Exploring synthesis of functionalized tetrahydroquinoline and N-substituted hydrazine via a reductive process using Hantzsch ester as hydrogen source

A dissertation submitted to the

Indian Institute of Technology Guwahati

in partial fulfilment for the degree of

Doctor of Philosophy



Submitted by

Siddhartha Kumar Senapati

Roll no.: 196122031

Supervisor: Dr. Animesh Das

Department of Chemistry

Indian Institute of Technology Guwahati

Guwahati, Assam-781039

TH-3765_196122031

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Dedicated

To

My Family

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INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
Department of Chemistry
Guwahati, Assam-781039, INDIA

STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Exploring synthesis of functionalized tetrahydroquinoline and N-substituted hydrazine via a reductive process using Hantzsch ester as hydrogen source***" is the outcome of the research work carried out by me under the supervision of Dr. **Animesh Das, Department of Chemistry, Indian Institute of Technology Guwahati, India**, for the award of the degree of Doctor of Philosophy. In harmony with the general practice of reporting scientific observations, due acknowledgements have been made if the work is established on the findings of other investigators.

Siddhartha Kumar Senapati

Guwahati
August, 2025

Siddhartha Kumar Senapati
Roll No: 196122031
Department of Chemistry
IIT Guwahati, Assam, India-781039

TH-3765_196122031

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

Guwahati, Assam-781039, INDIA

Dr. Animesh Das,

Associate Professor, Department of Chemistry

E-mail: adas@iitg.ac.in

Phone: +91-361-2583478

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Exploring synthesis of functionalized tetrahydroquinoline and N-substituted hydrazine via a reductive process using Hantzsch ester as hydrogen source***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by **Mr. Siddhartha Kumar Senapati** (Roll No: 196122031) was carried out by him under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Animesh Das

Guwahati

August, 2025

Dr. Animesh Das

(Thesis Supervisor)

Associate Professor

Department of Chemistry

IIT Guwahati, Assam, India-781039

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Acknowledgements

The PhD journey is filled with challenges, and it would be incomplete without acknowledging the wonderful individuals who, in various ways, have supported me during times of need. At the forefront, I wish to express my utmost respect and heartfelt gratitude to my supervisor, Dr. Animesh Das, for his unwavering guidance and insightful mentorship throughout my thesis work. His encouragement to stay dedicated while enjoying the research process was a constant source of motivation, especially during difficult phases. His deep commitment to research and his inspiring enthusiasm greatly helped me navigate and overcome many obstacles during my PhD.

I would like to thank all my doctoral committee members Prof. Prof. Subhendu Sekhar Bag (chairman), Dr. Krishna Pada Bhabak and Dr. Pavan Kumar Kancharla for their timely evaluation, insightful comments and valuable suggestions which helped me to improve my research work. I extend my regards to all the faculty members for their valuable advices during my tenure. I will especially remember the well wishes of Mr. Imdadul Islam for NMR and Mr. Bhaskar Jyoti Hazarika for ESI-MS. I also want to thank all the non-teaching staff of our department for their cooperation and help during my research work. My sincere thanks to all the staff of Central Instrument Facility (CIF), IIT Guwahati, specially to all the student operators for the instrumental facilities required for my research. I sincerely acknowledge IIT Guwahati for the financial support without which it would have been very difficult for me to complete my work.

During my PhD tenure, I was fortunate enough to come across some wonderful people as my lab members. I want to express my sincere thanks to my seniors Dr. Dipanjan Bhattacharyya and Dr. Bikash Kumar Sarmah for mentoring me during the initial phase of my research. I would like to acknowledge Monu da and Priyanka di for teaching me all the experimental skills which help me in completing my work. I want to express my gratitude towards my wonderful current and former lab juniors, Kritartha, Rahul, Nitumoni, Kamal, Tapashi, Asish, Anit, Nitish and Manash, Swagata for creating a friendly and joyous environment in the lab. I also like to acknowledge Nitumoni, for his help for in solving SC-XRD, Tapashi, for her help in nmr booking and analysis and Anit, Ashish, and Swagata for his/her help in revision work. I would also like to acknowledge project students Shivani, Ramakant, Vivek, Soumya, Arpan, Mayur, Neel. I am greatly thankful to my friend amlan and bubul bhai for always helping me in solving single crystal XRD data.

I acknowledge all my PhD batchmates & juniors; Prabhat, Saurav, Bubul bhai, Amlan, Jagnyesh, Priyam, Sukesh, Tripti, Surya, Ujjala, Bijoy, Rabu, Suravi, Sanchari, Mona, Rimjhim, Krisangi, Debika, Himani, Subhra, Golu, Himadree, Shivani (moti), Prateechee (chichi), Suraj, Rupresha, Rockey, Abir, Anshika, Abhaya, Sulekha, for making my days memorable in IITG. I also want to thank my seniors, colleagues, it always remains in my heart forever. Also, I would like to acknowledge my odia community people where I found some good souls during my PhD journey; Chinmayee, Limahree, Anandita, Sunil, Aswini, Seema, Tapashi, Subhashree, Soumya, Ankita Swati, Sampurnana, thank you all for all the good memories, which I always cherish forever.

TH-3765_196122031

Teachers influence the life of a student in many ways and I am fortunate to have some amazing personalities as my teachers who have taught valuable lessons and motivated me to do good in life. I would like to thank all of my teachers at, M.P.H School, Maharishi College of Natural Law, B.J.B College, CUK for their contributions in my education. I would like to my school teachers Chandra Sir for their contribution on my education. I greatly thankful to my postgraduate teacher, Prof. K Hanumae Gowd, Prof. Harish Holla, and Dr. Sunil Sir for his contribution to my passion in research and always encouraging me to achieve greatness in life.

I would like to express my heartfelt gratitude to my father Mr. Kumuda Chandra Senapati (bapa), mother Mrs. Babita Senapati (maa) for their unwavering support and encouragement throughout every phase of my life. Their constant motivation and efforts ensured that no obstacle ever stood in the way of my career. Thank you, Bapa and Maa, for the countless sacrifices you have made for my education and well-being, and for your boundless love. I also thank my brother, Biswaranjan (nanudu), brother in law, Surabhi (bhauja), and my niece, Avni (tungu mama) and other family members for their presence, support, and blessings. Their love and good wishes have been instrumental in helping me reach this milestone and successfully complete my doctoral journey, above all, I remain ever thankful to God for all the blessings that life has brought my way.

Sincerely,

Siddhartha Kumar Senapati

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Abbreviation

Ac	Acetyl
α	Alpha
Å	Angstrom
Ar	Argon
ACN	Acetonitrile
AD	Acceptorless dehydrogenation
ADC	Acceptorless dehydrogenative coupling
BA	Boronic acid
BAC	Boronic acid catalysis
BAIL	Brønsted acidic ionic liquid
br.	Broad
brs	Broad singlet
bi pyridine	2,2′-bipyridine
β	Beta
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
CCDC	Cambridge crystallographic data centre
COD	1,5-Cyclooctadiene
$CDCl_3$	Chloroform-d
CSA	Camphor sulphonic acid
Cy	Cyclohexyl
Cat	Catalyst
°C	Degree Celsius
d	Doublet or day
dd	Doublet of doublet
δ	Chemical shift or delta
DA	Donor-acceptor
DCE	Dichloroethane
DCM	Dichloromethane

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DFT	Density functional theory
DMSO	Dimethylsulfoxide
DMF	Dimethylformamide
DMA	Dimethylacetamide
dt	Doublet of triplet
EtOAc	Ethyl acetate
equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
EDG	Electron donating group
FDA	Food and drug Administration
GP	General procedure
g	Grams
γ	Gamma
HE	Hantzsch ester
HBD	Hydrogen bond donor
HFIP	Hexafluoroisopropanol
h	Hours
HRMS	High resolution mass spectrometry
Hz	Hertz
MHz	Mega Hertz
i	Iso
FT-IR	Fourier transform infrared spectroscopy
J	Coupling constant
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
MAGL	Monoacylglycerol lipase
MRSA	Anti-methicillin-resistant staphylococcus aureus
m	Meta
Me	Methyl
mg	Milligram
mL	Milliliter

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mmol	Millimole
Mp	Melting point
MS	Molecular sieve
NMR	Nuclear magnetic resonance
OHE	Oxidized Hantzsch ester
p-QMs	Para-quinone methides
Ts	Tosylate
Tol	Tolyl
o	Ortho
ω	Omega
ORTEP	Oak ridge thermal ellipsoid plot program
p	Para
Py	Phenyl
Pr	Pyridine
PNP	propyl
	2,6-bis- (di-tert-butylphosphinomethyl)pyridine
ppm	Parts per million
q	Quartet
rt	Room temperature
s	Singlet
THF	Tetrahydrofuran
TFE	2,2-Trifluoroethanol
THQ	1,2,3,4-tetrahydroquinoline
TLC	Thin-layer chromatography
t	Tert
TMS	Tetramethylsilane
TsOH	Para-toluene sulfonic acid
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
UHPLC - Q-TOF – HRMS	Ultra-High-Performance Liquid Chromatography-Quadrupole Time-of-Flight-High-Resolution Mass Spectrometry
XRD	X-ray diffraction

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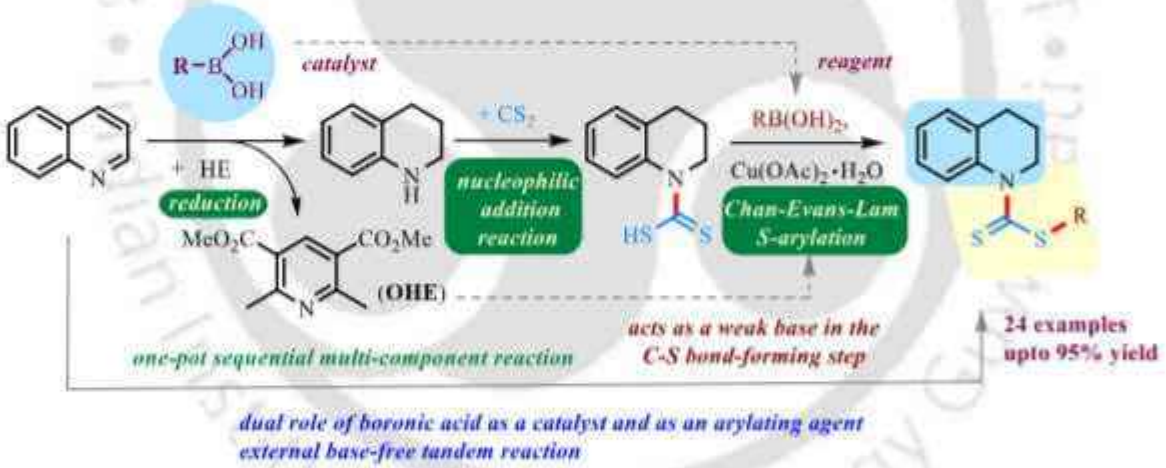
Abstract

The present thesis, entitled "***Exploring synthesis of functionalized tetrahydroquinoline and N-substituted hydrazine via a reductive process using Hantzsch ester as hydrogen source***" is divided into six chapters based on the results obtained from the experimental works during the course of PhD research period.

Chapter 1 includes boronic acid catalysis (BAC) and hexafluoroisopropanol (HFIP), focusing on their roles in organic synthesis, particularly in reduction chemistry. It highlights how BAC and HFIP contribute to improving reaction efficiency and selectivity.

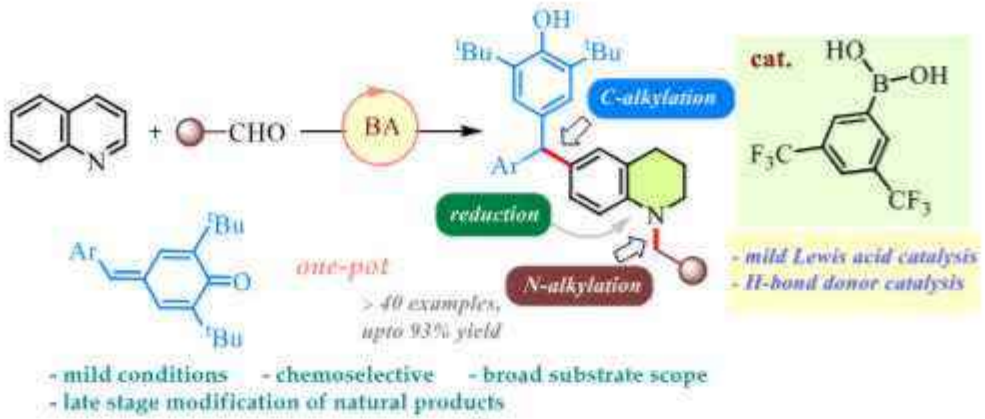
Each of the following chapters (Chapter 2 to Chapter 6) contains an introduction, previous literature reports, present results and discussion, experimental section and references. The spectral data for selected synthesized molecules are provided in the **Annexure I-V**.

Chapter 2 reports an arylboronic acid-catalyzed one-pot multicomponent reaction. It involves the reduction of quinolines to tetrahydroquinolines, nucleophilic addition with carbon disulfide to form dithiocarbamic acids, and final *S*-arylation *via* the Chan–Evans–Lam reaction to yield dithiocarbamate-functionalized tetrahydroquinolines. The protocol demonstrates the dual role of boronic acid, acting both as a catalyst in the quinoline reduction and as a coupling partner in the *S*-arylation reaction.

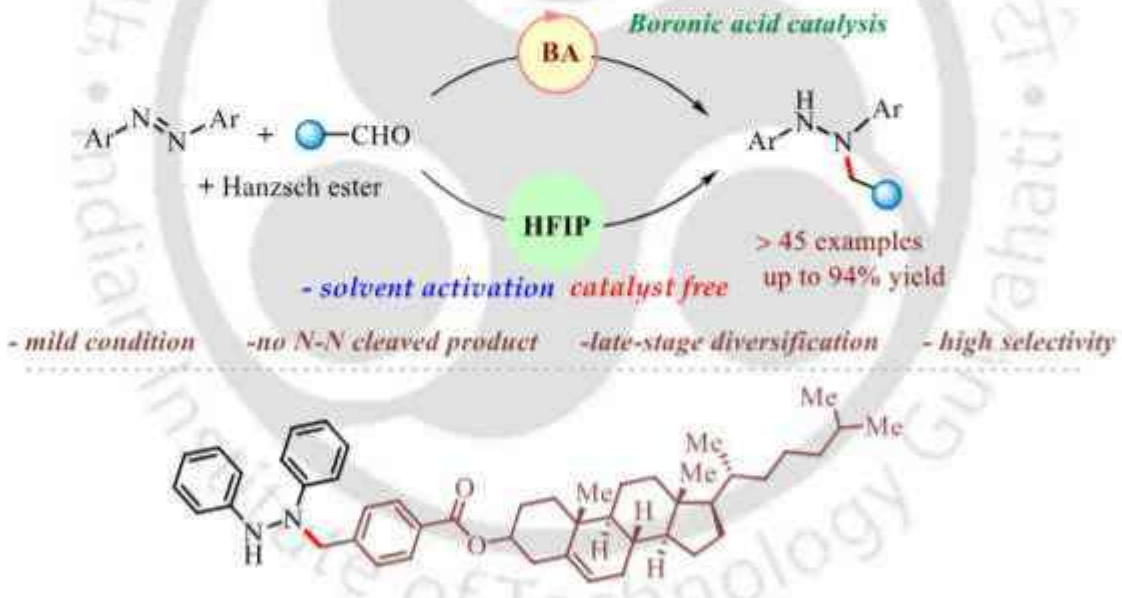


Chapter 3 illustrates the triple role of arylboronic acid as a catalyst in the alkylation of quinoline to *N*-substituted tetrahydroquinoline with diaryl motif at the C6-position. The reaction involved tandem reduction of quinoline to tertrahydroquinoline, followed by reductive *N*-alkylation with aldehyde to form *N*-alkylated tertrahydroquinoline and subsequent regioselective alkylation at the C6-position using *para*-quinone methide (*p*-QM) in a one-pot operation. The mechanistic study demonstrates the existence of organoboron catalysts as both Lewis acids and hydrogen-bond donors.

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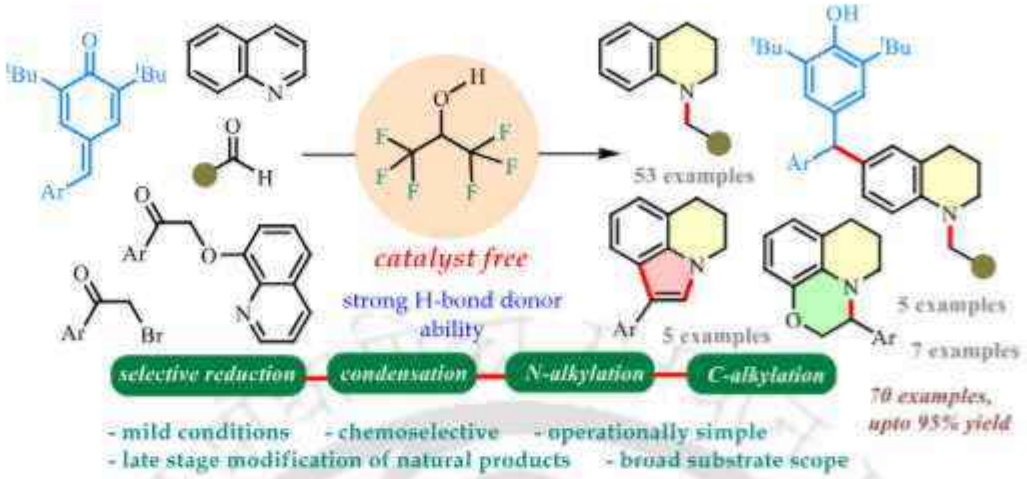


Chapter 4 describes a one-pot tandem reduction of azoarene with subsequent reductive alkylation using aldehydes to form *N*-alkylated hydrazine derivatives under mild conditions. The protocol shows notable selectivity as formation of *N*-*N* cleaved product amines and/or imines is completely suppressed and selectively provided *N*-alkyl-*N*, *N*'-diarylhydrazines. This study sheds light on the activation mode of boronic acid catalysis involves both H-bond donor catalysis and Brønsted acid catalysis. The strong hydrogen-bond donor ability of HFIP is also utilized in the reductive alkylation of azoarenes.

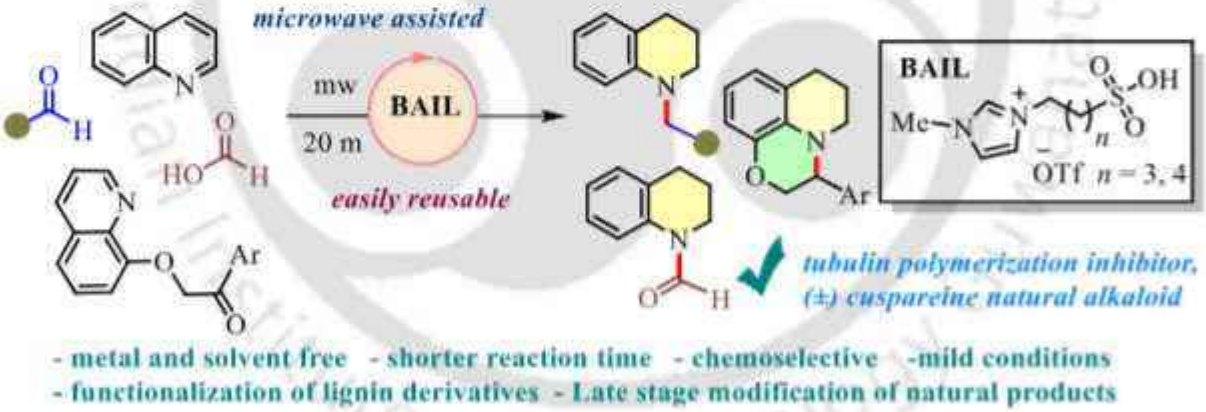


Chapter 5 introduces a hexafluoroisopropanol (HFIP)-mediated a one-pot tandem reduction of quinolines to tetrahydroquinolines followed by reductive alkylation by the aldehyde has been demonstrated through H-bonding network-enabled substrate activation. This step-economical synthetic approach is well suited for late-stage functionalization of complex bioactive molecules. The current reductive *N*-alkylation approach was also successfully utilized to synthesize novel tricyclic oxazino-fused-tetrahydroquinoline/ benzoxazine compounds and Lilolidine derivatives under ambient conditions. Scope of the reaction has been further extended to *C*-functionalized *N*-alkylated THQ derivatives in a one-pot by using *para*-quinone methides (*p*-QMs) or nitroolefins as alkylating precursors. The multifunctional role of HFIP has been demonstrated not only to facilitate the reduction of quinoline but also to improve

the stability of hemiaminal and/or iminium ion species through hydrogen-bonding network of HFIP.



Chapter-6 reports a green, cost-effective synthesis of *N*-alkyl tetrahydroquinolines using a Brønsted acidic ionic liquid (BAIL) that functions as both catalyst and solvent. This method operates efficiently under mild conditions and offers the advantage of BAIL reusability for at least five cycles with minimal loss of activity. The reaction follows a one-pot tandem reduction of quinolines to tetrahydroquinolines, followed by reductive alkylation with aldehydes. The workup process is also optimized for easy separation, recovery, and reuse of the Hantzsch ester.



Chapter 1

A brief introduction to boronic acid catalysis (BAC) and hexafluoroisopropanol (HFIP) mediated reactions in organic synthesis

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1.1. Brief introduction of boronic acids

1.1.1. Background and applications of boronic acids

Over the last few decades, boronic acids have emerged as a prevalent and important class of compounds used in a wide range of research areas, although they have no natural source and can be obtained only synthetically.[1] The landmark of boronic acids is attributed to their use in the well-known Suzuki–Miyaura cross-coupling reaction and their unique properties as well as reactivity.

In 1860, Frankland and Duppa reported the preparation and isolation of the very first boronic acid, ethylboronic acid, from the reaction of diethyl zinc and triethyl borate.[2] Ethylboronic acid was obtained after two subsequent oxidations of a highly reactive triethylborane intermediate under ambient aerial condition. Following this initial discovery, the synthesis and isolation of the first arylboronic acid, phenylboronic acid, was reported in 1880 by Michaelis and Becker using diphenylmercury ($HgPh_2$) with boron trichloride through a reactive dichlorophenylborane intermediate.[3] A century after these discoveries, boronic acids started to gain more attention from chemists with the revolutionary palladium catalyzed C–C cross-coupling reaction reported by Suzuki and Miyaura in 1979.[4] In recognition of the great significance that the Suzuki–Miyaura cross-coupling reaction holds in different areas of chemistry, in medicinal and materials chemistry, Professor Akira Suzuki was awarded the Nobel Prize in 2010.[5] Soon after synthetic utilities of boronic acids have expanded to other well-known reactions, such as Matteson homologation,[6] carbonyl allylboration,[7] the Petasis reaction,[8] Chan–Lam coupling,[9] and Liebeskind–Srogl coupling.[10] The wide recognition of boronic acids as versatile building blocks has led to major advances in the preparation of boronic acids and their derivatives, which also led to an increase of their commercial availability.

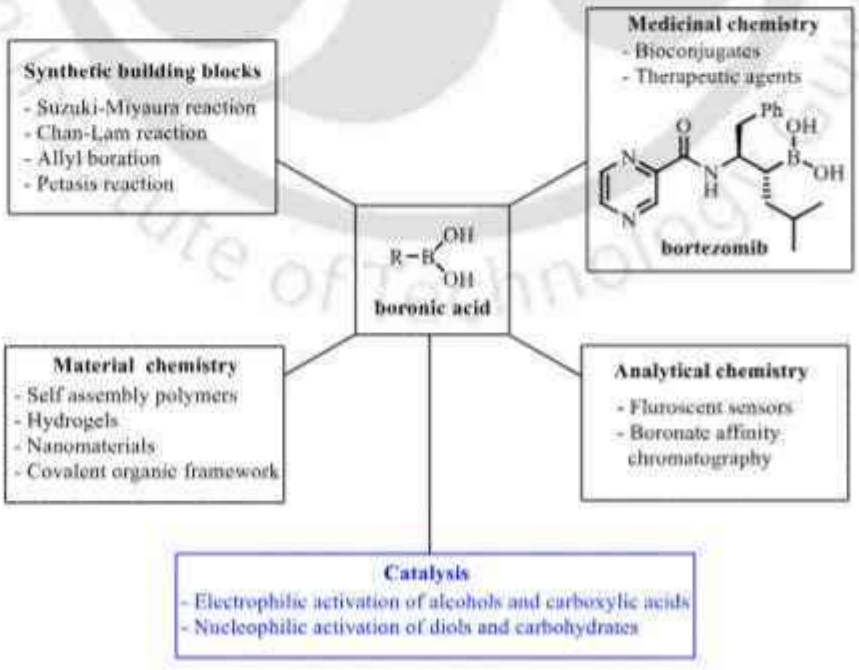


Figure 1.1. The application of boronic acids in various research fields.

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Recently, boronic acids have emerged as useful components in medicinal chemistry as therapeutic agents[11] and bioconjugates.[12,13] In this regard, the most notable example is the bortezomib, the first boronic acid containing drug, approved by the FDA in 2003. Since then, the number of bioactive boronic acids disclosed has increased exponentially. Additionally, the use of boronic acids is well-appreciated in materials and analytical chemistry. Boronic acids have been used extensively in the construction of covalent organic frameworks, hydrogels, polymers, and nanomaterials for various applications including drug delivery.[14–16] Boronic acid-based fluorescent sensors[17,18] and chromatography supports[19] have also become a valuable tool for analytical scientists for the detection and separation of carbohydrates, diols, and some ionic compounds.

1.1.2 Physicochemical properties

Structurally, boronic acids are trivalent organoboron compounds bearing one carbon substituent and two hydroxy groups on the central boron atom. With a deficiency of two valence electrons, the boron atom possesses a vacant *p*-orbital and is sp^2 hybridized (Figure 1.2A). Most boronic acids, especially arylboronic acids, exist as air stable crystalline solids with extended shelf-stability and can be handled without special precaution. Moreover, boronic acids generally possess low toxicity, and are deemed as environmentally friendly compounds since they ultimately degrade into benign boric acid.[20]

With the vacant *p*-orbital on the boron center, boronic acids are regarded as a mild class of organic Lewis acids that are capable of establishing reversible covalent bonds with basic compounds and nucleophiles. The pK_a of boronic acids lies in the of 5–9 and can be tuned by manipulating the nearby substituents. This characteristic nature of boronic acids also enables facile exchange of the B–OH groups with the hydroxy group of alcohols and carboxylic acids, generating boronic esters, and with vicinal nucleophiles, such as polyol, carbohydrates, and amino alcohols, forming cyclic boronic esters (Figure 1.2B). This dynamic exchange occurs at a higher rate with boronic acids with a lower pK_a due to the increase in electrophilicity at the boron center. Furthermore, under basic conditions of (pH greater than the pK_a of a boronic acid), Lewis acid–base interaction results in a tetrahedral anionic boronate species. In spite of two hydroxy groups, boronic acids hardly ever act as Brønsted acids in aqueous or basic conditions by losing a proton from one of the hydroxy groups (Figure 1.2C). Boronic acids also can behave as hydrogen bond donors and acceptors, as evidenced by X-ray crystallographic structures of boronic acids, where they generally exist as hydrogen-bonded dimers (Figure 1.2D).[21] The above-mentioned physicochemical properties of boronic acids are highly beneficial for various applications and led to a renaissance of research surrounding the chemistry of boronic acids.

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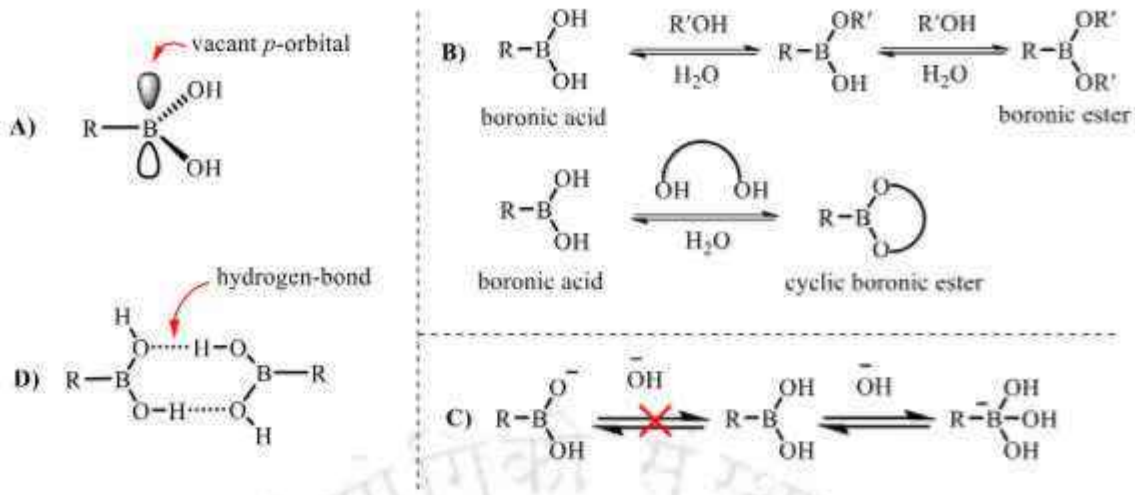
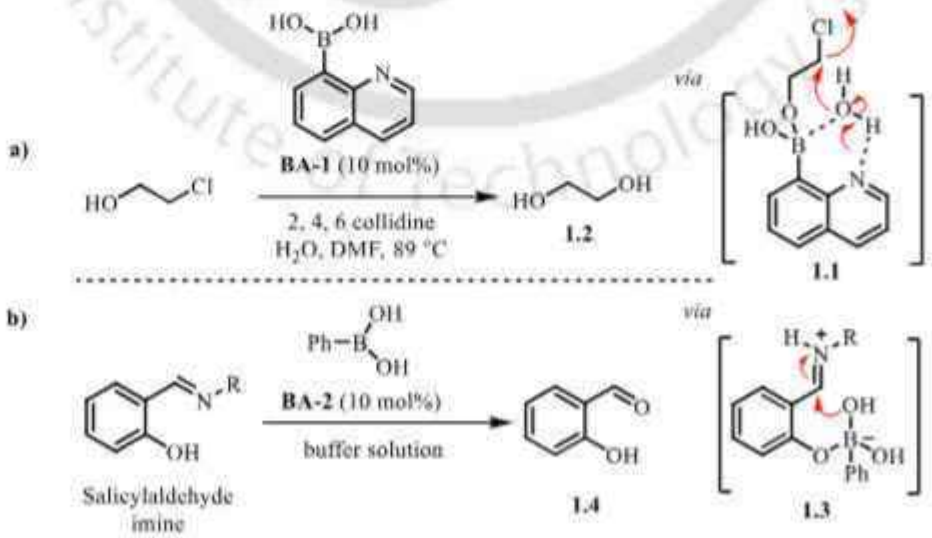


Figure 1.2. A) Structure; B) Reversible B-O bond exchange; C) in basic conditions; D) hydrogen-bonded dimer in solid states.

1.2. Boronic acid catalysis (BAC)

In history, the first boronic acid catalyzed reaction was reported in 1963 by Letsinger and co-workers.[22] The authors disclosed the use of 8-quinolineboronic acid (**BA-1**) to facilitate the hydrolysis of 2-chloroethanol in the presence of collidine (Scheme 1.1a). In this reaction, **BA-1** acts as a bifunctional catalyst, where the boronic acid unit brings the alcohol substrate and water together by formation of boronic ester **1.1**, and the nitrogen atom of the quinoline assists in the nucleophilic substitution of the chloride, presumably *via* hydrogen bonding and a cooperative base effect. Another early example of BAC with phenylboronic acid (**BA-2**) was disclosed by Philipp and Rao in 1991 for the hydrolysis of salicylaldehyde imine (Scheme 1.1b).[23] The coordination of the *ortho*-phenoxy group to **BA-2** generates the anionic boronate **1.3**, which not only holds and properly orients the substrates but also increases the nucleophilicity of the hydroxy group on the boron center for the subsequent nucleophilic attack onto the imine moiety.



Scheme 1.1. Boronic acid catalyzed hydrolysis a) 2-chloroethanol b) salicylaldehyde imine.

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1.2.1. Lewis acid catalysis *via* electrophilic activation

1.2.1.1. Electrophilic activation of carboxylic acids by BAC

Next, boronic acids have been utilized to affect both electrophilic and nucleophilic activation of hydroxy-containing compounds in various organic reactions. One of the most studied areas is the electrophilic activation of carboxylic acid using BAC for direct amide formation with amines (Figure 1.3). In 1996, Yamamoto and co-workers disclosed the use of 3,4,5-trifluorophenylboronic acid (**BA-3**) as an efficient catalyst for direct amidation in non-polar solvent under azeotropic reflux conditions.[24] Since then, several boronic acid catalysts (**BA-4**–**BA-10**) have been reported for direct amidation.[25–31] Generally, the activation of carboxylic acids by a boronic acid catalyst is proposed to originate from the formation of hydrogen-bonded intermediate **1.5**. However, in a recent work with extensive experimental and computational studies, Whiting and co-workers claimed that a dimeric intermediate, **1.6**, which is bridged by two carboxylates, is more likely to be the reactive intermediate.[32] Beside amines, the use of other nucleophiles, such as sodium azide, sodium borohydride, and urea, were also reported.

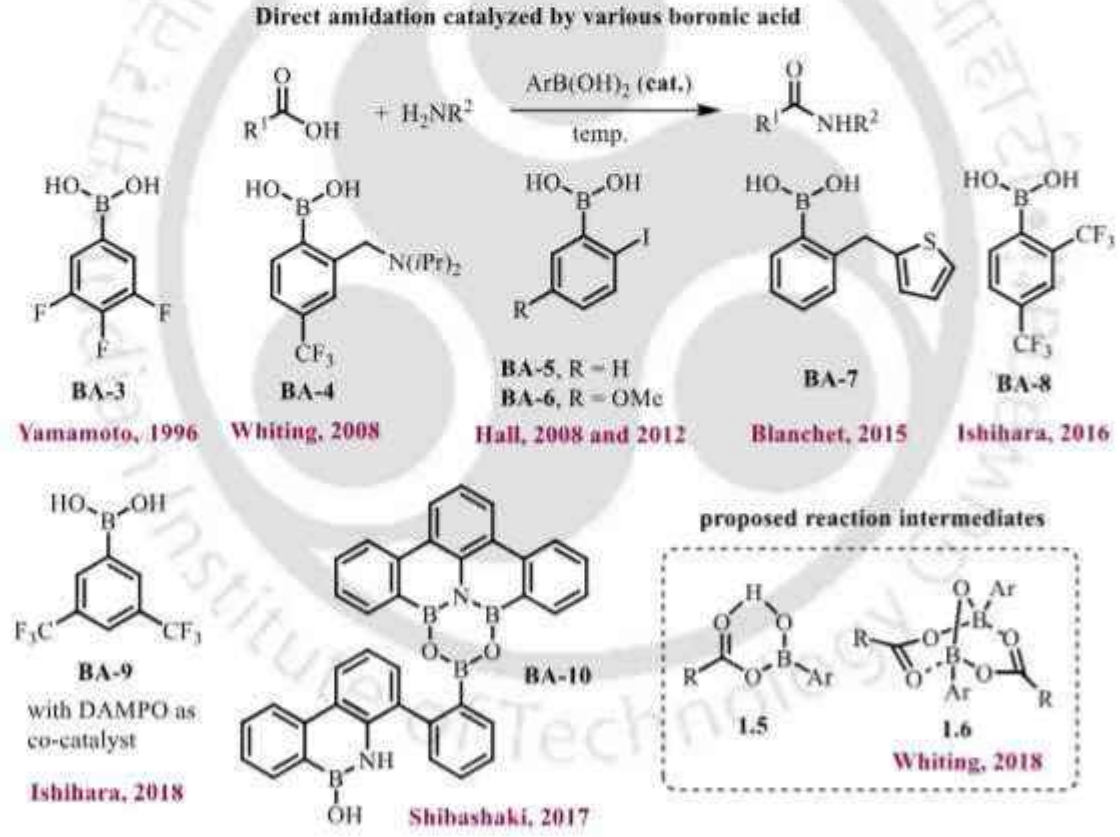


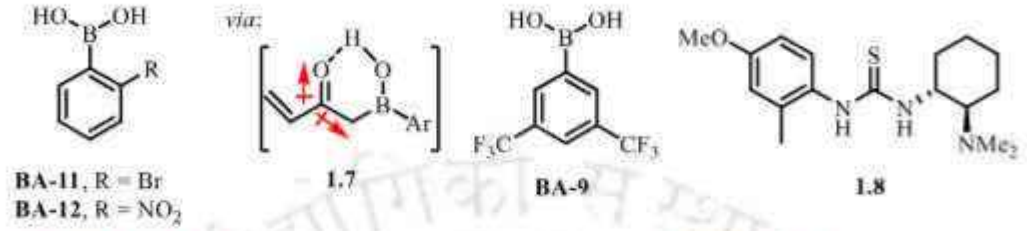
Figure 1.3. Examples of boronic acid catalysts for electrophilic activation of carboxylic acids and proposed reactive intermediate.

1.2.1.2. Electrophilic activation of α,β-unsaturated carboxylic acids by BAC

The concept of BAC was also extended to the electrophilic activation of α, β-unsaturated carboxylic acids towards cycloadditions and conjugate additions (Figure 1.4). 2-Bromophenylboronic acid (**BA-11**) and 2-nitrophenylboronic acid (**BA-12**) were reported by Hall and co-

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workers to be suitable catalysts for the Diels–Alder cycloaddition[33] and Huisgen cycloaddition[34] of α, β-unsaturated carboxylic acids. As evidenced by NMR spectroscopic studies, the hydrogen-bonded acylboronate intermediate **1.7** provides activation by lowering the LUMO energy of the unsaturated carboxylic acids.[34] In 2014, a dual catalytic system using **BA-9** and a chiral aminothiourea, **1.8**, for the asymmetric intramolecular conjugate additions of unsaturated carboxylic acid was disclosed by Takemoto and co-workers.[35]



BA-11, R = Br
BA-12, R = NO_2

Hall, 2008 and 2010

1.7

BA-9

1.8

Takemoto, 2014

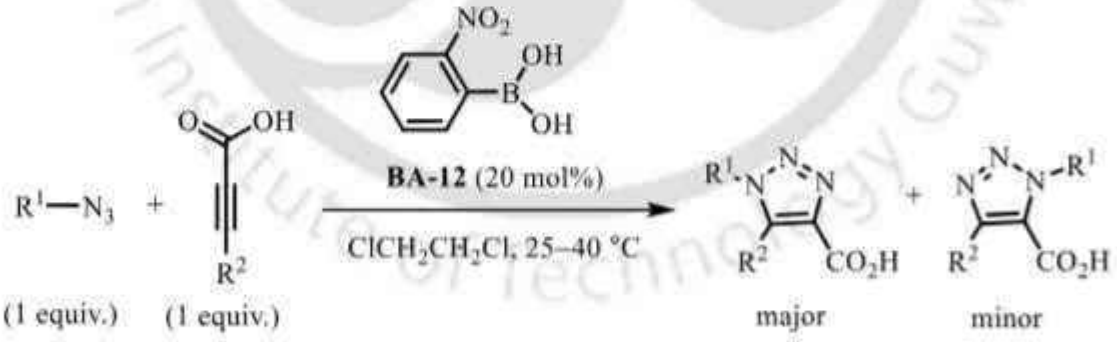
(a) Diels–Alder cycloaddition



1 equiv. 1 equiv.

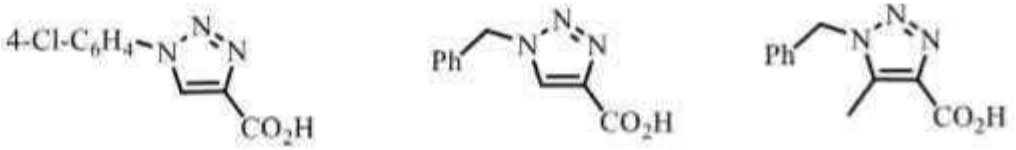
1.9, 90%
[no catalyst: < 5%]

(b) Huisgen cycloaddition



(1 equiv.) (1 equiv.)

major minor



25 °C, 4 h

1.10, 73%, > 20:1 regio.
[no cat.; 12%, 3:1]

25 °C, 4 h

1.11, 96%, > 98:2 regio.
[no cat.; 23%, 95:5]

40 °C, 48 h

1.12, 73%, > 98:2 regio.
[no cat.; 12%, 6:1]

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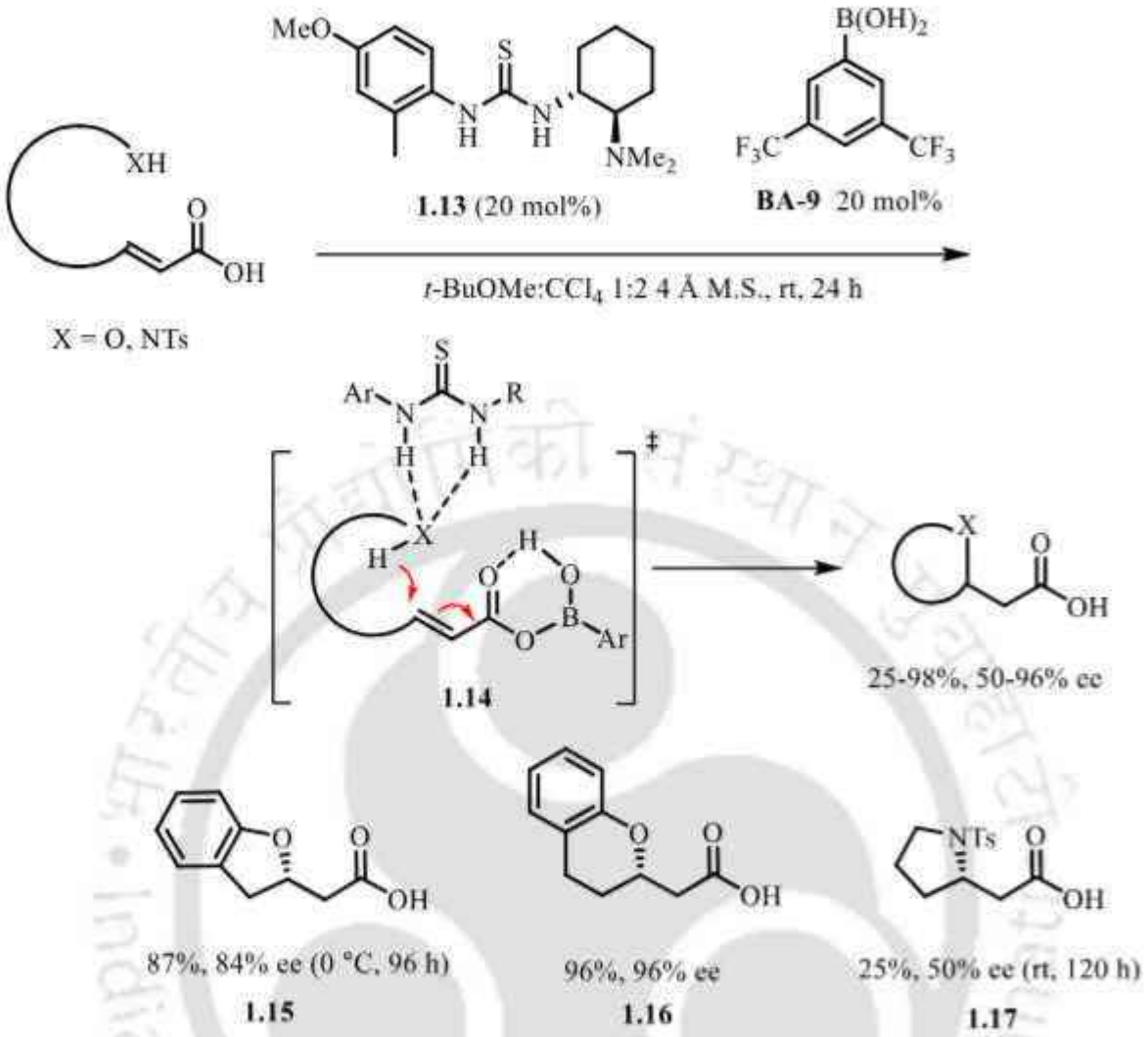


Figure 1.4. Examples of boronic acid catalysts for electrophilic activation of α,β-unsaturated carboxylic acids and proposed reactive intermediate.

The utilization of BAC also has been expanded to the electrophilic activation of alcohols *via* dynamic interaction of alcohols and boronic acids. The first example of such activation was discovered by McCubbin and co-workers in 2010 using highly Lewis acidic boronic acid, pentafluoroboronic acid (**BA-13**), for the direct use of allylic alcohols for Friedel–Crafts allylation with electron rich arenes.[36] Soon after, Hall and co-workers reported the use of 2,3,4,5-tetrafluorophenylboronic acid (**BA-14**) and hexafluoronaphthalene boronic acid (**BA-18**) to catalyze the 1,3-transposition of allylic and propargylic alcohols.[37] In 2012, *N*-methyl-difluoro-pyridinium boronic acid (**BA-16**), along with **BA-14** and **BA-15**, also were recognized as effective catalysts for the intramolecular cyclization of allylic alcohols with pendant nucleophiles.[38] In 2015, Hall and co-workers discovered improved conditions for the Friedel–Crafts allylation and alkylation of benzylic alcohols with less activated arenes using catalyst **BA-14** and ferrocenium boronic acid (**BA-17**) in a solvent mixture containing hexafluoroisopropanol (HFIP).[39,40]

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Activation of allylic alcohols with boronic acid catalysis

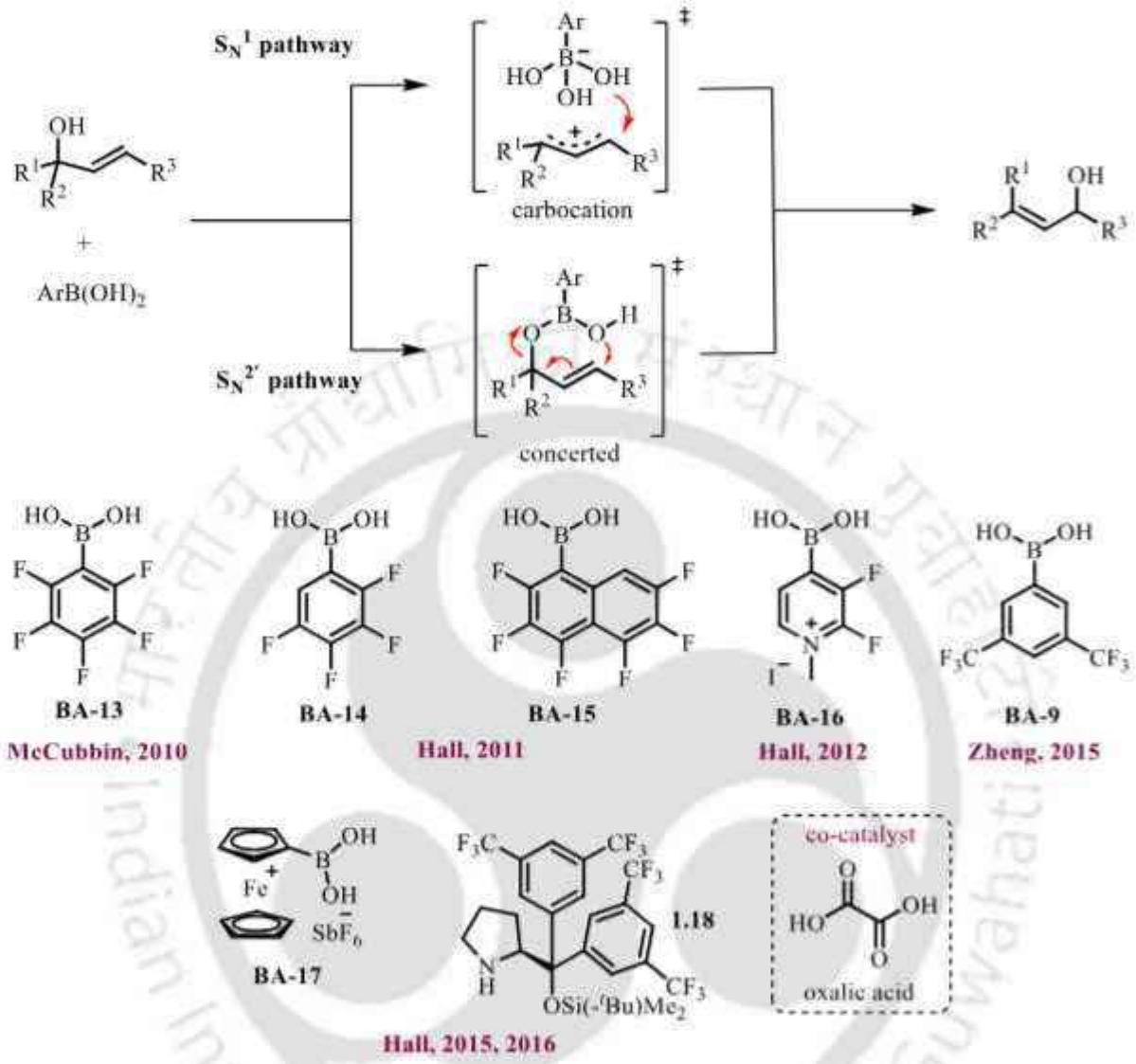


Figure 1.5. Examples of boronic acid catalysis for the electrophilic activation of allylic and benzylic alcohols.

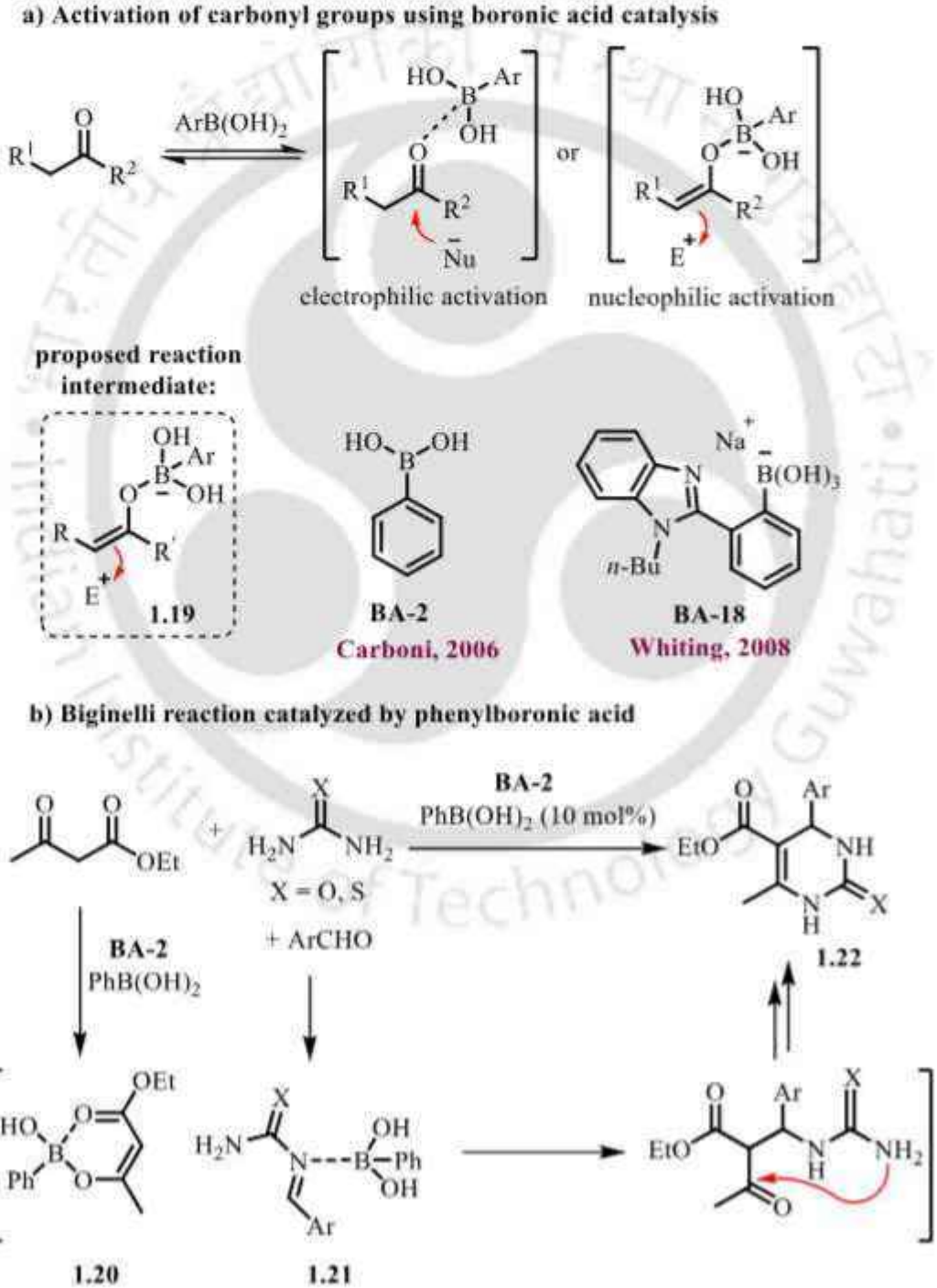
1.2.1.3. Lewis acid catalysis *via* nucleophilic activation

Due to their Lewis acidity, aryl boronic acids may activate carbonyl compounds by increasing the electrophilicity of the carbonyl carbon (or an imine) in a manner similar to traditional Lewis acids, or by promoting the nucleophilicity of the α-carbon by facilitating enolate formation.

In 2006, Carboni and co-workers reported the use of catalytic phenylboronic acid (**BA-2**) to accelerate the three-component Biginelli reaction involving ethyl acetoacetate, aryl aldehyde, and urea.[41] It was envisioned that **BA-2** not only provides nucleophilic activation to ethyl acetoacetate *via* the formation of enolate intermediate **1.20** but, also provides electrophilic activation to the acylimine intermediate **1.21**, which was generated from the condensation between aldehyde and urea *via* a boron–nitrogen covalent interaction. Later, an anionic boronate **BA-18**, was disclosed by Whiting and co-workers as an excellent catalyst for the

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cross-aldol reaction of α-hydroxyketones and aldehydes in water.[42,43] Toshima and co-workers proposed multiple roles of boronic acid **BA-19** in their regioselective and 1,2-cis-α-stereoselective glycosylation BAC protocol.[44] As depicted in Scheme 1.2, **BA-19** not only serves as a template to bring both the glycosyl donor and acceptor together, it also provides electrophilic activation to the 1,2-anhydro glycosyl donor *via* complex **1.24**, which triggers the epoxide ring opening, generating the anionic boronate intermediate **1.25**. The formation of intermediate **1.24** then enhances the nucleophilicity of the glycosyl acceptor and facilitates the glycosylation through the addition of more accessible 6-alkoxy group to the bottom face of the oxonium cation.



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c) Aldol reaction and condensation catalyzed by boronic acid

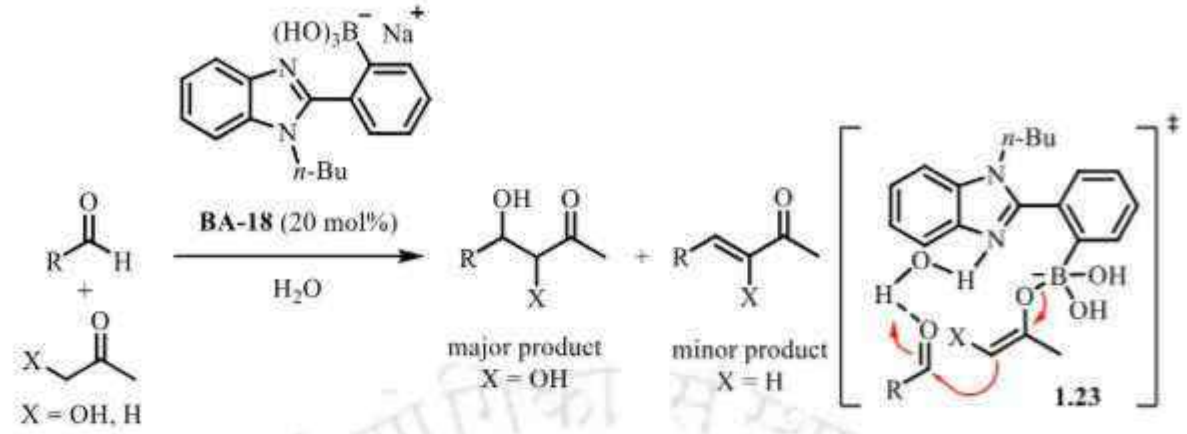
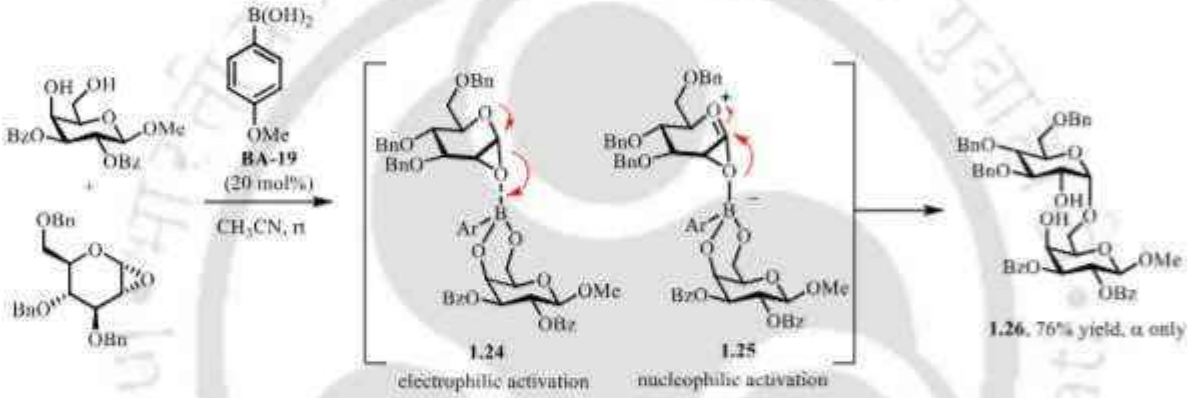


Figure 1.6. Examples of boronic acid catalysts for the nucleophilic activation of carbonyl compounds.

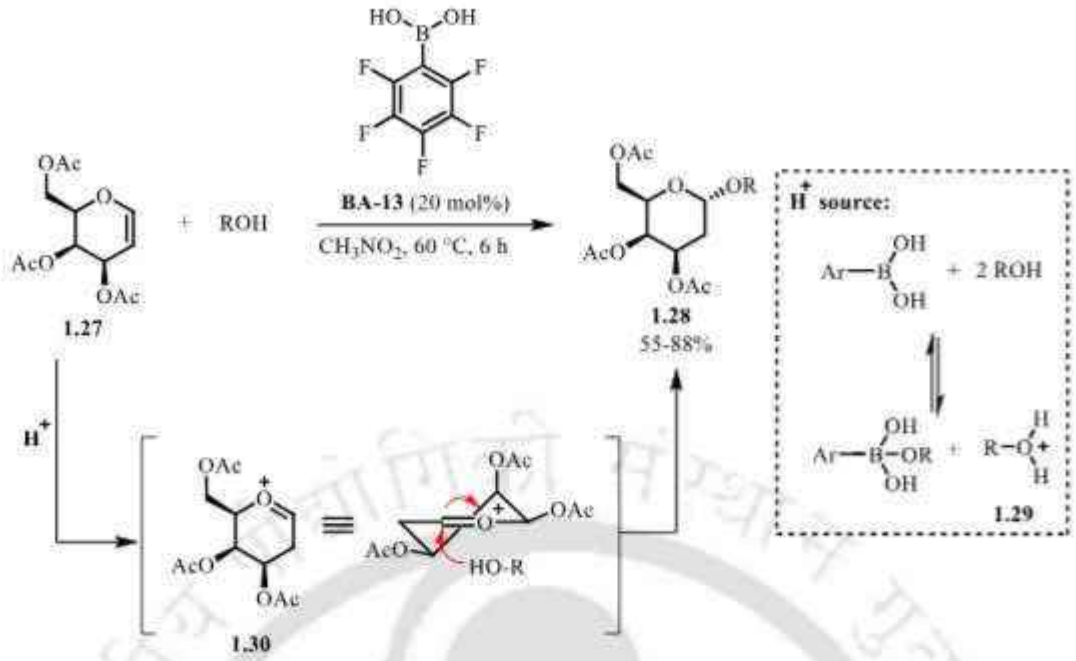


Scheme 1.2. Examples of dual role of boronic acid in BAC.

1.3. Indirect Brønsted acid catalysis

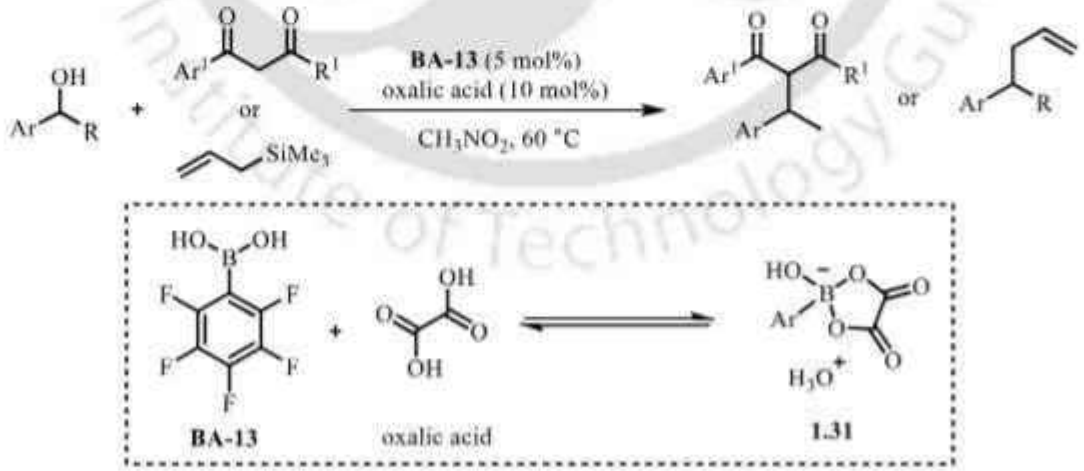
In 2019, Judeh and co-workers described a boronic acid catalyzed direct α-stereoselective addition of alcohols to deactivated peracetylated D-galactal **1.27** to yield a series of 2-deoxygalactosides, **1.28**, in moderate to good yields (Scheme 1.3).[45] To investigate the reaction mechanism, ^{1}H NMR studies of the reaction mixtures in CD_3NO_2 were performed. However, no clear changes in chemical shift of the olefinic proton of **1.27** was observed, which rules out any activation of substrates by **BA-13** *via* Lewis acid–base interaction. Based on these observations, the authors proposed that **BA-13** likely acts as an indirect Brønsted acid source through the generation of alkyloxonium ions **1.29** by a Lewis acid-mediated ionization equilibrium of **BA-13** and two moles of alcohols. Hydronium ions also can be formed in a similar fashion with adventitious water in the reaction. To this end, it is proposed that the reaction proceeds through the formation of oxonium intermediate **1.30** induced by a Brønsted acid.

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Scheme 1.3. Direct a-stereoselective synthesis of 2-deoxygalactosides **1.28** from acetylated D-galactal and alcohols catalyzed by **BA-13**.

In 2020, Taylor and co-workers extended the application of their **BA-13**/oxalic acid co-catalytic protocol to enable the construction of new C–C bonds with secondary benzylic alcohols as the electrophiles and 1,3-dicarbonyl compounds or allyltrimethylsilane as the nucleophiles (Scheme 1.4).[46] Similar to their previous work on dehydrative etherification of benzylic alcohols, a Brønsted acid-promoted electrophilic activation of alcohols involving the hydronium boronate ester **1.31**, was proposed which is formed by the condensation of **BA-13** and oxalic acid, was proposed. The formation of the hydronium species **1.31** was supported by X-ray crystallographic analysis and NMR spectroscopy from their previous report.[47]

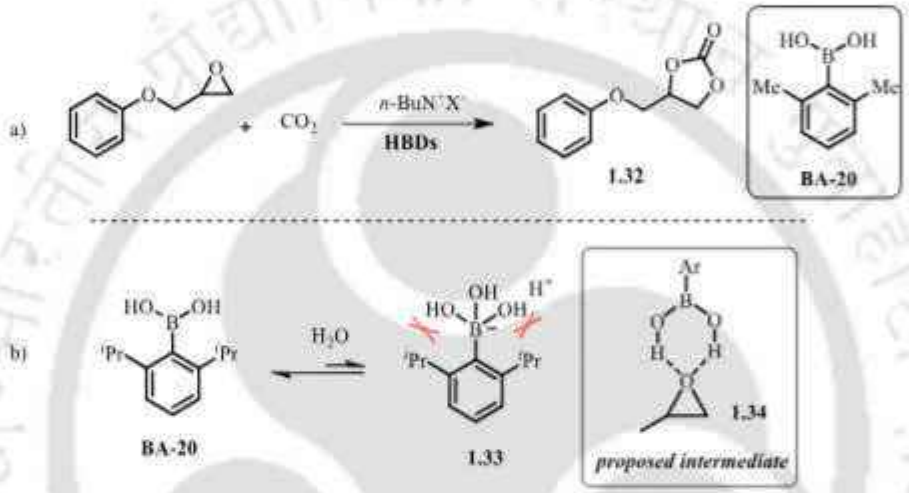


Scheme 1.4. Examples of dual role of boronic acid in BAC.

1.4. Hydrogen-bond donor catalysis

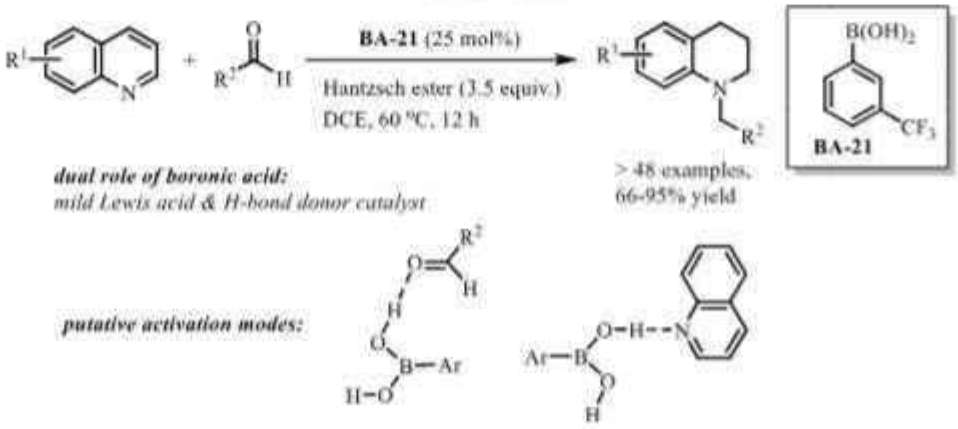
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The ability of boronic acids to act as hydrogen-bond donors to facilitate reactions has been proposed in the past, where secondary interactions are provided *via* hydrogen-bonding to bind and hold reagents in close proximity. The direct activation of nitrogen- and oxygen-containing compounds *via* hydrogen-bonding mechanism was proposed recently. In 2016, Zhang and co-workers reported 2,6-subtituted arylboronic acid as a hydrogen bond donor catalyst in the reaction of CO_2 with epoxide in water.[48] Various epoxides were transformed into corresponding cyclic carbonates with excellent yields under environmentally benign conditions. In general, higher positive charge on boron increases the Lewis acidity of boronic acid, while substitution on 2, 6-position will apparently affect its Lewis acid strength due to the F-strain effect (Scheme 1.5). This phenomenon makes the catalysts in the red circle behave like a strong Brønsted acid, providing strong hydrogen bond donor catalyst.



Scheme 1.5. Proposed intermediate.

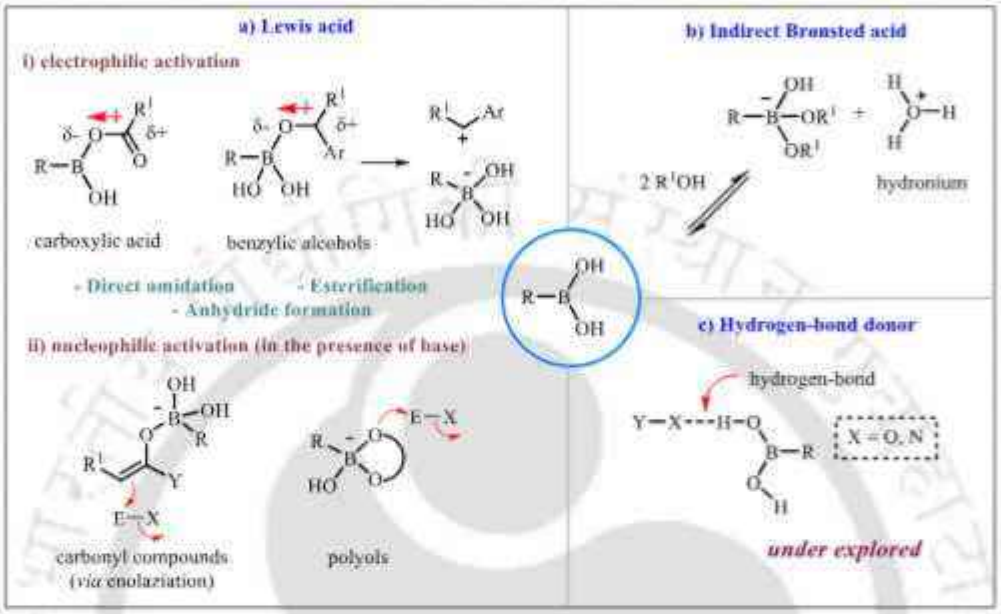
In 2021, reductive alkylation of quinolines to *N*-alkyl tetrahydroquinolines catalyzed by 3-trifluoromethyl-phenylboronic acid (**BA-21**) was reported by Das and co-workers (Scheme 1.6).[49] This protocol features a mild and step-economical synthesis of tetrahydroquinoline from readily available quinolines and aldehydes using Hantzsch ester (HE) as the reductant. Based on extensive NMR studies, a dual-role of **BA-21** was proposed in this transformation *via* Lewis acid catalysis and H-bond donor catalysis. **BA-21** activates quinoline, aldehyde as well as HE *via* hydrogen bonding interactions. **BA-21** also assists in the condensation of aldehydes with the tetrahydroquinoline intermediate as a Lewis acid.



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Scheme 1.6. Arylboronic acid as HBDs catalyst in reductive alkylation of quinoline.

In a nutshell, boronic acids confer multiple mode of activation in the reaction mechanism. These are associated with (a) Lewis acid catalysis *via* electrophilic activation, and nucleophilic activation in the presence of base (b) indirect Brønsted acid catalysis and (c) H-bond donor catalysis (Scheme 1.7).



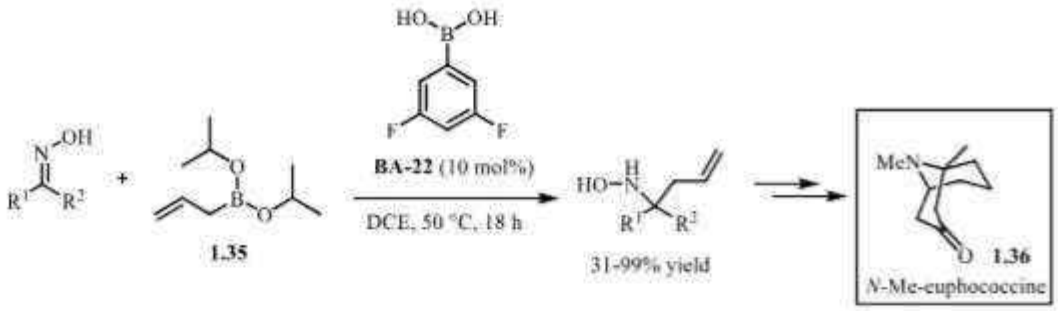
Scheme 1.7. Putative activation modes *via* BAC.

1.5. Practicality and versatility of BAC

As mentioned above, the physicochemical properties of arylboronic acids make them good candidates as catalysts with high practicality. Due to their high stability, boronic acid catalysts can be recovered easily by column chromatography or acid–base extraction. Although aryl boronic acids are generally inexpensive, the ability to recover them after a reaction would be highly advantageous in industrial settings, specifically, in terms of improving atom-economy and reducing the cost of manufacturing, where the reactions are conducted in large scale. The recoverability of boronic acids has also been demonstrated on the direct amidation of carboxylic acid and intramolecular cyclization of allylic alcohols bearing a pendant nucleophile.[50,51]

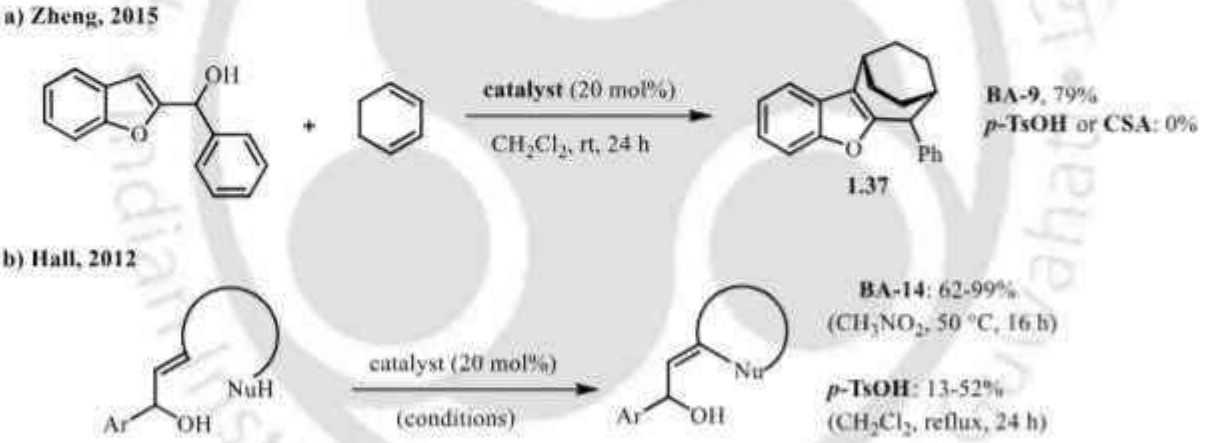
Recently, the concept of BAC was expanded further to total synthesis of *N*-Me-Euphococcine **1.36** by Kürti and co-workers in their work on the use of 3,5-difluorophenylboronic acid (**BA-22**) in promoting the *C*-allylation of oximes with allyl diisopropyl boronate **1.35** (Scheme 1.8).[52] The use of **BA-22** was found to be crucial in the transformation, as only a trace amount of product was obtained in the absence of **BA-22**.

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Scheme 1.8. The se of boronic acid catalyst in total synthesis of *N*-Me-Euphococcine.

The mildness of BAC protocols offers higher efficiency and tolerance of sensitive functional groups compared to the conventional protic acid systems. For example, in the boronic acid catalyzed [4+3] cycloaddition with indolyl alcohols by Zheng and co-workers, while BAC protocols afforded the desired products in moderate to high yields, strong protic acids, such as *p*-toluenesulfonic acid (TsOH) or camphorsulfonic acid (CSA), failed to deliver the desired products and resulted in undesired self-condensation (Scheme 1.9a).[53] The superiority of boronic acid over protic acids was testified also by Hall and co-workers in the intramolecular cyclization of allylic alcohols, where compared to the use of TsOH, **BA-14** resulted in higher product yields and cleaner reactions (Scheme 1.9b).[51]



Scheme 1.9. Examples illustrating the mildness of BAC system.

BAC also imparts better atom- and step-economy compared to conventional methods, which is beneficial in the concept of green chemistry. For example, the direct electrophilic activation of hydroxy group via BAC not only avoids the need of pre-activation of the hydroxy group into more reactive intermediates using excess reagents, it also generates water as the only by-product. Lastly, the operational simplicity of BAC, which does not require special precautions, is also an attractive aspect regarding practicality.

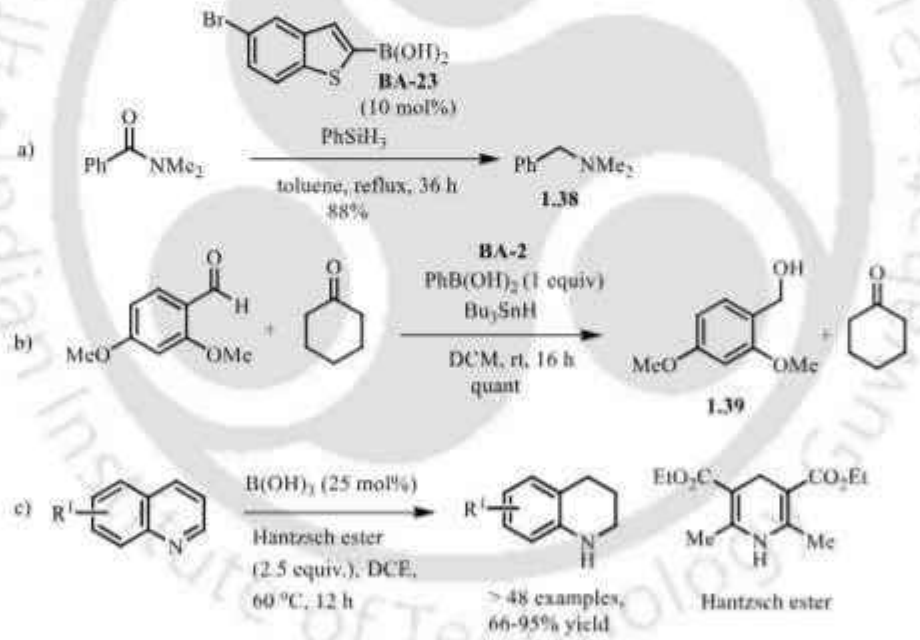
1.6. Challenges and current limitations of BAC

i) High catalyst loading: Compared to transition-metal catalysis, BAC generally requires higher catalyst loading (5–25 mol%). However, this disadvantage of BAC is offset easily by the price and recoverability of boronic acids.

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ii) Scarcity of boronic acid in reduction chemistry: Despite the impressive breakthroughs achieved in BAC, only handful examples of reduction reactions have been reported. This limitation is likely due to the instability of boronic acid under harsh reaction conditions.[54] Chemists have overcome this problem partially by employing mild reductants. Therefore, there is an ample opportunity for the development of more general and selective BAC in the future.

For instance, Beller and co-workers reported that benzothiophene boronic acids were effective catalysts for the chemoselective reduction of tertiary, secondary, and primary amides by hydrosilylation using phenylsilane (Scheme 1.10).[55] Data from mechanistic studies were inconsistent with direct activation of the amide carbonyl group by complexation to the boron. Instead, the data suggest activation by a hydrogen bond, though that explanation does not explain the observed changes in the boronic acid structure observed by NMR spectroscopy. Yu and Wang showed that arylboronic acids can promote the reduction of aldehydes with tributyltin hydride; however, attempts to use the boronic acid in sub-stoichiometric amounts resulted in poor yields, likely due to preferential complexation with the reaction product, and the reaction failed with ketones.[56] Finally, simple boric acid has been used to promote the reduction of quinolines using Hantzsch esters through coordination of the quinoline nitrogen to the boron.[57]



Scheme 1.10. The use of boronic acid in reduction chemistry.

iii) Scarcity of boronic acid in the multicomponent reactions: Although boronic acids are recognized primarily for their utility as reagents in transition metal-catalyzed transformations, other applications are emerging, including their use as reaction catalysts. However, the merging both as reagents and catalysts in an organic transformation is not explored. For example, our group has recently developed a boronic acid catalyzed one-pot reduction of quinolines with Hantzsch ester followed by *N*-arylation via external base-free Chan–Evans–Lam coupling has been demonstrated.[58] The dual role of boronic acid as a catalyst (in the reduction of quinolines) and a reagent (in the *N*-arylation) has been attained.

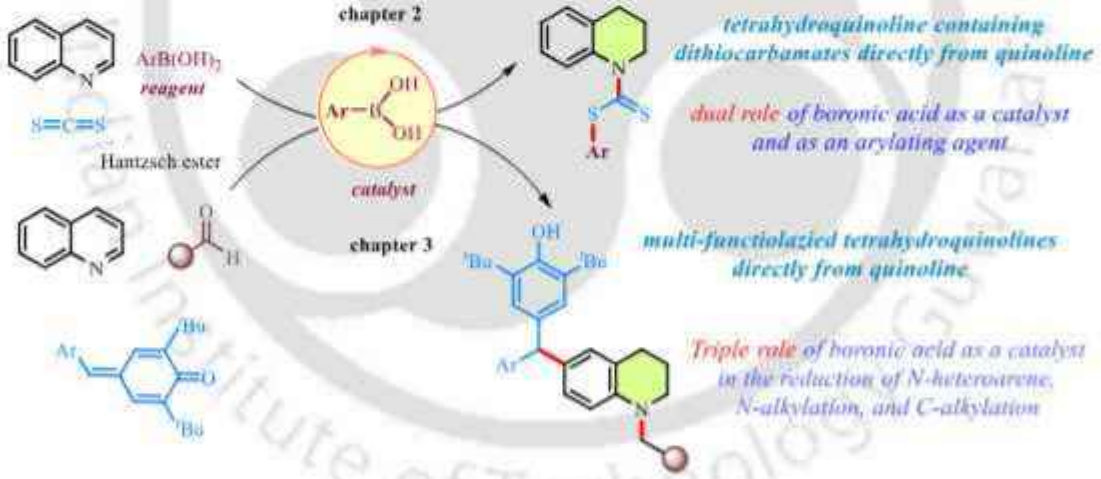
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1.7. Thesis objectives on BAC catalysis

As a promising emerging area of catalysis, it is believed strongly that the potential of BAC has not been realized fully yet, as several limitations remain to be addressed. Therefore, the goals of this thesis are: (1) to expand the scope of reactions amenable to BAC, including tandem transformations and multicomponent reactions; (2) to improve the efficiency of the existing BAC protocols; and (3) to learn more about the role of the boronic acid functionality in the BAC. It can be anticipated that achievement of these goals will provide important insights enabling future advances of BAC.

Chapter 2 will describe an efficient sequential multi-component method for the synthesis of tetrahydroquinoline containing dithiocarbamates involving a boronic acid-catalysed reduction of quinolines to tertrahydroquinolines, followed by nucleophilic addition reaction with carbon disulphide and subsequent *S*-arylation *via* external base free Chan–Evans–Lam coupling in a one-pot operation. The dual role of the boronic acid as a catalyst (in the reduction of quinolines) and as a reagent (in the *S*-arylation) will be established for the first time herein.

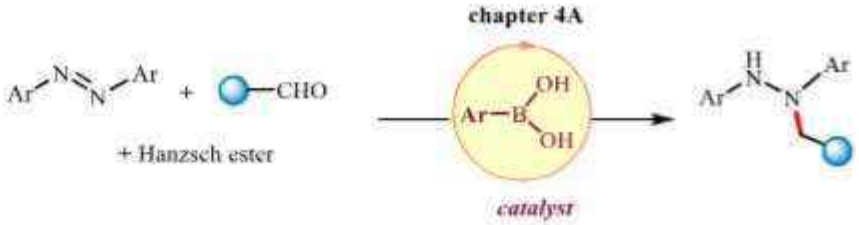
Chapter 3 will describe efforts made in the triple role of boronic acid as a catalyst in the reduction of quinoline to tetrahydroquinoline, followed by reductive *N*-alkylation with aldehyde and subsequent regioselective alkylation at the C6-position using *para*-quinone methides (*p*-QMs) in a one-pot operation. Mechanistic studies were conducted to gain insights into the role of the catalyst in the transformation.



Scheme 1.11. Synthesis of multi-functionalized tetrahydroquinolines directly from quinoline.

Chapter 4 will introduce a facile method for the synthesis of *N*-alkyl-*N*, *N'*-diarylhydrazines by boronic acid-catalyzed one-pot tandem reduction of azoarene to hydrazoarene followed by reductive alkylation with the aldehyde. The mild reaction conditions suppress N-N cleaved products and selectively provide trisubstituted hydrazine derivatives. Mechanistic study sheds light on the activation mode of boronic acid catalysis of azobenzene and aldehyde, showing Brønsted acid and H-bond donor catalysis, rather than Lewis acid activation.

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Scheme 1.12. Synthesis of *N*-alkyl-*N*, *N'*-diarylhydrazines *via* boronic acid-catalyzed reductive alkylation of azobenzene.

1.8. Brief introduction of hexafluoroisopropanol (HFIP)

Hexafluoroisopropanol (HFIP) is a polar, strongly hydrogen bond-donating solvent that has found numerous uses in organic synthesis due to its ability to stabilize ionic species, transfer protons, and engage in a range of other intermolecular interactions. The use of this solvent has exponentially increased in the past decade and has become a solvent of choice in various areas in chemistry, such as C-C bond-forming reactions, C-H functionalization reactions, condensations, heteroatom additions and eliminations, cyclization reactions, pericyclic reactions, oxidations and reductions, hypervalent iodine chemistry and photocatalysis.

In 1960, Knunyants and co-workers reported the first synthesis of HFIP through the reduction of hexafluoroacetone with sodium borohydride.[59] Soon after, Middleton and Lindsey showed remarkable hydrogen bonding ability of HFIP which was dictated by cumulative inductive effect of the six fluorine atoms. In the late 1970s, HFIP was demonstrated in the Ugi four-component condensation, representing one of its earliest uses in organic synthesis.[60] Later, Kopple and co-workers examined further utility of as a solvent for peptide coupling.[61] In the span of few decades, HFIP has infrequently used solvent to a mainstream choice in many areas of chemistry including organic, inorganic, and organometallic chemistry, further extent to electrochemistry. Lastly, some interesting applications in the field of chemical biology and polymer science also illustrates the role of HFIP beyond small molecule chemistry.

1.8.1. Physical and chemical properties of HFIP

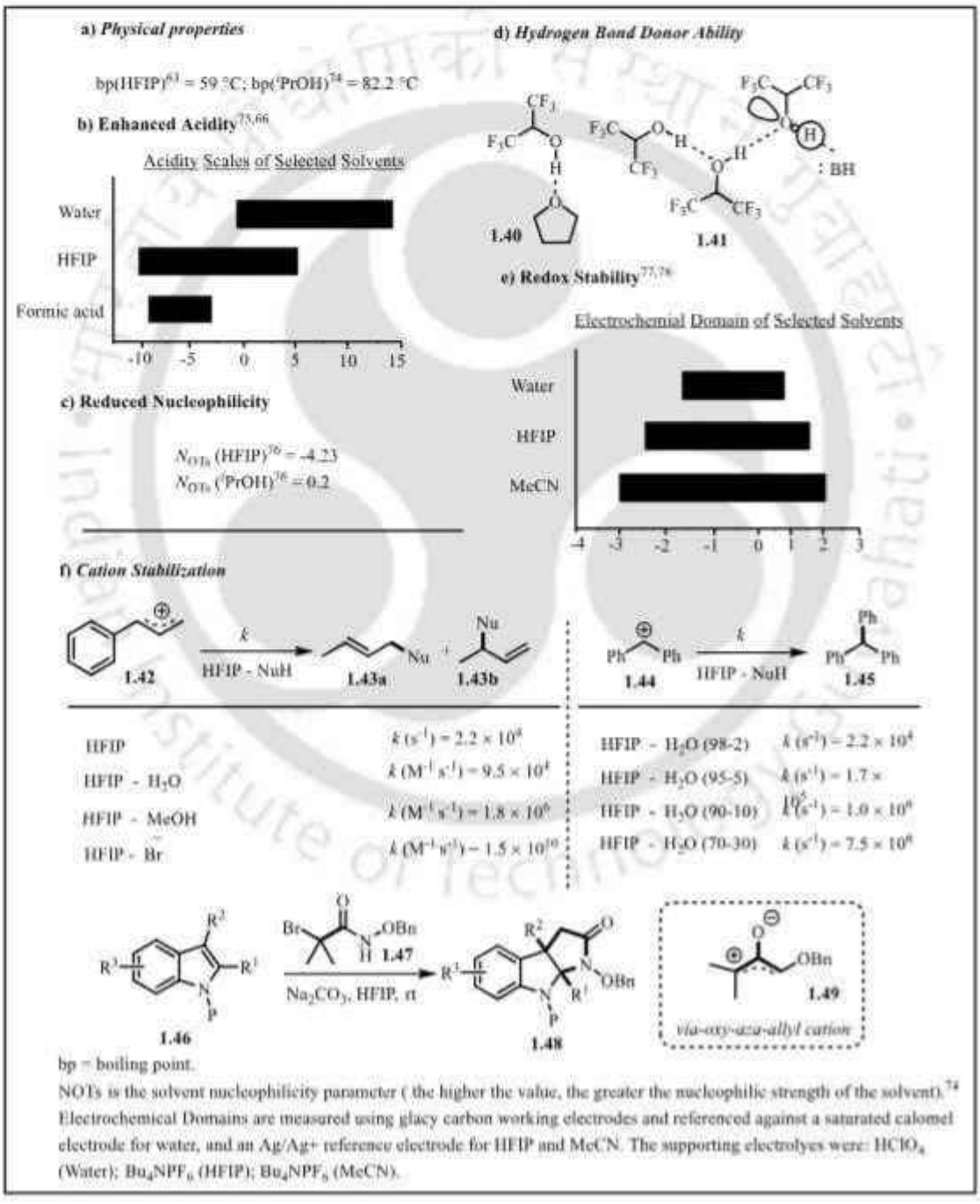
a) Physical properties: HFIP does not absorb UV light, is thermally stable and is also miscible with water and most common polar organic solvents.[62] The low boiling point (59 °C)[63] permits facile recovery by distillation, resulting in reduced solvent waste. The industrial procedures for HFIP recovery on large scale have been developed involving co-distillation with heptanes and separation of the immiscible distillate.[64]

b) Enhanced acidity: The negative inductive effect as a consequence of fluorination results in a significantly enhanced acidity for HFIP in aqueous solution ($pK_a = 9.3$)[63] than observed for *i*PrOH (pKa = 17.1).[65] Interestingly, the range of acidities achievable in HFIP is more directly comparable to that of formic acid.[66]

c) Reduced nucleophilicity: A comparison of the solvent nucleophilicity parameters (N_{OTs}) for *i*PrOH and HFIP highlights the dramatically decreased nucleophilicity of fluorinated alcohols compared to their non-fluorinated counterparts.

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d) Hydrogen bond donating ability: A striking example of the hydrogen bond donating ability of HFIP has been reported by Lindsey, where HFIP (bp 59 °C) and THF (bp 66 °C) were observed to form a stable, equimolar complex with a boiling point of 100 °C (see figure 1.7d).[67] Work by Anderson investigated the effect of mixing HFIP with tertiary amines.[68,69] With increasing amine basicity, enthalpies of hydrogen bond formation become increasingly exothermic, approaching a maximum of –31 kJ mol^{-1} for quinuclidine.[69] More recently, an aggregation-induced hydrogen bonding enhancement of HFIP was demonstrated (see figure1.7d), and it was concluded that the upper limit of this effect was a trimer of HFIP monomers.[70]



bp = boiling point.

NOTs is the solvent nucleophilicity parameter (the higher the value, the greater the nucleophilic strength of the solvent).[74] Electrochemical Domains are measured using glacy carbon working electrodes and referenced against a saturated calomel electrode for water, and an Ag/Ag+ reference electrode for HFIP and MeCN. The supporting electrolyes were: $HClO_4$ (Water); Bu_4NPF_6 (HFIP); Bu_4NPF_6 (MeCN).

Figure 1.7. Key physical and chemical properties of HFIP.

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e) Redox stability: The oxidative stability of HFIP makes it an ideal solvent for electrochemical investigations.[71]

f) Cation stabilisation: The reasonably high dielectric constant (ε = 15.7) and low nucleophilicity mean that HFIP is an ideal solvent in which to generate and study cations. Very recently, Jeffrey[72] and Wu[73] have exploited this property, reporting the first [3+2] cycloaddition of indoles **1.46** using aza-oxyallyl cation (see Figure 1.7f) generated in-situ from bromoamide **1.47**. Wu speculates that azaoxyallyl cation formation occurs by a hydrogen bond mediated tautomerisation followed by unimolecular ionisation of bromide. DFT calculations indicate that strong hydrogen bond donor solvents lower the transition state energy and stabilise the intermediate, thus accelerating the rate of the reaction.

1.8.2. HFIP in organic synthesis

Although most of the traditional reactions whereby HFIP activates organic molecules rely on carbonyl and epoxide substrates,[76,79] recent developments involving other reactive functional groups such as alcohols, halides, imines, sulfonates, hypervalent iodine reagents have also been reported. For some of the most recent examples, the actual role of HFIP is still unknown and mechanistic studies are required for a complete understanding and further development of these synthetic methods.

a) Carbonyl activation: The Aubé group reported the intramolecular Schmidt reaction using catalytic Lewis acid (10 mol% of TiCl4) in HFIP, see (Figure 1.8a). Use of this solvent overcomes one of the previous limitations of the reaction, namely the requirement for excess Lewis or Bronsted acid in order to achieve complete conversion, because of strong product binding and reaction inhibition.[80] In this case, inhibition was not observed due to competitive and strong hydrogen bonding of the amide product to HFIP itself. More recently, this methodology has been extended to an intermolecular Schmidt reaction with triflic acid employed as the optimal catalyst.[81] The same group has also reported the HFIP promoted intramolecular Friedel-Crafts reaction of acyl chlorides requiring no additional catalyst (Figure 1.8a).[82] Mechanistic experiments supported acyl chloride activation promoted *via* hydrogen bonding to HFIP. In the intermolecular version, electron rich arenes, including pyrrole, indole and benzothiophenes were used to good effect.[83]

b) Epoxide activation: Qu investigated the intra- and intermolecular Friedel-Crafts alkylation of electron rich arenes with epoxides **1.56** being activated by HFIP (Figure 1.8b). Remarkably, no catalyst was required and no reaction was observed in other commonly used solvents including toluene, acetone or acetonitrile.[84] The authors proposed an acid catalysed pathway involving concerted C–O bond cleavage and C–C bond formation, supported by an inversion of stereochemistry.

c) Imine activation: The addition of alkynes to imines in HFIP has been reported by Tehrani, leading to β-amino-ketones (see **1.61** in Figure 1.8c).[85] The presence of the α,α-dichloro moiety is crucial for the intermediate to be sufficiently electrophilic in this solvent. Mechanistic experiments suggest protonation of the imine, followed by alkyne addition to afford a stabilised vinyl cation, which may be trapped by HFIP, before being hydrolysed to the final product.

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d) Alcohols: The metal-free substitution of allylic alcohols **1.62**, reported by Baeza and Nájera in 2012, represents one of the first examples of alcohol activation in HFIP (Figure 1.8d).[86] Nucleophiles including amines, sulfonamides and carbamates were used, affording allylic amines with modest to good yields. Additionally, C-C bond formation was achieved using allyl silanes, 1,3-dicarbonyl compounds or electron-rich aromatic compounds, in a Friedel-Crafts-type reaction.

e) Halides: The effect of HFIP on activating halides has few examples. The reported examples relied on a neighbouring activating group, e.g. β-thioether.[87] However, Paquin has recently shown a very interesting Friedel-Crafts arylation of benzyl fluorides **1.66** with electron-rich arenes *via* selective C-F bond activation using HFIP as a H-bond donor (Figure 1.8e).[88]

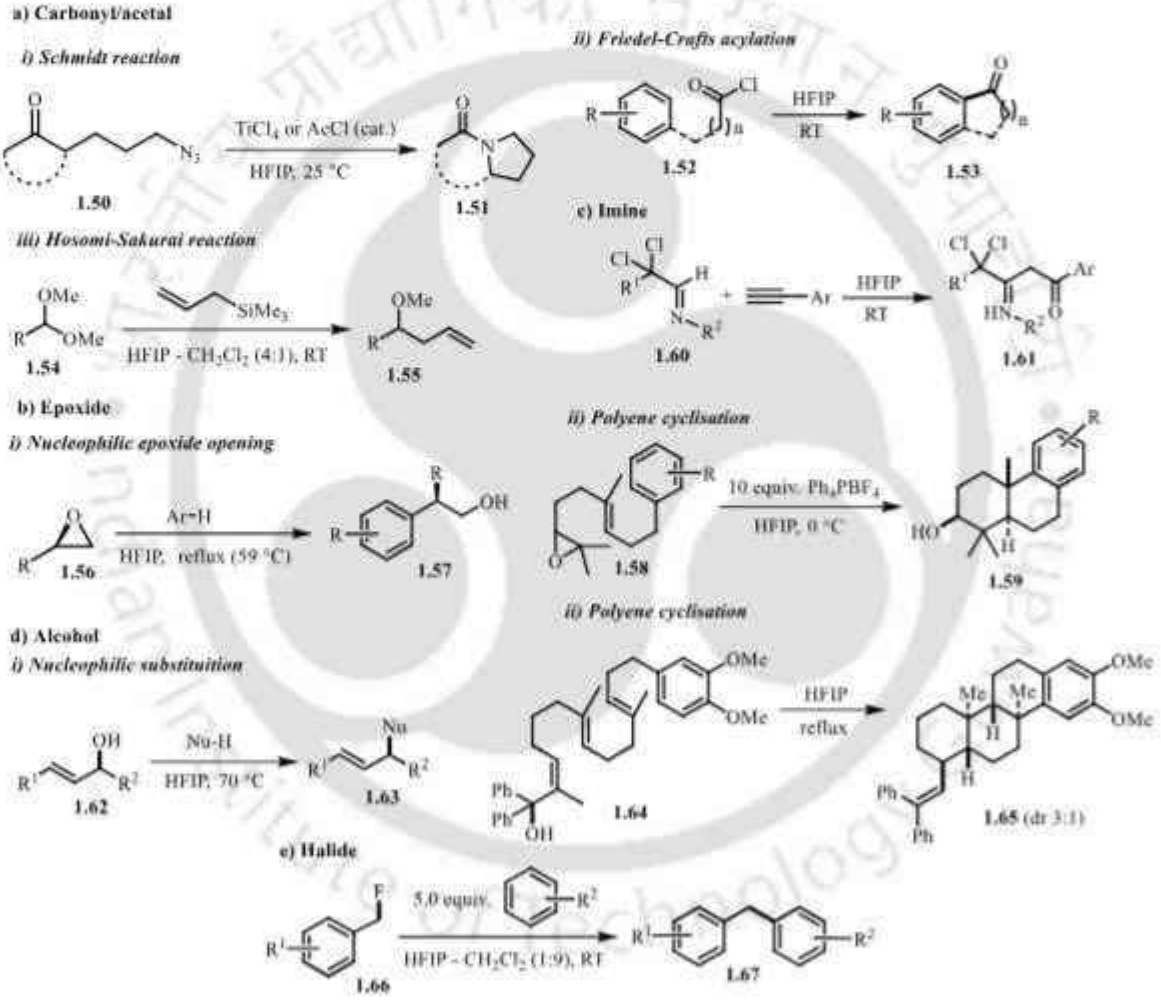


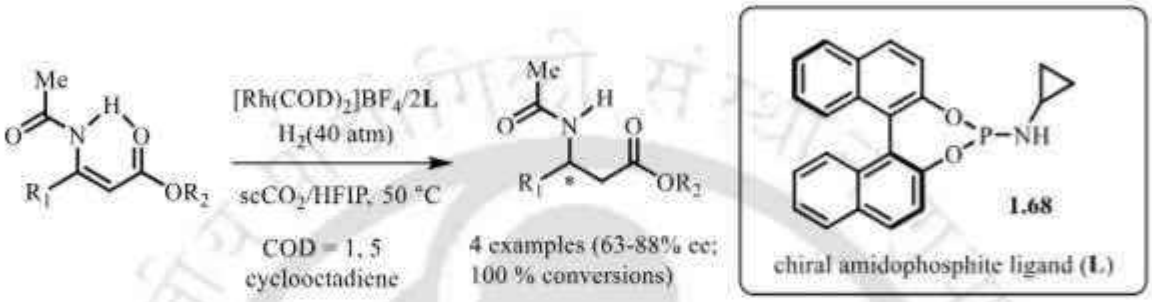
Figure 1.8. Selected examples for the reactivity of organic molecules, based on the functional group that HFIP can activate: a) carbonyl b) imines c) epoxides d) alcohols e) halides.

1.8.3. Use of HFIP in reduction reactions

The high acidity of the fluorinated alcohols, their coordinative nature, as well as their potential ability to serve as a hydrogen source have been utilized to promote various reduction reactions, including asymmetric hydrogenations.[79]

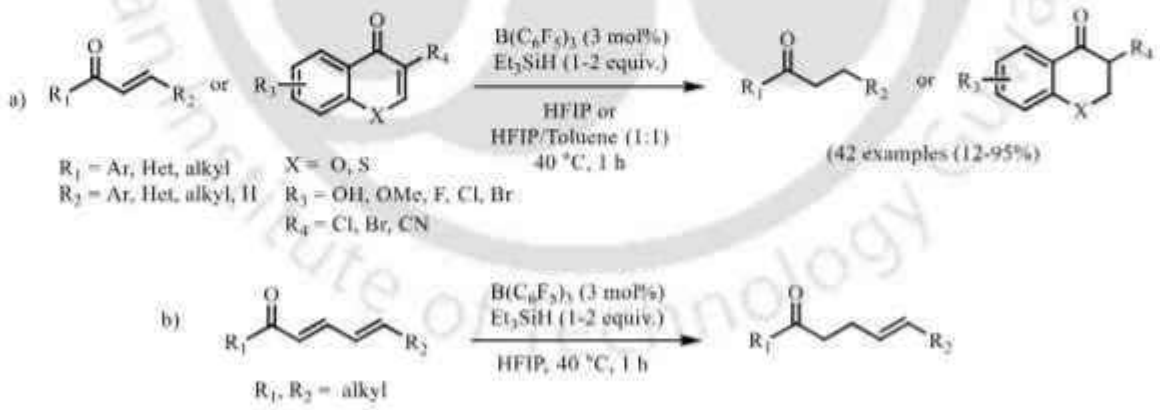
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A rhodium (Rh)-catalyzed asymmetric hydrogenation of a small set of (Z)-β-(acylamino)acrylates using a chiral amidophosphite ligand **1.68** in supercritical carbon dioxide ($scCO_2$) with HFIP as a co-solvent resulted in complete conversions to the corresponding β-amino acids with good enantioselectivities Scheme 1.13.[89,90] The significant improvements in the enantioselectivity and conversion with HFIP compared to methanol (MeOH) and *i*-PrOH were attributed to its increased acidity and stronger hydrogen-bond donor ability, which by interrupting the intramolecular hydrogen bond in the substrates, allowed coordination of the chiral catalyst complex and permitted the asymmetric hydrogenation to proceed.



Scheme 1.13. Rh-catalyzed asymmetric hydrogenation of *β*-(acylamino)acrylates.

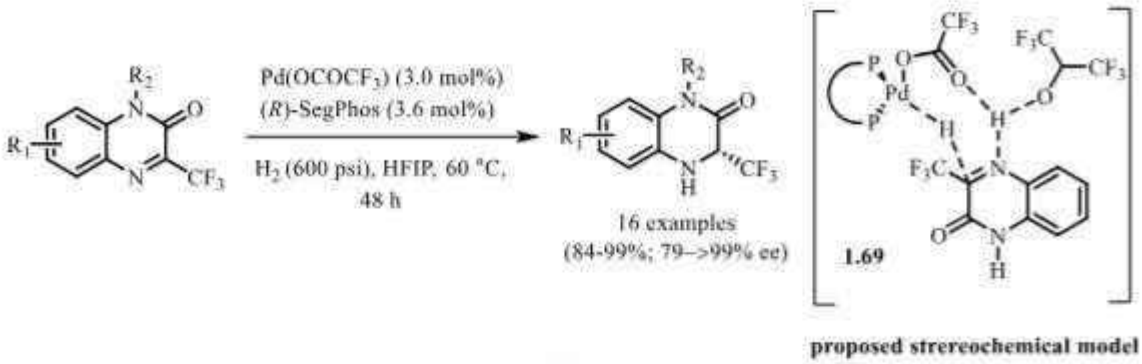
The frustrated Lewis pair combination of $B(C_6F_5)_3$ and Et_3SiH in HFIP promoted the chemoselective hydrosilylation of *α,β*- and *α,β,γ,δ*-unsaturated ketones (Scheme 1.14).[91] HFIP provided the highest yield of the protic solvents screened (MeOH, EtOH, *i*-PrOH), while THF and toluene gave only trace amounts of product. Deuterium labelling control experiments using HFIP-d_2 suggested that HFIP is the proton source for the transformation.



Scheme 1.14. Chemoselective hydrosilylation of *αβ*-and *αβγδ*-unsaturated ketones.

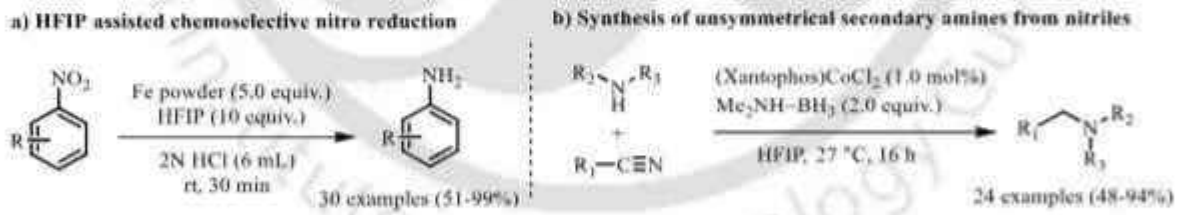
A Pd-catalyzed asymmetric hydrogenation of 3-(trifluoromethyl) quinoxalinones in HFIP under H_2 atmosphere was reported for the enantioselective synthesis of 3- (trifluoromethyl)-3,4-dihydroquinoxalinones (Scheme 1.15).[92] HFIP was identified as the optimal solvent for this transformation in comparison to TFE and DCM. HFIP was proposed to strengthen the complex between catalyst and substrate through hydrogen bonding.

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Scheme 1.15. Enantioselective hydrogenation of 3-(trifluoromethyl) quinoxalinones.

An iron-catalyzed chemoselective reduction of a nitro group using HCl solution as a hydrogen source was found to be facilitated by added HFIP (Scheme 1.16a).[93] A significant reduction in yield was obtained when other solvents like MeOH, EtOH, *i*-PrOH, THF, dioxane, as well as ethanolic solutions of HFIP, were used as additives. HFIP was proposed to activate the protonated nitro group *via* hydrogen bonding and facilitate the dehydration process. A variety of nitro compounds underwent chemoselective reduction in the presence of functional groups such as ester, nitrile, aldehyde, quinone, or halogens. Selective hydrogenation/reductive amination of nitriles were catalyzed by a (Xantphos)$CoCl_2$ complex using boranes as hydrogen sources in HFIP to produce secondary amines (Scheme 1.16b).[94] Reaction in MeOH, EtOH, and *i*-PrOH resulted in lower conversions. Symmetrical secondary amines were obtained from the corresponding aryl nitriles using ammonia borane (NH_3–BH_3) as a hydrogen source. On the other hand, dimethylamine borane (Me_2NH–BH_3) was utilized for the reductive amination of nitriles with external amines to give unsymmetrical secondary and tertiary amines.



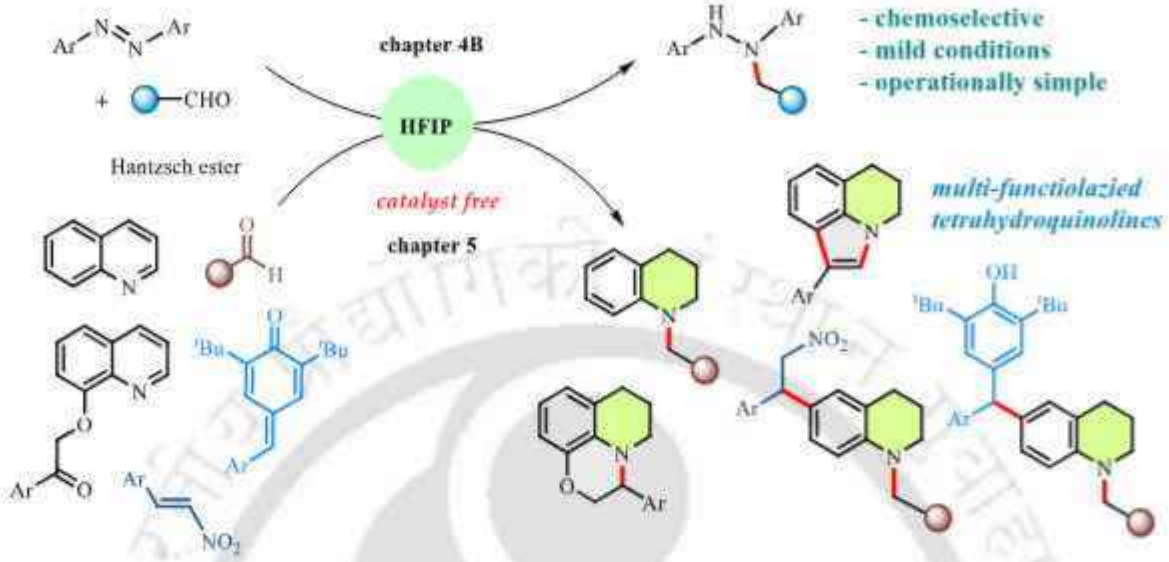
Scheme 1.16. HFIP-assisted reduction for the synthesis of amines.

1.9. Thesis objectives HFIP mediated reaction in reduction chemistry

Despite the notable advances achieved using HFIP, only handful examples of reduction reactions have been reported. Therefore, there is an ample opportunity for the development of more general and new method for the C-C and C-N bond forming reactions in the future. Specifically, the tandem reductive functionalization of *N*-containing heteroarenes and *N-N* multiple bonded species is not explored. Hence, another goals of this thesis are: (1) tandem reductive alkylation of quinolines to functionalized tetrahydroquinolines using HFIP under catalyst-free conditions (chapter 5). The mild reaction conditions are hoped to tolerate a wide

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range of reducible-sensitive functional groups, (2) improve the efficiency of the protocols towards synthesis of *N*-alkyl-*N*, *N'*-diarylhydrazines (chapter 4). The ambient reaction conditions may suppress *N*-*N* cleaved products and selectively provide trisubstituted hydrazine derivatives, (3) to learn more about the role of the HFIP functionality in the transformation.



Scheme 1.17. HFIP mediated reaction in tandem reductive alkylation of quinoline and azobenzene.

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Chapter 2

Facile synthesis of tetrahydroquinoline containing dithiocarbamate derivatives via a one-pot sequential multicomponent reaction

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2.1. Introduction

Organic dithiocarbamates are an important class of compounds that are widely utilized in the pharmaceutical,[1] agrochemical,[2] materials science[3] and rubber industries.[4] They are useful as anticancer agents,[5] anti-methicillin-resistant Staphylococcus aureus (MRSA) agents,[6] and monoacylglycerol lipase (MAGL) inhibitors.[7] In addition, they are found as useful building blocks and synthetic intermediates in the synthesis of natural products and biologically active compounds.[8] Besides their phenomenal bioactivities, they serve as linkers in solid-phase organic synthesis[9] and are used as radical chain transfer agents in reversible addition–fragmentation chain transfer (RAFT) polymerizations.[3] Likewise, 1,2,3,4-tetrahydroquinoline (THQ) derivatives have received much attention in pharmaceutical chemistry due to their remarkable therapeutic potential.[10] They are ubiquitous in many pharmacologically active synthetic and natural products including cuspareine, galipinine, and angustrureine.[11] Hybrids of tetrahydroquinoline with dithiocarbamate have exhibited potent antiproliferative activity (see Figure 2.1).[12]

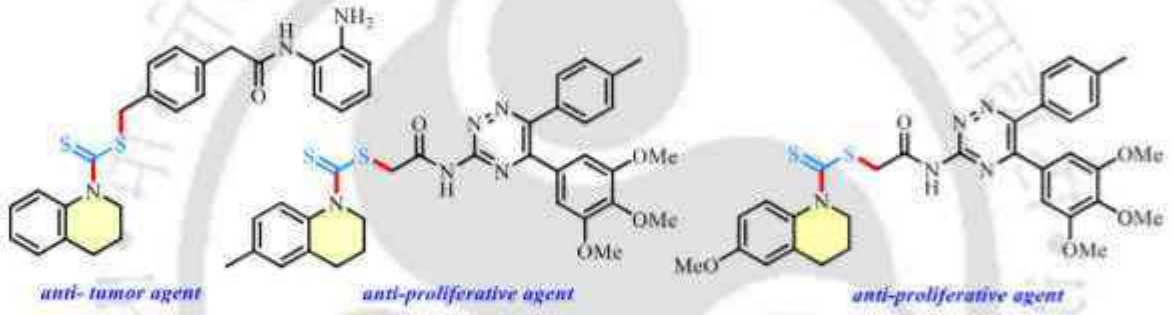
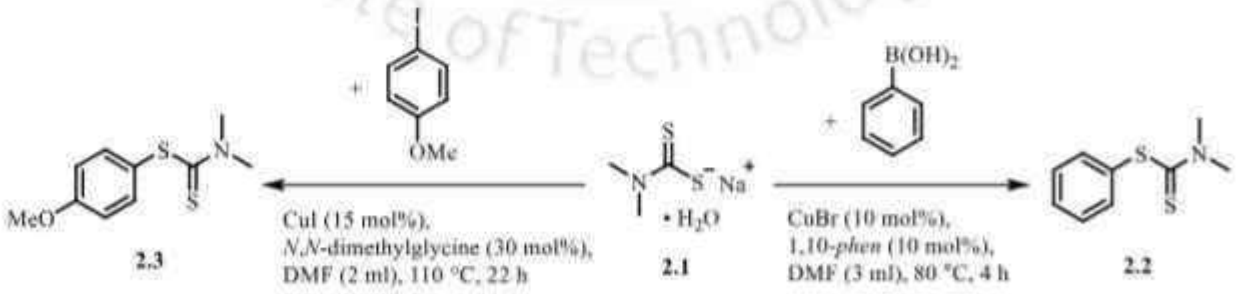


Figure 2.1. Representation of bioactive compound with THQ containing dithiocarbamate derivatives.

Owing to their importance and usefulness, synthesis of these hybrid molecules in an easy and straightforward way is highly desired. Conventionally, Conventionally, aryl dithiocarbamates have been synthesized by using toxic organometallic reagents with tetramethylthiuram disulphide[13] or facilitated by copper-catalyzed cross-coupling reaction of the sodium salt of dithiocarbamic acid with iodoarenes[14] and aryl boronic acids.[15]

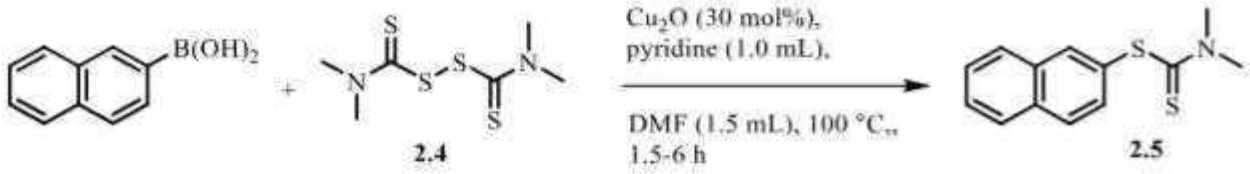


Scheme 2.1. Synthesis of aryl dithiocarbamates with iodoarenes and boronic acids.

However, sodium dithiocarbamate precursors are toxic, and difficult to prepare and store, and therefore, the scope of the reaction is quite limited.

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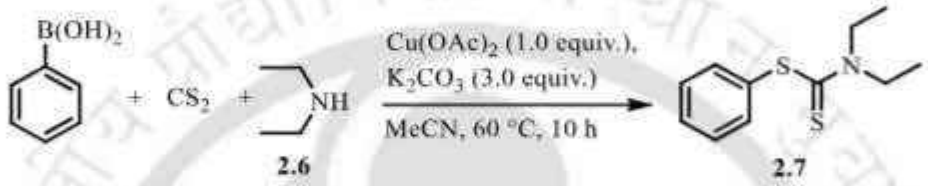
Alternatively, aryl dithiocarbamates are prepared *via* copper(I) oxide-catalyzed *S*-arylation using arylboronic acids and tetraalkylthiuram disulphides (Scheme 2.2).[16]



2.4 2.5

Scheme 2.2. Synthesis of aryl dithiocarbamates with tetraalkylthiuram disulphides.

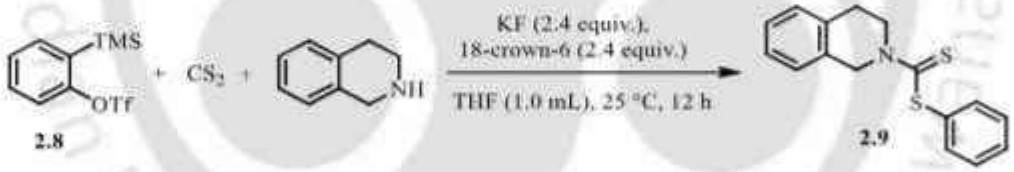
Furthermore, copper-mediated one-pot three-component coupling of acyclic amines, carbon disulfide, and boronic acids was reported (Scheme 2.3).[17]



2.6 2.7

Scheme 2.3. Synthesis of aryl dithiocarbamates with acyclic amine.

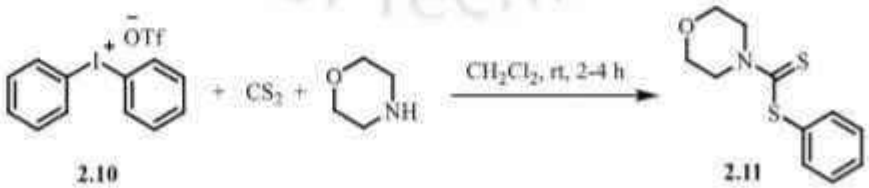
In recent studies, a few encouraging reports also documented the synthesis of *S*-aryl dithiocarbamates, one each from the groups of Biju[18] and Murarka[19] describing the transition metal-free direct *S*-arylation approach. For instance, the Biju group described a one-pot three-component coupling reaction involving arynes, aliphatic amine, and CS_2 (Scheme 2.4).[18]



2.8 2.9

Scheme 2.4. Synthesis of *S*-aryl dithiocarbamates by the aryne three-component coupling involving cyclic aliphatic amines and carbon disulphide.

The Muraka group used diphenyliodonium triflate as an arylating agent with aliphatic amine and CS_2 as the coupling partners (Scheme 2.5).[19a, c]



2.10 2.11

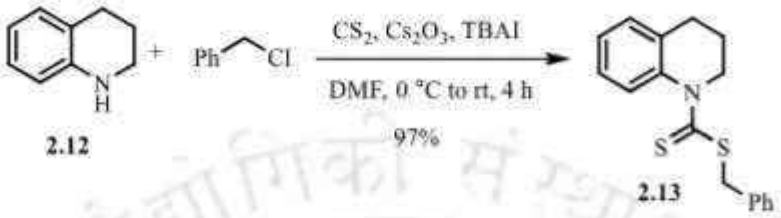
Scheme 2.5. Synthesis of *S*-aryl dithiocarbamates by diaryliodonium triflates, cyclic aliphatic amines, and carbon disulphide.

Although a number of synthetic methods have been developed for the synthesis of dithiocarbamate derivatives, the scope of the reaction is restricted by the electronic and steric

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nature of the amine-based coupling partner.[19a] For instance, piperidine containing dithiocarbamates have been widely studied with respect to benzo-fused piperidine analogues possibly due to the relatively low reactivity of benzofused piperidines in the nucleophilic addition reaction.

To date, only a handful of examples have been reported for the synthesis of tetrahydroquinoline containing dithiocarbamate derivatives (Scheme 2.6).[20]



Scheme 2.6. Synthesis of tetrahydroquinoline containing dithiocarbamate derivatives.

2.2. Present work

Very recently we have demonstrated a boronic acid catalyzed reduction of quinoline with Hantzsch ester (HE) to provide reduced heterocycle 1,2,3,4-THQs and concomitantly release oxidized Hantzsch ester (OHE).[21] Herein, I envisaged that in situ formed THQs can take part in nucleophilic reaction with carbon disulphide to form dithiocarbamic acids, and subsequent *S*-arylation using arylboronic acids *via* Chan– Evans–Lam coupling reaction would afford tetrahydroquinoline containing aryldithiocarbamate derivatives. Moreover, the released OHE can serve as a weak Lewis base (pKa 2.81) in the subsequent *S*-arylation reaction (Scheme 2.7), thereby (a) avoiding the use of an external base in the C–S bond-forming step and (b) bypassing the isolation of THQ intermediates, which may further increase the product scope and reduce the number of steps, thereby making the process a step-economic and cost-efficient tool.



Scheme 2.7. One-pot multi-component synthesis of THQ containing dithiocarbamate derivatives.

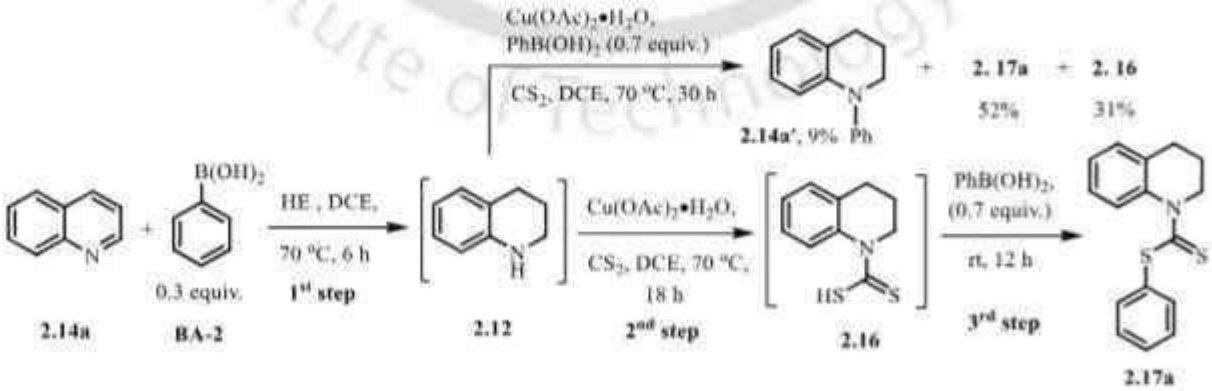
2.3. Results and discussion

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2.3.1. Optimization of reaction conditions

The reaction was initiated with quinoline (**2.14a**, 1 mmol), Hantzsch ester (2.2 mmol), and $PhB(OH)_2$ (**BA-2**, 0.3 mmol) in dichloroethane (DCE) at 70 °C for 6 h in air.[21, 22] Then, the required phenylboronic acid (**BA-2**, 0.7 mmol), carbon disulfide (2.2 mmol) and copper (II) acetate monohydrate (1 mmol) were added to the reaction mixture and stirred at the same temperature for 30 h. To our delight, the desired S-aryldithiocarbamate THQ **2.17a** was obtained in 52% yield, along with intermediate 3,4-dihydroquinoline-1(2H)-carbodithioic acid **2.16** (31%) and by-product *N*-phenyl THQ **2.14a′** (9%) (Table 2.1). To improve the yield of **2.17a**, a one-pot sequential reaction was performed. After obtaining complete conversion of quinoline **2.14a** to THQ **2.12**, a mixture of carbon disulfide (2.2 mmol) and copper (II) acetate monohydrate (1 mmol) was added to the reaction mixture and the mixture was stirred for 18 h. Subsequently, the remaining 0.7 mmol of phenylboronic acid **BA-2** was added to the reaction mixture and the resulting solution was stirred at room temperature overnight. The desired product **2.17a** was obtained in 91% yield (Table 2.1, entry 1). Then, on reducing the equivalency of copper (II) acetate loading to 0.2 mmol, the yield of the product **2.17a** was decreased to 26% (entries 2–5). In the absence of copper acetate, no desired product **2.17a** was obtained (entry 6). Furthermore, with the use of different copper salts, such as $CuSO_4{\cdot}5H_2O$, $CuCl_2{\cdot}2H_2O$, CuO and CuI, low conversion or no conversion was acquired (entry 7). These results suggested that the role of the copper (II) salts and corresponding counter anions are important in this transformation. The yield of **2.17a** was dramatically decreased when the reaction temperature was changed to room temperature in the 2nd step (entry 8) and to 70 °C for the 3rd step (entry 9). To examine the reactivity of other organoboron compounds in this multi-component reaction, phenylboronic acid pinacol ester (**2.15aa**) and potassium phenyl trifluoroborate (**2.15ab**) were employed as the coupling partner to individually react with **2.14a**, Hantzsch ester, and CS_2 under the standard reaction conditions. Target product **2.17a** was not obtained, indicating that these are not suitable coupling partners for this transformation (entry 10).

Table 2.1. Optimization studies for *S*-phenyl dithiocarbamate THQs[a]



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Entry	Deviation from above	Yield of **2.17a** (%)
1	none	91, 87[b]
2	with 0.8 equiv. of $Cu(OAc)_2 \cdot H_2O$	76
3	with 0.6 equiv. of $Cu(OAc)_2 \cdot H_2O$	65
4	with 0.4 equiv. of $Cu(OAc)_2 \cdot H_2O$	47
5	with 0.2 equiv. of $Cu(OAc)_2 \cdot H_2O$	26
6	no $Cu(OAc)_2 \cdot H_2O$	0
7	Copper (II) salts	41,[c] 0,[d] 0,[e] 49,[f]
8	For 2nd step, at rt, 18 h	52
9	For 3rd step, at 70 °C, 12 h	53
10	with organoboron compounds (**2.15aa**, **2.15ab**)	0[g]

[a]Reaction conditions: quinoline **2.14a** (1 mmol), phenylboronic acid **BA-2** (0.30 mmol), HE (2.2 mmol), DCE (2 mL) at 70 °C for 6 h under air; then copper (II) acetate monohydrate (1 mmol), CS_2 (2.2 mmol), at 70 °C for 18 h under air; then phenylboronic acid **BA-2** (0.70 mmol) at room temperature for 12 h. isolated yields. [b]Under argon atmosphere. [c]With $CuSO_4 \cdot 5H_2O$. [d]With $CuCl_2 \cdot 2H_2O$. [e]With CuI. [f]With CuO. [g]with other organoboron compounds.

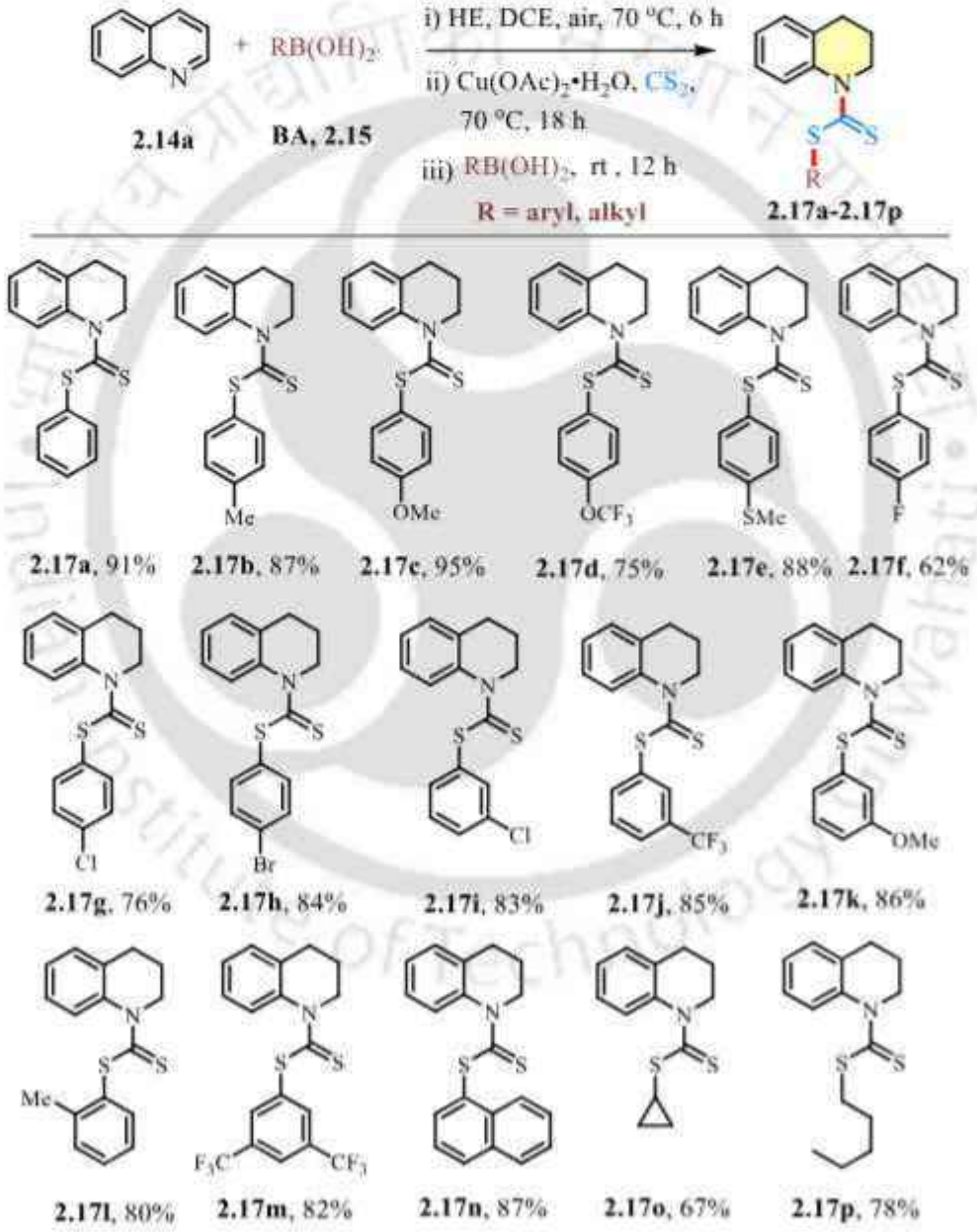
2.3.2 Substrate scope for synthesis of THQ containing dithiocarbamate derivatives

With the optimized conditions in hand, I intended the substrate scope of this reaction by employing varieties of substituted boronic acid with quinoline **2.14a** as the standard substrate. The *para*-position substituted aryl boronic acid having electron-donating *p*-Me (**2.15b**), *p*-OMe (**2.15c**), *p*-OCF_3 (**2.15d**), *p*-SMe (**2.15e**) and electron-withdrawing *p*-F (**2.15f**), *p*-Cl (**2.15g**), *p*-Br (**2.15h**) group were efficiently reacted with **2.14a** to obtain the desired products **2.17b-17h** with moderate to good yields (62–95%). Arylboronic acid with electron-donating substituents such as **2.15b-15c**, **2.15e** gave higher yields for the corresponding dithiocarbamate products than the boronic acid containing electron-withdrawing substituent like **2.15f-15h**. Since the current reaction condition tolerates the halogen functional groups; this can be beneficial for further functionalization. The reaction of *meta*-substituted aryl boronic acid having *m*-Cl (**2.15i**), *m*-CF_3 (**BA-22**), *m*-OMe (**2.15k**) afforded corresponding product **2.17i** (83%), **2.17j** (85%), and **2.17k** (86%), respectively. Interestingly, synthetically challenging sterically hindered *ortho*-substituted boronic acid **2.15l** was well tolerated as validated from the 80% yield of **2.17l.** Besides monosubstituted boronic acids, the bis-substituted boronic acid such as **BA-9** was also well suited under the reaction conditions. 1-Napthalene boronic acid also led to the products **2.17n** efficiently. Furthermore, protocol is successfully applicable to more challenging alkylboronic acid substrates, such as cyclopropylboronic acid (**2.15o**) and pentylboronic acid (**2.15p**) could also undergo the reaction smoothly, delivering the corresponding products **2.17o** and **2.17p** in 67% and 78% yield, respectively. The scope of the reaction was further extended to a series of quinoline while keeping phenylboronic acid as the standard substrate. Quinoline

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bearing 6-methyl (**2.14b**), 6-methoxy (**2.14c**), 6-aryloxy (**2.14d**), and 6-chloro (**2.14e**) substituents afforded the desired products **2.18a-18d** in 76-90% yields. Similarly, the reaction of 4-methyl (**2.14e**), 3-methyl (**2.14f**), 2-methyl (**2.14g**) quinoline afforded **2.18e**, 88%, **2.18f**, 82% and **2.18g**, 81% yield respectively. Considering potential usefulness of the THQ containing dithiocarbamate motif in various biologically and pharmaceutically relevant complex molecular settings,[12] a substrate containing nonsteroidal anti-inflammatory drug naproxen derivative **2.14h** was successfully converted into dithiocarbamate derivative **2.18h** in 52% yield.

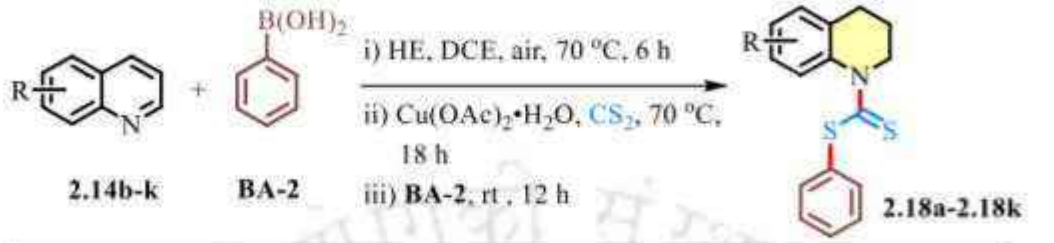
Table 2.2 The reaction scope with various boronic acid[a]

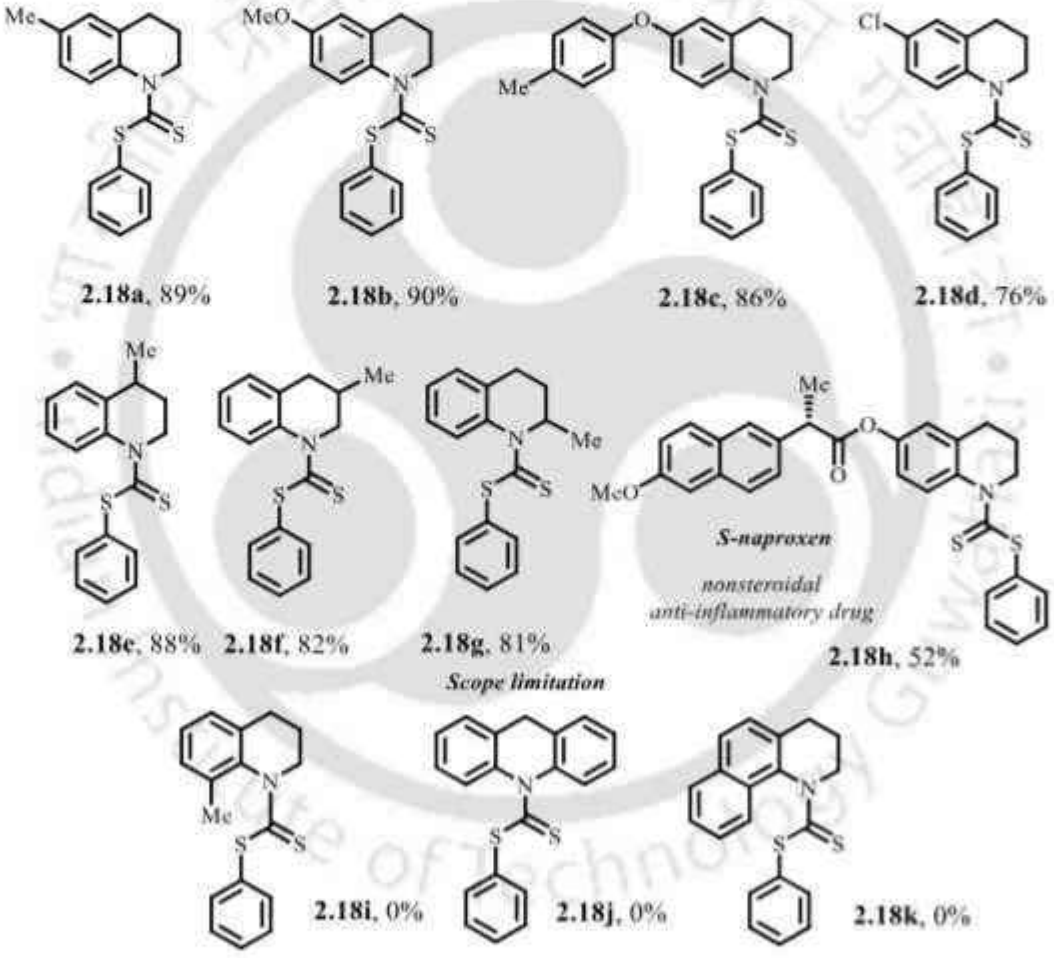


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[a]Reaction conditions: i) quinoline **2.14a** (1 mmol), aryl (or alkyl) boronic acid (0.30 mmol), HE (2.2 mmol), DCE (2 mL) at 70 °C for 6 h under air; ii) then added copper (II) acetate monohydrate (1.0 mmol), CS_2 (2.2 mmol) at 70 °C for 18 h under air; iii) then added aryl (or alkyl) boronic acid (0.70 mmol) at room temperature for 12 h. isolated yields.

Table 2.3 The reaction scope with various quinoline[a]





[a]Reaction conditions: i) substituted quinoline (1 mmol), phenyl boronic acid **BA-2** (0.30 mmol), HE (2.2 mmol), DCE (2 mL) at 70 °C for 6 h under air; ii) then added copper (II) acetate monohydrate (1.0 mmol), CS_2 (2.2 mmol) at 70 °C for 18 h under air; iii) added phenyl boronic acid **BA-2** (0.70 mmol) at room temperature for 12 h. isolated yields.

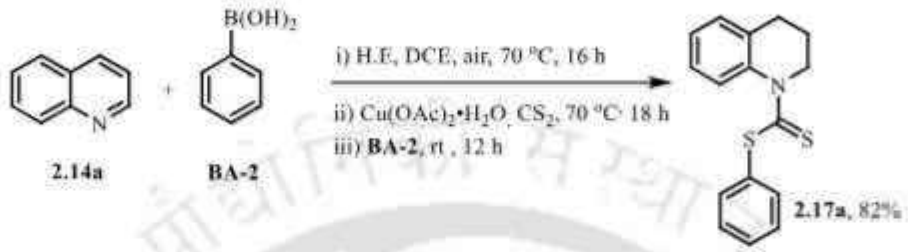
Nevertheless, 8-methylquinoline (**2.14i**), and other *N*- heteroarene such as acridine (**2.14j**), benzo[*h*]quinoline (**2.14k**) were not given the target dithiocarbamate product **2.18i-18k**. The

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result suggests that steric and electronic nature of *N*-heteroarene plays an important role in the outcome of the process.

2.3.3. Gram-scale reaction

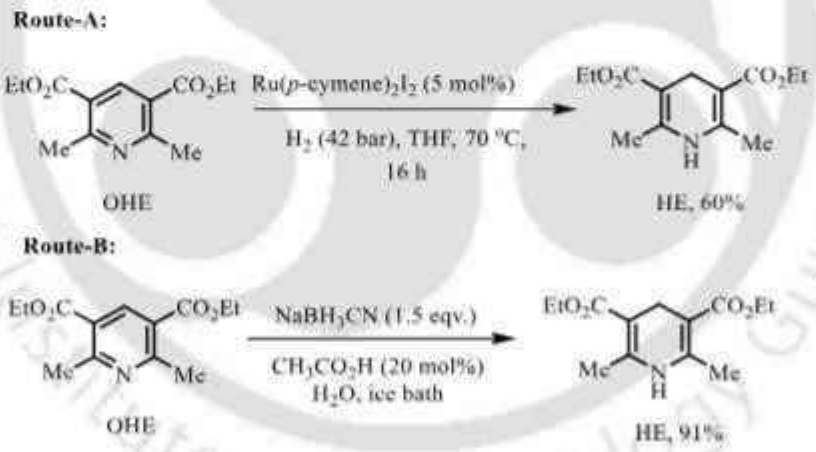
To understand the efficiency of this process, gram-scale reaction was performed for bulk utilization. The use of 1-gram quinoline **2.14a** afforded the desired dithiocabamate product **2.17a** in 82% yield (Scheme 2.8).



Scheme 2.8. Gram-scale reaction.

2.3.4. Procedure for oxidised Hantzsch ester (OHE) to Hantzsch-1,4-dihydropyridine (HE) recovery

Moreover, regeneration of Hantzsch ester can be achieved by reducing the oxidised Hantzsch ester by using the synthetic protocols given in (Scheme 2.9).



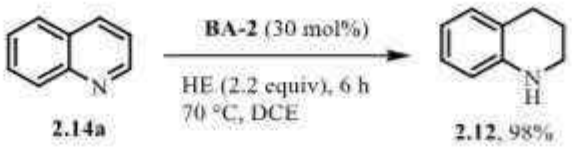
Scheme 2.9. Reduction of oxidised Hantzsch ester (OHE) to Hantzsch ester (HE).

2.3.5. Mechanistic studies

i) Proof of 1,2,3,4 THQ as the reaction intermediate

To gain insights into the reaction pathway, I have performed several control experiments. The reaction of quinoline **2.14a**, Hantzsch ester and phenylboronic acid (**BA-2**, 30 mol%) under the standard reaction conditions, afforded 1,2,3,4-tetrahydroquinoline **2.12** in 98% yield (Scheme 2.10).

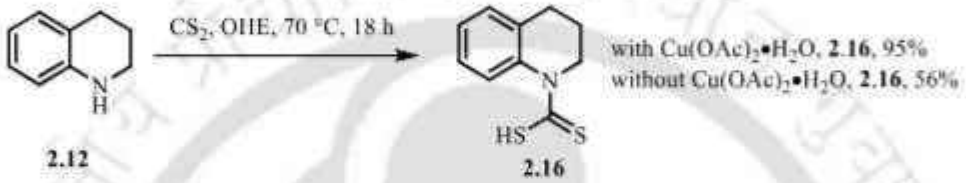
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Scheme 2.10. Proof of 1,2,3,4 THQ as the reaction intermediate.

ii) Proof of carbodithioic acid as the reaction intermediate

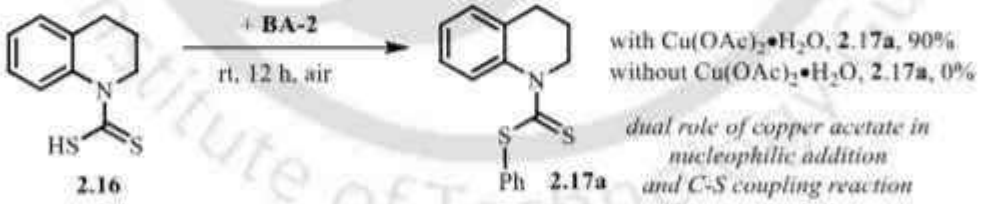
Then treating **2.12** with carbon disulfide, copper (II) acetate monohydrate and oxidized Hantzsch ester (OHE), a 3,4-dihydroquinoline-1(2H)-carbodithioic acid **2.16** was achieved in 95% yield (Scheme 2.11).



Scheme.2.11. Proof of carbodithioic acid as the reaction intermediate.

iii) Role of copper salts in the *S*-arylation step

Under the identical reaction conditions in the absence of copper acetate, a low yield of dithiocarbamic acid **2.16** (56%) was attained indicating the importance of copper salt in the nucleophilic addition reaction. Beside this, the role of copper salt is critical in the *S*-arylation step validated by performing the reaction as shown in (Scheme 2.12). A 90% yield of dithiocarbamate product **2.17a** was obtained in the presence of copper acetate and no product **2.17a** was formed in the absence of copper acetate.

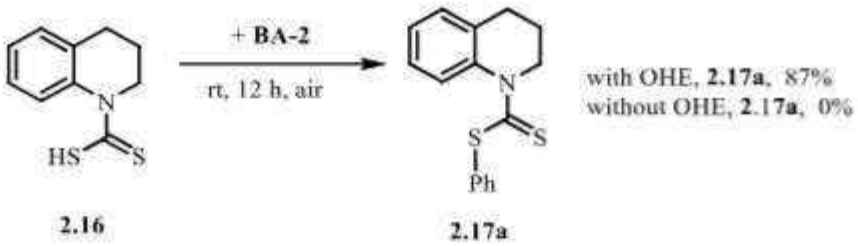


Scheme.2.12. Role of copper salts in the *S*-arylation step.

iv) Role of oxidized Hantzsch ester in the *S*-arylation step

Likewise, no conversion of dithiocarbamic acid **2.16** to **2.17a** was attained in the absence of OHE and a quantitative product **2.17a** (91%) was accomplished in the presence of OHE, suggesting the role of the oxidized Hantzsch ester (OHE) significant in the *S*-arylation step also (Scheme 2.13).

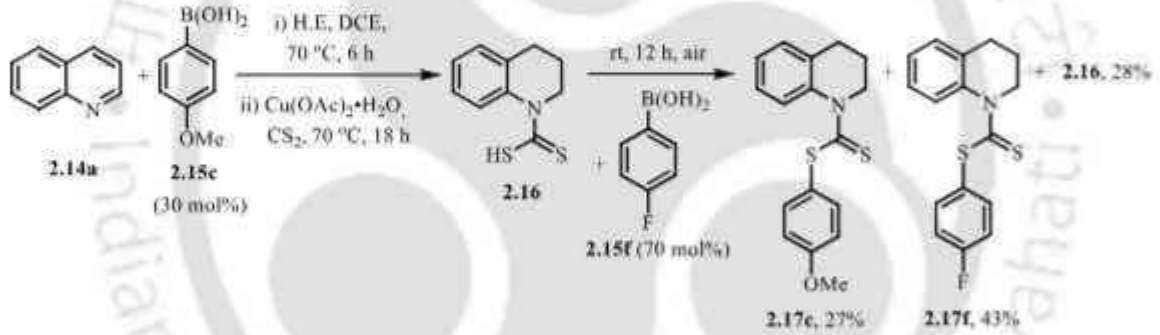
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Scheme.2.13. Role of oxidized Hantzsch ester in the *S*-arylation step.

v) Reactivity studies with two different arylboronic acid

To understand the reactivity of two different arylboronic acids in the *S*-arylation step, I performed an experiment using 4-methoxyphenylboronic acid (0.3 mmol) and 4-fluorophenylboronic acid (0.7 mmol) (Scheme 2.14). Interestingly, analytically pure dithiocarbamate **2.17c** and **2.17f** were isolated in 27% and 43% yields, respectively, along with 28% intermediate dithiocarbamic acid **2.16**. The result suggests that the reactivity of the boronic acid containing an electron-donating group is likely to be higher with respect to an electron-withdrawing substituent in the *S*-arylation segment.



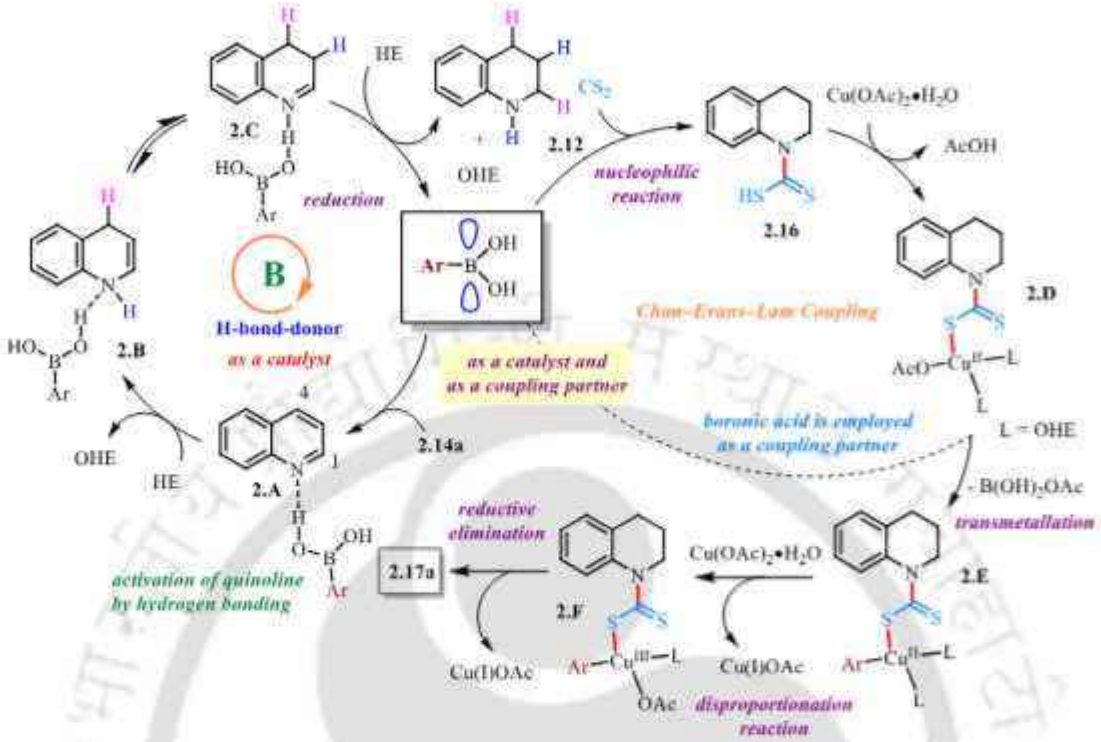
Scheme.2.14. Reactivity studies with two different arylboronic acid.

vi) Plausible mechanism

Based on the above-mentioned controlled experiments, taking our earlier reports into account,[21-23] a possible reaction pathway has been proposed as shown in scheme 2.15. First, the quinoline ring **2.A** was activated by the hydroxyl group of boronic acid *via* hydrogen bonding interaction as previously described.[21] Subsequently, Hantzsch esters hydride atom attack to the C-4 position of quinoline moiety and generate 1,4-dihydroquinoline species **2.B**. This could be readily isomerized to give 3,4-dihydroquinoline **2.C** and then 1,2-hydride transfer occurs, produce the 1,2,3,4-THQ **2.12**. The reaction of **2.12** with CS_2 generated dithiocarbamic acid **2.16**, which subsequent coordination exchange with copper (II)acetate produced **2.D**. Upon transmetallation with phenyl boronic acid generated complex **2.E**. Then, complex **2.E** underwent disproportionation reaction with copper (II) acetate hydrate generated oxidized copper (III) complex **2.F** and formed reduced copper(I) species. Lastly, high-

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valent copper (III) complex **2.F** participate in the reductive elimination reaction give product **2.17a**.



Scheme.2.15. Plausible mechanism.

2.4. Summary

In summary, I have developed a one-pot tandem reaction involving reduction of quinolines to tetrahydroquinolines, subsequent nucleophilic addition reaction with carbon disulphide to generate corresponding dithiocarbamic acid, followed by *S*-arylation using boronic acid to form tertrahydroquinoline containing dithiocarbamate derivatives *via* Chan–Evans–Lam reaction. From the 1st step released oxidised Hantzsch ester was successfully utilized in the subsequent *S*- arylation reaction; hence method does require any external base source in the C-S bond-forming step. The present study demonstrates the dual role of boronic acid as a catalyst (in the reduction of quinoline) and as a coupling partner (in the *S*-arylation segments). Method proved to be versatile and compatible with various functional groups at both the quinoline and boronic acid moiety. I believe that this method will find useful applications for the synthesis of a library of biologically important dithiocarbamate derivatives to facilitate the identification of the more potent bioactive molecules.

2.5. Experimental Section

A. General information

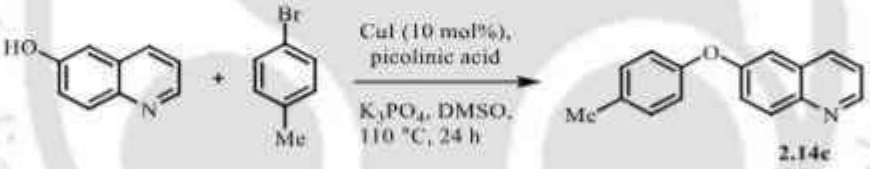
All the reagents and chemicals were purchased from common commercial suppliers like Sigma-Aldrich, Alfa Aesar, Merck, Spectrochem, Avra Synthesis Pvt. Ltd., Finar Chemicals, and BLD Pharma directly used as received without any further purification unless otherwise

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mentioned. Hantzsch ester was synthesized according to the reported literature.[24] ^1H, $^{13}C\{^1H\}$, and $^{19}F\{^1H\}$ NMR spectra of the compounds were measured in $CDCl_3$, D_2O, as a solvent by using TMS as an internal standard. Chemical shifts, δ (in ppm), are reported relative to TMS δ (^1H) 0.0 ppm, δ (^{13}C) 0.0 ppm, which was used as the internal reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.16 ppm; D_2O, (^1H) 4.790 ppm, were also used for calibration. Bruker Avance III 600, 500 and 400 spectrometers were used to record the NMR spectra. Chemical shifts (δ) values were reported in ppm and spin-spin coupling constant (J) were expressed in Hz, and other data were reported as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quartet, pent = pentate, sext = sextet, br = broad, and brs = broad singlet. IR spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass (UHPLC - Q-TOF - HRMS). Merck silica gel 60 - 120 was used for column chromatography. otherwise stated. All the final reactions were carried out under air and in preheated oil baths unless otherwise mentioned. Completion of reactions was examined by thin layer chromatography carried out on pre-coated Merck silica gel-60 F_{254} aluminium plates with ultraviolet light (UV) or iodine as visualizing agents.

B. Synthesis of starting material

Synthesis of 6-(*p*-tolyloxy) quinoline (2.14c) [25]



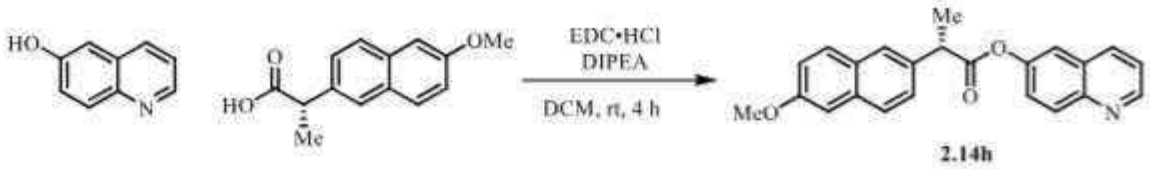
Scheme 2.16. Synthesis of 6-(*p*-tolyloxy) quinoline.

Experimental procedure: 6-hydroxyquinoline (0.400 g, 2.75 mmol, 1.0 equiv.), picolinic acid (0.068 g, 0.55 mmol, 20 mol%), copper(I) iodide (0.052 g, 0.275 mmol, 10 mol%), potassium phosphate (1.172 g, 5.51 mmol, 2.0 equiv.), and 1-bromo-4- methylbenzene (0.471 g, 2.75 mmol,1.0 equiv.) in dimethyl sulfoxide (5.0 mL) was taken in a 15 ml reaction tube, Solution was stirred at 110 °C with reflux condenser. After 24 h, the reaction mixture was cooled to room temperature and quenched with water (1 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with saturated ammonium chloride solution (20 mL × 2). The resulting mixture was dried over anhydrous Na_2SO_4, and then filtered. The resulting filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel to afford the product as brownish oil. Isolated yield: (0.543 g, 84%)

^1H NMR (600 MHz, $CDCl_3$): δ 8.79 (dd, J = 4.1, 1.4 Hz, 1H), 8.07 (d, J = 9.1 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.47 (dd, J = 9.1, 2.7 Hz, 1H), 7.30 (dd, J = 8.3, 4.2 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 2.6 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 2.35 (s, 3H).

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Preparation of quinolin-6-yl 2-(6-methoxynaphthalen-2-yl) propanoate (2.14h)



2.14h

Scheme 2.17. Preparation of quinolin-6-yl 2-(6-methoxynaphthalen-2-yl) propanoate.

Experimental procedure: A mixture of 6-hydroxy quinoline (0.189 g, 1.0 mmol, 1.0 equiv.), (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid (0.253 g, 1.1 mmol, 1.1 equiv.), EDC·HCl (0.230 g, 1.2 mmol, 1.2 equiv.) were combined in a round bottom flask and DCM (25 mL) and DIPEA (0.53 mL, 3.0 mmol, 3.0 equiv.) were added. The reaction mixture was stirred at room temperature for 4 h. 1N HCl (50 mL) and DCM (50 mL) were added to the reaction mixture. The organic layer is washed with saturated $NaHCO_3$ (25 mL) and brine (25 mL) then dried and concentrated under reduced pressure. The crude compound was purified through silica gel column chromatography as brownish solid (0.321 g, 90%).

^1H NMR (400 MHz, $CDCl_3$): δ 8.88 – 8.87 (m, 1H), 8.08 – 8.05 (m, 2H), 7.81 – 7.75 (m, 3H), 7.54 (dd, J = 8.5, 1.7 Hz, 1H), 7.47 (d, J = 2.5 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.20 – 7.16 (m, 2H), 4.17 (q, J = 7.1 Hz, 1H), 3.93 (s, 3H), 1.74 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 173.3, 158.0, 150.3, 148.8, 146.4, 135.9, 135.0, 134.0, 131.1, 129.5, 129.2, 128.6, 127.6, 126.3, 126.2, 124.7, 121.7, 119.3, 118.4, 105.8, 55.5, 45.8, 18.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{20}NO_3$: 358.1438; found: 358.1439.

C. General procedure for synthesis of tetrahydroquinoline containing dithiocarbamate derivatives (GP)

A mixture of substituted quinoline (1.0 mmol, 1.0 equiv.), HE (2.2 mmol, 2.2 equiv.), aryl/alkyl boronic acid (0.30 mmol, 30 mol%) and DCE (2 mL) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 70 °C with continuous stirring for 6 h. To the reaction mixture, copper (II) acetate monohydrate (1.0 mmol) and carbon disulphide (2.2 mmol) was added and stirred at 70 °C for 18 h. To the resulting mixture, remaining boronic acid (0.70 mmol, 70 mol%) was added and stirred at room temperature for 12 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

D. Gram-scale reaction (Scheme 2.8)

A mixture of quinoline (1.000 gm, 7.742 mmol, 1.0 equiv.), HE (4.324 gm, 17.03 mmol, 2.2 equiv.), phenyl boronic acid (0.283 gm, 2.323 mmol, 30 mol%) and DCE (10 mL) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 70 °C with continuous stirring for 16 hours. To the reaction

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mixture, copper (II) acetate monohydrate (1.545 gm, 7.742 mmol, 1.0 equiv.) and carbon disulphide (1.296 gm, 17.03 mmol, 2.2 equiv.) was added and stirred at 70 °C for 18 hours. To the resulting mixture, phenyl boronic acid (0.661 gm, 5.42 mmol, 70 mol%) was added and stirred at room temperature for 12 hours. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography to get pure compound as yellow oil of (1.834 g, 82%).

E. Procedure for oxidised Hantzsch ester (OHE) to Hantzsch-1,4-dihydropyridine (HE) recovery (Scheme 2.9)

Experimental procedure for route A[26]: A mixture of $[Ru(p\text{-cymene})I_2]_2$ (10 mg, 0.01 mmol) and oxidized Hantzsch ester (50.0 mg, 0.2 mmol) in THF (10 mL) was stirred at room temperature for 10 min in glove box, then the mixture was loaded to an autoclave. The hydrogenation was performed at 70 °C under H_2 (42 bar) for 16 h. After carefully release of the hydrogen, the autoclave was opened. Isolated yield (yellow solid, 30 mg, 60%).

Experimental procedure for route B[22]: In a 50 mL round bottom flask, OHE (1 gm, 3.9 mmol), water (10 mL) and acetic acid (45 µL, 20 mol%) were charged and placed in an ice bath. In the reaction mixture $NaBH_3CN$ (0.294 gm, 1.2 equiv.) was slowly added and stirred for overnight. The reaction was monitored by thin layered chromatography (TLC) in hexane and ethyl acetate solvent system. Once the reaction was completed, solid precipitate was filtered, washed thoroughly by water and ice-cold acetone and dried on vacuum desiccator. Isolated yield: (0.899 g, 91%).

F. Reaction mechanistic studies

i) Proof of 1,2,3,4 THQ (2.12) as the reaction intermediate (Scheme 2.10)

In a reaction tube (15 mL), quinoline (0.065 g, 0.5 mmol, 1.0 equiv.), HE (0.280 g, 1.1 mmol, 2.2 equiv.), phenylboronic acid (0.018 g, 0.15 mmol, 30 mol%) and DCE (2 mL) were charged. The reaction tube was properly closed and placed in a preheated oil bath (70 °C) with continuous stirring. After completion of the reaction, the crude compound was purified by column chromatography on silica gel for pure compound as yellow oil of **2.12** (0.065 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 – 6.95 (m, 2H), 6.61 (t, J = 8.1 Hz, 1H), 6.48 (d, J = 7.9 Hz, 1H), 3.32 – 3.29 (m, 2H), 2.77 (t, J = 6.4 Hz, 2H), 1.98 – 1.92 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.9, 129.6, 126.8, 121.6, 117.1, 114.3, 42.1, 27.1, 22.3. Spectral data is in accordance with the literature.[22]

ii) Proof of 3,4-dihydroquinoline-1(2H)-carbodithioic acid (2.16) as the reaction intermediate (Scheme 2.11)

In a reaction tube (15 mL), 1,2,3,4 tetrahydroquinoline (0.066 g, 0.5 mmol, 1.0 equiv.), Carbon disulphide (0.084 g, 1.1 mmol, 2.2 equiv.), copper (II) acetate monohydrate (0.099 g, 0.5 mmol,

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1.0 equiv.), OHE (0.188 g, 0.75 mmol, 1.5 equiv.) and DCE (2 mL) were added. The reaction tube was properly closed and placed in a preheated oil bath at 70 °C with continuous stirring for 18 hours. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the volatiles were removed under reduced pressure. The crude compound was purified through silica gel to get pure compound as yellow powder of **2.16** (0.099 g, 95%). Under the identical reaction condition in the absence of copper salt, the intermediate **2.16** was obtained in 56% yield (0.058 g).

^{1}H NMR (400 MHz, D_2O): δ 7.67 – 7.65 (m, 1H), 7.29 – 7.26 (m, 1H), 7.22 – 7.19 (m, 2H), 4.40 (t, J = 6.7 Hz, 2H), 2.71 (t, J = 7.0 Hz, 2H), 2.05 (pent, J = 6.8 Hz, 2H). ^{13}C NMR (151 MHz, D_2O): δ 212.6, 143.3, 134.4, 128.2, 127.4, 126.4, 125.1, 52.6, 25.4, 23.6. Characteristic IR band: $\nu_{(C=S)}$: 973 cm^{-1}. Spectral data is in accordance with the lietrature.[27]

iii) Role of copper salt in the *S*-arylation step (Scheme 2.12)

In a reaction tube (15 mL), **2.16** (0.104 g, 0.5 mmol, 1.0 equiv.), **BA-2** (0.061 g, 0.5 mmol, 1.0 equiv.), copper (II) acetate monohydrate (0.099 g, 0.5 mmol, 1.0 equiv.), OHE (0.277 g, 0.75 mmol, 1.5 equiv.) and DCE (2 mL) were added. The reaction tube was properly closed and placed in a preheated oil bath at rt with continuous stirring for 12 hours. After completion of the reaction, the crude compound was purified through silica gel to get pure compound as yellow oil of (0.128 g, 90%).

Under the same reaction condition in the absence of copper salt, there is no conversition of desired product **2.17a**. Both the study suggests that role of copper (II) acetate monohydrate is significant in nucleophic addition reaction as well as C-S coupling reaction.

iv) Role of oxidised Hantzsch ester in the *S*-arylation step (Scheme 2.13)

In a reaction tube (15 mL), **2.16** (0.104 g, 0.5 mmol, 1.0 equiv.), **BA-2** (0.061 g, 0.5 mmol, 1.0 equiv.), copper (II) acetate monohydrate (0.100 g, 0.5 mmol, 1.0 equiv.), OHE (0.188 g, 0.75 mmol, 1.5 equiv.) and DCE (2 mL) were added. The reaction tube was properly closed and placed in a preheated oil bath at room temperature with continuous stirring for 12 hours. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, the crude compound was purified through silica gel column chromatography to get the pure compound **2.17a** as yellow oil (0.124 g, 87%).

Under the same reaction condition in the absence of OHE, there is no formation of desired product **2.17a**. Study suggests that role of in-stu generated OHE in the *S*-arylation step is critical.

v) Reactivity studies with two different arylboronic acid (Scheme 2.14)

2.14a (0.065 g, 0.5 mmol, 1.0 equiv.), HE (0.280 g, 1.1 mmol, 2.2 equiv.), **2.15c** (0.023 g, 0.15 mmol, 30 mol%) and DCE (2 mL) were added into a reaction tube (15 mL) equipped with

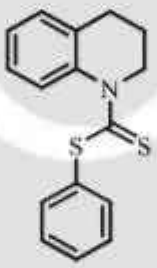
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stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 70 °C with continuous stirring for 6 hours. To the resulting mixture, copper (II) acetate monohydrate (0.099 g, 0.5 mmol, 1.0 equiv.) and carbon disulphide (0.084 g, 1.1 mmol, 2.2 equiv.) was added and stirred at 70 °C for 18 hours. To the resulting mixture, **2.15f** (0.049 g, 0.35 mmol, 70 mol%) was added and stirred at room temperature for 12 hours. After completion of the reaction, the crude compound was purified through silica gel column chromatography.

Gratifyingly, analytically pure *S*-aryl dithiocarbamate **2.17c** and **2.17f** were isolated in 27% (0.042 g) and 43% (0.067 g) yields, respectfully along with 28% (0.030 g) of **2.16** intermediate. The result suggests that the reactivity of the boronic acid containing an electron-donating group is likely to be higher than that with an electron-withdrawing substituent in the *S*-arylation segment.

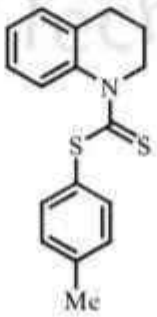
2.6. Analytical data of the products

Phenyl 3,4-dihydroquinoline-1(2H)-carbodithioate (2.17a)



By following the **GP**, the title compound **2.17a** was isolated as light-yellow oil (0.259 g, 91%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 – 7.73 (m, 1H), 7.45 – 7.39 (m, 5H), 7.29 – 7.24 (m, 3H), 4.43 – 4.41 (m, 2H), 2.76 (t, J = 6.8 Hz, 2H), 2.09 (pent, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 199.3, 140.4, 136.8, 134.9, 132.5, 130.0, 129.1, 128.7, 127.7, 126.5, 126.1, 52.8, 26.5, 23.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{16}H_{16}NS_2$: 286.0719; found: 286.0742. Significant IR band: $\nu_{(C=S)}$: 974 cm^{-1}.

***p*-tolyl 3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17b)**

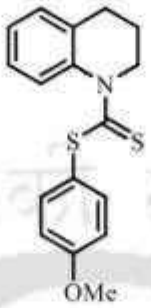


By following the **GP**, the title compound **2.17b** was isolated as light-yellow oil (0.260 g, 87%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 – 7.73 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.27 – 7.21

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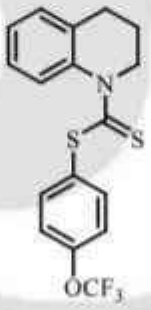
(m, 5H), 4.42 (t, J = 6.5 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 2.39 (s, 3H), 2.09 (pent, J = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 199.9, 140.4, 140.3, 136.7, 135.0, 130.1, 129.1, 128.7, 127.7, 126.6, 126.0, 52.8, 26.5, 23.8, 21.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{18}NS_2$: 300.0876; found: 300.0875. Significant IR band: $\nu_{(C=S)}$: 974 cm^{-1}.

Phenyl 4-methoxy-3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17c)



By following the **GP**, the title compound **2.17c** was isolated as light-yellow oil (0.300 g, 95%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.66). ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.73 (m, 1H), 7.34 (d, 8.7 Hz, 2H), 7.28 – 7.24 (m, 3H), 6.95 (d, J = 8.8 Hz, 2H), 4.43 (m, 2H), 3.84 (s, 3H), 2.76 (t, J = 6.8 Hz, 2H), 2.09 (pent, J = 6.8 Hz, 2H).^{13}C NMR (151 MHz, $CDCl_3$): δ 200.4, 161.1, 140.5, 138.4, 134.9, 128.7, 127.7, 126.6, 126.0, 123.4, 114.8, 55.4, 52.9, 26.6, 23.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{18}NOS_2$: 316.0825; found: 316.0823. Significant IR band: $\nu_{(C=S)}$: 974 cm^{-1}.

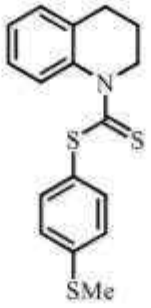
4-(trifluoromethoxy) phenyl 3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17d)



By following the **GP**, the title compound **2.17d** was isolated as light-yellow oil (0.277 g, 75%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^1H NMR (600 MHz, $CDCl_3$): δ 7.71 – 7.69 (m, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.28 – 7.25 (m, 3H), 7.22 (d, J = 8.1 Hz, 2H), 4.42 – 4.40 (m, 2H), 2.75 (t, J = 6.8 Hz, 2H), 2.09 (pent, J = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 198.2, 150.5, 140.3, 138.4, 135.0, 130.9, 128.8, 127.9, 126.4, 126.2, 121.2, 52.9, 26.5, 23.8. ^{19}F NMR (377 MHz, $CDCl_3$): δ -57.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{15}F_3NOS_2$: 370.0542; found: 370.0545. Significant IR band: $\nu_{(C=S)}$: 975 cm^{-1}.

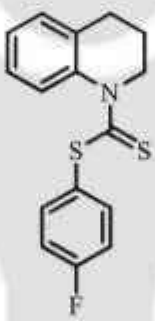
4-(methylthio) phenyl 3,4-dihydroquinoline-1(2H)-carbodithioate (2.17e)

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By following the **GP**, the title compound **2.17e** was isolated as light-yellow oil (0.292 g, 88%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 – 7.71 (m, 1H), 7.33 – 7.31 (m, 2H), 7.28 – 7.23 (m, 5H), 4.42 (t, J = 6.6 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 2.50 (s, 3H), 2.09 (pent, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 199.5, 141.7, 140.4, 137.0, 135.0, 128.7, 128.2, 127.7, 126.5, 126.2, 126.1, 52.9, 26.5, 23.8, 15.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{18}NS_3$: 332.0596; found 332.0595. Significant IR band: $\nu_{(C=S)}$: 975 cm^{-1}.

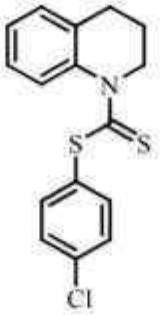
4-fluorophenyl 3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17f)



By following the **GP**, the title compound **2.17f** was isolated as light-yellow oil (0.188 g, 62%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 – 7.71 (m, 1H), 7.41 – 7.39 (m, 2H), 7.28 – 7.25 (m 3H), 7.09 (t, 8.6 Hz, 2H), 4.43 – 4.40 (m, 2H), 2.76 (t, J =6.8 Hz, 2H), 2.09 (pent, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 199.1, 165.2 – 162.7 (C-F, $^1J_{C\text{-}F}$ = 251.7 Hz), 140.3, 139.0 – 138.9 (C-F, $^2J_{C\text{-}F}$ = 8.8 Hz), 135.0, 128.7, 128.0 – 127.9 (C-F, $^3J_{C\text{-}F}$ = 3.5 Hz), 127.8, 126.4, 126.1, 116.5, 116.3, 52.9, 26.5, 23.8. ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$): δ -110.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{15}FNS_2$: 304.0625; found: 304.0624. Significant IR band: $\nu_{(C=S)}$: 973 cm^{-1}.

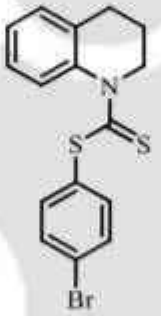
4-chlorophenyl 3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17g)

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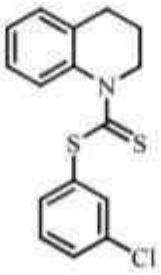
By following the **GP**, the title compound **2.17g** was isolated as light-yellow oil (0.243 g, 76%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 – 7.69 (m, 1H), 7.38 – 7.34 (m, 4H), 7.27 – 7.25 (m, 3H), 4.43 – 4.40 (m, 2H), 2.77 – 2.75 (m, 2H), 2.12 – 2.07 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 198.4, 140.2, 138.1, 136.5, 135.0, 130.9, 129.4, 128.7, 127.9, 126.4, 126.1, 52.9, 26.5, 23.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{15}ClNS_2$: 320.0329; found: 320.0328. Significant IR band: $\nu_{(C=S)}$: 974 cm^{-1}.

4-bromophenyl 3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17h)



By following the **GP**, the title compound **2.17h** was isolated as light-yellow oil (0.306 g, 84%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 – 7.69 (m, 1H), 7.53 (d, 8.4 Hz, 2H), 7.29 – 7.26 (m, 5H), 4.42 – 4.40 (m, 2H), 2.76 (t, J = 6.8 Hz, 2H), 2.09 (pent, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 198.2, 140.2, 138.3, 135.0, 132.4, 131.5, 128.8, 127.9, 126.4, 126.1, 124.9, 52.9, 26.5, 23.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{15}BrNS_2$: 363.9824; found: 363.9825. Significant IR band: $\nu_{(C=S)}$: 975 cm^{-1}.

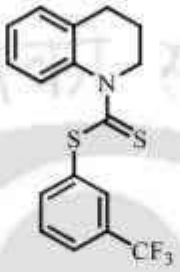
3-chlorophenyl 3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17i)



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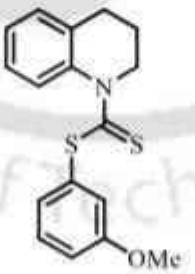
By following the **GP**, the title compound **2.17i** was isolated as light-yellow oil (0.265 g, 83%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.42 – 7.24 (m, 7H), 4.42 – 4.39 (m, 2H), 2.75 (t, J = 6.9 Hz, 2H), 2.12 – 2.06 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.9, 140.4, 136.4, 135.0, 134.8, 134.5, 134.2, 130.1, 130.0, 128.7, 127.8, 126.4, 126.2, 52.9, 26.5, 23.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{15}ClNS_2$: 320.0329; found: 320.0328. Significant IR band: $\nu_{(C=S)}$: 978 cm^{-1}.

3-(trifluoromethyl) phenyl 3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17j)



By following the **GP**, the title compound **2.17j** was isolated as light-yellow oil (0.300 g, 85%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 – 7.70 (m, 1H), 7.67 (d, 9.0 Hz, 2H), 7.61 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.29 – 7.25 (m, 3H), 4.41 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 2.10 (pent, J = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.4, 140.2, 140.1, 135.0, 133.8, 133.5 (C-F, q, $^1J_{C\text{-}F}$ = 3.8 Hz), 131.6, 131.3, 129.4, 128.7, 127.9, 126.7 (C-F, q, $^2J_{C\text{-}F}$ = 3.7 Hz), 126.3, 126.2, 52.9, 26.5, 23.8. $^{19}F\{^1H\}$ NMR (565 MHz, $CDCl_3$): δ -62.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{15}F_3NS_2$: 354.0593; found: 354.0594. Significant IR band: $\nu_{(C=S)}$: 974 cm^{-1}.

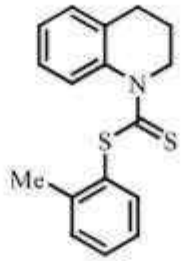
Phenyl 3-methoxy-3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17k)



By following the **GP**, the title compound **2.17k** was isolated as light-yellow oil (0.271 g, 86%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:1, R_f = 0.66).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 – 7.71 (m, 1H), 7.31 – 7.23 (m, 4H), 7.03 (d, J = 7.5 Hz, 1H), 6.98 – 6.95 (m, 2H), 4.41 (t, J = 6.9 Hz, 2H), 3.80 (s, 3H), 2.74 (t, J = 6.9 Hz, 2H), 2.11 – 2.06 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 199.0, 159.9, 140.5, 134.9, 133.4, 129.8, 128.9, 128.6, 127.6, 126.5, 126.1, 121.7, 116.2, 55.5, 52.7, 26.5, 23.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{18}NOS_2$: 316.0825; found: 316.0830. Significant IR band: $\nu_{(C=S)}$: 974 cm^{-1}.

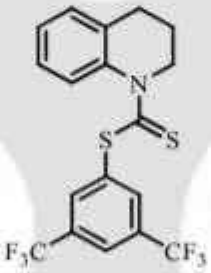
TH-3765_196122031

O-tolyl 3,4-dihydroquinoline-1(2H)-carbodithioate (2.17l)



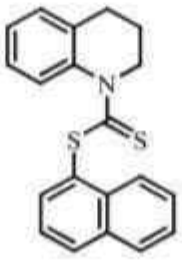
By following the **GP**, the title compound **2.17l** was isolated as light-yellow oil (0.240 g, 80%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.73 (m, 1H), 7.40 – 7.35 (m, 2H), 7.32 – 7.30 (m, 1H), 7.29 – 7.21 (m, 4H), 4.43 (t, J = 6.6 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H), 2.41 (s, 3H), 2.09 (pent, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 198.3, 143.7, 140.6, 137.6, 134.9, 131.9, 130.8, 130.7, 128.7, 127.7, 126.8, 126.4, 126.1, 52.7, 26.6, 23.9, 21.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{17}H_{18}NS_2$: 300.0876; found: 300.0873. Significant IR band: $\nu_{(C=S)}$: 974 cm^{-1}.

3,5-bis(trifluoromethyl)phenyl 3,4-dihydroquinoline-1(2H)-carbodithioate (2.17m)



By following the **GP**, the title compound **2.17m** was isolated as light-yellow oil (0.346 g, 82%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:1, R_f = 0.66). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.86 (s, 2H), 7.69 – 7.67 (m, 1H), 7.30 – 7.25 (m, 3H), 4.42 – 4.39 (m, 2H), 2.76 (t, J = 6.7 Hz, 2H), 2.10 (pent, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 195.5, 139.9, 136.78, 136.76, 135.5, 135.1, 132.07 (C-F, q, $^1J_{C\text{-}F}$ = 33.6 Hz), 128.8, 128.2, 126.3, 126.2, 124.0, 123.6 (C-F, q, $^2J_{C\text{-}F}$ = 3.4 Hz), 122.2, 53.1, 26.5, 23.8. ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$): δ -62.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{14}F_6NS_2$: 422.0467; found: 422.0466. Significant IR band: $\nu_{(C=S)}$: 974 cm^{-1}.

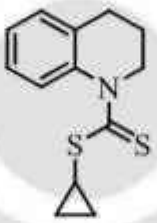
Naphthalen-1-yl 3, 4-dihydroquinoline-1(2H)-carbodithioate (2.17n)



TH-3765_196122031

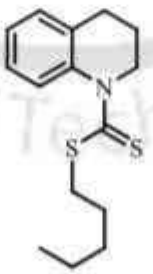
By following the **GP**, the title compound **2.17n** was isolated as light-yellow oil (0.292 g, 87%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f= 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.86 (d , J =7.8 Hz, 2H), 7.65 (d, J =7.1Hz, 1H), 7.56 – 7.54 (m, 1H), 7.50 (s, 1H), 7.45 – 7.44 (m, 1H), 7.30 – 7.27 (m, 3H), 7.23 – 7.21 (m, 1H), 4.40 (t, J = 6.6 Hz, 2H), 2.69 (t, J = 6.7 Hz, 2H), 2.07 (pent, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 198.2, 140.5, 136.5, 135.0, 134.9, 134.2, 131.3, 129.9, 128.8, 128.6, 127.6, 127.3, 126.4, 126.3, 126.2, 125.9, 125.8, 52.7, 26.5, 24.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{18}NS_2$: 336.0876; found: 336.0877. Significant IR band: $\nu_{(C=S)}$: 971 cm^{-1}.

Cyclopropyl 3,4-dihydroquinoline-1(2H)-carbodithioate (2.17o)



By following the **GP**, the title compound **2.17o** was isolated as light-yellow oil (0.167 g, 67%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f= 0.80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 6.9 Hz, 1H), 7.21 – 7.17 (m, 3H), 4.41 (t, J = 6.6 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 2.44 – 2.39 (m, 1H), 2.06 (pent, J = 6.7 Hz, 2H), 1.12 – 1.08 (m, 2H), 0.69 – 0.66 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 200.9, 140.4, 134.7, 128.7, 127.5, 126.3, 125.9, 51.8, 26.5, 23.8, 17.5, 8.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{13}H_{16}NS_2$: 250.0719; found: 250. 0721. Significant IR band: $\nu_{(C=S)}$: 977 cm^{-1}.

Pentyl 3,4-dihydroquinoline-1(2H)-carbodithioate (2.17p)

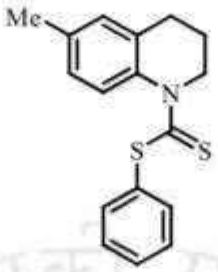


By following the **GP**, the title compound **2.17p** was isolated as light-yellow oil (0.217 g, 78%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f= 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.60 (m, 1H), 7.22 – 7.20 (m, 3H), 4.43 (t, J = 6.7 Hz, 2H), 3.28 – 3.20 (m, 2H), 2.72 (t, J = 6.8 Hz, 2H), 2.07 (pent, J = 6.8 Hz, 2H), 1.70 – 1.63 (m, 2H), 1.39 – 1.30 (m, 4H), 0.90 – 0.87 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 199.8, 140.5, 134.8, 128.7, 127.4, 126.6, 125.8, 52.0, 37.9, 31.4, 28.2, 26.4, 23.7, 22.4, 14.1. HRMS

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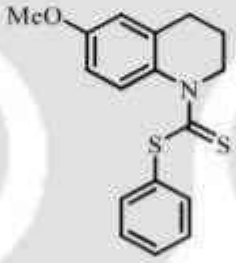
(ESI) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{22}NS_2$: 280.1189; found: 280. 1191.Significant IR band: $\nu_{(C=S)}$: 978 cm^{-1}.

Phenyl 6-methyl-3, 4-dihydroquinoline-1(2H)-carbodithioate (2.18a)



By following the **GP**, the title compound **2.18a** was isolated as light-yellow oil (0.266 g, 89%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 1H), 7.45 – 7.38 (m, 5H), 7.11 – 7.06 (m, 2H), 4.41 (t, J = 6.8 Hz, 2H), 2.72 (t, J = 6.6 Hz, 2H), 2.37 (s, 3H), 2.10 – 2.05 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 199.0, 137.9, 137.7, 136.9, 134.7, 132.6, 129.9, 129.4, 129.3, 129.1, 126.7, 126.2, 122.7, 52.9, 26.5, 23.8, 21.3. HRMS (ESI) *m/z*: $[M+H]^+$calculated for $C_{17}H_{18}NS_2$: 300.0876; found: 300.0848. Significant IR band: $\nu_{(C=S)}$: 973 cm^{-1}.

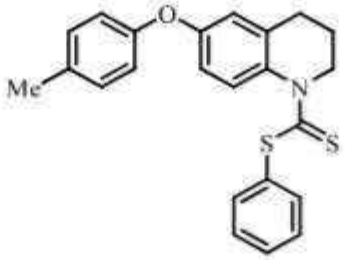
Phenyl 6-methoxy-3, 4-dihydroquinoline-1(2H)-carbodithioate (2.18b)



By following the **GP**, the title compound **2.18b** was isolated as light-yellow oil (0.284 g, 90%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.66). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.8 Hz, 1H), 7.45 – 7.38 (m, 5H), 6.82 – 6.77 (m, 2H), 4.41 (t, J = 6.8 Hz, 2H), 3.84 (s, 3H), 2.73 (t, J = 6.8 Hz, 2H), 2.07 (pent, J = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 198.9, 158.9, 136.9, 136.5, 133.5, 132.7, 129.9, 129.1, 127.6, 113.6, 111.4, 55.6, 52.8, 26.9, 23.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{18}NOS_2$: 316.0825; found: 316.0828. Significant IR band: $\nu_{(C=S)}$: 974 cm^{-1}.

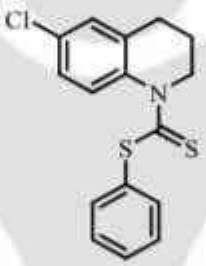
phenyl 6-(*p*-tolyloxy)-3,4-dihydroquinoline-1(2H)-carbodithioate (2.18c)

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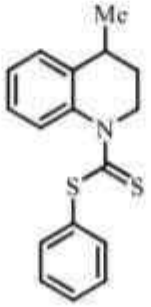
By following the **GP**, the title compound **2.18c** was isolated as light-yellow oil (0.337 g, 86%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.7 Hz, 1H), 7.46 – 7.38 (m, 5H), 7.18 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 6.86 – 6.81 (m, 2H), 4.41 (t, J = 6.6 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H), 2.36 (s, 3H), 2.07 (pent, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 199.0, 157.3, 154.0, 136.8, 136.6, 134.9, 133.8, 132.5, 130.6, 130.0, 129.2, 127.7, 119.9, 117.3, 115.2, 52.8, 26.8, 23.7, 20.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{23}H_{22}NOS_2$: 392.1138; found: 392.1139. Significant IR band: $\nu_{(C=S)}$: 977 cm^{-1}.

Phenyl 6-chloro-3,4-dihydroquinoline-1(2H)-carbodithioate (2.18d)



By following the **GP**, the title compound **2.18d** was isolated as light-yellow oil (0.243 g, 76%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.42 – 7.40 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.20 – 7.19 (m, 1H), 7.15 (dd, J = 8.8, 2.4 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 4.29 (t, J = 6.3 Hz, 2H), 2.83 (t, J = 6.7 Hz, 2H), 2.13 – 2.09 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 187.6, 154.0, 136.8, 134.1, 131.4, 129.5, 129.2, 128.6, 127.1, 126.3, 126.2, 122.6, 52.6, 27.0, 23.5. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{16}H_{15}ClNS_2$: 320.0329; found: 320.0325. Significant IR band: $\nu_{(C=S)}$: 963 cm^{-1}.

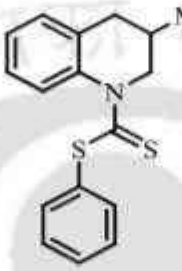
Phenyl 4-methyl-3, 4-dihydroquinoline-1(2H)-carbodithioate (2.18e)



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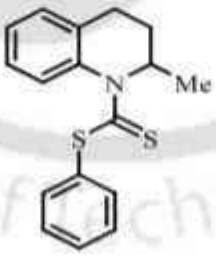
By following the **GP**, the title compound **2.18e** was isolated as light-yellow oil (0.264 g, 88%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 7.4 Hz, 1H), 7.44 – 7.38 (m, 5H), 7.31 – 7.29 (m, 3H), 4.63 – 4.58 (m, 1H), 4.33 – 4.26 (m, 1H), 2.90 – 2.83 (m, 1H), 2.29 – 2.22 (m, 1H), 1.70 – 1.63 (m, 1H), 1.37 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 199.3, 139.7, 139.6, 136.9, 132.5, 129.9, 129.4, 129.1, 127.9, 126.5, 126.2, 126.1, 122.7, 52.3, 32.4, 31.0, 19.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{18}NS_2$: 300.0876; found: 300.0900. Significant IR band: $\nu_{(C=S)}$: 970 cm^{-1}

Phenyl 3-methyl-3, 4-dihydroquinoline-1(2H)-carbodithioate (2.18f)



By following the **GP**, the title compound **2.18f** was isolated as light-yellow oil (0.246 g, 82%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 – 7.75 (m, 1H), 7.44 – 7.39 (m, 4H), 7.26 – 7.23 (m, 4H), 4.74 – 4.71(m, 1H), 3.82 – 3.78 (m, 1H), 2.89 (dd, J = 15.5, 5.8 Hz, 1H), 2.44 – 2.40 (m, 1H), 2.31 – 2.25 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 199.4, 140.0, 136.8, 134.2, 132.6, 130.0, 129.4, 129.2, 128.9, 127.5, 126.4, 126.0, 122.7, 59.7, 35.4, 31.1, 20.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{18}NS_2$: 300.0876; found: 300.0885. Significant IR band: $\nu_{(C=S)}$: 960 cm^{-1}.

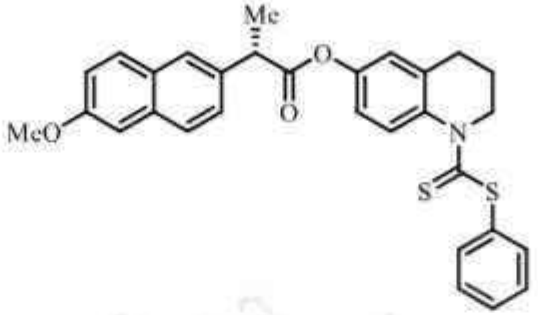
Phenyl 2-methyl-3,4-dihydroquinoline-1(2H)-carbodithioate (2.18g)



By following the **GP**, the title compound **2.18g** was isolated as light-yellow oil (0.243 g, 81%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.62 (m, 1H), 7.45 – 7.37 (m, 4H), 7.31 – 7.26 (m, 3H), 7.22 – 7.17 (m, 1H), 5.76 – 5.71 (m, 1H), 2.73 – 2.57 (m, 2H), 2.54 – 2.47 (m, 1H), 1.43 – 1.33 (m, 1H), 1.21 (d, J = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 198.9, 138.2, 137.2, 137.0, 132.5, 129.9, 129.4, 129.1, 128.1, 128.0, 127.6, 126.3, 122.7, 58.3, 33.1, 26.5, 20.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{18}NS_2$: 300.0876; found: 300.0875. Significant IR band: $\nu_{(C=S)}$: 957 cm^{-1}.

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1-((phenylthio)carbonothioyl)-1, 2, 3,4-tetrahydroquinolin-6-yl 2-(6-methoxynaphthalen-2-yl) propanoate (2.18h)



By following the **GP**, the title compound **2.18h** was isolated as light-yellow oil (0.267 g, 52%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 10:1, R_f = 0.48). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 – 7.72 (m, 4H), 7.50 – 7.48 (m, 2H), 7.40 – 7.38 (m, 1H), 7.26 (s, 4H), 7.17 – 7.14 (m, 2H), 6.81 – 6.77 (m, 1H), 4.09 – 4.05 (m, 1H), 3.92 (s, 3H), 3.84 – 3.81 (m, 2H), 2.76 – 2.73 (m, 2H), 2.03 – 1.97 (m, 2H), 1.68 (d, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 204.3, 173.4, 157.1, 144.7, 143.7, 136.7, 134.00, 133.98, 131.4, 134.0, 129.5, 129.21, 129.16, 129.1, 127.5, 126.3, 125.9, 121.9, 121.4, 119.3, 119.1, 116.0, 110.5, 105.8, 55.5, 45.7, 29.8, 27.1, 23.5, 18.7. HRMS (ESI) *m/z*: $[M+H]^+$calculated for $C_{30}H_{28}NO_3S_2$: 514.1506; found: 514.1505. Significant IR band: $\nu_{(C=S)}$: 963 cm^{-1}.

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Chapter 3

Triple role of boronic acid as a catalyst in the alkylation of quinoline to functionalized tetrahydroquinoline using para-quinone methides

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3.1. Introduction

Tetrahydroquinoline (THQ) derivatives are an important class of benzo-fused heteroaromatic compounds that are extensively employed in pharmaceuticals, bioactive natural products, ligands, and functional materials.[1,2] Among the various tetrahydroquinoline derivatives, *N*-benzyl tetrahydroquinolines (BTHQs) are of utmost interest in drug discovery due to their importance as therapeutics.[3,4] They are utilized as HDAC6 inhibitor,[3a] UCM1014 melatonin receptor agonists,[3b] β^3-adrenergic receptor antagonist,[3c] antitumor, antibiotic and anti-proliferative activities (Figure 3.1).[3d] Besides their bioactivities, they are suitable as pesticides, antioxidants, corrosion inhibitors, and active component of various dyes.[4] Notably, *N*-substituted tetrahydroquinoline with diaryl motif showed potent antiproliferative activity.[5]

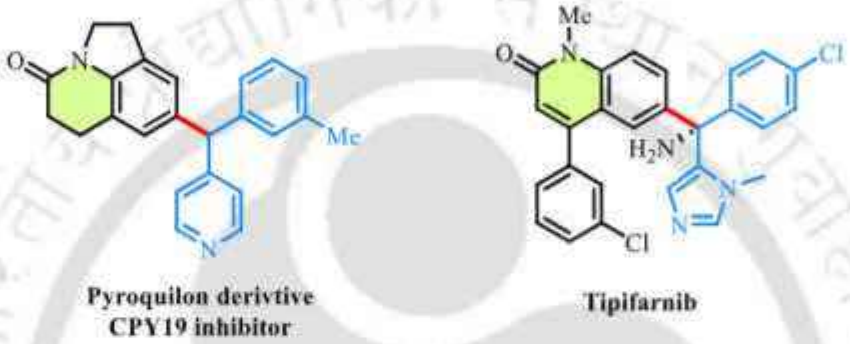
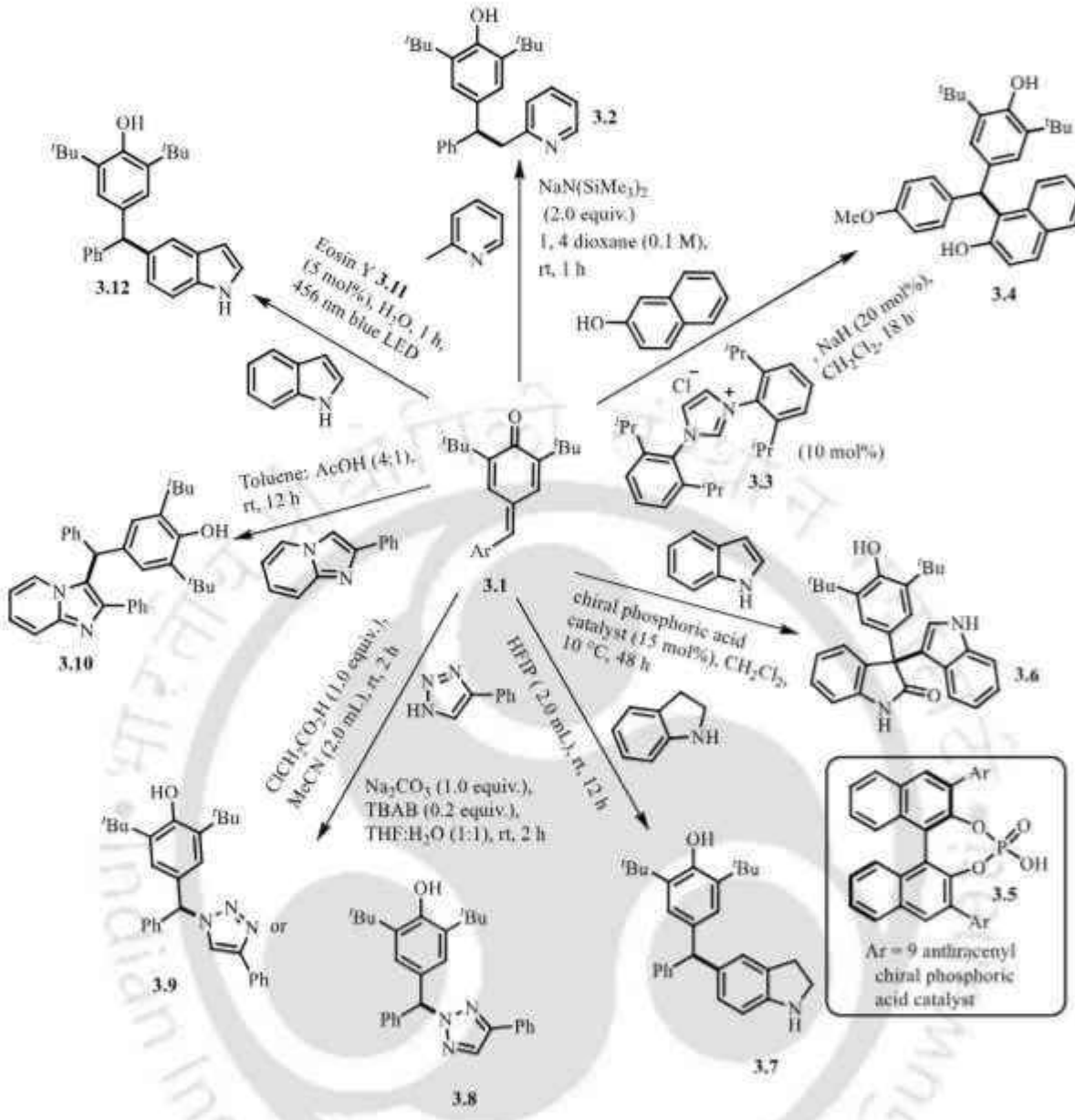


Figure 3.1. Representative bioactive compounds containing *N*-alkyl tetrahydroquinolines containing diaryl motif framework.

In recent years, *para*-quinone methides (*p*-QMs) have been recognized as a particularly unique and notable category of conjugate addition acceptors in organic synthesis, due to their highly electrophilic characteristics and versatile structure. These reactive intermediates possess an exocyclic carbon–carbon double bond that is conjugated with a quinonoid framework, making them especially prone to nucleophilic 1,6-conjugate addition. Consequently, *p*-QMs have been extensively utilized as important synthetic building blocks for creating functionalized aromatic compounds.[6] A variety of nucleophiles have been effectively employed in reactions with *p*-QMs, including alkylazaarenes,[7] naphthols,[8] isatins,[9] indolines,[10] 1,2,3-NH-triazoles,[11] imidazopyridines,[12] and indoles[13] (Scheme 3.1). These additions generally take place at the terminal carbon of the exocyclic double bond, generated 1,6-addition product with diaryl motif.

Nitrogen-containing aromatic compounds, such as dialkyl anilines and *N*-methyltetrahydroquinoline, serve as appealing nucleophiles because of their electron-rich characteristics. A significant development involves the use of $BF_3 \cdot Et_2O$ as a catalyst for Friedel–Crafts-type alkylation with *para*-quinone methides (*p*-QMs),[14] where the Lewis acid facilitates the activation of the *p*-QM, allowing for selective 1,6-conjugate addition at the benzylic site (Scheme 3.2).

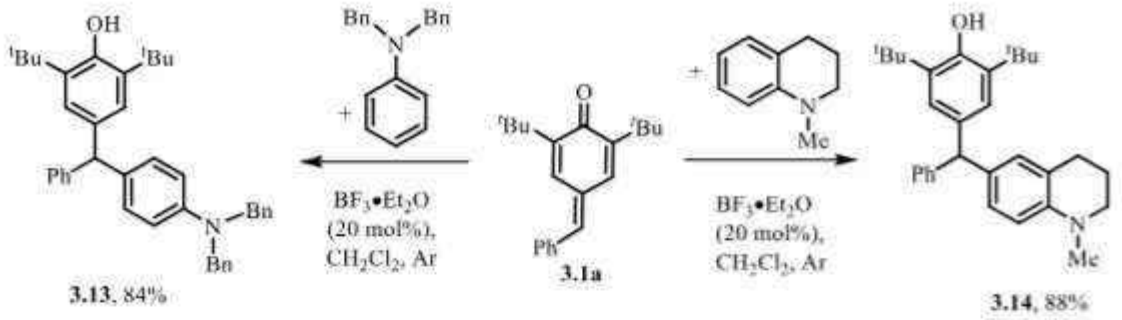
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Scheme 3.1. Synthesis of functionalized aromatic compounds using *para*-quinone methides as synthetic building block.

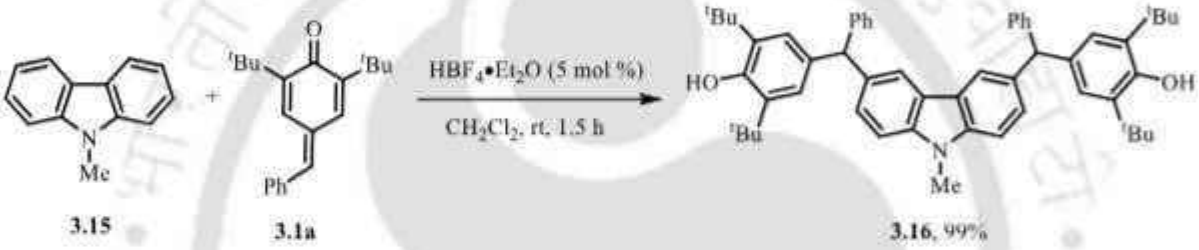
This mild and regioselective approach broadens the application of Friedel–Crafts chemistry to extended conjugated systems, providing an efficient pathway to obtain functionalized amines pertinent to the synthesis of complex molecules and medicinal chemistry. It highlights the increasing synthetic capabilities of *p*-QMs and introduces a practical strategy.

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Scheme 3.2. Lewis acid-catalyzed alkylation of dialkyl anilines and *N*-methyltetrahydroquinoline with *p*-QMs.

Later, *Anand* and *his co-workers* have demonstrated an alternative approach by using HBF_4 as Brønsted acid catalyst for the 1,6-conjugate addition of carbazoles to *p*-QMs to access diarylmethyl carbazoles under mild conditions (Scheme 3.3).[15]



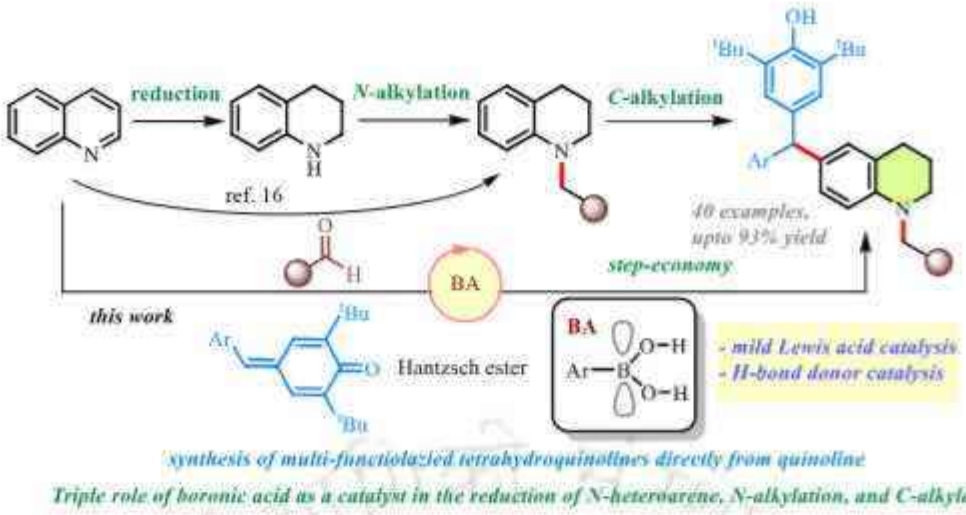
Scheme 3.3. Brønsted acid-catalyzed addition of carbazoles with *para*-quinone methides.

This demonstrates the adaptability of *p*-QMs in Friedel–Crafts-type alkylations and expands the range of nucleophiles that can be used in these reactions. In this study, it suggests that Friedel–Crafts-type alkylation with *p*-QMs can proceed by boron-based Lewis acid catalyst and also Brønsted acid catalyst.

3.2. Present work

Very recently we have demonstrated arylboronic acid-catalyzed reduction of quinolines to tetrahydroquinolines followed by reductive alkylation by the aldehyde to form the *N*-alkylated THQ product.[16] Herein, I envisaged that *in-situ* formed *N*-alkylated THQ can take part in *C*-alkylation reaction using *p*-QM affording tetrahydroquinoline derivatives containing diaryl motif at the C6-position (Scheme 3.4). The process is not only avoiding the prefunctionalized starting materials but also bypassing the isolation of THQ, and *N*-alkylated THQ intermediate, which may further increase the product scope and reduce the number of steps, thereby process become step-economic and cost-efficient tool.

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Scheme 3.4. One-pot multi-component synthesis of tetrahydroquinoline derivatives containing diaryl motif.

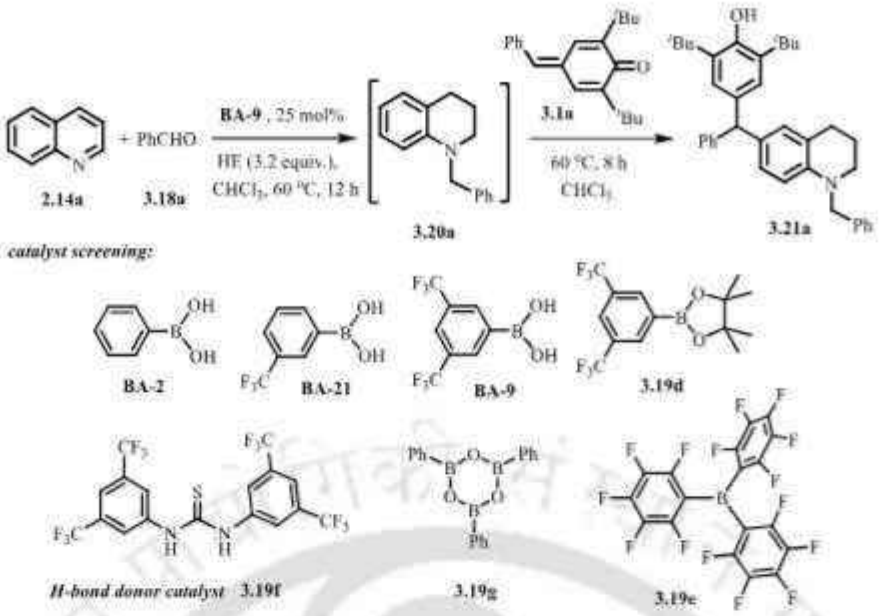
3.3. Results and discussion

3.3.1. Optimization of reaction conditions

The reaction was initiated with quinoline (**2.14a**, 1 mmol), benzaldehyde (**3.18a**, 1 mmol) Hantzsch ester (3.2 mmol), and phenylboronic acid **BA-2** (0.25 mmol)[16] in chloroform at a 60 °C for 12 h under air. Then, required *p*-QM (**3.1a**, 1 mmol) was added to the reaction mixture and stirred the reaction mixture at the same temperature for 8 h. Gratifyingly, *C*-alkylated THQ with diphenyl motif **3.21a** was obtained in 62% yield, along with 24% *N*-benzyl THQ (**3.20a**, Table 3.1, entry 1). To improve the yield of desired product **3.21a**, arylboronic acid with electron-withdrawing $-CF_3$ substituent (**BA-21**, **BA-9**) were examined (entries 2-3). The 3,5-bis(trifluoromethyl)phenyl boronic acid **BA-9** have been found to be superior catalyst for the current transformation with the product **3.21a** obtained in 87% yield (entry 3). Next, I examine the reaction by $-CF_3$ functionalized boronic ester **3.19d** under the reaction conditions, product **3.21a** was obtained in 48% yield (entry 4). When pentafluorotriphenylboron **3.19e** is used as Lewis acid catalyst, product **3.21a** was obtained in 73% yield (entry 5). Then the reaction was performed with hydrogen-bond donor catalyst, $-CF_3$ functionalized thiourea **3.19f**, product **3.21a** was obtained in 56% yield (entry 6). The study suggests that the mode of boronic acid catalysis likely involves both H-bond donor catalysis and Lewis acid catalysis. Brønsted acids such as benzoic acid, and trifluoracetic acid provided the product **3.21a** in low yield (entry 8). The reaction temperature was also found as an important factor affecting the results.

Table 3.1. Optimization studies for functionalized-THQ[a]

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entry	deviation from above	yield of **3.21a** (%)
1	with **BA-2**	62%, (24% of **3.20a**), 49%[b]
2	with **BA-21**	79%, 77%[b]
3	none	87%, 87%[b]
4	with **3.19d**	48%
5	with **3.19e**	73%
6	with **3.19f**	56%
7	with **3.19g**	38%
8	with Brønsted acid	4%[c] 37%[d]
9	at 45 °C	25%
10	at 80 °C	74%
11	no catalyst	0%
12	with 15 mol% **BA-9**	65%
13	with DCE	78%
14	with CH_3CN	62%
15[e]	adding **3.1a** from the beginning	22%, (39% of **3.20a**, 31% of **3.1a'**)

[a]Reaction conditions: quinoline (**2.14a**, 1 mmol), aldehyde (**3.18a**, 1 mmol), Hantzsch ester (3.2 mmol) and **BA-9** (0.25 mmol) in $CHCl_3$ (2 mL) at 60 °C for 12 h under air; then *p*-QMs **3.1a** (1 mmol) at 60 °C for 8 h, isolated yields. [b]with unrecrystallized phenylboronic acid **BA-2**, [c]with $PhCO_2H$, [d]with TFA, [e]by adding *p*-QMs **3.1a** from the beginning.

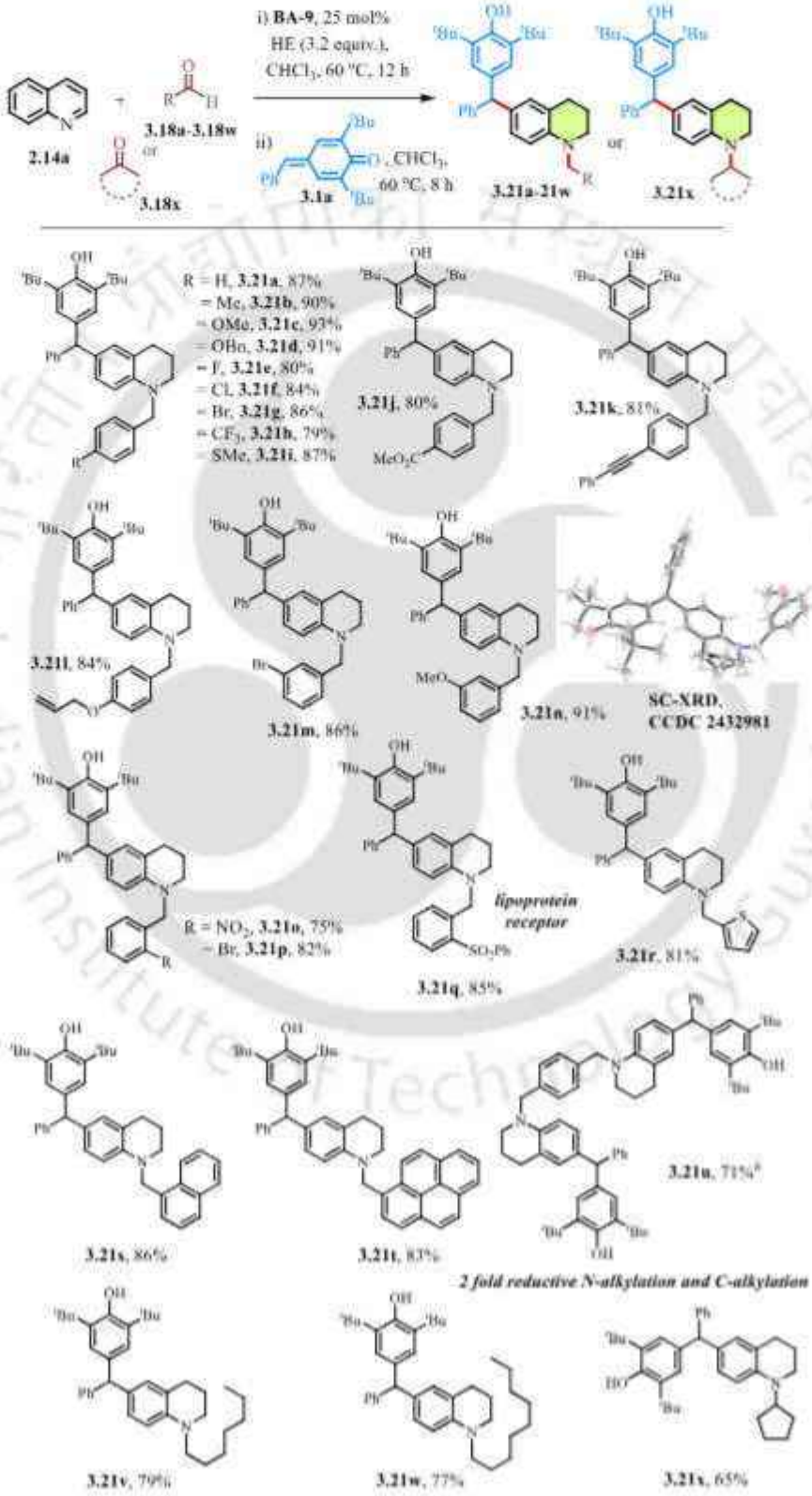
When the reaction temperature decreased to 45 °C, a lower yield of 25% was achieved (entry 9). Further, the lower catalyst loading significantly reduced the reaction efficiency (entry 12). Nevertheless, when the reaction was performed in a one-pot fashion, by adding *p*-QM **3.1a** from the beginning, the desired *C*-alkylated product **3.21a** was obtained in only 22% yield, along with 39% yield *N*-benzyl THQ **3.20a** and 31% yield hydrogenated product **3.1a'**(entry 15). This suggests that it is necessary to

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add *p*-QMs after the formation of *N*-alkylated THQ **3.20a**, otherwise, *p*-QMs readily reacts with Hantzsch ester to provide **3.1a'**.

3.3.2. Substrates scope for synthesis of functionalized tetrahydroquinolines

Table 3.2. The reaction scope with various aldehydes and ketone[a]

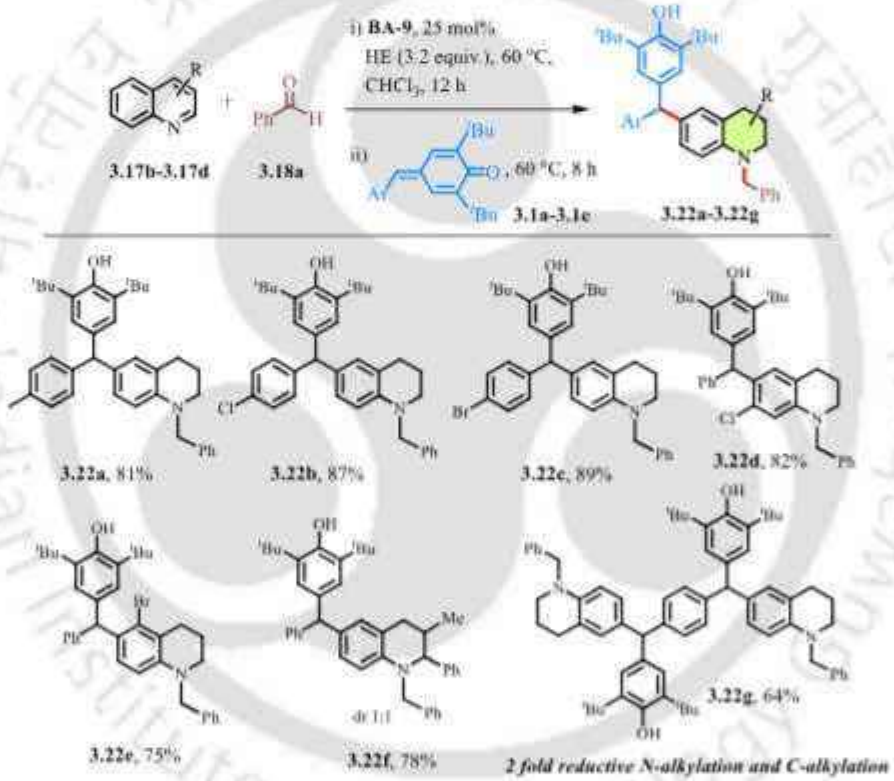


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[a]Reaction conditions: quinoline (**2.14a**, 1 mmol), aldehyde or ketone (1 mmol), Hantzsch ester (3.2 mmol) and **2.6m** (0.25 mmol) in $CHCl_3$ (2 mL) at 60 °C for 12 h under air; then *p*-QM **3.1a** (1 mmol) at 60 °C for 8 h, isolated yields. [b]with 0.5 mmol of **3.18u**, Hantzsch ester (6.5 mmol).

With the optimized conditions in hand, I intended the substrate scope of this reaction by employing varieties of substituted aldehydes **3.18a-w** with quinoline **2.14a** as the standard substrate (Table 3.2). The substrates containing both electron-donating and electron-withdrawing groups at the *para*-position in the aryl moiety were efficiently reacted to get the desired products **3.21a-3.21l** in 80-93% yields, and slightly higher yield were realized for electron-donating groups. Likewise, *meta*- substituent bearing aldehyde provided the corresponding *N*-alkylated products **3.21m-3.21n** in good yields.

Table 3.3. The reaction scope with various *p*-QMs, and quinolines[a]



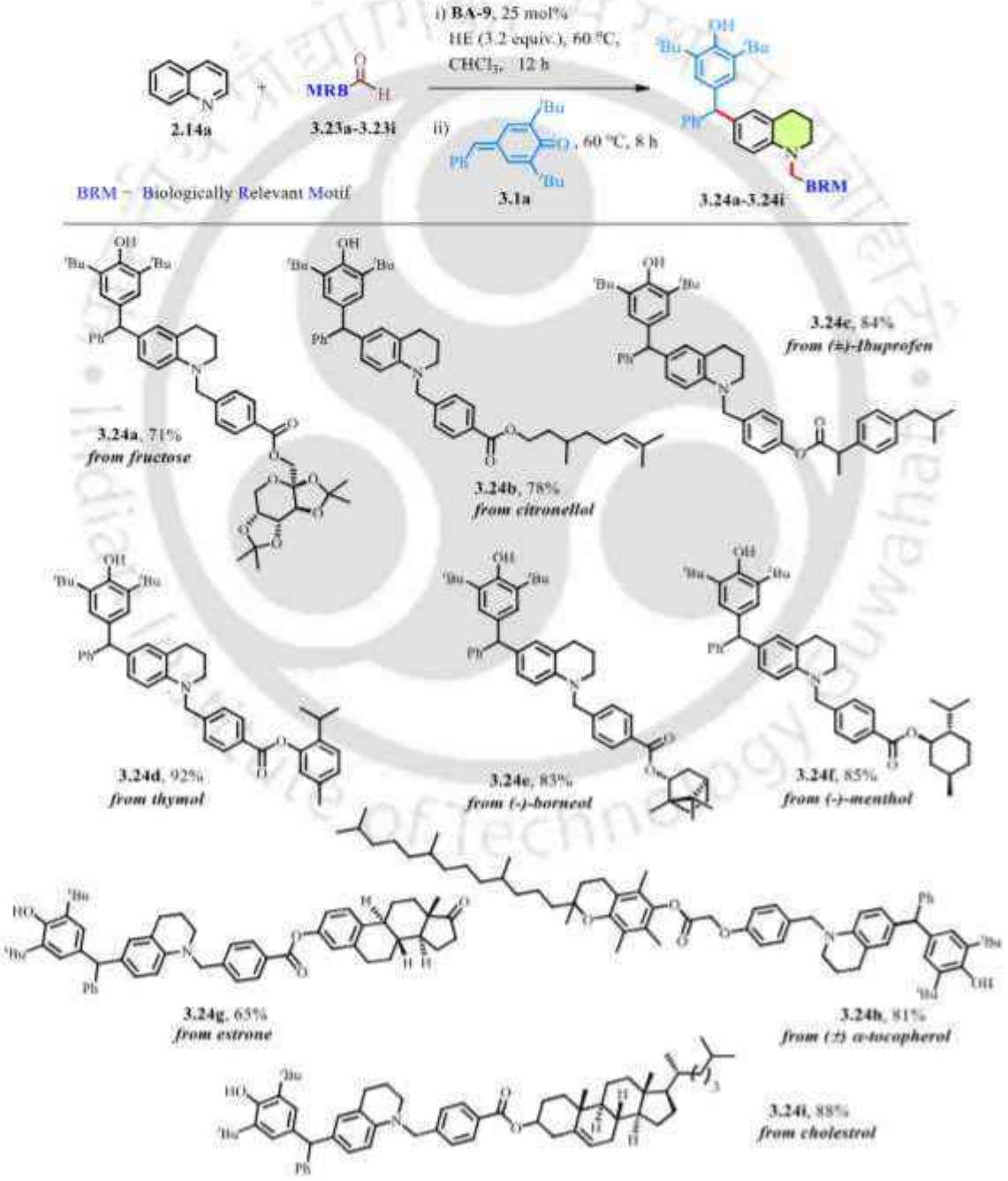
[a]Reaction conditions: substituted quinoline **3.17b-3.17d** (1 mmol), aldehyde **3.18a** (1 mmol), Hantzsch ester (3.2 mmol) and **BA-9** (0.25 mmol) in $CHCl_3$ (2 mL) at 60 °C for 12 h under air; then different *p*-QM **3.1a-3.1e** (1 mmol) at 60 °C for 8 h, isolated yields.

The structure of the product **3.21n** was further confirmed by single-crystal X-ray diffraction analyses. The synthetically challenging sterically hindered *ortho*-substituted aldehyde **3.18o**, **3.18p** was well tolerated as validated from the 75% yield of **3.21o** and 82% yield of **3.21p**, respectively. The current alkylation approach was also successfully employed to synthesize of a lipoprotein receptor **3.21q**. Since the reaction condition tolerates the halogen functional groups (**3.21g**, **3.21m**, **3.21p**), this can be beneficial for further functionalization. Notably, the retention of reducible functional groups (4-Br, 4-OBn, 4-CF_3, 4-C≡CPh, 4-*O*-allyl, 4-SMe, 4-CO_2Me, 3-Br, 2-Br, 2-NO_2, 2-SO_2Ph) in

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the final products showcasing the excellent chemoselectivity of the present protocol under reductive conditions. Moreover, heteroatom aldehyde **3.18r** and polyaromatic aldehydes **3.18s**, **3.18t** were also well suited under the reaction conditions and provided the products **3.21r**, **3.21s** and **3.21t**, respectively. When 1,4-benzenedialdehyde was used as an alkylating agent the polyfunctionalized *C*-alkylated THQ **3.21u** was obtained with notable selectivity. Besides aromatic aldehydes, scope of the reaction was expanded to a variety of aliphatic aldehydes and cyclic ketones, yielding **3.21v**-**3.21w** and **3.21x**, respectively. I failed to obtain the desired product when isoquinoline **2.14f** or quinoxaline **2.14g** was used as a substrate.

Table 3.4. The reaction scope with various BRM-bearing aldehyde[a]



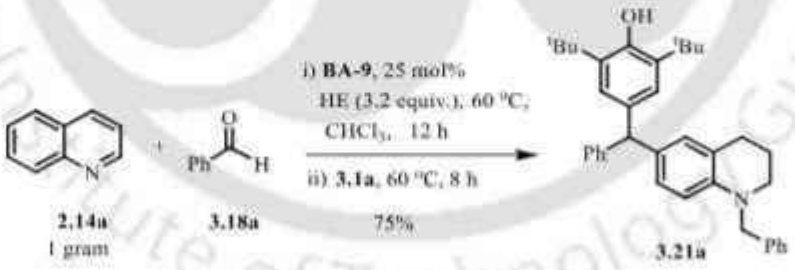
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[a]Reaction conditions: quinoline (**2.14a**, 1 mmol), BRM containing aldehydes **3.23a-3.23i** (1 mmol), Hantzsch ester (3.2 mmol) and **BA-9** (0.25 mmol) in $CHCl_3$ (2 mL) at 60 °C for 12 h under air; then *p*-QM **3.1a** (1 mmol) at 60 °C for 8 h, isolated yields.

The scope of the reaction was further extended to a series of *p*-QMs **3.1a-3.1e** and substituted quinoline **3.17b-3.17d** while keeping aldehyde **3.18a** as the standard substrate (Table 3.3). The *p*-QMs bearing 6-methyl (**3.1b**), 6-chloro (**3.1c**) and 6-bromo (**3.1d**) substituents afforded the desired products **3.22a-3.22c** in 81-89% yields. Similarly, the reaction of 7-chloro (**3.17b**), 5-bromo (**3.17c**), and 2-phenyl-3-methyl (**3.17d**) quinoline afforded **3.22d**, 82%, **3.22e**, 75% and **3.22f**, 78% yield respectively. Furthermore, *p*-QM of terephthalaldehyde **3.1e** gave tandem double 1,6-conjugate addition product **3.22g** in 64% yield. Encouraged by the performance of the catalyst, I further expanded scope of the reaction using highly functionalized substrates with complex molecular settings. A range of biologically relevant motifs (BRM) were targeted and were independently subjected to the optimized reaction conditions, afforded corresponding THQ derivatives containing fructose (**3.24a**, 71%), citronellol (**3.24b**, 78%), (±)-ibuprofen (**3.24c**, 84%), thymol (**3.24d**, 92%), (-)-borneol (**3.24e**, 83%), (-)-menthol (**3.24f**, 85%), estrone (**3.24g**, 65%), tocopherol (**3.24h**, 81%), cholesterol (**3.24i**, 88%) moiety without any structural changes of the complex architecture (Table 3.4).

3.3.4. Gram-scale reaction

To understand the efficiency of this process, gram-scale reaction was performed for bulk utilization. The use of 1-gram quinoline **2.14a** afforded the desired *C*-alkylated product **3.21a** in 75% yield (Scheme 3.5).



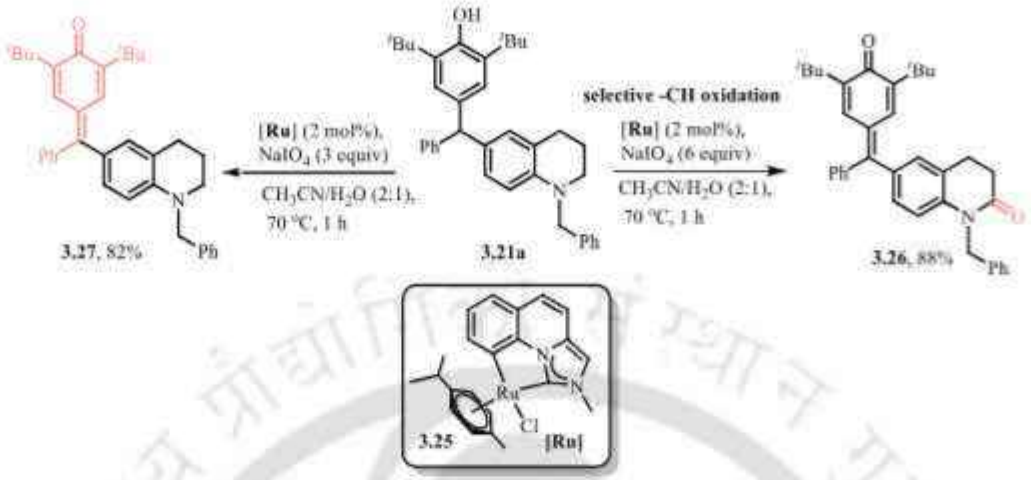
Scheme 3.5. Gram-scale reaction.

3.3.5. Post-synthetic modifications

Given the importance of the lactam motif in various biologically and pharmaceutically relevant complex molecular settings, synthesized compound **3.21a** was successfully converted into lactam **3.26** in 88% yield using the cyclometalated ruthenium catalyst (**3.25**)[17] and periodate under oxidative conditions (Scheme 3.6). Under the similar reaction conditions with lowering the equivalency of periodate, -CH proton at the tertiary carbon in **3.21a** can readily oxidized to give **3.27** in 82% yield (Scheme 3.6). It

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is worth mentioning that cyclic-α-methylene C–H bond is selectively oxidized under the reaction conditions even in the presence of benzyl C–H bonds.



Scheme 3.6. Post-synthetic modification.

3.3.6. Mechanistic investigation

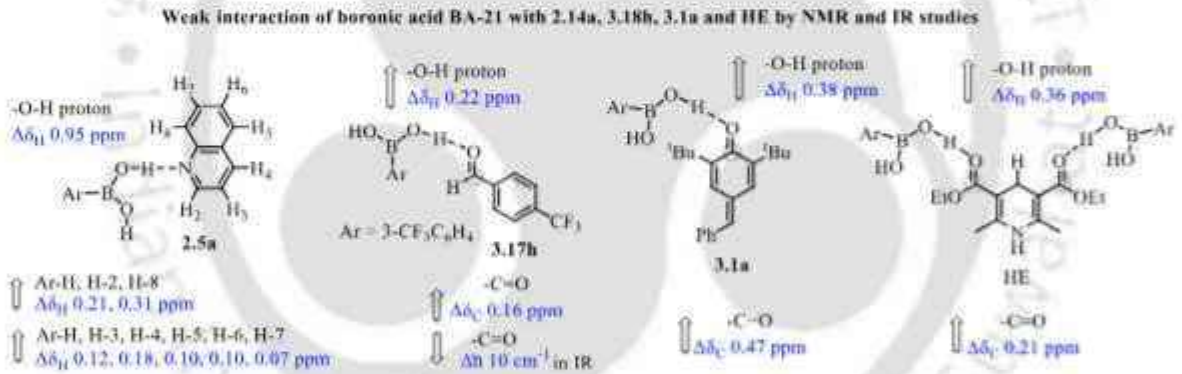


Figure 3.2. Weak interaction of boronic acid with substartes and HE.

Next, the mechanism of the catalytic reaction was investigated with both Lewis acid and hydrogen bonding properties of boronic acid (Figure 3.3, 3.4) A close inspection of the nature of binding in solution indicates that there is a weak hydrogen bond interaction between B-OH of **BA-21** and N-atom of quinoline moiety. The study was initiated with 1:1 mixture of quinoline **2.14a**: **BA-21** in $CDCl_3$ and record the ^1H NMR. A slight downfield shift of the hydroxyl group signal in **BA-21** from 4.92 ppm to 5.07 ppm upon mixing with **2.14a** was observed, indicating a weak hydrogen bonding between the B-OH of **BA-21** and N-atom of quinoline moiety. Furthermore, the chemical shift of the aromatic proton H2 and H8 of **2.5a** adjacent to the quinyl nitrogen shifted significantly from 8.90 to 9.11 ppm, and 8.12 to 8.43 ppm, respectively, upon addition of **BA-21**. In addition, the chemical shifts of the aromatic protons H3, H4, H5, H6, and H7 of the **2.14a** shifted from 7.36, 8.11, 7.78, 7.52 and 7.70 ppm to 7.48, 8.29, 7.88, 7.62 and 7.77 ppm, respectively. Such a noteworthy change in the ^1H NMR

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pattern of the quinyl region is consistent with the existence of a strong hydrogen bonding between **2.14a** and B-OH of **BA-21**.

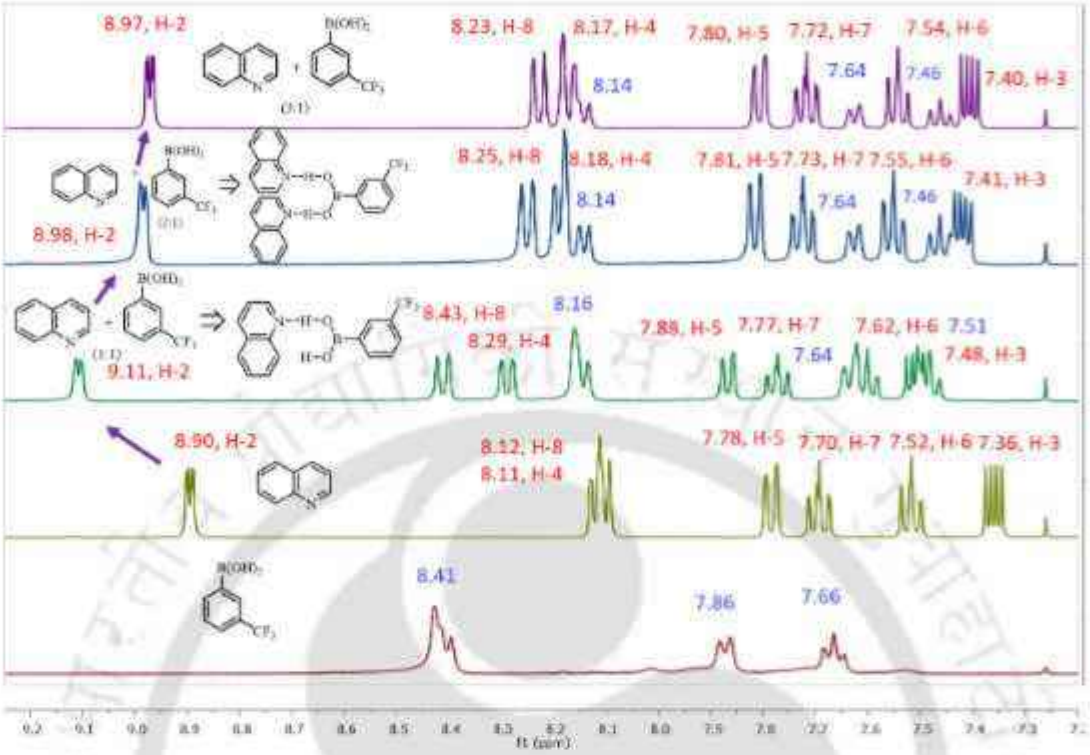
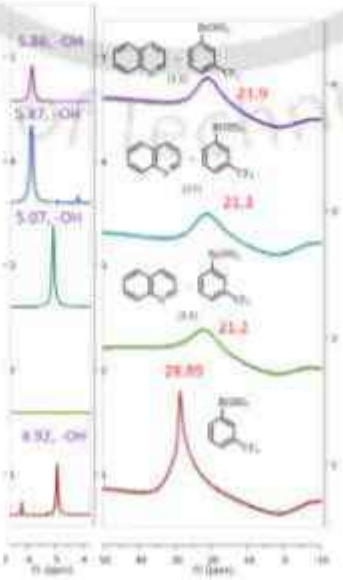


Figure 3.3. ^{1}H NMR spectra of quinoline (**2.14a**) (10 mg, 0.079 mmol), 3-trifluoromethylphenylboronic acid (**BA-21**) (16 mg, 0.079 mmol), and the mixture of quinoline and 3-trifluoromethylphenylboronic acid (**BA-21**) (molar ratio 1:1) in $CDCl_3$ at 298 K.

In ^{11}B NMR, approximately 7 ppm upfield shift was observed, which suggests complexation may take place between boronic acid **BA-21** and quinoline **2.14a**. The above upfield shift in ^{11}B NMR for boronic acid likely to be attributed as hydrogen bonding interaction rather than complexation with quinoline in solution.



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Figure 3.4. ^{11}B NMR spectra of quinoline (**2.14a**) (10 mg, 0.079 mmol), 3-trifluoromethylphenylboronic acid (**BA-21**) (16 mg, 0.079 mmol), and the mixture of quinoline and 3-trifluoromethylphenylboronic acid (**BA-21**) (molar ratio 1:1) in $CDCl_3$ at 298 K.

In order to illustrate the interaction of boronic acid and aldehyde, I performed the ^{1}H, ^{13}C, ^{11}B NMR, and IR spectroscopic experiments by using 3-trifluoromethylphenylboronic acid (**BA-21**), and 4-trifluoromethyl benzaldehyde, respectively. While one equivalent of 3-trifluoromethyl phenylboronic acid (**BA-21**) was added to 4-trifluoromethyl benzaldehyde (**3.18h**) in $CDCl_3$, a downfield shift of approximately 0.22 ppm for hydroxyl peak of boronic acid in ^{1}H NMR and 0.16 ppm for carbonyl signal of aldehyde in ^{13}C NMR were observed (Figure 3.5, 3.6). On the other hand, no shift was observed in ^{11}B NMR, which rules out the possibility of adduct formation with boron (Figure 3.7).

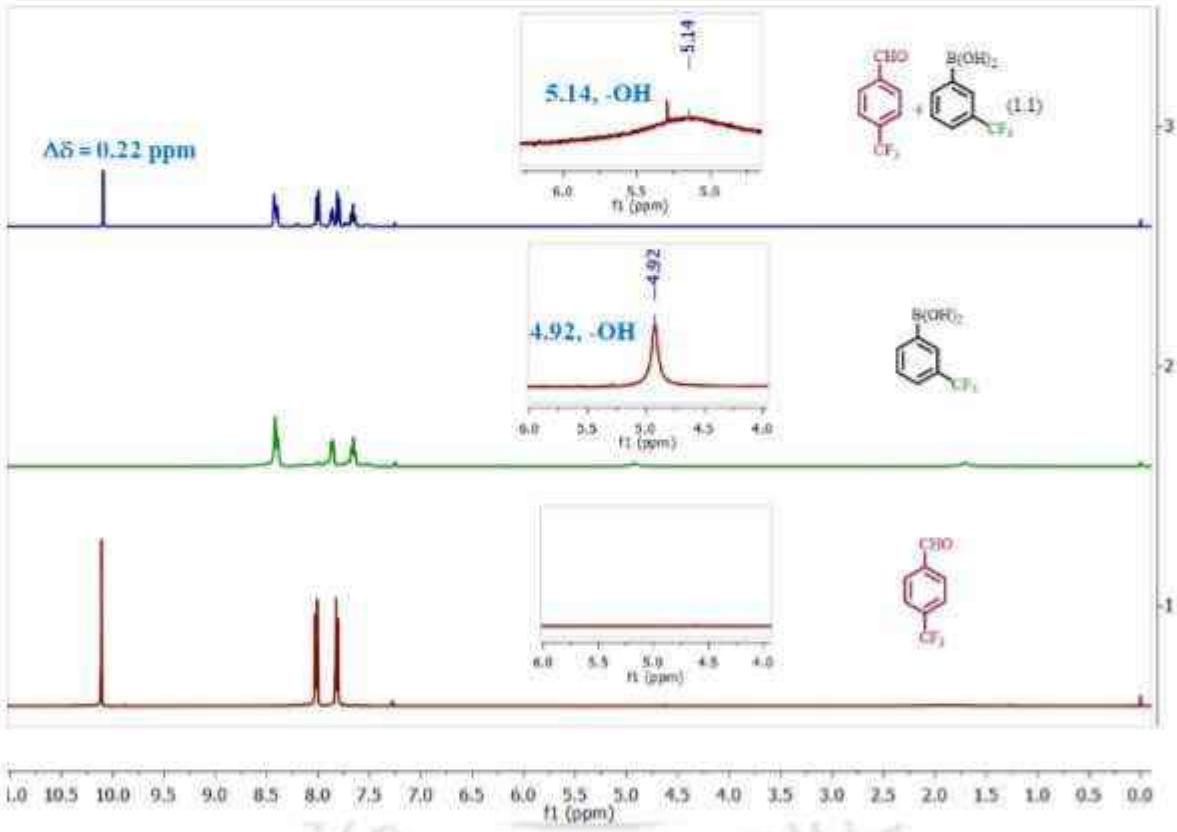


Figure 3.5. ^{1}H NMR spectra of 4-trifluoromethylbenzaldehyde (**3.18h**) (14 mg, 0.079 mmol), 3-trifluoromethylphenylboronic acid (**BA-21**) (16 mg, 0.079 mmol), and the mixture of 4-trifluoromethylbenzaldehyde (**3.18h**) and 3-trifluoromethylphenylboronic acid (**BA-21**) (molar ratio 1:1) in $CDCl_3$ at 298 K.

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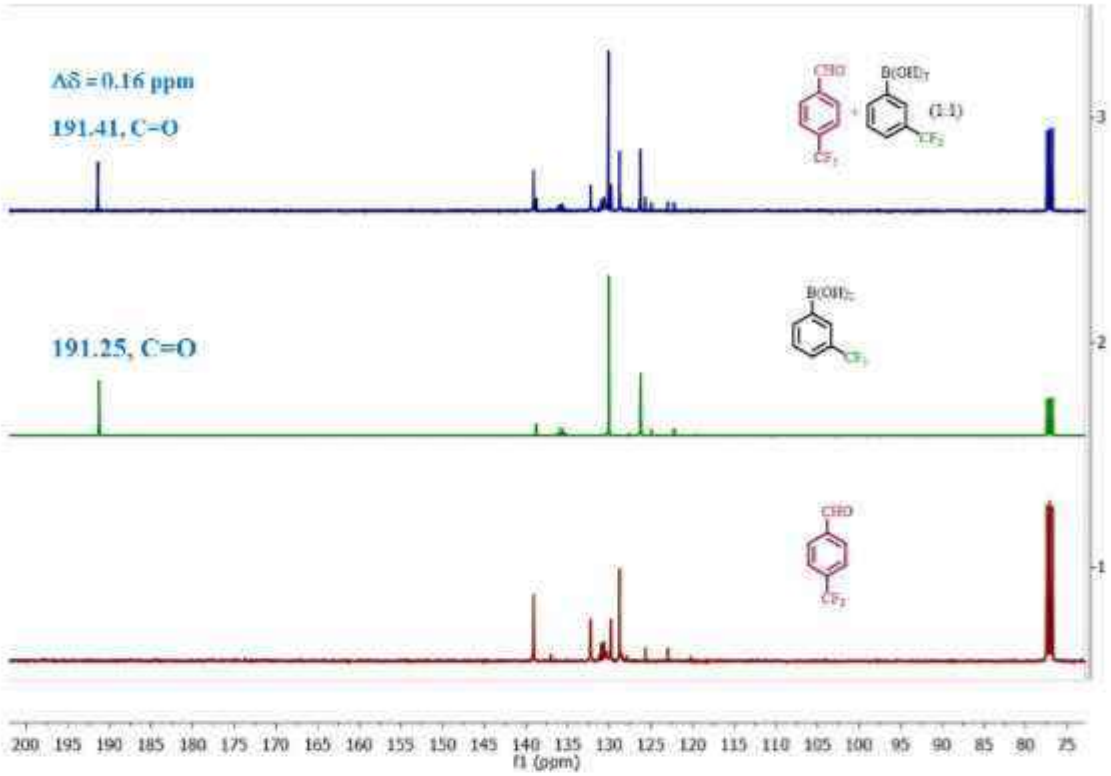
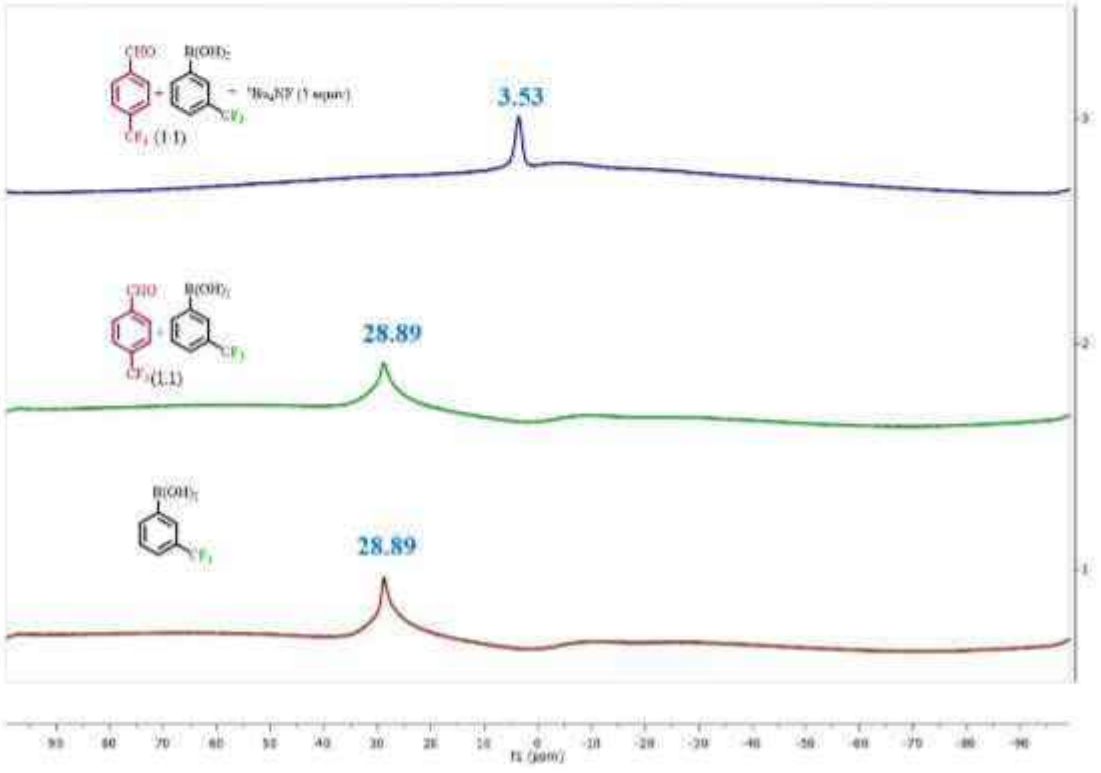


Figure 3.6. $^{13}C\{^{1}H\}$ NMR spectra of 4-trifluoromethylbenzaldehyde (**3.18h**) (14 mg, 0.079 mmol), 3-trifluoromethylphenylboronic acid (**BA-21**) (16mg, 0.079mmol), and the mixture of 4-trifluoromethylbenzaldehyde (**3.18h**) and 3-trifluoromethylphenylboronic acid (**BA-21**) (molar ratio 1:1) in $CDCl_3$ at 298 K.



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Figure 3.7. ^{11}B NMR spectra of 4-trifluoromethylbenzaldehyde (**3.18h**) (14 mg, 0.079 mmol), 3-trifluoromethylphenylboronic acid (**BA-21**) (16 mg, 0.079 mmol), and the mixture of 4-trifluoromethylbenzaldehyde (**3.18h**) and 3-trifluoromethylphenylboronic acid (**BA-21**) (molar ratio 1:1), 4-trifluoromethylbenzaldehyde, 3-trifluoromethylphenylboronic acid (**BA-21**) (molar ratio 1:1) and with TBAF (0.534 mmol) in $CDCl_3$ at 298 K.

For comparison, one equivalent of TBAF was added to the same reaction mixture, about 25 ppm upfield shift was observed, which indicates the same boron acts as a Lewis acid and take part in complexation with TBAF within. In IR, the carbonyl value shifted to a lower wave number from 1712.4 cm^{-1} to 1701.3 cm^{-1} after mixing with 3-trifluoromethylphenylboronic acid at room temperature (Figure 3.8). Approximately 10 cm^{-1} lower wave number has been observed for the carbonyl group in a mixture compared to free aldehyde, which supports hydrogen bonding interaction between aldehyde and boronic acid. A downfield shift for hydroxyl peak of boronic acid in ^1H NMR and ensuing downfield shift for carbonyl in aldehyde in ^{13}C NMR supports hydrogen bonding interaction with aldehyde and boronic acid. It has been further reinforced by using IR spectroscopic experiments in the solid-state.

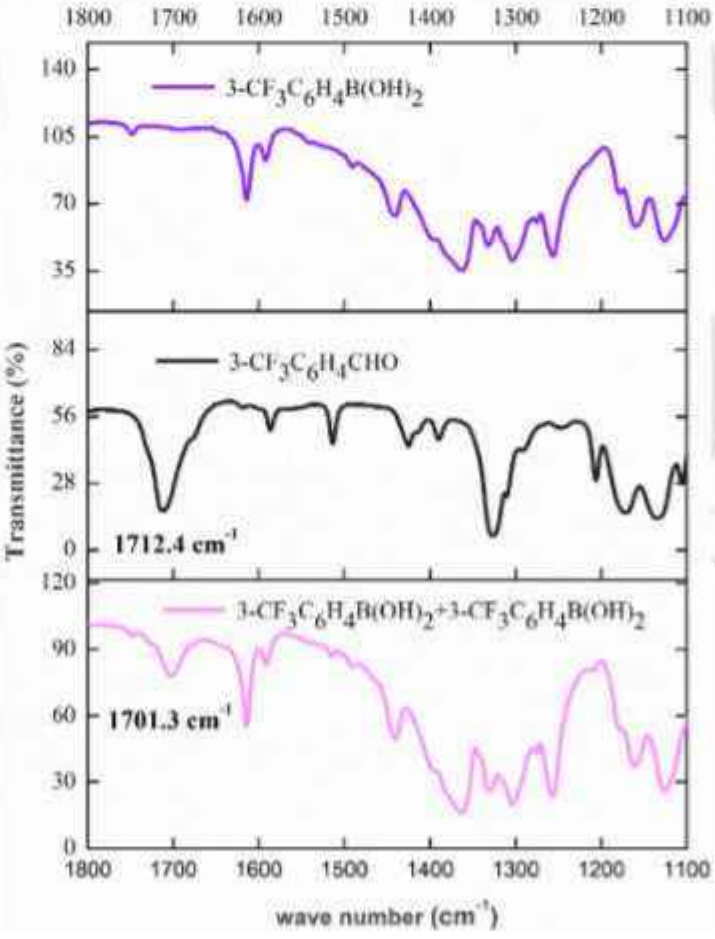


Figure 3.8. IR spectroscopy to support the interaction of 4-trifluoromethyl benzaldehyde (**3.17h**) and 3-trifluromethylphenylboronic acid (**BA-21**).

In order to illustrate the interaction of boronic acid and *p*-QMs, I performed the ^1H, ^{13}C, by using 3-trifluoromethylphenylboronic acid (**BA-21**), and 4-benzylidene-2,6-di-*tert*-

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butylcyclohexa-2,5-dien-1-one **3.1a**, respectively. While one equivalent of 3- trifluoromethyl phenylboronic acid (**BA-21**) was added to 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one **3.1a** in $CDCl_3$, a downfield shift of approximately 0.39 ppm for hydroxyl peak of boronic acid in ^1H NMR and 0.07 ppm for carbonyl signal of aldehyde in ^{13}C NMR were observed (Figure 3.9, 3.10).

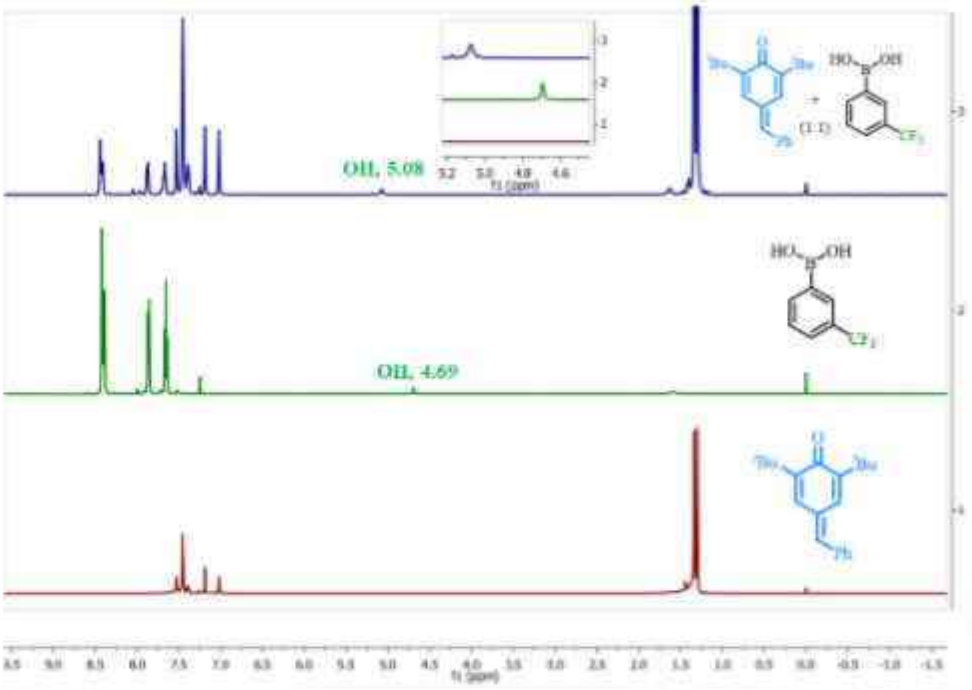
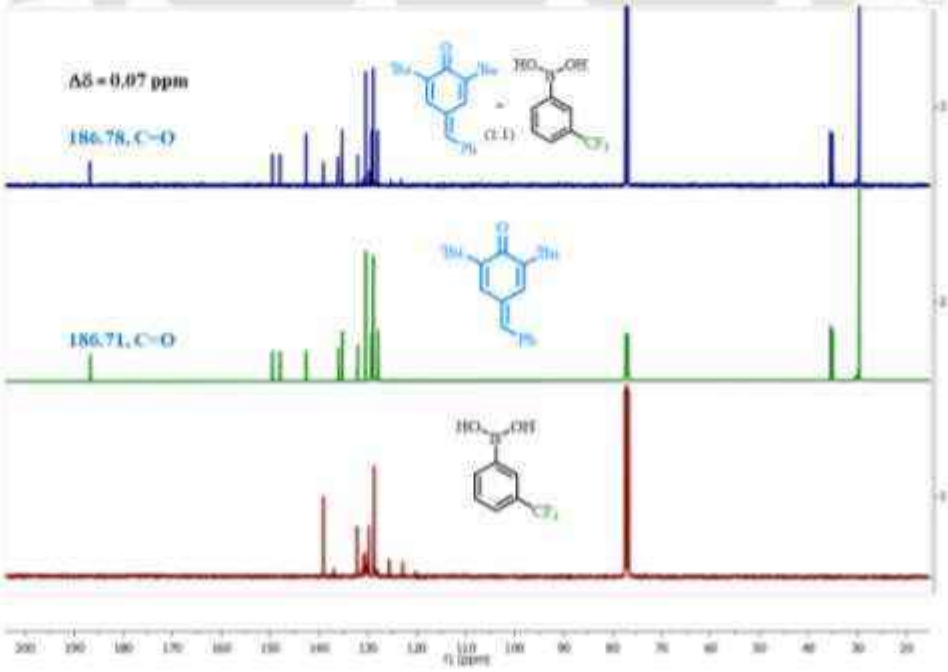


Figure 3.9. ^1H NMR spectra of 3-trifluoromethylphenylboronic acid (**BA-21**) (15 mg, 0.079 mmol), **3.1a** (0.023 g, 0.079 mmol), and the mixture of 3-trifluoromethylphenylboronic acid (**BA-21**) and **3.1a** (molar ratio 1:1) in $CDCl_3$ at 298 K.



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Figure 3.10. $^{13}C\{^{1}H\}$ NMR spectra of 3-trifluoromethylphenylboronic acid (**BA-21**) (15 mg, 0.079 mmol), **3.1a** (0.023 g, 0.079 mmol), and the mixture of 3-trifluoromethylphenylboronic acid (**BA-21**) and **3.1a** (molar ratio 1:1) in $CDCl_3$ at 298 K.

To examine the interaction of boronic acid and Hantzsch ester, I have checked the ^{1}H NMR with the combination of (a) Hantzsch ester and phenylboronic acid (**BA-2**) (molar ratio 1:1) (b) Hantzsch ester and 3-trifluoromethyl boronic acid (**BA-21**) (molar ratio 1:2) in $CDCl_3$ at rt. In the case of phenylboronic acid (**BA-2**) approximately 0.41 ppm downfield was shifted for the hydroxyl peak, whereas no characteristic –OH proton signal was observed while mixing with 3- trifluoromethyl phenylboronic acid (**BA-21**) (Figure 3.11, 3.12).

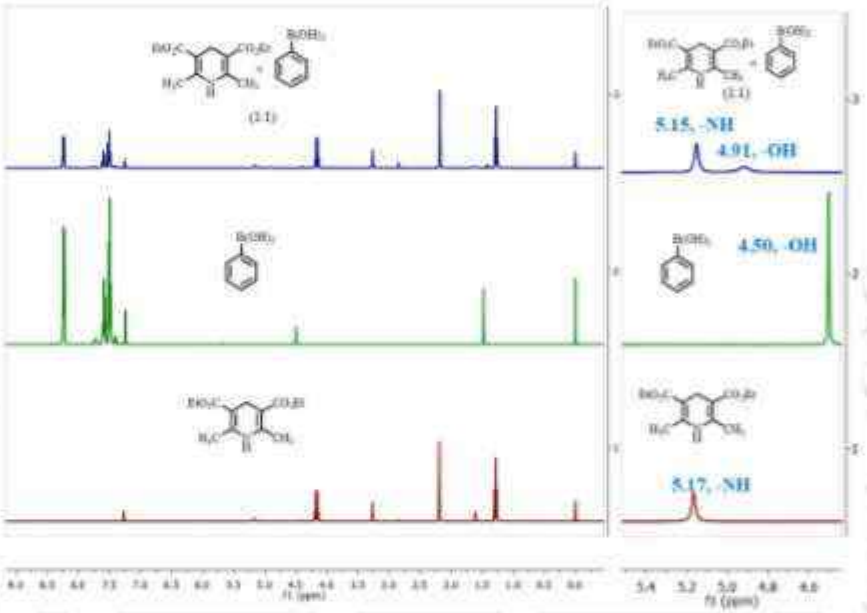
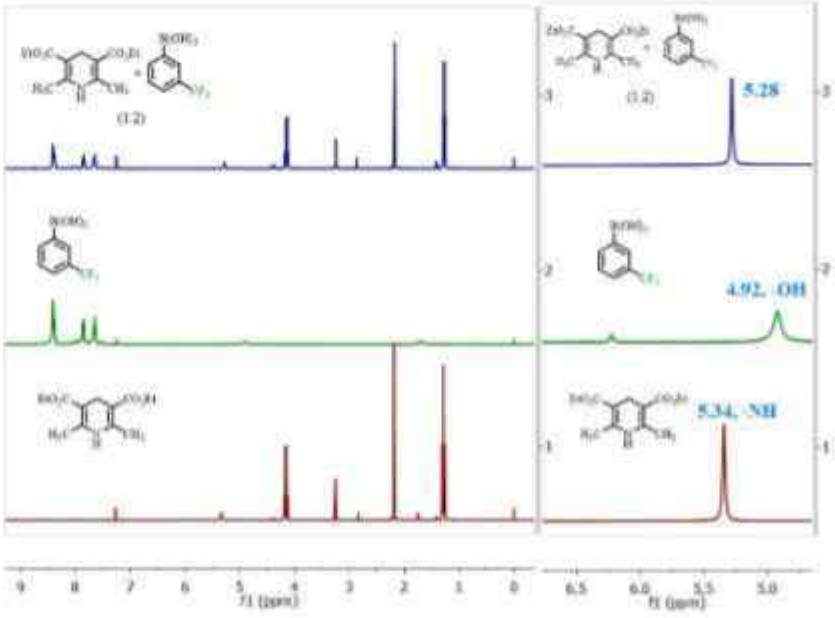


Figure 3.11. ^{1}H NMR spectra of Phenylboronic acid (**BA-2**) (10 mg, 0.079 mmol), Hantzsch ester (10 mg, 0.079 mmol), and the mixture of Phenylboronic acid (**BA-2**) and Hantzsch ester (molar ratio 1:1) in $CDCl_3$ at 298 K.



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Figure 3.12. ^{1}H NMR spectra of 3-trifluoromethylphenylboronic acid (**BA-21**) (15 mg, 0.079 mmol), Hantzsch ester (5 mg, 0.039 mmol), and the mixture of 3-trifluoromethylphenylboronic acid (**BA-21**) and Hantzsch ester (molar ratio 2:1) in $CDCl_3$ at 298 K.

However, in ^{13}C NMR, the carbonyl value in Hantzsch ester was shifted downfield from 168.22 to 168.43 ppm ($\Delta\delta$ = 0.21 ppm). Using ^{11}B NMR spectroscopy, no noticeable shift was observed in boronic acid, which implies exclude Lewis acid-base adduct, and hydrogen bonding interaction may exist between Hantzsch ester and –OH of boronic acid (Figure 3.13).

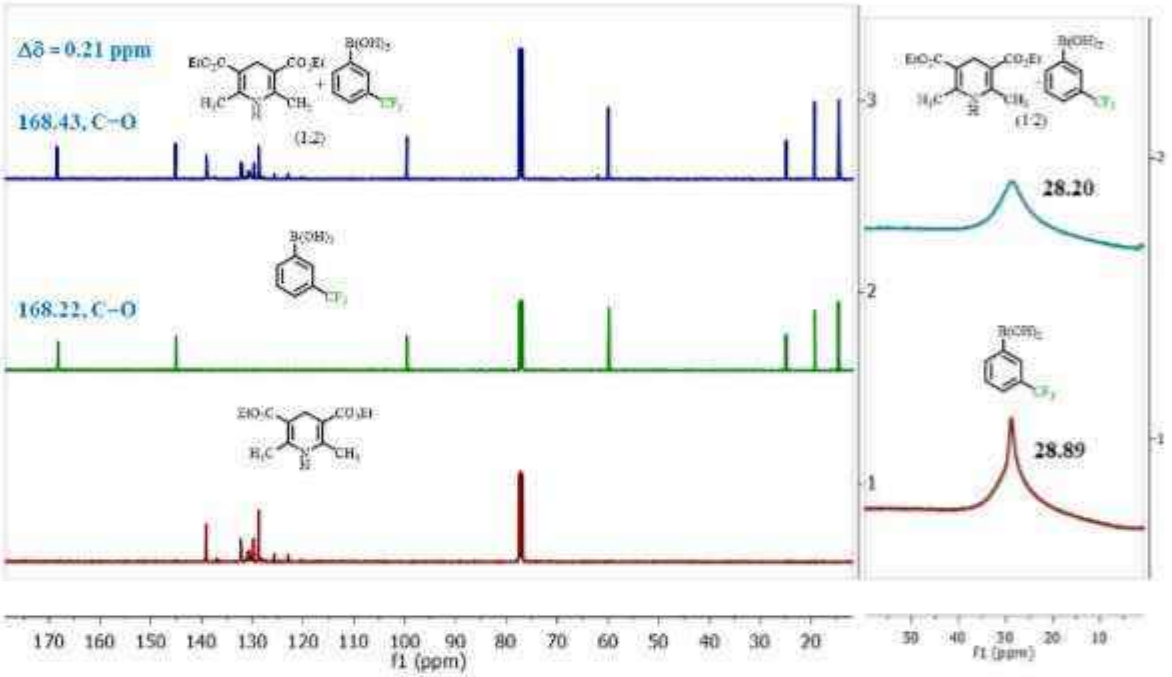
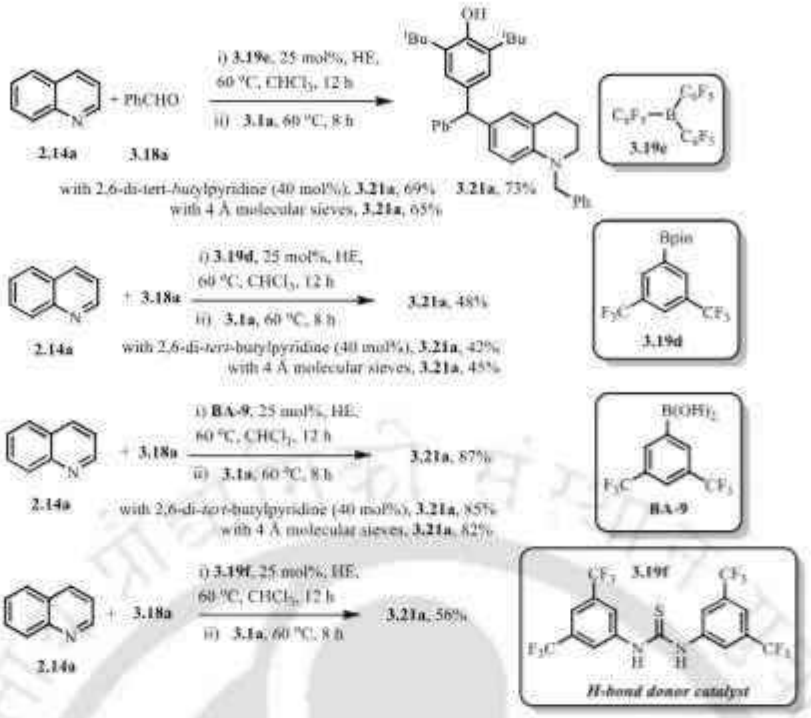


Figure 3.13. ^{13}C{^{1}H}, and ^{11}B NMR spectra of 3-trifluoromethylphenylboronic acid (**BA-21**) (15 mg, 0.079 mmol), Hantzsch ester (5 mg, 0.039 mmol), and the mixture of 3-trifluoromethylphenylboronic acid (**BA-21**) and Hantzsch ester (molar ratio 2:1) (left, right) in $CDCl_3$ at 298 K.

In general, the mode of boronic acid catalysis involves three possible pathways such as (a) Lewis acid catalysis, (b) Brønsted acid catalysis, and (c) H-bond donor catalysis (see Scheme 3.7). The bulky pyridine 2,6-di-*tert*-butylpyridine (DTBP) is commonly used to distinguish between boron Lewis acids and Brønsted acids because it does not form a complex with boron.[18] As the reaction produces H_2O as one of the by-products, the effect of water in this transformation was also studied. When pentafluorotriphenylboron **3.19e** is used as a catalyst, product **3.21a** was obtained in 73% yield. Then the yield of **3.21a** was not decreased in the presence of DTBP or with 4 Å molecular sieves, indicating the possible involvement of Lewis acid catalysis and not likely involvement of *in-situ* generated water-mediated Bronsted acid catalysis.

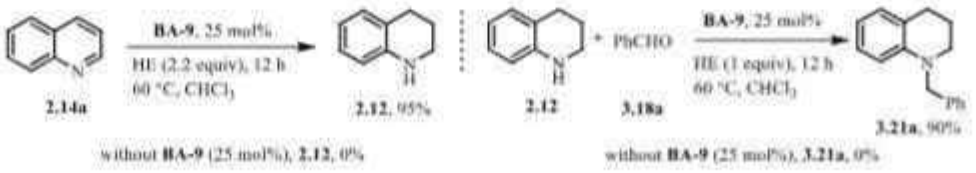
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Scheme 3.7. Mode of boronic acid catalysis in the alkylation of quinoline.

Likewise, the use of pinacol ester, **3.19d**, product **3.21a** was obtained in 48% yield, and boronic acid **BA-9** provided the product **3.21a** in 87% yield. In both the case, hindered Brønsted base 2,6-di-*tert*-butylpyridine has failed to inhibit the reactivity of the pinacol ester and boronic acid in the reaction, further, the yield of product is not suppressed in the presence of 4 Å molecular sieves, indicating possible involvement of Lewis acid catalysis, not protic acid catalysis. The higher yield of **3.21a** in **BA-9** (87%) with respect to **3.19d** (48%) suggests that the possible involvement of H-bonding catalysis. Furthermore, the reaction was performed within an authentic hydrogen-bond donor catalyst, $-CF_3$ functionalized thiourea (**3.19f**),[19] also led to the desired product **3.21a** in 56% yield. Based on these control studies, it can be concluded that the mode of boronic acid catalysis involves both H-bond donor catalysis and Lewis acid catalysis.

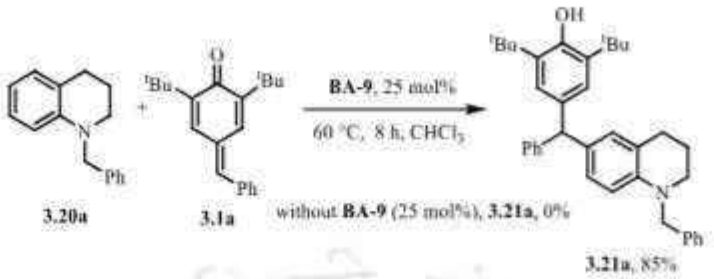
Next, a few control experiments were carried out to gain mechanistic insights into the synthesis of functionalized THQs. The reaction of quinoline **2.14a** in the absence of aldehyde under standard conditions afforded THQ **2.12** in 95% yield. Then the reaction was conducted with the formed **2.12**, and aldehyde **3.18a** under standard conditions, afforded the *N*-alkylated product **3.20a** in 90% yield (Scheme 3.8).



Scheme 3.8. Proof of 1,2,3,4-tetrahydroquinoline as the intermediate.

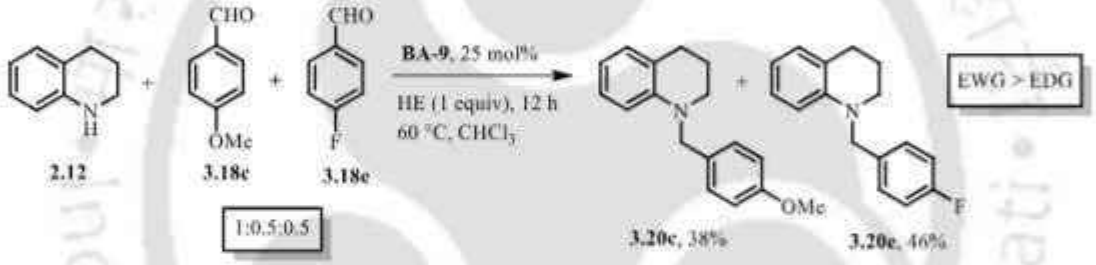
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Subsequently compound **3.20a** was treated with *p*-QMs **3.1a**, obtaining the desired product **3.21a** in 85% yield (Scheme 3.9). From this experimental observation, it can infer that THQ **2.12**, and *N*-alkylated THQ **3.20a** are the intermediates in the process.



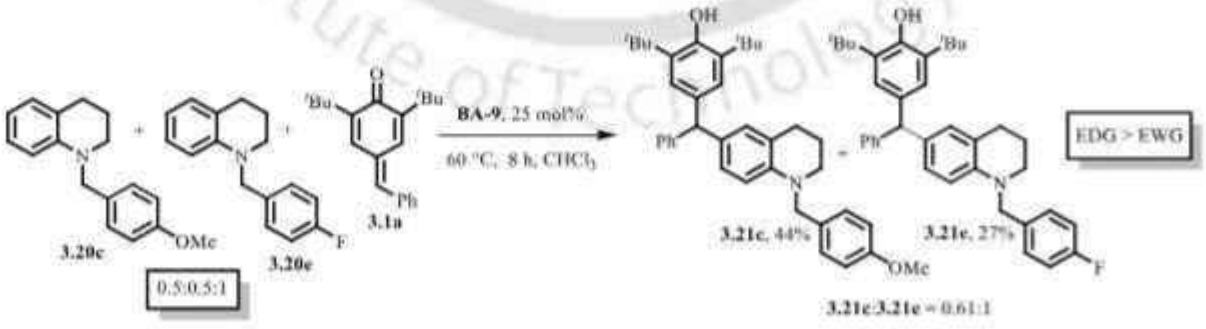
Scheme 3.9. Proof of *N*-benzyl THQ as the intermediate.

To know the electronic effect in the 2nd step, at first the reaction was examined with substituted aldehyde. A competitive reaction with aldehyde suggested that electron-withdrawing group (*p*-F) on the benzaldehyde enhanced the rate of the reaction with respect to an electron-donating group (*p*-OMe) (Scheme 3.10).



Scheme 3.10. Competitive reaction with substituted aldehyde.

To know the electronic effect in the 3rd step, at first the reaction was examined with substituted *N*-benzyl THQ. A competitive reaction suggested that the electron-donating group (-OMe) on the quinoline enhanced the rate of the reaction with respect to an electron-withdrawing group (*p*-F) (Scheme 3.11).

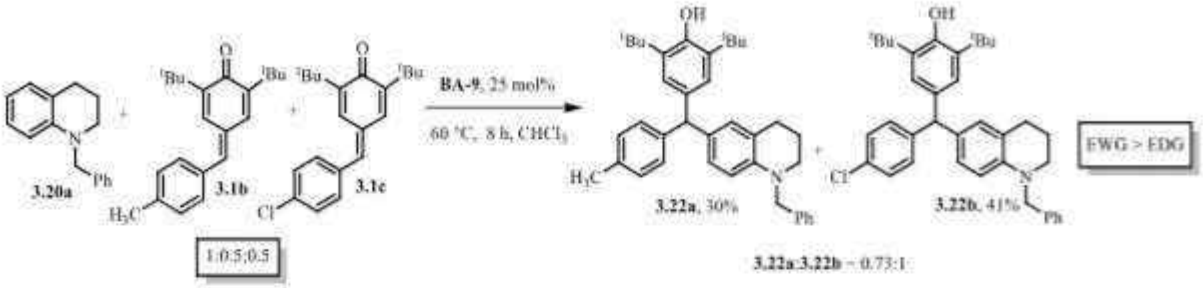


Scheme 3.11. Competitive reaction with substituted *N*-benzyl THQ.

To know the electronic effect in the 3rd step, at first the reaction was examined with substituted *p* -QMs. A competitive reaction suggested that the electron-donating group (-Me) on the

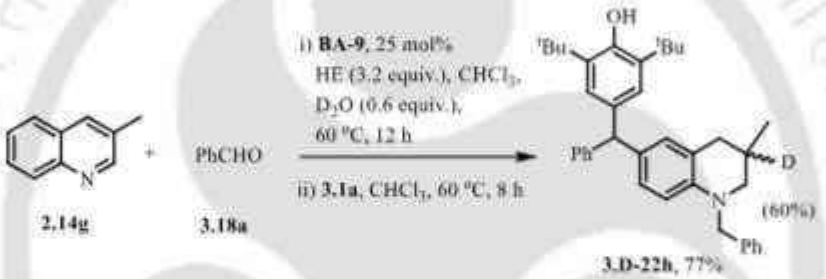
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quinoline enhanced the rate of the reaction with respect to an electron-withdrawing group (*p*-Cl) (Scheme 3.12).



Scheme 3.12. Competitive reaction with substituted *p* -QMs.

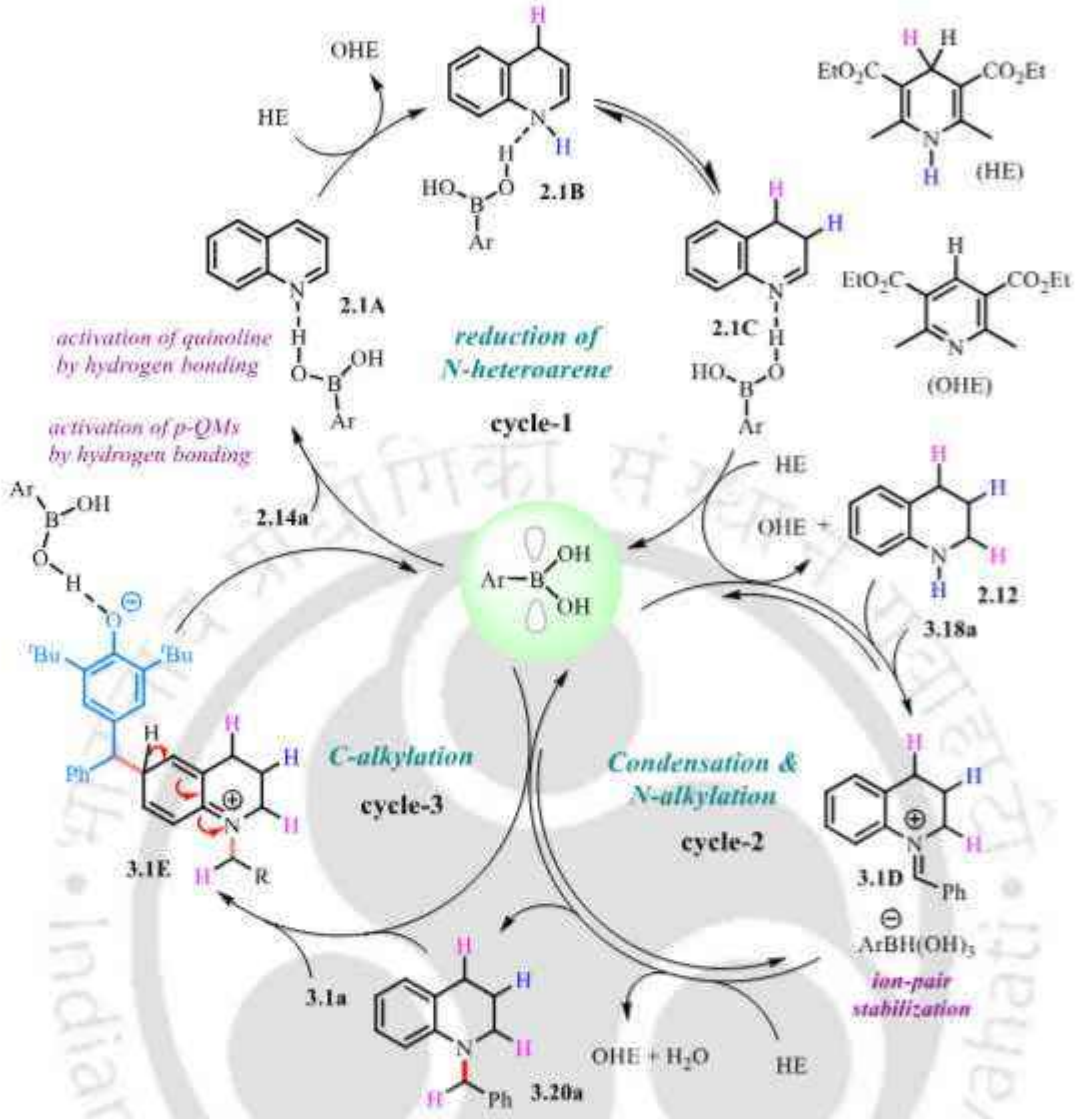
In order to locate the hydridic proton and acidic proton in the *N*-benzyl-THQ product, I have performed the catalytic experiment with 3-methyl quinoline **2.14g** in the presence of D_2O. The outcome demonstrated that the deuterium atom was incorporated at the C-3 position of *N*-functionalized THQ **3.D-22h** (Scheme 3.13).



Scheme 3.13. Deuterium-labelled experiment with 3-methyl quinoline.

Based on the above-mentioned controlled experiments, taking our earlier reports into account,[15,16,20] a possible reaction pathway has been proposed as shown in Scheme 3.14. First, the quinoline ring **2.1A** was activated by the hydroxyl group of boronic acid *via* hydrogen bonding interaction (cycle-1). Afterward, Hantzsch ester hydride atom attacks to C-4 position of quinoline moiety and generates 1,4-dihydroquinoline species **2.1B**. This could be readily isomerized to give 3,4-dihydroquinoline **2.1C**, followed by 1,2-hydride transfer, giving to THQ **2.12**. Next, the *in situ* generated THQ **2.12** can take part in boronic acid-assisted condensation reaction with the aldehyde **3.18a** to form iminium intermediate **3.1D**, which is subsequently reduced by HE to provide *N*-alkylated THQ **3.20a** (cycle-2). Finally, **3.20a** was reacted with *p*-QM **3.1a** to give the desired *C*-alkylated THQ **3.21a** *via* Friedel–Crafts alkylation and regenerates the catalyst (cycle-3). Alternatively, Lewis acid catalysis can also be the active mode of the catalysis which is shown in Scheme 3.18 in the experimental section.

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Scheme 3.14. Plausible mechanistic pathway of this study.

3.4. Summary

In summary, I have developed a one-pot tandem reaction involving reduction of quinolines to tetrahydroquinolines, subsequent reductive alkylation using aldehydes to *N*-alkylated tetrahydroquinolines, followed by *C*-alkylation using *p*-QM to form functionalized tetrahydroquinoline containing diaryl motif at the C6-position without the aid of any transition metals. The present study demonstrates the triple role of boronic acid as a catalyst in the reduction of quinoline, reductive *N*-alkylation and *C*-alkylation sequence. This convenient method tolerates a wide variety of hydrogenation-sensitive functional groups, such as ester, halo, nitro, nitrile, alkyne, allyl, benzyl and further has been successfully utilized in the late-stage functionalization, diversification of pharmaceuticals. The post transformations of the synthesized product have also been carried out to demonstrate the potential of the developed methodology. A combination of hydrogen bonding and Lewis acidity property of the boronic acids has been

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demonstrated, highlighting the multiple modes of activation available to boronic acids. This study demonstrates the general utility of the BA catalysis, specifically in reduction chemistry.

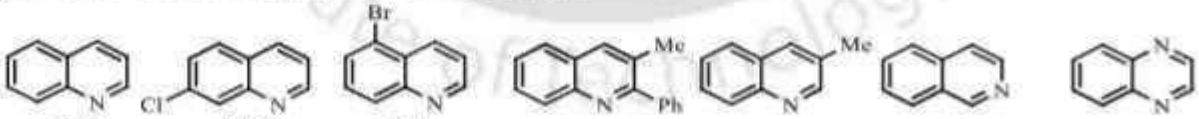
3.5. Experimental section

A. General information

All the reagents and chemicals were purchased from common commercial suppliers like Sigma-Aldrich, Alfa Aesar, Merck, Spectrochem, Avra Synthesis Pvt. Ltd., Finar Chemicals, and BLD Pharma directly used as received without any further purification unless otherwise mentioned. Hantzsch ester was synthesized according to the reported literature.[21] ^{1}H, ^{13}C, ^{11}B and ^{19}F NMR spectra of the compounds were measured in $CDCl_3$, as a solvent by using TMS as an internal standard. Chemical shifts, δ (in ppm), are reported relative to TMS δ (^{1}H) 0.0 ppm, δ (^{13}C) 0.0 ppm, which was used as the internal reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.16 ppm), were also used for calibration. Bruker Avance III 600, 500 and 400 spectrometers were used to record the NMR spectra. Chemical shifts (δ) values were reported in ppm and spin-spin coupling constant (J) were expressed in Hz, and other data were reported as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quartet, pent = pentate, sext = sextet, hept = heptane, br = broad, and brs = broad singlet. IR spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass (UHPLC - Q-TOF - HRMS). Merck silica gel 60 - 120 was used for column chromatography. otherwise stated. All the final reactions were carried out under air and in preheated oil baths unless otherwise mentioned. Completion of reactions was examined by thin layer chromatography carried out on pre-coated Merck silica gel-60 F_{254} aluminium plates with ultraviolet light (UV) or iodine as visualizing agents.

B. Synthesis of starting material

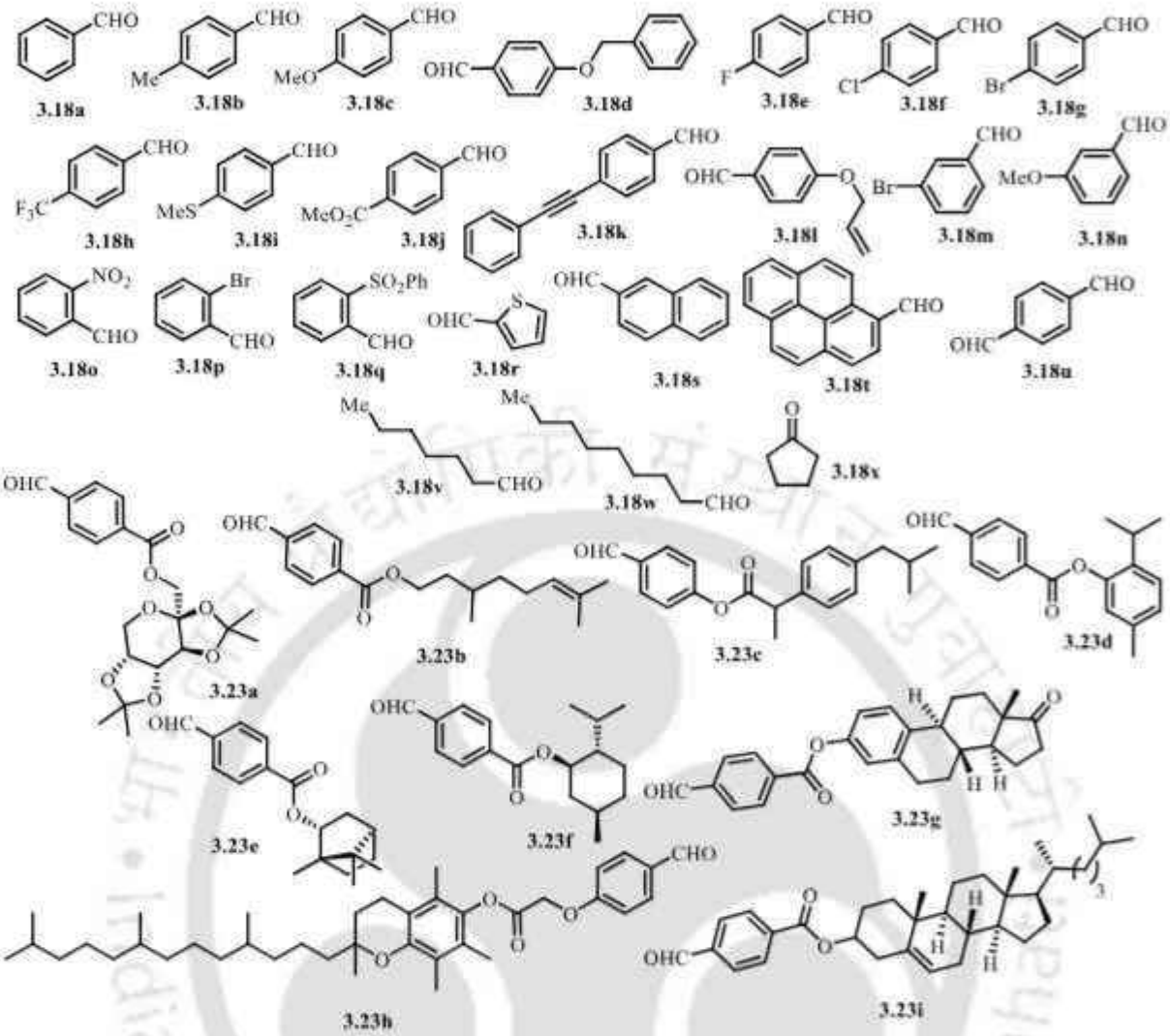
i) *N*-heteroarenes employed in the reaction:



2.14a 3.17b 3.17c 3.17d 2.14g 3.17f 3.17g

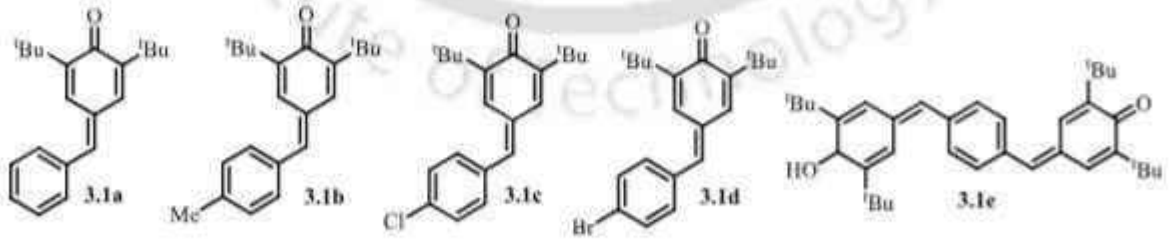
ii) Aldehydes and ketone employed in the reaction:

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Compounds **3.18d**,[22] **3.18k**,[23] **3.18l**,[24] are synthesized by known procedure. The biologically relevant motifs containing aldehyde derivatives **3.23a**,[25] **3.23b**,[26] **3.23c**,[27] **3.23e**,[28] **3.23f**,[29] **3.23g**,[30] **3.23h**,[16c], **3.23i** [29] were synthesized by the known procedure.

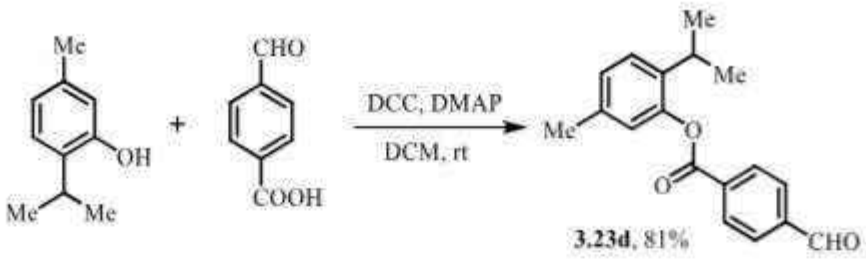
iii) *Para*-quinone methides (*p*-QMs) employed in the reaction:



Compounds **3.1b-3.1c**[31], **3.1d**[32] are synthesized by known procedures.

Synthesis of 2-isopropyl-5-methylphenyl 4-formylbenzoate (3.23d)

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Scheme 3.15. Synthesis of 2-isopropyl-5-methylphenyl 4-formylbenzoate (**3.23d**).

Reaction conditions: To a 100 mL round-bottom flask were added 4-formylbenzoic acid (0.225 g, 1.5 mmol, 0.5 equiv.), 2-isopropyl-5-methylphenol (0.225 g, 1.5 mmol, 0.5 equiv.), *N, N'*-dicyclohexylcarbodiimide (0.340 g, 1.65 mmol, 0.55 equiv.) and DMAP (0.018 g, 0.15 mmol, 0.05 equiv.), DCM (15 mL) was then added at room temperature. The mixture was stirred at room temperature until the acid was consumed as monitored by TLC. Then, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 10:1, v/v) to yield the desired compound **3.23d** as yellow oil (0.343 g, 81%). Compound **3.23d** was prepared for the first time following a known procedure.[29]

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.28 (d, J = 8.2 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 7.9 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.86 (s, 1H), 2.98 – 2.91 (m, 1H), 2.25 (s, 3H), 1.13 (d, J = 7.0 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 191.6, 164.5, 148.0, 139.7, 137.1, 136.9, 134.6, 130.8, 129.8, 127.6, 126.7, 122.7, 27.4, 23.1, 20.9. HRMS (ESI) *m/z*: $[M+Na]^+$ calculated for $C_{18}H_{18}NaO_3$: 305.1149; found: 305.1163.

C. General procedure for synthesis of *C*-functionalized THQ derivatives

i) General procedure for synthesis of *C*-functionalized THQ derivatives with different carbonyls (GP-1)

A mixture of quinoline **2.14a** (1.0 mmol, 1.0 equiv.), substituted aldehyde or cyclic ketone **3.18** (1.0 mmol, 1.0 equiv.), HE (3.2 mmol, 3.2 equiv.) and **BA-9** (25 mol%) in $CHCl_3$ (2 ml) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 12 h. Then *p*-QMs **3.1a** (1.0 mmol) was added in the same reaction tube at 60 °C with continuous stirring for 8 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

ii) General procedure for synthesis of *C*-functionalized THQ derivatives with different quinolines and *p*-QMs (GP-2)

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A mixture of substituted quinolines **3.16** (1.0 mmol, 1.0 equiv.), benzaldehyde **3.18a** (1.0 mmol, 1.0 equiv.), HE (3.2 mmol, 3.2 equiv.) and **BA-9** (25 mol%) in $CHCl_3$ (2 ml) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 12 h. Then substituted *p*-QMs **3.1** (1.0 mmol, 1.0 equiv.) was added in the same reaction tube at 60 °C with continuous stirring for 8 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

D. Gram scale reaction (Scheme 3.5)

Reaction conditions: A mixture of quinoline **2.14a** (1.0 g, 7.7 mmol, 1.0 equiv), benzaldehyde **3.18a** (0.817 g, 7.7 mmol, 1.0 equiv.), HE (6.257 g, 24.6 mmol, 3.2 equiv.) and **BA-9** (25 mol%) in $CHCl_3$ (10.0 ml) were added into a reaction tube (25 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 12 h. Then *p*-QMs **3.1a** (2.264 g, 7.7 mmol, 1.0 equiv.) was added in the same reaction tube at 60 °C with continuous stirring for 8 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography to get pure compound as dark-red liquid of **3.21a** (2.990 g, 75%).

E. Post synthetic modification (Scheme 3.6)

Synthesis of 1-benzyl-6-((3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene) (phenyl)methyl)-3,4-dihydroquinolin-2(1*H*)-one (3.26)

Reaction conditions: $NaIO_4$ (0.640 g, 3.0 mmol, 6 equiv.) was taken in a screw-capped reaction tube and dissolved it in water (1.0 mL). The **3.21a** (0.147 g, 0.5 mmol, 1 equiv.), **Ru-2** (**3.25**, 4 mol%), and acetonitrile (2.0 mL) were added to the reaction tube and stirred the reaction mixture at 70 °C for 1 hour. After the completion of the reaction as confirmed by TLC, the reaction mixture was worked up with CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was again extracted with CH_2Cl_2 (two times, 5 mL). The combined organic layer was washed with brine solution (8 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under a vacuum. The crude product was purified through silica-gel column chromatography to yield the desired compound **3.26** as orange solid (88%, 0.233 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.38 (m, 3H), 7.34 – 7.30 (m, 2H), 7.25 – 7.20 (m, 5H), 7.16 (d, J = 2.6 Hz, 1H), 7.09 (d, J = 2.6 Hz, 1H), 7.04 (s, 1H), 7.01 – 6.98 (m, 1H), 6.90 (d, J = 8.4 Hz, 1H), 5.22 (s, 2H), 2.99 – 2.96 (m, 2H), 2.85 – 2.81 (m, 2H), 1.24 (s, 9H), 1.21 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 186.2, 170.5, 155.2, 147.54, 147.46, 140.9, 140.8, 136.8, 135.4, 132.13, 132.08, 131.9, 131.8, 131.7, 129.8, 129.4, 128.9, 128.2, 127.4, 126.6,

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126.0, 115.2, 46.4, 35.45, 35.40, 31.9, 29.7, 29.6, 25.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{40}NO_2$: 530.3054; found 530.3058. Spectral data is in accordance to the reported literature. [17]

Synthesis of 4-((1-benzyl-1,2,3,4-tetrahydroquinolin-6-yl) (phenyl)methylene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one (3.27) [17]

Reaction conditions: $NaIO_4$ (0.320 g, 1.5 mmol, 3.0 equiv.) was taken in a screw-capped reaction tube and dissolved it in water (1.0 mL). The **3.21a** (0.147 g, 0.5 mmol, 1.0 equiv.), **Ru-2** (**3.25**, 2 mol%), and acetonitrile (2.0 mL) were added to the reaction tube and stirred the reaction mixture at 70 °C for 1 hour. After the completion of the reaction as confirmed by TLC, the reaction mixture was worked up with CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was again extracted with CH_2Cl_2 (two times, 5.0 mL). The combined organic layer was washed with brine solution (8.0 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under a vacuum. The crude product was purified through silica-gel column chromatography to yield the desired compound **3.27** as orange solid (82%, 0.211 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.37 (m, 4H), 7.31 (d, J = 8.2 Hz, 2H), 7.27 – 7.26 (m, 3H), 7.19 (d, J = 8.1 Hz, 2H), 7.01 (s, 1H), 6.91 (s, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.46 (d, J = 8.6 Hz, 1H), 4.52 (s, 2H), 3.44 – 3.42 (m, 2H), 2.78 (t, J = 6.1 Hz, 2H), 2.06 – 2.01 (m, 2H), 1.30 (s, 9H), 1.21 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 186.0, 158.1, 146.1, 136.6, 134.2, 133.1, 132.9, 132.8, 132.5, 129.2, 129.1, 128.4, 128.1, 128.0, 127.9, 121.6, 110.1, 54.6, 50.2, 35.4, 35.3, 29.8, 29.6, 28.1, 22.2. Spectral data is in accordance to the reported literature. [17]

F. Mechanistic investigation

i) Proof of THQ, *N*-benzyl THQ as the intermediate (Scheme 3.8)

Reaction conditions: Quinoline **2.14a** (0.065 g, 0.5 mmol, 1.0 equiv.), HE (0.279 g, 1.1 mmol, 2.2 equiv), and **BA-9** (20 mol%) were taken in a reaction tube. Then sealed with screw-cap, the resulting solution was heated at 60 °C for 12 h. As expected tetrahydroquinoline **2.12** obtained in 95% yield (0.063 g). For the subsequent step the reaction was conducted with the formed **2.12**, and benzaldehyde **3.18a** (0.050 g, 0.47 mmol, 1.0 equiv), HE (0.132 g, 0.52 mmol, 1.1 equiv), and **BA-9** (25 mol%) were taken in a reaction tube. Then sealed with screw-cap, the resulting solution was heated at 60 °C for 12 h), the desired product **3.21a** was obtained in 90% yield (0.094 g).

For the subsequent step the reaction was conducted with the formed **3.20a**, *p* -QM **3.1a** (0.132 g, 0.45 mmol, 1.0 equiv), and **BA-9** (25 mol%) at 60 °C for 8 h under standard conditions the desired product **3.21a** was obtained in 85% yield (0.198 g).

ii) Electronic effect for the 2nd step (Scheme 3.9, 3.10)

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Reaction conditions: 1,2,3,4 tetrahydroquinoline **2.12** (0.067 g, 0.5 mmol, 1.0 equiv), substituted aldehyde **3.18c** (0.034 g, 0.25 mmol, 0.5 equiv.), **3.18e** (0.031 g, 0.25 mmol, 0.5 equiv), HE (0.140 g, 0.55 mmol, 1.1 equiv), and **BA-9** (25 mol%) were taken in a reaction tube. Then sealed with screw-cap, the resulting solution was heated at 60 °C for 12 h under standard conditions, the product **3.20c** and **3.20e** was obtained in 38% yield (0.054 g) and 46% yield (0.056 g) respectively.

iii) Electronic effect for the 3rd step (Scheme 3.11, 3.12)

Reaction conditions: substituted *N*-benzyl THQs **3.20c** (0.063 g, 0.25 mmol, 0.5 equiv), **3.20e** (0.060 g, 0.25 mmol, 0.5 equiv), *p* -QM **3.1a** (0.147 g, 0.5 mmol, 1.0 equiv), and **BA-9** (25 mol%) were taken in a reaction tube. Then sealed with screw-cap, the resulting solution was heated at 60 °C for 8 h under standard conditions, the product **3.21c** and **3.21e** was obtained in 44% yield (0.120 g) and 27% yield (0.072 g) respectively.

Reaction conditions: *N*-benzyl THQ **3.20a** (0.112 g, 0.5 mmol, 1.0 equiv), substituted *p* -QMs **3.1b** (0.077 g, 0.25 mmol, 1.0 equiv), **3.1c** (0.082 g, 0.25 mmol, 1.0 equiv), and **BA-9** (25 mol%) were taken in a reaction tube. Then sealed with screw-cap, the resulting solution was heated at 60 °C for 8 h under standard conditions, the product **3.22a** and **3.22b** was obtained in 30% yield (0.080 g) and 41% yield (0.113 g) respectively.

iv) Deuterium-labelling experiment (Scheme 3.13)

Reaction conditions: In a reaction tube (15 mL), 3-methyl quinoline **2.14g** (0.072 g, 0.5 mmol, 1.0 equiv.), **3.18a** (0.053 g, 0.5 mmol, 1.0 equiv.), HE (0.406 g, 1.6 mmol, 3.2 equiv.), **BA-9** (25 mol%), and D_2O (0.3 mmol, 0.6 equiv.) were charged, then sealed with screw-cap, the resulting solution was heated at 60 °C for 12 h under standard conditions. Then *p*-QM **3.1a** (0.147 g, 0.5 mmol, 1.0 equiv.) was added in the same reaction tube at 60 °C with continuous stirring for 8 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography to get pure compound as dark-red liquid of **3.D-22h** (0.205 g, 77%).

^{1}H NMR spectrum of deuterated 4-((1-benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-6-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3.22h + 3.D-22h):

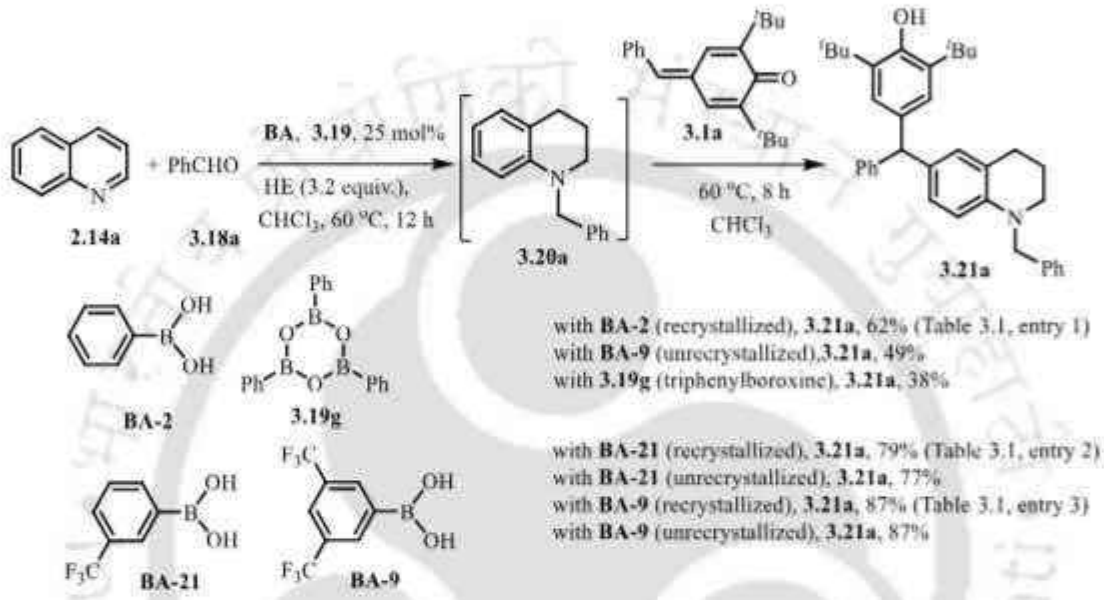
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 14H, **3.22h + 3.D-22h**), 7.16 – 7.11 (m, 6H, **3.22h + 3.D-22h**), 6.91 (s, 4H, **3.22h + 3.D-22h**), 6.75 – 6.73 (m, 2H, **3.22h + 3.D-22h**), 6.68 – 6.63 (m, 2H, **3.22h + 3.D-22h**), 6.42 (d, J = 8.4 Hz, 2H, **3.22h + 3.D-22h**), 5.26 (s, 2H, **3.22h + 3.D-22h**), 5.03 (s, 2H, **3.22h + 3.D-22h**), 4.44 (s, 4H, **3.22h + 3.D-22h**), 3.25 – 3.22 (m, 2H, **3.22h + 3.D-22h**), 3.01 – 2.96 (m, 2H, **3.22h + 3.D-22h**), 2.73 – 2.69 (m, 2H, **3.22h + 3.D-22h**), 2.47 – 2.40 (m, 2H, **3.22h + 3.D-22h**), 2.19 – 2.10 (m, 1H, **3.22h**), 1.36 (s, 36H, **3.22h + 3.D-22h**), 1.01 (s, 6H, **3.22h + 3.D-22h**). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.0, 146.0, 143.5, 139.4, 135.3, 135.1, 132.25, 130.2, 130.2, 129.48, 129.47, 128.6, 128.1, 128.0, 127.9,

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126.8, 126.1, 125.8, 121.7, 110.6, 57.0, 56.17, 56.17, 55.5, 55.4, 36.7, 34.5, 31.4, 30.5, 27.60, 27.57, 19.21, 19.18.

V) The effect of unrecrystallized boronic acid in the catalysis

The commercial boronic acids contain variable amounts of water and also triarylboroxine, which can affect the reaction. Hence, all the boronic acids used in the current manuscript were recrystallized from water prior to their use.



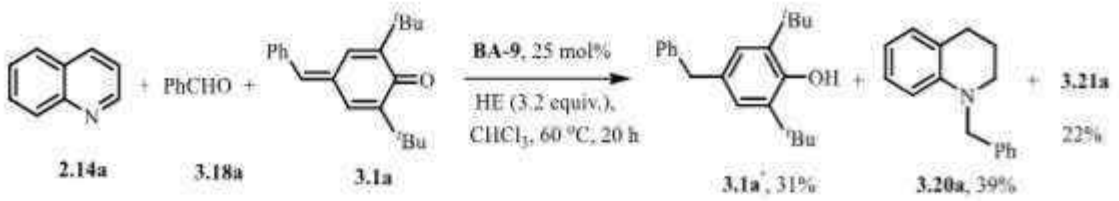
Scheme 3.16. Effect of unrecrystallized boronic acid in the catalysis.

When the reaction was examined with unrecrystallized phenyl boronic acid, **BA-2**, the yield of product **3.21a** was obtained in 49% yield and with triphenylboroxine, **3.19g**, product **3.21a** was obtained in 38% yield. It suggests that the reaction likely occur *via* the combinatorial effect of triphenylboroxine and residual boronic acid in the case of unrecrystallized phenylboronic acid **BA-2**. But, for electron-withdrawing $-CF_3$ substituent boronic acid **BA-21** or **BA-9** the reaction is most likely to proceed through boronic acid and not by the catalysis of triarylboroxine, since the yield of desired product **3.21a** is not altered under the reaction conditions.

vi) Synthesis of *C*-alkylated *N*-benzyl THQ in a one-pot fashion (Table 3.1)

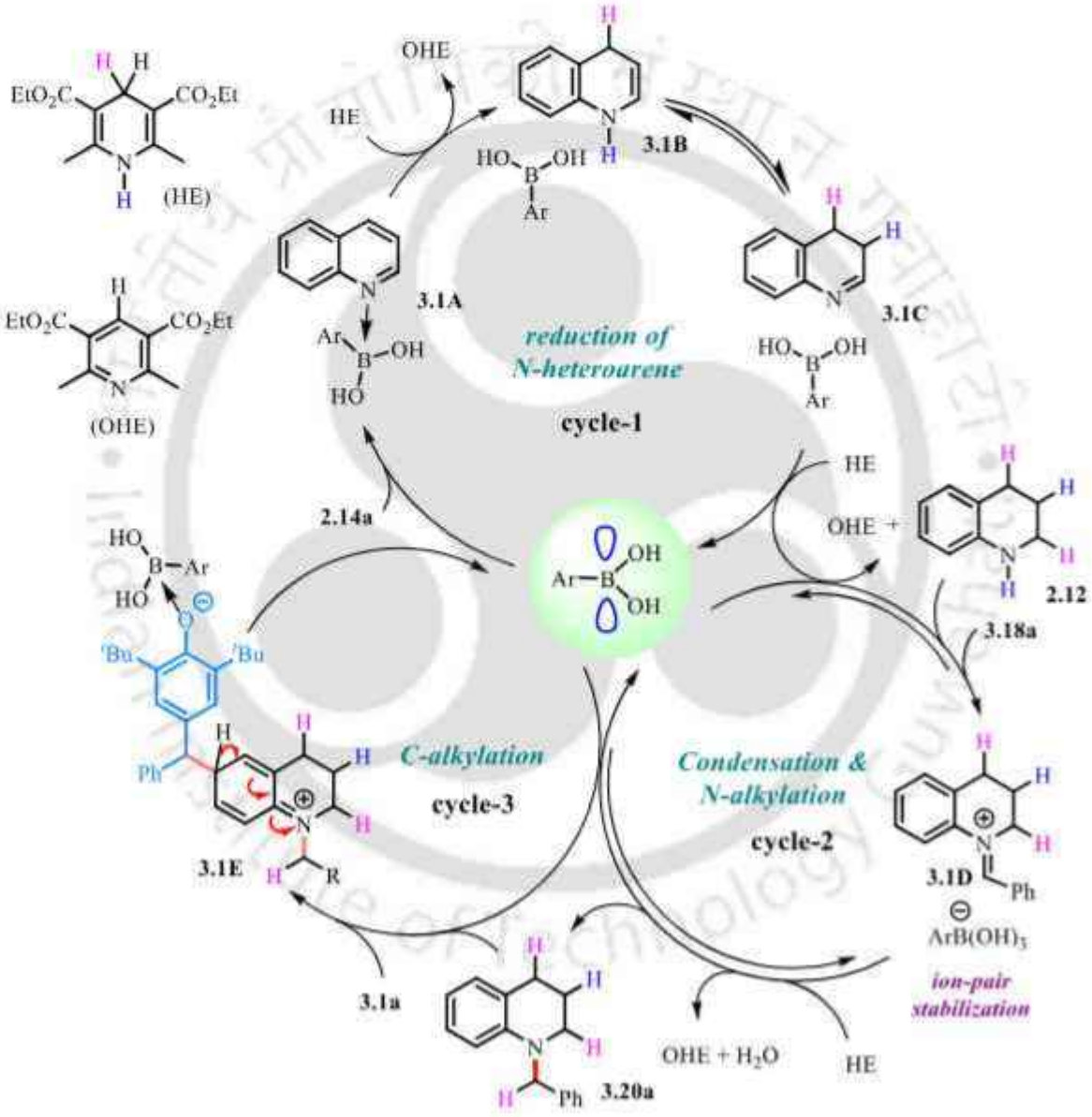
I have attempted to synthesize *C*-alkylated product **3.21a** in a one-pot fashion, by adding *p*-QMs **3.1a** from the beginning, the desired *C*-alkylated product **3.21a** was obtained in only 22% yield, along with 39% *N*-benzyl THQ **3.20a** and 31% hydrogenated product **3.1a'**. This indicates that it is necessity to add *p*-QMs **3.1a** after the formation of *N*-alkylated THQ **3.20a**, otherwise, *p*-QMs readily react with Hantzsch ester to provide **3.1a'**.

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Scheme 3.17. Synthesis of *C*-alkylated *N*-benzyl THQ in a one-pot fashion.

vii) Mechanistic pathway by Lewis acid catalysis



Scheme 3.18. Mechanistic pathway by Lewis acid catalysis

G. Crystallographic data

Crystallographic data of 3.21n

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Single crystals of compound **3.21n** suitable for X-ray diffraction were obtained by slow evaporation of the saturated solution of the compound in petroleum ether at room temperature. X-ray crystallographic data were collected using Bruker D8 QUEST diffractometer. Data refinement and cell reduction were carried out by APEX4. Structures were solved by direct methods using Olex2 v1.5 and refined by a full-matrix least-squares method using Olex2 v1.5. All of the non-H atoms were refined anisotropically. The ORTEP diagram was obtained with ORTEP3 software with 30% thermal ellipsoid (see below, Figure 3.14). The crystallographic parameters and refinement data were listed in Table 3.5.

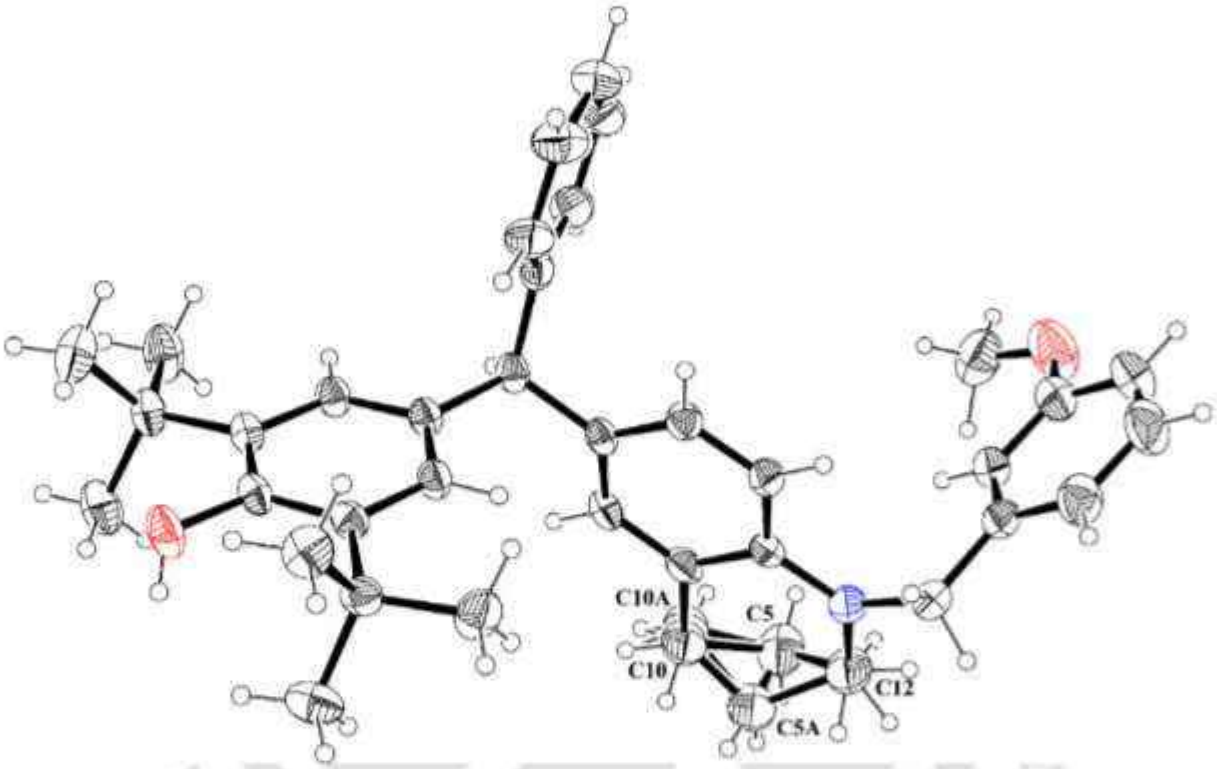


Figure 3.14. Molecular structure of compound **3.21n** (thermal ellipsoid 30% probability level).

Please note that the saturated carbon atoms of the tetrahydroquinoline moiety is unequally disordered over two sites. The disorder atoms C5, C10 and C12 are splitted over two positions with occupancy 0.68, and 0.32.

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Table 3.5. Crystal data and structure refinement for **3.21n**

Identification code	SK_381_0m_a
CCDC	2432981
Empirical formula	$C_{38}H_{45}NO_2$
Formula weight	547.75
Temperature/K	296.00
Crystal system	triclinic
Space group	P-1
a/Å	11.629(3)
b/Å	12.102(3)
c/Å	13.779(3)
α/°	68.406(6)
β/°	85.378(7)
γ/°	66.181(6)
Volume/Å^3	1644.1(7)
Z	2
ρ_{calc}g/cm^3	1.106
μ/mm^{-1}	0.067
F (000)	592.0
Crystal size/mm^3	0.38 × 0.34 × 0.31
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.258 to 52.748
Index ranges	-14 ≤ h ≤ 14, -15 ≤ k ≤ 15, -17 ≤ l ≤ 17
Reflections collected	48983
Independent reflections	6662 [R_{int} = 0.0367, R_{sigma} = 0.0214]
Data/restraints/parameters	6662/23/387
Goodness-of-fit on F^2	1.051
Final R indexes [I>=2σ (I)]	R_1 = 0.0543, wR_2 = 0.1392
Final R indexes [all data]	R_1 = 0.0706, wR_2 = 0.1583
Largest diff. peak/hole / e Å^{-3}	0.27/-0.33

Table 3.6. Atomic Occupancy for **3.21n**

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
C10	0.681(8)	H10A	0.681(8)	H10B	0.681(8)
C5	0.681(8)	H5A	0.681(8)	H5B	0.681(8)
H12A	0.681(8)	H12B	0.681(8)	H12C	0.319(8)
H12D	0.319(8)	C5A	0.319(8)	H5AA	0.319(8)

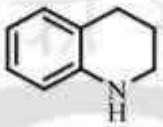
TH-3765_196122031

Table 3.6. Atomic Occupancy for **3.21n**

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
H5AB	0.319(8)	C10A	0.319(8)	H10C	0.319(8)
H10D	0.319(8)				

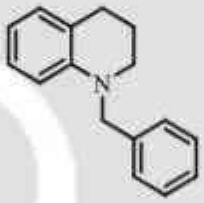
3.6. Analytical data of the products

1,2,3,4-tetrahydroquinoline (2.12)



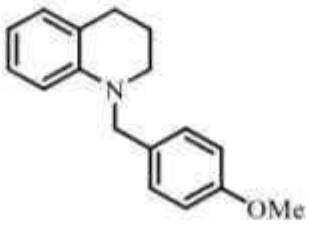
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 – 6.95 (m, 2H), 6.61 (t, J = 8.1 Hz, 1H), 6.48 (d, J = 7.9 Hz, 1H), 3.32 – 3.29 (m, 2H), 2.77 (t, J = 6.4 Hz, 2H), 1.98 – 1.92 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.9, 129.6, 126.8, 121.6, 117.1, 114.3, 42.1, 27.1, 22.3. Spectral data is in accordance with the literature.[33]

1-benzyl-1, 2, 3, 4-tetrahydroquinoline (3.20a)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.20 (m, 5H), 6.97 – 6.94 (m, 2H), 6.56 (t, J = 7.3 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 4.46 (s, 2H), 3.37 – 3.34 (m, 2H), 2.80 (t, J = 6.2 Hz, 2H), 2.03 (pent, 6.2 Hz, 2H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.7, 139.1, 129.1, 128.7, 127.3, 126.8, 126.7, 122.3, 115.9, 111.1, 55.3, 50.0, 28.3, 22.5. Spectral data is in accordance to the reported literature.[16c]

1-(4-methoxybenzyl)-1, 2, 3, 4-tetrahydroquinoline (3.20b)

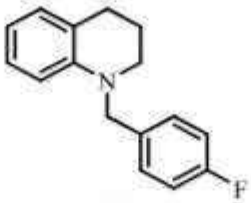


^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 6.8 Hz, 2H), 7.03 – 7.00 (m, 2H), 6.86 (d, J = 7.6 Hz, 2H), 6.62 – 6.57 (m, 2H), 4.45 (s, 2H), 3.82 (s, 3H), 3.37 (t, J = 5.7 Hz, 2H), 2.85 (t, J = 6.3 Hz, 2H), 2.06 – 2.01 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.7, 145.8, 131.0,

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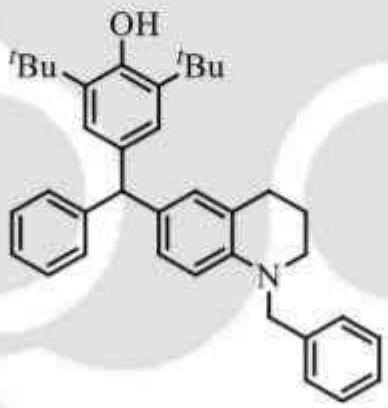
129.1, 127.9, 127.3, 122.4, 115.9, 114.1, 111.1, 55.4, 54.7, 49.8, 28.4, 22.5. Spectral data is in accordance to the reported literature.[16c]

1-(4-fluorobenzyl)-1, 2, 3, 4-tetrahydroquinoline (3.20d)



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 2H), 7.01 – 6.96 (m, 4H), 6.59 (t, J = 7.3 Hz, 1H), 6.48 (d, J = 8.6 Hz, 1H), 4.44 (s, 2H), 3.34 (t, J = 5.6 Hz 2H), 2.81 (t, J = 6.3 Hz, 2H), 2.01 (pent, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 162.9 – 161.0 (C-F, $^1J_{C\text{-}F}$ = 244.3 Hz), 145.6, 134.6 (C-F, $^4J_{C\text{-}F}$ = 3 Hz), 129.2, 128.2 (C-F, $^3J_{C\text{-}F}$ = 7.9 Hz), 127.3, 122.5, 116.2, 115.6 - 115.4 (C-F, $^2J_{C\text{-}F}$ = 21.4 Hz, 111.1, 54.8, 50.0, 28.3, 22.5. ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$): δ -116.45. Spectral data is in accordance to the reported literature.[16c]

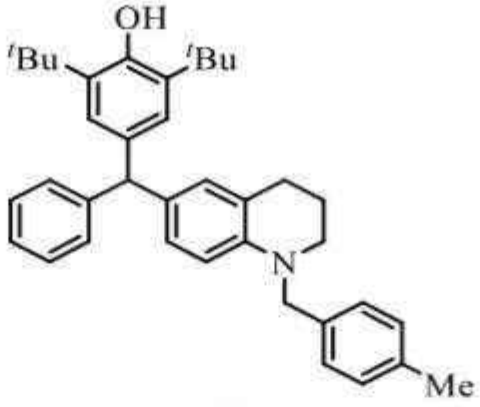
4-((1-benzyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl)-2, 6-di-*tert*-butylphenol (3.21a)



By following the **GP-1**, the title compound **3.21a** was isolated as dark-red liquid (0.450 g, 87%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 2H), 7.25 – 7.18 (m, 5H), 7.13 (t, J = 7.6 Hz, 3H), 6.92 (s, 2H), 6.75 (s, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.42 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 5.01 (brs, 1H), 4.42 (s, 2H), 3.30 (t, J = 5.6 Hz, 2H), 2.72 (t, J = 6.2 Hz, 2H), 1.96 (pent, J = 6.0 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.0, 146.0, 144.0, 139.3, 135.4, 135.0, 132.3, 130.1, 129.5, 128.6, 128.1, 128.0, 126.85, 126.83, 126.1, 125.8, 122.09, 110.9, 56.2, 55.5, 50.0, 34.5, 30.5, 28.4, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{44}NO$: 518.3418; found: 518.3419.

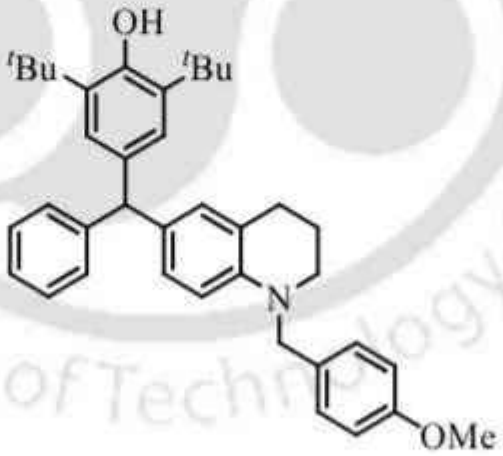
2, 6-di-*tert*-butyl-4-((1-(4-methylbenzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl)methyl) phenol (3.21b)

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By following the **GP-1**, the title compound **3.21b** was isolated as dark-red liquid (0.479 g, 90%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, J = 7.4 Hz, 2H), 7.14 (d, J = 8.5 Hz, 4H), 7.10 (t, J = 6.1 Hz, 3H), 6.92 (s, 2H), 6.74 (s, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 8.5 Hz, 1H), 5.25 (s, 1H), 5.01 (brs, 1H), 4.39 (s, 2H), 3.32 – 3.27 (m, 2H), 2.72 (t, J = 6.2 Hz, 2H), 2.31 (s, 3H), 1.96 (pent, J = 6.1 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.0, 146.0, 144.1, 136.4, 135.7, 135.4, 132.2, 130.1, 129.5, 129.3, 128.1, 128.0, 126.9, 126.2, 125.8, 122.1, 110.9, 56.2, 55.2, 49.9, 34.5, 30.5, 28.4, 22.7, 21.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{38}H_{46}NO$: 532.3574; found: 532.3577

2, 6-di-*tert*-butyl-4-((1-(4-methoxybenzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) phenol (3.21c)

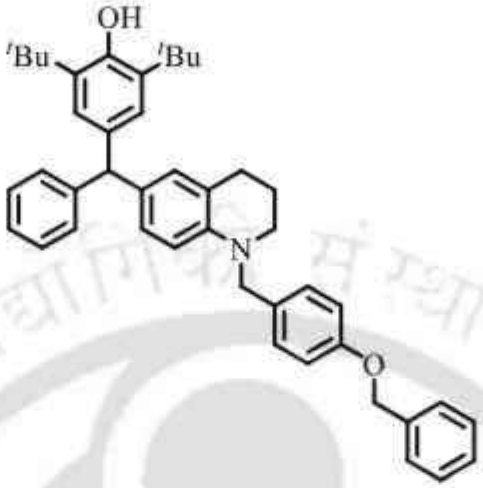


By following the **GP-1**, the title compound **3.21c** was isolated as dark-red liquid (0.509 g, 93%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (t, J = 7.6 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 7.5 Hz, 3H), 6.93 (s, 2H), 6.81 (d, J = 8.6 Hz, 2H), 6.75 (s, 1H), 6.67 (d, J = 9.4 Hz, 1H), 6.45 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 5.02 (s, 1H), 4.35 (s, 2H), 3.73 (s, 3H), 3.26 (t, J = 5.7 Hz, 2H), 2.70 (t, J = 6.5 Hz, 2H), 1.93 (pent, J = 6.1 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.6, 152.0, 145.9, 144.0, 135.3, 135.0, 132.2, 131.2, 130.1, 129.4, 128.1,

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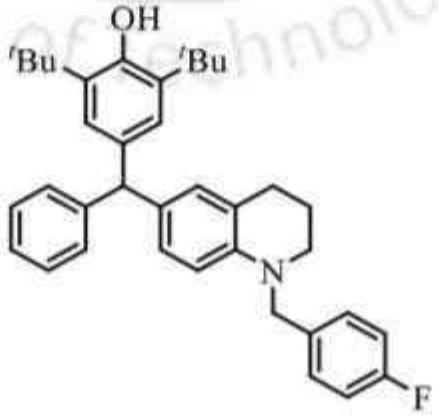
128.0, 127.9, 126.1, 125.8, 122.1, 114.0, 110.9, 56.2, 55.3, 54.8, 49.8, 34.4, 30.5, 28.3, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{38}H_{46}NO_2$: 548.3524; found: 548.3528.

4-((1-(4-(benzyloxy) benzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl)-2, 6-di-tert-butylphenol (3.21d)



By following the **GP-1**, the title compound **3.21d** was isolated as dark-red liquid (0.568 g, 91%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, J = 7.3 Hz, 2H), 7.35 (t, J = 7.2 Hz, 2H), 7.30 – 7.28 (m, 1H), 7.24 - 7.21 (m, 2H), 7.15 – 7.12 (m, 5H), 6.93 (s, 2H), 6.90 (d, J = 7.5 Hz, 2H), 6.75 (s, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.44 (d, J = 8.3 Hz, 1H), 5.26 (s, 1H), 5.01 (brs, 3H), 4.36 (s, 2H), 3.28 – 3.26 (m, 2H), 2.72 – 2.69 (m, 2H), 1.94 (pent, J = 5.8 Hz, 2H), 1.35 (s, 18H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 157.8, 152.0, 146.0, 144.0, 137.2, 135.3, 135.0, 132.2, 131.5, 130.1, 129.5, 128.7, 128.1, 128.0, 127.9, 127.6, 126.1, 125.8, 122.1, 115.0, 110.9, 70.2, 56.2, 54.8, 49.8, 34.4, 30.5, 28.4, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{44}H_{50}NO_2$: 624.3837; found: 624.3836.

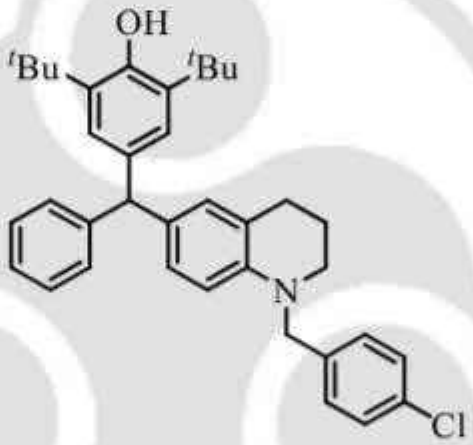
2, 6-di-*tert*-butyl-4-((1-(4-fluorobenzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) phenol (3.21e)



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By following the **GP-1**, the title compound **3.21e** was isolated as dark-red liquid (0.429 g, 80%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (q, J = 7.3 Hz, 3H), 7.19 (d, J = 5.6 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.12 (d, J = 7.4 Hz, 2H), 6.96 (t, J = 8.6 Hz, 2H), 6.92 (s, 2H), 6.75 (s, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.39 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 5.02 (s, 1H), 4.38 (s, 2H), 3.31 – 3.26 (m, 2H), 2.72 (t, J = 6.3 Hz, 2H), 1.96 (pent, J = 6.1 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 162.9 – 161.0 (C-F, $^1J_{C\text{-}F}$ = 244.8 Hz), 152.0, 145.9, 143.8, 135.4, 135.0, 134.9 (C-F, $^4J_{C\text{-}F}$ = 2.99 Hz), 132.5, 130.2, 129.5, 128.3 (C-F, $^3J_{C\text{-}F}$ = 7.9 Hz), 128.1, 128.0, 126.1, 125.8, 122.2, 115.5 – 115.4 (C-F, $^2J_{C\text{-}F}$ = 21.5 Hz), 110.9, 56.2, 54.9, 50.0, 34.5, 30.5, 28.3, 22.7. ^{19}F{^{1}H) NMR (471 MHz, $CDCl_3$): δ -116.45. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}FNO$: 536.3324; found: 536.3225.

2, 6-di-*tert*-butyl-4-((1-(4-chlorobenzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) phenol (3.21f)

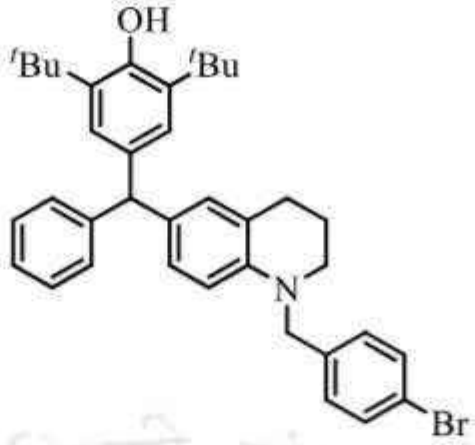


By following the **GP-1**, the title compound **3.21f** was isolated as dark-red liquid (0.464 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.24 (m, 2H), 7.24 – 7.22 (m, 2H), 7.19 – 7.17 (m, 2H), 7.16 - 7.14 (m, 1H), 7.12 (d, J = 7.6 Hz, 2H), 6.91 (s, 2H), 6.76 (s, 1H), 6.66 (d, J = 8.9 Hz, 1H), 6.36 (d, J = 8.4 Hz, 1H), 5.25 (s, 1H), 5.02 (brs, 1H), 4.39 (s, 2H), 3.29 (t, J = 5.5 Hz, 2H), 2.73 (t, J = 6.2 Hz, 2H), 1.99 – 1.95 (m, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.0, 145.9, 143.7, 137.9, 135.4, 135.0, 132.7, 132.5, 130.2, 129.5, 128.8, 128.3, 128.1, 128.0, 126.1, 125.8, 122.3, 111.0, 56.2, 55.1, 50.1, 34.5, 30.5, 28.3, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}ClNO$: 552.3028; found: 552.3011.

4-((1-(4-bromobenzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl)

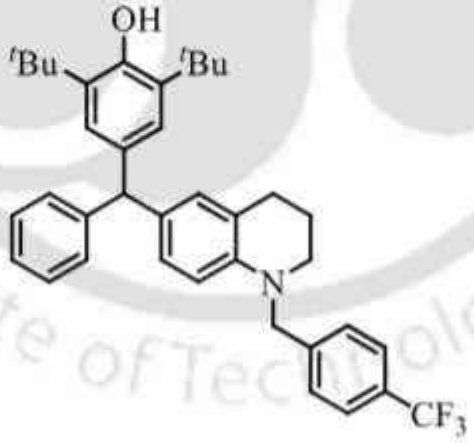
-2, 6-di-*tert*-butylphenol (3.21g)

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By following the **GP-1**, the title compound **3.21g** was isolated as dark-red liquid (0.513 g, 86%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, J = 8.2 Hz, 2H), 7.23 (t, J = 7.4 Hz, 2H), 7.15 (d, J = 7.0 Hz, 1H), 7.13 – 7.10 (m, 4H), 6.91 (s, 2H), 6.75 (s, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.5 Hz, 1H), 5.25 (s, 1H), 5.02 (s, 1H), 4.36 (s, 2H), 3.29 (t, J = 5.7 Hz, 2H), 2.72 (t, J = 6.4 Hz, 2H), 1.96 (pent, J = 6.0 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.0, 145.9, 143.7, 138.4, 135.4, 134.9, 132.6, 131.7, 130.2, 129.5, 128.6, 128.1, 128.0, 126.1, 125.8, 122.2, 120.5, 110.9, 56.2, 55.1, 50.1, 34.5, 30.5, 28.3, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}BrNO$: 596.2523; found: 596.2524.

2,6-di-*tert*-butyl-4-(phenyl (1-(4-(trifluoromethyl) benzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) methyl) phenol (3.21h)

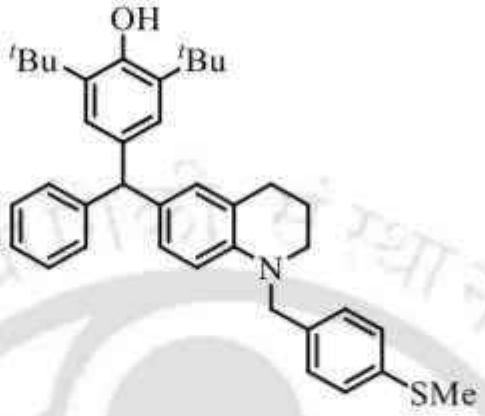


By following the **GP-1**, the title compound **3.21h** was isolated as dark-red liquid (0.463 g, 79%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.55 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.24 (t, J = 7.4 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 7.4 Hz, 2H), 6.91 (s, 2H), 6.77 (s, 1H), 6.65 (d, J = 8.3 Hz, 1H), 6.32 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 5.03 (s, 1H), 4.48 (s, 2H), 3.35 – 3.31 (m, 2H), 2.75 (t, J = 6.2 Hz, 2H), 2.00 (pent, J = 6.1 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.0, 145.9, 143.7, 143.6, 135.4, 134.9, 132.8, 130.3, 129.5, 128.1, 128.0, 127.0, 126.1, 125.8, 125.6 (CF_3, q, $J_{C\text{-}F}$ = 3.7 Hz), 122.3, 110.9, 56.2, 55.4, 50.3,

TH-3765_196122031

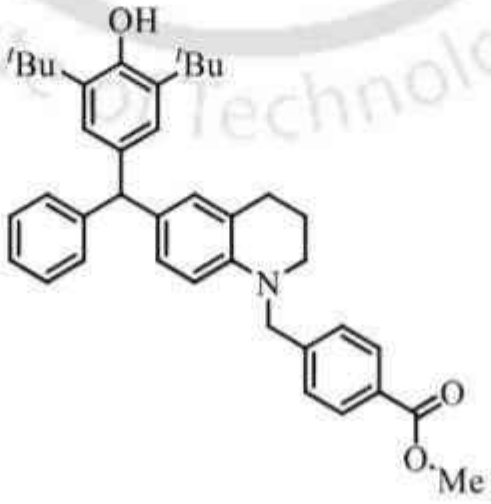
34.5, 30.5, 28.3, 22.7. $^{19}F\{^{1}H\}$ NMR (471 MHz, $CDCl_3$): δ -62.34. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{38}H_{43}F_3NO$: 586.3292; found: 586.3278.

2, 6-di-*tert*-butyl-4-((1-(4-(methylthio) benzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) phenol (3.21i)



By following the **GP-1**, the title compound **3.21i** was isolated as dark-red liquid (0.490 g, 87%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^1H NMR (600 MHz, $CDCl_3$): δ 7.23 (t, J = 7.3 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.4 Hz, 1H), 7.12 (d, J = 7.7 Hz, 2H), 6.92 (s, 2H), 6.75 (s, 1H), 6.65 (d, J = 8.3 Hz, 1H), 6.40 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 5.02 (s, 1H), 4.38 (s, 2H), 3.29 (t, J = 5.7 Hz, 2H), 2.72 (t, J = 6.4 Hz, 2H), 2.45 (s, 3H), 1.96 (pent, J = 6.1 Hz, 2H), 1.36 (s, 18H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 152.0, 145.9, 143.9, 136.5, 136.4, 135.3, 135.0, 132.3, 130.1, 129.5, 128.1, 127.9, 127.5, 127.2, 126.1, 125.8, 122.1, 110.9, 56.2, 55.1, 50.0, 34.5, 30.5, 28.3, 22.6, 16.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{38}H_{46}NOS$: 564.3295; found: 564.3296.

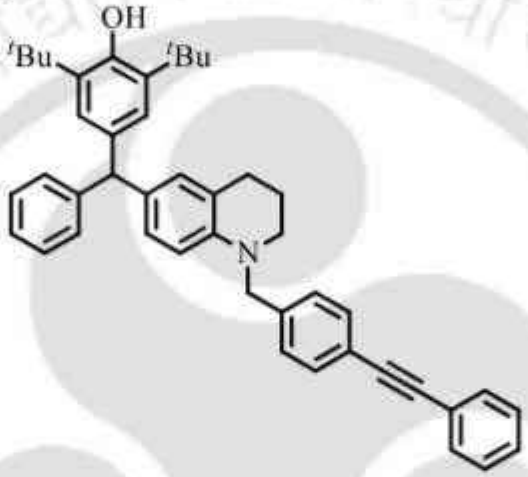
Methyl 4-((6-((3,5-di-*tert*-butyl-4-hydroxyphenyl) (phenyl)methyl)-3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (3.21j)



TH-3765_196122031

By following the **GP-1**, the title compound **3.21j** was isolated as dark-red liquid (0.461 g, 80%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.27 – 7.21 (m, 2H), 7.17 – 7.09 (m, 3H), 6.91 (s, 2H), 6.76 (s, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.33 (d, J = 8.4 Hz, 1H), 5.26 (s, 1H), 5.02 (s, 1H), 4.47 (s, 2H), 3.89 (s, 3H), 3.35 – 3.31 (m, 2H), 2.74 (t, J = 6.1 Hz, 2H), 1.99 (pent, J = 5.6 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.2, 152.0, 145.9, 145.1, 143.7, 135.4, 134.9, 132.7, 130.2, 130.0, 129.5, 128.9, 128.1, 128.0, 126.7, 126.1, 125.8, 122.2, 110.9, 56.2, 55.6, 52.2, 50.3, 34.5, 30.5, 28.3, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{39}H_{46}NO_3$: 576.3473; found:576.3470.

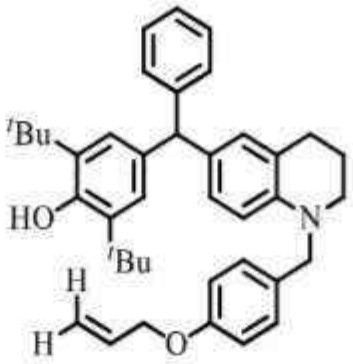
2, 6-di-*tert*-butyl-4-(phenyl (1-(4-(phenyl ethynyl) benzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) methyl) phenol (3.21k)



By following the **GP-1**, the title compound **3.21k** was isolated as dark-red liquid (0.500 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51 – 7.50 (m, 2H), 7.45 (d, J = 8.1Hz, 2H), 7.32 – 7.29 (m, 3H), 7.24 - 7.21 (m, 4H), 7.15 – 7.12 (m, J = 8.2 Hz, 3H), 6.93 (s, 2H), 6.76 (s, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.37 (d, J = 8.5 Hz, 1H), 5.27 (s, 1H), 5.02 (brs, 1H), 4.41 (s, 2H), 3.31 – 3.29 (m, 2H), 2.73 (t, J = 6.2 Hz, 2H), 1.97 (pent, J = 6.1 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.0, 145.9, 143.8, 139.9, 134.0, 135.4, 135.0, 132.5, 131.9, 131.7, 130.2, 129.5, 128.4, 128.3, 128.1, 128.0, 126.9, 126.1, 125.8, 123.5, 122.2, 121.7, 111.0, 89.5, 89.2, 56.2, 55.5, 50.1, 34.5, 30.5, 28.3, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{45}H_{48}NO$: 618.3731; found:618.3727.

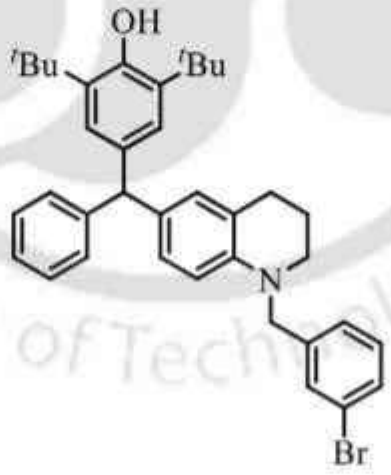
4-((1-(4-(allyloxy) benzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl)-2, 6-di-*tert*-butylphenol (3.21l)

TH-3765_196122031



By following the **GP-1**, the title compound **3.21l** was isolated as dark-red liquid (0.482 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25-7.22 (m, 2H), 7.16 – 7.14(m, 3H), 7.12 (d, J = 7.7 Hz, 2H), 6.92 (s, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.74 (s, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.44 (d, J = 8.5 Hz, 1H), 6.07 – 6.01 (m, 1H), 5.40 (d, J = 16.4 Hz, 1H), 5.28 – 5.26 (m, 2H), 5.02 (s, 1H), 4.50 (d, J = 5.2 Hz, 2H), 4.37 (s, 2H), 3.29– 3.27 (m, 2H), 2.72 (t, J = 6.2 Hz, 2H), 1.95 (pent, J = 5.9 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 157.7, 152.0, 146.0, 144.1, 135.3, 135.0, 133.6, 132.2, 131.4, 130.1, 129.5, 128.1, 128.02, 127.95, 126.1, 125.8, 122.1, 117.75, 114.9, 110.9, 69.0, 56.2, 54.9 49.8, 34.5, 30.5, 28.4, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{40}H_{48}NO_2$: 574.3680; found: 574.3677.

4-((1-(3-bromobenzyl)-1,2,3,4-tetrahydroquinolin-6-yl) (phenyl) methyl)-2, 6-di-*tert*-butylphenol (3.21m)

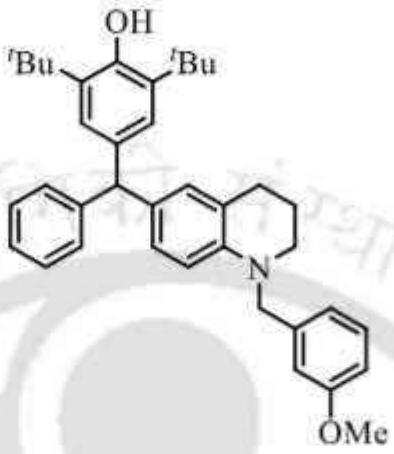


By following the **GP-1**, the title compound **3.21m** was isolated as dark-red liquid (0.513 g, 86%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.34 (d, J = 7.3 Hz, 1H), 7.23 (t, J = 7.1 Hz, 2H), 7.19 – 7.14 (m, 2H), 7.14 – 7.10 (m, 3H), 6.92 (s, 2H), 6.76 (s, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.36 (d, J = 8.4 Hz, 1H), 5.26 (s, 1H), 5.01 (s, 1H), 4.38 (s, 2H), 3.30 (t, J = 5.6 Hz, 2H), 2.73 (t, J = 6.3 Hz, 2H), 1.98 (pent, J = 6.0 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.0, 145.9, 143.7, 142.1, 135.4, 135.0, 132.7, 130.3, 130.2, 130.0, 129.8, 129.5,

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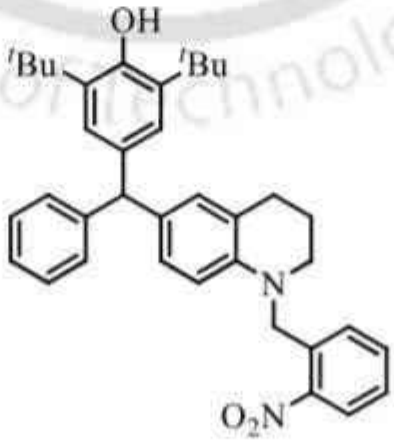
128.1, 128.0, 126.1, 125.8, 125.4, 122.9, 122.3, 111.0, 56.2, 55.3, 50.2, 34.5, 30.5, 28.3, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}BrNO$: 596.2523; found: 596.2523.

2, 6-di-*tert*-butyl-4-((1-(3-methoxybenzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) Phenol (3.21n)



By following the **GP-1**, the title compound **3.21n** was isolated as dark-red liquid (0.498 g, 91%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (q, J = 9.2, 8.3 Hz, 3H), 7.12 (d, J = 6.0 Hz, 3H), 6.93 (d, J = 2.7 Hz, 2H), 6.88 – 6.78 (m, 2H), 6.75 (s, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.41 (dd, J = 8.4, 2.3 Hz, 1H), 5.26 (s, 1H), 5.01 (s, 1H), 4.39 (s, 2H), 3.74 (s, 3H), 3.34 – 3.28 (m, 2H), 2.72 (t, J = 5.5 Hz, 2H), 1.97 (pent, J = 6.5 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.1, 152.0, 146.0, 144.0, 141.2, 135.4, 135.1, 132.3, 130.1, 129.7, 129.5, 128.1, 128.0, 126.1, 125.8, 122.1, 119.2, 112.5, 112.1, 111.0, 56.2, 55.5, 55.2, 50.1, 34.5, 30.5, 28.4, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{38}H_{46}NO_2$: 548.3524; found: 548.3522.

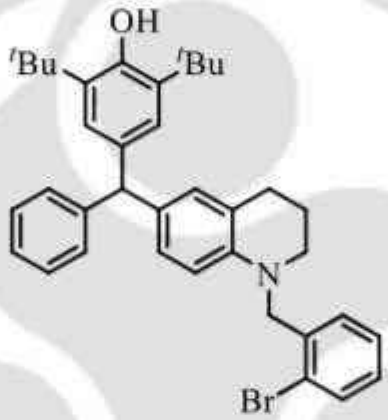
2, 6-di-*tert*-butyl-4-((1-(2-nitrobenzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) Phenol (3.21o)



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By following the **GP-1**, the title compound **3.21o** was isolated as dark-red liquid (0.422 g, 75%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.12 (d, J = 8.1 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.27 – 7.22 (m, 3H), 7.15 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 7.5 Hz, 2H), 6.91 (s, 2H), 6.79 (s, 1H), 6.62 (d, J = 8.3 Hz, 1H), 6.15 (d, J = 8.4 Hz, 1H), 5.27 (s, 1H), 5.05 (brs, 1H), 4.80 (s, 2H), 3.38 – 3.35 (m, 2H), 2.78 (t, J = 6.1 Hz, 2H), 2.03 (m, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.0, 148.2, 145.8, 135.3, 134.8, 134.0, 132.8, 130.2, 129.4, 128.7, 128.1, 128.0, 127.8, 126.1, 125.8, 125.6, 122.1, 110.6, 56.1, 54.2, 50.4, 34.4, 30.4, 28.2, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}N_2O_3$: 563.3269; found: 563.3254.

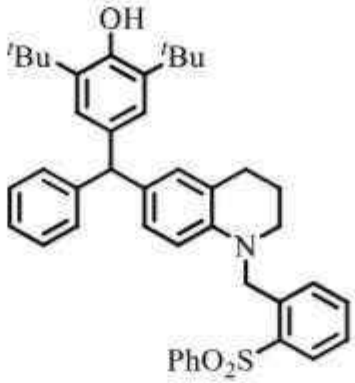
4-((1-(2-bromobenzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl)-2, 6-di-*tert*-butylphenol (3.21p)



By following the **GP-1**, the title compound **3.21p** was isolated as dark-red liquid (0.489 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.55 (d, J = 7.7 Hz, 1H), 7.25 – 7.21 (m, 4H), 7.16 – 7.09 (m, 4H), 6.91 (s, 2H), 6.77 (s, 1H), 6.63 (d, J = 8.4 Hz, 1H), 6.20 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 5.02 (s, 1H), 4.43 (s, 2H), 3.40 – 3.34 (m, 2H), 2.76 (t, J = 6.2 Hz, 2H), 2.02 (pent, J = 6.1 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.0, 145.9, 143.5, 137.5, 135.4, 132.9, 132.5, 130.1, 129.5, 128.4, 128.09, 128.05, 128.0, 127.6, 126.1, 125.8, 123.0, 122.0, 110.7, 56.5, 56.2, 50.3, 34.5, 30.5, 28.3, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}BrNO$: 596.2523; found: 596.2524.

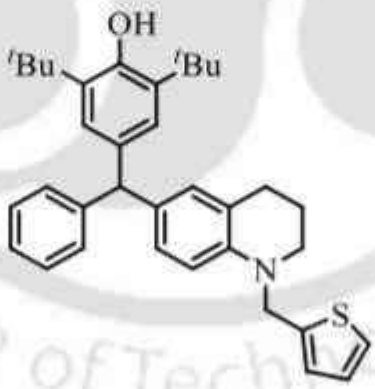
2, 6-di-*tert*-butyl-4-(phenyl (1-(2-(phenylsulfonyl) benzyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) methyl) phenol (3.21q)

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By following the **GP-1**, the title compound **3.21q** was isolated as dark-red liquid (0.559 g, 85%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, J = 7.7 Hz, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.53 – 7.40 (m, 6H), 7.24 - 7.21 (m, 2H), 7.14 (t, J = 7.1 Hz, 1H), 7.07 (d, J = 7.6 Hz, 2H), 6.86 (s, 2H), 6.70 (s, 1H), 6.33 (d, J = 8.3 Hz, 1H), 5.45 (d, J = 8.4 Hz, 1H), 5.19 (s, 1H), 5.03 (brs, 1H), 4.58 (s, 2H), 3.26 – 3.24 (m, 2H), 2.70 (t, J = 6.1 Hz, 2H), 1.95 (p, J = 6.2 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.0, 145.8, 143.1, 141.2, 139.1, 138.0, 135.4, 134.9, 134.2, 133.4, 132.5, 130.1, 130.0, 129.4, 129.3, 128.07, 128.05, 127.9, 127.8, 127.4, 126.1, 125.8, 121.9, 110.2, 56.1, 53.2, 50.5, 34.5, 30.5, 28.2, 22.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{43}H_{48}NO_3S$: 658.3350; found: 658.3349.

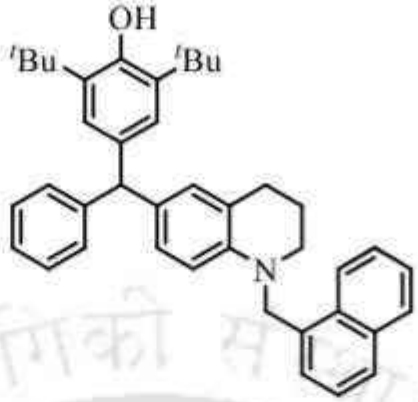
2, 6-di-*tert*-butyl-4-(phenyl (1-(thiophen-2-ylmethyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) methyl) phenol (3.21r)



By following the **GP-1**, the title compound **3.21r** was isolated as dark-red liquid (0.425 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.20 (m, 2H), 7.17 – 7.09 (m, 4H), 6.91 (d, J = 8.8 Hz, 4H), 6.72 (d, J = 12.9 Hz, 2H), 6.61 (d, J = 8.3 Hz, 1H), 5.27 (s, 1H), 5.02 (s, 1H), 4.57 (s, 2H), 3.33 – 3.27 (m, 2H), 2.68 (t, J = 6.3 Hz, 2H), 1.94 (pent, J = 6.0 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.0, 143.3, 145.9, 142.7, 135.4, 135.0, 132.9, 130.3, 129.5, 128.1, 127.9, 126.8, 126.2, 125.8, 124.9, 124.2, 122.8, 111.5, 56.2, 50.8, 49.6, 34.5, 30.5, 28.2, 22.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{35}H_{42}NOS$: 524.2982; found: 524.2975.

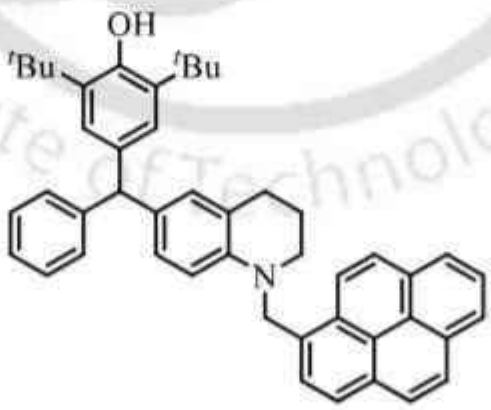
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2, 6-di-*tert*-butyl-4-((1-(naphthalen-2-ylmethyl)-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) phenol (3.21s)



By following the **GP-1**, the title compound **3.21s** was isolated as dark-red liquid (0.488 g, 86%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.73 (d, J = 7.3 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.39 – 7.35 (m, 2H), 7.23 (t, J = 7.6 Hz, 2H), 7.14-7.13 (m, 3H), 6.94 (s, 2H), 6.80 (s, 1H), 6.64 (s, 1H), 6.36 (d, J = 8.5 Hz, 1H), 5.27 (s, 1H), 5.01 (brs, 1H), 4.86 (s, 2H), 3.33 (t, J = 5.6 Hz, 2H), 2.77 (t, J = 6.4 Hz, 2H), 1.99 (pent, J = 6.2 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.0, 146.0, 135.3, 135.0, 133.2, 130.0, 129.4, 128.9, 128.1, 128.0, 127.4, 126.1, 126.1, 125.8, 125.7, 123.9, 122.9, 122.2, 110.8, 56.2, 53.5, 49.7, 34.4, 30.5, 28.4, 22.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{41}H_{46}NO$: 568.3574; found: 568.3577.

2,6-di-*tert*-butyl-4-((1-((4,6-dihydropyren-1-yl) methyl)-1,2,3,4-tetrahydroquinolin-6-yl) (phenyl)methyl) phenol (3.21t)

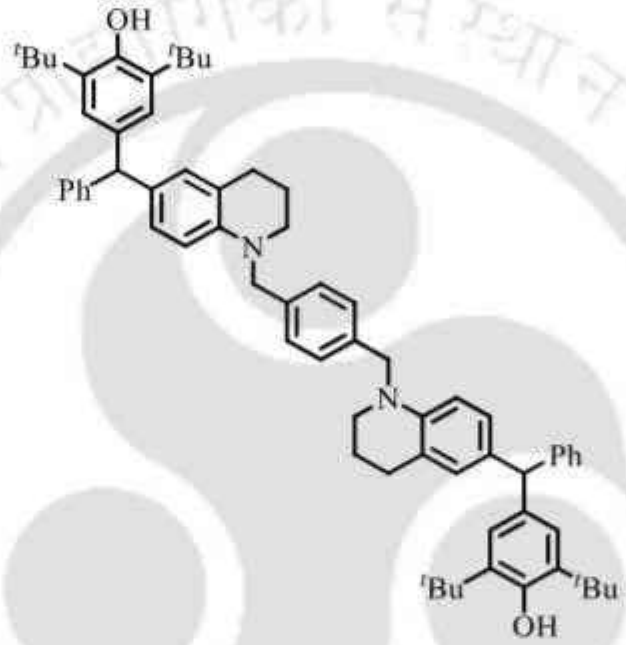


By following the **GP-1**, the title compound **3.21t** was isolated as dark-red liquid (0.533 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, J = 9.2 Hz, 1H), 8.14 (t, J = 7.0 Hz, 2H), 8.08 – 8.05 (m, 2H), 7.99 (s, 2H), 7.97 – 7.94 (m, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.23 (t, J = 7.5 Hz, 2H),

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7.15 (d, J = 7.8 Hz, 3H), 6.95 (s, 2H), 6.84 (s, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.46 (d, J = 8.5 Hz, 1H), 5.29 (s, 1H), 5.10 (s, 2H), 5.00 (brs, 1H), 3.34 (t, J = 5.6 Hz, 2H), 2.79 (t, J = 6.4 Hz, 2H), 2.00 (pent, J = 6.2 Hz, 2H), 1.35 (s, 18H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 152.0, 146.0, 135.4, 135.0, 132.5, 131.9, 131.5, 130.9, 130.2, 129.5, 128.5, 128.1, 128.1, 127.6, 127.00, 126.1, 126.0, 125.8, 125.2, 125.2, 125.0, 124.9, 122.5, 122.5, 111.0, 56.3, 53.8, 49.7, 34.5, 30.5, 28.4, 22.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{47}H_{48}NO$: 642.3731; found: 642.3722.

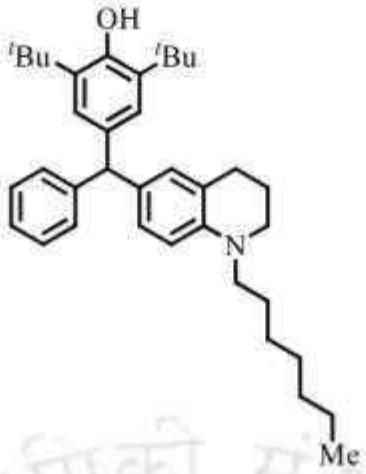
4,4'-((1,1'-(1,4-phenylenebis(methylene)) bis(1,2,3,4-tetrahydroquinoline-6,1-diyl)) bis (phenyl methylene)) bis(2,6-di-*tert*-butylphenol) (3.21u)



By following the **GP-1**, with 0.5 mmol of **3.18a**, and Hantzsch ester 6.5 mmol, the title compound **3.21u** was isolated as dark-red liquid (0.340 g, 71%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.23 (m, 2H), 7.21 (s, 1H), 7.17 (s, 4H), 7.15 (s, 1H), 7.15 – 7.11 (m, 5H), 6.91 (s, 4H), 6.85 – 6.78 (m, 1H), 6.74 (s, 2H), 6.65 (d, J = 8.3 Hz, 2H), 6.42 (d, J = 8.5 Hz, 2H), 5.25 (s, 2H), 5.01 (brs, 2H), 4.40 (s, 4H), 3.30 – 3.28 (m, 4H), 2.73 – 2.70 (m, 4H), 1.98 – 1.93 (m, 4H), 1.35 (s, 36H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 152.0, 146.0, 144.0, 137.8, 135.3, 135.0, 132.2, 130.1, 129.5, 128.1, 128.0, 127.0, 126.1, 125.8, 122.1, 110.9, 56.2, 55.2, 50.0, 34.5, 30.5, 28.4, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{68}H_{81}N_2O_2$: 957.6293; found: 957.6264.

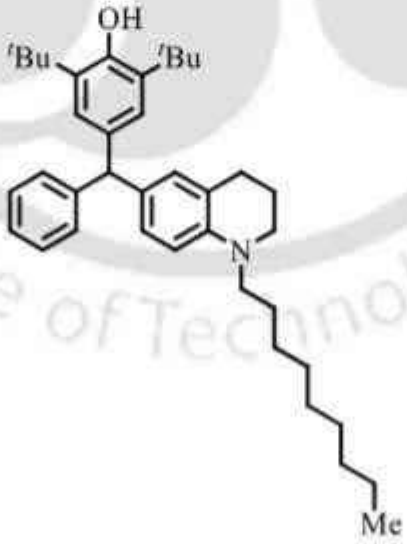
2, 6-di-*tert*-butyl-4-((1-heptyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) phenol (3.21v)

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By following the **GP-1**, the title compound **3.21v** was isolated as dark-red liquid (0.415 g, 79%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 (d, J = 7.5 Hz, 2H), 7.16 - 7.13 (m, 3H), 6.93 (s, 2H), 6.72 - 6.70 (m, 2H), 6.45 (d, J = 8.1 Hz, 1H), 5.25 (s, 1H), 5.02 (s, 1H), 3.24 – 3.22 (m, 2H), 3.19 – 3.17 (m, 2H), 2.66 (t, J = 6.2 Hz, 2H), 1.91 (pent, J = 6.1 Hz, 2H), 1.36 (s, 18H), 1.31-1.25 (m, 9H), 0.88-0.86 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.0, 146.1, 143.7, 135.3, 135.1, 131.6, 130.2, 129.5, 128.1, 127.8, 126.2, 125.7, 122.0, 110.4, 56.2, 51.8, 49.5, 34.5, 32.0, 30.5, 29.4, 28.4, 27.4, 26.4, 22.8, 22.6, 14.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{52}NO$: 526.4044; found: 526.4032.

2, 6-di-*tert*-butyl-4-((1-nonyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) phenol (3.21w)

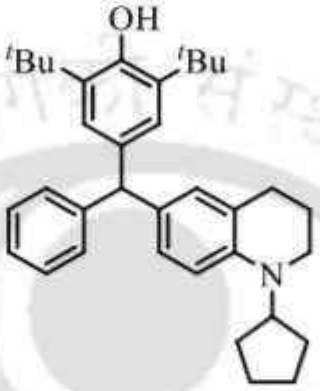


By following the **GP-1**, the title compound **3.21w** was isolated as dark-red liquid (0.426 g, 77%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25-7.22 (m, 2H), 7.16-7.13 (m, 3H), 6.94 (s, 2H), 6.72-6.70 (m, 2H), 6.45 (d, J = 8.1 Hz, 1H), 5.26 (s, 1H), 5.02 (brs, 1H), 3.25 – 3.21 (m, 2H), 3.21

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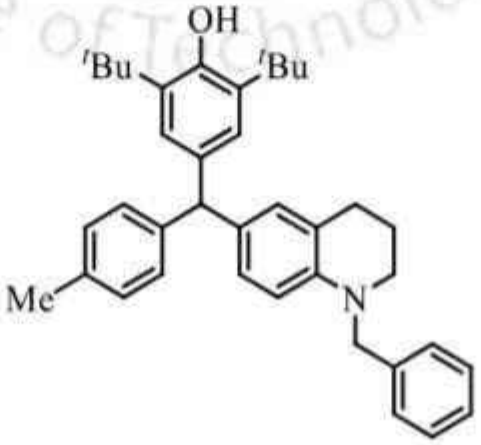
– 3.15 (m, 2H), 2.66 (t, J = 6.2 Hz, 2H), 1.91 – 1.89 (m, 2H), 1.56 – 1.54 (m, 2H), 1.36 (s, 18H), 1.30 (m, 12H), 0.88 - 0.86 (m, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 152.0, 146.1, 143.7, 135.3, 135.1, 131.6, 130.2, 129.5, 128.1, 127.8, 126.15, 125.7, 122.0, 110.4, 56.2, 51.8, 49.5, 34.5, 32.0, 30.5, 29.8, 29.7, 29.4, 28.4, 27.45, 26.4, 22.8, 22.6, 14.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{39}H_{56}NO$: 554.4357; found: 554.4364.

2, 6-di-*tert*-butyl-4-((1-cyclopentyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl) phenol (3.21x)



By following the **GP-1**, the title compound **3.21x** was isolated as dark-red liquid (0.322 g. 65%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 - 7.21 (m, 2H), 7.14-7.12 (m, 3H), 6.94 (s, 2H), 6.74 – 6.71 (m, 2H), 6.61 (d, J = 8.4 Hz, 1H), 5.26 (s, 1H), 5.01 (brs, 1H), 4.15 (pent, J = 7.8 Hz, 1H), 3.14 (t, J = 5.8 Hz, 2H), 2.64 (t, J = 6.4 Hz, 2H), 1.88 – 1.84 (m, 4H), 1.68 (br, 2H), 1.58 (br, 4H), 1.36 (s, 18H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 152.0, 146.1, 144.5 135.3, 135.1, 131.7, 130.1, 129.5, 128.0, 127.8, 126.1, 125.7, 123.1, 110.9, 58.8, 56.2, 42.1, 34.5, 30.5, 28.6, 28.1, 24.3, 22.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{35}H_{46}NO$: 496.3574; found: 496.3575.

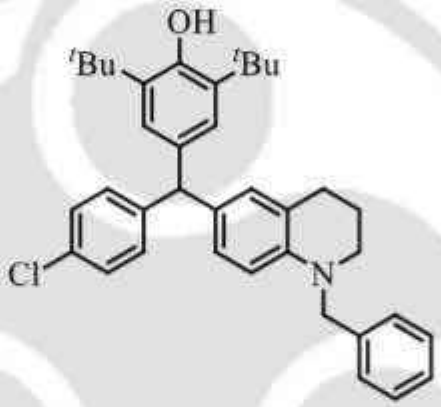
4-((1-benzyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (*p*-tolyl) methyl)-2, 6-di-*tert*-butylphenol (3.22a)



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By following the **GP-2**, the title compound **3.22a** was isolated as dark-red liquid (0.431 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.27 (m, 2H), 7.25 (d, J = 6.0 Hz, 3H), 7.21 (t, J = 7.1 Hz, 1H), 7.04 (d, J = 7.9 Hz, 2H), 7.00 (d, J = 7.9 Hz, 2H), 6.92 (s, 2H), 6.75 (s, 1H), 6.65 (d, J = 7.5 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.21 (s, 1H), 5.00 (s, 1H), 4.43 (s, 2H), 3.31 (t, J = 5.7 Hz, 2H), 2.73 (t, J = 6.4 Hz, 2H), 2.29 (s, 3H), 1.97 (pent, J = 6.0 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.0, 144.0, 143.0, 139.4, 135.4, 135.2, 135.1, 132.6, 130.1, 129.3, 128.8, 128.6, 127.9, 126.9, 126.8, 126.1, 122.1, 111.0, 55.9, 55.6, 50.0, 34.5, 30.5, 28.4, 22.7, 21.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{38}H_{46}NO$: 532.3574; found: 532.3574.

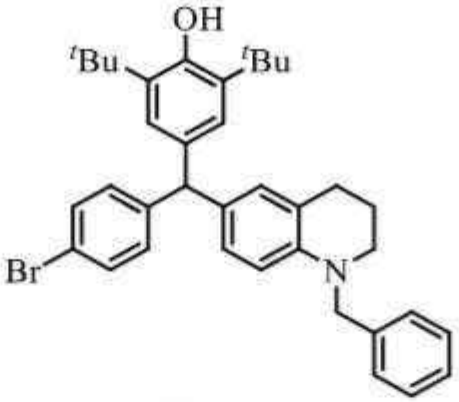
4-((1-benzyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (4-chlorophenyl) methyl)-2, 6-di-*tert*-butyl Phenol (3.22b)



By following the **GP-2**, the title compound **3.22b** was isolated as dark-red liquid (0.480 g, 87%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (t, J = 7.4 Hz, 2H), 7.27 – 7.21 (m, 4H), 7.20 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.88 (s, 2H), 6.71 (s, 1H), 6.62 (d, J = 8.5 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.22 (s, 1H), 5.04 (s, 1H), 4.44 (s, 2H), 3.33 (t, J = 5.6 Hz, 2H), 2.73 (t, J = 6.4 Hz, 2H), 1.98 (pent, J = 6.2 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.1, 144.6, 144.1, 139.2, 135.5, 134.5, 131.6, 131.5, 130.8, 130.0, 128.7, 128.2, 127.9, 126.9, 126.8, 126.0, 122.2, 110.9, 55.54, 55.47, 50.0, 34.5, 30.5, 28.4, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{42}ClNO$: 552.3028; found: 552.3025.

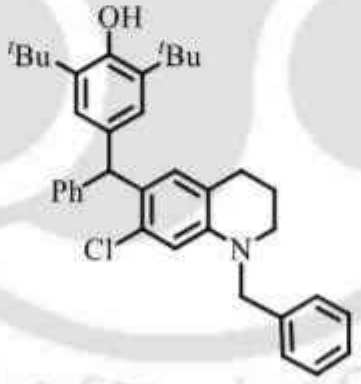
4-((1-benzyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (4-bromophenyl) methyl)-2, 6-di-*tert*-butylphenol (3.22c)

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By following the **GP-2**, the title compound **3.22c** was isolated as dark-red liquid (0.531 g, 89%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 7.2 Hz, 2H), 7.23 (d, J = 6.9 Hz, 2H), 7.22 – 7.17 (m, 1H), 6.99 (d, J = 8.2 Hz, 2H), 6.89 (s, 2H), 6.71 (s, 1H), 6.63 (d, J = 7.2 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.20 (s, 1H), 5.03 (s, 1H), 4.42 (s, 2H), 3.31 (t, J = 5.6 Hz, 2H), 2.72 (t, J = 6.3 Hz, 2H), 1.96 (pent, J = 6.0 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.2, 145.2, 144.1, 139.2, 135.6, 134.48, 134.46, 131.5, 131.2, 131.1, 130.0, 128.6, 127.9, 126.9, 126.8, 126.0, 122.2, 119.6, 111.0, 55.6, 55.5, 50.0, 34.5, 30.5, 28.4, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}BrNO$: 596.2523; found: 596.2526.

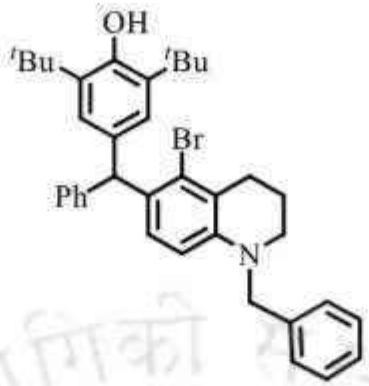
4-((1-benzyl-7-chloro-1,2,3,4-tetrahydroquinolin-6-yl)(phenyl)methyl)-2,6-di-*tert*-butylphenol (3.22d)



By following the **GP-2**, the title compound **3.22d** was isolated as dark-red liquid (0.453 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.30 (m, 2H), 7.25 – 7.23 (m, 5H), 7.17 – 7.15 (m, 1H), 7.10 (d, J = 7.6 Hz, 2H), 6.89 (s, 2H), 6.55 (s, 1H), 6.52 (s, 1H), 5.69 (s, 1H), 5.04 (s, 1H), 4.42 (s, 2H), 3.29 – 3.27 (m, 2H), 2.65 – 2.63 (m, 2H), 1.95 – 1.91 (m, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.1, 144.9, 144.7, 138.5, 135.4, 133.9, 132.7, 131.0, 129.5, 129.2, 128.8, 128.1, 127.1, 126.8, 126.3, 125.9, 120.9, 111.3, 55.2, 52.4, 49.5, 34.5, 30.5, 28.0, 22.4. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}ClNO$: 552.3028; found: 552.3026.

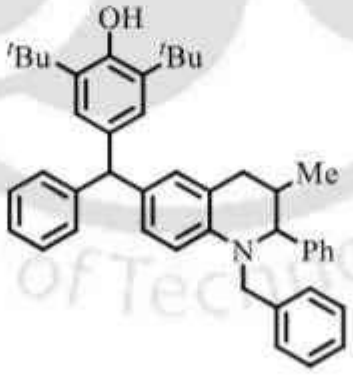
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4-((1-benzyl-5-bromo-1,2,3,4-tetrahydroquinolin-6-yl)(phenyl)methyl)-2,6-di-tert-butylphenol (3.22e)



By following the **GP-2**, the title compound **3.22e** was isolated as dark-red liquid (0.447 g, 75%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.28 (m, 2H), 7.23 – 7.22 (m, 5H), 7.16 – 7.13 (m, 1H), 7.07 (d, J = 7.7 Hz, 2H), 6.84 (s, 2H), 6.53 (d, J = 8.6 Hz, 1H), 6.38 (d, J = 8.6 Hz, 1H), 5.79 (s, 1H), 5.01 (s, 1H), 4.49 – 4.40 (m, 2H), 3.33 – 3.31 (m, 2H), 2.89 – 2.87 (m, 2H), 2.05 – 2.00 (m, 2H), 1.33 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.0, 145.6, 144.6, 138.85, 135.35, 134.3, 131.8, 129.6, 129.1, 128.7, 128.0, 127.0, 126.7, 126.5, 125.8, 122.0, 110.2, 56.0, 55.9, 49.7, 34.4, 30.5, 29.9, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}BrNO$: 596.2523; found: 596.2509.

4-((1-benzyl-3-methyl-2-phenyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl)-2, 6-di-*tert*-butylphenol (3.22f)

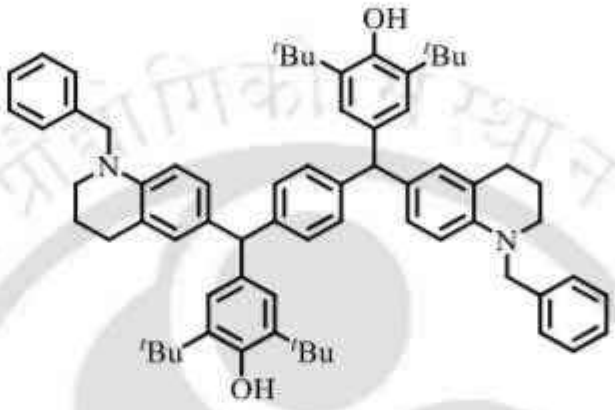


By following the **GP-2**, the title compound **3.22f** was isolated as dark-red liquid (0.474 g, 78%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). cis: trans = 1:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.24 (m, 14H), 7.22 – 7.21 (m, 6H), 7.18 – 7.14 (m, 6H), 7.12 – 7.10 (m, 4H), 6.92 (s, 4H), 6.81 (s, 1H), 6.76 – 6.73 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.37 (t, J = 8.4 Hz, 2H), 5.31 (d, J = 5.7 Hz, 2H), 5.04 (d, J = 3.2 Hz, 2H), 4.50 (dd, J = 17.3, 5.9 Hz, 2H), 4.39 (s, 2H), 4.17 (d, J = 17.4 Hz, 2H), 2.52 – 2.48 (m, 6H), 1.37 (s, 36H), 0.86 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 5.1 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$):

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δ 152.0, 146.1, 145.9, 143.5, 140.81, 140.79, 139.32, 139.28, 135.3, 135.1, 131.8, 131.7, 130.0, 129.8, 129.6, 129.5, 128.72, 128.68, 128.3, 128.2, 128.11, 128.09, 128.0, 127.3, 126.8, 126.4, 126.22, 126.17, 125.8, 121.27, 121.25, 109.78, 109.75, 67.2, 56.14, 56.06, 53.4, 34.5, 31.72, 31.68, 30.51, 30.5, 18.7, 18.6. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{44}H_{50}NO$: 608.3887; found: 608.3895.

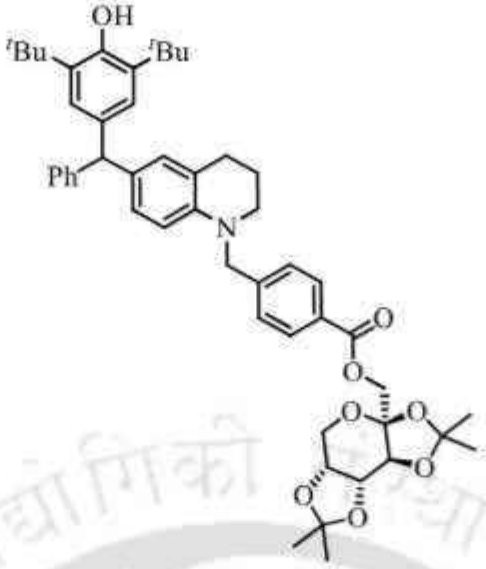
4,4'-(1,4-phenylenebis((1-benzyl-1,2,3,4-tetrahydroquinolin-6-yl) methylene)) bis(2,6-di-*tert*-butylphenol) (3.22g)



By following the **GP-2**, the title compound **3.22g** was isolated as dark-red liquid (0.613 g, 64%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.28 (m, 5H), 7.25 – 7.20 (m, 5H), 6.99 (s, 4H), 6.91 (s, 4H), 6.74 (s, 2H), 6.66 – 6.63 (m, 2H), 6.40 (d, J = 8.4 Hz, 2H), 5.22 (s, 2H), 5.00 (brs, 2H), 4.43 (s, 4H), 3.32 – 3.30 (m, 4H), 2.72 (t, J = 6.1 Hz, 4H), 1.97 (pent, J = 6.1 Hz, 4H), 1.35 (s, 36H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 151.9, 143.9, 143.14, 143.08, 139.4, 135.4, 135.3, 135.2, 132.5, 130.1, 129.0, 128.6, 128.0, 126.85, 126.81, 126.1, 122.00, 121.99, 110.87, 110.85, 55.8, 55.5, 50.0, 34.5, 30.5, 28.4, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{68}H_{81}N_2O_2$: 957.6293; found: 957.6284.

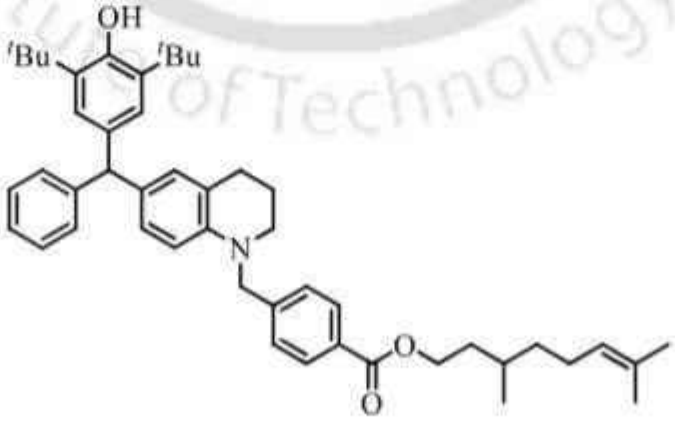
((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl 4-((6-((R)-(3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-3,4-dihydroquinolin-1(2H)-yl)methyl)benzoate (3.24a)

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By following the **GP-1**, the title compound **3.24a** was isolated as dark-red liquid (0.571 g, 71%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 60/40, R_f = 0.38). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.23 (t, J = 7.5 Hz, 2H), 7.17 – 7.09 (m, 3H), 6.92 (s, 2H), 6.77 (s, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 5.03 (s, 1H), 4.68 – 4.61 (m, 2H), 4.49 – 4.44 (m, 3H), 4.33 (d, J = 11.8 Hz, 1H), 4.25 (d, J = 8.5 Hz, 1H), 3.96 (dd, J = 13.0, 1.6 Hz, 1H), 3.80 (d, J = 13.0 Hz, 1H), 3.35 – 3.30 (m, 2H), 2.74 (t, J = 6.2 Hz, 2H), 1.99 (pent, J = 6.1 Hz, 2H), 1.54 (s, 3H), 1.46 (s, 3H), 1.39 – 1.33 (m, 24H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.0, 152.0, 145.8, 145.3, 143.6, 135.4, 134.9, 132.7, 130.2, 129.4, 128.6, 128.1, 127.95, 126.7, 126.1, 125.8, 122.2, 110.9, 109.3, 108.9, 101.8, 71.0, 70.6, 70.2, 65.4, 61.5, 56.2, 55.6, 50.3, 34.4, 30.5, 28.3, 26.7, 26.0, 25.8, 24.2, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{50}H_{62}NO_8$:804.4470; found:804.4473.

3,7-dimethyloct-6-en-1-yl 4-((6-((3, 5-di-*tert*-butyl-4-hydroxyphenyl) (phenyl)methyl)-3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (3.24b)

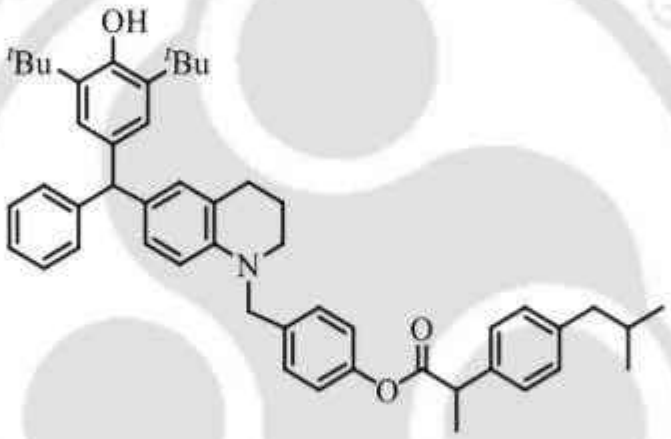


By following the **GP-1**, the title compound **3.24b** was isolated as dark-red liquid (0.546 g, 78%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f =

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0.62). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.23 (t, J = 7.6 Hz, 2H), 7.15 (d, J = 7.3 Hz, 1H), 7.12 (d, J = 7.4 Hz, 2H), 6.91 (s, 2H), 6.76 (s, 1H), 6.64 (d, J = 10.3 Hz, 1H), 6.33 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 5.09 (t, J = 7.1 Hz, 1H), 5.02 (s, 1H), 4.47 (s, 2H), 4.34 (d, J = 7.1 Hz, 2H), 3.34 – 3.31 (m, 2H), 2.74 (t, J = 6.3 Hz, 2H), 2.05 – 1.95 (m, 4H), 1.78 (d, J = 12.6 Hz, 1H), 1.66 (s, 3H), 1.63 (d, J = 13.0 Hz, 1H), 1.59 (s, 3H), 1.57 (d, J = 14.0 Hz, 1H), 1.42 (s, 1H), 1.35 (s, 18H), 1.25 (d, J = 13.5 Hz, 1H), 0.96 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 166.7, 152.0, 145.9, 144.9, 143.7, 135.4, 134.9, 132.7, 131.5, 130.2, 130.0, 129.46, 129.29, 128.08, 127.98, 126.72, 126.11, 125.80, 124.72, 122.22, 110.91, 63.51, 56.19, 55.6, 50.3, 37.1, 35.7, 34.5, 30.5, 29.7, 28.3, 25.8, 25.5, 22.7, 19.7, 17.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{48}H_{62}NO_3$:700.4725; found: 700.4721.

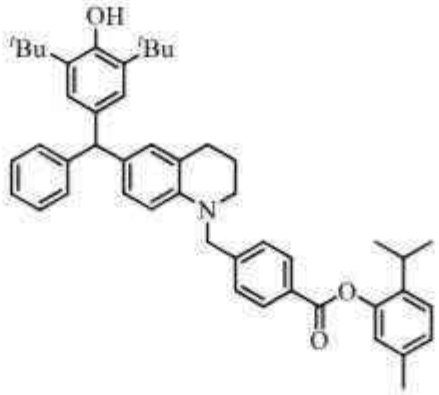
4-((6-((3, 5-di-*tert*-butyl-4-hydroxyphenyl) (phenyl) methyl)-3, 4-dihydroquinolin-1(2H)-yl) methyl) phenyl 2-(4-isobutylphenyl) propanoate (3.24c)



By following the **GP-1**, the title compound **3.24c** was isolated as dark-red liquid (0.607 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.68). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, J = 8.0 Hz, 2H), 7.26 – 7.24 (m, 1H), 7.23 – 7.21 (m, 3H), 7.16 – 7.11 (m, 6H), 6.93 (s, 1H), 6.92 (s, 3H), 6.75 (br, 1H), 6.65 (d, J = 8.2 Hz, 1H), 5.26 (s, 1H), 5.03 (s, 1H), 4.40 (s, 2H), 3.92 (q, J = 7.1 Hz, 1H), 3.29 – 3.27 (m, 2H), 2.72 (t, J = 6.2 Hz, 2H), 2.47 (d, J = 7.2 Hz, 2H), 1.98 – 1.94 (m, 2H), 1.89 – 1.85 (m, 2H), 1.60 (s, 2H), 1.36 (s, 18H), 0.91 (d, J = 6.6 Hz, 6H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 173.5, 152.0, 149.8, 145.9, 140.9, 137.4, 135.4, 135.0, 130.2, 129.6, 129.5, 128.1, 128.0, 127.4, 126.1, 125.8, 121.5, 56.2, 49.9, 45.4, 45.2, 34.5, 30.54, 30.51, 30.48, 30.3, 28.3, 22.5, 18.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{50}H_{60}NO_3$: 722.4568; found: 722.4566.

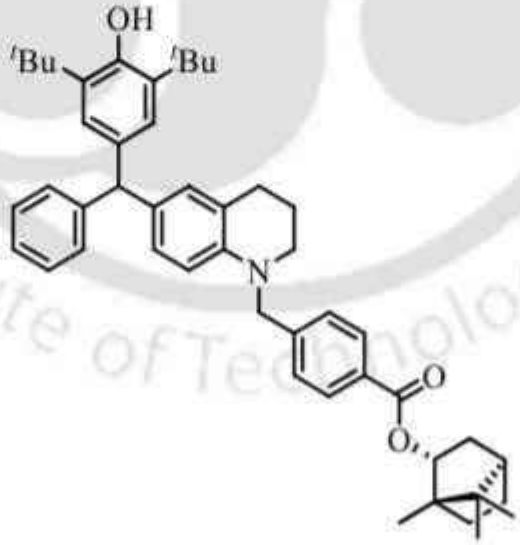
2-isopropyl-5-methylphenyl 4-((6-((3, 5-di-*tert*-butyl-4-hydroxyphenyl) (phenyl) methyl)-3, 4-dihydroquinolin-1(2H)-yl) methyl) benzoate (3.24d)

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By following the **GP-1**, the title compound **3.24d** was isolated as dark-red liquid (0.638 g, 92%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.25 – 7.22 (m, 3H), 7.16 – 7.12 (m, 3H), 7.05 (d, J = 7.8 Hz, 1H), 6.92 (s, 3H), 6.78 (s, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.5 Hz, 1H), 5.27 (s, 1H), 5.03 (brs, 1H), 4.52 (s, 2H), 3.38 – 3.35 (m, 2H), 3.07 – 3.02 (m, 1H), 2.76 (t, J = 6.2 Hz, 2H), 2.33 (s, 3H), 2.04 – 1.99 (m, 2H), 1.36 (s, 18H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 165.4, 152.0, 148.3, 145.89, 145.85, 143.6, 137.3, 136.7, 135.4, 134.9, 132.7, 130.6, 130.3, 129.5, 128.4, 128.1, 128.0, 127.2, 127.0, 126.6, 126.1, 125.8, 123.0, 122.2, 110.9, 56.2, 55.6, 50.4, 34.5, 30.5, 28.3, 27.4, 23.2, 22.7, 21.0.(ESI) *m/z*: $[M+H]^+$ calculated for: $C_{48}H_{56}NO_3$:694.4255; found:694.4248.

(1S,2R,4R)-1,7,7-trimethylbicyclo [2.2.1] heptan-2-yl 4-((6-((3,5-di-*tert*-butyl-4-hydroxyphenyl) (phenyl)methyl)-3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (3.24e)

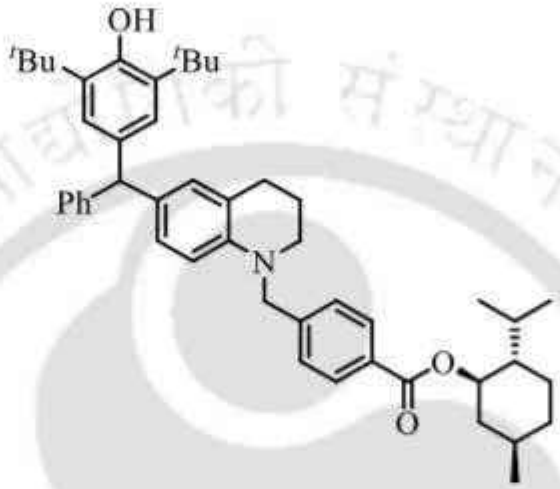


By following the **GP-1**, the title compound **3.24e** was isolated as dark-red liquid (0.579 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.23 – 7.20 (m, 2H), 7.12 (d, J = 6.7 Hz, 3H), 6.92 (s, 2H), 6.78 (s, 1H), 6.65 (d, J = 8.3 Hz, 1H), 6.33 (d, J = 8.5 Hz, 1H), 5.27 (s, 1H), 5.03 (brs, 1H), 4.92 – 4.90 (m, 1H), 4.45 (s, 2H), 3.32 – 3.30 (m, 2H), 2.73 (t, J = 6.2 Hz, 2H), 1.99 – 1.95 (m, 2H), 1.91 - 1.88 (m, 2H), 1.79 – 1.78 (m, 1H),

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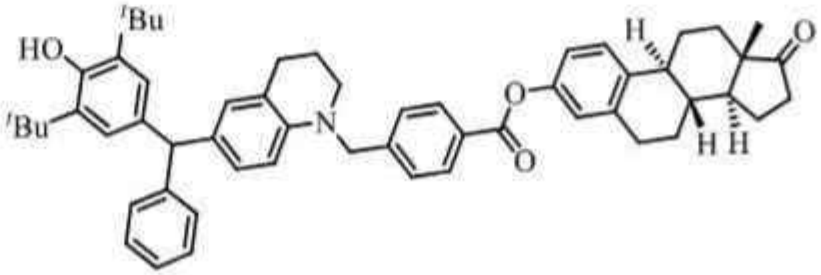
1.62 – 1.56 (m, 1H), 1.36 (s, 18H), 1.29 (d, J = 3.8 Hz, 2H), 1.11 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 166.0, 152.0, 145.8, 144.8, 143.5, 135.3, 134.9, 132.5, 130.2, 129.9, 129.5, 129.4, 128.0, 127.9, 126.7, 126.1, 125.7, 122.1, 110.8, 81.5, 56.1, 55.4, 50.2, 49.1, 47.1, 45.2, 39.0, 34.4, 33.8, 30.5, 28.2, 27.2, 22.6, 20.3, 20.2, 11.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{48}H_{60}NO_3$:698.4568; found: 698.4567.

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl4-((6-((3,5-di-*tert*-butyl-4-hydroxyphenyl) (phenyl)methyl)-3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (3.24f)



By following the **GP-1**, the title compound **3.24f** was isolated as dark-red liquid (0.595 g, 85%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.68). ^1H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.29 – 7.26 (m, 2H), 7.17 (dd, J = 21.4, 7.3 Hz, 3H), 6.95 (s, 2H), 6.80 (s, 1H), 6.68 (d, J = 8.5 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 5.30 (s, 1H), 5.06 (s, 1H), 4.95 (td, J = 10.8, 4.4 Hz, 1H), 4.51 (s, 2H), 3.39 – 3.34 (m, 2H), 2.78 (t, J = 6.3 Hz, 2H), 2.15 (d, J = 11.9 Hz, 1H), 2.05 – 1.97 (m, 3H), 1.76 (d, J = 11.5 Hz, 2H), 1.58 (t, J = 12.5 Hz, 3H), 1.39 (s, 18H), 0.97 – 0.93 (m, 8H), 0.82 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 166.3, 152.0, 145.9, 144.9, 143.7, 135.4, 135.0, 132.7, 130.2, 130.0, 129.6, 129.5, 128.1, 128.0, 126.7, 126.1, 125.8, 122.2, 110.9, 75.0, 56.2, 55.5, 50.3, 47.4, 41.1, 34.5, 31.6, 30.5, 28.3, 26.7, 23.8, 22.7, 22.2, 20.9, 16.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{48}H_{62}NO_3$:700.4725; found: 700.4714.

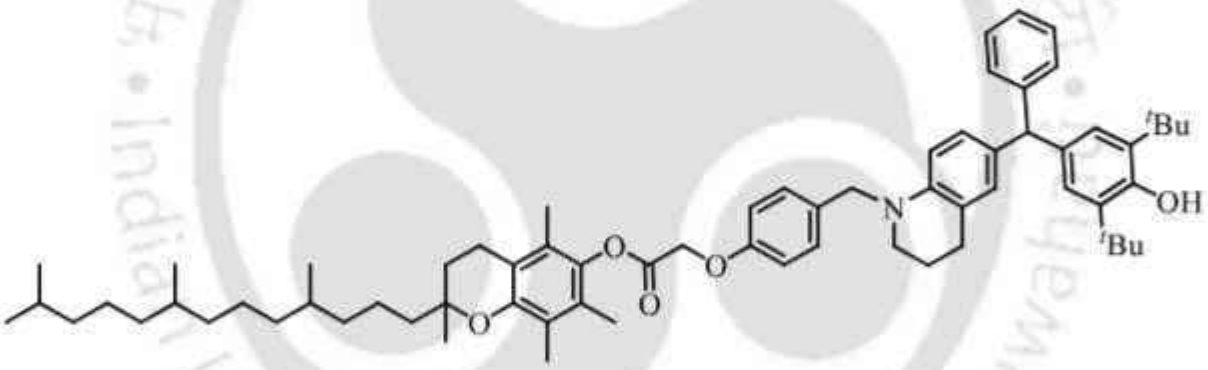
(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-((6-((3,5-di-*tert*-butyl-4-hydroxyphenyl) (phenyl)methyl)-3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (3.24g)



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By following the **GP-1**, the title compound **3.24g** was isolated as dark-red liquid (0.529 g, 65%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 60/40, R_f = 0.38). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.12 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 7.2 Hz, 1H), 7.12 (d, J = 7.5 Hz, 2H), 6.98 – 6.96 (m, 1H), 6.93 (s, 1H), 6.91 (s, 2H), 6.77 (s, 1H), 6.68 – 6.63 (m, 1H), 6.34 (d, J = 8.5 Hz, 1H), 5.26 (s, 1H), 5.03 (s, 1H), 4.51 (s, 2H), 3.37 – 3.35 (m, 2H), 2.95 – 2.93 (m, 2H), 2.76 (t, J = 6.2 Hz, 2H), 2.54 – 2.48 (m, 1H), 2.45 – 2.41 (m, 1H), 2.34 – 2.30 (m, 1H), 2.18 – 2.12 (m, 1H), 2.06 – 1.97 (m, 4H), 1.66 – 1.63 (m, 1H), 1.62 (d, J = 2.9 Hz, 1H), 1.59 – 1.56 (m, 3H), 1.55 – 1.52 (m, 2H), 1.36 (s, 18H), 0.92 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 220.9, 165.5, 152.0, 149.0, 145.90, 145.88, 143.6, 138.2, 137.5, 135.4, 134.9, 132.8, 130.6, 130.3, 129.5, 128.4, 128.1, 128.0, 126.9, 126.6, 126.1, 125.8, 122.3, 121.9, 119.0, 110.9, 56.2, 55.7, 50.6, 50.4, 48.1, 44.4, 38.2, 36.0, 34.5, 31.7, 30.5, 29.6, 28.3, 26.5, 26.0, 22.7, 21.8, 14.0.HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{56}H_{64}NO_4$: 814.4830; found: 814.4824.

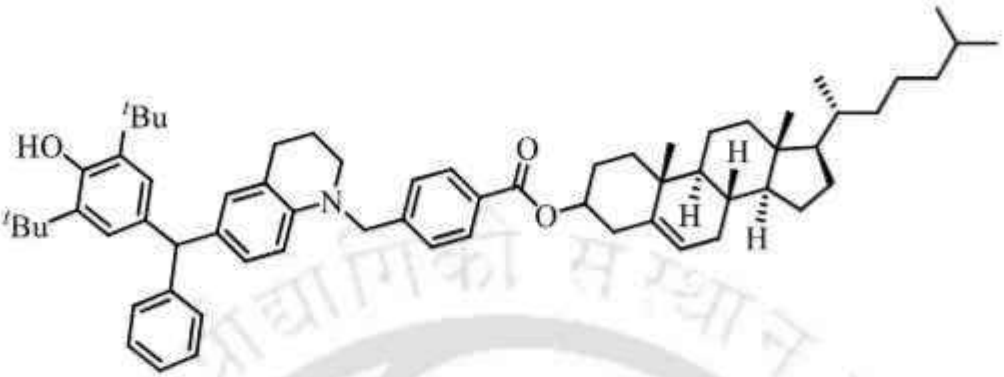
2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl) chroman-6-yl 2-(4-((6-((3,5-di-*tert*-butyl-4-hydroxyphenyl) (phenyl)methyl)-3,4-dihydroquinolin-1(2H)-yl) methyl) phenoxy) acetate (3.24h)



By following the **GP-1**, the title compound **3.24h** was isolated as dark-red liquid (0.814 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.68). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.19 (m, 3H), 7.15 – 7.10 (m, 4H), 6.94 – 6.93 (m, 4H), 6.76 (s, 1H), 6.68 (d, J = 8.5 Hz, 1H), 6.44 (d, J = 8.5 Hz, 1H), 5.27 (s, 1H), 5.02 (s, 1H), 4.90 (s, 2H), 4.37 (s, 2H), 3.31 – 3.25 (m, 2H), 2.72 (t, J = 6.0 Hz, 2H), 2.57 (t, J = 6.4 Hz, 2H), 2.07 (s, 3H), 1.99 (s, 3H), 1.97 – 1.95 (m, 4H), 1.83 – 1.71 (m, 3H), 1.58 – 1.48 (m, 4H), 1.38 – 1.31 (m, 22H), 1.28 – 1.22 (m, 11H), 1.16 – 1.06 (m, 6H), 0.87 – 0.84 (m, 12H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.1, 156.9, 152.0, 149.8, 146.0, 144.0, 140.0, 135.4, 135.0, 132.7, 132.3, 130.2, 129.5, 128.2, 128.1, 128.0, 126.7, 126.1, 125.8, 124.9, 123.4, 122.2, 117.7, 115.0, 111.0, 75.3, 65.5, 56.2, 54.9, 49.8, 39.5, 37.69, 37.67, 37.6, 37.55, 37.53, 37.51, 37.48, 37.43, 34.5, 32.93, 32.91, 32.85, 32.82, 30.5, 28.4, 28.1, 24.9, 24.6, 22.9, 22.8, 22.6, 21.2, 20.7, 19.9, 19.83, 19.80, 19.77, 19.7, 13.1, 12.3, 11.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{68}H_{94}NO_5$:1004.7127; found:1004.7129.

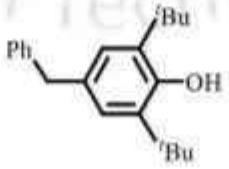
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(8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-((6-((3,5-di-*tert*-butyl-4-hydroxyphenyl) (phenyl)methyl)-3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (3.24i)



By following the **GP-1**, the title compound **3.24i** was isolated as dark-red liquid (0.819 g, 88%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.68). ^{1}H NMR (500 MHz, CDcl$_3$): δ 7.97 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.25 – 7.22 (m, 2H), 7.15 (d, J = 7.3 Hz, 1H), 7.11 (d, J = 7.4 Hz, 2H), 6.91 (s, 2H), 6.76 (s, 1H), 6.63 (d, J = 8.2 Hz, 1H), 6.33 (d, J = 8.5 Hz, 1H), 5.45 – 5.38 (m, 1H), 5.26 (s, 1H), 5.02 (s, 1H), 4.84 (q, J = 12.1, 11.6 Hz, 1H), 4.47 (s, 2H), 3.37 – 3.29 (m, 2H), 2.74 (t, J = 6.1 Hz, 2H), 2.44 (d, J = 7.7 Hz, 2H), 2.03 – 1.94 (m, 5H), 1.91 (d, J = 13.5 Hz, 1H), 1.86 (s, 1H), 1.75 – 1.67 (m, 1H), 1.57 (d, J = 17.1 Hz, 3H), 1.54 – 1.50 (m, 2H), 1.47 (d, J = 13.5 Hz, 2H), 1.35 (s, 20H), 1.26 (t, J = 12.0 Hz, 2H), 1.22 – 1.18 (m, 1H), 1.17 – 0.95 (m, 11H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (dd, J = 6.6, 2.1 Hz, 6H), 0.69 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$): δ 166.0, 152.0, 145.9, 144.8, 143.7, 139.8, 135.4, 134.9, 132.6, 130.2, 130.0, 129.6, 129.5, 128.1, 128.0, 126.7, 126.1, 125.8, 122.9, 122.2, 110.9, 74.6, 56.9, 56.3, 56.2, 55.6, 50.3, 50.2, 42.5, 39.9, 39.7, 38.4, 37.2, 36.8, 36.3, 36.0, 34.5, 32.1, 32.0, 30.5, 28.4, 28.3, 28.2, 28.0, 24.4, 24.0, 23.0, 22.72, 22.66, 21.2, 19.5, 18.9, 12.0. HRMS (ESI) *m/z*: [M+H]$^+$ calculated for: $C_{65}H_{88}NO_3$:930.6759; found: 930.6758.

4-benzyl-2,6-di-*tert*-butylphenol (3.1a')[34]:



Light yellow solid (0.092 g, 31%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.29 – 7.26 (m, 2H), 7.22 – 7.16 (m, 3H), 6.98 (s, 2H), 5.05 (s, 1H), 3.90 (s, 2H), 1.40 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$): δ 152.2, 141.9, 136.0, 131.7, 129.0, 128.5, 126.0, 125.6, 42.0, 34.4, 30.5. Spectral data is in accordance to the reported literature.[34]

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3.7. References

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Chapter 4

Reductive alkylation of azoarenes to N-alkylated hydrazines under mild conditions

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4.1. Introduction

Hydrazine derivatives are widely used compounds in the pharmaceutical, agrochemical, and polymer industries and are also found as important building blocks in organic synthesis, such as in the preparation of nonsteroidal anti-inflammatory drugs.[1] Further, they were shown to be effective for the treatment of tuberculosis, Parkinson's disease and hypertension. Hydrazine-based peptidomimetics (azapeptides) were also found as potent agents against diseases such as hepatitis, AIDS, and SARS, Additionally, they can be aligned to synthesize a diamine-based polyimide monomer. Polyimides, typically synthesized from aromatic dianhydrides and diamines, are widely utilized in electronic, information, and optical material applications.[2] Few selected examples are listed in Figure 4.1. Nevertheless, synthesis of target-based *N*-alkyl-*N*,*N*′-diarylhydrazines is difficult, which seriously restricts their bioactivity and application research.

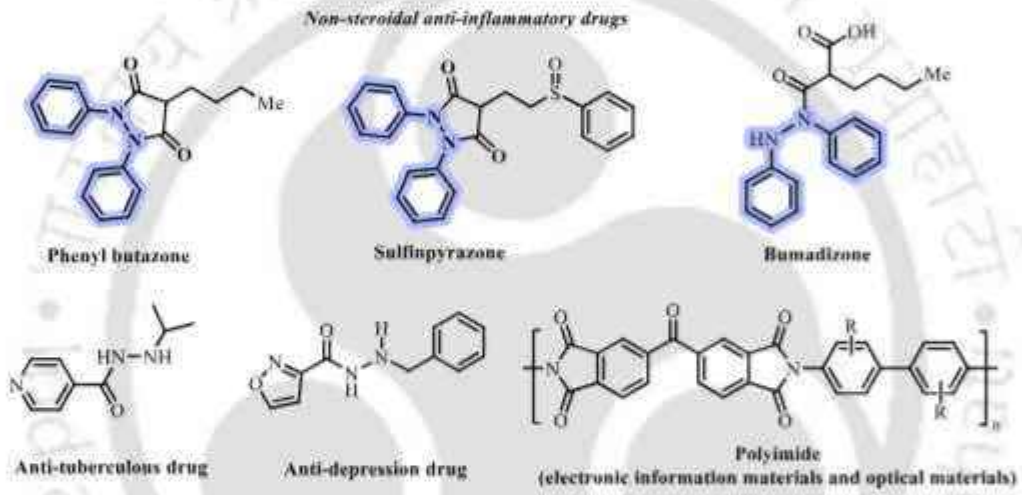


Figure 4.1. Representation of bioactive compounds with hydrazine derivatives.

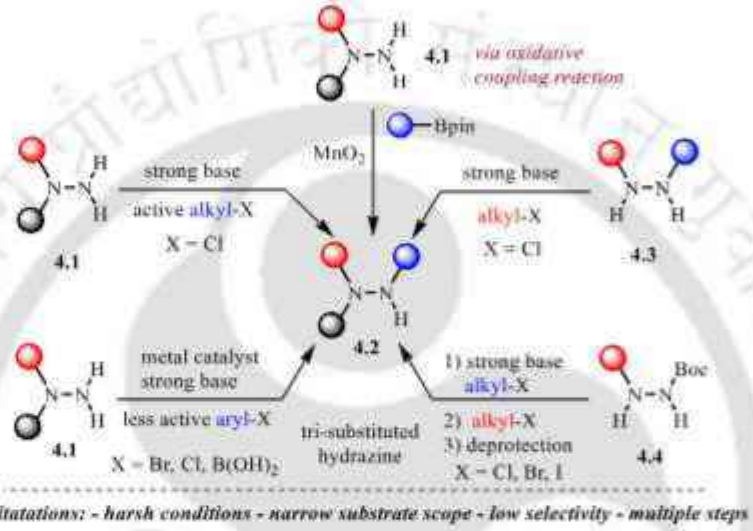
Besides their biological activity, they are being used for the derivatization of nanostructures to enhance specific functions.[3] Substituted hydrazines are also frequently applied in the study of single electron transfer reactions and as charge transfer quenchers of singlet oxygen.[4] They also have useful synthetic applications in the synthesis of nitrogen-containing compounds and coupling reactions.[5] Given their importance and usefulness, a significant research effort has been devoted towards the development of effective synthetic methodologies for the construction of hydrazine derivatives.

The trisubstituted hydrazine derivatives are difficult to prepare despite their appealing structural simplicity. The synthetic challenge may arise from either the similar reactivity or the relatively low activity of the two nitrogen atoms in a hydrazine precursor.[6] The former would lead to severe regioselectivity issues while the latter would require harsh reaction conditions. It is challenging to precisely prepare the target-based *N*-alkyl-*N*,*N*′-diarylhydrazines.

When *N*,*N*-disubstituted hydrazine **4.1** is used as a precursor, its substitution reaction with highly active alkyl halides along with a strong base to prepare *N*′-alkyl trisubstituted hydrazine

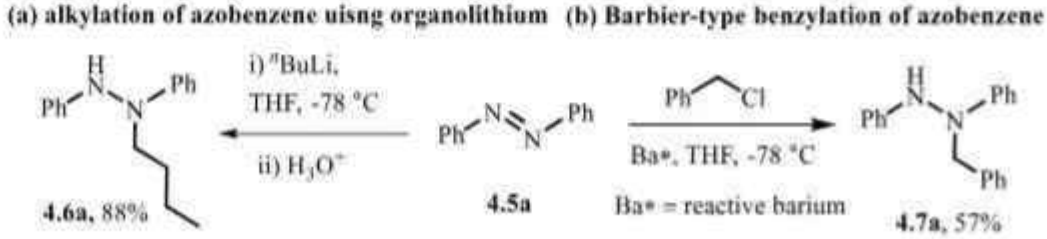
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4.2 (Scheme 4.1).[7] Furthermore, the use of metal catalyst and relatively high temperature are essential for the synthesis of the corresponding *N'*-aryl trisubstituted hydrazines **4.2**.[8] On the other hand, when *N,N'*-disubstituted hydrazines **4.3** are used as the precursor, the reaction proceed unselectively as well as side products of fully substituted hydrazines.[6a] In recent study, various hydrazide precursors **4.4** also have been employed as precursors based on the orthogonal protective group strategy. Although there are certain specific advantages but require additional steps (protection and deprotection) to afford the targeted trisubstituted hydrazine.[6b,9] Nevertheless, reported methodology are limited to the formation of hydrazines with specific substituents, and only very few of these methods are truly general and can be carried out under mild conditions.[10]



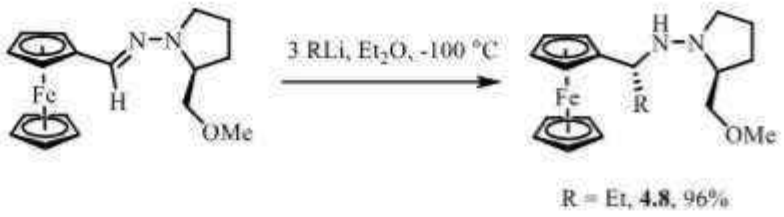
Scheme 4.1. Synthesis of trisubstituted hydrazine from disubstituted hydrazine *via* substitution reactions or metal-catalyzed reactions or oxidative coupling reaction.

The direct N=N functionalization of azobenzenes is alternative synthetic approaches to obtain *N,N'*-diaryl hydrazine derivatives. Unlike highly reactive alkyl azodicarboxylates with a strongly electrophilic N=N double bond, azobenzenes typically exist in a stable and nonpolar trans form, showing low N=N bond reactivity.[11] Early study was attempted with the addition of organolithium or organobarium to the N=N bond of an azobenzene however, it is limited by the type and accessibility of the nucleophiles (Scheme 4.2).[12] The electrophilic aminations of amines, additions of organometallic reagents to hydrazines (Scheme 4.3), and oxidative coupling reaction of hydrazines with boronic ester are also mentioned (Scheme 4.1).[10,13]



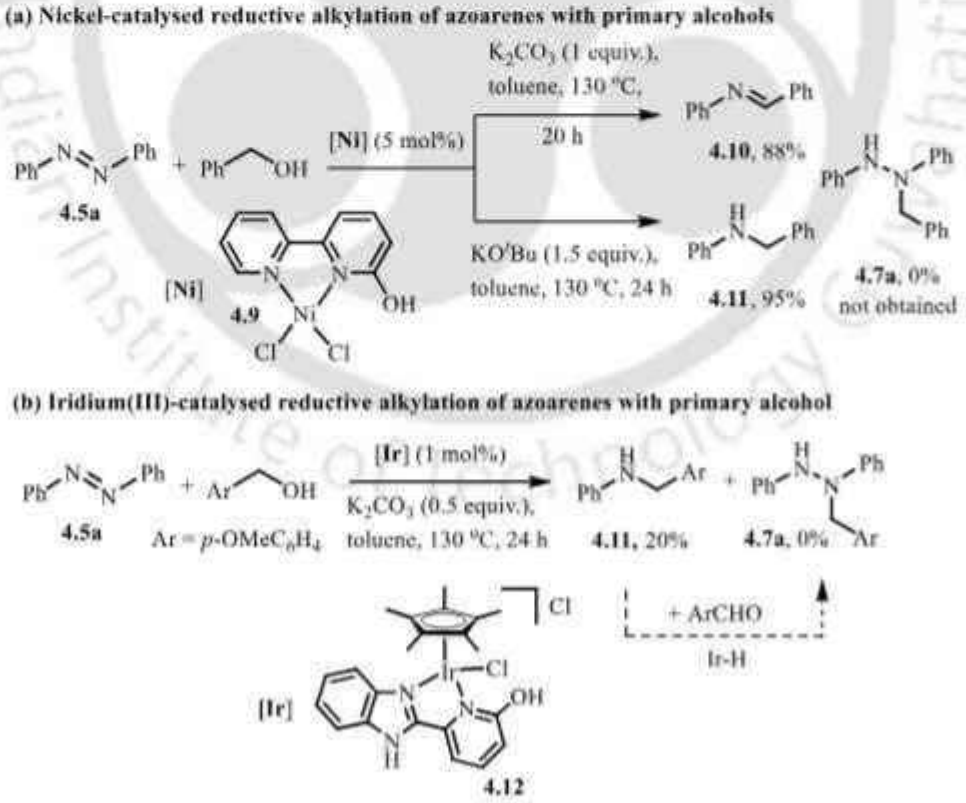
Scheme 4.2. Alkylation of azobenzene using organolithium or organobarium compounds.

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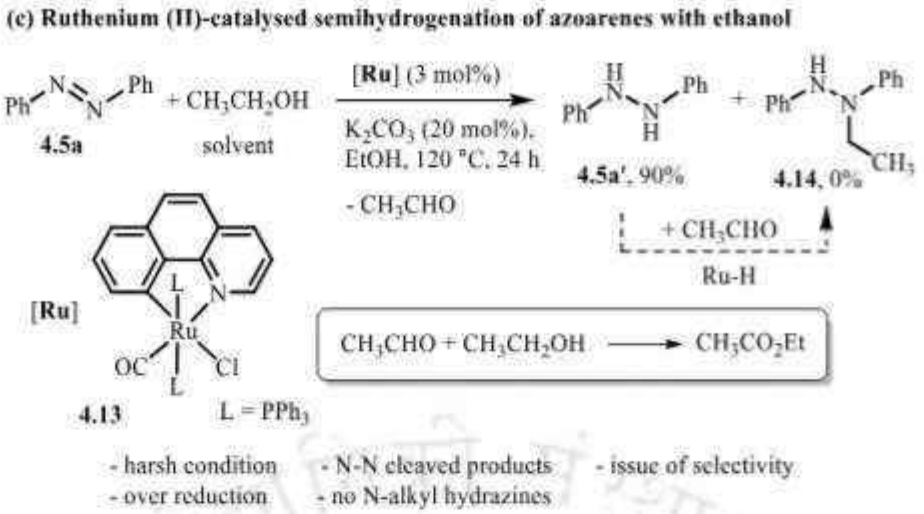


Scheme 4.3. Alkylation of hydrazones using organolithium compounds.

Later, various transition-metal catalysed reductive alkylation of azoarenes with primary alcohols is attempted (Scheme 4.4). In 2023, Punji and co-workers reported (de)hydrogenative coupling of azoarenes with benzyl alcohols by (6-OH-bpy)$NiCl_2$ catalyst **4.9** (Scheme 4.4a).[14] The employment of a K_2CO_3 base provided secondary imines, whereas secondary amines were obtained in the presence of KO^{t}Bu. Method showed the promising selectivity based on the different base. However, over-reduction of azoarene to amine/imine derivative renders the process less efficient for the synthesis of *N*-alkylated hydrazine. Kundu group described reductive alkylation of azobenzene with primary alcohols using Ir(III)-based cooperative catalyst **4.12** (Scheme 4.4b). The reaction afforded monoalkylated aniline **4.11** with poor yield, no *N*-alkylated hydrazine is obtained.[15] Very recently, Xu group attempted alkylation of azobenzene with ethanol as alkylating agent in the presence of a bidentate Ru(II)-NC catalyst **4.13** (Scheme 4.4c). Unlike *N*-alkylated hydrazine product **4.14**, hydrazoarene is obtained *via* Meerwein-Ponndorf-Verley mechanism and the by-product is ethyl acetate.[16]



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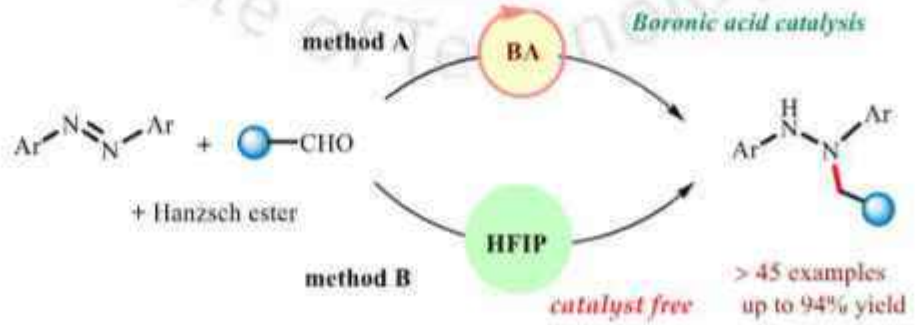


Scheme 4.4. Transition metal-catalysed reductive alkylation of azoarenes with primary alcohol.

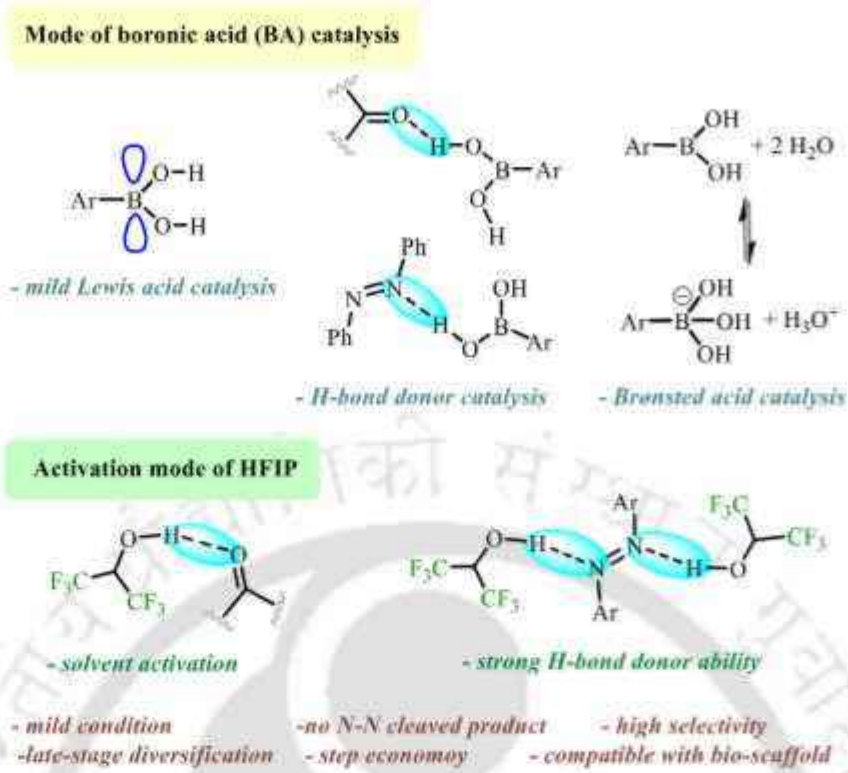
Overall, transition metal-catalysed alkylation of azoarene with alcohols leads to the formation of N-N cleaved products and failed to obtain *N*-alkylated 1,2-diarylhydrazines. The methods require harsh reaction conditions, and lack of tolerance with hydrogenation-sensitive functional groups. Therefore, I am interested to develop a mild and efficient catalytic method for the construction of *N*-alkyl-*N*,*N*'-diarylhydrazine with a wide scope of substrates.

4.2. Present work

In this chapter, I have developed new and efficient methods for constructing *N*-alkyl-*N*, *N*'-diarylhydrazines by arylboronic acid-catalyzed one-pot tandem reduction of azoarene to hydrazoarene followed by reductive alkylation by the aldehyde (method A). Owing to the use of mild reaction conditions, method is completely suppressed *N-N* cleaved product amines and/or imines and selectively provided trisubstituted hydrazine derivatives. The similar transformation can also be achieved by hexafluoroisopropanol (HFIP) under catalyst-free conditions (method B).



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Scheme 4.5. Synthesis of *N*-alkyl-*N, N'*-diarylhydrazines *via* reductive alkylation of azoarenes with aldehyde.

4.3. Results and discussion

4.3.1. Optimization of reaction conditions for *N*-alkylated trisubstituted hydrazine

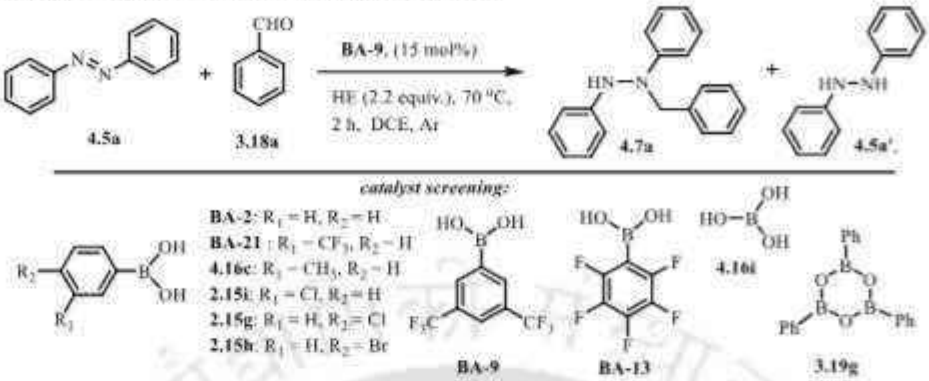
For method A:

optimization studies were initiated with azobenzene (**4.5a**), benzaldehyde (**3.18a**), Hantzsch ester (HE) (2.2 equiv.) and 15 mol% of phenylboronic acid (**BA-2**) in DCE at 70 °C. Gratifyingly, after 2 h, the desired *N*-alkylated product **4.7a** was obtained in 58% yield, along with 32% intermediate hydrogenated product hydrazobenzene (**4.5a'**, Table 4.1, entry 1). To improve the yield of the desired product **4.7a**, arylboronic acids with different substituents (**BA**, **2.15**, **4.16**) were examined (entries 2-10).[17] Boronic acids **BA-9** and **4.16h** with electron-withdrawing $-CF_3$ and –F group, respectively, have been found to be the best catalysts for the current transformation with the product **4.7a** obtained in 91% yield in both the cases (entries 7 and 8). Next, I examine the reaction by replacing boron-based catalysts with transition-metal catalysts such as AgOTf and $FeCl_3$ (entries 11 and 12). The use of AgOTf provided the product **4.7a** in 28% yield, along with intermediate hydrogenated product hydrazobenzene **4.5a'** (31%). $FeCl_3$ has failed to catalyze this transformation. Brønsted acids such as oxalic acid, *p*-TsOH, pyridinium *p*-toluenesulfonate, and AcOH provided the product **4.7a** in low yield (entry 13). Next, the reaction was examined with readily available reductants such as Et_3SiH, HBpin, and HCO_2H under identical reaction conditions (entry 14). However, the desired product **4.7a** was not obtained. This suggests that Hantzsch ester was found to be a suitable reductant for the

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current catalytic reaction. **BA-9** has been opted as the suitable catalyst for exploring the substrate scope of this reaction.

Table 4.1. Optimization of reaction conditions[a]



entry	deviation from above	yield of **4.7a** (%)
1	**BA-2**	58%, (32% of **4.5a'**)
2	**BA-21**	74%
3	**4.16c**	52%
4	**2.15i**	62%[b]
5	**2.15g**	60%[b]
6	**2.15h**	61%
7	none	91%, 71%,[b,c] 12%,[d] 82%[e], [0%][f]
8	**BA-13**	91%
9	**4.16i**	10%
10	**3.19g**	42%
11	AgOTf	28%, (31% of **4.5a'**)
12	$FeCl_3$	0%
13	Brønsted acid	23%,[g] 9%,[h] 12%,[i] 15%[j]
14	Reductant (Et_3SiH, HBpin and HCO_2H)	0%

[a]Reaction conditions: **4.5a** (0.5 mmol), **3.18a** (0.5 mmol), HE (2.2 equiv.), **BA**, **2.15**, **3.19**, **4.16** (15 mol%) in DCE (2 mL) at 70 °C for 2 h under Ar, isolated yields. [b]the same has been repeated three times, average data is given. [c]with 4 Å M.S. [d]at 45 °C. [e]at 90 °C. [f]no catalyst. [g]with oxalic acid. [h]with *p*-TsOH. [i]with pyridinium *p*-toluenesulfonate. [j]with AcOH.

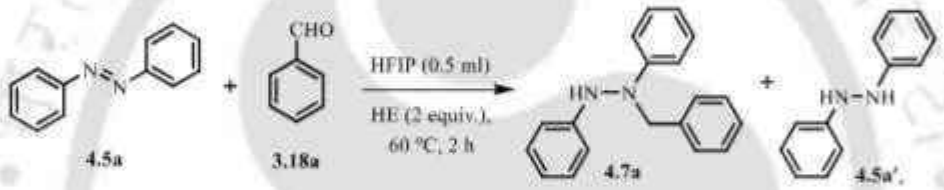
For method B:

Herein, I envisaged that the strong H-bond donor properties of HFIP can not only aid in the hydrogenation of azoarenes to hydrazoarenes but also in the reductive *N*-alkylation of the resulting *N*-alkylated hydrazine product. The study was initiated with the reaction of

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azobenzene (**4.5a**, 0.5 mmol), benzaldehyde (**3.18a**, 0.5 mmol), Hantzsch ester (HE) (1 mmol) in HFIP (0.1 ml) at 60 °C. After 2 h, *N*-alkylated hydrazine **4.7a** was obtained in 22% yield, along with 32% intermediate hydrogenated product hydrazobenzene (**4.5a'**, Table 4.2, entry 1). To improve the yield of desired product **4.7a**, equivalency of HFIP was gradually increased (entry 2). When HFIP was used in 0.5 ml, product **4.7a** was obtained in 92% yield (entry 3). A decrease in the yield of **4.7a** has been observed when the reaction was examined with a mixture of solvents (entries 4-6). The yield of **4.7a** was also decreased by reducing the reaction time (entry 7) or by reducing the reaction temperature (entry 8). Then, reaction was examined with $-CF_3$ functionalized thiourea as hydrogen-bond donor catalyst in DCE, provided the product **4.7a** in 60% yield, indicating hydrogen-bonding donor property important in this transformation (entry 9). I have examined the reaction by replacing HFIP with a relatively weak hydrogen bond donor solvent, isopropanol which failed to provide any desired product (entry 10). This reiterates the significance of the role of HFIP in the current transformation as strong H-bond donor solvent.

Table 4.2. Optimization of reaction conditions



entry	deviation from above	yield of **4.7a** (%)
1	HFIP (0.1 ml)	22%, (32% of **4.5a'**)
2	HFIP (0.2 ml, 0.3 ml, 0.4 ml)	41%, 65%, 81%
3	none	92%
4	HFIP: DCE (1:3, 0.5 ml)	25%
5	HFIP:CH_3OH (1:3, 0.5 ml)	21%
6	HFIP: toluene (1:3, 0.5 ml)	18%
7	with 0.5 h, 1 h, 1.5 h	26%, 48%, 74%
8	at 25 °C, at 45 °C	0%, 14%
9[b]	with HBD catalyst (**3.19f**)	60%
10	with isopropanol (0.5 ml)	0%

[a]Reaction conditions: **4.5a** (0.5 mmol), **3.18a** (0.5 mmol), HE (1 mmol) in HFIP (0.5 mL) at 60 °C for 2 h under Ar, isolated yields. [b]with HBD catalyst 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea **3.19f** (15 mol%) in DCE (0.5 ml).

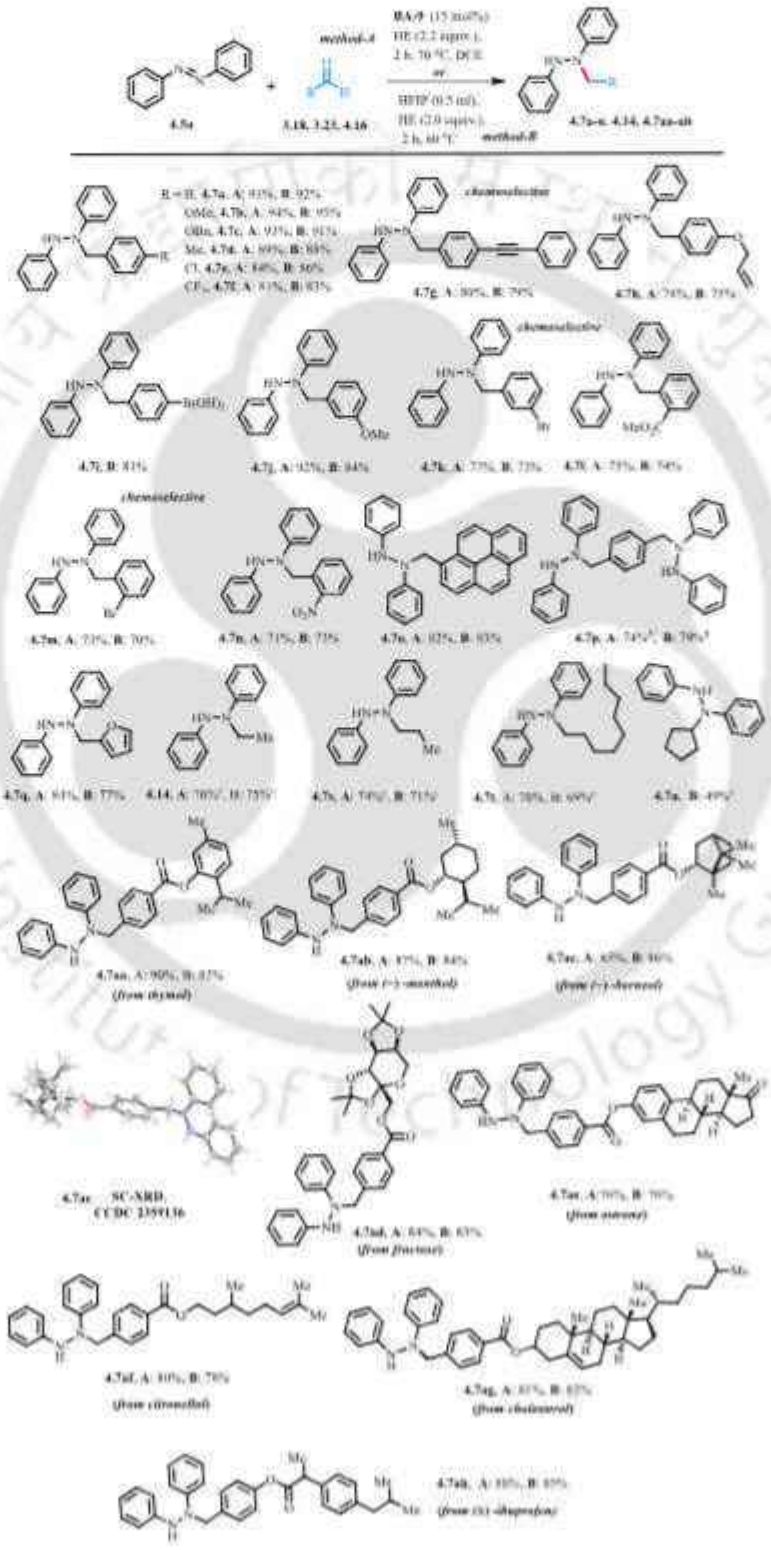
4.3.2. Substrate scope *N*-alkyl-*N*,*N'*-diarylhydrazines

I next intended to explore the scope of the *N*-alkylation reaction with a variety of aldehydes **3.18, 4.16** using **4.5a** as the standard substrate (Table 4.3). Both the methods (method A and method B) have been employed in the scope of the reaction. The substrates having both electron-donating (e.g., -Me, -OMe, -OBn) and electron-withdrawing groups (e.g., -Cl, $-CF_3$) at the *para*-position in the aryl moiety were efficiently reacted to obtain the desired products

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4.7a-4.7f in excellent yields. Slightly higher yields were realized for electron-donating groups. With boronic acid containing aldehyde, the desired product **4.7i** was formed with good yield. Since, the present reaction condition tolerates the $-B(OH)_2$ group functional groups, it can be useful for further functionalization in Pd-catalyzed Suzuki-Miyaura cross-coupling reaction.

Table 4.3. Substrate scope of carbonyls with azobenzene[a]

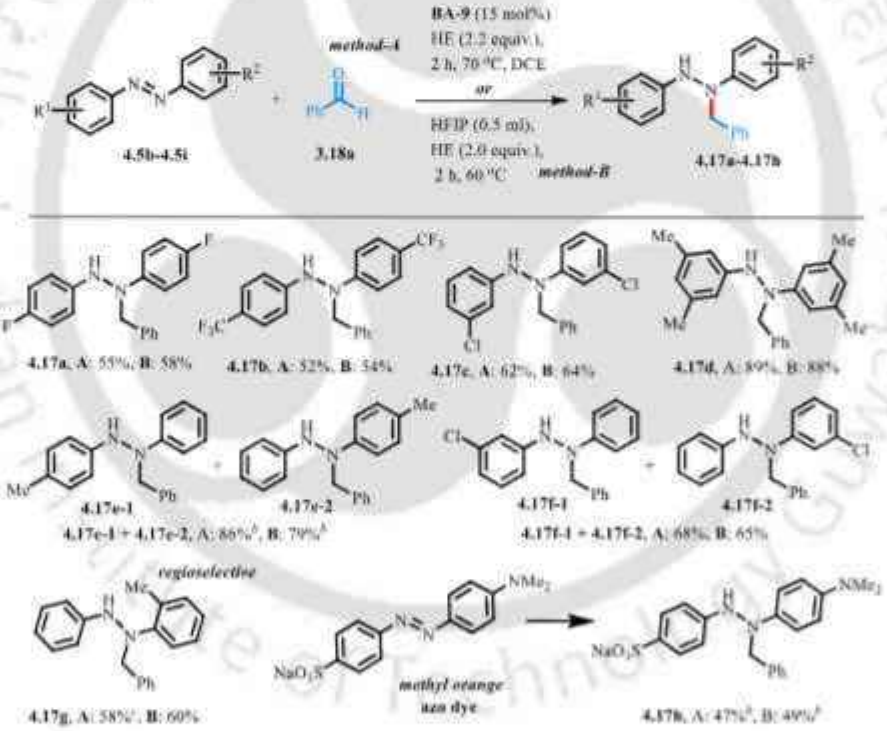


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[a]Reaction conditions: ***method A***: **4.5a** (1.0 equiv.), aldehyde **3.18**, **3.23**, **4.16** (1.0 equiv.), **BA-9** (15 mol%), HE (2.2 equiv.) in DCE (2 mL), at 70 °C for 2 h, isolated yields. [b]with 0.25 mmol of terephthalaldehyde, HE (4.2 equiv.) in DCE (2 mL). [c]with 0.25 mmol scale. ***method B***: **4.5a** (1.0 equiv.), aldehyde or ketone **3.18**, **4.16** (1.0 equiv.), HE (2.0 equiv.), HFIP (0.5 mL), at 60 °C for 2 h, isolated yields.[b]with 0.25 mmol of terephthalaldehyde, HE (4 equiv.). [c]0.25 mmol scale.

Further, *meta*-and *ortho*-substituent bearing aldehyde afforded the corresponding hydrazine products **4.7j-4.7k**, **4.7l-4.7n** in moderate to good yields. Notably, the retention of reducible-functional groups (4-Cl, 4-OBn, 4-CF_3, 4-C≡CPh, 4-O-allyl, 3-Br, 2-Br, 2-CO_2Me, 2-NO_2) in the final products showcases the excellent chemoselectivity of the present reductive protocol. Interestingly, 1-pyrene aldehyde led to the product **4.7o** in good yields. When 1,4-benzenedialdehyde was used as an alkylating agent the poly *N*-alkylated hydrazine **4.7p** was readily obtained with notable selectivity. Besides aromatic aldehydes, scope of the reaction was expanded to heteroaromatic aldehyde and a variety of aliphatic aldehydes yielding **4.7q**, **4.14**, **4.7s-t**. The cyclic ketone afforded the product **4.7u** in 49% yield using method B.

Table 4.4 Substrate scope of azobenzene[a]



[a]Reaction condition: ***method A:*** **4.5b-i** (0.5 mmol), **3.18a** (0.5 mmol), **BA-9** (15 mol%), HE (2.2 equiv.) in DCE (2 mL), at 70 °C for 2 h, isolated yields. [b] with 0.25 mmol. [c] along with **4.5h** (21%) recovered. ***method B***: **4.5b-i** (0.5 mmol), **3.18a** (0.5 mmol), HE (1 mmol), HFIP (0.5 mL), at 60 °C for 2 h, isolated yields. [b]0.25 mmol scale. [d]with HE (3.2 equiv.). [c] along with **4.5h** (25%) recovered.

Considering the efficiency of the present protocol, scope of the reaction was further expanded using highly functionalized substrates with complex molecular settings. A range of

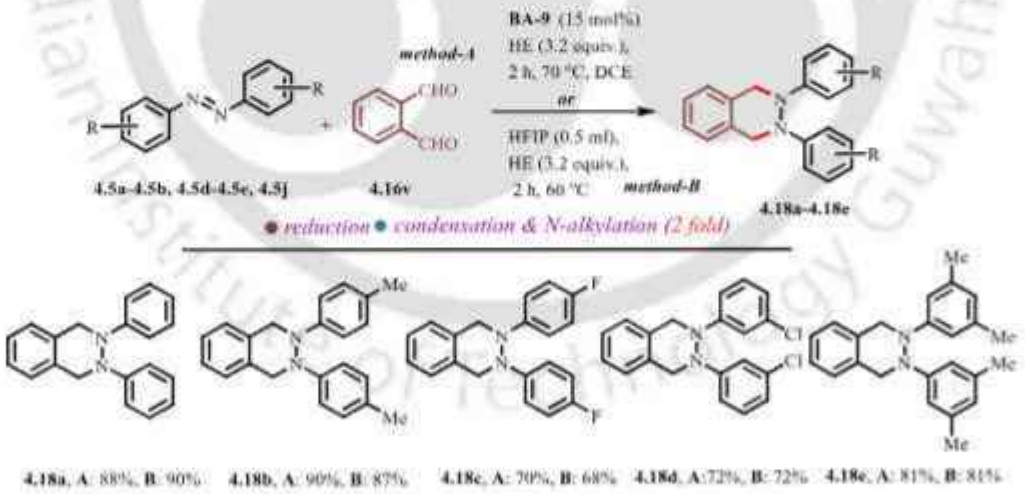
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biologically relevant motifs (BRM) were tested and were independently subjected to the optimized reaction conditions, afforded corresponding hydrazine derivatives containing thymol (**4.7aa**, 82%), (-)-menthol (**4.7ab**, 84%), (-)-borneol (**4.7ac**, 86%), fructose (**4.7ad**, 83%), estrone (**4.7ae**, 76%), citronellol (**4.7af**, 78%), cholesterol (**4.7ag**, 83%), (±)-ibuprofen (**4.7ah**, 85%) moiety. The structure of the product **4.7ac** was further confirmed by single-crystal X-ray diffraction analyses. This suggests that there is no any structural (chemical and stereochemical) changes of the complex architecture in the entity.

To further broaden the substrate scope, the reaction was examined with substituted azobenzene **4.5b-4.5e** while keeping aldehyde **3.18a** as the standard substrate (Table 4.4). A series of symmetrical azobenzenes having *p*-F (**4.5b**), *p*-CF_3 (**4.5c**), *m*-Cl (**4.5d**) and *m*, *m'*-$(CH_3)_2$ (**4.5e**) all efficiently provided the corresponding alkylated products **4.17a-4.17d** in good to excellent yields. Later, unsymmetrical azobenzenes such as 1-phenyl-2-(*p*-tolyl)diazene (**4.5f**) and 1-(3-chlorophenyl)-2-phenyldiazene (**4.5g**) provided an inseparable mixture of the alkylated products **4.17e**, **4.17f** respectively, whereas *ortho*-substituted azobenzene afforded a single regioisomeric product **4.17g**. The methodology was further extended to commercially used azo dye such as methyl orange, obtaining *N*-alkylated product **4.17h**.

It is worth mentioning that when the reaction was examined with phthalaldehyde **4.16v** under the identical reaction conditions, tetrahydrophthalazine derivatives **4.18a-4.18e** were obtained in good yield (Table 4.5), which are widely utilized in pharmaceutical research.[17]

Table 4.5. Scope of azobenzenes with benzene-1,2-dicarbaldehyde[a]

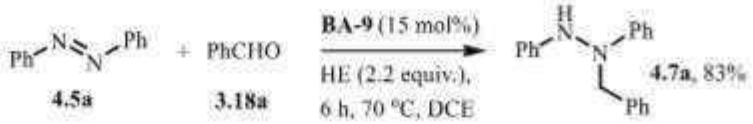


[a]Reaction condition: ***method A***: **4.5** (0.5 mmol), **4.16v** (0.5 mmol), **BA-9** (15 mol%), HE (3.2 equiv.) in DCE (2 mL), at 70 °C for 2 h, isolated yields. ***method B***: **4.5** (0.5 mmol), **4.16v** (0.5 mmol), HE (3.2 equiv.), HFIP (0.5 mL), at 60 °C for 2 h, isolated yields.

4.3.3. Scale-up reaction

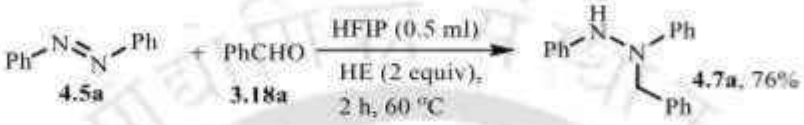
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To understand the efficiency of this process, gram-scale reaction was performed for bulk utilization. The use of 1-gram azobenzene **4.5a** afforded the desired *N*-alkylated product **4.7a** in 83% yield (Scheme 4.6) (method A).



Scheme 4.6. Gram-scale reaction.

Using method B, 2 mmol of azobenzene **4.5a** afforded the *N*-alkylated product **4.7a** in 76% yield (Scheme 4.7)

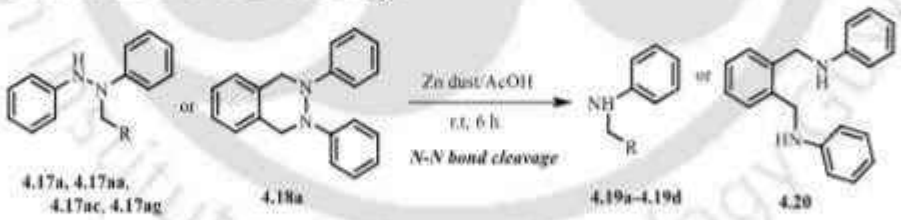


Scheme 4.7. 2 mmol-scale reaction.

4.3.4. Post-synthetic modifications

i) Reductive N-N bond cleavage of various hydrazine derivatives

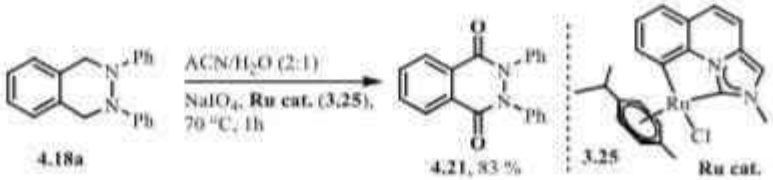
For the downstream purpose, the synthesized molecules can be easily transformed into useful molecules (Scheme 4.8). For example, the N-N bond cleavage of various hydrazine derivatives **4.17a**, **4.17aa**, **4.17ac**, **4.17ag** proceeded smoothly using Zn in AcOH, delivering the secondary amine **6a-6d** in moderate to good yield. It is worth mentioning that the current reductive approach applies to the synthesis of the secondary amines **4.19a-4.19d** with complex molecular settings. Compound **4.18a** can also be easily transformed into CXCR4 antagonist 712[18] (87% yield) *via* the reductive N-N bond cleavage.



Scheme 4.8. Reductive N-N bond cleavage of various hydrazine derivatives.

ii) *α*-methylene oxidation of compound 4.18a

Further, compound **4.18a** was converted to 2, 3-diphenyl-2, 3-dihydro phthalazine-1, 4-dione **4.21** (83%) under oxidative conditions by cyclometalated ruthenium catalyst (**3.25**) and periodate (Scheme 4.9).[19]



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Scheme 4.9. α-methylene oxidation of compound **4.18a**.

4.3.5. Mechanistic investigation for method A:

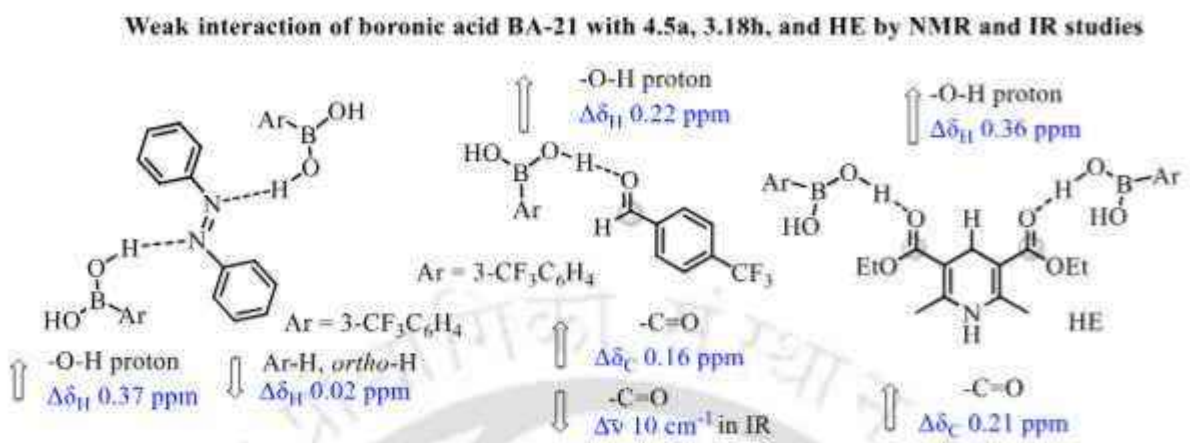
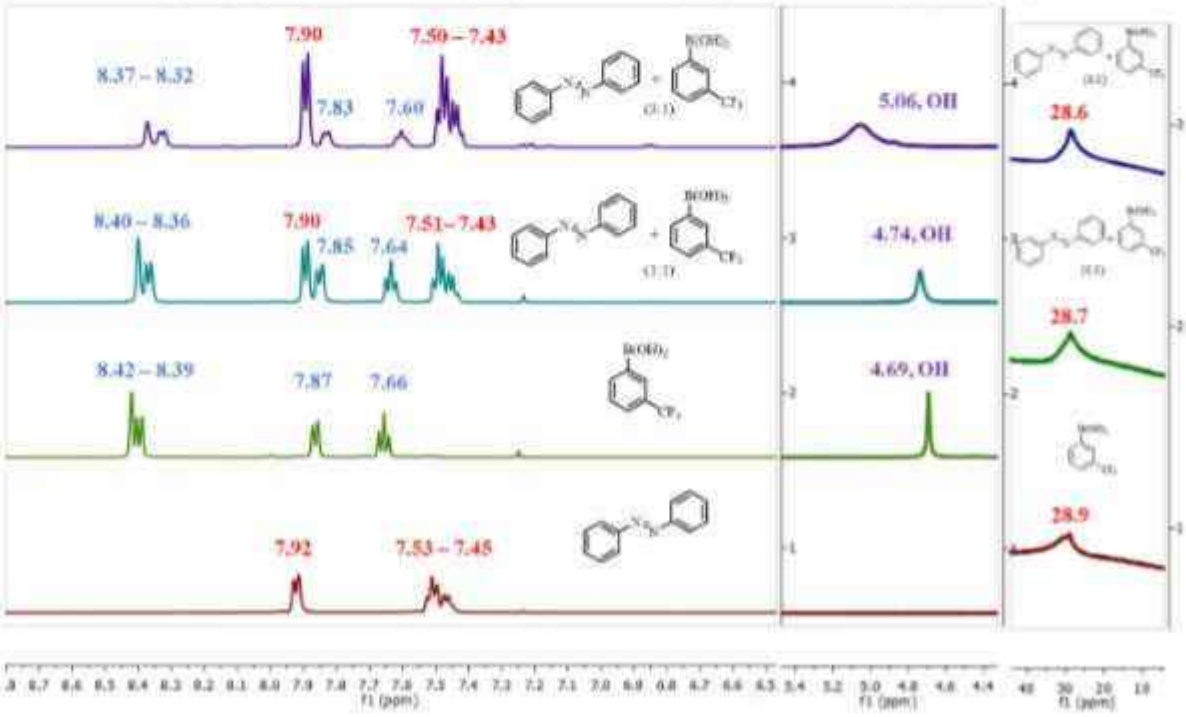


Figure 4.2. Weak interaction of boronic acid with substrate and HE.

The mechanism of the catalytic reaction was investigated with both Lewis acid[20-22] and hydrogen bonding[23] properties of boronic acid. A close inspection of the nature of the binding in solution indicates that there is a weak hydrogen bond interaction between B-OH of **BA-21** and *N*-atom of azobenzene moiety. It was proven by the ^{1}H NMR with a downfield shift (from δ = 4.69 to 5.06 ppm) of the signal of B-OH protons in **BA-21** and upfield shift of aromatic protons of boronic acid in **BA-21** on the other hand, the signals corresponding to aromatic protons in **4.5a** was shifted in the slightly upfield ($\Delta\delta$ 0.2 ppm) possibly due to n→π* transitions[24] in the B-OH to **4.5a** (Figure 4.3).



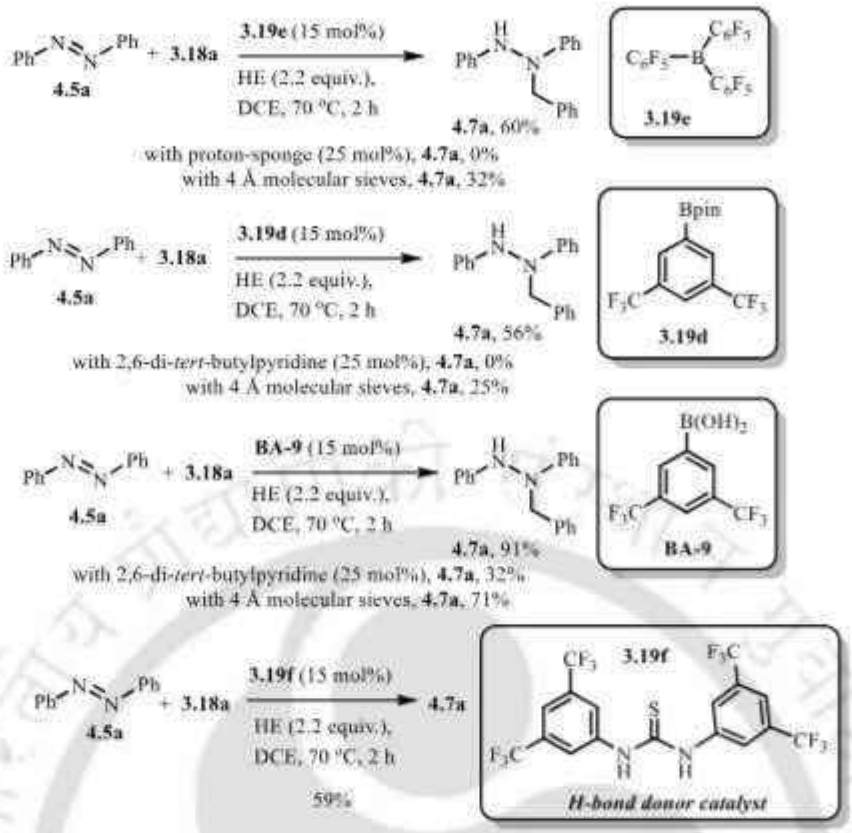
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Figure 4.3. ^{1}H, ^{11}B NMR spectra of azobenzene **4.5a** (14 mg, 0.079 mmol), 3-trifluoromethylphenylboronic acid (**2.6j**) (16 mg, 0.079 mmol), and the mixture of azobenzene **4.5a** and 3-trifluoromethylphenylboronic acid (**BA-21**) (molar ratio 1:1, 3:1) in $CDCl_3$ at 298 K.

The interaction of boronic acid with the aldehyde and carbonyl group in HE was also confirmed by NMR, and IR spectroscopic experiments. Upon addition of freshly distilled aldehyde **3.18h**, there was no change in the ^{11}B NMR, however, the hydroxyl peak of boronic acid was slightly shifted downfield by nearly 0.22 ppm in the ^{1}H NMR, and the carbonyl value moved to downfield ($\Delta\delta$ 0.16 ppm) in the corresponding ^{13}C NMR, Furthermore, the carbonyl band was shifted to the lower frequency (from 1712.4 to 1701.3 cm^{-1}) in the IR spectrum. The study suggests that there is a weak hydrogen bonding interaction of boronic acid with the aldehyde group rather than direct complexation with boron (see details in subsection 3.3.6 of chapter 3).

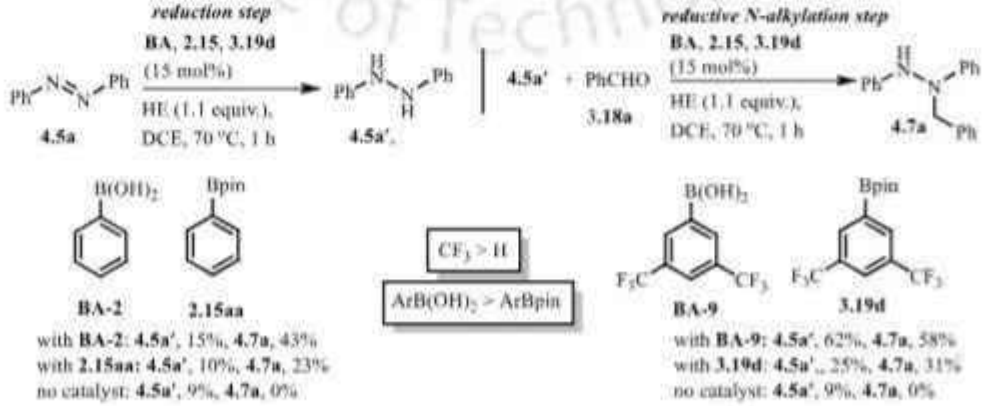
As mentioned in chapter 3, the mode of boronic acid catalysis involves three possible pathways such as (a) Lewis acid catalysis, (b) Brønsted acid catalysis, and (c) H-bond donor catalysis (see Scheme 4.10).[21, 25] When pentafluorotriphenylboron **3.19e** is used as a catalyst, product **4.7a** was obtained in 60% yield (Scheme 4.10a). To know the mode of catalysis in **3.19e**, the reaction is performed with a proton sponge (pK_a 12.1). Under the reaction conditions, no desired product **4.7a** was obtained, only **4.5a** was recovered. Further, the yield of **4.7a** was decreased in the presence of 4 Å molecular sieves, indicating the role of water in the catalysis. Strong boron Lewis acid pentafluoro-triphenylboron was known to rapidly react with adventitious water to form hydrates that are strong Brønsted acids.[26] This is likely responsible for the observed reactivity rather than Lewis acid catalysis. The bulky pyridine 2,6-di-*tert*-butylpyridine (DTBP) is then used to distinguish between Lewis and Brønsted acid catalysis in **3.19d** and **BA-9** respectively, as it does not form a complex with boron.[27] When the reaction was screened with a pinacol ester, **3.19d**, product **4.7a** was obtained in 56% yield, and in the presence of DTBP (25 mol%), no desired product **4.7a** was obtained (Scheme 4.10b). The hindered Brønsted base 2,6-di-*tert*-butylpyridine entirely inhibits the reactivity of the pinacol ester in the reaction. In addition, a decrease in the yield has been observed in the presence of 4 Å molecular sieves (**4.7a**, 25%), indicating the role of an *in-situ* generated water-mediated Bronsted acid catalysis in the presence of pinacol ester. On the other hand, the reaction was not completely shut down when boronic acid **BA-9**, was used as a catalyst in the presence of 25 mol% of DTBP (Scheme 4.10c).. The desired product **4.7a** was obtained with 32% yield. The inability of the hindered base to completely inhibit the reactivity suggests the possible involvement of H-bonding catalysis with **BA-9** However, the partial inhibition of the catalysis also indicates an alternate Bronsted acidic pathway involving the an *in-situ* generated water in the reaction. Furthermore, the reaction was performed within an authentic hydrogen-bond donor catalyst, $-CF_3$ functionalized thiourea (**3.19f**),[27] also led to the formation of the desired product **4.7a** in 59% yield (Scheme 4.10d).. Based on all these observations, it can be concluded that the mode of boronic acid catalysis involves both H-bond donor catalysis and Brønsted acid catalysis.

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Scheme 4.10. Mode of boronic acid catalysis in the alkylation of azoarene.

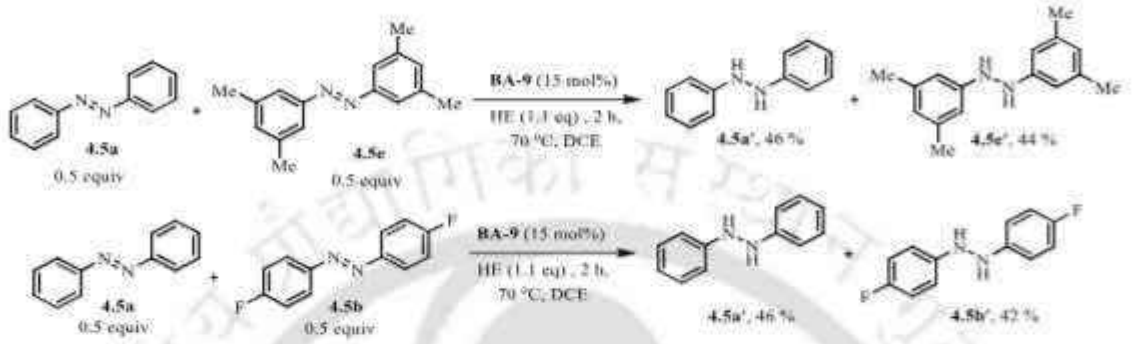
To further support the hydrogen bonding activation mode of boronic acids in the catalysis, the conversion of **4.5a** to **4.5a'** (for reduction step) and **4.5a'** to **4.7a** (for reductive *N*-alkylation step) were examined by using different electronic substituents of boronic acids (**BA-2**, **BA-9**). And for comparison, the corresponding boronic esters (**2.15aa**, **3.19d**) were also inspected (Scheme 4.11). In both the cases, catalytic activity is enhanced with electron-with-drawing substituent. In addition, the boronic acid **BA-2** and **BA-9** gave higher yields for the corresponding products **4.5a'** and **4.7a** than the boronic esters **2.15aa**, and **3.19d** (**BA-2**; **4.5a'**, 15%, **4.7a**, 43% vs **BA-2a**; **4.5a'**, 10%, **4.7a**, 23%; **BA-9**; **4.5a'**, 62%, **4.7a**, 58% *vs* **3.19d**; **4.5a'**, 25%, **4.7a**, 31%) indicating the role of hydroxyl group in the boronic acid catalysis.



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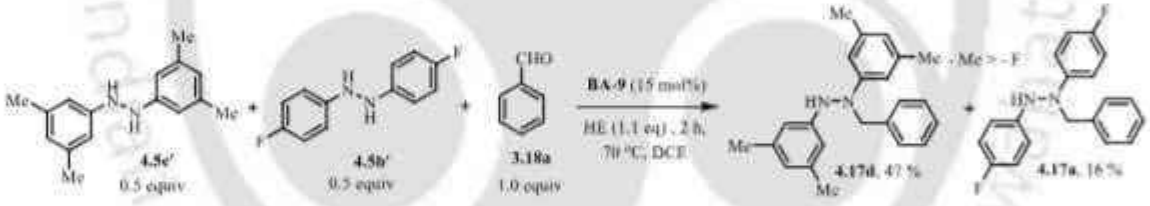
Scheme 4.11. Impact of hydrogen bonding ability and Lewis acidic properties in boronic acid catalysis.

Next, the electronic effect of the substrate on the rate of the reaction was examined (Scheme 4.12). To know the electronic effect in the 1st step, A competitive reaction suggested that the electron-donating group (Me) on the azobenzene enhanced the rate of the reaction with respect to an electron-withdrawing group (*p*-F).



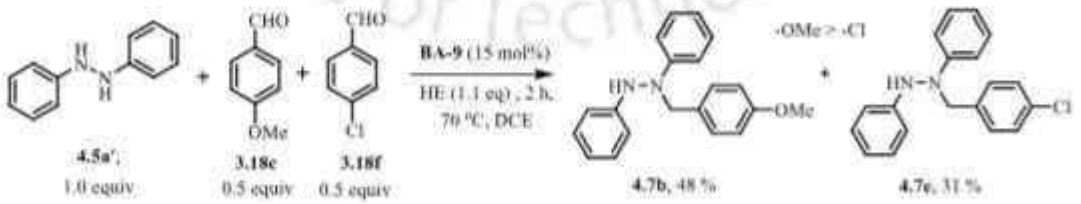
Scheme 4.12. Electronic effect of the azobenzene hydrogenation step.

To know the electronic effect in the 2nd step, at first the reaction was examined with substituted azobenzenes. A competitive reaction suggested that the electron-donating group (Me) on the hydrazobenzene enhanced the rate of the reaction with respect to an electron-withdrawing group (*p*-F) (Scheme 4.13).



Scheme 4.13. Competitive reaction with substituted azobenzene.

Likewise, competitive reaction with aldehyde suggested that electron-donating group (*p*-OMe) on the benzaldehyde enhanced the rate of the reaction with respect to an electron-withdrawing group (*p*-Cl) (Scheme 4.14).

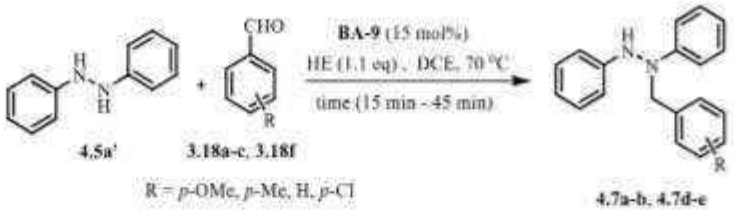


Scheme 4.14. Competitive reaction with aldehyde.

Furthermore, I have examined the kinetic Hammett correlation study using various *para*-substituted benzaldehydes under standard reaction conditions (Scheme 4.15). The reaction rates are in the order OMe>Me>H>Cl. The least-squares fit to the plot of [$\log(k_X/k_H)$] *vs.* Hammett σ^+ constant gave a straight line with a ρ^+ value of -0.86. A negative ρ^+ value suggests

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that in the transition state, electrons are flowing away, which is stabilised by the electron-donating substituents.



Scheme 4.15. Kinetic Hammett studies.

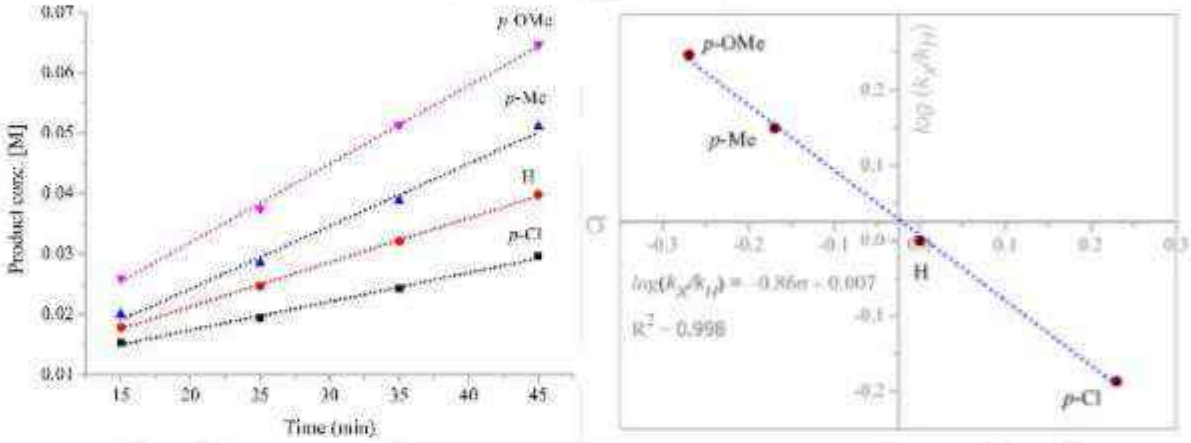
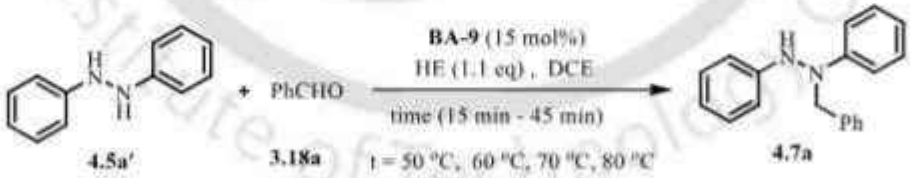


Figure 4.4. Concentration [Product] *vs* time plot for different substrates (left figure) and Hammett plot (right figure).

The effect of temperature on the rate of annulation reaction was examined by using Eyring analysis (Scheme 4.16). The activation parameters were found to be $\Delta H^{\ddagger} = 28.37 \pm 1.7$ kcal mol^{-1} and $\Delta S^{\ddagger} = +9.45 \pm 0.8$ cal mol^{-1} K^{-1}. The positive entropy of activation suggested the involvement of a dissociative process in the turnover-limiting step.



Scheme 4.16. Eyring studies

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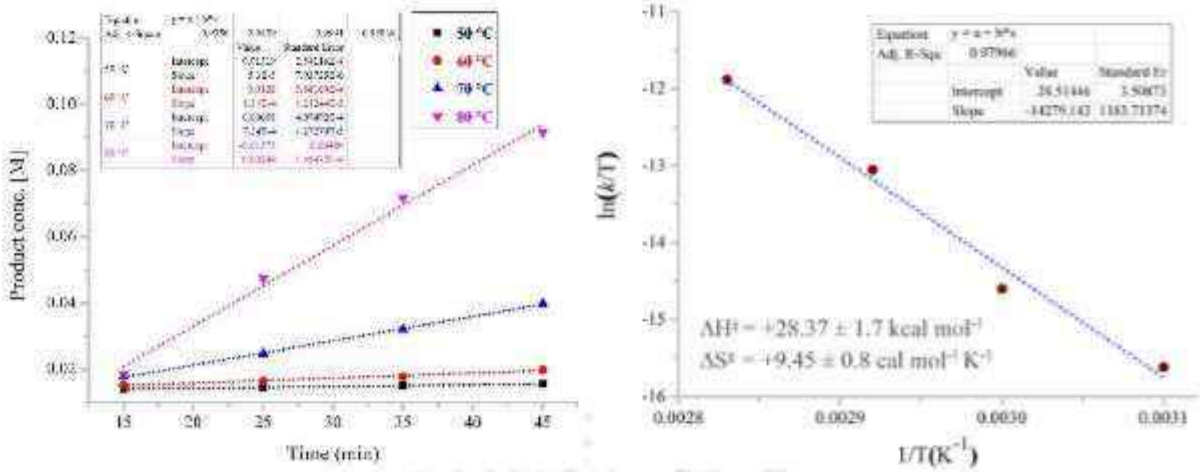


Figure 4.5. Concentration [Product] *vs* time plot at different temperatures (left figure) Arrhenius-Eyring plot (right figure).

Activation enthalpy ($\Delta H^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) values were obtained from the slope and intercept of plots of $\ln(k/T)$ vs $1/T$ (Figure 4.4) using the following equation:

$$\ln(k/T) = -\Delta H^{\#}/R.(1/T) + \ln k_B/h + \Delta S^{\#}/R$$

where k_B = Boltzmann constant, R = universal gas constant, and h = Planck's constant. From the plot of $\ln(k/T)$ vs $1/T$,

$$\text{Slope} = -14279.14$$

$$Or, -\Delta H^{\ddagger}/R = -14279.14$$

$$Or, \Delta H^{\ddagger} = -(-14279.14) \times (1.987 \text{ cal K}^{-1}\text{mol}^{-1})$$

$$= 28372.65 \text{ cal mol}^{-1}$$

$$= 28.37 \text{ kcal mol}^{-1}$$

And,

$$\text{Intercept} = 28.51$$

$$Or, \ln (k_B/h) + \Delta S^{\#}/R = 28.51$$

$$Or, \ln (1.38 \times 10^{-23} \text{ J K}^{-1}/6.626 \times 10^{-34} \text{ J s}) + \Delta S^{\#}/1.987 \text{ cal K}^{-1} \text{ mol}^{-1} = 28.51$$

$$Or, \ln (2.083 \times 10^{10} \text{ K}^{-1} \text{ s}^{-1}) + \Delta S^{\#}/1.987 \text{ cal K}^{-1} \text{ mol}^{-1} = 28.51$$

$$Or, 23.76 + \Delta S^{\#}/1.987 \text{ cal K}^{-1} \text{ mol}^{-1} = 28.51$$

$$Or, \Delta S^{\#}/1.987 \text{ cal K}^{-1} \text{ mol}^{-1} = 4.75$$

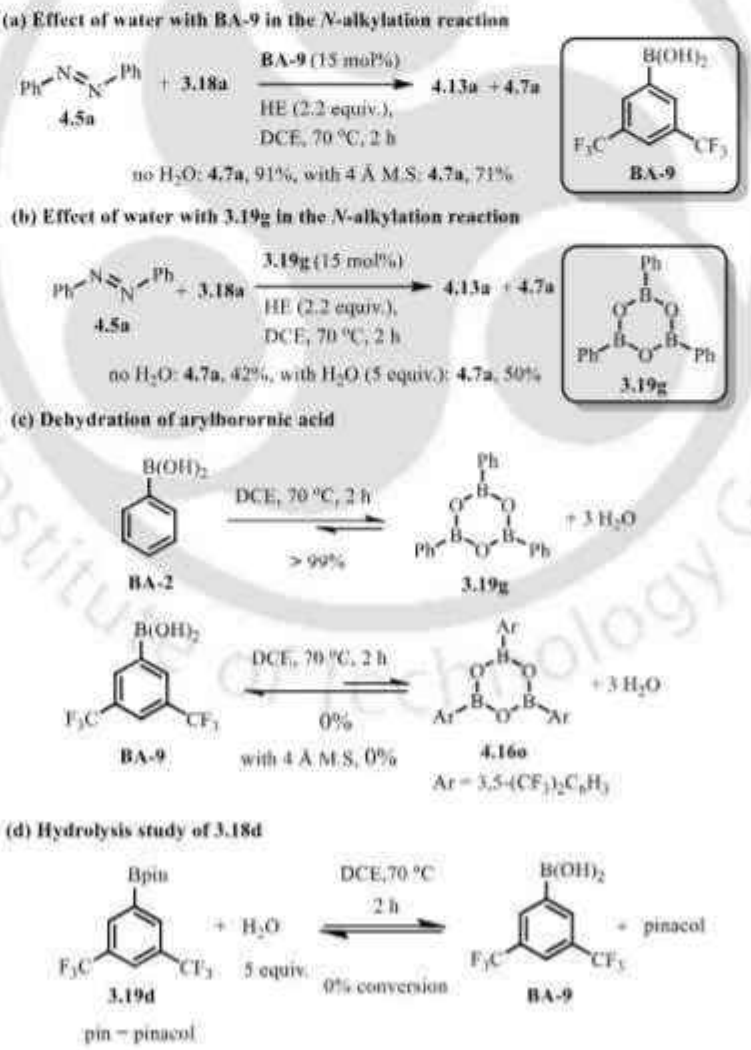
$$Or, \Delta S^{\#} = 9.45 \text{ cal K}^{-1} \text{ mol}^{-1}$$

The positive entropy of activation suggested the involvement of dissociative process in the turnover-limiting step.

As the reaction produces H_2O as one of the by-products, the effect of water in this transformation was studied using **BA-9** and **3.19g** (Scheme 4.17a). When the reaction was carried out with 5 equiv. water under the optimized conditions, the yield of *N*-alkylated product **4.7a** is increased to 50% in the case of triphenylboroxine **3.19g**. A slightly higher yield suggests that the triphenylboroxine possibly hydrolyze under the reaction conditions to give free phenyl boronic acid. To understand the possible involvement of boronic anhydride in the current

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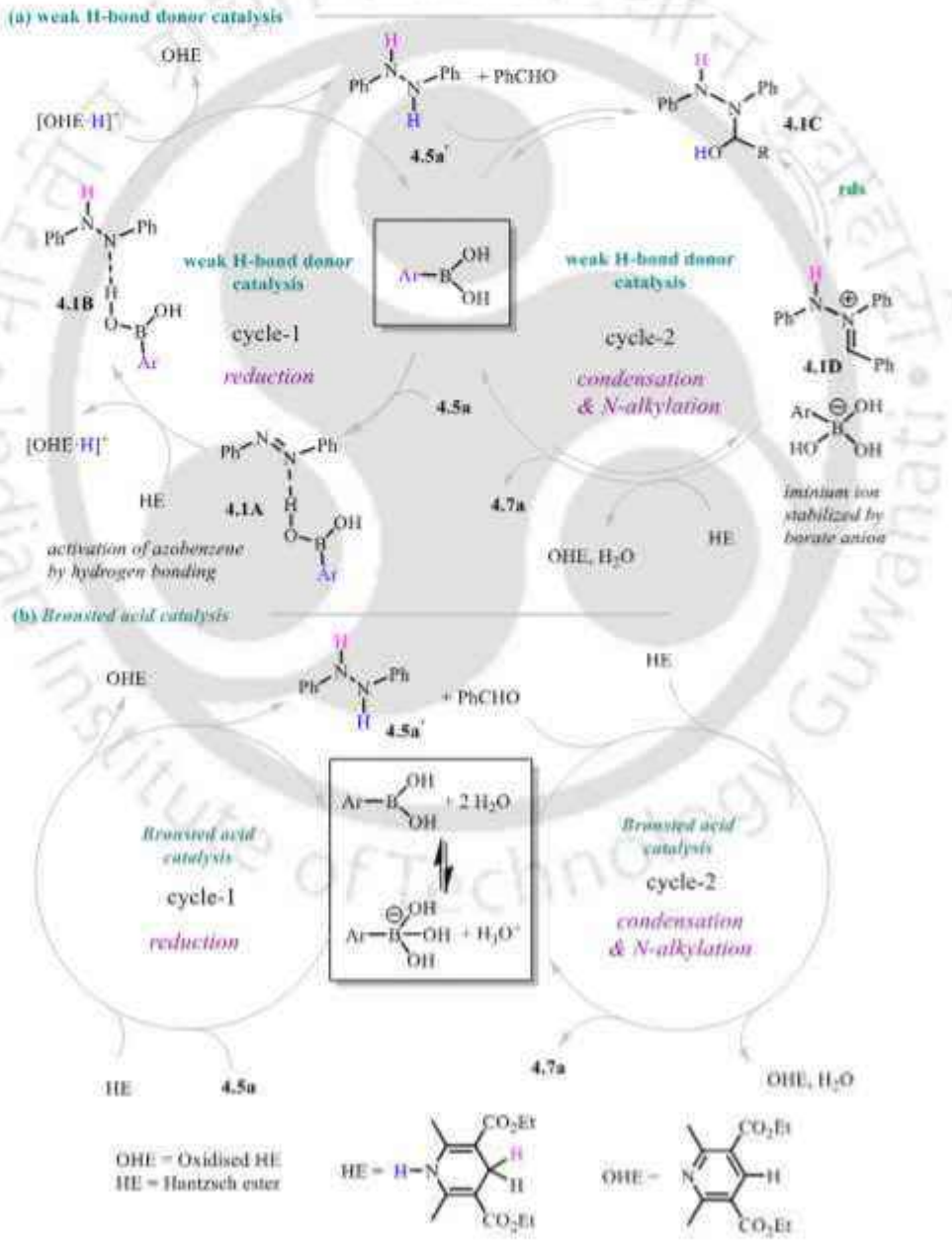
boronic acid catalysis, I have examined the dehydration of phenyl boronic acid (**BA-2**), and (3,5-bis(trifluoromethyl)phenyl) boronic acid (**BA-9**), independently in DCE at 70 °C for 2 h under our reaction conditions (Scheme 4.17b, Scheme 4.17c). Interestingly, complete conversion of phenylboronic acid (**BA-2**) to triphenyl boroxine (**3.19g**) was observed using **BA-2**, and no conversion was observed from **BA-9** to tris(3,5-bis(trifluoromethyl)phenyl) boroxine (**4.16o**). Based on these observations one can postulate that the reaction possibly occurs *via* the combined effect of boronic anhydride and the residual boronic acid in the case of phenylboronic acid (**BA-2**). However, for **BA-9** the reaction is most likely to proceed through boronic acid and not by the catalysis of boronic anhydride as there is no formation of corresponding boroxine under the reaction conditions. To understand the partial hydrolysis of arylboronic acid pinacol ester in presence of water, I have performed the NMR reaction with (3,5-bis(trifluoromethyl)phenyl) boronic acid pinacol ester (**3.19d**) and H_2O (5 equiv.) in DCE at 70 °C for 2 h (Scheme 4.17d). I have not observed any partial hydrolysis product (such as corresponding aryl boronic acid **BA-9** and free pinacol) under our reaction conditions. This control experiment suggests that the possibility of partial hydrolysis for arylboronic acid pinacol ester is unlikely under the reaction conditions.



Scheme 4.17. Role of water in the reductive alkylation of azoarene.

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Based on all of the above experimental findings, Brønsted acid and hydrogen-bond interaction[23,25] promoted a catalytic cycle of boronic acid is proposed for tandem-reduction and reductive *N*-alkylation of azobenzene (Scheme 4.18). First, the azobenzene is activated by the hydroxyl group of boronic acid *via* hydrogen bonding interaction to form **4.1A** (Cycle 1), which is then reduced by Hantzsch ester to provide hydrazobenzene **4.5a'** (Scheme 4.18a). The *in-situ* generated hydrazobenzene can take part in boron assisted condensation reaction with the aldehyde to form iminium intermediate **4.1D**, which is subsequently reduced by Hantzsch ester to deliver the desired *N*-alkylated hydrazine **4.7a** and regenerating the arylboronic acid catalyst (Cycle 2). Alternatively, Brønsted acid catalysis by hydronium ions can also be the active mode of the catalysis (Scheme 4.18b).



Scheme 4.18. Plausible mechanism.

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4.3.6. Mechanistic investigation for method B:

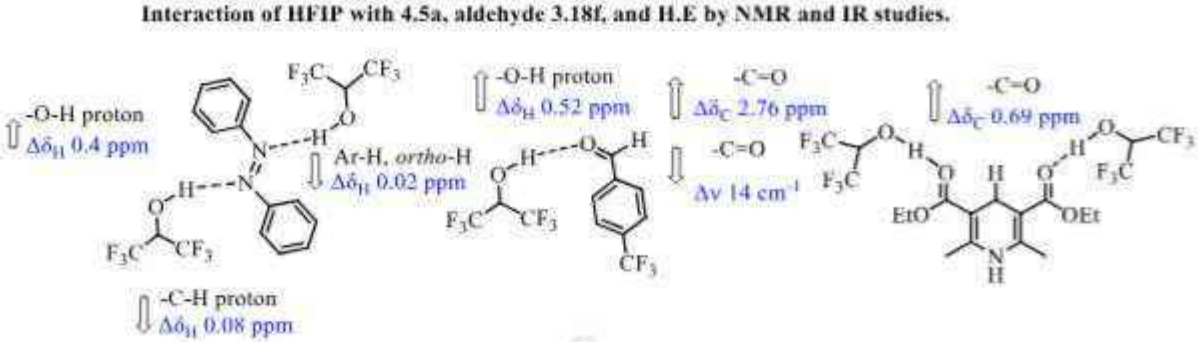


Figure 4.6. Weak interaction of HFIP with substrate and HE.

To probe the nature of binding interaction with HFIP and azobenzene, the combination of azobenzene and HFIP (molar ratio 1:1, 1:2) in $CDCl_3$ at rt has been examined. The hydroxyl peak of HFIP was shifted to downfield from δ = 3.21 ppm to 3.61 ppm, supporting the weak hydrogen bonding interaction between quinoline '*N*'-atom and the hydrogen atom of – OH in the HFIP. -CH proton of HFIP was shifted to upfield from 4.39 ppm to 4.31 ppm. The signals corresponding to *ortho*-aromatic protons in azobenzene was slightly shifted in the upfield ($\Delta\delta$ 0.2 ppm)[29] (Figure 4.7).

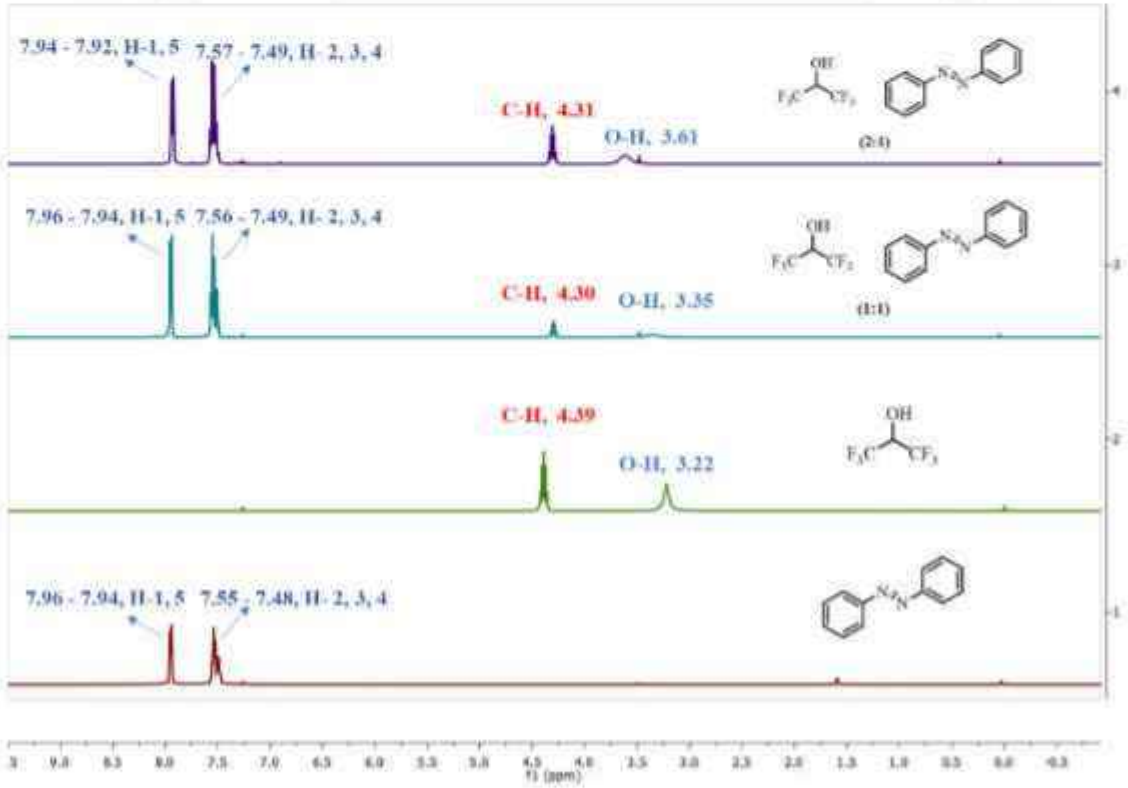


Figure 4.7. H NMR spectra of azobenzene (14 mg, 0.079 mmol), HFIP (13.2 mg, 0.079 mmol), and the mixture of azobenzene and HFIP (molar ratio 1:1, 1:2) in $CDCl_3$ at 298 K.

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In order to illustrate the interaction of HFIP and aldehyde, I performed the ^{1}H, ^{13}C NMR, and IR spectroscopic experiments by using HFIP and 4-trifluoromethyl benzaldehyde, respectively. While two equivalents of HFIP was added to 4-trifluoromethyl benzaldehyde[30] in $CDCl_3$, a downfield shift of nearly 0.52 ppm for hydroxyl peak of HFIP in ^{1}H NMR and 2.76 ppm for carbonyl signal of aldehyde in ^{13}C NMR were observed (Figure 4.8, 4.9).

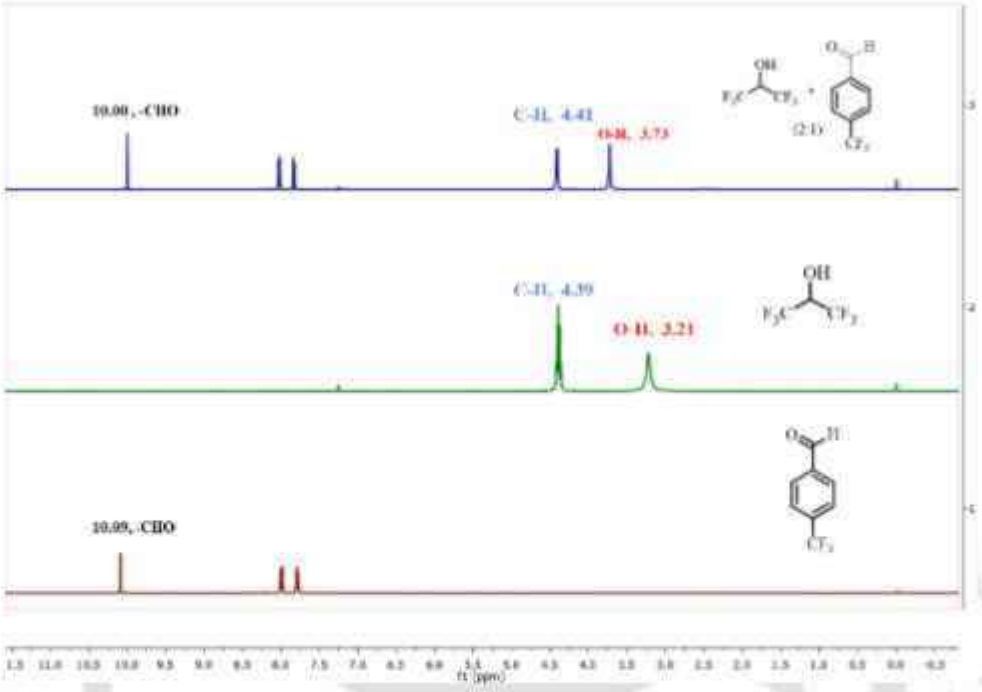
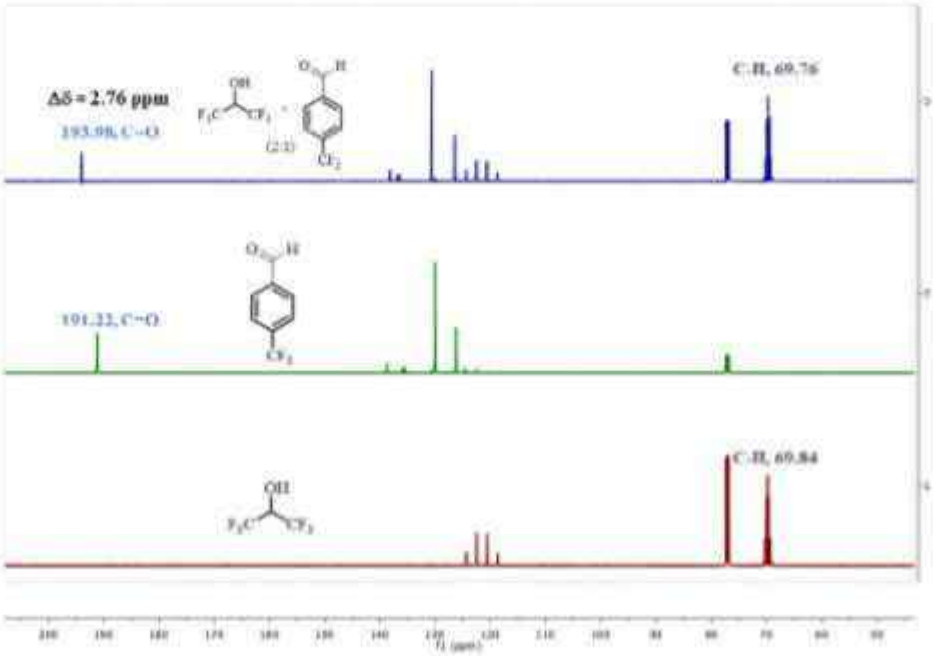


Figure 4.8. ^{1}H NMR spectra of 4-trifluoromethylbenzaldehyde (14 mg, 0.079 mmol), HFIP (26.4 mg, 0.158 mmol), and the mixture of 4-trifluoromethylbenzaldehyde and HFIP (molar ratio 1:2) in $CDCl_3$ at 298 K.



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Figure 4.9. ^{13}C NMR spectra of 4-trifluoromethylbenzaldehyde (14 mg, 0.079 mmol), HFIP (26.4 mg, 0.158mmol), and the mixture of 4-trifluoromethylbenzaldehyde and HFIP (molar ratio 1:2) in $CDCl_3$ at 298 K.

In IR, the carbonyl value shifted to a lower wave number from 1708.03 cm^{-1} to 1694.12 cm^{-1} after mixing with HFIP at room temperature (Figure 4.8). Approximately 14 cm^{-1} lower wave number has been observed for the carbonyl group in a mixture compared to free aldehyde, which supports hydrogen bonding interaction between aldehyde and HFIP (Figure 4.9). A downfield shift for hydroxyl peak of HFIP in ^1H NMR and ensuing downfield shift for carbonyl of aldehyde in ^{13}C NMR supports weak hydrogen bonding interaction with aldehyde and HFIP.[30] It has been further reinforced by using IR spectroscopic experiments in the solid-state.

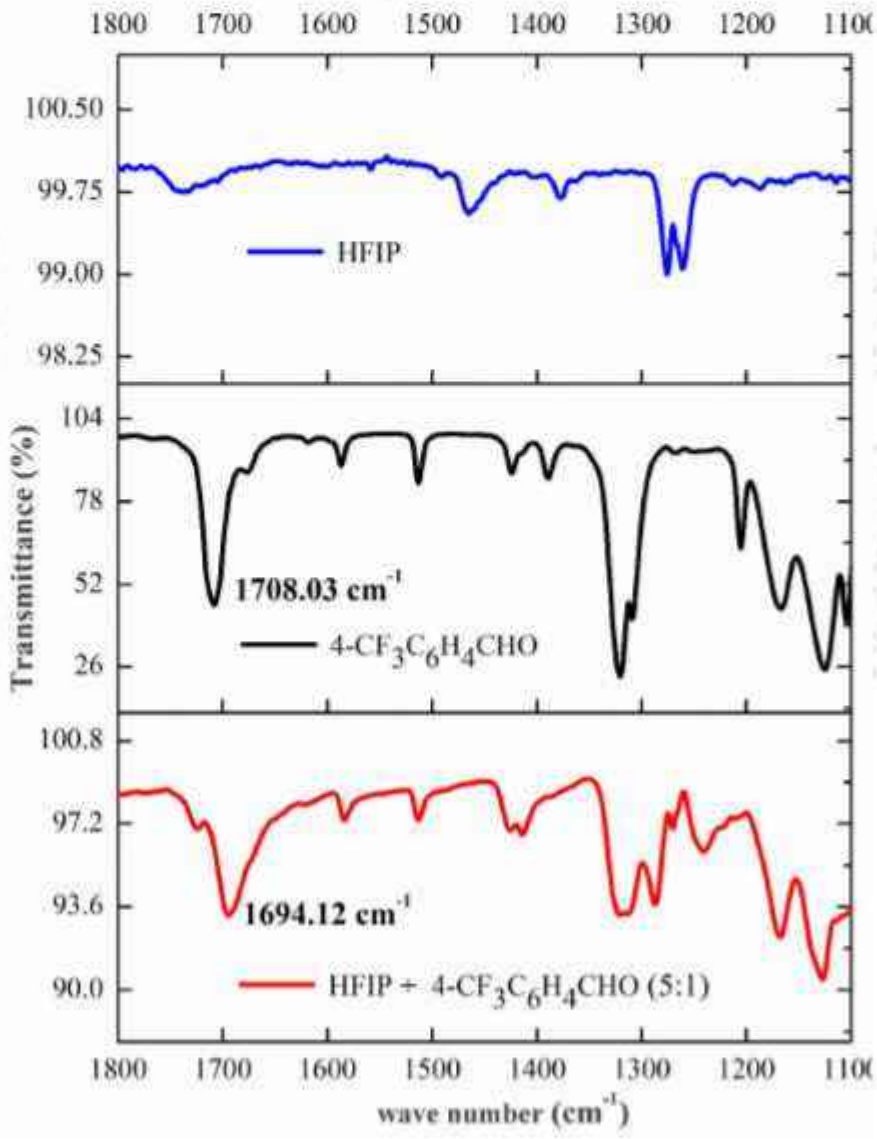


Figure 4.10. IR spectroscopy to support the interaction of 4-trifluoromethyl benzaldehyde **3.18h** and HFIP.

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To examine the interaction of HFIP and Hantzsch ester, I have checked the ^{1}H NMR with the combination of Hantzsch ester and HFIP (molar ratio 1:2) in $CDCl_3$ at rt. whereas no characteristic –OH proton signal was shifted while mixing with HFIP (Figure 4.11).

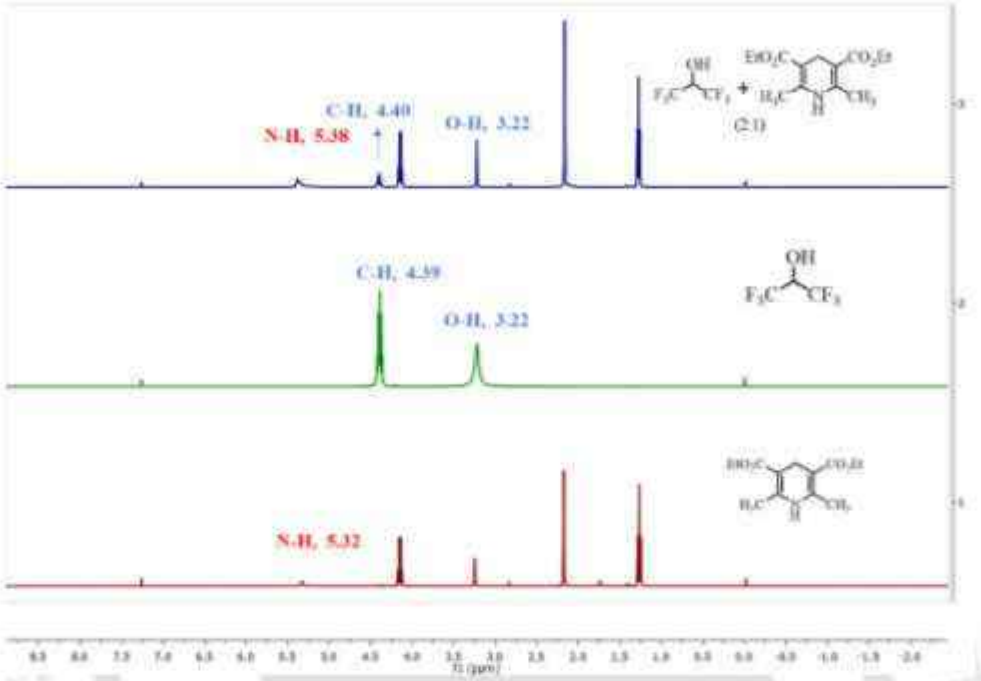
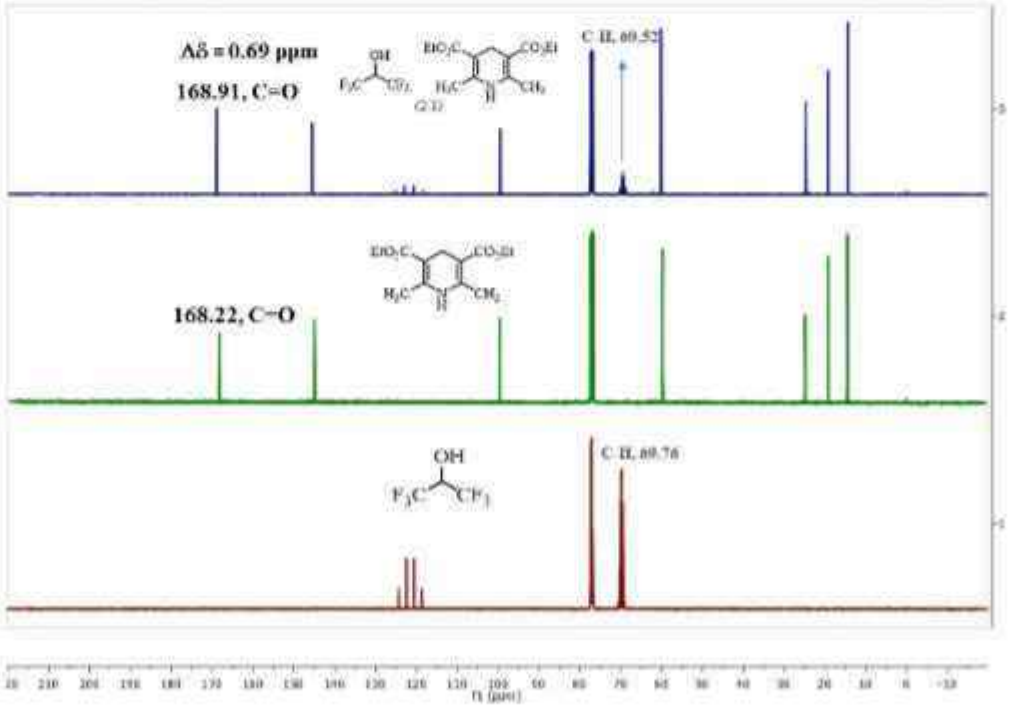


Figure 4.11. ^{1}H NMR spectra of HFIP (26.4 mg, 0.158 mmol), Hantzsch ester (20 mg, 0.079 mmol), and the mixture of HFIP and Hantzsch ester (molar ratio 2:1) in $CDCl_3$ at 298 K.

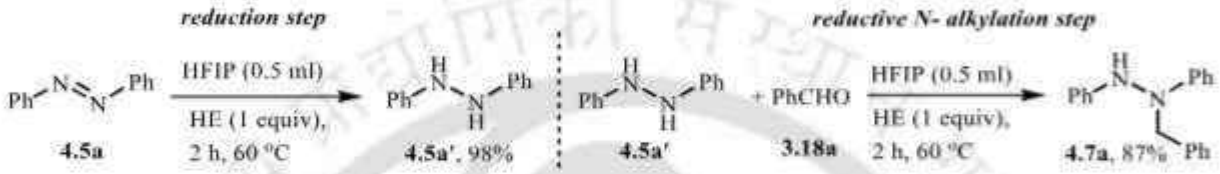
However, in ^{13}C NMR, the carbonyl value in Hantzsch ester was shifted downfield from 168.22 to 168.91 ppm ($\Delta\delta$ = 0.7 ppm). A weak hydrogen bonding interaction may exist between Hantzsch ester and –OH of HFIP. (Figure 4.12).



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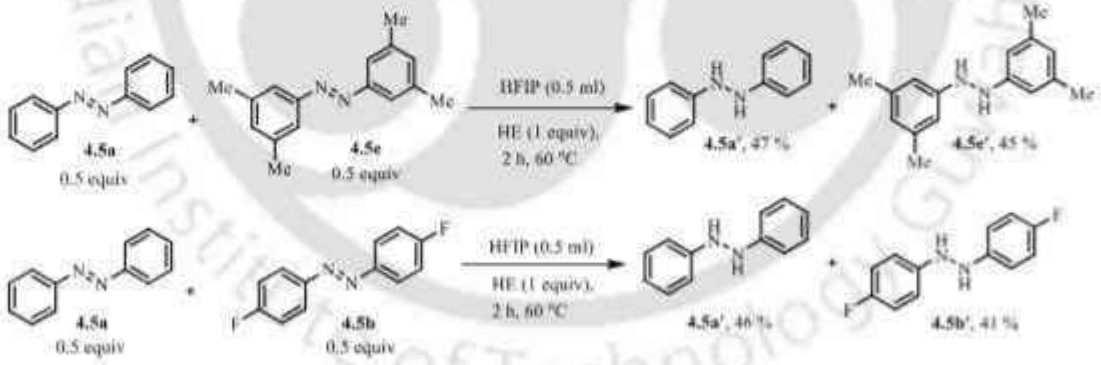
Figure 4.12. ^{13}C spectra of HFIP (26.4 mg, 0.158 mmol), Hantzsch ester (20 mg, 0.079 mmol), and the mixture of HFIP and Hantzsch ester (molar ratio 2:1) in $CDCl_3$ at 298 K.

Next, a few control experiments were carried out to gain mechanistic insights into the synthesis of hydrazine derivatives. The reaction of azobenzene **4.5a** in the absence of aldehyde under standard conditions afforded 1, 2-diphenyl hydrazine **4.5a'** in 98% yield. For the subsequent step the reaction was conducted with the formed **4.5a'**, and aldehyde **3.18a** under standard conditions the desired product **4.7a** was obtained in 87% yield (Scheme 4.19). From which it can infer that reaction possibly occurs in two steps, i.e., reduction of azobenzene, followed by reductive *N*-alkylation of hydrazobenzene to *N*-alkylated hydrazine.



Scheme 4.19. Proof of 1, 2-diphenylhydrazine as the intermediate.

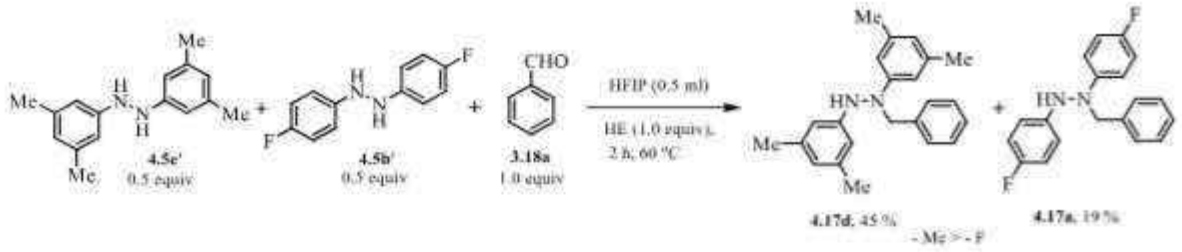
Next, the electronic effect of the substrate on the rate of the reaction was examined. To know the electronic effect in the 1st step, A competitive reaction suggested that the electron-donating group (Me) on the azobenzene enhanced the rate of the reaction with respect to an electron-withdrawing group (*p*-F). Since a comparable yield was obtained in both the case, one can infer that there is no considerable effect on the electronics in the azobenzene reduction step (Scheme 4.20).



Scheme 4.20. Electronic effect of the azobenzene hydrogenation step.

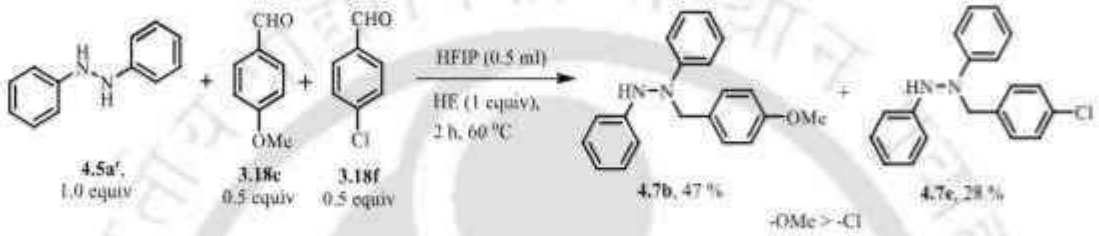
To know the electronic effect in the 2nd step, at first the reaction was examined with substituted azobenzenes. A competitive reaction suggested that the electron-donating group (-Me) on the hydrazobenzene enhanced the rate of the reaction with respect to an electron-withdrawing group (*p*-F) (Scheme 4.21).

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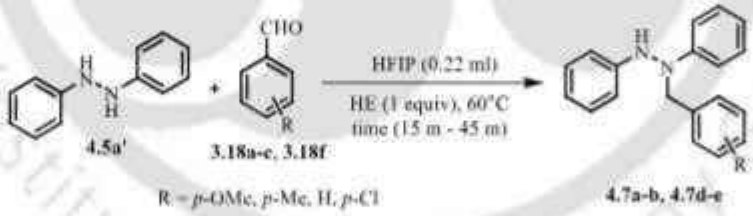
Scheme 4.21. Competitive reaction with substituted azobenzene.

Likewise, competitive reaction with aldehyde suggested that electron-donating group (*p*-OMe) on the benzaldehyde enhanced the rate of the reaction with respect to an electron-withdrawing group (*p*-Cl) (Scheme 4.22).



Scheme 4.22. Competitive reaction with aldehyde.

Furthermore, I have investigated the kinetic Hammett correlation study using various *para*-substituted benzaldehydes under standard reaction conditions. The reaction rates are in the order OMe>Me>H>Cl. The least-squares fit to the plot of [$\log(k_X/k_H)$] *vs.* Hammett σ^+ constant gave a straight line with a ρ^+ value of -1.3. A negative ρ^+ value suggests that in the transition state, electrons are flowing away, which is stabilised by the electron-donating substituents.



Scheme 4.23. Kinetic Hammett studies.

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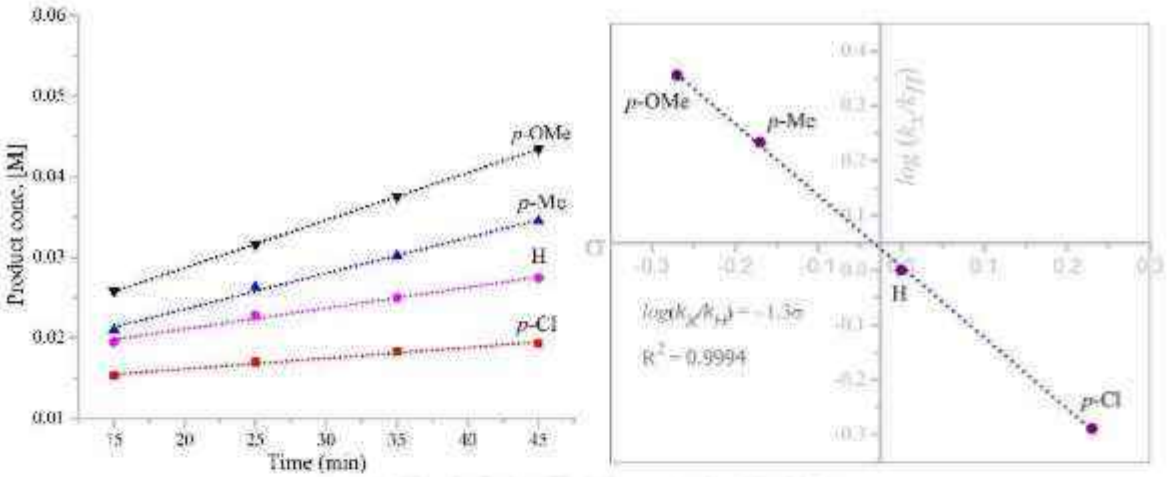
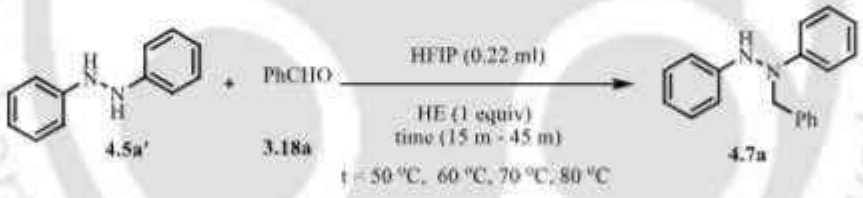


Figure 4.13. Concentration [Product] *vs* time plot for different substrates (left figure) and Hammett plot (right figure).

The effect of temperature on the rate of condensation reaction was examined by using Eyring analysis. The activation parameters were found to be $\Delta H^{\ddagger} = 29.2 \pm 1.6$ kcal mol^{-1} and $\Delta S^{\ddagger} = +12.02 \pm 0.9$ cal K^{-1} mol^{-1}. The positive entropy of activation suggests that the involvement of a dissociative process is the turnover-limiting step. Based on the thermodynamic activation parameters, kinetic Hammett studies, and competitive reaction on the substrate, one can postulate that iminium formation step is likely to be the rate-limiting step.



Scheme 4.24. Eyring studies.

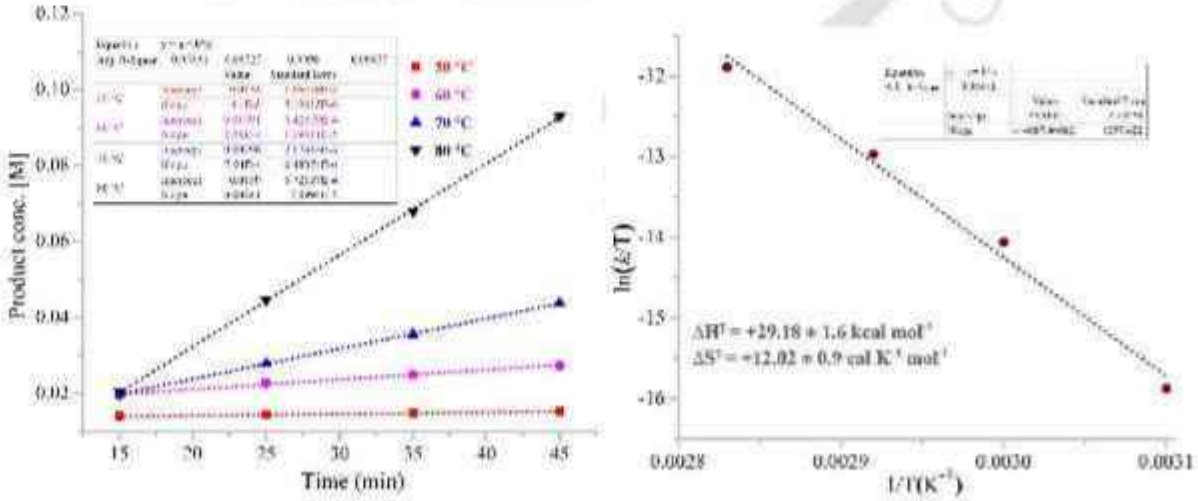


Figure 4.14. Concentration [Product] *vs* time plot at different temperatures (left figure).

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Arrhenius-Eyring plot (right figure).

Activation enthalpy ($\Delta H^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) values were obtained from the slope and intercept of plots of $\ln(k/T)$ vs $1/T$ (Figure S10) using the following equation:

$$\ln(k/T) = -\Delta H^{\ddagger}/R.(1/T) + \ln k_B/h + \Delta S^{\ddagger}/R$$

where k_B = Boltzmann constant, R = universal gas constant, and h = Planck's constant.

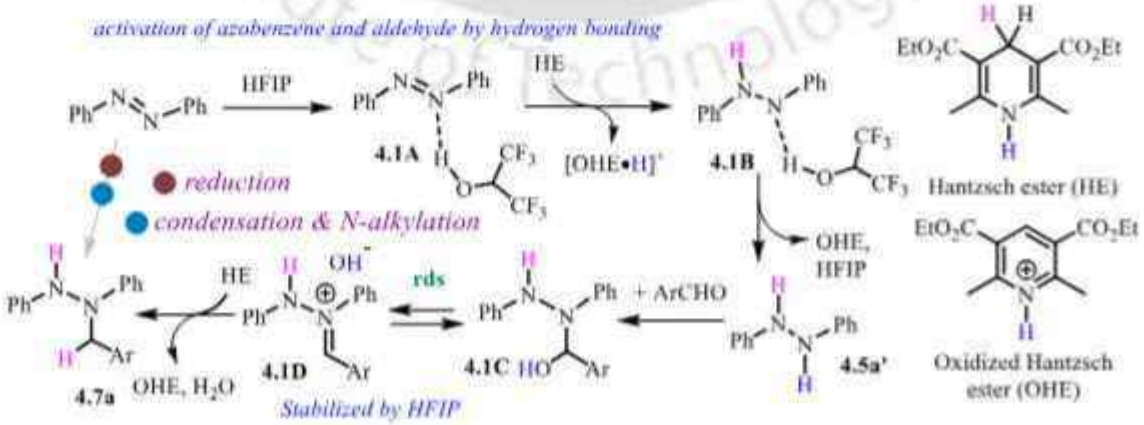
From the plot of $\ln(k/T)$ vs $1/T$,

$$\text{Slope} = -14687.2$$
$$Or, -\Delta H^{\ddagger}/R = -14687.2$$
$$Or, \Delta H^{\ddagger} = -(-14687.2) \times (1.987 \text{ cal K}^{-1}\text{mol}^{-1})$$
$$= 29183.4 \text{ cal mol}^{-1}$$
$$= 29.18 \text{ kcal mol}^{-1}$$

And,

$$\text{Intercept} = 29.81$$
$$Or, \ln (k_B/h) + \Delta S^{\ddagger}/R = 29.81$$
$$Or, \ln (1.38 \times 10^{-23} \text{ J K}^{-1}/6.626 \times 10^{-34} \text{ J s}) + \Delta S^{\ddagger}/1.987 \text{ cal K}^{-1}\text{ mol}^{-1} = 29.81$$
$$Or, \ln (2.083 \times 10^{10} \text{ K}^{-1}\text{ s}^{-1}) + \Delta S^{\ddagger}/1.987 \text{ cal K}^{-1}\text{ mol}^{-1} = 29.81$$
$$Or, 23.76 + \Delta S^{\ddagger}/1.987 \text{ cal K}^{-1}\text{ mol}^{-1} = 29.81$$
$$Or, \Delta S^{\ddagger}/1.987 \text{ cal K}^{-1}\text{ mol}^{-1} = 6.05$$
$$Or, \Delta S^{\ddagger} = 12.02 \text{ cal K}^{-1}\text{ mol}^{-1}$$

On the basis of above experimental findings, proposed pathway for the formation of *N*-alkylated hydrazine has been demostrated in Scheme 3. First, the azobenzene **4.5a** is activated by the hydroxyl group of HFIP *via* hydrogen bonding interaction, which is then reduced by Hantzsch ester to provide hydrazobenzene **4.5a'**. The *in-situ* generated hydrazobenzene can react with aldehyde to form hemiaminal species **4.2C**, followed by condensation leading to the formation of iminium intermediate **4.2D**. Then, this was readily reduced by Hantzsch ester to provide the *N*-alkylated hydrazine **4.7a**.



Scheme 4.25. Proposed pathway for the formation of *N*-alkylated hydrazine (method B).

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4.4. Summary

I have developed aryl boronic acid-catalyzed one-pot tandem reduction of azoarene with subsequent reductive alkylation using aldehydes to form *N*-alkylated hydrazine derivatives. The same transformation was also proceeded well by hexafluoroisopropanol under catalyst-free conditions. Both the protocol shows notable selectivity as formation of N-N cleaved product amines and/or imines[14-16] is completely suppressed and selectively provided *N*-alkyl-*N, N'*-diarylhydrazines. Method tolerates a wide variety of hydrogenation-sensitive functional groups, such as ester, halo, nitro, nitrile, alkyne, allyl, and benzyl. This has been successfully utilized in the late-stage functionalization, and diversification of pharmaceuticals. The post transformations of the synthesized product have also been carried out to demonstrate the significance of the developed methodology. In the BA catalysis, this study sheds light on the activation mode of boronic acid catalysis of azobenzene and aldehyde, showing that Brønsted acid and H-bond donor catalysis, rather than Lewis acid activation, are likely responsible for the observed reactivity. Lastly, this study demonstrates the general utility of the HFIP in the reduction chemistry.

4.5. Experimental section

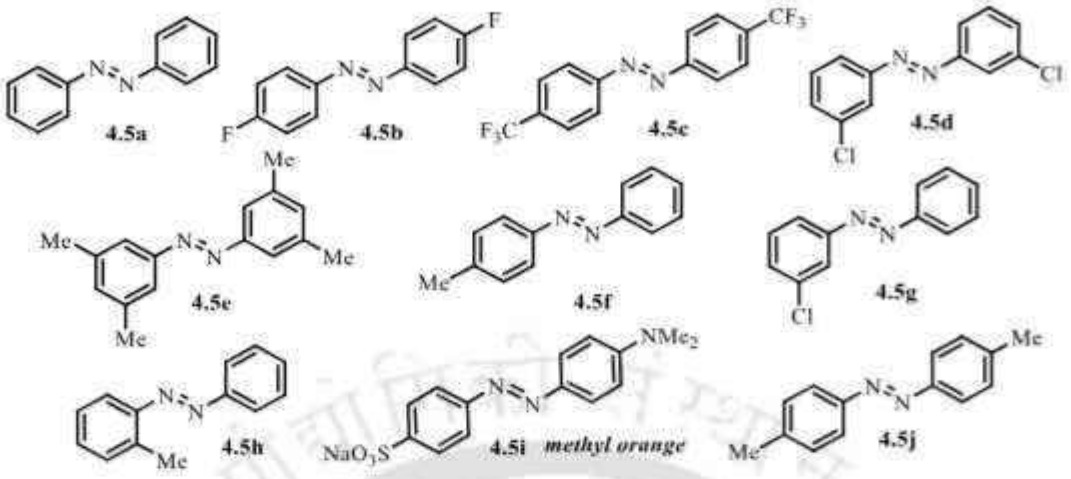
A. General Information

All the reagents and chemicals were purchased from common commercial suppliers like Sigma-Aldrich, Alfa Aesar, Merck, Spectrochem, Avra Synthesis Pvt. Ltd., Finar Chemicals, and BLD Pharma directly used as received without any further purification unless otherwise mentioned. Hantzsch ester was synthesized according to the reported literature.[31] ^{1}H, ^{13}C, and ^{19}F NMR spectra of the compounds were measured in $CDCl_3$, as a solvent by using TMS as an internal standard. Chemical shifts, δ (in ppm), are reported relative to TMS δ (^{1}H) 0.0 ppm, δ (^{13}C) 0.0 ppm, which was used as the internal reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.16 ppm), were also used for calibration. Bruker Avance III 600, 500 and 400 spectrometers were used to record the NMR spectra. Chemical shifts (δ) values were reported in ppm and spin-spin coupling constant (J) were expressed in Hz, and other data were reported as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quartet, pent = pentate, sext = sextet, hept = heptane, br = broad, and brs = broad singlet. IR spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass (UHPLC - Q-TOF - HRMS). Merck silica gel 60 - 120 was used for column chromatography. otherwise stated. All the final reactions were carried out under air and in preheated oil baths unless otherwise mentioned. Completion of reactions was examined by thin layer chromatography carried out on pre-coated Merck silica gel-60 F_{254} aluminium plates with ultraviolet light (UV) or iodine as visualizing agents.

B. Synthesis of starting material

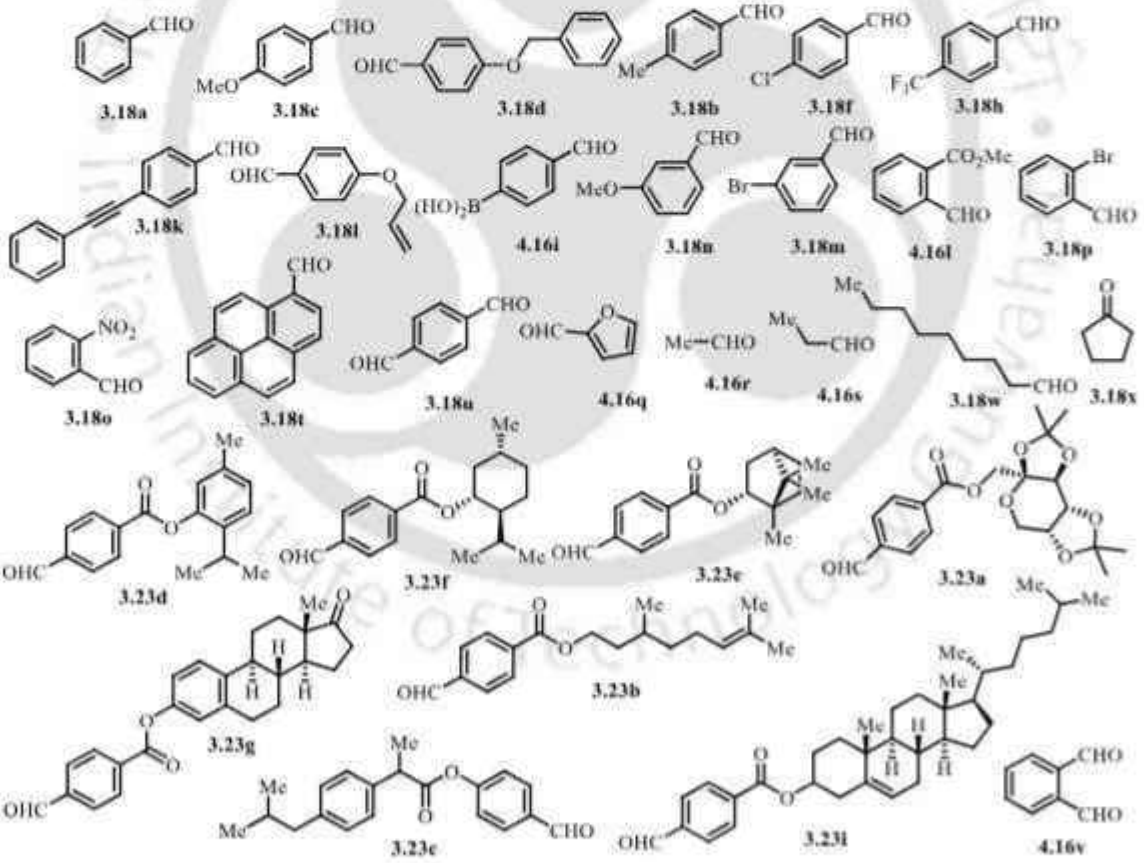
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i) Azoarenes employed in the reaction:



Compounds **4.5b-4.5h, 4.5j** are synthesized by known procedures.[16,32-34]

ii) Aldehydes and ketone employed in the reaction:



Compounds **3.18d**,[35] **3.18k**,[36] **3.18l**,[37] are synthesized by known procedure. The biologically relevant motifs containing aldehyde derivatives **3.23f**,[38] **3.23e**,[39] **3.23a**,[40] **3.23g**,[41] **3.23b**,[42] **3.23i**,[38] **3.23c**,[43] were synthesized by the known procedure.

C. General procedure for synthesis of *N*-alkyl trisubstituted hydrazines

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General procedure for synthesis of *N*-substituted hydrazines with different carbonyls (GP-1)

Reaction condition for method A: A mixture of azobenzene **4.5a** (0.5 mmol), aldehyde (0.5 mmol), HE (2.2 equiv.), **BA-9** (15 mol%) and DCE (2 mL) were added into a reaction tube (25 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 70 °C with continuous stirring for 2 h under argon. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

Reaction condition for method B: A mixture of azobenzene **4.5a** (0.5 mmol), aldehyde or cyclic ketone (0.5 mmol), HE (1 mmol) and HFIP (0.5 ml) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 2 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

General procedure for synthesis of *N*-substituted hydrazines with substituted azobenzene (GP-2)

Reaction condition for method A: A mixture of symmetrical or unsymmetrical azobenzene (0.5 mmol), benzaldehyde **3.18a** (0.5 mmol), HE (2.2 equiv.), **BA-9** (15 mol%) and DCE (2 mL) were added into a reaction tube (25 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 70 °C with continuous stirring for 2 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

Reaction condition for method B: A mixture of symmetrical or unsymmetrical azobenzene (0.5 mmol), benzaldehyde **3.18a** (0.5 mmol), HE (2 equiv) and HFIP (0.5 ml) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 2 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

General procedure for synthesis of tetrahydrophthalazine derivative (GP-3)

Reaction condition for method A: A mixture of substituted azobenzene (0.5 mmol), phthalaldehyde **4.16v** (0.5 mmol), HE (3.2 equiv.) and **BA-9** (15 mol%) and DCE (2 mL) were added into a reaction tube (25 mL) equipped with stirring bar. The reaction tube was properly

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closed and placed in a preheated oil bath at 70 °C with continuous stirring for 2 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

Reaction condition for method B: A mixture of substituted azobenzene (0.5 mmol), phthalaldehyde **4.16v** (0.5 mmol), HE (3.2 equiv.) and HFIP (0.5 ml) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 2 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

D. Scale-up reaction (Scheme 4.6, 4.7)

Experimental procedure for method A: A mixture of **4.5a** (1 gm, 5.487 mmol), **3.18a** (1.0 equiv.), HE (2.2 equiv.), **BA-9** (15 mol%) and DCE (10 mL) were added into a round bottom flak (50 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 70 °C with continuous stirring for 6 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography to get pure compound as yellow oil of (1.250 g, 83%).

Experimental procedure for method B: A mixture of **4.5a** (0.364 g, 2 mmol), **3.18a** (1.0 equiv), HE (2 equiv) and HFIP (2 mL) were added into a round bottom flak (50 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 2 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography to get pure compound as yellow oil of (0.417 g, 76%).

E. Post-synthetic modification

i) Reductive N-N bond cleavage of various hydrazine derivatives (Scheme 4.8)

Reaction condition:[12a] A mixture of hydrazine derivatives (0.216 mmol), Zn dust (100 equiv.), AcOH (1.5 mL) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at r.t with continuous stirring for 6 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified

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through silica gel column chromatography. Compound **4.19a**, **4.19b**, **4.19c** and **4.19d** were prepared using the following procedure.

Synthesis of *N, N'*-(1,2-phenylenebis(methylene)) dianiline (4.20) (Scheme 4.8)

Experimental procedure: A mixture of **4.18a** (0.216 mmol), Zn dust (100.0 equiv.), AcOH (1.5 mL) were added into a round bottom flask (50 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at rt with continuous stirring for 6 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography to yield the desired compound **4.20** as white solid (87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.41 (m, 2H), 7.32 – 7.28 (m, 2H), 7.20 – 7.15 (m, 4H), 6.75 – 6.71 (m, 2H), 6.65 – 6.63 (m, 4H), 4.39 (s, 4H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 148.2, 137.4, 129.4, 128.1, 118.0, 113.2, 46.4. Spectroscopic characterization data are in accordance with reported literature.[18]

ii) ***α*-methylene oxidation of compound 4.18a (Scheme 4.9)**

Synthesis of 2, 3-diphenyl-2, 3-dihydrophthalazine-1, 4-dione (4.21)

Experimental procedure: $NaIO_4$ (0.209 g) was taken in a screw- capped reaction tube and dissolved it in water (1 mL). Then compound **4.18a** (0.056 g), **Ru cat. (3.25)**[19] (4 mol%) acetonitrile (2 mL) were added to the reaction tube and stirred the reaction mixture in a preheated oil bath at 70 °C for 1 h. After the completion of the reaction as confirmed by TLC, the reaction mixture was worked up with CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was again extracted with CH_2Cl_2 (two times, 5 mL). The combined organic layer was washed with brine solution. The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under a vacuum. The crude product was purified through silica-gel column chromatography to get the pure product **4.21** as white solid (83%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 – 8.42 (m, 2H), 7.89 – 7.88 (m, 2H), 7.31 – 7.28 (m 5H), 7.26 – 7.25 (m, 3H), 7.18 (t, J = 7.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.6, 137.8, 134.1, 129.8, 128.9, 128.8, 128.5, 128.4. Spectroscopic characterization data are in accordance with reported literature.[44]

D. Mechanistic investigation

For method A:

i) Impact of hydrogen bonding ability and Lewis acidic properties in boronic acid catalysis (Scheme 4.11)

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Reaction conditions: For **4.5a'**: A mixture of azobenzene **4.5a** (0.5 mmol) HE (1.1 equiv.), **BA**, **2.15**, **3.19** (15 mol%) and DCE (2 mL) were added into a reaction tube (25 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 70 °C with continuous stirring for 1 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography. the same has been repeated three times, average data is given.

For **4.7a**: A mixture of **4.5a'** (0.5 mmol), **3.18a** (1 equiv.), and HE (1.1 equiv.), **BA**, **2.15**, **3.19** (15 mol%) and DCE (2 mL) were added into a reaction tube (25 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 70 °C with continuous stirring for 1 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography. The same has been repeated three times, average data is given.

ii) Proof of 1, 2-diphenyl hydrazine as the intermediate (Scheme 4.12)

To gain more insight into the reaction pathway, I performed the reaction with azobenzene **4.5a** (0.5 mmol), HE (1.1 equiv.), and **BA-9** (15 mol%) in DCE (2 mL) at 70 °C for 2 h. As expected 1, 2-diphenyl hydrazine **4.5a'** obtained in 96% yield. For the subsequent step the reaction was conducted with the formed **4.5a'**, and aldehyde **3.18a** (1 equiv.), HE (1.1 equiv.) and **BA-9** (15 mol%) in DCE (2 mL) at 70 °C for 2 h under standard conditions the desired product **4.7a** was obtained in 91%, yield, from I can conclude reaction possibly occurs in two steps i) reduction of azobenzene and ii) reductive *N*-alkylation of hydrazobenzene.

iii) Electronic effect for the 1st step (Scheme 4.13)

To know the electronic effect in the 1st step, I performed **4.5a** (0.5 mmol), **4.5e** (0.5 mmol), and HE (1.1 equiv.), and **BA-9** (15 mol%) in DCE (2 mL) at 70 °C for 2 h. As expected I obtained its corresponding hydrogenated product **4.5a'** (46%) and **4.5e'** (44%). Then I performed **4.5a** (0.5 mmol), **4.5b** (0.5 mmol), and HE (1.1 equiv.), **BA-9** (15 mol%) in DCE (2 mL) at 70 °C for 2 h, providing the hydrogenated product **4.5a'** (46%) and **4.5b'** (42%). Since there is a comparable yield was obtained, one can infer that there is no considerable effect on the electronics in the azobenzene hydrogenation step.

iv) Electronic effect for the 2nd step (Scheme 4.14)

Reaction conditions: substituted azobenzene **4.5e'** (0.5 equiv.), **4.5b'** (0.5 equiv.), aldehyde **3.18a** (0.5 mmol), HE (1.1 equiv.), and **BA-9** (15 mol%) in DCE (2 mL) at 70 °C for 2 h, the product **4.17d** and **4.17a** was obtained in 47% yield and 16 % yield respectively.

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Reaction conditions: hydrazobenzene **4.5a'** (0.5 mmol), substituted aldehyde **3.18c** (0.5 equiv.), **3.18f** (0.5 equiv.), HE (1.1 equiv.), and **BA-9** (15 mol%) in DCE (2 mL) at 70 °C for 2 h, the product **4.7b** and **4.7e** was obtained in 48% yield and 31% yield respectively.

v) Kinetic Hammett Studies (Scheme 4.15)

Reaction conditions: A mixture of **4.5a'** (0.217 mmol), substituted aldehyde **3.18a-c, 3.18f** (1.0 equiv.), HE (1.1 equiv.), **BA-9** (15 mol%), DCE (2 mL) were taken in the reaction tube. The reaction tube was properly closed and placed in a pre-heated oil bath at 70 °C for the specified times. The measure yield of product was plotted against to obtain the slope which gave the rate constant for each substrate.

substrate	k (min^{-1})	k_X/k_H	log (k_X/k_H)	σ_p	ρ
p-OMe	1.3×10^{-3}	1.77	+0.247	-0.27	-0.864
p-Me	1.04×10^{-3}	1.41	+0.149	-0.17	
H	0.734×10^{-3}	1	0	0	
p-Cl	0.477×10^{-3}	0.649	-0.187	+0.23	

vi) Eyring Studies (Scheme 4.16)

Reaction conditions: A mixture of **4.5a'** (0.217 mmol), **3.178a** (1.0 equiv.), HE (1.1 equiv.), **BA-9** (15 mol%), DCE (2 mL) were taken in the reaction tube. The reaction tube was properly closed and placed in a pre-heated oil bath at respective temperature for the specified times. The measure yield of product was plotted against to obtain the slope which gave the rate constant for each substrate.

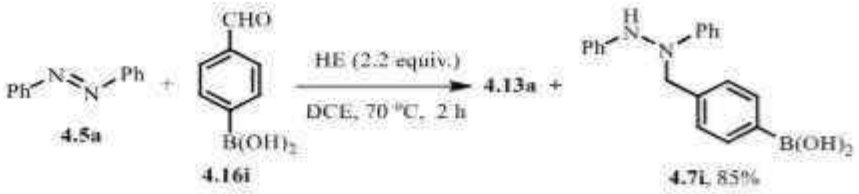
Temp	$1/T$	k	ln(k/T)
323 K (50 °C)	0.003095	0.053×10^{-3}	-15.62
333 K (60 °C)	0.003003	0.151×10^{-3}	-14.60
343 K (70 °C)	0.002915	0.734×10^{-3}	-13.05
353 K (80 °C)	0.002832	2.4×10^{-3}	-11.88

The positive entropy of activation suggested the involvement of dissociative process in the turnover-limiting step.

vii) *N*-alkylation with boronic acid bearing aromatic aldehyde

N-alkylation was examined with a boronic acid containing aldehyde in the absence of catalyst under standard conditions. The desired product **4.7i** was obtained in 85% yield without the disruption of the boron moiety (Scheme 4.26). Herein, 4-formylbenzeneboronic acid **4.16i** not only serves as a coupling partner, but also promote reaction.

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Scheme 4.26. *N*-alkylation with boronic acid containing aldehyde.

For method B:

i) Proof of 1, 2-diphenyl hydrazine as the intermediate (Scheme 4.19)

To gain more insight into the reaction pathway, I performed the reaction with azobenzene **4.5a** (0.5 mmol), HE (1 equiv), and HFIP (0.5 mL) at 60 °C for 2 h. As expected 1, 2-diphenyl hydrazine **4.5a'** obtained in 98% yield. For the subsequent step the reaction was conducted with the formed **4.5a'**, and aldehyde **3.18a** (1 equiv), HE (1 equiv), and HFIP (0.5 mL) at 60 °C for 2 h under standard conditions the desired product **4.7a** was obtained in 87%, yield, from I can conclude reaction possibly occurs in two steps i) reduction of azobenzene and ii) reductive *N*-alkylation of hydrazobenzene

ii) Electronic effect for the 1st step (Scheme 4.20)

To know the electronic effect in the 1st step, I performed **4.5a** (0.25 mmol), **4.5e** (0.25 mmol), and HE (0.5 mmol), and HFIP (0.5 mL) at 60 °C for 2 h. As expected I obtained its corresponding hydrogenated product **4.5a'** (47%) and **4.5e'** (45%). Then I performed **4.5a** (0.25 mmol), **4.5b** (0.25 mmol), and HE (0.5 mmol) in HFIP (0.5 mL) at 60 °C for 2 h, providing the hydrogenated product **4.5a'** (46%) and **4.5b'** (41%). Since a comparable yield was obtained in both the case, one can infer that there is no considerable effect on the electronics in the azobenzene reduction step.

iii) Electronic effect for the 2nd step (Scheme 4.21, 4.22)

Reaction conditions: substituted azobenzene **4.5e'** (0.5 equiv), **4.5b'** (0.5 equiv), aldehyde **3.18a** (0.5 mmol), HE (1 equiv), and HFIP (0.5 mL) at 60 °C for 2 h, the product **4.17d** and **4.17a** was obtained in 45% yield and 19% yield respectively.

Reaction conditions: hydrazobenzene **4.5a'** (0.5 mmol), substituted aldehyde **3.18c** (0.5 equiv), **3.18f** (0.5 equiv), HE (1 equiv), and HFIP (0.5 mL) at 60 °C for 2 h, the product **4.7b** and **4.7e** was obtained in 47% yield and 28% yield respectively.

iv) Hammett Studies (Scheme 4.23)

Reaction conditions: An oven dried reaction tube, a mixture of **4.5a'** (0.217 mmol, 1 equiv), substituted aldehyde derivative **3.18a-c, 3.18f** (0.217 mmol, 1 equiv), HE (0.217 mmol, 1 equiv), and HFIP (0.22 mL) at 60 °C for different time intervals were taken. The reaction tube was properly closed and placed in a pre-heated oil bath at 60 °C for the specified times. The progress of the reaction was analyzed by NMR using 1,3,5 trimethoxy benzene as an internal

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standard. The measure yield of product was plotted against to obtain the slope which gave the rate constant for each substrate.

substrate	k (min^{-1})	k_X/k_H	log (k_X/k_H)	σ_p	ρ
p-OMe	0.590×10^{-3}	2.27	+0.356	-0.27	**-1.298**
p-Me	0.444×10^{-3}	1.71	+0.234	-0.17	
H	0.259×10^{-3}	1	0	0	
p-Cl	0.133×10^{-3}	0.513	-0.289	+0.23	

v) Eyring Studies (Scheme 4.24)

Reaction conditions: An oven dried reaction tube, **4.5a'** (0.217 mmol, 1 equiv), benzaldehyde **3.18a** (0.217 mmol, 1 equiv), HE (0.217 mmol, 1 equiv), and HFIP (0.22 mL) were taken. The reaction tube was properly closed and placed in a pre-heated oil bath at respective temperature for the specified times. The progress of the reaction was analyzed by NMR using 1, 3, 5 trimethoxy benzene as an internal standard. The measure yield of product was plotted against to obtain the slope which gave the rate constant for each substrate.

Temp	$1/T$	k	$\ln(k/T)$
323 K (50 °C)	0.003095	0.041×10^{-3}	-15.87
333 K (60 °C)	0.003003	0.259×10^{-3}	-14.06
343 K (70 °C)	0.002915	0.794×10^{-3}	-12.97
353 K (80 °C)	0.002832	2.41×10^{-3}	-11.89

E. Crystallographic data

Crystallographic data of 4.7ac

Single crystals of compound **4.7ac** suitable for X-ray diffraction were obtained by slow evaporation of the saturated solution of the compound in petroleum ether at room temperature. X-ray crystallographic data were collected using Bruker D8 QUEST diffractometer. Data refinement and cell reduction were carried out by APEX4. Structures were solved by direct methods using Olex2 v1.5 and refined by a full-matrix least-squares method using Olex2 v1.5. All of the non-H atoms were refined anisotropically. The ORTEP diagram was obtained with ORTEP3 software with 40% thermal ellipsoid (see below, Figure 4.15). The crystallographic parameters and refinement data were listed in Table 4.6.

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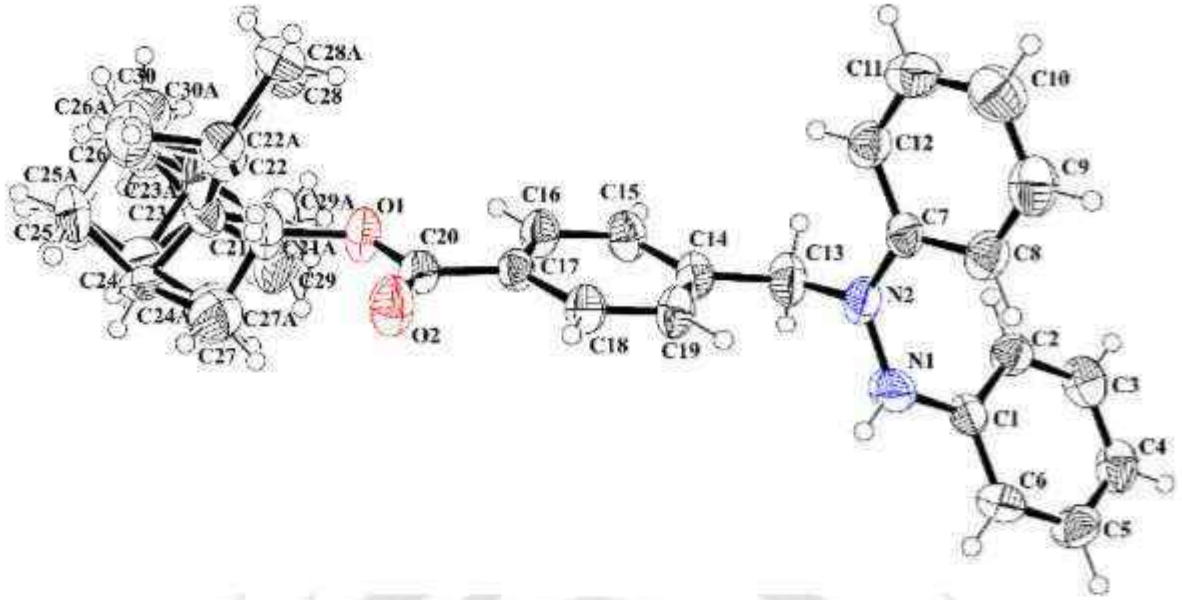


Figure 4.15. Molecular structure of compound **4.7ac** (thermal ellipsoid 40% probability level).

Please note that the terminal ligand bonded to O1 is unequally disordered over two sites. The disorder atoms C21 to C30, C21A to C30A and H21 to H30, H21A to H30A are splitted over two positions with occupancy 0.6, and 0.4 respectively.

Table 4.6. Crystal data and structure refinement for **4.7ac**

Identification code	SK_716_0m_a	
CCDC	2359136	
Empirical formula	$C_{30}H_{34}N_2O_2$	
Formula weight	454.59	
Temperature/K	295.00	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 11.5525(8)Å	α = 90°
	b = 7.9187(6) Å	β =96.854(2) °
	c = 28.056(2) Å	γ = 90°
Volume/Å^3	2548.2(3)	
Z	4	
ρ_{calc}g/cm^3	1.185	
μ/mm^{-1}	0.074	
F (000)	976.0	
Crystal size/mm^3	0.39 × 0.37 × 0.18	

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Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.676 to 49.996
Index ranges	$-13 \leq h \leq 13$, $-9 \leq k \leq 9$, $-33 \leq l \leq 33$
Reflections collected	53951
Independent reflections	4482 [R_{int} = 0.0632, R_{sigma} = 0.0324]
Data/restraints/parameters	4482/213/375
Goodness-of-fit on F^2	1.142
Final R indexes [I>=2σ (I)]	R_1 = 0.0994, wR_2 = 0.2239
Final R indexes [all data]	R_1 = 0.1246, wR_2 = 0.2439
Largest diff. peak/hole / e $Å^{-3}$	0.94/-0.31

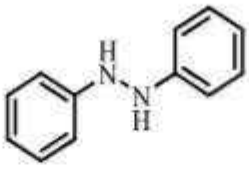
Table 4.7. Atomic Occupancy for **4.7ac**

Atom	***Occupancy***	**Atom**	***Occupancy***	**Atom**	***Occupancy***
C21	0.60(2)	H21	0.60(2)	C22	0.60(2)
C23	0.60(2)	C24	0.60(2)	H24	0.60(2)
C25	0.60(2)	H25A	0.60(2)	H25B	0.60(2)
C26	0.60(2)	H26A	0.60(2)	H26B	0.60(2)
C27	0.60(2)	H27A	0.60(2)	H27B	0.60(2)
C28	0.60(2)	H28A	0.60(2)	H28B	0.60(2)
H28C	0.60(2)	C29	0.60(2)	H29A	0.60(2)
H29B	0.60(2)	H29C	0.60(2)	C30	0.60(2)
H30A	0.60(2)	H30B	0.60(2)	H30C	0.60(2)
C21A	0.40(2)	H21A	0.40(2)	C27A	0.40(2)
H27C	0.40(2)	H27D	0.40(2)	C24A	0.40(2)
H24A	0.40(2)	C25A	0.40(2)	H25C	0.40(2)
H25D	0.40(2)	C26A	0.40(2)	H26C	0.40(2)
H26D	0.40(2)	C22A	0.40(2)	C23A	0.40(2)
C29A	0.40(2)	H29D	0.40(2)	H29E	0.40(2)
H29F	0.40(2)	C30A	0.40(2)	H30D	0.40(2)
H30E	0.40(2)	H30F	0.40(2)	C28A	0.40(2)
H28D	0.40(2)	H28E	0.40(2)	H28F	0.40(2)

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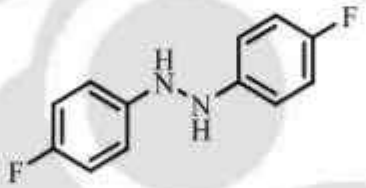
4.6. Analytical data of the products

1, 2-diphenylhydrazine (4.5a')



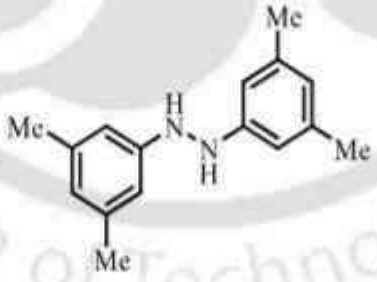
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.20 (m, 4H), 6.87 – 6.83, 6H), 5.62 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.0, 129.5, 120.1, 112.5. Spectroscopic characterization data are in accordance with reported literature.[16]

1, 2-bis(4-fluorophenyl) hydrazine (4.5b')



^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 – 6.90 (m, 4H), 6.81 – 6.77 (m, 4H), 5.55 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.3 (d, $J_{C\text{-}F}$ = 237.7 Hz), 145.0 (d, $J_{C\text{-}F}$ = 2.2 Hz), 116.0 (d, $J_{C\text{-}F}$ = 22.8 Hz), 113.5 (d, $J_{C\text{-}F}$ = 7.7 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -124.96. Spectroscopic characterization data are in accordance with reported literature.[21]

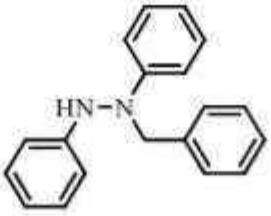
1,2-bis(3,5-dimethylphenyl) hydrazine (4.5e')



^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (s, 6H), 5.46 (s, 2H), 2.25 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.4, 139.3, 121.9, 110.2, 21.6. Spectroscopic characterization data are in accordance with reported literature.[22]

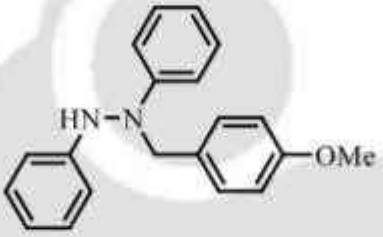
1-benzyl-1, 2-diphenylhydrazine (4.7a)

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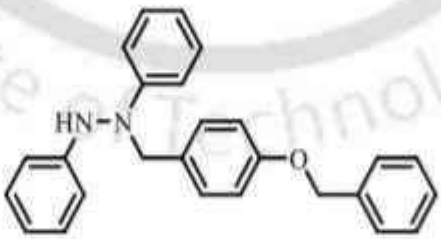
By following the **GP-1**, the title compound **4.7a** was isolated as light-yellow oil (0.126 g, 92%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.20 (m, 9H), 7.01 (d, J = 7.9 Hz, 2H), 6.86 – 6.76 (m, 4H), 5.66 (s, 1H), 4.76 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.0, 147.0, 136.9, 129.5, 129.4, 128.9, 127.9, 127.6, 120.1, 118.8, 113.04, 112.96, 54.4. Spectral data is in accordance to the reported literature.[10]

1-(4-methoxybenzyl)-1, 2-diphenylhydrazine (4.7b)



By following the **GP-1**, the title compound **4.7b** was isolated as light-yellow oil (0.145 g, 95%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.19 (m, 4H), 7.15 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 6.85 – 6.79 (m, 4H), 6.77 (d, J = 7.9 Hz, 2H), 5.59 (s, 1H), 4.68 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.2, 150.1, 147.1, 129.5, 129.41, 129.39, 128.6, 120.0, 118.8, 114.2, 113.2, 113.1, 55.4, 53.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{21}N_2O$: 305.1649; found: 305.1648.

1-(4-(benzyloxy) benzyl)-1, 2-diphenylhydrazine (4.7c)

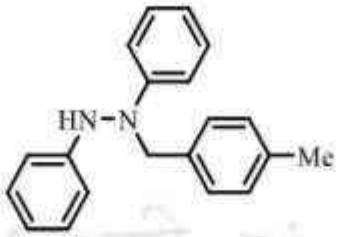


By following the **GP-1**, the title compound **4.7c** was isolated as light-yellow oil (0.173 g, 91%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.36 (m, 4H), 7.34 – 7.29 (m, 1H), 7.25 – 7.19 (m, 4H), 7.14 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 7.9 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.85 – 6.78 (m, 2H), 6.78 – 6.75 (m, 2H), 5.60 (s, 1H), 5.03 (s, 2H), 4.67 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4, 150.1, 147.1, 137.1, 129.5, 129.42, 129.38, 128.9, 128.7, 128.1, 127.6, 123.0,

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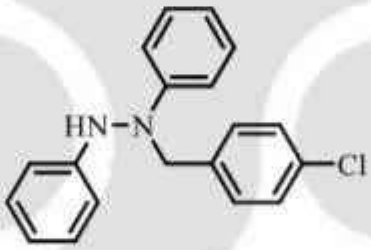
120.0, 118.8, 115.2, 113.10, 113.08, 70.2, 53.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{26}H_{25}N_2O$: 381.1962; found: 381.1961.

1-(4-methylbenzyl)-1, 2-diphenylhydrazine (4.7d)



By following the **GP-1**, the title compound **4.7d** was isolated as light-yellow oil (0.127 g, 88%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1 R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.19 (m, 4H), 7.14 – 7.10 (m, 4H), 7.02 (d, J = 8.1 Hz, 2H), 6.85 – 6.76 (m, 4H), 5.64 (s, 1H), 4.71 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.1, 147.1, 137.2, 136.8, 136.4, 133.7, 129.54, 129.52, 129.4, 129.0, 128.8, 127.9, 120.0, 118.7, 113.1, 113.0, 54.0, 21.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{21}N_2$: 289.1700; found: 289.1701.

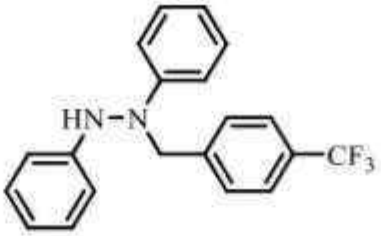
1-(4-chlorobenzyl)-1, 2-diphenylhydrazine (4.7e)



By following the **GP-1**, the title compound **4.7e** was isolated as light-yellow oil (0.133 g, 86%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.21 (m, 5H), 7.19 – 7.17 (m, 3H), 6.98 (d, J = 8.1 Hz, 2H), 6.86 – 6.81 (m, 2H), 6.76 (d, J = 7.9 Hz, 2H), 5.62 (s, 1H), 4.71 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.7, 146.8, 135.5, 133.4, 129.6, 129.5, 129.3, 129.0, 123.0, 120.2, 119.2, 113.1, 113.0, 54.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{18}ClN_2$: 309.1154; found: 309.1152.

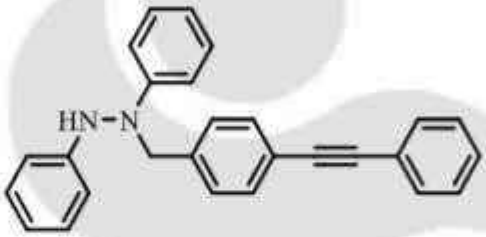
1, 2-diphenyl-1-(4-(trifluoromethyl) benzyl) hydrazine (4.7f)

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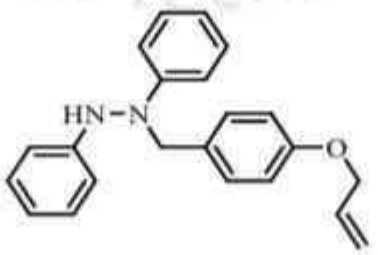
By following the **GP-1**, the title compound **4.7f** was isolated as light-yellow oil (0.142 g, 83%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.26 – 7.21 (m, 4H), 6.97 (d, J = 8.0 Hz, 2H), 6.87 – 6.83 (m, 2H), 6.78 (d, J = 7.7 Hz, 2H), 5.68 (s, 1H), 4.81 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 149.6, 146.7, 141.4, 129.64, 129.57, 128.0, 125.8 (CF_3, q, $J_{C\text{-}F}$ = 3.7 Hz), 120.3, 119.3, 113.0, 112.9, 54.8. ^{19}F NMR (471 MHz, $CDCl_3$): δ -62.48. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{18}F_3N_2$: 343.1417; found: 343.1416.

1, 2-diphenyl-1-(4- (phenyl ethynyl) benzyl) hydrazine (4.7g)



By following the **GP-1**, the title compound **4.7g** was isolated as light-yellow oil (0.148 g, 79%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.51 (m, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.36 – 7.33 (m, 3H), 7.26 – 7.20 (m, 6H), 7.00 (d, J = 7.9 Hz, 2H), 6.87 – 6.81 (m, 2H), 6.77 (d, J = 7.6 Hz, 2H), 5.67 (s, 1H), 4.76 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.9, 146.9, 137.3, 132.1, 131.7, 129.6, 129.5, 128.5, 128.4, 127.9, 123.3, 123.0, 122.6, 120.2, 119.1, 113.04, 113.01, 89.8, 89.2, 54.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{23}N_2$: 375.1856; found: 375.1858.

1-(4-(allyloxy) benzyl)-1, 2-diphenylhydrazine (4.7h)

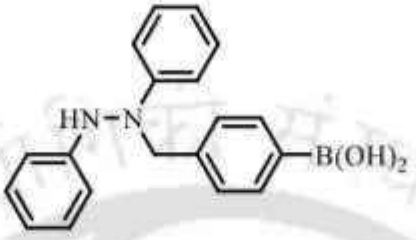


By following the **GP-1**, the title compound **4.7h** was isolated as light-yellow oil (0.124 g, 75%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.19 (m, 4H), 7.13 (d, J = 7.9 Hz, 2H), 7.02 (d, J

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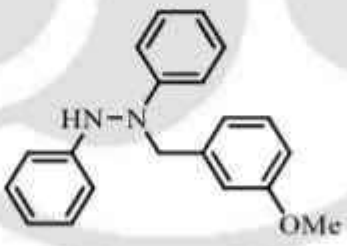
= 8.1 Hz, 2H), 6.85 – 6.79 (m, 4H), 6.76 (d, J = 7.9 Hz, 2H), 6.06 – 6.00 (m, 1H), 5.60 (s, 1H), 5.39 (d, 17.3 Hz, 1H), 5.27 (d, J = 10.4 Hz, 1H), 4.67 (s, 2H), 4.50 (d, J = 4.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 158.1, 150.0, 147.0, 133.3, 129.5, 129.4, 129.3, 128.8, 120.0, 118.7, 117.9, 115.0, 113.07, 113.05, 68.9, 53.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{22}H_{23}N_2O$: 331.1805; found: 331.1803.

(4-((1,2-diphenylhydrazineyl) methyl) phenyl) boronic acid (4.7i)



By following the **GP-1**, the title compound **4.7i** was isolated as white powder (0.129 g, 81%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 2:8, R_f = 0.25). m.p. 127 – 130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.27 – 7.21 (m, 4H), 7.03 – 6.99 (m, 2H), 6.88 – 6.81 (m, 3H), 6.79 – 6.76 (m, 1H), 5.72 (s, 1H), 4.84 – 8.79 (m, 3H), 4.64 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.9, 147.0, 142.0, 136.2, 134.1, 129.6, 129.5, 127.5, 120.2, 119.1, 113.0, 55.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{20}BN_2O_2$: 319.1613; found: 319.1614.

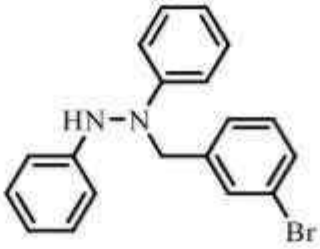
1-(3-methoxybenzyl)-1, 2-diphenylhydrazine (4.7j)



By following the **GP-1**, the title compound **4.7j** was isolated as light-yellow oil (0.128 g, 84%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.19 (m, 5H), 7.02 – 7.00 (m, 2H), 6.86 – 6.76 (m, 4H), 6.78 – 6.77 (m, 3H), 5.68 (s, 1H), 4.72 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.0, 150.0, 147.0, 138.6, 129.9, 129.5, 129.4, 120.1, 118.8, 113.4, 113.0, 112.93, 112.90, 55.3, 54.4. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{21}N_2O$: 305.1649; found: 305.1638.

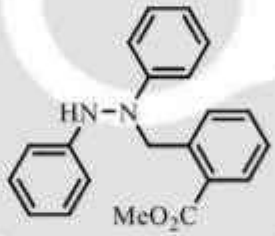
1-(3-bromobenzyl)-1, 2-diphenylhydrazine (4.7k)

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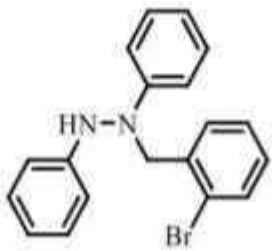
By following the **GP-1**, the title compound **4.7k** was isolated as light-yellow oil (0.132 g, 75%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 – 7.57 (m, 1H), 7.25 – 7.20 (m, 6H), 7.15 – 7.12 (m, 1H), 6.93 – 6.91 (m, 2H), 6.85 – 6.81 (m, 2H), 6.78 – 6.76 (m, 2H), 5.83 (s, 1H), 4.80 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.6, 147.0, 136.1, 133.3, 129.6, 129.5, 128.9, 128.8, 127.7, 123.5, 123.0, 120.2, 119.0, 112.8, 112.7, 56.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{17}BrN_2$: 353.0648; found: 353.0649.

Methyl 2-((1, 2-diphenylhydrazineyl) methyl) benzoate (4.7l)



By following the **GP-1**, the title compound **4.7l** was isolated as white powder (0.123 g, 74%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). m.p. 124 – 126 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, J = 7.7 Hz, 1H), 7.47 – 7.45 (m, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.24 – 7.19 (m, 4H), 6.93 (d, J = 8.3 Hz, 2H), 6.84 – 6.80 (m, 2H), 6.75 (d, J = 8.0 Hz, 2H), 5.87 (s, 1H), 5.17 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 167.8, 149.9, 147.0, 139.3, 132.6, 131.4, 129.5, 129.42, 129.37, 128.0, 127.2, 120.0, 118.7, 112.8, 112.5, 54.1, 52.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{21}H_{21}N_2O_2$: 333.1598; found: 333.1591. Characteristic IR band: $\nu_{(C=O)}$: 1713 cm^{-1}.

1-(2-bromobenzyl)-1, 2-diphenylhydrazine (4.7m)

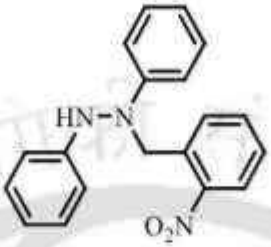


By following the **GP-1**, the title compound **4.7m** was isolated as light-yellow oil (0.123 g, 70%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2,

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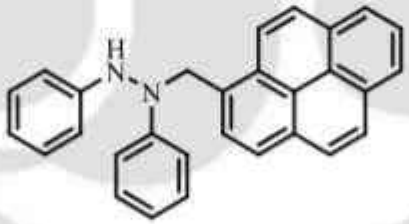
R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.38 (m, 2H), 7.24 – 7.19 (m, 4H), 7.17 – 7.14 (m, 2H), 6.97 (d, J = 8.1 Hz, 2H), 6.86 – 6.80 (m, 2H), 6.75 (d, J = 7.9 Hz, 2H), 5.68 (s, 1H), 4.71 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.6, 146.7, 139.6, 130.8, 130.7, 130.4, 129.6, 129.5, 126.4, 123.0, 120.2, 119.2, 113.0, 112.9, 54.4. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{18}BrN_2$: 353.0648; found: 353.0645.

1-(2-nitrobenzyl)-1, 2-diphenylhydrazine (4.7n)



By following the **GP-1**, the title compound **4.7n** was isolated as light-yellow oil (0.117 g, 73%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 8.1 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.52 – 7.50 (m, 1H), 7.45 – 7.42 (m, 1H), 7.25 – 7.19 (m, 5H), 6.89 (d, J = 8.1 Hz, 2H), 6.84 (t, J = 7.3 Hz, 2H), 6.75 (d, J = 7.9 Hz, 2H), 5.80 (s, 1H), 5.15 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.4, 148.7, 146.6, 133.9, 133.7, 129.64, 129.59, 129.3, 128.3, 125.7, 120.4, 119.5, 112.8, 112.7, 54.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{18}N_3O_2$: 320.1394; found: 320.1395.

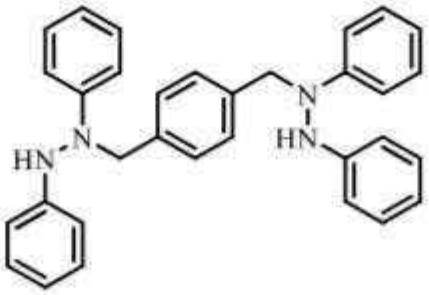
1, 2-diphenyl-1-(pyren-1-ylmethyl) hydrazine (4.7o)



By following the **GP-1**, the title compound **4.7o** was isolated as light-yellow oil (0.165 g, 83%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 – 8.17 (m, 3H), 8.09 – 8.04 (m, 3H), 8.03 – 7.99 (m, 2H), 7.84 (d, J = 7.7 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.18 (t, J = 7.3 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6.87 – 6.81 (m, 2H), 6.71 (d, J = 8.1 Hz, 2H), 5.74 (s, 1H), 5.48 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.1, 147.0, 131.4, 131.0, 130.9, 129.7, 129.6, 129.5, 129.2, 128.0, 127.6, 127.5, 126.2, 126.1, 125.5, 125.4, 125.2, 124.89, 124.86, 122.7, 120.1, 118.9, 113.1, 112.9, 52.4. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{29}H_{23}N_2$: 399.1856; found: 399.1835.

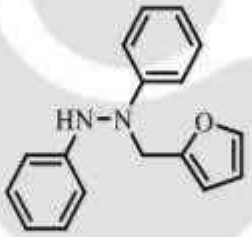
1, 4-bis ((1, 2-diphenylhydrazineyl) methyl) benzene (4.7p)

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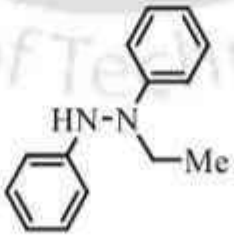
By following the **GP-1**, the title compound **4.7p** was isolated as light-yellow oil (0.186 g, 79%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (600 MHz, $CDCl_3$): 7.24 – 7.18 (m, 12H), 7.00 (d, J = 7.9 Hz, 4H), 6.85 – 6.80 (m, 4H), 6.76 (d, J = 7.7 Hz, 4H), 5.63 (s, 2H), 4.72 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.0, 147.0, 136.2, 129.54, 129.45, 128.4, 120.1 118.9, 113.02, 113.00, 54.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{32}H_{31}N_4$: 471.2544; found: 471.2535.

1-(furan-2-ylmethyl)-1, 2-diphenylhydrazine (4.7q)



By following the **GP-1**, the title compound **4.7q** was isolated as light-yellow oil (0.102 g, 77%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 1H), 7.25 – 7.21 (m, 4H), 7.06 (d, J = 7.8 Hz, 2H), 6.87 – 6.80 (m, 4H), 6.29 – 6.28 (m, 1H), 6.20 (d, J = 2.7 Hz, 1H), 5.78 (s, 1H), 4.66 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 150.8, 149.5, 147.3, 142.6, 129.5, 129.3, 120.1, 119.3, 113.5, 112.9, 110.4, 108.9, 47.3. Spectral data is in accordance to the reported literature.[9a]

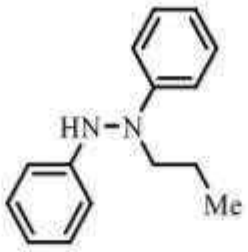
1-ethyl-1, 2-diphenylhydrazine (4.14)



By following the **GP-1**, the title compound **4.14** was isolated as light-yellow oil (0.040 g, 75%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.18 (m, 4H), 6.90 (d, J = 7.9 Hz, 2H), 6.82 – 6.77 (m, 4H), 5.55 (s, 1H), 3.56 (q, J = 7.0 Hz, 2H), 1.20 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.7, 148.1, 129.5, 129.4, 119.6, 118.7, 113.2, 112.3, 46.0, 10.9. Spectral data is in accordance to the reported literature.[45]

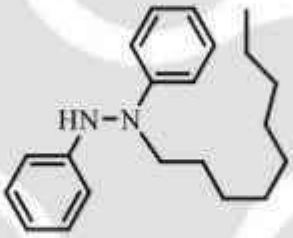
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1, 2-diphenyl-1-propylhydrazine (4.7s)



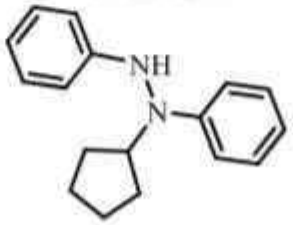
By following the **GP-1**, the title compound **4.7s** was isolated as light-yellow oil (0.040 g, 71%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.20 (m, 4H), 6.89 (d, J = 7.8 Hz, 2H), 6.83 – 6.78 (m, 4H), 5.59 (s, 1H), 3.47 – 3.44 (m, 2H), 1.73 – 1.68 (m, 2H), 0.97 (t, J = 8.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.0, 147.8, 129.5, 129.4, 119.6, 118.6, 112.9, 112.3, 54.0, 19.6, 11.7. Spectral data is in accordance to the reported literature.[9a]

1-nonyl-1, 2-diphenylhydrazine (4.7t)



By following the **GP-1**, the title compound **4.7t** was isolated as light-yellow oil (0.054 g, 69%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 – 7.20 (m, 4H), 6.89 (d, J = 8.0 Hz, 2H), 6.83 – 6.77 (m, 4H), 5.60 (s, 1H), 3.50 – 3.47 (m, 2H), 1.66 (p, J = 7.3 Hz, 2H), 1.34 – 1.25 (m, 12H), 0.89 – 0.86 (m, 3H).^{13}C NMR (151 MHz, $CDCl_3$): δ 149.9, 147.8, 129.5, 129.4, 119.6, 118.5, 112.9, 112.3, 52.1, 32.0, 29.7, 29.6, 29.4, 27.3, 26.1, 22.8, 14.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{21}H_{31}N_2$: 311.2482; found: 311.2483.

1-cyclopentyl-1, 2-diphenylhydrazine (4.7u)

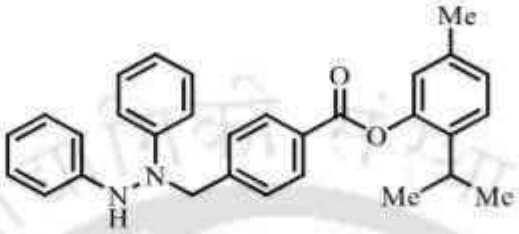


By following the **GP-1**, the title compound **4.7u** was isolated as light-yellow oil (0.031 g, 49%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 – 7.92 (m, 2H), 7.54 – 7.42 (m, 3H), 7.31 – 7.29 (m,

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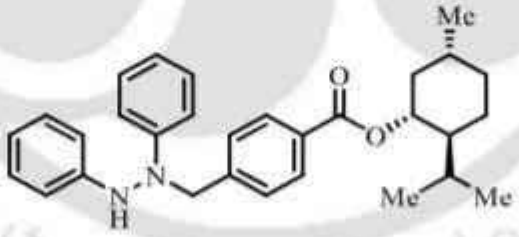
1H), 7.22 – 7.19 (m, 1H), 7.10 – 7.06 (m, 1H), 6.91 – 6.72 (m, 2H), 3.76 – 3.74 (m, 2H), 2.88 – 2.86 (m, 1H), 2.84 – 2.82 (m, 1H), 2.56 – 2.52 (m, 1H), 1.87 – 1.84 (m, 2H), 1.28 – 1.25 (brs, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 131.1, 129.4, 129.2, 128.8, 123.0, 120.6, 119.6, 118.6, 114.3, 111.8, 111.4, 68.1, 28.8, 26.0, 25.8, 24.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{21}N_2$: 253.1700; found: 253.1701.

2-isopropyl-5-methylphenyl 4-((1, 2-diphenylhydrazineyl) methyl) benzoate (4.7aa)



By following the **GP-1**, the title compound **4.7aa** was isolated as light-yellow oil (0.185 g, 82%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.27 – 7.21 (m, 5H), 7.07 – 7.05 (m, 1H), 7.00 – 6.98 (m, 2H), 6.92 (s, 1H), 6.88 – 6.82 (m, 2H), 6.80 – 6.78 (m, 2H), 5.74 (s, 1H), 4.85 (s, 2H), 3.08 – 2.98 (m, 1H), 2.33 (s, 3H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 165.3, 149.6, 148.2, 146.8, 143.4, 137.3, 136.8, 130.7, 129.6, 129.5, 128.9, 127.9, 127.3, 126.6, 122.9, 120.3, 119.3, 113.0, 112.9, 55.1, 27.4, 23.2, 21.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{30}H_{31}N_2O_2$: 451.2381; found: 451.2382.

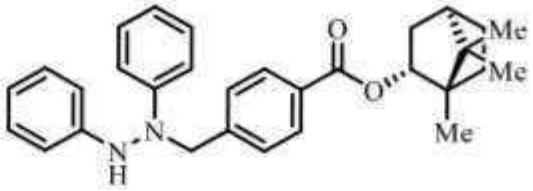
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 4-((1,2-diphenylhydrazineyl) methyl) benzoate (4.7ab)



By following the **GP-1**, the title compound **4.7ab** was isolated as light-yellow oil (0.192 g, 84%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.25 – 7.21 (m, 4H), 6.98 (d, J = 8.3 Hz, 2H), 6.87 – 6.81 (m, 2H), 6.78 (d, J = 8.1 Hz, 2H), 5.70 (s, 1H), 4.94 – 4.89 (m, 1H), 4.81 (s, 2H), 2.12 – 2.10 (m, 1H), 1.96 – 1.92 (m, 1H), 1.73 – 1.71 (m, 2H), 1.57 – 1.51 (m, 3H), 1.15 – 1.05 (m, 2H), 0.93 – 0.90 (m, 6H), 0.78 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.0, 149.7, 146.8, 142.2, 130.2, 129.6, 129.5, 127.6, 120.2, 119.2, 113.0, 112.9, 75.0, 54.8, 47.4, 41.1, 34.4, 31.6, 26.6, 23.7, 22.2, 20.9, 16.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{30}H_{37}N_2O_2$: 457.2850; found: 457.2848.

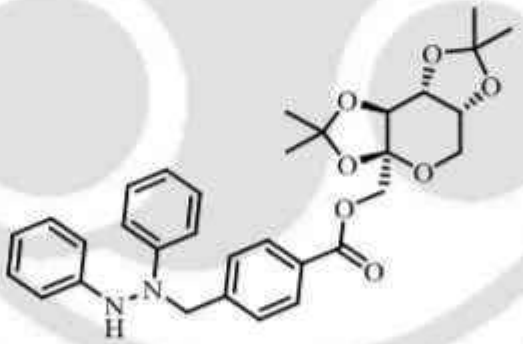
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(1S,2R,4R)-1,7,7-trimethylbicyclo [2.2.1] heptan-2-yl 4-((1,2-diphenylhydrazineyl) methyl) benzoate (4.7ac)



By following the **GP-1**, the title compound **4.7ac** was isolated as light-yellow solid (0.195 g, 86%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). m.p. 136 – 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.26 – 7.20 (m, 4H), 6.99 – 6.97 (m, 2H), 6.87 – 6.81 (m, 2H), 6.79 – 6.77 (m, 2H), 5.69 (s, 1H), 4.92 – 4.89 (m, 1H), 4.81 (s, 2H), 1.94 – 1.87 (m, 2H), 1.80 – 1.78 (m, 1H), 1.75 – 1.70 (m, 1H), 1.64 – 1.60 (m, 1H), 1.26 – 1.20 (m, 1H), 1.17 – 1.13 (m, 1H), 1.10 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.9, 149.7, 146.8, 142.3, 130.2, 130.1, 129.6, 129.5, 127.7, 120.3, 119.2, 112.98, 112.95, 81.8, 54.8, 49.2, 47.2, 45.3, 39.1, 33.9, 27.2, 20.3 20.2, 11.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{30}H_{35}N_2O_2$: 455.2694; found: 455.2693.

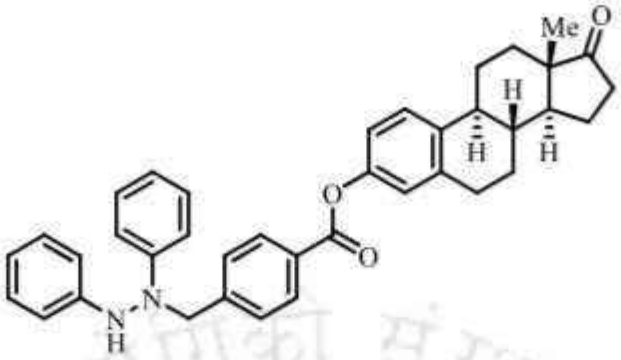
((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis ([1,3] dioxolo) [4,5-b:4',5'-d] pyran-3a-yl) methyl 4-((1,2-diphenylhydrazineyl) methyl) benzoate (4.7ad)



By following the **GP-1**, the title compound **4.7ad** was isolated as light-yellow oil (0.233 g, 83%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.25 – 7.19 (m, 4H), 6.97 (d, J = 8.1 Hz, 2H), 6.86 – 6.81 (m, 2H), 6.76 (d, J = 7.8 Hz, 2H), 5.69 (s, 1H), 4.80 (s, 2H), 4.66 – 4.62 (m, 2H), 4.44 (d, J = 2.5 Hz, 1H), 4.32 (d, J = 11.8 Hz, 1H), 4.25 (d, J = 8.0 Hz, 1H), 3.95 (d, J = 12.8 Hz, 1H), 3.80 (d, J = 13.0 Hz, 1H), 1.54 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.8, 149.7, 146.8, 142.8, 130.3, 129.6, 129.5, 129.2, 127.7, 120.2, 119.2, 113.0, 112.9, 109.3, 109.0, 101.8, 70.9, 70.7, 70.2, 65.5, 61.5, 55.0, 26.7, 26.0, 25.7, 24.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{32}H_{37}N_2O_7$: 561.2596; found: 561.2597.

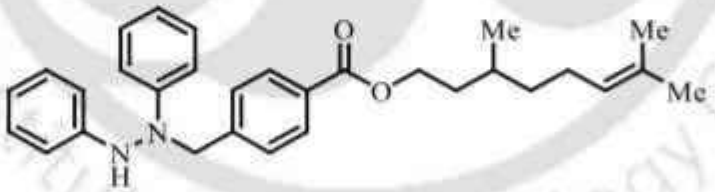
TH-3765_196122031

(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-((1, 2-diphenylhydrazineyl) methyl) benzoate (4.7ae)



By following the **GP-1**, the title compound **4.7ae** was isolated as light-yellow oil (0.217 g, 76%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.5 Hz, 1H), 7.26 – 7.21 (m, 4H), 6.99 – 6.96 (m, 3H), 6.93 (s, 1H), 6.88 – 6.83 (m, 2H), 6.79 (d, J = 7.8 Hz, 2H), 5.72 (s, 1H), 4.84 (s, 2H), 2.94 – 2.92 (m, 2H), 2.54 – 2.49 (m, 1H), 2.44 – 2.41 (m, 1H), 2.35– 2.29 (m, 1H), 2.19 – 2.12 (m, 1H), 2.09 – 1.97 (m, 4H), 1.66 – 1.61 (m, 2H),1.56 – 1.43 (m, 5H), 0.92 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 220.9, 165.3, 149.7, 148.9, 146.8, 143.3, 138.2, 137.6, 130.8, 129.64, 129.55, 129.0, 127.9, 126.6, 121.8, 120.3, 119.3, 119.0, 113.1, 113.0, 55.2, 50.6, 48.1, 44.3, 38.2, 36.0, 31.7, 29.6, 26.5, 25.9, 21.7, 14.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{38}H_{39}N_2O_3$: 571.2956; found: 571.2957.

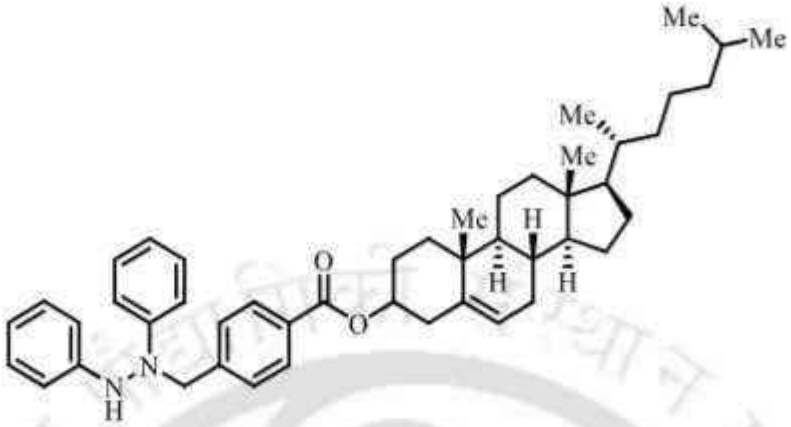
3,7-dimethyloct-6-en-1-yl 4-((1, 2-diphenylhydrazineyl) methyl) benzoate (4.7af)



By following the **GP-1**, the title compound **4.7af** was isolated as light-yellow oil (0.178 g, 78%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.26 – 7.20 (m, 4H), 6.98 (d, J = 8.0 Hz, 2H), 6.87 – 6.81 (m, 2H), 6.77 (d, J = 7.8 Hz, 2H), 5.68 (s, 1H), 5.09 (t, J = 7.1 Hz, 1H), 4.81 (s, 2H), 4.37 – 4.30 (m, 2H), 2.07 – 1.93 (m, 2H), 1.84 – 1.76 (m, 2H), 1.66 (s, 3H), 1.60 (s, 3H), 1.43 – 1.36 (m, 1H), 1.25 – 1.19 (m, 2H), 0.96 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.5, 149.7, 146.8, 142.4, 131.5, 130.1, 129.9, 129.6, 129.5, 129.2, 127.7, 124.7, 123.0, 120.3, 119.2, 113.03, 112.95, 63.7, 54.9, 37.1, 35.6, 29.7, 25.9, 25.5, 19.6, 17.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{30}H_{37}N_2O_2$: 457.2850; found: 457.2846.

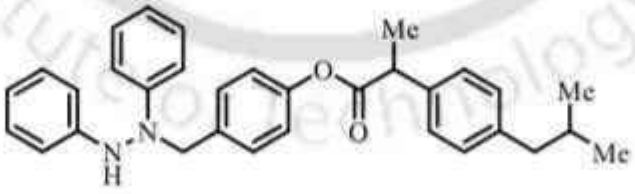
TH-3765_196122031

(8S, 9S, 10R, 13R, 14S, 17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-((1, 2-diphenyl-2l2-diazaneyl) methyl) benzoate (4.7ag)



By following the **GP-1**, the title compound **4.7ag** was isolated as light-yellow solid (0.285 g, 83%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). m.p. 130 – 133 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.25 – 7.20 (m, 4H), 6.97 (d, J = 8.2 Hz, 2H), 6.86 – 6.81 (m, 2H), 6.77 (d, J = 7.9 Hz, 2H), 5.69 (s, 1H), 5.41 (m, 1H), 4.87 – 4.80 (m, 3H), 2.44 (d, J = 7.8 Hz, 2H), 2.04 – 1.97 (m, 3H), 1.92 – 1.90 (m, 1H), 1.86 – 1.82 (m, 1H), 1.74 – 1.68 (m, 1H), 1.57 – 1.42 (m, 6H), 1.38 – 1.33 (m, 3H), 1.20 – 1.08 (m, 7H), 1.06 (s, 3H), 1.03 – 0.96 (m, 4H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 – 0.86 (m, 6H), 0.69 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 165.8, 149.7, 146.8, 142.2, 139.7, 130.3, 130.1, 129.6, 129.5, 127.6, 123.0, 120.2, 119.2, 113.0, 112.9, 74.8, 56.8, 56.2, 54.9, 50.2, 42.4, 39.9, 39.6, 38.3, 37.1, 36.8, 36.3, 35.9, 32.1, 32.0, 28.4, 28.2, 28.0, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{47}H_{63}N_2O_7$: 687.4885; found: 687.4884.

4-((1, 2-diphenylhydrazineyl) methyl) phenyl 2-(4-isobutylphenyl) propanoate (4.7ah)

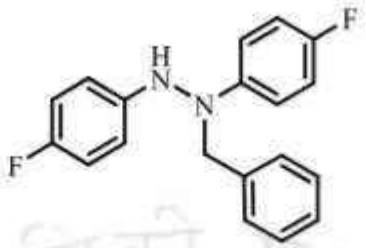


By following the **GP-1**, the title compound **4.7ah** was isolated as light-yellow oil (0.203 g, 85%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.25 (m, 3H), 7.23 – 7.19 (m, 5H), 7.15 – 7.13 (m, 2H), 7.00 – 6.98 (m, 2H), 6.95 – 6.93 (m, 2H), 6.87 – 6.83 (m, 1H), 6.83 – 6.79 (m, 1H), 6.77 – 6.75 (m, 2H), 5.64 (s, 1H), 4.72 (s, 2H), 3.92 (q, J = 7.2 Hz, 1H), 2.47 (d, J = 7.2 Hz, 2H), 1.92 – 1.81 (m, 1H), 1.60 (d, J = 7.2 Hz, 3H), 0.91 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.4, 150.3, 149.8, 149.0, 146.9, 141.0, 137.3, 134.3, 131.1, 129.7, 129.6, 129.50, 129.47, 129.2, 128.9, 127.3, 123.0, 121.8, 120.12, 120.05, 118.9, 113.02, 113.01,

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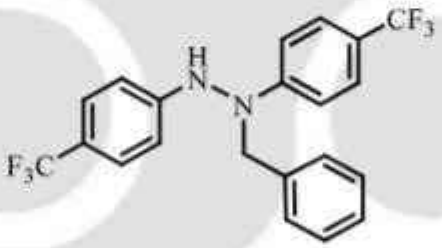
112.5, 53.9, 45.4, 45.2, 30.3, 22.5, 18.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{32}H_{35}N_2O_2$: 479.2694; found: 479.2693.

1-benzyl-1, 2-bis(4-fluorophenyl) hydrazine (4.17a)



By following the **GP-2**, the title compound **4.17a** was isolated as light-yellow oil (0.090 g, 58%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 3H), 7.19 (d, J = 6.9 Hz, 2H), 6.95 – 6.90 (m, 6H), 6.73 – 6.70 (m, 2H), 5.52 (s, 1H), 4.67 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.4 (*d*, $J_{C\text{-}F}$ = 237.8 Hz), 156.8 (*d*, $J_{C\text{-}F}$ = 237.8 Hz) 146.5 (*d*, $J_{C\text{-}F}$ = 1.8 Hz), 143.1 (*d*, $J_{C\text{-}F}$ = 1.8 Hz), 136.2, 128.9, 128.1, 127.8, 116 (*d*, $J_{C\text{-}F}$ = 22.6 Hz), 115.8 (*d*, $J_{C\text{-}F}$ = 22.6 Hz), 114.6 (*d*, $J_{C\text{-}F}$ = 7.6 Hz), 114.2 (*d*, $J_{C\text{-}F}$ = 7.6 Hz), 55.3. ^{19}F NMR (471 MHz, $CDCl_3$): δ -124.82, -126.39. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{17}F_2N_2$: 311.1355; found: 311.1356.

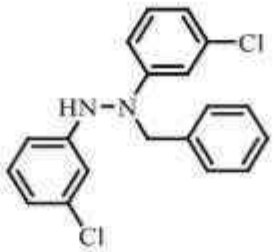
1-benzyl-1,2-bis(4-(trifluoromethyl) phenyl) hydrazine (4.17b)



By following the **GP-2**, the title compound **4.17b** was isolated as light-yellow oil (0.111 g, 54%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:4, R_f = 0.52). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (t, J = 7.0 Hz, 4H), 7.36 – 7.30 (m, 3H), 7.21 (d, J = 7.0 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.2 Hz, 2H), 5.97 (s, 1H), 4.53 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.9, 149.1, 135.5, 129.2, 128.2, 127.8, 127.1 (CF_3, q, $J_{C\text{-}F}$ = 3.6 Hz), 127.0 (CF_3, q, $J_{C\text{-}F}$ = 3.6 Hz), 112.4, 112.2, 54.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ -61.29, -61.44. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{21}H_{17}F_6N_2$: 411.1291; found: 411.1292.

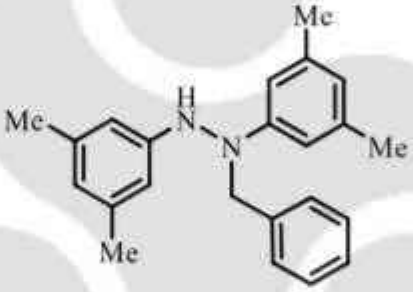
1-benzyl-1, 2-bis(3-chlorophenyl) hydrazine (4.17c)

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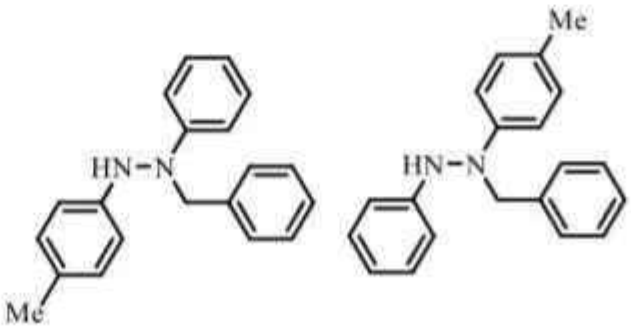
By following the **GP-2**, the title compound **4.17c** was isolated as light-yellow oil (0.110 g, 64%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.29 (m, 3H), 7.20 – 7.12 (m, 4H), 7.05 (s, 1H), 6.89 – 6.80 (m, 3H), 6.76 (s, 1H), 6.61 (d, J = 7.9 Hz, 1H), 5.67 (s, 1H), 4.73 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.9, 147.9, 135.7, 135.54, 134.52, 130.7, 130.5, 129.1, 128.0, 127.9, 120.5, 119.1, 113.1, 112.9, 111.2, 111.0, 54.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{17}Cl_2N_2$: 343.0764; found: 343.0765.

1-benzyl-1, 2-bis(3,5-dimethylphenyl) hydrazine (4.17d)



By following the **GP-2**, the title compound **4.17d** was isolated as light-yellow oil (0.145 g, 88%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.33 – 7.31 (m, 1H), 7.30 – 7.28 (m, 1H), 7.23 – 7.22 (m, 2H), 6.69 (s, 2H), 6.50 – 6.48 (m, 2H), 6.42 (s, 2H), 5.53 (s, 1H), 4.74 (s, 2H), 2.26 (s, 6H), 2.24 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.1, 150.4, 147.2, 139.3, 139.1, 138.9, 137.0, 132.7, 128.9, 127.9, 127.4, 122.0, 120.7, 120.6, 110.8, 110.6, 53.5, 21.9, 21.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{27}N_2$: 331.2169; found: 331.2168.

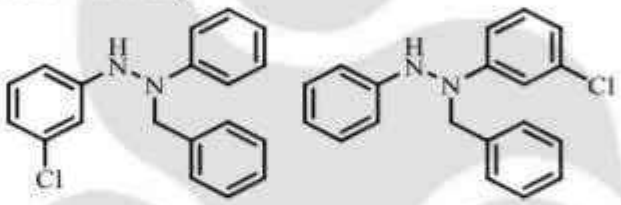
1-benzyl-1-phenyl-2-(*p*-tolyl) hydrazine and 1-benzyl-2-phenyl-1-(*p*-tolyl) hydrazine (4.17e-1 + 4.17e-2)



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By following the **GP-2**, an inseparable mixture of the title compound **4.17e-1** + **4.17e-2** was isolated as light-yellow oil (0.057 g, 79%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR analysis of the reaction mixture showed 2:1, as determined by comparison of the following signals: δ 5.62 (s, N*H*)-major, 5.59 (s, N*H*)-minor.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.19 (m, 7H, **4.17e-1**, major, 67% + m, 7H, **4.17e-2**, minor, 33%), 7.04 – 7.01 (m, 4H, **4.17e-1**, major, 67%), 6.92 – 6.91 (m, 4H, **4.17e-2**, minor, 33%), 6.84 – 6.81 (m, 2H, **4.17e-2**, minor, 33%), 6.79 – 6.77 (m, 2H, **4.17e-1**, major, 67%), 6.69 – 6.67 (m, 1H, **4.17e-1**, major, 67%), 6.65 – 6.63 (m, 1H, **4.17e-2**, minor, 33%), 5.62 (s, 1H, **4.17e-1**, major, 67%), 5.59 (s, 1H, **4.17e-2**, minor, 33%), 4.74 – 4.72 (brs, 2H, **4.17e-1**, major, 67% + 2H, **4.17e-2**, minor, 33%), 2.26 (s, 3H, **4.17e-1**, major, 67% + 3H, **4.17e-2**, minor, 33%). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.2, 147.8, 147.3, 144.6, 137.0, 130.0, 129.9, 129.5, 129.4, 129.0, 128.9, 128.8, 128.8, 128.1, 128.0, 127.9, 127.7, 127.5, 127.5, 127.4, 125.7, 122.5, 119.9, 118.6, 117.7, 113.2, 113.0, 112.9, 54.9, 54.2, 20.7, 20.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{17}Cl_2N_2$: 289.1700; found: 289.1691.

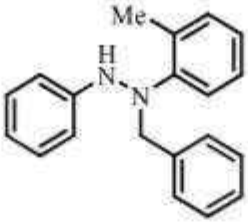
1-benzyl-1-(3-chlorophenyl)-2-phenylhydrazine and 1-benzyl-2-(3-chlorophenyl)-1-phenylhydrazine (4.17f-1 + 4.17f-2)



By following the **GP-2**, an inseparable mixture of the title compound **4.17f-1** + **4.17f-2** was isolated as light-yellow oil (0.100 g, 65%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR analysis of the reaction mixture showed 75:25, as determined by comparison of the following signals: δ 5.67 (s, N*H*)-major, 5.65 (s, N*H*)-minor. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 4H, **4.17f-1**, major, 75%), 7.25 – 7.19 (m, 11H, **4.17f-2**, minor, 25%), 7.15 – 7.06 (m, 2H, **4.17f-1**, major, 75% + m, 1H, **4.17f-2**, minor, 25%), 7.01 – 6.99 (m, 2H, **4.17f-1**, major, 75% + m, 1H, **4.17f-2**, minor, 25%), 6.89 – 6.82 (m, 2H, **4.17f-1**, major, 75%), 6.80 – 6.73 (m, 3H, **4.17f-1**, major, 75% + m, 1H, **4.17f-2**, minor, 25%), 6.63 (d, J = 6.8 Hz, 1H, **4.17f-1**, major, 75%), 5.67 (s, 1H, **4.17f-1,** major, 75%), 5.65 (s, 1H, **4.17f-2**, minor, 25%), 4.73 (brs, 2H, **4.17f-1**, major, 75% + brs, 2H, **4.17f-2**, minor, 25%). ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.3, 149.6, 148.5, 146.4, 136.4, 136.2, 135.5, 135.4, 130.6, 130.4, 129.6, 129.5, 129.0, 128.9, 128.0, 127.8, 127.7, 120.5, 120.0, 119.3, 118.6, 113.21, 113.18, 112.9, 112.8, 111.1, 110.8, 54.7, 53.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{18}ClN_2$: 309.1154; found: 309.1153.

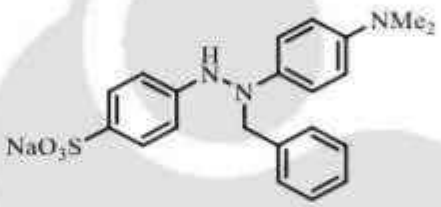
1-benzyl- 2-phenyl-1-(o-tolyl) hydrazine (4.17g)

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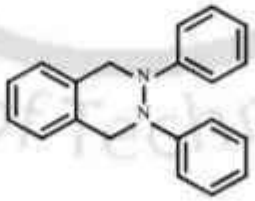
By following the **GP-2**, the title compound **4.17g** was isolated as light-yellow oil (0.086 g, 60%) along with 25% of corresponding azobenzene **4.5h** is recovered using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.22 (m, 7H), 7.12 – 7.06 (m, 2H), 7.02 (d, J = 8.1 Hz, 2H), 6.88 (d, J = 8.0 Hz, 1H), 6.82 – 6.76 (m, 2H), 5.56 (s, 1H), 4.74 (s, 2H), 2.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.0, 144.3, 136.9, 130.7, 129.4, 128.9, 128.1, 127.6, 127.4, 121.6, 119.5, 118.8, 112.9, 112.1, 54.3, 17.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{17}Cl_2N_2$: 289.1700; found: 289.1696.

Sodium 4-(2-benzyl-2-(4-(dimethylamino) phenyl) hydrazineyl) benzenesulfonate (4.17h)



By following the **GP-2**, the title compound **4.17h** was isolated as light-yellow oil (0.103 g, 49%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 5:1, R_f = 0.30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 5H), 7.28 – 7.24 (m, 4H), 6.74 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.6 Hz, 2H), 4.28 (s, 2H), 2.99 (brs, 1H), 2.82 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 140.1, 128.8, 128.7, 128.5, 127.7, 127.2, 122.4, 116.1, 114.5, 113.1, 49.6, 42.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{21}H_{23}N_3NaO_3S$: 420.1353; found: 420.1360.

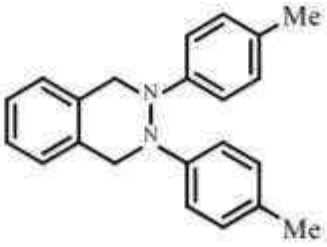
2, 3-diphenyl-1, 2, 3, 4-tetrahydrophthalazine (4.18a)



By following the **GP-3**, the title compound **4.18a** was isolated as light-yellow oil (0.129 g, 90%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.20 (m, 4H), 7.18 – 7.12 (m, 4H), 6.99 – 6.97 (m, 4H), 6.82 – 6.77 (m, 2H), 4.65 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.4, 132.7, 129.6, 126.8, 126.7, 119.3, 113.5, 45.3. Spectral data is in accordance to the reported literature.[46]

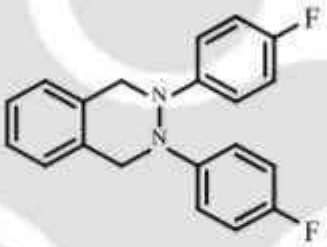
2, 3-di-*p*-tolyl-1, 2, 3, 4-tetrahydrophthalazine (4.18b)

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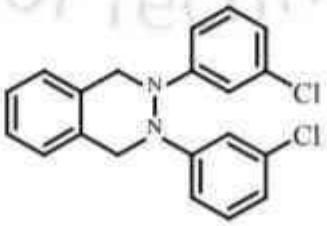
By following the **GP-3**, the title compound **4.18b** was isolated as light-yellow oil (0.137 g, 87%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 – 7.11 (m, 4H), 7.03 (d, J = 8.3 Hz, 4H), 6.90 – 6.88 (m, 4H), 4.61 (s, 4H), 2.24 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.2, 132.9, 130.0, 128.4, 126.7, 126.6, 113.7, 45.3, 20.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{22}H_{23}N_2$: 315.1856; found: 315.1856.

2, 3-bis(4-fluorophenyl)-1, 2, 3, 4-tetrahydrophthalazine (4.18c)



By following the **GP-3**, the title compound **4.18c** was isolated as light-yellow oil (0.110 g, 68%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 – 7.19 (m, 2H), 7.15 – 7.13 (m, 2H), 6.92 – 6.90 (m, 8H), 4.57 (s, 4H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 132.3, 127.0, 126.7, 116.1, 115.9, 115.03, 114.99, 45.6. ^{19}F NMR (565 MHz, $CDCl_3$): δ -125.77. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{17}F_2N_2$: 323.1355; found: 323.1345.

2, 3-bis(3-chlorophenyl)-1, 2, 3, 4-tetrahydrophthalazine (4.18d)

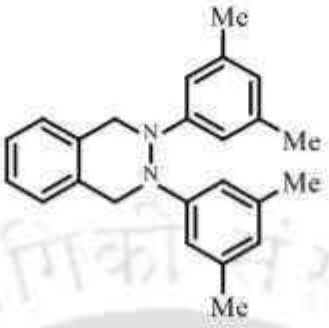


By following the **GP-3**, the title compound **4.18d** was isolated as light-yellow oil (0.128 g, 72%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 – 7.20 (m, 2H), 7.16 – 7.13 (m, 4H), 6.97 (s, 2H), 6.82 – 6.79 (m, 4H), 4.64 (s, 4H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 149.3, 135.6, 131.9,

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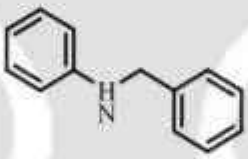
130.7, 127.1, 126.8, 119.6, 113.6, 111.6, 45.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{17}Cl_2N_2$: 355.0764; found: 355.0763.

2,3-bis(3,5-dimethylphenyl)-1,2,3,4-tetrahydrophthalazine (4.18e)



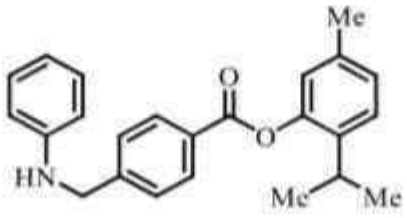
By following the **GP-3**, the title compound **4.18e** was isolated as light-yellow oil (0.139 g, 81%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 – 7.13 (m, 4H), 6.65 (s, 4H), 6.48 (s, 2H), 4.64 (s, 4H), 2.26 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.5, 139.2, 132.8, 126.6, 126.6, 121.1, 111.2, 44.8, 21.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{24}H_{27}N_2$: 343.2169; found: 343.2168.

***N*-benzyl aniline (4.19a)**



Using the reaction condition given in Scheme 4.8, the title compound **4.19a** was isolated as light-yellow oil (99%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.29 – 7.28 (m, 1H), 7.20 – 7.17 (m, 2H), 6.72 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 8.1 Hz, 2H), 4.34 (s, 2H), 4.01 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.3, 139.6, 129.4, 128.8, 127.7, 127.4, 117.7, 113.0, 48.5. Spectral data is in accordance to the reported literature.[47]

2-isopropyl-5-methylphenyl 4-((phenylamino)methyl) benzoate (4.19b)

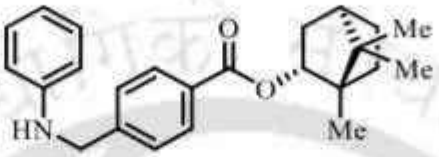


Using the reaction condition given in Scheme 4.8, the title compound **4.19b** was isolated as light-yellow oil (95%) using silica gel column chromatography with petroleum ether/ethyl

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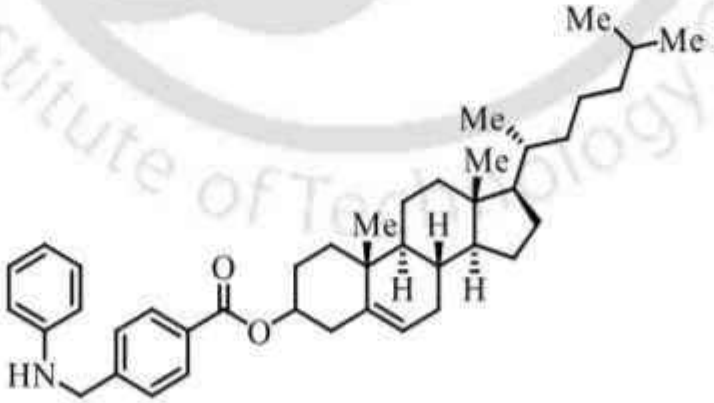
acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz,CDCl$_3$): δ 8.18 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.26 – 7.23 (m, 1H), 7.18 (t, J = 7.8 Hz, 2H), 7.06 (d, J = 7.9 Hz, 1H), 6.93 (s, 1H), 6.74 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 7.9 Hz, 2H), 4.46 (s, 2H), 3.04 (hept, J = 6.6 Hz, 1H), 2.34 (s, 3H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 165.3, 148.3, 147.8, 145.9, 137.3, 136.8, 130.7, 129.5, 128.7, 127.5, 127.3, 126.6, 123.0, 118.1, 113.1, 48.1, 27.4, 23.2, 21.0. HRMS (ESI) *m/z*: [M+H]$^+$ calculated for $C_{24}H_{26}NO_2$: 360.1959; found: 360.1960

(1S,2R,4R)-1,7,7-trimethylbicyclo [2.2.1] heptan-2-yl 4-((phenylamino)methyl) benzoate (4.19c)



Using the reaction condition given in Scheme 4.8, the title compound **4.19c** was isolated as light-yellow oil (85%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.97 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.18 – 7.15 (m, 2H), 6.74 – 6.71 (m, 1H), 6.61 – 6.60 (m, 2H), 4.92 – 4.89 (m, 1H), 4.41 (s, 2H), 1.94 – 1.88 (m, 2H), 1.80 (t, J = 3.9 Hz, 1H), 1.77 – 1.70 (m, 1H), 1.63 – 1.57 (m, 1H), 1.26 – 1.21 (m, 2H), 1.17 – 1.13 (m, 1H), 1.11 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (151 MHz, CDCl$_3$): δ 166.0, 147.9, 144.9, 130.0, 129.5, 127.3, 118.0, 113.0, 81.7, 49.2, 48.1, 47.2, 45.2, 39.1, 33.9, 27.2, 20.3, 20.2, 11.8. HRMS (ESI) *m/z*: [M+H]$^+$ calculated for $C_{24}H_{30}NO_2$: 364.2272; found: 364.2275.

(8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-((phenylamino)methyl) benzoate (4.19d)



Using the reaction condition given in Scheme 4.8, the title compound **4.19d** was isolated as light-yellow oil (81%) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.01 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 7.6 Hz, 2H), 6.72 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 7.8 Hz, 2H), 5.42 – 5.41 (m, 1H), 4.88 – 4.81 (m, 1H), 4.41 (s, 2H), 4.14 (s, 1H), 2.45 (d, J = 7.8 Hz, 2H),

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2.04 – 1.97 (m, 3H), 1.93 – 1.90 (m, 1H), 1.86 – 1.80 (m, 1H), 1.76 – 1.72 (m, 1H), 1.58 – 1.44 (m, 6H), 1.40 – 1.34 (m, 3H), 1.21 – 1.10 (m, 7H), 1.07 (s, 3H), 1.04 – 0.96 (m, 4H), 0.92 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 6H), 0.69 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 147.9, 144.9, 139.8, 130.1, 129.9, 129.4, 127.2, 122.9, 118.0, 113.1, 74.7, 56.8, 56.3, 50.2, 48.2, 42.5, 39.9, 39.7, 38.4, 37.2, 36.8, 36.3, 35.9, 32.1, 32.0, 28.4, 28.2, 28.0, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{41}H_{58}NO_2$: 596.4463; found: 596.4464.

4.7. References

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Chapter 5

Tandem reductive alkylation of quinolines to functionalized tetrahydroquinolines enabled by HFIP

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5.1. Introduction

1,2,3,4-Tetrahydroquinoline (THQ) derivatives are an important class of bioactive compounds that are widely utilized in the pharmaceutical, and agrochemical industries and also found as important building blocks in organic synthesis.[1] Further, they are ubiquitous in many pharmacologically active synthetic and natural products including cuspareine, galipinine, and angustrureine.[2] Among the various tetrahydroquinoline derivatives, the *N*-benzyl tetrahydroquinolines (BTHQs) are of foremost interest in pharmaceutical chemistry due to their excellent therapeutic potential.[3,4] They are employed as HDAC6 inhibitor,[3a] UCM1014 melatonin receptor agonists,[3b] β_3-adrenergic receptor agonists,[3c] and antitumor, and anti-HIV agents.[3d] Besides their bioactivities, they are useful as pesticides, antioxidants, corrosion inhibitors, and active components of various dyes.[4] In addition, they are widely applied as organic electronic device materials and hole transporting materials for electrophotography in material science.[5] Likewise, tricyclic oxazino-fused tetrahydroquinolines have received much attention in pharmaceutical chemistry as cannabinoid receptor agonists for potential therapeutic targets of inflammatory, neuropathic pain, and also show promising antioxidant activity.[6] Further, Lilolidine derivatives are employed as fungicides active against rice blast disease, and in potential treatments for asthma, and epilepsy.[7] Some of the selected bioactive compounds containing functionalized-THQs are listed in Figure 5.1.

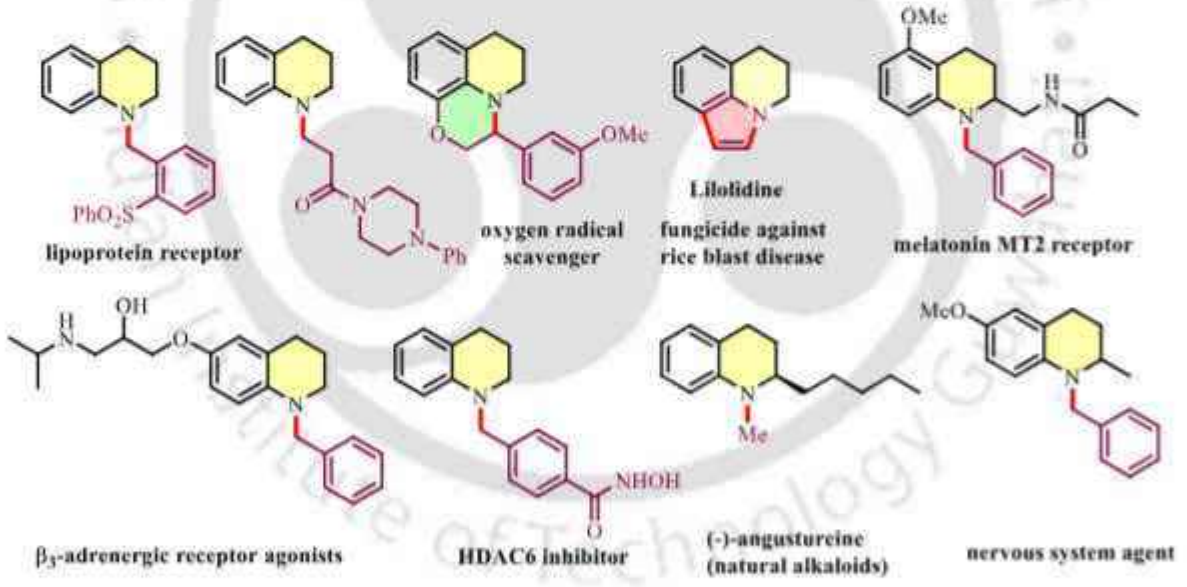


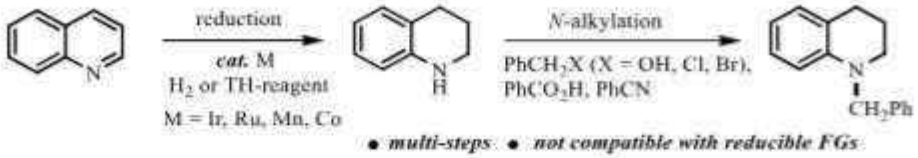
Figure 5.1. Representative bioactive compounds containing functionalized-THQs

Thus, given their importance and usefulness, considerable research efforts have been devoted towards the development of effective synthetic methodologies for constructing functionalized tetrahydroquinolines.

In general, THQs were employed as starting materials for the synthesis of *N*-benzyl THQs using *N*-alkylation with various alkylating agents such as benzyl halide, carboxylic acid, and nitrile.[8-19] However, methods suffer from limited substrate scope and low yields. Alternatively,

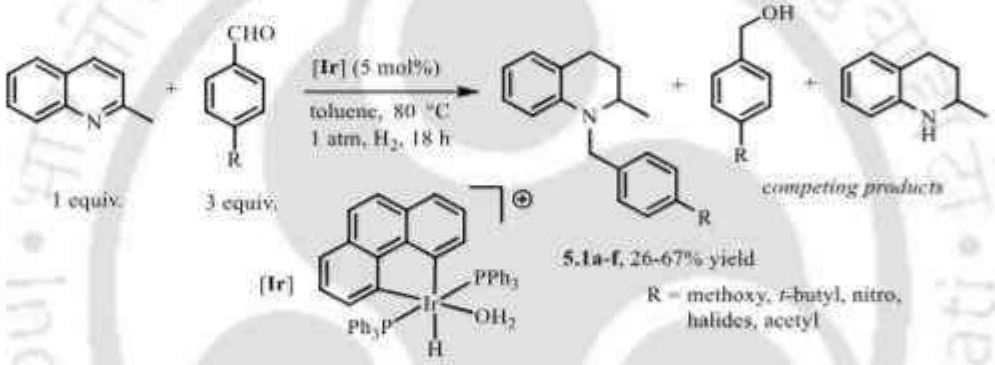
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the reduction of quinoline displays the most common and well-studied approach for the synthesis of THQs. Thus, direct *N*-alkylation of readily available quinolines can offer an upfront approach to construct *N*-benzyl THQs with synthetic ease.



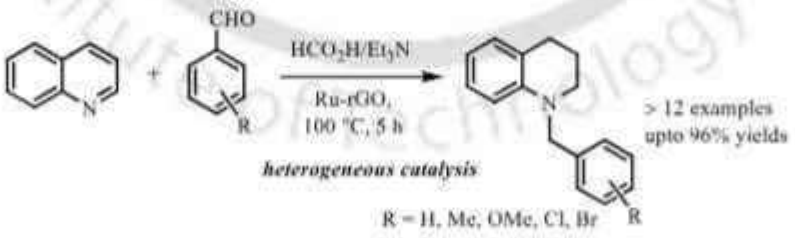
Scheme 5.1. *N*-Benzylation of quinolines to BTHQs.

Earlier research included reductive *N*-benzylation of 2-methyl quinoline with aldehyde using an iridium-benzoquinoline catalyst (Scheme 5.2).[20] The process afforded the desired *N*-benzylation product along with the hydrogenated 2-methyl-THQs and benzyl alcohol as competitive products. Further, strongly electron-donating or withdrawing groups bearing aromatic aldehydes were not suitable under the reaction conditions



Scheme 5.2. Iridium catalyzed reductive *N*-alkylation of quinaldine.

Later, the Lee group developed another method for the direct reductive *N*-benzylation by using a bifunctional Ru-rGO NSs catalyst (Scheme 5.3).[21] However, method failed to obtain the desired *N*-benzylated product with reducible functional groups such as ester, nitro, alkyne, and nitrile groups. Further, both the methods require the use of precious metals.

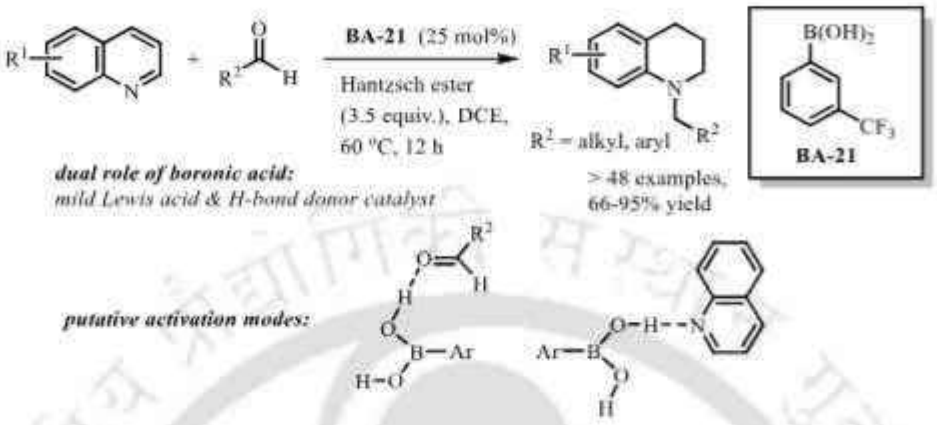


Scheme 5.3. Bifunctional Ru-rGO NSs catalyzed reductive benzylation of quinoline.

In 2021, our group have developed 3-trifluoromethyl-phenylboronic acid-catalysed reductive alkylation of quinoline with aldehyde and Hantzsch ester to *N*-alkyl tetrahydroquinoline (Scheme 5.4).[22]. This protocol features a mild and step-economical synthesis of tetrahydroquinoline from readily available quinolines and aldehydes using Hantzsch ester (HE) as the reductant. The method tolerates a wide variety of reducible-sensitive functional groups,

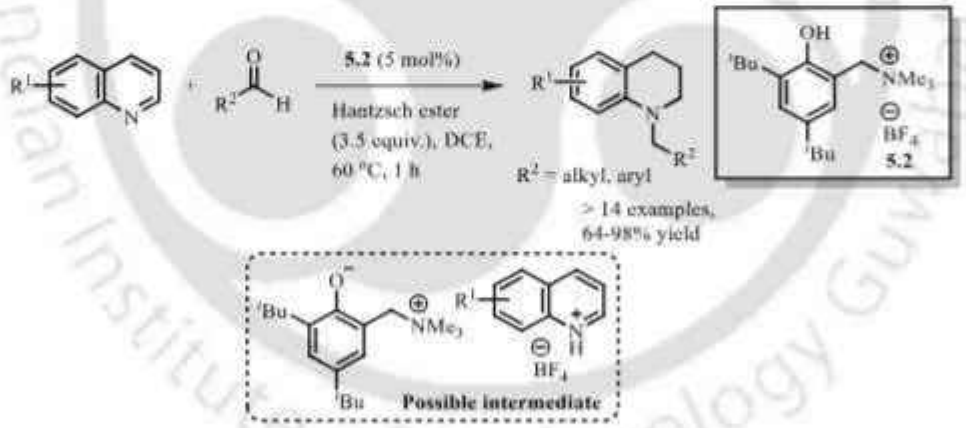
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such as ester, halo, nitro, nitrile, alkyne, allyl, benzyl, thioether etc, and not required any transition metals. Based on extensive NMR studies, a dual role of **BA-21** was proposed in this transformation, where **BA-21** activates quinoline, aldehyde, as well as HE *via* hydrogen bonding interactions. **BA-21** also assists in the condensation of aldehydes with the tetrahydroquinoline intermediate as a Lewis acid.



Scheme 5.4. Arylboronic acid-catalyzed reductive alkylation of quinoline.

Later, Subramanian group reported the same transformation using electrostatically tuned phenol (ETP) (**5.2**) as an organocatalyst (Scheme 5.5).[23]. Various control experiments and NMR spectroscopic investigations suggests that the role of the charged environment in the catalytic transformation.



Scheme 5.5. Electrostatically tuned phenols-catalyzed reductive alkylation of quinoline.

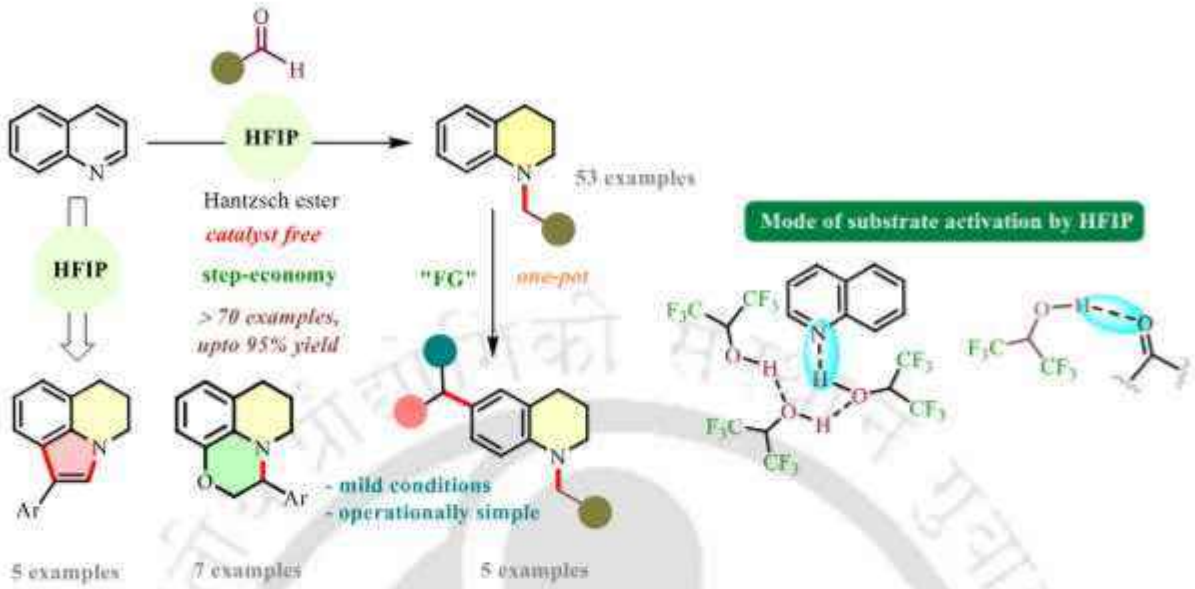
With this brief introduction, my interest is to develop a new method for the synthesis of functionalized tetrahydroquinolines with a wide scope of substrates under mild conditions.

5.2. Present work

In the previous chapter (Chapter 4), I have demonstrated hexafluoroisopropanol (HFIP)-promoted reductive alkylation of azoarenes to *N*-alkylated hydrazines using Hantzsch ester as hydrogen source. A strong hydrogen-bond donor ability of HFIP and cation stabilization of iminium ion species play important role in the transformation. Herein I envisaged that the quinoline moiety can be activated by the hydroxyl group of HFIP *via* hydrogen bonding

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interaction which is then reduced by Hantzsch ester to provide THQs. The in-situ generated THQs subsequently react with aldehyde to form *N*-alkylated THQs.



Scheme 5.5. Tandem reductive alkylation of quinolines to functionalized tetrahydroquinolines enabled by HFIP.

In this chapter, I have developed a new and efficient catalyst-free method for constructing *N*-alkyl tetrahydroquinoline by hexafluoroisopropanol (HFIP)-mediated a one-pot tandem reduction of quinoline with subsequent reductive alkylation using aldehydes. The hydrogen-bonding network-enabled substrate activation is key feature in the process. Further, this was encouraged to design a convenient route for synthesis of tricyclic oxazino-fused-tetrahydroquinoline/ benzoxazine compounds *via* tandem reductive cyclization of 1-aryl-2-(8-quinolinyloxy)ethanones and step-economical synthesis of lilolidine derivatives from readily available quinoline.

5.3. Results and discussion

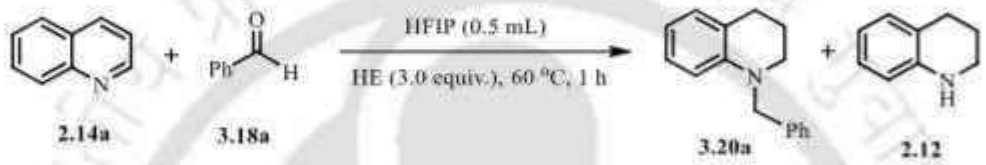
5.3.1. Optimization of reaction condition

The study was initiated with the reaction of quinoline (**2.14a**, 0.5 mmol), benzaldehyde (**3.18a**, 0.5 mmol), Hantzsch ester (HE) (1.5 mmol) in HFIP (0.1 mL) at 60 °C. After 2 h, the desired *N*-alkylated product **3.20a** was obtained in 25% yield, along with 34% intermediate hydrogenated product THQ (**2.12**, Table 5.1, entry 1). The equivalency of HFIP was gradually increased. to improve the yield of desired product **3.20a** (entry 2). When HFIP was used in 0.5 mL, product **3.20a** was obtained in 93% yield (entry 3). Notably, a decrease in the yield of **3.20a** has been observed when the reaction was performed with a mixture of solvents (entries 4-6). The reaction was then examined with other fluorinated polar solvents such as pentafluorophenol and trifluoroethanol, respectively (entries 7-8). The use of pentafluorophenol provided the product **3.20a** in 89% yield, and the use of trifluoroethanol

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furnished the product **3.20a** in 78% yield. Furthermore, a variety of strong polar solvents such as DMF and DMSO were investigated. They have failed to promote the reaction (entries 10-11). The yield of **3.20a** was decreased by reducing the reaction time (entry 12) and also by reducing the reaction temperature (entry 13). Then, the reaction was examined with $-CF_3$ functionalized thiourea as hydrogen-bond donor catalyst in DCE, providing the product **3.20a** in 56% yield, indicating that hydrogen-bonding donor property plays a role in this transformation (entry 14). I have also checked the reaction by replacing HFIP with a relatively weak hydrogen bond donor solvent, isopropanol, which failed to provide any desired product **3.20a** (entry 15).

Table 5.1. Optimization of reaction conditions[a]



2.14a 3.18a 3.20a 2.12

entry	deviation from above	yield of **3.20a** (%)
1	HFIP (0.1 mL)	25%, (34% of **2.12**)
2	HFIP (0.2 mL, 0.3 mL, 0.4 mL)	38%, 67%, 83%
3	none	93%
4	HFIP: DCE (1:3, 0.5 mL)	28%
5	HFIP:CH_3OH (1:3, 0.5 mL)	19%
6	HFIP: toluene (1:3, 0.5 mL)	16%
7	with pentafluorophenol (0.5 mL)	89%
8	with trifluoroethanol (0.5 mL)	78%
9	with CH_3OH (0.5 mL)	10%
10	with DMF (0.5 mL)	0%
11	with DMSO (0.5 mL)	0%
12	with 15 min, 30 min, 45 min	17%, 32%, 67%
13	at 25 °C, at 45 °C	0%, 11%
14[b]	with HBD catalyst (**3.19f**)	56%
15	with isopropanol (0.5 mL)	0%

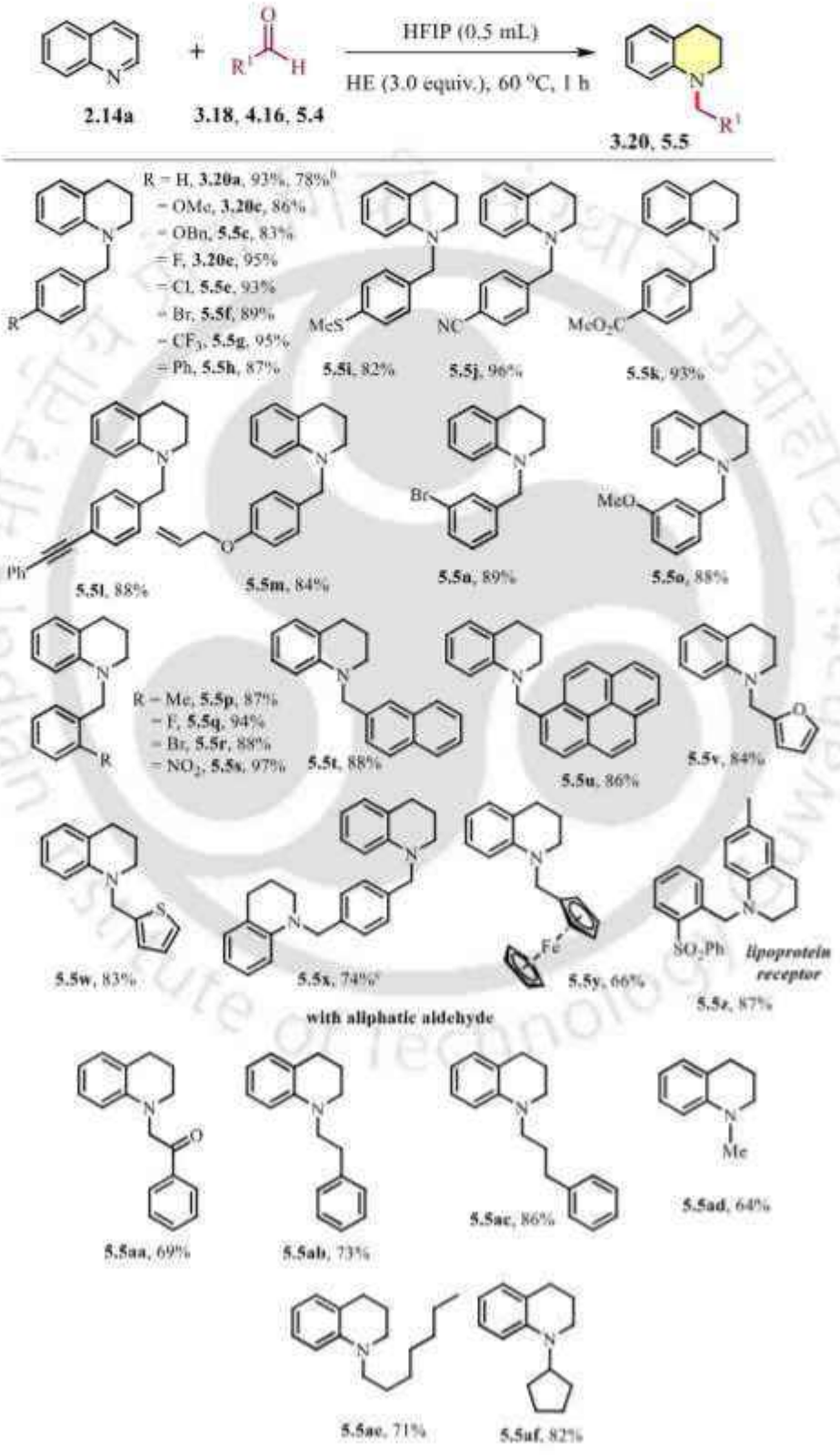
[a]Reaction conditions: **2.14a** (0.5 mmol), **3.18a** (0.5 mmol), HE (1.5 mmol) in HFIP (0.5 mL) at 60 °C for 1 h, isolated yields. [b]with HBD catalyst 1,3-bis(3,5-bis(trifluoromethyl)phenyl) thiourea (**3.19f**, 15 mol%) in DCE (0.5 mL).

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5.3.2. Substrate scope of the synthesis of *N*-functionalized tetrahydroquinolines:

Next, the scope of the reaction was initiated with a variety of aldehydes **3.18**, **4.16**, **5.4** using **2.14a** as the model substrate (Table 5.1). The substrates bearing different kinds of electron-

Table 5.2. The reaction scope with various aldehydes and ketone[a]

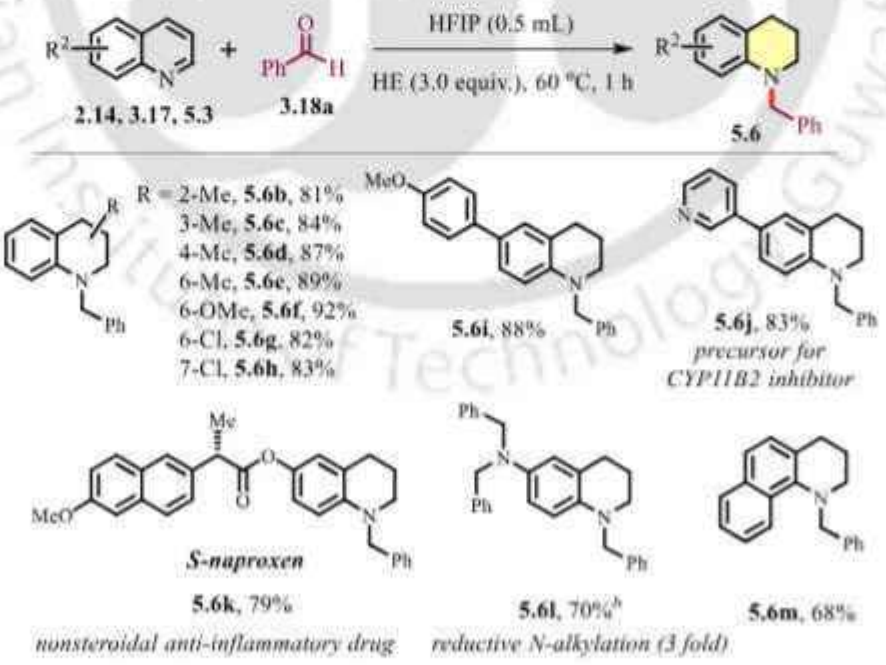


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[a]Reaction conditions: **2.14a** (0.5 mmol), aldehyde or ketone (0.5 mmol), HE (3 equiv.) in HFIP (0.5 mL), at 60 °C for 1 h, isolated yields. [b]5 mmol scale, with 2 h. [c]with 0.25 mmol of terephthalaldehyde, HE (6 equiv.) in HFIP (0.5 mL). [d]with 0.25 mmol scale.

donating and electron-withdrawing groups at the *para*-position in the aryl moiety were efficiently reacted to get the desired products **3.20**, **5.5** in 83-95% yields. The electron-withdrawing group containing aldehyde provided the higher yield compared to electron-donating substituents. Then, *meta*-and *ortho*-substituent-bearing aldehyde **3.18**, **5.4** also delivered the corresponding *N*-alkylated THQs **5.5n**-**5.5s** in 87-97% yield. It is worth mentioning that the reducible-functional groups such as 4-Cl, 4-Br, 4-OBn, 4-CN, 4-SMe, 4-CO_2Me, 4-C≡CPh, 4-O-allyl, 3-Br, 2-Br, 2-CO_2Me, 2-NO_2 remained intact in the final products, displaying the excellent chemoselectivity of the present reductive protocol. Then, polycyclic aromatic hydrocarbons (PAHs) containing aldehyde such as 1-naphthyl aldehyde **3.18s** and 1-pyrene aldehyde **3.18t** provided the desired product **5.5t** and **5.5u** in 88% and 86%, respectively. Heteroatom containing aldehyde **4.16q** and **3.18r** also led to the products **5.5v** (84%) and **5.5w** (83%) efficiently. Next, the reaction proceeded well on polysubstituted aldehyde with multiple aldehyde sites, and product **5.5x** were obtained with notable selectivity. Further, redox-active ferrocene-bearing aldehyde **5.4y** also participated in the reaction to provide the desired *N*-alkylated product **5.5y**. The current reaction was also successfully utilized to synthesize a lipoprotein receptor **5.5z**. Besides aromatic aldehydes, the scope of the reaction was expanded to a variety of aliphatic aldehydes and cyclic ketones, yielding **5.5aa**-**5.5ae** and **5.5af**. In the case of **5.4aa**, selective *N*-alkylation occurs in the presence of reactive $-CH_2COPh$ functionality.

Table 5.3. The reaction scope with various quinolines and other heteroarene[a]

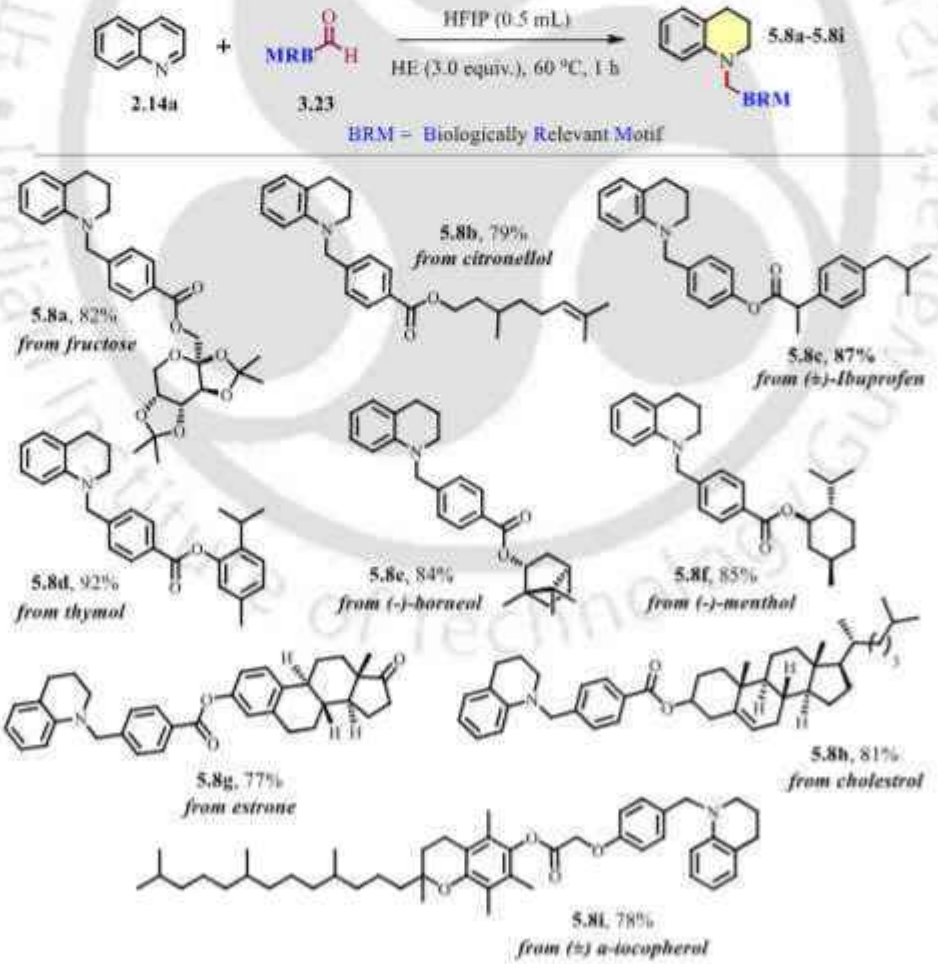


[a]Reaction condition: **2.14**, **3.17**, **5.3** (0.5 mmol), **3.18a** (0.5 mmol), HE (3 equiv.) in HFIP (0.5 mL), at 60 °C for 1 h, isolated yields. [b]with 0.25 mmol scale, **3.18a** (3 equiv.), HE (5 equiv.).

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To further broaden the substrate scope, the reaction was examined with variously substituted quinolines (**2.14, 3.17, 5.3**) and *N*-heteroarene while keeping aldehyde **3.18a** as the standard substrate (Table 5.3). The substrate having both electron-donating (e.g., -OMe) and electron-withdrawing (e.g., -F, -Cl, and -Br) groups as substituents was efficiently reacted to obtain the desired products **5.6** with moderate to good yields (81−92%). Relatively higher yields were realized for electron-donating groups. Pyridine-containing quinoline **5.3j** successfully participated in the reaction to provide 1-benzyl-6-(pyridin-4-yl)-1,2,3,4-tetrahydroquinoline **5.6j** in 83% yield. Further, a substrate containing nonsteroidal anti-inflammatory drugs naproxen **2.14i** was successfully converted into functionalized THQ **5.6k** in 79% yield. Scope of the reaction was extended to multi-functionalization of quinoline with -NH_2 bearing substituent at the 6-position, afforded **5.4l** in 70% yield. Further, it has been extended to another *N*-heteroaromatic scaffold such as benzo[*h*]quinoline (**2.14l**) effectively. However, I failed to obtain the desired *N*-alkylated product when isoquinoline **3.17f**, quinoxaline **3.17g** and acridine **2.14k** were used as the substrate. In the case of acridine, I have obtained 9,10-dihydroacridine **5.18p** in 96% yield.

Table 5.4. The reaction scope with various bilogically relevant motif bearing aldehyde[a]



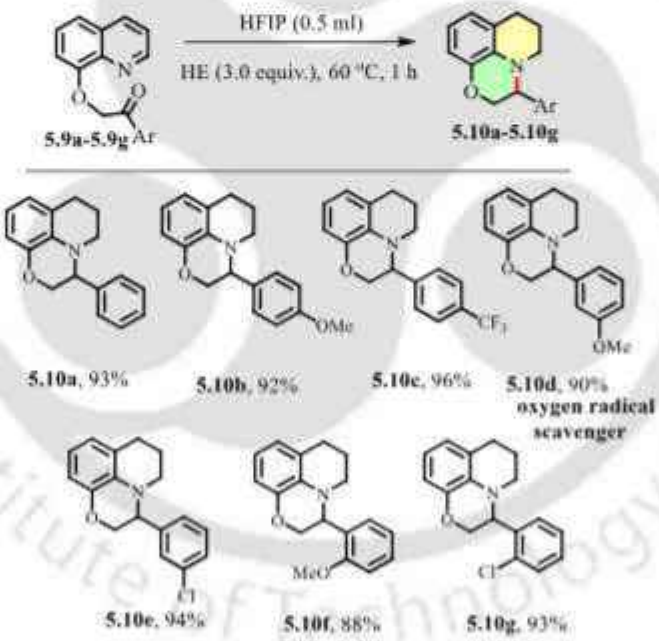
[a]Reaction condition: **2.14a** (0.5 mmol), **3.23** (0.5 mmol), HE (3 equiv.) in HFIP (0.5 mL), at 60 °C for 1 h, isolated yields.

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Since the *N*-alkylated THQ motif is found in various biologically and pharmaceutically relevant compounds, I further expanded the scope of the reaction using highly functionalized substrates with complex molecular settings. A range of biologically relevant motifs (BRM) were targeted and were independently subjected to the optimized reaction conditions, afforded corresponding *N*-alkyl tetrahydroquinoline derivatives containing fructose (**5.8a**, 82%), citronellol (**5.8b**, 79%), (±)-ibuprofen (**5.8c**, 87%), thymol (**5.8d**, 92%), (-)-borneol (**5.8e**, 84%), (-)-menthol (**5.8f**, 85%), estrone (**5.8g**, 77%), cholesterol (**5.8h**, 81%), (±)-tocopherol (**5.8i**, 78%) moieties without any structural changes of the complex architecture (Table 5.4).

Next, I attempted to synthesize novel tricyclic oxazino-fused-tetrahydroquinoline/benzoxazine compounds **5.10a**-**5.10g** *via* tandem reductive cyclization of 1-aryl-2-(8-quinolinyloxy)ethenone **5.9a**-**5.9g** under ambient conditions. Substrates having electron-donating *p*-OMe (**5.9b**), *o*-OMe (**5.9f**) and electron-withdrawing *p*-CF_3 (**5.9c**), *m*-OMe (**5.9d**), *m*-Cl (**5.9e**), and *o*-Cl (**5.9g**) all efficiently provided the corresponding cyclized products **5.10a**-**5.10g** in 88-96% yields (Table 5.5). It is worth noting that most of the resulting compounds were found to have promising antioxidant activity.[4,6]

Table 5.5. Scope of 1-aryl-2-(quinolin-8-yloxy)ethan-1-one[a]



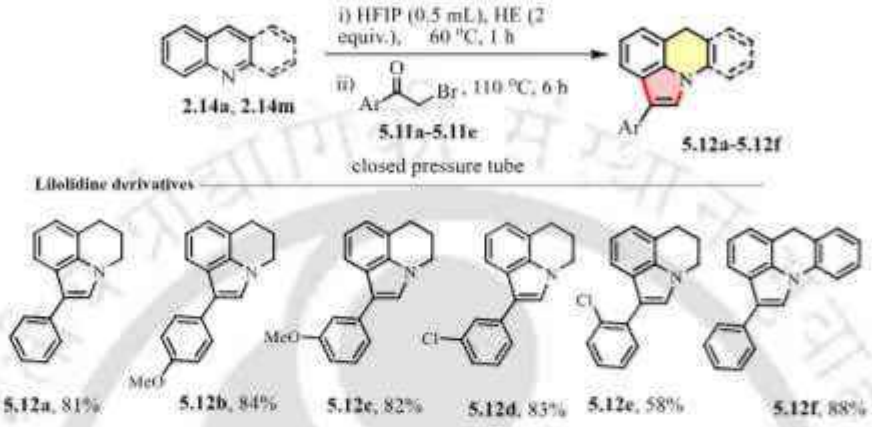
[a]Reaction condition: **5.9a**-**5.9g** (0.5 mmol), HE (3 equiv.) in HFIP (0.5 mL), at 60 °C for 1 h, isolated yields.

Owing to the excellent compatibility of this method with the carbonyl group, I became interested in the direct synthesis of 5,6-dihydro-4H-pyrrolo[3,2,1-*ij*]quinolines from readily available quinoline in one-pot through the tandem reduction of quinoline, *N*-alkylation using α-bromoacetophenone, and dehydration cyclization sequence. Generally, the dehydration process is facilitated by high temperature, so I choose 110 °C as the optimal reaction temperature. As expected, both electron-donating groups (such as *p*-OMe) and electron-

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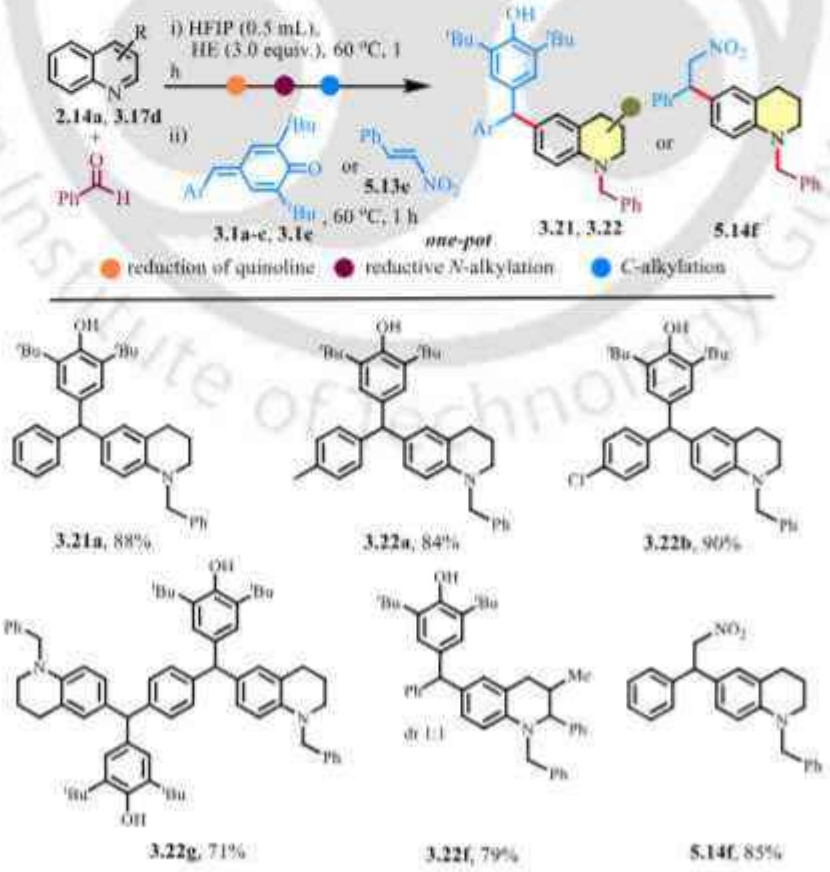
withdrawing groups (such as *o*-Cl, *m*-Cl) could achieve **5.12a-5.12e** in 58-83% yield. Furthermore, scope of the reaction has been extended to other *N*-heteroarenes such as acridine (**2.14p**), leading to the 2-phenyl-6H-pyrrolo[3,2,1-*de*]acridine **5.12f** in 88% yield (Table 5.6). It is worth to mentioning that resulting compounds are shown as leading candidates for fungicides active against rice blast disease[7] and as potential treatments for asthma.[24]

Table 5.6. Scope of α-bromoacetophenone with quinoline and acridine [a]



[a]Reaction condition: **2.14a, 2.14m** (0.5 mmol), HE (2 equiv.) in HFIP (0.5 mL), at 60 °C for 1 h, then added **5.11a-5.11e**, stirred at 110 °C for 6 h in closed pressure tube.

Table 5.7. Scope of quinolines and *p*-QMs, nitroolefin with aldehyde[a]



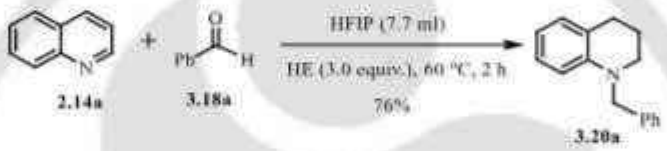
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[a]Reaction condition: **2.14a**, **3.17d** (0.5 mmol), **3.18a** (0.5 mmol), HE (3 equiv.) in HFIP (0.5 mL), at 60 °C for 1 h, then added **3.1a-c**, **3.1e** (0.5 mmol), stirred at 60 °C for 1 h in closed pressure tube, isolated yields.

The scope of the reaction has been extended to *C*-functionalized THQ derivatives in a one-pot by using *para*-quinone methides (*p*-QMs) or nitroolefins as alkylating precursors. Herein, I postulated that *in situ* formed *N*-alkylated THQ **3.20a** act as *C*-nucleophiles, which readily reacted with *p*-QM or nitroolefin to provide C6-functionalized *N*-alkylated THQs **3.21**, **3.22**, **5.14f**. It's worth mentioning that the *p*-QM of terephthalaldehyde **5.13e** gave tandem double 1,6-conjugate addition product **3.22g** in 71% yield (Table 5.7).

5.3.3. Gram-scale reaction

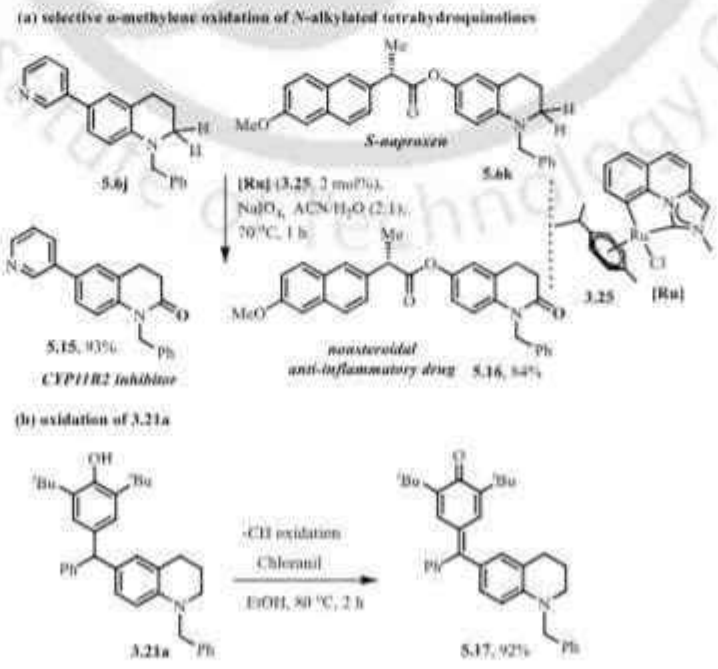
The efficiency of the reaction was demonstrated on a gram scale (Scheme 5.6). For this, I have performed the reaction with 1 gram of quinoline under optimized conditions. The desired product **3.20a** was obtained in 76% yield.



Scheme 5.6. Gram-scale reductive *N*-alkylation of quinoline.

5.3.4. Post-synthetic modifications

Considering the importance of the lactam motif in various biologically and pharmaceutically relevant complex molecular settings, synthesized *N*-alkylated THQs containing nonsteroidal anti-inflammatory drug naproxen **5.6k** was successfully converted into lactam derivative **5.16** in 84% yield using ruthenium catalyst and periodate under oxidative conditions.[25]



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Scheme 5.7. Post synthetic modification.

The method was also useful for the concise synthesis of bioactive molecule CYP11B2 inhibitor **5.15**[26] *via* late-stage α-methylene C−H oxidation of **5.6j**, further showcasing the potential of this protocol for practical utility (Scheme 5.7a). Then compound **5.17** could be readily obtained by selective -CH oxidation of **3.21a** using chloronil oxidant (Scheme 5.7b).

5.3.5. Mechanistic investigation

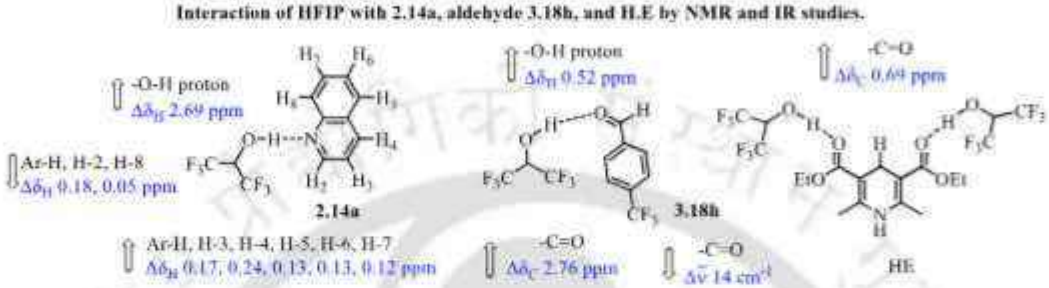
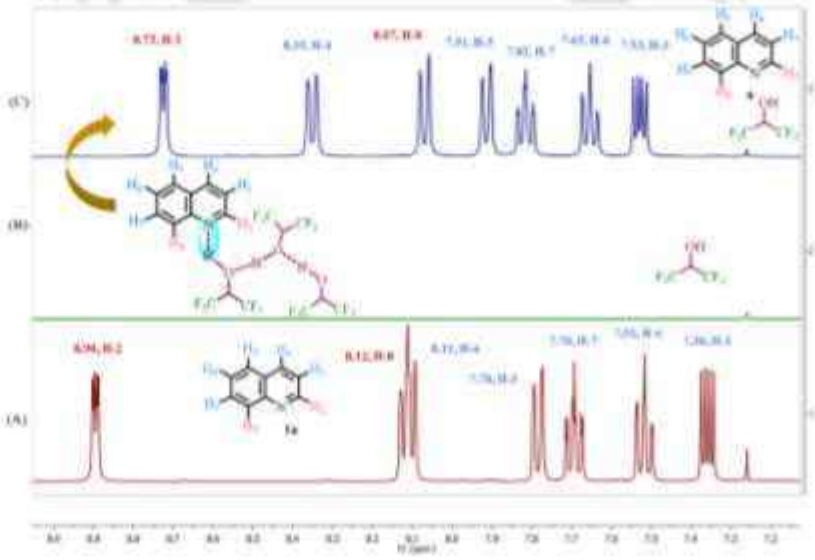


Figure 5.2. Weak interaction of HFIP with substrate and HE.

To probe the nature of binding interaction with HFIP and quinoline, the combination of quinoline and HFIP (molar ratio 1:5) in $CDCl_3$ at rt has been examined. The study was initiated with 1:5 mixture of quinoline **2.14a**: HFIP in $CDCl_3$, and record the ^1H NMR (Figure 5.3). A notable deshielded shift of the hydroxyl group signal in HFIP from 3.22 to 5.91 ppm upon mixing with **2.14a** was observed, indicating a strong hydrogen bonding between the -OH of HFIP and *N*-atom of quinoline moiety. Furthermore, the chemical shift of the aromatic proton H_2 and H_8 of **2.14a** adjacent to the quinyl nitrogen shifted significantly from 8.90 to 8.72 ppm, and 8.12 to 8.0 ppm, respectively, upon addition of HFIP, while the chemical shifts of the aromatic protons H_3, H_4, H_5, H_6, and H_7 of the **2.14a** shifted from 7.36, 8.11, 7.78, 7.52 and 7.70 ppm to 7.53, 8.35, 7.91, 7.65 and 7.82 ppm, respectively. Such a noteworthy change in the ^1H NMR pattern of the quinyl region is consistent with the existence of a strong hydrogen bonding between **2.14a** and HFIP.[27]



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Figure 5.3. H-bonding between the substrate **2.14a** and HFIP (zoom-in region of the aromatic protons). (A) ^{1}H NMR of **2.14a** (10 mg, 0.077 mmol), (B) ^{1}H NMR of HFIP, (C) after addition of HFIP into the solution of **2.14a** in $CDCl_3$ (molar ratio 1:5) at 298 K.

Then 1D Nuclear Overhauser effect (NOE) experiment was carried out in order to gain insight the dipolar spatial interactions between protons nuclei spatially close to each other. Upon irradiating the hydroxyl proton signal of a 1:5 mixture of **2.14a**: HFIP at 5.91 ppm, clear interaction of the hydroxyl peak of HFIP with the neighbouring protons was observed with the aromatic proton H_2 signal at 8.72 ppm and H_8 signal at 8.07 ppm (Figure 5.4). These correlation study further suggests that strong indication of the presence of a strong hydrogen bonding between **2.14a** and HFIP.

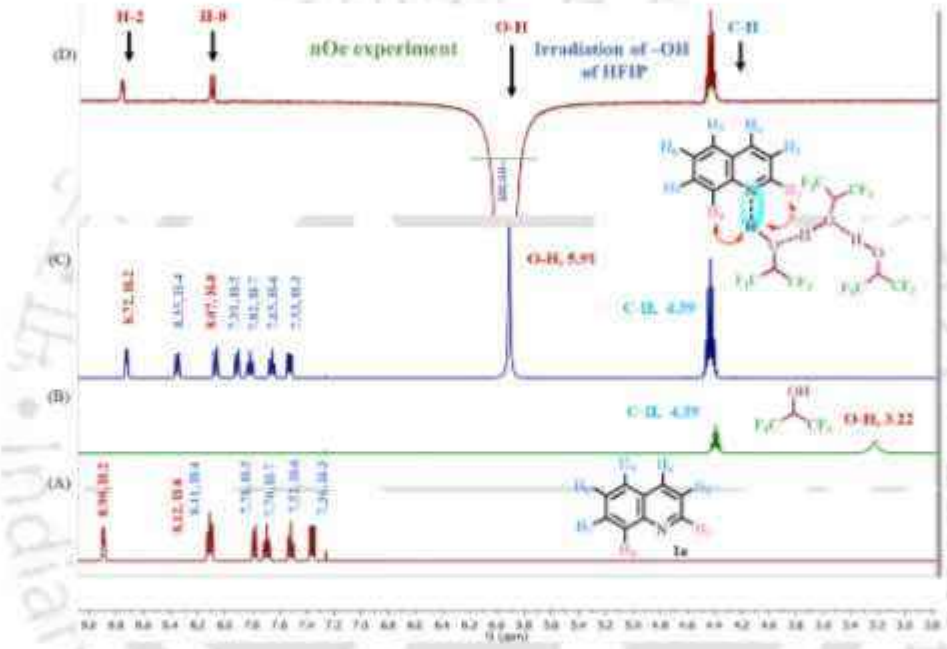


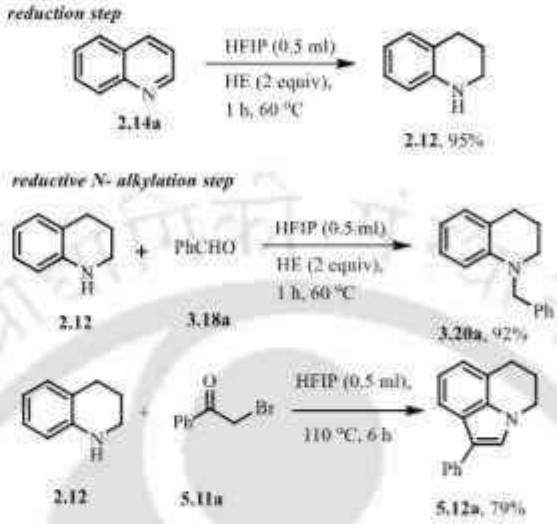
Figure 5.4. H-bonding between the substrate **2.14a** and HFIP. (A) ^{1}H NMR of **2.14a**, (B) ^{1}H NMR of HFIP, (C) after addition of HFIP into the solution of **2.14a** in $CDCl_3$ (molar ratio 1:5) and (D) 1D NOE of (C) at 298 K.

The interaction of HFIP with the freshly distilled aldehyde and carbonyl group in HE was also confirmed by ^{1}H and ^{13}C NMR, and IR spectroscopic experiments. Upon the addition of aldehyde **3.18f**, the hydroxyl peak of HFIP was shifted downfield by nearly 0.52 ppm in the ^{1}H NMR, and the carbonyl value moved to downfield ($\Delta\delta$ 2.76 ppm) in the ^{13}C NMR. Moreover, the carbonyl band shifted to a lower frequency (from 1708 to 1694 cm^{-1}) in the IR spectrum. Experimental observation suggests a weak hydrogen bonding interaction exist between HFIP and aldehyde group.[28] Likewise, interaction of HFIP with the carbonyl group in HE was also confirmed by the ^{13}C NMR with a downfield shift ($\Delta\delta$ 0.7 ppm) (see details in subsection 4.3.5 of chapter 4).

Next, a few control experiments were carried out to gain mechanistic insights into the synthesis of *N*-alkylated THQ derivatives. The reaction of quinoline **2.14a** in the absence of aldehyde under standard conditions afforded THQ **2.12** in 95% yield. Then reaction was conducted with

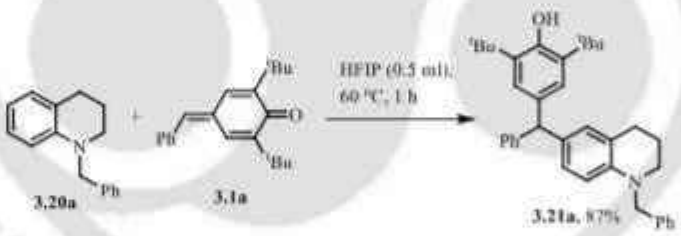
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the formed **2.12**, and aldehyde **3.18a** under standard conditions, the desired product **3.20a** was obtained in 92% yield (Scheme 5.8). From this experimental observation, it can be inferred that the reaction involves a two-step process, and THQ is found as an intermediate in the *N*-alkylation process. The intermediate **2.12** was also validated for the formation of **5.12a** by the following control experiment using the α-bromo acetophenone **5.11a** (Scheme 5.8).



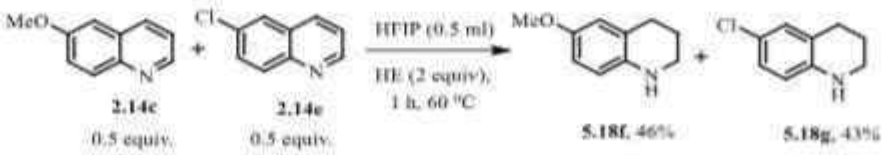
Scheme 5.8. Proof of 1,2,3,4-tetrahydroquinoline as the intermediate.

Likewise, **3.20a** was found as an intermediate for the formation of **3.21a** by the following control experiment using *p*-QM **3.1a** under the reaction conditions (Scheme 5.9).



Scheme 5.9. Proof of *N*-benzyl THQ as the intermediate.

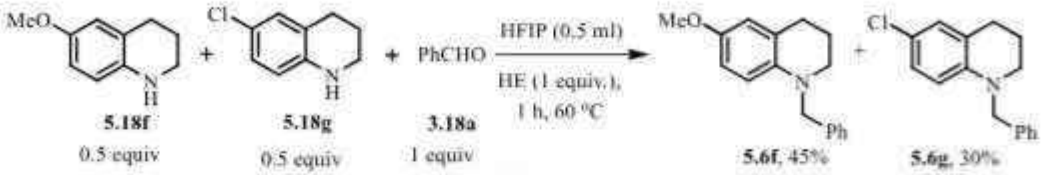
Next, the electronic effect of the substrate on the rate of the reaction was examined for both steps (Scheme 5.10). In the 1st step (i.e., reduction of quinoline to THQ), a comparable yield of THQ (**5.18f**, 46%; **5.18g**, 43%) was obtained when the reaction was performed with an equal ratio of 6-methoxyquinoline and 6-chloroquinoline. It suggests that there is no considerable electronic effect in the reduction step.



Scheme 5.10. Electronic effect of the quinoline hydrogenation step.

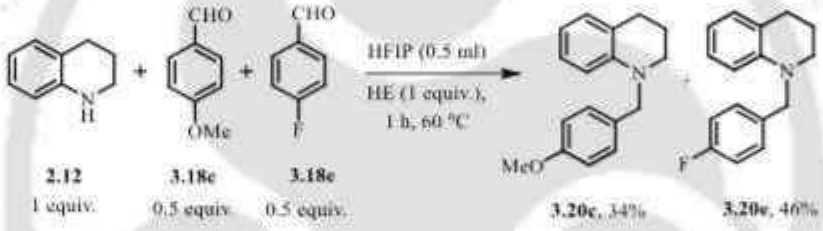
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To know the electronic effect in the 2nd step, the reaction was initiated with equal ratio of C6-substituted THQ **5.18f** and **5.18g**, respectively, in the presence of **3.18a** under identical conditions. A competitive reaction suggested that the electron-donating group (-OMe) on the THQ enhanced the rate of the reaction with respect to an electron-withdrawing group (-Cl) (Scheme 5.11).



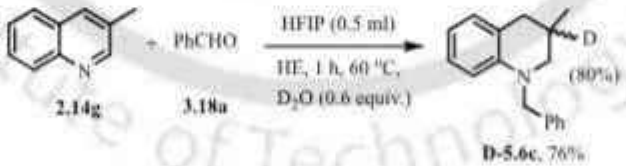
Scheme 5.11. Competitive reaction with substituted quinoline.

Likewise, the reaction was examined with equal ratio of 4-methoxy benzaldehyde **3.18c** and 4-fluoro benzaldehyde **3.18e** in the presence of THQ **2.12** under identical conditions. A competitive reaction suggested that electron-withdrawing group (*p*-F) on the benzaldehyde enhanced the rate of the reaction with respect to an electron-donating group (*p*-OMe) (Scheme 5.12).



Scheme 5.12. Competitive reaction with aldehyde.

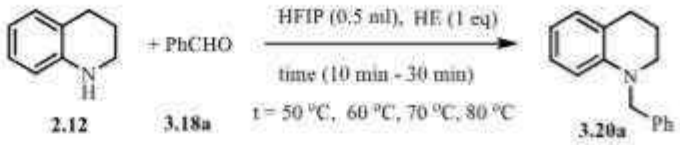
Additionally, the deuterium-labelled experiment was performed with **2.14g** in the presence of D_2O under standard conditions where 80% D-incorporation at the C3 position of *N*-benzylated THQ has been observed (Scheme 5.13).



Scheme 5.13. Deuterium-labelled experiment with 3-methyl quinoline.

The effect of temperature on the rate of *N*-alkylation reaction was examined by using Eyring analysis (Scheme 5.14). The activation parameters were found to be $\Delta H^{\ddagger} = 4.6 \pm 0.8$ kcal mol^{-1} and $\Delta S^{\ddagger} = -54.18 \pm 0.6$ cal K^{-1} mol^{-1}. The negative entropy of activation suggests that the rate-limiting step in a reaction involves the two or more molecules coming together to form a more ordered transition state, leading to a decrease in disorder. This is often observed in an associative process. The intermediate THQ **2.12** and aldehyde **3.18a** are likely combined in the rate-limiting step, leading to a decrease in entropy.

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Scheme 5.14. Eyring studies.

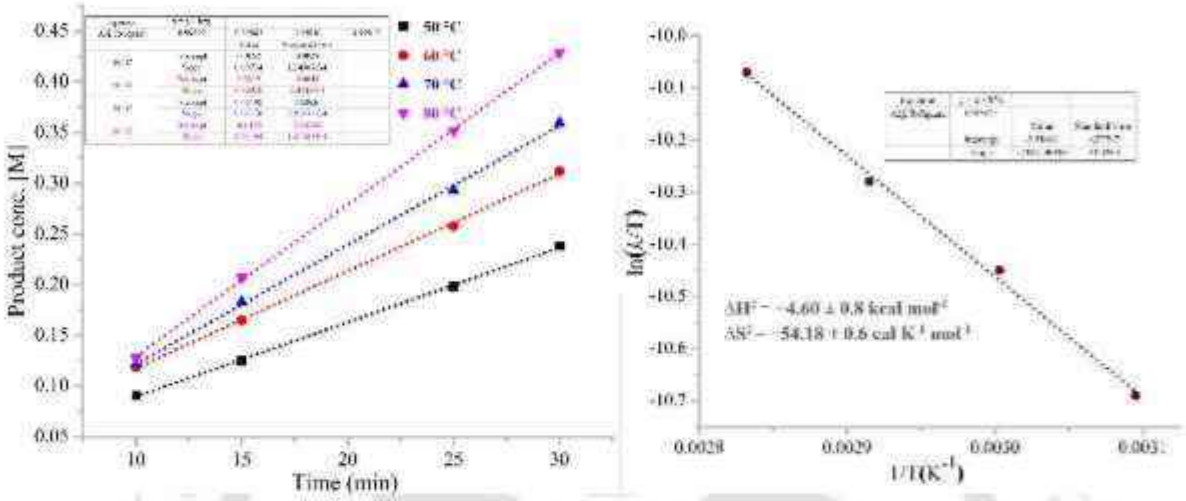


Figure 5.5. Concentration [Product] *vs* time plot at different temperatures (left figure) Arrhenius-Eyring plot (right figure).

Activation enthalpy ($\Delta H^{\#}$) and activation entropy ($\Delta S^{\#}$) values were obtained from the slope and intercept of plots of $\ln(k/T)$ vs $1/T$ (Figure S12) using the following equation:

$$\ln(k/T) = -\Delta H^{\#}/R.(1/T) + \ln k_B/h + \Delta S^{\#}/R$$

where k_B = Boltzmann constant, R = universal gas constant, and h = Planck's constant.

From the plot of $\ln(k/T)$ vs $1/T$,

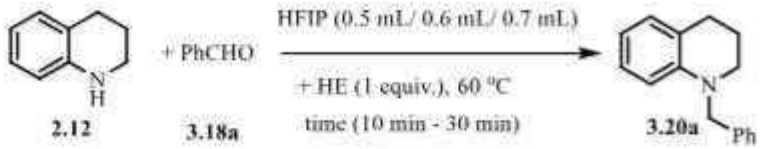
$$\text{Slope} = -2315.1$$
$$Or, -\Delta H^{\ddagger}/R = -2315.1$$
$$Or, \Delta H^{\ddagger} = -(-2315.1) \times (1.987 \text{ cal K}^{-1}\text{mol}^{-1})$$
$$= 4600.1 \text{ cal mol}^{-1}$$
$$= 4.60 \text{ kcal mol}^{-1}$$

And,

$$\text{Intercept} = -3.51$$
$$Or, \ln (k_B/h) + \Delta S^{\#}/R = -3.51$$
$$Or, \ln (1.38 \times 10^{-23} \text{ J K}^{-1}/6.626 \times 10^{-34} \text{ J s}) + \Delta S^{\#}/1.987 \text{ cal K}^{-1}\text{mol}^{-1} = -3.51$$
$$Or, \ln (2.083 \times 10^{10} \text{ K}^{-1} \text{ s}^{-1}) + \Delta S^{\#}/1.987 \text{ cal K}^{-1}\text{mol}^{-1} = -3.51$$
$$Or, 23.76 + \Delta S^{\#}/1.987 \text{ cal K}^{-1}\text{mol}^{-1} = -3.51$$
$$Or, \Delta S^{\#}/1.987 \text{ cal K}^{-1}\text{mol}^{-1} = -27.27$$
$$Or, \Delta S^{\#} = -54.18 \text{ cal K}^{-1}\text{mol}^{-1}$$

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Furthermore, it was found that the rate of the reaction is increased by increasing the volume of HFIP from 0.5 mL to 0.7 mL (Scheme 5.15). Based on the thermodynamic activation parameters and competitive reaction on the substrate, one can postulate that the hemiaminal species formation step is likely to be the rate-limiting step.



Scheme 5.15. Effect of HFIP volume in the initial rate of the reaction.

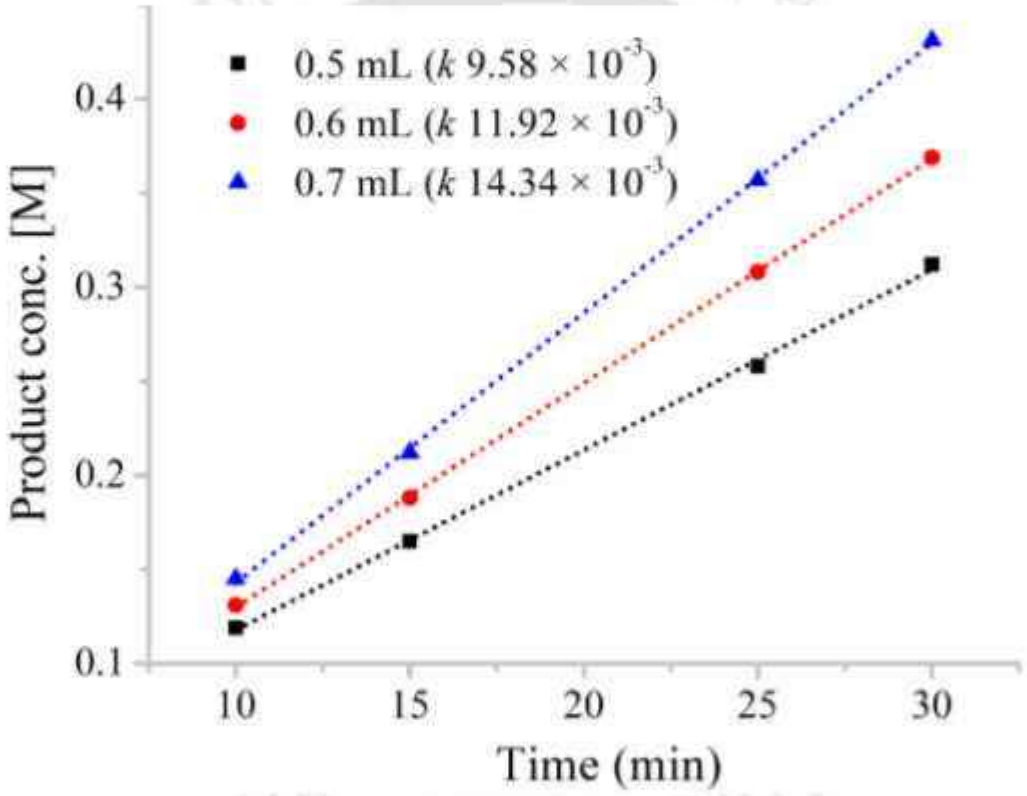
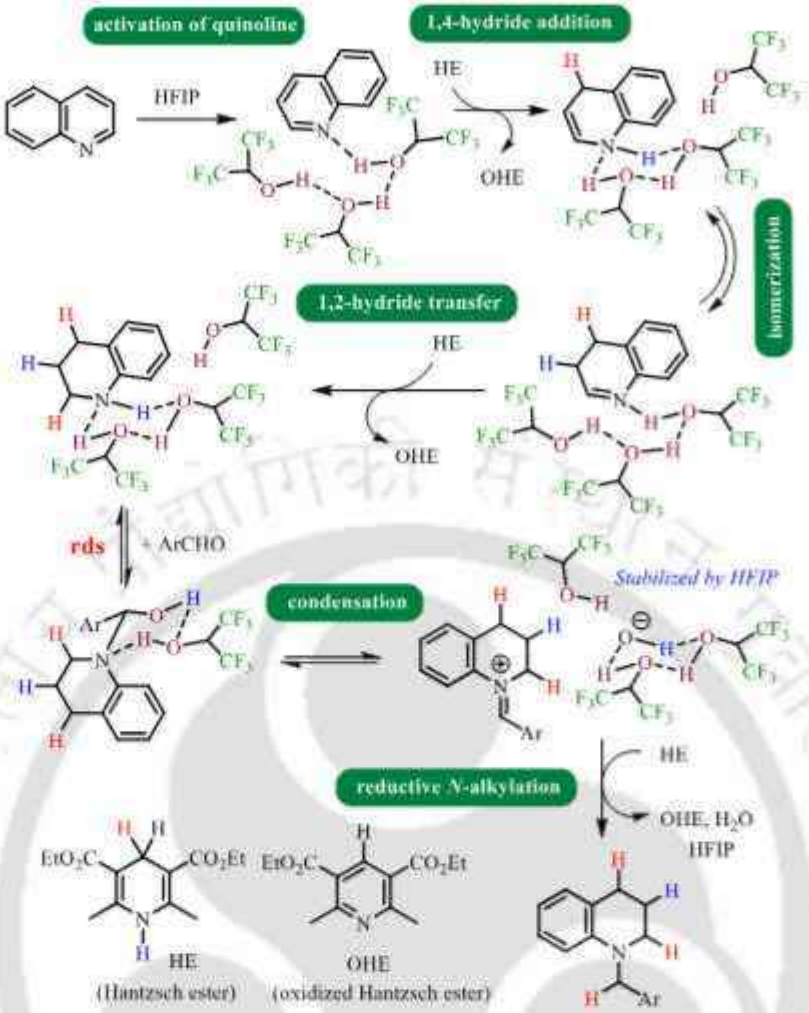


Figure 5.6. Concentration [Product] *vs* time plot at different volume of HFIP.

On the basis of above experimental findings, the proposed pathway for the formation of *N*-alkylated tetrahydroquinoline has been demonstrated in Scheme 5.16. First, the quinoline **2.14a** is activated by the hydroxyl group of HFIP *via* hydrogen bonding interaction, which is then reduced by Hantzsch ester to provide THQ **2.12**.[20-23,29] The *in situ* generated THQ can take part in HFIP-assisted condensation reaction with the aldehyde to form the hemiaminal species, followed by condensation leading to the formation of iminium intermediate. Then, this was readily reduced by Hantzsch ester to provide the desired *N*-alkylated THQ **3.20a**.

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Scheme 5.16. Plausible mechanism.

5.4. Summary

In summary, I have developed a one-pot tandem reduction of quinoline with subsequent reductive alkylation using aldehydes and Hantzsch ester to produce *N*-alkylated THQ derivatives. Because of mild reaction conditions, this convenient method tolerates a wide variety of reducible-sensitive functional groups, such as ester, halo, nitro, nitrile, alkyne, allyl, benzyl, thioether. Futhermore, it has been successfully utilized in the late-stage functionalization, diversification of pharmaceuticals. The post-transformations of the synthesized product have also been carried out to demonstrate the potential of the developed methodology. The current reductive *N*-alkylation approach was also successfully utilized to synthesize tricyclic oxazino-fused-tetrahydroquinoline/benzoxazine, lilolidine, and *C*-functionalized *N*-alkylated THQ derivatives in a one-pot. Mechanistic studies reveal the existence of a strong hydrogen bonding between the quinoline 'N's and HFIP. The multifunctional role of HFIP has been demonstrated not only to facilitate the reduction of quinoline but also to improve the stability of hemiaminal or iminium ion species through the hydrogen-bonding network of HFIP.

5.5. Experimental section

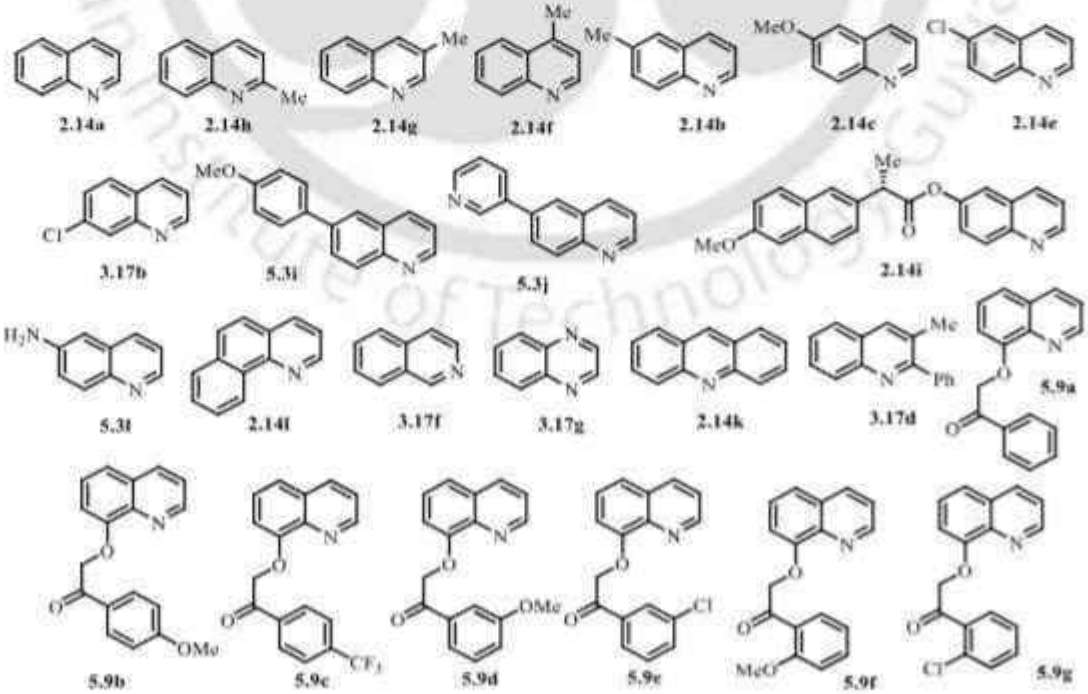
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A. General information

All the reagents and chemicals were purchased from common commercial suppliers like Sigma-Aldrich, Alfa Aesar, Merck, Spectrochem, Avra Synthesis Pvt. Ltd., Finar Chemicals, and BLD Pharma directly used as received without any further purification unless otherwise mentioned. Hantzsch ester was synthesized according to the reported literature.[30] ^{1}H, ^{13}C, and ^{19}F NMR spectra of the compounds were measured in $CDCl_3$, as a solvent by using TMS as an internal standard. Chemical shifts, δ (in ppm), are reported relative to TMS δ (^{1}H) 0.0 ppm, δ (^{13}C) 0.0 ppm, which was used as the internal reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.16 ppm), were also used for calibration. Bruker Avance III 600, 500 and 400 spectrometers were used to record the NMR spectra. Chemical shifts (δ) values were reported in ppm and spin-spin coupling constant (J) were expressed in Hz, and other data were reported as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quartet, p = pentate, sext = sextet, hept = heptane, br = broad, and brs = broad singlet. IR spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass (UHPLC - Q-TOF - HRMS). Merck silica gel 60 - 120 was used for column chromatography. otherwise stated. All the final reactions were carried out under air and in preheated oil baths unless otherwise mentioned. Completion of reactions was examined by thin layer chromatography carried out on pre-coated Merck silica gel-60 F_{254} aluminium plates with ultraviolet light (UV) or iodine as visualizing agents.

B. Synthesis of starting material

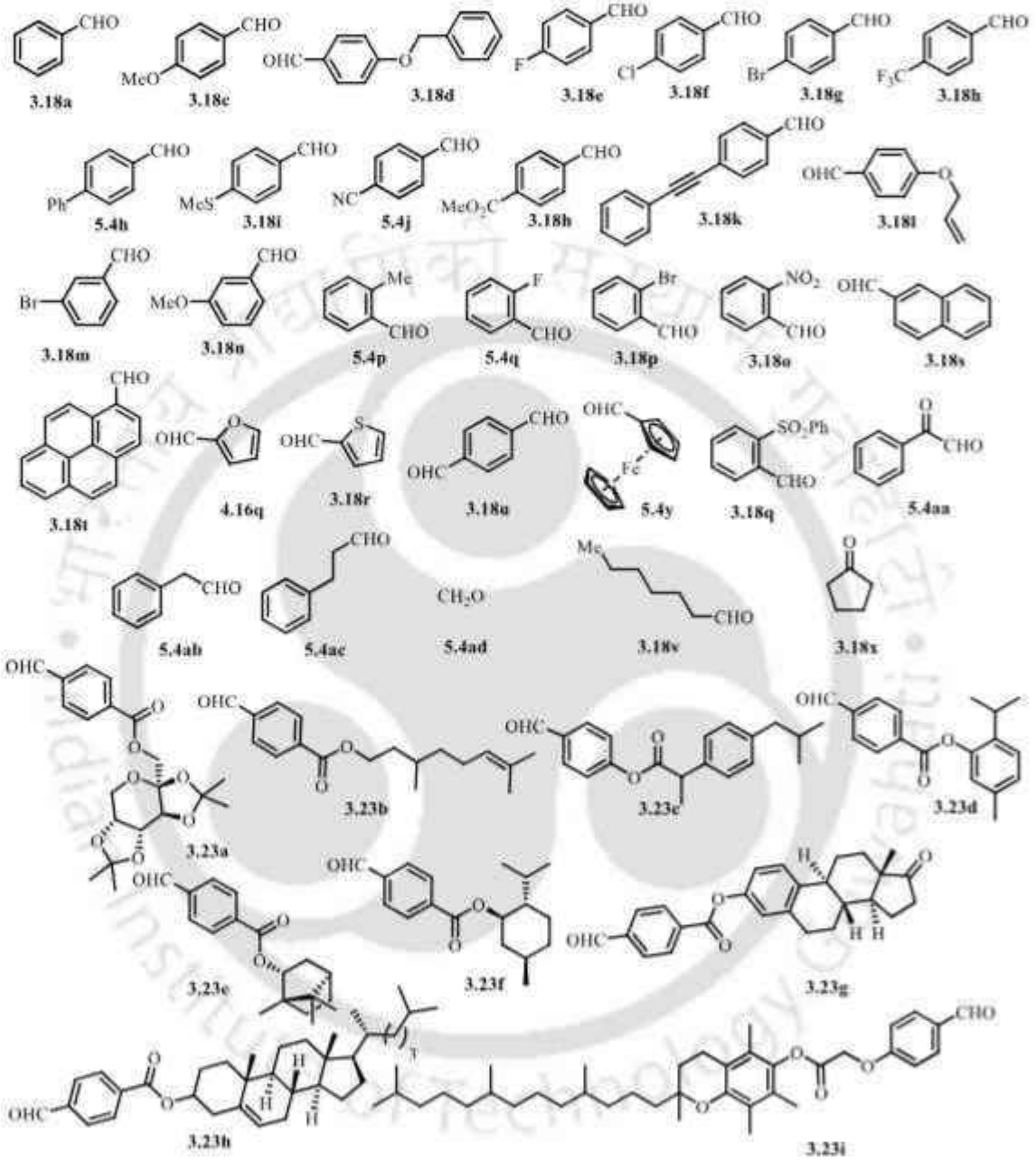
i) *N*-heteroarenes employed in the reaction:



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Compounds **5.3i**[31], **5.3j**[25], **2.14i**[32], **5.9a-5.9b**[6], **5.9d**[6], **5.9f**[6] are synthesized by known procedures.

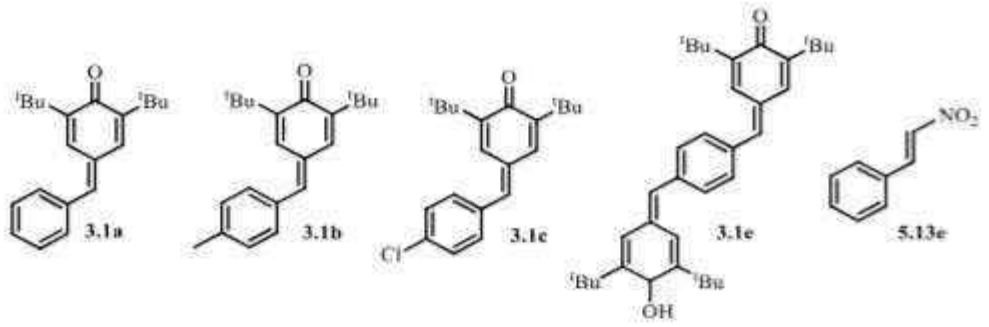
ii) Aldehydes and ketone employed in the reaction:



Compounds **3.18d**,[33] **3.18k**,[34] **3.18l**,[35] are synthesized by known procedure. The biologically relevant motifs containing aldehyde derivatives **3.23a**,[36] **3.23b**,[37] **3.23c**,[38] **3.23e**,[39] **3.23f**,[40] **3.23g**,[41] **3.23h**,[40], **3.23i**[22] were synthesized by the known procedure.

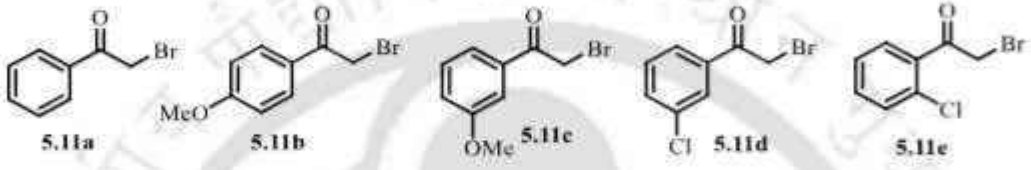
iii) Alkylating precursors employed in the reaction:

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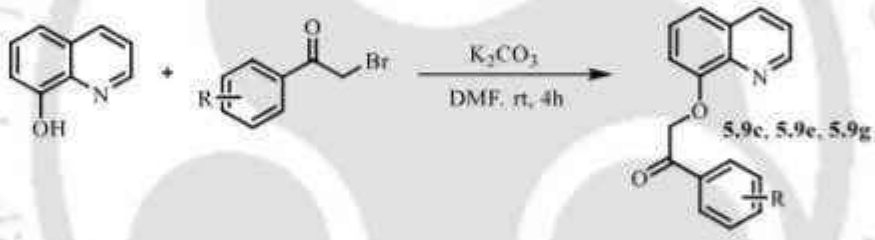


Compounds **3.1b-3.1c**[42], **3.1d**[43] are synthesized by known procedures.

iv) α-bromoacetophenone employed in the reaction:



v) General procedure for the synthesis of 1-aryl-2-(quinolin-8-yloxy) ethanone



Scheme 5.17. Synthesis of 1-aryl-2-(quinolin-8-yloxy) ethenone derivatives.

Experimental procedure: To a stirred solution of substituted Quinolin-8-o1 (1.7 mmol), K_2CO_3 (1.7 mmol) in dry DMF (5 mL) were stirred at room temperature for 10-15 mins. To this solution desired substituted 2-bromoacetophenone (1.7 mmol) in dry DMF (5 mL) was added in one portion. The resulting mixture was stirred at rt for 4 h (TLC monitoring) and then poured into ice-water (40 mL). The filtrate was concentrated and purified on a silica gel column (petroleum ether/ethyl acetate) to yield the 1-aryl-2-(quinolin-8-yloxy) ethanone **(5.9c, 5.9e, 5.9g)**. Compound **5.9c, 5.9e, 5.9g** was prepared for the first time following a known procedure.[6]

2-(quinolin-8-yloxy)-1-(4-(trifluoromethyl) phenyl) ethan-1-one (5.9c)

(Pale yellow solid, 78%) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.93 (dd, J = 4.2, 1.7 Hz, 1H), 8.22 (d, J = 8.2 Hz, 2H), 8.13 (dd, J = 8.3, 1.6 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.45 – 7.43 (m, 2H), 7.39 (t, J = 7.7 Hz, 1H), 7.00 – 6.99 (m, 1H), 5.60 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 194.4, 153.7, 149.6, 140.3, 137.3, 136.2, 135.1 (q, J = 32.7 Hz), 129.8, 128.9, 126.5, 126.0 (q, J = 3.6 Hz), 124.5, 122.7, 122.0, 121.4, 72.5. ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$): δ -63.24. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{13}F_3NO_2$:332.0893; found: 332.0892.

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1-(3-chlorophenyl)-2-(quinolin-8-yloxy) ethan-1-one (5.9e)

(Pale yellow solid, 86%) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.94 (dd, J = 4.2, 1.7 Hz, 1H), 8.13 (dd, J = 8.3, 1.7 Hz, 1H), 8.08 (t, J = 1.8 Hz, 1H), 7.99 – 7.97 (m, 1H), 7.56 – 7.54 (m, 1H), 7.44 – 7.42 (m, 3H), 7.41 – 7.37 (m, 1H), 6.98 (dd, J = 7.6, 1.3 Hz, 1H), 5.58 (s, 2H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 193.7, 153.8, 149.6, 140.3, 136.14, 136.11, 135.3, 133.9, 130.3, 129.8, 128.5, 126.5, 121.9, 121.2, 110.5, 72.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{13}ClNO_2$:298.0630; found: 298.0629.

1-(2-chlorophenyl)-2-(quinolin-8-yloxy) ethan-1-one (5.9g)

(Pale yellow solid, 82%) ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.92 (dd, J = 4.2, 1.7 Hz, 1H), 8.09 (dd, J = 8.3, 1.6 Hz, 1H), 7.67 (dd, J = 7.6, 1.4 Hz, 1H), 7.42 – 7.38 (m, 5H), 7.34 – 7.31 (m, 1H), 6.99 (dd, J = 6.6, 2.3 Hz, 1H), 5.56 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 197.2, 153.6, 149.4, 140.1, 136.1, 135.9, 132.7, 131.5, 130.6, 130.0, 129.6, 127.1, 126.4, 121.7, 120.9, 110.1, 73.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{13}ClNO_2$:298.0630; found: 298.0628.

C. General procedure for synthesis of *N*-alkyl tetrahydroquinolines

i) General procedure for synthesis of *N*- alkyl tetrahydroquinolines with different carbonyls (GP-1)

Reaction condition: A mixture of quinoline **2.14a** (0.5 mmol), aldehyde or cyclic ketone (0.5 mmol), HE (1.5 mmol) and HFIP (0.5 mL) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 1 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

ii) General procedure for synthesis of *N*-alkyl tetrahydroquinolines with substituted quinolines (GP-2)

Reaction condition: A mixture of substituted quinolines (0.5 mmol), benzaldehyde **3.18a** (0.5 mmol), HE (3.0 equiv) and HFIP (0.5 mL) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 1 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

iii) General procedure for synthesis of benzoxazine derivative (GP-3)

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Reaction condition: A mixture of 1-aryl-2-(8-quinolinyloxy)ethanone (0.5 mmol), HE (3.0 equiv.) and HFIP (0.5 mL) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 1 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

iv) General procedure for synthesis of lilolidine derivative (GP-4)

Reaction condition: In the first step, a mixture of quinoline **2.14a** (0.5 mmol), HE (2.0 equiv.) and HFIP (0.5 mL) were added into a closed pressure tube (15 mL) equipped with stirring bar. The pressure tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 1 h. Then in the same pressure tube, substituted α-bromoacetophenone (0.5 mmol) were added and placed in a preheated oil bath at 110 °C with continuous stirring for 6 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

v) General procedure for synthesis of *C*-functionalized THQ derivatives (GP-5)

Reaction condition: A mixture of substituted quinolines (0.5 mmol), benzaldehyde **3.18a** (0.5 mmol), HE (1.5 mmol) and HFIP (0.5 mL) were added into a reaction tube (15 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 1 h. Then *p*-QMs or nitroolefins (0.5 mmol) was added in the same reaction tube at 60 °C with continuous stirring for 1 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

D. Gram scale reaction (Scheme 5.6)

Experimental procedure: A mixture of **2.14a** (1.0 g, 7.7 mmol), **3.18a** (1.0 equiv), HE (3.0 equiv) and HFIP (7.7 mL) were added into a round bottom flak (100 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 60 °C with continuous stirring for 2 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography to get pure compound as yellow oil of **3.20a** (1.309 g, 76%).

E. Post synthetic modification (Scheme 5.7)

i) Selective α-methylene oxidation of *N*-alkylated tetrahydroquinolines (Scheme 5.7a)

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Synthesis of CYP11B2 inhibitor (5.15)

Reaction condition: $NaIO_4$ (1.5 mmol, 3 equiv.) was taken in a screw-capped reaction tube and dissolved it in water (1 mL). Then **5.6j** (0.5 mmol, 1 equiv.), **[Ru-2(3.25)]**[25] (2 mol%), and acetonitrile (2 mL) were added to the reaction tube and stirred the reaction mixture at 70 °C for 1 hour. After the completion of the reaction as confirmed by TLC, the reaction mixture was worked up with CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was again extracted with CH_2Cl_2 (two times, 5 mL). The combined organic layer was washed with brine solution (8 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under a vacuum. The crude product was purified through silica-gel column chromatography to get the pure product **5.15** as white solid (93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 2.4 Hz, 1H), 8.55 (d, J = 6.4 Hz, 1H), 7.81 – 7.79 (m, 1H), 7.40 – 7.39 (m, 1H), 7.35 – 7.30 (m, 4H), 7.26 – 7.23 (m, 3H), 6.98 (d, J = 8.4 Hz, 1H), 5.22 (s, 2H), 3.09 – 3.05 (m, 2H), 2.86 – 2.83 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 170.5, 148.4, 148.0, 140.0, 136.9, 135.8, 134.0, 132.5, 128.9, 127.3, 127.2, 126.6, 126.5, 126.2, 123.7, 116.3, 46.2, 31.9, 25.8. Spectral data is in accordance to the reported literature.[25]

Synthesis of nonsteroidal anti-inflammatory drug (5.16)

Reaction condition: $NaIO_4$ (1.5 mmol, 3 equiv.) was taken in a screw-capped reaction tube and dissolved it in water (1 mL). Then **5.6k** (0.5 mmol, 1 equiv.), **[Ru-2(3.25)]**[25] (2 mol%), and acetonitrile (2 mL) were added to the reaction tube and stirred the reaction mixture at 70 °C for 1 hour. After the completion of the reaction as confirmed by TLC, the reaction mixture was worked up with CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was again extracted with CH_2Cl_2 (two times, 5 mL). The combined organic layer was washed with brine solution (8 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under a vacuum. The crude product was purified through silica-gel column chromatography to get the pure product **5.16** as pale-yellow oil (84%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 – 7.71 (m, 3H), 7.47 – 7.46 (m, 1H), 7.28 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 7.17 – 7.13 (m, 4H), 6.81 – 6.78 (m, 2H), 6.71 (dd, J = 8.8, 2.6 Hz, 1H), 5.13 (s, 2H), 4.06 (q, J = 7.1 Hz, 1H), 3.92 (s, 3H), 2.92 – 2.90 (m, 2H), 2.77 – 2.74 (m, 2H), 1.67 (d, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 173.5, 170.4, 157.9, 146.1, 137.7, 136.8, 135.1, 133.9, 129.4, 129.1, 128.9, 127.6, 127.5, 127.3, 126.5, 126.24, 126.16, 121.0, 120.1, 119.3, 116.4, 105.7, 55.5, 46.4, 45.6, 31.6, 25.6, 18.6. Spectral data is in accordance to the reported literature.[25]

ii) Functionalization of (3.21a) (Scheme 5.7b)

Synthesis of 4-((1-benzyl-1,2,3,4-tetrahydroquinolin-6-yl) (phenyl)methylene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one (5.17)

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Experimental procedure: A mixture of **3.21a** (0.193 mmol, 1.0 equiv), chloranil (1.5 equiv), EtOH (5 mL) were added into a round bottom flask (50 mL) equipped with stirring bar. The reaction tube was properly closed and placed in a preheated oil bath at 80 ℃ with continuous stirring for 2 h. The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, all the solvent and volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography to yield the desired compound **5.17** as orange solid (92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.37 (m, 4H), 7.31 (d, J = 8.2 Hz, 2H), 7.27 – 7.26 (s, 3H), 7.19 (d, J = 8.1 Hz, 2H), 7.01 (s, 1H), 6.91 (s, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.46 (d, J = 8.6 Hz, 1H), 4.52 (s, 2H), 3.44 – 3.42 (m, 2H), 2.78 (t, J = 6.1 Hz, 2H), 2.06 – 2.01 (m, 2H), 1.30 (s, 9H), 1.21 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 186.0, 158.1, 146.1, 136.6, 134.2, 133.1, 132.9, 132.8, 132.5, 129.2, 129.1, 128.4, 128.1, 128.0, 127.9, 121.6, 110.1, 54.6, 50.2, 35.4, 35.3, 29.8, 29.6, 28.1, 22.2. Spectral data is in accordance to the reported literature.[25]

F. Mechanistic investigation

i) Proof of 1,2,3,4-tetrahydroquinoline and *N*-benzyl THQ as the intermediate (Scheme 5.8, 5.9)

To gain more insight into the reaction pathway, I performed the reaction with quinoline **2.14a** (0.065 g, 0.5 mmol, 1.0 equiv.), HE (0.253 g, 1.0 mmol, 2.0 equiv.), and HFIP (0.5 mL) at 60 °C for 1 h. As expected tetrahydroquinoline **2.12** obtained in 95% yield (0.063 g). For the subsequent step the reaction was conducted with the formed **2.12** (0.063 g, 0.47 mmol, 1.0 equiv.), and aldehyde **3.18a** (0.050 g, 0.47 mmol, 1.0 equiv), HE (0.119 g, 0.47 mmol, 1.0 equiv), and HFIP (0.5 mL) at 60 °C for 1 h under identical conditions the desired product **3.20a** was obtained in 92% yield (0.098 g). From the following experimental observation, one can infer that the reaction is involved in two steps i) reduction of quinoline to THQ and ii) then reductive *N*-alkylation with the aldehyde. Then the reaction was examined with the THQ **2.12** (0.047 mmol, 1.0 equiv.), α-bromoacetophenone **5.11a** (0.094 g, 0.047 mmol, 1.0 equiv.), and HFIP (0.5 mL) at 110 °C for 6 h, the desired product **5.12a** was obtained in 79% yield (0.087 g). It suggests that THQs **2.12** is as an intermediate in the process.

Likewise, when the reaction was performed with **3.20a** (0.104 g, 0.47 mmol, 1.0 equiv), *p*-QM **3.1a** (0.138 g, 0.47 mmol, 1.0 equiv.) at 60 °C for 1 h under standard conditions, the desired product **3.21a** was obtained in 87% yield (0.212 g). This indicates that compound **3.20a** is an intermediate for the *C*-functionalized *N*-alkylated THQ **3.21a**.

ii) Electronic effect for the 1st step (Scheme 5.10)

To know the electronic effect of the substrate in the 1st step, I performed the reaction with **2.14c** (0.040 g, 0.25 mmol, 0.5 equiv.), **2.14e** (0.041 g, 0.25 mmol, 0.5 equiv.), HE (0.253 g, 1.0 mmol, 2.0 equiv.), and HFIP (0.5 mL) at 60 °C for 1 h. As expected, the desired hydrogenated product **5.18f** and **5.18g** was obtained in 46% yield and 43% yield, respectively. Since a

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comparable yield was obtained in both the cases, one can infer that there is no considerable electronic effect in the reduction step.

iii) Electronic effect for the 2nd step (Scheme 5.11, 5.12)

Reaction conditions: The 6-methoxy tetrahydroquinoline **5.18f** (0.041 g, 0.25 mmol, 0.5 equiv), 6-chloro tetrahydroquinoline **5.18g** (0.042 g, 0.25 mmol, 0.5 equiv), aldehyde **3.18a** (0.053 g, 0.5 mmol, 1.0 equiv.), HE (0.127 g, 0.5 mmol, 1.0 equiv), and HFIP (0.5 mL) at 60 °C for 1 h, the product **5.6f** and **5.6g** was obtained in 45% yield (0.057 g) and 30% yield (0.039 g), respectively.

Reaction conditions: Tetrahydroquinoline **2.12** (0.067 g, 0.5 mmol, 1.0 equiv.), 4-methoxy benzaldehyde **3.18c** (0.034 g, 0.25 mmol, 0.5 equiv), 4-fluoro benzaldehyde **3.18e** (0.031 g, 0.25 mmol, 0.5 equiv), HE (0.127 g, 0.5 mmol, 1.0 equiv), and HFIP (0.5 mL) at 60 °C for 1 h, the product **3.20c** and **3.20e** was obtained in 34% yield (0.043 g) and 46% yield (0.056 g), respectively.

iv) Deuterium-labelling experiment (Scheme 5.13)

Reaction conditions: In a reaction tube (15 mL), 3-methyl quinoline **2.14g** (0.071 g, 0.5 mmol), **3.18a** (0.053 g, 0.5 mmol), HE (0.76 g, 1.5 mmol, 3 equiv.), HFIP (0.5 mL), and D_2O (0.6 equiv.) were charged, then sealed with screw-cap, the resulting solution was heated at 60 °C for 1 h under standard conditions, the desired product **D-5.6c** was obtained in 76% yield.

^{1}H NMR spectrum of deuterated 1-benzyl-3-methyl-1,2,3,4-tetrahydroquinoline (5.6c + D-5.6c):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.21 (m, 10H, **5.6c + D-5.6c**), 6.98 – 6.95 (m, 4H, **5.6c + D-5.6c**), 6.57 (t, J = 7.3 Hz, 2H, **5.6c + D-5.6c**), 6.50 (d, J = 8.5 Hz, 2H, **5.6c + D-5.6c**), 4.47 (s, 4H, **5.6c + D-5.6c**), 3.30 – 3.26 (m, 2H, **5.6c + D-5.6c**), 3.05 – 3.00 (m, 2H, **5.6c + D-5.6c**), 2.84 – 2.79 (m, 2H, **5.6c + D-5.6c**), 2.53 – 2.47 (m, 2H, **5.6c+ D-5.6c**), 2.23–2.12 (m, 1H, **5.6c**) 1.05 (s, 6H, **5.6c + D-5.6c**).

v) Eyring Studies (Scheme 5.14)

An oven dried reaction tube, **2.12** (0.066 g, 0.5 mmol, 1.0 equiv.), aldehyde **3.18a** (0.053 g, 0.5 mmol, 1.0 equiv.), and HE (0.126 g, 0.5 mmol, 1 equiv.) in HFIP (0.5 mL) were taken. The reaction tube was properly closed and placed in a pre-heated oil bath at respective temperature for the specified times. The measure yield of product was plotted against to obtain the slope which gave the rate constant for each case.

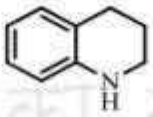
Temp	1/T	k	ln(k/T)
323 K (50 °C)	0.003095	7.34×10^{-3}	-10.69
333 K (60 °C)	0.003003	9.58×10^{-3}	-10.45

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343 K (70 °C)	0.002915	11.76×10^{-3}	-10.28
353 K (80 °C)	0.002832	14.94×10^{-3}	-10.07

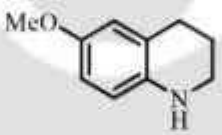
5.6. Analytical data of the products

1,2,3,4-tetrahydroquinoline (2.12)



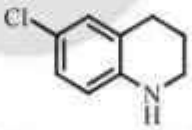
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 – 6.95 (m, 2H), 6.61 (t, J = 8.1 Hz, 1H), 6.48 (d, J = 7.9 Hz, 1H), 3.32 – 3.29 (m, 2H), 2.77 (t, J = 6.4 Hz, 2H), 1.98 – 1.92 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.9, 129.6, 126.8, 121.6, 117.1, 114.3, 42.1, 27.1, 22.3. Spectral data is in accordance with the literature. [44]

6-methoxy-1,2,3,4-tetrahydroquinoline (5.18f)



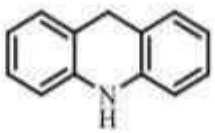
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 – 6.56 (m, 2H), 6.46 (d, J = 8.5 Hz, 1H), 3.73 (s, 3H), 3.01 (brs, 1H), 3.27 – 3.24 (m, 2H), 2.76 (t, J = 6.5 Hz, 2H), 1.96-1.90 (m, 2H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.0, 139.0, 123.0, 115.7, 115.0, 113.0, 55.9, 42.5, 27.3, 22.6. Spectral data is in accordance to the reported literature. [44]

6-chloro-1,2,3,4-tetrahydroquinoline (5.18g)



^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.38 (d, J = 8.0 Hz, 1H), 3.76 (brs, 1H), 3.30 – 3.27 (m, 2H), 2.73 (t, J = 6.4 Hz, 2H), 1.95 – 1.89 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.4, 129.1, 126.6, 122.9, 121.2, 115.2, 41.9, 27.0, 21.8 Spectral data is in accordance to the reported literature. [44]

9,10-dihydroacridine (5.18p)

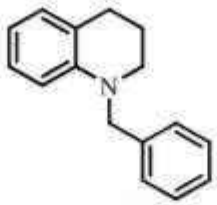


White solid (0.087 g, 96%); M.p: 171~173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 – 7.05 (m, 4H), 6.86 – 6.82 (M, 2H), 6.65 (dd, J = 7.8, 1.2 Hz, 2H), 5.93 (brs, 1H), 4.04 (s, 2H). ^{13}C{^{1}H}

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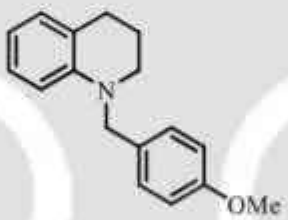
NMR (101 MHz, $CDCl_3$): δ 140.3, 128.7, 127.1, 120.8, 120.2, 113.6, 31.5. Spectral data is in accordance to the reported literature. [45]

1-benzyl-1, 2, 3, 4-tetrahydroquinoline (3.20a)



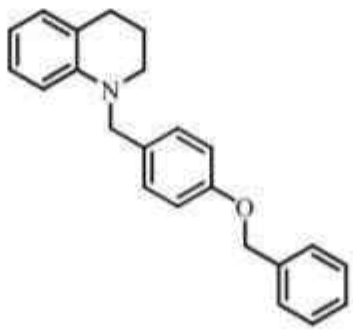
By following the **GP-1**, the title compound **3.20a** was isolated as light-yellow oil (0.104 g, 93%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.21 (m, 5H), 6.98 – 6.95 (m, 2H), 6.57 (t, J = 7.3 Hz, 1H), 6.50 (d, J = 8.3 Hz, 1H), 4.47 (s, 2H), 3.37 – 3.35 (m, 2H), 2.82 (t, J = 6.2 Hz, 2H), 2.03 – 1.99 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.8, 139.1, 129.1, 128.7, 127.3, 126.9, 126.7, 122.4, 116.0, 111.1, 55.3, 50.0, 28.4, 22.5. Spectral data is in accordance to the reported literature. [22]

1-(4-methoxybenzyl)-1, 2, 3, 4-tetrahydroquinoline (3.20c)



By following the **GP -1**, the title compound **3.20c** was isolated as light-yellow oil (0.109 g, 86%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, J = 8.5 Hz, 2H), 7.00 – 6.97 (m, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.59 – 6.54 (m, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.34 (t, J = 5.6 Hz, 2H), 2.82 (t, J = 6.3 Hz, 2H), 2.03 – 1.98 (m, 2H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 158.7, 145.8, 131.0, 129.1, 127.9, 127.3, 122.4, 115.9, 114.1, 111.1, 55.4, 54.7, 49.8, 28.4, 22.5. Spectral data is in accordance to the reported literature. [22]

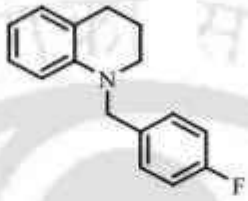
1-(4-(benzyloxy) benzyl)-1,2,3,4-tetrahydroquinoline (5.5c)



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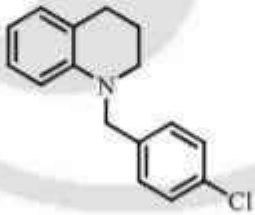
By following the **GP -1**, the title compound **5.5c** was isolated as light-yellow oil (0.137 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.28 (m, 5H), 7.16 – 7.14 (m, 2H), 6.97 – 6.89 (m, 4H), 6.57 – 6.50 (m, 2H), 4.99 (s, 2H), 4.37 (s, 2H), 3.30 – 3.28 (m, 2H), 2.77 (t, J = 6.3 Hz, 2H), 1.98 – 1.93 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 157.8, 145.7, 137.2, 131.2, 129.1, 128.6, 128.0, 127.9, 127.5, 127.2, 122.3, 115.9, 115.0, 111.1, 70.1, 54.6, 49.7, 28.3, 22.4. Spectral data is in accordance to the reported literature. [22]

1-(4-fluorobenzyl)-1, 2, 3, 4-tetrahydroquinoline (3.20e)



By following the **GP-1**, the title compound **3.20e** was isolated as light-yellow oil (0.115 g, 95%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.20 (m, 2H), 7.01 – 6.96 (m, 4H), 6.58 (t, J = 7.3 Hz, 1H), 6.47 (d, J = 8.5 Hz, 1H), 4.43 (s, 2H), 3.34 (t, J = 5.6 Hz 2H), 2.81 (t, J = 6.3 Hz, 2H), 2.03 – 1.98 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 162.9 – 161.0 (C-F, $^1J_{C\text{-}F}$ = 244.5 Hz), 145.6, 134.6 (C-F, $^4J_{C\text{-}F}$ = 3.1 Hz), 129.2, 128.2 (C-F, $^3J_{C\text{-}F}$ = 7.9 Hz), 127.3, 122.5, 116.2, 115.6 - 115.4 (C-F, $^2J_{C\text{-}F}$ = 21.5 Hz, 111.1, 54.8, 50.0, 28.3, 22.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ -116.46. Spectral data is in accordance to the reported literature. [22]

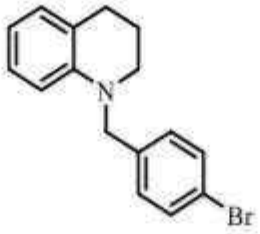
1-(4-chlorobenzyl)-1,2,3,4-tetrahydroquinoline (5.5e)



By following the **GP-1**, the title compound **5.5e** was isolated as light-yellow oil (0.120 g, 93%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.00 – 6.97 (m, 2H), 6.60 (d, J = 7.3 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.44 (s, 2H), 3.36 (t, J = 5.6 Hz, 2H), 2.83 (t, J = 6.3 Hz, 2H), 2.05 – 2.01 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.5, 137.6, 132.5, 129.2, 128.8, 128.1, 127.3, 122.5, 116.3, 111.1, 54.8, 50.1, 28.3, 22.5. Spectral data is in accordance to the reported literature. [22]

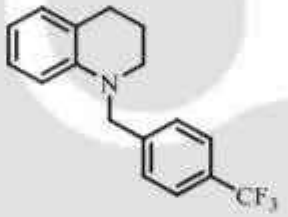
1-(4-bromobenzyl)-1, 2, 3, 4-tetrahydroquinoline (5.5f)

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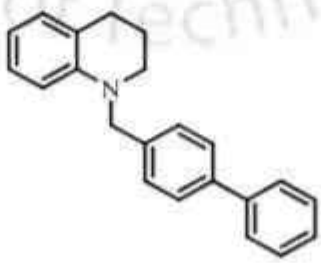
By following the **GP-1**, the title compound **5.5f** was isolated as light-yellow oil (0.134 g, 89%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.99 – 6.95 (m, 2H), 6.59 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 8.1 Hz, 1H), 4.41 (s, 2H), 3.34 (t, J = 5.6 Hz, 2H), 2.82 (t, J = 6.2 Hz, 2H), 2.04 – 1.99 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.5, 138.2, 131.8, 129.2, 128.5, 127.3, 122.5, 120.6, 116.3, 111.1, 54.9, 50.1, 28.3, 22.5. Spectral data is in accordance to the reported literature. [22]

1-(4-(trifluoromethyl) benzyl)-1,2,3,4-tetrahydroquinoline (5.5g)



By following the **GP-1**, the title compound **5.5g** was isolated as light-yellow oil (0.138 g, 95%) solid using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.04 – 6.99 (m, 2H), 6.64 (t, J = 7.2 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 4.55 (s, 2H), 3.42 – 3.40 (m, 2H), 2.87 (t, J = 6.2 Hz, 2H), 2.07 (p, J = 6.1 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.3, 143.5, 129.2, 127.3, 126.9, 125.6 (q, J = 3.7 Hz), 122.5, 116.4, 111.0, 55.1, 50.2, 28.2, 22.5. ^{19}F NMR (565 MHz, $CDCl_3$): δ -62.28. Spectral data is in accordance to the reported literature. [22]

1-([1,1'-biphenyl]-4-ylmethyl)-1,2,3,4-tetrahydroquinolines (5.5h)

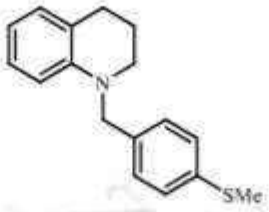


By following the **GP -1**, the title compound **5.5h** was isolated as light-yellow oil (0.130 g, 87 %) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 – 7.56 (m, 4H), 7.46 – 7.43 (s, 2H), 7.37 – 7.35 (s, 3H), 7.02 – 7.01 (m, 2H), 6.62 – 6.56 (m, 2H), 4.54 (s, 2H), 3.42 – 3.41 (m, 2H), 2.87 – 2.85 (m,

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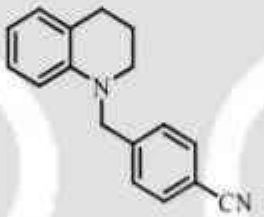
2H), 2.08 – 2.05 (m, 2H).$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 145.7, 141.1, 139.9, 138.2, 129.2, 128.9, 127.5, 127.35, 127.28, 127.2, 122.4, 116.0, 111.1, 55.1, 50.1, 28.4, 22.5. Spectral data is in accordance to the reported literature. [22]

1-(4-(methylthio) benzyl)-1,2,3,4-tetrahydroquinoline (5.5i)



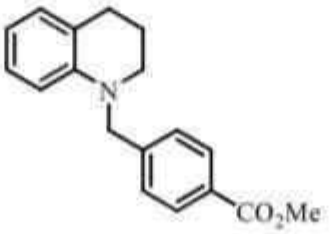
By following the **GP-1**, the title compound **5.5i** was isolated as light-yellow oil (0.110 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 – 7.17 (m, 4H), 6.97 – 6.94 (m, 2H), 6.56 (t, J = 7.3 Hz, 1H), 6.48 (d, J = 8.6 Hz, 1H), 4.41 (s, 2H), 3.33 (t, J = 5.7 Hz, 2H), 2.80 (t, J = 6.3 Hz, 2H), 2.45 (s, 3H), 2.02 – 1.97 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 145.6, 136.6, 136.1, 129.1, 127.32, 127.28, 127.26, 122.4, 116.0, 111.1, 54.9, 50.0, 28.3, 22.5, 16.3. Spectral data is in accordance to the reported literature. [22]

4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzonitrile (5.5j)



By following the **GP-1**, the title compound **5.5j** was isolated as white solid (0.119 g, 96%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80).m.p. 62-64°C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.02 – 6.96 (m, 2H), 6.62 (t, J = 7.3 Hz, 1H), 6.37 (d, J = 8.2 Hz, 1H), 4.52 (s, 2H), 3.38 (t, J = 5.6 Hz 2H), 2.85 (t, J = 6.3 Hz, 2H), 2.05 (p, J = 6.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 145.1, 132.6, 129.3, 127.34, 127.33, 122.6, 119.0, 116.7, 111.0, 110.8, 55.4, 50.4, 28.2, 22.5. Spectral data is in accordance to the reported literature. [22]

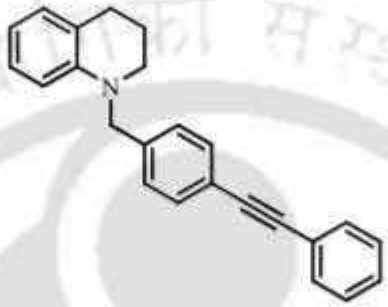
Methyl 4-((3, 4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.5k)



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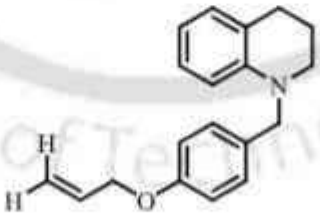
By following the **GP -1**, the title compound **5.5k** was isolated as light-yellow oil (0.131 g, 93%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.59 (t, J = 7.3 Hz, 1H), 6.41 (d, J = 8.2 Hz, 1H), 4.52 (s, 2H), 3.90 (s, 3H), 3.39 – 3.37 (m, 2H), 2.83 (t, J = 6.2 Hz, 2H), 2.06 – 2.01 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.2, 145.4, 144.8, 130.1, 129.2, 128.9, 127.3, 126.6, 122.5, 116.3, 111.0, 55.4, 52.2, 50.3, 28.3, 22.5. IR (KBr, selected band): 1722.60 cm^{-1}. Spectral data is in accordance to the reported literature. [22]

1-(4-(phenylethynyl) benzyl)-1,2,3,4-tetrahydroquinoline (5.5l)



By following the **GP -1**, the title compound **5.5l** was isolated as yellow oil (0.142 g, 88%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53 – 7.51 (m, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.35 – 7.31 (m, 3H), 7.25 – 7.23 (m, 2H), 6.99 – 6.96 (m, 2H), 6.59 (t, J = 7.3 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 4.47 (s, 2H), 3.37 – 3.35 (m, 2H), 2.82 (t, J = 6.2 Hz, 2H), 2.02 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.6, 139.6, 132.0, 131.7, 129.2, 128.5, 128.3, 127.3, 126.7, 123.4, 122.4, 121.8, 116.2, 111.1, 89.5, 89.2, 55.3, 50.1, 28.3, 22.5. IR (KBr, selected band): 2217.5 cm^{-1}. Spectral data is in accordance to the reported literature. [22]

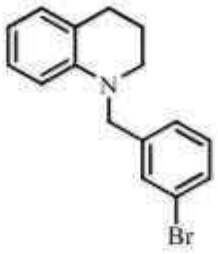
1-(4-(allyloxy) benzyl)-1, 2, 3, 4-tetrahydroquinoline (5.5m)



By following the **GP -1**, the title compound **5.5m** was isolated as light-yellow oil (0.117 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.59 – 6.53 (m, 2H), 6.09 – 6.02 (m, 1H), 5.41 (d, J = 17.2 Hz, 1H), 5.29 (m, 1H), 4.52 (d, J = 5.2 Hz, 2H), 4.41 (s, 2H), 3.35 – 3.32 (m, 2H), 2.81 (t, J = 5.8 Hz, 2H), 2.02 – 1.98 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 157.7, 145.8, 133.5, 131.2, 129.1, 127.9, 127.3, 122.4, 117.8, 115.9, 115.0, 111.1, 69.0, 54.7, 49.8, 28.4, 22.5. Spectral data is in accordance to the reported literature. [22]

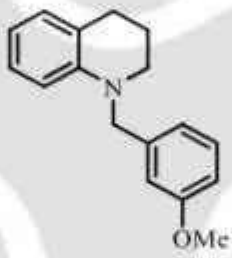
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1-(3-bromobenzyl)-1,2,3,4-tetrahydroquinoline (5.5n)



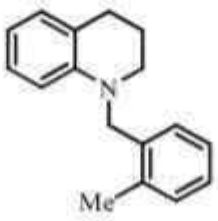
By following the **GP -1**, The title compound **5.5n** was isolated as light-yellow oil (0.134 g, 89%,) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.36 – 7.33 (m, 1H), 7.18 – 7.12 (m, 2H), 6.98 – 6.94 (m, 2H), 6.58 (t, J = 7.4 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.40 (s, 2H), 3.34 – 3.31 (m, 2H), 2.80 (t, J = 6.2 Hz, 2H), 2.00 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.4, 141.8, 130.3, 130.0, 129.6, 129.2, 127.3, 125.2, 122.9, 122.5, 116.3, 111.1, 55.1, 50.2, 28.2, 22.5. Spectral data is in accordance to the reported literature. [22]

1-(3-methoxybenzyl)-1, 2, 3, 4-tetrahydroquinoline (5.5o)



By following the **GP -1**, the title compound **5.5o** was isolated as light-yellow oil (0.111 g, 88 %) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (t, J = 7.8 Hz, 1H), 6.96 – 6.94 (m, 2H), 6.84 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 6.76 – 6.74 (m, 1H), 6.55 (t, J = 7.3 Hz, 1H), 6.48 (d, J = 8.6 Hz, 1H), 4.41 (s, 2H), 3.73 (s, 3H), 3.34 – 3.32 (m, 2H), 2.79 (t, J = 6.3 Hz, 2H), 1.98 (p, J = 6.1 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.0, 145.7, 140.9, 129.7, 129.0, 127.2, 122.3, 118.9, 116.0, 112.4, 112.0, 111.1, 55.3, 55.2, 50.0, 28.3, 22.5. Spectral data is in accordance to the reported literature. [25]

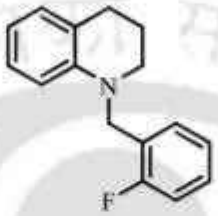
1-(2-methylbenzyl)-1,2,3,4-tetrahydroquinoline (5.5p)



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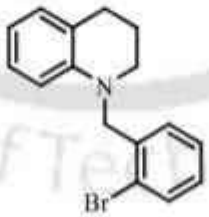
By following the **GP -1**, the title compound **5.5p** was isolated as light-yellow oil (0.103 g, 87%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 – 7.12 (m, 4H), 7.01 – 6.95 (m, 2H), 6.61 – 6.57 (m, 1H), 6.39 (d, J = 8.2 Hz, 1H), 4.41 (s, 2H), 3.38 – 3.35 (m, 2H), 2.86 (t, J = 6.2 Hz, 2H), 2.34 (s, 3H), 2.08 – 2.02 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.8, 136.1, 135.7, 130.4, 129.0, 127.3, 126.8, 126.21, 126.15, 122.4, 115.9, 111.0, 53.6, 49.9, 28.4, 22.6, 19.1. Spectral data is in accordance to the reported literature. [22]

1-(2-fluorobenzyl)-1,2,3,4-tetrahydroquinoline (5.5q)



By following the **GP -1**, the title compound **5.5q** was isolated as white solid (0.113 g, 94%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). m.p. 61-63 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.20 (m, 2H), 7.07 – 7.03 (m, 2H), 6.99 – 6.96 (m, 2H), 6.58 (t, J = 7.3 Hz, 1H), 6.45 (d, J = 8.3 Hz, 1H), 4.52 (s, 2H), 3.39 – 3.37 (m, 2H), 2.83 – 2.81 (m, 2H), 2.02 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 161.9 – 160.2 (C-F, $^1J_{C\text{-}F}$ = 245.1 Hz), 145.5, 129.2, 128.42, 128.38, 128.4 – 124.3 (C-F, $^3J_{C\text{-}F}$ = 2.31 Hz), 127.4, 125.7 – 125.6 (C-F, $^2J_{C\text{-}F}$ = 14.61 Hz), 124.2 (C-F, $^3J_{C\text{-}F}$ = 3.55 Hz), 122.4, 116.1, 115.4 – 115.3 (C-F, $^2J_{C\text{-}F}$ = 21.1 Hz), 110.9, 50.1, 49.30, 49.27, 28.3, 22.5. ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$): δ -118.61. Spectral data is in accordance to the reported literature. [22]

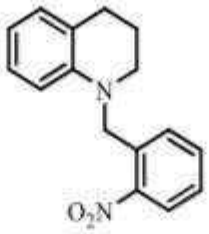
1-(2-bromobenzyl)-1,2,3,4-tetrahydroquinoline (5.5r)



By following the **GP -1**, the title compound **5.5r** was isolated as light-yellow oil (0.133 g, 88%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, J = 7.7 Hz, 1H), 7.21 – 7.20 (m, 2H), 7.12 – 7.09 (m, 1H), 6.98 (d, J = 7.3 Hz, 1H), 6.96 – 6.93 (m, 1H), 6.59 – 6.57 (m, 1H), 6.29 (d, J = 8.2 Hz, 1H), 4.45 (s, 2H), 3.41 – 3.39 (m, 2H), 2.84 (t, J = 5.8 Hz, 2H), 2.07 – 2.03 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.2, 137.1, 132.9, 129.1, 128.4, 127.8, 127.6, 127.4, 123.0, 122.2, 116.2, 110.9, 56.3, 50.3, 28.3, 22.6. Spectral data is in accordance to the reported literature. [22]

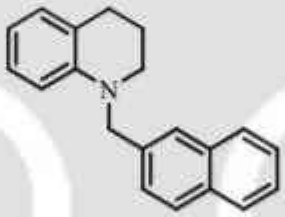
TH-3765_196122031

1-(2-nitrobenzyl)-1, 2, 3, 4-tetrahydroquinoline (5.5s)



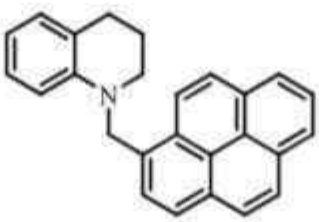
By following the **GP -1**, the title compound **5.5s** was isolated as light-red solid (0.130 g, 97%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.1Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.62 (t, J = 7.3 Hz, 1H), 6.27 (d, J = 8.2 Hz, 1H), 4.85 (s, 2H), 3.41 – 3.39 (m, 2H), 2.87 (t, J = 6.2 Hz, 2H), 2.10 – 2.05 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 148.3, 145.1, 135.3, 134.1, 129.2, 128.6, 127.9, 127.4, 125.6, 122.5, 116.6, 110.9, 54.0, 50.4, 28.2, 22.5. Spectral data is in accordance to the reported literature. [22]

1-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinoline (5.5t)



By following the **GP -1**, the title compound **5.5t** was isolated as white solid (0.120 g, 88%,) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). m.p. 100-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 – 8.01 (m, 1H), 7.93 – 7.91 (m, 1H), 7.79 – 7.77 (m, 1H), 7.58 – 7.52 (m, 2H), 7.41 (d, J = 5.5 Hz, 2H), 7.04 (d, J = 7.9 Hz, 1H), 6.99 – 6.95 (m, 1H), 6.63 – 6.59 (m, 1H), 6.46 (d, J = 8.2 Hz, 1H), 4.93 (s, 2H), 3.43 – 3.40 (m, 2H), 2.89 (t, J = 6.2 Hz, 2H), 2.10 – 2.04 (m, 2H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.8, 134.0, 132.9, 131.4, 129.1, 129.0, 127.5, 127.4, 126.1, 125.81, 125.79, 123.7, 122.8, 122.5, 116.0, 111.1, 53.4, 49.8, 28.4, 22.6. Spectral data is in accordance to the reported literature. [22]

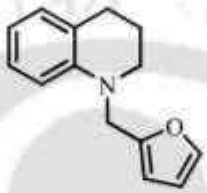
1-(pyren-1-ylmethyl)-1,2,3,4-tetrahydroquinoline (5.5u)



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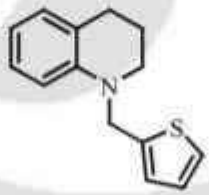
By following the **GP -1**, the title compound **5.5u** was isolated as light-green solid (0.149 g, 86%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). m.p. 175-177 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.27 (d, J = 9.1 Hz, 1H), 8.22 – 8.19 (m, 2H), 8.15 (d, J = 9.1 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 8.04 (s, 2H), 8.03 – 8.01 (m, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.63 (t, J = 7.1 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 5.20 (s, 2H), 3.45 – 3.43 (m, 2H), 2.91 (t, J = 5.8 Hz, 2H), 2.11 – 2.07 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.9, 131.6, 131.5, 130.9, 130.6, 129.2, 128.5, 127.73, 127.68, 127.4, 127.1, 126.1, 125.31, 125.26, 125.1, 125.0, 124.7, 122.8, 122.4, 116.2, 111.2, 53.7, 49.8, 28.4, 22.7. Spectral data is in accordance to the reported literature. [22]

1-(furan-2-ylmethyl)-1,2,3,4-tetrahydroquinoline (5.5v)



By following the **GP -1**, the title compound **5.5v** was isolated as light-yellow oil (0.090 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 1.2 Hz, 1H), 7.04 (t, J = 8.8 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.62 – 6.59 (m, 1H), 6.30 – 6.29 (m, 1H), 6.17 – 6.16 (m, 1H), 4.42 (s, 2H), 3.38 – 3.35 (m, 2H), 2.76 (t, J = 6.4 Hz, 2H), 2.01 – 1.95 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.5, 145.1, 141.9, 129.2, 127.1, 122.9, 116.4, 111.4, 110.3, 107.2, 49.7, 48.5, 28.2, 22.4. Spectral data is in accordance to the reported literature. [22]

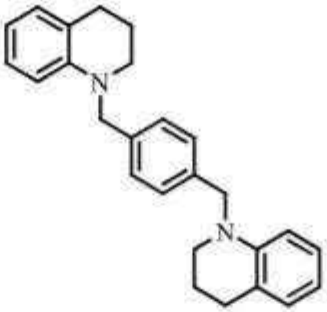
1-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroquinoline (5.5w)



By following the **GP-1**, the title compound **5.5w** was isolated as light-yellow oil (0.095 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 – 7.17 (m, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.00 – 6.95 (m, 3H), 6.72 (d, J = 8.2 Hz, 1H), 6.63 (t, J = 7.3 Hz, 1H), 4.64 (s, 2H), 3.39 – 3.36 (m, 2H), 2.79 (t, J = 6.3 Hz, 2H), 2.04 – 1.98 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.1, 142.6, 129.3, 127.2, 126.9, 124.8, 124.3, 123.0, 116.6, 111.6, 50.7, 49.6, 28.2, 22.4. Spectral data is in accordance to the reported literature. [22]

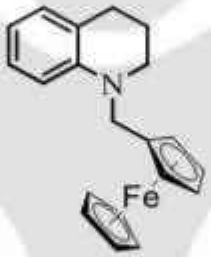
1,4-bis((3,4-dihydroquinolin-1(2H)-yl) methyl) benzene (3x)

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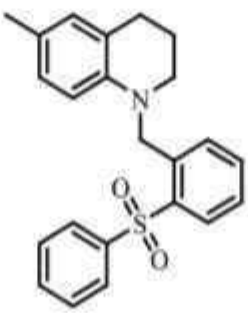
By following the **GP -1**, the title compound **5.5x** was isolated as yellow oil (0.136 g, 74%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 4H), 7.00– 6.96 (m, 4H), 6.58 (t, J = 7.3 Hz, 2H), 6.52 (d, J = 8.6 Hz, 2H), 4.46 (s, 4H), 3.38 – 3.35 (m, 4H), 2.81 (t, J = 6.2 Hz, 4H), 2.04 – 1.99 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.7, 137.6, 129.1, 127.3, 127.0, 122.4, 115.9, 111.1, 55.1, 50.0, 28.4, 22.5. Spectral data is in accordance to the reported literature. [22]

Cyclopenta-2,4-dien-1-yl(2-((3,4-dihydroquinolin-1(2H)-yl) methyl) cyclopenta-2,4-dien-1-yl) iron (5.5y)



By following the **GP-1**, the title compound **5.5y** was isolated as light-yellow oil (0.109 g, 66%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.04 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.3 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.55 (t, J = 7.2 Hz, 1H), 4.22 (s, 2H), 4.20 (t, J = 1.9 Hz, 2H), 4.16 (s, 5H), 4.08 (t, J = 1.9 Hz, 2H), 3.27 – 3.25 (m, 2H), 2.71 (t, J = 6.4 Hz, 2H), 1.94 – 1.90 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.5, 129.3, 127.0, 122.7, 115.9, 111.4, 69.1, 68.7, 67.9, 50.7, 49.0, 28.3, 22.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{22}FeN$:332.1097; found: 332.1057.

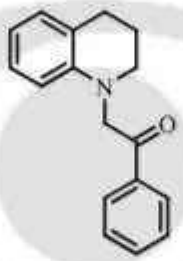
6-methyl-1-(2-(phenylsulfonyl) benzyl)-1,2,3,4-tetrahydroquinoline (5.5z)



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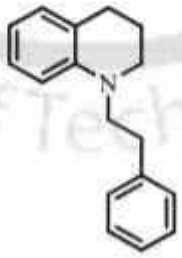
By following the **GP-1**, the title compound **5.5z** was isolated as white solid (0.164 g, 87%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). m.p. 175-177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (dd, J = 7.6, 1.6 Hz, 1H), 7.91 – 7.89 (m, 2H), 7.64 – 7.60 (m, 1H), 7.55 – 7.41 (m, 5H), 6.77 (s, 1H), 6.47 – 6.44 (m, 1H), 5.44 (d, J = 8.2 Hz, 1H), 4.57 (s, 2H), 3.28 – 3.25 (m, 2H), 2.76 (t, J = 6.3 Hz, 2H), 2.13 (s, 3H), 2.01 – 1.96 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 142.6, 141.2, 139.0, 137.8, 134.3, 133.4, 130.0, 129.9, 129.4, 128.0, 127.8, 127.5, 127.4, 125.3, 122.2, 110.5, 53.2, 50.5, 28.1, 22.6, 20.2. Spectral data is in accordance to the reported literature. [22]

2-(3,4-dihydroquinolin-1(2H)-yl)-1-phenylethan-1-one (5.5aa)



By following the **GP-1**, the title compound **5.5aa** was isolated a light-yellow oil (0.087 g, 69%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.52). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 7.5 Hz, 2H), 7.59 – 7.56 (m, 1H), 7.46 (t, J = 7.7 Hz, 2H), 6.97 – 6.92 (m, 2H), 6.58 (t, J = 7.2 Hz, 1H), 6.29 (d, J = 8.1 Hz, 1H), 4.67 (s, 2H), 3.38 – 3.35 (m, 2H), 2.81 (t, J = 6.2 Hz, 2H), 2.04 – 1.98 (m, 2H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.5, 145.1, 135.7, 133.5, 129.2, 128.8, 127.1, 122.8, 116.6, 110.4, 57.7, 50.6, 28.1, 22.4. Spectral data is in accordance to the reported literature. [25]

1-phenethyl-1,2,3,4-tetrahydroquinoline (5.5ab)

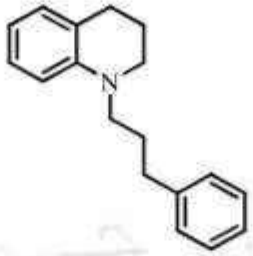


By following the **GP-1**, the title compound **5.5ab** was isolated as yellow oil (0.087 g, 73%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.29 (m, 2H), 7.25 – 7.22 (m, 3H), 7.08 (t, J = 7.8 Hz, 2H), 6.95 (d, J = 7.3 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.57 (t, J = 7.3 Hz, 1H), 3.50 – 3.47 (m, 2H), 3.22 – 3.20 (m, 2H), 2.88 – 2.85 (m, 2H), 2.74 (t, J = 6.3 Hz, 2H), 1.90 (p, J = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.9, 140.1, 129.4, 129.0, 128.6, 127.3, 126.3,

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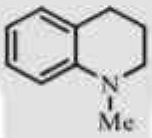
122.5, 115.7, 110.5, 53.5, 49.7, 32.6, 28.3, 22.3. Spectral data is in accordance to the reported literature. [22]

1-(3-phenylpropyl)-1,2,3,4-tetrahydroquinoline (5.5ac)



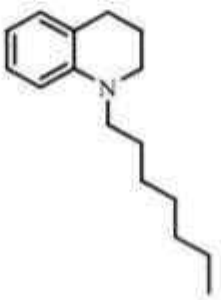
By following the **GP-1**, The title compound **5.5ac** was isolated as light-yellow oil (0.108 g, 86%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (t, J = 7.8 Hz, 2H), 7.21 – 7.19 (m, 3H), 7.02 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 7.1 Hz, 1H), 6.55 (t, J = 7.3 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 3.29 – 3.25 (m, 4H), 2.75 (t, J = 6.3 Hz, 2H), 2.69 – 2.66 (m, 2H), 1.96 – 1.91 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.4, 142.0, 129.3, 128.50, 128.48, 127.2, 126.0, 122.4, 115.5, 110.6, 51.1, 49.6, 33.6, 28.3, 27.8, 22.4. Spectral data is in accordance to the reported literature. [22]

1-methyl-1,2,3,4-tetrahydroquinoline (5.5ad)



By following the **GP-1**, the title compound **5.5ad** was isolated as colourless oil (0.047 g, 64%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.2 Hz, 1H), 6.66 – 6.63 (m, 2H), 3.27 – 3.24 (m, 2H), 2.92 (s, 3H), 2.81 (t, J = 6.4 Hz, 2H), 2.05 – 1.99 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.9, 128.9, 127.2, 123.0, 116.3, 111.1, 51.4, 39.2, 27.9, 22.6. Spectral data is in accordance to the reported literature. [22]

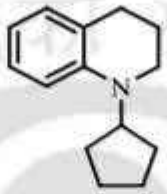
1-heptyl-1,2,3,4-tetrahydroquinoline (5.5ae)



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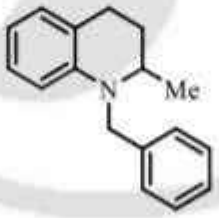
By following the **GP -1**, The title compound **5.5ae** was isolated as light-green oil (0.082 g, 71%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 – 7.02 (m, 1H), 6.94 (d, J = 7.2 Hz, 1H), 6.59 – 6.52 (m, 2H), 3.29 – 3.21 (m, 4H), 2.75 (t, J = 6.3 Hz, 2H), 1.98 – 1.92 (m, 2H), 1.62 – 1.55 (m, 2H), 1.34 – 1.30 (m, 8H), 0.91 – 0.88 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.5, 129.2, 127.2, 122.3, 115.3, 110.6, 51.7, 49.6, 32.0, 29.4, 28.4, 27.4, 26.3, 22.8, 22.4, 14.2. Spectral data is in accordance to the reported literature. [22]

1-cyclopentyl-1,2,3,4-tetrahydroquinoline (5.5af)



By following the **GP-1**, The title compound **5.5af** was isolated as light-yellow oil (0.082 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): 7.08 – 7.06 (m, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.56 (t, J = 7.1 Hz, 1H), 4.20 (p, J = 7.9 Hz, 1H), 3.21 – 3.18 (m, 2H), 2.75 (t, J = 6.4 Hz, 2H), 1.95 – 1.86 (m, 4H), 1.77 – 1.59 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.4, 129.1, 127.1, 123.5, 115.4, 111.2, 58.7, 42.1, 28.6, 28.1, 24.3, 22.8. Spectral data is in accordance to the reported literature. [22]

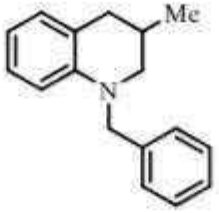
1-benzyl-2-methyl-1,2,3,4-tetrahydroquinoline (5.6b)



By following the **GP-2**, the title compound **5.6b** was isolated as light-yellow oil (0.096 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.19 (m, 5H), 7.00 (d, J = 7.3 Hz, 1H), 6.94 (t, J = 6.8 Hz, 1H), 6.58 – 6.54 (m, 1H), 6.39 (d, J = 8.2 Hz, 1H), 4.57 – 4.43 (m, 2H), 3.61 – 3.54 (m, 1H), 2.96 – 2.88 (m, 1H), 2.78 – 2.72 (m, 1H), 2.08 – 2.00 (m, 1H), 1.86 – 1.80 (m, 1H), 1.18 (d, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.9, 139.6, 128.9, 128.7, 127.2, 126.7, 126.4, 121.9, 115.6, 111.5, 53.5, 53.1, 28.3, 24.2, 19.1. Spectral data is in accordance to the reported literature. [22]

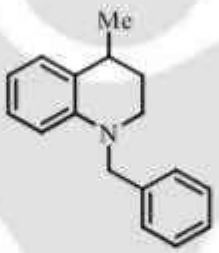
1-benzyl-3-methyl-1,2,3,4-tetrahydroquinoline (5.6c)

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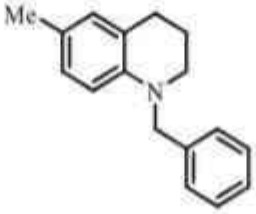
By following the **GP-2**, the title compound **5.6c** was isolated as light-yellow oil (0.100 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.21 (m, 5H), 6.98 – 6.95 (m, 2H), 6.57 (t, J = 7.2 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 4.48 (s, 2H), 3.30 – 3.26 (m, 1H), 3.06 – 3.01 (m, 1H), 2.84 – 2.79 (m, 1H), 2.54 – 2.47 (m, 1H), 2.23 – 2.12 (m, 1H), 1.05 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.3, 139.1, 129.2, 128.7, 127.3, 126.9, 126.7, 122.0, 116.0, 110.8, 57.0, 55.3, 36.6, 27.4, 19.2. Spectral data is in accordance to the reported literature. [22]

1-benzyl-4-methyl-1,2,3,4-tetrahydroquinoline (5.6d)



By following the **GP-2**, the title compound **5.6d** was isolated as light-yellow oil (0.103 g, 87%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.22 (m, 5H), 7.07 (d, J = 7.2 Hz, 1H), 6.99 – 6.95 (m, 1H), 6.62 – 6.59 (m, 1H), 6.50 (d, J = 8.2 Hz, 1H), 4.49 (s, 2H), 3.45 – 3.39 (m, 1H), 3.34 – 3.29 (m, 1H), 2.96 – 2.95 (m, 1H), 2.09 – 2.02 (m, 1H), 1.77 – 1.72 (m, 1H), 1.33 – 1.31 (m, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.0, 139.0, 128.7, 128.0, 127.4, 127.2, 126.9, 126.7, 115.9, 111.1, 55.3, 46.7, 31.2, 29.8, 22.4. Spectral data is in accordance to the reported literature. [22]

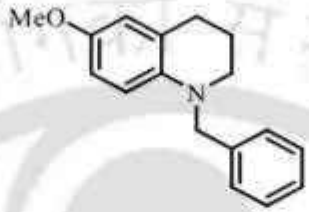
1-benzyl-6-methyl-1,2,3,4-tetrahydroquinoline (5.6e)



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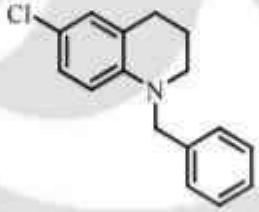
By following the **GP-2**, the title compound **5.6e** was isolated as colorless oil (0.106 g, 89%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 – 7.21 (m, 5H), 6.81 (s, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 4.44 (s, 2H), 3.33 (t, J = 5.6 Hz, 2H), 2.79 (t, J = 6.3 Hz, 2H), 2.19 (s, 3H), 2.00 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.6, 139.3, 129.9, 128.7, 127.6, 126.81, 126.76, 125.1, 122.4, 111.3, 55.5, 50.0, 28.3, 22.7, 20.3. Spectral data is in accordance to the reported literature. [22]

1-benzyl-6-methoxy-1,2,3,4-tetrahydroquinoline (5.6f)



By following the **GP-2**, the title compound **5.6f** was isolated as yellow oil (0.116 g, 92%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/1, R_f = 0.70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.23 (m, 5H), 6.61 – 6.56 (m, 2H), 6.45 (d, J = 8.8 Hz, 1H), 4.41 (s, 2H), 3.71 (s, 3H), 3.30 – 3.28 (m, 2H), 2.81 – 2.79 (m, 2H), 2.02 – 1.97 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 151.0, 140.5, 139.5, 128.7, 126.9, 126.8, 123.9, 115.4, 112.5, 112.4, 56.1, 55.9, 50.1, 28.5, 22.7. Spectral data is in accordance to the reported literature. [22]

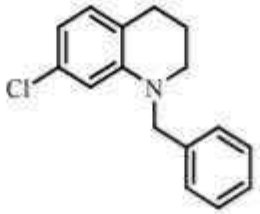
1-benzyl-6-chloro-1,2,3,4-tetrahydroquinoline (5.6g)



By following the **GP-2**, the title compound **5.6g** was isolated as yellow oil (0.106 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.31 (m, 2H), 7.24 – 7.22 (m, 3H), 6.93 (s, 1H), 6.90 – 6.88 (m, 1H), 6.39 – 6.37 (d, J = 8.8 Hz, 1H), 4.46 (s, 2H), 3.37 – 3.35 (m, 2H), 2.78 (t, J = 6.3 Hz, 2H), 2.02 – 1.98 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 144.2, 138.5, 128.8, 128.7, 127.0, 126.9, 126.6, 123.9, 120.4, 112.1, 55.3, 50.0, 28.2, 22.3. Spectral data is in accordance to the reported literature. [22]

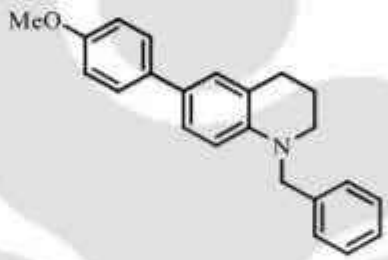
1-benzyl-7-chloro-1,2,3,4-tetrahydroquinoline (5.6h)

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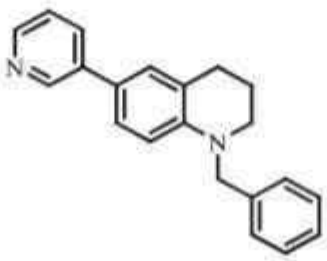
By following the **GP-2**, the title compound **5.6h** was isolated as light-yellow oil (0.107 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.30 (m, 2H), 7.26 – 7.22 (m, 3H), 6.86 (d, J = 7.9 Hz, 1H), 6.53 – 6.50 (m, 1H), 6.47 – 6.46 (m, 1H), 4.44 (s, 2H), 3.35 – 3.32 (m, 2H), 2.75 (t, J = 6.2 Hz, 2H), 1.97 (p, J = 6.1 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.6, 138.1, 132.7, 129.9, 128.8, 127.1, 126.6, 120.7, 115.6, 110.6, 55.0, 49.6, 27.8, 22.2. Spectral data is in accordance to the reported literature. [22]

1-benzyl-6-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (5.6i)



By following the **GP-2**, the title compound **5.6i** was isolated as colorless oil (0.145 g, 88%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 – 7.41 (m, 2H), 7.32 – 7.28 (m, 4H), 7.25 – 7.22 (m, 1H), 7.18 – 7.16 (m, 2H), 6.91 – 6.90 (m, 2H), 6.56 – 6.54 (m, 1H), 4.50 (s, 2H), 3.80 (s, 3H), 3.39 – 3.37 (m, 2H), 2.88 – 2.85 (m, 2H), 2.05 – 2.03 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 158.2, 144.8, 139.0, 134.2, 128.7, 128.6, 127.5, 127.3, 126.9, 126.7, 125.5, 122.6, 114.2, 111.4, 55.43, 55.37, 50.1, 28.5, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{24}NO$:330.1853; found: 330.1855.

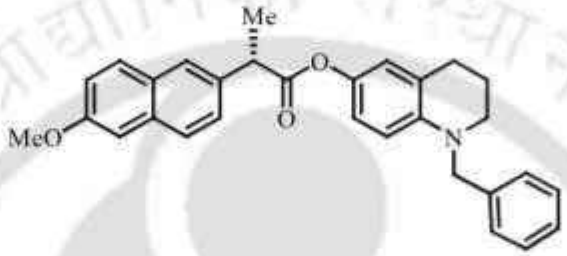
1-benzyl-6-(pyridin-3-yl)-1,2,3,4-tetrahydroquinoline (5.6j)



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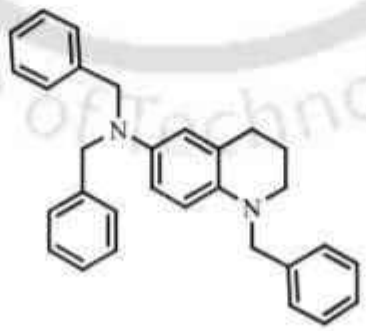
By following the **GP-2**, the title compound **5.6j** was isolated as yellow solid (0.125 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 2.4 Hz, 1H), 8.45 (d, J = 3.9 Hz, 1H), 7.79 (dt, J = 8.0, 2.0 Hz, 1H), 7.35 – 7.21 (m, 8H), 6.59 (d, J = 8.3 Hz, 1H), 4.54 (s, 2H), 3.43 (t, J = 5.7 Hz, 2H), 2.90 (t, J = 6.3 Hz, 2H), 2.09 – 2.03 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 147.5, 146.9, 145.8, 138.6, 136.9, 133.4, 128.8, 127.7, 127.1, 126.6, 126.0, 124.9, 123.6, 122.9, 111.5, 55.2, 50.1, 28.5, 22.4. Spectral data is in accordance to the reported literature. [25]

1-benzyl-1,2,3,4-tetrahydroquinolin-6-yl (S)-2-(6-methoxynaphthalen-2-yl) propanoate (5.6k)



By following the **GP-2**, the title compound **5.6k** was isolated as colourless oil (0.178 g, 79%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 – 7.70 (m, 3H), 7.49 – 7.47 (m, 1H), 7.30 – 7.27 (m, 2H), 7.22 – 7.21 (m, 3H), 7.15 – 7.11 (m, 2H), 6.61 – 6.60 (m, 1H), 6.58 – 6.56 (m, 1H), 6.38 – 6.36 (m, 1H), 4.40 (s, 2H), 4.05 – 4.01 (m, 1H), 3.90 (s, 3H), 3.31 – 3.29 (m, 2H), 2.73 (t, J = 6.2 Hz, 2H), 1.97 – 1.92 (m, 2H), 1.65 (d, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.0, 157.8, 143.6, 141.0, 138.8, 135.6, 133.9, 129.4, 129.1, 128.7, 127.3, 126.9, 126.7, 126.4, 126.2, 123.0, 121.6, 119.5, 119.1, 111.3, 105.7, 55.6, 55.4, 49.9, 45.6, 28.3, 22.3, 18.7. Spectral data is in accordance to the reported literature. [25]

***N*, *N*,1-tribenzyl-1,2,3,4-tetrahydroquinolin-6-amine (5.6l)**

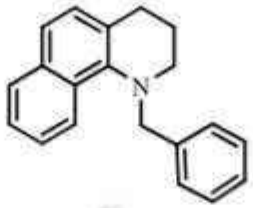


By following the **GP -2**, the title compound **5.6l** was isolated as purple-oil (0.146 g, 70%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.20 (m, 15H), 6.52 – 6.40 (m, 3H), 4.47 (s, 4H), 4.34 (s, 2H), 3.24 – 3.22 (m, 2H), 2.72 (t, J = 6.1 Hz, 2H), 1.98 – 1.95 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 141.2, 140.0, 139.7, 138.6, 128.6, 128.5, 127.2, 127.0, 126.8, 123.8, 115.4, 113.2,

TH-3765_196122031

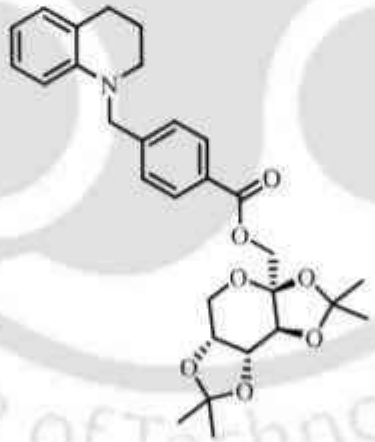
112.9, 56.4, 55.1, 50.1, 28.6, 22.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{30}H_{31}N_2$:419.2482; found: 419.2485.

1-benzyl-1,2,3,4-tetrahydrobenzo[*h*]quinoline (5.6m)



By following the **GP-2**, the title compound **5.6m** was isolated as colourless oil (0.093 g, 68%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.13 (m, 1H), 7.78 – 7.76 (m, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.47 – 7.43 (m, 3H), 7.40 – 7.33 (m, 3H), 7.18 (d, J = 8.4 Hz, 1H), 4.35 (s, 2H), 3.18 – 3.15 (m, 2H), 2.97 – 2.94 (m, 2H), 1.93 – 1.86 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.3, 139.9, 133.6, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 127.5, 127.1, 127.0, 125.45, 125.38, 125.1, 123.0, 122.2, 59.2, 47.0, 28.1, 16.6. Spectral data is in accordance to the reported literature. [22]

((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methyl 4-((3,4-dihydroquinolin-1(2H)-yl)methyl)benzoate (5.8a)

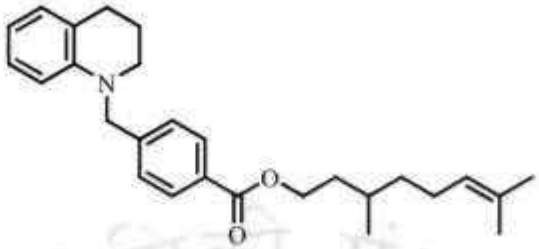


By following the **GP -1**, the title compound **5.8a** was isolated as light-yellow oil (0.209 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.60 (t, J = 7.3 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 4.67 – 4.64 (m, 2H), 4.52 (s, 2H), 4.47 (d, J = 2.5 Hz, 1H), 4.34 (d, J = 11.8 Hz, 1H), 4.26 (d, J = 7.9 Hz, 1H), 3.98 – 3.95 (m, 1H), 3.81 (d, J = 13.0 Hz, 1H), 3.39 – 3.35 (m, 2H), 2.84 (t, J = 6.2 Hz, 2H), 2.04 (p, J = 6.2 Hz, 2H), 1.56 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 165.9, 145.4, 145.1, 130.3, 129.2, 128.7, 127.3, 126.6, 122.5, 116.4, 111.1, 109.3,

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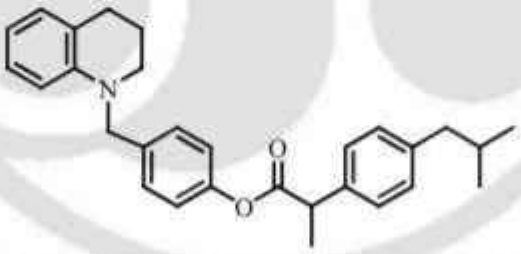
108.9, 101.8, 70.9, 70.6, 70.2, 65.4, 61.5, 55.4, 50.3, 28.2, 26.7, 26.0, 25.7, 24.2, 22.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{29}H_{36}NO_7$: 510.2487; found: 510.2488.

3,7-dimethyloct-6-en-1-yl 4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8b)



By following the **GP-1**, the title compound **5.8b** was isolated as light-yellow oil (0.160 g, 79%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.99 – 6.94 (m, 2H), 6.59 (t, J = 7.3 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 5.09 (t, J = 6.6 Hz, 1H), 4.51 (s, 2H), 4.37 – 4.30 (m, 2H), 3.38 – 3.36 (m, 2H), 2.83 (t, J = 6.2 Hz, 2H), 2.06 – 1.95 (m, 4H), 1.84 – 1.77 (m, 1H), 1.67 (s, 3H), 1.64 – 1.63 (m, 1H), 1.60 (s, 3H), 1.57 – 1.53 (m, 1H), 1.43 – 1.36 (m, 1H), 1.24 – 1.19 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.7, 145.5, 144.7, 131.5, 130.1, 129.4, 129.2, 127.3, 126.6, 124.7, 122.5, 116.4, 111.1, 63.6, 55.4, 50.3, 37.1, 35.7, 29.7, 28.3, 25.8, 25.6, 22.5, 19.6, 17.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{36}NO_2$: 406.2741; found: 406.2741.

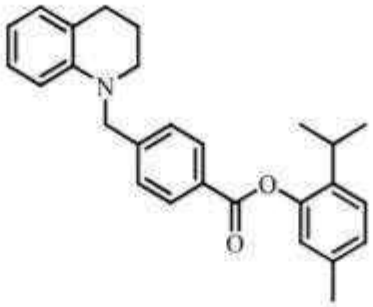
4-((3,4-dihydroquinolin-1(2H)-yl) methyl) phenyl 2-(4-isobutylphenyl) propanoate (5.8c)



By following the **GP-1**, the title compound **5.8c** was isolated as light-yellow oil (0.186 g, 87%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, J = 7.9 Hz, 2H), 7.24 – 7.20 (m, 2H), 7.13 (d, J = 7.9 Hz, 2H), 6.96 – 6.92 (m, 4H), 6.56 (t, J = 7.3 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 4.42 (s, 2H), 3.92 (q, J = 7.1 Hz, 1H), 3.32 – 3.30 (m, 2H), 2.79 (t, J = 6.2 Hz, 2H), 2.46 (d, J = 7.2 Hz, 2H), 1.98 (p, J = 6.1 Hz, 2H), 1.90 – 1.82 (m, 1H), 1.59 (d, J = 7.1 Hz, 3H), 0.90 (d, J = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 173.5, 149.8, 145.6, 140.9, 137.4, 136.5, 129.6, 129.1, 127.6, 127.34, 127.32, 122.4, 121.6, 116.1, 111.1, 54.9, 50.0, 45.4, 45.2, 30.3, 28.3, 22.53, 22.50, 18.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{29}H_{34}NO_2$: 428.2585; found: 428.2584.

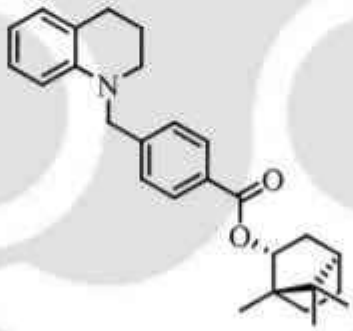
2-isopropyl-5-methylphenyl 4-((3, 4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8d)

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By following the **GP-1**, the title compound **5.8d** was isolated as light-yellow oil (0.184 g, 92%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.25 – 7.23 (m, 1H), 7.06 (d, J = 7.8 Hz, 1H), 7.01 – 6.97 (m, 2H), 6.93 (s, 1H), 6.62 – 6.59 (m, 1H), 6.45 (d, J = 8.1 Hz, 1H), 4.56 (s, 2H), 3.42 – 3.40 (m, 2H), 3.07 – 3.01 (m, 1H), 2.85 (t, J = 6.3 Hz, 2H), 2.34 (s, 3H), 2.08 – 2.03 (m, 2H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 165.4, 148.3, 145.6, 145.4, 137.3, 136.8, 130.7, 129.3, 128.4, 127.4, 127.3, 126.9, 126.6, 123.0, 122.6, 116.4, 111.1, 55.5, 50.4, 28.3, 27.4, 23.2, 22.5, 21.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{30}NO_2$: 400.2272; found: 400.2271.

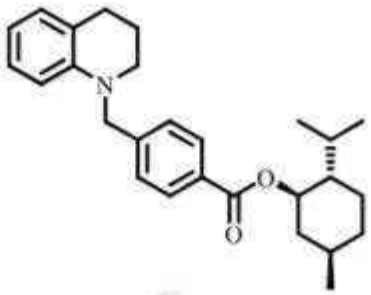
(1S,2R,4R)-1,7,7-trimethylbicyclo [2.2.1] heptan-2-yl 4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8e)



By following the **GP-1**, the title compound **5.8e** was isolated as light-yellow oil (0.170 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.01 – 6.95 (m, 2H), 6.60 (t, J = 7.2 Hz, 1H), 6.43 (d, J = 8.1 Hz, 1H), 4.93 – 4.91 (m, 1H), 4.53 (s, 2H), 3.40 – 3.38 (m, 2H), 2.84 (t, J = 6.2 Hz, 2H), 2.05 (p, J = 6.2 Hz, 2H), 1.96 – 1.89 (m, 2H), 1.81 – 1.80 (m, 1H), 1.77 – 1.72 (m, 1H), 1.65 – 1.58 (m, 1H), 1.28 – 1.15 (m, 2H), 1.12 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.0, 145.4, 144.5, 130.0, 129.7, 129.2, 127.3, 126.6, 122.5, 116.3, 111.0, 81.6, 55.3, 50.3, 49.1, 47.1, 45.2, 39.1, 33.9, 28.3, 27.2, 22.5, 20.3, 20.2, 11.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{34}NO_2$: 404.2585; found: 404.2584.

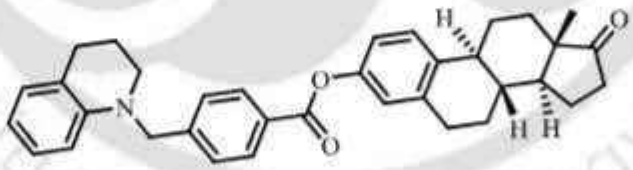
TH-3765_196122031

(1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl 4-((3, 4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8f)



By following the **GP-1**, the title compound **5.8f** was isolated as light-yellow oil (0.172 g, 85%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.60 (t, J = 7.3, 1H), 6.47 (d, J = 8.2 Hz, 1H), 4.95 – 4.90 (m, 1H), 4.52 (s, 2H), 3.39 – 3.37 (m, 2H), 2.84 (t, J = 6.3 Hz, 2H), 2.14 – 2.12 (m, 1H), 2.06 – 2.01 (m, 2H), 1.99 – 1.94 (m, 1H), 1.74 – 1.72 (m, 2H), 1.57 – 1.53 (m, 2H), 1.18 – 1.06 (m, 2H), 0.94 – 0.91 (m, 7H), 0.80 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.1, 145.4, 144.5, 130.1, 129.7, 129.2, 127.3, 126.6, 122.5, 116.3, 111.1, 74.9, 55.4, 50.2, 47.4, 41.1, 34.5, 31.6, 28.3, 26.6, 23.8, 22.5, 22.2, 20.9, 16.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{36}NO_2$: 406.2741; found: 406.2741.

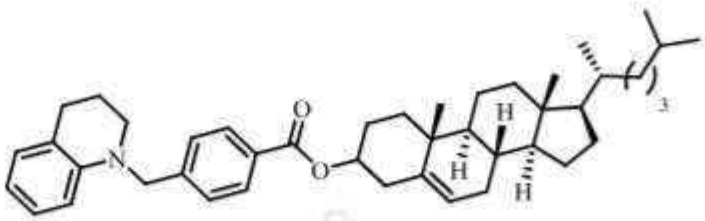
(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8g)



By following the **GP-1**, the title compound **5.8g** was isolated as light-yellow oil (0.208 g, 77%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/5, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.5 Hz, 1H), 6.99 – 6.94 (m, 4H), 6.61 (t, J = 7.3 Hz, 1H), 6.43 (d, J = 8.2 Hz, 1H), 4.55 (s, 2H), 3.41 – 3.39 (m, 2H), 2.95 – 2.93 (m, 2H), 2.85 (t, J = 6.2 Hz, 2H), 2.55 – 2.49 (m, 1H), 2.45 – 2.42 (m, 1H), 2.34 – 2.30 (m, 1H), 2.19 – 2.14 (m, 1H), 2.10 – 2.04 (m, 3H), 1.99 – 1.97 (m, 1H), 1.68 – 1.59 (m, 3H), 1.56 – 1.43 (m, 4H), 0.93 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 221.0, 165.4, 149.0, 145.6, 145.4, 138.2, 137.5, 130.7, 129.3, 128.4, 127.3, 126.8, 126.6, 122.6, 121.9, 119.0, 116.4, 111.1, 55.5, 50.6, 50.4, 48.1, 44.3, 38.2, 36.0, 31.7, 29.6, 28.3, 26.5, 25.9, 22.5, 21.7, 14.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{35}H_{38}NO_3$: 520.2847; found: 520.2849.

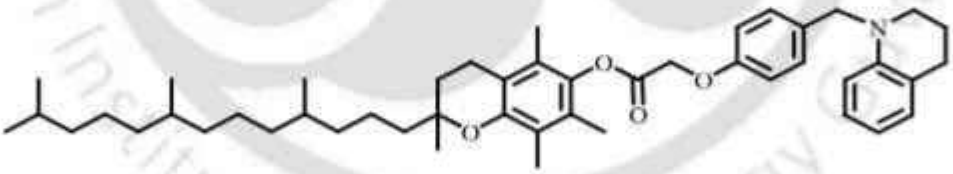
TH-3765_196122031

(8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8h)



By following the **GP-1**, the title compound **5.8h** was isolated as white solid (0.257 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.60 (t, J = 7.3 Hz, 1H), 6.43 (d, J = 8.2 Hz, 1H), 5.41 (d, J = 4.1 Hz, 1H), 4.89 – 4.83 (m, 1H), 4.52 (s, 2H), 3.39 – 3.37 (m, 2H), 2.84 (t, J = 6.2 Hz, 2H), 2.46 (d, J = 7.8 Hz, 2H), 2.05 – 1.99 (m, 5H), 1.93 – 1.88 (m, 1H), 1.88 – 1.82 (m, 1H), 1.78 – 1.69 (m, 1H), 1.61 – 1.47 (m, 6H), 1.42 – 1.35 (m, 3H), 1.25 – 1.11 (m, 7H), 1.08 (s, 3H), 1.05 – 0.99 (m, 4H), 0.94 (d, J = 6.5 Hz, 3H), 0.89 – 0.88 (m, 6H), 0.71 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.0, 145.5, 144.5, 139.8, 130.1, 129.7, 129.2, 127.3, 126.6, 122.9, 122.5, 116.3, 111.1, 74.6, 56.8, 56.3, 55.4, 50.23, 50.19, 42.5, 39.9, 39.7, 38.4, 37.2, 36.8, 36.3, 35.9, 32.1, 32.0, 28.4, 28.3, 28.2, 28.0, 24.4, 24.0, 23.0, 22.7, 22.5, 21.2, 19.5, 18.9, 12.0. Spectral data is in accordance to the reported literature. [22]

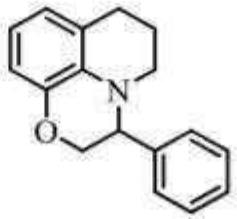
2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl) chroman-6-yl 2-(4-((3,4-dihydroquinolin-1(2H)-yl) methyl) phenoxy) acetate (5.8i)



By following the **GP-1**, the title compound **5.8i** was isolated as light-yellow oil (0.277 g, 78%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (d, J = 7.9 Hz, 2H), 7.00 – 6.96 (m, 4H), 6.59 (t, J = 7.2 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 4.91 (s, 2H), 4.43 (s, 2H), 3.35 – 3.33 (m, 2H), 2.82 (t, J = 6.1 Hz, 2H), 2.60 – 2.58 (m, 2H), 2.09 (s, 3H), 2.03 – 2.00 (m, 5H), 1.95 (s, 3H), 1.84 – 1.73 (m, 3H), 1.56 – 1.51 (m, 3H), 1.45 – 1.35 (m, 7H), 1.32 – 1.26 (m, 8H), 1.16 – 1.07 (m, 6H), 0.88 – 0.85 (m, 12H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.9, 157.0, 149.8, 145.7, 140.1, 132.4, 129.2, 128.0, 127.3, 126.7, 125.0, 123.4, 122.5, 117.7, 116.0, 115.1, 111.2, 75.3, 65.5, 54.7, 49.9, 39.5, 37.6, 37.5, 37.4, 32.9, 32.8, 28.3, 28.1, 25.0, 24.9, 24.6, 22.9, 22.8, 22.5, 21.2, 20.7, 19.9, 19.8, 19.7, 13.1, 12.3, 12.0. Spectral data is in accordance to the reported literature. [22]

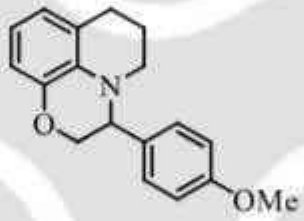
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3-phenyl-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10a)



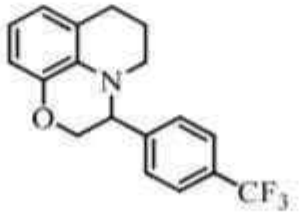
By following the **GP-3**, the title compound **5.10a** was isolated as white solid (0.117 g, 93%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). m.p.102-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.25 (m, 5H), 6.67 – 6.64 (m, 2H), 6.59 – 6.56 (m, 1H), 4.25 – 4.19 (m, 2H), 4.16 – 4.11 (m, 1H), 3.09 – 3.04 (m, 1H), 2.84 – 2.76 (m, 3H), 2.04 – 1.88 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.6, 139.0, 133.0, 128.9, 128.1, 127.6, 123.5, 122.2, 117.3, 114.0, 70.3, 60.3, 46.2, 27.1, 22.3. Spectral data is in accordance to the reported literature. [6]

3-(4-methoxyphenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10b)



By following the **GP-3**, the title compound **5.10b** was isolated as white solid (0.129 g, 92%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.60). m.p. 84 -86 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.66 (t, J = 7.8, 2H), 6.58 (t, J = 7.7 Hz, 1H), 4.22 – 4.09 (m, 3H), 3.81 (s, 3H), 3.07 – 3.04 (m, 1H), 2.87 – 2.74 (m, 3H), 2.01 – 1.88 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 159.5, 143.6, 133.1, 130.9, 128.7, 123.6, 122.1, 117.3, 114.3, 113.9, 70.4, 59.6, 55.4, 46.0, 27.2, 22.3. Spectral data is in accordance to the reported literature. [6]

3-(4-(trifluoromethyl) phenyl)-2,3,6,7-tetrahydro-5H-[1,4] oxazino[2,3,4-ij] quinoline (5.10c)

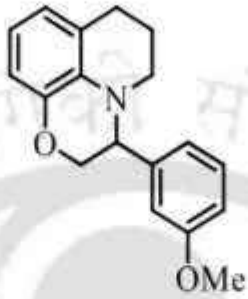


By following the **GP-3**, the title compound **5.10c** was isolated as white solid (0.153 g, 96%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). m.p. 92 -94 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz,

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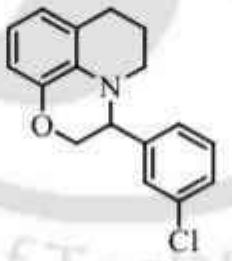
2H), 6.68 (d, J = 7.6 Hz, 2H), 6.61 – 6.58 (m, 1H), 4.31 – 4.29 (m, 1H), 4.26 – 4.24 (m, 1H), 4.14 – 4.11 (m, 1H), 3.06 – 3.02 (m, 1H), 2.89 – 2.81 (m, 3H), 2.05 – 1.93 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 143.6, 143.4, 139.4, 132.4, 127.9, 127.0, 125.9 (CF_3, $J_{C\text{-}F}$ = 3.7 Hz), 124.04, 124.02, 123.4, 122.4, 117.4, 114.2, 69.7, 60.2, 46.6, 27.1, 22.2. $^{19}F\{^1H\}$ NMR (565 MHz, $CDCl_3$): δ -62.53. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{17}F_3NO$. 320.1257; found: 320.1253.

3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10d)



By following the **GP-3**, the title compound **5.10d** was isolated as white solid (0.127 g, 90%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.60). m.p. 90 -91 °C ^1H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.26 (m, 1H), 6.89 (d, J = 7.3 Hz, 1H), 6.85 – 6.84 (m, 2H), 6.66 – 6.64 (m, 2H), 6.59 – 6.56 (m, 1H), 4.24 – 4.22 (m, 1H), 4.18– 4.11 (m, 2H), 3.79 (s, 3H), 3.10 – 3.08 (m, 1H), 2.84 – 2.76 (m, 3H), 2.05 – 1.89 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.2, 143.6, 140.7, 133.0, 130.0, 123.6, 122.2, 120.0, 117.4, 114.0, 113.4, 113.2, 70.3, 60.3, 55.4, 46.2, 27.1, 22.3. Spectral data is in accordance to the reported literature. [6]

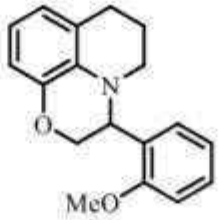
3-(3-chlorophenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10e)



By following the **GP-3**, the title compound **5.10e** was isolated as white solid (0.134 g, 94%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). m.p. 93 -94 °C ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.29 (m, 3H), 7.20 – 7.17 (m, 1H), 6.68 – 6.66 (m, 2H), 6.61 – 6.58 (m, 1H), 4.25 – 4.19 (m, 2H), 4.15 – 4.09 (m, 1H), 3.09 – 3.04 (m, 1H), 2.87 – 2.79 (m, 3H), 2.07 – 1.90 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 143.4, 141.4, 134.8, 132.6, 130.3, 128.3, 127.7, 125.7, 123.5, 122.3, 117.4, 114.1, 69.9, 60.1, 46.4, 27.1, 22.2. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{17}ClNO$. 286.0994; found: 286.0997.

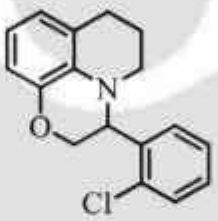
3-(2-methoxyphenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10f)

TH-3765_196122031



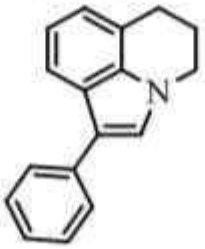
By following the **GP-3**, the title compound **5.10f** was isolated as white solid (0.124 g, 88%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.60). m.p. 101 -103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.23 (m, 1H), 7.17 (d, J = 7.5 Hz, 1H), 6.92 – 6.89 (m, 2H), 6.65 – 6.63 (m, 2H), 6.53 – 6.50 (m, 1H), 4.76 (m, 1H), 4.23 – 4.17 (m, 2H), 3.85 (s, 3H), 3.20 – 3.18 (m, 1H), 2.97 – 2.93 (m, 1H), 2.85 – 2.82 (m, 2H), 2.01 – 1.95 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 157.1, 143.2, 133.0, 128.6, 127.7, 127.2, 122.5, 122.1, 120.9, 116.1, 114.1, 110.6, 68.3, 55.4, 53.9, 46.8, 27.3, 22.2. Spectral data is in accordance to the reported literature. [6]

3-(2-chlorophenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10g)



By following the **GP-3**, the title compound **5.10g** was isolated as white solid (0.133 g, 93%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). m.p. 97 -99 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.37 (m, 1H), 7.28 – 7.25 (m, 1H), 7.23 – 7.20 (m, 2H), 6.67 – 6.66 (m, 2H), 6.55 (t, J = 7.7 Hz, 1H), 4.81 (t, J = 3.8 Hz, 1H), 4.28 – 4.20 (m, 2H), 3.15 – 3.11 (m, 1H), 2.85 – 2.82 (m, 1H), 2.84 (t, J = 5.6 Hz, 2H), 1.98 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.1, 136.7, 133.1, 132.5, 130.0, 128.9, 128.6, 127.4, 122.6, 122.3, 116.6, 114.2, 67.8, 57.1, 46.9, 27.2, 22.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{17}H_{17}ClNO$: 286.0994; found: 286.0996.

1-phenyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij] quinoline (5.12a)

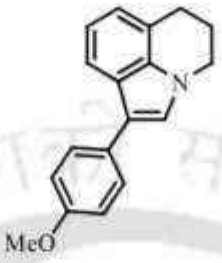


By following the **GP-4**, the title compound **5.12a** was isolated as pale-yellow oil (0.094 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 7.4 Hz, 2H), 7.42

TH-3765_196122031

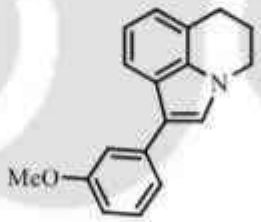
(t, J = 7.6 Hz, 2H), 7.28 (s, 1H), 7.25 – 7.22 (m, 1H), 7.09 (t, J = 7.3 Hz, 1H), 6.96 (d, J = 7.0 Hz, 1H), 4.19 (t, J = 5.7 Hz, 2H), 3.02 (t, J = 6.2 Hz, 2H), 2.27 (p, J = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 136.3, 135.1, 128.9, 127.0, 125.6, 123.9, 123.8, 122.2, 120.5, 119.1, 117.7, 116.7, 44.4, 24.9, 22.9. Spectral data is in accordance to the reported literature. [45]

1-(4-methoxyphenyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij] quinoline (5.12b)



By following the **GP-4**, the title compound **5.12b** was isolated as white solid (0.111 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.60). m.p. 126 -128 °C ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.21 (s, 1H), 7.09 (t, J = 7.2 Hz, 1H), 7.00 – 6.95 (m, 3H), 4.20 (t, J = 5.5 Hz, 2H), 3.86 (s, 3H), 3.03 (t, J = 5.9 Hz, 2H), 2.28 (p, J = 5.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 157.9, 135.0, 129.0, 128.1, 123.9, 123.2, 122.1, 120.3, 119.0, 117.6, 116.4, 114.4, 55.5, 44.3, 24.9, 23.0. Spectral data is in accordance to the reported literature. [45]

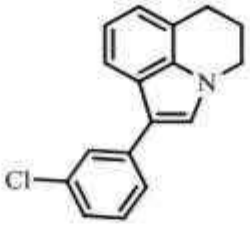
1-(3-methoxyphenyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij] quinoline (5.12c)



By following the **GP-4**, the title compound **5.12c** was isolated as pale-yellow solid (0.108 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.60). m.p. 128 -130 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.28 – 7.26 (m, 2H), 7.24 (s, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 7.0 Hz, 1H), 6.81 – 6.79 (s, 1H), 4.20 – 4.18 (m, 2H), 3.87 (s, 3H), 3.01 (t, J = 6.0 Hz, 2H), 2.26 (p, J = 5.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 160.1, 137.7, 135.1, 129.8, 124.0, 123.8, 122.2, 120.5, 119.6, 119.1, 117.7, 116.6, 112.6, 111.0, 55.4, 44.4, 24.9, 22.9. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{18}H_{18}NO$: 264.1383; found: 264.1384.

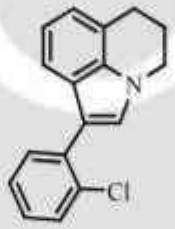
1-(3-chlorophenyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij] quinoline (5.12d)

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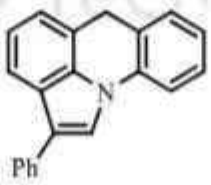
By following the **GP-4**, the title compound **5.12d** was isolated as light-yellow oil (0.111 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 1H), 7.65 (m, 1H), 7.56 – 7.54 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.27 (s, 1H), 7.20 – 7.17 (m, 1H), 7.13 – 7.09 (m, 1H), 6.97 (d, J = 7.6 Hz, 1H), 4.19 – 4.16 (m, 2H), 3.00 (t, J = 6.1 Hz, 2H), 2.25 (p, J = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 138.2, 135.1, 134.6, 130.1, 126.7, 125.4, 124.9, 124.3, 123.6, 122.3, 120.8, 119.4, 117.4, 115.3, 44.4, 24.8, 22.9. Spectral data is in accordance to the reported literature. [45]

1-(2-chlorophenyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij] quinoline (5.12e)



By following the **GP-4**, the title compound **5.12e** was isolated as light-yellow oil (0.078 g, 58%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 8.7 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.41 (s, 1H), 7.32 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 7.0 Hz, 1H), 4.25 – 4.23 (m, 2H), 3.04 (t, J = 6.1 Hz, 2H), 2.31 (t, J = 6.1 Hz, 2H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 134.5, 134.3, 132.8, 131.7, 130.3, 127.1, 126.8, 126.4, 124.8, 122.1, 120.4, 119.0, 117.9, 113.1, 44.4, 24.9, 23.0. Spectral data is in accordance to the reported literature. [46]

2-phenyl-6H-pyrrolo[3,2,1-de]acridine (5.12f):

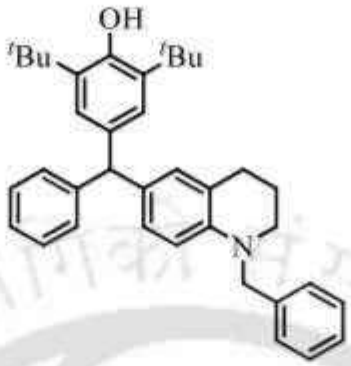


By following the **GP-4**, the title compound **5.12f** was isolated as white solid (0.123 g, 88%); M.p: 131-133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.73 (d, J = 7.5 Hz, 2H), 7.69 (d, J = 7.9 Hz, 1H), 7.46 (t, J = 7.3 Hz, 2H), 7.37 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.25 – 7.24 (m, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.07 – 7.04 (m, 2H), 4.46 (s, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 135.4, 135.3, 134.6, 130.4, 129.0, 127.7, 127.2, 126.4, 125.4, 124.2,

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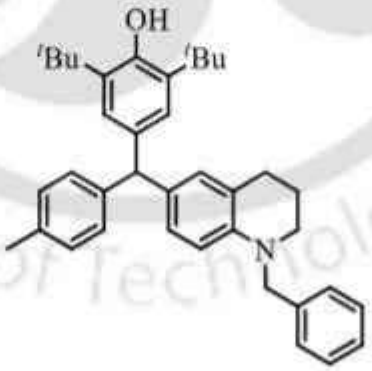
123.9, 122.9, 120.5, 120.4, 120.2, 118.0, 117.7, 113.3, 29.9. HRMS (ESI) *m/z*: $[M-H]^+$ calculated for $C_{21}H_{14}N$: 280.1121; found: 280.1117.

4-((1-benzyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl)-2, 6-di-*tert*-butylphenol (3.21a)



By following the **GP-5**, the title compound **3.21a** was isolated as dark-red liquid using (0.228 g, 88%) silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.18 (m, 7H), 7.13 (t, J = 7.6 Hz, 3H), 6.92 (s, 2H), 6.75 (s, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.42 (d, J = 8.4 Hz, 1H), 5.26 (s, 1H), 5.01 (brs, 1H), 4.42 (s, 2H), 3.32 – 3.29 (m, 2H), 2.72 (t, J = 6.2 Hz, 2H), 1.96 (p, J = 6.1 Hz, 2H), 1.35 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.0, 146.0, 144.0, 139.3, 135.4, 135.0, 132.3, 130.1, 129.5, 128.6, 128.1, 128.0, 126.85, 126.83, 126.1, 125.8, 122.1, 110.9, 56.2, 55.5, 50.0, 34.5, 30.5, 28.4, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{44}NO$: 518.3418; found: 518.3419.

4-((1-benzyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (*p*-tolyl) methyl)-2, 6-di-*tert*-butylphenol (3.22a)

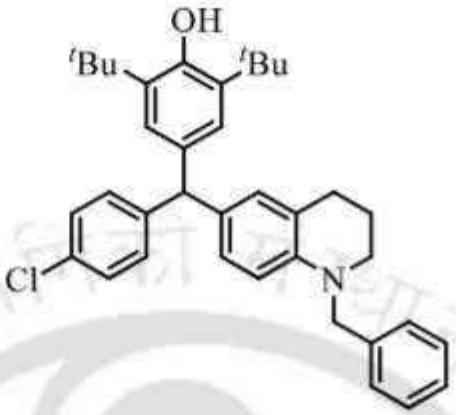


By following the **GP-5**, the title compound **3.22a** was isolated as dark-red liquid (0.223 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.20 (m, 5H), 7.05 – 6.99 (m, 2H), 6.92 (s, 2H), 6.75 (s, 1H), 6.65 (d, J = 7.5 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.21 (s, 1H), 5.00 (s, 1H), 4.43 (s, 2H), 3.32 – 3.30 (m, 2H), 2.73 (t, J = 6.3 Hz, 2H), 2.29 (s, 3H), 1.97 (p, J = 6.0 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 152.0, 144.0, 143.0, 139.4, 135.4, 135.2, 135.1, 132.6, 130.1, 129.3, 128.8, 128.6, 127.9, 126.9, 126.8, 126.1, 122.1, 111.0, 55.9, 55.6,

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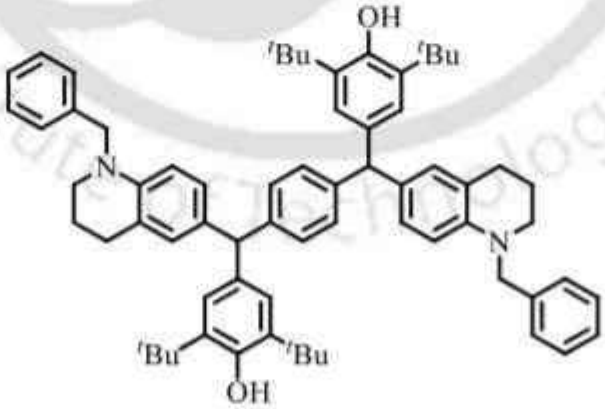
50.0, 34.5, 30.5, 28.4, 22.7, 21.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{38}H_{46}NO$: 532.3574; found: 532.3574.

4-((1-benzyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (4-chlorophenyl) methyl)-2, 6-di-*tert*-butyl phenol (3.22b)



By following the **GP-5**, the title compound **3.22b** was isolated as dark-red liquid (0.248 g, 90%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 – 7.28 (m, 2H), 7.26 – 7.22 (m, 3H), 7.20 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.88 (s, 2H), 6.71 (s, 1H), 6.62 (d, J = 8.5 Hz, 1H), 6.41 (d, J = 8.3 Hz, 1H), 5.22 (s, 1H), 5.04 (s, 1H), 4.44 (s, 2H), 3.34 – 3.32 (m, 2H), 2.73 (t, J = 6.4 Hz, 2H), 1.98 (p, J = 6.4 Hz, 2H), 1.36 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 152.1, 144.6, 144.1, 139.2, 135.5, 134.5, 131.6, 131.5, 130.8, 130.0, 128.7, 128.2, 127.9, 126.9, 126.8, 126.0, 122.2, 110.9, 55.54, 55.47, 50.0, 34.5, 30.5, 28.4, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{37}H_{43}ClNO$: 552.3028; found: 552.3025.

4,4'-(1,4-phenylenebis((1-benzyl-1,2,3,4-tetrahydroquinolin-6-yl) methylene)) bis(2,6-di-*tert*-butylphenol) (3.22g)

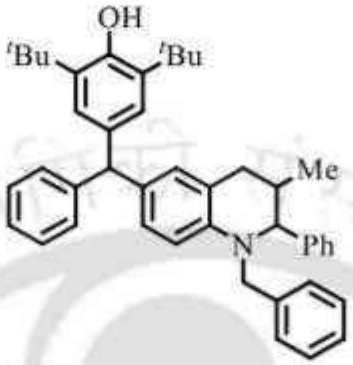


By following the **GP-5**, the title compound **3.22g** was isolated as dark-red liquid (0.340 g, 71%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.28 (m, 5H), 7.25 – 7.20 (m, 5H), 6.99 (s, 4H), 6.91 (s, 4H), 6.74 (s, 2H), 6.66 – 6.63 (m, 2H), 6.40 (d, J = 8.4 Hz, 2H), 5.22 (s, 2H), 5.00 (brs, 2H), 4.43 (s, 4H), 3.32 – 3.30 (m, 4H), 2.72 (t, J = 6.1 Hz, 4H), 1.97 (p, J = 6.1 Hz, 4H), 1.35

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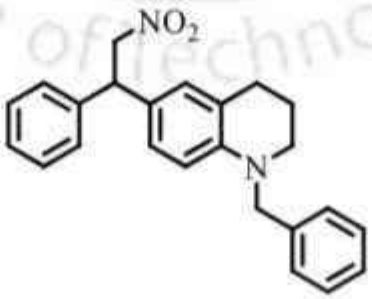
(s, 36H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 151.9, 143.9, 143.14, 143.08, 139.4, 135.4, 135.3, 135.2, 132.5, 130.1, 129.0, 128.6, 128.0, 126.85, 126.81, 126.1, 122.00, 121.99, 110.87, 110.85, 55.8, 55.5, 50.0, 34.5, 30.5, 28.4, 22.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{68}H_{81}N_2O_2$: 957.6293; found: 957.6284.

4-((1-benzyl-3-methyl-2-phenyl-1, 2, 3, 4-tetrahydroquinolin-6-yl) (phenyl) methyl)-2, 6-di-tert-butylphenol (3.22f)



By following the **GP-5**, the title compound **3.22f** was isolated as dark-red liquid (0.240 g, 79%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.62). cis: trans = 1:1. ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.24 (m, 14H), 7.22 – 7.21 (m, 6H), 7.18 – 7.14 (m, 6H), 7.12 – 7.10 (m, 4H), 6.92 (s, 4H), 6.81 (s, 1H), 6.76 – 6.73 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.37 (t, J = 8.4 Hz, 2H), 5.31 (d, J = 5.7 Hz, 2H), 5.04 (d, J = 3.2 Hz, 2H), 4.50 (dd, J = 17.3, 5.9 Hz, 2H), 4.39 (s, 2H), 4.17 (d, J = 17.4 Hz, 2H), 2.52 – 2.48 (m, 6H), 1.37 (s, 36H), 0.86 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 5.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 152.0, 146.1, 145.9, 143.5, 140.81, 140.79, 139.32, 139.28, 135.3, 135.1, 131.8, 131.7, 130.0, 129.8, 129.6, 129.5, 128.72, 128.68, 128.3, 128.2, 128.11, 128.09, 128.0, 127.3, 126.8, 126.4, 126.22, 126.17, 125.8, 121.27, 121.25, 109.78, 109.75, 67.2, 56.14, 56.06, 53.4, 34.5, 31.72, 31.68, 30.51, 30.5, 18.7, 18.6. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{44}H_{50}NO$: 608.3887; found: 608.3895.

(R)-1-benzyl-6-(2-nitro-1-phenylethyl)-1, 2, 3, 4-tetrahydroquinoline (5.14f)



By following the **GP -5**, the title compound **5.14f** was isolated as pale-yellow oil (0.158 g, 85%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.52). ^1H NMR (600 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 4H), 7.22 – 7.18 (m, 6H), 6.79 – 6.76 (m, 2H), 6.40 (d, J = 8.4 Hz, 1H), 4.90 – 4.82 (m, 2H), 4.72 – 4.69 (m, 1H), 4.40 (s, 2H), 3.32 – 3.30 (m, 2H), 2.73 (t, J = 6.2 Hz, 2H), 1.95 (p, J = 6.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz,

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$CDCl_3$): δ 145.0, 140.2, 138.8, 128.9, 128.7, 128.4, 127.7, 127.3, 126.9, 126.6, 126.3, 126.2, 122.7, 111.2, 79.7, 55.3, 49.9, 48.4, 28.3, 22.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for: $C_{24}H_{25}N_2O_2$:373.1911; found: 373.1912.

5.7. References

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Chapter 6

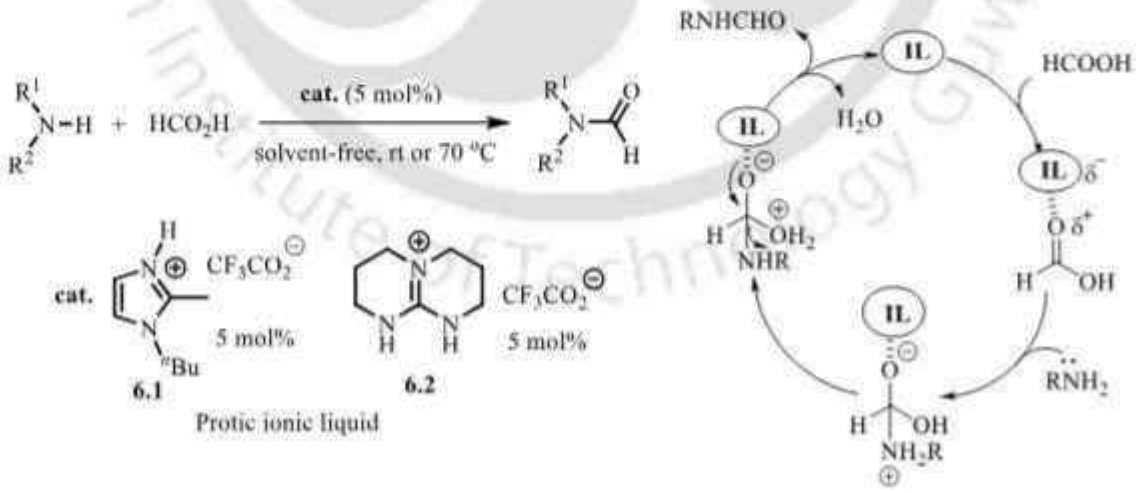
Reusable Brønsted acidic ionic liquid catalyzed reductive alkylation of quinolines to functionalized tetrahydroquinolines

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6.1. Introduction

Brønsted acids are widely used in various organic transformation such as alkylation, dehydration, condensation, esterification and synthesis of pharmaceutical products from both laboratory and industrial scales.[1] However, several drawbacks have been encountered by using these chemicals. They liberate explosive hydrogen gas by reacting with metals. They are often corrosive and release the metallic wastes of a reaction reactor and cause cracks within the reactor body and/or pollute the products. In this regard, the replacement of the mentioned homogeneous acid catalyst with safe or less hazardous heterogeneous acid catalysts based on porous materials have been explored.[2-5] Despite a remarkable improvement in catalyst separation and recovery, they mainly suffer from a "lazy" kinetic since the catalytic centers are fixed on the surface of a support. Other limitations of these materials refer to the weak mass transfer, deactivation of the hydrophilic surface with water and blocking the entrance of the solid support (especially in the case of microporous materials) with organic molecules.[6-8]

As "solvent or catalyst", ionic liquids (ILs) is found as useful alternative owing to their excellent solubility, high thermal and chemical stability, negligible vapor pressure, and easy recyclability.[9] The judiciously designed task-specific ILs have shown noticeable performance in the organic synthesis.[10] For example, protic ionic liquids [Bmim]TFA **6.1** (Bmim = 1-butyl-3-methylimidazolium) and [TBD][TFA] **6.2** (TBD = 1,5,7-triazabicyclo [4.4.0]dec-5-ene) were used as recyclable and reusable catalyst for the synthesis of formamides under solvent-free condition (Scheme 6.1).[11] It has been postulated that the activation of carbonyl of formic acid by the protic ionic liquid, followed by the nucleophilic attack by amine on the carbonyl carbon. The protonation and subsequent dehydration produce formamide and regenerate catalyst.

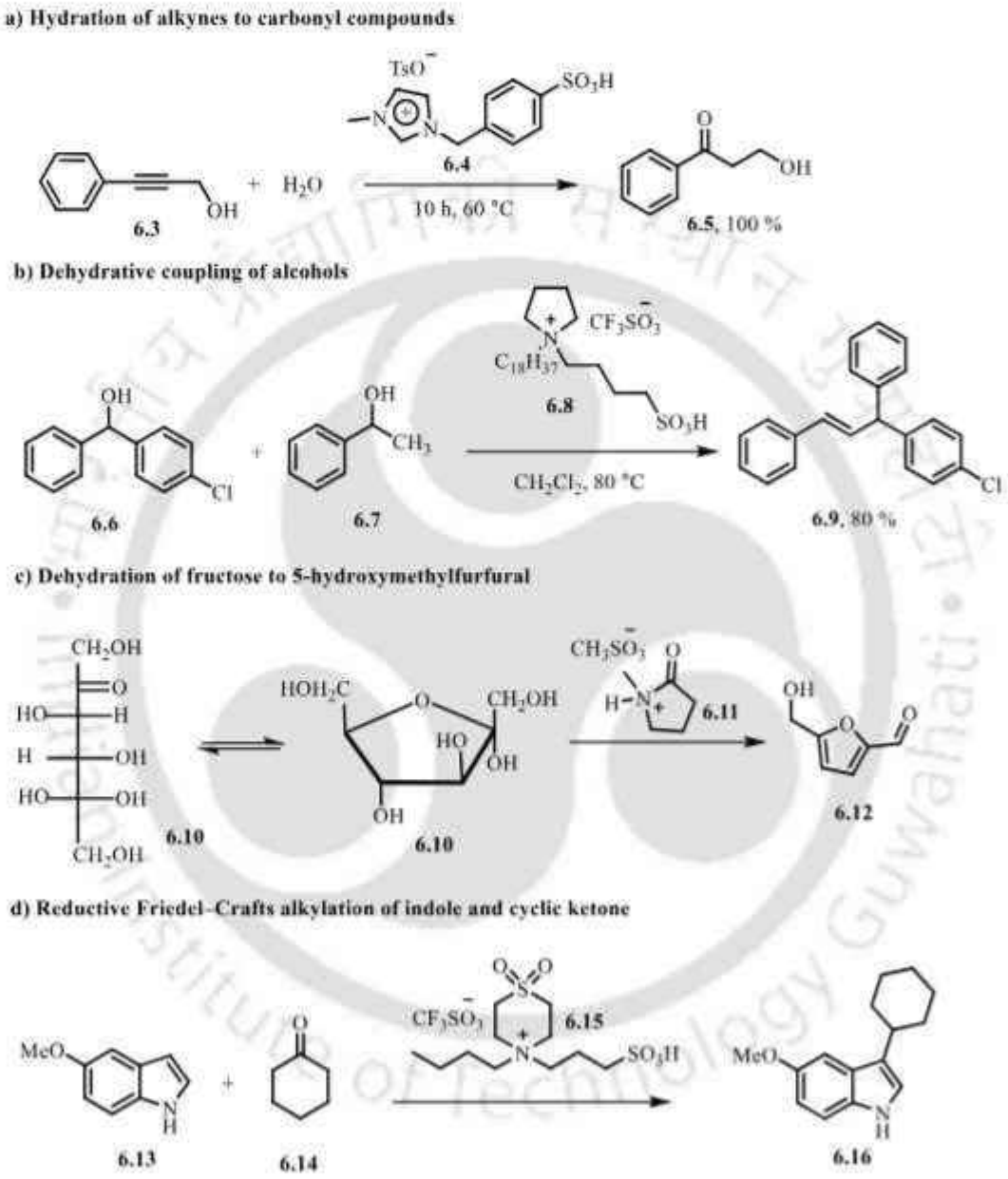


Scheme 6.1. Protic ionic liquids-catalysed formylation of amines under solvent-free condition.

Likewise, Brønsted acidic ionic liquids (BAILs) have gained considerable attention because of their high thermal stability, high acidity, simple separation, nontoxicity, and

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inertness toward air and water.[12,13] BAILs are used as a catalyst in a various organic transformation such as, hydration of alkynes to the carbonyl compounds , dehydrative coupling of alcohols to polysubstituted olefins, dehydration of fructose to 5-hydroxymethylfurfural, reductive Friedel–Crafts alkylation of indole and cyclic ketone (Scheme 6.2).[13]

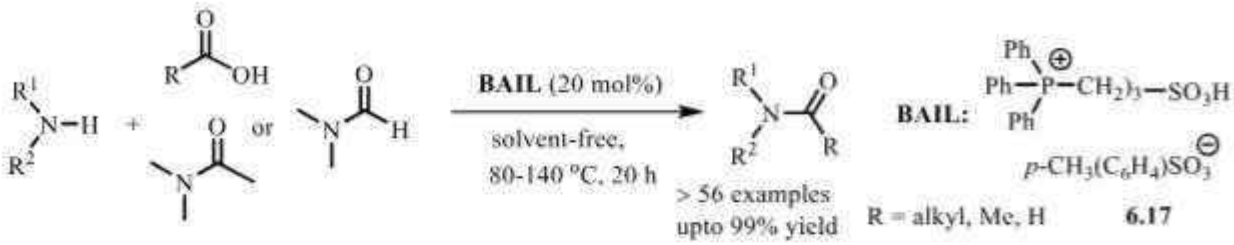


Scheme 6.2. The reactions involving BAILs as catalyst.

Further, **BAIL**-catalysed *N*-formylation and *N*-acylation of aliphatic, aromatic, and heterocyclic amines with carboxylic acids have been documented under solvent-free conditions.[14] A control experiment with only *p*-TsOH as the catalyst, there was no formation of formamide indicating the combination of zwitterionic precursors and donor

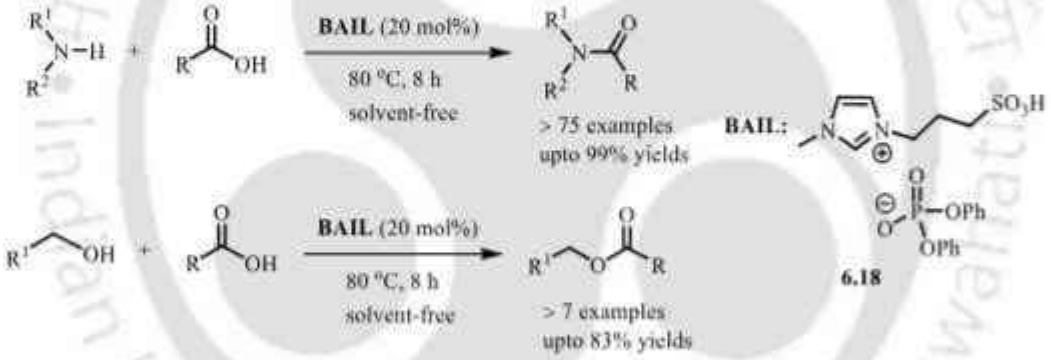
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acids certified the activities of the BAILs. The catalyst was recycled for up to five consecutive cycles with slight loss of activity (Scheme 6.3).



Scheme 6.3. *N*-formylation and *N*-acylation of amines catalysed by BAILs.

Very recently, direct amidation of carboxylic acid and amine in a stoichiometric proportion catalysed by ionic **BAIL** is developed. The esterification of alcohols with carboxylic acids was also reported (Scheme 6.4).[15] This protocol was not sensitive to water formed in the condensation process. The methodology is applicable on a multigram scale, and a significant sustainability improvement (PMI < 3) over existing catalytic amidation.

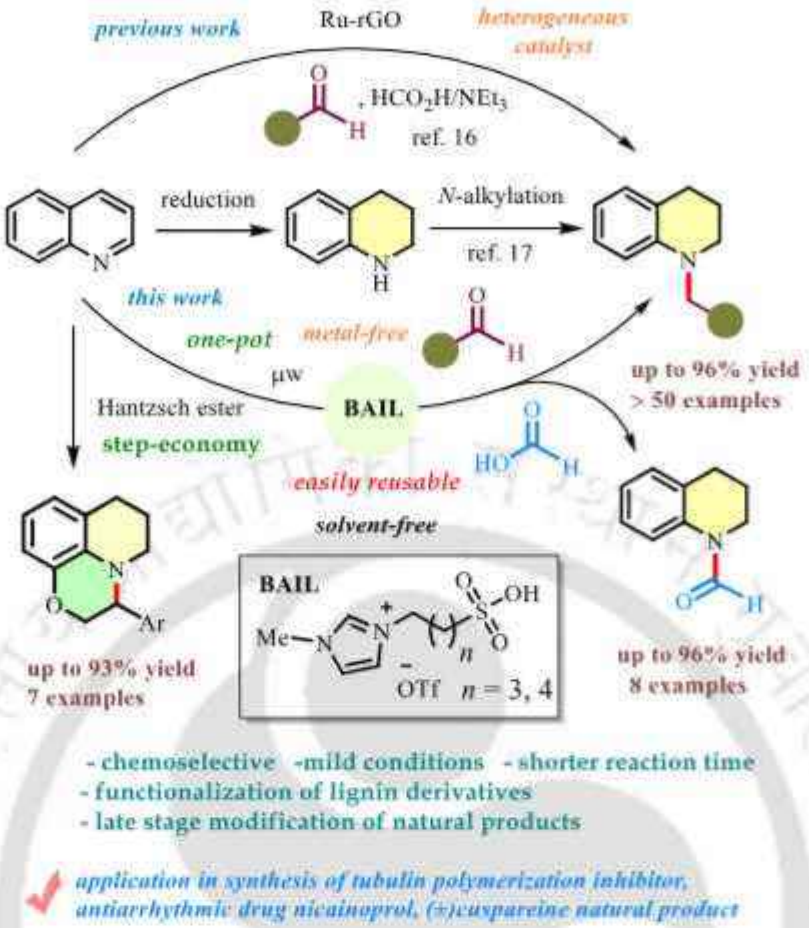


Scheme 6.4. BAIL-catalyzed amide bond formation.

6.2. Present work

Considering the importance and usefulness of THQ derivatives (Chapter 5, section 5.1), herein I report transition-metal-free, reusable protocol for the direct *N*-alkylation of quinoline with aldehyde using a **BAIL** under mild reaction conditions. This new strategy offered significant improvements in the efficiency and sustainability of direct alkylation of *N*-heteroarenes. Current reductive protocol has been successfully applied to synthesize tetrahydroquinoline-1-carbaldehyde *via* direct amidation of quinoline and formic acid. In addition, synthesis of tricyclic oxazino-fused-tetrahydroquinoline/benzoxazine compounds *via* tandem reductive cyclization of 1-aryl-2-(8-quinolinyloxy)ethanones is developed.

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Scheme 6.5. Reusable Brønsted acidic ionic liquid catalyzed reductive alkylation of quinolines to functionalized tetrahydroquinolines.

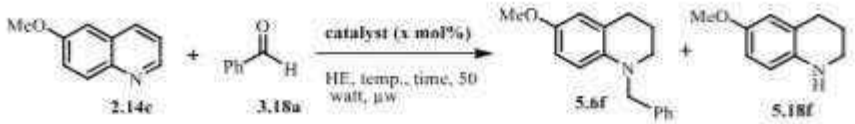
6.3. Results and discussion

6.3.1. Optimization of reaction conditions

Herein I anticipated that **BAIL** can help the tandem reaction in which the quinoline is first hydrogenated by Hantzsch ester (HE) to form a THQ, then it is subsequently reductively alkylated by the aldehyde to provide the *N*-alkylated product. The study was initiated under microwave irradiation (μw) since this method is emerging as an alternative to conventional heating practice and leads to accelerated reaction rates.[18] I began our investigation with the reaction of 6-methoxy quinoline (**2.14c**, 0.5 mmol), benzaldehyde (**3.18a**, 0.5 mmol), Hantzsch ester (HE) (1.6 mmol), **6.21a** (15 mol%) at 70 °C under microwave irradiation (μw). Gratifyingly, the reaction is completed within 20 minutes and give the desired *N*-alkylated product **5.6f** in 79% yield, along with 19% intermediate hydrogenated product THQ (**5.18f**, Table 6.1, entry 1).

Table 6.1 Optimization studies for functionalized-THQ[a]

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Brønsted Acidic Ionic liquid (BAIL)



entry	**catalyst** (equiv.)	temp (°C)	time (m)	Yield of **5.6f** (%)
1	**6.21a** (15 mol%)	70 °C	20 m	79%, 19% of **5.18f**
2	**6.21b** (15 mol%)	70 °C	20 m	85%, 11% of **5.18f**
3	**6.21b** (20 mol%)	70 °C	20 m	95%
4	**6.21c** (20 mol%)	70 °C	20 m	84%[b]
5	**6.21d** (20 mol%)	70 °C	20 m	81%[b]
6	**6.21e** (20 mol%)	70 °C	20 m	55%
7	**6.21f** (20 mol%)	70 °C	20 m	52%[b]
8	**6.21g** (20 mol%)	70 °C	20 m	50%[b]
9	**CF_3SO_3H** (20 mol%)	70 °C	20 m	71%
10	**CH_3SO_3H** (20 mol%)	70 °C	20 m	47%
11	***p*-$CH_3C_6H_4SO_3H$** (20 mol%)	70 °C	20 m	60%
12	**CF_3CO_2H** (20 mol%)	70 °C	20 m	64%
13	**6.21b'** (20 mol%)	70 °C	20 m	5%
14	**6.21b** (20 mol%)	80 °C	20 m	85%
15	**6.21b** (20 mol%)	100 °C	20 m	80%
16	**6.21b** (20 mol%)	60 °C	20 m	78%
17	**6.21b** (20 mol%)	50 °C	20 m	66%
18	**6.21b** (20 mol%)	25 °C	20 m	44%
19	**6.21b** (20 mol%)	70 °C	15 m	79%
20	**6.21b** (20 mol%)	70 °C	10 m	58%
21[c]	**6.21b** (20 mol%)	70 °C	12 h	82%
22	-	70 °C	20 m	-
23	**6.21b** (20 mol%) with reductant (Et_3SiH, HBpin and HCO_2H)	70 °C	20 m	0%

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[a]Reaction conditions: **2.14c** (0.5 mmol), **3.18a** (0.5 mmol), HE (1.6 mmol), **catalyst** (x mol%) under the microwave (50 W), isolated yields. [b]The same has been repeated three times, average data is given. [c]Under the conventional method.

Then the reaction was screened with **6.21b** under the same conditions, product **5.6f** was obtained in 85% yield (entry 2). When equivalency of **6.21b** was slightly increased to 20 mol%, the yield of product **5.6f** is further improved to 95% (entry 3). Next, I investigated the effect of the **6.21b** counterion in the current catalytic process under the same reaction conditions (entries 4-8). The $CF_3SO_3^-$, *p*-$CH_3C_6H_4SO_3^-$, and $CF_3CO_2^-$ counter anion bearing **6.21b** provided the product **5.6f** (81-95%) in a higher yield than HSO_4^-, Cl^-, and NO_3^- counter anion bearing **6.21b** (**5.6f**, 50-55%). This suggests that anion in **6.21b** play an important role in enhancing the substrate reactivity. Nevertheless, **6.21b** was found to be the best catalyst among the **BAIL** employed in this study. Additionally, a control experiment was conducted with corresponding Brønsted acid as the catalyst, a decrease in the yield of product **5.6f** has been observed (entries 9-12). Further, this study suggests that the activities of the **6.21b** depend on the combination of their precursor zwitterions and donor acids (entry 13). Then, the reaction temperature was an important factor affecting the results (entries 14-17). When the reaction temperature decreased to 25 °C, a lower yield was realized (entries 16, 17). The decrease in reaction time significantly reduced the reaction efficiency (entries 18-19). The reaction was also examined with readily available reductants such as Et_3SiH, HBpin, and HCO_2H under identical reaction conditions (entry 23). However, the desired product **5.6f** was not obtained. This suggests that Hantzsch ester was found to be a suitable reductant for the current transformation.

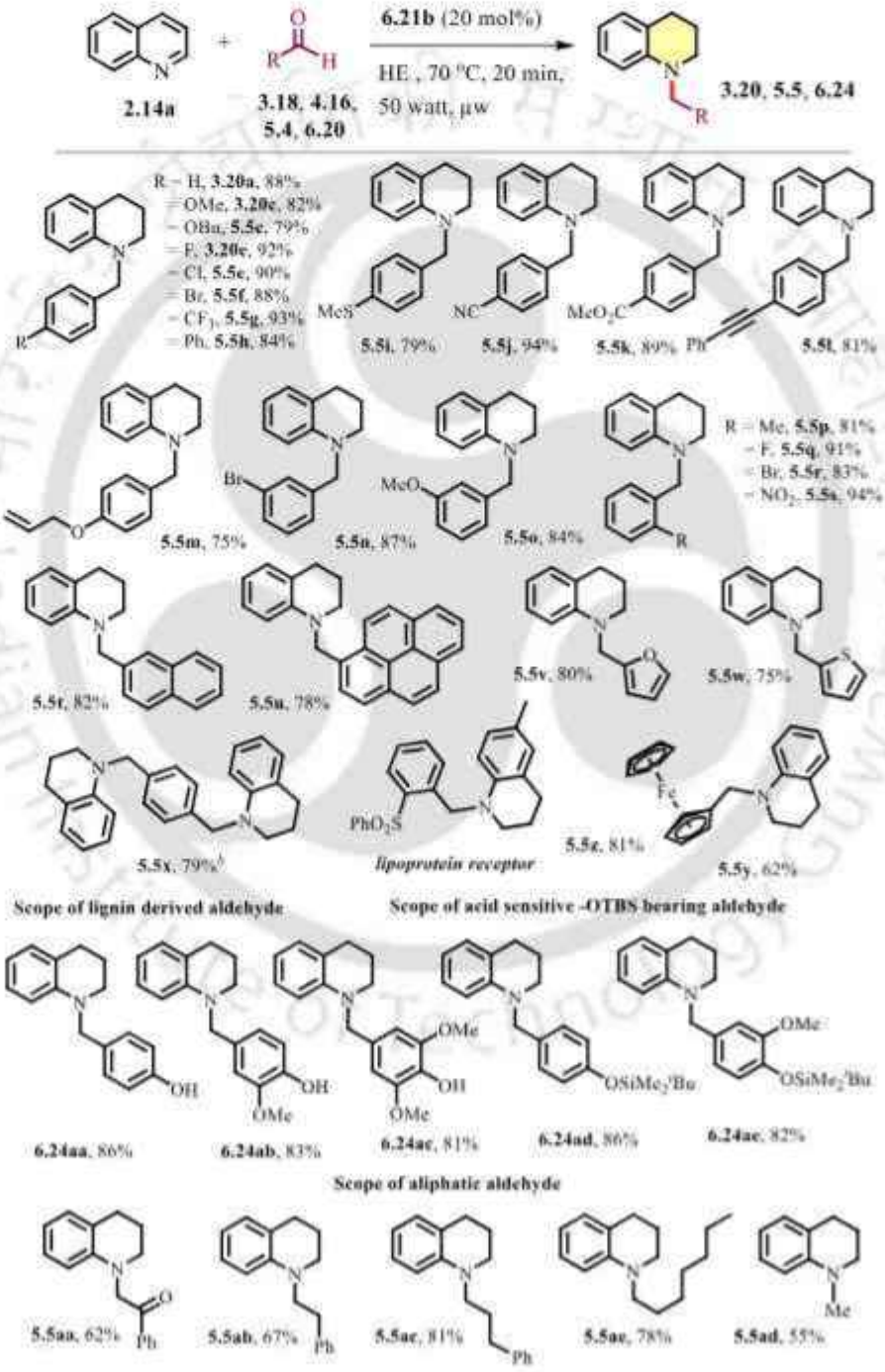
6.3.2. Substrate scope of the synthesis of *N*-functionalized tetrahydroquinolines:

With the optimized conditions in hand, I investigated the substrate scope of this reaction by employing varieties of substituted aldehyde **3.18**, **4.6**, **5.4** with quinoline **2.14a** as the standard substrate (Table 6.2). The aldehydes with a wide range of functional groups having both electron-donating (e.g., −Me, −OMe) and electron-withdrawing (e.g., −Cl, −Br, −CN) groups at the *para*-position in the aryl moiety were efficiently reacted to obtain the desired products **3.20, 5.5** in 82-93% yields. The electron-withdrawing group containing substrate provided slightly higher yield compared to electron-donating substituents. Then, *meta*-and *ortho*-substituent bearing aldehyde **3.18**, **5.4** also gave the corresponding *N*-alkylated THQs **5.5n**-**5.5s** in 81-94% yield. Notably, present reaction condition tolerates various reducible-functional groups such as 4-Cl, 4-OBn, 4-CF_3, 4-C≡CPh, 4-O-allyl, 3-Br, 2-Br, 2-CO_2Me, 2-NO_2 which display the excellent chemoselectivity of the current reductive protocol. Then, polycyclic aromatic hydrocarbons (PAHs) containing aldehyde such as 1-napthyl aldehyde **3.18s** and 1-pyrene aldehyde **3.18t** also well suited under the reaction conditions. The heteroatom containing aldehyde **4.16q** and **3.18r** also reacted efficiently with **2.14a** leading to the desired products **5.5v** and **5.5w** in 80% and 76% yield respectively. The reaction proceeded well on polysubstituted aldehyde **3.18u**, product **5.5x** was obtained with notable selectivity. The given reaction condition was also utilized in the synthesis of a lipoprotein receptor **5.5z**. Further, redox-active ferrocene moiety bearing aldehyde **5.4y**, lignin derived aldehyde **6.20aa**-**2ac**, and

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acid sensitive *tert*-butyldimethylsilyl (TBS) ether containing aldehyde **6.20ad-2ae** successfully participated in the reaction to provide the desired product **5.5y, 6.24aa-6.24ae**. Besides aromatic aldehyde, scope of the reaction was expanded to a variety of aliphatic aldehydes, yielding **5.5aa-5.5ae**. In the case of **5.4aa**, the reaction can occur with $-CH_2COPh$ functionality, indicating a notable selectivity of our present protocol.

Table 6.2. The reaction scope with various aldehydes[a]

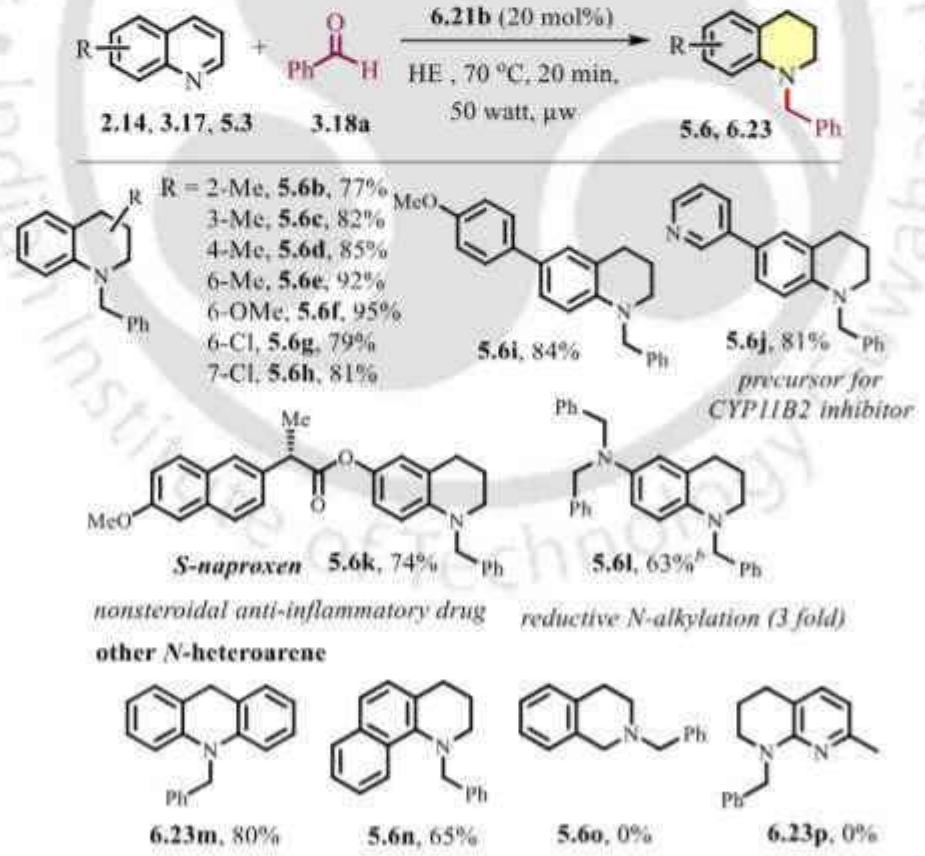


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[a]Reaction condition: **2.14a** (0.5 mmol), **3.18**, **4.16**, **5.4**, **6.20** (0.5 mmol), HE (3.2 equiv.), **6.21b** (20 mol%) at 70 °C for 20 minutes under the microwave (50 W), isolated yields. [b]with 0.25 mmol of terephthalaldehyde **3.18u**, HE (6.5 equiv.).

The scope of the reaction was further extended to a series of substituted quinolines **2.14**, **3.17**, **5.3** while keeping aldehyde **3.18a** as the standard substrate (Table 6.3). The substrate having both electron-donating (e.g., -OMe) and electron-withdrawing (e.g., -F, -Cl, and -Br) groups as substituents was efficiently reacted to obtain the desired products **5.6** with 77-95% yield. A slightly higher yields were realized for electron-donating groups. The pyridine-containing quinoline **5.3j** successfully participated in the reaction to provide1-benzyl-6-(pyridin-4-yl)-1,2,3,4-tetrahydro quinoline **5.6j** in 81% yield. A substrate containing nonsteroidal anti-inflammatory drugs naproxen **2.14i** was successfully converted into functionalized THQs **5.6k** in 74% yield. Then current strategy is extended to multi-alkylation of quinoline with amine bearing substituent at the 6-position, afforded **5.6l** in 63% yield. Further, it has been extended to another *N*-heteroaromatic scaffold such as acridine (**2.14k**), benzo[*h*]quinoline (**2.14l**), effectively. However, I failed to obtain the desired *N*-alkylated product when isoquinoline **3.17f**, 2-methyl-1,8-naphthyridine **6.19z**, and quinoxaline **3.17g** were used as the substrate.

Table 6.3. The reaction scope with various quinolines[a]

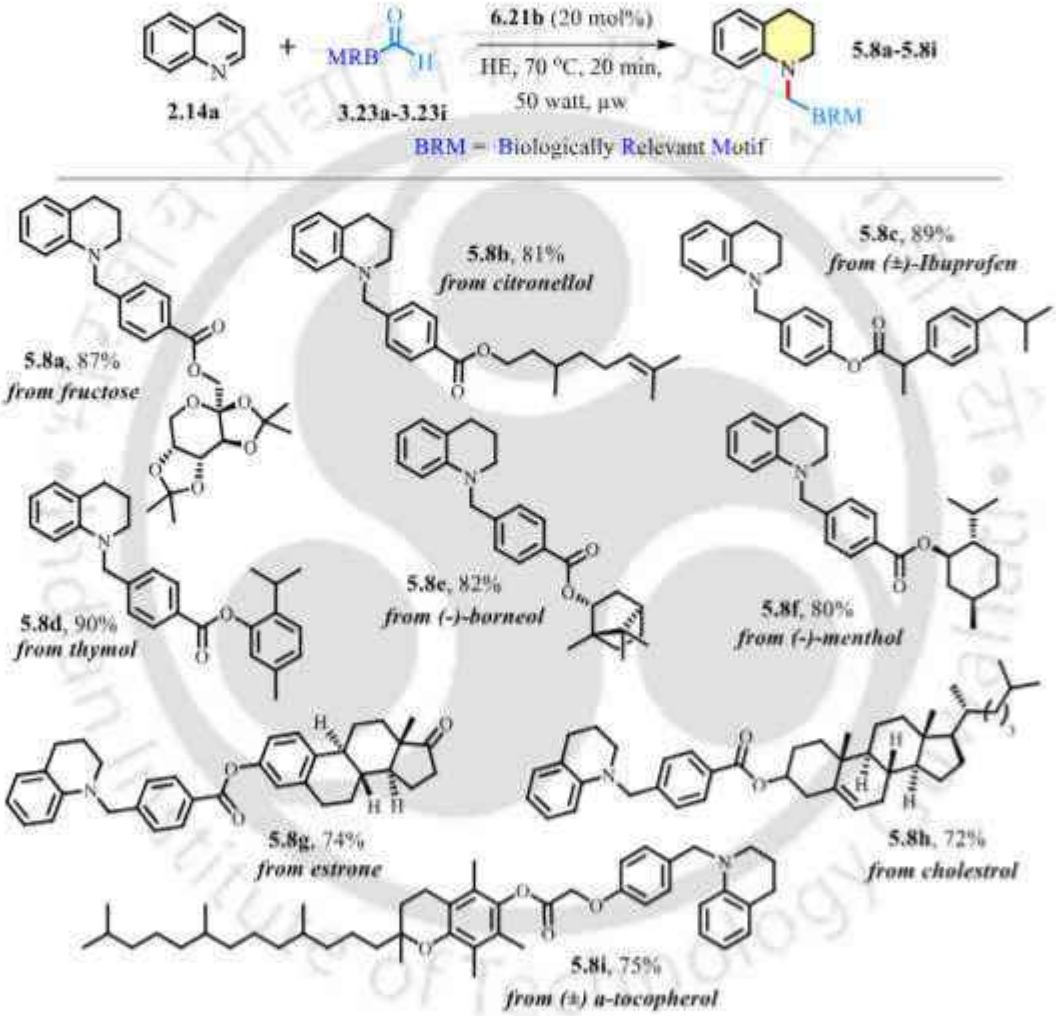


[a]Reaction condition: **2.14**, **3.17**, **5.3** (0.5 mmol), **3.18a** (0.5 mmol), HE (3.2 equiv.), **6.21b** (20 mol%) at 70 °C for 20 minutes under the microwave (50 W), isolated yields. [b]with 0.25 mmol scale of, **3.18a** (3 equiv.), HE (5.2 equiv.)

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Since the *N*-alkylated THQ motif is found in various biologically and pharmaceutically relevant compounds, I further expanded scope of the reaction using highly functionalized substrates with complex molecular settings. A range of biologically relevant motifs (BRM) were targeted and were independently subjected to the optimized reaction conditions, afforded corresponding *N*-alkyl tetrahydroquinoline derivatives containing fructose (**5.8a**, 87%), citronellol (**5.8b**, 81%), (±)-ibuprofen (**5.8c**, 89%), thymol (**5.8d**, 90%), (-)-borneol (**5.8e**, 82%), (-)-menthol (**5.8f**, 80%), estrone (**5.8g**, 74%), cholesterol (**5.8h**, 72%), (±)-tocopherol (**5.8i**, 75%) moieties without any structural changes of the complex architecture (Table 6.4).

Table 6.4. The reaction scope with various bilogically relevant motif bearing aldehyde[a]



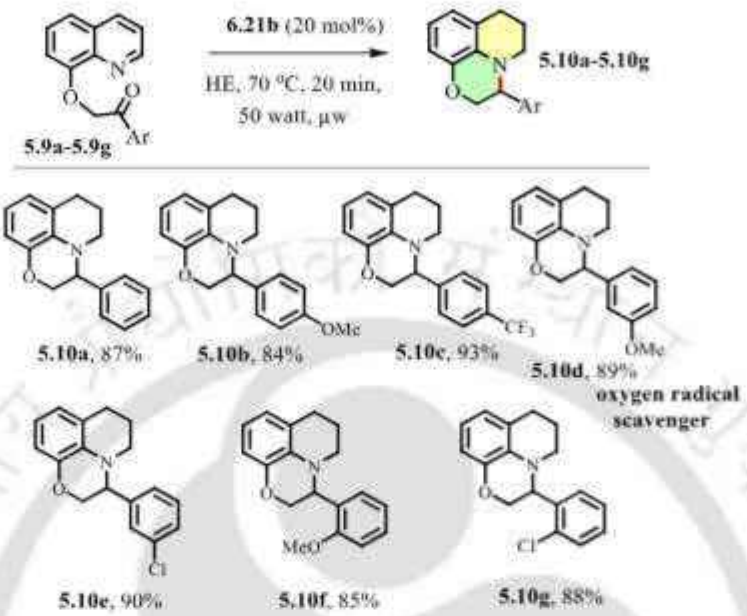
[a]Reaction condition: **2.14a** (0.5 mmol), **3.23a-3.23i** (0.5 mmol), HE (3.2 equiv.), **6.21b** (20 mol%) at 70 °C for 20 minutes under the microwave (50 W), isolated yields.

Next, I attempted to synthesize novel tricyclic oxazino-fused-tetrahydroquinoline/benzoxazine compounds **5.10a-5.10g** *via* tandem reductive cyclization of 1-aryl-2-(8-quinolinyloxy) ethenone **5.9a-5.9g** under ambient conditions (Table 6.5). Substrate having electron-donating *p*-OMe (**5.9b**) and *o*-OMe (**5.9f**) and electron-withdrawing *p*-CF_3 (**5.9c**), *m*-OMe (**5.9d**), *m*-Cl (**5.9e**), and *o*-Cl (**5.9g**) all efficiently provided the corresponding cyclized products **5.10a-5.10g**

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in 84-93% yields. It is worthy to note that most of the resulting benzoxazine compounds were found to have promising antioxidant activity.[19]

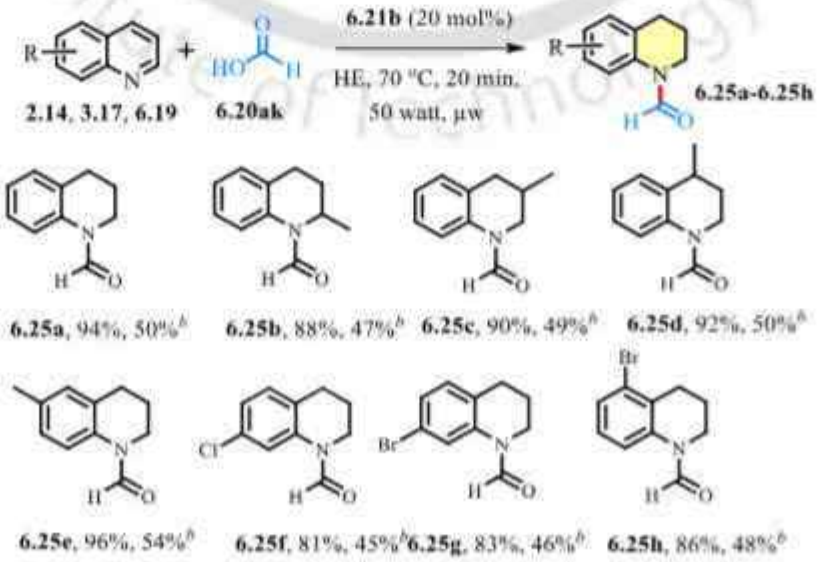
Table 6.5. Scope of 1-aryl-2-(quinolin-8-yloxy)ethan-1-one[a]



[a]Reaction condition: **5.9a-5.9g** (0.5 mmol), HE (3.2 equiv.), **6.21b** (20 mol%) at 70 °C for 20 minutes under the microwave (50 W), isolated yields.

Then, I have synthesized tetrahydroquinoline-1-carbaldehyde *via* direct amidation of formic acid and quinoline using **6.21b** (Table 6.6). As expected, both electron-donating groups (such as *p*-OMe) and electron-withdrawing groups (such as *o*-Cl, *m*-Cl) could achieve **6.25a-6.25h** in 81-96% yield.

Table 6.6. Scope of quinoline with formic acid

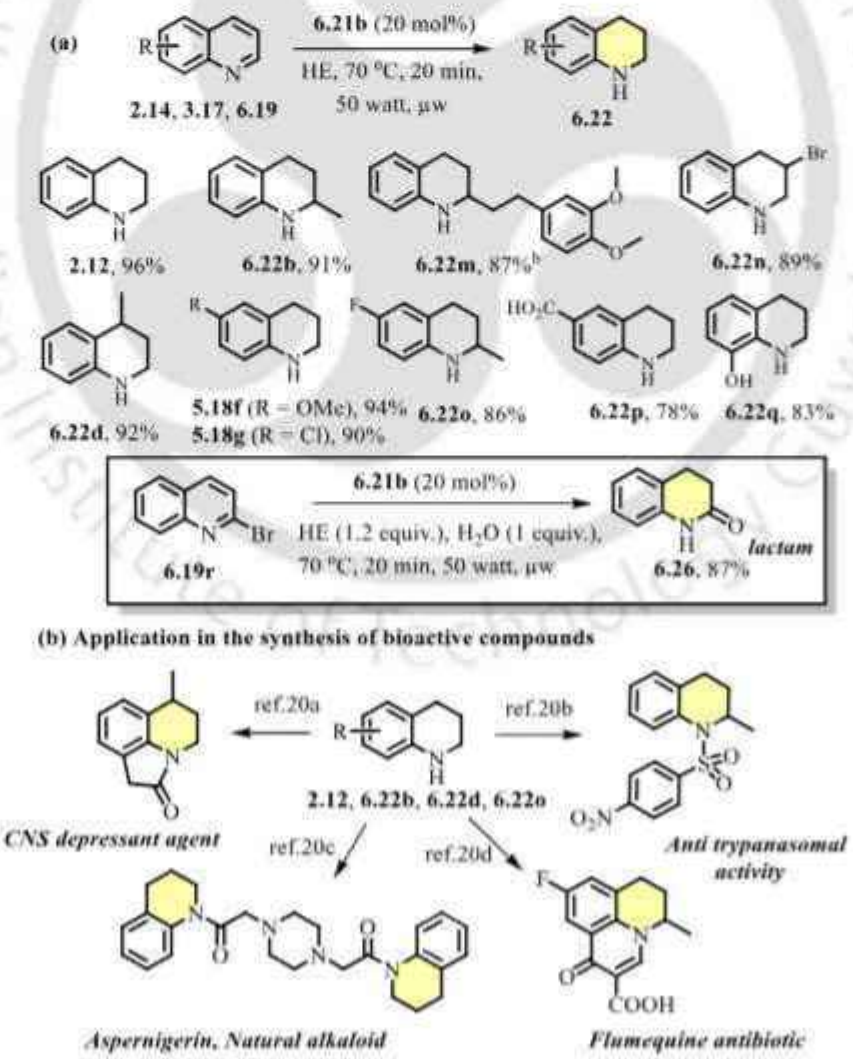


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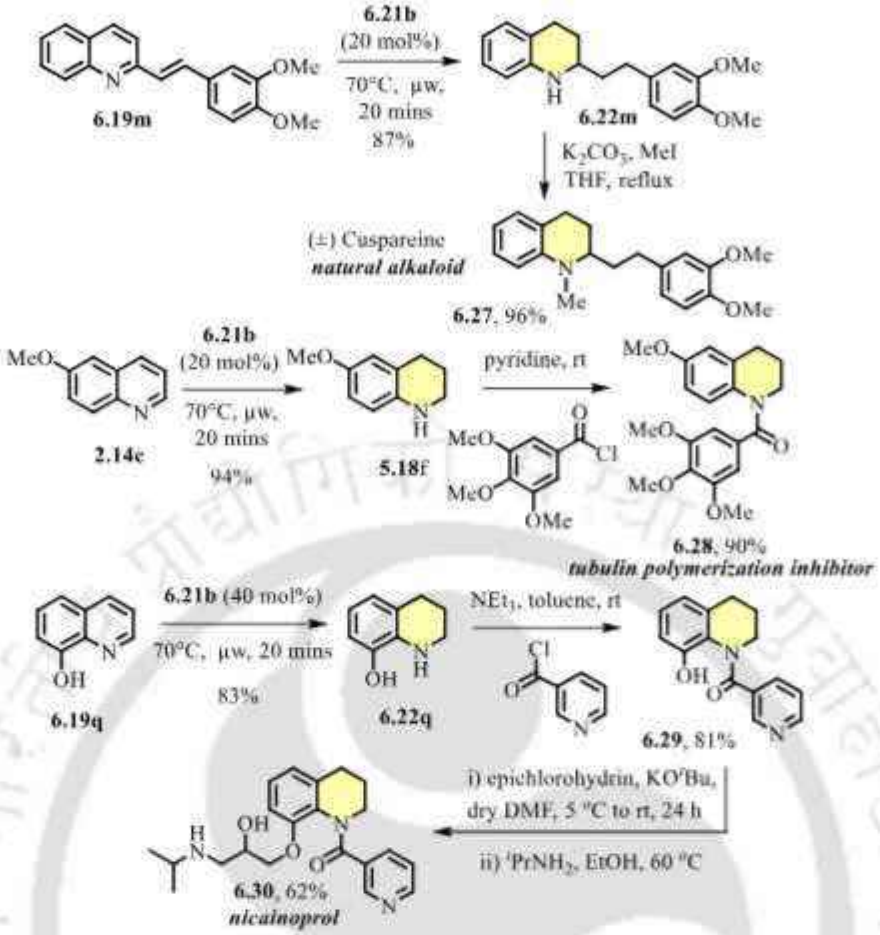
[a]Reaction condition: **2.14**, **3.17**, **6.19** (0.5 mmol), HCO_2H **6.20ak** (2.0 mmol), HE (2 equiv.), **6.21b** (20 mol%) at 70 °C for 20 minutes under the microwave (50 W), isolated yields. [b] In the absence of **6.21b**.

Synthetic utility of the current hydrogenative protocol was also explored towards THQs (**2.12**, **5.18**, **6.22**) (Scheme 6.7a). They are found as the important intermediate for the synthesis of various biological active molecules such as CNS depressant agent, anti trypanasomal activity, aspernigerin natural alkaloid and flumequine antibiotic.[20] Further, lactam **6.26** could also be readily obtained in 87% yield under the reaction conditions when 2-bromoquinoline **6.19r** is used as a substrate. Natural alkaloid (±) cuspareine has been prepared in 96% yield from the synthesized compound **6.19m**, followed by methylation with methyl iodide.[21] Tubulin polymerization inhibitor **6.28** was synthesized by the coupling of compound **2.14c** and 3,4,5-trimethoxy benzoyl chloride in presence of pyridine.[22] In addition, antiarrhythmic drug nicainoprol **6.30** was obtained in multi-steps.[23] The synthesized compound **6.19q** was treated with nicotinoyl chloride to give **6.29** in 81% yield, subsequently this was treated with epichlorohydrin, followed by isopropyl amine afforded the compound **6.30** in 77% yield.

Table 6.7. a) Scope of tetrahydroquinolines and (b) their utilization in the synthesis of bioactive compounds



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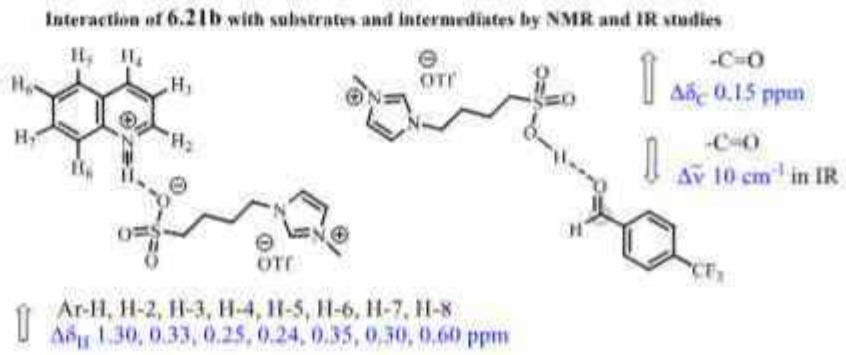


6.3.3. Post synthetic modification

Considering the importance of the lactam motif in various biologically and pharmaceutically relevant complex molecular settings, synthesized *N*-alkylated THQs containing nonsteroidal anti-inflammatory drug naproxen **5.6k** was successfully converted into lactam derivative **5.16** in 83% yield using ruthenium catalyst and periodate under oxidative conditions.[24] The method was also useful for the concise synthesis of bioactive molecule CYP11B2 inhibitor **5.15**[25] *via* late-stage α-methylene C−H oxidation of **5.6j**, further showcasing the potential of this protocol for practical utility (see details in subsection 5.3.4 of chapter 5).

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6.3.4. Mechanistic investigation



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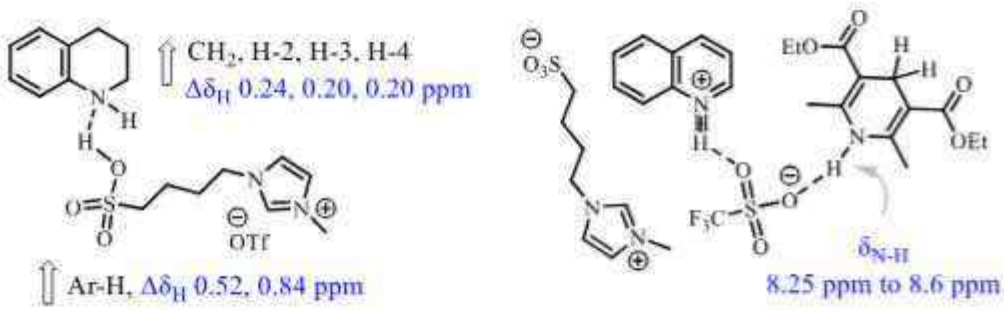


Figure 6.1. Weak interaction of **6.21b** with substrate and HE.

To gain insight into the role of **BAIL** in the *N*-alkylation process, systematic nuclear magnetic resonance (NMR) studies were performed to provide experimental evidence for the existence of interaction between the quinoline 'N's and the **6.21b** (Figure 6.2). The study was initiated with 1:1 mixture of quinoline **2.14a**: **6.21b** in DMSO-d_6, and record the ^{1}H NMR. A notable downfield shift of the aromatic proton H_2 and H_8 of **2.14a** adjacent to the quinyl nitrogen shifted significantly from 8.90 to 9.20 ppm, and 8.36 to 8.96 ppm, respectively, and the chemical shifts of the aromatic protons H_3, H_4, H_5, H_6, and H_7 of the **2.14a** shifted from 7.53, 8.02, 7.96, 7.60 and 7.76 ppm to 7.86, 8.27, 8.20, 7.95 and 8.06 ppm, respectively, upon addition of **6.21b**. Such a noteworthy change in the ^{1}H NMR consists of an initial quinolinium salt formation.

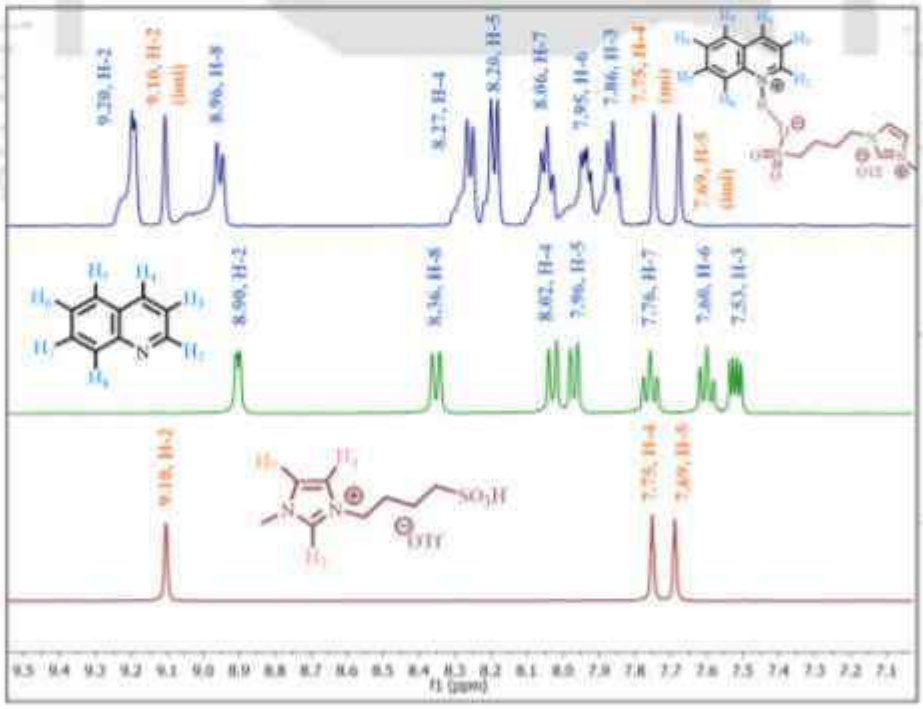


Figure 6.2. ^{1}H NMR spectra of quinoline **2.14a** (11 mg, 0.079 mmol), **6.21b** (29 mg, 0.0.079 mmol) molar ratio 1:1 in DMSO at 298K.

Then interaction of **6.21b** with the freshly distilled aldehyde was also confirmed by ^{13}C NMR. Upon addition of aldehyde **3.18h**, carbonyl value moved to downfield from 192.67 to 192.82

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ppm (Δδ 0.15 ppm) in the ^{13}C NMR. Study suggests that there is a weak hydrogen bonding interaction between **6.21b** and aldehyde group (Figure 6.3).

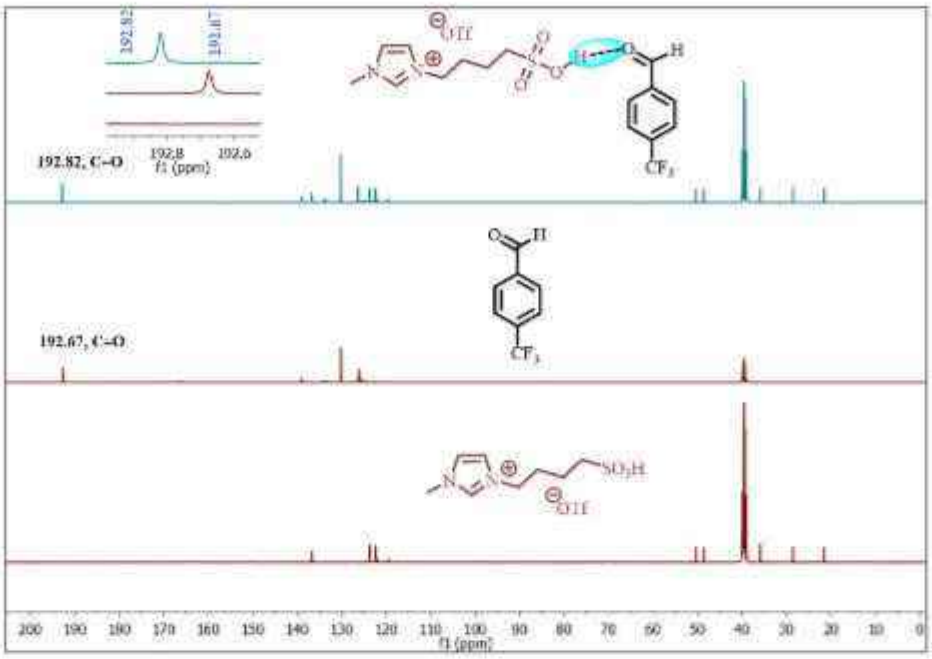
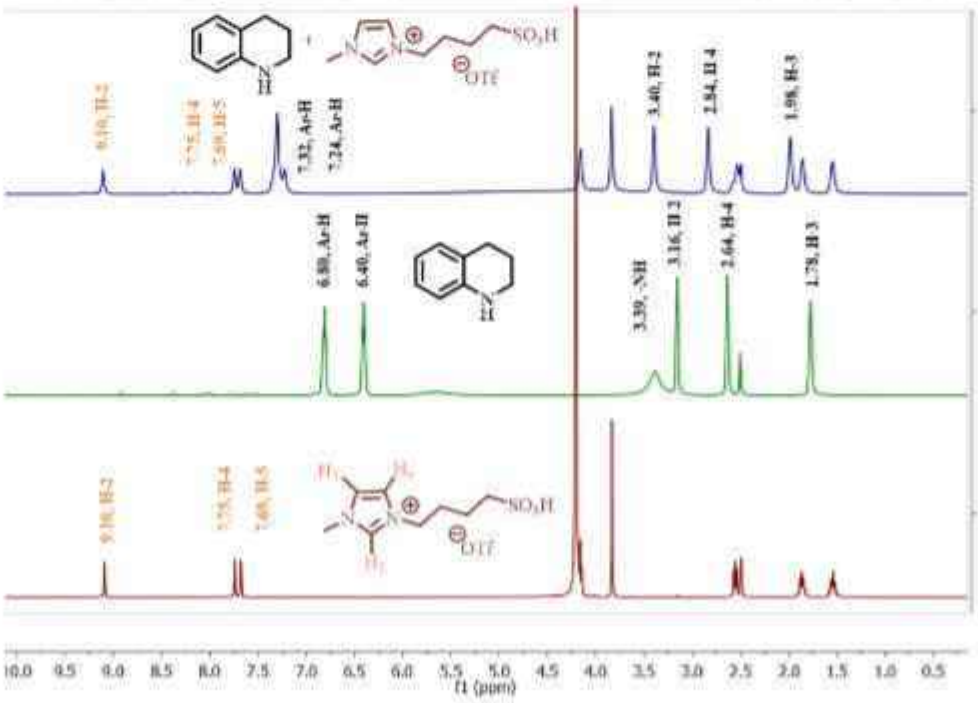


Figure 6.3. ^{13}C NMR spectra of 4-trifluoromethylbenzaldehyde **3.18h** (11 mg, 0.079 mmol), **6.21b** (29 mg, 0.079 mmol), and the mixture of 4-trifluoromethylbenzaldehyde **3.18h** and **6.21b** (molar ratio 1:1) in DMSO-d_6 at 298 K.

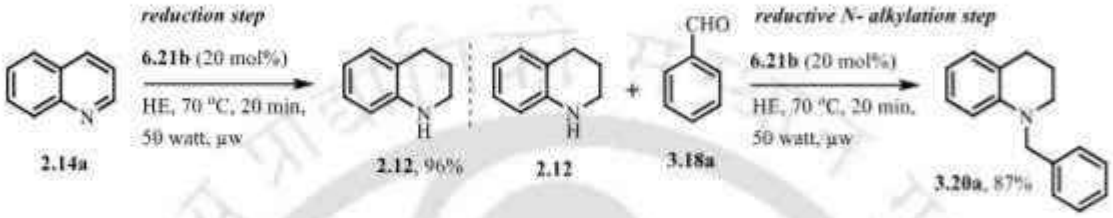
Then interaction of **6.21b** with the THQ **2.12** was also confirmed by ^{1}H NMR. Study suggests that both aromatic protons and aliphatic protons of the THQ **2.12** is shifted in the downfield upon addition of **6.21b** (Figure 6.4).



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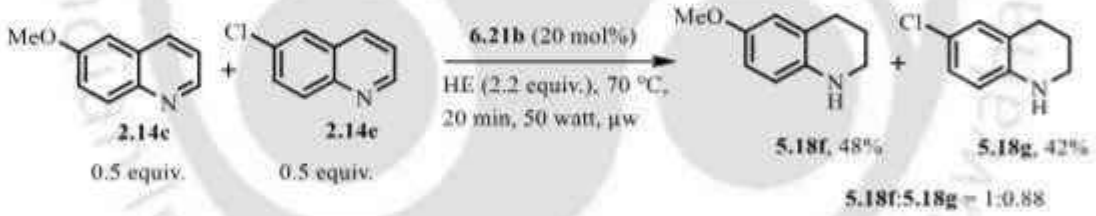
Figure 6.4. ^{1}H NMR spectra of THQ **2.12** (11 mg, 0.082 mmol), **6.21b** (30 mg, 0.0.082 mmol) molar ratio 1:1 in DMSO at 298K.

Next, a few control experiments were carried out to gain mechanistic insights into the synthesis of *N*-alkylated THQ derivative. The reaction of quinoline **2.14a** in the absence of aldehyde afforded THQ 4a in 96% yield. Then reaction was conducted with the formed **2.12**, and aldehyde **3.18a** under standard conditions the desired product 3.20a was obtained in 87% yield (Scheme 6.7). From the experimental observation, it can infer that THQs is an intermediate in the process.



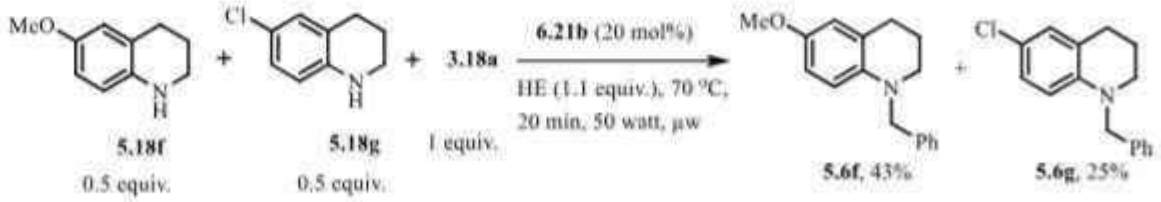
Scheme 6.7. Proof of 1,2,3,4-tetrahydroquinoline as the intermediate.

Then electronic effect of the substrate on the rate of the reaction was examined (Scheme 6.8). In the 1st step (i.e., reduction of quinoline to THQ), a comparable yield of THQ (**5.18f**, 48%; **5.18g**, 42%) was obtained when the reaction was performed with an equal ratio of 6-methoxyquinoline and 6-chloroquinoline, indicating no considerable electronic effect in the reduction step.



Scheme 6.8: Electronic effect of the quinoline hydrogenation step.

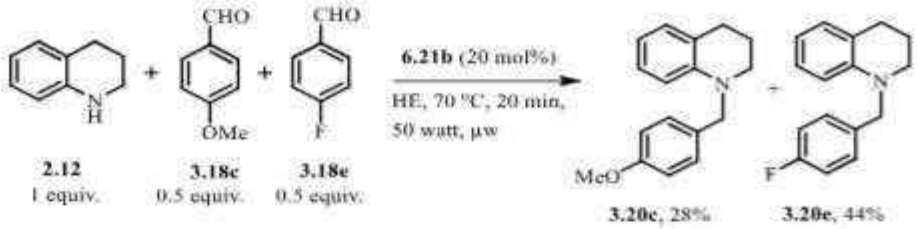
To know the electronic effect in the 2nd step, the reaction was examined with substituted THQ. A competitive reaction suggested that the electron-donating group (-OMe) on the THQ enhanced the rate of the reaction with respect to an electron-withdrawing group (*p*-Cl) (Scheme 6.9).



Scheme 6.9. Competitive reaction with substituted quinoline.

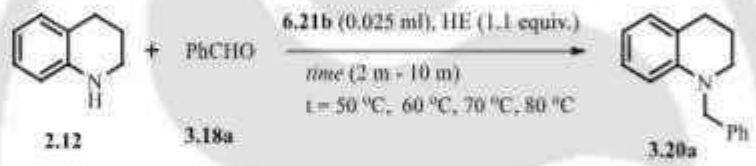
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Likewise, competitive reaction with aldehyde suggested that electron-withdrawing group (*p*-F) on the benzaldehyde slightly enhanced the rate of the reaction with respect to an electron-donating group (*p*-OMe) (Scheme 6.10).



Scheme 6.10. Competitive reaction with aldehyde.

Then effect of temperature on the rate of reaction was examined by using Eyring analysis (Scheme 6.11). The activation parameters were found to be $\Delta H^{\ddagger} = 6.84 \pm 0.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = -38.88 \pm 0.9$ cal K^{-1} mol^{-1}. The negative entropy of activation suggests that the involvement of associative process is the turnover-limiting step. Based on the thermodynamic activation parameters, and competitive reaction on the substrate, one can postulate that hemiaminal species formation step is likely to be the rate-limiting step.



Scheme 6.11. Eyring studies.

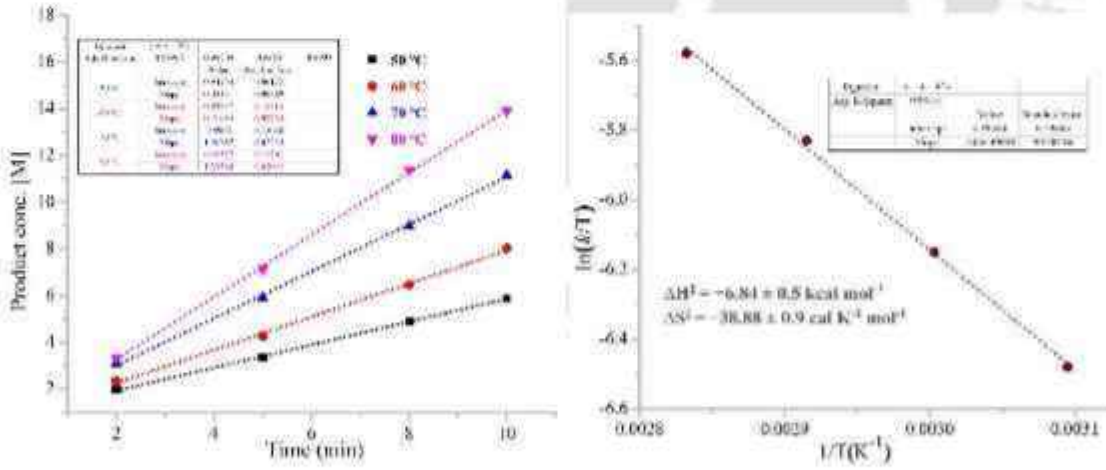


Figure 6.5. Concentration [Product] *vs* time plot at different temperatures (left side) Arrhenius-Eyring plot (right side).

Activation enthalpy ($\Delta H^{\#}$) and activation entropy ($\Delta S^{\#}$) values were obtained from the slope and intercept of plots of $\ln(k/T)$ vs $1/T$ (Figure S6) using the following equation:

$$\ln(k/T) = -\Delta H^{\#}/R.(1/T) + \ln k_B/h + \Delta S^{\#}/R$$

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where k_B = Boltzmann constant, R = universal gas constant, and h = Planck's constant.

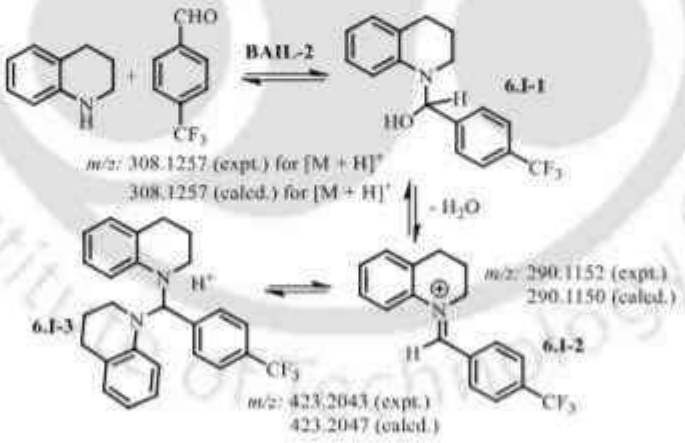
From the plot of $\ln(k/T)$ vs $1/T$,

$$\text{Slope} = -3446.5$$
$$Or, -\Delta H^{\ddagger}/R = -3446.5$$
$$Or, \Delta H^{\ddagger} = -(-3446.5) \times (1.987 \text{ cal } K^{-1}mol^{-1})$$
$$= 6848.2 \text{ cal } mol^{-1}$$
$$= 6.84 \text{ kcal } mol^{-1}$$

And,

$$\text{Intercept} = 4.19$$
$$Or, \ln (k_B/h) + \Delta S^{\#}/R = 4.19$$
$$Or, \ln (1.38 \times 10^{-23} \text{ J } K^{-1}/6.626 \times 10^{-34} \text{ J s}) + \Delta S^{\#}/1.987 \text{ cal } K^{-1} mol^{-1} = 4.19$$
$$Or, \ln (2.083 \times 10^{10} K^{-1} s^{-1}) + \Delta S^{\#}/1.987 \text{ cal } K^{-1} mol^{-1} = 4.19$$
$$Or, 23.76 + \Delta S^{\#}/1.987 \text{ cal } K^{-1} mol^{-1} = 4.19$$
$$Or, \Delta S^{\#}/1.987 \text{ cal } K^{-1} mol^{-1} = -19.57$$
$$Or, \Delta S^{\#} = -38.88 \text{ cal } K^{-1} mol^{-1}$$

To understand the impact of **6.21b** in the condensation reaction, the investigation has been illustrated with **6.21b** in the equal molar ratio THQ, and 4-trifluoromethylbenzaldehyde under reaction conditions and monitored the reaction mixture by ESI-MS spectrometry. The study suggests that there is formation of hemiaminal intermediate **6.I-1** and iminium ion intermediate **6.I-2** (Scheme 6.12).



Scheme 6.12. Plausible mechanistic pathway for the condensation reaction.

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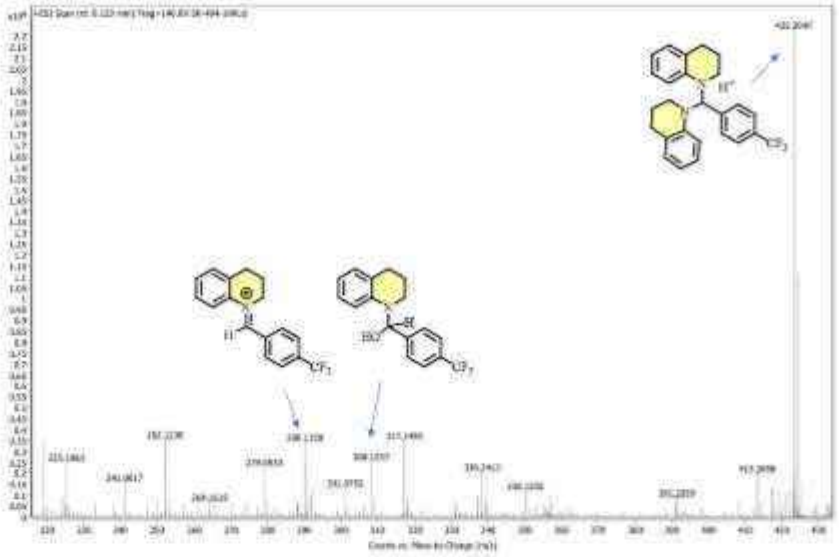


Figure 6.6. MS(ESI) spectra of the reaction mixture obtained from **6.21b**, THQ, 4-trifluoromethyl benzaldehyde (molar ratio 1:1:1) under the above reaction condition.

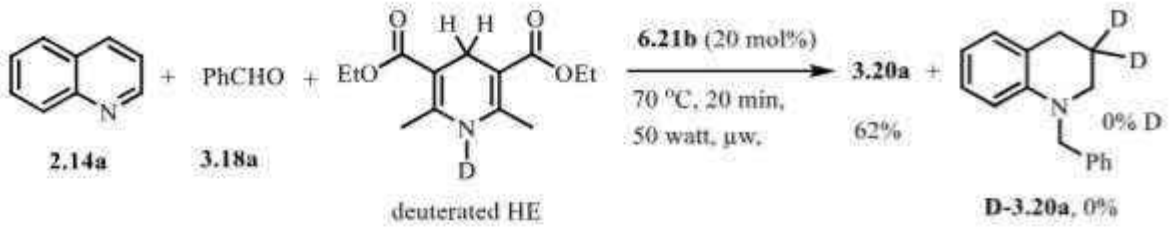
The deuterium labelled experiment was performed with **2.14g** and **6.19u** in the presence of D_2O under standard conditions. In both cases, D-incorporation was observed at the C3 position (SchemE 6.13).



Scheme 6.13: Deuterium-labelled experiment with 3-methyl quinoline and 3-phenyl quinoline.

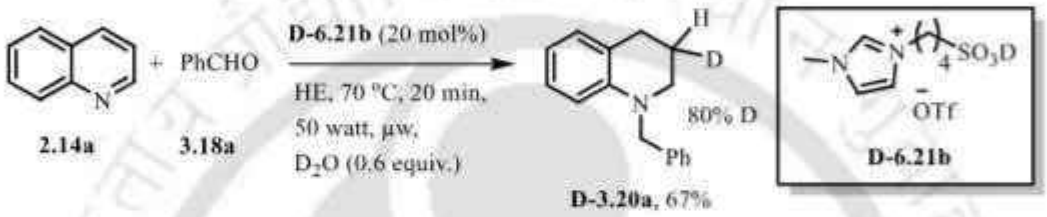
Then I have performed deuterium labelling experiments with N-D bearing Hantzsch ester under the reaction conditions (Scheme 6.14). The resulting product **3.20a** showed no deuterium incorporation at the C3 position, suggest that hydrogen transfer possibly not take place from the N-H of Hantzsch ester to the product **3.20a**. Additionally, the lower yield of **3.20a** (62%) indicates that the replacement of the N-H with N-D likely affects the reaction with **6.21b** and Hantzsch ester under the reaction conditions.

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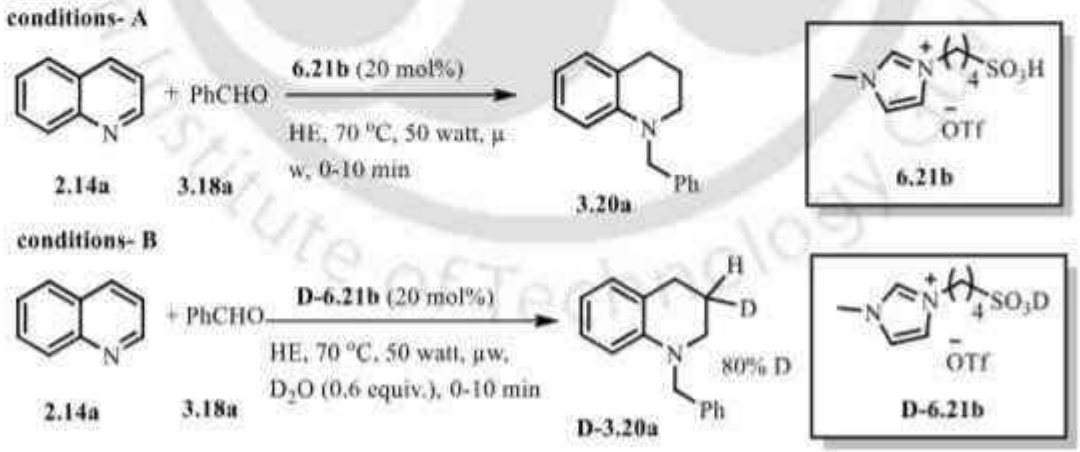
Scheme 6.14: Reaction with deuterated Hantzsch ester.

Further, the reaction was examined with deuterium **6.21b** and D_2O under the same optimized conditions, a lower yield of **3.20a** (67%), suggesting that the presence of a proton in **6.21b** play a significant role in hydrogen bonding interactions with the nitrogen atom of the quinoline moiety (Scheme 6.15).

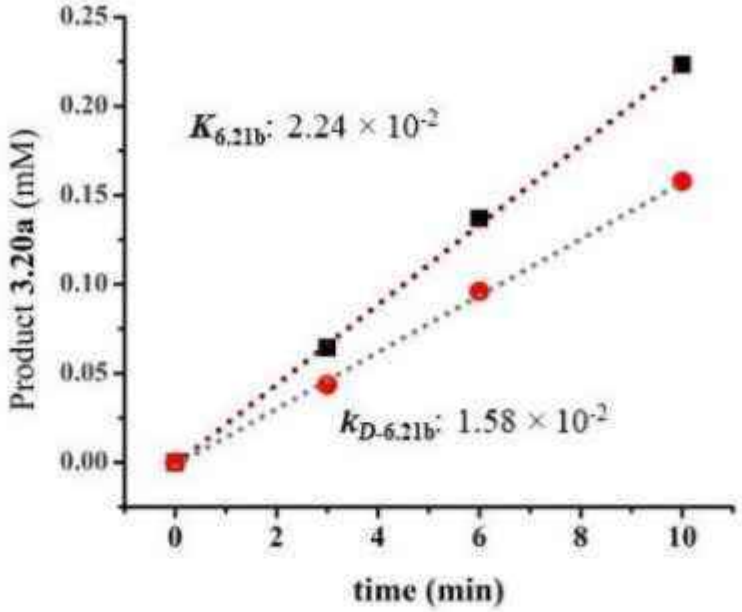


Scheme 6.15: Reaction with deuterated **6.21b** in the presence of D_2O.

The deuterium kinetic isotope effects were calculated by **conditions A** and **conditions B**. At different time interval, the crude compound was purified through silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.80). The Deuterium kinetic isotope effect (KIE) was calculated as $k_{6.21b}/k_{D\text{-}6.21b}$ = **1.41** indicating the importance of proton interactions (Scheme 6.16).

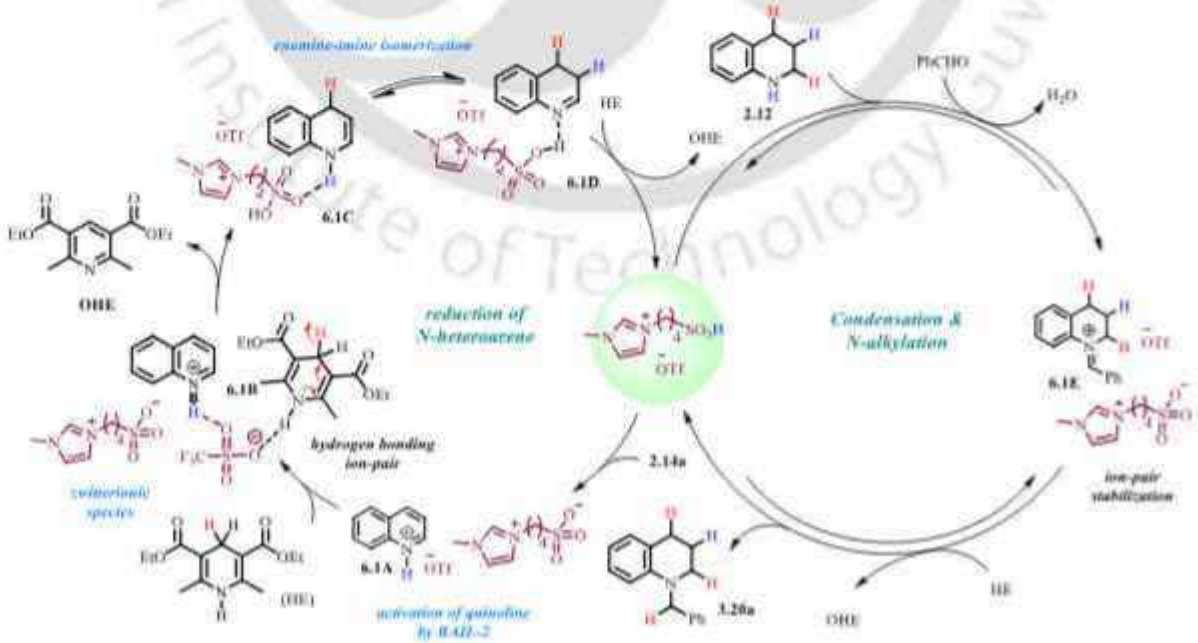


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Scheme 6.16. Kinetic isotopic experiment.

On the basis of above experimental findings and taking earlier reports into account,[12-16,26-28] proposed reaction pathways for the formation of *N*-alkylated tetrahydroquinoline has been demonstrated in Scheme 6.17. First, the quinoline **2.14a** is protonated by the **6.21b** to form quinolinium salt **6.1A** which is then reduced by Hantzsch ester to provide THQ *via* hydrogen bonding ion-pair mechanism.[28] The *in situ* generated THQ **2.12** can take part in reaction with the aldehyde to form hemiaminal species, followed by condensation leading to the formation of iminium intermediate **6.1E**. Finally, this was readily reduced by Hantzsch ester to provide the *N*-alkylated THQ **3.20a**.

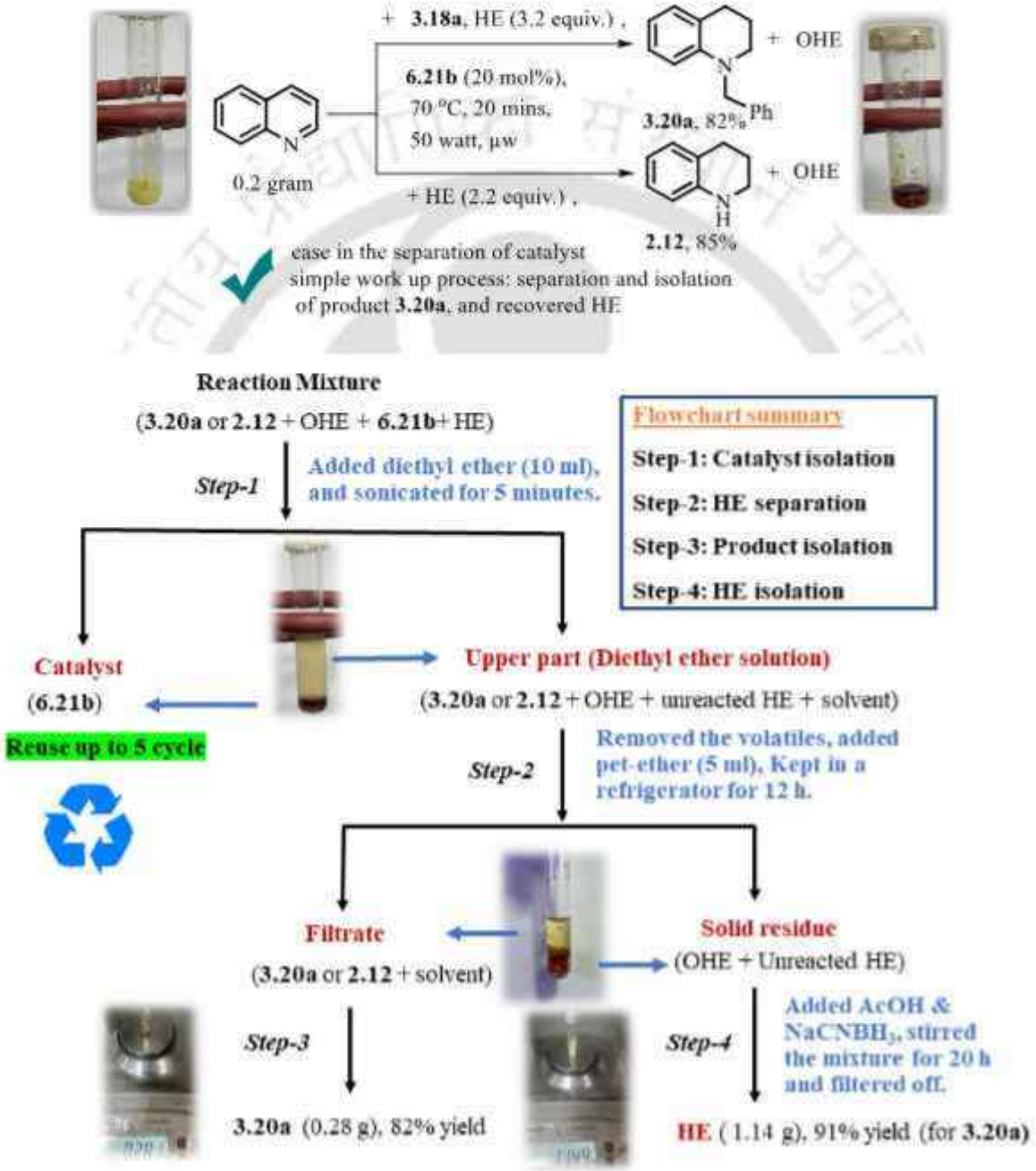


Scheme 6.17. Plausible mechanism.

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6.4. Scaling up, separation and isolation of product, recovered HE and recyclability of 6.21b

Next, scale-up studies and purification process has been examined for both the steps. Generally, a stoichiometric amount of oxidized Hantzsch ester (OHE) was produced in the Hantzsch ester-based transfer hydrogenation process.

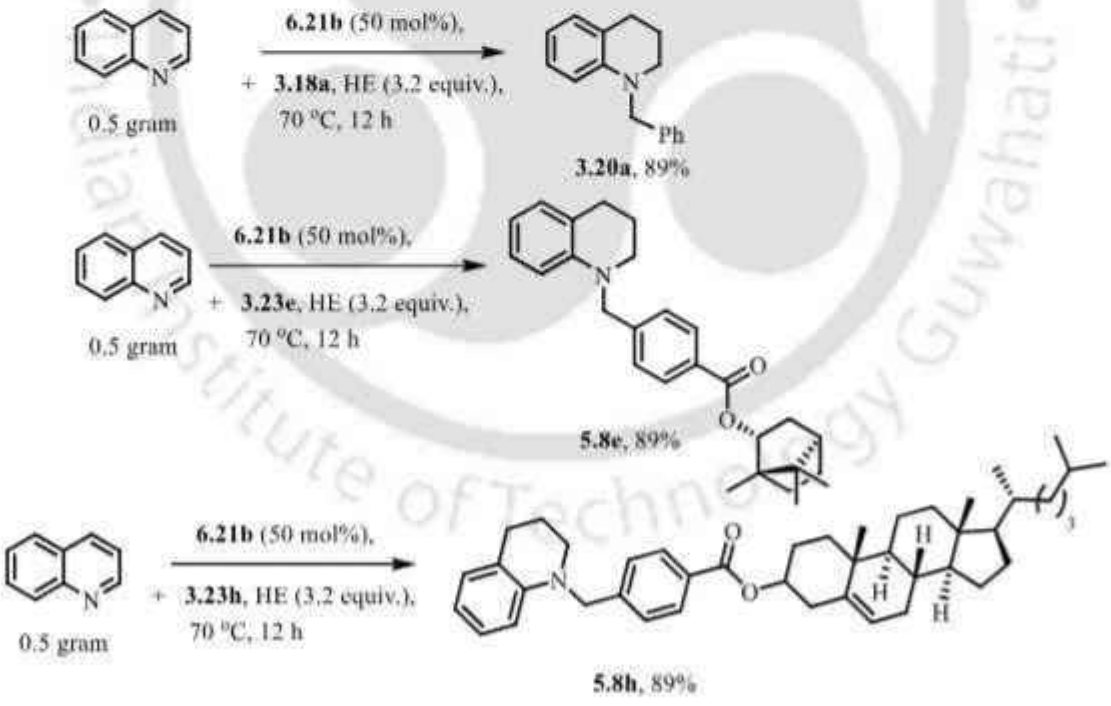


Scheme 6.18. Scaling up, separation and isolation of product and recovered HE.

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The use of conventional column chromatography is required to get the analytically pure product from the reaction mixture reaction, I further investigated the post workup procedure with the aim of efficiently separating, recovering, regenerating and reusing the Hantzsch ester (Scheme 6.18). In view of the charged imidazolium arm in the **6.21b** this polar compound can be easily separated out in diethyl ether solvent (see Figure 6.8, Schematic diagram for recyclability of **6.21b**) and the solution contains product BTHQ **3.20a**, by-product OHE, and unreacted HE (<5%). After removing all the volatiles, added petroleum-ether to the reaction mixture, and kept the solution in the refrigerator for overnight. The desired *N*-alkylated product **3.20a** was obtained in 82% yield. Likewise, intermediate THQ **2.12** was obtained in 85% yield. The solid residue of by-product OHE and unreacted HE was then collected by vacuum filtration. Finally, this solid compound was treated with glacial acetic acid and sodium cyanoborohydride at room temperature, recovered the HE in quantitative yield and thereby, limits its practical applicability.

To broaden the methods utility, the reaction was examined under thermal conditions in an oil bath with a slightly higher catalyst loading (50 mol%) using 0.5 gram of quinoline **2.14a** for 12 h (Scheme 6.19). The product **3.20a** was obtained with 89% yield. This thermal condition is also successfully applied in complex molecule settings, for instance, products **5.8e** and **5.8h**, were obtained in 78% and 69% yield, respectively.



Scheme 6.19: Alternative thermal conditions for the *N*-alkylated product.

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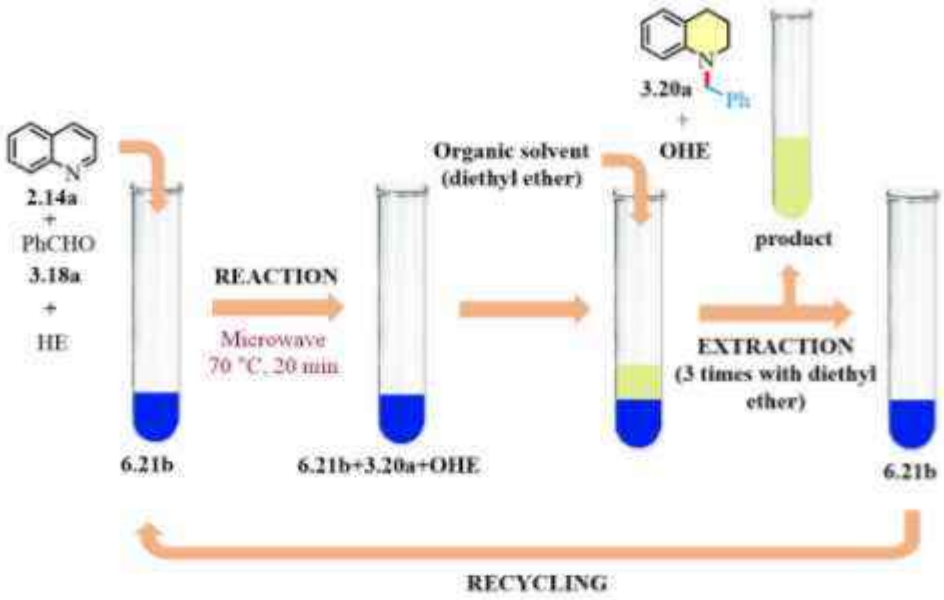


Figure 6.7. Schematic diagram for recyclability and reusability of the catalytic system.

To address this limitation and to enhance the practicality of the present Next, I explored the recycle performance of **6.21b** using **2.14a** and **3.18a** as model substrates under the optimal reaction condition (Figure 6.7). After completion of the reaction (monitored by TLC), diethyl ether was added to the reaction mixture, leading to the recovery of the catalyst. As depicted in Figure 6.8, the catalyst could be reused six times for the synthesis of **3.20a** with slight loss of activity, suggesting that the system had a good catalytic recyclability. Further validity of recycled **6.21b** is elucidated by the ^{1}H NMR (Figure 6.9).

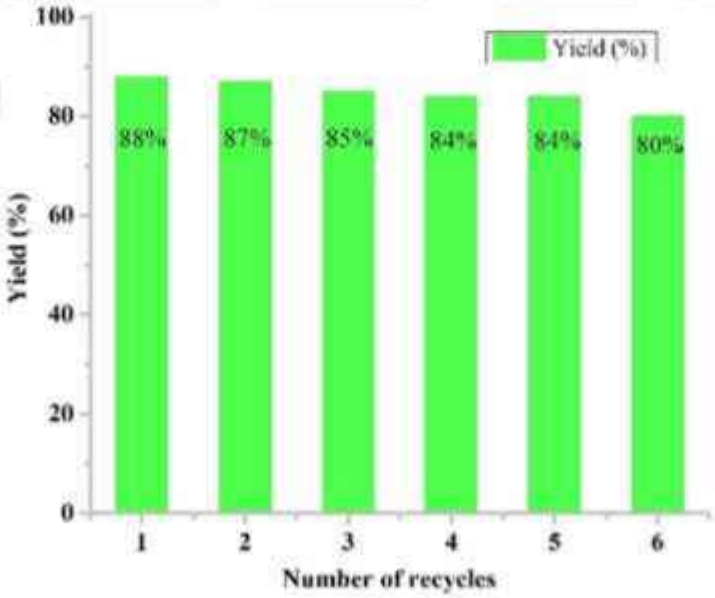


Figure 6.8. Recyclability study of **6.21b**.

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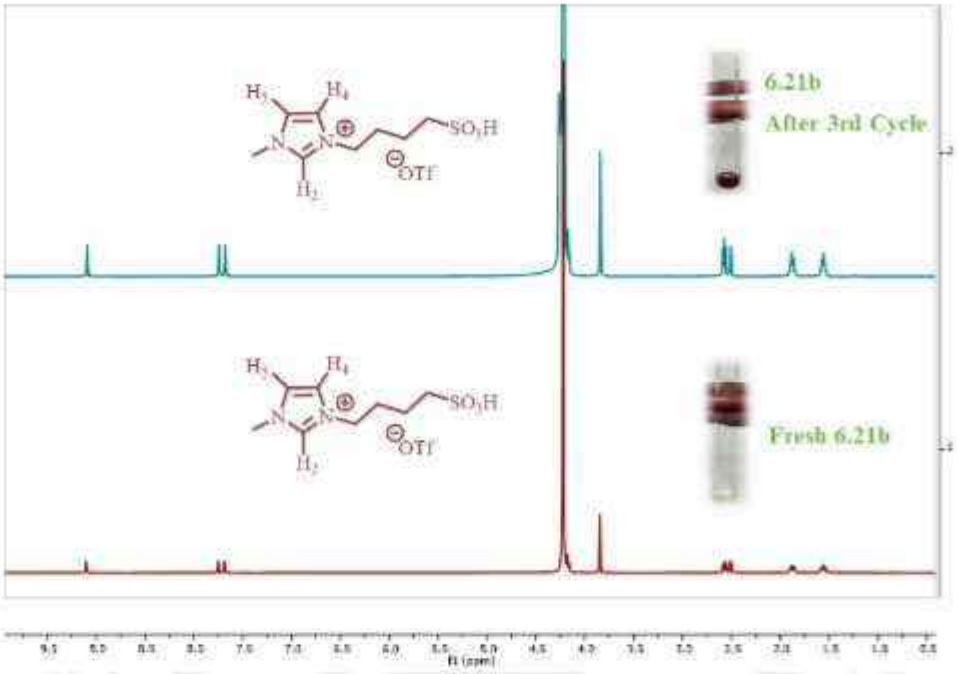


Figure 6.9. ^{1}H NMR of recycled **6.21b**.

6.5. Summary

In summary, I have developed **BAIL**-catalyzed a one-pot tandem reduction of quinoline with subsequent reductive alkylation using aldehydes to produce *N*-alkylated THQ derivatives. The catalyst could be easily recovered and reused five times without a considerable decrease in catalytic activity. This convenient method tolerates a wide variety of reducible-sensitive functional groups, such as ester, halo, nitro, nitrile, alkyne, allyl, benzyl, thioether. Further, it has been successfully utilized in the late-stage functionalization, diversification of pharmaceuticals. The post transformations of the synthesized product have also been carried out to demonstrate the potential of the developed methodology. The current reductive strategy was also successfully utilized to synthesize tricyclic oxazino-fused-tetrahydroquinoline/ benzoxazine, antiarrhythmic drug nicainoprol tubulin polymerization inhibitor and (±) cuspareine natural alakaloid efficiently. The multifunctional role of **BAIL** has been demonstrated not only to facilitate the reduction of quinoline but also to improve the stability of iminium ion species through ion-pair effect.

6.6. Experimental section

A. General information

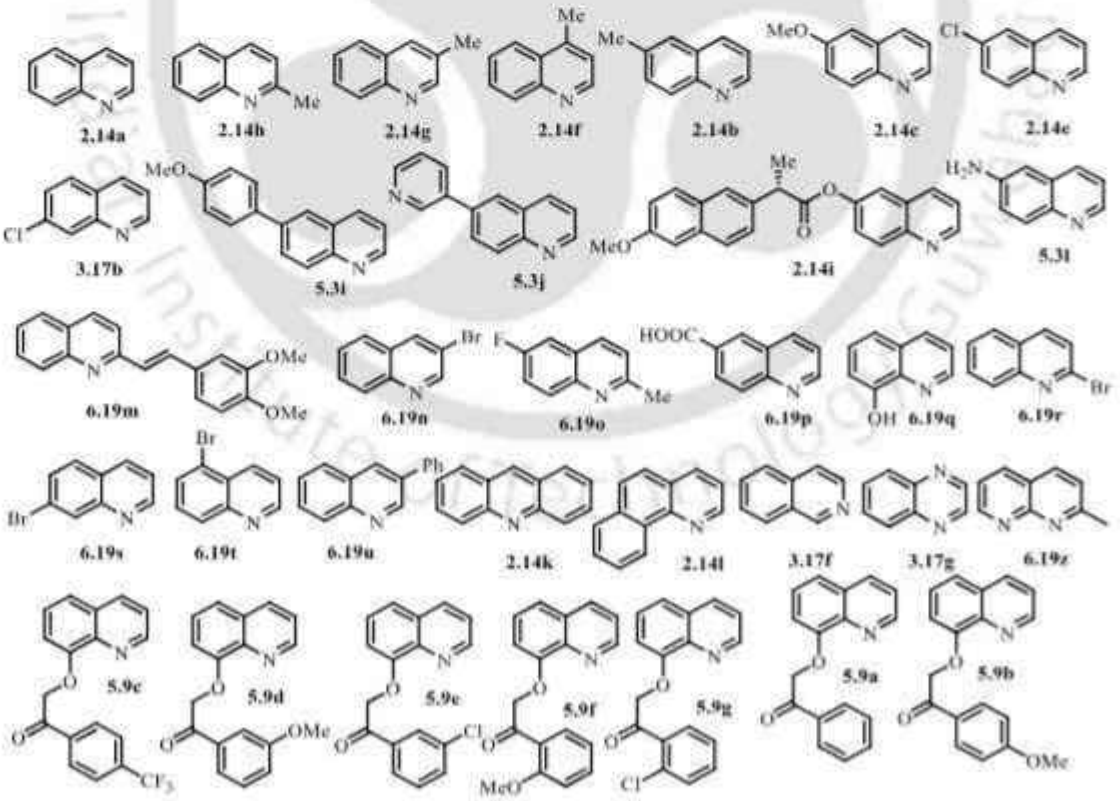
All the reagents and chemicals were purchased from common commercial suppliers like Sigma-Aldrich, Alfa Aesar, Merck, Spectrochem, Avra Synthesis Pvt. Ltd., Finar Chemicals, and BLD Pharma directly used as received without any further purification unless otherwise mentioned. Hantzsch ester was synthesized according to the reported literature.[29] All the reductive *N*-alkylation reactions were performed in a microwave reaction tube. All synthesized compounds were characterized by spectroscopic methods and compared to reported literature wherever applicable, otherwise stated. ^{1}H, ^{13}C, and ^{19}Fspectra of all the compounds were

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measured in $CDCl_3$, DMSO-d_6, D_2O as a solvent by using TMS as an internal standard. Chemical shifts, δ (in ppm), are reported relative to TMS δ (^1H) 0.0 ppm, δ (^{13}C) 0.0 ppm, which was used as the inner reference. Otherwise the solvents residual proton resonance and carbon resonance ($CDCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.16 ppm; DMSO-d_6, (^1H) 2.50 ppm, δ (^{13}C) 39.52 ppm); D_2O, δ (^1H) 4.790 ppm, were also used for calibration. Bruker Avance III 600, 500 and 400 spectrometers were used to record the NMR spectra. Chemical shifts (δ) values were reported in ppm and spin-spin coupling constant (J) were expressed in Hz, and other data were reported as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet, q = quartet, p = pentate, sext = sextet, hept = heptane, br = broad, and brs = broad singlet. IR spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass (UHPLC - Q-TOF - HRMS). Merck silica gel 60 - 120 was used for column chromatography. otherwise stated. All the final reactions were carried out under air and in preheated oil baths unless otherwise mentioned. Completion of reactions was examined by thin layer chromatography carried out on pre-coated Merck silica gel-60 F_{254} aluminium plates with ultraviolet light (UV) or iodine as visualizing agents.

B. Synthesis of starting material

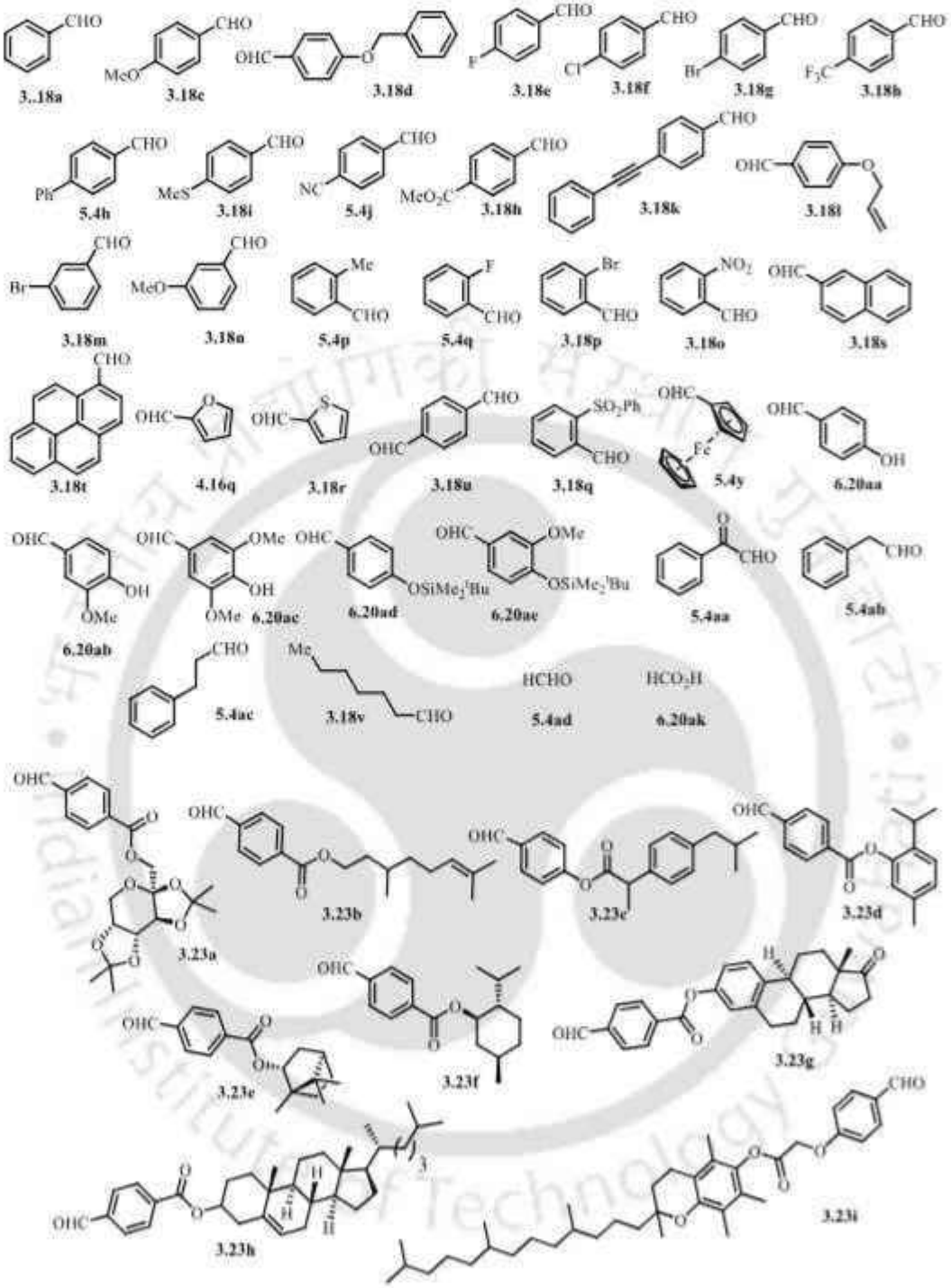
i) *N*-heteroarenes employed in the reaction:



Compounds **5.3i**[30], **5.3j**[24], **2.14i**[31], **6.19m**[32], **5.9a-5.9b**[19], **5.9d**[19], **5.9f**[19] are synthesized by known procedures.

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ii) Aldehydes and formic acid employed in the reaction:

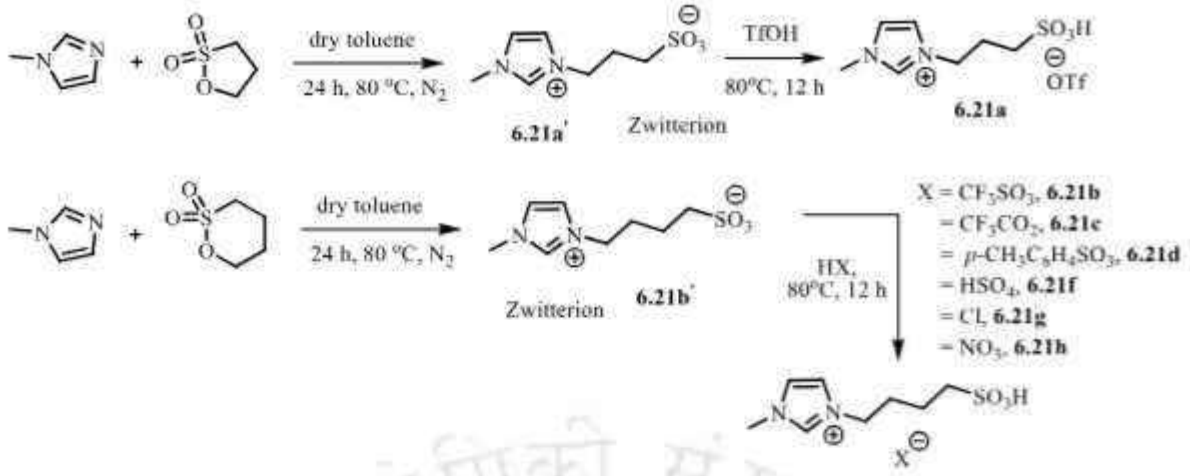


Compounds **3.18d**,[33] **3.18k**,[34] **3.18l**,[35] are synthesized by known procedure. The biologically relevant motifs containing aldehyde derivatives **3.23a**,[36] **3.23b**,[37] **3.23c**,[38] **3.23e**,[39] **3.23f**,[40] **3.23g**,[41] **3.23h**,[40], **3.23i**[27b] were synthesized by the known procedure.

C. General procedure for preparation of Brønsted acidic ionic liquids (GP-1)

i) Synthesis of Brønsted acidic ionic liquid (6.21a to 6.21g)

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Scheme 6.16. Preparation of BAILs.

A mixture of 1-methyl imidazole (240 mmol) and 1,3-propane sultone (240 mmol) or 1,4-butane sultone (240 mmol) were charged into a 100 ml round bottom flask in 20 ml of dry toluene and refluxed for 16 h. The white solid zwitterion species was washed with diethyl ether (3×10 ml), toluene (3×10 ml), and cyclohexane (3×10 ml) and dried under vacuum. The zwitterions species of **6.21a'** or **6.21b'** were formed quantitively. A stochiometric amount of Bronsted acid (4.58 mmol, TfOH, TFA, *p*-TSA, 98% H_2SO_4, 38% HCl or 70% HNO_3) was subsequently added drop wise to the reaction mixture of **6.21a'** (4.58 mmol) or **6.21b'** (4.58 mmol) and stirred the reaction mixture at 80 °C for 12 h. The obtained viscous liquid was washed with diethyl ether (3×10 ml), and dried under vacuum overnight.

ii) Analytical data of BAILs

1-methyl-3-(4-sulfopropyl) imidazolium trifluoromethane sulfonate (6.21a):

Using GP-1 with 4.58 mmol of **6.21a'** and trifluoromethanesulfonic acid, the title compound was isolated as colourless liquid, 97% yield (1.57 g). ^{1}H NMR (500 MHz, D_2O): δ 8.60 (s, 1H), 7.38 (m, 1H), 7.31 (m, 1H), 4.22 (t, J = 7.1 Hz, 2H), 3.76 (s, 3H), 2.78 (t, J = 7.2 Hz, 2H), 2.18 (p, J = 7.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, D_2O): δ 136.0, 123.7, 122.1, 119.57 (q, J = 327.6 Hz), 47.7, 47.2, 35.6, 25.0. ^{19}F NMR (471 MHz, D_2O): δ -78.95. Spectral data is in accordance to the reported literature. [42]

1-methyl-3-(4-sulfobutyl) imidazolium trifluoromethane sulfonate (6.21b):

Using GP-1 with 4.58 mmol of **6.21b'** and trifluoromethanesulfonic acid, the title compound was isolated as colourless liquid, 98% yield (1.65 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (s, 1H), 7.74 (t, J = 1.8 Hz, 1H), 7.68 (t, J = 1.8 Hz, 1H), 4.16 (d, J = 7.0 Hz, 2H), 3.84 (s, 3H), 2.58 – 2.52 (m, 2H), 1.87 (p, J = 7.2 Hz, 2H), 1.55 (p, J = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 136.7, 123.8, 122.4, 120.79 (q, J = 315.0 Hz), 119.5, 50.5, 48.6, 35.9, 28.6,

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21.6. $^{19}F\{^{1}H\}$ NMR (565 MHz, DMSO-d_6): δ -77.86. Spectral data is in accordance to the reported literature. [43]

4-(1-methyl-1H-imidazol-3-ium-3-yl) butane-1-sulfonate (6.21b'):

Using GP-1 with 240 mmol of 1,4-butane sultone, the title compound was isolated as white solid, 99% yield (5.21 g). ^{1}H NMR (500 MHz, D_2O): δ 8.77 (s, 1H), 7.53 – 7.52 (m, 1H), 7.47 – 7.46 (m, 1H), 4.29 – 4.26 (m, 2H), 3.92 (s, 3H), 2.98 – 2.95 (m, 2H), 2.08 – 2.02 (m, 2H), 1.80 – 1.74 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, D_2O): δ 136.0, 123.7, 122.2, 50.1, 48.9, 35.7, 28.1, 21.0, 20.9. Spectral data is in accordance to the reported literature. [44]

1-methyl-3-(4-sulfobutyl) imidazolium trifluoroacetate (6.21c):

Using GP-1 with 4.58 mmol of **6.21b'** and trifluoracetic acid, the title compound was isolated as colourless liquid, 95% yield (1.45 g). ^{1}H NMR (500 MHz, D_2O): δ 8.76 (s, 1H), 7.52 (m, 1H), 7.46 (m, 1H), 4.27 (t, J = 7.0 Hz, 2H), 3.92 (s, 3H), 2.98 – 2.95 (m, 2H), 2.08 – 2.02 (m, 2H), 1.77 (p, J = 8.1 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, D_2O): δ 136.0, 123.7, 122.2, 50.1, 48.9, 35.7, 28.1, 20.9. ^{19}F NMR (471 MHz, D_2O): δ -75.53.

1-methyl-3-(4-sulfobutyl)-1H-imidazolium *p*-tolyl sulfonate (6.21d):

Using GP-1 with 4.58 mmol of **6.21b'** and *p*-TsOH, the title compound was isolated as colourless liquid, 97% yield (1.73 g). ^{1}H NMR (500 MHz, D_2O): δ 8.64 (s, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.41 (m, 1H), 7.36 – 7.35 (m, 1H), 7.31 (d, J = 8.1 Hz, 2H), 4.15 (t, J = 7.1 Hz, 2H), 3.81 (s, 3H), 2.90 – 2.86 (m, 2H), 2.34 (s, 3H), 1.94 (p, J = 7.3 Hz, 2H), 1.71 – 1.65 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, D_2O): δ 142.4, 139.5, 135.8, 129.4, 125.3, 123.6, 122.1, 50.0, 48.9, 35.6, 28.0, 20.9, 20.4. Spectral data is in accordance to the reported literature. [42]

1-methyl-3-(4-sulfobutyl) imidazolium hydrogen sulfate (6.21e):

Using GP-1 with 4.58 mmol of **6.21b'** and sulfuric acid, the title compound was isolated as colourless liquid, 94% yield (1.15 g). ^{1}H NMR (500 MHz, D_2O): δ 8.65 (s, 1H), 7.42 – 7.41 (m, 2H), 7.36 (m, 2H), 4.17 (t, J = 7.1 Hz, 3.81 (s, 3H), 2.92 – 2.81 (m, 2H), 1.95 (p, J = 7.2 Hz, 2H), 1.70 – 1.64 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, D_2O): δ 135.9, 123.6, 122.1, 50.0, 48.9, 35.6, 28.1, 20.9. Spectral data is in accordance to the reported literature. [42]

1-methyl-3-(4-sulfobutyl)-1H-imidazol-3-ium chloride (6.21f):

Using GP-1 with 4.58 mmol of **6.21b'** and hydrochloric acid, the title compound was isolated as colourless liquid, 96% yield (1.12 g). ^{1}H NMR (500 MHz, D_2O): δ 8.59 (s, 1H), 7.33 (d, J = 28.6 Hz, 2H), 4.16 – 4.10 (m, 2H), 3.76 (s, 3H), 2.88 – 2.85 (m, 2H), 1.95 – 1.83 (m, 2H), 1.67 – 1.56 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, D_2O): δ 135.9, 123.6, 122.1, 50.0, 48.8, 35.6, 28.0, 20.9. Spectral data is in accordance to the reported literature. [45]

1-methyl-3-(4-sulfobutyl) imidazolium nitrate (6.21g):

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Using GP-1 with 4.58 mmol of **6.21b'** and nitric acid, the title compound was isolated as colourless liquid, 98% yield (1.26 g). ^{1}H NMR (600 MHz, D_2O): δ 8.62 (s, 1H), 7.38 (t, J = 1.7 Hz, 1H), 7.32 (t, J = 1.7 Hz, 1H), 4.13 (t, J = 7.1 Hz, 2H), 3.78 (s, 3H), 2.85 – 2.82 (m, 2H), 1.91 (p, J =7.3 Hz, 2H), 1.66 – 1.61 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, D_2O): δ 135.9, 123.6, 122.1, 50.0, 48.9, 35.6, 28.1, 20.9.

D General procedure for synthesis of *N*-alkyl tetrahydroquinolines

i) General procedure for synthesis of *N*-alkyl tetrahydroquinolines with different aldehydes (GP-2)

Reaction condition: In a microwave tube, a mixture of quinoline **2.14a** (0.5 mmol), substituted aldehyde (0.5 mmol), HE (1.6 mmol), and **6.21b** (20 mol%) were taken. This was sealed with screw-cap and the resulting solution was then heated at 70 °C for 20 min under microwave irradiation (50 W). The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, $CHCl_3$ (2 mL) was added to the reaction mixture and transferred the reaction mixture into round bottom flask. All the volatiles were then removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

ii) General procedure for synthesis of *N*-alkyl tetrahydroquinolines with substituted quinolines (GP-3)

Reaction condition: In a microwave tube, a mixture of substituted quinoline (0.5 mmol), benzaldehyde **3.18a** (0.5 mmol), HE (1.6 mmol), and **6.21b** (20 mol%) were taken. This was sealed with screw-cap, the resulting solution was then heated at 70 °C for 20 min under microwave irradiation (50 W). The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, $CHCl_3$ (2 mL) was added to the reaction mixture and transferred the reaction mixture into round bottom flask. All the volatiles were then removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

iii) General procedure for synthesis of benzoxazine derivative (GP-4)

Reaction condition: In a microwave tube, a mixture of 1-aryl-2-(8-quinolinyloxy) ethanone (0.5 mmol), HE (3.2 equiv.) and and **6.21b** (20 mol%) were taken. This was sealed with screw-cap, the resulting solution was then heated at 70 °C for 20 min under microwave irradiation (50 W). The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, $CHCl_3$ (2 mL) was added to the reaction mixture and transferred the reaction mixture into round bottom flask. All the volatiles were then removed under reduced pressure. The crude compound was then purified through silica gel column chromatography.

iv) General procedure for the synthesis of tetrahydroquinoline-1-carbaldehyde derivative (GP-5):

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Reaction conditions: In a microwave tube, substituted quinoline (0.5 mmol), formic acid 6.**20ak** (2.0 mmol), HE (1.1 mmol), and **6.21b** (20 mol%) were taken. Then this was sealed with screw-cap, the resulting solution was heated at 70 °C for 20 mins under microwave irradiation (50W). The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, $CHCl_3$ (2 mL) was added to the reaction mixture and transferred the reaction mixture into round bottom flask. All the volatiles were then removed under reduced pressure. The crude compound was purified through silica gel column chromatography.

v) Scope of tetrahydroquinolines and their utilization in the synthesis of bioactive compounds

General procedure for the synthesis of tetrahydroquinoline derivatives (GP-6)

Reaction conditions: In a microwave tube, substituted quinoline (0.5 mmol, 1.0 equiv.), HE (0.279 g, 1.1 mmol, 2.2 equiv.), and **6.21b** (20 mol%) were taken. Then this was sealed with screw-cap, the resulting solution was heated at 70 °C for 20 mins under microwave irradiation (50 W). The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, $CHCl_3$ (2 mL) was added to the reaction mixture and transferred the reaction mixture into round bottom flask. All the volatiles were then removed under reduced pressure. The crude compound was purified through silica gel column chromatography. For **6.22m**, 1.75 mmol of HE was used.

vi) Procedure for the synthesis of lactam

Reaction conditions: In a microwave tube, 2-bromo quinoline **6.19r** (0.104 g, 0.5 mmol, 1.0 equiv.), HE (0.153 g, 0.6 mmol, 1.2 equiv.), H_2O (0.5 mmol, 1.0 equiv.) and **6.21b** (20 mol%) were taken. This was sealed with screw-cap, the resulting solution was then heated at 70 °C for 20 mins under microwave irradiation (50 W). The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, $CHCl_3$ (2 mL) was added to the reaction mixture and transferred the reaction mixture into round bottom flask. All the volatiles were then removed under reduced pressure.

The residue was purified by column chromatography on silica gel (eluent: pet-ether/ethyl acetate 5:1, v/v) to yield the desired compound **6.26** as white solid (0.064 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (brs, 1H), 7.20 – 7.16 (m, 2H), 6.99 (t, J = 6.9 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 2.97 (t, J = 7.4 Hz, 2H), 2.66 – 2.63 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 171.7, 137.3, 128.2, 127.7, 123.8, 123.3, 115.4, 30.9, 25.5. Spectral data is in accordance to the reported literature. [24]

vi) Application in the synthesis of bioactive compounds (Table 6.7b)

Synthesis of cuspareine (6.27)

Step 1: (*E*)-2-(3,4-dimethoxystyryl) quinoline (1m) to 2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline (6.22m)

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In a microwave tube, **6.19m** (0.146 g, 0.5 mmol, 1.0 equiv.), HE (0.442 g, 1.75 mmol, 3.5 equiv.), and **6.21b** (20 mol%) were taken. Then sealed with screw-cap, the resulting solution was heated at 70 °C for 20 mins under microwave irradiation (50 W). After completion of the reaction, $CHCl_3$ (2 ml) was added to the reaction mixture and transferred the reaction mixture into round bottom flask. All the volatiles were then removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: pet-ether/ethyl acetate 10:1, v/v) to yield the desired compound **6.22m** as yellow oil (0.129 g, 87%).

Step 2: Synthesis of 2-(3,4-dimethoxyphenethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (6.27) [21a]

In a reaction tube (15 mL), 2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline **6.22m** (0.100 g, 0.34 mmol, 1.0 equiv.), methyl iodide (0.144 g, 3.0 equiv.), potassium carbonate (0.047 g, 0.34 mmol, 1.0 equiv.) and dry THF (5 mL) were charged. The reaction mixture was allowed to reflux in a pre-heated oil bath for 20 h. Once the substrates were consumed, volatiles were evaporated using rotary evaporator and directly purified by column chromatography on silica gel (pet-ether/ ethyl acetate) to afford the pure product as yellow oil (0.102 g, 96%).

Synthesis of tubulin polymerization inhibitor (6.28)

Step 1: 6-methoxyquinoline (2.14c) to 6-methoxy-1,2,3,4-tetrahydroquinoline (5.18f)

In a microwave tube, **2.14c** (0.080 g, 0.5 mmol, 1.0 equiv.), HE (0.279 g, 1.1 mmol, 2.2 equiv.), and **6.21b** (20 mol%) were taken. This was sealed with screw-cap, the resulting solution was then heated at 70 °C for 20 mins under microwave irradiation (50W). The reaction was monitored by thin layered chromatography (TLC) in petroleum ether and ethyl acetate solvent system. After completion of the reaction, $CHCl_3$ (2 ml) was added to the reaction mixture and transferred the reaction mixture into round bottom flask. All the volatiles were then removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 5:1, v/v) to yield the desired compound **5.18f** as yellow oil (0.076 g, 94%).

Step 2: Synthesis of compound 6.28 [26c]

In a 100 mL Schlenk flask, 6-methoxy-1,2,3,4-tetrahydroquinoline **5.18f** (0.05 g, 0.3 mmol, 1.0 equiv.), was dissolved in pyridine (2 mL). Next, 3,4,5-trimethoxybenzoyl chloride (0.104 g, 0.45 mmol, 1.5 equiv.) was added to the above solution and resulting mixture was allowed to stir at room temperature for overnight. Once the reaction was completed, water was added to the reaction mixture and extracted by using ethyl acetate. The organic layer was further washed with diluted HCl solution to remove the pyridine in traces. Then, the solvent was removed under reduced pressure, the microwave tube was brought to room temperature, then $CHCl_3$ (2 ml) was added to it, then transferred into round bottom flask, then all the volatiles were then removed under reduced pressure, the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 5:1, v/v) to yield the desired compound **6.28** as yellow oil (0.096 g, 90%).

Synthesis of nicainoprol (6.30)

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Step 1: 8-hydroxyquinoline (6.19q) to 8-hydroxy-1,2,3,4-tetrahydroquinoline (6.22q)

In a microwave tube, **6.19q** (0.073 g, 0.5 mmol, 1.0 equiv.), HE (0.0279 g, 1.1 mmol, 2.2 equiv.), and **6.21b** (20 mol%) were taken. Then sealed with screw-cap, the resulting solution was heated at 70 °C for 20 mins under microwave irradiation (50 W). After completion of the reaction, the reaction tube was brought to room temperature. The $CHCl_3$ (2 ml) was added to the reaction mixture and removed all the volatiles under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: DCM/MeOH, v/v) to yield the desired compound **6.22q** as colourless oil (0.062 g, 83%).

Step-2: Synthesis of compound 6.30

In a 50 mL Schlenk flask, 8-hydroxy-1,2,3,4-tetrahydroquinoline **6.22q** (0.06 g, 0.4 mmol, 1.0 equiv.), nicotinoyl chloride (0.068 g, 0.48 mmol, 1.20 equiv.), triethyl amine (0.061 g, 0.6 mmol, 1.50 equiv.) and dry toluene (2 mL) were charged and stirred overnight in argon atmosphere at room temperature. Once the reaction was complete, toluene was evaporated by using rotary evaporator. The solid crude was purified by silica column chromatography using DCM:MeOH (5-10% MeOH mixture) solvent system to yield the desired compound **6.29** as white solid (0.082 g, 81%). m.p: 120~126 °C.

In a 50 mL schlenk flask, compound **6.29** (0.08 g, 0.32 mmol, 1.0 equiv.) was dissolved in dry DMF (0.3 mL) and potassium *tert*-butoxide (0.042 g, 0.38 mmol, 1.2 equiv.) was charged onto it. The entire solution was stirred in ice cold bath (~0-5 °C) for 30 min followed by the dropwise addition of epichlorohydrin (0.044 g, 0.48 mmol, 1.5 equiv.). After complete addition the reaction mixture, stirred the reaction mixture at ice cold bath for next 30 minutes, subsequently stirred it at room temperature for another 24 h. The reaction mixture was monitored by thin layered chromatography (TLC) in CH_2Cl_2 and methanol solvent system. The crude reaction mixture was concentrated in rotary evaporator and purified by using liquid-liquid separation method (water/ ethyl acetate). The organic layer (ethyl acetate fraction) was added with Na_2SO_4 to remove the excess water and concentrated in a rotary evaporator. Afterwards, the solid crude (0.083 g, 75%) was directly proceeded for the next step without any further purification. The resulting compound is sensitive towards an air and moisture, recommendable to store under argon at -20 °C.

In a 50 mL pyrex tube, above crude compound (0.080 g, 0.23 mmol, 1 equiv.) was dissolved in dry ethanol (2 mL) and isopropylamine (0.027 g, 0.46 mmol, 2 equiv.) was charged onto it. The reaction tube was closed under argon flow and the entire solution was stirred at 60 °C for 12 hours. The reaction was monitored using thin layered chromatography (TLC). Upon complete consumption of the starting material, the reaction mixture is concentrated in rotary evaporator to remove ethanol and unreacted isopropylamine. Compound **6.30** was obtained by neutral alumina column chromatography using CH_2Cl_2 : MeOH (4% MeOH mixture) to obtain the product as white solid (0.070 g, 83%); m.p: 120~125 °C. Overall yield in the last step: 62%.

E. Post synthetic modification (see details in the experimental section of chapter 5)

Selective α-methylene oxidation of *N*-alkylated tetrahydroquinolines

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Synthesis of CYP11B2 inhibitor (5.15)

Reaction condition: $NaIO_4$ (1.5 mmol, 3.0 equiv.) was taken in a screw-capped reaction tube and dissolved it in water (1 mL). Then synthesized compound **5.6j** (0.5 mmol, 1 equiv.), **[Ru]**[24] (2 mol%), and acetonitrile (2 mL) were added to the reaction tube and stirred the reaction mixture at 70 °C for 1 hour. After the completion of the reaction as confirmed by TLC, the reaction mixture was worked up with CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was again extracted with CH_2Cl_2 (two times, 5 mL). The combined organic layer was washed with brine solution (8 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under a vacuum. The crude product was purified through silica-gel column chromatography to get the pure product **5.15** as white solid (0.137 g, 87%).

^1H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 2.4 Hz, 1H), 8.55 (d, J = 6.4 Hz, 1H), 7.81 – 7.79 (m, 1H), 7.40 – 7.39 (m, 1H), 7.35 – 7.30 (m, 4H), 7.26 – 7.23 (m, 3H), 6.98 (d, J = 8.4 Hz, 1H), 5.22 (s, 2H), 3.09 – 3.05 (m, 2H), 2.86 – 2.83 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 170.5, 148.4, 148.0, 140.0, 136.9, 135.8, 134.0, 132.5, 128.9, 127.3, 127.2, 126.6, 126.5, 126.2, 123.7, 116.3, 46.2, 31.9, 25.8. Spectral data is in accordance to the reported literature. [46]

Synthesis of nonsteroidal anti-inflammatory drug (5.16)

Reaction condition: $NaIO_4$ (1.5 mmol, 3 equiv.) was taken in a screw-capped reaction tube and dissolved it in water (1 mL). Then **5.6k** (0.5 mmol, 1 equiv.), **[Ru-2]**[21] (2 mol%), and acetonitrile (2 mL) were added to the reaction tube and stirred the reaction mixture at 70 °C for 1 hour. After the completion of the reaction as confirmed by TLC, the reaction mixture was worked up with CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was again extracted with CH_2Cl_2 (two times, 5 mL). The combined organic layer was washed with brine solution (8 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under a vacuum. The crude product was purified through silica-gel column chromatography to get the pure product **5.16** as pale-yellow oil (0.193 g, 83%).

^1H NMR (600 MHz, $CDCl_3$): δ 7.74 – 7.71 (m, 3H), 7.47 – 7.46 (m, 1H), 7.28 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 7.17 – 7.13 (m, 4H), 6.81 – 6.78 (m, 2H), 6.71 (dd, J = 8.8, 2.6 Hz, 1H), 5.13 (s, 2H), 4.06 (q, J = 7.1 Hz, 1H), 3.92 (s, 3H), 2.92 – 2.90 (m, 2H), 2.77 – 2.74 (m, 2H), 1.67 (d, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 173.5, 170.4, 157.9, 146.1, 137.7, 136.8, 135.1, 133.9, 129.4, 129.1, 128.9, 127.6, 127.5, 127.3, 126.5, 126.24, 126.16, 121.0, 120.1, 119.3, 116.4, 105.7, 55.5, 46.4, 45.6, 31.6, 25.6, 18.6. Spectral data is in accordance to the reported literature. [24]

F. Mechanistic investigation

i) Interaction of BAIL with quinoline and HE

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Adding one equivalent of Hantzsch ester to the reaction mixture, -NH proton of HE is shifted in the downfield from 8.25 ppm to 8.6 ppm. This is likely due to the hydrogen bonding interaction between the -NH of HE and triflate anion. Further, triflate anion is shifted from -77.76 ppm to -77.86 ppm in ^{19}F NMR (Figure 6.9).

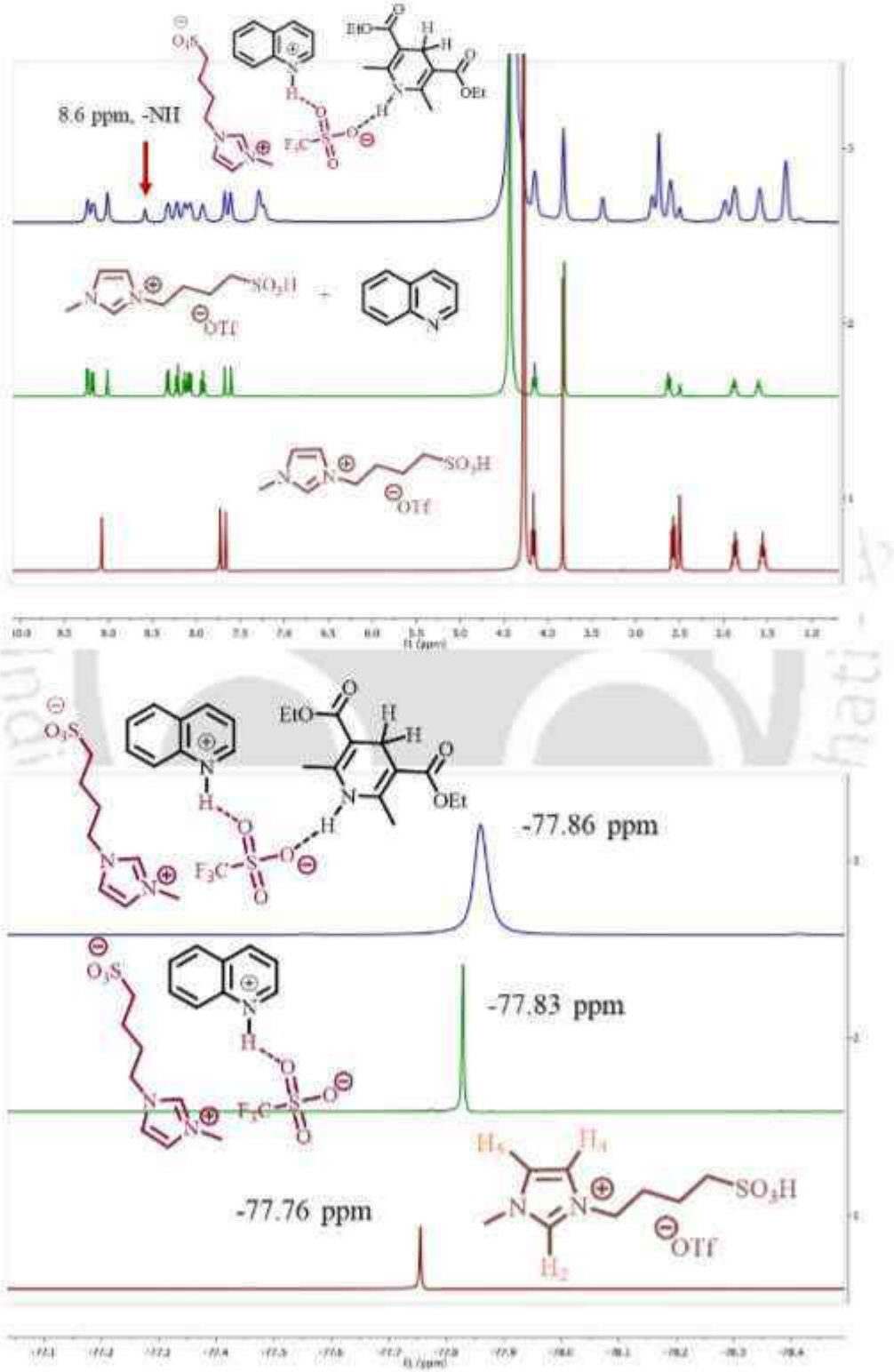


Figure 6.9. ^{1}H NMR and ^{19}F NMR spectra of quinoline **2.14a** (11 mg, 0.079 mmol), **6.21b** (29 mg, 0.0.079 mmol), and HE (20 mg, 0.079 mmol) molar ratio 1:1:1 in DMSO at 298K.

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ii) Proof of 1,2,3,4-tetrahydroquinoline as the intermediate (Scheme 6.7)

To gain more insight into the reaction pathway, I performed the reaction with quinoline **2.14a** (0.065 g, 0.5 mmol, 1.0 equiv.), HE (0.279 g, 1.1 mmol, 2.2 equiv), and **6.21b** (20 mol%) were taken in a microwave tube. Then sealed with screw-cap, the resulting solution was heated at 70 °C for 20 mins under microwave irradiation (50 W). As expected tetrahydroquinoline **2.12** obtained in 96% yield (0.063 g). For the subsequent step the reaction was conducted with the formed **2.12** (0.062 g, 0.47 mmol), and benzaldehyde **3.18a** (0.050 g, 0.47 mmol, 1.0 equiv), HE (0.132 g, 0.52 mmol, 1.1 equiv), and **6.21b** (20 mol%) were taken in a microwave tube. Then sealed with screw-cap, the resulting solution was heated at 70 °C for 20 mins under microwave irradiation (50 W), the desired product **3.20a** was obtained in 87% yield (Scheme S17). The study suggests that tetrahydroquinoline **2.12** is the intermediate in the alkylation process.

iii) Electronic effect for the 1st step (Scheme 6.8)

To know the electronic effect in the 1st step, I performed **2.14c** (0.040 g, 0.25 mmol, 0.5 equiv.), **2.14e** (0.041 g, 0.25 mmol, 0.5 equiv.), and HE (0.279 g, 1.1 mmol, 2.2 equiv.), and **6.21b** (20 mol%) were taken in a microwave tube and then sealed with screw-cap. The resulting solution was heated at 70 °C for 20 mins under microwave irradiation (50 W). As expected I obtained corresponding hydrogenated product **5.18f** (48%) and **5.18g** (42%), respectively. Since a comparable yield was obtained in both the case, one can infer that there is no considerable electronic effect in the the 1st step i.e., quinoline reduction step.

iv) Electronic effect for the 2nd step (Scheme 6.9, 6.10)

Reaction conditions: The 6-methoxy-1,2,3,4-tetrahydroquinoline **5.18f** (0.041 g, 0.25 mmol, 0.5 equiv), 6-chloro-1,2,3,4-tetrahydroquinoline **5.18g** (0.042 g, 0.25 mmol, 0.5 equiv), aldehyde **3.18a** (0.053 g, 0.5 mmol, 1.0 equiv.), HE (0.140 g, 0.55 mmol, 1.1 equiv), and **6.21b** (20 mol%) were taken in a microwave tube. Then sealed with screw-cap, the resulting solution was heated at 70 °C for 20 mins under microwave irradiation (50 W), the product **5.6f** and **5.6g** was obtained in 43% yield (0.054 g) and 25% yield (0.032 g) respectively.

Reaction conditions: The tetrahydroquinoline **2.12** (0.067 g, 0.5 mmol, 1.0 equiv), 4-methoxybenzaldehyde **3.18c** (0.034 g, 0.25 mmol, 0.5 equiv.), 4-fluorobenzaldehyde **3.18e** (0.031 g, 0.25 mmol, 0.5 equiv), HE (0.140 g, 0.55 mmol, 1.1 equiv), and **6.21b** (20 mol%) were taken in a microwave tube. Then sealed with screw-cap, the resulting solution was heated at 70 °C for 20 mins under microwave irradiation (50W), the product **3.20c** and **3.20e** was obtained in 28% yield (0.035 g) and 44% yield (0.053 g), respectively.

v) Eyring Studies (Scheme 6.11)

Reaction conditions: An oven dried reaction tube, **2.12** (0.067 g, 0.5 mmol, 1.0 equiv.), benzaldehyde **3.18a** (0.053 g, 0.5 mmol, 1.0 equiv.), HE (0.140 g, 0.55 mmol, 1.1 equiv.), and **6.21b** (0.025 mL) were taken in a microwave tube. Then sealed with screw-cap, the resulting solution was heated under microwave irradiation (50 W) at respective temperature for the specified times. Afterward, the reaction mixture was poured into a round bottom flask. The solvent was evaporated under reduced pressure, and the residue was purified by column

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chromatography on a silica column using EtOAc/Petroleum ether as the eluent. The isolated yields of the products at different time intervals have been calculated. Then the initial rates of product formation were obtained from the plot of the product concentration vs time.

Temp	1/T	k	ln(k/T)
323 K (50 °C)	0.003095	0.493	-6.48
333 K (60 °C)	0.003003	0.710	-6.15
343 K (70 °C)	0.002915	1.008	-5.83
353 K (80 °C)	0.002832	1.333	-5.58

vi) Deuterium-labelling experiment (Scheme 6.13, 6.14, 6.15)

Reaction conditions: In a microwave reaction tube (15 mL), 3-methyl quinoline **2.14g** (0.072 g, 0.5 mmol, 1.0 equiv.), **3.18a** (0.053 g, 0.5 mmol, 1.0 equiv.) HE (0.406 g, 1.6 mmol, 3.2 equiv.), **6.21b** (20 mol%), and D_2O (0.3 mmol, 0.6 equiv.) were charged and sealed with screw-cap. The reaction mixture was heated at 70 °C for 20 mins under microwave irradiation (50 W). After completion of the reaction, the microwave tube was brought to room temperature, and $CHCl_3$ (2 ml) was added to it, then all the volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.80) (0.082 g, 69%).

^{1}H NMR spectrum of deuterated 1-benzyl-3-methyl-1,2,3,4-tetrahydroquinoline (5.6c + D-5.6c):

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 – 7.29 (m, 4H, **5.6c + D-5.6c**), 7.26 – 7.21 (m, 6H, **5.6c + D-5.6c**), 6.97 – 6.95 (m, 4H, **5.6c + D-5.6c**), 6.57 (t, J = 7.3 Hz, 2H, **5.6c + D-5.6c**), 6.50 (d, J = 8.5 Hz, 2H, **5.6c + D-5.6c**), 4.47 (s, 4H, **5.6c + D-5.6c**), 3.28 – 3.26 (m, 2H, **5.6c + D-5.6c**), 3.04 – 3.01 (m, 2H, **5.6c + D-5.6c**), 2.82 – 2.79 (m, 2H, **5.6c + D-5.6c**), 2.51 – 2.48 (m, 2H, **5.6c+ D-5.6c**), 2.20 – 2.14 (m, 1H, **5c**) 1.04 (s, 6H, **5.6c + D-5.6c**). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.3, 139.2, 129.3, 129.1, 128.7, 127.3, 127.2, 126.9, 126.7, 122.0, 116.0, 110.9, 57.0, 56.9, 55.3, 36.6, 36.5, 27.5, 27.0 (t, J=19.9 Hz), 19.2, 19.1.

Reaction conditions: In a microwave reaction tube (15 mL), 3-phenyl quinoline (0.102 g, 0.5 mmol, 1.0 equiv.), HE (0.279 g, 1.1 mmol, 2.2 equiv.), **6.21b** (20 mol%), and D_2O (0.006 g, 0.3 mmol, 0.6 equiv.) were charged, and sealed with screw-cap. The reaction mixture was heated at 70 °C for 20 mins under microwave irradiation (50 W). After completion of the reaction, the microwave tube was brought to room temperature, and $CHCl_3$ (2 ml) was added to it, then all the volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.80) (0.095 g, 84%).

^{1}H NMR spectrum of deuterated 3-phenyl-1,2,3,4-tetrahydroquinoline (6.22u + D-6.22u):

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^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.32 (m, 4H, **6.22u** + **D-6.22u**), 7.24 (d, J = 7.1 Hz, 6H, **6.22u** + **D-6.22u**), 7.01 – 7.00 (m, 4H, **6.22u** + **D-6.22u**), 6.64 (t, J = 7.3 Hz, 2H, **6.22u** + **D-6.22u**), 6.54 (d, J = 7.8 Hz, 2H, **6.22u** + **D-6.22u**), 4.01 (s, 2H, **6.22u** + **D-6.22u**), 3.46 – 3.44 (m, 2H, **6.22u** + **D-6.22u**), 3.35 – 3.31 (m, 2H, **6.22u** + **D-6.22u**), 3.16 – 3.12 (m, 1H, **6.22u**), 3.06 – 2.93 (m, 4H, **6.22u** + **D-6.22u**). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.2, 144.0, 129.7, 129.6, 128.7, 127.35, 127.34, 127.1, 127.0, 126.8, 121.5, 117.2, 114.2, 48.5, 38.8, 38.4 (t, J =20.1 Hz), 34.8, 34.7.

Reaction conditions: In a microwave reaction tube (15 mL), quinoline **2.14a** (0.065 g, 0.5 mmol, 1.0 equiv.), deuterated HE (0.406 g, 1.6 mmol, 3.2 equiv.), and **6.21b** (20 mol%) were charged, and sealed with screw-cap. The reaction mixture was heated at 70 °C for 20 mins under microwave irradiation (50 W). After completion of the reaction, the microwave tube was brought to room temperature, and $CHCl_3$ (2 ml) was added to it, then all the volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.80) (**3.20a**, 0.069 g, 62%). No **D-3.20a** product was obtained.

^{1}H NMR of **3.20a** (400 MHz, $CDCl_3$): δ 7.31 – 7.20 (m, 5H), 6.97 – 6.94 (m, 2H), 6.56 (t, J = 7.3 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 4.46 (s, 2H), 3.37 – 3.34 (m, 2H), 2.80 (t, J = 6.2 Hz, 2H), 2.03 (p, 6.2 Hz, 2H).
1-deuterated HE was prepared.[47] The solution of Hantzsch ester (0.25 g, 0.01 mol) in 2 mL of CD_3OD was stirred under argon atmosphere overnight. After evaporation of the volatiles, pale green solid was obtained. Yield. 0.245 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, J = 7.2 Hz, 4H), 3.26 (s, 2H), 2.19 (s, 6H), 1.28 (t, J = 6.8 Hz, 6H).

Reaction conditions: In a microwave reaction tube (15 mL), quinoline **2.14a** (0.065 g, 0.5 mmol, 1.0 equiv.), HE (0.404 g, 1.6 mmol, 3.2 equiv.), deuterated **6.21b** (20 mol%), and D_2O (0.3 mmol, 0.6 equiv.) were charged and sealed with screw-cap. The reaction mixture was heated at 70 °C for 20 mins under microwave irradiation (50 W). After completion of the reaction, the microwave tube was brought to room temperature, and $CHCl_3$ (2 mL) was added to it, then all the volatiles were removed under reduced pressure. The crude compound was purified through silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 50:1, R_f = 0.80) (0.075 g, 67%). The 80% deuterium atom was incorporated at the C3 position of **D-3.20a**.

The deuterated **6.21b** was prepared by stirring the solution of **6.21b** in D_2O, followed by the removing the volatiles, obtained the viscous liquid.

G. Scaling up, separation and isolation of product and recovered HE in the *N*-alkylation process (Scheme6.18)

Reaction condition A: In a microwave tube, a mixture of quinoline **2.14a** (0.200 g, 1.55 mmol, 1.0 equiv.), benzaldehyde **3.18a** (0.164 g, 1.55 mmol, 1.0 equiv.), HE (1.270 g, 5.0 mmol, 3.2

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equiv.), and **6.21b** (20 mol%) were taken. Then sealed with screw-cap, the resulting solution was heated at 70 °C for 20 min under microwave irradiation (50 W). After completion of the reaction, the reaction tube was brought to room temperature.

Reaction condition B: In a microwave tube, a mixture of quinoline (0.200 g, 1.55 mmol, 1.0 equiv.), HE (0.863 g, 3.4 mmol, 2.2 equiv.), and **6.21b** (20 mol%) were taken. Then sealed with screw-cap, the resulting solution was heated at 70 °C for 20 min under microwave irradiation (50 W). After completion of the reaction, the reaction tube was brought to room temperature.

Step-1: In the crude reaction mixture, diethyl ether (10 mL) was added and sonicated for 5 mins. After that two distinct layers was formed where at upper layer consists of (**3.20a** or **2.12**, OHE, unreacted OHE and diethyl ether), whereas in the lower layer, **6.21b** was lying, then we separated out both the layer.

Step-2: The diethyl ether solution was removed under reduced pressure, added pet-ether (5 mL) and kept it in the refrigerator for 12 h. After 12 h, there are two distinct layers were formed. Solid residue contains OHE and unreacted HE, where as in the filtrate part, only **3.20a** or **2.12** along with pet ether solvent.

Step-3: Remove pet ether from filtrate part under reduced pressure, the desired product **3.20a** or **2.12** was obtained in 82% yield and 85% yield respectively from the pet ether solution.

Step-4: Lastly, this solid residue was easily converted into HE (1.14 g, 91% yield) by treating glacial acetic acid and sodium cyanoborohydride at room temperature for **3.20a**. likewise, HE (0.73 g, 93% yield) was recovered for **2.12**.

H. Alternative thermal conditions for the *N*-alkylated product (Scheme 6.19)

Reaction condition: In a reaction tube, a mixture of quinoline **2.14a** (0.5 g, 3.87 mmol), benzaldehyde **3.18a** (0.41 g, 3.87 mmol), HE (3.15 g, 12.4 mmol), and **6.21b** (1.93 mmol, 50 mol%) were taken. This was sealed with screw-cap and the resulting solution was placed in a preheated oil bath at 70 °C for 12 h. After completion of the reaction, $CHCl_3$ (12 mL) was added to the reaction mixture and transferred the reaction mixture into round bottom flask. All the volatiles were then removed under reduced pressure. The crude compound was purified through silica gel column chromatography. Isolated yield: 0.76 g, 89%.

This thermal condition is also tested with complex molecules settings using 0.5 mmol of precursor **3.23e** and **3.23h**, respectively, the product **5.8e** and **5.8h** were obtained in 78%, and 69% yield, respectively.

I. Recyclability and reusability of the catalytic system

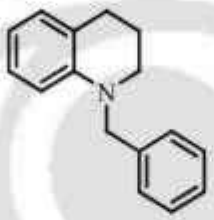
To investigate the reusability of the catalyst, quinoline **2.14a** (0.5 mmol), aldehyde **3.18a** (0.5 mmol), HE (1.6 mmol) and **6.21b** (20 mol%) were taken in a microwave tube and kept the reaction mixture under microwave irradiation (50 W) for 20 minutes at 70 °C. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with diethyl ether, and shaken well. Two layers were generated, the upper layer of diethyl ether contains product

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3.20a and OHE, which was purified through silica gel column chromatography as mentioned above (90% yield of **3.20a** from 1st cycle). The lower layer contains **6.21b** that was directly used for the next cycle by adding substrate **2.14a** (0.5 mmol), **3.18a** (0.5 mmol) and HE (1.6 mmol) under the same reaction conditions. This process was repeated five times without any significant loss in catalytic activity. As depicted in Figure 6.7, the catalyst **6.21b** could be reused five times for the synthesis of **3.20a** with a slight loss of activity, indicating that the catalytic system exhibits good recyclability. Further, catalyst **6.21b** was able characterize spectroscopically by ^{1}H NMR after 3 cycles.

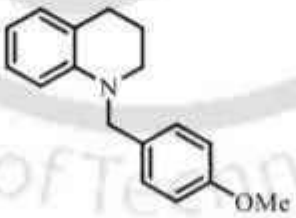
6.7. Analytical data of the products

1-benzyl-1, 2, 3, 4-tetrahydroquinoline (3.20a)



By following the **GP-2**, the title compound **3.20a** was isolated as light-yellow oil (0.098 g, 88%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.20 (m, 5H), 6.97 – 6.94 (m, 2H), 6.56 (t, J = 7.3 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 4.46 (s, 2H), 3.37 – 3.34 (m, 2H), 2.80 (t, J = 6.2 Hz, 2H), 2.03 (p, 6.2 Hz, 2H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.7, 139.1, 129.1, 128.7, 127.3, 126.8, 126.7, 122.3, 115.9, 111.1, 55.3, 50.0, 28.3, 22.5. Spectral data is in accordance to the reported literature. [16]

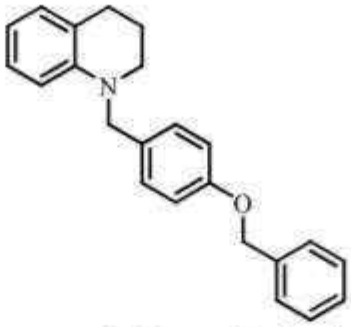
1-(4-methoxybenzyl)-1, 2, 3, 4-tetrahydroquinoline (3.20c)



By following the **GP-2**, the title compound **3.20c** was isolated as colourless oil (0.104 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 6.8 Hz, 2H), 7.03 – 7.00 (m, 2H), 6.86 (d, J = 7.6 Hz, 2H), 6.62 – 6.57 (m, 2H), 4.45 (s, 2H), 3.82 (s, 3H), 3.37 (t, J = 5.7 Hz, 2H), 2.85 (t, J = 6.3 Hz, 2H), 2.06 – 2.01 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.7, 145.8, 131.0, 129.1, 127.9, 127.3, 122.4, 115.9, 114.1, 111.1, 55.4, 54.7, 49.8, 28.4, 22.5. Spectral data is in accordance to the reported literature. [16]

1-(4-(benzyloxy) benzyl)-1,2,3,4-tetrahydroquinoline (5.5c)

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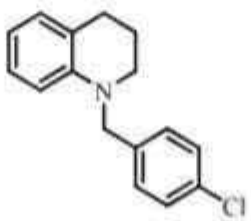
By following the **GP-2**, the title compound **5.5c** was isolated as yellow oil (0.130 g, 79%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40. – 7.28 (m, 5H), 7.16 – 7.14 (m, 2H), 6.97 – 6.89 (m, 4H), 6.57 – 6.50 (m, 2H), 4.99 (s, 2H), 4.37 (s, 2H), 3.30 – 3.28 (m, 2H), 2.77 (t, J = 6.3 Hz, 2H), 1.98 – 1.93 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 157.8, 145.7, 137.2, 131.2, 129.1, 128.6, 128.0, 127.9, 127.5, 127.2, 122.3, 115.8, 115.0, 111.1, 70.1, 54.6, 49.7, 28.3, 22.4. Spectral data is in accordance to the reported literature. [27a]

1-(4-fluorobenzyl)-1, 2, 3, 4-tetrahydroquinoline (3.20e)



By following the **GP-2**, the title compound **3.20e** was isolated as colourless oil (0.111 g, 92%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 2H), 7.01 – 6.96 (m, 4H), 6.59 (t, J = 7.3 Hz, 1H), 6.48 (d, J = 8.6 Hz, 1H), 4.44 (s, 2H), 3.34 (t, J = 5.6 Hz 2H), 2.81 (t, J = 6.3 Hz, 2H), 2.01 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 162.9 – 161.0 (C-F, $^1J_{C\text{-}F}$ = 244.3 Hz), 145.6, 134.6 (C-F, $^4J_{C\text{-}F}$ = 3 Hz), 129.2, 128.2 (C-F, $^3J_{C\text{-}F}$ = 7.9 Hz), 127.3, 122.5, 116.2, 115.6 - 115.4 (C-F, $^2J_{C\text{-}F}$ = 21.4 Hz, 111.1, 54.8, 50.0, 28.3, 22.5. ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$): δ -116.45. Spectral data is in accordance to the reported literature. [27b]

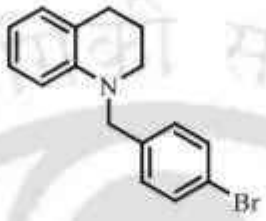
1-(4-chlorobenzyl)-1,2,3,4-tetrahydroquinoline (5.5e)



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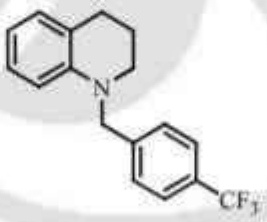
By following the **GP-2**, the title compound **5.5e** was isolated as colourless oil (0.116 g, 90%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 6.99 (t, J = 8.2 Hz, 2H), 6.60 (d, J = 7.3 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.44 (s, 2H), 3.36 (t, J = 5.4 Hz, 2H), 2.83 (t, J = 6.3 Hz, 2H), 2.05 – 2.01 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.5, 137.6, 132.5, 129.2, 128.8, 128.1, 127.3, 122.5, 116.3, 111.1, 54.8, 50.1, 28.3, 22.5. Spectral data is in accordance to the reported literature. [27e]

1-(4-bromobenzyl)-1, 2, 3, 4-tetrahydroquinoline (5.5f)



By following the **GP-2**, the title compound **5.5f** was isolated as light-yellow oil (0.133 g, 88%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 – 7.42 (m, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.97 (t, J = 8.1 Hz, 2H), 6.59 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 8.1 Hz, 1H), 4.41 (s, 2H), 3.34 (t, J = 5.7 Hz, 2H), 2.82 (t, J = 6.3 Hz, 2H), 2.01 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.5, 138.2, 131.8, 129.2, 128.5, 127.3, 122.5, 120.6, 116.3, 111.1, 55.0, 50.1, 28.3, 22.5. Spectral data is in accordance to the reported literature. [16]

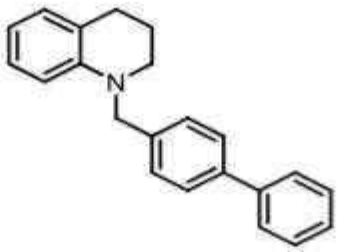
1-(4-(trifluoromethyl) benzyl)-1,2,3,4-tetrahydroquinoline (5.5g)



By following the **GP-2**, the title compound **5.5g** was isolated as colourless oil (0.135 g, 93%) solid using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.01 – 6.92 (m, 2H), 6.59 (t, J = 7.3 Hz, 1H), 6.41 (d, J = 8.2 Hz, 1H), 4.49 (s, 2H), 3.37 – 3.32 (m, 2H), 2.82 (t, J = 6.3 Hz, 2H), 2.01 (p, J = 6.1 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.3, 143.5, 129.2, 127.3, 126.9, 125.6 (q, J = 3.7 Hz), 122.5, 116.4, 111.0, 55.1, 50.2, 28.2, 22.5. ^{19}F NMR (565 MHz, $CDCl_3$): δ -62.28. Spectral data is in accordance to the reported literature. [27b]

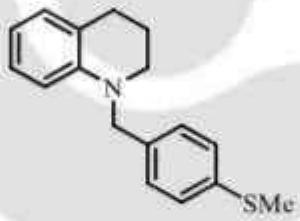
1-([1,1'-biphenyl]-4-ylmethyl)-1,2,3,4-tetrahydroquinolines (5.5h)

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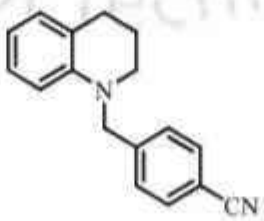
By following the **GP-2**, the title compound **5.5h** was isolated as yellow oil (0.126 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 – 7.56 (m, 4H), 7.47 – 7.43 (m, 2H), 7.36 – 7.35 (m, 3H), 7.02 – 7.01 (m, 2H), 6.63 – 6.56 (m, 2H), 4.54 (s, 2H), 3.42 – 3.41 (m, 2H), 2.87 – 2.85 (m, 2H), 2.08 – 2.06 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.7, 141.1, 139.9, 138.2, 129.2, 128.9, 127.5, 127.35, 127.28, 127.2, 122.4, 116.0, 111.1, 55.1, 50.1, 28.4, 22.5. Spectral data is in accordance to the reported literature. [27b]

1-(4-(methylthio) benzyl)-1,2,3,4-tetrahydroquinoline (5.5i)



By following the **GP-2**, the title compound **5.5i** was isolated as yellow oil (0.106 g, 79%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (q, J = 8.4 Hz, 4H), 6.95 (t, J = 6.6 Hz, 2H), 6.56 (t, J = 7.3 Hz, 1H), 6.48 (d, J = 8.5 Hz, 1H), 4.41 (s, 2H), 3.34 – 3.31 (m, 2H), 2.80 (t, J = 6.3 Hz, 2H), 2.44 (s, 3H), 2.01 – 1.96 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.6, 136.6, 136.1, 129.1, 127.3, 127.27, 127.25, 122.4, 116.0, 111.1, 54.9, 49.9, 28.3, 22.5, 16.3. Spectral data is in accordance to the reported literature. [27b]

4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzonitrile (5.5j)

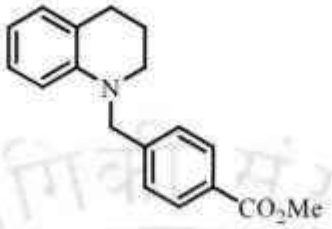


By following the **GP-2**, The title compound **5.5j** was isolated as white solid (0.117 g, 94%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). M.p. 62-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.02 – 6.96 (m, 2H), 6.62 (t, J = 7.2 Hz, 1H), 6.37 (d, J = 8.2 Hz, 1H), 4.52 (s, 2H), 3.38

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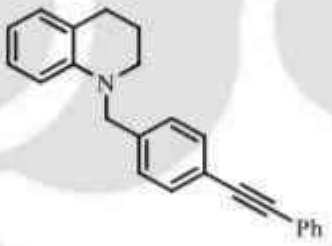
(t, J = 5.6 Hz, 2H), 2.85 (t, J = 6.0 Hz, 2H), 2.05 (p, J = 6.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 145.1, 132.6, 129.3, 127.3, 127.3, 122.6, 119.0, 116.7, 111.0, 110.8, 55.4, 50.4, 28.2, 22.5. IR (KBr, selected band): 2227.78 cm^{-1}. Spectral data is in accordance to the reported literature. [27b]

Methyl 4-((3, 4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.5k)



By following the **GP-2**, the title compound **5.5k** was isolated as colourless oil (0.125 g, 89%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^1H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.60 (t, J = 7.2 Hz, 1H), 6.43 (d, J = 8.2 Hz, 1H), 4.52 (s, 2H), 3.91 (s, 3H), 3.38 (t, J = 5.7 Hz, 2H), 2.84 (t, J = 6.3 Hz, 2H), 2.04 (p, J = 6.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.1, 145.4, 144.8, 130.1, 129.2, 129.0, 127.3, 126.6, 122.5, 116.4, 111.1, 55.4, 52.2, 50.3, 28.3, 22.5. IR (KBr, selected band): 1722.6 cm^{-1}. Spectral data is in accordance to the reported literature. [27b]

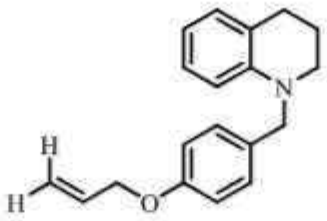
1-(4-(phenylethynyl) benzyl)-1,2,3,4-tetrahydroquinoline (5.5l)



By following the **GP-2**, the title compound **5.5l** was isolated as yellow oil (0.131 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^1H NMR (600 MHz, $CDCl_3$): δ 7.52 – 7.50 (m, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.33 – 7.30 (m, 3H), 7.23 (d, J = 7.8 Hz, 2H), 6.98 – 6.95 (m, 2H), 6.59 – 6.57 (m, 1H), 6.45 (d, J = 8.0 Hz, 1H), 4.55 (s, 2H), 3.35 – 3.33 (m, 2H), 2.87 (t, J = 6.2 Hz, 2H), 2.06 (p, J = 6.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 145.6, 139.6, 132.0, 131.7, 129.2, 128.4, 128.3, 127.3, 126.7, 123.5, 122.4, 121.8, 116.2, 111.1, 89.5, 89.2, 55.3, 50.1, 28.3, 22.5. IR (KBr, selected band): 2217.5 cm^{-1}. Spectral data is in accordance to the reported literature. [27b]

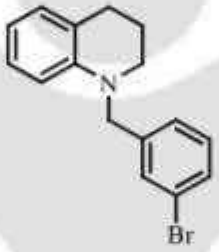
1-(4-(allyloxy) benzyl)-1, 2, 3, 4-tetrahydroquinoline (5.5m)

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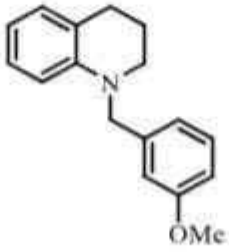
By following the **GP-2**, the title compound **5.5m** was isolated as colourless oil (0.105 g, 75%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, J = 8.3 Hz, 2H), 7.00 – 6.97 (m, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.60 – 6.54 (m, 2H), 6.10 – 6.03 (m, 1H), 5.42 (d, J = 17.2 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 4.53 (d, J = 5.2 Hz, 2H), 4.42 (s, 2H), 3.37 – 3.32 (m, 2H), 2.82 (t, J = 6.2 Hz, 2H), 2.01 (p, J = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 157.7, 145.8, 133.6, 131.2, 129.1, 127.9, 127.3, 122.4, 117.7, 115.9, 115.0, 111.2, 69.0, 54.7, 49.8, 28.4, 22.5. Spectral data is in accordance to the reported literature. [27b]

1-(3-bromobenzyl)-1,2,3,4-tetrahydroquinoline (5.5n)



By following the **GP-2**, The title compound **5.5n** was isolated as yellow oil (0.131 g, 87%,) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.34 (d, J = 7.2 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.98 – 6.94 (m, 2H), 6.58 (t, J = 7.4 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.40 (s, 2H), 3.34 – 3.31 (m, 2H), 2.80 (t, J = 6.2 Hz, 2H), 2.00 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.4, 141.8, 130.3, 130.0, 129.6, 129.2, 127.3, 125.2, 122.9, 122.5, 116.3, 111.1, 55.1, 50.2, 28.4, 22.5. Spectral data is in accordance to the reported literature. [27b]

1-(3-methoxybenzyl)-1, 2, 3, 4-tetrahydroquinoline (5.5o)

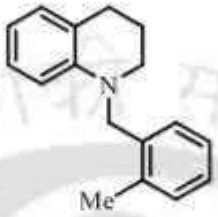


By following the **GP-2**, the title compound **5.5o** was isolated as light-yellow oil (0.106 g, 84 %) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75).

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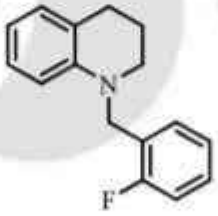
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, J = 7.9 Hz, 1H), 6.97 – 6.94 (m, 2H), 6.87 – 6.85 (m, 1H), 6.82 (s, 1H), 6.78 – 6.76 (m, 1H), 6.58 – 6.55 (m, 1H), 6.50 – 6.48 (m, 1H), 4.43 (s, 2H), 3.76 (s, 3H), 3.39 – 3.32 (m, 2H), 2.80 (t, J = 6.3 Hz, 2H), 2.00 (p, J = 6.1 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 160.1, 145.7, 141.0, 129.7, 129.1, 127.3, 122.4, 119.0, 116.0, 112.4, 112.0, 111.2, 55.4, 55.3, 50.1, 28.3, 22.5. Spectral data is in accordance to the reported literature. [27b]

1-(2-methylbenzyl)-1,2,3,4-tetrahydroquinoline (5.5p)



By following the **GP-2**, the title compound **5.5p** was isolated as light-yellow oil (0.096 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 – 7.12 (m, 4H), 7.01 – 6.95 (m, 2H), 6.59 (t, J = 6.6 Hz, 1H), 6.39 (d, J = 8.2 Hz, 1H), 4.41 (s, 2H), 3.38 – 3.35 (m, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.34 (s, 3H), 2.08 – 2.02 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.8, 136.1, 135.7, 130.4, 129.0, 127.3, 126.7, 126.21, 126.15, 122.4, 115.9, 111.0, 53.6, 49.9, 28.4, 22.6, 19.1. Spectral data is in accordance to the reported literature. [16]

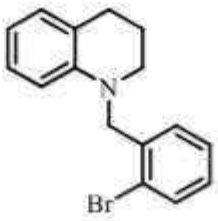
11-(2-fluorobenzyl)-1,2,3,4-tetrahydroquinoline (5.5q)



By following the **GP-2**, the title compound **5.5q** was isolated as white solid (0.110 g, 91%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). M.p. 61-63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.19 (m, 2H), 7.07 – 7.02 (m, 2H), 6.99 – 6.95 (m, 2H), 6.60 – 6.56 (m, 1H), 6.46 (d, J = 8.5 Hz, 1H), 4.52 (s, 2H), 3.39 – 3.36 (m, 2H), 2.84 – 2.81 (m, 2H), 2.02 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 161.9, 160.3, 145.5, 129.2, 128.4, 128.4, 128.4, 127.4, 125.7, 125.6, 124.2, 124.2, 122.4, 116.2, 115.4, 115.3, 110.1, 50.1, 49.3, 49.3, 28.3, 22.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ -118.6. Spectral data is in accordance to the reported literature. [27b]

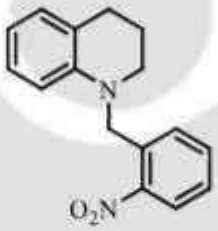
1-(2-bromobenzyl)-1,2,3,4-tetrahydroquinoline (5.5r)

TH-3765_196122031



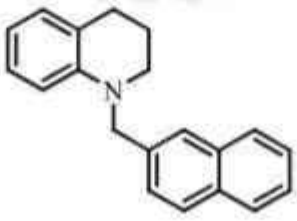
By following the **GP-2**, the title compound **5.5r** was isolated as yellow oil (0.125 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, J = 7.7 Hz, 1H), 7.22 – 7.21 (m, 2H), 7.12 – 7.09 (m, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.96 – 6.94 (m, 1H), 6.60 – 6.57 (m, 1H), 6.29 (d, J = 8.2 Hz, 1H), 4.46 (s, 2H), 3.41 – 3.39 (m, 2H), 2.85 (t, J = 6.3 Hz, 2H), 2.07 – 2.03 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.2, 137.1, 132.9, 129.1, 128.4, 127.8, 127.6, 127.4, 123.0, 122.2, 116.2, 110.9, 56.3, 50.3, 28.3, 22.6. Spectral data is in accordance to the reported literature. [27b]

1-(2-nitrobenzyl)-1, 2, 3, 4-tetrahydroquinoline (5.5s)



By following the **GP-2**, the title compound **5.5s** was isolated as red solid (0.126 g, 94%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). M.p. 120-122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, J = 7.6 Hz, 1H), 7.58 – 7.56 (m, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.63 (t, J = 7.2 Hz, 1H), 6.28 (d, J = 8.2 Hz, 1H), 4.86 (s, 2H), 3.44 – 3.38 (m, 2H), 2.88 (t, J = 6.3 Hz, 2H), 2.12 – 2.05 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 148.3, 145.1, 135.3, 134.0, 129.2, 128.6, 127.8, 127.4, 125.6, 122.5, 116.6, 110.8, 54.0, 50.3, 28.2, 22.5. Spectral data is in accordance to the reported literature. [27b]

1-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinoline (5.5t)

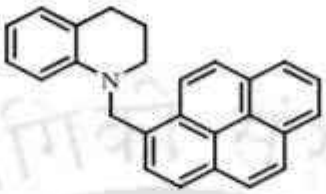


By following the **GP-2**, the title compound **5.5t** was isolated as white solid (0.112 g, 82%,) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). M.p. 100-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 – 7.98 (m, 1H), 7.91 – 7.89 (m, 1H), 7.79 – 7.77 – 7.75 (m, 1H), 7.55 – 7.50 (m, 2H), 7.41 (d, J = 5.5 Hz, 2H), 7.04 (d, J = 7.9 Hz,

TH-3765_196122031

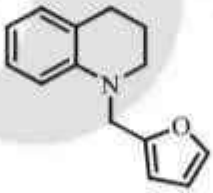
1H), 6.97 (t, J = 8.5 Hz, 1H), 6.61 – 6.57 (m, 1H), 6.46 (d, J = 8.2 Hz, 1H), 4.93 (s, 2H), 3.43 – 3.40 (m, 2H), 2.89 (t, J = 6.2 Hz, 2H), 2.10 – 2.04 (m, 2H). $^{113}C\{^1H\}$NMR (151 MHz, $CDCl_3$): δ 145.8, 134.0, 132.9, 131.4, 129.1, 129.0, 127.5, 127.4, 126.1, 125.81, 125.79, 123.7, 122.8, 122.5, 116.0, 111.1, 53.4, 49.8, 28.4, 22.6. Spectral data is in accordance to the reported literature. [16]

1-(pyren-1-ylmethyl)-1,2,3,4-tetrahydroquinoline (5.5u)



By following the **GP-2**, the title compound **5.5u** was isolated as light green solid (0.135 g, 78%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). M.p. 175-177 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 8.27 (d, J = 9.2 Hz, 1H), 8.21 – 8.18 (m, 2H), 8.15 (d, J = 9.2 Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H), 8.04 (s, 2H), 8.01 (t, J = 7.6 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 6.62 (t, J = 7.3 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 5.19 (s, 2H), 3.45 – 3.43 (m, 2H), 2.90 (t, J = 6.3 Hz, 2H), 2.08 (p, J = 6.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 146.0, 131.6, 130.9, 130.6, 129.2, 128.5, 127.7, 127.7, 127.4, 127.1, 126.1, 125.3, 125.3, 125.1, 125.0, 124.7, 122.8, 122.4, 116.2, 111.2, 53.7, 49.8, 28.4, 22.7. Spectral data is in accordance to the reported literature. [27e]

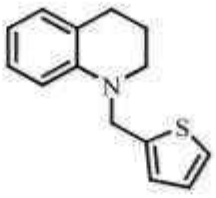
1-(furan-2-ylmethyl)-1,2,3,4-tetrahydroquinoline (5.5v)



By following the **GP-2**, the title compound **5.5v** was isolated as light-yellow oil (0.085 g, 80%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 1.2 Hz, 1H), 7.03 (t, J = 8.8 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 1H), 6.29 – 6.28 (m, 1H), 6.16 – 6.15 (m, 1H), 4.42 (s, 2H), 3.38 – 3.35 (m, 2H), 2.76 (t, J = 6.4 Hz, 2H), 2.01 – 1.95 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 152.5, 145.1, 141.9, 129.2, 127.1, 122.9, 116.4, 111.4, 110.3, 107.2, 49.7, 48.5, 28.2, 22.4. Spectral data is in accordance to the reported literature. [16]

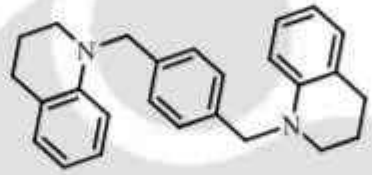
1-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroquinoline (5.5w)

TH-3765_196122031



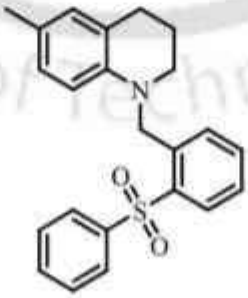
By following the **GP-2**, the title compound **5.5w** was isolated as light-yellow oil (0.086 g, 75%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.17 (m, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.00 – 6.95 (m, 3H), 6.72 (d, J = 8.2 Hz, 1H), 6.63 (t, J = 7.3 Hz, 1H), 4.64 (s, 2H), 3.39 – 3.36 (m, 2H), 2.79 (t, J = 6.3 Hz, 2H), 2.04 – 1.98 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.1, 142.6, 129.3, 127.2, 126.9, 124.8, 124.3, 123.0, 116.6, 111.6, 50.7, 49.6, 28.2, 22.4. Spectral data is in accordance to the reported literature. [16]

1,4-bis((3,4-dihydroquinolin-1(2H)-yl) methyl) benzene (5.5x)



By following the **GP-2** with 0.25 mmol of terephthalaldehyde, **3.18u** and HE (6.5 equiv.), the title compound **5.5x** was isolated as white solid (0.073 g, 79%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). M.p. 139-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (s, 4H), 6.98 – 6.95 (m, 4H), 6.57 (t, J = 7.2 Hz, 2H), 6.50 (d, J = 8.6 Hz, 2H), 4.45 (s, 4H), 3.37 – 3.34 (m, 4H), 2.81 (t, J = 6.2 Hz, 4H), 2.03 – 1.97 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.7, 137.6, 129.1, 127.3, 127.0, 122.4, 116.0, 111.1, 55.1, 50.0, 28.4, 22.5. Spectral data is in accordance to the reported literature. [27b]

6-methyl-1-(2-(phenylsulfonyl) benzyl)-1,2,3,4-tetrahydroquinoline (5.5z)

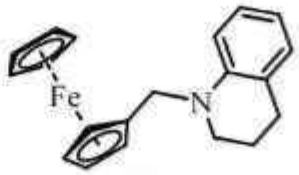


By following the **GP-2**, the title compound **5.5z** was isolated as white solid (0.153 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). M.p. 175-177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (dd, J = 7.6, 1.6 Hz, 1H), 7.91 – 7.89 (m, 2H), 7.64 – 7.60 (m, 1H), 7.55 – 7.41 (m, 5H), 6.76 (s, 1H), 6.47 – 6.44 (m, 1H), 5.44 (d, J = 8.2 Hz, 1H), 4.57 (s, 2H), 3.28 – 3.25 (m, 2H), 2.76 (t, J = 6.3 Hz, 2H), 2.13 (s, 3H), 2.01

TH-3765_196122031

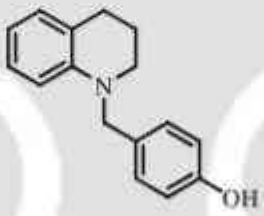
– 1.96 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 142.6, 141.2, 139.0, 137.8, 134.3, 133.4, 130.0, 129.9, 129.4, 128.0, 127.8, 127.5, 127.4, 125.3, 122.2, 110.5, 53.2, 50.5, 28.1, 22.6, 20.2. Spectral data is in accordance to the reported literature. [27b]

Cyclopenta-2,4-dien-1-yl(2-((3,4-dihydroquinolin-1(2H)-yl) methyl) cyclopenta-2,4-dien-1-yl) iron (5.5y)



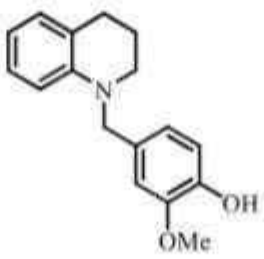
By following the **GP-2**, the title compound **5.5z** was isolated as light-yellow oil (0.103 g, 62%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^1H NMR (600 MHz, $CDCl_3$): δ 7.04 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.3 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.55 (t, J = 7.2 Hz, 1H), 4.22 (s, 2H), 4.20 (t, J = 1.9 Hz, 2H), 4.16 (s, 5H), 4.08 (t, J = 1.9 Hz, 2H), 3.27 – 3.25 (m, 2H), 2.71 (t, J = 6.4 Hz, 2H), 1.94 – 1.90 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 145.5, 129.3, 127.0, 122.7, 115.9, 111.4, 69.1, 68.7, 67.9, 50.7, 49.0, 28.3, 22.3. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{22}FeN$ 332.1097; found: 332.1057.

4-((3, 4-dihydroquinolin-1(2H)-yl) methyl) phenol (6.24aa)



By following the **GP-2**, the title compound **6.24aa** was isolated as light-yellow oil (0.104 g, 86%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.52). ^1H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 8.3 Hz, 2H), 7.01 – 6.98 (m, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.60 – 6.54 (m, 2H), 4.84 (brs, 1H), 4.41 (s, 2H), 3.35 – 3.33 (m, 2H), 2.82 (t, J = 6.3 Hz, 2H), 2.03 – 1.98 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 154.5, 145.8, 131.1, 129.1, 128.1, 127.3, 122.4, 115.9, 115.5, 111.2, 54.7, 49.8, 28.4, 22.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{18}NO$ 240.1383; found 240.1383.

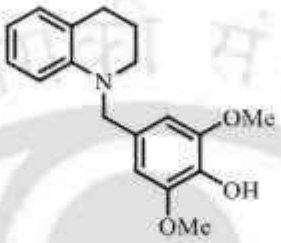
4-((3, 4-dihydroquinolin-1(2H)-yl) methyl)-2-methoxyphenol (6.24ab)



TH-3765_196122031

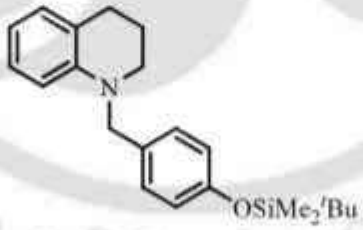
By following the **GP-2**, the title compound **6.24ab** was isolated as light-yellow oil (0.112 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.48). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 – 6.97 (m, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6.79 – 6.76 (m, 2H), 6.60 – 6.56 (m, 2H), 5.53 (brs, 1H), 4.39 (s, 2H), 3.84 (s, 3H), 3.32 (t, J = 5.7 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.02 – 1.97 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.9, 145.9, 144.6, 131.0, 129.2, 127.3, 122.5, 119.5, 116.1, 114.5, 111.3, 109.3, 56.0, 55.2, 49.8, 28.4, 22.5. HRMS (ESI) *m/z*: [M+H]$^+$ calculated for $C_{17}H_{20}NO_2$ 270.1489; found 270.1490.

4-((3, 4-dihydroquinolin-1(2H)-yl) methyl)-2, 6-dimethoxyphenol (6.24ac)



By following the **GP-2**, the title compound **6.24ac** was isolated as light-yellow oil (0.121 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 – 6.97 (m, 2H), 6.60 – 6.56 (m, 2H), 6.51 (s, 2H), 5.43 (brs, 1H), 4.38 (s, 2H), 3.84 (s, 6H), 3.31 (t, J = 5.7 Hz, 2H), 2.81 (t, J = 6.3 Hz, 2H), 2.00 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 147.4, 146.0, 133.6, 130.3, 129.2, 127.3, 122.6, 116.2, 111.4, 103.3, 56.4, 55.7, 49.8, 28.3, 22.6. HRMS (ESI) *m/z*: [M+H]$^+$ calculated for $C_{18}H_{22}NO_3$ 300.1595; found 300.1608.

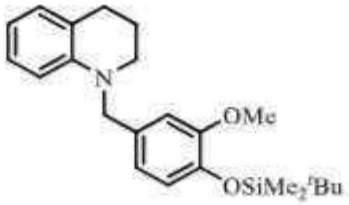
1-(4-((*tert*-butyldimethylsilyl) oxy) benzyl)-1, 2, 3, 4-tetrahydroquinoline (6.24ad)



By following the **GP-2**, the title compound **6.24ad** was isolated as colourless oil (0.152 g, 86%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 8.6 Hz, 2H), 7.01 – 6.97 (m, 2H), 6.80 – 6.78 (m, 2H), 6.60 – 6.54 (m, 2H), 4.41 (s, 2H), 3.34 (t, J = 5.7 Hz, 2H), 2.82 (t, J = 6.3 Hz, 2H), 2.04 – 1.98 (m, 2H), 0.99 (s, 9H), 0.20 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.6, 145.8, 131.5, 129.1, 127.8, 127.3, 122.4, 120.2, 115.9, 111.2, 54.8, 49.8, 28.4, 25.8, 22.5, 18.3, -4.3. HRMS (ESI) *m/z*: [M+H]$^+$ calculated for $C_{22}H_{32}NOSi$: 354.2248; found: 354.2248.

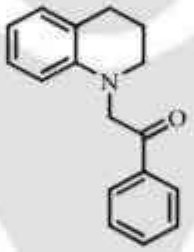
1-(4-((*tert*-butyldimethylsilyl) oxy)-3-methoxybenzyl)-1, 2, 3, 4-tetrahydroquinoline (6.24ae)

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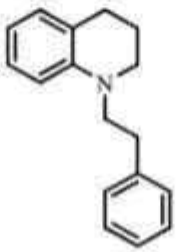
By following the **GP-2**, The title compound **6.24ae** was isolated as colourless oil (0.157 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.65). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 – 6.98 (m, 2H), 6.81 – 6.78 (m, 2H), 6.74 – 6.72 (m, 1H), 6.61 – 6.57 (m, 2H), 4.41 (s, 2H), 3.77 (s, 3H), 3.35 – 3.32 (m, 2H), 2.83 (t, J = 6.3 Hz, 2H), 2.04 – 1.98 (m, 2H), 1.01 (s, 9H), 0.17 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 151.2, 146.0, 143.9, 132.4, 129.1, 127.2, 122.5, 120.9, 119.0, 116.0, 111.3, 110.7, 55.6, 55.2, 49.7, 28.4, 25.9, 22.5, 18.6, -4.45. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{34}NO_2Si$ 384.2354; found 384.2353.

2-(3,4-dihydroquinolin-1(2H)-yl)-1-phenylethan-1-one (5.5aa)



By following the **GP-2**, the title compound **5.5aa** was isolated a light-yellow oil (0.078 g, 62%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.52). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 8.1 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 6.97 – 6.92 (m, 2H), 6.58 (t, J = 7.3 Hz, 1H), 6.29 (d, J = 8.2 Hz, 1H), 4.67 (s, 2H), 3.38 – 3.36 (m, 2H), 2.81 (t, J = 6.2 Hz, 2H), 2.01 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 196.6, 145.1, 135.6, 133.5, 129.3, 128.8, 127.9, 127.1, 122.8, 116.6, 110.3, 57.7, 50.6, 28.1, 22.4. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{18}NO$:252.1383; found: 252.1381.

1-phenethyl-1,2,3,4-tetrahydroquinoline (5.5ab)

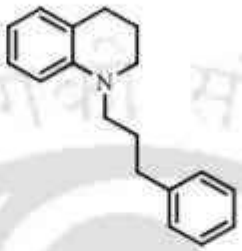


By following the **GP-2**, the title compound **5.5ab** was isolated as colourless oil (0.080 g, 67%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80).

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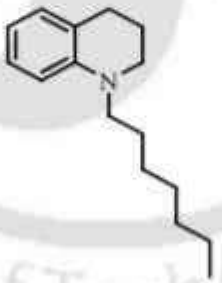
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.31 (m, 2H), 7.24 – 7.22 (m 3H), 7.12 – 7.08 (m, , 2H), 6.95 (d, J = 7.0 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.57 (t, J = 7.3 Hz, 1H), 3.53 – 3.49 (m, 2H), 3.24 – 3.21 (m, 2H), 2.91 – 2.87 (m, 2H), 2.74 (t, J = 6.3 Hz, 2H), 1.90 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 144.9, 140.1, 129.4, 128.9, 128.6, 127.3, 126.3, 122.5, 115.6, 110.5, 53.5, 49.7, 32.6, 28.3, 22.3. Spectral data is in accordance to the reported literature. [27b]

1-(3-phenylpropyl)-1,2,3,4-tetrahydroquinoline (5.5ac)



By following the **GP-2**, The title compound **5.5ac** was isolated as colourless oil (0.102 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (t, J = 7.8 Hz, 2H), 7.21 -7.19 (m, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.55 (t, J = 7.3 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 3.29 – 3.25 (m, 4H), 2.75 (t, J = 6.3 Hz, 2H), 2.69 – 2.66 (m, 2H), 1.96 -1.91 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 142.0, 129.3, 128.50, 128.48, 127.2, 126.0, 122.4, 115.5, 110.6, 51.1, 49.6, 33.6, 28.3, 27.8, 22.4. Spectral data is in accordance to the reported literature. [27b]

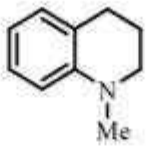
1-heptyl-1,2,3,4-tetrahydroquinoline (5.5ae)



By following the **GP-2**, The title compound **5.5ae** was isolated as light green oil (0.090 g, 78%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 – 7.02 (m, 1H), 6.94 (d, J = 7.2 Hz, 1H), 6.59 – 6.52 (m, 2H), 3.29 – 3.26 (m, 2H), 3.25 – 3.21 (m, 2H), 2.75 (t, J = 6.3 Hz, 2H), 1.98 – 1.92 (m, 2H), 1.60 – 1.57 (m, 2H), 1.34 – 1.30 (m, 8H), 0.91 – 0.88 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.5, 129.2, 127.2, 122.3, 115.3, 110.6, 51.7, 49.6, 32.0, 29.4, 28.4, 27.4, 26.3, 22.8, 22.4, 14.2. Spectral data is in accordance to the reported literature. [27b]

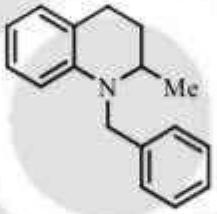
1-methyl-1,2,3,4-tetrahydroquinoline (5.5ad)

TH-3765_196122031



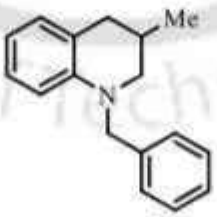
By following the **GP-2**, the title compound **5.5ad** was isolated as light-yellow oil (0.041 g, 55%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.2 Hz, 1H), 6.67 – 6.63 (m, 2H), 3.27 – 3.24 (m, 2H), 2.92 (s, 3H), 2.81 (t, J = 6.4 Hz, 2H), 2.06 – 2.00 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.9, 128.9, 127.2, 123.0, 116.3, 111.1, 51.4, 39.2, 27.9, 22.6. Spectral data is in accordance to the reported literature. [48]

1-benzyl-2-methyl-1,2,3,4-tetrahydroquinoline (5.6b)



By following the **GP-3**, the title compound **5.6b** was isolated as colourless oil (0.091 g, 77%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.19 (m, 5H), 7.00 (d, J = 7.3 Hz, 1H), 6.94 (t, J = 6.8 Hz, 1H), 6.58 – 6.54 (m, 1H), 6.39 (d, J = 8.2 Hz, 1H), 4.57 – 4.43 (m, 2H), 3.61 – 3.54 (m, 1H), 2.96 – 2.88 (m, 1H), 2.78 – 2.72 (m, 1H), 2.08 – 2.00 (m, 1H), 1.86 – 1.80 (m, 1H), 1.18 (d, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.9, 139.6, 128.9, 128.7, 127.2, 126.7, 126.4, 121.9, 115.6, 111.53, 53.5, 53.1, 28.3, 24.2, 19.1. Spectral data is in accordance to the reported literature. [27b]

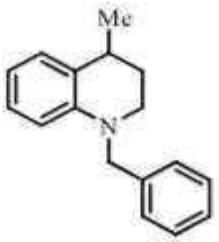
1-benzyl-3-methyl-1,2,3,4-tetrahydroquinoline (5.6c)



By following the **GP-3**, the title compound **56c** was isolated as yellow oil (0.097 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.21 (m, 5H), 6.98 – 6.95 (m, 2H), 6.57 (t, J = 7.2 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 4.48 (s, 2H), 3.30 -3.26 (m, 1H), 3.06 – 3.01 (m, 1H), 2.84 – 2.79 (m, 1H), 2.54 – 2.47 (m, 1H), 2.23 – 2.12 (m, 1H), 1.05 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.3, 139.1, 129.2, 128.7, 127.3, 126.9, 126.7, 122.0, 116.0, 110.8, 57.0, 55.3, 36.6, 27.4, 19.2. Spectral data is in accordance to the reported literature. [49]

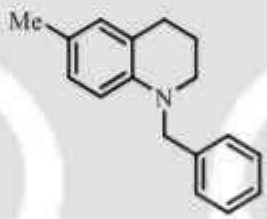
TH-3765_196122031

1-benzyl-4-methyl-1,2,3,4-tetrahydroquinoline (5.6d)



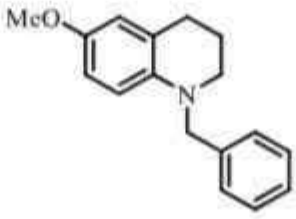
By following the **GP-3**, the title compound **5.6d** was isolated as yellow oil (0.101 g, 85%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.22 (m, 5H), 7.07 (d, J = 7.2 Hz, 1H), 6.99 – 6.95 (m, 1H), 6.62 – 6.59 (m, 1H), 6.50 (d, J = 8.2 Hz, 1H), 4.49 (s, 2H), 3.45 – 3.39 (m, 1H), 3.34 – 3.29 (m, 1H), 2.96 – 2.95 (m, 1H), 2.09 – 2.02 (m, 1H), 1.77 – 1.72 (m, 1H), 1.33 – 1.31 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.0, 139.0, 128.7, 128.0, 127.4, 127.2, 126.9, 126.7, 115.9, 111.1, 55.3, 46.7, 31.2, 29.8, 22.4. Spectral data is in accordance to the reported literature. [27b]

1-benzyl-6-methyl-1,2,3,4-tetrahydroquinoline (5.6e)



By following the **GP-3**, the title compound **5.6e** was isolated as colorless oil (0.109 g, 92%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 – 7.21 (m, 5H), 6.81 (s, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 4.44 (s, 2H), 3.33 (t, J = 5.6 Hz, 2H), 2.79 (t, J = 6.3 Hz, 2H), 2.19 (s, 3H), 2.00 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.6, 139.3, 129.9, 128.7, 127.6, 126.81, 126.76, 125.1, 122.4, 111.3, 55.5, 50.0, 28.3, 22.7, 20.3. Spectral data is in accordance to the reported literature. [49]

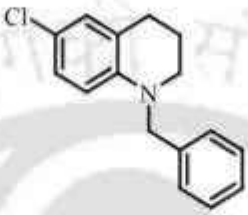
1-benzyl-6-methoxy-1,2,3,4-tetrahydroquinoline (5.6f)



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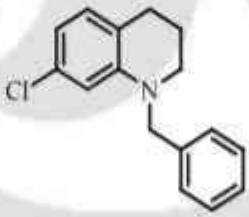
By following the **GP-3**, the title compound **5.6f** was isolated as light-yellow oil (0.120 g, 95%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/1, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 4H), 7.23 – 7.21 (m, 2H), 6.61 – 6.56 (m, 2H), 6.45 (d, J = 8.8 Hz, 1H), 4.41 (s, 2H), 3.71 (s, 3H), 3.30 – 3.28 (m, 2H), 2.80 (m, 2H), 2.03 – 1.97 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 151.0, 140.5, 139.5, 128.7, 126.9, 126.8, 123.9, 115.4, 112.5, 112.4, 56.1, 55.9, 50.1, 28.5, 22.7. Spectral data is in accordance to the reported literature. [49]

1-benzyl-6-chloro-1,2,3,4-tetrahydroquinoline (5.6g)



By following the **GP-3**, the title compound **5.6g** was isolated as colourless oil (0.102 g, 79%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.30 (m, 2H), 7.25 – 7.22 (m, 3H), 6.93 (s, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.38 (d, J = 8.7 Hz, 1H), 4.45 (s, 2H), 3.37 – 3.34 (m, 2H), 2.78 (t, J = 6.2 Hz, 2H), 2.02 – 1.97 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.3, 138.5, 128.8, 128.7, 127.1, 126.9, 126.6, 124.0, 120.5, 112.2, 55.4, 50.0, 28.2, 22.3. Spectral data is in accordance to the reported literature. [27b]

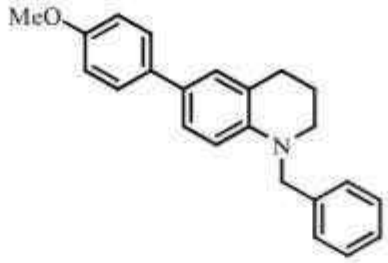
1-benzyl-7-chloro-1,2,3,4-tetrahydroquinoline (5.6h)



By following the **GP-3**, the title compound **5.6h** was isolated as colourless oil (0.104 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.30 (t, J = 7.2 Hz, 2H), 7.26 – 7.22 (m, 3H), 6.86 (d, J = 7.9 Hz, 1H), 6.53 – 6.50 (m, 1H), 6.47 -6.46 (m, 1H), 4.44 (s, 2H), 3.35 – 3.32 (m, 2H), 2.75 (t, J = 6.2 Hz, 2H), 1.97 (p, J = 6.1 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.6, 138.1, 132.7, 129.9, 128.8, 127.1, 126.6, 120.7, 115.6, 110.6, 55.0, 49.6, 27.8, 22.2. Spectral data is in accordance to the reported literature. [27b]

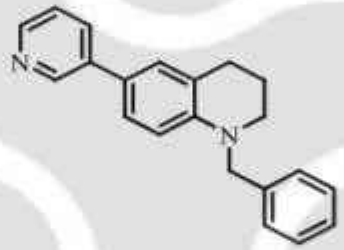
1-benzyl-6-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (5.6i)

TH-3765_196122031



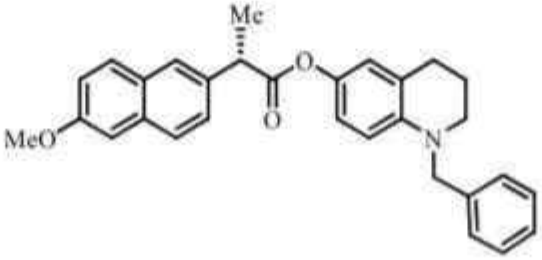
By following the **GP-3**, the title compound **5.6i** was isolated as colourless oil (0.138 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 7.2 Hz, 2H), 7.33 – 7.31(m, 2H), 7.29 – 7.27 (m, 2H), 7.25 – 7.22 (m, 1H), 7.19 – 7.16 (m, 2H), 6.91 – 6.90 (m, 2H), 6.55 – 6.54 (m, 1H), 4.50 (s, 2H), 3.80 (s, 3H), 3.39 – 3.37 (m, 2H), 2.88 – 2.86 (m, 2H), 2.06 – 2.02 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 158.2, 144.8, 139.0, 134.2, 128.7, 128.6, 127.5, 127.3, 126.9, 126.7, 125.5, 122.6, 114.2, 111.4, 55.43, 55.37, 50.1, 28.5, 22.6. HRMS (ESI) *m/z*: $[M+H]^+$calculated for $C_{23}H_{24}NO$: 330.1853; found: 330.1855.

1-benzyl-6-(pyridin-3-yl)-1,2,3,4-tetrahydroquinoline (5.6j)



By following the **GP-3**, the title compound **5.6j** was isolated as yellow solid (0.122 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.75). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.45 (d, J = 3.9 Hz, 1H), 7.80 – 7.77 (m, 1H), 7.35 – 7.32 (m, 1H), 7.28 – 7.26 (m, 4H), 7.24 – 7.21 (m, 2H), 6.59 (d, J = 8.3 Hz, 1H), 4.54 (s, 2H), 3.43 (t, J = 5.7 Hz, 2H), 2.90 (t, J = 6.3 Hz, 2H), 2.09 – 2.03 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 147.5, 146.9, 145.8, 138.6, 136.9, 133.4, 128.8, 127.7, 127.1, 126.6, 126.0, 124.9, 123.6, 122.9, 111.5, 55.2, 50.1, 28.5, 22.4. Spectral data is in accordance to the reported literature. [24]

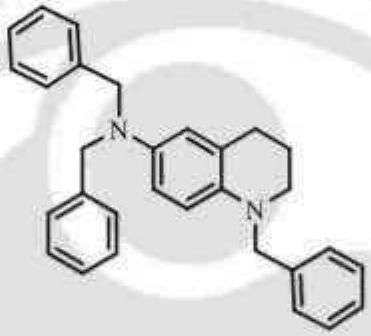
1-benzyl-1,2,3,4-tetrahydroquinolin-6-yl (S)-2-(6-methoxynaphthalen-2-yl) propanoate (5.6k)



TH-3765_196122031

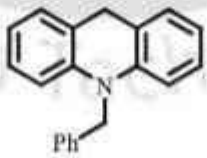
By following the **GP-3**, the title compound **5.6k** was isolated as colourless oil (0.167 g, 74%) using compound **2.14i** ($[\alpha]_D^{25.0}$ = +123.3° (0.15 M, $CHCl_3$) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 – 7.69 (m, 3H), 7.49 – 7.47 (m, 1H), 7.29 – 7.27 (m, 2H), 7.22 – 7.20 (m, 3H), 7.14 – 7.11 (m, 2H), 6.60 – 6.56 (m, 2H), 6.38 – 6.36 (m, 1H), 4.40 (s, 2H), 4.05 – 4.01 (m, 1H), 3.90 (s, 3H), 3.31 – 3.29 (m, 2H), 2.73 (t, J = 6.2 Hz, 2H), 1.97 – 1.92 (m, 2H), 1.65 (d, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 174.0, 157.8, 143.6, 141.0, 138.8, 135.6, 133.9, 129.4, 129.1, 128.7, 127.3, 126.9, 126.7, 126.4, 126.2, 123.0, 121.6, 119.5, 119.1, 111.3, 105.7, 55.6, 55.4, 49.9, 45.6, 28.3, 22.3, 18.7. Spectral data is in accordance to the reported literature.[24] $[\alpha]_D^{25.0}$ = +24.01° (0.15 M, $CHCl_3$).

_N_, _N_,1-tribenzyl-1,2,3,4-tetrahydroquinolin-6-amine (5.6l)



By following the **GP-3** with 0.25 mmol of 6-amino quinoline and HE (5.2 equiv.), the title compound **5.6l** was isolated as purple-oil (0.064 g, 63%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.62). ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.25 (m, 12H), 7.22– 7.20 (m, 3H), 6.52 – 6.40 (m, 3H), 4.47 (s, 4H), 4.34 (s, 2H), 3.24 – 3.22 (m, 2H), 2.72 (t, J = 6.1 Hz, 2H), 1.98 – 1.95 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 141.2, 140.0, 139.7, 138.6, 128.6, 128.5, 127.2, 127.0, 126.8, 123.8, 115.4, 113.2, 112.9, 56.4, 55.1, 50.1, 28.6, 22.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{30}H_{31}N_2$: 419.2482; found: 419.2485.

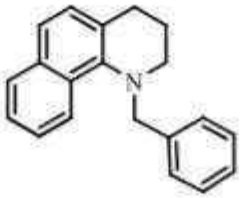
10-benzyl-9,10-dihydroacridine (6.23m)



Using the **GP-3**, the title compound **6.23m** was isolated as brown oil using silica gel column chromatography with petroleum ether/ethyl acetate (v/v 50:1, R_f = 0.70); (108 mg, 80%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 – 7.16 (m, 2H), 7.12 (d, J = 6.9 Hz, 1H), 7.08 – 7.07 (m, 2H), 7.03 (d, J = 7.1 Hz, 2H), 6.93 – 6.89 (m, 2H), 6.76 (t, J = 7.3 Hz, 2H), 6.55 (d, J = 8.1 Hz, 2H), 4.99 (s, 2H), 3.96 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 142.3, 137.1, 128.8, 128.1, 127.1, 126.9, 126.3, 123.3, 120.7, 113.3, 50.9, 32.7. Spectral data is in accordance to the reported literature.[50]

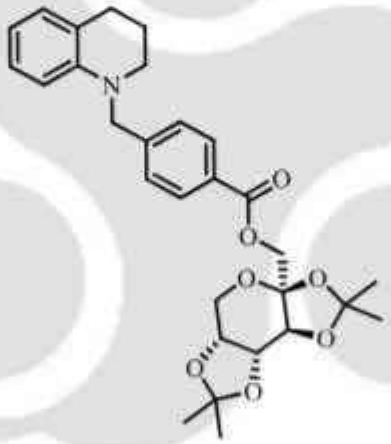
1-benzyl-1,2,3,4-tetrahydrobenzo[*h*]quinoline (5.6n)

TH-3765_196122031



By following the **GP-3**, the title compound **5.6n** was isolated as colourless oil (0.093 g, 68%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/1, R_f = 0.80). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.13 (m, 1H), 7.78 – 7.76 (m, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.47 – 7.43 (m, 3H), 7.40 – 7.33 (m, 3H), 7.18 (d, J = 8.4 Hz, 1H), 4.35 (s, 2H), 3.18 – 3.15 (m, 2H), 2.97 – 2.94 (m, 2H), 1.93 – 1.86 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.3, 139.9, 133.6, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 127.5, 127.1, 127.0, 125.45, 125.38, 125.1, 123.0, 122.2, 59.2, 47.0, 28.1, 16.6. Spectral data is in accordance to the reported literature. [27b]

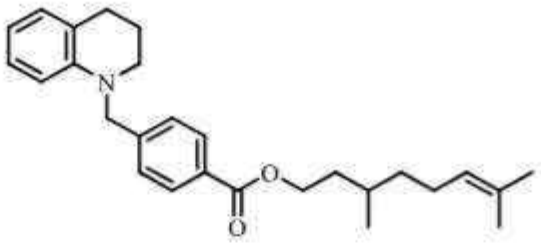
((3aS,5aR,8aR,8bS)-2,2,7,7-tetramethyltetrahydro-3aH-bis ([1,3] dioxolo) [4,5-b:4',5'-d] pyran-3a-yl) methyl 4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8a)



By following the **GP-2**, the title compound **5.8a** was isolated as light-yellow oil (0.222 g, 87%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/4, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.60 (t, J = 7.3 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 4.67 – 4.64 (m, 2H), 4.52 (s, 2H), 4.47 (d, J = 2.6 Hz, 1H), 4.34 (d, J = 11.8 Hz, 1H), 4.27 (d, J = 7.9 Hz, 1H), 3.98 – 3.95 (m, 1H), 3.81 (d, J = 13.0 Hz, 1H), 3.39 – 3.37 (m, 2H), 2.84 (t, J = 6.2 Hz, 2H), 2.04 (p, J = 6.2 Hz, 2H), 1.56 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 165.9, 145.1, 130.3, 129.2, 128.7, 127.3, 126.6, 122.5, 116.4, 111.1, 109.3, 108.9, 101.8, 70.9, 70.6, 70.2, 65.4, 61.5, 55.4, 50.3, 28.2, 26.7, 26.0, 25.7, 24.2, 22.5. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{29}H_{36}NO_7$: 510.2487; found: 510.2488.

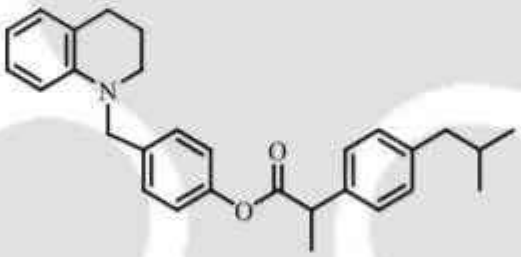
3,7-dimethyloct-6-en-1-yl 4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8b)

TH-3765_196122031



By following the **GP-2**, the title compound **5.8b** was isolated as light-yellow oil (0.164 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.60 (t, J = 7.0 Hz, 1H), 6.43 (d, J = 8.2 Hz, 1H), 5.12 – 5.09 (m, 1H), 4.52 (s, 2H), 4.39 – 4.33 (m, 2H), 3.39 – 3.37 (m, 2H), 2.84 (t, J = 6.3 Hz, 2H), 2.06 – 2.02 (m, 3H), 2.00 – 1.95 (m, 1H), 1.84 – 1.78 (m, 1H), 1.68 (s, 3H), 1.65 – 1.63 (m, 1H), 1.61 (s, 3H), 1.59 – 1.56 (m, 1H), 1.44 – 1.38 (m, 1H), 1.26 – 1.22 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 145.5, 144.7, 131.5, 130.1, 129.4, 129.2, 127.3, 126.6, 124.7, 122.5, 116.4, 111.1, 63.5, 55.4, 50.3, 37.1, 35.7, 29.7, 28.3, 25.8, 25.5, 22.5, 19.6, 17.8. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{36}NO_2$ 406.2741; found 406.2741.

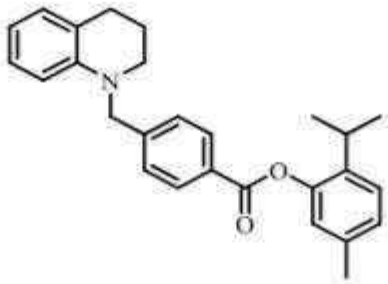
4-((3,4-dihydroquinolin-1(2H)-yl) methyl) phenyl 2-(4-isobutylphenyl) propanoate (5.8c)



By following the **GP-2**, the title compound **5.8c** was isolated as light-yellow oil (0.190 g, 89%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.19 – 7.17 (m, 2H), 7.02 – 6.97 (m, 4H), 6.63 – 6.60 (m, 1H), 6.51 (d, J = 8.0 Hz, 1H), 4.48 (s, 2H), 3.99 – 3.95 (m, 1H), 3.37 – 3.36 (m, 2H), 2.85 (t, J = 6.2 Hz, 2H), 2.51 (d, J = 7.2 Hz, 2H), 2.03 (p, J = 6.2 Hz, 2H), 1.91 (hept, J = 6.8 Hz, 1H), 1.64 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 173.5, 149.8, 145.6, 140.9, 129.6, 129.1, 127.6, 127.34, 127.32, 122.4, 121.6, 116.1, 111.1, 54.9, 49.9, 45.4, 45.2, 30.3, 28.3, 22.53, 22.51, 18.6. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{29}H_{34}NO_2$: 428.2585; found: 428.2584.

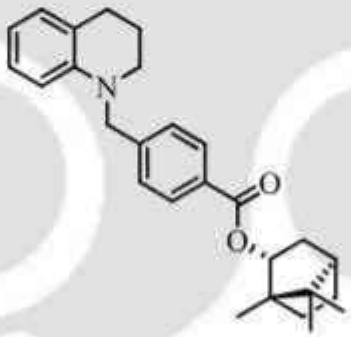
2-isopropyl-5-methylphenyl 4-((3, 4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8d)

TH-3765_196122031



By following the **GP-2**, the title compound **5.8d** was isolated as light-yellow oil (0.180 g, 90%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.24 – 7.22 (m, 1H), 7.05 (d, J = 7.8 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.93 (s, 1H), 6.60 (t, J = 7.3 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 4.56 (s, 2H), 3.42 – 3.39 (m, 2H), 3.04 (p, J = 6.9 Hz, 1H), 2.84 (t, J = 6.3 Hz, 2H), 2.34 (s, 3H), 2.05 (p, J = 6.1 Hz, 2H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 165.3, 148.3, 145.6, 145.4, 136.8, 130.7, 129.3, 128.5, 127.4, 127.3, 126.9, 126.6, 122.6, 116.5, 55.5, 50.4, 28.3, 27.4, 23.2, 22.6, 21.0. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{30}NO_2$: 400.2271; found: 400.2271.

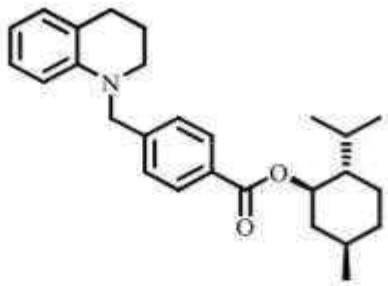
(1S,2R,4R)-1,7,7-trimethylbicyclo [2.2.1] heptan-2-yl 4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8e)



By following the **GP-2**, the title compound **5.8e** was isolated as light-yellow oil (0.165 g, 82%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.97 – 6.93 (m, 2H), 6.63 (t, J = 7.3 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 4.91 – 4.89 (m, 1H), 4.55 (s, 2H), 3.36 – 3.35 (m, 2H), 2.87 (t, J = 6.3 Hz, 2H), 2.07 (p, J = 6.2 Hz, 2H), 1.92 – 1.88 (m, 2H), 1.84 (t, J = 4.2 Hz, 1H), 1.73 – 1.69 (m, 1H), 1.62 – 1.57 (m, 1H), 1.24 – 1.20 (m, 1H), 1.15 – 1.13 (m, 1H), 1.10 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 144.5, 129.9, 129.2, 127.3, 126.6, 122.4, 116.3, 111.0, 81.5, 55.3, 50.2, 49.1, 47.1, 45.2, 39.0, 33.8, 28.2, 27.2, 22.5, 20.23, 20.17, 11.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{34}NO_2$ 404.2585; found 404.2584.

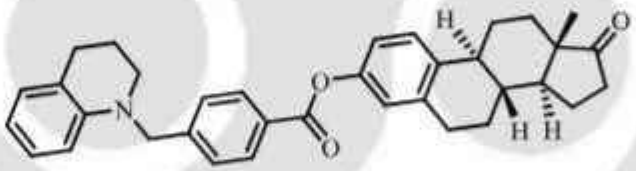
(1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl 4-((3, 4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8f)

TH-3765_196122031



By following the **GP-2**, the title compound **5.8f** was isolated as light-yellow oil (0.162 g, 80%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.03 – 6.99 (m, 2H), 6.64 (t, J = 7.3, 1H), 6.47 (d, J = 8.2 Hz, 1H), 5.00 – 4.96 (m, 1H), 4.55 (s, 2H), 3.41 (t, J = 6.2 Hz, 2H), 2.87 (t, J = 6.2 Hz, 2H), 2.19 – 2.17 (m, 1H), 2.09 – 2.04 (m, 2H), 2.04 – 1.99 (m, 1H), 1.78 – 1.77 (m, 2H), 1.62 – 1.58 (m, 2H), 1.21 – 1.11 (m, 2H), 0.98 – 0.96 (m, 7H), 0.85 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 166.0, 145.4, 144.5, 130.0, 129.6, 129.2, 127.3, 126.5, 122.4, 116.3, 111.0, 74.8, 55.3, 50.2, 47.4, 41.1, 34.4, 31.5, 28.2, 26.6, 23.8, 22.5, 22.1, 20.9, 16.7. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{27}H_{36}NO_2$: 406.2741; found: 406.2741.

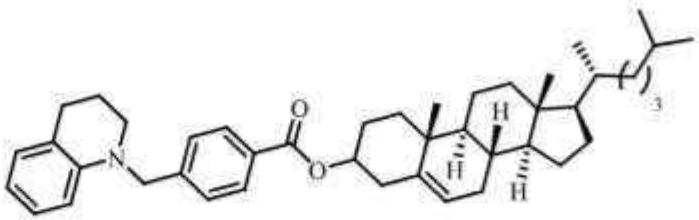
8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8g)



By following the **GP-2**, the title compound **5.8g** was isolated as light-yellow oil (0.192 g, 74%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/5, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.5 Hz, 1H), 7.01 – 6.94 (m, 4H), 6.61 (t, J = 7.2 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 4.56 (s, 2H), 3.42 – 3.39 (m, 2H), 2.95 – 2.93 (m, 2H), 2.85 (t, J = 6.2 Hz, 2H), 2.55 – 2.49 (m, 1H), 2.45 – 2.41 (m, 1H), 2.35 – 2.30 (m, 1H), 2.20 – 2.12 (m, 1H), 2.10 – 2.05 (m, 4H), 2.00 – 1.97 (m, 1H), 1.67 – 1.60 (m, 3H), 1.54 – 1.47 (m, 3H), 0.93 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 220.9, 165.4, 149.0, 145.6, 145.4, 138.2, 137.5, 130.7, 129.3, 128.4, 127.3, 126.8, 126.6, 122.6, 121.8, 119.0, 116.4, 111.1, 55.5, 50.6, 50.3, 48.1, 44.3, 38.2, 36.0, 31.7, 29.6, 28.3, 26.5, 25.9, 22.5, 21.7, 14.0.HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{35}H_{38}NO_3$ 520.2847; found 520.2849.

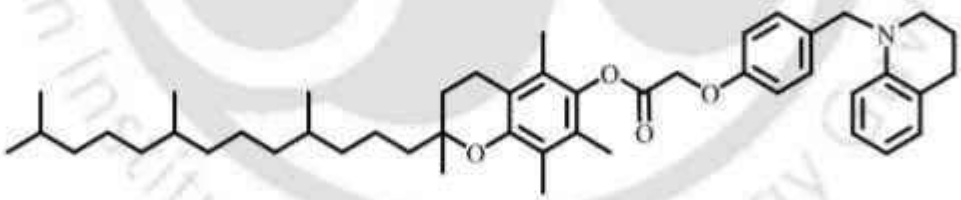
TH-3765_196122031

(8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-((3,4-dihydroquinolin-1(2H)-yl) methyl) benzoate (5.8h)



By following the **GP-2**, the title compound **5.8h** was isolated as white solid (0.229 g, 72%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.01 – 6.96 (m, 2H), 6.61 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 5.41 (d, J = 4.0 Hz, 1H), 4.90 – 4.84 (m, 1H), 4.53 (s, 2H), 3.38 (t, J = 5.6 Hz, 2H), 2.85 (t, J = 6.2 Hz, 2H), 2.48 (d, J = 7.7 Hz, 2H), 2.07 – 2.00 (m, 5H), 1.95 – 1.92 (m, 1H), 1.90 – 1.84 (m, 1H), 1.78 – 1.71 (m, 1H), 1.64 – 1.59 (m, 2H), 1.57 – 1.48 (m, 4H), 1.41 – 1.37 (m, 3H), 1.23 – 1.09 (m, 11H), 1.06 – 0.99 (m, 3H), 0.95 (d, J = 6.5 Hz, 3H), 0.91 – 0.89 (m, 6H), 0.72 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 166.0, 145.4, 144.5, 139.8, 130.0, 129.2, 127.3, 126.5, 122.9, 122.5, 116.3, 111.1, 74.6, 56.8, 56.3, 55.4, 50.21, 50.18, 42.4, 39.9, 39.7, 38.4, 37.2, 36.8, 36.3, 35.9, 32.1, 32.0, 28.4, 28.3, 28.1, 28.0, 24.4, 24.0, 23.0, 22.7, 22.5, 21.2, 19.5, 18.9, 12.0. Spectral data is in accordance to the reported literature. [27b]

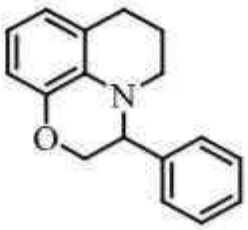
2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl) chroman-6-yl 2-(4-((3,4-dihydroquinolin-1(2H)-yl) methyl) phenoxy) acetate (5.8i)



By following the **GP-2**, the title compound **5.8i** was isolated as light-yellow oil (0.266 g, 75%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 8.4 Hz, 2H), 7.00 – 6.95 (m, 4H), 6.58 (t, J = 7.3 Hz, 1H), 6.52 (d, J = 8.6 Hz, 1H), 4.91 (s, 2H), 4.43 (s, 2H), 3.34 (t, J = 5.6 Hz, 2H), 2.82 (t, J = 6.3 Hz, 2H), 2.58 (t, J = 6.7 Hz, 2H), 2.09 (s, 3H), 2.04 – 2.00 (s, 5H), 1.95 (s, 3H), 1.84 – 1.75 (m, 2H), 1.55 – 1.50 (m, 2H), 1.46 – 1.36 (m, 4H), 1.33 – 1.24 (m, 12H), 1.17 – 1.06 (m, 6H), 0.88 – 0.84 (m, 12H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.8, 157.0, 149.8, 145.7, 140.1, 132.4, 129.2, 128.0, 127.30, 126.7, 125.0, 123.4, 122.5, 117.6, 116.0, 115.1, 111.2, 75.3, 65.5, 54.7, 49.9, 39.5, 37.6, 37.5, 37.4, 32.9, 32.8, 28.3, 28.1, 25.0, 24.6, 22.9, 22.8, 22.5, 21.2, 20.7, 19.9, 19.8, 19.7, 13.1, 12.3, 12.0. Spectral data is in accordance to the reported literature. [27b]

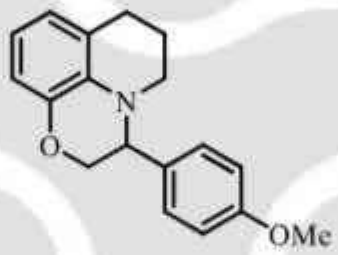
TH-3765_196122031

3-phenyl-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10a)



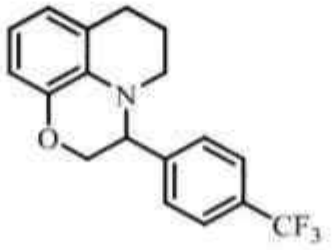
By following the **GP-4**, the title compound **5.10a** was isolated as white solid (0.109 g, 87%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). M.p.102-104 °C .^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.34 (m, 2H), 7.32 – 7.28 (m, 3H), 6.67 (t, J = 6.9 Hz, 2H), 6.59 (t, J = 7.6 Hz, 1H), 4.25 – 4.19 (m, 2H), 4.14 – 4.11 (m, 1H), 3.09 – 3.05 (m, 1H), 2.84 – 2.77 (m, 3H), 2.01 – 1.88 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.6, 139.1, 133.0, 128.9, 128.1, 127.6, 123.5, 122.2, 117.3, 114.0, 70.3, 60.4, 46.2, 27.2, 22.3. Spectral data is in accordance to the reported literature. [19]

3-(4-methoxyphenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10b)



By following the **GP-4**, the title compound **5.10b** was isolated as white solid (0.118 g, 84%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). M.p. 84 -86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.66 (t, J = 7.7, 2H), 6.58 (t, J = 7.7 Hz, 1H), 4.23 – 4.20 (m, 1H), 4.16 – 4.08 (m, 2H), 3.81 (s, 3H), 3.08 – 3.04 (m, 1H), 2.84 – 2.74 (m, 3H), 2.00 – 1.91 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.5, 143.6, 133.1, 131.0, 128.8, 123.6, 122.1, 117.3, 114.4, 114.0, 70.4, 59.6, 55.4, 46.0, 27.2, 22.3. Spectral data is in accordance to the reported literature. [19]

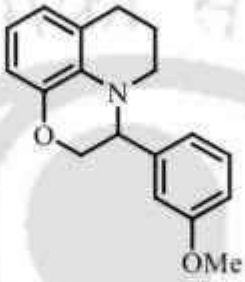
3-(4-(trifluoromethyl) phenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10c)



TH-3765_196122031

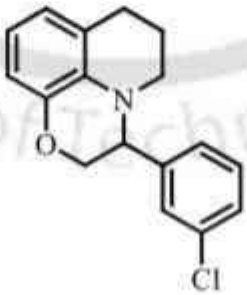
By following the **GP-4**, the title compound **5.10c** was isolated as white solid (0.148 g, 93%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). M.p. 92 -94 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 – 7.61 (m, 2H), 7.55 – 7.54 (m, 1H), 7.41 (d, J = 8.1 Hz, 2H), 6.68 (d, J = 7.6 Hz, 1H), 6.61 – 6.58 (m, 1H), 4.31 – 4.29 (m, 1H), 4.26 – 4.24 (m, 1H), 4.14 – 4.11 (m, 1H), 3.06 – 3.02 (m, 1H), 2.89 – 2.82 (m, 3H), 2.01 – 1.96 (m, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 143.6, 143.4, 139.4, 132.4, 127.9, 127.0, 125.9 (q = 3.7 Hz), 124.0, 123.4, 122.4, 117.4, 114.2, 69.7, 60.2, 46.6, 27.1, 22.2. ^{19}F NMR (565 MHz, $CDCl_3$): δ -62.53. Spectral data is in accordance to the reported literature. [19]

3-(3-methoxyphenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10d)



By following the **GP-4**, the title compound **5.10d** was isolated as white solid (0.125 g, 89%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). M.p. 90 -91 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.25 (m, 1H), 6.89 (d, J = 7.3 Hz, 1H), 6.85 – 6.84 (m, 2H), 6.67 – 6.64 (m, 2H), 6.59 – 6.56 (m, 1H), 4.24 – 4.22 (m, 1H), 4.18 – 4.11 (m, 2H), 3.79 (s, 3H), 3.11 – 3.07 (m, 1H), 2.87 – 2.76 (m, 3H), 2.04 – 1.94 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.2, 143.6, 140.7, 133.0, 130.0, 123.6, 122.2, 120.0, 117.4, 114.0, 113.4, 113.2, 70.3, 60.3, 55.4, 46.2, 27.1, 22.3. Spectral data is in accordance to the reported literature. [19]

3-(3-chlorophenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10e)



By following the **GP-4**, the title compound **5.10e** was isolated as white solid (0.129 g, 90%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). M.p. 93 -94 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.29 (m, 3H), 7.20 – 7.18 (m, 1H), 6.68 – 6.66 (m, 2H), 6.61 – 6.58 (m, 1H), 4.24 – 4.19 (m, 2H), 4.13 – 4.10 (m, 1H), 3.09 – 3.05 (m, 1H), 2.86 – 2.82 (m, 3H), 2.04 – 1.93 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.4, 141.5, 134.9, 132.6, 130.2, 128.3, 127.7, 125.7, 123.5, 122.3, 117.4, 114.1, 69.9, 60.1, 46.4, 27.1, 22.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{17}H_{17}ClNO$: 286.0994; found: 286.0997.

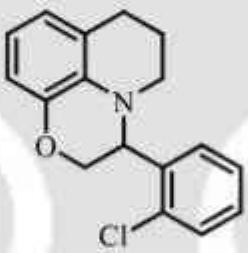
TH-3765_196122031

3-(2-methoxyphenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10f)



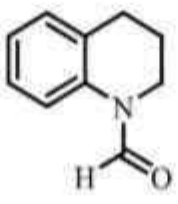
By following the **GP-4**, the title compound **5.10f** was isolated as white solid (0.120 g, 85%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). M.p. 101 -103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.23 (m, 1H), 7.17 (d, J = 6.7 Hz, 1H), 6.92 – 6.89 (m, 2H), 6.65 – 6.63 (m, 2H), 6.53 – 6.50 (m, 1H), 4.76 (t, J = 3.6 Hz, 1H), 4.23 – 4.17 (m, 2H), 3.85 (s, 3H), 3.21 – 3.17 (m, 1H), 2.98 – 2.93 (m, 1H), 2.83 (t, J = 6.5 Hz, 2H), 1.99 – 1.95 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.1, 143.2, 133.0, 128.6, 127.7, 127.2, 122.5, 122.1, 120.9, 116.1, 114.1, 110.6, 68.3, 55.4, 53.9, 46.8, 27.3, 22.2. Spectral data is in accordance to the reported literature. [19]

3-(2-chlorophenyl)-2,3,6,7-tetrahydro-5H- [1,4] oxazino[2,3,4-ij] quinoline (5.10g)



By following the **GP-4**, the title compound **5.10g** was isolated as white solid (0.126 g, 88%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 50/2, R_f = 0.70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.38 (m, 1H), 7.28 – 7.24 (m, 1H), 7.23 – 7.21 (m, 2H), 6.67 – 6.66 (m, 2H), 6.55 (t, J = 7.5 Hz, 1H), 4.81 (t, J = 3.4 Hz, 1H), 4.27 – 4.25 (m, 1H), 4.23 – 4.20 (m, 1H), 3.15 – 3.11 (m, 1H), 3.01 – 2.97 (m, 1H), 2.84 (t, J = 5.9 Hz, 2H), 1.98 (p, J = 6.1 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.1, 136.6, 133.1, 132.5, 130.0, 128.9, 128.6, 127.4, 122.6, 122.3, 116.6, 114.2, 67.8, 57.0, 46.9, 27.2, 22.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{17}H_{17}ClNO$: 286.0994; found: 286.0996.

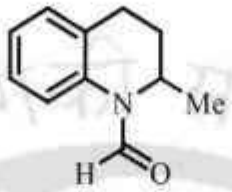
3, 4-dihydroquinoline-1(2*H*)-carbaldehyde (6.25a)



TH-3765_196122031

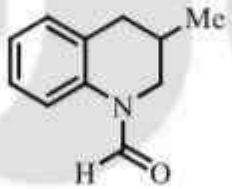
By following the **GP-5**, the title compound **6.25a** was isolated as light-yellow oil (0.076 g, 94%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (s, 1H), 7.10 – 6.98 (m, 4H), 3.71 – 3.68 (m, 2H), 2.71 – 2.69 (t, J = 6.2 Hz, 2H), 1.84 (m, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.0, 137.2, 129.6, 128.9, 127.1, 124.5, 117.0, 40.3, 27.1, 22.2. Spectral data is in accordance to the reported literature. [51]

2-methyl-3, 4-dihydroquinoline-1(2*H*)-carbaldehyde (6.25b)



By following the **GP-5**, the title compound **6.25b** was isolated as light-yellow oil (0.077 g, 88%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.23 – 7.20 (m, 2H), 7.13 – 7.11 (m, 2H), 4.84 – 4.78 (m, 1H), 2.86 – 2.80 (m, 1H), 2.76 – 2.67 (m, 1H), 2.17 – 2.10 (m, 1H), 1.73 – 1.68 (m, 1H), 1.21 (d, J = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.3, 136.4, 130.0, 129.3, 127.4, 124.9, 118.6, 45.4, 29.4, 24.4, 18.3. Spectral data is in accordance to the reported literature. [51]

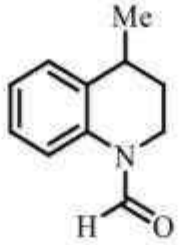
3-methyl-3, 4-dihydroquinoline-1(2*H*))-carbaldehyde (6.25c)



By following the **GP-5**, The title compound **6.25c** was isolated as light-yellow oil (0.079 g, 90%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.20 – 7.14 (m, 3H), 7.11 – 7.08 (m, 1H), 4.18 – 4.14 (m, 1H), 3.11 – 3.07 (m, 1H), 2.91 – 2.84 (m, 1H), 2.52 – 2.44 (m, 1H), 2.07 – 1.99 (m, 1H), 1.09 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.2, 137.0, 129.9, 128.4, 127.1, 124.7, 116.8, 46.5, 35.6, 28.0, 18.8. Spectral data is in accordance to the reported literature. [51]

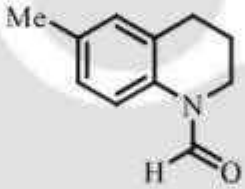
4-methyl-3, 4-dihydroquinoline-1(2*H*))-carbaldehyde (6.25d)

TH-3765_196122031



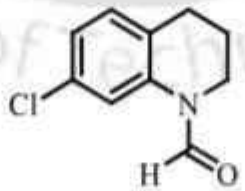
By following the **GP-5**, the title compound **6.25d** was isolated as light-yellow oil (0.081 g, 92%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.23 – 7.20 (m, 1H), 7.16 – 7.13 (m, 2H), 3.89 – 3.84 (m, 1H), 3.80 – 3.75 (m, 1H), 2.97 – 2.90 (m, 1H), 2.09 – 2.02 (m, 1H), 1.72 – 1.65 (m, 1H), 1.34 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.4, 136.7, 134.2, 128.2, 127.3, 124.9, 117.4, 38.4, 30.9, 30.2, 21.0. Spectral data is in accordance to the reported literature. [51]

6-methyl-3, 4-dihydroquinoline-1(2*H*))-carbaldehyde (6.25e)



By following the **GP-5**, the title compound **6.25e** was isolated as light-yellow oil (0.084 g, 96%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.04 – 6.98 (m, 3H), 3.80 – 3.77 (m, 2H), 2.77 (t, J = 6.4 Hz, 2H), 2.30 (s, 3H), 1.94 (p, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 161.1, 134.8, 134.3, 130.2, 128.8, 127.7, 116.9, 40.3, 27.1, 22.4, 20.7. Spectral data is in accordance to the reported literature. [52]

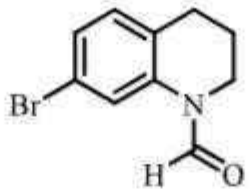
7-chloro-3,4-dihydroquinoline-1(2*H*))-carbaldehyde (6.25f)



By following the **GP-5**, the title compound **6.25f** was isolated as light-yellow oil (0.079 g, 81%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.42). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.15 (brs, 1H), 7.08 – 7.05 (m, 2H), 3.78 (t, J = 6.0 Hz, 2H), 2.77 (t, J = 6.4 Hz, 2H), 1.94 (p, J = 6.3 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.0, 138.4, 132.6, 130.8, 127.3, 124.6, 117.2, 40.4, 26.9, 22.1. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{10}H_{11}ClNO$: 196.0524; found: 196.0522.

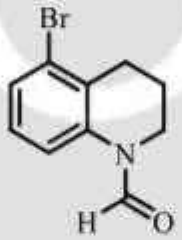
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7-bromo-3,4-dihydroquinoline-1(2*H*))-carbaldehyde (6.25g)



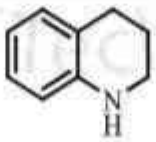
By following the **GP-5**, the title compound **6.25g** was isolated as light-yellow oil (0.100 g, 83%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.30 (s, 1H), 7.23 – 7.21 (m, 1H), 7.04 (d, J = 7.9 Hz, 1H), 3.80 – 3.78 (m, 2H), 2.77 – 2.75 (m, 2H), 1.97 – 1.92 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.0, 138.7, 131.1, 127.9, 127.6, 120.3, 120.1, 40.4, 27.0, 22.1. Spectral data is in accordance to the reported literature. [53]

5-bromo-3,4-dihydroquinoline-1(2*H*))-carbaldehyde (6.25h)



By following the **GP-5**, the title compound **6.25h** was isolated as light-yellow oil (0.103 g, 86%) using silica gel column chromatography with pet-ether/ ethyl acetate (v/v = 25/2, R_f = 0.42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H), 7.40 – 7.39 (m, 1H), 7.10 – 7.06 (m, 2H), 3.80 (t, J = 5.9 Hz, 2H), 2.85 (t, J = 6.8 Hz, 2H), 1.97 (p, J = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.1, 139.2, 128.9, 128.7, 128.0, 126.0, 116.7, 39.6, 28.2, 22.5. HRMS (ESI) *m/z*: $[M+H]^+$ calculated for $C_{10}H_{11}BrNO$: 240.0019; found: 240.0015.

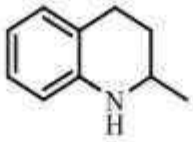
1,2,3,4-tetrahydroquinoline (2.12)



Using the reaction condition given in Table 6.7a, the title compound **2.12** was isolated as Colourless oil (96%, 0.064 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 – 6.95 (m, 2H), 6.61 (t, J = 8.1 Hz, 1H), 6.48 (d, J = 7.9 Hz, 1H), 3.32 – 3.29 (m, 2H), 2.77 (t, J = 6.4 Hz, 2H), 1.98 – 1.92 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.9, 129.6, 126.8, 121.6, 117.1, 114.3, 42.1, 27.1, 22.3. Spectral data is in accordance with the literature. [27c]

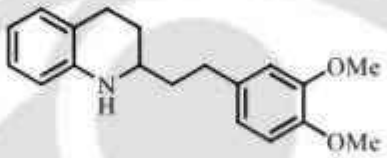
2-methyl-1,2,3,4-tetrahydroquinoline (6.22b)

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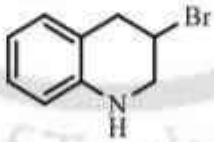
Using the reaction condition given in Table 6.7a, the title compound **6.22b** was isolated as Colourless oil (91%, 0.067 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 – 6.93 (m, 2H), 6.61 – 6.57 (m, 1H), 6.46 – 6.44 (m, 1H), 3.64 (brs, 1H), 3.42 – 3.34 (m, 1H), 2.87 – 2.79 (m, 1H), 2.74 – 2.68 (m, 1H), 1.94 – 1.88 (m, 1H), 1.62 – 1.53 (m, 1H), 1.19 (d, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.8, 129.3, 126.7, 121.1, 116.9, 114.0, 47.1, 30.1, 26.6, 22.6. Spectral data is in accordance with the literature. [26h]

2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline (6.22m)



Using the reaction condition given in Table 6.7a, the title compound **6.22m** was isolated as yellow sticky solid (87%, 0.065 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.62). Using 3.5 equivalent of HE. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.00 – 6.97 (m, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.78 – 6.76 (m, 2H), 6.60 (t, J = 7.2 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.35 – 3.30 (m, 1H), 2.86 – 2.81 (m, 1H), 2.79 – 2.75 (m, 1H), 2.68 (t, J = 8.0 Hz, 2H), 2.04 – 2.00 (m, 1H), 1.86 – 1.82 (m, 2H), 1.73 – 1.67 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 148.9, 147.3, 144.6, 134.5, 129.3, 126.8, 121.3, 120.2, 117.1, 114.2, 111.6, 111.3, 56.0, 55.9, 51.2, 38.5, 31.9, 28.1, 26.3. Spectral data is in accordance with the literature. [27e]

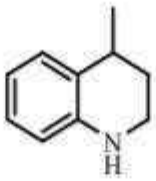
3-bromo-1,2,3,4-tetrahydroquinoline (6.22n)



Using the reaction condition given in Table 6.7a, the title compound **6.22n** was isolated as brown oil (89%, 0.094 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 – 7.00 (m, 1H), 6.93 (d, J = 7.3 Hz, 1H), 6.69 – 6.65 (m, 1H), 6.53 (d, J = 7.9 Hz, 1H), 4.52 – 4.46 (m, 1H), 3.67 – 3.63 (m, 1H), 3.50 – 3.45 (m, 1H), 3.41 – 3.36 (m, 1H), 3.22 – 3.16 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 142.7, 129.6, 127.7, 118.7, 118.2, 114.7, 49.5, 44.3, 38.0. Spectral data is in accordance to the reported literature. [26h]

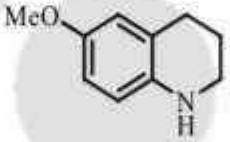
4-methyl-1,2,3,4-tetrahydroquinoline (6.22d)

TH-3765_196122031



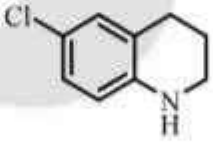
Using the reaction condition given in Table 6.7a, the title compound **6.22d** was isolated as Colourless oil (92%, 0.068 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 7.4 Hz, 1H), 6.96 (t, J = 7.3 Hz, 1H), 6.63 (t, J = 7.4 Hz, 1H), 6.47 (d, J = 7.9 Hz, 1H), 3.36 – 3.27 (m, 2H), 2.94 – 2.89 (m, 1H), 2.02 – 1.95 (m, 1H), 1.71 – 1.65 (m, 1H), 1.29 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.4, 128.6, 126.9, 126.8, 117.1, 114.3, 39.2, 30.4, 30.0, 22.8. Spectral data is in accordance to the reported literature. [26h]

6-methoxy-1,2,3,4-tetrahydroquinoline (5.18f)



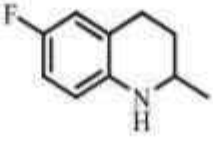
Using the reaction condition given in Table 6.7a, the title compound **5.18f** was isolated as Colourless oil (94%, 0.077 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.62). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 – 6.56 (m, 2H), 6.46 (d, J = 8.5 Hz, 1H), 3.73 (s, 3H), 3.01 (brs, 1H), 3.27 – 3.24 (m, 2H), 2.76 (t, J = 6.5 Hz, 2H), 1.96-1.90 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.0, 139.0, 123.0, 115.7, 115.0, 113.0, 55.9, 42.5, 27.3, 22.6. Spectral data is in accordance to the reported literature. [27c]

6-chloro-1,2,3,4-tetrahydroquinoline (5.18g)



Using the reaction condition given in Table 6.7a, the title compound **5.18g** was isolated as pale-yellow sticky liquid (90%, 0.075 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 – 6.89 (m, 2H), 6.38 (d, J = 8.0 Hz, 1H), 3.76 (NH, brs, 1H), 3.30 – 3.27 (m, 2H), 2.73 (t, J = 6.4 Hz, 2H), 1.95 – 1.89 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.4, 129.1, 126.6, 122.9, 121.2, 115.2, 41.9, 27.0, 21.8. Spectral data is in accordance to the reported literature. [26h]

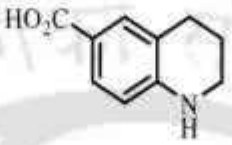
6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (6.22o)



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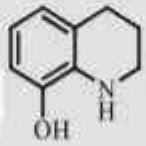
Using the reaction condition given in Table 6.7a, the title compound **6.22o** was isolated as Colourless sticky liquid (86%, 0.071 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 – 6.65 (m, 2H), 6.42 – 6.38 (m, 1H), 3.55 (NH, brs, 1H), 3.38 – 3.31 (m, 1H), 2.86 – 2.78 (m, 1H), 2.73 – 2.66 (m, 1H), 1.94 – 1.88 (m, 1H), 1.61 – 1.51 (m, 1H), 1.20 (d, J = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 155.6 (d, $^1J_{C\text{-}F}$ = 235.3 Hz), 141.1 (d, $^4J_{C\text{-}F}$ = 1.8 Hz), 122.6 (d, $^3J_{C\text{-}F}$ = 6.6 Hz), 115.5 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 114.8 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 113.3 (d, $^2J_{C\text{-}F}$ = 22.5 Hz), 47.4, 30.0, 26.8, 22.6. Spectral data is in accordance to the reported literature. [26h]

1,2,3,4-tetrahydroquinoline-6-carboxylic acid (6.22p)



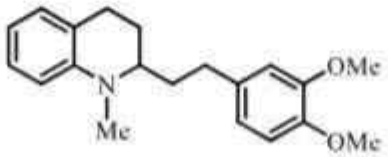
Using the reaction condition given in Table 6.7a, the title compound **6.22p** was isolated as light-yellow oil (78%, 0.069 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.2 Hz, 2H), 6.41 (d, J = 8.3 Hz, 1H), 3.37 (t, J = 5.5 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 1.94 (p, J = 6.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0, 149.6, 132.1, 130.1, 120.0, 116.5, 112.8, 41.9, 27.0, 21.5. Spectral data is in accordance to the reported literature. [26a]

8-hydroxy-1,2,3,4-tetrahydroquinoline (6.22q)



Using the reaction condition given in Table 6.7a, the title compound **6.22q** was isolated as white solid (83%, 0.062 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 6.45 – 6.26 (m, 3H), 4.60 (NH, brs, 1H), 3.20 (brs, 2H), 2.64 – 2.61 (m, 2H), 1.79 – 1.76 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 143.2, 133.7, 120.4, 119.9, 114.7, 111.4, 40.8, 26.4, 21.8. Spectral data is in accordance to the reported literature. [26h]

2-(3,4-dimethoxyphenethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (6.27)

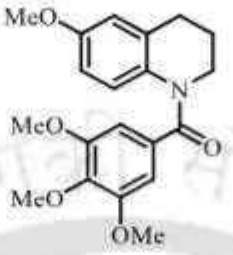


Using the reaction condition given in Table 6.7b, the title compound **6.27** was isolated as yellow oil (96%, 0.102 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.62). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 – 7.07 (m, 1H), 6.98 (d, J = 7.2 Hz, 1H), 6.80 – 6.78 (m, 1H), 6.74 – 6.71 (m, 2H), 6.60 (t, J = 7.2 Hz, 1H), 6.53 (d, J =

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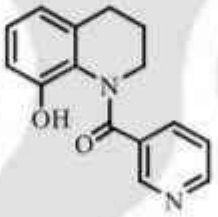
8.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.32 – 3.27 (m, 1H), 2.92 (s, 3H), 2.88 – 2.81 (m, 1H), 2.73 – 2.64 (m, 2H), 2.57 – 2.50 (m, 1H), 1.98 – 1.88 (m, 3H), 1.78 – 1.69 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 149.1, 147.4, 145.5, 134.8, 128.8, 127.3, 121.9, 120.2, 115.6, 111.8, 111.5, 110.8, 58.6, 56.1, 56.0, 38.2, 33.2, 32.1, 24.6, 23.7. Spectral data is in accordance to the reported literature. [54]

(6-methoxy-3,4-dihydroquinolin-1(2H)-yl) (3,4,5-trimethoxyphenyl) methanone (6.28)



Using the reaction condition given in Table 6.7b, the title compound **6.28** was isolated as yellow oil (90%, 0.096 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.50). ^1H NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 2H), 6.55 (s, 2H), 6.45 (d, J = 8.4, 1H), 3.85 – 3.81 (m, 2H), 3.79 (d, J = 1.9 Hz, 3H), 3.70 (d, J = 2.1 Hz, 3H), 3.65 (d, J = 2.1 Hz, 6H), 2.76 (t, J = 6.0, 2H), 2.02 –1.95 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 169.4, 156.6, 152.7, 139.6, 133.0, 132.6, 131.2, 126.3, 113.1, 111.4, 106.2, 60.9, 56.0, 55.4, 44.6, 27.2, 24.2. Spectra data is in accordance to the reported literature. [26c]

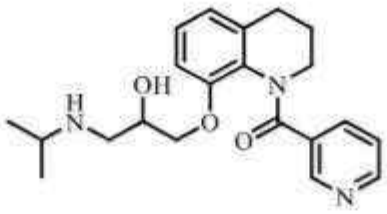
(8-hydroxy-3,4-dihydroquinolin-1(2H)-yl) (pyridin-3-yl) methanone (6.29)



Using the reaction condition given in Table 6.7b, the title compound **6.29** was isolated white solid (81%, 0.082 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^1H NMR (400 MHz, DMSO-d_6): δ 9.43 (s, 1H), 8.47 – 8.45 (m, 1H), 8.38 (d, J = 2.3 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.25 – 7.22 (m, 1H), 6.89 (t, J = 7.7 Hz, 1H), 6.72 (d, J = 7.2 Hz, 1H), 6.42 (d, J = 7.8 Hz, 1H), 3.91 (brs, 2H), 2.73 (t, J = 6.5 Hz, 2H), 1.91 (brs, 2H). ^1H NMR (400 MHz, CD_3CN): δ 8.51 (br, 2H), 7.71 – 7.69 (m, 1H), 7.26 – 7.25 (m, 1H), 7.01 (t, J = 8.0 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.56 – 6.55 (m, 1H), 3.67 (brs, 2H), 2.81 (t, J = 6.6 Hz, 2H), 2.21 (brs, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 167.6, 150.2, 149.2, 148.2, 136.3, 135.0, 133.3, 127.1, 126.6, 122.6, 118.2, 114.2, 42.9, 26.3, 24.5. Spectra data is in accordance to the reported literature. [26h]

(8-(2-hydroxy-3-(isopropylamino) propoxy)-3,4-dihydroquinolin-1(2H)-yl) (pyridin-3-yl) methanone (6.30)

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Using the reaction condition given in Table 6.7b, the title compound **6.30** was isolated as white solid (62%, 0.053 g) using silica gel column chromatography with petroleum ether/ethyl acetate (v/v = 25:2, R_f = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 – 8.55 (m, 2H), 7.74 (s, 1H), 7.21 – 7.17 (m, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.64 – 6.61 (m, 1H), 4.22 (br, 1H), 3.83 – 3.74 (m, 2H), 3.65 – 3.48 (m, 2H), 2.88 – 2.66 (m, 4H), 2.56 – 2.51 (m, 1H), 2.22 (br, 2H), 1.89 – 1.82 (m, 2H), 1.06 (d, J = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.6, 151.13, 151.08, 149.1, 135.7, 132.4, 128.6, 127.0, 122.9, 122.8, 120.8, 111.3, 71.9, 71.0, 68.7, 68.1, 49.1, 26.7, 24.8, 23.1, 23.0. Spectra data is in accordance to the reported literature. [26h]

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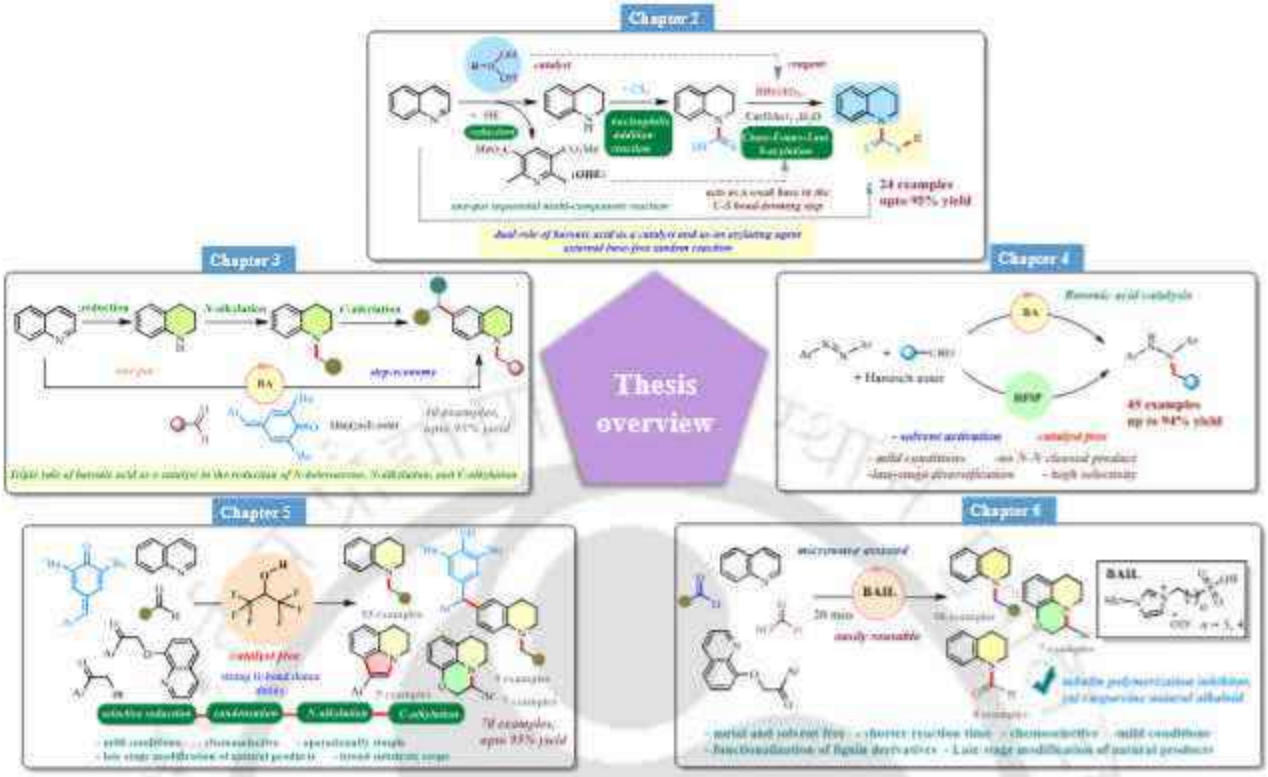
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Chapter 1 outlines includes boronic acid catalysis (BAC) and hexafluoroisopropanol (HFIP), focusing on their roles in organic synthesis, particularly in reduction chemistry. It highlights how BAC and HFIP contribute to improving reaction efficiency and selectivity.

Chapter 2 deals with the one-pot tandem reaction involving reduction of quinolines to tetrahydroquinolines, subsequent nucleophilic addition reaction with carbon disulphide to generate corresponding dithiocarbamic acid, followed by *S*-arylation using boronic acid to form tertrahydroquinoline containing dithiocarbamate derivatives *via* Chan–Evans–Lam reaction. From the 1st step released Hantzsch pyridine was successfully utilized in the subsequent *S*-arylation reaction; hence method does require any external base source in the C-S bond-forming step. The present study demonstrates the dual role of boronic acid as a catalyst (in the reduction of quinoline) and as a coupling partner (in the *S*-arylation segments). Method proved to be versatile and compatible with various functional groups at both the quinoline and boronic acid moiety. We believe that this method will find useful applications for the synthesis of a library of biologically important dithiocarbamate derivatives to facilitate the identification of the more potent bioactive molecules.

Chapter 3 deals with the one-pot tandem reaction involving reduction of quinolines to tetrahydroquinolines, subsequent reductive alkylation using aldehydes to *N*-alkylated tetrahydroquinolines, followed by *C*-alkylation using *p*-QM to form functionalized tetrahydroquinoline containing diaryl motif at the C6-position without the aid of any transition metals. The present study demonstrates the triple role of boronic acid as a catalyst in the reduction of quinoline, reductive *N*-alkylation, and *C*-alkylation sequence. This convenient method tolerates

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a wide variety of hydrogenation-sensitive functional groups, such as ester, halo, nitro, nitrile, alkyne, allyl, benzyl, and further has been successfully utilized in the late-stage functionalization, and diversification of pharmaceuticals. The post- transformations of the synthesized product have also been carried out to demonstrate the potential of the developed methodology. A combination of hydrogen bonding and Lewis acidity property of the boronic acids has been demonstrated, highlighting the multiple modes of activation available to boronic acids. This study demonstrates the general utility of the BA catalysis, specifically in reduction chemistry.

Chapter 4 describes a one-pot tandem reduction of azoarene with subsequent reductive alkylation using aldehydes to form *N*-alkylated hydrazine derivatives under mild conditions. The protocol shows notable selectivity as formation of *N-N* cleaved product amines and/or imines is completely suppressed and selectively provided *N*-alkyl-*N, N'*-diarylhydrazines. This convenient method tolerates a wide variety of hydrogenation-sensitive functional groups, such as ester, halo, nitro, nitrile, alkyne, allyl, and benzyl. This has been successfully utilized in the late-stage functionalization, and diversification of pharmaceuticals. The post transformations of the synthesized product have also been carried out to demonstrate the significance of the developed methodology.This study sheds light on the activation mode of boronic acid catalysis involves both H-bond donor catalysis and Brønsted acid catalysis. The strong hydrogen-bond donor ability of HFIP is also utilized in the reductive alkylation of azoarenes.

Chapter 5 describes a one-pot tandem reduction of quinoline with subsequent reductive alkylation using aldehydes and Hantzsch ester to produce *N*-alkylated THQ derivatives. Because of mild reaction conditions, this convenient method tolerates a wide variety of reducible-sensitive functional groups, such as ester, halo, nitro, nitrile, alkyne, allyl, benzyl, thioether. Futhermore, it has been successfully utilized in the late-stage functionalization, diversification of pharmaceuticals. The post-transformations of the synthesized product have also been carried out to demonstrate the potential of the developed methodology. The current reductive *N*-alkylation approach was also successfully utilized to synthesize tricyclic oxazino-fused-tetrahydroquinoline/benzoxazine, lilolidine, and *C*-functionalized *N*-alkylated THQ derivatives in a one-pot. Mechanistic studies reveal the existence of a strong hydrogen bonding between the quinoline 'N's and HFIP. The multifunctional role of HFIP has been demonstrated not only to facilitate the reduction of quinoline but also to improve the stability of hemiaminal or iminium ion species through the hydrogen-bonding network of HFIP.

Chapter 6 demonstrates BAIL-catalyzed a one-pot tandem reduction of quinoline with subsequent reductive alkylation using aldehydes to produce *N*-alkylated THQ derivatives. The catalyst could be easily recovered and reused five times without a considerable decrease in catalytic activity. This convenient method tolerates a wide variety of reducible-sensitive functional groups, such as ester, halo, nitro, nitrile, alkyne, allyl, benzyl, thioether. Further, it has been successfully utilized in the late-stage functionalization, diversification of pharmaceuticals. The post transformations of the synthesized product have also been carried out to demonstrate the potential of the developed methodology. The current reductive strategy was also successfully utilized to synthesize tricyclic

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oxazino-fused-tetrahydroquinoline/ benzoxazine, antiarrhythmic drug nicainoprol tubulin polymerization inhibitor and (±) cuspareine natural alakaloid efficiently. The multifunctional role of BAIL has been demonstrated not only to facilitate the reduction of quinoline but also to improve the stability of iminium ion species through ion-pair effect.

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Annexure I

^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ spectra of representative compounds (*Chapter 2*)

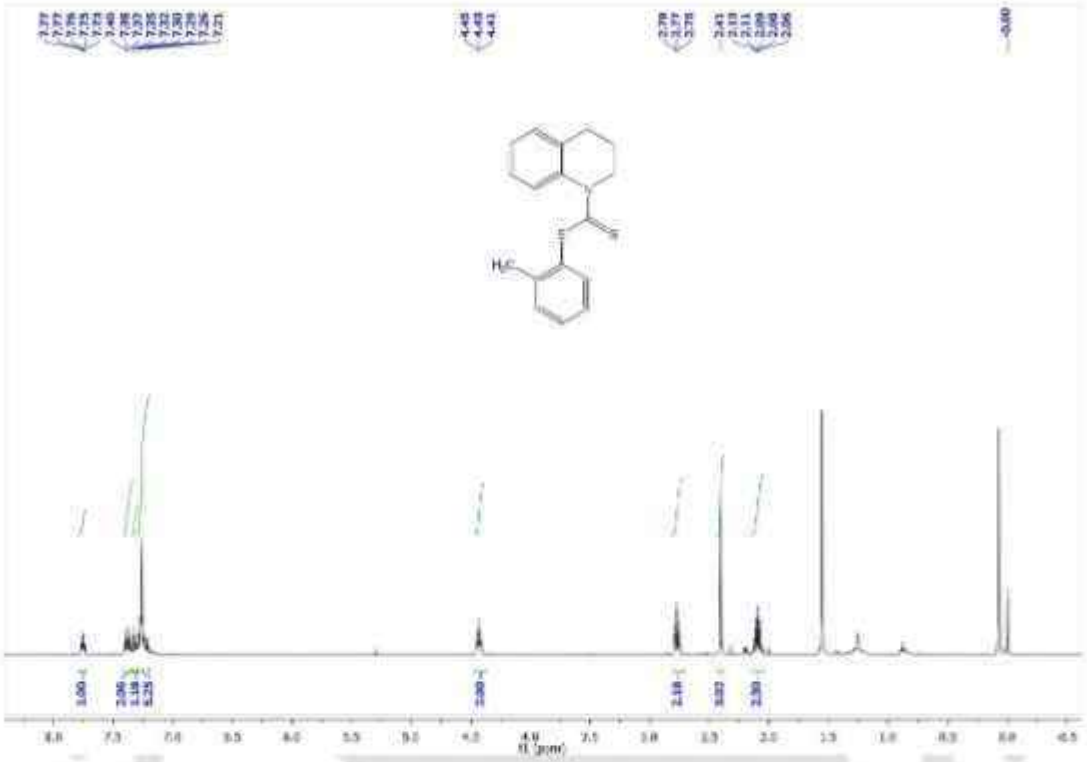


Figure S1: ^{1}H NMR Spectrum of **2.17l** ($CDCl_3$, 400 MHz, 298 K)

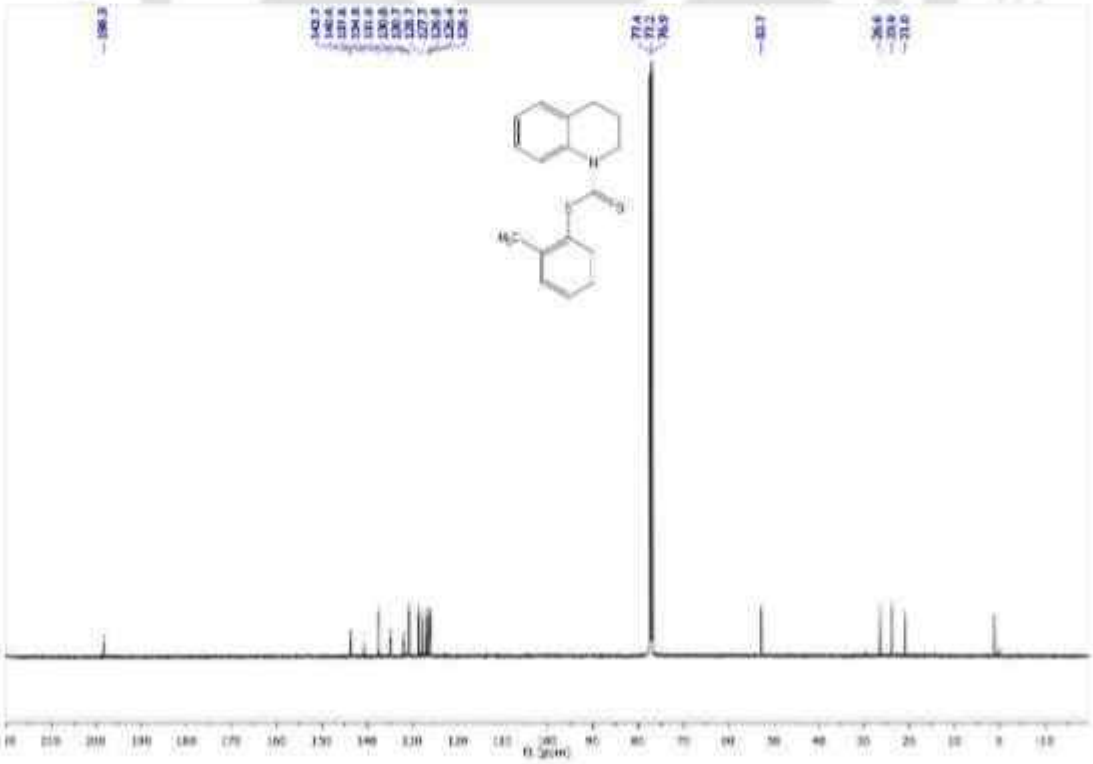


Figure S2: ^{13}C $\{^{1}H\}$ NMR Spectrum of **2.17l** ($CDCl_3$, 151 MHz, 298 K)

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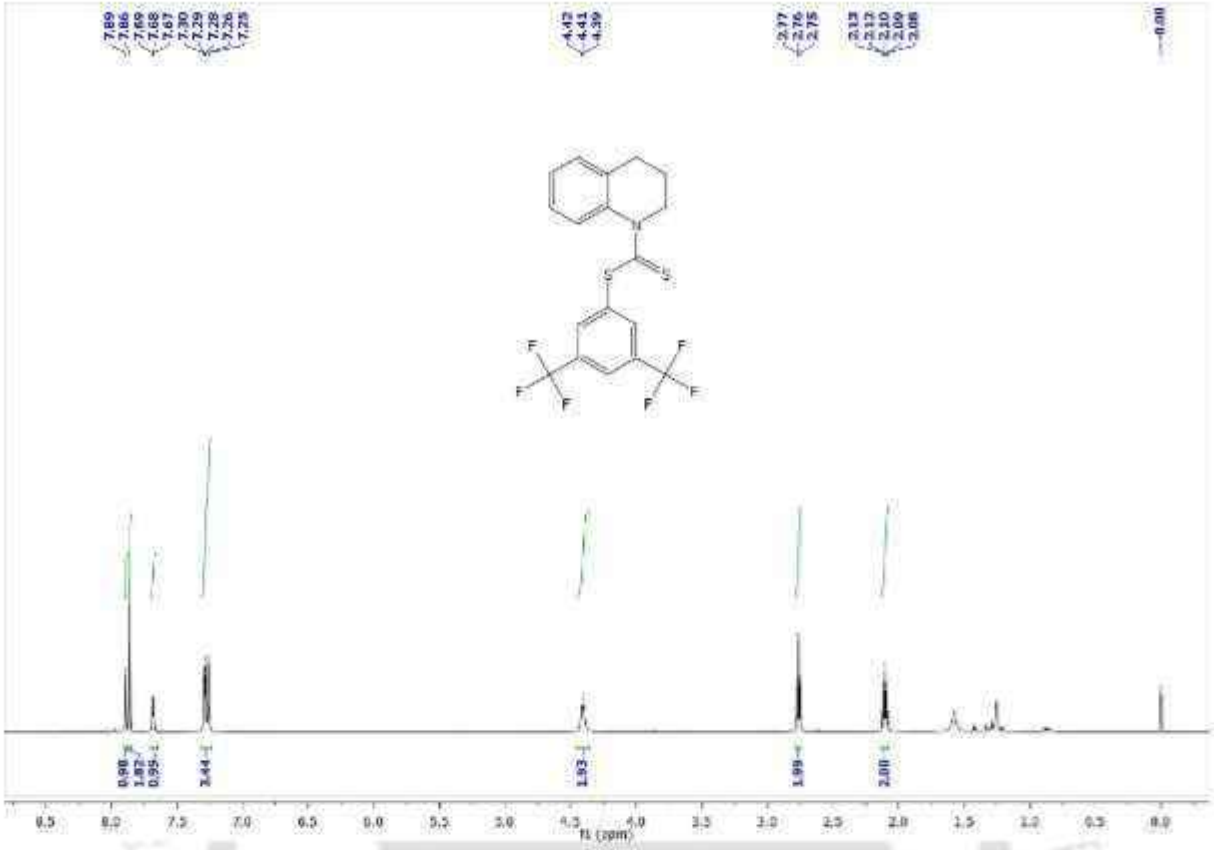


Figure S3: ^{1}H NMR Spectrum of **2.17m** ($CDCl_3$, 600 MHz, 298 K)

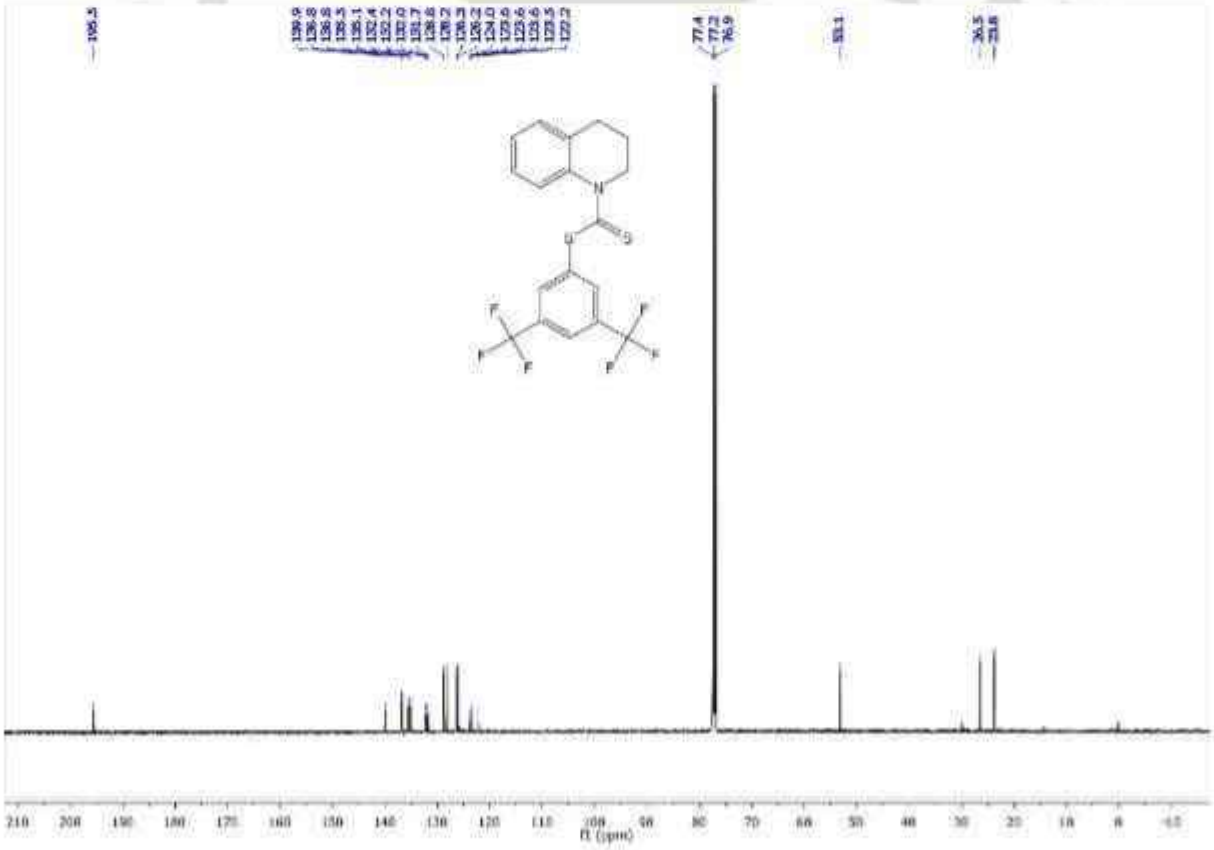


Figure S4: ^{13}C {^{1}H} NMR Spectrum of **2.17m** ($CDCl_3$, 151 MHz, 298 K)

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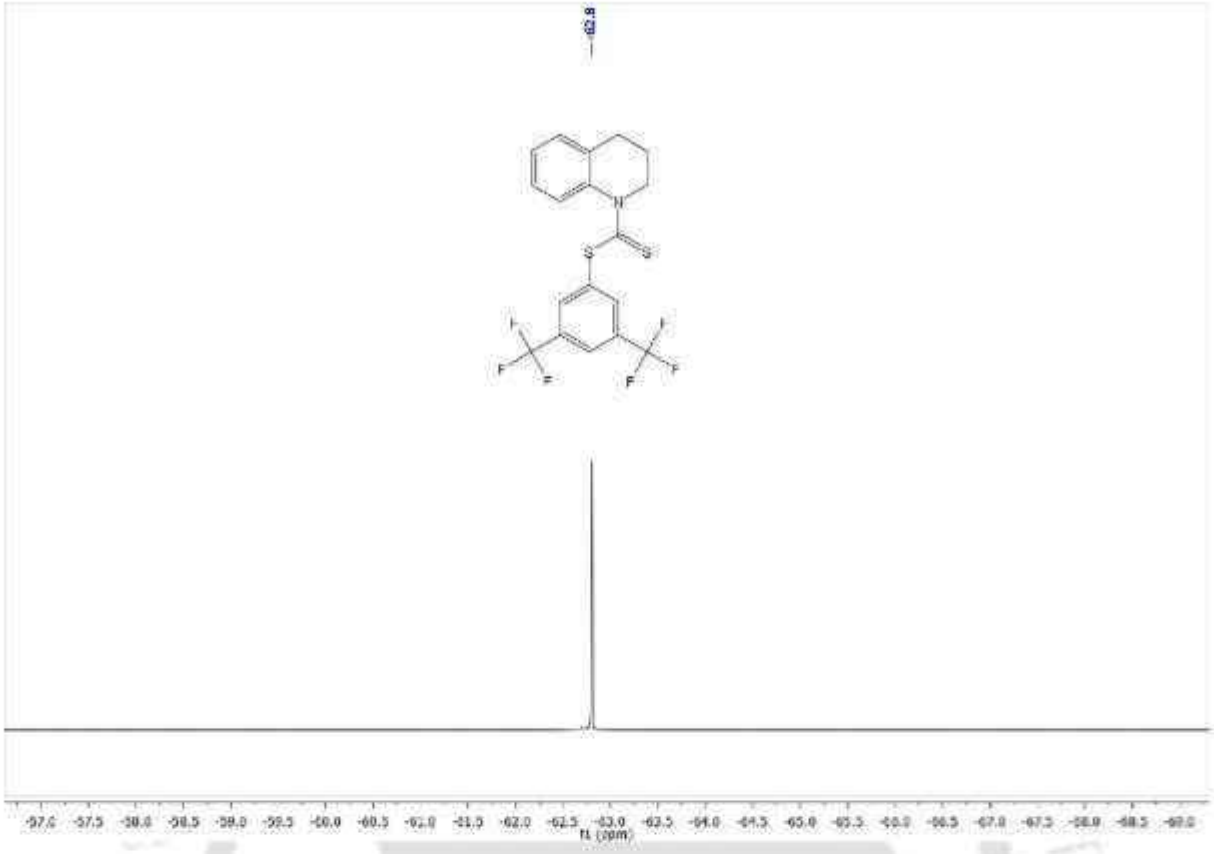


Figure S5: ^{19}F {^{1}H} NMR Spectrum of **2.17m** ($CDCl_3$, 565 MHz, 298 K)

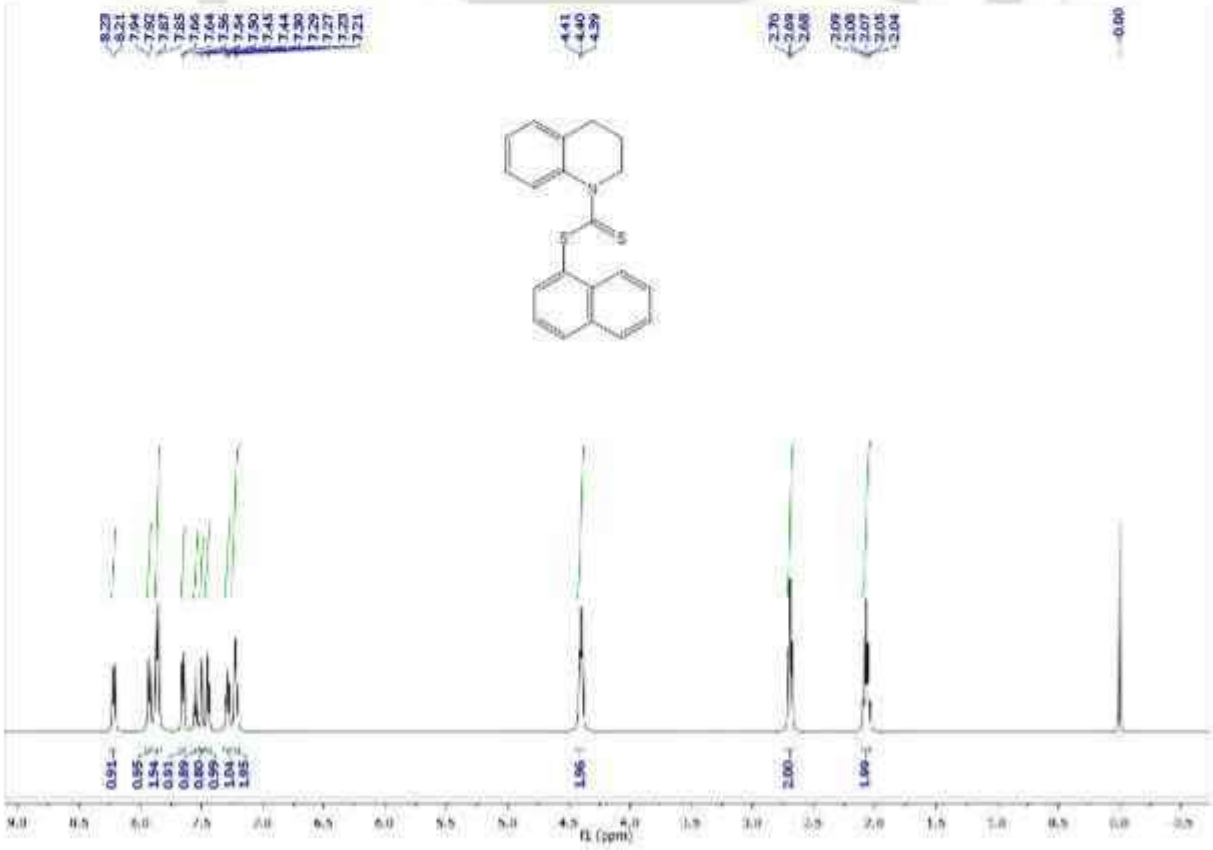


Figure S6: ^{1}H NMR Spectrum of **2.17n** ($CDCl_3$, 500 MHz, 298 K)

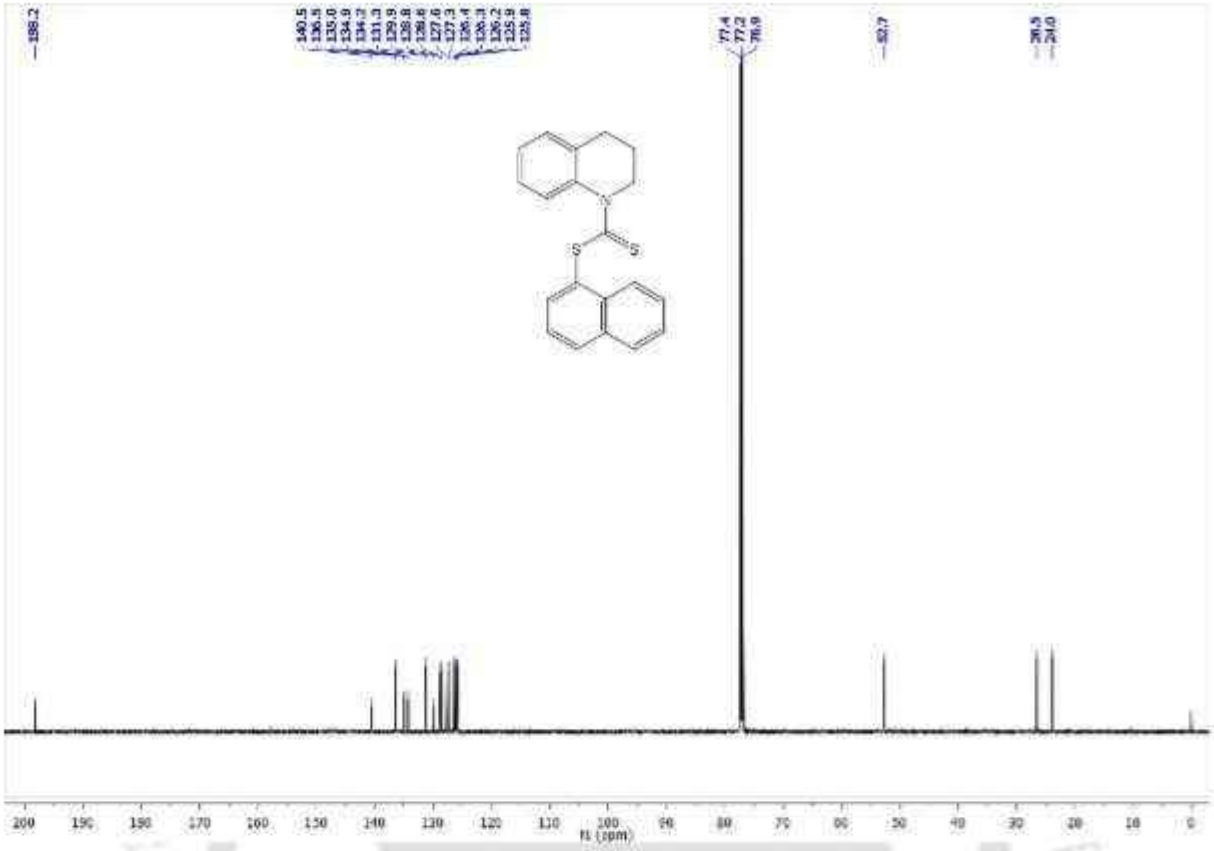


Figure S7: ^{13}C {^{1}H} NMR Spectrum of **2.17n** ($CDCl_3$, 151 MHz, 298 K)

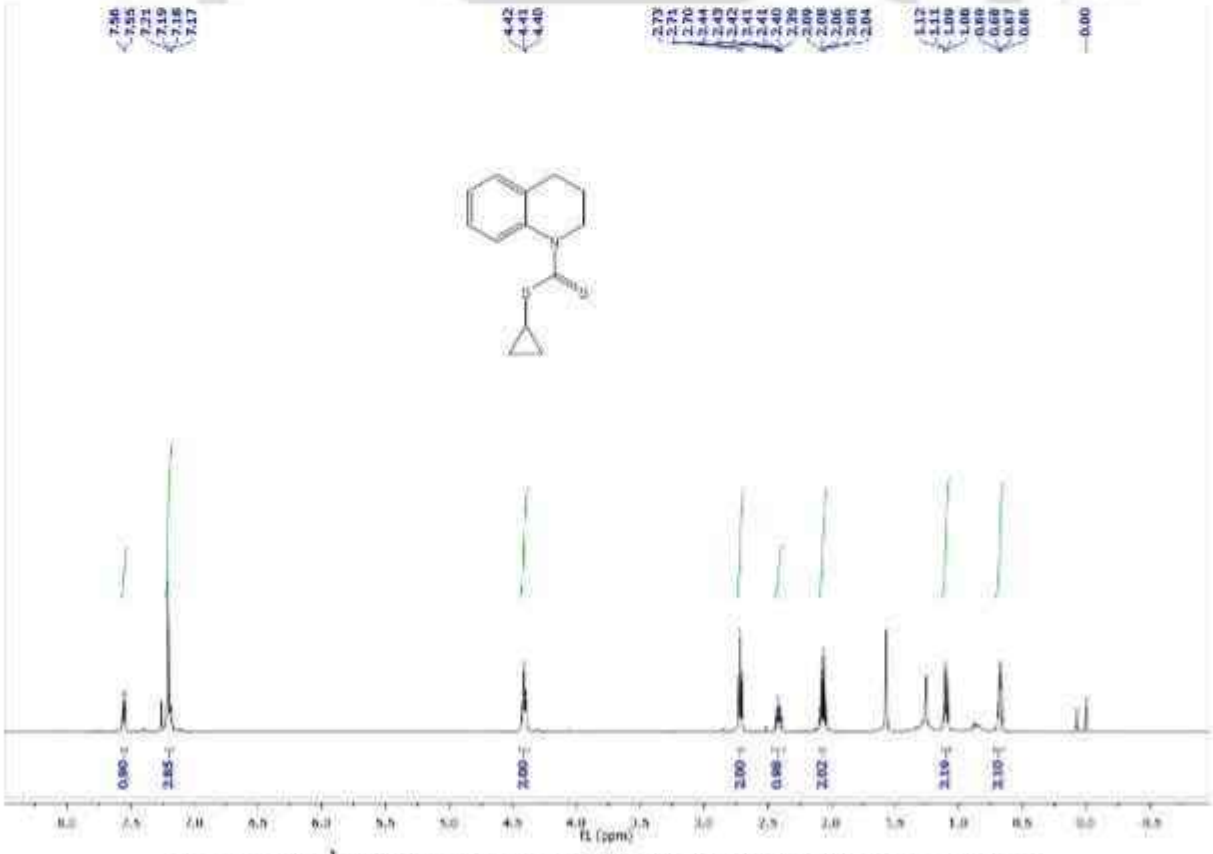


Figure S8: ^{1}H NMR Spectrum of **2.17o** ($CDCl_3$, 500 MHz, 298 K)

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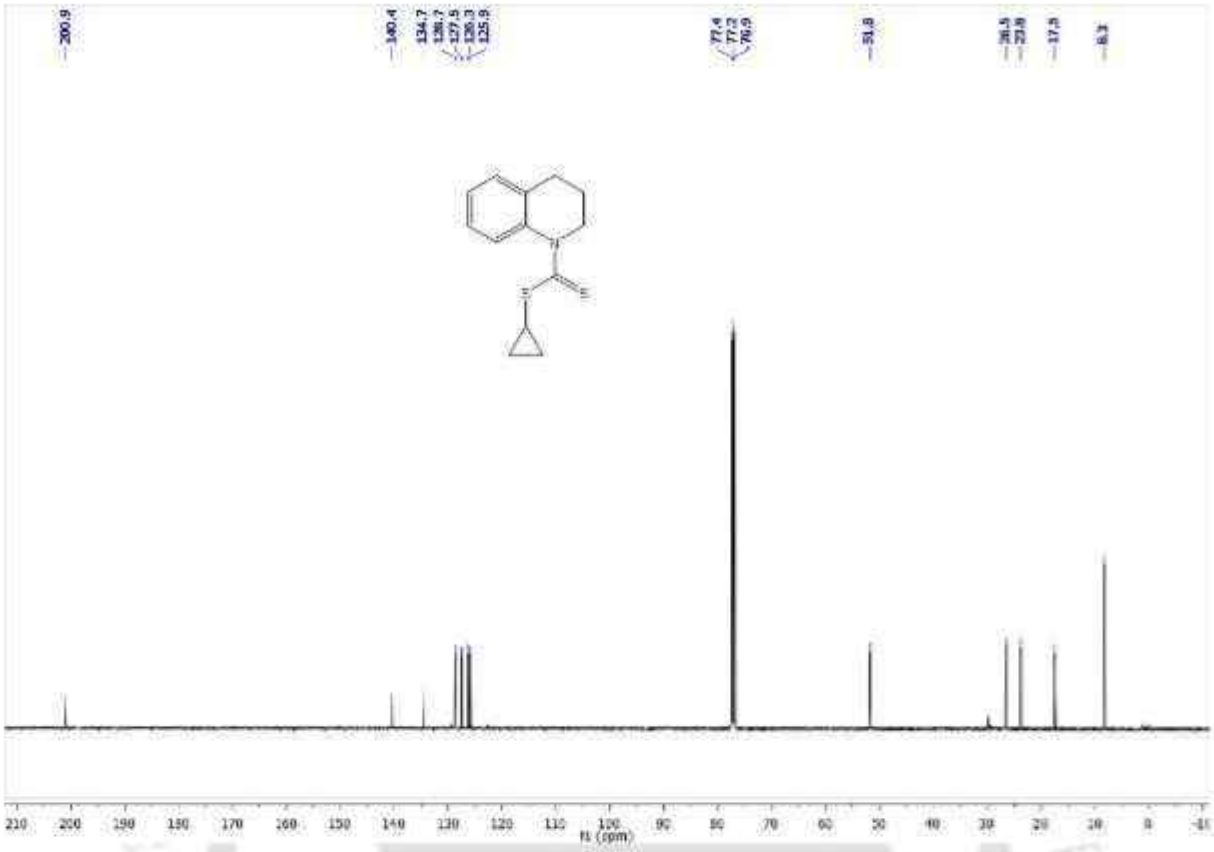


Figure S9: ^{13}C {^{1}H} NMR Spectrum of **2.17o** ($CDCl_3$, 126 MHz, 298 K)

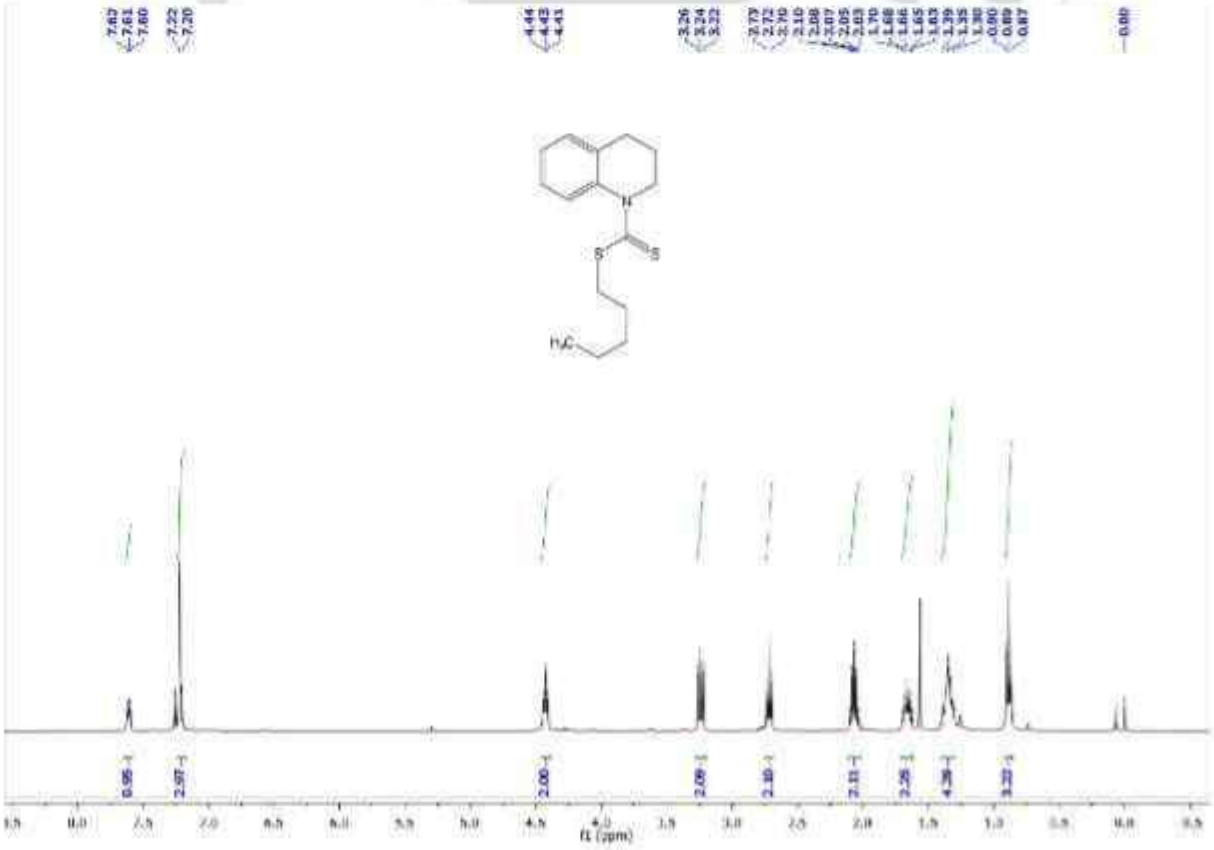


Figure S10: ^{1}H NMR Spectrum of **2.17p** ($CDCl_3$, 400 MHz, 298 K)

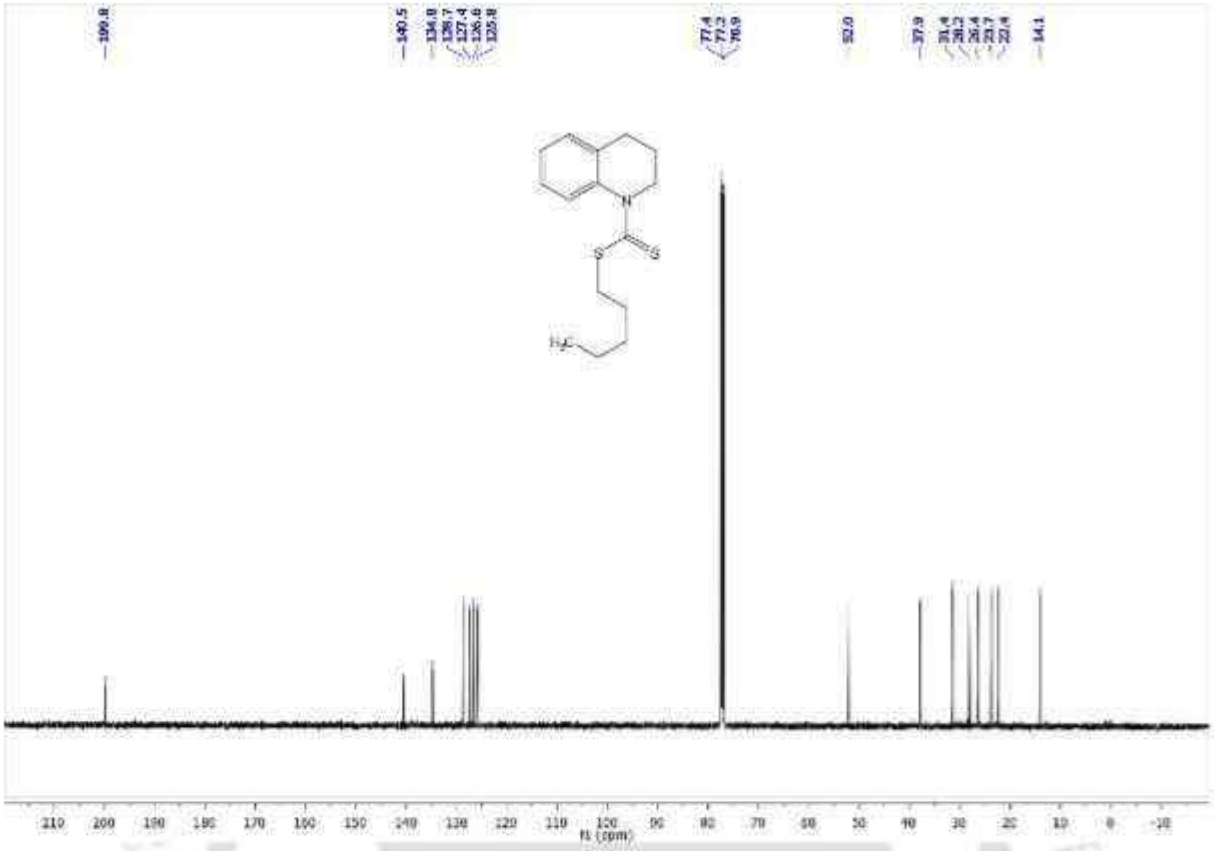


Figure S11: ^{13}C {^{1}H} NMR Spectrum of **2.17p** ($CDCl_3$, 126 MHz, 298 K)

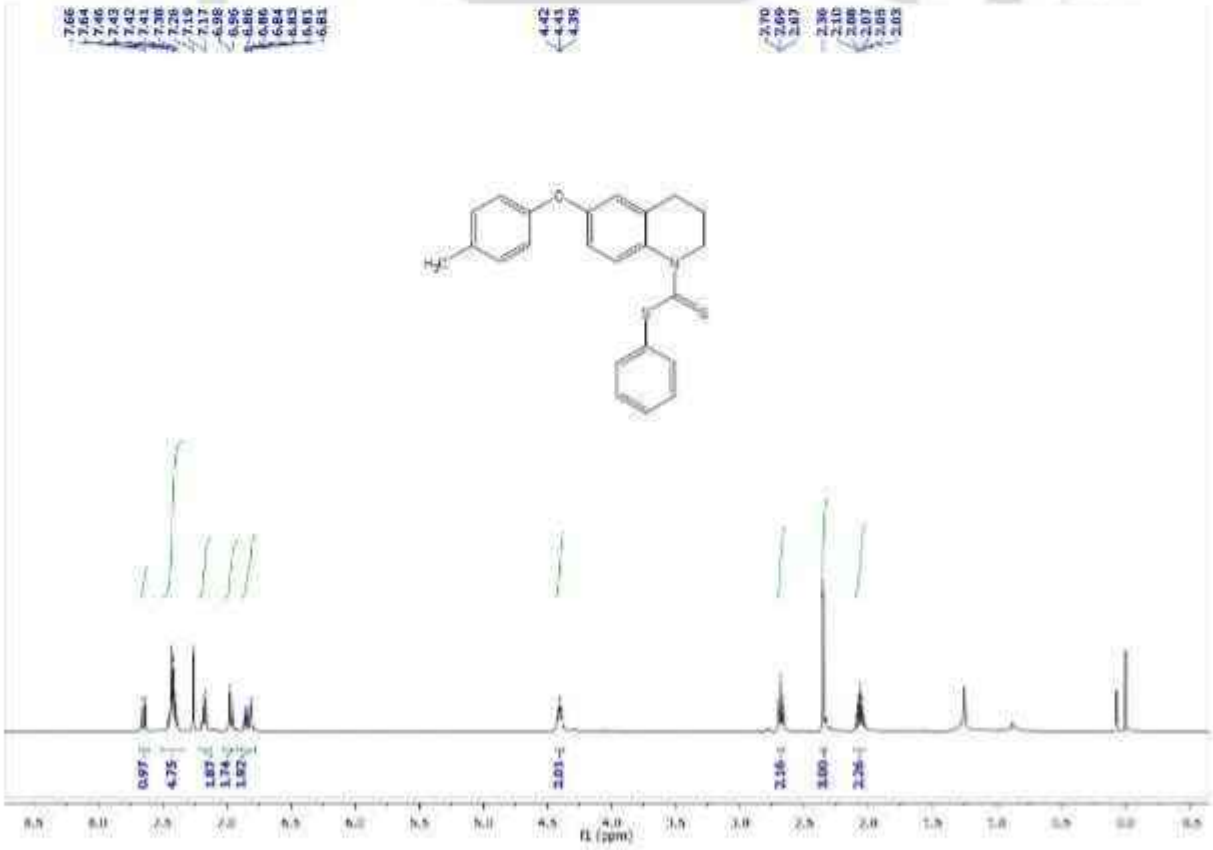


Figure S12: ^{1}H NMR Spectrum of **2.18c** ($CDCl_3$, 400 MHz, 298 K)

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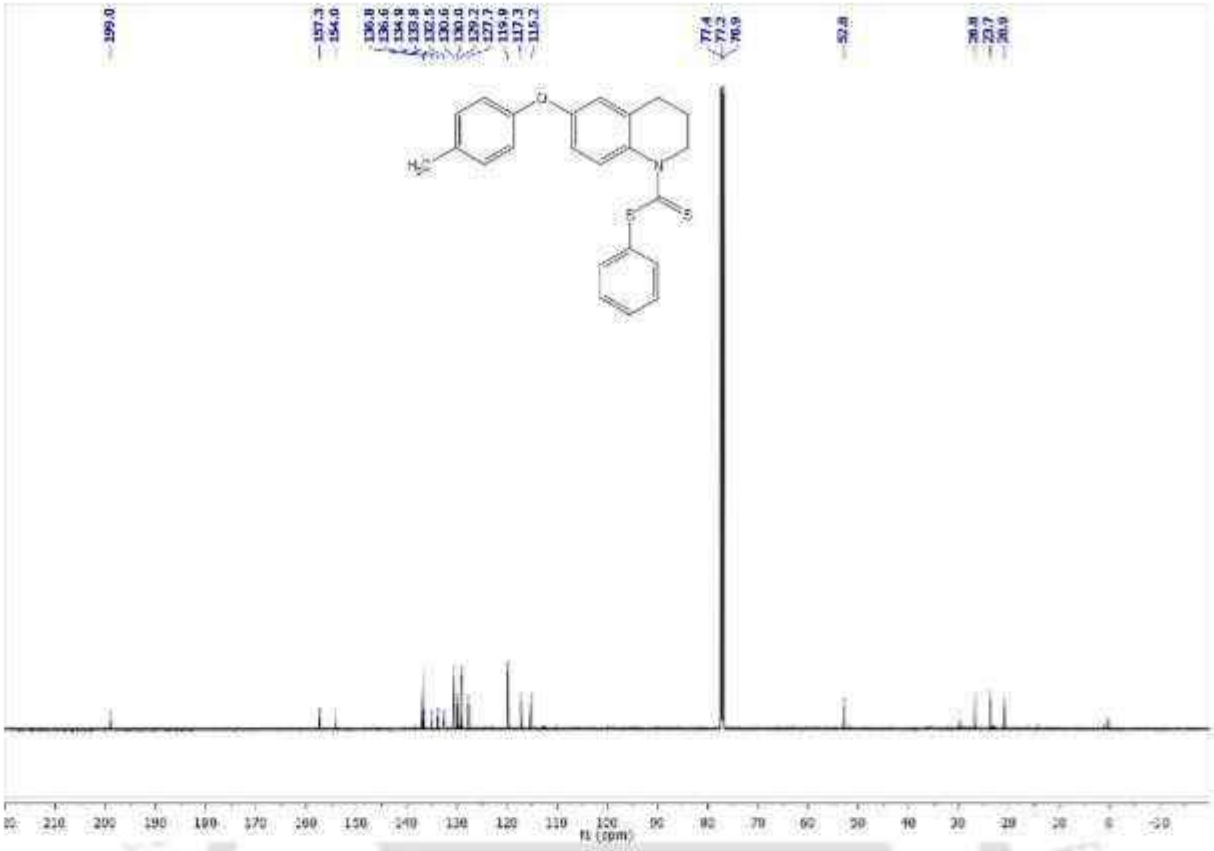


Figure S13: ^{13}C {^{1}H} NMR Spectrum of **2.18c** ($CDCl_3$, 151 MHz, 298 K)

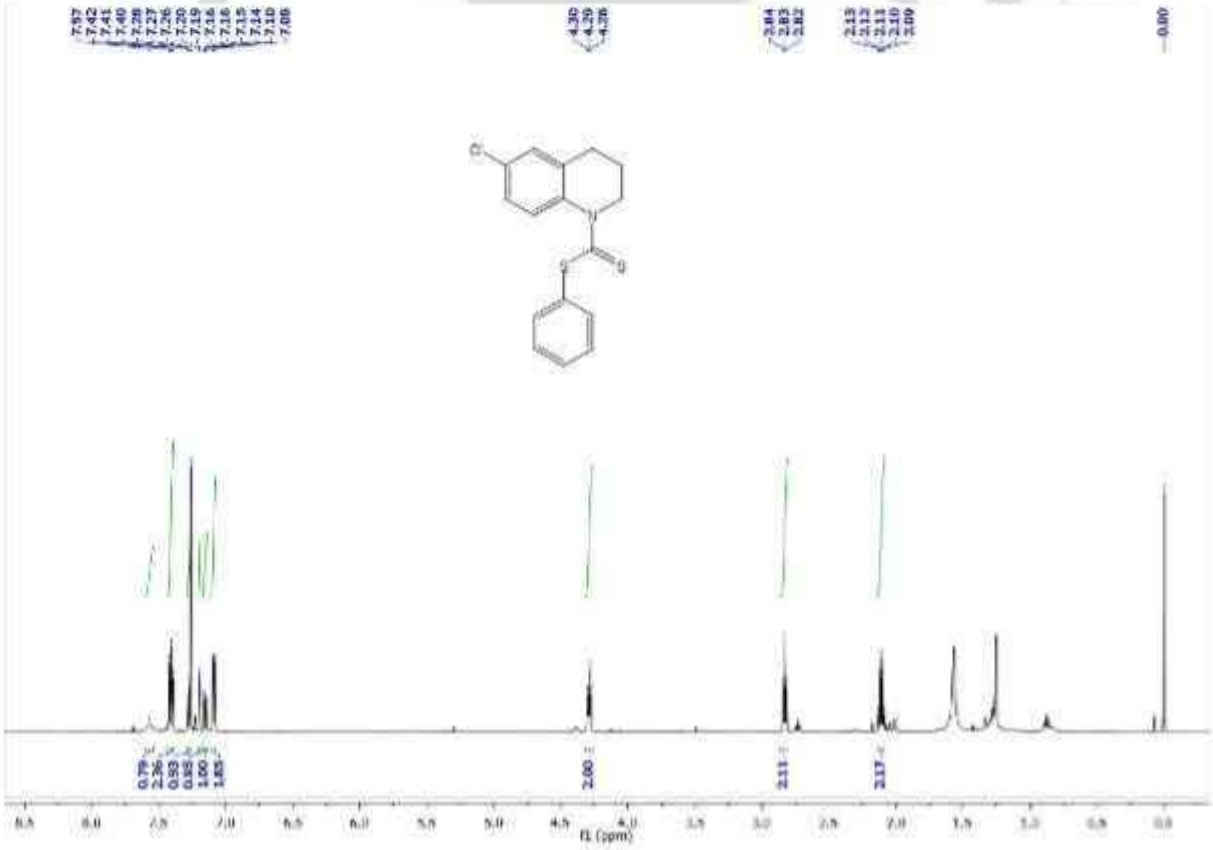


Figure S14: ^{1}H NMR Spectrum of **2.18d** ($CDCl_3$, 600 MHz, 298 K)

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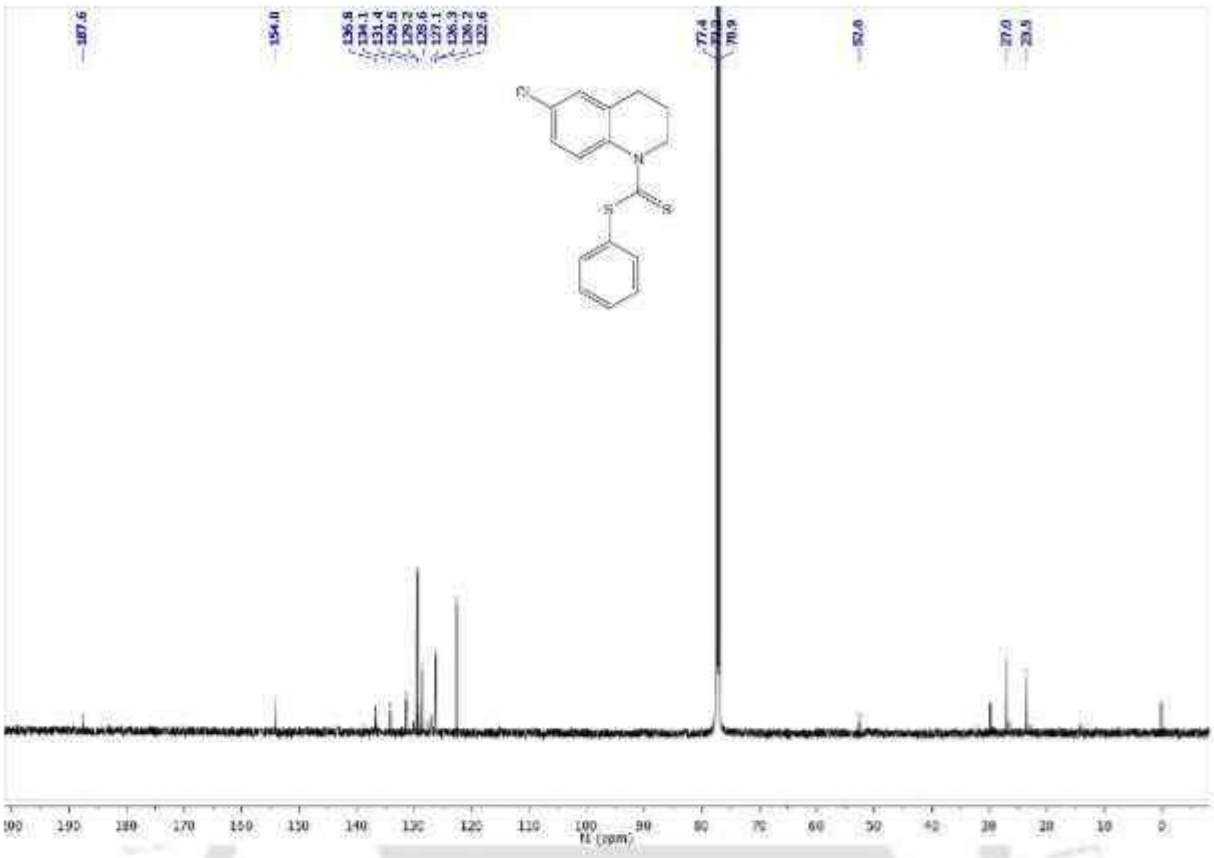


Figure S15: ^{13}C {^{1}H} NMR Spectrum of **2.18d** ($CDCl_3$, 151 MHz, 298 K)

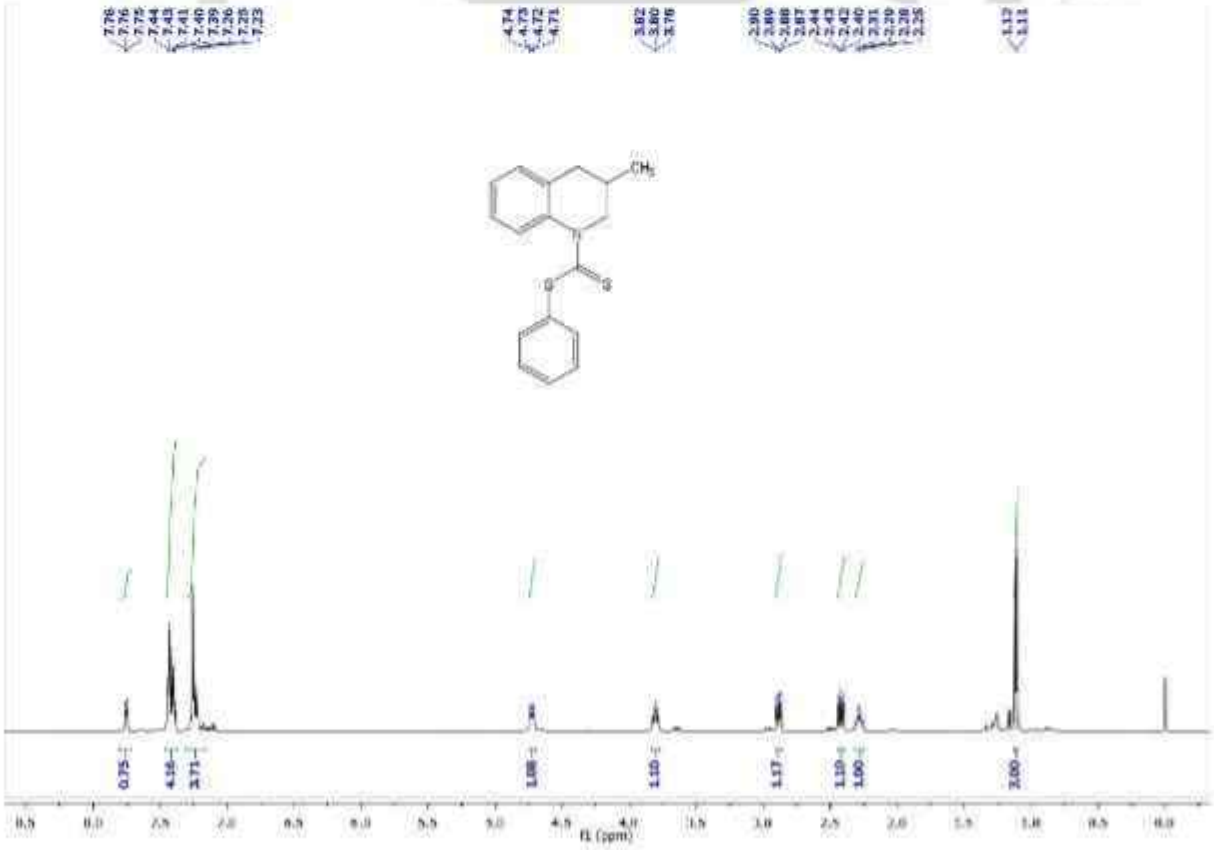


Figure S16: ^{1}H NMR Spectrum of **2.18f** ($CDCl_3$, 600 MHz, 298 K)

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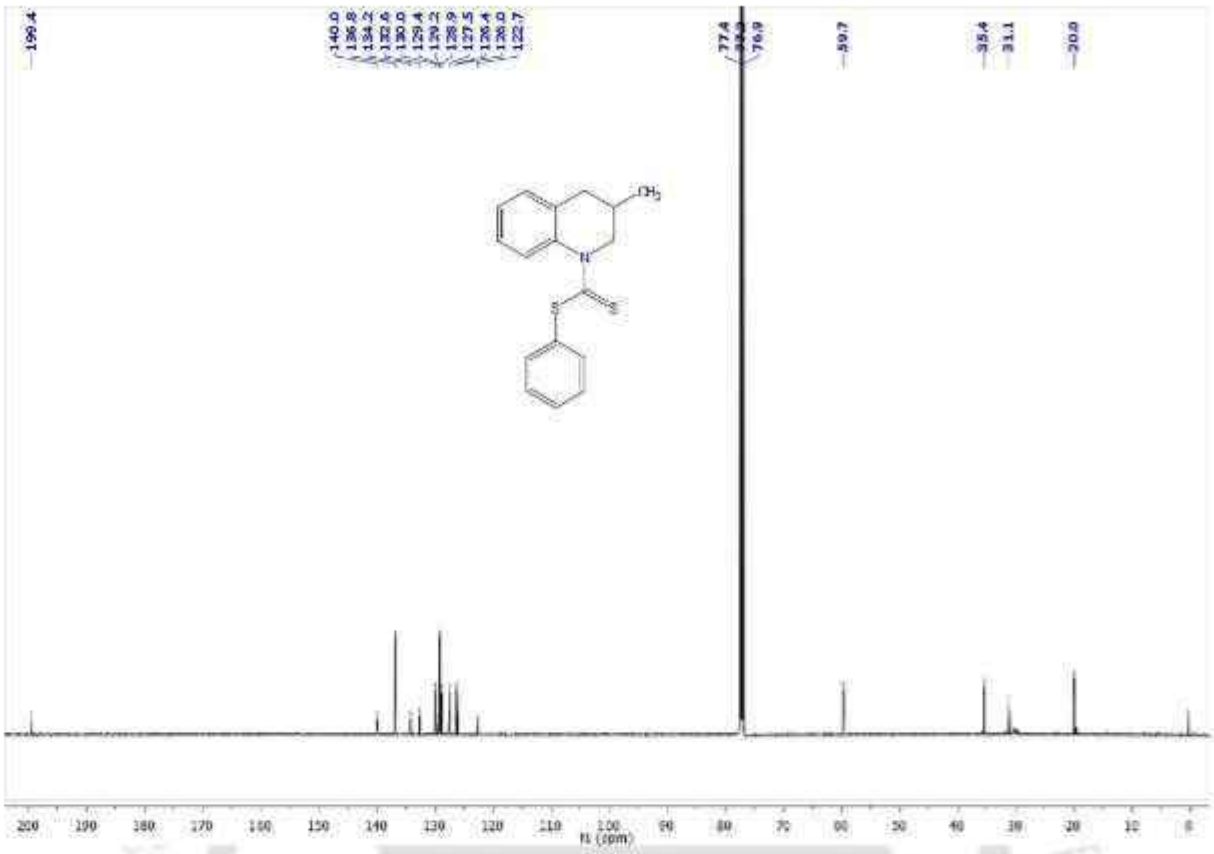


Figure S17: ^{13}C {^{1}H} NMR Spectrum of **2.18f** ($CDCl_3$, 151 MHz, 298 K)

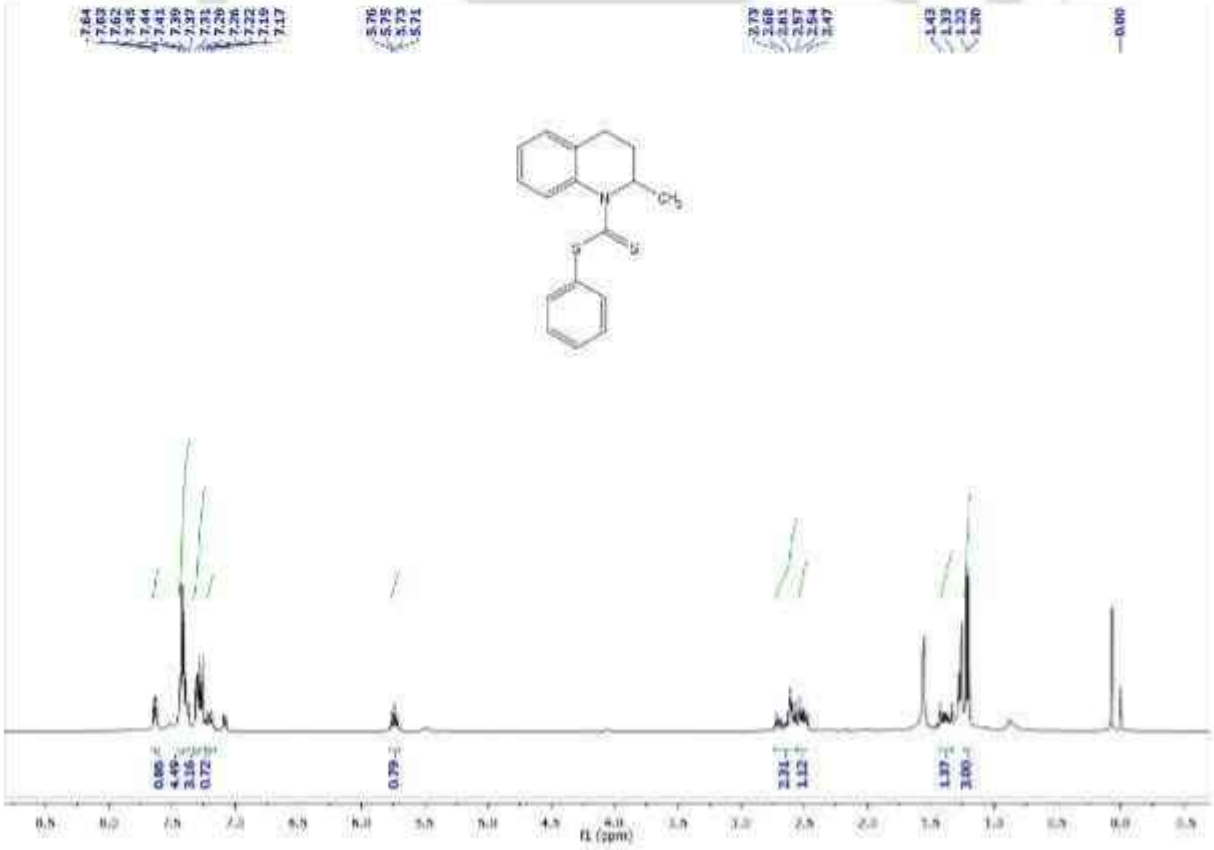


Figure S18: ^{1}H NMR Spectrum of **2.18g** ($CDCl_3$, 400 MHz, 298 K)

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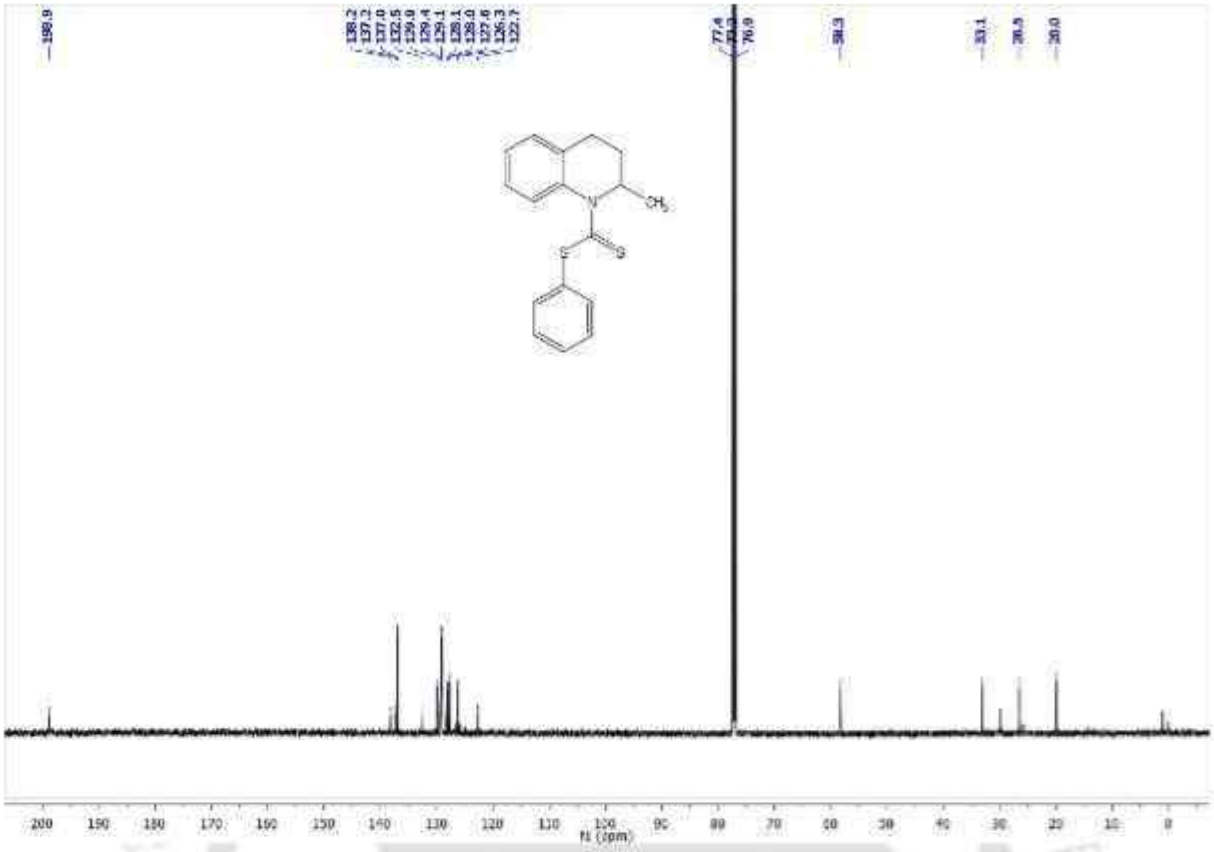


Figure S19: ^{13}C {^{1}H} NMR Spectrum of **2.18g** ($CDCl_3$, 151 MHz, 298 K)

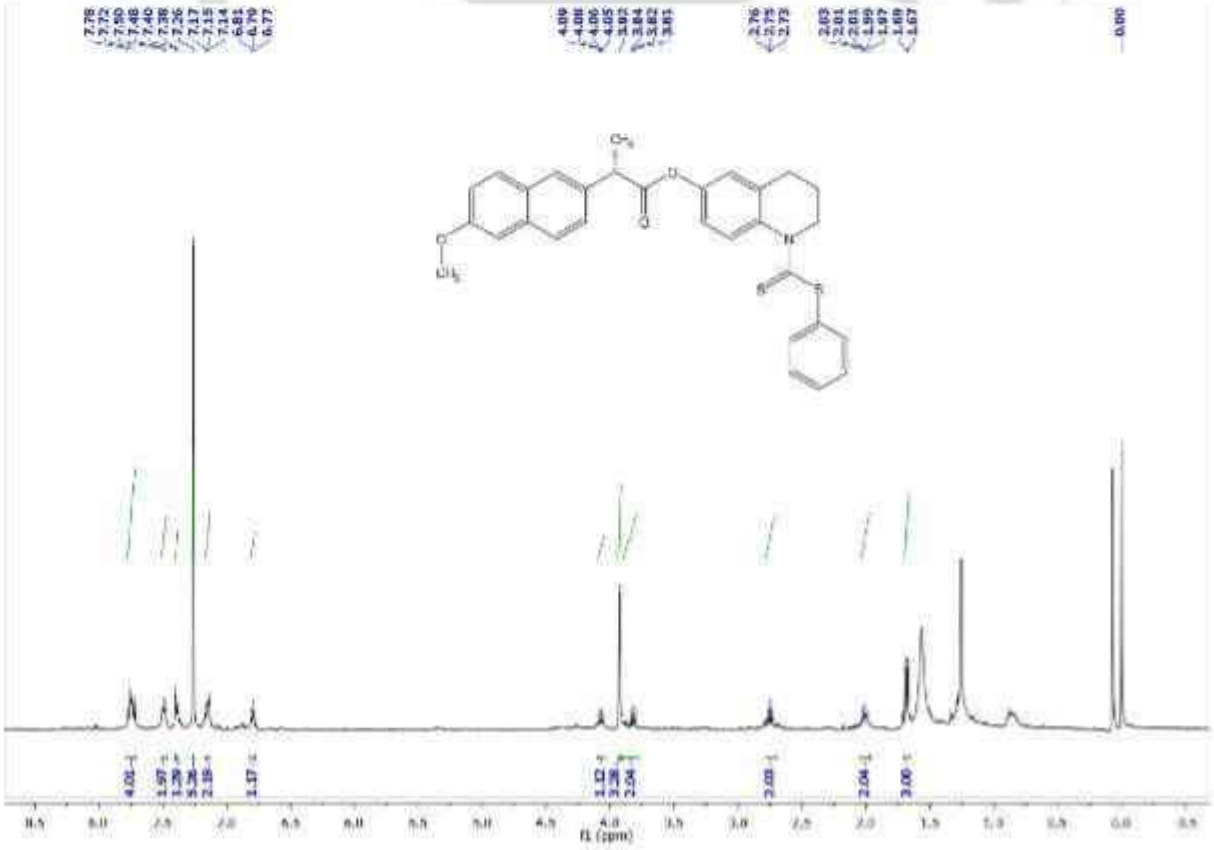


Figure S20: ^{1}H NMR Spectrum of **2.18h** ($CDCl_3$, 400 MHz, 298 K)

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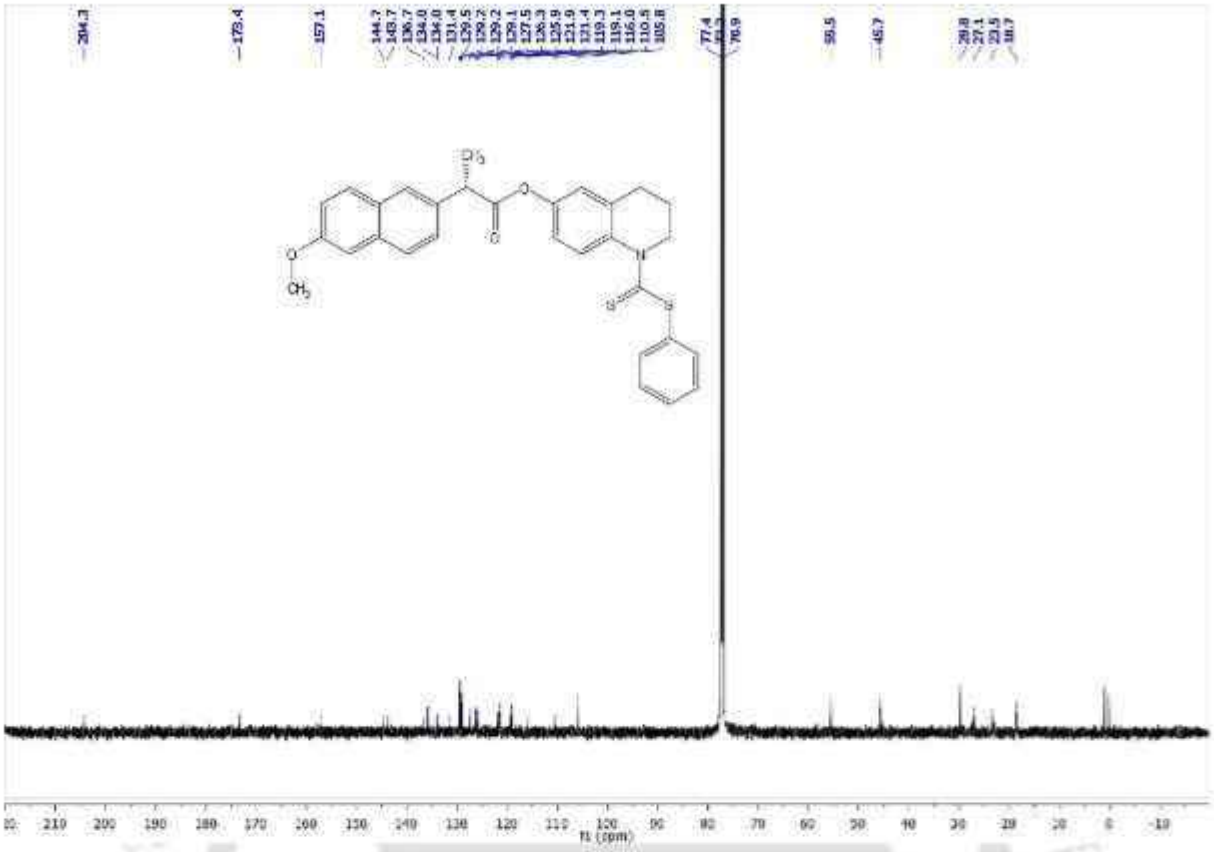


Figure S21: ^{13}C {^{1}H} NMR Spectrum of **2.18h** ($CDCl_3$, 151 MHz, 298 K)

The supporting information and all other product spectra for chapter 2 is available at https://doi.org/10.1039/D4OB00490F

Annexure II

^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ spectra of representative compounds (*Chapter 3*)

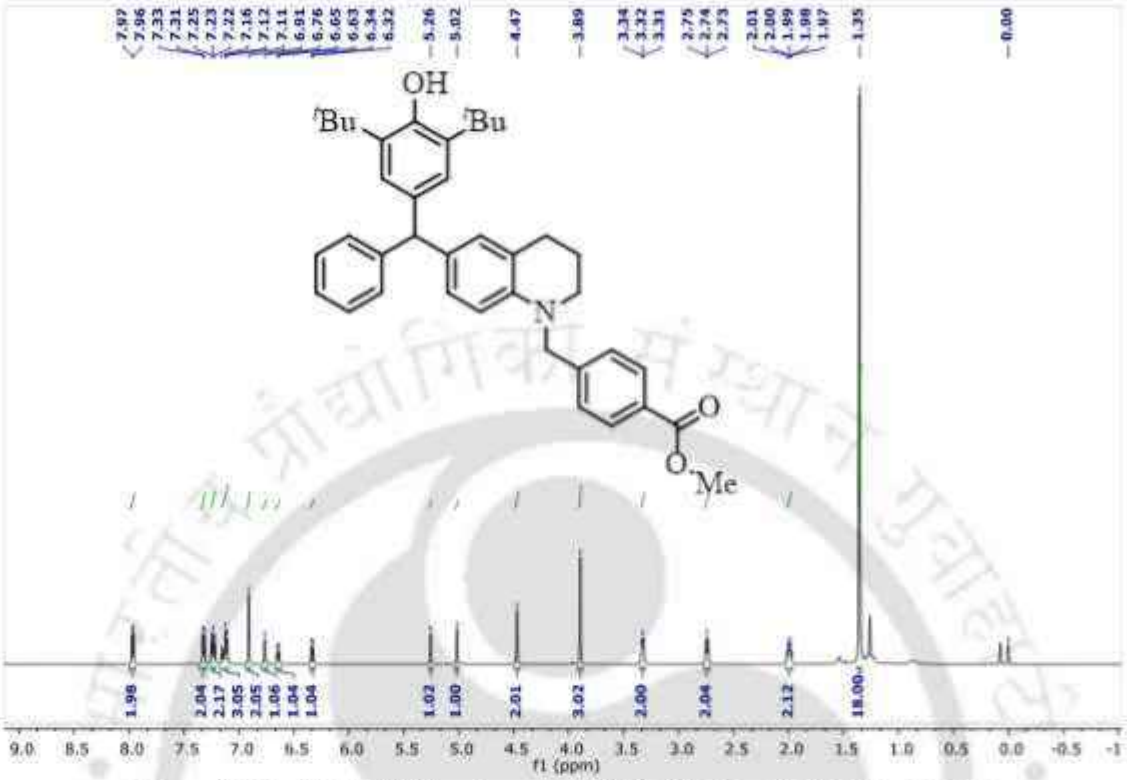


Figure S22: ^{1}H NMR Spectrum of **3.21j** ($CDCl_3$, 500 MHz, 298 K)

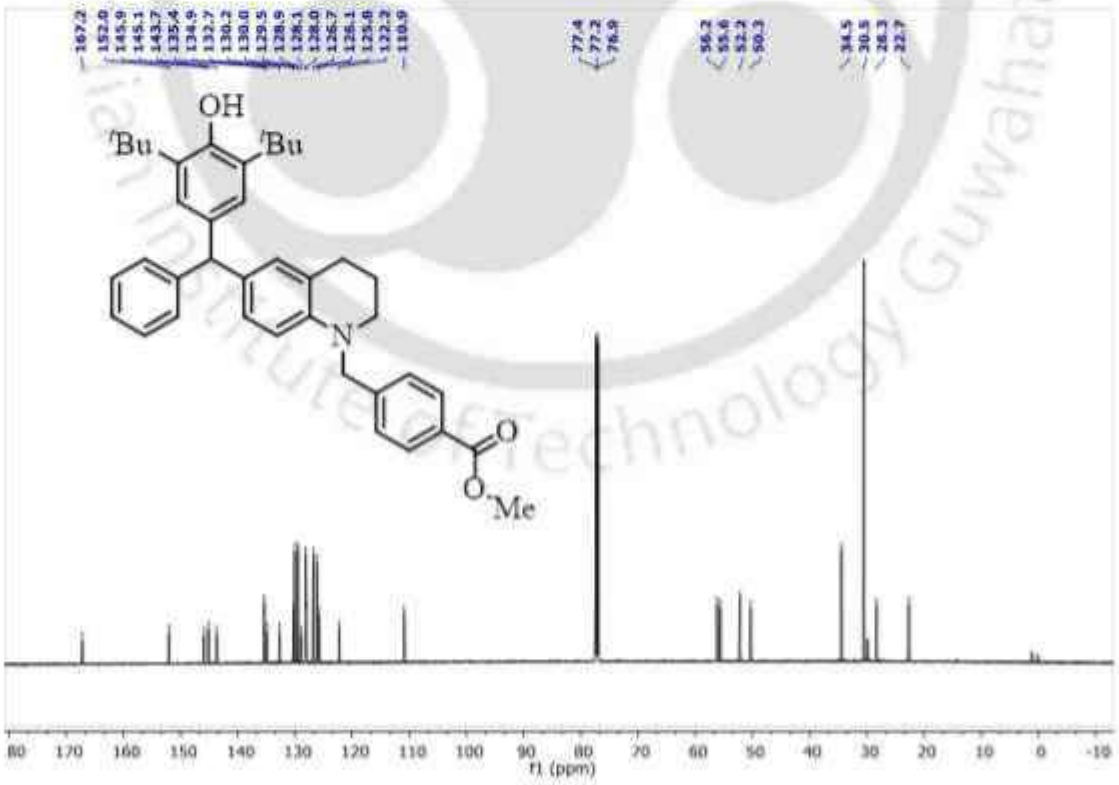


Figure S23: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.21j** ($CDCl_3$, 151 MHz, 298 K)

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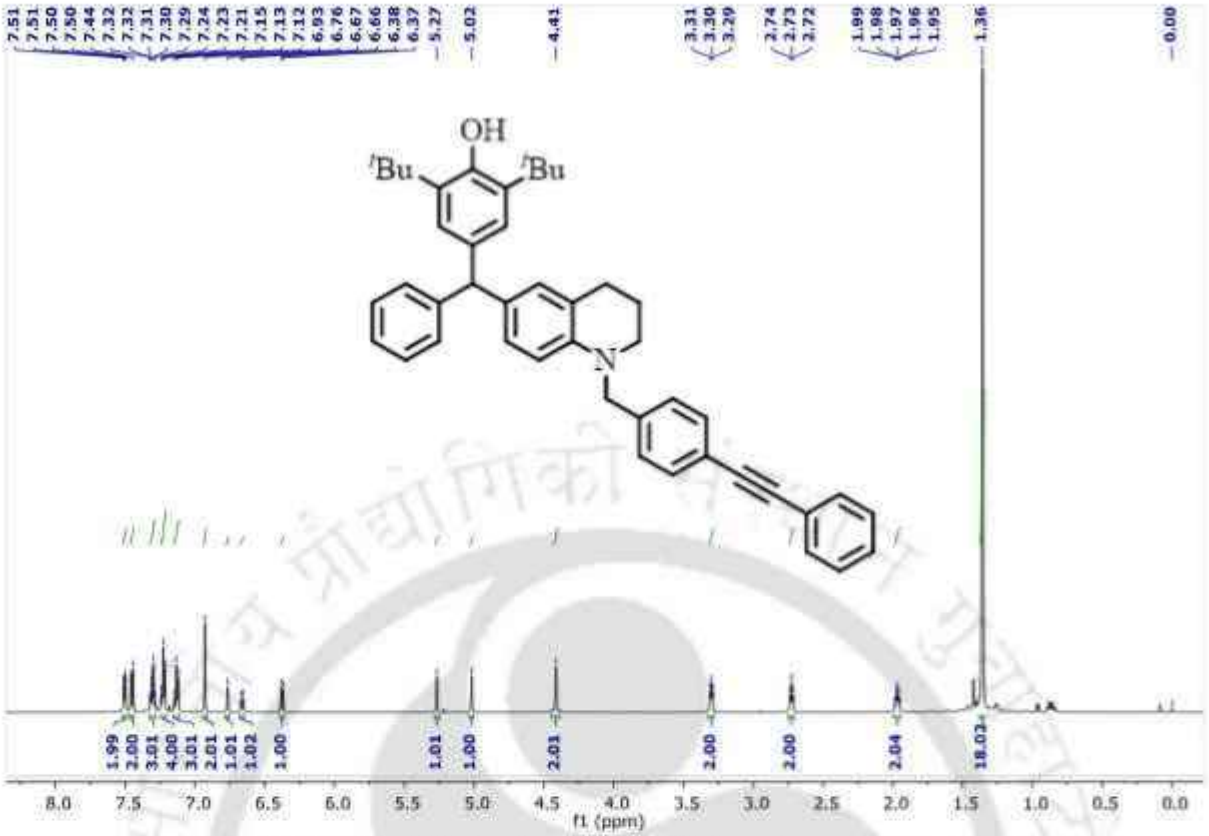


Figure S24: ^{1}H NMR Spectrum of **3.21k** ($CDCl_3$, 600 MHz, 298 K)

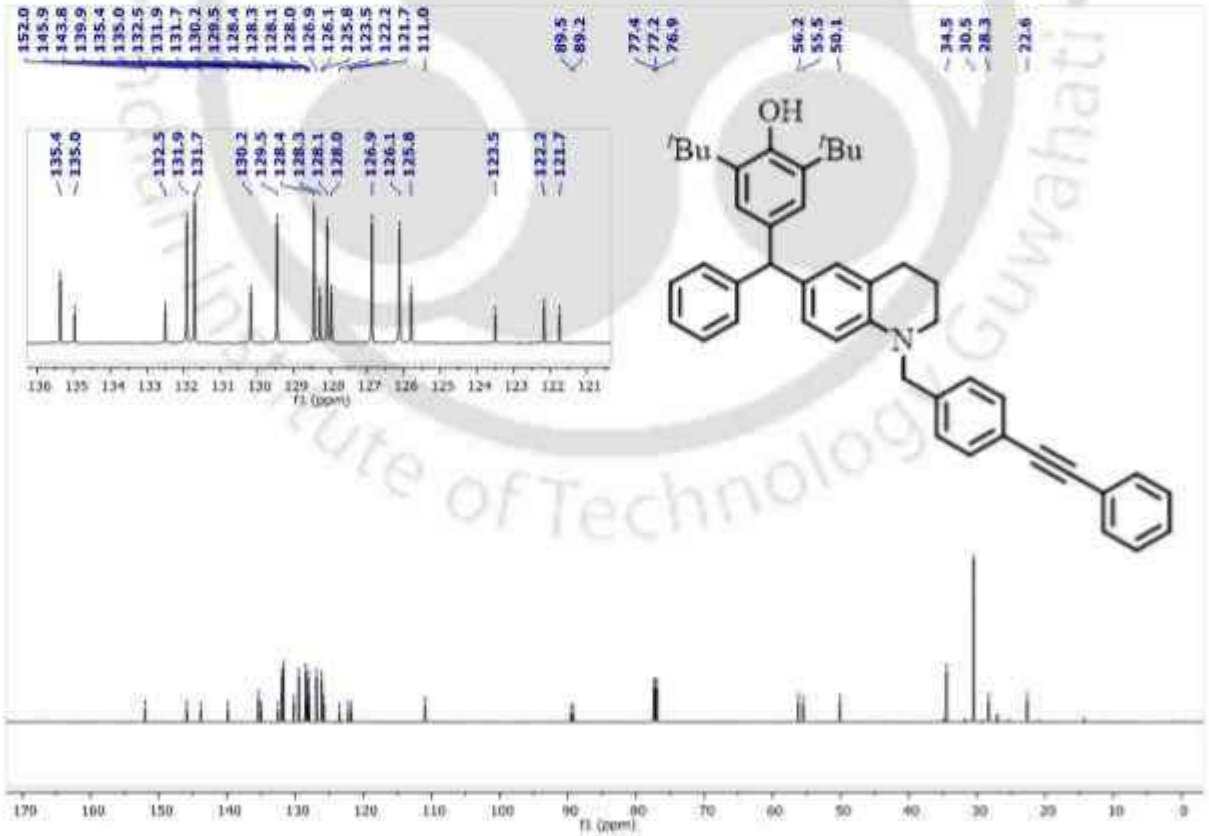


Figure S25: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.21k** ($CDCl_3$, 151 MHz, 298 K)

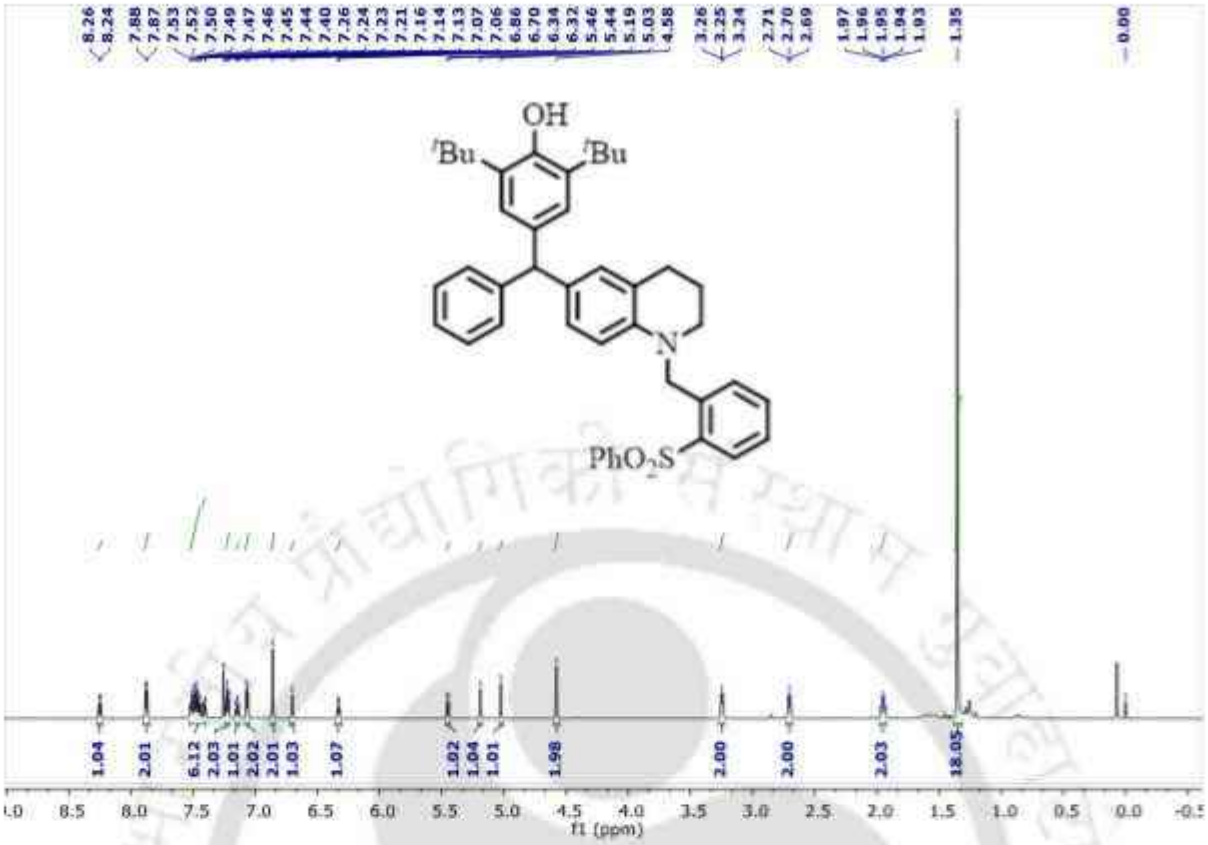


Figure S26: ^{1}H NMR Spectrum of **3.21q** ($CDCl_3$, 600 MHz, 298 K)

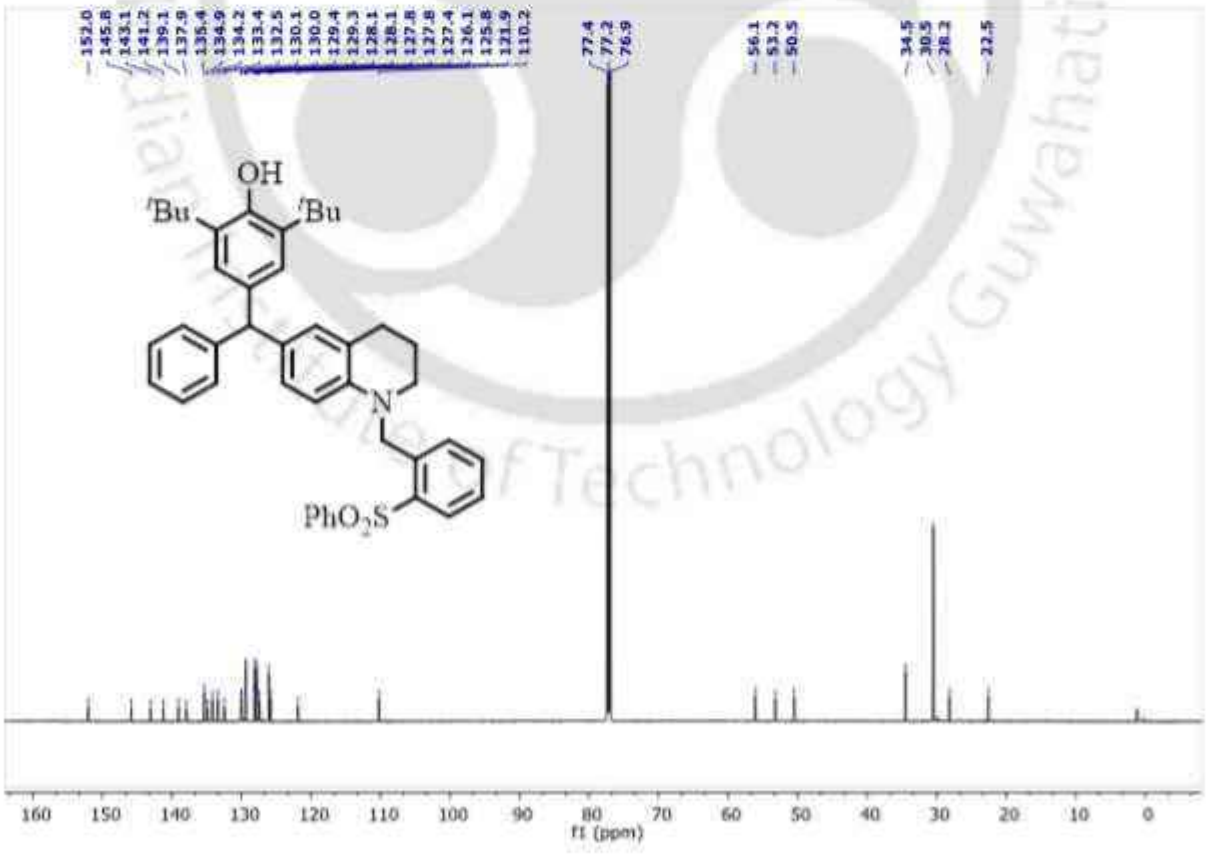


Figure S27: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.21q** ($CDCl_3$, 151 MHz, 298 K)

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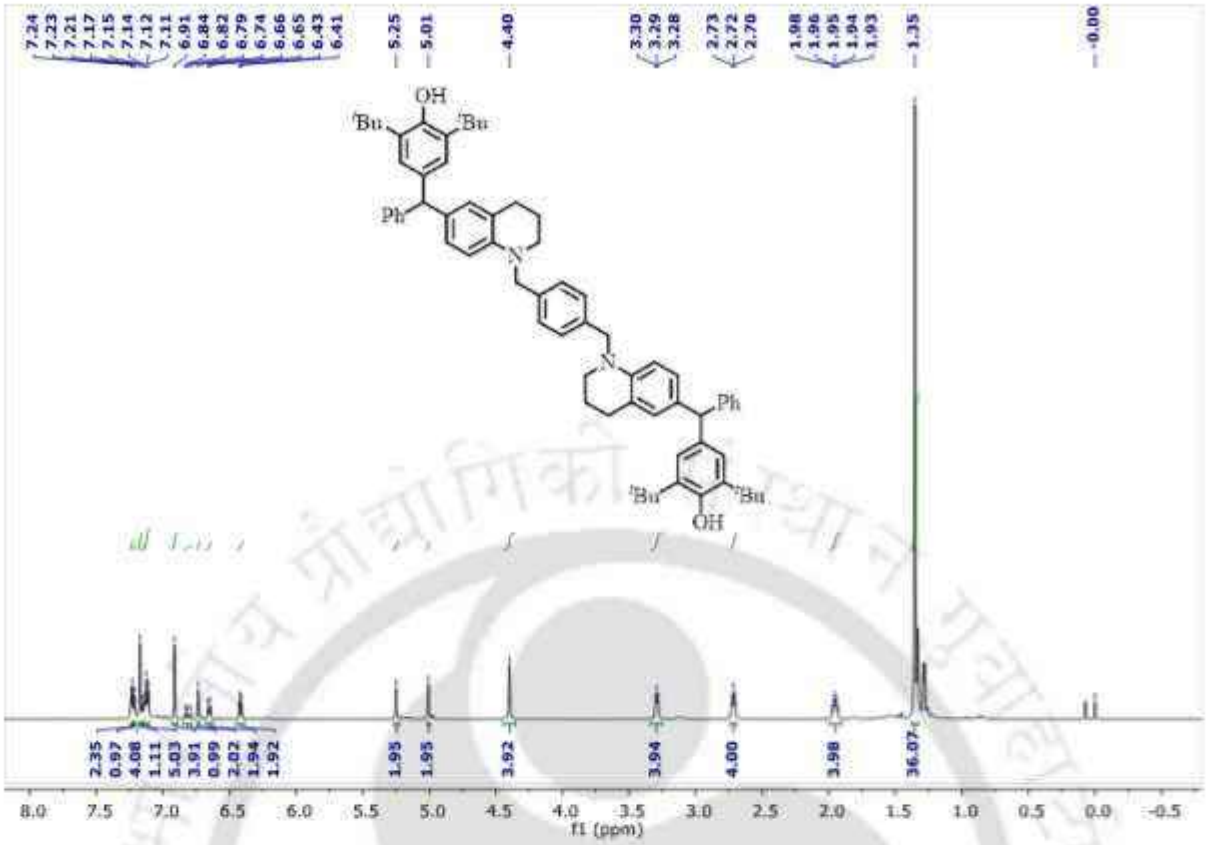


Figure S28: ^{1}H NMR Spectrum of **3.21u** ($CDCl_3$, 500 MHz, 298 K)

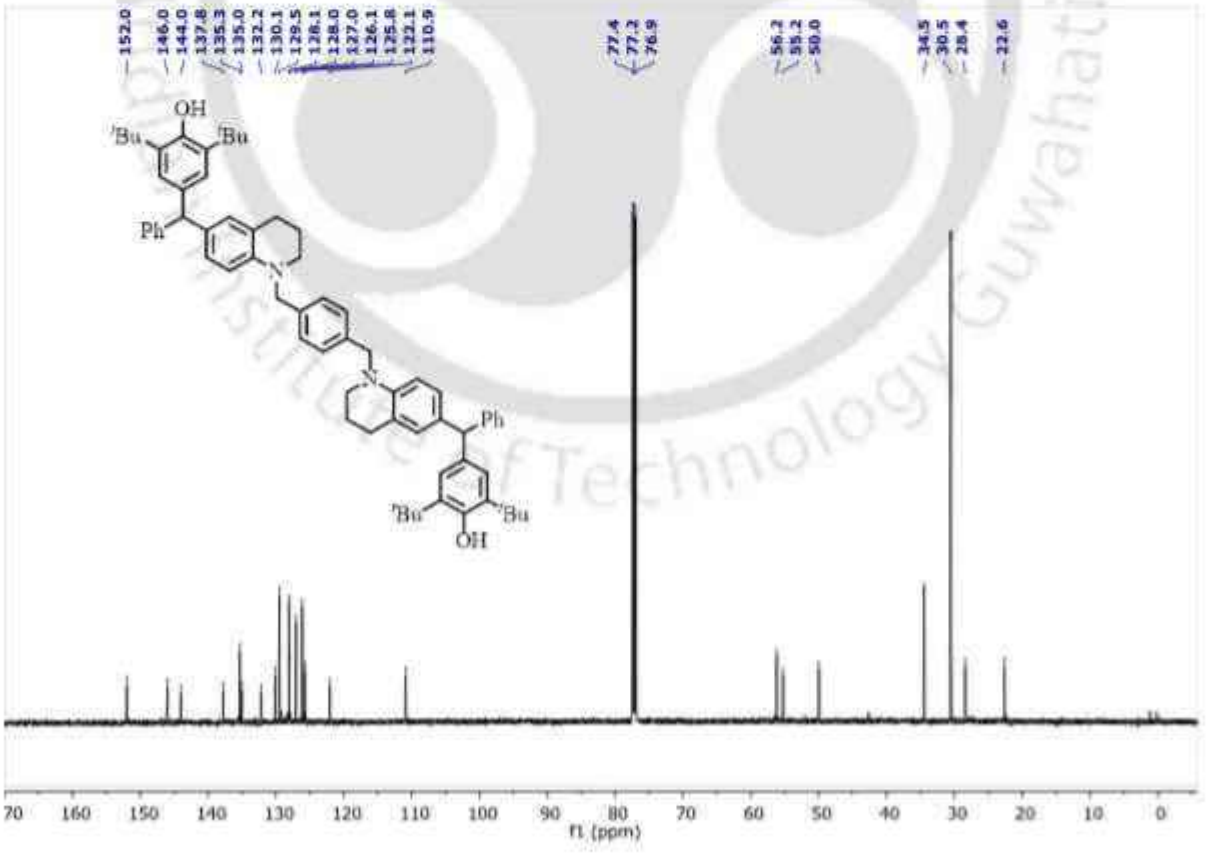


Figure S29: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.21u** ($CDCl_3$, 151 MHz, 298 K)

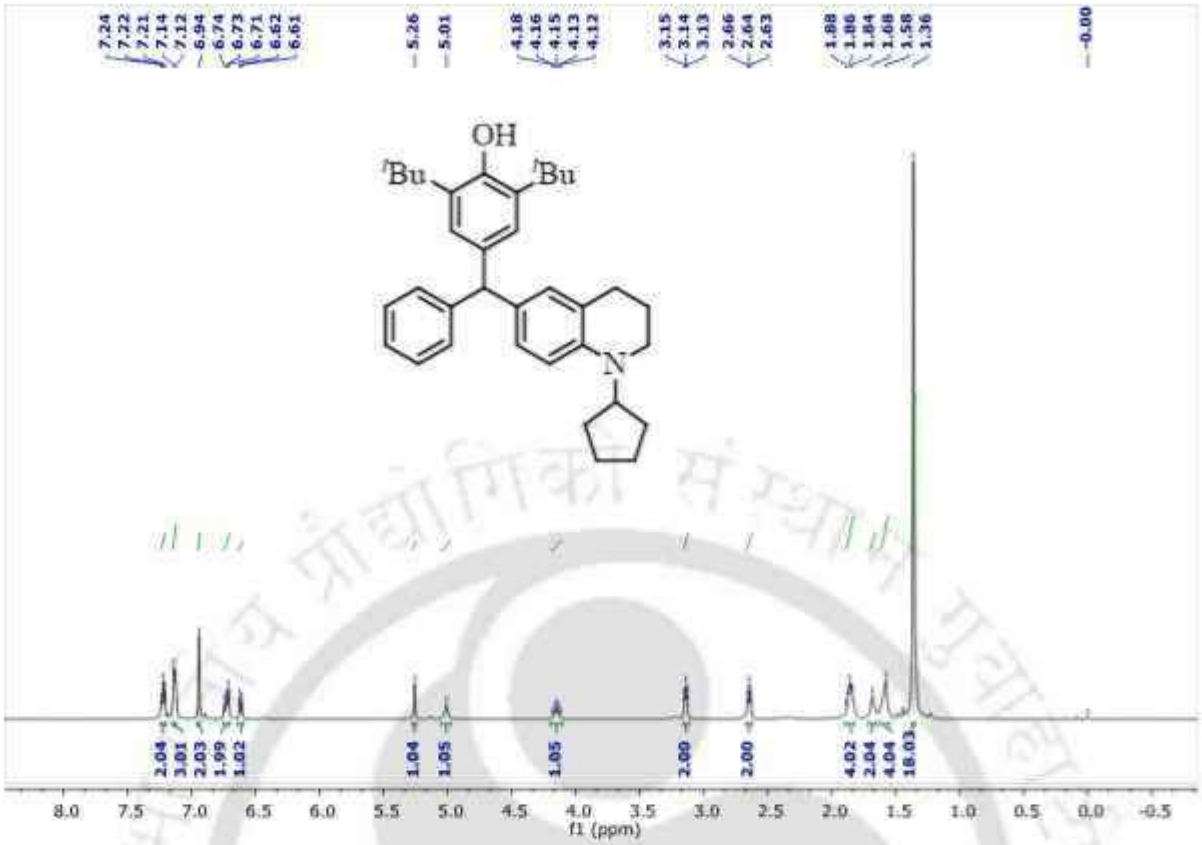


Figure S30: ^{1}H NMR Spectrum of **3.21x** ($CDCl_3$, 500 MHz, 298 K)

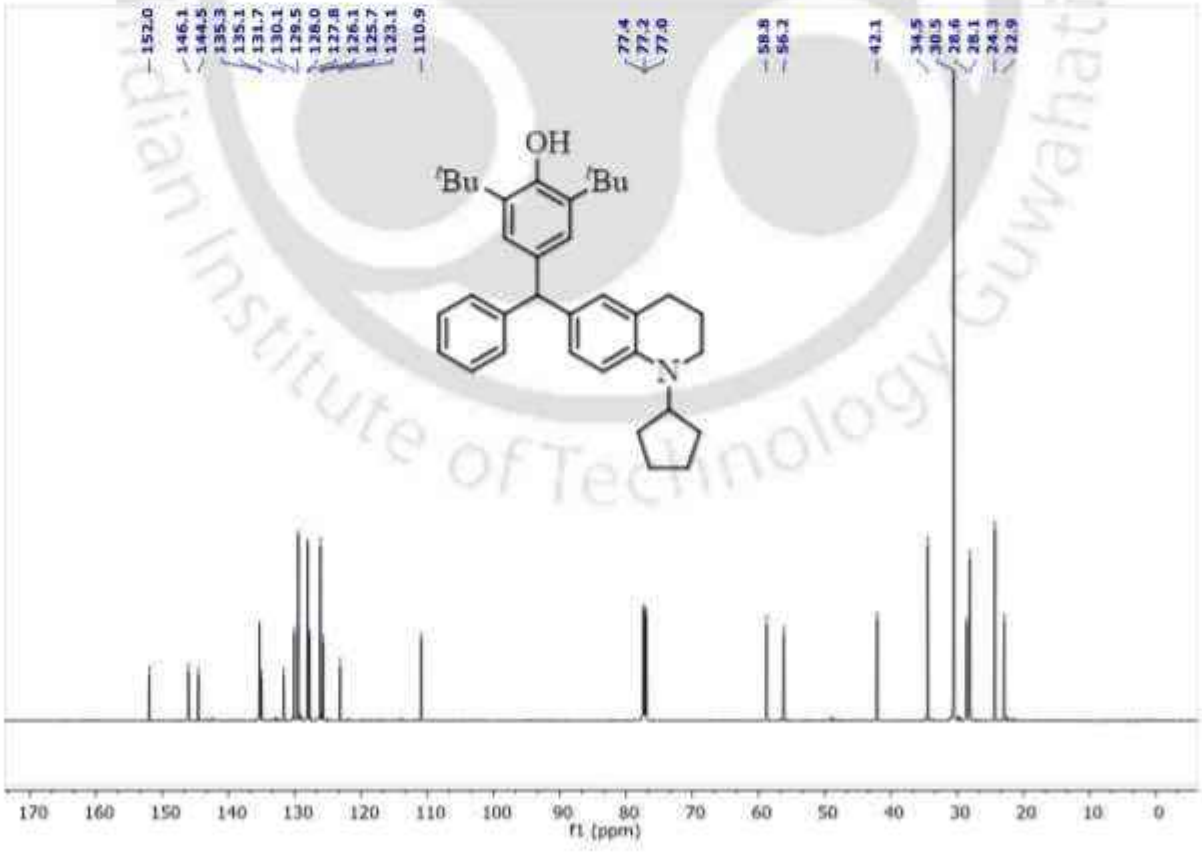


Figure S31: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.21x** ($CDCl_3$, 151 MHz, 298 K)

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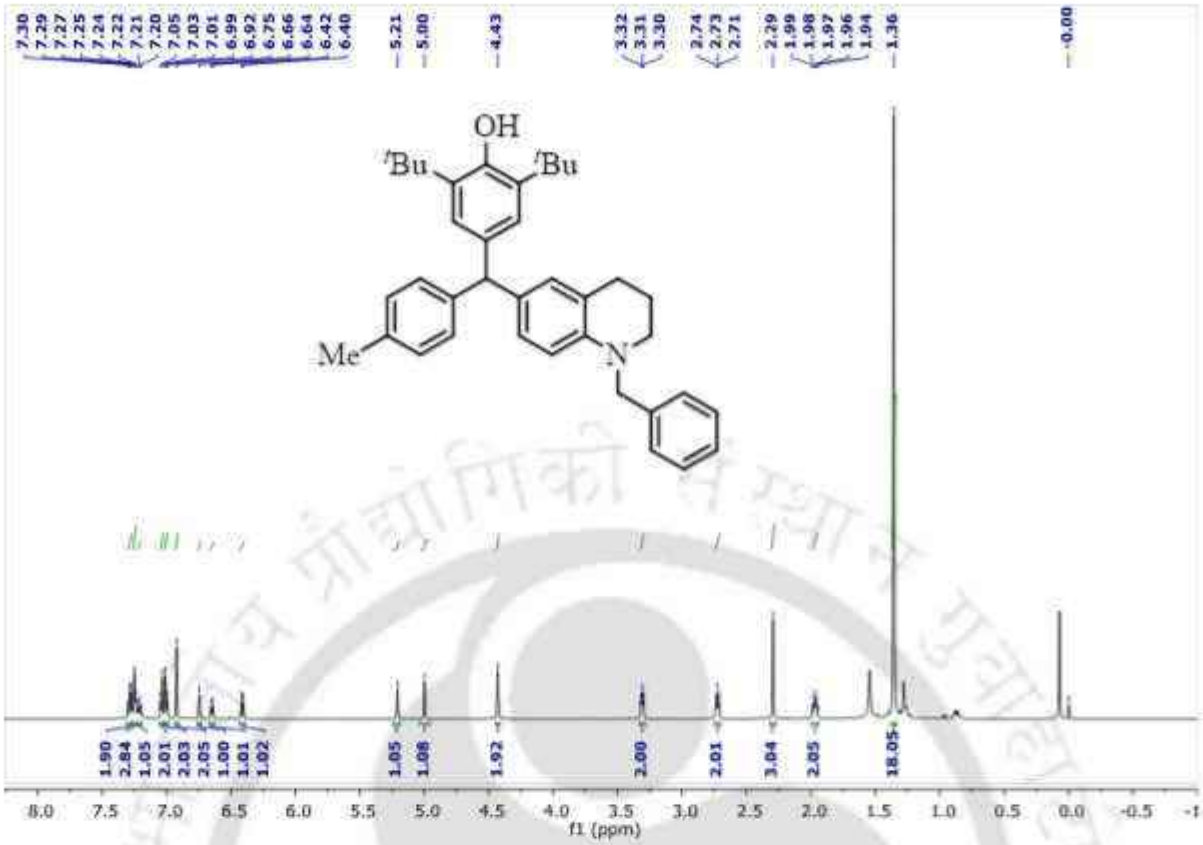


Figure S32: ^{1}H NMR Spectrum of **3.22a** ($CDCl_3$, 500 MHz, 298 K)

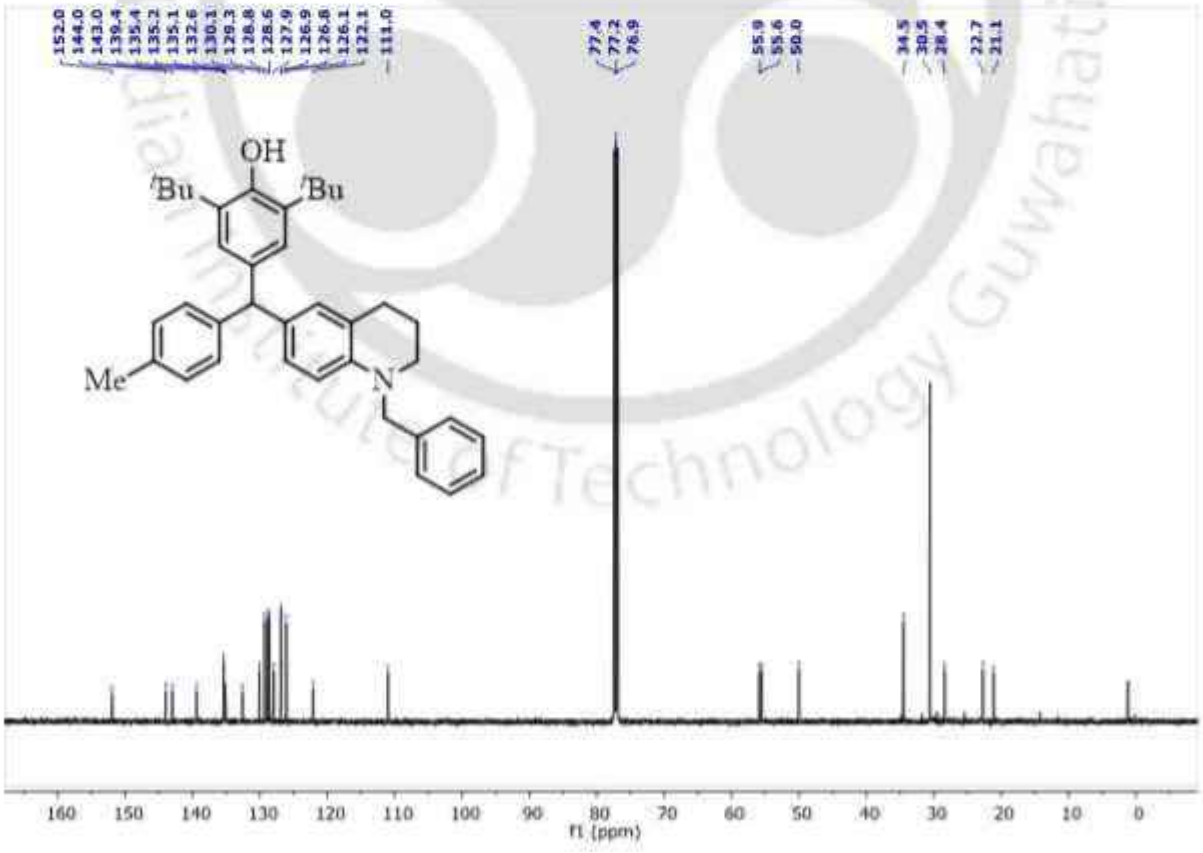


Figure S33: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.22a** ($CDCl_3$, 126 MHz, 298 K)

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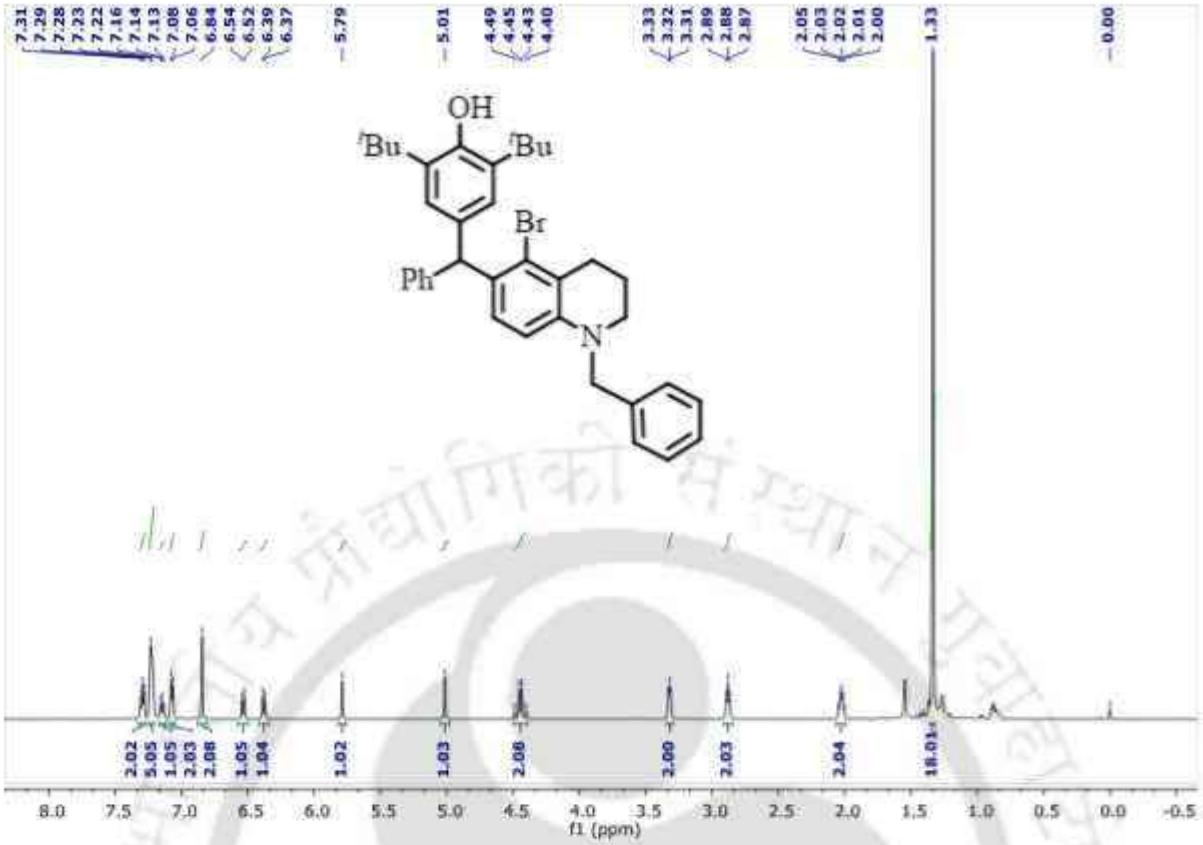


Figure S34: ^{1}H NMR Spectrum of **3.22e** ($CDCl_3$, 500 MHz, 298 K)

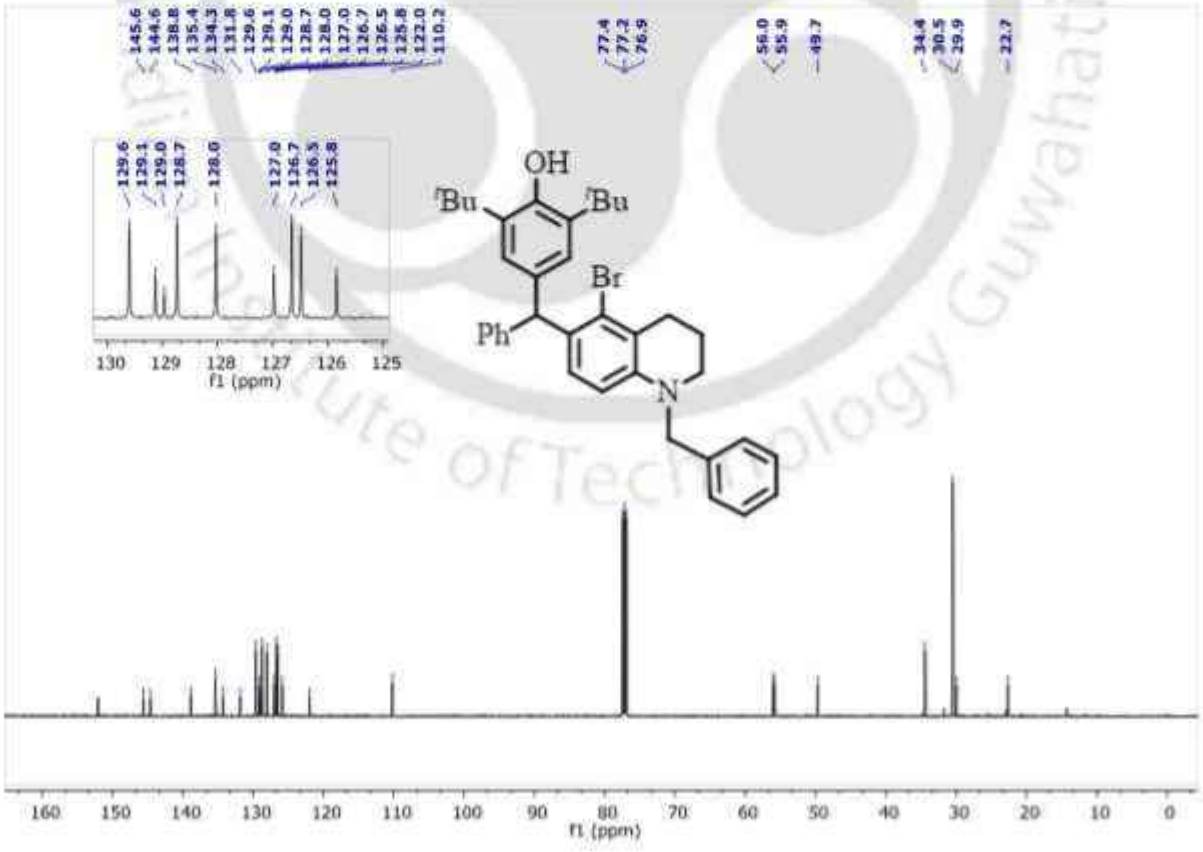


Figure S35: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.22e** ($CDCl_3$, 126 MHz, 298 K)

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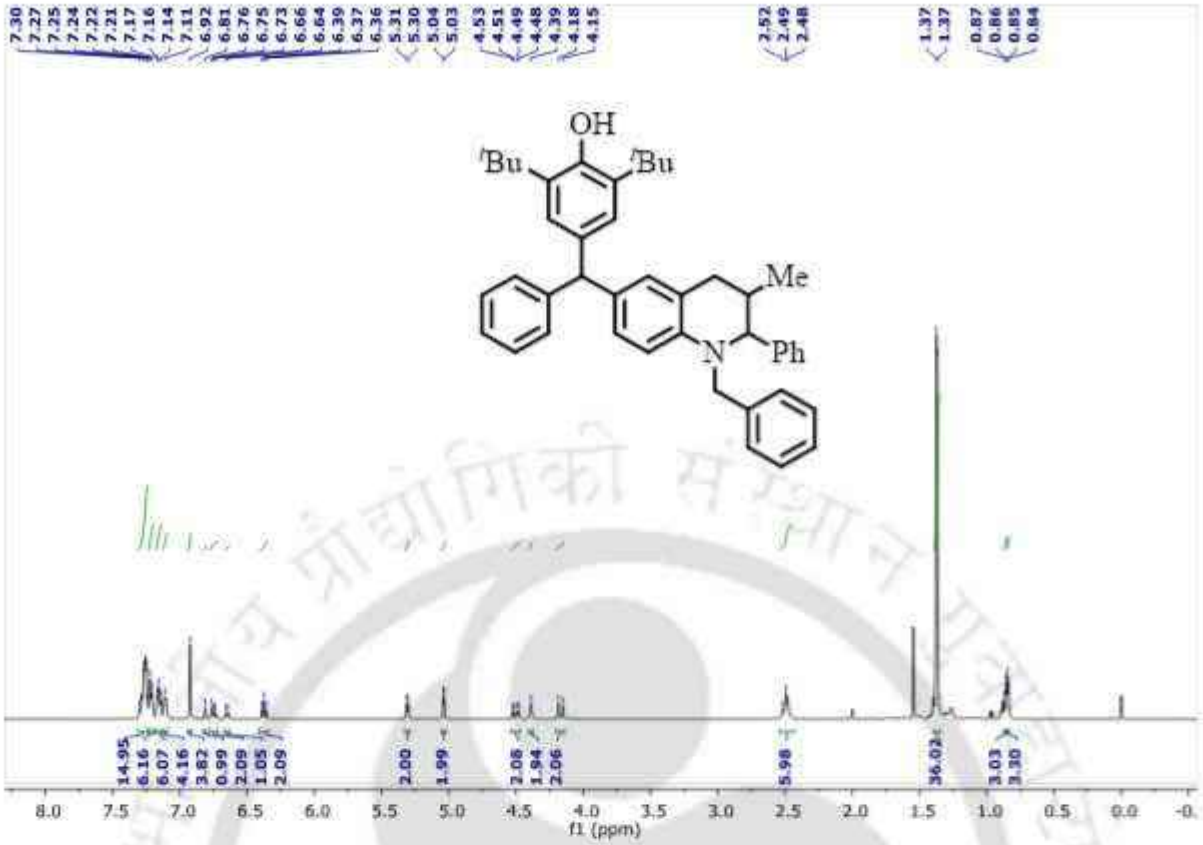


Figure S36: ^{1}H NMR Spectrum of **3.22f** ($CDCl_3$, 500 MHz, 298 K)

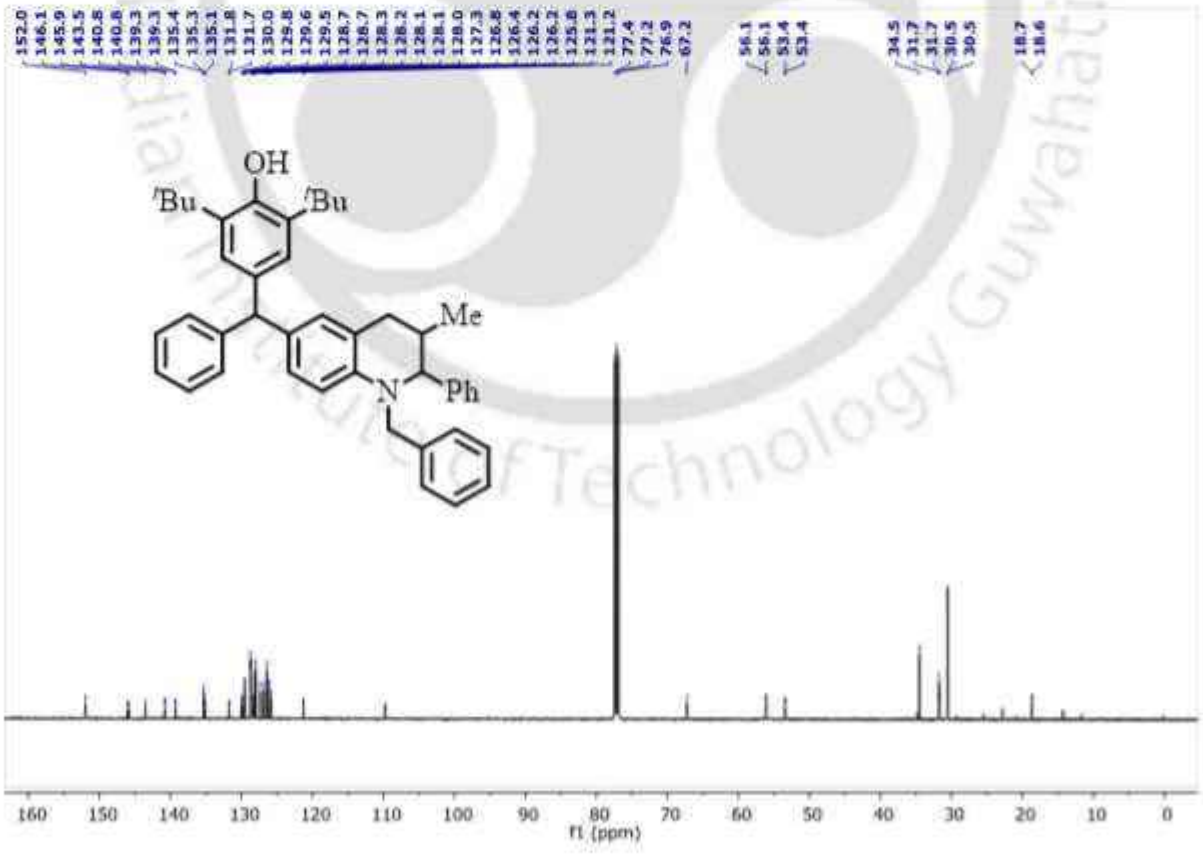


Figure S37: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.22f** ($CDCl_3$, 126 MHz, 298 K)

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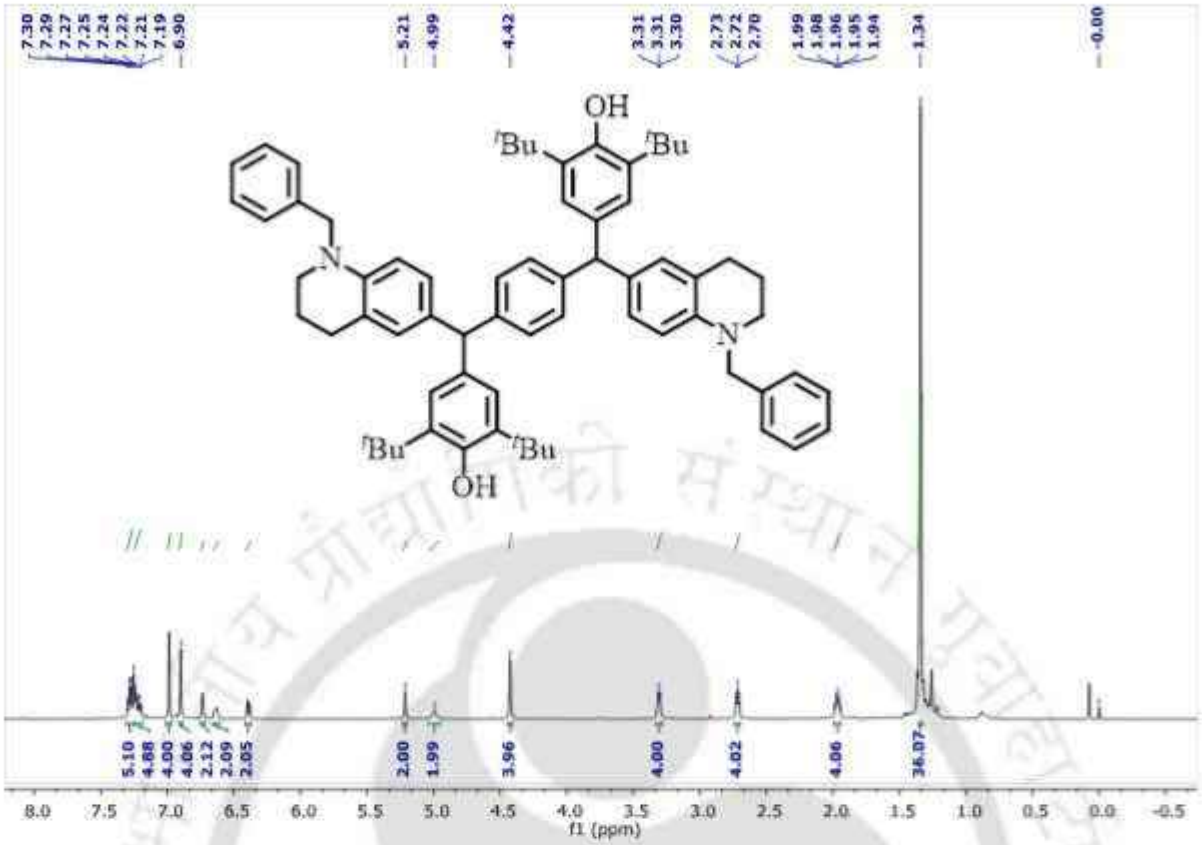


Figure S38: ^{1}H NMR Spectrum of **3.22g** ($CDCl_3$, 500 MHz, 298 K)

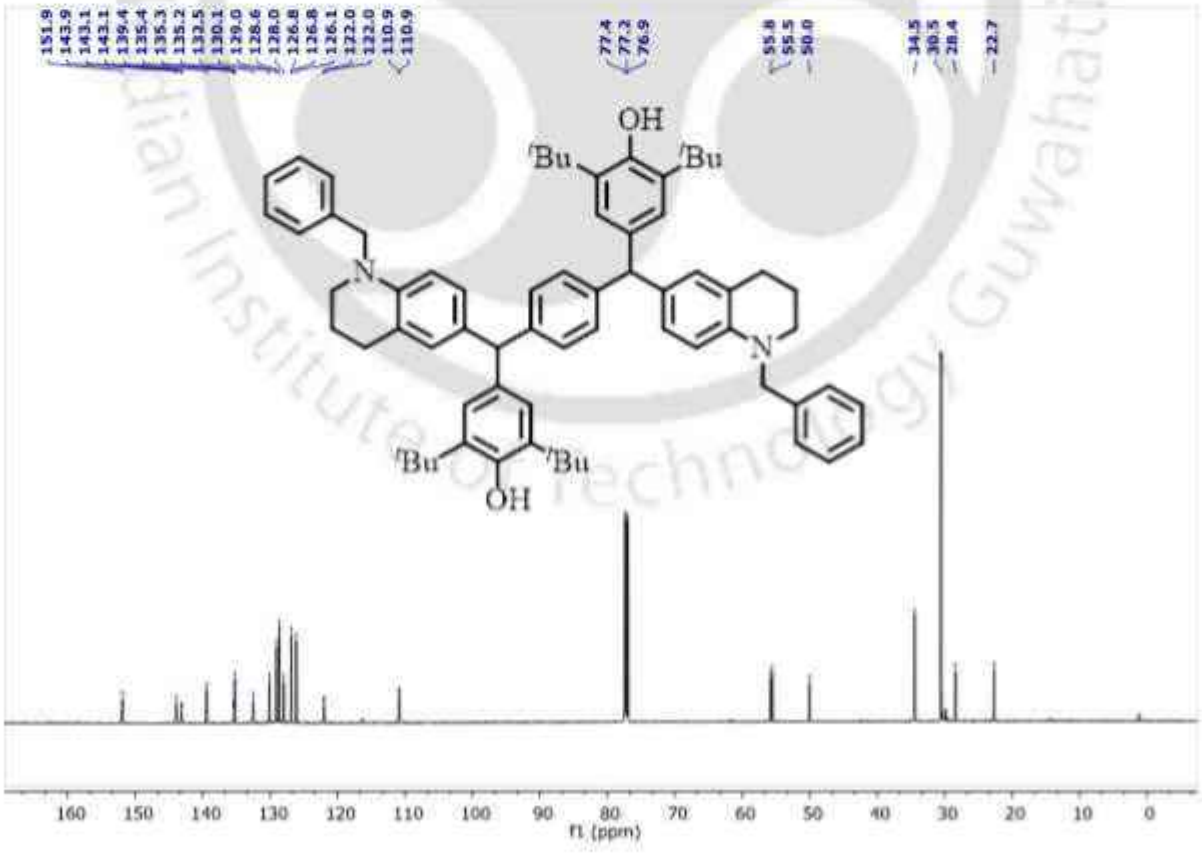


Figure S39: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.22g** ($CDCl_3$, 151 MHz, 298 K)

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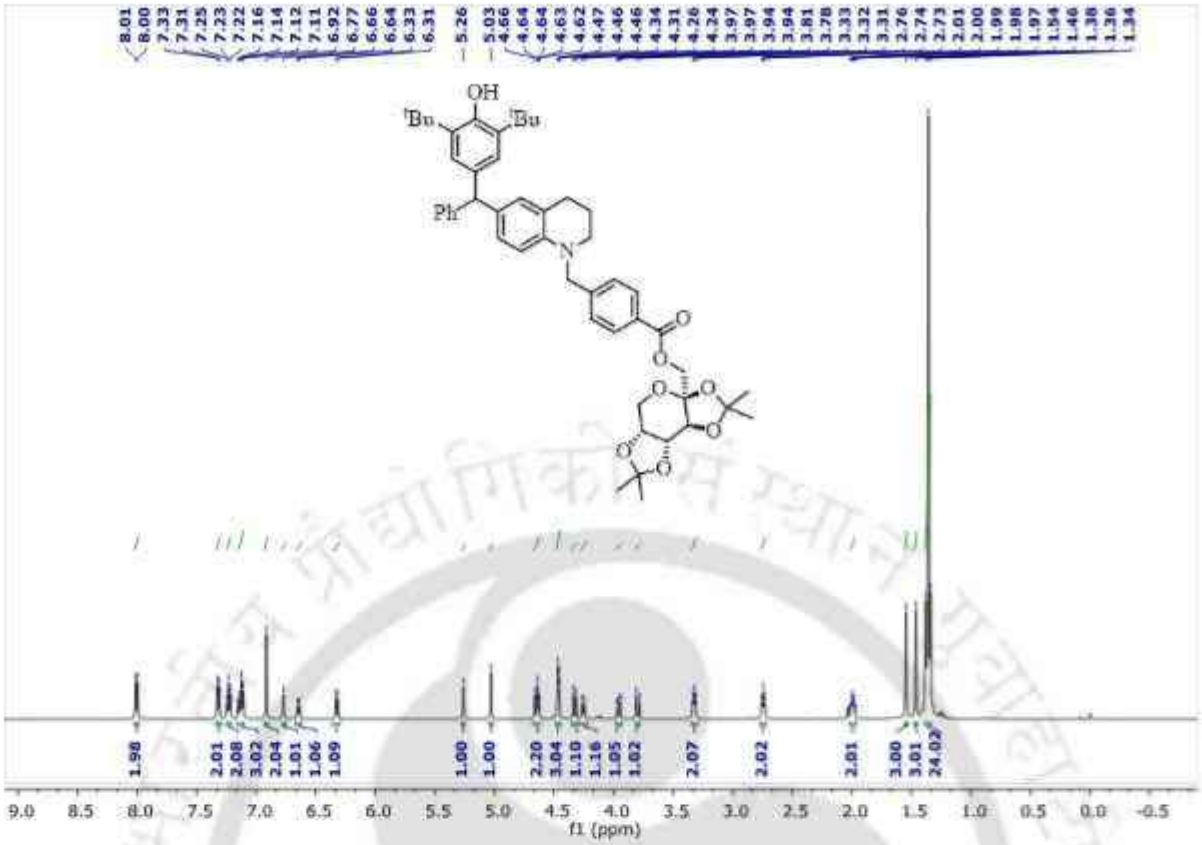


Figure S40: ^{1}H NMR Spectrum of **3.24a** ($CDCl_3$, 500 MHz, 298 K)

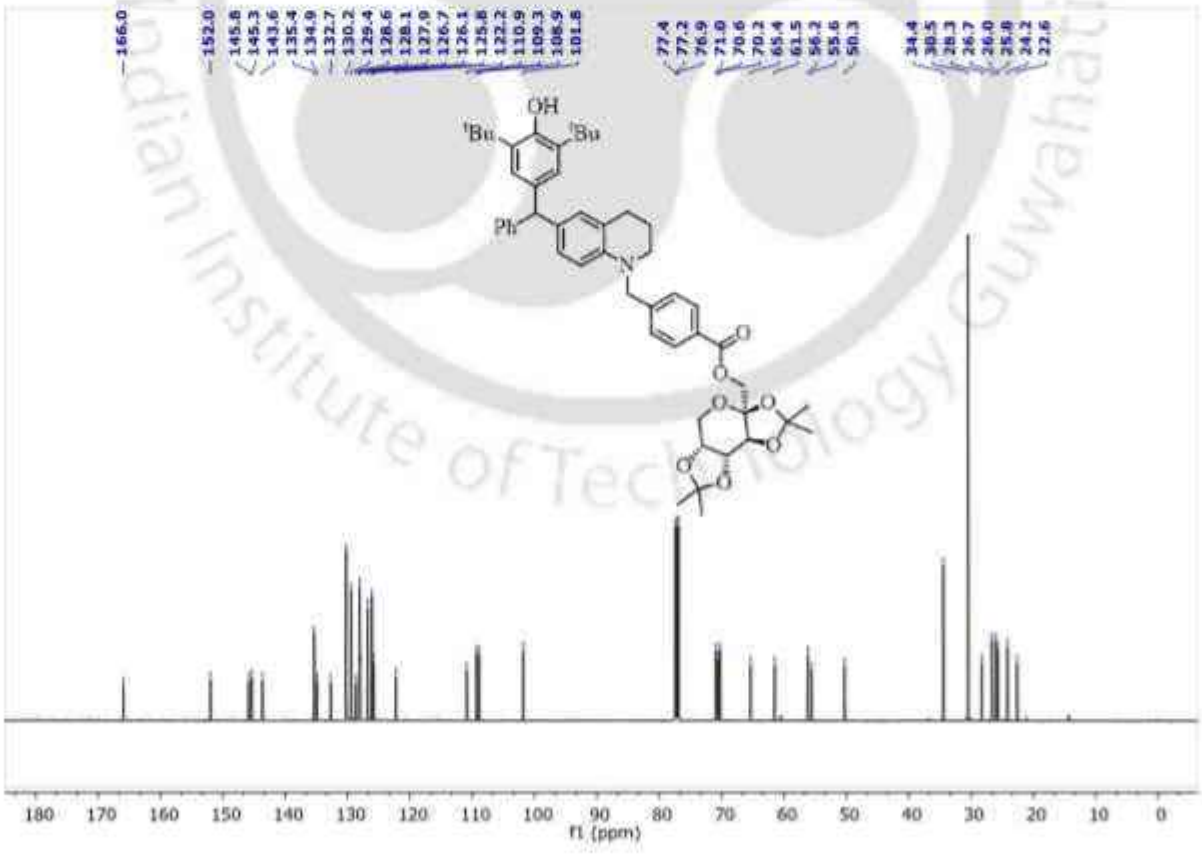


Figure S41: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.24a** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

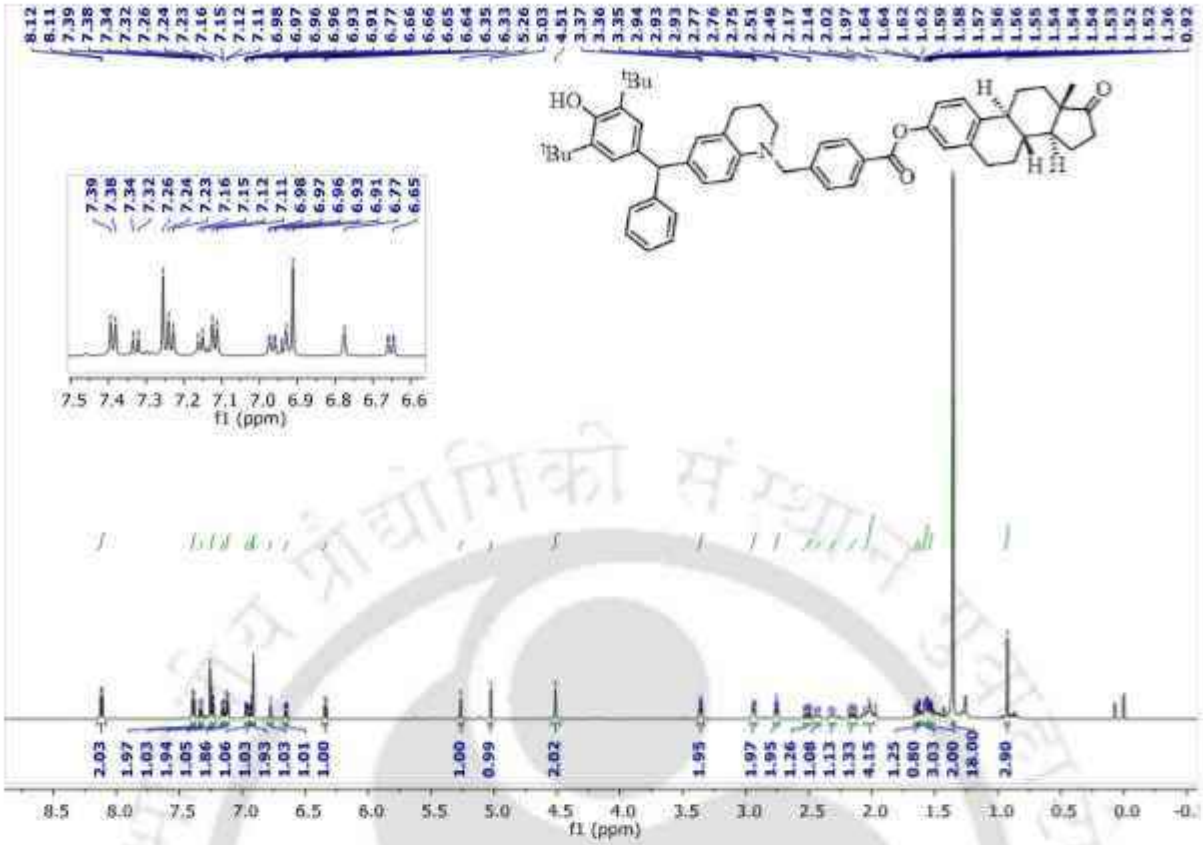


Figure S42: ^{1}H NMR Spectrum of **3.24g** ($CDCl_3$, 600 MHz, 298 K)

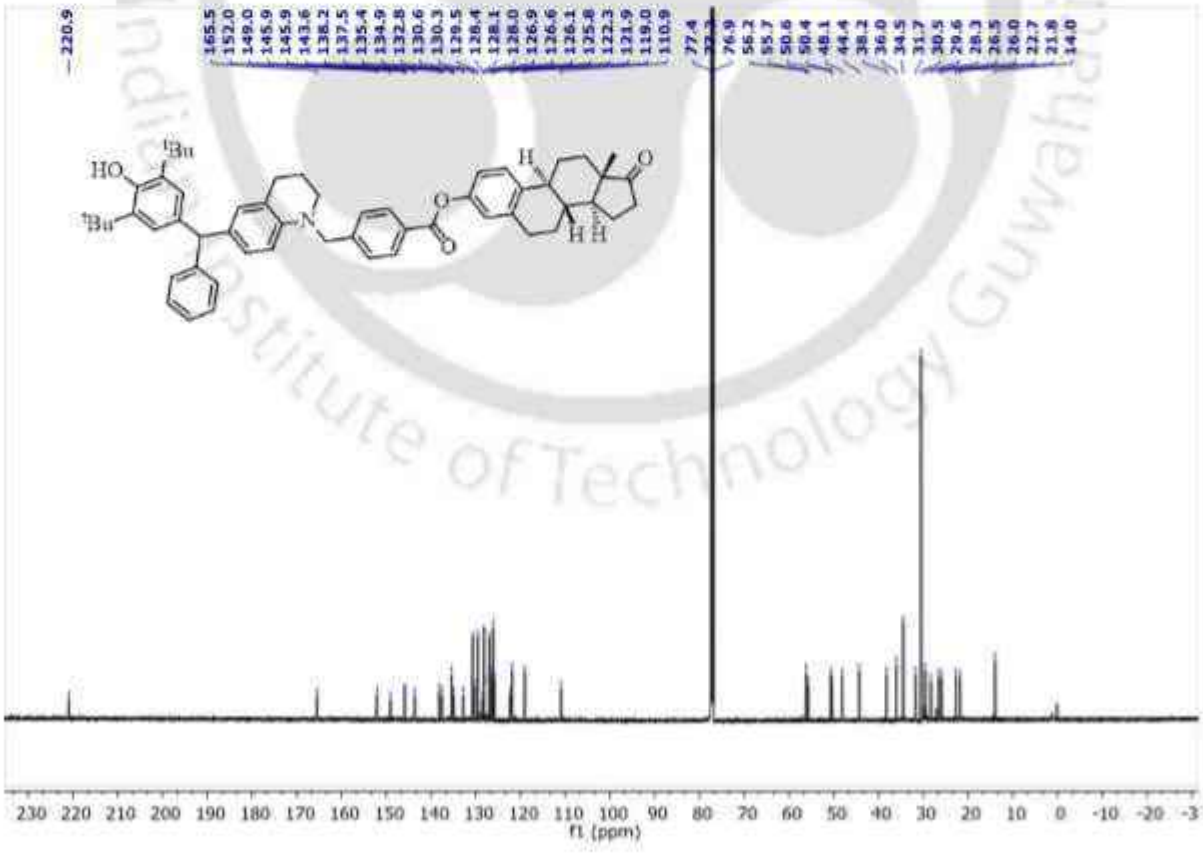


Figure S43: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.24g** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

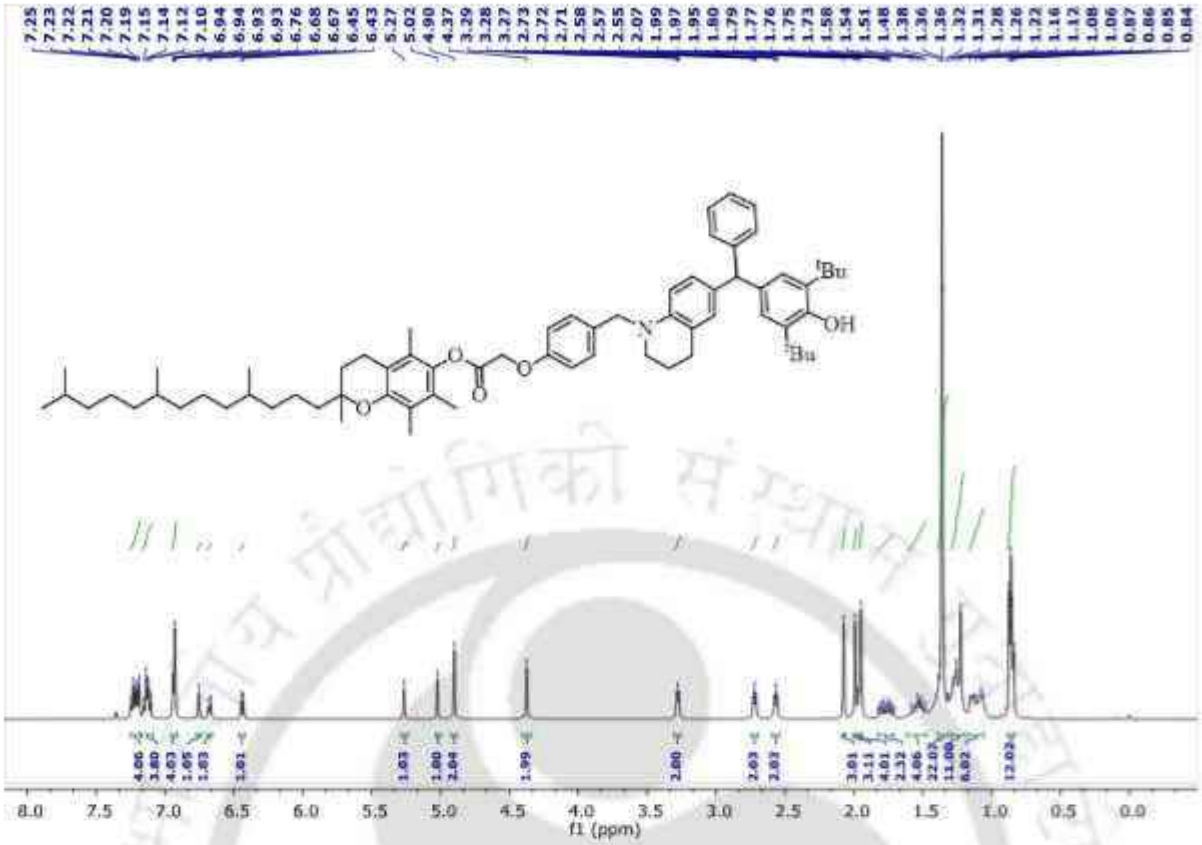


Figure S44: ^{1}H NMR Spectrum of **3.24h** ($CDCl_3$, 500 MHz, 298 K)

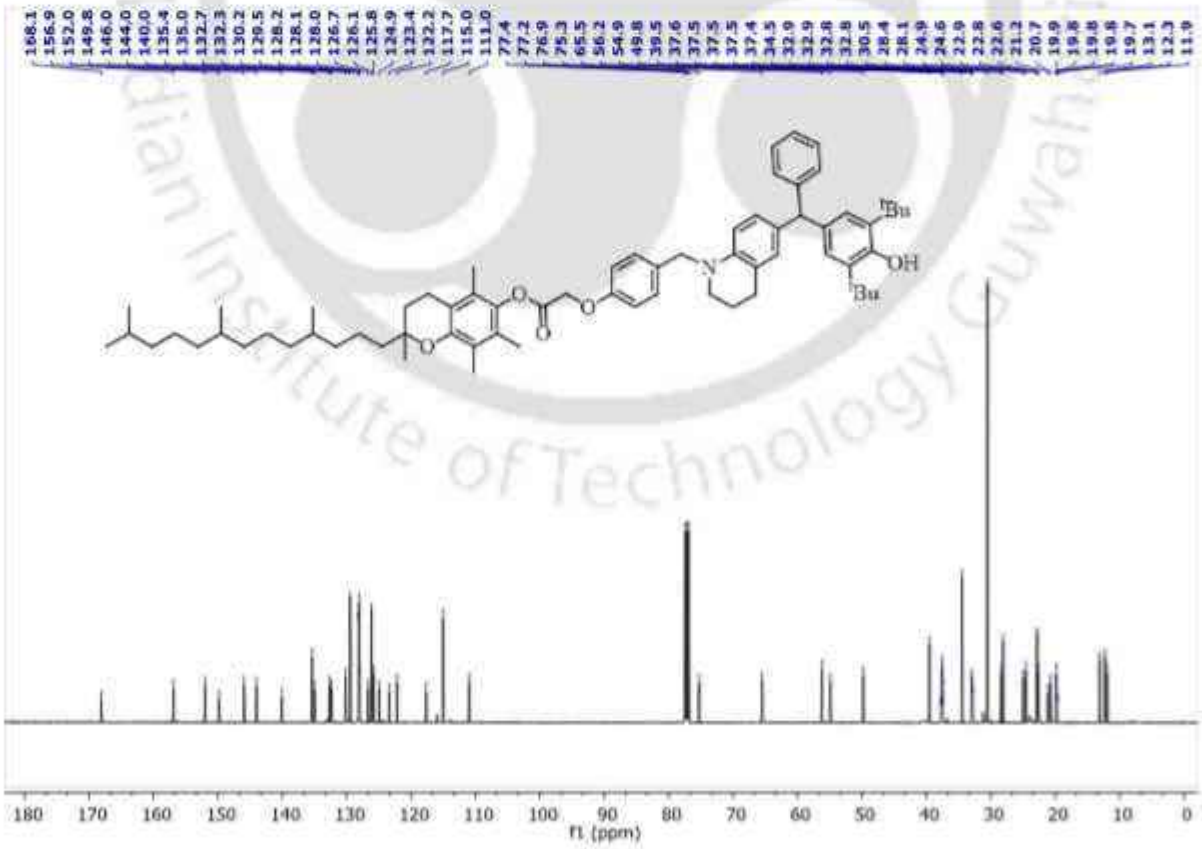


Figure S45: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.24h** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

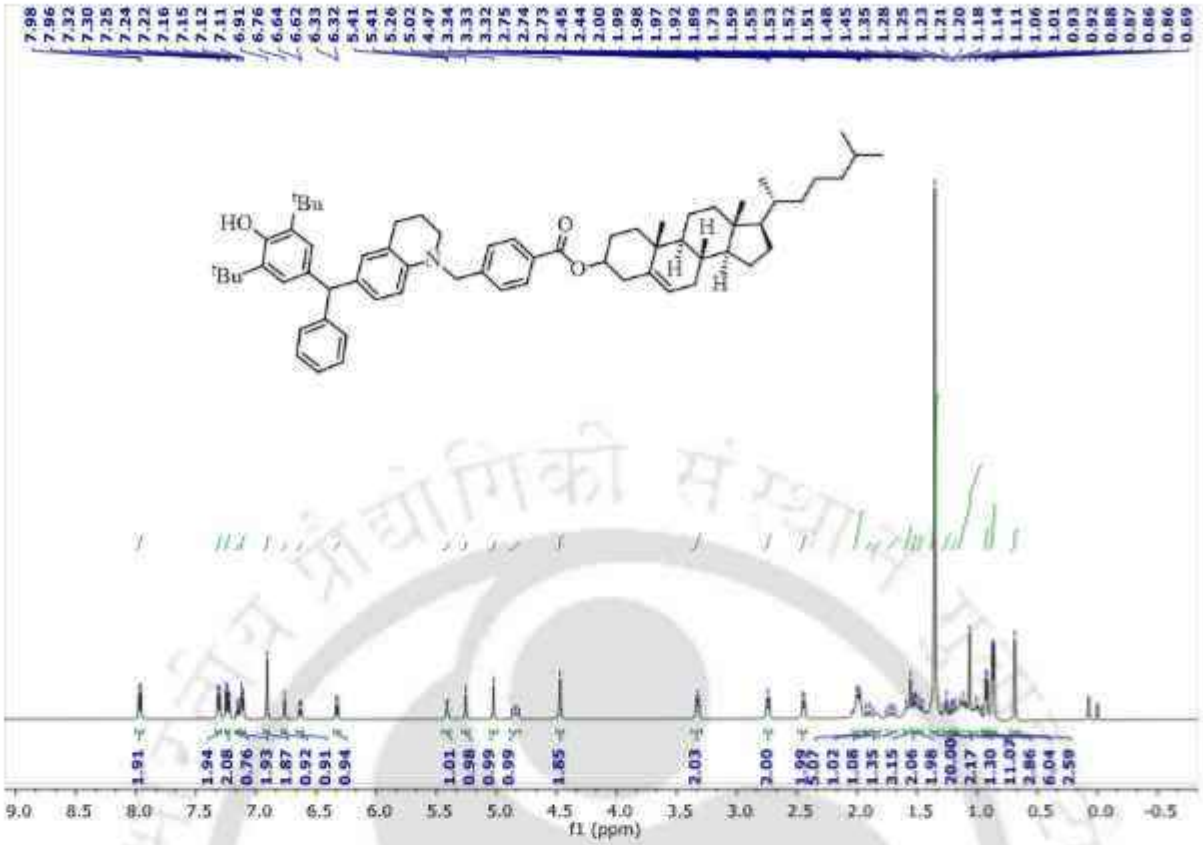


Figure S46: ^{1}H NMR Spectrum of **3.24i** ($CDCl_3$, 500 MHz, 298 K)

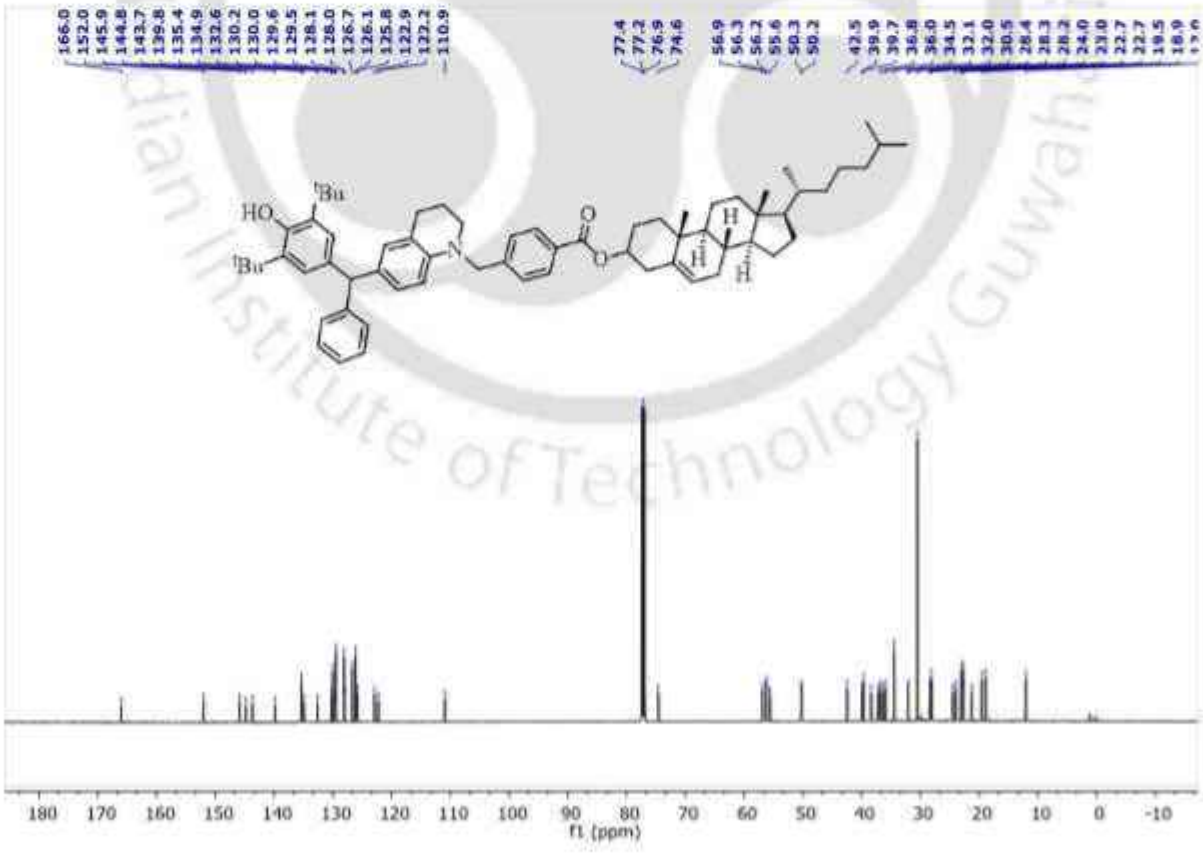


Figure S47: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.24i** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

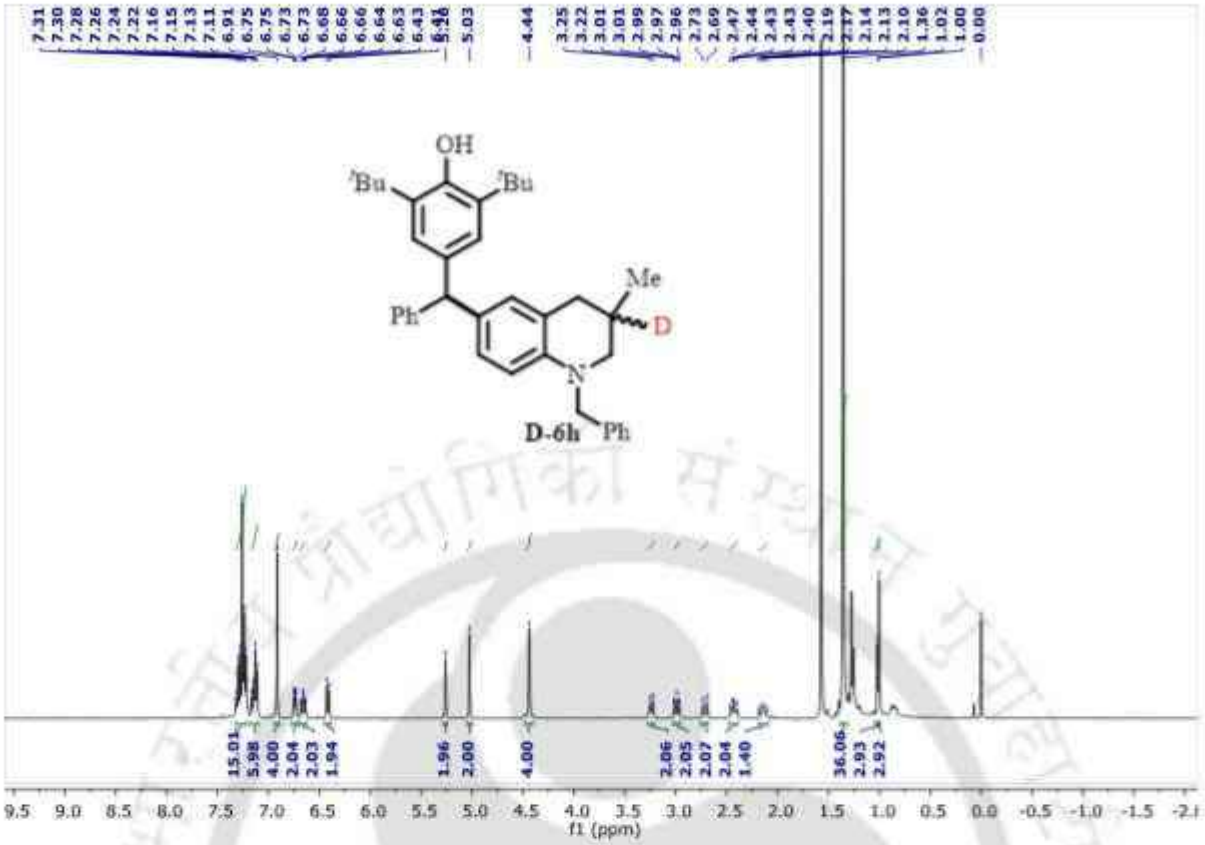


Figure S48: ^{1}H NMR Spectrum of **3.D-22h** ($CDCl_3$, 400 MHz, 298 K)

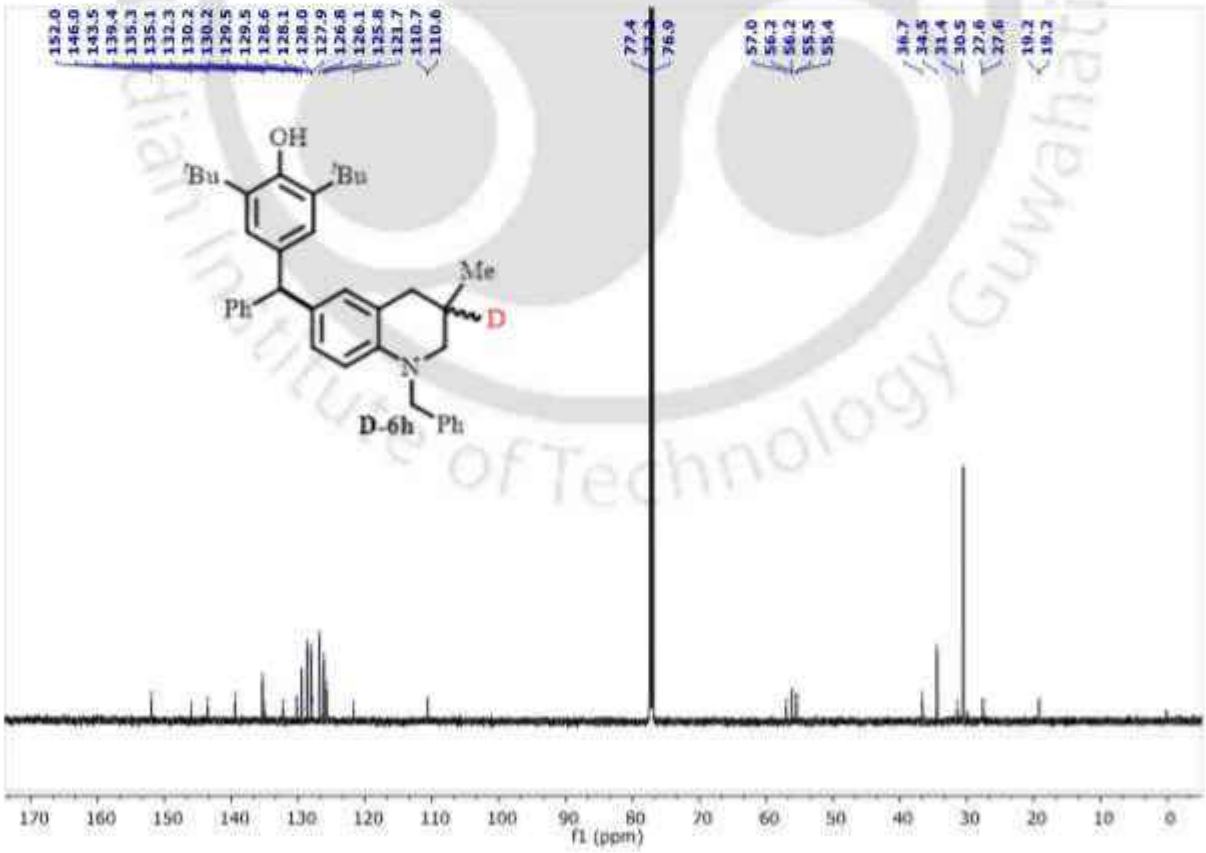


Figure S49: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.D-22h** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

The supporting information and all other product spectra for chapter 3 is available at https://doi.org/10.1039/D5OB00895F

Annexure III

^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ spectra of representative compounds (*Chapter 4*)

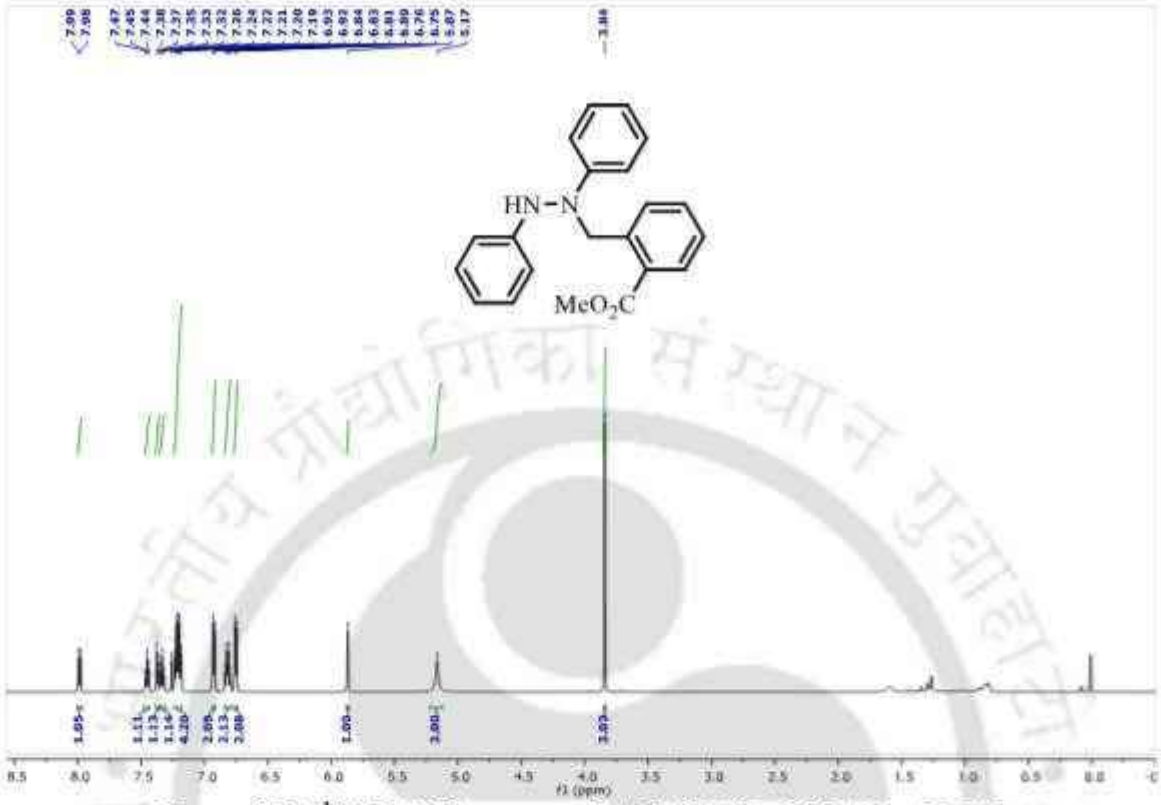


Figure S50: ^{1}H NMR Spectrum of **4.7l** ($CDCl_3$, 600 MHz, 298 K)

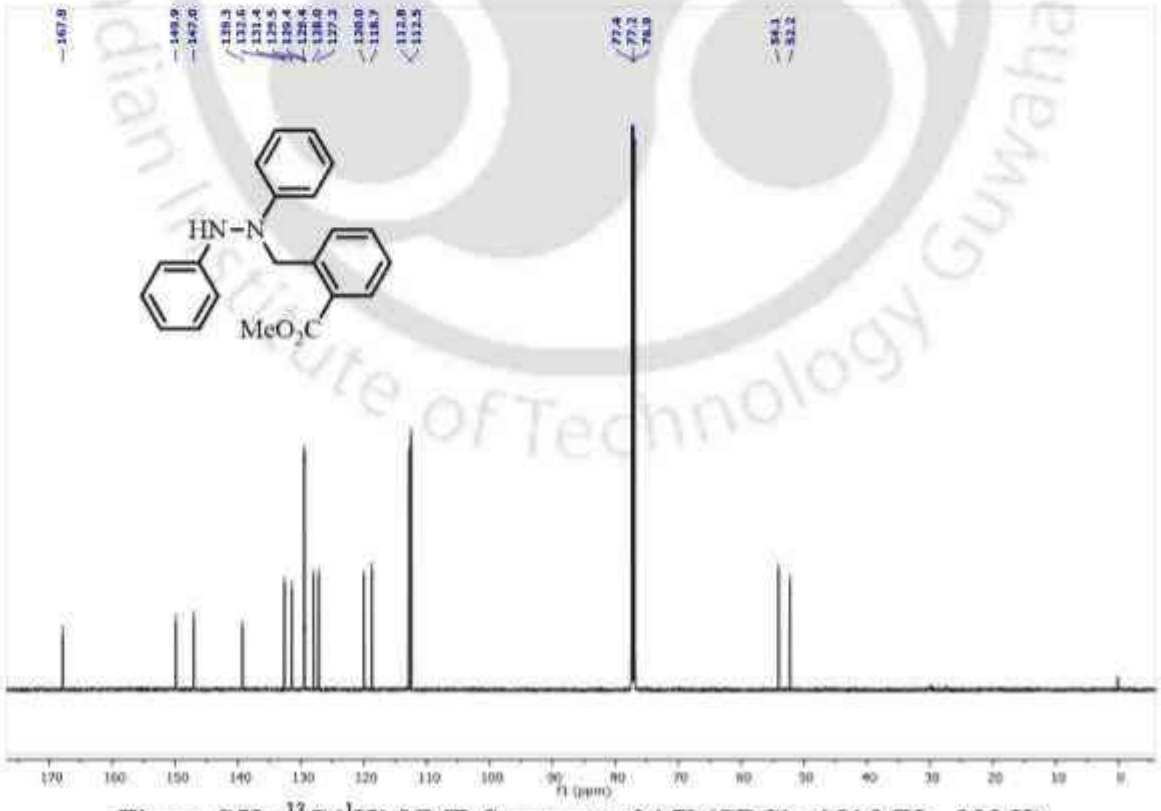


Figure S51: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.7l** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

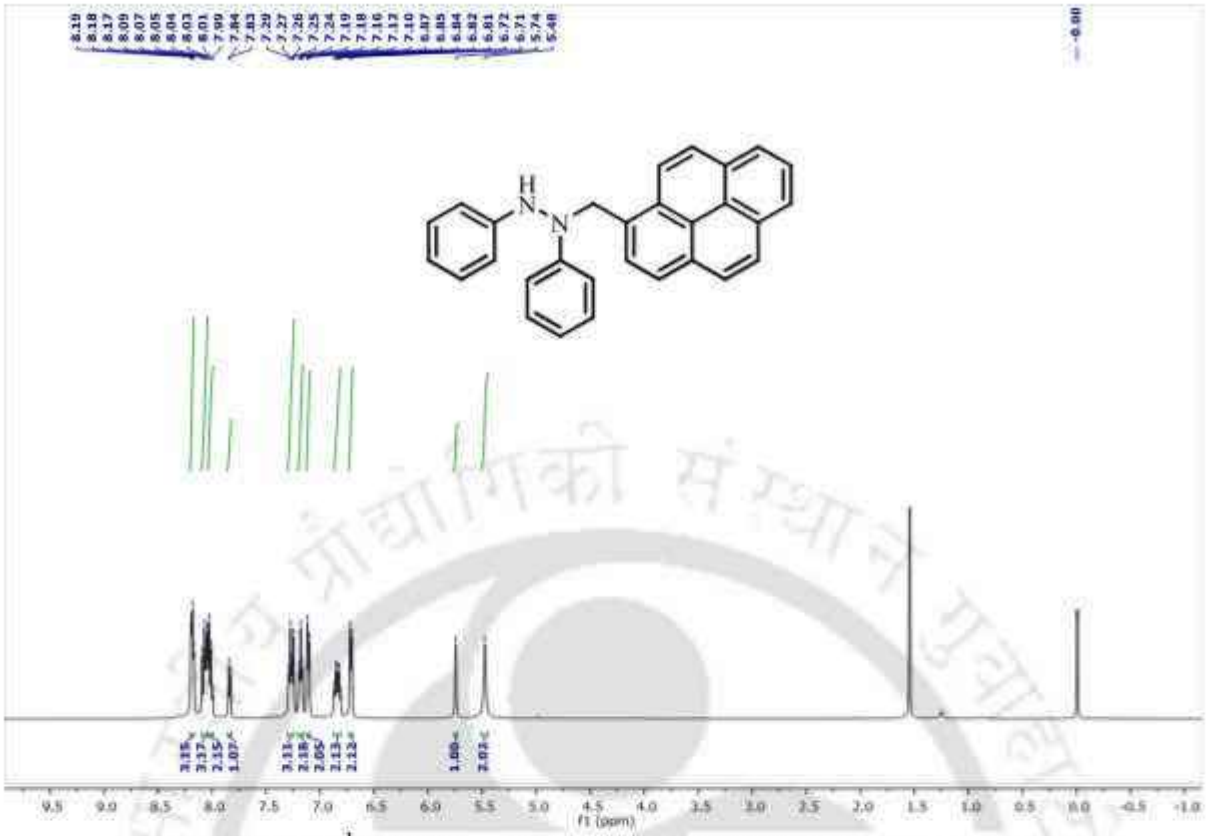


Figure S52: ^{1}H NMR Spectrum of **4.7o** ($CDCl_3$, 500 MHz, 298 K)

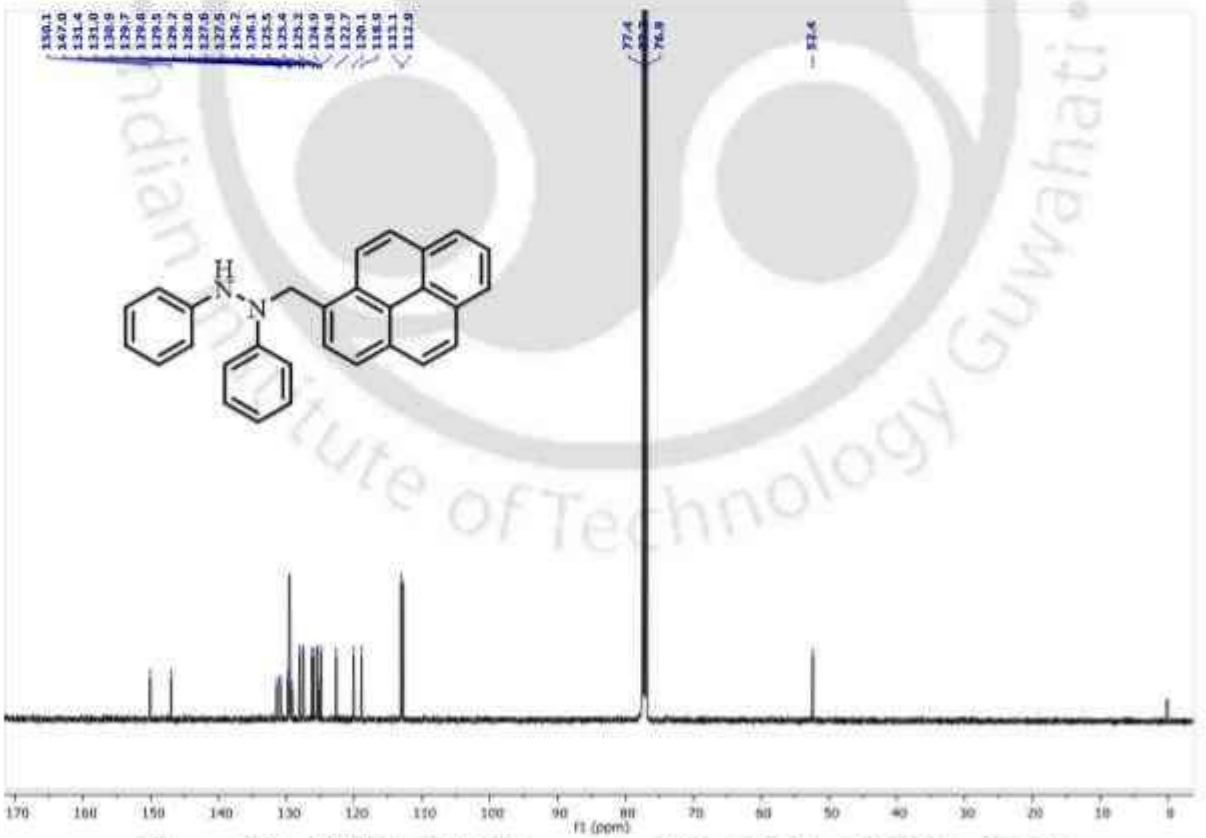


Figure S53: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.7o** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

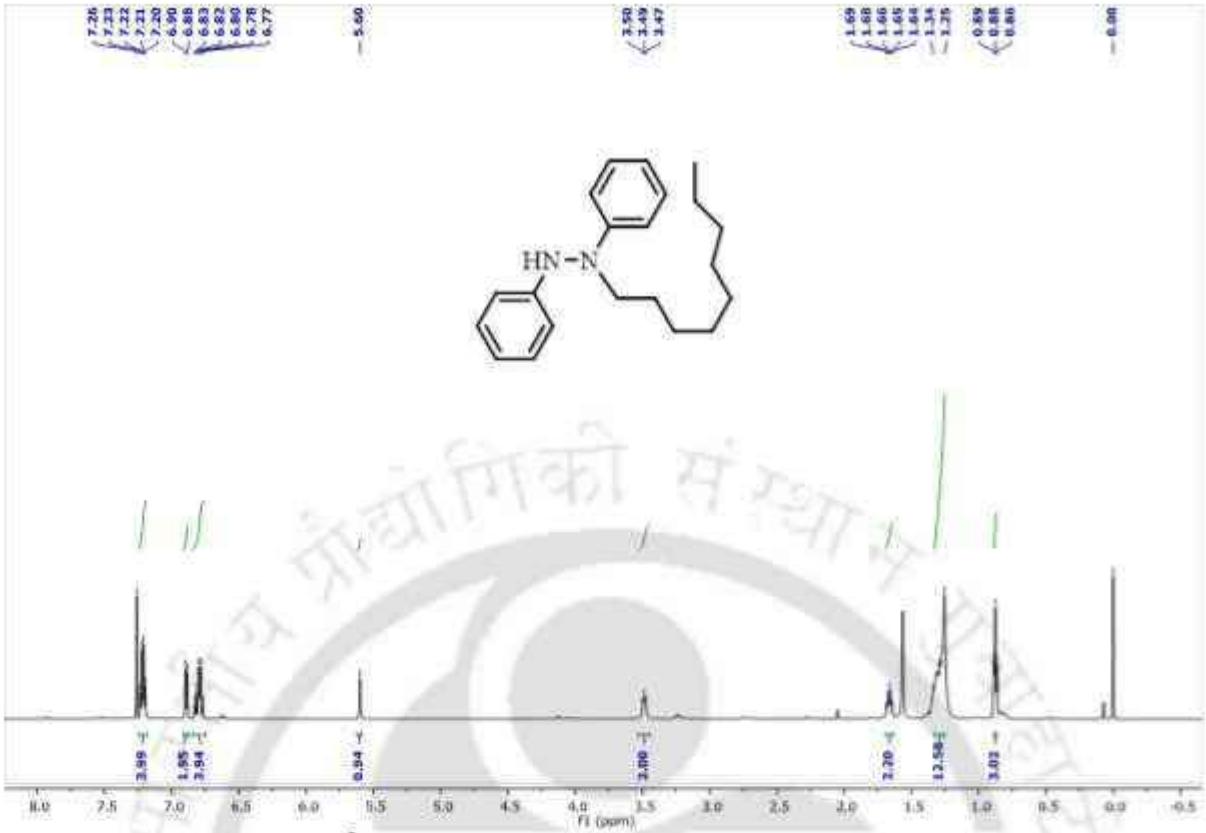


Figure S54: ^{1}H NMR Spectrum of **4.7t** ($CDCl_3$, 600 MHz, 298 K)

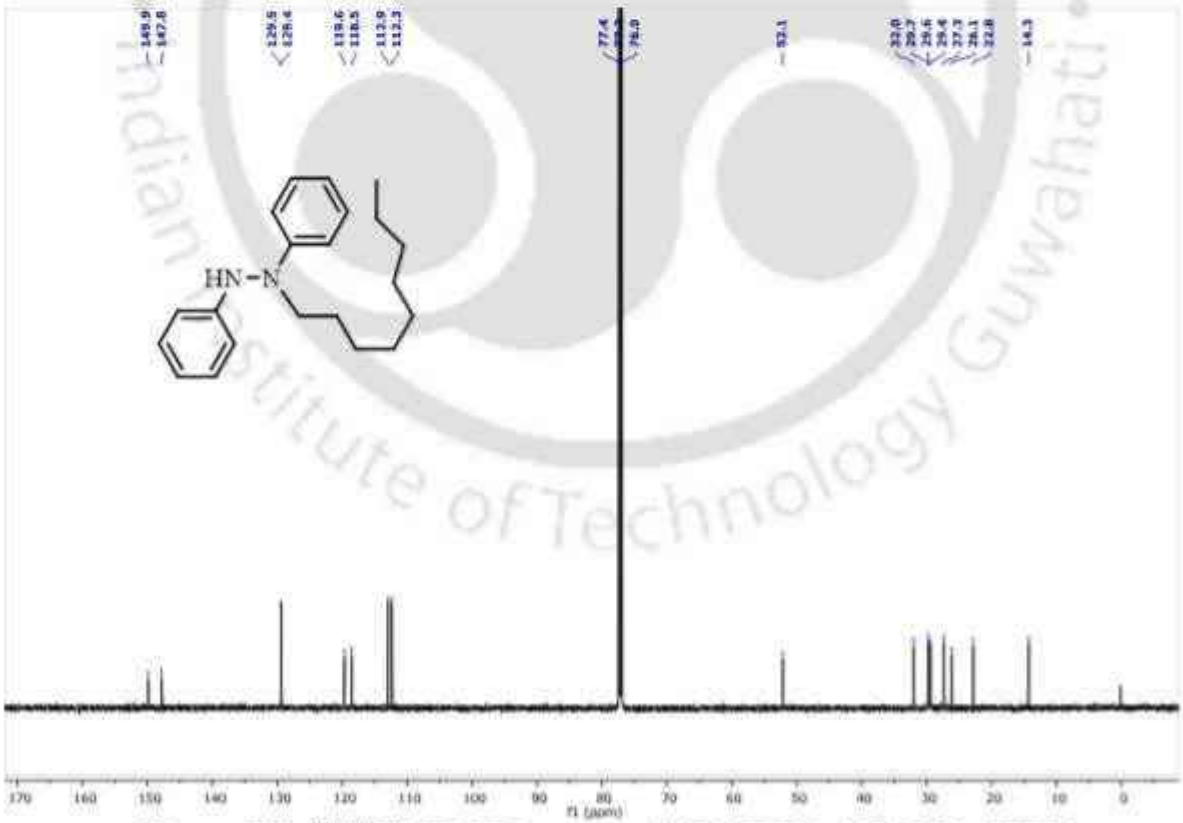


Figure S55: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.7t** ($CDCl_3$, 151 MHz, 298 K)

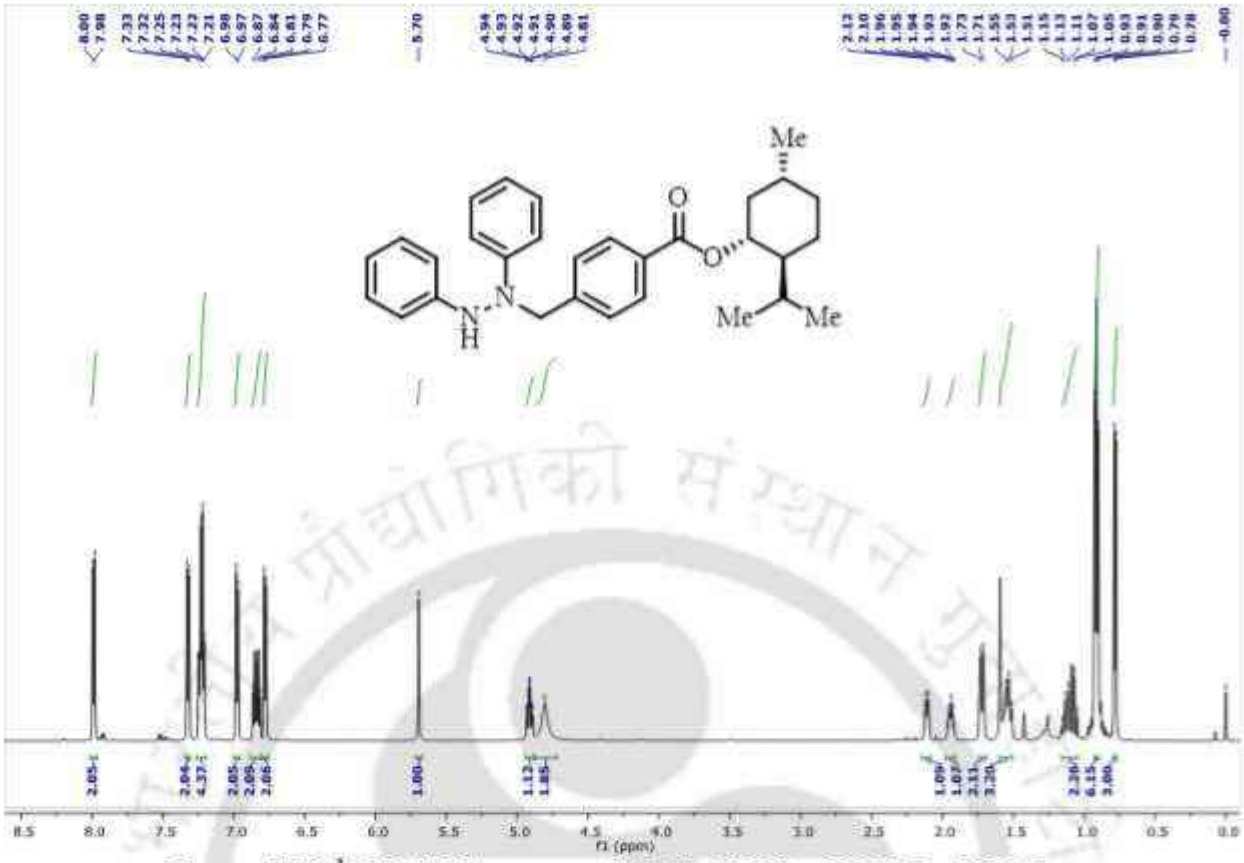


Figure S56: ^{1}H NMR Spectrum of **4.7ab** ($CDCl_3$, 600 MHz, 298 K)

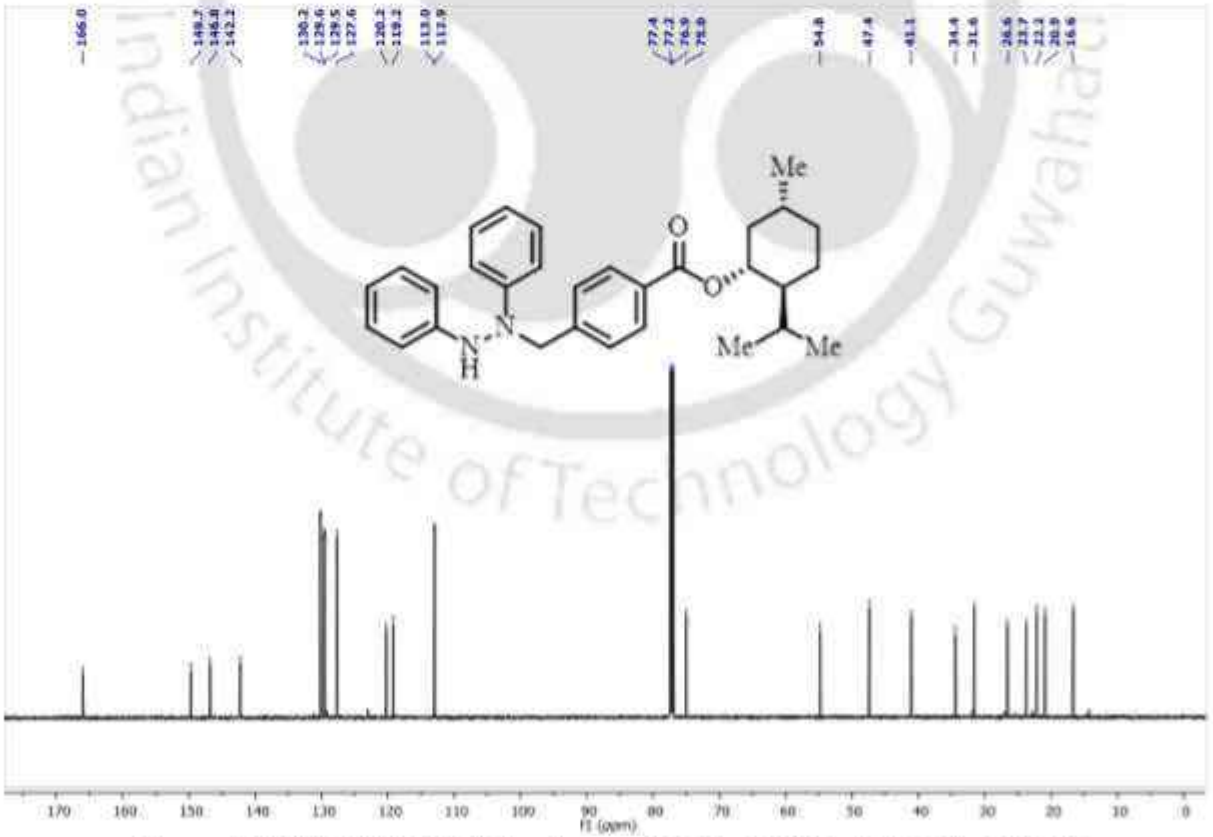


Figure S57: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.7ab** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

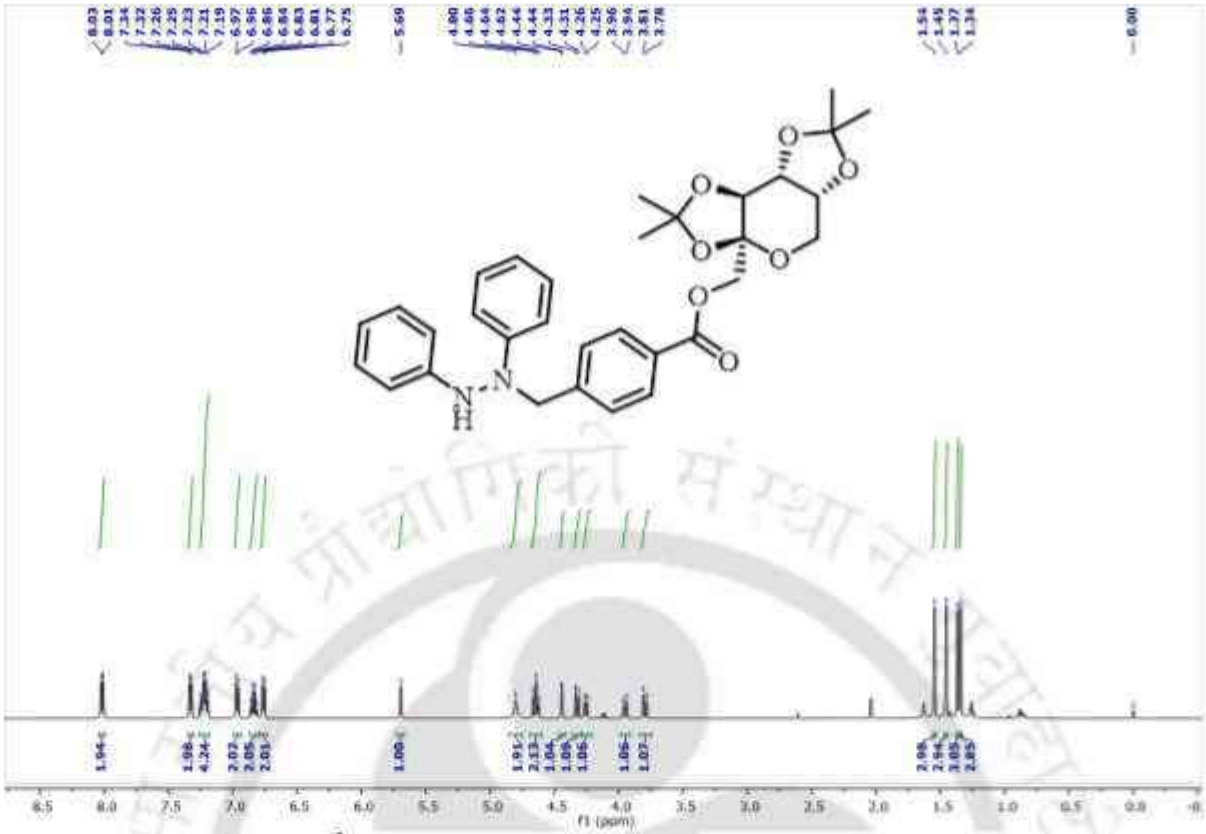


Figure S58: ^{1}H NMR Spectrum of **4.7ad** ($CDCl_3$, 500 MHz, 298 K)

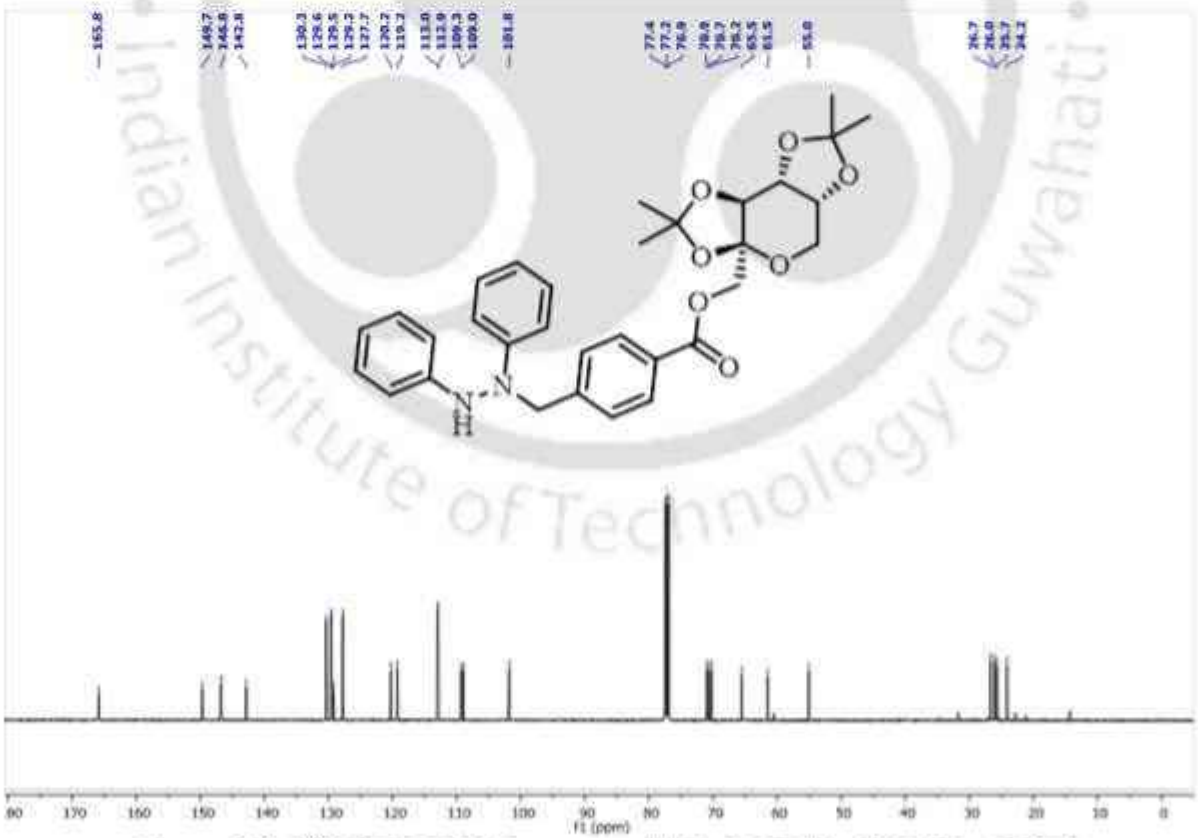


Figure S59: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.7ad** ($CDCl_3$, 126 MHz, 298 K)

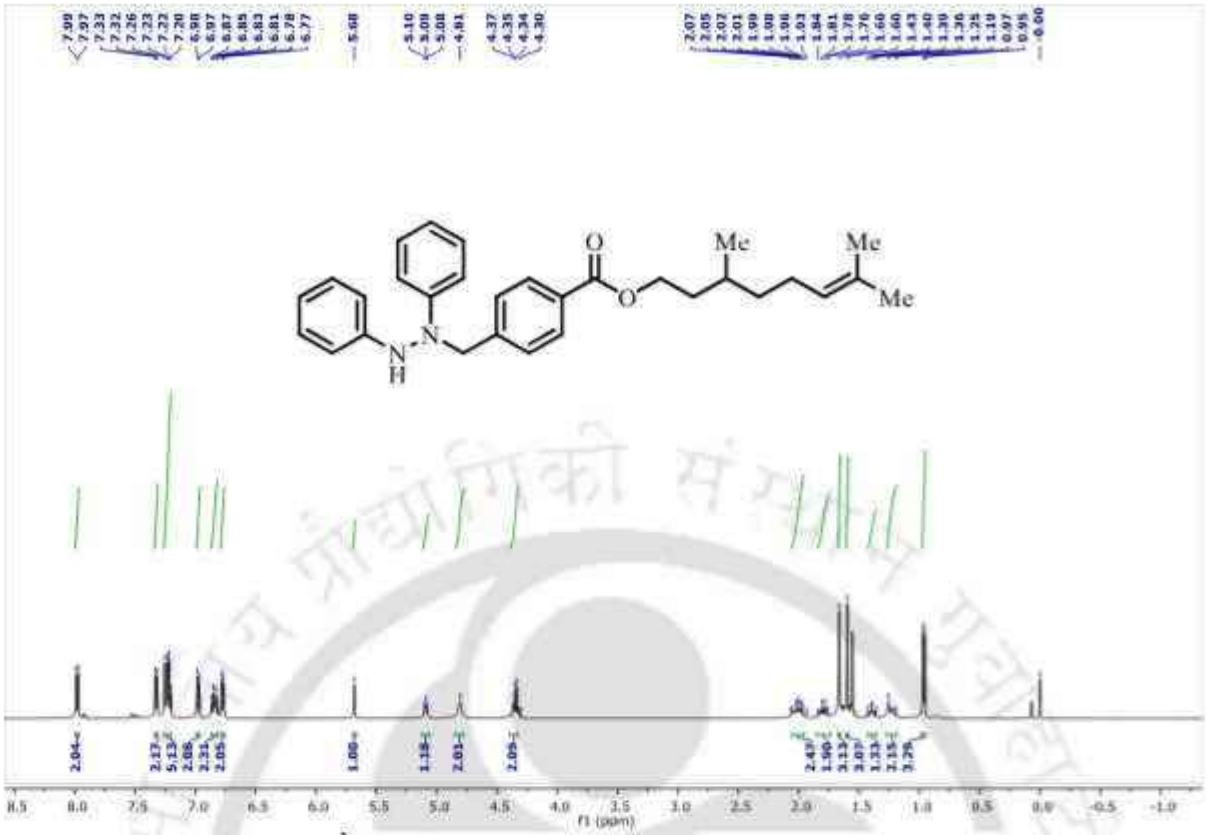


Figure S60: ^{1}H NMR Spectrum of **4.7af** ($CDCl_3$, 500 MHz, 298 K)

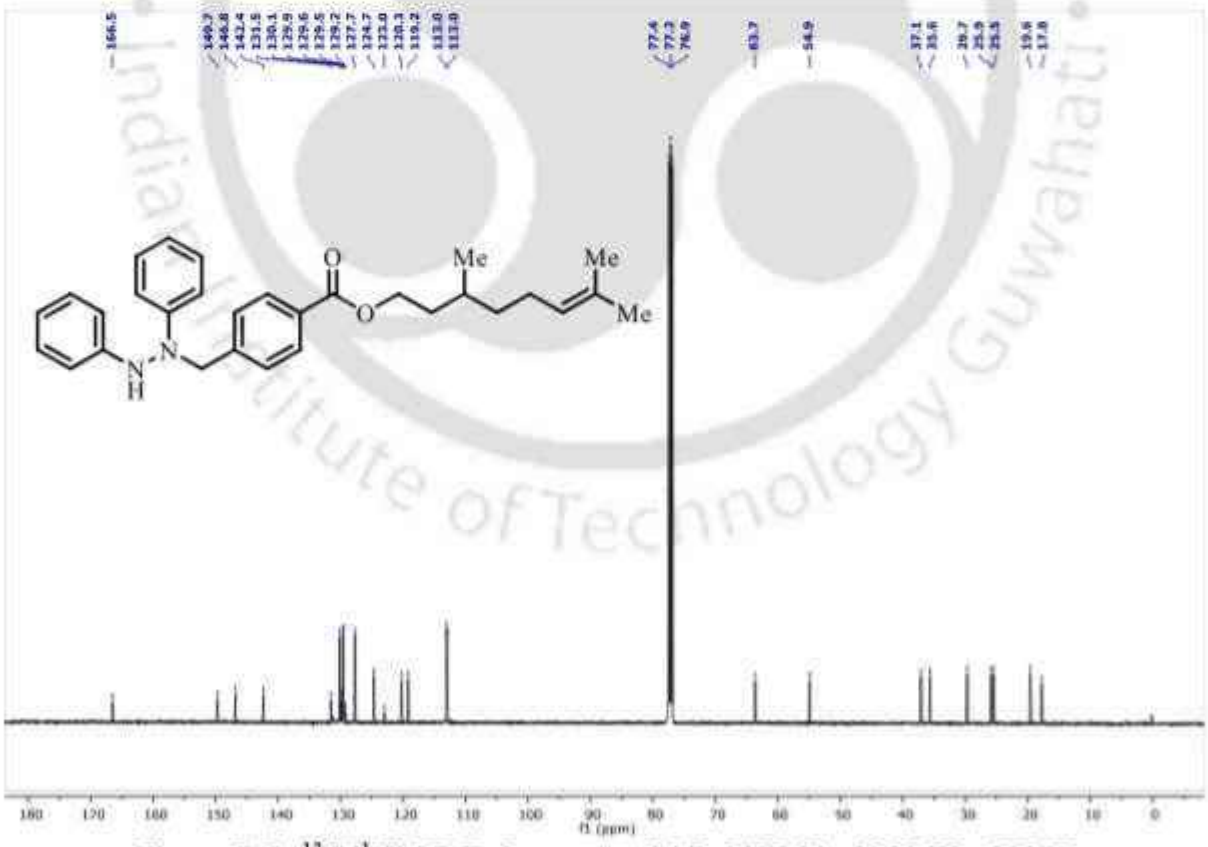


Figure S61: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.7af** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

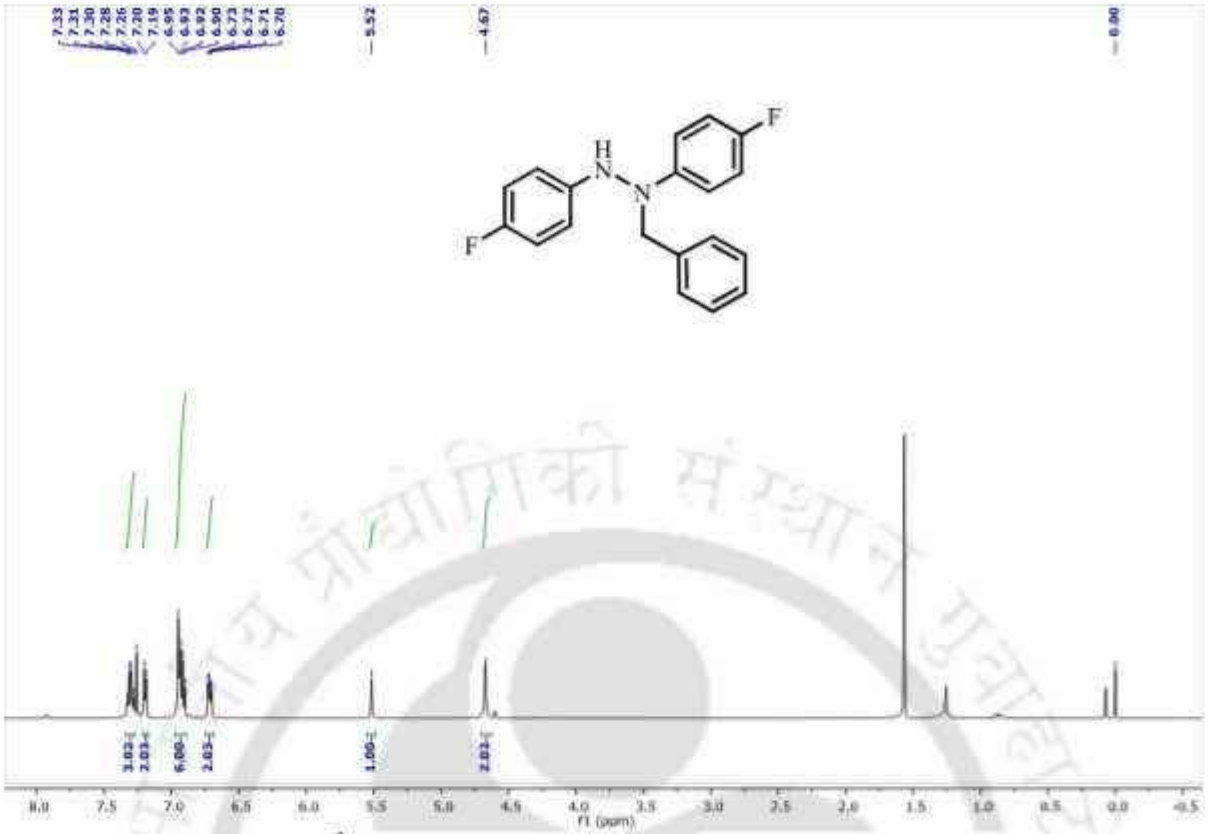


Figure S62: ^{1}H NMR Spectrum of **4.17a** ($CDCl_3$, 500 MHz, 298 K)

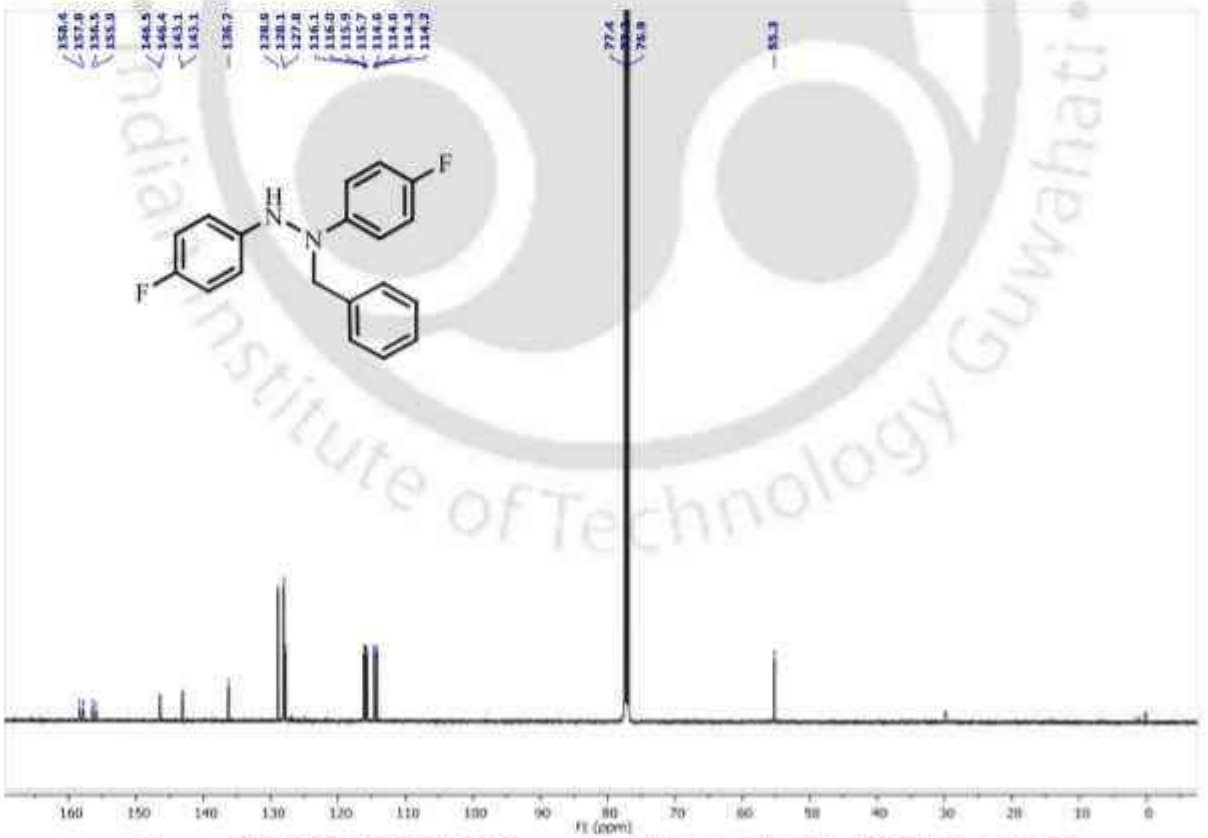


Figure S63: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.17a** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

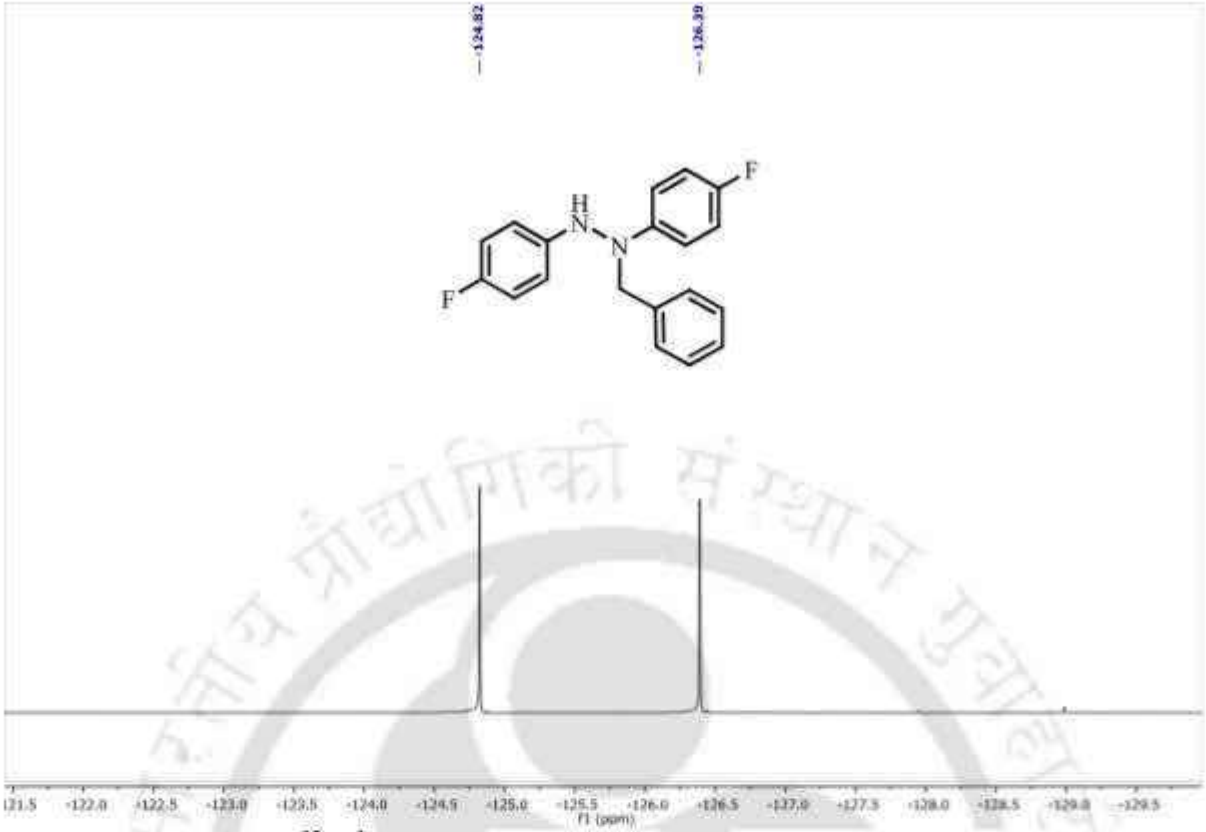


Figure S64: $^{19}F\{^{1}H\}$ NMR Spectrum of **4.17a** ($CDCl_3$, 471 MHz, 298 K)

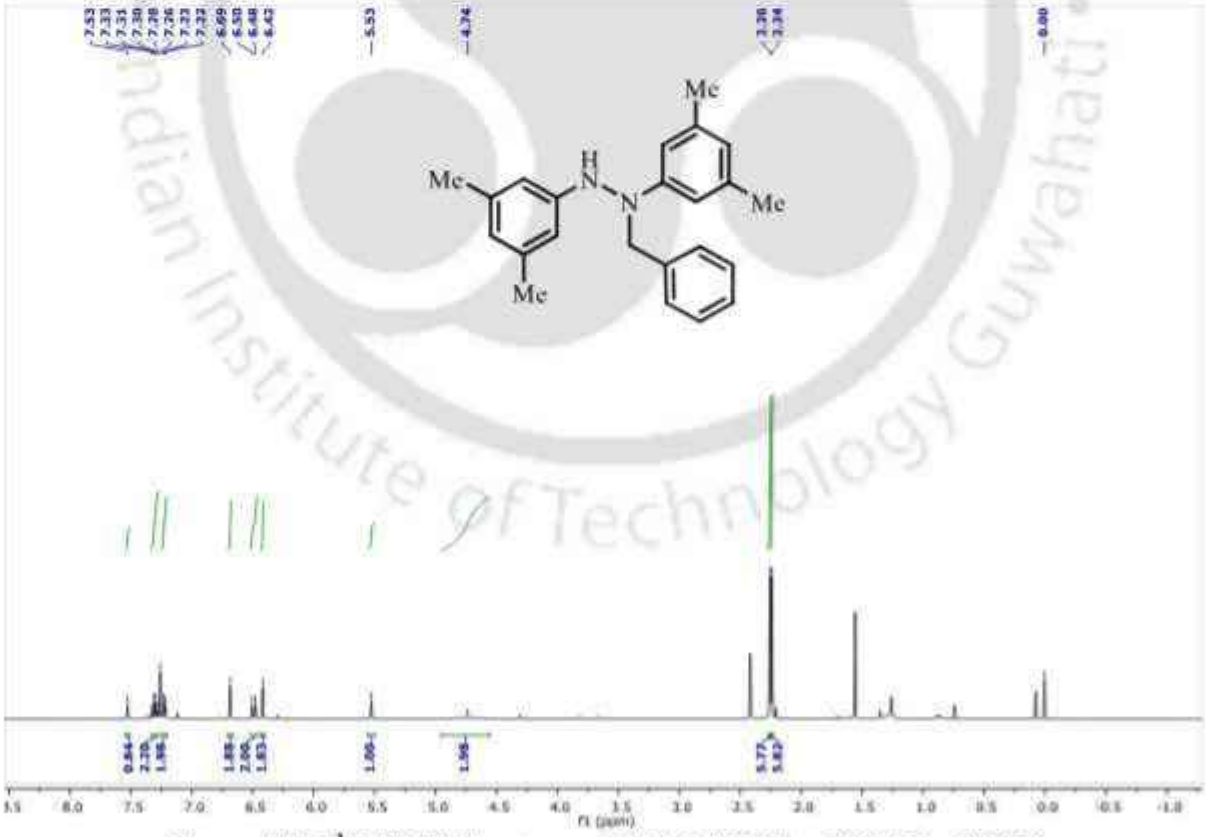


Figure S65: ^{1}H NMR Spectrum of **4.17d** ($CDCl_3$, 500 MHz, 298 K)

TH-3765_196122031

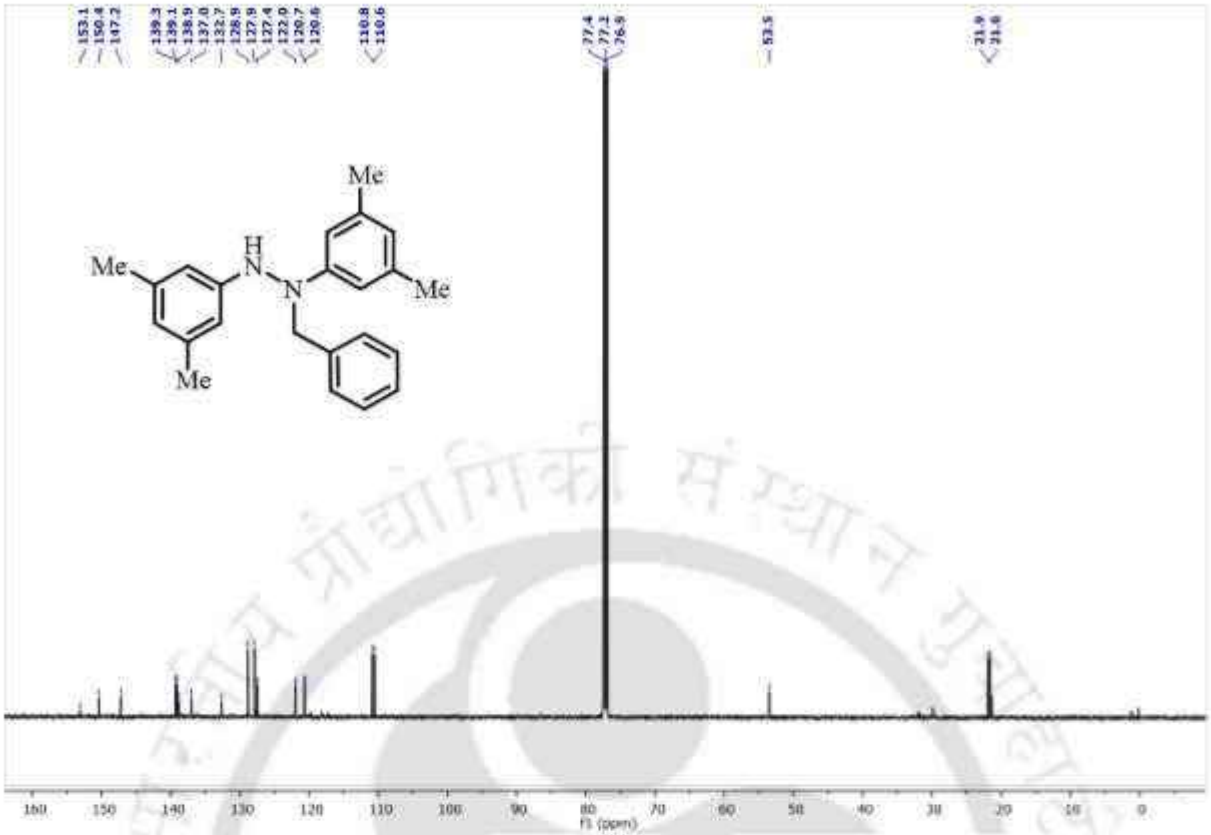


Figure S66: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.17d** ($CDCl_3$, 126 MHz, 298 K)

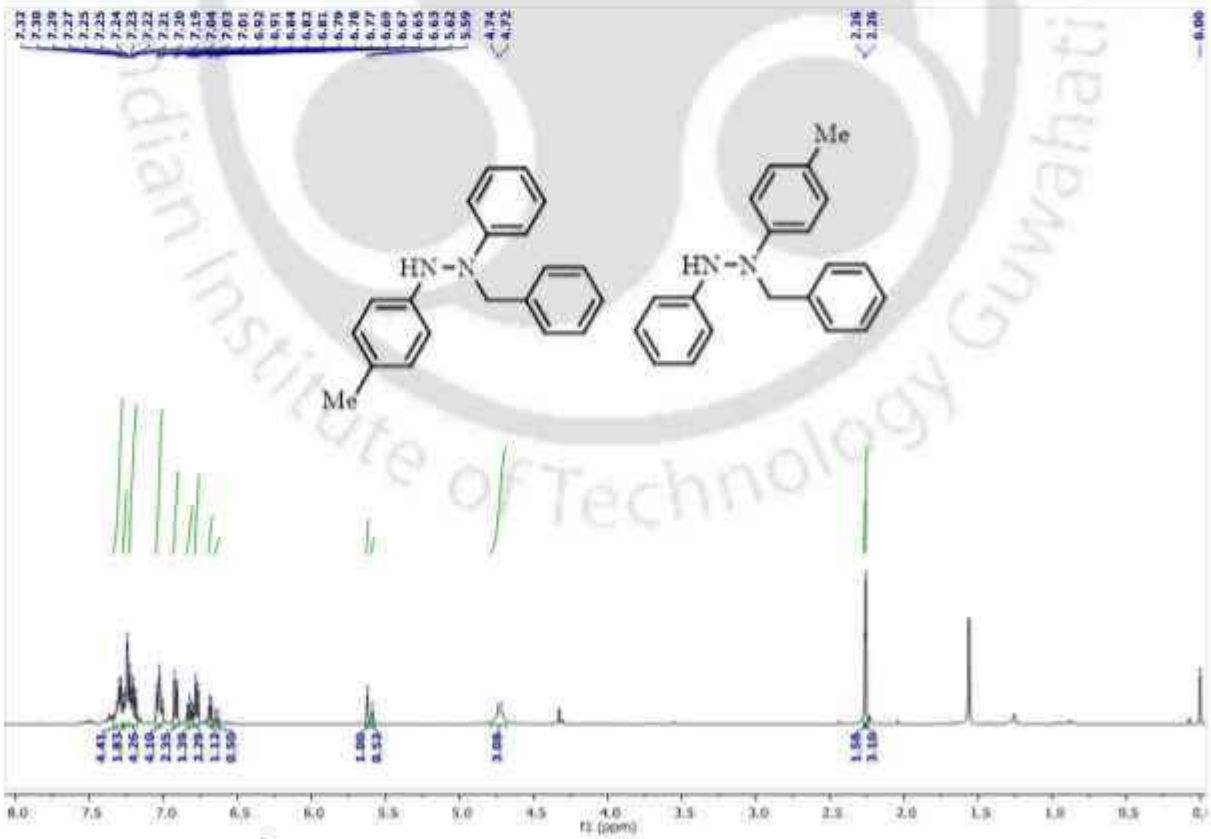


Figure S67: ^{1}H NMR Spectrum of **4.17e-1** + **4.17e-2** ($CDCl_3$, 500 MHz, 298 K)

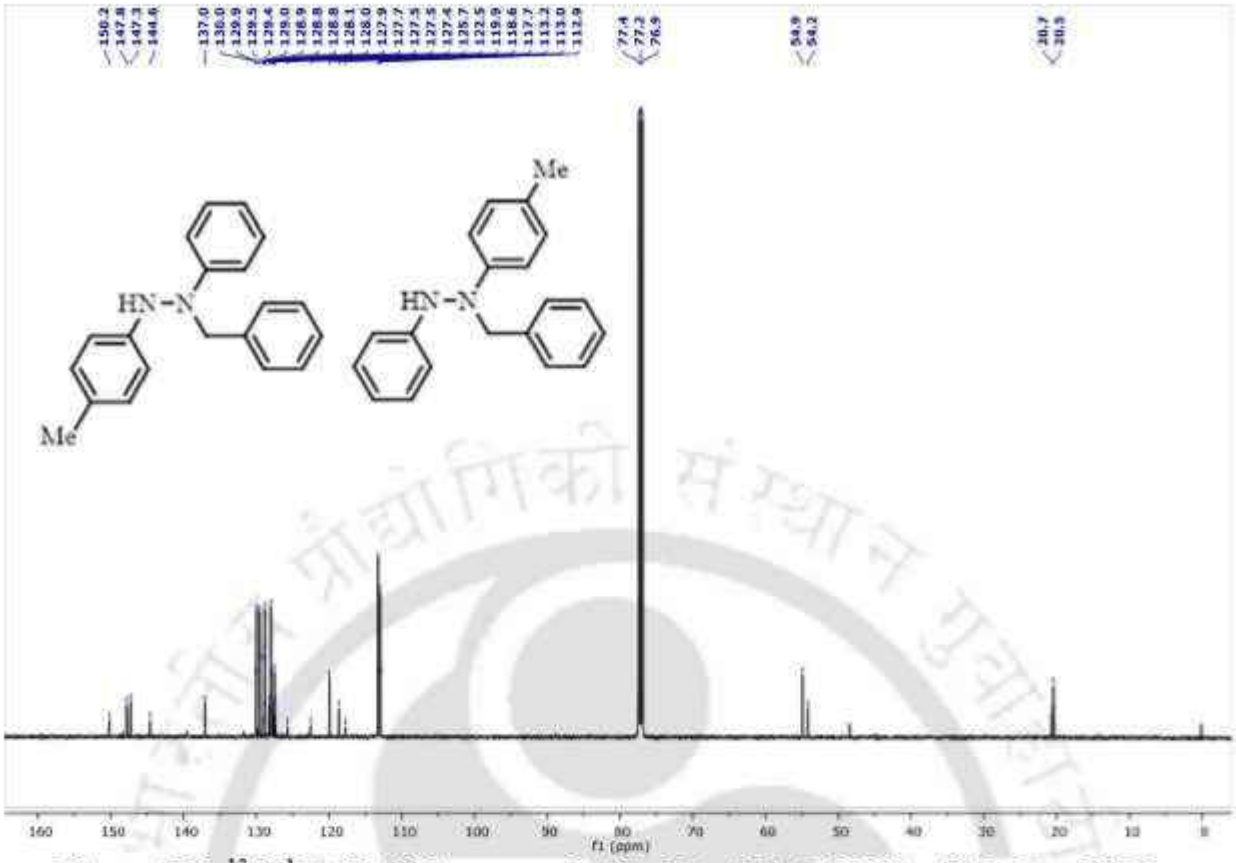


Figure S68: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.17e-1** + **4.17e-2** ($CDCl_3$, 126 MHz, 298 K

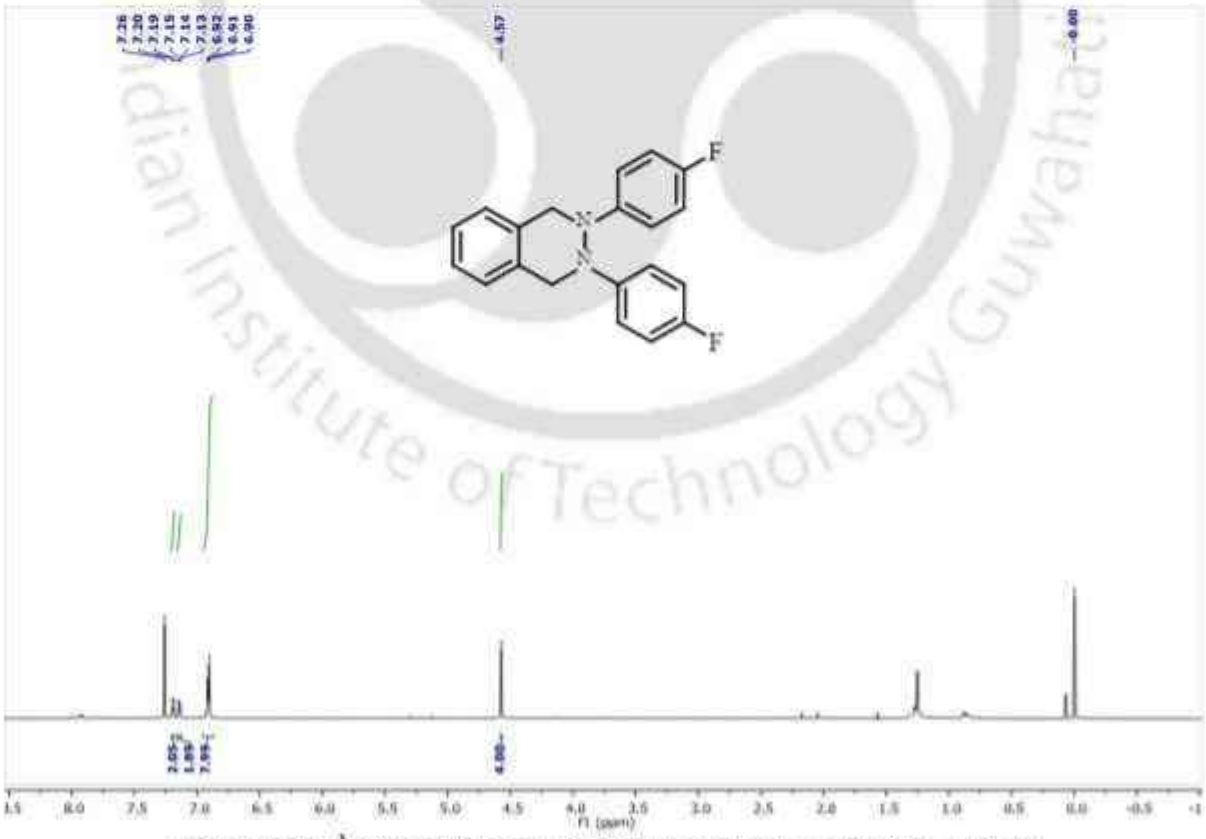


Figure S69: ^{1}H NMR Spectrum of **4.18c** ($CDCl_3$, 600 MHz, 298 K)

TH-3765_196122031

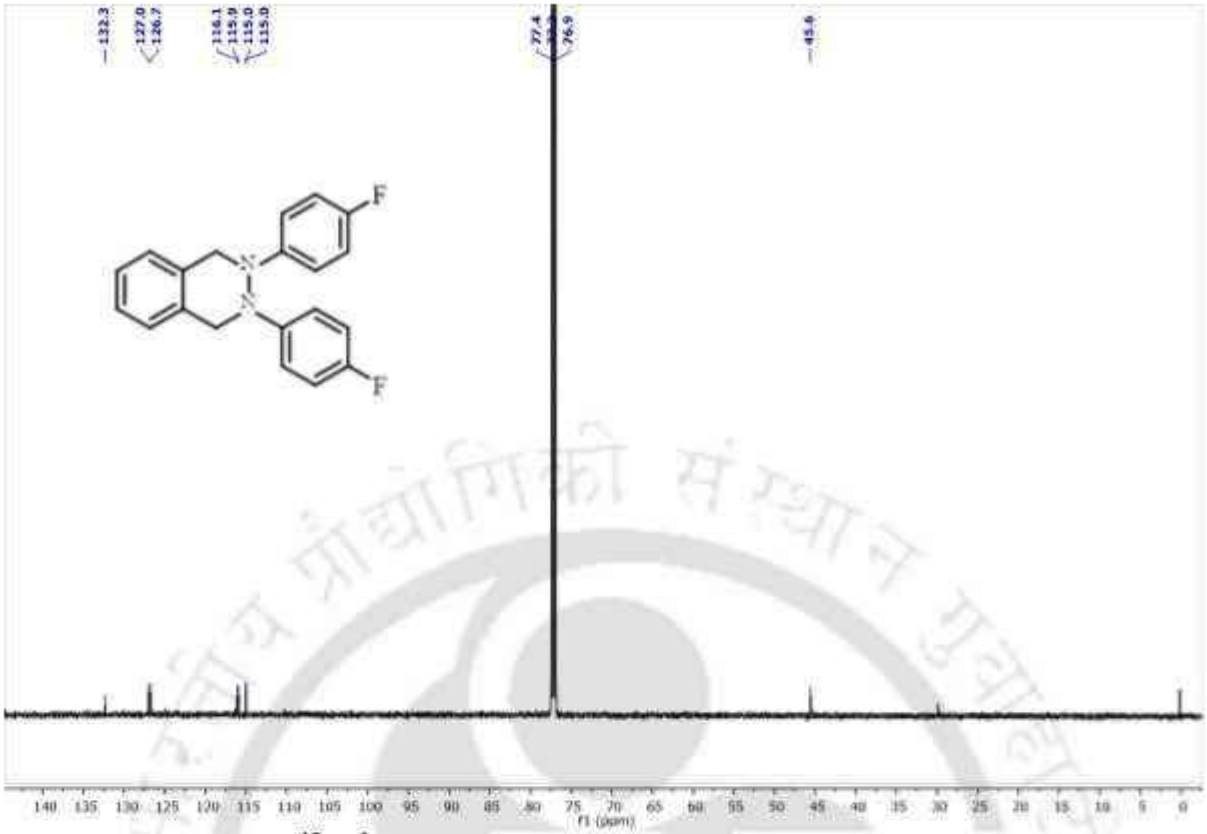


Figure S70: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.18c** ($CDCl_3$, 151 MHz, 298 K)

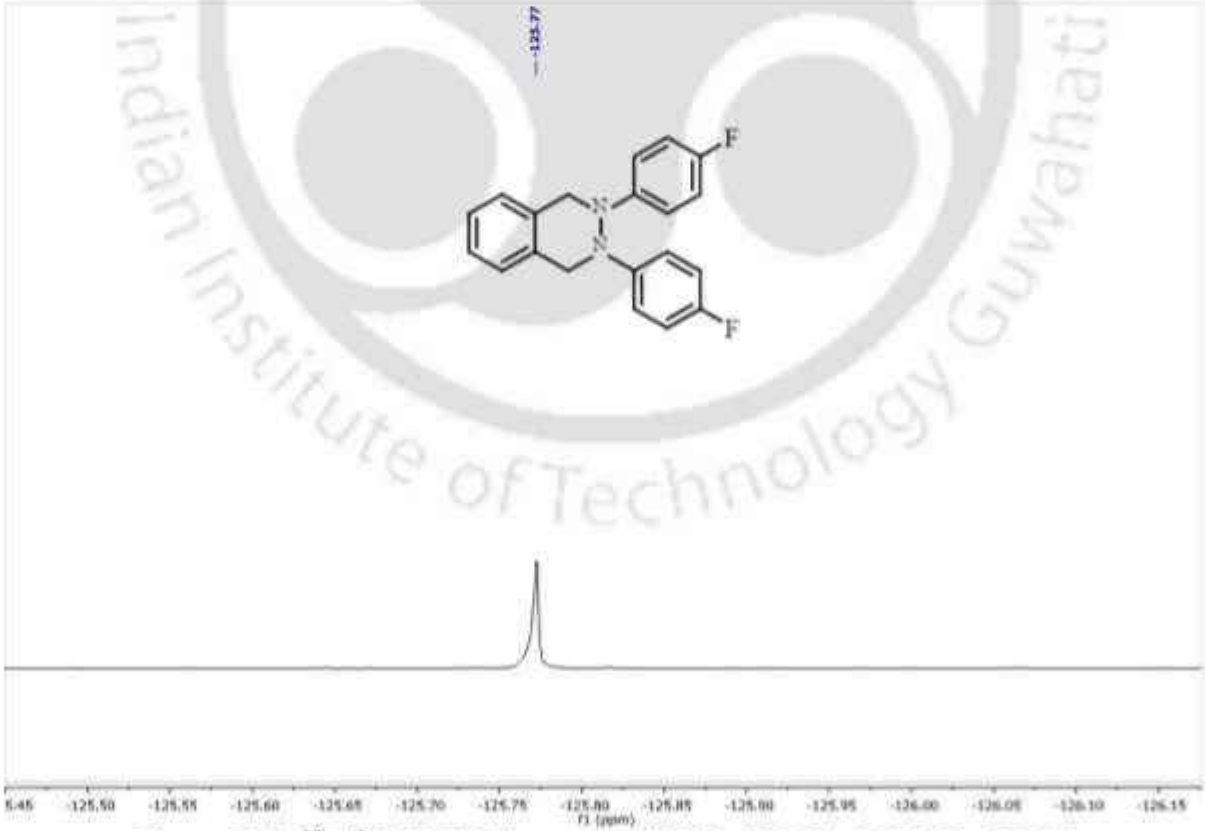


Figure S71: $^{19}F\{^{1}H\}$ NMR Spectrum of **4.18c** ($CDCl_3$, 565 MHz, 298 K)

TH-3765_196122031

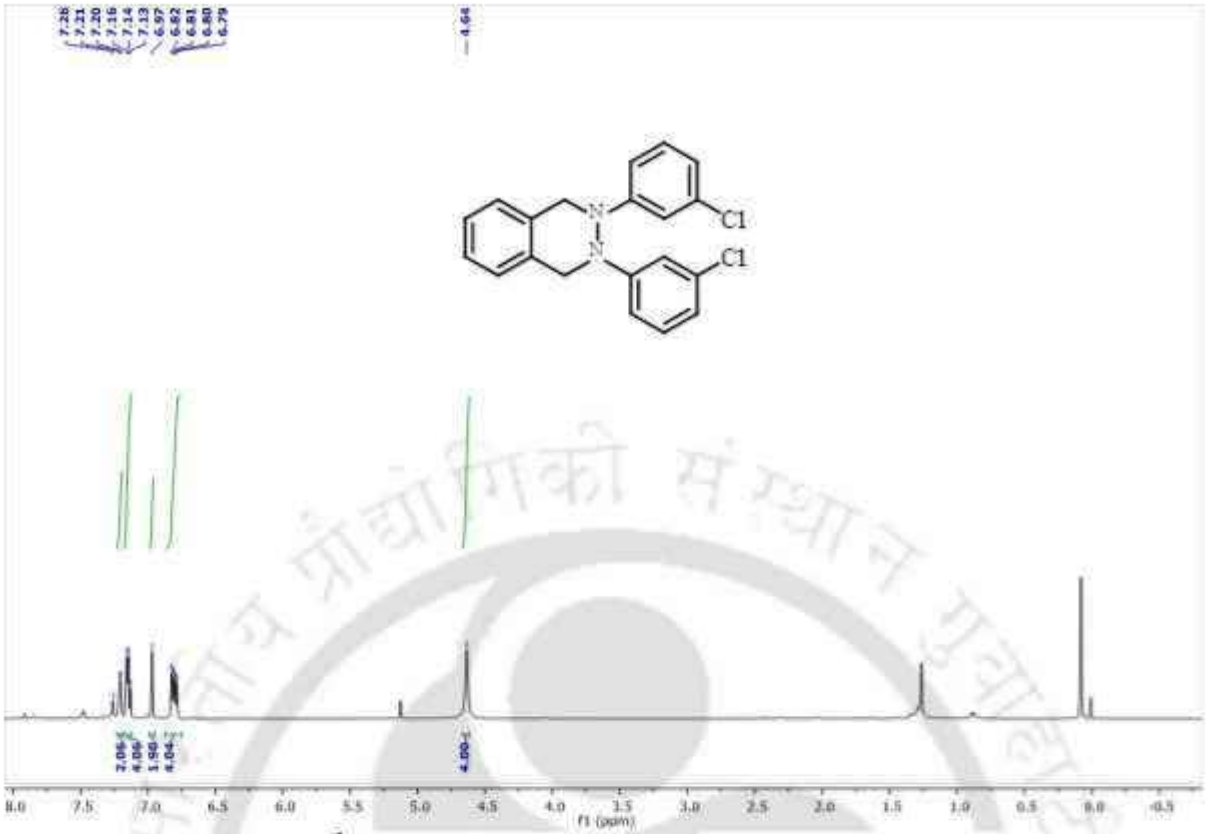


Figure S72: ^{1}H NMR Spectrum of **4.18d** ($CDCl_3$, 600 MHz, 298 K)

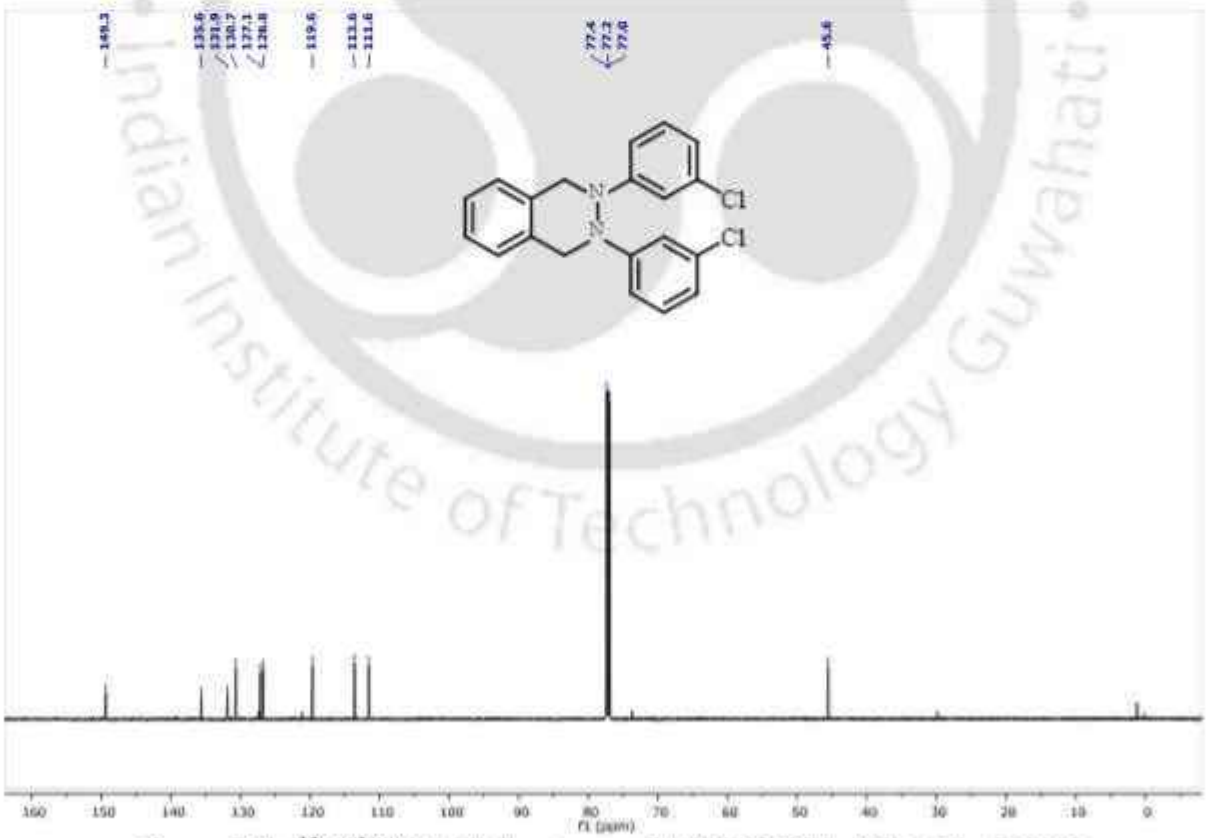


Figure S73: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.18d** ($CDCl_3$, 151 MHz, 298 K)

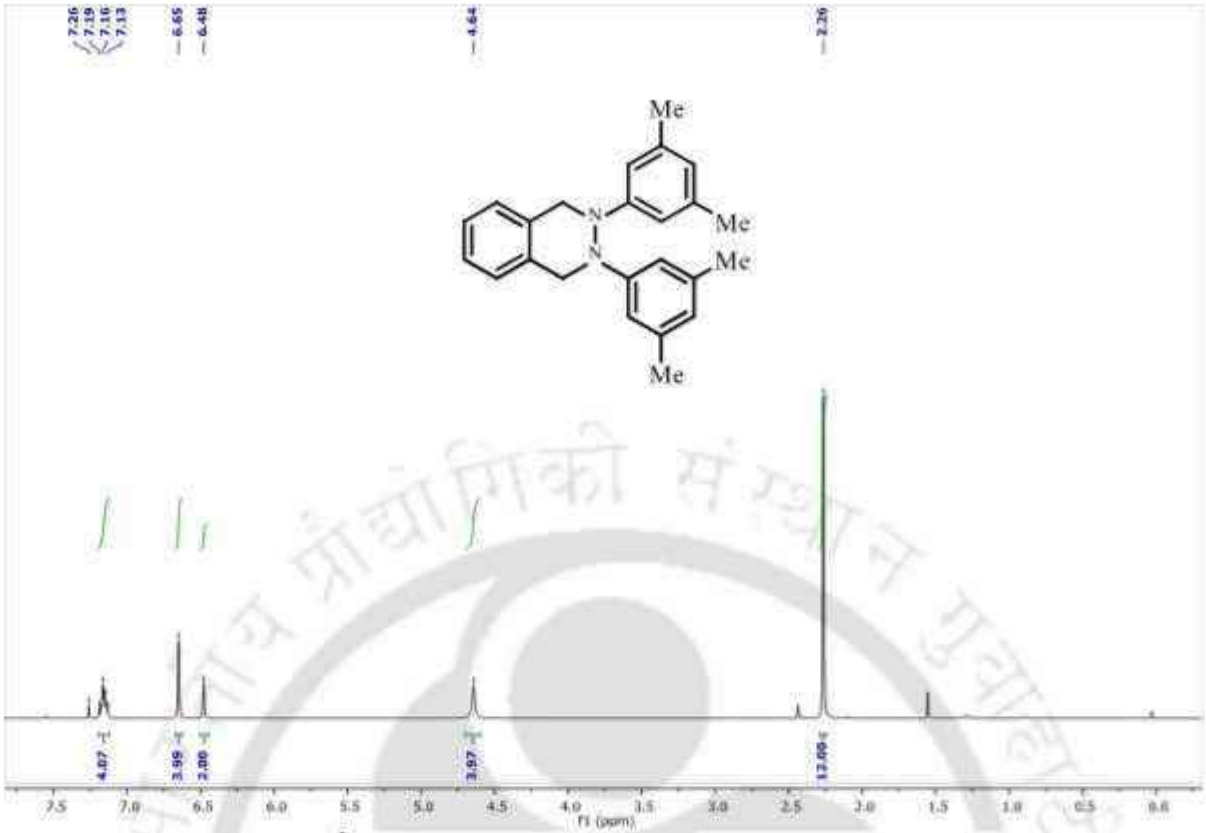


Figure S74: ^{1}H NMR Spectrum of **4.18e** ($CDCl_3$, 400 MHz, 298 K)

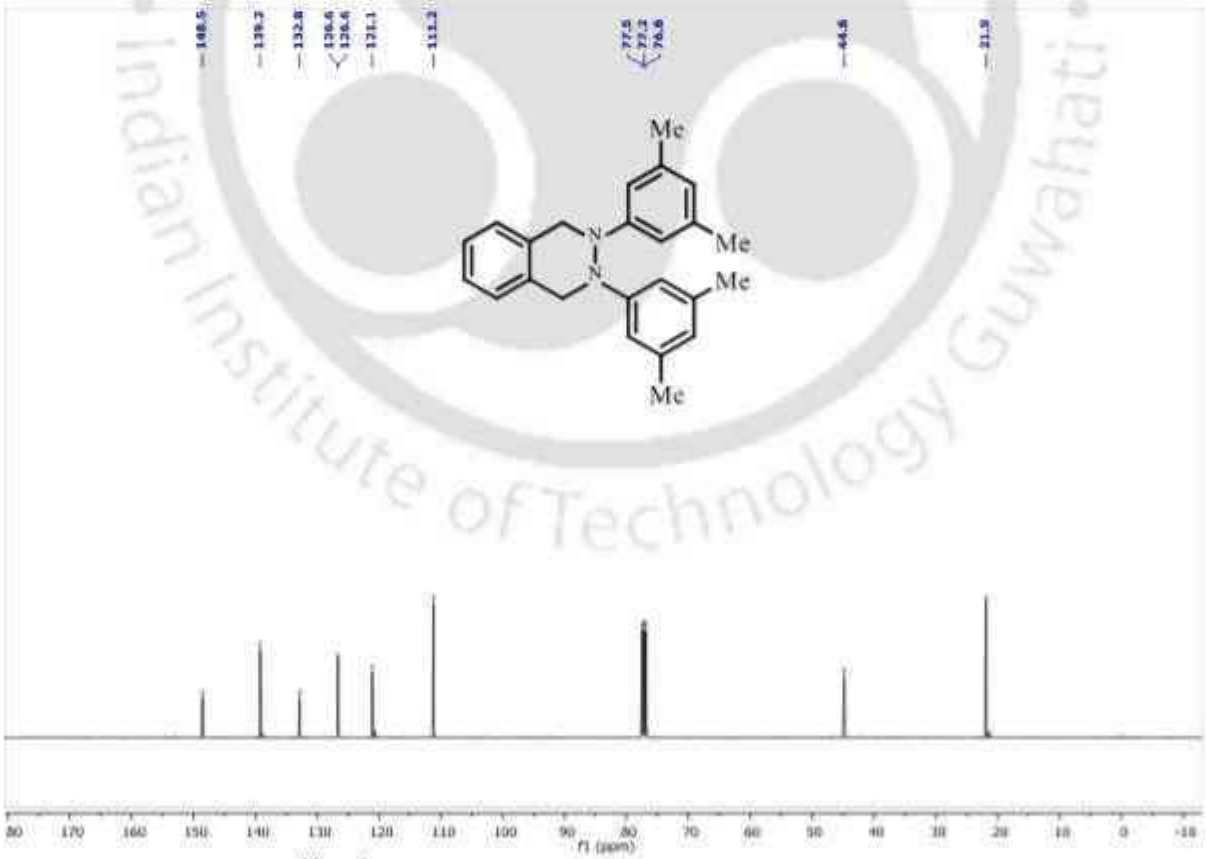


Figure S75: $^{13}C\{^{1}H\}$ NMR Spectrum of **4.18e** ($CDCl_3$, 101 MHz, 298 K)

TH-3765_196122031

The supporting information and all other product spectra for chapter 4 is available at

https://doi.org/10.1002/chem.202500953

https://doi.org/10.1039/D5CC00425J

Annexure IV

^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ spectra of representative compounds (*Chapter 5*)

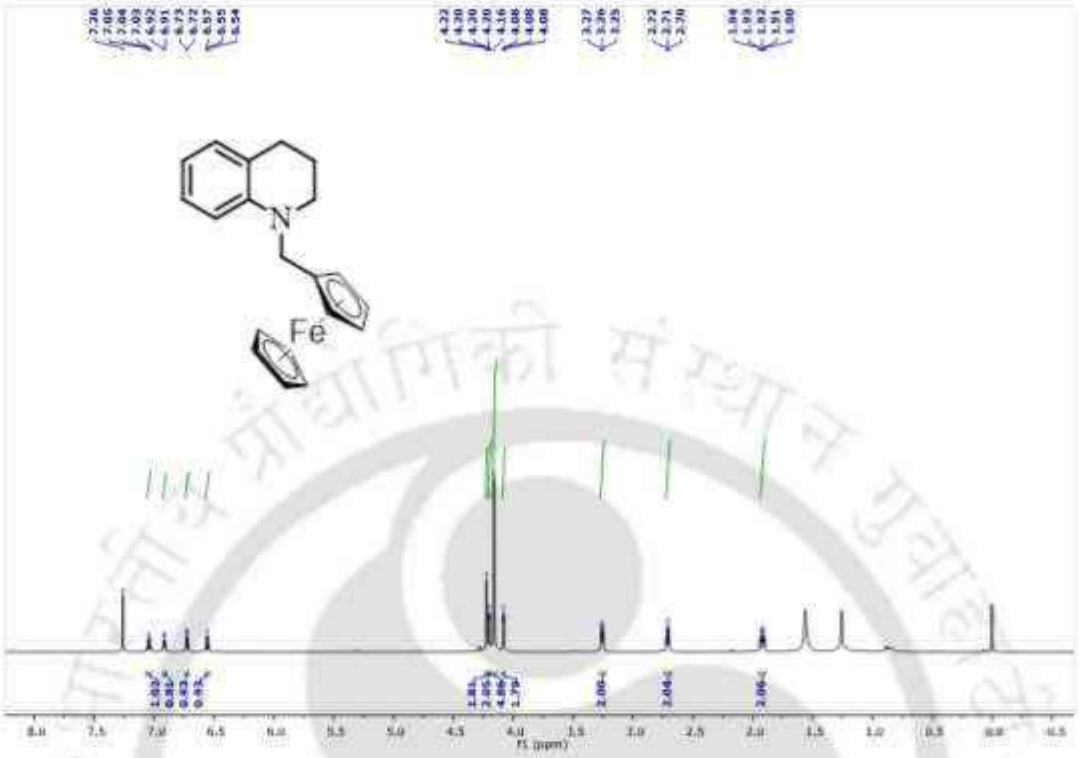


Figure S76: ^{1}H NMR Spectrum of **5.5y** ($CDCl_3$, 600 MHz, 298 K)

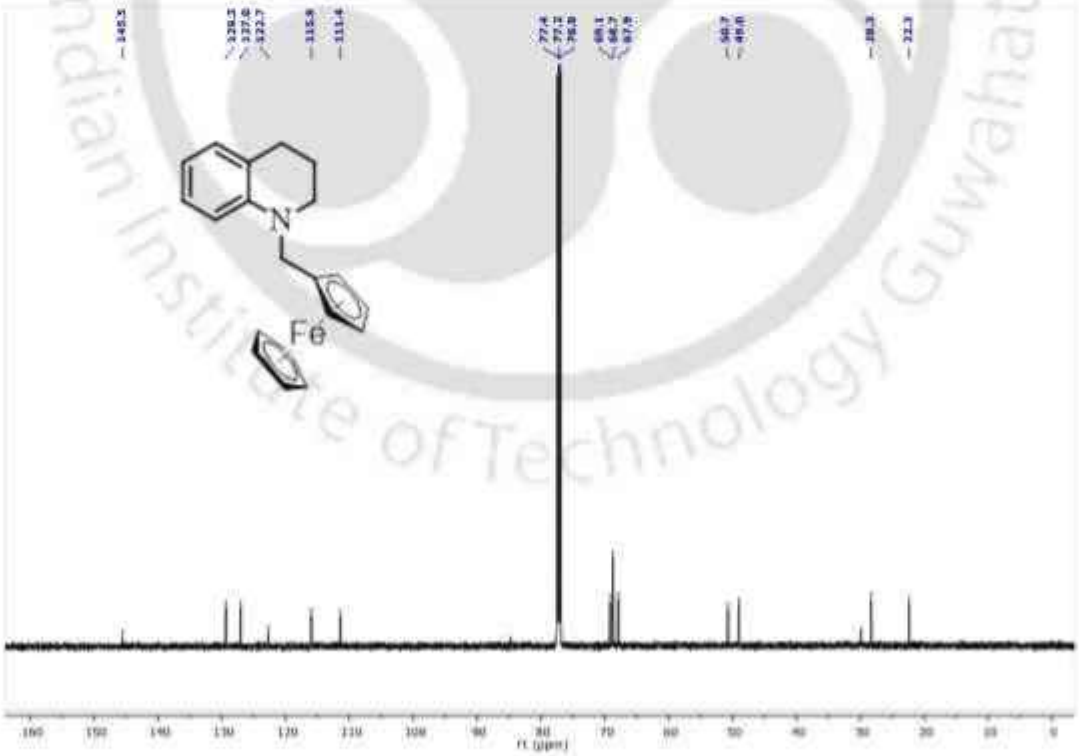


Figure S77: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.5y** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

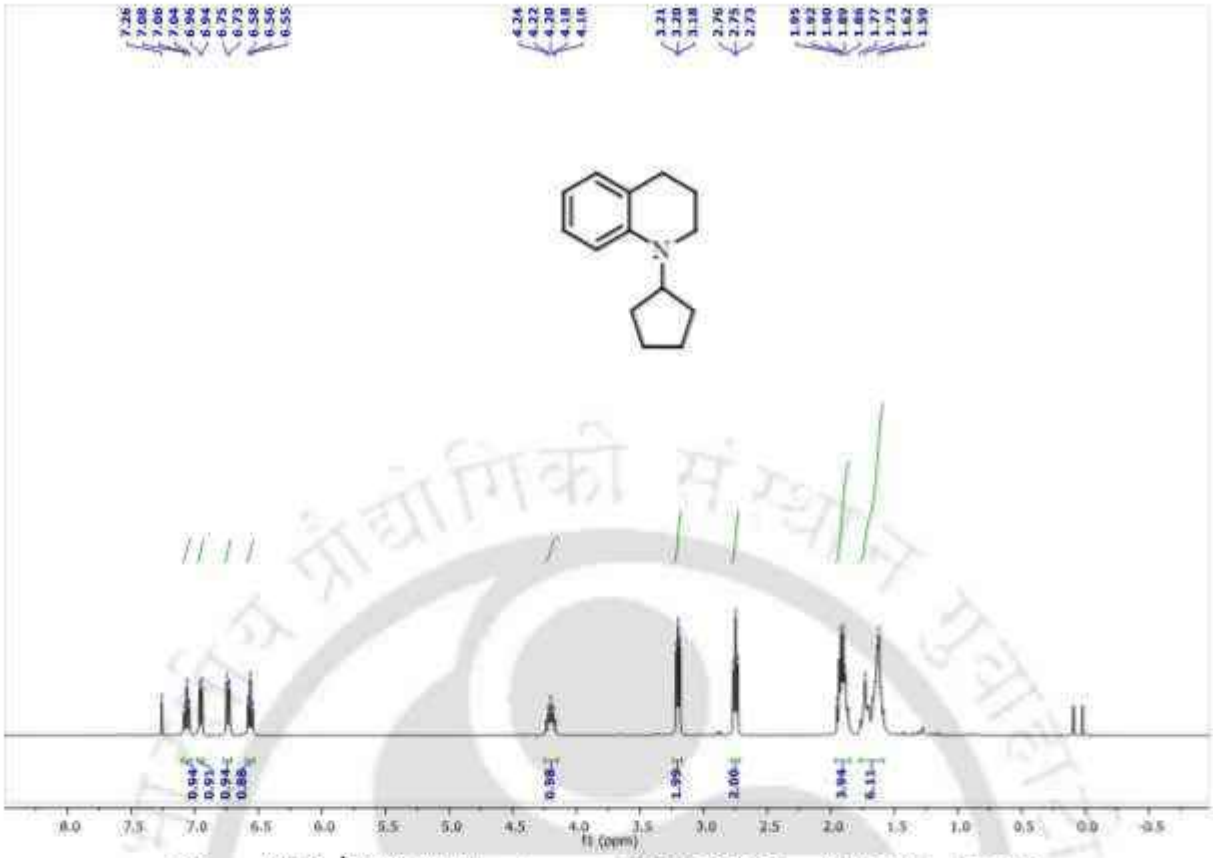


Figure S78: ^{1}H NMR Spectrum of **5.5af** ($CDCl_3$, 400 MHz, 298 K)

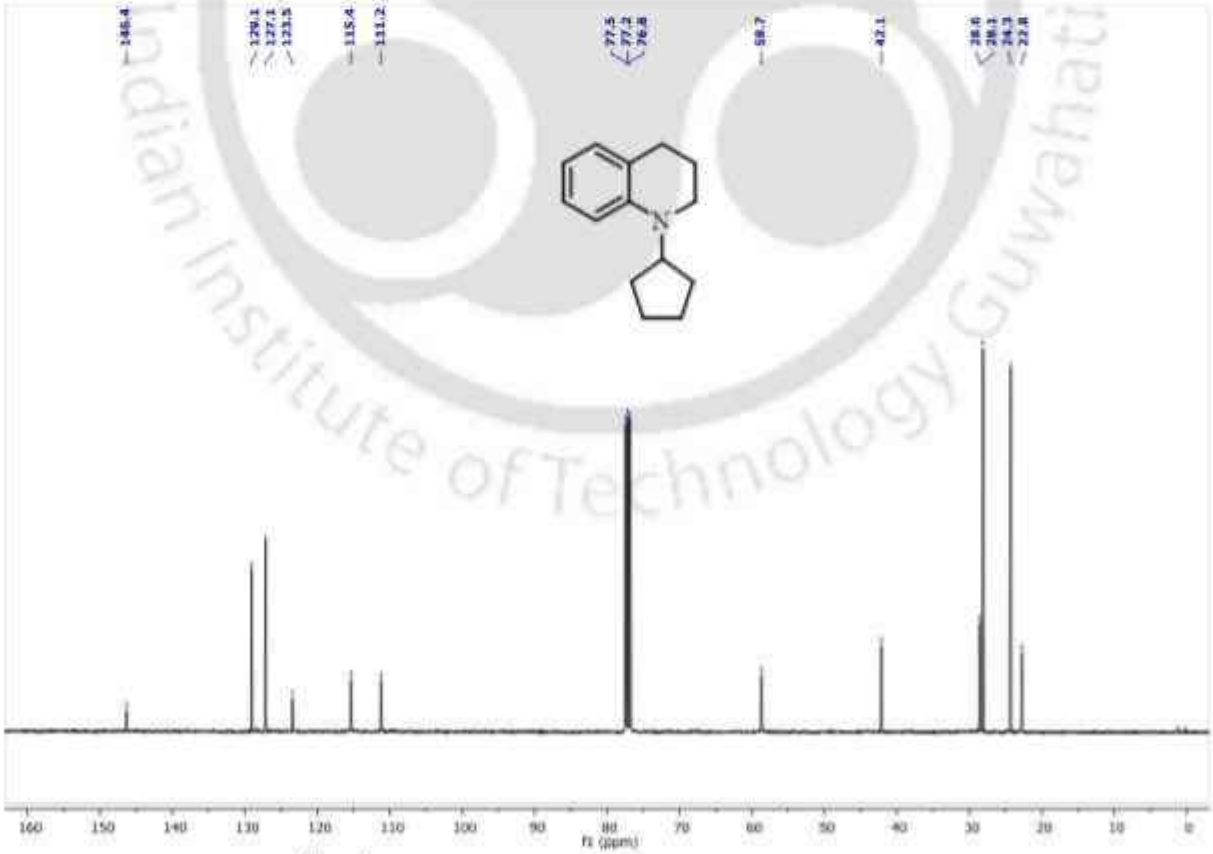


Figure S79: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.5af** ($CDCl_3$, 101 MHz, 298 K)

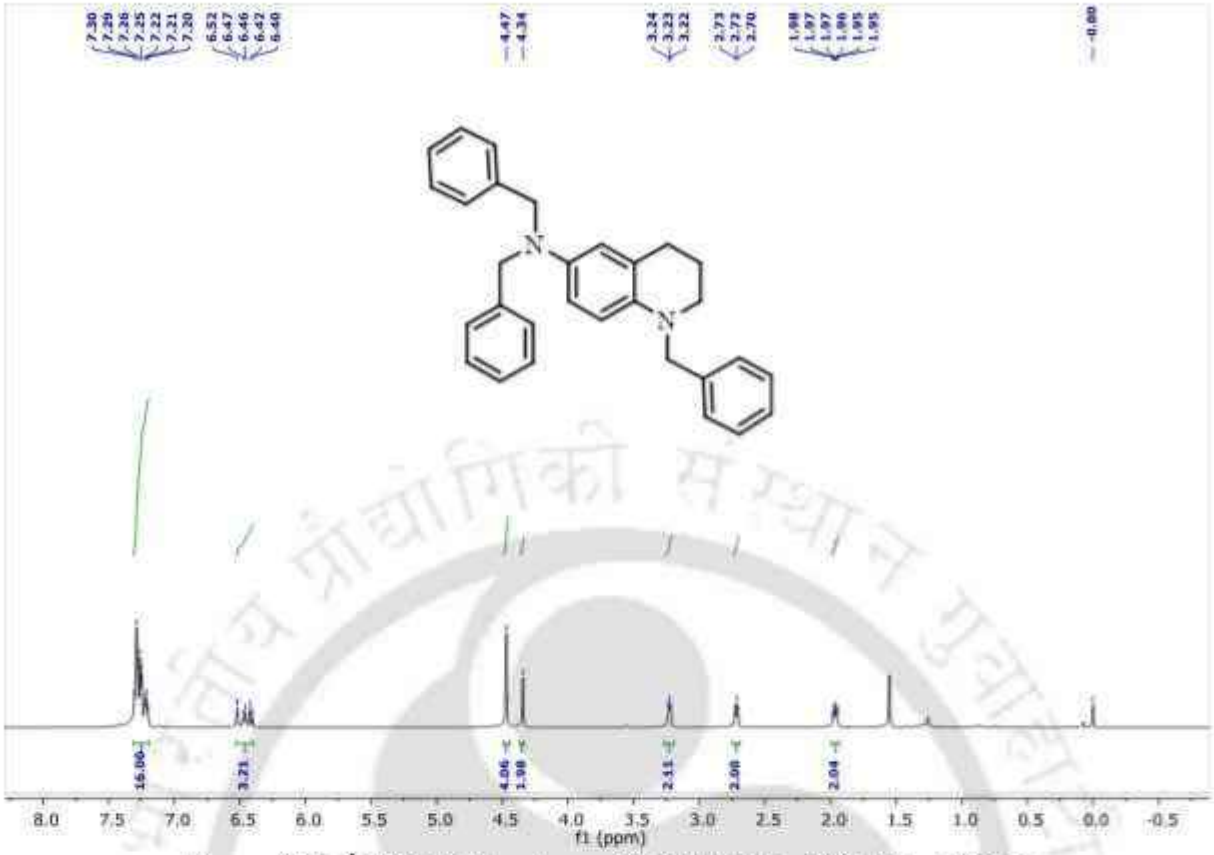


Figure S80: ^{1}H NMR Spectrum of **5.6l** ($CDCl_3$, 500 MHz, 298 K)

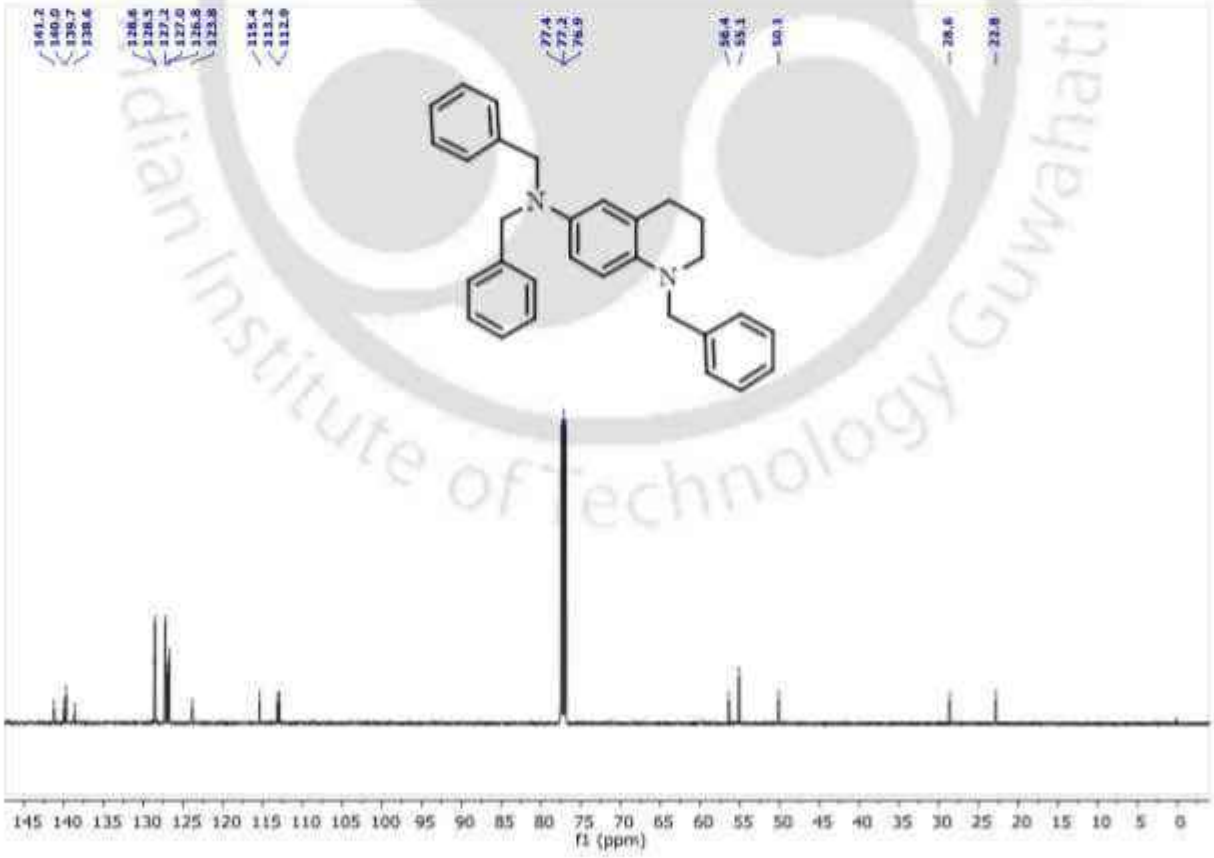


Figure S81: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.6l** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

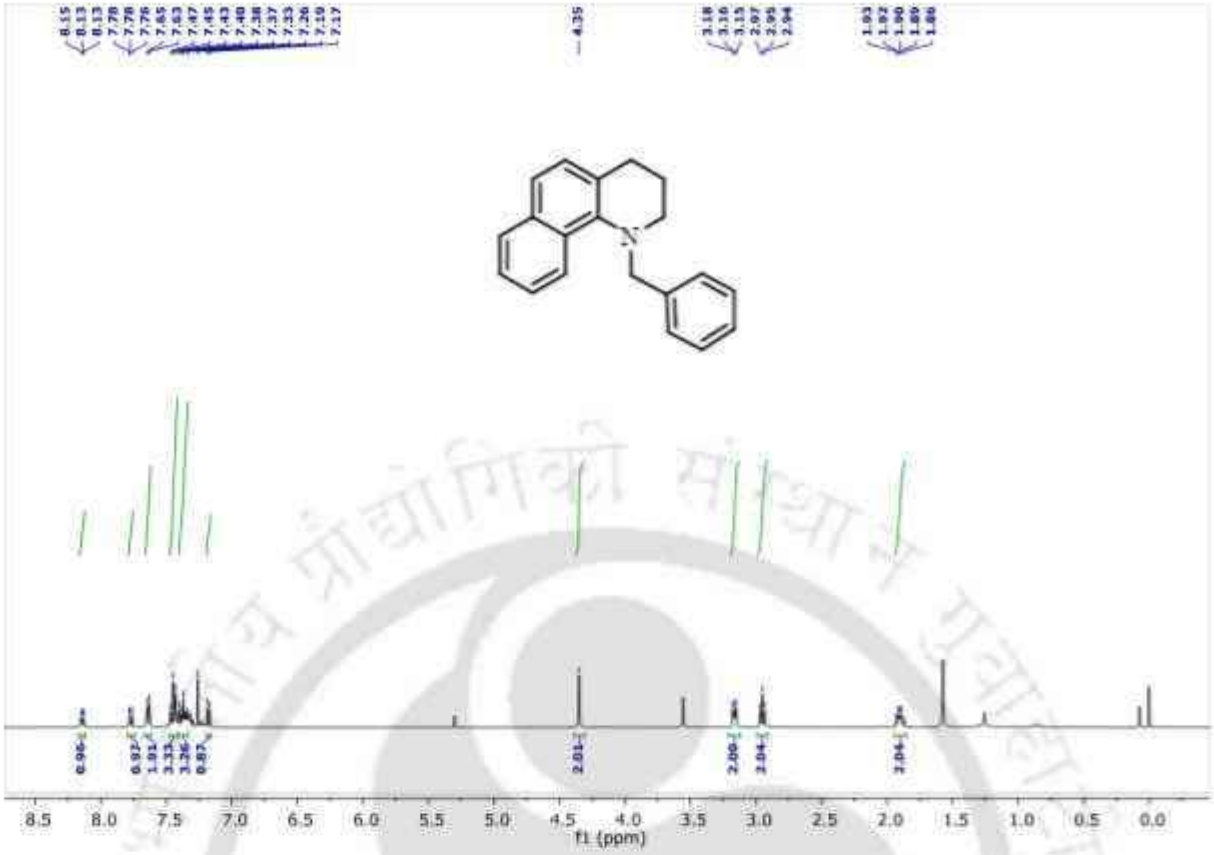


Figure S82: ^{1}H NMR Spectrum of **5.6m** ($CDCl_3$, 400 MHz, 298 K)

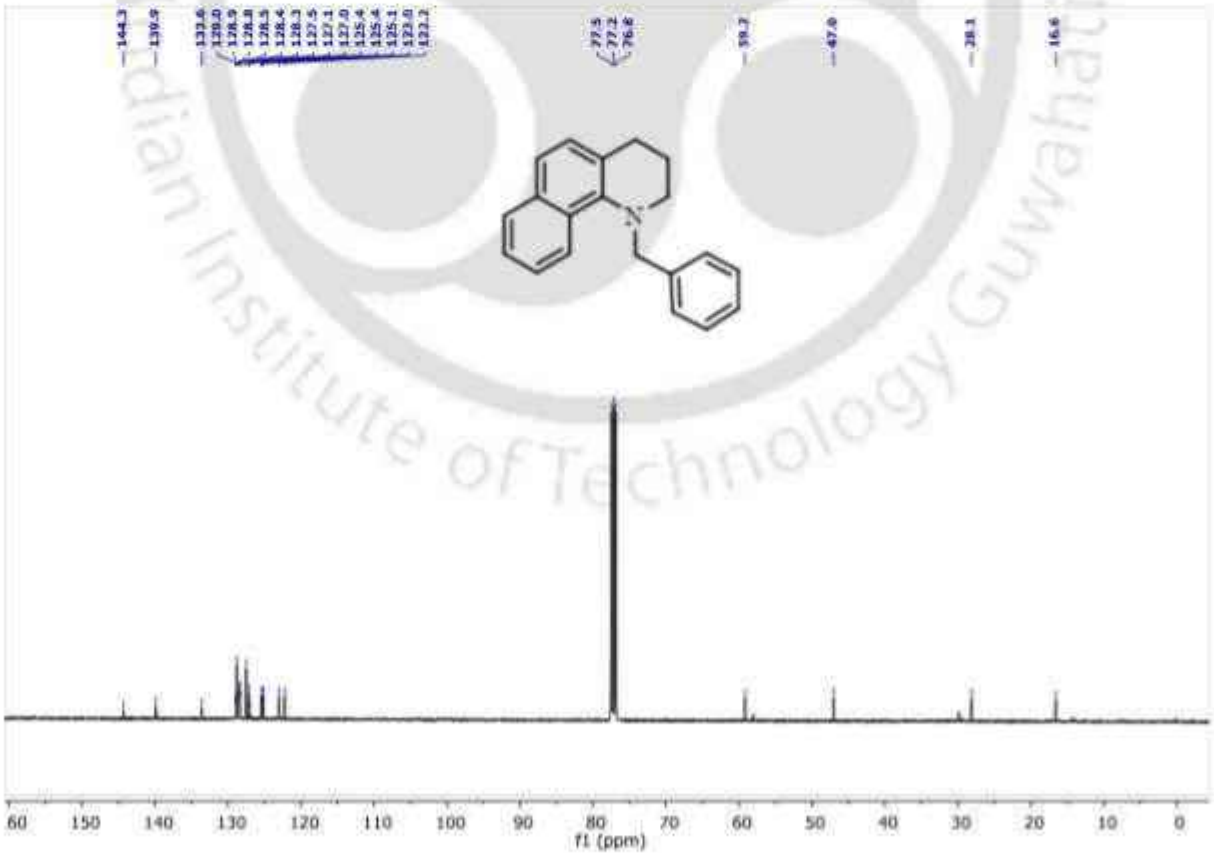


Figure S83: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.6m** ($CDCl_3$, 101 MHz, 298 K)

TH-3765_196122031

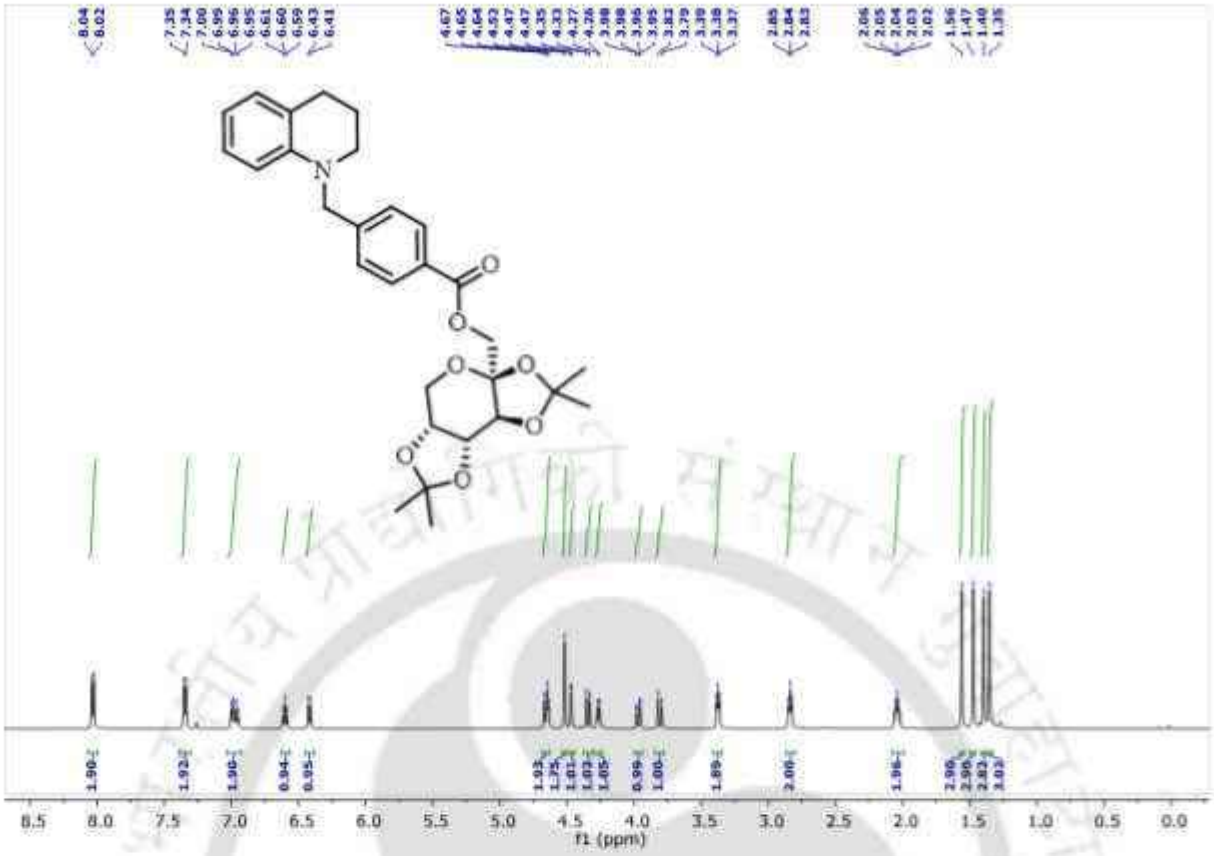


Figure S84: ^{1}H NMR Spectrum of **5.8a** ($CDCl_3$, 500 MHz, 298 K)

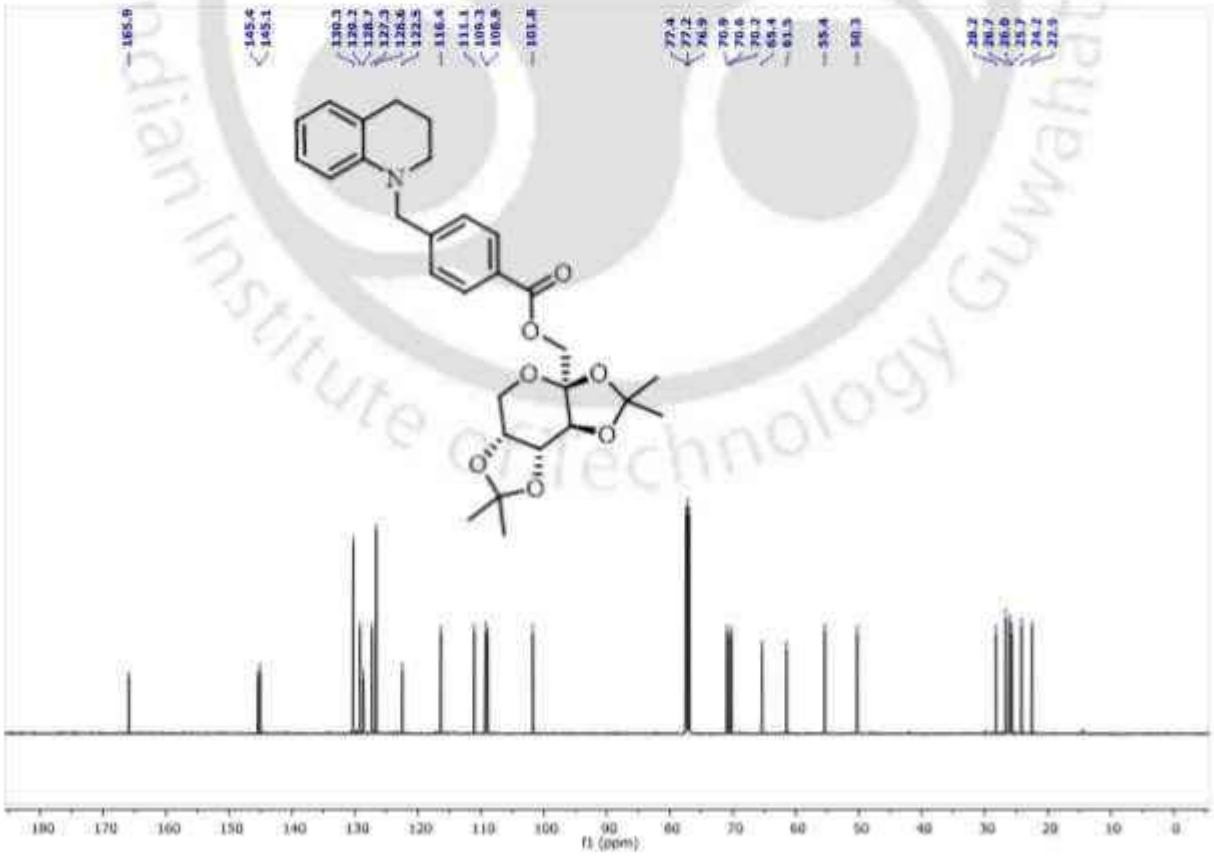


Figure S85: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.8a** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

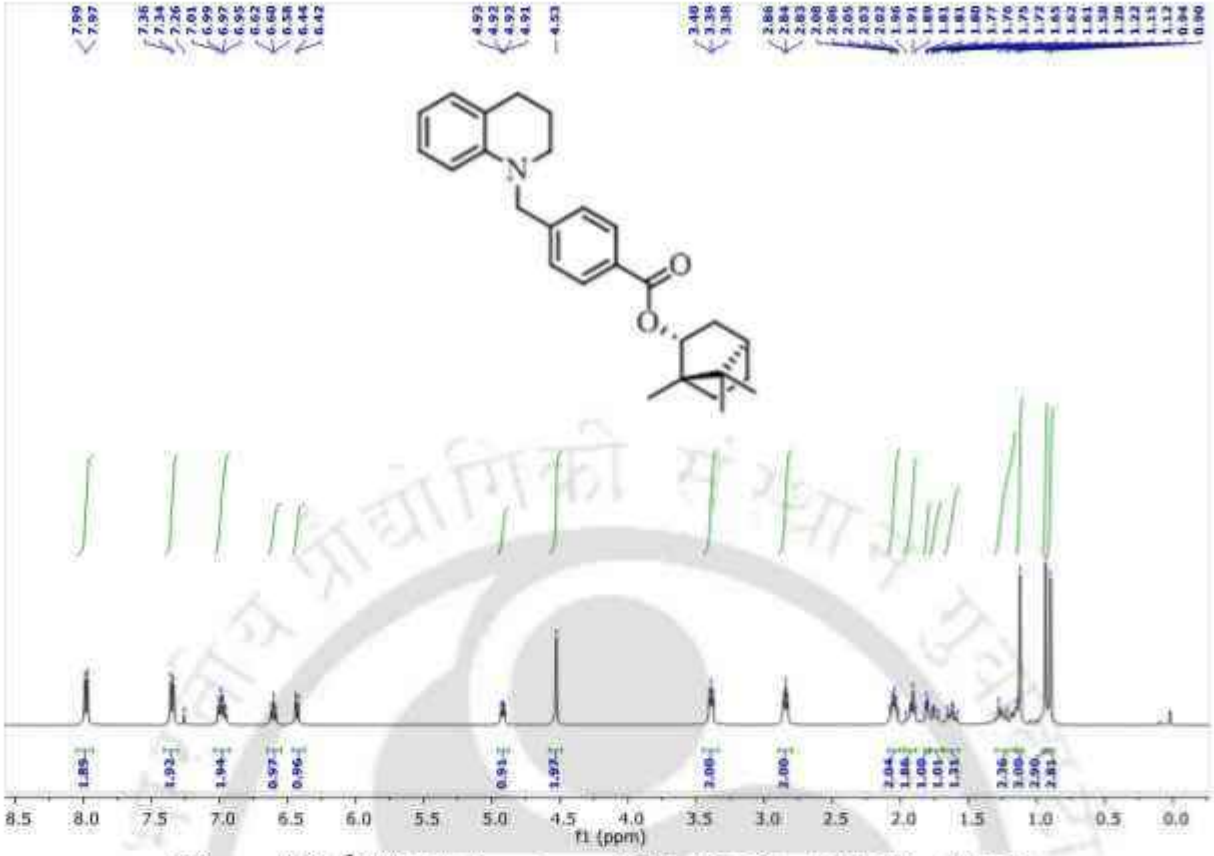


Figure S86: ^{1}H NMR Spectrum of **5.8e** ($CDCl_3$, 400 MHz, 298 K)

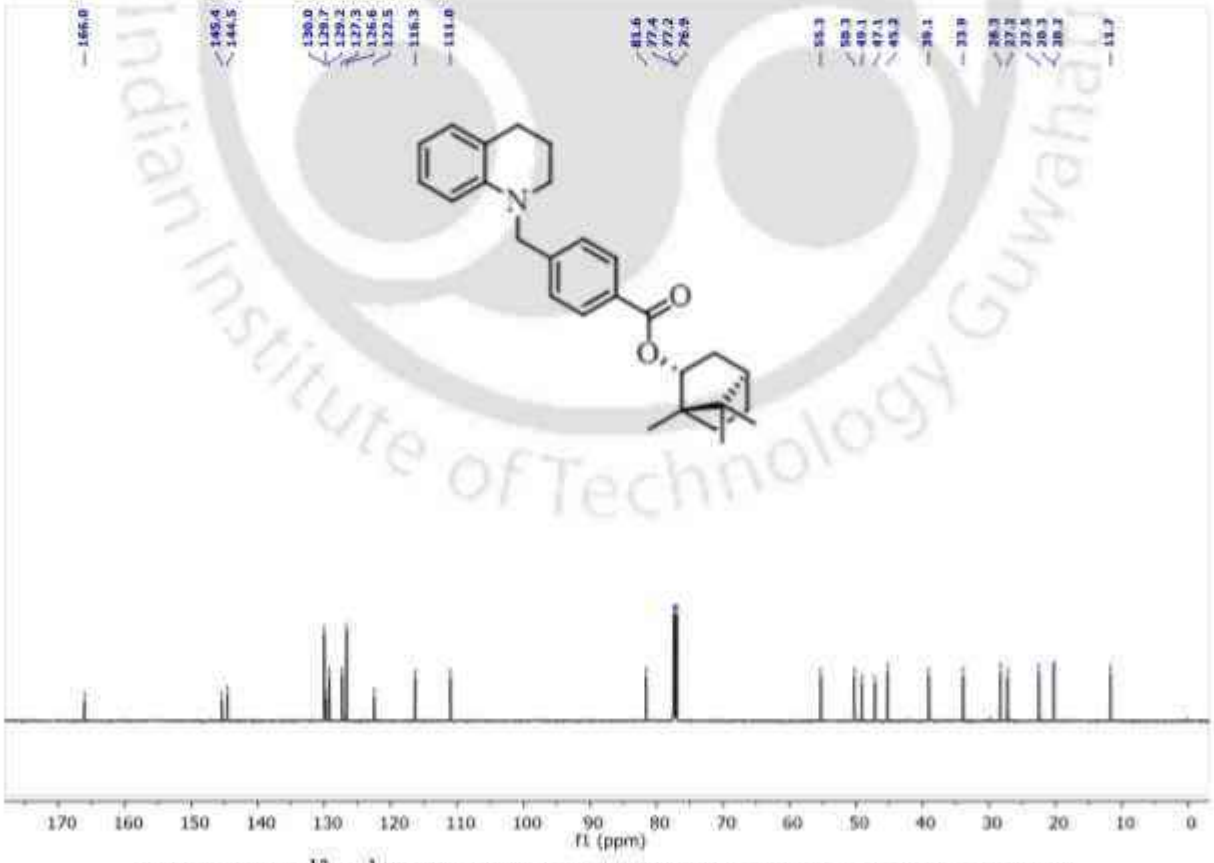


Figure S87: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.8e** ($CDCl_3$, 126 MHz, 298 K)

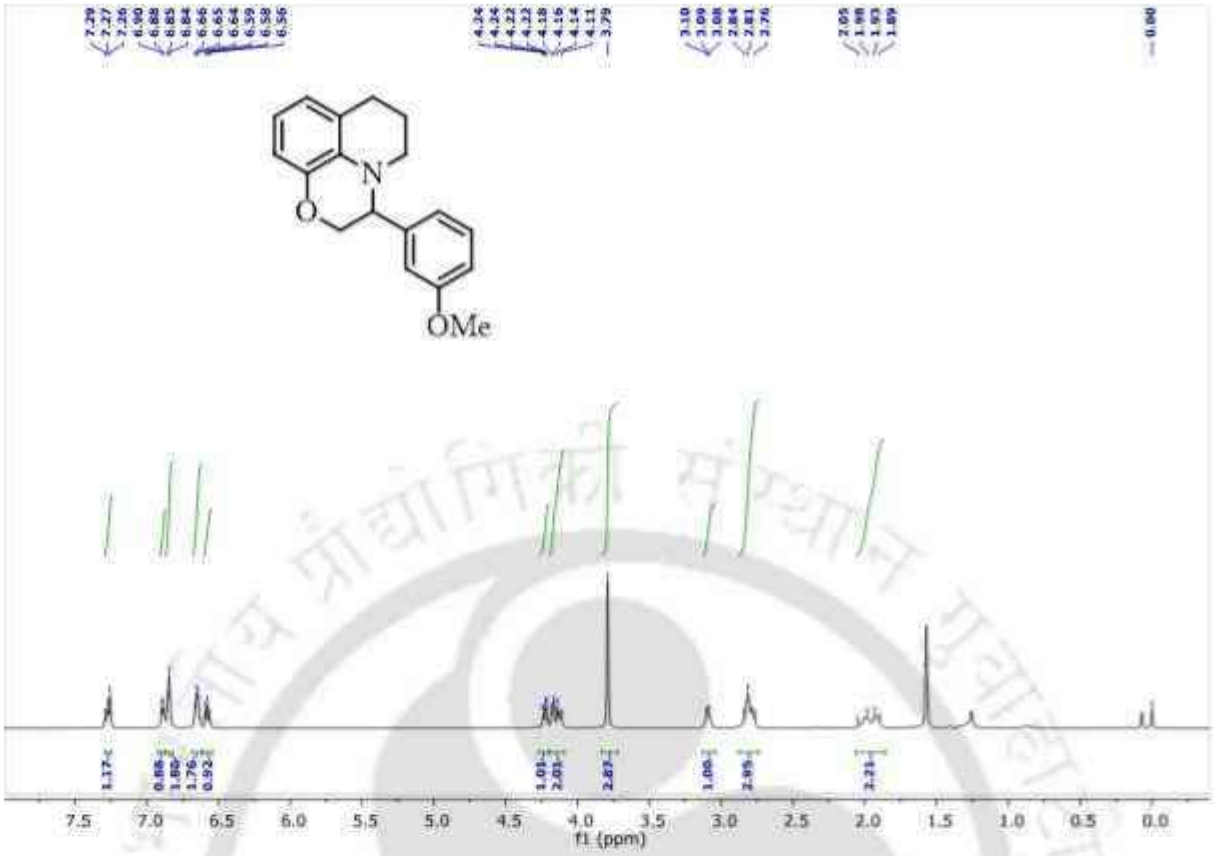


Figure S88: ^{1}H NMR Spectrum of **5.10d** ($CDCl_3$, 500 MHz, 298 K)

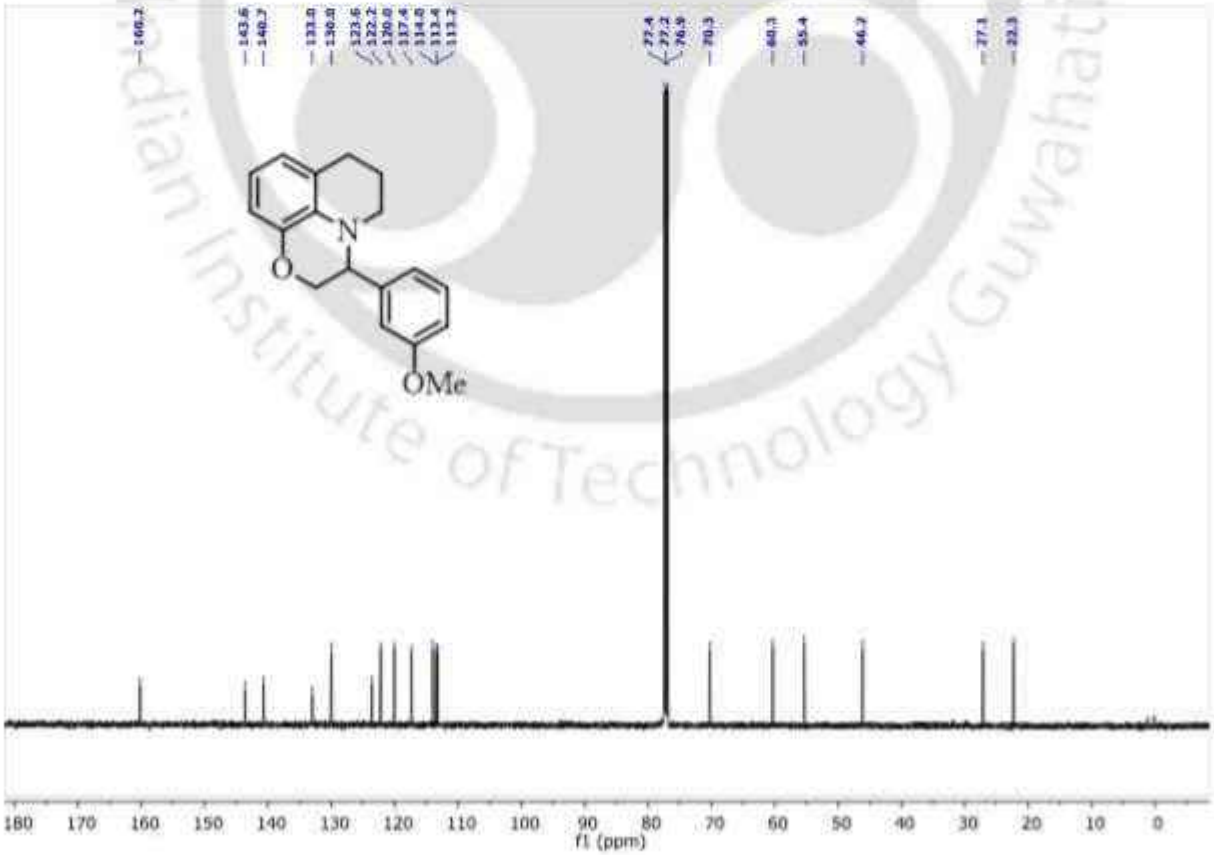


Figure S89: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.10d** ($CDCl_3$, 126 MHz, 298 K)

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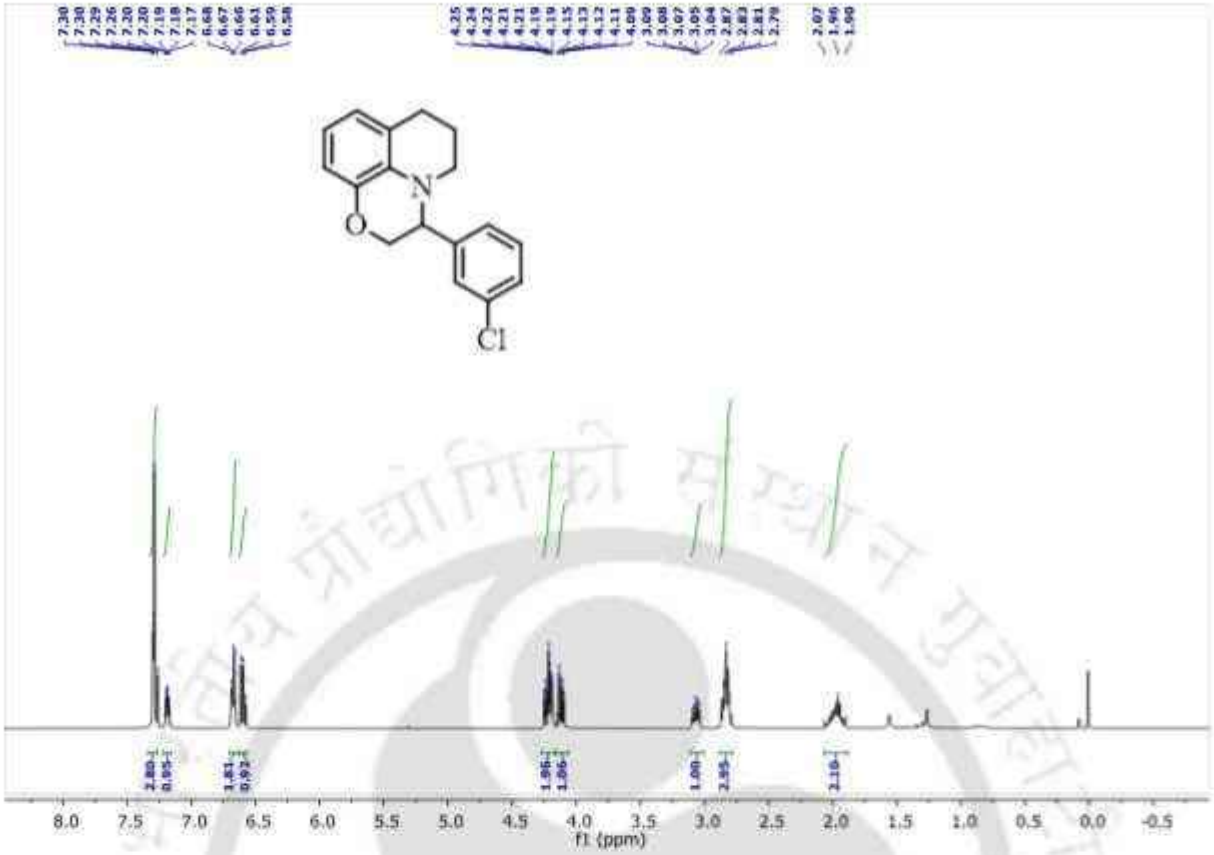


Figure S90: ^{1}H NMR Spectrum of **5.10e** ($CDCl_3$, 400 MHz, 298 K)

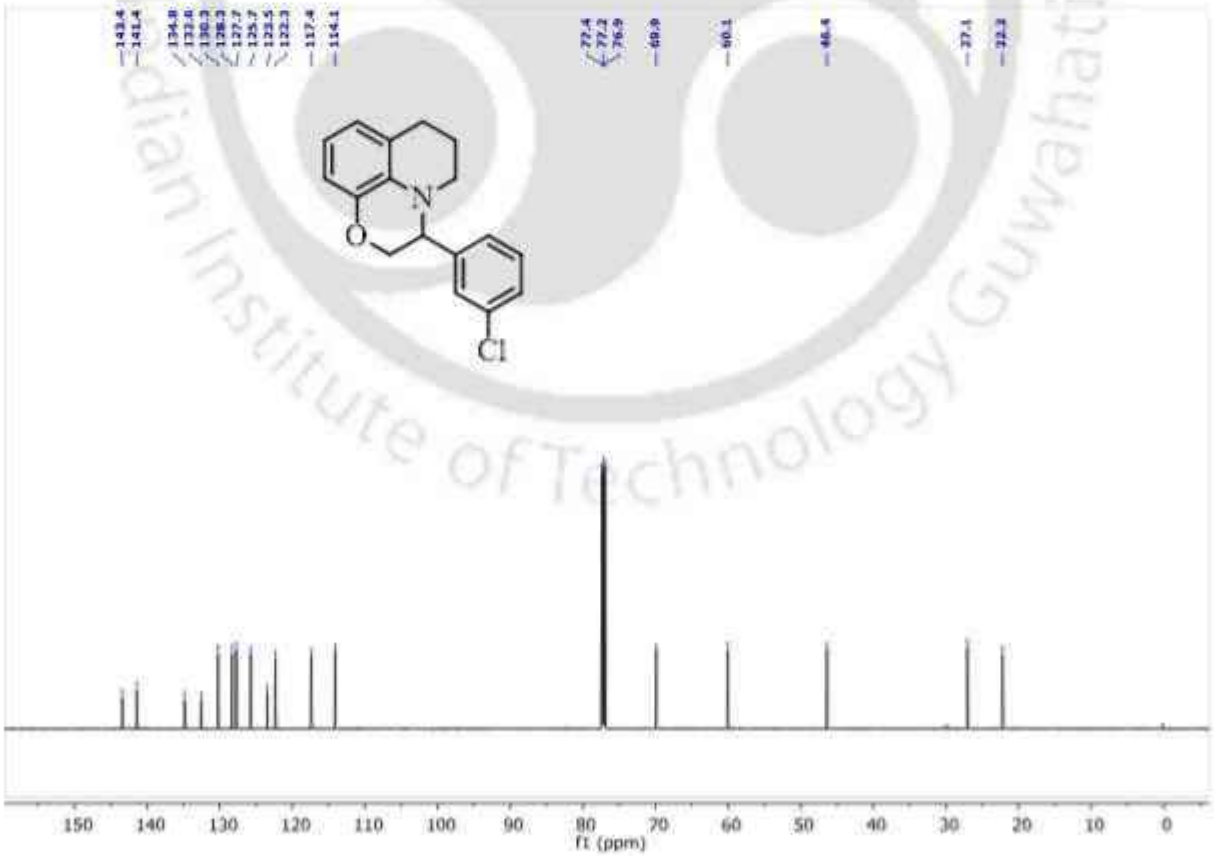


Figure S91: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.10e** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

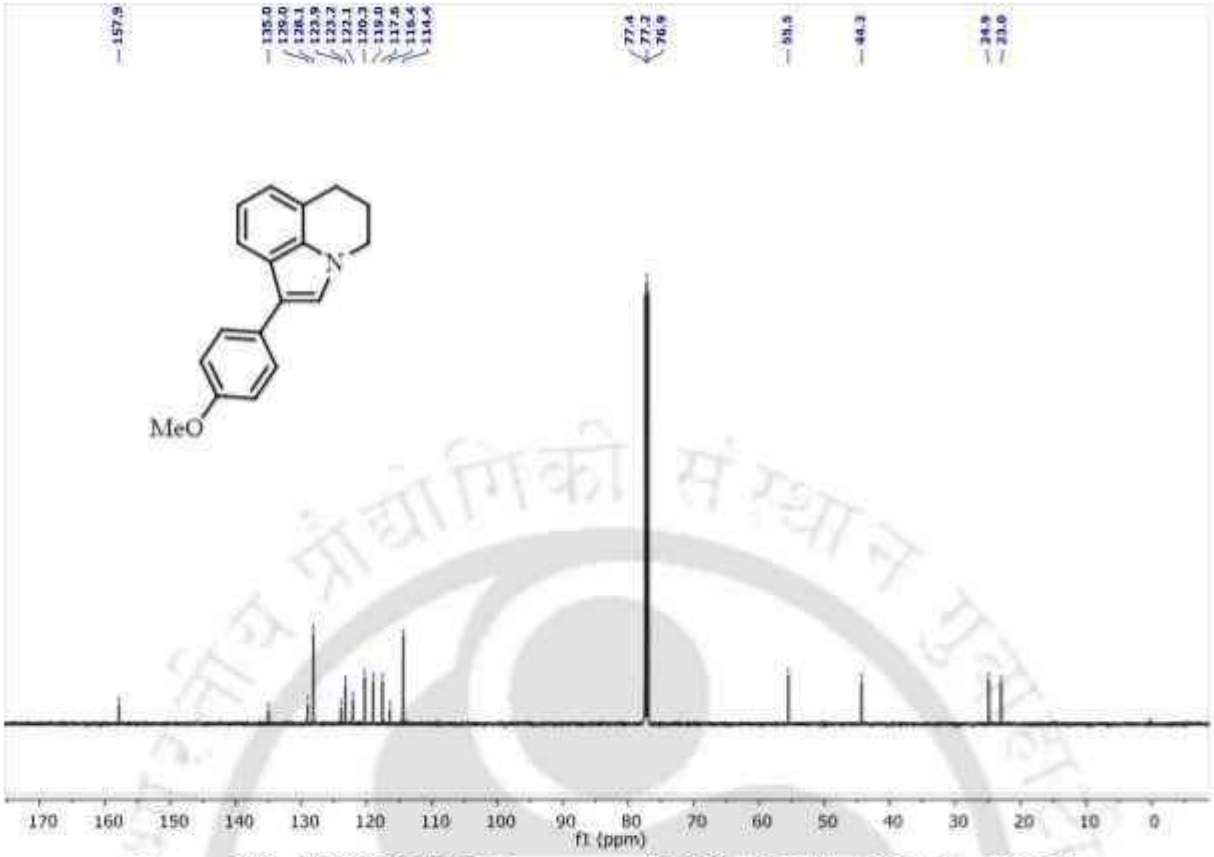


Figure S92: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.12b** ($CDCl_3$, 126 MHz, 298 K)

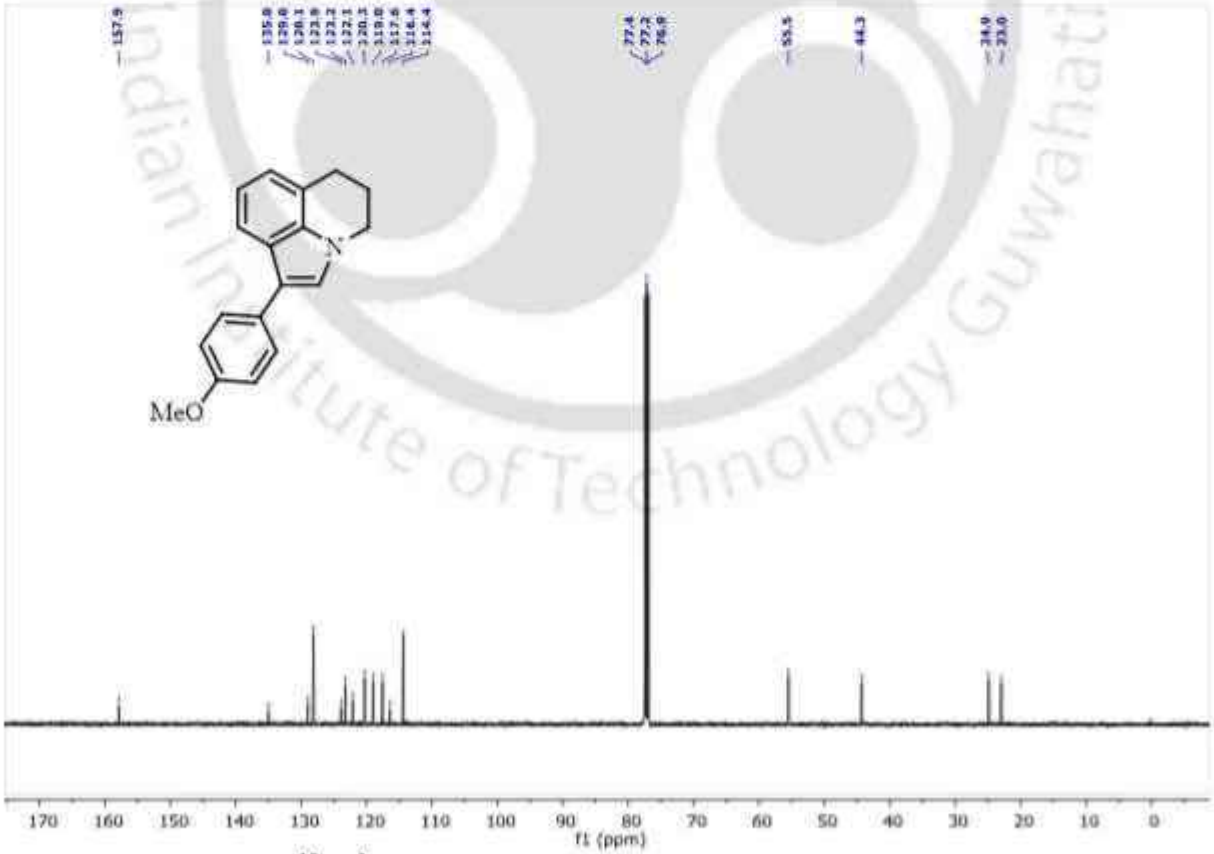


Figure S93: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.12b** ($CDCl_3$, 126 MHz, 298 K)

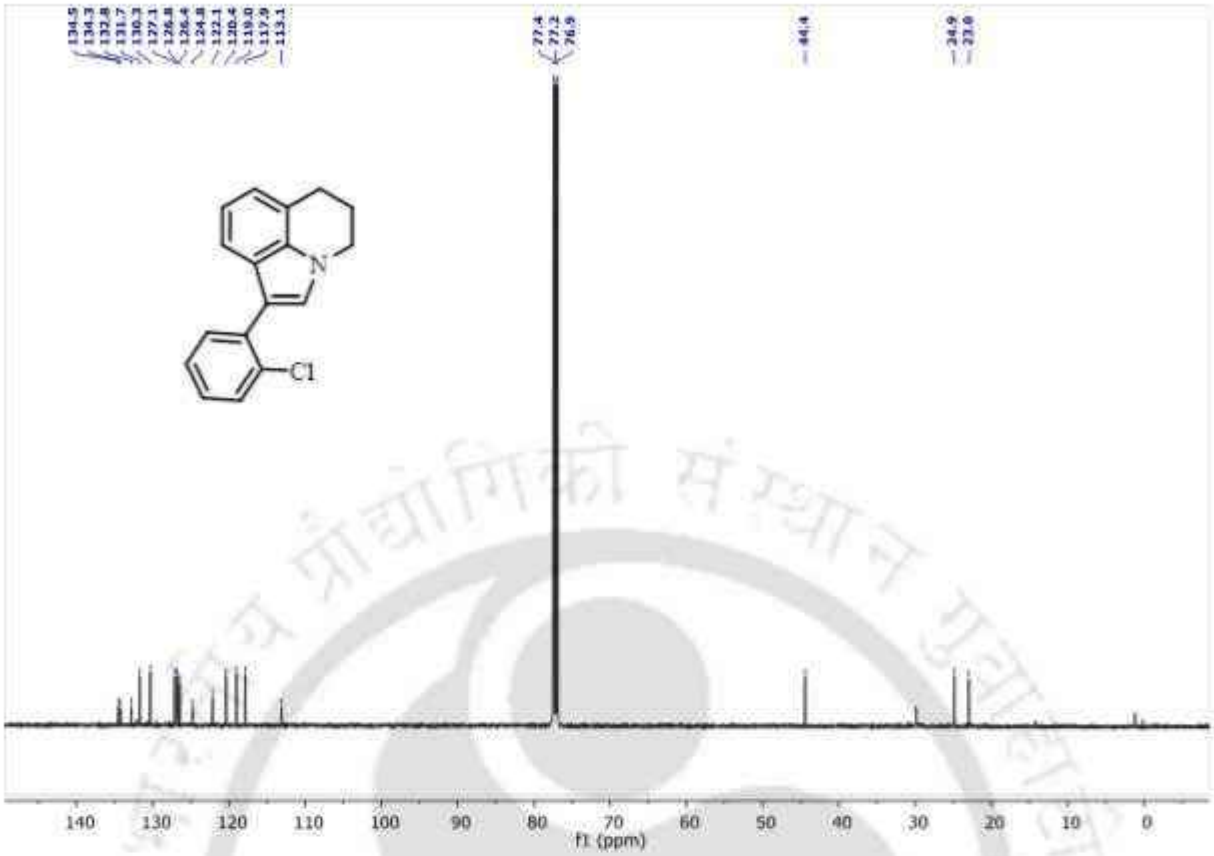


Figure S94: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.12e** ($CDCl_3$, 126 MHz, 298 K)

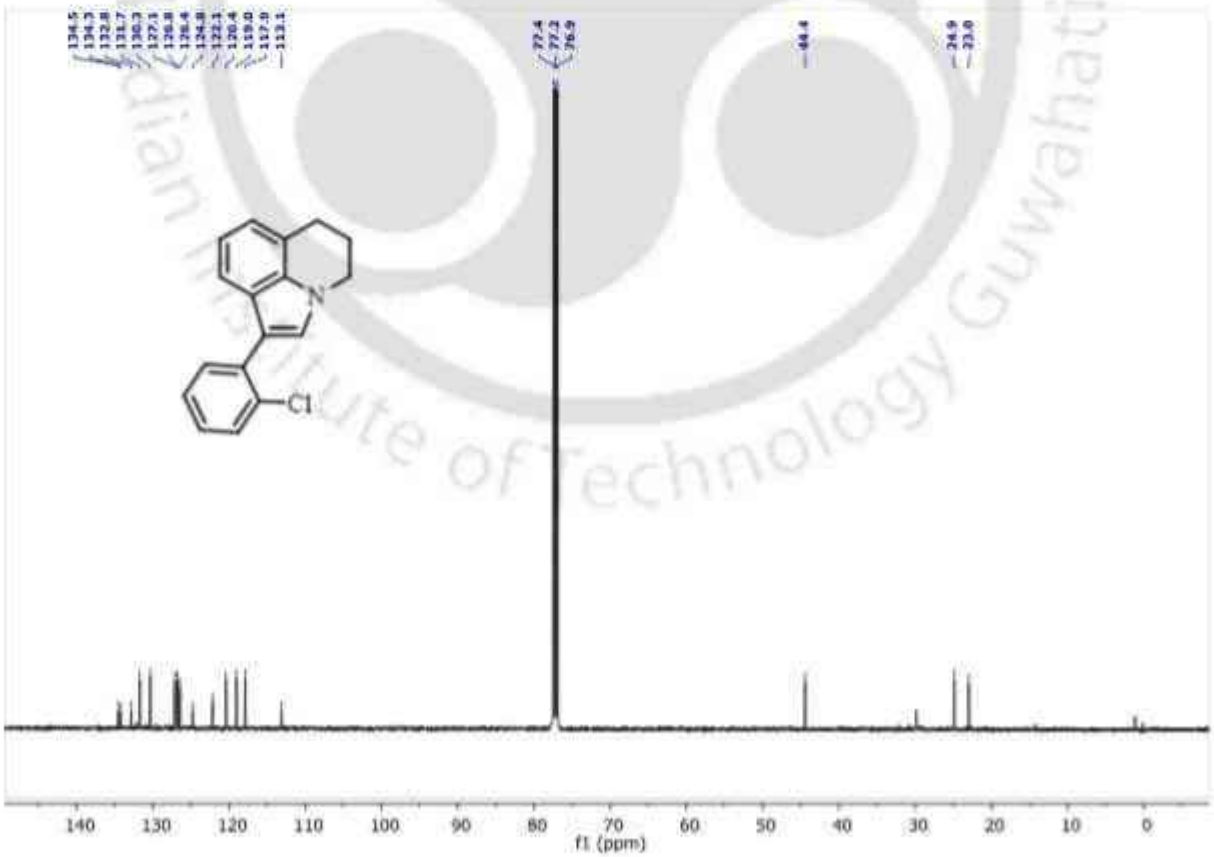


Figure S95: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.12e** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

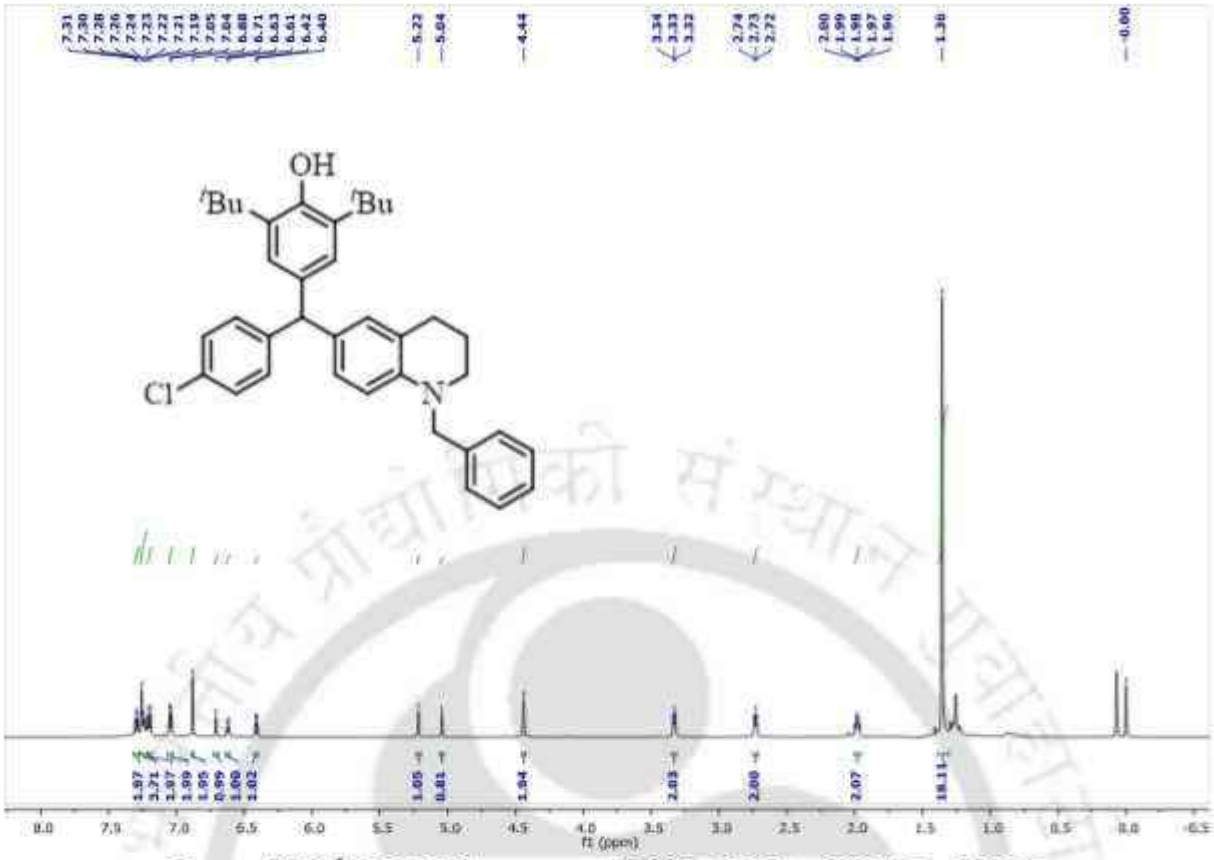


Figure S96: ^{1}H NMR Spectrum of **3.22b** ($CDCl_3$, 600 MHz, 298 K)

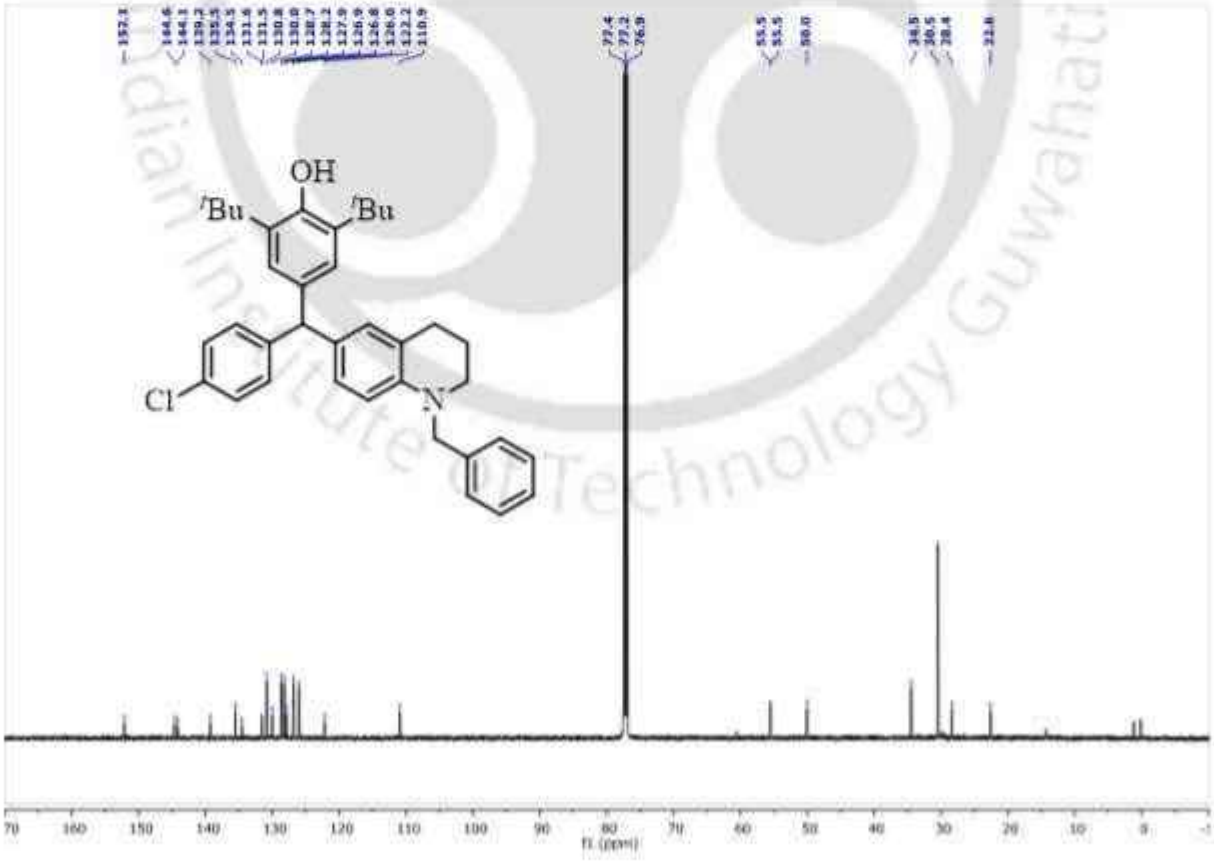


Figure S97: $^{13}C\{^{1}H\}$ NMR Spectrum of **3.22b** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

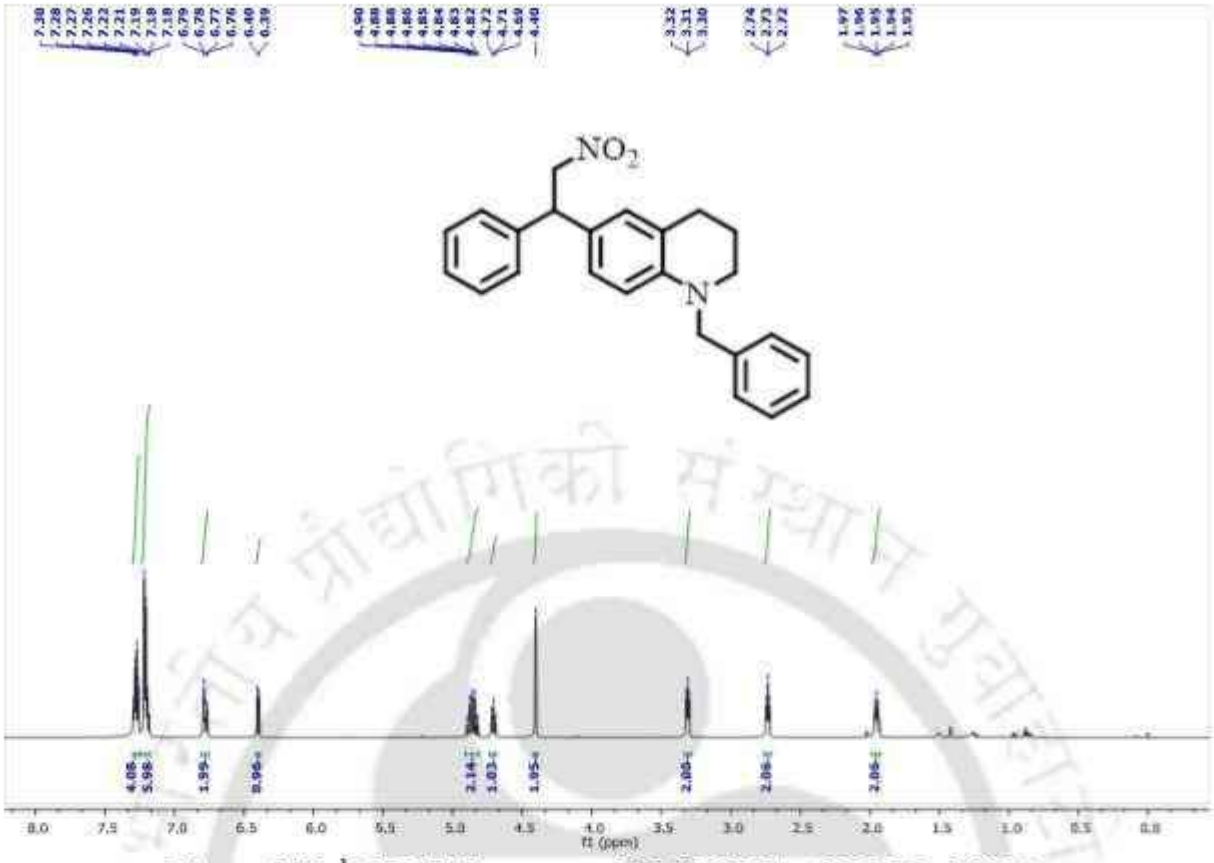


Figure S98: ^{1}H NMR Spectrum of **5.14f** ($CDCl_3$, 600 MHz, 298 K)

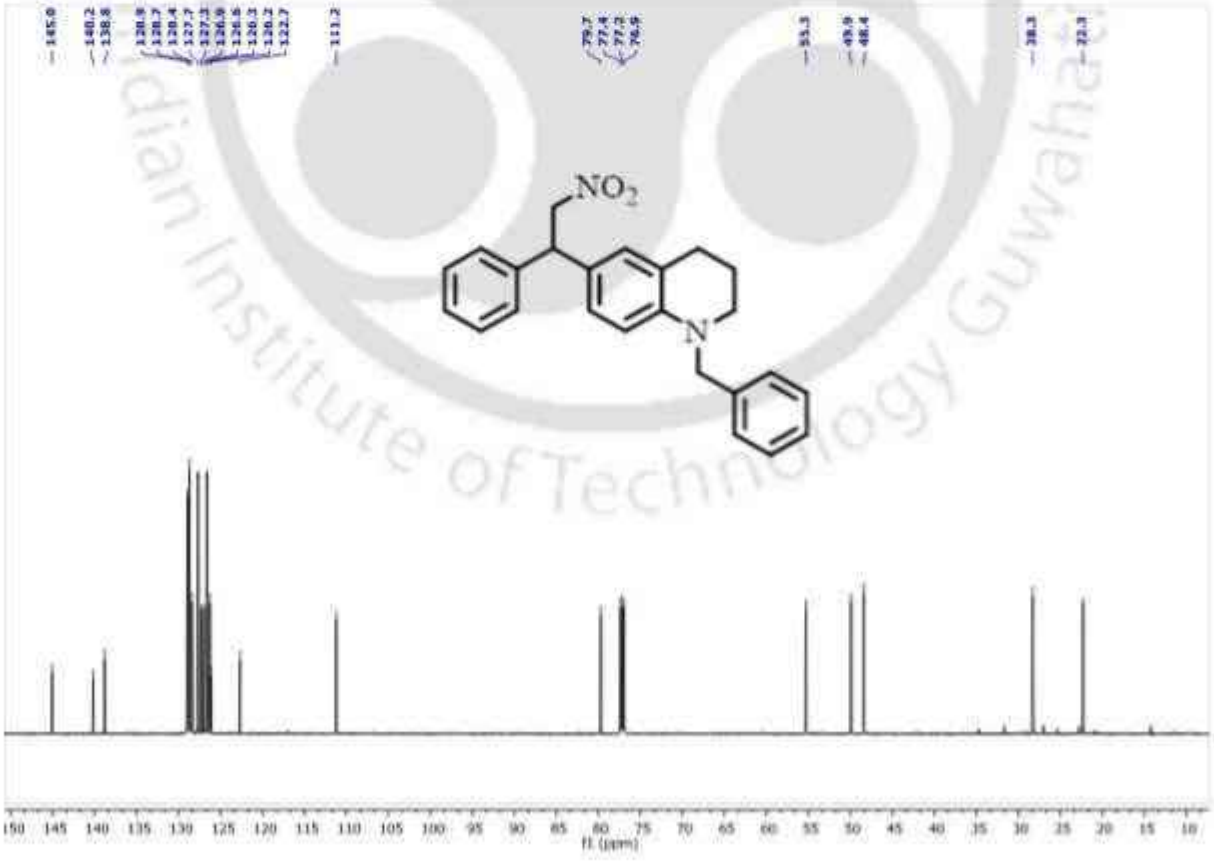


Figure S99: $^{13}C\{^{1}H\}$ NMR Spectrum of **5.14f** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

The supporting information and all other product spectra for chapter 5 is available at https://doi.org/10.1039/D5QO00519A

Annexure V

^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ spectra of representative compounds (*Chapter 6*)

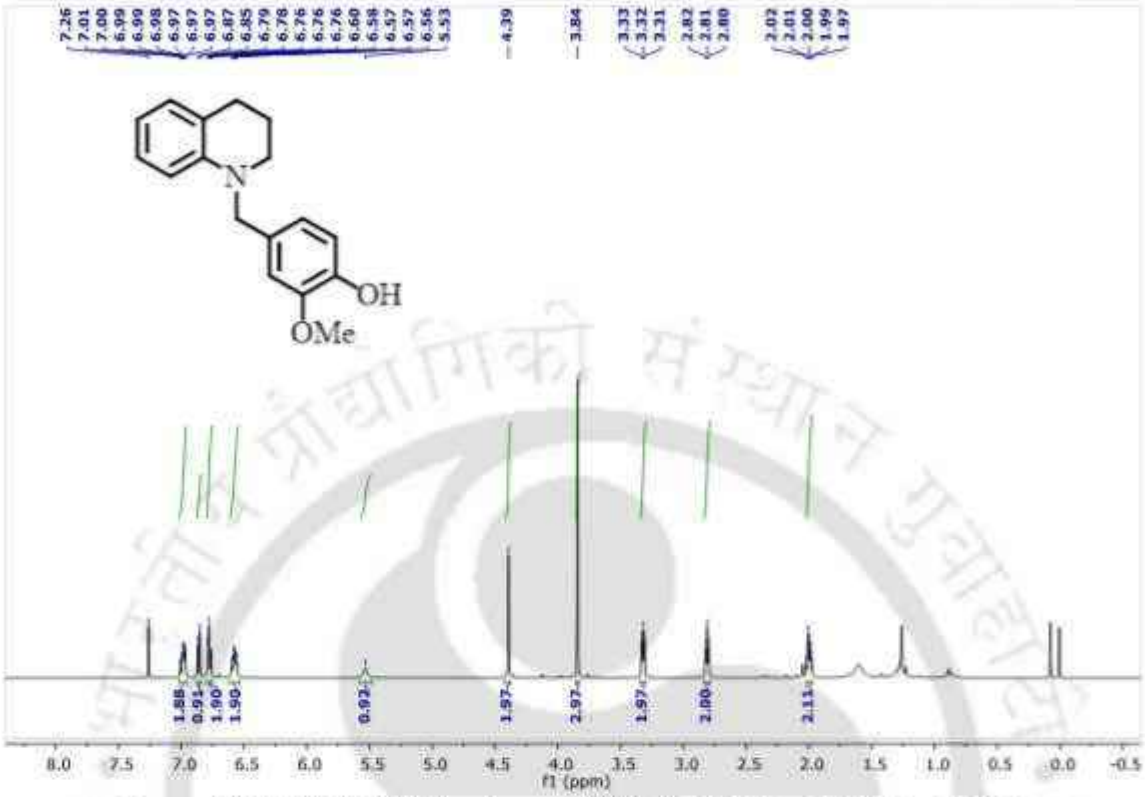


Figure S100: ^{1}H NMR Spectrum of **6.24ab** ($CDCl_3$, 500 MHz, 298 K)

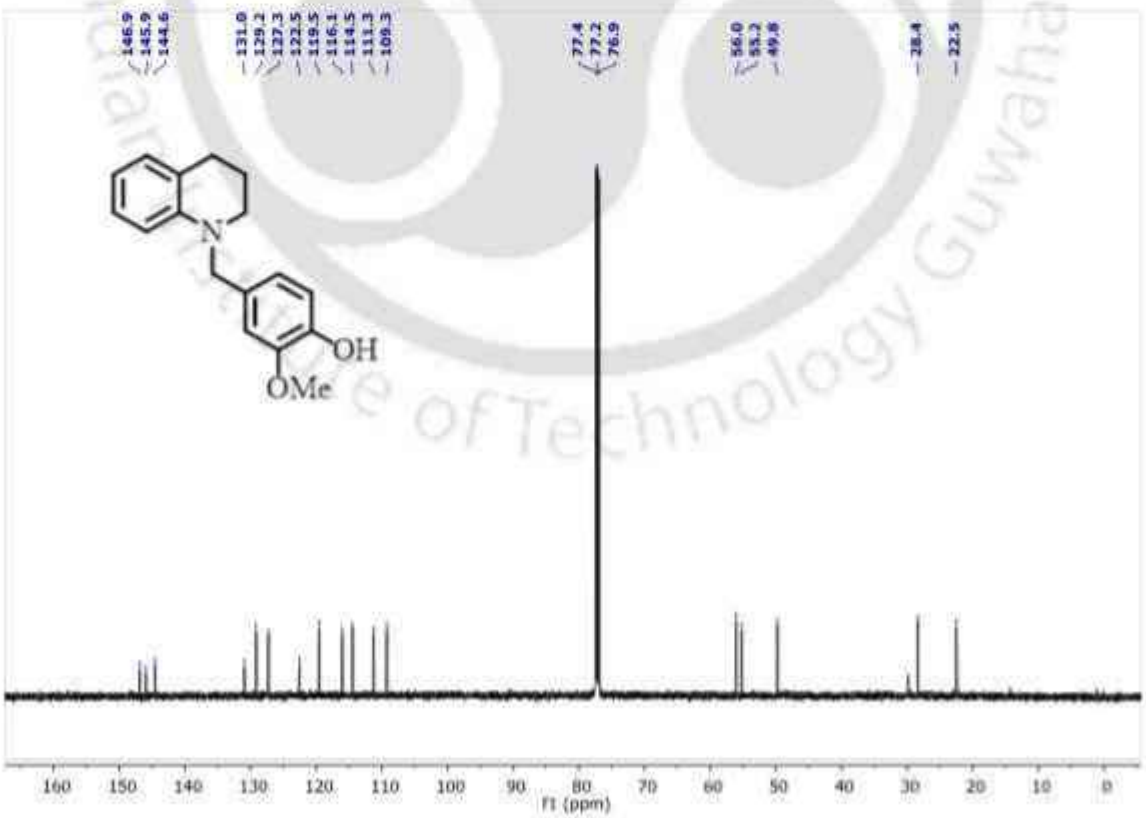


Figure S101: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.24ab** ($CDCl_3$, 101 MHz, 298 K)

TH-3765_196122031

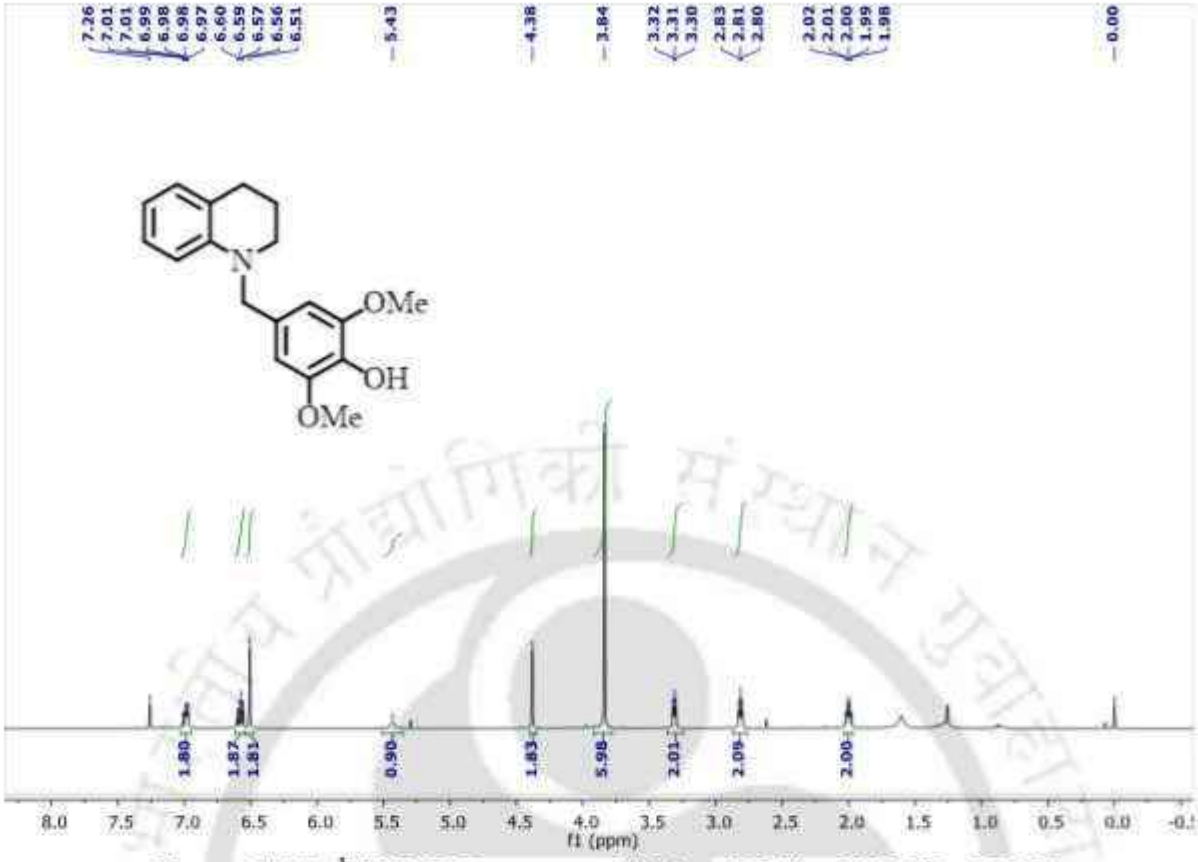


Figure S102: ^{1}H NMR Spectrum of **6.24ac** ($CDCl_3$, 500 MHz, 298 K)

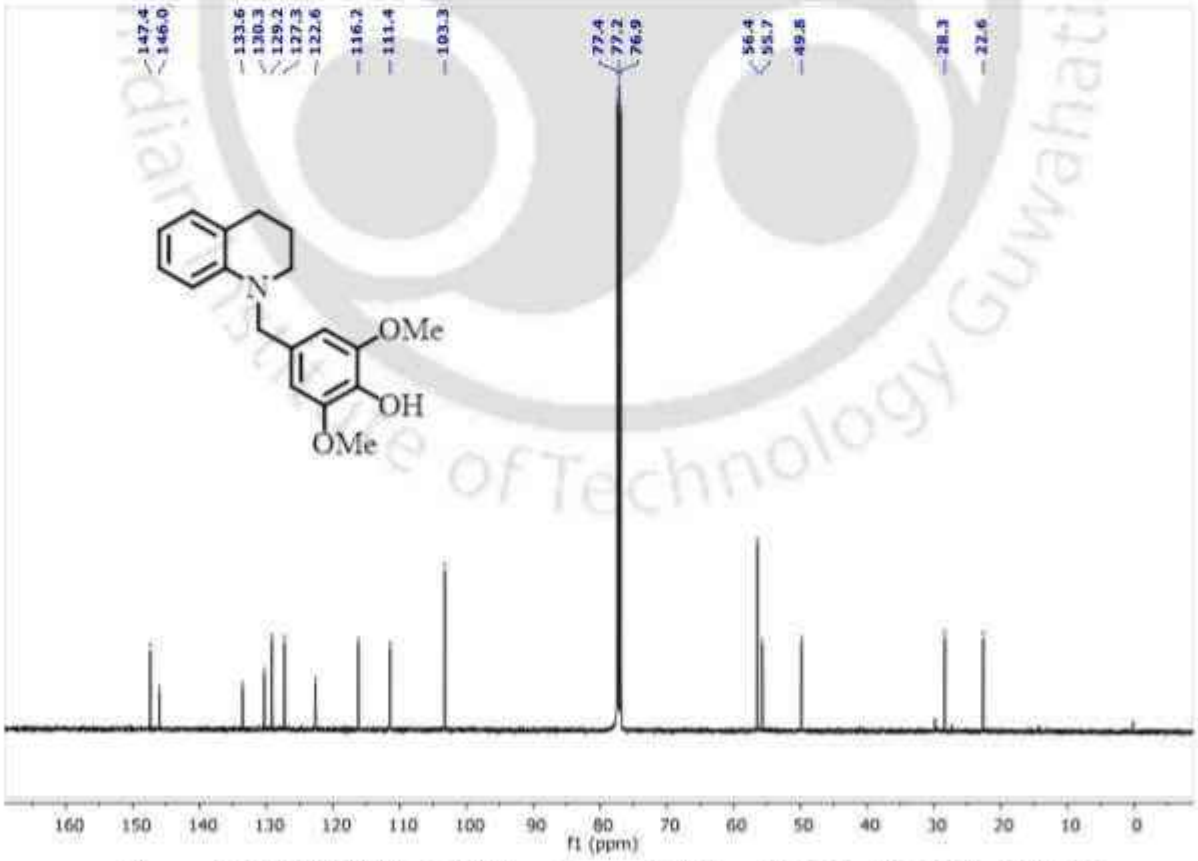


Figure S103: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.24ac** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

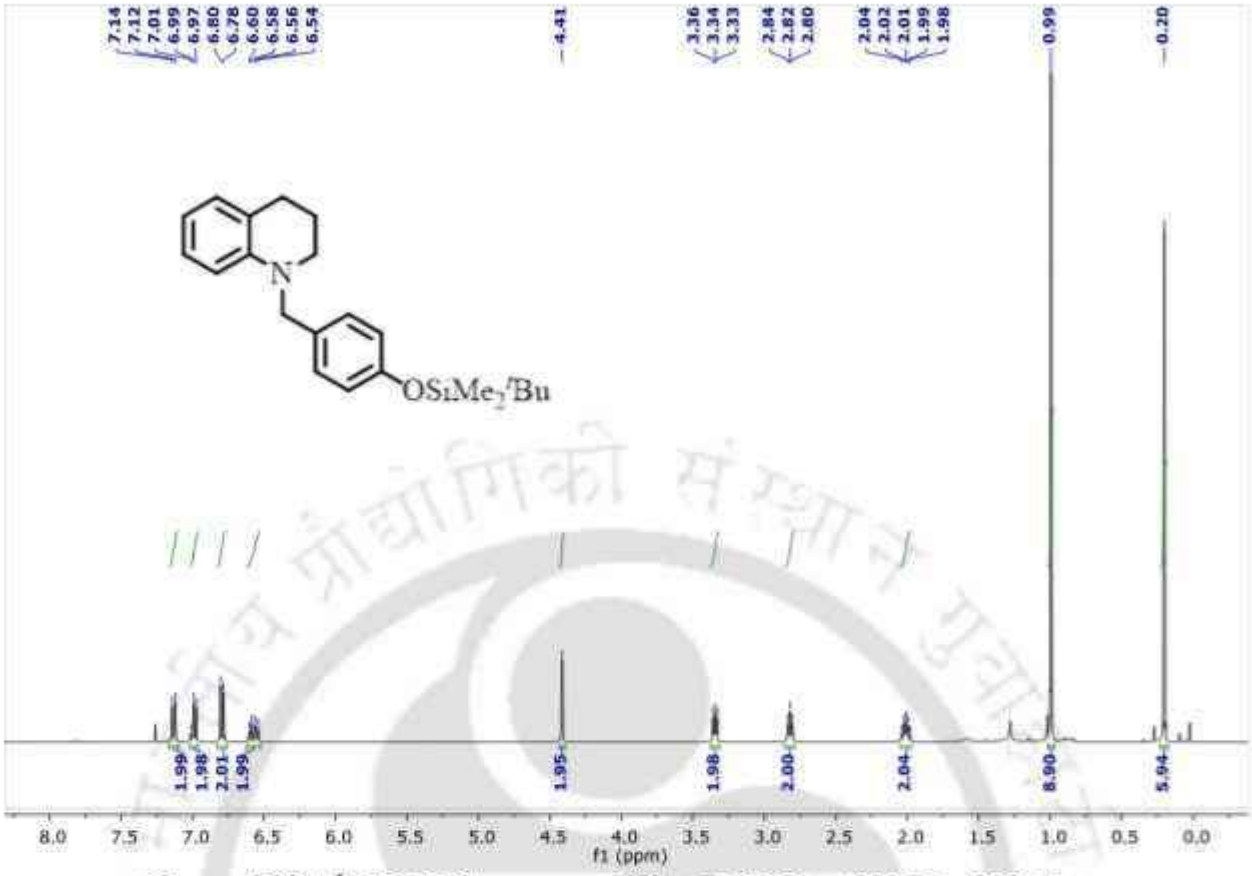


Figure S104: ^{1}H NMR Spectrum of **6.24ad** ($CDCl_3$, 400 MHz, 298 K)

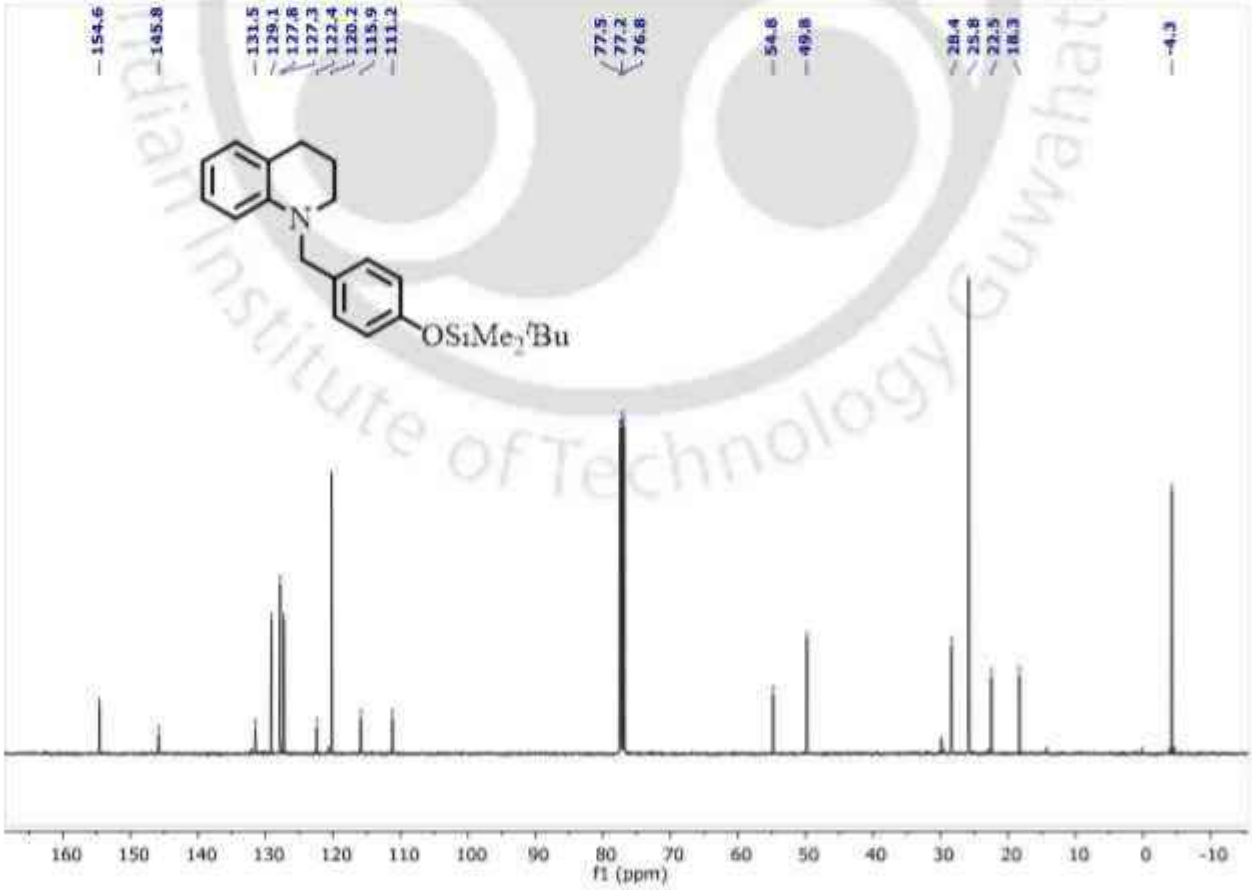


Figure S105: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.24ad** ($CDCl_3$, 101 MHz, 298 K)

TH-3765_196122031

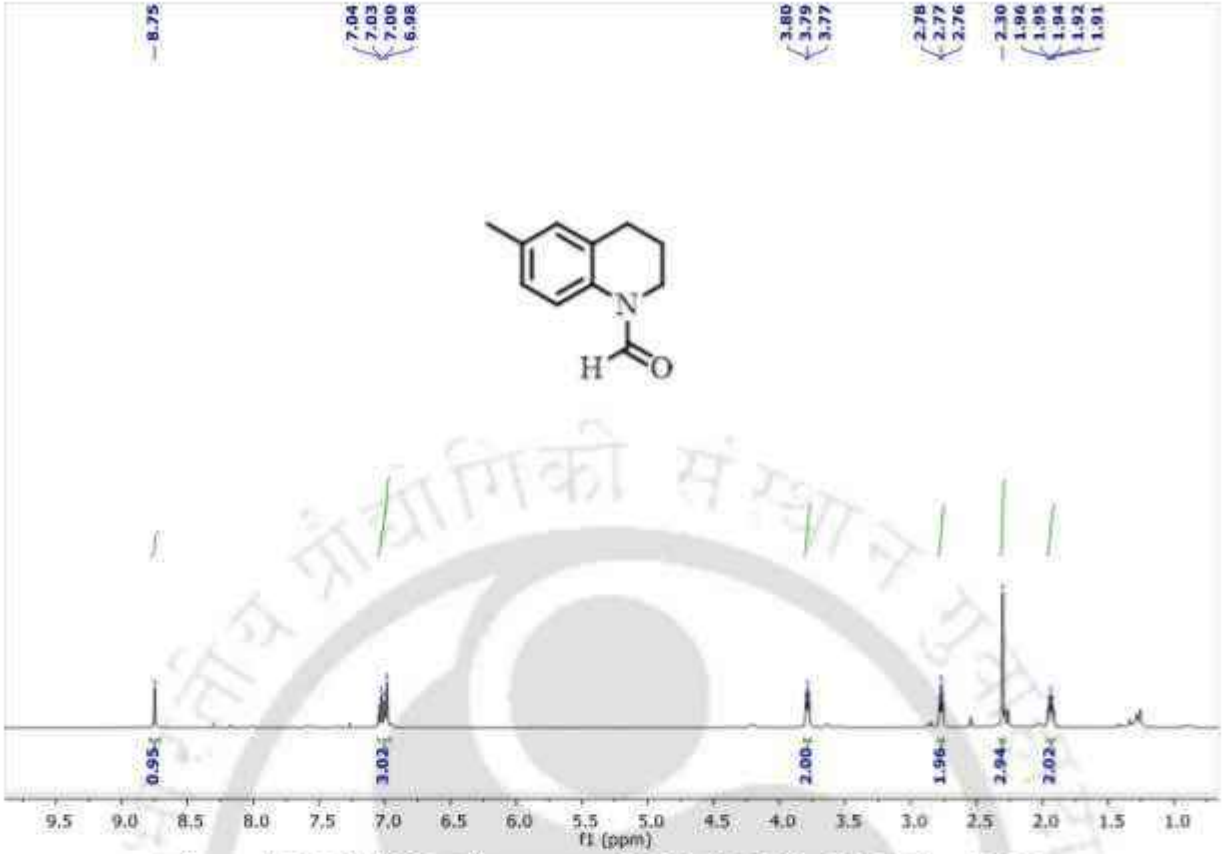


Figure S106: ^{1}H NMR Spectrum of **6.25e** ($CDCl_3$, 500 MHz, 298 K)

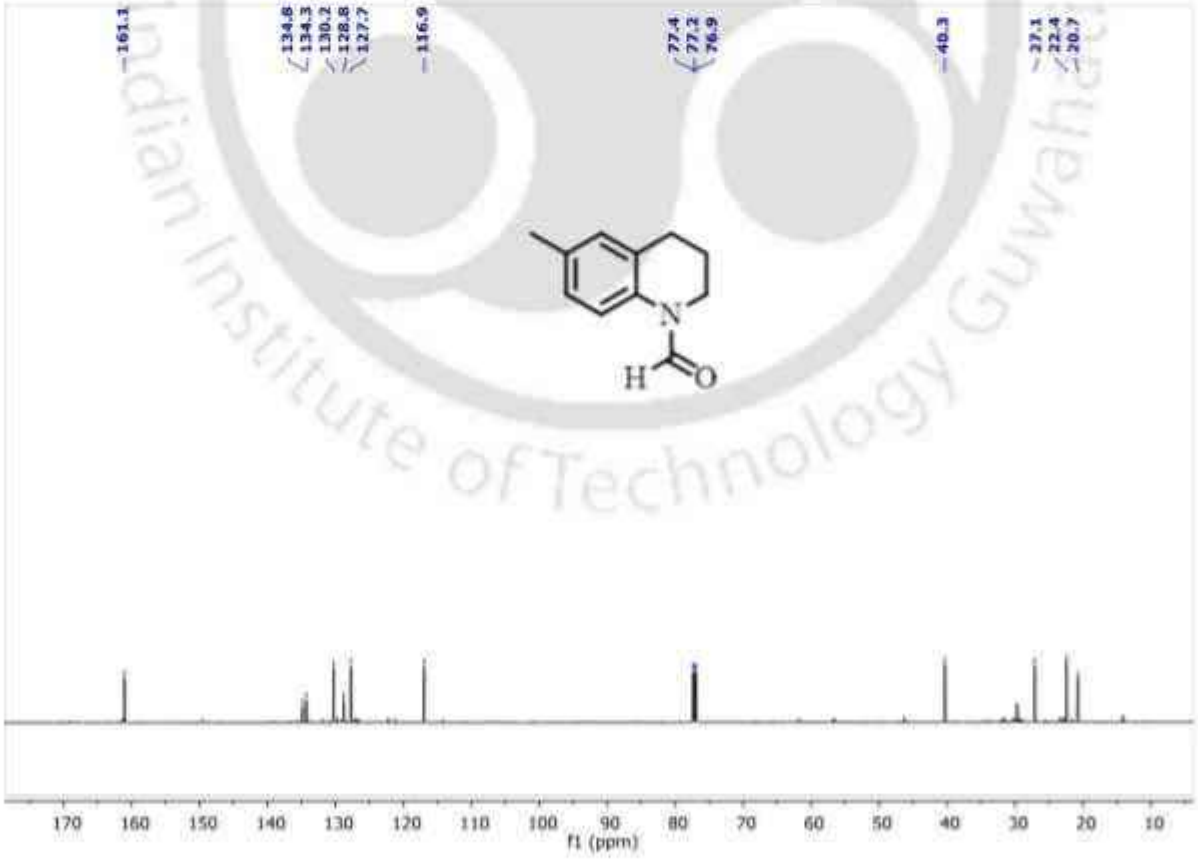


Figure S107: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.25e** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

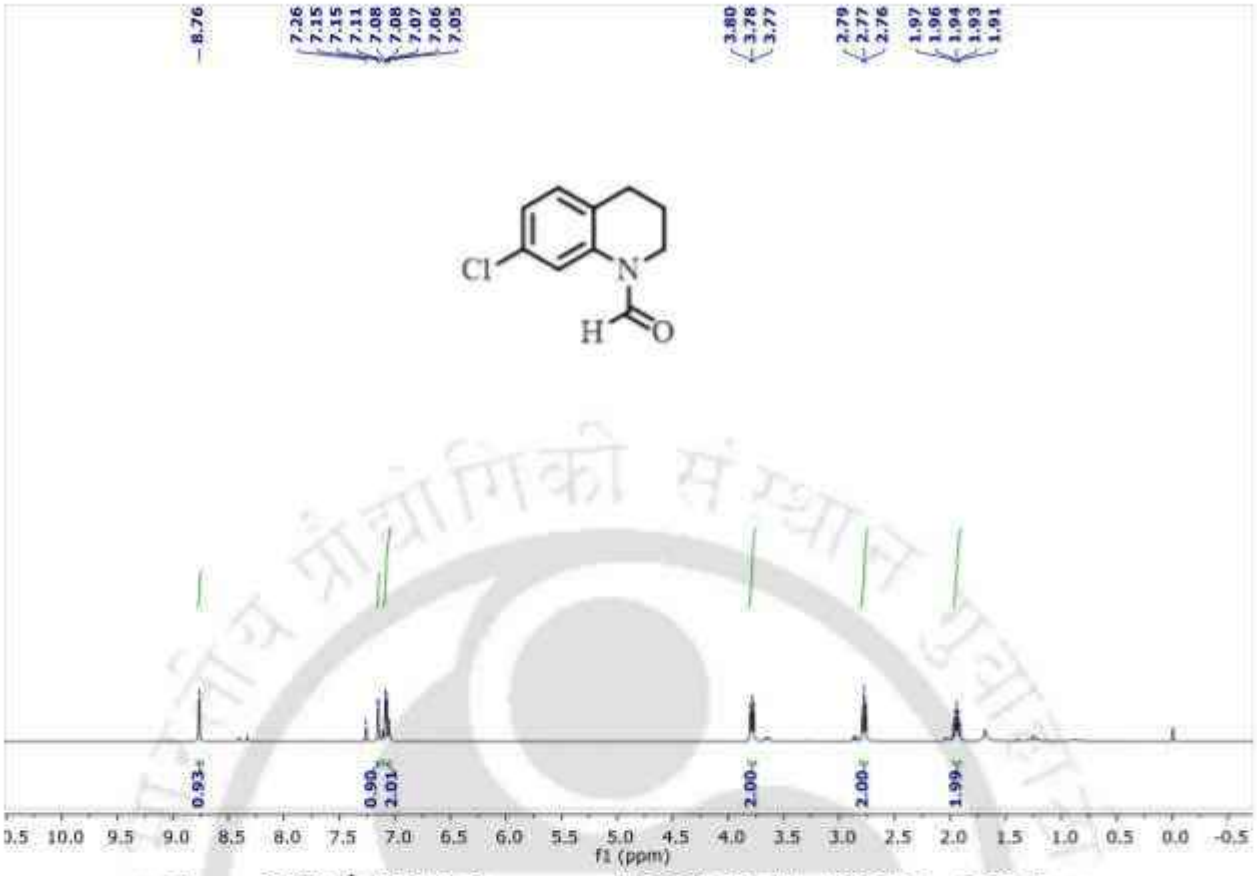


Figure S108: ^{1}H NMR Spectrum of **6.25f** ($CDCl_3$, 400 MHz, 298 K)

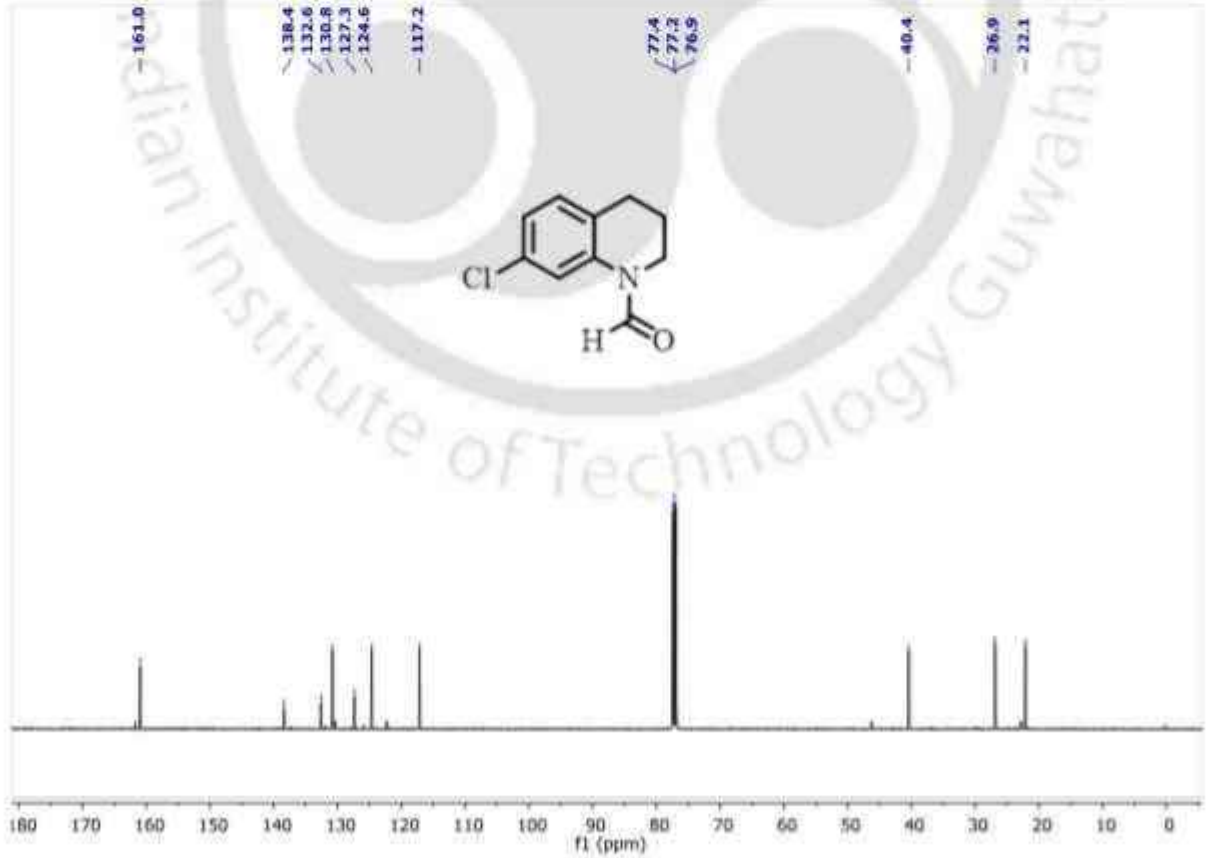


Figure S109: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.25f** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

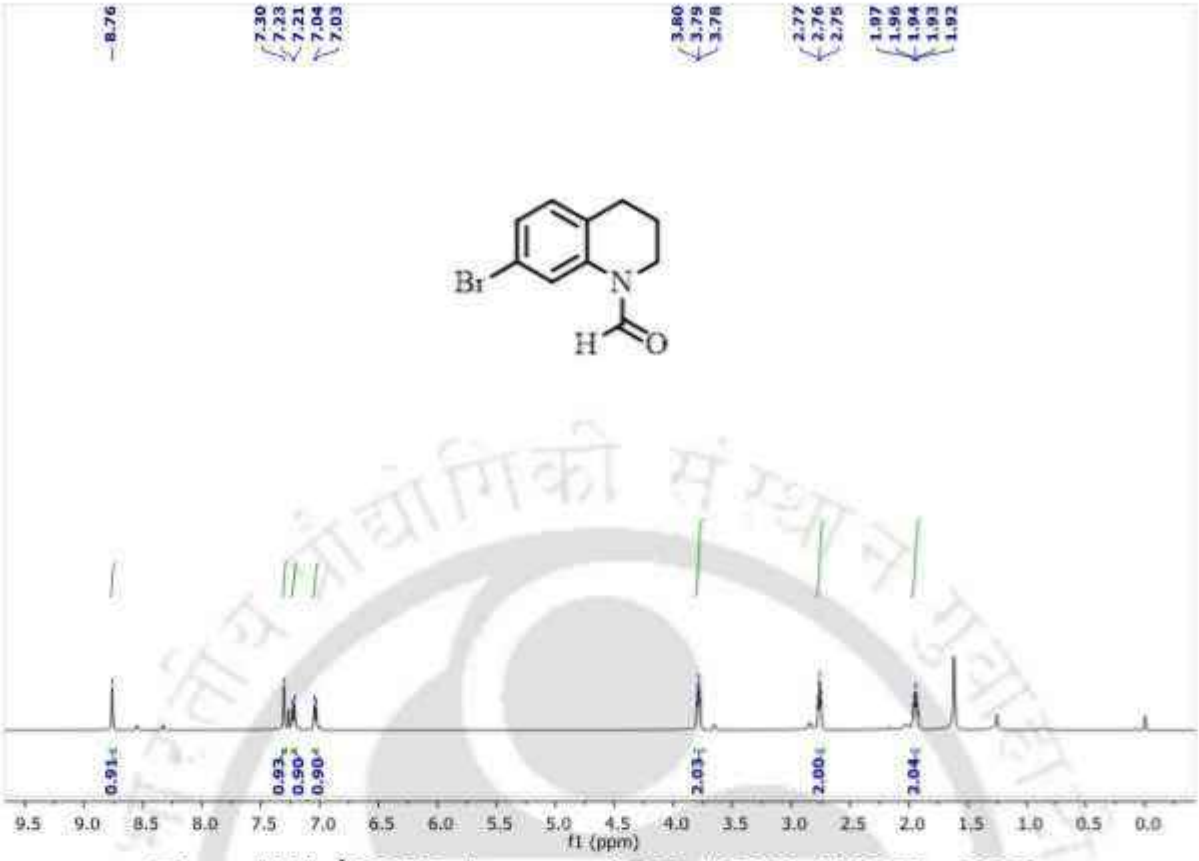


Figure S110: ^{1}H NMR Spectrum of **6.25g** ($CDCl_3$, 500 MHz, 298 K)

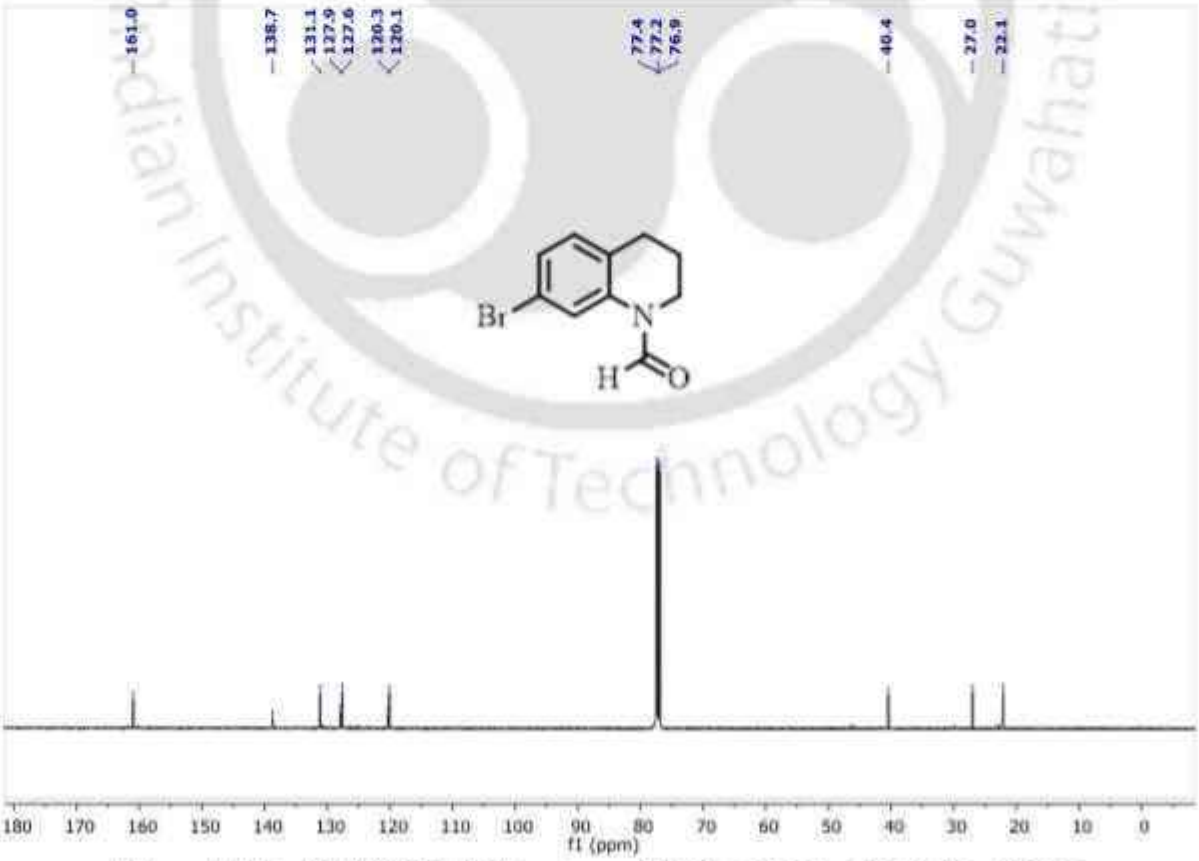


Figure S111: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.25g** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

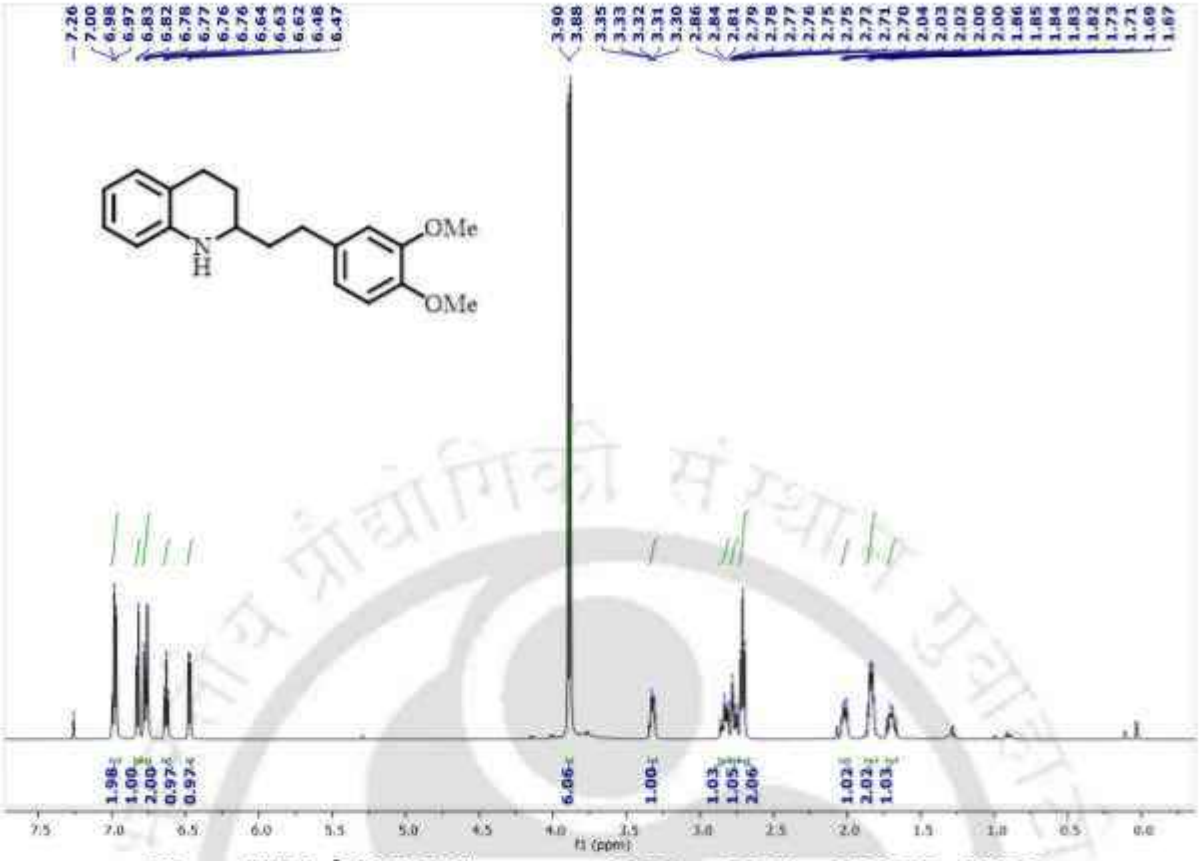


Figure S112: ^{1}H NMR Spectrum of **6.22m** ($CDCl_3$, 600 MHz, 298 K)

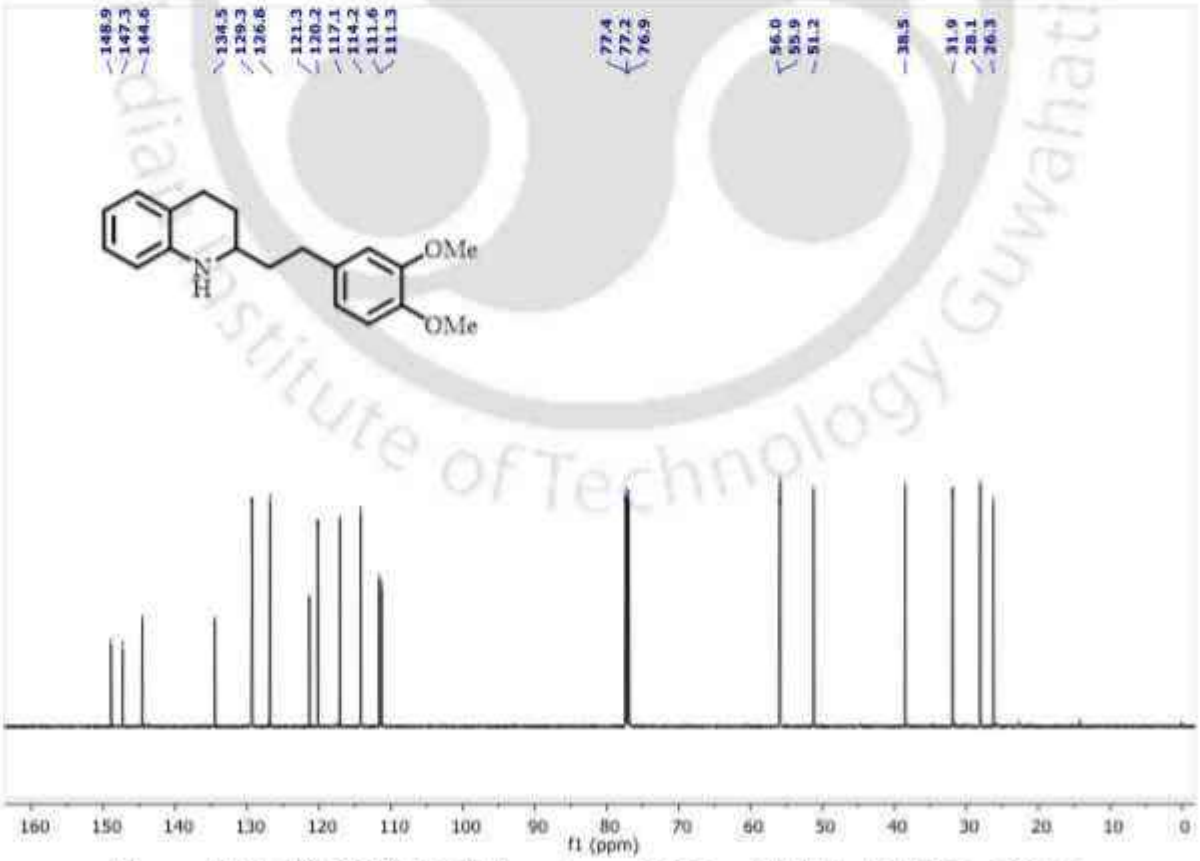


Figure S113: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.22m** ($CDCl_3$, 151 MHz, 298 K)

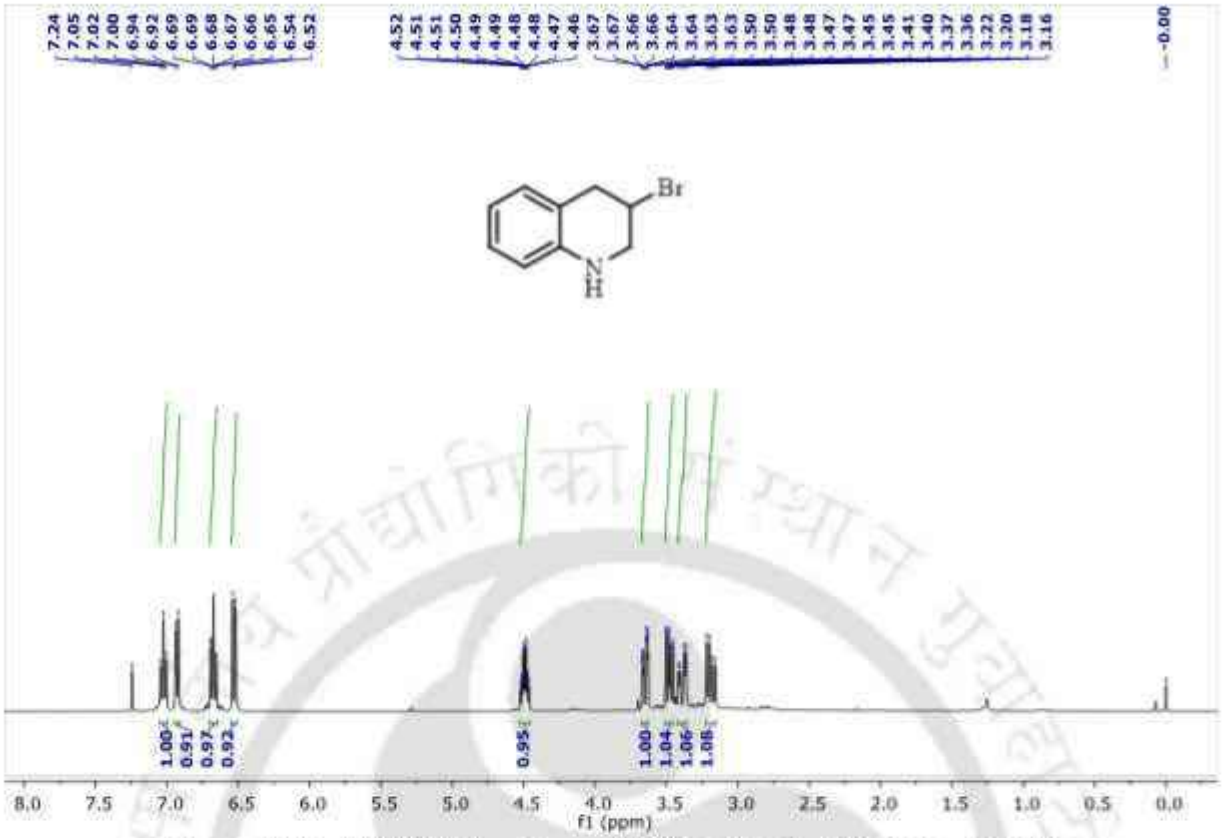


Figure S114: ^{1}H NMR Spectrum of **6.22n** ($CDCl_3$, 400 MHz, 298 K)

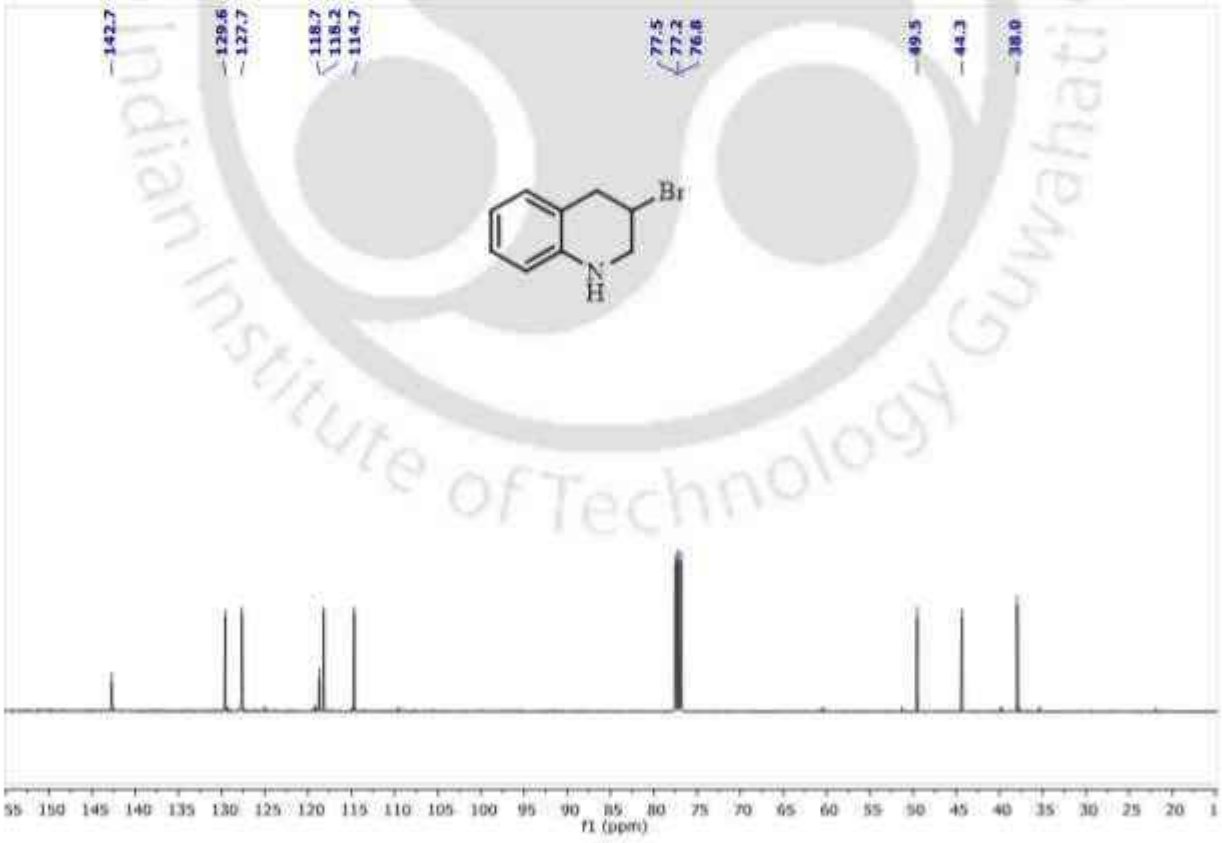


Figure S115: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.22n** ($CDCl_3$, 101 MHz, 298 K)

TH-3765_196122031

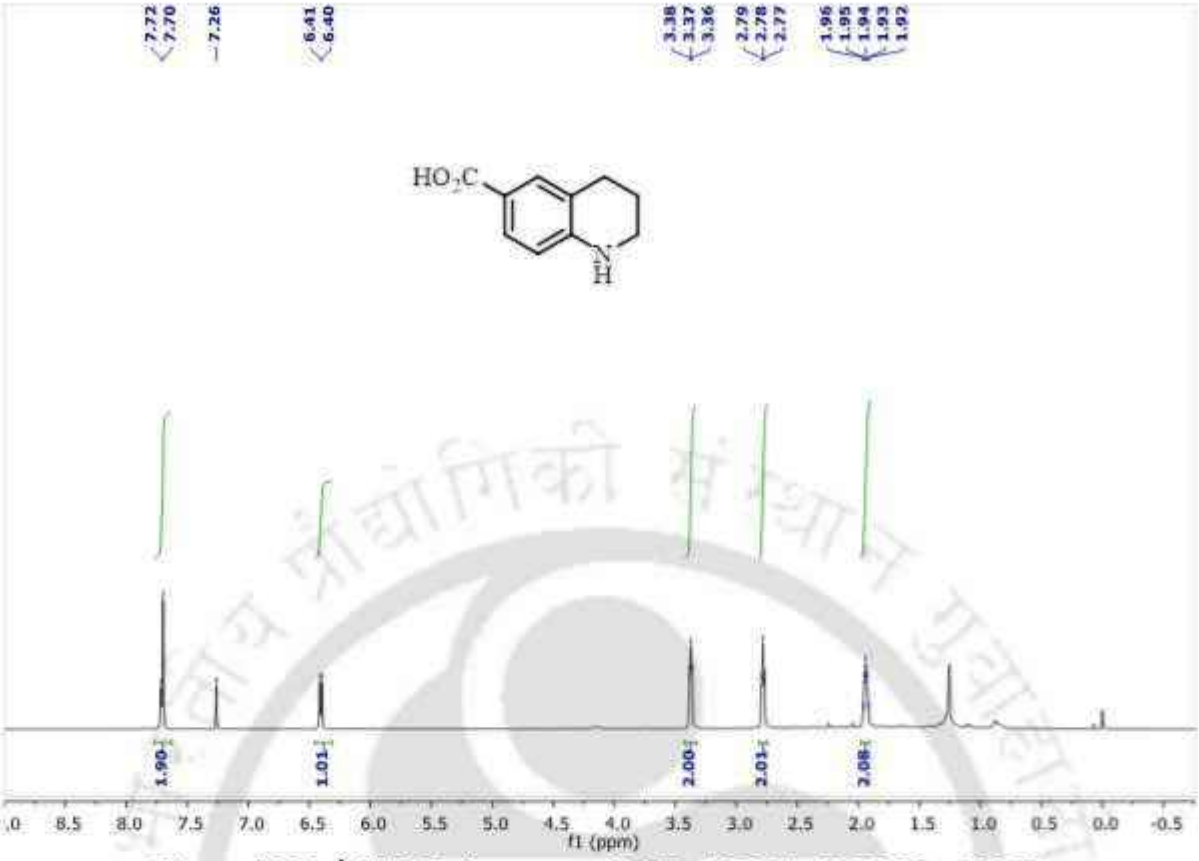


Figure S116: ^{1}H NMR Spectrum of **6.22p** ($CDCl_3$, 500 MHz, 298 K)

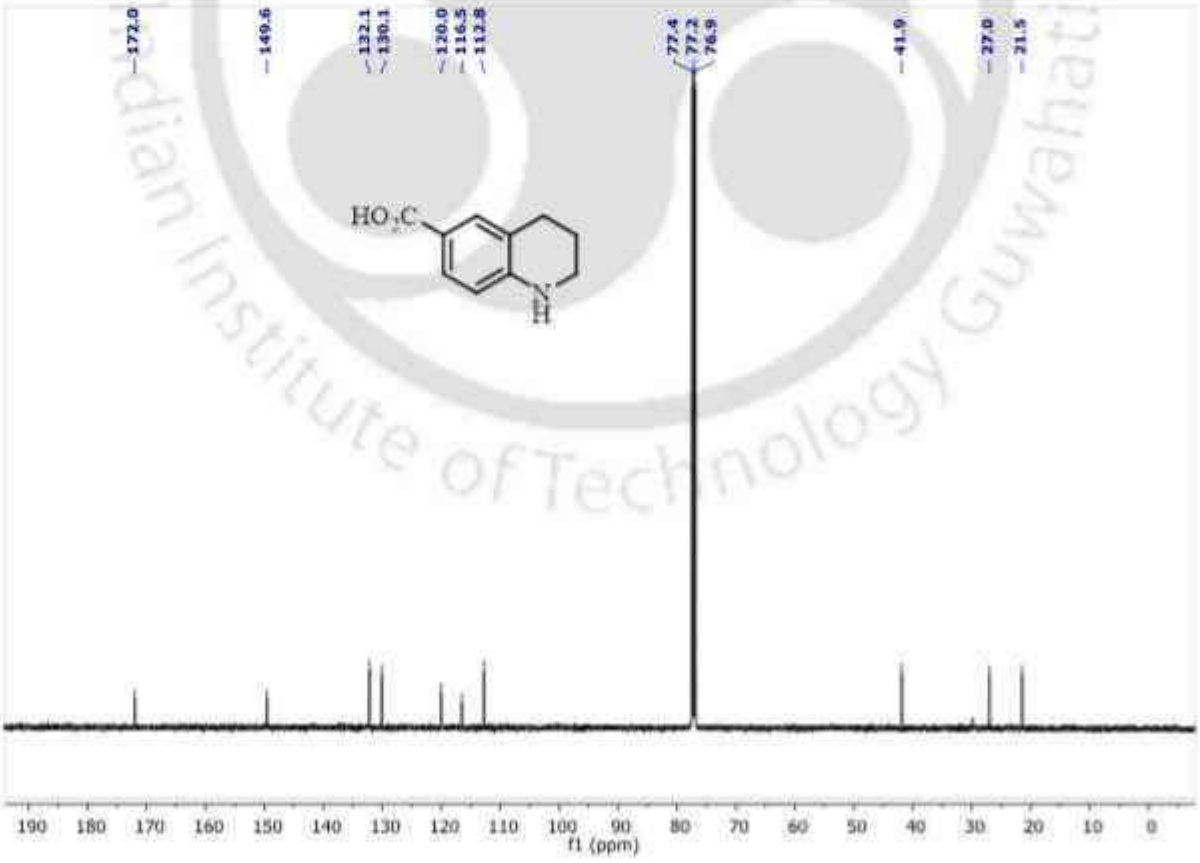


Figure S117: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.22p** ($CDCl_3$, 126 MHz, 298 K)

TH-3765_196122031

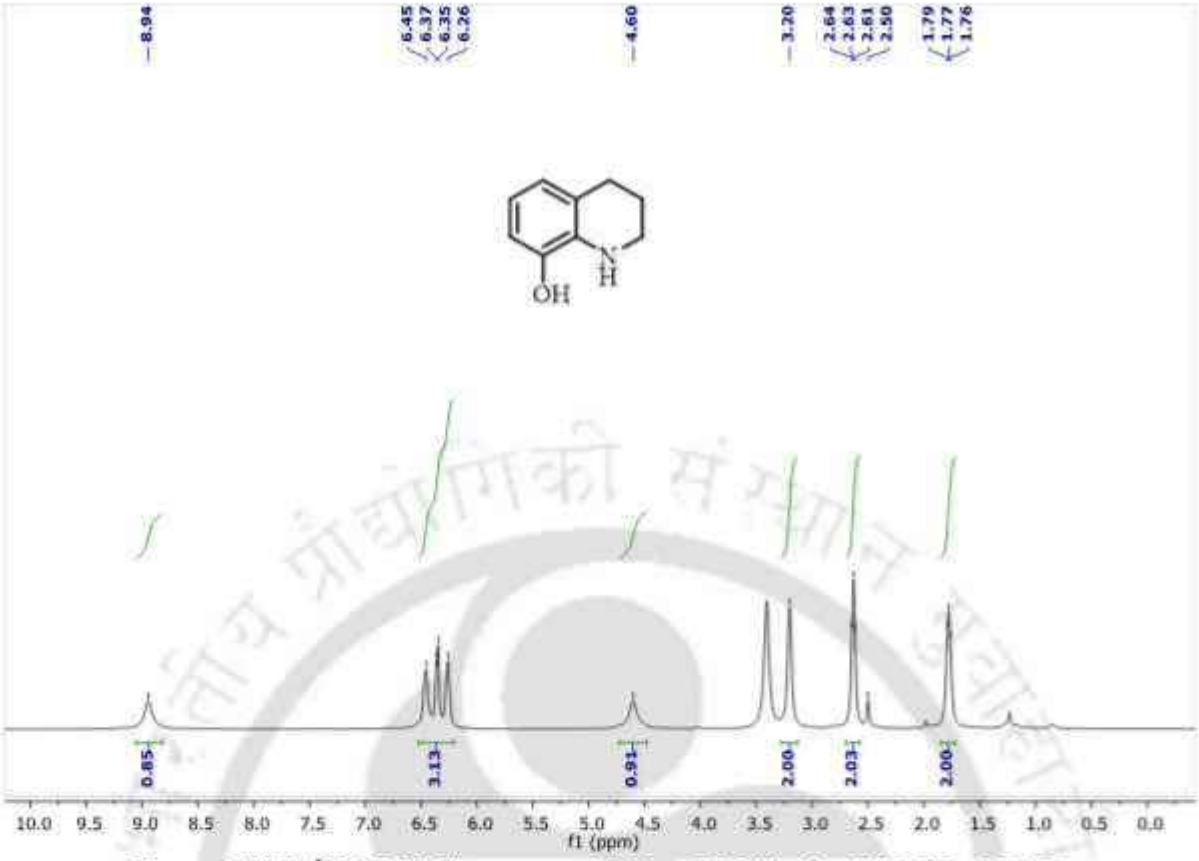


Figure S118: ^{1}H NMR Spectrum of **6.22q** (DMSO-d_6, 400 MHz, 298 K)

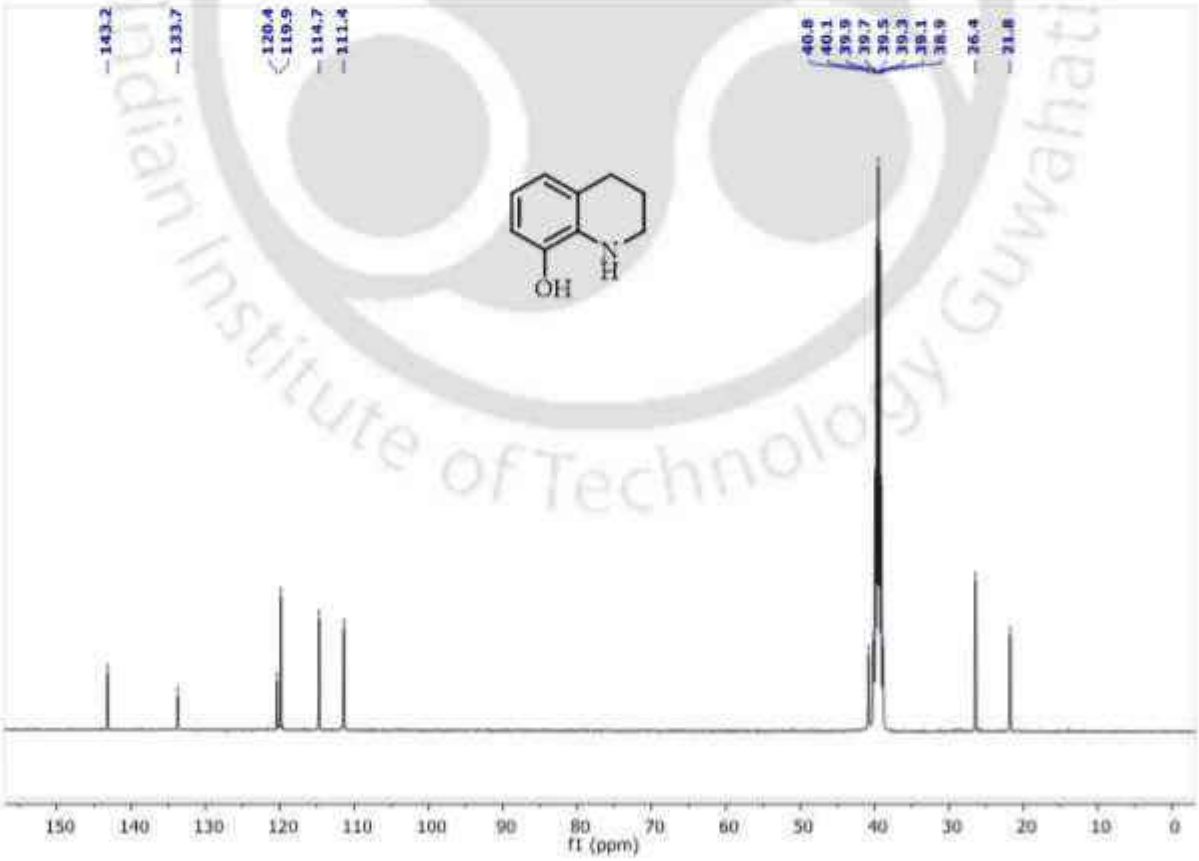


Figure S119: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.22q** (DMSO-d_6, 101 MHz, 298 K)

TH-3765_196122031

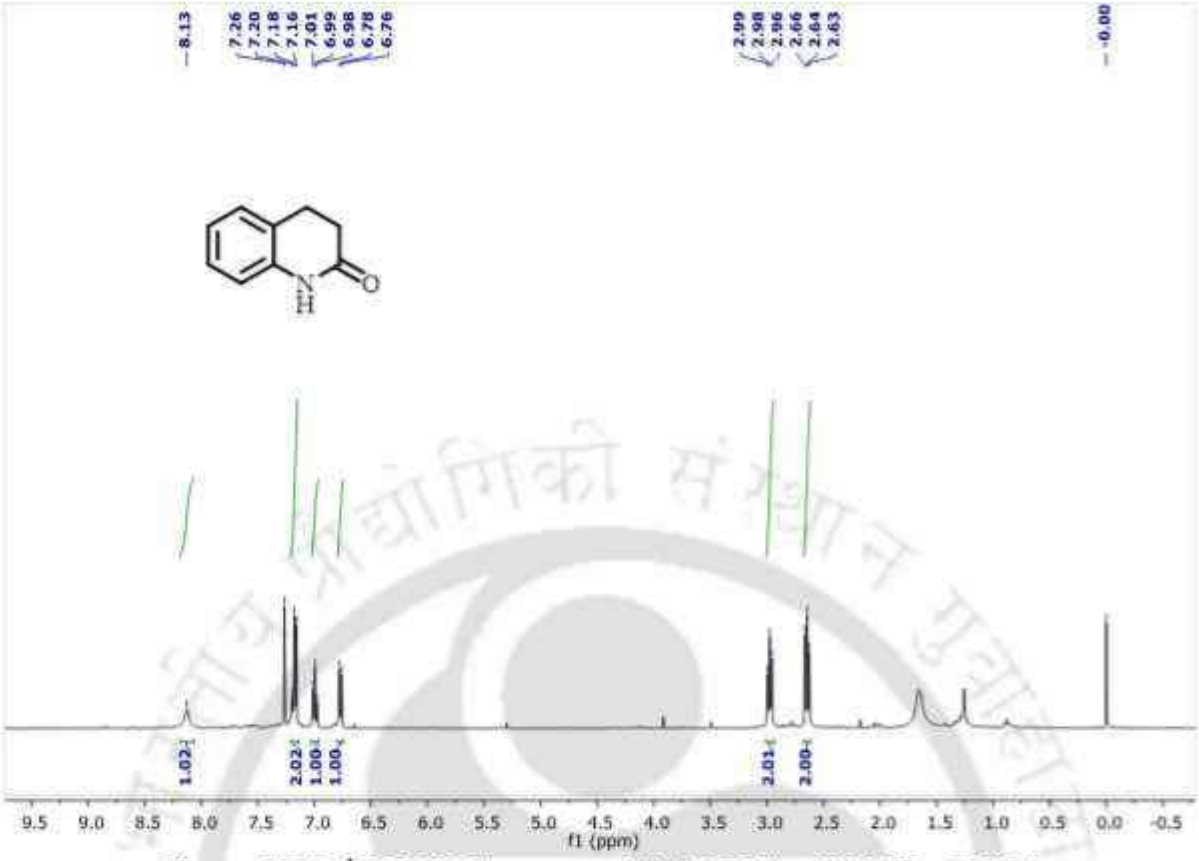


Figure S120: ^{1}H NMR Spectrum of **6.26** ($CDCl_3$, 400 MHz, 298 K)

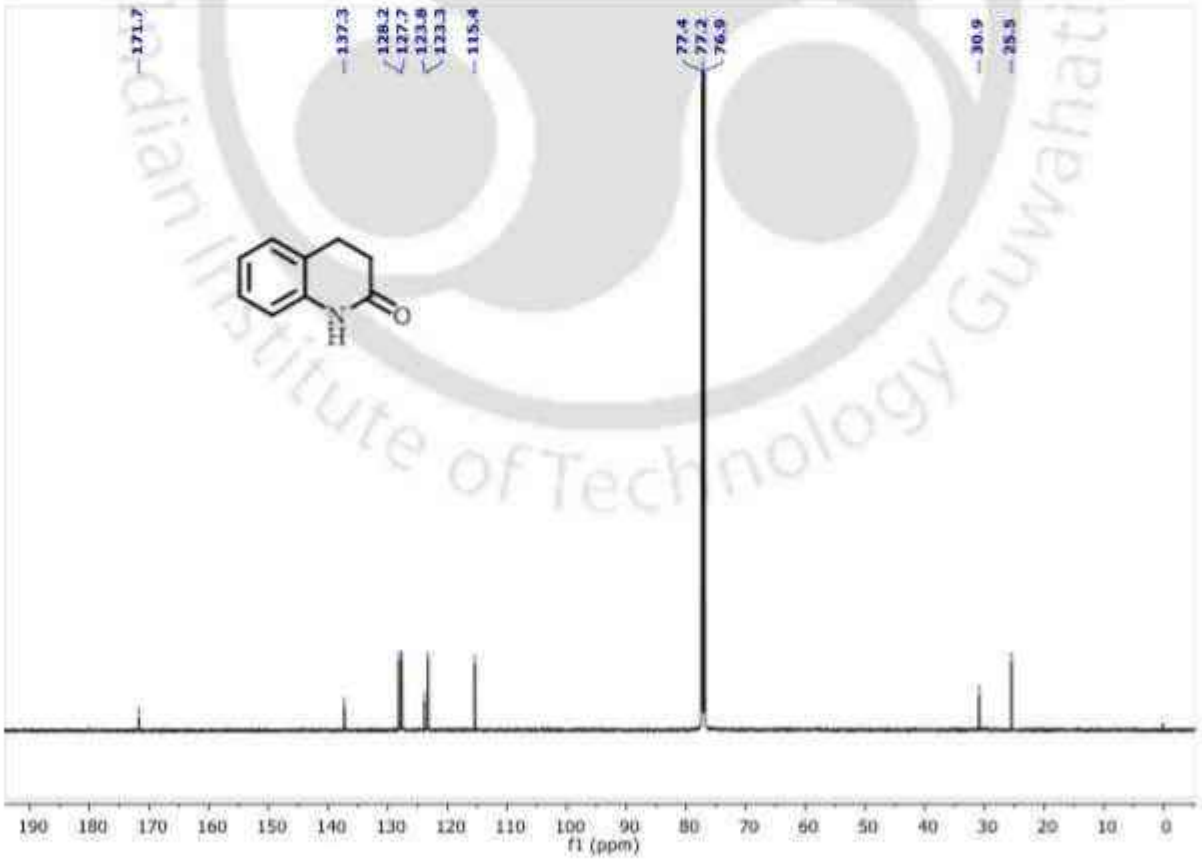


Figure S121: $^{13}C\{^{1}H\}$ NMR Spectrum of **6.26** ($CDCl_3$, 151 MHz, 298 K)

TH-3765_196122031

The supporting information and all other product spectra for chapter 6 is available at https://doi.org/10.1002/chem.202502094

TH-3765_196122031

List of Publications

1. Facile synthesis of tetrahydroquinoline containing dithiocarbamate derivatives *via* one-pot sequential multicomponent reaction.

S. K. Senapati, A. Pal, and A. Das, *Org. Biomol. Chem.*, 2024, **22**, 4041- 4056.

2. Triple role of boronic acid as a catalyst in the alkylation of quinoline to functionalized tetrahydroquinoline.

S. K. Senapati, A Borah, S Hazarika, A Das, *Org. Biomol. Chem.*, 2025, **23**, 7275-7282.

3. Arylboronic acid catalyzed reductive alkylation of azoarenes to *N*-alkylated hydrazines.

S. K. Senapati and A. Das, *Chem. Eur. J.*, **31**, e202500953.

4. Reductive alkylation of azoarenes to *N*-alkylated hydrazines enabled by hexafluoroisopropanol.

S. K. Senapati and A. Das, *Chem. Commun.*, 2025, **61**, 8596-8599.

5. Tandem reductive alkylation of quinolines to functionalized tetrahydroquinolines enabled by HFIP.

S. K. Senapati, T. Das and A. Das, *Org. Chem. Front.*, 2025, ASAP. DOI: 10.1039/D5QO00519A

6. Reusable Brønsted acidic ionic liquid catalyzed reductive alkylation of quinolines to functionalized tetrahydroquinolines

S. K. Senapati, A. Pal, P. Adhikari and A. Das, *Chem. Eur. J.*, 2025, ASAP. DOI: 10.1002/chem.202502094

7. Concise Synthesis of *N*-Aryl Tetrahydroquinolines *via* a One-Pot Sequential Reduction of Quinoline/Chan–Evans–Lam Coupling Reaction.

D. Bhattacharyya, **S. K. Senapati** and A. Das. *Synlett*, 2023, **34**, 651–656.

TH-3765_196122031

List of Conferences

1. **30th International Conference on Organometallic Chemistry (ICOMC-2024)** from 14th-18th July 2024, Agra. Poster presentation with entitled "Microwave Assisted Tandem Reductive Alkylation of Quinolines to *N*-Alkyl Tetrahydroquinolines Using a Reusable Brønsted Acidic Ionic Liquid as a Catalyst and a Solvent."
2. **Research and Industrial Conclave-Integration'24 (RIC-2024)** from 9th-11th August 2024, IIT Guwahati, Guwahati. Oral presentation with entitled "Facile synthesis of tetrahydroquinoline containing dithiocarbamate derivatives *via* one-pot sequential multicomponent reaction."
3. **Frontiers in Chemical Sciences - 2022 (FICS-2022)** from 2nd-4th December 2022, IIT Guwahati. Poster presentation with entitled "Concise Synthesis of *N*-Aryl Tetrahydroquinolines *via* One-pot Sequential Reduction of Quinoline/Chan-Evans-Lam Coupling Reaction."

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