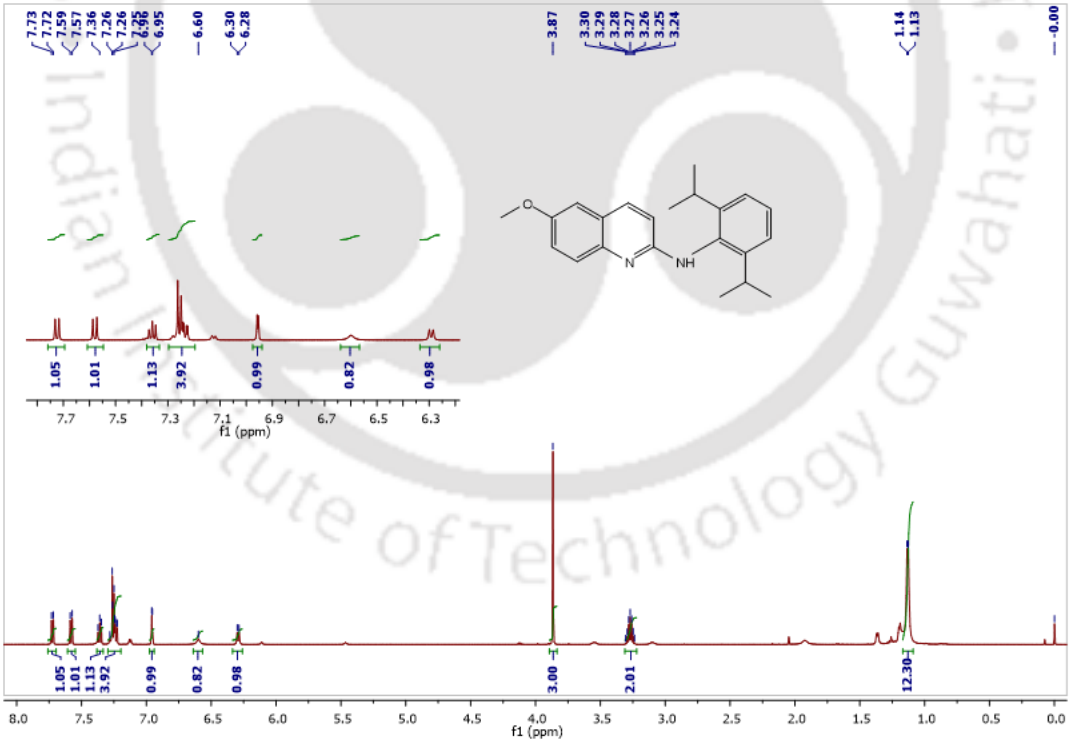


Figure S138. ^{1}H NMR Spectrum of **3.4j** ($CDCl_3$, 600 MHz, 298 K)

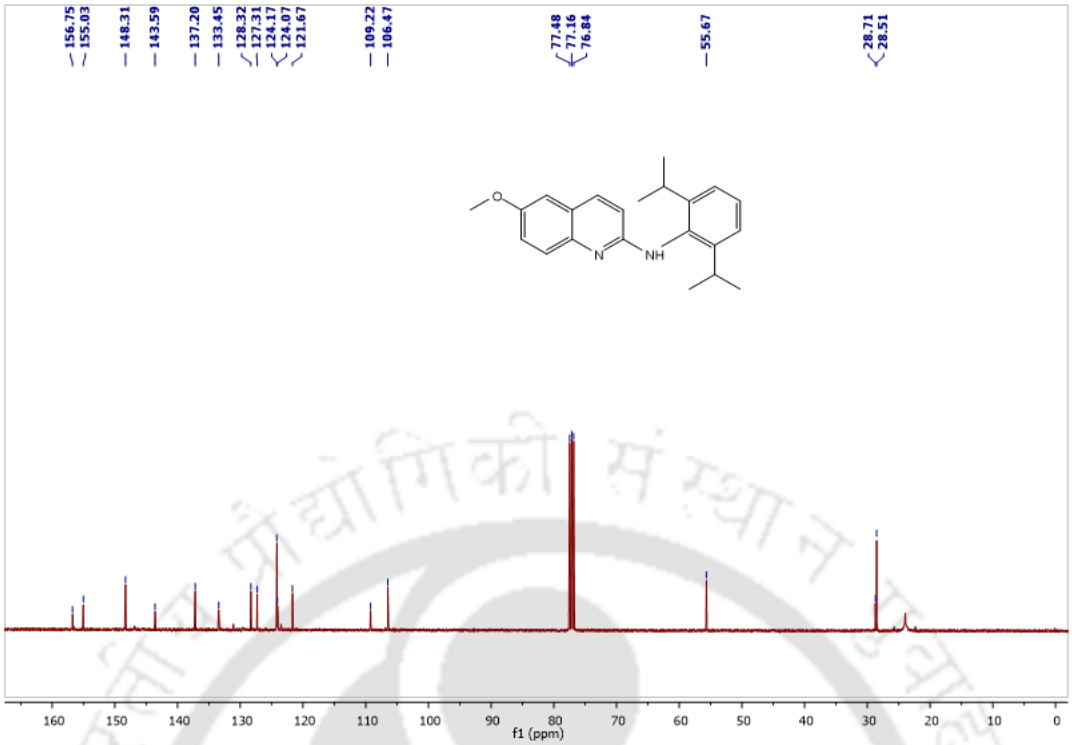


Figure S139. ^{13}C NMR Spectrum of **3.4j** ($CDCl_3$, 101 MHz, 298 K)

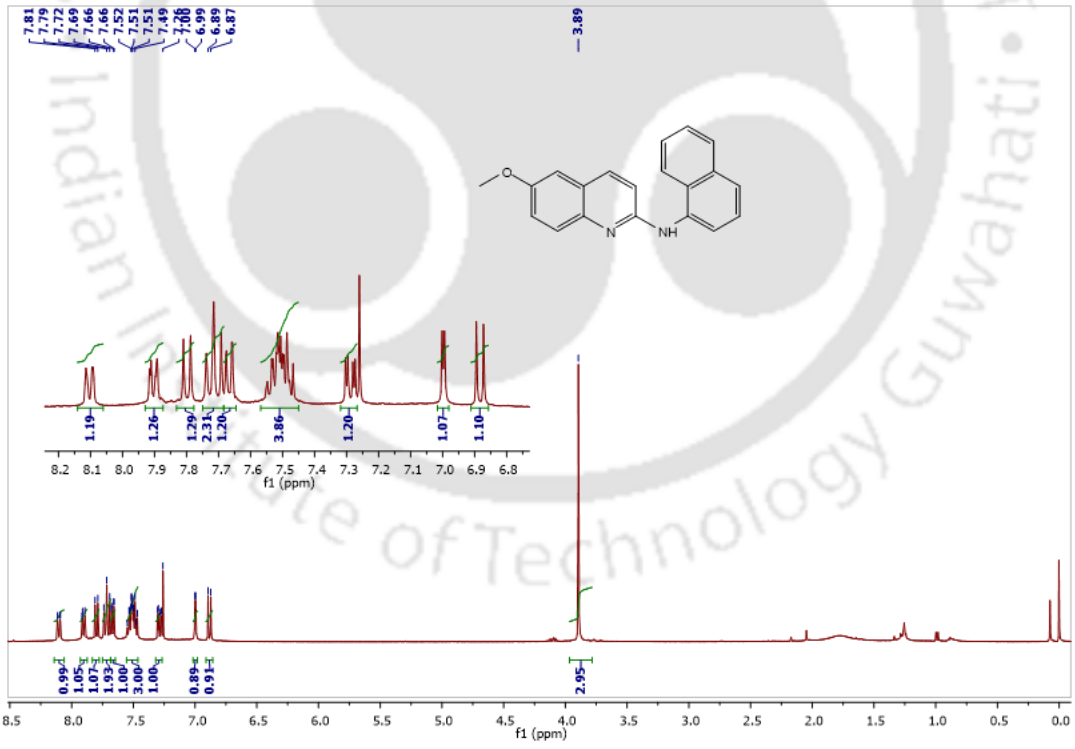


Figure S140. ^{1}H NMR Spectrum of **3.4k** ($CDCl_3$, 600 MHz, 298 K)

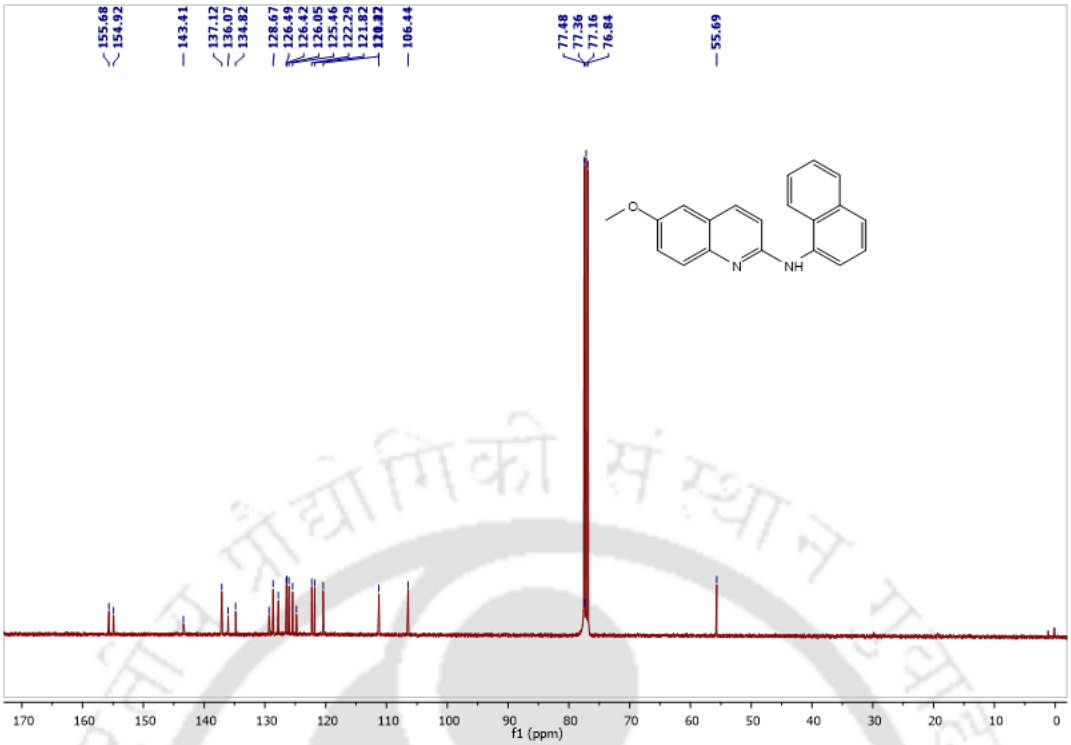


Figure S141. ^{13}C NMR Spectrum of **3.4k** ($CDCl_3$, 101 MHz, 298 K)

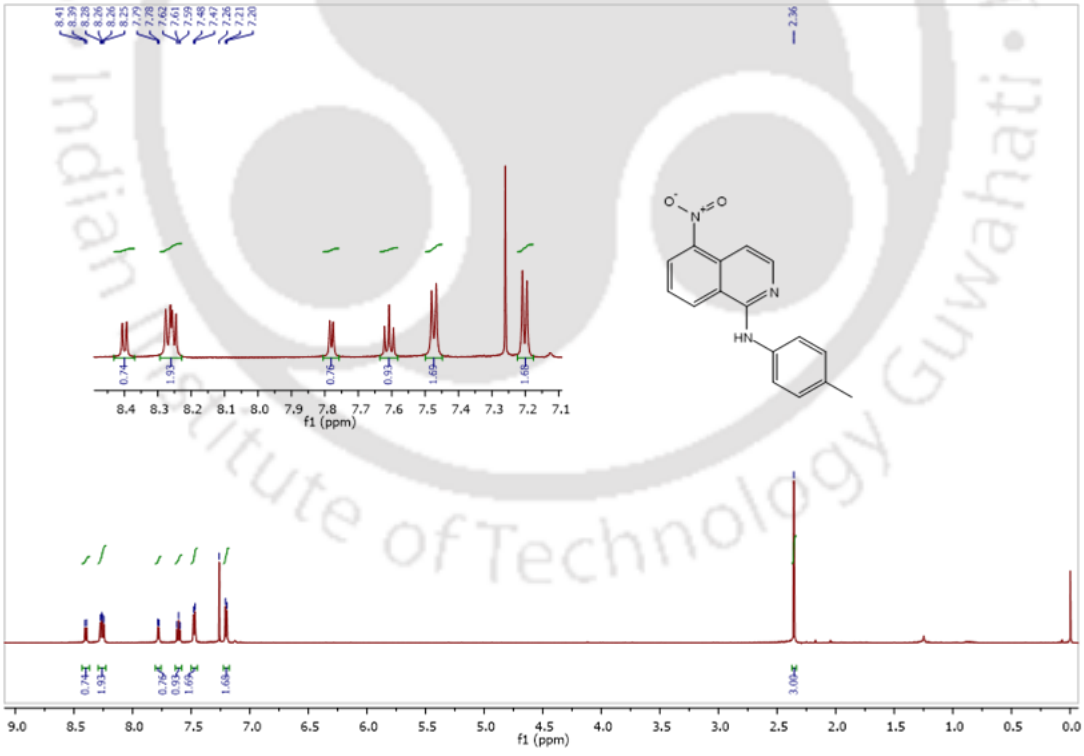


Figure S142. ^{1}H NMR Spectrum of **3.5a** ($CDCl_3$, 600 MHz, 298 K)

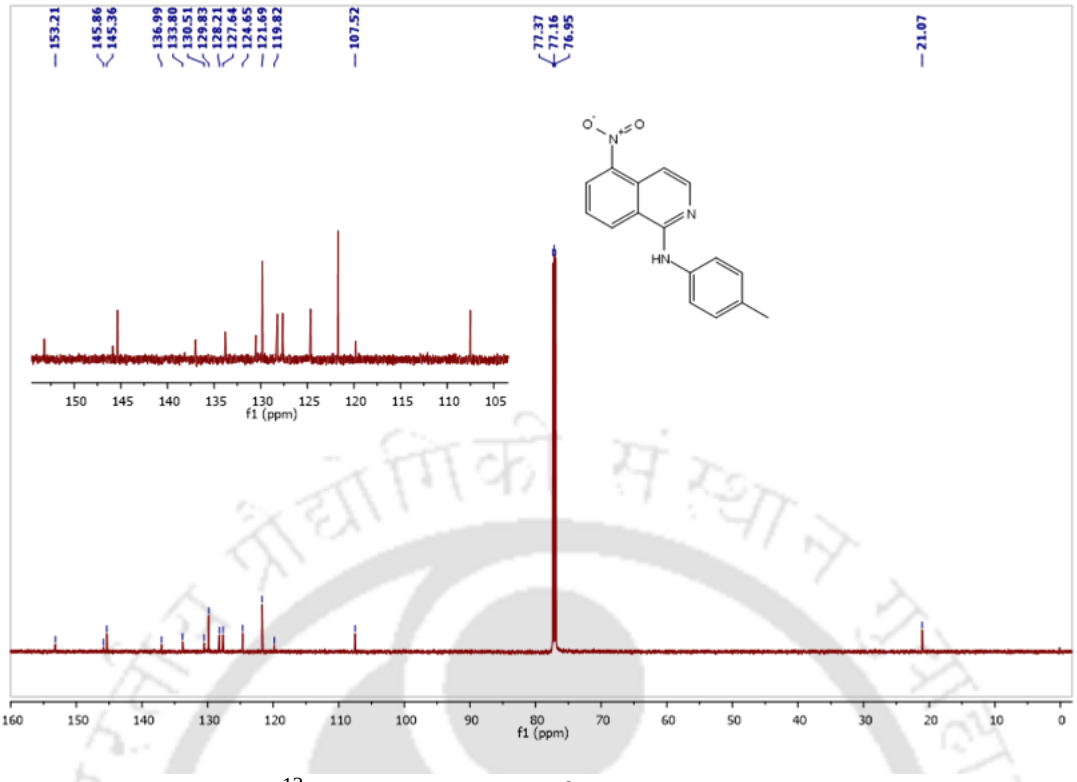


Figure S143. ^{13}C NMR Spectrum of **3.5a** ($CDCl_3$, 151 MHz, 298 K)

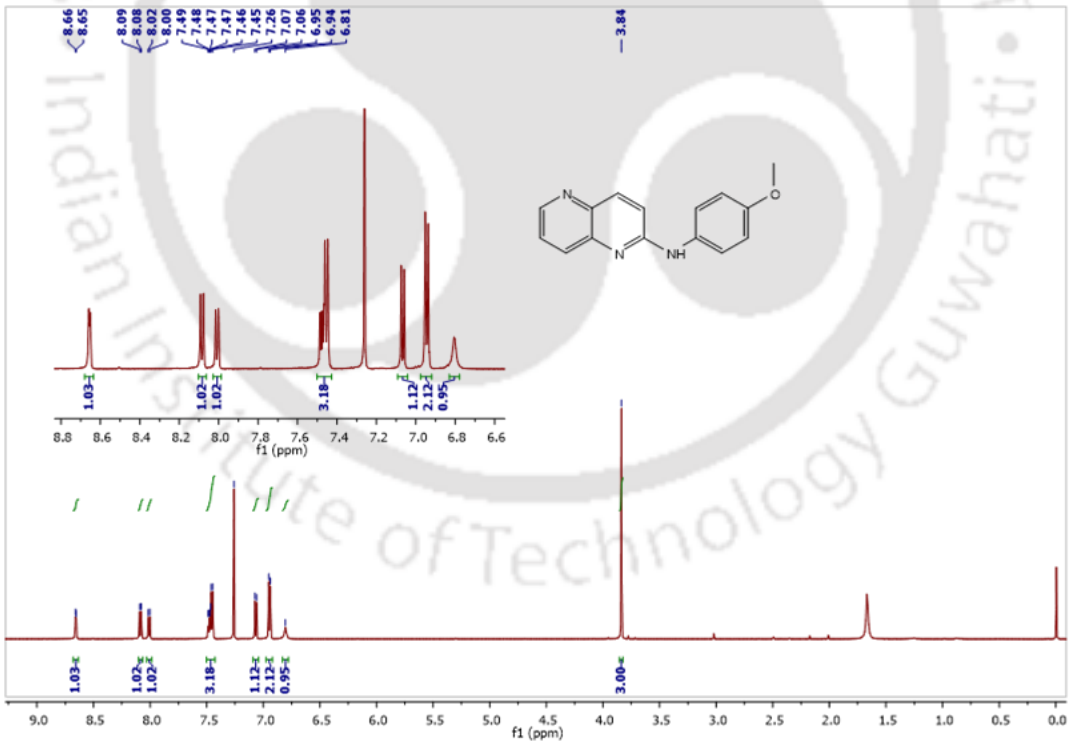


Figure S144. ^{1}H NMR Spectrum of **3.5b** ($CDCl_3$, 600 MHz, 298 K)

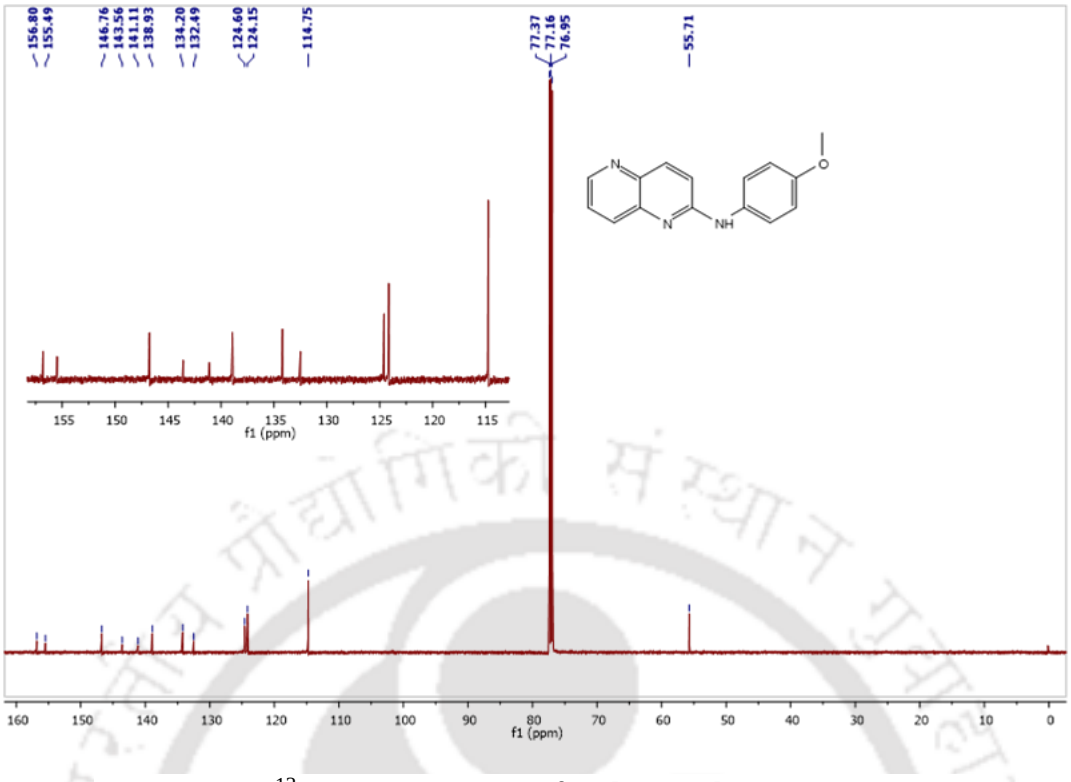


Figure S145. ^{13}C NMR Spectrum of **3.5b** ($CDCl_3$, 151 MHz, 298 K)

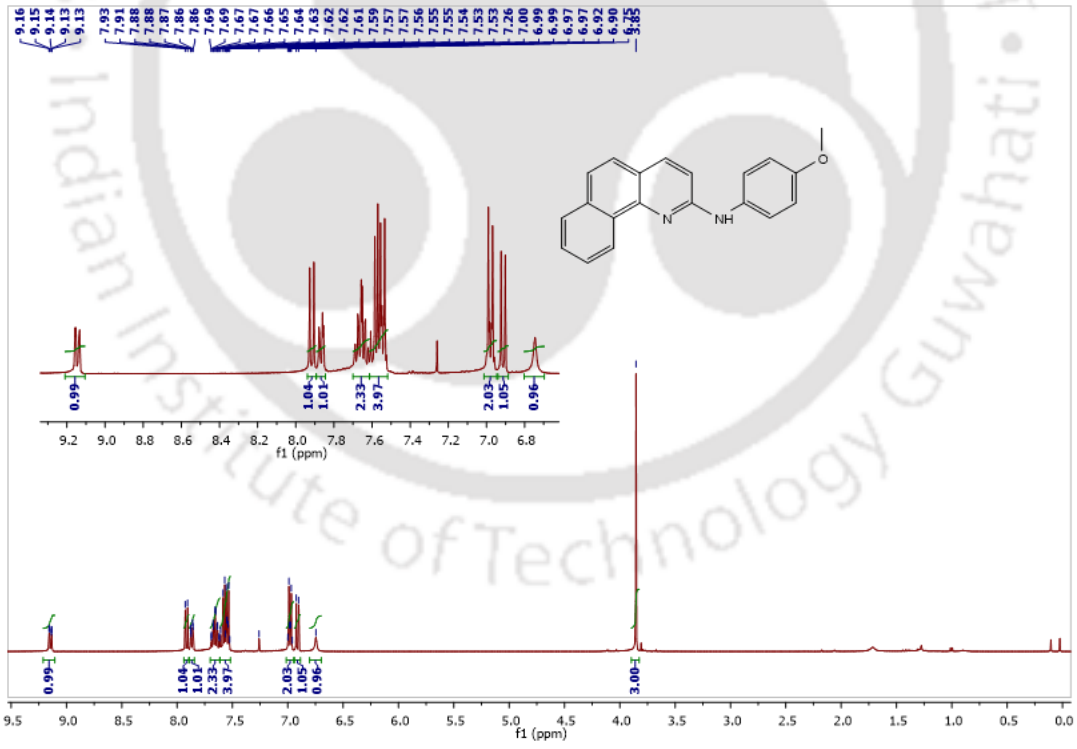


Figure S146. ^{1}H NMR Spectrum of **3.5c** ($CDCl_3$, 400 MHz, 298 K)

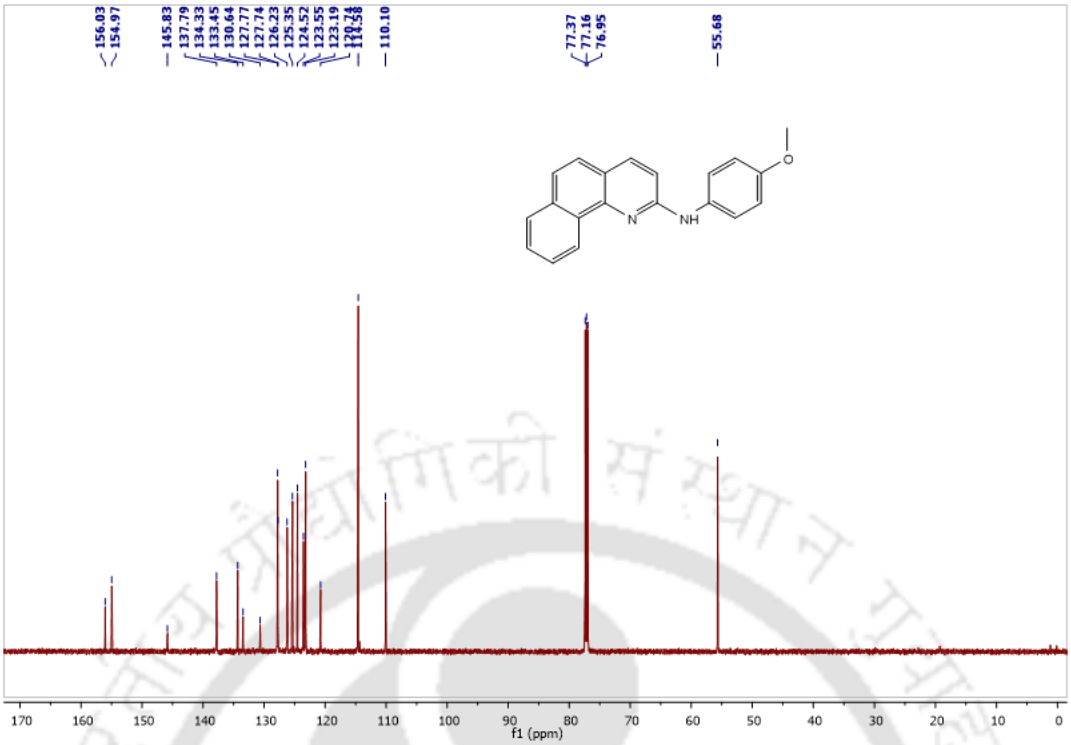


Figure S147. ^{13}C NMR Spectrum of **3.5c** ($CDCl_3$, 151 MHz, 298 K)

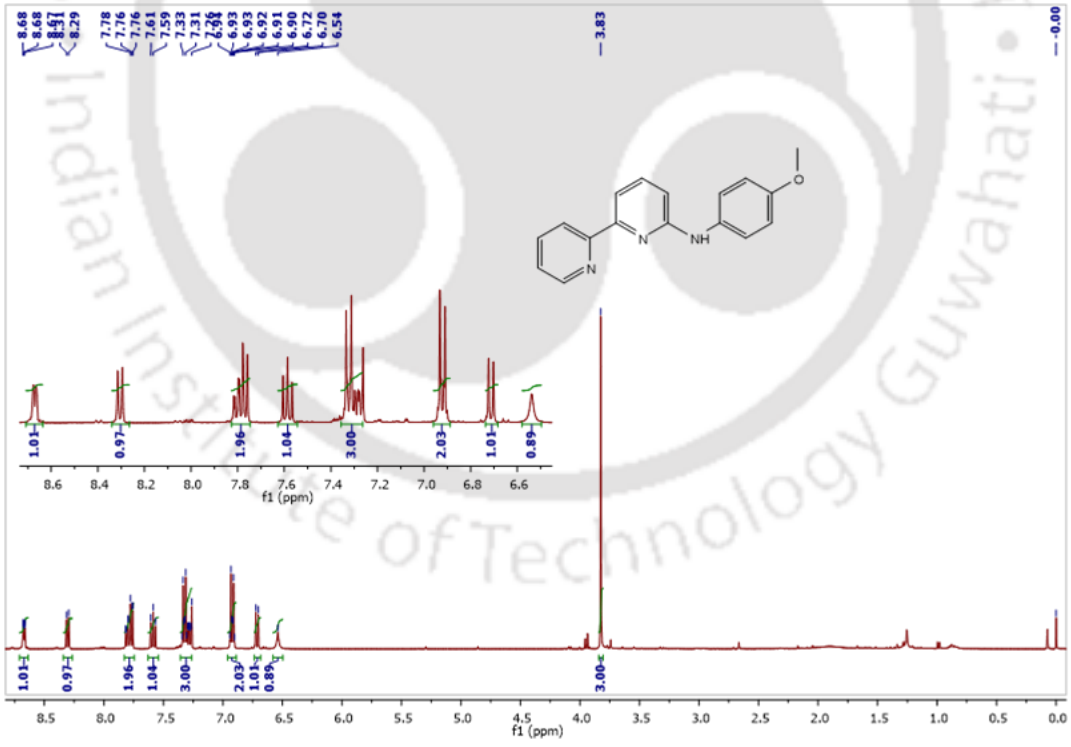


Figure S148. ^{1}H NMR Spectrum of **3.5d** ($CDCl_3$, 400 MHz, 298 K)

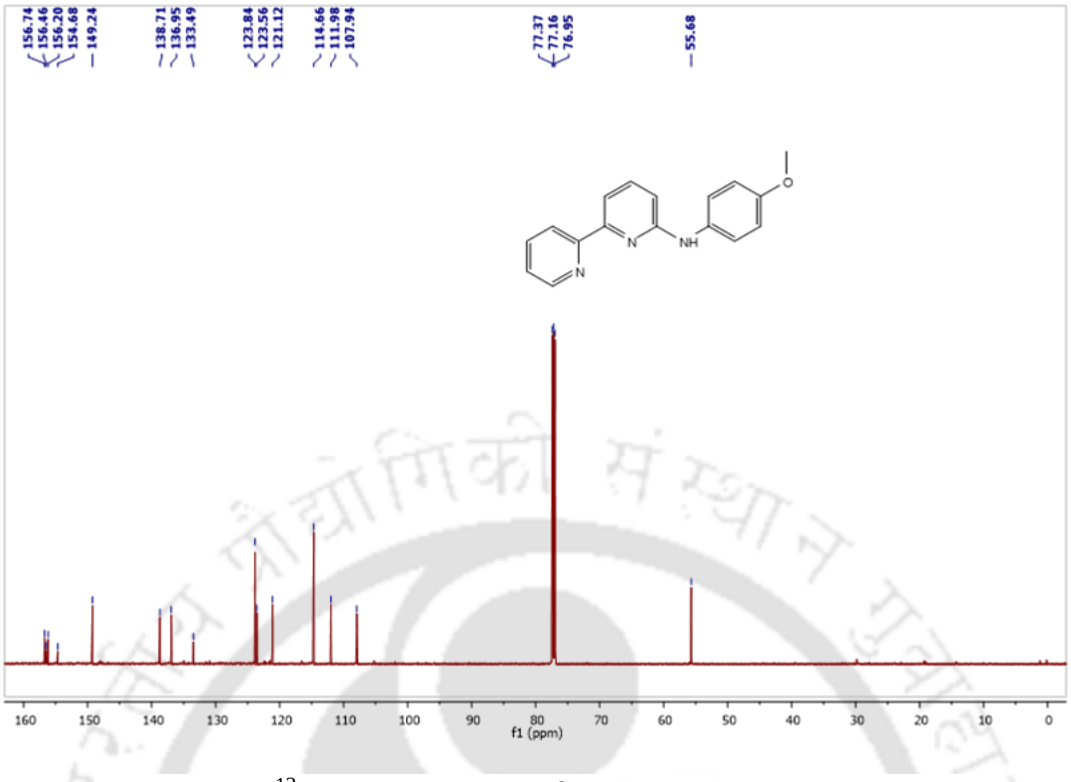


Figure S149. ^{13}C NMR Spectrum of **3.5d** ($CDCl_3$, 151 MHz, 298 K)

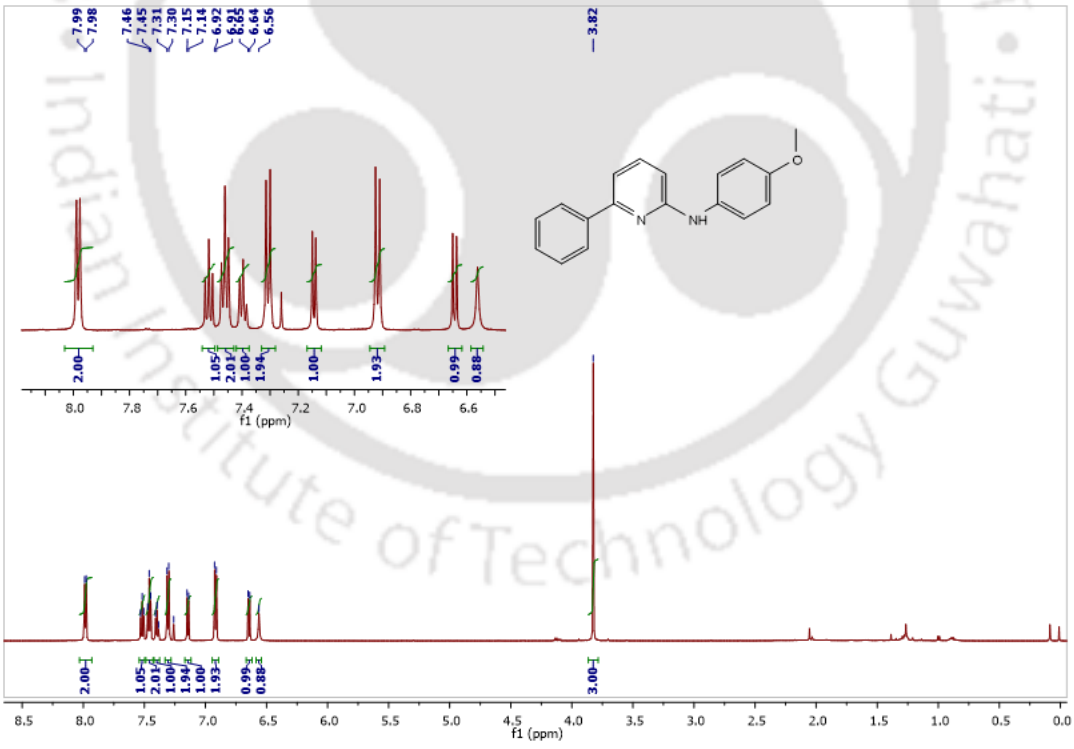


Figure S150. ^{1}H NMR Spectrum of **3.5e** ($CDCl_3$, 600 MHz, 298 K)

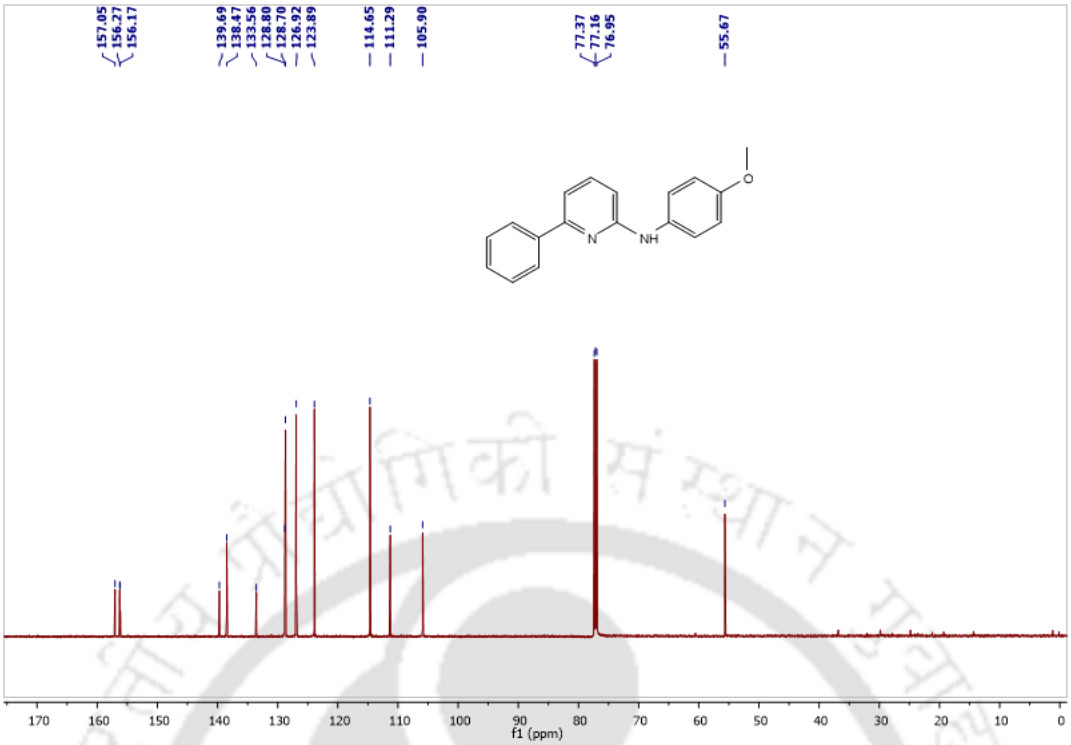


Figure S151. ^{13}C NMR Spectrum of **3.5e** ($CDCl_3$, 151 MHz, 298 K)

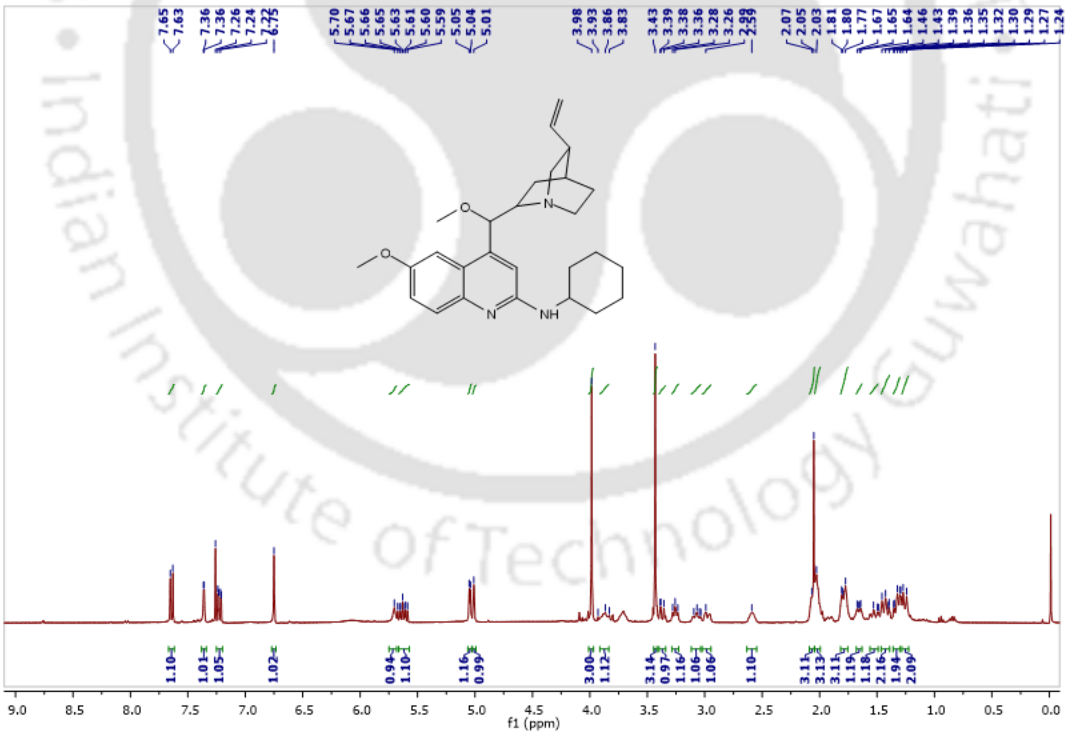


Figure S152. ^{1}H NMR Spectrum of **3.2u** ($CDCl_3$, 400 MHz, 298 K)

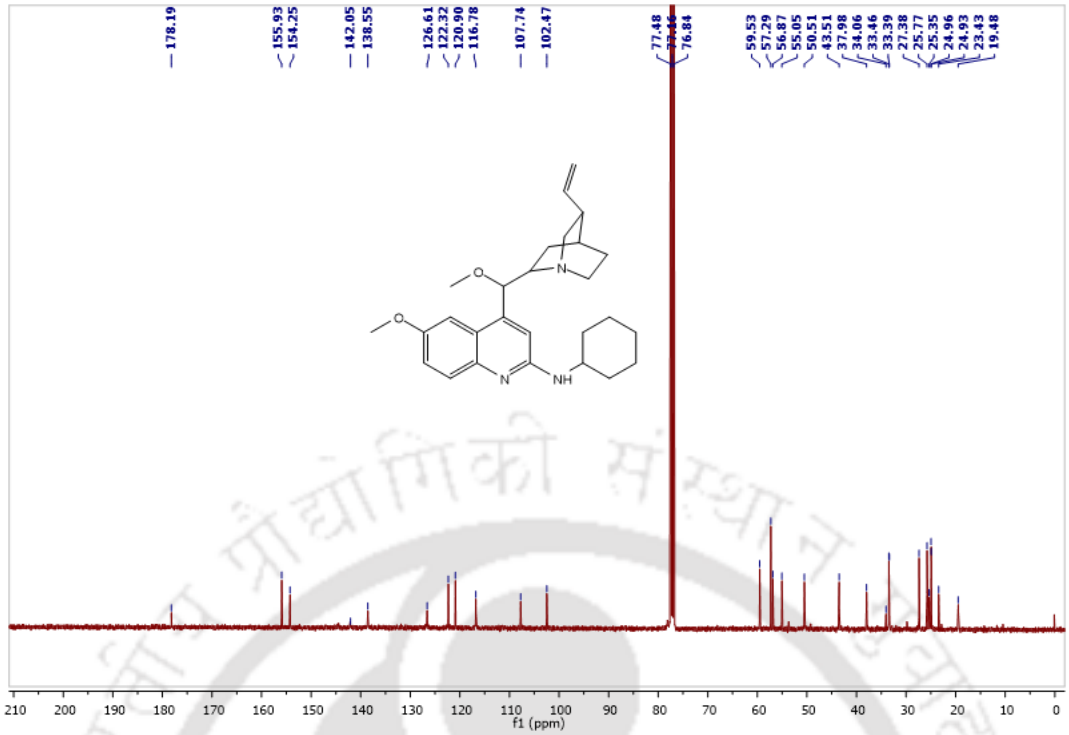


Figure S153. ^{13}C NMR Spectrum of **3.2u** ($CDCl_3$, 101 MHz, 298 K)

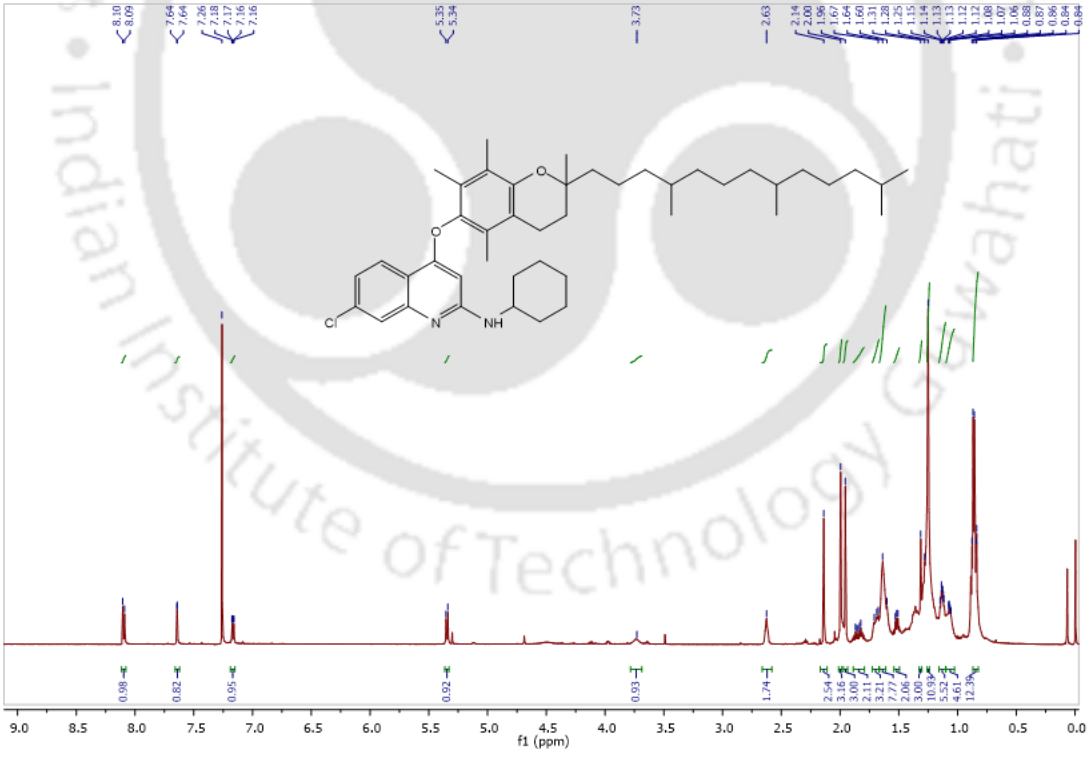


Figure S154. ^{1}H NMR Spectrum of **3.2v** ($CDCl_3$, 600 MHz, 298 K)

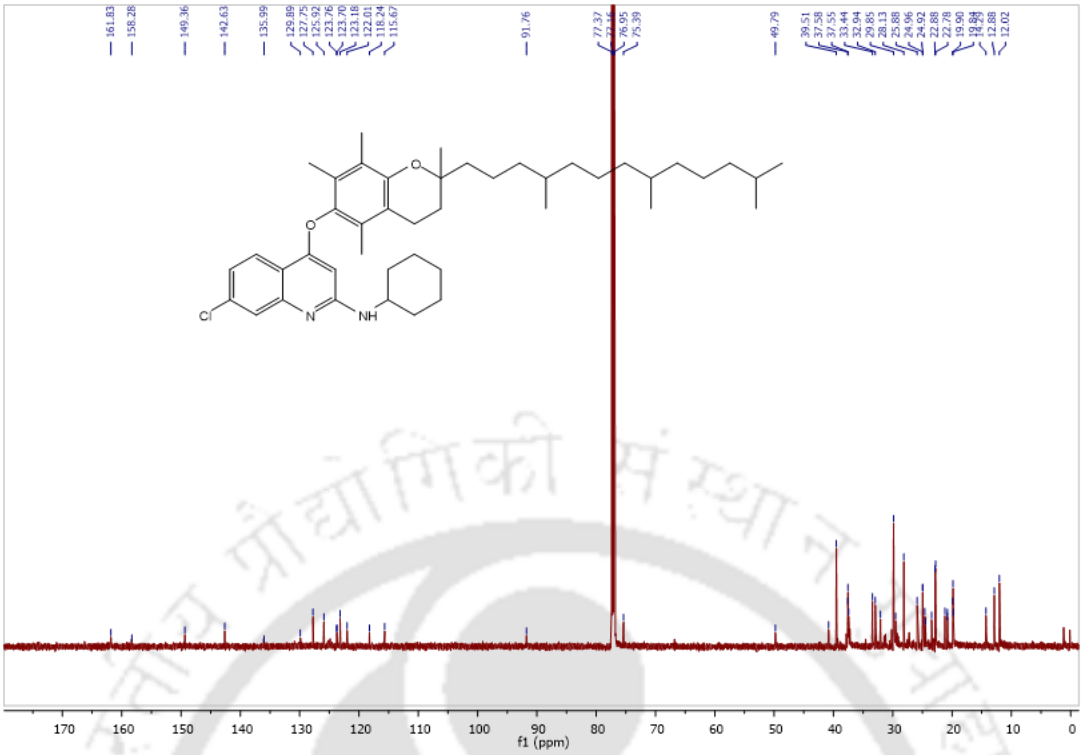


Figure S155. ^{13}C NMR Spectrum of **3.2v** ($CDCl_3$, 151 MHz, 298 K)

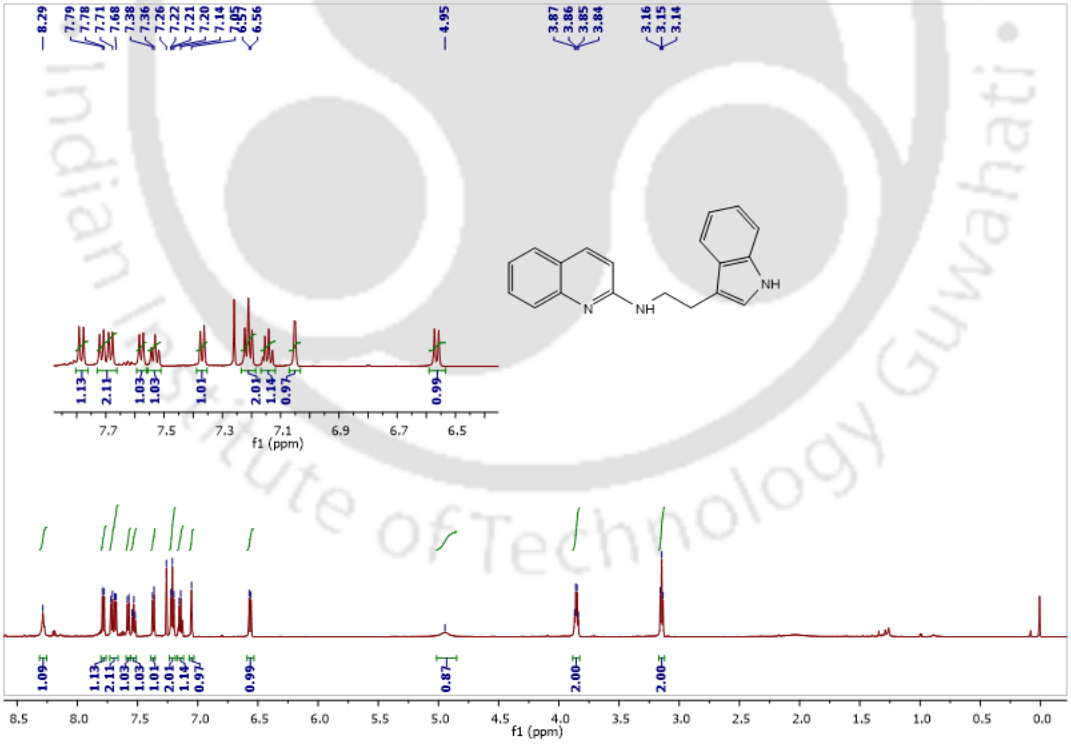


Figure S156. ^{1}H NMR Spectrum of **3.2w** ($CDCl_3$, 600 MHz, 298 K)

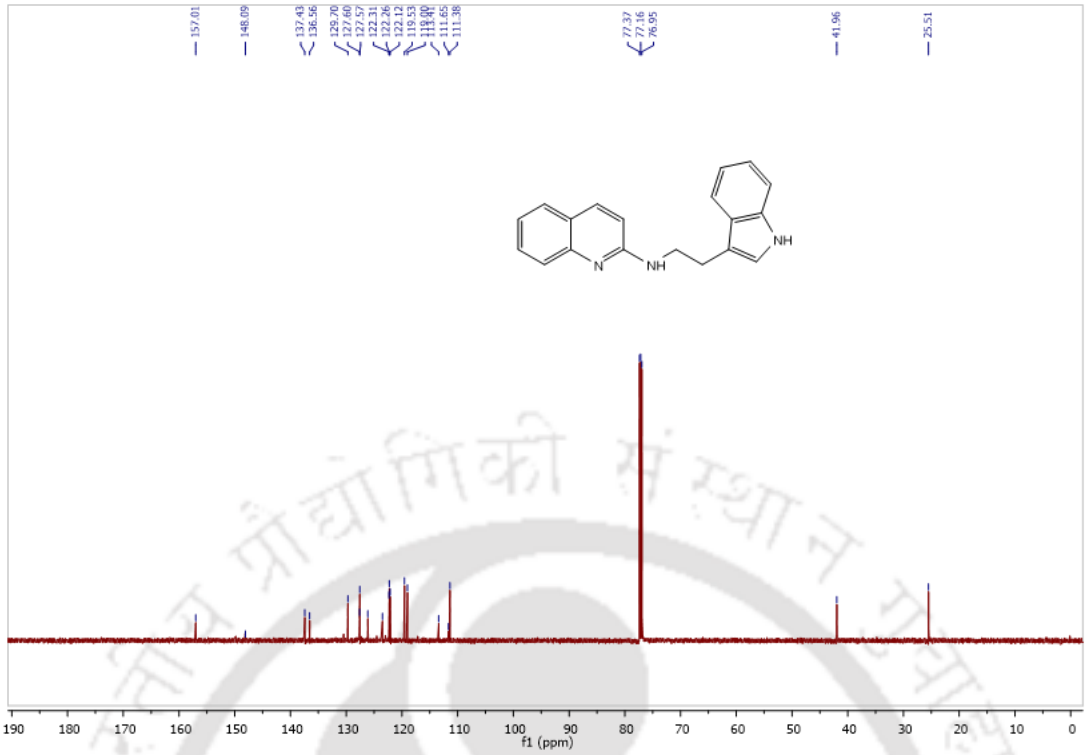


Figure S157. ^{13}C NMR Spectrum of **3.2w** ($CDCl_3$, 151 MHz, 298 K)

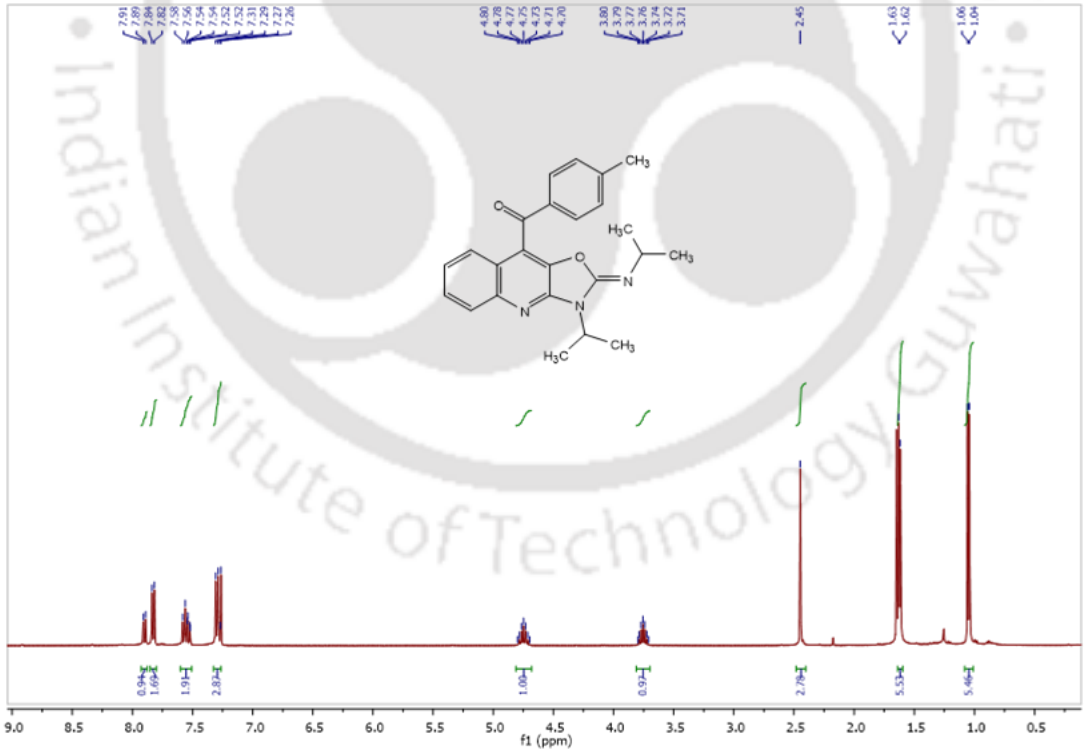


Figure S158. ^{1}H NMR Spectrum of **3.9** ($CDCl_3$, 400 MHz, 298 K)

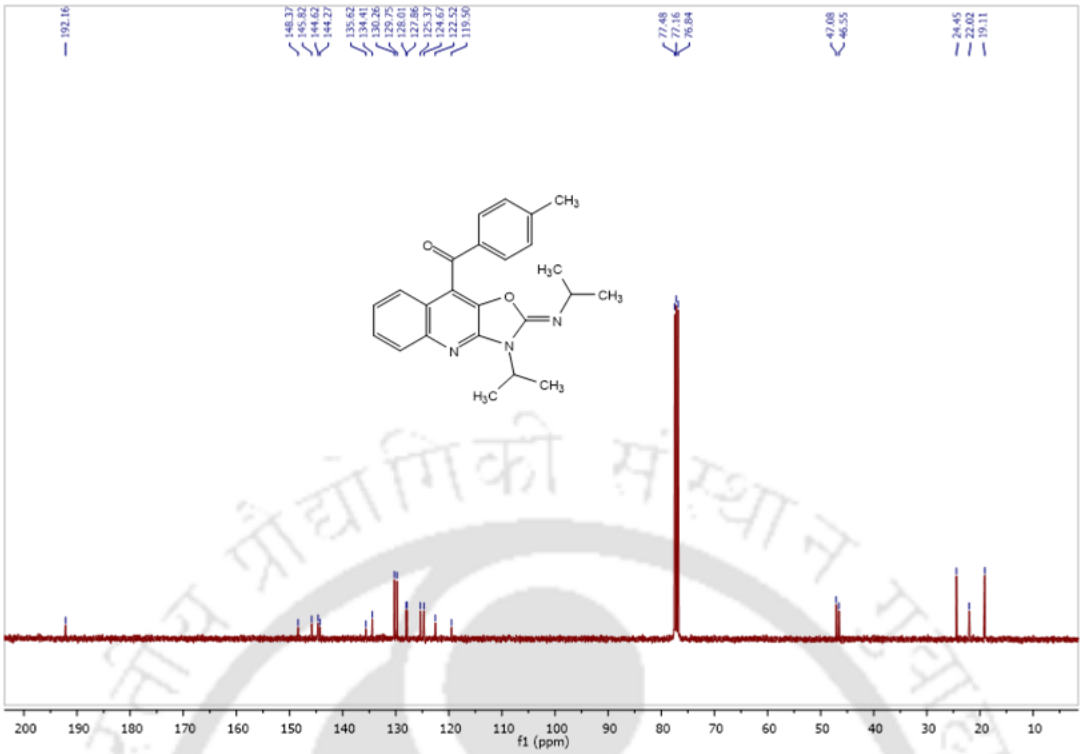


Figure S159. ^{13}C NMR Spectrum of **3.9** ($CDCl_3$, 101 MHz, 298 K)

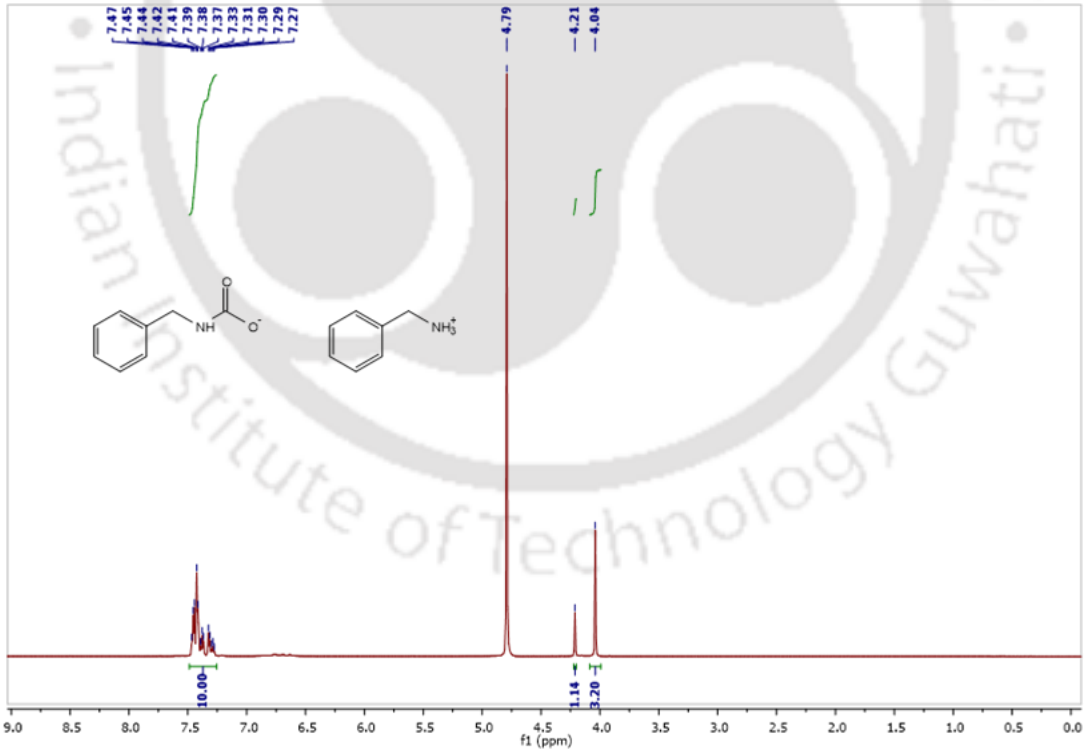


Figure S160. ^{1}H NMR Spectrum of **3.10** (D_2O, 600 MHz, 298 K)

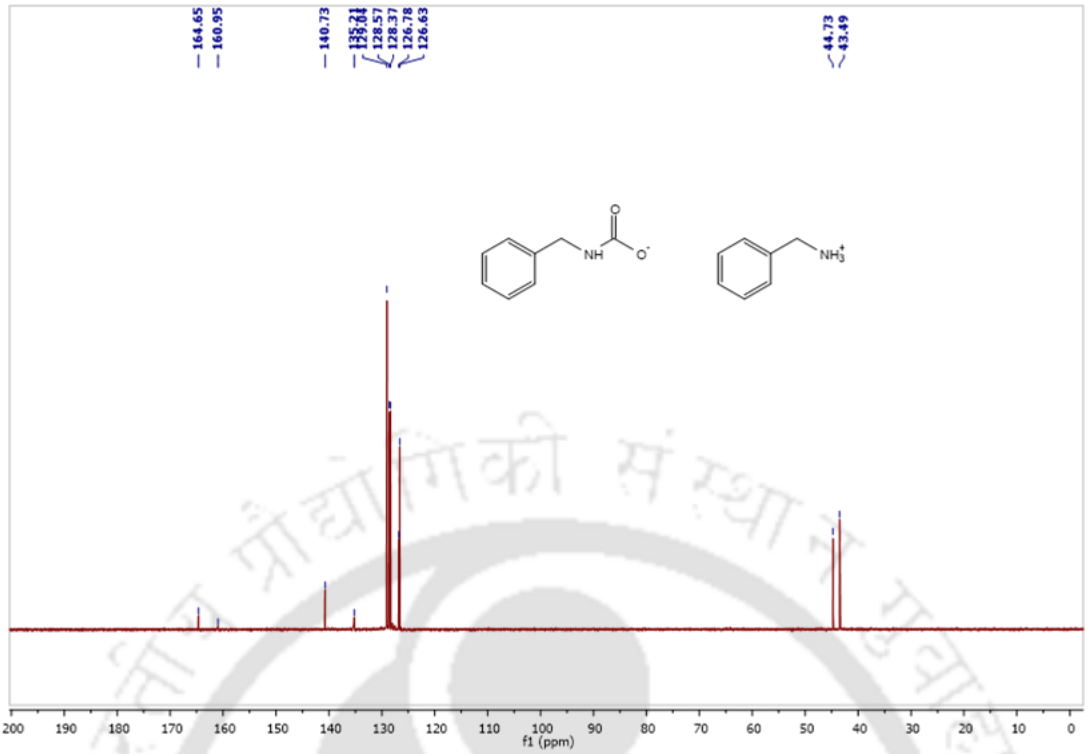


Figure S161. ^{13}C NMR Spectrum of **3.10** (D_2O, 151 MHz, 298 K)

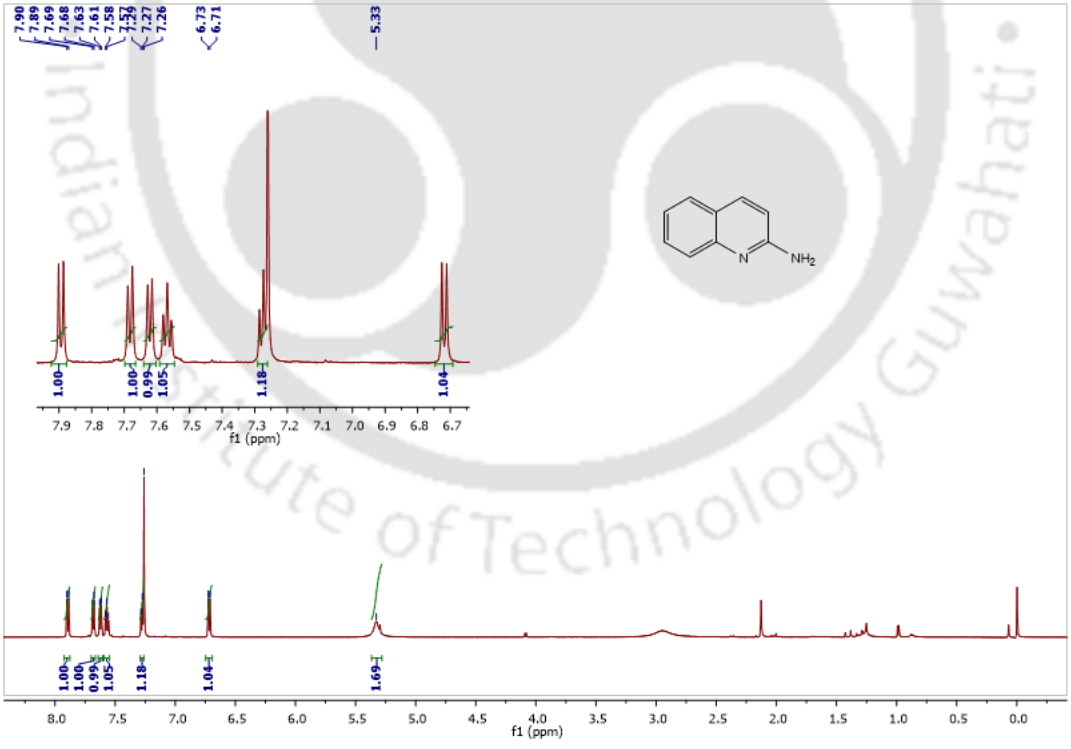


Figure S162. ^{1}H NMR Spectrum of **3.11** ($CDCl_3$, 600 MHz, 298 K)

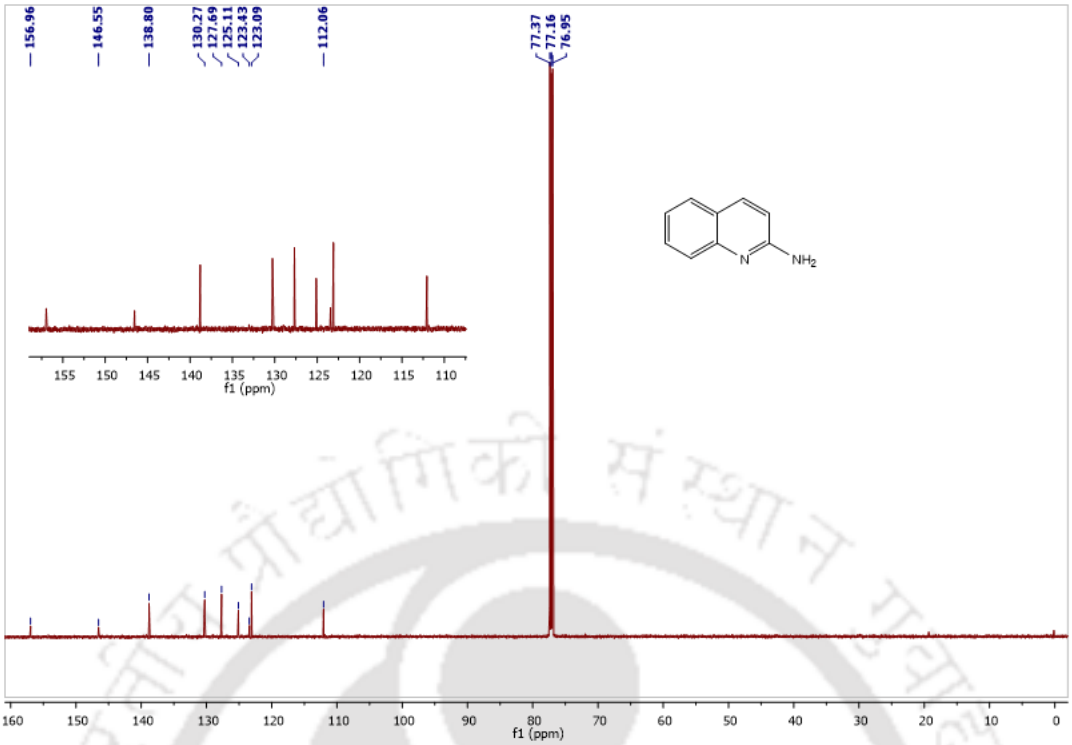


Figure S163. ^{13}C NMR Spectrum of **3.11** ($CDCl_3$, 151 MHz, 298 K)

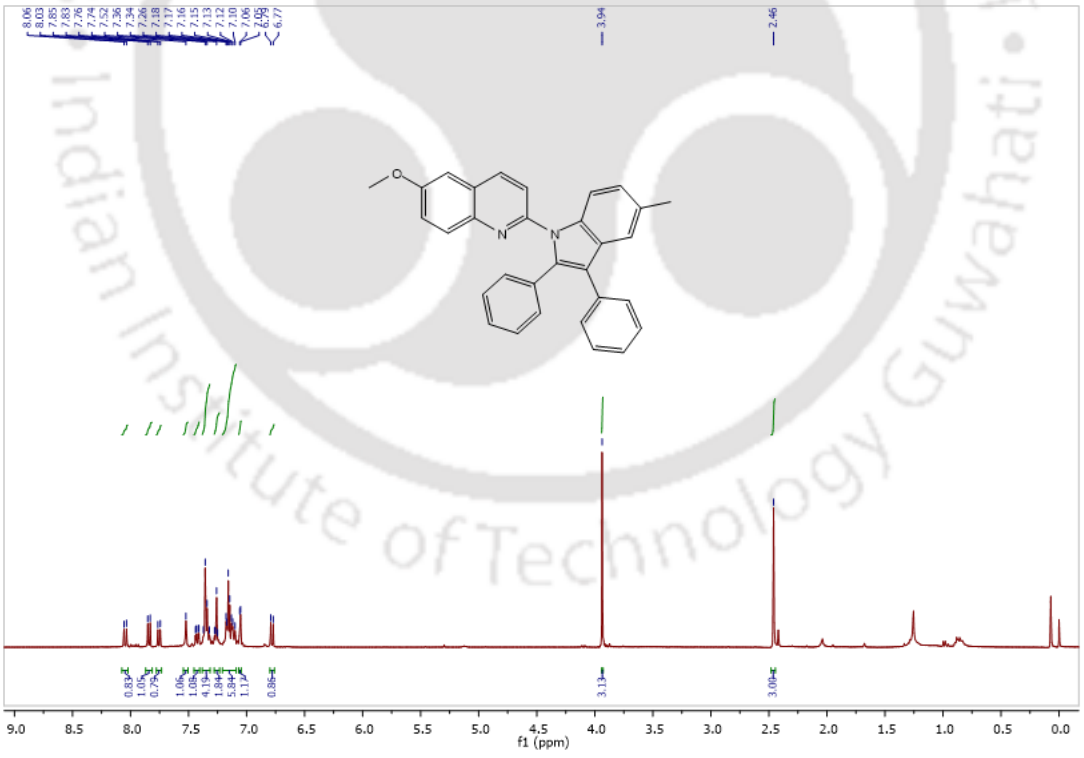


Figure S164. ^{1}H NMR Spectrum of **3.13** ($CDCl_3$, 600 MHz, 298 K)

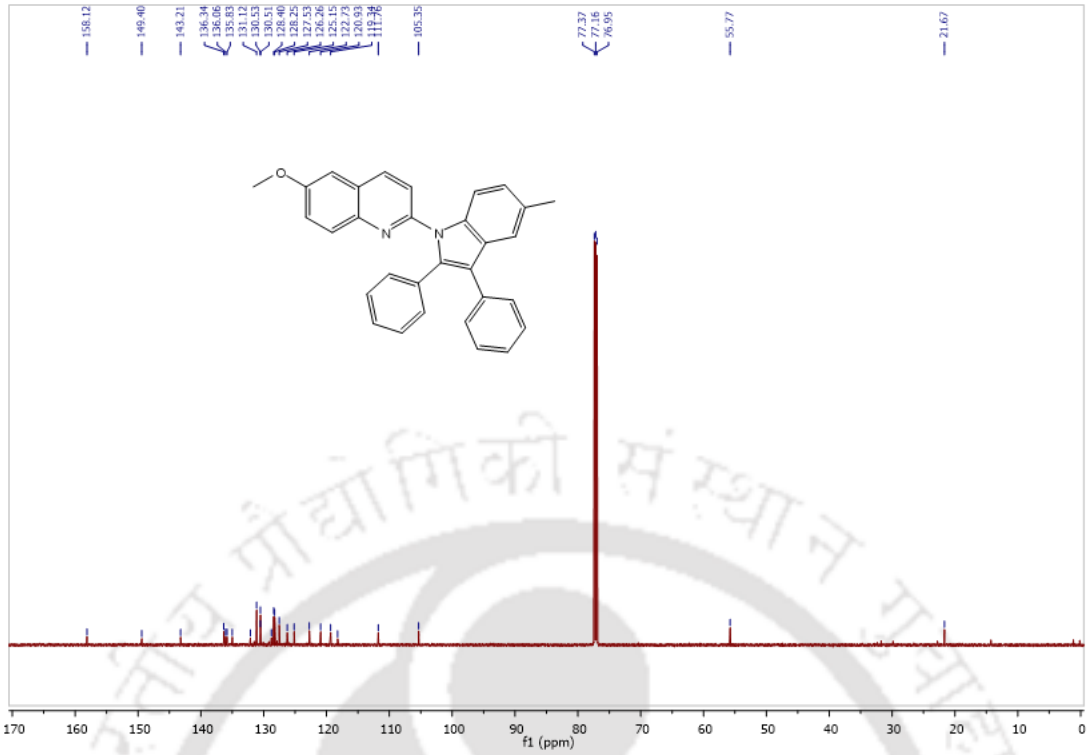


Figure S165. ^{13}C NMR Spectrum of **3.13** ($CDCl_3$, 151 MHz, 298 K)

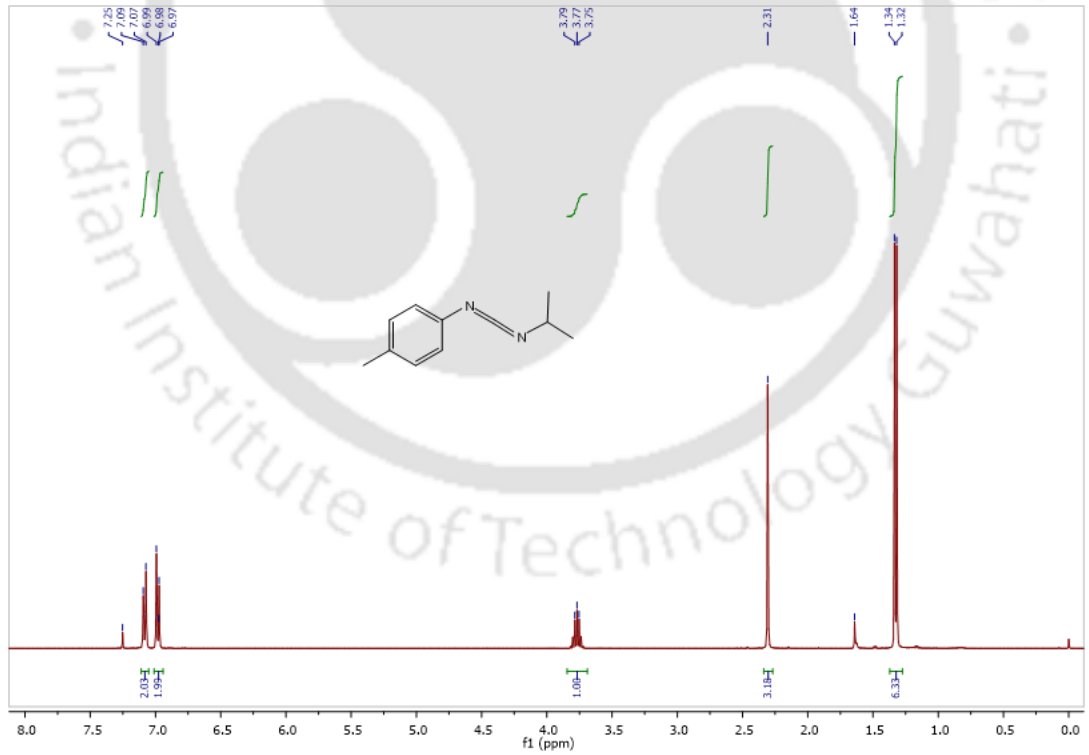


Figure S166. ^{1}H NMR Spectrum of **3.8** ($CDCl_3$, 400 MHz, 298 K)

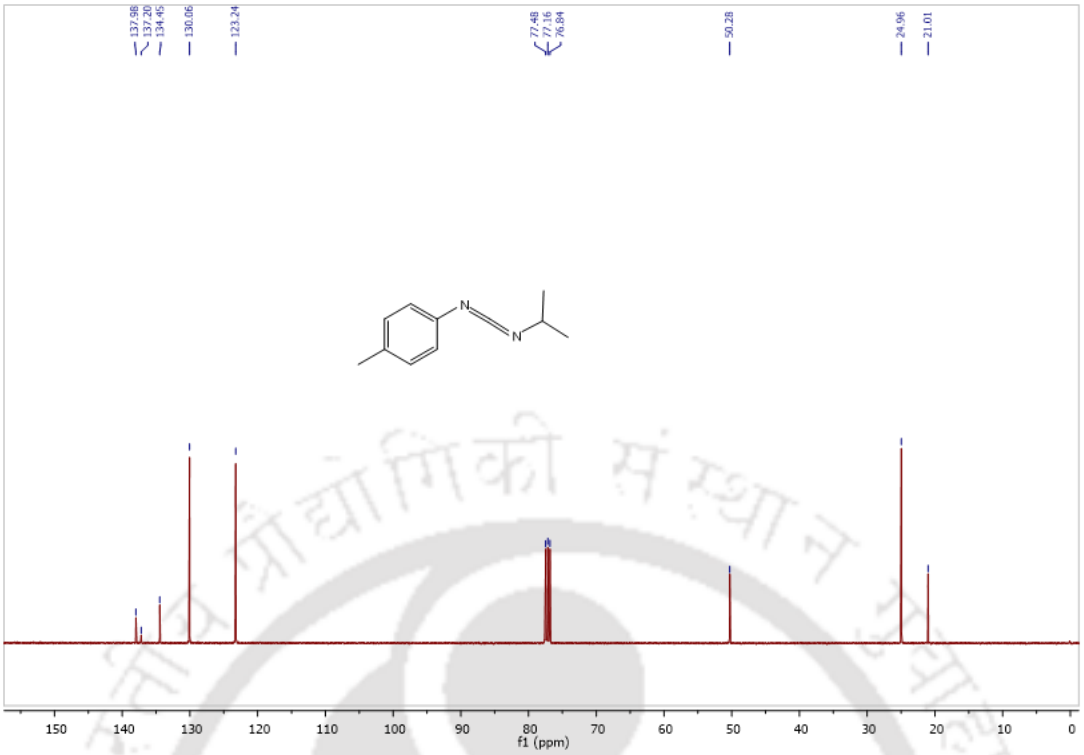


Figure S167. ^{13}C NMR Spectrum of **3.8** ($CDCl_3$, 101 MHz, 298 K)

Annexure III

^{1}H, ^{13}C, 2D NMR and HRMS spectra of compounds (*Chapter 4*)

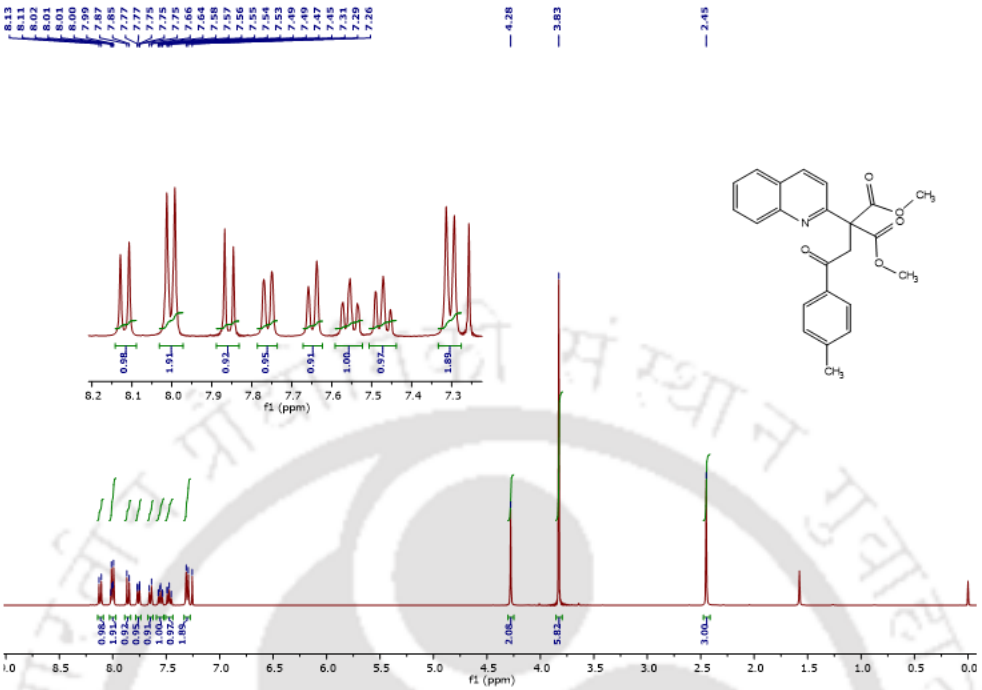


Figure S168. ^{1}H NMR Spectrum of **4.2a** ($CDCl_3$, 400 MHz, 298 K)

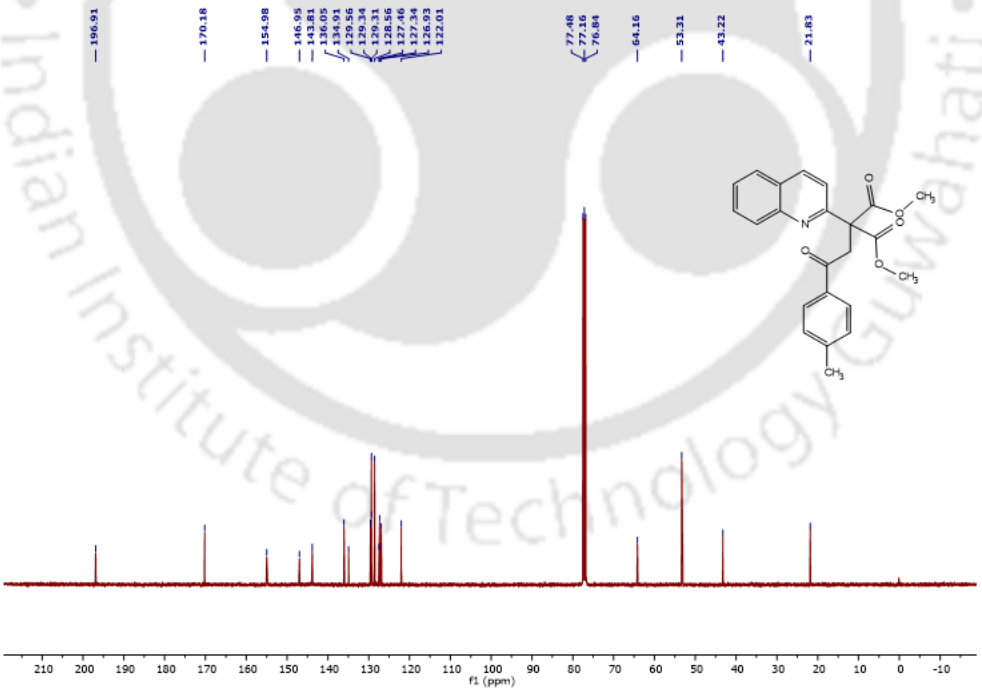


Figure S169. ^{13}C NMR Spectrum of **4.2a** ($CDCl_3$, 101 MHz, 298 K)

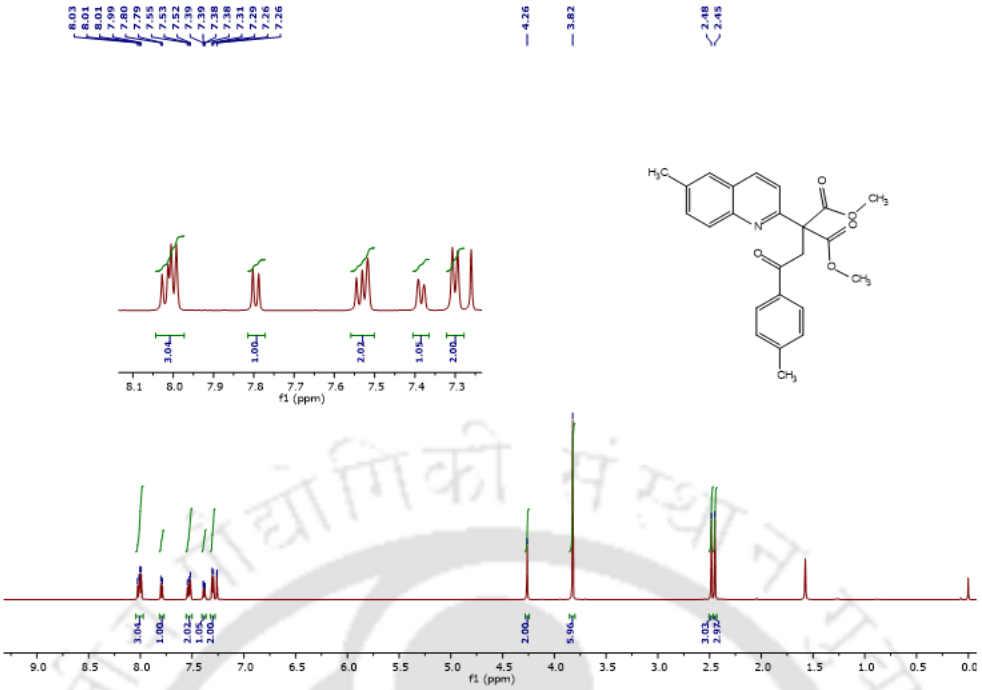


Figure S170. ^{1}H NMR Spectrum of **4.2b** ($CDCl_3$, 600 MHz, 298 K)

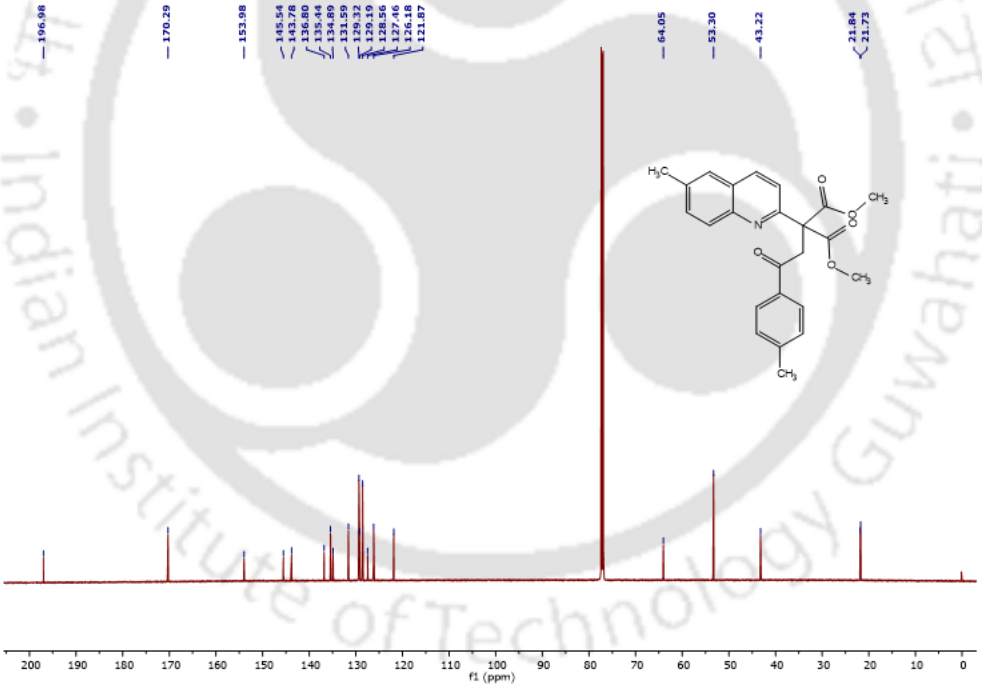


Figure S171. ^{13}C NMR Spectrum of **4.2b** ($CDCl_3$, 151 MHz, 298 K)

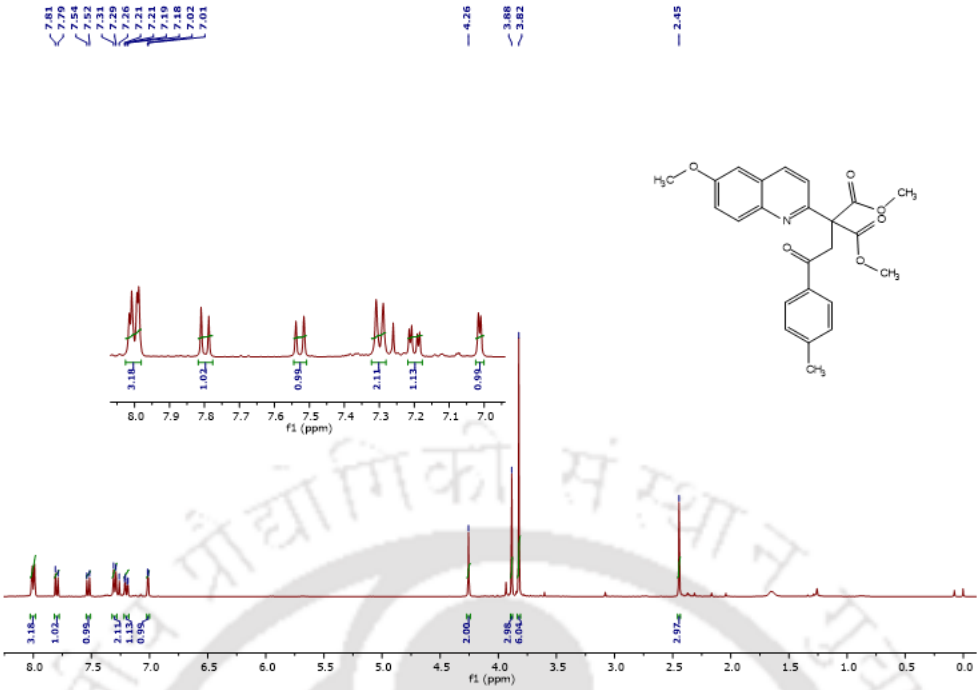


Figure S172. ^{1}H NMR Spectrum of **4.2c** ($CDCl_3$, 400 MHz, 298 K)

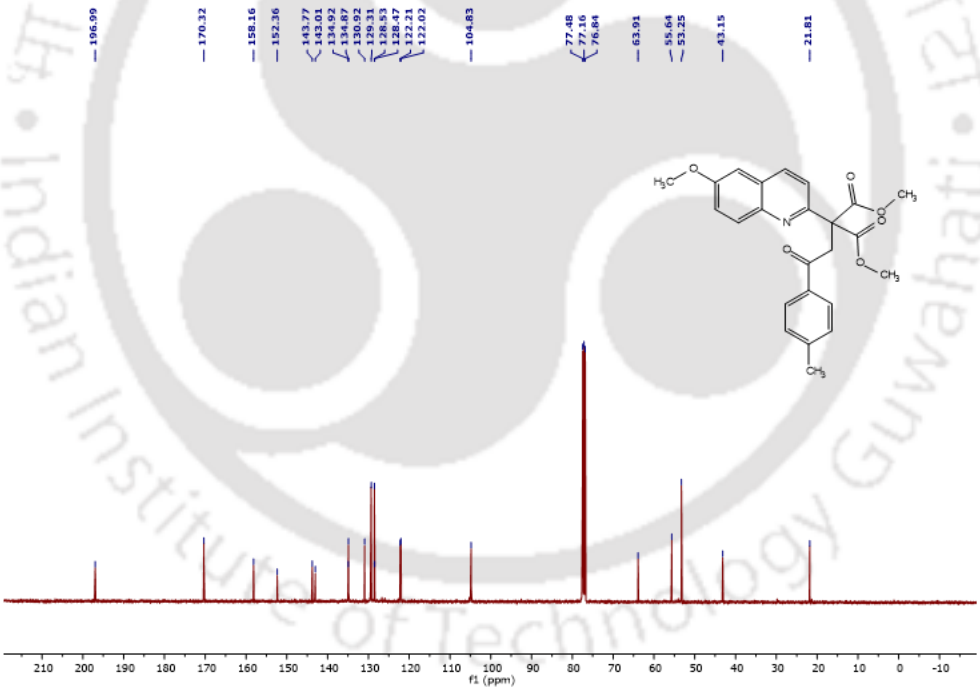


Figure S173. ^{13}C NMR Spectrum of **4.2c** ($CDCl_3$, 101 MHz, 298 K)

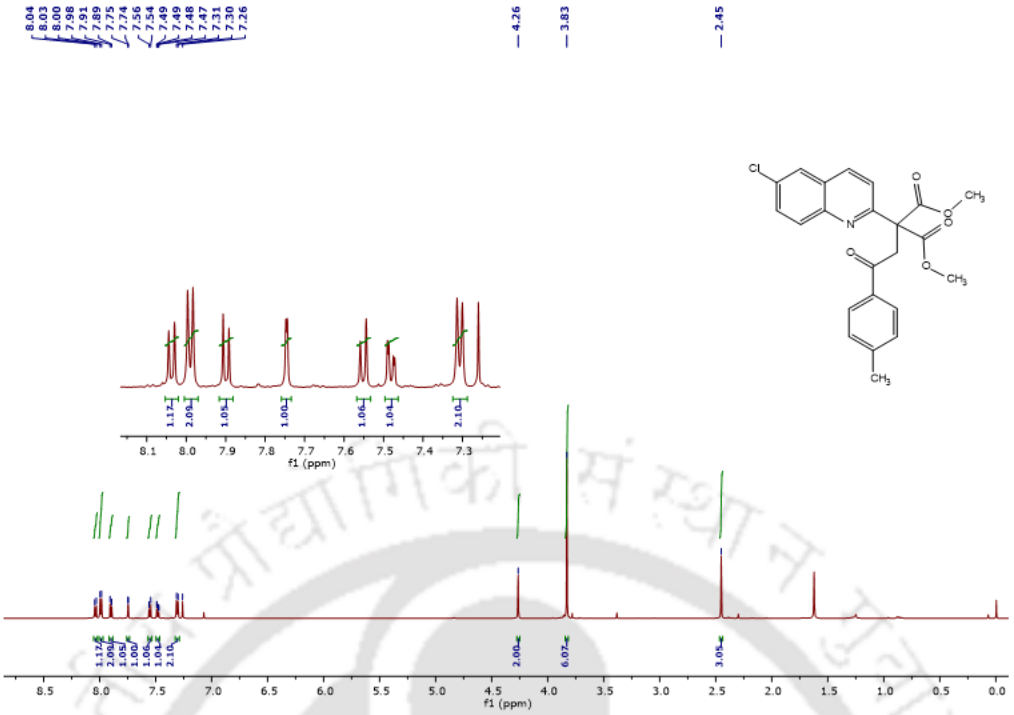


Figure S174. ^{1}H NMR Spectrum of **4.2d** ($CDCl_3$, 600 MHz, 298 K)

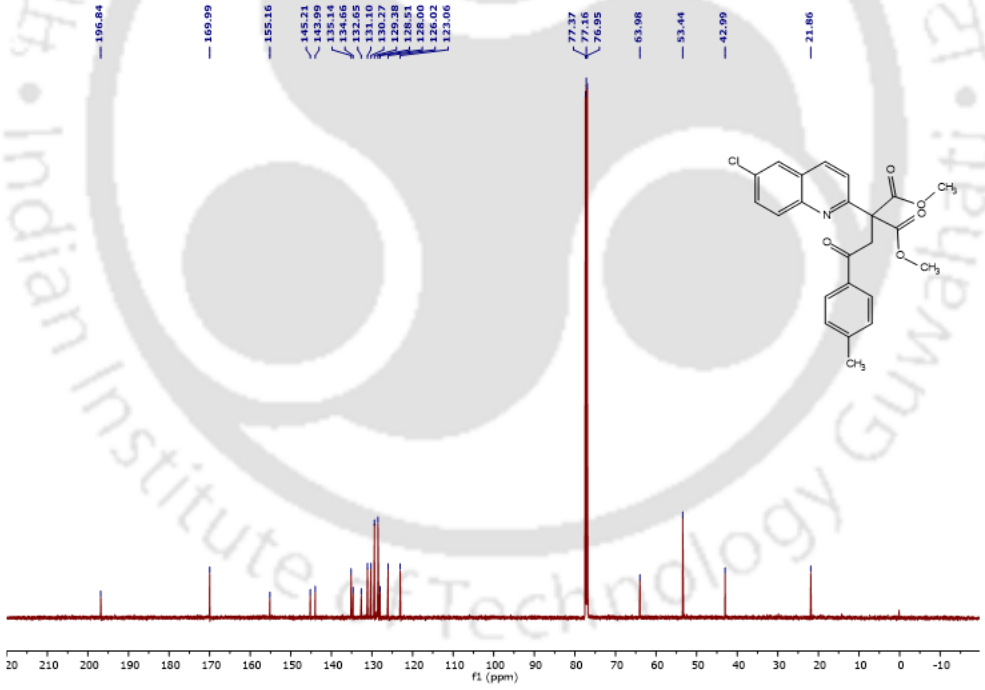


Figure S175. ^{13}C NMR Spectrum of **4.2d** ($CDCl_3$, 151 MHz, 298 K)

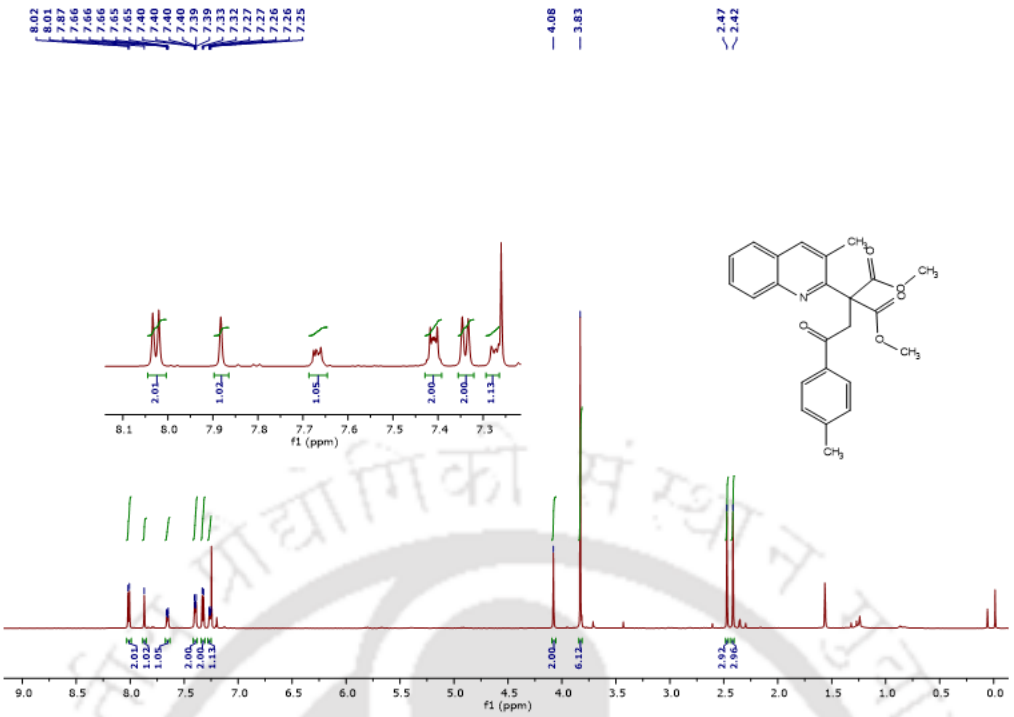


Figure S176. ^{1}H NMR Spectrum of **4.2e** ($CDCl_3$, 600 MHz, 298 K)

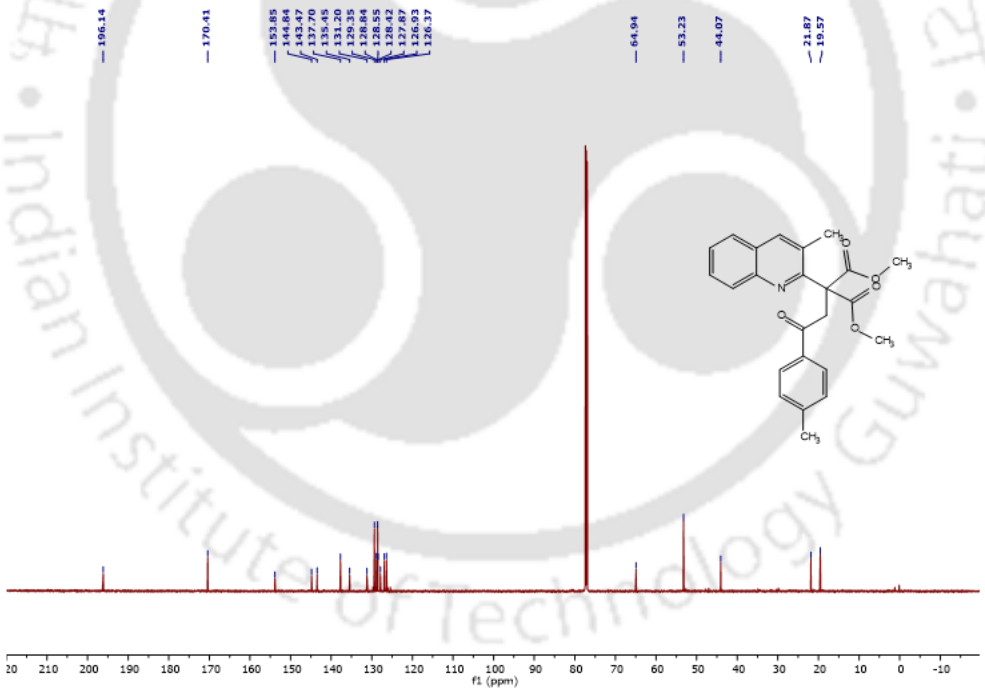


Figure S177. ^{13}C NMR Spectrum of **4.2e** ($CDCl_3$, 151 MHz, 298 K)

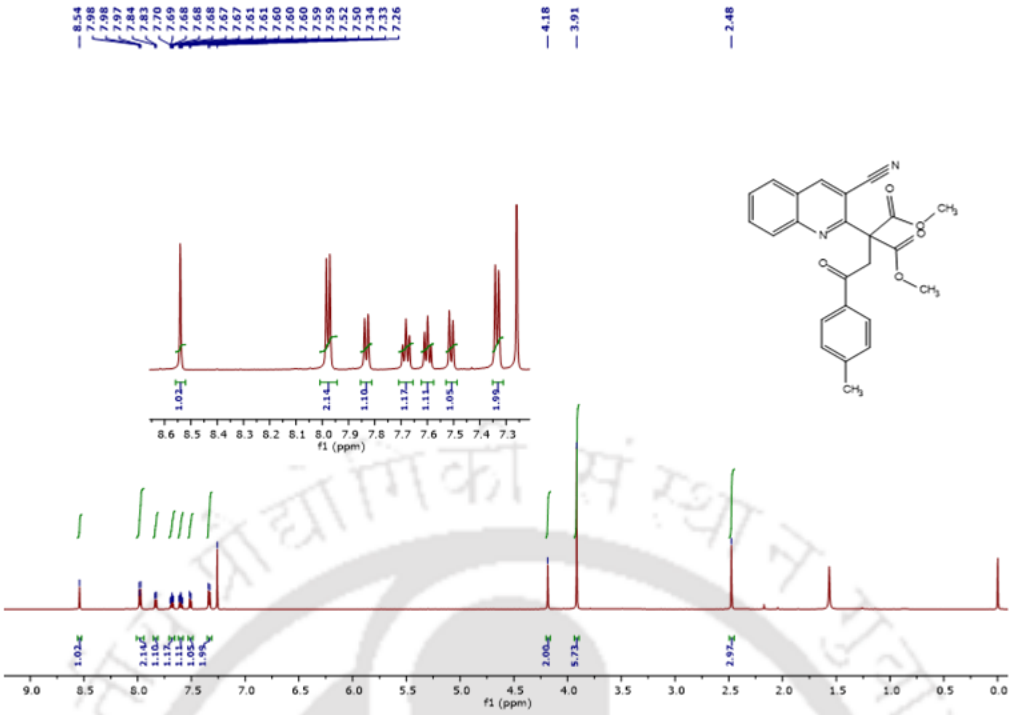


Figure S178. ^{1}H NMR Spectrum of **4.2f** ($CDCl_3$, 400 MHz, 298 K)

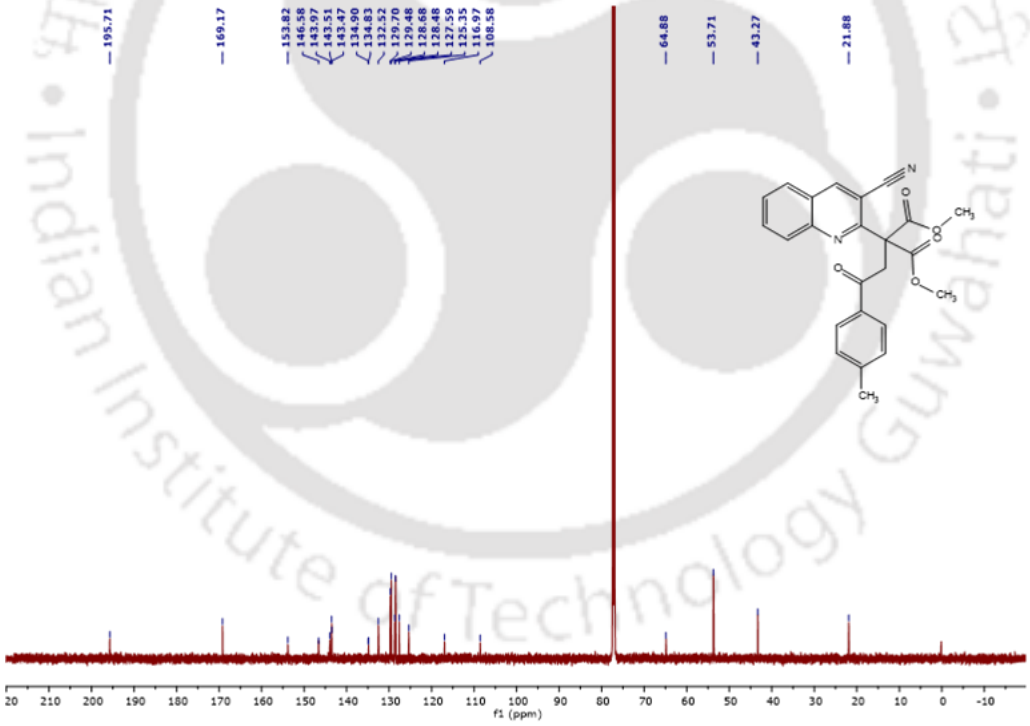


Figure S179. ^{13}C NMR Spectrum of **4.2f** ($CDCl_3$, 101 MHz, 298 K)

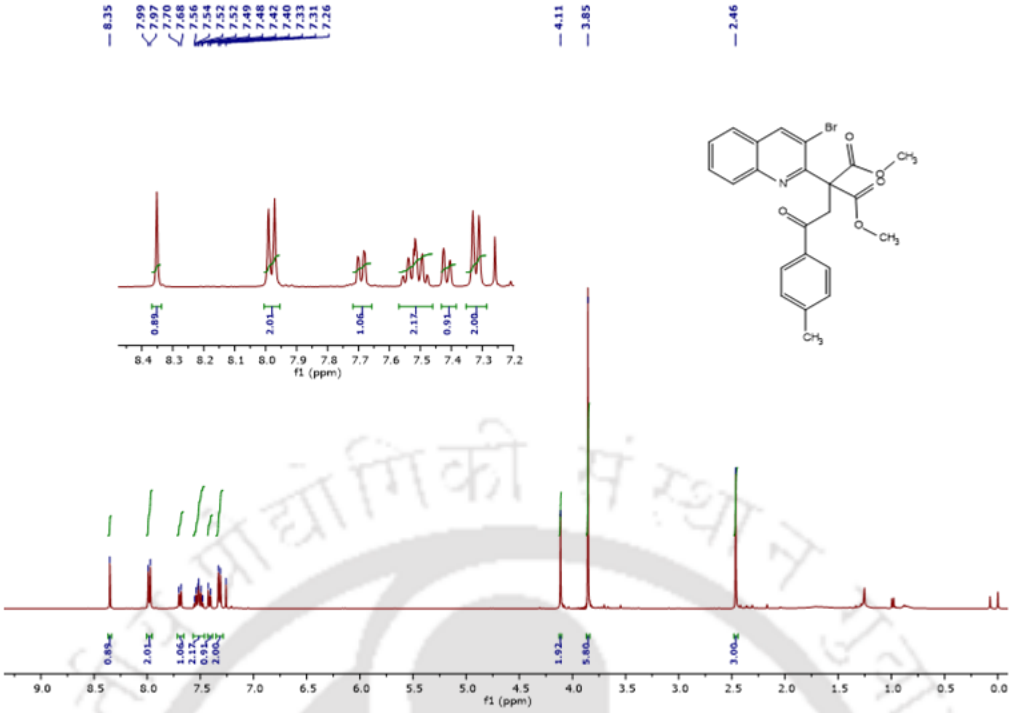


Figure S180. ^{1}H NMR Spectrum of **4.2g** ($CDCl_3$, 600 MHz, 298 K)

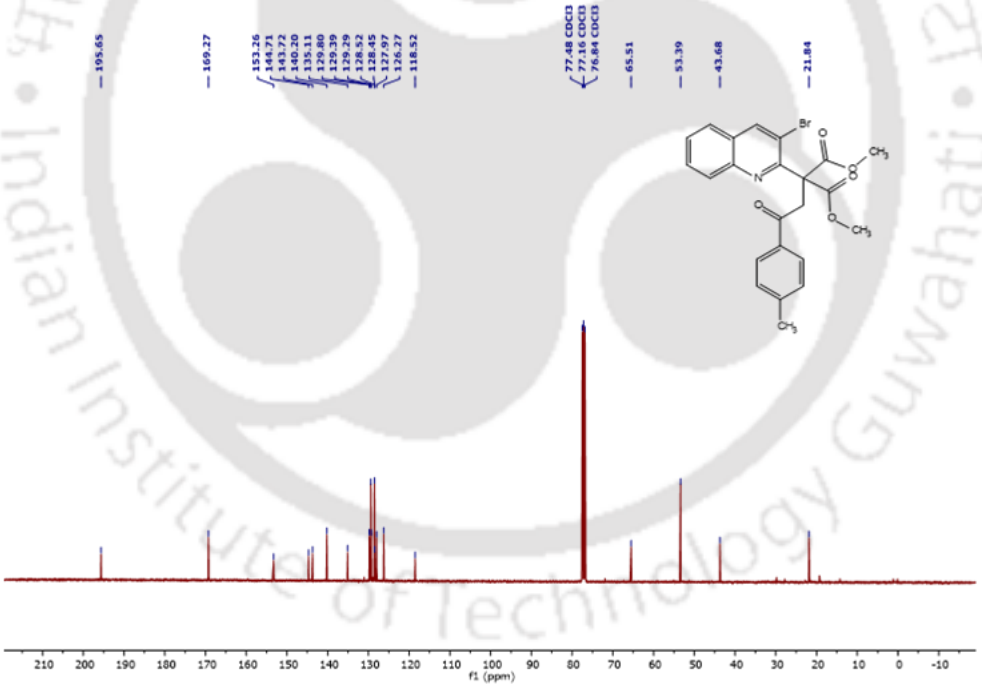


Figure S181. ^{13}C NMR Spectrum of **4.2g** ($CDCl_3$, 151 MHz, 298 K)

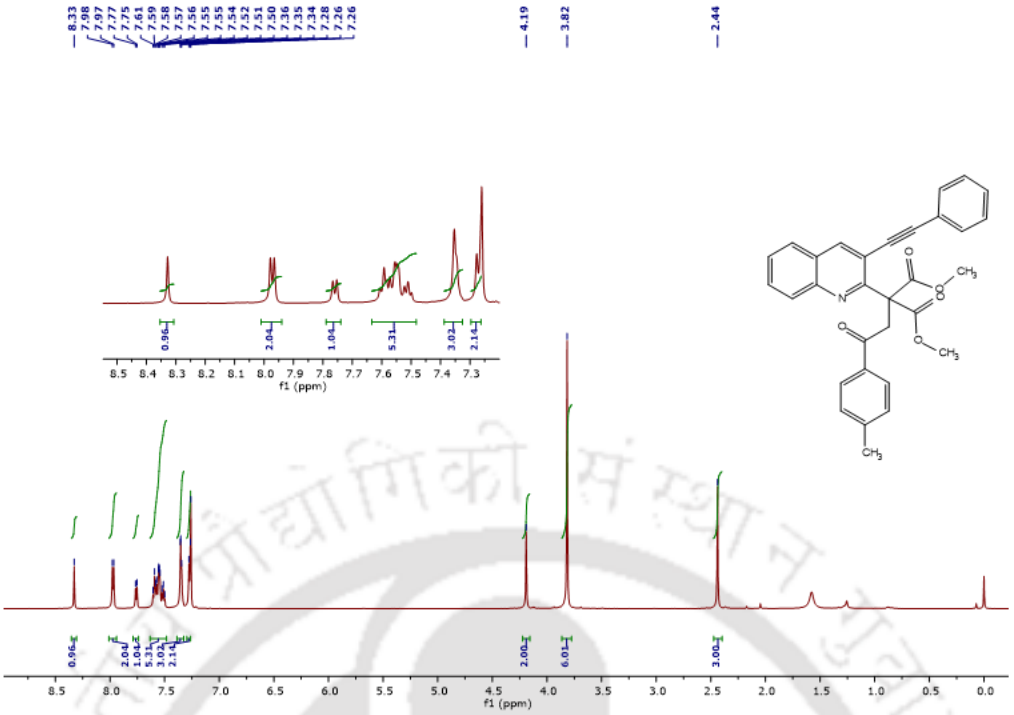


Figure S182. ^{1}H NMR Spectrum of **4.2h** ($CDCl_3$, 600 MHz, 298 K)

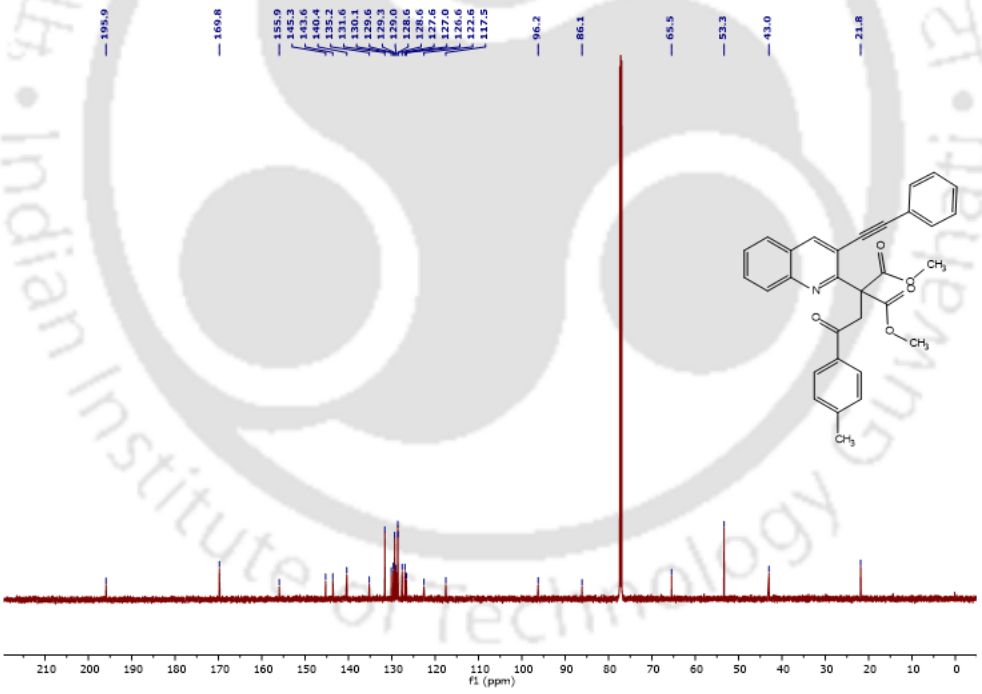


Figure S183. ^{13}C NMR Spectrum of **4.2h** ($CDCl_3$, 151 MHz, 298 K)

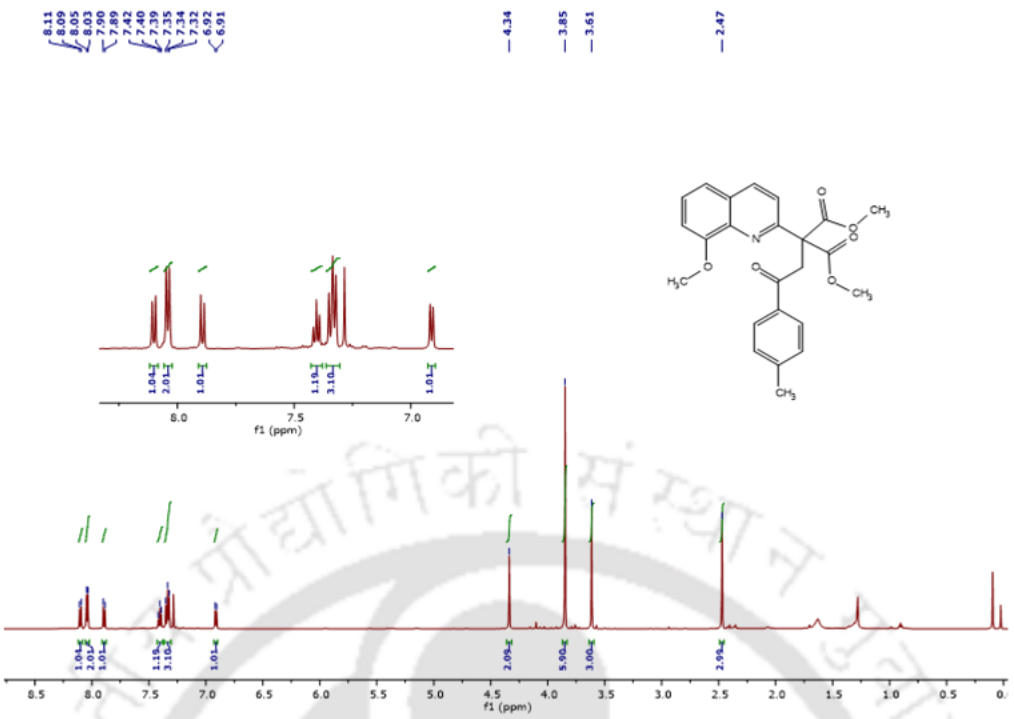


Figure S184. ^{1}H NMR Spectrum of **4.2i** ($CDCl_3$, 400 MHz, 298 K)

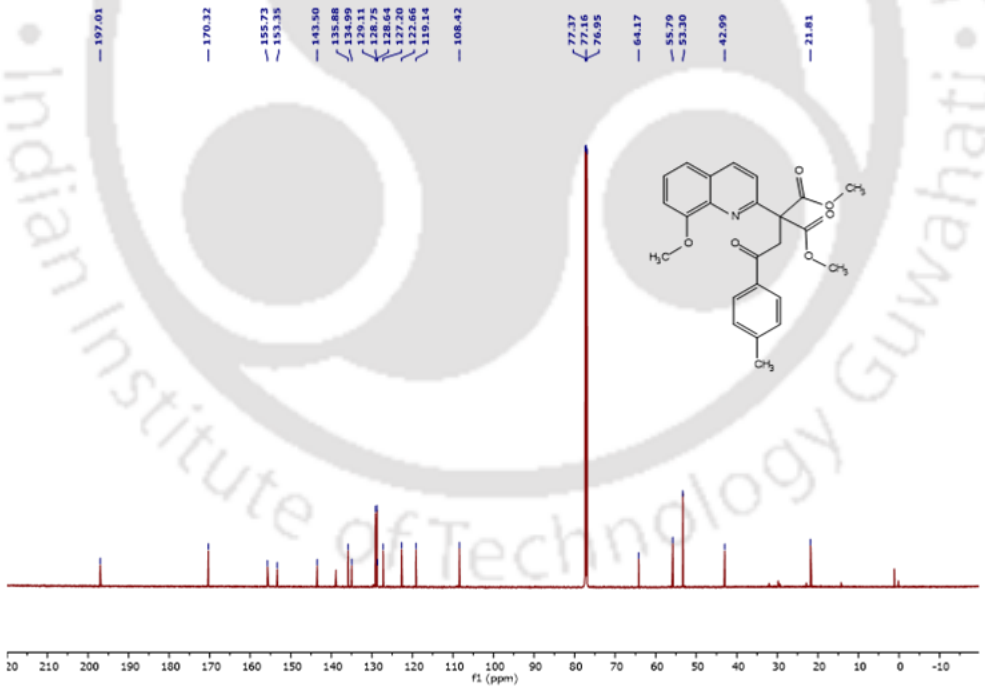


Figure S185. ^{13}C NMR Spectrum of **4.2i** ($CDCl_3$, 101 MHz, 298 K)

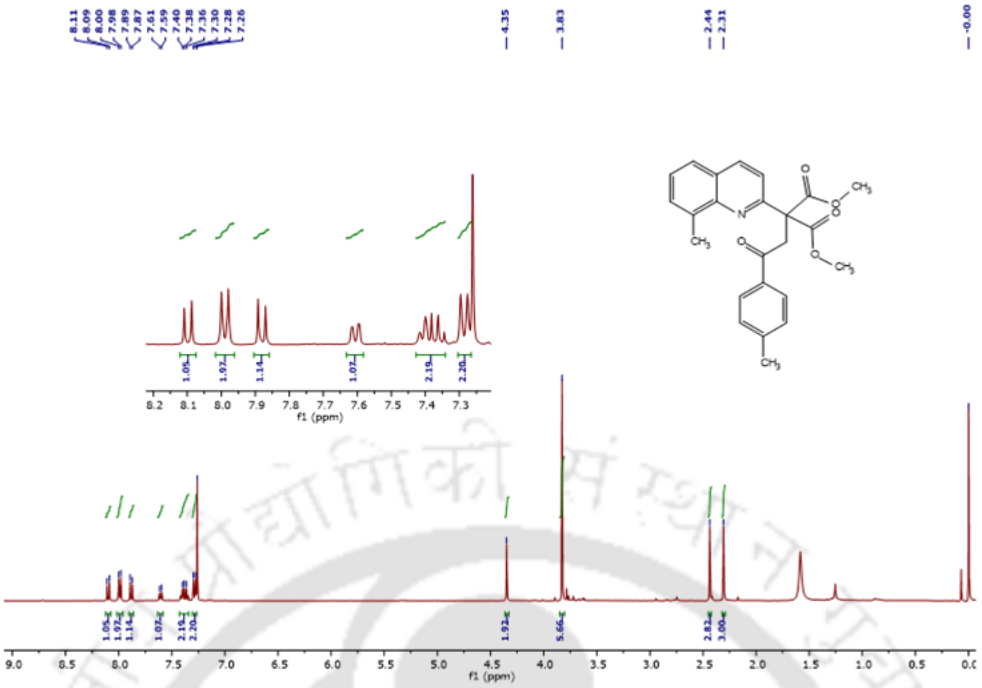


Figure S186. ^{1}H NMR Spectrum of **4.2j** ($CDCl_3$, 600 MHz, 298 K)

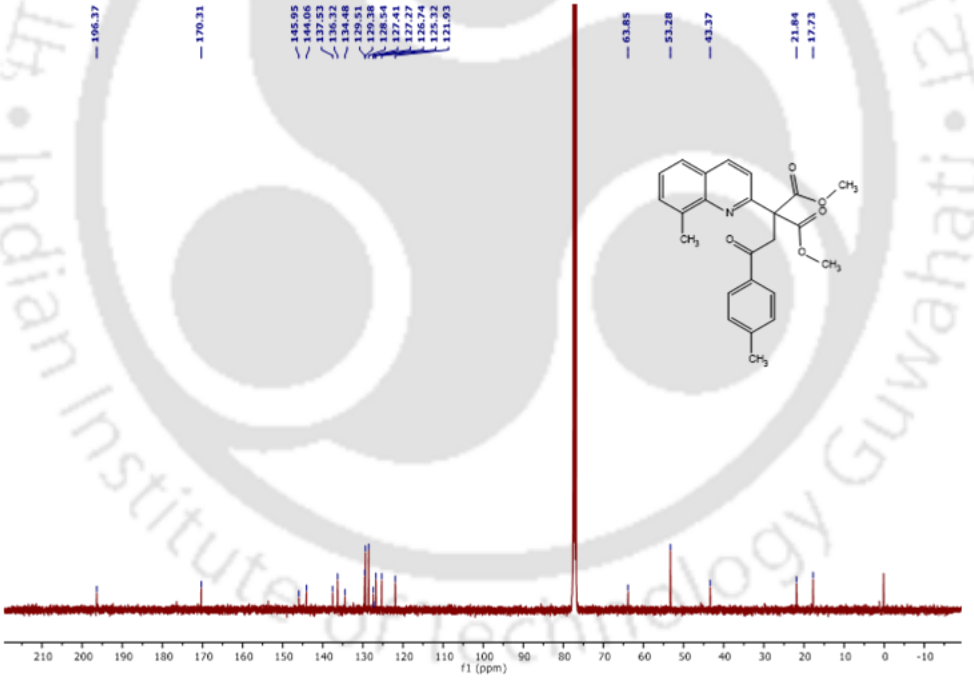


Figure S187. ^{13}C NMR Spectrum of **4.2j** ($CDCl_3$, 151 MHz, 298 K)

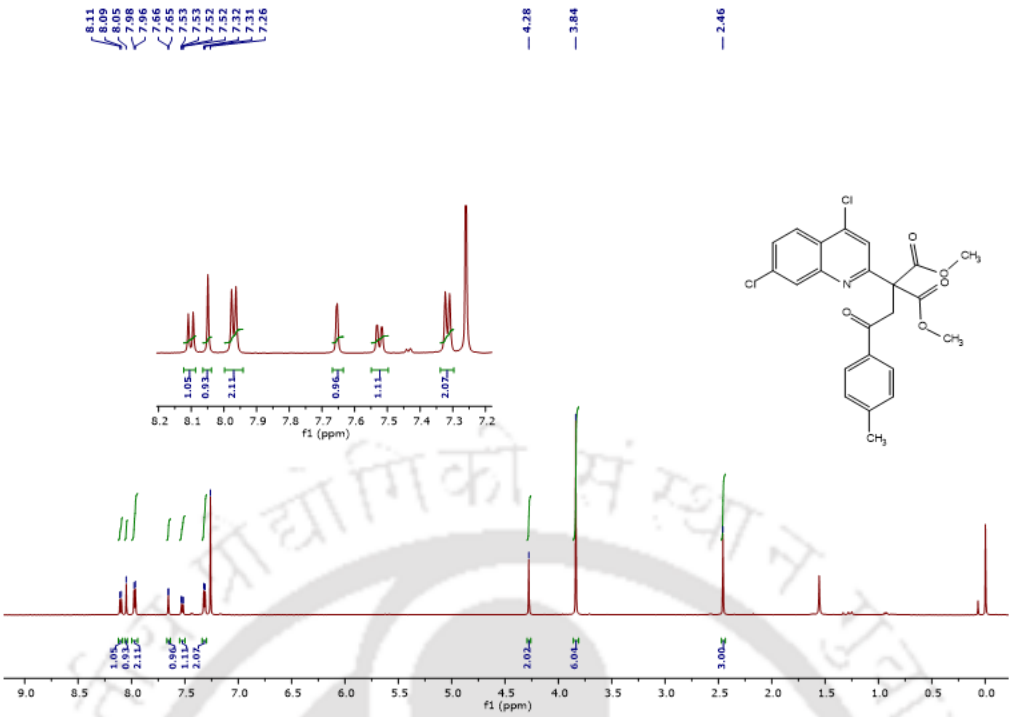


Figure S188. ^{1}H NMR Spectrum of **4.2k** ($CDCl_3$, 600 MHz, 298 K)

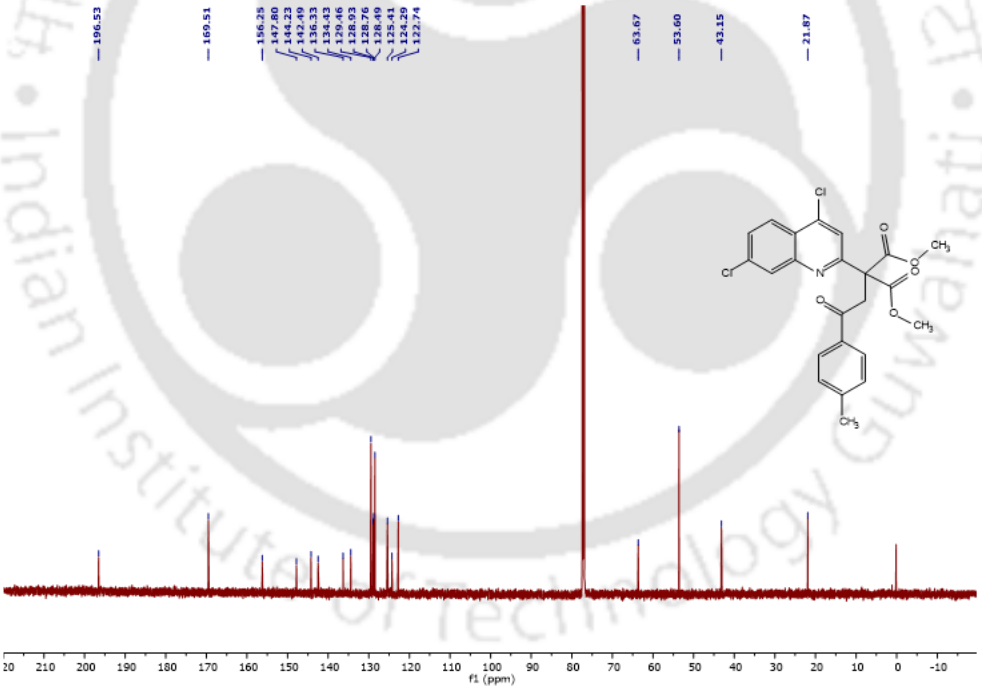


Figure S189. ^{13}C NMR Spectrum of **4.2k** ($CDCl_3$, 151 MHz, 298 K)

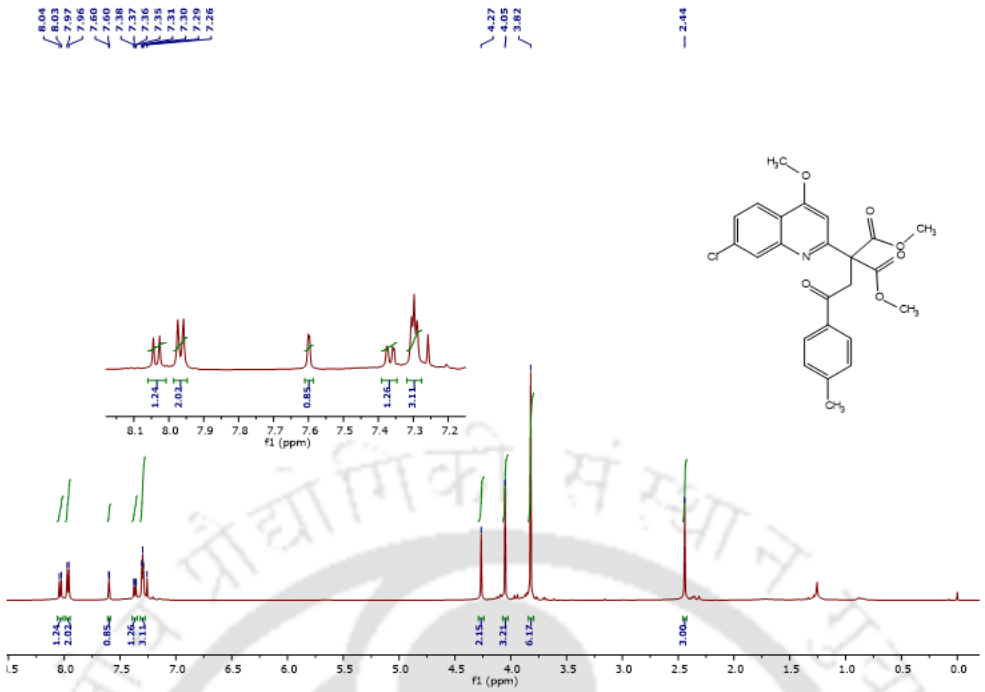


Figure S190. ^{1}H NMR Spectrum of **4.2l** ($CDCl_3$, 400 MHz, 298 K)

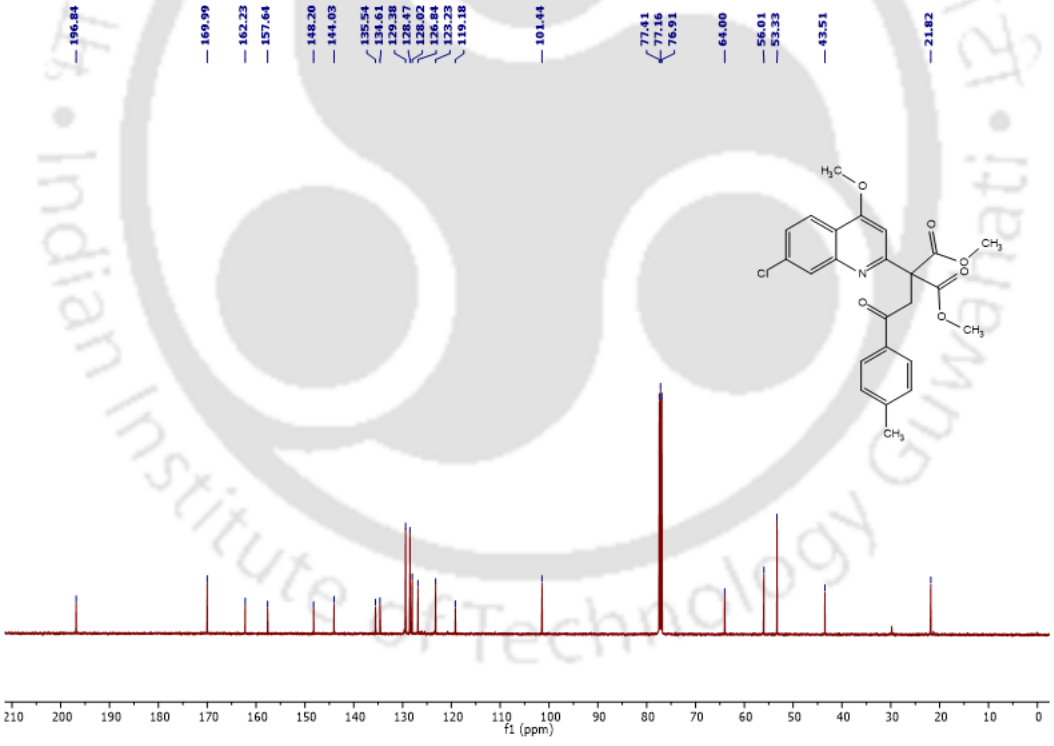


Figure S191. ^{13}C NMR Spectrum of **4.2l** ($CDCl_3$, 101 MHz, 298 K)

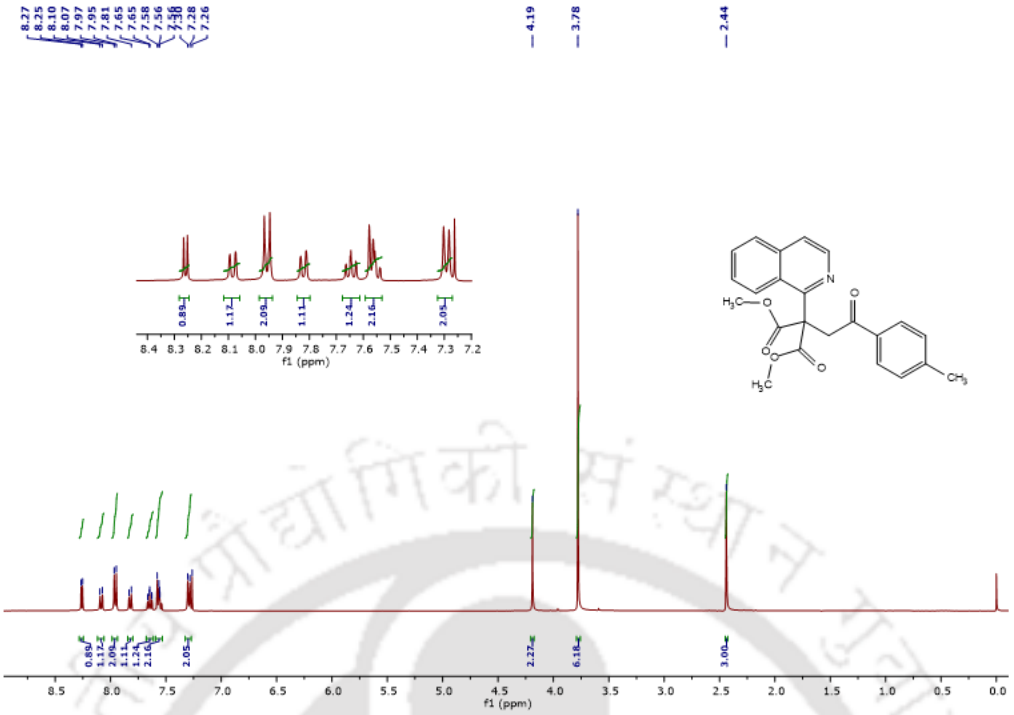


Figure S192. ^{1}H NMR Spectrum of **4.3a** ($CDCl_3$, 400 MHz, 298 K)

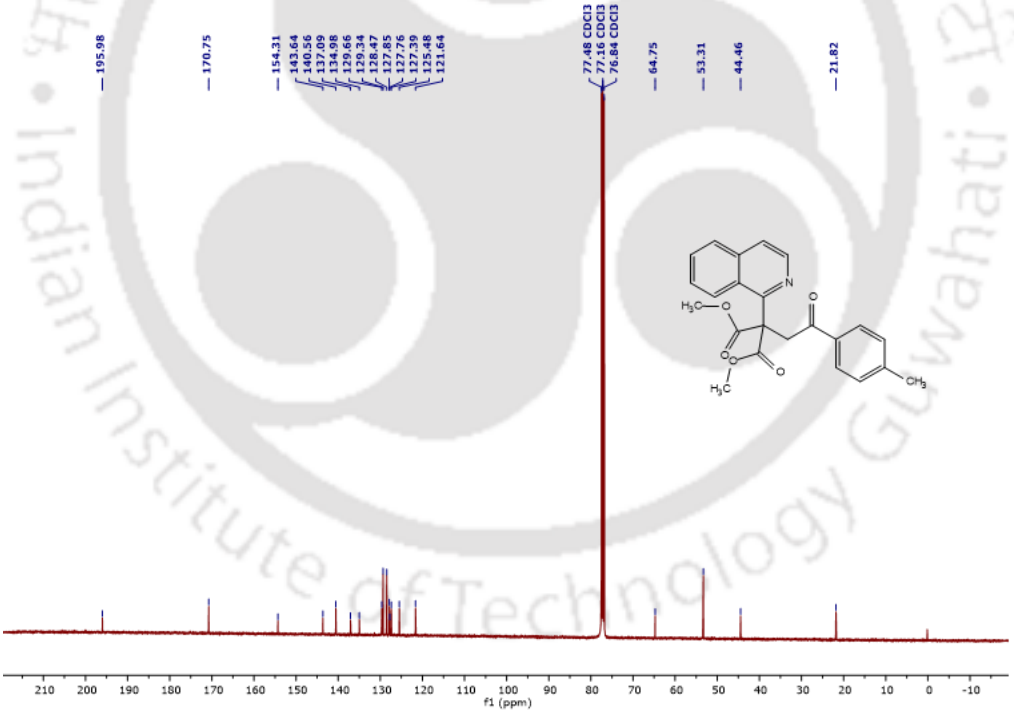


Figure S193. ^{13}C NMR Spectrum of **4.3a** ($CDCl_3$, 101 MHz, 298 K)

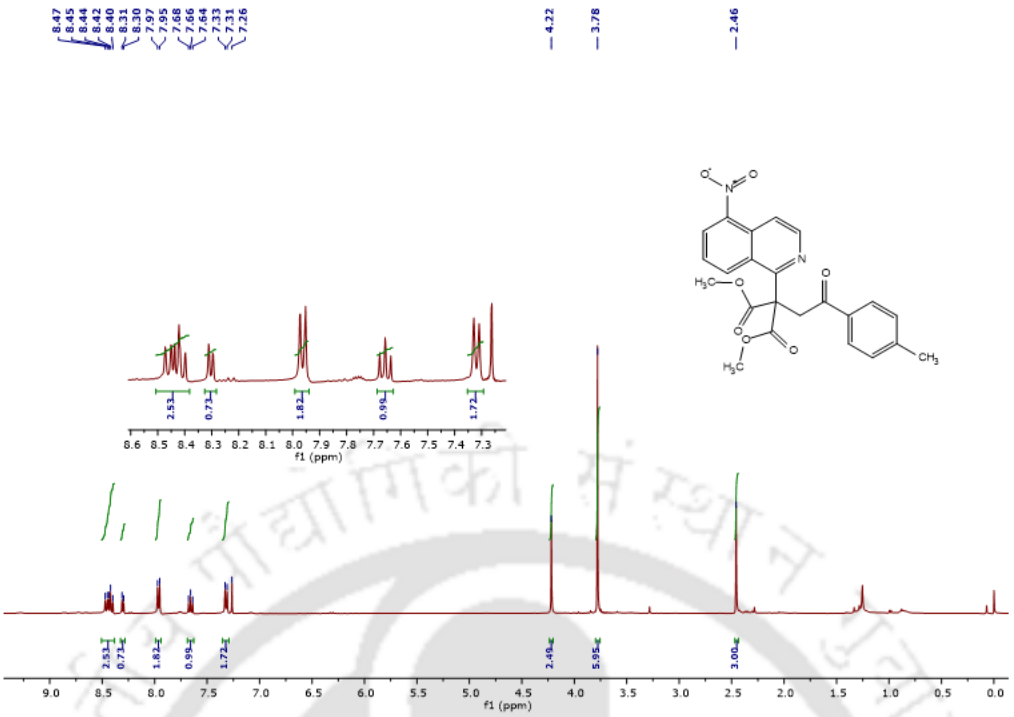


Figure S194. ^{1}H NMR Spectrum of **4.3b** ($CDCl_3$, 400 MHz, 298 K)

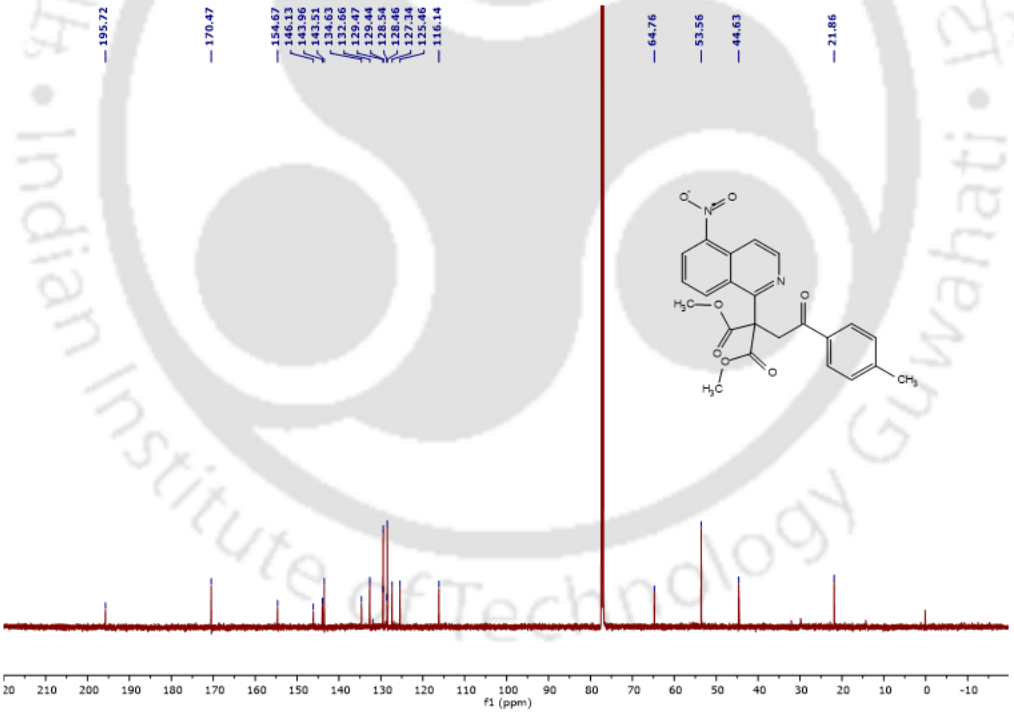


Figure S195. ^{13}C NMR Spectrum of **4.3b** ($CDCl_3$, 151 MHz, 298 K)

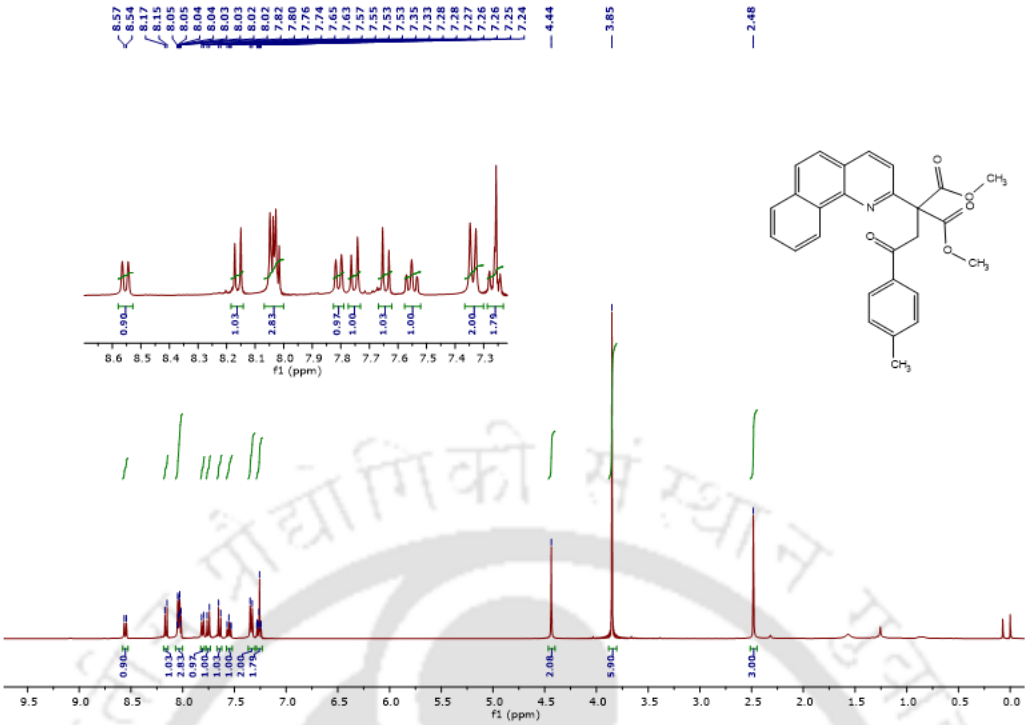


Figure S196. ^{1}H NMR Spectrum of **4.3c** ($CDCl_3$, 600 MHz, 298 K)

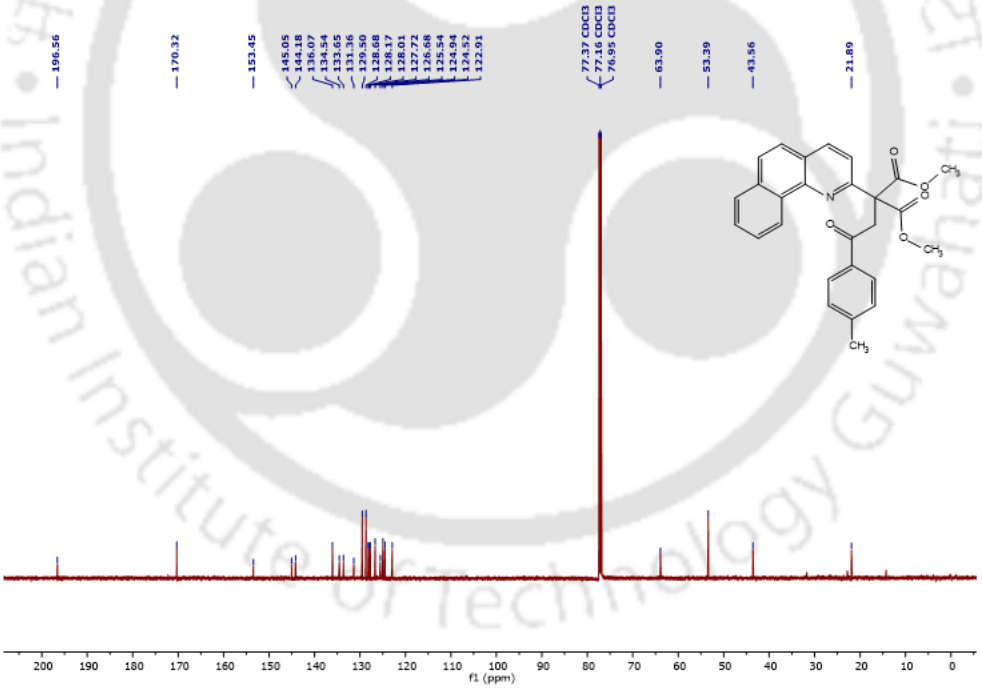


Figure S197. ^{13}C NMR Spectrum of **4.3c** ($CDCl_3$, 151 MHz, 298 K)

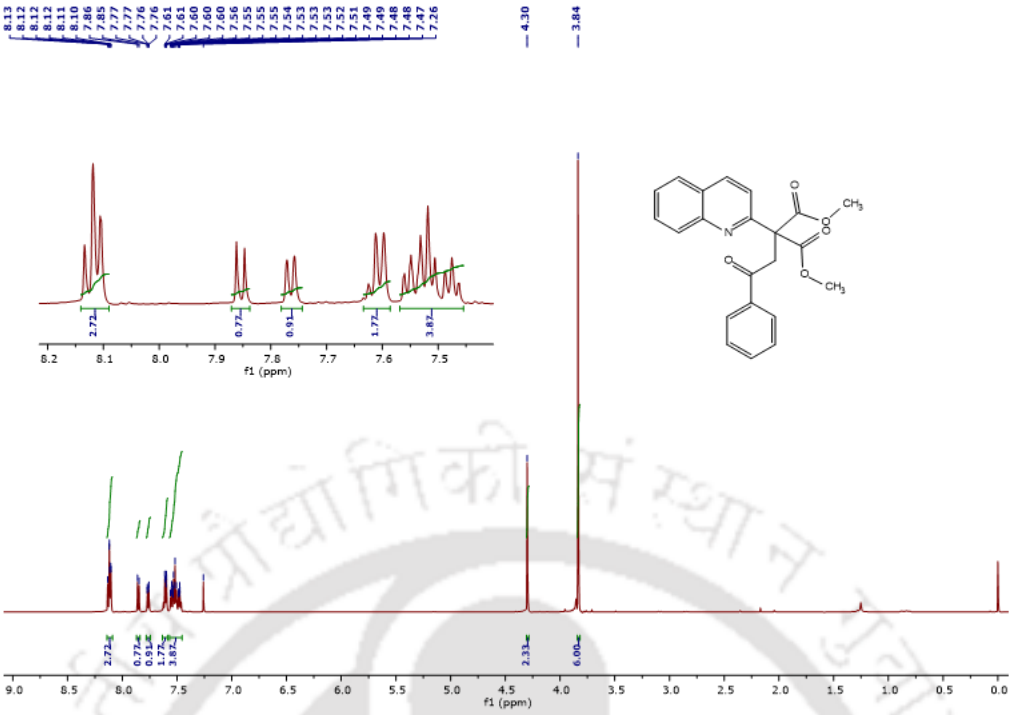


Figure S198. ^{1}H NMR Spectrum of **4.4a** ($CDCl_3$, 600 MHz, 298 K)

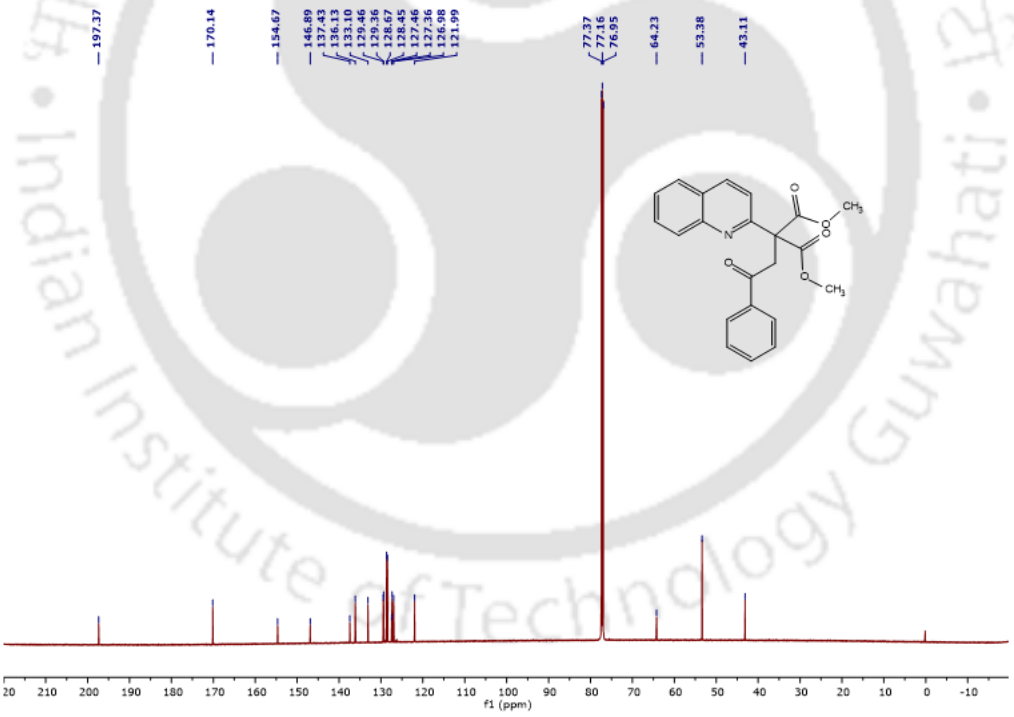


Figure S199. ^{13}C NMR Spectrum of **4.4a** ($CDCl_3$, 151 MHz, 298 K)

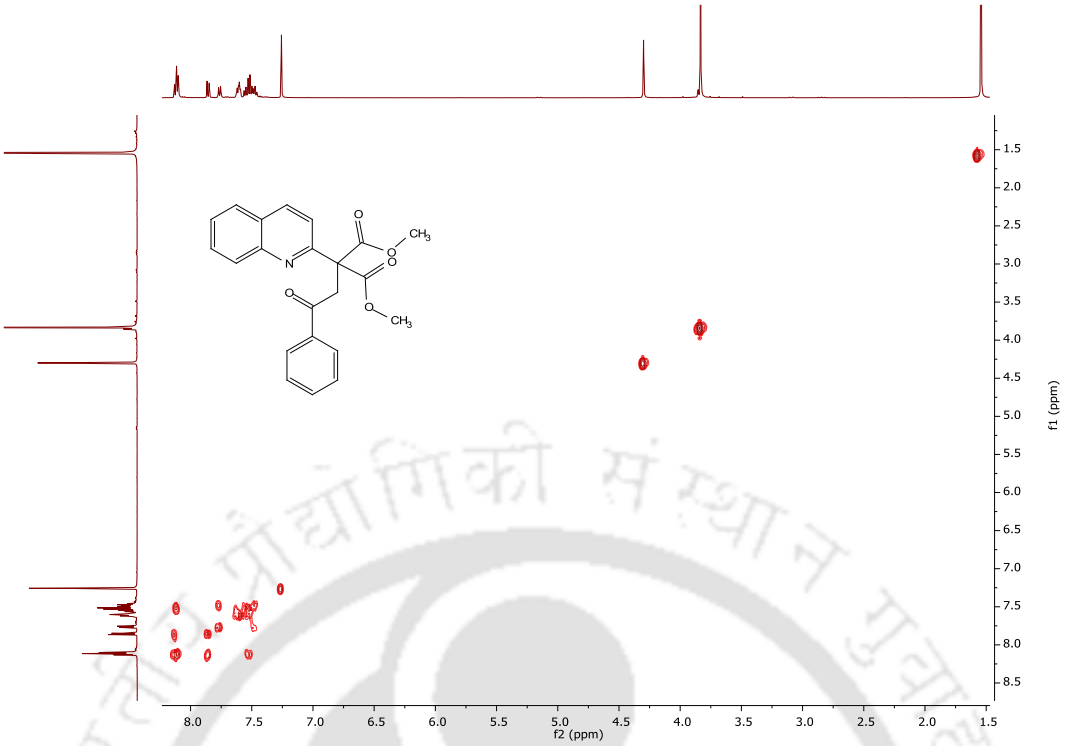


Figure S200. ^{1}H-^{1}H COSY NMR Spectrum of **4.4a** ($CDCl_3$, 298 K).

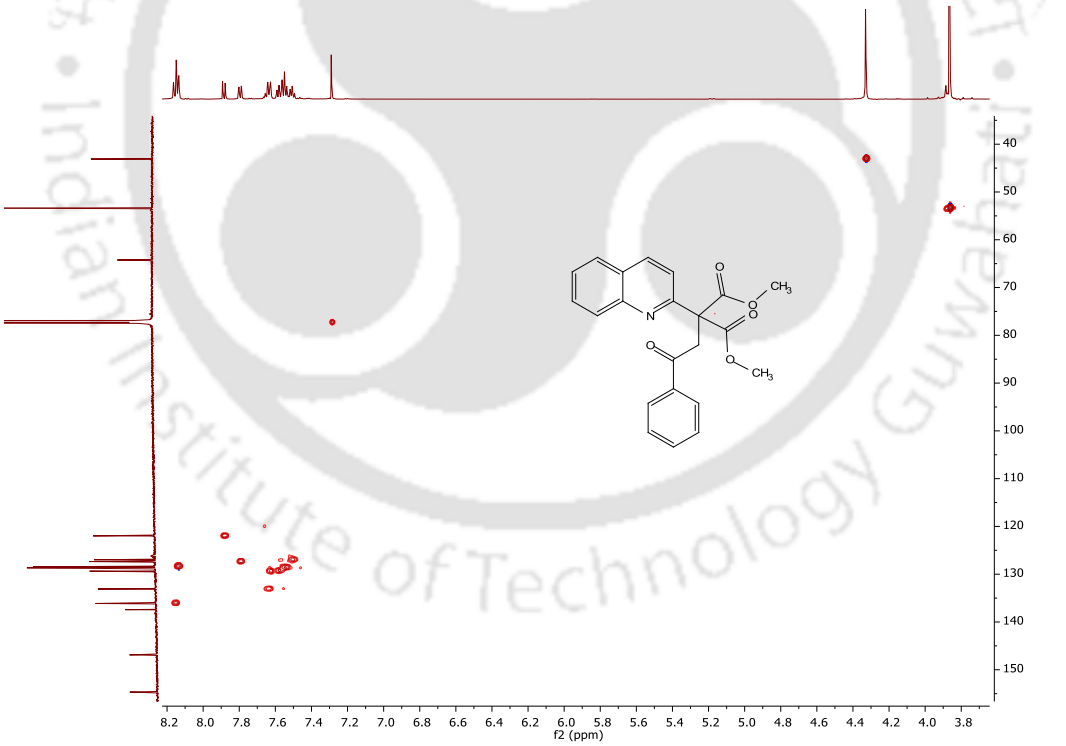


Figure S201. ^{1}H-^{13}C HSQC NMR Spectrum of **4.4a** ($CDCl_3$, 298 K).

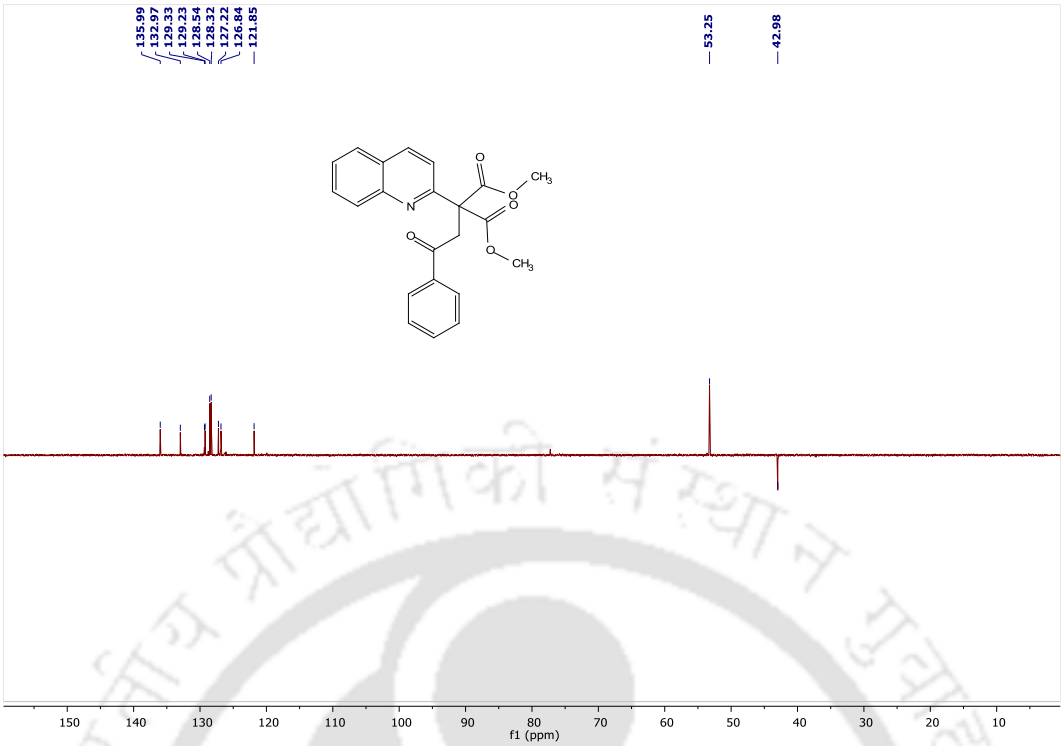


Figure S202. ^{13}C DEPT-135 NMR Spectrum of **4.4a** ($CDCl_3$, 298 K).

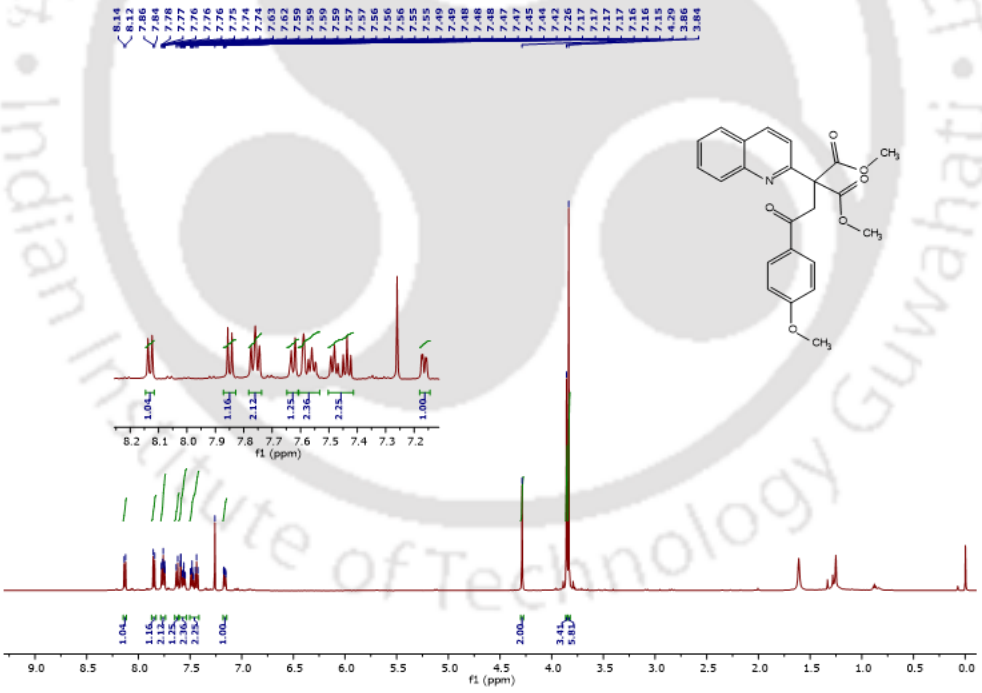


Figure S203. ^{1}H NMR Spectrum of **4.4b** ($CDCl_3$, 400 MHz, 298 K)

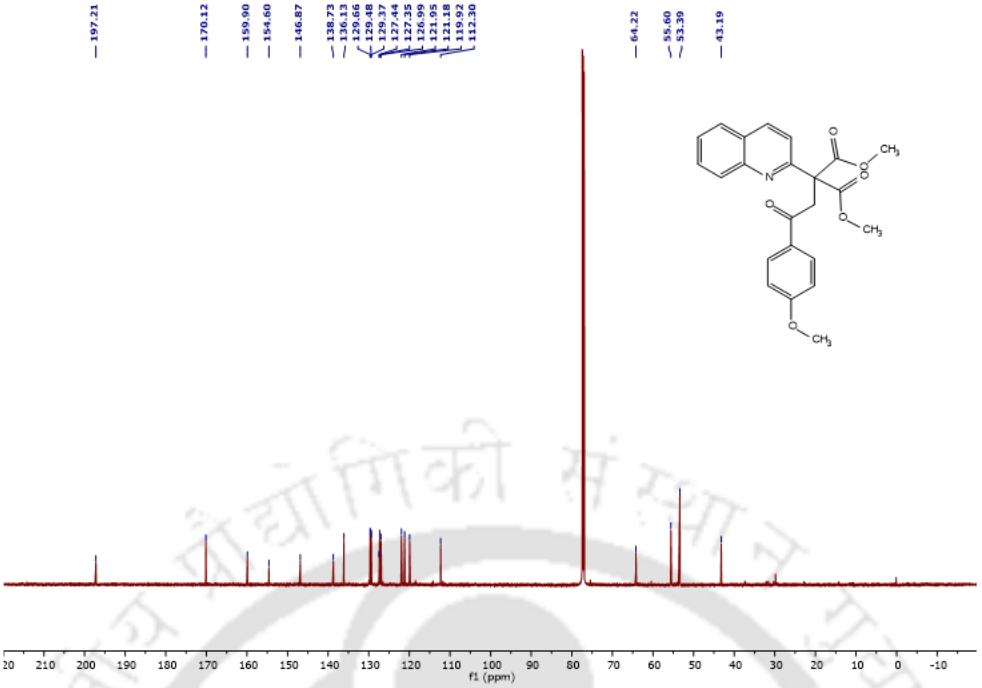


Figure S204. ^{13}C NMR Spectrum of **4.4b** ($CDCl_3$, 101 MHz, 298 K)

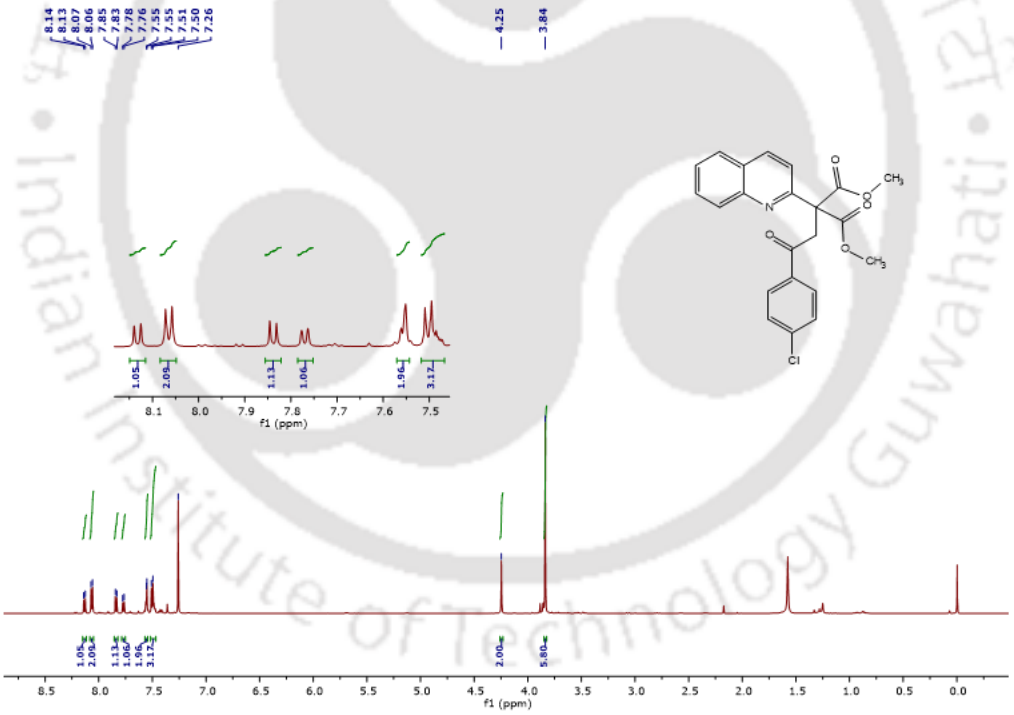


Figure S205. ^{1}H NMR Spectrum of **4.4c** ($CDCl_3$, 600 MHz, 298 K)

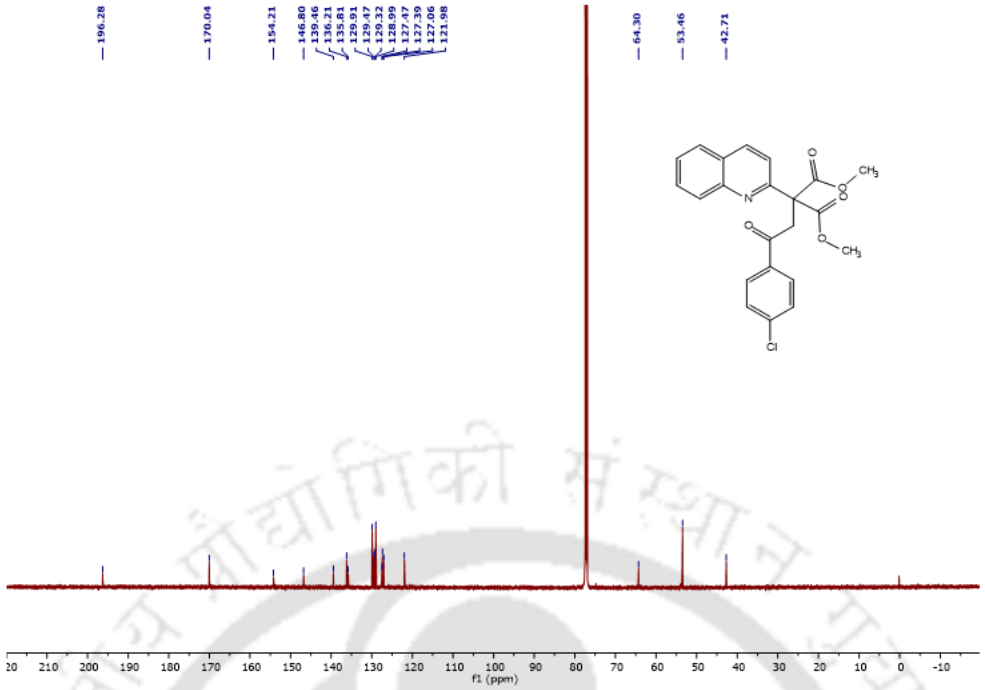


Figure S206. ^{13}C NMR Spectrum of **4.4c** ($CDCl_3$, 151 MHz, 298 K)

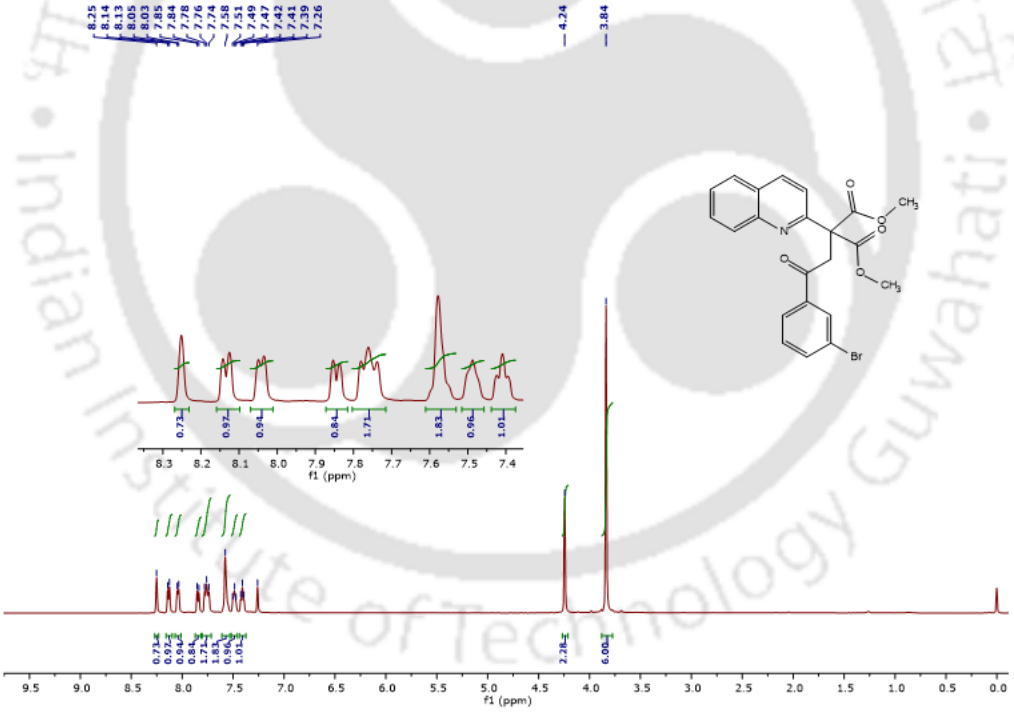


Figure S207. ^{1}H NMR Spectrum of **4.4d** ($CDCl_3$, 500 MHz, 298 K)

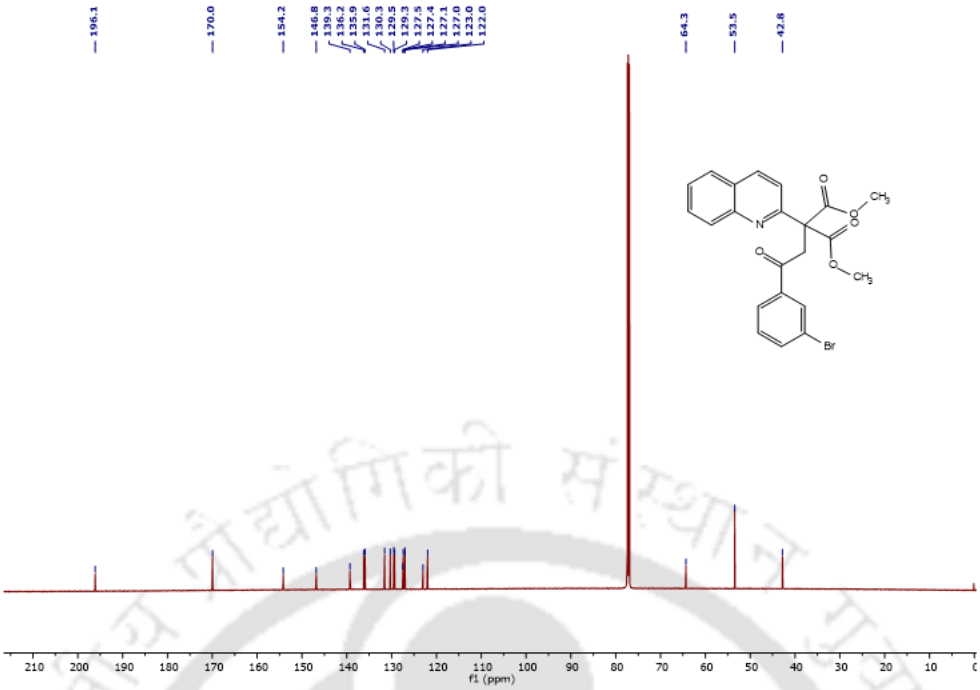


Figure S208. ^{13}C NMR Spectrum of **4.4d** ($CDCl_3$, 151 MHz, 298 K)

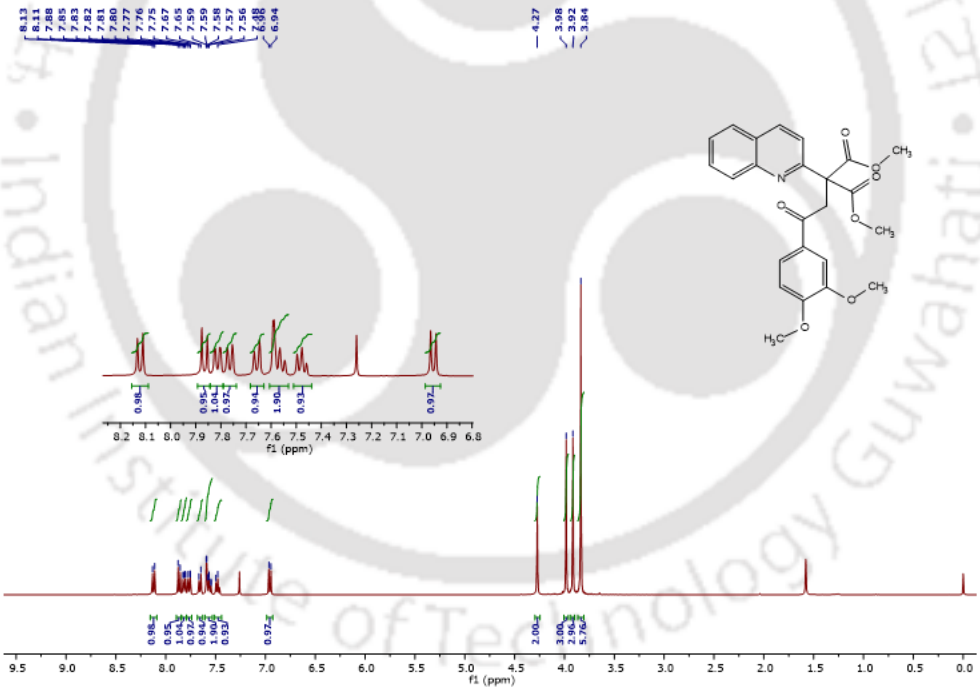


Figure S209. ^{1}H NMR Spectrum of **4.4e** ($CDCl_3$, 400 MHz, 298 K)

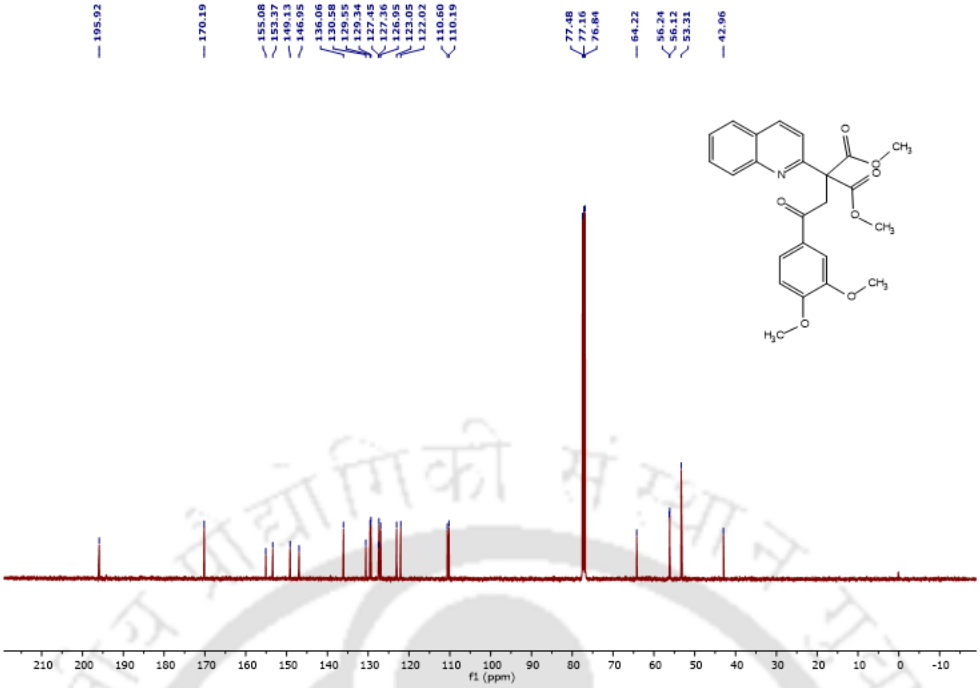


Figure S210. ^{13}C NMR Spectrum of **4.4e** ($CDCl_3$, 101 MHz, 298 K)

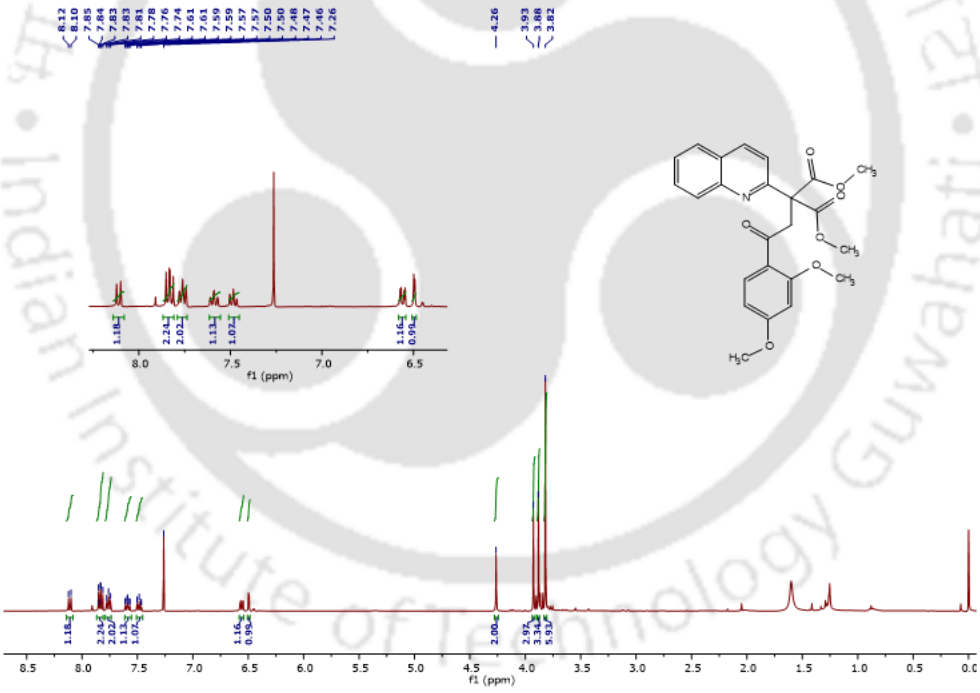


Figure S211. ^{1}H NMR Spectrum of **4.4f** ($CDCl_3$, 400 MHz, 298 K)

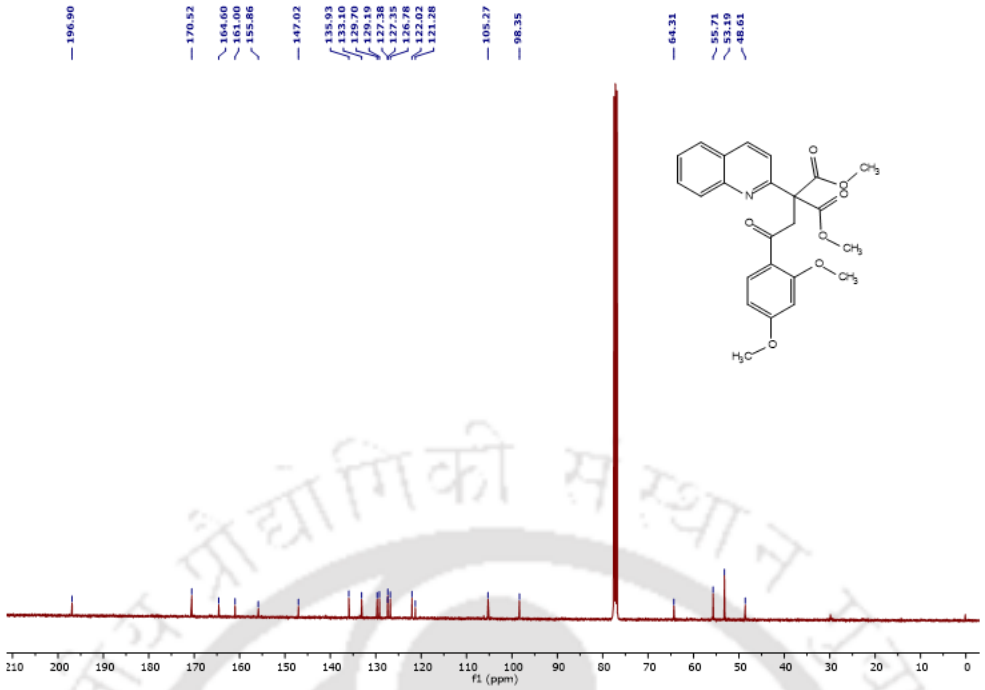


Figure S212. ^{13}C NMR Spectrum of **4.4f** ($CDCl_3$, 101 MHz, 298 K)

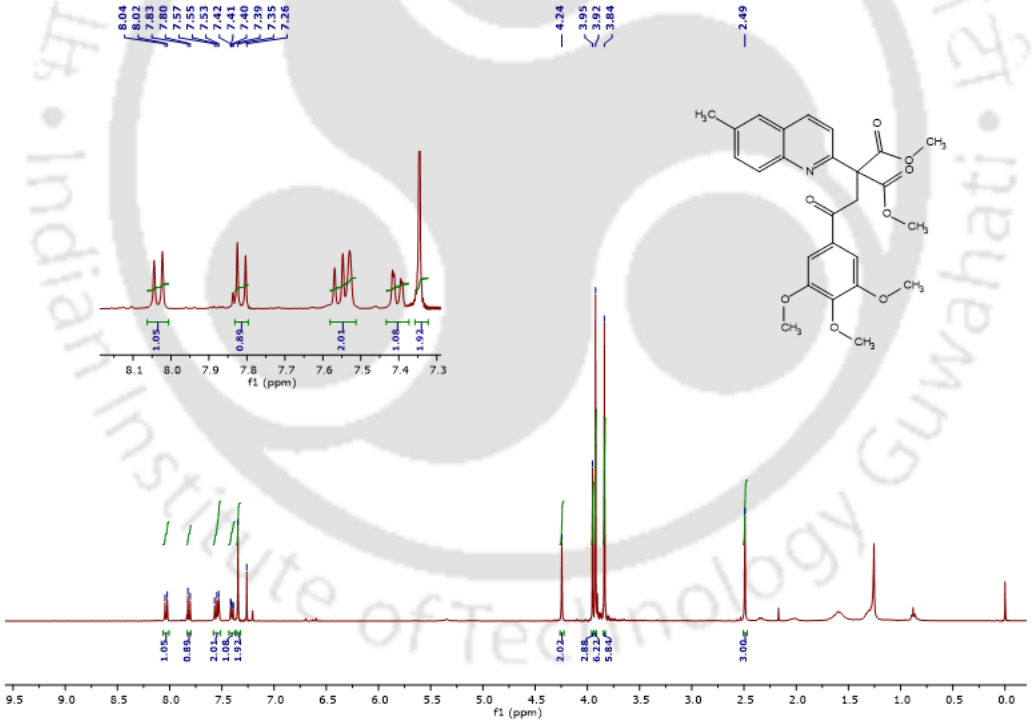


Figure S213. ^{1}H NMR Spectrum of **4.4g** ($CDCl_3$, 400 MHz, 298 K)

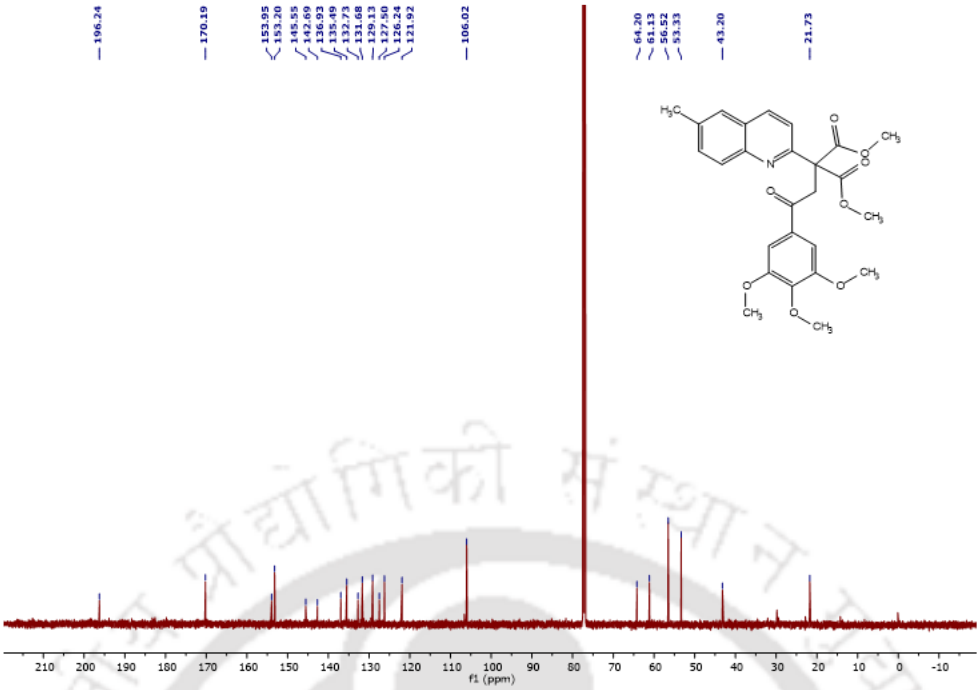


Figure S214. ^{13}C NMR Spectrum of **4.4g** ($CDCl_3$, 126 MHz, 298 K)

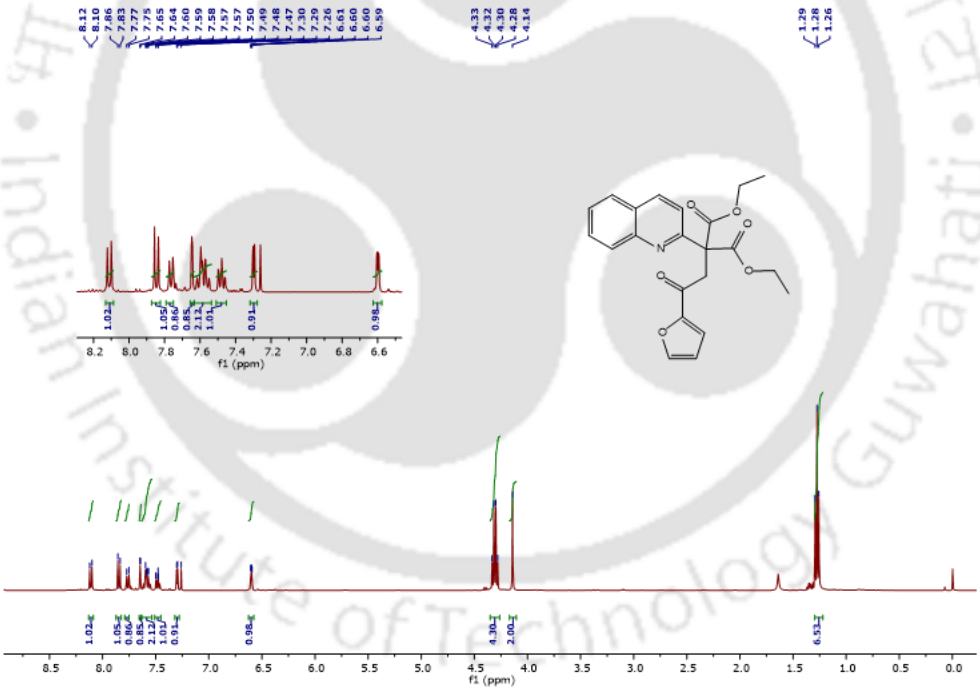


Figure S215. ^{1}H NMR Spectrum of **4.4i** ($CDCl_3$, 400 MHz, 298 K)

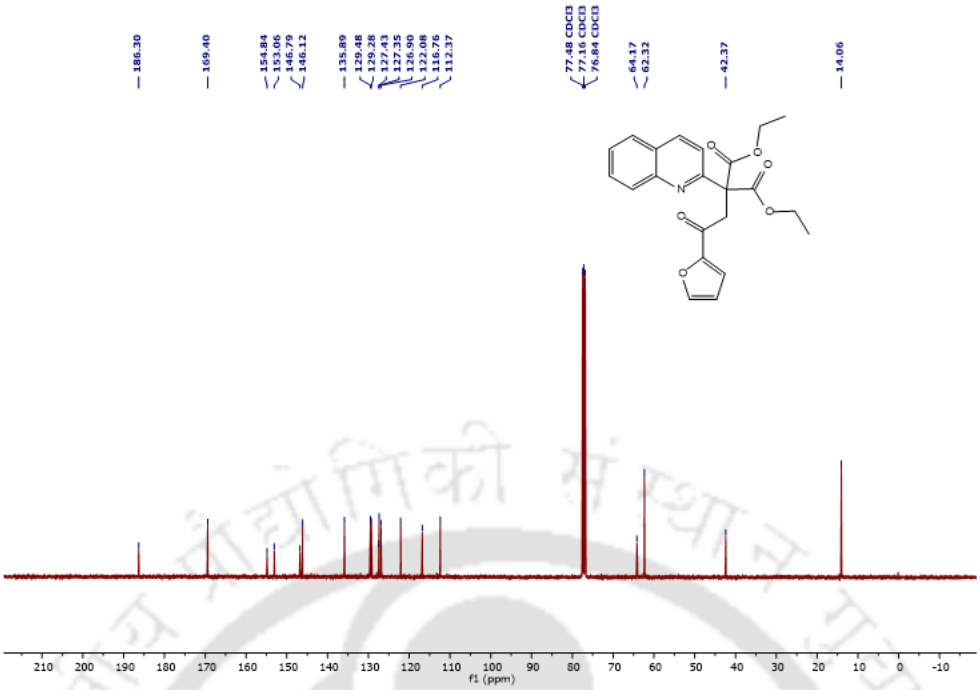


Figure S216. ^{13}C NMR Spectrum of **4.4i** ($CDCl_3$, 101 MHz, 298 K)

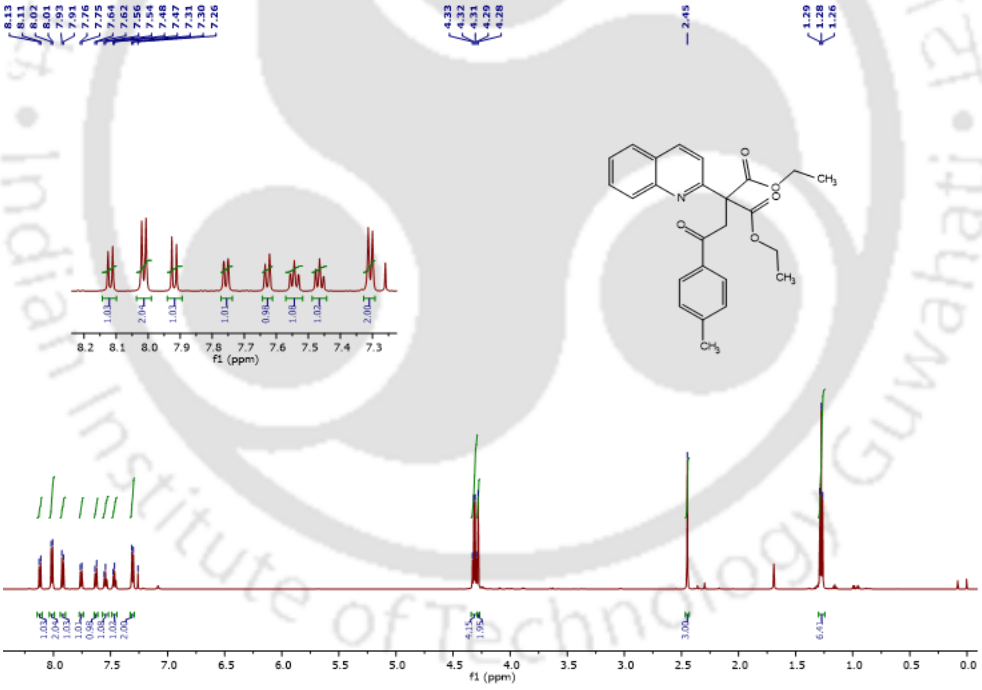


Figure S217. ^{1}H NMR Spectrum of **4.4j** ($CDCl_3$, 600 MHz, 298 K)

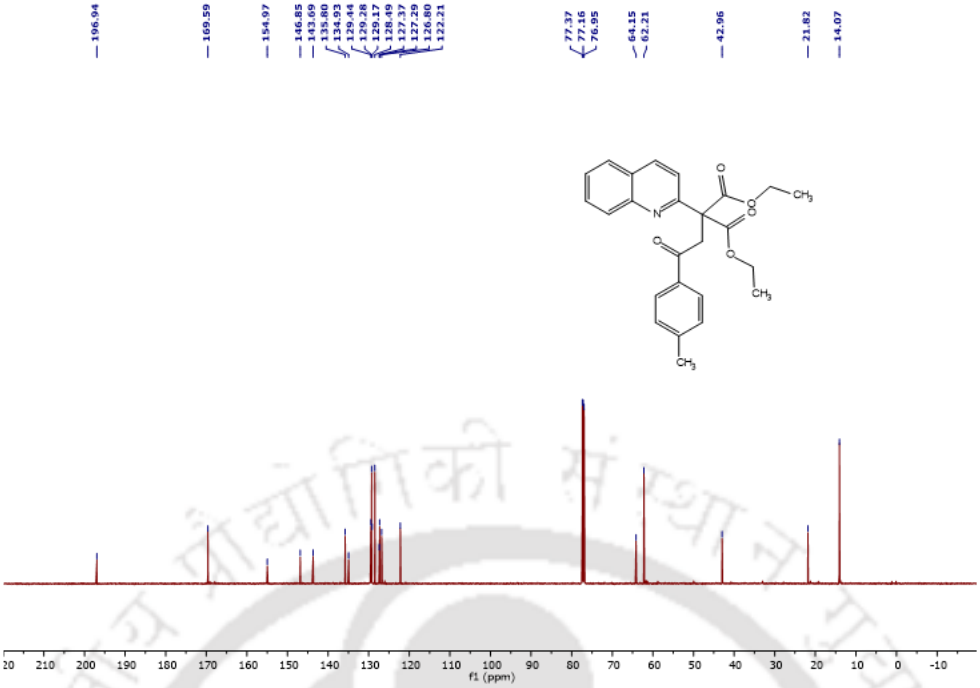


Figure S218. ^{13}C NMR Spectrum of **4.4j** ($CDCl_3$, 151 MHz, 298 K)

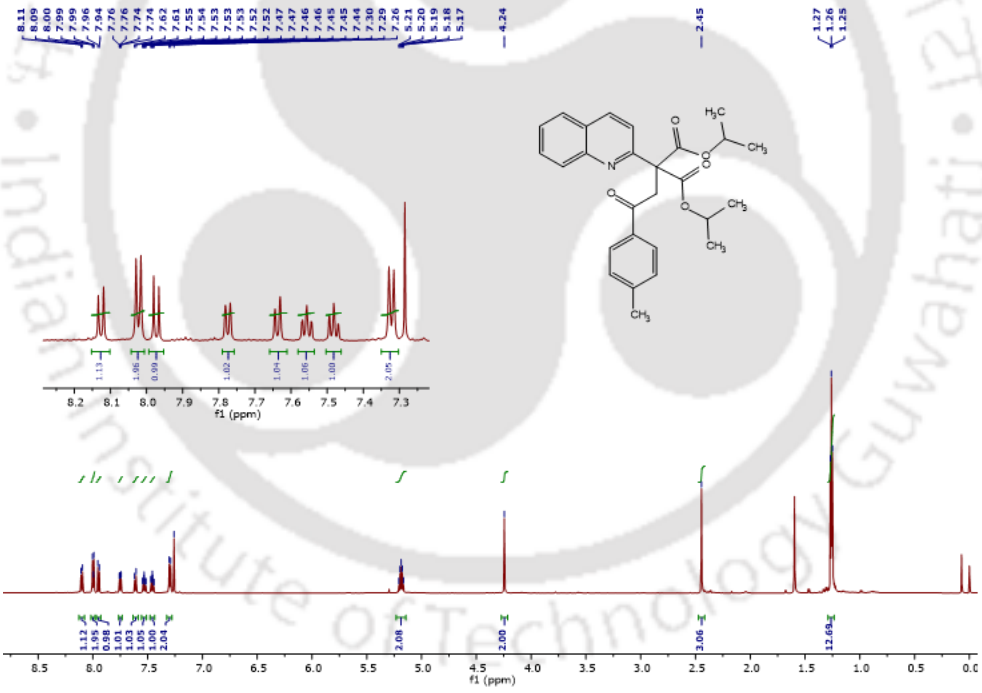


Figure S219. ^{1}H NMR Spectrum of **4.4k** ($CDCl_3$, 600 MHz, 298 K)

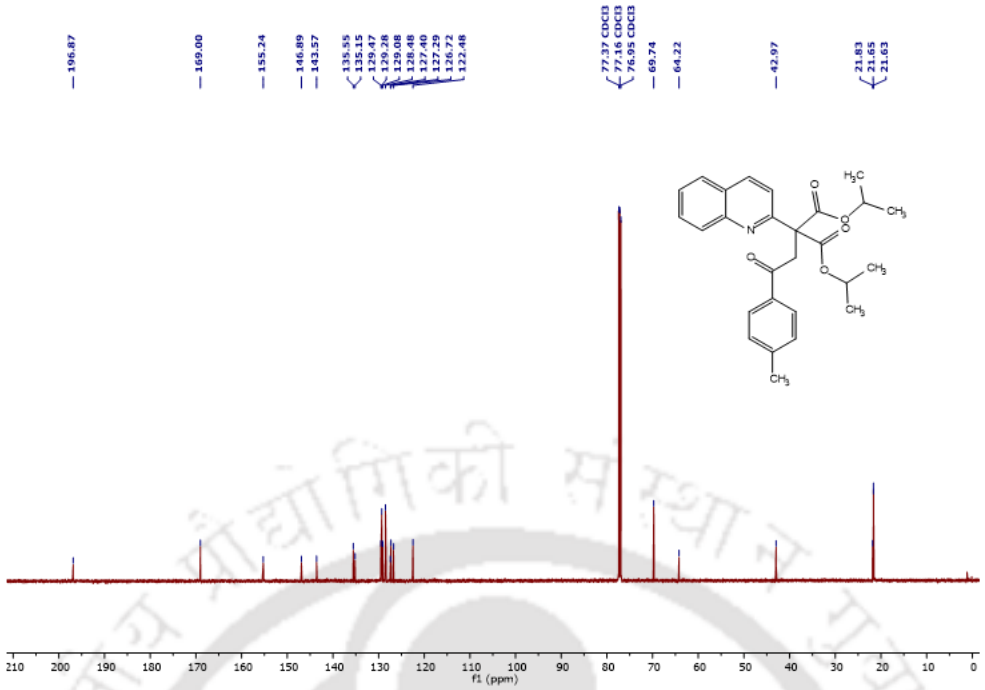


Figure S220. ^{13}C NMR Spectrum of **4.4k** ($CDCl_3$, 151 MHz, 298 K)

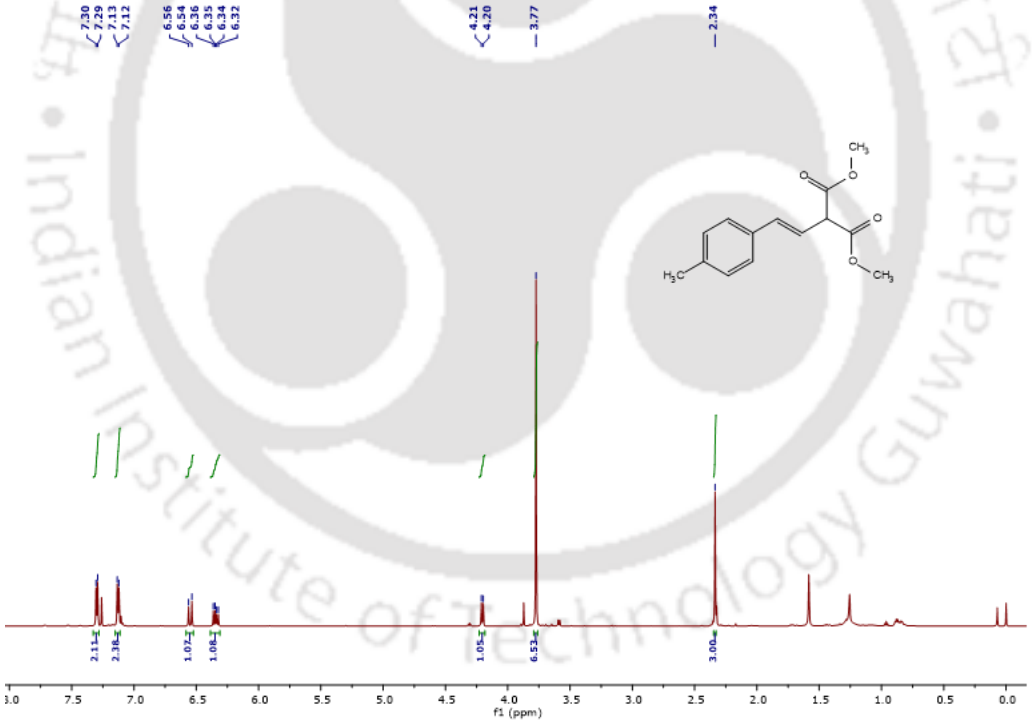


Figure S221. ^{1}H NMR Spectrum of **4.5** ($CDCl_3$, 600 MHz, 298 K).

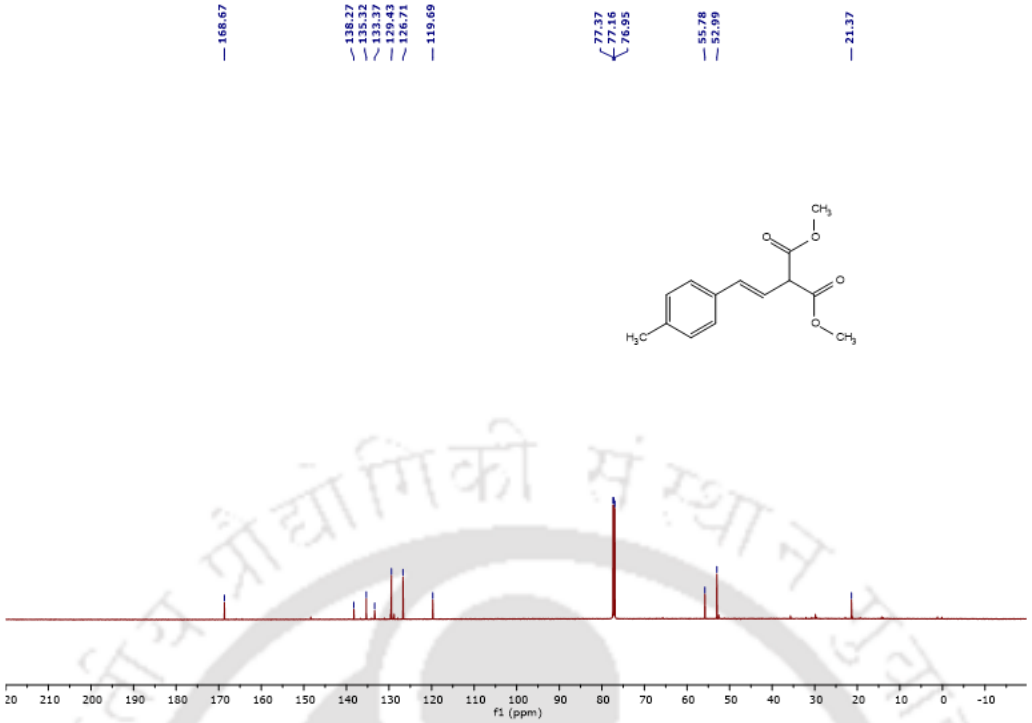


Figure S222. ^{1}H NMR Spectrum of **4.5** ($CDCl_3$, 151 MHz, 298 K).

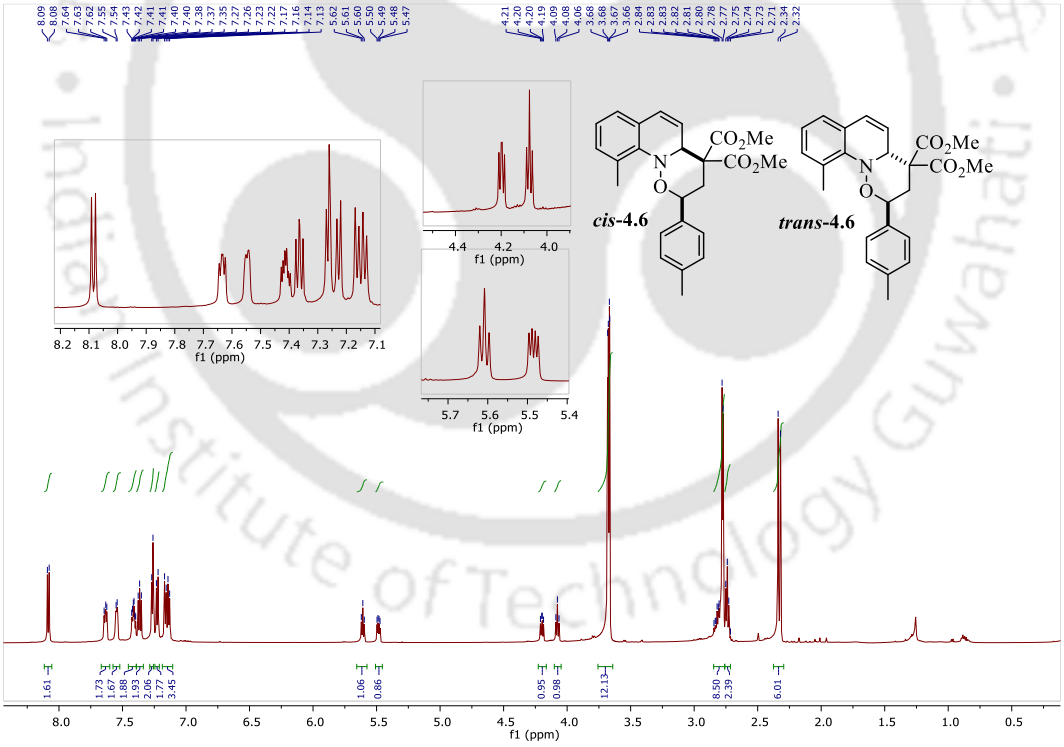


Figure S223. ^{1}H NMR Spectrum of **4.6** ($CDCl_3$, 600 MHz, 298 K)

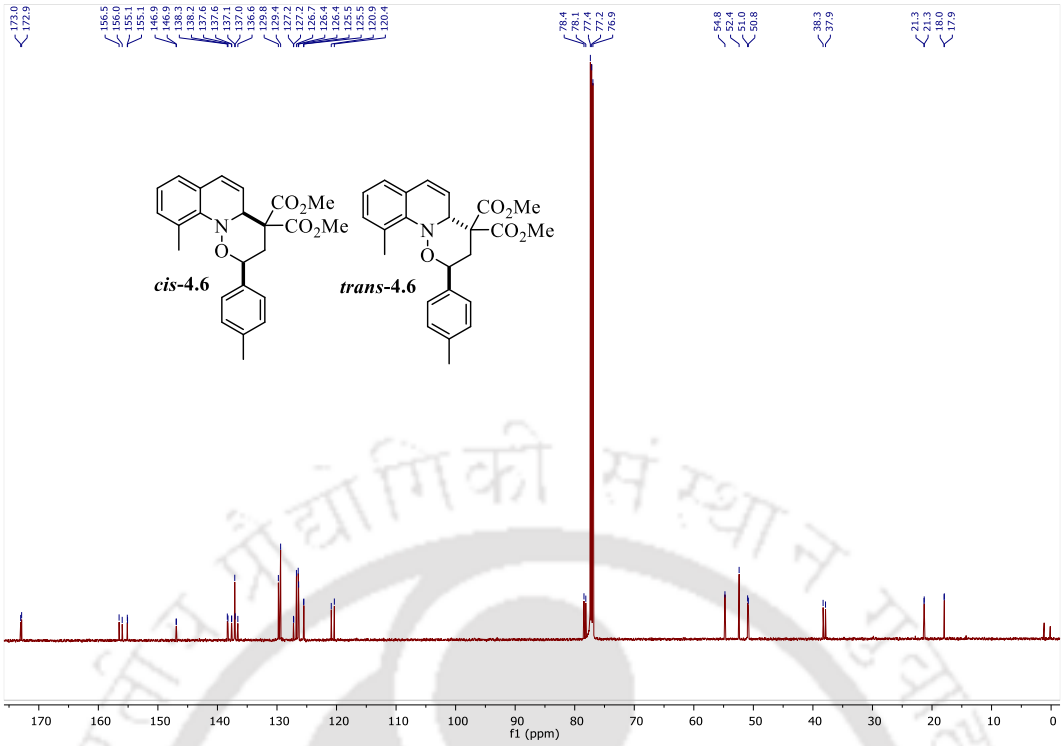


Figure S224. ^{13}C NMR Spectrum of **4.6** ($CDCl_3$, 151 MHz, 298 K)

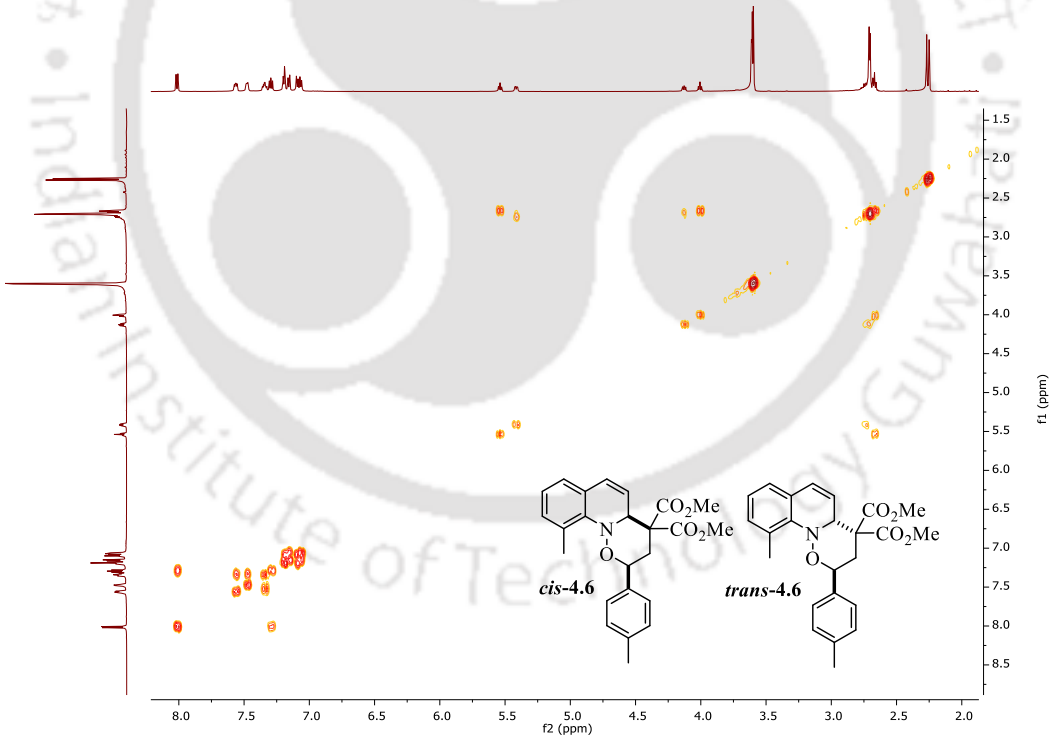


Figure S225. ^{1}H-^{1}H COSY NMR Spectrum of **4.6** ($CDCl_3$, 298 K).

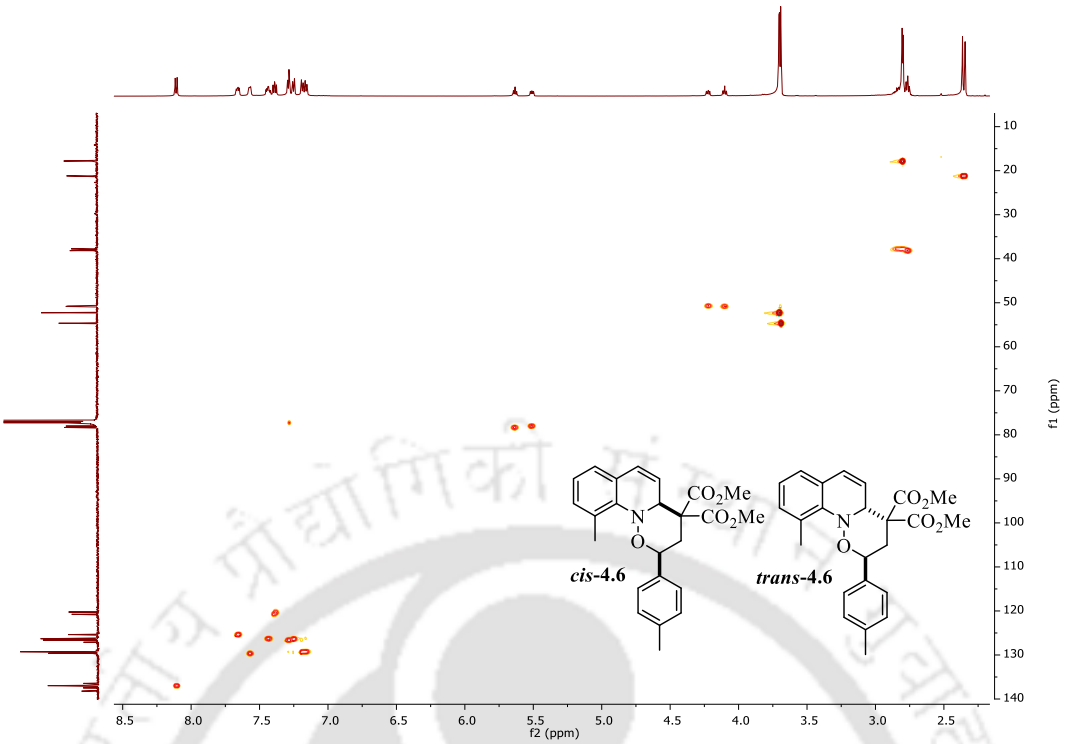


Figure S226. ^{1}H-^{13}C HSQC NMR Spectrum of **4.6** ($CDCl_3$, 298 K).

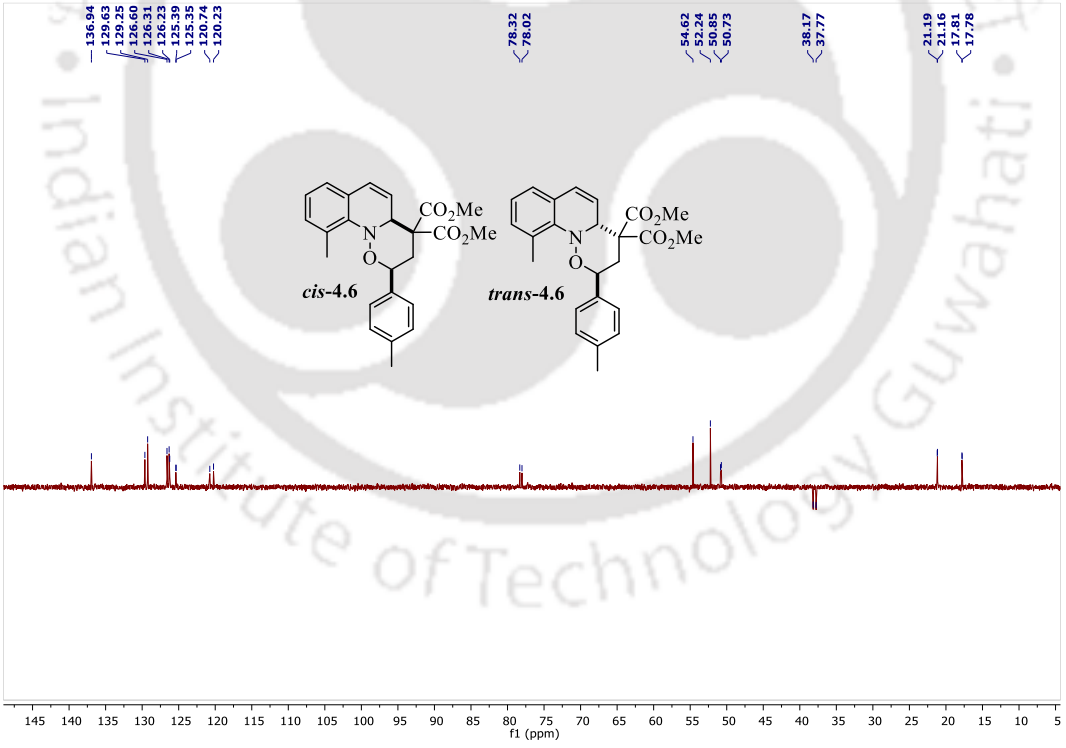


Figure S227. ^{13}C DEPT-135 NMR Spectrum of **4.6** ($CDCl_3$, 298 K).

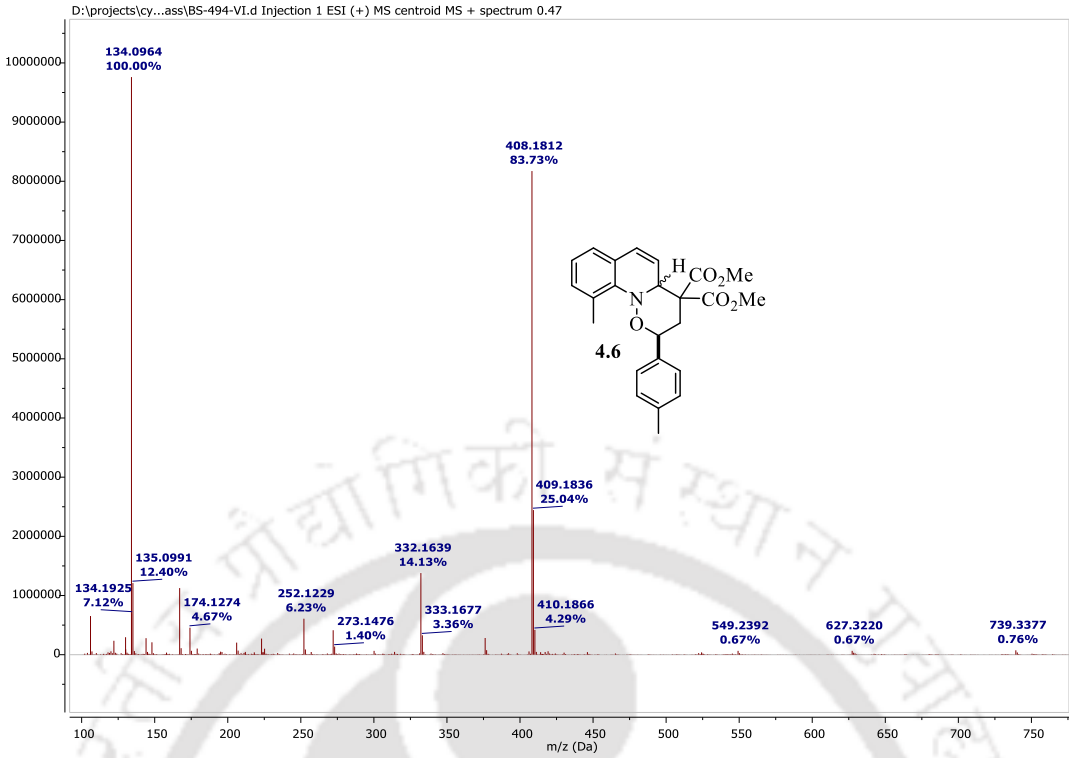


Figure S228. HRMS Spectrum of **4.6**.

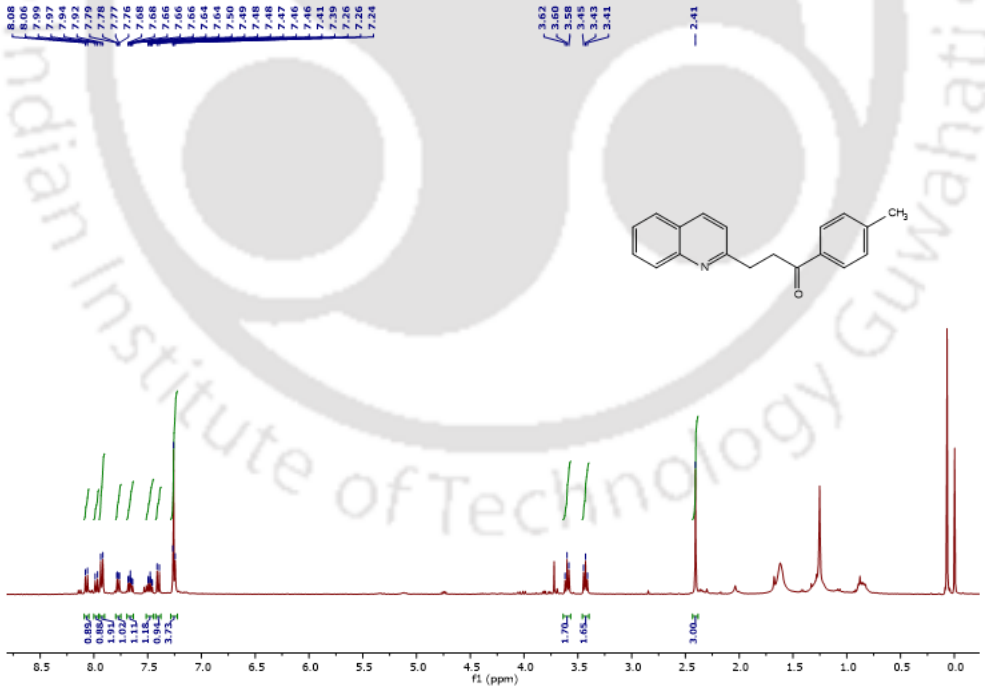


Figure S229. ^{1}H NMR Spectrum of **4.8** ($CDCl_3$, 400 MHz, 298 K)

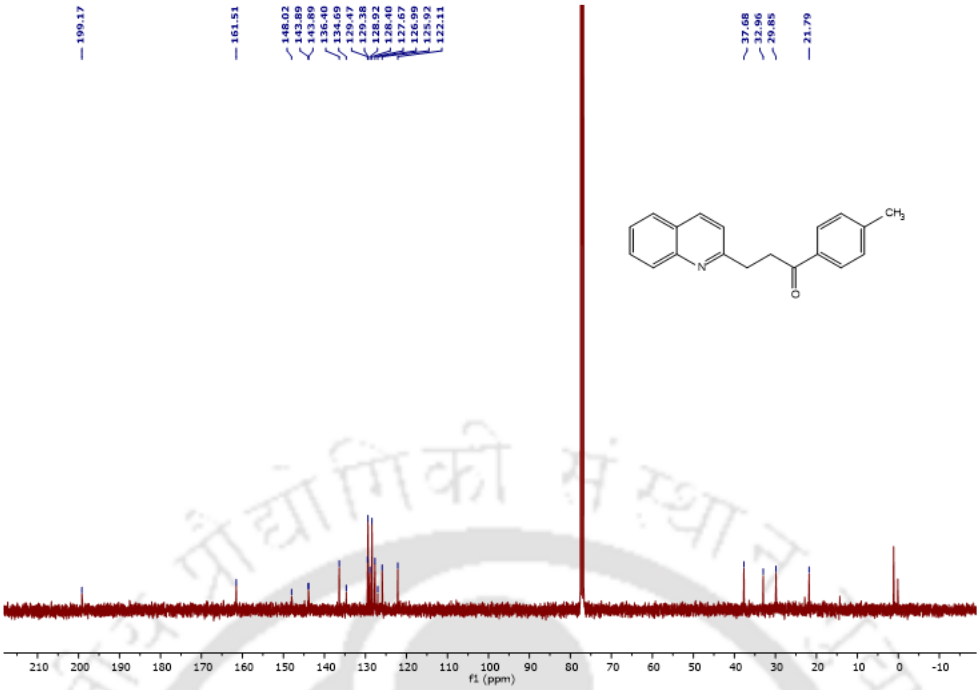


Figure S230. ^{13}C NMR Spectrum of **4.8** ($CDCl_3$, 101 MHz, 298 K)

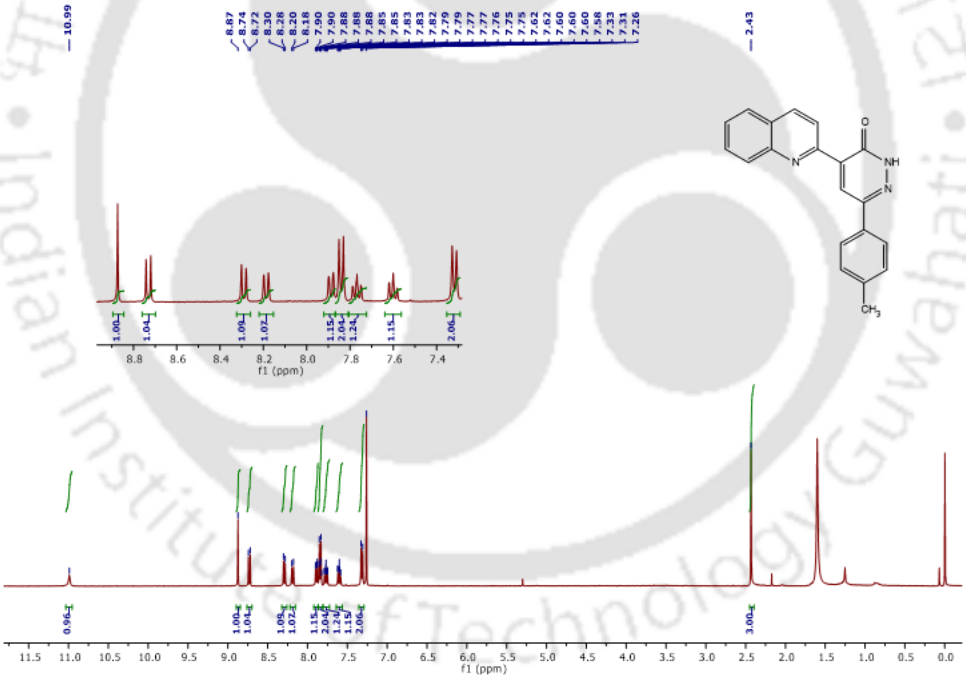


Figure S231. ^{1}H NMR Spectrum of **4.9** ($CDCl_3$, 400 MHz, 298 K)

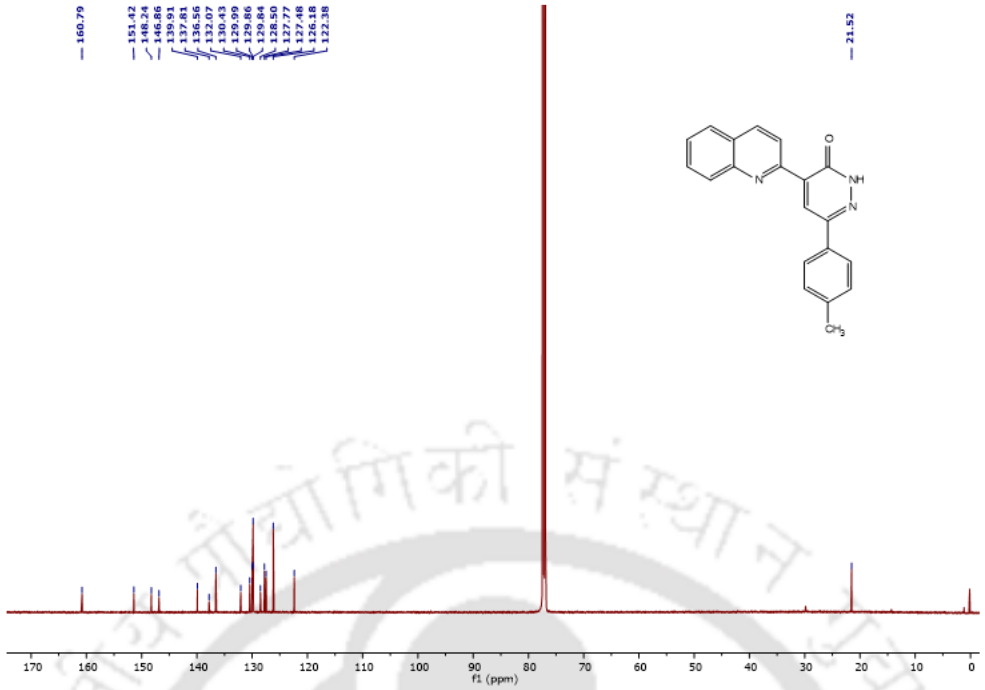


Figure S232. ^{13}C NMR Spectrum of **4.9** ($CDCl_3$, 101 MHz, 298 K)

Annexure IV

^{1}H and ^{13}C NMR spectra of compounds (*Chapter 5*)

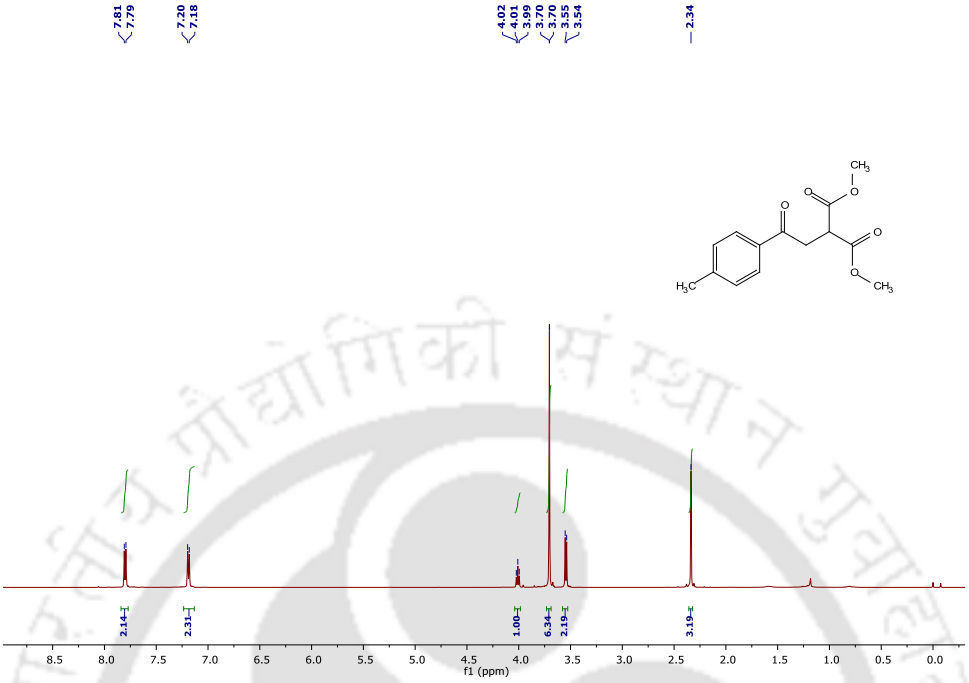


Figure S233. ^{1}H NMR Spectrum of **5.1a** ($CDCl_3$, 500 MHz, 298 K)

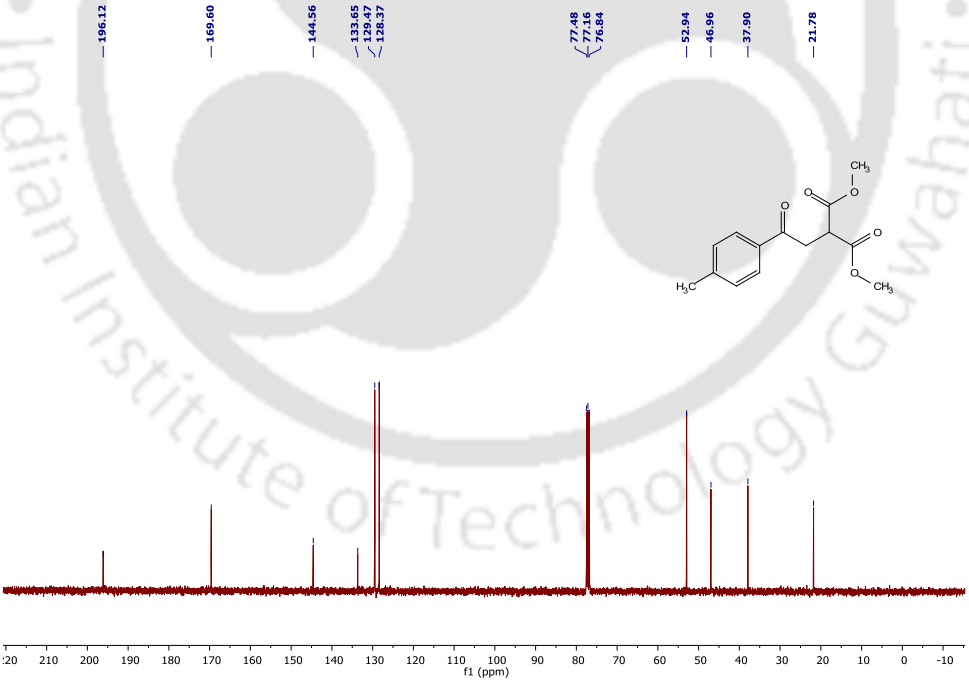


Figure S234. ^{13}C NMR Spectrum of **5.1a** ($CDCl_3$, 101 MHz, 298 K)

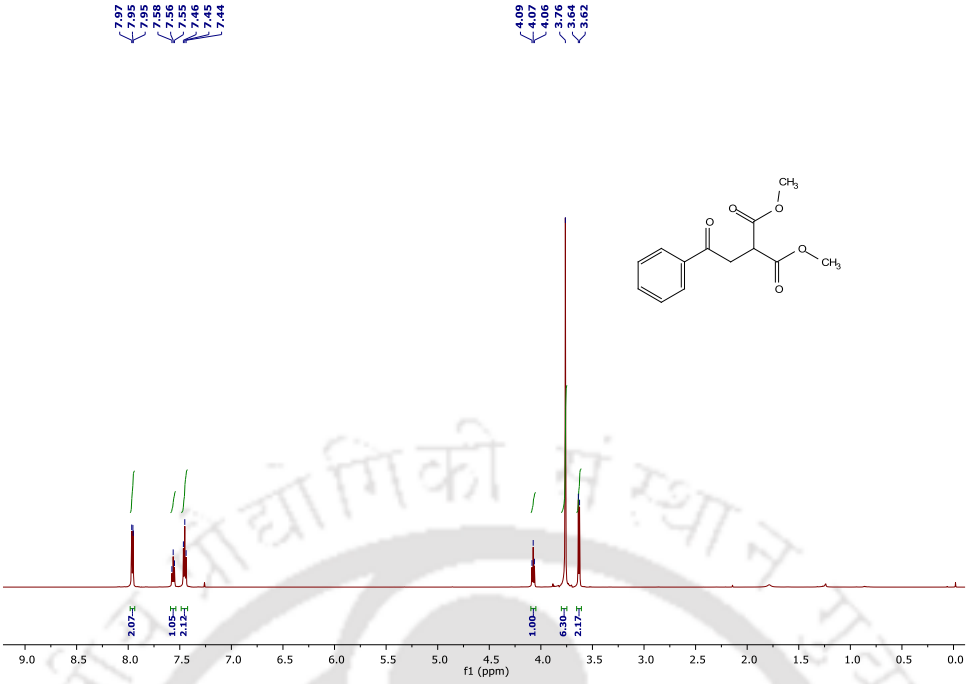


Figure S235. ^{1}H NMR Spectrum of **5.1b** ($CDCl_3$, 600 MHz, 298 K)

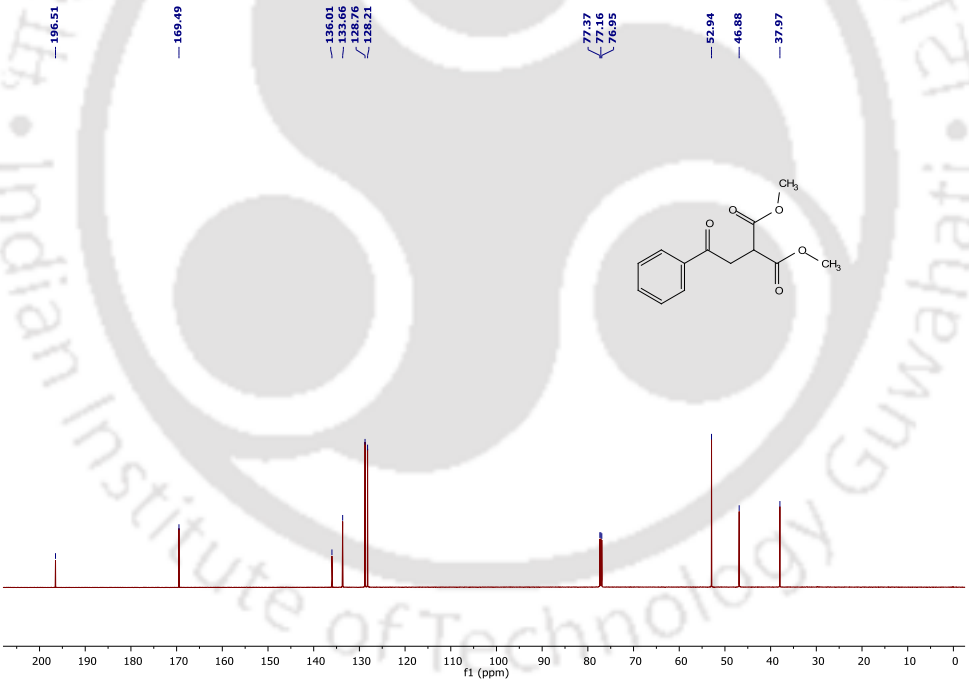


Figure S236. ^{13}C NMR Spectrum of **5.1b** ($CDCl_3$, 151 MHz, 298 K)

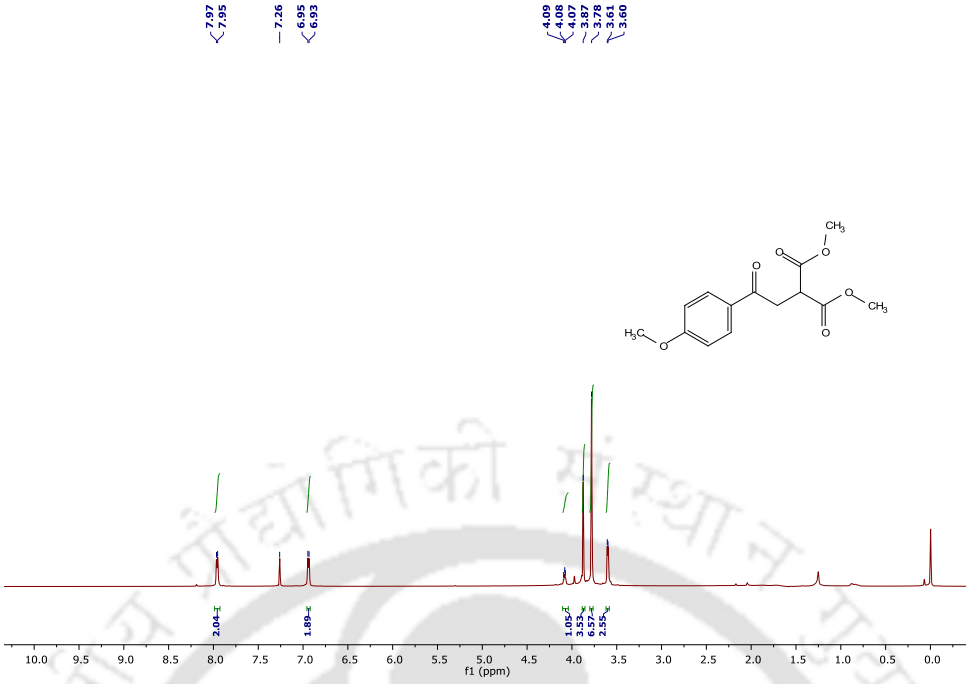


Figure S237. ^{1}H NMR Spectrum of **5.1c** ($CDCl_3$, 600 MHz, 298 K)

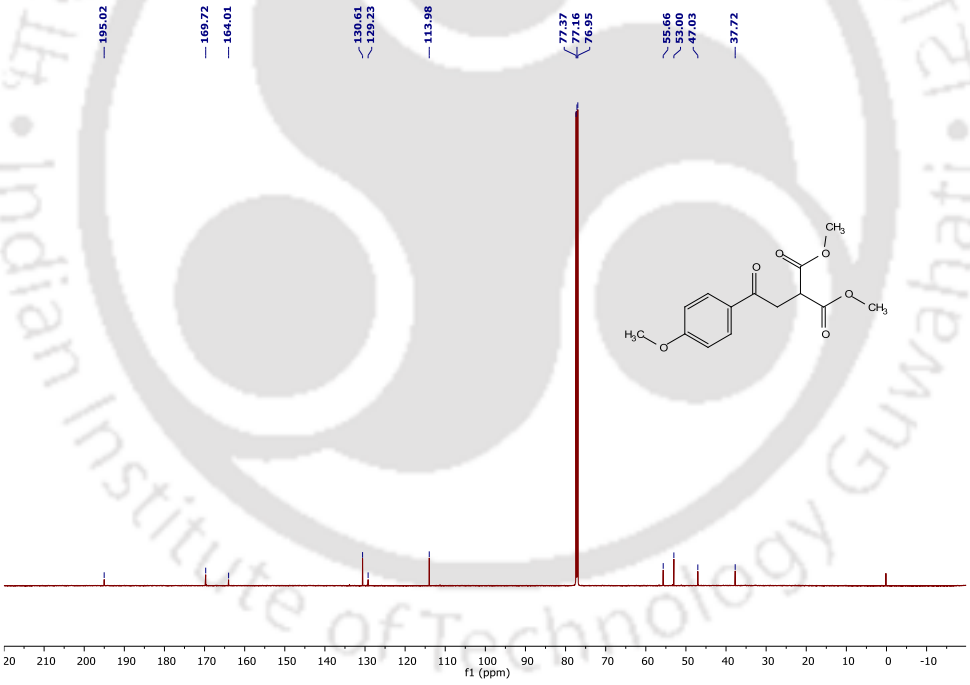


Figure S238. ^{13}C NMR Spectrum of **5.1c** ($CDCl_3$, 151 MHz, 298 K)

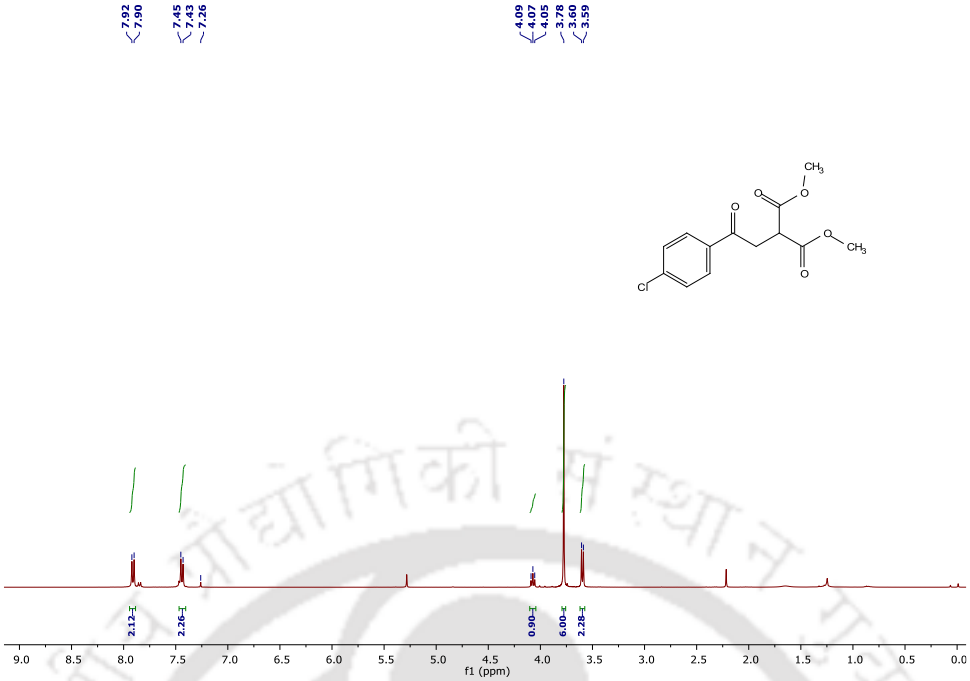


Figure S239. ^{1}H NMR Spectrum of **5.1d** ($CDCl_3$, 600 MHz, 298 K)

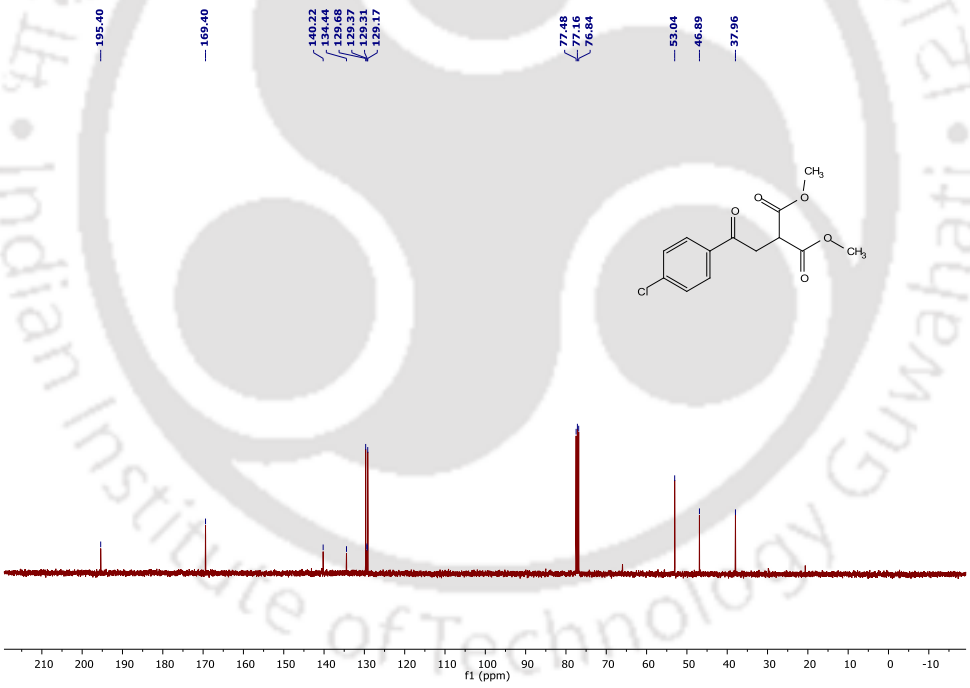


Figure S240. ^{13}C NMR Spectrum of **5.1d** ($CDCl_3$, 101 MHz, 298 K)

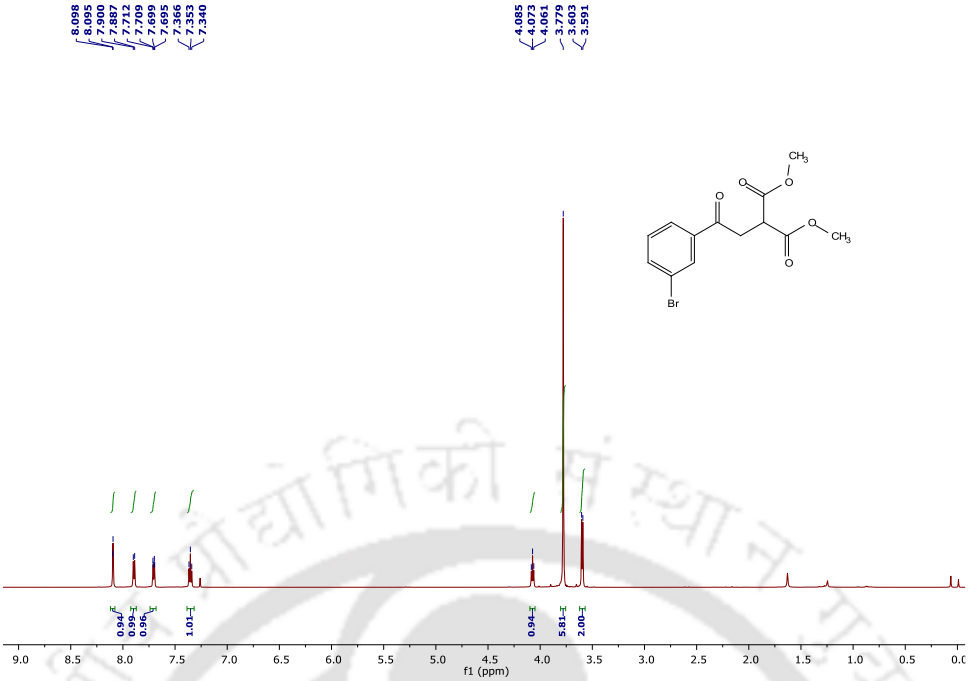


Figure S241. ^{1}H NMR Spectrum of **5.1e** ($CDCl_3$, 600 MHz, 298 K)

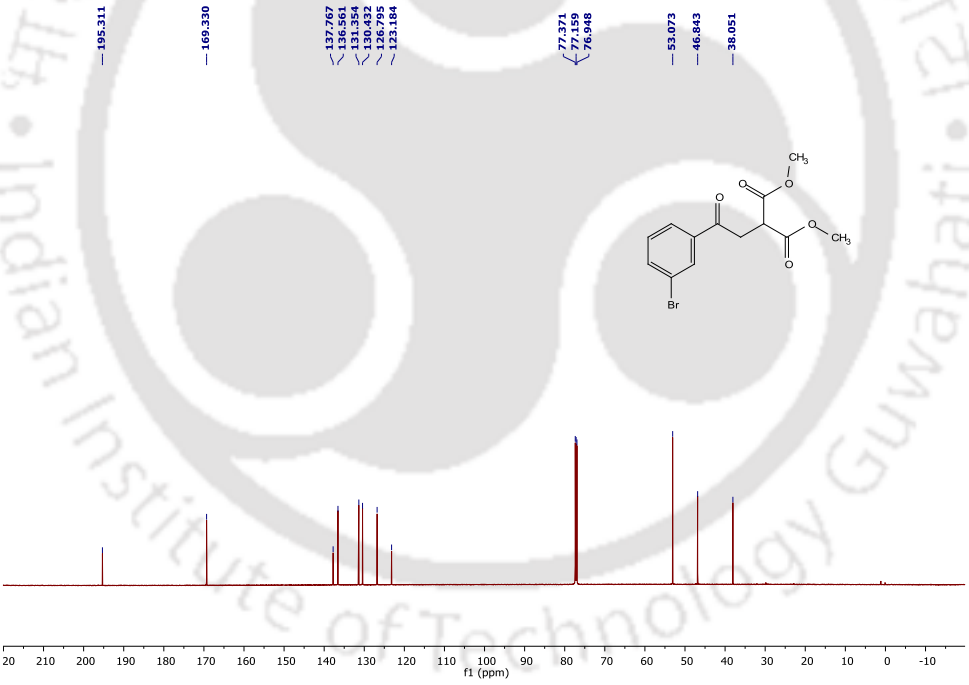


Figure S242. ^{13}C NMR Spectrum of **5.1e** ($CDCl_3$, 151 MHz, 298 K)

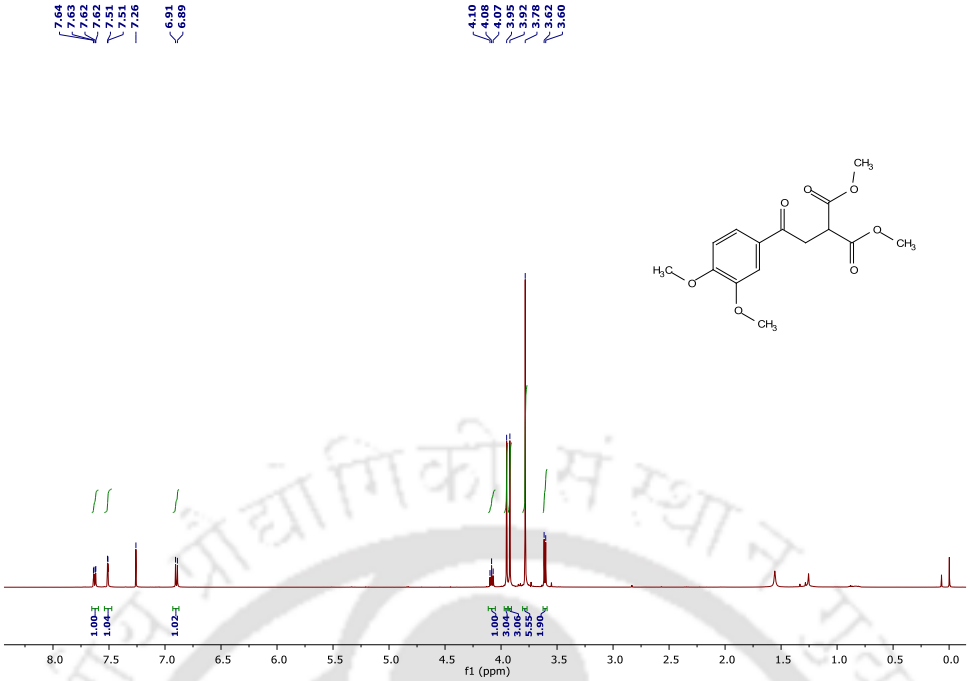


Figure S243. ^{1}H NMR Spectrum of **5.1f** ($CDCl_3$, 500 MHz, 298 K)

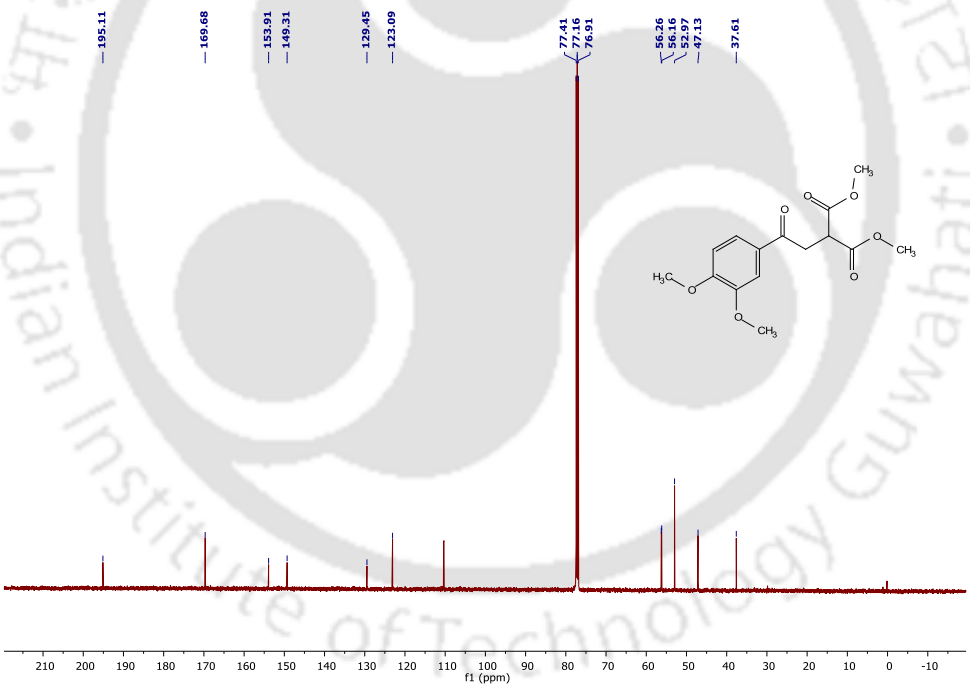


Figure S244. ^{13}C NMR Spectrum of **5.1f** ($CDCl_3$, 126 MHz, 298 K)

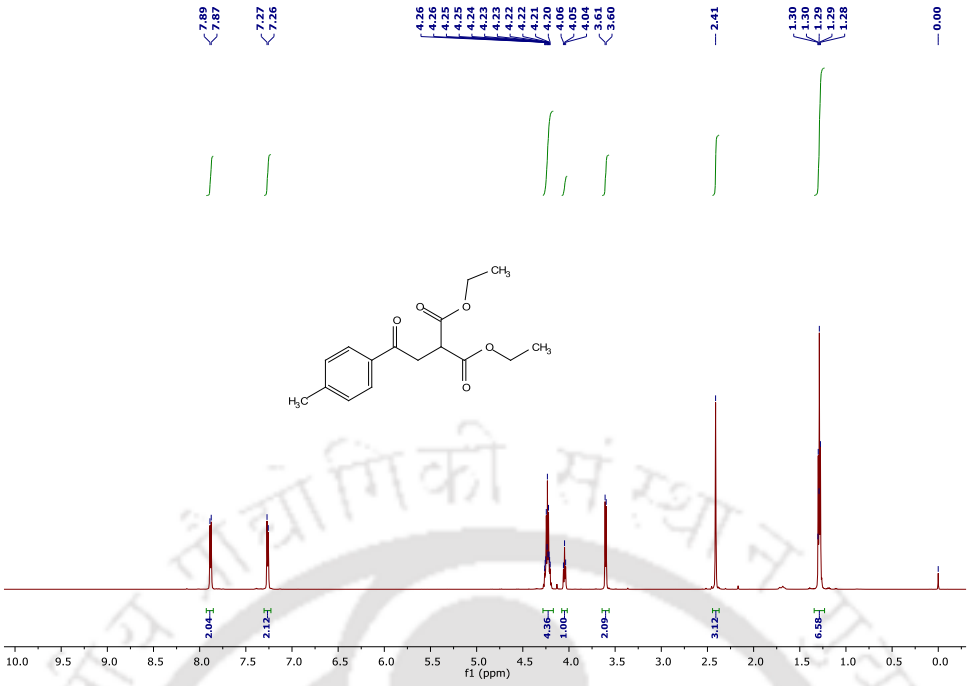


Figure S245. ^{1}H NMR Spectrum of **5.1g** ($CDCl_3$, 600 MHz, 298 K)

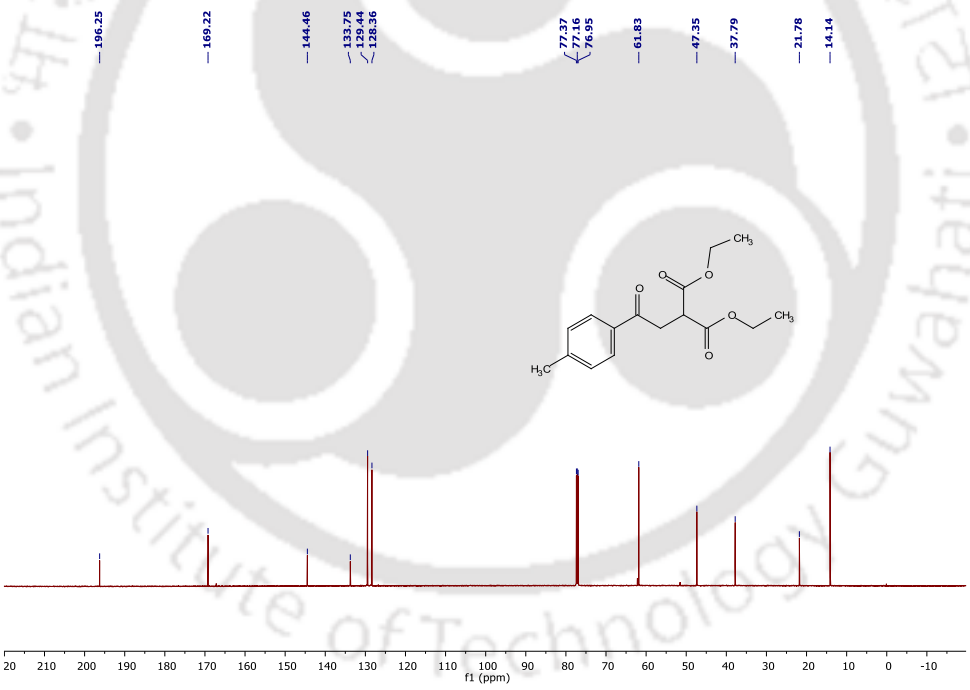


Figure S246. ^{13}C NMR Spectrum of **5.1g** ($CDCl_3$, 151 MHz, 298 K)

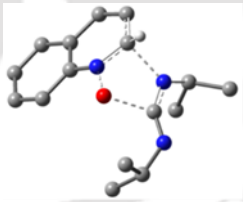
Annexure V

Cartesian coordinates (xyz) of all the optimized structures (*Chapter 3*)

1a + 2a (for reaction with alkyl carbodiimide)

C	2.45204	2.08714	-0.74706
H	1.49369	1.91772	-0.24515
C	2.73152	-0.29851	-0.57839
C	2.4428	-2.25861	0.7962
H	1.52754	-2.85889	0.82317
N	3.17143	0.80147	-0.86541
N	2.33846	-1.44691	-0.43084
C	2.19664	2.63859	-2.15198
H	1.58473	1.94849	-2.73766
H	1.67181	3.59669	-2.09264
H	3.14086	2.79201	-2.68211
C	3.29473	3.04536	0.09611
H	3.45502	2.64295	1.09885
H	4.27145	3.20799	-0.3685
H	2.78915	4.01069	0.19141
C	2.50666	-1.41203	2.06948
H	3.42385	-0.81493	2.09285
H	1.6499	-0.73654	2.12795
H	2.50321	-2.0577	2.95259
C	3.63271	-3.21549	0.66688
H	3.6633	-3.90107	1.51877
H	3.55854	-3.80412	-0.25005
H	4.57357	-2.65802	0.63978
C	-3.53009	-0.13351	-0.12669
C	-2.11664	-0.11455	0.02775
C	-2.3178	1.59283	1.67048
C	-3.71077	1.5907	1.53633
C	-4.32831	0.74227	0.64996
H	-1.77826	2.23674	2.34944
H	-4.28104	2.27656	2.15025
H	-5.4055	0.7328	0.53682
C	-4.07657	-1.04394	-1.06825
C	-1.28743	-0.96785	-0.72313
C	-3.26177	-1.87407	-1.80086
C	-1.86045	-1.83532	-1.62646
H	-5.15287	-1.07026	-1.19811
H	-3.69458	-2.56333	-2.51687
H	-1.22615	-2.49337	-2.20864
H	-0.21688	-0.92479	-0.57543
N	-1.52855	0.77403	0.94725
O	-0.25305	0.79526	1.08676

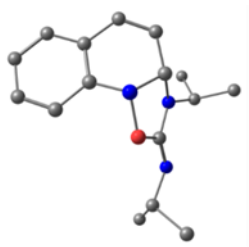
TS1A



C	1.79684	-1.89771	0.05558
C	1.69436	-0.58299	-0.4292
C	2.72706	0.3577	-0.17596
C	3.858	-0.0634	0.55249
C	3.95612	-1.35716	1.02669
C	2.91634	-2.27063	0.77634
H	0.99714	-2.59334	-0.15538
H	4.65139	0.65252	0.74051
H	4.82878	-1.6687	1.5881

H	2.99336	-3.28572	1.14956
C	2.56798	1.69334	-0.66888
C	1.44612	2.05991	-1.33864
H	3.37475	2.40327	-0.5187
H	1.32606	3.05718	-1.74207
N	0.61514	-0.19757	-1.2077
C	0.37087	1.11241	-1.52897
O	-0.51233	-0.92397	-1.21905
C	-1.74177	0.24507	-0.24824
N	-1.08882	1.34347	-0.33322
C	-1.11849	2.40128	0.6879
H	-0.31757	3.09312	0.40117
C	-0.80578	1.87064	2.09218
H	0.16113	1.36234	2.11153
H	-0.77434	2.69518	2.81015
H	-1.57419	1.16544	2.41941
C	-2.45316	3.15459	0.63826
H	-2.44995	3.98185	1.35421
H	-2.63093	3.56184	-0.35977
H	-3.28095	2.48568	0.88605
N	-2.79005	-0.30728	0.08643
C	-3.14033	-1.71741	0.24522
H	-4.1482	-1.70664	0.67331
C	-3.22321	-2.43346	-1.11058
H	-2.23882	-2.50016	-1.57575
H	-3.62226	-3.4432	-0.97202
H	-3.88986	-1.89329	-1.78712
C	-2.21914	-2.43992	1.23457
H	-2.20804	-1.92706	2.19982
H	-2.56919	-3.46367	1.39758
H	-1.19917	-2.47684	0.8488
H	-0.27537	1.22817	-2.3882

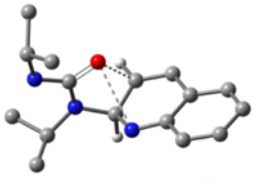
I-1A



C	-2.97233	2.58513	0.37347
C	-1.85165	2.05137	-0.26028
C	-1.77255	0.67748	-0.48242
C	-2.8196	-0.17021	-0.06696
C	-3.94266	0.39232	0.5477
C	-4.02516	1.76289	0.77294
H	-3.02278	3.65407	0.54736
H	-1.04281	2.69121	-0.58545
C	-2.6735	-1.60524	-0.27028
H	-4.74871	-0.2622	0.86322
H	-4.89825	2.18527	1.25565
C	-1.52113	-2.13688	-0.68974
C	-0.33027	-1.27257	-0.99646
H	-3.52568	-2.24179	-0.05417
H	-1.4056	-3.20435	-0.82912
H	0.1646	-1.63517	-1.90775
O	0.51776	0.83588	-1.04284
C	1.29213	0.10609	-0.13362
N	0.67184	-1.11043	0.08315
N	2.37957	0.50973	0.36024
C	1.44901	-2.21514	0.67339
H	2.29264	-1.70851	1.14614
C	2.00665	-3.17199	-0.39006
H	1.21403	-3.72792	-0.90118
H	2.59006	-2.63112	-1.13941

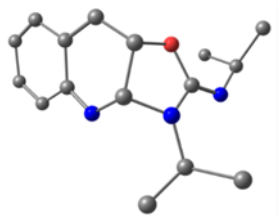
H	2.66547	-3.90569	0.08132
C	0.65609	-2.94463	1.7623
H	-0.19927	-3.48905	1.35514
H	1.30217	-3.66739	2.2689
H	0.28487	-2.23538	2.50462
C	2.87176	1.86443	0.09473
H	2.06276	2.50946	-0.27127
C	3.40323	2.45513	1.40439
H	4.21418	1.83567	1.79823
H	3.78411	3.46872	1.24676
H	2.61391	2.49721	2.15894
C	3.96553	1.81412	-0.98052
H	4.78429	1.16441	-0.65778
H	3.56993	1.42406	-1.92169
H	4.37015	2.8134	-1.16787
N	-0.71218	0.11846	-1.24332

TS2A



C	1.27689	-1.19011	-1.42899
C	4.23512	0.57103	-0.05295
C	2.97612	-0.03924	-0.18484
C	2.04103	0.03412	0.92696
C	4.57188	1.24685	1.10421
C	3.65624	1.35803	2.18318
H	1.69406	0.84554	2.89797
H	4.9365	0.51934	-0.87863
H	5.54766	1.71204	1.18774
C	2.51742	-0.64035	-1.38913
H	3.9459	1.90344	3.07354
H	3.12186	-0.56071	-2.28607
C	0.47823	-1.39139	-0.18364
C	2.41878	0.78317	2.09577
N	-2.60804	0.34612	-0.63354
H	0.85986	-1.5849	-2.3475
H	-1.2189	-3.21556	0.25087
O	-0.3703	0.78118	-1.07701
N	-0.95165	-1.29763	-0.42131
C	-1.33233	0.03823	-0.70621
C	-1.85423	-2.32867	0.14204
H	-2.56323	-2.98795	-1.8053
C	-2.97599	-2.69885	-0.8351
H	-3.54095	-3.54658	-0.4357
H	-3.64938	-1.8556	-0.98052
H	-2.96632	-2.80025	1.94598
C	-2.39201	-1.96466	1.53409
H	-1.57512	-1.73277	2.22148
H	-3.04171	-1.091	1.45965
H	-4.11181	1.70935	-0.64902
N	0.86644	-0.56245	0.93305
C	-3.03858	1.71457	-0.88183
H	-1.31451	2.86368	-0.19527
C	-2.37802	2.76512	0.02714
H	-2.85909	3.73884	-0.11341
H	-2.48735	2.48242	1.07796
H	-3.415	1.35498	-2.99973
C	-2.92025	2.1001	-2.3714
H	-3.3928	3.07111	-2.5518
H	-1.8683	2.15697	-2.65987
H	0.66625	-2.42933	0.15548

I-2A



C	4.69119	-0.92143	-0.27403
C	3.7807	-1.24164	0.66932
C	2.49155	-0.57289	0.72255
C	2.22358	0.53511	-0.24645
C	3.24437	0.78556	-1.26112
C	4.40912	0.10402	-1.26352
H	1.6405	-1.79549	2.23333
H	5.64464	-1.43557	-0.31227
H	3.98073	-2.01925	1.39892
C	1.50759	-0.95272	1.56269
H	3.0272	1.55982	-1.98673
H	5.16192	0.31949	-2.0139
C	0.17915	1.08593	0.8237
C	0.17908	-0.27199	1.53747
N	1.16467	1.26868	-0.24123
H	-0.22975	-0.16175	2.54663
H	0.34319	1.89801	1.54006
O	-0.76197	-1.06622	0.76618
N	-1.19088	1.10207	0.33209
C	-1.59728	-0.20129	0.07703
C	-1.83164	2.2387	-0.36775
H	-1.87052	1.98531	-1.43358
C	-1.03179	3.53162	-0.19345
H	-0.01611	3.43953	-0.57701
H	-1.53701	4.33081	-0.74083
H	-0.99017	3.83356	0.85836
C	-3.26693	2.42608	0.13968
H	-3.84437	1.51147	0.01511
H	-3.26372	2.70786	1.19749
H	-3.75673	3.22412	-0.42612
N	-2.56772	-0.53788	-0.65738
C	-2.98699	-1.9318	-0.83862
H	-3.85886	-1.87288	-1.49949
C	-3.46034	-2.5926	0.46615
H	-3.90632	-3.56944	0.25439
H	-2.63081	-2.73769	1.16145
H	-4.21782	-1.97425	0.9553
C	-1.93232	-2.78065	-1.56619
H	-2.3457	-3.76225	-1.81877
H	-1.62545	-2.29257	-2.49488
H	-1.04589	-2.92943	-0.94606

3aa+2a′

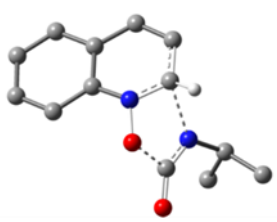
C	-0.53851	1.38391	-0.47302
C	0.33681	1.46337	0.65178
C	1.57094	2.14371	0.53502
C	1.93847	2.7299	-0.65775
C	1.07606	2.6504	-1.77316
C	-0.13276	1.9937	-1.68634
H	2.22252	2.19891	1.40133
H	2.88317	3.25485	-0.74069
H	1.36858	3.11597	-2.70822
H	-0.80387	1.93072	-2.53493
C	-0.09926	0.83561	1.85431
C	-2.12226	0.19011	0.70908
C	-1.30736	0.20854	1.89293
H	-1.66233	-0.26953	2.79964
H	0.54073	0.85849	2.7301
N	-1.74344	0.74485	-0.42778

N	-3.35348	-0.41043	0.77371
H	-3.553	-0.95024	1.60166
C	-4.23347	-0.60782	-0.37935
H	-4.1415	0.29568	-0.98576
C	-5.67553	-0.7411	0.11361
H	-6.3575	-0.86533	-0.73083
H	-5.79195	-1.61837	0.7608
H	-5.98187	0.14371	0.67653
C	-3.80122	-1.80774	-1.23426
H	-2.77058	-1.6829	-1.57049
H	-3.87362	-2.7394	-0.66322
H	-4.44004	-1.90067	-2.11771
C	3.02959	-1.4026	-0.85142
H	2.64358	-0.39597	-1.03995
C	3.34038	-0.95241	1.58958
N	3.56667	-1.42201	0.51113
C	1.88181	-2.40798	-0.97574
H	1.07432	-2.16825	-0.28087
H	1.47605	-2.38524	-1.99055
H	2.23405	-3.42125	-0.76497
C	4.16386	-1.69302	-1.83354
H	4.96758	-0.96162	-1.72745
H	4.57988	-2.68854	-1.6571
H	3.79031	-1.64964	-2.8597
O	3.21775	-0.55096	2.68906

1a+2a′ (for reaction with alkyl isocyanate)

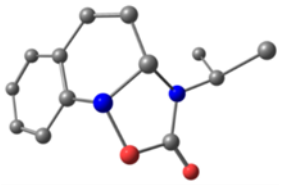
C	-3.58302	-0.94047	-0.15596
H	-2.62962	-1.13304	-0.65408
C	-3.13373	1.50908	-0.06082
N	-3.78694	0.51057	-0.15836
C	-4.71777	-1.59846	-0.94007
H	-4.75802	-1.21672	-1.96253
H	-4.56592	-2.68027	-0.98159
H	-5.68203	-1.40256	-0.46301
C	-3.49365	-1.45142	1.28378
H	-2.6489	-0.99167	1.7993
H	-4.41277	-1.22669	1.83216
H	-3.34679	-2.53526	1.28436
C	3.10668	0.40708	-0.04482
C	1.86587	-0.28425	0.00209
C	0.70237	1.78865	0.05916
C	1.91319	2.48998	0.01372
C	3.11315	1.82362	-0.0383
H	-0.26749	2.26419	0.09863
H	1.86921	3.57183	0.0206
H	4.05425	2.35875	-0.07386
C	4.29211	-0.37182	-0.09628
C	1.81436	-1.68999	-0.00141
C	4.23492	-1.74515	-0.10009
C	2.98802	-2.40792	-0.05209
H	5.24686	0.14108	-0.13257
H	5.14961	-2.32534	-0.13973
H	2.95574	-3.49118	-0.05492
H	0.84436	-2.16481	0.037
N	0.66304	0.44189	0.05339
O	-0.45668	-0.18954	0.09538
O	-2.61285	2.5634	0.01857

TS3A



C	2.13318	-1.51672	-0.16912
C	1.57601	-0.25063	-0.40451
C	2.19544	0.9231	0.09559
C	3.40649	0.79115	0.8077
C	3.95984	-0.45312	1.03024
C	3.31342	-1.60525	0.54501
H	1.62525	-2.39331	-0.54631
H	3.88893	1.68554	1.18676
H	4.88738	-0.54637	1.58203
H	3.74656	-2.58099	0.73256
C	1.54608	2.17823	-0.11872
C	0.35645	2.24891	-0.7766
H	2.02579	3.08082	0.2448
H	-0.14354	3.19201	-0.95164
N	0.42558	-0.10642	-1.16268
C	-0.26595	1.05261	-1.24429
O	-0.36518	-1.20252	-1.36173
C	-1.65185	-1.07541	-0.43603
N	-1.72199	0.14485	-0.01674
C	-2.84481	0.63186	0.78847
H	-2.63231	1.69254	0.97047
C	-2.90264	-0.07219	2.15248
H	-1.95379	0.03957	2.68295
H	-3.6956	0.36051	2.77008
H	-3.10456	-1.13822	2.02707
C	-4.18077	0.53694	0.03679
H	-4.98786	0.9701	0.63531
H	-4.13295	1.0797	-0.91143
H	-4.42974	-0.5051	-0.17607
H	-1.0276	1.0841	-2.00609
O	-2.23937	-2.12582	-0.36661

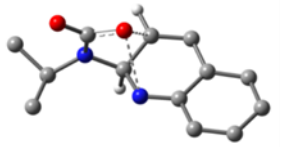
I-3A



C	-3.6168	0.99444	0.5626
C	-2.40085	1.32008	-0.03559
C	-1.52331	0.30352	-0.40871
C	-1.85769	-1.04548	-0.17713
C	-3.09286	-1.34683	0.40557
C	-3.97349	-0.33631	0.77792
H	-4.29142	1.79098	0.85518
H	-2.12936	2.35155	-0.2137
C	-0.88318	-2.07175	-0.52103
H	-3.34956	-2.38678	0.5794
H	-4.925	-0.58204	1.23383
C	0.35729	-1.7582	-0.90823
C	0.79419	-0.32725	-1.04482
H	-1.18414	-3.11115	-0.43634
H	1.08613	-2.52111	-1.15135
H	1.38832	-0.20877	-1.96019
O	0.21582	1.86013	-0.74487
C	1.28496	1.60454	0.11233
N	1.54767	0.26364	0.08927
C	2.80748	-0.24749	0.65781
H	3.21251	0.61056	1.1994
C	3.81116	-0.64038	-0.43429
H	3.46979	-1.50261	-1.01533
H	3.99479	0.18996	-1.12061
H	4.76457	-0.914	0.02394
C	2.5585	-1.37549	1.6641
H	2.1594	-2.27144	1.18312

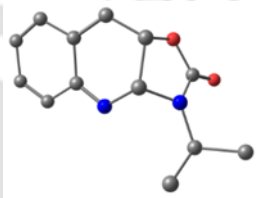
H	3.49728	-1.64647	2.15506
H	1.85011	-1.05615	2.43089
N	-0.34057	0.5936	-1.14167
O	1.83601	2.49193	0.70739

TS4A



C	-0.08517	-2.00017	0.79915
C	3.23167	-1.104	-0.61565
C	2.00368	-0.99053	0.04505
C	1.55268	0.2874	0.43193
C	3.98986	0.02297	-0.91467
C	3.51747	1.28221	-0.54515
H	1.94672	2.3953	0.42985
H	3.57894	-2.08952	-0.90853
H	4.93596	-0.07743	-1.43276
C	1.15499	-2.14175	0.31909
H	4.09615	2.16861	-0.77891
H	1.55178	-3.13006	0.10942
C	-0.64997	-0.64083	1.09525
C	2.30809	1.4202	0.13297
N	0.38479	0.38417	1.2355
H	-0.71922	-2.85525	0.99834
H	-2.46308	-1.79072	-0.4309
O	-2.06362	2.18383	-0.36102
N	-1.50314	-0.04629	0.03848
C	-1.39748	1.31044	0.12807
O	-0.32438	1.60982	0.97415
C	-2.68997	-0.72416	-0.51936
H	-1.94125	-0.65686	-2.55703
C	-3.95886	-0.42096	0.28964
H	-3.06774	0.65283	-2.15959
H	-3.67702	-0.99153	-2.42193
H	-4.80043	-0.99767	-0.10313
C	-2.85182	-0.40548	-2.00881
H	-4.21023	0.63962	0.22704
H	-1.215	-0.66703	2.03706
H	-3.83423	-0.68685	1.34315

I-4a



C	4.3905	0.15027	-0.26115
C	3.61193	-0.80819	0.2826
C	2.17477	-0.62619	0.4029
C	1.58396	0.68026	-0.02576
C	2.49128	1.6442	-0.64251
C	3.81361	1.394	-0.74149
H	1.73395	-2.59342	1.06373
H	5.45938	-0.0009	-0.35755
H	4.03578	-1.74571	0.62629
C	1.35038	-1.60891	0.81703
H	2.05199	2.57171	-0.98856
H	4.47262	2.13163	-1.18613
C	-0.55268	0.08002	0.80226
C	-0.12627	-1.39622	0.87841
N	0.34242	0.99822	0.10605
H	-0.55222	-1.85943	1.77381
H	-0.6998	0.48879	1.80743
O	-0.76329	-2.01005	-0.26996
N	-1.82662	-0.06958	0.10823

C	-1.81422	-1.21103	-0.66074
O	-2.57084	-1.53	-1.54069
C	-2.79188	1.02208	-0.17519
H	-2.67053	1.30039	-1.22818
C	-2.50977	2.24989	0.6925
H	-1.50428	2.63904	0.53467
H	-3.22692	3.03215	0.43393
H	-2.64335	2.02203	1.75498
C	-4.22715	0.52766	0.04101
H	-4.44644	-0.33918	-0.58042
H	-4.38459	0.26156	1.09088
H	-4.92993	1.32423	-0.21878

3aa + CO_2

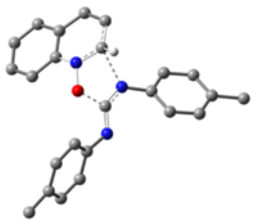
C	4.8469	-1.78668	0.22074
O	3.89224	-1.27326	-0.19961
O	5.79835	-2.29911	0.63862
C	-2.30466	0.23497	-0.00327
C	-2.41687	-1.18366	-0.11366
C	-3.68598	-1.79741	-0.01281
C	-4.81845	-1.03897	0.19089
C	-4.71086	0.36453	0.30052
C	-3.48598	0.98886	0.20659
H	-3.75517	-2.87753	-0.09921
H	-5.78946	-1.51452	0.26688
H	-5.60514	0.95718	0.46052
H	-3.39245	2.06535	0.28876
C	-1.20943	-1.90903	0.32262
C	-0.01334	0.18471	-0.29114
C	-0.02253	-1.2478	-0.41273
H	0.90832	-1.77818	-0.57978
H	-1.24616	-2.99039	-0.41168
N	-1.11068	0.89006	-0.08656
N	1.18397	0.84117	-0.41719
H	2.01713	0.2721	-0.41215
C	1.35286	2.27679	-0.18941
H	0.45957	2.75389	-0.59771
C	2.58175	2.76321	-0.96026
H	2.7151	3.83942	-0.82626
H	3.49306	2.27132	-0.60099
H	2.48107	2.55843	-2.02872
C	1.437	2.61601	1.30604
H	0.54833	2.25663	1.82765
H	2.32043	2.15525	1.76086
H	1.50528	3.69825	1.45278

1a + 4b (for reaction with aryl carbodiimide)

C	-1.70428	-0.44955	0.67574
N	-2.61665	0.24139	1.1046
N	-0.68221	-1.022	0.34536
C	4.23994	2.63909	0.28859
C	3.39488	1.56427	-0.10218
C	5.17171	0.62931	-1.37625
C	6.02062	1.67808	-1.00555
C	5.57591	2.68268	-0.18096
H	5.46566	-0.18597	-2.02086
H	7.03355	1.67052	-1.38835
H	6.22448	3.49887	0.11298
C	3.69068	3.62922	1.14416
C	2.06244	1.48354	0.34142
C	2.38815	3.54474	1.5753
C	1.5704	2.46576	1.17196
H	4.3222	4.45556	1.45142
H	1.9837	4.30909	2.22901

H	0.54543	2.40763	1.51873
H	1.4533	0.64921	0.02287
N	3.89536	0.55621	-0.94806
O	3.13742	-0.41401	-1.303
C	-0.34438	-2.39092	0.29249
C	-1.21479	-3.39325	0.73734
C	0.9063	-2.74064	-0.22109
C	-0.83014	-4.72736	0.66723
H	-2.18842	-3.12641	1.13456
C	1.27319	-4.08206	-0.28434
H	1.58041	-1.96575	-0.56862
C	0.42032	-5.09841	0.15805
H	-1.51674	-5.49388	1.01291
H	2.24648	-4.33898	-0.68992
C	-3.73002	0.79287	0.44194
C	-3.92321	0.68377	-0.94108
C	-4.67535	1.47936	1.20735
C	-5.04302	1.25454	-1.53505
H	-3.19691	0.15176	-1.54616
C	-5.79209	2.0447	0.59915
H	-4.52485	1.55805	2.27741
C	-5.99808	1.94709	-0.7806
H	-5.17785	1.15696	-2.60776
H	-6.51803	2.56987	1.21166
C	0.84291	-6.54703	0.11446
H	1.33048	-6.84408	1.04986
H	-0.01424	-7.20922	-0.03047
H	1.55283	-6.73001	-0.69552
C	-7.19476	2.58808	-1.44072
H	-6.95183	3.59045	-1.81077
H	-7.54096	2.00111	-2.29501
H	-8.02766	2.6908	-0.74141

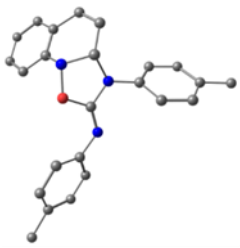
TS1B



C	1.20946	3.04574	0.59599
C	0.05355	2.81056	-0.16134
C	-1.05082	3.6985	-0.10635
C	-0.94656	4.84533	0.70824
C	0.19379	5.08135	1.4495
C	1.26619	4.17323	1.39527
H	2.02907	2.34249	0.5458
H	-1.78447	5.53251	0.75101
H	0.26284	5.96141	2.0773
H	2.15504	4.3574	1.98741
C	-2.22714	3.3724	-0.85167
C	-2.29706	2.2284	-1.58766
H	-3.06671	4.05861	-0.82427
H	-3.18086	1.96426	-2.15204
N	-0.03445	1.72627	-1.02279
C	-1.19099	1.33335	-1.60614
O	0.84225	0.69001	-0.84745
C	0.12568	-0.49124	-0.20387
N	-1.16704	-0.25818	-0.16401
N	0.87114	-1.43825	0.20111
H	-1.10025	0.57003	-2.36284
C	-2.14804	-1.22936	0.0348
C	-1.94963	-2.6068	-0.16637
C	-3.42827	-0.79759	0.42358
C	-2.99883	-3.50193	0.01861

H	-0.9688	-2.96685	-0.44582
C	-4.46669	-1.70451	0.59796
H	-3.59009	0.26089	0.59413
C	-4.2752	-3.07745	0.40286
H	-2.81687	-4.56081	-0.14105
H	-5.44416	-1.33902	0.89903
C	-5.39345	-4.06515	0.63365
H	-5.28107	-4.94945	0.00122
H	-5.41176	-4.40966	1.67415
H	-6.36944	-3.62094	0.42139
C	2.26467	-1.51961	0.09613
C	2.97805	-1.98128	1.21418
C	2.98927	-1.26461	-1.08038
C	4.35737	-2.14984	1.1657
H	2.42618	-2.20154	2.12077
C	4.36866	-1.44762	-1.11931
H	2.46751	-0.92495	-1.96624
C	5.08392	-1.88958	-0.00167
H	4.87854	-2.49797	2.0528
H	4.89987	-1.24213	-2.0443
C	6.57571	-2.11617	-0.06315
H	7.04479	-1.48108	-0.81894
H	7.05189	-1.90323	0.89766
H	6.81138	-3.15572	-0.31895

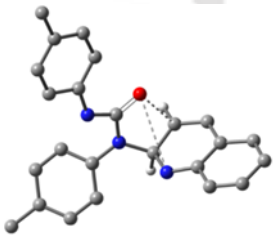
I-1B



C	0.77717	4.49724	0.98134
C	0.80776	3.38375	0.14424
C	-0.38831	2.837	-0.31728
C	-1.62359	3.39883	0.0642
C	-1.62562	4.53015	0.88709
C	-0.43487	5.08163	1.34824
H	1.71109	4.91274	1.34228
H	1.748	2.93724	-0.1493
C	-2.85032	2.75168	-0.38032
H	-2.57702	4.9644	1.17663
H	-0.45029	5.9539	1.99057
C	-2.83117	1.57438	-1.01432
C	-1.53481	0.88601	-1.3245
H	-3.7942	3.24045	-0.16057
H	-3.73928	1.07106	-1.31998
H	-1.57163	0.4449	-2.32991
O	0.72446	0.90071	-1.09672
C	0.27182	-0.22785	-0.40969
N	-1.10712	-0.17093	-0.36157
N	1.00309	-1.13693	0.07312
N	-0.39316	1.79035	-1.27771
C	2.40655	-1.1659	0.06355
C	3.02516	-1.88787	1.09685
C	3.22854	-0.59216	-0.91966
C	4.40745	-2.00821	1.15958
H	2.39469	-2.34678	1.84948
C	4.61329	-0.73268	-0.8522
H	2.78827	-0.03989	-1.73901
C	5.23299	-1.4356	0.18425
H	4.85371	-2.56334	1.9794
H	5.22391	-0.27963	-1.62761
C	6.73286	-1.60094	0.23695
H	7.03706	-2.58997	-0.12398

H	7.23715	-0.85666	-0.38372
H	7.11038	-1.4991	1.25821
C	-1.92135	-1.31386	-0.09766
C	-2.96403	-1.20851	0.82236
C	-1.71858	-2.52279	-0.76867
C	-3.80293	-2.29627	1.05593
H	-3.10719	-0.27701	1.3562
C	-2.55494	-3.60489	-0.51889
H	-0.89716	-2.61806	-1.46787
C	-3.61216	-3.51282	0.39494
H	-4.61074	-2.19815	1.7739
H	-2.3829	-4.53876	-1.04462
C	-4.49485	-4.70394	0.67855
H	-4.70591	-5.26953	-0.23259
H	-4.01219	-5.39009	1.38295
H	-5.44746	-4.39918	1.11704

TS2B

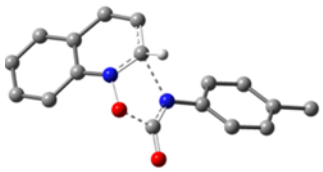


C	5.14187	2.88303	0.83309
C	4.68302	2.53852	-0.42542
C	3.72298	1.5277	-0.58978
C	3.22682	0.82813	0.58818
C	3.71224	1.23933	1.88062
C	4.64888	2.22954	1.99236
H	3.43794	1.75349	-2.73017
H	5.88212	3.66785	0.93899
H	5.05498	3.0583	-1.30198
C	3.15614	1.18505	-1.85076
H	3.31618	0.71985	2.74445
H	5.01986	2.52314	2.96745
C	1.86721	-0.61181	-0.73508
C	2.18353	0.24337	-1.91797
N	2.38709	-0.18528	0.53633
H	1.68947	0.00319	-2.85019
H	2.31775	-1.60437	-0.93161
O	0.01386	1.26563	-1.21311
N	0.42437	-0.88184	-0.60313
C	-0.41783	0.26652	-0.60546
N	-1.56218	0.08617	0.06933
C	-2.55628	1.01816	0.06286
C	-2.61255	2.22528	-0.69203
C	-3.66171	0.7389	0.91851
C	-3.6863	3.09155	-0.55165
H	-1.8087	2.45136	-1.37612
C	-4.7162	1.6187	1.04673
H	-3.63292	-0.18713	1.48043
C	-4.75373	2.82137	0.31614
H	-3.70462	4.00389	-1.14031
H	-5.53484	1.37817	1.71845
C	0.00536	-2.19442	-0.2793
C	-1.20497	-2.70286	-0.78155
C	0.81732	-3.04	0.48669
C	-1.57757	-4.01089	-0.51811
H	-1.84053	-2.06657	-1.38112
C	0.42834	-4.35601	0.73737
H	1.72381	-2.65454	0.93513
C	-0.77107	-4.86899	0.24556
H	-2.51389	-4.38042	-0.92517
H	1.07167	-4.98569	1.34371

C	-1.19526	-6.29132	0.51658
H	-1.30615	-6.85777	-0.41388
H	-0.46438	-6.81209	1.13862
H	-2.16003	-6.3268	1.03257
C	-5.90394	3.78065	0.46971
H	-6.86608	3.26091	0.43044
H	-5.8587	4.29711	1.43588
H	-5.89657	4.54268	-0.31223
5ab + 4b′			
C	2.96307	-3.5322	1.08103
C	1.95841	-2.9162	1.79327
C	0.79738	-2.44284	1.13736
C	0.66768	-2.60411	-0.27622
C	1.71864	-3.24357	-0.98345
C	2.83628	-3.69467	-0.31782
H	-0.24447	-1.69285	2.88771
H	3.84892	-3.89627	1.58847
H	2.04322	-2.78893	2.868
C	-0.28557	-1.81589	1.81001
H	1.60924	-3.36408	-2.05473
H	3.62985	-4.18523	-0.87122
C	-1.40255	-1.57599	-0.30528
C	-1.37737	-1.38375	1.11269
H	-2.21627	-0.92726	1.61811
N	-2.48296	-1.20014	-1.07704
H	-2.43469	-1.56276	-2.01886
C	-3.60552	-0.4134	-0.74431
C	-4.85146	-0.75583	-1.28467
C	-3.51329	0.73482	0.05138
C	-5.97314	0.02544	-1.02849
H	-4.93715	-1.64147	-1.90566
C	-4.6503	1.49251	0.31882
H	-2.55603	1.06036	0.43823
C	-5.90069	1.15754	-0.21005
H	-6.92486	-0.25984	-1.46566
H	-4.55028	2.38003	0.93561
C	-7.12935	1.97556	0.10597
H	-7.63706	1.59759	1.00052
H	-6.87363	3.02105	0.29413
H	-7.85025	1.94662	-0.71468
N	-0.4197	-2.1667	-0.96507
N	1.50731	3.07027	0.71758
C	0.40089	2.76239	1.06391
O	-0.70046	2.58344	1.42879
C	2.69543	2.5284	0.20976
C	2.83223	1.15856	-0.03971
C	3.76522	3.38693	-0.04555
C	4.03081	0.66556	-0.54159
H	2.0077	0.48376	0.15952
C	4.95823	2.87602	-0.54844
H	3.65407	4.44562	0.15436
C	5.11455	1.51113	-0.8087
H	4.11959	-0.39998	-0.72566
H	5.78271	3.55502	-0.73974
C	6.39976	0.9657	-1.3822
H	6.64428	-0.00977	-0.95443
H	6.32201	0.8351	-2.46715
H	7.23835	1.63899	-1.19188
1a+4b′ (for reaction with aryl isocyanate)			
C	1.82305	2.7543	-0.00217
N	2.87626	2.18389	-0.0015
C	-4.27514	-0.01596	-0.00059

C	-2.93486	-0.48847	0.0003
C	-2.13569	1.75084	-0.00158
C	-3.44803	2.23833	-0.00245
C	-4.51988	1.37933	-0.002
H	-1.25981	2.38377	-0.00194
H	-3.58634	3.31223	-0.00351
H	-5.5383	1.74827	-0.00268
C	-5.31339	-0.98374	-0.00001
C	-2.64711	-1.86532	0.00171
C	-5.02569	-2.32786	0.00134
C	-3.68406	-2.77096	0.00221
H	-6.34163	-0.63926	-0.00068
H	-5.83041	-3.05403	0.00176
H	-3.46984	-3.83332	0.00328
H	-1.61007	-2.16928	0.00231
N	-1.86995	0.42998	-0.00023
O	-0.66046	-0.00349	0.00053
O	0.86233	3.43173	-0.00313
C	3.45999	0.91019	0.00047
C	4.85208	0.81678	0.00364
C	2.68066	-0.25244	0.00362
C	5.46167	-0.43473	0.00783
H	5.44461	1.72359	0.00595
C	3.3105	-1.49188	0.00802
H	1.59883	-0.18081	0.0055
C	4.70607	-1.61076	0.00739
H	6.54518	-0.494	0.01333
H	2.69767	-2.38779	0.0136
C	5.36816	-2.96723	-0.01541
H	5.35844	-3.39411	-1.02436
H	6.41026	-2.90727	0.30593
H	4.85234	-3.67345	0.64053

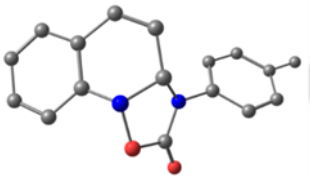
TS3B



C	3.4515	1.02077	-0.64314
C	2.66156	0.18876	0.16271
C	2.88572	-1.21057	0.20703
C	3.94587	-1.7444	-0.55429
C	4.72945	-0.92472	-1.34179
C	4.47181	0.45699	-1.38785
H	3.24527	2.08164	-0.67025
H	4.12673	-2.81321	-0.5196
H	5.53822	-1.34332	-1.92829
H	5.08249	1.09503	-2.0161
C	2.00424	-2.01647	0.99519
C	0.96209	-1.46349	1.67252
H	2.18644	-3.08458	1.04892
H	0.2863	-2.05983	2.27009
N	1.66632	0.70938	0.97586
C	0.73096	-0.0564	1.58814
O	1.19321	1.96907	0.69419
C	-0.20199	1.86495	0.06225
N	-0.62655	0.6289	0.16171
H	0.13024	0.44699	2.33029
O	-0.58421	2.92051	-0.37069
C	-1.95583	0.24417	-0.05193
C	-2.21391	-1.09202	-0.39187
C	-3.04758	1.11501	0.10077
C	-3.51818	-1.54208	-0.56906
H	-1.3774	-1.76911	-0.52258

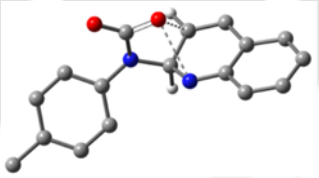
C	-4.34519	0.65102	-0.08789
H	-2.87164	2.15374	0.3489
C	-4.61114	-0.68105	-0.42503
H	-3.68838	-2.58185	-0.8318
H	-5.17199	1.34483	0.03216
C	-6.02386	-1.1605	-0.65677
H	-6.72976	-0.66081	0.01177
H	-6.34869	-0.95627	-1.68338
H	-6.11123	-2.23766	-0.49508

I-3B



C	4.60845	0.27052	-1.10429
C	3.57168	0.93039	-0.44769
C	2.61771	0.19038	0.24901
C	2.69297	-1.21652	0.28386
C	3.75598	-1.85316	-0.36561
C	4.71249	-1.11963	-1.05949
H	5.34355	0.85209	-1.64883
H	3.49726	2.00897	-0.47197
C	1.63413	-1.95412	0.95876
H	3.81472	-2.93628	-0.33433
H	5.52765	-1.62463	-1.56354
C	0.53993	-1.34288	1.42551
C	0.37398	0.14248	1.30738
H	1.74293	-3.02976	1.05516
H	-0.26367	-1.88887	1.90279
H	-0.0448	0.55039	2.2368
O	1.21486	2.07882	0.44951
C	-0.01574	1.87568	-0.17823
N	-0.47	0.62998	0.1748
N	1.62966	0.83477	1.03953
O	-0.51237	2.72193	-0.86645
C	-1.82575	0.22373	-0.01616
C	-2.09529	-1.01309	-0.60215
C	-2.88467	1.03572	0.39595
C	-3.41248	-1.43711	-0.75866
H	-1.27322	-1.63223	-0.93968
C	-4.19623	0.60686	0.22121
H	-2.68144	2.00494	0.83487
C	-4.48498	-0.63533	-0.35566
H	-3.60772	-2.4024	-1.21427
H	-5.0096	1.25029	0.5407
C	-5.91233	-1.07774	-0.56699
H	-6.55832	-0.74287	0.24818
H	-6.31666	-0.66085	-1.49578
H	-5.98729	-2.16511	-0.63539

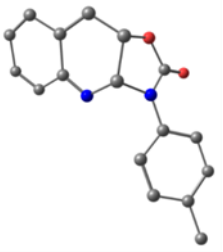
TS4B



C	5.27255	-0.98394	0.05302
C	4.63992	-0.18881	-0.87877
C	3.24938	0.02265	-0.80763
C	2.49646	-0.6407	0.24954
C	3.20822	-1.42878	1.22316
C	4.55714	-1.60253	1.11638
H	3.10593	1.5597	-2.32689
H	6.34471	-1.13205	-0.01414
H	5.21075	0.29679	-1.66223
C	2.5516	0.92807	-1.64176

H	2.62355	-1.87972	2.01515
H	5.09384	-2.20797	1.83663
C	0.41733	0.12532	-0.64123
C	1.20227	1.05335	-1.50521
N	1.19677	-0.52493	0.39173
H	0.63689	1.76758	-2.09233
H	0.06288	-0.6982	-1.29259
O	0.94329	1.89933	0.91932
N	-0.73407	0.78285	-0.08482
C	-0.33181	1.80272	0.87205
C	-2.02619	0.19664	-0.09081
C	-3.16198	1.01802	-0.09957
C	-2.20529	-1.19046	-0.09368
C	-4.43231	0.45491	-0.11372
H	-3.03593	2.09091	-0.07226
C	-3.48661	-1.73941	-0.13521
H	-1.34959	-1.85295	-0.03202
C	-4.62514	-0.93162	-0.14328
H	-5.29551	1.11366	-0.11159
H	-3.59608	-2.81948	-0.14037
C	-6.01328	-1.52356	-0.18901
H	-6.65402	-1.0966	0.58809
H	-6.49841	-1.32874	-1.15164
H	-5.98827	-2.60602	-0.04495
O	-1.16495	2.44524	1.49408

I-4B



C	5.12072	-1.25386	0.32638
C	4.68254	-0.107	-0.23285
C	3.26083	0.15645	-0.38342
C	2.29137	-0.90135	0.04164
C	2.84929	-2.09469	0.67157
C	4.18281	-2.25977	0.79465
H	3.45447	2.15238	-1.07676
H	6.18269	-1.43555	0.44389
H	5.37851	0.65389	-0.56937
C	2.7847	1.33568	-0.82856
H	2.14094	-2.8402	1.01111
H	4.5769	-3.16085	1.25153
C	0.44694	0.32097	-0.8013
C	1.31689	1.58417	-0.93349
N	1.01374	-0.82223	-0.10141
O	0.88088	2.43786	0.15292
H	1.07751	2.1042	-1.86634
N	-0.7061	0.87206	-0.09231
H	0.13491	-0.0388	-1.78868
C	-0.38013	2.05873	0.54199
C	-1.97711	0.23309	-0.04508
C	-3.13602	0.94603	0.29155
C	-2.09106	-1.11718	-0.3917
C	-4.37103	0.30823	0.27438
H	-3.06839	1.98593	0.57349
C	-3.34127	-1.73192	-0.4125
H	-1.2059	-1.69648	-0.61395
C	-4.50547	-1.03906	-0.07776
H	-5.25385	0.88222	0.53862
H	-3.40157	-2.78047	-0.68664
C	-5.8534	-1.71826	-0.06592
H	-6.6288	-1.0734	-0.48834

H	-5.83644	-2.64634	-0.6417
H	-6.16096	-1.96951	0.95512
O	-1.03427	2.71122	1.30916

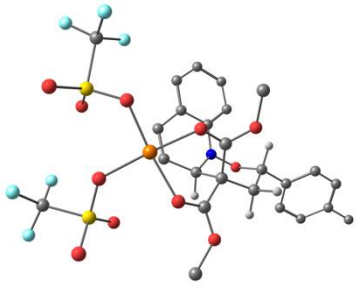
5ab+CO_2

C	2.34031	4.36404	-0.39853
O	1.87859	3.58759	0.33433
O	2.79986	5.13972	-1.12537
C	-2.69542	-0.69799	-0.07007
C	-3.46739	0.47748	0.16869
C	-4.87612	0.42463	0.0664
C	-5.5108	-0.75334	-0.26226
C	-4.74939	-1.91848	-0.49881
C	-3.37489	-1.89468	-0.40575
H	-5.45062	1.32704	0.25117
H	-6.59128	-0.78934	-0.33946
H	-5.25465	-2.84282	-0.75668
H	-2.7821	-2.78374	-0.58496
C	-2.74944	1.65945	0.50499
C	-0.70256	0.39587	0.32548
C	-1.39046	1.63108	0.58514
H	-0.82498	2.51951	0.84319
H	-3.29361	2.57859	0.69768
N	-1.33202	-0.7168	0.0113
N	0.67481	0.43129	0.42304
H	1.05017	1.33875	0.65328
C	1.65119	-0.56545	0.25606
C	2.98644	-0.19063	0.4877
C	1.38713	-1.88834	-0.11955
C	4.01947	-1.10507	0.34318
H	3.21083	0.82738	0.79249
C	2.44142	-2.79091	-0.25782
H	0.36843	-2.19485	-0.29359
C	3.77126	-2.43007	-0.03676
H	5.03847	-0.78228	0.53393
H	2.20999	-3.81146	-0.54729
C	4.90109	-3.41521	-0.21568
H	5.62855	-3.34246	0.5979
H	4.53037	-4.44226	-0.24255
H	5.44219	-3.23638	-1.15161

Annexure VI

The Cartesian coordinates (xyz) for all the optimized structures (*Chapter 4*)

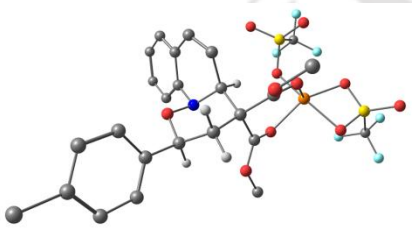
I1



C	2.85265	2.97951	-1.59049
C	1.89528	1.95528	-1.48892
C	0.50707	2.26837	-1.53883
C	0.11765	3.61425	-1.66619
C	1.06631	4.63136	-1.74367
C	2.43038	4.30354	-1.71122
H	3.91292	2.72964	-1.58284
H	-0.94903	3.84711	-1.70239
H	0.75178	5.67267	-1.83749
H	3.18182	5.09383	-1.78357
C	-0.4417	1.17099	-1.52506
C	-0.04997	-0.10324	-1.28672
H	-1.49501	1.38318	-1.72585
H	-0.7434	-0.94318	-1.38068
N	2.24666	0.61387	-1.41657
C	1.37547	-0.41662	-0.95536
H	1.69526	-1.36477	-1.41411
C	1.69266	-0.7076	0.67164
O	3.59186	0.29083	-1.35964
C	4.05119	0.16161	0.01691
H	3.93072	1.1358	0.5108
C	3.22494	-0.90957	0.7514
H	3.45454	-1.88568	0.30626
H	3.55062	-0.94745	1.80052
C	5.51907	-0.18609	-0.04584
C	6.44545	0.51389	0.73693
C	5.98548	-1.2234	-0.87141
C	7.80337	0.17925	0.70641
H	6.10568	1.33085	1.37948
C	7.3417	-1.54575	-0.9062
H	5.28361	-1.77512	-1.50116
C	8.27749	-0.85435	-0.11466
H	8.50702	0.73874	1.32896
H	7.68388	-2.35242	-1.56104
C	0.90781	-1.95612	1.01552
C	1.17015	0.44326	1.51297
O	1.57216	-3.06995	0.91552
O	2.09408	1.2166	2.01341
O	-0.29983	-1.95528	1.29428
O	-0.02852	0.68023	1.70959
C	0.8587	-4.32118	1.09999
H	1.56875	-5.10203	0.81129
H	0.57426	-4.42224	2.15552
H	-0.03414	-4.32994	0.46306
C	1.69008	2.36845	2.79299
H	1.11996	2.0377	3.67053
H	2.62275	2.85644	3.0917
H	1.0769	3.03558	2.1735

C	9.74032	-1.22216	-0.15529
H	10.13735	-1.1664	-1.18225
H	10.34294	-0.55677	0.47972
H	9.89928	-2.25704	0.19155
Cu	-1.55274	-0.43131	1.08755
O	-2.99862	-1.61496	0.5479
O	-2.72142	1.11432	1.20207
S	-3.98231	1.38447	0.36995
S	-2.90064	-2.92762	-0.23943
O	-5.21195	0.90957	1.00634
O	-3.79786	1.13086	-1.06542
O	-3.18789	-4.10326	0.58336
O	-1.73533	-2.98357	-1.13926
C	-4.03646	3.24852	0.53373
C	-4.3773	-2.73164	-1.37313
F	-4.13859	3.60461	1.81143
F	-5.09387	3.71222	-0.12999
F	-2.93369	3.79615	0.02013
F	-5.47363	-2.46621	-0.66939
F	-4.16404	-1.74879	-2.24097
F	-4.5571	-3.86951	-2.04243

I1′



C	-2.59764	3.02672	-2.25348
C	-2.37636	2.50513	-0.97816
C	-2.29171	3.35422	0.15123
C	-2.40933	4.7412	-0.04486
C	-2.61159	5.26412	-1.3239
C	-2.70957	4.40923	-2.42939
H	-2.67203	2.33976	-3.09901
H	-2.34397	5.40995	0.81754
H	-2.69683	6.34483	-1.46107
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C	-2.86896	-1.36943	0.51196
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H	-2.89438	-2.46402	0.42861
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C	-5.87946	-2.04995	-1.11269
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F	3.70104	3.49887	-1.13879
F	4.51652	-1.77041	-2.20127
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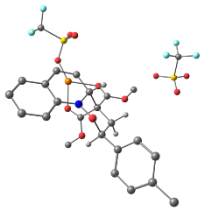
I2



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C	-3.14741	-0.14649	-0.9573
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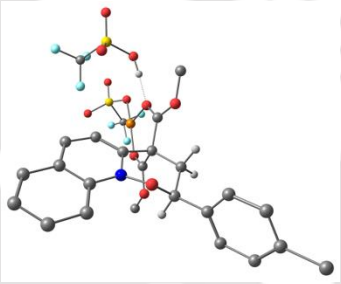
I3



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O	4.12619	0.57714	0.21815
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H	3.95535	-1.2492	1.184
C	2.82838	-1.2203	-0.68406
H	3.03064	-0.8899	-1.70775
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C	6.0342	-2.43106	0.12466
C	5.87747	-0.75904	-1.60678
C	7.21629	-2.91061	-0.44934
H	5.64397	-2.90336	1.03037
C	7.06267	-1.23362	-2.1679
H	5.36534	0.09018	-2.06543
C	7.75383	-2.32142	-1.60321
H	7.73303	-3.75507	0.015
H	7.46122	-0.7511	-3.06509
C	0.6014	-0.18499	-1.39598
C	0.82037	-1.40756	0.86924
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H	0.6425	-3.55254	2.48002
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C	9.0326	-2.82652	-2.22489
H	9.80025	-2.03545	-2.25484
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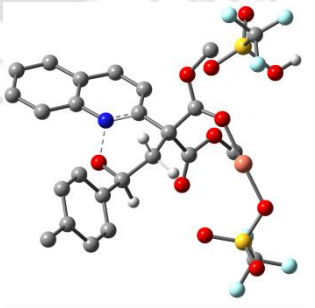
TS-1



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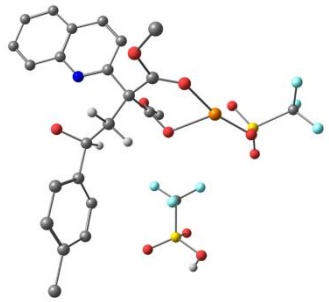
I4



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F	4.43322	4.35173	0.9743	C	5.29205 3.57843 -0.52298
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H	2.32933	-1.65841	-2.40029
Cu	1.04693	-0.65486	0.91943
O	-0.68346	-0.85691	0.11632
S	-0.78999	-1.52121	-1.24924
O	0.23122	-2.56244	-1.46688
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C	-2.39174	-2.46115	-1.04099
F	-2.67068	-3.12262	-2.1649
F	-2.29233	-3.33812	-0.04225
F	-3.39377	-1.6226	-0.77864
S	-12.66302	1.44541	0.44222
C	-14.33828	0.6232	0.21737
O	-12.43616	2.26774	0.72934
O	-11.7364	0.41761	0.88784
O	-13.01324	2.45365	1.65234
H	-12.8317	2.03258	2.51548
F	-15.2362	1.53013	-0.13332
F	-14.70368	0.04456	1.35323
F	-14.22819	-0.29162	0.73502
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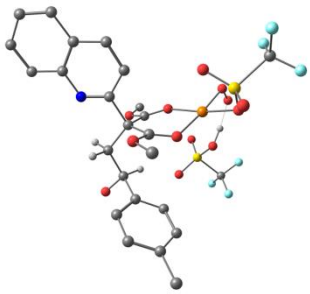
O	-5.712	-5.10915	-0.64487

I5



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C	-5.14374	-1.43399	-1.06648
C	-6.07959	-2.47079	-1.33516
C	-7.38482	-2.16212	-1.65949
H	-4.89731	1.98784	-0.89503
H	-8.85044	-0.58685	-1.98834
H	-7.25115	1.25988	-1.52615
C	-4.6099	0.93399	-0.85791
H	-5.73281	-3.50444	-1.27654
H	-8.09943	-2.96279	-1.86512
C	-2.99599	-0.8141	-0.49701
C	-3.31961	0.57299	-0.54015
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N	-3.86041	-1.76388	-0.7495
C	-1.53124	-1.24409	-0.17179
C	-1.46183	-2.75901	0.16494
C	-0.05203	-3.31607	0.44586
H	-2.13769	-2.95477	1.00666
H	-1.87133	-3.29796	-0.69651
C	-0.73431	-0.93551	-1.4524
C	-1.04716	-0.43615	1.04018
O	-0.03341	0.05558	-1.66339
O	-0.93881	-1.82871	-2.38113
O	-0.06119	0.29371	1.08116
O	-1.81826	-0.62152	2.07984
C	-1.50248	0.07737	3.30813
H	-2.37116	-0.07063	3.95738
H	-0.60487	-0.36801	3.75724
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C	-0.33677	-1.62903	-3.68329
H	0.75384	-1.55859	-3.58501
H	-0.6242	-2.50638	-4.27093
H	-0.73471	-0.70975	-4.1332

Cu	0.71578	1.44703	-0.43498
O	1.14194	2.92049	0.8243
S	-0.11999	3.57092	1.38434
O	-1.322	3.1243	0.65024
O	1.35168	2.557	-1.98681
O	2.41837	2.19142	-2.56789
H	0.69033	-2.88865	-0.25963
O	-0.17435	3.58778	2.84876
C	0.12501	5.35666	0.88641
F	0.22637	5.45299	-0.4372
F	1.23162	5.84191	1.44324
F	-0.91785	6.07684	1.29451
C	0.50479	-3.10423	1.86538
C	-0.23987	-3.51714	2.98414
C	1.79948	-2.59217	2.06
C	0.28074	-3.37211	4.27076
H	-1.232	-3.95341	2.85165
C	2.30766	-2.44558	3.34967
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C	1.5605	-2.83026	4.47974
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C	2.11624	-2.64883	5.86867
H	2.03488	-1.59485	6.18686
H	1.57452	-3.25961	6.60539
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O	3.23117	-1.10513	-3.34605
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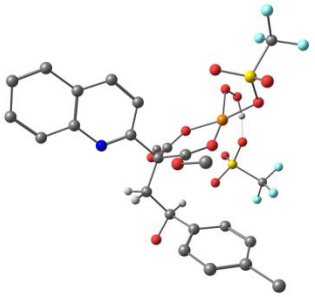
F	5.90015	-2.13876	-2.32094

I6



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C	-5.35632	-0.44042	-0.74282
C	-6.48855	-1.23529	-1.07342
C	-7.73699	-0.65679	-1.17532
H	-4.46168	2.79396	-0.00804
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H	-6.95868	2.60299	-0.45776
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H	-6.33632	-2.30336	-1.24088
H	-8.60365	-1.27173	-1.42965
C	-3.08957	-0.30782	-0.33972
C	-3.1497	1.09528	-0.10225
H	-2.25933	1.67224	0.15751
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C	-1.708	-1.04052	-0.27371
C	-1.90601	-2.577	-0.17403
C	-0.61507	-3.42086	-0.15009
H	-2.52722	-2.78513	0.70619
H	-2.49111	-2.88002	-1.04925

C	-1.00346	-0.64603	-1.58144
C	-0.96213	-0.53636	0.96629
O	-0.24086	0.31453	-1.73184
O	-1.36749	-1.37847	-2.59124
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O	-1.59179	-0.82485	2.06807
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H	-0.14238	-1.02992	3.55239
H	-0.72749	0.65124	3.28187
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H	-1.17323	-0.07707	-4.21528
Cu	0.93051	1.23524	-0.42935
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C	0.10064	-3.54211	1.20731
C	-0.57754	-4.08235	2.31427
C	1.45724	-3.20065	1.33896
C	0.07958	-4.2398	3.5353
H	-1.62364	-4.38193	2.22236
C	2.10177	-3.35364	2.56626
H	1.99749	-2.79456	0.48184
C	1.42891	-3.87655	3.68699
H	-0.46399	-4.6583	4.38659
H	3.15257	-3.06399	2.65604
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H	2.19987	-3.04768	5.52714
H	1.60318	-4.71453	5.67959
H	3.16541	-4.3838	4.87887
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O	1.99211	-1.93428	-1.78656
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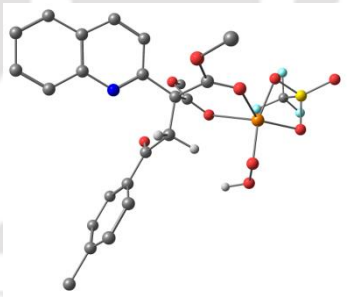
I7



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C	5.79845	-4.77156	-0.96545
C	6.81918	-5.61316	-1.36081
H	7.79766	-1.06093	-2.88763

H	8.72503	-5.79152	-2.39632	O	5.36461	0.73494	0.53883
H	8.8488	-3.37814	-2.98064	O	2.21534	1.21593	-1.78022
C	6.96531	-1.48973	-2.32358	O	3.16082	-0.3681	-3.01836
H	4.93863	-5.14083	-0.40278	C	2.47728	0.12488	-4.19078
H	6.7774	-6.67612	-1.11069	H	2.78615	-0.53382	-5.00877
C	4.85453	-1.29737	-1.17038	H	1.39074	0.07546	-4.03881
C	5.92349	-0.69974	-1.90265	H	2.77829	1.16175	-4.39082
H	5.91281	0.36813	-2.12366	C	5.81381	1.69787	1.51175
N	4.82282	-2.57753	-0.88498	H	5.5204	1.36356	2.51682
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C	3.66352	-0.44796	-0.68968	H	5.3727	2.68189	1.30687
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C	2.24604	-3.15991	1.76121	S	1.85556	5.04047	-0.03257
C	2.63759	-3.70668	2.99984	O	0.72874	4.29234	0.61509
C	1.17965	-3.76203	1.07134	O	1.52326	6.21263	-0.83707
C	1.98852	-4.81836	3.52387	C	2.87006	5.70162	1.39344
H	3.46226	-3.23741	3.53924	F	2.13101	6.53368	2.12256
C	0.5279	-4.87534	1.60601	F	3.28697	4.70072	2.16831
H	0.8403	-3.3681	0.11213	F	3.92987	6.35679	0.92664
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H	2.31087	-5.22809	4.48527	O	0.04135	1.36905	1.7938
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H	-0.17998	-6.41118	4.41702	O	-14.77853	1.10488	1.03319
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H	2.26864	-2.10549	-0.78862	H	-13.77051	-1.58324	2.61596
C	4.07087	0.63048	0.34264	F	-13.58295	-0.39009	1.43663
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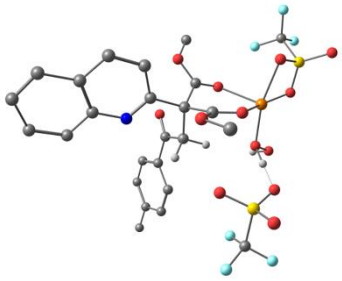
I8



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C	-4.95542	-3.03437	-0.39871
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C	-1.4221	-2.45643	-0.81966
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H	0.05833	-3.66533	-1.89595
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C	-1.13827	-0.20622	0.36592
C	-1.6731	-0.58003	1.73614
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C	0.70237	-1.91224	0.53162
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O	1.58062	-1.18927	0.98426
O	0.66113	-3.20368	0.73899
O	1.23718	0.02088	-1.55866
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C	-0.01479	-0.14935	-3.90352
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Cu	2.55352	0.44002	-0.10227
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S	5.11822	-0.13671	0.03094
O	4.33099	0.93067	0.77756
O	6.36431	0.25855	-0.59955
C	5.56932	-1.40187	1.33943
F	6.46412	-0.87325	2.16149

F	4.48495	-1.74586	2.0228
F	6.0815	-2.47226	0.74874
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O	-0.43678	3.67719	-3.46981
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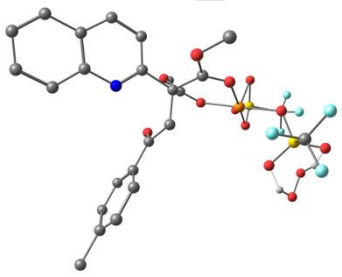
I9



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C	7.79965	-0.8634	0.3942
H	4.65113	-4.49554	1.34238
H	9.06878	-2.56795	0.8629
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C	4.51084	-3.44933	1.05923
H	6.30539	0.64346	-0.02258
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H	2.36825	-3.55516	1.06308
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C	1.81906	0.61118	0.15073
C	2.40001	0.98503	-1.20758
C	3.05657	2.30679	-1.3844
C	3.5404	2.64225	-2.66562
C	3.20088	3.24388	-0.34614
C	4.15102	3.86905	-2.89488
H	3.42476	1.91835	-3.47416
C	3.81093	4.47642	-0.58515
H	2.83636	3.02854	0.65937
C	4.29888	4.81229	-1.85806
H	4.52162	4.1084	-3.89545
H	3.91069	5.19147	0.23534
C	4.96592	6.13725	-2.11932
H	4.46209	6.67814	-2.93713
H	4.96066	6.77901	-1.22702
H	6.01377	5.9939	-2.43203
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H	2.41148	1.01924	0.97575
C	0.95991	-1.55236	-0.84737
C	0.83564	-1.08933	1.60079
O	-0.20308	-1.24013	-1.12864
O	1.58974	-2.48833	-1.48739
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O	1.50584	-1.24775	2.69987
C	0.784	-1.30126	3.95831
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C	-5.26117	-1.51854	-1.53408	F	-2.79039	3.12139	3.42098
F	-5.89065	-2.6887	-1.62713	F	-1.19755	1.71042	3.00751
F	-5.45816	-1.01662	-0.3188				

Annexure VII

The Cartesian coordinates (xyz) for all the optimized structures (*Chapter 5*)

A

C	8.60286	-1.92988	-0.52164
C	7.61421	-2.89249	-0.5262
C	6.25744	-2.52947	-0.31036
C	5.92829	-1.15332	-0.08605
C	6.96845	-0.1839	-0.08635
C	8.27636	-0.56703	-0.3005
H	5.38968	-4.52196	-0.46225
H	9.64456	-2.21454	-0.68913
H	7.86115	-3.94408	-0.69622
C	5.18378	-3.46032	-0.29929
H	6.69327	0.85854	0.08467
H	9.07137	0.18294	-0.30114
C	3.6742	-1.62841	0.12342
C	3.89846	-3.0221	-0.08581
H	3.05884	-3.71714	-0.07294
N	4.64633	-0.74841	0.12936
O	2.42043	0.93034	-1.51215
C	2.24769	-1.09116	0.39215
C	2.28803	0.39872	0.79384
C	2.66444	1.29574	-0.37064
C	3.24193	2.64703	-0.10908
C	3.48998	3.14645	1.17959
C	3.53352	3.46873	-1.21475
C	4.01198	4.42957	1.35496
H	3.27448	2.54107	2.06139
C	4.05752	4.7432	-1.03371
H	3.33501	3.07746	-2.21413
C	4.30567	5.25061	0.25616
H	4.19477	4.80037	2.36717
H	4.27843	5.36463	-1.90654
C	4.86057	6.64039	0.43914
H	5.78777	6.77967	-0.14077
H	4.14455	7.40094	0.08394
H	5.08264	6.85525	1.49447
H	1.28598	0.69913	1.14763
H	2.97602	0.51218	1.63596
C	1.30956	-1.27163	-0.81642
C	1.64448	-1.96085	1.51992
O	0.13036	-0.9141	-0.81141
O	1.82565	-1.9029	-1.83635
O	1.04632	-2.98891	1.31039
O	1.92594	-1.48421	2.7291
C	1.39062	-2.21092	3.84309
H	1.76407	-1.70409	4.7405
H	0.29181	-2.18284	3.81443
H	1.72648	-3.2576	3.81968
C	1.01747	-2.05351	-3.01577
H	0.77921	-1.06143	-3.42356
H	1.63039	-2.62555	-3.72103
H	0.08975	-2.59121	-2.77674
Al	-1.4753	-0.52783	0.28297
C	-2.5245	0.90571	-0.62201
H	-3.43146	0.95752	0.0184
H	-2.90476	0.53217	-1.595
C	-2.31782	-2.34235	0.22072

H	-1.58681	-3.0793	0.60745
H	-2.44414	-2.59786	-0.85115
C	-1.98117	2.33863	-0.80948
H	-1.47521	2.64446	0.12767
C	-3.66553	-2.56927	0.93807
H	-4.39676	-1.83469	0.53295
C	-0.94169	2.40787	-1.93681
H	-1.40087	2.13148	-2.90298
H	-0.53005	3.42544	-2.04751
H	-0.09722	1.72318	-1.76689
C	-3.10441	3.35663	-1.0645
H	-2.71283	4.38293	-1.17656
H	-3.65564	3.10691	-1.98838
H	-3.83357	3.36441	-0.23749
C	-3.56206	-2.31929	2.44945
H	-4.52853	-2.47505	2.95741
H	-2.83216	-3.01215	2.90396
H	-3.22294	-1.29491	2.67555
C	-4.24134	-3.96742	0.66547
H	-4.35964	-4.1463	-0.4157
H	-3.5623	-4.7455	1.05606
H	-5.22736	-4.10881	1.14038
H	-0.75826	-0.08437	1.66692
Al	-7.06039	-0.6196	0.31453
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C	-6.84335	0.16116	-1.49066
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H	-7.58077	0.98873	-1.5469
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C	-6.63218	1.94519	1.92803
H	-5.92145	2.24147	1.13287
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H	-7.97856	-1.28049	-2.63623
C	-7.04064	0.04942	-4.03107
H	-6.09272	0.59592	-4.17809
H	-7.19031	-0.6034	-4.90814
H	-7.85349	0.79416	-4.02407
C	-5.91241	-1.82871	-2.77596
H	-4.91254	-1.36582	-2.84642
H	-5.92159	-2.4654	-1.87567
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C	-6.10645	2.5303	3.2477
H	-6.03472	3.63067	3.20664
H	-6.77615	2.26941	4.08601
H	-5.10551	2.13707	3.48865
C	-7.99565	2.5568	1.57635
H	-8.36484	2.20228	0.59898
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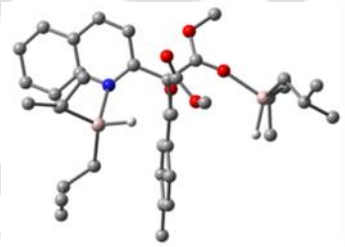

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H	-2.42384	-2.60916	4.11202

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C	-2.30056	-1.92357	3.26941	H	0.44069	2.18529	-2.06588
H	-3.95703	1.48447	0.67635	C	0.61568	5.42574	-1.00258
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C	-1.05294	-1.1313	1.35224	H	0.45066	4.48252	-2.94052
C	-1.19664	-2.0145	2.45706	C	0.6304	6.83563	-1.53528
H	-0.43832	-2.76626	2.64339	H	1.59603	7.3261	-1.32503
N	-2.05858	-0.33276	0.98624	H	0.46874	6.86239	-2.62247
C	0.25757	-1.09234	0.52983	H	-0.15085	7.44986	-1.05801
C	0.42387	0.21122	-0.29019	H	-0.41982	0.35053	-0.97242
H	1.311	0.11568	-0.93744	Al	-2.85167	-0.45078	-1.11135
C	1.5516	-1.18419	1.38422	H	-1.66688	-1.33928	-1.7239
C	0.30464	-2.37385	-0.36623	C	-2.91194	1.43511	-1.80676
O	2.65462	-1.0323	0.86764	H	-2.12576	1.52706	-2.58345
O	1.43794	-1.5167	2.64373	H	-2.58809	2.13699	-1.01424
O	-0.16097	-3.42782	-0.01084	C	-4.56714	-1.45287	-0.83355
O	0.97511	-2.17535	-1.49106	H	-5.38882	-0.73911	-1.03827
C	1.0635	-3.28253	-2.39825	H	-4.71845	-1.75125	0.2211
H	1.74076	-2.9601	-3.19689	C	-4.23986	1.94123	-2.41527
H	1.4612	-4.16949	-1.88596	H	-5.04878	1.78348	-1.6742
H	0.06559	-3.50853	-2.80166	C	-4.75557	-2.70807	-1.72129
C	2.63218	-1.52503	3.44855	H	-4.42177	-2.47155	-2.75189
H	3.07201	-0.51864	3.46278	C	-4.19831	3.44657	-2.72194
H	2.30614	-1.82075	4.45176	H	-3.41207	3.67212	-3.46356
H	3.35986	-2.24291	3.04627	H	-5.15721	3.80909	-3.13121
C	0.63457	1.41772	0.60754	H	-3.97402	4.0351	-1.81703
O	0.86932	1.24734	1.798	C	-4.6202	1.15098	-3.67531
C	0.60713	2.78304	0.01763	H	-5.58096	1.49166	-4.09586
C	0.71035	3.88856	0.88435	H	-3.85201	1.27435	-4.45883
C	0.51125	3.01715	-1.36394	H	-4.71393	0.07165	-3.47143
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H	-6.36501	-4.01452	-2.45853
H	-6.63238	-3.3717	-0.81807
H	-6.85276	-2.31545	-2.23235
C	-3.89943	-3.88126	-1.22463
H	-2.83268	-3.61684	-1.15868
H	-4.22377	-4.19565	-0.2165
H	-3.99017	-4.75793	-1.88793
Al	4.18396	-0.65314	-0.35835
H	3.43836	0.17097	-1.52618
C	5.37764	0.34054	0.89683
H	5.53753	-0.33742	1.76108
H	6.38106	0.41487	0.42809
C	4.73418	-2.52038	-0.83057
H	5.46823	-2.88479	-0.08266
H	3.85524	-3.18468	-0.71139
C	5.32363	-2.73257	-2.2425
H	4.56908	-2.39499	-2.98038
C	6.58253	-1.8828	-2.46778
H	7.00055	-2.03093	-3.47766
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C	5.61632	-4.21239	-2.53545
H	6.37562	-4.60649	-1.83716
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H	5.99618	-4.36353	-3.56105
C	4.97417	1.73741	1.41853
H	3.93684	1.68248	1.80587
C	5.86326	2.20006	2.58412
H	6.9169	2.27993	2.26333
H	5.55599	3.18754	2.97102
H	5.83061	1.48565	3.4241
C	4.98121	2.78468	0.29585
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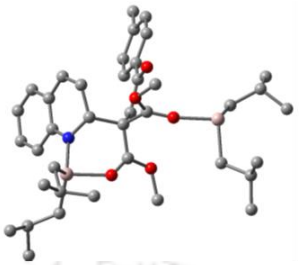
H	4.65599	3.77351	0.66077

I2



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C	3.92694	3.8114	1.32617
H	1.10897	3.74677	-2.64808
H	3.6242	5.90966	0.84983
H	2.10979	5.39438	-1.07317
C	1.38745	2.93777	-1.96573
H	4.05011	1.68162	1.59905
H	4.5966	4.01187	2.16723
C	1.34265	0.55054	-1.27927
C	0.98494	1.67865	-2.21159
H	0.3761	1.43915	-3.08388
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C	0.08588	0.04097	-0.42317
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C	0.60193	-0.96776	0.61571
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O	-0.59241	-0.9394	-2.51405

O	1.68269	-1.5594	0.51528	H	4.29129	-2.06058	1.94386
O	-0.20237	-1.19672	1.61595	H	3.71917	-0.50312	2.50644
C	0.17964	-2.17612	2.60786	C	4.49009	-3.14747	-1.59806
H	-0.58058	-2.10497	3.39227	H	5.2157	-3.27057	-0.77176
H	0.16916	-3.17645	2.15564	C	5.82569	-0.53594	1.97664
H	1.17994	-1.94565	2.99762	H	5.90732	0.54801	1.76813
C	-1.50602	-1.62554	-3.39465	C	3.29731	-4.06654	-1.29716
H	-2.45082	-1.06827	-3.44293	H	2.5227	-3.97229	-2.07912
H	-1.00992	-1.64529	-4.37107	H	3.60183	-5.12572	-1.26187
H	-1.70134	-2.64298	-3.03149	H	2.82231	-3.82496	-0.33272
C	-1.61098	1.95201	-0.62934	C	5.19625	-3.59515	-2.88709
O	-2.06063	1.38622	-1.61608	H	5.5232	-4.64772	-2.83146
C	-2.06718	3.31814	-0.25269	H	4.52167	-3.50045	-3.75635
C	-1.5385	4.0418	0.82932	H	6.08578	-2.97727	-3.09158
C	-3.08989	3.9087	-1.02161	C	6.81015	-1.2481	1.03892
C	-2.02152	5.31572	1.13248	H	7.84704	-0.92213	1.22366
H	-0.73749	3.62688	1.44248	H	6.77565	-2.34151	1.18797
C	-3.5663	5.17645	-0.71284	H	6.58484	-1.05178	-0.02127
H	-3.49852	3.34356	-1.8611	C	6.24123	-0.74172	3.44191
C	-3.04182	5.90599	0.37195	H	5.57612	-0.19333	4.12923
H	-1.59316	5.8635	1.97587	H	6.19223	-1.81027	3.71623
H	-4.36276	5.61578	-1.32035	H	7.27294	-0.39693	3.62674
C	-3.5708	7.27917	0.69723	H	1.60946	-0.32027	-1.89842
H	-3.04206	7.72881	1.54989	Al	-3.56165	-2.34064	-0.34745
H	-3.46754	7.95864	-0.16507	H	-4.07396	-2.6883	-1.83459
H	-4.64467	7.23991	0.94578	C	-2.74137	-3.83479	0.71468
H	0.1042	1.87228	0.72554	H	-1.77918	-4.12718	0.24215
Al	3.43439	-0.74534	-0.01444	H	-2.46123	-3.39822	1.69457
C	4.0759	-1.65881	-1.65867	C	-4.60428	-0.92834	0.61048
H	4.95381	-1.06382	-1.98439	H	-4.32002	-0.91494	1.68335
H	3.34962	-1.53105	-2.48613	H	-4.26291	0.04696	0.20991
C	4.36229	-0.97193	1.73451	C	-3.56137	-5.11972	0.96999

H	-4.53978	-4.82614	1.39825
C	-3.84318	-5.8858	-0.33046
H	-4.37629	-5.26204	-1.06508
H	-2.89906	-6.21328	-0.80164
H	-4.45031	-6.78797	-0.14597
C	-2.88547	-6.04232	1.99682
H	-3.48849	-6.94416	2.20076
H	-1.89879	-6.37808	1.6304
H	-2.72429	-5.52422	2.95706
C	-6.14387	-0.98377	0.50582
H	-6.41102	-0.96337	-0.56862
C	-6.71136	-2.28621	1.08772
H	-6.44905	-2.38814	2.15577
H	-7.81105	-2.32384	1.01091
H	-6.31641	-3.17381	0.56465
C	-6.8142	0.23314	1.16268
H	-7.91186	0.21349	1.04534
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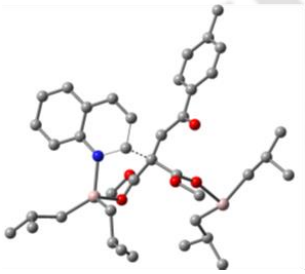
H	-6.44586	1.17576	0.72523

TS-1



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C	-3.50961	2.93562	-1.10574
C	-3.6559	4.1431	-1.77945
H	-0.02239	4.56087	1.43889
H	-2.91064	6.165	-2.06405
H	-1.0968	5.88921	-0.37027
C	-0.59543	3.68516	1.12028
H	-4.19796	2.11911	-1.31205
H	-4.46196	4.24951	-2.51029
C	-1.15303	1.30929	1.24033
C	-0.38522	2.4758	1.68799
H	0.35787	2.32726	2.47133
N	-2.34863	1.55132	0.54534
C	0.08511	0.20178	0.17976
C	1.26734	0.99401	-0.37838
H	1.77777	0.42574	-1.17578
C	0.57461	-0.9671	1.02367
C	-0.81552	-0.31549	-0.85466
O	1.44004	-1.72708	0.58988
O	-0.0085	-1.16098	2.17847
O	-1.90764	-0.87174	-0.58881
O	-0.47436	-0.08024	-2.10486
C	-1.36076	-0.49852	-3.15794
H	-0.86094	-0.21359	-4.09025
H	-1.50546	-1.58643	-3.11651
H	-2.32935	0.01213	-3.06772
C	0.47054	-2.23529	3.01491
H	1.49543	-2.00598	3.33875
H	-0.21141	-2.26489	3.87153
H	0.46329	-3.18624	2.46645
C	2.31917	1.33217	0.66672
O	2.28499	0.79587	1.76556
C	3.40853	2.28822	0.31419
C	3.50783	2.91663	-0.93857
C	4.39109	2.56538	1.28419
C	4.55836	3.79429	-1.21009

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H	4.31362	2.07209	2.25469	C	-7.21963	0.13369	-1.86125
C	5.53917	4.07366	-0.24616	H	-6.78091	0.47383	-2.81385
H	4.61839	4.27159	-2.19184	H	-7.42177	-0.94737	-1.95856
H	6.18626	3.64344	1.7754	H	-8.18943	0.64495	-1.73665
C	6.68381	5.00962	-0.53836	H	-1.27791	0.55175	2.01362
H	6.56541	5.50804	-1.51129	Al	2.38416	-3.2879	-0.17555
H	6.77115	5.78773	0.23743	H	2.04821	-4.39772	0.94441
H	7.64295	4.46447	-0.55369	C	1.37952	-3.43536	-1.9072
H	0.89671	1.91247	-0.8558	H	0.30676	-3.62048	-1.68543
Al	-3.39702	-0.09007	0.41401	H	1.40919	-2.43426	-2.38407
C	-3.57259	-0.94713	2.19835	C	4.25289	-2.60239	-0.32236
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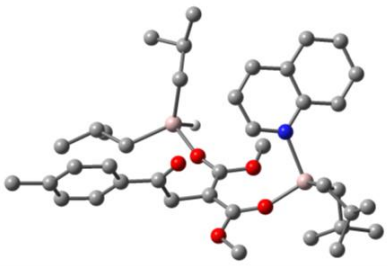
I3



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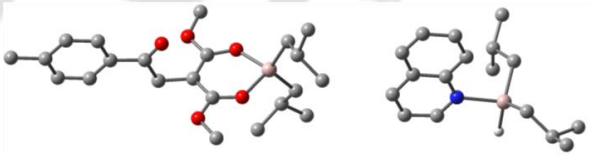
I4



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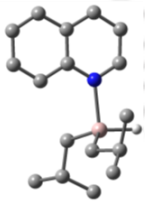

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H	0.59896	3.39382	-0.61476

H	0.00566	4.51277	0.63547
H	0.51657	0.14532	2.92546

List of publications

1**. Sarmah, B. K**.; Konwar, M.; Bhattacharyya, D.; Adhikari, P.; Das, A. Regioselective Cyanation of Six-Membered *N*-Heteroaromatic Compounds Under Metal-, Activator-, Base- and Solvent-Free Conditions. *Adv. Syn. Cat.* **2019,** *361*, 5616-5625.

2. **Sarmah, B. K**.; Konwar, M.; Das, A. Site-Selective Deoxygenative Amination of Azine *N*-Oxides with Carbodiimides under Catalyst-, Activator-, Base-, and Solvent-Free Conditions. *J. Org. Chem.* **2021**, *86*, 10762–10772.

3. **Sarmah, B. K.**; Konwar, M.; Das, A. Copper-Catalyzed Oxidative Dehydrogenative Reaction of Quinoline-*N*-Oxides with Donor−Acceptor Cyclopropanes: Installation of a Tertiary Alkyl Motif at C2 Position. *Org. Lett.* **2021**, *23*, 8390−8395.

4. Bhattacharyya, D.; **Sarmah, B. K.**; Nandi, S.; Srivastava, H. K.; Das, A. Selective Catalytic Synthesis of α-Alkylated Ketones and β-Disubstituted Ketones via Acceptorless Dehydrogenative Cross-Coupling of Alcohols. *Org. Lett.* **2021,** *23*, 869-875.

5. Bhattacharyya, D.; Nandi, S.; Adhikari, P.; **Sarmah, B. K**.; Konwar, M.; Das, A. Boric acid catalyzed chemoselective reduction of quinolines. *Org. Biomol. Chem.* **2020,** *18*, 1214-1220.

List of conferences attended

1. Research Conclave 2018 (IIT- Guwahati) - Poster presentation (3rd best poster award)
2. Frontiers in Chemical Sciences 2018 (IIT- Guwahati) - Poster presentation
3. Modern Trends in Inorganic Chemistry XVIII 2019 (IIT- Guwahati) - Poster presentation
4. Recent Trends in Chemical Sciences 2020 - Oral presentation (Best presentation award)
5. North-East Research Conclave 2022 (IIT Guwahati) – Poster presentation