Catalytic (De)hydrogenative Annulation by Well-defined Mn(I) and Co(II)-complexes for the Construction of N-Heterocycles

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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Dedicated

to

My Parents

&

Teachers

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Statement

I, hereby declare that the work comprised in this thesis entitled "***Catalytic (De)hydrogenative Annulation by Well-defined Mn(I) and Co(II)-complexes for the Construction of N-Heterocycles***" is the outcome of the research work carried out by me under the supervision of **Prof. Dipankar Srimani, 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 acknowledgments 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 **"*Catalytic (De)hydrogenative Annulation by Well-defined Mn(I) and Co(II)-complexes for the Construction of N-Heterocycles*"** which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by **Mr. Debjyoti Pal** (Roll No: **186122010**) was carried out by him under my supervision at this institute. The work presented in his thesis is original and has not been submitted elsewhere for a degree.

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Thank You

-Debjyoti

Contents

Abbreviation

Ac	Acetyl
α	Alpha
Å	Angstrom
Ar	Argon
ACN	Acetonitrile
AD	Acceptorless dehydrogenation
ADC	Acceptorless Dehydrogenative coupling
Br	Broad
β	Beta
Bn	Benzyl
Bu	Butyl
Cat	Catalyst
D	doublet
Dd	Doublet of doublet
δ	Chemical shift
DA	Donor-acceptor
DCE	Dichloroethane
DCM	Dichloromethane
DMSO	Dimethylsulfoxide
DMF	Dimethylformamide
DMA	Dimethyacetamide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
EtOAc	Ethyl acetate
Equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
EDG	Electron donating group
g	Grams
γ	Gamma
HA	Hydrogen-autotransfer
HRMS	High resolution mass spectrometry

Hz	Hertz
MHz	Mega Hertz
i	Iso
FT-IR	Fourier transform infrared spectroscopy
J	Coupling constant
m	multiplet
mg	Milligram
mmol	Millimole
MS	Molecular sieves
Mp	Melting point
MLC	Metal-ligand cooperation
NMR	Nuclear magnetic resonance
Ts	Tosylate
o	*Ortho*
m	*Meta*
p	*Para*
PNP	2,6-bis-(di-*tert*-butylphosphinomethyl)pyridine
ppm	Parts per million
THF	Tetrahydrofuran
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
t	Tert
TMS	Tetramethylsilane
TS	Transition state
XRD	X-ray diffraction
rt	Room temperature
ORTEP	Oak ridge thermal ellipsoid plot program

Abstract

The contents of the present thesis entitled as "**Catalytic (De)hydrogenative Annulation by Well-defined Mn(I) and Co(II)-complexes for the Construction of N-Heterocycles**" have been divided into five chapters. The first chapter contains a brief literature overview on construction of various (de)hydrogenative heterocycle synthesis and the last four chapters were based on the results achieved from the experimental works performed during the entire course of the PhD research programme.

Chapter I: A brief introduction about the catalytic (de)hydrogenative transformation towards the construction of heterocycles

The synthesis of N-heterocycles has always been considered an emergent topic of chemical research due to its widespread usage in medicinal chemistry, material science, and natural product synthesis. The development of green, atom economical and sustainable strategies to construct those N-heterocycles employing readily available renewable starting material is a high priority for the scientific community. Alcohol is a suitable candidate to meet this demand, as it is an economically viable and widely abundant greener starting material derived from a diverse range of sustainable resources. Therefore, envisaging both noble and earth-abundant 3d-transition metal-based catalytic protocol for the benign synthesis of those N-heterocycles via Acceptorless Dehydrogenative Annulation (ADA) pathway where water and molecular hydrogen were solely liberated as eco-friendly by-products is a demanding process. **Chapter I** shed light on a brief overview about the documented literatures on the transition metal catalyzed synthesis of both saturated and unsaturated N/O/S-heterocycles employing acceptorless dehydrogenation (AD) and borrowing hydrogen (BH) or hydrogen auto-transfer (HA) strategy accessing alcohols as a key coupling partner.

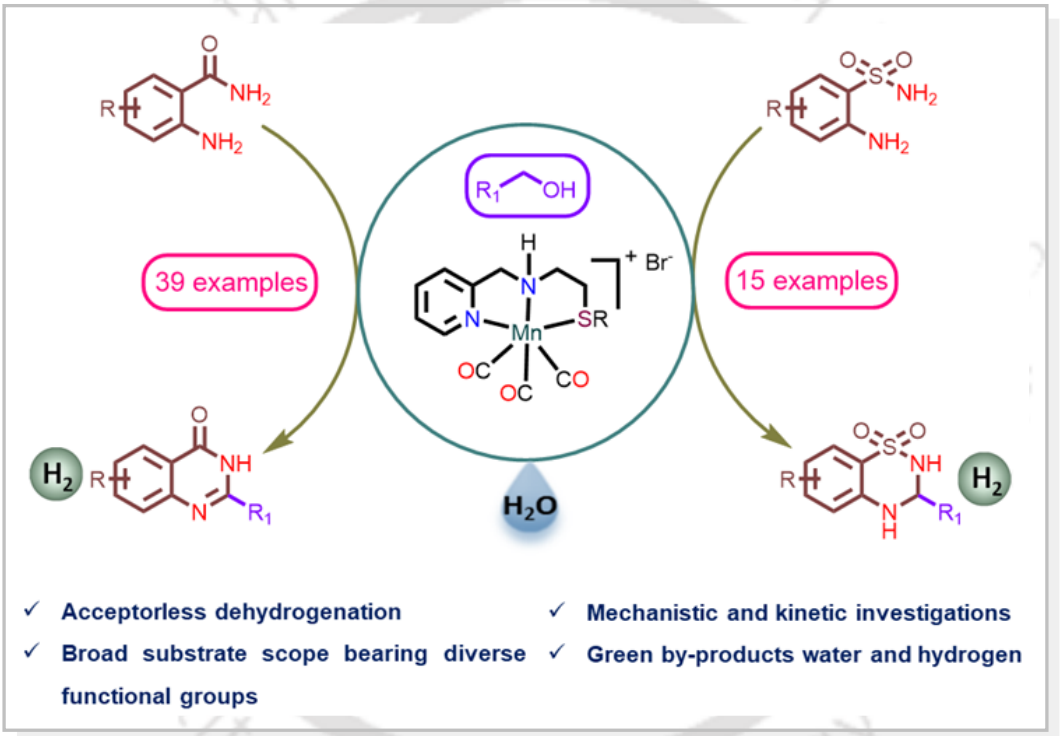
Aim of the Thesis:

The documented literature reports on the synthesis of both saturated and unsaturated heterocycles displayed that over the last few decades, this was mainly dominated by air, moisture sensitive, costly, sophisticated phosphine ligand bearing both noble and 3d-transition metal-based catalysts. Henceforth, the present thesis is focused on designing and synthesizing various phosphine-free, air and moisture stable ligands and their easily accessible Mn(I) and Co(II) complexes which are well characterized by various spectroscopic and spectrometric techniques. Afterwards, the intension was to explore their catalytic activity towards the synthesis of various N-heterocycles, which are basic structural unit or building block of several natural products.

Chapter II: Well-defined Manganese Complex Catalyzed Dehydrogenative Synthesis of Quinazolin-4(3H)-ones and 3,4-Dihydro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides

Manganese is the third most abundant transition metal in the earth's crust (950 mg kg^{-1}), less toxic as compared to its higher analogs and plays an important role in several biological systems. Apart from that, the existence of wide range of oxidation state (-3 to +7) and coordination number (up to 7) makes it a suitable candidate for catalysis. However, it's applicability towards acceptorless dehydrogenation

and hydrogenation reaction was untapped until 2016. Since then, there has been significant advancement in this field. However, the synthesis of N-heterocycles via the Mn-catalyzed acceptorless dehydrogenative coupling (ADC) method was in nascent stage. Intrigued by this report, **chapter II** described about Mn-catalyzed synthesis of quinazoline-4(3H)-ones and 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides via acceptorless dehydrogenative annulation (ADA). This method features the usage of various primary alcohols including benzyl alcohol bearing tolerable functional groups, heteroaryl and aliphatic alcohols as coupling partners furnishing good to excellent yields. The synthetic value of this procedure was showcased by the efficient construction of 2-(quinolin-2-yl)quinazolin-4(3H)-one, which is an intermediate for Luotonins A, B, and E. Detailed mechanistic investigations and kinetic monitoring were performed to understand the reaction sequence and the role of the catalyst in different steps.



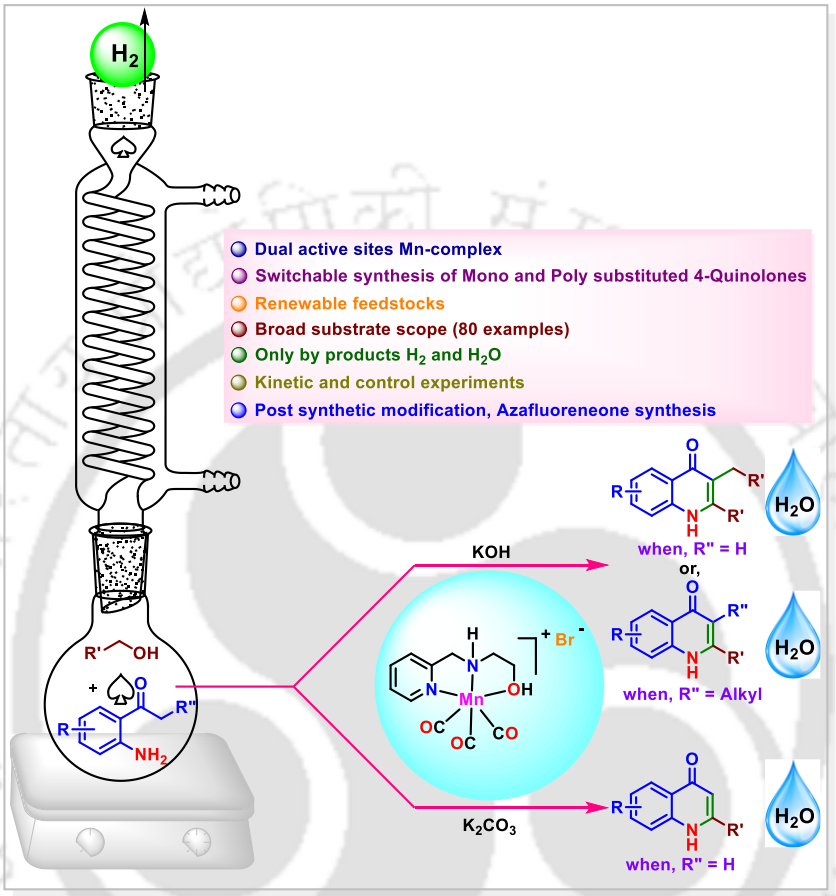
Scheme 1: A schematic representation of the research work covered in chapter **II**.

Publication: *Catal. Sci. Technol.* **2022**,*12*, 3202-3208.

Chapter III: Manganese Complex Catalyzed (De)hydrogenative Cyclization toward the Selective Synthesis of 2-Substituted and 2, 3-Disubstituted 4-Quinolones

4-quinolones and its derivatives displayed a broad spectrum of biological and pharmaceutical activity. Furthermore, they have the potentiality to regulate and cure various acute and chronic diseases including ischemia, pain, inflammation, immunomodulation, malarial, bacterial, fungal infection, HIV, cancer etc. This prolific importance of aforementioned N-heterocycle lured scientific community to develop green, atom-economical and energetically efficient synthetic strategies to construct employing an

economically viable and widely abundant renewable starting material like alcohol. Hence, the development of new and efficient base metal catalysts to manifest these selective transformations via Acceptorless Dehydrogenative Annulation (ADA) and Borrowing Hydrogen (BH) pathway offered a sustainable and ever demanding route, as eco-friendly by-products water and molecular hydrogen get liberated.



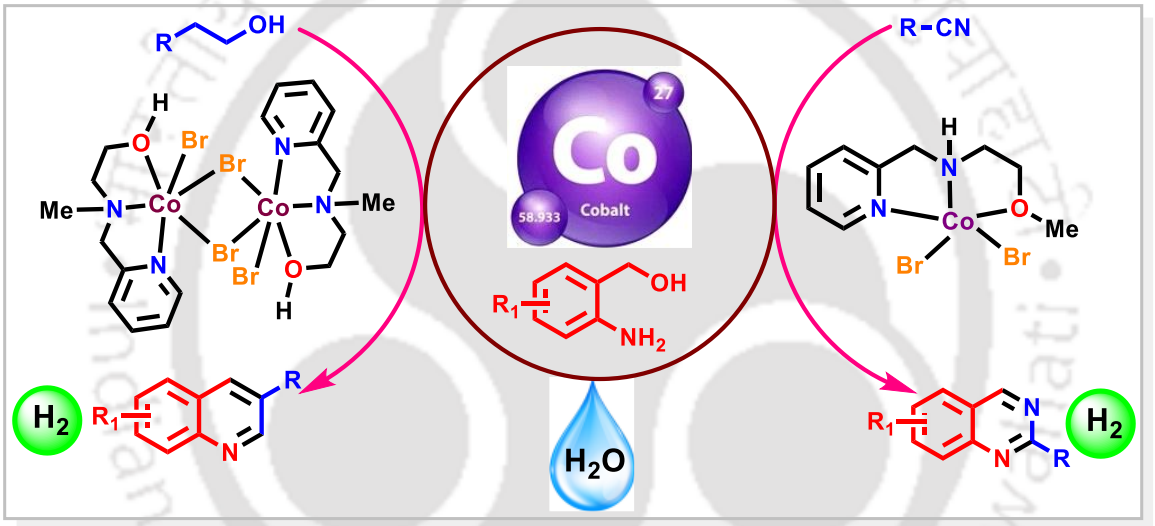
Scheme 2: A schematic imprint of the research work covered in chapter **III**.

In **chapter III**, it has been highlighted about phosphine-free well-defined bifunctional NNO-Mn(I) catalyzed switchable synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one and 2-phenylquinolin-4(1H)-one via dehydrogenative annulation of alcohols with 2-amino phenyl ketones. The developed protocol showcased ample substrate scope with good selectivity for a host of alcohols with diverse acetophenones. To demonstrate the utility and efficacy of that present catalytic strategy, some post synthetic modification was conducted where some 4-quinolones with antibiotic properties and azafluoreneone derivative have accomplished. In order to underpin the mechanistic investigation, a series of control and kinetic experiments were performed, which displayed that for the construction of both heterocycles, formation of the C-C bond get priority over the C-N bond formation and dehydrogenation of alcohol is the slowest or rate determining step.

Publication: *Manuscript under preparation*.

Chapter IV: Designing Cobalt(II) Complexes for Tandem Dehydrogenative Synthesis of Quinoline and Quinazoline Derivatives

Chapter IV highlighted about the cascade dehydrogenative synthesis of wide range of C-3-substituted quinoline and quinazoline derivatives with good to excellent isolated yields employing 2-aminobenzyl alcohol as a stable and inexpensive key coupling partner. To pursue these objectives, in this work, three new phosphine-free tridentate NNO-Co(II) complexes employing inexpensive and easily accessible precursor $CoBr_2$ was constructed. The metal ligand-cooperation behavior of the alkoxy arm was utilized to explore the catalytic activities of these complexes towards dehydrogenation. The selective synthesis of C-3-substituted quinolines of this catalytic protocol depend on the slow dehydrogenative transformation of 2-aminobenzyl alcohol into 2- aminobenzaldehyde as well as primary alcohol to its aldehyde by circumventing and suppressing its deoxygenative self-coupling nature and Guerbet reaction possibility.



Scheme 3: A schematic demonstration of the research work covered in chapter **IV**.

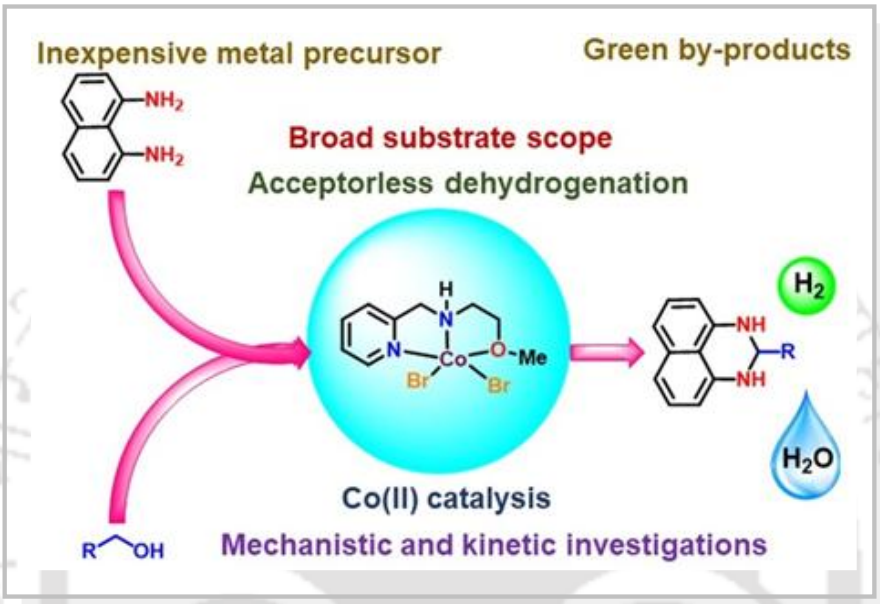
Apart from that, the developed protocol's usefulness was enhanced by the chemoselective transformation of natural monoterpenoids and different fatty acid derived alcohols to synthesize heterocycles having distal unsaturation and synthetic efficacy was enhanced by demonstrating some post-synthetic modifications. Various kinetic, mechanistic, and control studies were conducted to comprehend the reaction route.

Publication: *Org. Lett.* **2024**, *26*, 514–518.

Chapter V: Well-defined Cobalt(II) Catalyzed Synthesis of 2,3-Dihydro-1*H*-Perimidines via Acceptorless Dehydrogenative Annulation

The versatility of the perimidine moiety offers a rich playground for researchers in fields ranging from medical science to industrial chemistry. Upon spurred by its fascinating structural architecture and prolific biological eminence, in **chapter V** the tandem synthesis of 2,3-dihydro-1*H*-perimidine derivatives employing pre-synthesized well-defined phosphine-free NNO-Co(II)-complex via

acceptorless dehydrogenative annulation (ADA) of 1,8-diaminonaphthalene (DAN) with a diverse range of primary alcohols including benzylic, heteroaryl containing and cyclic/acyclic aliphatic alcohols was presented where they have furnished good to excellent isolated yields. Furthermore, the catalytic protocol was also suitable for naturally occurring unsaturated fatty acid derived alcohols such as oleyl alcohol, 9-decen-1-ol with whom they reacted well affording the targeted heterocycles chemoselectively in good yields keeping distal unsaturation intact. Several kinetic and control tests were carried out in order to understand the reaction sequence.



Scheme 4: A schematic showcased of the research work covered in chapter **V**.

Publication: *Org. Biomol. Chem.* **2024**, *22,* 8602–8607.

Chapter 1

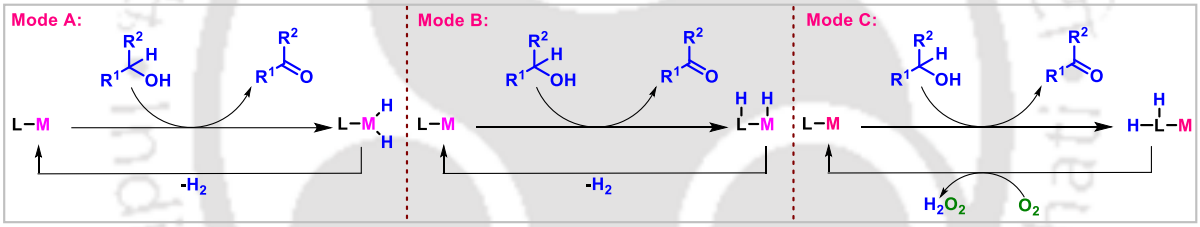
General Introduction: (De)hydrogenative Heterocycle Synthesis

1.1. Introduction:

Heterocycles are one of the immense, diverse and fascinating arenas of chemistry, which is identified by their profound application in many biological processes. In fact, they are the fundament of modern medicinal chemistry and pharmacology, used as key building blocks in the realm of drug design and discovery[1] evident from the FDA approved database revealing that 60% of structurally unique small molecule drugs contain these N-heterocyclic scaffolds[2] and also one report in 2021 displaying that 8 out of 20 top seller blockbuster drugs contain at least one active heterocycle. Aside from that, they are the essential structural scaffolds of numerous natural products,[3] catalysts, advanced materials[4] and exhibit omnipresence in agrochemical industry,[5] dye industry.[6] Due to the high prevalence of this, the creation of efficacious strategies has been instigated as a central goal for both academic and industrial perspectives. In that quest, over the decades, a series of classical approaches have been developed and documented, however, many of these approaches involve the usage of expensive reagents, harsher reaction conditions, cumbersome work-up procedures, longer reaction times and especially generating over-stoichiometric amounts of wastages.[7] To circumvent these issues scientific fraternity very much prompt to design and develop a clean, green, selective and efficient synthetic process which rely on homogeneous transition metal catalyzed sustainable chemical transformation utilizing simple and abundant starting material derived from renewable resources under relatively milder conditions. In the modern era, the relentless march of population growth and technological development has not only taken a severe toll on the delicate balance of our natural world but also has placed an unprecedented strain on the planet by confining the resources, intensifying the usage of various chemical feedstocks and energy to meet the ongoing demand. Reports suggested that the majority of the chemical compounds are currently produced from finite fossil fuel resources such as oil or coal.[8] However, the anticipation of rapid depletion of fossil fuels and their usage in which the natural cycle and biosphere get manifold disrupted leading to global climate change remained as an alarming point. Thus, there is a growing impetus to hunt for alternative raw materials. Lignocellulosic biomass is a proper candidate as it is widely abundant, generating from food and agricultural waste.[9] Nevertheless, lignocellulose can be processed to alcohols.[10] Henceforth, transition metal catalyst mediated dehydrogenative construction of diverse range of N-heteroarenes is still a demanding process. The high atom-efficiency and excellent redox economy of the Acceptorless Dehydrogenation (AD) and Borrowing Hydrogen (BH) or Hydrogen Auto-transfer (HA) strategies brings an unwavering attention and substantial motivation to the contemporary science.

1.2. Catalytic dehydrogenative approach behind the formation of C-heteroatom bond:

The major step involved for construction of C-heteroatom bond *i.e.* for the formation of N-heteroarenes from abundantly available and key renewable starting material alcohols is the catalytic dehydrogenative activation of alcohols.[11] The dehydrogenation of alcohols can be proceed via three different pathways which are outlined in scheme **1.1**. In pathways 'A' and 'B', H_2 get released whilst in pathway 'C' the necessity of O_2 is to get back the active catalytic species with the concomitant liberation of H_2O_2. Both pathways 'A' and 'B' well-known as Acceptorless Alcohol Dehydrogenation (AAD) which is potentially operated by redox-innocent ligand bearing transition metal catalysts, whereas, the pathway 'C' accessed by transition metal complex bearing redox-active ligands.[12] Again, amidst of that, pathway 'A' which is named as classical AAD undergoes via initial oxidative addition with the subsequent β-H elimination of the metal-alkoxide species leads to the generation of metal-dihydride intermediate along with the carbonyl product. The metal-dihydride intermediate undergoes reductive elimination regenerated the active catalyst and liberated H_2 molecule. However, in pathway 'B' the AAD undergoes via metal-ligand cooperation (MLC) strategy[13] where metal centre, ligand motif actively participate in bond-making as well as bond-breaking process in a concerted manner and during the course of bond activation both centres have chemically adjusted.

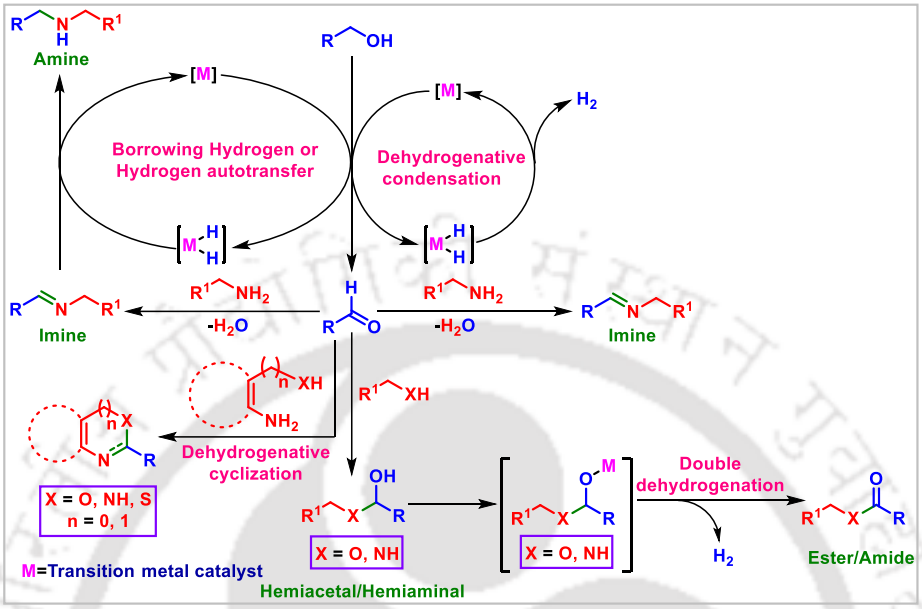


Scheme 1.1. General scheme on different modes of catalytic dehydrogenation of alcohols.

Acceptorless dehydrogenative coupling (ADC) is a coupling reaction where one or more substrates will undergo dehydrogenation furnishing a reactive nucleophilic or electrophilic intermediate. Subsequently, an added nucleophile or a nucleophile of the parent substrate will couple with the electrophilic intermediate forming an another transient intermediate viable for either dehydrogenation or condensation to afford the final product. The concomitantly liberated hydrogen will not involve in the reaction.[14] Nevertheless, during the dehydrogenation of one or more hydrogen rich or hydrogen donor substrate, if the liberated hydrogen get stored into its catalytic metal fragment forming $[MH_2]$-species and released in the final hydrogenation step transforming the unsaturated transient intermediate into the saturated product with concomitant formation of active catalyst, then this principle was named as 'Borrowing Hydrogen (BH)' or 'Hydrogen Auto-transfer (HA)', first coined by *Williams et. al.* in 2004 (Scheme **1.2**).[15]

For the dehydrogenative construction of heterocycles, it involved the transformation of highly stable alcohol into its potential electrophilic analogue carbonyl compounds. Then there is a nucleophilic attack by amine forming imine with the liberation of water as byproduct. This imine can be converted into amine by borrowing hydrogen catalysis or it may be converted to N-heteroarenes depending on the

catalyst and reaction conditions. Sometimes depending on the nature of the catalyst, its structural property and activity, double dehydrogenation of hemiaminal or hemiacetal takes place, leading to the formation of amide or ester before eliminating water (Scheme **1.2**).[16] These are the subsequent phenomenon noticed during the construction of heterocyclic moieties.



Scheme 1.2. General mechanistic outline enroute to Dehydrogenative formation of C-heteroatom bond.

1.3. Synthesis of heterocyclic compounds via dehydrogenative coupling of alcohols:

For the sake of green and sustainable transformations, manufacturing a plethora of both saturated and unsaturated biologically and industrially important heterocyclic scaffold employing readily available, biomass derived, renewable and greener starting material alcohol with the aid of transition metal catalyst via 'ADC' or 'BH' approached lured a substantial attraction for its high atom-efficiency, excellent redox-economy, low cost and waste-free feature.[17] In this strategy, first alcohol undergoes metal mediated dehydrogenation furnishing the corresponding carbonyl analogue releasing H_2 as a greener by-product, which then coupled with suitable nucleophile (N, O and S) delivered the desired heterocycle eliminating H_2O as another greener by product. Instead of releasing H_2 if it gets stored into the metal cavity which get transformed in the final step to the coupling product, it accomplished saturated heterocyclic scaffold. Therefore, both saturated and unsaturated heterocycle can be furnished from same set of coupling partner upon designing suitable catalytic scaffold and varying reaction condition.

1.3.1. Unsaturated N-heterocycles synthesis via dehydrogenative pathway:

Unsaturated N-heterocycles are ubiquitous and privileged scaffolds in pharmaceuticals and biological compounds and they are commercially available at low cost. Due to their manifold usefulness, over the years, construction of unsaturated N-heterocycles provides an implausible interest and realm over saturated N-heterocycles.

1.3.1.1. Dehydrogenative approach towards 5-membered N-heterocycles synthesis:

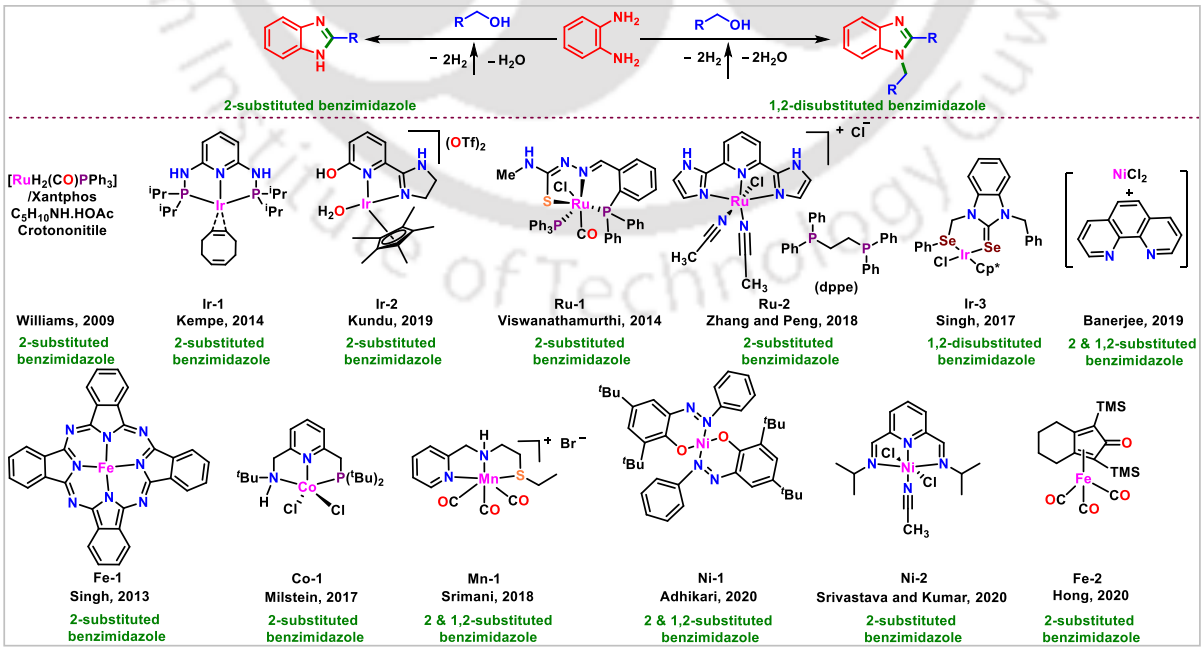
1.3.1.1.1. Benzimidazole (2-substituted and 1,2-disubstituted) synthesis via dehydrogenative pathway:

The sustainable synthesis of benzimidazole and its derivatives has gained an unwavering attention due to its promising biological activity and essential building block for pharmaceutical industry.[18] Traditionally upon condensation of 1,2-diaminobenzenes with carboxylic acids, acid chlorides or anhydrides under harsh reaction condition benzimidazoles and their derivatives can be synthesized however, these methods suffered from lack of atom-economy and incompatible in presence of tolerable functional group.[19] Alternatively, in the sustainable strategy it can be fabricated by transition metal catalyst mediated acceptorless dehydrogenative coupling of 1,2-diaminobenzenes with alcohols where H_2O and H_2 released as sole by-products. Apart from that, it can also be synthesized from 2-nitroaniline derivatives.

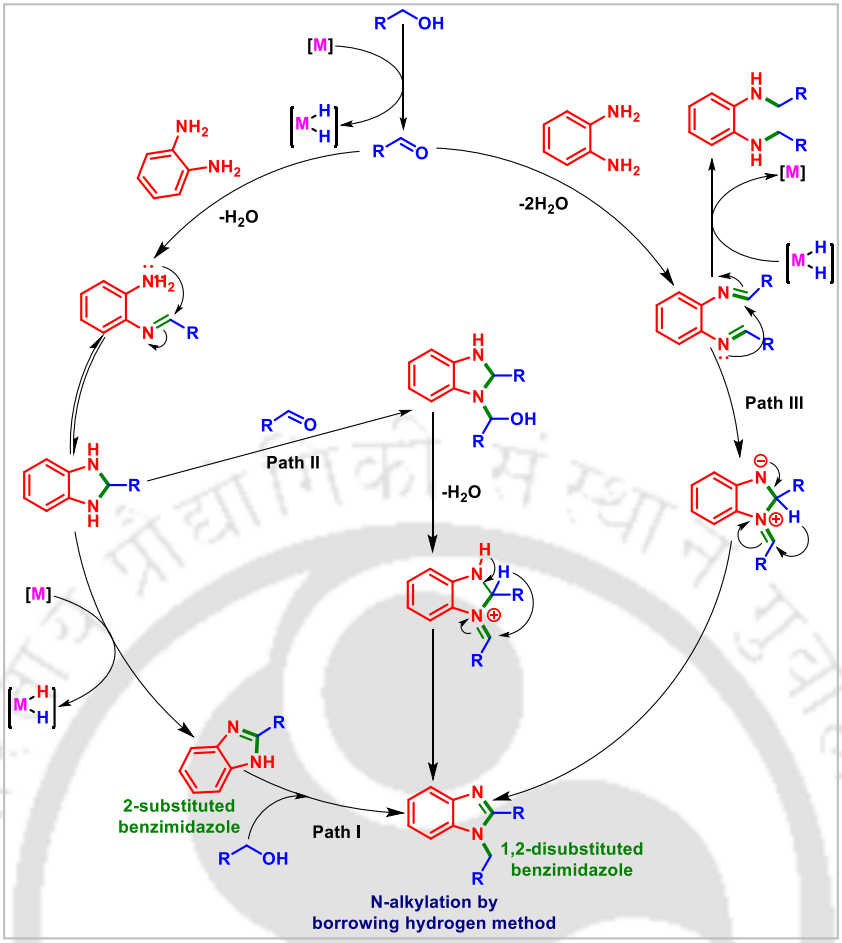
1.3.1.1.1.1. From *o*-phenylenediamines:

In 1991, *Watanabe group* introduced sustainable synthesis of benzimidazole first via ADC employing precious Ru-complex at elevated temperature (215 °C).[20a] Afterwards, in 2009, *the William group* developed a catalytic system based on easily accessible Ru(II) precursor, $[RuH_2(CO)(PPh_3)_3]$ with assortment of bidentate ligand xantphos and hydrogen acceptor crotononitrile and applied them towards the construction of aforementioned heterocycle via dehydrogenative coupling of o-aminoaniline and primary alcohol in refluxing toluene.[20b] However, the catalytic protocol is limited for only aromatic alcohol with moderate isolated yield. Later on, in 2014, *Kempe et. al.* demonstrated tridentate PNP-ligand stabilized Ir(I)-complex (**Ir-1**) catalyzed benzimidazole synthesis.[20c] Their catalytic system exhibits high efficiency for various aliphatic and good chemoselectivity for olefin containing aromatic primary alcohol. Recently, *the Kundu group* reported bidentate phosphine free 2-hydroxypyridine based water soluble Ir(III) complex (**Ir-2**) catalyzed similar transformation in green, nontoxic and non-flammable solvent water under base-free condition.[20d] Later, there are several catalytic protocol has been developed by various groups employing Ru[20e,f] and Pd[20g] to conduct the synthesis of aforesaid heterocycle, however, in terms of cost-effectiveness, availability and sustainability, a continuous hunt is going on to develop base metal based catalytic system in scientific community. In that quest, in 2013, *Singh and co-workers* manifested an inexpensive and efficient Fe(II)-phthalocyanine complex (**Fe-1**) to catalyse the coupling between alcohols with diamines towards construction of 2-substituted benzimidazole with few examples.[20h] In 2017, the pioneering *Milstein group* first time reported PNN-Co(II)-complex (**Co-1**) catalyzed 2-substituted benzimidazole synthesis form the same set of coupling partners with the concomitant release of water and two molecules of hydrogen as green by-products under base free condition.[20i] To pursue this the active catalytic paramagnetic Co(I)-species has been generated upon combination of 5 mol% of $NaHBEt_3$ as a hydride source with equal amount of **Co-1** complex and KO^{t}Bu as a base at 140 °C. 4Å MS plays a crucial role to achieve the highest yield.

Mechanistic studies comprises that the initial formed paramagnetic (PNNH)Co(I)-Cl species performs the actual dehydrogenative transformation of alcohol to aldehyde by liberating H_2 which then coupled with *o*-phenylenediamine formed benzimidazole and H_2O. In the very next year, *Srimani and co-workers* reported a tridentate NNS-MN(I)-complex (**Mn-1**) which is phosphine free for the selective synthesis of both benzimidazoles (2-substituted and 1,2-disubstituted) upon fine adjustment of the reaction parameters.[20j] Both benzylic and heteroaromatic alcohols furnished good yield whilst aliphatic alcohol delivered poor yield. Mechanistic investigation for the formation of both benzimidazoles (2-substituted and 1,2-disubstituted) has been documented by the author which underpin that out of three possible pathways the reaction followed path III via intermediate bisimine formation (Scheme **1.4**). In 2019, *Banerjee et. al.* accomplished both employing simple and inexpensive Ni-precatalyst, $NiCl_2$ with the assortment of 1,10-phenanthroline ligand from *o*-phenylenediamine and alcohols.[20k] In the very next year, *the Adhikari group* communicate molecularly well-defined, isolable and bench-stable redox-active azo-backbone containing Ni-complex (**Ni-1**) which by hydrogen atom transfer (HAT) mechanism enable to commensurate both 2-substituted and 1,2-disubstituted benzimidazoles.[20l] They conducted it by employing **Ni-1** catalyst with catalytic quantity of base KO^{t}Bu at 80 °C affording ample scope and till date it is the mildest, selective and efficient approach to construct aforesaid both. In the same year, *Srivastava and Kumar* reported NNN-Ni(II)-pincer complex (**Ni-2**) catalyzed sustainable synthesis of 2-substituted benzimidazoles at 200 °C under an open atmosphere in solventless condition displaying 12 examples with a moderate turnover number (TON).[20m] Later, *Hong et. al.* selectively synthesized 1,2-disubstituted benzimidazoles employing their Knölker type tricarbonyl Fe-complex (**Fe-2**) in accordance with the oxidant trimethyl N-oxide (TMAO) from 1 equiv. of *o*-phenylenediamine with an array of alcohols of 2.5 equiv. (Scheme **1.3**).[20n]



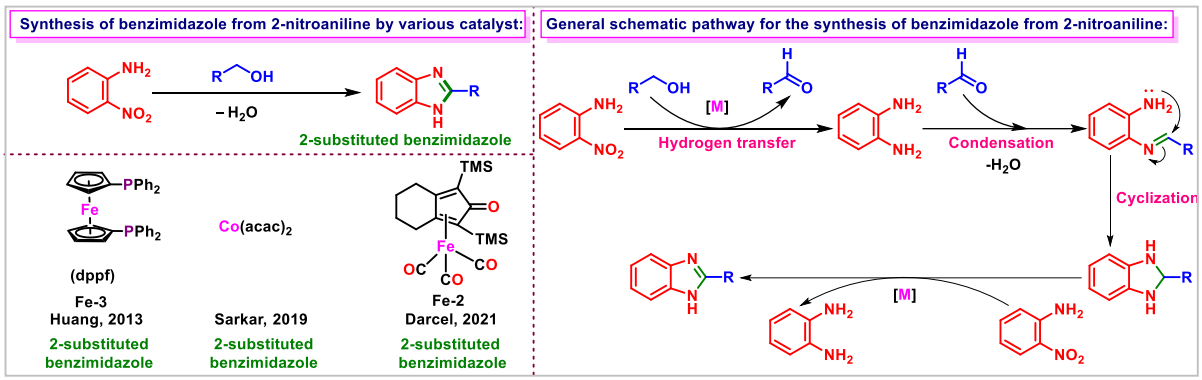
Scheme 1.3. Selective construction of 2-substitued and 1,2-disubstituted benzimidazoles by different catalysts.



Scheme 1.4. Probable mechanistic cycle for the construction of 2-substitued and 1,2-disubstituted benzimidazoles.

1.3.1.1.1.2. From *o*-nitroanilines:

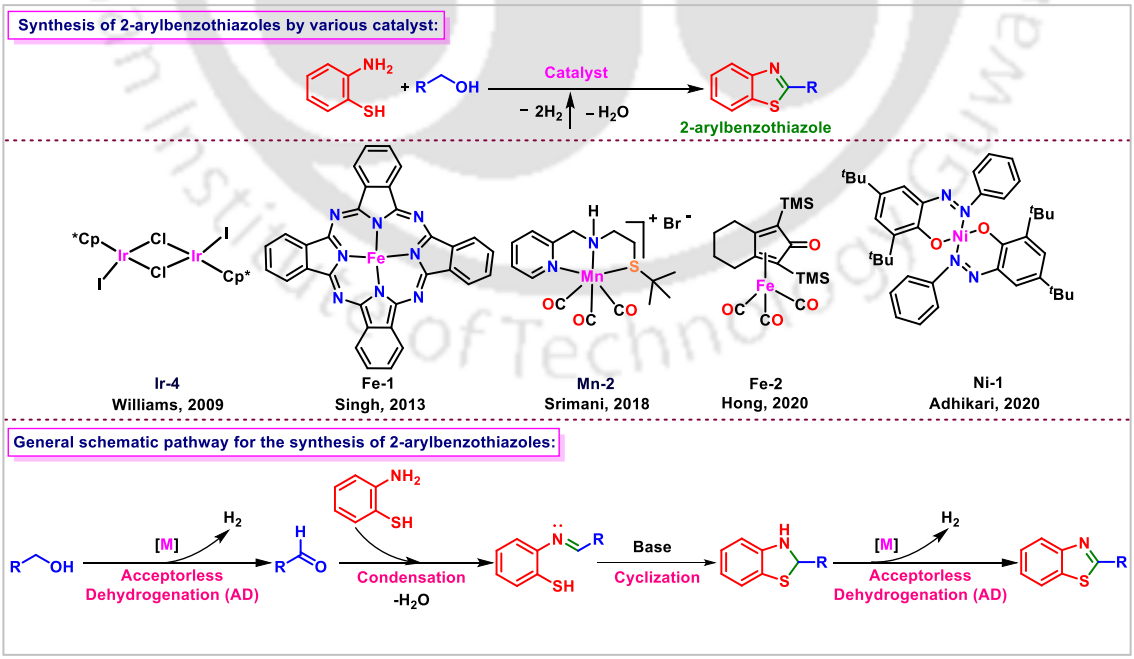
Construction of benzimidazoles taken with alcohol is mostly explored employing *o*-phenylenediamine as a coupling partner, however, the *o*-phenylenediamine are preliminary synthesized from 2-nitroaniline, which is stable as compared to *o*-phenylenediamine. Therefore, fabrication of benzimidazole via direct transformation of 2-nitroaniline to *o*-phenylenediamine using alcohol in absence of foreign reducing agents followed by coupling of alcohol is a step-economical and eco-friendly process. In that parenthesis, alcohol act as a hydrogen donor and nitro act as a hydrogen acceptor. Based on that concept, in 2013, the cyclization employing dppf (**Fe-3**) as a catalyst via hydrogen transfer pathway demonstrated by *Huang and co-workers*.[21a] However, in 2019, *the Sarkar group* reported $Co(acac)_2$ catalyzed coupling of 2-nitroanilines and alcohols in selective formation of 2-substituted benzimidazoles in any additional ligand system absence.[21b] The kinetic experiment revealed that electron-releasing group bearing alcohol get faster oxidized as compared to its electron-withdrawing analogue. In the very next year, *Darcel et. al.* applied the **Fe-2** complex in assortment with Me_3NO.[21c] In that strategy they used DDQ as an additional additive at very high temperature whose role is to oxidize the dihydrobenzimidazole intermediate towards the formation of 2-substituted benzimidazole with a few examples (Scheme **1.5**).



Scheme 1.5. Synthesis and general mechanistic pathway for 2-substitued benzimidazoles from 2-nitroanilines.

1.3.1.1.2. Benzothiazole synthesis via dehydrogenative pathway:

C-S bond is ubiquitous in pharmaceutical and biological species.[22] Therefore, construction of a heterocycle via subsequent fabrication of C-N and C-S bond is still demanding process. Especially, 2-arylbenzothiazoles is a basic structural unit of various medicinal and agrochemical products. For that, synthesis of 2-arylbenzothiazoles via 'ADC' strived an unusual paradigm over conventional methods as they involved costly and prefunctionalized starting material employing toxic reagent, generating stoichiometric amount of waste. In that quest, in 2009, *Madsen, Williams and co-workers* first reported dimeric $[Cp^*IrI_2]_2$-catalyzed (**Ir-4**) oxidative cyclization of *p*-tolualdehyde and *o*-aminothiophenol to generate benzothiazole in refluxing toluene.[23a] Later, in 2013, *the Singh group* demonstrated an efficient and inexpensive phthalocyanine based Fe(II)-complex (**Fe-1**) catalyzed dehydrogenative coupling with *o*-aminothiophenol with an array of benzyl alcohols and one aliphatic alcohol where aliphatic one afforded low yield.[20h] The catalyst exhibit good selectivity with its low loading.



Scheme 1.6. Synthesis and general mechanistic pathway for 2-arylbenzothiazoles.

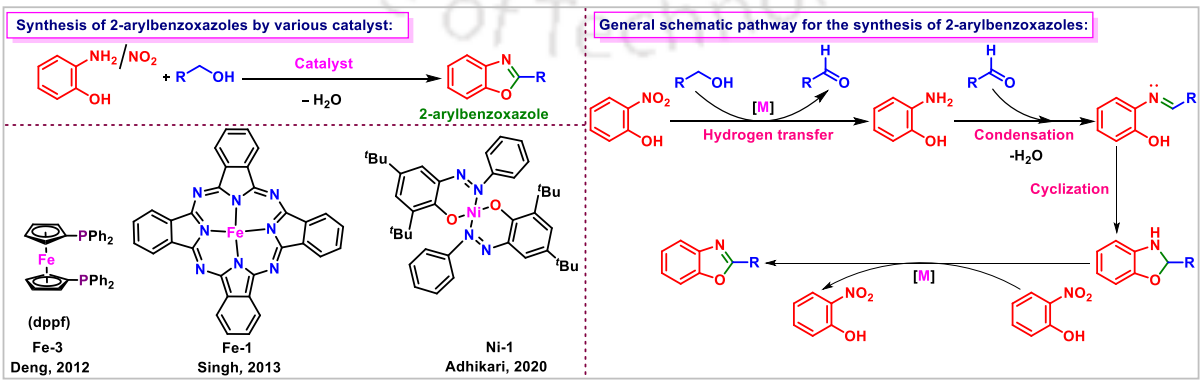
In 2018, the synthesis of aforementioned heterocycle accomplishing their tridentate ligand derived NNS-Mn(I)-complex (**Mn-2**) was illustrated by *Srimani and co-workers* departing environmentally

benign by-products water and molecular hydrogen.[23b]The lower loading of base and **Mn-2** catalyst makes this protocol efficacious over the previous one. After two years of this report, the efficiency of **Fe-2** complex was checked by *Hong and co-workers* for 2-arylbenzothiazole synthesis at 150 °C.[20n] Recently, *the Adhikari group* employed their redox-active azo-backbone bearing isolable, bench-stable, homogeneous Ni(II)-complex (**Ni-1**) towards the accomplishment of aforesaid one via hydrogen atom transfer (HAT) based dehydrogenative coupling of *o*-aminothiophenol and a few benzyl alcohols in more milder and advantageous way (Scheme **1.6**).[20l]

1.3.1.1.3. Benzoxazole and benzofuran synthesis via dehydrogenative pathway:

1.3.1.1.3.1. Benzoxazole synthesis via dehydrogenative pathway:

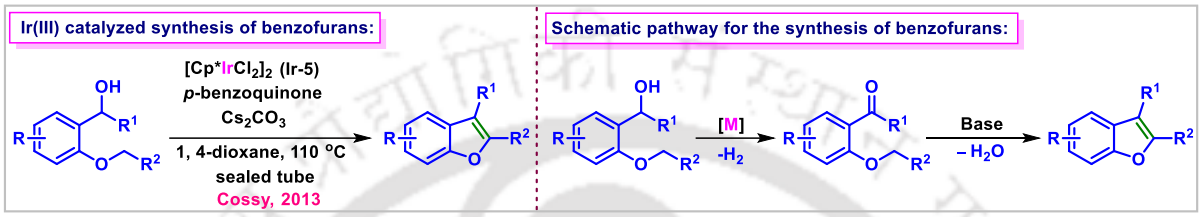
Synthesis of benzoxazole derivatives is an elegant approach and adorable areas to investigate due to its wide range of applications.[24] For that scientific community dedicated to develop sustainable approaches over traditional methods as it suffers from non-negligible shortcomings. In that respect, in 2009, *Madsen, Williams and co-workers* first reported dimeric $[Cp^*IrI_2]_2$-catalyzed (**Ir-4**) synthesis of benzoxazole, however, they have taken aldehyde for this oxidative coupling.[23a] In 2012, *Deng and co-workers* reported 2-arylbenzoxazole employing the Fe-catalyzed 'HA' strategy from *o*-nitrophenols and aromatic alcohols.[25] In this methodology, DPPF *i.e.* [1,1´-bis(diphenylphosphino)ferrocene] (**Fe-3**) (2 mol%) played an important role to conduct the coupling reaction at 150 °C. Herein, excess alcohol initiated borrowing hydrogen mediated reduction of nitro to amine and in the whole process, role of nitro group was hydrogen acceptor. On the basis of different control experiments, the author comprised that initially the alcohol gets dehydrogenated to aldehyde where the liberated hydrogen reduced nitro to amine which soon after undergoes condensation with that aldehyde forming an imine intermediate which followed dehydrogenative annulation leads to the benzoxazoles (Scheme **1.7**). The lower loading of catalyst and base-free approach makes this protocol efficient. Later, *Singh and co-workers* reported their Fe(II)-phthalocyanine catalyzed (**Fe-1**) 2-phenyl benzoxazole synthesis.[20h] Very recently, *the Adhikari group* applied their **Ni-1** complex to commenced the benzoxazole derivatives via hydrogen atom transfer (HAT) mediated coupling of 2-aminophenol and alcohols with few examples and good isolated yield by dehydrogenative pathway.[20l]



Scheme 1.7. Synthesis and general mechanistic pathway for 2-arylbenzoxazoles.

1.3.1.1.3.2. Benzofuran synthesis via dehydrogenative pathway:

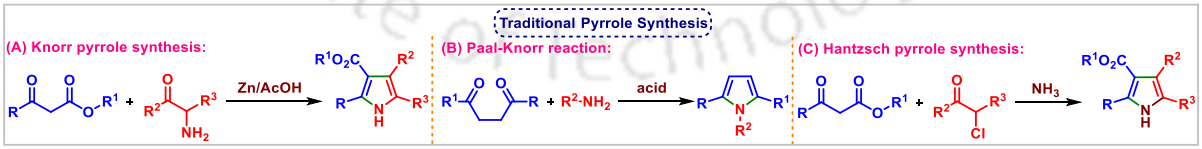
Benzofuran is a beautiful structural scaffold found in different natural and pharmaceutically active compounds.[26] The proliferative biological property lured researchers to find an efficient, sustainable and greener method to access benzofurans. In 2013, *the Cossy group* reported benzofurans using dimeric $[Cp^*IrCl_2]_2$ as a catalyst (**Ir-5**) in assortment with *p*-benzoquinone as a co-oxidant by hydrogen transfer method.[27] Under the optimized reaction conditions they have furnished 20 examples with excellent isolated yield. The role of *p*-benzoquinone was to accept hydrogen to inhibit the next reduction of benzofuran by [Ir]-H intermediate (Scheme **1.8**).



Scheme 1.8. Ir-catalyzed synthesis and mechanistic pathway for benzofurans.

1.3.1.1.4. Pyrrole synthesis via dehydrogenative pathway:

Pyrroles are essential building blocks and valuable intermediates for synthetically important various natural products, agrochemicals, flavones, dyes and advanced functional materials.[28] Different types of classical approaches involve for pyrrole synthesis such as Knorr,[29a] Paal-knorr, [29b] and Hantzsch reaction (Scheme **1.9**).[29c] Later various metal-catalyzed multicomponent coupling reactions and cyclization reactions have been developed to construct the aforesaid heterocycle. However, this protocol suffers from need of prefunctionalized substrate, poor atom-economy, multistep substrate acquisition, cumbersome work-up procedure, toxic reagents generating copious waste. In order to overcome these shortcomings construction of pyrrole from readily available and renewable feedstock like different varieties of alcohols and polyols via transition metal assisted 'ADC' and 'BH' or 'HA' strategy is quite attractive since these alcohols or polyols can be derived from lignocellulosic biomass or industrial products. In recent times, notable progress in sustainable pyrrole synthesis has been achieved from varieties of alcohols like 1,4-unsaturated diols, 2,5-diols, β-amino alcohols etc.

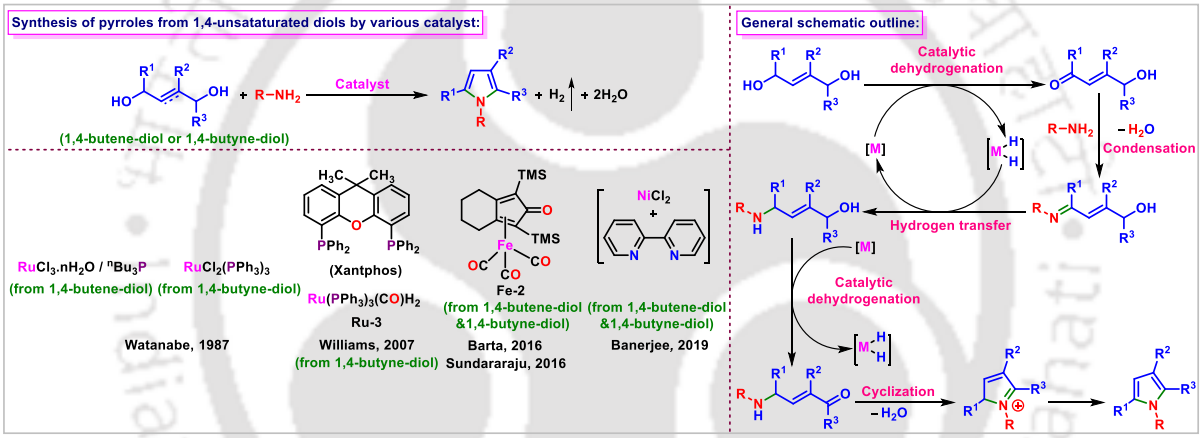


Scheme 1.9. Traditional pyrrole synthesis.

1.3.1.1.4.1. Synthesis of Pyrrole from 1,4-unsataturated diols:

Reaction of amine and 1,4-butene-diol or 1,4-butyne-diol towards the synthesis of N-substituted pyrrole is one of the strategies to construct this. However, the main problem for working with 1,4-unsaturated diol is at elevated temperature it gets oligomerized. In 1974, Pd-catalyzed N-substituted pyrrole synthesis was reported by *the Murahasi group* employing 1,4-butene-diol and a few amines.[30a] Later on in 1987, *Watanabe and co-workers* accomplished that from 1,4-butene-diol using $RuCl_3.nH_2O$ in

combination with $^{n}Bu_3P$ and 1,4-butyne-diol using $RuCl_2(PPh_3)_3$ catalyst, however, it is well-suited for aromatic amines, limited for aliphatic ones.[30b] In 2007, *Williams group* developed a catalytic protocol based on $Ru(PPh_3)_3(CO)H_2$ with (**Ru-3**) Xantphos on coupling of 1,4-substituted butyne-1,4-diols with amines. Here, the reaction involves isomerisation of 1,4-alkyne diol into a 1,4-diketone followed by Paal-Knorr cyclisation towards the pyrrole formation.[30c]In 2016, *Barta et. al.* first described Knölker homogeneous Fe-catalyzed (**Fe-2**) formation of pyrroles in combination with Me_3NO by coupling of unsaturated diols with both aliphatic and aromatic primary amines.[30d]In the same year, the similar catalytic protocol was applied by *Sundararaju et. al.* to broaden the substrate scope, albeit their catalytic protocol suffers from high catalyst loading and reaction temperature with respect to previous one.[30e] Afterwards, in 2018, *Banerjee and co-workers* accomplish this transformation by developing a simple catalytic protocol containing $NiCl_2$ in accordance with phosphine-free, bench stable, inexpensive bipyridine ligand and their substrate scope is quite broader as compared to all the aforesaid reports (Scheme **1.10**).[30f]

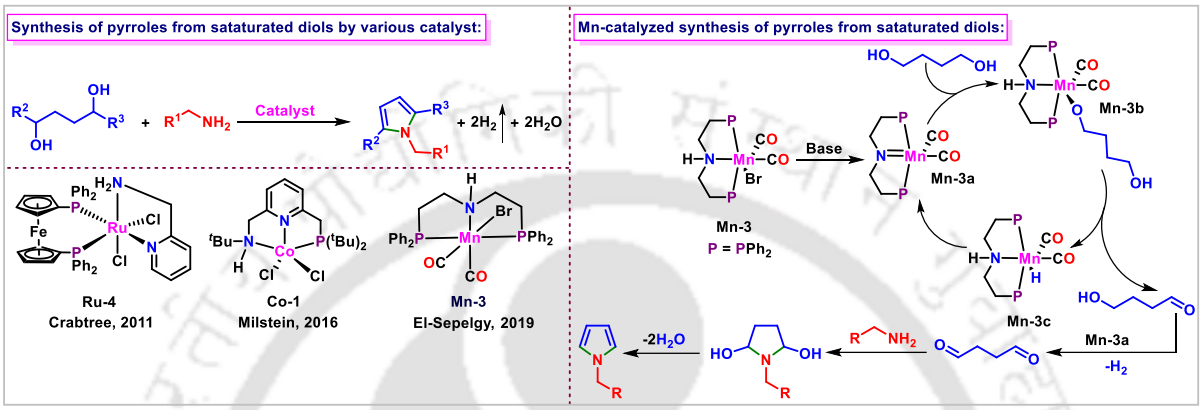


Scheme 1.10. Synthesis and general mechanistic pathway for pyrroles from 1,4-unsataturated diols.

1.3.1.1.4.2. Pyrrole synthesis from 2,5-diols or 1,4-diols:

Apart from unsaturated-diol N-alkylated pyrrole can be synthesized from saturated-diol also. In that quest, in 2011, *Crabtree and co-workers* reported chelated diphosphine diamine-based Ru-complex (**Ru-4**) catalyzed reaction of 2,5-hexane-diol with 1-hexylamine/1-decylamine towards the synthesis of pyrrole in presence of HCOONa.[31a] After this seminal report, in 2016, the pioneering *Milstein group* first reported base metal mediated pyrrole synthesis from saturated diol where they have employed PNN-Co(II)-complex (**Co-1**) with equivalent ration of $NaBHEt_3$ and KO^{t}Bu at 150 °C. Hexane-2,5-diols and primary amines were the reaction partner here (Scheme **1.11**).[31b]Various primary amines were explored affording quite satisfactory result, however, benzyl amines bearing electron-withdrawing group delivered low yield because of detriment in its basicity. Low nucleophilicity of anilines with substitution also give low yield. The mechanistic investigation comprised that initially formed active paramagnetic (PNNH)Co(I)-species was responsible for dehydrogenation of alcohol to ketone via in situ generation of Co-alkoxy species. The ketone then coupled with the corresponding amine accomplishing N-substituted pyrrole. Recently, *Rueping, Elsepelgy and co-workers* presented

commercially available 'MACHO' PNP-pincer ligand-based Mn-complex (**Mn-3**) catalyzed synthesis of N-alkyl-2,5-disubstituted pyrrole using 1,4-diol with primary amine with lower loading of catalyst and catalytic amount of base.[31c]The plausible mechanistic cycle suggested that the active catalytic species **Mn-3a** formed from **Mn-3** upon treatment with base which transformed diols to its electrophilic species dicarbonyl compound via acceptorless dehydrogenation. Afterwards, upon reaction of amine with this dicarbonyl compound followed by liberation of two molecules of H_2O furnished the corresponding pyrroles (Scheme **1.11**).

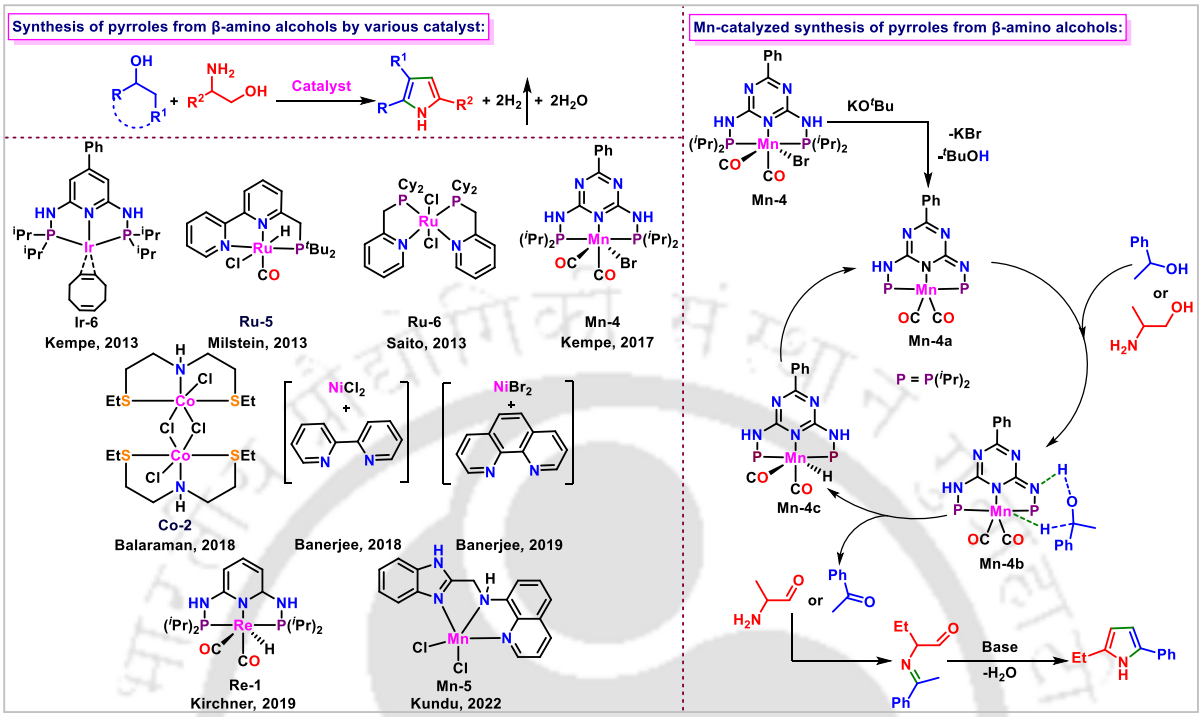


Scheme 1.11. Previous reports and Mn-catalyzed synthesis of pyrroles from saturated diols.

1.3.1.1.4.3. Pyrrole from β-amino alcohols:

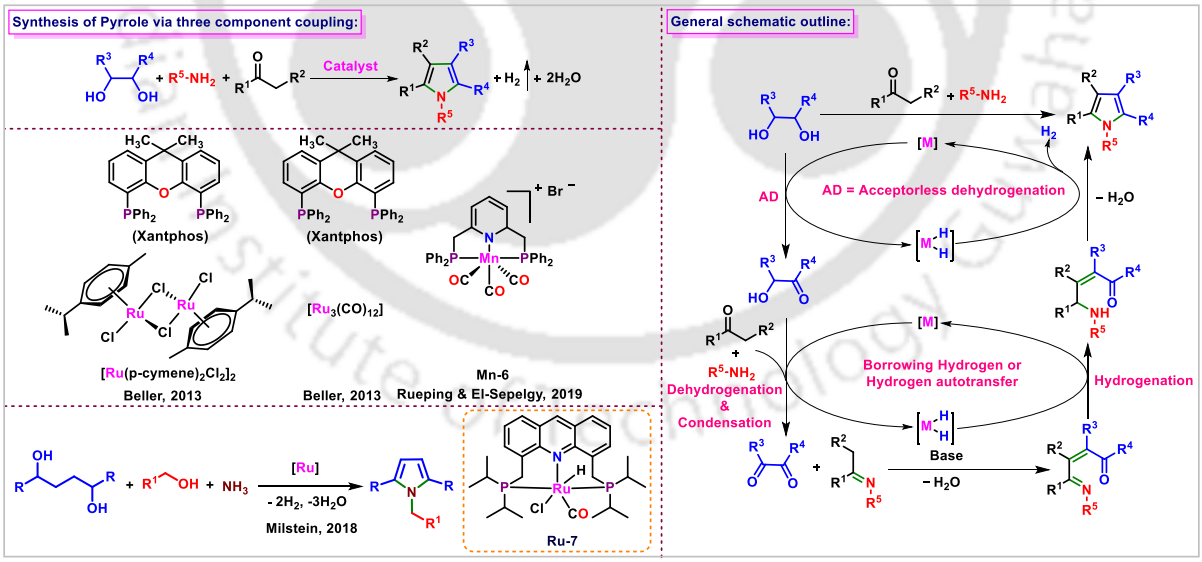
N-substituted pyrrole can be synthesized upon reaction of secondary alcohol and amino alcohol. Based on that concept, in 2013, there was a report on Ir(I)-catalyzed (**Ir-6**) by *the Kempe group*.[32a]The author stated that during the reaction iridium trihydride complex was formed at its resting state and key step involved was the formation of imine intermediate and intramolecular cyclization. *The Milstein group* also demonstrated **Ru-5** catalyzed pyrrole synthesis.[32b]In the intramolecular cyclization step both catalyst and base play crucial role defined by control experiments. Later, *Saito group* employed their Ru(II)-complex (**Ru-6**) to conduct this, however their reaction temperature is very high.[32c] In 2017, *Kempe and co-workers* illustrated triazine backbone based PN_5P-ligand stabilized Mn-complex (**Mn-4**) catalyzed construction of pyrrole derivatives via dehydrogenative coupling between β-amino alcohol with secondary alcohol, under milder way compared to previous reports.[32d] Indeed, the similar Fe and also Co-catalyst of that scaffold failed to show any activity. The author depicted that **Mn-4a**, the dearomatized active species, dehydrogenate alcohols to its desired carbonyl compound via subsequent generation with Mn-H species (**Mn-4c**). Then the in situ generated β-amino aldehyde and ketone gets coupled to give the desired pyrrole product (Scheme **1.12**). Vey next, *Balaraman and co-workers* demonstrated ^{Et}SNS-Co complex (**Co-2**) for the formation of aforesaid heterocycle from same set of starting material.[32e] Later, *Banerjee et. al.* constructed the same devising both $NiBr_2$/1,10-phenanthroline system[32f] and also $NiCl_2$/bipyridine system[32g] in KO^{t}Bu. In 2019, *Kirchner and co-workers* reported well-defined PNP-Re(I)-pincer complex (**Re-1**) assisted dehydrogenative coupling between 1,2-amino alcohols with secondary alcohols, obtaining good isolated yield.[32h] Very recently,

Kundu and co-workers developed an nitrogen containing proton responsive benzimidazole and 8-aminoquinoline combining unsymmetrical NNN-Mn(II)-pincer complex (**Mn-5**) for the dehydrogenative coupling between *β*-amino alcohol and acetophenone derivatives.[32i]



Scheme 1.12. Previous reports and Mn-catalyzed construction of pyrroles from β-amino alcohols.

1.3.1.1.4.4. A three-component strategy for pyrrole synthesis:



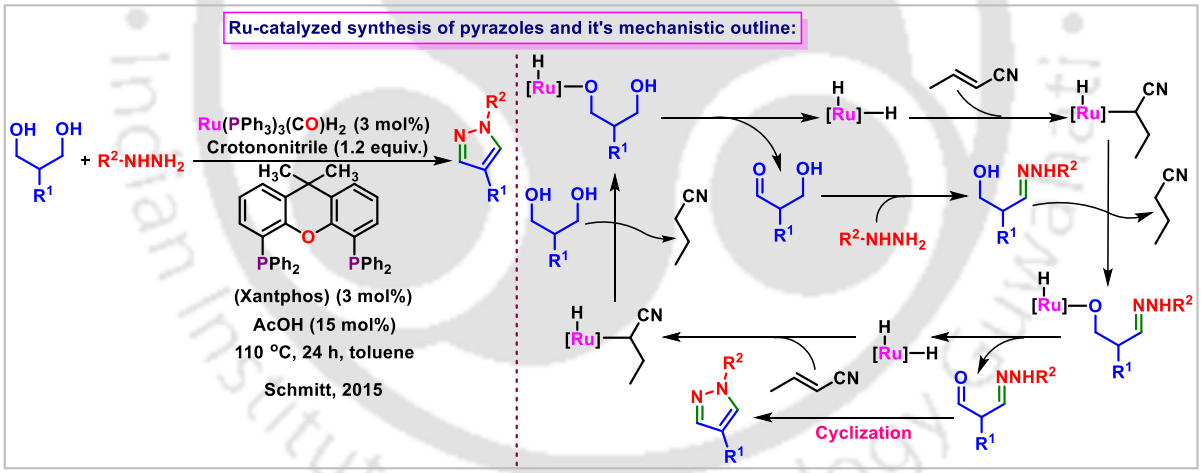
Scheme 1.13. Synthesis of pyrrole via three component strategy and it's general mechanistic outline.

Multicomponent reactions are advantageous and effective process for the generation of intricate molecular scaffold where three or more substrates get coupled in one pot by minimizing the waste amount and simplifying the purification process. In 2013, *Beller and co-workers* represented [Ru (p-cymene)$_2$Cl$_2$]$_2$ / Xanthphos-catalyzed construction of pyrroles via three component coupling.[33a] As herein, the synthesis of pyrrole involved coupling reaction of 1,2-diol, amine and *α*-methylene ketone

(Scheme **1.13)**, that's why the reaction was designated as a three-component coupling reaction. Interestingly, by varying the Ru-precursor in the same year they have documented another report on this.[33b] In 2019, *Rueping, Elsepelgy and co-workers* introduced potential **Mn-6** complex for three component pyrrole synthesis via 'AD' and 'BH' process by varying amines, vicinal diol and ketones.[33c] Computational study comprises that reaction goes via C-H alkylation of in situ formed enamine and glyoxal where enamine get selectively hydrogenated followed by condensation delivered highly substituted pyrrole. Herein, a general mechanistic pathway has been depicted in scheme **1.13**. Recently, the pioneering *Milstein group* reported acridine based Ru-pincer complex (**Ru-7**) catalyzed pyrrole synthesis via 'ADC' of diols with gaseous NH_3 (7 bar) as a nitrogen source in absence of any external additive (Scheme **1.13**).[33d]

1.3.1.1.5. Pyrazole synthesis via dehydrogenative pathway:

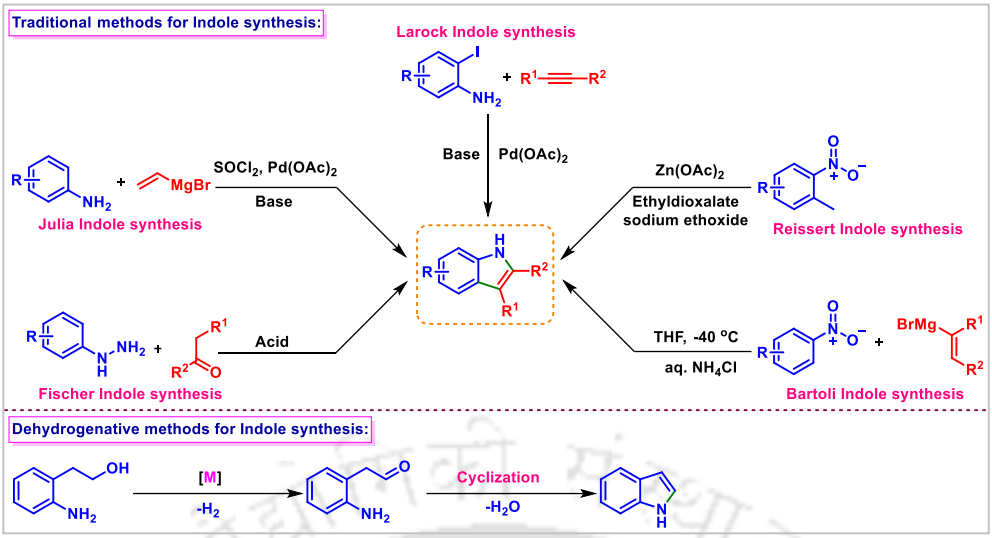
Pyrazoles are basic structural subunit present in numerous biologically important species.[34] In 2015, *Schmitt and co-workers* conveyed Ru-catalyzed pyrazole synthesis where they have taken 2-alkyl-1,3-diol and alkyl hydrazines as coupling partner.[35]They have screened several Ir and Ru-complex, amidst of that $[RuH_2(PPh_3)_3CO]$ with xantphos ligand, and hydrogen acceptor crotononitrile displayed the optimal yield. This catalytic protocol exhibits ample substrate scope by varying both the coupling partners. Herein, a plausible mechanism was outlined in scheme **1.14**.



Scheme 1.14. Ru-catalyzed synthesis of pyrazole and it's mechanistic outline.

1.3.1.1.6. Indole synthesis via dehydrogenative pathway:

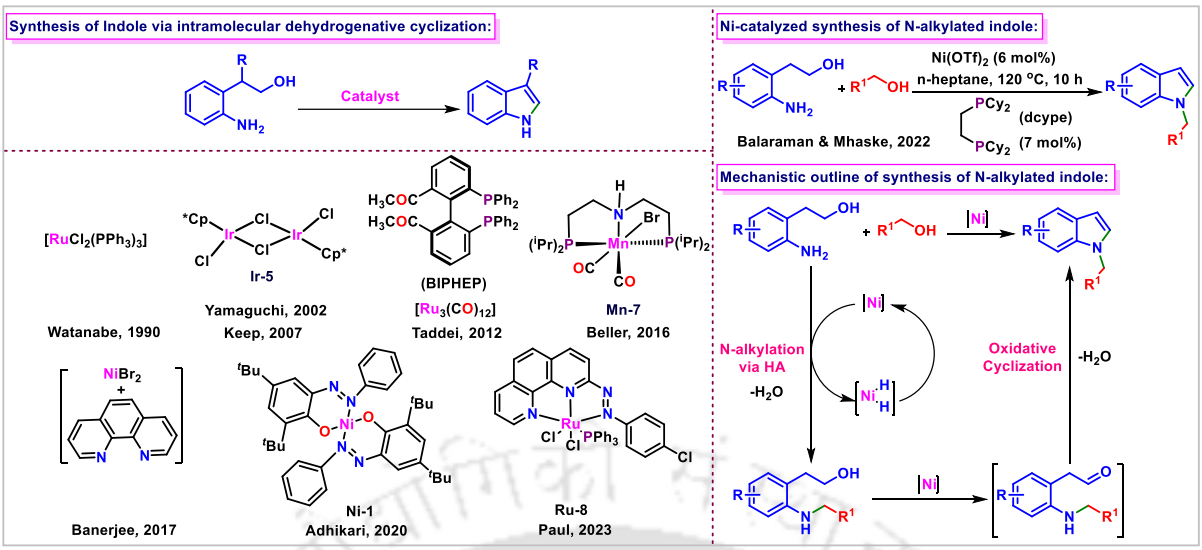
Indole, a pervasive and key structural units present in various biologically active scaffolds, natural products, pharmaceuticals, dyes, agrochemicals and in fine chemicals.[36] Due to its large structural diversity and plethora of biological significance, various synthetic procedures have been developed for fabrication of indoles over the years.[37a] Amidst of that, Fischer reaction was one of the efficient strategy where enolizable N-aryl hydrazones get transformed into indoles upon acid catalyzed assisted heating of ketone or aldehyde with the arylhydrazine.[37b] Herein, for indole synthesis some classical approaches have been represented in scheme **1.15**.[37c,d]However, these methods need prefunctionalized starting material, toxic reagent generating stoichiometric wastages.



Scheme 1.15. Traditional and dehydrogenative methods for indole synthesis.

To avoid this synthesis of indole via transition metal catalyzed intramolecular 'ADC' of amino alcohol is an elegant approach in terms of green and sustainable transformation since H_2 and H_2O get liberated. Herein, a general schematic approach has been outlined in scheme **1.15**. Based on that concept, in 1990, the *Watanabe group* first described $RuCl_2(PPh_3)_3$-catalyzed intramolecular dehydrogenative cyclization of 2-nitrophenethyl alcohol and 2-aminophenethyl alcohol towards the synthesis of indole.[38a] Later, they have devised N-substituted indole broadly at elevated temperature.[38b] In 2002, the *Yamaguchi group* extended this concept employing commercially available $[Cp^*IrCl_2]_2$ -catalyst (**Ir-5**) in presence of weak base K_2CO_3.[38c] The author claimed that 2-propanol can be used as an external hydrogen source when they have employed 2-nitrophenethyl alcohol as starting material. Later, *the Keep group*[38d] and *the Taddei group*[38e] independently developed **Ir-5** and Ru-catalyst to conduct this aforesaid heterocycle. However, the journey of base metal starts from 2016, when *Beller and co-workers* demonstrated PNP-Mn(I)-catalyzed (**Mn-7**) indole synthesis by intramolecular dehydrogenative coupling between amino alcohol.[38f]In the very next year, *Banerjee et. al.* manifested this intramolecular cyclization reaction by developing easily accessible operationally simple catalytic protocol bearing $NiBr_2$ with 1,10-phenanthroline ligand (1:2).[38g] In 2020, **Ni-1** complex catalyzed in situ indole formation via intramolecular hydrogen atom transfer (HAT) based dehydrogenative cyclization with cvoncomitant chemoselective C-3 alkylation with alcohol under aerobic condition was reported by *the Adhikari group*.[38h]Very recently, *Paul and his team* applied the same strategy with their developed redox-innocent arylazo 1,10-phenanthroline ligand base tridentate **Ru-8** complex (Scheme **1.16**).[38i]

Compared to the synthesis of C3 or C2-functionalized indole, construction of N-alkylated indole via functionalizing the N-H bond is still a challenging process. However, in 2022, *Balaraman, Mhaske and co-workers* first successfully disclosed the selective one-pot cascade synthesis of N-alkylated indole employing $Ni(OTf)_2$ as an efficient Ni-precursor with dcype ligand in n-heptane solvent in milder, base-free condition (Scheme **1.16**).[38j] Their catalytic protocol is viable for aryl, heteroaryl and primary alkyl alcohol, albeit moderate yield was isolated for primary alkyl alcohol.



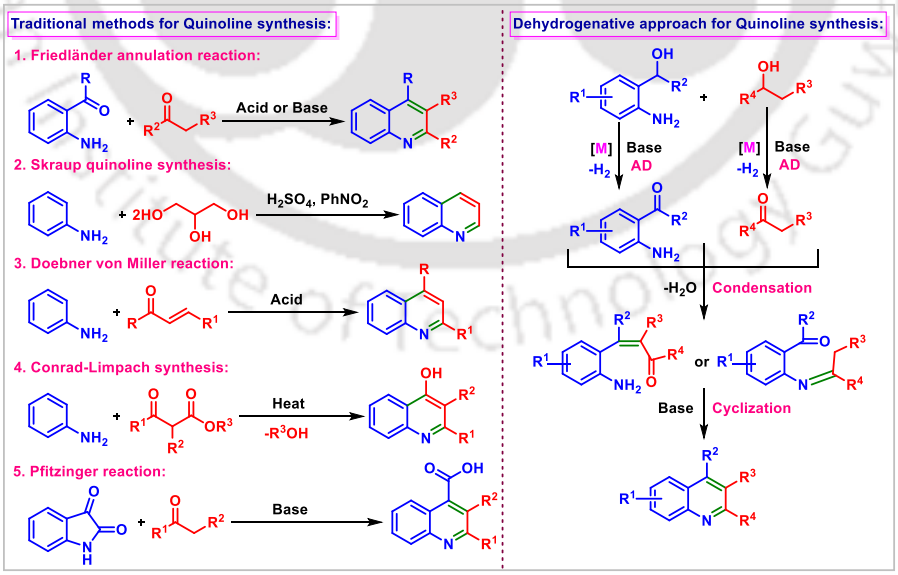
Scheme 1.16. Synthesis of indole and N-alkylated indole.

1.3.1.2. Dehydrogenative approach towards the synthesis of 6-membered N-heterocycles:

1.3.1.2.1. Quinoline synthesis via dehydrogenative pathway:

1.3.1.2.1.1. 2-Aryl/ Alkyl Quinoline synthesis via dehydrogenative pathway:

Like other heterocycles, quinoline derivatives imposes myriads of medicinal applications, biological properties, used as important organocatalyst, photoelectric material and dyes.[39] Therefore, there is a continuous hunt going on to develop innovative synthetic approaches to build highly functionalized quinoline moiety. The most popular approach for that heterocycle is known as Friedländer annulation reaction where it involved acid or base assisted condensation of 2-aminobenzaldehydes with active methylene group bearing carbonyl derivatives.



Scheme 1.17. Traditional and dehydrogenative methods for quinoline synthesis.

Apart from that 'Skraup', 'Doebner von Miller', 'Conrad-Limpach', 'Pfitzinger' reactions are there to construct quinoline moiety under acidic condition (Scheme **1.17**).[40] However, these methods suffer from the instability and prone self-condensation behaviour of 2-aminobenzaldehydes and harsh reaction

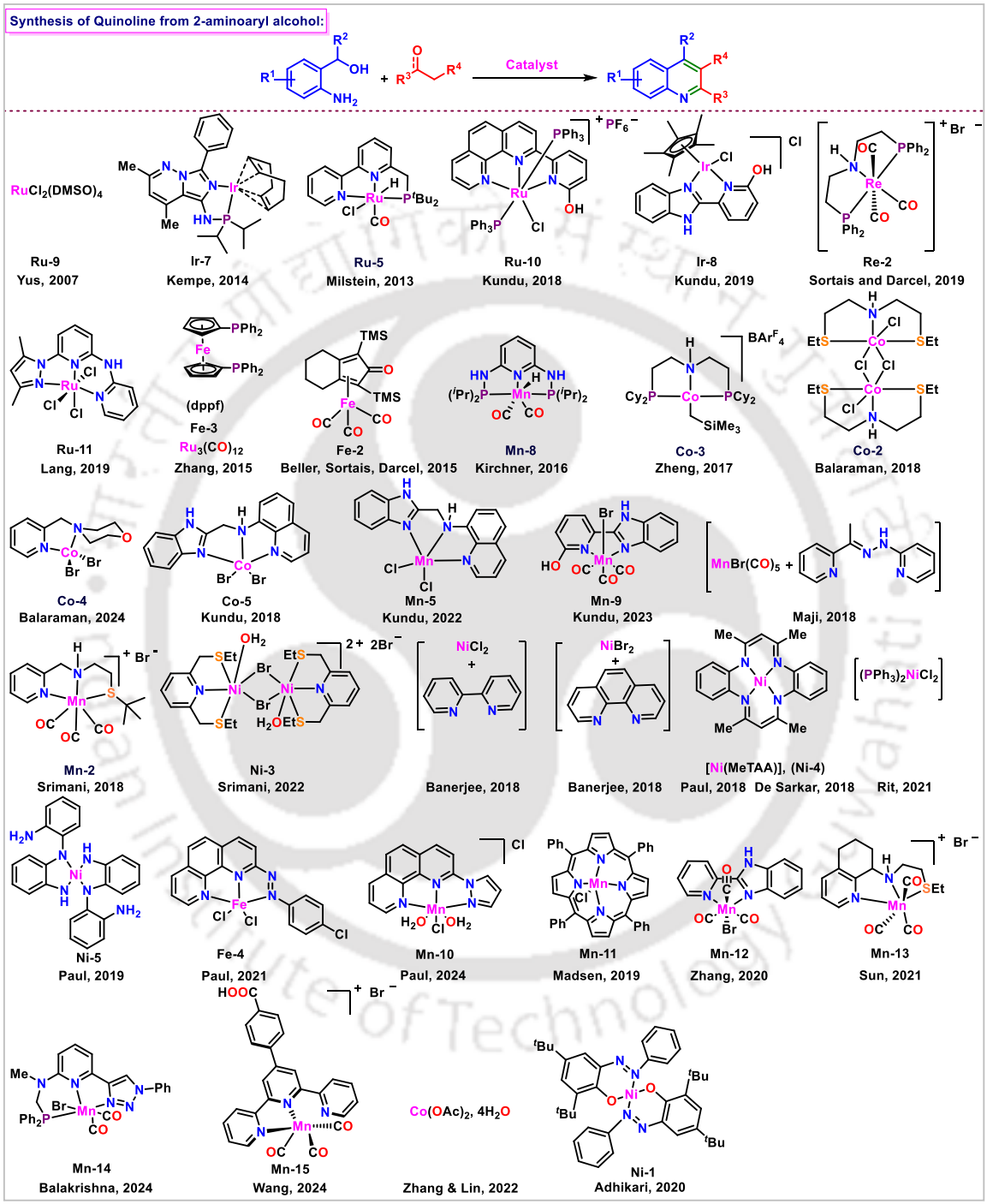
condition. To devoid from this, over the years various reports on transition metal catalyzed 'ADC' or 'BH' strategy has been documented using alcohol as a renewable starting material. Quinoline can be synthesized either from 2-aminoaryl alcohols or from nitrobenzene derivatives in coupling with secondary alcohol. In the ADC pathway, under the streamlined reaction condition, both get dehydrogenated forming their corresponding aldehyde or ketone counterpart, which undergoes intermolecular condensation. Now, there are two possibilities: i) formation of imine followed by aldol reaction, ii) first aldol adduct then cyclization by imine formation. Both pathways are possible, however, according to the literature reports [41o, 41p, 42a] aldol adduct followed by imine formation towards the synthesis of substituted quinoline is the most preferable pathway.

1.3.1.2.1.1.1. Synthesis of Quinoline from 2-aminoaryl alcohol:

In 2007, $[RuCl_2(dmso)_4]$ *i.e.* Ru(II)-catalyzed (**Ru-9**) dehydrogenative Quinoline synthesis reaction between 2-aminoaryl alcohols/ketones with alcohols under solvent free condition was introduced by *Yus and co-workers*, however, their catalytic protocol required prolonged reaction time and stoichiometric sacrificial hydrogen acceptor.[41a] In 2014, *the Kempe group* first applied the acceptorless dehydrogenation (AD) strategy for the synthesis of 2-aryl/alkyl quinoline by developing bidentate PN-Ir(I)-complex (**Ir-7**) with the liberation of H_2 and H_2O.[41b] To furnish the reaction low loading of catalyst and catalytic amount of base is employed, however, the acquisition of alcohol is high (5 equiv.). Later, *the Milstein group* also demonstrated well-defined bipyridine based PNN-Ru-pincer complex (**Ru-5**) catalyzed synthesis of aforementioned heterocycle.[41c] In 2018, *Kundu and co-workers* also accomplished the quinoline synthesis by (2-hydroxy-2-pyridyl)-1,10-phenanthroline ligand bearing bifunctional NNN-Ru(II)-complex (**Ru-10**) taking *o*-aminoaryl alcohols and secondary alcohols in an equimolar ration under milder reaction condition.[41d] Later, they have extended this catalytic transformation from both 2-aminoaryl alcohols and from nitrobenzenes by developing 2-hydroxypyridine-based bifunctional Ir(III)-complex (**Ir-8**) in green solvent water.[41e] In the very next year, *Sortais and Darcel group* illustrated tridentate PN^HP-Re(I)-complex (**Re-2**) catalyzed catalytic amount of base assisted synthesis of aforesaid heterocycle from same set of starting material with ample substrate scope.[41f] Later, *Lang and co-workers* developed pyrazole-pyridine based unsymmetrical NNN-Ru(III)-pincer complex (**Ru-11**) to conduct the similar reaction.[41g] On the basis of control experiments the author suggested that in presence of base and alcohol the active Ru(II)-species generated from Ru(III)-complex. However, in terms of cost-effectiveness and abundance 3d-metal based catalyst outperformed over noble-metal catalyst. In that respect, in 2015, *Sortais, Darcel and co-workers* explored **Fe-2** catalyzed coupling of 2-aminobenzylalcohol with ketone in presence of 10 mol% of KO^{t}Bu towards the synthesis of quinoline. The active catalytic species has been generated by equimolar mixture of PPh_3 and Knölker Fe-complex (**Fe-2**) and PPh_3 plays a crucial role to afford the optimal yield.[41h] Intrigued by this report, *Kirchner and co-workers* in the very next year, reported pyridine backbone bearing PNP-Mn(I)-complex (**Mn-8**) catalyzed dehydrogenative condensation between 2-aminobenzyl alcohol with secondary alcohol for quinoline synthesis.[41i] Combination of base KO^{t}Bu

and KOH at the ration 2.1:1 was required for catalyst activation. Later, a PNP-Co(II)-complex (**Co-1**) was introduced by *Zheng et. al.* to pursue this.[41j] In 2018, *the Balaraman group* introduced air-stable, operationally simple dimeric SNS-Co(II)-pincer complex (**Co-2**) mediated C2-functionalized quinoline synthesis via acceptorless dehydrogenative annulation (ADA) with limited substrate scope.[32e] The same group also reported $(NN)^{Mor}$-bidentate ligand based Co(II)-complex (**Co-4**) to pursue the objective from both secondary alcohol and ketone where nitrile and amino functional group bearing secondary alcohol or ketone well-survived furnishing good yield.[41k] *Kundu et .al.* accomplished this employing their nitrogen containing proton responsive benzimidazole and 8-aminoquinoline combining paramagnetic NNN-Co(II)-complex (**Co-5**). They have also constructed one acridine derivative from inexpensive α-tetralone.[41l] In 2022, they have developed a Mn(II)-complex (**Mn-5**) of that same ligand scaffold[32i] and 2-hydroxypyridine appended benzimidazole ligand backbone bearing Mn(I)-complex (**Mn-9**)[41m] for this dehydrogenative coupling reaction where in the latter case low loading of both catalyst and base was employed. In 2018, an in situ generated Mn-complex upon mixing hydrazole type NNN-ligand with $MnBr(CO)_5$ was constructed by *Maji and co-workers* to do this.[41n] In the same year, *Srimani group* conducted similar transformation with their pre-synthesized NNS-Mn(I) complex (**Mn-2**) where **Mn-2** showed similar selectivity and reactivity like *Sortais* **Mn-8**.[23b] Later, the same group pursed this by their well-defined SNS-Ni(II)-complex (**Ni-3**) from 2-aminobenzyl alcohols and acetophenone derivatives.[41o] In 2018, *Banerjee* reported the tandem intermolecular cyclization towards the synthesis of 2-alkyl/aryl quinoline by $NiCl_2$/bipyridine[31g] and $NiBr_2$/1,10-phenanthroline ligand system.[41p] *De sarkar*[41q]and *Paul*[41r] independently delineated an operationally simple catalytic protocol based on square planar Ni(II)-complex *i.e.* [Ni(MeTAA)] (**Ni-4**) via 'ADC' of 2-aminoayl alcohols with both 2° alcohols or ketones with ample substrate scope, however, previous group report with low catalyst loading and weak base whilst latter one manifested an aerobic condition. Currently, commercially available $NiCl_2(PPh_3)_3$ catalyst was illustrated by *Rit and co-workers*.[41s] In 2019, *Paul and co-workers* envisaged a singlet diradical Ni(II)-complex (**Ni-5**) catalyzed quinoline synthesis having redox non-innocent diamine type ligand from the similar set of starting materials.[41t] Author suggested that there was a cooperative involvement of both metal centre and ligand in the dehydrogenation reaction and aerial oxygen played an essential role in this dehydrogenation process, for which H_2O_2 was generated instead of H_2. Recently, the same group conducted this with their tridentate arylazo pincer ligand bearing **Fe-4** complex[41u] and 1,10-phenanthroline ligand based air and water stable Mn(II)-complex (**Mn-10**) respectively.[41v] *Madsen and co-workers* reported tetraphenylporphyrin (TPP)Mn(III)-complex (**Mn-11**) for 2-arylquinoline synthesis via 'ADC' of *o*-aminobenzyl alcohols and secondary alcohols (1:1.5) in a smooth combination of KOH, KO^{t}Bu and pyridine in 10:10:1 ration.[41w] Later, *Zhang and co-workers* accomplished this transformation employing lower loading of pyridyl-imidazolyl ligand stabilized simple bidentate NN-Mn(I)-complex (**Mn-12**) compared to *Madsen and co-workers* report (**Mn-11**).[41x] Later, *Sun* (**Mn-13**),[41y] *Balakrishna* (**Mn-14**),[41z] *Wang* (**Mn-15**)[41za] and *Zhang* devised Co-complex[41zb] to catalyse the synthesis of this heterocycle. Recently, *the Adhikari group* demonstrated the

dehydrogenative synthesis of 2-aryl/alkyl quinoline derivatives between coupling of 2-aminobenzyl alcohol with an array of aromatic and aliphatic alcohols in presence of 5 mol% of phosphine free redox active **Ni-1** complex under aerobic condition at 80 °C which is milder and serendipitous as compared to aforementioned documented reports (Scheme **1.18**).[41zc]

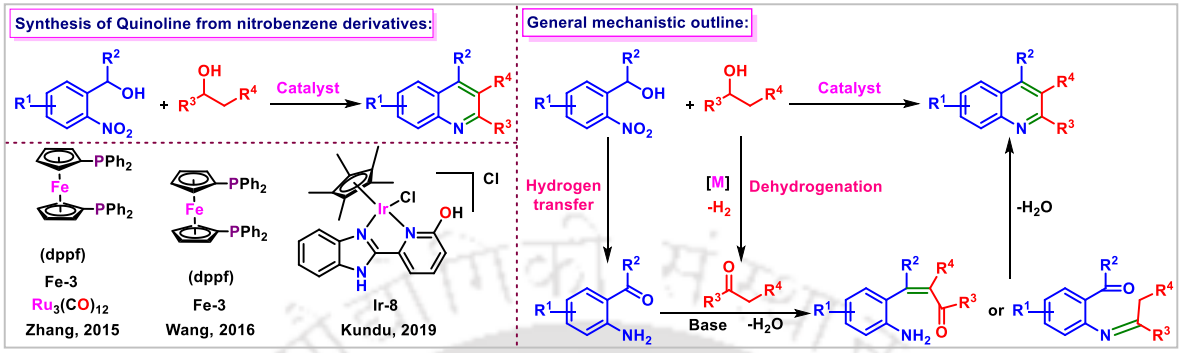


Scheme 1.18. Synthesis of quinolines from 2-aminoaryl alcohol.

1.3.1.2.1.1.2. Synthesis of quinoline from nitrobenzene derivatives:

Synthesis of Quinoline from nitrobenzene derivatives is less explored as compared to its amine analogue. In 2015, *Zhang and co-workers* demonstrated $Ru_3(CO)_{12}$ with bidentate phosphine ligand dppf (**Fe-3**) catalyzed quinoline synthesis by dehydrogenative coupling between 2-nitroaryl alcohol

with secondary alcohol.[42a]In that case, the final product was obtained by coupling with generated ketone from alcohol which in situ reduced the nitro group. Later, *Wang and co-workers* disclosed this seminal work via Fe-catalyzed *i.e.* dppf-catalyzed (**Fe-3**) redox condensation of aforementioned same set of starting materials (Scheme **1.19**).[42b]

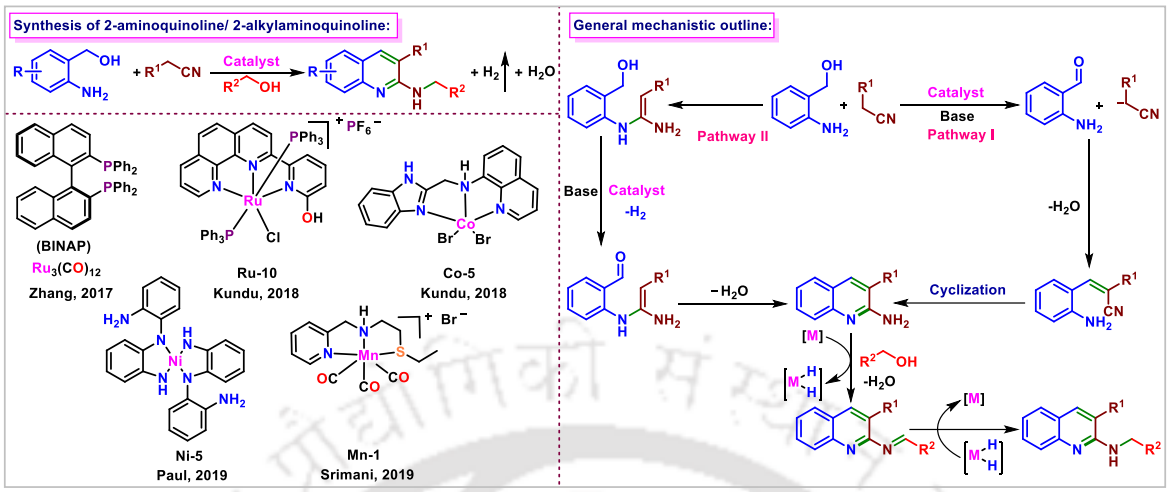


Scheme 1.19. Synthesis of quinolines from nitrobenzene derivatives and its mechanistic outline.

1.3.1.2.1.2. 2-Aminoquinoline/ 2-alkylaminoquinoline synthesis via dehydrogenative pathway:

2-aminoquinoline or 2-alkylaminoquinoline synthesis via tandem dehydrogenative cyclization or dehydrogenative annulation with N-alkylation is an attractive approach since they are potential scaffold in medicinal chemistry.[43] In that quest, in 2017, $Ru_3(CO)_{12}$/BINAP catalyzed operationally simple, three component coupling of 2-aminoarylmethanols with alkyl nitriles and alcohols towards the synthesis of 2-alkylaminoquinolines was reported by *Zhang and co-workers*.[44a] Pathway-**I** (Scheme **1.20**) preferentially supported by the experimental observation. In the very next year, *Kundu and co-workers* demonstrated alkyl phosphine free (2-hydroxy-2-pyridyl)-1,10-phenanthroline ligand bearing well-defined bifunctional NNN-Ru(II)-complex (**Ru-10**) mediated efficient synthesis of 2-alkylaminoquinolines under mild condition.[41d] Later, in the same year, they have developed nitrogen containing proton responsive tridentate ligand containing NNN-Co(II)-paramagnetic complex (**Co-5**) to catalyzed the synthesis of aforesaid one via 'ADA' of 2-aminobenzyl alcohol and benzyl cyanide along with N-alkylation of various alcohol under CsOH.[41l] *Paul and co-workers* accomplished **Ni-5** catalyzed synthesis of 2-aminoquinoline under aerobic condition eliminating H_2O_2 as by-product.[41t] In 2019, *the Srimani group* disclosed first Mn-catalyzed one pot synthesis of 2-alkylaminoquinolines employing their tridentate NNS-Mn(I)-complex (**Mn-1**).[44b] A combination of **Mn-1** and KOH pursued the acceptorless dehydrogenative coupling of 2-aminobenzyl alcohols with alkyl nitriles (1:1.5), in which addition of primary alcohols in presence of further imposition of 5 mol% of **Mn-1** delivered the desired 2-alkylaminoquinoline products. The author proposed two possible pathways in which pathway-**I** proceeds via dehydrogenation, condensation and annulation whilst in pathway-**II** nucleophilic addition of $-NH_2$ to -CN formed amidine which successive dehydrogenation and cyclization furnished the intended product. The experimental results support pathway-**I** is more likely. Herein, a plausible

mechanistic was outlined for 2-aminoquinoline/ 2-alkylaminoquinoline which is depicted in scheme **1.20**.



Scheme 1.20. Synthesis of 2-aminoquinoline/ 2-alkylaminoquinoline and its mechanistic outline.

1.3.1.2.2. Quinazoline synthesis via dehydrogenative pathway:

Quinazolines belongs to a class of N-heterocycles, widespread structural unit exclusively found in various natural products and pharmaceutical compounds having an array of biological and physiological properties.[45] These prolific applications lured scientific fraternity to develop an atom-economical, environmentally benign strategy to accomplish the aforesaid N-heterocycle. Over the years, although several approaches have been devised to pursue this but transition metal catalyzed 'ADC' and 'BH' mediated C-N bond-formation gained a different attention as compared to well-documented conventional methods.[46] Quinazolines can be constructed either from 2-aminobenzylalcohols or 2-aminobenzylamines and also via multicomponent pathway which are discussed below.

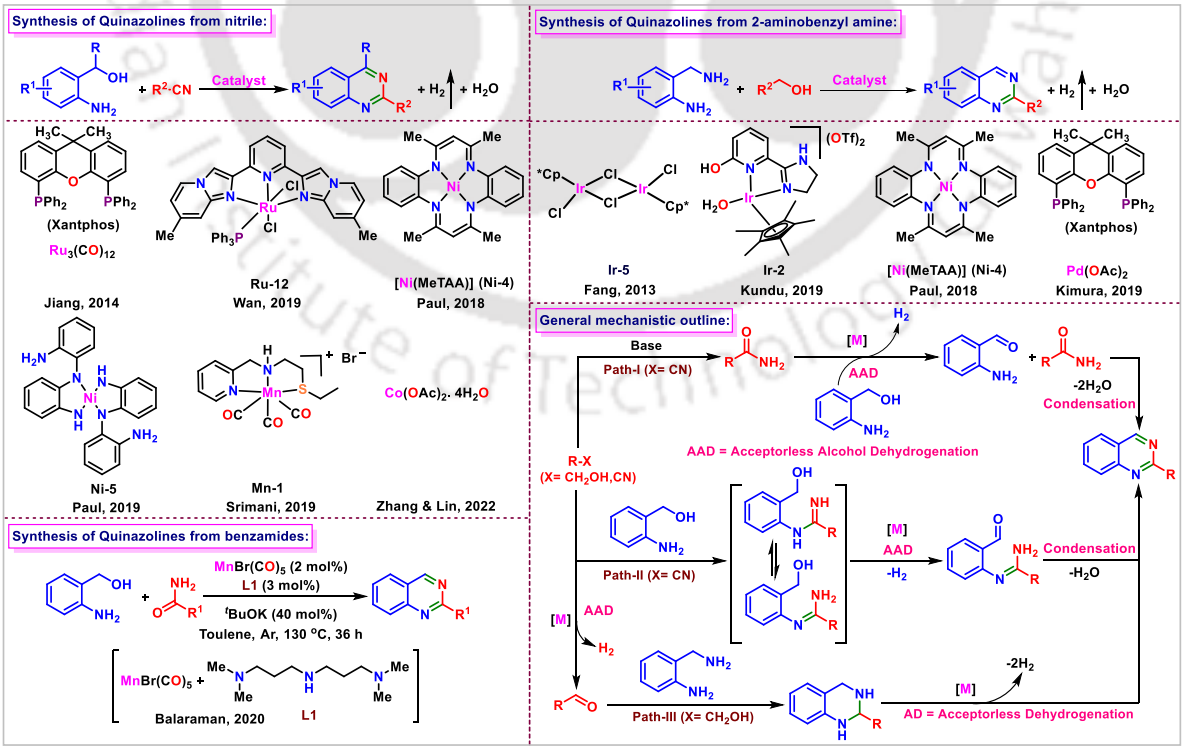
1.3.1.2.2.1. Synthesis of quinazolines from 2-aminobenzylalcohol:

The first report on cascade synthesis of quinazolines was by *Wu's grou*p in 2013, however, this method suffers from excess usage of Lewis acid as well as strong oxidant.[47a] Devoid from this, in the very next year, $Ru_3(CO)_{12}$/ Xantphos mediated dehydrogenative synthesis of 2-arylquinazolines was demonstrated by *Jiang and co-workers* employing 2-aminoarylalcohol and benzonitriles as coupling partners.[47b]In 2019, *Wan et al.* disclosed the construction of derivatives of aforementioned heterocycles employing their phosphine free NNN-Ru(II) pincer complex (**Ru-12**) via acceptorless dehydrogenative annulation of 2-aminobenzylalcohols with an array of nitriles delivering good to excellent yields.[47c] Again, in terms of cost-effectiveness, abundance and sustainability 4d metal catalyst were replaced by 3d metal based catalyst. In that case, in 2018, *Paul and co-workers*[47d] applied their tetraazaannulene based Ni(II) complex (**Ni-4**) *i.e.* [Ni(MeTAA)] to synthesize the quinazoline derivatives from 2-aminobenzylalcohol with aryl nitrile under argon atmosphere. Mechanistic elucidation underpins that in the acceptorless dehydrogenative coupling there was an involvement of $2e^-$ hydride transfer pathway for conversion of alcohol to aldehyde. The author proposed two possible pathways: 1) Nitrile in presence of base get hydrolyzed transformed to amide which further coupled with in situ generated 2-

amino benzaldehyde formed the desired product (pathway-I) and 2) 2-aminobenzylalcohol react with nitrile generate an amidine intermediate which upon subsequent condensation furnish the intended product (pathway-II). Interestingly, the control experiments validate the presence of pathway-I (Scheme **1.21**). In the very next year, the same group[41t] accomplished quinazoline construction upon coupling between 2-aminobenzylalcohol and aryl nitrile in 1:1 equivalent ratio. 4 mol% of that Ni(II) catalyst (**Ni-5**) with 0.75 mol% of KO^{t}Bu was essential to furnish the reaction. In 2019, *Srimani and co-workers*[81b] applied their pre-synthesized Mn-complex (**Mn-1**) mediated quinazoline derivatives synthesis upon coupling of 2-aminobenzylalcohol with an array of aryl nitrile. The optimal condition of the reaction furnished that 1 equiv. of 2-aminobenzylalcohol with 1.5 equiv. of aryl nitrile catalyzed by 5 mol% of Mn-catalyst and 1 equiv. of KO^{t}Bu in xylene solvent accomplished an excellent yield after 30 h. Very recently, *Zhang and co-workers* developed a simple catalytic system in combination of $Co(OAc)_2{\cdot}4H_2O$ and stoichiometric base for quinazolines synthesis via dehydrogenative cyclization of 2-aminobenzylalcohol with an array of aryl nitrile (Scheme **1.21**).[41zb] In 2020, *Balaraman and co-workers*[47e] demonstrated an in situ generated active Mn-catalyst from $MnBr(CO)_5$ (2 mol%) and Ligand (**L1**)(3 mol%) mediated benign approach towards the dehydrogenative construction of quinazoline upon coupling of 2-aminobenzylalcohols and benzamides (Scheme **1.21**).

1.3.1.2.2.2. Synthesis of Quinazolines from 2-aminobenzyl amine:

In 2013, *the Fang group* described $[Cp^*IrCl_2]_2$ (**Ir-5**) catalyzed dehydrogenative synthesis of 2-substituted quinazolines, coupling between 2-aminobenzylamines with aldehydes and alcohols.[47f]Here, styrene act as a hydrogen acceptor, in the absence of which, N-benzylation product formed as a major

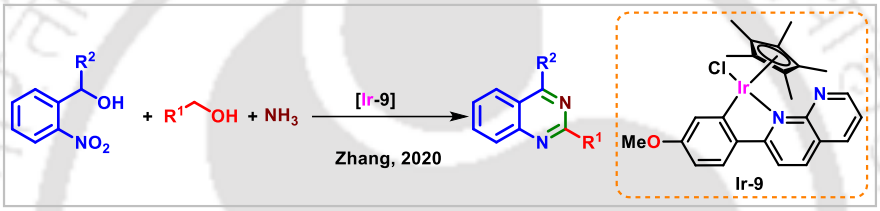


Scheme 1.21. Quinazolines synthesis from 2-aminobenzylalcohol and 2-aminobenzyl amine and their mechanistic outline.

product. Here, the catalytic reaction proceeds in water rather than organic solvents. Intrigued by that strategy, in 2019, various water-soluble Ir catalysts was developed by *the Kundu group* and its catalytic applicability was tested on the fabrication of quinazolines in water.[20d] The **Ir-2** catalyst furnished considerable substrate scopes bearing tolerable functional group with good isolated yield. In 2018, *Paul and co-workers*[47d] furnished the quinazoline derivatives upon implementation of their **Ni-4** complex for coupling of 2-aminobenzylamine and benzyl alcohol in an 1:1 equivalent ratio in a dehydrogenative way with good isolated yield. Lately, in 2019, $Pd(OAc)_2$/ Xantphos catalyzed intermolecular oxidative synthesis of quinazoline reported by *Kimura and co-workers* (Scheme **1.21**).[47g]

1.3.1.2.2.3. Synthesis of Quinazolines via multicomponent pathway:

In 2020, *the Zhang group*[47h] first displayed the multicomponent strategy for the cascade synthesis of aforesaid valuable heterocycle in one pot from readily available 2-nitrobenzyl alcohols along with alcohols employing ammonia as a nitrogen source. They found that 2-(4-methoxyphenyl)-1,8-naphthyridyl ligand supported iridium complex (**Ir-9**) exhibit remarkable catalytic performance in that



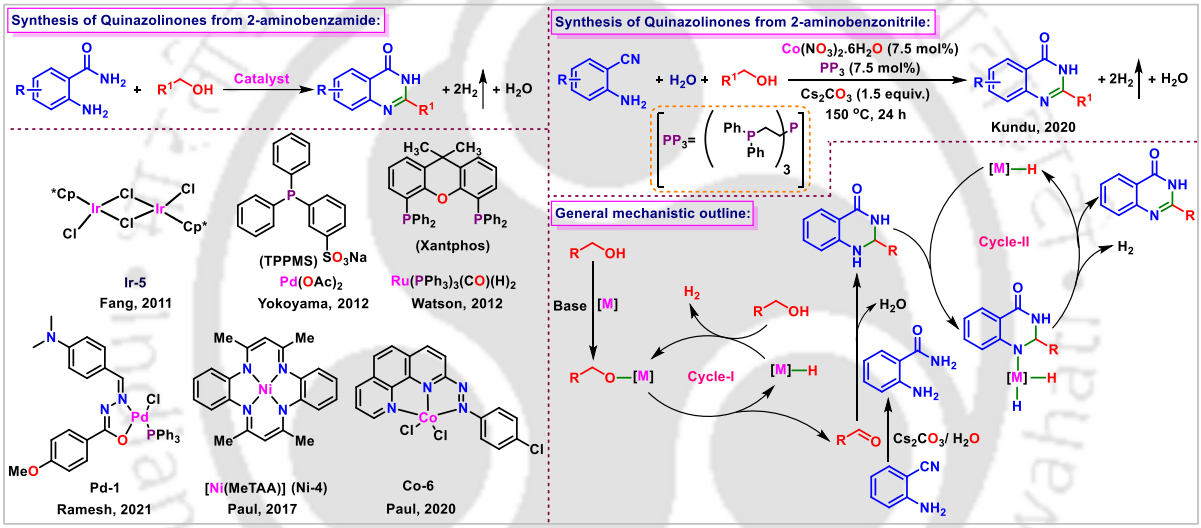
Scheme 1.22. Multicomponent quinazoline synthesis from nitro alcohol, alcohols and ammonia.

current protocol. The non-coordinated N-arm in the ligand backbone accelerated the condensation of step via hydrogen bonding, suggested by mechanistic study (Scheme **1.22**).

1.3.1.2.3. Quinazolinone synthesis via dehydrogenative pathway:

Quinazolinones were considered as renowned N-heterocycles as several bio-active compounds and naturally occurring alkaloids comprise with that scaffold, which makes its synthesis worthy of emphasis. There were various traditional synthetic approaches involved[48] however, these processes are not green, atom-economical and sustainable approached at all. In that perspective, the acceptorless dehydrogenation is a useful synthetic tool for that important heterocyclic scaffold. Upon implementation of that idea, in current years, lot of reports are well-documented towards the dehydrogenative synthesis of quinazolin-4(3H)-ones directly from primary alcohol and *o*-aminobenzamide with noble metals. In that quest, in 2011, *Zhou and co-workers* demonstrated Quinazolin-4(3H)-ones synthesis via oxidative cyclization of primary alcohols with 2-aminobenzamides.[49a]The domino reaction has been carried out by 2.5 mol% of $[Cp^*IrCl_2]_2$ catalyst (**Ir-5**) in absence of base under hydrogen transfer condition. In the very next year, *Yokoyama et al.* manifested the synthesis of quinazolinone derivatives[49b] upon refluxing a mixture of 2-aminobenzamide with the excess acquisition of benzyl alcohol in presence of 5 mol% of $Pd(OAc)_2$ with 10 mol% of sodium (diphenylphosphino)benzene-3-sulfonate (TPPMS) in aqueous media in a closed vessel. The usage of aqueous media makes the protocol green, however, it suffers from very limited substrate scope.

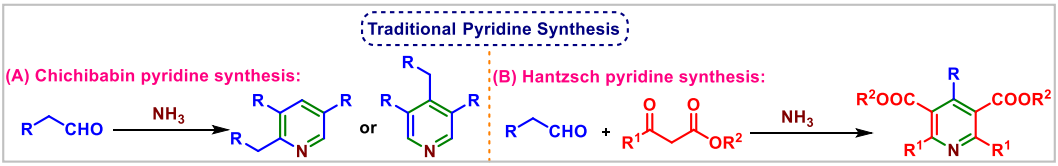
Later, *the group of Watson* achieved the access of quinazolinones employing Ru catalyst combine with Xantphos ligand (1:1) under inert atmosphere[49c] in the same year. In 2021, *Ramesh and co-workers* accomplished the dehydrogenative synthesis of Quinazolin-4(3H)-one[49d] upon coupling of 2-aminobenzamide with an assortment of benzyl alcohols accounting 1 mol% of well-defined bidentate Pd(II) N^O chelating complex (**Pd-1**). The straightforward protocol operates in presence of 1.5 equiv. of KOH base at aerobic condition. In 2017, *Paul and co-workers*[49e] first reported a square planar Ni(II) complex ([Ni(MeTAA)]) catalyzed (**Ni-4**) quinazolin-4(3H)-one synthesis with excess loading of base NaO^{t}Bu (1.5 equiv.) under inert atmosphere. Later, the same group conducted the similar kind of reaction[49f] by exploring their well-defined Co(II) complex (**Co-6**). In 2020, *the group of Kundu*[49g] demonstrated it by employing $Co(NO_3)_2.6H_2O$ with the assortment of tris[2-(diphenylphosphino)ethyl]phosphine (PP_3) ligand in presence of base Cs_2CO_3 (1.5 equiv.) and 20 equiv. of water at 150 °C using 2-aminobenzonitrile as a substrate (Scheme **1.23**).



Scheme 1.23. Quinazolinones synthesis by various catalyst and its mechanistic outline.

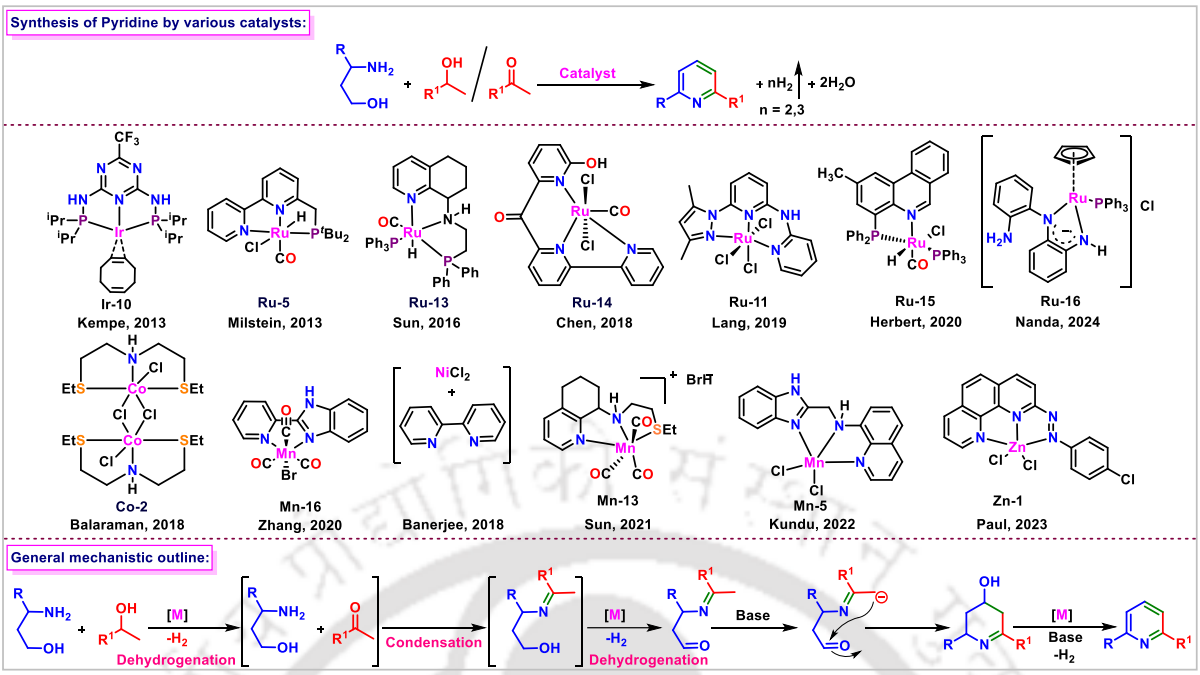
1.3.1.2.4. Pyridine synthesis via dehydrogenative pathway:

Like quinoline, the pyridine skeleton is one of the basic structural unit and prevalent scaffold of various natural products, functional materials and active therapeutic agent. From its medicinal significancy, pyridine is the second most prevalent heterocyclic compound. It has profound application in biomedical usages as a cardiovascular, anti-inflammatory, anti-malarial, anxiolytic and neurogenic drug agent. Not only that it can also act as an organocatalyst and ligands to synthesize different transition metal catalysts.[50]For the industrial synthesis of pyridine derivatives one of the well-known reaction is the Chichibabin reaction where α, β-unsaturated ketone/aldehydes undergoes condensation with ammonia.



Scheme 1.24. Traditional pyridine synthesis.

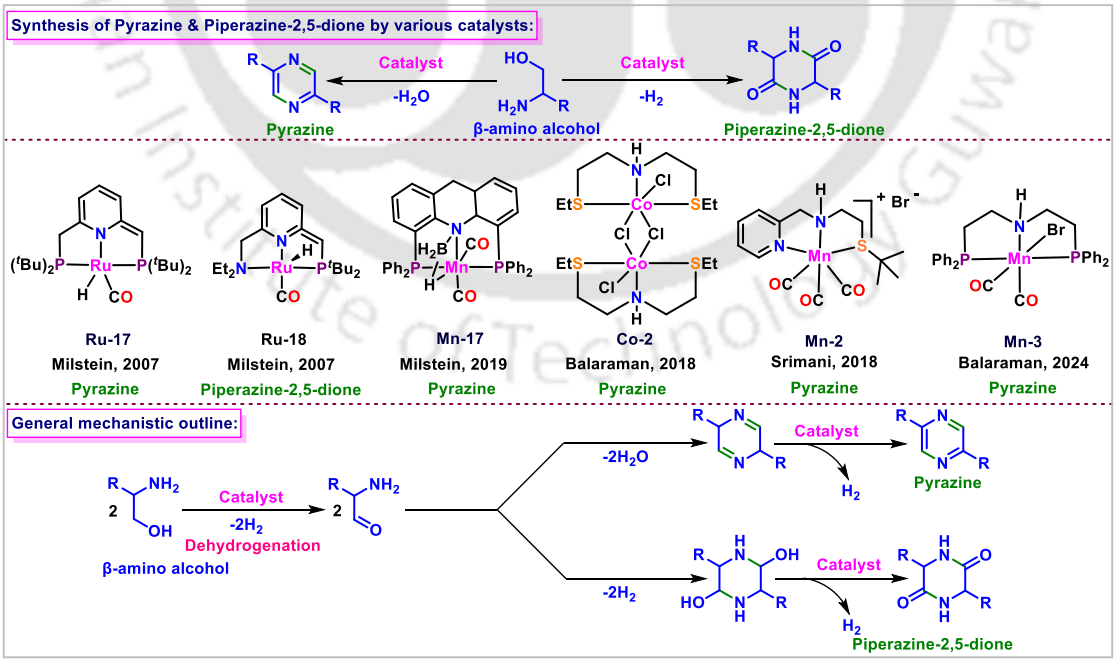
Another well-known reaction is Hantzsch pyridine synthesis (Scheme **1.24**).[51] However, these classical approaches required high temperature and suffer from relatively less stable starting material. Thus, synthesis of pyridine employing readily available, stable and renewable starting material alcohol via ADC is highly desirable. In 2013, dehydrogenative synthesis of various substituted pyridine derivatives by triazine backbone bearing PN_5P-Ir(I)-catalyzed (**Ir-10**) was first disclosed by *Kempe and co-workers* upon coupling of 1,3-amino alcohols with both 1° and 2° alcohols by liberating 3 equiv. of H_2 and 2 equiv. of H_2O.[52a] Several bicyclic pyridine scaffolds were also devised to conduct this. Later, in the same year, the pioneering *Milstein group* demonstrated Ru-bipyridine mediated pincer complex (**Ru-5**) catalyzed synthesis of fused bicyclic pyridine derivatives with moderate isolated yield by two component dehydrogenative coupling between γ-amino alcohol with secondary alcohol via metal-ligand cooperation pathway.[41c] Later, *Sun and co-workers* developed PNN-tridentate Ru-complex (**Ru-13**) taking commercially available $RuHCl(CO)(PPh_3)_3$ as precursor to conduct the aforesaid heterocycle synthesis from same set of coupling partners.[52b] The author comprises that extra stability and higher catalytic activity was imposed by fused ring in the pincer ligand. Later, *Chen,*[52c] *Lang,*[41g] *Herbert*[52d] independently developed various Ru-catalyst to pursue their objectives. Very recently, *Paul and co-workers* delineated substituted 2-aryl pyridine synthesis from secondary alcohol and ammonium acetate as nitrogen donor employing their well-defined newly developed Ru-catalyst (**Ru-16**) bearing a cyclopentadienyl group, one PPh_3 and a redox-active scaffold N^1-(2-aminophenyl)benzene-1,2-diamine having a pendant -NH_2 arm.[52e] The author proposed that the -NH_2 arm of the catalyst facilitates the formation of active species by enhancing the electrophilicity of the carbonyl carbon centre of the diols or diketones by forming hydrogen bonds. However, the usage of precious and inadequate noble metals and air-sensitive phosphine ligands confined that protocol for industrial process and assist to find an alternative 3d-metal based catalytic system. In that quest, in 2018, *Balaraman and co-workers* first introduced dimeric ^{Et}SNS-Co(II) complex (**Co-2**) for the formation of pyridine via coupling of γ-amino alcohol and secondary alcohol.[31e] Both aliphatic and aromatic congeners provided good yield (Scheme **1.25**). Very recently, *Zhang, Ma and co-workers* devised pyridyl-imidazolyl ligand based bidentate NN-Mn(I)-complex (**Mn-16**) for this dehydrogenative transformation reaction.[41x] Intrigued by *Balaraman and co-workers* report, the *Banerjee group* employed their in situ generated $NiCl_2$/bipyridine catalyst to conduct this from γ-amino alcohol and ketone.[31g] Later, *Sun et. al.* reported NN^HS-coordinated Mn(I)-complex (**Mn-13**) catalyzed synthesis of bi, tri, tetracyclic pyridine derivatives from the same set of starting materials in a combining THF and Toluene solvent.[41y] In 2022, *the Kundu group* explored the fabrication of 2,6-disubstituted pyridine derivatives from γ-amino alcohol and ketone employing their nitrogen containing proton responsive unsymmetrical NNN-Mn(II)-pincer complex (**Mn-5**) derived from commercially available cheap precursor $MnCl_2$.[32i] *Paul and co-workers* reported air-stable Zn(II)-complex (**Zn-1**) catalyzed synthesis of unsymmetrical 2,4,6-substituted pyridines via A^3 coupling reaction of primary, secondary alcohols with ammonium acetate at 100 °C under aerobic condition by liberating H_2O_2 instead of H_2 as sole by-product (Scheme **1.25**).[52f]



Scheme 1.25. Synthesis of pyridines by various catalyst and its mechanistic outline.

1.3.1.2.5. Pyrazine and cyclic dipeptide piperazine-2,5-dione synthesis via dehydrogenative pathway:

Pyrazines and cyclic peptides constitute an important class of compounds in chemcalbiology. They exhibit potential application in cancer experimental drugs.[53] Pyrazine or 2,5-dione selectively can be constructed by self-coupling followed intermolecular cyclization of β-amino alcohol upon fine tuning of reaction parameters.



Scheme 1.26. Synthesis of pyrazine and piperazine-2,5-dione and its mechanistic outline.

In that context, the pioneering group *Milstein* first demonstrated the synthesis of cyclic peptide piperazine-2,5-dione and pyrazine derivatives from β-amino alcohol by their Ru-complex.[54a] They

observed that upon fine tuning of ligand arm of Ru-complex it can be selectively synthesized. When the reaction was catalyzed by dearomatized PNN-Ru complex (**Ru-18**) it leads to the formation of cyclic dipeptides with the extrusion of H_2 whilst when it was catalyzed by dearomatized PNP-Ru complex (**Ru-17**) where the amine side arm is substituted by the bulky tert-butyl phosphine arm it leads to pyrazine with the concomitant extrusion of H_2 and H_2O with excellent isolated yield. Later the same group reported acridine based Acr-PNP^{Ph}-Mn(I) complex (**Mn-17**) catalyzed dehydrogenative pyrazine synthesis via self-coupling of β-amino alcohol in presence of catalytic amount (3 mol%) of base KH.[54b] In 2018, *Balaraman and co-workers* demonstrated the pyrazine synthesis via ADC of β-amino alcohol employing their well-defined phosphine-free dimeric ^{Et}SNS-Co(II) complex (**Co-2**).[31e] Vey recently, they have carried out the similar experiment using commercially available 'MACHO' PNP-pincer ligand-based Mn-complex (**Mn-3**) under solventless condition .[54c] At the same time *the Srimani group* also delivered the aforesaid heterocycle using cyclic 1,2-diamine and 1,2-diol by their well-defined tridentate NNS-Mn(I)-complex (**Mn-2**).[23b] Mechanistically for the formation of pyrazine, initially β-amino alcohol undergoes transition metal catalyzed dehydrogenation reaction to furnish amino aldehyde which furthermore undergoes homocoupling reaction fabricating 2,5-dihydropyrazine upon elimination of two H_2O. Afterwards, the 2,5-dihydropyrazine readily undergoes catalytic dehydrogenation to transform into its stable aromatic analogue pyrazine derivative (Scheme **1.26**).

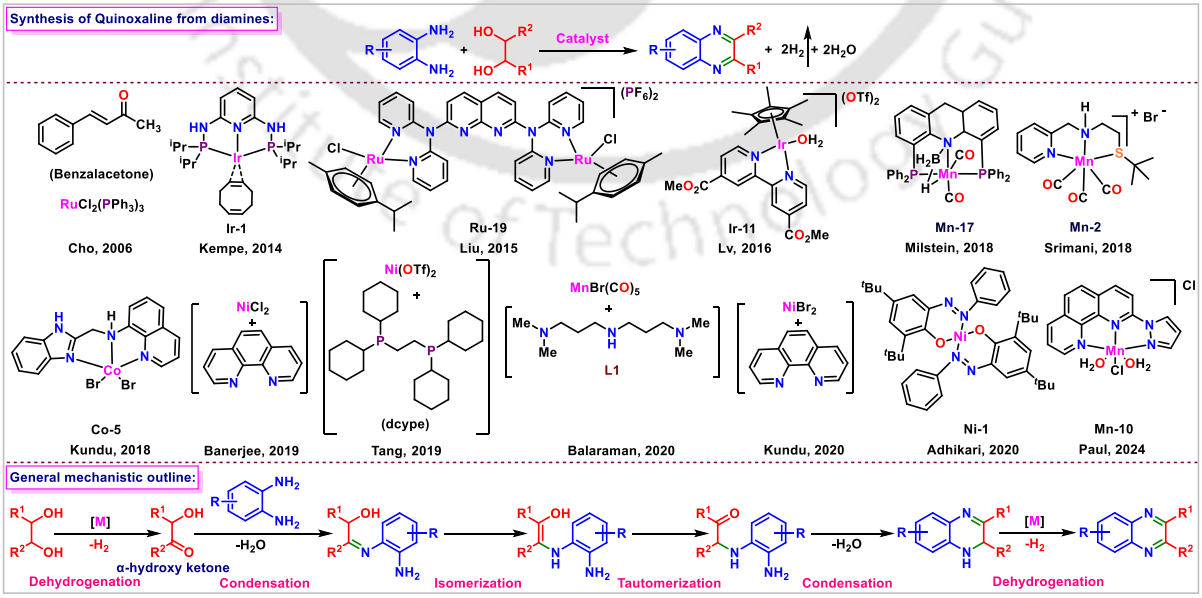
1.3.1.2.6. Quinoxaline synthesis via dehydrogenative pathway:

Quinoxalines, well-known as benzopyrazines, an N-heterocycles and basic structural unit of different naturally important synthetic compounds having profound significance in the field of medicinal chemistry.[55] Despite its prolific biological and physiological significance, traditionally, upon coupling of diamine and diketone, quinoxalines can be synthesized. Later, 'AD' and 'BH' strategy with diamines/nitroamines and alcohols basically diols are more sustainable approaches than coupling with highly reactive diketone. When the reaction was conducted by diol instead of diketone, at the outset terminal alcohol of the 1,2-diol gets catalytically dehydrogenated to α-hydroxy ketone which undergoes condensation reaction with amino group of 1,2-diaminobenzene followed by proton shift, tautomerization and successive intramolecular condensation afforded 1,2-dihydroquinoxaline which concomitant release of H_2 molecule formed the desired quinoxaline derivative (Scheme **1.27**).

1.3.1.2.6.1. Synthesis of Quinoxaline from diamines:

In 2006, *Cho and co-workers* first demonstrated homogeneous Ru-catalyzed i.e. $RuCl_2(PPh_3)_3$ catalyzed synthesis of quinoxalines from *o*-phenylenediamines and vicinal diols, however, they have used benzalacetone as hydrogen acceptor.[56a] In 2014, the pioneering *Kempe* group reported dearomatized pyridine backbone bearing PNP-Ir complex (**Ir-1**) catalyzed aforesaid dehydrogenative transformation reaction with the implementation of lower catalyst loading and relatively lower temperature as compared to the previous one.[56b] In the same year, *Liu* reported this seminal work by developing Ru(II) η^6 -arene complex featuring a dimeric chelating 1,8-napthyridine based ligand (**Ru-19**) under aerobic

condition.[56c] Later, the quinoxaline synthesis from various substituted diamines and 1,2-diols catalyzed by phosphine free bipyridine based NN-Ir(II)-aqua complex (**Ir-11**) was demonstrated by *Lv, Wu and co-workers*.[56d] In 2018, *the Milstein group* first established acridine based Acr-PNP^{Ph}-Mn(I) complex (**Mn-17**) for the aforementioned heterocycle construction from same set of coupling partners in combination of catalytic amount of KH.[54b] However, stoichiometric amount of base was required for 1,2-diols with shorter chains. The author suggested that a five coordinated amido species may play an active role in the alcohol dehydrogenation process and due to the less basic nature of the amido nitrogen of the ligand alkoxy assisted dehydrogenation of alcohol via liberation of molecular hydrogen takes place. In the same year, *Srimani and co-workers* reported construction of quinoxaline from their well-defined NNS-Mn(I)-complex (**Mn-2**) under solventless condition.[23b] Afterwards, *Kundu and co-workers* devised this by their NNN-Co(II)-complex (**Co-5**) via acceptorless dehydrogenative coupling of *o*-phenylenediamine and 1,2-diols.[41l] Nevertheless, *Banerjee and co-workers* carried out the synthesis from 1,2-diamnobenzene with more challenging ethylene glycol as a diol partner in presence of $NiCl_2$ in accordance with 1,10-phenanthroline ligand (1:2) with comparatively lower yield.[20k] In the same year, the Tang group prudently accomplished $Ni(OTf)_2$ and 1,2-bis(dicyclohexylphosphino)ethane (dcype) ligand bearing catalytic system to catalyzed the synthesis of quinoxaline.[56e] Herein, extra two equivalent of 4-methylcinnamic acid was used to reproduce the active catalyst from in situ formed Ni-H species. Afterwards, *Balaraman and his group* applied a catalytic system upon combining $MnBr(CO)_5$ as metal precursor and phosphine free NNN-ligand (**L1**) for this sustainable tandem transformation from of *o*-phenylenediamines and 1-phenyl-1,2-ethanediols.[47e] *Kundu and co-workers*, in 2020, synthesized this employing and operationally simple $NiBr_2$ and 1,10-phenanthroline ligand system by dehydrogenative coupling of various vicinal diols.[56f] Upon conducting the mercury poisoning experiment it revealed that both homogeneous and heterogeneous Ni-materials were actively

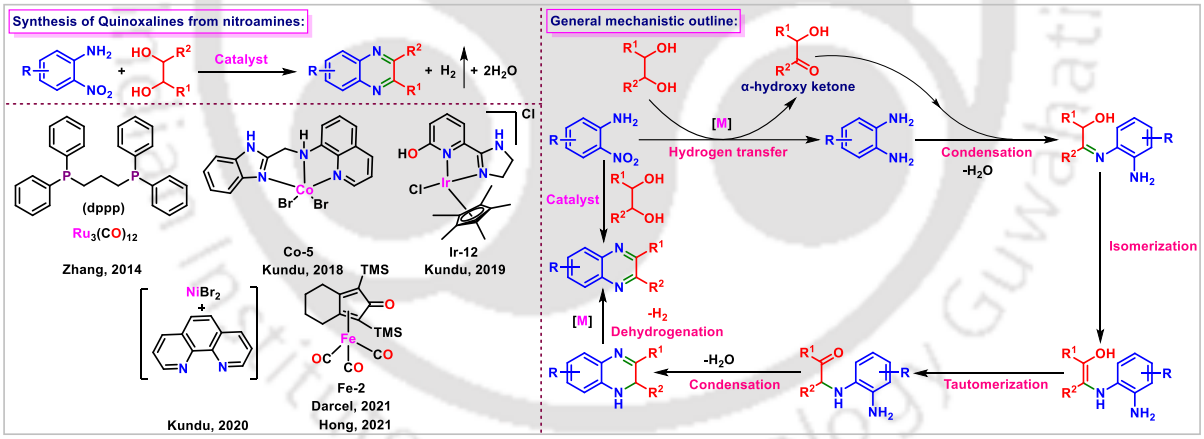


Scheme 1.27. Synthesis of quinoxalines from diamines by various catalyst and its general mechanistic outline.

participated in the catalytic reaction. Recently, *the Adhikari group* demonstrated the coupling of an array of *o*-phenylene diamines and various diols with their inexpensive, redox-active ligand bearing **Ni-1** complex.[41zc] *Paul and co-workers* accomplished this developing 1,10-phenanthroline ligand based NNN-Mn(II) pincer complex (**Mn-10**) in water (Scheme **1.27**).[41v]

1.3.1.2.6.2. Synthesis of Quinoxaline from nitroamines:

$Ru_3(CO)_{12}$ in combination of dppp ligand mediated synthesis of quinoxaline derivatives via dehydrogenative annulation of nitroamines and biomass derived 1,2-diols in absence of any external reducing agent was first reported by *Zhang group*.[56g]In that strategy, the vicinal diol serves as the hydrogen donors and the role of nitro group of 2-nitroaniline was to accept hydrogen. In 2018, *Kundu and his co-workers* demonstrated benzimidazole and 8-aminoquinoline combining paramagnetic NNN-Co(II)-complex (**Co-5**) for the synthesis of different quinoxalines upon coupling of nitroamines with diols.[41l] In the very next year, they have pursued this from the same set of coupling partners with their developed 2-hydroxy pyridine based water soluble Ir(III)-complex (**Ir-12**).[20d] Later, they employed $NiBr_2$/1,10-phenanthroline based catalytic protocol for this sustainable transformation.[56f] The direct synthesis of quinoxalines from 2-nitroaniline and vicinal diol using Knölker Fe-complex (**Fe-2**) in combination of oxidant Me_3NO was reported by *Darcel and co-workers*. Here, the role of Me_3NO is upon oxidizing CO ligand create a vacant site on iron carbonyl complex.[21c] Later, *Hong* modified the strategy displaying ample substrate scope with good to excellent yield (Scheme **1.28**).[56h]

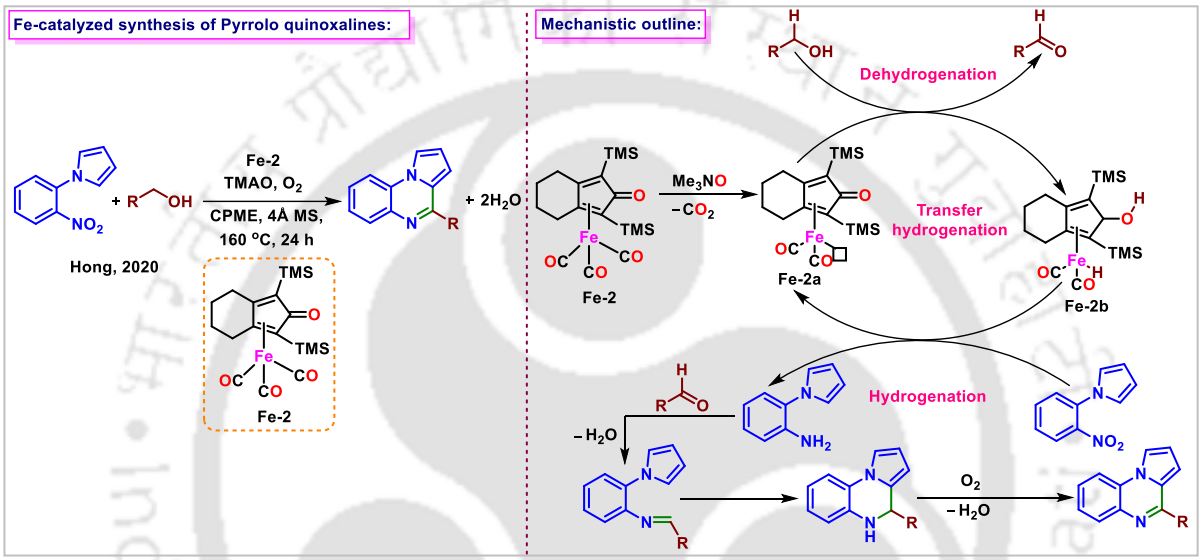


Scheme 1.28. Construction of quinoxalines from nitroamines by various catalyst and its general mechanistic outline.

1.3.1.2.7. Pyrrolo[1,2-α]quinoxaline synthesis via dehydrogenative pathway:

Pyrrolo[1,2-α]quinoxalines are structurally imperative component displayed in various biologically active scaffolds. In addition to their diverse biological activities, their photophysical properties sparked interest in the creation of dyes and materials.[57] Pictet-Spengler-type condensation is one of the most common method for synthesis which involve coupling between aldehydes and reduction product of 1-(2-nitrophenyl)pyrroles i.e. 1-(2-aminophenyl)pyrroles. Previous literature reports documented for this by noble metals are mainly based on oxidation-reduction chemistry where elevated temperature and predesigned substrate required. In contrast, the reports based on 'ADC' and 'HA' is quite operationally

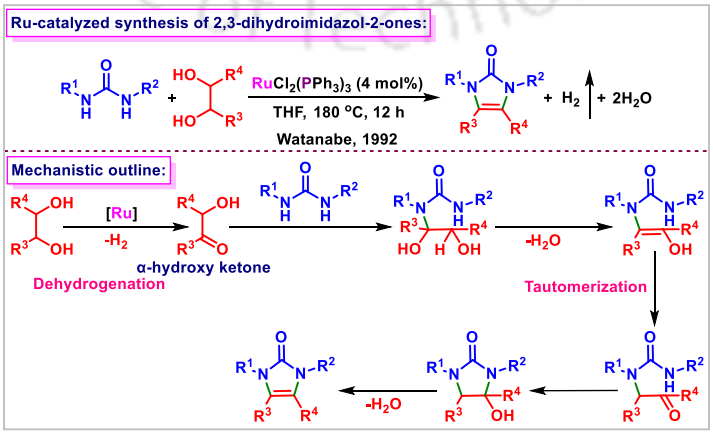
simple and mild. In 2020, direct construction of Pyrrolo[1,2-α]quinoxalines by Fe-catalyzed transfer hydrogenation between alcohols and 1-(2-nitrophenyl)pyrroles with ample substrate scope was reported by *Hong and co-workers*.[58] They have conducted the reaction in presence of 6 mol% of Knölker tricarbonyl Fe-complex (**Fe-2**) in combination with 12 mol% of oxidant Me_3NO which was used to activate **Fe-2** by in situ generation of vacant site in cyclopentyl methyl ether (CPME) under aerobic condition. In this reaction the active Fe-complex catalyzed the dehydrogenation of alcohol and the reduction of nitroarenes generating in situ aldehyde and aniline respectively which further undergoes Pictet-Spengler-type annulation/oxidation reaction furnishing the desired quinoxaline derivative. The primary role of O_2 was to oxidize the intermediate to its final resultant product (Scheme **1.29**).



Scheme 1.29. Knölker Fe-complex mediated construction of pyrrolo[1,2-α]quinoxalines and its mechanistic outline.

1.3.1.2.8. 2,3-dihydroimidazol-2-one synthesis via dehydrogenative pathway:

$RuCl_2(PPh_3)_3$-catalyzed dehydrogenative annulation of vicinal diols with N, N′-disubstituted ureas enroute to synthesis of 1,3-disubstituted-2,3-dihydroimidazol-2-ones was reported by *Watanabe and co-workers* in 1992.[59] The catalytic protocol displayed limited substrate scope (6 examples) with good isolated yield at elevated temperature (180 °C) (Scheme **1.30**).

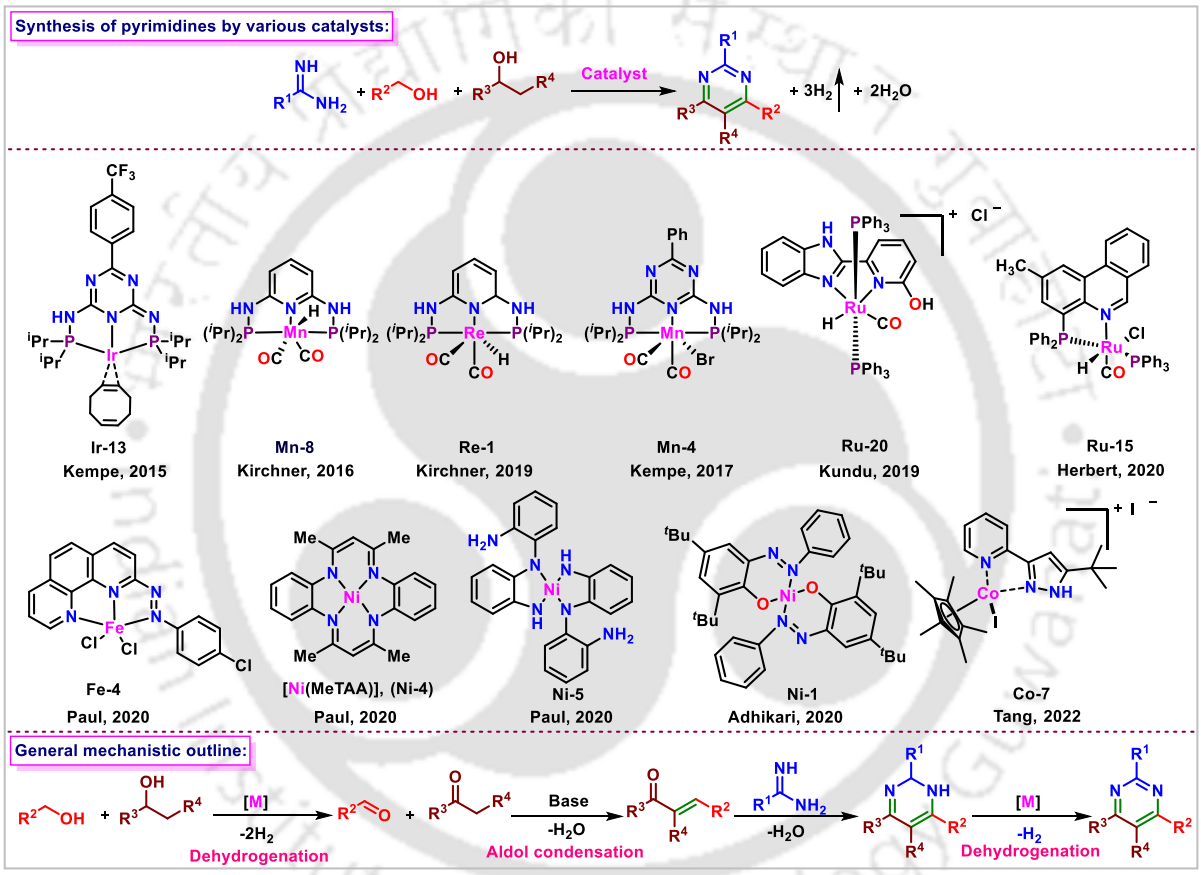


Scheme 1.30. Ru-catalyzed construction of 2,3-dihydroimidazol-2-ones and its mechanistic outline.

1.3.1.2.9. Pyrimidine synthesis via dehydrogenative pathway:

The construction of pyrimidine derivatives has drawn an utmost consideration towards scientific community due to their immense biological importance and potential application in pharmacological industry.[60] Traditionally, pyrimidine can be constructed Lewis acid $ZnCl_2$ catalyzed condensation of formamide with acetophenone, condensation between amidines with malononitriles. However, these classical approaches involve the usage of stoichiometric reagents, harsher reaction condition, moisture sensitive starting materials, multistep procedures, generation of copious toxic waste. Henceforth need to develop for sustainable methodologies. In that, initially, both primary and secondary alcohol undergoes acceptorless catalytic dehydrogenation transforming to their corresponding aldehyde and ketone respectively by liberating two equiv. of molecular hydrogen, which then undergoes base mediated aldol condensation and upon eliminating H_2O it formed α, β-unsaturated ketone which in turn react with amidine followed by dehydrogenation furnished substituted pyrimidines (Scheme **1.31**). Based on that concept, in 2015, PNP-Ir complex catalyzed (**Ir-13**) multicomponent trisubstituted pyrimidine synthesis was first reported by *Kempe and co-workers* with good to excellent yield.[61a] They have also able to synthesize highly substituted pyrimidine derivatives via four component one pot acceptorless dehydrogenative coupling of β-alkylated secondary alcohol with primary alcohol and amidine. In the very next year, *Kirchner and co-workers* reported this seminal work employing their **Mn-8** complex via A^3 coupling reaction in presence of equimolar mixture of base KO^{t}Bu and KOH.[41i] Both of the bases play a crucial role, as absence of either of them exhibit detrimental effect in the yield. The author suggested that base has two roles; one is to deprotonate the -NH proton of PNP-ligand of **Mn-8** and another is to drive the condensation step. In 2019, they reported the similar transformation by developing the Re-complex of that same ligand scaffold *i.e.* hydride Re(I)-PNP pincer complex (**Re-1**).[32h]Although both Re and Mn-complex are isoelectronic in nature, the lower loading of **Re-1** and shorter reaction time makes this protocol more efficacious than previous **Mn-8** complex catalyzed report. Soon after these reports, *Kempe and co-workers* demonstrated the multicomponent tri and tetra-substituted pyrimidine synthesis reacting amidine with three different alcohols catalyzed by triazine backbone based PN_5P-Mn(I)-pincer complex (**Mn-4**).[61b]The author suggested that **Mn-4** complex displayed similar activity to **Ir-13** complex whereas, its Co-complex remain catalytically inactive. The high reactivity of **Mn-4** facilitates the reaction with lower loading of base compared to *Kirchner and his group* report. Recently, benzimidazole-hydroxypyridine based bidentate NN-Ru(III)-complex (**Ru-20**) catalyzed three component synthesis of aforesaid heterocycle was reported by *Kundu and co-workers*.[61c] Later, *Herbert et. al.* developed PN-Ru(II)-complex (**Ru-15**) for this similar transformation.[52d] *Paul and co-workers* introduced in 2019, a penta-coordinated Fe(II)-complex (**Fe-4**) bearing 2-phenylazo-(1,10-phenanthroline) ligand for this sustainable transformation employing guanidine, primary and secondary alcohol as dehydrogenative coupling partner with lower loading of base under aerobic condition.[61d] Mechanistic investigation tells that there was a synergistic participation of both arylazo ligand and Fe in the dehydrogenative transformation of alcohols which avoid the

energetically demanding iron-centred two electron Fe(II)/Fe(IV) redox events. Later, they have employed **Ni-4** and **Ni-5**, tetradentate catalysts to accomplish the aforementioned heterocycle using amidine, primary and secondary alcohol as coupling partner.[61e] **Ni-4** dehydrogenated alcohol by thermodynamically unfavourable $2e^-$ hydride transfer pathway, to pursue this required higher temperature and longer reaction time whilst **Ni-5** carried out this via 1 e^- hydrogen atom transfer pathway. In the same year, *the Adhikari group* presented **Ni-1** catalyzed reaction in relatively milder condition via 'HAT' pathway.[61f] Very recently, *Tang et. al.* reported Co(III)-pyridyl-pyrazole bifunctional catalyst (**Co-7**) mediated acceptorless dehydrogenative coupling (ADC) towards various pyrimidine synthesis with good to excellent yield (Scheme **1.31**).[61g]

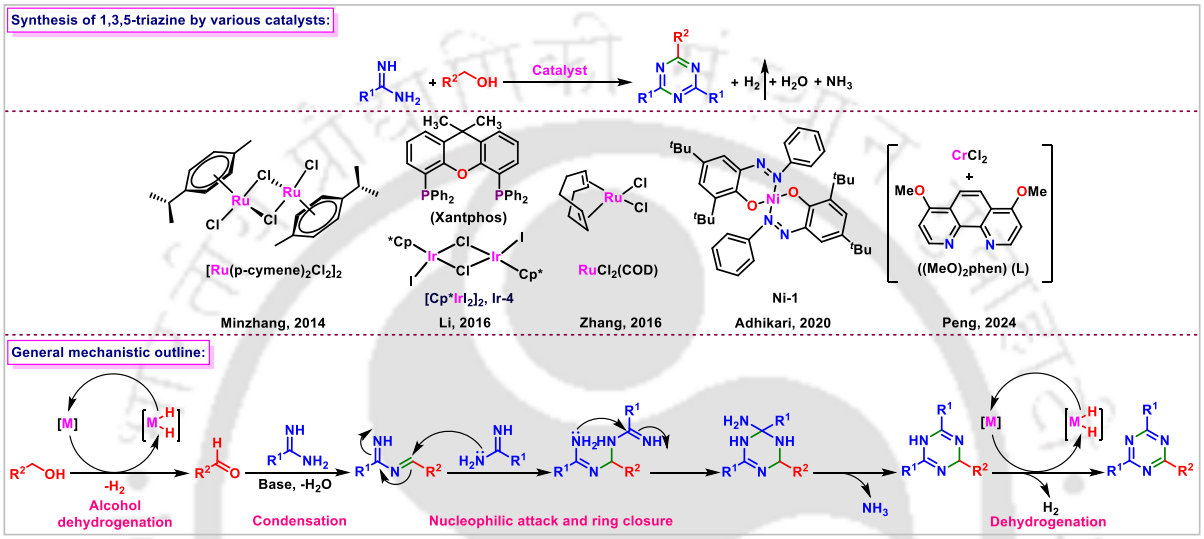


Scheme 1.31. Synthesis of pyrimidines by various catalysts and its general mechanistic outline.

1.3.1.2.10. 1,3,5-triazine synthesis via dehydrogenative pathway:

Like pyrimidine, aryl substituted 1,3,5-triazine derivatives are also synthesized by multicomponent 'ADC' strategy from renewable starting material alcohol (Scheme **1.32**), exhibit diverse biological activities.[62] In 2014, *Minzhang and co-workers* reported $[RuCl_2(p\text{-cymene})]_2$ mediated reaction between amidine hydrochloride and aryl alcohols towards the synthesis of trisubstituted 1,3,5-triazines in presence of weak base K_2CO_3, however, for aliphatic alcohol it remain inactive.[63a] Next, in 2016, *the Li group* accomplished this aforesaid heterocycle from same set of coupling partners using dimeric Ir(III) complex (**Ir-4**) *i.e.* $[Cp^*IrI_2]_2$ in accordance with xantphos ligand.[63b] In this catalytic protocol both aliphatic and aromatic alcohol smoothly underwent under streamline reaction condition. In the same

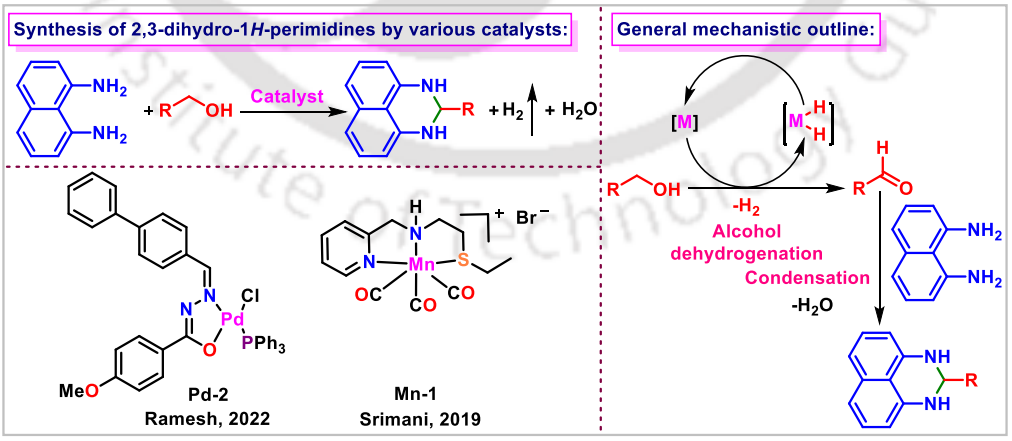
year, *Zhang et. al.* synthesized trisubstituted 1,3,5-triazines from various alcohols and biguanides catalyzed by $RuCl_2(COD)$.[63c] In 2020, *Adhikari and co-workers* showcased **Ni-1** catalyzed aforementioned heterocycle synthesis via dehydrogenative coupling between 1 equiv. of substituted benzyl alcohols with 2 equiv. of benzamidine under mild reaction condition (80 °C).[61f] Very recently, *Peng et. al.* demonstrated dehydrogenative construction of 1,3,5-triazine derivatives upon coupling of alcohols with amidines using $CrCl_2$ with nitrogen ligand 4,7-dimethoxy-1,10-phenanthroline ($(MeO)_2$phen) (**L**) in presence of 18-crown-6 additive in mesitylene solvent with broad substrate scope (Scheme **1.32**).[63d]



Scheme 1.32. Synthesis of 1,3,5-triazine by various catalysts and its general mechanistic outline.

1.3.1.2.11. 2,3-dihydro-1*H*-perimidine and Fertigine derivative synthesis via dehydrogenative pathway:

1.3.1.2.11.1. 2,3-dihydro-1*H*-perimidine synthesis via dehydrogenative pathway:



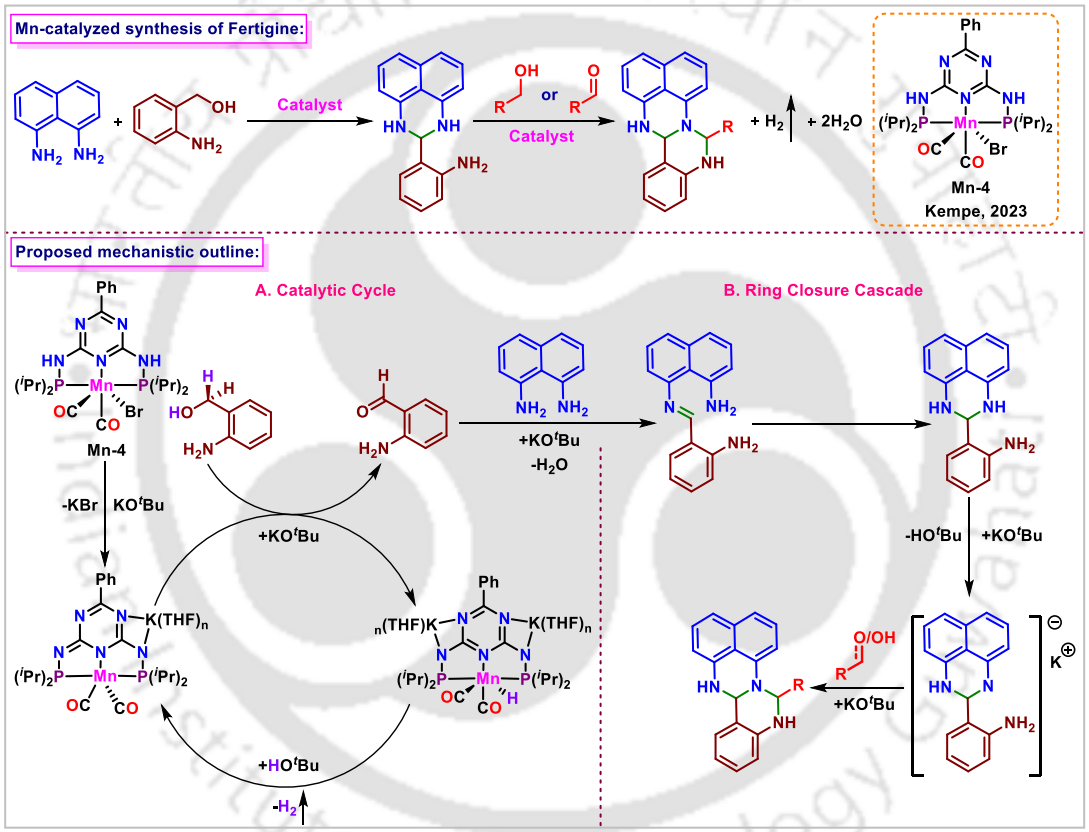
Scheme 1.33. Dehydrogenative construction of 2,3-dihydro-1*H*-perimidines by various catalysts and its general mechanistic outline.

Synthetically and naturally important Perimidine scaffolds exhibit a wide range of biological activity.[64, 65]Intrigued by this significant importance, in 2022, *Ramesh and co-workers* reported Pd(II)-catalyzed (**Pd-2**) synthesis of 2,3-dihydro-1*H*-perimidine employing KOH as a base with a limited substrate

scope.[66a] However, toxicity and high cost was the major drawbacks which confined their use of noble metals and enhanced the implementation of 3d metals in homogeneous catalysis. In that quest, in 2019 *Srimani et. al.*[66b] demonstrated the synthesis of aforementioned heterocycle upon coupling between 1,8-diaminonapthalene and primary alcohols via acceptorless dehydrogenation (AD) upon intake of phosphine free NNS-Mn(I) complex (**Mn-1**) with KOH base in toluene solvent at 24 h, however, it offered moderate substrate scope because of involvement of activated primary alcohol (Scheme **1.33**).

1.3.1.2.11.2. Consecutive multicomponent strategy for Fertigine synthesis:

In 2023, *Kempe and co-workers* devised a new heterocyclic scaffold named as 'Fertigine' in a modified multicomponent strategy employing specific set of substrates via acceptorless dehydrogenation followed by cyclization.



Scheme 1.34. Mn-catalyzed synthesis of fertigines and its mechanistic outline.

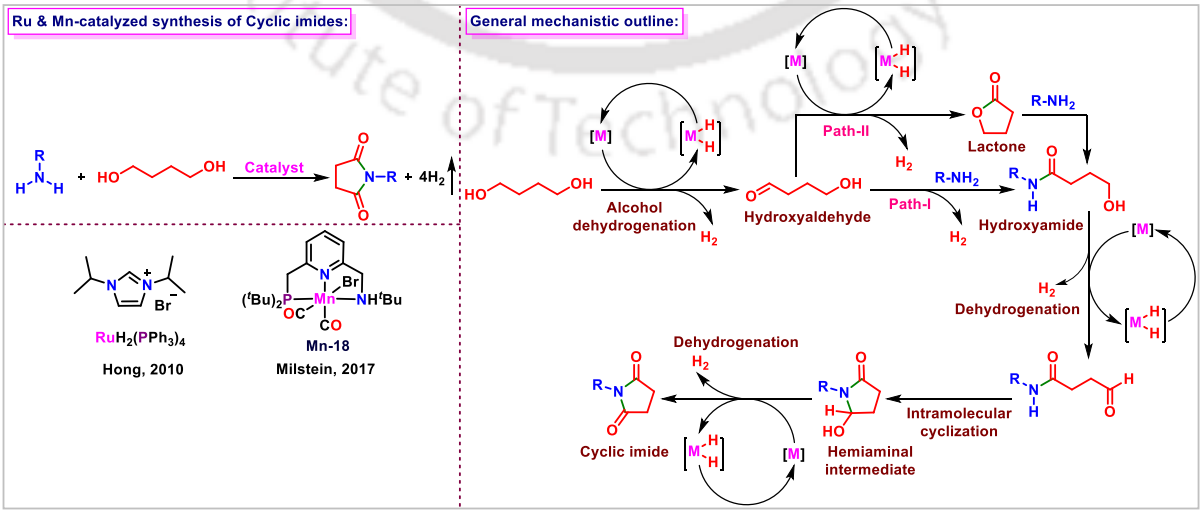
In this synthetic protocol, it involved Mn-catalyst mediated dehydrogenative transformation of amino alcohol followed with condensation and cyclization with original set of diamines regenerate a new set of diamine which further reacts aldehydes or carbonyldiimidazoles furnished the targeted heterocyclic scaffolds. This consecutive multicomponent strategy named as 'regenerative cyclisation' or 'iterative synthesis'. For that, the author have screened with their previously developed triazine and pyridine backbone PN_5P and PN_3P-ligand based Mn(I)-complexes, out of which **Mn-4** exhibits excellent reactivity with good selectivity.[66c] However, its Co(II) and Fe(III) congeners failed to exhibit reactivity. Based on the previous literature reports on **Mn-4** mediated dehydrogenation and some control experiments on that current reaction, they sketched a catalytic cycle which is outlined in scheme **1.34**.

1.3.2. Saturated N-heterocycles synthesis via ADC pathway:

Construction of saturated N-heterocycles via inter or intra molecular dehydrogenative coupling of hemiaminal/hemiacetal intermediate is also an important area of research since it is completely untapped. Last few years, some pioneering groups have devised some elegant protocols to unravel the synthesis of cyclic imides, lactams and lactones.

1.3.2.1. Cyclic imide synthesis via ADC:

Cyclic imide is a key structural building block in synthetic, medicinal, biological and polymer chemistry.[67] It is a potential scaffold found in several drugs and highly bioactive compounds. Despite their utility, the conventional methods involved for this is Ir-catalyzed three components coupling of nitriles, olefins and water,[68a] Ru-catalyzed carbonylation of aromatic amides to form phthalimides[68b] etc. These methods suffer from non-negligible drawbacks. To devoid from this 'ADC' of diol with amine is employed as an alternative, green and sustainable approach. In that quest, in 2010, *Hong and co-workers* first postulated Ru-hydride based catalyst i.e. $[RuH_2(PPh_3)_4]$ in accordance with NHC ligand mediated synthesis of cyclic imides via acceptorless dehydrogenation followed by cyclisation of amine with biomass derived renewably obtained simple diol.[69a,b] The catalytic protocol is viable for both aliphatic and aromatic diols and amines furnishing good isolated yield, however, it is limited for five and six-membered cyclic imides, seven-membered cyclic imide was not successful. Later, they have conducted the reaction taking readily available nitriles instead of amines as coupling partner with the implementation of same catalytic system in NaH base.[69c] In 2017, the pioneering *Milstein group* displayed an unprecedented reported on pyridine based PNNH-Mn(I)-pincer complex (**Mn-18**) catalyzed dehydrogenative synthesis of cyclic imides upon coupling of diols with primary amines with the concomitant release of H_2. Herein, the catalytic amount of base KH is sufficient to accelerate the reaction.[69d]The author suggested that the N-H proton of the -NH^{t}Bu arm plays a crucial role towards the formation of active catalyst, since it's -NEt_2 arm is catalytically inactive. The formation of a hydride intermediate via an 'amine arm' opening is assumed to be the key step of the catalytic cycle. They have

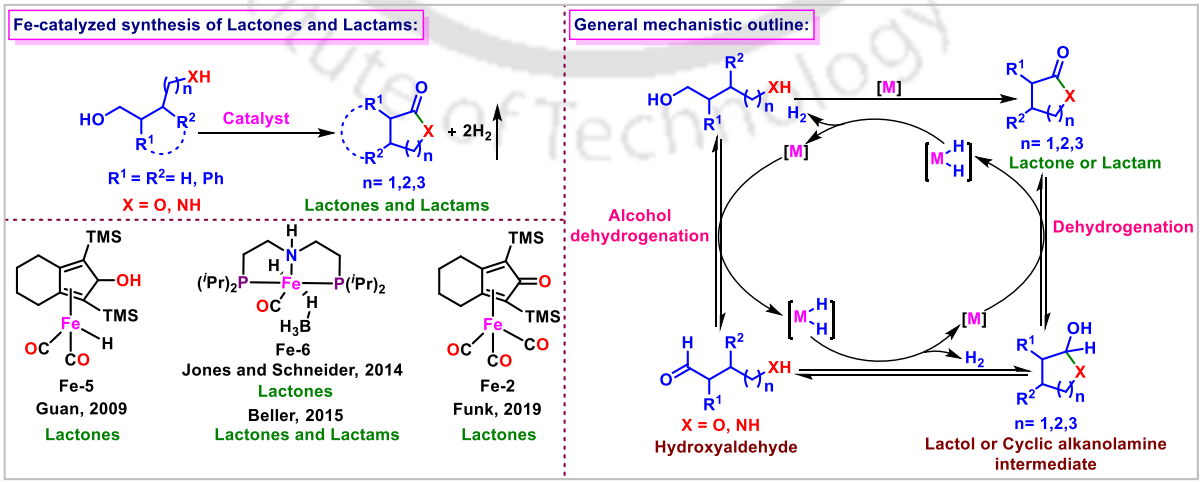


Scheme 1.35. Ru & Mn-catalyzed construction of cyclic imides and its general mechanistic outline.

proposed a mechanistic pathway on the basis of control experiments where initially the diol undergoes catalytic dehydrogenation forming hydroxyaldehyde or lactone which upon reaction with amine formed hydroxyamide. Furthermore, the subsequent dehydrogenation and intramolecular cyclization generates the hemiaminal intermediate which upon thermodynamically favorable hydrogen molecule loss furnished the desired cyclic imides product (Scheme **1.35**).

1.3.2.2. Lactam and Lactone via ADC:

Lactones and lactams are utilised as useful building blocks to create biodegradable polyesters and polyamides via ring-opening polymerisation and useful structural unit for various natural products and biologically active compounds.[70] Over the years, various group have synthesized these scaffolds via 'ADA' of biomass derived diols. In 2009, *Guan and co-workers* first described a well-defined (hydroxycyclopentadienyl)iron dicarbonyl hydride (**Fe-5**) catalyzed dehydrogenative cyclization of diol to convert it into its corresponding lactones based on the previously studied activity of **Fe-5** complex in dehydrogenation reaction.[71a] They have conducted the reaction in presence of 3 mol% of **Fe-5** at relatively lower temperature (60 °C) under base-free condition in presence of acetone, which has dual role i.e. act as a solvent as well as a hydrogen acceptor. In 2014, *Schneider and co-workers* accomplished the synthesis of lactones via intramolecular acceptorless dehydrogenative coupling of PNP-pincer ligand-based Fe-MACHO-BH catalyst (**Fe-6**) with limited substrate scope.[71b]In the very next year, both lactone and lactam employing similar **Fe-6** complex was accomplished by *Beller and co-workers*.[71c]The catalyst enable to construct five to seven membered lactone, however failed to furnish four membered lactone. Similarly, for lactam six and seven membered rings are furnished with excellent isolated yield whilst four and five membered rings are ineffective. In 2020, *the group of Funk* explored their **Fe-2** complex towards dehydrogenative lactonization of various symmetrical and unsymmetrical diol employing acetone as solvent and the hydrogen acceptor.[71d] Five, six and seven membered lactone ring successfully formed with no over oxidation to carboxylic acids, however, for unsymmetrical diol the selectivity is low. Catalyst having sterically bulk TMS or 3,5-dimethylphenyl



Scheme 1.36. Fe-catalyzed synthesis of lactones and lactams and its general mechanistic outline.

group nearer to cyclopentadienone carbonyl exhibit large effect in its reactivity as well as activity. The proposed mechanism suggested that initially diol get catalytically dehydrogenated to form hydroxyaldehyde which get cyclized to lactol or cyclic alkanolamine intermediate. It furthermore undergoes second dehydrogenation formed lactone or lactam (Scheme **1.36**)

1.4. Borrowing Hydrogenation (BH) mediated construction of saturated N-heterocycles:

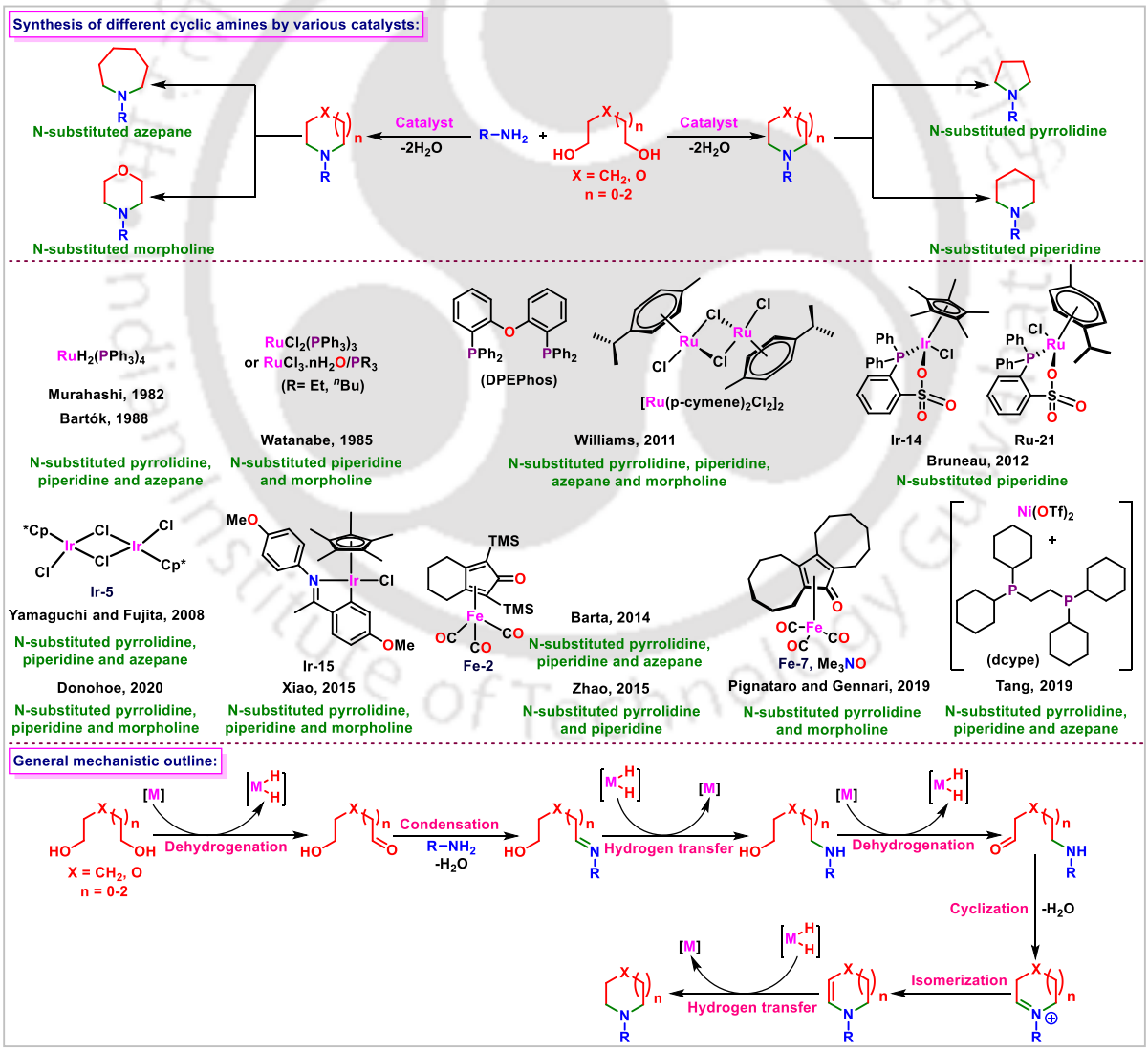
Owing to the prolific importance of saturated N-heterocycles in the arena of drug molecules and organic synthesis, construction of these scaffolds offers an utmost attention towards researchers.[72] Amidst of that saturated cyclic amines have witnessed in past few decades.

1.4.1. Borrowing Hydrogenation (BH) mediated cyclic amine synthesis:

1.4.1.1. Borrowing Hydrogenation (BH) mediated N-substituted piperidine, pyrrolidine, azepane and morpholine synthesis:

Classically, these amines can be synthesized from 1,5-dihalogenopentanes, diethanol amines diethylenetriamines through intramolecular cyclization reaction.[73] Later these strategies have been replaced by dehydrogenative condensation of renewably available diol followed via 'BH' or 'HA' approach. In 1982, *Murashi and co-workers* studied and reported the synthesis of cyclic amines by $RuH_2(PPh_3)_3$-catalyzed intramolecular and intermolecular cyclization of aminoalcohol/alcohol and diol/primary amines at elevated temperature i.e. 160-180 °C.[74a]On the basis of conducted control experiments the author proposed that more convenient pathway was reaction between diol and primary amines than the reaction between aminoalcohol and primary alcohol to furnish the resultant product in higher yield. This strategy provides good to excellent yield of pyrrolidine, piperidine and azepane of various chain length via intramolecular cyclization of aminoalcohol under solvent-free condition. Later, *Bartók et. al.* pursued similar reaction employing $RuCl_2(PPh_3)_3$ catalyst.[74b]In 1985, *the group of Watanabe* reported N-substituted piperidine and morpholine derivative synthesis via N-heterocyclization of primary amines with commercially available 1,5-diols such as 1,5-pentanediol and diethylene glycol catalyzed by $RuCl_2(PPh_3)_3$ or $RuCl_3.nH_2O$/phosphine ligand.[74c]The alkyl phosphine like PEt_3 or P^tBu_3 was efficacious for aliphatic amines whilst PPh_3 was suitable for aromatic amines. The basicity of amines attributed a striking difference here. Aliphatic amines are more basic, for that it may require more basic phosphine as ligands. The author also suggested that like basicity steric modulation also plays an important role. Therefore, in presence of $RuCl_3.nH_2O$/ P^tBu_3 they have prepared N-substituted morpholines and N-substituted pyrrolidine from aliphatic amine with diethylene glycol and primary amine with 1,4-butane diol respectively with excellent yield. Later, *Williams and his group* also reported [Ru(p-cymene)Cl_2] in accordance with diphosphine ligand DPEphos mediated synthesis of 5, 6 and 7 membered cyclic amines via hydrogen autotransfer mediated annulation of primary amine with the corresponding diol under microwave condition.[74d]In 2004, *Fujita et. al.* devised dimeric $[Cp^*IrCl_2]_2$ (**Ir-5**) catalyzed N-alkylated cyclic amines from diol and primary amine at milder condition as compared to the previous Ru-catalyzed reports.[74e] In 2012, a tandem multicomponent

synthesis of C3-functionalized N-aryl piperidines from 1,5-diol, aniline and aldehydes in more eco-friendly diethyl carbonate solvent was catalyzed by chelating phosphine sulfonate ligand bearing piano-tool geometry based Ir(III)-complex (**Ir-14**) was reported by *Bruneau and co-workers*.[74f] They have also achieved Ru(II)-arene complex of that same chelating ligand (**Ru-21**), however, **Ir-14** catalyst outperformed over **Ru-21** catalyst. In order to get better selectivity, the author used camphorsulfonic acid (CSA) as a Bronsted acid. Later, *Xiao group* accomplished N-aryl pyrrolidine, piperdidine and morpholine with their cyclometallated Ir-complex (**Ir-15**).[74g]Recently, the pioneering *Donohoe group* demonstrated $[Cp^*IrCl_2]_2$ complex (**Ir-5**) catalyzed C3 and C4-substituted N-alkylated pyrrolidine, piperidine and morpholine derivatives via borrowing hydrogen annulation strategy.[74h]In 2015, **Fe-2** complex catalyzed synthesis of various benzyl protected 5, 6 and 7-membered cyclic amine from 4, 5 and 6-membered acyclic diol with several benzyl amines in presence of Me_3NO oxidantwas first manifested by *Feringa, Barta and co-workers*.[74i]The role of using cyclopentyl methyl ether (CPME) is to stabilize the key iron intermediate. The reaction proceeds via intermolecular N-alkylation followed

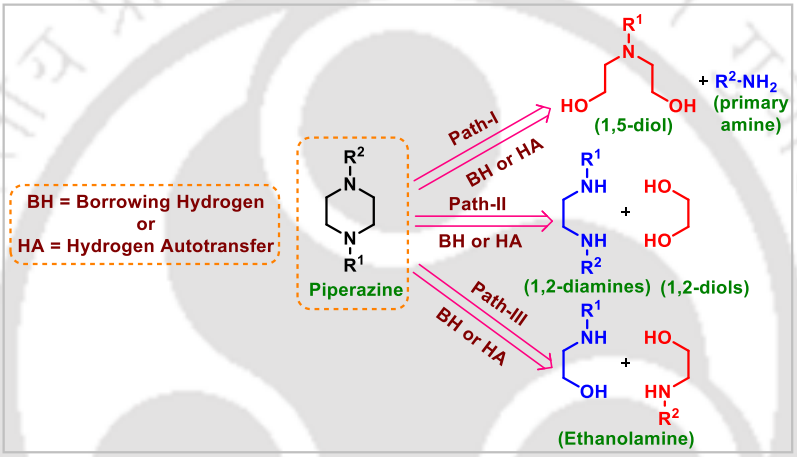


Scheme 1.37. Synthesis of N-substituted piperidines, pyrrolidines, azepanes and morpholines by various catalysts and its general mechanistic outline.

by second intramolecular alkylation with free alcohol. This catalytic protocol also able to fabricate challenging seven membered azepane type N-heterocycle. In the very next year, *Zhao and his team* applying aniline and diol synthesized saturated N-heterocycles using **Fe-2** complex in combination with Lewis acid AgF whose role is to facilitate the imine condensation and activate the imine intermediate towards reduction by the Fe-H complex.[74j] Later, *Pignataro, Gennari and co-workers* modified this catalytic protocol obviating the usage of semi-precious co-catalyst AgF.[74k]In the same year, *Tang et. al.* devised $Ni(OTf)_2$ in accordance with 1,2-bis(dicyclohexylphosphino)ethane (dcype) ligand mediated catalytic protocol to furnish N-substituted pyrrolidine, piperidine and azepanes with good isolated yield in slightly acidic HFIP *i.e.* 1,1,1,3,3,3-hexafluoroisopropanol solvent (Scheme **1.37**).[56e]

1.4.1.2. Borrowing Hydrogenation (BH) mediated piperazine synthesis:

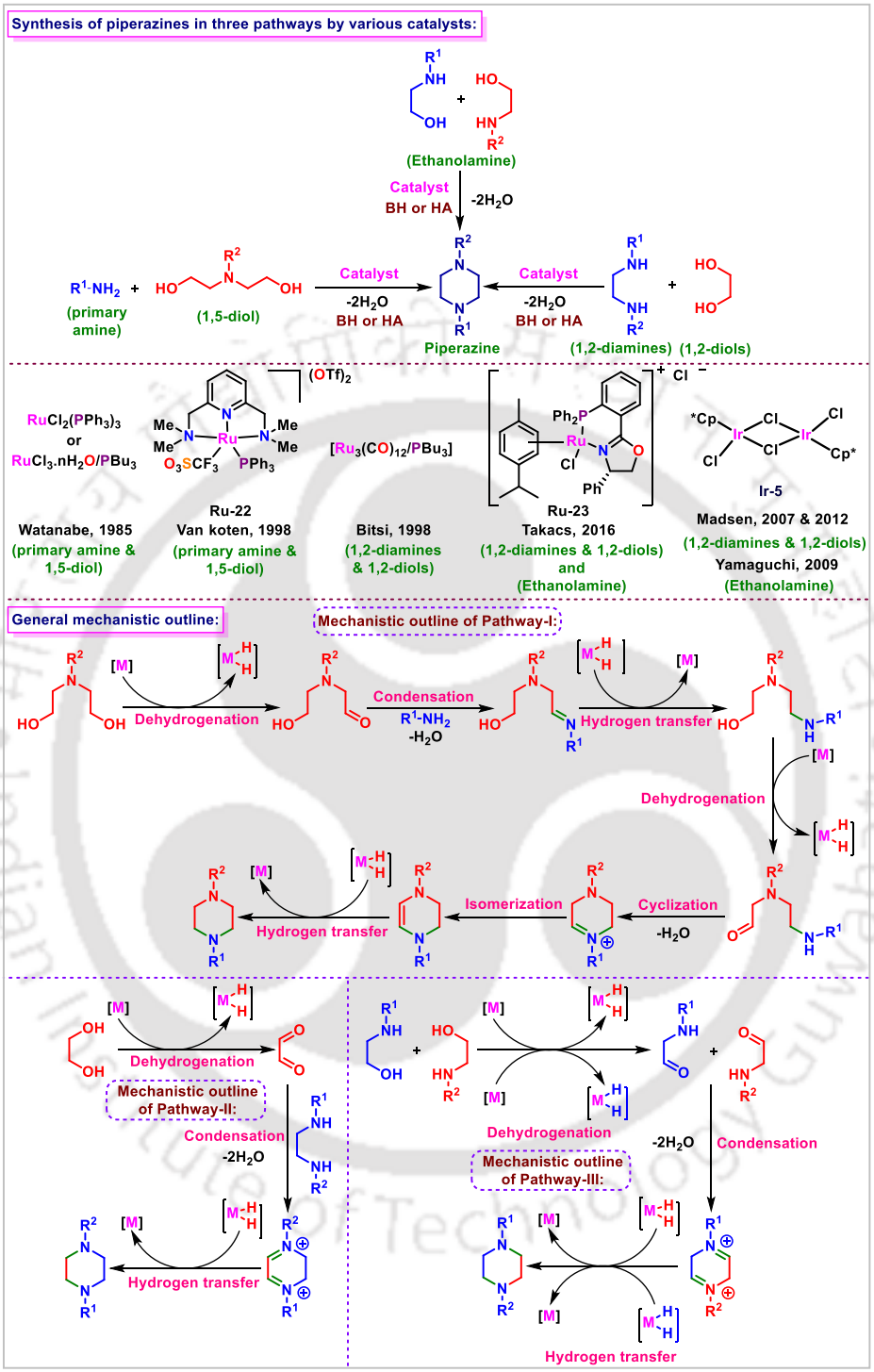
Piperazines can be synthesized via three pathways employing the 'BH' strategy (Scheme **1.38**).



Scheme 1.38. Schematic representation of three pathways for synthesis of piperazines via 'BH' or 'HA'.

So far, noble metal based catalytic protocol has been implemented to fabricate this. In that context, in 1985, Ru-catalyzed synthesis of N-arylated or N-alkylated piperazines via borrowing hydrogen mediated annulation of primary amines with diethanolamines as a source of 1,5-diols was first demonstrated by the pioneering *Watanabe group*.[74c] Following that protocol, the author have synthesized five piperazine derivatives with moderate isolated yield and they also conveyed that for aromatic amine $RuCl_2(PPh_3)_3$ provided the optimal result whilst for aliphatic amine $RuCl_3.nH_2O$/ P^tBu_3 displayed most effective result (Scheme **1.39**). Later, in 1998, *Van koten et. al.* explored the similar reaction with their developed phosphine free NNN-Ru(II)-pincer complex (**Ru-22**), although this protocol is limited only for aromatic amines furnishing moderate yield.[75a] In the same year, *the Bitsi group* also constructed some aforementioned heterocycles employing simple 1,2-diamine and 1,2-diols by their $[Ru_3(CO)_{12}/PBu_3]$-catalytic system, however, elevated temperature i.e. 220 °C is required for this.[75b] Later, *the Takacs group* also conducted similar transformation employing their **Ru-23** complex.[75c] Both *Madsen*[75d,e] *and Yamaguchi*[75f] independently accomplished a plethora of bicyclic piperazines via cyclocondensation of diols and diamines and N-alkylation of ethanolamine respectively

in aqueous media in presence of catalytic amount of commercially available $[Cp^*IrCl_2]_2$ complex (**Ir-5**) employing weak base $NaHCO_3$ (Scheme **1.39**).

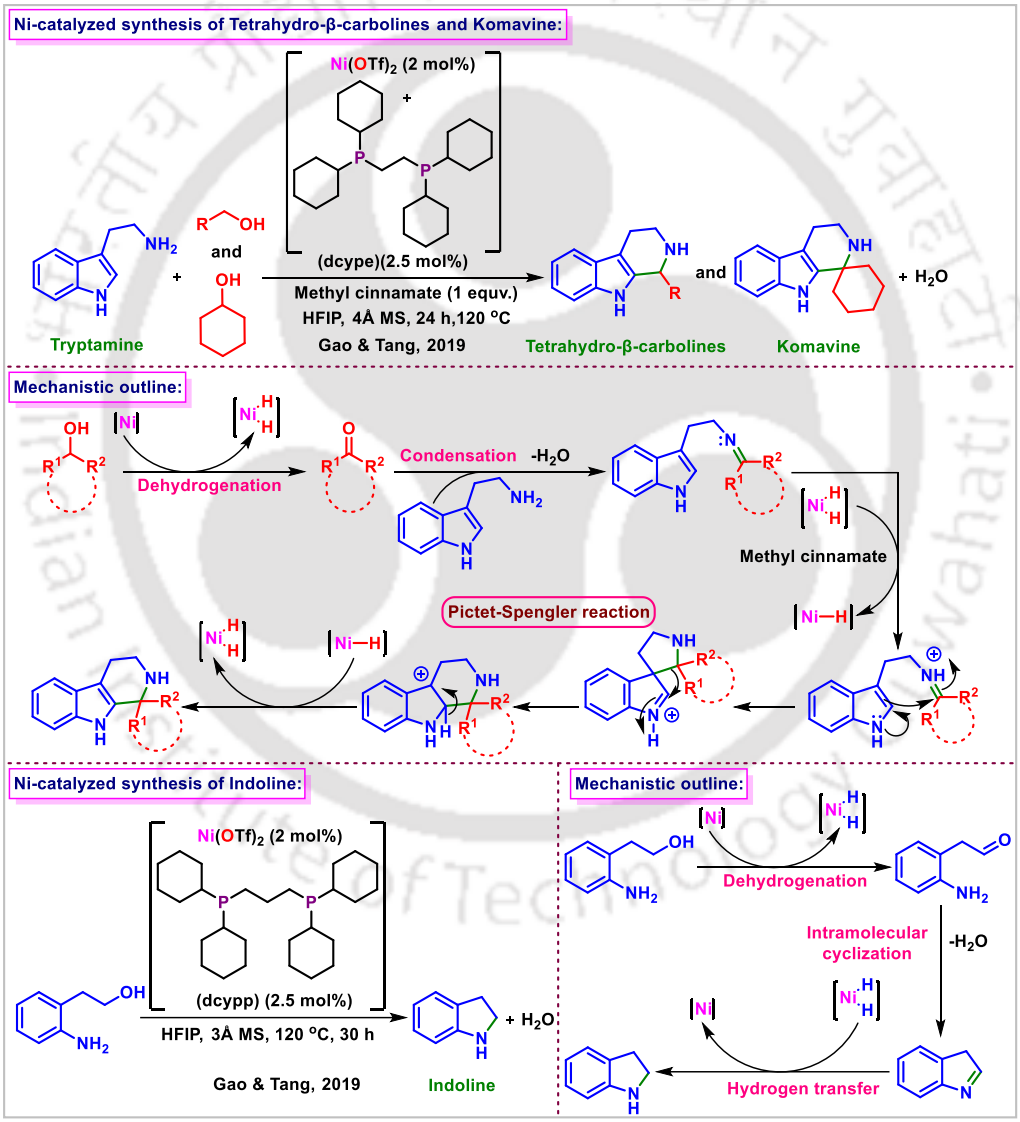


Scheme 1.39. Synthesis of piperazines via 'BH' or 'HA' by various catalysts and its general mechanistic outline.

1.4.2. Borrowing Hydrogenation (BH) mediated Indoline and its derivative synthesis:

In 2019, $Ni(OTf)_2$ in combination of 1,2-bis(dicyclohexylphosphino)ethane (dcype) ligand mediated synthesis of tetrahydro-β-carbolines in slightly acidic HFIP solvent via dehydrogenation of aryl and alkyl alcohol followed by Pictet-Spengler reaction with tryptamine was reported by *Tang and co-*

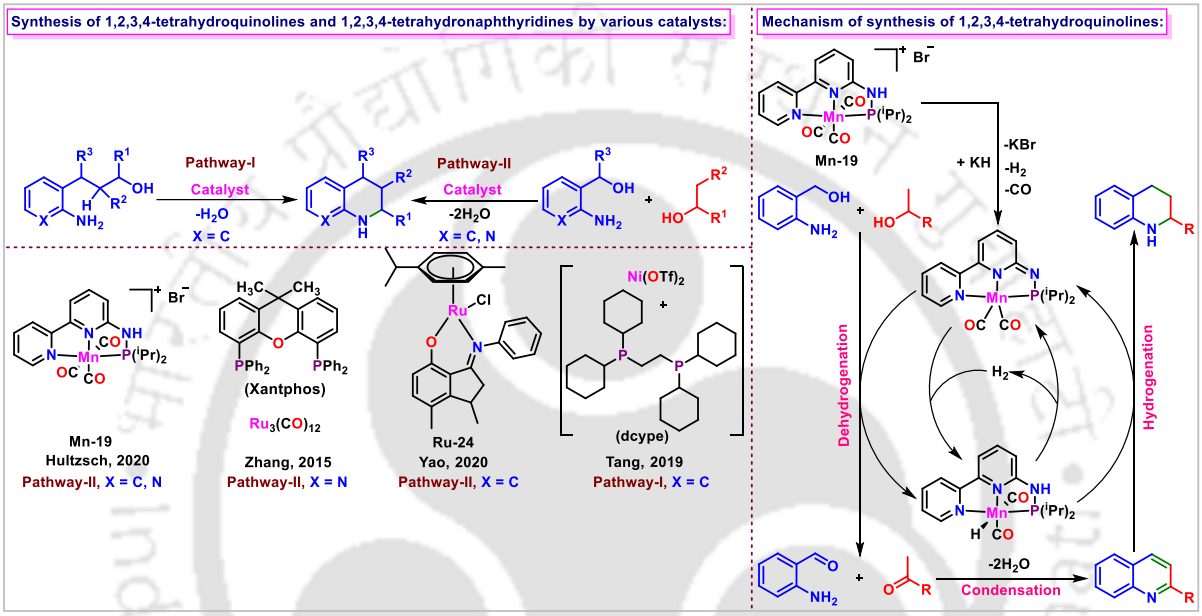
workers.[56e] However, only 30% yield was furnished, whereas employing methyl cinnamate drastic increase in the yield has been noticed as it captured the in situ formed Ni-H species. Both aliphatic and aromatic alcohol well-tolerated furnishing excellent yields. Later, they have extended their protocol by constructing natural product komavine employing cyclohexanol instead of benzyl alcohol as transfer hydrogenating coupling partner. In that manuscript, they have also explored intramolecular cyclization of amino alcohol and for that when they have employed 2-aminophenethyl alcohol as a starting material under the same catalytic environment furnished Indoline with moderate isolated yield. The author slightly changed the ligand motif from dcype to 1,3-bis(dicyclohexylphosphino)propane (dcypp) in order to get good result where they enacted with an equal proportion of indolines and indole (Scheme **1.40**).



Scheme 1.40. Ni-catalyzed synthesis of indoline and its derivatives and their mechanistic outline.

1.4.3. Borrowing Hydrogenation (BH) mediated synthesis of 1,2,3,4-tetrahydroquinoline and 1,2,3,4-tetrahydronaphthyridine:

The construction of saturated analogue of quinoline i.e. 1,2,3,4-tetrahydroquinoline are scarce. 1,2,3,4-tetrahydroquinoline is a substantially important scaffold and building block present in various natural products and pharmacological active substances.[76] Although a plethora of synthetic approaches to construct that heterocycle has been culminated, the 'BH' or 'HA' methodology provides an atom-economical pathway via concomitant generation of C-C and C-N bonds utilizing inexpensive, renewable and abundant starting material alcohol.



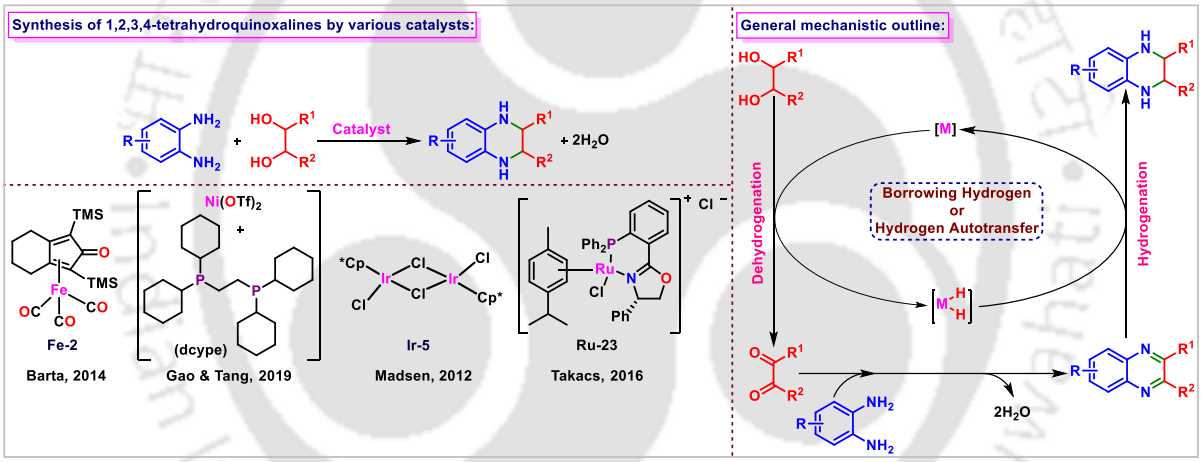
Scheme 1.41. Synthesis of 1,2,3,4-tetrahydroquinolines and 1,2,3,4-tetrahydronaphthyridines and its mechanism.

In that perspective, *Hultzsch and co-workers* utilized their bipyridine based NNP-Mn(I) complex (**Mn-19**) for the sake of construction of 1,2,3,4-tetrahydroquinoline employing 2-aminobenzyl alcohols with an array of secondary alcohols via 'BH' pathway.[77a]By proper tuning of base and reaction temperature, they have selectively synthesized both quinoline and tetrahydroquinoline. Upon employing KO^{t}Bu it selectively formed quinoline whilst in presence of KH tetrahydroquinoline is the major product with low yield. Combination of 1.5 equiv. of KH and 0.3 equiv. of KOH in DME solvent it showed optimal reactivity and selectivity towards 1,2,3,4-tetrahydroquinoline. Later, they have extended their catalytic protocol by constructing 1,2,3,4-tetrahydronaphthyridines via 'BH' mediated cyclization between 2-aminopyridyl methanols with secondary alcohols with limited substrate scope. *Zhang and co-workers* exclusively synthesized this tetrahydronaphthyridines employing $Ru_3(CO)_{12}$ with xantphos in polar protic ^{t}AmOH solvent from the same set of redoxtake.[77b]In that, the pyridyl ring act as hydrogen acceptor i.e. oxidant and two alcohol units play as hydrogen donors i.e. reductants and the transfer hydrogenation mainly takes place at the pre-existing pyridyl ring. Recently, *Yao and co-workers* demonstrated the synthesis of 1,2,3,4-tetrahydroquinoline by their well-defined hydroxyindanone-

amine ligand bearing half-sandwich NO-Ru(II)-complex (**Ru-24**) starting from 2-aminobenzyl alcohols and ketones employing 6 atm H_2 pressure in the final step.[77c] In 2019, *Tang and co-workers* also devised the aforesaid heterocycle via intramolecular cyclization of amino alcohol in presence of $Ni(OTf)_2$ and 1,2-bis(dicyclohexylphosphino)ethane (dcype) ligand mediated catalytic protocol in slightly acidic HFIP solvent with good isolated yield (Scheme **1.41**).[56e]

1.4.4. Borrowing Hydrogenation (BH) mediated synthesis of 1,2,3,4-tetrahydroquinoxaline:

In comparison to quinoxalines, synthesis of 1,2,3,4-tetrahydroquinoxalines, a saturated or hydrogenated analogue of the previous one, constructed by 'BH' approach is still in nascent stage. In 2014, *Feringa and Barta* first reported Knölker Fe(II) complex (**Fe-2**) catalyzed synthesis of 1,2,3,4-tetrahydroquinoxalines employing 1,2-benzenediamine and with more challenging ethylene glycol as a source of 1,2-diol as coupling partner.[78]The catalytic protocol proceeds 5 mol% of **Fe-2** in combination with 10 mol% of Me_3NO oxidant under base free and in CPME green solvent with excess acquisition of vicinal diol (Scheme **1.42**).

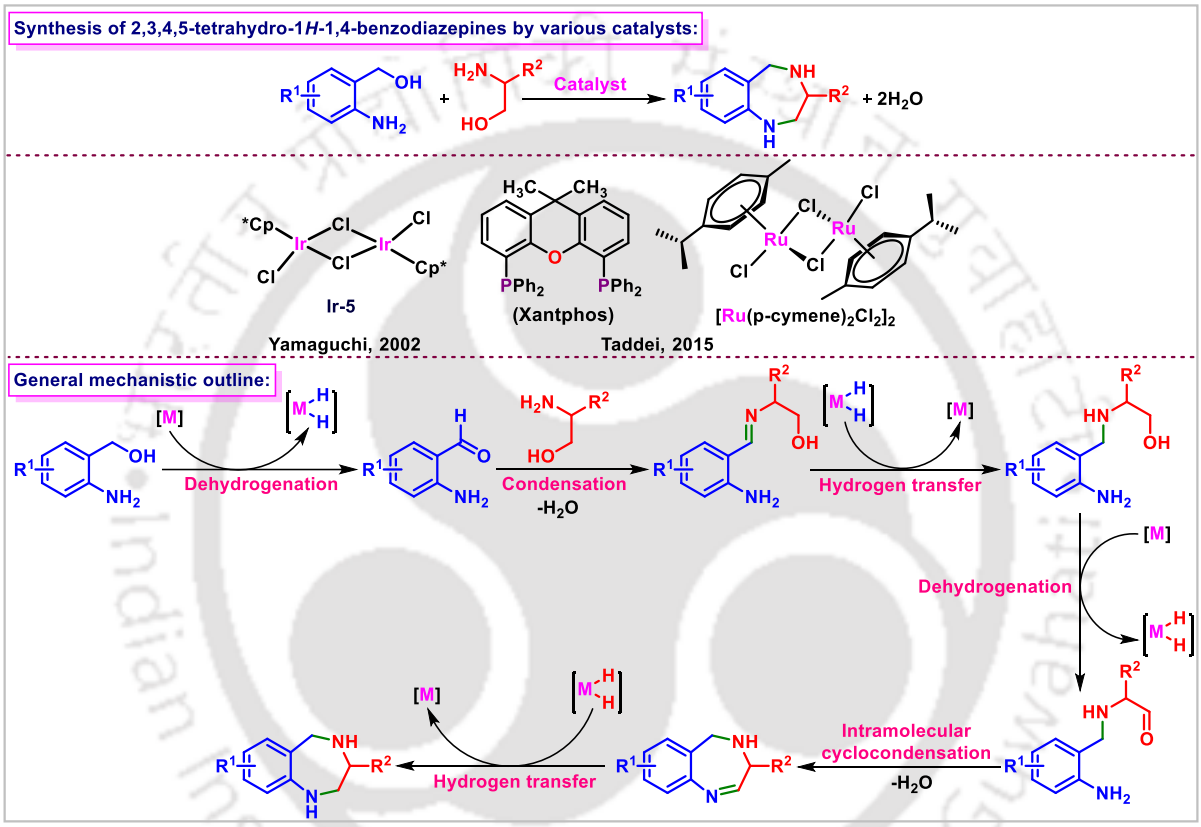


Scheme 1.42. Construction of 1,2,3,4-tetrahydroquinoxalines by various catalysts and its general mechanism.

Later, *Tang and co-workers* accomplished the aforesaid heterocycle in presence of $Ni(OTf)_2$ and 1,2-bis(dicyclohexylphosphino)ethane (dcype) ligand in refluxing ^{t}AmOH.[56e] Both aliphatic and aromatic congeners of vicinal diols smoothly react with diamines under 'BH' mediated annulation reaction affording various 2,3-disubstituted tetrahydroquinoxalines and 2-substituted tetrahydroquinoxalines with excellent isolated yield. Later, *Madsen group* employed their commercially available dimeric Ir (III)-complex *i.e.* $[Cp^*IrCl_2]_2$ complex (**Ir-5**) to promote the fabrication of 1,2,3,4-tetrahydroquinoxalines in presence of catalytic amount of weak base $NaHCO_3$.[75e]In 2016, *Takacs group* reported Ru-phosphinooxazoline complex (**Ru-23**) mediated construction of aforementioned heterocycle in presence of stoichiometric amount of base (Scheme **1.42**).[75c]

1.4.5. Borrowing Hydrogenation (BH) mediated synthesis of 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine:

Amidst of various bioactive benzannulated nitrogen heterocyclic scaffolds Benzazepines and their hydrogenated analogue proved to be important for drug discovery and as a versatile buildingblocks.[79] It conventionally constructed via Pd-catalyzed amonocarbonylation,[80a] the Beckamann rearrangement,[80b] the Dickmenn cyclization,[80c] etc. However, the non-negligible disadvantageous of these elegant classical strategies considerably conquer their implementation in organic synthesis. In order to devoid from these 'BH' or 'HA' approach with the aid of transition metal catalyzed cascade reaction with alcohol is highly efficient, facile, green and sustainable approach. In that quest, in 2002, *Yamaguchi and co-workers* reported dimeric $[Cp^*IrCl_2]_2$ complex (**Ir-5**) catalyzed synthesis of 2,3,4,5-tetrahydro-1*H*-1,4-



Scheme 1.43. Ir and Ru-catalyzed construction of 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines and its general mechanistic outline.

benzodiazepines via dehydrogenative N-heterocyclization of 4-(2-aminophenyl)butanol in presence of catalytic amount of weak base K_2CO_3.[38c] In 2015, *Taddei group* demonstrated the fabrication of aforesaid N-heterocycle from 2-amnoaryl alcohol and β-amino alcohol by developing an eye catching catalytic system bearing equimolar mixture of $[Ru(p\text{-cymene})Cl_2]_2$ with bidentate P-ligand xantphos for this one pot reaction encompassed with two successive borrowing hydrogen cycles with excellent yield.[81] In the plausible mechanism initially the 2-aminoaryl alcohol in presence of transition metal catalyst get dehydrogenated to its corresponding aldehydes which undergoes condensation with more nucleophilic $-NH_2$ group of β-amino alcohol formed the imine intermediate where the first 'BH' takes place. Afterwards, the aliphatic alcohol get dehydrogenated undergoes cyclocondensation followed by second 'BH' furnished the desired benzodiazepine products (Scheme **1.43**).

1.5. Concluding remarks and aim of the present thesis:

1.5.1. Concluding remarks:

The above discussion demonstrated that Acceptorless Dehydrogenative Annulation (ADA) and Borrowing Hydrogen (BH) strategy with the aid of transition metal catalysts brought a significant attention and becomes an indispensable tool in the arena of synthetic organic chemistry for the development of green, sustainable, eco-friendly and atom-economical methodologies for the preparation of important building blocks specially N-heterocyclic scaffolds which are the fundamental core of modern promising intricate drug molecules. Over the years, a number of reports dominated and documented on air, moisture sensitive, less cost-effective sophisticated phosphine ligand bearing both noble and 3d-transition metal-based catalyst. However, in that current century, both academic and industrial perspective witnessed on cheap, cost-effective, mild and economically viable approach. Therefore, to conquer this aspect, modern scientific research underlying and envisaged on replacement of phosphine-based ligand frame work by phosphine free arms such as NNN, NNO, NNS, NNC, CNC, CNS etc. ligands, albeit, their application in their corresponding catalyst remain infancy, especially non-precious 3d-metals.

1.5.2. Aim of the present thesis:

Amidst of 3d-transition metals Mn and Co, these two metals engrossed a special attention towards the scientific community because i) their abundance in earth's crust (*e.g.* Manganese is the third most abundant transition metal in the earth's crust (950 mg kg^{-1})), ii) their wide range of oxidation state, spin state, coordination number and geometry, iii) unique redox chemistry and substitutional lability. Apart from that, employing ADA and BH approach synthesis of various medicinally promising N-heterocycles by designing suitable and easily accessible ligands alongside their corresponding Mn and Co-complexes is still in nascent as well as a demanding process. Henceforth, in this thesis, we have developed new bifunctional NNS, NNO-Mn(I) and NNO-Co(II)-complexes from their respective precursor $MnBr(CO)_5$ and $CoBr_2$ and explored their catalytic activity in various control (de)hydrogenative transformations enroute to construction of N-heterocycles.

1.6. References:

1. a) J. A. Joule and K. Mills in *Heterocyclic Chemistry*, Blackwell, Oxford, UK, **2000**; b) A. Gomtsyan, *Chem. Heterocycl. Compd.* **2012**, *48*, 7–10; c) T. Baladi, V. Abet, S. Piguel, *Eur. J. Med. Chem.* **2015**, *105*, 220-237; d) M. Chauhan, R. Kumar, *Med. Chem. Res.* **2015**, *24*, 2259−2282; e) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem Rev.* **2003**, *103*, 893−930.

2. E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257−10274.

3. a) J. Kim, M. Movassaghi, *Chem. Soc. Rev.* **2009**, *38*, 3035–3050; b) J. G. Cannon, *J. Med. Chem.* **1997**, *40*, 4165–4166.

4. D. Chen, S. J. Su, Y. Cao, *J. Mater. Chem. C.* **2014**, *2*, 9565−9578.

5. G. R. Tombo, H. Blaser, G. Brooks, T. Roberts in *Pesticide Chemistry and Bioscience, RSC, Cambridge*, **1999**.

6. A. Loudet, K. Burgess, *Chem. Rev.* **2007**, *107*, 4891–4932.

7. a) V. Estevez, M. Villacampa, J. C. Menendez, *Chem. Soc. Rev.* **2014**, *43*, 4633−4657; b) G. Bartoli, R. Dalpozzo, M. Nardib, *Chem. Soc. Rev.* **2014**, *43*, 4728−4750; c) N. R. Candeias, L. C. Branco, P. M. P.Gois, A. M. Afonso, A. F. Trindade, *Chem Rev.* **2009**, *109*, 2703−2802; d) G. Jones, *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, New York, **1984**, vol. 2, p. 395; e) I. Khan, A. Ibrar, N. Abbas, A. Saeed, *Eur. J. Med. Chem.* **2014**, *76*, 193–244.

8. a) H.-J. Arpe, *Industrielle Organische Chemie*, 6th ed., Wiley-VCH, Weinheim, **2007**, p. 15 – 21; b) H.-J. Arpe, *Industrielle Organische Chemie*, 6th ed., Wiley-VCH, Weinheim, **2007**, p. 137 – 154; c) A. Kumar, P. Daw, D. Milstein, *Chem. Rev*. **2022**, *122*, 385–441.

9. C. O. Tuck, E. Perez, I. T. Horvath, R. A. Sheldon, M. Poliakoff, *Science* **2012**, *337*, 695–699.

10. a) T. P. Vispute, H. Zhang, A. Sanna, R. Xiao, G. W. Huber, *Science* **2010**, *330*, 1222 – 1227; b) Z. Sun, G. Bottari, A. Afanasenko, M. C. A. Stuart, P. J. Deuss, B. Fridrich, K. Barta, *Nat. Catal.* **2018**, *1*, 82–92; c) C. O. Tuck, E. Perez, I. T. Horvath, R. A. Sheldon, M. Poliakoff, *Science* **2012**, *337*, 695–699.

11. a) R. H. Crabtree, *Chem. Rev.* **2017**, *117*, 9228–9246; b) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681 – 703.

12. a) V. Lyaskovskyy, B. de Bruin, *ACS Catal.* **2012**, *2*, 270– 279; b) R. Mondal, A. K. Guin, G. Chakraborty, N. D. Paul, *Org. Biomol. Chem.* **2022**, *20*, 296– 328.

13. a) J. Khusnutdinova, D. Milstein, *Angew. Chem. Int. Ed*. **2015**, *54*, 12236 – 12273; b) H. Li, T. Gonc¸alves, D. Lupp, K.-W. Huang, *ACS Catal*. **2019**, *9*, 1619 – 1629; c) P. Pandey, I. Dutta, J. K. Bera, *Proc. Natl. Acad. Sci., India, Sect. A Phys. Sci.* **2016**, *86*, 561–579.

14. C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712.

15. a) M. G. Edwards, R. F. R. Jazzar, B. M. Paine, D. J. Shermer, M. K. Whittlesey, J. M. J. Williams, D. D. Edney, *Chem. Commun*. **2004**, 90 – 91; b) M. H.-S. A. Hamid, P. A. Slatford, J. M.-J. Williams, *Adv. Synth. Catal.*, **2007**, *349*, 1555–1575; c) A. Corma, J. Navas, M. J. Sabater, *Chem. Rev.* **2018**, *118*, 1410–1459; d) B. G. Reed-Berendt, K. Polidano, L. C. Morrill, *Org. Biomol. Chem.* **2019,** *17*, 1595-1607; e) B. G. Reed-Berendt, D. E. Latham, M. B. Dambatta, L. C. Morrill, *ACS Cent. Sci.* **2021**, *7*, 570–585.

16. a) C. Gunanathan, D. Milstein, *Chem. Rev.* **2014**, *114*, 12024−12087; b) Q. Yang, Q. Wang, Z. Yu, *Chem. Soc. Rev.* **2015**, *44*, 2305−2329; c) A. Mukherjee, D. Milstein, *ACS Catal.* **2018**, *8*, 11435−11469; d) K. Junge, V. Papa, M. Beller, *Chem.–Eur. J.* **2019**, *25*, 122 – 143; e) K. Das, S. Waiba, A. Jana, B. Maji, *Chem. Soc. Rev.* **2022**, *51*, 4386−4464; f) T. Irrgang, R. Kempe, *Chem. Rev.* **2019**, *119*, 2524−2549.

17. a) A. Mondal, R. Sharma, D. Pal, D. Srimani, *Eur. J. Org. Chem*. **2021**, 3690–3720; b) M. Maji, D. Panja, I. Borthakur, S. Kundu, *Org. Chem. Front*. **2021**, *8*, 2673–2709; c) N. Hofmann, K. C. Hultzsch, *Eur. J. Org. Chem.* **2021**, 6206 –6223; d) K. Bera, A. Mukherjee, *Tetrahedron Lett.* **2021**, *81*, 153326.

18. a) J. B. Wright, *Chem. Rev.* **1951**, *48*, 397–541; b) O. O. Ajani, D. V. Aderohunmu, C. O. Ikpo, A. E. Adedapo, I.O. Olanrewaju, *Arch. Pharm.* **2016**, *349*, 475−506; c) L. B. Townsend, G. V. Revankar, *Chem. Rev.* **1970**, *70*, 389−438; d) S. Bhattacharya, P. Chaudhuri, *Curr. Med. Chem.* **2008**, *15*, 1762−1777.

19. a) M. A. Phillips, *J. Chem. Soc.* **1928**, 2393–2399; b) D. W. Hein, R. J. Alheim, J. J. Leavitt, *J. Am. Chem. Soc.* **1957**, *79*, 427–429.

20. a) T. Kondo, S. Yang, K. Huh, M. Kobayashi, S. Kotachi, Y. Watanabe, Y. *Chem. Lett*. **1991**, *20*, 1275-1278.; b) A. J. Blacker, M. M. Farah, M. I. Hall, S. P. Marsden, O. Saidi, J. M. J. Williams, *Org. Lett.* **2009**, *11*, 2039– 2042; c) T. Hille, T. Irrgang, R. Kempe, *Chem. Eur. J*. **2014**, *20*, 5569-5572; d) K. Chakrabarti, M. Maji, S. Kundu, *Green Chem.* **2019**, *21*, 1999–2004; e) R. Ramachandran, G. Prakash, S. Selvamurugan, P. Viswanathamurthi, J. G. Malecki, V. Ramkumar, *Dalton Trans*. **2014**, *43*, 7889-7902; f) L. Li, Q. Luo, H. Cui, R. Li, J. Zhang, T. Peng, T. *ChemCatChem* **2018**, *10*, 1607-1613; g) P. Anandaraj, R. Ramesh, J. G. Malecki, *J. Organomet. Chem.* **2023**, *985*, 122577–122588; h) M. Bala, P. K. Verma, U. Sharma, N. Kumar, B. Singh, *Green Chem.* **2013**, *15*, 1687–1693; i) P. Daw, Y. Ben-David, D. Milstein, *ACS Catal.* **2017**, *7*, 7456−7460; j) K. Das, A. Mondal, D. Srimani, *J. Org. Chem.* **2018**, *83*, 9553−9560; k) A. Bera, M. Sk, K. Singh, D. Banerjee *Chem. Commun.* **2019**, *55*, 5958−5961; l) A. K. Bains, D. Dey, S. Yadav, A. Kundu, D. Adhikari, *Catal. Sci. Technol.* **2020**, *10*, 6495−6500; m) V. Arora, M. Dutta, K. Das, B. Das, H. K. Srivastava, A. Kumar, *Organometallics* **202**0, *39*, 2162–2176; n) R. R. Putta, S. Chun, S. B. Lee, D.-C. Oh, S. Hong, *Front. Chem.* **2020**, *8*, 429.

21. a) G. Li, J. Wang, B. Yuan, D. Zhang, Z. Lin, P. Li, H. Huang, *Tetrahedron Lett.* **2013**, *54*, 6934–6936; b) S. Das, S. Mallick, S. De Sarkar, *J. Org. Chem.* **2019**, *84*, 12111−12119; c) J. Wu, C. Darcel, *J. Org. Chem.* **2021**, *86*, 1023−1036.

22. a) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor, X. Liu, *Chem. Soc. Rev.* **2015**, *44*, 291−314; b) T. Castanheiro, J. Suffert, M. Donnard, M. Gulea, *Chem. Soc. Rev.* **2016**, *45*, 494−505.

23. a) A. J. Blacker, M. M. Farah, M. I. Hall, S. P. Marsden, O. Saidi, J. M. J. Williams, *Org. Lett.* **2009**, *11*, 2039–2042; b) K. Das, A. Mondal, D. Srimani, *Chem. Commun.* **2018**, *54*, 10582−10585.

24. a) J. Jiang, X. Tang, W. Dou, H. Zhang, W. Liu, C. Wang, J. Zheng, *J. Inorg. Biochem.* **2010**, *104*, 583–591; b) Y. Ooyama, Y. Kagawa, H. Fukuoka, G. Ito, Y. Harima, *Eur. J. Org. Chem.* **2009**, *31*, 5321–5326; c) C. S. Demmer, L. Bunch, *Eur. J. Med. Chem.* **2015**, *97*, 778−785; d) A. Kaur, D. P. Pathak, V. Sharma, S. Wakode, *Bioorg. Med. Chem.* **2018**, *26*, 891−902.

25. M. Wu, X. Hu, J. Liu, Y. Liao, G. J. Deng, *Org. lett.* **2012**, *14*, 2722−2725.

26. M. M. Heravi, V. Zadsirjan, H. Hamidi, P. H. Tabar Amiri, *RSC Adv.* **2017**, *7*, 24470–24521.

27. B. Anxionnat, D. Gomez Pardo, G. Ricci, K. Rossen, J. Cossy, *Org. Lett.* **2013**, *15*, 3876–3879.

28. a) N. Amishiro, S. Nagamura, E. Kobayashi, A. Okamoto, K. Gomi, M. Okabe, H. Saito, *Bioorg. Med. Chem.* **2000**, *8*, 1637-1643; b) S. Lunak, M. Vala, J. Vynuchal, I. Ouzzane, P. Horakova, P. Moziskova, Z. Elias, M. Weiter, *Dyes Pigm.* **2011**, *91*, 269-278; c) V. Blangy, C. Heiss, V. Khlebnikov, C. Letondor, H. S. Evans, R. Neier, *Angew. Chem. Int. Ed.* **2009**, *48*, 1688−1691; d) M. M. Wienk, M. Turbiez, J. Gilot, R. A. J. Janssen, *Adv.Mater.* **2008**, *20*, 2556−2560.

29. a) T. A. Moss, T. Nowak, *Tetrahedron Lett.* **2012**, *53*, 3056–3060; b) A. Balakrishna, A. Aguiar, P. J. M. Sobral, M. Y. Wani, J. Almeida e Silva, A. J. F. N. Sobral, *Catal. Rev.* **2019**, *61*, 84–110; c) Z. Wang, Knorr Pyrrole Synthesis, in Comprehensive Organic Name Reactions and Reagents, **2010**, pp. 1634–1637.

30. a) S.-I. Murahashi, T. Shimamura, I. Moritani, *J. Chem. Soc., Chem. Commun.* **1974**, 931–932; b) Y. Tsuji, Y. Yokoyama, H. T. Hwh, Y. Watanabe, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3456–3458; c) S. J. Pridmore, P. A. Slatford, A. Daniel, M. K. Whittlesey, J. M. J. Williams, *Tetrahedron Lett.* **2007**, *48*, 5115–5120; d) T. Yan, K. Barta, *ChemSusChem* **2016**, *9*, 2321 – 2325; e) B. Emayavaramban, M. Sen, B. Sundararaju, *Org. Lett.* **2017**, *19*, 6−9; f) K. Singh, L. M. Kabadwal, S. Bera, A. Alanthadka, D. Banerjee, *J. Org. Chem.* **2018**, *83*, 15406−15414.

31. a) N. D. Schley, G. E. Dobereiner, R. H. Crabtree, *Organometallics* **2011**, *30*, 4174–4179; b) P. Daw, S. Chakraborty, J. A. Garg, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2016**, *55*, 14373−14377; c) C. J. Borghs, Y. Lebedev, M. Rueping, O. El-Sepelgy, *Org. Lett.* **2019**, *21*, 70−74.

32. a) S. Michlik and R. Kempe, *Nat. Chem.* **2013**, *5*, 140–144; b) D. Srimani, Y. Ben-David, D. Milstein, *Angew. Chem., Int. Ed.* **2013**, *52*, 4012– 4015; c) K. Iida, T. Miura, J. Ando, S. Saito, *Org. Lett.* 2013, 15, 1436 – 1439; d) F. Kallmeier, B. Dudziec, T. Irrgang, R. Kempe, *Angew. Chem. Int. Ed.* **2017**, *56*, 7261 –7265; e) S. P. Midya, V. G. Landge, M. K. Sahoo, J. Rana, E. Balaraman, *Chem. Commun.* **2018**, *54*, 90−93; f) A. Alanthadka, S. Bera, M. Vellakkaran, D. Banerjee, *J. Org. Chem.* **2019**, *84*, 13557−13564; g) K. Singh, M. Vellakkaran, D. Banerjee, *Green Chem.* **2018**, *20*, 2250−2256; h) M. Mastalir, M. Glatz, E. Pittenauer, G. Allmaier, K. Kirchner, *Org. Lett.* **2019**, *21*, 1116–1120; i) A. Maji, S. Gupta, M. Maji, S. Kundu, *J. Org. Chem.* **2022**, *87*, 8351−8367.

33. a) M. Zhang, X. Fang, H. Neumann, M. Beller, *J. Am. Chem. Soc*. **2013**, *135*, 11384–11388; b) M. Zhang, H. Neumann, M. Beller, *Angew. Chem. Int. Ed*. **2013**, *52*, 597–601; *Angew. Chem*. **2013**, *125*, 625–629; c) J. C. Borghs, L. M. Azofra, T. Biberger, O. Linnenberg, L. Cavallo, M. Rueping, O. El-Sepelgy, *ChemSusChem*, **2019**,*12*, 3083–3088; d) P. Daw, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc*. **2018**, *140*, 11931– 11934.

34. a) J. Zablocki, V. Palle, B. Blackburn, E. Elzein, G. Nudelman, S. Gothe, Z. Gao, Z. Li, S. Meyer, L. Belardinelli, *Nucleosides, Nucleotides, Nucleic Acids* **2001**, *20*, 343-360; b) N. K. Terrett, A. S. Bell, D. Brown, P. Ellis, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819-1824.

35. D. C. Schmitt, A. P. Taylor, A. C. Flick, R. E. Kyne, *Org. Lett.* **2015**, *17*, 1405–1408.

36. a) F. R. Chen, J. Huang, *Chem. Rev.* **2005**, *105*, 4671–4706; b) I. Ninomiya, *J. Nat. Prod.* **1992**, *55*, 541–564; c) C. Trilok, G. Neha, K. Ashok, *Int. J. ChemTech Res.* **2010**, *2*, 762–773; d) A. A. E. Gendy,

M. M. Said, N. Ghareb, Y. M. Mostafa, E. Sayed, H. E. Ashry, *Arch. Pharm.* **2008**, *341*, 294–300; e) S. N. Pandeya, P. Yogeeswari, D. Sriram, G. Nath, *Boll. Chim. Farm.* **1998**, *137*, 321–324; d) K. Lalit, B. Shashi, J. Kamal, *IJRPS* **2012**, *2*, 23–33; f) R. J. Sundberg in Indoles; Academic Press: London, 1996; g) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73−103.

37. a) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195–7210; b) B. Robinson, *Chem. Rev.* **1969**, *69*, 227–250; c) G. W. Gribble, in *Indole Ring Synthesis* **2016**, pp. 137–138; d) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690.

38. a) Y. Tsuji, K.-T. Huh, Y. Watanabe, *Tetrahedron Lett.* **1986**, *27*, 377–380; b) Y. Tsuji, K. T. Huh, Y. Watanabe, *J. Org. Chem.* **1987**, *52*, 1673–1680; c) K.-I. Fujita, K. Yamamoto, R. Yamaguchi, *Org. Lett.* **2002**, *4*, 2691–2694; d) S. Whitney, R. Grigg, A. Derrick, A. Keep, *Org. Lett.* **2007**, *9*, 3299–3302; e) A. Porcheddu, M. G. Mura, L. De Luca, M. Pizzetti, M. Taddei, *Org. Lett.* **2012**, *14*, 6112–6115; f) S. Elangovan1, J. Neumann, J. B. Sortais, K. Junge, C. Darcel, M. Beller, *Nat. Commun.* **2016**, *7*, 1−8; g) M. Vellakkaran, K. Singh, D. Banerjee, *ACS Catal.* **2017**, *7*, 8152−8158; h) A. K. Bains, A. Biswas, D. Adhikari, *Chem. Commun.* **2020**, *56*, 15442−15445; i) A. K. Guin, S. Pal, S. Chakraborty, S. Chakraborty, N. D. Paul, *J. Org. Chem.* **2023**, *88*, 16755–16772; j) V. Yadav, S. G. Jagtap, E. Balaraman, S. B. Mhaske, *Org. Lett.* **2022**, *24*, 9054−9059.

39. a) J. P. Michael, *Nat. Prod. Rep*. **2002**, *19*, 742–760; b) A. Joshi, C. L. Viswanathan, *Bioorg. Med. Chem*. *Lett.* **2006**, *16*, 2613–2617; c) Y. L. Chen, K. C. Fang, J. Y. Sheu, S. L. Hsu, C. C. Tzeng, *J. Med. Chem.* **2001**, *44*, 2374–2377; d) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; e) M. M. Biddle, M. Lin, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 3830–3831.

40. R. H. Manske, *Chem. Rev.* **1942**, *30*, 113–144.

41. a) R. Martínez, D. J. Ramón. M. Yus, *Eur. J. Org. Chem.* **2007**, 1599–1605; b) S. Ruch, T. Irrgang, R. Kempe, *Chem. – Eur. J.* 2014, 20, 13279–13285; c) D. Srimani, Y. Ben-David, D. Milstein, *Chem. Commun.* **2013**, *49*, 6632–6634; d) M. Maji, K. Chakrabarti, B. Paul, B. C. Roy, S. Kundu, *Adv. Synth. Catal.* **2018**, *360*, 722–729; e) M. Maji, K. Chakrabarti, D. Panja, S. Kundu, *J. Catal.* **2019**, *373*, 93–102; f) D. Wei, V. Dorcet, C. Darcel, J.-B. Sortais, *ChemSusChem* **2019**, *12*, 3078–3082; g) B. Guo, T.-Q. Yu, H.-X. Li, S.-Q. Zhang, P. Braunstein, D. J. Young, H.-Y. Li, J.-P. Lang, *ChemCatChem* **2019**, *11*, 2500–2510; h) S. Elangovan, J.-B. Sortais, M. Beller, C. Darcel, *Angew. Chem. Int. Ed*. **2015**, *54*, 14483 – 14486; i) M. Mastalir, M. Glatz, E. Pittenauer, G. Allmaier, K. Kirchner, *J. Am. Chem. Soc.* **2016**, *138*, 15543−15546; j) R. Kumar, R. Babu, S. Chakrabortty, V. Madhu, E. Balaraman, J. Org. Chem. 2024, 89, 14720−14739; k) G. Zhang, J. Wu, H. Zeng, S. Zhang, Z. Yin, S. Zheng, *Org. Lett.* **2017**, *19*, 1080-1083; l) S. Shee, K. Ganguli, K. Jana, S. Kundu, *Chem. Commun.* **2018**, *54*, 6883−6886; m) S. Nandi, I. Borthakur, K. Ganguli, S. Kundu, *Organometallics* **2023**, *42*, 1793−1802; n) M. K. Barman, A. Jana, B. Maji, *Adv. Synth. Catal.* **2018**, *360*, 3233−3238; o) S. Das, D. Maiti, S. D. Sarkar, *J. Org. Chem*. **2018**, *83*, 4, 2309−2316; p) S. Parua, R. Sikari, S. Sinha, S. Das, G. Chakraborty, N. D. Paul, *Org. Biomol. Chem.* **2018**, *16*, 274−284; q) R. Sharma, A. Mondal, A. Samanta, N. Biswas, B.

Das, D. Srimani, *Adv. Synth. Catal.* **2022**, *364*, 2429–2437; r) J. Das, K. Singh, M. Vellakkaran, D. Banerjee, *Org. Lett.* **2018**, *20*, 5587–5591; s) S. N. R. Donthireddy, V. K. Pandey, A. Rit, *J. Org. Chem.* **2021**, *86*, 6994−7001; t) G. Chakraborty, R. Sikari, S. Das, R. Mondal, S. Sinha, S. Banerjee, N. D. Paul, *J. Org. Chem.* **2019**, *84*, 2626−2641; u) R. Mondal, G. Chakraborty, A. K. Guin, S. Pal and N. D. Paul, *Tetrahedron* **2021**, *100*, 132479; v) S. Mondal, S. Chakraborty, S. Khanra, S. Chakraborty, S. Pal, P. Brandao, N. D. Paul, *J. Org. Chem.* **2024**, *89*, 5250−5265; w) K. Azizi, S. Akrami, R. Madsen, *Chem. Eur. J.* **2019**, *25*, 6439−6446; x) H. Chai, W. Tan, Y. Lu, J. Ma, G. Zhang, *Appl. Organomet. Chem.* **2020**, *34*, e5685; y) Z. Wang, Q. Lin, N. Ma, S. Liu, M. Han, X. Yan, Q. Liu, G. A. Solan, W.-H. Sun, *Catal. Sci. Technol.* **2021**, *11*, 8026– 8036; z) M. A. Mohite, S. Sheokand, D. Mondal, M. S. Balakrishna, *Dalton Trans.* **2024**, *53*, 5580–5591; za) S. Wu, P. Zhang, X. Wang, Z. Wang, Y. Wang, *Appl. Organomet. Chem.* **2024**, *34*, e7797; zb) Z. Hao, X. Zhou, Z. Ma, C. Zhang, Z. Han, J. Lin, G. L. Lu, *J. Org. Chem.* **2022**, *87*, 12596−12607; zc) A. K. Bains, V. Singh, D. Adhikari, *J. Org. Chem.* **2020**, *85*, 14971–14979.

42. a) F. Xie, M. Zhang, M. Chen, W. Lv, H. Jiang, *ChemCatChem* **2015**, *7*, 349– 353; b) Q. Wang, M. Wang, H.-J. Li, S. Zhu, Y. Liu and Y.-C. Wu, *Synthesis* **2016**, 3985–3995.

43. a) J. R. Pfister, *J. Nat. Prod*. **1988**, *51*, 969−970; b) S. R. Inglis, R. K. Jones, G. W. Booker, S. M. Pyke, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 387−390.

44. a) W. Lv, B. Xiong, H. Jiang, M. Zhang, *Adv. Synth. Catal.* **2017**, *359*, 1202–1207; b) K. Das, A. Mondal, D. Pal, D. Srimani, *Org. Lett.* **2019**, *21*, 3223−3227.

45. a) A. K. Parhi, Y. Zhang, K. W. Saionz, P. Pradhan, M. Kaul, K. Trivedi, D. S. Pilch, E. J. LaVoie, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4968–4974; b) J. Kuneš, J. Bažant, M. Pour, K. Waisser, M. Šlosárek, J. Janota, *Farmaco* **2000**, *55*, 725–729; c) K. Juvale, J. Gallus, M. Wiese, *Bioorg. Med. Chem.* **2013**, *21*, 7858–7873.

46. a) A. Witt, J. Bergman, *Curr. Org. Chem.* **2003**, *7*, 659– 677; b) D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry, *Tetrahedron* **2005**, *61*, 10153–10202.

47. a) Z. Chen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang, H. Wu, *J. Org. Chem.* **2013**, *78*, 11342–11348; b) M. Chen, M. Zhang, B. Xiong, Z. Tan, W. Lv, H. Jiang, *Org. Lett.* **2014**, *16*, 6028–6031; c) X.-M. Wan, Z.-L. Liu, W.-Q. Liu, X.-N. Cao, X. Zhu, X.-M. Zhao, B. Song, X.-Q. Hao, G. Liu, *Tetrahedron* **2019**, *75*, 2697–2705; d) S. Parua, R. Sikari, S. Sinha, G. Chakraborty, R. Mondal, N. D. Paul, *J. Org. Chem.* **2018**, *83*, 11154–11166; e) A. Mondal, M. K. Sahoo, M. Subaramanian, E. Balaraman, *J. Org. Chem.* **2020**, *85*, 7181–7191; f) J. Fang, J. Zhou, Z. Fang, *RSC Adv.* **2013**, *3*, 334–336; g) T. Mori, C. Ishii, M. Kimura, *Org. Process Res. Dev.* **2019**, *23*, 1709–1717; h) Z. Tan, Z. Fu, J. Yang, Y. Liang, H. Jiang, M. Zhang, *iScience* **2020**, *23*, 101003.

48. a) D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry, *Tetrahedron*, **2005**, *61*, 10153–10202; b) D. Zhan, T. Li, H. Wei, W. Weng, K. Ghandi, Q. Zeng, *RSC Adv.* **2013**, *3*, 9325–9329; c) W. Ge, X. Zhu and Y. Wei, *RSC Adv.* **2013**, *3*, 10817–10822; d) N. Y. Kim, C.-H. Cheon, *Tetrahedron Lett.* **2014**,

55, 2340-2344; e) R. J. Abdel-Jalil, W. Voelter and M. Saeed, *Tetrahedron Lett.* **2004**, *45*, 3475−3476; f) F.-C. Jia, Z.-W. Zhou, C. Xu, Y.-D. Wu, A.-X. Wu, *Org. Lett.* **2016**, *18*, 2942−2945.

49. a) J. Zhou, J. Fang, *J. Org. Chem.* **2011**, *76*, 7730-7736; b) H. Hikawa, Y. Ino, H. Suzuki, Y. Yokoyama, *J. Org. Chem.* **2012**, *77*, 7046-7051; c) A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *Org. Biomol. Chem.* **2012**, *10*, 240-243; d) S. Balaji, G. Balamurugan, R. Ramesh, D. Semeril, *Organometallics* **2021**, *40*, 725-734; e) S. Parua, S. Das, R. Sikari, S. Sinha, N. D. Paul, *J. Org. Chem.* **2017**, *82,* 7165−7175; f) S. Sinha, S. Das, R. Mondal, S. Mondal, N. D. Paul, *Dalton Trans.* **2020**, *49*, 8448−8459; g) A. Sk Samim, B. C. Roy, S. Nayak, S. Kundu, *J. Org. Chem.* **2020**, *85*, 11359−11367.

50. a) T. J. Donohoe, C. R. Jones, A. F. Kornahrens, L. C. Barbosa, L. J. Walport, M. R. Tatton, M. O'Hagan, A. H. Rathi, D. B. Baker, *J. Org. Chem.* **2013**, *78*, 12338–12350; b) P. Fu, S. Wang, K. Hong, X. Li, P. Liu, Y. Wang, W. Zhu, *J. Nat. Prod.* **2011**, *74*, 1751–1756; c) A. A. Altaf, A. Shahzad, Z. Gul, N. Rasool, A. Badshah, B. Lal, E. Khan, *J. Drug Design Med. Chem.* **2015**, *1*, 1-11; d) A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem. Int. Ed.* **2001**, *40*, 650–679; e) J. M. J. Fr_chet, M. V. de Meftahi, *Br. Polym. J.* **1984**, *16*, 193 –198.

51. M. Movassaghi, M. D. Hill, O. K. Ahmad, *J. Am. Chem. Soc.* **2007**, *129*, 10096–10097.

52. a) S. Michlik, R. Kempe, *Angew. Chem., Int. Ed.* **2013**, *52*, 6326–6329; b) B. Pan, B. Liu, E. Yue, Q. Liu, X. Yang, Z. Wang, W.-H. Sun, *ACS Catal.* **2016**, *6*, 1247–1253; c) D.Deng, B. Hu, M. Yang, D. Chen, *Organometallics* **2018**, *37*, 2386−2394; d) R. Mondal, D. E. Herbert, *Organometallics* **2020**, *39*, 1310–1317; e) S. Chakraborty, R. Sikari, S. Chakraborty, M. Sharma. P. Brandão, N. D. Paul, *Adv. Synth. Catal.* **2024**, *366*, 1 –13; f) S. Pal, S. Das, S. Chakraborty, S. Khanra, N. D. Paul, *J. Org. Chem.* **2023**, 88, 3650−3665.

53. a) P. A. Keller, *In Comprehensive Heterocyclic Chemistry III*; A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, Eds.; Elsevier: Oxford, U.K., 2008; Vol. 7, pp 217-308; b) *Pharmaceuticals: Classes, Therapeutic Agents, Areas of Application; McGuire,* J. L., Ed.; Wiley- VCH: Weinheim, Germany, 2000; Vols. 1-4.

54. a) B. Gnanaprakasam, E. Balaraman, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed*. **2011**, *50*, 12240–12244; b) P. Daw, A. Kumar, N. A. Espinosa-Jalapa, Y. Diskin-Posner, Y. Ben-David, D. Milstein, *ACS Catal*. **2018**, *8*, 7734–7741; c) G. Sivakumar, A. K. Suresh, S. R. Padhy, E. Balaraman, *Chem. Commun.*, **2024**, DOI: 10.1039/D4CC03595J.

55. a) P. N. Kalaria, S. C. Karad, D. K. Raval, *Eur. J. Med. Chem.* **2018**, *158*, 917–936; b) S. Cascioferro, B. Parrino, D. Carbone, D. Schillaci, E. Giovannetti, G. Cirrincione, P. Diana, *J. Med. Chem.* **2020**, *63*, 7923–7956; c) A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones, O. Fadeyi, *Org. Biomol. Chem.* **2016**, *14*, 6611–6637.

56. a) C. S. Cho, S. G. Oh, *Tetrahedron Lett.* **2006**, *47*, 5633–5636; b) T. Hille, T. Irrgang, R. Kempe, *Chem. – Eur. J.* **2014**, *20*, 5569–5572; c) W.-H. Tang, Y.-H. Liu, S.-M. Peng, S.-T. Liu, *J. Organomet. Chem.* **2015**, *775*, 94–100; d) D. Lv, Z. Xie, B. Gu, H. Wu, H. Wan, *Russ. J. Genet.* **2016**, *86*, 2887–2890; e) P. Yang, C. Zhang, W.-C. Gao, Y. Ma, X. Wang, L. Zhang, J. Yue, B. Tang, *Chem. Commun.*

2019, *55*, 7844−7847; f) S. Shee, D. Panja, S. Kundu, *J. Org. Chem.* **2020**, *85*, 2775−2784; g) F. Xie, M. Zhang, H. Jiang, M. Chen, W. Lv, A. Zheng, X. Jian, *Green Chem.* **2015**, *17*, 279–284; h) R. R. Putta, S. Chun, S. B. Lee, J. Hong, D. -C. Oh, S. Hong, *RSC Adv.* **2021**, *11*, 18225–18230.

57. a) H. Prunier, S. Rault, J.-C. Lancelot, M. Robba, P. Renard, P. Delagrange, B. Pfeiffer, D.-H. Caignard, R. Misslin, M. Hamon, *J. Med. Chem.* **1997**, *40*, 1808–1819; b) J. Guillon, P. Dallemagne, B. Pfeiffer, P. Renard, D. Manechez, A. Kervran, S. Rault, *Eur. J. Med. Chem.* **1998**, *33*, 293–308.

58. a) S. Chun, J. Ahn, R. R. Putta, S. B. Lee, D.-C. Oh, S. Hong, *J. Org. Chem.* **2020**, *85*, 23, 15314–15324; b) M. d. F. Pereira, V. Thiéry, *Org. Lett.* **2012**, *14*, 4754−4757.

59. T. Kondo, S. Kotachi, Y. Watanabe, *J. Chem. Soc., Chem. Commun.* **1992**, 1318–1319.

60. a) V. Sharma, N. Chitranshi and A. K. Agarwal, *Int. J. Med. Chem.* **2014**, *2014*, 1–31; b) A. R. Bhat, *Org. Med. Chem. Int. J.* **2017**, *2*, 1–4.

61. a) N. Deibl, K. Ament, R. Kempe, *J. Am. Chem. Soc.* **2015**, *137*, 12804–12807; b) N. Deibl, R. Kempe, *Angew. Chem. Int. Ed.* **2017**, *56*, 1663−1666; c) M. Maji, S. Kundu, *Dalton Trans.* **2019**, *48*, 17479–17487; d) R. Mondal, S. Sinha, S. Das, G. Chakraborty, N. D. Paul, *Adv. Synth. Catal.* **2020**, *362*, 594–600; e) G. Chakraborty, R. Sikari, R. Mondal, S. Mandal, N. D. Paul, *Asian J. Org. Chem.* **2020**, *9*, 431-436; f) A. K. Bains, D. Adhikari, *Catal. Sci. Technol.* **2020**, *10*, 6309−6318; g) H. Tian, W. Xue, J. Wu, Z. Yang, H. Lu, C. Tang, *Org. Chem. Front.* **2022**, *9*, 4554–4560.

62. a) N. Nishimura, A. Kato, I. Maeba, *Carbohydr. Res.* **2001**, *331*, 77–82; b) B. Klenke, M. Stewart, M. P. Barrett, R. Brun, I. H. Gilbert, *J. Med. Chem.* **2001**, *44*, 3440– 3452.

63. a) F. Xie, M. Chen, X. Wang, H. Jiang, M. Zhang, *Org. Biomol. Chem.* **2014**, *12*, 2761–2768; b) G. Shi, F. He, Y. Che, C. Ni, Y. Li, *Russ. J. Gen. Chem.* **2016**, *86*, 380–386; c) M. Zeng, T. Wang, D.-M. Cui, C. Zhang, *New J. Chem.* **2016**, *40*, 8225– 8228; d) B. Feng, W. Yue, D. Wei, Q. Chen, C. Liu, X. Wang, Y. Wang, Z. Peng, *Eur. J. Org. Chem.* **2024**, e202400993.

64. a) M. Elce, C. E. Dearden, E. Matutes, J. Garcia-Talavera, A. Z. S. Rohatiner, S. A. N. Johnson, N. T. J. O'Connor, A. Haynes, N. Osuji, F. Forconi, F. Lauria, D. Catovsky, *Br. J. Haematol.* **2009**, *145*, 733–740; b) J. A. Joule, E. F. V. Scriven, C. A. Ramsden, *Adv. Heterocycl. Chem.* **2016**, *119*, 81−106.

65. a) M. M. Belmonte, E. C. Escudero-Ada´ n, J. Benet-Buchholz, R. M. Haak, A. W. Kleij, *Eur. J. Org. Chem.* **2010**, 4823–4831; b) N. A. Harry, R. M. Cherian, S. Radhika, G. Anilkumar, *Tetrahedron Lett.* **2019**, *60*, 150946; c) K. Bahrami, S. Saleh, *Synth. React. Inorg. Met.-Org. Nano-Met. Chem.,* **2016**, *46*, 852–856; d) M. Kalhor, N. Khodaparast, *Res. Chem. Intermed.* **2015**, *41*, 3235–3242; e) H. Alinezhad, A. Ahmadi, P. Hajiabbasi, *J. Chem. Sci.* **2019**, *131*, 34; f) M. Kalhor, F. Rezaee-Baroonaghi, A. Dadras, Z. Zarnegar, *Appl. Organometal. Chem.* **2019**, *33*, 4784; g) M. Kalhor, Z. Zarnegar, F. Janghorban, S. A. Mirshokraei, *Res. Chem. Intermed.* **2020**, *46*, 821–836; h) P. B. Shelke, S. N. Mali, H. K. Chaudhari, A. P. Pratap, *J. Heterocycl. Chem.* **2019**, *56*, 3048.

66. a) S. S. Clinton, R. Ramesh, J. G. Małecki, *Appl. Organomet. Chem.*, 2022, **36**, No. e6708; b) K. Das, A. Mondal, D. Pal, H. K. Srivastava, D. Srimani, *Organometallics* **2019**, *38*, 1815 –1825; c) R. Fertig, F. L. -Künstler, T. Irrgang, R. Kempe, *Nat. Commun*. **2023**, *14*, 5.

67. a) M. K. Hargreaves, J. G. Pritchard, H. R. Dave, *Chem. Rev.* **1970**, *70*, 439; b) S. M. Sondhi, R. Rani, A. D. Diwvedi, P. Roy, *J. Heterocycl. Chem.* **2009**, *46*, 1369.

68. a) H. Takaya, K. Yoshida, K. Isozaki, H. Terai, S.-I. Murahashi, *Angew. Chem., Int. Ed.* **2003**, *42*, 3302; b) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898.

69. a) J. Zhang, M. Senthilkumar, S. C. Ghosh, S. H. Hong, *Angew. Chem., Int. Ed.* **2010**, *49*, 6391; b) S. Muthaiah, S. H. Hong, *Synlett* **2011**, *2011*, 1481; c) J. Kim, S. H. Hong, *Org. Lett.* **2014**, *16*, 4404; d) N. A. Espinosa-Jalapa, A. Kumar, G. Leitus, Y. Diskin-Posner, D. Milstein, *J. Am. Chem. Soc.* **2017**, *139*, 11722−11725.

70. a) T. Janecki, T. *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity.*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2014**; b) M. Chadwick, H. Trewin, F. Gawthrop, C. Wagstaff, *Int. J. Mol. Sci.* **2013**, *14*, 12780-12805.

71. a) M. G. Coleman, A. N. Brown, B. A. Bolton, H. Guan, *Adv. Synth. Catal.* **2010**, *352*, 967–970.; b) S. Chakraborty, P. O. Lagaditis, M. Förster, E. A. Bielinski, N. Hazari, M. C. Holthausen, W. D. Jones, S. Schneider, *ACS Catal*. **2014**, *4*, 3994−4003; c) M. Peña-López, H. Neumann, M. Beller, *ChemCatChem* **2015**, *7*, 865−871; d) Y. Tang, R. IL Meador, C. T. Malinchak, E. E. Harrison, K. A. McCaskey, M. C. Hempel, T. W. Funk, *J. Org. Chem.* **2020**, *85*, 1823−1834.

72. E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257−10274.

73. a) M. Haniti, S. A. Hamid, J. M. J. Williams, *Chem. Commun.* **2007**, 725; b) J. He, J. W. Kim, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2009**, *48*, 9888.

74. a) S.-I. Murahashi, K. Kondo, T. Hakata, *Tetrahedron Lett.* **1982**, *23*, 229–232; b) K. Felföldi, M. S. Klyavlin, M. Bartók, *J. Organomet. Chem.* **1989**, *362*, 193–195; c) Y. Tsuji, K. T. Huh, Y. Ohsugi, Y. Watanabe, *J. Org. Chem.* **1985**, *50*, 1365–1370; d) A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *J. Org. Chem.* **2011**, *76*, 2328–2331; e) K.-I. Fujita, T. Fujii, R. Yamaguchi, *Org. Lett.* **2004**, *6*, 3525–3528; f) K. Yuan, F. Jiang, Z. Sahli, M. Achard, T. Roisnel, C. Bruneau, *Angew. Chem., Int. Ed.* **2012**, *51*, 8876–8880; g) Q. Zou, C. Wang, J. Smith, D. Xue, J. Xiao *Chem.–Eur. J.* **2015**, *21*, 9656–9661; h) A. E. R. Chamberlain, K. J. Paterson, R. J. Armstrong, H. C. Twinb, T. J. Donohoe, *Chem. Commun.* **2020**, *56*, 3563–3566; i) T. Yan, B. L. Feringa, K. Barta, T. Yan, B. L. Feringa, K. Barta, *Nat. Commun.* **2014**, *5*, 1−7; j) H.-J. Pan, T. W. Ng, Y. Zhao, *Chem. Commun.* **2015**, *51*, 11907-11910; k) X. Bai, F. Aiolfi, M. Cettolin, U. Piarulli, A. Dal Corso, L. Pignataro, C. Gennari, *Synthesis* **2019**, *51*, 3545–3555.

75. a) R. A. T. M. Abbenhuis, J. Boersma, G. van Koten, *J. Org. Chem.* **1998**, *63*, 4282–4290; b) G. Jenner, G. Bitsi, *J. Mol. Catal.* **1988**, *45*, 165–168; c) K. O. Marichev, J. M. Takacs, *ACS Catal.* **2016**, *6*, 2205–2210; d) L. U. Nordstrøm, R. Madsen, *Chem. Commun.* **2007**, 5034–5036; e) L. L. R. Lorentz-Petersen, L. U. Nordstrøm, R. Madsen, *Eur. J. Org. Chem.* **2012**, 6752– 6759; f) K. Fujita, Y. Kida, R. Yamaguchi, *Heterocycles* **2009**, *77*, 1371–1377.

76. a) *Amino Group Chemistry: From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, **2008**; b) V. Sridharan, P. A. Suryavanshi, J. C. Menendez, *Chem. Rev.* **2011**, *111*, 7157–7259; c) I. Muthukrishnan, V. Sridharan, J. C. Menendez, *Chem. Rev.* **2019**, *119*, 5057-5191.

77. a) N. Hofmann, L. Homberg, K. C. Hultzsch, *Org. Lett.* **2020**, *22*, 7964– 7970; b) B. Xiong, Y. Li, W. Lv, Z. Tan, H. Jiang, M. Zhang, *Org. Lett.* **2015**, *17*, 4054–4057; c) X.-J. Yun, J.-W. Zhu, Y. Jin, W. Deng, Z.-J. Yao, *Inorg. Chem.* **2020**, *59*, 7841–7851.

78. T. Yan, B. L. Feringa, K. Barta, *Nat. Commun.* **2014**, *5*, 5602.

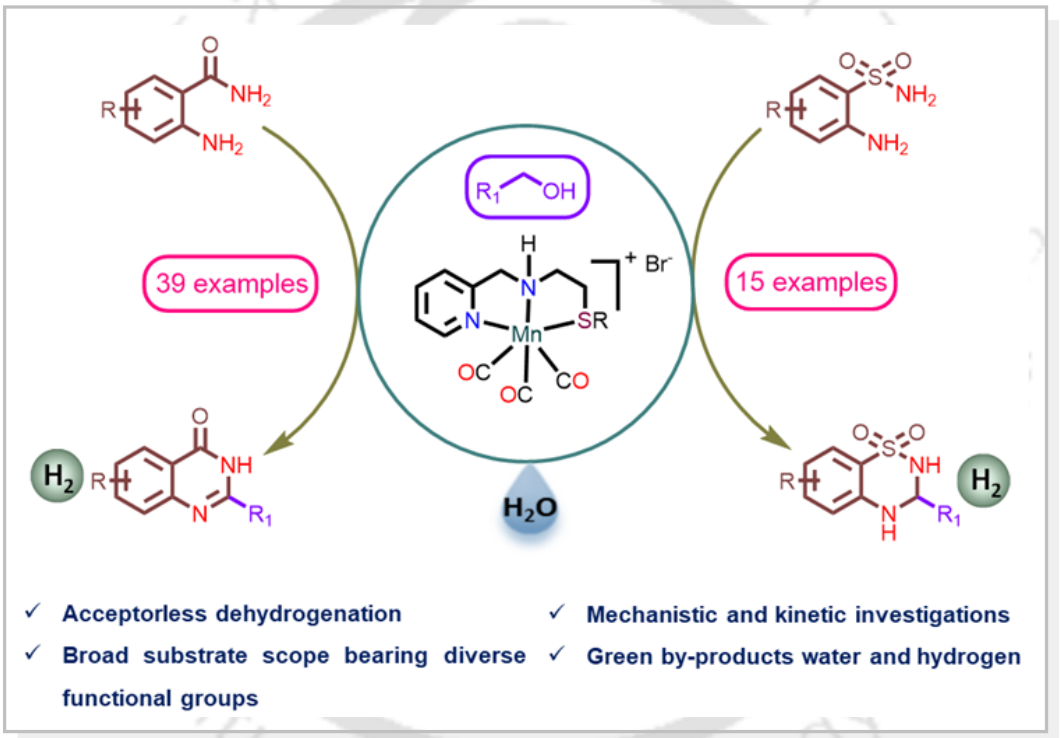
79. a) N. Kaur, *Int. J. Pharm. Bio. Sci.* **2013**, *4*, 485–513; b) J. Spencer, R. P. Rathnam, B. Z. Chowdhry, *Future Med. Chem.* **2010**, *2*, 1441–1449; c) B. Ahmed, M. Rashid, *Org. Chem. Indian J.* **2008**, *4*, 486–507; d) L. Costantino, D. Barlocco, *Curr. Med. Chem.* **2006**, *13*, 65– 85; e) C. M. S. Menezes, G. Rivera, M. A. Alves, D. N. Do Amaral, J. P. B. Thibaut, F. Noel, E. J. Barreiro, L. M. Lima, *Chem. Biol. Drug Des.* **2012**, *79*, 943–949.

80. a) Y. Torisawa, T. Furuta, T. Nishi, S. Aki, J. Minamikawa, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6455– 645; b) S. Kotha, V. R. Shah, *Eur. J. Org. Chem.* **2008**, 1054–1064; c) Y. Kawakita, M. Seto, T. Ohashi, T. Tamura, T. Yusa, H. Miki, H. Iwata, H. Kamiguchi, T. Tanaka, S. Sogabe, Y. Ohta, T. Ishikawa, *Bioorg. Med. Chem.* **2013**, *21*, 2250–2261.

81. V. R. Jumde, E. Cini, A. Porcheddu, M. Taddei, *Eur. J. Org. Chem.* **2015**, *2015*, 1068–1074.

Chapter 2

Well-defined Manganese Complex Catalyzed Dehydrogenative Synthesis of Quinazolin-4(3H)-ones and 3,4-Dihydro-2H-1,2,4-benzothiadiazine 1,1-Dioxides



D. Pal, A. Mondal, D. Srimani, *Catal. Sci. Technol.* **2022**,*12,* 3202-3208.

2.1. Introduction:

Nitrogen heterocycles are active structural units of numerous natural products, drug molecules, advanced materials and crop protecting agents.[1] Amidst of that the quinazolinone scaffolds are an important class of fused structural motifs, which are present in naturally occurring alkaloids, biologically active[2] and pharmaceutically important compounds. These compounds are known for their antimicrobial,[3] anticonvulsant,[4] sedative,[5] antitubercular,[6] antivirial,[7] antimalarial,[8] anti-inflammatory[9] and anticancer[10] properties (Figure **2.1**).

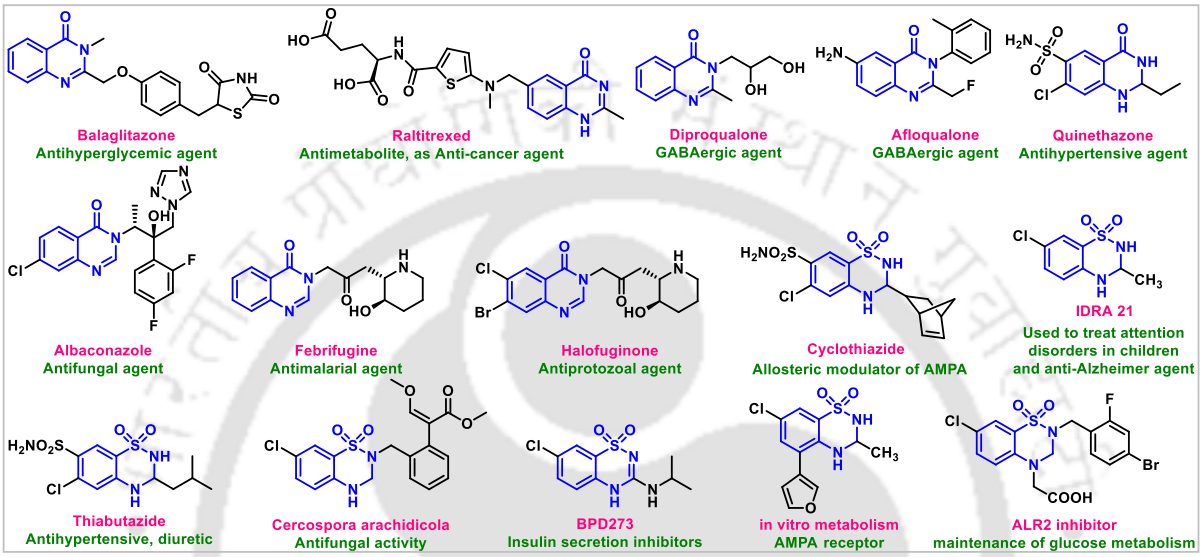


Figure 2.1. Biologically important molecules bearing quinazolinone and benzothiadiazine scaffold

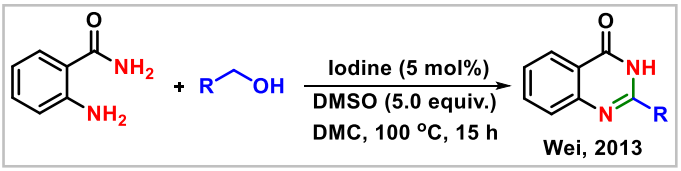
Due to its profound importance, a plethora of synthetic approaches was accomplished in the literature during the last few decades.

2.2. Literature survey:

2.2.1. Synthesis of Quinazolin-4(3H)-one:

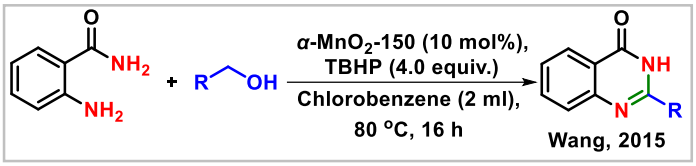
The majority of these classical synthetic procedures involved the condensation of aldehydes with 2-aminobenzamides and successive oxidation of the aminal intermediate, amidation of *o*-aminobenzoic acid and coupling of anthranilic acid with amides.[11] Herein, in this chapter, some literature synthetic approaches have been briefly demonstrated.

In 2013, *Wei and co-workers* carried out the synthesis of quinazolin-4(3H)-one[11a] in an environmentally benign solvent dimethyl carbonate (DMC), in presence of 5 equiv. of mild oxidant DMSO, using 5 mol% of inexpensive, nontoxic and nonmetallic iodine as a catalyst under a nitrogen atmosphere. (Scheme **2.1**).



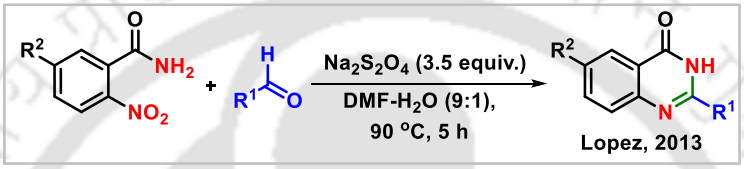
Scheme 2.1. Molecular iodine catalyzed synthesis of quinazolinones

In 2015, *the group of Wang* reported a synthetic protocol to afford the quinazolin-4(3H)-one derivatives employing nanocrystalline oxide α-MnO_2-150 in presence of TBHP oxidant [11b] (Scheme **2.2**)



Scheme 2.2. α-MnO_2-catalyzed synthesis of quinazolinones

In 2013, *Lopez and co-workers* sought a direct one-pot procedure for the synthesis of quinazolin-4(3H)-one[11c] derivatives by the reaction of 2-nitrobenzamides with aldehydes in the presence of sodium dithionite ($Na_2S_2O_4$) under aerobic condition (Scheme **2.3**). In the catalytic system the presence of water is required for the reduction of 2-nitroaryl amines by $Na_2S_2O_4$.



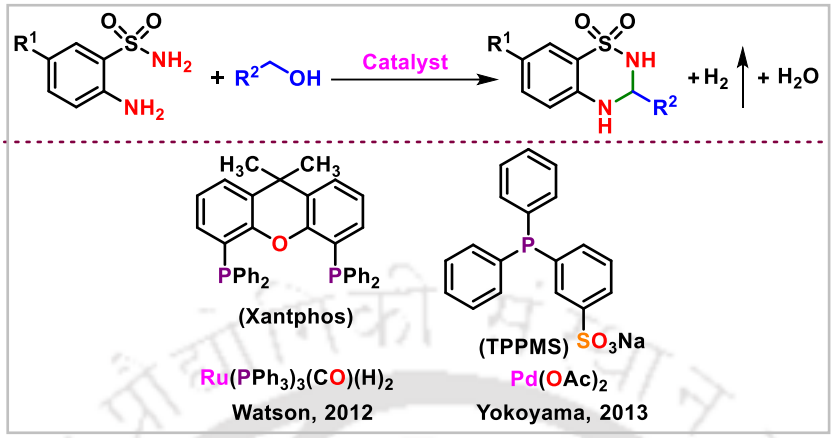
Scheme 2.3. Synthesis of 2-Substituted Quinazolin-4(3*H*)-ones using $Na_2S_2O_4$

These processes necessitate the usage of excess or stoichiometric amounts of oxidizing agents, elevated temperature and the need of preformed aldehydes, which are relatively unstable under the reaction conditions. Furthermore, these approaches are also generating copious stoichiometric wastages.[12] To address these issues scientific communities urge their interest to develop green, atom-economical and sustainable strategies for the construction of quinazolinone derivatives. In that perspective, the acceptorless dehydrogenation[13, 14] evolved as an emerging tool for the synthesis of this important heterocyclic scaffold. Upon implementation of that idea, in recent years, notable progress was made towards the dehydrogenative synthesis of quinazolin-4(3H)-ones directly from primary alcohol and *o*-aminobenzamide with noble metals as well as 3d-metals which has been discussed in Chapter I of Section, 1.3.1.2.1.4.

2.2.2. Synthesis of 3,4-Dihydro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides:

3,4-Dihydro benzothiadiazine 1,1-oxides are an important structural motif found in many bioactive compounds[15] and pharmaceuticals (Figure **2.1**).[16] Classically these can be synthesized via condensation of aldehydes or ethyl hemiacetals with 2-aminobenzenesulfonamide in acidic medium liberating toxic by-products.[17] However, dehydrogenative construction of this structurally important scaffold is completely untapped. In that quest, in 2012, *Watson research group* described the construction of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (DHBDs) using 5 mol% of $Ru(PPh_3)_3(CO)(H)_2$, 5 mol% of Xantphos, 20 mol % of NH_4Cl, and 2.5 mmol crotononitrile at 115 °C for 14 h. Herein, NH_4Cl plays a crucial role in the dehydrogenation strep, however, this catalytic protocol suffers from limited substrate scope.[18a] In the very next year, *the group of Yokoyama* reported $Pd(OAc)_2$ catalyzed TPPMS ligand mediated synthesis of aforementioned heterocycle using *o*-aminobenzenesulfonamide and

primary alcohols as starting materials.[18b] In the catalytic system, water plays an important role in activation of benzyl alcohol and stabilization of hydroxide ion by hydration, followed by formation of water-soluble activated (η^3-benzyl)palladium cationic species.



Scheme 2.4. Noble and 3d metal catalyzed dehydrogenative synthesis of 3,4-dihydro benzothiadiazine 1,1-oxides

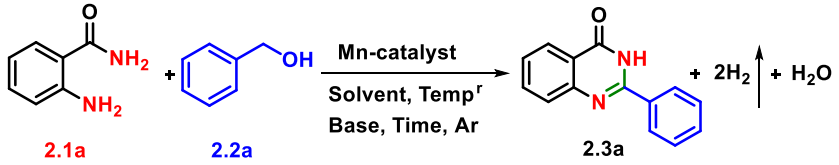
2.3. Present work:

Hence, the development of well-defined phosphine-free 3d-metal complex, which can trigger the synthesis of these N-heterocycles via ADC using a stoichiometric amount of alcohol and lower loading of a base, is extremely beneficial. Notably, the use third most earth-abundant transition metal manganese is completely unexplored for the dehydrogenative synthesis of quinazolinone. Moreover, the dehydrogenative construction of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-oxide is completely untapped. Henceforth, this present chapter demonstrated Mn-catalyzed synthesis of quinazolin-4(3H)-one and 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (DHBDs) derivatives via ADC of aminobenzamide or aminobenzenesulfonamide with primary alcohols.

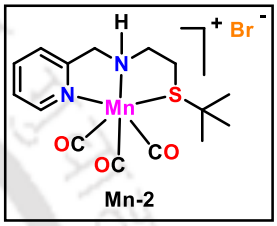
2.3.1. Results and discussion:

At the outset, the applicability of three NNS-Mn(I)-complexes *i.e.* **Mn-1, Mn-2** and **Mn-20** has been checked towards the synthesis of quinazolin-4(3H)-one via acceptorless dehydrogenative annulation process. To determine the optimal reaction conditions, the investigations was started taking 2-aminobenzamide (**2.1a**) and benzyl alcohol (**2.2a**) as a model system. In that regard, when a 1,4-dioxane solution containing an equimolar mixture of 2-aminobenzamide (**2.1a**) and benzyl alcohol (**2.2a**) refluxed in the presence of 5 mol% of **Mn-2** and 0.5 equiv. of NaO^{t}Bu for 36 h 80% of the desired 2-phenylquinazolin-4(3H)-one (**2.3a**) isolated (Table 2.3.1.1., entry 1). Furthermore, increasing the ratio of 2-aminobenzamide and benzyl alcohol there was no improvement in the isolated yield (Table 2.3.1.1., entry 2) was noticed. Under a similar reaction condition, upon reducing the reaction time by 12 h a detrimental effect in the yield was observed (Table 2.3.1.1., entry 3).

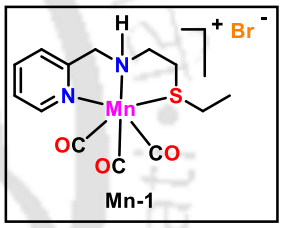
Table 2.3.1.1. Reaction Optimization for the Mn-catalyzed synthesis of Quinazolin-4(3H)-ones[a]



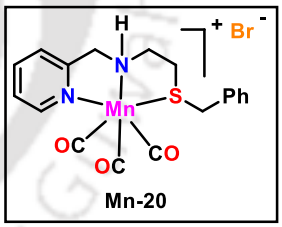
Entry	Cat.	Solvent	Base (equiv.)	2.1a:2.2a	Temp^r (°C)	Time (h)	Yield^b (%)
1	Mn-2	1,4-dioxane	NaO^{t}Bu(0.5)	1:1	100	36	80
2	Mn-2	1,4-dioxane	NaO^{t}Bu(0.5)	1:1.5	100	36	80
3	Mn-2	1,4-dioxane	NaO^{t}Bu(0.5)	1:1	100	24	68
4	Mn-2	1,4-dioxane	NaO^{t}Bu(0.3)	1:1	100	36	70
5	Mn-2	1,4-dioxane	KO^{t}Bu(0.5)	1:1	100	36	62
6	Mn-2	1,4-dioxane	NaOH(0.5)	1:1	100	36	70
7	Mn-2	1,4-dioxane	KOH(0.5)	1:1	100	36	60
8	Mn-2	1,4-dioxane	Na_2CO_3(0.5)	1:1	100	36	30
9	Mn-2	Xylene	NaO^{t}Bu(0.5)	1:1	100	36	80
10	Mn-2	Xylene	NaO^{t}Bu(0.5)	1:1	140	36	86
11	Mn-2	Toluene	NaO^{t}Bu(0.5)	1:1	140	36	76
12	Mn-2	^{t}AmOH	NaO^{t}Bu(0.5)	1:1	140	36	---
13^c	Mn-2	Xylene	NaO^{t}Bu(0.5)	1:1	140	36	68
14	Mn-1	Xylene	NaO^{t}Bu(0.5)	1:1	140	36	82
15	Mn-20	Xylene	NaO^{t}Bu(0.5)	1:1	140	36	72
16	-	Xylene	NaO^{t}Bu(0.5)	1:1	140	36	Trace
17	Mn-2	Xylene	-	1:1	140	36	Trace
18	$MnBr(CO)_5$	Xylene	NaO^{t}Bu(0.5)	1:1	140	36	24



Mn-2



Mn-1



Mn-20

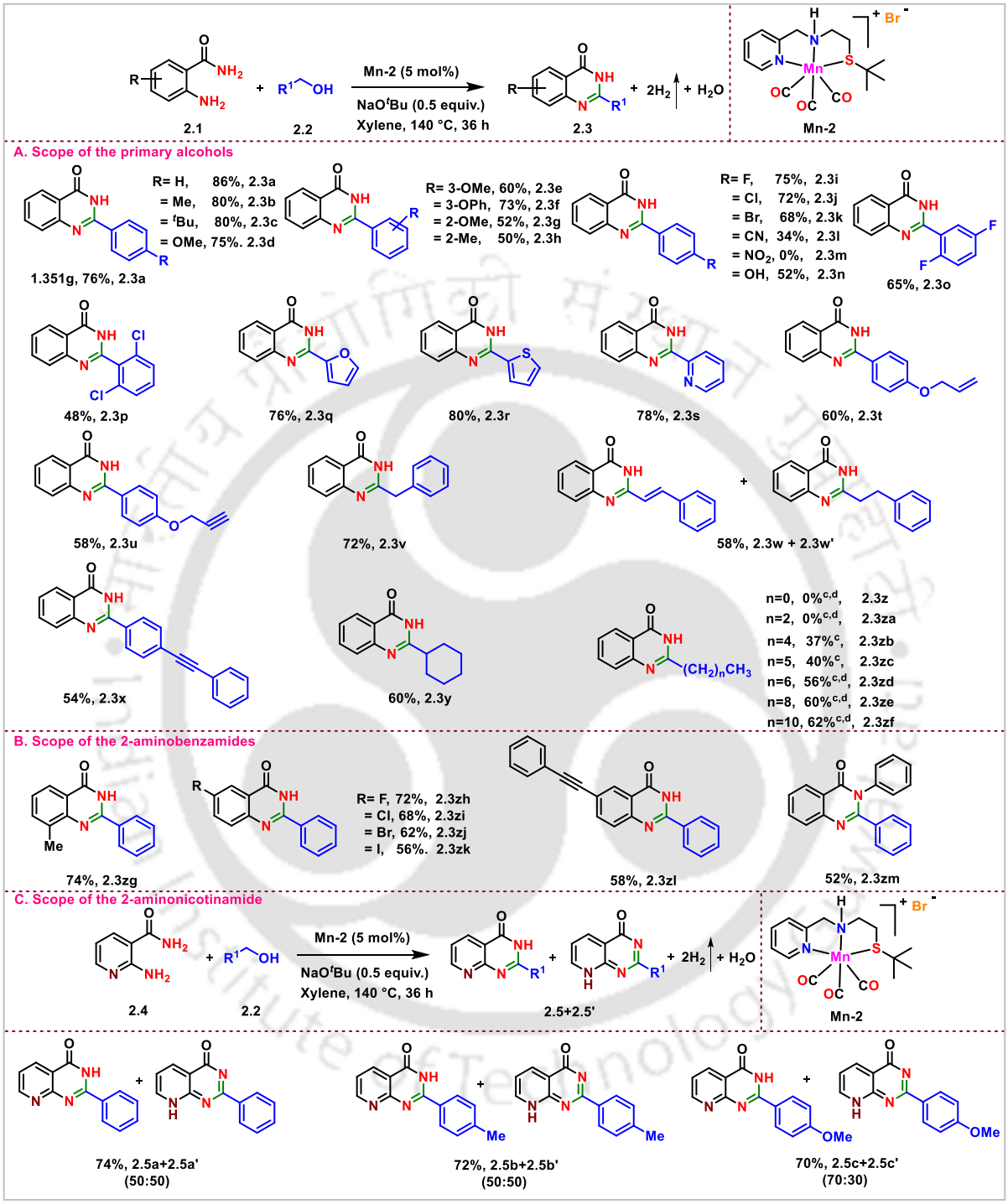
[a] Reaction conditions: **2.1a** (0.5 mmol), **2.2a** (0.5 – 0.75 mmol), base (0.15 – 0.25 mmol), Mn-catalyst (5 mol%), solvent (2 mL), at temperature 100 °C – 140 °C of a preheated oil bath under argon. [b]Isolated yield, [c]Catalyst loading 2 mol%.

Keeping the other conditions unaltered; decrease of the base loading from 0.5 equiv. to 0.3 equiv. reduced the isolated yield of **2.3a** (Table 2.3.1.1., entry 4). Further study on the effect of base show NaO^{t}Bu is more effective than NaOH or Na_2CO_3 (Table 2.3.1.1., entry 6-8). Slight improvement of the yield was noticed when the reaction performed at 140 °C at xylene solvent under the standard reaction conditions. (Table 2.3.1.1., entry 10). Afterwards, the catalytic applicability of **Mn-1** and **Mn-20** are compared. **Mn-1** shows almost similar reactivity to that of **Mn-2,** whereas **Mn-20** afforded lower yield

(Table 2.3.1.1., entry 14-15). There was no detectable conversion of the product in the absence of either the catalyst or the base, showing that both played a vital role for this method (Table 2.3.1.1., entry 16-17). In presence of the precursor, $MnBr(CO)_5$, only 24% isolated yield of **2.3a** was delivered under the optimal reaction conditions (Table 2.3.1.1., entry 18).

Next, the efficacy of this current protocol was explored by examining the scope of both primary alcohols and 2-aminobenzamides. Initially, a diverse range of benzylic alcohols bearing electronically neutral and electronically biased groups at the *o*-, *m*- and *p*-positions of the aryl ring was tested, which were found to be well tolerated under the optimal reaction conditions affording good to excellent yields of the desired products (**2.3a-2.3h**). Halide substituted aromatic alcohols were well-survived furnishing good isolated yields without forming any dehalogenated by-products (**2.3i-2.3k**). Benzyl alcohol containing strong electron withdrawing substituent fluoro at the 2, 5-position gave moderate yield (**2.3o**). However, presence of nitro group at *p*-position was found to be catalytically incompatible. Benzyl alcohol containing cyano and hydroxyl functional group was effective under the reaction condition furnishing moderate isolated yield (**2.3l** and **2.3n** respectively). When sterically hindered 2, 6-dichlorobenzyl alcohol was executed as a reaction partner 48% of isolated yield was accomplished (**2.3p**). Heteroaromatic alcohols like 2-furyl, 2-thiophene and 2-pyridyl methanol smoothly reacted to afford the respective quinazolinone products (**2.3q-2.3s**) in excellent yield. Of note, the reducible functional groups such as –C≡C–Ph, $–OCH_2CH{=}CH_2$ and $–OCH_2C{\equiv}CH$ present at the *p*-position of benzyl alcohol can survive under the streamlined reaction conditions to give the desired products (**2.3x**, **2.3t** and **2.3u** respectively). Albeit, in case of cinnamyl alcohol apart from the desired product **2.3w** a small amount of –C=C reduction product **2.3w'** was also obtained (**2.3w**: **2.3w'** = **3**:**1**). Primary alcohol with an extended carbon chain worked uneventfully furnishing good yield (**2.3v**). Aliphatic alcohols were also compatible and afforded moderate to good yield at higher temperature (**2.3zb - 2.3zf**). Diversely substituted 2-aminobenzamide were also furnished corresponding qunazolinones in good yield (**2.3zg-2.3zl**). In addition, N-phenyl substituted 2-aminobenzamide also provided 52% isolated yield (**2.3zm**). When 2-aminonicotinamide was taken as a coupling partner a mixture of two isomeric pyridopyrimidinone derivatives was isolated in good yields (**2.5a-2.5c**).

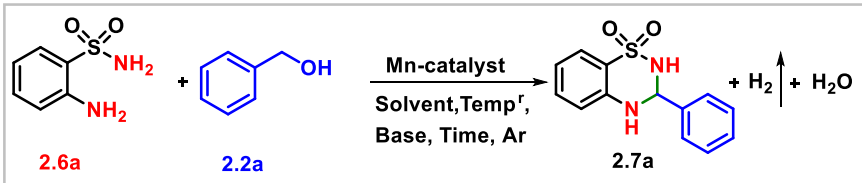
2.3.1.2. Mn-catalyzed synthesis of Quinazolin-4(3H)-one and Pyridopyrimidin-4(3H)-one: substrate scope[a,b]



[a] Reaction conditions: **2.1** (0.5 mmol), **2.2** (0.5 mmol), **2.4** (0.5 mmol), NaO^{t}Bu (0.25 mmol), **Mn-2** (5 mol %), 36 h, 140 ˚C (oil bath), under argon, Xylene (2 mL), [b]Isolated yield, [c]72 h, [d]170 ˚C.

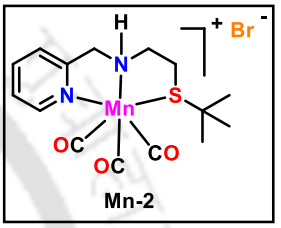
Furthermore, efficacy of the developed catalytic protocol was extended by conducting the synthesis of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-oxide directly from 2-aminobenzenesulfonamide and alcohols employing as prepared phosphine-free well-defined NNS-Mn(I) complexes via Acceptorless Dehydrogenative Coupling (ADC). When equimolar mixture of 2-aminobenzenesulfonamide (**2.6a**)

Table 2.3.1.3: Reaction Optimization for the Mn-catalyzed synthesis of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-oxide[a]

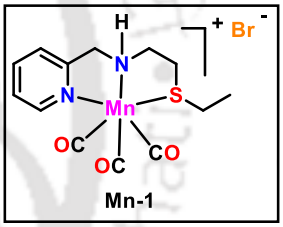


2.6a 2.2a 2.7a

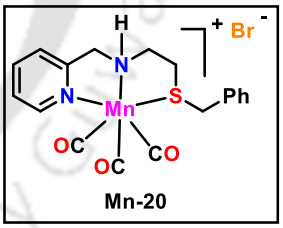
Entry	Cat.	Solvent	Base (equiv.)	2.6a:2.2a	Temp^r (°C)	Time (h)	Yield^b (%)
1	Mn-2	1,4-dioxane	NaO^{t}Bu(1)	1:1	100	36	45
2	Mn-2	1,4-dioxane	NaO^{t}Bu(1)	1:1.5	100	36	62
3	Mn-2	1,4-dioxane	NaO^{t}Bu(1)	1:2	100	36	62
4	Mn-2	1,4-dioxane	NaO^{t}Bu(1)	1:1.5	100	48	62
5	Mn-2	1,4-dioxane	NaO^{t}Bu(0.75)	1:1.5	100	36	52
6	Mn-2	1,4-dioxane	KO^{t}Bu(1)	1:1.5	100	36	42
7	Mn-2	1,4-dioxane	NaOH(1)	1:1.5	100	36	50
8	Mn-2	1,4-dioxane	KOH(1)	1:1.5	100	36	40
9	Mn-2	1,4-dioxane	Na_2CO_3(1)	1:1.5	100	36	28
10	Mn-2	Xylene	NaO^{t}Bu(1)	1:1.5	100	36	30
11	Mn-2	Xylene	NaO^{t}Bu(1)	1:1.5	140	36	30
12	Mn-2	Toluene	NaO^{t}Bu(1)	1:1.5	100	36	25
13	Mn-2	-	NaO^{t}Bu(1)	1:1.5	100	36	45
14^c	Mn-2	1,4-dioxane	NaO^{t}Bu(1)	1:1.5	100	36	48
15	Mn-1	1,4-dioxane	NaO^{t}Bu(1)	1:1.5	100	36	60
16	Mn-20	1,4-dioxane	NaO^{t}Bu(1)	1:1.5	100	36	51
17	-	1,4-dioxane	NaO^{t}Bu(1)	1:1.5	100	36	Trace
18	Mn-2	1,4-dioxane	-	1:1.5	100	36	Trace



Mn-2



Mn-1



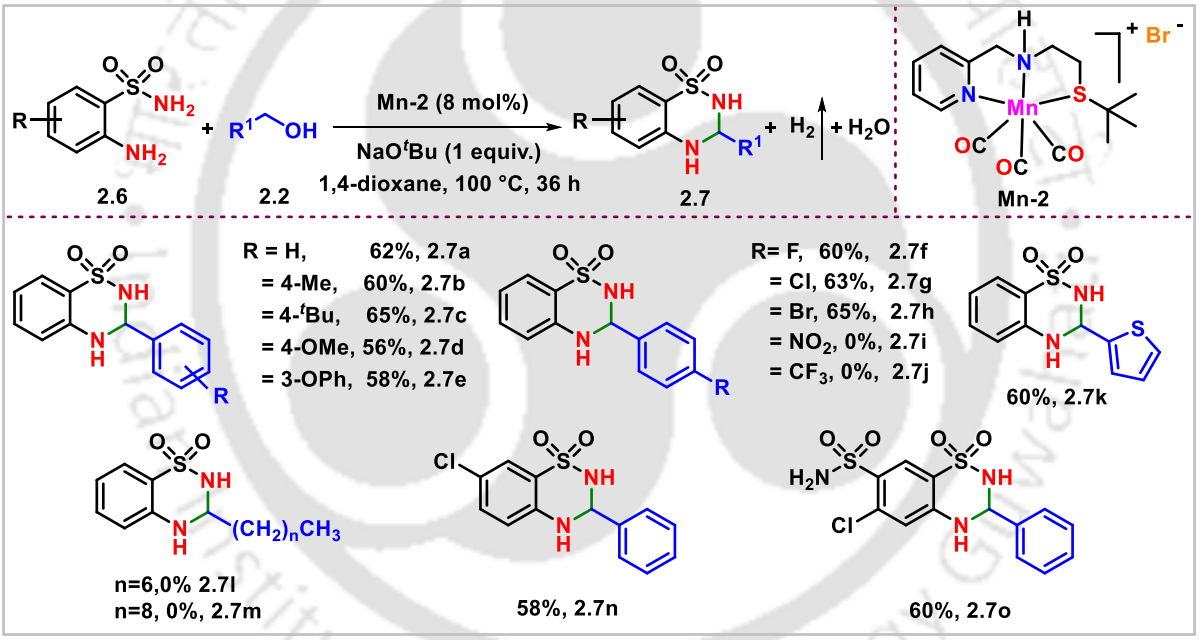
Mn-20

[a] Reaction conditions: **2.6a** (0.5 mmol), **2.2a** (0.5 – 1.0 mmol), base (0.375 – 0.5 mmol), Mn-catalyst (8 mol%), solvent (2 mL), at temperature 100 ˚C– 140 ˚C of a preheated oil bath under argon. [b]Isolated yield. [c]Catalyst loading 5 mol%.

and benzyl alcohol (**2.2a**) were refluxed in 1,4-dioxane at 100 ˚C for 36 h in presence of 8 mol% of **Mn-2** and 1.0 equiv. of NaO^{t}Bu, it afforded 45% isolated yield (Table 2.3.1.3., entry 1).Upon increasing of loading of benzyl alcohol (**2.2a**) from 1.0 equiv. to 1.5 equiv. an increment in the yield from 45% to 62% has been observed (Table 2.3.1.3., entry 2). The result remains unaltered furthermore increasing

of loading of **2.2a** (Table 2.3.1.3., entry 3). Afterwards, several reaction parameters such as base loading, nature of base, time, temperature, solvent and catalyst loading were screened (Table 2.3.1.3., entry 4-14), albeit, they are failed to afford the optimal result. Therefore, to get the optimum yield of the desired product **2.7a**, 1.5 equiv. of benzyl alcohol (**2.2a**) is required as a coupling partner with 1.0 equiv. of 2-aminobenzenesulfonamide (**2.6a**) at 100 ˚C for 36 h upon implementation of 8 mol% of **Mn-2** and 1.0 equiv. of NaO^{t}Bu base in 1,4-dioxane solvent (Table 2.3.1.3., entry 2). Again, the catalytic applicability of other two complexes has been checked which manifested that although **Mn-1** displayed similar kind of reactivity like **Mn-2** albeit **Mn-20** exhibited some detrimental effect (Table 2.3.1.3., entry 15-16). The control experiment demonstrated that both the catalyst and base are necessary components of the reaction mixture as only trace amount of product were formed in their absence (Table 2.3.1.3., entry 17-18).

2.3.1.4. Mn-catalyzed synthesis of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-oxide: substrate scope[a,b]

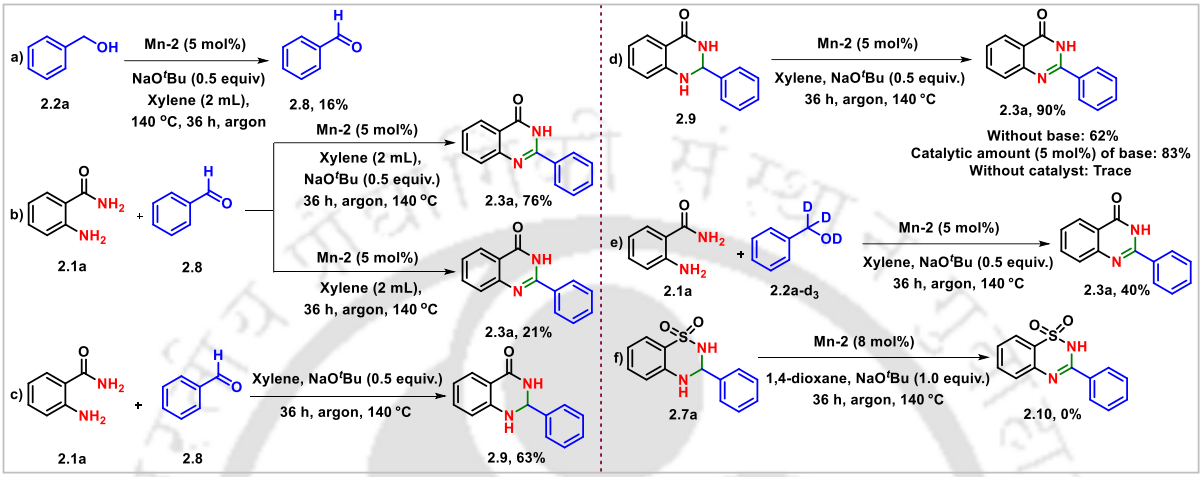


[a] Reaction conditions: **2.6** (0.5 mmol), **2.2** (0.75 mmol), NaO^{t}Bu (0.5 mmol), **Mn-2** (8 mol %), 36 h, 100 ˚C (Oil bath), under argon, 1, 4-dioxane (2 mL), [b]Isolated yield.

With the set of optimized reaction conditions in hand, the feasibility of current catalytic protocol was explored with an array of 2-aminobenzenesulfonamide and primary alcohols whose pertinent results were summarized in **2.3.1.4**. Initially, the scope of *p*- and *m*-substituted benzyl alcohols were tested where electronically neutral and electronically rich functional groups embrace at the aromatic nucleus of the phenyl ring furnished good isolated yield (**2.7a-2.7e**). Halide substituted aromatic alcohols were well compatible affording good isolated yields where the carbon-halogen moiety remains intact under the reaction unravelling the scope for further derivatization (**2.7f-2.7h**). Of note, benzyl alcohol bearing nitro group and electronically deficient -CF_3 group failed to accomplish their desired product (**2.7i-**

2.7j). Interestingly, 2-Thiophenemethanol (**2.2k**) reacted well with 2-aminobenzenesulfonamide (**2.6a**) delivering the intended product (**2.7k**) with 60% isolated yield. Unfortunately, aliphatic alcohols remained inactive in that streamline reaction condition (**2.7l & 2.7m**). Afterwards, the scope of different 2-aminobenzenesulfonamide derivatives has been tested which furnished their desired products (**2.7n-2.7o**) in good yields without forming any dehalogenated by-products.

2.3.1.5. Mechanistic investigation:



Scheme 2.7. Control experiments

The successful accomplishment of both N-heterocycles using air and moisture stable, phosphine-free manganese catalyst promoted to elucidate its mechanistic details by performing various control reactions (Scheme **2.7**). In that quest, at the outset, in presence of **Mn-2** conversion of alcohol to its corresponding aldehyde was observed (Scheme **2.7**, a). Then, to disclose the role of catalyst the condensation reaction between benzaldehyde (**2.8**) with 2-aminobenzamide (**2.1a**) was performed (Scheme **2.7**, b). Notably, when the reaction was carried out in presence of only 0.5 equiv. of NaO^{t}Bu, 63% of the intermediate 2-phenyl-2,3-dihydroquinazolinone (**2.9**) was isolated whereas formation of 2-phenylquinazolinone (**2.3a**) was not observed (Scheme **2.7**, c). Of note, to convert intermediate (**2.9**) to the desired product (**2.3a**) **Mn-2** was highly essential whereas only NaO^{t}Bu failed to perform this step (Scheme **2.7**, d). These experiments suggested that the base was assisting the condensation of 2-aminobenzamide with the aldehyde to afford intermediate 2-phenyl-2,3-dihydroquinazolinone (**2.9**) whereas **Mn-2** had a profound role in converting **2.9** to **2.3a.** Furthermore, during the catalysis evolved H_2 gas was utilized in the hydrogenation reaction using Wilkinson catalyst (experimental section **2.5.12.3**), confirmed by GC-TCD and estimated by a gas-burette method which revealed that 83% liberation of dihydrogen. When the representative reaction was conducted with deuterated benzyl alcohol (**2.2a-d$_3$**) 40% of the desired product (**2.3a**) was isolated resulting k_H/k_D= 2.15 (Scheme **2.7**, e). Interestingly, during the preparation of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide, formation of **2.10** was not observed. Thus, under the optimized condition dehydrogenation of **2.7a** was failed to give **2.10.** This reveals that **Mn-2** failed to activate the dehydrogenation of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**2.7a**) (Scheme **2.7**, f). This might be due to the difficulty in the

dehydrogenation of the electron deficient **2.7a** compare to the electron sufficient 2-phenyl-2,3-dihydroquinazolinone (**2.9**) intermediate.[19]

2.3.1.6. Kinetic experiments:

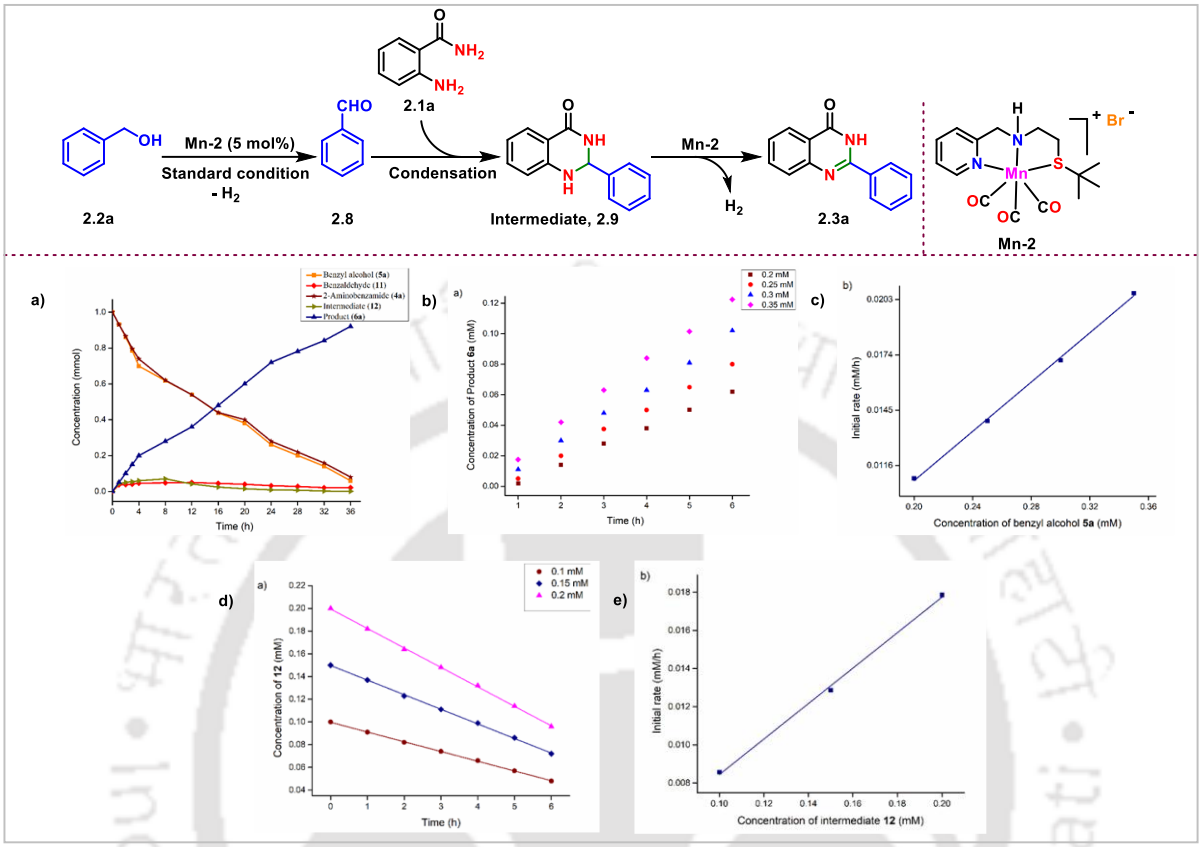


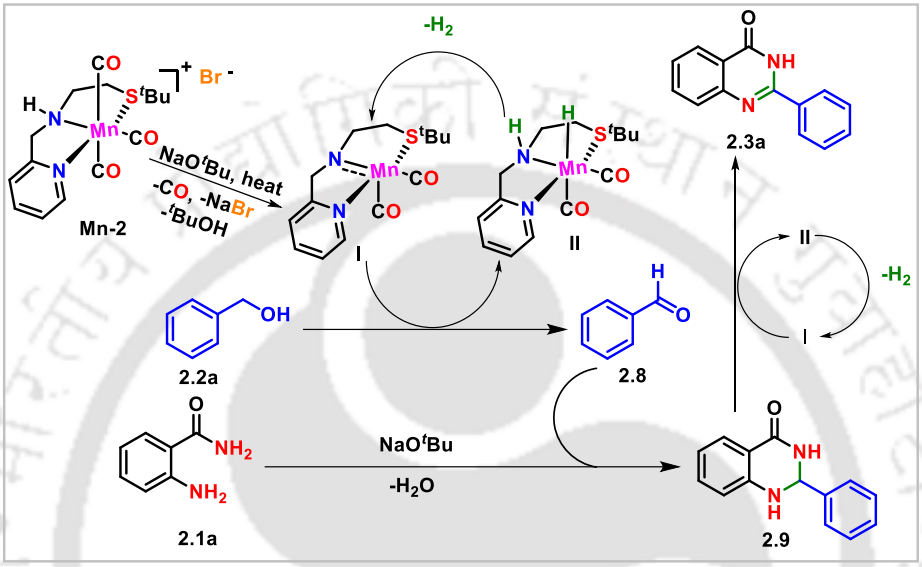
Figure 2.2. a) Kinetic monitoring of the Mn(I)-catalyzed synthesis of 2-phenyl quinazolin-4(3H)-one (**2.3a**); b) Concentration of **2.3a** vs time plot at various concentration of benzyl alcohol (**2.2a**); c) Plot for determining the order of the reaction with respect to benzyl alcohol (**2.2a**). d) Concentration vs time plot at various concentration of intermediate (**2.9**); e) Plot for determining the order of the reaction with respect to intermediate (**2.9**).

The kinetic data indicate a steady formation of **2.3a** during the reaction**.** Throughout the reaction, the concentration of formed aldehyde **2.8** or intermediate **2.9** was less, which indicate that the dehydrogenation of alcohol **2.2a** is slower compared to the dehydrogenation of intermediate **2.9** or condensation step (Figure **2.2**, a). Furthermore, the rate order for this acceptorless dehydrogenative annulation (ADA) reaction was established using an initial rate technique to understand the role of alcohol in this process. The reaction order with respect to benzyl alcohol (**2.2a**) is 1.09, indicating that the reaction is first order with respect to alcohol. This is crucial in the synthesis of 2-phenyl quinazolin-4(3H)-one (**2.3a**), as the rate of product formation increases with the increase of initial concentration of benzyl alcohol (**2.2a**) (Figure **2.2** b and c). Moreover, for the kinetic monitoring of dehydrogenation of intermediate (**2.9**) to product (**2.3**) was performed which also exhibited first order kinetics with respect

to intermediate (**2.9**) and the rate of desired product (**2.3**) formation gradually increases with the increase of initial concentration of the intermediate (**2.9**) (Figure **2.2** d and e).

2.3.1.7. Proposed catalytic cycle:

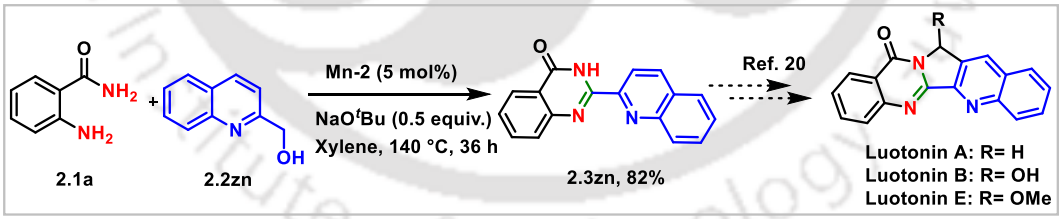
A plausible mechanistic cycle was presented based on aforesaid experimental results and previous literatures[13k,19] (Scheme **2.8**) in which **Mn-2** was first converted to the amido complex (**I**), which dehydrogenate alcohol **2.2a** to aldehyde **2.8** via metal-ligand cooperation (MLC) with simultaneous formation of Mn-H species (**II**). The *in situ* formed aldehyde (**2.8**) undergoes condensation with **2.1a**



Scheme 2.8. Plausible catalytic cycle

to furnish the intermediate (**2.9**) by liberating a water molecule. Finally, dehydrogenation of **2.9** lead to the formation of the final product **2.3a**.

2.3.1.8. Synthetic application:



Scheme 2.9. Synthetic application towards the formal synthesis of Luotonins

In order to unveil the synthetic utility and practical applicability, gram scale synthesis of the representative reaction was also conducted where 1.351 g (**2.3a**, 76% yield) of the desired product was isolated (Table 2.3.1.2). Delightfully, 2-(quinolin-2-yl)quinazolin-4(3H)-one (**2.3zn**) which is an intermediate for the synthesis of pyrroloquinazolinoquinoline alkaloids Luotonins A, B and E,[20] was successfully synthesized (82%) employing the current catalytic protocol (Scheme **2.9**).

2.4. Conclusion:

In summary, herein, manganese catalyzed sustainable synthesis of quinazolin-4(3H)-ones and 3, 4-dihydro-2*H*-1, 2, 4-benzothiadiazine 1, 1-oxides via ADC has been demonstratted. This operationally

simple catalytic approach illustrated a wide variety of substrate scope including aromatic, heteroaromatic, aliphatic alcohols and substrate containing reducible functional groups with good to excellent yields. Mechanistic study strongly indicates the double-dehydrogenative pathway to afford quinazolinone scaffold. The use of phosphine free earth-abundant manganese complex with renewable starting materials makes this approach environmentally green and sustainable.

2.5. Experimental Section:

2.5.1. Ligands synthesis:

All three ligands were prepared according to previous reported literature methods.[13] Pyridine-2-carboxaldehyde (10 mmol) and amino-thiol compound (10 mmol,) were dissolved in dry CH_2Cl_2 (30 mL) and then Na_2SO_4 (40 mmol) was added to it. The resulting suspension was stirred for 20 h at room temperature. Then, it was filtered and the residue was washed thoroughly with CH_2Cl_2 and the combined solvent was removed under reduced pressure. The residue obtained was directly used for the next step without further purification. The residue was dissolved in methanol (30 mL) and $NaBH_4$ (30 mmol) was added portion wise in stirring condition at 0 °C and the stirring was continued for overnight at room temperature. Then the solvent was evaporated and 30 mL of water was added. After that, it was extracted by CH_2Cl_2 and the organic portion was collected and passed through Na_2SO_4. Then the solvent was evaporated to get the crude product, which was purified further by silica gel (100-200 mess) column chromatography using 20-40 % ethyl acetate in hexane.

2.5.2. Complex preparation:

All three complexes (**Mn-1**, **Mn-2** and **Mn-20**) were prepared according to previous reported literature methods.[13] Ligand [$(PyCH_2)HN(CH_2CH_2SR)$, R= Et, ^{t}Bu, Bn] (2.0 mmol) was taken in 5 mL dry THF and was added dropwise to the orange-yellow suspension of $[MnBr(CO)_5]$ (2.0 mmol) in 5 mL degassed dry THF. Afterward, the suspension was refluxed for overnight under argon atmosphere. After the completion of the reaction, the reaction mixture was cooled down to the room temperature, then the solvent was evaporated to obtain the residue, which was further washed with hexane and dried under vacuum to get yellow solid of Mn-complex.

2.5.3. General experimental procedure for the synthesis of Quinazolin-4(3H)-ones:

To an oven dried 10 mL round bottomed flask, 2-aminobenzamide **2.1** (0.5 mmol), alcohol **2.2** (0.5 mmol), NaO^{t}Bu (0.25 mmol) and **Mn-2** (5 mol%) were taken under argon atmosphere, after that 2 mL of xylene was added to the reaction mixture. The resulting mixture was heated in an oil bath at 140 °C for 36 h. After the completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate and methanol were added to dilute the mixture and filtered through celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel (100-200 mess) column chromatography using 20% ethyl acetate in hexane to obtain pure compound.

2.5.4. General experimental procedure for the synthesis of Pyridopyrimidin-4(3H)-one:

A mixture of 2-aminonicotinamide **2.4** (0.5 mmol), aromatic primary alcohol **2.2** (0.5 mmol), NaO^{t}Bu (0.25 mmol) and **Mn-2** (5 mol%) were stirred in xylene (2 mL) under argon atmosphere at 140 °C for 36 h. After the reaction was completed, it was cooled to room temperature and methanol was added to dilute the mixture and filtered through celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel (100-200 mess) column chromatography using 50% ethyl acetate in hexane to get pure compound.

2.5.5. General experimental procedure for the synthesis of 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-oxide:

To an oven dried 10 mL round bottom flask, 2-aminobenzenesulfonamide **2.6** (0.5 mmol), alcohol **2.2** (0.75 mmol), **Mn-2** (8 mol%), NaO^{t}Bu (0.5 mmol) and 1, 4-dioxane (2 mL) were added under argon atmosphere. The reaction mixture was kept for refluxing in a preheated oil bath at 100 °C for 36 h. Then, the reaction was subjected to cool at room temperature and ethyl acetate and methanol were added to dilute the mixture and filtered through celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel (100-200 mess) column chromatography using 20% ethyl acetate in hexane as an eluent to obtain pure compound.

2.5.6. Manganese catalyzed dehydrogenation of alcohol:

To an oven-dried 10 mL round bottomed flask, **Mn-2** (5 mol%), benzyl alcohol **2.2a** (1.0 mmol), NaO^{t}Bu (0.5 mmol) and xylene (2 mL) were added under argon. The reaction mixture was kept for refluxing in a preheated oil bath at 140 °C for 36 h. Then, the reaction mixture was subjected to cool, submitted and analysed by ^{1}H-NMR confirming that 16% of benzaldehyde **2.8** was detected.

2.5.7. Manganese catalyzed synthesis of Quinazolin-4(3H)-one (2.3a) from 2-aminobenzamide (2.1a) and benzaldehyde (2.8):

To an oven-dried 10 mL round bottomed flask, 2-aminobenzamide **2.1a** (0.5 mmol), benzaldehyde **2.8** (0.5 mmol), **Mn-2** (5 mol%), NaO^{t}Bu (0.25 mmol) and xylene (2 mL) were added under argon atmosphere. The reaction vessel was then placed in a preheated oil bath at 140 °C for refluxing. After 36 h, the crude reaction mixture was diluted by ethyl acetate, methanol and filter through celite. The filtrate was concentrated under vacuum and resultant residue was purified by column chromatography using 100-200 mesh size silica employing 20% ethyl acetate in hexane as an eluent. The 76% of the desired product (**2.3a**) was isolated under standard reaction conditions. Whereas, only 21% of the product (**2.3a**) was formed in the absence of base NaO^{t}Bu.

2.5.8. Synthesis of the intermediate 2-phenyl-2,3-dihydroquinazolin-4(1H)-one (2.9)[2] from 2-aminobenzamide (2.1a) and benzaldehyde (2.8):

2-aminobenzamide **2.1a** (0.5 mmol), benzaldehyde **2.8** (0.5 mmol), NaO^{t}Bu (0.25 mmol) and xylene (2 mL) were added under argon atmosphere in an oven-dried 10 mL round bottomed flask. The reaction vessel was placed in a preheated oil bath at 140 °C for 36 h. Afterwards, the crude reaction mixture was

subjected to cool to room temperature, diluted by ethyl acetate, methanol and filter through celite. Then, the filtrate was concentrated under vacuum and resultant residue was purified by column chromatography using 100-200 mesh silica employing 25% ethyl acetate in hexane as an eluent. It was found that 63% of the intermediate product **2.9** was isolated as a white solid in absence of Mn-catalyst.

2.5.9. Manganese catalyzed dehydrogenation of intermediate 2-phenyl-2, 3-dihydroquinazolin-4(1H)-one (2.9) to product Quinazolin-4(3H)-one (2.3a):

To an oven-dried 10 mL round bottomed flask, the intermediate 2-phenyl-2, 3-dihydroquinazolin-4(1H)-one **2.9** (0.5 mmol), **Mn-2** (5 mol%), NaO^{t}Bu (0.25 mmol) and xylene (2 mL) were taken under argon atmosphere. The reaction vessel was then placed in a preheated oil bath at 140 °C for refluxing. After 36 h, the crude reaction mixture was diluted by ethyl acetate, methanol and filter through celite. The filtrate was concentrated under vacuum, taking an aliquot amount to perform gas chromatography, which showed full conversion and furthermore, resultant residue was purified by column chromatography using 100-200 mesh size silica employing 20% ethyl acetate in hexane as an eluent to get 90% yield of the desired product **2.3a**. 62% of the product **2.3a** was formed in absence of base NaO^{t}Bu whilst trace amount of the product detected in absence of catalyst. Albeit, 83% of desired product was isolated in presence of catalytic *i.e.* 5 mol% of base loading instead of 50 mol% of base.

2.5.10. Determination of the kinetic isotope effect:

In an oven dried 10 mL round bottomed flask 2-aminobenzamide **2.1a** (0.5 mmol), deuterated benzyl alcohol **2.2a-d$_3$**[21] (0.5 mmol), **Mn-2** (5 mol%), NaO^{t}Bu (0.25 mmol) were taken and then 2 mL xylene was added under argon atmosphere. The resulting mixture was placed in an oil bath at 140 °C for 36 h. After completion of the reaction, it was cooled to room temperature and ethyl acetate, methanol was poured into the reaction mixture to make it dilute and filtered through celite. The filtrate was concentrated under vacuum and the residue was purified by column chromatography over silica gel (100–200 mesh) employing 20% ethyl acetate/hexane as an eluent obtaining 40% of the desired product **2.3a**. When the same reaction was performed employing benzyl alcohol **2.2a** as a coupling partner under the similar reaction conditions 86% of **2.3a** was isolated which reveals that the value of KIE= k_H/k_D= 2.15.

2.5.11. Manganese catalyzed dehydrogenation of 3-phenyl-3,4-dihydro-2*H*-1,2,4 benzothiadiazine 1, 1-dioxide (4.7a) to 3-phenyl-2*H*-1,2,4 benzothiadiazine 1, 1-dioxide (4.10):

To an oven-dried 10 mL round bottomed flask, 3-phenyl-3,4-dihydro-2*H*-1,2,4 benzothiadiazine 1,1-dioxide **2.7a** (0.5 mmol), **Mn-2** (8 mol%), NaO^{t}Bu (0.5 mmol) and 1,4-dioxane (2 mL) were taken under argon atmosphere. The reaction vessel was placed in a preheated oil bath at 100 °C for refluxing. After 36 h, the crude reaction mixture was diluted by ethyl acetate, methanol and filter through celite. Then, the filtrate was concentrated under vacuum and subjected to do ^{1}H NMR, upon analysis, which

indicates that the reaction was failed to deliver the formation of dehydrogenated product 3-phenyl-2*H*-1,2,4 benzothiadiazine 1,1-dioxide **2.10**.

2.5.12. Determination of hydrogen gas formation:

2.5.12.1. Hydrogen gas quantification- A volumetric quantitative analysis:

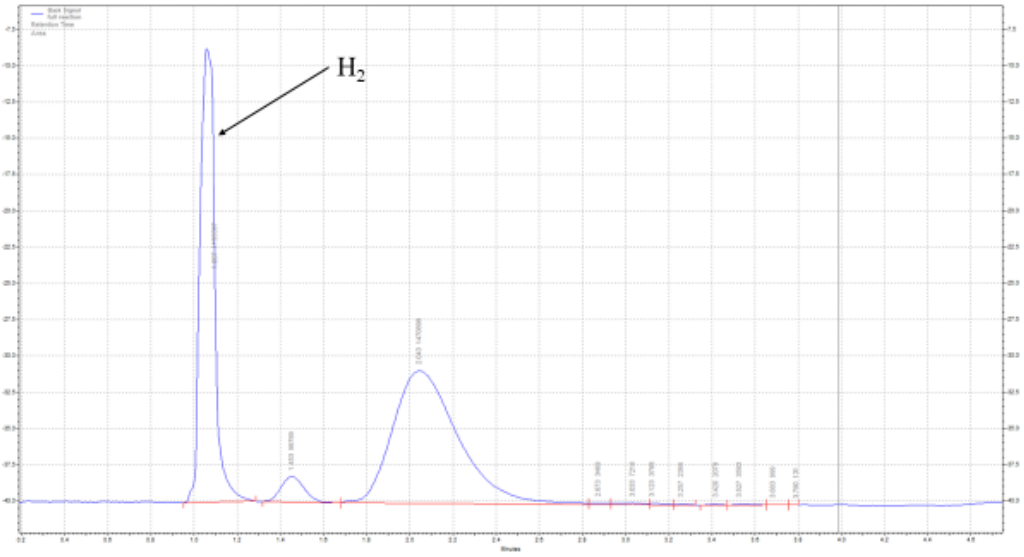
The volumetric quantification of hydrogen gas was accomplished according to the previously reported literature methods.[22] To an oven dried 10 mL round bottomed flask, 2-aminobenzamide **2.1a** (0.5 mmol, 1.0 equiv.), benzyl alcohol **2.2a** (0.5 mmol, 1.0 equiv.), NaO^{t}Bu (0.25 mmol, 50 mol%) and **Mn-2** (0.025 mmol, 5 mol%) were taken under argon atmosphere, after that 2 mL of xylene was added to the reaction mixture and joined with an one neck adapter condenser set up. The adapter was connected to the gas collection apparatus (standard water displacement apparatus, using a graduated cylinder to determine the volume) and the entire system was flushed with argon for 5 minutes and allowed to equilibrate for 5 minutes. The reaction vessel was placed in a preheated oil-bath to the appropriate temperature (140 °C). The reaction was stirred vigorously at a constant temperature until gas evolution ceased. The volume of collected gas was noted. After 36 h, the reaction mixture was removed from preheated oil-bath, subjected to cool at room temperature. It was filtered, purified by silica gel (100-200 mess) column chromatography using 20% ethyl acetate in hexane, analysed by ^{1}H-NMR which conformed that 86% isolated yield of the desired 2-phenylquinazolinone (**2.3a**) was delivered. The collected volume of gas in that experiment was 21 mL. The experiment was repeated twice to obtain consistent readings and the number of moles of hydrogen was evolved was calculated taking into account the vapor pressure of water at 298K = 23.7695 Torr. Volume of water displaced = 21 mL. Atmospheric Pressure = 758.3124 Torr, R = 62.3635 L Torr K^{-1} mol^{-1}

$$nH_2 = [(P_{atm} - P_{water}) \times V] / RT = 0.00083 \text{ moles} = 0.83 \text{ mmoles}$$

Therefore, the collected volume of gas in that experiment was 21 mL, which corresponds to 0.83 mmoles of dihydrogen and consisted with the release of 2 equiv. of H_2 per mole of reactant benzyl alcohol **2.2a**.

2.5.12.2. Detection of evolved gas by GC-Thermal Detector (GC-TCD):

To an oven dried Ace pressure tube (100 mL), 2-aminobenzamide **2.1a** (0.5 mmol, 1equiv.), benzyl alcohol **2.2a** (0.5 mmol, 1equiv.), NaO^{t}Bu (0.25 mmol, 50 mol%) and **Mn-2** (0.025 mmol, 5 mol%) were taken under argon atmosphere, after that 2 mL of xylene was added to the reaction mixture and placed in a preheated oil-bath at 140 °C for 36 h. Afterwards, the crude reaction mixture was subjected to cool at room temperature and the head gas was collected by a 1 mL gas-tight syringe and analysed by GC-TCD with a Carbon plot capillary column gas chromatography which showed the presence of H_2 gas at retention time 1.097 (Figure **2.3**).



Back Signal
Results

Retention Time	Area	Area %	Height	Height %
1.097	1135597	41.61	119888	57.58
1.453	98789	3.62	13423	6.45
2.043	1470898	53.90	70167	33.70

Figure 2.3. Gas Chromatography Spectrum for evolved gas (TCD mode)

2.5.12.3. Detection of hydrogen gas by dual catalysis:

Initially, the intermediate 2-phenyl-2, 3-dihydroquinazolin-4(1H)-one **2.9** (2 mmol), **Mn-2** (5 mol%) and NaO^{t}Bu (1 mmol, 50 mol%) were taken in an oven dried 10 mL round bottomed flask (**A**). The entire system was degassed, flushed with argon for 5 minutes (three times) and packed with 14 joint rubber septa upon which dry xylene (2 mL) was added. To an another 10 mL round bottomed flask (**B**) Wilkinson's catalyst *i.e.* $RhCl(PPh_3)_3$ (6 mol%) catalyst, and styrene (0.5 mmol) were dissolved in benzene (2 mL) and also packed with 14 joint rubber septum. Both the flasks (**A** & **B**) were connected through a double headed syringe and allowed to equilibrate for 5 minutes. The mixture in the flask (**A**) was heated at 140 °C (oil-bath temperature), whilst the mixture in the flask (**B**) was stirred at 60 °C (oil-bath temperature).

2.5.12.4. Manganese catalyzed dehydrogenation of intermediate 2-phenyl-2, 3-dihydroquinazolin-4(1H)-one (4.9) to product Quinazolin-4(3H)-one (4.3a) in presence of catalytic amount (5 mol%) of base:

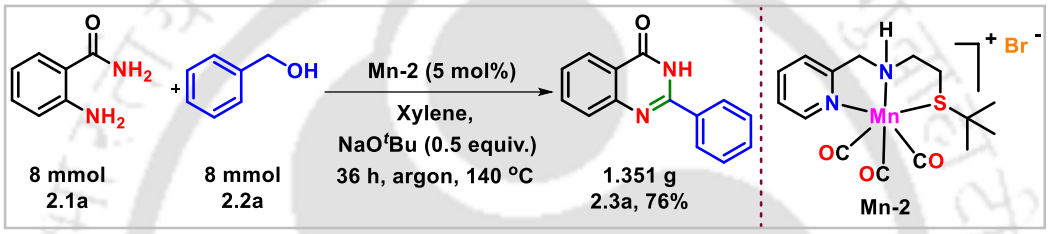
To an oven dried Ace pressure tube (100 mL), the intermediate 2-phenyl-2, 3-dihydroquinazolin-4(1H)-one **2.9** (0.5 mmol), **Mn-2** (5 mol%), NaO^{t}Bu (0.025 mmol, 5 mol%) and xylene (2 mL) were taken under argon atmosphere and the pressure tube was then placed in a preheated oil bath at 140 °C for 36 h. Afterwards, the crude reaction mixture was subjected to cool at room temperature and the head gas

was collected by a 1 mL gas-tight syringe and analysed by GC-TCD with a Carbon plot capillary column gas chromatography which underpin the presence of H_2 gas in the reaction.

2.5.13. Gram scale synthesis:

To an oven dried 50 mL round bottomed flask 2-aminobenzamide **2.1a** (8 mmol), benzyl alcohol **2.2a** (8 mmol), NaO^{t}Bu (4 mmol, 50 mol%) and **Mn-2** (5 mol%) were taken under argon atmosphere, then xylene was added to the reaction mixture. The resulting mixture was then placed into a preheated oil bath at 140 °C for 36 h. Upon completion, the reaction was cooled to room temperature, ethyl acetate and methanol was added to it to make it dilute and filtered through celite. The filtrate was concentrated under vacuum, the residue was purified by column chromatography over silica gel (100-200 mesh) with hexane/ethyl acetate mixture (20%) as eluent. 76% of the desired product 2-phenyl quinazolin-4(3H)-one **2.3a** was obtained. Yield 76% (1.351 g).

2.5.14. Calculation of green chemistry metrics:



2-aminobenzamide — Chemical formula: $C_7H_8N_2O$ — Molecular weight = 136.15 — Exact mass = 136. 0637

Benzyl alcohol — Chemical formula: C_7H_8O — Molecular weight = 108.14 — Exact mass = 108.0575

2-phenyl quinazolin-4(3H)-one — Chemical formula: $C_{14}H_{10}N_2O$ — Molecular weight = 222.25 — Exact mass = 222.0793

Total molecular weight of the reactant = (136. 0637+ 108.0575) = 244.1212

Product yield = 76%

Reactant-1	2-aminobenzamide	1.089 g	FW= 136.15
Reactant-2	Benzyl alcohol	0.865 g	FW= 108.14
Base	NaO^{t}Bu	0.384 g	FW= 96.105
Solvent	Xylene	6.943 g	FW= 106.16
Auxiliary	-	-	-
Product	2-phenyl quinazolin-4(3H)-one	1.351 g	FW= 222.25

Total weight = (1.089+0.865+0.384) g = 2.338 g

1. **E factor** = [(2.338–1.351)/1.351] = 0.987/1.351 = 0.731 *i.e.* 0.731 kg waste per 1 kg of product

2. **Atom economy** = [(Molecular mass of desired product/ Molecular masses of reactants) × 100%]

= [{222.0793/ (136.0637+108.0575)} × 100%]

= [{222.0793/ 244.1212} × 100%] = 91%

3. **Atom efficiency** = [Percentage yield × (Atom economy/ 100)]
= [76 × (91/ 100] = 69.16%

4. **Carbon efficiency** = [(Number of carbon atoms in desire product/ Number of carbon atoms in reactants) × 100%]

Here, number of carbon atoms in desire product = 14 and total number of carbon atoms in reactants = (7+7) = 14

Therefore, **carbon efficiency** = [(14/14) × 100] = 100%

5. **Reaction mass efficiency** = [(Actual mass of desired product/ Actual mass of reactants) × 100%]
= [{1.351/ (1.089+0.865)} × 100]
= [(1.351/1.954) × 100] = 69.14%

2.5.15. Kinetic experiments:

2.5.15.1. Monitoring the kinetics of the reaction:

2.5.15.1.1. Experimental procedure: To an oven dried 10 mL 2-neck round bottomed flask, 2-aminobenzamide **2.1a** (1.0 mmol, 1equiv.), benzyl alcohol **2.2a** (1.0 mmol, 1equiv.), NaO^{t}Bu (0.5 mmol, 50 mol%) and **Mn-2** (0.05 mmol, 5 mol%), mesitylene (1.0 mmol, 1 equiv.) as an internal standard and xylene as a solvent were added under argon to make up the total volume of the reaction mixture 2 mL. Afterwards, the reaction mixture was kept in a preheated oil bath for stirring at 140 °C. At regular intervals (1 h, 2 h, 3 h, 4 h, 8 h, 12 h, 16 h, 20 h, 24 h, 28 h, 32 h, 36 h) the reaction mixture was cooled to ambient temperature and an aliquot of mixture was taken in a GC vial. The GC sample was diluted with methanol and subjected to gas chromatographic analysis. The concentration of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of the product (mmol) *vs* time (h) plot **(Figure 2.2, a)**.

2.5.15.2. Rate order determination:

The initial rate method was used to determine the rate order of the 2-phenyl quinazolin-4(3H)-one **2.3a** synthesis reaction with respect to various components of the reaction. The data of the concentration (mM) *vs* time (h) plot was fitted to linear using origin pro 9. The slope of the linear fitted curve represents the initial rate of the reaction. The order of the reaction was determined by plotting initial rate (mM/h) *vs* concentration (mM) of that particular component.

2.5.15.2.1. Rate order determination with respect to benzyl alcohol (2.2a):

To determine the order of the 2-phenyl quinazolin-4(3H)-one **2.3a** synthesis reaction, initial rates at different initial concentration of benzyl alcohol **2.2a** were recorded.

2.5.15.2.1.1. Experimental procedure: To an oven dried 10 mL 2-neck round bottomed flask, 2-aminobenzamide **2.1a** (0.5 mmol, 1equiv.), NaO^{t}Bu (0.25 mmol, 50 mol%) and **Mn-2** (0.025 mmol, 5 mol%), mesitylene (0.5 mmol, 1 equiv.) as an internal standard, specific amount of benzyl alcohol **2.2a** and xylene as a solvent were added under argon to make up the total volume of the reaction mixture 2 mL. Afterwards, the reaction mixture was kept in an oil bath of 140 °C for stirring. At regular intervals

(1 h, 2 h, 3 h, 4 h, 5 h, 6 h) the reaction mixture was cooled to ambient temperature and an aliquot of mixture was taken in a GC vial. The GC sample was diluted with methanol and subjected to gas chromatographic analysis. The concentration of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of the product (mM) *vs* time (h) plot **(Figure 2.2, b)**. The rate of the reaction at different initial concentration of benzyl alcohol **2.2a** was given below and used to plot the initial rate (mM/h) *vs* concentration of benzyl alcohol **2.2a** (mM) to determine the order of the reaction with respect to benzyl alcohol **2.2a (Figure 2.2, c)**.

2.5.15.3. Rate order determination of third step of the reaction with respect to intermediate 2.9:

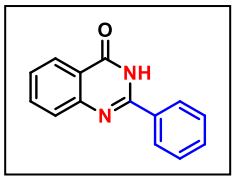
2.5.15.3.1. Experimental procedure: To an oven dried 10 mL 2-neck round bottomed flask, intermediate **2.9** (0.2 mmol), NaO^{t}Bu (0.1 mmol, 50 mol%) and **Mn-2** (0.01 mmol, 5 mol%), mesitylene (0.2 mmol, 1 equiv.) as an internal standard and xylene as a solvent were added under argon to make up the total volume of the reaction mixture 2 mL. Afterwards, the reaction mixture was kept in an oil bath of 140 °C for stirring. At regular intervals (1 h, 2 h, 3 h, 4 h, 5 h, 6 h) the reaction mixture was cooled to ambient temperature and an aliquot of mixture was taken in a GC vial. The GC sample was diluted with methanol and subjected to gas chromatographic analysis. The concentration of the consumption of intermediate **2.9** was determined with respect to mesitylene internal standard. The same analysis was repeated taking 0.3 mmol and 0.4 mmol of the intermediate **2.9** and with respect to its internal standard, base and catalyst were taken. The data was accomplished to draw the concentration of the consumption of intermediate **2.9** (mM) *vs* time (h) plot **(Figure 2.2, d)**. The rate of the reaction (mM/h) at different initial concentration of intermediate **2.9** was plotted with respect to concentration of initial concentration of intermediate **2.9** (mM) to determine the order of the reaction with respect to intermediate **2.9 (Figure 2.2, e)**.

2.5.16. Post-synthetic modification:

To an oven dried 10 mL round bottomed flask, 2-aminobenzamide **2.1** (1.0 mmol), Quinolin-2-ylmethanol **2.2zn** (1.0 mmol), NaO^{t}Bu (0.5 mmol) and **Mn-2** (5 mol%) were taken under argon atmosphere, after that 3 mL of xylene was added to the reaction mixture. The resulting mixture was heated in an oil bath at 140 °C for 36 h. After the completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate and methanol were added to dilute the mixture and filtered through celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel (100-200 mess) column chromatography using 20% ethyl acetate in hexane to obtain the desired 2-(quinolin-2-yl)quinazolin-4(3H)-one (**2.3zn**) in 82% yield as a white solid. The remaining steps towards the synthesis of alkaloids Luotonins A, B and E were reported in literature.[20]

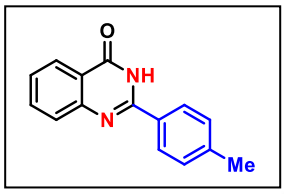
2.5.17. Analytical data:

2-phenylquinazolin-4(3H)-one (2.3a):[23]



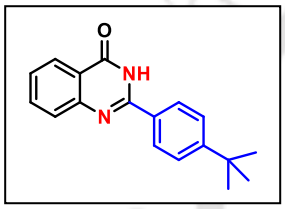
White solid, 86% Yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 11.71 (brs, 1H, NH), 8.34 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.28 – 8.25 (m, 2H), 7.85 – 7.80 (m, 2H), 7.62 – 7.59 (m, 3H), 7.53 – 7.50 (m, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.8, 151.8, 149.6, 135.1, 132.9, 131.8, 129.2, 128.1, 127.4, 127.0, 126.5, 121.0.

2-(p-tolyl)quinazolin-4(3H)-one (2.3b):[23]



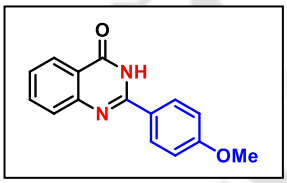
White solid, 80% Yield. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 12.49 (brs, 1H, NH), 8.14 (d, *J* = 7.9, 1H), 8.10 (d, *J* = 8.2 Hz, 2H), 7.84 –7.81 (m, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 162.3, 152.3, 148.9, 141.5, 134.6, 129.9, 129.2, 127.7, 127.5, 126.5, 125.9, 120.9, 21.0.

2-(4-(tert-butyl)phenyl)quinazolin-4(3H)-one (2.3c):[24]



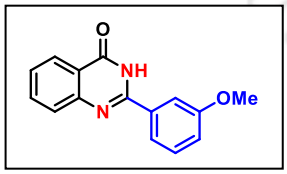
White solid, 80% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.31 (brs, 1H, NH), 8.16 – 8.12 (m, 3H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 1.32 (s, 9H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 162.3, 154.3, 152.3, 148.8, 134.6, 129.9, 127.6, 127.3, 126.4, 125.8, 125.4, 120.9, 34.7, 30.9.

2-(4-methoxyphenyl)quinazolin-4(3H)-one (2.3d):[23]



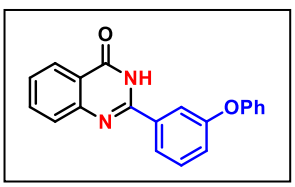
White solid, 75% Yield. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 12.43 (brs, 1H, NH), 8.19 (d, *J* = 8.9 Hz, 2H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.83 –7.80 (m, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 7.1 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 162.4, 161.9, 151.9, 149.0, 134.7, 129.5, 127.4, 126.2, 125.9, 124.8, 120.7, 114.1, 55.5.

2-(3-methoxyphenyl)quinazolin-4(3H)-one (2.3e):[23]



White solid, 60% Yield. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 12.55 (brs, 1H, NH), 8.15 (d, *J* = 7.7 Hz 1H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.75 – 7.74 (m, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.14 (dd, *J* = 8.2, 2.7 Hz, 1H), 3.86 (s, 3H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 162.3, 159.4, 152.1, 148.6, 134.6, 134.1, 129.8, 127.5, 126.7, 125.9, 121.0, 120.2, 117.6, 112.5, 55.4.

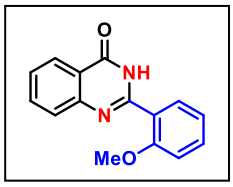
2-(3-phenoxyphenyl)quinazolin-4(3H)-one (2.3f):[25]



White solid, 73% Yield. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 12.60 (brs, 1H, NH), 8.14 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.23 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.19 (t, *J* = 7.4 Hz,

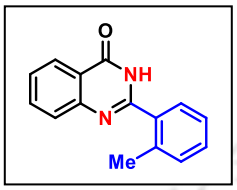
1H), 7.09 (d, *J* = 7.8 Hz, 2H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 162.2, 156.9, 156.4, 151.6, 148.6, 134.7, 130.4, 130.2, 127.6, 126.8, 125.9, 123.8, 122.9, 121.7, 121.1, 118.9, 117.9.

2-(2-methoxyphenyl)quinazolin-4(3H)-one (2.3g):[26]



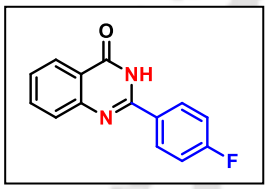
White solid, 52% Yield. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 12.09 (brs, 1H, NH), 8.15 (d, *J* = 8.0 Hz, 1H), 7.84 – 7.81 (m, 1H), 7.72 – 7.69 (m, 2H), 7.55 – 7.51 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 3.86 (s, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 161.2, 157.2, 152.3, 149.0, 134.3, 132.2, 130.4, 127.3, 126.5, 125.7, 122.6, 121.0, 120.4, 111.9, 55.8.

2-(o-tolyl)quinazolin-4(3H)-one (2.3h):[23]



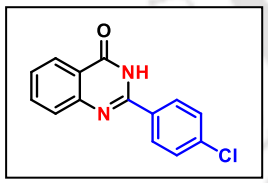
White solid, 50% Yield. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 10.79 (brs, 1H, NH), 8.26 (d, *J* = 7.9 Hz, 1H), 7.80 – 7.79 (m, 2H), 7.58 – 7.56 (m, 1H), 7.51 – 7.48 (m, 1H), 7.43 – 7.40 (m, 1H), 7.35 – 7.32 (m, 2H), 2.53 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 163.3, 153.6, 149.3, 137.0, 135.0, 133.8, 131.6, 130.7, 128.9, 128.0, 127.1, 126.53, 126.4, 120.9, 20.2.

2-(4-fluorophenyl)quinazolin-4(3H)-one (2.3i):[23]



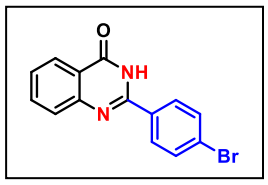
White solid, 75% Yield. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.57 (brs, 1H, NH), 8.27 – 8.24 (m, 2H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 8.8 Hz, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 164.0 (d, *J* = 247.9 Hz), 162.2, 151.4, 148.6, 134.6, 130.4 (d, *J* = 8.8 Hz), 129.2 (d, *J* = 3.0 Hz), 127.4, 126.6, 125.8, 120.9, 115.6 (d, *J* = 21.8 Hz). ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -109.07.

2-(4-chlorophenyl)quinazolin-4(3H)-one (2.3j):[23]



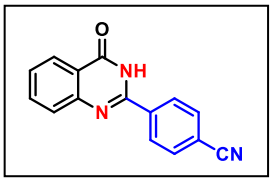
White solid, 72% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.60 (brs, 1H, NH), 8.20 (d, *J* = 8.3 Hz, 2H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 162.1, 151.3, 148.6, 136.3, 134.6, 131.5, 129.6, 128.6, 127.5, 126.74, 125.8, 121.0.

2-(4-bromophenyl)quinazolin-4(3H)-one (2.3k):[23]



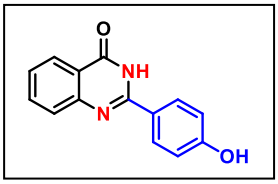
White solid, 68% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.59 (brs, 1H, NH), 8.16 – 8.11 (m, 3H), 7.86 – 7.75 (m, 4H), 7.55 – 7.52 (m, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 162.1, 151.4, 148.6, 134.6, 131.9, 131.6, 129.8, 127.5, 126.8, 125.9, 125.2, 121.0.

4-(4-oxo-3,4-dihydroquinazolin-2-yl)benzonitrile (2.3l):[27]



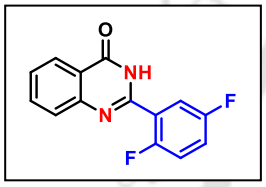
White solid, 34% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.73 (brs, 1H, NH), 8.33 (d, *J* = 8.2 Hz, 2H), 8.17 (d, *J* = 7.7 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.86 (t, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 162.1, 150.9, 148.4, 136.9, 134.8, 132.5, 128.6, 127.7, 127.2, 125.9, 121.2, 118.3, 113.6.

2-(4-hydroxyphenyl)quinazolin-4(3H)-one (2.3n):[28]



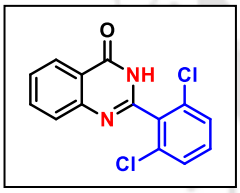
White solid, 52% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.29 (brs, 1H, NH), 10.16 (s, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 2H), 7.78 (t, *J* = 7.2 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 162.3, 160.6, 152.1, 149.1, 134.5, 129.6, 127.2, 125.9, 125.8, 123.3, 120.6, 115.4.

2-(2,5-difluorophenyl)quinazolin-4(3H)-one (2.3o):[29]



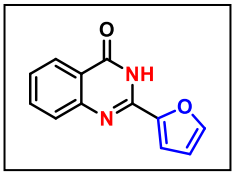
White solid, 65% Yield. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.62 (brs, 1H, NH), 8.17 (d, *J* = 8.4 Hz, 1H), 7.86 (t, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.66 – 7.62 (m, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.50 – 7.44 (m, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 161.5, 157.8 (dd, *J* = 239.8 Hz, 2.2 Hz), 155.8 (dd, *J* = 245.4 Hz, 2.4 Hz), 148.8, 148.4, 134.7, 129.2, 127.3, 125.9, 123.5 (dd, *J* = 15.7 Hz, 8.5 Hz), 121.2, 119.3 (dd, *J* = 24.0 Hz, 9.0 Hz), 118.0 (dd, *J* = 24.4 Hz, 8.7 Hz), 117.4 (dd, *J* = 25.9, 2.9 Hz).

2-(2,6-dichlorophenyl)quinazolin-4(3H)-one (2.3p):[23]



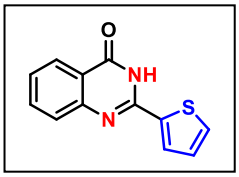
White solid, 48% Yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 11.52 (brs, 1H, NH), 8.16 (d, *J* = 8.0 Hz, 1H), 7.83 – 7.82 (m, 2H), 7.55 – 7.52 (m, 1H), 7.44 – 7.42 (m, 2H), 7.41 – 7.38 (m, 1H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 163.3, 149.2, 148.9, 135.0, 134.7, 132.8, 131.8, 128.4, 128.2, 127.7, 126.6, 121.4.

2-(furan-2-yl)quinazolin-4(3H)-one (2.3q):[23]



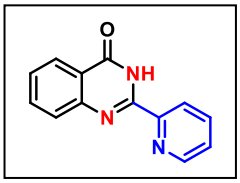
Yellow solid, 76% Yield. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 11.97 (brs, 1H, NH), 8.28 (d, *J* = 7.9 Hz, 1H), 7.79 – 7.77 (m, 1H), 7.76 – 7.72 (m, 1H), 7.67 – 7.66 (m, 2H), 7.46 – 7.42 (m, 1H), 6.63 – 6.62 (m, 1H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 163.4, 149.5, 146.4, 145.8, 143.8, 135.0, 127.8, 126.7, 126.5, 121.0, 114.3, 112.8.

2-(thiophen-2-yl)quinazolin-4(3H)-one (2.3r):[24]



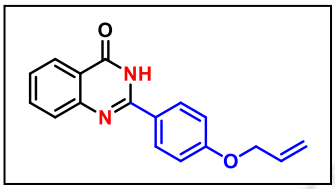
White solid, 80% Yield. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 12.66 (brs, 1H, NH), 8.23 (d, *J* = 3.7 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 5.2 Hz, 1H), 7.81 – 7.78 (m, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 5.0 Hz, 1H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 161.8, 148.6, 147.9, 137.4, 134.7, 132.2, 129.4, 128.5, 127.0, 126.4, 126.0, 120.9.

2-(pyridin-2-yl)quinazolin-4(3H)-one (2.3s):[23]



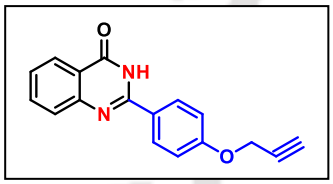
White solid, 78% Yield. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.85 (brs, 1H, NH), 8.75 (d, *J* = 4.5 Hz, 1H), 8.44 (d, *J* = 8.2 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 8.07 (t, *J* = 7.7 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.56 (t, *J* = 7.5 Hz, 1H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 160.8, 150.0, 149.0, 148.7, 148.4, 138.0, 134.7, 127.7, 127.3, 126.6, 126.1, 122.2, 122.0.

2-(4-(allyloxy)phenyl)quinazolin-4(3H)-one (2.3t):



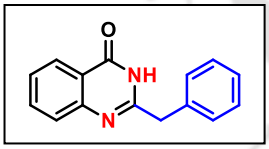
White solid, 60% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.36 (brs, 1H, NH), 8.19 – 8.16 (m, 2H), 8.13 (dd, *J* = 7.8 Hz, 1.0 Hz, 1H), 7.81 – 7.78 (m, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.10 – 7.08 (m, 2H), 6.09 – 6.02 (m, 1H), 5.42 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.29 (dd, *J* = 10.5, 1.8 Hz, 1H), 4.67 – 4.65 (m, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 162.3, 160.8, 151.8, 148.9, 134.5, 133.3, 131.3, 129.4, 127.3, 126.1, 125.8, 124.9, 120.7, 117.7, 114.7, 114.4, 68.4. HRMS (ESI) m/z (M+H): 279.1134, found: 279.1164.

2-(4-(prop-2-yn-1-yloxy)phenyl)quinazolin-4(3H)-one (2.3u):



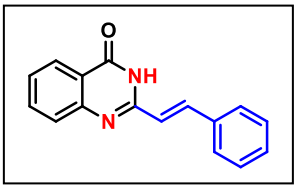
White solid, 58% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.39 (brs, 1H, NH), 8.19 (d, *J* = 8.5 Hz, 2H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 4.91 (s, 2H), 3.60 (s, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 162.3, 159.7, 151.8, 148.9, 134.5, 129.4, 128.3, 127.3, 126.2, 125.8, 125.6, 120.7, 114.9, 78.9, 78.6, 55.7. HRMS (ESI) m/z (M+H): 277.0977, found: 277.0976.

2-benzylquinazolin-4(3H)-one (2.3v):[14a]



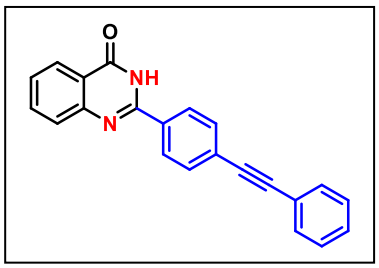
White solid, 72% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.38 (brs, 1H, NH), 8.10 – 8.07 (m, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.96 (s, 1H), 7.91 (d, *J* = 7.4 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.67 (t, *J* = 8.8 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.38 – 7.32 (m, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 162.2, 141.4, 137.9, 134.6, 132.6, 132.0, 129.9, 129.2, 128.5, 128.3, 127.7, 126.5, 126.4, 125.8, 124.9, 120.9, 20.9.

(E)-2-styrylquinazolin-4(3H)-one (2.3w):[30]



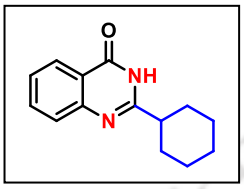
White solid, 58% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.30 (brs, 1H, NH), 8.11 (d, *J* = 7.9 Hz, 1H), 7.95 (d, *J* = 16.2 Hz, 1H), 7.80 (t, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 8.8 Hz, 3H), 7.48 – 7.44 (m, 3H), 7.42 –7.39 (m, 1H), 7.01 (d, *J* = 16.2 Hz, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 161.7, 151.4, 149.0, 138.2, 135.0, 134.4, 129.7, 129.0, 127.6, 127.1, 126.2, 125.8, 121.1.

2-(4-(phenylethynyl)phenyl)quinazolin-4(3H)-one (2.3x):



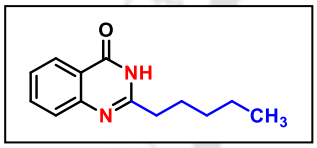
White solid, 54% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.65 (brs, 1H, NH), 8.30 (d, *J* = 8.2 Hz, 2H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.90 (t, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.67 – 7.65 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.52 – 7.50 (m, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 162.1, 151.5, 148.6, 134.6, 132.5, 131.5, 131.4, 129.2, 128.8, 128.0, 127.5, 126.7, 125.9, 125.1, 121.9, 121.0, 91.7, 88.7. HRMS (ESI) m/z (M+H): 323.1184, found: 323.1214.

2-cyclohexylquinazolin-4(3H)-one (2.3y):[31]



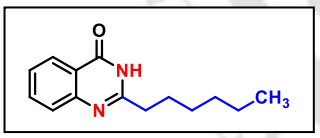
White solid, 60% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.04 (brs, 1H, NH), 8.07 (dd, *J* = 7.9 Hz, 1.4 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 2.59 – 2.53 (m, 1H), 1.90 (d, *J* = 11.4 Hz, 2H), 1.78 (d, *J* = 13.0 Hz, 2H), 1.67 (d, *J* = 12.1 Hz, 1H), 1.61 – 1.53 (m, 2H), 1.37 – 1.11 (m, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 161.8, 160.7, 148.9, 134.1, 126.9, 125.8, 125.6, 120.9, 42.8, 30.1, 25.5, 25.3.

2-pentylquinazolin-4(3H)-one (2.3zb):[32]



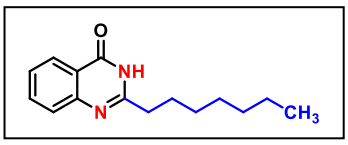
White solid, 50% Yield. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 11.82 (brs, 1H, NH), 8.29 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 2.79 (t, J = 7.5 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.48 – 1.38 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 164.4, 157.1, 149.6, 134.9, 127.4, 126.5, 126.4, 120.7, 36.1, 31.5, 27.4, 22.5, 14.1.

2-hexylquinazolin-4(3H)-one (2.3zc):



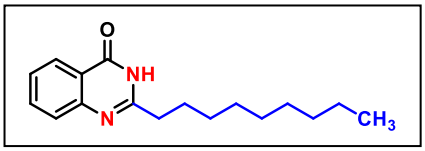
White solid, 53% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.12 (brs, 1H, NH), 8.07 (d, *J* = 7.9 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 2.58 (t, *J* = 7.6 Hz, 2H), 1.73 – 1.67 (m, 2H), 1.31 – 1.23 (m, 6H), 0.83 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 161.8, 157.4, 148.9, 134.1, 126.7, 125.8, 125.6, 120.7, 34.4, 30.9, 28.1, 26.7, 21.9, 13.8. HRMS (ESI) m/z (M+H): 231.1497, found: 231.1519.

2-heptylquinazolin-4(3H)-one (2.3zd):[33]



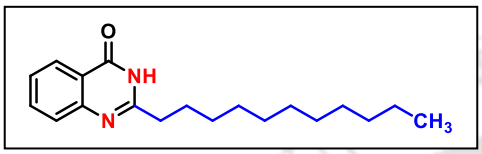
White solid, 56% Yield. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 12.14 (brs, 1H, NH), 8.20 (d, *J* = 7.9 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 2.72 (t, *J* = 7.9 Hz, 2H), 1.83 – 1.77 (m, 2H), 1.41 – 1.20 (m, 8H), 0.78 (t, *J* = 6.2 Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 164.6, 157.3, 149.7, 134.8, 127.3, 126.4, 126.3, 120.6, 36.0, 31.8, 29.3, 29.0, 27.7, 22.7, 14.1.

2-nonylquinazolin-4(3H)-one (2.3ze):[34]



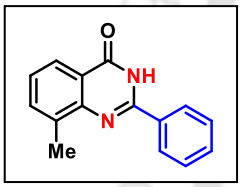
White solid, 60% Yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 12.28 (brs, 1H, NH), 8.18 (d, *J* = 7.9 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.37 – 7.33 (m, 1H), 2.71 (t, *J* = 7.9 Hz, 2H), 1.83 – 1.77 (m, 2H), 1.40 – 1.34 (m, 2H), 1.26 – 1.15 (m, 10H), 0.77 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 164.7, 157.4, 149.6, 134.8, 127.2, 126.3, 126.2, 120.5, 36.0, 31.9, 29.5, 29.4, 27.7, 22.7.

2-undecylquinazolin-4(3H)-one (2.3zf):[35]



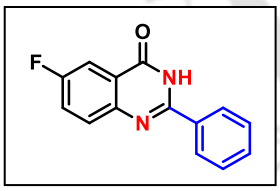
White solid, 62% Yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 12.11 (brs, 1H, NH), 8.27 (d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 2.79 (t, *J* = 7.9 Hz , 2H), 1.90 – 1.84 (m, 2H), 1.47 – 1.42 (m, 2H), 1.28 – 1.23 (m, 14H), 0.86 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 164.6, 157.2, 149.7, 134.9, 127.3, 126.4, 126.3, 120.6, 36.0, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 27.7, 22.8, 14.2.

8-methyl-2-phenylquinazolin-4(3H)-one (2.3zg):[24]



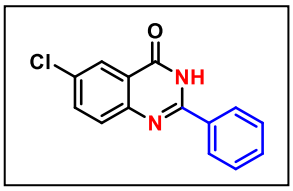
White solid, 74% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.50 (brs, 1H, NH), 8.23 (d, *J* = 7.7 Hz, 2H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.58 – 7.53 (m, 3H), 7.39 (t, *J* = 7.6 Hz, 1H), 2.62 (s, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 162.5, 151.0, 147.1, 135.6, 134.9, 133.0, 131.3, 128.6, 127.7, 126.0, 123.5, 120.9, 17.1.

6-fluoro-2-phenylquinazolin-4(3H)-one (2.3zh):[36]



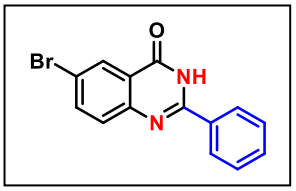
White solid, 72% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.63 (brs, 1H, NH), 8.16 (d, *J* = 7.4 Hz, 2H), 7.83 – 7.80 (m, 2H), 7.72 (t, *J* = 8.7 Hz, 1H), 7.60 – 7.53 (m, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 161.7, 160.1 (d, *J* = 244.0 Hz), 151.9, 145.6, 132.5, 131.4, 130.3, 128.6, 127.7, 123.0 (d, *J* = 24.1 Hz), 122.2 (d, *J* = 8.4 Hz), 110.5 (d, *J* = 23.2 Hz).

6-chloro-2-phenylquinazolin-4(3H)-one (2.3zi):[36]



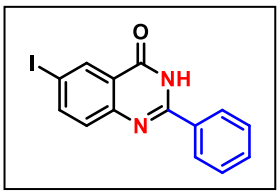
White solid, 68% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.68 (brs, 1H, NH), 8.18 (d, *J* = 7.2 Hz, 2H), 8.09 (d, *J* = 2.5 Hz, 1H), 7.86 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.62 – 7.54 (m, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 161.2, 152.8, 147.5, 134.6, 132.4, 131.5, 130.7, 129.7, 128.6, 127.8, 124.8, 122.2.

6-bromo-2-phenylquinazolin-4(3H)-one (2.3zj):[23]



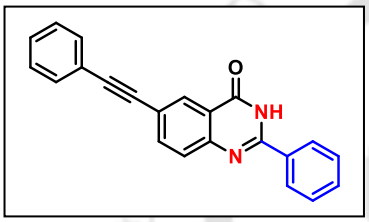
White solid, 62% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.68 (brs, 1H, NH), 8.22 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 2H), 7.96 (d, *J* = 6.8 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.61 – 7.53 (m, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 161.1, 152.8, 147.7, 137.3, 132.4, 131.5, 129.8, 128.5, 127.9, 127.8, 122.6, 118.8.

6-iodo-2-phenylquinazolin-4(3H)-one (2.3zk):[23]



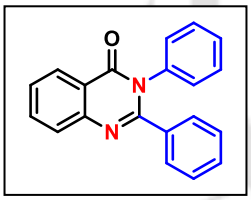
White solid, 56% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.50 (brs, 1H, NH), 8.19 – 8.14 (m, 3H), 7.82 (t, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.49 (m, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 162.2, 152.3, 148.7, 134.5, 132.7, 131.3, 128.6, 127.7, 127.5, 126.5, 125.8, 121.0.

2-phenyl-6-(phenylethynyl)quinazolin-4(3H)-one (2.3zl):



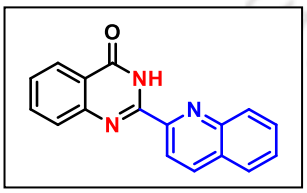
White solid, 58% Yield. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 12.68 (brs, 1H, NH), 8.25 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.61 – 7.54 (m, 5H), 7.45 – 7.44 (m, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 161.4, 153.1, 148.5, 136.7, 132.4, 131.5, 131.4, 129.0, 128.8, 128.7, 128.6, 128.1, 127.8, 122.0, 121.2, 120.1, 90.5, 88.5. HRMS (ESI) m/z (M+H): 323.1184, found: 323.1177.

2,3-diphenylquinazolin-4(3H)-one (2.3zm):[37]



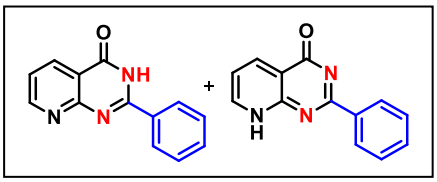
White solid, 52% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 8.21 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.92 – 7.88 (m, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.38 – 7.36 (m, 2H), 7.33 – 7.28 (m, 4H), 7.27 – 7.19 (m, 4H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 161.3, 155.1, 147.2, 137.8, 135.6, 134.7, 129.5, 128.9, 128.8, 128.5, 128.1, 127.4, 127.4, 127.1, 126.4, 120.7.

2-(quinolin-2-yl)quinazolin-4(3H)-one (2.3zn):[23]



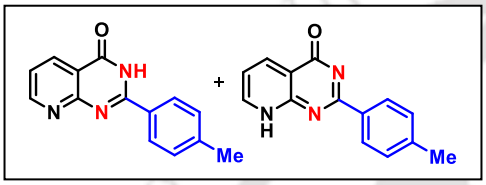
White solid, 82% Yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 11.13 (brs, 1H, NH), 8.57 (d, *J* = 8.6 Hz, 1H), 8.33 (d, *J* = 7.9 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.83 – 7.81 (m, 2H), 7.75 (q, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 161.4, 149.2, 149.0, 148.1, 146.8, 137.6, 134.6, 130.5, 129.7, 129.3, 128.3, 128.2, 127.8, 127.6, 126.8, 122.7, 118.5.

2-phenylpyrido[2,3-d]pyrimidin-4(3H)-one and 2-phenylpyrido[2,3-d]pyrimidin-4(8H)-one (2.5a+2.5a'):[38]



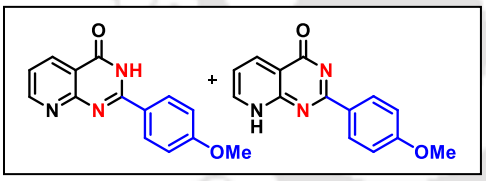
White solid, 74% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.79 (brs, 1H, NH), 8.97 – 8.96 (m, 1H), 8.55 – 8.51 (m, 2H), 8.22 (d, *J* = 7.6 Hz, 2H), 8.14 – 8.13 (m, 1H), 7.96 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.63 – 7.61 (m, 1H), 7.58 – 7.55 (m, 2H), 7.54 – 7.51 (m, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.35 (m, 1H), 7.32 – 7.29 (m, 1H), 6.70 – 6.68 (m, 1H), 5.83 (brs, 1H, NH). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 162.7, 157.4, 156.0, 155.4, 152.8, 142.2, 135.7, 135.5, 132.4, 131.9, 128.6, 128.4, 128.3, 128.0, 126.2, 122.2, 116.1, 113.7, 109.5, 65.1.

2-(p-tolyl)pyrido[2,3-d]pyrimidin-4(3H)-one and 2-(p-tolyl)pyrido[2,3-d]pyrimidin-4(8H)-one (2.5b+2.5b'):



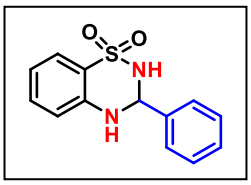
White solid, 72% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.68 (brs, 1H, NH), 8.95 (s, 1H), 8.52 (s, 2H), 8.13 (s, 3H), 7.93 – 7.83 (m, 2H), 7.51 (s, 1H), 7.37 – 7.30 (m, 3H), 7.16 (s, 1H), 6.69 (s, 1H), 5.79 (brs, 1H, NH), 2.39 (s, 3H), 2.26 (s, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 163.0, 162.7, 159.0, 157.4, 156.0, 155.3, 152.6, 142.1, 139.2, 137.5, 135.7, 135.5, 129.6, 129.2, 128.8, 128.0, 126.1, 122.0, 116.0, 113.6, 109.6, 65.0, 21.0, 20.6. HRMS (ESI) m/z (M+H): 238.0980, found: 238.0974.

2-(4-methoxyphenyl)pyrido[2,3-d]pyrimidin-4(3H)-one and 2-(4-methoxyphenyl)pyrido[2,3-d]pyrimidin-4(8H)-one (2.5c+2.5c'):



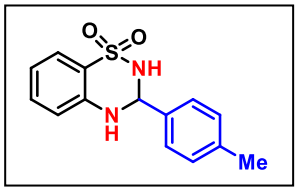
White solid, 70% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.65 (brs, 1H, NH), 8.94 (s, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 8.24 (d, *J* = 8.7 Hz, 2H), 7.50 – 7.47 (m, 1H), 7.36 – 7.34 (m, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 1H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 162.8, 162.4, 159.3, 158.7, 157.5, 156.0, 155.0, 152.7, 135.7, 135.5, 134.1, 129.9, 128.3, 127.6, 124.4, 121.8, 115.8, 114.1, 113.7, 109.5, 64.9, 55.5, 55.1. HRMS (ESI) m/z (M+H): 254.0930, found: 254.0923.

3-phenyl-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7a):[18b]



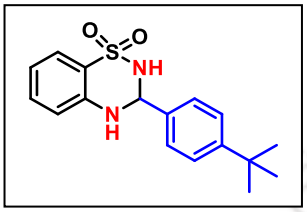
White solid, 62% Yield. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 7.89 (d, *J* = 12.1 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.38 (s, 1H), 7.35 – 7.31 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 5.81 (d, *J* = 12.1 Hz, 1H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 143.9, 137.3, 132.8, 129.1, 128.5, 127.5, 123.7, 121.7, 116.7, 116.4, 68.4.

3-(p-tolyl)-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7b):[18b]



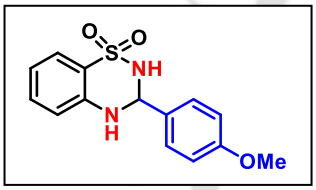
White solid, 60% Yield. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 7.84 (d, *J* = 12.1 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 5.74 (d, *J* = 12.1 Hz, 1H), 2.35 (s, 3H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 143.9, 138.5, 134.4, 132.8, 129.0, 127.4, 123.7, 121.6, 116.6, 116.4, 68.2, 20.8.

3-(4-(tert-butyl)phenyl)-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7c):



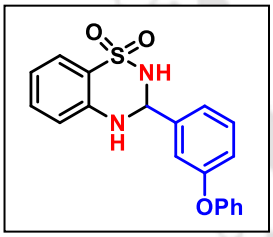
White solid, 65% Yield. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.84 (d, *J* = 12.0 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.36 (s, 1H), 7.33 – 7.28 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 5.75 (d, *J* = 12.0 Hz, 1H), 1.31 (s, 9H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 151.7, 143.9, 134.4, 132.7, 127.2, 125.2, 123.6, 121.6, 116.6, 116.3, 68.1, 34.4, 31.0. HRMS (ESI) m/z (M+H): 317.1324, found: 317.1349.

3-(4-methoxyphenyl)-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7d):[39]



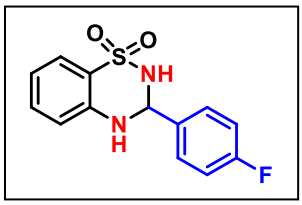
White solid, 56% Yield. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 7.83 (d, *J* = 12.1 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.33 – 7.30 (m, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 5.74 (d, *J* = 12.0 Hz, 1H), 3.79 (s, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 159.8, 143.9, 132.8, 129.5, 128.9, 123.7, 121.6, 116.6, 116.4, 113.8, 68.0, 55.3.

3-(3-phenoxyphenyl)-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7e):[40]



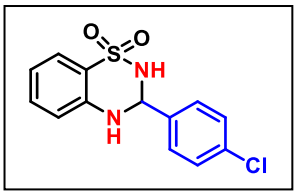
White solid, 58% Yield. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 7.96 (d, *J* = 11.8 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.47 – 7.40 (m, 6H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.07 – 7.05 (m, 3H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 5.80 (d, *J* = 11.8 Hz, 1H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 156.7, 156.4, 143.8, 139.3, 132.9, 130.2, 130.1, 123.8, 123.7, 122.8, 121.7, 119.3, 118.7, 117.8, 116.9, 116.4, 68.0.

3-(4-fluorophenyl)-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7f):[40]



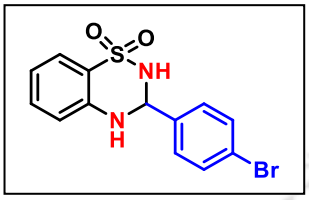
White solid, 60% Yield. **^{1}H NMR (600 MHz, $CDCl_3$ + DMSO-d_6)** δ 7.66 – 7.60 (m, 3H), 7.32 – 7.27 (m, 1H), 7.14 – 7.10 (m, 2H), 6.86 – 6.78 (m, 2H), 6.52 – 6.49 (m, 1H), 5.95 – 5.91 (m, 1H), 5.51 – 5.49 (m, 1H). **^{13}C NMR (150 MHz, $CDCl_3$ + DMSO-d_6)** δ 163.3 (d, *J* = 247.9 Hz), 143.0, 133.2, 133.0, 129.0 (d, *J* = 8.3 Hz), 124.5, 122.8, 118.6, 116.7, 115.9 (d, *J* = 21.7 Hz), 68.4.

3-(4-chlorophenyl)-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7g):[39]



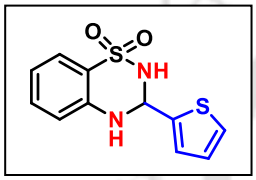
White solid, 63% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 7.93 (d, *J* = 12.0 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 3H), 7.38 (s, 1H), 7.35 – 7.31 (m, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.78 (t, *J* = 7.7 Hz, 1H), 5.82 (d, *J* = 12.0 Hz, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 143.7, 136.2, 133.6, 132.8, 129.4, 128.4, 123.7, 121.7, 116.9, 116.4, 67.6.

3-(4-bromophenyl)-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7h):[40]



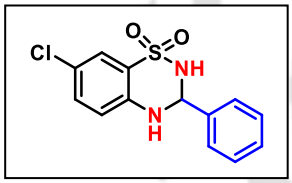
White solid, 65% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 7.92 (d, *J* = 12.0 Hz, 1H), 7.68 – 7.62 (m, 4H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.38 (s, 1H), 7.34 – 7.30 (m, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 5.80 (d, *J* = 12.0 Hz, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 143.7, 136.6, 132.8, 131.4, 129.7, 123.7, 122.2, 121.7, 116.9, 116.4, 67.7.

3-(thiophen-2-yl)-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7k):[40]



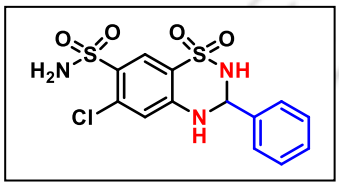
White solid, 60% Yield. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.08 (d, *J* = 11.7 Hz, 1H), 7.62 (d, *J* = 5.0 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.43 (d, *J* = 3.5 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.12 – 7.09 (m, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.08 (d, *J* = 11.6 Hz, 1H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 143.5, 140.1, 132.9, 126.8, 126.7, 126.6, 123.6, 121.8, 117.1, 116.5, 64.2.

7-chloro-3-phenyl-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide (2.7n):[41]



White solid, 58% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 8.03 (d, *J* = 12.0 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.60 (s, 1H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.48 -7.45 (m, 3H), 7.38 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 5.79 (d, *J* = 12.0 Hz, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 142.7, 136.8, 132.8, 129.2, 128.5, 127.5, 122.8, 122.2, 120.1, 118.4, 68.3.

6-chloro-3-phenyl-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide (2.7o):



White solid, 60% Yield. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 8.26 (s, 1H), 8.22 (d, *J* = 11.9 Hz, 1H), 8.07 (s, 1H), 7.68 – 7.66 (m, 2H), 7.52 – 7.48 (m, 5H), 7.10 (s, 1H), 5.90 (d, *J* = 11.8 Hz, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 146.6, 136.1, 134.4, 129.5, 128.6, 128.3, 127.5, 125.4, 118.6, 117.4, 68.3. HRMS (ESI) m/z (M+H): 374.0036, found: 374.0043.

2.6. References:

1. a) A. R. Katritzky, C. W. Rees, *Comprehensive Heterocyclic Chemistry II*, Eds., Elsevier, Oxford, **1996**; b) T. Nomura, Z. Z. Ma, Y. Hano, Y. J. Chen, *Heterocycles* **1997**, *46*, 541–546; c) I. J. S. Fairlamb, *Chem. Soc. Rev.* **2007**, *36*, 1036–1045; d) J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Blackwell, Oxford, UK, **2000**; e) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; f) B. Willy, T. J. J. Müller, *Curr. Org. Chem.* **2009**, *13*, 1777–1790.

2. a) I. Khan, A. Ibrar, N. Abbas, A. Saeed, *Eur. J. Med. Chem.* **2014**, *76*, 193–244; b) J. P. Michael, *Nat. Prod. Rep*. **2008**, *25*, 166–187; c) Y. Deng, R. Xu, Y. Ye, *J. Chin. Pharm. Sci.* **2000**, *9*, 116–118.

3. M. M. Ghorab, Z. H. Ismail, M. Abdalla, A. A. Radwan, *Arch. Pharm. Res.* **2013**, *36*, 660–670.

4. M. Zappala, S. Grasso, N. Micale, G. Zuccala, F. S. Menniti, G. Ferreri, G. De Sarro, C. De Micheli, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4427–4430.

5. N. K. Terrett, A. S. Bell, D. Brown, P. Ellis, *Bioorg. Med. Chem. Lett.***1996**, *6*, 1819–1822.

6. J. Kunes, J. Baz˘ant, M. Pour, K. Waisser, M. S˘losarek, J.´Janota, *Farmaco* **2000**, *55*, 725–729.

7. M. Chen, P. Li, D. Hu, S. Zeng, T. Li, L. Jin, W. Xue and B. Song, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 168–173.

8. a) H. Kikuchi, K. Yamamoto, S. Horoiwa, S. Hirai, R. Kasahara, N. Hariguchi, M. Matsumoto, Y. Oshima, *J. Med. Chem.* **2006**, *49*, 4698–4706; b) S. Kobayashi, M. Ueno, R. Suzuki, H. Ishitani, *Tetrahedron Lett.* **1999**, *40*, 2175–2178.

9. K.-i. Ozaki, Y. Yamada, T. Oine, T. Ishizuka, Y. Iwasawa, *J. Med. Chem.* **1985**, *28*, 568–576.

10. a) S.-L. Cao, Y.-P. Feng, Y.-Y. Jiang, S.-Y. Liu, G.-Y. Ding, R.-T. Li, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1915–1917; b) P. M. Chandrika, T. Yakaiah, A. R. R. Rao, B. Narsaiah, N. C. Reddy, V. Sridhar, J. V. Rao, *Eur. J. Med. Chem.* **2008**, *43*, 846–852.

11. a) W. Ge, X. Zhu, Y. Wei, *RSC Adv.*, **2013**, *3*, 10817–10822; b) Z. Zhang, M. Wang, C. Zhang, Z. Zhang, J. Lu, F. Wang, *Chem. Commun.* **2015**, *51*, 9205–9207; c) A. H. Romero, J. Salazar, S. E. Lopez, *Synthesis*, **2013**, *45*, 2043-2050.

12. a) R. J. Abdel-Jalil, W. Voelter, M. Saeed, *Tetrahedron Lett.* **2004**, *45*, 3475−3476; b) C. Balakumar, P. Lamba, D. Pran Kishore, B. Lakshmi Narayana, K. Venkat Rao, K. Rajwinder, A. Raghuram Rao, B. Shireesha, B. Narsaiah, *Eur. J. Med. Chem.* **2010**, *45*, 4904−4913; c) T. Hisano, M. Ichikawa, A. Nakagawa, M. Tsuji, *Chem. Pharm. Bull.* **1975**, *23*, 1910−1916; d) M. Bakavoli, A. Shiri, Z. Ebrahimpour, M. Rahimizadeh, *Chin. Chem. Lett.* **2008**, *19*, 1403−1406; e) M. Sharif, J. Opalach, P. Langer, M. Beller, X. Wu, *RSC Adv.* **2014**, *4*, 8−17; f) F.-C. Jia, Z.-W. Zhou, C. Xu, Y.-D. Wu, A.-X. Wu, *Org. Lett.* **2016**, *18*, 2942−2945.

13. a) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712; b) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140–144; c) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681–703; d) M. Maji, D. Panja, I. Borthakur, S. Kundu, *Org. chem. Front*. **2021**, *8*, 2673−2709; e) M. J. Hulsey, H. Yang, N. Yan, *ACS Sustainable Chem. Eng.* **2018**, *6*, 5694−5707; f) Q. Yang, Q. Wang, Z. Yu, *Chem. Soc. Rev.* **2015**, *44*, 2305−2329; g) K. Barta, P. C. Ford, *Acc. Chem. Res.* **2014**, *47*, 1503–1512; h) A. Mondal, R. Sharma, D. Pal, D. Srimani, *Eur. J. Org. Chem.* **2021**, *2021*, 3690–3720; i) K. Das, A. Mondal, D. Srimani, *J. Org. Chem*. **2018**, *83*, 9553−9560; j) K. Das, A. Mondal, D. Pal, D. Srimani, *Org. Lett*. **2019**, *9*, 3223–3227; k) K. Das, A. Mondal, D. Pal, H. K. Srivastava, D. Srimani, *Organometallics* **2019**, *8*, 1815–1825; l) K. Das, A. Mondal, D. Srimani, *Chem. Commun*. **2018**, *54*, 10582−10585; m) L. Alig, M. Fritz, S. Schneider, *Chem. Rev*. **2019**, *119*, 2681−2751; n) A. Kumar, P. Daw, D. Milstein, *Chem. Rev.* **2022**, *122*, 385−441.

14. a) J. Zhou, J. Fang, *J. Org. Chem.* **2011**, *76*, 7730-7736; b) F. Li, L. Lu, J. Ma, *Org. Chem. Front.* **2015**, *2*, 1589-1597; c) F. Li, L. Lu, P. Liu, *Org. Lett.* **2016**, *18*, 2580-2583; d) S. M. A. H. Siddiki, K. Kon, A. S. Touchy, K.-i. Shimizu, *Catal. Sci. Technol.* **2014**, *4*, 1716-1719; e) H. Hikawa, Y. Ino, H. Suzuki, Y. Yokoyama, *J. Org. Chem.* **2012**, *77*, 7046-7051; f) A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *Org. Biomol. Chem.* **2012**, *10*, 240-243. g) S. Balaji, G. Balamurugan, R. Ramesh, D. Semeril, *Organometallics* **2021**, *40*, 725-734; h) S. Parua, S. Das, R. Sikari, S. Sinha, N. D. Paul, *J. Org. Chem.* **2017**, *82,* 7165−7175; i) S. Sinha, S. Das, R. Mondal, S. Mondal, N. D. Paul, *Dalton Trans.* **2020**, *49*, 8448−8459; j) A. Sk Samim, B. C. Roy, S. Nayak, S. Kundu, *J. Org. Chem.* **2020**, *85*, 11359−11367.

15. a) J. G. Topiliss, M. D. Yudis, *J. Med. Chem.* **1972**, *15*, 394–400; b) A. Tait, A. Luppi, S. Franchini, E. Preziosi, C. Parenti, M. Buccioni, G. Marucci, A. Leonardi, E. Poggessi, L. Brasili, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1185–1188; c) M. Dibella, M. Rinaldi, U. Fabio, G. Manicard, *Farmaco* **1973**, *28*, 777–783; d) P. Zhan, X. Y. Liu, E. De Clercq, *Curr. Med. Chem.* **2008**, *15*, 1529–1540.

16. a) F. Impagnatiello, A. Oberto, P. Longone, E. Costa, A. Guidotti, *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 7053–7058; b) N. Nagarajan, C. Quast, A. R. Boxall, M. Shahid and C. Rosenmund, *Neuropharmacology* **2001**, *41*, 650–663; c) I. Zivkovic, D. M. Thompson, M. Bertolino, D. Uzunov, M. Dibella, E. Costa, A. Guidotti, *J. Pharmacol. Exp. Ther.* **1995**, *272*, 300–309.

17. a) P. de Tullio, S. Boverie, B. Becker, M. H. Antoine, Q. A. Nguyen, P. Francotte, S. Counerotte, S. Sebille, B. Pirotte, P.Lebrun, *J. Med. Chem.* **2005**, *48*, 4990–5000; b) S. Boverie, M. H. Antoine, F. Somers, B. Becker, S. Sebille, R. Ouedraogo, S. Counerotte, B. Pirotte, P. Lebrun, P. de Tullio, *J. Med. Chem.* **2005**, *48*, 3492–3503; c) D. Braghiroli, G. Puia, G. Cannazza, A. Tait, C. Parenti, G. Losi, M. Baraldi, *J. Med. Chem.* **2002**, *45*, 2355–2357; d) J. M. Loynes, H. F. Ridley, R. G. Spickett, *J. Med. Chem.* **1965**, *8*, 691–694.

18. a) Watson, A. J.; Maxwell, A. C.; Williams, J. M. *Org. Biomol. Chem.* **2012**, *10*, 240−243; b) H. Hikawa, N. Matsuda, H. Suzuki, Y. Yokoyama, I. Azumaya, *Adv. Synth. Catal.* **2013**, *355*, 2308–2320.

19. a) V. Yadav, V. G. Landge, M. Subaramanian, E. Balaraman, *ACS Catal.* **2020**, *10*, 947−954; b) S. Chakraborty, U. K. Das, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2017**, *139*, 11710−11713.

20. S. B. Mhaske, N. P. Argade, *J. Org. Chem.* **2004**, *69*, 4563–4566.

21. B. Chatterjee, C. Gunanathan, *Org. Lett.* **2015**, *17*, 4794−4797.

22. a) A. Sarbajna, I. Dutta, P. Daw, S. Dinda, S. W. Rahaman, A. Sarkar, J. K. Bera, *ACS Catal.* **2017**, *7*, 2786–2790; b) G. Jaiswal, V. G. Landge, D. Jagadeesan, E. Balaraman, *Nat. Commun.* **2017**, *8*, 2147–2160; c) P. Hu, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2016**, *138*, 6143−6146.

23. P. R. Thorve, B. Maji, *Catal. Sci. Technol.* **2021**, *11*, 1116 – 1124.

24. S. Das, S. Sinha, D. Samanta, R. Mondal, G. Chakraborty, P. Brandao, N. D. Paul, *J. Org. Chem.* **2019**, *84*, 10160-10171.

25. J. Sun, T. Tao, D. Xu, H. Cao, Q. Kong, X. Wang, Y. Liu, J. Zhao, Y. Wang, Y. Pan, *Tetrahedron Lett.* **2018**, *59*, 2099-2102.

26. N. Ghorashi, Z. Shokri, R. Moradi, A. Abdelrasoul, A. Rostami, *RSC Adv.* **2020**, *10*, 14254 – 14261.

27. X. F. Wu, L. He, H. Neumann, M. Beller, *Chem. Eur. J.* **2013**, *19*, 12635 – 12638.

28. R. Gupta, G. Arora, P. Yadav, R. Dixit, A. Srivastava, R. K. Sharma, *Dalton Trans.* **2021**, *50*, 890 – 898.

29. S. Verma, A. S. Pathania, S. Baranwal, P. Kumar, *Lett. Drug Des. Discov.* **2020**, *17*, 1552-1565.

30. S. Sahoo, S. Pal, *J. Org. Chem.* **2021**, *86*, 18067−18080.

31. Z. Ma, T. Song, Y. Yuan, Y. Yang, *Chem. Sci.* **2019**, *10*, 10283–10289.

32. Y. Hu, H. Hou, L. Yu, S. Zhou, X. Wu, W. Sun, F. Ke, *RSC Adv.* **2021**, *11*, 31650–31655.

33. K. Upadhyaya, R. K. Thakur, S. K. Shukla, R. P. Tripathi, *J. Org. Chem.* **2016**, *81*, 5046-5055.

34. S. H. Siddiki, K. Kon, A. S. Touchy, K. I. Shimizu, *Catal. Sci. Technol.* **2014**, *4*, 1716–1719.

35. M. R. Mahmoud, E. A. El-Bordany, N. F. Hassan, F. S. A. El-Azm, *J. Chem. Res.* **2007**, *9*, 541-544. doi: 10.3184/030823407X248315.

36. P. Mehara, A. Kumar, P. Das, *ChemCatChem* **2021**, *13*, 2459 –2464.

37. H. S. Hwang, E. J. Cho, *Org. Lett.* **2021**, *23*, 5148−5152.

38. Y. Jang, S. B. Lee, J. Hong, S. Chun, J. Lee, S. Hong, *Org. Biomol. Chem.* **2020**, *18*, 5435–5441.

39. K. Gopalaiah, A. Tiwari, R. Choudhary, K. Mahiya, *ChemistrySelect* **2019**, *4*, 5200 –520.

40. B. N. Patil, J. J. Lade, A. S. Karpe, B. Pownthurai, K. S. Vadagaonkar, V. Mohanasrinivasan, A. C. Chaskar, *Tetrahedron Lett*. **2019**, *60*, 891−894.

41. D. Braghiroli, G. Puia, G. Cannazza, A. Tait, C. Parenti, G. Losi, M. Baraldi, *J. Med. Chem.* **2002**, *45*, 2355–2357.

2.7. Selected NMR copies of the compounds:

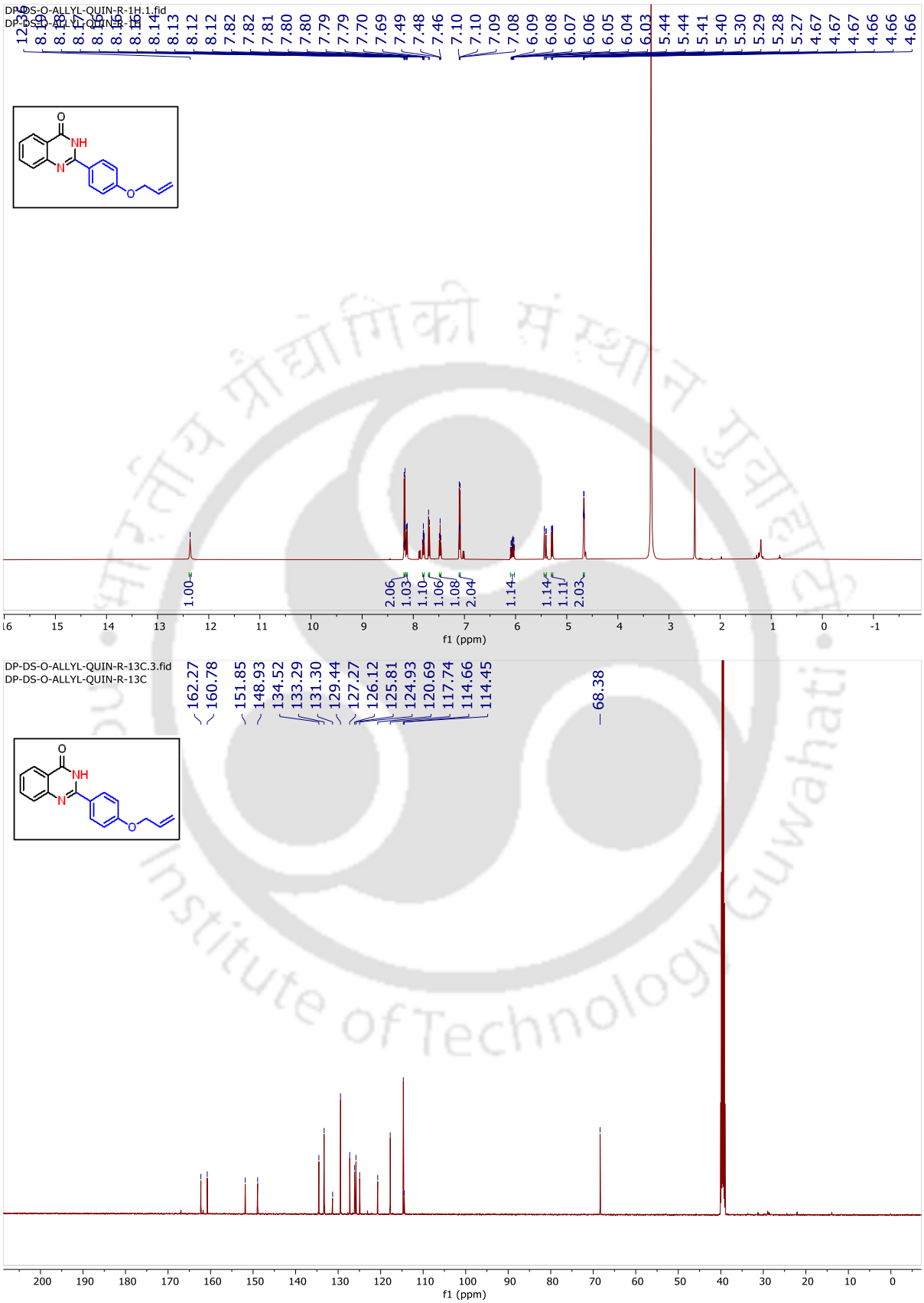


Figure 2.4. ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of 2-(4-(allyloxy)phenyl)quinazolin-4(3H)-one **(2.3t)** in DMSO-d_6.

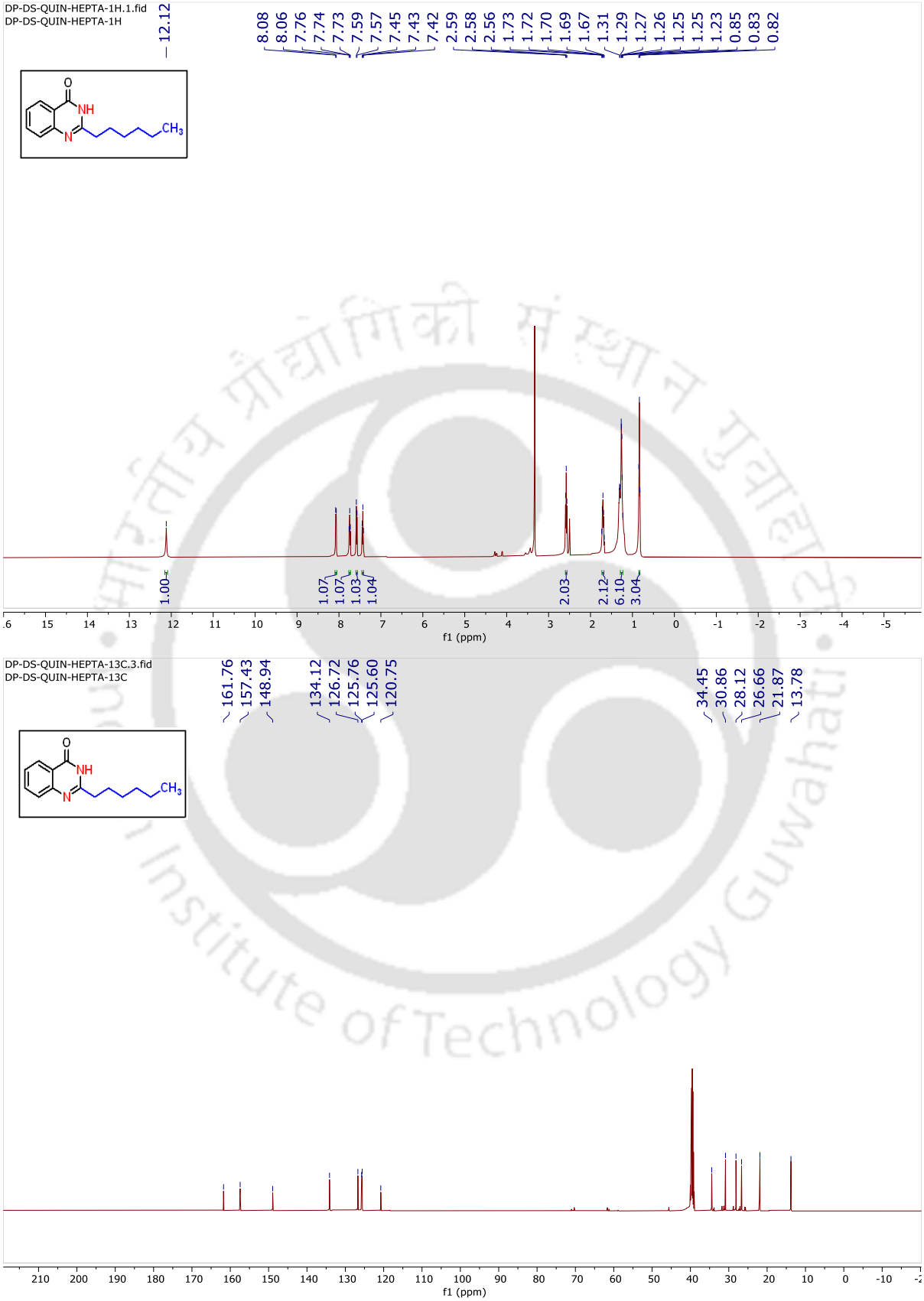


Figure 2.5. ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of 2-hexylquinazolin-4(3H)-one **(2.3zc)** in DMSO-d_6.

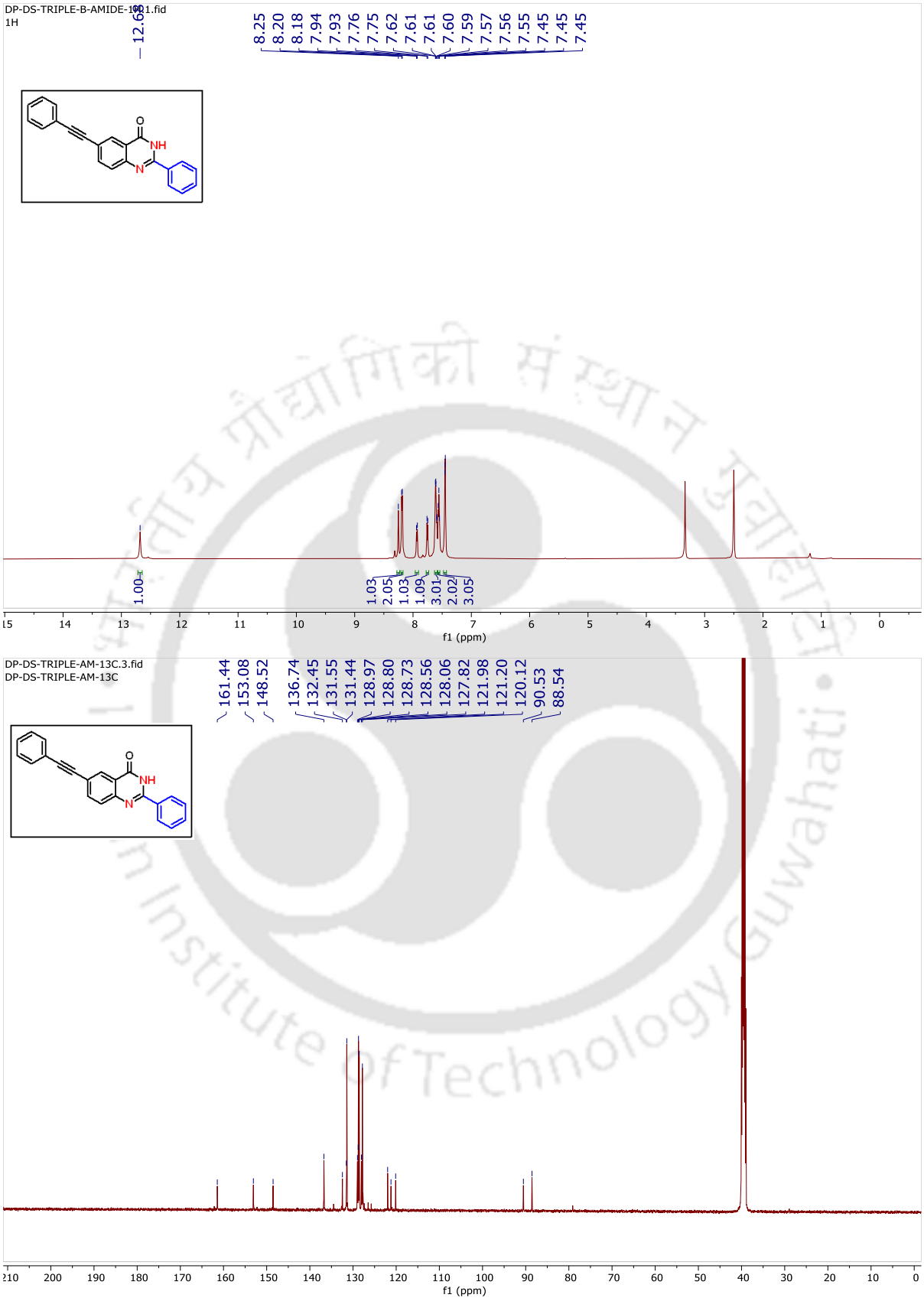


Figure 2.6. ^{1}H (600 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of 2-phenyl-6-(phenylethynyl)quinazolin-4(3H)-one **(2.3zl)** in DMSO-d_6.

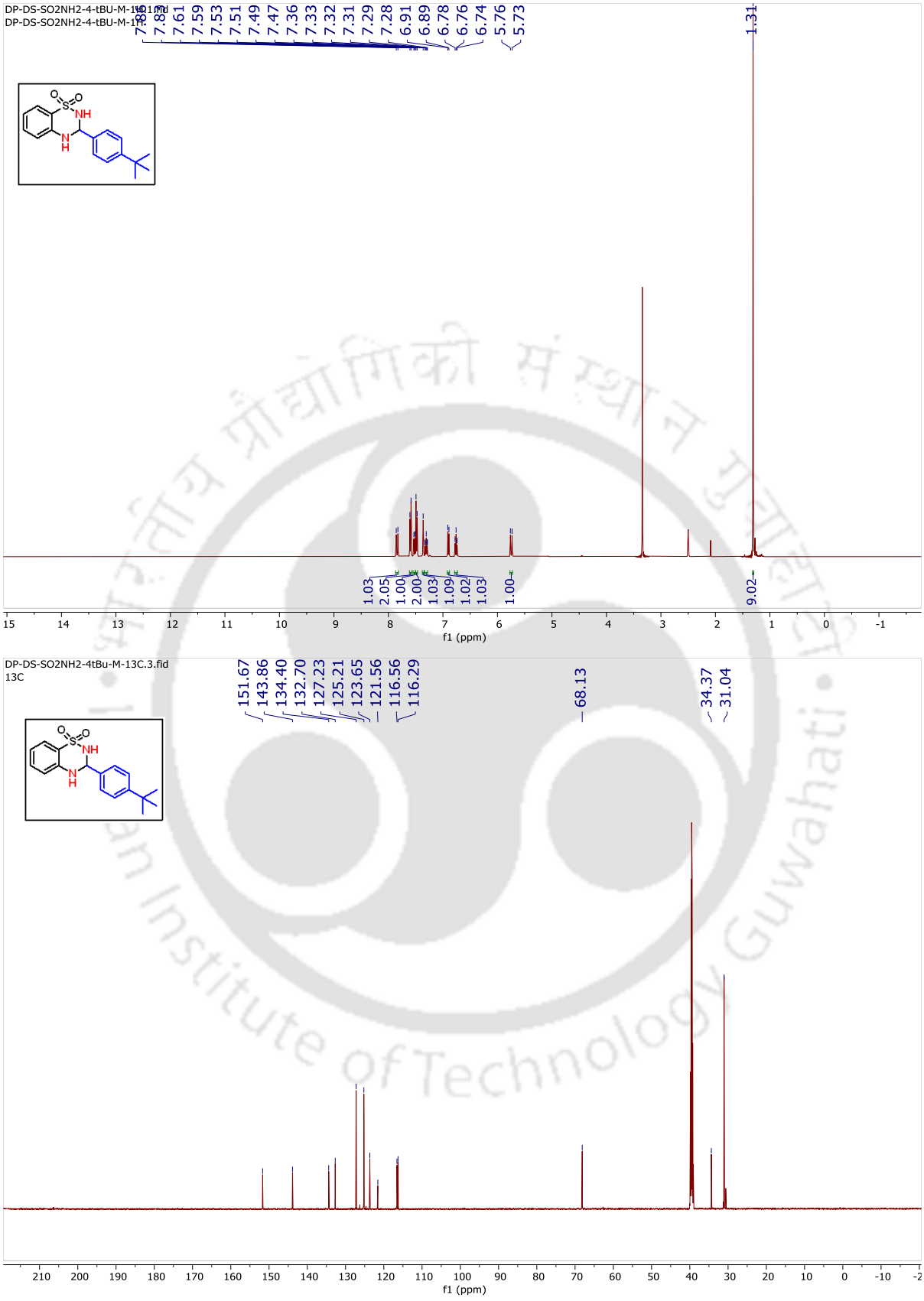


Figure 2.7. ^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (150 MHz) NMR Spectrum of 3-(4-(tert-butyl)phenyl)-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine 1,1-dioxide **(2.7c)** in DMSO-d_6.

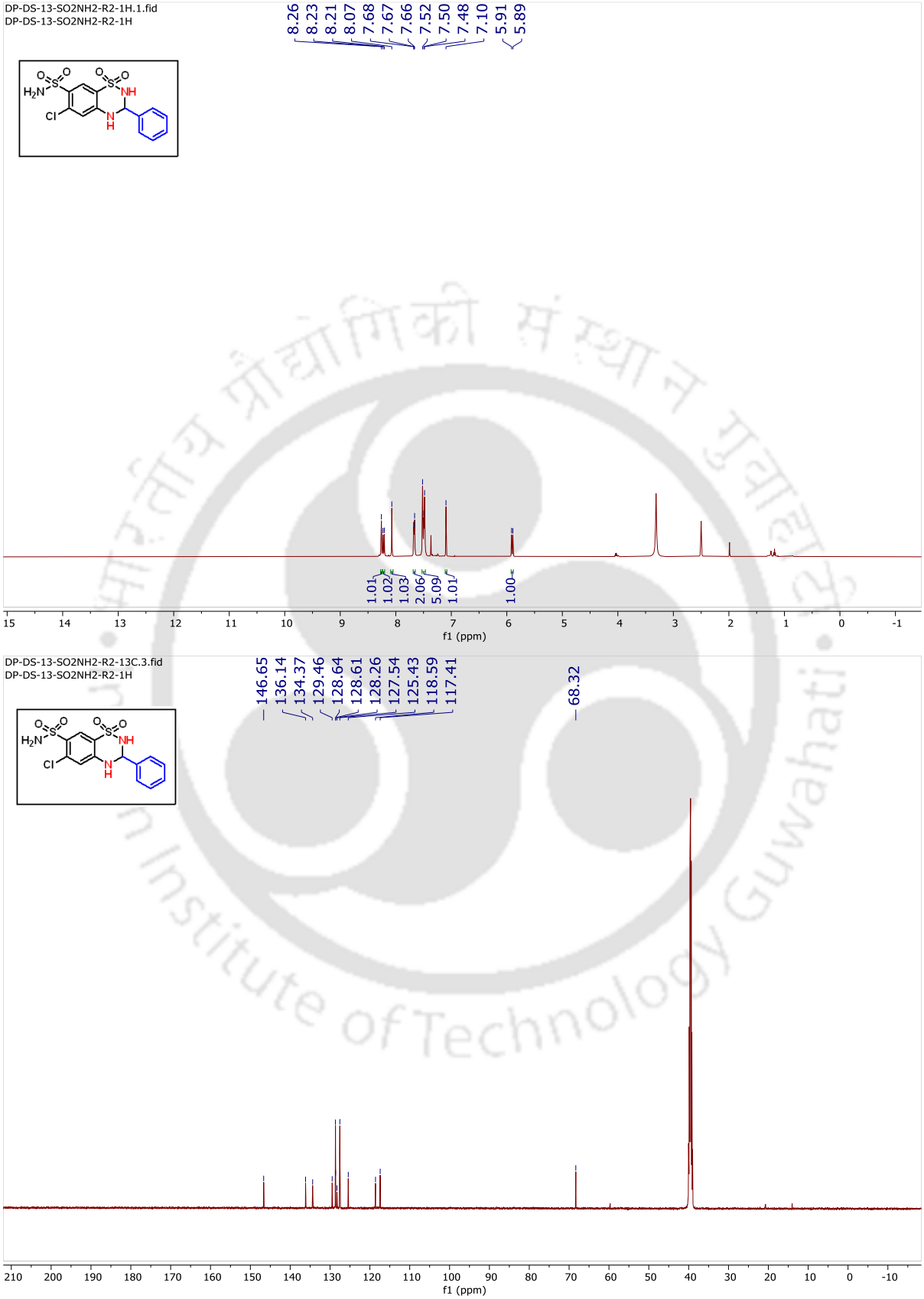
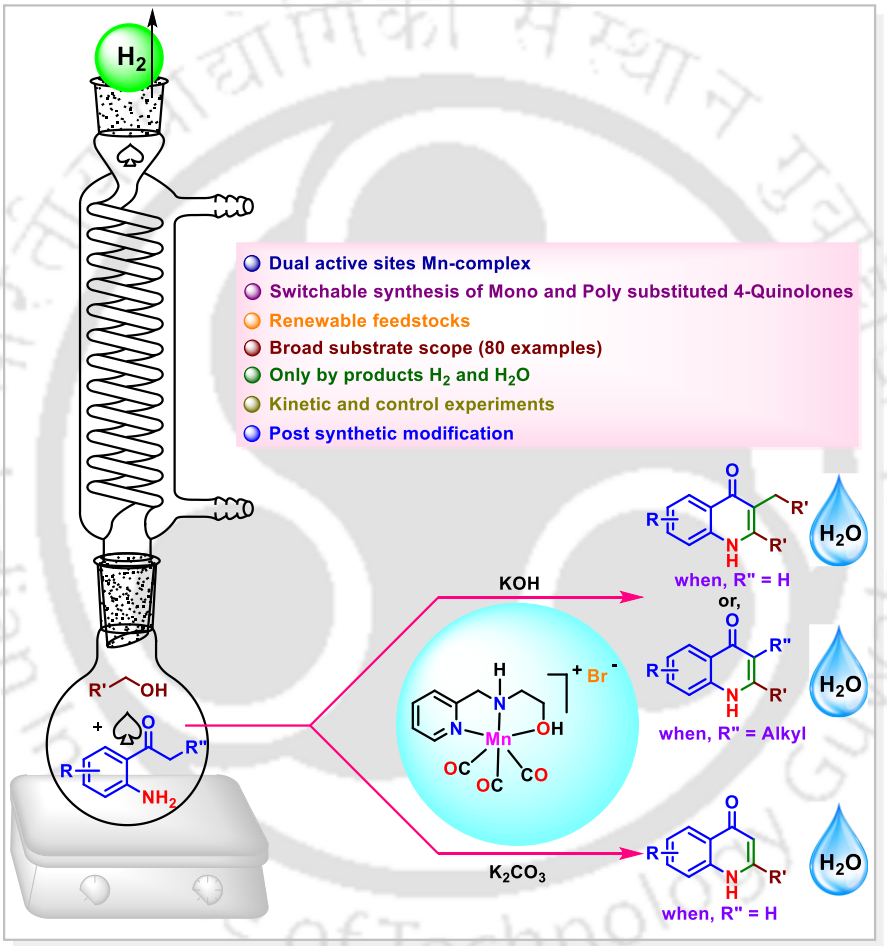


Figure 2.8. ^{1}H (500 MHz) and ^{13}C{^{1}H} (125 MHz) NMR Spectrum of 6-chloro-3-phenyl-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide **(2.7o)** in DMSO-d_6.

Chapter 3

Manganese Complex Catalyzed (De)hydrogenative Cyclization toward the Selective Synthesis of 2-Substituted and 2, 3-Disubstituted 4-Quinolones



D. Pal, B. Sardar, A. Mondal, K. Mohar, R. Sarmah, H. J. Phukan and D. Srimani* *Org. Lett.* **2025**, **https://doi.org/10.1021/acs.orglett.5c01721**.

3.1. Introduction:

Saturated and unsaturated N-heterocyclic compounds are omnipresent and indispensable, as they are the basic structural scaffolds of various life-saving medications and innovative materials that drive technological progress. The FDA approved database revealing that 60% of structurally unique small molecule drugs contain these N-heterocyclic scaffolds as a key structural unit.[1] Due to its myriad applications over the last two decades they realm in the pivotal of organic synthesis. Amidst of these vast array, 4-quinolones engrossed a widespread attention and regarded as a privileged scaffold towards medicinal and natural product synthetic chemists as it imparted a diverse range of biological activities.[2] More than 50 years ago, Nalidixic acid,[3a] an antibacterial drug, the first prototype 4-quinolone analogue dive into the market. Since then, several generations of antibacterial drug bearing 4-quinolone scaffold such as ciprofloxacin,[3b] norfloxacin,[3a] fleroxacin,[3c] and marbofloxacin[3d] has been evolved which captured a remarkable attention towards numerous researchers from various scientific disciplines. Apart from that, 2-aryl-4-quinolone, an aza analogue of flavone paraded an inhibitory effect on tubulin polymerization and act as a potent antitumor,[4] antiviral,[5] antimalarial[6] and antiplatelet[7] agent.

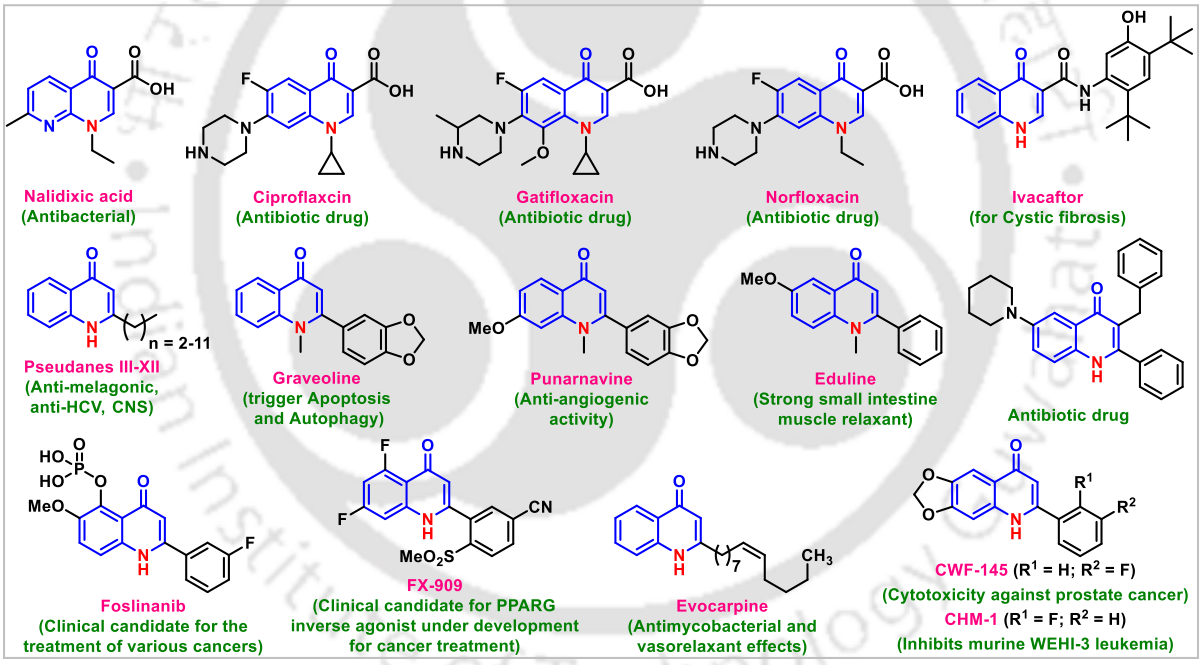
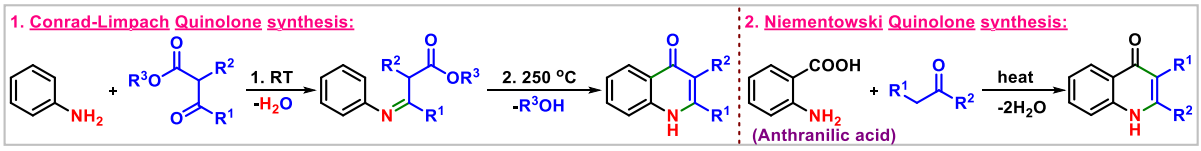


Figure 3.1. Biologically important molecules bearing 4-quionolone scaffold.

Owing to its fascinating structural architecture and prolific biological eminence, it has lured researchers to create various synthetic approaches to attain aforementioned scaffold in recent years. Henceforth, in the next segment, some of the literature reports on synthesis of both 2-substituted and 2, 3-disubstituted 4-Quinolones were discussed.

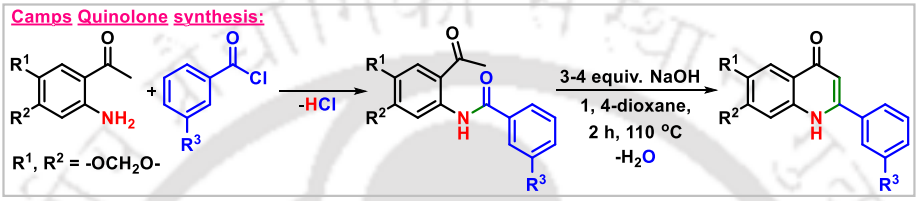
3.2. Literature survey:

Conventionally, *Conrad-Limpach*[8] and *Niementowski* reaction[9] which proceeds via cyclocondensation of amine and carbonyl groups were accomplished towards the synthesis of 4-quinolone scaffolds (Scheme **3.1**). But these classical methods suffer from harsh condition and inadequate substrate scope.



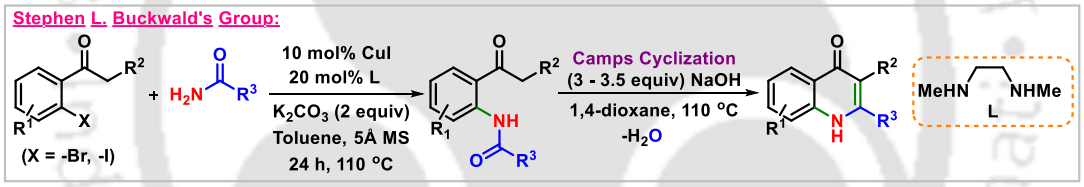
Scheme 3.1. Conrad-Limpach and Niementowski reaction for Quinolone synthesis.

Afterwards, base-assisted cyclocondensation of N-(2-ketoaryl)amides known as the *Camps cyclization*[10] received an unwavering attention. Previously, these Camps precursors were made by condensation of *o*-aminoacetophenones and carboxylic acids or acid chlorides, Friedel-Crafts acylation of anilides (which often result in a complex mixture of products) or synthesis and subsequent opening of a benzoxazinone with the dianion of an N-substituted acetamide (Scheme **3.2**).



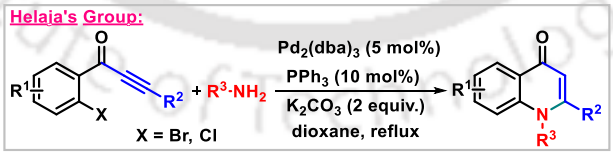
Scheme 3.2. Conventional synthetic route to *N*-(2-ketoaryl)amides and quinolones.

Later, based on this Cu(I)-catalyzed amidation of *o*-haloacetophenones to manifest 2-aryl-4-quinolones was reported by the *Buchwald group* (Scheme **3.3**).



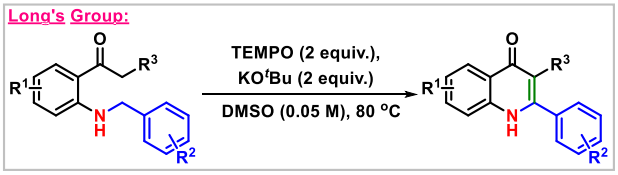
Scheme 3.3. Sequential Cu-catalyzed amidation, base mediated Camps cyclization to synthesize 4-quinolones.

Recently, some improved and milder routes have been devised to establish 2-aryl-4-quinolones employing transition metal catalyzed tandem reaction of *o*-haloaryl acetylenic ketones/amines[11] and *o*-aminoaryl acetylenic ketones (Scheme **3.4**).[12]



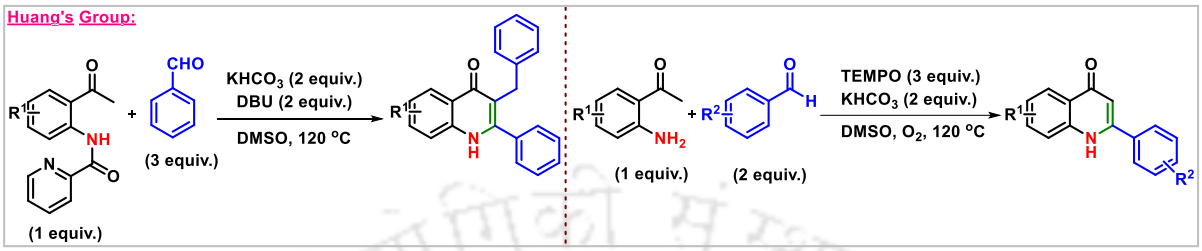
Scheme 3.4. Pd-catalyzed tandem amination reaction for the synthesis of 4-quinolones.

Nonetheless, most of these methods rely on expensive metal catalyst, relatively strident reaction condition, time involve multistep or specific substrate acquisition, cumbersome work-up procedures.



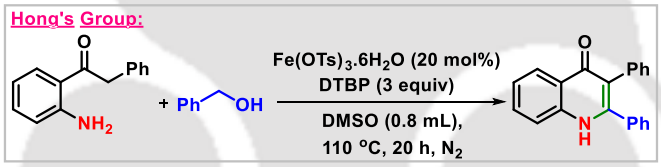
Scheme 3.5. Transition metal-free intramolecular oxidative synthesis of 2-aryl-4-quinolones.

In order to circumvent from these, in 2015, *Long and coworkers* reported TEMPO mediated oxidative annulation of N-benzyl-2-aminoacetophenone via C(sp^3)-H/C(sp^3)-H coupling towards the synthesis of quinolones (Scheme **3.5**).[13] In 2017, *Huang's group* demonstrated transition metal free oxidative intermolecular cyclization of 2-amino acetophenones and benzaldehydes enroute to 2-aryl-4-quinolones (Scheme **3.6**).[14]



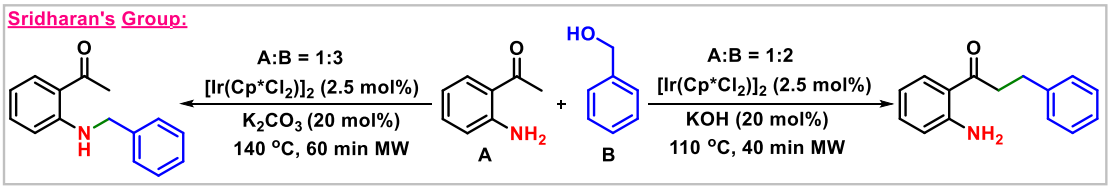
Scheme 3.6. Transition metal-free intramolecular oxidative synthesis of 2-substituted and 2, 3-disubstituted 4-quinolones.

Although the employment of aldehyde as an oxidation level coupling partner confined the generality of the reaction. Very recently, *Hong's group* described Fe-catalyzed one step synthesis of 4-quinolones via oxidative annulation of 2-amino aryl ketone with alcohol or methyl arene as reaction partner, nevertheless, this strategy suffers from excessive acquisition of strong oxidants and reactants (Scheme **3.7**).[15]



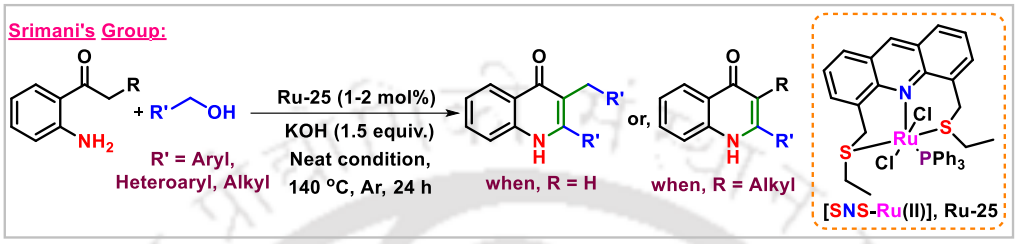
Scheme 3.7. Fe-catalyzed oxidative coupling of alcohol towards one-pot synthesis of 4-quinolones.

Henceforth, there is a growing impetus to build an atom-economical, energetically efficient, environmentally benign and sustainable synthetic route towards the accomplishment of quinolone derivatives. In that quest, catalytic (de)hydrogenative coupling reactions sparked unswerving attention in the arena of green and sustainable catalysis.[16] This strategy is very much fascinated to giving room to build diverse range of heterocyclic scaffolds from the identical set of starting materials upon fine tuning of the reaction parameters with designing of new efficient catalysts. In pursuit of that, in 2012, *Sridharans's group* reported Ir-catalyzed chemoselective alkylation of 2′-aminoacetophenone with primary benzyl alcohol under microwave conditions in which by fine tuning of the nature of the base they selectively furnished mono C-alkylated and mono N-alkylated product (**Scheme 3.8**).[17]



Scheme 3.8. Ir-catalyzed Chemoselective alkylation of 2′-aminoacetophenone.

Intrigued by this report, *Srimani group* prompted to investigate and found that during the course of the reaction apart from self-condensation of 2′-aminoacetophenone, it can furnished mono N-alkylated, C-alkylated, N, C-dialkylated product or annulated product (Scheme 1). Therefore, chemoselective synthesis of biologically important annulated product via controlling the selectivity devising sustainable catalytic protocol is still a demanding process. Very recently, they have reported Ru-catalyzed (**Ru-25**) (de)hydrogenative annulation between alcohol and 2-amino phenyl ketone towards the synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one (Scheme **3.9**).[18]



Scheme 3.9. Ru-catalyzed (de)hydrogenative synthesis of 2, 3-disubstituted 4-quinolones.

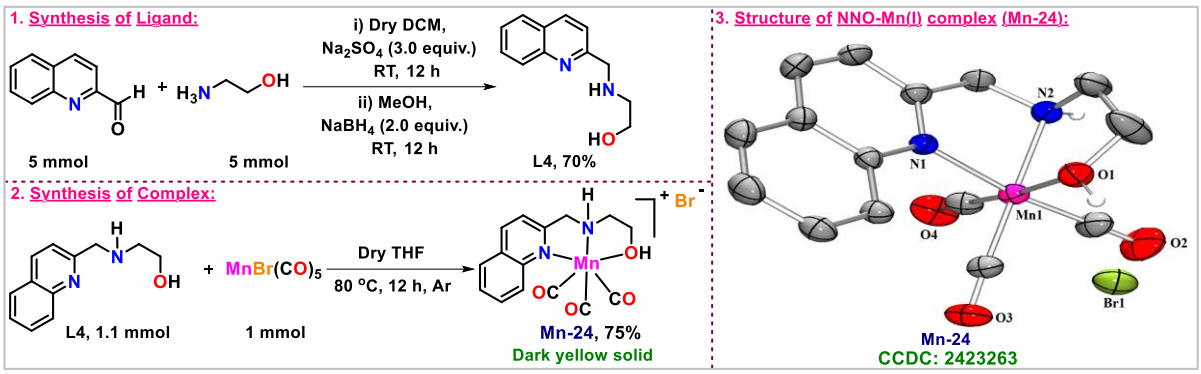
3.3. Present work:

However, environmental and economic pressure has confined the continual use of noble metals and witnessed an exigency for developing new and efficient base metal catalysts for useful organic transformations.[19] Despite being the third-most earth-abundant transition metal and a non-toxic element found in several biological system,[20] the use of manganese in the tandem (de)hydrogenative synthesis of both 2-substituted and 2, 3-disubstituted 4-quinolones was completely untapped. Spurred by that, this present chapter demonstrated first Mn(I)-catalyzed synthesis of both 2-substituted and 2, 3-disubstituted 4-quinolones upon fine tuning of reaction parameter using alcohols as key renewable[16f] starting material. In this chapter, four NNO-ligand-derived Mn(I)-complexes were employed, amidst of that, pyridine based three NNO-Mn(I) complexes were pre-synthesized[21] and herein, quinoline based NNO-Mn(I) complex was synthesized, well characterized with ATIR, HRMS and SC-XRD and their catalytic activity has been explored upon towards the synthesis of a wide range of both 2-substituted and 2, 3-disubstituted 4-Quinolones. Not only that, pre-synthesized NNS-Mn(I) complexes[21] were also used to check the reactivity towards the synthesis of both aforementioned N-heterocycles.

3.3.1. Results and discussion:

3.3.1.1. Synthesis of Quinoline based NNO Ligand and its Mn-complex (Mn-24):

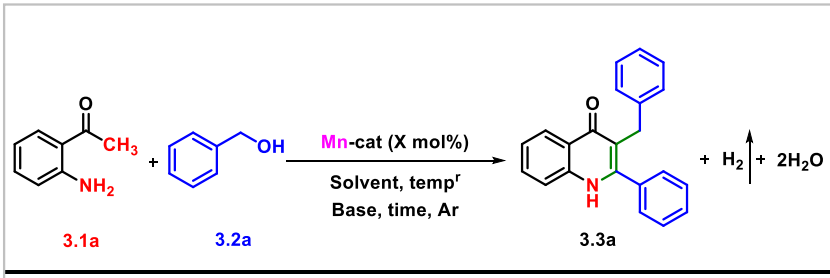
At the outset, quinoline based NNO Ligand and its Mn-complex (**Mn-24**) was synthesized upon reacting with the precursor $MnBr(CO)_5$ (Scheme **3.10**). Afterwards, the molecular structure was confirmed with SC-XRD upon growing their single crystals and with IR (experimental section **3.5.2.2**).



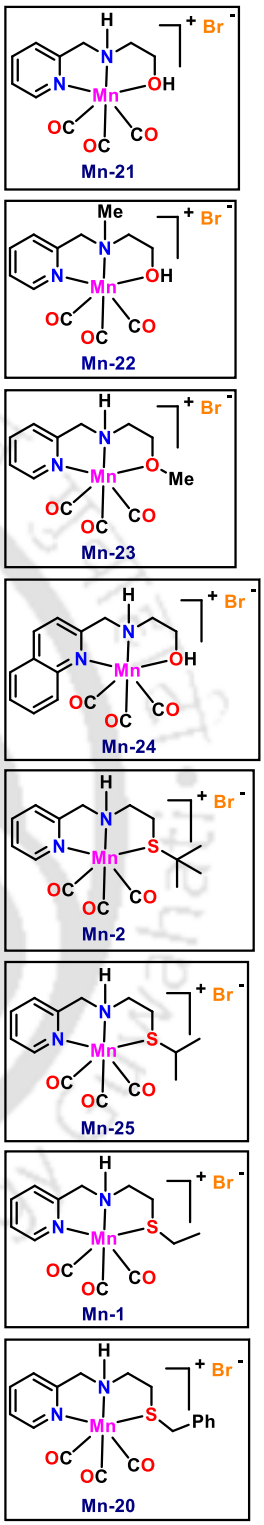
Scheme 3.10. Synthesis of quinoline based NNO-Mn(I) complex (**Mn-24**) and its structure.

Initially, the investigation in this (de)hydrogenative annulation reaction was commenced by scrutinizing the feasibility of the developed eight phosphine free Mn(I)-complexes employing 2′-aminoacetophenone (**3.1a**) and benzyl alcohol (**3.2a**) as the model coupling partners. Interestingly, during the course of the reaction a clean selectivity towards the synthesis of 3-benzyl-2-phenylquinolin-4(1H)- one (**3.3a**) was observed with none of the C/N-alkylated derivatives. At the outset, reaction of 2′-aminoacetophenone (**3.1a**) (1 equiv.) and benzyl alcohol (**3.2a**) (4 equiv.) using **Mn-21** complex (5 mol%) and KO^{t}Bu (1 equiv.) in solventless condition under argon atmosphere at 140 °C for 36 h resulted only 40% formation of the product (**3.3a**) (Table 3.3.1.2, entry 1). Furthermore, keeping other parameters intact upon increasing the base loading from 1 equiv. to 1.5 equiv. yield also increased, however, switching the base from KO^{t}Bu to KOH it delivered 76% isolated yield of the intended product (**3.3a**) (Table 3.3.1.2, entry 2-4). Pleasingly, decrease of alcohol loading from 4 equiv. to 3 equiv. does not hamper, however, furthermore decrease showcased some negative impacts in the yield of the desired product (**3.3a**) (Table 3.3.1.2, entry 5-6). Afterwards, the catalytic activity of the as prepared three NNO-Mn(I) complexes (**Mn-22**, **Mn-23** and **Mn-24**) were checked in which **Mn-22** showed almost similar catalytic activity like **Mn-21** whilst **Mn-23** and **Mn-24** shows some detrimental effect in the yield, amidst of that **Mn-24** exhibit better reactivity over **Mn-23** displaying the prominence role of ligand hydroxyl arm over amine arm and presence of both makes the catalytic system more active (Table 3.3.1.2, entry 12-14). Previously developed NNS-Mn(I)-complexes (**Mn-2**, **Mn-25**, **Mn-1** and **Mn-20**) accomplished an inferior result (Table 3.3.1.2, entry 15-18). Then, several reaction parameters such as catalyst loading, base loading, reaction time, temperature, nature of base, solvent was also screened albeit all of them failed to raise the yield of the intended product (**3.3a**) (Table 3.3.1.2, entry 7-11, 19-26). Therefore, (de)hydrogenative annulation of 1 equiv. of 2′-aminoacetophenone (**3.1a**) with 3 equiv. of benzyl alcohol (**3.2a**) in presence of 5 mol% of **Mn-21** catalyst and 1.5 equiv. of KOH in solventless condition under argon atmosphere at 140 °C for 36 h furnished the optimal yield of the desired 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) product (Table 3.3.1.2, entry 5). Herein, some control experiments were carried out to prove that both catalyst and base manifested a more decisive impact to pursue the reaction.

Table 3.3.1.2: Reaction Optimization for the Mn-catalyzed synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one[a,b]



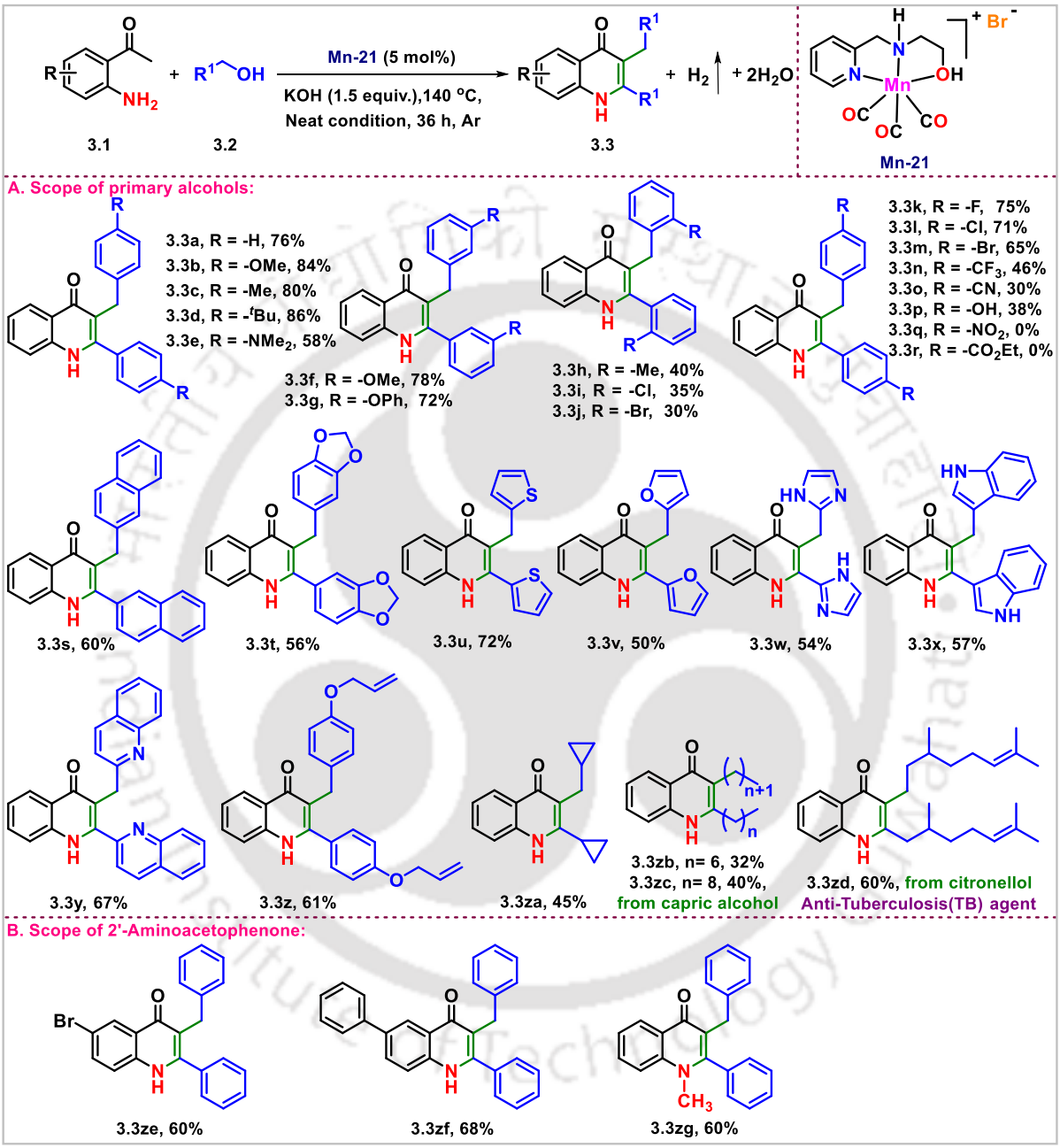
Entry	Cat. (mol%)	Solvent	Base (equiv.)	3.1a:3.2a	Temp^r (°C)	Time (h)	Yield^b (%)
1.	Mn-21 (5)	-	KO^{t}Bu (1.0)	1:4	140 °C	36	40
2.	Mn-21 (5)	-	KO^{t}Bu (1.2)	1:4	140 °C	36	52
3.	Mn-21 (5)	-	KO^{t}Bu (1.5)	1:4	140 °C	36	63
4.	Mn-21 (5)	-	KOH (1.5)	1:4	140 °C	36	76
5.	Mn-21 (5)	-	KOH (1.5)	1:3	140 °C	36	76
6.	Mn-21 (5)	-	KOH (1.5)	1:2	140 °C	36	50
7.	Mn-21 (5)	-	KOH (1.2)	1:3	140 °C	36	63
8.	Mn-21 (5)	-	KOH (1.5)	1:3	140 °C	48	77
9.	Mn-21 (5)	-	KOH (1.5)	1:3	140 °C	24	51
10.	Mn-21 (4)	-	KOH (1.5)	1:3	140 °C	36	65
11.	Mn-21 (5)	-	KOH (1.5)	1:3	120 °C	36	61
12.	Mn-22 (5)	-	KOH (1.5)	1:3	140 °C	36	73
13.	Mn-23 (5)	-	KOH (1.5)	1:3	140 °C	36	54
14.	Mn-24 (5)	-	KOH (1.5)	1:3	140 °C	36	65
15.	Mn-2 (5)	-	KOH (1.5)	1:3	140 °C	36	50
16.	Mn-25 (5)	-	KOH (1.5)	1:3	140 °C	36	47
17.	Mn-1 (5)	-	KOH (1.5)	1:3	140 °C	36	45
18.	Mn-20 (5)	-	KOH (1.5)	1:3	140 °C	36	32
19.	Mn-21 (5)	-	NaOH (1.5)	1:3	140 °C	36	60
20.	Mn-21 (5)	-	CsOH (1.5)	1:3	140 °C	36	50
21.	Mn-21 (5)	-	NaO^{t}Bu(1.5)	1:3	140 °C	36	45
22[c].	Mn-21 (5)	-	K_2CO_3(1.5)	1:3	140 °C	36	-
23.	Mn-21 (5)	-	Na_2CO_3(1.5)	1:3	140 °C	36	Trace
24.	Mn-21 (5)	Toluene	KOH (1.5)	1:3	140 °C	36	30
25.	Mn-21 (5)	Xylene	KOH (1.5)	1:3	140 °C	36	38
26.	Mn-21 (5)	^{t}AmOH	KOH (1.5)	1:3	140 °C	36	ND
27.	-	-	KOH (1.5)	1:3	140 °C	36	15
28.	Mn-21 (5)	-	-	1:3	140 °C	36	ND
29.	$MnBr(CO)_5$ (5)	-	KOH (1.5)	1:3	140 °C	36	18



[a]Reaction conditions: **3.1a** (0.5 mmol), **3.2a** (1.5-2.0 mmol), base (0. 5-0.75 mmol), **Mn**-cat. (4-5 mol %), solvent (0-2 ml), at temperature 120 °C – 140 °C of a preheated oil bath for 24 – 48 h in a 10 mL round-bottom flask under argon. [b]Isolated yield. [c]Yield of compound 2-phenylquinolin-4(1H)-one (**3.6a**), 30%. N.D. = Not detected.

In presence of the metal precursor, $MnBr(CO)_5$ only 18% yield of the desired product (**3.3a**) was obtained (Table 3.3.1.2, entry 27-29).

3.3.1.3. Mn-catalyzed synthesis of 2, 3-disubstituted 4-quinolone derivatives from various alcohols and 2′-aminoacetophenones: substrate scope[a,b]



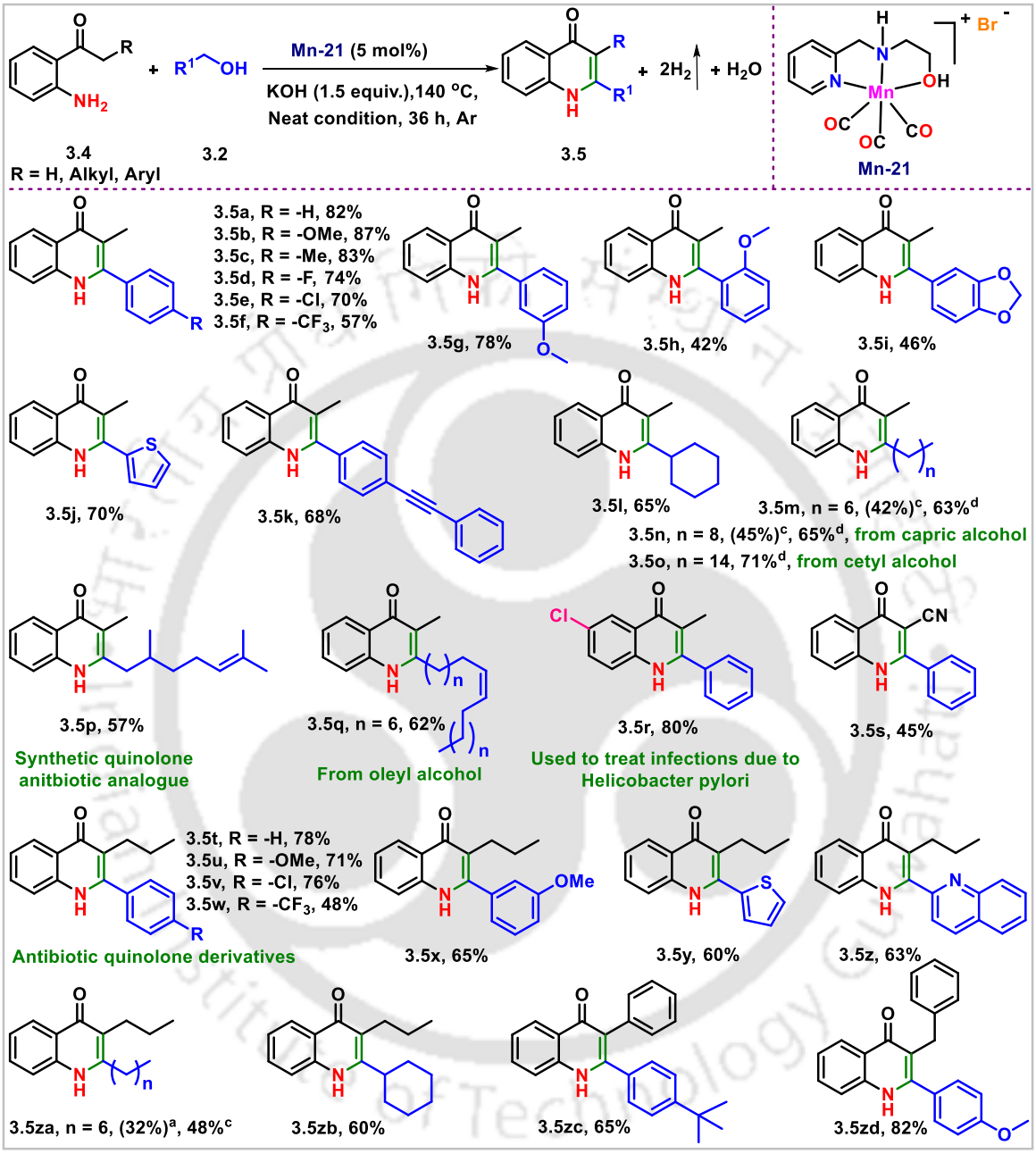
[a] Reaction conditions: **3.1** (0.5 mmol), **3.2** (1.5 mmol), KOH (1.5 equiv.), **Mn-1** (5 mol%), Neat condition, 36 h, 140 ˚C, under argon. [b]Isolated yield.

With the set of optimized reaction conditions in hand, the feasibility of the current catalytic protocol was explored with an array of 2′-aminoacetophenones and primary alcohols whose pertinent results were summarized below. Initially, the scope of electronically neutral, rich and deficient functional groups embraces at the *p*-, *m*- and *o*-position of the aromatic nucleus of the phenyl ring was tested where

the *p*- and *m*-substituted functional groups furnished the desired product with good to excellent yield whilst *o*-substituted were accomplished moderate result because of steric encumbrance (**3.3a**-**3.3n**). Of note, benzyl alcohol containing cyano and hydroxyl functional group was effective furnishing moderate isolated yield whilst nitro and ester group were incompatible under the streamlined reaction condition (**3.3o**-**3.3r**). Significantly, extended Π-conjugated system such as 2-Napthylalcohol led to the desired product **3.3s** with good isolated yield. Nevertheless, heteroaromatic alcohols underwent smoothly manifesting moderate to good isolated yield (**3.3t**-**3.3y**). Indeed, the reducible functional groups such as $–OCH_2CH═CH_2$ present at the *p*-position of benzyl alcohol can survive under the current reaction conditions to give the desired product (**3.3z**). Remarkably, more challenging cyclic and acyclic aliphatic primary alcohols such as cyclopropylmethanol, 1-octanol and fatty alcohol *e.g.* capric alcohol respond well accomplishing the desired product (**3.3za**-**3.3zc**), albeit for acyclic aliphatic primary alcohols there was a tendency to form 3-substituted quinoline.[15] Then the reaction was conducted with natural monoterpenoid, citronellol which chemoselectively converted to the intended product (**3.3zd**) with good isolated, act as a potent anti-Tuberculosis (TB) drug.[4d] Afterwards, the scope of 2′-aminoacetophenone was also checked which afforded good isolated yields (**3.3ze**-**3.3zg**).

Furthermore, the potentiality of the current catalytic protocol was investigated by implementing functionally diverse *α*-alkylated 2′-aminoacetophenone based derivatives. Herein, the intension was to examine challenging aliphatic alcohols rather than evaluating the scope of traditional benzylic alcohols featuring electron donating and electron withdrawing substituents. Indeed, cyclohexyl methanol (**3.5l**) and 1-octanol (**3.5m**) underwent smoothly towards (de)hydrogenative annulation furnishing the expected product in moderate yield at slightly higher loading of alcohol and reaction time. Remarkably, fatty alcohols such as capric, cetyl alcohols natural monoterpenoid, citronellol and naturally occurring unsaturated oleyl alcohol were chemoselectively transformed to the desired product with good isolated yield (**3.5n**-**3.5q**). A biologically active compound (**3.5r**) used for the treatment of stomach infections caused by the bacteria Helicobacter pylori[22] additionally have been synthesized. Apart from that, functional group like –CN (**3.5s**) was steadily participated and well tolerated in the streamline reaction condition affording the intended product in modest yield. Next, the envisioned was to explore the scope of 2'-aminobutyrophenone moiety based 4-quinolone derivatives, which were potent antibiotics[3] furnishing good isolated yield for aromatic, heteroaromatic, cyclic and acyclic aliphatic alcohols (**3.5t**-**3.5zb**). Aside from that, presence of bulky -Ph group at *α*-position of 2′-aminoacetophenone also afforded appeasement result (**3.5zc**) circumventing the peri-steric interaction. Nevertheless, a hybrid 2, 3-disubstituted quinolone was achieved successfully delivering good yield (**3.5zd**).

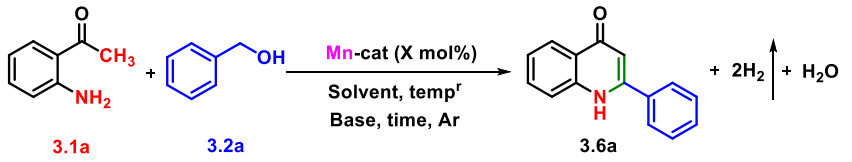
3.3.1.4. Mn-catalyzed synthesis of 2, 3-disubstituted 4-quinolone derivatives from aliphatic alcohols and functionally diverse *α*-alkylated 2'-aminoacetophenone based derivatives: substrate scope[a,b]



[a] Reaction conditions: **3.4** (0.5 mmol), **3.2** (1.0 mmol), KOH (1.5 equiv.), **Mn-1** (5 mol%), Neat condition, 36 h, 140 ˚C, under argon. [b]Isolated yield. [c]Alcohol (1.5 mmol). [d]72 h.

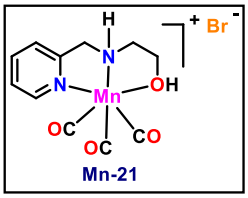
In search of optimal condition towards the synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) product, when the reaction was carried out taking 1 equiv. of 2′-aminoacetophenone (**3.1a**) with 3 equiv. of benzyl alcohol (**3.2a**) at 140 °C in presence of 5 mol% of **Mn-21** complex and 1.5 equiv. of K_2CO_3 in solventless and additive free condition under argon atmosphere for 36 h, rather than furnishing **3.3a**, it afforded 30% yield of 2-phenylquinolin-4(1H)-one (**3.6a**) product (Table 3.3.1.5, entry 1).

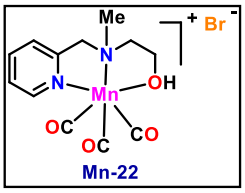
Table 3.3.1.5: Reaction Optimization for the Mn-catalyzed synthesis of 2-phenylquinolin-4(1H)-one [a,b]



3.1a 3.2a 3.6a

Entry	Cat. (mol%)	Solvent	Base (equiv.)	Additive (equiv.)	3.1a:3.2a	Temp^r (°C)	Time (h)	Yield^b (%)
1.	Mn-21 (5)	-	K_2CO_3 (1.5)	-	1:3	140 °C	36	30
2.	Mn-21 (5)	-	K_2CO_3 (1.5)	$ZnCl_2$ (1.0)	1:3	140 °C	36	ND
3.	Mn-21 (5)	-	K_2CO_3 (1.5)	$InCl_3$ (1.0)	1:3	140 °C	36	ND
4.	Mn-21 (5)	-	K_2CO_3 (1.5)	$FeCl_3$ (1.0)	1:3	140 °C	36	Trace
5.	Mn-21 (5)	-	K_2CO_3 (2.0)	-	1:3	140 °C	36	42
6.	Mn-21 (5)	-	K_2CO_3 (3.0)	-	1:3	140 °C	36	55
7.	Mn-21 (5)	-	K_2CO_3 (4.0)	-	1:3	140 °C	36	65
8.	Mn-21 (5)	-	K_2CO_3 (5.0)	-	1:3	140 °C	36	67
9.	Mn-21 (5)	-	K_2CO_3 (4.0)	-	1:3	140 °C	48	74
10.	Mn-21 (5)	-	K_2CO_3 (4.0)	-	1:3	140 °C	40	74
11.	Mn-21 (5)	-	K_2CO_3 (4.0)	-	1:3	120 °C	40	54
12.	Mn-21 (5)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	72
13.	Mn-21 (5)	-	K_2CO_3 (4.0)	-	1:1	140 °C	40	45
14.	Mn-21 (4)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	64
15.	Mn-22 (5)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	67
16.	Mn-23 (5)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	48
17.	Mn-24 (5)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	62
18.	Mn-2 (5)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	45
19.	Mn-25 (5)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	42
20.	Mn-1 (5)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	40
21.	Mn-20 (5)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	28
22.	Mn-21 (5)	-	Na_2CO_3 (4.0)	-	1:2	140 °C	40	53
23.	Mn-21 (5)	-	Cs_2CO_3 (4.0)	-	1:2	140 °C	40	ND
24.	Mn-21 (5)	Xylene	K_2CO_3 (4.0)	-	1:2	140 °C	40	ND
25.	Mn-21 (5)	^{t}AmOH	K_2CO_3 (4.0)	-	1:2	140 °C	40	ND
26.	Mn-21 (5)	Diglyme	K_2CO_3 (4.0)	-	1:2	140 °C	40	ND
27.	-	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	ND
28.	Mn-21 (5)	-	-	-	1:2	140 °C	40	ND
29.	$MnBr(CO)_5$ (5)	-	K_2CO_3 (4.0)	-	1:2	140 °C	40	12


Mn-21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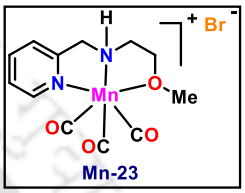
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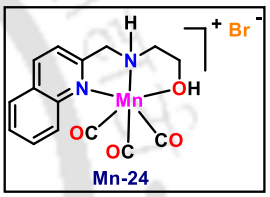
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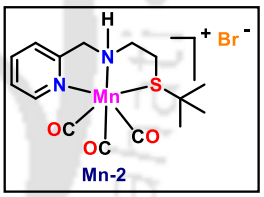
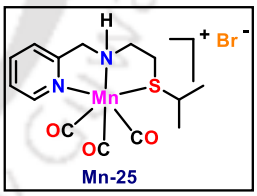

Mn-2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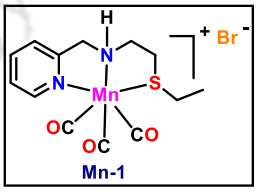
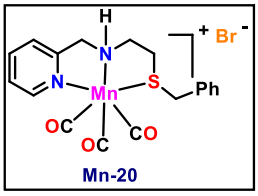

Mn-1


Mn-20

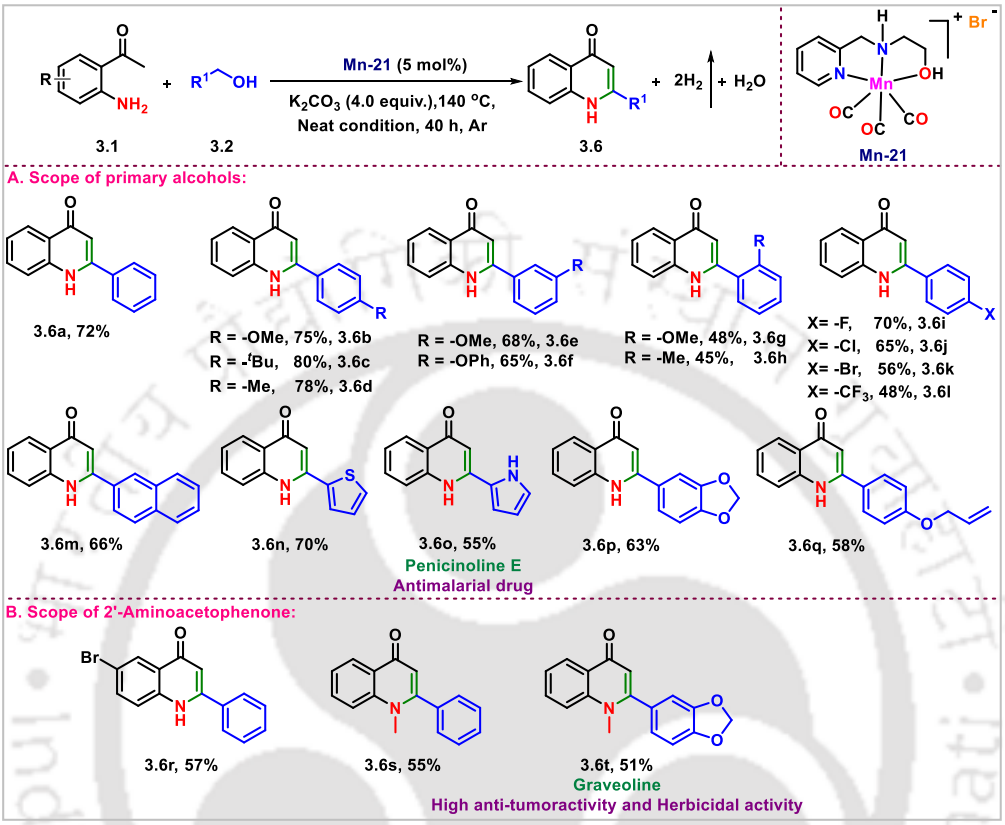
[a]Reaction conditions: **3.1a** (0.5 mmol), **3.2a** (1.0-1.5 mmol), base (0. 75-2.5 mmol), **Mn**-cat. (4-5 mol %), solvent (0-2 ml), at temperature 120 °C – 140 °C of a preheated oil bath for 36 – 48 h in a 10 mL round-bottom flask under argon. [b]Isolated yield. N.D. = Not detected.

Afterwards, in order to increase the yield, the reaction was accomplished upon adding some Lewis acid such as $ZnCl_2$, $InCl_3$, $FeCl_3$ albeit all of them failed to deliver a detectable conversion of the intended product (**3.6a**) (Table 3.3.1.5, entry 2-4). Then, the base loading was increased and found that employing 4 equiv. of weak base K_2CO_3 it afforded 65% yield and furthermore increase of base loading no notable increment has been observed (Table 3.3.1.5, entry 5-8). However, increase of reaction time by 12 h keeping other parameters intact it furnished 74% isolated yield of the desired 2-phenylquinolin-4(1H)-one (**3.6a**) product (Table 3.3.1.5, entry 9). Pleasingly, decrease of alcohol loading from 3 equiv. to 2 equiv. does not hamper in the yield of the desired product (**3.6a**) but furthermore reduction of alcohol loading from 2 equiv. to 1 equiv. gave inferior yield (Table 3.3.1.5, entry 12-13). Herein, the catalytic applicability of other three NNO-Mn(I) complexes was also checked, amidst of that, **Mn-22** and **Mn-24** showed almost similar catalytic activity like **Mn-21** whilst **Mn-23** delivered a detrimental result (Table 3.3.1.5, entry 15-17). Previously developed NNS-Mn(I)-complexes (**Mn-2**, **Mn-25**, **Mn-1** and **Mn-20**) afforded an inferior result (Table 3.3.1.5, entry 18-21). Afterwards, several reaction parameters such as catalyst loading, reaction temperature, nature of base and solvent (Table 3.3.1.5, entry 11, 14, 22-26) have also screened, amidst of them, (de)hydrogenative annulation of 1 equiv. of 2′-aminoacetophenone (**3.1a**) with 2 equiv. of benzyl alcohol (**3.2a**) at 140 °C in presence of 5 mol% of **Mn-21** catalyst and 4 equiv. of K_2CO_3 in solvent free condition under argon atmosphere for 40 h furnished the best result of desired 2-phenylquinolin-4(1H)-one (**3.6a**) product (Table 3.3.1.5, entry 12). Herein also some control experiments were conducted which manifested that either in absence of catalyst or base no detectable conversion of the desired product (**3.6a**) obtained. In presence of the metal precursor, $MnBr(CO)_5$ only 12% yield of the desired product (**3.6a**) was obtained (Table 3.3.1.5, entry 27-29).

After getting the optimal conditions, the developed protocol was applied towards various 2′-aminoacetophenones and primary alcohols to afford a wide range of 2-phenylquinolin-4(1H)-one derivatives. Initially, the versatility of this (de)hydrogenative annulation reaction was tested upon employing *o*-, *m*-, and *p*-substituted benzyl alcohols as coupling partner bearing electronically biased and electronically poor functional groups at its aromatic nucleus delivering the desired product selectively in moderate to good isolated yield (**3.6a-3.6l**) (45-80%). Remarkably, extended Π-conjugated system such as 2-Napthylalcohol also furnished moderate isolated yield (**3.6m**). Nevertheless, heteroaromatic alcohols also respond well under the streamline reaction condition manifesting moderate to good isolated yield (**3.6n-3.6p**). Of note, benzyl alcohol bearing the reducible functional groups such as $–OCH_2CH{=}CH_2$ present at its *p*-position also catalytically compatible under the current reaction conditions to give the desired product (**3.6q**). Next, the scope of both 2′-aminoacetophenones and N-methylated 2′-aminoacetophenones also checked which furnished their intended products in moderate isolated yields (**3.6r-3.6t**). Indeed, the catalytic protocol able to

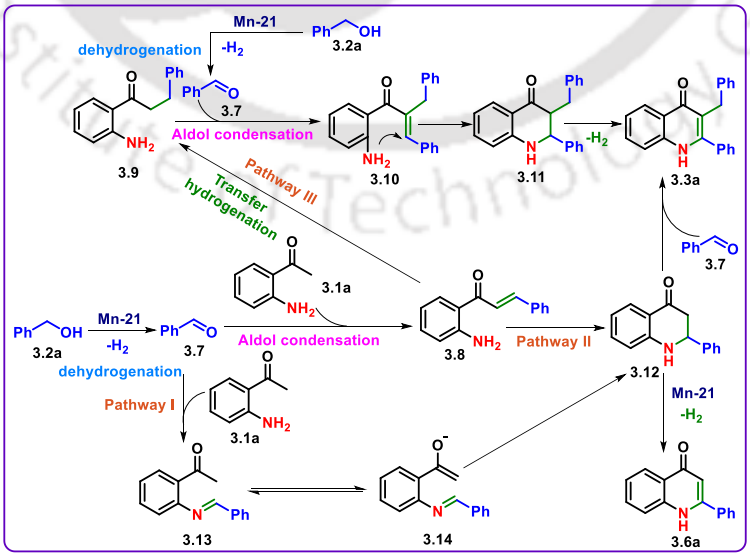
synthesize Penicinoline E, an antimalarial drug (**3.6o**) and Graveoline, an antitumor and herbicidal drug (**3.6t**) successfully and in more convenient and greener way as compared to the classical procedures.[23]

3.3.1.6. Mn-catalyzed synthesis of 2-substituted 4-quinolone derivatives from various alcohols and 2′-aminoacetophenones: substrate scope[a,b]



[a] Reaction conditions: **3.1** (0.5 mmol), **3.2** (1.0 mmol), K_2CO_3 (4.0 equiv.), **Mn-1** (5 mol%), Neat condition, 40 h, 140 ˚C, under argon. [b]Isolated yield.

3.3.1.7. Mechanistic investigation:

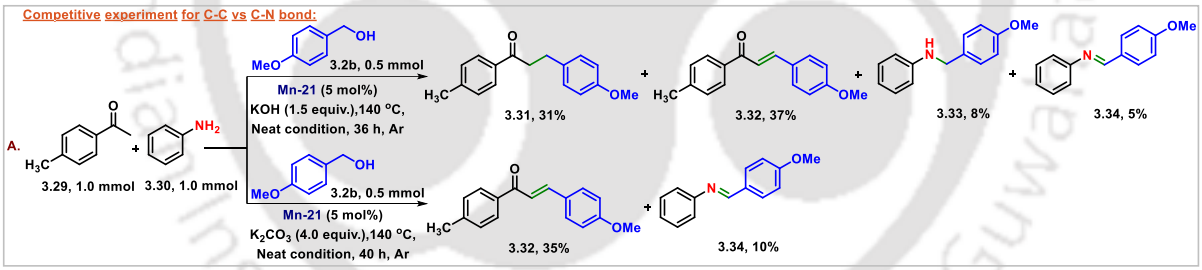


Scheme 3.11. Plausible pathways involved for the construction of 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) and 2-phenylquinolin-4(1H)-one (**3.6a**).

In prior to enter into the mechanistic investigations, three possible mechanistic pathways for the synthesis 2,3-disubstituted 4-quinolones and two possible pathways for 2-substituted 4-quinolones was proposed in that tandem multistep (de)hydrogenative process which has been outlined in Scheme **3.11**, At the outset, in presence of **Mn-21** complex benzyl alcohol (**3.2a**) get dehydrogenated into its corresponding benzaldehyde (**3.7**). Once benzaldehyde (**3.7**) was formed, in reaction with 2′-aminoacetophenone (**3.1a**), there was two possibilities. In pathway-**I**, it may undergo condensation with amine to form imine which via Mannich type cyclization furnished intermediate 2-substituted 2,3-dihydro-4-quinolone (**3.12**) or in pathway-**II**, that benzaldehyde (**3.7**) will undergo base assisted Claisen-Schmidt condensation furnishing the chalcone intermediate (**3.8**), which upon further cyclization generate intermediate **3.12**. Now, the intermediate **3.12** upon condensation with benzaldehyde (**3.7**) can produce 2,3-disubstituted 4-quinolone (**3.3a**). The intermediate **3.12** upon dehydrogenation can also form 2-substituted 4-quinolone (**3.6a**). Now, there was another possibility (pathway-**III**), in which the chalcone intermediate (**3.8**) undergo in situ generated **Mn-H** mediated transfer hydrogenation and furnish intermediate **3.9** which upon successive condensation with preformed benzaldehyde (**3.7**) followed by Aza-Michael type reaction manifested the intended product **3.3a**.

In pursuit to elucidate the reaction mechanism and to know which one was the dominant pathway, a series of control experiments was conducted.

Initially, the borrowing hydrogen mediated selective construction of C-C and C-N bond was examined.

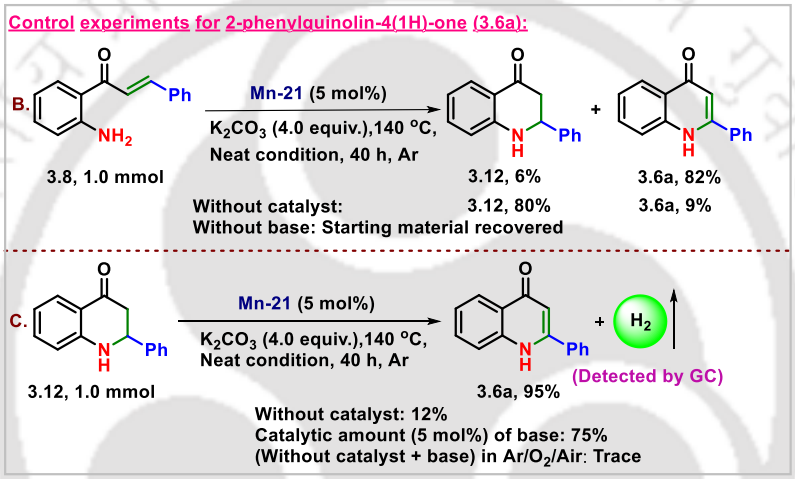


Scheme 3.12. A. Competitive experiment for C-C vs C-N bond.

Henceforth, when the competitive experiment was pursued upon treating 4-methoxy benzyl alcohol (**3.2b**) with an equimolar mixture of aniline and 4′-methylacetophenone, in presence of KOH a high selectivity towards the formation of C-C bond was observed whilst in case of K_2CO_3 although the selectivity is somewhat lower but formation of C-C bond surpluses over C-N bond formation (Scheme **3.11**, A). This outcome underpins that for the synthesis of 2-substituted 4-quinolone (**3.6a**) it followed pathway-**II** and for the synthesis of 2,3-disubstituted 4-quinolone (**3.3a**), it may follow either pathway-**II** or pathway-**III**.

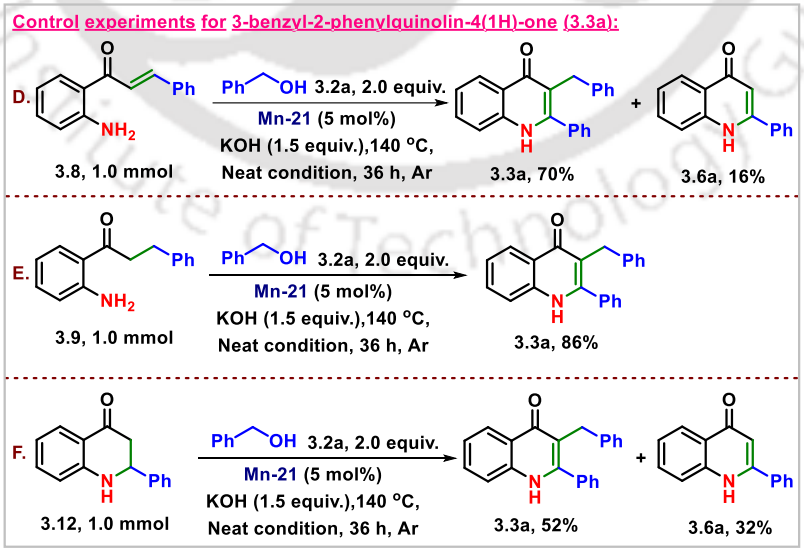
Afterwards, the intension was to unveil the probable intermediate involved and the role of base as well as catalyst towards the synthesis of 2-substituted 4-quinolone (**3.6a**). For that, the experiment was started upon treating the chalcone intermediate **3.8** with its streamline reaction conditions and it furnished only 6% of 2-substituted 2,3-dihydro-4-quinolone (**3.12**) and 82% of its dehydrogenated

analogue *i.e.* desired 2-phenylquinolin-4(1H)-one (**3.6a**). However, it was noted that in absence of catalyst 80% of **3.12** and only 9% of **3.6a** was observed whereas in absence of base the reaction does not proceed (Scheme **3.12**, B). These results indicated that in Aza-Michael type cyclization reaction, base plays key role whilst in the transformation of **3.12** to **3.6a** catalyst have important role. To materialize this hypothesis, when the intermediate **3.12** was treated in its optimal reaction condition, 95% of **3.6a** was obtained whereas in absence of **Mn-21** only 12% was manifested, which emphasized the essential role of **Mn-21** in that transformation (Scheme **3.12**, C). The evolved hydrogen gas was detected upon GC analysis of the reaction headspace confirming the involvement of dehydrogenative pathway (experimental section **3.5.15**). These two control experiments underpin that the chalcone **3.8** and 2-substituted 2,3-dihydro-4-quinolone, **3.12** was the most probable intermediate towards the synthesis of 2-substituted 4-quinolone (**3.6a**).



Scheme 3.12. Control experiments for 2-substituted 4-quinolone (**3.6a**).

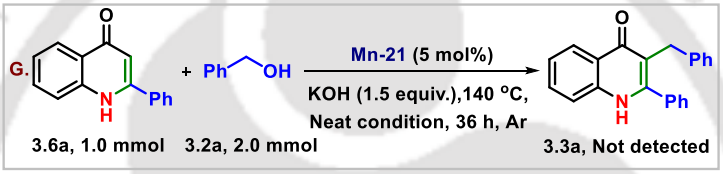
Next intension was the pathway involved for synthesis of 2,3-disubstituted 4-quinolones (**3.3a**).



Scheme 3.12. Control experiments for 2,3-disubstituted 4-quinolones (**3.3a**).

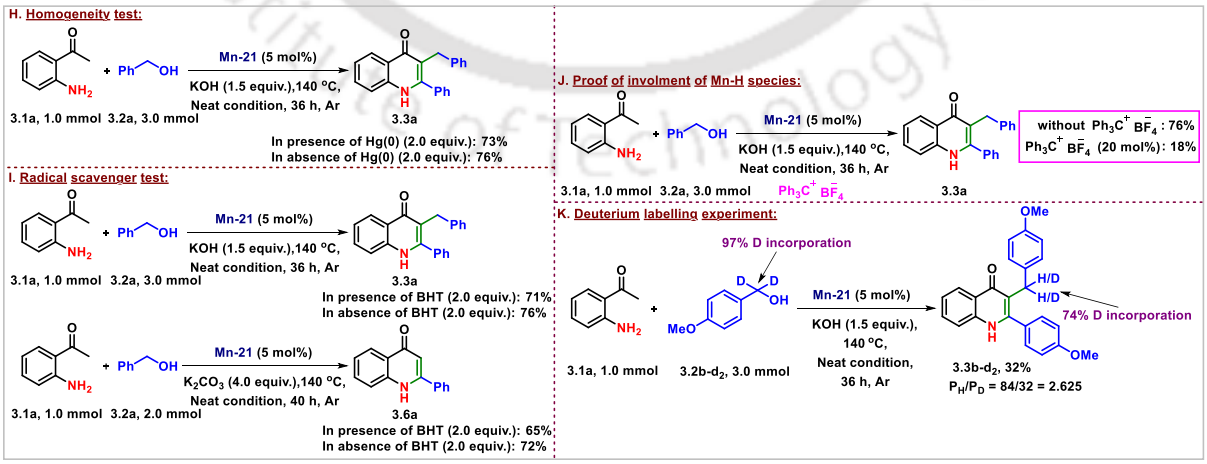
For that, when the reaction was carried out between the chalcone intermediate **3.8** (Scheme **3.12**, D) and it's hydrogenated analogue intermediate **3.9** (Scheme **3.11**, E) with primary alcohol (**3.2a**) respectively, it furnished the desired 2,3-disubstituted 4-quinolone (**3.3a**) with an appeasement result close to the optimal yield whilst performing the reaction between 2-substituted 2,3-dihydro-4-quinolone intermediate (**3.12**) with benzyl alcohol (**3.2a**) under the streamlined condition, a mixture of 2,3-disubstituted 4-quinolone (**3.3a**, 52%) and 2-substituted 4-quinolone (**3.6a**, 32%) was formed (Scheme **3.11**, F). However, in the optimal reaction condition formation of **3.6a** was not detected. These results highlighted that **3.8** and **3.9** were the most probable intermediates and also suggested that pathway-**III** was more preferable over pathway-**II** for the construction of 2,3-disubstituted 4-quinolone (**3.3a**).

Furthermore, the participation of **3.6a** in the synthesis of **3.3a** was invalidated as no detectable conversion of **3.3a** was obtained during the reaction of **3.6a** with benzyl alcohol (**3.2a**) under the streamline reaction condition (Scheme **3.11**, G).



Scheme 3.12. Control experiments for 2,3-disubstituted 4-quinolones (**3.3a**).

The reaction's homogenous nature was probed by adding mercury drops, where no detrimental effect has been manifested (Scheme **3.12**, H). The radical trapping experiment was conducted employing 2,6-di-tert butyl-4-methylphenol (BHT) as a radical scavenger which negated the involvement of single electron in the catalytic cycle towards the construction of both 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) and 2-phenylquinolin-4(1H)-one (**3.6a**) product (Scheme **3.11**, I). In presence of 20 mol% of trityl cation (with respect to catalyst) there was a significant decrement in the yield has been noticed which underpins the involvement of **Mn-H** species in reaction pathway (Scheme **3.11**, J).[24]



Scheme 3.12. Control experiments for 2,3-disubstituted 4-quinolones (**3.3a**).

The deuterium kinetic isotope effect experiment shows P_H/P_D = 2.625 with 74% 'D' incorporation implying that the *α*-cleavage of C-H bond of primary alcohol *i.e.* the dehydrogenation of primary alcohol could be the slowest step or rate-determining step of the catalytic cycle which also get supported form kinetic profile diagram (Scheme **3.11**, K).

3.3.1.8. Kinetic experiments:

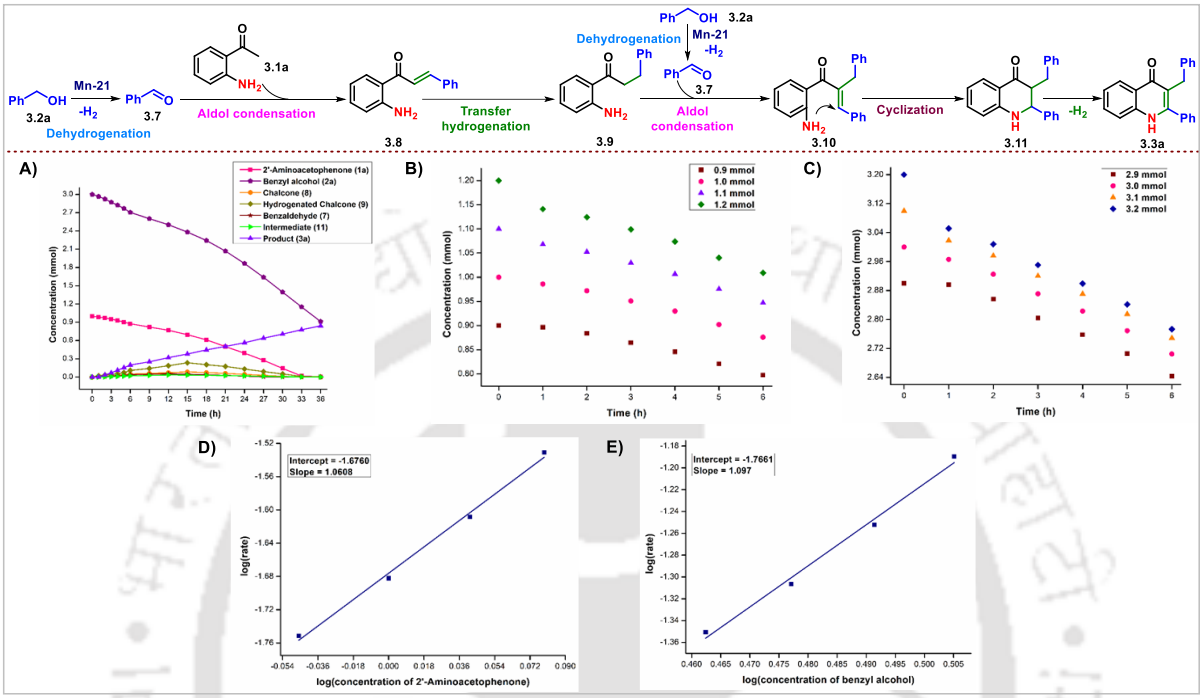


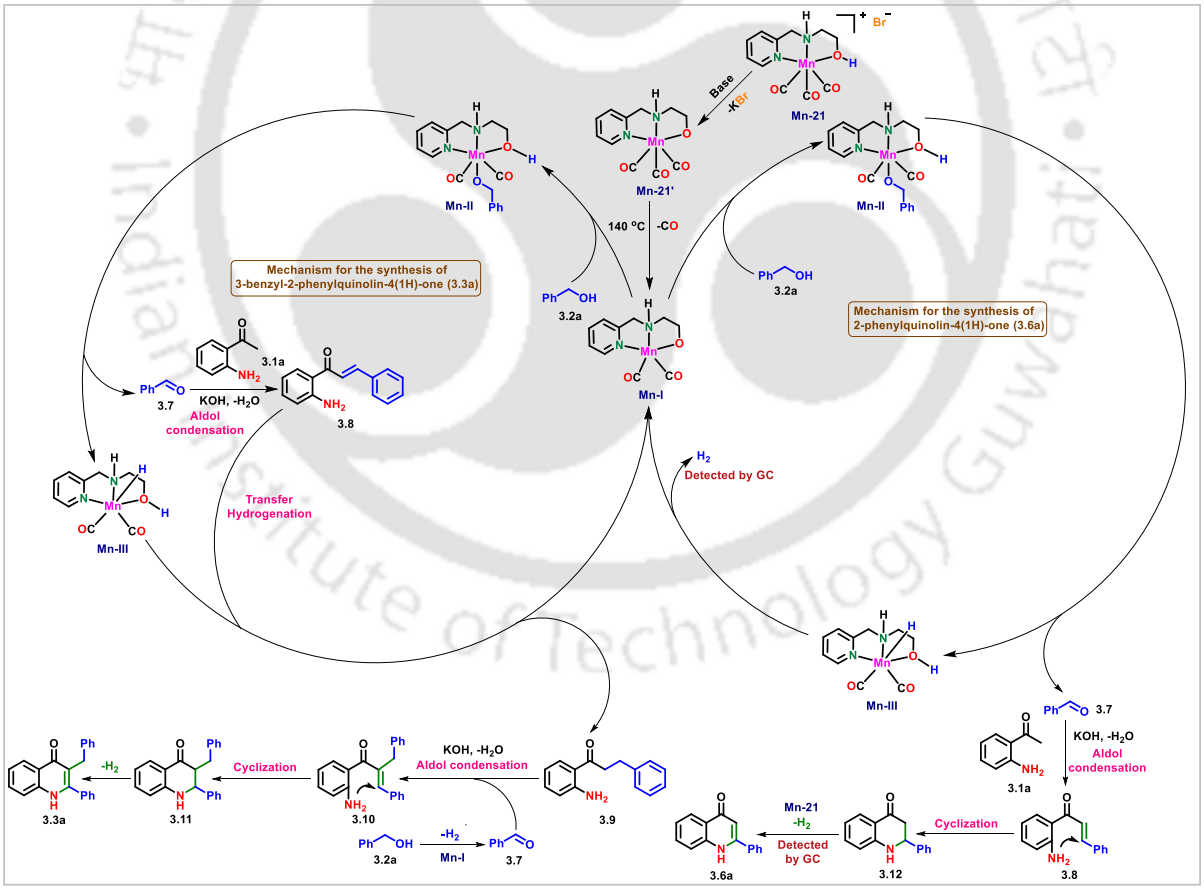
Figure 3.2. A) Kinetic monitoring of Mn(I)-catalyzed (de)hydrogenative synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**), B) Concentration versus time plot at various concentration of 2′-aminoacetophenone (**3.1a**), C) Concentration versus time plot at various concentration of Benzyl alcohol (**3.2a**), D) Plot for determining the order of the reaction with respect to log (concentration of 2′-aminoacetophenone (**3.1a**)), E) Plot for determining the order of the reaction with respect to log (concentration of benzyl alcohol (**3.2a**)).

Furthermore, to understand the reactivity pattern of this cascade (de)hydrogenative annulation reaction the reaction profile was examined. Kinetic monitoring of the reaction between 2′-aminoacetophenone (**3.1a**) and benzyl alcohol (**3.2a**) revealed that the concentration of the formed aldehyde (**3.7**), chalcone (**8**) and the intermediate 2-substituted 2,3-dihydro-4-quinolone (**3.11**) was low throughout the reaction. This indicated that the dehydrogenation of alcohol (**3.2a**) to its corresponding aldehyde (**3.7**) was relatively slower than the base assisted Claisen-Schmidt condensation, which was slower than **Mn-H** mediated transfer hydrogenation of chalcone (**3.8**). Once the chalcone get hydrogenated it further undergoes base assisted aldol condensation with another molecule of in situ formed aldehyde (**3.7**) which undergoes intramolecular Aza-Michael type reaction followed by dehydrogenation furnishing the desired 3-benzyl-2-phenylquinolin-4(1H)-one product (**3.3a**).

Furthermore, the effect of concentration of both reactant with the formation of product of 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) was also determined using initial rate law method. The order value derived from the time course profile diagram indicative that the first order dependence of rate on the concentration of both 2′-aminoacetophenone (**3.1a**) and benzyl alcohol (**3.2a**) underpinning the steady increase of product formation with increasing the initial concentration of both 2′-aminoacetophenone (**3.1a**) and benzyl alcohol (**3.2a**) (Figure **3.2** B – **3.2** E).

3.3.1.9. Proposed catalytic cycle:

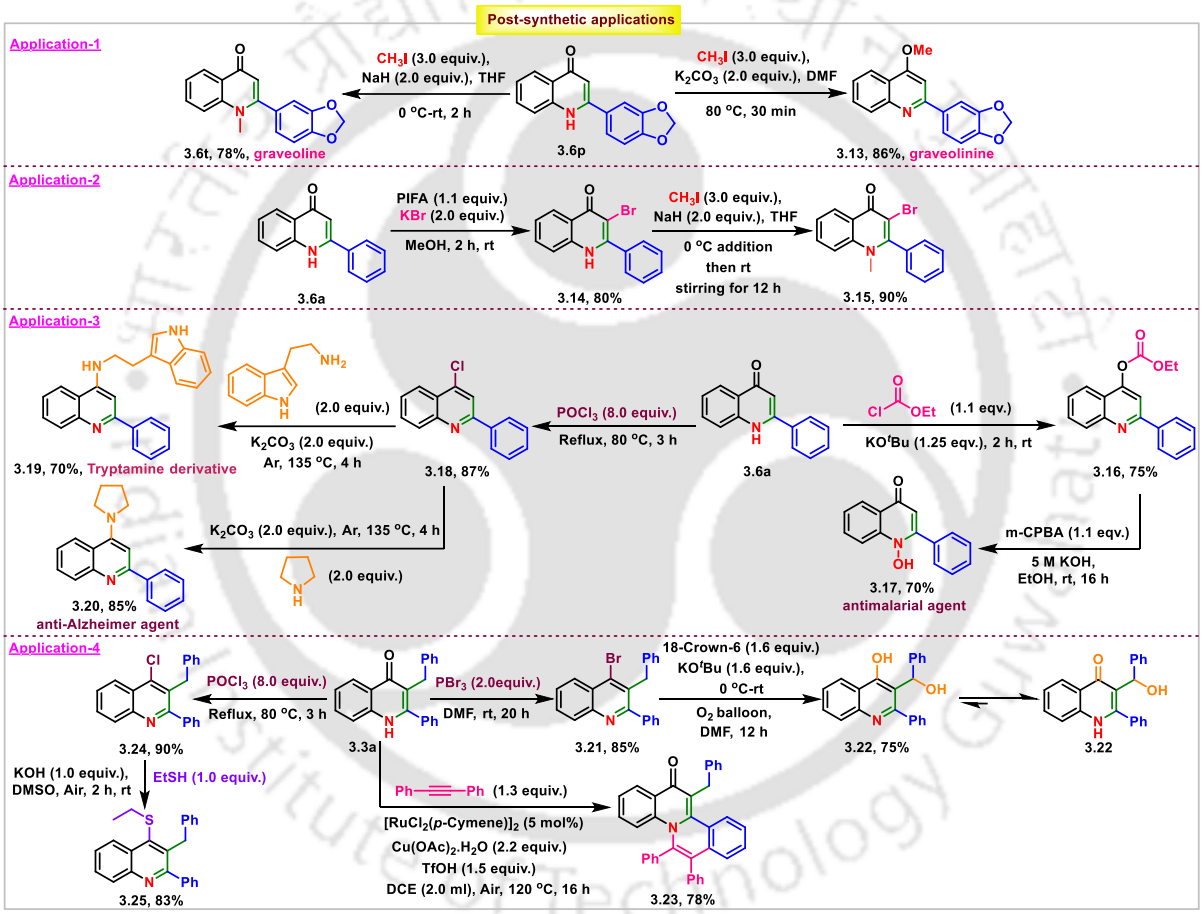
Accounting all the experiment results and literature reports[17, 18, 25] herein, the plausible catalytic cycle of the current catalytic protocol has depicted (Scheme **3.13**) where due to less steric hindrance and lower acidity at hydroxyl bifunctional site, it easily accommodated alcohols, various bulky unstable intermediates and participated in metal-ligand cooperation (MLC). At the outset, under the optimal conditions, the precatalyst *i.e.* hexacoordinate tricarbonyl cationic bromide complex **Mn-21** converted to its active catalytic species *i.e.* pentacoordinate dicarbonyl oxido complex **Mn-I** which dehydrogenate primary alcohol (**3.2a**) into its corresponding aldehyde (**3.7**) via MLC with the concomitant formation of **Mn-H** intermediate **Mn-III** (Scheme **3.13**).



Scheme 3.13. Plausible catalytic cycle of Mn-oxido arm mediated synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) and 2-phenylquinolin-4(1H)-one (**3.6a**).

Afterwards, the generated aldehyde (**3.7**) undergoes base assisted Claisen-Schmidt condensation furnishing the chalcone intermediate (**3.8**) upon removal of H_2O. Then, for the synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) the C=C bond of the chalcone intermediate (**3.8**) get hydrogenated via concerted transfer of hydride from the **Mn-H** and proton from the O-H site. The reduced intermediate **3.9** underwent base assisted second aldol condensation with preformed aldehyde (**3.7**) followed by consecutive cyclization and dehydrogenation resulted the desired 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) (Scheme **3.13**). However, for the construction of 2-phenylquinolin-4(1H)-one (**3.6a**) rather than transfer hydrogenation, chalcone (**3.8**) preferred the intramolecular Aza-Michael type reaction followed by successive dehydrogenation.

3.3.1.10. Post-synthetic modification:



Scheme 3.14. Post synthetic modifications.

To demonstrate the utility and efficacy of present catalytic strategy the attention was turned towards the construction of quinolone alkaloid graveoline (**3.6t**) and its aromatic sibling graveolinine (**3.13**) isolated from Ruta graveolens.[26] Both **3.6t** and **3.13** displayed diverse bioactivities ranging from antibacterial, antiplatelet aggregator, spasmolytic, and autophagy activity to apoptosis trigger and cytotoxic activity.[27] To execute the synthesis of graveoline (**3.6t**), the N-methylation reaction was conducted upon treatment of 2-(benzo[d][1,3]dioxol-5-yl)quinolin-4(1H)-one (**3.6p**) with NaH (2.0 equiv.) and MeI (3.0 equiv.) in anhydrous THF stirring at room temperature for 3 h (Scheme 2). The quinoline-based natural product

graveolinine (**3.13**) was synthesized from **3.6p** under thermodynamic alkylation−aromatization conditions found to be spectroscopically identical[28] with the natural product (Scheme **3.14**). The direct transformation of C(sp^2)−H bonds to C(sp^2)−X (X = heteroatom) bonds was desired for creating new and useful molecules, and halide groups were the most frequent functional groups in chemical transformations, particularly late stage C-H functionalization offered an efficient route to facilitate the development of pharmaceutically and biologically active compounds. In that arena, hypervalent iodine reagents were considered as environmentally benign synthetic tools due to their readily available property and unique reactivities similar to those of heavy metals. Again, it has been reported that aryl substituents at the C2 position of 4-quinolones significantly enhance their antitumor and antimitotic activities, while variation of substituents located at the C3 position of 4-quinolones influences their cytotoxicities.[29] Intrigued by these documented literature reports, the synthetic potential of current developed protocol was exaggerated upon treating 2-phenylquinolin-4(1H)-one (**3.6a**) product with hypervalent iodine (III) reagent (Bis(trifluoroacetoxy)iodo)benzene (PIFA) (1.1 equiv.) with KBr (2.0 equiv.) in MeOH solvent at room temperature for 2 h which furnished **3.14** with an 80% yield which upon N-methylation with MeI afforded compound **3.15** with excellent isolated yield (Scheme **3.14**)[30] The naturally occurring 1-hydroxy-4(1H)-quinolones were known for their antimalarial activity, inhibitors of respiratory and photosynthetic electron transport chains.[31] The synthesis of the N−OH compounds was achieved by reacting the quinolone **3.6a** with ethyl chloroformate to give carbonate **3.16** in 75% yield. This was then oxidized using m-CPBA (1.1 equiv.) followed by hydrolysis with KOH accomplished the desired N-hydroxy compound **3.17** in 70% yield (Scheme **3.14**).[32] Furthermore, halogenation of **3.6a** with $POCl_3$ provided the corresponding 4-chloroquinoline (**3.18**)[15] which upon treatment with tryptamine and pyrrolidine furnished the desired nucleophilic substituted product **3.19** and **3.20** in which **3.20** act as an anti-Alzheimer agent (Scheme **3.14**).[33] Next, the envisioned was that the 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) product could provide a new synthetic route to azafluorene via benzylic C-H hydroxylation and annulation. For that **3.3a** was transformed into **3.21** where the halogenation reaction was performed employing 2.0 equiv. of PBr_3 in DMF solvent.[15] Afterwards, the quinoline moiety (**3.21**) was reacted in presence of 18-Crown-6 (1.6 equiv.) and KO^{t}Bu (1.6 equiv.) under O_2 atmosphere at 0 °C to room temperature for 12 h where 75% of direct C3-hydroxylated quinoline (**3.22**) was isolated. This new C(sp^3)-H hydroxylation strategy[34] prompted to open a new window to construct various synthetically important molecules.[35] Furthermore, Ru(II)-catalyzed C-H annulation reaction was conducted over 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) where extended Π-conjugated polycyclic scaffold **3.23** has been furnished. Because of their strong Π-Π staking interaction these polycyclic scaffolds may have applications in “turn-on” or “light-up” biosensors or chemosensors, optoelectronics, bioimaging, DNA visualization etc (Scheme **3.14**).[36, 37] Furthermore, halogenation of **3.3a** with $POCl_3$ provided the corresponding 4-chloroquinoline (**3.24**) which direct nucleophilic substitution with ethanethiol afforded 4-sulfide quinoline (**3.25**) with good isolated yield (Scheme **3.14**).[15]

3.4. Conclusion:

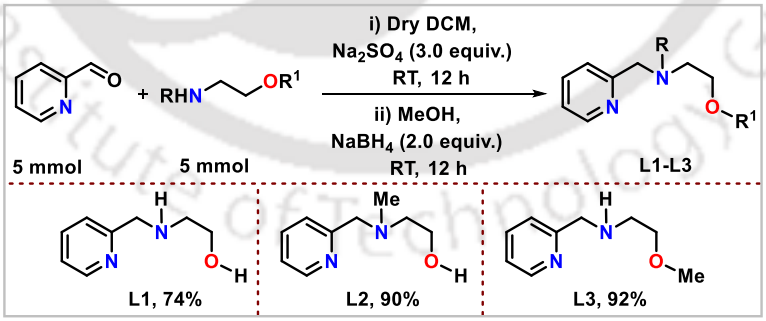
In conclusion, the current chapter demonstrated well-defined, sterically less hindered bifunctional Mn(I)-complex catalyzed switchable synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one and 2-phenylquinolin-4(1H)-one and their related analogues via ADC and BH or HA strategy employing renewable feedstock. The selective construction of that aforementioned heterocycles regulated by the nature of base. Notably, this integrated two-component coupling protocol offered an ample substrate scope bearing primary aromatic, hetero-aromatic and challenging aliphatic alcohols. The potentiality of this developed strategy was enhanced by chemoselective transformation of fatty acid derived alcohols keeping their distal double bond intact and efficacy was manifested by furnishing diverse range of synthetically and medicinally important molecules with good to excellent yields. The reaction route of that designed protocol was analysed and comprehended through conducting various control, kinetic and mechanistic experiments. The reduced steric assistance of the ligand oxido arm of bifunctional Mn(I)-complex at metal-ligand cooperative site hinges the entire catalytic cycle towards the accomplishment of intended N-heterocycles.

3.5. Experimental Section:

3.5.1. Ligands synthesis:

3.5.1.1. Synthesis and characterization of Pyridine based NNO Ligands:

Pyridine based all three NNO ligands were prepared according to previous reported literature methods.[38] To an oven dried 50 mL round bottomed flask equipped with a magnetic stir bar, Pyridine-2-carboxaldehyde (0.535 g, 5.0 mmol, 1.0 equiv.) and 2-Aminoethanol or their derivatives (5.0 mmol, 1.0 equiv.) were dissolved in 15 mL of dry CH_2Cl_2 and then Na_2SO_4 (2.131 g, 15.0 mmol, 3.0 equiv.) was added to the reaction mixture. The resulting suspension was stirred for 12 h at room temperature. Then, it was filtered, the residue was washed thoroughly with CH_2Cl_2 and the combined solvent was

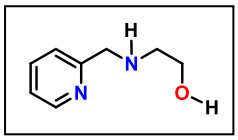


Scheme 3.14. Synthesis of PyNNO-ligands.

removed under reduced pressure. The residue obtained was directly used for the next step without further purification. The residue was dissolved in 30 mL of methanol and $NaBH_4$ (0.378 g, 10.0 mmol,2.0 equiv.) was added in a portion wise manner under stirring condition at 0 °C and the stirring was continued for overnight at room temperature. Then the solvent was evaporated and 15 mL of water was added. After that, it was extracted by CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4. Then the solvent was evaporated to get the crude product, which was further purified by silica

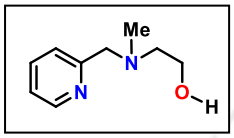
gel (100-200 mesh size) column chromatography using 60 –80% ethyl acetate in Petroleum ether (**Scheme 3.14**).[38]

2-((pyridin-2-ylmethyl)amino)ethan-1-ol (L1):[38]



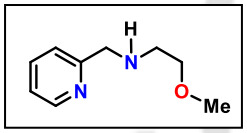
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 74% yield (0.563 g, 3.70 mmol) as a yellow liquid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.54 (d, *J* = 5.0 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 6.3 Hz, 1H), 3.97 (s, 2H), 3.95 (brs, 2H), 3.69 (t, *J* = 5.2 Hz, 2H), 2.83 (t, *J* = 5.2 Hz, 2H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 159.0, 149.2, 136.7, 122.5, 122.2, 60.6, 54.2, 51.1.

2-(methyl(pyridin-2-ylmethyl)amino)ethan-1-ol (L2):[38]



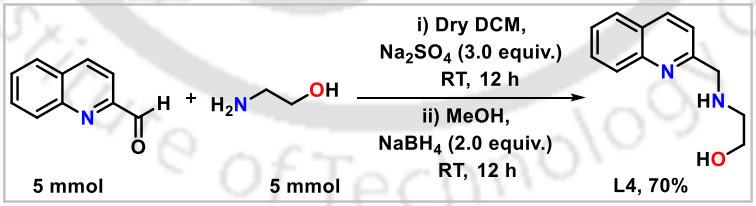
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 90% yield (0.748 g, 4.5 mmol) as a yellow liquid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.48 (d, *J* = 4.9 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.11 (t, *J* = 6.1 Hz, 1H), 3.68 (s, 2H), 3.59 (t, *J* = 5.3 Hz, 2H), 2.60 (t, *J* = 5.3 Hz, 2H), 2.27 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 158.7, 149.3, 136.7, 123.3, 122.3, 63.3, 59.0, 58.9, 42.6.

2-methoxy-N-(pyridin-2-ylmethyl)ethan-1-amine (L3):[38]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 92% yield (0.764 g, 4.6 mmol) as a brown liquid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.55 (d, *J* = 4.3 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.16 – 7.14 (m, 1H), 3.94 (s, 2H), 3.53 (t, *J* = 5.2 Hz, 2H), 3.36 (s, 3H), 2.85 (t, *J* = 5.2 Hz, 2H). 2.23 (brs, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 159.9, 149.4, 136.5, 122.3, 122.0, 72.2, 58.9, 55.3, 49.0.

3.5.1.2. Synthesis and characterization of Quinoline based NNO Ligand:

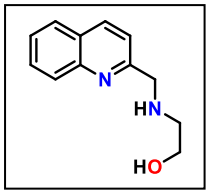


Scheme 3.15. Synthesis of QuinNNO-ligand.

To an oven dried 50 mL round bottomed flask equipped with a magnetic stir bar, 2-quinolinecarboxaldehyde (0.785 g, 5.0 mmol, 1.0 equiv.) and 2-aminoethanol (0.305 g, 5.0 mmol, 1.0 equiv.) were dissolved in 15 mL of dry CH_2Cl_2 and then Na_2SO_4 (2.131 g, 15.0 mmol, 3.0 equiv.) was added to the reaction mixture. The resulting suspension was stirred for 12 h at room temperature. Then, it was filtered, the residue was washed thoroughly with CH_2Cl_2 and the combined solvent was removed under reduced pressure. The residue obtained was directly used for the next step without further purification. The residue was dissolved in 30 mL of methanol and $NaBH_4$ (0.378 g, 10.0 mmol, 2.0

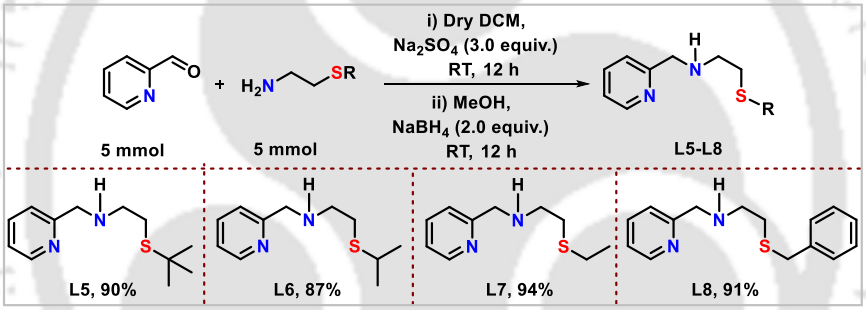
equiv.) was added in a portion wise manner under stirring condition at 0 °C and the stirring was continued for overnight at room temperature. Then the solvent was evaporated and 15 mL of water was added. After that, it was extracted by CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4. Then the solvent was evaporated to get the crude product, which was further purified by silica gel (100-200 mesh size) column chromatography using 60 –70% ethyl acetate in Petroleum ether (**Scheme 3.15**).[2]

2-((quinolin-2-ylmethyl)amino)ethan-1-ol (L4):[39]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 30/70) to afforded the title compound in 70% yield (0.708 g, 3.50 mmol) as a yellow liquid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.06 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 4.10 (s, 2H), 3.86 (brs, 2H), 3.70 (t, *J* = 5.1 Hz, 2H), 2.88 (t, *J* = 5.1 Hz, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 159.7, 147.4, 136.8, 129.7, 128.6, 127.6, 127.3, 126.3, 120.5, 60.7, 54.7, 51.4.

3.5.1.3. Synthesis of Pyridine based NNS Ligands (L5-L8):

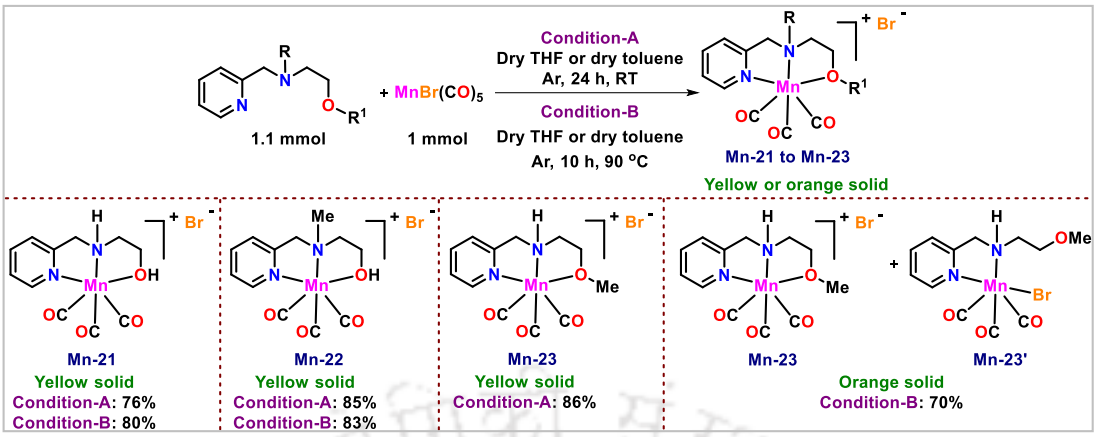


Scheme 3.16. Synthesis of PyNNS-ligands.

Pyridine based all four NNS ligands were prepared according to previous reported literature methods.[21] To an oven dried 50 mL round bottomed flask equipped with a magnetic stir bar, Pyridine-2-carboxaldehyde (0.535 g, 5.0 mmol, 1.0 equiv.) and amino-thiol compound (5.0 mmol, 1.0 equiv.) were dissolved in 15 mL of dry CH_2Cl_2 and then Na_2SO_4 (2.131 g, 15.0 mmol, 3.0 equiv.) was added to the reaction mixture. The resulting suspension was stirred for 12 h at room temperature. Then, it was filtered, the residue was washed thoroughly with CH_2Cl_2 and the combined solvent was removed under reduced pressure. The residue obtained was directly used for the next step without further purification. The residue was dissolved in 30 mL of methanol and $NaBH_4$ (0.378 g, 10.0 mmol, 2.0 equiv.) was added in a portion wise manner under stirring condition at 0 °C and the stirring was continued for overnight at room temperature. Then the solvent was evaporated and 15 mL of water was added. After that, it was extracted by CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4. Then the solvent was evaporated to get the crude product, which was further purified by silica gel (100-200 mesh size) column chromatography using 20-40 % ethyl acetate in Petroleum ether (Scheme **3.16**).[21]

3.5.2. Complexes synthesis: Synthesis and characterization of NNO-Mn(I) and NNS-Mn(I) complexes:

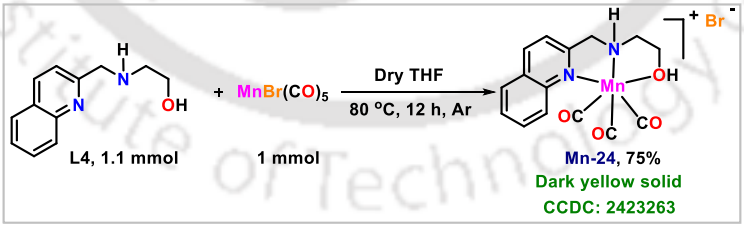
3.5.2.1. Procedure for synthesis of Pyridine based NNO-Mn(I) complexes (Mn-21 to Mn-23):



Scheme 3.17. Synthesis of Pyridine based NNO-Mn(I) complexes.

Pyridine based all three NNO-Mn(I) complexes were prepared according to the previous reported literature methods.[21] In an oven dried 25 mL round bottomed flask equipped with a condenser and a magnetic stir bar, 3 mL degassed dry colourless THF or Toluene solution of NNO ligands (**L1-L3**) (1.1 mmol, 1.1 equiv.) was added to the orange-yellow suspension of [$MnBr(CO)_5$] (0.275 g, 1.0 mmol, 1.0 equiv.) in 5 mL degassed dry THF or Toluene in a dropwise manner. Afterward, the resulting mixture was stirred at 90 °C for 12 h or for 24 h at room temperature under argon atmosphere. After the completion of the reaction, the reaction mixture was cooled down to the room temperature and the solvent was evaporated under reduced pressure to obtain the residue, which was further washed with n-hexane and diethyl ether, and dried under vacuum to get a yellow solid or orange solid of Mn-complexes (**Mn-21 to Mn-23**) (Scheme **3.17**). The structural elucidation of these complexes was accomplished with the help of ATIR, ^{1}H, $^{13}C\{^{1}H\}$ NMR and SCXRD and their characterization data were documented in previous literature report.[21]

3.5.2.2. Procedure for synthesis of Quinoline based NNO-Mn(I) complex (Mn-24):

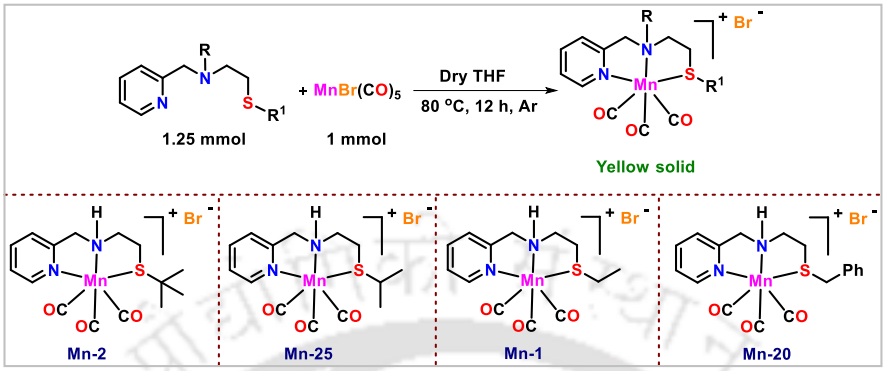


Scheme 3.18. Synthesis of Quinoline based NNO-Mn(I) complex.

In an oven dried 25 mL round bottomed flask equipped with a condenser and a magnetic stir bar, 3 mL degassed dry colourless THF solution of NNO ligand (**L4**) (1.1 mmol, 1.1 equiv.) was added to the orange-yellow suspension of [$MnBr(CO)_5$] (0.275 g, 1.0 mmol, 1.0 equiv.) in 5 mL degassed dry THF in a dropwise manner. Afterward, the resulting mixture was stirred at 80 °C for 12 h under argon atmosphere. After the completion of the reaction, the reaction mixture was cooled down to the room temperature and the solvent was evaporated under reduced pressure to obtain the residue, which was further washed with n-hexane and diethyl ether, and dried under vacuum to get a dark yellow solid of

Mn-complex (**Mn-24**) in 75% yield (0.514 g, 0.75 mmol) (Scheme **3.18**). The single crystal for **Mn-24** complex was grown by slow diffusion of diethyl ether in the saturated solution of **Mn-24** in acetonitrile in 5 mL glass vial kept at room temperature. **IR** (ATIR, in cm^{-1}): γ_{CO}2032.38, 1927.70, 1910.54.

3.5.2.3. Procedure for synthesis of NNS-Mn(I) complexes:



Scheme 3.19. Synthesis of Pyridine based NNS-Mn(I) complexes.

All four NNS-Mn(I) complexes were prepared according to the previous reported literature methods.[21] In an oven dried 25 mL round bottomed flask, 3 mL degassed dry THF solution of ligand [$(PyCH_2)HN(CH_2CH_2SR)$, R= ^{t}Bu, ^{i}Pr, Et, Bn] *i.e.* NNS ligands (**L5-L8**) (1.25 mmol, 1.25 equiv.) was added to the orange-yellow suspension of [$MnBr(CO)_5$] (0.275 g, 1.0 mmol, 1.0 equiv.) in 5 mL degassed dry THF in a dropwise manner. Afterward, the resulting reaction mixture was refluxed for 12 h under argon atmosphere. After the completion of the reaction, the reaction mixture was cooled down to the room temperature and the solvent was evaporated under reduced pressure to obtain the residue, which was further washed with n-hexane and diethyl ether, and dried under vacuum to get a yellow solid of Mn-complexes (Scheme **3.19**).

3.5.3. General experimental procedure for the synthesis of 2, 3-disubstituted 4-quinolone derivatives from various alcohols and 2′-aminoacetophenones:

To an oven dried 10 mL round-bottom flask equipped with a condenser and a magnetic stir bar, 2′-Aminoacetophenone analogue, **3.1** (0.5 mmol, 1.0 equiv.), primary aryl, heteroaryl or alkyl alcohol **3.2** (1.5 mmol, 3.0 equiv.), KOH (0.042 g, 0.75 mmol, 1.5 equiv.) and **Mn-21** (0.010 g, 0.025 mmol, 5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent to get the pure desired product.

3.5.4. General experimental procedure for the synthesis of 2, 3-disubstituted 4-quinolone derivatives from alcohols and functionally diverse *α*-alkylated 2'-aminoacetophenone based derivatives:

To an oven dried 10 mL round-bottom flask equipped with a condenser and a magnetic stir bar, α-alkylated 2'-aminoacetophenones, **3.1** (0.5 mmol, 1.0 equiv.), primary aryl, heteroaryl or cycloalkyl alcohol **3.2** (1.0 mmol, 2.0 equiv.), KOH (0.042 g, 0.75 mmol, 1.5 equiv.) and **Mn-21** (0.010 g, 0.025 mmol, 5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent to get the pure desired product.

3.5.5. General experimental procedure for the synthesis of 2, 3-disubstituted 4-quinolone derivatives from aliphatic alcohols and functionally diverse *α*-alkylated 2'-aminoacetophenone based derivatives:

To an oven dried 10 mL round-bottom flask equipped with a condenser and a magnetic stir bar, α-alkylated 2'-aminoacetophenones, **3.1** (0.5 mmol, 1.0 equiv.), primary aliphatic alcohol **3.2** (1.5 mmol, 3.0 equiv.), KOH (0.042 g, 0.75 mmol, 1.5 equiv.) and **Mn-21** (0.010 g, 0.025 mmol, 5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h or 72 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent to get the pure intended product.

3.5.6. General experimental procedure for the synthesis of 2-substituted 4-quinolone derivatives from various alcohols and 2′-aminoacetophenones:

To an oven dried 10 mL round-bottom flask equipped with a condenser and a magnetic stir bar, 2′-Aminoacetophenone analogue, **3.1** (0.5 mmol, 1.0 equiv.), primary aryl or heteroaryl alcohol **3.2** (1.0 mmol, 2.0 equiv.), K_2CO_3 (0.276 g, 2.0 mmol, 4.0 equiv.) and **Mn-21** (0.010 g, 0.025 mmol, 5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 140 °C in a preheated oil bath for 40 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent to get the pure desired product.

3.5.7. Manganese catalyzed dehydrogenation of alcohol:

To an oven dried 10 mL round bottomed flask equipped with a reflux condenser and a magnetic stir bar, benzyl alcohol, **3.2a** (0.108 g, 1.0 mmol, 1.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture

was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude reaction mixture was submitted and analysed by ^{1}H-NMR spectroscopy confirming that 18% of benzaldehyde **(3.7)** was detected.

3.5.8. Manganese catalyzed competitive experiment for C-C vs C-N bond formation:

To an oven dried 10 mL round bottomed flask equipped with a reflux condenser and a magnetic stir bar, 4′-Methylacetophenone, **3.29** (0.134 g, 1.0 mmol, 2.0 equiv.), aniline, **3.30** (0.093 g, 1.0 mmol, 2.0 equiv.), 4-methoxybenzyl alcohol, **3.2b** (0.069 g, 0.5 mmol, 1.0 equiv.), KOH (0.042 g, 0.75 mmol, 1.5 equiv.) and **Mn-21** (0.010 g, 0.025 mmol, 5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude reaction mixture was submitted and analysed by ^{1}H-NMR suggesting that 3-(4-methoxyphenyl)-1-(p-tolyl)propan-1-one, **(3.31)** was 31%, (*E*)-3-(4-methoxyphenyl)-1-(p-tolyl)prop-2-en-1-one **(3.32)** was 37%, N-(4-methoxybenzyl)aniline **(3.33)** was 8% and (*E*)-1-(4-methoxyphenyl)-N-phenylmethanimine **(3.34)** was 5% formed (Figure **3.3**).

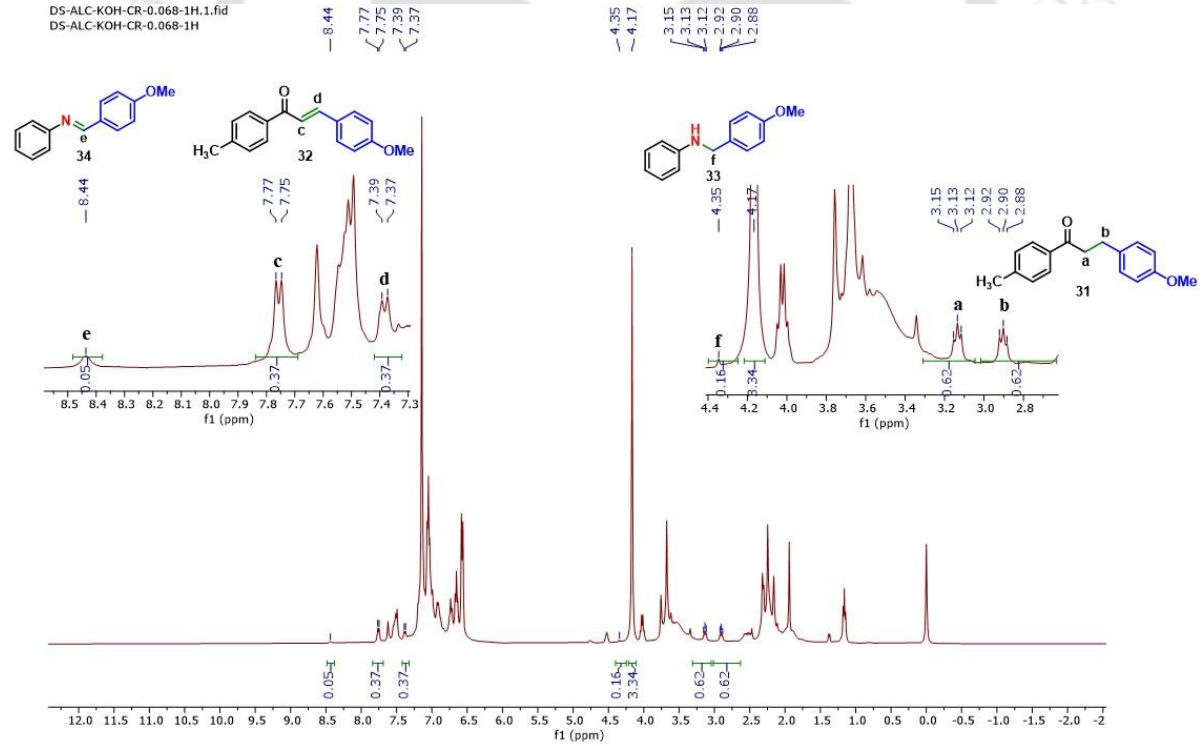


Figure 3.3. ^{1}H (400 MHz) NMR Spectrum of crude reaction mixture in $CDCl_3$.

To an oven dried 10 mL round bottomed flask equipped with a reflux condenser and a magnetic stir bar, 4′-Methylacetophenone, **3.29** (0.134 g, 1.0 mmol, 2.0 equiv.), aniline, **3.30** (0.093 g, 1.0 mmol, 2.0 equiv.), 4-methoxybenzyl alcohol, **3.2b** (0.069 g, 0.5 mmol, 1.0 equiv.), K_2CO_3 (0.276 g, 2.0 mmol, 4.0 equiv.) and **Mn-21** (0.010 g, 0.025 mmol, 5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 140 °C in a preheated oil bath for 40 h. After completion of the reaction, the

reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude reaction mixture was submitted and analysed by ^{1}H-NMR suggesting that (*E*)-3-(4-methoxyphenyl)-1-(p-tolyl)prop-2-en-1-one (**3.32**) was 32%, and (*E*)-1-(4-methoxyphenyl)-N-phenylmethanimine (**3.34**) was 13% formed (Figure **3.4**).

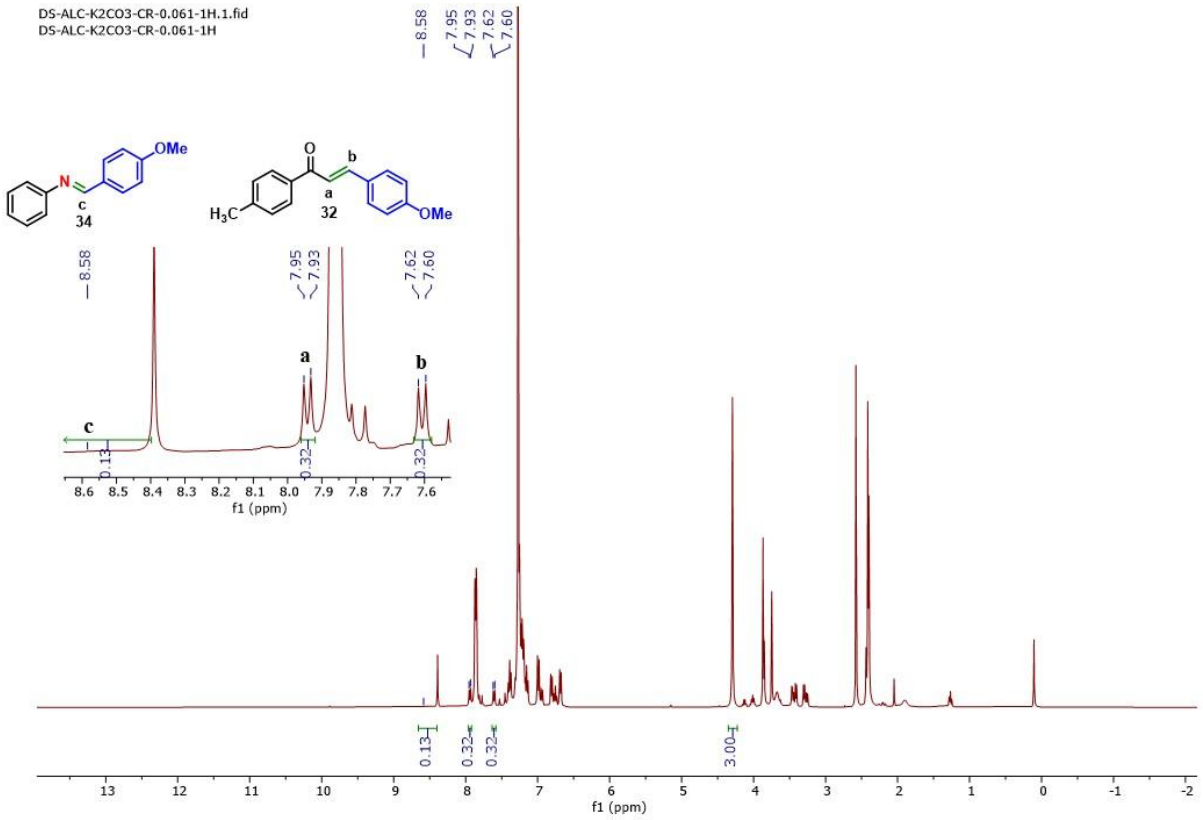


Figure 3.4. ^{1}H (400 MHz) NMR Spectrum of crude reaction mixture in $CDCl_3$.

3.5.9. Identification of possible intermediates involved in Manganese catalyzed synthesis of 2-phenylquinolin-4(1H)-one (3.6a):

These controlled experiments were performed to find out the possible intermediates which were involved in the synthesis of 2-phenylquinolin-4(1H)-one **(3.6a)**.

3.5.9.1. Manganese catalyzed reaction of (*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one (3.8):

To an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar, (*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one, **3.8** (0.223, 1.0 mmol, 1.0 equiv.), K_2CO_3 (0.553 g, 4.0 mmol, 4.0 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) were taken under argon atmosphere. Then, the reaction mixture was heated at 140 °C in a preheated oil bath for 40 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent (eluent: Pet. ether/EtOAc =

ranging from 70/30 to 20/80). In that isolation process, 2-phenyl-2,3-dihydroquinolin-4(1H)-one (**3.12**) was obtained in 6% yield (0.014 g, 0.06 mmol) as a bright yellow solid and 2-phenylquinolin-4(1H)-one (**3.6a**) was obtained in 82% yield (0.181 g, 0.82 mmol) as a white solid. Furthermore, when the reaction was conducted in absence of catalyst 80% yield (0.123 g, 0.80 mmol) of 2-phenyl-2,3-dihydroquinolin-4(1H)-one (**3.12**) was formed and 9% yield (0.020 g, 0.09 mmol) of 2-phenylquinolin-4(1H)-one (**3.6a**) has been detected. However, performing reaction in absence of base neither 2-phenyl-2,3-dihydroquinolin-4(1H)-one (**3.12**) nor 2-phenylquinolin-4(1H)-one (**3.6a**) was formed, the starting material get recovered.

3.5.9.2. Manganese catalyzed reaction of 2-phenyl-2,3-dihydroquinolin-4(1H)-one (3.12):

At the onset, 2-phenyl-2,3-dihydroquinolin-4(1H)-one, **3.12** (0.223, 1.0 mmol, 1.0 equiv.), K_2CO_3 (0.553 g, 4.0 mmol, 4.0 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) were taken to an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar. Then, the round-bottom flask was evacuated, backfilled with argon for three times and the reaction mixture was heated at 140 °C in a preheated oil bath for 40 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure, monitored by thin layer chromatography (TLC) and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 20/80) which afforded 95% yield (0.210 g, 0.95 mmol) of 2-phenylquinolin-4(1H)-one (**3.6a**) as a white solid. Furthermore, when the reaction was conducted in absence of catalyst only 12% yield (0.026 g, 0.12 mmol) of 2-phenylquinolin-4(1H)-one (**3.6a**) was formed. Again, 75% of **3.6a** (0.166 g, 0.75 mmol) was accomplished in presence of catalytic *i.e.* 5 mol% of base loading instead of 4.0 equiv. of base. Nevertheless, trace amount of the product **3.6a** was detected in absence of both catalyst and base irrespective of the environment of the reaction *i.e.* whether it was manifested under argon, oxygen or air.

3.5.10. Identification of possible intermediates involved in Manganese catalyzed synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one (3.3a):

These controlled experiments were performed to find out the possible intermediates which were involved in the synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one **(3.3a)**.

3.5.10.1. Manganese catalyzed reaction between (*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one (3.8) and benzyl alcohol (3.2a):

To an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar, (*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one, **3.8** (0.223, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.216 g, 2.0 mmol, 2.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) were taken under argon atmosphere. Then, the reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to

cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent (eluent: Pet. ether/EtOAc = ranging from 65/35 to 20/80). In that isolation process, 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) was obtained in 70% yield (0.218 g, 0.70 mmol) as a white solid and 2-phenylquinolin-4(1H)-one (**3.6a**) was obtained in 16% yield (0.035 g, 0.16 mmol) as a white solid.

3.5.10.2. Manganese catalyzed reaction between 1-(2-aminophenyl)-3-phenylpropan-1-one (3.9) and benzyl alcohol (3.2a):

To an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar, 1-(2-aminophenyl)-3-phenylpropan-1-one, **3.9** (0.225, 1.0 mmol, 1.0 equiv.), benzyl alcohol, 3.**2a** (0.216 g, 2.0 mmol, 2.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) were taken under argon atmosphere. Then, the reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature, ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure, monitored by thin layer chromatography (TLC) and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 65/35) which afforded 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) in 86% yield (0.268 g, 0.86 mmol) as a white solid.

3.5.10.3. Manganese catalyzed reaction between 2-phenyl-2,3-dihydroquinolin-4(1H)-one (3.12) and benzyl alcohol (3.2a):

To an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar, 2-phenyl-2,3-dihydroquinolin-4(1H)-one, **3.12** (0.223, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.216 g, 2.0 mmol, 2.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) were taken under argon atmosphere. Then, the reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent (eluent: Pet. ether/EtOAc = ranging from 65/35 to 20/80). In that isolation process, 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) was obtained in 52% yield (0.162 g, 0.52 mmol) as a white solid and 2-phenylquinolin-4(1H)-one (**3.6a**) was obtained in 32% yield (0.071 g, 0.32 mmol) as a white solid. However, in the optimal reaction only 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) was obtained, no 2-phenylquinolin-4(1H)-one (**3.6a**) has been isolated.

3.5.10.4. Manganese catalyzed reaction between 2-phenylquinolin-4(1H)-one (3.6a) and benzyl alcohol (3.2a):

To an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar, 2-phenylquinolin-4(1H)-one, **3.6a** (0.221, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.216 g, 2.0 mmol, 2.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) were taken under argon atmosphere. Then, the reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure, monitored by thin layer chromatography (TLC) and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent (eluent: Pet. ether/EtOAc = ranging from 65/35 to 20/80). However, in that isolation process, no 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) was isolated and the reactant, 2-phenylquinolin-4(1H)-one (**3.6a**) was recovered as a white solid.

3.5.11. Hg-dropping experiment:

To an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar, 2′-Aminoacetophenone, **3.1a** (0.135 g, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.324 g, 3.0 mmol, 3.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and metallic Hg (0.401 g, 2.0 mmol, 2.0 equiv.) were taken together and connected with high vacuum for 10 minutes. Then **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) was added under gentle flow of argon. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 65/35) which afforded 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) in 73% yield (0.227 g, 0.73 mmol) as a white solid. In absence of 2.0 equiv. metallic Hg, it afforded 76% yield (0.237 g, 0.76 mmol) of **3.3a** as a white solid.

3.5.12. Radical involvement test in the catalysis:

To an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar, 2′-Aminoacetophenone, **3.1a** (0.135 g, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.324 g, 3.0 mmol, 3.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and BHT (0.441 g, 2.0 mmol, 2.0 equiv.) were taken together and remove air through high vacuum upon connecting for 10 minutes. Then **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) was added under gentle stream of argon. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 65/35) which afforded 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) in 71% yield (0.221

g, 0.73 mmol) as a white solid. In absence of radical scavenger BHT, it afforded 76% yield (0.237 g, 0.76 mmol) of **3.3a** as a white solid.

To an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar, 2′-Aminoacetophenone, **3.1a** (0.135 g, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.216 g, 2.0 mmol, 2.0 equiv.), K_2CO_3 (0.553 g, 4.0 mmol, 4.0 equiv.) and BHT (0.441 g, 2.0 mmol, 2.0 equiv.) were taken together and remove air through high vacuum upon connecting for 10 minutes. Then **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) was added under gentle stream of argon. The reaction mixture was heated at 140 °C in a preheated oil bath for 40 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 20/80) which afforded 2-phenylquinolin-4(1H)-one (**3.6a**) in 65% yield (0.144 g, 0.65 mmol) as a white solid. In absence of radical scavenger BHT, it afforded 72% yield (0.159 g, 0.72 mmol) of **3.6a** as a white solid.

3.5.13. Metal hydride trapping experiment:

To an oven dried 100 mL Ace pressure tube equipped with a magnetic stir bar, 2′-Aminoacetophenone, **3.1a** (0.135 g, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.324 g, 3.0 mmol, 3.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) was added sequentially inside the argon filled glove box. Then the reaction mixture was stirred at room temperature. After stirring for 0.5 h, tritylium tetrafluoroborate ($Ph_3C^+ BF_4^-$) (0.066 g, 0.20 mmol, 20 mol%) was added to the reaction mixture. Then, the tube was sealed and placed at 140 °C in a preheated oil bath. After stirring for 36 h, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 65/35) which afforded 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) in 18% yield (0.056 g, 0.18 mmol) as a white solid. The detrimental effect in the yield indicated the involvement of in situ formed Mn-H in the catalytic cycle.

3.5.14. Deuterium scrambling experiment:

At the onset, 2′-Aminoacetophenone, **3.1a** (0.135 g, 1.0 mmol, 1.0 equiv.), (4-methoxyphenyl)methan-d_2-ol, **3.2b-d$_2$**[40] (0.422 g, 3.0 mmol, 3.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) were charged successively to an oven dried 10 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar. Then, the round-bottom flask was evacuated, backfilled with argon for three times and the reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through a small pad of celite. The resultant volatiles were evaporated under reduced pressure, monitored by thin layer chromatography

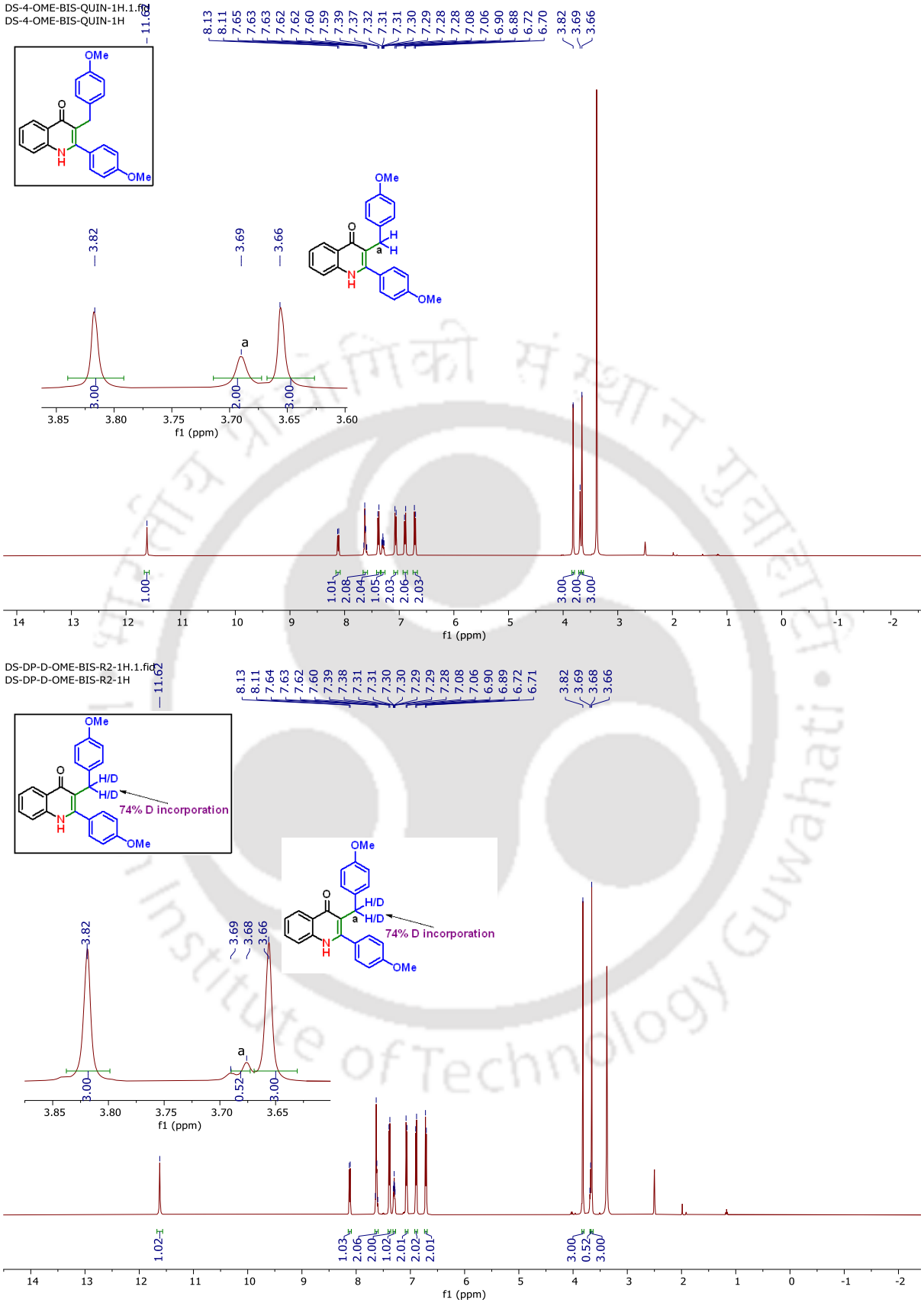


Figure 3.5. ^{1}H (400 MHz) and ^{1}H (500 MHz) NMR Spectrum of **3-(4-methoxybenzyl)-2-(4-methoxyphenyl)quinolin-4(1H)-one (3.3b)** and **3.3b-d$_2$** in DMSO-d_6 respectively.

(TLC) and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 65/35) which afforded the desired **3.3b-d_2** in 32% yield with 74% deuterium incorporation in the benzylic position as a white solid. The percentage of deuterium incorporation was analysed by ^{1}H-NMR spectroscopy. When the same reaction was conducted employing 4-Methoxybenzyl alcohol, **3.2b** (0.405 g, 3.0 mmol, 3.0 equiv.) as a coupling partner under the similar reaction conditions 84% yield (0.312 g, 0.84 mmol) of 3-(4-methoxybenzyl)-2-(4-methoxyphenyl)quinolin-4(1H)-one (**3.3b**) was isolated as a white solid which revealed that the value of P_H/P_D = 2.625 (Figure **3.5**).

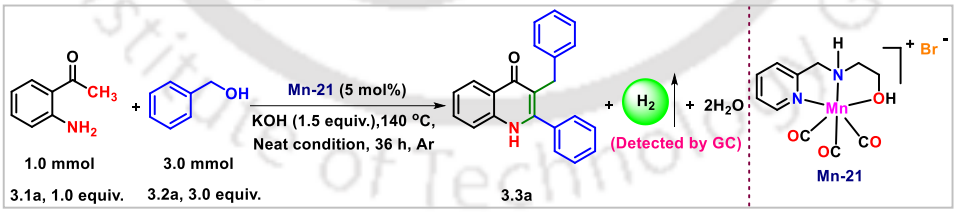
3.5.15. Detection of evolved hydrogen gas by GC-Thermal Detector (GC-TCD):

3.5.15.1. Detection of evolved hydrogen gas by GC-Thermal Detector (GC-TCD) for Mn-catalyzed synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one (3.3a) from 2′-aminoacetophenone (3.1a) and benzyl alcohol (3.2a):

To an oven dried 100 mL Ace pressure tube equipped with a magnetic stir bar, 2′-Aminoacetophenone, **3.1a** (0.135 g, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.324 g, 3.0 mmol, 3.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) was added sequentially inside the argon filled glove box. Then the reaction mixture was stirred at room temperature for 0.5 h. Then, the tube was sealed and placed at 140 °C in a preheated oil bath for next 36 h. After completion of the reaction, the Ace pressure tube was cooled at 0 °C, the evolved gas was syringed out and detected from PerkinElmer clarus-590 GC instrument using Elite-Q PLOT Capillary Column (30 m length x 530 µm x 20 µm ID) employing the following method:

TCD starting temperature: 40 °C, Oven temperature: 60 °C, Time at starting temperature: 0 min, Hold time: 5 min, Ramp: 28 °C/ min up to 200 °C, Flow rate: 5 mL/ min (N_2), Split ration: 20, Inlet temperature: 40 °C, Detector temperature TCD: 200 °C,

The detected gas chromatogram was shown in figure **3.6** (right).



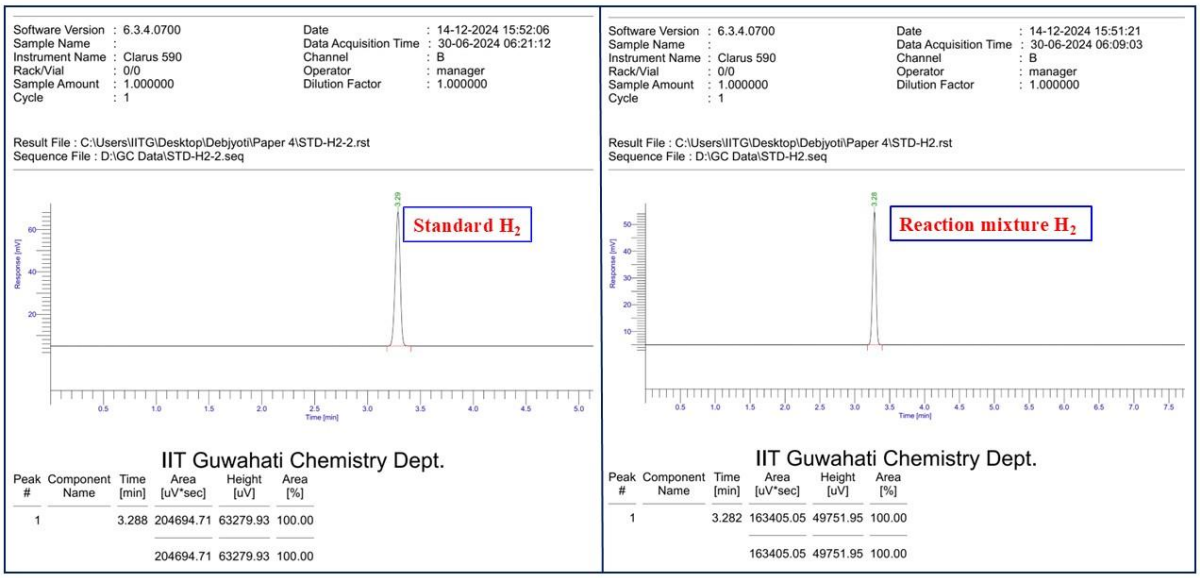


Figure 3.6. Chromatogram of standard hydrogen gas (left) and evolved hydrogen gas during catalysis (right).

3.5.15.2. Detection of evolved hydrogen gas by GC-Thermal Detector (GC-TCD) for Mn-catalyzed synthesis of 2-phenylquinolin-4(1H)-one (3.6a) from 2′-aminoacetophenone (3.1a) and benzyl alcohol (3.2a):

To an oven dried 100 mL Ace pressure tube equipped with a magnetic stir bar, 2′-Aminoacetophenone, **3.1a** (0.135 g, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.216 g, 2.0 mmol, 2.0 equiv.), K_2CO_3 (0.553 g, 4.0 mmol, 4.0 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) was added sequentially inside the argon filled glove box. Then the reaction mixture was stirred at room temperature for 0.5 h. Then, the tube was sealed and placed at 140 °C in a preheated oil bath for next 40 h. After completion of the reaction, the Ace pressure tube was cooled at 0 °C, the evolved gas was syringed out and detected from PerkinElmer clarus-590 GC instrument using Elite-Q PLOT Capillary Column (30 m length x 530 µm x 20 µm ID) employing the following method:

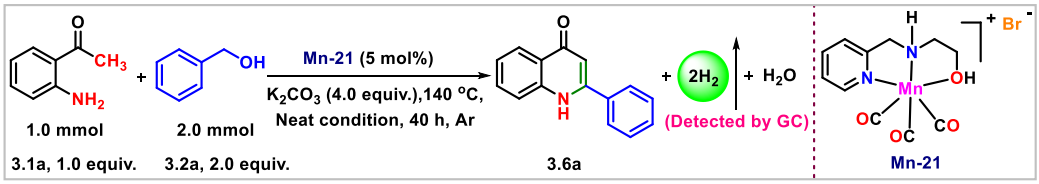
TCD starting temperature: 40 °C

Oven temperature: 60 °C, Time at starting temperature: 0 min, Hold time: 5 min

Ramp: 28 °C/ min up to 200 °C, Flow rate: 5 mL/ min (N_2), Split ration: 20

Inlet temperature: 40 °C, Detector temperature TCD: 200 °C

The detected gas chromatogram was shown in figure **3.7** (right).



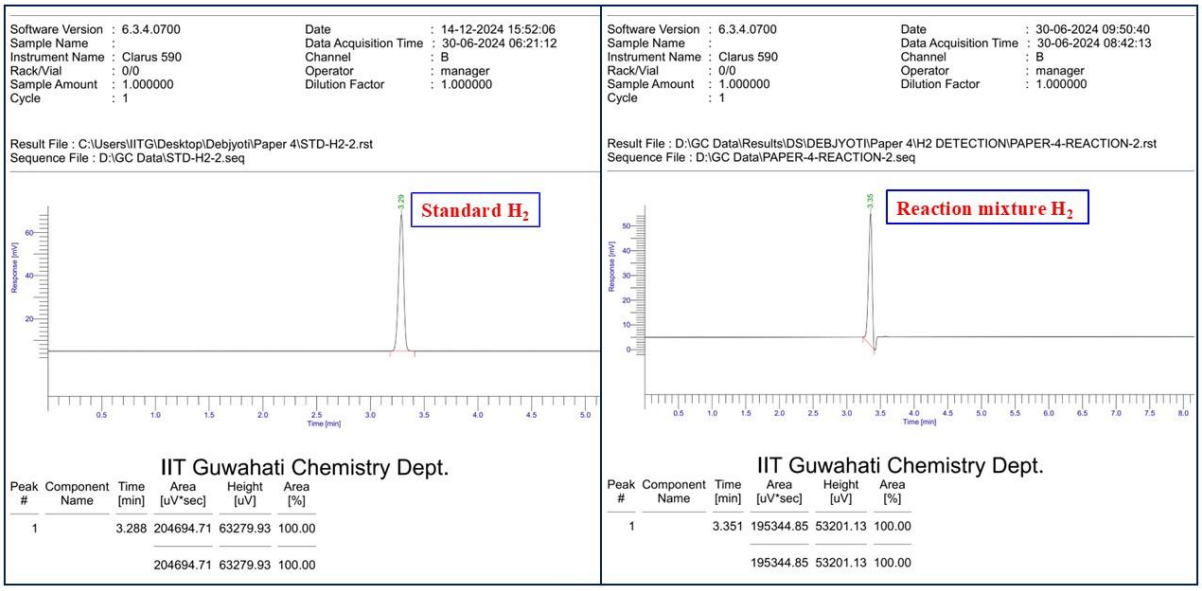


Figure 3.7. Chromatogram of standard hydrogen gas (left) and evolved hydrogen gas during catalysis (right).

3.5.15.3. Detection of evolved hydrogen gas by GC-Thermal Detector (GC-TCD) during Mn-catalyzed transformation of 2-phenyl-2,3-dihydroquinolin-4(1H)-one (3.12) to 2-phenylquinolin-4(1H)-one (3.6a):

To an oven dried 100 mL Ace pressure tube equipped with a magnetic stir bar, 2-phenyl-2,3-dihydroquinolin-4(1H)-one, **3.12** (0.223, 1.0 mmol, 1.0 equiv.), K_2CO_3 (0.553 g, 4.0 mmol, 4.0 equiv.) and **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) was added sequentially inside the argon filled glove box. Then the reaction mixture was stirred at room temperature for 0.5 h. Then, the tube was sealed and placed at 140 °C in a preheated oil bath for next 40 h. After completion of the reaction, the Ace pressure tube was cooled at 0 °C, the evolved gas was syringed out and detected from PerkinElmer clarus-590 GC instrument using Elite-Q PLOT Capillary Column (30 m length x 530 µm x 20 µm ID) employing the following method:

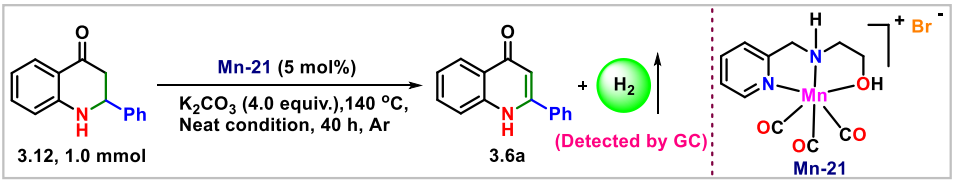
TCD starting temperature: 40 °C

Oven temperature: 60 °C, Time at starting temperature: 0 min, Hold time: 5 min

Ramp: 28 °C/ min up to 200 °C, Flow rate: 5 mL/ min (N_2), Split ration: 20

Inlet temperature: 40 °C, Detector temperature TCD: 200 °C

The detected gas chromatogram was shown in figure **3.8** (right).



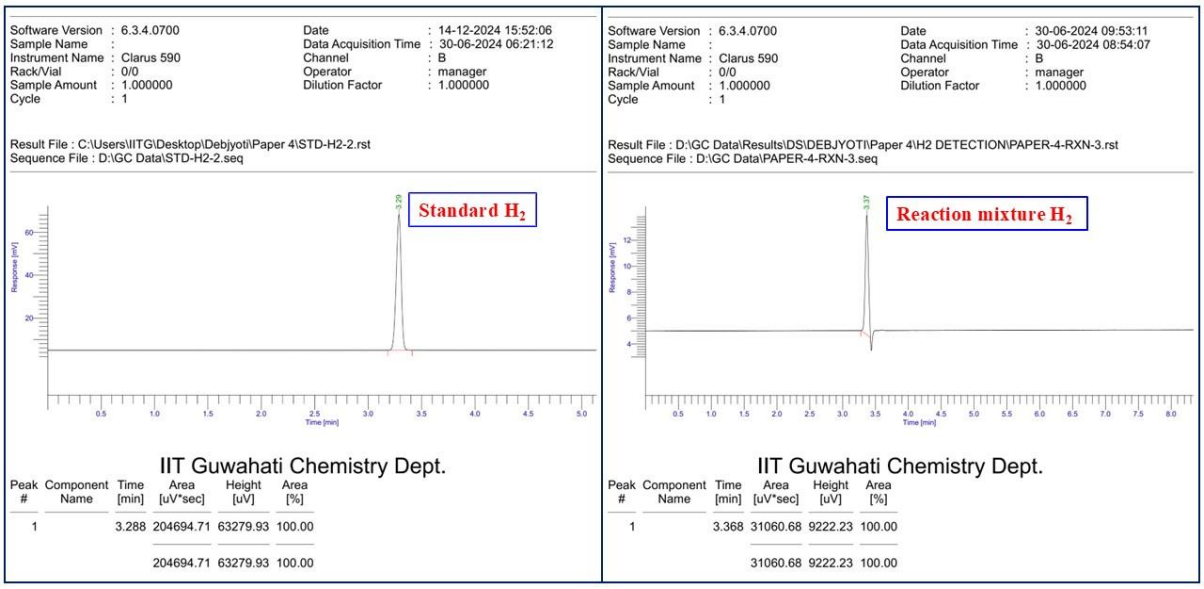


Figure 3.8. Chromatogram of standard hydrogen gas (left) and evolved hydrogen gas during catalysis (right).

3.5.16. Kinetic experiments:

3.5.16.1. Monitoring the kinetics of the reaction:

Experimental procedure: To an oven dried 10 mL two neck round bottomed flask equipped with a reflux condenser and a magnetic stir bar, 2′-Aminoacetophenone, **3.1a** (0.135 g, 1.0 mmol, 1.0 equiv.), benzyl alcohol, **3.2a** (0.324 g, 3.0 mmol, 3.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) were taken sequentially and connected with high vacuum for 15 minutes. Then, **Mn-21** (0.020 g, 0.05 mmol, 5 mol%) and mesitylene (0.121 g, 1.0 mmol, 1.0 equiv.) as an internal standard were added to the mixture under gentle flow of argon. In that way, sixteen different reactions were set up and kept in a preheated oil bath for stirring at 140 °C. At regular intervals (1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 9 h, 12 h, 15 h, 18 h, 21 h, 24 h, 27 h, 30 h, 33 h, 36 h) the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (2 mL) and taken in a GC vial. The GC sample was then subjected to gas chromatographic analysis in PerkinElmer clarus-590 GC instrument using Elite-5 Capillary Column (30 m x 0.25 mm I.D. x 0.25 µm) employing the following method: Inlets: 280 °C; FID 280 °C; Carrier Gas: N_2; Flow: 1 mL/min; Oven: 60 °C, hold 1 min; 12 °C/min to 320 °C. The concentration of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of the product (mmol) *vs* time (h) plot (**Figure 3.2** A).

3.5.16.2. Rate order determination:

The initial rate method was used to determine the rate order for the synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one (**3.3a**) with respect to 2′-Aminoacetophenone, **3.1a** and benzyl alcohol, **3.2a**. The data of the concentration (mM) *vs* time (h) plot was fitted to linear using origin pro 8.5. The slope of the linear fitted curve represents the initial rate of the reaction. The order of the reaction was determined by plotting initial rate (mM/h) *vs* concentration (mM) of that particular component.

3.5.16.2.1. Rate order determination with respect to 2′-Aminoacetophenone (3.1a):

To determine the order for the synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one, **3.3a** initial rates at different initial concentration of 2′-Aminoacetophenone, **3.1a** were recorded.

Experimental procedure: To an oven dried 10 mL two neck round bottomed flask equipped with a reflux condenser and a magnetic stir bar, benzyl alcohol, **3.2a** (0.324 g, 3.0 mmol, 3.0 equiv.) and KOH (0.084 g, 1.5 mmol, 1.5 equiv.) were taken sequentially and connected with high vacuum for 15 minutes. Then, **Mn-21** (0.020 g, 0.05 mmol, 5 mol%), mesitylene (0.121 g, 1.0 mmol, 1.0 equiv.) as an internal standard and specific amount of 2′-Aminoacetophenone, **3.1a** were added to the mixture under gentle stream of argon. In that way, twenty-four different reactions were set up and kept in a preheated oil bath for stirring at 140 °C. At regular intervals (1 h, 2 h, 3 h, 4 h, 5 h, 6 h) the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (2 mL) and taken in a GC vial. The GC sample was then subjected to gas chromatographic analysis in PerkinElmer clarus-590 GC instrument using Elite-5 Capillary Column (30 m x 0.25 mm I.D. x 0.25 µm) employing the following method: Inlets: 280 °C; FID 280 °C; Carrier Gas: N_2; Flow: 1 mL/min; Oven: 60 °C, hold 1 min; 12 °C/min to 320 °C. The concentration of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of the product (mmol) *vs* time (h) plot (**Figure 3.2** B). The rate of the reaction at different initial concentration of 2′-Aminoacetophenone, **3.1a** was given below and used to plot the log(rate) *vs* log(concentration of 2′-Aminoacetophenone, **3.1a**) to determine the order of the reaction with respect to 2′-Aminoacetophenone, **3.1a** (**Figure 3.2** C).

3.5.16.2.2. Rate order determination with respect to benzyl alcohol (2a):

To determine the order for the synthesis of 3-benzyl-2-phenylquinolin-4(1H)-one, **3.3a** initial rates at different initial concentration of benzyl alcohol, **3.2a** were recorded.

Experimental procedure: To an oven dried 10 mL two neck round bottomed flask equipped with a reflux condenser and a magnetic stir bar, 2′-Aminoacetophenone, **3.1a** (0.135 g, 1.0 mmol, 1.0 equiv.) and KOH (0.084 g, 1.5 mmol, 1.5 equiv.) were taken sequentially and connected with high vacuum for 15 minutes. Then, **Mn-21** (0.020 g, 0.05 mmol, 5 mol%), mesitylene (0.121 g, 1.0 mmol, 1.0 equiv.) as an internal standard and specific amount of benzyl alcohol, **3.2a** were added to the mixture under gentle stream of argon. In that way, twenty-four different reactions were set up and kept in a preheated oil bath for stirring at 140 °C. At regular intervals (1 h, 2 h, 3 h, 4 h, 5 h, 6 h) the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (2 mL) and taken in a GC vial. The GC sample was then subjected to gas chromatographic analysis in PerkinElmer clarus-590 GC instrument using Elite-5 Capillary Column (30 m x 0.25 mm I.D. x 0.25 µm) employing the following method: Inlets: 280 °C; FID 280 °C; Carrier Gas: N_2; Flow: 1 mL/min; Oven: 60 °C, hold 1 min; 12 °C/min to 320 °C. The concentration of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of the product (mmol) *vs* time (h) plot (**Figure 3.2** D). The rate of the reaction at different initial concentration of benzyl alcohol, **3.2a** was given below and used to

plot the log(rate) *vs* log(concentration of benzyl alcohol, **3.2a**) to determine the order of the reaction with respect to benzyl alcohol, **3.2a** (**Figure 3.2** E).

3.5.17. Post-synthetic modification:

3.5.17.1. Experimental procedure for the synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-1-methylquinolin-4(1H)-one, graveoline (3.6t):[41]

The title compound was prepared according to previous reported literature method.[12] To an oven dried 25 mL round bottomed flask equipped with a magnetic stir bar**,** 2-(benzo[d][1,3]dioxol-5-yl)quinolin-4(1H)-one (**3.6p**) (0.265 g, 1.0 mmol, 1.0 equiv.) was dissolved in 10 mL of degassed dry THF solvent and the mixture was subjected to cool at 0 °C, stirred for 10 min. Then, NaH (0.096 g, 2.0 mmol, 2.0 equiv.) was added portionwise for 15 min. Iodomethane (0.426 g, 186.8 µL, 3.0 mmol, 3.0 equiv.) was added to the mixture via syringe under gentle stream of argon. After completion of addition the reaction mixture was promoted to room temperature and continued stirring for 3 h. Next, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl, diluted with 20 mL of water and extracted three times with ethyl acetate (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 20/80) to afford the desired 2-(benzo[d][1,3]dioxol-5-yl)-1-methylquinolin-4(1H)-one, graveoline **(3.6t)** in 78% yield (0.218 g, 0.78 mmol) as a pale brown solid.

3.5.17.2. Experimental procedure for the synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxyquinoline, graveolinine (3.13):[41]

To an oven dried 25 mL round bottomed flask equipped with a magnetic stir bar**,** 2-(benzo[d][1,3]dioxol-5-yl)quinolin-4(1H)-one (**3.6p**) (0.265 g, 1.0 mmol, 1.0 equiv.) was dissolved in 10 mL of anhydrous DMF solvent and stirred for 10 min. Then, K_2CO_3 (0.276 g, 2.0 mmol, 2.0 equiv.) was added into it. Iodomethane (0.426 g, 186.8 µL, 3.0 mmol, 3.0 equiv.) was added to the mixture via syringe under gentle stream of argon. After completion of addition, the reaction mixture was heated at 80 °C in a preheated oil bath for 30 min. Next, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl, diluted with 20 mL of water and extracted three times with ethyl acetate (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 85/15) to afford the desired 2-(benzo[d][1,3]dioxol-5-yl)-4-methoxyquinoline, graveolinine (**3.13**) in 86% yield (0.240 g, 0.86 mmol) as a pale brown solid.

3.5.17.3. Experimental procedure for the synthesis of 3-bromo-2-phenylquinolin-4(1H)-one (3.14) and 3-bromo-1-methyl-2-phenylquinolin-4(1H)-one (3.15):[30]

At the onset, a mixture of 2-phenylquinolin-4(1H)-one (**3.6a**) (0.221 g, 1.0 mmol, 1.0 equiv.) and KBr (0.238 g, 2.0 mmol, 2.0 equiv.) was taken in 10 mL MeOH in an oven dried 50 mL round bottomed

flask equipped with a magnetic stir bar and the mixture was stirred at room temperature for 15 min. Then, a methanolic solution (5 mL) of PIFA (0.473 g, 1.1 mmol, 1.1 equiv.) was added in a dropwise manner to the mixture via syringe. Next, it was subjected to stir at room temperature for 2 h. The completion of the reaction was monitored by thin layer chromatography (TLC) and the contents were concentrated under reduced pressure. Then, the residue was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 40/60) to afford the desired 3-bromo-2-phenylquinolin-4(1H)-one (**3.14**) in 80% yield (0.240 g, 0.80 mmol) as a light pink solid.

Next, 3-bromo-2-phenylquinolin-4(1H)-one (**3.14**) (0.150 g, 0.5 mmol, 1.0 equiv.) was dissolved in 5 mL of degassed dry THF solvent in an oven dried 25 mL round bottomed flask equipped with a magnetic stir bar and the mixture was subjected to cool at 0 °C, stirred for 10 min. Then, NaH (0.048 g, 1.0 mmol, 2.0 equiv.) was added portionwise for 15 min. Iodomethane (0.213 g, 93.4 µL, 1.5 mmol, 3.0 equiv.) was added to the mixture via syringe under gentle stream of argon. After completion of addition the reaction mixture was promoted to room temperature and continued stirring for 3 h. Next, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl, diluted with 10 mL of water and extracted three times with ethyl acetate (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 40/60) to afford the intended 3-bromo-1-methyl-2-phenylquinolin-4(1H)-one (**3.15**) in 90% yield (0.142 g, 0.45 mmol) as a white solid.

3.5.17.4. Experimental procedure for the synthesis of ethyl (2-phenylquinolin-4-yl) carbonate (3.16) and 1-hydroxy-2-phenylquinolin-4(1H)-one (3.17):[31, 32]

To an oven dried 25 mL round bottomed flask equipped with a magnetic stir bar, a mixture of 2-phenylquinolin-4(1H)-one (**3.6a**) (0.663 g, 3.0 mmol, 1.0 equiv.) and KO^{t}Bu (0.420 g, 3.75 mmol, 3.0 equiv.) was added in 20 mL of anhydrous THF and stirred for 1 h at room temperature under argon gas. Then, ethyl chloroformate (0.358 g, 3.3 mmol, 1.1 equiv.) was added into it and the stirring was continued for another 30 min. Next, the reaction mixture was quenched with 10 mL of water and extracted three times with ethyl acetate (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 90/10) to afford the intended ethyl (2-phenylquinolin-4-yl) carbonate (**3.16**) in 75% yield (0.660 g, 2.25 mmol) as a light-yellow liquid.

Afterwards, a solution of ethyl (2-phenylquinolin-4-yl) carbonate, **3.16** (0.439 g, 1.5 mmol, 1.0 equiv.) and m-CPBA (77% purity, 0.280 g, 1.62 mmol, 1.08 equiv.) were suspended in 8 mL of anhydrous DCM and stirred for 3 h at room temperature. The solution was washed with 0.5 M aqueous Na_2CO_3 (2×10 mL) and water (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was used in the next step without any further purification. Next, 3 mL

of aqueous 5M KOH solution was added into the ethanolic solution (6 mL) of that crude product. After 1 h at room temperature 15 mL water was added and the pH was adjusted to 1-2 using concentrated HCl to give a milky solution which soon crystallized. The product was collected under vacuum and washed with water to give the desired 1-hydroxy-2-phenylquinolin-4(1H)-one (**3.17**) in 70% yield (0.249 g, 1.05 mmol) as a yellow solid.

3.5.17.5. Experimental procedure for the synthesis of 4-chloro-2-phenylquinoline (3.18):[15]

To an oven dried 25 mL round bottomed flask equipped with a condenser and a magnetic stir bar, a mixture of 2-phenylquinolin-4(1H)-one (**3.6a**) (0.221 g, 1.0 mmol, 1.0 equiv.) and $POCl_3$ (0.753 ml, 8.0 mmol, 8.0 equiv.) was charged with argon gas and stirred at 80 °C in a preheated oil bath for 3 h. The completion of the reaction was monitored by thin layer chromatography (TLC) and quenched with saturated aqueous solution of $NaHCO_3$ to make a mixture neutral. Then, the mixture was extracted three times with ethyl acetate (3×15 mL). The combined organic layer was washed with water (2 x 15 ml), brine (15 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 85/15) to afford the desired 4-chloro-2-phenylquinoline (**3.18**) in 87% yield (0.209 g, 0.87 mmol) as a white solid.

3.5.17.6. Experimental procedure for the synthesis of N-(2-(1H-indol-3-yl)ethyl)-2-phenylquinolin-4-amine (3.19) and 2-phenyl-4-(pyrrolidin-1-yl)quinoline (3.20):[33]

A mixture of 4-chloro-2-phenylquinoline (**3.18**) (0.240 g, 1.0 mmol, 1.0 equiv.) and K_2CO_3 (0.276 g, 2.0 mmol, 2.0 equiv.) was taken to an oven dried 25 mL round bottomed flask equipped with a condenser and a magnetic stir bar and then tryptamine (0.320 g, 2.0 mmol, 2.0 equiv.) was charged into that under gentle stream of argon. Later, the reaction mixture was stirred at 135 °C in a preheated oil bath for 4 h. After 4 h, the reaction mixture was subjected to cool at room temperature, added 10 mL of distilled water and extracted three times with ethyl acetate (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 50/50) to afford the targeted N-(2-(1H-indol-3-yl)ethyl)-2-phenylquinolin-4-amine (**3.19**) in 70% yield (0.255 g, 0.70 mmol) as a brown solid.

A mixture of 4-chloro-2-phenylquinoline (**3.18**) (0.240 g, 1.0 mmol, 1.0 equiv.) and K_2CO_3 (0.276 g, 2.0 mmol, 2.0 equiv.) was taken to an oven dried 25 mL round bottomed flask equipped with a condenser and a magnetic stir bar and then pyrrolidine (0.142 g, 2.0 mmol, 2.0 equiv.) was charged into that under gentle stream of argon. Later, the reaction mixture was stirred at 135 °C in a preheated oil bath for 4 h. After 4 h, the reaction mixture was subjected to cool at room temperature, added 10 mL of distilled water and extracted three times with ethyl acetate (3×10 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent:

Pet. ether/EtOAc = 10/90) to afford the targeted 2-phenyl-4-(pyrrolidin-1-yl)quinoline (**3.20**) in 85% yield (0.233 g, 0.85 mmol) as a light-yellow liquid.

3.5.17.7. Experimental procedure for the synthesis of 3-benzyl-4-bromo-2-phenylquinoline (3.21),[15] 3-(hydroxy(phenyl)methyl)-2-phenylquinolin-4-ol (3.22) or 3-(hydroxy(phenyl)methyl)-2-phenylquinolin-4(1H)-one (3.22):[21]

To an oven dried 25 mL round bottomed flask equipped with a magnetic stir bar, 3-benzyl-2-phenylquinolin-4(1H)-one, **3.3a** (0.311 g, 1.0 mmol, 1.0 equiv.) was added in 10 mL of anhydrous DMF under argon gas. The mixture was cooled to 0 °C and then, PBr_3 (0.192 ml, 2.0 mmol, 2.0 equiv.) was added slowly to a stirred mixture. The reaction mixture was warmed to room temperature, and stirred for 20 h. The mixture was monitored by TLC and quenched with saturated aqueous solution of $NaHCO_3$ to make a mixture neutral. Then, the mixture was extracted three times with ethyl acetate (3×15 mL). The combined organic layer was washed with water (2 x 15 ml), brine (15 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 3-benzyl-4-bromo-2-phenylquinoline (**3.21**) in 85% yield (0.318 g, 0.85 mmol) as a white solid.

Next, KO^{t}Bu (0.224 g, 2.0 mmol, 1.6 equiv.) and 18-Crown-6 (0.528 g, 2.0 mmol, 1.6 equiv.) was added in 7 mL of anhydrous DMF under argon gas taken to an oven dried 25 mL round bottomed flask equipped with a magnetic stir bar and the mixture was subjected to cool at 0 °C. Then 3-benzyl-4-bromo-2-phenylquinoline, **3.21** (0.468 g, 1.25 mmol, 1.0 equiv.) was added into the mixture slowly. Then, the argon gas in the reaction mixture was removed under vacuum and the reaction vessel was filled with O_2. This procedure was repeated for three to four times. The reaction mixture was then stirred under an O_2 balloon at room temperature for 12 h. Afterwards, the completion of the reaction was monitored by thin layer chromatography (TLC) and DMF was removed under vacuum. The resulting residue was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 40/60) to afford the intended 3-(hydroxy(phenyl)methyl)-2-phenylquinolin-4-ol (**3.22**) in 75% yield (0.307 g, 0.94 mmol) as a white solid.

3.5.17.8. Experimental procedure for the synthesis of 12-benzyl-6,7-diphenyl-13H-isoquinolino[2,1-a]quinolin-13-one (3.23):[37]

To an oven dried 25 mL round bottomed flask fitted with a reflux condenser, a magnetic pellet and stirrer was charged with 3-benzyl-2-phenylquinolin-4(1H)-one, **3.3a** (0.311 g, 1.0 mmol, 1.0 equiv.), diphenylacetylene (0.232 g, 1.3 mmol, 1.3 equiv.), $[RuCl_2(p\text{-Cymene})]_2$ (0.031 g, 0.05 mmol, 5 mol%), $Cu(OAc)_2.H_2O$ (0.400 g, 2.2 mmol, 2.2 equiv.), TfOH (0.225 g, 1.5 mmol, 1.5 equiv.) and DCE (4 mL). The combined reaction mixture was heated at 120 °C in a preheated oil bath for 16 h under aerobic condition. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, DCE was removed under reduced pressure. The crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 90/10) to afford

the desired 12-benzyl-6,7-diphenyl-13H-isoquinolino[2,1-a]quinolin-13-one (**3.23**) in 78% yield (0.380 g, 0.78 mmol) as a white solid.

3.5.17.8. Experimental procedure for the synthesis of 3-benzyl-4-chloro-2-phenylquinoline (3.24) and 3-benzyl-4-(ethylthio)-2-phenylquinoline (3.25):[15]

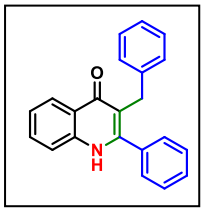
To an oven dried 25 mL round bottomed flask equipped with a reflux condenser and a magnetic stir bar, a mixture of 3-benzyl-2-phenylquinolin-4(1H)-one, **3.3a** (0.311 g, 1.0 mmol, 1.0 equiv.) and $POCl_3$ (0.753 ml, 8.0 mmol, 8.0 equiv.) was charged with argon gas and stirred at 80 °C in a preheated oil bath for 3 h. The completion of the reaction was monitored by thin layer chromatography (TLC) and quenched with saturated aqueous solution of $NaHCO_3$ to make a mixture neutral. Then, the mixture was extracted three times with ethyl acetate (3×15 mL). The combined organic layer was washed with water (2 x 15 ml), brine (15 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 85/15) to afford the desired 3-benzyl-4-chloro-2-phenylquinoline (**3.24**) in 90% yield (0.297 g, 0.90 mmol) as a white solid.

To an oven dried 25 mL round bottomed flask equipped with a magnetic stir bar was charged with 3-benzyl-4-chloro-2-phenylquinoline, **3.25** (0.330 g, 1.0 mmol, 1.0 equiv.), KOH (0.056 g, 1.0 mmol, 1.0 equiv.), Ethanethiol (0.062 g, 1.0 mmol, 1.0 equiv.) and DMSO (5 mL). The combined reaction mixture was stirred at room temperature under air. The progress of the reaction was monitored by thin layer chromatography (TLC). After 2 h, the mixture was diluted with ethyl acetate (10 mL) and water (10 mL) and extracted three times with ethyl acetate (3×15 mL). The combined organic layer was washed with water (2 x 15 ml), brine (15 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 98/2) to afford the targeted 3-benzyl-4-(ethylthio)-2-phenylquinoline **(3.25)** in 83% yield (0.295 g, 0.83 mmol) as a white solid.

3.5.18. Analytical data:

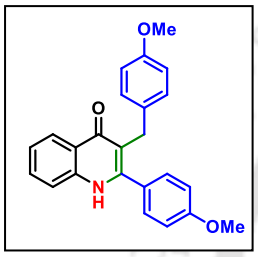
3.5.18.1. Analytical data for substrate scopes:

3-benzyl-2-phenylquinolin-4(1H)-one (3.3a):[42]



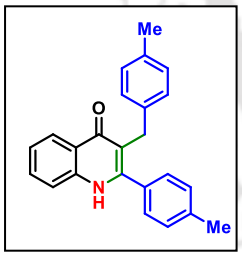
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 65/35) to afforded the title compound in 76% yield (0.237 g, 0.76 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.72 (brs, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.56 – 7.50 (m, 3H), 7.45 – 7.43 (m, 2H), 7.30 – 7.30 (m, 1H), 7.13 (t, *J* = 7.4 Hz, 2H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 7.1 Hz, 2H), 3.74 (s, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 176.3, 149.1, 141.5, 139.6, 134.8, 131.6, 129.5, 128.7, 128.6, 127.9, 127.8, 125.4, 125.1, 123.8, 122.9, 118.3, 117.6, 31.1.

3-(4-methoxybenzyl)-2-(4-methoxyphenyl)quinolin-4(1H)-one (3.3b):[42]



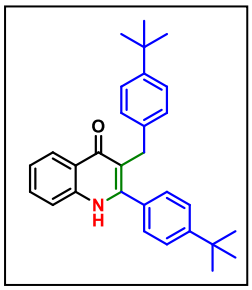
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 84% yield (0.312 g, 0.84 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.62 (brs, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.28 (m, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.69 (s, 2H), 3.66 (s, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.3, 160.1, 157.1, 148.8, 139.6, 133.6, 131.4, 130.1, 128.7, 127.2, 125.1, 123.7, 122.8, 118.2, 118.1, 113.9, 113.4, 55.4, 54.9, 30.3.

3-(4-methylbenzyl)-2-(p-tolyl)quinolin-4(1H)-one (3.3c):[42]



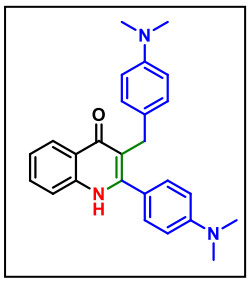
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 80% yield (0.272 g, 0.80 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.64 (brs, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.62 (m, 2H), 7.37 – 7.29 (m, 5H), 6.94 (d, *J* = 7.7 Hz, 2H), 6.86 (d, *J* = 7.4 Hz, 2H), 3.68 (s, 2H), 2.38 (s, 3H), 2.19 (s, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.3, 149.1, 139.6, 139.1, 138.5, 134.1, 132.1, 131.4, 129.0, 128.6, 128.5, 127.7, 125.1, 123.7, 122.8, 118.2, 117.7, 30.7, 20.9, 20.5.

3-(4-(tert-butyl)benzyl)-2-(4-(tert-butyl)phenyl)quinolin-4(1H)-one (3.3d):[18]



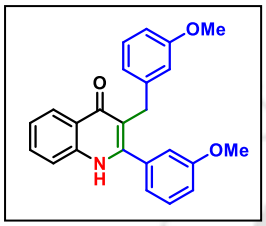
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 86% yield (0.364 g, 0.86 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.66 (brs, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.31 – 7.28 (m, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.70 (s, 2H), 1.31 (s, 9H), 1.19 (s, 9H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.3, 152.2, 149.0, 147.5, 139.7, 138.4, 132.2, 131.5, 128.5, 127.5, 125.4, 125.1, 124.6, 123.7, 122.8, 118.3, 117.7, 34.6, 34.0, 31.2, 31.1, 30.8.

3-(4-(dimethylamino)benzyl)-2-(4-(dimethylamino)phenyl)quinolin-4(1H)-one (3.3e):[18]



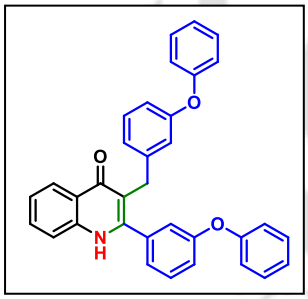
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 58% yield (0.231 g, 0.58 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.44 (brs, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.30 – 7.25 (m, 3H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 8.6 Hz, 2H), 3.69 (s, 2H), 2.96 (s, 6H), 2.78 (s, 6H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.3, 150.9, 149.3, 148.5, 139.6, 131.1, 129.7, 129.5, 128.3, 125.0, 123.6, 122.5, 122.2, 118.1, 117.9, 112.5, 111.5, 40.5, 39.9, 30.3.

3-(3-methoxybenzyl)-2-(3-methoxyphenyl)quinolin-4(1H)-one (3.3f):[18]



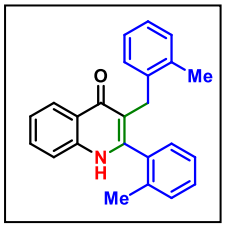
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 78% yield (0.290 g, 0.78 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.76 (brs, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.11 – 7.02 (m, 3H), 6.96 (s, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.52 (s, 1H), 3.73 (s, 2H), 3.68 (s, 3H), 3.62 (s, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.4, 159.1, 159.0, 149.0, 143.3, 139.6, 136.1, 131.6, 129.8, 129.0, 125.2, 123.8, 123.0, 120.8, 120.3, 118.4, 117.5, 115.4, 114.2, 113.8, 110.7, 55.2, 54.8, 31.2.

3-(3-phenoxybenzyl)-2-(3-phenoxyphenyl)quinolin-4(1H)-one (3.3g):[18]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 72% yield (0.357 g, 0.72 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.76 (brs, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.33 – 7.29 (m, 3H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.16 – 7.12 (m, 3H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 3H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.74 – 6.69 (m, 2H), 6.57 (s, 1H), 3.76 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.3, 156.7, 156.7, 156.3, 156.1, 148.5, 143.8, 139.5, 136.3, 131.7, 130.4, 130.3, 130.2, 129.9, 129.5, 125.1, 123.9, 123.8, 123.6, 123.2, 123.1, 119.5, 119.3, 118.8, 118.5, 118.4, 118.2, 117.4, 115.7, 30.8.

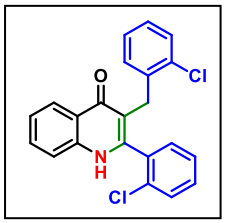
3-(2-methylbenzyl)-2-(o-tolyl)quinolin-4(1H)-one (3.3h):



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 40% yield (0.136 g, 0.40 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.75 (brs, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 6.97 – 6.88 (m, 3H), 6.78 (d, *J* = 7.5 Hz, 1H), 3.65 – 3.62 (m, 1H), 3.49 – 3.46 (m, 1H), 1.94 (s, 3H), 1.88 (s, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.5, 149.0, 139.6, 139.1, 135.9, 135.3, 134.4, 131.5,

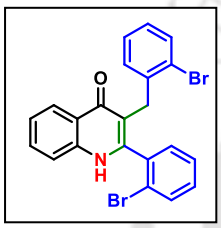
130.2, 129.4, 129.2, 128.7, 127.4, 125.8, 125.4, 125.2, 125.1, 123.8, 122.9, 118.2, 118.2, 27.6, 19.0, 18.7. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{24}H_{22}NO$ is 340.1701 Found 340.1678.

3-(2-chlorobenzyl)-2-(2-chlorophenyl)quinolin-4(1H)-one (3.3i):



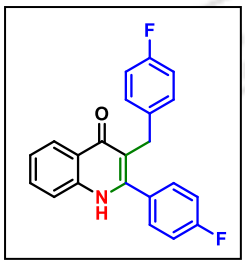
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 35% yield (0.133 g, 0.35 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.98 (brs, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 2H), 7.53 – 7.50 (m, 1H), 7.39 – 7.35 (m, 3H), 7.27 - 7.25 (m, 1H), 7.12 – 7.07 (m, 2H), 7.01 – 6.99 (m, 1H), 3.88 – 3.85 (m, 1H), 3.50 – 3.47 (m, 1H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.3, 146.9, 139.7, 137.7, 133.2, 132.8, 132.1, 131.9, 131.4, 130.7, 129.7, 129.2, 128.6, 127.4, 127.2, 126.8, 125.2, 123.9, 123.3, 118.3, 116.9, 28.5. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{22}H_{16}Cl_2NO$ is 380.0609 Found 380.0594.

3-(2-bromobenzyl)-2-(2-bromophenyl)quinolin-4(1H)-one (3.3j):



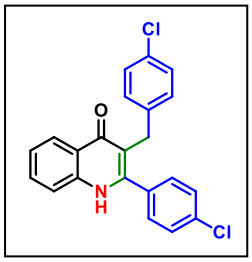
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 30% yield (0.141 g, 0.30 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.98 (brs, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 7.3 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.38 – 7.34 (m, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.04 – 7.00 (m, 2H), 3.91 – 3.88 (m, 1H), 3.39 – 3.36 (m, 1H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.3, 148.3, 139.7, 139.2, 135.2, 132.8, 131.8, 131.5, 130.6, 129.3, 128.5, 127.8, 127.5, 127.4, 125.2, 123.9, 123.9, 123.3, 122.1, 118.4, 116.8, 31.5. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{22}H_{16}Br_2NO$ is 469.9578 Found 469.9568.

3-(4-fluorobenzyl)-2-(4-fluorophenyl)quinolin-4(1H)-one (3.3k):[42]



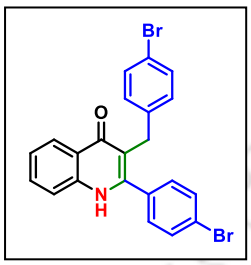
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 75% yield (0.261 g, 0.75 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.74 (brs, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.51 – 7.47 (m, 2H), 7.39 – 7.31 (m 3H), 6.99 – 6.92 (m, 4H), 3.71 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.2, 162.6 (d, *J* = 245.2 Hz), 160.3 (d, *J* = 239.2 Hz), 148.3, 139.5, 137.5 (d, *J* = 2.8 Hz), 131.6, 131.2, 131.1, 131.09, 131.0, 129.4 (d, *J* = 7.8 Hz), 125.1, 123.8, 123.0, 118.3, 117.9, 115.5 (d, *J* = 21.6 Hz), 114.6 (d, *J* = 20.7 Hz), 30.2. **^{19}F NMR (470 MHz, DMSO-*d*$_6$)** δ -111.5, -118.1.

3-(4-chlorobenzyl)-2-(4-chlorophenyl)quinolin-4(1H)-one (3.3l):[18]



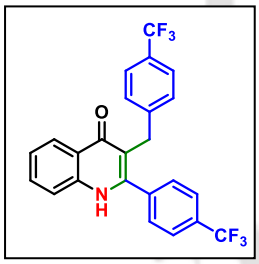
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 71% yield (0.270 g, 0.71 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.80 (brs, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 8.1 Hz, 2H), 3.70 (s, 2H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.3, 148.3, 140.4, 139.6, 134.5, 133.4, 131.8, 130.6, 130.1, 129.7, 128.7, 127.9, 125.2, 123.9, 123.2, 118.4, 117.5, 30.5.

3-(4-bromobenzyl)-2-(4-bromophenyl)quinolin-4(1H)-one (3.3m):[42]



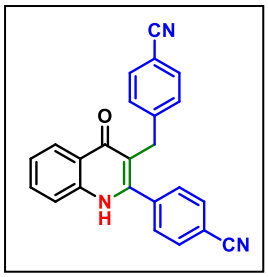
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 65% yield (0.305 g, 0.65 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.74 (brs, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 4.0 Hz, 2H), 7.53 – 7.49 (m, 2H), 7.44 – 7.42 (m, 2H), 7.34 – 7.31 (m, 1H), 7.14 – 7.06 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 2H), 3.74 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.4, 149.3, 141.6, 139.6, 134.9, 131.7, 129.6, 128.7, 128.6, 128.0, 127.9, 125.4, 125.2, 123.8, 123.1, 118.4, 117.8, 31.1.

3-(4-(trifluoromethyl)benzyl)-2-(4-(trifluoromethyl)phenyl)quinolin-4(1H)-one (3.3n):[18]



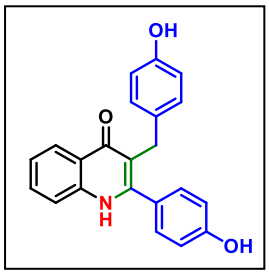
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 46% yield (0.206 g, 0.46 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.91 (brs, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 2H), 7.69 – 7.61 (m, 4H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 3.80 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.3, 147.2 (d, *J* = 253.6 Hz), 139.7, 138.6, 132.0, 130.4 (q, *J* = 31.6 Hz), 129.8, 128.6, 127.8, 127.3, 126.4 (q, *J* = 31.5 Hz), 125.6 (q, *J* = 3.5 Hz), 125.2, 125.1, 124.9 (q, *J* = 3.6 Hz), 123.9, 123.4, 123.0, 121.3, 120.8, 118.5, 117.1, 31.1. **^{19}F NMR (470 MHz, DMSO-*d*$_6$)** δ -60.7, -61.3.

4-(3-(4-cyanobenzyl)-4-oxo-1,4-dihydroquinolin-2-yl)benzonitrile (3.3o):



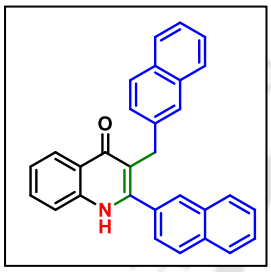
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 30% yield (0.108 g, 0.30 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.93 (brs, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 2H), 7.70 – 7.59 (m, 6H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 3.77 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.1, 147.9, 147.3, 139.6, 138.9, 132.6, 131.9, 131.9, 129.8, 128.9, 125.1, 123.8, 123.3, 119.1, 118.4, 118.3, 116.7, 112.4, 108.3, 31.2. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{24}H_{16}N_3O$ is 362.1293 Found 362.1311.

3-(4-hydroxybenzyl)-2-(4-hydroxyphenyl)quinolin-4(1H)-one (3.3p):



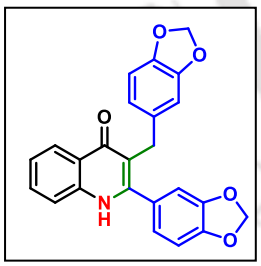
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 30/70) to afforded the title compound in 38% yield (0.108 g, 0.38 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.54 (brs, 1H), 9.90 (s, 1H), 9.02 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.61(q, *J* = 8.3 Hz, 2H), 7.32 – 7.23 (m, 3H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.77 (d, *J* = 8.1 Hz, 2H), 6.55 (d, *J* = 8.1 Hz, 2H), 3.65 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.3, 158.4, 155.0, 149.2, 139.6, 131.9, 131.3, 130.1, 128.7, 125.6, 125.1, 123.7, 122.7, 118.3, 118.2, 115.1, 114.7, 30.3. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{22}H_{18}NO_3$ is 344.1287 Found 344.1290.

2-(naphthalen-2-yl)-3-(naphthalen-2-ylmethyl)quinolin-4(1H)-one (3.3s):[42]



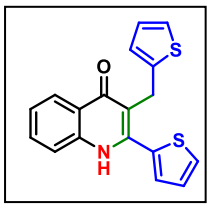
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 60% yield (0.247 g, 0.60 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.91 (brs, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.07 (s, 1H), 8.00 (t, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.68 – 7.67 (m, 3H), 7.62 – 7.55 (m, 4H), 7.38 – 7.33 (m, 4H), 7.21 (d, *J* = 8.3 Hz, 1H), 3.96 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.5, 149.4, 139.7, 139.3, 133.1, 133.0, 132.4, 132.3, 131.7, 131.5, 128.4, 128.3, 128.1, 127.8, 127.4, 127.3, 127.3, 127.3, 127.3, 127.0, 126.1, 125.8, 125.5, 125.3, 125.0, 124.0, 123.1, 118.4, 117.8, 31.5.

2-(benzo[d][1,3]dioxol-5-yl)-3-(benzo[d][1,3]dioxol-5-ylmethyl)quinolin-4(1H)-one (3.3t):[18]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 56% yield (0.224 g, 0.56 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.63 (brs, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 3.7 Hz, 2H), 7.32 – 7.29 (m, 1H), 7.06 – 7.03 (m, 2H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.58 (s, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 6.11 (s, 2H), 5.89 (s, 2H), 3.68 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.3, 148.7, 148.1, 147.2, 146.9, 144.9, 139.5, 135.5, 131.5, 128.4, 125.1, 123.8, 122.9, 122.8, 120.5, 118.3, 117.9, 109.2, 108.5, 108.3, 107.7, 101.5, 100.5, 30.8.

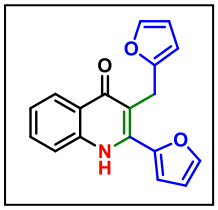
2-(thiophen-2-yl)-3-(thiophen-2-ylmethyl)quinolin-4(1H)-one (3.3u):[18]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 72% yield (0.233 g, 0.72 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.78 (brs, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 5.0 Hz, 1H), 7.67 – 7.64 (m, 2H), 7.42 (d, *J* = 3.6, 1H), 7.35 – 7.32 (m, 1H), 7.26 (t, *J* = 4.3 Hz, 1H), 7.17 (d, *J* = 5.1 Hz, 1H), 6.83 (t, *J* = 4.3 Hz, 1H), 6.63 (d, *J* = 3.5 Hz, 1H), 4.03 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.0, 144.3,

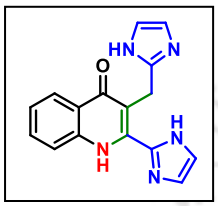
142.2, 139.7, 134.2, 132.1, 130.0, 129.2, 127.7, 126.6, 125.2, 124.4, 123.7, 123.5, 123.4, 119.0, 118.5, 26.4.

2-(furan-2-yl)-3-(furan-2-ylmethyl)quinolin-4(1H)-one (3.3v):[18]



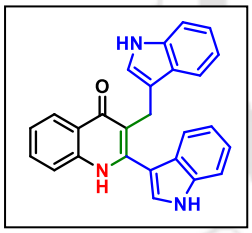
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 50% yield (0.146 g, 0.50 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.64 (brs, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 8.03 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.45 (s, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 3.5 Hz, 1H), 6.76 (s, 1H), 6.27 (s, 1H), 5.86 (s, 1H), 4.06 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.1, 154.2, 146.2, 145.2, 141.1, 139.7, 137.8, 132.0, 125.1, 123.4, 123.2, 118.5, 114.2, 113.9, 112.4, 110.5, 105.2, 24.4.

3-((1H-imidazol-2-yl)methyl)-2-(1H-imidazol-2-yl)quinolin-4(1H)-one (3.3w):



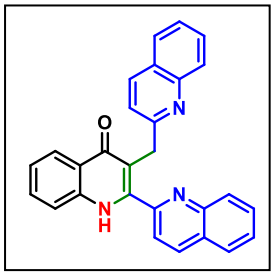
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 54% yield (0.157 g, 0.54 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.78 (brs, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.63(t, *J* = 7.9 Hz ,1H), 7.48 (s, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.98 (s, 2H), 3.98 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.2, 147.7, 140.7, 139.7, 138.7, 132.0, 131.6, 131.5, 128.9, 128.8, 124.8, 123.4, 123.2, 118.8, 114.8, 23.9. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{16}H_{14}N_5O$ is 292.1198 Found 292.1211.

3-((1H-indol-3-yl)methyl)-2-(1H-indol-3-yl)quinolin-4(1H)-one (3.3x):



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 30/70) to afforded the title compound in 57% yield (0.222 g, 0.57 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.61 (brs, 1H), 10.78 (s, 2H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 5.8 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 2H), 6.86 – 6.83 (m, 3H), 3.59 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 175.3, 139.5, 137.4, 137.0, 136.8, 136.5, 133.2, 131.3, 127.2, 126.8, 125.5, 124.9, 124.6, 124.0, 123.7, 123.5, 122.8, 120.9, 119.5, 119.1, 118.7 ,118.3, 118.2, 117.7, 111.6, 30.0. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{26}H_{20}N_3O$ is 390.1606 Found 390.1610.

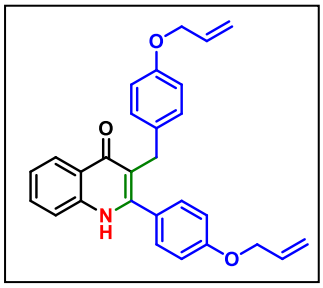
3-(quinolin-2-ylmethyl)-[2,2'-biquinolin]-4(1H)-one (3.3y):



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 67% yield (0.277 g, 0.67 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.05 (brs, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.04 (t, *J* = 9.5 Hz, 3H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.72 -7.68 (m, 3H), 7.63 – 7.60 (m, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.17 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.7, 153.3, 147.8, 147.1, 139.7, 137.1, 135.9, 132.0, 130.4, 129.2, 129.2, 128.3, 128.1, 127.7, 127.6, 127.6, 126.4,

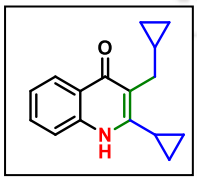
125.6, 125.2, 123.9, 123.3, 122.1, 121.7, 118.6, 117.0, 34.7. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{28}H_{20}N_3O$ is 414.1606 Found 414.1586.

3-(4-(allyloxy)benzyl)-2-(4-(allyloxy)phenyl)quinolin-4(1H)-one (3.3z):



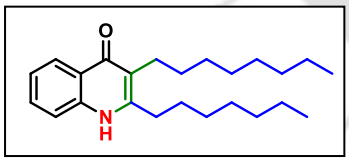
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 61% yield (0.258 g, 0.61 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.64 (brs, 1H), 8.13 (d, *J* = 7.6 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.09 – 5.95 (m, 2H), 5.42 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.34 (dd, *J* = 17.3, 2.0 Hz, 1H), 5.28 (dd, *J* = 10.5, 1.8 Hz, 1H), 5.23 – 5.18 (m, 1H), 4.64 (d, *J* = 5.1 Hz, 2H), 4.45 (d, *J* = 4.8 Hz, 2H), 3.70 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.4, 159.0, 156.1, 148.9, 139.6, 133.9, 133.8, 133.4, 131.4, 130.1, 128.8, 127.3, 125.1, 123.8, 122.8, 118.3, 118.2, 117.7, 117.2, 114.6, 114.2, 68.3, 68.1, 30.3. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{28}H_{26}NO_3$ is 424.1293 Found 424.1311.

2-cyclopropyl-3-(cyclopropylmethyl)quinolin-4(1H)-one (3.3za):



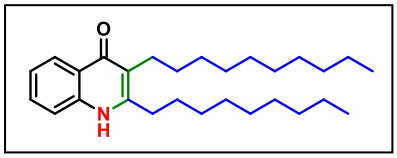
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 45% yield (0.108 g, 0.45 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.34 (brs, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 2.66 (d, *J* = 6.6 Hz, 2H), 2.28 – 2.21 (m, 1H), 1.11 – 0.98 (m, 5H), 0.33 – 0.30 (m, 2H), 0.23 – 0.21 (m, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 175.7, 149.8, 139.2, 130.9, 125.0, 123.5, 122.4, 119.9, 118.0, 28.4, 12.7, 10.9, 7.6, 4.4. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{16}H_{18}NO$ is 240.1388 Found 240.1379.

2-heptyl-3-octylquinolin-4(1H)-one (3.3zb):[18]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 70/30) to afforded the title compound in 32% yield (0.114 g, 0.32 mmol) as a brown solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 11.48 (brs, 1H), 8.27 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 2.65 (t, *J* = 8.1 Hz, 2H), 2.57 (t, *J* = 7.8 Hz, 2H), 1.63 – 1.56 (m, 2H), 1.50 – 1.44 (m, 2H), 1.25 – 1.09 (m, 16H), 0.81 – 0.74 (m, 8H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 177.8, 151.4, 139.8, 131.1, 125.7, 124.1, 123.0, 120.3, 118.3, 32.5, 32.0, 31.8, 30.3, 30.0, 29.9, 29.8, 29.7, 29.5, 29.3, 29.1, 22.8, 22.7, 14.2, 14.2.

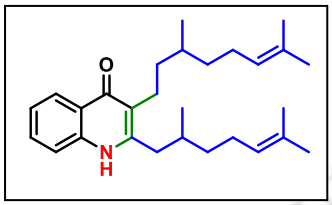
3-decyl-2-nonylquinolin-4(1H)-one (3.3zc):



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 70/30) to afforded the title compound in 40% yield (0.165 g, 0.40 mmol) as a brown solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 11.64 (brs, 1H), 8.32 (d, *J* = 8.2 Hz, 1H), 7.67 (d,

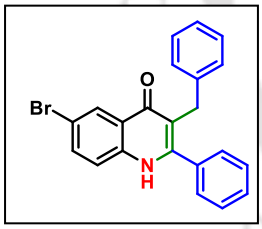
J = 8.1 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 2.69 (t, *J* = 8.2 Hz, 2H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.38 (t, *J* = 7.7 Hz, 2H), 1.67 – 1.64 (m, 4H), 1.56 – 1.49 (m, 2H), 1.36 – 1.19 (m, 20H), 0.89 – 0.84 (m, 8H).**^{13}C NMR (125 MHz, CDCl$_3$)** δ 177.7, 151.5, 139.5, 131.1, 125.6, 123.8, 123.1, 120.3, 118.1, 34.5, 32.3, 32.0, 32.0, 30.2, 29.8, 29.8, 29.8, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 25.8, 25.0, 22.8, 22.8, 14.2, 14.2. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{28}H_{46}NO$ is 412.3579 Found 412.3583.

2-(2,6-dimethylhept-5-en-1-yl)-3-(3,7-dimethyloct-6-en-1-yl)quinolin-4(1H)-one (3.3zd):



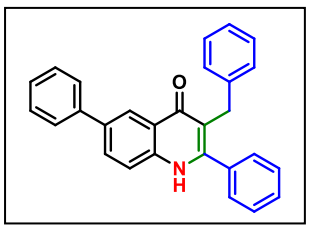
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 75/25) to afforded the title compound in 60% yield (0.245 g, 0.60 mmol) as a yellow liquid. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 11.71 (brs, 1H), 8.33 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 5.05 (t, *J* = 7.2 Hz, 1H), 4.98 (t, *J* = 7.1 Hz, 1H), 2.79 – 2.52 (m, 2H), 2.42 – 2.17 (m, 2H), 2.06 – 1.83 (m, 6H), 1.67 (s, 3H), 1.64 (d, *J* = 6.7 Hz, 2H), 1.60 (s, 3H), 1.56 (s, 3H), 1.52 (s, 3H), 1.42 – 1.28 (m, 1H), 1.26 – 1.12 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 2H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 177.5, 150.4, 139.6, 131.5, 131.44, 131.42, 131.0, 130.91, 130.90, 125.5, 125.0, 124.4, 124.3, 123.9, 123.1, 121.3, 118.4, 42.1, 39.6, 37.1, 37.1, 36.9, 36.7, 33.4, 33.4, 33.3, 30.1, 25.8, 25.7, 25.7, 25.7, 25.5, 23.7, 19.7, 19.5, 19.5, 19.2, 17.7. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{28}H_{42}NO$ is 408.3266 Found 408.3260.

3-benzyl-6-bromo-2-phenylquinolin-4(1H)-one (3.3ze):[42]



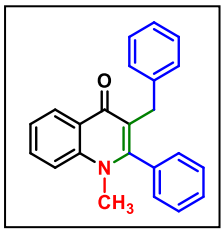
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 60% yield (0.234 g, 0.60 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.92 (brs, 1H), 8.22 (s, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.53 (t, *J* = 9.2 Hz, 3H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 2H), 7.08 – 7.06 (m, 1H), 6.94 (d, *J* = 7.5 Hz, 2H), 3.73 (s, 2H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 175.1, 149.6, 141.2, 138.4, 134.5, 134.3, 129.7, 128.7, 128.6, 128.0, 127.8, 127.3, 125.5, 125.2, 121.0, 118.3, 115.6, 31.1.

3-benzyl-2,6-diphenylquinolin-4(1H)-one (3.3zf):[18]



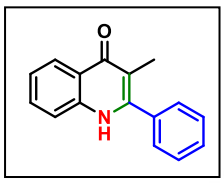
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 68% yield (0.264 g, 0.68 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.86 (brs, 1H), 8.39 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 6.9 Hz, 3H), 7.57 – 7.45 (m, 7H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 2H), 3.76 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.4, 149.2, 141.5, 139.6, 139.0, 134.8, 130.3, 129.6, 129.2, 128.7, 128.6, 128.0, 127.9, 127.5, 126.6, 125.4, 124.0, 122.5, 119.2, 117.9, 31.2.

3-benzyl-1-methyl-2-phenylquinolin-4(1H)-one (3.3zg):[18]



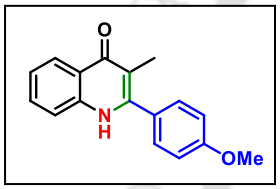
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 60% yield (0.195 g, 0.60 mmol) as a yellow solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 8.29 (d, *J* = 7.8 Hz, 1H), 7.78 – 7.77 (m, 2H), 7.52 – 7.48 (m, 3H), 7.45 – 7.42 (m, 1H), 7.27 – 7.26 (m, 2H), 7.09 (t, *J* = 7.3 Hz, 2H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 6.8 Hz, 2H), 3.56 (s, 2H), 3.42 (s, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 175.5, 152.6, 141.2, 140.9, 134.5, 132.2, 129.2, 128.9, 128.5, 127.9, 127.8, 125.8, 125.3, 125.1, 123.3, 119.7, 117.1, 37.3, 32.3.

3-methyl-2-phenylquinolin-4(1H)-one (3.5a):[18]



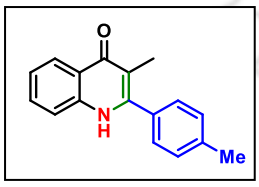
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 82% yield (0.193 g, 0.82 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.64 (brs, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.60 – 7.54 (m, 5H), 7.31 – 7.29 (m, 1H), 1.89 (s, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.9, 147.9, 139.5, 135.2, 131.4, 129.5, 129.0, 128.7, 125.0, 123.1, 122.8, 118.2, 114.5, 12.3.

2-(4-methoxyphenyl)-3-methylquinolin-4(1H)-one (3.5b):[18]



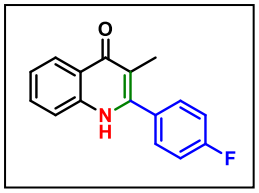
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 87% yield (0.231 g, 0.87 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.52 (brs, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.28 (t, *J* = 7.1 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H), 1.91 (s, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.8, 160.0, 147.6, 139.5, 131.2, 130.4, 127.3, 124.9, 123.0, 122.6, 118.1, 114.3, 113.9, 55.4, 12.3.

3-methyl-2-(p-tolyl)quinolin-4(1H)-one (3.5c):[43]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 83% yield (0.231 g, 0.83 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.55 (brs, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 2.40 (s, 3H), 1.90 (s, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.7, 147.7, 139.5, 139.0, 132.3, 131.2, 129.0, 128.8, 124.9, 123.0, 122.6, 118.1, 114.3, 20.9, 12.2.

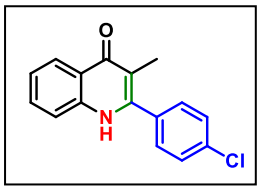
2-(4-fluorophenyl)-3-methylquinolin-4(1H)-one (3.5d):[43]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 74% yield (0.187 g, 0.74 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.62 (brs, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.60 (m, 4H), 7.41 (t, *J* = 8.7 Hz, 2H), 7.32 – 7.27 (m, 1H), 1.88 (s, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.7, 162.6 (d, *J* = 245.3 Hz), 146.8,

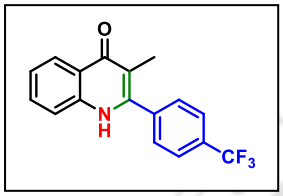
139.5, 131.5 (d, J = 3.3 Hz), 131.42, 131.35, 131.33, 125.0, 123.1, 122.7, 118.2, 115.5 (d, J = 21.5 Hz), 114.6, 12.1. **^{19}F NMR (470 MHz, DMSO-d_6)** δ -111.8.

2-(4-chlorophenyl)-3-methylquinolin-4(1H)-one (3.5e):[18]



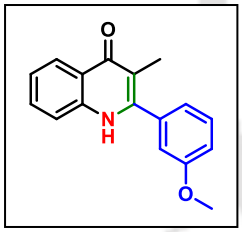
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 70% yield (0.189 g, 0.70 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 11.63 (brs, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.64 – 7.58 (m, 6H), 7.31 – 7.28 (m, 1H), 1.88 (s, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 176.7, 146.5, 139.5, 134.2, 133.8, 131.3, 130.9, 128.6, 125.0, 123.1, 122.7, 118.1, 114.5, 12.1.

3-methyl-2-(4-(trifluoromethyl)phenyl)quinolin-4(1H)-one (3.5f):[18]



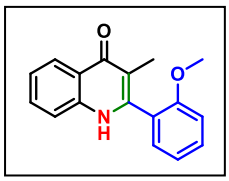
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 30/70) to afforded the title compound in 57% yield (0.173 g, 0.57 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 11.70 (brs, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 7.9 Hz, 2H), 7.65 – 7.58 (m, 2H), 7.31 (t, J = 7.1 Hz, 1H), 1.87 (s, 3H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 176.7, 146.2, 139.5, 139.0, 131.5, 130.1, 129.7 (q, J = 22.2 Hz), 125.5 (q, J = 3.8 Hz), 125.1, 125.0, 123.1, 122.9, 122.8, 118.2, 114.6, 12.0. **^{19}F NMR (470 MHz, DMSO-d_6)** δ -61.2.

2-(3-methoxyphenyl)-3-methylquinolin-4(1H)-one (3.5g):[18]



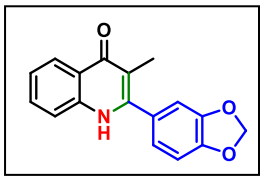
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 30/70) to afforded the title compound in 78% yield (0.207 g, 0.78 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 11.60 (brs, 1H), 8.13 (s, 1H), 7.63 – 7.60 (m, 2H), 7.48 (t, J = 6.4 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.12 – 7.11 (m, 3H), 3.83 (s, 3H), 1.90 (s, 1H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 176.8, 159.2, 147.5, 139.5, 136.4, 131.3, 129.8, 124.9, 123.1, 122.7, 121.2, 118.2, 115.0, 114.5, 114.3, 55.4, 12.2.

2-(2-methoxyphenyl)-3-methylquinolin-4(1H)-one (3.5h):[18]



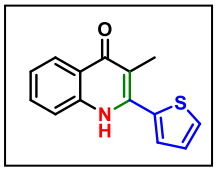
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 42% yield (0.111 g, 0.42 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 11.60 (brs, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.55 – 7.52 (m, 2H), 7.36 (d, J = 7.3 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 3.78 (s, 3H), 1.74 (s, 3H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 176.5, 156.4, 145.2, 139.5, 131.1, 131.1, 130.2, 124.9, 123.8, 123.2, 122.5, 120.5, 118.0, 115.6, 111.8, 55.6, 11.9.

2-(benzo[d][1,3]dioxol-5-yl)-3-methylquinolin-4(1H)-one (3.5i):[18]



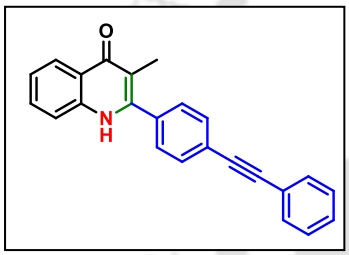
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 46% yield (0.128 g, 0.46 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.55 (brs, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.30 – 7.27 (m, 1H), 7.15 (s, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.12 (s, 2H), 1.91 (s, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.9, 148.1, 147.5, 147.3, 139.5, 131.3, 128.8, 125.0, 123.2, 123.1, 122.7, 118.2, 114.5, 109.5, 108.4, 101.6, 12.4.

3-methyl-2-(thiophen-2-yl)quinolin-4(1H)-one (3.5j):[18]



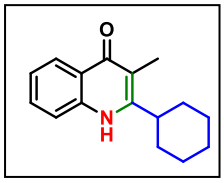
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 70% yield (0.169 g, 0.70 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.59 (brs, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 5.0 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.50 (d, *J* = 3.5 Hz, 1H), 7.31 – 7.28 (m, 2H), 2.05 (s, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.6, 140.9, 139.5, 135.0, 131.5, 129.9, 128.9, 127.6, 125.0, 123.0, 122.9, 118.2, 115.6, 12.4.

3-methyl-2-(4-(phenylethynyl)phenyl)quinolin-4(1H)-one (3.5k):



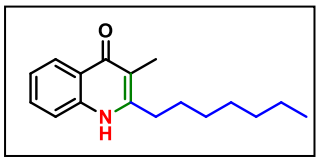
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 68% yield (0.228 g, 0.68 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.66 (brs, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.63 – 7.59 (m, 6H), 7.46 – 7.45 (m, 3H), 7.33 – 7.29 (m, 1H), 1.91 (s, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.7, 146.8, 139.5, 135.1, 131.5, 131.5, 131.4, 129.5, 129.1, 128.8, 125.0, 123.3, 123.1, 122.8, 122.0, 118.2, 114.5, 90.6, 88.8, 12.1. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{24}H_{18}NO$ is 336.1388 Found 336.1406.

2-cyclohexyl-3-methylquinolin-4(1H)-one (3.5l):[18]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 30/70) to afforded the title compound in 65% yield (0.157 g, 0.65 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.69 (brs, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 2.99 – 2.91 (m, 1H), 2.04 (s, 3H), 1.86 – 1.72 (m, 7H), 1.46 – 1.29 (m, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.4, 153.0, 139.4, 130.8, 124.9, 122.8, 122.3, 117.9, 112.9, 40.0, 29.7, 26.0, 25.3, 10.1.

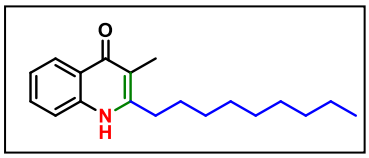
2-heptyl-3-methylquinolin-4(1H)-one (3.5m):[18]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 63% yield (0.162 g, 0.63 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.34 (brs, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.49 (d, *J* =

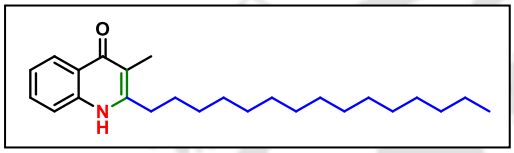
8.4 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 2.67 (t, *J* = 7.9 Hz, 2H), 1.98 (s, 3H), 1.64 – 1.59 (m, 2H), 1.37 – 1.22 (m, 8H), 0.85 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.3, 149.7, 139.2, 130.9, 125.0, 122.9, 122.3, 117.6, 113.7, 31.7, 31.2, 28.8, 28.5, 28.3, 22.1, 14.0, 10.3.

3-methyl-2-nonylquinolin-4(1H)-one (3.5n):[18]



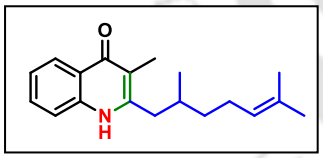
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 65% yield (0.186 g, 0.65 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.39 (brs, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 7.0 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 2.66 (t, *J* = 7.7 Hz, 2H), 1.98 (s, 3H), 1.64 – 1.56 (m, 2H), 1.36 – 1.21 (m, 12H), 0.83 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 176.4, 149.9, 139.2, 131.0, 125.1, 122.9, 122.4, 117.6, 113.8, 31.7, 31.3, 29.0, 28.9, 28.8, 28.7, 28.4, 22.1, 14.0, 10.4.

3-methyl-2-pentadecylquinolin-4(1H)-one (3.5o):



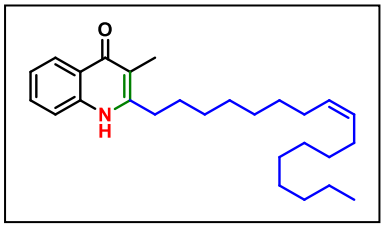
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 71% yield (0.262 g, 0.71 mmol) as a white solid. **^{1}H NMR (500 MHz, CDCl$_3$ + CD$_3$OD)** δ 8.17 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 8.0 Hz, 2H), 2.04 (s, 3H), 1.59 – 1.53 (m, 2H), 1.32 – 1.27 (m, 2H), 1.24 – 1.17 (m, 22H), 0.79 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$ + CD$_3$OD)** δ 178.3, 151.1, 139.0, 131.1, 125.3, 123.2, 123.1, 117.3, 115.1, 32.6, 31.9, 29.6, 29.6, 29.6, 29.6, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 28.8, 22.6, 14.0, 10.4. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{25}H_{40}NO$ is 370.3110 Found 370.3111.

2-(2,6-dimethylhept-5-en-1-yl)-3-methylquinolin-4(1H)-one (3.5p):[18]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 57% yield (0.162 g, 0.57 mmol) as a white solid. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 10.01 (brs, 1H), 8.37 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.29 – 7.26 (m, 1H), 5.01 (t, *J* = 7.1 Hz, 1H), 2.79 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.54 (dd, *J* = 13.7, 8.6 Hz, 1H), 2.18 (s, 3H), 2.05 – 1.89 (m, 2H), 1.79 – 1.75 (m, 1H), 1.65 (s, 3H), 1.55 (s, 3H), 1.41 – 1.33 (m, 1H), 1.29 – 1.21 (m, 1H), 0.91 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 178.2, 149.0, 139.2, 131.9, 131.3, 126.1, 124.3, 123.7, 123.1, 117.5, 116.4, 40.3, 37.0, 33.0, 25.8, 25.6, 19.4, 17.8, 11.4.

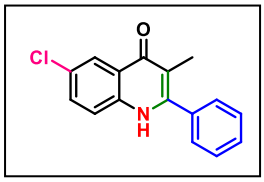
(Z)-2-(heptadec-8-en-1-yl)-3-methylquinolin-4(1H)-one (3.5q):



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 60/40) to afforded the title compound in 62% yield (0.245 g, 0.62 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$ + C$_6$D$_6$)** δ 11.38 (brs, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.56 (m, 2H), 7.28 – 7.23 (m, 1H), 5.36 (s, 2H), 2.68 (t, *J* = 7.4 Hz, 2H), 2.06 (s, 3H), 1.97 (d, *J* = 17.0 Hz, 4H), 1.63 (m, 1H), 1.36 – 1.22 (m, 22H), 1.12 – 1.08

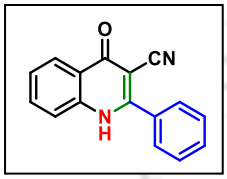
(m,1SSH), 0.85 (dd, *J* = 6.7, 3.8 Hz, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.3, 149.7, 139.2, 130.9, 129.7, 129.6, 125.0, 122.9, 122.3, 117.6, 113.7, 31.7, 31.3, 29.1, 29.1, 28.8, 28.7, 28.6, 28.6, 28.5, 28.3, 26.6, 22.1, 14.0, 10.3. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{27}H_{42}NO$ is 396.3266 Found 396.3260.

6-chloro-3-methyl-2-phenylquinolin-4(1H)-one (3.5r):[18]



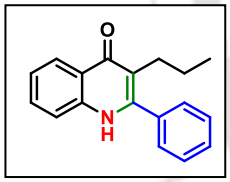
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 80% yield (0.216 g, 0.80 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.78 (brs, 1H), 8.05 (s, 1H), 7.64 (s, 2H), 7.58 – 7.54 (m, 5H), 1.88 (s, 3H). **^{13}C NMR (125MHz, DMSO-*d*$_6$)** δ 175.6, 148.1, 138.0, 134.8, 131.5, 129.6, 128.9, 128.6, 127.3, 124.0, 123.8, 120.7, 114.9, 12.2.

4-oxo-2-phenyl-1,4-dihydroquinoline-3-carbonitrile (3.5s):[18]



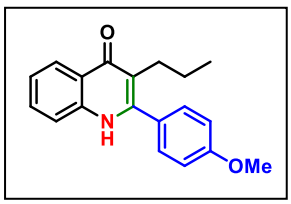
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 45% yield (0.111 g, 0.45 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 12.31 (brs, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.81 – 7.79 (m, 3H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.67 (m, 3H), 7.50 (t, *J* = 7.5 Hz, 1H). **^{13}C NMR (125MHz, DMSO-*d*$_6$)** δ 175.1, 157.3, 139.3, 133.5, 132.3, 131.5, 128.9, 128.8, 125.6, 124.9, 123.9, 119.6, 117.0, 93.4.

2-phenyl-3-propylquinolin-4(1H)-one (3.5t):[18]



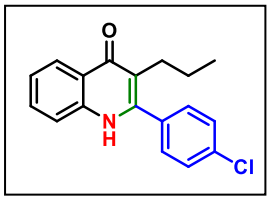
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 78% yield (0.205 g, 0.78 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.57 (brs, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.62 – 7.56 (m, 5H), 7.51 (d, *J* = 6.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.40 – 1.34 (m, 2H), 0.71 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.5, 148.3, 139.5, 135.2, 131.4, 129.3, 128.7, 128.6, 125.0, 123.6, 122.7, 119.2, 118.2, 28.0, 22.1, 14.2.

2-(4-methoxyphenyl)-3-propylquinolin-4(1H)-one (3.5u):[18]



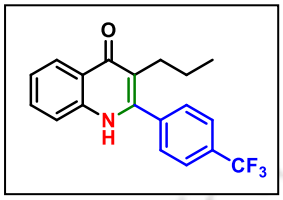
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 71% yield (0.208 g, 0.71 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.48 (brs, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 3.84 (s, 3H), 2.32 (t, *J* = 7.6 Hz, 2H), 1.42 – 1.35 (m, 2H), 0.73 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.4, 159.9, 148.0, 139.4, 131.2, 130.1, 127.5, 125.0, 123.5, 122.5, 119.3, 118.1, 113.9, 55.3, 28.0, 22.1, 14.2.

2-(4-chlorophenyl)-3-propylquinolin-4(1H)-one (3.5v):[18]



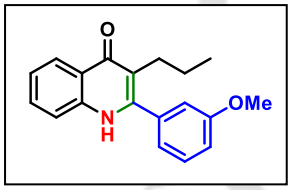
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 76% yield (0.226 g, 0.76 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.58 (brs, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.65 – 7.54 (m, 6H), 7.31 – 7.27 (m, 1H), 2.28 (t, *J* = 7.7 Hz, 2H), 1.42 – 1.32 (m, 2H), 0.72 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.4, 147.0, 139.4, 134.1, 133.9, 131.4, 130.7, 128.6, 125.0, 123.6, 122.8, 119.3, 118.1, 27.9, 22.0, 14.2.

3-propyl-2-(4-(trifluoromethyl)phenyl)quinolin-4(1H)-one (3.5w):[18]



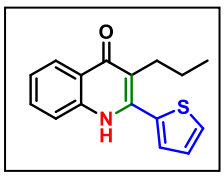
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 48% yield (0.159 g, 0.48 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.63 (brs, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.56 – 7.55 (m, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 2.30 (t, *J* = 7.7 Hz, 2H), 1.41 – 1.35 (m, 2H), 0.71 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.3, 146.7, 139.5, 139.1, 131.5, 129.7 (q, *J* = 26.5 Hz), 125.5 (q, *J* = 3.7 Hz), 125.0, 124.9, 123.6, 123.1, 122.8, 119.2, 118.1, 27.8, 22.0, 14.1. **^{19}F NMR (470 MHz, DMSO-*d*$_6$)** δ -61.2.

2-(3-methoxyphenyl)-3-propylquinolin-4(1H)-one (3.5x):[18]



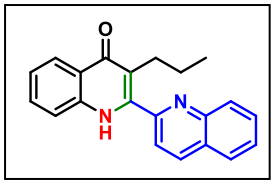
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 65% yield (0.191 g, 0.65 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.57 (brs, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.08 – 7.07 (m, 2H), 3.82 (s, 3H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.44 – 1.37 (m, 2H), 0.74 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.4, 159.2, 147.9, 139.4, 136.5, 131.3, 129.8, 125.0, 123.6, 122.6, 120.9, 119.1, 118.1, 114.9, 114.3, 55.4, 28.1, 22.1, 14.2.

3-propyl-2-(thiophen-2-yl)quinolin-4(1H)-one (3.5y):[18]



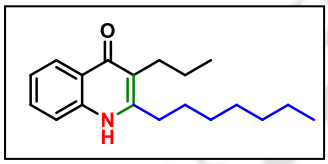
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 60% yield (0.162 g, 0.60 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.59 (brs, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 5.1 Hz, 1H), 7.62 – 7.59 (m, 2H), 7.44 (d, *J* = 3.4 Hz, 1H), 7.33 – 7.22 (m, 2H), 2.45 (t, *J* = 7.8 Hz, 2H), 1.48 – 1.41 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.3, 141.0, 139.6, 134.9, 131.6, 129.5, 128.7, 127.5, 125.0, 123.4, 122.9, 120.8, 118.2, 28.3, 22.5, 14.2.

3-propyl-[2,2'-biquinolin]-4(1H)-one (3.5z):



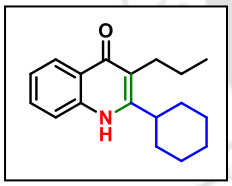
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 63% yield (0.198 g, 0.63 mmol) as a yellow solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.81 (brs, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.18 – 8.11 (m, 3H), 7.88 (t, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.35 – 7.31 (m, 1H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.48 – 1.38 (m, 2H), 0.69 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.7, 153.7, 147.1, 146.5, 139.5, 137.1, 131.6, 130.5, 129.2, 128.1, 127.7, 127.4, 125.1, 123.7, 122.9, 121.9, 119.5, 118.3, 27.6, 22.1, 14.2. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{21}H_{19}N_2O$ is 315.1497 Found 315.1502.

2-heptyl-3-propylquinolin-4(1H)-one (3.5za):[18]



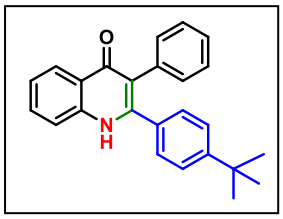
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 48% yield (0.137 g, 0.48 mmol) as a white solid. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 11.43 (brs, 1H), 8.33 (d, *J* = 8.1 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 2.70 (t, *J* = 8.1 Hz, 2H), 2.61 (t, *J* = 7.7 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 1H), 1.69 – 1.61 (m, 2H), 1.59 – 1.52 (m, 2H), 1.34 – 1.17 (m, 5H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 2H), 0.83 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 177.8, 139.7, 131.2, 125.7, 123.9, 123.1, 120.1, 118.2, 34.5, 32.4, 31.8, 29.7, 29.2, 29.1, 27.8, 25.0, 22.7, 14.5, 14.1.

2-cyclohexyl-3-propylquinolin-4(1H)-one (3.5zb):[18]



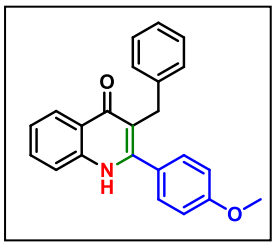
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 60% yield (0.162 g, 0.60 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 10.70 (brs, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 2.92 (t, *J* = 12.0 Hz, 1H), 2.56 – 2.53 (m, 2H), 1.87 – 1.79 (m, 4H), 1.75 – 1.68 (m, 3H), 1.45 – 1.30 (m, 5H), 0.91 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.2, 153.1, 139.5, 130.9, 125.0, 123.1, 122.3, 117.8, 117.7, 40.1, 30.3, 26.4, 26.0, 25.2, 22.9, 14.1.

2-(4-(tert-butyl)phenyl)-3-phenylquinolin-4(1H)-one (3.5zc):



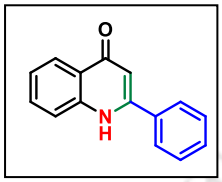
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 65% yield (0.230 g, 0.65 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.71 (brs, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.36 – 7.32 (m, 3H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 2H), 7.13 (d, *J* = 6.9 Hz, 1H), 7.07 (d, *J* = 6.8 Hz, 2H), 1.24 (s, 9H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 175.4, 151.5, 148.4, 139.7, 135.8, 132.4, 131.7, 131.6, 129.3, 127.2, 126.0, 125.3, 124.9, 124.6, 123.1, 120.3, 118.4, 34.4, 30.9. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{25}H_{24}NO$ is 354.1858 Found 354.1811.

3-benzyl-2-(4-methoxyphenyl)quinolin-4(1H)-one (3.5zd):[18]



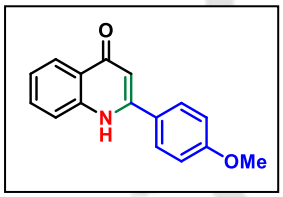
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 82% yield (0.280 g, 0.82 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.62 (brs, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 4.0 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.29 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 3H), 6.98 (d, *J* = 7.6 Hz, 2H), 3.82 (s, 3H), 3.76 (s, 2H). **^{13}C NMR (125MHz, DMSO-*d*$_6$)** δ 176.3, 160.1, 149.0, 141.6, 139.6, 131.4, 130.1, 127.9, 127.8, 127.1, 125.3, 125.0, 123.7, 122.8, 118.2, 117.6, 113.9, 55.4, 31.2.

2-phenylquinolin-4(1H)-one (3.6a):[15]



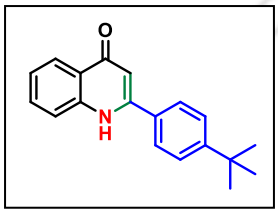
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 72% yield (0.159 g, 0.72 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.78 (brs, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.84 – 7.82 (m, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.59 – 7.57 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 6.37 (s, 1H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 177.0, 150.1, 140.5, 134.2, 131.8, 130.5, 129.0, 127.4, 124.9, 124.8, 123.3, 118.7, 107.4.

2-(4-methoxyphenyl)quinolin-4(1H)-one (3.6b):[41]



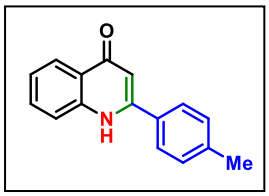
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 75% yield (0.189 g, 0.75 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.61 (brs, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.31 (s, 1H), 3.84 (s, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.9, 161.1, 149.8, 140.5, 131.7, 128.9, 126.2, 124.8, 124.7, 123.2, 118.6, 114.4, 106.5, 55.5.

2-(4-(tert-butyl)phenyl)quinolin-4(1H)-one (3.6c):[44]



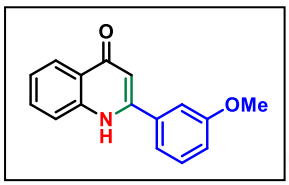
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 80% yield (0.222 g, 0.80 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.67 (brs, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.74 (m, 3H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.32 (s, 1H), 1.33 (s, 9H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 177.0, 153.3, 150.0, 140.5, 131.8, 131.4, 127.2, 125.8, 124.9, 124.7, 123.2, 118.7, 107.0, 34.6, 31.0.

2-(p-tolyl)quinolin-4(1H)-one (3.6d):[44]



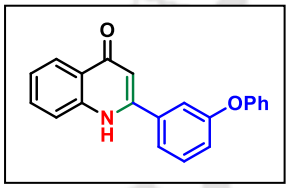
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 78% yield (0.183 g, 0.78 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.66 (brs, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.79 – 7.65 (m, 4H), 7.38 – 7.32 (m, 3H), 6.33 (s, 1H), 2.39 (s, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 177.0, 149.9, 140.5, 140.4, 131.8, 131.3, 129.6, 127.2, 124.9, 124.7, 123.2, 118.7, 106.9, 20.9.

2-(3-methoxyphenyl)quinolin-4(1H)-one (3.6e):[44]



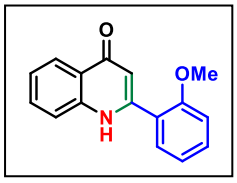
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 68% yield (0.171 g, 0.68 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.70 (brs, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.40 – 7.32 (m, 3H), 7.14 (d, *J* = 7.1 Hz, 1H), 6.36 (s, 1H), 3.87 (s, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 177.0, 159.6, 149.9, 140.5, 135.6, 131.8, 130.2, 124.9, 124.7, 123.3, 119.6, 118.8, 116.1, 112.8, 107.4, 55.4.

2-(3-phenoxyphenyl)quinolin-4(1H)-one (3.6f):[45]



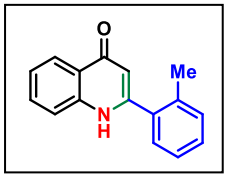
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 65% yield (0.204 g, 0.65 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.74 (brs, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.62 – 7.56 (m, 2H), 7.51 (s, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.33 (s, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 177.0, 157.1, 156.2, 149.2, 140.5, 136.1, 131.9, 130.8, 130.2, 130.0, 124.9, 124.7, 123.9, 123.4, 122.5, 120.1, 118.9, 118.8, 118.7, 117.5, 107.5.

2-(2-methoxyphenyl)quinolin-4(1H)-one (3.6g):[44]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 48% yield (0.121 g, 0.48 mmol) as a white solid. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 10.06 (brs, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.42 (s, 1H), 3.85 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 179.1, 156.8, 148.5, 139.7, 132.1, 132.0, 130.6, 126.0, 125.3, 123.8, 122.2, 121.9, 117.9, 112.1, 109.6, 56.2.

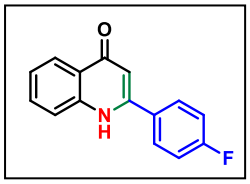
2-(o-tolyl)quinolin-4(1H)-one (3.6h):[14]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 45% yield (0.106 g, 0.45 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.81 (brs, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 7.1 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.43

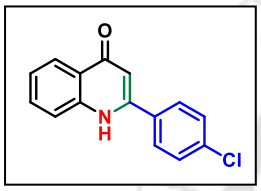
(m, 2H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.35 (q, *J* = 7.0 Hz, 2H), 5.97 (s, 1H), 2.31 (s, 3H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.7, 150.7, 140.2, 135.6, 135.0, 131.8, 130.5, 129.6, 129.1, 126.1, 124.8, 123.2, 118.4, 109.3, 19.4.

2-(4-fluorophenyl)quinolin-4(1H)-one (3.6i):[41]



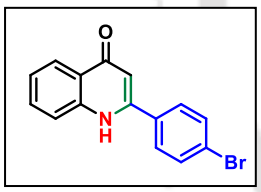
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 70% yield (0.168 g, 0.70 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.74 (brs, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.91 – 7.88 (m, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8.5 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 6.33 (s, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 177.0, 163.4 (d, *J* = 246.6 Hz), 149.1, 140.5, 131.9, 130.7, 129.9 (d, *J* = 8.5 Hz), 124.8, 124.7, 123.3, 118.7, 116.0 (d, *J* = 21.7 Hz), 107.4. **^{19}F NMR (470 MHz, DMSO-*d*$_6$)** δ -110.5.

2-(4-chlorophenyl)quinolin-4(1H)-one (3.6j):[14]



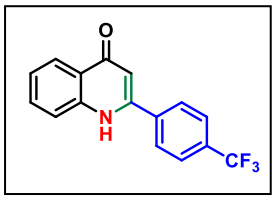
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 65% yield (0.166 g, 0.65 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.76 (brs, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.69 – 7.65 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 6.35 (s, 1H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 177.0, 148.8, 140.5, 135.3, 133.0, 132.0, 129.3, 129.0, 124.9, 124.8, 123.4, 118.8, 107.5.

2-(4-bromophenyl)quinolin-4(1H)-one (3.6k):[46]



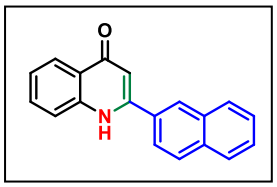
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 56% yield (0.168 g, 0.56 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.76 (brs, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.84 – 7.74 (m, 5H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 6.35 (s, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 177.0, 148.9, 140.5, 133.3, 132.0, 130.9, 129.5, 124.9, 124.8, 124.0, 123.4, 118.7, 107.5.

2-(4-(trifluoromethyl)phenyl)quinolin-4(1H)-one (3.6l):[47]



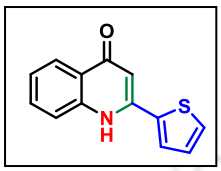
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 48% yield (0.139 g, 0.48 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.87 (brs, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.77 – 7.75 (m, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.57 – 7.53 (m, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 6.41 (s, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 177.0, 148.5, 140.5, 138.2, 133.1, 132.3, 132.1, 131.5, 131.4, 130.4 (q, *J* = 31.2 Hz), 128.8, 128.7, 128.5 125.9 (q, *J* = 3.8 Hz), 125.0, 124.9, 124.8, 123.6, 122.8, 118.8, 115.6, 108.1. **^{19}F NMR (470 MHz, DMSO-*d*$_6$)** δ -61.3.

2-(naphthalen-2-yl)quinolin-4(1H)-one (3.6m):[14]



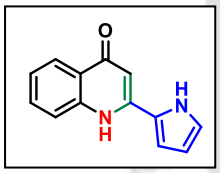
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 66% yield (0.179 g, 0.66 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.88 (brs, 1H), 8.46 (s, 1H), 8.14 – 8.12 (m, 2H), 8.11 – 8.09 (m, 1H), 8.04 – 8.02 (m, 1H), 7.94 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.65 – 7.62 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 6.50 (s, 1H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 177.0, 149.9, 140.6, 133.6, 132.6, 131.9, 131.5, 128.7, 128.7, 127.7, 127.6, 127.2, 127.0, 124.9, 124.8, 124.5, 123.3, 118.8, 107.8.

2-(thiophen-2-yl)quinolin-4(1H)-one (3.6n):[48]



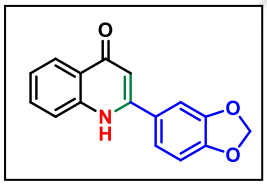
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 5/95) to afforded the title compound in 70% yield (0.159 g, 0.70 mmol) as a brown solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.65 (brs, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.90 (s, 1H), 7.85 (t, *J* = 3.5 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.34 – 7.29 (m, 2H), 6.33 (s, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.7, 143.6, 140.3, 136.1, 132.0, 129.7, 128.6, 128.2, 124.9, 124.7, 123.4, 118.5, 115.7, 106.1.

2-(1H-pyrrol-2-yl)quinolin-4(1H)-one (3.6o):



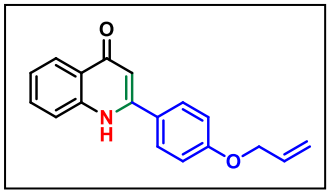
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 5/95) to afforded the title compound in 55% yield (0.116 g, 0.55 mmol) as a brown solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.74 (brs, 1H), 11.28 (brs, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 11.8 Hz, 2H), 6.47 (s, 1H), 6.28 (s, 1H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 176.9, 142.7, 140.4, 131.7, 124.8, 124.7, 123.1, 122.9, 118.2, 115.8, 110.6, 110.0, 102.6. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{13}H_{11}N_2O$ is 211.0871 Found 211.0880.

2-(benzo[d][1,3]dioxol-5-yl)quinolin-4(1H)-one (3.6p):[41]



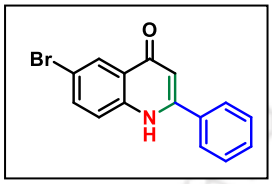
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 5/95) to afforded the title compound in 63% yield (0.167 g, 0.63 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.57 (brs, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.42 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.30 (s, 1H), 6.14 (s, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.9, 149.6, 149.2, 147.9, 140.4, 131.7, 128.0, 124.8, 124.7, 123.1, 121.8, 118.6, 108.7, 107.6, 106.8, 101.8.

2-(4-(allyloxy)phenyl)quinolin-4(1H)-one (3.6q):



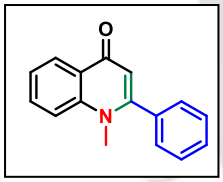
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 5/95) to afforded the title compound in 58% yield (0.161 g, 0.58 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-*d*$_6$)** δ 11.61 (brs, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.80 – 7.75 (m, 3H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.31 (s, 1H), 6.11 – 6.02 (m, 1H), 5.43 (d, *J* = 17.1 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 4.67 (d, *J* = 5.2 Hz, 2H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 176.9, 160.0, 149.7, 140.5, 133.4, 131.7, 128.9, 126.4, 124.7, 123.1, 118.6, 117.8, 115.7, 115.3, 106.5, 68.4. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{18}H_{16}NO_2$ is 278.1181 Found 278.1184.

6-bromo-2-phenylquinolin-4(1H)-one (3.6r):[49]



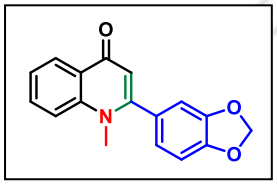
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 57% yield (0.171 g, 0.57 mmol) as a white solid. **^{1}H NMR (600 MHz, DMSO-*d*$_6$)** δ 11.76 (brs, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.84 – 7.81 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.58 – 7.57 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 6.35 (s, 1H). **^{13}C NMR (150 MHz, DMSO-*d*$_6$)** δ 177.0, 150.1, 140.6, 134.2, 131.9, 130.5, 129.1, 129.0, 127.5, 124.8, 123.3, 118.8, 107.4.

1-methyl-2-phenylquinolin-4(1H)-one (3.6s):[50]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 55% yield (0.129 g, 0.55 mmol) as a white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.48 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.51 – 7.49 (m, 3H), 7.43 – 7.39 (m, 3H), 6.37 (s, 1H), 3.63 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 177.7, 155.2, 141.8, 135.6, 132.6, 129.7, 128.9, 128.6, 126.6, 126.4, 123.9, 116.1, 112.3, 37.4.

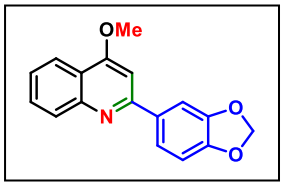
2-(benzo[d][1,3]dioxol-5-yl)-1-methylquinolin-4(1H)-one (3.6t):[41]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 20/80) to afforded the title compound in 51% yield (0.142 g, 0.51 mmol) as a pale brown solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.49 (d, *J* = 7.6 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.44 – 7.41 (m, 1H), 6.94 – 6.86 (m, 3H), 6.30 (s, 1H), 6.07 (s, 2H), 3.64 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 177.8, 154.5, 148.9, 148.1, 142.1, 132.5, 129.6, 127.0, 126.9, 123.8, 122.9, 116.1, 112.8, 109.1, 108.8, 101.8, 37.4.

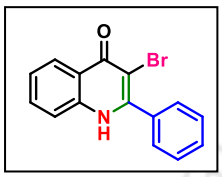
3.5.18.2. Analytical data for post synthetic modifications:

2-(benzo[d][1,3]dioxol-5-yl)-4-methoxyquinoline (3.13):[41]



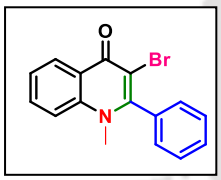
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 85/15) to afforded the title compound in 86% yield (0.240 g, 0.86 mmol) as a pale brown solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.06 (s, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.02 (s, 2H), 4.07 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 162.8, 158.2, 149.2, 148.8, 148.4, 134.9, 130.1, 129.1, 125.3, 121.7, 121.7, 120.4, 108.5, 108.1, 101.5, 97.6, 55.7.

3-bromo-2-phenylquinolin-4(1H)-one (3.14):[30]



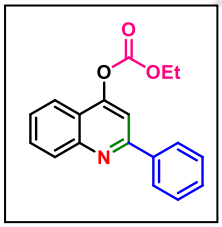
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 80% yield (0.240 g, 0.80 mmol) as a light pink solid. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 12.33 (brs, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.64 – 7.62 (m, 2H), 7.59 – 7.58 (m, 3H), 7.41 (t, *J* = 7.2 Hz, 1H). **^{13}C NMR (125 MHz, DMSO-d_6)** δ 171.7, 149.9, 139.0, 135.0, 132.2, 130.0, 129.0, 128.5, 125.3, 124.1, 123.0, 118.5, 105.3.

3-bromo-1-methyl-2-phenylquinolin-4(1H)-one (3.15):[51]



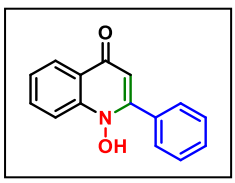
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 90% yield (0.283 g, 0.90 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.61 (d, *J* = 2.4 Hz, 1H), 7.74 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.60 – 7.53 (m, 4H), 7.42 (d, *J* = 9.1 Hz, 1H), 7.33 (d, *J* = 6.7 Hz, 2H), 3.55 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 171.39, 153.06, 139.45, 135.88, 135.57, 130.02, 129.87, 129.39, 128.36, 126.06, 118.15, 118.04, 109.38, 38.75.

ethyl (2-phenylquinolin-4-yl) carbonate (3.16):[31, 32]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 90/10) to afforded the title compound in 75% yield (0.220 g, 0.75 mmol) as a light-yellow liquid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (d, *J* = 8.6 Hz, 1H), 8.16 – 8.13 (m, 2H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.89 (s, 1H), 7.73 (t, *J* = 7.9 Hz, 1H), 7.55 – 7.49 (m, 3H), 7.46 – 7.43 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 158.3, 154.9, 152.5, 150.0, 139.2, 130.4, 129.8, 129.7, 128.9, 127.6, 126.7, 121.0, 120.9, 109.9, 65.6, 14.3.

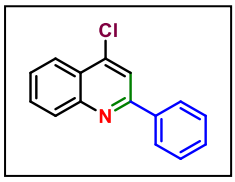
1-hydroxy-2-phenylquinolin-4(1H)-one (3.17):[31, 32]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 70% yield (0.166 g, 0.70 mmol) as a yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 11.76 (brs, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.84 – 7.82 (m, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.5

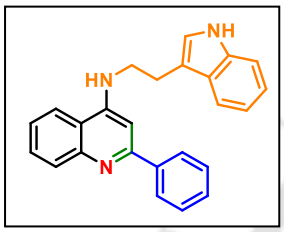
Hz, 1H), 7.59 – 7.56 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 6.35 (s, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$)** δ 177.0, 150.1, 140.5, 134.2, 131.8, 130.5, 129.0, 127.4, 124.9, 124.7, 123.3, 118.7, 107.4.

4-chloro-2-phenylquinoline (3.18):[15]



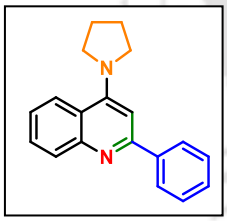
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 85/15) to afforded the title compound in 87% yield (0.209 g, 0.87 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.13 (d, *J* = 8.4 Hz, 2H), 8.08 (d, *J* = 6.9 Hz, 2H), 7.87 (s, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.1 Hz, 2H), 7.42 (t, *J* = 7.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 157.2, 149.1, 143.1, 138.6, 130.5, 130.1, 129.8, 128.9, 127.5, 127.2, 125.3, 123.9, 119.1.

N-(2-(1H-indol-3-yl)ethyl)-2-phenylquinolin-4-amine (3.19):[33]



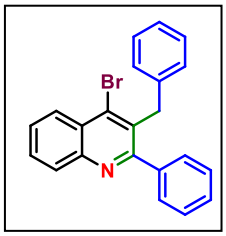
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 70% yield (0.255 g, 0.70 mmol) as a brown solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.31 (s, 1H), 8.07 – 8.02 (m, 3H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.39 (m, 3H), 7.36 – 7.29 (m, 2H), 7.24 – 7.20 (m, 1H), 7.17 – 7.13 (m, 1H), 7.03 (s, 1H), 6.89 (s, 1H), 5.14 (t, *J* = 5.3 Hz, 1H), 3.71 (q, *J* = 6.2 Hz, 2H), 3.24 (t, *J* = 6.6 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 158.6, 150.2, 148.7, 141.0, 136.6, 130.2, 129.3, 129.0, 128.7, 127.7, 127.4, 124.5, 122.5, 122.4, 119.8, 119.3, 118.6, 118.0, 112.7, 111.6, 97.1, 43.4, 24.8.

2-phenyl-4-(pyrrolidin-1-yl)quinoline (3.20):[33]



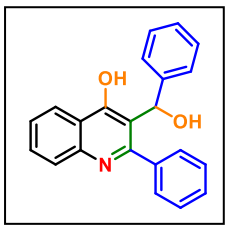
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 10/90) to afforded the title compound in 85% yield (0.233 g, 0.85 mmol) as a light-yellow liquid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.12 (d, *J* = 8.6 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 3H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.82 (s, 1H), 3.61 – 3.58 (m, 4H), 1.93 – 1.90 (m, 4H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 157.4, 153.2, 150.4, 141.1, 130.0, 128.7, 128.6, 128.5, 127.5, 124.9, 122.8, 120.4, 100.7, 52.1, 25.9.

3-benzyl-4-bromo-2-phenylquinoline (3.21):[15]



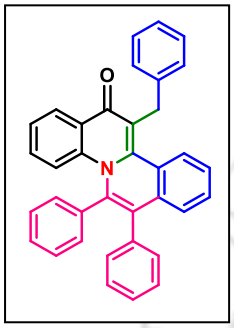
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 85% yield (0.318 g, 0.85 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.26 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.38 – 7.34 (m, 5H), 7.19 – 7.12 (m, 3H), 6.90 (d, *J* = 7.2 Hz, 2H), 4.40 (s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 161.4, 147.1, 140.6, 138.9, 138.0, 132.4, 130.0, 129.9, 128.7, 128.5, 128.4, 128.3, 128.2, 127.9, 127.6, 127.3, 126.2, 39.7.

3-(hydroxy(phenyl)methyl)-2-phenylquinolin-4-ol (3.22):



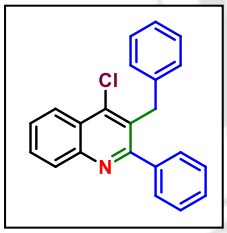
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 75% yield (0.246 g, 0.75 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 10.41 (brs, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.29 – 7.13 (m, 11H), 5.45 (s, 1H), 4.66 (brs, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 179.0, 149.2, 144.3, 139.3, 133.5, 132.6, 130.2, 128.9, 128.6, 128.2, 127.1, 126.2, 125.5, 124.8, 124.3, 119.3, 118.0, 72.9. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{22}H_{18}NO_2$ is 328.1338 Found 328.1341

12-benzyl-6,7-diphenyl-13H-isoquinolino[2,1-a]quinolin-13-one (3.23):



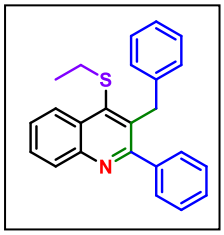
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 90/10) to afforded the title compound in 78% yield (0.380 g, 0.78 mmol) as a white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.41 – 7.35 (m, 5H), 7.28 – 7.20 (m, 6H), 7.13 (t, *J* = 7.1 Hz, 3H), 7.05 (t, *J* = 7.6 Hz, 2H), 6.89 (d, *J* = 7.8 Hz, 2H), 6.66 (d, *J* = 7.4 Hz, 1H), 4.13 (s, 2H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 162.9, 157.6, 149.3, 148.2, 140.8, 140.6, 134.9, 133.4, 131.2, 131.1, 130.8, 129.3, 129.0, 129.0, 128.7, 128.5, 128.4, 128.3, 128.3, 128.1, 127.8, 126.1, 125.4, 119.2, 117.2, 116.1, 113.4, 32.5. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{36}H_{26}NO$ is 489.2048 Found 489.2037.

3-benzyl-4-chloro-2-phenylquinoline (3.24):[15]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 90% yield (0.297 g, 0.90 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.29 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.41 – 7.36 (m, 5H), 7.20 – 7.13 (m, 3H), 6.92 (d, *J* = 6.2 Hz, 2H), 4.36 (s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 161.6, 147.2, 143.5, 140.6, 139.0, 130.1, 130.0, 129.9, 128.8, 128.6, 128.5, 128.4, 128.2, 127.7, 126.2, 126.0, 124.4, 36.8.

3-benzyl-4-(ethylthio)-2-phenylquinoline (3.25):



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) to afforded the title compound in 83% yield (0.295 g, 0.83 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.40 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.22 – 7.20 (m, 2H), 7.19 – 7.16 (m, 3H), 6.97 (t, *J* = 7.2 Hz, 2H), 6.92 (d, *J* = 7.1 Hz, 1H), 6.67 (d, *J* = 7.3 Hz, 2H), 4.44 (s, 2H), 2.62 (q, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 161.1, 146.9, 144.3, 141.1, 140.5, 136.4, 130.3, 129.2, 129.0, 128.6, 128.2, 128.1, 128.1, 128.0, 127.1, 126.5, 125.7, 37.9, 31.1, 14.9. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{24}H_{22}NS$ is 357.1507 Found 357.1512.

3.6. References:

1. E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257−10274.

2. a) P. Hradil, J. Hlavac, M. Soural, M. Hajdu´ch, M. Kola´r, R.´ Vecerova, *Mini-Rev. Med. Chem.* **2009**, *9*, 696−702; b) C. Mugnaini, S. Pasquini, F. Corelli, *Curr. Med. Chem.* **2009**, *16*, 1746−1767; c) H. Huse, M. Whiteley, *Chem. Rev.* **2011**, *111*, 152−159; d) G. Manfroni, R. Cannalire, M. L. Barreca, N. Kaushik-Basu, P. Leyssen, J. Winquist, N. Iraci, D. Manvar, J. Paeshuyse, R. Guhamazumder, A. Basu, S. Sabatini, O. Tabarrini, U. H. Danielson, J. Neyts, V. Cecchetti, *J. Med. Chem.* **2014**, *57*, 1952−1963; e) Y. Zhi, L. Gao, Y. Jin, C. Tang, J. Li, J. Li, Y. Long, *Bioorg. Med. Chem.* **2014**, *22*, 3670−3683; f) J. A. Wiles, B. J. Bradbury, M. J. Pucci, *Expert Opin. Ther. Pat.* **2010**, *20*, 1295−1319; g) G. S. Bisacchi, *J. Med. Chem.* **2015**, *58*, 4874−4882; h) G. Zhang, S. Zhang, B. Pan, X. Liu, L. Feng, *Eur. J. Med. Chem.* **2018**, *143*, 710−723.

3. a) M. Kresken, B. Wiedemann, *Antimicrob. Agents Chemother.* **1988**, *32*, 1285−1288; b) T. D. M. Pham, Z. M. Ziora, M. A. T. Blaskovich, *Med. Chem. Commun.* **2019**, *10*, 1719–1739; c) P. J. Barry, A. L. Donaldson, A. M. Jones, *BMJ.* **2018**, *361*, k1783; d) M. Spreng, J. Deleforge, V. Thomas, B. Boisrame, H. Drugeon, *J. Vet. Pharmacol. Ther.* **1995**, *18*, 284.

4. a) Y. Xia, Z. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S. Kuo, E. Hamel, T. Hackl, K. Lee, *J. Med. Chem.* **1998**, *41*, 1155−1162; b) S. Zhang, Jj. Feng, S. Kuo, A. Brossi, E. Hamel, A. Tropsha, K. Lee, *J. Med. Chem.* **2000**, *43*, 167−176; c) M. G. Ferlin, G. Chiarelotto, V. Gasparotto, L. Dalla Via, V. Pezzi, L. Barzon, G. Palu, I.`, Castagliuolo, *J. Med. Chem.* **2005**, *48*, 3417−3427; d) A. Lawer, C. Tyler, K. Hards, K.; L. M. Keighley, C. Y. Cheung, F. Kierek, S. Su, S. S. Matikonda, T. McInnes, J. D. A. Tyndall, K. L. Krause, G. M. Cook, A. B. Gamble, *ACS Med. Chem. Lett.* **2022**, *13*, 1663-1669.

5. a) R. P. Frutos, N. Haddad, I. N. Houpis, M. Johnson, L. L. Smith-Keenan, V. Fuchs, N. K. Yee, V. Farina, A. Faucher, C. Brochu, B. Hache, J. Duceppe, B.´ Beaulieu, *Synthesis* **2006**, *15*, 2563-2567; b) A. Baxter, M. Chambers, F. Edfeldt, K. Edman, A. Freeman, A., Johansson, S. King, A. Morley, J. Petersen, P. Rawlins, L. Spadola, B. Thong, H. V. Poel, N. Williams, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 777-780.

6. a) Y. Zhang, J. A. Clark, M. C. Connelly, F. Zhu, J. Min, W. A. Guiguemde, A. Pradhan, L. Iyer, A. Furimsky, J. Gow, T. Parman, F. El Mazouni, M. A. Phillips, D. E. Kyle, J. Mirsalis, R. K. Guy, *J. Med. Chem.* **2012**, *55*, 4205−4219; b) Y. Fan, X. Cheng, J. Wu, M. Liu, F. Zhang, Z. Xu, L. Feng, *Eur. J. Med. Chem.* **2018**, *146*, 1−14.

7. L. Huang, M. Hsieh, C. Teng, K. Lee, S. Kuo, *Bioorg. Med. Chem.* **1998**, *6*, 1657−1662.

8. A. Romek, T. Opatz, *Eur. J. Org. Chem.* **2010**, *2010*, 5841.

9. S. Niementowski, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1394.

10. a) C. P. Jones, K. W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 7968−7973; b) J. Huang, Y. Chen, A. O. King, M. Dilmeghani, R. D. Larsen, M. M. Faul, *Org. Lett.* **2008**, *10*, 2609− 2612; c)

R. T. McGuire, T. Lundrigan, J. W. M. MacMillan, K. N. Robertson, A. A. Yadav, M. Stradiotto, *Angew. Chem. Int. Ed.* **2022**, *61*, e202200352.

11. T. Zhao, B. Xu, *Org. Lett.* **2010**, *12*, 212−215.

12. O. Seppanen, M. Muuronen, J. Helaja, *Eur. J. Org. Chem.* **2014**, *19*, 4044−4052.

13. W. Hu, J. Lin, L. Song, Y. Long, *Org. Lett.* **2015**, *17*, 1268− 1271.

14. H. Ma, C. Guo, Z. Zhan, G. Lu, Y. Zhang, X. Luo, X. Cui, G. Huang, *New J. Chem.* **2017**, *41*, 5280−5283.

15. S. B. Lee, Y. Jang, J. Ahn, S. Chun, D. Oh, S. Hong, *Org. Lett.* **2020**, *22*, 8382–8386.

16. a) C. Gunanathan, D. Milstein, *Science*, **2013**, *341*, 1229712; b) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681−703; c) S. Budweg, K. Junge, M. Beller, *Catal. Sci. Technol.* **2020**, *10*, 3825–3842; d) A. Kumar, T. M. Bhatti, A. S. Goldman, *Chem. Rev.* **2017**, *117*, 12357–12384; e) C. Gunanathan, D. Milstein, *Chem. Rev.* **2014**, *114*, 12024–12087; f) A. Kumar, P. Daw, D. Milstein, *Chem. Rev.* **2022**, *122*, 385–441; g) B. Gnanaprakasam, E. Balaraman, Y. Ben-David, D. Milstein, *Angew. Chem., Int. Ed.* **2011**, *50*, 12240–12244; h) T. Hille, T. Irrgang, R. Kempe, *Angew. Chem. Int. Ed.* **2017**, *56*, 371 –374.

17. S. Bhat, V. Sridharan, *Chem. Commun.* **2012**, *48*, 4701–4703.

18. B. Sardar, D. Pal, R. Sarmah, D. Srimani, *Chem. Commun.* **2023**, *59*, 9267-9270.

19. a) D. Srimani, Y. Ben-David, D. Milstein, *Chem. Commun.* **2013**, *49*, 6632−6634; b) M. Chen, M. Zhang, B. Xiong, Z. Tan, W. Lv, H. Jiang, *Org. Lett.* **2014**, *16*, 6028−6031; c) K. Junge, V. Papa, M. Beller, *Chem. - Eur. J.* **2019**, *25*, 122−143; d) A. Mukherjee, D. Milstein, *ACS Catal.* **2018**, *8*, 11435−11469; e) I. Borthakur, A. Sau, S. Kundu, *Coord. Chem. Rev.* **2022**, *451*, 214−257; f) A. Samanta, P. Behera, A. Chaubey, A. Mondal, D. Pal, K. Mohar, L. Roy, D. Srimani, *Chem. Commun.* **2024**, *60*, 4056–4059; g) E. Balaraman, A. Nandakumar, G. Jaiswal, M. K. Sahoo, *Catal. Sci. Technol.* **2017**, *7*, 3177–3195; h) M. Subaramanian, G. Sivakumar, E. Balaraman, *Org. Biomol. Chem.* **2021**, *19*, 4213–4227; i) A. Mondal, R. Sharma, D. Pal, D. Srimani, *Eur. J. Org. Chem*. **2021**, *2021*, 3690–3720; j) M. Maji, D. Panja, I. Borthakur, S. Kundu, *Org. Chem. Front*. **2021**, *8*, 2673–2709; l) N. Hofmann, K. C. Hultzsch, *Eur. J. Org. Chem.* **2021**, 6206 –6223; m) K. Bera, A. Mukherjee, *Tetrahedron Lett.* **2021**, *81*, 153326

20. a) D. A. Valyaev, G. Lavigne, N. Lugan, *Coord. Chem. Rev.* **2016**, *308*, 191– 235; b) K. Das, S. Waiba, A. Jana, B. Maji, *Chem. Soc. Rev.* **2022**, *51*, 4386−4464; c) S. Elangovan, J. Neumann, J.-B. Sortais, K. Junge, C. Darcel, M. Beller, *Nat. Commun.* **2016**, *7*, 12641; d) M. Peña-López, P. Piehl, S. Elangovan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 14967–14971; e) S. Chakraborty, P. Daw, Y. Ben David, D. Milstein, *ACS Catal.* **2018**, *8*, 10300–10305; f) F. Sun, J. Huang, Z. Wei, C. Tang, W. Liu, *Angew. Chem. Int. Ed.* **2023**, *62*, e202303433; g) Y. Wang, M. Wang, Y. Li, Q. Liu, Chem **2021**, *7*, 1180–1223; h) K. Das, A. Mondal, D. Pal, D. Srimani, *Org. Lett.* **2019**, *21*, 3223–322; i) D. Pal, A. Mondal, D. Srimani, *Catal. Sci. Technol.* **2022**, *12*, 3202−3208; j) A. Mondal, H. J. Phukan, D. Pal, S. Kumar, M. Roy, D. Srimani, *Chem. Eur. J.* **2024**, *30*, e2023033; k) A. Mondal, D. Pal, H. J.

Phukan, M. Roy, S. Kumar, S. Purkayastha, A. K. Guha, D. Srimani, *ChemSusChem* **2024**,*17*, e202301138; l) A. Maji, S. Gupta, M. Maji, S. Kundu, *J. Org. Chem.* **2022**, *87*, 8351–8367.

21. A. Mondal, H. J. Phukan, K. Mohar, D. Pal, R. Sharma, S. Purkayastha, A. K. Guha, D. Srimani, *Chem. Commun.* **2025**, *61*, 4796-4799.

22. B. M. Frank, European Patent Organization, EP811613 A1, **1997**.

23. S. Tummanapalli, K. C. Gulipalli, S. Bodige, A. K. Pommidi, R. Boya, S. Choppadandi, M. R. Bakangari, S. K. Punna, S. Medaboina, D. Y. Mamindla, A. Kanuka, S. Endoori, V. K. Ganapathi, S. D. kottam, D. Kalbhor, M. Valluri, *J. Org. Chem.* **2024**, *89*, 1609−1617.

24. a) S. N. R. Donthireddy, M. Siddique, A. Rit, *J. Org. Chem.* **2023**, *88*, 1135−1146; b) T.-Y. Cheng, B. S. Brunschwig, R. M. Bullock, *J. Am. Chem. Soc.* **1998**, *120*, 13121–13137.

25. Q. Fan, C. Yang, M. Li, G. Wang, X. Kong, Q. Zhu, *Dalton Trans.* **2025**, DOI: https://doi.org/10.1039/d4dt02744b.

26.a) S. Ghosh, K. Bishayee, A. R. Khuda-Bukhsh, *Phytother. Res.* **2014**, *28*, 1153; b) A. L. Hale, K. M. Meepagala, A. Oliva, G. Aliotta, S. O. Duke, *J. Agric. Food Chem.* **2004**, *52*, 3345; c) A. Oliva, K. M. Meepagala. D. E. Wedge, D. Harries, A. L. Hale, G. Aliotta, S. O. Duke, *J. Agric. Food Chem.* **2003**, *51*, 890.

27. a) S. R. Bandatmakuru, V. R. Arava, *Synth. Commun.* **2018**, *48*, 2635−2641; b) S. J. Gharpure, S. K. Nanda, P.A. Adate, Y. G. Shelke, *J. Org. Chem.* **2017**, *82*, 2067−2080; c) W.-S. Chen, F. Yang, T. Wang, G.-Q. Zhang, Y. Wei, M.-H. Wang, Z.-S. Chen, K. Ji, *Org. Lett.* **2023**, *25*, 5762–5767.

28. a) O. M. Sampaio, L. C. C. Vieira, B. S. Bellete, B. King-Diaz, B. Lotina-Hennsen, M. F. D. G. F da Silva, T. A. M. Veiga, *Molecules* **2018**, *23*, 2693; b) S. Singh, S. Nerella, S. Pabbaraja, G. Mehta, *Org. Lett.* **2020**, *22*, 1575–1579.

29. M. Miliutina, S. A. Ejaz, S. U. Khan, V. O. Iaroshenko, A. Villinger, J. Iqbal, P. Langer, *Eur. J. Med. Chem.* **2017**, *126*, 408−420.

30. F. Yang, X. Wang, W. Zhao, F. Yu, Z. Yu, *ACS Omega* **2021**, *6*, 34044−34055.

31. G. Hofle, B. Bohlendorf, T. Fecker, F. Sasse, B. E. Kunze, *J. Nat. Prod.* **2008**, *71*, 1967−1969.

32. C. Pidathala, R. Amewu, G. A. Biagini, S. A. Ward, P. M. O'Neill, *J. Med. Chem.* **2012**, *55*, 1831−1843.

33. W. Luo, J.-W. Lv, T. Wang, Z.-Y. Zhang, H.-Y. Guo, Z.-Y. Song, C.-J. Wang, J. Ma, Y. Chen, *Bioorg. Med. Chem.* **2020**, *28*, No. 115190.

34. a) J. Genovino, D. Sames, L. G. Hamann, B. B. Touré, *Angew. Chem. Int. Ed.* **2016**, *55*, 14218–14238; b) F. Burg, M. Gicquel, S. Breitenlechner, A. Pçthig, T. Bach, *Angew. Chem. Int. Ed.* **2018**, *57*, 2953–2957; c) L. Tanwar, J. Bçrgel, T. Ritter, *J. Am. Chem. Soc.* **2019**, *141*, 17983 – 17988; d) M. S. Chen, M. C. White, *Science* **2007**, *318*, 783; e) Y. Zhang, C. Cao, Y. She, Y-F. Yang, K. N. Houk, *J. Am. Chem. Soc*. **2023**, *145*, 14446–14455.

35. a) Y.-C. Wu, C.-Y. Duh, S.-K. Wang, K.-S. Chen, T.-H. Yang, *J. Nat. Prod.* **1990**, *53*, 1327−1331; b) K. C. Agrawal, *J. Med. Chem.* **1967**, *10*, 99−101; c) Y. Li, J. Ding, M. Day, Y. Tao, J. Lu, M. D'iorio,

Chem. Mater. **2004**, *16*, 2165− 2173; (d) C. Li, X. Du, Y. Zhou, J. Ye, L. Fu, M. G. Humphrey, C. Wu, J. Zhao, Y. Du, S. Tao, J. Wu, C. A. Zhang, *J. Mater. Chem. C* **2018**, *6*, 6949−6957.

36. a) Y. Hong, J. W. Lam, B. Z. Tang, *Chem. Commun.* **2009**, 4332; b) E. Zhao, Y. Hong, S. Chen, C. W. T. Leung, C. Y.; Chan, R. T. Kwok, J. W. Y. Lam, B. Z. Tang, *Adv. Healthcare Mater.* **2014**, *3*, 88; c) Y. Hong, S. Chen, S.; C. W. T. Leung, C. W. T.; J. W. Y. Lam, B. Z. Tang, *Chem.-Asian J.* **2013**, *8*, 1806.

37. S. Ghosh, S. Pal, S. Rajamanickam, R. Shome, P. R. Mohanta, S. S. Ghosh, B. K. Patel, *ACS Omega* **2019**, *4*, 5565−5577.

38. S. A. Stoian, Y. -R. Peng, C. C. Beedle, Y.-J. Chung, G.-H. Lee, E.-C. Yang, S. Hil, *Inorg. Chem.* **2017**, *56*, 10861−10874; b) A. Mondal, J. H. Phukan, D. Pal, S. Kumar, M. Roy and D. Srimani, *Chem. Eur. J.* 2024, **30**, e202303315; c) D. Pal, A. Mondal, R. Sarmah, D. Srimani, *Org. Lett.* **2024**, *26*, 514−518.

39. V. A. Rao, P. C. Jain, N. Anand, R. C. Srimal, P. R. Dua, *J. Med. Chem.* **1970**, *13*, 516–522.

40. B. Chatterjee, C. Gunanathan, *Org. Lett.* **2015**, *17*, 4794−4797.

41. S. Singh, S. Nerella, S. Pabbaraja, G. Mehta, *Org. Lett.* **2020**, *22*, 1575–1579.

42. H. Ma, X. Zhou, D. Wei, J. Cao, C. Shi, Y. Fan, G. Huang, *Chem. Asian J.* **2016**, *11*, 2829 – 2833.

43. X. Wu, L.-L. Zheng, L.-P. Zhao, C.-F. Zhu, Y.-G. Li, *Chem. Commun.* **2019**, *55*, 14769–14772.

44. X. Xu, R. Sun, S. Zhang, X. Zhang, W. Yi, *Org. Lett.* **2018**, *20*, 1893–1897.

45. N. Shridhar, S. R. Krishan; G. C. Sekhar, R. G. Renukaiah, WO2024189504A1·2024-09-19.

46. J. Wu, Y. Zhou, T. Wu, Y. Zhou, C.-W. Chiang, A. Lei, *Org. Lett.* **2017**, *19*, 6432–6435.

47. W. Hu, J.-P. Lin, L.-R. Song, Y.-Q. Long, *Org. Lett.* **2015**, *17*, 1268–1271.

48. 28. L. Akerbladh, P. Nordeman, M. Wejdemar, L. R. Odell, M. Larhed, *J. Org. Chem.* **2015**, *80*, 1464–1471.

49. V. K. Rai, F. Verma, G. P. Sahu, M. Singh, A. Rai, *Eur. J. Org. Chem.* **2018**, *48*, 537–544.

50. W.-S. Chen, F. Yang, T. Wang, G.-Q. Zhang, Y. Wei, M.-H. Wang, Z.-S. Chen, K. Ji, *Org. Lett.* **2023**, *25*, 5762–5767.

51. M. J. Mphahlele, M. S. Nwamadi, P. Mabeta, *J. Heterocycl. Chem.* **2006**, *43*, 255–260.

3.7. Selected NMR copies of the compounds:

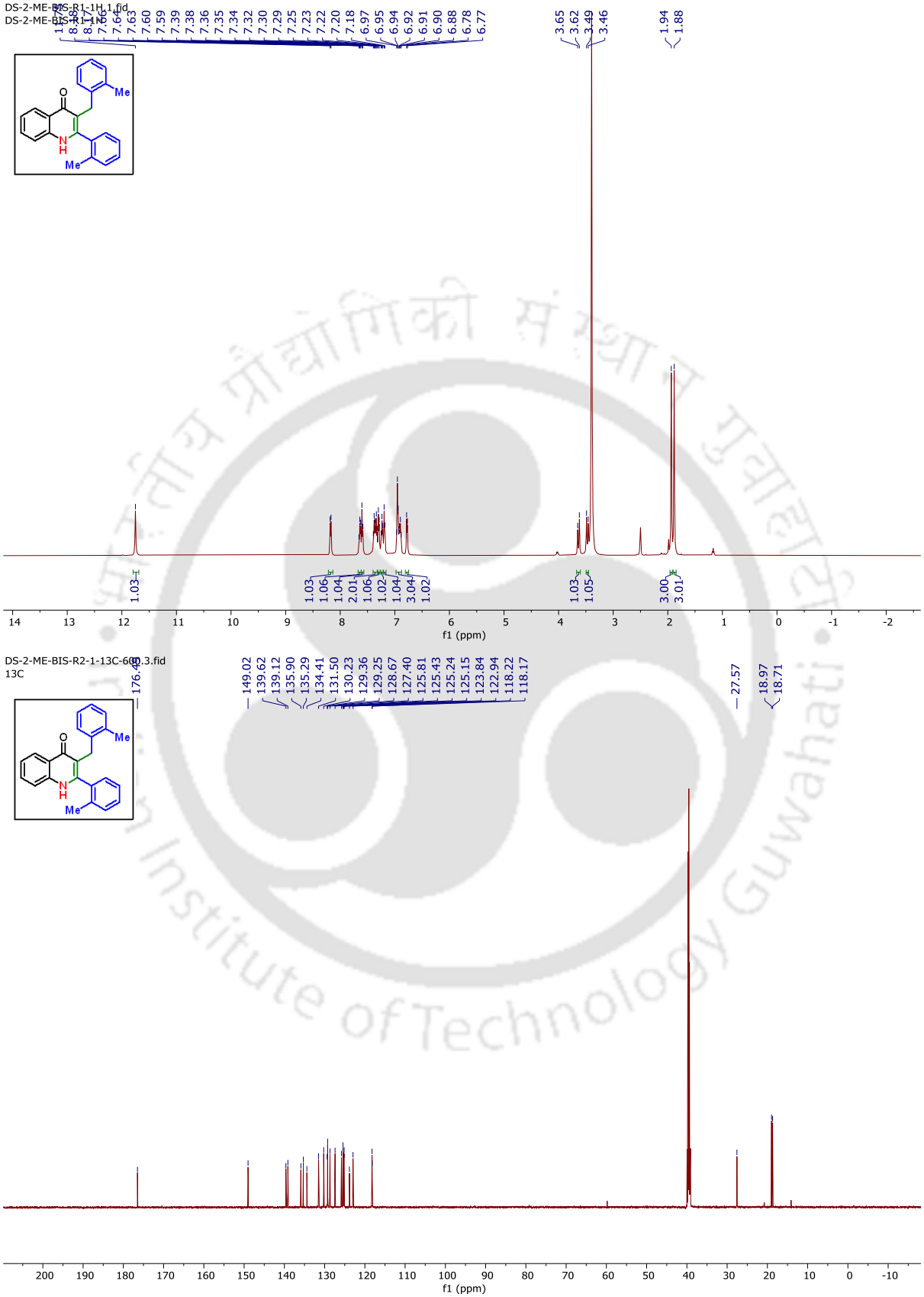


Figure 3.9. ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (150 MHz) NMR Spectrum of **3-(2-methylbenzyl)-2-(o-tolyl)quinolin-4(1H)-one (3.3h)** in DMSO-d_6.

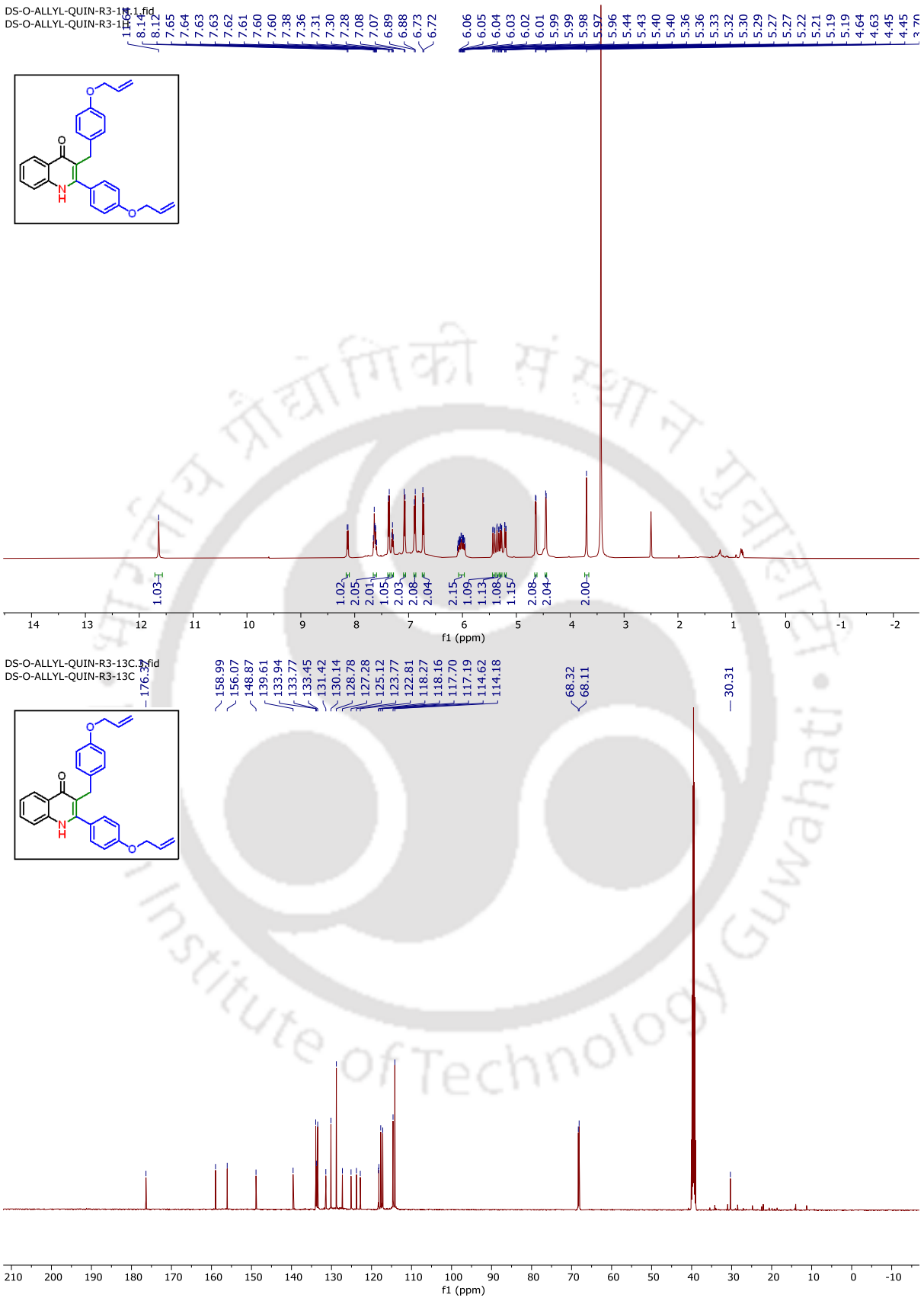


Figure 3.10. ^{1}H (500 MHz) and ^{13}C{^{1}H} (125 MHz) NMR Spectrum of **3-(4-(allyloxy)benzyl)-2-(4-(allyloxy)phenyl)quinolin-4(1H)-one (3.3z)** in DMSO-d_6.

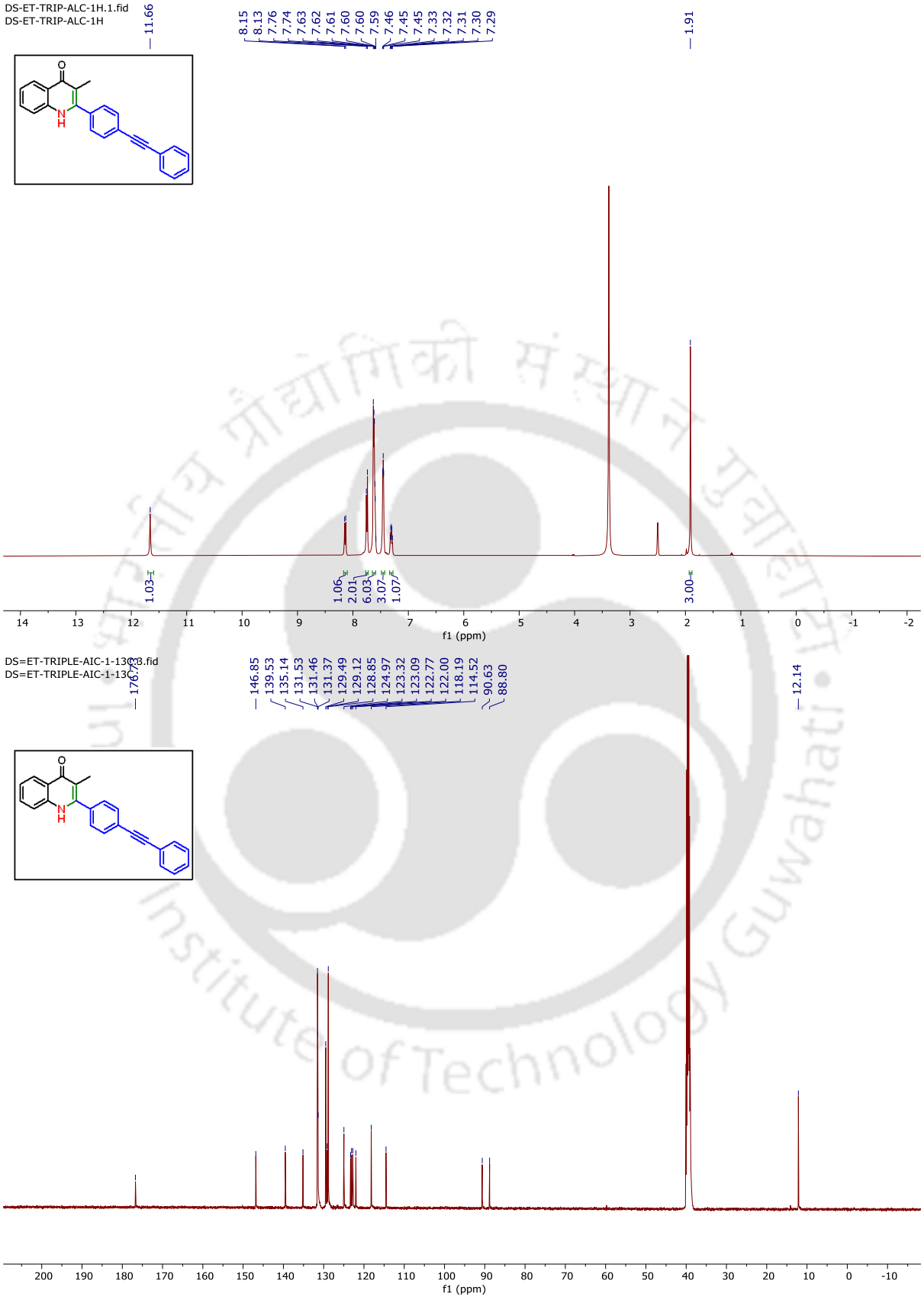


Figure 3.11. ^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of **3-methyl-2-(4-(phenylethynyl)phenyl)quinolin-4(1H)-one (3.5k)** in DMSO-d_6.

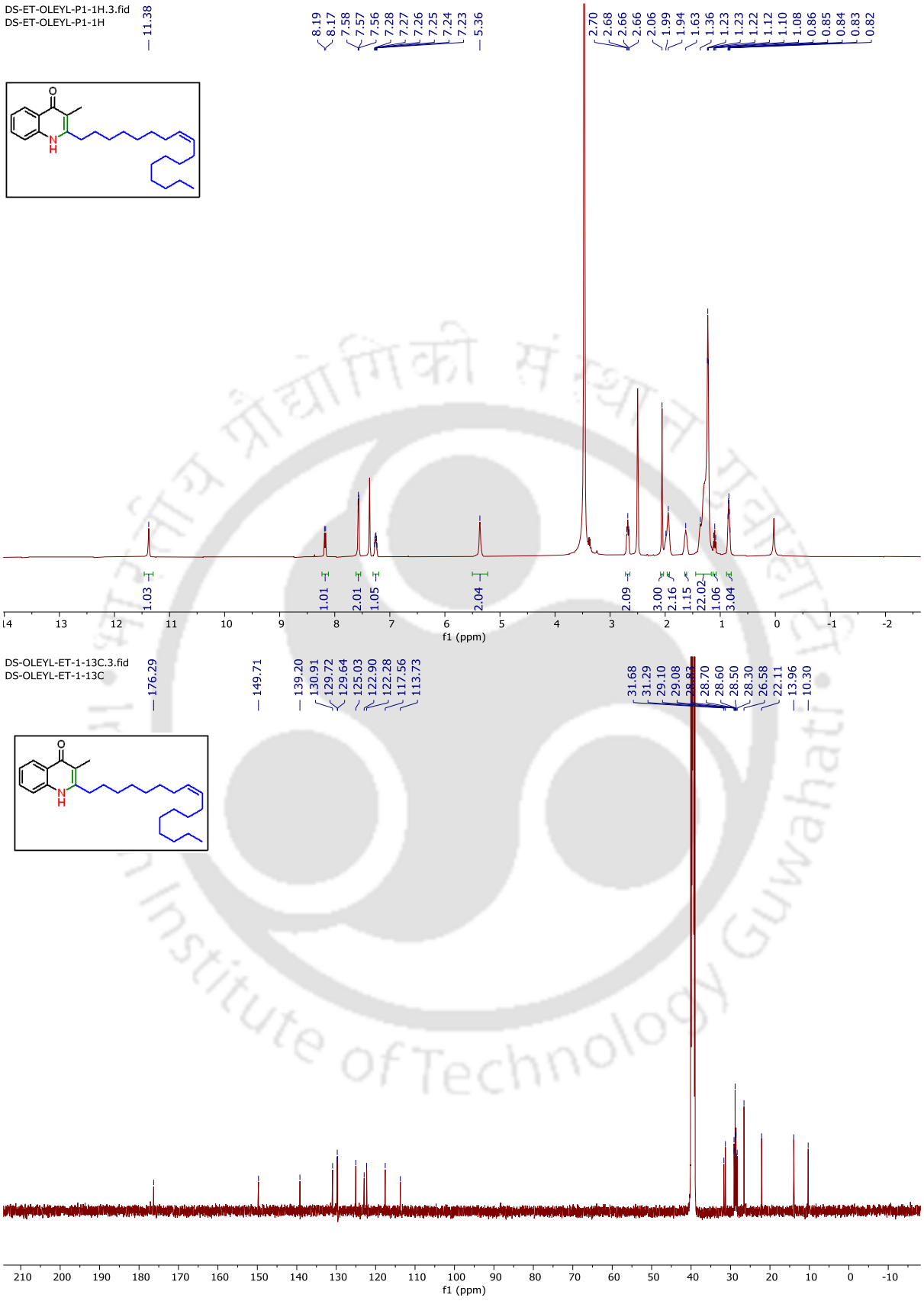


Figure 3.12. ^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of **(Z)-2-(heptadec-8-en-1-yl)-3-methylquinolin-4(1H)-one (3.5q)** in (DMSO-d_6 + C_6D_6) and DMSO-d_6 respectively.

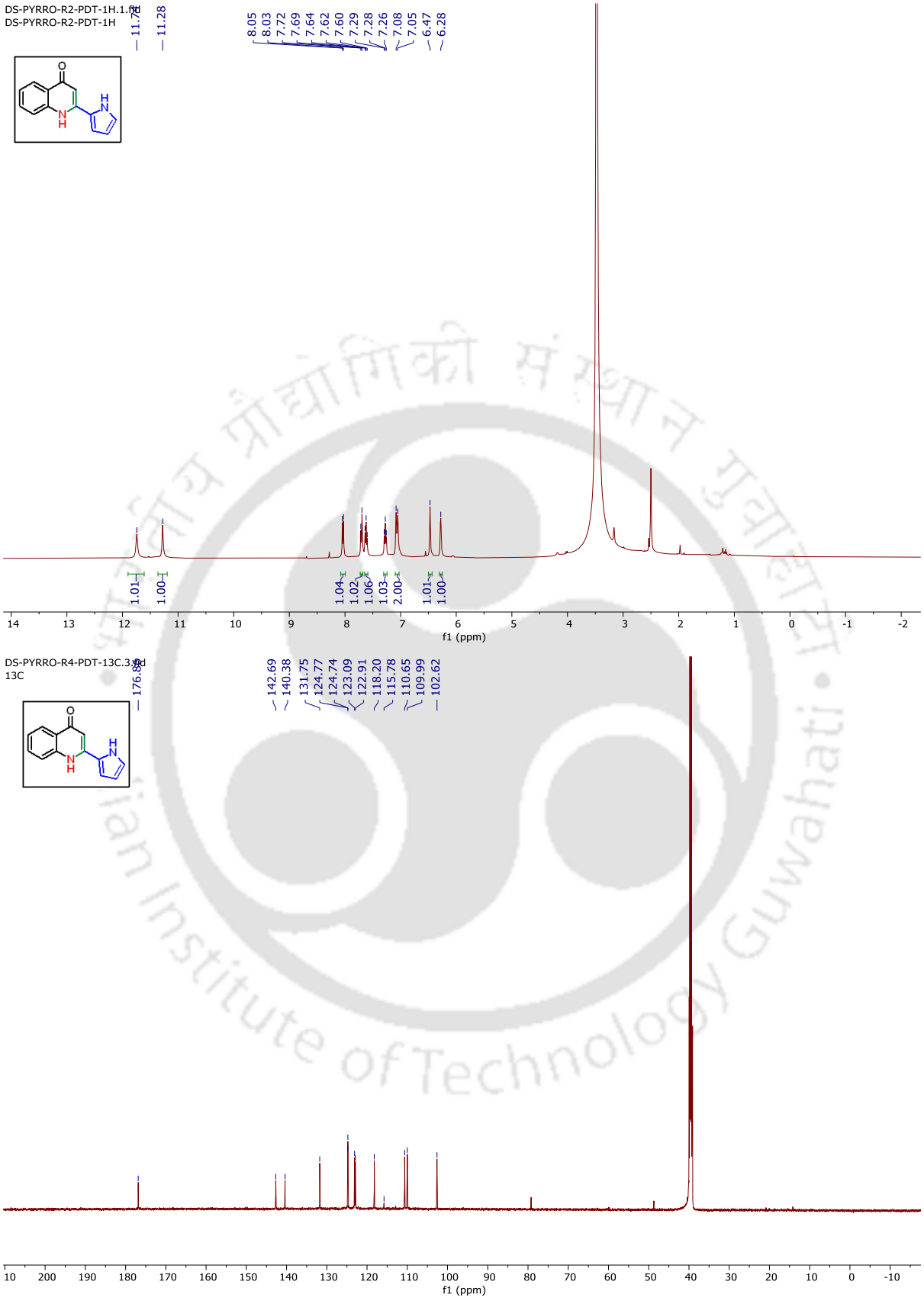


Figure 3.13. ^{1}H (400 MHz) and ^{13}C{^{1}H} (150 MHz) NMR Spectrum of **2-(1H-pyrrol-2-yl)quinolin-4(1H)-one (3.6o)** in DMSO-d_6.

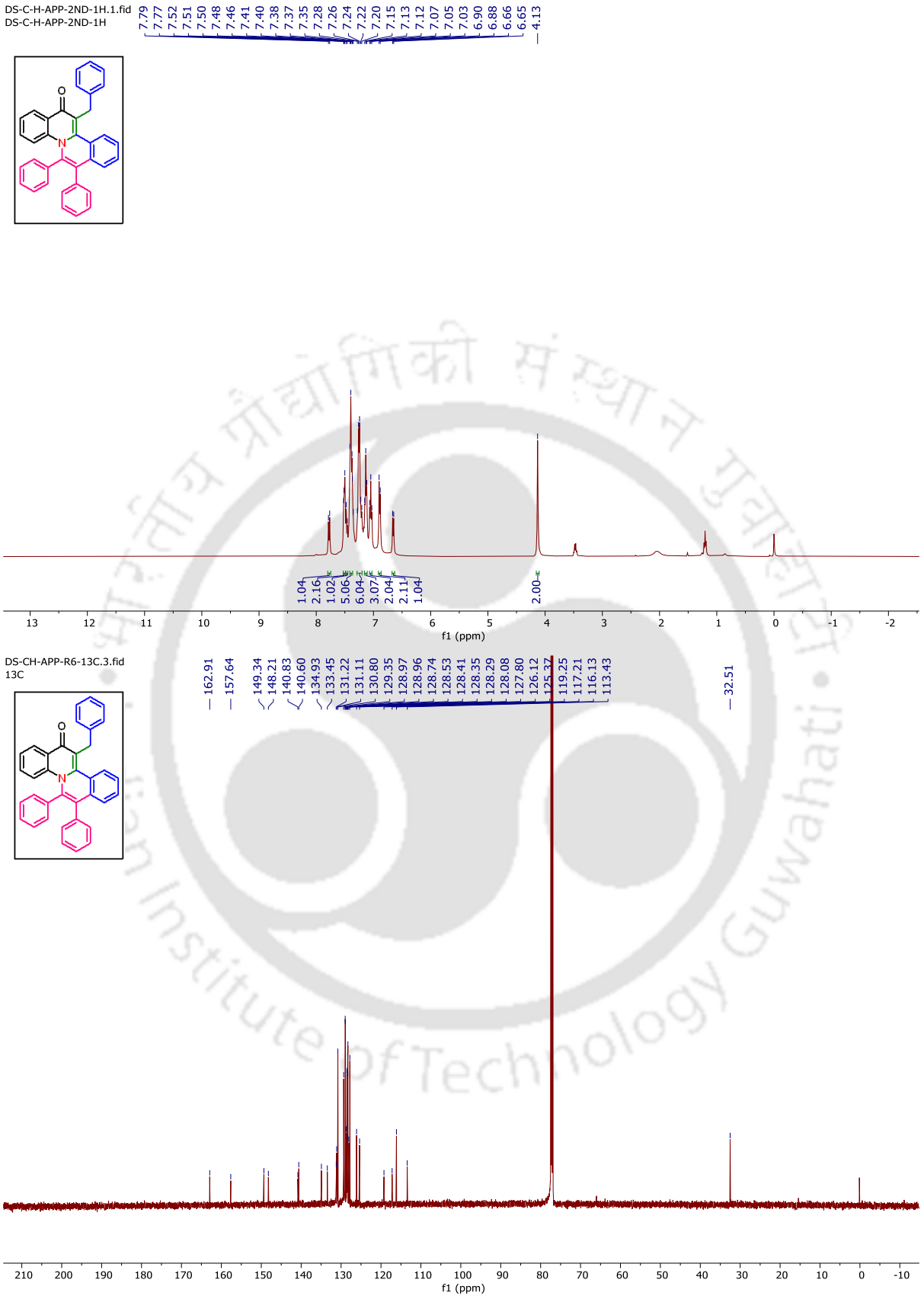


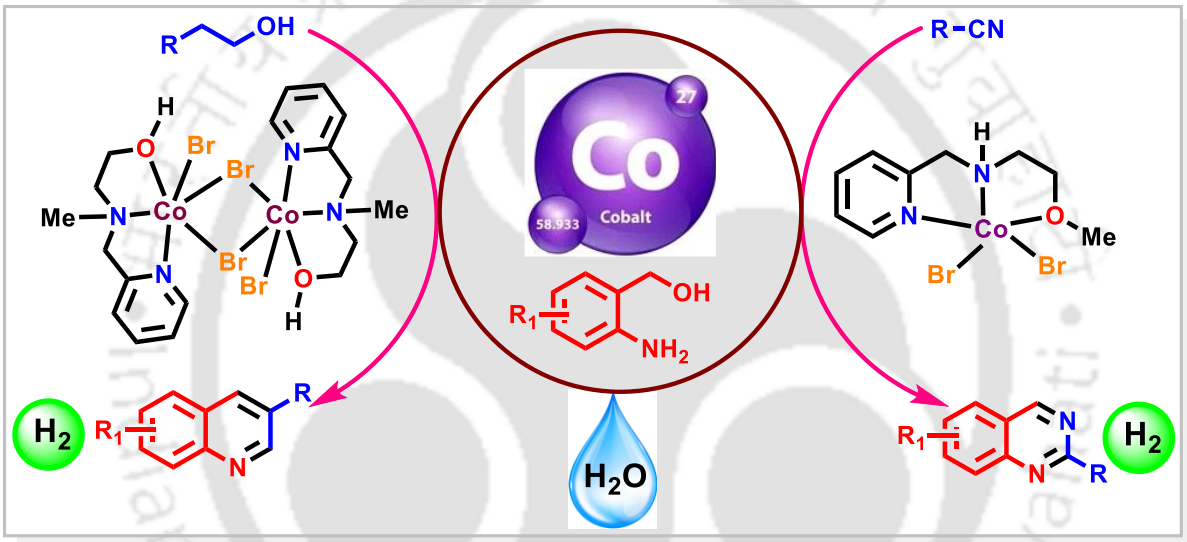
Figure 3.14. ^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ (150 MHz) NMR Spectrum of **12-benzyl-6,7-diphenyl-13H-isoquinolino[2,1-a]quinolin-13-one (3.24)** in $CDCl_3$.

3.8. Important crystal parameters of Mn-24:

	Mn-24
Empirical formula	$C_{15}H_{14}BrMnN_2O_4$
Formula weight	421.1290
Temperature, T	296 K
Crystal system	'monoclinic'
Space group	P 2_1/n
Unit cell dimensions	a= 11.6809(12), b= 15.4785(16), c= 11.8805(12) α= 90, β= 107.629(3), γ= 90
Volume, V (Å^3)	2047.2(4)
Z	4
Index ranges	$-14 \leq h \leq 14$, $-19 \leq k \leq 19$, $-14 \leq l \leq 14$
Final R indices [I>2sigma(I)]	R_1= 0.0393, wR_2= 0.1007
R indices (all data)	R_1= 0.0522, wR_2= 0.1102

Chapter 4

Designing Cobalt(II) Complexes for Tandem Dehydrogenative Synthesis of Quinoline and Quinazoline Derivatives



D. Pal, A. Mondal, R. Sarmah, D. Srimani, *Org. Lett.* **2024**, *26*, 514–518

4.1. Introduction:

Saturated and unsaturated N-heterocyclic compounds are highly appealing and emergent structural scaffolds as they frequently appear as key structural units in several life-saving drugs which aim to treat a variety of medical issues.[1] Such privileged scaffolds are ubiquitous in various natural products, agrochemicals, pharmaceuticals as well as bulk and fine chemicals.[2] Owing to its growing impetus and profound applications, the development of concise, efficient and greener protocols to synthesize these N-heterocyclic scaffolds directly from renewable and widely available starting materials is very enticing.[3] In this perspective, acceptorless dehydrogenation (AD) and borrowing hydrogen catalysis have become an elegant toolbox for the benign construction of these intricate molecular scaffolds; where only H_2 and/or H_2O are liberated as nontoxic byproducts.[4]

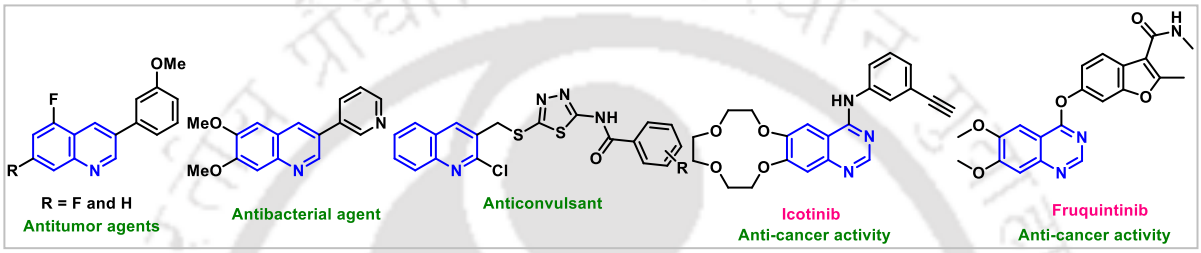


Figure 4.1. Biologically important molecules bearing 3-substituted quinoline and quinazoline scaffold.

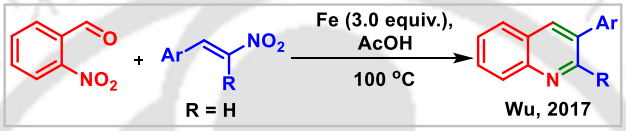
The precious noble metal-based catalytic system has advanced significantly in recent decades.[5] However, environmental and economic pressure has confined the continual use of noble metals in homogeneous catalysis. Thus, recent years have witnessed an exigency for developing new and efficient base metal catalysts for useful organic transformations.[6] In this regard cobalt complex catalyzed reactions have gained unwavering attention because of their lower toxicity and diverse electronic structural behaviour, substitutional lability and ability to adopt different coordination geometry, which offers unique selectivity and reactivity patterns.[7] However, the construction of diversely functionalized heterocyclic scaffolds via dehydrogenative coupling of alcohols with an assortment of nucleophiles catalyzed by cobalt complex is still in the budding phase.[8] The synthesis of various N-heterocyclic scaffolds was made possible by the use of 2-aminobenzaldehydes as key precursors.[9] However, 2-aminobenzaldehydes and their analogues are quite unstable at room temperature and they are polymerized by self-condensation.[10] This creates a storage problem and also promotes side reactions during heterocycle synthesis. Thus, the use of 2-aminobenzyl alcohols as stable and inexpensive feedstocks for heterocycle synthesis has garnered considerable interest. The method's effectiveness hinges on the slow dehydrogenation-based in situ formation of 2-aminobenzaldehydes which further undergoes quick condensation with various coupling partners to produce diverse N-heterocycles. Consequently, there is an exponential growth in the dehydrogenative synthesis of various heterocycles like 2-aminoquinolies,[11] poly-substituted quinolines[12] and quinazolines[13] through the dehydrogenative condensation of 2-aminobenzyl alcohols with different coupling partners. However, until recently, the dehydrogenative construction of C-3 substituted quinolines directly from 2-aminobenzyl alcohols with

primary alkyl alcohols remained unknown. The deoxygenative self-coupling of 2-aryl ethanol and the Guerbet reaction of aliphatic alcohols[14] obfuscate the selective synthesis of C-3 substituted quinolines. In the next segment, literature reports on C-3 substituted quinolines and quinazolines synthesis was discussed.

4.2. Literature survey:

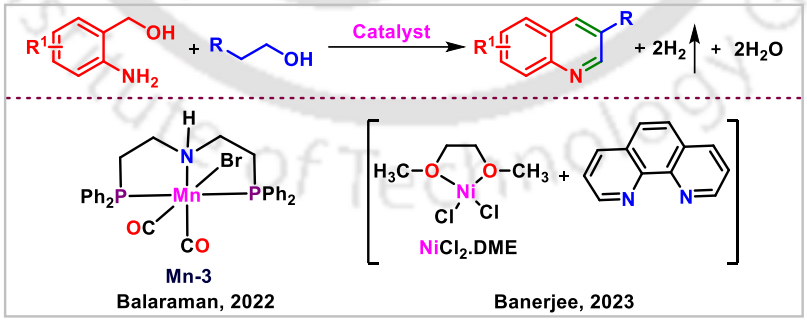
4.2.1. Synthesis of C-3 substituted quinolines:

In 2017, *Wu and co-workers* reported an iron-mediated domino reductive cyclization of *o*-nitro benzaldehydes and *β*-nitrostyrenes to synthesize 3-arylquinolines (Scheme **4.1**).[15a] To conduct the reaction they have used 3.0 equiv. of Fe in presence of AcOH which delivered good isolated yield of the targeted 3-arylquinolines. However, the generation of toxic by-products and cumbersome work-up procedures confined the applicability of this protocol in green and sustainable methodology.



Scheme 4.1. Fe-catalyzed synthesis of C-3 substituted quinoline.

Therefore, there is a need of an atom-economical, environmentally benign, and sustainable approach for the synthesis of C-3 substituted quinolines, where catalytic dehydrogenative reactions are suitable approach. In that quest, in 2022, *Balaraman and his group* utilized Mn(I)-MACHO^{Ph} catalyst (**Mn-3**) to produce C-3 substituted quinolines in good yield under solventless condition via double dehydrogenative pathway.[15b] However, in this catalytic protocol they have utilized air and moisture sensitive phosphine containing ligand and relatively costly Mn(I) metal precursor. Later Banerjee *et al.* employed their nickel system for this purpose circumventing the aforementioned problem, nevertheless, this methodology suffers from relatively high catalyst loading with an assortment of acquisition of excess amount of primary alcohols (Scheme **4.2**).[15c]

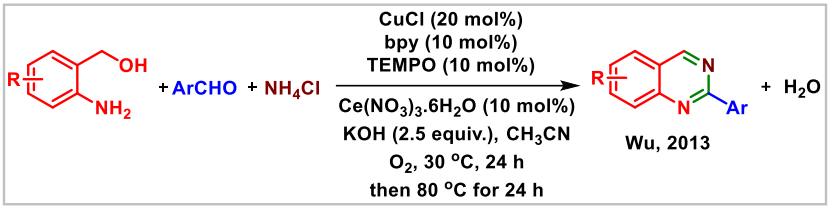


Scheme 4.2. Mn and Ni-catalyzed synthesis of C-3 substituted quinoline.

4.2.2. Synthesis of Quinazolines from 2-aminobenzylalcohol:

In 2013, *Wu's group* reported the first example of Cu-catalyzed cascade synthesis of substituted quinazolines employing 2-aminobenzylalcohol, aldehyde and ammonium chloride as substrates. In order to improvise the yield of the desired product they have used strong oxidants like cerium nitrate

hexahydrate and TEMPO together with Cu-catalyst under the environment of oxygen balloon (Scheme **4.3**) which generates toxic waste.[13]



Scheme 4.3. Cu-catalyzed synthesis of Quinazolines.

Therefore, to circumvent this problem scientific community accomplished the synthesis of quinazolines either from 2-aminobenzylalcohols or 2-aminobenzylamines via Acceptorless Dehydrogenative Coupling (ADC) pathway which has been discussed in Chapter I of Section, 1.3.1.2.1.3.

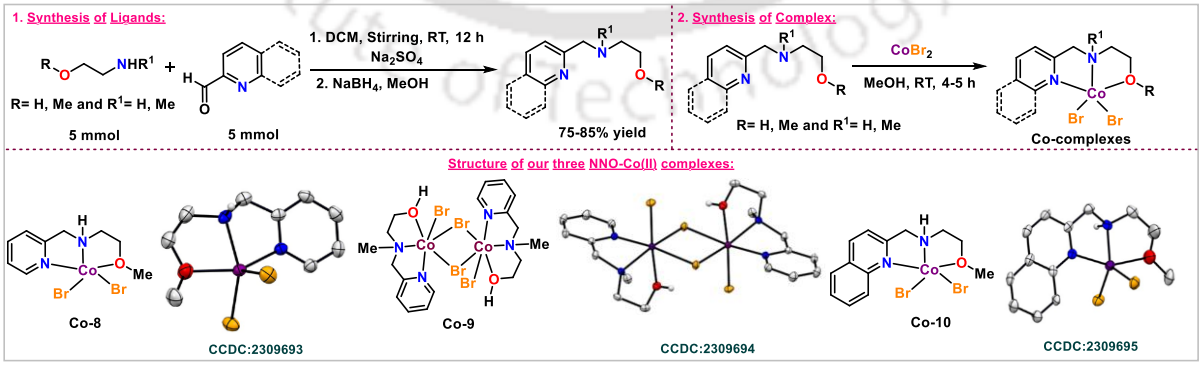
4.3. Present work:

Thus, there is a demand to devise a sustainable catalytic route to synthesize functionally diverse C-3 substituted quinolines using earth-abundant nontoxic metals like cobalt. In this chapter, NNO-ligand-derived Co(II)-complexes were synthesized, well characterized with HRMS and SC-XRD and their catalytic activity has been explored upon synthesizing a wide range of functionalized C-3 substituted quinoline. Furthermore, the developed protocol was also used to synthesize quinazolines via dehydrogenative condensation of 2-aminobenzyl alcohols with nitriles.

4.3.1. Results and discussion:

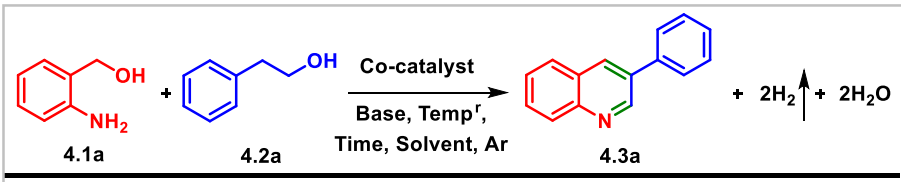
4.3.1.1. Synthesis of ligands and their Co-complexes:

At the outset, three NNO-based phosphine-free ligands and their Co(II) complexes upon reacting with their precursor $CoBr_2$ was synthesized. Afterwards, their molecular structures were confirmed with SC-XRD upon growing their single crystals in suitable combination of solvent (experimental section **4.5.2.**) which revealed that **Co-8** and **Co-10** have monomeric structures albeit **Co-9** bearing N-methylated ligand delivered the μ2-bromobridged dinuclear structure in which the ligand coordinated in a facial manner (preparation procedure is mentioned in experimental section) (Scheme **4.4**).

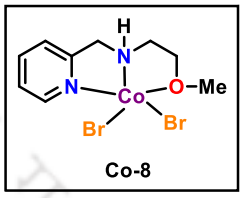


Scheme 4.4. Synthesis of NNO-Co(II)-based complexes and their structures.

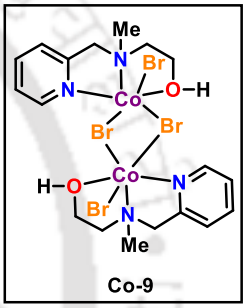
Table 4.3.1.2: Reaction Optimization for the Co-catalyzed synthesis of 3-Phenylquinoline[a,b]



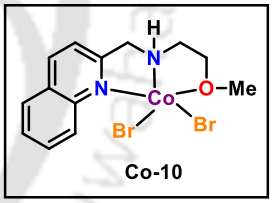
Entry	Cat. (mol%)	Solvent	Base (equiv.)	4.1a:4.2a	Temp^{r} (°C)	Time (h)	Yield^{b} (%)
1.	Co-8 (5)	Xylene	KO^{t}Bu(1.0)	1:1.5	130	36	40
2.	Co-8 (5)	Xylene	KO^{t}Bu(1.5)	1:1.5	130	36	45
3.	Co-8 (5)	-	KO^{t}Bu(1.5)	1:1.5	130	36	60
4.	Co-8 (5)	-	KOH(1.5)	1:1.5	130	36	70
5.	Co-8 (5)	-	KOH(2.0)	1:1.5	130	36	72
6.	Co-9 (2.5)	-	KOH(1.5)	1:1.5	130	36	76
7.	Co-10 (5)	-	KOH(1.5)	1:1.5	130	36	57
8.	Co-9 (2.5)	-	KOH(1.5)	1:1.5	130	48	78
9.	Co-9 (2.5)	-	KOH(1.5)	1:1.5	130	24	51
10.	Co-9 (2.5)	-	KOH(1.5)	1:1.2	130	36	58
11.	Co-9 (2.5)	-	KOH(1.5)	1:1.5	110	36	67
12.	Co-9 (2.5)	-	NaO^{t}Bu(1.5)	1:1.5	130	36	48
13.	Co-9 (2.5)	-	NaOH(1.5)	1:1.5	130	36	62
14.	Co-9 (2.5)	-	K_2CO_3(1.5)	1:1.5	130	36	40
15.	Co-9 (2.5)	Toluene	KOH(1.5)	1:1.5	130	36	30
16.	Co-9 (2.5)	^{t}AmOH	KOH(1.5)	1:1.5	130	36	ND
17.	-	-	KOH(1.5)	1:1.5	130	36	15
18.	Co-9 (2.5)	-	-	1:1.5	130	36	ND
19.	$CoBr_2$ (5)	-	KOH(1.5)	1:1.5	130	36	12



Co-8



Co-9



Co-10

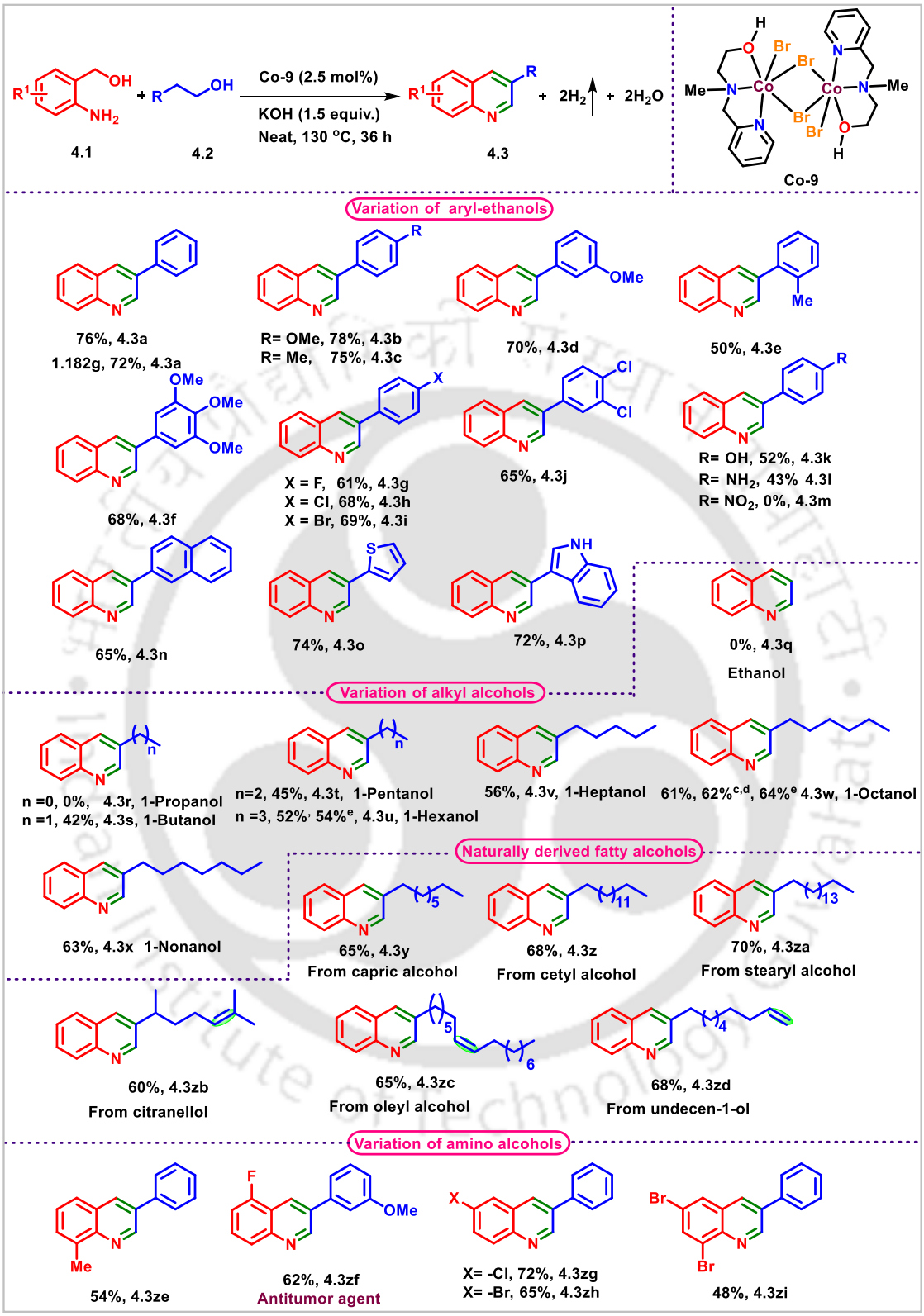
[a] **Reaction conditions: 4.1a** (0.5 mmol), **4.2a** (0.6 – 0.75 mmol), base (0.5 – 1.0 mmol), Co-cat. (2.5 – 5 mol %), solvent (0 – 2 mL), at temperature 110 °C – 130 °C of a preheated oil bath under argon. [b]Isolated yield. ND = Not detected.

Initially, the potentiality of three phosphine free NNO-Co(II) complexes towards the synthesis of 3-phenylquinoline (**4.3a**) was checked. In this acceptorless double dehydrogenative coupling (ADDC) pathway 2-aminobenzyl alcohol (**4.1a**) and 2-phenylethanol (**4.2a**) was chosen as model substrate to investigate the optimal reaction conditions. In that regard, when a xylene solution containing 1.0 equiv. of 2-aminobenzyl alcohol (**4.1a**) and 1.5 equiv. of 2-phenylethanol (**4.2a**) was refluxed at 140 °C for 36 h in presence of 5 mol% of **Co-8** and 1.0 equiv. of KO^{t}Bu only 40% yield of the desired product (**4.3a**) was isolated (Table 4.3.1.2, entry 1). However, increasing the base loading from 1.0 equiv. to 1.5 equiv.

and pursuing the reaction under solvent free condition there was a drastic increase in the yield was noticed (Table 4.3.1.2, entry 2-3). Pleasingly, changing of base from KO^{t}Bu to KOH yield again increased albeit increase of base loading does not exhibit such remarkable effect in the yield (Table 4.3.1.2, entry 4-5). Afterwards, the catalytic applicability of other two as prepared catalysts was checked in which **Co-9** exhibit better catalytic activity over **Co-8** whilst **Co-10** showed lower activity (Table 4.3.1.2, entry 6-7). Nevertheless, several reaction parameters such as reaction time, alcohol loading, nature of base, solvent have been screened, however, all of them failed to afford the optimal reaction condition (Table 4.3.1.2, entry 8-16). Therefore, acceptorless double dehydrogenative coupling of 1.0 equiv. of 2-aminobenzyl alcohol (**4.1a**) with 1.5 equiv. of 2-phenylethanol (**4.2a**) in presence of 2.5 mol% of **Co-9** catalyst and 1.5 equiv. of KOH base at 140 °C for 36 h under solventless condition furnished the optimal yield of the desired 3-Phenylquinoline (**4.3a**) product (Table 4.3.1.2, entry 6). Upon conducting the control experiments, it underpins that both catalyst and base were essential to accomplish a detectable conversion of the desired product (**4.3a**). In presence of the metal precursor $CoBr_2$, 12% of desired product **4.3a** was furnished (Table 4.3.1.2, entry 17-19).

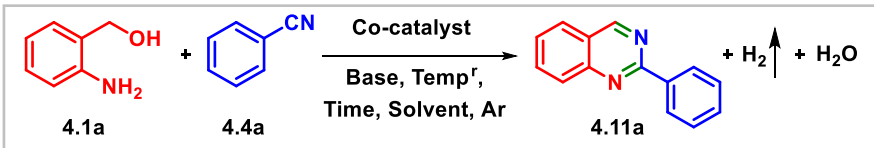
Next, the efficacy of this developed protocol was accomplished upon examining the spectrum of 2-aryl ethanols and primary alkyl alcohols with various 2-aminobenzyl alcohols under the optimized reaction conditions. Various electronically neutral and electronically biased groups present at the *o*-, *m*-, and *p*-positions of the aromatic nucleus of 2- phenylethyl alcohols are well tolerated, resulting in moderate to good yields of the desired 3-aryl quinoline (**4.3a-4.3f**). Of note, halide substituted aryl ethanols survived well achieving good yields without dehalogenation (**4.3g-4.3j**). 2-Phenylethanol containing hydroxyl, and amino functional group was effective furnishing moderate isolated yield, however, presence of strong electron withdrawing group -NO_2 was found to be catalytically incompatible in the current catalytic protocol (**4.3k-4.3m**). 2-heteroaryl ethyl alcohols such as 2-thiophene ethanol, 3-indolyl ethanol are well compatible under those Co-catalyzed conditions (**4.3o-4.3p**). Next, the intension was moved towards the activation of a series of more challenging aliphatic primary alcohols to construct short to long chain 3-alkyl substituted quinoline derivatives, which were difficult to synthesize under conventional pathway. Interestingly, the current catalytic protocol activates these aliphatic alcohols except ethanol and 1-propanol and delivers **4.3s-4.3x** in good to moderate yields. Notably, natural monoterpenoids, citronellol and fatty alcohols such as capric, cetyl, stearyl alcohols reacted well to form the targeted heterocycles in good yields (60-70%) (**4.3y-4.3zb**). Naturally occurring unsaturated oleyl alcohol and undecen-1-ol chemoselectively reacted and furnished the 3-substituted quinolines under double dehydrogenative reaction conditions (**4.3zc-4.3zd**). Afterwards, the scope of 2-aminobenzyl alcohol was scrutinized. (2-amino-3-methyl phenyl) methanol (**4.1b**) reacted with 2-phenylethanol (**4.2a**) to furnish the expected product **4.3ze** in moderate yield. 2-aminobenzyl alcohols with halide (-F, -Cl, -Br) group successfully furnished the corresponding 3-substituted quinolines in 48-72% yields harnessing in late-stage functionalization (**4.3zf-4.3zi**). Of note, synthesized **4.3zf** exhibits antitumor activity.

4.3.1.3. Co-catalyzed synthesis of 3-Substituted Quinoline: substrate scope[a,b]

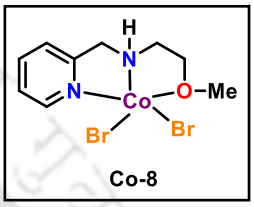


[a] **Reaction conditions: 4.1** (0.5 mmol), **4.2** (0.75 mmol), KOH (0.75 mmol), **Co-9** (2.5 mol % i.e. 5 mol% w.r.t. monomeric form of **Co-9**), Neat condition, 36 h, 130 °C, under argon. [b]Isolated yield. [c]Alcohol 3.0 equiv. [d]**Co-9** (5.0 mol %) [e]72 h.

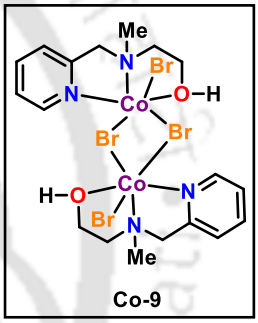
Table 4.3.1.4: Reaction optimization for the Co-catalyzed synthesis of 2-phenylquinazoline[a]



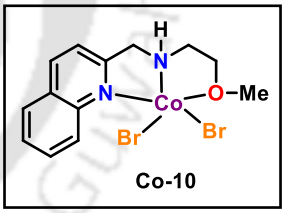
Entry	Cat. (mol%)	Solvent	Base (equiv.)	4.1a:4.4a	Temp^r (°C)	Time (h)	Yield[b] (%)
1.	Co-8 (5)	Toluene	NaO^{t}Bu(1.0)	1:1	130	36	45
2.	Co-8 (5)	Toluene	NaO^{t}Bu(1.0)	1:1.5	130	36	68
3.	Co-8 (5)	Xylene	NaO^{t}Bu(1.0)	1:1.5	130	36	82
4.	Co-8 (5)	^{t}AmOH	NaO^{t}Bu(1.0)	1:1.5	130	36	ND
5.	Co-8 (4)	Xylene	NaO^{t}Bu(1.0)	1:1.5	130	36	72
6.	Co-8 (5)	Xylene	NaO^{t}Bu(1.0)	1:1.5	130	24	68
7.	Co-8 (5)	Xylene	NaO^{t}Bu(1.0)	1:1.5	110	36	70
8.	Co-8 (5)	Xylene	NaO^{t}Bu(0.75)	1:1.5	130	36	70
9.	Co-8 (5)	Xylene	KO^{t}Bu(1.0)	1:1.5	130	36	65
10.	Co-8 (5)	Xylene	NaOH(1.0)	1:1.5	130	36	60
11.	Co-8 (5)	Xylene	KOH(1.0)	1:1.5	130	36	50
12.	Co-8 (5)	Xylene	CsOH(1.0)	1:1.5	130	36	45
13.	Co-8 (5)	Xylene	Na_2CO_3(1.0)	1:1.5	130	36	35
14.	Co-8 (5)	Xylene	K_2CO_3(1.0)	1:1.5	130	36	26
15.	Co-9 (2.5)	Xylene	NaO^{t}Bu(1.0)	1:1.5	130	36	64
16.	Co-10 (5)	Xylene	NaO^{t}Bu(1.0)	1:1.5	130	36	62
17.	-	Xylene	NaO^{t}Bu(1.0)	1:1.5	130	36	17
18.	Co-8 (5)	Xylene	-	1:1.5	130	36	ND
19.	$CoBr_2$ (5)	Xylene	NaO^{t}Bu(0.5)	1:1.5	130	36	14



Co-8



Co-9



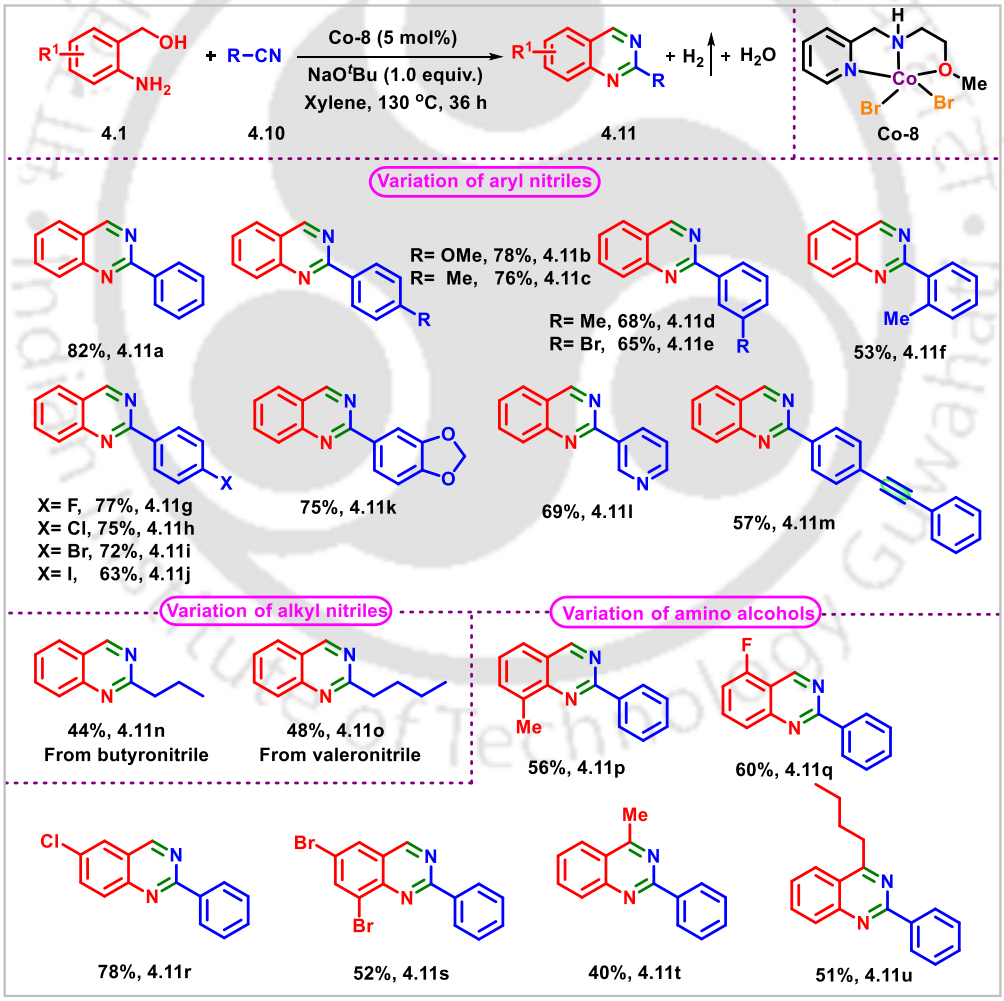
Co-10

[a] **Reaction conditions: 4.1a** (0.5 mmol), **4.4a** (0.5 – 0.75 mmol), base (0.375 – 0.5 mmol), Co-cat. (2.5 – 5 mol %), solvent (2 mL), at temperature 110 °C – 130 °C of a preheated oil bath under argon. [b]Isolated yield. ND = Not detected.

Then the potentiality of the developed catalyst was investigated towards the dehydrogenative coupling of 2-aminobenzyl alcohols with other coupling partners such as nitriles to furnish quinazolines. In that regard, when a toluene solution containing an equimolar mixture of 2-aminobenzylalcohol (**4.1a**) and benzonitrile (**4.4a**) has been refluxed at 130 °C in the presence of 5 mol% of **Co-8** and 1 equiv. of NaO^{t}Bu for 36 h only 45% yield of the desired product (**4.11a**) was isolated (Table 4.3.1.4, entry 1). The yield was improved to 68% upon increasing the loading of benzonitrile (**4.4a**) (Table 4.3.1.4, entry

2) however, furthermore switching of the solvent from toluene to high boiling xylene it manifested the optimal yield of the desired 2-phenylquinazoline (**4.11a**) product (Table 4.3.1.4, entry 3). Here, the loadings of the catalyst and alcohol are relatively lower as compared to the previously reported Co-catalyzed synthesis of quinazolines.[13b] Afterwards, several other reaction parameters such as nature of solvent and base, base loading, catalyst loading, reaction time were screened nevertheless, all of them failed to deliver better yield of the intended product **4.11a** (Table 4.3.1.4, entry 4-14). Herein also, the catalytic applicability of other two as prepared complexes *i.e.* **Co-9** and **Co-10** were checked albeit, both of them furnished detriment result under the optimal reaction condition (Table 4.3.1.4, entry 15-16). The control experiments were conducted which underpin that both catalyst and base were essential to accomplish a detectable conversion of the desired product (**4.11a**) (Table 4.3.1.4, entry 17-18). In presence of the metal precursor, $CoBr_2$ trace amount of desired product (**4.11a**) was delivered (Table 4.3.1.4, entry 19).

4.3.1.5. Co-catalyzed synthesis of quinazoline: substrate scope[a,b]

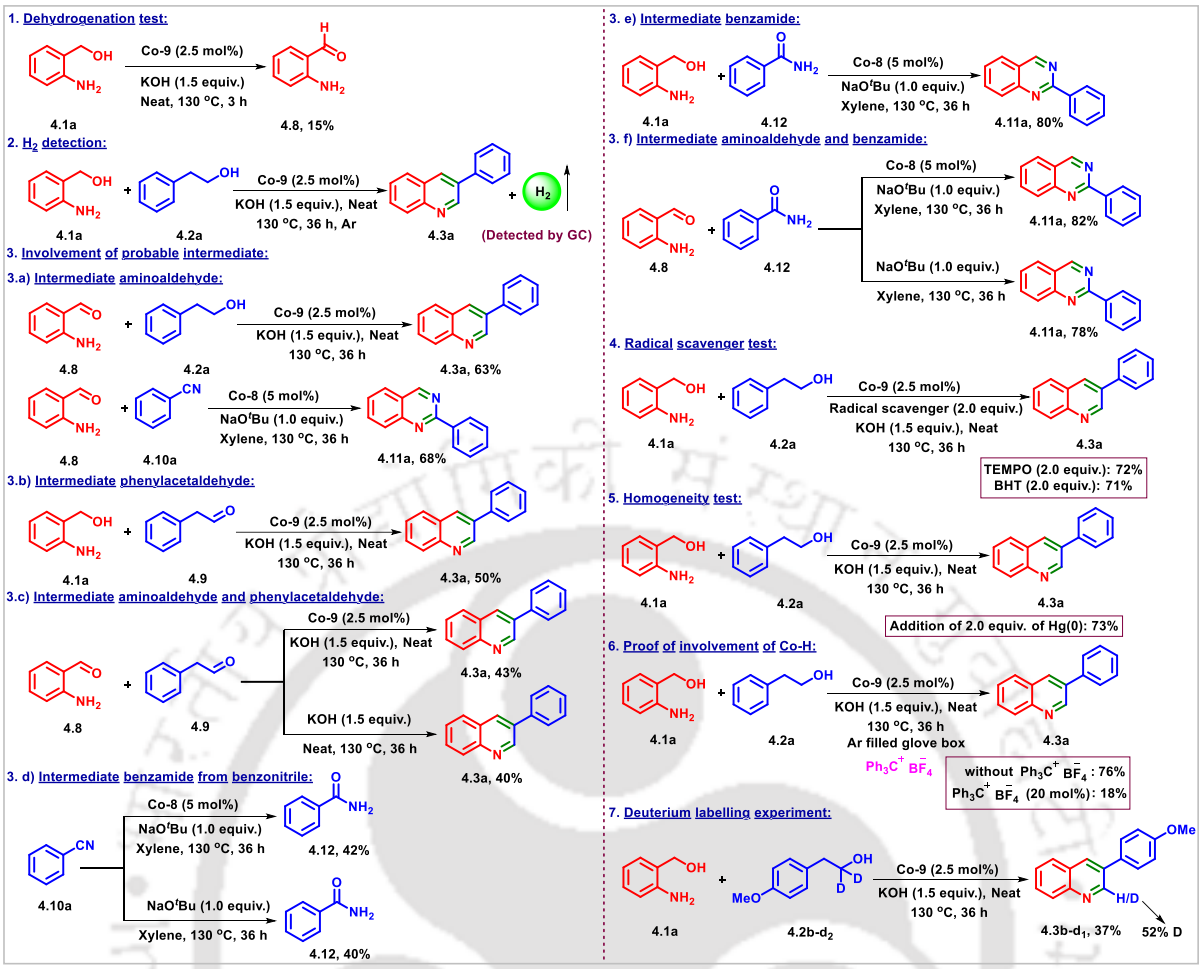


[a] **Reaction conditions: 4.1** (0.5 mmol), **4.10** (0.75 mmol), NaO^{t}Bu (0.5 mmol), **Co-8** (5 mol %), under argon in xylene (2 mL) at 130 °C (oil bath temperature), for 36 h. [b] Isolated yield.

After accomplishing the optimal reaction condition, the applicability and limitation of the current protocol towards the synthesis of diverse range of quinazolines was investigated from 2-aminobenzylalcohols with an array of benzonitriles. At the outset, electronically neutral as well as electronically biased groups bearing at the *o*-, *m*- and *p*-position of aromatic nucleus of benzonitrile were tested which found to be well tolerated under the streamline reaction condition furnishing moderate to good isolated yield of the desired products (**4.11a-4.11f**). Furthermore, halo substituted aromatic nitriles were well compatible under the standard catalytic protocol manifesting good yield without achieving dehalogenated product (**4.11g-4.11j**). Encouragingly, heterocyclic nitriles such as piperonyl and 2-pyridine nitriles were well susceptible to afford the respective quinazoline products (**4.11k-4.11l**) in nearly 70% isolated yield. Indeed, the reducible functional groups such as –C≡C–Ph present at the *p*-position of benzonitrile can survive under the current conditions to give the desired product in moderate yield (**4.11m**). The reaction is somewhat sluggish for butyronitrile (**4.10n**) and valeronitrile (**4.10o**), which furnish moderate yield of the products (**4.11n-4.11o**). Afterwards, the scope of 2-aminobenzylalcohol was explored where, it has been found that halo substituted alcohols were survived furnishing good yields (**4.11q-4.11s**) giving room for further derivatizations. Secondary amino alcohols were also catalytically compatible furnishing moderate isolated yield (**4.11t-4.11u**).

4.3.1.6. Mechanistic investigation:

In order to gain mechanistic insight towards the synthesis of C-3 substituted quinolines and quinazolines several control experiments were carried out (Scheme **4.5**). Initially, the conversion of 2-aminobenzyl alcohol (**4.1a**) to its corresponding aldehyde **4.8** was observed in presence of **Co-9** (Scheme **4.5**, 1). Further, the dehydrogenative pathway was confirmed by the detection of evolved H_2 gas during the synthesis of 3-phenylquinoline (**4.3a**) under the optimal reaction conditions (Scheme **4.5**, 2). Afterwards, the involvement of the intermediates (**4.8, 4.9** and **4.12**) towards the construction of both 3-phenylquinoline (**4.3a**) and 2-phenylquinazoline (**4.11a**) product was checked which was confirmed by reacting **4.8** with **4.2a**, **4.8** with **4.10a** (Scheme **4.5**, 3a), **4.1a** with **4.9** (Scheme **4.5**, 3b) and **4.1a** with **4.12** (Scheme **4.5**, 3e) under their respective standard conditions. However, the lower yield of **4.3a** and **4.11a** have been resulted from the initial high concentration of **4.8** as it promotes the self-condensation[10] and the high concentration of **4.9** furnished yield several side reactions[16] before converting to **4.3a**. This also underpins the usefulness of dehydrogenative approach for such a process to get maximum efficacy. Then an intermolecular coupling of **4.8** with **4.9** was conducted under streamlined reaction conditions and even in absence of **Co-9** complex, whereas a similar yield of **4.3a** was isolated (Scheme **4.5**, 3c) which underpin that catalyst has no role in the condensation and intermolecular cyclization step. Afterwards, in order to check the possibility of *in situ* formation of intermediate benzamide (**4.12**) from benzonitrile via NaO^{t}Bu mediated transformation towards the



Scheme 4.5. Control experiments.

synthesis of 2-phenylquinazoline (**4.11a**) when only benzonitrile **4.10a** was treated under the optimal reaction condition it afforded only 42% of **4.12**, however, in absence of catalyst, it accomplished a similar yield of **4.12** (Scheme **4.5**, 3d). The involvement of intermediate **4.12** was proved upon conducting the reaction of **4.1a** with intermediate **4.12** under the standard reaction (Scheme **4.5**, 3e). The intermolecular coupling of **4.8** with **4.12** under streamlined reaction conditions and even in absence of **Co-8** complex furnishes similar yield of **4.11a** (Scheme **4.5**, 3f). The aforementioned three control experiments (Scheme **4.5,** 3d-3f) underpin that other than the dehydrogenation of 2-aminobenzyl alcohol (**4.1a**) to its corresponding aldehyde **4.8** the catalyst has no role during the construction of 2-phenylquinazoline (**4.11a**) product, only base plays the crucial role. The involvement of single electron in the catalytic cycle has been invalidated upon accomplishing the radical trapping experiment (Scheme **4.5**, 4). The reaction's homogenous nature was probed by adding mercury drops, where no detrimental effect has been manifested (Scheme **4.5**, 5). In presence of 20 mol% of trityl cation (with respect to catalyst) there was a significant decrement in the yield has been noticed which underpins the involvement of Co-H species in the reaction pathway (Scheme **4.5**, 6). In addition, the deuterium labelling experiment confirms the dehydrogenative pathway and underpins dehydrogenation of alcohols might be the rate-determining step (Scheme **4.5**, 7).

4.3.1.7. Kinetic experiments:

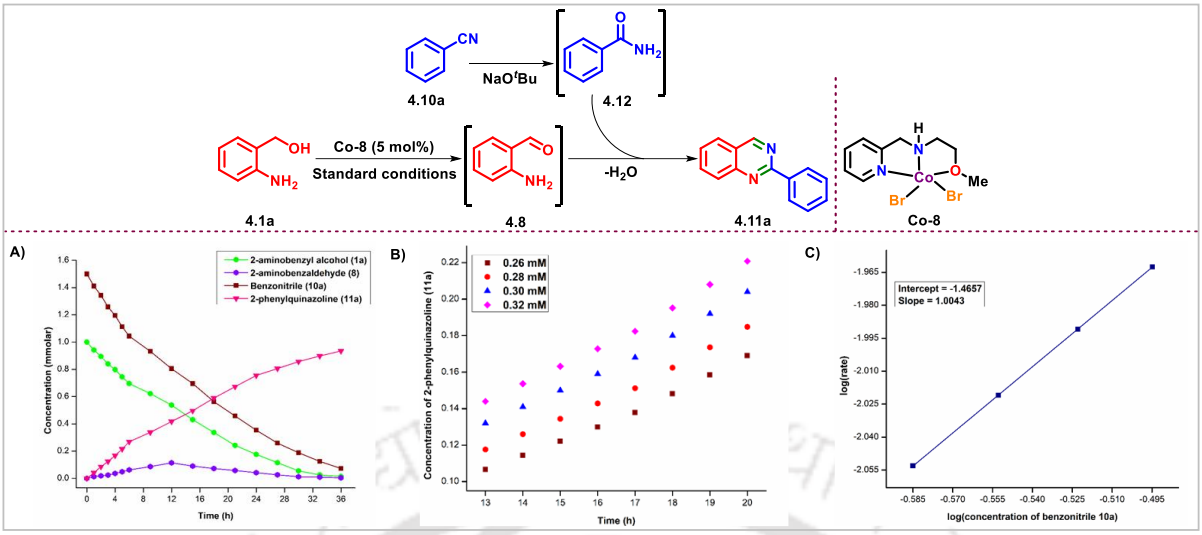


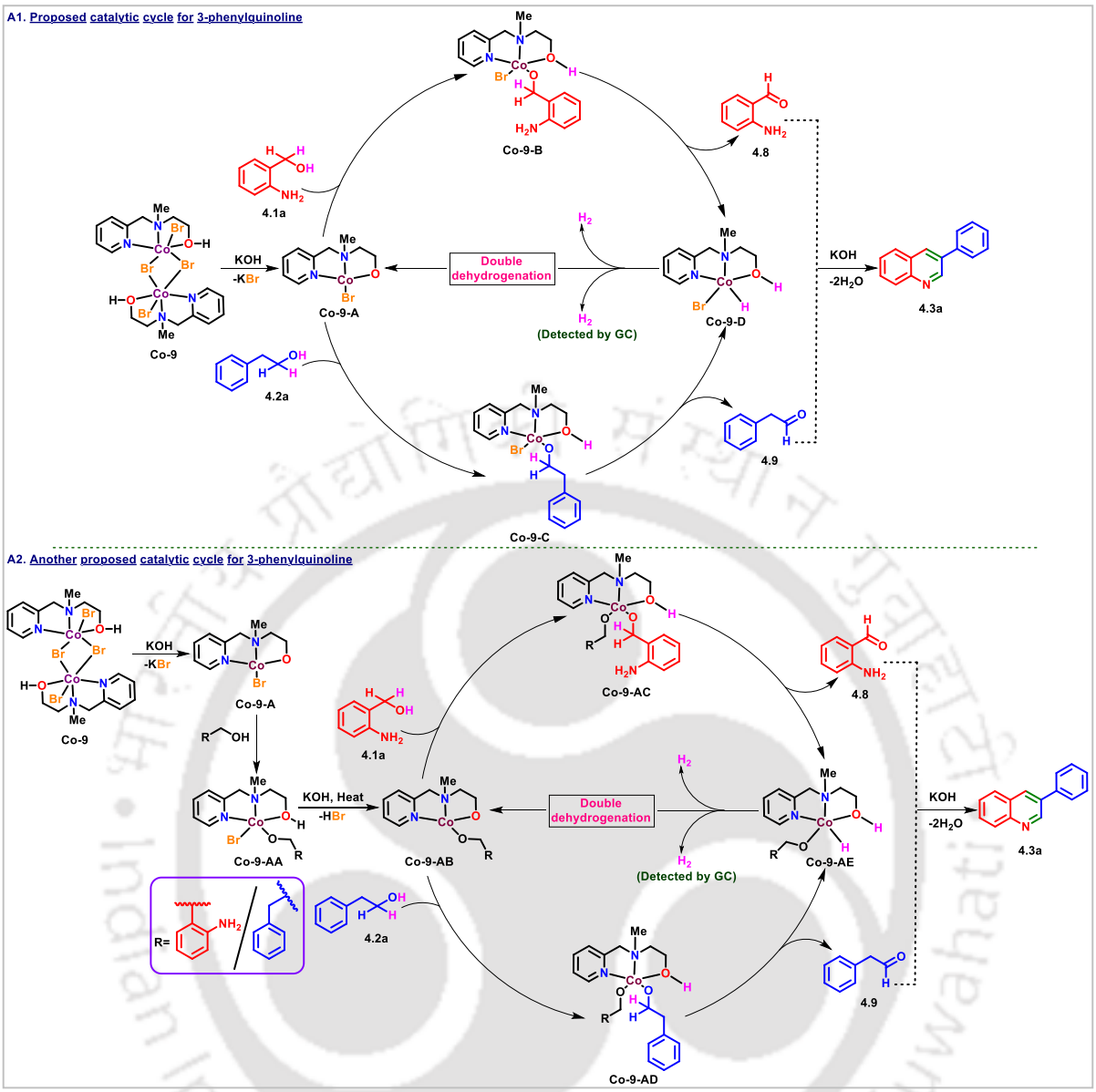
Figure 4.2. A) Kinetic monitoring of Co(II)-catalyzed acceptorless dehydrogenative coupling (ADC) of 2-aminobenzyl alcohol **4.1a** with benzonitrile **4.10a** towards the synthesis of 2-phenylquinazoline **4.11a**; B) Concentration of **4.11a** vs time plot with various concentration of benzonitrile **4.10a**; C) log (rate) vs log (conc. **4.10a**).

To understand the reactivity pattern for the synthesis of 2-phenylquinazoline (**4.11a**) via ADC a kinetic profile diagram was drawn (Figure **4.2**) which showed that the formation of the product (**4.11a**) steadily increases and the concentration of the formed 2-aminobenzaldehyde (**4.8**) was lower throughout the reaction which indicated dehydrogenation of alcohol was slower as compare to the condensation step (Figure **4.2** A). The time course profile of the reaction at various concentrations of benzonitrile (**4.10a**) points that the reaction was first order with respect to benzonitrile (**4.10a**) (Figure **4.2** B and **4.2** C).

4.3.1.8. Proposed catalytic cycle:

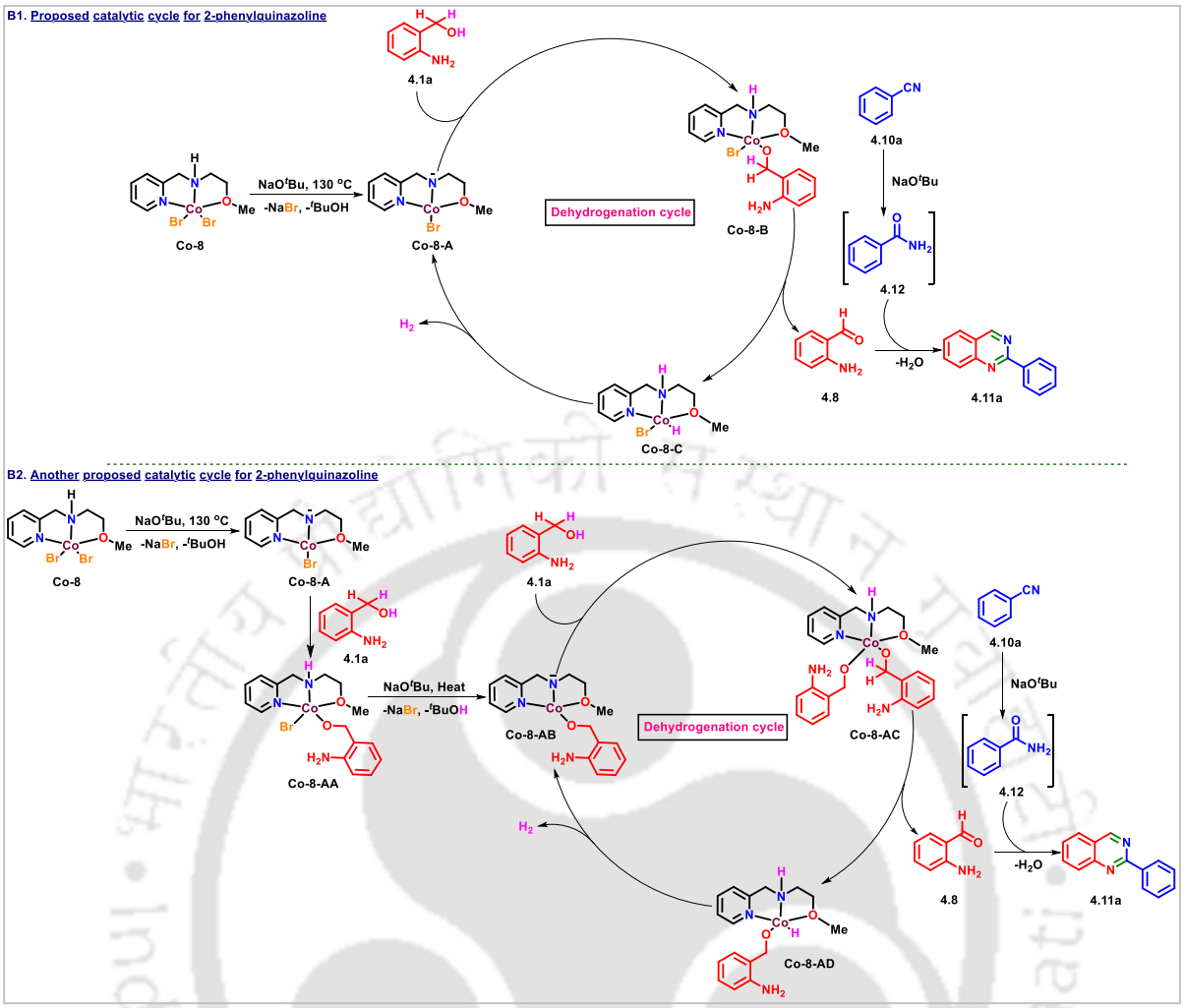
Accounting for all controlled experiments and preceding literature reports,[15,13] hereby, a plausible mechanistic cycle for the synthesis of both 3-phenylquinoline (**4.3a**) and 2-phenylquinazoline (**4.11a**) have been proposed (Scheme **4.8** and **4.9**). For the synthesis of 3-phenylquinoline (**4.3a**) initially, the active Co-catalyst (**Co-9-A**) was generated from the precatalyst **Co-9** in presence of KOH which dehydrogenates both alcohol (**4.1a** and **4.2a**) to their corresponding aldehydes (**4.8** and **4.9**) via metal-ligand cooperation (MLC) at the alkoxy site to form Co-H species (**Co-9-D**). The *in situ* formed aldehydes (**4.8** and **4.9**) undergoes base mediated condensation and subsequent intermolecular cyclization to form 3-substituted quinoline (**4.3a**) upon eliminating two water molecules. By liberation of H_2 gas via MLC the active Co-catalyst (**Co-9-A**) was regenerated from the intermediate Co(II)-hydrido complex (**Co-9-D**) species (Scheme **4.8 A1**). Nonetheless, the involvement of Co(I)-H also cannot be ignored. Again, the Co(II)-alkoxy species also may behave as an active catalyst in the synthesis of intended product 3-phenylquinoline (**4.3a**) (Scheme **4.8 A2**).

In case of synthesis of 2-phenylquinazoline (**4.11a**) initially, the precatalyst **Co-8** was transformed into its active Co-catalyst (**Co-8-A**) in presence of NaO^{t}Bu which dehydrogenates 2-aminobenzyl alcohol



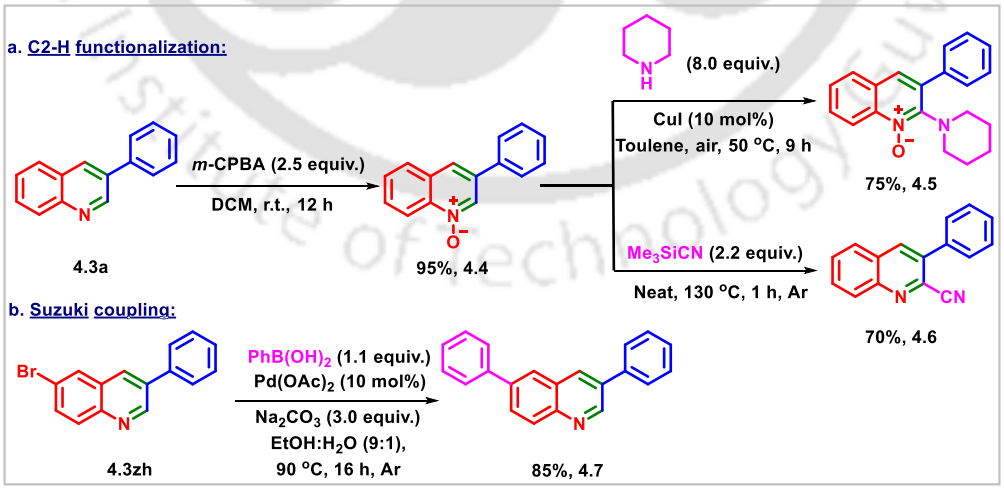
Scheme 4.8. Plausible catalytic cycle of 3-phenylquinoline (**4.3a**).

(**4.1a**) to its corresponding aldehyde **4.8** via metal-ligand cooperation (MLC) forming Co-H species (**Co-8-C**). Then, the *in situ* formed aldehydes **4.8** undergoes base mediated condensation with another *in situ* formed intermediate benzamide (**4.12**) via NaO^{t}Bu mediated transformation of benzonitrile furnishing the desired 2-phenylquinazoline (**4.11a**) by eliminating a single water molecule and the active species Co-catalyst (**Co-8-A**) was regenerated upon liberation of H_2 gas via MLC from Co-H species (**Co-8- C**) (Scheme **4.8 B1**). Again, herein also, the Co(II)-alkoxy species also may behave as an active catalyst in the synthesis of intended product 2-phenylquinazoline (**4.11a**) (Scheme **4.8 B2**).



Scheme 4.9. Plausible catalytic cycle of 2-phenylquinazoline (**4.11a**).

4.3.1.9. Post-synthetic modification:



Scheme 4.10. Post functionalization.

The synthetic applicability of the current catalytic protocol was manifested by converting **4.3a** into other valuable molecules via N-oxide directed C2-H functionalization (Scheme **4.10**, a). When **4.3a** was treated with 2.5 equiv. of *m*-CPBA in DCM for 12 h at room temperature, the corresponding N-

oxide product (**4.4**) was formed. The reaction of **4.4** with piperidine in presence of CuI delivered the amination product (**4.5**) in 75% yield (Scheme **4.10**, a). The C-H cyanation product (**4.6**) was furnished in moderate isolated yield upon treatment of the corresponding N-Oxide (**2.4**) with trimethylsilyl cyanide (Scheme **4.10**, a). In addition, a Suzuki coupling reaction with **4.3zh** was also conducted accomplishing the desired compound **4.7** in excellent yield (Scheme **4.10**, b).

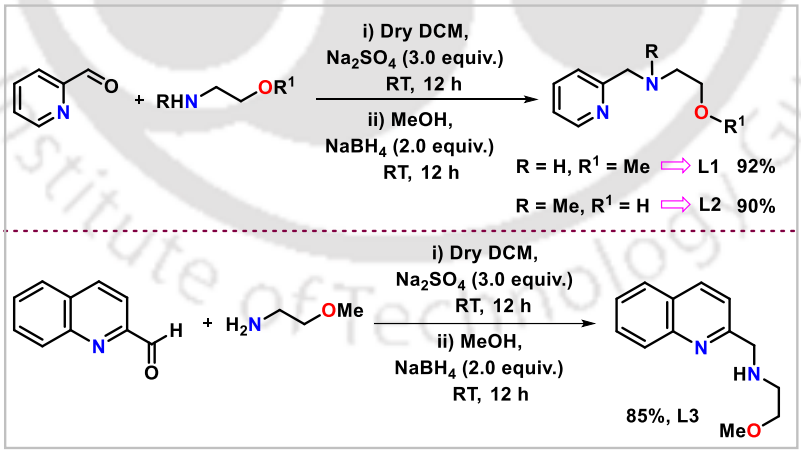
4.4. Conclusion:

This catalytic process showed excellent tolerance to a large variety of reducible functional groups as well as a broad substrate scope. The mechanistic investigation strongly suggests that slow in situ dehydrogenation of amino alcohol and the primary alcohol are crucial in the pathway to afford the 3-substituted quinolines. The use of readily accessible starting materials and an earth-abundant phosphine-free cobalt complex makes this strategy atom-economical, environmentally green and sustainable.

4.5. Experimental Section:

4.5.1. Ligands synthesis:

To an oven dried 50 mL round bottomed flask, Pyridine-2-carboxaldehyde (0.535 g, 5.0 mmol, 1.0 equiv.) and 2-amino ethanol derivatives (5.0 mmol, 1.0 equiv.) were dissolved in 15 mL of dry CH_2Cl_2 and then Na_2SO_4 (2.131 g, 15.0 mmol, 3.0 equiv.) was added to the reaction mixture. The resulting suspension was stirred for 12 h at room temperature. Then, it was filtered, the residue was washed thoroughly with CH_2Cl_2 and the combined solvent was removed under reduced pressure. The residue obtained was directly used for the next step without further purification. The residue was dissolved in 30 mL of methanol and $NaBH_4$ (0.378 g, 10.0 mmol, 2.0 equiv.) was added in a portion wise manner

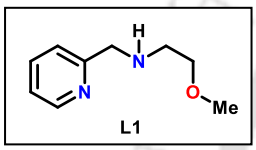


Scheme 4.11. Schematic representation of ligand synthesis.

under stirring condition at 0 °C and the stirring was continued for overnight at room temperature. Then the solvent was evaporated and 15 mL of water was added. After that, it was extracted by CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4. Then the solvent was evaporated to get the crude product, which was further purified by silica gel (100-200 mess) column chromatography using 60 – 70% ethyl acetate in Petroleum ether (Scheme **4.11**).[17]

To an oven dried 50 mL round bottomed flask, 2-Quinolinecarboxaldehyde (0.785 g, 5.0 mmol, 1.0 equiv.) and 2-Methoxyethylamine (0.375 g, 5.0 mmol, 1.0 equiv.) were dissolved in 15 mL of dry CH_2Cl_2 and then Na_2SO_4 (2.131 g, 15.0 mmol, 3.0 equiv.) was added to the reaction mixture. The resulting suspension was stirred for 12 h at room temperature. Then, it was filtered, the residue was washed thoroughly with CH_2Cl_2 and the combined solvent was removed under reduced pressure. The residue obtained was directly used for the next step without further purification. The residue was dissolved in 30 mL of methanol and $NaBH_4$ (0.378 g, 10.0 mmol, 2.0 equiv.) was added in a portion wise manner under stirring condition at 0 °C and the stirring was continued for overnight at room temperature. Then the solvent was evaporated and 15 mL of water was added. After that, it was extracted by CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4. Then the solvent was evaporated to get the crude product, which was further purified by silica gel (100-200 mess) column chromatography using 60 –70% ethyl acetate in Petroleum ether (Scheme **4.11**).[18]

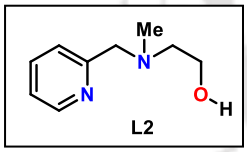
2-methoxy-N-(pyridin-2-ylmethyl)ethan-1-amine (L1):[17]



L1

Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 92% yield (0.764 g, 4.6 mmol) as a brown liquid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.55 (d, *J* = 4.3 Hz, 1H), 7.64 (td, *J* = 7.7, 1.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.25 – 6.94 (m, 1H), 3.94 (s, 2H), 3.53 (t, *J* = 5.2 Hz, 2H), 3.36 (s, 3H), 2.85 (t, *J* = 5.2 Hz, 2H). 2.23 (brs, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 159.87, 149.39, 136.55, 122.29, 122.00, 72.17, 58.90, 55.31, 48.98.

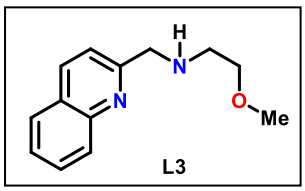
2-(methyl(pyridin-2-ylmethyl)amino)ethan-1-ol (L2):[17]



L2

Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 40/60) to afforded the title compound in 90% yield (0.748 g, 4.5 mmol) as a yellow liquid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.48 (d, *J* = 4.9 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.11 (dd, *J* = 7.5, 4.9 Hz, 1H), 3.68 (s, 2H), 3.59 (t, *J* = 5.3 Hz, 2H), 2.97 (s, 1H), 2.60 (t, *J* = 5.3 Hz, 2H), 2.27 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 158.74, 149.27, 136.75, 123.26, 122.35, 63.29, 58.98, 58.95, 42.57.

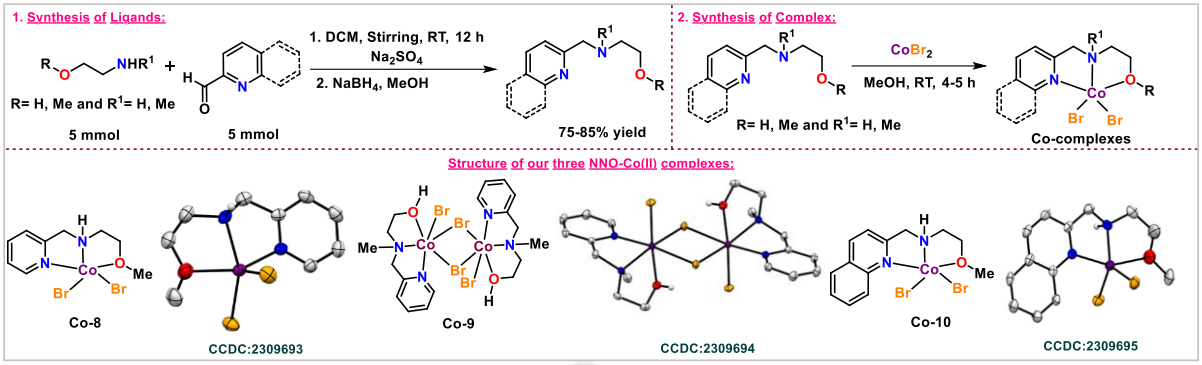
2-methoxy-N-(quinolin-2-ylmethyl)ethan-1-amine (L3):[18]



L3

Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 30/70) to afforded the title compound in 85% yield (0.919 g, 4.25 mmol) as a yellow liquid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.11 – 7.92 (m, 2H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.64 (d, *J* = 6.8 Hz, 1H), 7.44 (ddd, *J* = 11.4, 8.1, 2.8 Hz, 2H), 4.10 (d, *J* = 2.7 Hz, 2H), 3.53 (td, *J* = 5.3, 2.4 Hz, 2H), 3.34 (d, *J* = 2.9 Hz, 3H), 2.88 (td, *J* = 5.3, 2.4 Hz, 2H), 2.42 (s, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 160.16, 147.52, 136.10, 129.12, 128.79, 127.31, 127.04, 125.75, 120.19, 71.90, 58.51, 55.59, 48.77.

4.5.2. Procedure for synthesis of Co (II) complexes (Co8-Co10):



In an oven dried 25 mL round bottomed flask, $CoBr_2$ (0.219 g, 1.0 mmol, 1.0 equiv.) and methanolic solution of [$(PyCH_2)RN(CH_2CH_2OR_1)$, R = H, Me, R_1 = H, Me] (0.166 g, 1.0 mmol, 1.0 equiv.) was added drop wise. Then, the suspension was stirred at room temperature under argon atmosphere for 6 h. After 6 h, the solvent was removed under reduced pressure and the residue was rinsed with diethyl ether and dried under vacuum to get deep violet crystalline solid. The single crystal for **Co-8** complex was grown by slow diffusion of diethyl ether in the CH_2Cl_2 solution of the complex whilst for **Co-9** complex the single crystal was grown by slow diffusion of diethyl ether in the CH_3CN solution of the complex. After 3 – 4 days crystals were come which are suitable for single crystal analysis to obtain molecular structure of the complex.

In an oven dried 25 mL round bottomed flask, $CoBr_2$ (0.219 g, 1.0 mmol, 1.0 equiv.) and methanolic solution of 2-methoxy-N-(quinolin-2-ylmethyl)ethan-1-amine **(L3)** (0.217 g, 1.0 mmol, 1.0 equiv.) was added drop wise. Then, the suspension was stirred at room temperature under argon atmosphere for 6 h. After 6 h, the solvent was removed under reduced pressure and the residue was rinsed with diethyl ether and dried under vacuum to get deep violet crystalline solid. The single crystal for **Co-10** complex was grown by slow diffusion of diethyl ether in the in the CH_3CN solution of the complex. After 3 – 4 days crystals were come which are suitable for single crystal analysis to obtain molecular structure of the complex.

4.5.3. General experimental procedure for the synthesis of 3-substituted Quinoline derivatives:

To an oven dried 10 mL round bottomed flask, 2-aminobenzyl alcohols **4.1** (0.5 mmol, 1.0 equiv.), primary aryl or alkyl alcohols **4.2** (0.75 mmol, 1.5 equiv.), KOH (0.042 g, 0.75 mmol, 1.5 equiv.) and **Co-9** (0.010 g, 0.0125 mmol, 2.5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent to get the desired products.

4.5.4. General experimental procedure for the synthesis of Quinazoline derivatives:

To an oven dried 10 mL round bottomed flask, 2-aminobenzyl alcohols **4.1** (0.5 mmol, 1.0 equiv.), nitriles **4.10** (0.75 mmol, 1.5 equiv.), NaO^{t}Bu (0.048 g, 0.5 mmol, 1.0 equiv.) and **Co-8** (0.010 g, 0.025 mmol, 5 mol%) in xylene (2 mL) were taken under argon atmosphere. The reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using Petroleum ether/ethyl acetate as eluent to get the desired products.

4.5.5. Cobalt catalyzed dehydrogenation of alcohol:

To an oven dried 10 mL round bottomed flask, 2-aminobenzyl alcohol **4.1a** (0.123 g, 1.0 mmol, 1.0 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Co-9** (0.019 g, 0.025 mmol, 2.5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 130 °C in a preheated oil bath for 3 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude reaction mixture was submitted and analysed by ^{1}H-NMR confirming that 15% of 2-aminobenzaldehyde **(4.8)** was detected. After analysing the ^{1}H-NMR of the crude reaction mixture it was isolated by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 98/2) which afforded the desired 2-aminobenzaldehyde **(8)** as a yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.84 (s, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 6.71 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.16 (s, 2H).

4.5.6. Detection of evolved gas by GC-Thermal Detector (GC-TCD):

A mixture of 2-aminobenzyl alcohol **4.1a** (0.246 g, 2.0 mmol, 1.0 equiv.), 2-phenylethanol **4.2a** (0.366 g, 3.0 mmol, 1.5 equiv.), KOH (0.168 g, 3.0 mmol, 1.5 equiv.) were taken in an oven dried Ace pressure tube (100 mL) containing a stirring bar and connected with high vacuum for 10 mins, then **Co-9** (0.039 g, 0.05 mmol, 2.5 mol%) was added to the mixture under gentle flow of argon. Afterwards, the reaction mixture was kept for stirring into preheated oil bath at 130 °C for next 36 h. After completion of the reaction, the Ace pressure tube was cooled at 0 °C, the evolved gas was syringe out and detected from PerkinElmer clarus-590 GC instrument using Elite Plot-Q column (30 m length x 530 µm x 20 µm ID) employing the following method:

TCD starting temperature: 40 °C

Oven temperature: 60 °C

Time at starting temperature: 0 min

Hold time: 5 min

Ramp: 28 °C/ min up to 200 °C

Flow rate: 5 mL/ min (N_2)

Split ration: 20

Inlet temperature: 40 °C

Detector temperature TCD: 200 °C

The detected gas chromatogram was shown in figure **4.3.** (right).

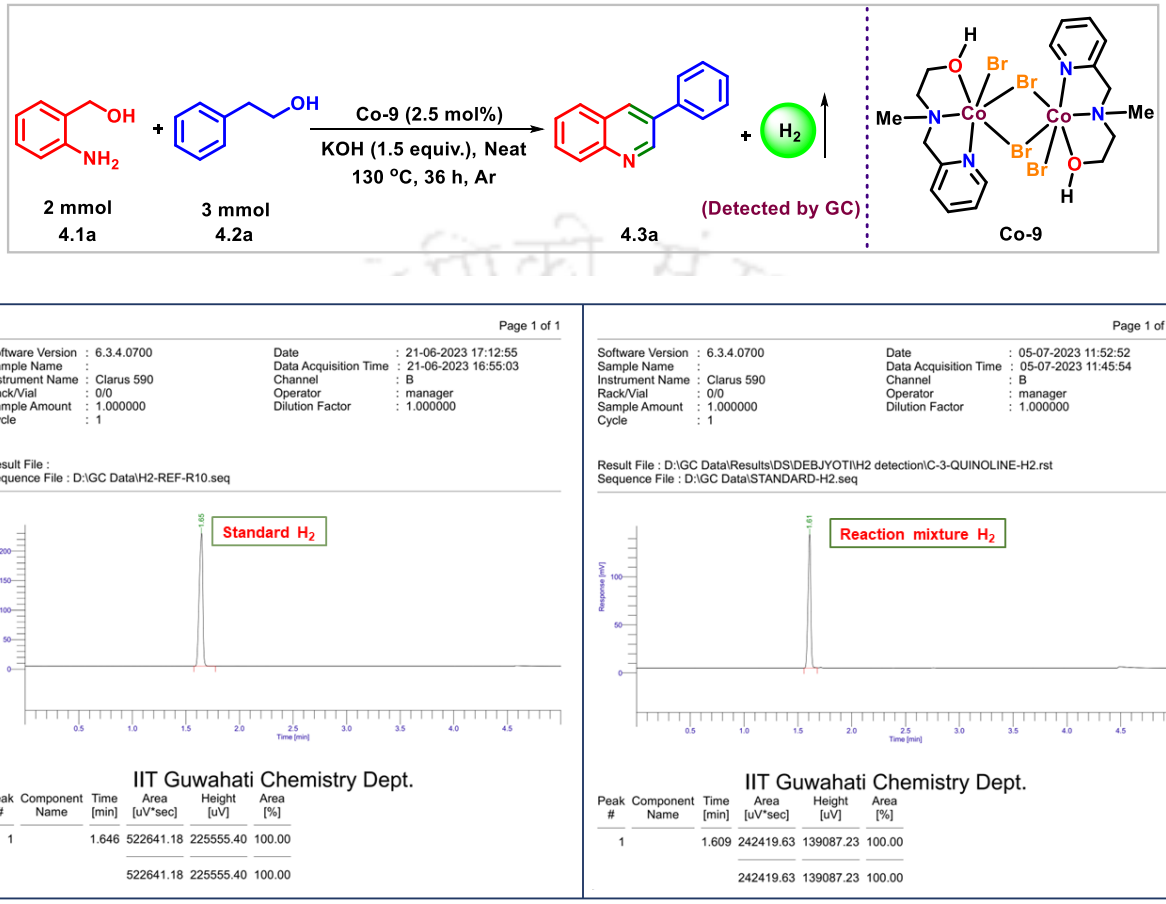


Figure 4.3. Chromatogram of standard hydrogen gas (left) and evolved hydrogen gas during catalysis (right).

4.5.7. Cobalt catalyzed synthesis of 3-phenylquinoline (4.3a) from 2-aminobenzaldehyde (4.8) and 2-phenylethanol (4.2a):

To an oven dried 10 mL round bottomed flask, 2-aminobenzaldehyde **4.8** (0.061 g, 0.5 mmol, 1.0 equiv.), 2-phenylethanol **4.2a** (0.092 g, 0.75 mmol, 1.5 equiv.), KOH (0.042 g, 0.75 mmol, 1.5 equiv.) and **Co-9** (0.010 g, 0.0125 mmol, 2.5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 3-phenylquinoline **(4.3a)** in 63% yield (0.065 g, 0.315 mmol) as a white solid.

4.5.8. Cobalt catalyzed synthesis of 2-phenylquinazoline (4.11a) from 2-aminobenzaldehyde (4.8) and benzonitrile (4.10a):

To an oven dried 10 mL round bottomed flask, 2-aminobenzaldehyde **4.8** (0.061 g, 0.5 mmol, 1.0 equiv.), benzonitrile **4.10a** (0.077 g, 0.75 mmol, 1.5 equiv.) and NaO^{t}Bu (0.048 g, 0.5 mmol, 1.0 equiv.) were taken together and connected with high vacuum for 10 minutes. Then dry xylene (2 mL) and **Co-8** (0.010 g, 0.025 mmol, 5 mol%) were added to the mixture under gentle flow of argon. The reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 2-phenylquinazoline **(4.11a)** in 68% yield (0.07 g, 0.34 mmol) as a yellow solid.

4.5.9. Cobalt catalyzed synthesis of 3-phenylquinoline (4.3a) from 2-aminobenzyl alcohol (4.1a) and phenylacetaldehyde (4.9):

To an oven dried 10 mL round bottomed flask, 2-aminobenzyl alcohol **4.1a** (0.062 g, 0.5 mmol, 1.0 equiv.), phenylacetaldehyde **4.7** (0.090 g, 0.75 mmol, 1.5 equiv.), KOH (0.042 g, 0.75 mmol, 1.5 equiv.) and **Co-9** (0.010 g, 0.0125 mmol, 2.5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 3-phenylquinoline **(4.3a)** in 50% yield (0.051g, 0.25 mmol) as a white solid.

4.5.10. Cobalt catalyzed synthesis of 3-phenylquinoline (4.3a) from 2-aminobenzaldehyde (4.8) and phenylacetaldehyde (4.9):

To an oven dried 10 mL round bottomed flask, 2-aminobenzaldehyde **4.8** (0.061 g, 0.5 mmol, 1.0 equiv.), phenylacetaldehyde **4.9** (0.090 g, 0.75 mmol, 1.5 equiv.), KOH (0.042 g, 0.75 mmol, 1.5 equiv.) and **Co-9** (0.010 g, 0.0125 mmol, 2.5 mol%) were taken under argon atmosphere. The reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 3-phenylquinoline (**4.3a**) in 43% yield (0.044 g, 0.215 mmol) as a white solid. Afterwards, when the reaction was conducted in absence of **Co-9** catalyst 40% (0.041 g, 0.2 mmol) of the desired 3-phenylquinoline (**4.3a**) was isolated.

4.5.11. Synthesis of benzamide (4.12) from benzonitrile (4.10a):

To an oven dried 10 mL round bottomed flask, benzonitrile **4.10a** (0.103 g, 1.0 mmol, 1.0 equiv.) and NaO^{t}Bu (0.096 g, 1.0 mmol, 1.0 equiv.) were taken together and connected with high vacuum for 10 minutes. Then dry xylene (3 mL) and **Co-8** (0.019 g, 0.05 mmol, 5 mol%) were added to the mixture under gentle flow of argon. The reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 50/50) to afford the benzamide **(4.12)** in 42% yield (0.051 g, 0.42 mmol) as a white solid. Afterwards, when the reaction was conducted in absence of **Co-8** catalyst 40% (0.049 g, 0.40 mmol) of the benzamide **(4.12)** was isolated.

4.5.12. Cobalt catalyzed synthesis of 2-phenylquinazoline (4.11a) from 2-aminobenzyl alcohol (4.1a) and benzamide (4.12):

To an oven dried 10 mL round bottomed flask, 2-aminobenzyl alcohol **4.1a** (0.062 g, 0.5 mmol, 1.0 equiv.), benzamide **4.12** (0.091 g, 0.75 mmol, 1.5 equiv.) and NaO^{t}Bu (0.048 g, 0.5 mmol, 1.0 equiv.) were taken together and connected with high vacuum for 10 minutes. Then dry xylene (2 mL) and **Co-8** (0.010 g, 0.025 mmol, 5 mol%) were added to the mixture under gentle flow of argon. The reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 2-phenylquinazoline **(4.11a)** in 80% yield (0.082 g, 0.4 mmol) as a yellow solid.

4.5.13. Cobalt catalyzed synthesis of 2-phenylquinazoline (4.11a) from 2-aminobenzaldehyde (4.8) and benzamide (4.12):

To an oven dried 10 mL round bottomed flask, 2-aminobenzaldehyde **4.8** (0.061 g, 0.5 mmol, 1.0 equiv.), benzamide **4.12** (0.091 g, 0.75 mmol, 1.5 equiv.) and NaO^{t}Bu (0.048 g, 0.5 mmol, 1.0 equiv.) were taken together and connected with high vacuum for 10 minutes. Then dry xylene (2 mL) and **Co-8** (0.010 g, 0.025 mmol, 5 mol%) were added to the mixture under gentle flow of argon. The reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 2-phenylquinazoline **(4.11a)** in 82% yield (0.085 g, 0.41 mmol) as a yellow solid. Afterwards, when the reaction was conducted in absence of **Co-8** catalyst 78% (0.08 g, 0.39 mmol) of the 2-phenylquinazoline **(4.11a)** was isolated.

4.5.14. Radical involvement test in the catalysis:

To an oven dried 10 mL round bottomed flask, 2-aminobenzyl alcohol **4.1a** (0.123 g, 1.0 mmol, 1.0 equiv.), 2-phenylethanol **4.2a** (0.183 g, 1.5 mmol, 1.5 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and TEMPO or BHT (0.312 g or 0.441 g, 2.0 mmol, 2.0 equiv.) were taken and remove air through vacuum. Then **Co-9** (0.019 g, 0.025 mmol, 2.5 mol%) was added under gentle flow of argon. The resulting reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 3-phenylquinoline **(4.3a)** as a white solid (for TEMPO, 72% yield, 0.148 g, 0.72 mmol and for BHT, 71% yield, 0.146 g, 0.71 mmol).

4.5.15. Homogeneity test:

To an oven dried 10 mL round bottomed flask, 2-aminobenzyl alcohol **4.1a** (0.123 g, 1.0 mmol, 1.0 equiv.), 2-phenylethanol **4.2a** (0.183 g, 1.5 mmol, 1.5 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and 2.0 equiv. metallic Hg were taken together and connected with high vacuum for 10 minutes. Then **Co-9** (0.019 g, 0.025 mmol, 2.5 mol%) was added under gentle flow of argon. The resulting reaction mixture was heated at 130 °C in a preheated oil bath. After stirring for 36 h, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 3-phenylquinoline **(4.3a)** in 73% yield (0.150 g, 0.73 mmol) as a white solid.

4.5.16. Metal hydride trapping experiment:

To an oven dried 100 mL Ace pressure tube, 2-aminobenzyl alcohol **4.1a** (0.123 g, 1.0 mmol, 1.0 equiv.), 2-phenylethanol **4.2a** (0.183 g, 1.5 mmol, 1.5 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) and **Co-9** (0.019 g, 0.025 mmol, 2.5 mol%) were added sequentially inside the argon filled glove box. Then the reaction mixture is stirred at room temperature. After stirring for 0.5 h, tritylium tetrafluoroborate (Ph_3C^+ BF_4^-) (0.066 g, 0.20 mmol, 20 mol%) was added to the reaction mixture. Then, the tube was sealed and placed at 130 °C in a preheated oil bath. After stirring for 36 h, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude reaction mixture was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 3-phenylquinoline **(4.3a)** in 18% yield (0.040 g, 0.18 mmol) as a white solid which indicated that the in situ formed cobalt hydride involved in the catalytic cycle.

4.5.17. Determination of the kinetic isotope effect:

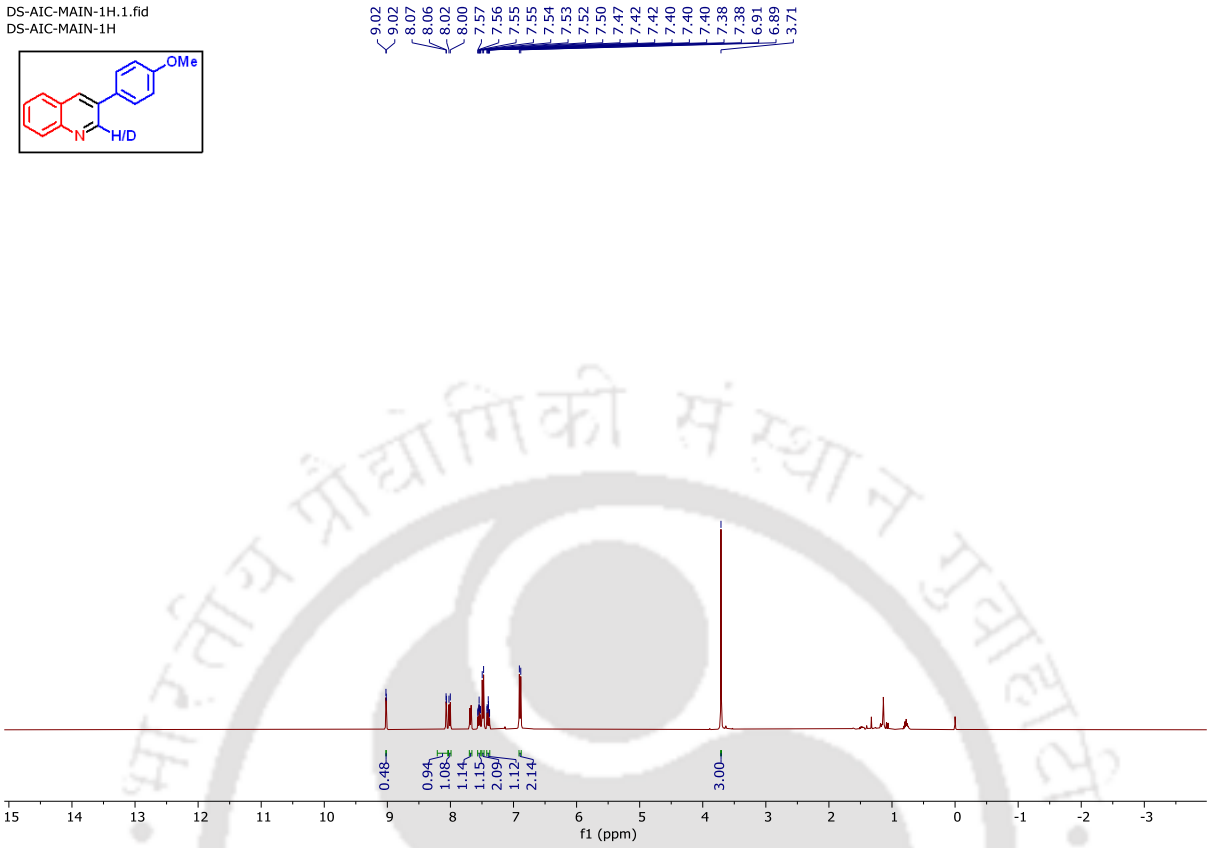


Figure 4.4. ^{1}H (400 MHz) NMR Spectrum of **4.3b-d$_1$** in $CDCl_3$.

To an oven dried 10 mL round bottomed flask, 2-aminobenzyl alcohol **4.1a** (0.123 g, 1.0 mmol, 1.0 equiv.), 2-(4-methoxyphenyl)ethan-1,1-d$_2$-1-ol **4.2b-d$_2$**[19] (0.231 g, 1.5 mmol, 1.5 equiv.), KOH (0.084 g, 1.5 mmol, 1.5 equiv.) were taken together and connected with high vacuum for 10 minutes. Then **Co-9** (0.019 g, 0.025 mmol, 2.5 mol%) was added under gentle flow of argon and the resulting reaction mixture was heated at 130 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired **4.3b-d$_1$** in 37% yield as a white solid. When the same reaction was performed employing 2-(4-methoxyphenyl)ethan-1-ol **4.2b** as a coupling partner under the similar reaction conditions 78% of **4.3b** was isolated which revealed that the value of KIE= k_H/k_D= 2.11.

4.5.18. Gram scale synthesis:

To an oven dried 50 mL round bottomed flask, 2-aminobenzyl alcohol **4.1a** (0.985 g, 8.0 mmol, 1.0 equiv.), 2-phenylethanol **4.2a** (1.46 g, 12.0 mmol, 1.5 equiv.) and KOH (0.673 g, 12.0 mmol, 1.5 equiv.) were taken sequentially and connected with high vacuum for 15 minutes. Then **Co-9** (0.154 g, 0.2 mmol, 2.5 mol%) was added under gentle flow of argon. The resulting reaction mixture was heated at 130 °C in a preheated oil bath. After stirring for 36 h, the reaction mixture was subjected to cool at room

temperature and ethyl acetate (30 mL) was added to dilute the mixture and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 3-phenylquinoline **(4.3a)** in 72% yield (1.182 g, 0.72 mmol) as a white solid.

4.5.19. Kinetic experiments:

4.5.19.1. Monitoring the kinetics of the reaction:

4.5.19.1.1. Experimental procedure: To an oven dried 10 mL 2-neck round bottomed flask, 2-aminobenzyl alcohol **4.1a** (0.616 g, 5.0 mmol, 1.0 equiv.), benzonitrile **4.10a** (0.773 g, 7.5 mmol, 1.5 equiv.) and NaO^{t}Bu (0.480 g, 5.0 mmol, 1.0 equiv.) were taken sequentially and connected with high vacuum for 15 minutes. Then, **Co-8** (0.096 g, 0.25 mmol, 5 mol%), mesitylene (0.601 g, 5.0 mmol, 1.0 equiv.) as an internal standard and dry xylene were added to the mixture under gentle flow of argon to make up the total volume of the reaction mixture 5 mL. Afterwards, the reaction mixture was kept in a preheated oil bath for stirring at 130 °C. At regular intervals (1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 9 h, 12 h, 15 h, 18 h, 21 h, 24 h, 27 h, 30 h, 33 h, 36 h) the reaction mixture was cooled to ambient temperature and an aliquot of mixture was taken in a GC vial. The GC sample was diluted with ethyl acetate and subjected to gas chromatographic analysis. The concentration of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of the product (mmolar) *vs* time (h) plot **(Figure 4.2 A)**.

4.5.19.2. Rate order determination:

The initial rate method was used to determine the rate order of the 2-phenylquinazoline **4.11a** synthesis reaction with respect to various components of the reaction. The data of the concentration (mM) *vs* time (h) plot was fitted to linear using origin pro 8.5. The slope of the linear fitted curve represents the initial rate of the reaction. The order of the reaction was determined by plotting initial rate (mM/h) *vs* concentration (mM) of that particular component.

4.5.19.2.1. Rate order determination with respect to benzonitrile (4.10a):

To determine the order of the 2-phenylquinazoline **4.11a** synthesis reaction, initial rates at different initial concentration of benzonitrile **4.10a** were recorded.

4.5.19.2.1.1. Experimental procedure: To an oven dried 10 mL 2-neck round bottomed flask, 2-aminobenzyl alcohol **4.1a** (0.123 g, 1.0 mmol, 1.0 equiv.) and NaO^{t}Bu (0.096 g, 1.0 mmol, 1.0 equiv.) were taken together and connected with high vacuum for 10 minutes. Then, **Co-8** (0.019 g, 0.05 mmol, 5 mol%), mesitylene (0.120 g, 1.0 mmol, 1.0 equiv.) as an internal standard, specific amount of benzonitrile **4.10a** and dry xylene were added to the mixture under gentle flow of argon to make up the total volume of the reaction mixture 5 mL. Afterwards, the reaction mixture was kept in an oil bath of 130 °C for stirring. At regular intervals (13 h, 14 h, 15 h, 16 h, 17 h, 18 h, 19 h, 20 h) the reaction mixture was cooled to ambient temperature and an aliquot of mixture was taken in a GC vial. The GC sample was diluted with ethyl acetate and subjected to gas chromatographic analysis. The concentration

of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of the product (mM) *vs* time (h) plot **(Figure 4.2 B)**. The rate of the reaction at different initial concentration of benzonitrile **4.10a** was given below and used to plot the log(rate) *vs* log(concentration of benzonitrile **4.10a)** to determine the order of the reaction with respect to benzonitrile **4.10a (Figure 4.3.C)**.

4.5.20. Post-synthetic modification:

4.5.20.1. Preparation procedure of 3-phenylquinoline 1-oxide (4.4):[20]

3-phenylquinoline **4.3a** (1.03 g, 5.0 mmol, 1.0 equiv.) and CH_2Cl_2 (10 mL) was added to an oven-dried 50 mL round bottom flask and the mixture was cooled to 0 °C. Afterwards, *m*-Chloroperoxybenzoic acid (*m*-CPBA, 2.16 g, 12.5 mmol, 2.5 equiv.) was added slowly in a portion wise manner under stirring condition at 0 °C and the stirring was continued for 12 h at room temperature. After 12 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (35 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 30/70) to afford the desired 3-phenylquinoline 1-oxide **(4.4)** in 95% yield (1.05 g, 9.5 mmol) as a brown liquid.

4.5.20.2. Preparation procedure of 3-phenyl-2-(piperidin-1-yl)quinoline 1-oxide (4.5):[21]

To an oven-dried 25 mL round bottom flask, piperidine (0.341 g, 4.0 mmol, 8.0 equiv.) in 3.75 mL toluene was added into a mixture of 3-phenylquinoline 1-oxide **(4.4)** (0.111 g, 0.5 mmol, 1.0 equiv.) and copper iodide (0.010 g, 0.05 mmol, 10 mol%) and the reaction mixture was stirred at 50 °C for 9 h under aerobic condition. After 9 h, the reaction mixture was subjected to cool at room temperature, diluted with 25 mL CH_2Cl_2 and washed with 25 mL H_2O. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 50/50) to afford the desired 3-phenyl-2-(piperidin-1-yl)quinoline 1-oxide **(4.5)** in 75% yield (0.114 g, 0.375 mmol) as a yellow solid.

4.5.20.3. Preparation procedure of 3-phenylquinoline-2-carbonitrile (4.6):[22]

3-phenylquinoline 1-oxide **(4.4)** (0.111 g, 0.5 mmol, 1.0 equiv.) and trimethylsilyl cyanide (0.109 g, 1.1 mmol, 2.2 equiv.) were added successively to an oven dried Ace pressure tube (15 mL) containing a stirring bar. Then the tube was flushed with argon and the resulting mixture was heated at 130 °C in a preheated oil bath for 1 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 3-phenylquinoline-2-carbonitrile **(4.6)** in 70% yield (0.081 g, 0.35 mmol) as a white solid.

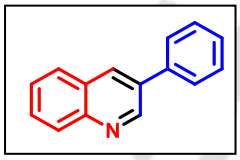
4.5.20.4. Preparation procedure of 3,6-diphenylquinoline (4.7):[23]

To an oven-dried 10 mL round bottom flask under argon atmosphere was charged with 6-bromo-3-phenylquinoline **(4.3zh)** (0.656 g, 2.31 mmol, 1.0 equiv.), phenylboronic acid (0.310 g, 2.55 mmol, 1.1 equiv.), $Pd(OAc)_2$ (0.052 g, 0.23 mmol, 10 mol%) and Na_2CO_3 (0.736 g, 6.94 mmol, 3.0 equiv.) in EtOH:H_2O (9:1) (1.0 mL) mixture. The resulting mixture was flushed with argon and was heated at 90 °C in a preheated oil bath for 16 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (30 mL) was added to dilute the mixture and filtered through a pad of celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 90/10) to afford the desired 3,6-diphenylquinoline **(4.7)** in 85% yield (0.552 g, 1.96 mmol) as a white solid.

4.5.21. Analytical data:

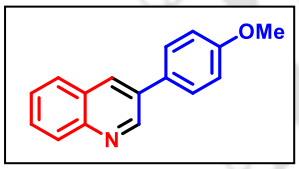
4.5.21.1. Analytical data for substrate scopes:

3-phenylquinoline (4.3a):[15b]



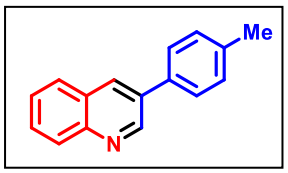
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 76% yield (0.156 g, 0.76 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.18 (s, 1H), 8.27 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.72 – 7.69 (m, 3H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 150.0, 147.5, 138.0, 134.0, 133.3, 129.5, 129.3, 129.3, 128.2, 128.2, 128.1, 127.5, 127.1.

3-(4-methoxyphenyl)quinoline (4.3b):[15b]



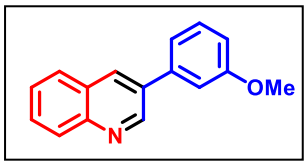
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 78% yield (0.183 g, 0.78 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.01 – 9.00 (m, 1H), 8.03 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.68 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 159.8, 149.7, 146.9, 133.4, 132.3, 130.1, 129.1, 129.0, 128.4, 128.1, 127.8, 126.9, 114.6, 55.3.

3-(*p*-tolyl)quinoline (4.3c):[15b]



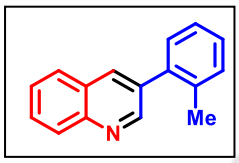
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 75% yield (0.164 g, 0.75 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.04 (s, 1H), 8.08 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 2H), 2.27 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 149.9, 147.2, 138.0, 134.9, 133.7, 132.8, 129.9, 129.2, 129.2, 128.1, 127.9, 127.2, 126.9, 21.2.

3-(3-methoxyphenyl)quinoline(4.3d):[24]



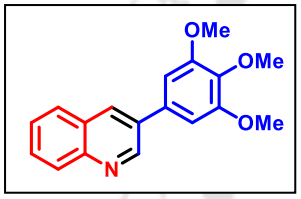
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 70% yield (0.165 g, 0.70 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.15 (s, 1H), 8.20 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.19 (s, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 3.83 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 160.1, 149.8, 147.3, 139.2, 133.6, 133.2, 130.1, 129.3, 129.13, 128.0, 127.9, 119.8, 113.3, 113.2, 55.3.

3-(*o*-tolyl)quinoline (4.3e):[15b]



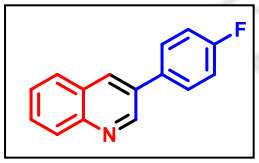
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 50% yield (0.110 g, 0.50 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.75 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.83 (s, 1H), 7.60 – 7.58 (m, 1H), 7.51 – 7.48 (m, 1H), 7.34 – 7.30 (m, 1H), 7.11 – 7.08 (m, 4H), 2.11 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 151.3, 146.9, 138.0, 135.6, 135.1, 134.7, 130.5, 130.0, 129.2, 129.2, 128.1, 127.7, 127.6, 126.7, 126.1, 20.3.

3-(3,4,5-trimethoxyphenyl)quinoline (4.3f):[25]



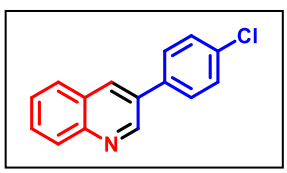
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 90/10) to afforded the title compound in 68% yield (0.201 g, 0.68 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.04 (s, 1H), 8.13 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 6.77 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 153.8, 149.8, 147.3, 138.3, 133.9, 133.7, 133.1, 129.4, 129.2, 127.9, 127.1, 104.7, 61.0, 56.3.

3-(4-fluorophenyl)quinoline (4.3g):[15b]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 92/8) to afforded the title compound in 61% yield (0.136 g, 0.61 mmol) as a brown solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.04 (s, 1H), 8.14 (s, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.78 – 7.76 (m, 1H), 7.64 – 7.62 (m, 1H), 7.58 – 7.55 (m, 2H), 7.50 – 7.47 (m, 1H), 7.14 – 7.10 (m, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 163.0 (d, *J* = 246.5 Hz), 149.8, 147.4, 134.1 (d, *J* = 3.2 Hz), 133.2, 133.0, 129.6, 129.4, 129.2 (d, *J* = 8.2 Hz), 128.0, 127.2, 116.3 (d, *J* = 21.5 Hz). **^{19}F NMR (470 MHz, $CDCl_3$)** δ -114.05.

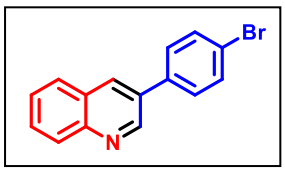
3-(4-chlorophenyl)quinoline (4.3h):[15b]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 92/8) to afforded the title compound in 68% yield (0.163 g, 0.68 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.02 (s, 1H), 8.13 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 2H). **^{13}C{^{1}H} NMR**

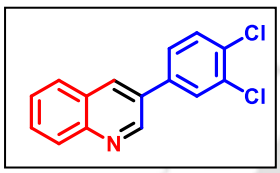
(150 MHz, $CDCl_3$) δ 149.5, 147.5, 136.4, 134.4, 133.2, 132.7, 129.7, 129.4, 129.3, 128.7, 128.1, 128.0, 127.2.

3-(4-bromophenyl)quinoline (4.3i):[15b]



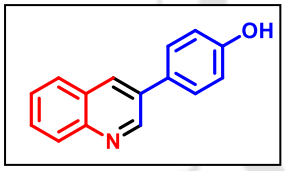
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 92/8) to afforded the title compound in 69% yield (0.196 g, 0.69 mmol) as a pale yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.17 (s, 1H), 8.25 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 150.0, 147.4, 137.9, 133.9, 133.3, 129.4, 129.3, 129.2, 128.2, 128.1, 127.5, 127.0.

3-(3,4-dichlorophenyl)quinoline (4.3j):[26]



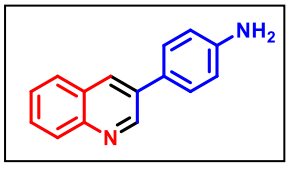
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 92/8) to afforded the title compound in 65% yield (0.178 g, 0.65 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.98 (s, 1H), 8.09 – 8.07 (m, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.71 – 7.69 (m, 1H), 7.60 – 7.56 (m, 1H), 7.46 – 7.40 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.30 – 7.23 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 149.4, 147.5, 139.7, 136.3, 135.1, 134.4, 133.3, 132.5, 130.4, 129.5, 128.6, 128.0, 127.5, 127.2, 125.5.

4-(quinolin-3-yl)phenol (4.3k):[27]



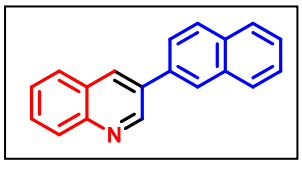
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 70/30) to afforded the title compound in 52% yield (0.115 g, 0.52 mmol) as a white solid. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 9.77 (s, 1H), 9.20 (s, 1H), 8.49 (s, 1H), 8.09 – 7.88 (m, 2H), 7.83 – 7.62 (m, 3H), 7.59 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 2H). **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 157.9, 149.3, 146.4, 132.9, 131.4, 129.0, 128.6, 128.4, 128.2, 127.9, 127.7, 126.9, 116.2.

4-(quinolin-3-yl)aniline (4.3l):[27]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 70/30) to afforded the title compound in 43% yield (0.095 g, 0.43 mmol) as a white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.16 (s, 1H), 8.22 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.63 – 7.46 (m, 3H), 6.83 (d, *J* = 8.4 Hz, 2H), 3.83 (s, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 150.0, 146.9, 146.8, 134.0, 131.9, 129.3, 128.9, 128.5, 128.4, 128.0, 127.9, 128.0, 115.8.

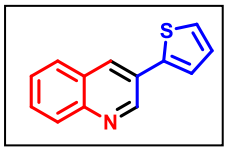
3-(naphthalen-2-yl)quinoline (4.3n):[15b]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 65% yield (0.166 g, 0.65 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.19 (s, 1H), 8.26 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.02 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H),

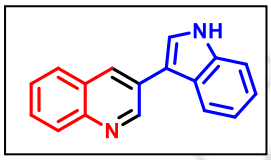
7.81 (d, *J* = 7.7 Hz, 1H), 7.77 – 7.75 (m, 2H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.39 (m, 2H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 150.1, 147.4, 135.2, 133.8, 133.7, 133.5, 133.0, 129.5, 129.3, 129.1, 128.4, 128.1, 128.1, 127.8, 127.1, 126.7, 126.6, 126.5, 125.3.

3-(thiophen-2-yl)quinoline (4.3o):[15c]



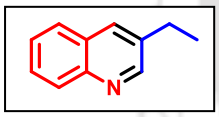
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 90/10) to afforded the title compound in 74% yield (0.156 g, 0.74 mmol) as a white solid. **^1H NMR (600 MHz, $CDCl_3$)** δ 9.04 (s, 1H), 8.05 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.30 (s, 1H), 7.27 – 7.13 (m, 1H), 6.99 – 6.97 (m, 1H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 148.5, 147.2, 140.7, 131.3, 129.3, 129.2, 128.4, 127.9, 127.8, 127.5, 127.2, 126.1, 124.4.

3-(1*H*-indol-3-yl)quinoline (4.3p):[28]



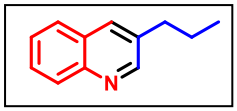
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 55/45) to afforded the title compound in 72% yield (0.176 g, 0.72 mmol) as a yellow solid. **^1H NMR (600 MHz, $CDCl_3$)** δ 9.20 (s, 1H), 9.17 (s, 1H), 8.32 (s, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.21 – 7.15 (m, 2H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 150.6, 146.4, 137.0, 132.4, 129.2, 129.0, 128.8, 128.7, 127.8, 127.1, 125.7, 123.0, 122.9, 120.9, 119.4, 114.5, 112.0

3-ethylquinoline (4.3s):[15c]



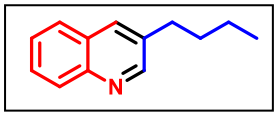
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 42% yield (0.066 g, 0.42 mmol) as a colourless liquid. **^1H NMR (600 MHz, $CDCl_3$)** δ 8.78 (s, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.87 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 2.79 (q, *J* = 7.7 Hz, 2H), 1.32 (t, *J* = 7.8 Hz, 3H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 151.8, 146.7, 136.6, 133.4, 129.1, 128.5, 128.2, 127.3, 126.5, 26.2, 15.2.

3-propylquinoline(4.3t):[15c]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 45% yield (0.077 g, 0.45 mmol) as a colourless liquid. **^1H NMR (600 MHz, $CDCl_3$)** δ 8.66 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.75 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.64 – 1.58 (m, 2H), 0.86 (t, *J* = 7.5 Hz, 3H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 152.1, 146.7, 135.1, 134.2, 129.1, 128.5, 128.2, 127.3, 126.5, 35.2, 24.2, 13.7.

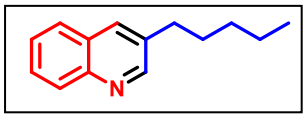
3-butylquinoline (4.3u):[15c]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 52% yield (0.096 g, 0.52 mmol) as a colourless liquid. **^1H NMR (600 MHz, $CDCl_3$)** δ 8.78 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.90 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.5

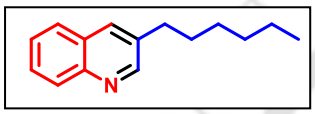
Hz, 1H), 2.79 (t, *J* = 7.8 Hz, 2H), 1.70 (p, *J* = 7.6 Hz, 2H), 1.41 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 152.2, 146.8, 135.5, 134.2, 129.2, 128.6, 128.3, 127.4, 126.6, 33.3, 33.0, 22.4, 14.0.

3-pentylquinoline (4.3v):[15c]



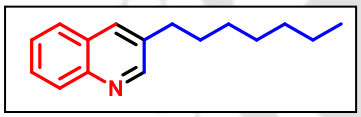
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 56% yield (0.112 g, 0.56 mmol) as a white solid. **^1H NMR (600 MHz, $CDCl_3$)** δ 8.76 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.83 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 2.71 (t, *J* = 7.9 Hz, 2H), 1.68 – 1.63 (m, 2H), 1.36 – 1.27 (m 4H), 0.88 (t, *J* = 6.7 Hz, 3H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 151.9, 146.6, 135.2, 134.0, 129.0, 128.3, 128.1, 127.2, 126.4, 33.0, 31.2, 30.6, 22.4, 13.9.

3-hexylquinoline (4.3w):[15c]



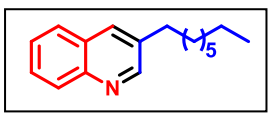
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 61% yield (0.130 g, 0.61 mmol) as a yellow liquid. **^1H NMR (600 MHz, $CDCl_3$)** δ 8.77 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.88 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 2.77 (t, *J* = 7.8 Hz, 2H), 1.72 – 1.67 (m, 2H), 1.39 – 1.35 (m, 2H), 1.32 – 1.26 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 152.1, 146.7, 135.4, 134.2, 129.1, 128.5, 128.3, 127.3, 126.6, 33.2, 31.7, 31.1, 28.9, 22.6, 14.1.

3-heptylquinoline (4.3x):[28]



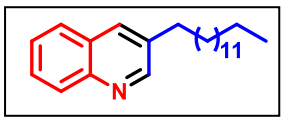
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 63% yield (0.143 g, 0.63 mmol) as a yellow liquid. **^1H NMR (600 MHz, $CDCl_3$)** δ 8.76 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.85 (s, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 2.73 (t, *J* = 7.8 Hz, 2H), 1.70 – 1.65 (m, 2H), 1.38 – 1.21 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 152.0, 146.6, 135.3, 134.0, 129.0, 128.4, 128.2, 127.2, 126.4, 33.1, 31.7, 31.1, 29.1, 29.1, 22.6, 14.0.

3-octylquinoline (4.3y):[15b]



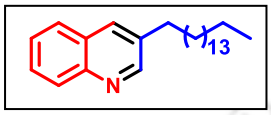
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 65% yield (0.157 g, 0.65 mmol) as a yellow liquid. **^1H NMR (600 MHz, $CDCl_3$)** δ 8.77 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.85 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 2.74 (t, *J* = 7.9 Hz, 2H), 1.68 (p, *J* = 7.5 Hz, 2H), 1.36 – 1.23 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 152.0, 146.7, 135.3, 134.0, 129.1, 128.4, 128.2, 127.3, 126.5, 33.2, 31.8, 31.1, 29.4, 29.2, 29.2, 22.6, 14.1.

3-tetradecylquinoline (4.3z):



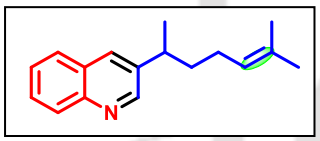
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 68% yield (0.221 g, 0.68 mmol) as a colourless liquid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.64 (s, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.71 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 2.61 (t, *J* = 7.9 Hz, 2H), 1.55 (p, *J* = 7.5 Hz, 2H), 1.24 – 1.10 (m, 22H), 0.76 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 152.0, 146.7, 135.3, 133.9, 129.1, 128.4, 128.1, 127.2, 126.4, 33.1, 31.9, 31.1, 29.70, 29.68, 29.66 (2C), 29.64, 29.6, 29.4, 29.36, 29.2, 22.7, 14.1. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{23}H_{35}N$ is 326.2848. Found 326.2855.

3-hexadecylquinoline (4.3za):[15c]



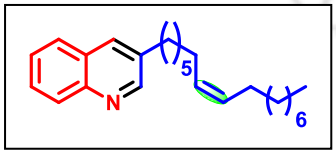
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 70% yield (0.247 g, 0.70 mmol) as a colourless liquid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.63 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.68 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 2.58 (t, *J* = 7.9 Hz, 2H), 1.53 (p, *J* = 7.5 Hz, 2H), 1.22 – 1.08 (m, 26H), 0.75 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 151.9, 146.6, 135.2, 133.8, 129.0, 128.3, 128.1, 127.1, 126.3, 33.1, 31.9, 31.0, 29.65, 29.63, 29.61, 29.6, 29.5, 29.4, 29.3, 29.1, 22.6, 14.0.

3-(6-methylhept-5-en-2-yl)quinoline (4.3zb):[15c]



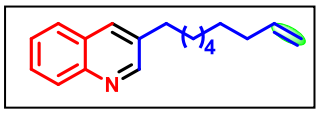
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 60% yield (0.144 g, 0.60 mmol) as a colourless liquid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.79 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.88 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 5.09 (t, *J* = 7.3 Hz, 1H), 2.94 – 2.88 (m, 1H), 1.99 – 1.88 (m, 2H), 1.80 – 1.68 (m, 2H), 1.66 (s, 3H), 1.49 (s, 3H), 1.34 (d, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 151.3, 147.0, 140.0, 132.7, 131.9, 129.1, 128.5, 128.2, 127.4, 126.5, 123.9, 38.0, 37.1, 26.0, 25.7, 22.1, 17.7.

(*Z*)-3-(pentadec-7-en-1-yl)quinoline (4.3zc):[15c]



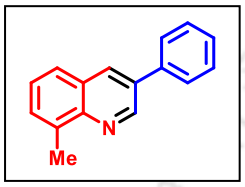
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 65% yield (0.219 g, 0.65 mmol) as a colourless liquid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.65 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 5.28 – 5.22 (m, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 1.98 – 1.83 (m, 4H), 1.62 – 1.54 (m, 2H), 1.25 – 1.15 (m, 18H), 0.76 (t, *J* = 6.3 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 152.0, 146.8, 135.3, 134.0, 130.5, 130.1, 129.6, 129.1, 128.4, 128.2, 127.2, 126.5, 33.2, 32.6, 31.9, 31.1, 29.8, 29.7, 29.5, 29.3, 29.2, 29.1, 29.1, 28.9, 27.2, 27.1, 22.7, 14.1.

3-(non-8-en-1-yl)quinoline (4.3zd):



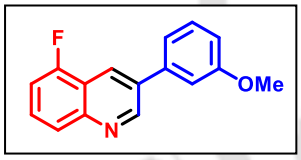
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 68% yield (0.172 g, 0.68 mmol) as a colourless liquid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.68 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.80 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 5.37 – 5.26 (m, 1H), 2.69 (t, *J* = 7.8 Hz, 2H), 1.95 – 1.86 (m, 2H), 1.65 – 1.59 (m, 2H), 1.55 – 1.49 (m, 2H), 1.31 – 1.17 (m, 6H), 0.79 (t, *J* = 6.5 Hz, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 152.2, 146.9, 134.1, 131.5, 128.5, 128.3, 127.4, 126.6, 124.8, 123.9, 33.3, 32.6, 32.0, 31.2, 29.6, 29.4, 29.3, 29.1, 29.0, 26.9, 22.7, 18.0, 14.2. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{18}H_{23}N$ is 254.1909. Found 254.1914.

8-methyl-3-phenylquinoline (4.3ze):[29]



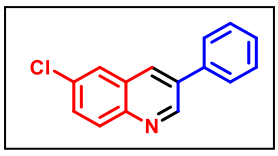
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 54% yield (0.118 g, 0.54 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.04 (s, 1H), 8.02 (s, 1H), 7.50 – 7.47 (m, 3H), 7.35 – 7.29 (m, 3H), 7.25 – 7.21 (m, 2H), 2.69 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 148.6, 146.4, 137.9, 136.9, 133.4, 133.36, 129.6, 129.1, 128.0, 127.3, 126.7, 126.1, 18.2.

5-fluoro-3-(3-methoxyphenyl)quinoline (4.3zf):[15b]



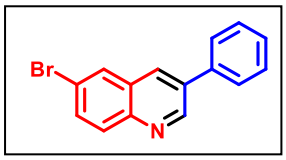
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 62% yield (0.157 g, 0.62 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.07 (s, 1H), 8.40 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.49 (q, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 8.3 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.11 – 7.06 (m, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 3.76 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 160.3, 158.02 (d, *J* = 253.5 Hz), 150.8, 149.9, 148.09 (d, *J* = 3.0 Hz), 147.4, 139.3, 138.9, 133.9, 133.7, 133.3, 130.3, 129.3 (d, *J* = 32.7 Hz), 129.2, 128.8 (d, *J* = 8.9 Hz), 128.1, 127.0, 126.4 (d, *J* = 4.4 Hz), 125.1 (d, *J* = 4.0 Hz), 119.9, 118.9 (d, *J* = 16.0 Hz) 113.7, 113.3, 110.6 (d, *J* = 19.1 Hz), 55.4. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -122.72.

6-chloro-3-phenylquinoline(4.3zg):[15b]



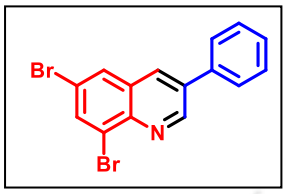
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 72% yield (0.173 g, 0.72 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.07 (s, 1H), 8.09 (s, 1H), 7.98 (d, *J* = 8.9 Hz, 1H), 7.75 (s, 1H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 150.2, 145.7, 137.4, 134.8, 132.9, 132.3, 130.9, 130.4, 129.4, 128.8, 128.5, 127.5, 126.7.

6-bromo-3-phenylquinoline (4.3zh):[15b]



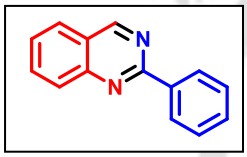
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 65% yield (0.185 g, 0.65 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.11 (s, 1H), 8.14 (s, 1H), 7.97 (s, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 150.2, 145.7, 137.4, 134.9, 133.1, 132.4, 130.9, 130.1, 129.4, 129.4, 128.6, 127.6, 121.2.

6,8-dibromo-3-phenylquinoline (4.3zi):[15b]



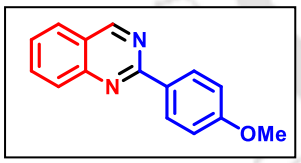
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 48% yield (0.174 g, 0.48 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.19 (s, 1H), 8.10 (s, 1H), 8.04 (s, 1H), 7.91 (s, 1H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 151.0, 143.2, 136.7, 135.8, 135.6, 132.7, 130.1, 130.0, 129.5, 128.9, 127.6, 125.8, 120.5.

2-phenylquinazoline (4.11a):[11]



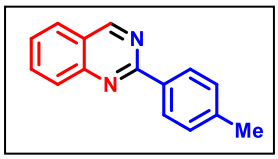
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 82% yield (0.169 g, 0.82 mmol) as a yellow solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.43 (s, 1H), 8.61 (d, *J* = 7.1 Hz, 2H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.57 – 7.48 (m, 4H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 161.1, 160.6, 150.8, 138.1, 134.2, 130.7, 128.7, 128.7, 128.7, 127.3, 127.2, 123.7.

2-(4-methoxyphenyl)quinazoline (4.11b):[11]



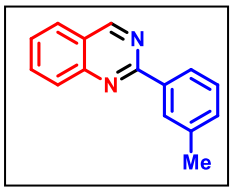
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 78% yield (0.184 g, 0.78 mmol) as a yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.32 (s, 1H), 8.49 (d, *J* = 8.2 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.80 – 7.76 (m, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 3.81 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 162.0, 161.0, 160.5, 151.0, 134.1, 130.9, 130.3, 128.5, 127.2, 126.9, 123.4, 114.1, 55.5.

2-(*p*-tolyl)quinazoline (4.11c):[11]



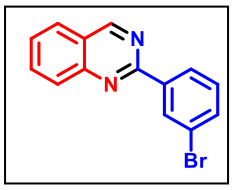
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 76% yield (0.167 g, 0.76 mmol) as a yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.28 (s, 1H), 8.40 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.74 – 7.71 (m, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 2.31 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 161.2, 160.4, 150.8, 140.9, 135.4, 134.0, 129.5, 128.6, 128.6, 127.1, 127.0, 123.5, 21.6.

2-(*m*-tolyl)quinazoline (4.11d):[11]



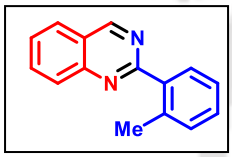
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 68% yield (0.150 g, 0.68 mmol) as a yellow solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.40 (s, 1H), 8.43 – 8.40 (m, 2H), 8.05 (d, *J* = 8.7 Hz, 1H), 7.85 – 7.82 (m, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 2.47 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 161.2, 160.5, 150.8, 138.3, 138.0, 134.1, 131.5, 129.2, 128.6, 128.6, 127.2, 127.1, 125.9, 123.6, 21.6.

2-(3-bromophenyl)quinazoline (4.11e):[11]



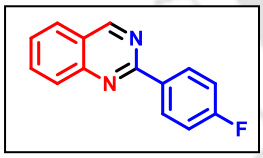
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 65% yield (0.184 g, 0.65 mmol) as a yellow solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.45 (s, 1H), 8.79 (s, 1H), 8.55 (d, *J* = 7.3 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.94 – 7.91 (m, 2H), 7.65 – 7.62 (m, 2H), 7.40 (t, *J* = 7.8 Hz, 1H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 160.7, 159.7, 150.8, 140.2, 134.5, 133.6, 131.7, 130.3, 128.8, 127.8, 127.3, 127.2, 123.9, 123.1.

2-(*o*-tolyl)quinazoline (4.11f):[30]



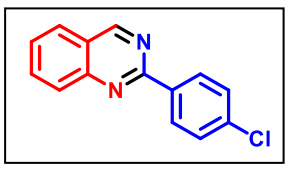
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 53% yield (0.117 g, 0.53 mmol) as a yellow solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.40 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.98 – 7.97 (m, 1H), 7.80 – 7.77 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.34 – 7.29 (m, 3H), 2.63 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 163.7, 159.8, 150.1, 138.4, 137.3, 133.8, 131.1, 130.6, 129.1, 128.2, 127.2, 126.8, 125.7, 122.6, 21.0.

2-(4-fluorophenyl)quinazoline (4.11g):[11]



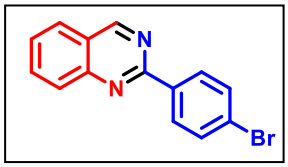
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 77% yield (0.173 g, 0.77 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.45 (s, 1H), 8.67 – 8.57 (m, 2H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.94 – 7.89 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 8.6 Hz, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 163.7 (d, *J* = 248.8 Hz), 159.5, 159.1, 149.7, 133.2, 132.8, 129.6 (d, *J* =8.5 Hz), 127.5, 126.3, 126.1, 125.9, 125.8, 125.1, 122.5, 114.5 (d, *J* = 21.5 Hz). **^{19}F NMR (470 MHz, $CDCl_3$)** δ -110.58.

2-(4-chlorophenyl)quinazoline (4.11h):[11]



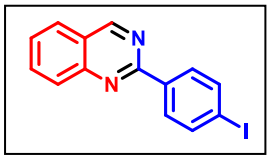
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 75% yield (0.180 g, 0.75 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.44 (s, 1H), 8.57 (d, *J* = 8.2 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.91 (t, *J* = 8.7 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 160.7, 160.2, 150.8, 137.0, 136.7, 134.4, 130.0, 129.0, 128.7, 127.6, 127.3, 123.8.

2-(4-bromophenyl)quinazoline (4.11i):[11]



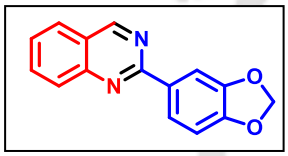
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 72% yield (0.205 g, 0.72 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.41 (s, 1H), 8.48 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.90 – 7.87 (m, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 160.6, 160.2, 150.8, 137.1, 134.4, 131.9, 130.3, 128.7, 127.6, 127.3, 125.5, 123.7.

2-(4-iodophenyl)quinazoline (4.11j):[13g]



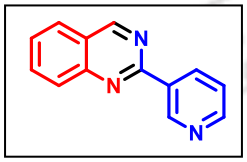
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 63% yield (0.209 g, 0.63 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.43 (s, 1H), 8.35 (d, *J* = 8.3 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.92 – 7.85 (m, 4H), 7.61 (t, *J* = 7.4 Hz, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 160.6, 160.4, 150.8, 137.9, 137.7, 134.4, 130.4, 128.8, 127.6, 127.3, 123.8, 97.9.

2-(benzo[d][1,3]dioxol-5-yl)quinazoline (4.11k):[11]



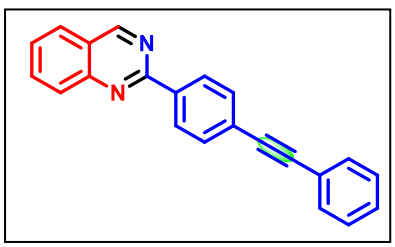
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 75% yield (0.188 g, 0.75 mmol) as a yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.39 (s, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 8.11 (s, 1H), 8.02 (d, *J* = 8.9 Hz, 1H), 7.88 – 7.85 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.05 (s, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 160.7, 160.5, 150.9, 150.0, 148.3, 134.2, 132.7, 128.6, 127.2, 127.0, 123.6, 123.5, 108.9, 108.4, 101.6.

2-(pyridin-3-yl)quinazoline (4.11l):[31]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 85/15) to afforded the title compound in 69% yield (0.143 g, 0.69 mmol) as a brown solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.80 (s, 1H), 9.45 (s, 1H), 8.85 (d, *J* = 7.8 Hz, 1H), 8.73 (d, *J* = 4.8 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.91 (t, *J* = 7.5 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.45 – 7.43 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 160.7, 159.2, 151.2, 150.6, 150.3, 135.9, 134.4, 133.6, 128.7, 127.8, 127.2, 123.8, 123.5.

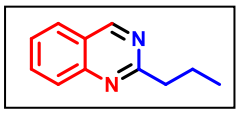
2-(4-(phenylethynyl)phenyl)quinazoline (4.11m):



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 57% yield (0.175 g, 0.57 mmol) as a brown solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.47 (s, 1H), 8.63 (d, *J* = 8.1 Hz, 2H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.94 – 7.90 (m, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.58 – 7.57 (m, 2H), 7.39 – 7.36 (m, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 160.6,

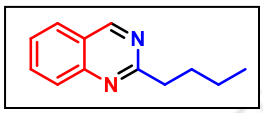
160.5, 150.9, 137.8, 134.4, 132.0, 131.8, 128.8, 128.6, 128.6, 128.5, 127.6, 127.3, 125.6, 123.8, 123.3, 91.4, 89.6. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{22}H_{14}N_2$ is 307.1235. Found 307.1239.

2-propylquinazoline (4.11n):[31]



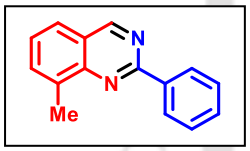
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) to afforded the title compound in 44% yield (0.076 g, 0.44 mmol) as a yellow solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.25 (s, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.79 – 7.77 (m, 2H), 7.50 – 7.48 (m, 1H), 3.01 (t, *J* = 7.7 Hz, 2H), 1.87 (h, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 167.7, 160.4, 150.4, 134.1, 127.9, 127.1, 127.0, 123.1, 41.9, 22.4, 14.1.

2-butylquinazoline (4.11o):[11]



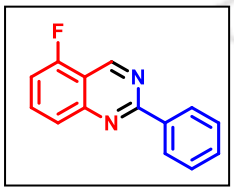
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) to afforded the title compound in 48% yield (0.089 g, 0.48 mmol) as a yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.22 (s, 1H), 7.88 – 7.85 (m, 1H), 7.76 – 7.73 (m, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 3.02 (t, *J* = 7.7 Hz, 2H), 1.85 – 1.77 (m, 2H), 1.40 – 1.31 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 167.9, 160.3, 150.3, 133.9, 127.8, 127.0, 126.9, 123.0, 39.7, 31.1, 22.6, 13.9.

8-methyl-2-phenylquinazoline (4.11p):[30]



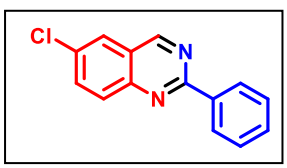
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 56% yield (0.123 g, 0.56 mmol) as a yellow solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.18 (s, 1H), 8.53 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 2.66 (s, 3H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 160.5, 159.8, 149.6, 138.4, 137.0, 133.8, 130.5, 128.6, 128.6, 126.9, 124.8, 123.4, 16.9.

5-fluoro-2-phenylquinazoline (4.11q):[31]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 60% yield (0.134 g, 0.60 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.66 (s, 1H), 8.56 – 8.54 (m, 1H), 7.82 – 7.80 (m, 1H), 7.78 – 7.73 (m, 1H), 7.49 – 7.45 (m, 3H), 7.15 (t, *J* = 8.8 Hz, 1H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 161.9, 158.4 (d, *J* = 257.6 Hz), 155.0 (d, *J* = 3.3 Hz), 151.7 (d, *J* = 2.1 Hz), 137.7, 134.3 (d, *J* = 9.2 Hz), 131.1, 128.9 (d, *J* = 7.1 Hz), 124.8 (d, *J* = 4.4 Hz), 114.6 (d, *J* = 15.5 Hz), 111.2 (d, *J* = 18.4 Hz). **^{19}F NMR (470 MHz, $CDCl_3$)** δ -122.94.

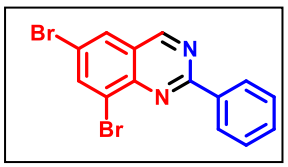
6-chloro-2-phenylquinazoline (4.11r):[11]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 78% yield (0.192 g, 0.78 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.29 (s, 1H), 8.52 – 8.50 (m, 2H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.80 – 7.79 (m, 1H), 7.74 – 7.71 (m,

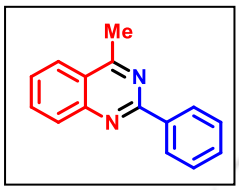
1H), 7.47 – 7.43 (m, 3H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 161.4, 159.6, 149.3, 137.7, 135.2, 132.9, 131.0, 130.5, 128.8, 128.7, 125.9, 124.1.

6,8-dibromo-2-phenylquinazoline (4.11s):[30]



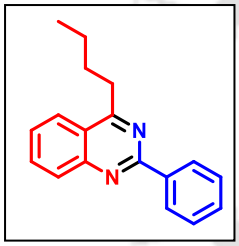
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 52% yield (0.189 g, 0.52 mmol) as a white solid. **^1H NMR (600 MHz, $CDCl_3$)** δ 9.31 (s, 1H), 8.67 – 8.66 (m, 2H), 8.26 (s, 1H), 8.00 (s, 1H), 7.54 – 7.53 (m, 3H). **$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$)** δ 162.0, 159.9, 147.2, 140.2, 137.2, 131.5, 129.0, 128.9, 128.9, 125.6, 125.2, 120.3.

4-methyl-2-phenylquinazoline (4.11t):[32]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) to afforded the title compound in 40% yield (0.088 g, 0.40 mmol) as a white solid. **^1H NMR (500 MHz, $CDCl_3$)** δ 8.62 (d, *J* = 6.8 Hz, 2H), 8.08 (t, *J* = 7.9 Hz, 2H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.54 – 7.47 (m, 3H), 3.01 (s, 3H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 168.4, 160.3, 150.5, 138.4, 133.6, 130.5, 129.4, 128.7, 127.7, 127.0, 125.1, 123.2, 22.1.

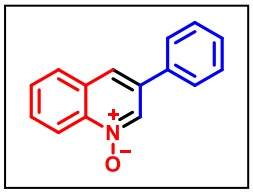
4-butyl-2-phenylquinazoline (4.11u):[33]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) to afforded the title compound in 51% yield (0.134 g, 0.51 mmol) as a white solid. **^1H NMR (500 MHz, $CDCl_3$)** δ 8.69 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 3.31 (t, *J* = 7.5 Hz, 2H), 1.98 – 1.92 (m, 2H), 1.56 – 1.48 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 170.7, 161.7, 149.8, 149.1, 133.3, 131.6, 128.8, 126.5, 124.7, 121.7, 119.7, 117.2, 117.0, 34.4, 30.6, 22.9, 14.1.

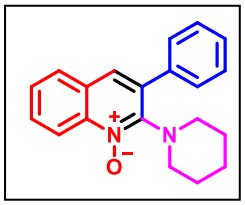
4.5.21.2. Analytical data for post synthetic modifications:

3-phenylquinoline 1-oxide (4.4):[20]



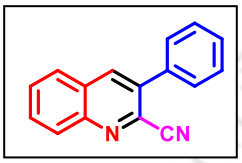
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 30/70) to afforded the title compound in 95% yield (0.210 g, 0.95 mmol) as a yellow liquid. **^1H NMR (500 MHz, $CDCl_3$)** δ 8.84 (s, 1H), 8.69 (d, *J* = 8.7 Hz, 1H), 7.87 – 7.85 (m, 2H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.62 – 7.59 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.41 – 7.38 (m, 1H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 140.3, 136.0, 135.5, 135.1, 130.5, 130.4, 129.5, 129.3, 129.2, 128.5, 127.2, 124.3, 119.9.

3-phenyl-2-(piperidin-1-yl)quinoline 1-oxide (4.5):



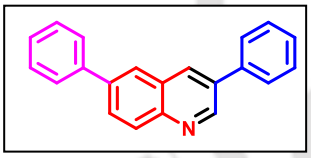
Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) to afforded the title compound in 75% yield (0.228 g, 0.75 mmol) as a yellow solid. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.04 (s, 1H), 8.21 (d, J = 8.1 Hz, 1H), 8.15 (d, J = 6.1 Hz, 1H), 7.72 (d, J = 7.6 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 3.31 – 3.17 (m, 3H), 3.30 – 2.90 (m, 1H), 1.67 – 1.42 (m, 4H), 1.33 – 1.22 (m, 2H). **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 174.8, 139.3, 138.2, 136.1, 131.6, 128.4, 127.9, 126.4, 125.9, 125.6, 123.3, 119.8, 118.2, 45.8, 43.8, 8.6. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{20}H_{20}N_2O$ is 305.1654. Found 305.1663.

3-phenylquinoline-2-carbonitrile (4.6):[22]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 70% yield (0.161 g, 0.70 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.75 – 7.72 (m, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 6.7 Hz, 2H), 7.47 – 7.39 (m, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 147.2, 137.1, 137.0, 135.8, 133.1, 131.1, 129.9, 129.8, 129.2, 129.1, 128.7, 127.9, 117.2.

3,6-diphenylquinoline (4.7):[23]



Purification by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) to afforded the title compound in 85% yield (0.239 g, 0.85 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.05 (s, 1H), 8.19 (s, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.91 (s, 1H), 7.85 (dd, J = 8.7, 2.1 Hz, 1H), 7.61 – 7.59 (m, 4H), 7.43 – 7.37 (m, 4H), 7.34 – 7.29 (m, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 150.0, 146.8, 140.4, 139.8, 137.9, 134.3, 133.4, 129.7, 129.3, 129.2, 129.1, 128.3, 128.2, 127.9, 127.5, 127.5, 125.7.

4.6. References:

1. R. E. Buntrock, Review of Heterocyclic Chemistry, 5th Edition. *J. Chem. Educ.* **2012**, *89*, 1349–1350;

2. E. Vitaku, T. D. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257−10274.

3. a) A. Nandakumar, S. P. Midya, V. G. Landge, E. Balaraman, *Angew. Chem., Int. Ed.* **2015**, *54*, 11022−11034; b) A. Mondal, R. Sharma, D. Pal, D. Srimani, *Eur. J. Org. Chem.* **2021**, *2021*, 3690−3720; c) M. Maji, D. Panja, I. Borthakur, S. Kundu, *Org. Chem. Front.* **2021**, *8*, 2673−2709.

4. a) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681−703; b) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712; c) A. Corma, J. Navas, M. J.; Sabater, *Chem. Rev.* **2018**, *118*, 1410−1459; d) K. Das, S. Waiba, A. Jana, B. Maji, *Chem. Soc. Rev.* **2022**, *51*, 4386−4464.

5. a) D. Srimani, Y. Ben-David, D. Milstein, *Chem. Commun.* **2013**, *49*, 6632−6634; b) M. Chen, M. Zhang, B. Xiong, Z. Tan, W. Lv, H. Jiang, *Org. Lett.* **2014**, *16*, 6028−6031.

6. a) K. Junge, V. Papa, M. Beller, *Chem. - Eur. J.* **2019**, *25*, 122−143; b) A. Mukherjee, D. Milstein, *ACS Catal.* **2018**, *8*, 11435−11469; c) D. Pal, A. Mondal, D. Srimani, *Catal. Sci. Technol.* **2022**, *12*, 3202−3208.

7. I. Borthakur, A. Sau, S. Kundu, *Coord. Chem. Rev.* **2022**, *451*, 214−257.

8. a) P. Daw, Y. Ben-David, D. Milstein, *ACS Catal.* **2017**, *7*, 7456−7460; b) D. R. Pradhan, S. Pattanaik, J. Kishore, C. Gunanathan, *Org. Lett.* **2020**, *22*, 1852−1857; c) A. Mishra, A. D. Dwivedi, S. Shee, S. Kundu, *Chem. Commun.* **2020**, *56*, 249−252; d) S. P. Midya, V. G. Landge, M. K. Sahoo, J. Rana, E. Balaraman, *Chem. Commun.* **2018**, *54*, 90−93.

9. J. Marco-Contelles, E. Pérez-Mayoral, A. Samadi, M. D. C. Carreiras, E. Soriano, *Chem. Rev.* **2009**, *109*, 2652−2671.

10. P. G. Owston, S. S. Leylâ, A. T. Peter, *J. Chem. Soc., Chem. Commun.* **1982**, *1*, 17−19.

11. K. Das, A. Mondal, D. Pal, D. Srimani, *Org. Lett.* **2019**, *21*, 3223−3227.

12. a) M. Mastalir, M. Glatz, E. Pittenauer, G. Allmaier, K. Kirchner, *J. Am. Chem. Soc.* **2016**, *138*, 15543−15546; b) A. Maji, S. Gupta, M. Maji, S. Kundu, *J. Org. Chem.* **2022**, *87*, 8351–8367.

13. a) Z. Chen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang, H. Wu, *J. Org. Chem.* **2013**, *78*, 11342–11348; b) M. Chen, M. Zhang, B. Xiong, Z. Tan, W. Lv, H. Jiang, *Org. Lett.* **2014**, *16*, 6028–6031.

14. a) D. Ainembabazi, J. Horlyck, D. Dolan, M. Finn, A. F. Lee, K. Wilson, A. Voutchkova-Kostal, *ACS Sustainable Chem. Eng.* **2021**, *9*,14657−14662; b) B. Sardar, N. Biswas, D. Srimani, *Organometallics* **2023**, *42*, 55–61.

15. a) D.-K. Li, Q. Cai, R.-R. Zhou, Y.-D. Wu, A.-X. Wu, *ChemistrySelect* **2017**, *2,* 1048−1051; b) G. Sivakumar, M. Subaramanian, E. Balaraman, *ACS Sustainable Chem. Eng.* **2022**, *10*, 7362−7373; c) M. Sk, A. Bera, D. Banerjee, *ChemCatChem* **2023**, *15*, e20230041.

16. J. L. E. Brickson, *J. Am. Chem. Soc.* **1958**, *80*, 5466−5469.

17. S. A. Stoian, Y. -R. Peng, C. C. Beedle, Y.-J. Chung, G.-H. Lee, E.-C. Yang, S. Hil, *Inorg. Chem.* **2017**, *56*, 10861−10874.

18. V. A. Rao, P. C. Jain, N. Anand, R. C. Srimal, P. R. Dua, *J. Med. Chem.* **1970**, *13*, 516–522.

19. B. Chatterjee, C. Gunanathan, *Org. Lett.* **2015**, *17*, 4794−4797.

20. B. Garai, R. A. Molla, R. Mandal, B. Sundararaju, *Org. Lett.* **2023**, *25*, 2018−2023.

21. C. Zhu, M. Yi, D. Wei, X. Chen, Y. Wu, X. Cui, *Org. Lett.* **2014**, *16*, 1840−1843.

22. B. K. Sarmah, M. Konwar, D. Bhattacharyya, P. Adhikari, A. Das, *Adv. Synth. Catal.* **2019**, *361*, 5616–5625.

23. M. Bollenbach, E. Salvat, F. Daubeuf, P. Wagner, I. Yalcin, M. Humo, B. Letellier, L. J. Becker, F. Bihel, J-J. Bourguignon, P. Villa, A. Obrecht, N. Frossard, M. Barrot, M. Schmitt, *Eur. J. Med. Chem.* **2018**, *147*, 163–182.

24. R. K. Saunthwal, M. Patel, A. K. Verma, *J. Org. Chem.* **2016**, *81*, 6563−6572.

25. R. Gattu, S. Mondal, S. Ali, A. T. Khan, *Org. Biomol. Chem.* **2019**, *17*, 347–353.

26. Y. He, Z. Wu, C. Ma, X. Zhou, X. Liu, X. Wang, G. Huang, *Adv. Synth. Catal.* **2016**, *358*, 375 – 379.

27. S. -H. Kim, R. D. Rieke, *Tetrahedron* **2010**, *66*, 3135–3146.

28. A. Krasovskiy, I. Thomé, J. Graff, V. Krasovskaya, P. Konopelski, C. Duplais, B. H. Lipshutz *Tetrahedron Lett.* **2011**, *52*, 2203–2205.

29. R. Yan, X. Liu, C. Pan, X. Zhou, X. Li, X. Kang, G. Huang, *Org. Lett.* **2013**, *15*, 4876–4879.

30. Z. Hao, X. Zhou, Z. Ma, C. Zhang, Z. Han, J. Lin, G. -L. Lu, *J. Org. Chem.* **2022**, *87*, 12596−12607.

31. C. U. Maheswari, G. S. Kumar, M. Venkateshwar, R. A. Kumar, M. L. Kantam, K. R. Reddy *Adv. Synth. Catal.* **2010**, *352*, 341 – 346.

32. C. Yu, X. Guo, M. Shen, B. Shen, M. Muzzio, Z. Yin, Q. Li, Z. Xi, J. Li, C. T. Seto, S. Sun, *Angew. Chem. Int. Ed.* **2018**, *57*, 451–455.

33. J. Zhang, C. Yu, S. Wang, C. Wan, Z. Wang, *Chem. Commun.* **2010**, *46*, 5244–5246.

4.7. Selected NMR copies of the compounds:

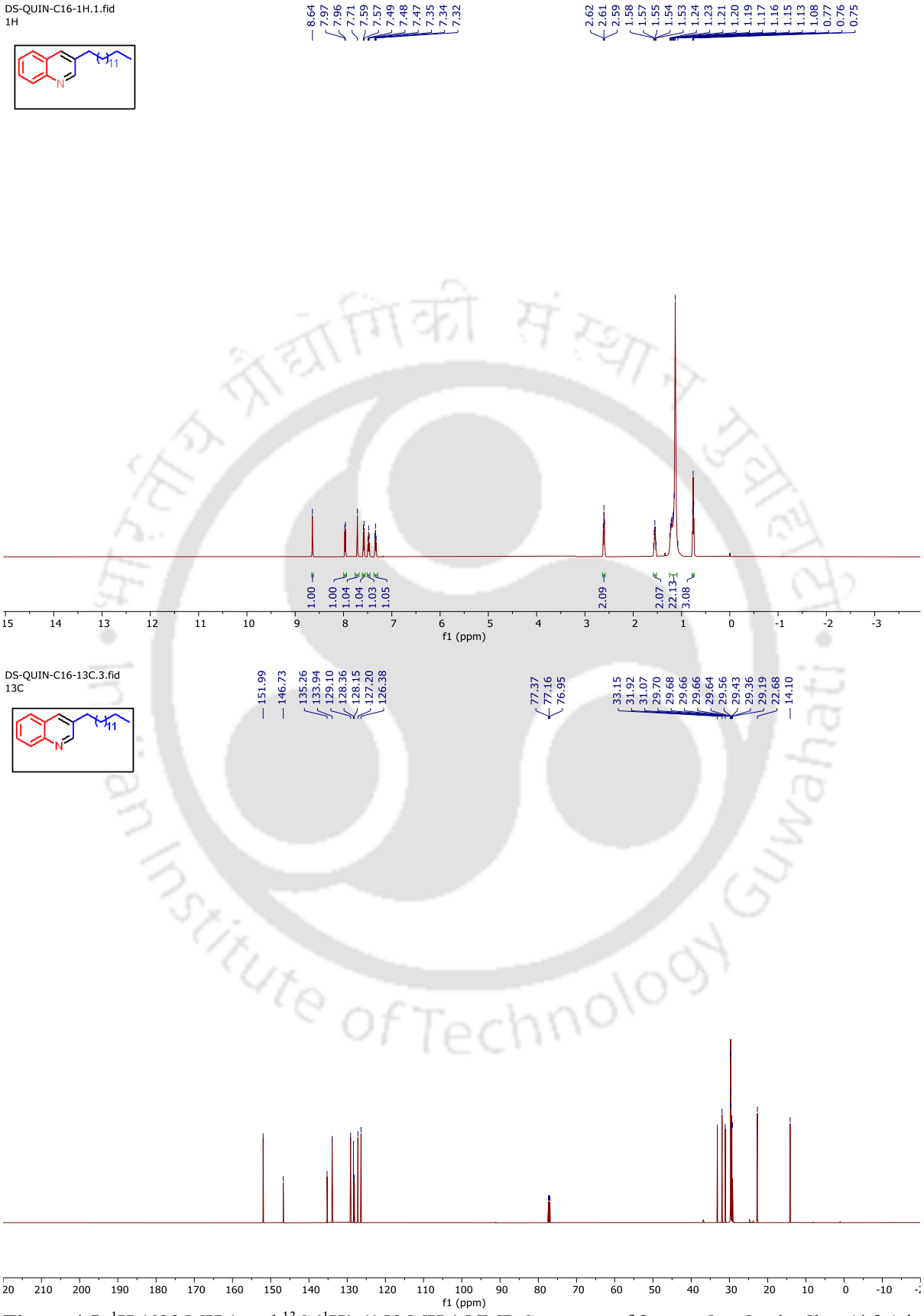


Figure 4.5. ^{1}H (600 MHz) and $^{13}C\{^{1}H\}$ (150 MHz) NMR Spectrum of **3-tetradecylquinoline (4.3z)** in $CDCl_3$.

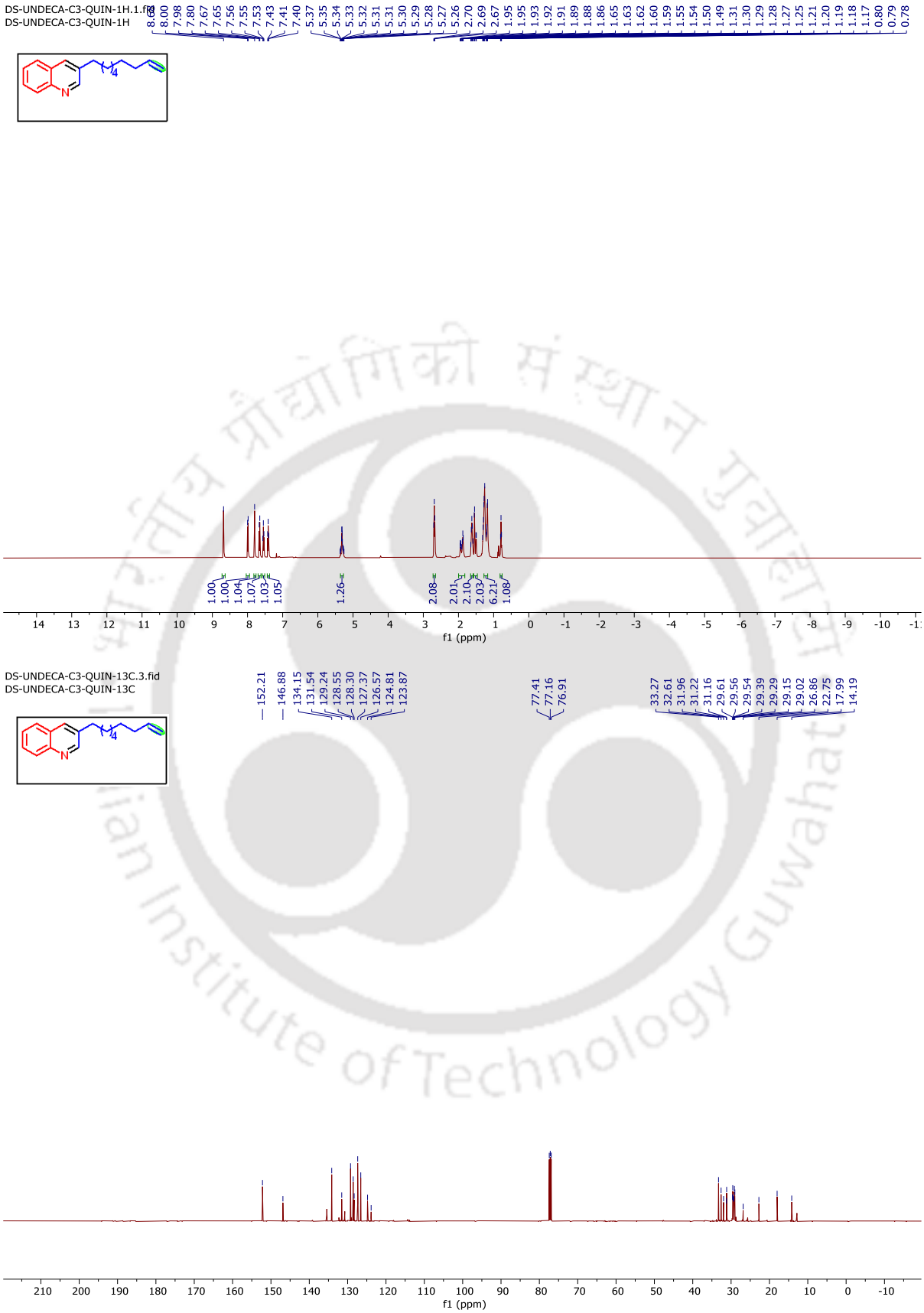


Figure 4.6. ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of **3-(non-8-en-1-yl)quinoline (4.3zd)** in $CDCl_3$.

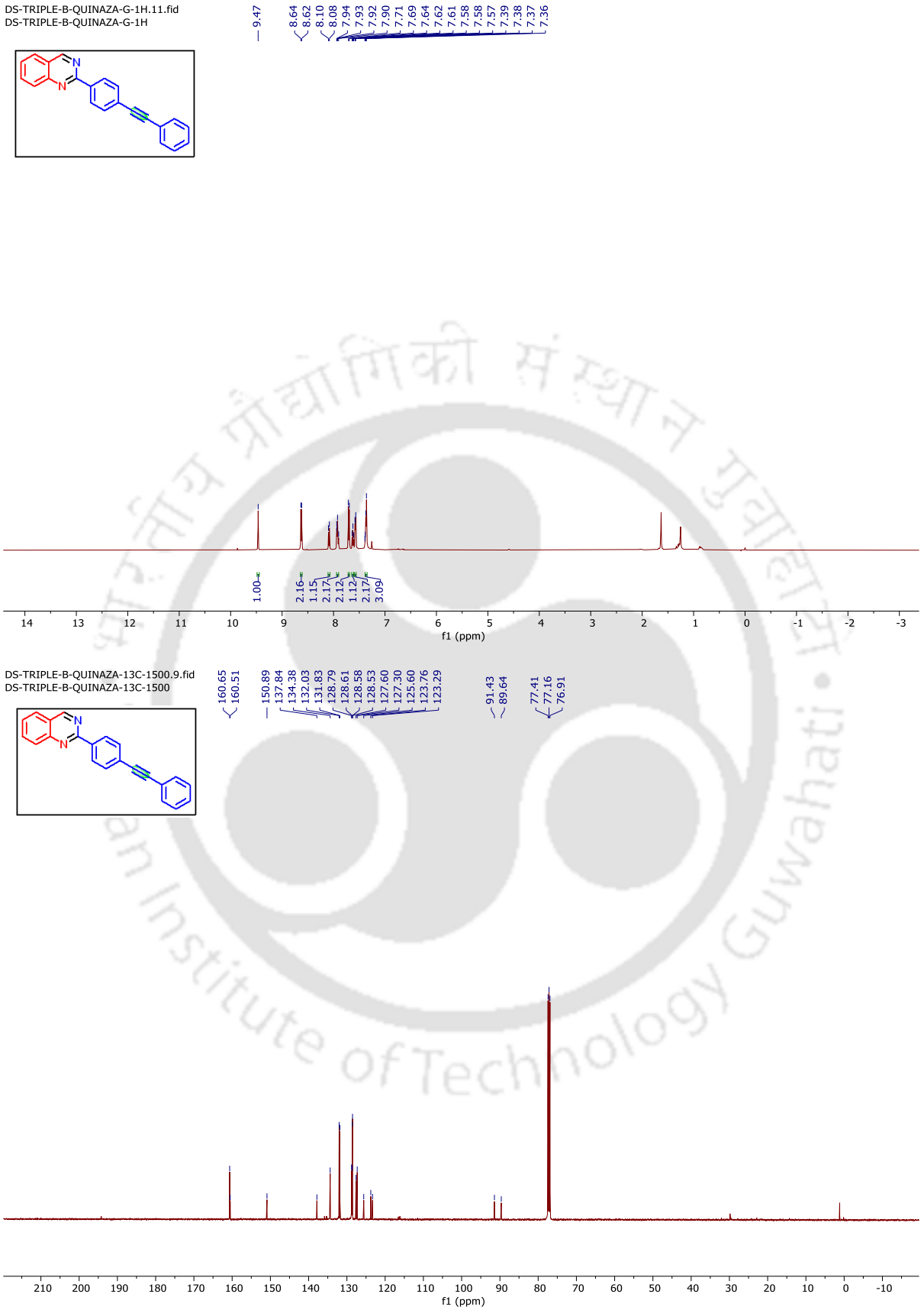


Figure 4.7. ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of **2-(4-(phenylethynyl)phenyl)quinazoline (4.11m)** in $CDCl_3$.

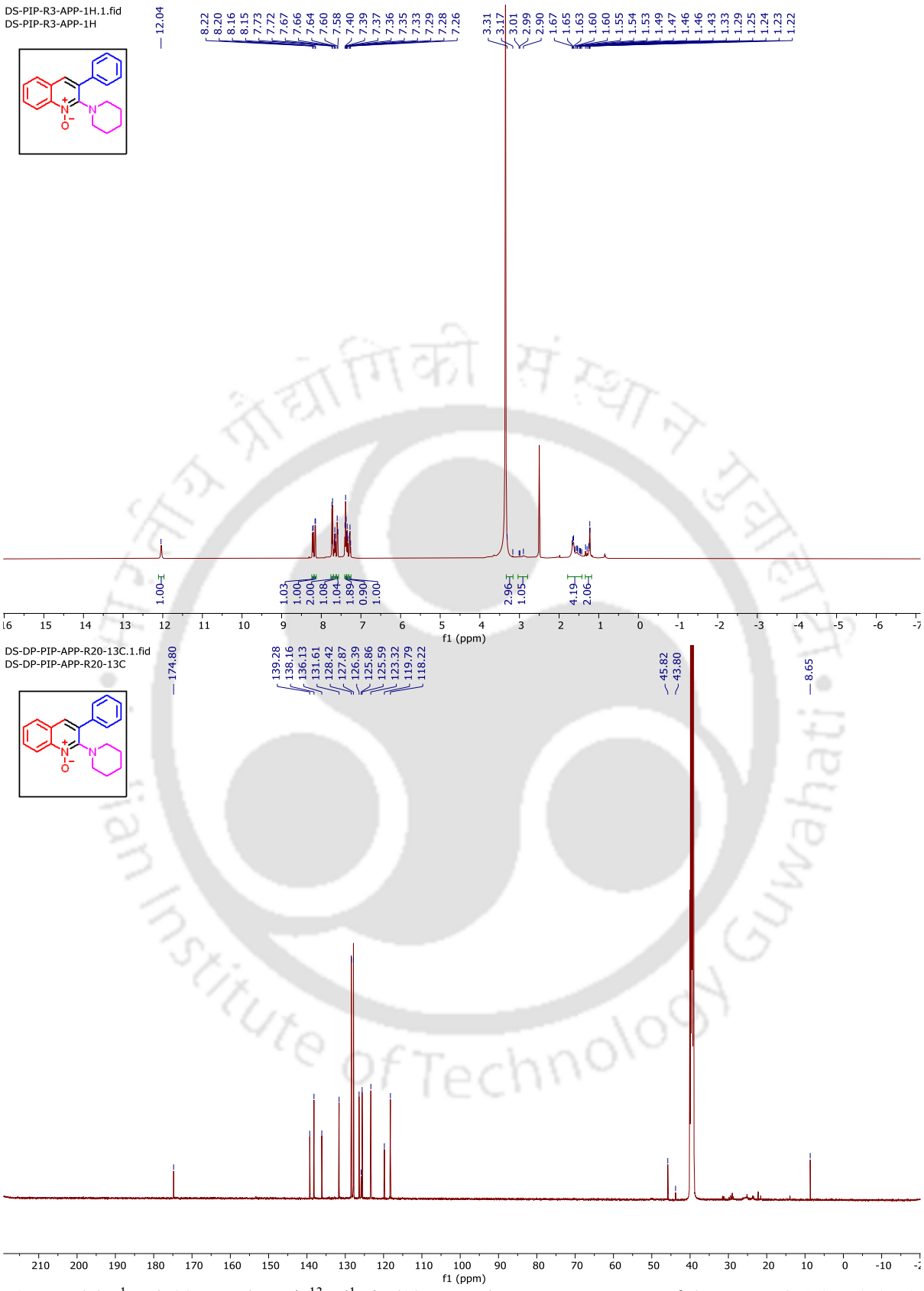


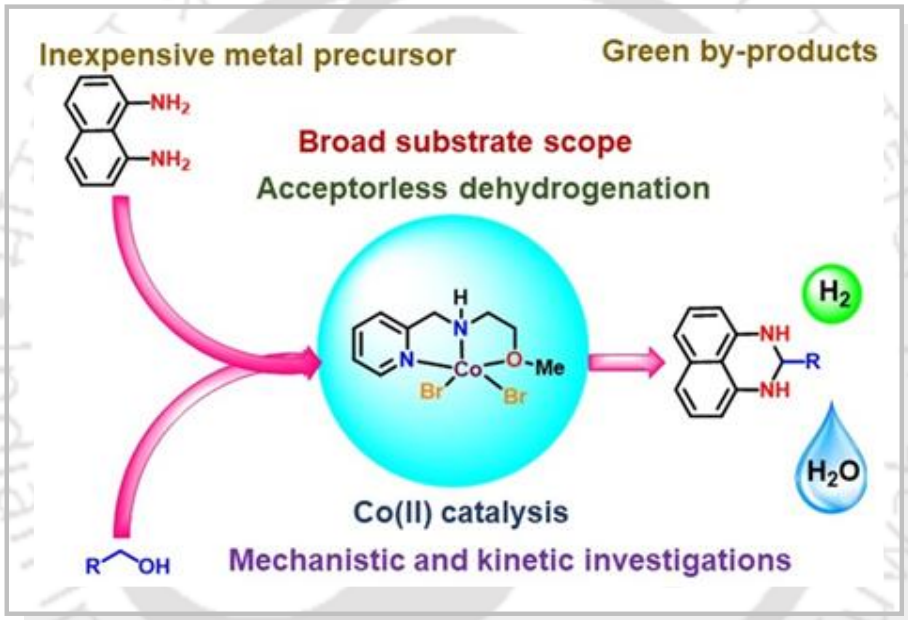
Figure 4.8. ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of **3-phenyl-2-(piperidin-1-yl)quinoline 1-oxide (4.5)** in DMSO-d_6.

4.8. Important crystal parameters of Co-8, Co-9 and Co-10:

	Co-8	**Co-9**	**Co-10**
Empirical formula	$C_9 H_{14} Br_2 Co N_2 O$	$C_{18} H_{28} Br_4 Co_2 N_4 O_2$	$C_{13} H_{15} Br_2 Co N_2 O$
Formula weight	384.97	769.94	434.00
Temperature, T	295 K	275 K	298 K
Crystal system	monoclinic	monoclinic	monoclinic
Space group	P 21/n	P 21/n	P 1 21/n 1
Unit cell dimensions	a= 8.132(3)Å, α= 90° b=11.134(4)Å, β=95.186(11)° c= 14.525(5)Å, γ= 90°	a=8.0193(5)Å, α= 90° b=13.3037(8)Å, β= 96.579(2)° c=11.5040(7)Å, γ= 90°	a=18.917(4) Å, α= 90 ° b=11.038(2)Å, β= 74.16(3)° c=15.945(3) (7)Å, γ= 90 °
Volume, V (Å3)	1309.8(8)	1219.24(13)	3203.0(12)
Z	4	2	8
Index ranges	$-9 \le h \le 9$, $-13 \le k \le 13$, $-17 \le l \le 17$	$-9 \le h \le 9$, $-15 \le k \le 15$, $-13 \le l \le 13$	$-22 \le h \le 22$, $-13 \le k \le 13$, $-18 \le l \le 18$
Final R indices [I>2sigma(I)]	R1= 0.0362(1708), wR2= 0.0915(2310)	R1= 0.0175(2057), wR2= 0.0451(2137)	R1 = 0.0909(3389), wR2= 0.1815(5638)
R indices (all data)	R1= 0.0185, wR2= 0.0445	R1= 0.0610, wR2= 0.0832	R1= 0.1572, wR2= 0.1673

Chapter 5

Well-defined Cobalt(II) Catalyzed Synthesis of 2,3-Dihydro-1H-Perimidines via Acceptorless Dehydrogenative Annulation



D. Pal, R. Sarmah, A. Mondal, I. Mallick, D. Srimani, *Org. Biomol. Chem.* **2024**, *22*, 8602–8607

5.1. Introduction:

The synthesis of N-containing heterocycles has piqued a lot of interest as they are the key structural units of various natural alkaloids, hormones, amino acids,[1] essential product of everyone daily lives[2] and have a distinctive ability to exhibit numerous applications in the field of medicinal and agricultural chemistry.[3] N-containing tricyclic perimidine scaffolds are ubiquitous in both synthetic and natural products, displaying a broad spectrum of biological activity.[4] De Aguiar discovered the perimidine moiety for the first time in 1874, and Sachs conducted a thorough investigation in 1909.[5] Since then, this heterocyclic motif has attracted significant attention for its prolific biological and pharmaceutical activities. Perimidine derivatives behave as an antitumor agent against the MCF-7 breast cancer cell line and HEPG-2 liver cancer cell line and also have antimicrobial, antifungal, antiulcer properties.[6] Apart from that, the perimidine moiety was also identified as a DNA-intercalating agent, fluorescent chemo-sensors and stoppers for supramolecules[7] an corrosion inhibitor (Figure **5.1**).[8]

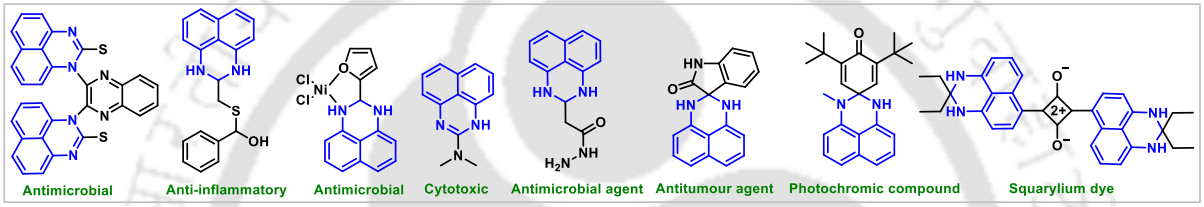


Figure 5.1. Representative examples of some important compounds bearing perimidine scaffold.

Due to the prevalence of this scaffold, the creation of new routes to attain this tricyclic N-heterocycle moiety remains a subject of current research.

5.2. Literature survey:

The classical approach involves the condensation reaction of 1,8-diaminonapthalene with a carbonyl group in presence of a Lewis or mineral acid[9] such as $Zn(OAc)_2$ $.2H_2O$,[9a] $NiCl_2$ $.6H_2O$,[9b] 2% W nano-CuY Zeolite,[9c] SiO_2 nanoparticles,[9d] nickel-decorated SBA-15 nanocomposite,[9e] Fe_3O_4 nanoparticles immobilized on zeolite – SO_3H,[9f] chitosan hydrochloride and so forth.[9g] Herein, in this chapter, one of the literature reports was delineated.

In 2019, *Kalhor and co-workers* developed a magnetic solid acid catalyst using Fe_3O_4 magnetic nanoparticles supported on zeolosulforic nanocomposite and applied them towards the synthesis of 2,3-dihydro-1*H*-perimidines (DHPs). After several screening the author found the optimal reaction condition in which equimolar ratio of benzaldehyde and 1,8-diaminonapthalene in presence of 0.008 g of Fe_3O_4/SO_3H@zeolite-Y in the ethanol solvent at 4 min delivered 98% yield of the desired product (Scheme **5.1**).[9f]

Scheme 5.1. Fe_3O_4/SO_3H@zeolite-Y- magnetic solid acid catalyzed synthesis of dihydroperimidine.

However, most of these methods suffer from prolonged reaction times, poor yields, and tedious work-up procedures, which generate plentiful waste. So, the development of new, efficient, environmentally benign and sustainable routes to access the perimidine derivatives from stable and readily accessible starting materials remains fascinating. Recently, the acceptorless dehydrogenative coupling (ADC) of alcohols derived from lignocellulosic biomass,[10] with suitable coupling partner to synthesize various heterocycles has sparked interest in green and sustainable catalysis where only H_2O and H_2 gas were formed as sole by-products.[11] Spurred by this, in Chapter I of Section, 1.4.5.1.2.1.12.1. the dehydrogenative synthesis of 2,3-dihydro-1*H*-perimidines (DHPs) by both noble metal ae well as 3d-metal was discussed.

5.3. Present work:

In chapter-4, new inexpensive, earth-abundant and nontoxic NNO-ligand-derived Co(II)-complexes were synthesized, well characterized with HRMS and SC-XRD and explored their ability in dehydrogenative reactions.[12] So, in the current chapter envisioned on developing a sustainable catalytic method for synthesizing a wide range of DHPs with the pre-synthesized cobalt(II)-complexes. Herein, Co-catalyzed synthesis of 2,3-dihydro-1*H*-perimidine derivatives via ADC of 1,8-diaminonapthalene (DAN) with diverse range of primary alcohols including benzylic, heteroaryl-containing, cyclic/acyclic aliphatic alcohols and various naturally occurring terpinols was described.

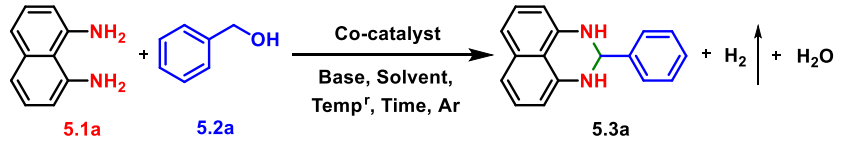
5.3.1. Results and discussion:

5.3.1.1. Synthesis of ligands and their Co-complexes:

The synthetic strategy of three ligands, their respective Co(II)-complexes and characterization techniques are mentioned in previous chapter *i.e.* in chapter-4 of section 4.3.1.1. in a detailed way.

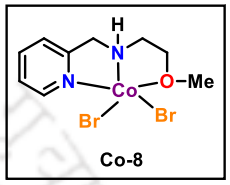
At the onset, the reactivity of three phosphine free NNO-Co(II) complexes towards the dehydrogenative construction of DHP derivatives was investigated. The screening of the reaction conditions was done by employing 1,8-diaminonapthalene (**5.1a**) and benzyl alcohol (**5.2a**) as substrates to obtain maximum yields. An equimolar mixture of 1,8-diaminonapthalene (**5.1a**) and benzyl alcohol (**5.2a**) generated a 64% isolated yield 2-phenyl-2,3-dihydro-1*H*-perimidine (**5.3a**) after 36 h reflux in xylene solvent at 140°C with 5 mol% of **Co-8** and 1.0 equiv. of KO^{t}Bu. (Table 5.3.1.2, entry 1). Upon increasing the amount of benzyl alcohol (**5.2a**) from 1.0 equiv. to 1.2 equiv. an increment in the yield from 64% to 78% was observed, however, furthermore increasing the yield remained similar (Table 5.3.1.2, entry 2-3). Afterwards, keeping other parameters intact upon decreasing the base loading (1 equiv. to 0.75 equiv.) it furnished a similar yield of **5.3a** (Table 5.3.1.2, entry 4), however, additional decrease of the base showed a detrimental effect (Table 5.3.1.2, entry 5). Later, several reaction parameters such as catalyst loading, reaction time, temperature, nature of base, solvent was screened, nevertheless, none of them was able to raise the yield (Table 5.3.1.2, entry 6-16). The catalytic applicability of other two as prepared catalysts *i.e.* **Co-9** and **Co-10** have also checked albeit both of them manifested

Table 5.3.1.2: Reaction Optimization for the Co-catalyzed synthesis of 2,3-Dihydro-1*H*-Perimidine[a]

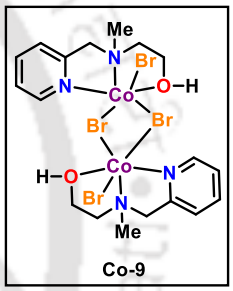


5.1a 5.2a 5.3a

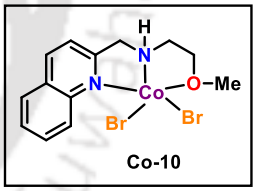
Entry	Cat. (mol%)	Solvent	Base (equiv.)	5.1a:5.2a	Temp (°C)	Time (h)	Yield[b] (%)
1.	Co-8 (5)	Xylene	KO^{t}Bu(1.0)	1:1	140	36	64
2.	Co-8 (5)	Xylene	KO^{t}Bu(1.0)	1:1.2	140	36	78
3.	Co-8 (5)	Xylene	KO^{t}Bu(1.0)	1:1.5	140	36	78
4.	Co-8 (5)	Xylene	KO^{t}Bu(0.75)	1:1.2	140	36	78
5.	Co-8 (5)	Xylene	KO^{t}Bu(0.5)	1:1.2	140	36	62
6.	Co-8 (4)	Xylene	KO^{t}Bu(0.75)	1:1.2	140	36	67
7.	Co-8 (5)	Xylene	KO^{t}Bu(0.75)	1:1.2	140	24	60
8.	Co-8 (5)	Xylene	KO^{t}Bu(0.75)	1:1.2	120	36	64
9.	Co-8 (5)	Xylene	NaO^{t}Bu(0.75)	1:1.2	140	36	65
10.	Co-8 (5)	Xylene	KOH(0.75)	1:1.2	140	36	68
11.	Co-8 (5)	Xylene	NaOH(0.75)	1:1.2	140	36	55
12.	Co-8 (5)	Xylene	CsOH(0.75)	1:1.2	140	36	46
13.	Co-8 (5)	Xylene	K_2CO_3(0.75)	1:1.2	140	36	35
14.	Co-8 (5)	Xylene	Na_2CO_3(1.0)	1:1.2	140	36	28
15.	Co-8 (5)	Toluene	KO^{t}Bu(0.75)	1:1.2	140	36	56
16.	Co-8 (5)	^{t}AmOH	KO^{t}Bu(0.75)	1:1.2	140	36	N.D.
17.	Co-9 (2.5)	Xylene	KO^{t}Bu(0.75)	1:1.2	140	36	63
18.	Co-10 (5)	Xylene	KO^{t}Bu(0.75)	1:1.2	140	36	61
19.	-	Xylene	KO^{t}Bu(0.75)	1:1.2	140	36	18
20.	Co-8 (5)	Xylene	-	1:1.2	140	36	N.D.
21.	$CoBr_2$ (5)	Xylene	KO^{t}Bu(0.75)	1:1.2	140	36	15



Co-8



Co-9

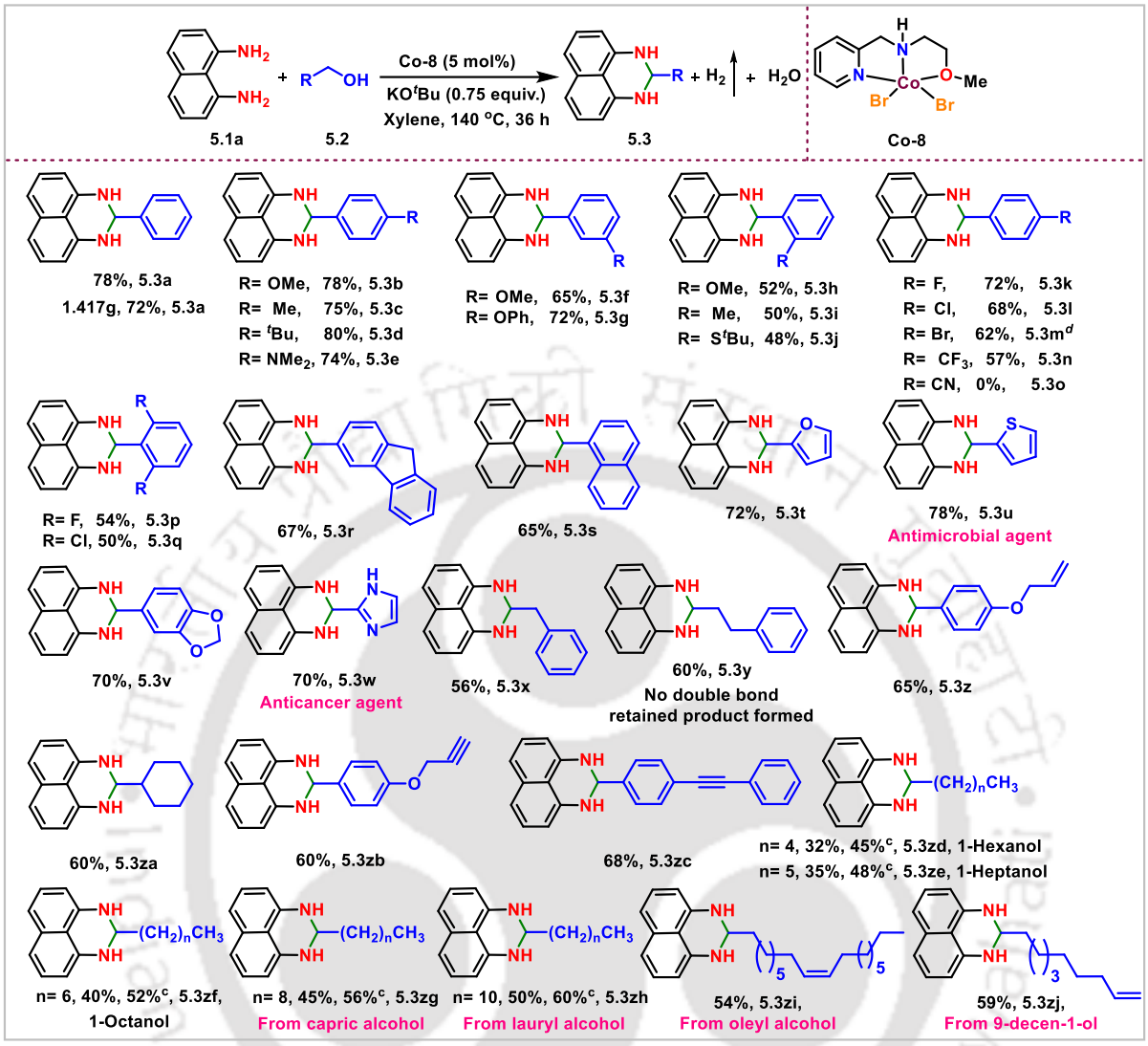


Co-10

[a] Reaction conditions: **5.1a** (0.5 mmol), **5.2a** (0.5-0.75 mmol), base (0.25-0.5 mmol), Co-cat. (2.5-5 mol %), solvent = 2 ml, 120 –140 °C, preheated oil bath under argon. [b]Isolated yield. N.D. = Not detected.

lower catalytic activity under the optimal reaction condition (Table 5.3.1.2, entry 17-18). Thus, after implementing 5 mol% of **Co-8** and 0.75 equiv. of KO^{t}Bu base in xylene solvent, 1.2 equiv. of benzyl alcohol (**5.2a**) and 1.0 equiv. of 1,8-diaminonapthalene (**5.1a**) would react at 140 °C for 36 h to generate the best yield of the intended product **5.3a** (Table 5.3.1.2, entry 4). The control studies demonstrated that both the catalyst and the base were necessary to achieve a high yield of the desired **5.3a**. In presence of the metal precursor, $CoBr_2$, only 15% of product (**5.3a**) was obtained (Table 5.3.1.2, entry 19-21).

5.3.1.3. Co-catalyzed synthesis of 2,3-Dihydro-1*H*-Perimidine: substrate scope[a,b]

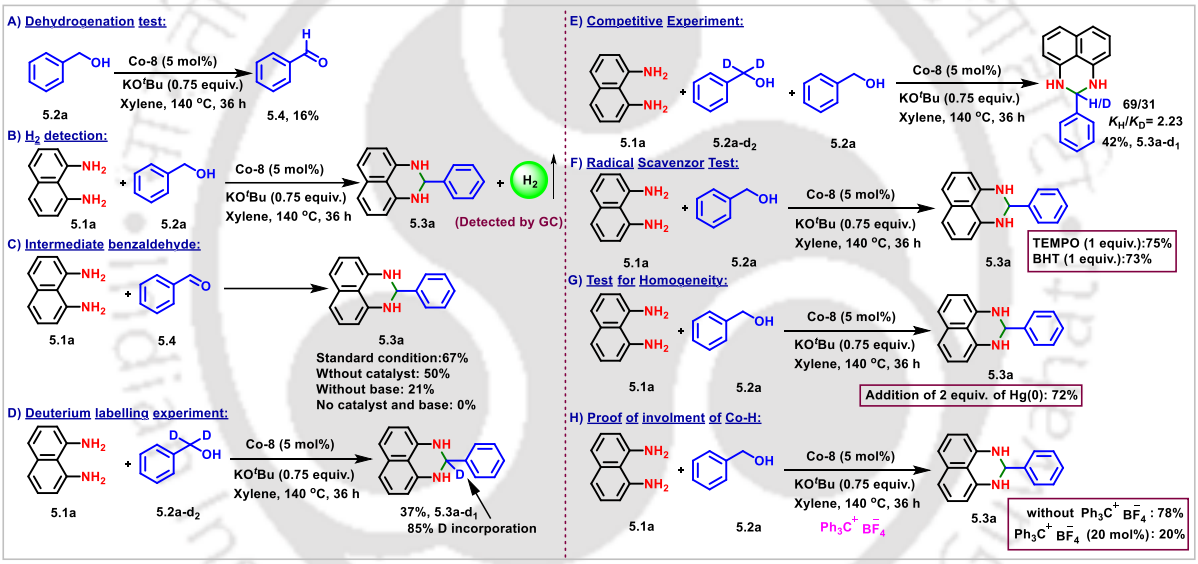


[a] Reaction conditions: **5.1a** (0.5 mmol), **5.2** (0.6 mmol), KO^{t}Bu (0.375 mmol), **Co-8** (5 mol %), Xylene (2 ml), 36 h, 140 ˚C (bath temperature), under argon, [b]Isolated yield. [c]72 h, [d]3:1 ratio of **5.3m** and its corresponding dehalogenated product (**5.3a**) was obtained.

After achieving the optimal reaction conditions, the generality of the discovered protocol was set out to explore the spectrum of potential DHP-derivative synthesis. Initially, a wide variety of benzylic alcohols with neutral and electronically biassed groups at the ortho, meta, and para-position of the phenyl ring were examined. It provided excellent yields of the desired products with good functional group tolerance (**5.3a-5.3j**). Good isolated yields were obtained with aromatic alcohols with halide substitutions, however, in case of **5.3m**, in the isolated mixture 25% of its corresponding dehalogenated product (**5.3a**) was present (**5.3k-5.3m**). Strong electron withdrawing substituent -CF_3 at *p*-position and -F at 2,6-position of phenyl ring reacted sluggishly to give moderate yield of **5.3n** and **5.3p**. However, 4-cyanobenzyl alcohol failed to deliver the desired product in the current catalytic protocol. When 2,6-dichlorobenzylalcohol was taken as a coupling partner only 50% yield was isolated (**5.3q**) probably due to steric encumbrance. Polyaromatic alcohols also afforded moderate isolated yield (**5.3r-5.3s**).

Heteroaromatic alcohols reacted smoothly to furnish the respective 2,3-dihydro-1*H*-perimidine products (**5.3t-5.3w**). Amidst of that, perimidine product **5.3u** and **5.3w** exhibit antimicrobial and anticancer activity respectively.[3c,e] Of note, the benzyl alcohol bearing reducible substituents such as, $–OCH_2CH═CH_2$, $–OCH_2C≡CH$ and –C≡C–Ph at its para-position couple chemoselectively with 1,8-diaminonapthalene (**5.1a**) accomplishing the desired product with good isolated yield without any disturbance (**5.3z, 5.3zb-5.3zc**), however, for cinnamyl alcohol the double bond hydrogenated product was obtained (**5.3y**). Interestingly, the current catalytic protocol able to activate both cyclic and acyclic aliphatic alcohols and delivered a good to moderate yields employing longer reaction time (**5.3za, 5.3zd-5.3zf**). Notably, fatty alcohols *e.g.* capric, lauryl alcohol, and naturally occurring unsaturated oleyl alcohol, 9-decen-1-ol reacted well affording the targeted heterocycles chemoselectively with good yields (**5.3zg-5.3zj**, 45-60%). Furthermore, to showcase the scalability and practical utility of the present protocol a gram-scale synthesis (**5.3a**, 72%, 1.417 g) was conducted.

5.3.1.4. Mechanistic investigation:



Scheme 5.3. Control experiments.

To gain mechanistic insight towards the synthesis of DHP, a series of control experiments were performed (Scheme **5.3**). Dehydrogenation of alcohol **5.2a** to its aldehyde (**5.4**) was observed using **Co-8** (Scheme **5.3**, A). Afterwards, the liberated H_2 gas was detected during the catalysis and confirmed by GC, which showed that the reaction involved the dehydrogenative pathway (Scheme **5.3**, B). Additionally, to demonstrate how the catalyst and base work together throughout the condensation process, reaction between benzaldehyde (**5.4**) and 1,8-diaminonapthalene (**5.1a**) was conducted (Scheme **5.3**, C). Notably, it was found that base plays an effective role in the condensation process probably by abstracting the amine proton and enhancing its nucleophilicity whereas catalyst enhances the electrophilicity of aldehyde through coordination. When 1,8-diaminonapthalene (**5.1a**) reacted with deuterated benzylalcohol-d_2 (**5.2a-d$_2$**), under standard reaction conditions, 85% of deuterium incorporation (**5a-d$_1$**) was noticed (Scheme **5.3**, D). A competition reaction was performed taking **5.2a**

and **5.2a-d$_2$** in 1:1 ratio, which resulted that K_H/K_D = 2.23, indicating that dehydrogenative transformation of benzyl alcohol (**5.2a**) to its corresponding aldehyde (**5.4**) might be the slowest step (Scheme **5.3**, E). Then, a radical scavenger experiment with TEMPO and BHT was carried out, where 75% and 73% of the desired product **5.3a** were isolated, respectively, invalidating the involvement of radical-pathway (Scheme **5.3**, F). Furthermore, the homogeneity of the present catalytic system was tested using a Hg(0) poisoning experiment, and the findings revealed no adverse impacts on the yield of the intended DHP product (**5.3a**) (Scheme **5.3**, G). In presence of 20 mol% of trityl cation (with respect to catalyst) there was a significant decrement in the yield has been noticed which underpins the involvement of Co-H species in reaction pathway (Scheme **5.3**, H).[13]

5.3.1.5. Kinetic experiments:

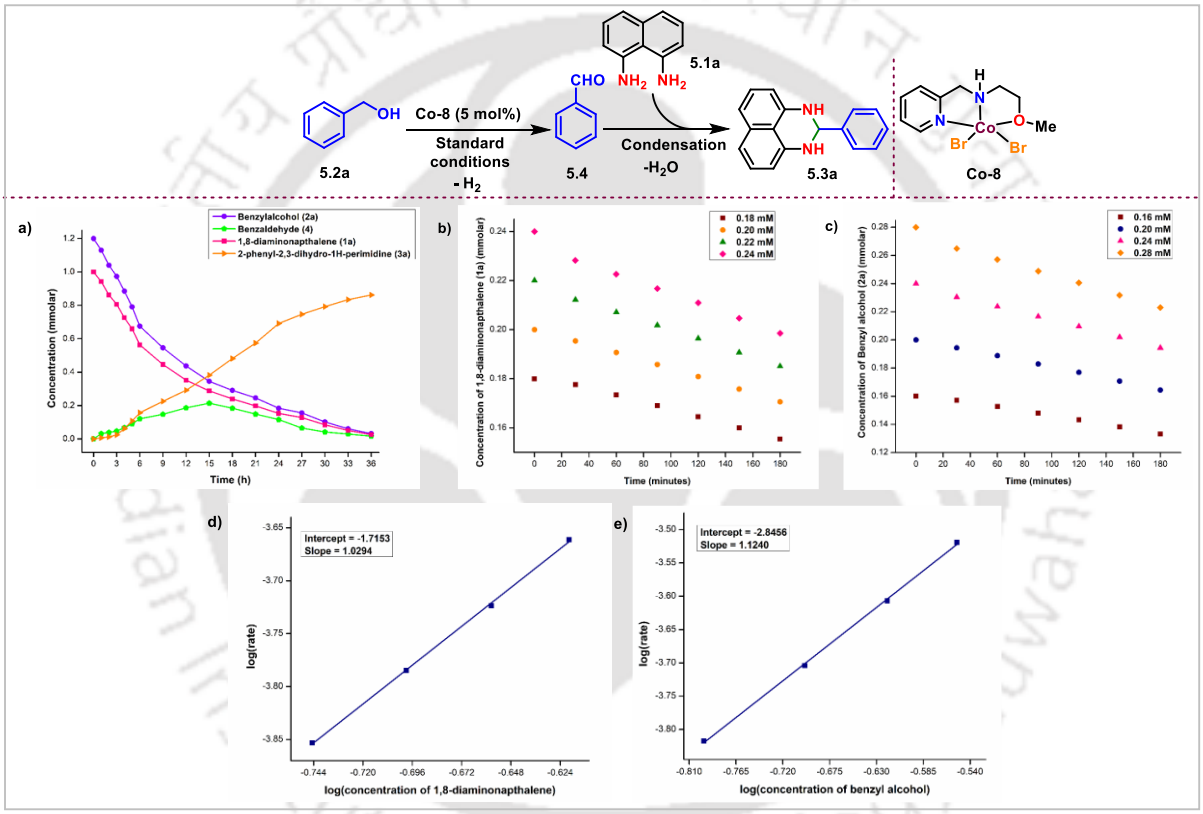
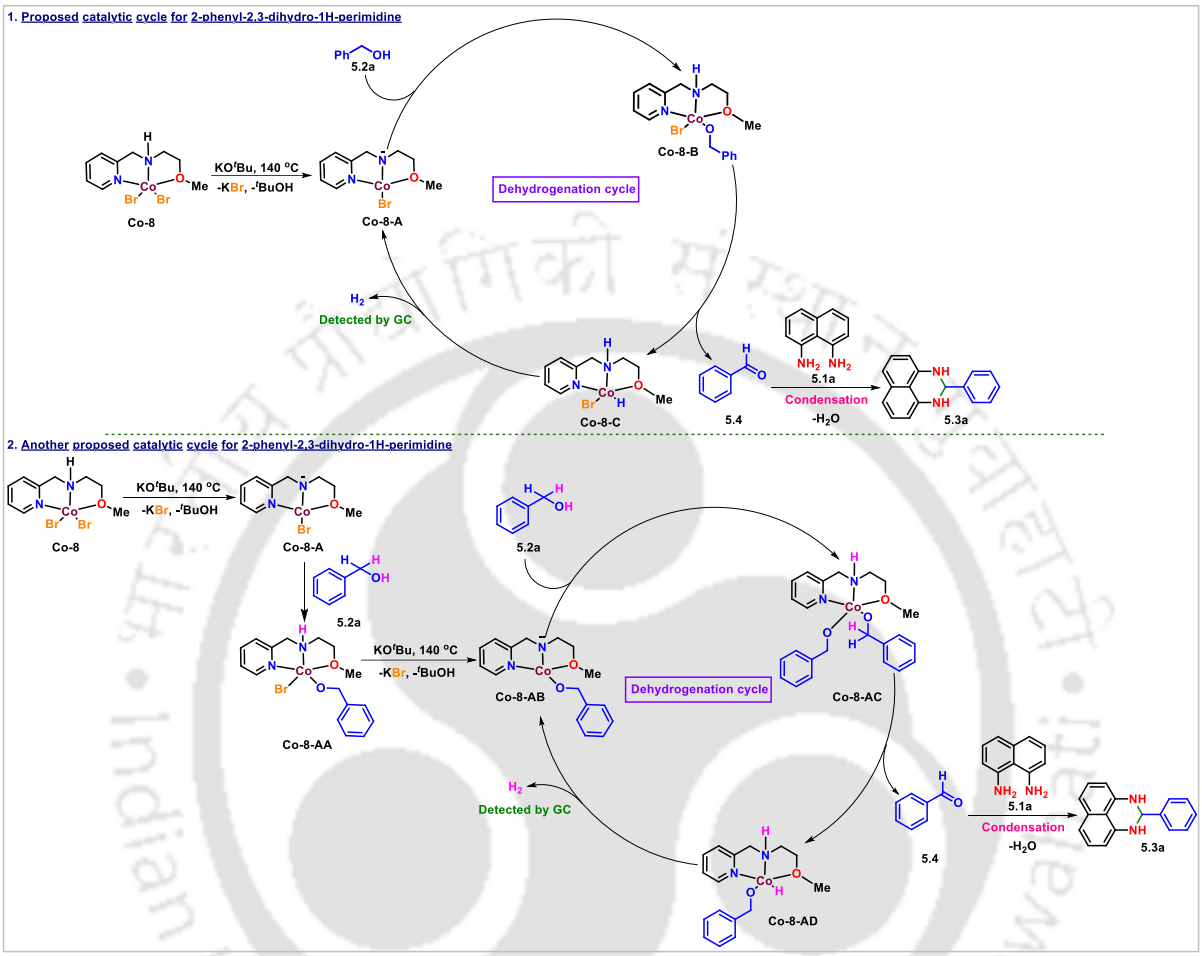


Figure 5.2. a) Kinetic profile of Co-catalyzed ADC of 1,8-diaminonapthalene **5.1a** and benzyl alcohol **5.2a** towards the synthesis of 2-phenyl-2,3-dihydro-1*H*-perimidine **5.3a**; b) Concentration vs time plot at various concentration of **5.1a**; c) Concentration vs time plot at various concentration of **5.2a**, d) log(rate) vs log (conc. of **5.1a**), e) log(rate) vs log (conc. of **5.2a**).

Time-dependent kinetic experiments were conducted to investigate the reactivity pattern of the Co-catalyzed ADC reaction. (Figure **5.2**). The kinetic monitoring displayed that the concentration of the *in situ* generated aldehyde **5.4** gradually increases and accumulation of it maximum at 9 h which gradually converted to the product **5.3a** formation (Figure **5.2**, a). Furthermore, an initial rate approach was used to determine the rate order for acceptorless dehydrogenative annulation (ADA) process to understand

the role of both the reactants **5.1a** and **5.2a** in this catalysis. This data suggests that the reaction is first order with respect to both 1,8-diaminonapthalene (**5.1a**) and benzyl alcohol (**5.2a**) (Figure **5.2**, b, **5.2**, c, **5.2**, d and **5.2**, e).

5.3.1.6. Proposed catalytic cycle:



Scheme 5.4. Plausible catalytic cycle.

Based on the previous literature reports and current control studies a plausible catalytic cycle was proposed where the in situ formation of cobalt hydride (**Co-8-C**) was responsible for the dehydrogenative transformation of alcohol **5.2a** to its corresponding aldehyde **5.4** which undergoes condensation with diamine **5.1a** to afford the desired 2-phenyl-2,3-dihydro-1*H*-perimidine (**5.3a**) upon liberating one water molecule (Scheme **5.4**, 1). Again, the Co(II)-alkoxy species also may behave as an active catalyst in the synthesis of intended product 2-phenyl-2,3-dihydro-1*H*-perimidine (**5.3a**) (Scheme **5.4**, 2).[14]

5.4. Conclusion:

In conclusion, herein, the present chapter presented cobalt complexes catalyzed dehydrogenative annulation between alcohol and 1,8-diaminonapthalene for synthesizing perimidine derivatives. A number of kinetic and control studies were conducted in order to understand the reaction pathway. The developed method exhibits wide range of substrate scope and the chemoselective transformation of

different fatty alcohols to produce perimidines with distal unsaturation demonstrates the utility of the approach.

5.5. Experimental Section:

5.5.1. Preparation of ligands and Co-complexes (Co-8, Co-9 and Co-10):

The synthetic procedures and their characterization data are described in chapter-4 (experimental section 4.5.1. and 4.5.2.).

5.5.2. General experimental procedure for the synthesis of 2,3-Dihydro-1*H*-Perimidine derivatives:

To an oven dried 10 mL round bottomed flask, 1,8-diaminonapthalene **5.1a** (0.50 mmol, 1.0 equiv.), primary aryl or alkyl alcohols **5.2** (0.60 mmol, 1.2 equiv.), KO^{t}Bu (0.042 g, 0.375 mmol, 0.75 equiv.) and **Co-8** (0.010 g, 0.025 mmol, 5 mol%) were taken under argon atmosphere, afterwards 2 ml of xylene was added to the reaction mixture. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography using 5-60% ethyl acetate in Petroleum ether as an eluent to get the desired products.

5.5.3. Cobalt catalyzed dehydrogenation of alcohol:

To an oven dried 10 mL round bottomed flask, Benzyl alcohol **5.2a** (0.108 g, 1.0 mmol, 1.0 equiv.), KO^{t}Bu (0.084 g, 0.75 mmol, 0.75 equiv.) and **Co-8** (0.020 g, 0.05 mmol, 5 mol%) were taken under argon atmosphere, afterwards 2 mL of xylene was added to the reaction mixture. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude reaction mixture was submitted and analysed by ^{1}H-NMR confirming that 16% of Benzaldehyde **(5.4)** was detected.

5.5.4. Detection of evolved gas by GC-Thermal Detector (GC-TCD):

A mixture of 1,8-diaminonapthalene **5.1a** (0.316 g, 2.0 mmol, 1.0 equiv.), benzyl alcohol **5.2a** (0.260 g, 2.4 mmol, 1.2 equiv.), KO^{t}Bu (0.168 g, 1.5 mmol, 0.75 equiv.) were taken in an oven dried Ace pressure tube (100 mL) containing a stirring bar and connected with high vacuum for 10 mins, then **Co-8** (0.039 g, 0.1 mmol, 5 mol%) and 5 mL of xylene was added to the mixture under gentle flow of argon. Afterwards, the reaction mixture was kept for stirring into preheated oil bath at 140 °C for next 36 h. After completion of the reaction, the Ace pressure tube was cooled at 0 °C, the evolved gas was syringe out and detected from PerkinElmer clarus-590 GC instrument using Elite Plot-Q column (30 m length x 530 µm x 20 µm ID) employing the following method:

TCD starting temperature: 40 °C, Oven temperature: 60 °C, Time at starting temperature: 0 min,

Hold time: 5 min, Ramp: 28 °C/ min up to 200 °C, Flow rate: 5 ml/ min (N_2), Split ration: 20

Inlet temperature: 40 °C, Detector temperature TCD: 200 °C

The detected gas chromatogram was shown in figure **5.3.** (right).

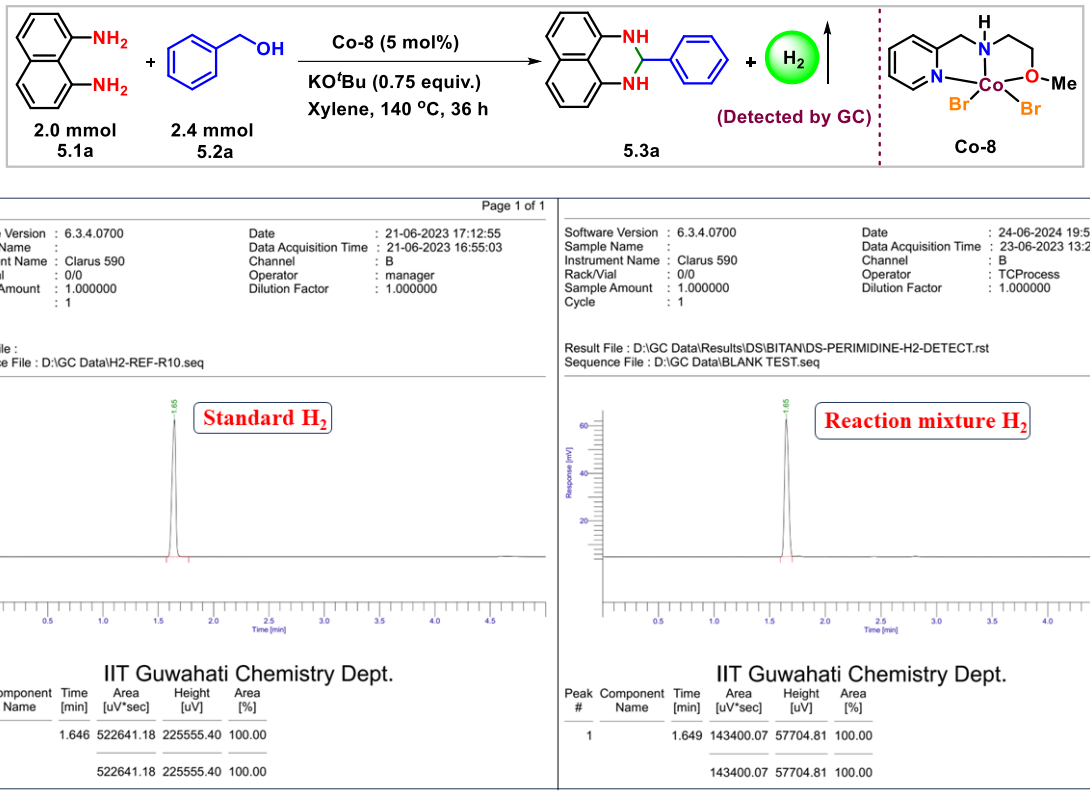


Figure 5.3. Chromatogram of standard hydrogen gas (left) and evolved hydrogen gas during catalysis (right).

5.5.5. Cobalt catalyzed synthesis of 2-phenyl-2,3-dihydro-1*H*-perimidine (5.3a) from 1,8-diaminonapthalene (5.1a) and benzaldehyde (5.4):

To an oven dried 10 mL round bottomed flask, 1,8-diaminonapthalene **5.1a** (0.079 g, 0.50 mmol, 1.0 equiv.), benzaldehyde **5.4** (0.064 g, 0.60 mmol, 1.2 equiv.), KO^{t}Bu (0.042 g, 0.375 mmol, 0.75 equiv.) and **Co-8** (0.010 g, 0.025 mmol, 5 mol%) were taken under argon atmosphere, afterwards 2 mL of xylene was added to the reaction mixture. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 2-phenyl-2,3-dihydro-1*H*-perimidine **(5.3a)** in 67% yield (0.083 g, 0.335 mmol) as a white solid. When the reaction was conducted either in absence of **Co-8** or in absence of KO^{t}Bu, it only furnished 50% (0.062 g, 0.25 mmol) and 21% yield (0.026 g, 0.105 mmol) of the desired product **5.3a** respectively, however, in absence of both **Co-8** and KO^{t}Bu no detectable conversion of the desired product **5.3a** was observed.

5.5.6. Cobalt catalyzed synthesis of 2-phenyl-2,3-dihydro-1*H*-perimidine-2-*d* (5.3a-d_1) from 1,8-diaminonapthalene (5.1a) and phenylmethan-d_2-ol (5.2a-d_2):

To an oven dried 10 mL round bottomed flask, 1,8-diaminonapthalene **5.1a** (0.079 g, 0.50 mmol, 1.0 equiv.), phenylmethan-d_2-ol **5.2a-d_2**[15] (0.066 g, 0.60 mmol, 1.2 equiv.), KO^{t}Bu (0.042 g, 0.375 mmol, 0.75 equiv.) and **Co-8** (0.010 g, 0.025 mmol, 5 mol%) were taken under argon atmosphere, afterwards 2 mL of xylene was added to the reaction mixture. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the 2-phenyl-2,3-dihydro-1*H*-perimidine-2-*d* **(5.3a-d_1)** in 37% yield (0.049 g, 0.20 mmol) as a white solid with 85% deuterium incorporation. The percentage of deuterium incorporation was analysed using ^{1}H NMR spectroscopy.

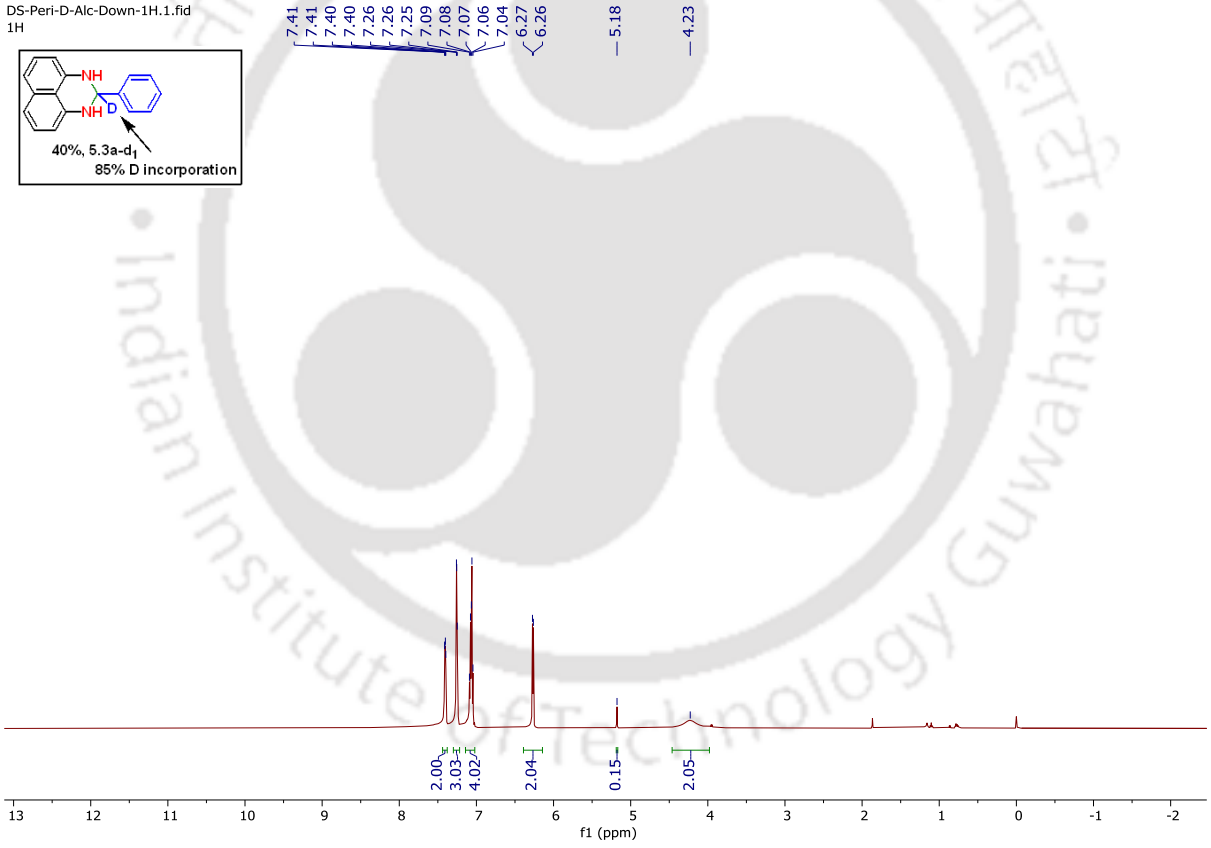


Figure 5.4. ^{1}H (400 MHz) NMR Spectrum of **2-phenyl-2,3-dihydro-1*H*-perimidine-2-*d* (5.3a-d_1)** in $CDCl_3$.

5.5.7. Competitive Experiment:

To an oven dried 10 mL round bottomed flask, 1,8-diaminonapthalene **5.1a** (0.079 g, 0.50 mmol, 1.0 equiv.), phenylmethan-d_2-ol **5.2a-d_2** (0.066 g, 0.60 mmol, 1.2 equiv.), benzyl alcohol **5.2a** (0.065 g, 0.60 mmol, 1.2 equiv.), KO^{t}Bu (0.042 g, 0.375 mmol, 0.75 equiv.) and **Co-8** (0.010 g, 0.025 mmol, 5

mol%) were taken under argon atmosphere, afterwards 2 mL of xylene was added to the reaction mixture. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford a mixture of 2-phenyl-2,3-dihydro-1*H*-perimidine **(5.3a)** and 2-phenyl-2,3-dihydro-1*H*-perimidine-2-*d* **(5.3a-d$_1$)** in 42% yield as a white solid. The experiment revealed that the value of KIE= k_H/k_D= 2.23.

5.5.8. Radical involvement test in the catalysis:

To an oven dried 10 mL round bottomed flask, 1,8-diaminonapthalene **5.1a** (0.079 g, 0.50 mmol, 1.0 equiv.), benzyl alcohol **5.2a** (0.065 g, 0.60 mmol, 1.2 equiv.), KO^{t}Bu (0.042 g, 0.375 mmol, 0.75 equiv.), **Co-8** (0.010 g, 0.025 mmol, 5 mol%) and TEMPO or BHT (0.078 g or 0.110 g, 0.50 mmol, 1.0 equiv.) were taken under argon atmosphere, afterwards 2 mL of xylene was added to the reaction mixture. The reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 2-phenyl-2,3-dihydro-1*H*-perimidine **(5.3a)** as a white solid. (for TEMPO, 75% yield, 0.092 g, 0.375 mmol and for BHT, 73% yield, 0.090 g, 0.365 mmol).

5.5.9. Homogeneity test:

To an oven dried 10 mL round bottomed flask, 1,8-diaminonapthalene **5.1a** (0.079 g, 0.50 mmol, 1.0 equiv.), benzyl alcohol **5.2a** (0.065 g, 0.60 mmol, 1.2 equiv.), KO^{t}Bu (0.042 g, 0.375 mmol, 0.75 equiv.) and 2.0 equiv. metallic Hg were taken together and connected with high vacuum for 10 minutes. Afterwards, **Co-8** (0.010 g, 0.025 mmol, 5 mol%) and 2 mL of xylene was added to the reaction mixture under gentle stream of argon. Then the resulting reaction mixture was heated at 140 °C in a preheated oil bath for 36 h. After completion of the reaction, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 2-phenyl-2,3-dihydro-1*H*-perimidine **(5.3a)** in 72% yield (0.089 g, 0.36 mmol) as a white solid.

5.5.10. Metal hydride trapping experiment:

To an oven dried 100 mL Ace pressure tube, 1,8-diaminonapthalene **5.1a** (0.079 g, 0.50 mmol, 1.0 equiv.), benzyl alcohol **5.2a** (0.065 g, 0.60 mmol, 1.2 equiv.), KO^{t}Bu (0.042 g, 0.375 mmol, 0.75 equiv.) and **Co-8** (0.010 g, 0.025 mmol, 5 mol%) were added sequentially inside the argon filled glove box. Afterwards 2 mL of xylene was added to the reaction mixture and the reaction mixture was allowed to

stir at room temperature. After stirring for 0.5 h, tritylium tetrafluoroborate ($Ph_3C^+ BF_4^-$) (0.033 g, 0.10 mmol, 20 mol%) was added to the reaction mixture. Then, the tube was sealed and placed at 140 °C in a preheated oil bath. After stirring for 36 h, the reaction mixture was subjected to cool at room temperature and ethyl acetate (15 mL) was added to dilute the mixture and filtered through celite. The resultant volatiles were evaporated under reduced pressure and the crude product was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 2-phenyl-2,3-dihydro-1*H*-perimidine **(5.3a)** in 20% yield (0.025 g, 0.10 mmol) as a white solid. The drastic detriment in the yield manifested that the in situ formed cobalt hydride involved in the catalytic cycle.

5.5.11. Gram scale synthesis:

To an oven dried 50 mL round bottomed flask, 1,8-diaminonapthalene **5.1a** (1.266 g, 8.0 mmol, 1.0 equiv.), benzyl alcohol **5.2a** (1.038 g, 9.6 mmol, 1.2 equiv.) and KO^{t}Bu (0.673 g, 6.0 mmol, 0.75 equiv.) were taken sequentially and connected with high vacuum for 15 minutes. Then **Co-8** (0.154 g, 0.40 mmol, 5 mol%) and 15 mL of xylene was added to the reaction mixture under gentle stream of argon. The resulting reaction mixture was heated at 140 °C in a preheated oil bath. After stirring for 36 h, the reaction mixture was subjected to cool at room temperature and ethyl acetate (30 mL) was added to dilute the mixture and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel (100−200 mesh size) column chromatography (eluent: Pet. ether/EtOAc = 95/5) to afford the desired 2-phenyl-2,3-dihydro-1*H*-perimidine **(5.3a)** in 72% yield (1.417 g, 5.6 mmol) as a white solid.

5.5.12. Kinetic experiments:

5.5.12.1. Monitoring the kinetics of the reaction:

5.5.12.1.1. Experimental procedure: To an oven dried 10 mL 2-neck round bottomed flask equipped with a condenser and a magnetic stir bar, 1,8-diaminonapthalene **5.1a** (0.791 g, 5.0 mmol, 1.0 equiv.), benzyl alcohol **5.2a** (0.649 g, 6.0 mmol, 1.2 equiv.) and KO^{t}Bu (0.421 g, 3.75 mmol, 0.75 equiv.) were taken sequentially and connected with high vacuum for 15 minutes. Then, **Co-8** (0.096 g, 0.25 mmol, 5 mol%), mesitylene (0.601 g, 5.0 mmol, 1.0 equiv.) as an internal standard and dry xylene were added to the mixture under gentle flow of argon to make up the total volume of the reaction mixture 5 mL. Afterwards, the reaction mixture was kept in a preheated oil bath for stirring at 140 °C. At regular intervals (1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 9 h, 12 h, 15 h, 18 h, 21 h, 24 h, 27 h, 30 h, 33 h, 36 h) the reaction mixture was cooled to ambient temperature and an aliquot of mixture was taken in a GC vial. The GC sample was diluted with ethyl acetate and subjected to gas chromatographic analysis. The concentration of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of the product (mmolar) *vs* time (h) plot (Figure **5.2,** a).

5.5.12.2. Rate order determination:

The initial rate method was used to determine the rate order for the synthesis of 2-phenyl-2,3-dihydro-1*H*-perimidine **5.3a** with respect to various components of the reaction. The data of the concentration (mM) *vs* time (h) plot was fitted to linear using origin pro 8.5. The slope of the linear fitted curve represents the initial rate of the reaction. The order of the reaction was determined by plotting initial rate (mM/h) *vs* concentration (mM) of that particular component.

5.5.12.2.1. Rate order determination with respect to 1,8-diaminonapthalene (5.1a):

To determine the order of the 2-phenyl-2,3-dihydro-1*H*-perimidine **5.3a** synthesis reaction, initial rates at different initial concentration of 1,8-diaminonapthalene **5.1a** were recorded.

5.5.12.2.1.1. Experimental procedure: To an oven dried 10 mL 2-neck round bottomed flask equipped with a condenser and a magnetic stir bar, benzyl alcohol **5.2a** (0.130 g, 1.2 mmol, 1.2 equiv.) and KO^{t}Bu (0.84 g, 0.75 mmol, 0.75 equiv.) were taken together and connected with high vacuum for 10 minutes. Then, **Co-8** (0.019 g, 0.05 mmol, 5 mol%), mesitylene (0.120 g, 1.0 mmol, 1.0 equiv.) as an internal standard, specific amount of 1,8-diaminonapthalene **5.1a** and dry xylene were added to the mixture under gentle flow of argon to make up the total volume of the reaction mixture 5 mL. Afterwards, the reaction mixture was kept in an oil bath of 140 °C for stirring. At regular intervals (0 min, 30 min, 60 min, 90 min, 120 min, 150 min, 180 min) the reaction mixture was cooled to ambient temperature and an aliquot of mixture was taken in a GC vial. The GC sample was diluted with ethyl acetate and subjected to gas chromatographic analysis. The concentration of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of 1,8-diaminonapthalene **5.1a** (mM) *vs* time (h) plot (Figure **5.2,** b). The rate of the reaction at different initial concentration of 1,8-diaminonapthalene **5.1a** was given below and used to plot the log(rate) *vs* log(concentration of 1,8-diaminonapthalene **5.1a**) to determine the order of the reaction with respect to 1,8-diaminonapthalene **5.1a** (Figure **5.2,** d).

5.5.12.2.2. Rate order determination with respect to benzyl alcohol (5.2a):

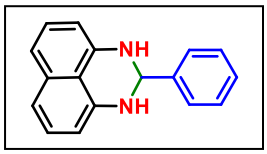
To determine the order of the 2-phenyl-2,3-dihydro-1*H*-perimidine **5.3a** synthesis reaction, initial rates at different initial concentration of benzyl alcohol **5.2a** were recorded.

5.5.12.2.2.1. Experimental procedure: To an oven dried 10 mL 2-neck round bottomed flask equipped with a condenser and a magnetic stir bar, 1,8-diaminonapthalene **5.1a** (0.158 g, 1.0 mmol, 1.0 equiv.) and KO^{t}Bu (0.84 g, 0.75 mmol, 0.75 equiv.) were taken together and connected with high vacuum for 10 minutes. Then, **Co-8** (0.019 g, 0.05 mmol, 5 mol%), mesitylene (0.120 g, 1.0 mmol, 1.0 equiv.) as an internal standard, specific amount of benzyl alcohol **5.2a** and dry xylene were added to the mixture under gentle flow of argon to make up the total volume of the reaction mixture 5 mL. Afterwards, the reaction mixture was kept in an oil bath of 140 °C for stirring. At regular intervals (0 min, 30 min, 60 min, 90 min, 120 min, 150 min, 180 min) the reaction mixture was cooled to ambient temperature and an aliquot of mixture was taken in a GC vial. The GC sample was diluted with ethyl

acetate and subjected to gas chromatographic analysis. The concentration of the product was determined with respect to mesitylene internal standard. The data was accomplished to draw the concentration of benzyl alcohol **5.2a** (mM) *vs* time (h) plot (Figure **5.2**, c). The rate of the reaction at different initial concentration of benzyl alcohol **5.2a** was given below and used to plot the log(rate) *vs* log(concentration of benzyl alcohol **5.2a**) to determine the order of the reaction with respect to benzyl alcohol **5.2a** (Figure **5.2**, e).

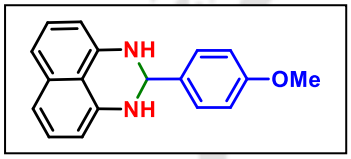
5.5.13. Analytical data for substrate scopes:

2-phenyl-2,3-dihydro-1*H*-perimidine (5.3a):[16]



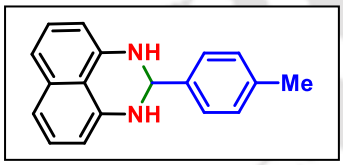
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 78% yield (0.192 g, 0.78 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.58 – 7.56 (m, 2H), 7.40 – 7.39 (m, 3H), 7.23 – 7.17 (m, 4H), 6.44 (d, *J* = 6.8 Hz, 2H), 5.37 (s, 1H), 4.45 (brs, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 142.2, 140.2, 135.0, 129.7, 128.9, 128.0, 126.9, 117.9, 113.5, 105.9, 68.4.

2-(4-methoxyphenyl)-2,3-dihydro-1*H*-perimidine (5.3b):[16]



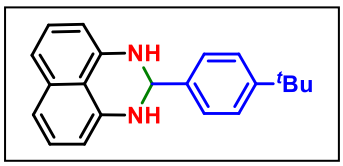
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 78% yield (0.215 g, 0.78 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.42 (d, *J* = 8.1 Hz, 2H), 7.15 – 7.09 (m, 4H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.37 (d, *J* = 7.1 Hz, 2H), 5.26 (s, 1H), 4.36 (brs, 2H), 3.72 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 160.6, 142.4, 135.0, 132.4, 129.2, 126.9, 117.8, 114.2, 113.5, 105.8, 68.0, 55.5.

2-(*p*-tolyl)-2,3-dihydro-1*H*-perimidine (5.3c):[16]



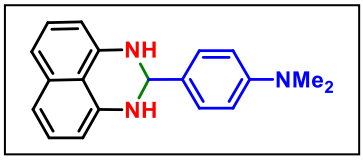
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 75% yield (0.195 g, 0.75 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.15 – 7.09 (m, 6H), 6.35 (d, *J* = 6.7 Hz, 2H), 5.26 (s, 1H), 4.34 (brs, 2H), 2.29 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 142.3, 139.5, 137.3, 135.0, 129.5, 127.9, 127.0, 117.9, 113.5, 105.9, 68.2, 21.4.

2-(4-(*tert*-butyl)phenyl)-2,3-dihydro-1*H*-perimidine(5.3d):[17]



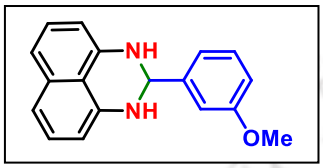
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 80% yield (0.242 g, 0.80 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.18 – 7.11 (m, 4H), 6.40 (d, *J* = 7.1 Hz, 2H), 5.35 (s, 1H), 4.41 (brs, 2H), 1.27 (s, 9H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 152.9, 142.3, 137.3, 135.1, 127.7, 127.0, 125.9, 117.9, 113.6, 105.9, 68.2, 34.9, 31.5.

4-(2,3-dihydro-1*H*-perimidin-2-yl)-N,N-dimethylaniline (5.3e):[18]



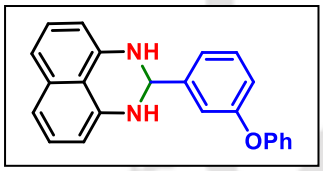
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 74% yield (0.214 g, 0.74 mmol) as a brown solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.44 (d, *J* = 8.7 Hz, 2H), 7.22 – 7.18 (m, 4H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 7.5 Hz, 2H), 5.31 (s, 1H), 4.43 (brs, 2H), 2.94 (s, 6H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 151.5, 142.7, 135.1, 128.8, 127.7, 126.9, 117.6, 113.5, 112.4, 105.7, 68.2, 40.6.

2-(3-methoxyphenyl)-2,3-dihydro-1*H*-perimidine (5.3f):[17]



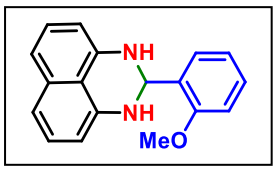
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 65% yield (0.180 g, 0.65 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.22 (t, *J* = 7.9 Hz, 1H), 7.16 – 7.10 (m, 5H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.88 – 6.85 (m, 1H), 6.39 (d, *J* = 7.0 Hz, 2H), 5.29 (s, 1H), 4.41 (brs, 2H), 3.71 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 160.1, 142.1, 141.7, 135.0, 129.9, 127.0, 120.2, 118.0, 115.7, 113.5, 112.8, 105.9, 68.4, 55.5.

2-(3-phenoxyphenyl)-2,3-dihydro-1*H*-perimidine (5.3g):



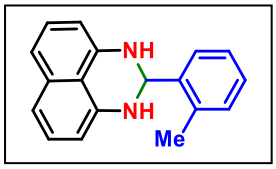
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 72% yield (0.244 g, 0.72 mmol) as a white solid. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.46 – 7.39 (m, 4H), 7.36 – 7.35 (m, 1H), 7.32 – 7.29 (m, 2H), 7.28 – 7.27 (m, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.14 – 7.11 (m, 3H), 6.54 (d, *J* = 7.5 Hz, 2H), 5.41 (s, 1H), 4.56 (brs, 2H). **^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$)** δ 157.8, 156.7, 142.1, 141.9, 134.8, 130.2, 130.0, 126.9, 123.7, 122.6, 119.7, 119.2, 118.0, 117.9, 113.4, 105.9, 68.0. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{23}H_{19}N_2O$ is 339.1497 Found 339.1480

2-(2-methoxyphenyl)-2,3-dihydro-1*H*-perimidine (5.3h):[16]



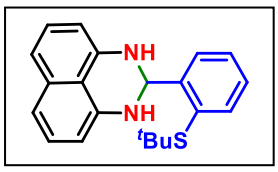
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 52% yield (0.144 g, 0.52 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 2H), 7.09 – 7.08 (m, 2H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.42 (d, *J* = 7.2 Hz, 2H), 5.80 (s, 1H), 4.55 (brs, 2H), 3.75 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 157.1, 142.2, 135.0, 129.8, 128.7, 127.5, 126.9, 121.1, 117.7, 113.5, 110.6, 106.0, 61.4, 55.6.

2-(*o*-tolyl)-2,3-dihydro-1*H*-perimidine (5.3i):[17]



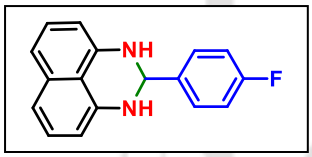
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 50% yield (0.130 g, 0.50 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.63 – 7.61 (m, 1H), 7.21 – 7.15 (m, 2H), 7.14 – 7.07 (m, 5H), 6.36 (d, *J* = 7.2 Hz, 2H), 5.56 (s, 1H), 4.28 (brs, 2H), 2.37 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 142.5, 137.6, 136.6, 135.0, 131.0, 129.1, 128.2, 126.9, 126.7, 117.9, 113.6, 106.0, 65.2, 19.2.

2-(2-(*tert*-butylthio)phenyl)-2,3-dihydro-1*H*-perimidine (3.3j):



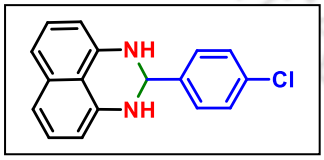
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 48% yield (0.161 g, 0.48 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.92 – 7.90 (m, 1H), 7.61 – 7.60 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.34 (td, *J* = 7.6 Hz, 1.7 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.20 – 7.18 (m, 2H), 6.49 (d, *J* = 7.0 Hz, 2H), 6.29 (s, 1H), 4.49 (brs, 2H), 1.28 (s, 9H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 145.0, 142.3, 138.9, 134.9, 131.9, 130.0, 128.9, 128.8, 127.0, 117.8, 113.4, 105.9, 64.9, 47.3, 31.1. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{21}H_{23}N_2S$ is 335.1582. Found 335.1604.

2-(4-fluorophenyl)-2,3-dihydro-1*H*-perimidine (5.3k):[16]



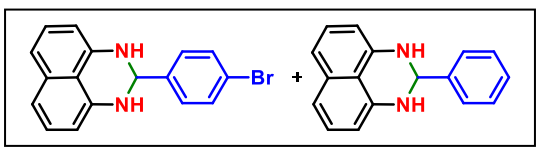
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 72% yield (0.190 g, 0.72 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.50 – 7.47 (m, 2H), 7.17 – 7.12 (m, 4H), 7.01 (t, *J* = 8.5 Hz, 2H), 6.41 (d, *J* = 6.9 Hz, 2H), 5.31 (s, 1H), 4.36 (brs, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 163.5 (d, *J* = 246.6 Hz), 142.1, 136.1 (d, *J* = 3.0 Hz), 135.0, 129.9 (d, *J* = 8.5 Hz), 127.0, 118.1, 115.8 (d, *J* = 21.5 Hz), 113.5, 106.0, 67.8. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -111.74.

2-(4-chlorophenyl)-2,3-dihydro-1*H*-perimidine (5.3l):[16]



Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 68% yield (0.191 g, 0.68 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.19 – 7.14 (m, 4H), 6.43 (d, *J* = 6.8 Hz, 2H), 5.34 (s, 1H), 4.38 (brs, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 141.9, 138.8, 135.5, 135.0, 129.4, 129.2, 127.0, 118.2, 113.5, 106.1, 67.8.

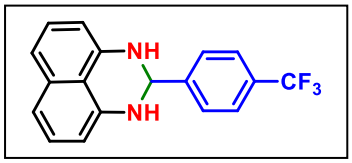
2-(4-bromophenyl)-2,3-dihydro-1*H*-perimidine (5.3m):[18]



Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 62% yield (0.202 g, 0.62 mmol) as a yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.53 – 7.51 (m, 1H), 7.46 – 7.44 (m, 2H), 7.37 – 7.35 (m, 2H), 7.34 – 7.33 (1H), 7.17 – 7.10

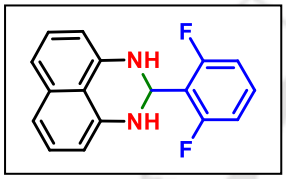
(m, 7H), 6.41 – 6.39 (m, 3H), 5.27 (s, 1H), 4.35 (brs, 3H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 142.2, 141.8, 140.2, 139.2, 135.0, 134.9, 132.1, 129.7, 128.9, 128.0, 127.0, 123.7, 118.2, 118.0, 113.6, 113.5, 106.1, 105.9, 68.5, 67.8.

2-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-perimidine (5.3n):[19]



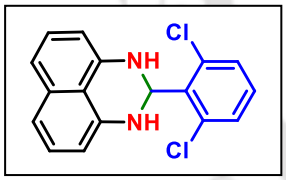
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 92/8) which afforded the title compound in 57% yield (0.179 g, 0.57 mmol) as a white solid. **^1H NMR (500 MHz, $CDCl_3$)** δ 7.71 – 7.66 (m, 4H), 7.25 – 7.21 (m, 4H), 6.52 – 6.50 (m, 2H), 5.46 (s, 1H), 4.45 (brs, 2H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 144.1, 141.6, 135.0, 131.9 (q, J = 32.3 Hz), 128.5, 127.0, 125.9 (q, J = 3.7 Hz), 124.1 (d, J = 270.7 Hz), 118.4, 113.6, 106.3, 67.8. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -62.63.

2-(2,6-difluorophenyl)-2,3-dihydro-1*H*-perimidine (5.3p):[20]



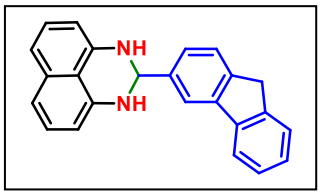
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 90/10) which afforded the title compound in 54% yield (0.152 g, 0.54 mmol) as a white solid. **^1H NMR (500 MHz, $CDCl_3$)** δ 7.27 – 7.21 (m, 1H), 7.18 – 7.15 (m, 4H), 6.85 (t, J = 8.7 Hz, 2H), 6.52 – 6.49 (m, 2H), 5.87 (s, 1H), 4.53 (brs, 2H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 161.8 (dd, J = 251.0, 7.0 Hz), 141.6, 135.0, 131.2 (t, J = 10.8 Hz), 126.8, 118.8, 115.4 (t, J = 14.5 Hz), 114.8, 112.4 (dd, J = 21.5, 4.5 Hz), 107.6, 60.3 (t, J = 3.1 Hz). **^{19}F NMR (470 MHz, $CDCl_3$)** δ -112.27.

2-(2,6-dichlorophenyl)-2,3-dihydro-1*H*-perimidine (5.3q):[20]



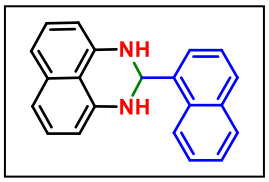
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 90/10) which afforded the title compound in 50% yield (0.158 g, 0.54 mmol) as a white solid. **^1H NMR (500 MHz, $CDCl_3$)** δ 7.40 (d, J = 8.0 Hz, 1H), 7.31 – 7.27 (m, 6H), 6.62 (dd, J = 5.9, 2.4 Hz, 2H), 6.36 (s, 1H), 4.56 (brs, 2H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 141.6, 136.6, 135.0, 133.0, 130.7, 130.1, 126.9, 118.6, 114.2, 107.5, 65.0.

2-(9*H*-fluoren-3-yl)-2,3-dihydro-1*H*-perimidine (5.3r):[21]



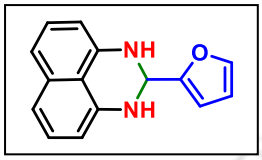
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 67% yield (0.224 g, 0.67 mmol) as a white solid. **^1H NMR (500 MHz, $CDCl_3$)** δ 7.81 – 7.79 (m, 3H), 7.58 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.26 – 7.20 (m, 4H), 6.50 (d, J = 6.9 Hz, 2H), 5.49 (s, 1H), 4.52 (brs, 2H), 3.91 (s, 2H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 144.0, 143.7, 143.3, 142.3, 141.2, 138.7, 135.1, 127.3, 127.0, 126.8, 125.3, 124.6, 120.3, 120.1, 118.0, 113.6, 106.0, 68.7, 37.0.

2-(naphthalen-1-yl)-2,3-dihydro-1*H*-perimidine (5.3s):[16]



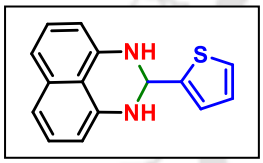
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 65% yield (0.193 g, 0.65 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.49 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 7.1 Hz, 1H), 7.42 – 7.38 (m, 3H), 7.18 – 7.13 (m, 4H), 6.40 (d, *J* = 6.3 Hz, 2H), 6.01 (s, 1H), 4.42 (brs, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 142.4, 135.2, 134.9, 134.3, 131.3, 130.2, 129.0, 127.0, 126.6, 126.5, 126.2, 125.5, 124.6, 118.0, 113.7, 106.1.

2-(furan-2-yl)-2,3-dihydro-1*H*-perimidine (5.3t):[16]



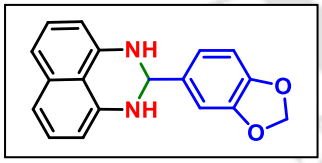
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 92/8) which afforded the title compound in 72% yield (0.170 g, 0.72 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.19 (s, 1H), 7.08– 7.03 (m, 4H), 6.31 (dd, *J* = 6.3, 2.4 Hz, 2H), 6.12 (s, 2H), 5.32 (s, 1H), 4.49 (brs, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 153.4, 142.4, 140.7, 134.6, 126.8, 118.0, 113.7, 110.4, 107.6, 106.5, 61.3.

2-(thiophen-2-yl)-2,3-dihydro-1*H*-perimidine (5.3u):[16]



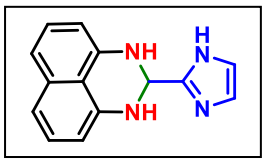
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 92/8) which afforded the title compound in 78% yield (0.197 g, 0.78 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.25 – 7.24 (m, 1H), 7.14 – 7.07 (m, 5H), 6.89– 6.88 (m, 1H), 6.37 (d, *J* = 8.2 Hz, 2H), 5.61 (s, 1H), 4.50 (brs, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 144.1, 141.4, 134.9, 127.0, 126.9, 126.5, 126.4, 118.2, 113.7, 106.2, 63.8.

2-(benzo[*d*][1,3]dioxol-5-yl)-2,3-dihydro-1*H*-perimidine (5.3v):[17]



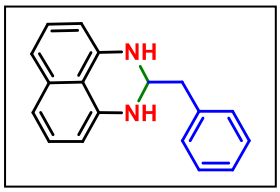
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 92/8) which afforded the title compound in 70% yield (0.203 g, 0.70 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.26 – 7.20 (m, 4H), 7.17 (s, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.50 (d, *J* = 7.0 Hz, 2H), 5.99 (s, 2H), 5.37 (s, 1H), 4.46 (brs, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 148.7, 148.3, 142.2, 135.0, 134.3, 127.0, 121.7, 118.0, 113.5, 108.3, 108.2, 105.9, 101.5, 68.2.

2-(1*H*-imidazol-2-yl)-2,3-dihydro-1*H*-perimidine (5.3w):[3e]



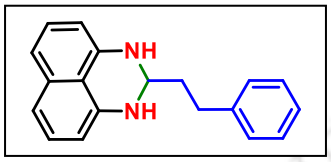
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 50/50) which afforded the title compound in 70% yield (0.184 g, 0.70 mmol) as a white solid. **^{1}H NMR (500 MHz, DMSO-d_6)** δ 12.33 (brs, 1H), 7.18 (t, *J* = 7.8 Hz, 2H), 7.04 – 7.02 (m, 4H), 6.87 (s, 2H), 6.56 (d, *J* = 7.5 Hz, 2H), 5.51 (s, 1H). **^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6)** δ 147.0, 142.6, 134.4, 127.1, 126.9 (2C), 115.7, 112.7, 104.8, 61.6.

2-benzyl-2,3-dihydro-1*H*-perimidine (5.3x):[22]



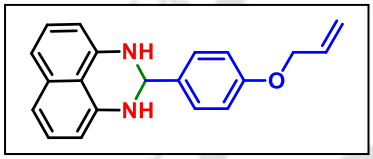
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 56% yield (0.146 g, 0.56 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.54 – 7.44 (m, 3H), 7.42 – 7.37 (m, 4H), 7.31 (d, *J* = 6.9 Hz, 2H), 6.56 (d, *J* = 7.8 Hz, 2H), 4.64 (t, *J* = 6.6 Hz, 1H), 4.49 (brs, 2H), 2.98 (d, *J* = 6.7 Hz, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 141.2, 135.9, 134.8, 129.4, 128.8, 127.0, 126.9, 117.4, 113.7, 105.9, 65.1, 42.0.

2-phenethyl-2,3-dihydro-1*H*-perimidine (5.3y):[23]



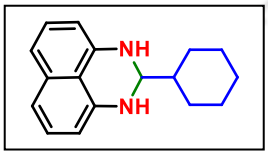
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 60% yield (0.165 g, 0.60 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.19 (t, *J* = 7.5 Hz, 2H), 7.13 – 7.07 (m, 7H), 6.31 (d, *J* = 7.2 Hz, 2H), 4.30 (t, *J* = 5.5 Hz, 1H), 4.10 (brs, 2H), 2.65 (t, *J* = 7.9 Hz, 2H), 1.88 – 1.82 (m, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 141.8, 141.0, 134.9, 128.7, 128.4, 126.9, 126.4, 117.7, 114.0, 106.1, 64.6, 37.2, 30.9.

2-(4-(allyloxy)phenyl)-2,3-dihydro-1*H*-perimidine (5.3z):



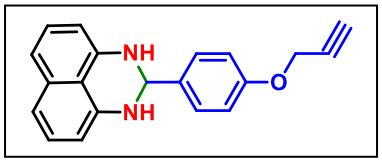
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 65% yield (0.196 g, 0.65 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.16 – 7.10 (m, 4H), 6.86 (d, *J* = 8.3 Hz, 2H), 6.38 (d, *J* = 7.1 Hz, 2H), 6.01 – 5.93 (m, 1H), 5.34 (d, *J* = 17.3 Hz, 1H), 5.28 (s, 1H), 5.22 (d, *J* = 10.5 Hz, 1H), 4.46 (d, *J* = 5.3 Hz, 2H), 4.37 (brs, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 159.7, 142.4, 135.1, 133.2, 132.6, 129.2, 127.0, 117.9 (2C), 115.1, 113.6, 105.8, 69.0, 68.0. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{20}H_{19}N_2O$ is 303.1497. Found 303.1481.

2-cyclohexyl-2,3-dihydro-1*H*-perimidine (5.3za):[24]



Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 60% yield (0.151 g, 0.60 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.13 (t, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.39 (d, *J* = 7.3 Hz, 2H), 4.26 (brs, 2H), 4.14 (d, *J* = 5.4 Hz, 1H), 1.80 – 1.72 (m, 4H), 1.65 – 1.62 (m, 1H), 1.52 – 1.47 (m, 1H), 1.22 – 1.03 (m, 5H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 142.1, 135.0, 127.0, 117.4, 113.9, 105.8, 69.0, 42.3, 27.9, 26.5, 26.1.

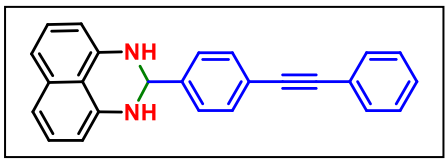
2-(4-(prop-2-yn-1-yloxy)phenyl)-2,3-dihydro-1*H*-perimidine (5.3zb):



Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 60% yield (0.180 g, 0.60 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.19 – 7.12 (m,

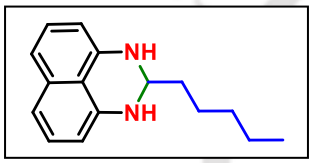
4H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 7.0 Hz, 2H), 5.34 (s, 1H), 4.65 (s, 2H), 4.40 (brs, 2H), 2.46 (s, 1H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 158.6, 142.3, 135.1, 133.4, 129.3, 127.0, 118.0, 115.3, 113.6, 105.9, 78.5, 75.9, 68.0, 56.0. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{20}H_{17}N_2O$ is 301.1341. Found 301.1339.

2-(4-(phenylethynyl)phenyl)-2,3-dihydro-1*H*-perimidine (5.3zc):



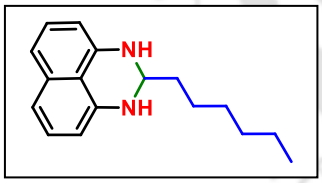
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 95/5) which afforded the title compound in 68% yield (0.235 g, 0.68 mmol) as a white solid. **^1H NMR (500 MHz, $CDCl_3$)** δ 7.57 (s, 4H), 7.55 – 7.53 (m, 2H), 7.35 – 7.33 (m, 3H), 7.24 – 7.20 (m, 4H), 6.49 (d, *J* = 6.9 Hz, 2H), 5.40 (s, 1H), 4.46 (brs, 2H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 142.0, 140.2, 132.1, 131.8, 128.6, 128.5, 128.0, 127.0, 124.7, 123.1, 118.1, 113.6, 106.1, 90.5, 89.0, 68.1. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{25}H_{19}N_2$ is 347.1548. Found 347.1538.

2-pentyl-2,3-dihydro-1*H*-perimidine (5.3zd):[25]



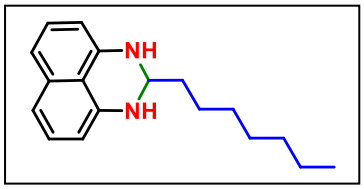
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) which afforded the title compound in 45% yield (0.108 g, 0.45 mmol) as a white solid. **^1H NMR (500 MHz, $CDCl_3$)** δ 7.11 (t, *J* = 7.7 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.37 (d, *J* = 7.3 Hz, 2H), 4.27 (t, *J* = 5.8 Hz, 1H), 4.18 (brs, 2H), 1.55 – 1.51 (m, 2H), 1.35 – 1.29 (m, 2H), 1.26 – 1.17 (m, 4H), 0.82 (t, *J* = 6.8 Hz, 3H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 142.1, 135.0, 126.9, 117.6, 114.1, 105.9, 64.9, 35.9, 31.8, 24.1, 22.6, 14.1.

2-hexyl-2,3-dihydro-1*H*-perimidine (5.3ze):[25]



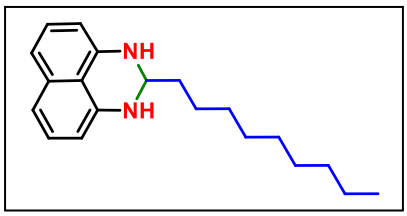
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) which afforded the title compound in 48% yield (0.122 g, 0.48 mmol) as a white solid. **^1H NMR (400 MHz, $CDCl_3$)** δ 7.15 (t, *J* = 8.5 Hz, 2H), 7.10 – 7.08 (m, 2H), 6.43 (d, *J* = 7.1 Hz, 2H), 4.40 (t, *J* = 5.7 Hz, 1H), 4.27 (brs, 2H), 1.69 – 1.64 (m, 2H), 1.46 – 1.39 (m, 2H), 1.35 – 1.29, (m, 2H), 1.28 – 1.23 (m, 4H), 0.8 (t, J = 6.6 Hz, 3H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 142.1, 135.1, 127.0, 117.8, 114.2, 106.1, 65.0, 36.1, 31.8, 29.4, 24.5, 22.7, 14.2.

2-heptyl-2,3-dihydro-1*H*-perimidine (5.3zf):[16]



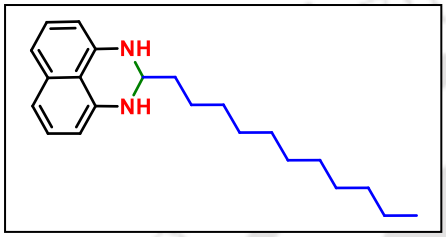
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) which afforded the title compound in 52% yield (0.140 g, 0.52 mmol) as a white solid. **^1H NMR (500 MHz, $CDCl_3$)** δ 7.14 (t, *J* = 7.7 Hz, 2H), 7.09 – 7.07 (m, 2H), 6.41 (d, *J* = 7.2 Hz, 2H), 4.36 (t, *J* = 5.8 Hz, 1H), 4.24 (brs, 2H), 1.65 – 1.60 (m, 2H), 1.42 – 1.36 (m, 2H), 1.28 – 1.18 (m, 8H), 0.82 (t, *J* = 6.8 Hz, 3H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$)** δ 142.1, 135.0, 126.9, 117.7, 114.1, 106.0, 65.0, 36.0, 31.9, 29.7, 29.3, 24.5, 22.7, 14.2.

2-nonyl-2,3-dihydro-1*H*-perimidine (5.3zg):[26]



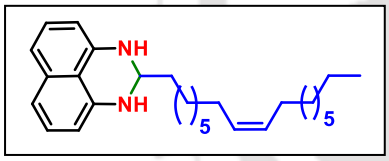
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) which afforded the title compound in 56% yield (0.166 g, 0.56 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.10 (t, *J* = 7.7 Hz, 2H), 7.06 – 7.04 (m, 2H), 6.35 (d, *J* = 7.2 Hz, 2H), 4.23 (t, *J* = 5.7 Hz, 1H), 4.15 (brs, 2H), 1.52 – 1.47 (m, 2H), 1.29 – 1.26 (m, 2H), 1.23 – 1.19 (s, 12H), 0.81 (t, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 142.0, 135.0, 126.8, 117.5, 114.0, 105.9, 64.8, 35.9, 31.9, 29.6 (3C), 29.4, 24.4, 22.7, 14.2.

2-undecyl-2,3-dihydro-1*H*-perimidine (5.3zh):[26]



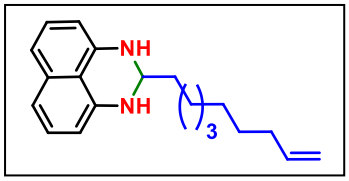
Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) which afforded the title compound in 60% yield (0.195 g, 0.60 mmol) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.09 (t, *J* = 7.7 Hz, 2H), 7.05 – 7.03 (m, 2H), 6.33 (d, *J* = 7.3 Hz, 2H), 4.20 (t, *J* = 5.7 Hz, 1H), 4.12 (brs, 2H), 1.48 – 1.44 (m, 2H), 1.27 – 1.22 (m, 4H), 1.21 – 1.18 (m, 14H), 0.80 (t, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 142.0, 134.9, 126.8, 117.5, 114.0, 105.9, 64.8, 35.8, 32.0, 29.7 (2C), 29.6 (2C), 29.4, 24.4, 22.7, 14.2.

(*Z*)-2-(heptadec-8-en-1-yl)-2,3-dihydro-1*H*-perimidine (5.3zi):



Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) which afforded the title compound in 54% yield (0.220 g, 0.54 mmol) as a yellow liquid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.09 – 7.04 (m, 4H), 6.34 (d, *J* = 7.1 Hz, 2H), 5.28 – 5.25 (m, 2H), 4.26 – 4.23 (m, 1H), 4.15 (brs, 2H), 1.95 – 1.91 (m, 4H), 1.52 – 1.49 (m, 2H), 1.30 – 1.15 (m, 22H), 0.8 (t, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 142.0, 134.9, 130.1, 129.8, 126.8, 117.5, 114.0, 105.9, 64.8, 35.9, 32.0, 29.8, 29.6, 29.5, 29.4, 29.2, 27.3, 24.4, 22.7, 14.2. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{28}H_{43}N_2$ is 407.3426. Found 407.3440.

2-(non-8-en-1-yl)-2,3-dihydro-1*H*-perimidine (5.3zj):



Purification was done by column chromatography (SiO_2, 100–200 mesh, eluent: Pet. ether/EtOAc = 98/2) which afforded the title compound in 59% yield (0.174 g, 0.59 mmol) as a yellow liquid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.12 – 7.04 (m, 4H), 6.34 (d, *J* = 7.2 Hz, 2H), 5.77 – 5.67 (m, 1H), 4.94 – 4.84 (m, 2H), 4.21 (t, *J* = 5.5 Hz, 1H), 4.15 (brs, 2H), 1.98 – 1.92 (m, 2H), 1.49 – 1.44 (m, 2H), 1.30 – 1.18 (m, 10H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 142.0, 139.1, 134.9, 126.8, 117.5, 114.3, 114.0, 105.8, 64.8, 35.8, 33.8, 29.5, 29.4, 29.0, 28.9, 24.4. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{20}H_{27}N_2$ is 295.2174. Found 295.2175.

5.6. References:

1. J. W. Daly, H. M. Garraffo, T. F. Spande, M. W. Decker, J. P. Sullivan, M. Williams, *Nat. Prod. Rep.* **2000**, *17*, 131–135.

2. a) J. J. O'Brien, D. M. Campoli-Richards, *Drugs* **1989**, *37*, 233–309; b) P. Arora, V. Arora, H. S. Lamba, D. Wadhwa, *Int. J. Pharm. Sci.* **2012**, *3*, 2947–2954; c) J. Walkembach, M. Brüss, B. W. Urban, M. Barann, *Br. J. Pharmacol.* **2005**, *146*, 543–552; d) A. Rudi, G. Shmul, Y. Benayahu, Y. Kashman, *Tetrahedron Lett.* **2006**, *47*, 2937–2939.

3. a) A. R. Katritzky, C. W. Rees, *Comprehensive Heterocyclic Chemistry II*, Eds., Elsevier, Oxford, **1996**; b) J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Blackwell, Oxford, UK, **2000**; c) N. Sahiba, S. Agarwal, *Top. Curr. Chem.* **2020**, *378*, 44; d) J. M. Herbert, P. D. Woodgate, W. A. Denny, *J. Med. Chem.***1987**, *30*, 2081-2086; e) Z. Petkova, R. Rusew, S. Bakalova, B. Shivachev, V. Kurteva, *Molbank* **2023**, *2023*, M1587.

4. a) M. Elce, C. E. Dearden, E. Matutes, J. Garcia-Talavera, A. Z. S. Rohatiner, S. A. N. Johnson, N. T. J. O'Connor, A. Haynes, N. Osuji, F. Forconi, F. Lauria, D. Catovsky, *Br. J. Haematol.* **2009**, *145*, 733–740; b) J. A. Joule, E. F. V. Scriven, C. A. Ramsden, *Adv. Heterocycl. Chem.* **2016**, *119*, 81−106.

5. a) A. de Aguiar, *Ber. Dtsch. Chem. Ges.* **1874**, *7*, 309–319; b) F. Sachs, *Justus Lieb. Ann. der Chem.* **1909**, *365*, 135–166.

6. a) M. Azam, I. Warad, S. I. Al-Resayes, N. Alzaqri, M. R. Khan, R. Pallepogu, S. Dwivedi, J. Musarrat, M. Shakir, *J. Mol. Struct.* **2013**, *1047*, 48–54; b) M. Azam, I. Warad, S. I. Al-Resayes, M. Zahin, I. Ahmad, M. Shakir, *Anorg. Allg. Chem.* **2012**, *638*, 881–886; c) F. A. Bassyouni, S. M. Abu-Bakr, K. H. Hegab, W. El-Eraky, A. A. El-Beih, M. E. A. Rehim, *Res. Chem. Intermed.* **2012**, *38*, 1527–1528; d) M. F. Braña, M. Garrido, M. L. LopezRodriguez, M. J. Morcillol, Y. Alvarez, Y. Valladares, G. Klebe, *Eur. J. Med. Chem.* **1990**, *25*, 209–215; e) B. Stefańska, M. Dzieduszycka, M. M. Bontemps-Gracz, E. Borowski, S. Martelli, R. Supino, G. Pratesi, M. A. de Cesare, F. Zunino, H. Kuśnierczyk, *J. Med. Chem.* **1999**, *42*, 3494–3501; f) X. Bu, W. L. Deady, G., J. Finlay, B. C. Baguley, W. A. Denny, *J. Med. Chem.* **2001**, *44*, 2004–2014.

7. S. Y. Fan, H. T. Xu, Q. G. Li, D. M. Fang, W. H. Yu, S. K. Xiang, *Liq. Cryst.* **2020**, *47*, 1041–1054.

8. a) P. Bazinet, G. P. A. Yap, D. S. Richeson, *J. Am. Chem. Soc.* **2003**, *125*, 13314–133155; b) K. Verlinden, C. Ganter, *J. Organomet. Chem.* **2014**, *750*, 23–29.

9. a) M. M. Belmonte, E. C. Escudero-Ada´ n, J. Benet-Buchholz, R. M. Haak, A. W. Kleij, *Eur. J. Org. Chem.* **2010**, *2010*, 4823–4831; b) N. A. Harry, R. M. Cherian, S. Radhika, G. Anilkumar, *Tetrahedron Lett.* **2019**, *60*, 150946; c) K. Bahrami, S. Saleh, *Synth. React. Inorg. Met.-Org. Nano-Met. Chem.* **2016**, *46*, 852–856; d) M. Kalhor, N. Khodaparast, *Res. Chem. Intermed.* **2015**, *41*, 3235–3242; e) H. Alinezhad, A. Ahmadi, P. Hajiabbasi, *J. Chem. Sci.* **2019**, *131*, 34; f) M. Kalhor, F. Rezaee-Baroonaghi, A. Dadras, Z. Zarnegar, *Appl. Organometal. Chem.* **2019**, *33*, 4784; g) M. Kalhor, Z. Zarnegar, F. Janghorban, S. A. Mirshokraei, *Res. Chem. Intermed.* **2020**, *46*, 821–836; h) P. B. Shelke, S. N. Mali, H. K. Chaudhari, A. P. Pratap, *J. Heterocycl. Chem.* **2019**, *56*, 3048.

10. a) M. Besson, P. Gallezot, C. Pinel, *Chem. Rev.* **2014**, *114*, 1827−1870; b) H. T. Luk, C. Mondelli, D. C. Ferre, J. A. Stewart, J. Pe´rez-´Ramírez, *Chem. Soc. Rev.* **2017**, *46*, 1358−1426; c) D. M. Alonso, J. Q. Bond, J. A. Dumesic, *Green Chem*. **2010**, *12*, 1493−1513; d) K. Barta, P. C. Ford, *Acc. Chem. Res.* **2014**, *47*, 1503−1512.

11. a) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712; b) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681−703; c) M. Maji, D. Panja, I. Borthakur, S. Kundu, *Org. Chem. Front.* **2021**, *8*, 2673−2709; d) Q. Yang, Q. Wang, Z. Yu, *Chem. Soc. Rev.* **2015**, *44*, 2305−2329; e) A. Kumar, P. Daw, D. Milstein, *Chem. Rev.* **2022**, *122*, 385−441.

12. D. Pal, A. Mondal, R. Sarmah, D. Srimani, *Org. Lett.* **2024**, *26*, 514−518.

13. a) S. N. R. Donthireddy, M. Siddique, A. Rit, *J. Org. Chem.* **2023**, *88*, 1135−1146; b) T.-Y. Cheng, B. S. Brunschwig, R. M. Bullock, *J. Am. Chem. Soc.* **1998**, *120*, 13121–13137.

14. S. Pattanaik, C. Gunanathan, *ACS Catal.* **2019**, *9*, 5552−5561.

15. B. Chatterjee, C. Gunanathan, *Org. Lett.* **2015**, *17*, 4794−4797.

16. K. Das, A. Mondal, D. Pal, H. K. Srivastava, D. Srimani, *Organometallics* **2019**, *38*, 1815−1825.

17. B. Zhang, J. Li, H. Zhu, X.-F. Xia, D. Wang, *Catal. Lett.* **2023**, *153*, 2388–2397.

18. M. Mannarsamy, M. Nandeshwar, G. Muduli, G. Prabusankar, *Chem.–Asian J.* **2022**, *17*, e202200594.

19. J. Soni, A. Sethiya, N. Sahiba, D. Joshi, S. Agarwal, *Polycyclic. Aromat. Compd.* **2023**, *43*, 674–685.

20. Z. Sadri, F. K. Behbahani, E. Keshmirizadeh, *Polycyclic Aromat. Compd.* **2023**, *43*, 1898−1913.

21. A. Mobinikhaledi, N. Forughifar, N. Bassaki, *Turk. J. Chem.* **2009**, *33*, 555-560.

22. C.-C. Chou, H.-J. Liu, L. H.-C. Chao, H.-B. Syu, T.-S. Kuo, *Polyhedron* **2012**, *37*, 60–65.

23. K. Bahrami, S. Saleh, *Synth. React. Inorg., Met.-Org., NanoMet. Chem.* **2016**, *46*, 852–856.

24. R. Parui, N. Zehraa, P. K. Iyer, *J. Mater. Chem. C* **2023**, *11*, 11243–11251.

25. S. Ernst, J. Mistol, B. Senns, L. Hennig, D. Keil, *Dyes Pigm.* **2018**, *154*, 216– 228.

26. R.F. Malherbe, US Patent 4389321 (**1983**).

5.7. Selected NMR copies of the compounds:

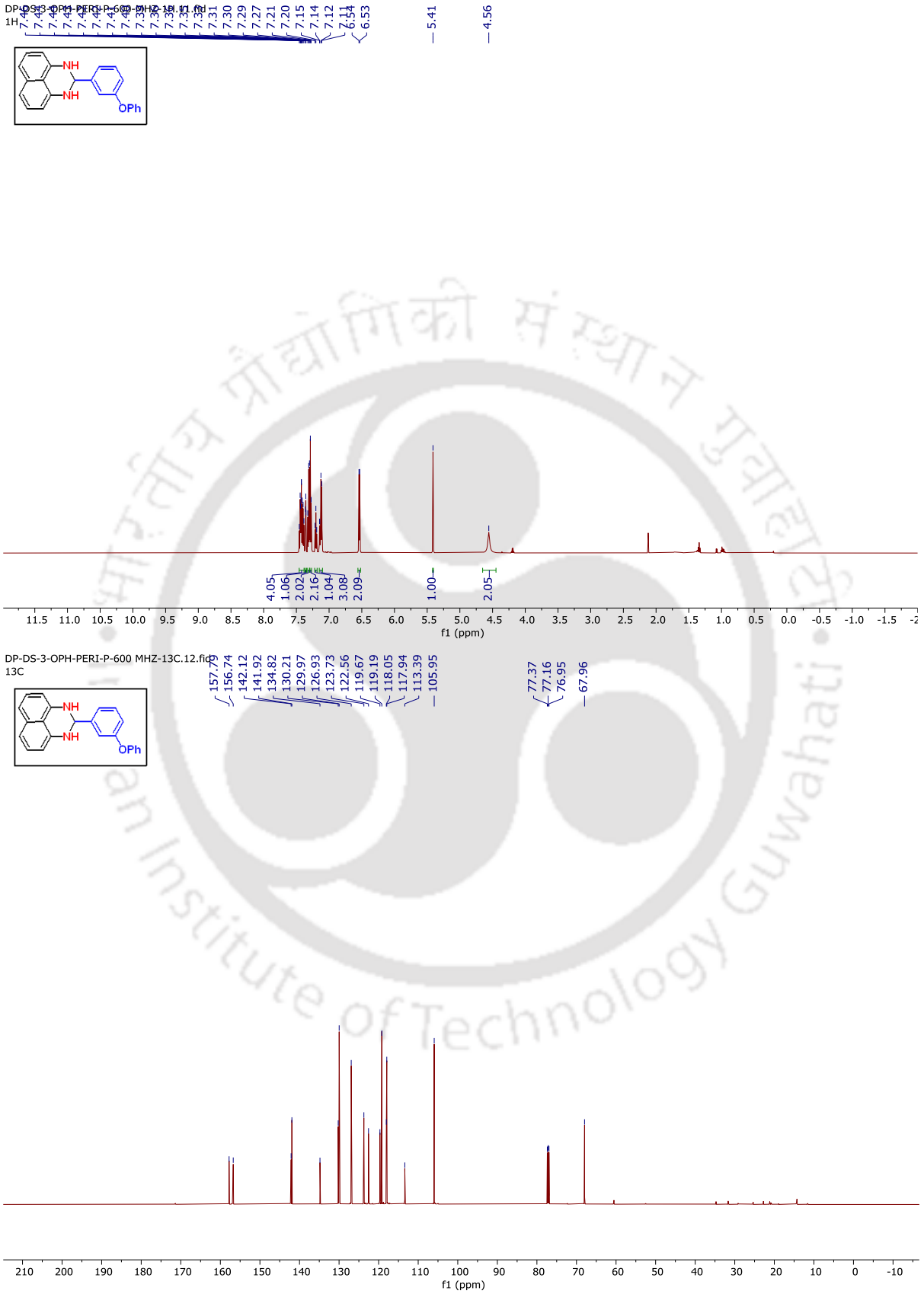


Figure 5.5. ^{1}H (600 MHz) and $^{13}C\{^{1}H\}$ (150 MHz) NMR Spectrum of **2-(3-phenoxyphenyl)-2,3-dihydro-1*H*-perimidine (5.3g)** in $CDCl_3$.

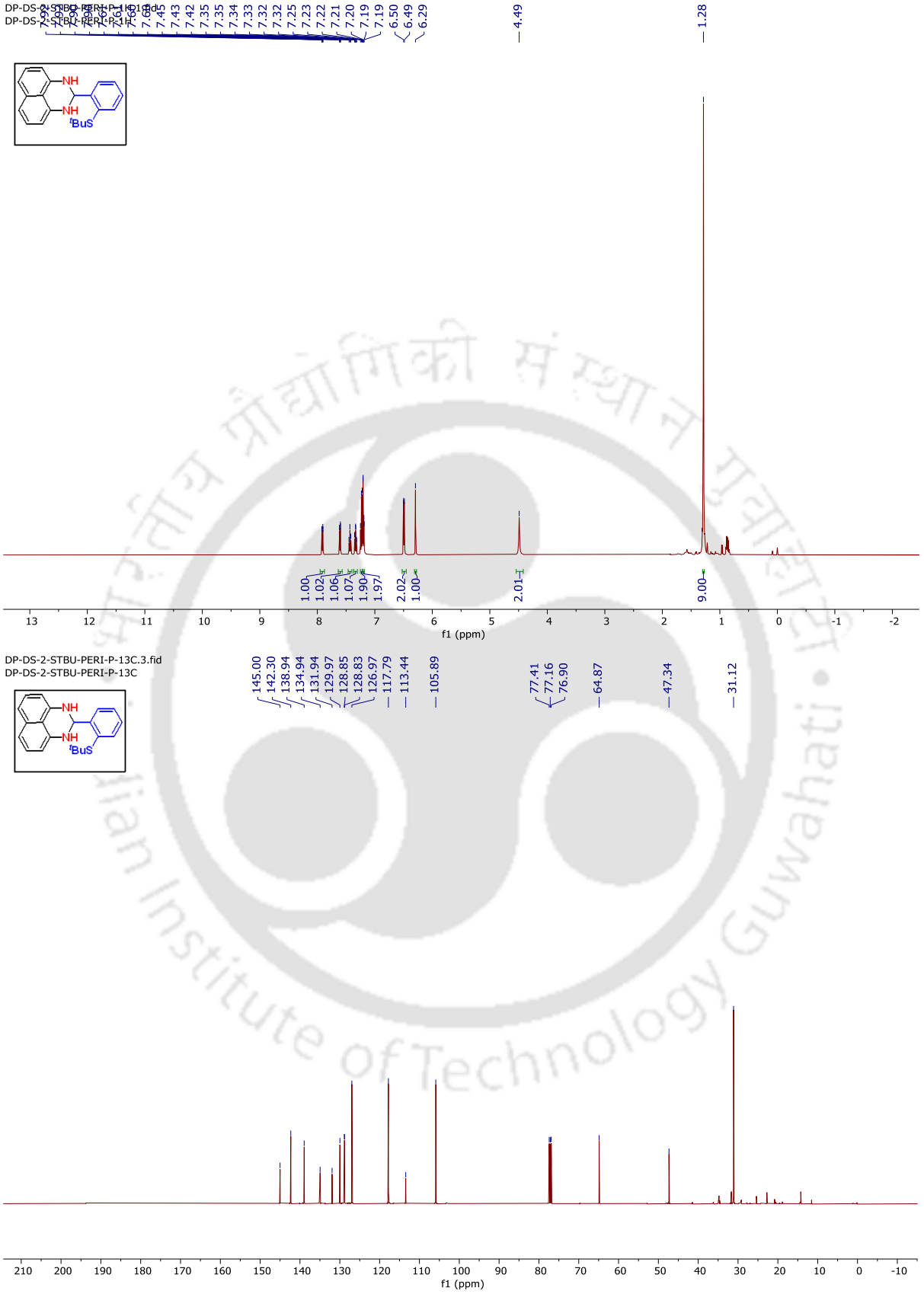


Figure 5.6. ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of **2-(2-(*tert*-butylthio)phenyl)-2,3-dihydro-1*H*-perimidine (5.3j)** in $CDCl_3$.

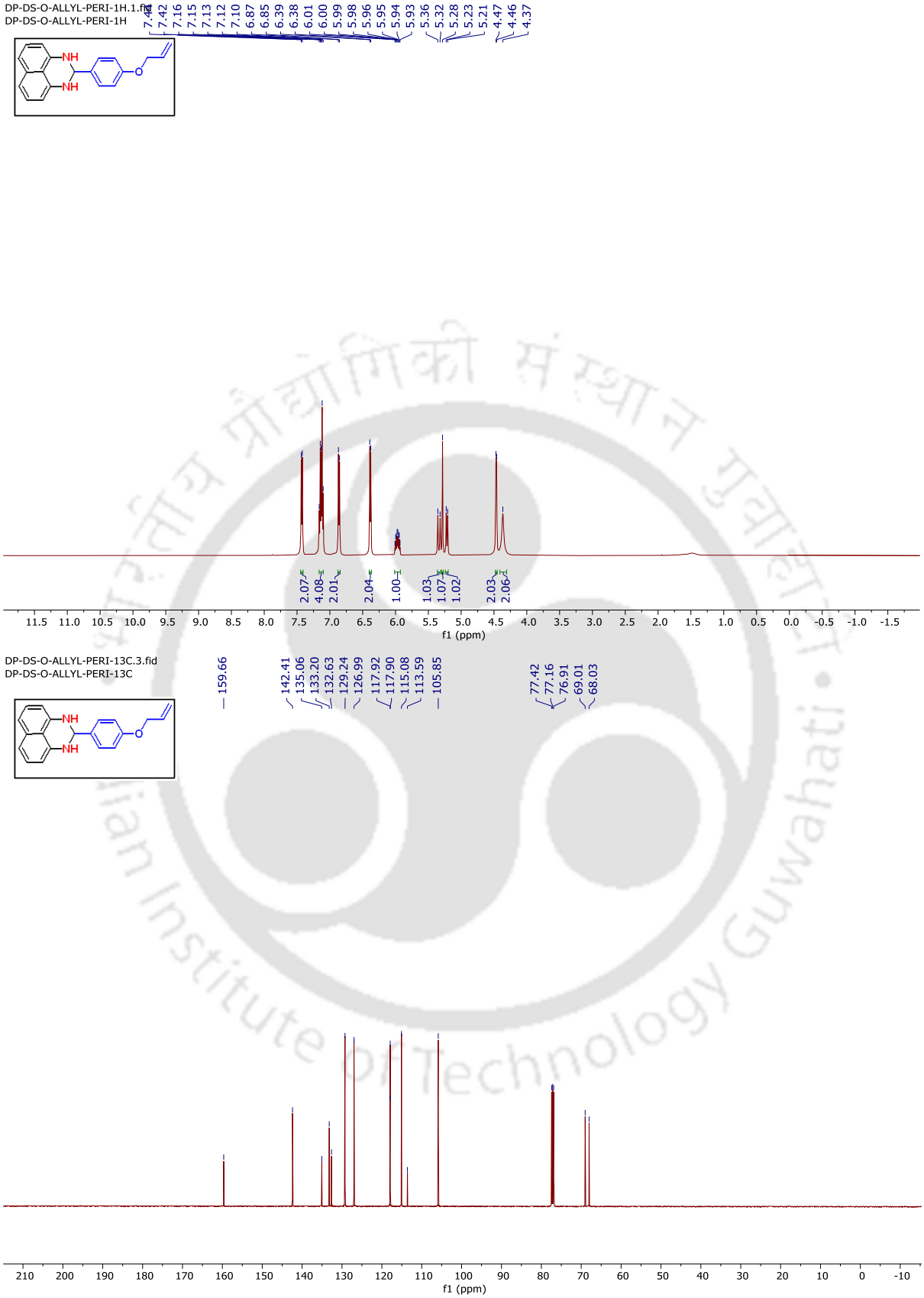


Figure 5.7. ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of **2-(4-(allyloxy)phenyl)-2,3-dihydro-1*H*-perimidine (5.3z)** in $CDCl_3$.

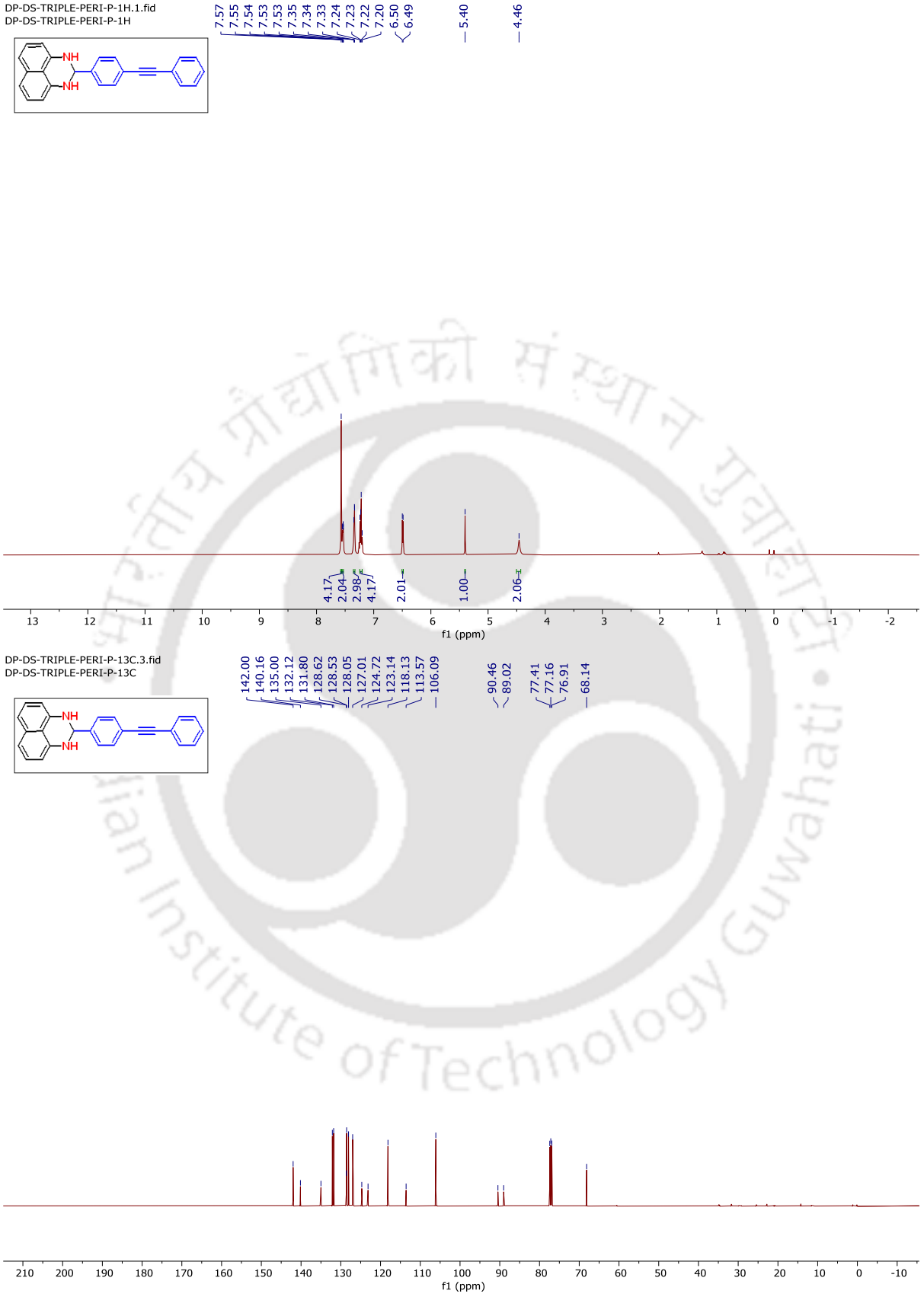


Figure 5.8. ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (125 MHz) NMR Spectrum of **2-(4-(phenylethynyl)phenyl)-2,3-dihydro-1*H*-perimidine (5.3zc)** in $CDCl_3$.

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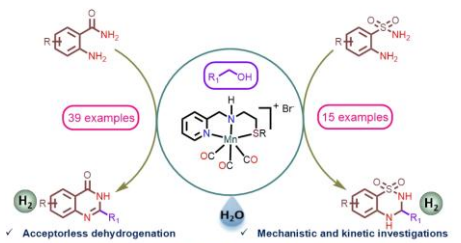
Chapter-2



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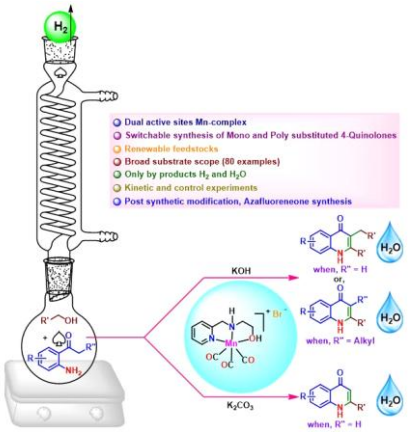

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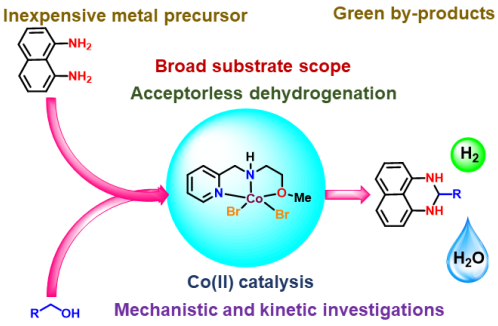

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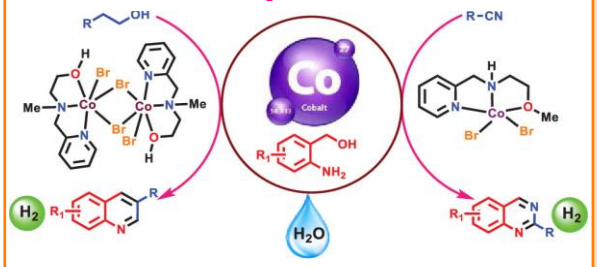
Chapter-4



Org. Lett. 2024, *26*, 514–518

List of publications

Thesis works:

1. **D. Pal**, A. Mondal and D. Srimani*, Well-defined Manganese Complex Catalyzed Dehydrogenative Synthesis of Quinazolin-4(3H)-ones and 3,4-Dihydro-2*H*-1,2,4- benzothiadiazine 1,1-Dioxides. *Catal. Sci. Technol*. **2022**, *12*, 3202-3208.

2. **D. Pal**, A. Mondal, R. Sarmah, D. Srimani*, Designing Cobalt(II) Complexes for Tandem Dehydrogenative Synthesis of Quinoline and Quinazoline Derivatives. *Org. Lett*. **2024**, *26*, 514–518.

3. **D. Pal**, R. Sarmah, A. Mondal, I. Mallick and D. Srimani*, Well-defined Cobalt(II) Catalyzed Synthesis of Perimidine derivatives via Acceptorless Dehydrogenative Annulation. *Org. Biomol. Chem.* **2024***, 22,* 8602–8607.

4. **D. Pal**, B. Sardar, A. Mondal, K. Mohar, R. Sarmah, H. J. Phukan and D. Srimani* Manganese Complex Catalyzed (De)hydrogenative Cyclization toward the Selective Synthesis of 2-Substituted and 2, 3-Disubstituted 4-Quinolones. *Org. Lett.* **2025**, **https://doi.org/10.1021/acs.orglett.5c01721**.

Non-Thesis works:

5. K. Das, A. Mondal, **D. Pal**, H. K. Srivastava* and D. Srimani*, Phosphine-Free Well-Defined Mn(I)Complex-Catalyzed Synthesis of Amine, Imine, and 2,3-Dihydro-1*H*-perimidine via Hydrogen Autotransfer or Acceptorless Dehydrogenative Coupling of Amine and Alcohol. *Organometallics* **2019**, *38*, 1815-1825.

6. K. Das, A. Mondal, **D. Pal** and D.Srimani*, Sustainable Synthesis of Quinazoline and 2-Aminoquinoline via Dehydrogenative Coupling of 2-Aminobenzyl Alcohol and Nitrile Catalyzed by Phosphine-Free Manganese Pincer Complex. *Org. Lett*. **2019**, *21*, 3223–3227.

7. A. Mondal, R. Sharma, **D. Pal** and D. Srimani*, Recent Progress in the Synthesis of Heterocycles via Base Metal-catalyzed Acceptorless Dehydrogenative and Borrowing Hydrogen Approach. *Eur. J. Org. Chem*. **2021**, *2021*, 3690.

8. B. Sardar, R. Jamatia, **D. Pal** and D. Srimani*, Multicomponent Dehydrogenative Synthesis of Acridine-1,8-diones Catalyzed by Ru-doped Hydrotalcite. *Asian J. Org. Chem.* **2021**, *10*, 2195.

9. A. Mondal, R. Sharma, **D. Pal** and D. Srimani*, Manganese Catalyzed Switchable C-Alkylation/Alkenylation of Fluorenes and Indene with Alcohols. *Chem. Commun*. **2021**, *57*, 10363-10366.

10. A. Mondal, R. Sharma, B. Dutta, **D. Pal** and D. Srimani*, Well-Defined NNS-Mn Complex Catalyzed Selective Synthesis of C-3 Alkylated Indoles and Bisindolylmethanes Using Alcohol. *J. Org. Chem*. **2022**, *87*, 3989–4000.

11. B. Sardar, **D. Pal**, R. Sarmah and D. Srimani*, Ruthenium Catalyzed Dehydrogenative Cyclization to Synthesize Polysubstituted 4-Quinolones under Solvent-Free Condition. *Chem. Commun.* **2023**, *59*, 9267-9270.

12. A. Mondal, H. J. Phukan, **D. Pal**, S. Kumar, M. Roy and D. Srimani*, Well-defined Mn(II)-complex Catalyzed Switchable De(hydrogenative) Csp3-H Functionalization of Methyl Heteroarenes: A Sustainable Approach for Diversification of Heterocyclic Motifs. *Chem. Eur. J.* **2024***, 30,* e20230331.

13. A. Mondal, **D. Pal**, H. J. Phukan, M. Roy, S. Kumar, S. Purkayastha, A. K. Guha, * and D, Srimani* Manganese Complex Catalyzed Sequential Multi-Component Reaction: Enroute to a Quinoline-Derived Azafluorenes, *ChemSusChem* **2024**, *17*, e202301138.

14. A. Samanta, P. Behera, A. Chaubey, A. Mondal, **D. Pal**, K. Mohar, L. Roy*, and D. Srimani*, Experimental and Theoretical Insights for Designing Zn^{2+} Complexes to Trigger Chemo-selective Hetero-Coupling of Alcohols, *Chem. Commun*. **2024**, *60*, 4056-4059.

15. A. Samanta, A. Chaubey, **D. Pal**, K. Majhi, and D. Srimani*, Redox-enabled cooperative catalysis by activating secondary alcohols using low-valent Zn complexes, *Chem. Commun.* **2024**, *60*, 10398-10401.

Conferences and workshop

1. The 2 days' online workshop on ***"Nuclear Magnetic Resonance: Technique and its Application"*** held from 23rd to 24th August 2021, organized by **North East Centre for Biological Sciences and Healthcare Engineering (NECBH)**, Indian Institute of Technology Guwahati, Assam in collaboration with **Bruker**, **India**, with support of Department of Biotechnology, Govt. of India as part of **Azadi ka Amrit Mahotsav**.

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3. ***International Conference on Modern trends in Inorganic Chemistry (MTIC-XIX)***, 2022, **Poster:** Well Defined Manganese Catalyzed Synthesis of Dehydrogenative Quinazolin-4(3H)-ones and 3,4-Dihydro-2*H*-1,2,4-benzothiadiazine 1,1-oxides.

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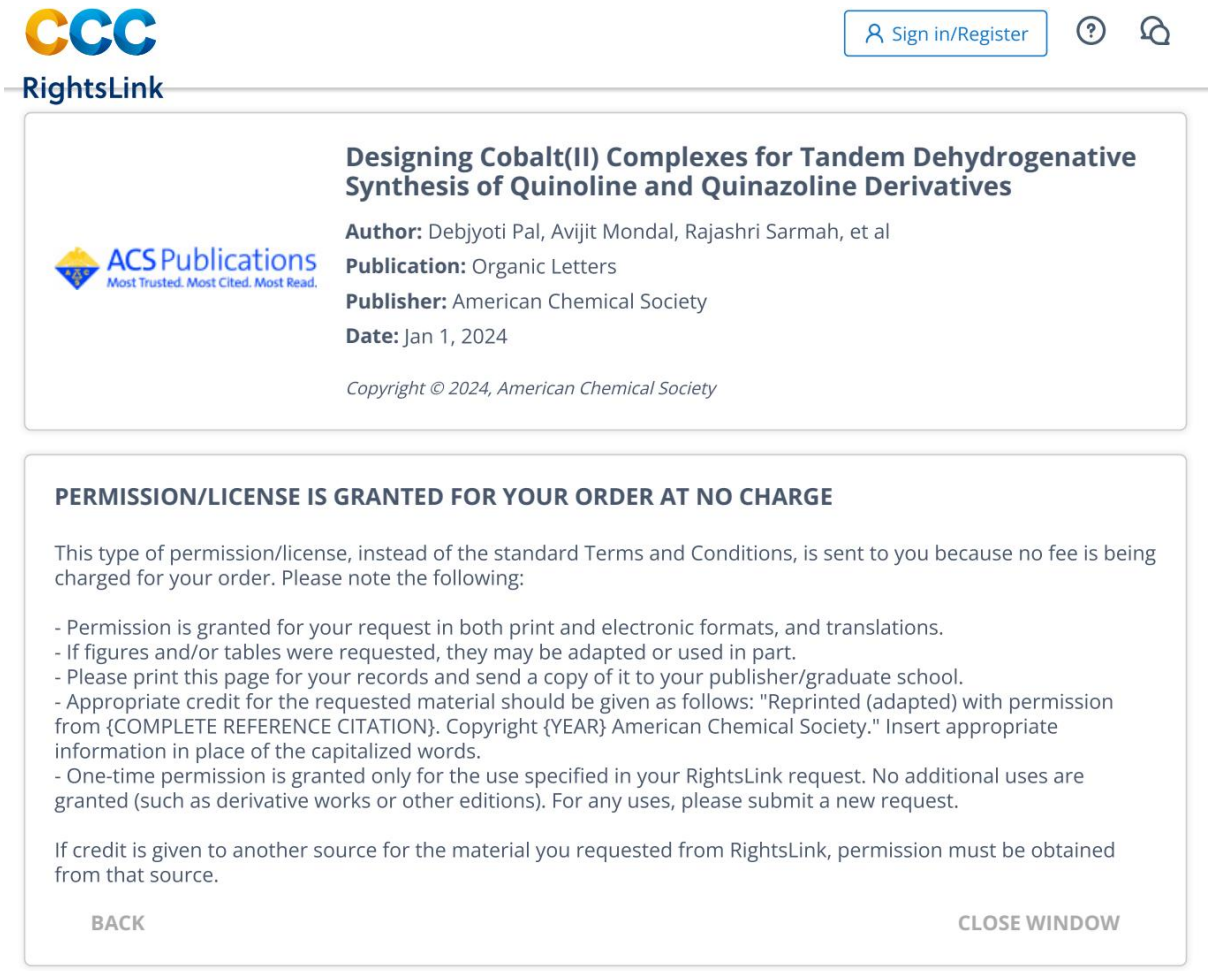

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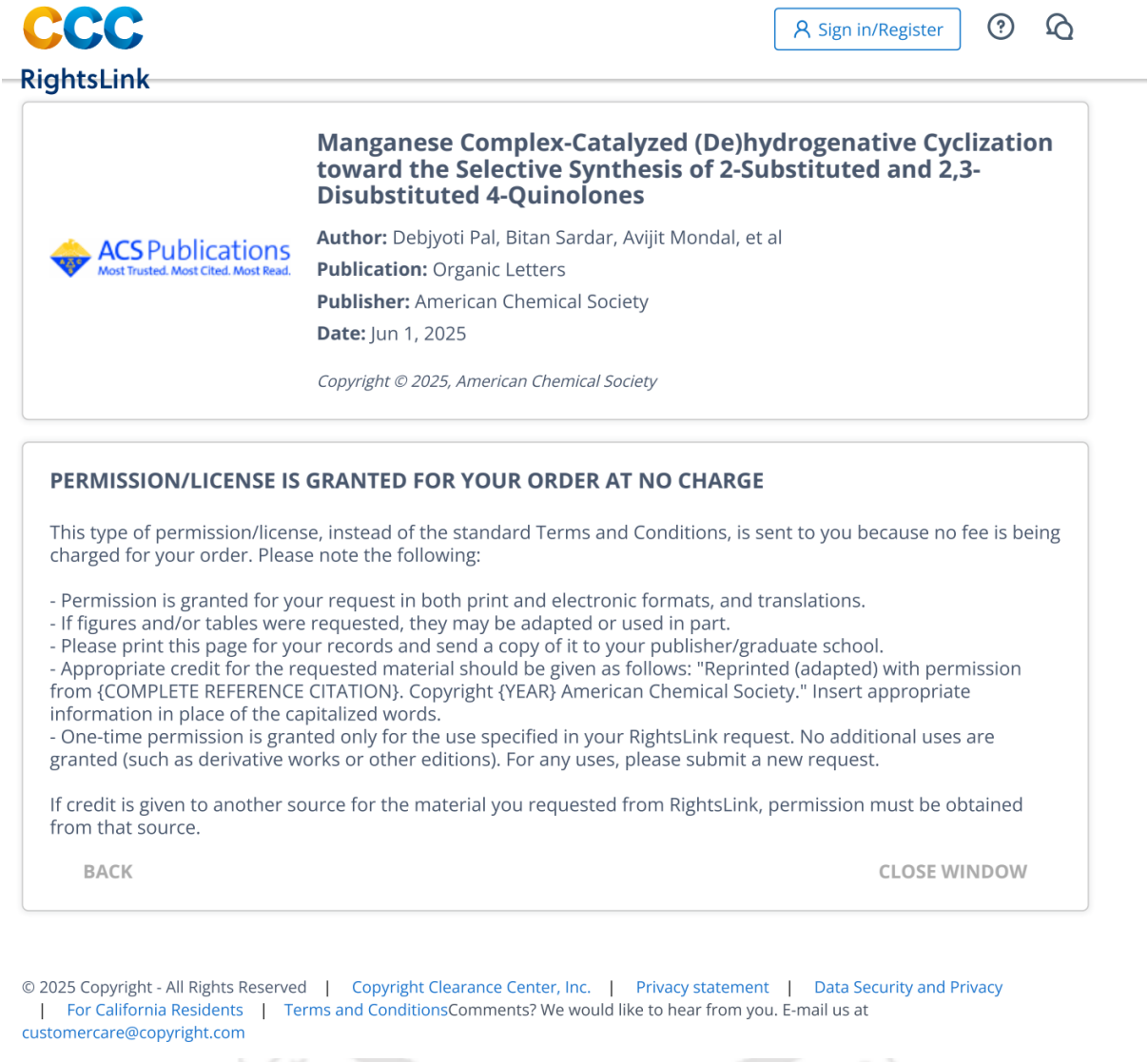

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