Syntheses of *N*-heterocycles *via* arene functionalization of nitrosoarenes

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

By

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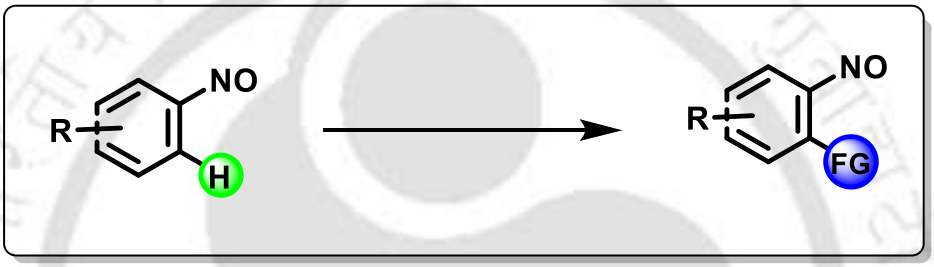
Syntheses of N-heterocycles via arene functionalization of nitrosoarenes



Department of Chemistry

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Department of Chemistry

STATEMENT

The work contained in this thesis entitled "**Syntheses of *N*-heterocycles *via* arene functionalization of nitrosoarenes**" is the outcome of the research work carried out by me under the supervision of Prof. Chandan K. Jana, Department of Chemistry, Indian Institute of Technology Guwahati, India. In the present thesis the general practice of the scientific observations is reported and whenever needed, the work on the findings of other investigators is described and thus due acknowledgements have been made.

22th June, 2021

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Syntheses of *N*-heterocycles *via* arene functionalization of nitrosoarenes**" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Ms. Anisha Purkait (Roll No: 156122036) was carried out by her under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati
22th June, 2021

Prof. Chandan K. Jana
(Thesis supervisor)

Dedicated to my parents and family members

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Sincerely
Anisha Purkait

List of Publications and Presentations:

1. **Anisha Purkait**, Subhra Kanti Roy, Hemant Kumar Srivastava, and Chandan K. Jana. *Metal-Free Sequential C(sp^2)–H/OH and C(sp^3)–H Aminations of Nitrosoarenes and N- Heterocycles to Ring-Fused Imidazoles*. *Org. Lett.* **2017**, *19*, 2540-2543.

2. **Anisha Purkait** and Chandan K. Jana. *N-aminations of Benzylamines and Alicyclic Amines with Nitro-soarenes to Hydrazones and Hydrazides*. *Synthesis*, **2019**, *51*, 2687-2696.

3. Subhra Kanti Roy, **Anisha Purkait**, SK Md Tarik Aziz and Chandan K. Jana. *Acid Mediated Coupling of Aliphatic Amines and Nitrosoarenes to Indoles*. *Chem. Commun.* **2020**, *56*, 3167-3170.

4. **Anisha Purkait**, Subhajit Saha, Santanu Ghosh and Chandan K. Jana. *Lewis Acid Catalyzed Reactivity Switch: Pseudo Three-Component Annulation of Nitrosoarenes and (Epoxy)styrenes*. *Chem. Commun.* **2020**, *56*, 15032-15035.

5. Santanu Ghosh, **Anisha Purkait**, and Chandan K. Jana. *Environmentally benign decarboxylative N-, O-, and S-acetylations and acylations*. *Green Chem.*, **2020**, *22*, 8721- 8727.

6. **A. Purkait** and C. K. Jana, 'Nitroso-azomethine ene reaction enabled three component annulations of nitrosoarene, azomethine and alkene to arylquinolines" (*manuscript under preparation*).

Conferences Attended:

1. Presented a poster in **CRSI-2017**, held at Department of Chemistry, Gauhati University, Guwahati, India.

2. Presented a poster in **Research Conclave-2017**, held at Department of Chemistry, IIT Guwahati, Guwahati, India.

3. Presented a poster in **CFOS-2017**, held at IIT Roorkee, Roorkee, India.

4. Presented a poster in **Chemconvene-2017**, held at Department of Chemistry, IIT Guwahati, Guwahati, India.

5. Presented a poster in **FICS-2018**, held at IIT Guwahati, Guwahati, India.

6. Oral presentation in **XV-JNOST-2019**, held at Department of Chemistry, Delhi University, Delhi, India.

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Dr. Akshai Kumar Alape Seetharam (Member)

Content

Abbreviation

Å	Angstrom
Ar	Argon
br.	Broad
Bn	Benzyl
Bu	Butyl
Boc	*tert*-butoxycarbonyl
1,4 BQ	Benzoquinone
^{n}Bu	*n*-Butyl
Cat.	Catalytic/Catalyst
Cbz	Carboxybenzyl
$CDCl_3$	Chloroform-*d*
CAN	Ceric ammonium nitrate
CDC	Cross Dehydrogenative Coupling
CH_3CN	Acetonitrile
CCDC	Cambridge crystallographic data centre
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
^{o}C	Degree Celsius
Cu	Cupper
d	Doublet or day
δ	Chemical shift or delta
DCM	Dichloromethane
DMF	*N*, *N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
EtOAc	Ethyl acetate
ee	Enantiomeric excess
equiv.	Equivalent
ESI	Electrospray ionization
FTIR	Fourier transform infrared spectroscopy
g	Grams
γ	Gamma
h	Hours
HFIP	Hexafluoroisopropanol
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
MOM	Methoxymethyl acetal
mg	Microgram
µL	Microliter
mL	Mililiter

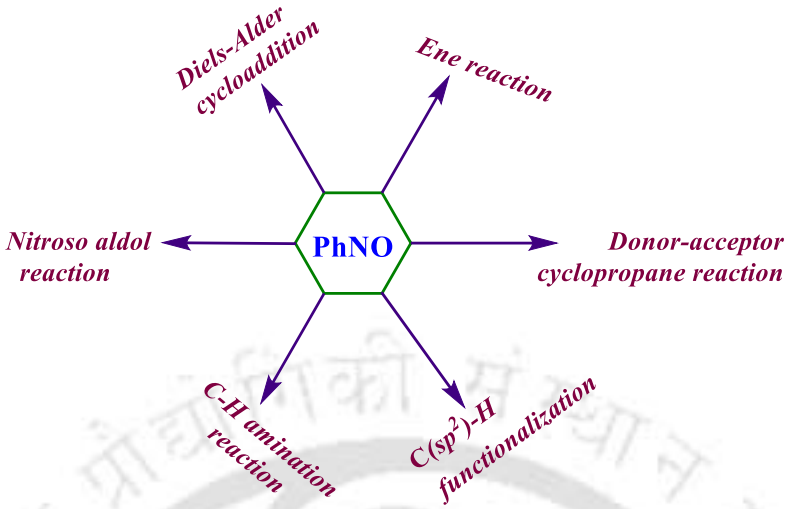
MS	Molecular sieve
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
PIFA	Bis(trifluoroacetoxy) iodobenzene
Ph	Phenyl
p-TSA	*p*-Toluenesulfonic acid
Py	Pyridine
rt	Room temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	Tetrahydrofuran
THIQ	1,2,3,4- Tetrahydroisoquinoline
TMS	Tetramethylsilane
X-RD	X-ray diffraction

Abstract:

Nitrosoarene is a versatile reagent for incorporation of N, O-functionality. However, the use of arene moiety in the reaction is not widely explored. Development of new protocols where the involvement of -N=O group as well as the arene moiety of nitrosoarene are applied towards the syntheses of valuable bio-active scaffolds is highly desirable. The contents of this thesis entitled "**Syntheses of *N*-heterocycles *via* arene functionalization of nitrosoarenes**" have been divided into six chapters. A brief review on different reactivity of nitrosoarene has been presented in the first chapter. Chapter 2 describes metal-free sequential C(sp^2)−H and C(sp^3)−H aminations of nitrosoarenes and N‑heterocycles to ring-fused imidazoles. Chapter 3 presents N-aminations of benzylamines and alicyclic amines with nitrosoarenes to hydrazones and hydrazides. Chapter 4 describes Lewis-acid catalyzed pseudo three-component annulation of nitrosoarenes and (epoxy)styrenes to provide arylquinolines. Chapter 5 describes nitroso- ene reaction of nitrosoarene and azomethine to nitrones. The strategy has been applied for one-pot three component synthesis of oxazolidines and aryl quinolines. Finally, the experimental details and copies of ^{1}H and ^{13}C NMR data have been provided in chapter six.

CHAPTER I. Reactivity of nitrosoarene:

Nitrosoarene, due to its high reactivity and easy availability was chosen for synthetic transformation in the organic syntheses. Owing to the high polarizability of N=O bond nitrosoarenes proved to be an important synthetic building block to install *N* and *O* -functionality in molecules. This chapter highlights an outline of diverse reactivity of nitrosoarenes, such as nitroso aldol reaction, diels alder reaction, pericyclic reaction, nitroso-ene, reaction with donor-acceptor cyclopropane etc. Since its discovery, nitrosoarenes have been used in various *N*-nitroso aldol as well as *O*-nitroso aldol reaction. Apart from aldol reactions, nitrosoarenes are well known for [3+2], [4+2], [2+2] cycloaddition reactions under different conditions. On the other way, nitroso ene reactions have been one of the most widely used approaches to direct regio- and stereo-selective allylic functionalization of olefins.



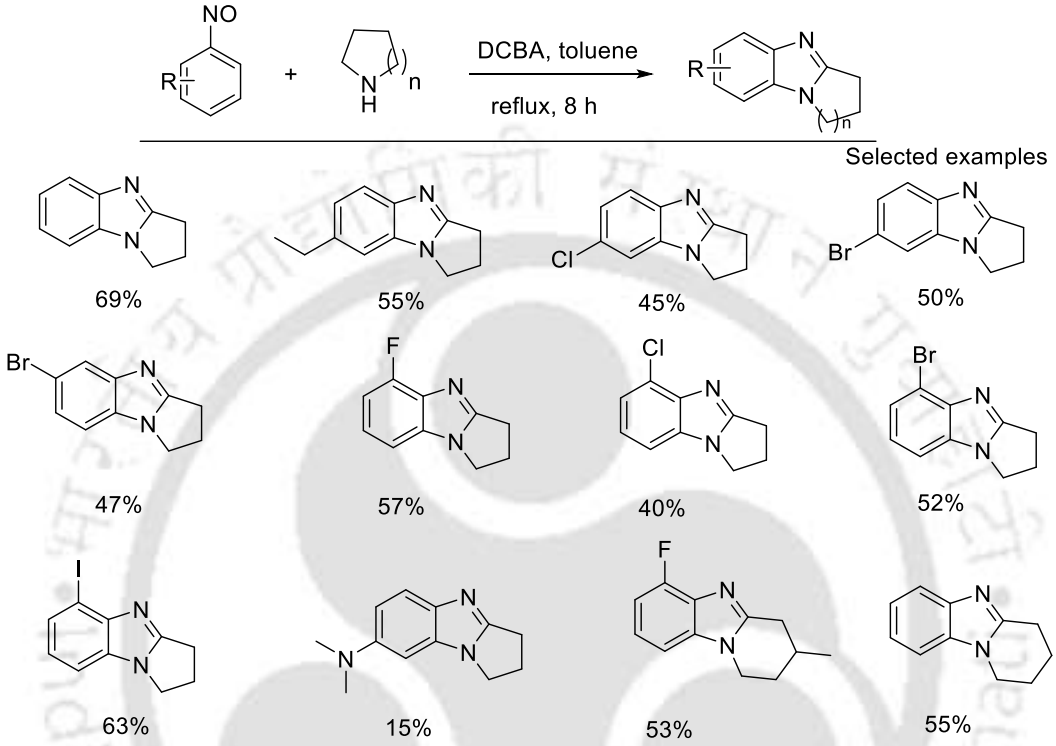
Scheme 1: Diverse reactivity of nitrosoarene.

However, there are very limited reports on C(sp^2)-H functionalization using nitrosoarene. From the previous reports on different reactions of nitrosoarenes, it is well anticipated that important heterocyclic cores *i.e.*, indoles, acridine, phenazine, carbazole *etc* can be synthesized using C-H functionalization of nitrosoarenes. Most of these strategies for C-H functionalization of nitrosoarenes are based on metal mediated pathway including external oxidants, along with the multistep synthesis with undesirable by-product. Therefore, the aim of this thesis is to develop novel synthetic methodologies for C-N bond formation using C-H functionalization of nitrosoarene under operationally simple conditions.

CHAPTER II: Metal-Free Sequential C(sp^2)−H and C(sp^3)−H Aminations of Nitrosoarenes and N-Heterocycles to Ring-Fused Imidazoles:

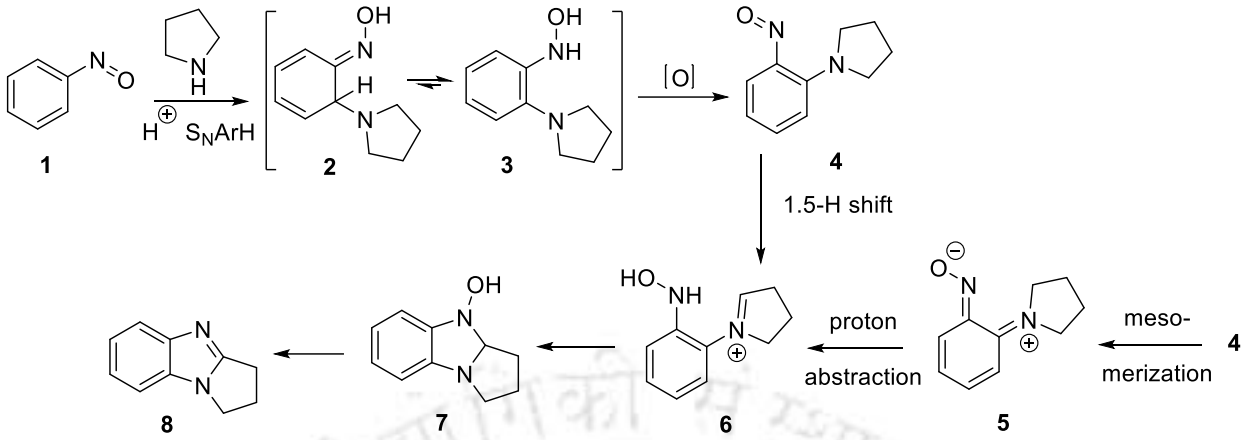
Fused imidazoles are privileged core structures which are present in many bioactive molecules including various natural products. The benzimidazole derivatives play a very significant role as therapeutic agent *e.g.*, anti-cancer, anti-ulcer, anti-helminthic drugs. Apart from this, the benzimidazole derivatives exhibit pharmacological activities such as antimicrobial, antiviral, anticancer, anti-inflammatory, analgesic, etc. Specially, ring-fused benzimidazole derivatives were documented as the important pharmacophore for anticancer activity. Most of the cases, syntheses of these important scaffolds mainly based on the multistep reaction sequences A metal-free protocol for the C(sp^3)-H functionalization enabled annulation of nitrosoarenes and *N*-heterocycles for the synthesis of ring-fused imidazoles has been developed. A wide range of

bioactive ring-fused benzimidazoles were easily prepared from readily available nitrosoarenes and N-heterocycles in a mild and simple operation. Further DFT-study proved that C(sp^2)−H amination via S_NArH reaction of o-halo-nitrosoarene was favored over conventional S_NAr to provide halogen (Cl, Br, I) containing products which are otherwise difficult to prepare.



Scheme 2: Scope of annulation of nitrosoarenes and *N*-heterocycles. *DCBA- 2,4-dichlorobenzoic acid

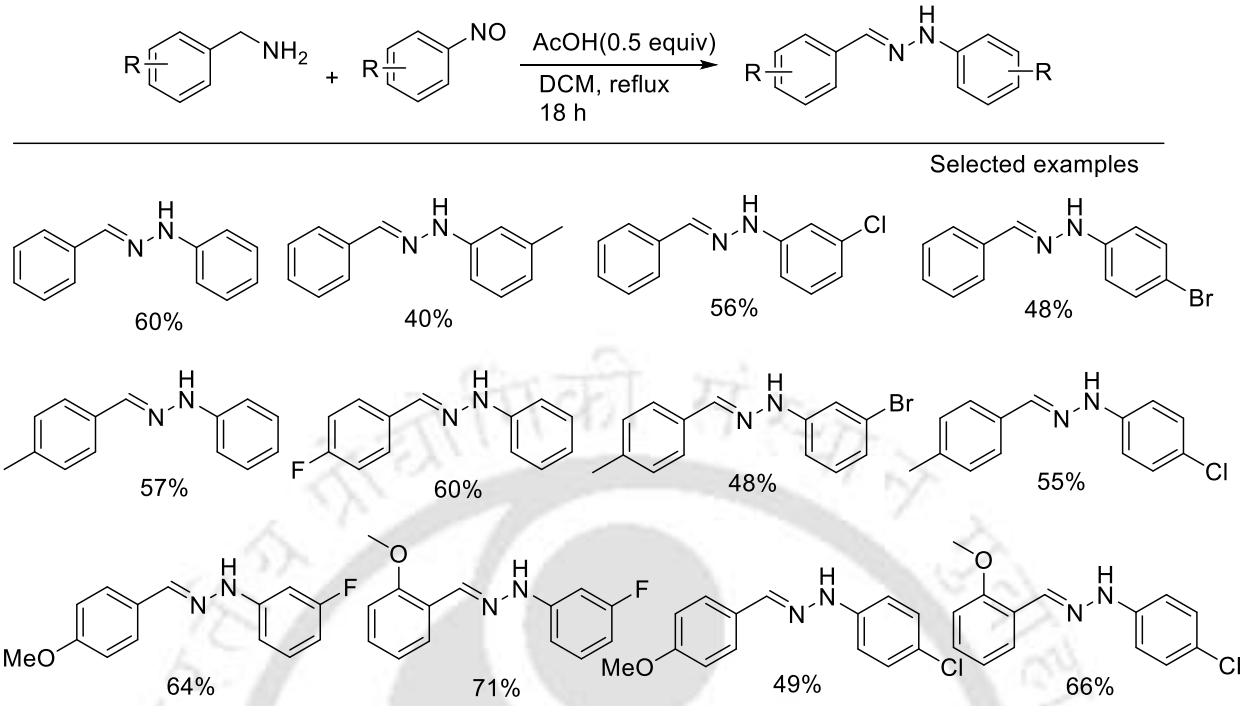
A plausible mechanism for unprecedented domino C(sp^2)−H and C(sp^3)−H amination reaction is described in **Scheme 3**. Nucleophilic addition of pyrrolidine to nitrosobenzene **1** occurred in the first step. The oxidation of resulting intermediate **2** and/or **3** could lead to corresponding 2-amino nitrosoarene **4**. Amino nitroso derivative **4** then readily undertook a 1,5-hydride shift to provide the iminium ion **6**. Alternatively, the iminium ion **6** could also be produced through deprotonation and consequent mesomerization of the corresponding isomeric iminium ion **5**, which resulted from **4**. Annulation of **6** followed by acid mediated dehydration of resulting N-hydroxy derivative **7** provided the desired imidazole **8**. Amino phenylhydroxylamine **3** was detected through mass spectrometry which support the intermediacy of **3** in the reaction.



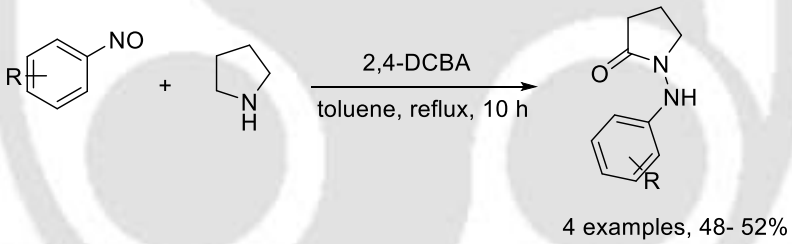
Scheme 3: Proposed mechanism for metal free annulation of nitrosoarene and *N*-heterocycles.

CHAPTER III: N-Aminations of Benzylamines and Alicyclic Amines with Nitrosoarenes to Hydrazones and Hydrazides:

Benzylamines unlike alkylamines upon reaction with a nitrosoarene undergo oxidation to the corresponding imines. A direct amination of benzylamines, which was difficult to achieve due to its facile oxidation, to the corresponding hydrazones is reported in this chapter. A wide variety of benzylamines and N-heterocycles were reacted with nitrosoarenes to provide structurally diverse hydrazones and hydrazides, respectively. The hydrazones are an important class of compounds that find application in organic synthesis, medicinal chemistry, and supramolecular chemistry including metal and covalent organic frameworks. Hydrazone derivatives are also found as a key unit of fluorescent chemosensors.

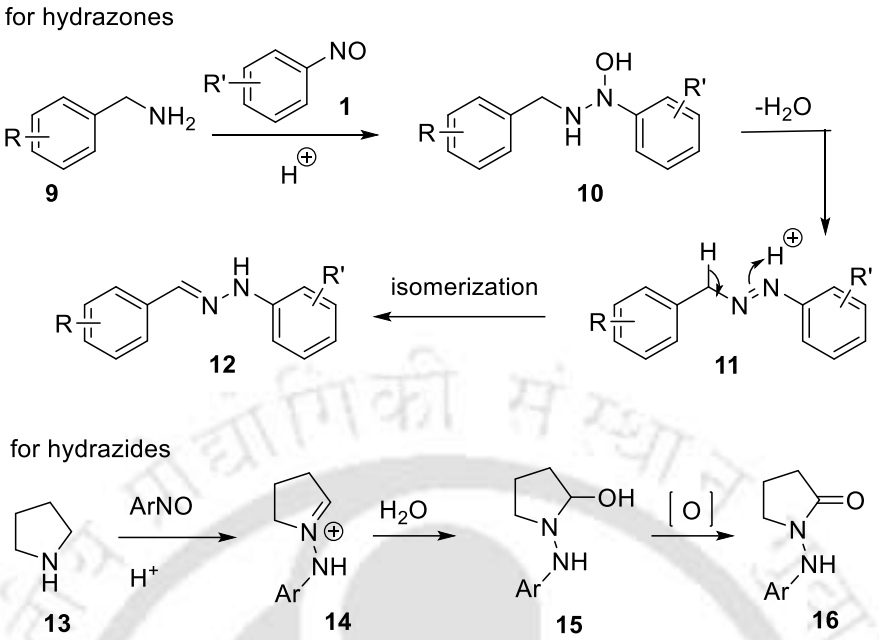


Scheme 4: Substrate scope of hydrazones.



Scheme 5: Substrate scope of hydrazides.

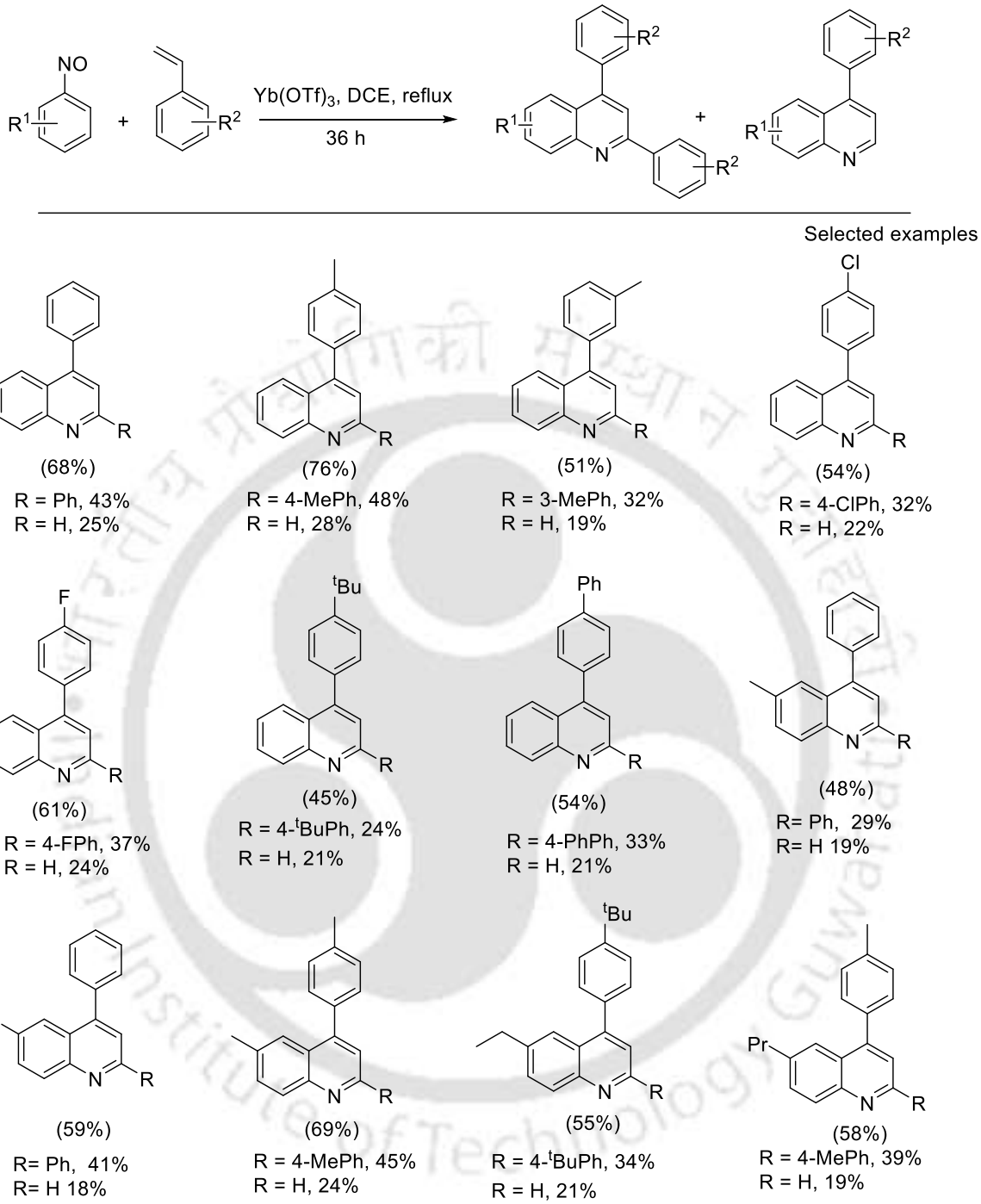
A plausible mechanism for the formation of hydrazone and hydrazide is described in **Scheme 5**. Analogous to the reaction of amines with the carbonyl compounds, nucleophilic addition of amines **9** to the nitrosoarenes **1** occurred to provide hydroxylamine derivative **10**. Acid mediated dehydration **10** produced corresponding arylazoalkanes derivative **11** which was isomerized readily to provide the observed hydrazone **12**. A similar intermediate was formed from the reaction of nitrosoarene **1** and N-heterocycles **13**. The iminium intermediate **14** was trapped by H_2O to provide the corresponding hemiaminal **15** which upon subsequent oxidation gave the hydrazide **16**.



Scheme 6: Proposed mechanism for hydrazone and hydrazides.

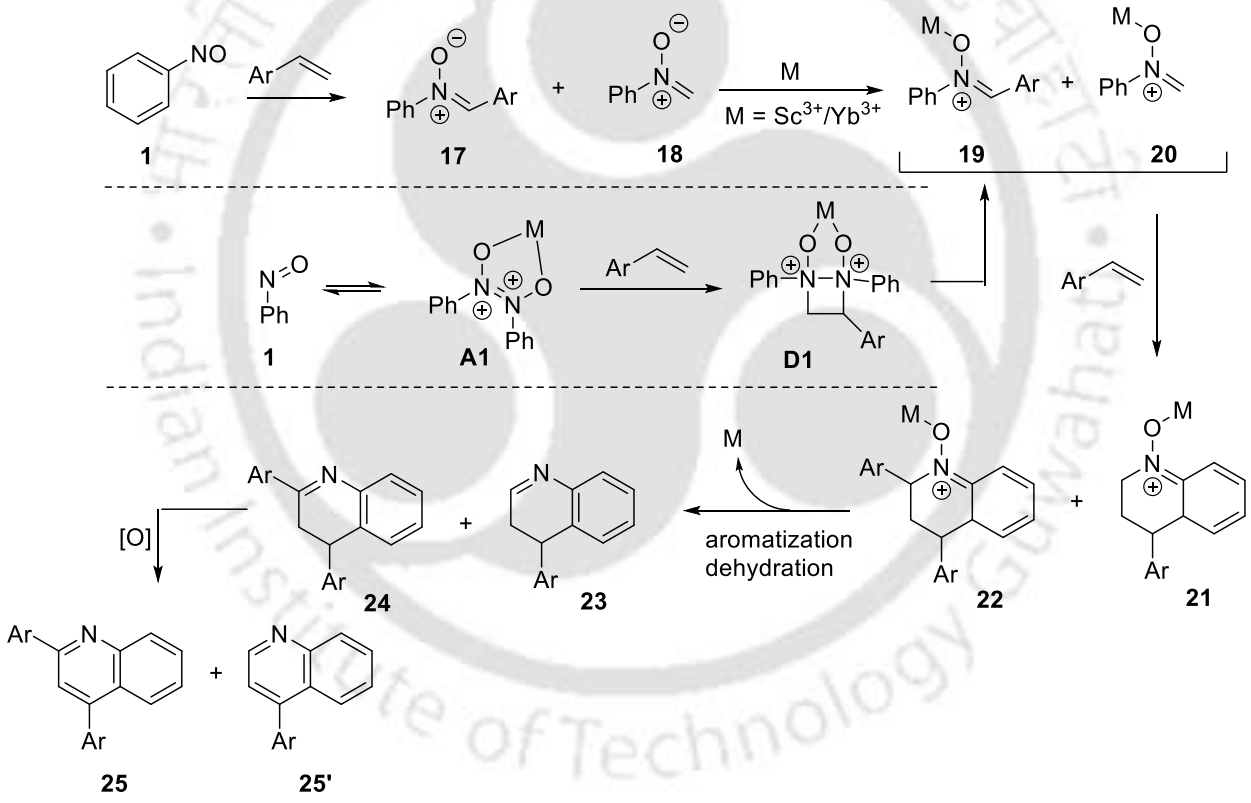
CHAPTER IV: Lewis Acid Catalyzed Reactivity Switch: Pseudo Three-Component Annulation of Nitrosoarenes and (Epoxy)styrenes

Functionalized quinoline, particularly, arylquinoline are widely found as the key scaffold of many natural products and bioactive molecules. Therefore, the efforts are being devoted to the development of novel and more efficient synthetic methods for the synthesis of functionalized quinoline derivatives. However, the development of novel synthetic methods to provide quinoline derivatives with wide structural diversity starting from readily available starting materials under simple reaction conditions still remains challenging and desirable. Lewis acid catalyzed annulation reaction via arene functionalization of nitrosoarenes, and C-C cleavage of (epoxy)styrene to provide arylquinolines has been developed. The lewis acid catalyst altered the annulation pattern of *insitu* generated nitrone providing arylquinolines *via* [4+2] annulations instead of oxazolidines which is commonly obtained through [3+2] cycloaddition. The reaction of nitrosoarene with styrene gave a mixture of 2,4- diarylquinoline and 4-arylquinoline.



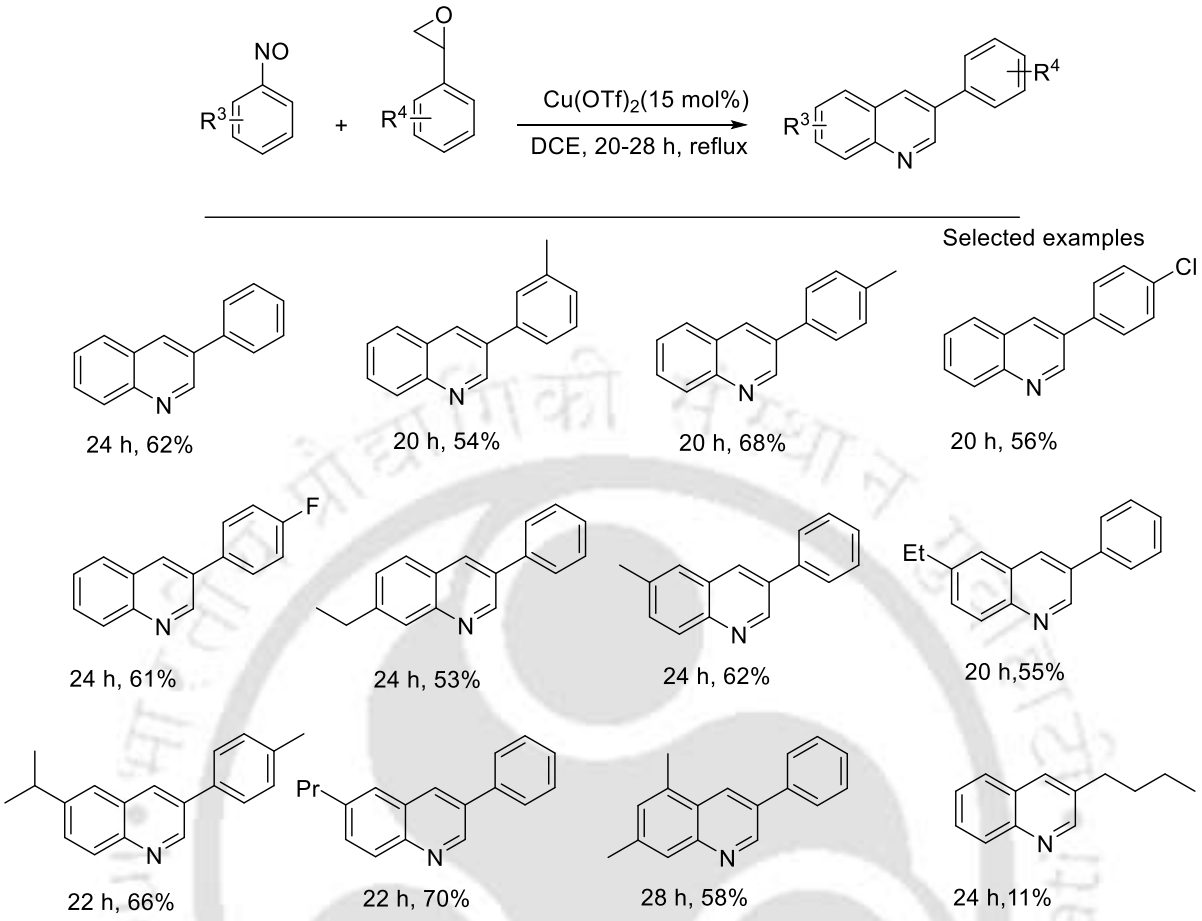
Scheme 7: Scope of 2,4-di-substituted and 4-substituted quinoline derivatives.

On the basis of our experimental outcomes and literature reports, a plausible mechanism for the formal [3+2+1] annulation of nitrosoarene and styrene is presented in **scheme 7**. The nitrones **19** and **20** were formed from the reaction of nitrosoarene **1** and styrene derivatives involving azodioxy dimer **A1** and diazetidine derivative **D1**. The nitrones could also be formed from nitrosoarene **1** and styrene following a radical pathway. Both the metal coordinated nitrone derivatives **19** and **20** reacted through the Povarov type reaction with another equivalent of styrene to provide the tetrahydroquinoline derivatives **22** and **21**, respectively. Aromatization and dehydration of **22** and **21** produced respective dihydroquinoline **24** and **23** which upon oxidation provided the observed aryl quinolines **25** and **25'**.



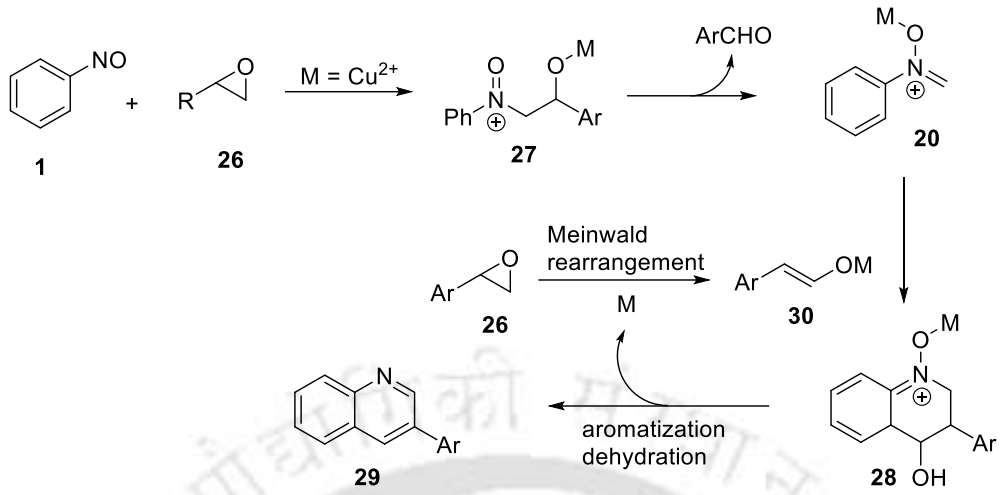
Scheme 8: Proposed mechanism for annulation of nitrosoarene and styrene.

Subsequently, $Cu(OTf)_2$ catalyzed annulation reaction of nitrosobenzene with epoxy-styrene has been developed to provide 3-arylquinolines.



Scheme 9: Scope of 3-aryl quinoline derivatives.

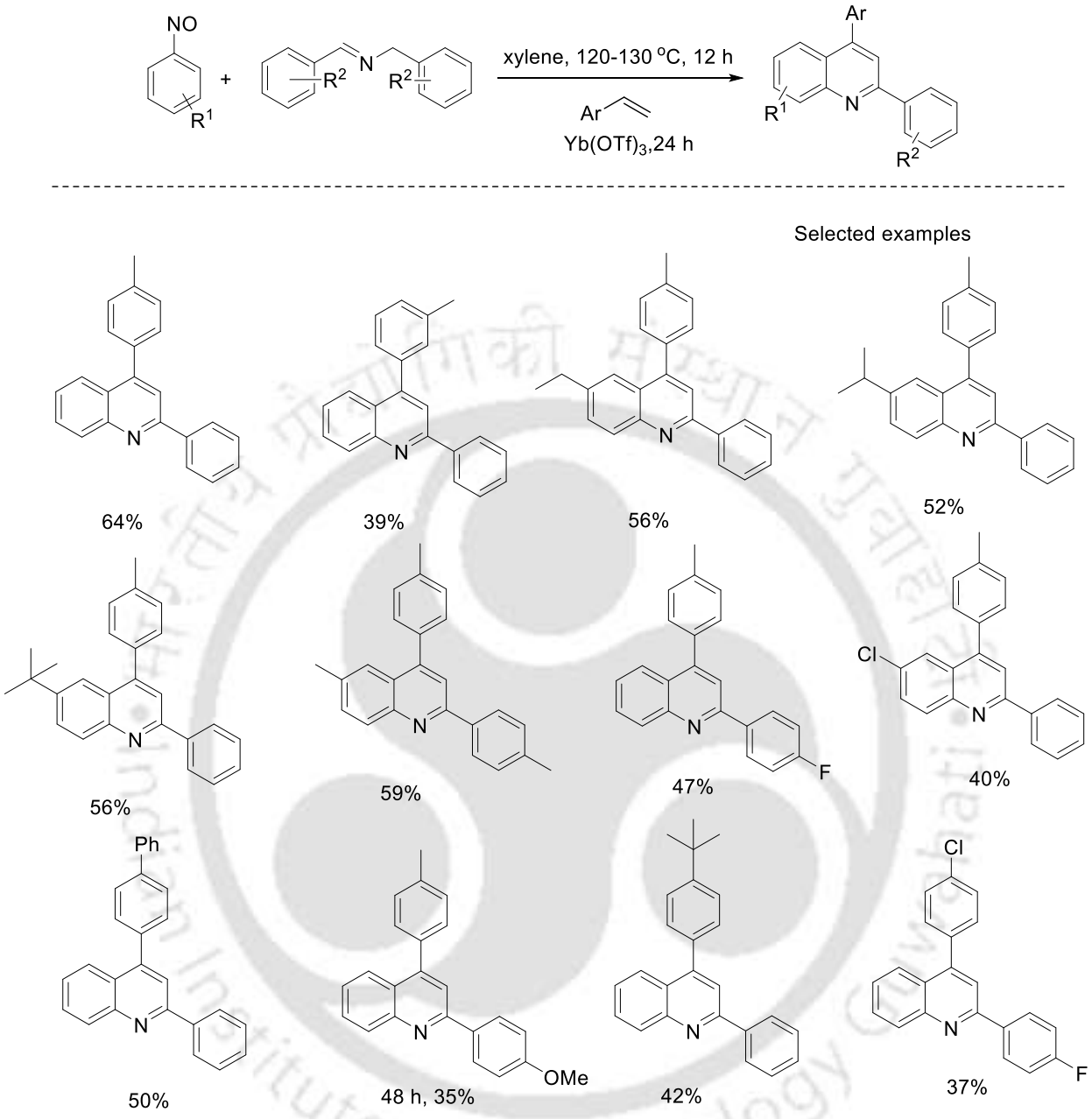
Based on these results, a plausible reaction mechanism has been depicted in **Scheme 9**. Nucleophilic nitrosoarene **1** added to the least hindered site of styrene oxide **26,** which is activated by the coordination with the Cu(II). C-C bond cleavage of the resulting ionic intermediate **27** occurred to provide the nitrone **20** and aldehyde. The metal coordinated nitrone **20** reacted with the enolate **30**, which was generated *in situ* from styrene oxide **26** via Meinwald rearrangement, either via a concerted or stepwise pathway to provide the N-oxide **28**. Fast aromatization followed by dehydration of **28** yielded observed 3-aryl quinoline **29** as the single regio-isomer.



Scheme 10: Proposed mechanism for annulation of nitrosoarene and epoxystyrene

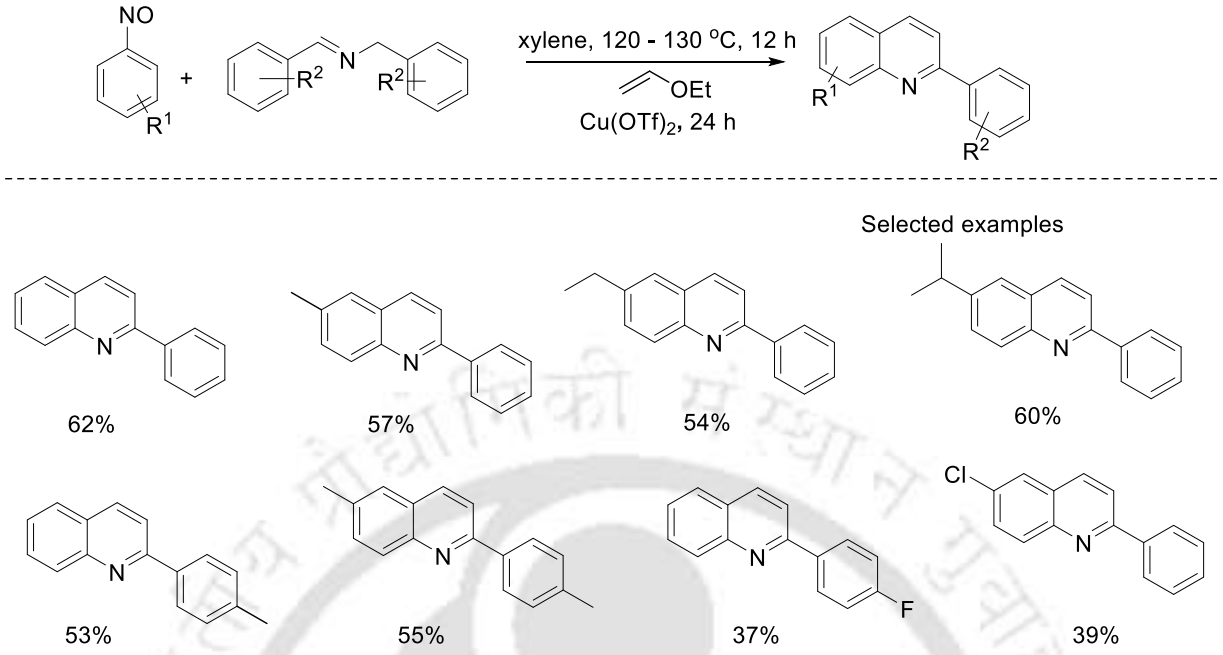
CHAPTER V: Nitroso-azomethine ene reaction enabled three component annulations of Nitrosoarene, azomethine and alkene to Arylquinolines:

Nitrones, take part in multifaceted applications including cycloaddition reactions with multiple bond formations leading to the assembly of a wide variety of heterocyclic ring systems. In the previous chapter, reactivity switch of nitrones from [3+2] to [4+2] cycloaddition has been achieved to obtain 2,4-substituted quinolines with the same aryl groups. In this chapter, a novel method for the synthesis of nitrone derivatives *via* nitroso-ene pathway has been demonstrated which is helpful to synthesize 2,4-differently substituted quinolines in one-pot operation. The imine synthesized from benzylamine and benzaldehyde derivatives was reacted with nitrosoarene *via* nitroso-ene reaction to produce nitrones which underwent [4+2] cyclization with different styrene derivatives in presence of Lewis acid to provide quinolines.



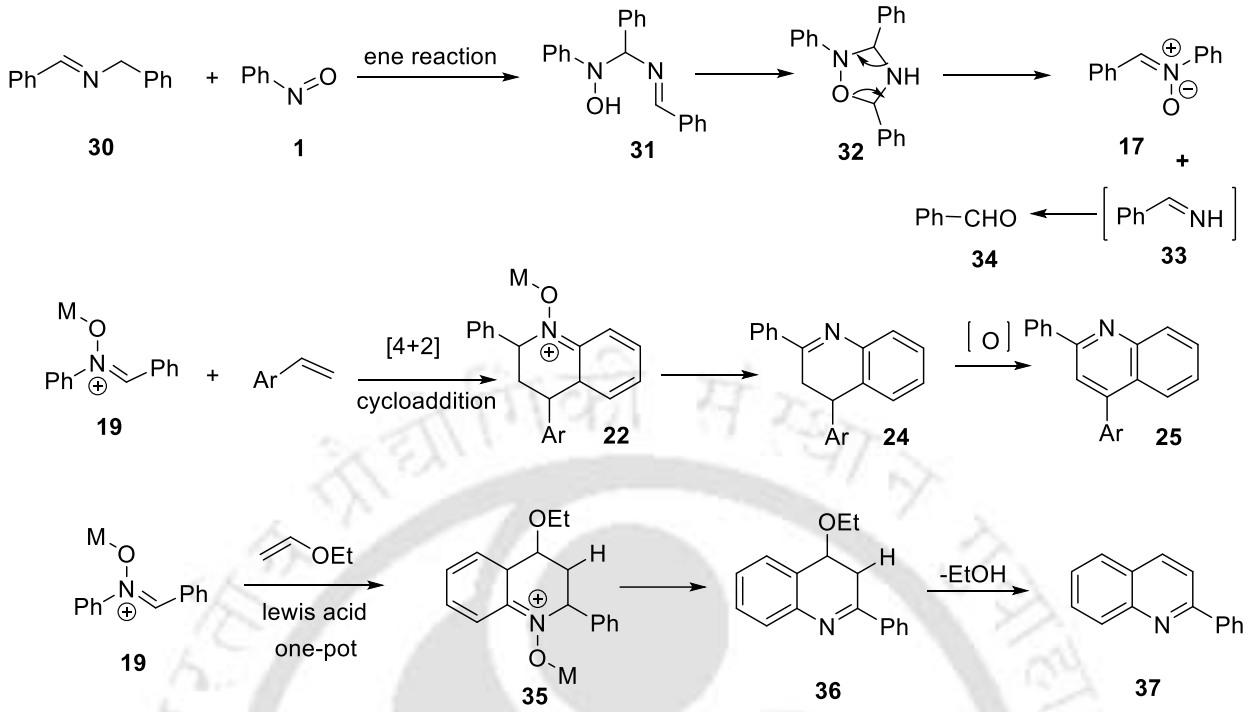
Scheme 11: Substrates of differently substituted quinolines

Apart from styrenes, [4+2] cycloaddition of other dienes *i.e.*, ethylvinyl ether provides 2-arylquinolines under the standard reaction conditions.



Scheme 12: Scope of 2-phenylquinolines

A plausible mechanism has been proposed for the three-component annulation reaction. The ene addition product **31** formed which further cyclized to five membered intermediate oxadiazolidine **32.** The intermediate **32** underwent reverse 3+2 cycloaddition reaction to get expected nitrone **17**. This step involved formation of the imine **33** which ultimately produced aldehyde **34**. Metal coordinated nitrone **19** underwent [4+2] cycloaddition with styrene to attain **22** which upon aromatization and deprotonation provide **24**. Oxidation of **24** leads to targeted quinoline **25**. Similar cycloaddition with ethyl vinyl ether formed **35** which upon aromatization provide **36**. Finally, elimination of ethanol from **36** provided 2-arylquinoline **37**.



Scheme 13: Proposed mechanism for nitrones and its annulation with styrene and vinylether

Summary:

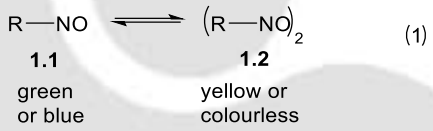
The thesis describes the development of novel synthetic methodologies for new C-C/C-N bond formation with the aid of diverse reactivity of nitrosoarene. Synthesis of ring-fused imidazole derivatives was obtained *via* one-pot dual C-H functionalization. A synthetic route for the synthesis of hydrazones and hydrazides has been established. Substituted quinolines were synthesized *via* Lewis-acid mediated reaction between nitrosoarene, styrenes and epoxy-styrenes. An advanced methodology for nitroso-azomethine ene reaction enabled three component annulations towards the synthesis of aryl quinolines has been developed. In future, the focus will be to investigate and explore the functionalization of nitrosoarenes varying the other counterparts to afford other valuable *N*-heterocycles.

CHAPTER - 1

Reactivity of Nitrosoarenes

1.1 Introduction:

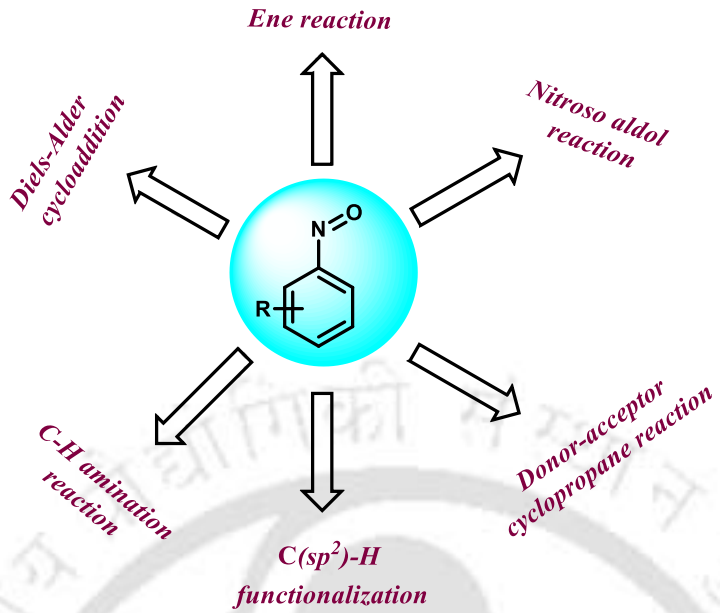
Since 1874, after the first report of the synthesis of nitrosobenzene by Adolf Baeyer[1], nitroso group (R−N=O) had a rich history in chemistry and biology. Various facets of C-nitroso compounds have been studied, including their syntheses,[2] reactivities,[3] and interactions with metals,[4] This renewed attention has been fueled in part by their many applications in synthetic organic chemistry,[5] their role as reactive metabolites,[6] and their use as spin traps.[7] Although heteroaryl C-nitroso compounds are less studied than nitrosoarenes,[8] they exhibit closely related behavior. The most interesting fact was discovered by Piloty in 1898 that C-nitroso compounds can generally exist in two distinct forms in equilibrium: dimeric **1.2** (usually colorless or yellow) or monomeric **1.1** (normally green or blue) (**Scheme 1**, eq. 1).[9]



Scheme 1: Monomer-dimer equilibrium of nitroso compounds.

With these unique characteristics, in due course of time, nitrosoarenes proved to be an important synthetic building block that can undergo a broad range of transformations in synthetic organic chemistry. As reactive intermediates, aromatic nitroso compounds exhibit a high reactivity towards nucleophiles, electrophiles, olefins *etc*. The polarization of the nitrogen-oxygen bond resembling that of the carbon-oxygen bond in carbonyl groups, results in a susceptibility of the -N=O group to additions of nucleophiles. The clarification for this reactivity is connected to their low LUMO energy which make them dominant electrophiles. However, the high energy of the HOMO, orthogonal to the LUMO, produces a lone pair at nitrogen so they can also react as nucleophiles.[10] Nevertheless, the dominant behavior of the nitroso group is its strong tendency to act as an electrophile.

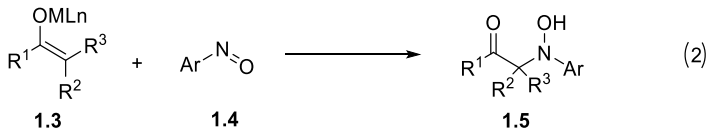
Therefore, nitrosoarenes are frequently used in various synthetic applications for incorporating nitrogen and oxygen functionality in a molecule.[5b,11,31,33,39-41,43] Nitroso groups have acted extensively as dienophile, dipolarophile, and enophile in different pericyclic reactions. Thus, the miscellaneous reactivity (**Scheme 2**) helped nitroso to be preferred as a key starting material for the synthesis of *N*-heterocycles.



Scheme 2: Diverse reactivities of nitrosoarenes.

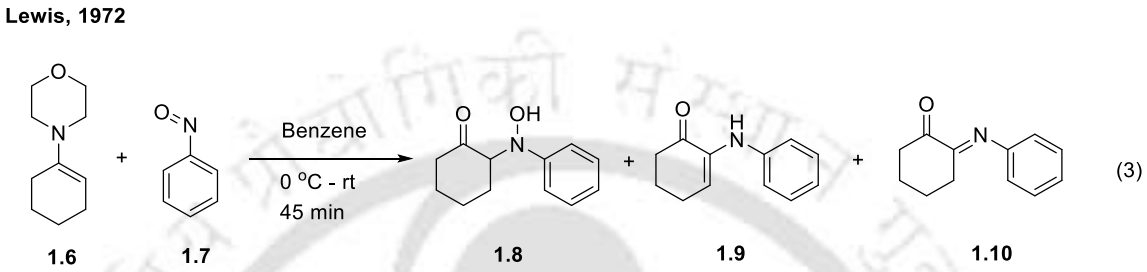
1.2 Nitroso-Aldol Reaction:

Nitrosobenzene analogues are important class of molecules as both the nitrogen and oxygen atoms are extremely reactive. Therefore, a challenge of controlling regioselectivity either *via* nitrogen or oxygen to react preferably with the nucleophile is of essential importance. A number of studies of the reaction of nitrosobenzene with metal-enolate exposed that the *O* versus *N* selectivity is dependent on the nature of the enolate and catalysts. Experiments showed that the reaction of various aromatic and aliphatic nitroso compounds with several enolate anions generate *α*-hydroxyamino ketones (**Scheme 3**, eq. 2)[12] *via* *N*-nitroso aldol pathway. The protocol proceeds smoothly using the *in situ* generated or pre-synthesized enolates **1.3** with nitrosoarene **1.4** to deliver a broad range of *N*-nitroso-aldol products **1.5**.



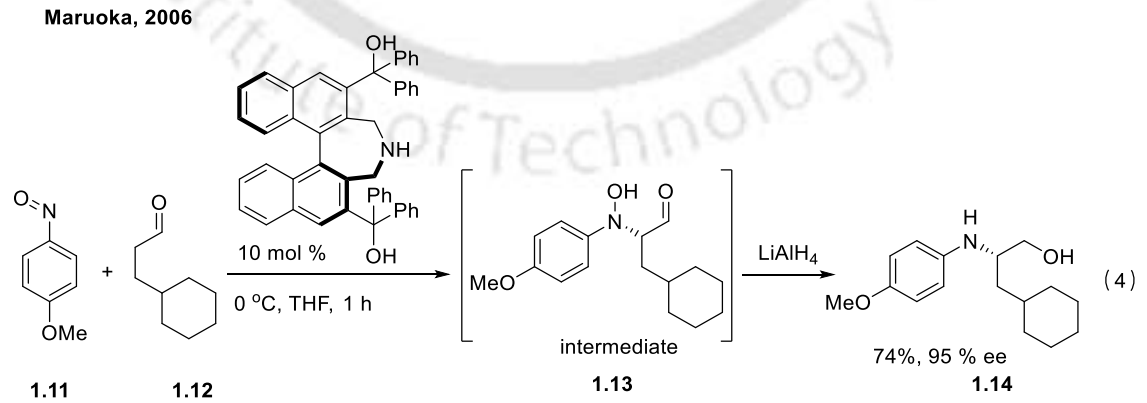
Scheme 3: General scheme for *N*-nitroso aldol reaction

The first synthesis of *α*-hydroxyamino ketones from nitrosobenzene was carried out by Lewis *et al.* in 1972. They reported the synthesis of *α*-hydroxyamino ketones **1.8** using nitrosobenzene **1.7**. The reaction was carried out in benzene at 0 ^{o}C to room temperature with 1-morpholino-1-cyclohexene **1.6** (**Scheme 4**, eq. 3), the corresponding aniline derivative **1.9** has been isolated from the reaction along with the *α*-hydroxyaminoketone.[13]



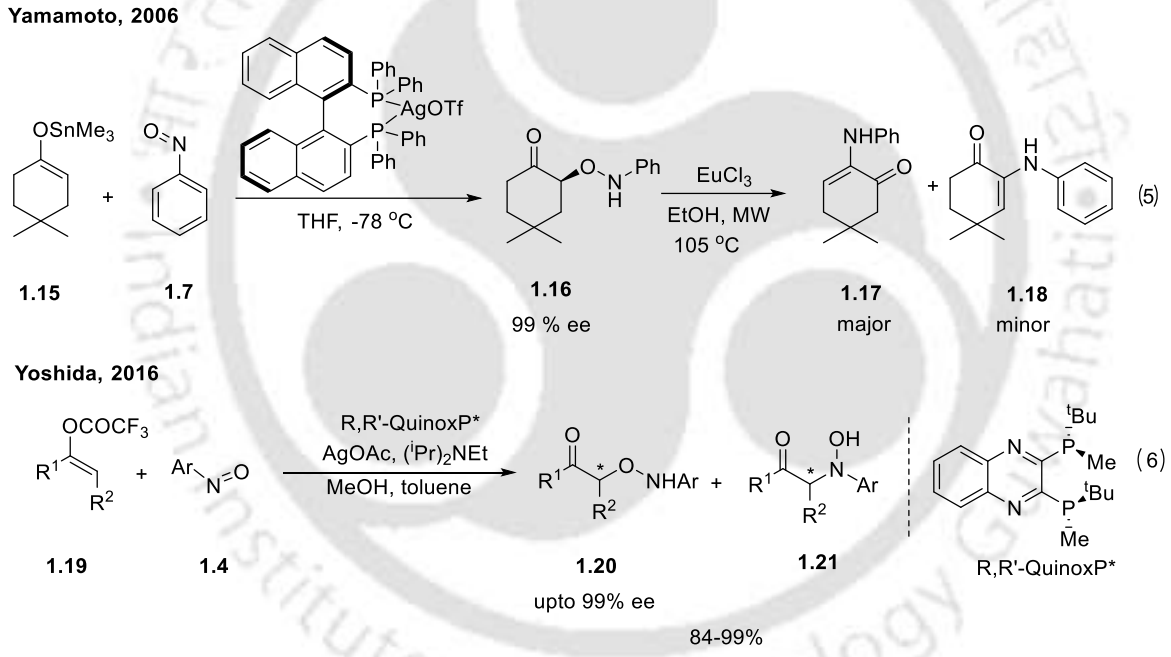
Scheme 4: *N*-nitroso-aldol reaction by Lewis *et al*.

The above example impelled the development of new methods for carbon-nitrogen bond formation *via N*-nitroso aldol reactions. Reactions of various aromatic and aliphatic nitroso compounds with several enolate anions to generate *α*-hydroxyamino carbonyl were well established by several research groups. Maruoka *et al.*, in 2006, established a hydroxyl amination protocol between nitrosoarene **1.11** and aldehyde **1.12** to afford *α*-*N*-hydroxylamino aldehyde **1.13**. Reduction of *N*-hydroxy derivative **1.13** with $LiAlH_4$ provided amino alcohol **1.14** (**Scheme 5**, eq. 4).[14]



Scheme 5: An example of *N*-nitroso-aldol reaction.

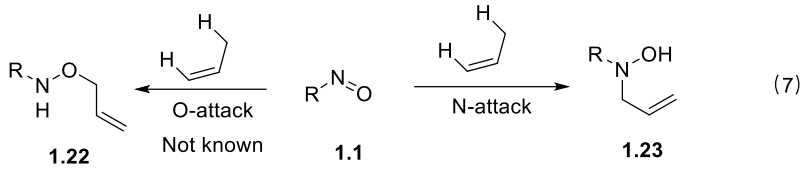
The significant contribution to nitroso chemistry was the discovery of acid promoted *O*-selective nucleophilic attack of silyl enol ethers to nitrosobenzene by Yamamoto *et al*. In 2006, they developed new methodology to achieve the synthesis of *α*-aminooxy carbonyl derivatives **1.16** from the reaction of nitrosobenzene **1.7** with metal enolate **1.15**. Next, Lewis acid ($EuCl_3$) catalyzed 1,2-rearrangement of **1.16** afforded the *α*-amino enone derivatives **1.17** and **1.18** (**Scheme 6**, eq. 5).[15] Later in 2016 Yoshida *et al.* introduced a catalytic asymmetric *O*-nitroso aldol reaction of alkenyl trifluoroacetates **1.19** with nitrosoarenes **1.4** by using QuinoxP*·AgOAc [(*R,R*)-QuinoxP* = (–)-(*R,R*)-2,3-bis(*tert*-butylmethylphosphino) quinoxaline] as the chiral pre-catalyst and *N,N*-diisopropylethylamine as the base pre-catalyst in methanol. Optically active α-aminooxy ketones **1.20** were obtained with up to 99 % ee along with *N*-nitroso aldol product **1.21**. The reaction proceeds through *in situ* generated chiral silver enolates (**Scheme 6**, eq. 6).[16]



Scheme 6: Selected example of *O*-nitroso-aldol reaction.

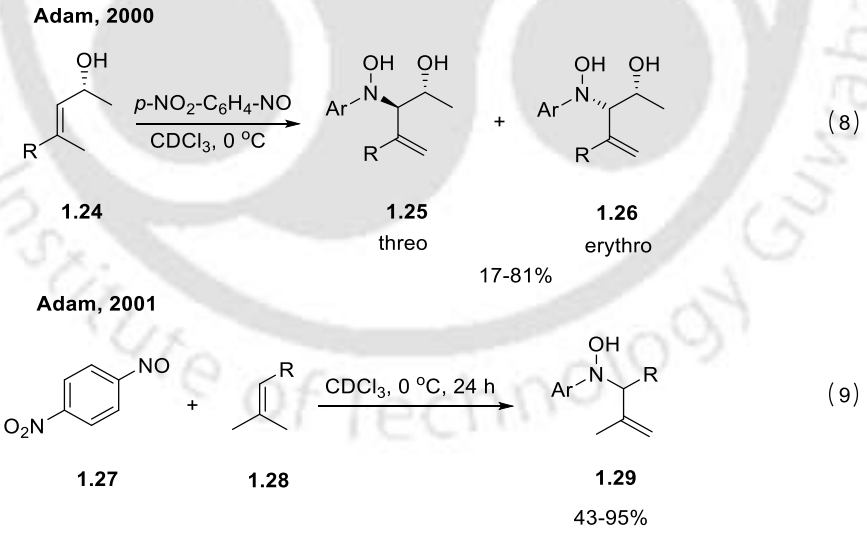
1.3 Nitroso-ene Reaction:

The capability of nitroso compounds to undergo the ene reaction was reported by Alesandri[17] in 1910 and Banks[18] in 1965. But a more efficient study was developed by Knight.[19] Nitroso ene reaction has become one of the most adaptable approaches to the direct regio- and stereo-selective allylic functionalization of olefins.[20] Although, the mechanism of the nitroso ene reaction may go *via* zwitterionic, diradical, concerted pathway, experimental outcome proved that the reaction adopted concerted way preferably (**Scheme 7**, eq. 7).



Scheme 7: Nitroso-ene reaction.

Adam *et al.*, in 2000, investigated nitroso-ene reaction of secondary chiral allylic alcohol **1.24** with *p*-nitro nitrosobenzene to provide the targeted product with erythro **1.26** and threo **1.25** isomer. The reaction was performed at low temperature with strong electron directing effect of the hydroxyl group. Tri- and tetra-substituted substrates displayed high diastereoselectivity in this protocol (**Scheme 8**, eq. 8).[21] Next year the same group established that 4-nitronitrosobenzene **1.27** as an enophile took part in reactions with tri- and tetra-substituted olefins **1.28** under lower temperature. The reactivity of the tri-substituted olefins **1.28** with a variety substituent toward this nitroso enophile has been demonstrated depending on steric, electronic and coordinative effects (**Scheme 8**, eq. 9).[22]

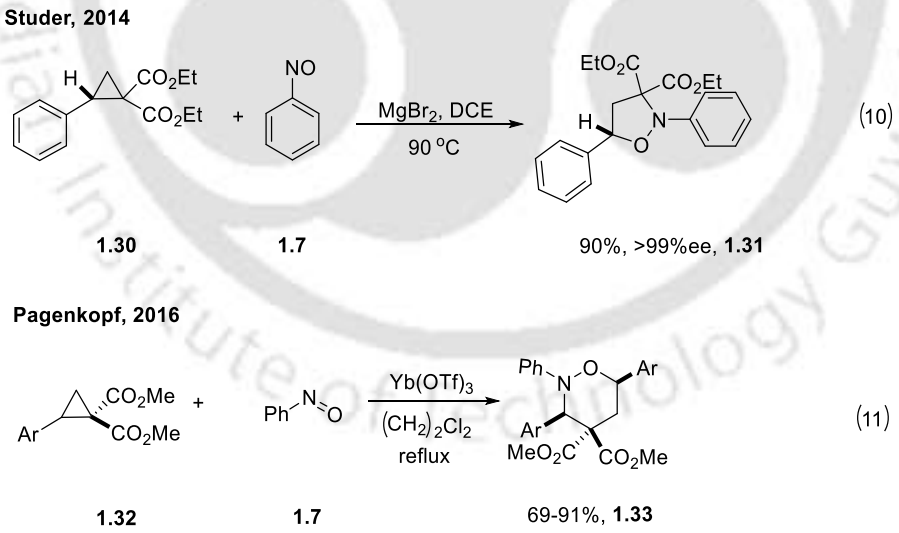


Scheme 8: Selected examples of Nitroso-ene reaction.

1.4 Reaction with Donor-Acceptor cyclopropane:

The use of ring strain in donor−acceptor (DA) cyclopropanes to generate 1,3-zwitterionic intermediates has been well documented in the literature. A number of reactive partners have been set up to undergo cycloaddition reactions with this zwitterion.[23] Nitrosoarene is one of them which can undergo [4+2] as well as [3+2] cycloaddition reaction.

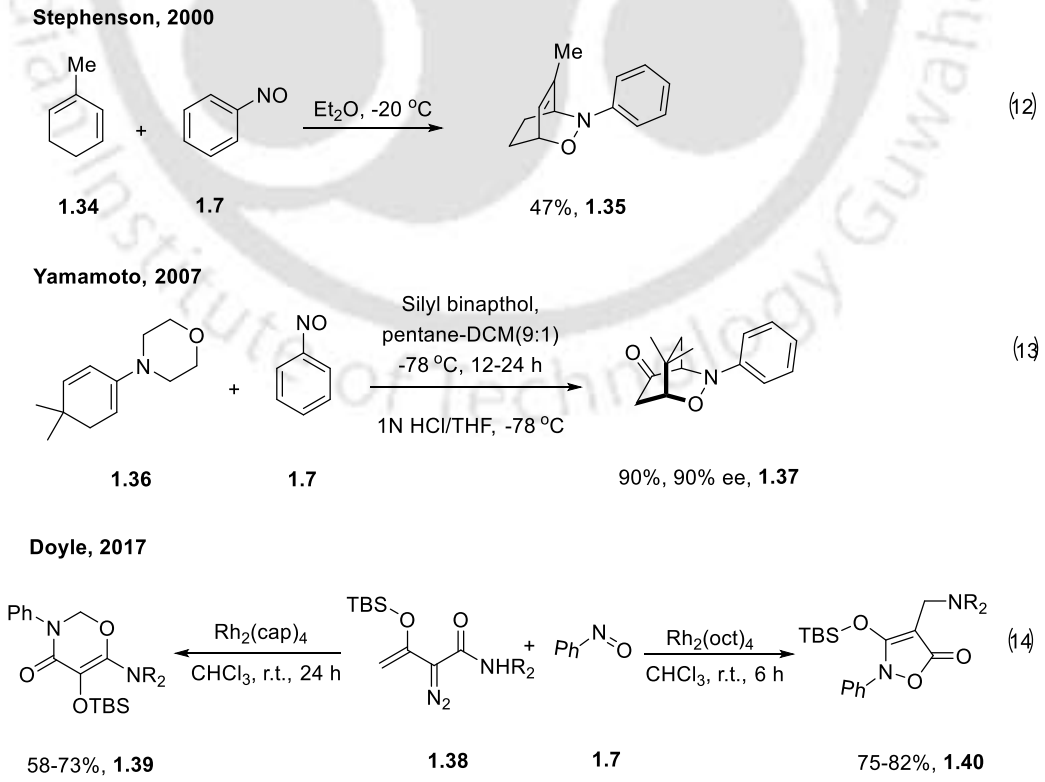
In 2014, Studer *et al.* developed $MgBr_2$-catalyzed formal [3+2] cycloaddition of donor–acceptor activated cyclopropanes **1.30** with nitrosobenzene **1.7**. The method provides a novel approach to structurally diverse isoxazolidines **1.31**. This cycloaddition method afforded the product isoxazolidine with complete stereospecificity starting from an enantiomerically pure cyclopropane. The reaction occurred with retention of stereochemistry at the stereo-genic center (**Scheme 9**, eq. 10).[24] In 2016, Pagenkopf *et al.* introduced tandem ring opening, elimination, and cycloaddition of donor−acceptor cyclopropanes **1.32** with nitrosoarenes **1.7** in presence of $Yb(OTf)_3$. The reaction results the formation of tetrahydro-1,2-oxazine **1.33** instead of the normal cycloadduct isoxazolidine *via in situ* nitrone formation (**Scheme 9**, eq. 11).[25]



Scheme 9: Reaction of nitrosoarene with donor-acceptor cyclopropanes.

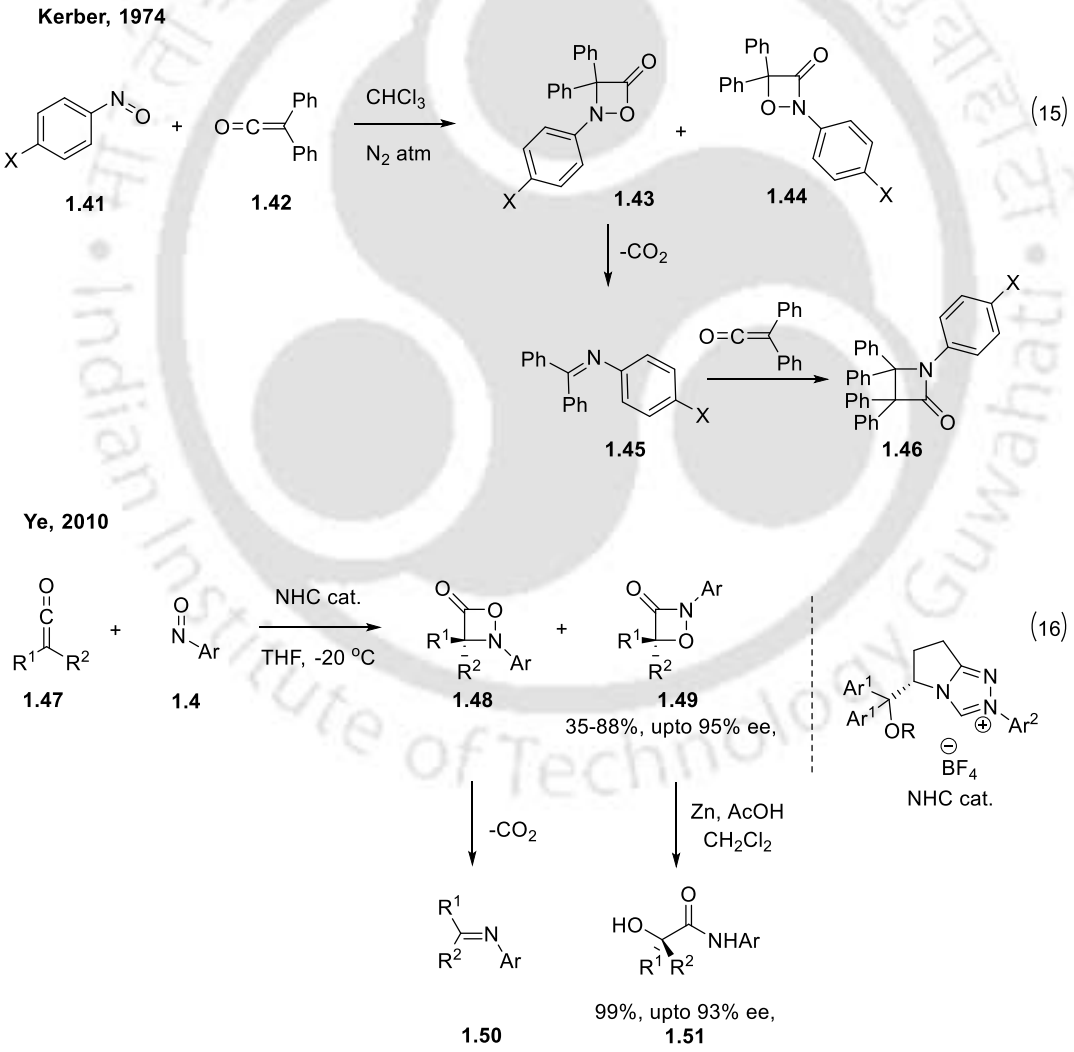
1.5 Cycloaddition reactions of nitrosoarenes:

Nitrosoarene participates in various reactions such as cycloaddition *i.e.* [4+2], [2+2], [3+2] to incorporate both –N and –O functionality in the molecules. Earlier in 2000, Stephenson *et al.* reported a novel low temperature cycloaddition protocol for nitrosobenzene **1.7** and diene **1.34** to provide **1.35** as the major product (**Scheme 10**, eq. 12).[26] This is a convenient and proficient method to introduce the new C–N and C–O substituents in the compound. In 2007, Yamamoto *et al.* reported the synthesis of bicyclic ketone **1.37** using nitroso Diels–Alder-type reaction of **1.36** and nitrosobenzene **1.7**. Silyl binaphthol possessing tris(*m*-xylyl)silyl groups at the 3,3′-positions ensures formation of 2-oxa-3-azabicyclo[2.2.2]octan-5-one **1.37** as a single regioisomer with high enantioselectivity (**Scheme 10**, eq. 13).[27] Doyle *et al.*, in 2017, developed the first cyclization reactions of enol-diazo compounds **1.38** with nitrosobenzene **1.7**. Rhodium(II) octanoate catalyzed [3 + 2] formal cycloaddition between enoldiazoacetamides **1.38** and nitrosobenzene **1.7** occurred through cleavages of the enol double bond and the amide bond, thus furnishing fully substituted 5- isoxazolone derivatives **1.40**. Upon changing the catalyst to rhodium(II) caprolactamate, the reaction pathway switched to an unprecedented formal [5 + 1]-cyclization that provided multifunctionalized 1,3-oxazin-4-ones **1.39** with near exclusivity (**Scheme 10**, eq. 14).[28]



Scheme 10: Cycloaddition reaction of nitrosoarene.

Nitroso compound is well-known for its [2+2]-cycloaddition with to provide 4-membered ring system. In 1974, Kerber *et al.* developed the cycloaddition reaction of aromatic nitroso compounds **1.41** with diphenylketene **1.42** to 1,2- oxazetidinones **1.43** and **1.44**. Due to instability of compound **1.43**, it decomposed to carbon dioxide and a Schiff base **1.45**, which reacted *in situ* with diphenylketene **1.42** to form an azetidinone **1.46** (**Scheme 11**, eq. 15).[29] Later in 2010, Ye *et al.* reported Chiral *N*-heterocyclic carbenes catalyzed formal [2 + 2] cycloaddition reaction of alkyl(aryl)ketenes **1.47** and nitrosoarenes **1.4** to obtain the corresponding 1,2-oxazetidin-4-ones **1.48** and 1,2-oxazetidin-3-ones **1.49** in moderate to good yields with high enantioselectivities. Reductive ring-opening of the oxazetidinones **1.49** provided the corresponding *α*-hydroxy acid derivatives **1.51** in good yields (**Scheme 11**, eq. 16).[30]

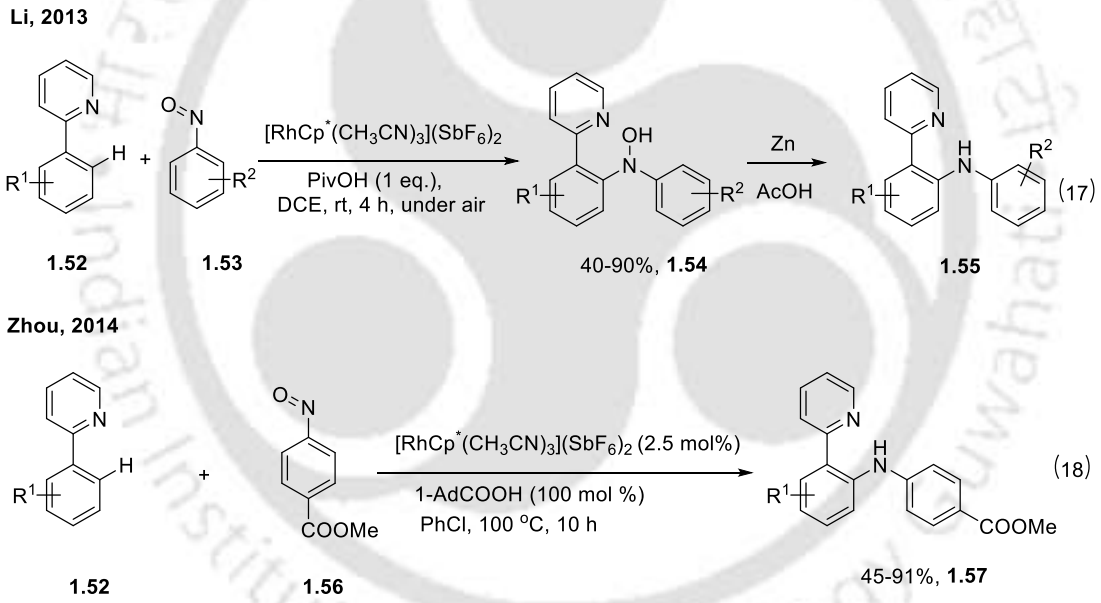


Scheme 11: Selected examples of [2+2]-cycloaddition reaction of nitrosoarene.

1.6 C-H amination using nitrosoarenes:

Various amination reactions have been developed using nitrosoarene as a source of aminating agent. There are few conventional reports on C(sp^2)-H amination involving nitrosoarene where nitroso group becomes amine source and sometimes in their potential application arene moiety is sacrificed after the reaction.

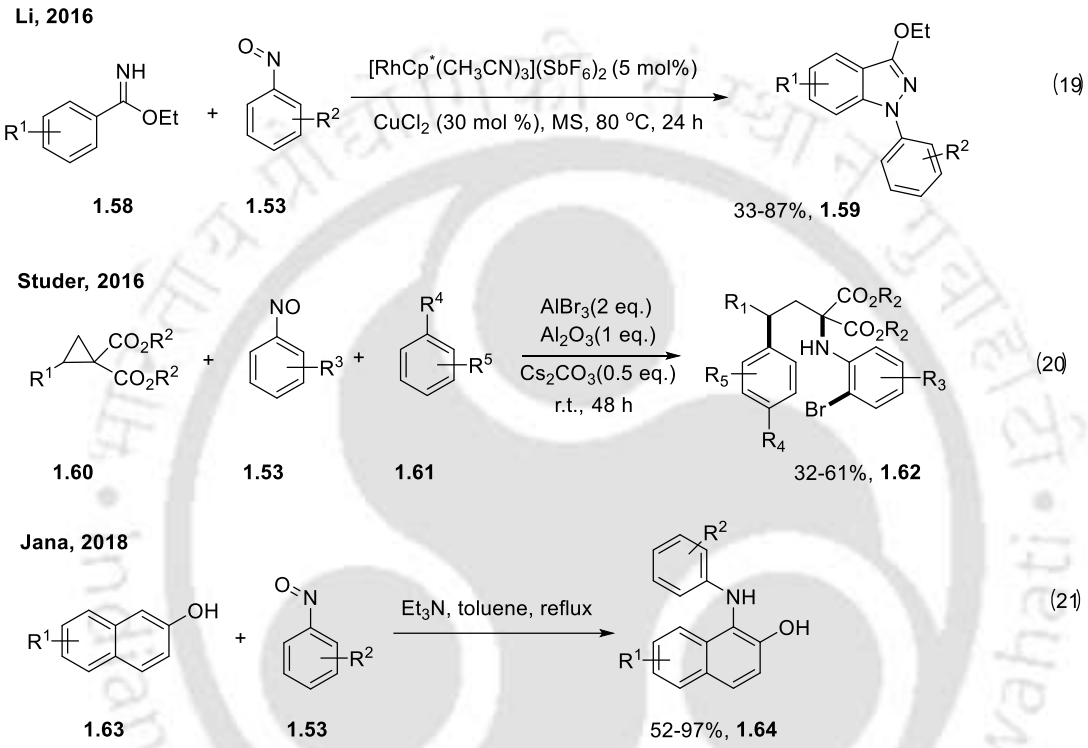
In 2013, Li *et al.* developed an unprecedented rhodium-catalyzed aryl C-H amination using nitrosoarene **1.53** and aryl substituted pyridine **1.52** to obtain synthetically important *N*-arylhydroxylamines **1.54**. Reduction of **1.54** with Zn/AcOH provided the valuable diarylamine **1.55** (**Scheme 12**, eq. 17).[31] In the next year the Zhou *et al.* reported a standard protocol of aryl C-H amination followed by *in situ* cleavage of the resulting hydroxylamines to access versatile diarylamines **1.57** (**Scheme 12**, eq. 18).[32]



Scheme 12: C-H amination using nitrosoarenes.

In 2016, Li *et al.* introduced a rhodium and copper catalyzed efficient synthesis of 1*H*-indazoles **1.59** through C-H activation and C-N, N-N bond formation using nitrosoarene **1.53** and the imine derivative **1.58** (**Scheme 13**, eq 19).[33] In 2016, Studer *et al.* presented $AlBr_3$-mediated multicomponent 1,3-bifunctionalization of donor−acceptor cyclopropanes **1.60** using arenes **1.61** and nitrosoarenes **1.53** as coupling partners (**Scheme 13**, eq 20).[34] In 2018, Jana *et al.* reported an unprecedented metal free arylamination reaction involving

nitrosoarenes **1.53** as the electrophilic aminating agents. The direct arylamination of naphthols **1.63** occurred to afford aminated product **1.64** (**Scheme 13**, eq 21). A broad range of other substrates, such as hydroxyquinolines, hydroxyquinones, coumarins and 1,3-cyclohexadienones could be aminated under operationally simple and mild conditions without the support of additional reagents for N–O bond reduction.[35]



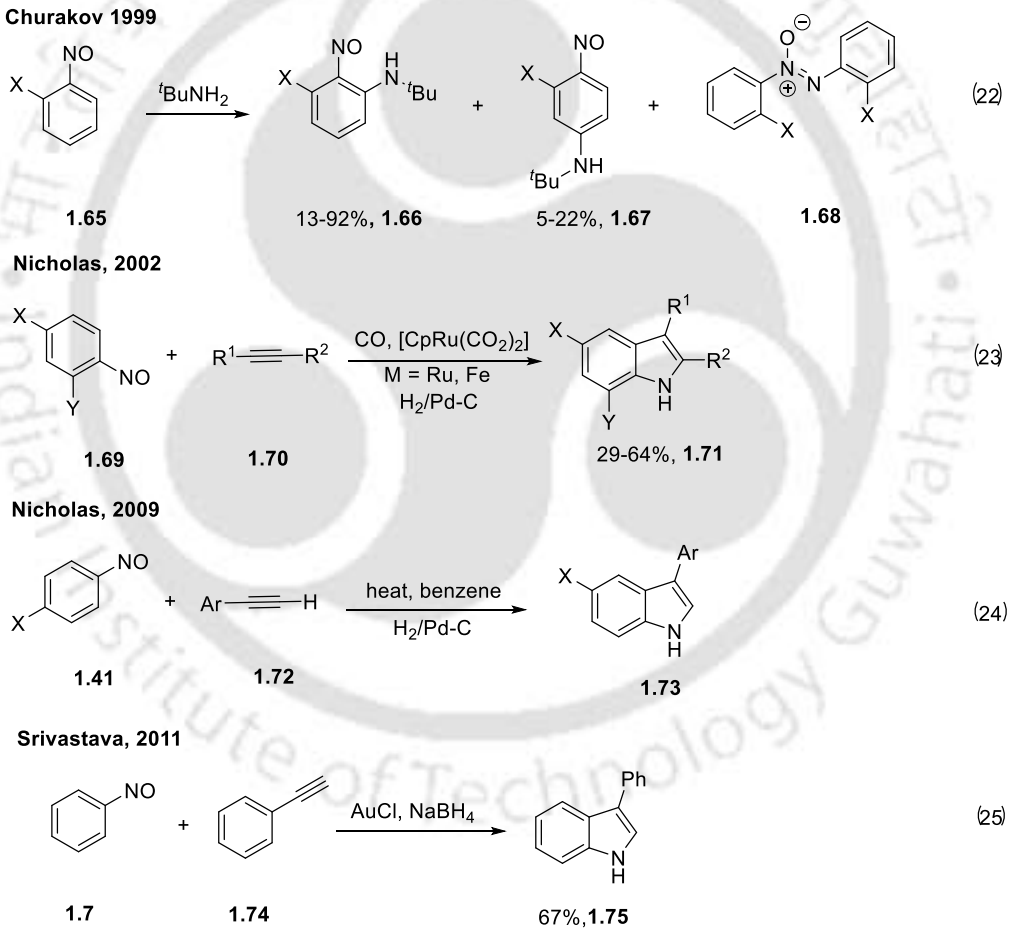
Scheme 13: C-H amination using nitrosoarenes.

1.7 C(sp^2)-H functionalization of nitrosoarene:

Nitrosoarenes, due to their availability and higher reactivity[36], are selected as starting materials for the various synthetic transformation. They are mostly used in pericyclic and aldol reactions. However, there are very fewer examples of aromatic functionalization of nitrosoarene.

In 1999, Churakov *et al.* described the reaction of primary amines bearing tertiary alkyl groups (*e.g.*, R–NH_2; R = ^{t}Bu, 1-adamantyl) with nitrosoarenes **1.65** to afford *N*-(*tert*-alkyl)-*ortho*- nitrosoanilines **1.66** and *para*-nitrosoanilines **1.67**. The replacement of hydrogen proceeds more rapidly than the replacement of *ortho*- or *para*-nitro or -bromo substituents

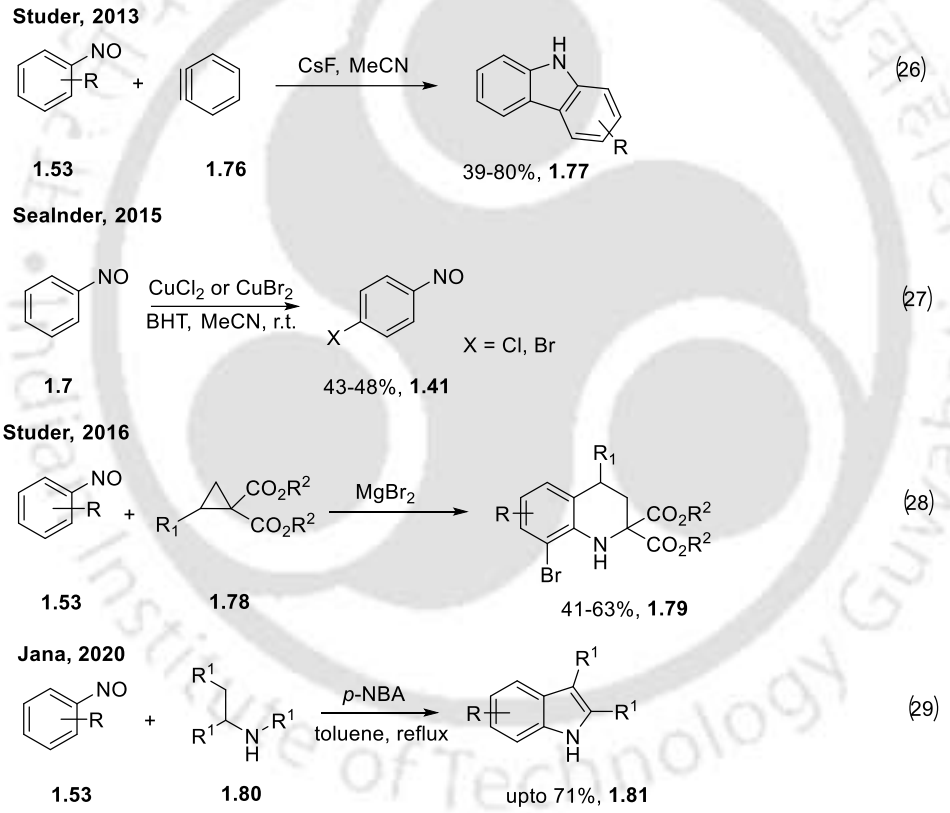
(**Scheme 14**, eq. 22).[37] In 2002, Nicholas *et al.* discovered a [Cp*Ru(CO)$_2$]$_2$-catalyzed novel annulation reaction to provide a direct and regioselective route to indoles **1.71** from nitrosoarenes **1.69** with alkynes **1.70** using carbon monoxide (**Scheme 14**, eq. 23).[38] In 2009, same group developed a thermal reaction between nitrosoarenes **1.41** and alkynes **1.72** to produce *N*-hydroxyindoles as the major products which upon treatment with Pd/C resulted indole derivative **1.73**. The mechanism of these novel reactions has been proved using a combination of experimental and computational methods (**Scheme 14**, eq. 24).[39] Srivastava *et al.* in 2011, developed an Au-catalyzed annulation reaction to produce substituted 3-arylindoles **1.75** from nitrosobenzene **1.7** with aryl-substituted acetylenes **1.74** under reductive conditions using sodium borohydride (**Scheme 14**, eq. 25).[40]



Scheme 14: C(sp^2)-H functionalization of nitrosoarenes.

In 2013, Studer *et al.* reported a novel method for the synthesis of carbazoles. Nitrosoarenes **1.53** and *in situ* generated aryne **1.76** reacted in the absence of any transition metal to provide the corresponding carbazoles **1.77** (**Scheme 15**, eq. 26).[41] In 2015, Selander *et al.* developed

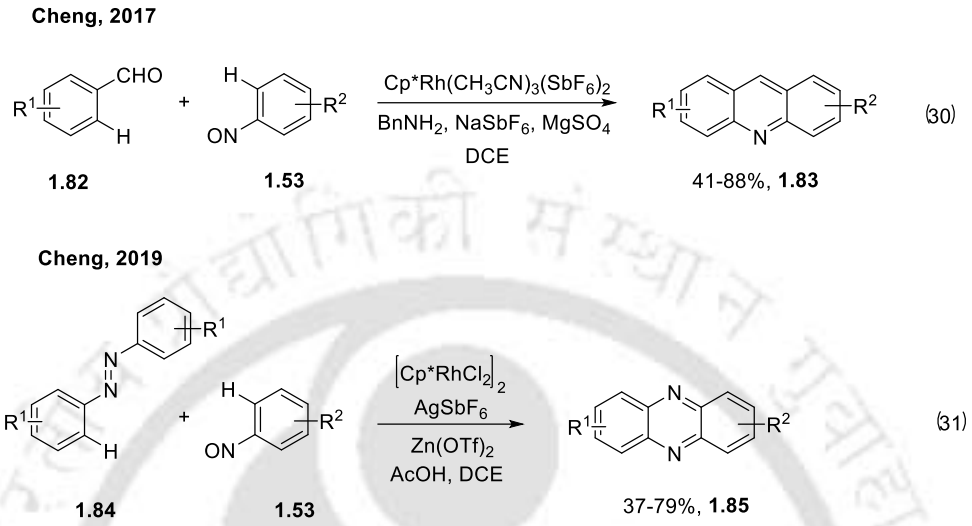
the *para*-selective direct bromination and chlorination of nitrosobenzene **1.7** with copper (II) bromide and chloride. Under mild reaction conditions, a range of halogenated arylnitroso compounds **1.41** are obtained in moderate to good yields with high regioselectivity (**Scheme 15**, eq. 27).[42] Studer *et al.*, in 2016, developed a stereospecific [3 + 3]-annulation of donor−acceptor cyclopropanes **1.78** with nitrosoarenes **1.53**. The method offers a novel approach to various structurally diverse C-8-brominated tetrahydroquinolines **1.79** (**Scheme 15**, eq. 28).[43] Most recently, in 2020, Jana *et al.* reported an acid mediated annulation reaction of aliphatic amines **1.80** and nitrosoarenes **1.53** to provide indole derivatives **1.81** under metal free conditions (**Scheme 15**, eq. 29). This conceptually novel method for indole synthesis does not require pre-functionalization steps for the new C–C and C–N bond formation.[44]



Scheme 15: C(sp^2)-H functionalization of nitrosoarenes.

Cheng *et al.*, in 2017, developed a Rh(III)-catalyzed bilateral cyclization for the efficient construction of acridines **1.83** (**Scheme 16**, eq. 30). In this transformation, a sequential Rh(III)-catalyzed C–H amination, cyclization, and aromatization processes were involved.[45]

Same group in 2019, described a rhodium-catalyzed annulation reaction between azobenzene **1.84** and nitrosoarenes **1.53**, leading to a series of phenazines **1.85** in moderate to good yields (**Scheme 16**, eq. 31). During this transformation, the azo group served as not only a traceless directing group but also a building block in the final products.[46]



Scheme 16: C(sp^2)-H functionalization of nitrosoarenes.

1.8 Conclusion:

Over the years diverse reactivity of nitrosoarenes have been developed in the different field of synthetic chemistry. Nitroso Diels-Alder, ene reaction, aldol, pericyclic, amination, annulation reactions *etc.* are conventional reactions of nitrosoarene known from the last few decades. Metal catalyzed nitroso-aldol reaction to synthesize *N*-nitroso or *O*-nitroso product have been widely used. On the other hand, the nitroso ene reaction is known to be a mild and selective process for the direct allylic nitrogen functionalization of alkenes. The metal free approach is a potentially useful for the synthesis of allylic amines, hydroxylamines *etc*. Regio- and enantioselective nitroso Diels-Alder-cycloaddition has been explored to synthesize bicyclic systems. Apart from that metal catalyzed cycloaddition of donor-acceptor cyclopropanes with nitrosoarenes have been discovered over the last few years. Moreover, fewer examples on C(sp^2)-H amination to form new C-N bond involving nitrosobenzenes as an amine source has been reported in the literature. C-H functionalization of nitrosoarene is gradually becoming more interesting in the chemistry of C-nitroso compound. However, very few reports on C(sp^2)-H functionalization using nitrosoarene are known till date. Therefore, the central importance of this thesis is to develop novel synthetic methodologies for new C-

C/C-N bond formation with the aid of C(sp^2)-H functionalization nitrosoarene under operationally simple conditions.

1.9 References:

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CHAPTER - 2

Metal-Free Sequential C(sp^2)−H and C(sp^3)−H Aminations of Nitrosoarenes and N-Heterocycles to Ring-Fused Imidazoles

2.1 Introduction:

Benzimidazoles are privileged moiety which are present in many bioactive molecules including natural products.[1] Imidazole derivatives exhibit a wide range of pharmacological activities including anti-fungal[2], anti-bacterial[3], anti-viral[4] activities *etc*. Particularly, ring-fused benzimidazole derivatives were identified as important pharmacophores for anticancer activity.[5, 10]

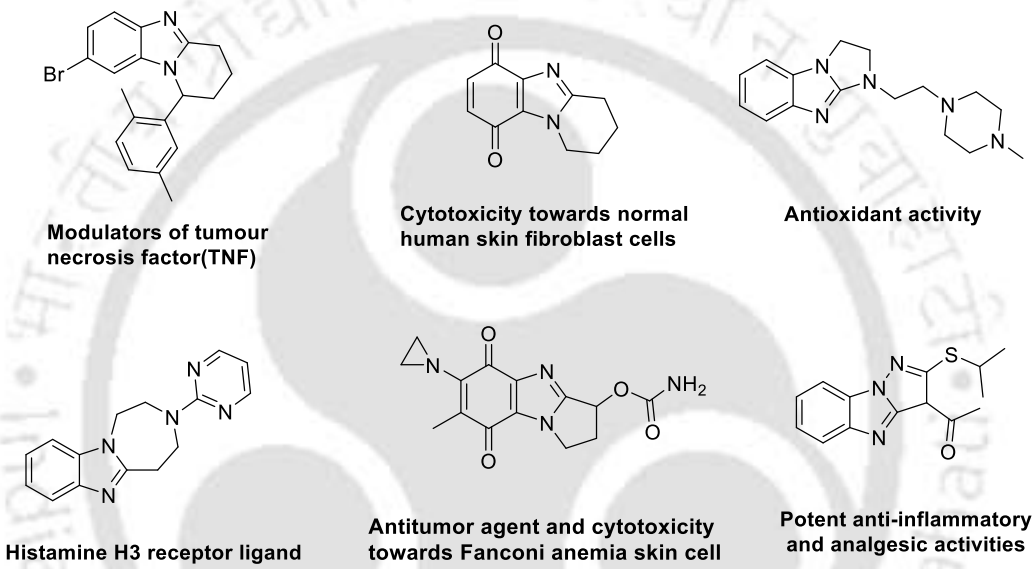


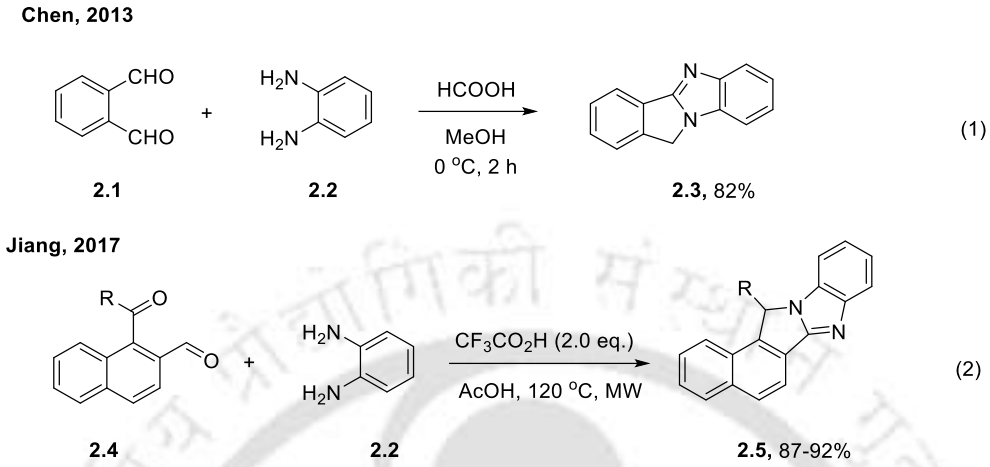
Figure 1: Biologically active ring fused imidazoles.

2.2 Known methods for the synthesis of ring-fused imidazoles:

The prevalent application of ring fused imidazole derivatives encouraged us to develop unique and well-organized methodologies for their synthesis. Several synthetic methodologies have been reported so far for the synthesis of ring-fused important scaffold.

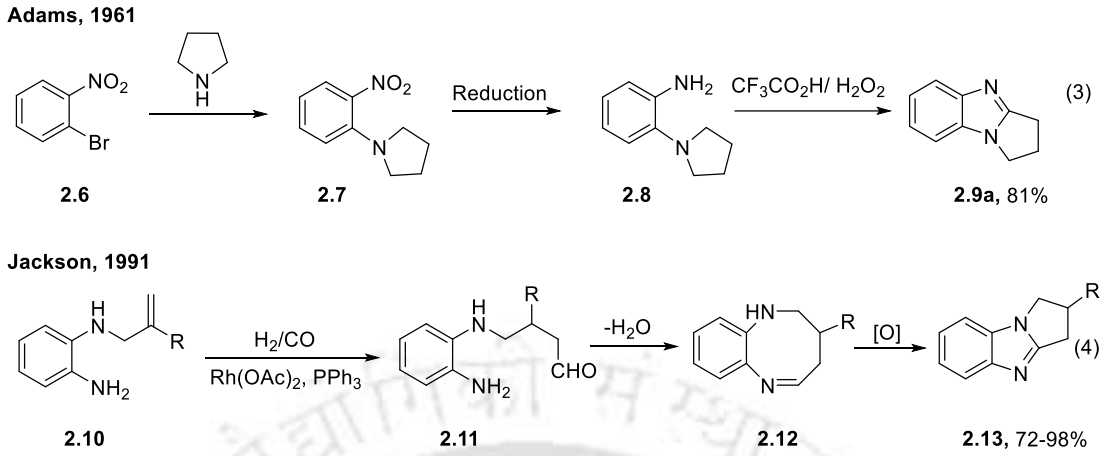
The traditional method for the synthesis of ring-fused imidazole is the redox condensation of *o*-phenylenediamines with 1,4-dialdehydes. In 2013, a metal-free acid-promoted coupling reaction between dialdehyde **2.1** and *o*-diaminobenzene **2.2** to benzo[4,5]imidazo[2,1-*a*]isoindole **2.3** (**Scheme 1**, eq. 1) was developed by Chen *et al*.[6] Later on in 2017, Jiang *et*

al. reported an acid-mediated condensation reaction of 1,4-dicarbonyl **2.4** and *o*-diaminobenzene **2.2** to obtain benzo[*e*]benzo[4,5]imidazo[2,1-*a*]isoindoles **2.5** (**Scheme 1**, eq. 2).[7]



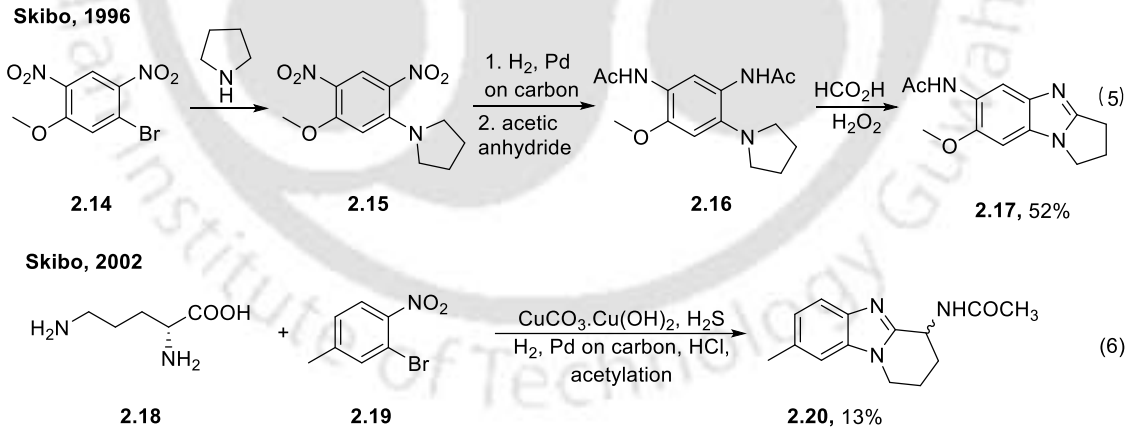
Scheme 1: Synthesis of ring fused imidazole *via* condensation reaction.

Other approaches for the synthesis of ring fused imidazoles mostly depend on different oxidative and dehydrogenative cyclizations. In 1961, Adam *et al.* discovered a multistep strategy for the synthesis of fused benzimidazoles with various heterocyclic secondary amines as nucleophiles. Substitution reaction of *o*-nitrobromobenzene **2.6** with pyrrolidine resulted the corresponding *o*-aminonitrobenzene **2.7** which was reduced to afford corresponding aromatic amine **2.8**. Peroxytrifluoroacetic acid promoted oxidative cyclization of the aromatic amine **2.8** provided fused imidazole ring **2.9a** (**Scheme 2**, eq. 3).[8] In 1991, Jackson *et al.* performed a rhodium catalyzed reaction for the synthesis of fused benzimidazoles. *N*-alkenyl-1,2-diaminobenzene **2.10** was reacted with hydrogen and carbon monoxide in the presence of $[Rh(OAc)_2]$, PPh_3 to achieve substituted amine **2.11**. Condensation of **2.11** provided cyclized product **2.12** which on oxidation provided the fused benzimidazole **2.13** (**Scheme 2**, eq. 4).[9]



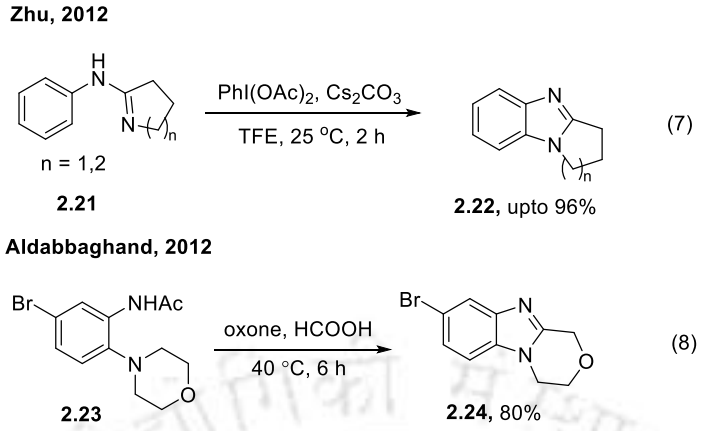
Scheme 2: Multistep synthesis of benzimidazoles.

In 1996, Skibo *et al.* developed similar substitution reaction between dinitrophenyl derivative **2.14** and pyrrolidine to afford **2.15** which upon reduction and acetylation resulted anilines derivative **2.16**. Acid catalysed annulation of **2.16** resulted fused imidazole **2.17** (**Scheme 3**, eq. 5).[10] Later in 2002, same group discovered copper mediated annulation reaction to obtain fused imidazole **2.20** starting from amino acid **2.18** and substituted nitrobenzene **2.19** (**Scheme 3**, eq. 6).[11]



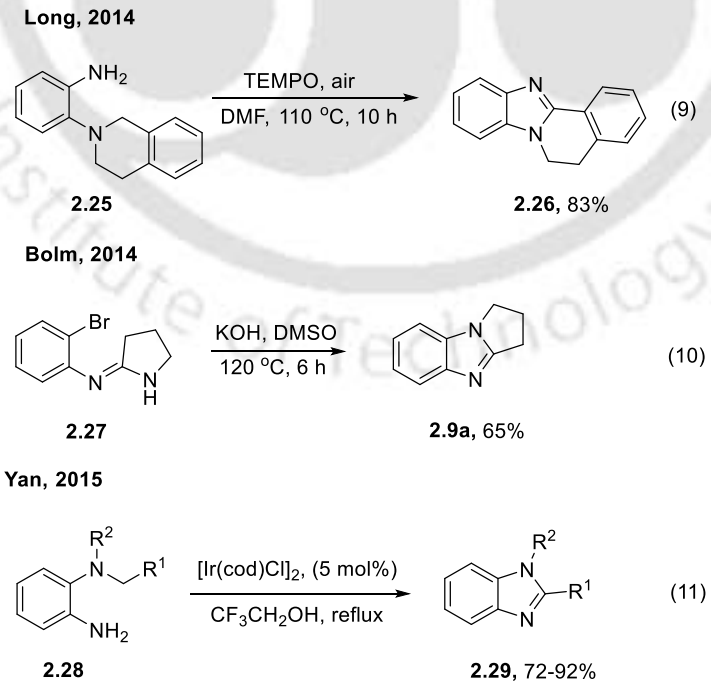
Scheme 3: Synthesis of fused imidazoles by Skibo *et al.*

Zhu *et al.*, in 2012, reported $PhI(OAc)_2$-promoted intramolecular oxidative imidation reaction of aromatic C-H bond of *N*-arylamidines **2.21** to obtain fused benzimidazole **2.22** (**Scheme 4**, eq. 7).[12] In the same year, Aldabbaghand *et al.* disclosed an oxidative cyclization of *o-tert*-amino acetanilide **2.23** using oxone in 90% formic acid to obtain ring-fused benzimidazole **2.24** (**Scheme 4**, eq. 8).[13]



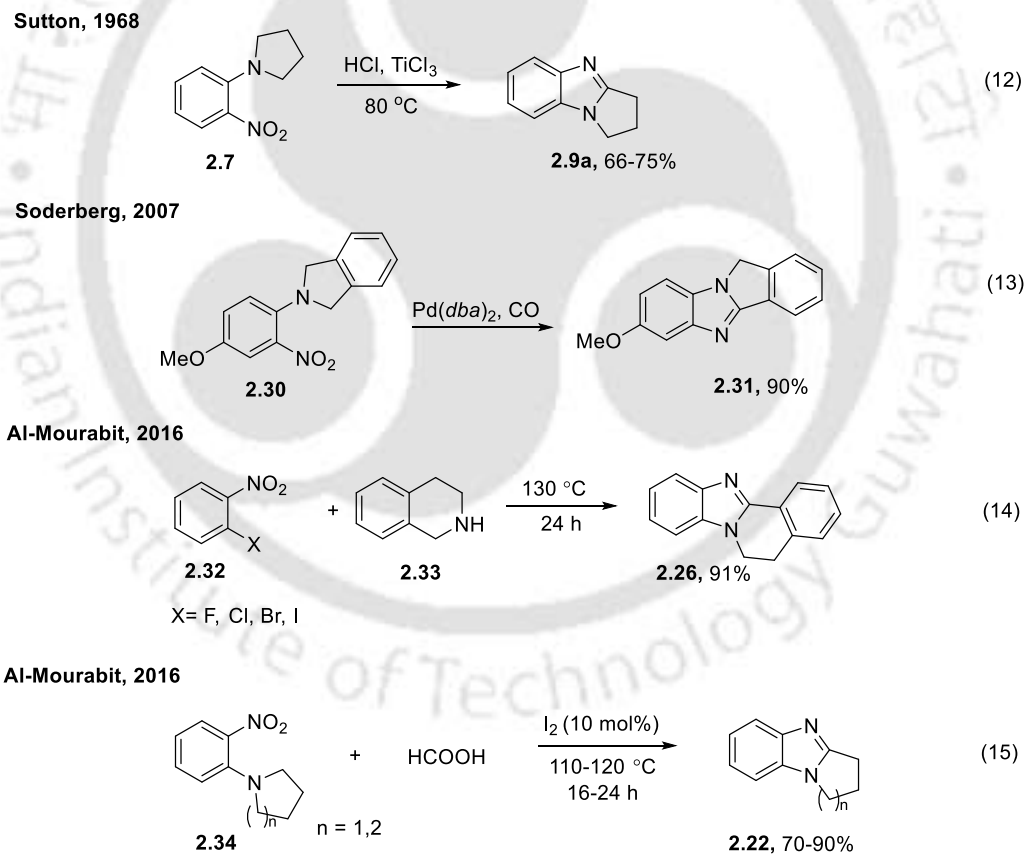
Scheme 4: Imidazole synthesis *via* metal free annulation reaction of substituted amines.

In 2014, Long *et al.* revealed a TEMPO promoted oxidative cyclization reaction to synthesize ring fused benzimidazoles. Oxidative C−N coupling between the C(sp^3)−H and free N−H of amine **2.25** afforded the targeted product **2.26** (**Scheme 5**, eq. 9).[14] In the same year, Bolm *et al.* reported intramolecular *N*-arylations of amidines **2.27** to imidazoles **2.9a** using potassium hydroxide in DMSO at 120 °C (**Scheme 5**, eq. 10).[15] Yan *et al.*, in 2015, disclosed Iridium-catalyzed intramolecular dehydrogenative coupling of tertiary amines **2.28** to afford fused benzimidazole **2.29** (**Scheme 5**, eq. 11).[16]



Scheme 5: Synthesis of imidazole through annulation reaction.

Earlier in 1968, Sutton *et al.* have developed a $TiCl_3$ mediated reductive cyclization reaction of *N*-2-nitrophenyl-heterocycles **2.7** to access fused benzimidazole **2.9a** using (**Scheme 6**, eq. 12).[17] Soderberg *et al*, in 2007, discovered a palladium-catalyzed reductive *N*-hetero-annulation of substituted-nitrobenzenamine **2.30**, using Pd(*dba*)$_2$ and carbon monoxide as the ultimate reducing agent to afford 2-substituted benzimidazoles **2.31** (**Scheme 6**, eq. 13).[18] Al-Mourbit *et al.* developed a protocol for the synthesis of fused imidazoles **2.26** *via* redox condensation of *o*-halonitrobenzene **2.32** with 1,2,3,4-tetrahydroisoquinoline **2.33** under solvent-free conditions (**Scheme 6**, eq. 14).[19] Later on , the same group developed a molecular iodine catalyzed approach for the synthesis of fused benzimidazoles **2.22** *via* reductive redox cyclization of *o*-nitro-*tert*-anilines **2.34** using formic acid as the hydrogen source (**Scheme 6**, eq. 15).[20]



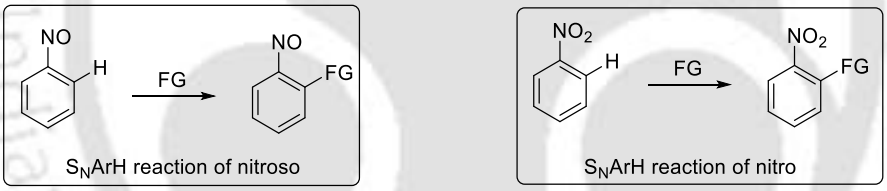
Scheme 6: Synthesis of ring fused imidazoles using substituted nitrobenzene.

2.3 Drawback of the known methods:

Syntheses of this valuable scaffold mainly relied on a multistep reaction sequence. The significant disadvantage of the known methods arises from the use of hazardous organic or metallic oxidants, reductants, and involvement of a multistep reaction sequence. In the context of the applicability, the syntheses of these important pharmacophores *via* direct annulation of nitrosoarenes with *N*-heterocycles under conditions free of metal and hazardous reagents would be advantageous as compared to the known protocols.

2.4 Hypothesis:

Arylnitroso compounds are versatile C-N building blocks that can undergo broad range of transformations.[21,22] In previous chapter the diverse reactivities of nitrosoarenes are discussed. In addition to that, the reactivity of nitrosoarene towards nucleophiles is different with the variation of reaction conditions.[22] Along the lines of the ongoing research for the development of novel C−H functionalization strategy, the possibility of direct C(sp^2)−H functionalization of a nitrosoarene was investigated.



Scheme 7: Electrophilicity comparison between nitro and nitroso compounds

S_NArH reactions of nitroarenes, which involve nucleophilic addition to the arene as the key step using C, N, O, and P nucleophiles, were well studied.[23a-d] Therefore, the Fukui electrophilicity indices of nitrobenzene and nitrosobenzene was compared to check the feasibility of S_NArH reactions of nitrosoarenes. Fukui indices are reactivity parameter that provide the information about which atoms or groups in a molecule have a higher tendency to accept or loose an electron during the reaction. According to that basis, the molecules can be interpreted as more prone to undergo a nucleophilic or an electrophilic attack, respectively.[23e] Fukui Electrophilicity indices (f_A^+) of an atom A in molecule having N electrons is computed according to the following equation:

$$f_A^+ = P_A^{(N+1)} - P_A^{(N)}$$

Population of an atom A ($P_A^{(N)}$) of a molecule having N electrons is obtained from the NBO (Natural Bond Orbital) analysis using DFT (B3LYP/6-31+ G(d)) calculation. Population of the same atom A ($P_A^{(N+1)}$) of the same molecule having (N+1) electrons is determined (without further optimization) similarly.

Electrophilicity indices revealed that nitrosobenzene, which has higher or analogous values of f+ as compared to nitrobenzene, could be a potential electrophile in the S_NArH reaction (**Figure 2**).

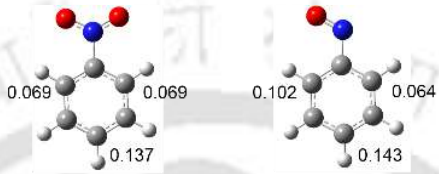
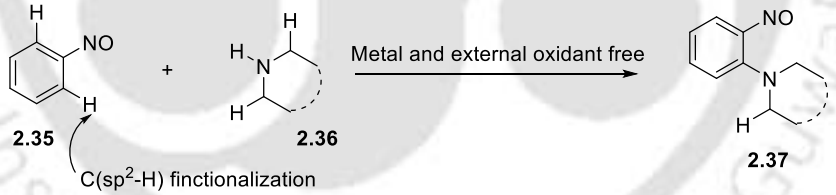


Figure 2: Fukui electrophilicity indices of nitrobenzene and nitrosobenzene

Therefore, it was anticipated that C(sp²)−H functionalization of nitrosoarene can be achieved *via* S_NArH reaction.

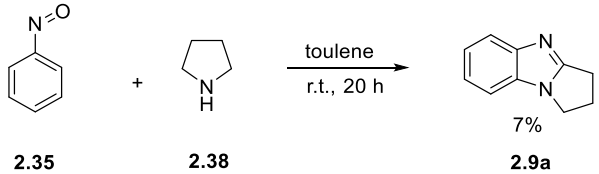
With the literature reports and the theoretical studies, it was anticipated that C-H functionalization of nitrsoarenes can be possible *via* secondary amines as a source of nucleophiles (**Scheme 8**).



Scheme 8: Hypothesis of C(sp²)-H functionalization of nitrosoarene.

2.5 Preliminary Result:

To test the hypothesis, nitrosobenzene was reacted with pyrrolidine in toluene at room temperature. Surprisingly, a ring-fused benzimidazole **2.9a** was formed with 7% yield **(Scheme 9)**.[24]

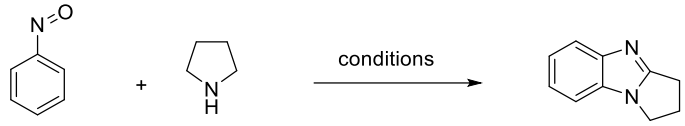


Scheme 9: Preliminary result.

2.6 Optimization of reaction conditions:

Encouraged by the initial result, several reaction conditions were screened for the improvement of the yield of benzimidazole **2.9a**.

Table 1: Optimization of the reaction conditions



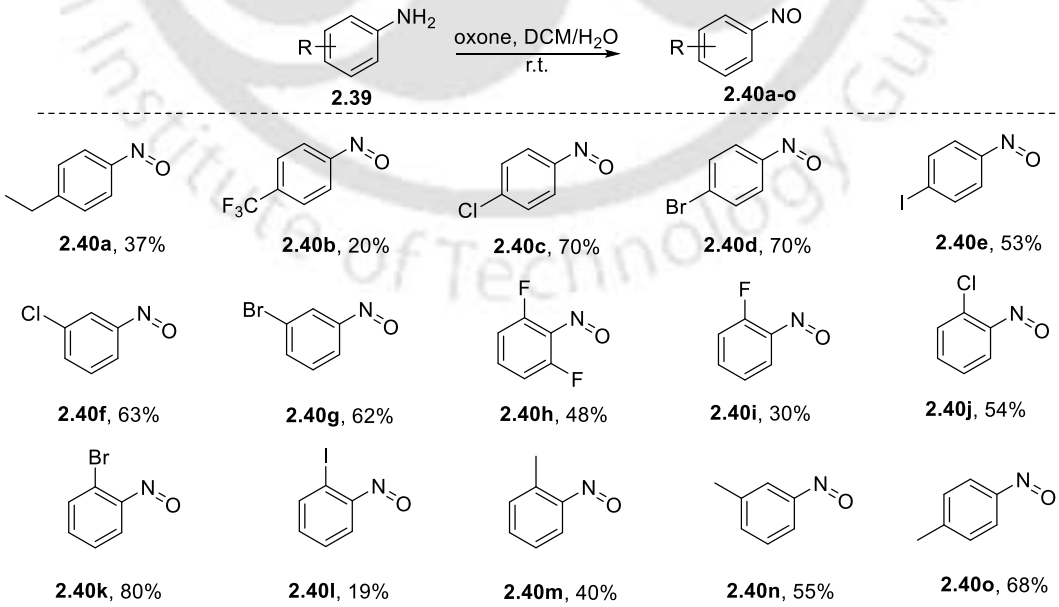
Entry	Pyrrolidine	Additives (eq.)	Solvent	Temperature	Time	Yield (%)
1	1	-	Toluene	r.t	20 h	7
2	4	-	Toluene	r.t	20 h	19
3	4	DCBA (0.6)	Toluene	r.t	12 h	36
4	4	DCBA (0.6)	Toluene	r.t	95 h	53
5	4	DCBA (0.6)	Toluene	50 °C	95 h	58
6	4	DCBA (0.6)	Toluene	110 °C	8 h	69
7	2	DCBA (0.6)	Toluene	110 °C	12 h	41
8	4	DCBA (0.6)	Toluene	110 °C	6 h	65
9	4	DCBA (0.6)	Toluene	110 °C	4 h	48
10	4	DCBA (0.6)	Toluene	110 °C	12 h	66
11	4	DCBA (1)	Toluene	110 °C	12 h	50
12	4	DCBA (0.2)	Toluene	110 °C	12 h	45
13	4	DCBA (0.6)	Toluene	110 °C (μw)	0.5 h	60
14	4	AcOH (0.6)	Toluene	110 °C	8 h	50
15	4	p-TSA (0.6)	Toluene	110 °C	8 h	14
16	4	DNBA (0.6)	Toluene	110 °C	8 h	62
17	4	H_3PO_4 (0.6)	Toluene	110 °C	8 h	44
18	4	DCBA (0.6)	Xylene	140 °C	8 h	47
19	4	DCBA (0.6)	Dioxane	101 °C	8 h	10
20[a]	4	DCBA (0.6)	Toluene	110 °C	12 h	Trace

All reactions were carried out with nitrosobenzene (0.47 mmol, 1 eq.) in solvent (4 mL). DCBA = 2,4-dichlorobenzoic acid. DNBA = 3,5-dinitrobenzoic acid. [a]reaction was carried out in the presence of O_2 bubbling.

The yield of the ring fused imidazole was slightly improved on increasing the relative stoichiometry of pyrrolidine (**Table 1**, entry 2). Further improvement in the yield was observed using 2,4-dichlorobenzoic (**Table 1**, entry 3). The yield of the benzimidazole **2.9a** was increased by increasing the reaction time and temperature (**Table 1**, entry 4, 5). However, best result was obtained when the reaction was performed in refluxing toluene for 8 h (**Table 1**, entry 6). Performing the reaction with less equivalency of pyrrolidine provided lower yield of the desired product (**Table 1**, entry 7). Further variation in reaction time did not affect the yield of the desired product (**Table 1**, entries 8 -10). Decrease in yield was observed with higher loading (**Table 1**, entry 11) as well as lower concentration (**Table 1**, entry 12) of additives. The better yield of the reaction was not found for the reaction performed under microwave irradiation (**Table 1**, entry 13). The presence of different acids *i.e.*, acetic acid (**Table 1**, entry 14), *p*-toluene sulphonic acid (**Table 1**, entry 15), 2,4-dinitro benzoic acid (**Table 1**, entry 16), *o*-phosphoric acid (**Table 1**, entry 17) lowered the formation of desired compound. Decrease in yield of the desired imidazole was observed in different other solvents *i.e.*, xylene (**Table 1**, entry 18), dioxane (**Table 1**, entry 19). Bubbling of oxygens in reaction medium provided trace amount of the desired product (**Table 1**, entry 20).

2.7 Scope of nitrosoarenes:

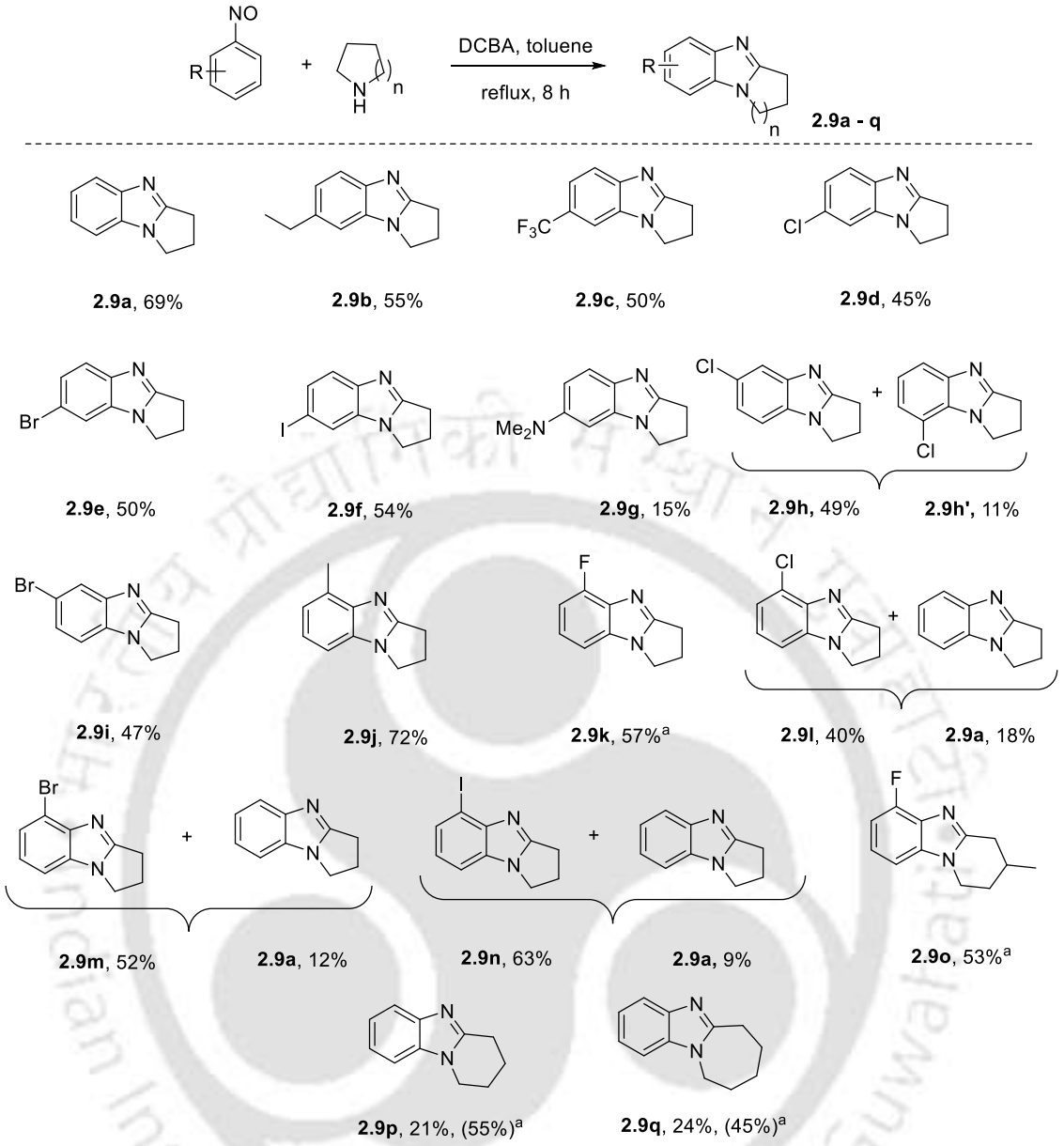
To explore the scope of the reaction, a series of nitroso compounds were readily prepared by the reaction of corresponding aniline with oxone in presence of DCM/H_2O as solvent at room temperature (**Scheme 10**).



Scheme 10: Preparation of aromatic nitroso compounds.

2.8 Scope of successive C(sp^2)-H / C(sp^3)-H amination with various nitroso compounds and cyclic secondary amines:

The optimized conditions were then used to check the scope of the reaction. Various nitrosoarenes **2.40a - m** containing different substituents were reacted with pyrrolidine to obtain the corresponding benzimidazoles **2.9a - q** with good yields (**Scheme 11**). Both electron-donating and -withdrawing substituents in the nitrosoarenes were tolerated in the reactions. The yield of imidazole derivative **2.9g** significantly reduced due to the presence of strongly electron-donating dimethyl-amino substituents. Regioisomeric products **2.9h** and **2.9h'** were obtained from the reaction of *m*-chloronitrosobenzene. C(sp^2)−H aminations para to the chloro substituent were preferred over the ortho-position to provide *p*-substituted products **2.9h** as the major isomers. In a reaction of *o*-fluoronitrosobenzene with pyrrolidine, classical nucleophilic aromatic substitution (S_NAr) followed by amine C−H functionalization occurred to provide **2.9a** in 79% yield. To my surprise, in cases of other *o*-halo-nitrosobenzenes, halogenated imidazoles **2.9l - n** were obtained as the major products *via* domino C(sp^2)−H and C(sp^3)−H amination reactions. Interestingly, the yields of halogenated imidazoles **2.9l - n**, which were formed through C(sp^2)−H functionalization, decrease with the increase in the electronegativity of halogens. Consequently, it was also found that the yield of imidazole **2.9a** that is formed *via* S_NAr reaction increases with the electronegativity. The reactions of nitrosobenzene with other *N*-heterocycles such as piperidine and homopiperidine provided lower yields of the corresponding benzimidazoles **2.9p - 2.9q**. Nevertheless, satisfactory yields of those were obtained when the reactions were carried out with 2-fluoronitrosobenzene.



Scheme 11: Scope of successive C(sp^2)-H and C(sp^3)-H amination. [a] Yields of the imidazoles starting from corresponding *o*-fluoro-nitrosobenzene.

2.9 Crystal structures of ring fused imidazoles:

The structure of the imidazole derivative **2.9l** was confirmed by X-ray crystallographic analysis. The structure of the compound have given below (**Table 2**).

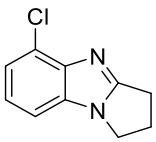
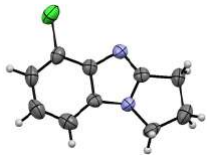
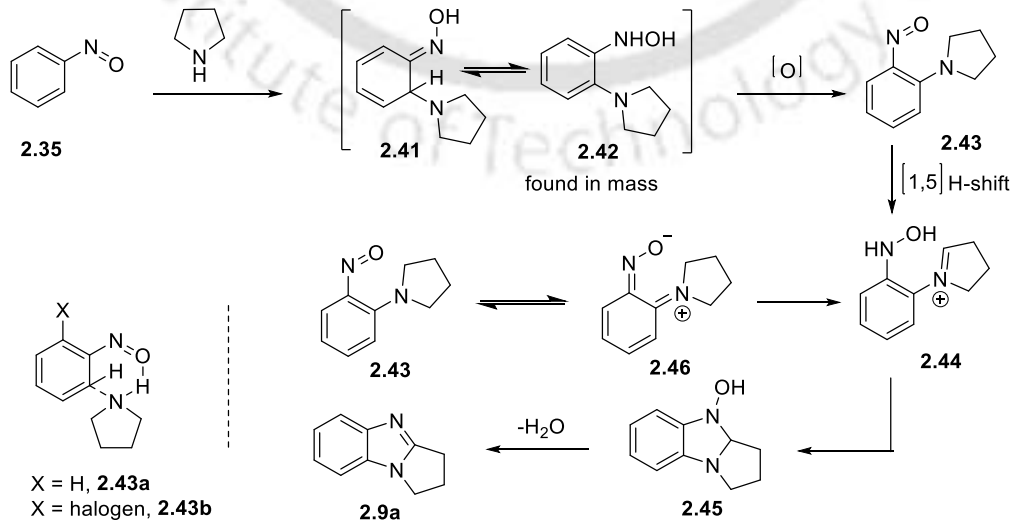
Compound	Crystal structure
 **2.9l**	

Table 2: X-ray crystal structure of ring fused imidazole.

2.10 Plausible mechanism:

A plausible mechanism for unprecedented domino C(sp^2)−H and C(sp^3)−H amination reaction is presented in **Scheme 12**. Nucleophilic addition of pyrrolidine to nitrosobenzene occurred in the first step. The oxidation of resulting intermediate **2.41** and/or **2.42** could lead to corresponding 2-amino nitrosoarene **2.43**.[25] Amino nitroso derivative **2.43** then readily undertook a 1,5-hydride shift to provide the iminium ion **2.44**.[26] A similar 1,5-*H* shift was reported for a related reaction involving an amino aldehyde corresponding to **2.43**.[26o] Alternatively, the iminium ion **2.44** could also be produced through deprotonation and consequent mesomerization of the corresponding isomeric iminium ion **2.46**, which resulted from **2.43**. Annulation of **2.44** followed by acid mediated dehydration of resulting *N*-hydroxy derivative **2.45** provided the desired imidazole **2.9a**. Amino phenylhydroxylamine **2.42** was detected through mass spectrometry. Further, the thermal/aerial oxidation of arylhydroxylamine to the corresponding nitroso compound is known to be facile.[25] These support the intermediacy of **2.42** and **2.43** in the reaction.



Scheme 12: Proposed mechanism for the annulation of nitrosoarene and secondary cyclic amines.

The preference of the S_NArH reaction at the *para*-carbon of nitrosobenzene would be expected because it has the highest Fukui electrophilicity coefficient value at that carbon (**Figure 2**). However, the substitution reaction occurred selectively at the *ortho*-position probably due to the hydrogen bond assisted directing effect of the nitroso group as shown in **2.43a** (**Scheme 12**). This hypothesis was supported by DFT studies.[27] The transition state for *ortho*-substitution (**TS** in **Figures 3**) in the S_NArH reaction between nitrosobenzene and pyrrolidine is obtained with an activation barrier of 18.23 kcal/mol. However, all attempts to obtain transition states for substitution at the *para*-position of nitrosobenzene remained unsuccessful. The presence of an intramolecular hydrogen bond (O···H = 1.925 Å) between the nitroso-oxygen and amine-hydrogen having a stable six-membered cyclic structure is evident from the optimized transition state geometry (**Figure 3, TS**).

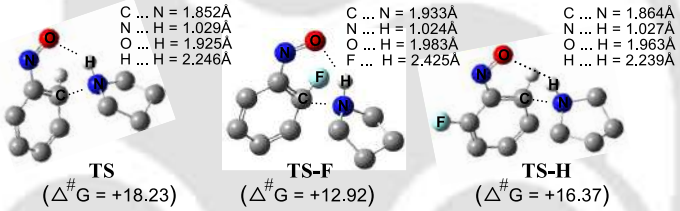
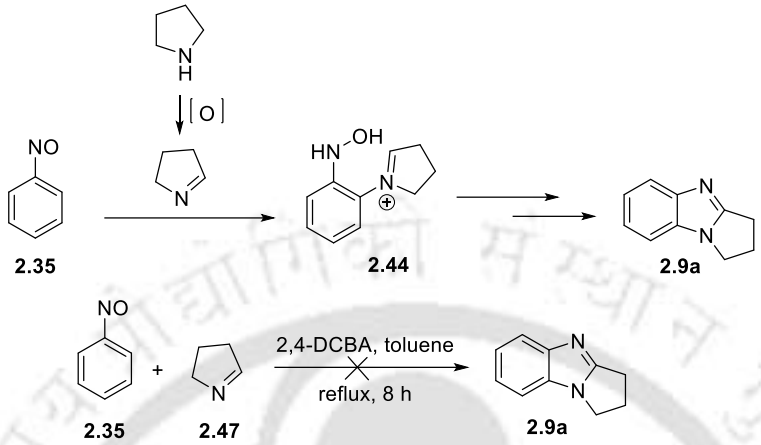


Figure 3. Optimized geometries of transition states and corresponding calculated activation barriers (in kcal/mol).

Except for 2-fluoronitrosobenzene, S_NArH was preferred over conventional S_NAr in the reaction of *o*-halo-nitrosobenzene. This is probably due to the H-bond aided nucleophilic attack as shown in the preferred conformation **2.43b**[28] (**Scheme 12**) where bulky halogens remain away from the nitroso to avoid unfavourable steric interaction. This is presumably the cause of the increase in the experimental yields of imidazoles (**2.9l** → **2.9m** → **2.9n**) with increasing sizes of the halogens (Cl → Br → I) in *o*-halonitrosobenzene. In contrast, fluorine that has comparable size with hydrogen and strong electron-withdrawing ability facilitates the nucleophilic addition at the carbon bearing a fluorine atom to exclusively provide imidazole **2.9a**. The calculated lower activation barrier for F-substitution (**TS-F**: 12.92 kcal/mol) as compared to H-substitution (**TS-H**: 16.37 kcal/mol) supported the experimental results on the exclusive formation of F-substituted products **2.9a** (**Figures 3**).

An alternative mechanistic possibility where pyrrolidine could be oxidized to pyrroline **2.47** which then can react with nitroso compound **2.35** to directly provide intermediate **2.44**

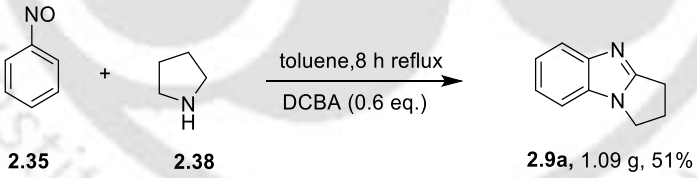
(**Scheme 13**) was considered. To examine this feasibility, pyrroline **2.47** was reacted separately with nitrosobenzene **2.35** under the standard reaction conditions. However, desired imidazole **2.9a** was not formed in the reaction, which eliminated the possibility of formation of imidazole involving pyrroline.



Scheme 13: Elimination of alternate mechanism.

2.11 Gram scale synthesis:

The desired benzimidazole **2.9a** can also be synthesized in gram scale following the standard procedure using nitrosobenzene **2.35**, pyrrolidine **2.38** and 2,4-DCBA in toluene refluxing conditions. The fused imidazole was obtained with 51% yield (**Scheme 14**).

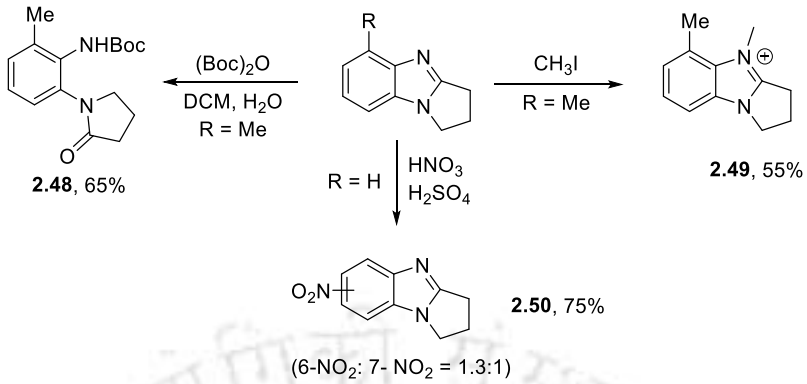


Scheme 14: Gram-scale synthesis.

2.12 Synthetic application:

Selected ring fused benzimidazoles were derivatized under different reaction conditions. *N*-methylation of benzimidazole **2.9j** was performed with methyl iodide to provide imidazolium iodide **2.49**. *N*-acylation of **2.9j** in the presence of di-*tert*-butyl dicarbonate followed by hydrolysis of resulting imidazolium salt led to the cleavage of C-N bond of imidazole ring to provide corresponding *o*-diamino arenes **2.48** with good yield. Nitro

imidazole derivative **2.50** was obtained from the reaction of **2.9a** in the nitrating mixture (1:1 HNO_3: H_2SO_4) with very good yield. (**Scheme 15**).



Scheme 15: Synthetic application of imidazole derivatives.

2.13 Conclusion:

In summary, a novel annulation reaction of nitrosoarene and aliphatic amines *via* an unprecedented sequential C(sp²)-H amination of nitrosoarene and *α*-C(sp³)-H amination of aliphatic amines without the aid of metallic reagent/catalyst and external oxidant has been developed. A wide variety of ring-fused benzimidazoles were easily prepared from readily available nitrosoarenes and *N*-heterocycles in a mild and simple operation. C(sp²)−H amination via S_NArH reaction of *o*-halo-nitrosoarene was favoured over conventional S_NAr to provide halogen (Cl, Br, I) containing products which are otherwise difficult to prepare. DFT studies revealed the involvement of H-bonding in controlling the *ortho*-selectivity of C(sp²)−H amination. The method was also applicable for gram-scale synthesis.

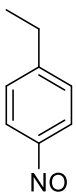
2.14 Experimental Section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus (V) oxide (P_2O_5). Commercial grade xylene, benzene and toluene were distilled over CaH_2 before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ^1H, ^{13}C NMR spectroscopy: *Varian Mercury plus 400 MHz, Bruker 600 MHz* (at 298 K). 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 ($CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.2 ppm; CD_3OD, (^1H) 3.31 ppm, δ (^{13}C) 49.0 ppm) were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity. IR: spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

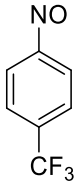
General procedure for synthesis nitroso compounds (GPI):

A solution of oxone (2 - 4 eq.) in (8 - 154 mL) water was added to a solution of aniline derivatives (1 eq.) in dichloromethane with vigorous stirring. The reaction mixture was stirred at room temperature under argon atmosphere for 30 min to 24 h. After disappearance of starting materials (indicated by TLC), the reaction was quenched by addition of saturated sodium bicarbonate solution (30 - 60 mL). The mixture was extracted with dichloromethane (3 X 20 mL). The combined organic layers were washed with 1(N) HCl (20 - 40 mL) then with brine solution (30 - 60 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was subjected to column chromatography (silica gel) to afford the analytically pure products.

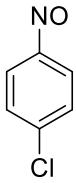
1-ethyl-4-nitrosobenzene (2.40a):[29] According to GP 1: 4-ethylaniline (1.5 mL, 12.07 mmol) in 15 mL of DCM, oxone (14.84 g, 48.28 mmol) in 70 mL of water were reacted for 0.5 h and column chromatography (silica gel; hexane) gave **2.40a** as green liquid (0.6 g, 37%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 2.74 (q, *J* = 7.8 Hz,2H), 1.31 - 1.28 (m, 3H) ppm.



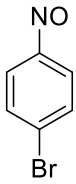
1-(trifluoromethyl)-4-nitrosobenzene (2.40b):[30] According to GP 1: 4-(trifluoromethyl)aniline (0.8 mL, 6.37 mmol) in 9 mL of DCM, oxone (5.87 g, 19.11 mmol) in 50 mL of water were reacted for 12 h and column chromatography (silica gel; hexane) gave **2.40b** as a yellow solid (0.22 g, 20%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.8 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H) ppm.



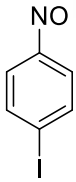
1-chloro-4-nitosobenzene (2.40c):[31] According to GP 1: 4-chloroaniline (0.63 g, 4.93 mmol) in 15 mL of DCM, oxone (3.04 g, 9.88 mmol) in 60 mL of water were reacted for 0.5 h and column chromatography (silica gel; hexane) gave **2.40c** as a yellow solid (0.49 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H) ppm.



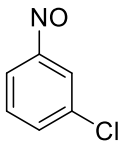
1-bromo-4-nitosobenzene (2.40d):[32] According to GP 1: 4-bromoaniline (0.5 g, 2.91 mmol) in 9 mL of DCM. oxone (1.79 g, 5.82 mmol) in 20 mL of water were reacted for 3.5 h and column chromatography (silica gel; hexane) gave **2.40d** as a yellow solid (0.38 g, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 (s, 4H) ppm.



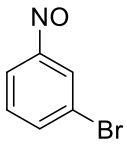
1-iodo-4-nitosobenzene (2.40e):[33] According to GP 1: 4-iodoaniline (0.5 g, 2.28 mmol) in 10 mL of DCM. oxone (1.40 g, 4.56 mmol) in 140 mL of water were reacted for 3.5 h and column chromatography (silica gel; hexane) gave **2.40e** as a green solid (0.28 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H) ppm.



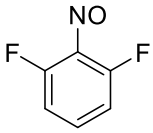
1-chloro-3-nitosobenzene (2.40f):[34] According to GP 1: 3-chloroaniline (0.8 mL, 7.56 mmol) in 33 mL of DCM, oxone (6.97 g, 22.68 mmol) in 22 mL of water were reacted for 4 h and column chromatography (silica gel; hexane) gave **2.40f** as a yellow solid (0.67 g, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.61 (s, 1H) ppm.



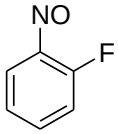
1-bromo-3-nitosobenzene (2.40g):[35] According to GP 1: 3-bromoaniline (0.3 mL, 2.76 mmol) in 14 mL of DCM, oxone (1.70 g, 5.52 mmol) in 27 mL of water were reacted for 5 h and column chromatography (silica gel; hexane) gave **2.40g** as a yellow solid (0.31 g, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 8.4 Hz, 1H), 7.85 - 7.83 (m, 1H), 7.77 (s, 1H), 7.58 - 7.56 (m, 1H) ppm.



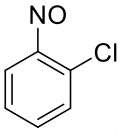
1,3-difluoro-2-nitrosobenzene (2.40h):[36] According to GP 1: 2,6-difluoroaniline (0.28 g, 2.16 mmol) in 7 mL of DCM, oxone (1.33 g, 4.33 mmol) in 8 mL of water were reacted for 15 h and column chromatography (silica gel; hexane) gave **2.40h** as a white solid (0.15 g, 48%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.65 - 7.60 (m, 1H), 7.16 - 7.11 (m, 2H) ppm.



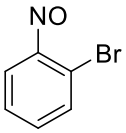
1-fluoro-2-nitosobenzene (2.40i):[37] According to GP 1: 2-fluroaniline (0.9 mL, 9.32 mmol) in 20 mL of DCM, oxone (11.0 g, 35.78 mmol) in 80 mL of water were reacted for 24 h with exclusion of light and column chromatography (silica gel; hexane) gave **2.40i** as a brown solid (0.35 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75 - 7.69 (m, 1H), 7.53 - 7.49 (m, 1H), 7.16 - 7.12 (m, 1H), 6.51 - 6.47 (m, 1H) ppm.



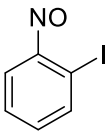
1-chloro-2-nitosobenzene (2.40j):[37] According to GP 1: 2-chloroaniline (0.5 mL, 4.75 mmol) in 10 mL of DCM, oxone (5.6 g, 18.24 mmol) in 40 mL of water were reacted for 24 h with exclusion of light and column chromatography (silica gel; hexane) gave **2.40j** as a light-yellow solid (0.36 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.0 Hz, 1H), 7.64 - 7.60 (m, 1H), 7.24 - 7.20 (m, 1H), 6.20 (d, *J* = 8.0 Hz, 1H) ppm.



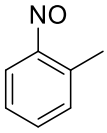
1-bromo-2-nitosobenzene (2.40k):[38] According to GP 1: 2-bromoaniline (0.6 mL, 5.30 mmol) in 12 mL of DCM, oxone (3.26 g, 10.60 mmol) in 50 mL of water were reacted for 24 h and column chromatography (silica gel; hexane) gave **2.40k** as a light-yellow solid (0.78 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.17 (d, *J* = 8.0 Hz, 1H) ppm.



1-iodo-2-nitosobenzene (2.40l):[39] According to GP 1: 2-iodoaniline (0.55 g, 2.51 mmol) in 7.5 mL of DCM, oxone (1.54 g, 5.02 mmol) in 154 mL of water were reacted for 2.5 h and column chromatography (silica gel; hexane) gave **2.40l** as a yellow solid (0.11 g, 19%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 7.8 Hz, 1H), 7.37 - 7.34 (m, 1H), 7.32 - 7.29 (m, 1H), 6.19 (d, *J* = 9.6 Hz, 1H) ppm.



1-methyl-2-nitrosobenzene (2.40m):[40] According to GP 1: o-toluidine (2.0 mL,18.67 mmol)

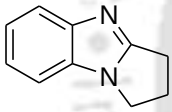


in 30 mL of DCM, oxone (9.25 g, 30.09 mmol) in 30 mL of water were reacted for 2 h and column chromatography (silica gel; hexane) gave **2.40m** as a yellow solid (0.90 g, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.60 - 7.57 (m, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.27 (d, *J* = 8.0 Hz, 1H), 3.34 (s, 3H) ppm.

General procedure for synthesis benzimidazole derivatives (GP II):

Freshly prepared nitrosoarenes (0.2 - 0.47 mmol) and 2,4-dichlorobenzoic acid (0.6 eq.) were successively added to a solution of secondary amines (4 eq.) in dry toluene (3 - 4 mL). The mixture was stirred at room temperature for 20 min. under argon atmosphere. Then the reaction mixture was refluxed for 8 - 24 h under argon atmosphere. Then the solvent was evaporated under reduced pressure and crude mixture was subjected to column chromatography (neutral alumina) to afford analytically pure products.

2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9a): According to GP II:

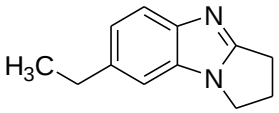


Nitrosobenzene (50 mg, 0.47 mmol), pyrrolidine (0.15 mL, 1.87 mmol) and 2,4-dichlorobenzoic acid (53 mg, 0.28 mmol) was reacted for 8 h in dry toluene (4 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9a** as white solid (51 mg, 69%). Under the same condition 2-fluoronitrosobenzene (35 mg, 0.28 mmol) gave **2.9a** (35 mg, 79 %). FTIR (KBr): $\tilde{\nu}$ = 2961, 2917, 2845, 1630, 1415, 1261, 1019, 802, 735 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 6.6 Hz, 1H), 7.29 (d, *J* = 6.0 Hz, 1H), 7.23 - 7.19 (m, 2H), 4.11 (t, *J* = 6.6 Hz, 2H), 3.08 - 3.05 (m, 2H), 2.74 - 2.69 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.3, 149.0, 132.6, 122.0, 121.9, 119.8, 109.7, 42.9, 26.3, 23.7 ppm. HRMS: Exact mass calculated for $C_{10}H_{11}N_2$ ($[M+H]^+$): 159.0917, Found: 159.0915.

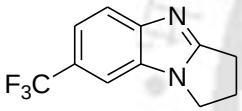
Gram-scale synthesis of 2.9a:

Nitrosobenzene (1.45 g, 13.54 mmol) and 2,4-dichlorobenzoic acid (1.55 g, 8.12 mmol) were successively added to a solution of pyrrolidine (4.5 mL, 54.15 mmol) in dry toluene (115 mL). The mixture was stirred at room temperature for 20 min. under argon atmosphere. Then the reaction mixture was refluxed for 8 h under argon atmosphere. Then the solvent was evaporated under reduced pressure and crude mixture was subjected to column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9a** as white solid (1.09 g, 51%).

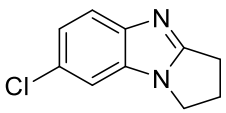
7-ethyl-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9b): According to GP 2: 1-ethyl-4-nitrosobenzene (50 mg, 0.37 mmol), pyrrolidine (0.12 mL, 1.48 mmol) and 2,4-dichlorobenzoic acid (42 mg, 0.22 mmol) was reacted for 8 h in dry toluene (4 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9b** as light yellow oil (38 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 2964, 2928, 2853, 1627, 1530, 1449, 1330, 1419, 1283, 1205, 816, 736, 644, 430 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.4 Hz, 1H), 7.12 (s, 1H), 7.07 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.10 - 4.07 (m, 2H), 3.06 - 3.02 (m, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.74 - 2.67 (m, 2H), 1.28 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 160.9, 147.3, 138.5, 132.8, 122.3, 119.3, 108.5, 42.8, 29.3, 26.3, 23.7, 16.5 ppm. HRMS: Exact mass calculated for $C_{12}H_{15}N_2$ ($[M+H]^+$): 187.1230, Found: 187.1228.



7-(trifluoromethyl)-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-*a*]imidazole (2.9c): According to GP 2: 1-(trifluoromethyl)-4-nitrosobenzene (50 mg, 0.29 mmol), pyrrolidine (0.10 mL, 1.16 mmol) and 2,4-dichlorobenzoic acid (33 mg, 0.17 mmol) were reacted for 8 h in dry toluene (4 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9c** as white solid (33 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 2956, 2917, 2854, 1637, 1461, 1384, 1317, 1264, 1106, 872, 667 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 4.18 (t, *J* = 7.2 Hz, 2H), 3.12 (t, *J* = 7.8 Hz, 2H), 2.80 - 2.75 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.0, 151.2, 132.0, 126.0, 124.4, 124.2, 120.0, 119.02, 118.99, 118.97, 118.95, 107.5, 43.3, 26.2, 23.9 ppm. HRMS: Exact mass calculated for $C_{11}H_{10}F_3N_2$ ($[M+H]^+$): 227.0791, Found: 227.0789.



7-chloro-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9d): According to GP 2: 1-chloro- 4-nitrosobenzene (30 mg, 0.21 mmol), pyrrolidine (70 µL ,0.85 mmol) and 2,4-dichlorobenzoic acid (25 mg ,0.13 mmol) were reacted for 8 h in dry toluene (3 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9d** as white solid (18 mg, 45%). FTIR (KBr): $\tilde{\nu}$ = 2962, 2924, 2853, 1611, 1449, 1384, 1262, 1022, 803, 668 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 9.0 Hz, 1H), 7.30 (s, 1H), 7.18 (dd, J_1= 9.0 Hz, J_2 = 1.8 Hz, 1H), 4.09 (t, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 7.8 Hz, 2H), 2.76 - 2.71 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.3,



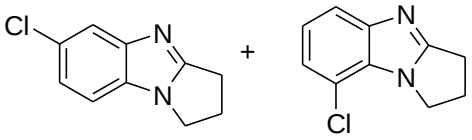
147.6, 133.1, 127.7, 122.5, 120.5, 109.9, 43.0, 26.3, 23.7 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}N_2Cl$ ([M+H]$^+$): 193.0527, Found: 193.0527.

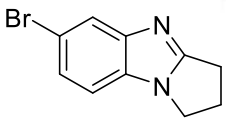
7-bromo-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9e): According to GP 2: 1-bromo-4-nitosobenzene (40 mg, 0.22 mmol), pyrrolidine (71 µL, 0.87 mmol) and 2,4-dichlorobenzoic acid (25 mg, 0.13 mmol) was reacted for 8 h in dry toluene (4 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9e** as white solid (26 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 2925, 2854, 1620, 1458, 1384, 1108, 874, 473 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 9.0 Hz, 1H), 7.45 (s, 1H), 7.32 (dd, *J*= 9.0, 1.8 Hz, 1H), 4.09 (t, *J* = 7.2 Hz, 2H), 3.07 - 3.05 (m, 2H), 2.75 - 2.71 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.1, 148.0, 133.6, 125.1, 121.0, 115.1, 112.9, 43.1, 26.3, 23.7 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}N_2Br$ ([M+H]$^+$): 237.0022, Found: 239.0023.

7-iodo-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9f): According to GP 2: 1-iodo-4-nitosobenzene (45 mg, 0.19 mmol), pyrrolidine (63 µL, 0.77 mmol) and 2,4-dichlorobenzoic acid (22 mg, 0.12 mmol) were reacted for 8 h in dry toluene (3 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9f** as white solid (29 mg, 54%). FTIR (KBr): $\tilde{\nu}$ = 2957, 2923, 2853, 1632, 1453, 1384, 1104, 874, 806, 472 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (s, 1H), 7.50 - 7.43 (m, 2H), 4.09 - 4.06 (m, 2H), 3.08 - 3.04 (m, 2H), 2.76 - 2.69 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.9, 148.6, 134.1, 130.8, 121.5, 118.8, 85.1, 43.0, 26.3, 23.6 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}N_2I$ ([M+H]$^+$): 284.9883, Found: 284.9881.

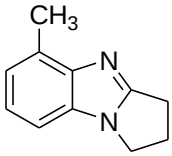
7-*N*, *N*-dimethyl-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9g): According to GP 2: N,N-dimethyl-4-nitrosoaniline (0.10 g, 0.67 mmol), pyrrolidine (0.22 mL, 2.66 mmol) and 2,4-dichlorobenzoic acid (77 mg, 0.40 mmol) were reacted for 24 h in dry toluene (8 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:1) gave **2.9g** as colorless gum (20 mg, 15%). FTIR (KBr): $\tilde{\nu}$ = 2957, 2924, 2853, 1632, 1455, 1384, 1261, 1101, 874, 802, 472 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, *J* = 9.2 Hz, 1H), 6.82 - 6.80 (m, 1H), 6.60 (s, 1H), 4.09 - 4.05 (m, 2H), 3.08 (t, *J* = 7.6 Hz, 2H), 2.98 (s, 6H), 2.75 - 2.68 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 159.0, 148.0, 133.2, 119.4, 110.8, 93.7, 43.0, 42.1 (2C), 26.4, 23.6 ppm (overlap

1C in aromatic). HRMS: Exact mass calculated for $C_{12}H_{16}N_3$ ($[M+H]^+$): 202.1339, Found: 202.1335.

6-chloro-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9h) and 8-chloro-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (2.9h'):  According to GP 2: 1-chloro-3-nitrosobenzene (40 mg, 0.28 mmol), pyrrolidine (93 µL, 1.13 mmol) and 2,4-dichlorobenzoic acid (32 mg, 0.17 mmol) were reacted for 8 h in dry toluene (3 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9h** as white solid (27 mg, 49%) and **2.9h'** as colorless gum (6 mg, 11%). Analytical data for **2.9h**: FTIR (KBr): $\tilde{\nu}$ = 2956, 2924, 2853, 1639, 1527, 1464, 1407, 1295, 1058, 739 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 7.20 - 7.16 (m, 2H), 4.11 (t, *J* = 7.2 Hz, 2H), 3.06 (t, *J* = 7.8 Hz, 2H), 2.76 - 2.71 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.7, 149.8, 131.2, 127.5, 122.4, 119.6, 110.3, 43.2, 26.3, 23.9 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}N_2Cl$ ($[M+H]^+$): 193.0527, Found: 193.0529. Analytical data for **2.9h'**: FTIR (KBr): $\tilde{\nu}$ = 2924, 2857, 1638, 1458, 1389, 1100, 808 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 7.8 Hz, 1H), 7.15 - 7.10 (m, 2H), 4.44 (t, *J* = 7.2 Hz, 2H), 3.06 (t, *J* = 7.8 Hz, 2H), 2.75 - 2.70 (m, 2H) ppm.^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.2, 150.2, 130.3, 122.6, 122.3, 118.4, 116.0, 45.2, 26.5, 23.5 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}N_2Cl$ ($[M+H]^+$): 193.0527, Found: 193.0527.

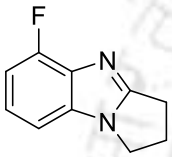
6-bromo-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9i):  According to GP 2 : 1-bromo-3-nitrosobenzene (40 mg, 0.22 mmol), pyrrolidine (71 µL, 0.87 mmol) and 2,4-dichlorobenzoic acid (25 mg, 0.13 mmol) were reacted for 8 h in dry toluene (3 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9i** as white solid (24 mg, 47%). FTIR (KBr): $\tilde{\nu}$ = 2957, 2924, 2853, 1633, 1462, 1384, 1107, 874, 800, 477 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.82 (s, 1H), 7.32 - 7.29 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 4.12 - 4.09 (m, 2H), 3.09 - 3.05 (m, 2H), 2.77 - 2.70 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.6, 150.2, 131.5, 125.0, 122.6, 114.9, 110.9, 43.2, 26.3, 23.8 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}N_2Br$ ($[M+H]^+$): 237.0022, Found: 239.0022.

5-methyl-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9j): According to GP 2: 1-



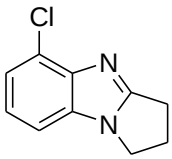
methyl-2-nitrosobenzene (50 mg, 0.41 mmol), pyrrolidine (0.14 mL, 1.65 mmol) and 2,4-dichlorobenzoic acid (47 mg, 0.25 mmol) were reacted for 8 h in dry toluene (4 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9n** as white solid (51 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 2967, 2920, 2850, 1641, 1523, 1402, 1208, 1080, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.13 - 7.08 (m, 2H), 7.02 (d, *J* = 6.4 Hz, 1H), 4.07 - 4.04 (m, 2H), 3.07 - 3.03 (m, 2H), 2.72 - 2.66 (m, 2H), 2.64 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 160.4, 148.1, 132.1, 129.5, 122.3, 121.8, 107.2, 42.9, 26.3, 23.7, 16.9 ppm. HRMS: Exact mass calculated for $C_{11}H_{13}N_2$ ($[M+H]^+$): 173.1073, Found: 173.1073.

5-fluoro-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9k): According to GP 2:



1,3-difluoro-2-nitrosobenzene (50 mg, 0.35 mmol), pyrrolidine (0.11 mL, 1.40 mmol) and 2,4-dichlorobenzoic acid (40 mg, 0.21 mmol) were reacted for 8 h in dry toluene (4 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9j** as white solid (35 mg, 57%). FTIR (KBr): $\tilde{\nu}$ = 2995, 2911, 2850, 1633, 1586, 1528, 1496, 1447, 1407, 1300, 1221, 1056, 1045, 778, 731 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.12 - 7.09 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.93 - 6.89 (m, 1H), 4.10 (t, *J* = 7.2 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.76 - 2.71 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.6, 154.4, 152.8, 137.2, 137.1, 135.3, 135.2, 122.32, 122.28, 107.7, 107.5, 105.8, 105.8, 43.2, 26.4, 23.6 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}FN_2$ ($[M+H]^+$): 177.0823; Found: 177.0823.

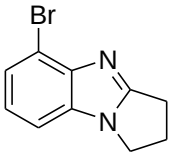
5-chloro-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9l): According to GP 2: 1-



chloro-2-nitrosobenzene (50 mg, 0.35 mmol), pyrrolidine (0.12 mL, 1.42 mmol) and 2,4-dichlorobenzoic acid (40 mg, 0.21 mmol) were reacted for 8 h in dry toluene (4 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9k** as white solid (27 mg, 40%), along with the substituted product **2** (10 mg, 18 %). FTIR (KBr): $\tilde{\nu}$ = 2989, 2931, 2850, 1618, 1567, 1520, 1481, 1439, 1397, 1297, 1191, 1118, 1047, 984, 852, 771, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.24 - 7.18 (m, 2H), 7.13 - 7.09 (m, 1H), 4.13 - 4.09 (m, 2H), 3.10 - 3.06 (m, 2H), 2.76 - 2.69 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.0, 145.9, 133.4, 124.1, 122.5, 121.9, 108.5,

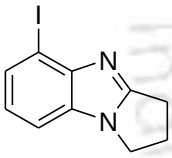
43.3, 26.3, 23.8 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}N_2Cl$ ($[M+H]^+$): 193.0527; Found: 193.0527.

5-bromo-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9m): According to GP 2: 1-



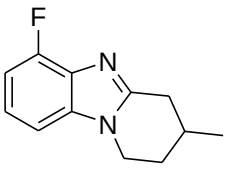
bromo-2-nitrosobenzene (50 mg, 0.27 mmol), pyrrolidine (89 µL, 1.08 mmol) and 2,4-dichlorobenzoic acid (31 mg 0.16 mmol) were reacted for 8 h in dry toluene (3 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9l** as white solid (33 mg, 52%), along with the substituted product **2** (5 mg, 12%) FTIR (KBr): $\tilde{\nu}$ = 2956, 2936, 2853, 1614, 1564, 1518, 1473, 1438, 1402, 1296, 1191, 1146, 1125, 1048, 979, 853, 774, 573 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41 - 7.39 (m, 1H), 7.24 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.12 - 3.09 (m, 2H), 2.77 - 2.70 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.0, 147.3, 133.0, 125.0, 122.9, 112.7, 109.1, 43.4, 26.3, 23.9 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}N_2Br$ ($[M+H]^+$): 237.0022; Found: 237.0023.

5-iodo-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.9n): According to GP 2: 1-



iodo-2-nitrosobenzene (50 mg, 0.21 mmol), pyrrolidine (71 µL, 0.86 mmol) and 2,4-dichlorobenzoic acid (25 mg, 0.13 mmol) were reacted for 8 h in dry toluene (4 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9m** as white solid (38 mg, 63%), along with the substituted product **2** (3 mg, 9%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2924, 2850, 1617, 1560, 1516, 1483, 1438, 1384, 1262, 1099, 802, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.64 - 7.62 (m, 1H), 7.28 - 7.26 (m, 1H), 6.99 - 6.95 (m, 1H), 4.14 - 4.11 (m, 2H), 3.14 - 3.10 (m, 2H), 2.77 - 2.70 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.6, 150.5, 131.5, 131.2, 123.5, 109.9, 86.2, 43.4, 26.3, 24.0 ppm. HRMS: Exact mass calculated for $C_{10}H_{10}N_2I$ ($[M+H]^+$) : 284.9883; Found: 284.9884.

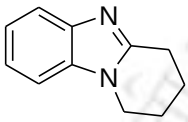
6-fluoro-3-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine(2.9o): According



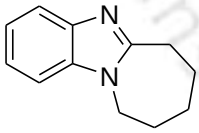
to GP 2: 1,3-difluoro-2-nitrosobenzene (35 mg, 0.24 mmol), 4-methylpiperidine (79 µL, 0.96 mmol) and 2,4-dichlorobenzoic acid (27 mg, 0.14 mmol) were reacted for 8 h in dry toluene (3 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9o** as white solid (26 mg, 53%). FTIR (KBr): $\tilde{\nu}$ = 2955, 2925, 2854, 1629, 1518, 1384, 1325, 1234,

1106, 1054, 784, 746, 481 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.15 - 7.11 (m, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.95 - 6.92 (m, 1H), 4.24 - 4.20 (m, 1H), 3.99 - 3.94 (m, 1H), 3.25 - 3.21 (m, 1H), 2.66 -2.62 (m, 1H), 2.20 - 2.14 (m, 2H), 1.83 - 1.79 (m, 1H), 1.20 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.5, 152.9 152.3, 137.8, 137.7, 131.8, 131.7, 122.3, 122.2, 108.0, 107.9, 105.1, 105.1, 42.2, 33.6, 30.6, 27.7, 21.2 ppm. HRMS: Exact mass calculated for $C_{12}H_{14}FN_2$ ($[M+H]^+$): 205.1136; Found: 205.1138.

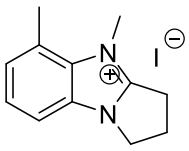
1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine (2.9p): According to GP 2: Nitrosobenzene (30 mg, 0.28 mmol), piperidine (0.11 mL, 1.12 mmol) and 2,4-dichlorobenzoic acid (32 mg, 0.17 mmol) were reacted for 8 h in dry toluene (3 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9p** as yellow oil (12 mg, 24%). Under the same condition 2-fluoronitrosobenzene (35 mg, 0.28 mmol) gave **2.9p** (27 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 2961, 2926, 2850, 1656, 1619, 1514, 1457, 1418, 1384, 1315, 1262, 1096, 1022, 801, 744 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.69 - 7.67 (m, 1H), 7.31 - 7.29 (m, 1H), 7.24 - 7.22 (m, 2H), 4.09 (t, *J* = 6 Hz, 2H), 3.10 (t, *J* = 6.5 Hz, 2H), 2.16 - 2.11 (m, 2H), 2.05 - 2.00 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 151.9, 143.0, 134.8, 122.3, 121.9, 119.1, 108.9, 42.7, 25.7, 22.9, 21.0 ppm. HRMS: Exact mass calculated for $C_{11}H_{13}N_2$ ($[M+H]^+$): 173.1073, Found: 173.1074.



7,8,9,10-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]azepine (2.9q): According to GP 2: Nitrosobenzene (30 mg, 0.28 mmol), azepane (0.13 mL, 1.12 mmol) and 2,4-dichlorobenzoic acid (32 mg, 0.17 mmol) were reacted for 8 h in dry toluene (3 mL) and column chromatography (neutral alumina; EtOAc : hexane, 1:3) gave **2.9q** as yellow oil (11 mg, 21%). Under the same condition 2-fluoronitrosobenzene (35 mg, 0.28 mmol) gave **2.9q** (24 mg, 45%). FTIR (KBr): $\tilde{\nu}$ = 3056, 2929, 2847, 1617, 1517, 1463, 1414, 1242, 1192, 1085, 801, 740 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 7.8 Hz, 1H), 7.27 (s, 1H), 7.25 - 7.20 (m, 2H), 4.17 - 4.15 (m, 2H), 3.12-3.10 (m, 2H), 1.97 - 1.93 (m, 2H), 1.86 - 1.84 (m, 2H), 1.83 - 1.79 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 157.7, 142.5, 135.9, 122.1, 121.8, 119.4, 108.9, 44.7, 31.1, 30.3, 28.9, 25.7 ppm. HRMS: Exact mass calculated for $C_{12}H_{15}N_2$ ($[M+H]^+$): 187.1230, Found: 187.1230.

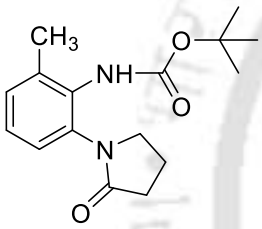


4,5-dimethyl-2,3-dihydro-1*H*-benzo[d]pyrrolo[1,2-*a*]imidazol-4-ium iodide (2.49):



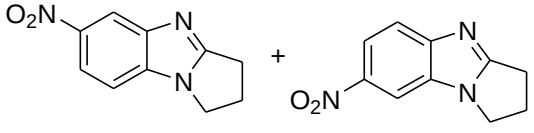
Imidazole **2.9n** (15 mg, 0.09 mmol) was dissolved in methyl iodide (0.14 mL, 2.25 mmol) and the mixture was stirred at room temperature for 12 h. The mixture with solid precipitate was diluted with diethyl ether (2 mL). The precipitate was filtered, washed with ethyl acetate (10 mL). The ion **2.49** was obtained as white solid (15 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 2956, 2920, 2853, 1627, 1571, 1458, 1383, 1119, 1055, 797, 461 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ = 7.71 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 4.44 (t, *J* = 7.2 Hz, 2H), 4.17 (s, 3H), 3.45 - 3.42 (m, 2H), 2.83 (s, 3H), 2.82 - 2.78 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 160.8, 135.5, 129.9, 128.7, 126.7, 126.2, 111.9, 47.5, 36.2, 25.7, 24.6, 18.4 ppm. HRMS: Exact mass calculated for $C_{12}H_{16}N_2$ ($[M+H]^+$): 187.1230, Found: 187.1235.

***tert*-butyl(2-methyl-6-(2-oxopyrrolidin-1-yl)phenyl)carbamate (2.48):**



Di-*tert*-butyl dicarbonate (0.16 g, 0.73 mmol) was added to a solution of imidazole **2.9n** (25 mg, 0.15 mmol) in dry DCM (1.5 mL). The reaction mixture was stirred at room temperature for 60 h. Then the reaction mixture was quenched with water (10 mL) and extracted with DCM (3x10 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (neutral alumina, EtOAc : hexane, 1:5) to give **2.48** as a white solid (28 mg, 65%). FTIR (KBr): $\tilde{\nu}$ = 2974, 2927, 2858, 1719, 1679, 1521, 1423, 1308, 1248, 1162, 1052, 795, 728 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.18 (s, 1H), 7.17 (s, 1H) 7.04 - 7.02 (m, 1H), 6.67 (s, 1H), 3.85 - 3.82 (m, 2H), 2.60 - 2.57 (m, 2H), 2.32 (s, 3H), 2.22 - 2.17 (m, 2H), 1.46 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.7, 154.0, 138.6, 135.5, 132.0, 129.9, 127.3 (2C), 122.1, 79.8, 51.1, 31.9, 28.5 (3C), 19.4, 18.6 ppm. HRMS: Exact mass calculated for $C_{16}H_{23}N_2O_3$ ($[M+H]^+$): 291.1703, Found: 291.1703.

6-nitro-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole and 7-nitro-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (2.50):

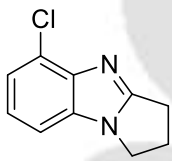
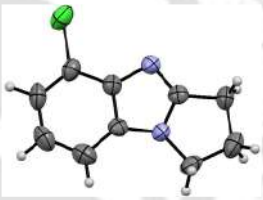


Conc. H_2SO_4 and conc. HNO_3 (1:1) mixture (4.7 mL) was slowly added to the imidazole **2.9a** (40 mg, 0.25 mmol) at 0 °C with continuous stirring and the reaction mixture was stirred 12 h at 0 °C. To this mixture aq. NH_4OH solution (20 mL) was added to maintain the pH≥8. The mixture was then extracted with ethyl acetate (3x20 mL) and combined organic layers were dried over

Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (neutral alumina, EtOAc : hexane, 1:3) to provide **2.50** (38 mg, 75%) as an inseparable mixture of two regioisomer with ratio (6-nitro: 7-nitro; 1.3:1). FTIR (KBr): $\tilde{\nu}$ = 2964, 2920, 2850, 1622, 1588, 1530, 1517, 1455, 1312, 1289, 1058, 819, 741 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.59 (d, *J* = 1.8 Hz, 1H, major), 8.26 (d, *J* = 2.4 Hz, 1H, minor), 8.17 - 8.15 (m, 2H, major+ minor), 7.72 (d, *J* = 9.0 Hz, 1H, minor), 7.34 (d, *J* = 9.0 Hz, 1H, major), 4.24 - 4.18 (m, 4H, major + minor), 3.16 -3.13 (m, 4H, major + minor), 2.84 - 2.77 (m, 4H, major + minor), ppm. ^{13}C NMR (151 MHz, $CDCl_3$) for major and minor isomer: δ = 166.6, 165.2, 153.6, 148.4, 143.5, 136.7, 119.6, 118.2, 118.0, 116.4, 109.4, 106.6, 43.5, 43.3, 26.3, 26.10, 24.1, 23.9 ppm (overlap in aromatic region). HRMS: Exact mass calculated for $C_{10}H_{11}N_3O_2$ ($[M+H]^+$): 204.0768; Found: 204.0767.

Crystallographic Data:

Crystal of **2.9l:**

	 CCDC 1536902
Empirical formula	C_{10} H_9 Cl N_2
Formula weight	192.64
Crystal habit, colour	needle / colorless
Crystal size, mm^3	0.4 X 0.3 X 0.3
Temperature, *T*	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'C 1 2/c 1'*
Unit cell dimensions	*a* = 12.412(2) Å *b* = 13.116(2) Å *c* = 11.694(2) Å α = 90.00°, γ = 90.00°, β = 110.85(2)°
Volume, *V*($Å^3$)	1779.1(6)
Z	8
Calculated density, $Mg·m^{-3}$	1.438
Absorption coefficient, μ(mm^{-1})	0.377
F(000)	800
θ range for data collection	3.11° to 24.99°
Limiting indices	$-11 \le h \le 14$, $-15 \le k \le 13$, $-13 \le l \le 13$
Reflection collected / unique	3154 / 1104 [*R*(int) = 0.0591]
Completeness to θ	99.4% (θ = 24.99°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'

Data / restraints / parameters	1104 / 0 / 118
Goodness–of–fit on F^2	1.060
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0603, *wR*2 = 0.1498
R indices (all data)	*R*1 = 0.0837, *wR*2 = 0.1736
Largest diff. peak and hole	0.376 and – 0.395e·Å^{-3}

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CHAPTER - 3

N-Aminations of Benzylamines and Alicyclic Amines with Nitrosoarenes to Hydrazones and Hydrazides

3.1 Introduction:

Hydrazones are an important class of compounds that find application in organic synthesis, medicinal chemistry, and supramolecular chemistry including metal and covalent organic frameworks.[1,7a] Hydrazone derivatives shown in **figure 1** are well known for anti-inflammatory[2], analgesic[3], anti-mycobacterial[4], COX-2 inhibitor[5] *etc*. Hydrazone derivatives are also found as a key unit of fluorescent chemosensors.[6] Moreover, hydrazones can also be used as ligands or directing groups in organic synthesis.[7] This widespread application has promoted the development of novel and efficient methodologies for the synthesis of hydrazone and their derivatives.

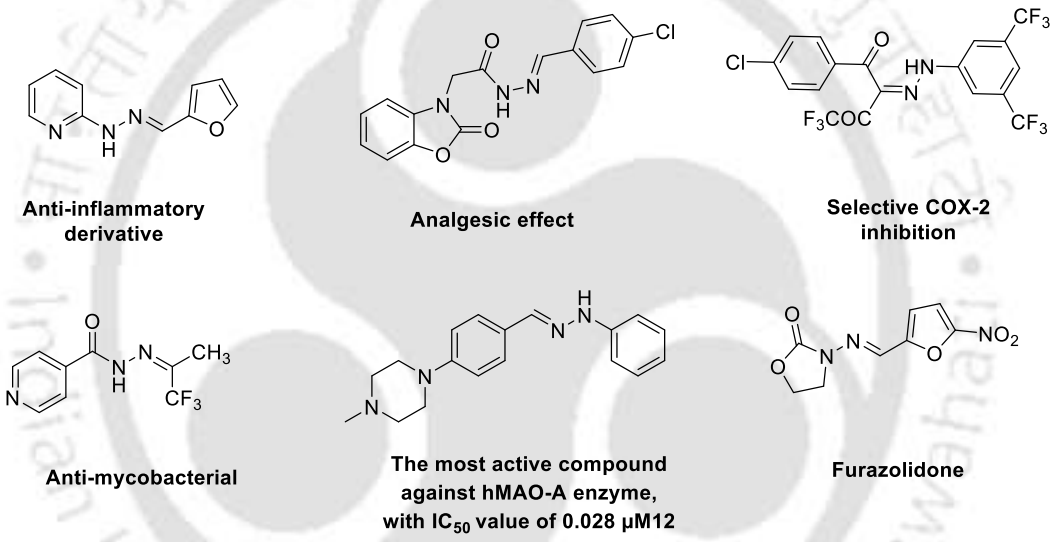


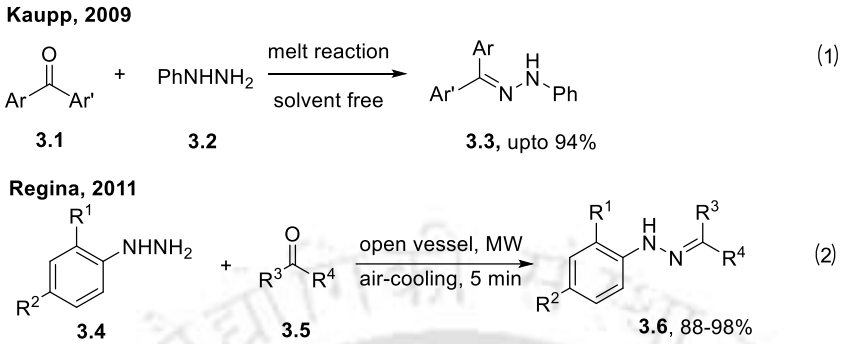
Figure 1: Biologically active hydrazone molecules.

3.2 Known methods for the synthesis of hydrazones:

The importance of these hydrazone core structure has drawn the attention of the synthetic chemists to develop novel and cost-effective methodologies for their synthesis. Several methods have already been established for the synthesis of the scaffold from different starting materials. The most classical approach to synthesize hydrazones is the condensation between carbonyl compounds with hydrazine.

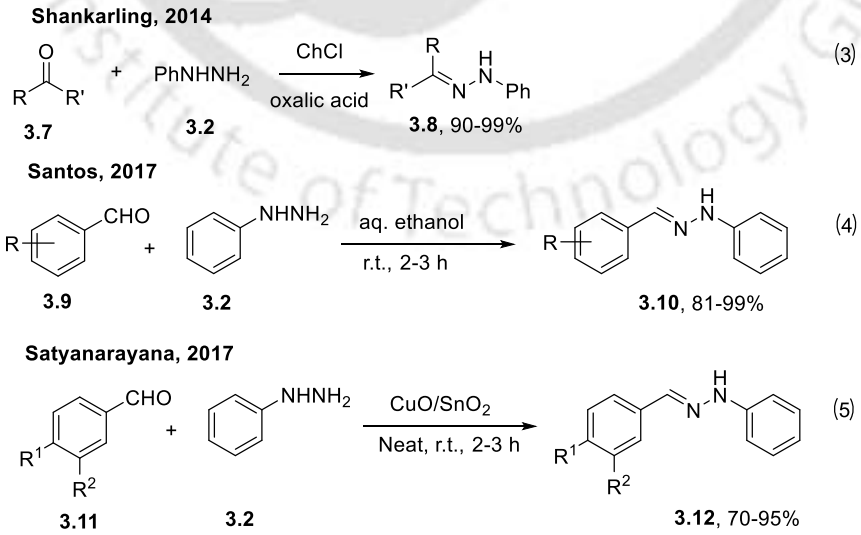
In 2009, Kaupp *et al.* developed a versatile method for the synthesis of hydrazones **3.3** from the reaction of phenylhydrazine **3.2** with low-melting aldehydes and ketones **3.1** (**Scheme 1**, eq. 1).[8] In 2011, Regina *et al.* reported a microwave-assisted open vessel synthesis of

pyridinyl *N*-aryl hydrazones **3.6** by reacting 4- and 2,4-di substituted phenylhydrazines **3.4**, having both electron-donating (4-CH_3, 4-OCH_3) and -withdrawing (4-Cl, 4-Br, 4-CF_3, 4-NO_2, 2,4-di-Cl) groups with carbonyl compound containing heteroatom **3.5** (**Scheme 1**, eq. 2).[9]



Scheme 1: Selected examples of syntheses of hydrazones using carbonyl compounds and hydrazine derivatives.

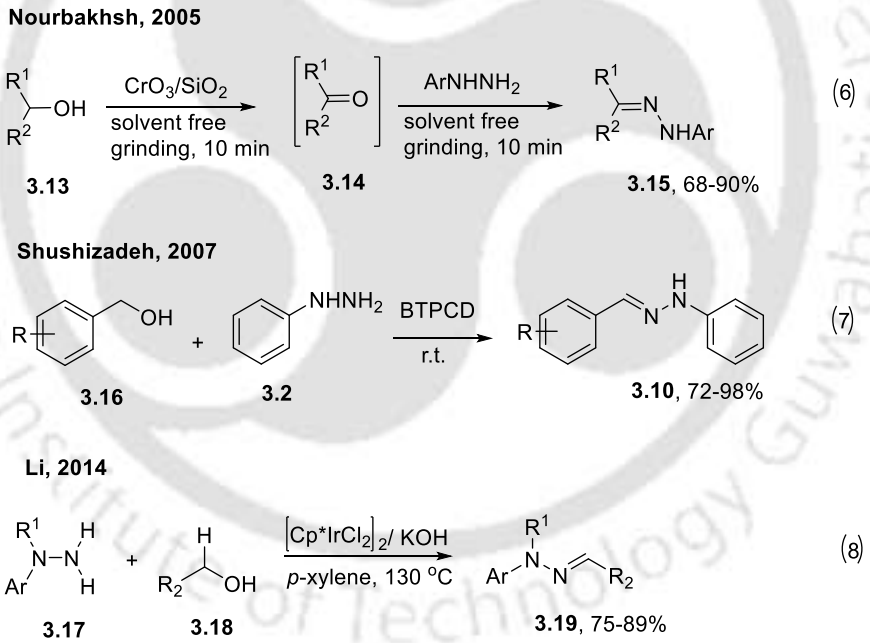
In 2014, an effective synthesis of hydrazones **3.8** from carbonyl partners **3.7** and phenylhydrazine **3.2** was introduced by Shangkarling *et al.* using ionic liquid choline chloride–oxalic acid (ChCl:Ox) (**Scheme 2**, eq. 3).[10] Later, in 2017 Santos *et al.* established a simple condensation reaction between benzaldehyde **3.9** and phenylhydrazine **3.2** in methanol at room temperature. Broad range of hydrazones **3.10** was afforded utilizing this method (**Scheme 2**, eq. 4).[11] In the same year, Satyanarayana *et al.* furnished a mixed metal oxide CuO/SnO_2 mediated synthesis of hydrazones **3.12** from phenylhydrazine **3.2** under solvent free condition at room temperature (**Scheme 2**, eq. 5).[12]



Scheme 2: Syntheses of hydrazones *via* condensation reaction.

3.3 Syntheses of hydrazones from alcohols:

Additional strategies for the synthesis of hydrazones from corresponding alcohols were well documented. In 2005, Nourbakhsh *et al.* described the synthesis of hydrazone **3.15** *via* one-pot transformation of primary and secondary alcohols **3.13** *via* carbonyl derivative **3.14** using chromium trioxide supported on silica gel under solvent-free conditions (**Scheme 3**, eq. 6).[13] In 2007, Shushizadeh *et al.* performed a 3,6-*bis*(triphenylphosphonium) cyclohexene dichromate (BTPCD) promoted efficient and facile one-step process for the synthesis of hydrazones **3.10** from the reaction of the oxidation product of benzyl alcohols **3.16** with phenylhydrazine **3.2** (**Scheme 3**, eq. 7).[14] Few years later in 2014, Li *et al.* developed a direct synthesis of arylhydrazone scaffolds **3.19** *via* catalytic acceptorless dehydrogenative coupling of arylhydrazines **3.17** and alcohols **3.18** (**Scheme 3**, eq. 8). The method provides complete selectivity for arylhydrazones excluding *N*-alkylated byproducts which exhibited a new prospect for the development of catalytic acceptorless dehydrogenative coupling reactions.[15]

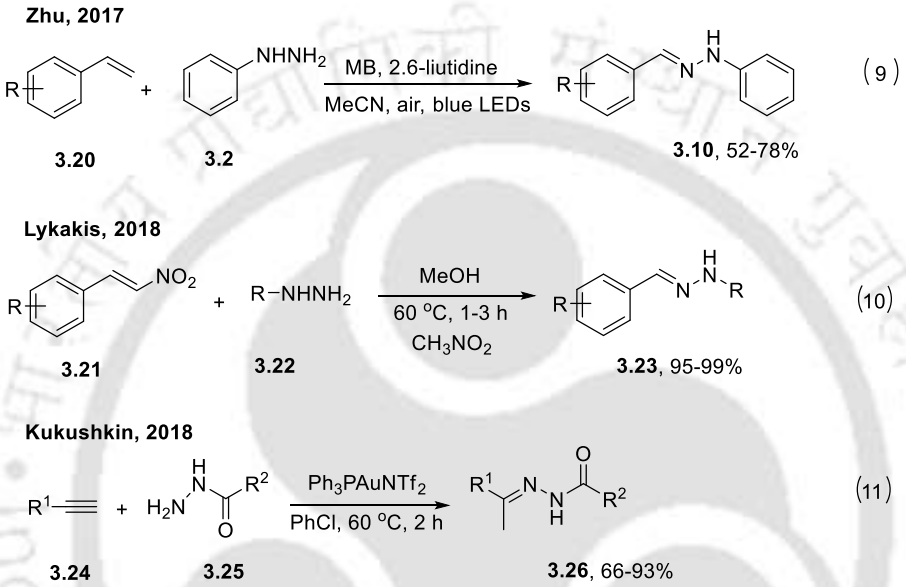


Scheme 3: Selected examples of syntheses of hydrazones from alcohols.

3.4 Syntheses of hydrazones from alkenes and alkynes:

Olefins are also found to be useful for the synthesis of hydrazone *via* C-C bond cleavage. In 2017, visible light mediated metal-free protocol of oxidative cleavage of C=C bonds of styrene **3.20** to construct C=N in hydrazone **3.10** has been demonstrated by Zhu *et al*. The reaction proceeded *via* diazetidine intermediate that is generated by [2+2] annulation of

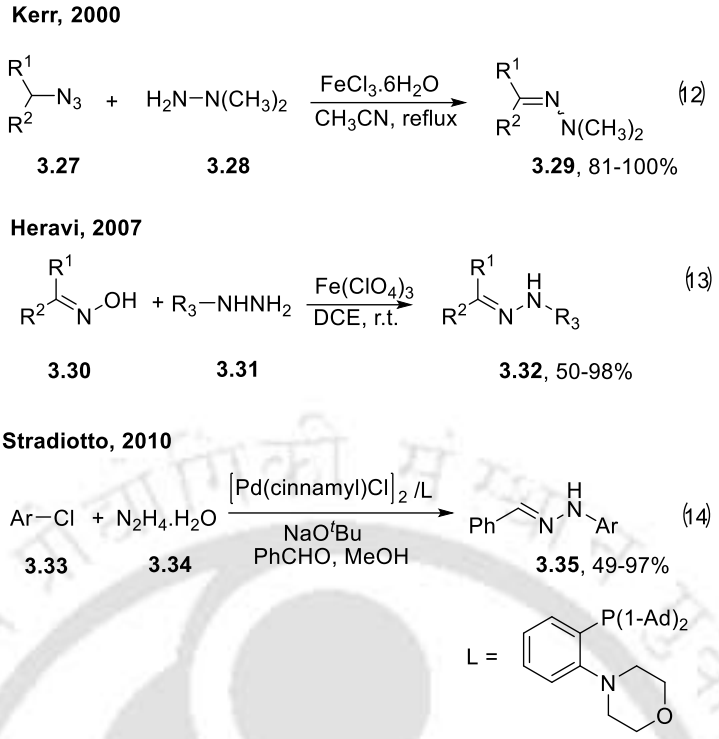
alkenes with *in situ* generated diazenes from arylhydrazines (**Scheme 4**, eq. 9).[16] Later in 2018, Lykakis *et al.* reported the synthesis of hydrazones **3.23** using nitroalkene **3.21** and hydrazines **3.22** *via* a retro-aza- Henry-type process (**Scheme 4**, eq. 10).[17] Also in 2018, Kukushkin *et al.* developed a facile gold-catalyzed hydro-hydrazidation of alkynes **3.24** with various hydrazides $R_2CONHNH_2$ (R = Alk or Ar) **3.25** in presence of $Ph_3PAuNTf_2$ (6 mol %). This protocol leads to a wide range of substituted keto-*N*-acylhydrazones **3.26** with good yields (**Scheme 4**, eq. 11).[18]



Scheme 4: Syntheses of hydrazones from olefins and alkynes.

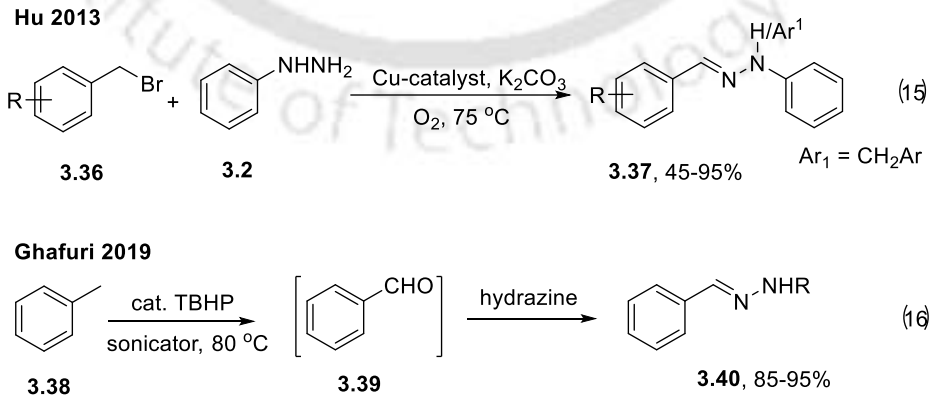
3.5 Various other methods for the syntheses of hydrazones:

Not only carbonyls, alcohols, olefins, but other substrates like oxime, toluene, azide, haloarenes, benzyl bromide *etc.* were also utilized as the starting materials for the syntheses of hydrazones. In 2000, Kerr *et al.* developed ferric chloride mediated synthesis of arylhydrazones **3.29** from the reaction of simple azides **3.27** with *N*,*N*-dimethylhydrazine **3.28** (**Scheme 5**, eq. 12).[19] In 2007, Heravi *et al.* described the conversion of oximes **3.30** into the corresponding arylhydrazones **3.32** in the presence of $Fe(ClO_4)_3$ (**Scheme 5**, eq. 13).[20] Stradiotto *et al.*, in 2010 developed base supported conversion of aryl chlorides **3.33** to corresponding hydrazones **3.35** using hydrazine hydrate **3.34** (**Scheme 5**, eq. 14).[21]



Scheme 5: Syntheses of hydrazones from azide, oxime and halo compounds.

In 2013, Hu *et al.* developed the mild and efficient Cu(I)-catalyzed one-pot synthesis of *N*-substituted (or NH) *bis*-arylhydrazones **3.37** from benzyl bromide **3.36** and phenylhydrazines **3.2** (**Scheme 6**, eq. 15).[22] In 2019, Ghafuri *et al.* demonstrated graphene oxide−imidazolium ionic liquid−CO_2H−Cu catalyzed conversion of toluene **3.38** to the corresponding benzaldehyde **3.39** which upon treatment with hydrazines provided the desired hydrazones **3.40** (**Scheme 7**, eq. 16).[23]



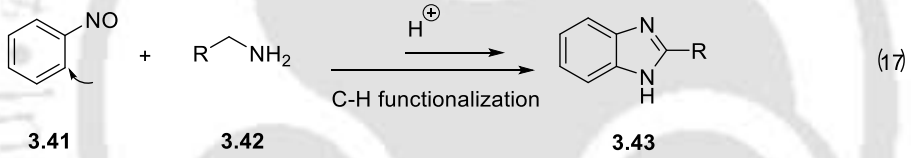
Scheme 6: Syntheses of hydrazones from halide, toluene compounds.

3.6 Drawback of the known methods:

Although, the classical condensation of arylhydrazines with an aldehyde and coupling of hydrazines with an alcohol are mainly used for the synthesis of hydrazone derivatives.[15,24a,b] However, the synthetic utility of these methods are greatly restricted because of the limited availability of arylhydrazines due to their inherent instability issues and difficulties in their synthesis.[24c] Therefore, the development of an alternative method for the synthesis of arylhydrazones from readily available starting material is essential.[16,25]

3.7 Hypothesis:

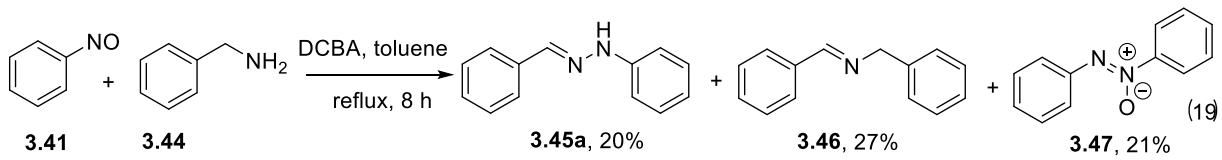
Secondary cyclic amines provide fused benzimidazole product *via* C-H functionalization (**Chapter 2**). If similar reactivity is followed by the primary amine, then the fused imidazole **3.43** will be obtained from the reaction of nitrosoarene **3.41** and arylamines **3.42** (**Scheme 7**, eq. 17).



Scheme 7: Expected imidazole from reaction with primary amine.

3.8 Preliminary Result:

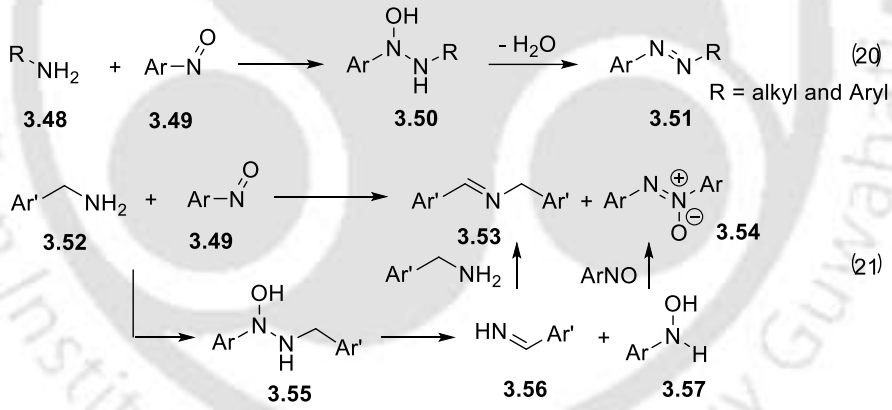
Based on the plan, nitrosobenzene **3.41** was reacted with benzylamine **3.44** in the presence of 2,4-dichlorobenzoic acid (DCBA) under toluene reflux. To my surprise, no C-H functionalized was obtained at all. However, hydrazone **3.45a** was formed in 20% yield along with the oxidized product **3.46** and azoxybenzene **3.47** (**Scheme 8**, eq. 19).[26]



Scheme 8: Preliminary result.

3.9 Known reaction of primary amines with nitroso:

The previous literature regarding the reactivity of nitrosoarene with primary amines revealed that nitrosoarenes **3.49** react with alkyl- and arylamines **3.48** to provide the corresponding azo derivatives **3.51** forming a N=N bond (**Scheme 9**, eq. 20).[27,28] Interestingly, a similar reaction of nitrosoarenes **3.49** with benzylamines **3.52** does not provide the desired azo derivative;[27b] the reaction produces azoxy derivatives **3.54** and the corresponding aldehyde. A careful analysis of the mechanistic rationalization revealed that the elimination of water involving N–H cleavage of initial *N*-hydroxyhydrazine derivative **3.50** provide the azo compound for alkyl- or arylamines (**Scheme 9**, eq. 20). In contrast, elimination of hydroxylamine **3.57** occurs (from **3.55**) involving the cleavage of the activated benzylic C–H bond of the benzylamine to provide the corresponding imine derivative **3.56**. Then the imine on subsequent reaction with water or another molecule of benzylamine produces an aldehyde and/or imine **3.53** (**Scheme 9**, eq. 21), respectively. Hydroxylamine **3.57** also reacts with another molecule of nitrosoarene **3.49** to provide the observed azoxyarene **3.54**.



Scheme 9: Reaction known for primary amines and nitrosoarenes.

To the best of knowledge, there are no previous reports of the reaction of nitrosoarenes and benzylamines providing a benzyl-aryl azo-compound or their tautomers. This is the first example of Brønsted acid mediated direct *N*-amination of benzylamines using nitrosoarenes to provide the corresponding hydrazones.

3.10 Optimization of reaction conditions:

Table 1: Optimization Table

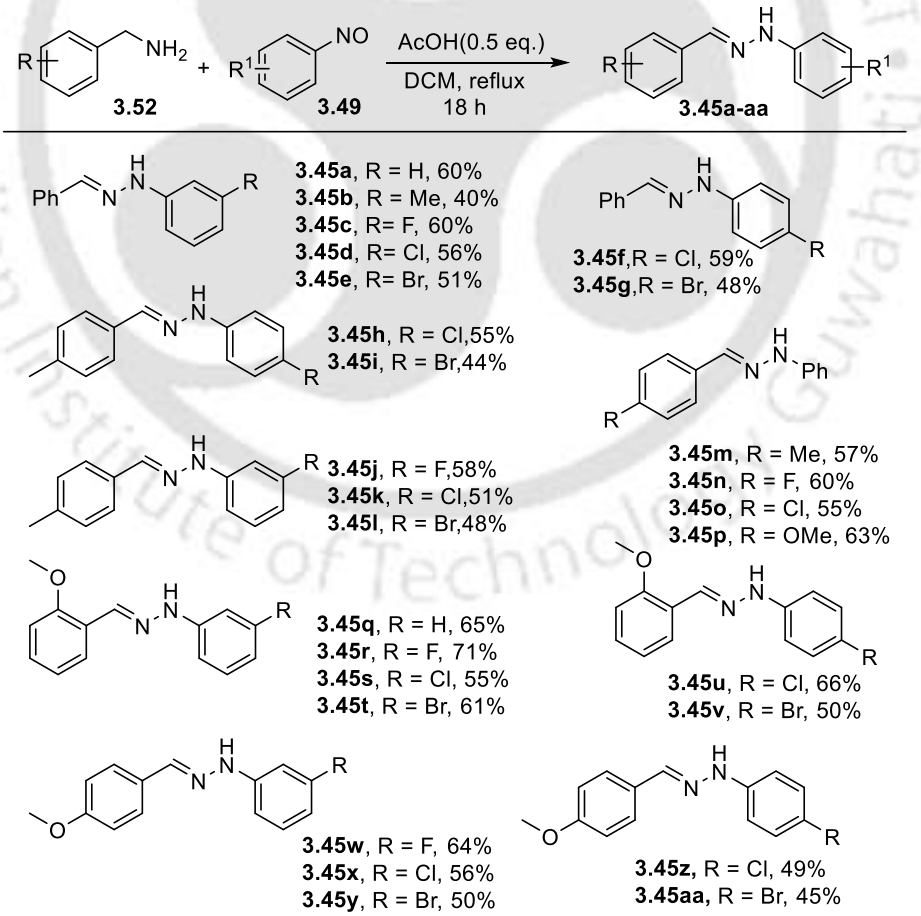
Entry	Conditions[a]	Yield of **3.45a**[b]	Yield of **3.46**[c]	Yield of **3.47**[c]
1[d].	DCBA (0.6 eq.), toluene, reflux, 8 h	20	27	21
2[d].	AcOH (0.6 eq.), toluene, reflux, 8 h	30	24	20
3[e].	AcOH (0.6 eq.), DCM, reflux, 8 h	38	36	17
4[e].	AcOH (0.6 eq.), DCM, reflux, 15 h	41	33	16
5.	AcOH (0.6 eq.), DCM, reflux, 15 h	53	Nd	Nd
6.	AcOH (0.5 eq.), DCM, reflux, 15 h	56	Nd	Nd
7.	AcOH (0.5 eq.), DCM, reflux, 18 h	60	9	11
8[f].	AcOH (0.5 eq.), DCM, reflux, 18 h	55	Nd	Nd
9.	DCM, reflux, 18 h	36	Nd	Nd
10.	AcOH (2.0 eq.), DCM, reflux, 18 h	47	Nd	Nd

[a]Reaction conditions: benzylamine (0.37 mmol), nitrosobenzene (0.37 mmol), solvent (3.0 mL), unless otherwise stated. [b]Isolated yield calculated with respect to nitrosobenzene. [c]Isolated yield of 3.50 and 3.51 were calculated with respect to benzylamine and nitrosobenzene, respectively, considering maximum possible yield as 50%; Nd = not determined. [d]Benzylamine (4 eq.) was used. [e]Benzylamine (2 eq.) was used. [f] Nitrosobenzene (1.5 eq.) was used.

With this initial result in hand, further experiments were carried out to optimize the reaction conditions towards better yields of the hydrazone. The yield of the reaction improved slightly when the reaction was carried out in the presence of acetic acid (**Table1**, entry 2). The reaction at a lower temperature in refluxing dichloromethane with decrease in amine equivalency provided slightly better yield (**Table1**, entry 3). Longer reaction time provided better yield of the desired product (**Table1**, entry 4). Further improvement in the yield was noticed with the decrease in the relative stoichiometry of benzylamine (**Table1**, entry 5). A little increase in the yield was observed with slight decrease in acid concentration (**Table1**, entry 6). However, the yield of the product increases with increasing reaction time (**Table1**, entry 7). More equivalency of nitroso did not alter the reaction outcome into better way (**Table1**, entry 8). Poor yields were obtained when the reaction was carried out either in the absence of acid or in the presence of higher amount of acetic acid (2 eq.) (**Table1**, entries 9 and 10 respectively).

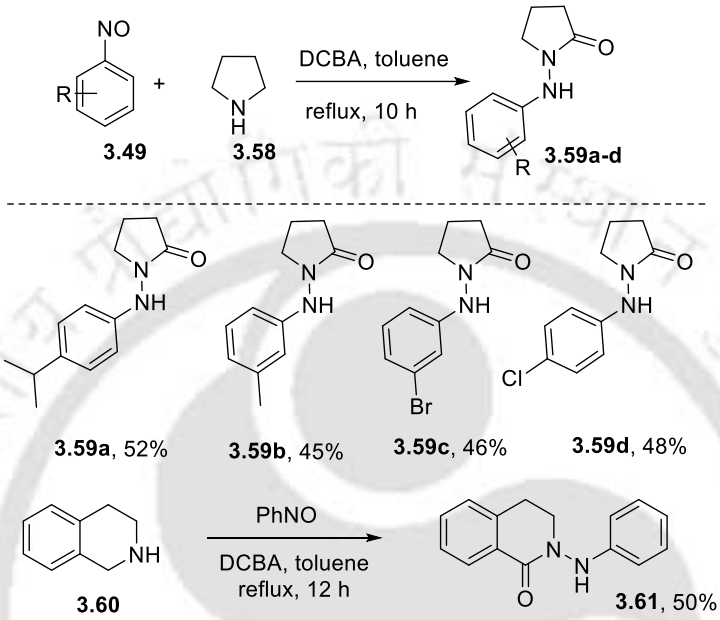
3.11 Substrate scopes of hydrazones and hydrazides:

Next, the substrate scope was investigated for this reaction using the optimal reaction condition. Reactions of benzylamine with various nitrosoarenes were studied first (**Scheme 10**). Nitrosoarenes as well as benzylamine containing both electron-donating and electron-withdrawing groups participated in the *N*-amination reaction to give the corresponding hydrazones **3.45a-aa** in moderate to good yields. The reaction with halogen-substituted nitrosoarenes provided the better yields of the desired hydrazones **3.45c-e** as compared to the hydrazone **3.45b** that is obtained from the reaction with methyl-substituted nitrosoarene. The reactions of various benzylamines with nitrosobenzene were investigated next. The studies revealed that the benzylamines containing -Me, -OMe, -Cl, -F, *etc*. provided the desired products in good yields. The electron-donating group in the benzylamine makes it more nucleophilic and an electron-withdrawing group makes the nitrosoarene more electrophilic. Therefore, benzylamines with electron-donating groups (-Me, -OMe) reacted efficiently with the nitrosoarene having electron-withdrawing groups (-Cl, -F, -Br, etc.) to provide the desired hydrazones **3.45h-aa** in good yields.



Scheme 10. Substrate scope of the *N*-amination reaction.

The reactions of alicyclic amines with the nitrosoarene were tested next. Accordingly, pyrrolidine **3.58** was reacted with an nitrosoarene under standard conditions. Surprisingly, the reaction of pyrrolidine with various nitrosoarenes provided hydrazide derivatives **3.59a-d** in 45–52% yields (**Scheme 11**). A similar result was also observed for the tetrahydroisoquinoline **3.60**, which gave the corresponding hydrazide **3.61** in 50% yield.



Scheme 11. Substrate scope of hydrazides.

3.12 Crystal structures of hydrazide:

The structure of the hydrazide derivative **3.59b** was confirmed by X-ray crystallographic analysis. The structure of the compound have been shown below (**Table 2**).

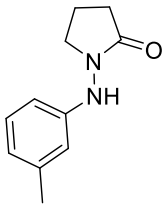
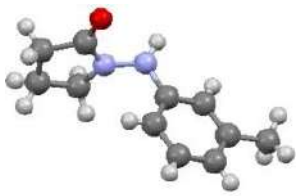
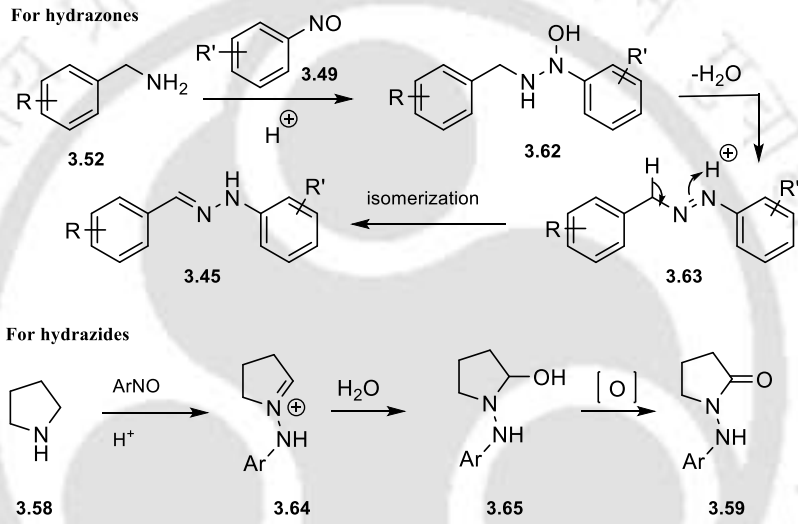
Compound	Crystal structure
 **3.59b**	

Table 2: X-ray crystal structure of hydrazide.

3.13 Plausible mechanism:

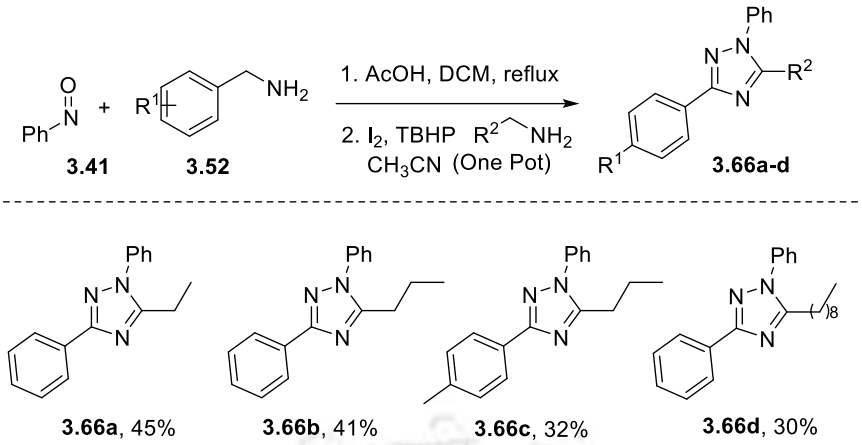
A plausible mechanism for the formation of hydrazones and hydrazides is presented in **Scheme 12**. Analogous to the reaction of amines with carbonyl compounds, nucleophilic addition of amines **3.52** to the nitrosoarenes **3.49** occurs to provide hydroxylamine derivative **3.62**.[27a, b] Acid-mediated dehydration of **3.62** produces the corresponding arylazoalkanes derivative **3.63**, which isomerizes readily to provide the observed hydrazone **3.45**.[29] A similar intermediate **3.64** is formed from the reaction of nitrosoarene and *N*-heterocycles **3.58**. The iminium intermediate **3.64** is trapped by H_2O to provide the corresponding hemiaminal **3.65** which upon subsequent oxidation gives the hydrazide **3.59**.[30]



Scheme 12: Proposed Mechanism of *N*-amination reaction.

3.14 Synthetic application:

Hydrazones are reacted with primary amines in the presence of iodine and *tert*-butyl hydroperoxide (TBHP) for the synthesis of triazoles.[31] Triazoles are an important scaffold in biological, pharmaceuticals, and medicinal chemistry.[32] Therefore, the *N*-amination reaction was employed for the synthesis of triazoles directly starting from amines **3.52** and nitrosobenzene **3.41**. Accordingly, benzylamines **3.52** were *N*-aminated under standard conditions to give the corresponding hydrazones that were further reacted with primary alkylamines in the presence of iodine and aq.TBHP in the same pot to provide the corresponding triazoles **3.66a-d** with acceptable yields (**Scheme 13**).



Scheme 13: One-pot triazole synthesis.

3.15 Conclusion:

In summary, an unprecedented *N*-amination reaction of benzylamines and *N*-heterocycles has been developed with the nitrosoarenes to provide hydrazones and hydrazides, respectively. The use of Brønsted acid facilitated dehydration reaction in comparison to undesired hydroxylamine elimination to achieve the difficult *N*-amination of benzylamines. A wide range of benzylamines and *N*-heterocycles reacted efficiently with the readily available nitrosoarenes to provide the corresponding hydrazone and hydrazide derivatives, respectively. This unconventional method for hydrazone synthesis does not involve hydrazines and thus issues relating to the preparation and the stability of hydrazines can be avoided. Moreover, this *N*-amination reaction was successfully applied in a one-pot syntheses of triazoles.

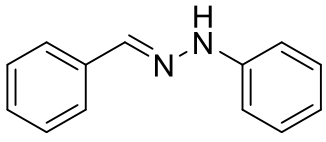
3.16 Experimental Section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus (V) oxide (P_2O_5). Commercial grade xylene, benzene and toluene were distilled over CaH_2 before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ^1H, ^{13}C NMR spectroscopy: *Varian Mercury plus 400 MHz, Bruker 600 MHz* (at 298 K). 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 ($CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.23 ppm); were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity. IR: spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade). MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak). Nitrosoarenes are prepared according to the known procedures.

Experimental procedure:

General procedure for the synthesis of hydrazone derivatives (I): Freshly prepared nitrosoarenes (1eq.) and and acetic acid were successively added to a solution of benzyl amines (1eq.) in DCM (3 - 4 mL). Then the reaction mixture was refluxed for 18 h under argon atmosphere. Then the solvent was evaporated under reduced pressure and crude mixture was subjected to column chromatography (silica gel) to afford analytically pure products.

(*E*)-1-benzylidene-2-phenylhydrazine (3.45a):[16] According to GP I: nitrosobenzene (40 mg, 0.37 mmol), benzylamine (40 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45a** as white solid (44 mg, 60%). ^1H NMR (600 MHz, $CDCl_3$) δ = 7.68 – 7.66 (m, 3H), 7.40-7.37 (m, 2H), 7.33 – 7.28 (m, 3H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.89 (t, *J* = 7.2 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 144.8, 137.5, 135.5, 129.5 (2C), 128.8 (2C), 128.6, 126.4 (2C), 120.3, 112.9 (2C) ppm.



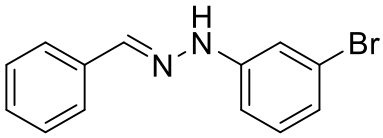
(*E*)-1-benzylidene-2-(*m*-tolyl)hydrazine (3.45b): According to GP I: 1-methyl-3-nitrosobenzene[34a] (45 mg, 0.37 mmol), benzylamine (40 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45b** as yellow gum (31 mg, 40%). FTIR (KBr): $\tilde{\nu}$ = 2956, 2924, 2854, 1587, 1490, 1464, 1376, 1262, 1209, 1097, 1020, 802, 691 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 7.66 (s, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.29 (m, 1H), 7.17 (t, *J* = 7.8, Hz, 1H), 6.98 (s, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.2 Hz, 1H), 2.36 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 144.8, 139.4, 137.3, 135.5, 129.4, 128.8 (2C), 128.6, 126.4 (2C), 121.2, 113.6, 110.2, 21.9 ppm. HRMS: Exact mass calculated for $C_{14}H_{15}N_2$ ($[M+H]^+$): 211.1230, Found: 211.1230.

(*E*)-1-benzylidene-2-(3-fluorophenyl)hydrazine (3.45c): According to GP I: 1-fluoro-3-nitrosobenzene[34b] (46 mg, 0.37 mmol), benzylamine (40 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45c** as white solid (48 mg, 60%). M.p. = 113 – 114 ºC. FTIR (KBr): $\tilde{\nu}$ = 3317, 2960, 2924, 1615, 1518, 1490, 1443, 1263, 1070, 798, 679 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.70 (s, 1H), 7.67 – 7.66 (m, 2H), 7.40 - 7.37 (m, 2H), 7.33 – 7.31 (m, 1H), 7.21 – 7.18 (m, 1H), 6.96 - 6.93 (m, 1H), 6.78 – 6.77 (m, 1H), 6.57 – 6.54 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.0, 163.4, 146.6, 146.5, 138.3, 135.1, 130.63, 130.57, 129.0, 128.9 (2C), 126.5 (2C), 108.43, 108.41, 106.8, 106.7, 100.3, 100.2 ppm. HRMS: Exact mass calculated for $C_{13}H_{12}N_2F$ ($[M+H]^+$): 215.0979, Found: 215.0979.

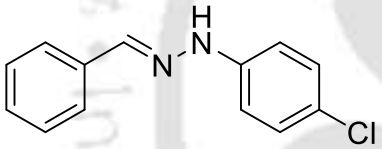
(*E*)-1-benzylidene-2-(3-chlorophenyl)hydrazine (3.45d):[11] According to GP I: 1-chloro-3-nitrosobenzene[33] (53 mg, 0.37 mmol), benzylamine (40 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45d** as white solid (48 mg, 56%). FTIR (KBr): $\tilde{\nu}$ = 3323, 2958, 2918, 1592, 1508, 1483, 1300, 1129, 1091, 991, 852, 694 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.67 – 7.66 (m, 3H), 7.40 – 7.38 (m, 2H), 7.34 – 7.31 (m, 1H), 7.19 – 7.16 (m, 2H), 6.92 – 6.90 (m, 1H), 6.83 (d, *J* = 7.8 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 145.9, 138.5, 135.4, 135.0, 130.5, 129.0, 128.9 (2C), 126.5 (2C), 120.1,

112.9, 111.1 ppm. HRMS: Exact mass calculated for $C_{13}H_{12}N_2Cl$ ($[M+H]^+$): 231.0684, Found: 231.0684.

(*E*)-1-benzylidene-2-(3-bromophenyl)hydrazine (3.45e):[34c] According to GP I: 1-bromo-3-nitrosobenzene[33] (69 mg, 0.37 mmol), benzylamine (40 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45e** as white solid (52 mg, 51%). FTIR (KBr): $\tilde{\nu}$ = 3322, 2956, 2923, 2855, 1589, 1567, 1478, 1287, 1240, 1131, 984, 776, 694 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.67 – 7.66 (m, 3H), 7.60 (s, 1H), 7.40 – 7.38 (m, 2H), 7.35 – 7.32 (m, 2H), 7.13 -7.10 (m, 1H), 6.99 – 6.95 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 146.0, 138.6, 135.0, 130.7, 129.0, 128.9 (2C), 126.6 (2C), 123.5, 123.0, 115.8, 111.5 ppm. HRMS: Exact mass calculated for $C_{13}H_{12}N_2Br$ ($[M+H]^+$): 275.0178, Found: 275.0178.

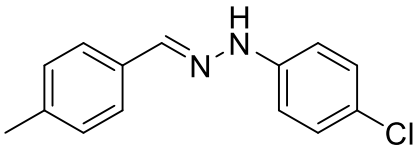


(*E*)-1-benzylidene-2-(4-chlorophenyl)hydrazine (3.45f):[16] According to GP I: 1-chloro-4-nitrosobenzene[33] (53 mg, 0.37 mmol), benzylamine (40 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45f** as white solid (50 mg, 59%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.69 (s, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.40 – 7.36 (m, 2H), 7.33-7.29 (m, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H) ppm. HRMS: Exact mass calculated for $C_{13}H_{12}N_2Cl$ ($[M+H]^+$): 231.0684, Found: 231.0684.



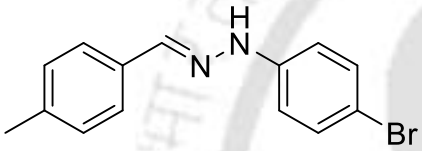
(*E*)-1-benzylidene-2-(4-bromophenyl)hydrazine (3.45g): According to GP I: 1-bromo-4-nitrosobenzene[33] (69 mg, 0.37 mmol), benzylamine (40 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45g** as white solid (49 mg, 48%). M.p. = 125 °C. FTIR (KBr): $\tilde{\nu}$ = 3339, 2962, 2923, 2853, 1650, 1484, 1401, 1257, 1067, 1027, 812, 691 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.69 (s, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.35 (m, 4H), 7.33 – 7.30 (m, 1H), 7.00 (d, *J* = 9.0 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 143.9, 138.2, 135.2, 132.3 (2C), 128.91, 128.86 (2C), 126.5 (2C), 114.5 (2C), 112.0 ppm. HRMS: Exact mass calculated for $C_{13}H_{12}N_2Br$ ($[M+H]^+$): 275.0178, Found: 275.0190.

(*E*)-1-(4-chlorophenyl)-2-(4-methylbenzylidene)hydrazine (3.45h): According to GP I: 1-



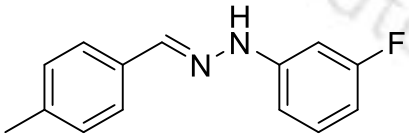
chloro-4-nitrosobenzene (53 mg, 0.37 mmol), 4-methylbenzylamine (45 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45h** as white solid (50 mg, 55%). M.p. = 155 -156 °C. FTIR (KBr): $\tilde{\nu}$ = 3320, 2960, 2923, 2856, 1598, 1500, 1408, 1253, 1092, 827 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.65 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 2.37 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 143.6, 139.0, 138.4, 132.4, 129.6 (3C), 129.4, 126.4 (3C), 124.6, 114.0, 21.6 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}N_2Cl$ ($[M+H]^+$): 245.0840, Found: 245.0840.

(*E*)-1-(4-bromophenyl)-2-(4-methylbenzylidene)hydrazine (3.45i): According to GP I: 1-



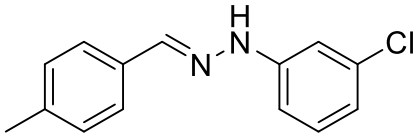
bromo-4-nitrosobenzene (69 mg, 0.37 mmol), 4-methylbenzylamine (45 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45i** as white solid (47 mg, 44%). M.p. = 160 -162 °C. FTIR (KBr): $\tilde{\nu}$ = 2923, 2854, 1592, 1501, 1402, 1248, 1068, 820 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 2.37 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 144.0, 139.0, 138.5, 132.4, 132.2 (2C), 129.6 (2C), 126.4 (2C), 114.5 (2C), 111.8, 21.6 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}N_2Br$ ($[M+H]^+$): 289.0335, Found: 289.0333.

(*E*)-1-(3-fluorophenyl)-2-(4-methylbenzylidene)hydrazine (3.45j): According to GP I: 1-



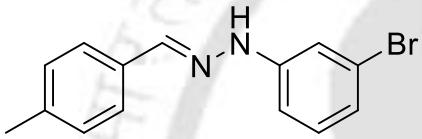
fluoro-3-nitrosobenzene (46 mg, 0.37 mmol), 4-methylbenzylamine (45 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45j** as white solid (49 mg, 58%). M.p. = 111 -113 °C. FTIR (KBr): $\tilde{\nu}$ = 3319, 2960, 1613, 1589, 1490, 1257, 1140, 764, 515 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.21 – 7.15 (m, 3H), 6.95 – 6.91 (m, 1H), 6.77 – 6.75 (m, 1H), 6.56 – 6.51(m, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.9, 146.7, 139.1, 138.7, 132.4, 130.6, 130.5, 129.6 (2C), 126.5 (2C), 108.43, 108.41, 106.7, 106.5, 100.4, 100.1, 21.6 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}N_2F$ ($[M+H]^+$): 229.1136, Found: 229.1147.

(*E*)-1-(3-chlorophenyl)-2-(4-methylbenzylidene)hydrazine (3.45k): According to GP I: 1-



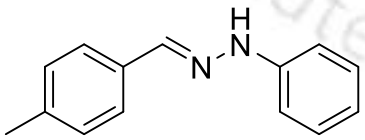
chloro-3-nitrosobenzene (53 mg, 0.37 mmol), 4-methylbenzylamine (45 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45k** as white solid (46 mg, 51%). M.p. = 116 -118 ºC. FTIR (KBr): $\tilde{\nu}$ = 3312, 2924, 2854, 1592, 1501, 1482, 1241, 1131, 1090, 991, 856, 684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.50 (s, 1H), 7.21 – 7.15 (m, 4H), 6.91 – 6.89 (m, 1H), 6.84 – 6.82 (m, 1H), 2.39 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.1, 139.1, 138.9, 135.3, 132.4, 130.4, 129.6 (2C), 126.5 (2C), 120.0, 112.9, 111.1, 21.6 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}N_2Cl$ ($[M+H]^+$): 245.0840, Found: 245.0840.

(*E*)-1-(3-bromophenyl)-2-(4-methylbenzylidene)hydrazine (3.45l): According to GP I: 1-

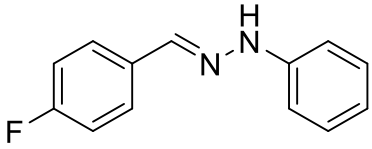


bromo-3-nitrosobenzene (69 mg, 0.37 mmol), 4-methylbenzylamine (45 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45l** as white solid (51 mg, 48%). M.p. = 116 -118 ºC. FTIR (KBr): $\tilde{\nu}$ = 3313, 3029, 2950, 2912, 1589, 1497, 1238, 1130, 1063, 988, 817, 682 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 2.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.98 – 6.93 (m, 2H), 2.38 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.2, 139.2, 138.9, 132.3, 130.7, 129.6 (2C), 126.6 (2C), 123.5, 122.9, 115.8, 111.5, 21.6 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}N_2Br$ ($[M+H]^+$): 289.0335, Found: 289.0337.

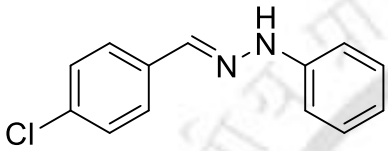
(*E*)-1-(4-methylbenzylidene)-2-phenylhydrazine (3.45m):[16] According to GP I:



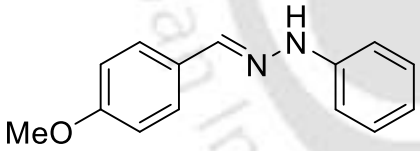
nitrosobenzene (40 mg, 0.37 mmol), p-tolylmethanamine (45 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45m** as white solid (44 mg, 57%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.68 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.86 (t, *J* = 7.2 Hz, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 145.0, 138.7, 137.7, 132.7, 129.54 (2C), 129.49 (2C), 126.4 (2C), 120.1, 112.9 (2C), 21.6 ppm.

(*E*)-1-(4-fluorobenzylidene)-2-phenylhydrazine (3.45n):[16] According to GP I: 

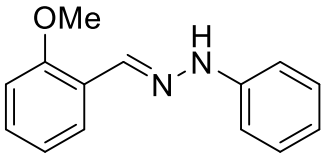
nitrosobenzene (40 mg, 0.37 mmol), 4-fluorobenzylamine (46 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45n** as white solid (47 mg, 60%).^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.67 – 7.62 (m, 3H), 7.30 – 7.27 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.08 – 7.05 (m, 2H), 6.90 – 6.87 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.3, 161.8, 144.8, 136.3, 131.7, 129.5 (2C), 128.0, 127.9, 120.4, 116.0, 115.8, 112.9 (2C) ppm.

(*E*)-1-(4-chlorobenzylidene)-2-phenylhydrazine (3.45o):[16] According to GP I: 

nitrosobenzene (40 mg, 0.37 mmol), 4-chlorobenzylamine (53 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) was reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:15) gave **3.45o** as white solid (47 mg, 55%).^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.64 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 9.0 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.90 – 6.88 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 144.6, 136.0, 134.2, 134.0, 129.5 (2C), 129.0 (2C), 127.5 (2C), 120.6, 113.0 (2C) ppm.

(*E*)-1-(4-methoxybenzylidene)-2-phenylhydrazine (3.45p):[16] According to GP I: 

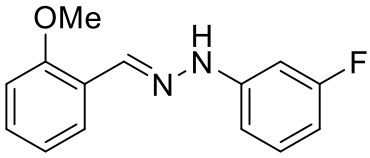
nitrosobenzene (40 mg, 0.37 mmol), 4-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) was reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45p** as white solid (53 mg, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.63 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.86 (t, *J* = 7.2 Hz, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.2, 145.2, 137.6, 129.5 (2C), 128.3, 127.8 (2C), 120.0, 114.3 (2C), 112.9 (2C), 55.5 ppm.

(*E*)-1-(2-methoxybenzylidene)-2-phenylhydrazine (3.45q):[34d] According to GP I: 

nitrosobenzene (40 mg, 0.37 mmol), 2-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45q** as yellow gum (54 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13 (s, 1H), 8.00 – 7.98 (m, 1H), 7.30 – 7.27 (m, 3H), 7.11 (d, *J* =

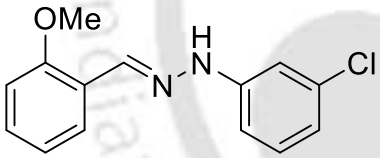
7.6 Hz, 2H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.91 – 6.85 (m, 2H), 3.87 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.2, 145.0, 133.7, 129.8, 129.5 (2C), 126.1, 124.0, 121.2, 120.2, 113.0 (2C), 111.2, 55.6 ppm.

(*E*)-1-(3-fluorophenyl)-2-(2-methoxybenzylidene)hydrazine (3.45r): According to GP I:



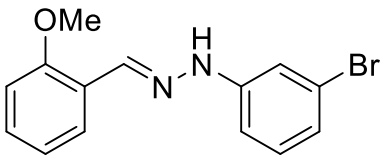
1-fluoro-3-nitrosobenzene (46 mg, 0.37 mmol), 2-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol mmol) were reacted for 18 h in DCM (4 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45r** as yellow gum (64 mg, 71%). FTIR (KBr): $\tilde{\nu}$ = 2926, 2847, 1613, 1601, 1518, 1486, 1288, 1248, 1139, 1023, 756, 683 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 8.00 – 7.98 (m, 1H), 7.67 (s, 1H), 7.32 – 7.28 (m, 1H), 7.21 – 7.15 (m, 2H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.95 – 6.92 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.77 – 6.75 (m, 1H), 6.56 – 6.51 (m, 1H), 3.86 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.5, 163.0, 157.2, 146.9, 146.8, 134.5, 130.6, 130.5, 130.0, 126.1, 123.7, 121.2, 111.2, 108.40, 108.38, 106.6, 106.3, 100.3, 100.0, 55.7 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}FN_2O$ ($[M+H]^+$): 245.1085, Found: 245.1089.

(*E*)-1-(3-chlorophenyl)-2-(2-methoxybenzylidene)hydrazine (3.45s): According to GP I:



1-chloro-3-nitrosobenzene (53 mg, 0.37 mmol), 2-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45s** as yellow gum (53 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 3068, 2956, 2924, 2849, 1597, 1518, 1478, 1326, 1241, 1095, 1020, 853, 756, 606 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 8.00 – 7.97 (m, 1H), 7.32 – 7.27 (m, 1H), 7.18 – 7.14 (m, 2H), 7.02 -6.98 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.82 – 6.80 (m, 1H), 3.86 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) = 157.3, 146.2, 135.4, 134.7, 130.4, 130.1, 126.1, 123.7, 121.2, 119.9, 112.9, 111.2, 111.0, 55.8 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}ClN_2O$ ($[M+H]^+$): 261.0789, Found: 261.0788.

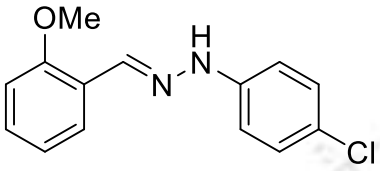
(*E*)-1-(3-bromophenyl)-2-(2-methoxybenzylidene)hydrazine (3.45t): According to GP I:



1-bromo-3-nitrosobenzene (69 mg, 0.37 mmol), 2-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45t** as yellow gum (69 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 2960, 2916, 2848, 1639, 1598, 1466, 1249, 1103,

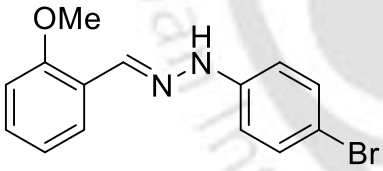
1022, 753, 674. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 7.99 – 7.98 (m, 1H), 7.33 (t, *J* = 1.8 Hz, 1H), 7.31 – 7.28 (m ,1H), 7.11 – 7.08 (m, 1H), 7.01 – 6.99 (m, 1H), 6.96 – 6.93 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 157.2, 146.3, 134.7, 130.7, 130.1, 126.1, 123.6, 123.5, 122.8, 121.2, 115.7, 111.4, 111.1, 55.7 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}BrN_2O$ ($[M+H]^+$): 305.0284, Found: 305.0279.

(*E*)-1-(4-chlorophenyl)-2-(2-methoxybenzylidene)hydrazine (3.45u): According to GP I:



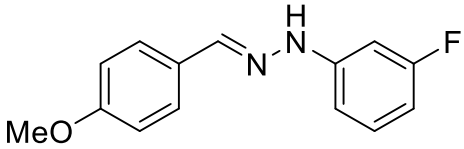
1-chloro-4-nitrosobenzene (53 mg, 0.37 mmol), 2-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45u** as yellow gum (64 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 3080, 2960, 2924, 2852, 1599, 1490, 1437, 1242, 1092, 1019, 822, 756, 606 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.98 - 7.96 (m, 1H), 7.30 – 7.27 (m, 1H), 7.22 – 7.19 (m, 2H), 7.04 – 7.02 (m, 2H), 7.00 – 6.98 (m, 1H), 6.90 – 6.88 (m, 1H), 3.86 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 157.1, 143.7, 134.2, 130.0, 129.3 (2C), 125.9, 124.5, 123.7, 121.1, 113.9 (2C), 111.1, 55.7 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}ClN_2O$ ($[M+H]^+$): 261.0789, Found: 261.0787.

(*E*)-1-(4-bromophenyl)-2-(2-methoxybenzylidene)hydrazine (3.45v): According to GP I:



1-bromo-4-nitrosobenzene (69 mg, 0.37 mmol), 2-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45v** as yellow gum (56 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 2958, 2924, 2849, 1598, 1488, 1437, 1243, 1070, 1020, 822, 755, 606 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.98 – 7.95 (m, 1H), 7.36 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.01 – 6.97 (m, 3H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.2, 144.2, 134.4, 132.2 (2C), 130.0, 126.0, 123.8, 121.2, 114.5 (2C), 111.8, 111.2, 55.8 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}BrN_2O$ ($[M+H]^+$): 305.0284, Found: 305.0291.

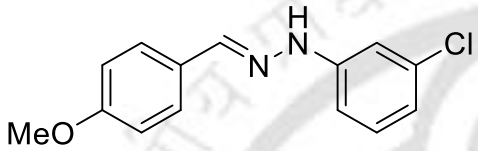
(*E*)-1-(3-fluorophenyl)-2-(4-methoxybenzylidene)hydrazine (3.45w): According to GP I:



1-fluoro-3-nitrosobenzene (46 mg, 0.37 mmol), 4-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol mmol) were reacted for 18 h

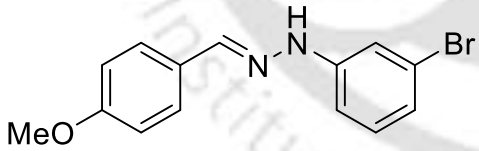
in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45w** as white solid (58 mg, 64%). M.p. = 120 -122 °C. FTIR (KBr): $\tilde{\nu}$ = 3310, 2964, 2921, 2837, 1614, 1495, 1413, 1261, 1175, 917, 840, 687 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.65 (s, 1H), 7.60 (d, *J* = 9.0 Hz, 2H), 7.20 – 7.16 (m, 1H), 6.92 (d, *J* = 9.0 Hz, 3H), 6.75 – 6.74 (m, 1H), 6.55 – 6.52 (m, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.0, 163.4, 160.4, 146.9, 146.8, 138.4, 130.6, 130.5, 127.94 (2C), 127.90, 114.3 (2C), 108.31, 108.29, 106.5, 106.3, 100.2, 100.0, 55.6 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}FN_2O$ ($[M+H]^+$): 245.1085, Found: 245.1085.

(*E*)-1-(3-chlorophenyl)-2-(4-methoxybenzylidene)hydrazine (3.45x): According to GP I:



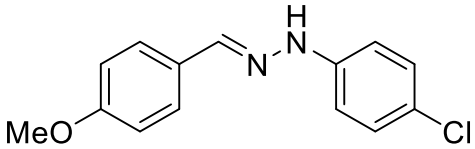
1-chloro-3-nitrosobenzene (53 mg, 0.37 mmol), 4-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45x** as white solid (54 mg, 56%). M.p. = 132 -133 °C. FTIR (KBr): $\tilde{\nu}$ = 3313, 2964, 2922, 2831, 1594, 1485, 1295, 1251, 1172, 1026, 917, 767, 684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.60 – 7.57 (m, 3H), 7.18 – 7.14 (m, 2H), 6.93 – 6.90 (m, 2H), 6.90 – 6.87 (m, 1H), 6.83 – 6.80 (m, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.5, 146.3, 138.7, 135.3, 130.4, 128.0 (2C), 127.9, 119.8, 114.4 (2C), 112.8, 111.0, 55.5 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}ClN_2O$ ($[M+H]^+$): 261.0789, Found: 261.0788.

(*E*)-1-(3-bromophenyl)-2-(4-methoxybenzylidene)hydrazine (3.45y): According to GP I:



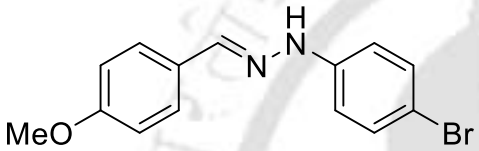
1-bromo-3-nitrosobenzene (69 mg, 0.37 mmol), 4-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (4 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45y** as white solid (56 mg, 50%). M.p. = 132 -133 °C. FTIR (KBr): $\tilde{\nu}$ = 3300, 2960, 2926, 2839, 1592, 1500, 1415, 1290, 1170, 1023, 840, 675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.60 – 7.57 (m, 2H), 7.31 (t, *J* = 2.0 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.97 – 6.90 (m, 4H), 3.84 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.5, 146.4, 138.7, 130.7, 128.0 (2C), 127.9, 123.5, 122.7, 115.7, 114.4 (2C), 111.4, 55.6 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}BrN_2O$ ($[M+H]^+$): 305.0284, Found: 305.0280.

(*E*)-1-(4-chlorophenyl)-2-(4-methoxybenzylidene)hydrazine (3.45z):[34e] According to GP



I: 1-chloro-4-nitrosobenzene (53 mg, 0.37 mmol), 4-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45z** as white solid (47 mg, 49%). FTIR (KBr): $\tilde{\nu}$ = 3310, 2958, 2925, 2839, 1606, 1488, 1459, 1411, 1252, 1171, 1092, 915, 818, 646 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.66 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{14}H_{14}ClN_2O$ ($[M+H]^+$): 261.0789, Found: 261.0788.

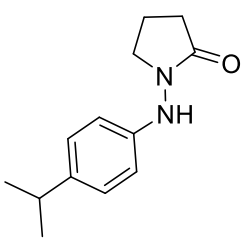
(*E*)-1-(4-bromophenyl)-2-(4-methoxybenzylidene)hydrazine (3.45aa):[34e] According to



GP I: 1-bromo-4-nitrosobenzene (69 mg, 0.37 mmol), 4-methoxybenzylamine (51 mg, 0.37 mmol) and acetic acid (11 µL, 0.19 mmol) were reacted for 18 h in DCM (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:10) gave **3.45aa** as white solid (51 mg, 45%). FTIR (KBr): $\tilde{\nu}$ = 3307, 2962, 2928, 2829, 1604, 1505, 1486, 1407, 1252, 1172, 1024, 818, 642 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.62 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.46 (s, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.4, 144.2, 138.3, 132.2 (2C), 128.0, 127.9 (2C), 114.43 (2C), 114.37 (2C), 111.7, 55.6 ppm. HRMS: Exact mass calculated for $C_{14}H_{14}BrN_2O$ ($[M+H]^+$): 305.0384, Found: 305.0275.

General Procedure for the synthesis of hydrazide derivatives (II): Freshly prepared nitrosoarenes (1 eq.) and 2,4-dichlorobenzoic acid (0.5 eq.) were successively added to a solution of cyclic secondary amines (4 eq.) in toluene (3 mL). Then the reaction mixture was refluxed for 10-12 h under argon atmosphere. Then the solvent was evaporated under reduced pressure and crude mixture was subjected to column chromatography (silica gel) to afford analytically pure products.

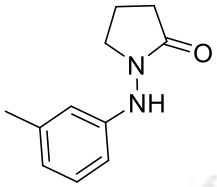
1-((4-isopropylphenyl)amino)pyrrolidin-2-one (3.59a): According to GP II: 1- isopropyl-



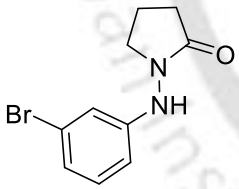
4-nitrosobenzene (37 mg, 0.25 mmol), pyrrolidine (82 µL, 1.00 mmol) and 2,4-DCBA (24 mg, 0.12 mmol) were reacted for 10 h in toluene (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:3) gave **3.59a** as brown gum (29 mg, 52%). FTIR (KBr): $\tilde{\nu}$ =

2962, 2924, 2853, 1696, 1589, 1514, 1455, 210, 1099, 803, 608 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.10 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.04 (s, 1H), 3.63 – 3.60 (m, 2H), 2.87 – 2.80 (m, 1H), 2.48 (t, *J* = 8.0 Hz, 2H), 2.18 – 2.11 (m, 2H), 1.20 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.1, 144.1, 142.5, 127.5 (2C), 114.2 (2C), 48.5, 33.6, 29.2, 24.4 (2C), 16.7 ppm. HRMS: Exact mass calculated for $C_{13}H_{19}N_2O$ ($[M+H]^+$): 219.1492, Found: 219.1502.

1-(m-tolylamino)pyrrolidin-2-one (3.59b): According to GP II: 1- methyl-3-nitrosobenzene (30 mg, 0.25 mmol), pyrrolidine (82 µL, 1.00 mmol) and 2,4-DCBA (24 mg, 0.12 mmol) were reacted for 10 h in toluene (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:3) gave **3.59b** as white solid (21 mg, 45%). M.p. = 123 -125 °C. FTIR (KBr): $\tilde{\nu}$ = 2956, 2923, 2854, 1697, 1609, 1490, 1415, 1264, 1381, 1019, 777, 541 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.14 – 7.10 (m, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.57 - 6.55 (m, 2H), 6.03 (s, 1H), 3.63 – 3.60 (m, 2H), 2.49 (t, *J* = 8.0 Hz, 2H), 2.29 (s, 3H), 2.19 – 2.12 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.2, 146.3, 139.5, 129.4, 122.6, 114.6, 111.0, 48.5, 29.1, 21.8, 16.7 ppm. HRMS: Exact mass calculated for $C_{11}H_{15}N_2O$ ($[M+H]^+$): 191.1179, Found: 191.1179.



1-((3-bromophenyl)amino)pyrrolidin-2-one (3.59c): According to GP II: 1- bromo-3-nitrosobenzene (46 mg, 0.25 mmol), pyrrolidine (82 µL, 1.00 mmol) and 2,4-DCBA (24 mg, 0.12 mmol) were reacted for 10 h in toluene (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:3) gave **3.59c** as light yellow gum (29 mg, 46%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2925, 2851, 1699, 1595, 1524, 1476, 1294, 1262, 1096, 1021, 801, 682 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.08 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 6.25 (s, 1H), 3.62 – 3.58 (m, 2H), 2.52 – 2.47 (m, 2H), 2.21 – 2.13 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.4, 147.8, 130.9, 124.4, 123.5, 116.4, 112.4, 48.4, 29.0, 16.6 ppm. HRMS: Exact mass calculated for $C_{10}H_{12}N_2BrO$ ($[M+H]^+$): 255.0128, Found: 255.0124.

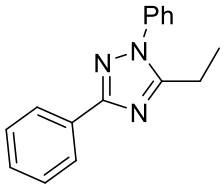


1-((4-chlorophenyl)amino)pyrrolidin-2-one (3.59d): According to GP II: 1- chloro-4-nitrosobenzene (35 mg, 0.25 mmol), pyrrolidine (82 µL, 1.00 mmol) and 2,4-DCBA (24 mg, 0.12 mmol) were reacted for 10 h in toluene (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:3) gave **3.59d** as light yellow gum (25 mg, 48%). FTIR (KBr): $\tilde{\nu}$ = 2960, 2924, 2853, 1696, 1596, 1491, 1417, 1261, 1091, 1020, 822, 630 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.12 (s, 1H), 3.62 – 3.58 (m, 2H), 2.51 – 2.47 (m, 2H), 2.22 – 2.12 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.3, 145.0, 129.5 (2C), 126.5, 115.1 (2C), 48.4, 29.0, 16.7 ppm. HRMS: Exact mass calculated for $C_{10}H_{12}N_2ClO$ ($[M+H]^+$): 211.0633, Found: 211.0634.

2-(phenylamino)-3,4-dihydroisoquinolin-1(2*H*)-one (3.61): According to GP II: nitrosobenzene (27 mg, 0.25 mmol), tetrahydroisoquinoline (0.13 mL, 1.00 mmol) and 2,4-DCBA (24 mg, 0.12 mmol) were reacted for 12 h in toluene (3 mL) and column chromatography of crude product (silica gel; EtOAc : hexane, 1:3) gave **3.61** as white solid (30 mg, 50%). M.P. = 155 -156 °C. FTIR (KBr): $\tilde{\nu}$ = 2956, 2925, 2854, 1599, 1464, 1211, 1071, 1019, 719, 606 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (d, *J* = 7.6 Hz, 1H), 7.49 – 7.46 (m, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.28 (s, 1H), 7.24 (s, 1H), 7.00 (s, 1H), 6.96 – 6.91 (m, 3H), 3.87 (t, *J* = 6.8 Hz, 2H), 3.26 – 3.23 (m, 2H) ppm. ^{13}C NMR (151 MHz, CDCl3) δ = 165.1, 147.1, 138.2, 132.5, 129.5 (2C), 128.7, 128.6, 127.5, 127.4, 121.9, 114.4 (2C), 49.8, 28.6 ppm. HRMS: Exact mass calculated for $C_{15}H_{15}N_2O$ ($[M+H]^+$): 239.1179, Found: 239.1178.

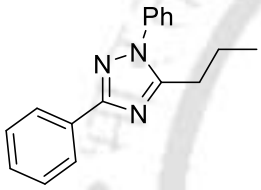
The general procedure for one pot synthesis of triazole (III): Freshly prepared nitrosoarenes (1eq.) and acetic acid were successively added to a solution of benzyl amines (1eq.) in DCM (3 - 4 mL). Then the reaction mixture was refluxed for 18 h under argon atmosphere. The reaction mixture was evaporated to dryness, acetonitrile (2 mL) added to it. Primary amine (3 eq.) followed by molecular iodine (20 mol%) and aq. TBHP (3 eq.) were successively added to the reaction mixture and the mixture was refluxed at 90 °C for additional 4 h. Then the reaction mixture was cooled to room temperature, 15 mL water was added to the mixture, and the mixture was extracted with DCM (3 ×30 mL). The combined organic layers were washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and concentrated in vacuo to provide a crude product, which was purified by column chromatography on silica gel to get analytically pure product.

1,3-diphenyl-5-ethyl-1*H*-1,2,4-triazole (3.66a):[31] According to GP III: nitrosobenzene (50



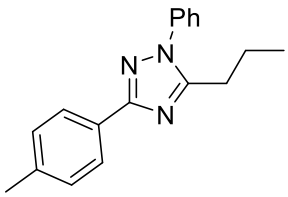
mg, 0.47 mmol), benzylamine (50 mg, 0.47 mmol) and acetic acid (14 µL, 0.24 mmol) were reacted for 18 h in DCM (4 mL), The reaction mixture was evaporated to dryness and diluted with acetonitrile (2 mL). n-Propylamine (83 mg, 1.41 mmol), molecular iodine (24 mg, 0.094 mmol) and aq. TBHP (127 mg, 1.41 mmol) were added to the mixture and the mixture was heated at 90 °C for additional 4 h and the crude product was purifying by column chromatography (silica gel; EtOAc : hexane, 1:10) gave **3.66a** as yellow gum (53 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 – 8.16 (m, 2H), 7.52 – 7.36 (m, 8H), 2.87 -2.82 (m, 2H), 1.35 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.5, 158.0, 137.7, 131.1, 129.5 (2C), 129.3, 129.0, 128.6 (2C), 126.5 (2C), 125.2 (2C), 20.3, 12.5 ppm.

1,3-diphenyl-5-propyl-1*H*-1,2,4-triazole (3.66b):[31] According to GP III, nitrosobenzene



(50 mg, 0.47 mmol), benzylamine (50 mg, 0.47 mmol) and acetic acid (14 µL, 0.24 mmol) were reacted for 18 h in DCM (4 mL), The reaction mixture was evaporated to dryness and diluted with acetonitrile (2 mL). n-Butylamine (0.10 g, 1.41 mmol), molecular iodine (24 mg, 0.094 mmol) and aq. TBHP (127 mg, 1.41 mmol) were added to the mixture and the mixture was heated at 90 °C for additional 4 h and the crude product was purifying by column chromatography (silica gel; EtOAc : hexane, 1:10) gave **3.66b** as yellow gum (51 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 – 8.17 (m, 2H), 7.52 – 7.36 (m, 8H), 2.80 (t, *J* = 7.6 Hz, 2H), 1.86 – 1.77 (m, 2H), 0.98 – 0.94 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.5, 157.0, 137.7, 131.1, 129.5 (2C), 129.3, 129.0, 128.6 (2C), 126.5 (2C), 125.3 (2C), 28.6, 21.5, 13.9 ppm.

1-phenyl-5-propyl-3-(*p*-tolyl)-1*H*-1,2,4-triazole (3.66c): According to GP III:



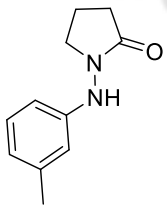
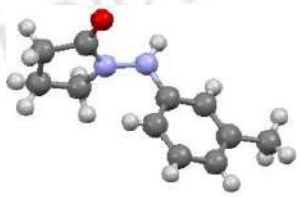
nitrosobenzene (50 mg, 0.47 mmol), 4-methylbenzylamine (57 mg, 0.47 mmol) and acetic acid (14 µL, 0.24 mmol) were reacted for 18 h in DCM (4 mL), The reaction mixture was evaporated to dryness and diluted with acetonitrile (2 mL). n-Butylamine (0.10 g, 1.41 mmol), molecular iodine (24 mg, 0.094 mmol) and aq. TBHP (127 mg, 1.41 mmol) were added to the mixture and the mixture was heated at 90 °C for additional 4 h and the crude product was purifying by column chromatography (silica gel; EtOAc : hexane, 1:10) gave **3.66c** as yellow gum (42 mg, 32%). FTIR (KBr): $\tilde{\nu}$ = 2960, 2926, 2854, 1639, 1598, 1501, 1468, 1347, 1111, 1020, 831, 751, 692. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 8.0 Hz,

2H), 7.54 – 7.44 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.82 – 2.78 (m, 2H), 2.39 (s, 3H), 1.86 – 1.77 (m, 2H), 0.98 – 0.94 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.7, 157.0, 139.3, 137.88, 129.6 (2C), 129.4 (2C), 129.1, 128.4, 126.6 (2C), 125.5 (2C), 28.7, 21.7, 21.6, 14.0 ppm. HRMS: Exact mass calculated for $C_{18}H_{20}N_3$ ($[M+H]^+$): 278.1651, Found: 278.1656.

5-nonyl-1,3-diphenyl-1*H*-1,2,4-triazole (3.66d): According to GP III: nitrosobenzene (50 mg, 0.47 mmol), benzylamine (50 mg, 0.47 mmol) and acetic acid (14 µL, 0.24 mmol) were reacted for 18 h in DCM (4 mL), The reaction mixture was evaporated to dryness and diluted with acetonitrile (2 mL). *n*-Decylamine (0.22 g, 1.41 mmol), molecular iodine (24 mg, 0.094 mmol) and aq. TBHP (127 mg, 1.41 mmol) were added to the mixture and the mixture was heated at 90°C for additional 4 h and the crude product was purifying by column chromatography (silica gel; EtOAc : hexane, 1:15) gave **3.66d** as yellow gum (49 mg, 30%). FTIR (KBr): $\tilde{\nu}$ = 3066, 2954, 2925, 2854, 1645, 1599, 1500, 1466, 1354, 1173, 1070, 1022, 763, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.18 - 8.15 (m, 2H), 7.54 – 7.37 (m, 8H), 2.84 – 2.80 (m, 2H), 1.81 – 1.74 (m, 2H), 1.35 – 1.23 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.6, 157.3, 137.8, 131.2, 129.6 (2C), 129.3, 129.1, 128.7 (2C), 126.6 (2C), 125.4 (2C), 32.0, 29.5, 29.38, 29.36, 29.3, 28.2, 26.8, 22.8, 14.3 ppm. HRMS: Exact mass calculated for $C_{23}H_{30}N_3$ ($[M+H]^+$): 348.2434, Found: 348.2434.

Crystallographic Data:

Crystal of **3.59b:**

	 CCDC:1915270
Empirical formula	$C_{11}H_{14}N_2O$
Formula weight	190.24
Crystal habit, colour	Block, colourless
Crystal size, mm^3	0.24×0.17×0.15
Temperature, T	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	Tetragonal

Space group	I 41/a
Unit cell dimensions	a = 17.5108(6) Å b = 17.5108(6) Å c = 13.8438(5) Å α = 90°, β = 90°, γ = 90°,
Volume, V(Å^3)	4244.9(3)
Z	16
Calculated density, Mg·m^{-3}	1.191
Absorption coefficient, μ(mm^{-1})	0.078
F(000)	1632
θ range for data collection	2.99 º to 24.98 º
Limiting indices	–12≤ h≤ 20, –20 ≤ k≤ 16, –10≤ l≤ 16
Reflection collected / unique	4257 / 1268
Completeness to θ	99.9% (θ = 24.98 º)
Refinement method	SHELXL- 97 (Sheldrick, 1997)
Data / restraints / parameters	1268 / 0 / 128
Goodness – of – fit on F^2	0.914
Final R indices [I>2sigma(I)]	R1 = 0.0638, wR2 = 0.1153
R indices (all data)	R1 = 0.0910, wR2 = 0.1286
Largest diff. peak and hole	0.334 and -0.308 e·Å^{-3}

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CHAPTER - 4

Lewis Acid Catalyzed Pseudo Three-Component Annulation of Nitrosoarenes and (Epoxy)styrenes to provide arylquinolines

4.1 Introduction:

Quinoline derivatives are ubiquitous substructures of natural products and unnatural compounds possessing valuable biological activities.[1] Functionalized quinolines, particularly aryl-quinolines, are widely found as the key scaffold of many natural products and bioactive molecules (**Figure 1**).[2] Therefore, efforts are being devoted to the development of novel and more efficient synthetic methods for the synthesis of functionalized quinoline derivatives.[3,13,21] However, the development of novel synthetic methods to obtain quinoline derivatives with a wide structural diversity starting from readily available starting materials under simple reaction conditions still remains challenging and desirable.

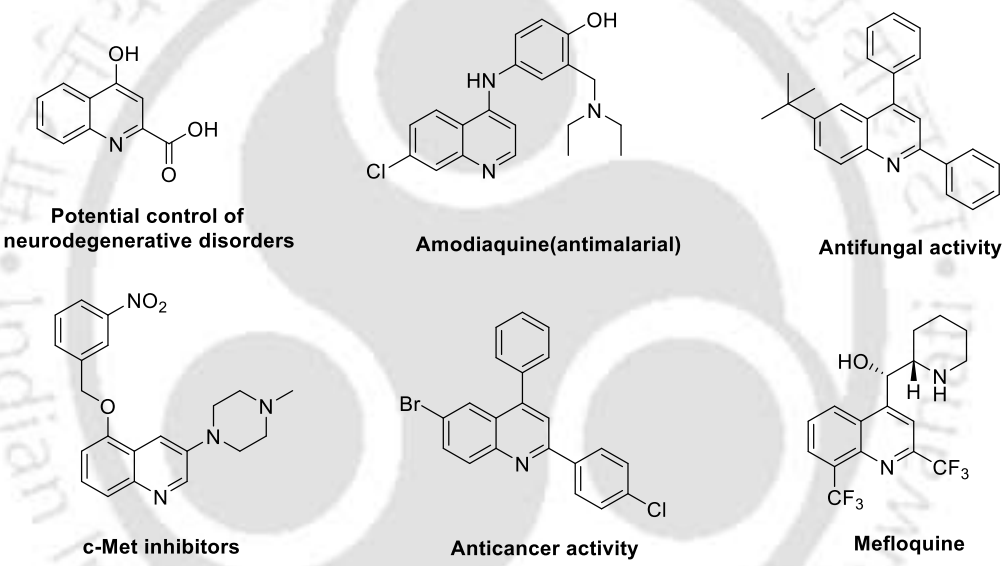
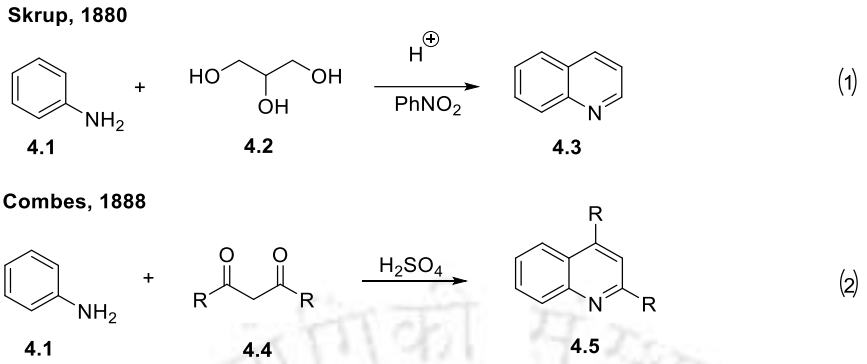


Figure 1: Bio-active quinoline molecules.

4.2 Name reaction for the synthesis of quinolines:

From last few decades, owing to the enormous pharmacological activity, continuous efforts have been made to develop clean and selective routes toward these heterocycles. Skrup synthesis[4] and Combes synthesis[5] are the very earlier report on acid catalyzed quinoline synthesis. In the reaction, aniline **4.1** and glycerol **4.2** were heated with sulfuric acid in presence of an oxidizing agent to produce quinoline **4.3** (**Scheme 1**, eq. 1). Later in 1888, Combes quinoline synthesis was first reported. It involved the condensation of unsubstituted anilines **4.1** with

β-diketones **4.4** to form substituted quinolines **4.5** *via* an acid-catalyzed ring closure of an intermediate Schiff base (**Scheme 1**, eq. 2).

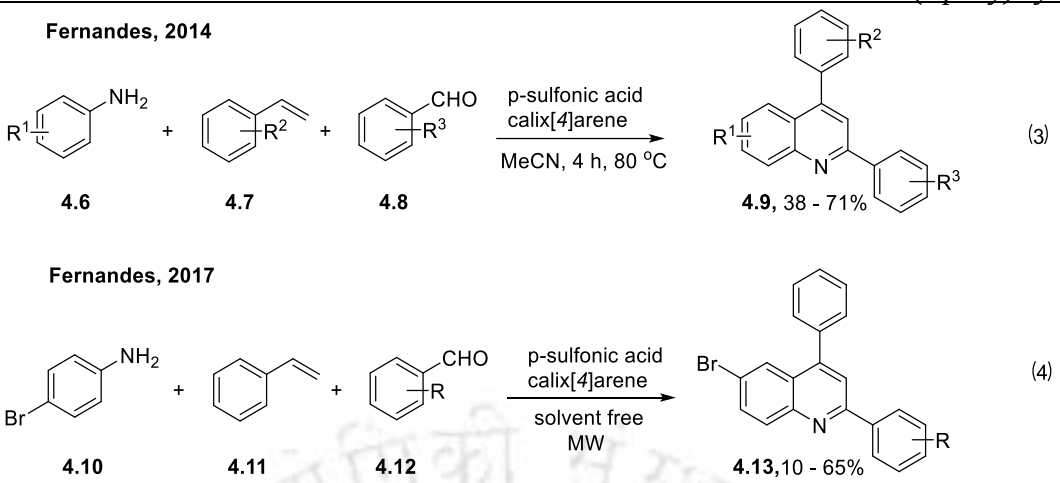


Scheme 1: Skrup and Combes quinolines synthesis.

4.3 Use of Povarov reaction for quinoline synthesis:

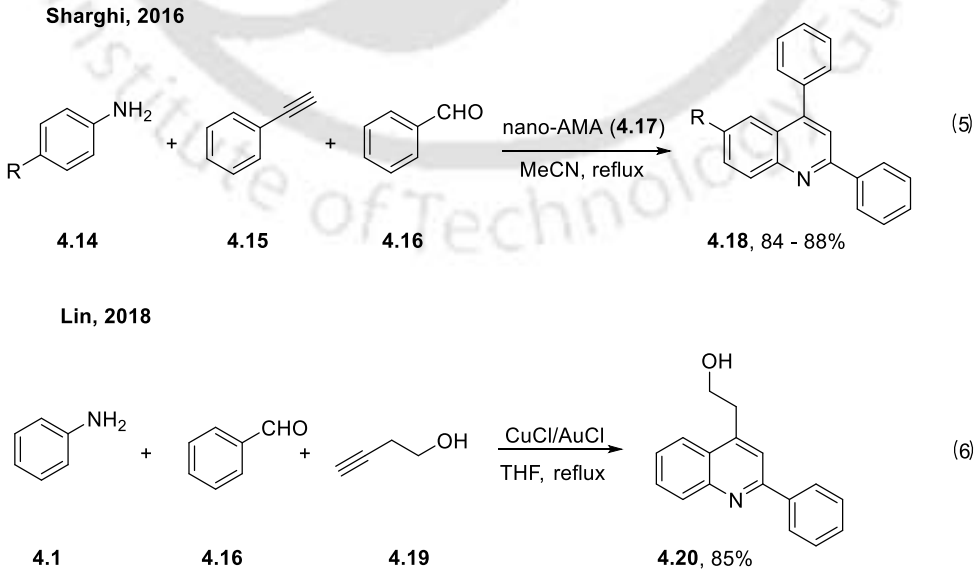
The Povarov reaction is a formal cycloaddition between an aromatic imine and an alkene. Notably, the reaction can be performed in a three-component fashion using a dienophile and an *N*-arylimine, generated *in situ* from a suitable arylamine and a carbonyl.[6] With this principle, the resulting tetrahydroquinolines can be transformed into the corresponding quinolines in one-pot by treatment with an oxidant.

In 2014, Fernandes *et al.* reported *p*-sulfonic acid calix[*4*]arene catalyzed cascade pathway involving the Povarov reaction and hydrogen transfer. Three component reaction of aniline derivatives **4.6**, arylaldehyde **4.8** and styrene derivative **4.7** afforded 2,4-disubstituted quinolines in good yields under heating conditions in a single pot process (**Scheme 2,** eq. 3).[7] Later in 2017, same group developed a microwave assisted method for the synthesis of quinolines **4.13** with good yields using 4-bromoquinoline **4.10**, styrene **4.11** and arylaldehyde **4.12** (**Scheme 2,** eq. 4).[8] Synthesized quinolines **4.13** were tested for their antifungal, anticancer and antioxidant properties and disclosed with high biological activities.



Scheme 2: Quinoline synthesis by Fernandes *et al.*

In 2016, Sharghi *et al.* described an efficient and useful procedure for the synthesis of 2,4-disubstituted quinolines **4.18** *via* one-pot three component reaction of aryl amines **4.14**, benzaldehyde **4.16** and phenylacetylene **4.15** using Al_2O_3 nanoparticles/methanesulfonic acid (nano-AMA, **4.17**) as a new catalyst (**Scheme 3**, eq. 5).[9] In 2018, Lin *et al.* reported a new method to construct 4-hydroxalkyl-quinoline **4.20** derivatives *via* Cu(I)/Au(I) catalyzed cyclization of anilines **4.1** with benzaldehyde **4.16** and aliphatic alkynes **4.19**. The three-component cascade reaction provided an effective approach for easy access to various quinoline containing an aliphatic chain substituent at the 4-position with high yields (**Scheme 3**, eq. 6).[10]

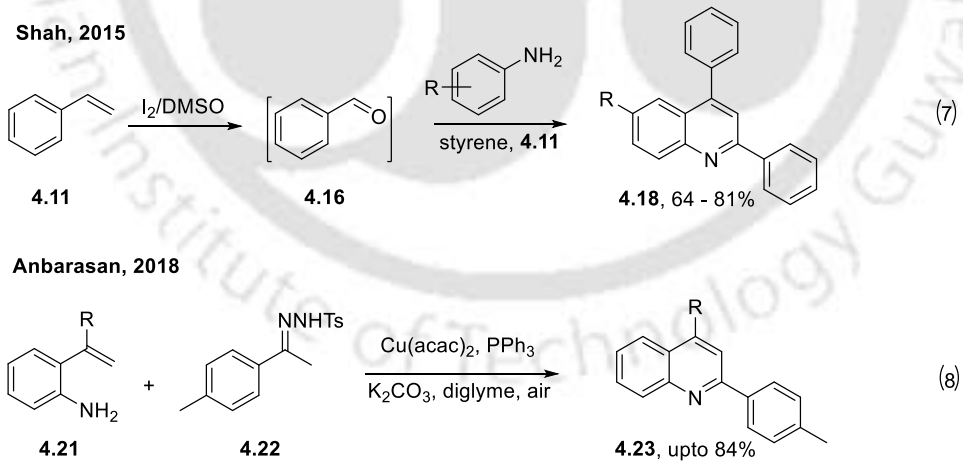


Scheme 3: Known methods of quinoline synthesis.

4.4 2,4-di aryl quinoline synthesis from other starting materials:

Due to important bioactivity of quinoline scaffolds, considerable research has been devoted to develop new methods for constructing substituted quinoline compounds not only *via* Povarov reaction but exploitation of other synthetic strategies. Recently, transition metal-catalyzed annulation reaction of anilines has been used as potent tools for the synthesis of these heterocyclic compounds.[11] Annulation reaction involving multi-component components is a powerful strategy for the synthesis of these cyclic compounds.[12] Multiple numbers of bond breaking and bond making can be achieved in a single operation, which makes the strategy advantageous in the context of step and atom economy.

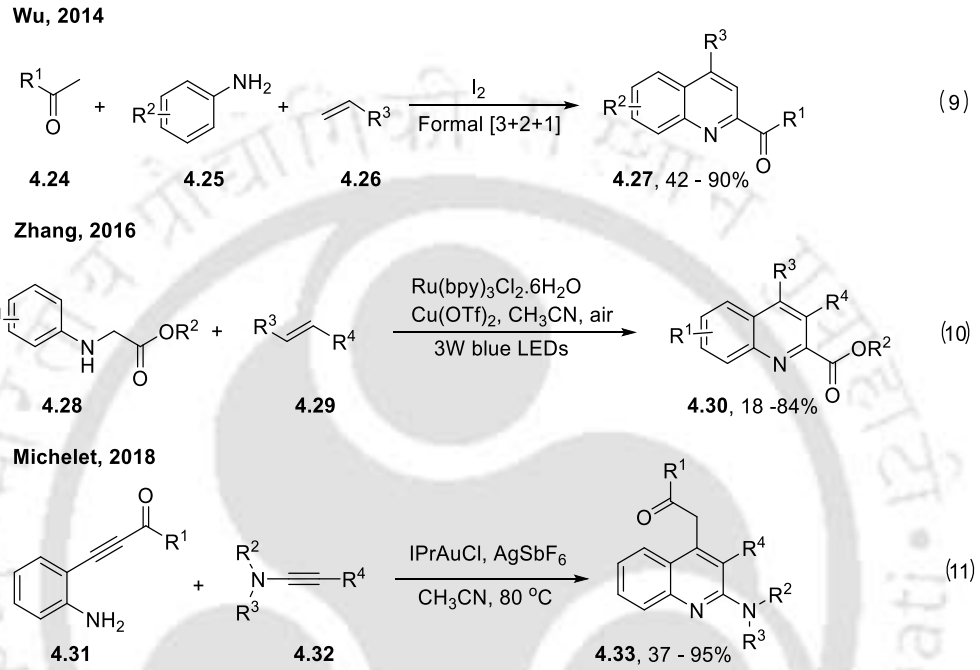
In 2015, Shah *et al.* established a new metal free self-sorting tandem reaction between styrenes **4.11** and anilines to access 2,4-disubstituted quinolines **4.18** proceeded *via* C=C bond cleavage to benzaldehyde **4.16**. The reaction was based on simultaneous C–C and C–N bond formation under metal free conditions (**Scheme 4**, eq. 7).[13] In 2018, Anbarasan *et al.* developed an efficient and general method *via* copper catalyzed oxidative cyclization of *o*-vinylaniline **4.21** employing *N*-tosylhydrazone **4.22** as coupling partner. Various substituted quinoline derivatives **4.23** of biological importance were achieved in good to excellent yield (**Scheme 4**, eq. 8).[14]



Scheme 4: Quinoline synthesis from different olefins.

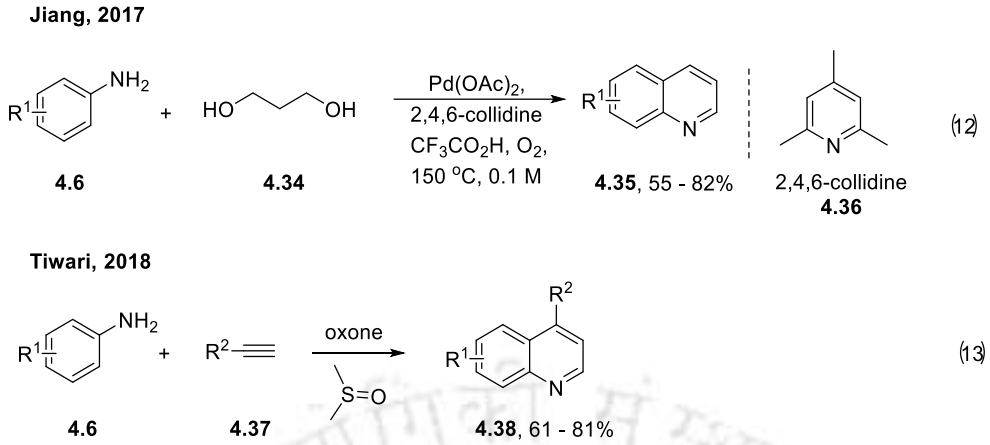
In 2014, Wu *et al.* developed molecular iodine mediated formal [3 + 2 + 1] cycloaddition reaction for the direct synthesis of substituted quinolines **4.27** from methyl ketones **4.24**, arylamines **4.25**, and olefins **4.26** (**Scheme 5**, eq. 9).[15] In 2016, Zhang *et al.* discovered a visible-light induced tandem reaction involving photocatalytic aerobic oxidative

dehydrogenative coupling reaction followed by aromatization. Highly substituted quinolines **4.30** were achieved from the reaction of glycine esters **4.28** with un-activated alkenes **4.29** at room temperature under air (**Scheme 5**, eq. 10).[16] In 2018, Michelet *et al.* reported a mild synthetic route for the preparation of 2-aminoquinolines **4.33** *via* a gold-catalyzed cascade reaction of *β*-(2-aminophenyl)-*α,β*-ynones **4.31** with ynamides **4.32** (**Scheme 5**, eq. 11).[17]



Scheme 5: Quinoline synthesis from aromatic amines.

In 2017, Jiang *et al.* developed an aerobic oxidative aromatization of simple aliphatic alcohols **4.34** and aniline derivatives **4.6** under the $Pd(OAc)_2$/2,4,6-Collidine/Brønsted acid catalytic system, providing a direct approach for the synthesis of diversely substituted quinolines **4.35** (**Scheme 6**, eq. 12).[18] Later in 2018, Tiwari *et al.* presented an efficient and transition-metal-free approach for the synthesis of 4-arylquinolines **4.38** from readily available anilines **4.6** and alkynes **4.37** in the presence of $K_2S_2O_8$ (oxone) and DMSO (**Scheme 6**, eq. 13). A wide range of alkynes and anilines containing a diverse range of substitution patterns successfully underwent the one-pot cyclization reaction.[19]

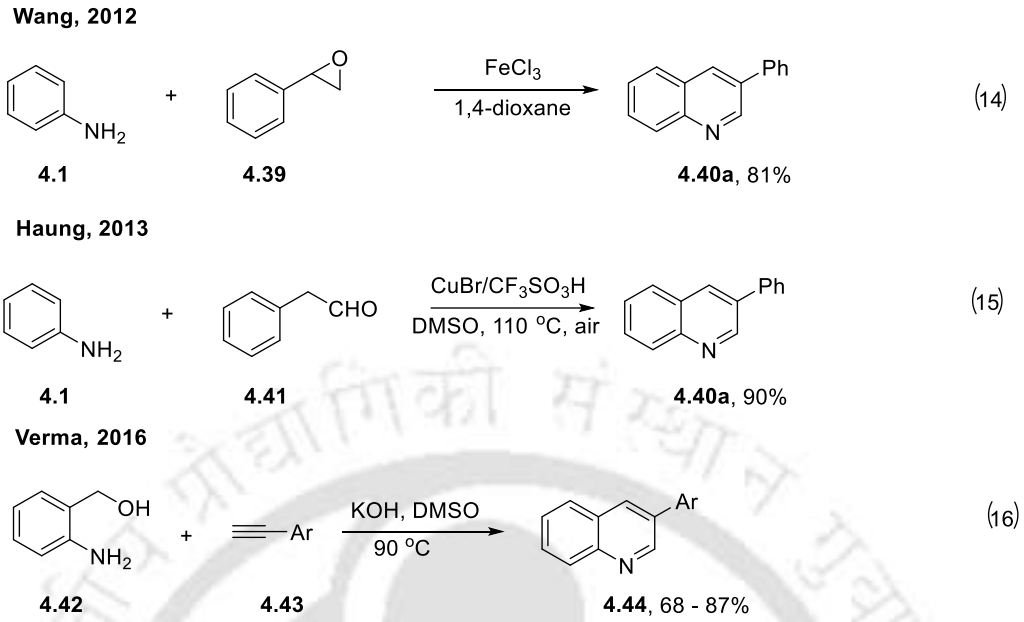


Scheme 6: Quinoline synthesis from alcohols and alkenes.

4.5. Known methods for 3-substituted quinoline synthesis:

3-Arylquinolines are an important class of compounds having biological activities.[20] Several methods have been reported so far for the synthesis of 3-arylquinolines.

In 2012, Wang *et al.* developed iron-promoted tandem reaction of aniline **4.1** with styrene oxide **4.39** *via* C-C cleavage and C-H activation. Utilization of an inexpensive $FeCl_3$ as promoter was suitable to provide a 3-phenyquinoline **4.40a** from the simple and readily available starting materials (**Scheme 7**, eq. 14).[21] Later on, in 2013, Huang *et al.* achieved an efficient, CuBr promoted, method for the direct synthesis of 3-phenylquinoline **4.40a** from readily available anilines **4.1** and phenylacetaldehyde **4.41** through C-H functionalization, C-C/C-N bond formation, and C-C bond cleavage (**Scheme 7**, eq. 15).[22] In 2016, Verma *et al.* accomplished a highly efficient metal free approach for the regioselective synthesis of C-3-functionalized quinolines **4.44** from azadienes which is *in situ* generated from 2-aminobenzyl alcohol **4.42** and terminal alkynes **4.43** *via* [4 + 2] cycloaddition (**Scheme 7**, eq. 16). [23]

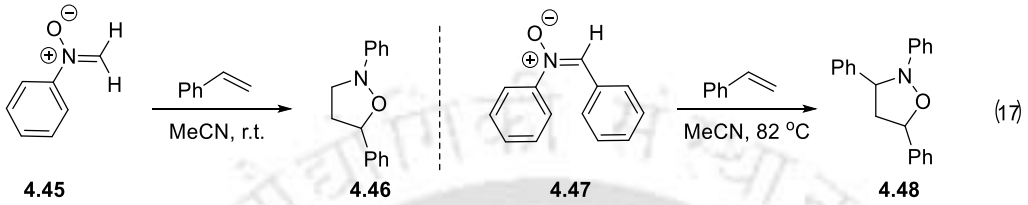


Scheme 7: Known methods for 3-arylquinolines synthesis.

Nitrosoarenes are used in a wide variety of reactions, such as Diels–Alder, ene, [3+2] cycloaddition, and aldol reactions, to install the amine and oxygen functionality in organic molecules.[24] In addition, nitrosoarenes also participate in different annulation reactions to provide a variety of heterocycles.[25] Primarily, the reactive nitroso functionality of nitrosoarenes participates in the reactions. In most of the cases, the arene moiety is sacrificed after the reaction. Therefore, the development of a reaction for the C–H functionalization of nitrosoarenes that incorporates the arene moiety into the product is of great interest. In this context, a few examples of reactions of nitrosoarenes involving both nitroso and arene moieties have been reported recently.[26,27] Highly reactive molecules, such as aryne, alkyne, enone and donor–acceptor cyclopropanes, react with nitrosoarenes acting as a three-atom unit (C–C–N) in the presence of suitable metal catalysts/reagents to afford different heterocycles.[27]

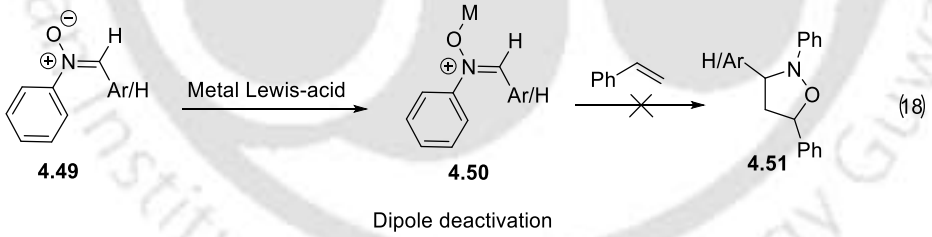
4.6 Hypothesis:

Nitrone, which is well known for their 1,3-dipolar cycloaddition reaction with the styrene/oliefin.[28] Connell *et al.* reported the synthesis of oxazolidine derivatives *via* the formation of nitrone *in situ* from the reaction of nitrosoarene and the styrene under metal-free conditions (**Scheme 8**, eq. 17). [29] The mechanistic path followed [3+2]-cycloaddition of nitrone with the styrene derivatives.



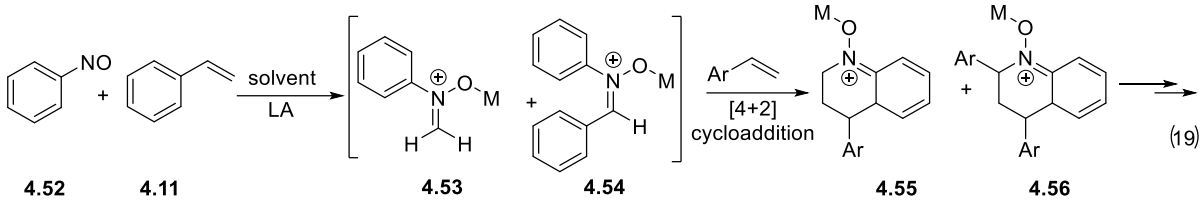
Scheme 8: Known reaction of nitrone with styrene.

It was anticipated that the use of oxophilic lanthanide-based Lewis's acid, such as Sc^{3+}, Yb^{3+} could deactivate the dipole of nitrone **4.49** through strong coordination with the anionic oxygen atom resulting the formation of the metal coordinated nitrone **4.50**. This would open the possibility of a different mode of reactivity of nitrone with the olefin.[30] As a result, oxazolidine **4.51** may not be obtained *via* well-known [3+2] cycloaddition (**Scheme 9**, eq. 18).



Scheme 9: Reactivity-switch in presence of Lewis acid.

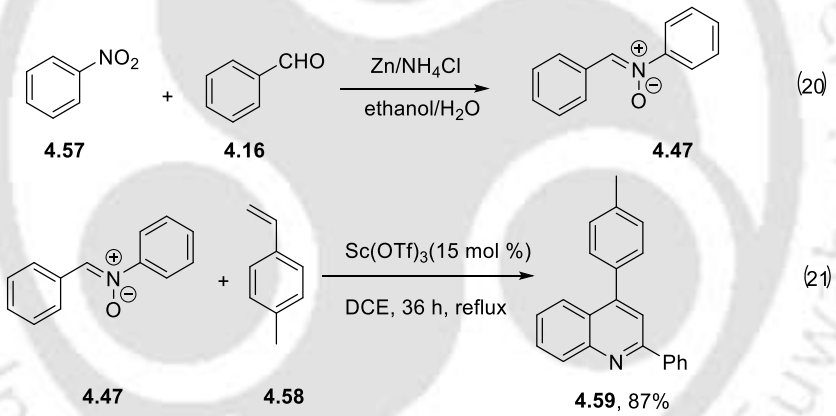
On the basis of this concept, it was considered that change in the mode of reactivity of nitrones may be altered by the addition of Lewis acid. Instead of classical [3+2] cycloaddition, metal coordinated nitrone **4.53** and **4.54** can participate in [4+2] cycloaddition reaction which may lead towards the formation of intermediate **4.55** and **4.56** (**Scheme 10**, eq. 19). For example, the desired C–H functionalization of nitrosoarenes could be achieved if nitrone reacts with styrene *via* a Povarov type reaction.



Scheme 10: Reaction of nitrosoarene and styrene with $Sc(OTf)_3$.

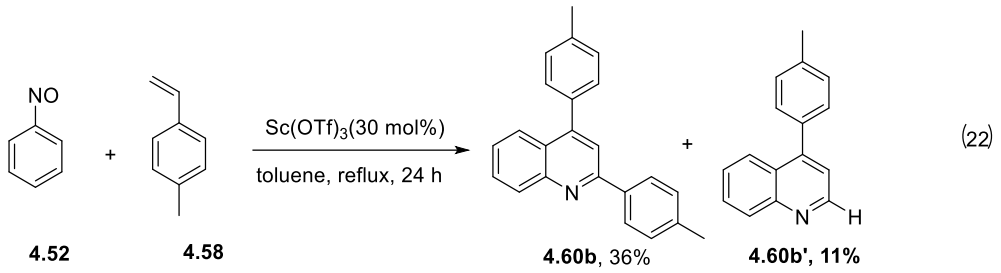
4.7 Preliminary Results:

To explore the proposed hypothesis, the investigation was started by performing a reaction of nitrone **4.47** with styrene **4.58** in the presence of a catalytic amount of $Sc(OTf)_3$. For that nitrone **4.47** was prepared from benzaldehyde **4.16** and nitrobenzene **4.57** using Zn and NH_4Cl following literature procedure (**Scheme 11**, eq. 20).[31] It was pleasure to observe that the reaction of **4.47** with **4.58** provided quinoline **4.59** with 87% yield instead of classical product, oxazolidine (**Scheme 11**, eq. 21).[32]



Scheme 11: Preliminary result with nitrone.

Then the stage was ready for testing a pseudo-three component reaction of nitrosoarene and styrene in the presence of $Sc(OTf)_3$. Accordingly, nitrosobenzene **4.52** was reacted with 4-methylstyrene **4.58** in the presence of 30 mol% of $Sc(OTf)_3$ in refluxing toluene for 24 h. As expected, the 2,4-diarylquinoline **4.60b** and 4-arylquinoline **4.60b'** were isolated as 3:1 ratio with a 47% combined yield.



Scheme 12: Preliminary result with nitrosobenzene.

To the best of the knowledge, there is no report on the reaction of styrene with the nitrosoarene towards the synthesis of quinoline known in the literature. Therefore, the scope of the reaction was studied further.

4.8 Optimization of reaction conditions:

Encouraged by the initial result, several reaction conditions were screened to optimize the reaction condition for the improvement of the yield of quinolines **4.60b** and **4.60b'**.

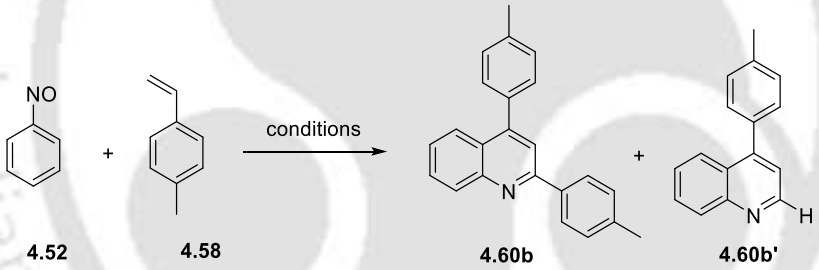


Table 1: Optimization of reaction conditions

Entry	Conditions	Yield of 4.60b (%)[d]	Yield of 4.60b'(%)[d]
1.[a]	$Sc(OTf)_3$ (30 mol%), toluene, reflux, 24 h	36	11
2.[b]	$Sc(OTf)_3$ (30 mol%), toluene, reflux, 24 h	43	18
3.	$Sc(OTf)_3$ (30 mol%), toluene, reflux, 24 h	46	22
4.	$Sc(OTf)_3$ (30 mol%), toluene, reflux, 36 h	47	25
5.	$Sc(OTf)_3$ (15 mol%), toluene, reflux, 36 h	45	18
6.	$Sc(OTf)_3$ (15 mol%), DCE, reflux, 36 h	49	28
7.	$Sc(OTf)_3$ (15 mol%), DCM, reflux, 36 h	46	21

8.	$Yb(OTf)_3$ (15 mol%), DCE, reflux, 36 h	48	28
9.[c]	$Yb(OTf)_3$ (15 mol%), DCE, reflux, 36 h	44	25
10.	$Yb(OTf)_3$ (5 mol%), DCE, reflux, 36 h	34	15
11.	$Yb(OTf)_3$ (5 mol%), DCE, reflux, 72 h	34	12
12.	$Yb(OTf)_3$ (15 mol%), DCE, reflux, 72 h	42	22
13.	$Bi(OTf)_3$ (15 mol%), DCE, reflux, 36 h	36	19
14.	$Cu(OTf)_2$ (15 mol%), DCE, reflux, 36 h	35	11
15.	TfOH (15 mol%), DCE, reflux, 36 h	33	21
16.	$FeCl_3$ (15 mol%), DCE, reflux, 36 h	-	-
17.	$Yb(OTf)_3$ (15 mol%), THF, reflux, 36 h	37	18
18.	$Yb(OTf)_3$ (15 mol%), EtOAc, reflux, 36 h	39	22
19.	$Yb(OTf)_3$ (15 mol%), benzene, reflux, 36 h	45	11
20.	$Yb(OTf)_3$ (15 mol%), CH_3CN, reflux, 36 h	46	19
21.	AcOH (15 mol%), DCE, reflux, 36 h	-	-
22.	*p*-NBA (15 mol%), DCE, reflux, 36 h	-	-

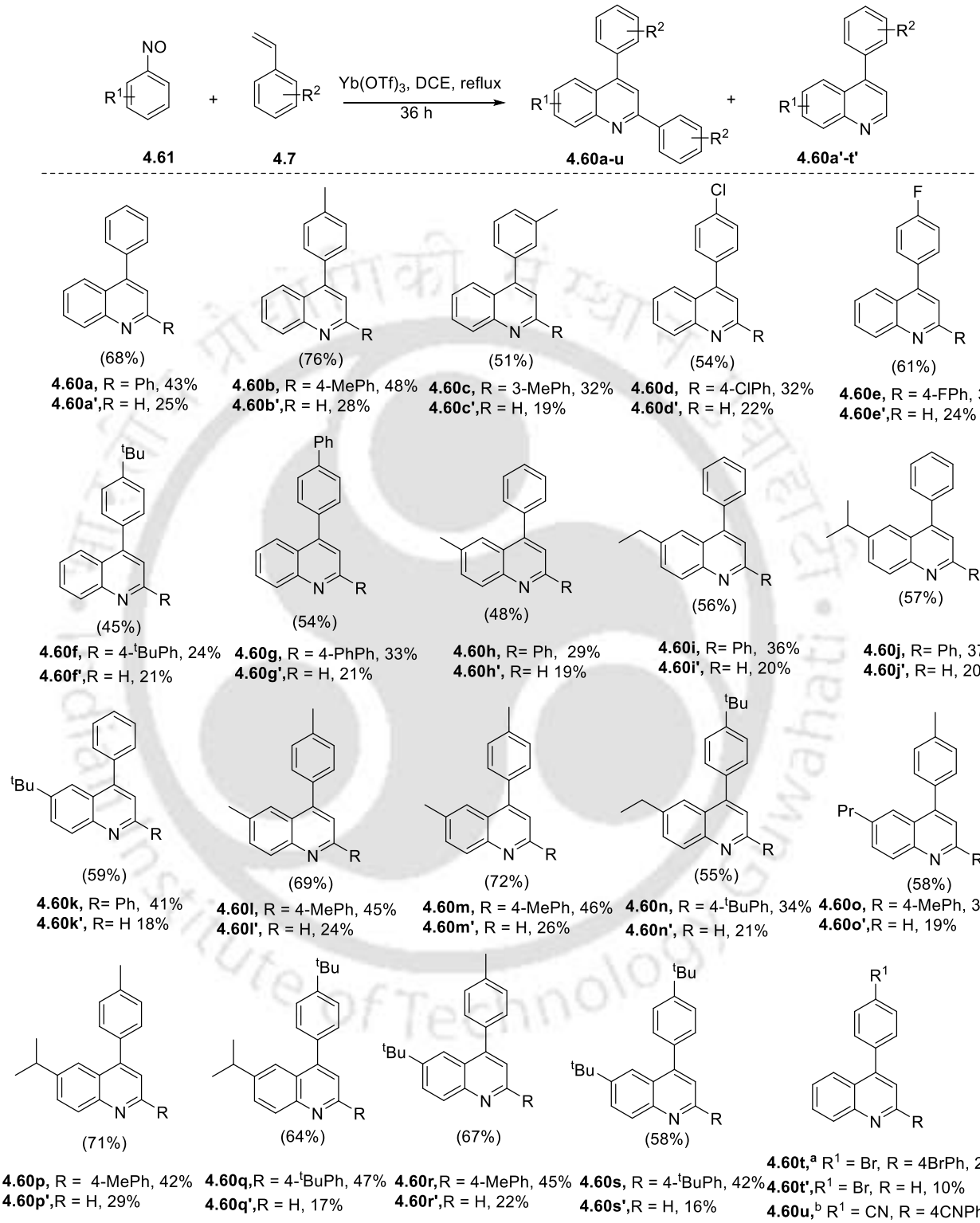
All reactions were carried out with 1 eq (0.40 mmol) of nitrosobenzene, 2.2 eq. of 4-methyl styrene and solvent (3 mL). [a]1 eq. 4-methyl styrene was used. [b]2 eq. 4-methyl styrene was used. [c]4 eq. 4-methyl styrene was used. [d]Separated yield. *p*-NBA - para nitrobenzoic acid.

The increase in yields of the desired products were obtained with an increase in the relative stoichiometry of 4-methyl styrene (**Table 1**, entry 2,3). The reaction yield was further improved with the increase in reaction time (**Table 1**, entry 4). A diminished yield was observed on lowering the catalyst loading to 15 mol% (**Table 1**, entry 5). However, the best yield of the desired quinoline was observed when the reaction was carried out in DCE instead of toluene (**Table 1**, entry 6). Decrease in yield was noted while reaction was performed in DCM (**Table 1**, entry 7). A similar result was obtained when $Yb(OTf)_3$ was used as the catalyst instead of $Sc(OTf)_3$ in DCE (**Table 1**, entry 8). The yields of the desired product are found to be reduced with the excess of 4-methylstyrene (**Table 1**, entry 9). Conducting the reaction with lower catalyst loading provided inferior yield of the desired product (**Table 1**,

entry 10) even if in higher reaction time (**Table 1**, entry 11). No enhancement in the yields was noticed with lengthening the reaction time (**Table 1**, entry 12). Several Lewis acids *i.e.*, $Bi(OTf)_3$, $Cu(OTf)_2$, TfOH were evaluated, but none of them provided better yield (**Table 1**, entry 13 - 15). No products were obtained with catalytic amount of $FeCl_3$ (**Table 1**, entry 16). It was found that the reaction proceeded smoothly with the other solvents *i.e.*, THF, EtOAc, benzene, CH_3CN with lesser yields (**Table 1**, entry 17-20). Use of other Bronsted acids *i.e.*, AcOH and *p*-nitrobenzoic acid failed to provide the desired quinolines (**Table 1**, entry 21, 22).

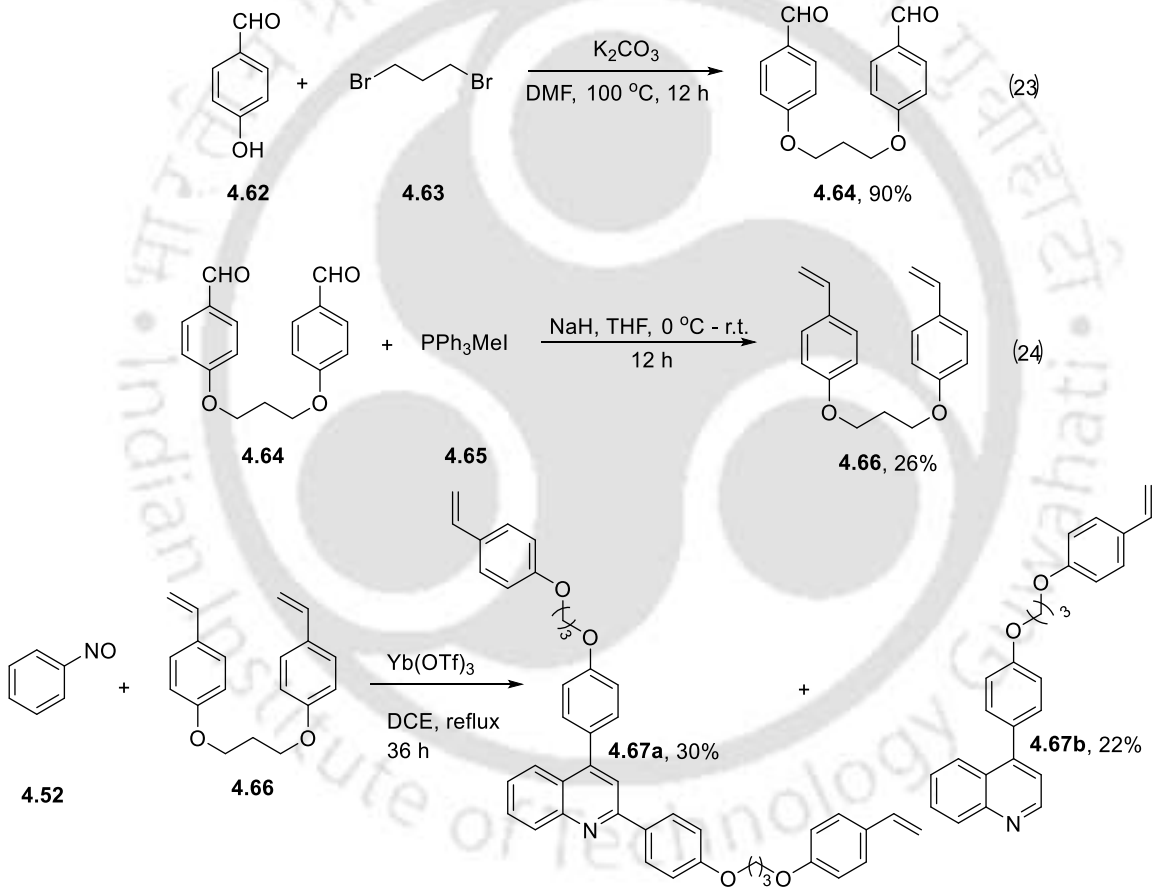
4.9 Scope of successive cycloaddition with various nitroso compounds and styrene derivatives:

The best reaction conditions were then used to investigate the substrate scope of this unprecedented annulation reaction. An extensive range of electronically modified styrenes as well as nitrosoarenes participated in the reaction. The desired quinolines **4.60a-g** and **4.60a'-g'** were isolated with good combined yields. Styrene having alkyl substitution at *p*-position provided better yield as compare to halogen substitution. In case of *m*-substituents styrene, drastic decrease the yield of the product **4.60c** and **4.60c'** was observed. Then the scope of the reaction using different nitrosoarenes was tested. Accordingly, alkyl substituted nitrosoarenes reacted smoothly with different styrene derivatives to provide the quinoline derivatives **4.60h-s** and **4.60h'-s'** with good combined yields. Lower yields were observed in case of electron withdrawing styrene derivative *i.e.* -Br, -CN (**4.60t**, **4.60u**). Interestingly, it was observed that the quinolines which are originated from the unsubstituted nitrones were obtained with a little lower yield as compared to the quinolines that are formed from the substituted nitrone. The observation can be rationalized based on the lower stability of the unsubstituted nitrones as compared to its substituted analogs.[33]



Scheme 13: Scope of the annulation reaction of nitrosoarenes and styrenes.

After successful annulation reaction of styrene derivatives with nitrosoarene, the standard reaction condition was applied for the *bis*-vinyl system. Firstly, 4-hydroxyaldehyde **4.62** was reacted with 1,3-dibromopropane **4.63** in DMF at 100 ^{o}C to synthesize *bis*-aldehyde **4.64** (**Scheme 14**, eq. 23). Wittig reaction of **4.64** in presence wittig salt (Methyltriphenylphosphonium iodide) **4.65** and NaH at 0 ^{o}C - r.t. provided styrene derivative **4.66 (Scheme 14**, eq. 24**)**. The reaction of substrate **4.66** having two styrene moieties was then investigated with nitrosobenzene. Both mono-substituted **4.67b** and 2,4-disubstituted **4.67a** quinolines were formed under standard conditions. Quinoline **4.67a** derivative having two styrene units can serve as the potential crosslinking agent in polystyrene synthesis.

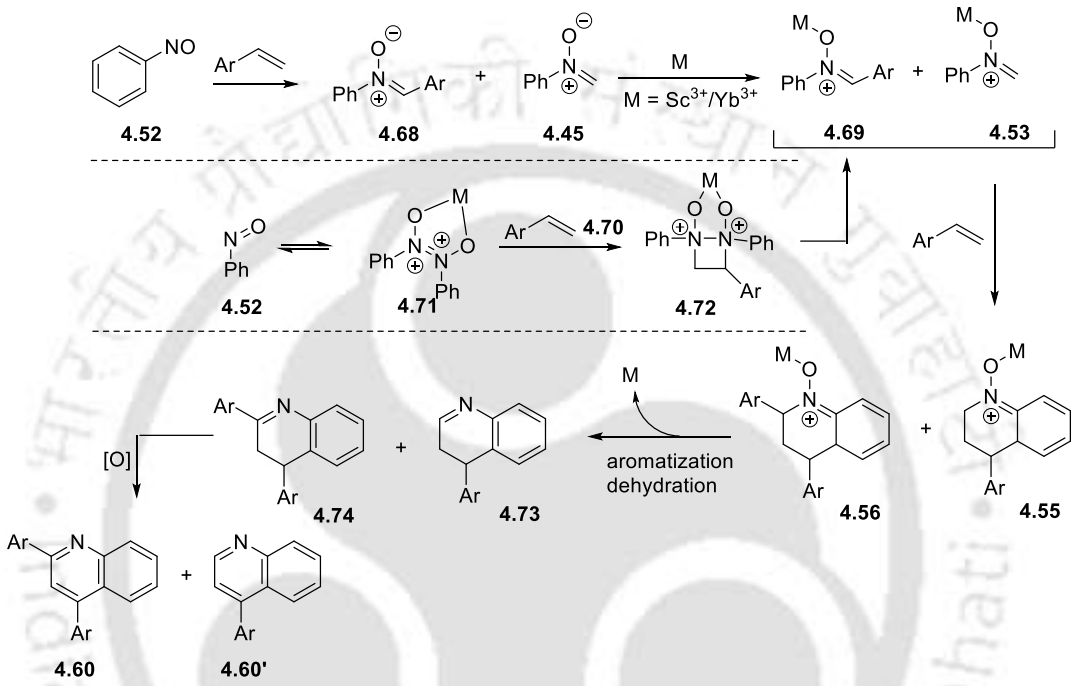


Scheme 14: Reaction of nitrosobenzene with *bis*-vinyl system.

4.10 Plausible mechanism:

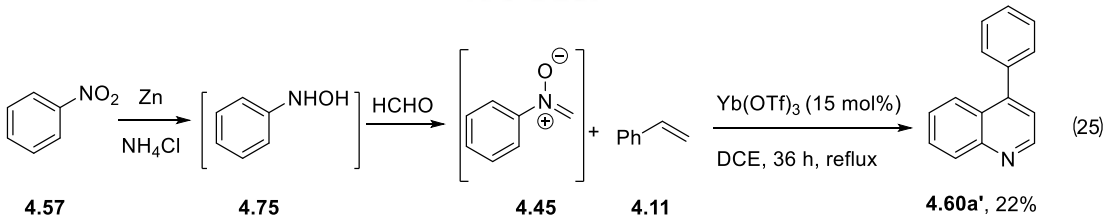
On the basis of the experimental results and literature reports, a plausible mechanism for the formal [3+2+1] annulation of nitrosoarene and styrene is depicted in **Scheme 15**. The nitrones **4.68** and **4.45** were formed from the reaction of nitrosoarene and styrene involving azodioxy dimer **4.71**[34] and diazetidine derivative **4.72**.[35] The nitrones could also be formed from

nitrosoarene **4.52** and styrene following a radical pathway.[36, 29] Both the metal coordinated nitrone derivatives **4.69** and **4.53** reacted through the Povarov type reaction with another equivalent of styrene to provide the tetrahydroquinoline derivatives **4.56** and **4.55**, respectively. Aromatization and dehydration of **4.56** and **4.55** produced respective dihydroquinoline **4.74** and **4.73** which upon areal oxidation provided the observed aryl quinolines **4.60** and **4.60'**.



Scheme 15: Proposed mechanism for annulation of nitrosoarene and styrene.

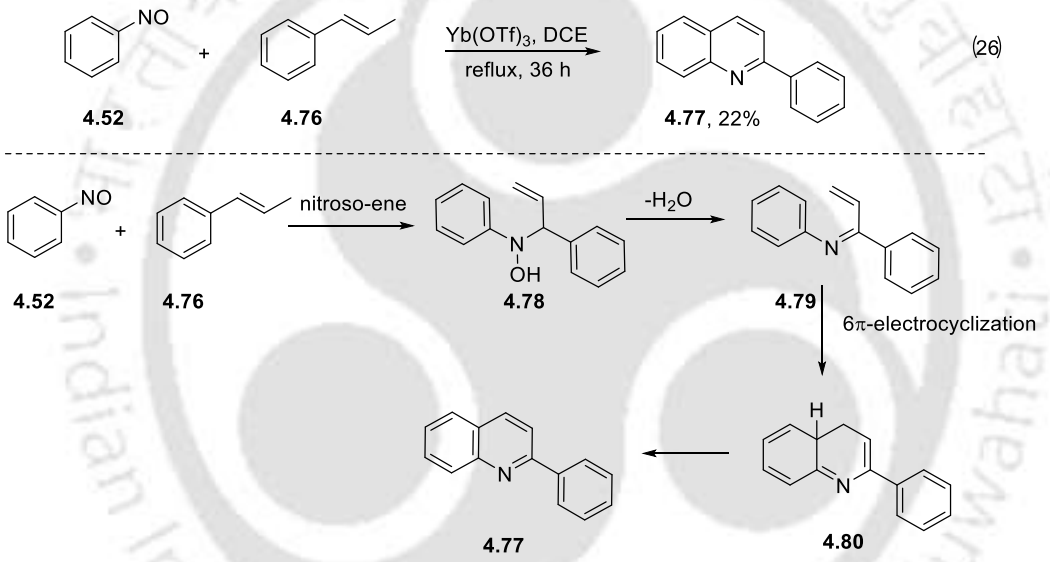
For the mechanistic interpretation, nitrone **4.45** was formed *in situ* from the reaction of nitrobenzene **4.57** with aq. formalin solution. Styrene **4.11** was reacted with the nitrone **4.45** *in situ* under standard condition. Expected quinoline **4.60a'** was isolated with 22% yield (**Scheme 16**, eq. 25).



Scheme 16: Controlled experiment for quinoline synthesis.

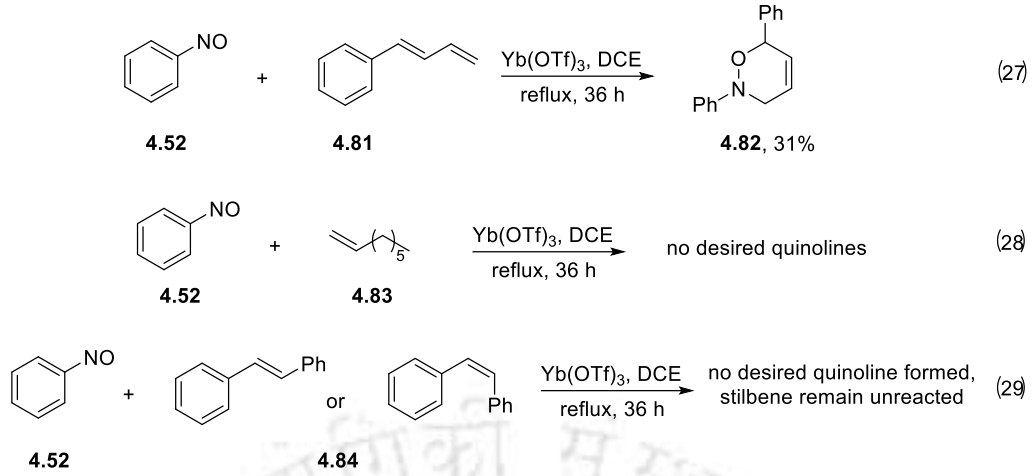
4.11 Additional Reactions:

After successful annulation reaction of nitrosoarene with styrene derivatives, reaction of nitrosobenzene with different olefin was tested. The reaction of *trans*-β methyl styrene **4.76** with nitrosobenzene **4.52** was performed under the standard condition. Instead of expected di-substituted quinolines, 2-phenylquinoline **4.77** was isolated with 22% yield (**Scheme 17**, eq. 26). The reaction proceeded *via* nitroso-ene pathway. Nitrosobenzene **4.52** was reacted with *trans*-β methyl styrene **4.76** to provide N-hydroxy intermediate **4.78** which after elimination of -H_2O produced **4.79**. 6π-electrocyclization of **4.79** produced **4.80** which upon aromatization resulted **4.77**.



Scheme 17: Proposed mechanism for annulation of nitrosoarene and *trans*-β methyl styrene.

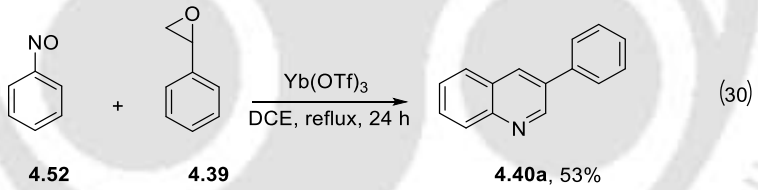
Then, the optimized reaction condition was applied to 1,4-diene system **4.81**. Cycloaddition product **4.82** was observed with 31% yield (**Scheme 18**, eq. 27). No desired quinolines were formed in case of reaction of 1-octene **4.83** with nitrosobenzene **4.52** (**Scheme 18**, eq. 28). Also, no desired quinoline was isolated when the reaction was carried out in presence of *cis* or *trans* stilbene **4.84**. The stilbene remained unreacted after the end of the reaction (**Scheme 18**, eq. 29).



Scheme 18: Reaction of nitrosobenzene with other olefin system.

4.12 Initial Result of 3-phenyl quinoline:

Subsequently, the scope of cycloaddition reaction of nitrosobenzene with epoxy-styrene was explored under metal-based Lewis's acid to check the reactivity of nitrosoarene with the epoxide. 3-substituted quinoline was obtained with moderate to good yield. Nitrosobenzene **4.52** was reacted with styrene epoxide **4.39** in presence of 15 mol% $Yb(OTf)_3$ in refluxing DCE. 3-phenylquinoline **4.40a** was isolated with 53% yield.



Scheme 19: Reaction of nitrosobenzene with epoxy-styrene.

4.13 Optimization Table:

With this initial attempt, screening of different reaction conditions was performed to increase the yield of the desired product.

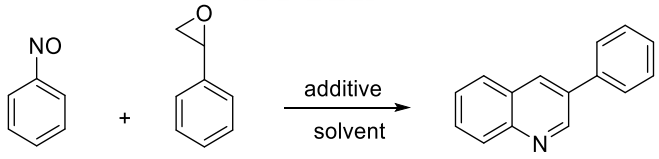


Table 2: Optimization table.

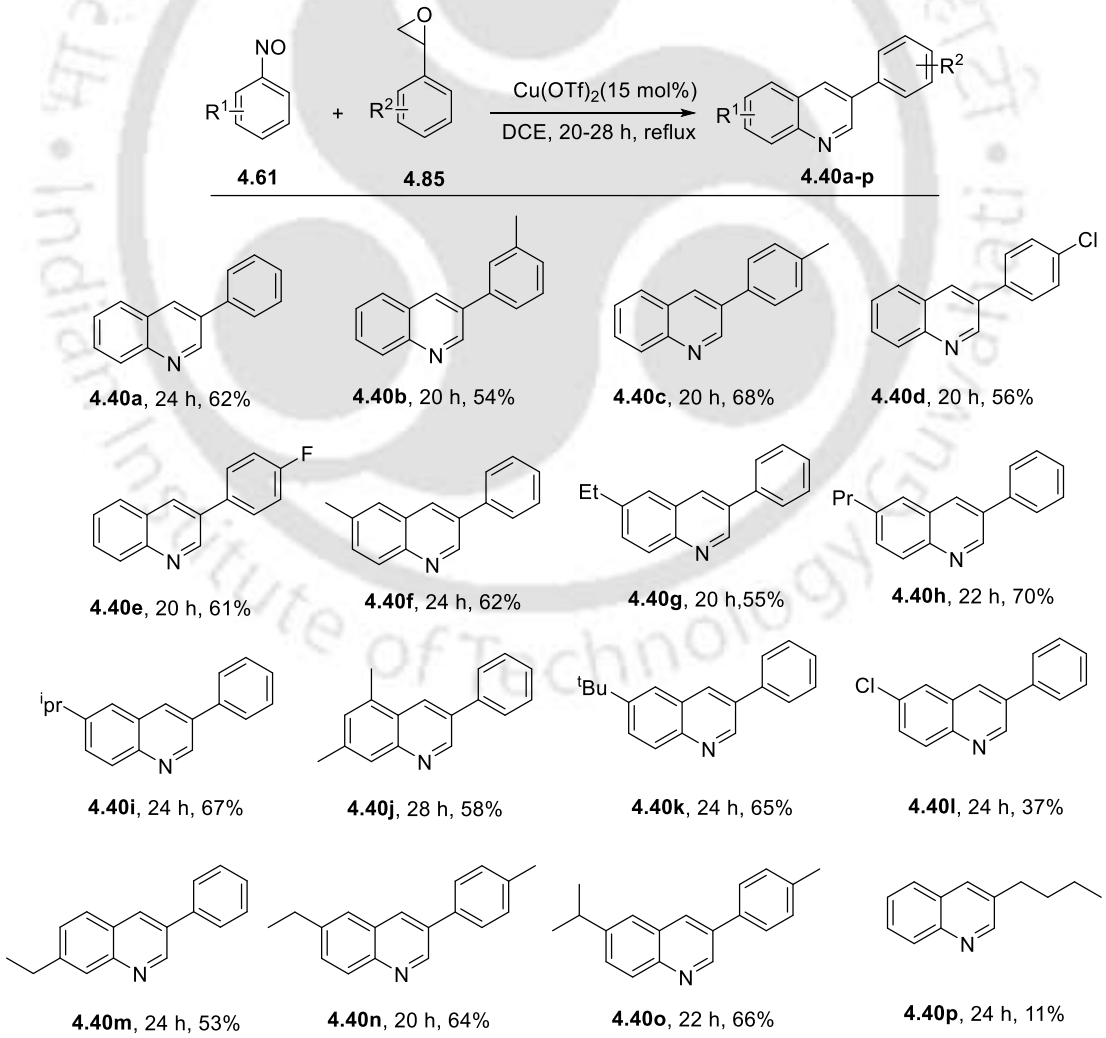
Entry	Conditions	Yield (%)[c]
1[a]	$Cu(OTf)_2$ (15 mol%), toluene, reflux, 24 h	39
2	$Cu(OTf)_2$ (15 mol%), toluene, reflux, 24 h	55
3	$Cu(OTf)_2$ (15 mol%), DCE, reflux, 24 h	62
4	$Sc(OTf)_3$ (15 mol%), DCE, reflux, 24 h	64
5	$Cu(OTf)_2$ (15 mol%), DCE, reflux, 36 h	61
6	$Cu(OTf)_2$ (15 mol%), DCE, reflux, 72 h	56
7	$Cu(OTf)_2$ (15 mol%), DCE, reflux, 12 h	51
8[b]	$Cu(OTf)_2$ (15 mol%), DCE, reflux, 24 h	61
9	$Yb(OTf)_3$ (15 mol%), DCE, reflux, 24 h	53
10	$CuBr_2$ (15 mol%), DCE, reflux, 24 h	-
11	$Cu(OTf)_2$ (15 mol%), benzene, reflux, 24 h	42
12	$Cu(OTf)_2$ (15 mol%), THF, reflux, 24 h	37

All reactions were carried out 0.33 mmol (1 eq.) of nitrosobenzene, 2 eq. of styrene epoxide and solvent (3 mL). [a]1 eq. epoxide was used. [b]2.5 eq. epoxide was used. [c]Separated yield.

The lower yield of the desired quinoline **4.40a** was observed with the equal ratio of both the reactants (**Table 2**, entry 1). Increase in the relative stoichiometry of styrene epoxide increases the yield of the product (**Table 2**, entry 2). DCE is found to be better solvent than toluene (**Table 2**, entry 3). The yield was slightly better with $Sc(OTf)_3$ than other Lewis acid *i.e.*, $Cu(OTf)_2$ (**Table 2**, entry 4) and $Yb(OTf)_3$ (**Table 2**, entry 9). However, no further improvement of the desired product was noticed with higher (**Table 2**, entry 5,6) or lower reaction time (**Table 2**, entry 7). No enhancement in yield was observed with increase in the stoichiometry of styrene oxide (**Table 2**, entry 8). $CuBr_2$ was unsuccessful to provide desired the product (**Table 2**, entry 10). The reaction worked moderately with other solvents *i.e.*, THF, benzene (**Table 2**, entry 11, 12). The reaction of nitrosobenzene with styrene oxide with 15 mol% of $Cu(OTf)_2$ in refluxing DCE was recognized to be the best condition for the formation of desired quinoline **4.40a** .

4.14 Scope of successive cycloaddition with various nitroso compounds and epoxy-styrenes:

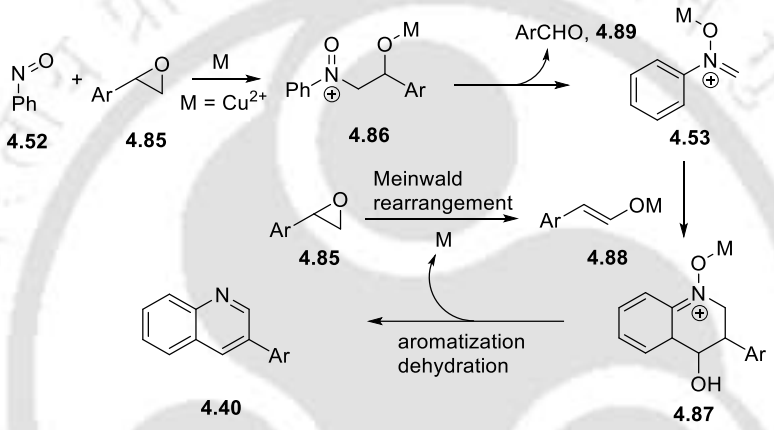
Optimized conditions using a cost-effective catalyst $Cu(OTf)_2$ were used to study the substrate scope of the reaction. Differently substituted styrene oxides were reacted with various nitrosoarenes to obtain a series of structurally diverse 3-aryl quinolines **4.40a-p** with good yields (**Scheme 20**). The substrates containing both the electron-donating and electron-withdrawing groups provided the desired quinolines in moderate to good yields. Alkyl substituted nitrosobenzene produced better yield than substitution with electron-withdrawing halogen group (**4.40f -m**). Only one isomer of **4.40m** was identified in case of 3-ethyl nitrosobenzene with moderate yield. The reaction of 4-oxiranylpyridine did not provide the desired quinoline. However, alkyl epoxide participated in the reaction to provide 3-alkylquinoline **4.40p**.



Scheme 20: Scope of the reaction of nitrosoarenes with styrene oxide derivatives.

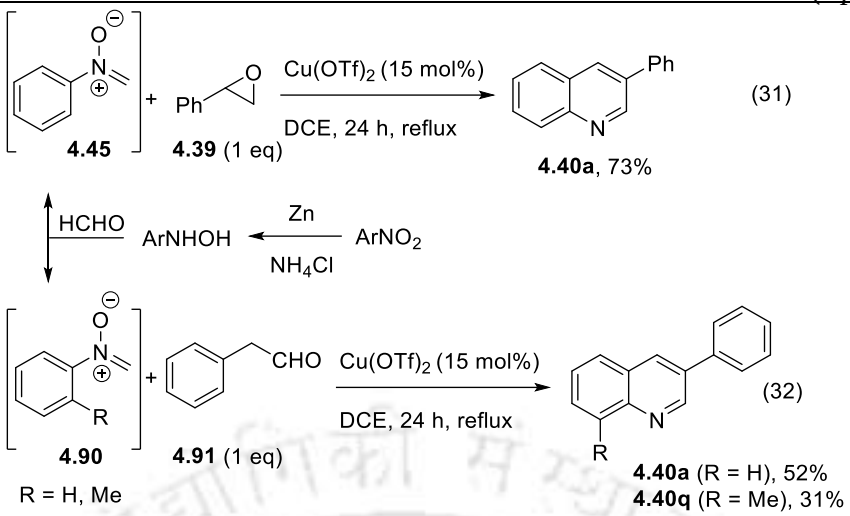
4.15 Plausible Mechanism:

Based on these results, a plausible reaction mechanism has been depicted in **Scheme 21**. Nucleophilic nitrosobenzene **4.52** added to the least hindered site of styrene oxide **4.85,** which is activated by the coordination with the Cu(II). C-C bond cleavage of the resulting ionic intermediate **4.86** occurred to provide the nitrone **4.53** and aldehyde **4.89**. The metal coordinated nitrone **4.53** reacted with the enolate **4.88**, which was generated *in situ* from styrene oxide **4.85** *via* Meinwald rearrangement,[37] either *via* a concerted or stepwise pathway to provide the N-oxide **4.87**. Dehydration of **4.87** followed by aromatization provided 3-arylquinoline **4.40**.



Scheme 21: Proposed mechanism for annulation of nitrosoarene and epoxystyrene

To understand the mechanism of annulation reaction between epoxy styrene **4.85** and nitrosobenzene **4.52**, epoxy styrene **4.85** was reacted with pre-formed nitrone **4.45** from nitroarene and formaldehyde (**Scheme 22**, eq 31). Under standard conditions, the 3-aryl quinoline **4.40a** was isolated with 73 % yield. This indicates the intermediacy of nitrone **4.45** in the annulation reaction of epoxy styrene and nitrosoarene. Moreover, the formation of aryl aldehyde **4.89** corresponding to the styrene oxide was observed in the reaction. A reaction of pre-formed nitrone **4.90** with aldehyde **4.91**, which is capable of generating enolate related to **4.88,** producing desired quinolines (**4.40a**, **4.40q**) supports the intermediacy of **4.88** in the reaction. Fast aromatization followed by dehydration yielded observed 3-aryl quinoline as the single regioisomer.



Scheme 22: Controlled experiments for the synthesis of 3-arylquinoline.

4.16 Conclusion:

In summary, an unprecedented annulation reaction of nitrosoarenes and epoxy-(styrene) has been developed that provides arylquinolines with wide structural diversity. The cleavage across C=C of styrene and epoxide of epoxy-styrene provided the nitrone intermediate. The use of the Lewis acid catalyst switched the reaction of nitrone and styrene from [3+2] to [4+2] cycloaddition and thus allowed to form quinoline derivatives instead of oxazolidines. The nitrones reacted with styrene to give a mixture of 2,4-diarylquinoline and 4-arylquinoline. On the other hand, 3-arylquinoline was formed selectively from the reaction of epoxy-styrene *via* cycloaddition of nitrone and enol/metal-enolate derived from epoxy-styrene through Meinwald rearrangement.

4.17 Experimental Section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus (V) oxide (P_2O_5). Commercial grade DCE, xylene, benzene and toluene were distilled over CaH2 before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ^1H, ^{13}C NMR spectroscopy: Bruker 600 MHz and Bruker 400 MHz (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS δ (1H) 0.0 ppm, δ (13C) 0.0 ppm) which was used as the inner reference. Otherwise, the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (1H) 7.26 ppm, δ (13C) 77.23 ppm) were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity. IR: spectra were recorded on Perkin Elmer Instrument at normal temperature. MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in m/z (% of basis peak). Nitrosoarenes were prepared from the reported method.

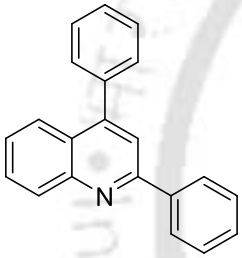
Procedure for the Synthesis of 2-phenyl-4-(p-tolyl)quinoline (4.59) :

2-phenyl-4-(*p*-tolyl)quinoline (4.59):[38] Freshly prepared (*Z*)-*N*,1-diphenylmethanimine oxide (79 mg, 0.40 mmol) and $Sc(OTf)_3$ (29 mg, 0.06 mmol) were successively added to a solution of 4-methyl styrene (57 mg, 0.48 mmol) in dry DCE (3 mL). Then the reaction mixture was refluxed for 36 h under argon atmosphere. Then the solvent was evaporated under reduced pressure. The reaction mixture was diluted with water (1X20 mL) and the reaction mixture was extracted with DCM (3X20 mL). The organic layer was washed with brine solution (1X30 mL) and evaporated under vacuum. The crude mixture was subjected to column chromatography (silica gel; EtOAc : hexane, 1:30) gave **4.59** as yellow gum (0.10 g, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 7.2 Hz, 2H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.82 (s, 1H), 7.76 - 7.72 (m, 1H), 7.56 - 7.52 (m, 2H), 7.49 - 7.47 (m, 4H), 7.37 (d, *J* = 8.0 Hz, 2H), 2.49 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{22}H_{18}N$ ($[M+H]^+$): 296.1434, Found: 296.1432.

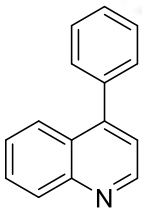
General Procedure for the Synthesis of mono and di substituted quinolines (I):

Freshly prepared nitrosoarenes (1 eq.) and $Yb(OTf)_3$ (15 mol%) were successively added to a solution of styrene derivatives (2.2 eq.) in dry DCE (3 mL). Then the reaction mixture was refluxed for 36 h under argon atmosphere. The reactions were carried out under an argon environment; however, without strictly maintaining the oxygen-free conditions. Then the solvent was evaporated under reduced pressure. The reaction mixture was diluted with water (1x20 mL) and the reaction mixture was extracted with DCM (3X20 mL). The organic layer was washed with brine solution (1X30 mL) and evaporated under vacuum. The crude mixture was subjected to column chromatography (silica gel) to afford analytically pure products.

2,4-diphenylquinoline (4.60a)[3c] **and 4-phenylquinoline (4.60a')**[45]: According to GP I,

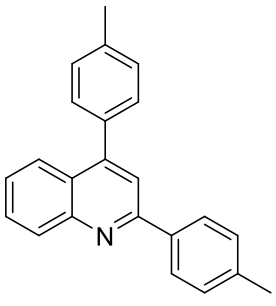


nitrosobenzene (43 mg, 0.40 mmol), styrene (92 mg, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60a** as yellow gum (48 mg, 43%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60a'** as yellow gum (21 mg, 25%). Analytical data for **4.60a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (d, *J* = 8.4 Hz, 1H), 8.23 - 8.18 (m, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.83 (s, 1H), 7.78 - 7.74 (m, 1H), 7.58 - 7.46 (m, 9H) ppm. HRMS: Exact mass calculated for $C_{21}H_{16}N$ ($[M+H]^+$): 282.1277, Found: 282.1285.



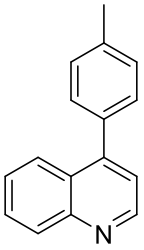
Analytical data for **4.60a'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.96 (d, *J* = 3.6 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.82 - 7.78 (m, 1H), 7.59 - 7.52 (m, 6H), 7.43 (d, *J* = 4.4 Hz, 1H) ppm. HRMS: Exact mass calculated for $C_{15}H_{12}N$ ($[M+H]^+$): 206.0964, Found:206.0974.

2,4-di-*p*-tolylquinoline (4.60b)[39] **and 4-(*p*-tolyl)quinoline (4.60b')**[46] : According to GP I,



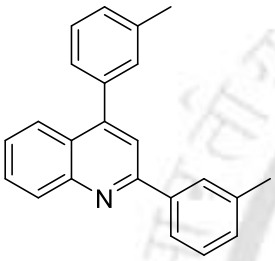
nitrosobenzene (43 mg, 0.40 mmol), 4-methyl styrene (0.10 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60b** as yellow gum (59 mg, 48%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60b'** as yellow gum (25 mg, 28%). Analytical data for **4.60b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ

= 8.27 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.94 - 7.92 (m, 1H), 7.80 (s, 1H), 7.75 - 7.71 (m, 1H), 7.48 - 7.45 (m, 3H), 7.38 - 7.33 (m, 4H), 2.49 (s, 3H), 2.44 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{23}H_{20}N$ ($[M+H]^+$): 310.1590, Found: 310.1604.

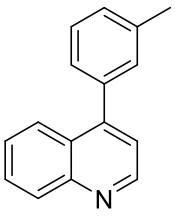


Analytical data for **4.60b'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.94 (d, *J* = 4.8 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.81 - 7.76 (m, 1H), 7.58 - 7.54 (m, 1H), 7.44 - 7.40 (m, 3H), 7.36 (d, *J* = 7.6 Hz, 2H), 2.48 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{16}H_{14}N$ ($[M+H]^+$): 220.1121, Found: 220.1127.

2,4-di-*m*-tolylquinoline (4.60c) and 4-(*m*-tolyl)quinoline (4.60c')[47] : According to GP I,

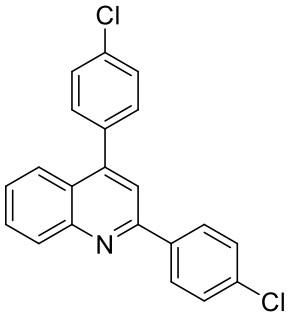


nitrosobenzene (43 mg, 0.40 mmol), 3-methyl styrene (0.10 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60c** as yellow gum (40 mg, 32%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60c'** as yellow gum (17 mg, 19%). Analytical data for **4.60c**: FT-IR: ($\tilde{\nu}$) = 2960, 2927, 2857, 1670, 1593, 1548, 1488, 1353, 1261, 1096, 876, 766 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (d, *J* = 8.8 Hz, 1H), 8.04 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 7.76 - 7.72 (m, 1H), 7.50 - 7.42 (m, 3H), 7.40 - 7.32 (m, 3H), 7.29 (d, *J* = 7.6 Hz, 1H), 2.48 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 157.3, 149.5, 149.0, 139.8, 138.7, 138.6, 138.5, 130.4, 130.3, 130.2, 129.7, 129.3, 128.9, 128.7, 128.5, 126.9, 126.4, 126.0, 125.9, 124.9, 119.7, 21.82, 21.75 ppm. HRMS: Exact mass calculated for $C_{23}H_{20}N$ ($[M+H]^+$): 310.1590, Found: 310.1590.

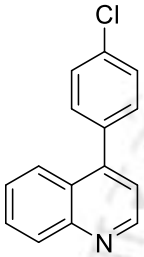


Analytical data for **4.60c'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.96 (d, *J* = 4.8 Hz, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.86 - 7.81 (m, 1H), 7.63 - 7.59 (m, 1H), 7.48 - 7.44 (m, 2H), 7.37 - 7.32 (m, 3H), 2.47 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{16}H_{14}N$ ($[M+H]^+$): 220.1121, Found: 220.1122.

2,4-*bis*(4-chlorophenyl)quinoline (4.60d)[40] **and 4-(4-chlorophenyl)quinoline (4.60d')**[48]: According to GP I, nitrosobenzene (43 mg, 0.40 mmol), 4-chloro styrene (0.12 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60d** as yellow

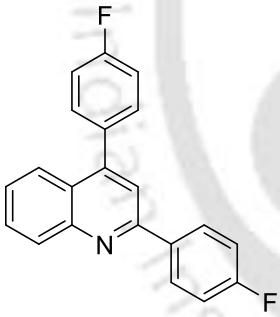


gum (45 mg, 32%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60d'** as yellow gum (21mg, 22%). Analytical data for **4.60d**: FT-IR: ($\tilde{\nu}$) = 2962, 2925, 2855, 1596, 1544, 1487, 1420, 1357, 1091, 1014, 830, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.24 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.78 - 7.74 (m, 2H), 7.55 - 7.49 (m, 7H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 155.5, 149.2, 148.0, 137.0, 136.5, 136.4, 135.2, 131.0, 130.6, 129.6, 129.4, 129.3, 129.2, 127.3, 125.8, 125.6, 119.3 ppm. HRMS: Exact mass calculated for $C_{21}H_{14}NCl_2$ ($[M+H]^+$): 350.0498, Found: 350.0497.

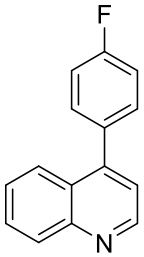


Analytical data for **4.60d'**: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.97 (d, *J* = 4.4 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.85 - 7.81 (m, 1H), 7.62 - 7.58 (m, 1H), 7.56 - 7.54 (m, 2H), 7.48 - 7.46 (m, 2H), 7.43 (d, *J* = 4.4 Hz, 1H) ppm. HRMS: Exact mass calculated for C15H11NCl ($[M+H]^+$): 240.0575, Found: 240.0576.

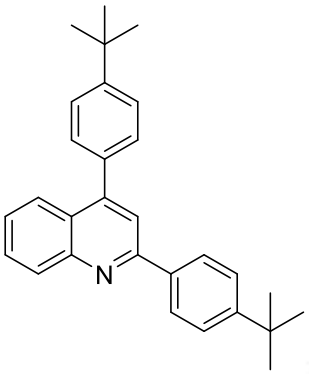
2,4-*bis*(4-fluorophenyl)quinoline (4.60e)[41] **and 4-(4-fluorophenyl)quinoline (4.60e')**[49]:



According to GP I, nitrosobenzene (43 mg, 0.40 mmol), 4-fluoro styrene (0.11 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60e** as yellow gum (47 mg, 37%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60e'** as yellow gum (22 mg, 24%). Analytical data for **4.60e**: ^1H NMR (600 MHz, $CDCl_3$) δ = 8.27 - 8.23 (m, 1H), 8.21 - 8.16 (m, 2H), 7.87 - 7.83 (m, 1H), 7.77 - 7.75 (m, 2H), 7.55 - 7.49 (m, 3H), 7.27 - 7.20 (m, 4H) ppm. HRMS: Exact mass calculated for $C_{21}H_{14}NF_2$ ($[M+H]^+$): 318.1089, Found: 318.1090.

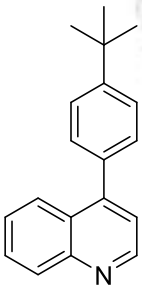


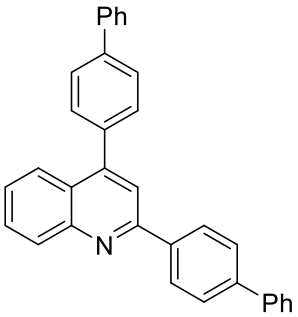
Analytical data for **4.60e'**: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.96 (d, *J* = 4.8 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.83 - 7.79 (m, 1H), 7.61 - 7.57 (m, 1H), 7.53 - 7.49 (m, 2H), 7.41 (d, *J* = 4.4 Hz, 1H), 7.28 - 7.27 (m, 1H), 7.26 - 7.24 (m, 1H) ppm. HRMS: Exact mass calculated for $C_{15}H_{11}NF$ ($[M+H]^+$): 224.0870, Found:224.0871.

2,4-*bis*(4-(*tert*-butyl)phenyl)quinoline (4.60f) and 4-(4-(*tert*-butyl)phenyl)quinoline (4.60f'): 

According to GP I, nitrosobenzene (43 mg, 0.40 mmol), 4-*tert* butyl styrene (0.14 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:40) gave **4.60f** as yellow gum (38 mg, 24%) and (silica gel; EtOAc : hexane, 1:10) gave **4.60f'** as yellow gum (22 mg, 21%). Analytical data for **4.60f**: FT-IR: ($\tilde{\nu}$) = 2961, 2930, 2867, 1660, 1591, 1497, 1363, 1268, 1018, 838, 765, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.24 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.83 (s, 1H), 7.74 - 7.70 (m, 1H), 7.59 - 7.57 (m, 3H), 7.55 - 7.51 (m, 3H), 7.48 - 7.45 (m, 1H), 1.44 (s, 9H), 1.39 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.2, 152.7, 151.7, 149.2, 149.1, 137.2, 135.8, 130.3, 129.5, 127.5, 126.2, 126.04, 125.99, 125.7, 119.5, 34.98, 34.96, 31.6, 31.5 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{29}H_{32}N$ ($[M+H]^+$): 394.2529, Found: 394.2533.

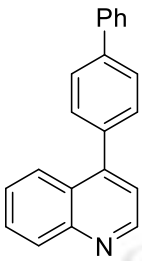
Analytical data for **4.60f'**: FT-IR: ($\tilde{\nu}$) = 2960, 2930, 2866, 1611, 1585, 1501, 1462, 1389, 1201, 1056, 873, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.93 (d, *J* = 4.4 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.74 - 7.70 (m, 1H), 7.56 - 7.54 (m, 2H), 7.52 - 7.48 (m, 1H), 7.47 - 7.45 (m, 2H), 7.34 (d, *J* = 4.4 Hz, 1H), 1.41 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.8, 150.2, 149.0, 148.8, 135.3, 130.0, 129.51, 129.45, 127.1, 126.7, 126.3, 125.7, 121.5, 35.0, 31.6 ppm. HRMS: Exact mass calculated for $C_{19}H_{20}N$ ($[M+H]^+$): 262.1590, Found: 262.1595.



2,4-di([1,1'-biphenyl]-4-yl)quinoline (4.60g) and 4-([1,1'-biphenyl]-4-yl)quinoline (4.60g'): 

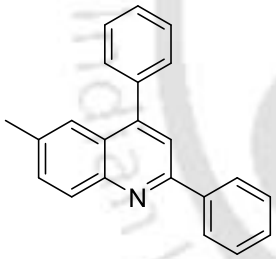
According to GP I, nitrosobenzene (43 mg, 0.40 mmol), 4-vinyl biphenyl (0.16 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60g** as yellow gum (58 mg, 33%) and (silica gel; EtOAc : hexane, 1:10) gave **4.60g'** as yellow gum (24 mg, 21%). Analytical data for **4.60g**: FT-IR: ($\tilde{\nu}$) = 2927, 2860, 1628, 1600, 1449, 1299, 1076, 907, 844,

734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.32 - 8.29 (m, 3H), 8.02 - 8.00 (m, 1H), 7.92 (s, 1H), 7.81 - 7.75 (m, 5H), 7.73 - 7.67 (m, 6H), 7.54 - 7.47 (m, 5H), 7.44 - 7.37 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.7, 149.1, 149.0, 142.3, 141.6, 140.8, 140.7, 138.7, 137.5, 130.4, 130.3, 129.9, 129.2, 129.1, 128.2, 127.9, 127.81, 127.79, 127.6, 127.41, 127.37, 126.6, 126.0, 125.9, 119.5 ppm. HRMS: Exact mass calculated for $C_{33}H_{24}N$ ($[M+H]^+$): 434.1903, Found: 434.1910.

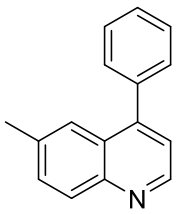


Analytical data for **4.60g'**: FT-IR: ($\tilde{\nu}$) = 2957, 2920, 2847, 1633, 1596, 1486, 1388, 1261, 1007, 839, 766 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.97 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.79 - 7.75 (m, 3H), 7.71 - 7.69 (m, 2H), 7.62 - 7.60 (m, 2H), 7.58 - 7.54 (m, 1H), 7.52 - 7.49 (m, 2H), 7.43 - 7.39 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.7, 149.0, 148.3, 141.8, 140.6, 136.9, 130.2, 129.9, 129.7, 129.2, 128.0, 127.6, 127.4, 127.1, 127.0, 126.2, 121.5 ppm. HRMS: Exact mass calculated for $C_{21}H_{16}N$ ($[M+H]^+$): 282.1277, Found: 282.1270.

6-methyl-2,4-diphenylquinoline (4.60h)[3c] **and 6-methyl-4-phenylquinoline (4.60h')**[19] **:**

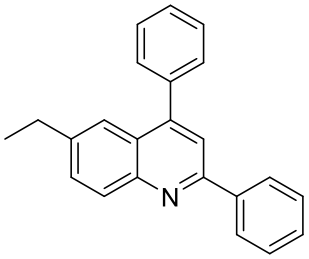


According to GP I, 1-methyl-4-nitrosobenzene (48 mg, 0.40 mmol), styrene (92 mg, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) was reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60h** as yellow gum (34 mg, 29%) and (silica gel; EtOAc : hexane, 1:7) gave 5h' as yellow gum (17 mg, 19%). Analytical data for **4.60h**: ^1H NMR (400 MHz, $CDCl_3$) δ = 8.21 - 8.17 (m, 3H), 7.78 (s, 1H), 7.66 (s, 1H), 7.60 - 7.51 (m, 8H), 7.48 - 7.44 (m, 1H), 2.48 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{22}H_{18}N$ ($[M+H]^+$): 296.1434, Found: 296.1438.

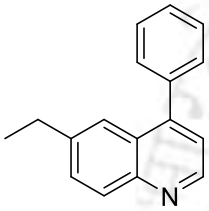


Analytical data for **4.60h'**: ^1H NMR (600 MHz, $CDCl_3$) δ = 8.88 (d, *J* = 4.2 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 7.70 (s, 1H), 7.63 - 7.62 (m, 1H), 7.57 - 7.51 (m, 5H), 7.38 (d, *J* = 4.2 Hz, 1H), 2.49 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{16}H_{14}N$ ($[M+H]^+$): 220.1121, Found: 220.1123.

6-ethyl-2,4-diphenylquinoline (4.60i)[42] **and 6-ethyl-4-phenylquinoline (4.60i')**[50] **:**

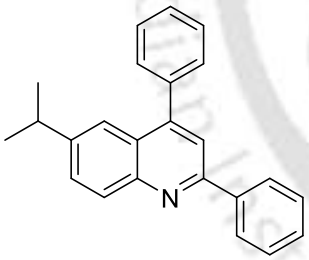


According to GP I, 1- ethyl-4-nitrosobenzene (54 mg, 0.40 mmol), styrene (92 mg, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60i** as yellow gum (44 mg, 36%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60i'** as yellow gum (19 mg, 20%). Analytical data for **4.60i**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 7.2 Hz, 2H), 7.79 (s, 1H), 7.68 (s, 1H), 7.64 - 7.62 (m, 1H), 7.58 - 7.51 (m, 7H), 7.48 - 7.45 (m, 1H), 2.78 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H) ppm. HRMS: Exact mass calculated for $C_{23}H_{20}N$ ($[M+H]^+$): 310.1590, Found: 310.1591.

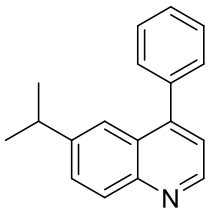


Analytical data for **4.60i'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.88 (d, *J* = 4.4 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.71 (s, 1H), 7.66 - 7.64 (m, 1H), 7.56 - 7.51 (m, 5H), 7.36 (d, *J* = 4.8 Hz, 1H), 2.78 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H) ppm. HRMS: Exact mass calculated for $C_{17}H_{16}N$ ($[M+H]^+$): 234.1277, Found: 234.1285.

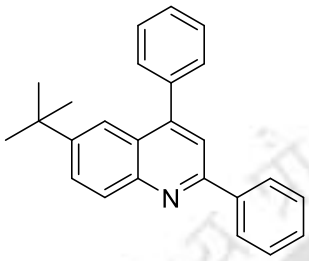
6-isopropyl-2,4-diphenylquinoline (4.60j) and 6-isopropyl-4-phenylquinoline (4.60j')[3g] **:**



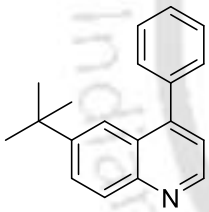
According to GP I, 1-isopropyl-4-nitrosobenzene (60 mg, 0.40 mmol), styrene (92 mg, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60j** as yellow gum (48 mg, 37%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60j'** as yellow gum (20 mg, 20%). Analytical data for **4.60j**: FT-IR: ($\tilde{\nu}$) = 2960, 2930, 2867, 1623, 1589, 1491, 1027, 835, 693 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.20 - 8.16 (m, 3H), 7.78 (s, 1H), 7.70 (s, 1H), 7.67 - 7.66 (m, 1H), 7.59 - 7.56 (m, 4H), 7.54 - 7.51 (m, 3H), 7.47 - 7.45 (m, 1H), 3.06 - 3.01 (m, 1H), 1.29 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.4, 148.9, 147.9, 147.2, 140.0, 138.8, 130.3, 129.8, 129.3, 129.2, 129.0, 128.8, 128.5, 127.7, 125.8, 122.1, 119.7, 34.6, 24.1 ppm. HRMS: Exact mass calculated for $C_{24}H_{22}N$ ($[M+H]^+$): 324.1747, Found: 324.1749.



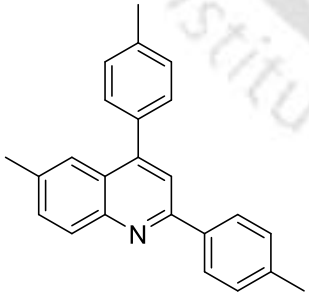
Analytical data for **4.60j'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.88 (d, *J* = 4.8 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 7.74 (s, 1H), 7.71 – 7.68 (m, 1H), 7.56 – 7.52 (m, 5H), 7.36 (d, *J* = 4.4 Hz, 1H), 3.07 – 3.05 (m, 1H), 1.28 (d, *J* = 6.8 Hz, 6H) ppm. HRMS: Exact mass calculated for $C_{18}H_{18}N$ ($[M+H]^+$): 248.1434, Found: 248.1432.

6-(*tert*-butyl)-2,4-diphenylquinoline (4.60k)[43] **and 6-(*tert*butyl)-4-phenylquinoline (4.60k')**[3g] : 

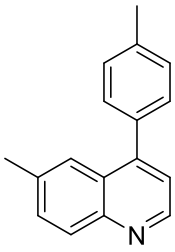
According to GP I, 1-tert butyl-4-nitrosobenzene (65 mg, 0.40 mmol), styrene (92 mg, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60k** as yellow gum (55 mg, 41%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60k'** as yellow gum (19 mg, 18%). Analytical data for **4.60k**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, *J* = 8.8 Hz, 1H), 8.19 - 8.17 (m, 2H), 7.87 - 7.83 (m, 2H), 7.79 (s, 1H), 7.60 - 7.51 (m, 7H), 7.48 - 7.44 (m, 1H), 1.35 (s, 9H) ppm. HRMS: Exact mass calculated for $C_{25}H_{24}N$ ($[M+H]^+$): 338.1903, Found: 338.1921.



Analytical data for **4.60k'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.89 (d, *J* = 4.8 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 7.92 - 7.87 (m, 2H), 7.56 - 7.53 (m, 5H), 7.39 (d, *J* = 4.8 Hz, 1H), 1.34 (s, 9H) ppm. HRMS: Exact mass calculated for $C_{19}H_{20}N$ ($[M+H]^+$): 262.1590, Found: 262.1594.

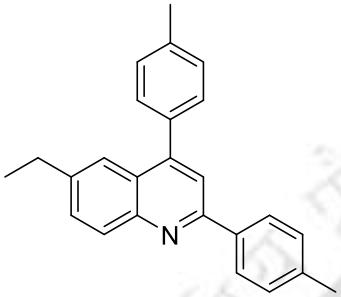
6-methyl-2,4-di-*p*-tolylquinoline (4.60l)[44] **and 6-methyl-4-(*p*-tolyl)quinoline (4.60l')**[19] **:** 

According to GP I, 1-methyl-4-nitrosobenzene (48 mg, 0.4 mmol), 4-methylstyrene (0.10 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) was reacted for 36 h in dry DCE (3 mL) and column chromatography (silica gel; EtOAc : hexane, 1:30) gave **4.60l** as yellow gum (58 mg, 45%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60l'** as yellow gum (22 mg, 24%). Analytical data for **4.60l**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.18 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 7.75 (s, 1H), 7.67 (s, 1H), 7.58 - 7.55 (m, 1H), 7.47 - 7.45 (m, 2H), 7.38 - 7.36 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.49 (s, 3H), 2.48 (s, 3H), 2.43 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{24}H_{22}N$ ($[M+H]^+$): 324.1747, Found: 324.1757.

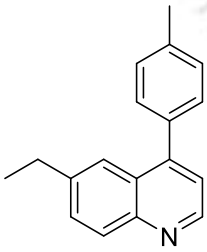


Analytical data for **4.60l'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.85 (d, *J* = 4.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.71 (s, 1H), 7.59 - 7.56 (m, 1H), 7.42 - 7.40 (m, 2H), 7.36 - 7.34 (m, 2H), 7.31 (d, *J* = 4.8 Hz, 1H), 2.48 (s, 6H) ppm. HRMS: Exact mass calculated for $C_{17}H_{16}N$ ($[M+H]^+$): 234.1277, Found: 234.1287.

6-ethyl-2,4-di-*p*-tolylquinoline (4.60m) and 6-ethyl-4-(*p*-tolyl)quinoline (4.60m'):



According to GP I, 1-ethyl-4-nitrosobenzene (54 mg, 0.4 mmol), 4-methylstyrene (0.10 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60m** as yellow gum (62 mg, 46%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60m'** as yellow gum (26 mg, 26%). Analytical data for **4.60m**: FT-IR: ($\tilde{\nu}$) = 2963, 2922, 2870, 1613, 1588, 1494, 1358, 1211, 1183, 1090, 890, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 7.75 (s, 1H), 7.70 (d, *J* = 1.2 Hz, 1H), 7.62 - 7.59 (m, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.50 (s, 3H), 2.43 (s, 3H), 1.27 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 149.5, 147.0, 142.8, 139.8, 138.6, 136.3, 135.7, 131.1, 129.8, 129.7, 129.5, 129.4, 127.8, 126.0, 123.5, 119.6, 29.3, 21.56, 21.54, 15.8 ppm. HRMS: Exact mass calculated for $C_{25}H_{24}N$ ($[M+H]^+$): 338.1903, Found:338.1903.



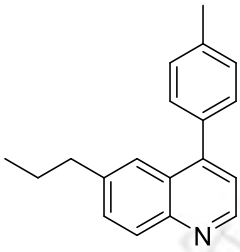
Analytical data for **4.60m'**: FT-IR: ($\tilde{\nu}$) = 2964, 2927, 2872, 1615, 1584, 1454, 1372, 1260, 1184, 1021, 817, 723 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.86 (d, *J* = 4.8 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.37 - 7.34 (m, 3H), 2.78 (q, *J* = 7.8 Hz, 2H), 2.48 (s, 3H), 1.26 (t, *J* = 7.8 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 149.2, 148.4, 146.7, 143.3, 138.7, 135.2, 131.1, 129.63, 129.55, 129.1, 127.1, 123.8, 121.5, 29.4, 21.5, 15.8 ppm. HRMS: Exact mass calculated for $C_{18}H_{18}N$ ($[M+H]^+$): 248.1434, Found: 248.1434.

2,4-bis(4-(*tert*-butyl)phenyl)-6-ethylquinoline (4.60n) and 4-(4-(*tert*-butyl)phenyl)-6-ethylquinoline (4.60n'): According to GP I, 1-ethyl-4-nitrosobenzene (54 mg, 0.4 mmol), 4-tertbutylstyrene (0.14 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:40) gave **4.60n** as yellow gum (57 mg, 34%) and (silica gel; EtOAc : hexane, 1:10) gave **4.60n'** as yellow gum (24 mg, 21%). Analytical data for **4.60n**: FT-IR: ($\tilde{\nu}$) = 2962, 2904, 2868, 1589, 1460, 1394, 1261, 1186, 1081, 965, 892, 799 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.16 (d, *J* = 8.8 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 1H), 7.74 (s, 1H), 7.61 - 7.57 (m, 3H), 7.55 - 7.51 (m, 4H), 2.78 (q, *J* = 7.6 Hz, 2H), 1.44 (s, 9H), 1.38 (s, 9H), 1.28 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.4, 152.5, 151.6, 148.6, 147.9, 142.4, 137.4, 136.0, 130.6, 130.2, 129.5, 127.4, 126.0, 125.9, 125.7, 123.6, 119.6, 35.0, 34.9, 31.6, 31.5, 29.4, 15.9 ppm. HRMS: Exact mass calculated for $C_{31}H_{36}N$ ($[M+H]^+$): 422.2822, Found:422.2851.

Analytical data for **4.60n'**: FT-IR: ($\tilde{\nu}$) = 2962, 2929, 2868, 1611, 1582, 1501, 1455, 1363, 1260, 1102, 1018, 891, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.86 (d, *J* = 4.4 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.76 (s, 1H), 7.61 - 7.59 (m, 1H), 7.57 - 7.55 (m, 2H), 7.48 - 7.46 (m, 2H), 7.29 (d, *J* = 4.4 Hz, 1H), 2.78 (q, *J* = 7.6 Hz, 2H), 1.42 (s, 9H), 1.27 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.6, 149.3, 148.2, 147.7, 142.9, 135.5, 130.6, 129.8, 129.5, 127.0, 125.7, 123.8, 121.7, 35.0, 31.6, 29.4, 15.9 ppm. HRMS: Exact mass calculated for $C_{21}H_{24}N$ ($[M+H]^+$): 290.1903, Found: 290.1900.

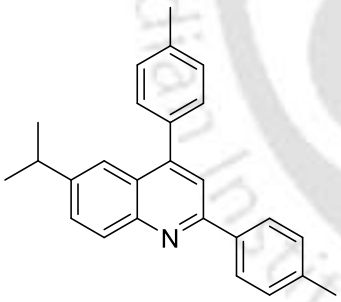
6-propyl-2,4-di-*p*-tolylquinoline (4.60o) and 6-propyl-4-(*p*-tolyl)quinoline (4.60o'): According to GP I, 1-propyl-4-nitrosobenzene (60 mg, 0.4 mmol), 4- methylstyrene (0.10 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60o** as yellow gum (55 mg, 39%) and (silica gel; EtOAc : hexane, 1:10) gave **4.60o'** as yellow gum (20 mg, 19%). Analytical data for **4.60o**: FT-IR: ($\tilde{\nu}$) = 2960, 2925, 2870, 1618, 1590, 1496, 1361, 1261, 1018, 820, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.15 (d, *J* =

8.8 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.75 (s, 1H), 7.68 (d, *J* = 1.6 Hz, 1H), 7.59 - 7.56 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.71(t, *J* = 7.6 Hz, 2H), 2.50 (s, 3H), 2.43 (s, 3H), 1.73 - 1.64 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.3, 148.7, 147.8, 140.9, 139.3, 138.4, 137.3, 136.0, 131.1, 129.9, 129.73, 129.68, 129.5, 127.6, 125.9, 124.2, 119.5, 38.4, 24.8, 21.6, 14.1 ppm. Total count of 13C is less than expected due to the merging of signals in the aliphatic region. HRMS: Exact mass calculated for $C_{26}H_{26}N$ ($[M+H]^+$): 352.2060, Found:352.2056.

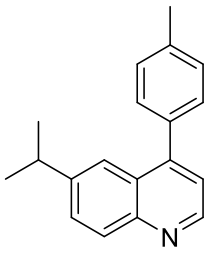


Analytical data for **4.60o'**: FT-IR: ($\tilde{\nu}$) = 2958, 2923, 2854, 1615, 1585, 1501, 1456, 1260, 1184, 1089, 858, 724 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.86 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.74 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.38 - 7.37 (m, 3H), 2.72(t, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 1.70 -1.64 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 150.1, 147.6, 145.7, 142.2, 139.0, 135.0, 132.0, 129.6, 128.3, 127.1, 124.6, 121.5, 38.4, 24.7, 21.6, 14.0 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{19}H_{20}N$ ($[M+H]^+$): 262.1590, Found:262.1596.

6-isopropyl-2,4-di-*p*-tolylquinoline (4.60p) and 6-isopropyl-4-(*p*-tolyl)quinoline (4.60p'):

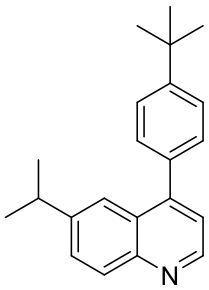


According to GP I, 1-isopropyl-4-nitrosobenzene (60 mg, 0.4 mmol), 4- methylstyrene (0.10 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60p** as yellow gum (59 mg, 42%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60p'** as yellow gum (30 mg, 29%). Analytical data for **4.60p**: FT-IR: ($\tilde{\nu}$) = 2960, 2922, 2867, 1613, 1593, 1548, 1456, 1358, 1266, 821, 751 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 2H), 7.76 (s, 1H), 7.73 (s, 1H), 7.66 - 7.64 (m, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 3.06 - 3.01 (m, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.29 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.3, 148.8, 147.9, 146.9, 139.3, 138.4, 137.3, 136.0, 130.1, 129.72, 129.67, 129.5, 129.1, 127.6, 125.8, 122.2, 119.5, 34.6, 24.1, 21.6 ppm. Total count of 13C is less than expected due to the merging of signals in the aliphatic region. HRMS: Exact mass calculated for $C_{26}H_{26}N$ ($[M+H]^+$): 352.2060, Found: 352.2072.



Analytical data for **4.60p'**: FT-IR: ($\tilde{\nu}$) = 2960, 2925, 2867, 1618, 1584, 1501, 1457, 1385, 1185, 1043, 859, 818, 684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.86 (d, *J* = 4.4 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 1.6 Hz, 1H), 7.69 - 7.66 (m, 1H), 7.44 - 7.42 (m, 2H), 7.37 - 7.32 (m, 3H), 3.07 – 3.00 (m, 1H), 2.48 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.4, 148.4, 147.8, 146.7, 138.8, 135.2, 129.7, 129.6, 129.1, 127.1, 122.5, 121.5, 34.6, 24.1, 21.6 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{19}H_{20}N$ ($[M+H]^+$): 262.1590, Found: 262.1591.

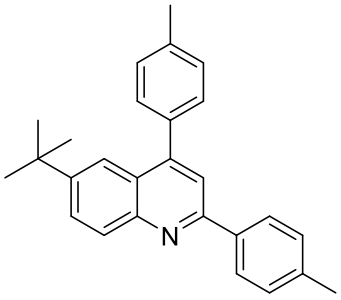
2,4-*bis*(4-(*tert*-butyl)phenyl)-6-isopropylquinoline (4.60q) and 4-(4-(*tert*-butyl)phenyl)-6- isopropylquinoline (4.60q'): According to GP I, 1-isopropyl-4- nitrosobenzene (60 mg, 0.4 mmol), 4-*tert*-butylstyrene (0.14 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:40) gave **4.60q** as yellow gum (81 mg, 47%) and (silica gel; EtOAc : hexane, 1:10) gave **4.60q'**as yellow gum (21mg, 17%). Analytical data for **4.60q**: FT-IR: ($\tilde{\nu}$) = 2962, 2902, 2867, 1610, 1590, 1463, 1368, 1273, 1113, 1016, 838, 750, 604 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.77 - 7.76 (m, 2H), 7.66 - 7.63 (m, 1H), 7.60 - 7.58 (m, 2H), 7.55 - 7.52 (m, 4H), 3.09 - 3.02 (m, 1H), 1.44 (s, 9H), 1.38 (s, 9H), 1.30 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.4, 152.5, 151.6, 148.7, 148.1, 146.9, 137.4, 136.0, 130.3, 129.5, 128.9, 127.4, 126.0, 125.7, 125.9, 122.3, 119.7, 35.0, 34.9, 34.6, 31.6, 31.5, 24.2 ppm. HRMS: Exact mass calculated for $C_{32}H_{38}N$ ($[M+H]^+$): 436.2999, Found: 436.2992.



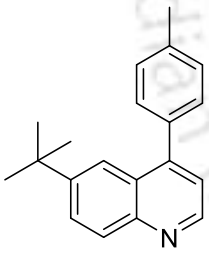
Analytical data for **4.60q'**: FT-IR: ($\tilde{\nu}$) = 2961, 2905, 2870, 1613, 1583, 1501, 1460, 1363, 1267, 1106, 1021, 838, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.86 (d, *J* = 4.4 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.66 - 7.63 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.48 - 7.46 (m, 2H), 7.29 (d, *J* = 4.4 Hz, 1H), 3.08 - 3.01 (m, 1H), 1.43 (s, 9H), 1.29 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.7, 149.4, 148.2,

147.9, 147.4, 135.5, 130.0, 129.5, 128.9, 127.0, 125.7, 122.5, 121.7, 35.0, 34.6, 31.6, 24.2 ppm. HRMS: Exact mass calculated for $C_{22}H_{26}N$ ($[M+H]^+$): 304.2060, Found: 304.2064.

6-*tert*-butyl-2,4-di-*p*-tolylquinoline (4.60r) and 6-*tert*-butyl-4-(*p*-tolyl)quinoline (4.60r'):

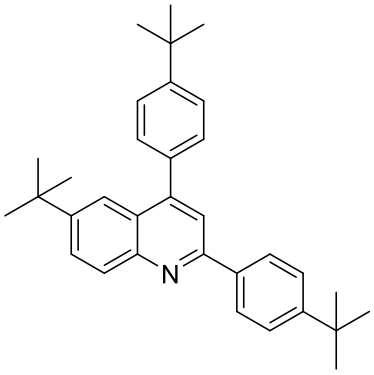


According to GP I, 1-tert-butyl-4-nitrosobenzene (65 mg, 0.4 mmol), 4- methylstyrene (0.10 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.60r** as yellow gum (65 mg, 45%) and (silica gel; EtOAc : hexane, 1:7) gave **4.60r'** as yellow gum (24 mg, 22%). Analytical data for **4.60r**: FT-IR: ($\tilde{\nu}$) = 2962, 2927, 2867, 1615, 1590, 1544, 1462, 1389, 1260, 1114, 1020, 820, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.85 - 7.82 (m, 1H), 7.77 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.39 - 7.32 (m, 4H), 2.50 (s, 3H), 2.44 (s, 3H), 1.36 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.3, 149.7, 149.3, 146.9, 139.7, 138.6, 136.6, 135.8, 129.8, 129.6, 129.5, 129.3, 128.8, 127.7, 125.5, 120.9, 119.6, 35.3, 31.4, 21.6 ppm. Total count of 13C is less than expected due to the merging of signals in the aliphatic region. HRMS: Exact mass calculated for $C_{27}H_{28}N$ ($[M+H]^+$): 366.2216, Found:366.2219.



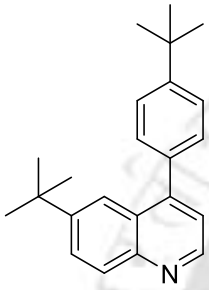
Analytical data for **4.60r'**: FT-IR: ($\tilde{\nu}$) = 2962, 2869, 1614, 1583, 1500, 1372, 1260, 1185, 1022, 859, 817, 724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.87 (s, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.93 (s, 1H), 7.85 - 7.82 (m, 1H), 7.45 - 7.43 (m, 2H), 7.36 - 7.31 (m, 3H), 2.48 (s, 3H), 1.35 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.7, 149.2, 149.0, 146.9, 138.6, 135.4, 129.7, 129.5, 129.1, 128.6, 126.6, 121.6, 121.1, 35.3, 31.4, 21.5 ppm. HRMS: Exact mass calculated for $C_{20}H_{22}N$ ($[M+H]^+$): 276.1747, Found: 276.1751.

2,4-*bis*(4-(*tert*-butyl)phenyl)-6-*tert*-butylquinoline (4.60s) and 4-(4-(*tert*-butyl)phenyl)-6-*tert*butylquinoline (4.60s'):



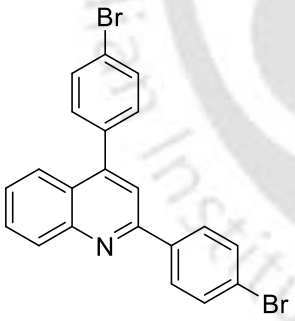
According to GP I, 1-tert-butyl-4-nitrosobenzene (65 mg, 0.4 mmol), 4-tertbutylstyrene (0.14 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:40) gave **4.60s** as yellow gum (76 mg, 42%) and (silica gel; EtOAc : hexane, 1:10) gave **4.60s'** as yellow gum (20 mg, 16%).

Analytical data for **4.60s**: FT-IR: ($\tilde{\nu}$) = 2961, 2905, 2868, 1589, 1514, 1493, 1393, 1201, 1110, 1017, 894, 834, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 (d, *J* = 8.4 Hz, 2H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 2.0 Hz, 2H), 7.85 - 7.82 (m, 1H), 7.79 (s, 1H), 7.61 - 7.54 (m, 6H), 1.44 (s, 9H), 1.39 (s, 9H), 1.38 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.5, 152.6, 151.6, 149.1, 147.4, 137.2, 135.9, 129.6, 129.5, 128.5, 127.5, 126.0, 125.7, 125.4, 120.8, 119.7, 35.3, 35.0, 34.9, 31.6, 31.5, 31.4 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{33}H_{40}N$ ($[M+H]^+$): 450.3155, Found: 450.3172.

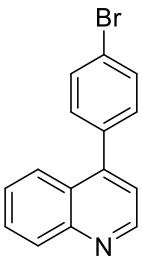


Analytical data for **4.60s'**: FT-IR: ($\tilde{\nu}$) = 2962, 2909, 2870, 1613, 1583, 1500, 1372, 1266, 1111, 1023, 839, 771 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.87 (d, *J* = 4.4 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.84 - 7.81 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 4.4 Hz, 1H), 1.43 (s, 9H), 1.36 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.7, 149.52, 149.45, 148.6, 147.4, 135.5, 129.49, 129.45, 128.4, 126.6, 125.7, 121.7, 121.1, 35.3, 35.0, 31.6, 31.4 ppm. HRMS: Exact mass calculated for $C_{23}H_{28}N$ ([M+H]): 318.2216, Found: 318.2206.

2,4-*bis*(4-bromophenyl)quinoline (4.60t) and 4-(4-bromophenyl)quinoline (4.60t')[51] :

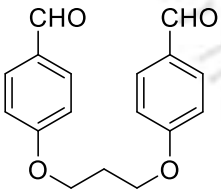


According to GP I, nitrosobenzene (43 mg, 0.40 mmol), 4-bromo styrene (0.16 g, 0.88 mmol) and $Yb(OTf)_3$ (74 mg, 0.12 mmol) were reacted for 48 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:40) gave **4.60t** as yellow gum (43 mg, 25%) and (silica gel; EtOAc : hexane, 1:10) gave **4.60t'** as yellow gum (12 mg, 11%). Analytical data for **4.60t**: FT-IR: ($\tilde{\nu}$) = 2958, 2924, 2851, 1596, 1542, 1485, 1355, 1072, 825, 764, 578, 470 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.78 – 7.74 (m, 2H), 7.71 – 7.65 (m, 4H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.7, 148.8, 148.6, 138.3, 137.2, 132.3, 132.1, 131.3, 130.2, 129.4, 127.1, 125.7, 125.5, 124.4, 123.2, 119.0 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{21}H_{14}Br_2N$ ($[M+H]^+$): 437.9488, Found: 437.9484.



Analytical data for **4.60t'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.96 (s, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.41 – 7.38 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.0, 148.8, 136.7, 132.2, 131.3, 130.4, 129.2, 127.6, 125.9, 123.5, 121.4 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region.

4,4'-(quinoline-2,4-diyl)dibenzonitrile (4.60u): According to GP I, nitrosobenzene (43 mg, 0.40 mmol), 4-cyano styrene (0.11 g, 0.88 mmol) and Yb(OTf)3 (37 mg, 0.06 mmol) were reacted for 5 days in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.60u** as yellow gum (13 mg, 10%). Analytical data for **4.60u**: FT-IR: ($\tilde{\nu}$) = 2960, 2930, 2852, 2228, 1595, 1499, 1451, 1278, 1188, 1076, 844, 747, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 – 8.32 (m, 3H), 7.89 – 7.78 (m, 7H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.61 – 7.57 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.6, 148.4, 142.7, 132.9, 132.8, 131.0, 130.5, 130.4, 128.5, 128.2, 119.1, 118.8, 118.5, 113.5, 113.1 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{23}H_{14}N_3$ ([M+H]$^+$): 332.1182, Found: 332.1177.

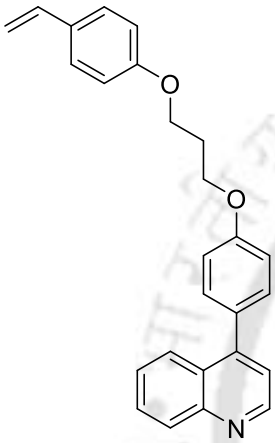


4,4'-(propane-1,3-diylbis(oxy))dibenzaldehyde (4.64):[52] 4-hydroxy benzaldehyde (1.47 g, 12.05 mmol) was added to the solution of 1,3-dibromoprpoape (1.0 g, 5.00 mmol) in DMF (5 mL) followed by the addition of K_2CO_3 (2.08 g, 15.07 mmol). The reaction mixture was heated at 100 ºC for 12 h. After that, the reaction mixture was cooled down to room temperature. The reaction mixture was diluted with cold water (70 mL) and extracted with DCM (3 X 50 mL). The organic layer was washed with brine solution (1 X 50 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum to provide 4,4'- (propane-1,3-diylbis(oxy))dibenzaldehyde **4.64** as a light yellow solid (1.28 g, 90%) which was used for the next step. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.87 (s, 2H), 7.82 (d, *J* = 8.4 Hz, 4H), 7.01 (d, *J* = 9.0 Hz, 4H), 4.25 (t, *J* = 6.0 Hz, 4H), 2.36 - 2.32 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 191.0, 163.9, 132.2, 130.2, 114.9, 64.7, 29.1 ppm.

1,3-*bis*(4-vinylphenoxy)propane (4.66): Methyltriphenylphosphonium iodide (2.19 g, 5.41 mmol) and sodium hydride (60% in mineral oil) (0.81 g (0.49 g), 20.29 mmol) were taken in 100 mL R.B. under argon. A solution of 4,4'-(propane-1,3- diylbis(oxy))dibenzaldehyde **4.64** (1.28 g, 4.51 mmol) in dry THF (20 mL) was added slowly to the mixture at 0 ^{o}C. Then the reaction mixture was stirred at room temperature for 12 h. Then the reaction was quenched with cold water (50 mL) and the mixture was extracted with DCM (3 X 50 mL). The organic layer was washed with brine solution (1X50 mL), dried over anhydrous Na2SO4 and evaporated under vacuum. The column chromatography of the crude product (silica gel; EtOAc : hexane, 1:50) gave **4.66** as white solid (0.33 g, 26%). FT-IR: ($\tilde{\nu}$) = 2955, 2922, 2853, 1603, 1509, 1468, 1378, 1289, 1242, 1176, 1065, 992, 903, 836 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.34 (d, *J* = 8.4 Hz, 4H), 6.87 (d, *J* = 9.0 Hz, 4H), 6.69 - 6.64 (m, 2H), 5.61 (d, *J* = 17.4 Hz, 2H), 5.13 (d, *J* = 10.8 Hz, 2H), 4.17 (t, *J* = 6.0 Hz, 4H), 2.29 - 2.25 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.8, 136.4, 130.7, 127.6, 114.7, 111.8, 64.6, 29.5 ppm.

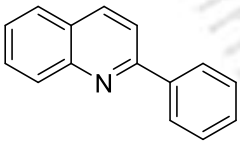
2,4-*bis*(4-(3-(4-vinylphenoxy)propoxy)phenyl)quinoline (4.67a) and 4-(4-(3-(4-vinylphenoxy)propoxy)phenyl)quinoline (4.67b): Nitrosobenzene (43 mg, 0.40 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were successively added to a solution of styrene derivative 6 (0.25 g, 0.88 mmol) in dry DCE (3 mL). Then the reaction mixture was refluxed for 36 h under argon atmosphere. Then the solvent was evaporated under reduced pressure. The reaction mixture was diluted with water (20 mL) and the mixture was extracted with DCM (3 X 20 mL). The combined organic layer was washed with brine solution (1 X 30 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum. Column chromatography of the crude product (silica gel; EtOAc : hexane, 1:10) gave **4.67a** as yellow gum (75 mg, 30%) and (silica gel; EtOAc : hexane, 1:4) gave **4.67b** as yellow gum (34 mg, 22%). Analytical data for **4.67a**: FT-IR: ($\tilde{\nu}$) = 2958, 2923, 2879, 2848, 1606, 1544, 1509, 1498, 1401, 1288, 1175, 1059, 833 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 (d, *J* = 8.0 Hz,

1H), 8.16 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H), 7.73 - 7.70 (m, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.47 - 7.43 (m, 1H), 7.37 - 7.34 (m, 4H), 7.10 - 7.05 (m, 4H), 6.91 - 6.88 (m, 4H), 6.70 - 6.62 (m, 2H), 5.64 - 5.59 (m, 2H), 5.15 - 5.11 (m, 2H), 4.29 - 4.18 (m, 8H), 2.37 - 2.28 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.6, 159.5, 158.8, 156.3, 136.41, 136.38, 131.0, 130.82, 130.78, 130.7, 130.0, 129.4, 127.6, 126.3, 126.0, 125.9, 119.2, 115.1, 114.9, 114.73, 114.72, 111.9, 111.8, 64.81, 64.80, 64.65, 64.56, 29.52, 29.50 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{43}H_{40}NO_4$ ([M+H]$^+$): 634.2952, Found: 634.2945.



Analytical data for **4.67b**: FT-IR: ($\tilde{\nu}$) = 2961, 2905, 2870, 1613, 1583, 1501, 1460, 1363, 1267, 1106, 1021, 838, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.92 (d, *J* = 4.8 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.80 - 7.76 (m, 1H), 7.58 - 7.54 (m, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.40 - 7.34 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.70 - 6.63 (m, 1H), 5.62 (d, *J* = 17.6 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H), 4.29 - 4.20 (m, 4H), 2.36 - 2.30 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.8, 158.8, 148.6, 147.2, 136.4, 131.1, 130.8, 130.4, 130.0, 128.8, 128.7, 127.6, 127.3, 127.2, 126.3, 121.4, 115.0, 114.7, 111.9, 64.8, 64.5, 29.5 ppm. HRMS: Exact mass calculated for $C_{26}H_{24}NO_2$ ([M+H]$^+$): 382.1802, Found: 382.1818.

2-phenylquinoline (4.77):[53] According to GP I, nitrosobenzene (43 mg, 0.40 mmol), trans β-methyl styrene (0.10 g, 0.88 mmol) and $Yb(OTf)_3$ (37 mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.77** as yellow gum (18 mg, 22%) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.4 Hz, 1H), 8.19 – 8.16 (m, 3H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.76 – 7.71 (m 1H), 7.56 – 7.52 (m, 3H), 7.49 – 7.45 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.6, 148.5, 139.9, 137.0, 129.94, 129.88, 129.5, 129.1, 127.8, 127.7, 127.4, 126.5, 119.3 ppm.

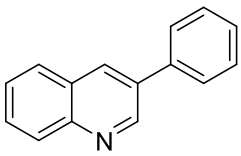


General Procedure for the Synthesis of 3-substituted quinolines (II):

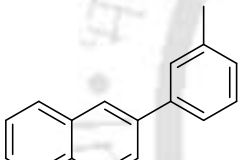
Freshly prepared nitrosoarenes (1 equiv.) and $Cu(OTf)_2$ (15 mol%) were successively added to a solution of styrene oxide derivatives (2 equiv.) in dry DCE (3 mL). Then the reaction mixture was refluxed for 20 - 28 h under argon atmosphere. Then the solvent was evaporated

under reduced pressure. The reaction mixture was diluted with water (1X20 mL) and the reaction mixture was extracted with DCM (3X20 mL). The organic layer was washed with brine solution (1X30 mL) and evaporated under vacuum. The crude mixture was subjected to column chromatography (silica gel) to afford analytically pure products.

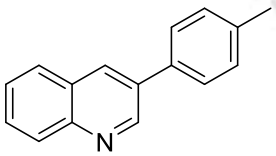
3-phenylquinoline (4.40a):[21] According to GP II, nitrosobenzene (35 mg, 0.33 mmol), styrene oxide (79 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 24 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40a** as yellow gum (42 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.19 (d, *J* = 2.4 Hz, 1H), 8.32 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.75 - 7.71 (m, 3H), 7.61 - 7.57 (m, 1H), 7.55 - 7.51 (m, 2H), 7.46 - 7.43 (m, 1H) ppm. HRMS: Exact mass calculated for $C_{15}H_{12}N$ ($[M+H]^+$): 206.0964, Found: 206.0974.



3-(*m*-tolyl)quinoline (4.40b):[23] According to GP II, nitrosobenzene (35 mg, 0.33 mmol), 3-methylstyrene oxide (88 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 20 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40b** as yellow gum (39 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.19 (d, *J* = 2.0 Hz, 1H), 8.37 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.77 - 7.74 (m, 1H), 7.63 -7.60 (m, 1H), 7.53 - 7.51 (m, 2H), 7.45 - 7.41 (m, 1H), 7.28 (s, 1H), 2.48 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{16}H_{14}N$ ($[M+H]^+$): 220.1121, Found: 220.1114.



3-(*p*-tolyl)quinoline (4.60c):[23] According to GP II, nitrosobenzene (35 mg, 0.33 mmol), 4-methyl styrene oxide (88 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 20 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.60c** as yellow gum (49 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.19 (d, *J* = 1.2 Hz, 1H), 8.36 (d, *J* = 1.6 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.77 - 7.73 (m, 1H), 7.63 - 7.59 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 2H), 2.45 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{16}H_{14}N$ ($[M+H]^+$): 220.1121, Found: 220.1122.



3-(4-chlorophenyl)quinoline (4.60d):[21] According to GP II, nitrosobenzene (35 mg, 0.33 mmol), 4- chlorostyrene oxide (0.10 g, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 20 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.60d** as yellow gum (44 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.15 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 25 1H), 7.78 - 7.74 (m, 1H), 7.66 - 7.60 (m, 3H), 7.52 - 7.49 (m, 2H) ppm. HRMS: Exact mass calculated for $C_{15}H_{11}NCl$ ($[M+H]^+$): 240.0575, Found: 240.0578.

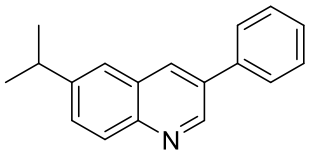
3-(4-fluorophenyl)quinoline (4.60e):[21] According to GP II, nitrosobenzene (35 mg, 0.33 mmol), 4- fluorostyrene oxide (91 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 15 mol %, 0.05 mmol) were reacted for 24 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.60e** as yellow gum (45 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.16 (d, *J* = 2.0 Hz, 1H), 8.36 (s, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.80 - 7.76 (m, 1H), 7.70 - 7.62 (m, 3H), 7.24 - 7.22 (m, 2H) ppm. HRMS: Exact mass calculated for $C_{15}H_{11}NF$ ($[M+H]^+$): 224.0870, Found: 224.0869.

6-methyl-3-phenylquinoline (4.60f):[21] According to GP II, 1-methyl-4-nitrosobenzene (40 mg, 0.33 mmol), styrene oxide (79 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 24 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.60f** as yellow gum (45 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.12 (d, *J* = 2.0 Hz, 1H), 8.30 (d, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.72 - 7.68 (m, 3H), 7.61 - 7.58 (m, 1H), 7.56 - 7.52 (m, 2H), 7.47 - 7.43 (m, 1H), 2.58 (s, 3H) ppm. HRMS: Exact mass calculated for C16H14N ($[M+H]^+$): 220.1121, Found: 220.1124.

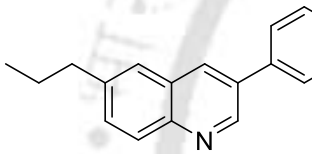
6-ethyl-3-phenylquinoline (4.60g):[21] According to GP II, 1-ethyl-4-nitrosobenzene (45 mg, 0.33 mmol), styrene oxide (79 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 20 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.60g** as yellow gum (42 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.13 (d, *J* = 2.0 Hz, 1H), 8.32 (d, *J* = 2.0 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.73 - 7.69 (m, 3H), 7.64 - 7.61 (m, 1H), 7.55 - 7.52 (m, 2H), 7.47 - 7.43 (m, 1H), 2.88 (q, *J* = 7.6 Hz, 2H), 1.36

(t, *J* = 7.6 Hz, 3H) ppm. HRMS: Exact mass calculated for $C_{17}H_{16}N$ ($[M+H]^+$): 234.1277, Found: 234.1280.

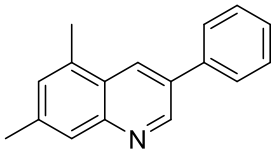
6-isopropyl-3-phenylquinoline (4.40h):[21] According to GP II, 1-isopropyl-4-nitrosobenzene (49 mg, 0.33 mmol), styrene oxide (79 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 24 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40h** as yellow gum (55 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.12 (d, *J* = 2.0 Hz, 1H), 8.27 (d, *J* = 2.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.72 - 7.71 (m, 2H), 7.68 (s, 1H), 7.65 - 7.63 (m, 1H), 7.55 - 7.51 (m, 2H), 7.45 - 7.42 (m, 1H), 3.16 - 3.09 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 6H) ppm. HRMS: Exact mass calculated for $C_{18}H_{18}N$ ($[M+H]^+$): 248.1434, Found: 248.1429.



3-phenyl-6-propylquinoline (4.40i): According to GP II, 1-nitroso-4-propylbenzene (49 mg, 0.33 mmol), styrene oxide (79 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 22 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40i** as yellow gum (57 mg, 70%). FT-IR: ($\tilde{\nu}$) = 2959, 2929, 2871, 1600, 1494, 1455, 1349, 1260, 1026, 800, 627 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.13 (d, *J* = 1.8 Hz, 1H), 8.33(d, *J* = 1.2 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.68 (s, 1H), 7.62 - 7.61 (m, 1H), 7.55 - 7.53 (m, 2H), 7.47 - 7.44 (m, 1H), 2.81 (t, *J* = 7.8 Hz, 2H), 1.79 - 1.75 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 148.1, 144.9, 142.5, 137.7, 134.21, 134.15, 132.0, 129.5, 128.5, 128.4, 128.1, 127.6, 126.6, 38.2, 24.5, 14.0 ppm. HRMS: Exact mass calculated for $C_{18}H_{18}N$ ($[M+H]^+$): 248.1434, Found: 248.1433.



5,7-dimethyl-3-phenylquinoline (4.40j):[21] According to GP II, 1,3-dimethyl-5-nitrosobenzene (45 mg, 0.33 mmol), styrene oxide (79 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 28 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40j** as yellow gum (45 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.13 (d, *J* = 2.4 Hz, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 7.82 (s, 1H), 7.73 - 7.71 (m, 2H), 7.56 - 7.52 (m, 2H), 7.46 - 7.42 (m, 1H), 7.28 (s, 1H), 2.72 (s, 3H), 2.55 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{17}H_{16}N$ ($[M+H]^+$): 234.1277, Found: 234.1280.



6-(*tert*-butyl)-3-phenylquinoline (4.40k):[22] According to GP II, 1-(*tert*-butyl)-4-nitrosobenzene (54 mg, 0.33 mmol), styrene oxide (79 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 24 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40k** as yellow gum (56 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.13 (s, 1H), 8.35 (d, *J* = 1.6 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.86 - 7.83 (m, 2H), 7.73 - 7.71 (m, 2H), 7.55 - 7.52 (m, 2H), 7.47 - 7.43 (m, 1H), 1.45 (s, 9H) ppm. HRMS: Exact mass calculated for $C_{19}H_{20}N$ ($[M+H]^+$): 262.1590, Found: 262.1593.

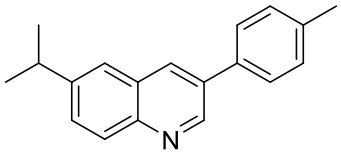
6-chloro-3-phenylquinoline (4.40l):[23] According to GP II, 1-chloro-4-nitrosobenzene (47 mg, 0.33 mmol), styrene oxide (79 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 24 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40l** as yellow gum (29 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.17 (d, *J* = 2.0 Hz, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 9.2 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.71 - 7.65 (m, 3H), 7.56 - 7.52 (m, 2H), 7.48 - 7.44 (m, 1H) ppm. HRMS: Exact mass calculated for $C_{15}H_{11}NCl$ ($[M+H]^+$): 240.0575, Found: 240.0574.

7-ethyl-3-phenylquinoline (4.40m):[54] According to GP II, 1-ethyl-3-nitrosobenzene (45 mg, 0.33 mmol), styrene oxide (79 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 24 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40m** as yellow gum (41 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.15 (d, *J* = 2.4 Hz, 1H), 8.35 (d, *J* = 2.0 Hz, 1H), 8.02 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.72 - 7.70 (m, 2H), 7.55 - 7.43 (m, 4H), 2.90 (q, *J* = 7.6 Hz, 2H), 1.37 (t, *J* = 7.6 Hz, 3H) ppm. HRMS: Exact mass calculated for $C_{17}H_{16}N$ ($[M+H]^+$): 234.1277, Found: 234.1279.

6-ethyl-3-(*p*-tolyl)quinoline (4.40n): According to GP II, 1-ethyl-4-nitrosobenzene (45 mg, 0.33 mmol), 4-methyl styrene oxide (88 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 20 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40n** as yellow gum (52 mg, 64%). FT-IR: ($\tilde{\nu}$) = 2964, 2927, 2871, 1604, 1516, 1455, 1374, 1261, 1040, 914, 834, 724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.11 (d, *J* = 2.0 Hz, 1H), 8.29 (d, *J* = 2.0 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.67 (s, 1H), 7.63 - 7.60 (m, 3H), 7.34 (d, J = 8.0 Hz, 2H), 2.87 (q, *J* = 7.6 Hz, 2H), 2.44 (s, 3H), 1.36 (t, *J*

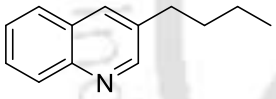
= 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.1, 144.8, 143.9, 138.5, 134.8, 134.1, 133.8, 131.5, 130.2, 128.6, 128.2, 127.4, 125.7, 29.1, 21.4, 15.5 ppm. HRMS: Exact mass calculated for $C_{18}H_{18}N$ ($[M+H]^+$): 248.1434, Found: 248.1435.

6-isopropyl-3-(*p*-tolyl)quinoline (4.40o): According to GP II, 1-isopropyl-4-nitrosobenzene



(49 mg, 0.33 mmol), 4-methyl styrene oxide (88 mg, 0.66 mmol) and $Cu(OTf)_2$ (18 mg, 0.05 mmol) were reacted for 22 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40** as yellow gum (57 mg, 66%). FT-IR: ($\tilde{\nu}$) = 2960, 2927, 2872, 1607, 1516, 1256, 1128, 817, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.12 (d, *J* = 2.4 Hz, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.67 (m, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 2H), 3.17 - 3.10 (m, 1H), 2.44 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.9, 147.4, 144.0, 138.8, 134.7, 134.4, 134.2, 130.7, 130.3, 128.7, 127.6, 127.4, 124.3, 34.4, 24.0, 21.4 ppm. HRMS: Exact mass calculated for $C_{19}H_{20}N$ ($[M+H]^+$): 262.1590, Found: 262.1592.

3-butylquinoline (4.40p):[53] According to GP II, nitrosobenzene (43 mg, 0.4 mmol), 1,2-



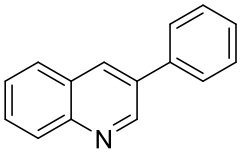
epoxyhexane (80 mg, 0.8 mmol) and $Cu(OTf)_2$ (22 mg, 0.06 mmol) were reacted for 24 h in dry DCE (3 mL) and column chromatography of the crude product (neutral alumina; EtOAc : hexane, 1:30) gave **4.40p** as yellow gum (8 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.78 (d, *J* = 2.0 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 2.83 – 2.67 (m, 2H), 1.77 – 1.67 (m, 2H), 1.44 – 1.38 (m, 2H), 1.00 – 0.94 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.8, 146.4, 135.7, 134.9, 129.0, 128.9, 128.5, 127.5, 126.9, 33.4, 33.1, 22.5, 14.1 ppm.

General Procedure for preparation of nitrone 4.45 and its reaction with 2-phenylacetaldehyde or styrene oxide (GP III):

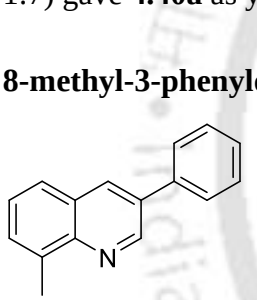
Formalin (37%, 1eq) solution was added to a mixture of nitrobenzene derivatives(1eq), ethanol, water and NH_4Cl (1eq). After the mixture was stirred 15 min, Zn powder (2 eq) was added under 0 ^oC. The reaction mixture was stirred overnight at room temperature. Then the solid was filtered, the filtrate was extracted with DCM (3X30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in DCE. 2-phenylacetaldehyde (1eq) or styrene epoxide (1 eq.) and $Cu(OTf)_2$ (15

mol%) were added and the mixture was refluxed for 24 h. Then the solvent was evaporated under reduced pressure. The reaction mixture was diluted with water and the reaction mixture was extracted with DCM. The organic layer was washed with brine solution and evaporated under vacuum. The crude mixture was subjected to column chromatography (silica gel) to afford analytically pure products.

3-phenylquinoline (4.40a): According to the GP III: 37% aq. Formalin (0.11 g (40 mg), 1.35 mmol), nitrobenzene (0.17 g, 1.35 mmol), ethanol (5 mL), water (5 mL) and NH_4Cl (72 mg, 1.35 mmol), Zn powder (0.18 g, 2.70 mmol), 2-phenylacetaldehyde (0.16 g, 1.35 mmol) and $Cu(OTf)_2$ (73 mg, 0.20 mmol) were reacted for 24 h in dry DCE (5 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40a** as yellow gum (0.14 g, 52%) and styrene oxide (0.16 g, 1.35 mmol) and $Cu(OTf)_2$ (73 mg, 0.20 mmol) were reacted for 24 h in dry DCE (5 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40a** as yellow gum (0.20 g, 73%).



8-methyl-3-phenylquinoline (4.40q):[55] According to the GP III: 37% aq. Formalin (0.11 g (40 mg), 1.35 mmol), 1-methy-2-nitrobenzene (0.19 g, 1.35 mmol), ethanol (5 mL), water (5 mL) and NH_4Cl(72 mg, 1.35 mmol), Zn powder (0.18 g, 2.70 mmol), 2-phenylacetaldehyde (0.16 g, 1.35 mmol) and $Cu(OTf)_2$ (73 mg, 0.20 mmol) were reacted for 24 h in dry DCE (5 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:7) gave **4.40q** as yellow gum (92 mg, 31%). Analytical data for **4.40q**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.25 (s, 1H), 8.34 (d, *J* = 2.0 Hz, 1H), 7.77 – 7.72 (m, 3H), 7.61 – 7.52 (m, 3H), 7.50 – 7.43 (m, 2H), 2.88 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{16}H_{14}N$ ($[M+H]^+$): 220.1121, Found: 220.1135.



2,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine (4.82):[56] According to GP I, nitrosobenzene (43 mg, 0.4 mmol), phenylbutadiene (0.11 g, 0.88 mmol) and $Yb(OTf)_3$ (37mg, 0.06 mmol) were reacted for 36 h in dry DCE (3 mL) and column chromatography of the crude product (silica gel; EtOAc : hexane, 1:30) gave **4.82** as yellow gum (29 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.38 (m, 2H), 7.32 – 7.25 (m, 3H), 7.22 – 7.18 (m, 2H), 7.04 – 7.02 (m, 2H), 6.89 (t, *J* = 7.2 Hz, 1H), 6.08 – 5.99 (m, 2H), 5.55 – 5.54 (m, 1H), 3.93 – 3.79 (m, 2H) 30 ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.5, 139.1, 129.2, 129.0, 128.7, 128.6, 128.4, 124.0, 122.4, 116.0, 80.1, 51.8 ppm.

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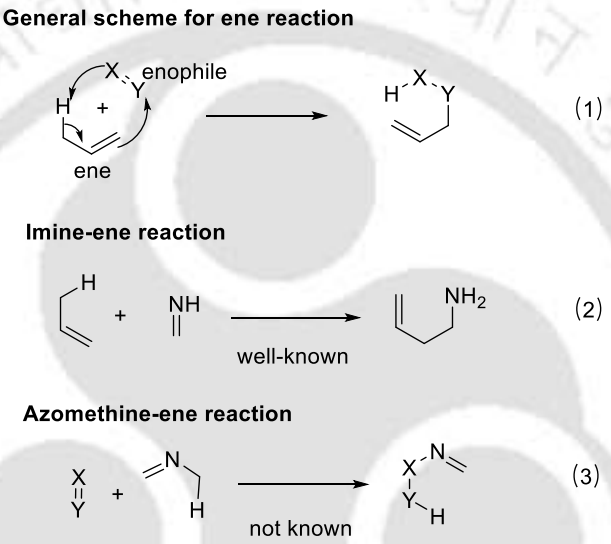
CHAPTER - 5

Nitroso-azomethine ene reaction enabled three component annulation of nitrosoarene, azomethine and alkene to arylquinolines

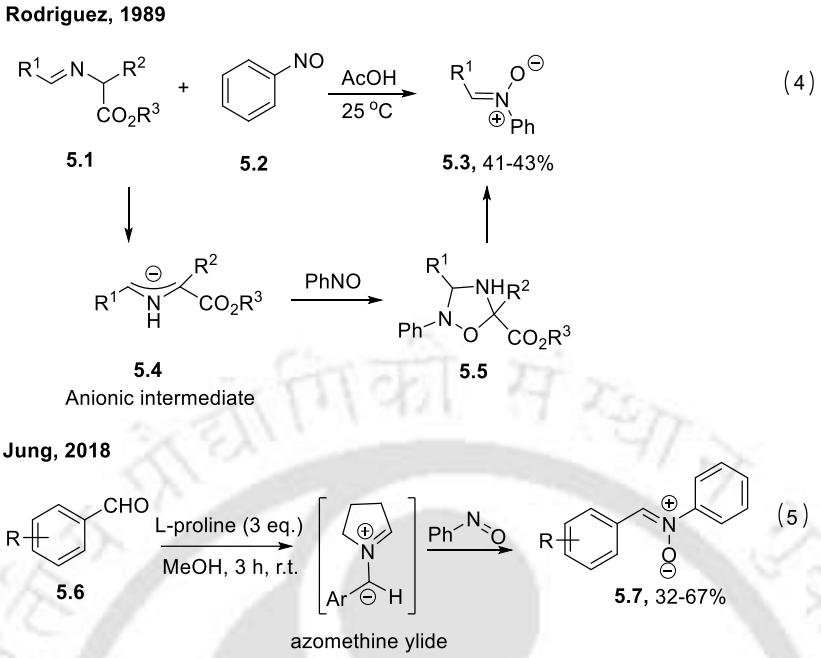
5.1 Introduction:

The ene reaction, an important transformation in organic synthesis, was discovered by Alder in 1943.[1] The reaction proceeds between an alkene having an allylic hydrogen (ene) and an enophile, in order to form a new σ-bond (**Scheme 1**, eq. 1).[1] Ene reaction, where a Schiff base is chosen as an enophile, is often known as an imino-ene reaction (**Scheme 1**, eq. 2). It provides a new strategy for C–C bond formation, and is potentially valuable for the synthesis of *N*-heterocycles.[2]



Scheme 1: Variety of ene reactions

On the other way, Schiff base as an alkene (as ene) for the ene reaction is not known in the literature (**Scheme 1**, eq. 3). Moreover, nitroso compounds as an enophile are also capable to undergo nitroso-ene reaction. The nitroso ene reaction has become one of the most versatile approaches to the direct regioselective and stereoselective allylic functionalization of alkenes (**Chapter 1**).[3] In 1989, Rodriguez *et al.* reacted nitrosoarene with azomethine amine derived from amino acid for the synthesis of nitrone **5.3**. It was believed that the reaction proceeded *via* [3+2] cycloaddition pathway (**Scheme 2**, eq. 4).[4] Similarly, later in 2018, Jung *et al.* reported *L*-proline mediated synthesis of nitrone **5.7** at room temperature using arylaldehyde **5.6** and nitrosobenzene **5.2** through azomethine ylide intermediate (**Scheme 2**, eq. 5).[5]



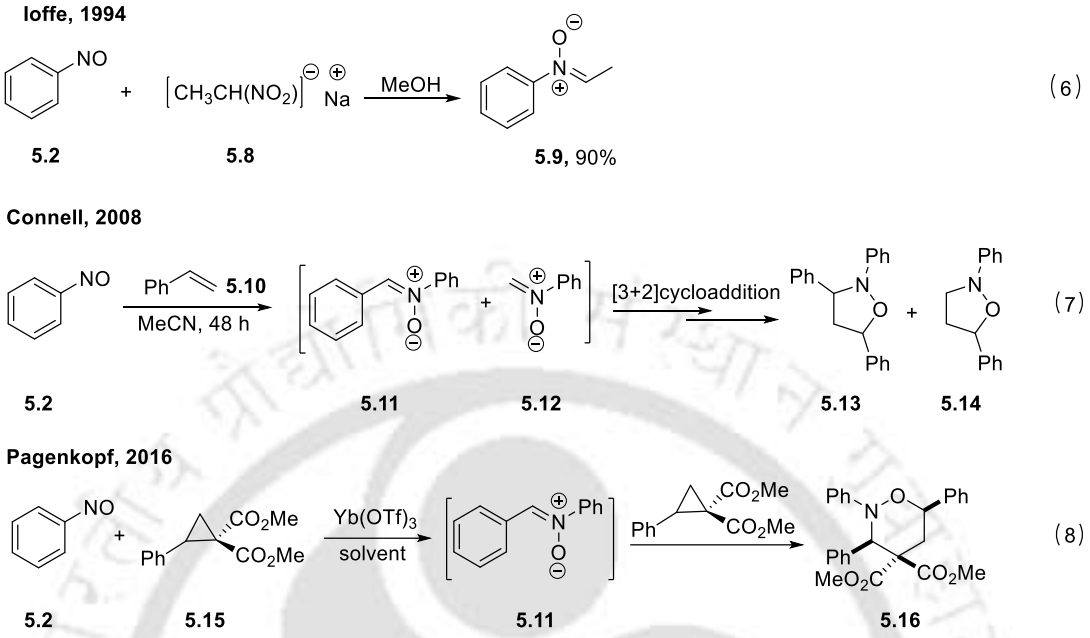
Scheme 2: Synthesis of nitrone using nitrosobenzene.

5.2 Literature Reports on Nitrone formation from nitrosobenzene:

Nitrone is a functional group in organic chemistry consisting of an *N*-oxide of an imine. Nitrone is mostly used as a 1,3-dipole mainly in 1,3-dipolar cycloadditions. Other reactions *i.e.*, radical addition, nucleophilic additions, electrophilic coordination are also well-known reactions for nitrone.[6] Very few strategies are known in the literature for the synthesis of nitrone from nitrosoarenes. Reaction of imine containing acidic proton with nitroso to synthesis nitrone through [3+2] cycloaddition pathway was well documented.[4] However, imine which can also be treated as pseudo-olefinic system, may undergo nitroso-ene reaction to afford the similar reactive species which will be helpful for further application.

In 1994, Ioffe *et al.* developed the method using salts of nitro compounds **5.8**, which can be reacted readily with nitroso compounds **5.2** in MeOH to afford the corresponding nitrones **5.9** (**Scheme 3**, eq. 6).[7] As discussed in previous chapter, in 2008, Connell *et al.* reported a reaction of nitrosobenzene **5.2** with styrene **5.10** to form oxazolines **5.13** and **5.14** *via in situ* formation of nitrones **5.11** and **5.12** (**Scheme 3**, eq. 7).[8] In addition to that , the nitroso group was reported recently to react well with the donor−acceptor cyclopropanes. In 2016, Pagenkopf *et al.* developed tandem ring opening, elimination, and cycloaddition of donor−acceptor cyclopropane **5.15** by $Yb(OTf)_3$-catalyzed cycloaddition with nitrosobenzene

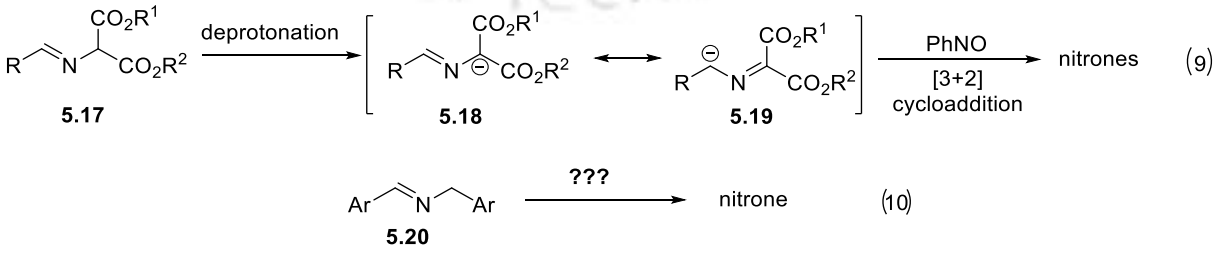
5.2. The reaction results in the formation of tetrahydro-1, 2-oxazine **5.16** instead of the normal cycloadduct isoxazolidine *via in situ* nitrone **5.11** formation (**Scheme 3**, eq. 8).[9]



Scheme 3: *In situ* formation of nitrone for the synthesis of *N*-heterocycles.

5.3 Hypothesis:

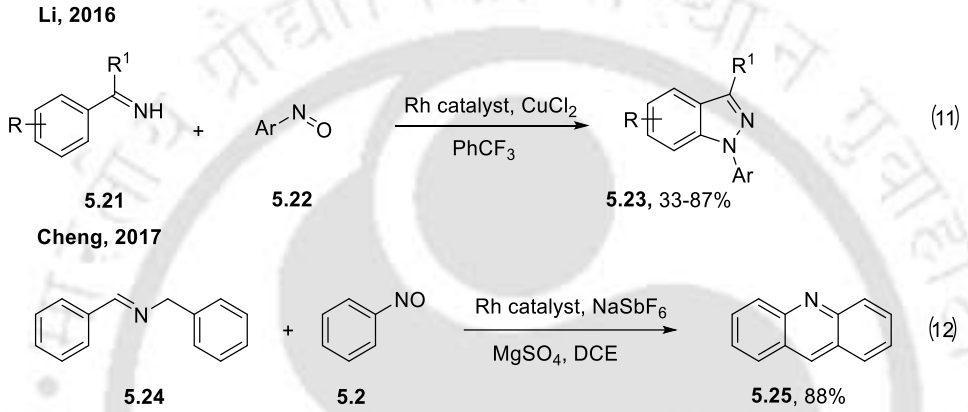
According to the literature, [3+2]-cycloaddition reaction of the imine **5.17** with nitroso is documented to form nitrones. Due to presence of acidic proton, deprotonation step will be facile for imine **5.17** to afford **5.18** or **5.19** which underwent [3+2] cycloaddition with nitrosoarene very easily to form nitrone (**Scheme 4**, eq. 9). However, similar reactivity of imine **5.20** without having electron withdrawing group was not known. Therefore, the study of the reactivity of imine with nitrosoarene would be important in the context of nitrone synthesis (**Scheme 4**, eq. 10).



Scheme 4: Hypothesis of the nitrone formation.

5.4 Literature known imine reaction with nitroso:

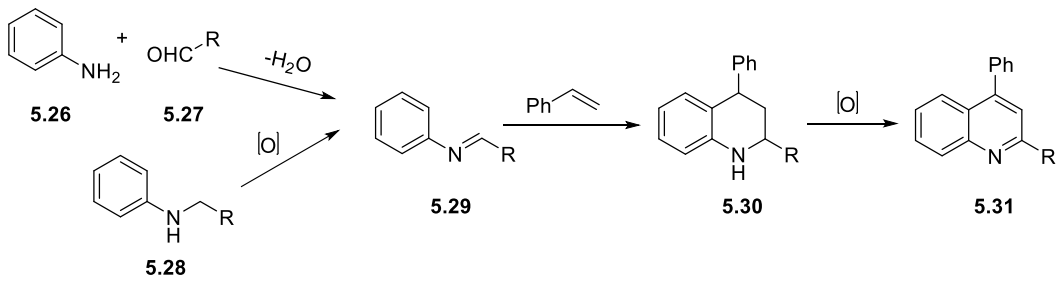
There are few reactions of imine derivatives with nitrosoarene are known. In 2016, Li *et al.* designed a pathway where nitrosoarene **5.22** has been used as a potential aminating reagent for the efficient synthesis of 1*H*-indazoles **5.23** with imine **5.21** *via* rhodium and copper catalyzed C−H activation and C−N/N−N coupling (**Scheme 5**, eq. 11).[10] In the next year, Cheng *et al.* developed a Rh(III)-catalyzed bilateral cyclization of nitrosobenzene **5.2** and imine **5.24** for the efficient construction of acridine **5.25** proceeding *via* C–H functionalization (**Scheme 5**, eq. 12).[11]



Scheme 5: Known reaction of imine with nitroso compounds.

5.5 Literature Report on 2,4-disubstituted quinolines:

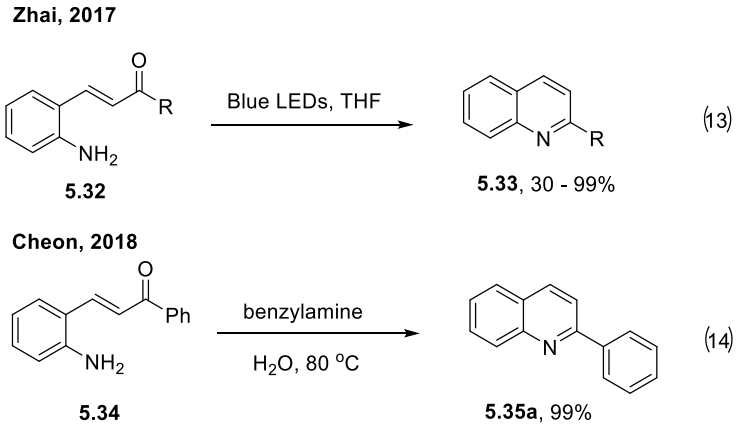
Povarov approach is one of the important protocols for the synthesis of 2,4-disubstituted quinolines (**Chapter 4**). Most of them involves use of aniline **5.26**, aldehyde **5.27**, olefins to synthesize the quinoline scaffolds through formation of imine **5.29**. Secondary amine **5.28** after facile oxidation was able to provide imine **5.29** which after Povarov cyclization provides tetrahydroquinoline **5.30**. Aerial oxidation of **5.30** provides di-substituted quinoline **5.31** (**Scheme 6**).[12]



Scheme 6: General protocol for quinoline syntheses.

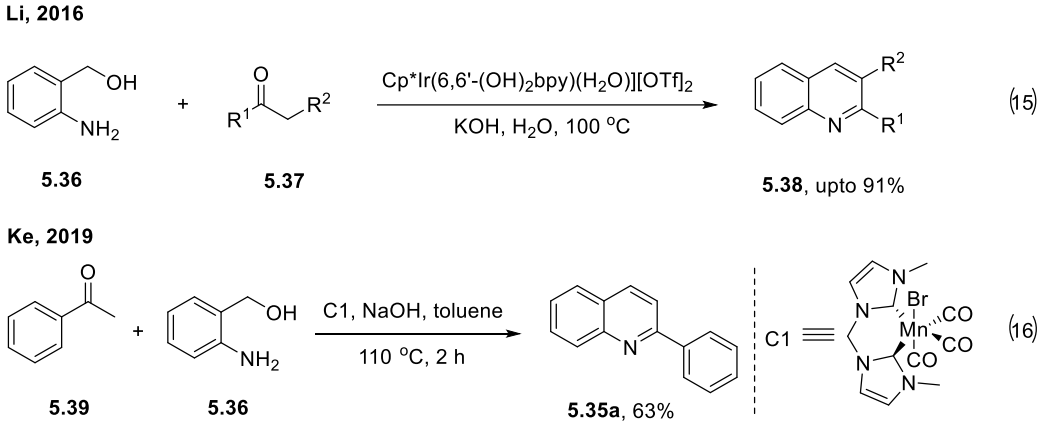
5.6 Selected known methods for 2-phenylquinolins:

In 2017, Zhai *et al*. synthesized a series of quinolines **5.33** in good to excellent yields under simple aerobic conditions through the cyclization of aminostyryl **5.32**. The reaction proceeded *via* blue-light-mediated carbon–carbon double bond isomerization of **5.32** in the absence of any photo-redox catalyst (**Scheme 7**, eq. 13).[13] Next year, Cheon *et al.* reported on-water synthesis of 2-substituted quinoline **5.35a** with excellent yield from 2-aminochalcone derivative **5.34** using benzylamine as the nucleophilic catalyst (**Scheme 7**, eq. 14).[14]



Scheme 7: Syntheses of 2-aryl quinoline from aminostyryl ketone.

In 2016, Li *et al.* reported a strategy for acceptorless dehydrogenative cyclization of *o*-amino benzyl alcohol **5.36** with ketone **5.37** to quinoline **5.38**. A series of desirable quinolines were synthesized in the presence of $[Cp^*Ir(6,6'\text{-}(OH)_2bpy)(H_2O)][OTf]_2$ in high yields (**Scheme 8**, eq. 15).[15] Later in 2019, Ke *et al.* designed an efficient protocol for the synthesis of quinoline **5.35a** from acetophenone **5.39** and *o*-amino benzyl alcohol **5.36** using the non-bifunctional *bis*-NHC-Mn catalyst (C1) (**Scheme 8**, eq. 16).[16]

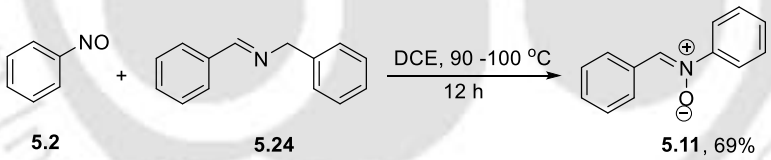


Scheme 8: Selected examples of 2-phenylquinoline from amino benzyl alcohol.

All the previous methods are mostly multi component and multistep reaction and associated with conventional condensation reaction followed imine formation and cycloaddition reaction.

5.7 Preliminary Result for nitrone:

Nitrosobenzene **5.2** was reacted with the imine **5.24** in DCE at 90-100 °C for 12 h. Expectedly, nitrone **5.11** was formed with 69% yield (**Scheme 9**). The imine **5.24** was synthesized from corresponding benzaldehyde and benzylamine using literature procedure.



Scheme 9: Preliminary result for nitrone synthesis.

5.8 Optimization of the reaction:

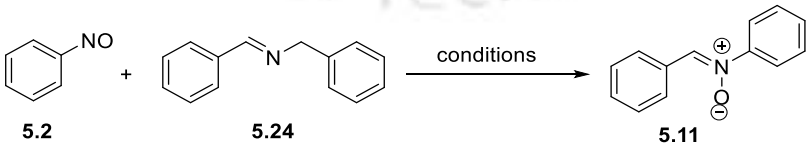


Table 1: Optimization Table:

Entry	Eq. of 5.2	Eq. of 5.24	Solvent	Time	Temp.	Yield[a] (%)
1.	1	1	DCE	12 h	90 -100 °C	69

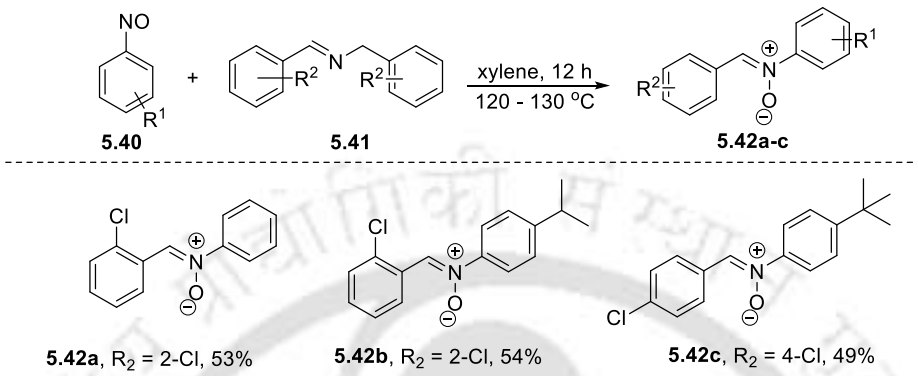
2.	1	1	toluene	12 h	110 -120 ^{o}C	66
3.	1	1	DCM	12 h	40 - 50 ^{o}C	49
4.	1	1	xylene	12 h	120 -130 ^{o}C	71
5.	1	1	CCl_4	12 h	80 ^{o}C	70
6.	1	1	DMF	12 h	150 ^{o}C	-
7.	1	1	MeOH	12 h	70 ^{o}C	32
8.	1	1	$CHCl_3$	12 h	65 ^{o}C	49
9.	1	1.5	xylene	12 h	120 -130 ^{o}C	73
10.	1	2	xylene	12 h	120 -130 ^{o}C	73
11.	2	1	xylene	12 h	120 -130 ^{o}C	21
12.	1	1.5	xylene	24 h	120 -130 ^{o}C	71
13.	1	1.5	xylene	6 h	120 -130 ^{o}C	70
14.	1	1.5	xylene	24 h	r.t.	trace
15.	1	1.5	Xylene (AcOH – 0.5 eq.)	12 h	120 -130 ^{o}C	59
16.	1	1.5	Xylene (Et_3N – 0.5 eq.)	12 h	120 -130 ^{o}C	trace

All reactions were carried out with nitrosobenzene (0.28 mmol, 1 eq.) in solvent (3 mL). AcOH = Acetic acid. [a]Isolated yield.

Encouraged by the initial result, various reaction conditions were screened for further improvement. Initially, the reaction of nitrosobenzene with imine was investigated in various solvents without changing the relative stoichiometry of both the reactants (**Table 1**, entry 1-8). Moderate yield was noticed with toluene (**Table 1**, entry 2) which was not improved using DCM (**Table 1**, entry 3). The yield was relatively improved using xylene (**Table 1**, entry 4). However, further enhancement was not observed in CCl_4 (**Table 1**, entry 5). DMF was unsuccessful to produce the product (**Table 1**, entry 6). Decreased in yields were noticed when MeOH and $CHCl_3$ were used (**Table 1**, entry 7, 8). Slight increase in the yield was observed while 1.5 eq. of the imine was used (**Table 1**, entry 9, 10). The yield was reduced while 2 equivalents of nitrosobenzene was used (**Table 1**, entry 11). Variation in reaction time did not provide better result (**Table 1**, entry 12, 13). Only trace amount of the product was isolated when reaction was performed at room temperature (**Table 1**, entry 14). No significant changes in the reaction yield were observed when the additives *i.e.*, AcOH or Et_3N were added in the reaction (**Table 1**, entry 15, 16).

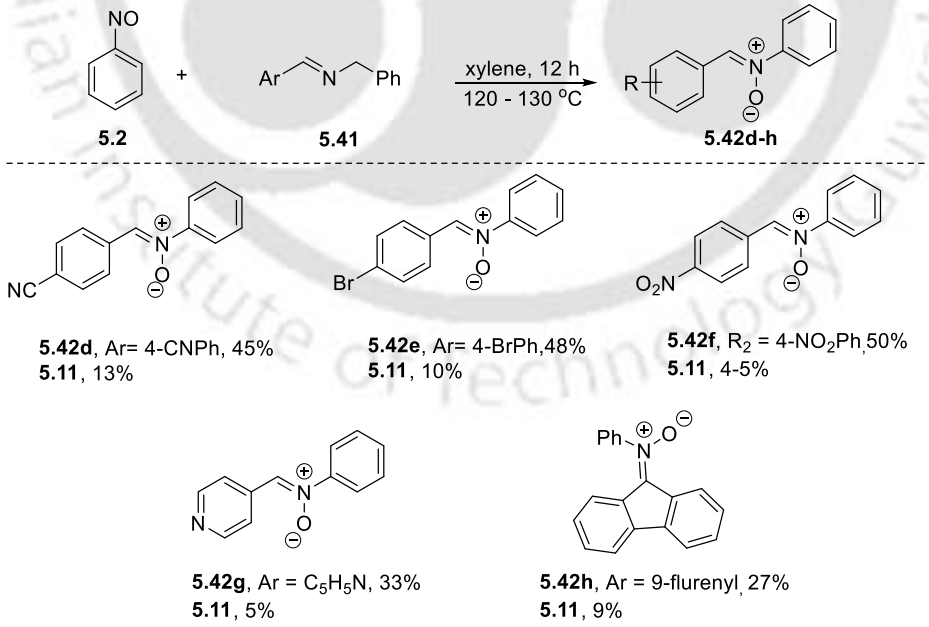
5.9 Scope of nitrone formation from symmetric and unsymmetric imines:

Having the optimized reaction condition in hand, the scope of the nitrone formation was examined. Substrates **5.42a-h** were prepared with the variation in nitrosoarene **5.40** as well as in imine **5.41** (**Scheme 10a**).



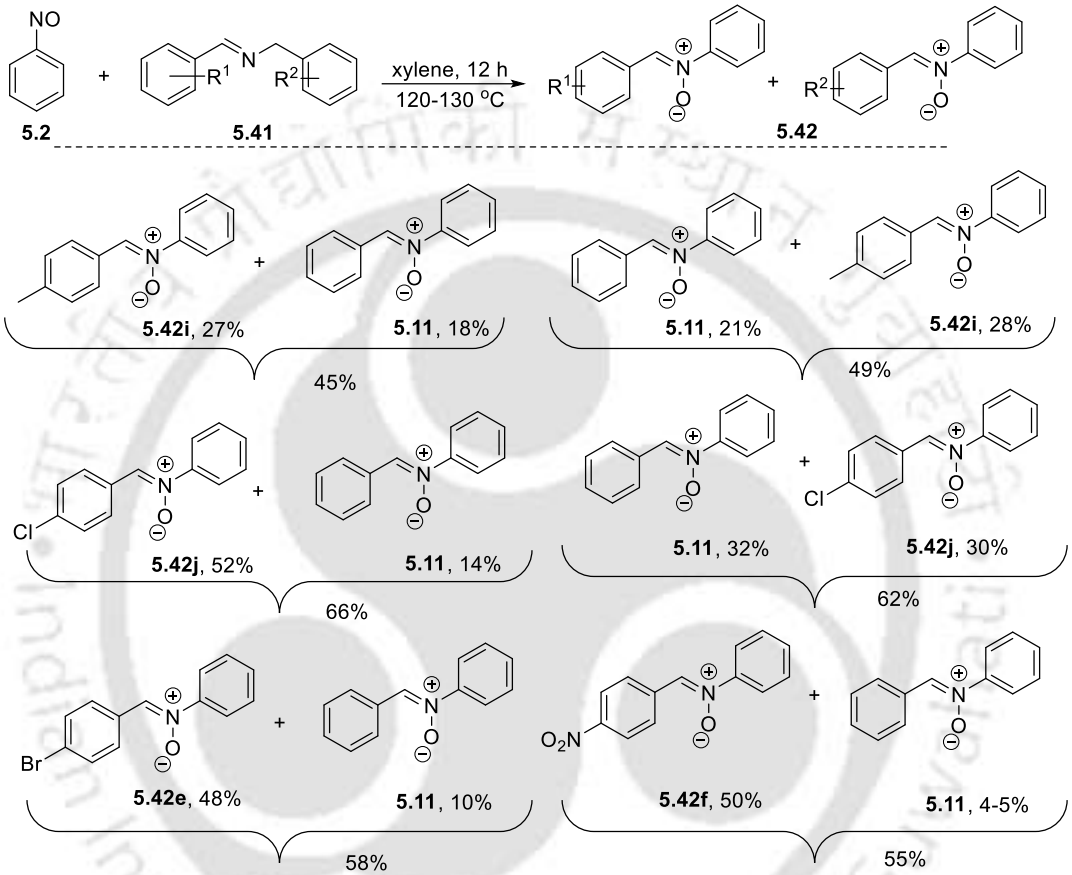
Scheme 10a: Synthesis of nitrones from symmetric imines

Electron withdrawing group *i.e.* -NO_2, -CN *etc*. in aldehyde part produced better result. Hetero-atom containing imine was also able to provide the corresponding nitrones **5.42g**. Nitrone **5.42h** containing 9-Flurenyl moiety could also be prepared with this method, however with lower yield (**Scheme 10b**).



Scheme 10b: Synthesis of nitrones from imines containing different substituents at aldehyde component.

Imines **5.41** containing different substitution in aldehyde as well as amine part were reacted with nitrosobenzene **5.2** to provide two different nitrones. A slight preference of forming nitrone having aldehyde component was observed. However, electron withdrawing group in aldehyde component further increases the preference (**Scheme 11**).

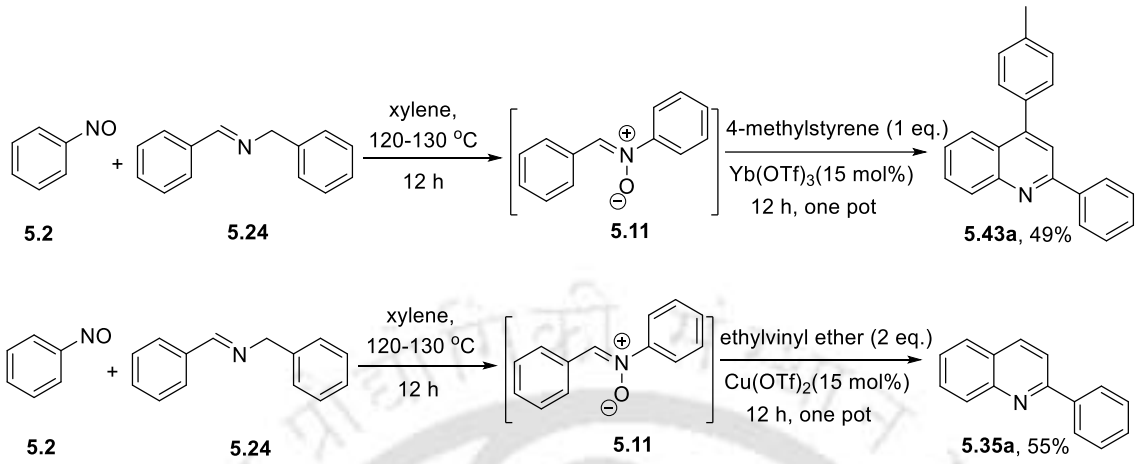


Scheme 11: Synthesis of nitrones from imines containing different substituents at aldehyde and amine component.

5.10 Preliminary result for the synthesis of quinoline:

The reactivity of nitrone in presence of Lewis acid was presented in **Chapter 4**. Presence of Lewis acid deactivated the dipole of nitrone which excludes the possibility of [3+2]-cycloaddition of nitrones with olefins. However, [4+2]-cycloaddition of nitrones with styrene derivatives or other olefin provided quinolines.[17] So, one-pot synthesis of quinoline was explored using the nitrone that is formed in this protocol. With the optimized condition of the nitrone **5.11**, one-pot reaction including 1 eq. of 4-methylstyrene as the third reactant was performed in presence of 15 mol% $Yb(OTf)_3$. Expectedly substituted quinoline **5.43a** was

isolated with 49% yield. The use of 2 eq. of ethylvinyl ether ended up with 2-substituted quinoline **5.35a** with 55% yield (**Scheme 12**).



Scheme 12: Preliminary result for quinoline synthesis.

5.11 One-pot optimization:

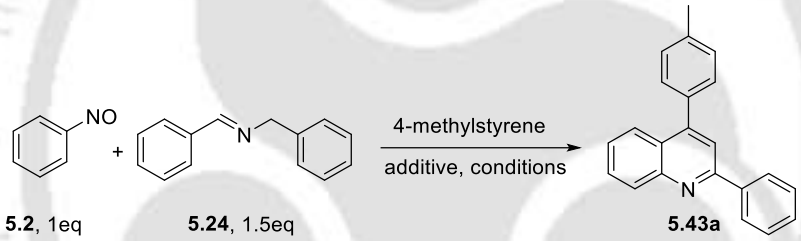


Table 2: Optimization Table:

Entry	Eq. of 4-Me-styrene	Additive	Solvent	Time	Temp.	Yield[b] (%)
1.	1	$Yb(OTf)_3$	xylene	12 h	120-130 °C	49
2.	1.5	$Yb(OTf)_3$	xylene	12 h	120 -130 °C	55
3.	2	$Yb(OTf)_3$	xylene	12 h	120-130 °C	61
4.	2	-	xylene	12 h	120 -130 °C	-
5.	2	$Sc(OTf)_3$	xylene	12 h	120-130 °C	66
6.	2	$Cu(OTf)_2$	xylene	12 h	120-130 °C	56
7.	2	$Yb(OTf)_3$	xylene	6 h	120-130 °C	35
8.	2	$Yb(OTf)_3$	xylene	24 h	120-130 °C	64
9.	2	$Yb(OTf)_3$	CCl_4	24 h	80 °C	55
10.	2	$Yb(OTf)_3$	toluene	24 h	110 -120 °C	60
11.	2	$Yb(OTf)_3$	DCE	24 h	90 °C	62

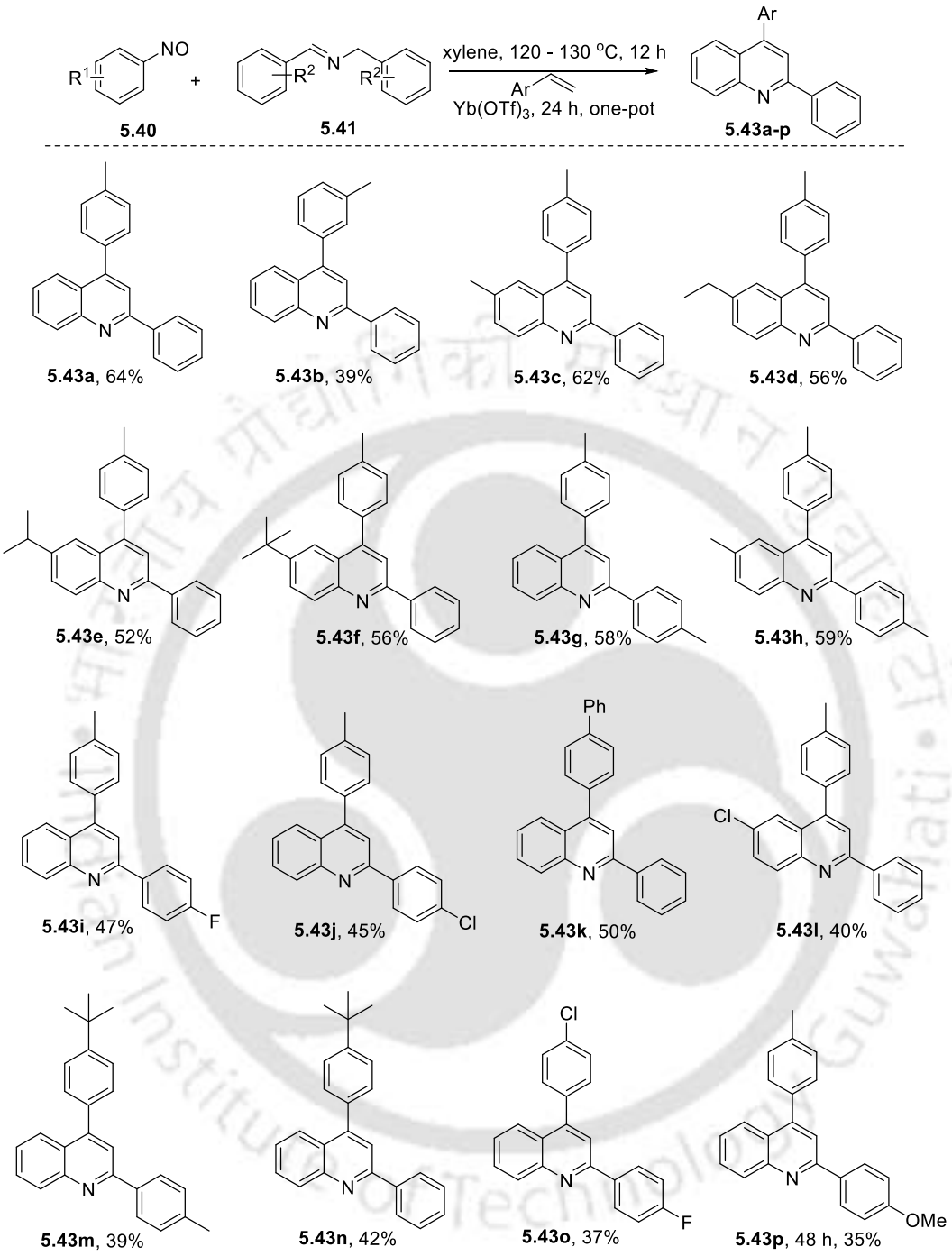
12.[a]	2	$Yb(OTf)_3$	xylene	24 h	120 -130 ^oC	68
13.	2	TfOH	xylene	24 h	120 -130 ^oC	32
14.	2	$Cu(OAc)_2$	xylene	24 h	120-130 ^oC	-

All reactions were carried out with nitrosobenzene (0.28 mmol, 1 eq.) in solvent (3 mL). TfOH = Triflic acid. [a] = 30 mol% of Lewis acid was used. [b] = isolated yields.

Based on the preliminary result, different reaction conditions were screened to obtain better yield of the quinolines. Firstly, relative stoichiometry of 4-methylstyrene was increased. The enhancement of the yield was observed (**Table 2**, entry 2, 3). Next, different Lewis acids were tested to improve the yields. Desired product was not achieved without any Lewis acid (**Table 2**, entry 4). $Sc(OTf)_3$ provided better outcome, however, the yields was lower with $Cu(OTf)_2$ (**Table 2**, entry 5, 6). Decrease in the reaction time ended up with less yield. Higher reaction time provided better result (**Table 2**, entry 7, 8). As various solvents were tested earlier, few of them were tested for the one-pot reaction. Unfortunately, no further enhancement in yield was observed (**Table 2**, entry 9-11). Higher amount of catalyst loading (30 mol%) provided a better yield (**Table 2**, entry 12). TfOH was also able to provide the desired product with lower yield (**Table 2**, entry 13). However, $Cu(OAc)_2$ failed to give desired product (**Table 2**, entry 14).

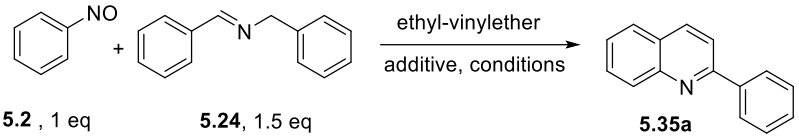
5.12 Substrate scope of quinolines:

The optimal condition has been explored to clarify the scope of this multicomponent reaction. A variety of nitrosoarenes, imines were reacted with styrene derivative under standard condition to obtain differently substituted quinolines derivatives **5.43a-p** with moderate to good yield. Electron donating *i.e.*, alkyl substitution at *p*-position on the nitroso part produced better yield of **5.43c-f**. The yield of the quinolines **5.43i-o** were decreased in presence of electron withdrawing group. The tolerance of the imine and styrene derivatives was also checked under the optimized condition. Electron donating group, *i.e.*, –OMe, provided the desired product **5.43p** with lower yield.



Scheme 13: Substrate scopes with differently substituted quinolines.

5.13 Optimization for 2-phenylquinoline:



5.2 , 1 eq **5.24**, 1.5 eq **5.35a**

Table 3: Optimization Table

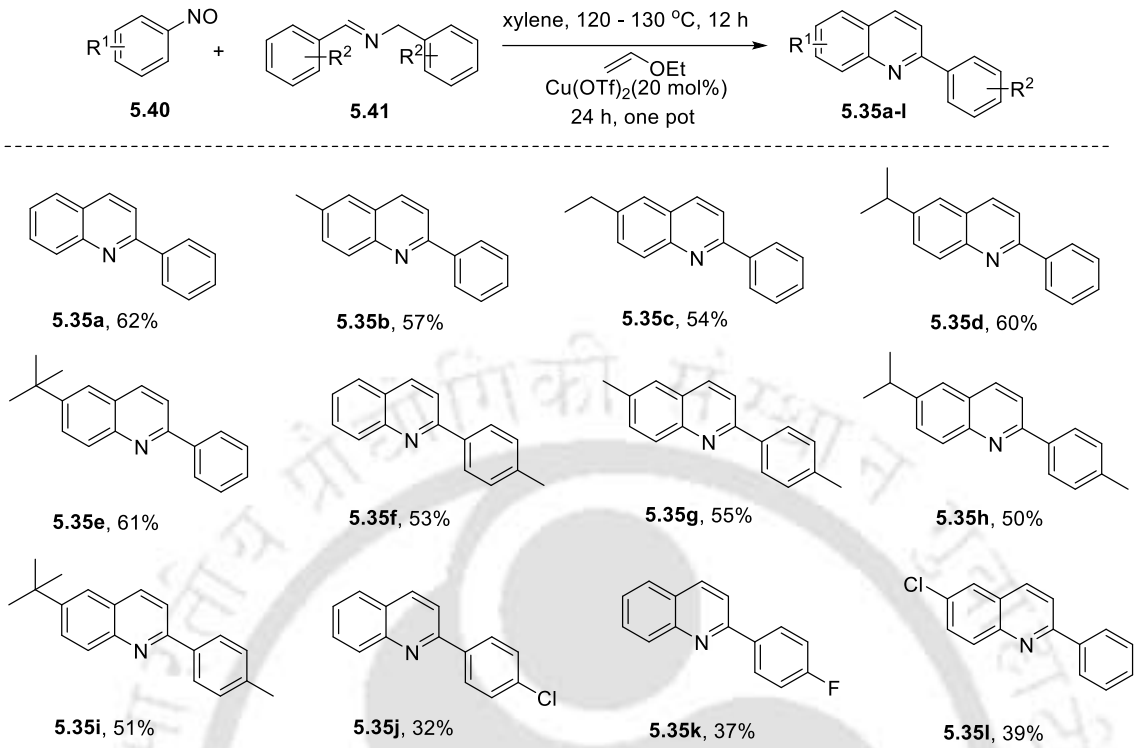
Entry	Eq. of ethylvinyl ether	Additive	Solvent	Time	Temp.	Yield[b] (%)
1.	2	$Yb(OTf)_3$	xylene	24 h	120-130 °C	59
2.	2	$Cu(OTf)_2$	xylene	24 h	120 -130 °C	60
3.[a]	2	$Cu(OTf)_2$	xylene	24 h	120-130 °C	62
4.	2	-	xylene	24 h	120 -130 °C	-
5.	2	$Cu(OTf)_2$	xylene	12 h	120-130 °C	55
6.[a]	1.5	$Cu(OTf)_2$	xylene	24 h	120-130 °C	54
7.	2	TfOH	xylene	24 h	120-130 °C	36
8.	2	$Cu(OAc)_2$	xylene	24 h	120-130 °C	-

All reactions were carried out with nitrosobenzene (0.28 mmol, 1 eq.) in solvent (3 mL). TfOH = Triflic acid. [a] = 20 mol% catalysed was used. [b] = Separated yield.

With the initial result for the reaction with ethylvinyl ether, different reaction conditions were tested for the improvement of the yield of 2-phenylquinoline **5.35a**. The reaction conditions were screened with the change in Lewis acids (**Table 3**, entry 1, 2). Slight increase in the catalyst loading provided better yield (**Table 3**, entry 3). No quinoline was formed in absence of Lewis acid (**Table 3**, entry 4). Decreased in the yield of the desired product was observed with lowering the reaction time (**Table 3**, entry 5). Yield of **5.35a** was reduced with the decrease of the stoichiometry of ethylvinyl ether (**Table 3**, entry 6). TfOH was able to provide the product with lower yield (**Table 3**, entry 7). However, no desired product was isolated with $Cu(OAc)_2$ (**Table 3**, entry 8).

5.14 Substrate scope of 2-phenylquinoline:

The substrate scope of 2-arylquinoline **5.35a-l** was also explored by reacting various nitrosoarenes and imines in the presence of ethylvinyl ether. As mentioned earlier, alkyl substitution in the both nitrosoarene and imine provided better result *i.e.*, **5.35b-e**. However, relatively lower yields were observed with halogens in both the counterpart, *i.e.*, **5.35j-l**.



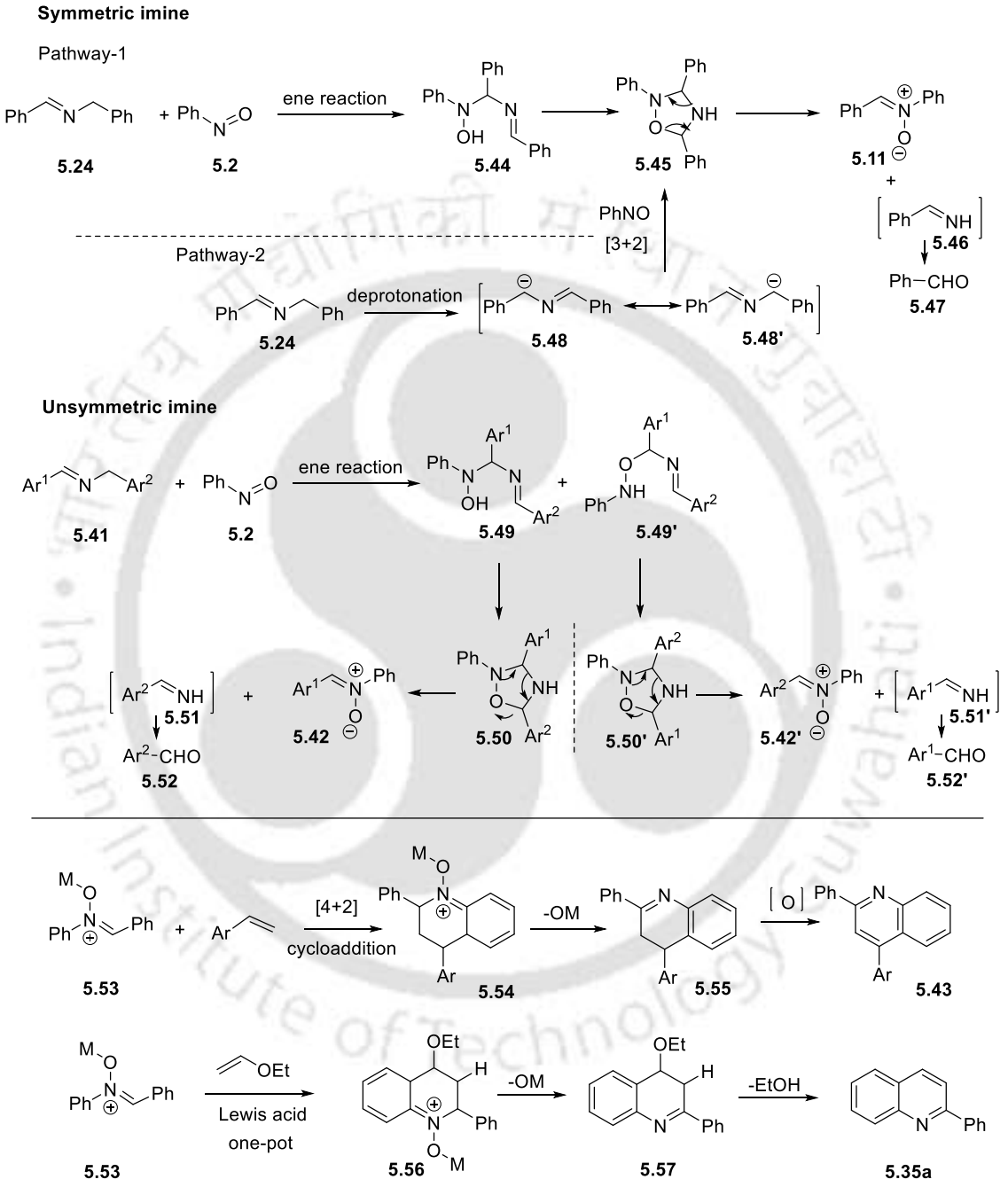
Scheme 14: Substrate scope of 2-arylquinolines.

5.15 Plausible Mechanism:

A plausible mechanism has been proposed for the three-component annulation reaction in **Scheme 15**. For symmetric imine, nitrone formation from nitrosobenzene **5.2** and imine **5.24** can be proceeded *via* two pathways. Firstly, the reaction may be progressed through nitroso-ene reaction between nitrosobenzene **5.2** and imine **5.24** which is considered to be the ene-component for the reaction. The ene addition product **5.44** further cyclized to provide five membered oxadiazolidine intermediate **5.45.** Deprotonation of imine **5.24** to **5.48** and **5.48'** followed by cyclization with nitrosobenzene *via* [3+2] to provide oxadiazolidine intermediate **5.45** is another possibility. Five membered oxadiazolidine **5.45** further cleaved to obtain expected nitrone **5.11**. This step involved formation of the imine **5.46** which ultimately provided aldehyde **5.47**. Metal coordinated nitrone **5.53** underwent [4+2] cycloaddition with styrene derivative to afford the final product **5.43** *via* the intermediate **5.54** and **5.55**. Similar cycloaddition with ethyl vinyl ether provided **5.56**. Aromatization of **5.56** followed by elimination afforded **5.35a**.

The reaction between nitrosobenzene **5.2** with unsymmetrical imine **5.41** provided two nitroso-ene addition products **5.49** and **5.49'** which cyclized to five membered oxadiazolidine

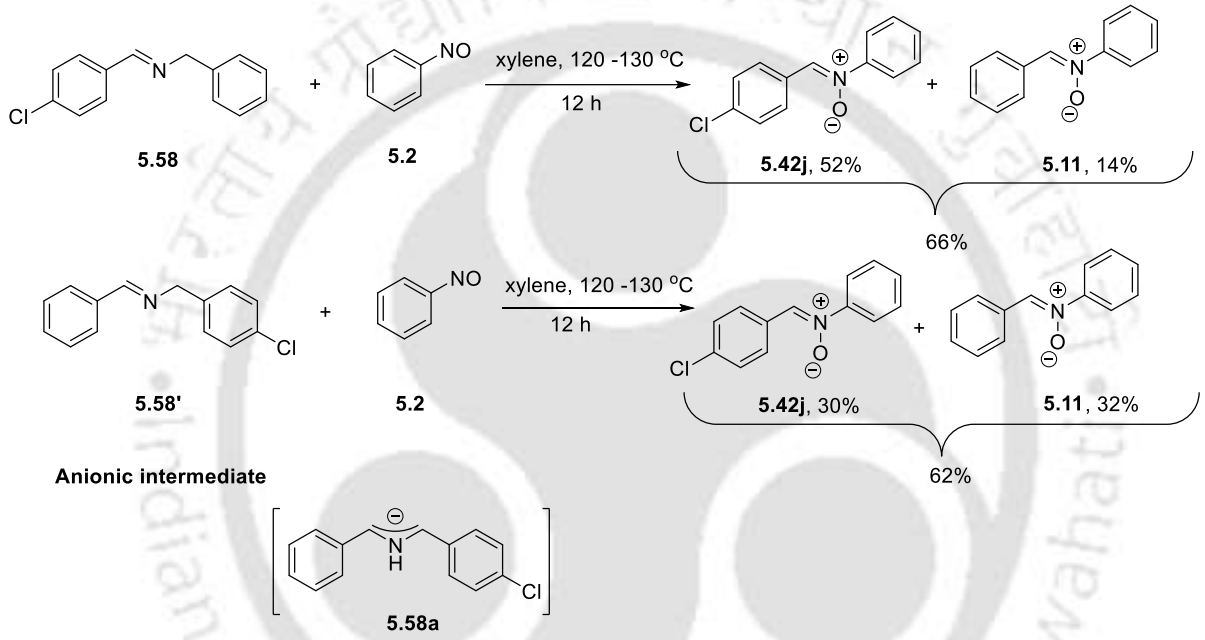
intermediates **5.50** and **5.50'** respectively. Similarly, both oxadiazolidine intermediates cleaved to obtain expected nitrones **5.42** and **5.42'.** Aldehydes **5.52** and **5.52'** were formed *via* formation of imine **5.51** and **5.51'** respectively.



Scheme 15: Plausible mechanism for the annulation.

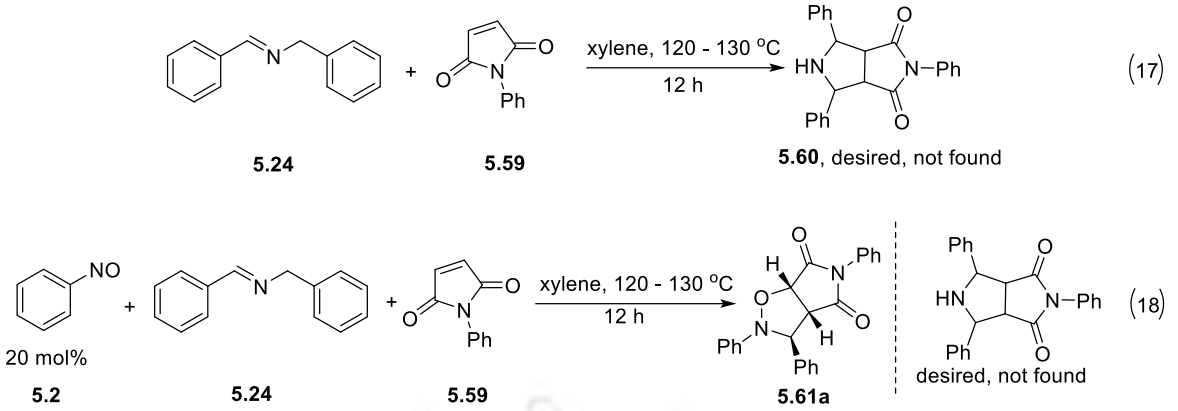
5.16 Controlled Experiments:

To investigate the mechanistic path of the reaction, controlled experiments have been performed (**Scheme 16**). Unsymmetrical imine **5.58** and **5.58'** were separately reacted with nitrosobenzene **5.2** to check the relative ratio of the two nitrones **5.42j** and **5.11**. Different outcomes were observed under same reaction condition with imine **5.58** and **5.58'**. If [3+2] cycloaddition pathway was followed, the equal ratio of the anionic intermediate **5.58a** was formed to provide the nitrone **5.42j** and **5.11** in both the experiments with equal ratio. This experiment excluded the possibility of [3+2] cycloaddition.



Scheme 16: Controlled reaction with unsymmetric imines.

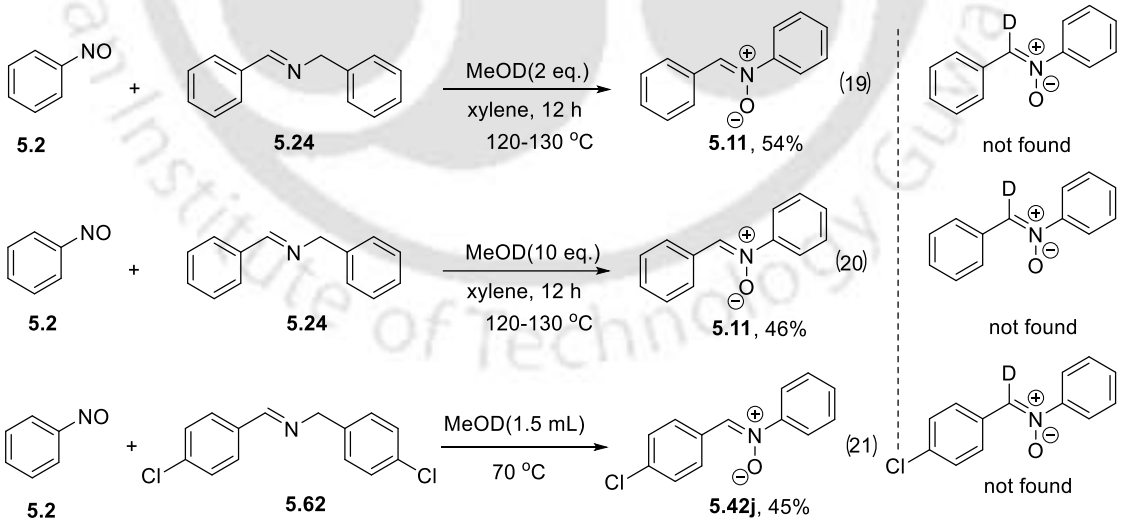
Another controlled experiment was performed for further support the mechanistic proposal. *N*-phenyl maleimide **5.59** was reacted with imine **5.24** under two different conditions. Firstly, without any additive under standard condition (**Scheme 17**, eq. 17) and another in presence of catalytic amount of nitrosobenzene **5.2** (**Scheme 17**, eq. 18). No expected [3+2] cycloadduct product **5.60** was obtained in both the experiments. Instead of obtaining **5.60**, cycloaddition product **5.61a** was isolated with single isomer from the reaction of *N*-phenylmaleimide **5.59** and nitrone **5.11** (**Scheme 17**, eq. 18). The relative stereochemistry of **5.61a** is confirmed by X-ray crystallography (**Table 4**).



Scheme 17: Controlled reactions with *N*-phenyl maleimide.

5.17 Deuterium exchanged reactions:

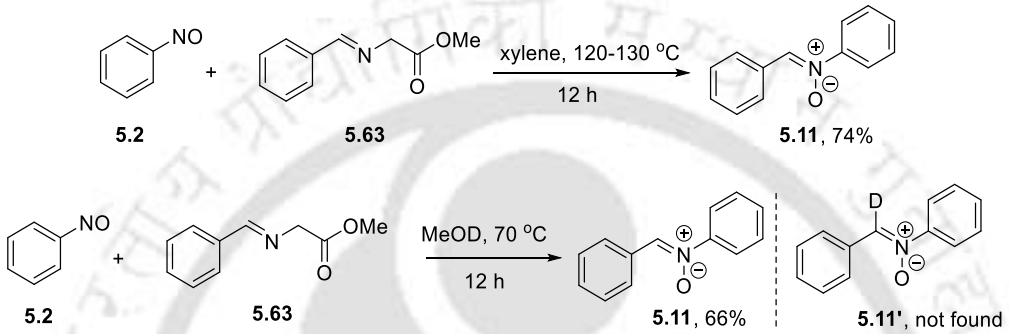
The mechanistic possibilities were investigated by performing experiments in the presence of MeOD-d_4. Deuterium would be incorporated into the nitrone **5.11**, if reaction proceeds *via* [3+2] cycloaddition through the azomethine anion **5.48/5.48'**. MeOD-d_4 was added to the reaction mixture with different equivalency. Gradually increase in MeOD-d_4 proportion in the reaction mixture did not alter the outcome (**Scheme 18**, eq. 19-21). No -D incorporated nitrone was isolated from the reaction. This outcome excluded the possibility of [3+2] cycloaddition pathway through the azomethine anion **5.48/5.48'**.



Scheme 18: Controlled reaction with MeOD-d_4.

5.18 Controlled experiment with other imine:

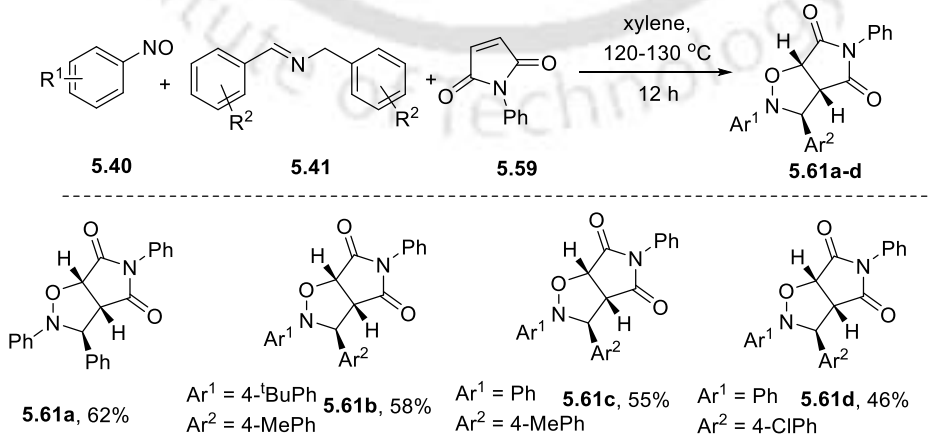
The deuterium exchanged experiments was performed in another way. The imine **5.63** was synthesized from corresponding aldehyde and glycine methyl ester following literature procedure. Nitrosobenzene **5.2** was reacted with the imine **5.63** under standard condition. Nitrone **5.11** was isolated with 74% yield. Then the experiment was performed in MeOD-d_4 to check the -D incorporation into the product. However, there was no deuterated nitrone **5.11'** was formed in the reaction (**Scheme 19**).



Scheme 19: Deuterium experiment with other imine.

5.19 Syntheses of oxazolidine:

The reaction of nitrosobenzene **5.40**, imine **5.41** and *N*-phenyl maleimide **5.59** were reacted under standard conditions. Substituted oxazolidine **5.61a-d** were isolated with moderate yields as single isomer (**Scheme 20**). ^{1}H-NMR of crude reaction mixture suggested that no other isomer was formed in the reaction mixture. Variation in nitrosoarene as well as imines were successful to provide the expected product **5.61b-d** with moderate yield.



Scheme 20: Substrate scope of oxazolidines.

5.20 Crystal structures of oxazolidine:

The structure of the oxazolidine derivative **5.61a** was confirmed by X-ray crystallographic analysis. The structure of the compound have given below (**Table 4**).

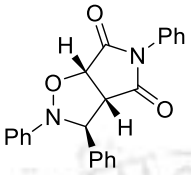
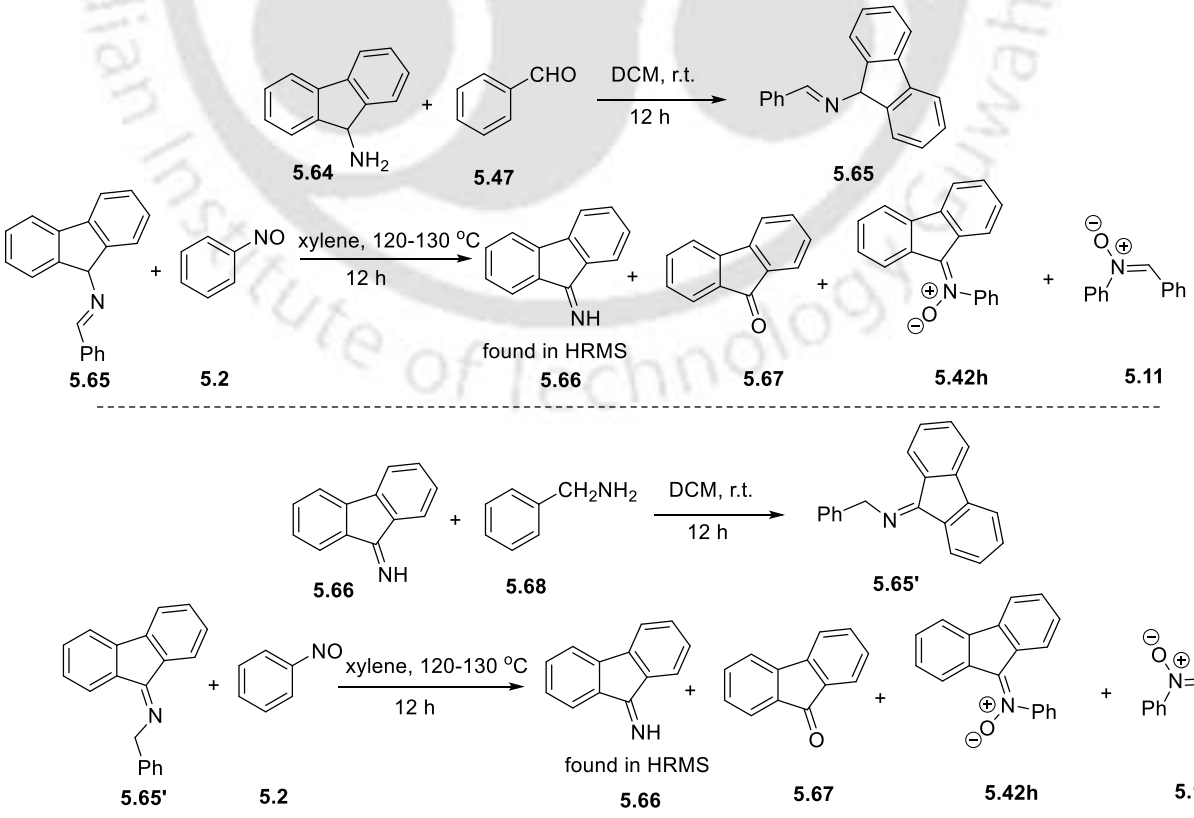
Compound	Crystal structure
 **5.61a**	

Table 4: X-ray crystal structure of oxazolidine.

5.21 Identification of imine as an intermediate:

According to the proposed mechanism, the imine **5.46** should be formed in the reaction. The imine **5.46** is unstable, could not be identified from the reaction mixture. The reaction of nitrosobenzene **5.2** with the imine **5.65** and **5.65'** separately provided 9-flurenone **5.67**, 9-flurenone imine **5.66** and the corresponding nitrones **5.42h** and **5.11 (Scheme 21)**. The imine **5.66** was identified in HRMS.



Scheme 21: Identification of imine in the reaction mixture.

5.22 Conclusion:

In summary, a new synthetic route for the synthesis of nitrone and its [4+2] and [3+2] annulation reaction with olefins to provide quinolines and oxazolidine has been developed. Differently substituted nitrones and di-substituted quinolines were prepared from the reaction of nitrosoarenes, imines and styrene derivatives. Moreover, 2-arylquinolines was achieved from cycloaddition reaction with ethylvinyl ether. Mechanistic investigation suggested that the reaction proceeds *via* nitroso-ene pathway (using azomethine as ene-component) rather than classical [3+2] cycloaddition reaction. Additionally, single isomer of oxazolidine and its derivatives were prepared using this methodology.

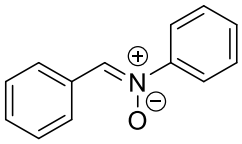
5.23 Experimental Section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus(V)oxide (P_2O_5). Commercial grade xylene, benzene and toluene were distilled over CaH_2 before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ^1H, ^{13}C NMR spectroscopy, *Bruker 400, 500, 600 MHz* (at 298 K). 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 ($CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.2 ppm) were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity. Flash chromatography: Merck or Spectrochem silica gel 230-400. IR: spectra were recorded on Perkin Elmer Instrument at normal temperature. MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak). Nitrosoarenes were prepared by following literature procedures.

General procedure for the synthesis of nitrones (I):

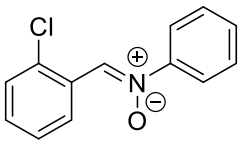
Nitrosoarene (1 eq.) was added to a solution of imine derivative (1.5 eq.) in xylene (3mL). The mixture was heated at 120-130 ^oC for 12 h under argon atmosphere. Then the solvent was evaporated under reduced pressure. The crude mixture was subjected to flash chromatography (silica-gel) to afford analytically pure products.

(*Z*)-N-(benzylidene)aniline oxide (5.11):[18] According to GP I: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, and flash chromatography of crude product (silica gel 230-400; EtOAc : hexane, 1:5) gave **5.11** as white solid (40 mg, 73%).



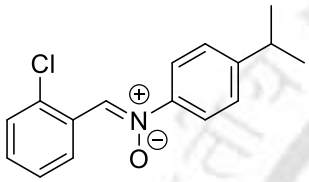
^1H NMR (600 MHz, $CDCl_3$) δ = 8.41 – 8.39 (m, 2H), 7.93 (s, 1H), 7.78 – 7.77 (m, 2H), 7.50 – 7.46 (m, 6H) ppm. HRMS: Exact mass calculated for $C_{13}H_{12}NO$ ($[M+H]^+$): 198.0913, Found: 198.0906.

(*Z*)-N-(2-chlorobenzylidene)aniline oxide (5.42a):[19] According to GP I: Nitrosobenzene



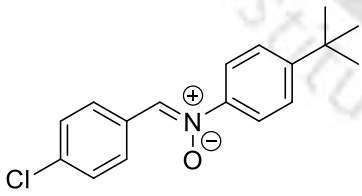
(30 mg, 0.28 mmol), (*E*)-*N*-(2-chlorobenzyl)-1-(2-chlorophenyl)methanimine (0.11 g, 0.42 mmol) were reacted for 12 h, and flash chromatography of crude product (silica gel 230-400; EtOAc : hexane, 1:5) gave **5.42a** as colorless gum (34 mg, 53%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.52 (d, *J* = 6.6 Hz, 1H), 8.43 (s, 1H), 7.80 – 7.78 (m, 2H), 7.52 – 7.47 (m, 4H), 7.43 – 7.38 (m, 2H) ppm. HRMS: Exact mass calculated for $C_{13}H_{11}NClO$ ($[M+H]^+$): 232.0524, Found: 232.0519.

(*Z*)-N-(2-chlorobenzylidene) (4-*isopropyl*-butyl)aniline oxide (5.42b): According to GP I:



1-isopropyl-4-nitrosobenzene (42 mg, 0.28 mmol), (*E*)-*N*-(2-chlorobenzyl)-1-(2-chlorophenyl)methanimine (0.11 g, 0.42 mmol) were reacted for 12 h, and flash chromatography of crude product (silica gel 230-400; EtOAc : hexane, 1:5) gave **5.42b** as colorless gum (41 mg, 54%). FT-IR ($\tilde{\nu}$) = 2960, 2927, 2857, 1667, 1602, 1496, 1326, 1285, 1096, 1014, 837, 750, 557 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.52 (d, *J* = 8.0 Hz, 1H), 8.41 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.47 – 7.45 (m, 1H), 7.41 – 7.33 (m, 4H), 3.02 – 2.96 (m, 1H), 1.29 (d, *J* = 7.0 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 151.6, 147.6, 133.8, 131.6, 130.4, 129.7, 129.4, 128.6, 127.4, 121.9, 34.1, 24.0 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{16}H_{17}NClO$ ($[M+H]^+$): 274.0993, Found: 274.0991.

(Z)-N-(4-chlorobenzylidene)(4-*tert*-butyl)aniline oxide (5.42c): According to GP I: 1-



*tert*butyl-4-nitrosobenzene (46 mg, 0.28 mmol), (*E*)-*N*-(4-chlorobenzyl)-1-(4-chlorophenyl)methanimine (0.11 g, 0.42 mmol) were reacted for 12 h, and flash chromatography of crude product (silica gel 230-400; EtOAc: hexane, 1:5) gave **5.42c** as colorless gum (39 mg, 49%). FT-IR ($\tilde{\nu}$) = 2963, 2936, 2870, 1593, 1543, 1419, 1262, 1179, 1089, 1013, 834 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 8.4 Hz, 2H), 7.89 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.50 – 7.43 (m, 4H), 1.35 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.8, 146.6, 136.5, 133.4, 130.4, 129.4, 129.1, 126.3, 121.5, 35.1, 31.4 ppm. HRMS: Exact mass calculated for $C_{17}H_{19}NClO$ ($[M+H]^+$): 288.1150, Found: 288.1150.

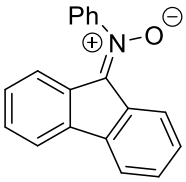
(*Z*)-N-(4-cyanobenzylidene)aniline oxide (5.42d):[19] According to GP I: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-4-((benzylimino)methyl)benzonitrile (92 mg, 0.42 mmol) were reacted for 12 h, and flash chromatography of crude product (silica gel 230-400; EtOAc : hexane, 1:4) gave **5.42d** as white solid (28 mg, 45%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.48 (d, *J* = 8.4 Hz, 2H), 8.00 (s, 1H), 7.78 – 7.74 (m, 4H), 7.52 – 7.51 (m, 3H) ppm. HRMS: Exact mass calculated for $C_{14}H_{11}N_2O$ ($[M+H]^+$): 223.0866, Found: 223.0871.

(*Z*)-N-(4-bromobenzylidene)aniline oxide (5.42e):[18] According to GP I: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-(4-bromophenyl)methanimine (0.12 g, 0.42 mmol) were reacted for 12 h, and flash chromatography of crude product (silica gel 230-400; EtOAc : hexane, 1:5) gave **5.42e** as white solid (37 mg, 48%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 8.4 Hz, 2H), 7.89 (s, 1H), 7.76 – 7.75 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.50 - 7.48 (m, 3H) ppm. HRMS: Exact mass calculated for $C_{13}H_{11}NBrO$ ($[M+H]^+$): 276.0019, Found: 276.0010.

(*Z*)-N-(4-nitrosobenzylidene)aniline oxide (5.42f):[18] According to GP I: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-(4-nitrophenyl)methanimine (0.10 g, 0.42 mmol) were reacted for 12 h, and flash chromatography of crude product (silica gel 230-400; EtOAc : hexane, 1:2) gave **5.42f** as white solid (34 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54 (d, *J* = 9.2 Hz, 2H), 8.30 (d, *J* = 9.2 Hz, 2H), 8.07 (s, 1H), 7.78 – 7.76 (m, 2H), 7.52 – 7.51 (m, 3H) ppm. HRMS: Exact mass calculated for $C_{13}H_{11}N_2O_3$ ($[M+H]^+$): 243.0764, Found: 243.0774.

(*Z*)-N-(4-pyridinebenzylidene)aniline oxide (5.42g):[20] According to GP I: Nitrosobenzene (43 mg, 0.40 mmol), (*E*)-*N*-benzyl-1-(pyridin-4-yl)methanimine (0.12 g, 0.60 mmol) were reacted for 12 h, and flash chromatography of crude product (silica gel 230-400; EtOAc : hexane, 1:1) gave **5.42g** as white solid (26 mg, 33%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.76 (d, *J* = 6.0 Hz, 2H), 8.28 (d, *J* = 6.0 Hz, 2H), 8.03 (s, 1H), 7.78 – 7.77 (m, 2H), 7.54 – 7.52 (m, 3H) ppm. HRMS: Exact mass calculated for $C_{12}H_{11}N_2O$ ($[M+H]^+$): 199.0866, Found: 199.0862.

(*Z*)-N-(9-flurenylbenzylidene)aniline oxide (5.42h):[21] According to GP I: Nitrosobenzene

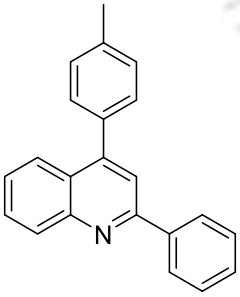


(43 mg, 0.40 mmol), *N*-benzyl-9*H*-fluoren-9-imine (0.16 g, 0.60 mmol) were reacted for 12 h, and flash chromatography of crude product (silica gel 230-400; EtOAc : hexane, 1:7) gave **5.42h** as white solid (29 mg, 27%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.85 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.54 – 7.53 (m, 3H), 7.46 – 7.41 (m, 3H), 7.37 – 7.34 (m, 1H), 7.18 – 7.16 (m, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 5.83 (d, *J* = 8.0 Hz, 1H) ppm. HRMS: Exact mass calculated for $C_{19}H_{14}NO$ ($[M+H]^+$): 272.1070, Found: 272.1064.

General procedure for the synthesis of quinolines (II):

Nitrosoarene (1 eq.) was added to a solution of azomethine (1.5 eq.) in xylene (3mL). The mixture was heated at 120 – 130 ^{o}C for 12 h under argon atmosphere. After that, the reaction mixture was cooled down to room temperature. Styrene derivatives (2 eq.) and $Yb(OTf)_3$ (15 mol%) were added to the reaction mixture. Then the reaction mixture was heated at 120 – 130 ^{o}C for another 24 under argon atmosphere. After the completion of reaction, the solvent was evaporated under reduced pressure. The reaction mixture was diluted with water (1x20 mL) and extracted with DCM (3x20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to column chromatography (neutral alumina) to afford analytically pure products.

2-phenyl-4-(*p*-tolyl)quinoline (5.43a):[22]According to GP II: Nitrosobenzene (30 mg, 0.28



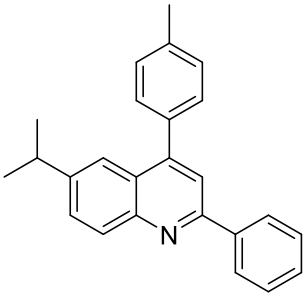
mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43a** as yellow gum (53 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.33 (d, *J* = 7.5 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.82 (s, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.55 – 7.47 (m, 6H), 7.37 (d, *J* = 8.0 Hz, 2H), 2.49 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{22}H_{18}N$ ($[M+H]^+$): 296.1434, Found: 296.1441.

2-phenyl-4-(*m*-tolyl)quinoline (5.43b):[22] According to GP II: Nitrosobenzene (30 mg, 0.28mmol), (*E*)-N-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, 3-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43b** as colorless gum (32 mg, 39%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.26 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 7.2 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.82 (s, 1H), 7.75 – 7.72 (m, 1H), 7.55 – 7.43 (m, 5H), 7.38 – 7.33 (m, 3H), 2.48 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{22}H_{18}N$ ($[M+H]^+$): 296.1434, Found: 296.1433.

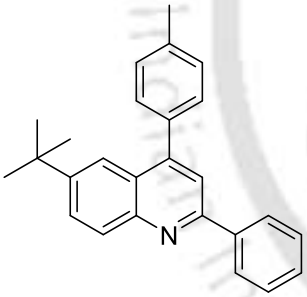
6-methyl-2-phenyl-4-(*p*-tolyl) quinoline (5.43c):[23] According to GP II: 1-methy-4-Nitrosobenzene (34 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43c** as yellow gum (54 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.18 – 8.13 (m, 3H), 7.77 (s, 1H), 7.68 (s, 1H), 7.58 – 7.55 (m, 1H), 7.54 – 7.50 (m, 2H), 7.48 – 7.45 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 2.50 (s, 3H), 2.48 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{23}H_{20}N$ ($[M+H]^+$): 310.1590, Found: 310.1595.

6-ethyl-2-phenyl-4-(*p*-tolyl) quinoline (5.43d): According to GP II: 1-ethy-4-Nitrosobenzene (38 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43d** as yellow gum (51 mg, 56%). FT-IR ($\tilde{\nu}$) = 2965, 2927, 1603, 1517, 1491, 1344, 1276, 839, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 – 8.16 (m, 3H), 7.77 (s, 1H), 7.71 (s, 1H), 7.63 – 7.60 (m, 1H), 7.54 – 7.51 (m, 2H), 7.49 – 7.46 (m, 3H), 7.38 (d, *J* = 7.6 Hz, 2H), 2.78 (q, *J* = 7.6 Hz, 2H), 2.50 (s, 3H), 1.27 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.3, 149.0, 147.6, 142.7, 139.9, 138.5, 135.9, 130.9, 130.0, 129.7, 129.5, 129.4, 129.0, 127.8, 126.0, 123.5, 119.7, 29.4, 21.6, 15.8 ppm. HRMS: Exact mass calculated for $C_{24}H_{22}N$ ($[M+H]^+$): 324.1747, Found: 324.1753.

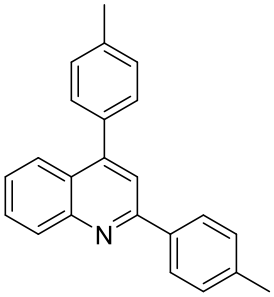
6-isopropyl-2-phenyl-4-(*p*-tolyl)quinoline (5.43e): According to GP II: 1-isopropyl-4-Nitrosobenzene (38 mg, 0.28 mmol), (*E*)-N-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43e** as yellow gum (49 mg, 52%). FT-IR ($\tilde{\nu}$) = 2960, 2928, 2876, 1588, 1494, 1357, 1259, 1026, 833, 822, 769, 584 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 8.25 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 7.5 Hz, 2H), 7.77 (s, 1H), 7.75 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.54 – 7.46 (m, 5H), 7.38 (d, *J* = 8.0 Hz, 2H), 3.07 – 3.02 (m, 1H), 2.50 (s, 2H), 1.30 (d, *J* = 7.0 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.2, 149.5, 147.4, 139.6, 138.6, 135.7, 129.8, 129.7, 129.6, 129.54, 129.50, 129.1, 127.9, 126.0, 122.2, 119.7, 34.6, 24.1, 21.6 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{25}H_{24}N$ ($[M+H]^+$): 338.1903, Found: 338.1904.



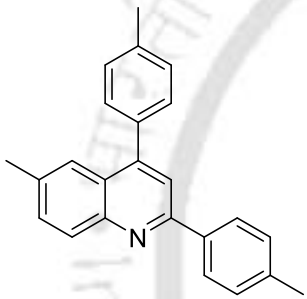
5. 6-(*tert*-butyl)-2-phenyl-4-(*p*-tolyl)quinoline (5.43f): According to GP II: 1-*tert*-butyl-4-Nitrosobenzene (46 mg, 0.28mmol), (*E*)-N-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43f** as yellow gum (55 mg, 56%). FT-IR ($\tilde{\nu}$) = 2958, 2928, 1617, 1588, 1494, 1360, 966, 823, 769, 590 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 9.0 Hz, 1H), 8.18 (d, *J* = 7.2 Hz, 2H), 7.93 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.55 – 7.47 (m, 5H), 7.38 (d, *J* = 6.6 Hz, 2H), 2.50 (s, 3H), 1.36 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.3, 150.0, 149.6, 146.8, 139.3, 138.7, 135.7, 129.7, 129.6, 129.3, 129.1, 129.0, 127.9, 125.6, 120.9, 119.8, 35.3, 31.4, 21.6 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{26}H_{26}N$ ($[M+H]^+$): 352.2060, Found: 352.2067.



2-phenyl-4-(*p*-tolyl)quinoline (5.43g):[24] According to GP II: Nitrosobenzene (30 mg ,0.28mmol), (*E*)-*N*-(4-methylbenzyl)-1-(*p*-tolyl)methanimine (94 mg, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were reacted further 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43g** as yellow gum (50 mg, 58%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.27 (d, *J* = 7.8 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.80 (s, 1H), 7.74 – 7.72 (m, 1H), 7.48 – 7.46 (m, 3H), 7.37 – 7.33 (m, 4H), 2.49 (s, 3H), 2.44 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{23}H_{20}N$ ($[M+H]^+$): 310.1590, Found: 310.1591.



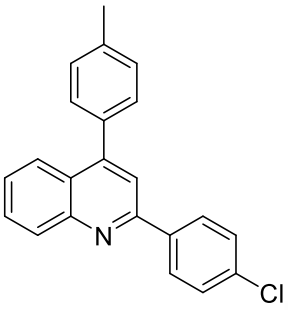
6-methyl-2,4-di-*p*-tolylquinoline (5.43h):[25] According to GP II: 1-methyl-4-Nitrosobenzene (34 mg, 0.28 mmol), (*E*)-N-(4-methylbenzyl)-1-(p-tolyl)methanimine (94 mg, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43h** as yellow gum (53 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.20 (d, *J* = 6.0 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 2H), 7.75 (s, 1H), 7.67 (s, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.38 - 7.32 (m, 4H), 2.49 (s, 3H), 2.48 (s, 3H), 2.43 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{24}H_{22}N$ ($[M+H]^+$): 324.1747, Found: 324.1739.



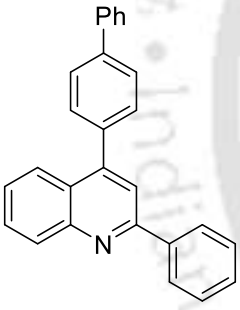
2-(4-fluorophenyl)-4-(*p*-tolyl)quinoline (5.43i): According to GP II: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-(4-fluorobenzyl)-1-(4-fluorophenyl)methanimine (97 mg, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43i** as colorless gum (41 mg, 47%). FT-IR ($\tilde{\nu}$) = 2923, 2854, 1592, 1497, 1358, 1230, 1156, 838, 764 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 6.6 Hz, 1H), 8.21 – 8.19 (m, 2H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.76 – 7.74 (m, 2H), 7.50 – 7.46 (m, 3H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 8.4 Hz, 2H), 2.49 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.1 (d, *J* = 249.5 Hz), 155.9, 149.3 (d, *J* = 186.3 Hz), 138.7, 135.7,

135.5, 129.9, 129.7 (d, *J* = 8.5 Hz), 129.7, 129.6, 126.6, 125.99, 125.97, 119.2, 116.0 (d, *J* = 21.6 Hz), 21.53 ppm. HRMS: Exact mass calculated for $C_{22}H_{17}NF$ ($[M+H]^+$): 314.1340, Found: 314.1342.

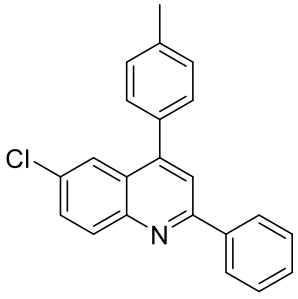
2-(4-chlorophenyl)-4-(*p*-tolyl)quinoline (5.43j):[26] According to GP II: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-(4-chlorobenzyl)-1-(4-chlorophenyl)methanimine (0.11 g, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43j** as colorless gum (41 mg, 45%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.25 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H), 7.76 – 7.73 (m, 1H), 7.51 – 7.45 (m, 5H), 7.37 (d, *J* = 7.8 Hz, 2H), 2.49 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{22}H_{17}NCl$ ($[M+H]^+$): 330.1044, Found: 330.1043.



4-([1,1'-biphenyl]-4-yl)-2-phenylquinoline (5.43k):[27] According to GP II: Nitrosobenzene (30 mg, 0.28mmol), (*E*)-N-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, 4-vinyl-1,1'-biphenyl (0.1 g, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:50) gave **5.43k** as colorless gum (50 mg, 50%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.80 -7.76 (m, 3H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.57 – 7.48 (m, 6H), 7.42 (t, *J* = 7.2 Hz, 1H) ppm. HRMS: Exact mass calculated for $C_{27}H_{20}N$ ($[M+H]^+$): 358.1590, Found: 358.1592.

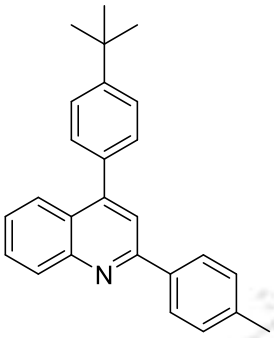


6-chloro-2-phenyl-4-(*p*-tolyl)quinoline (5.43l):[28] According to GP II: 1-chloro-4-Nitrosobenzene (40 mg, 0.28mmol), (*E*)-N-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:50) gave **5.43l** as colorless gum (37 mg, 40%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.21 – 8.17 (m, 3H), 7.90 (s, 1H), 7.83 (s, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.55 – 7.52 (m, 2H),

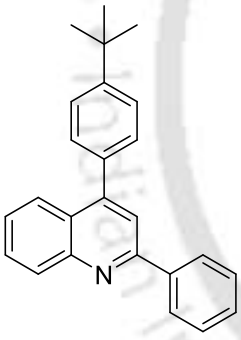


7.49 – 7.44 (m, 3H), 7.39 (d, *J* = 7.8 Hz, 2H), 2.50 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{22}H_{27}NCl$ ($[M+H]^+$): 330.1044, Found: 330.1049.

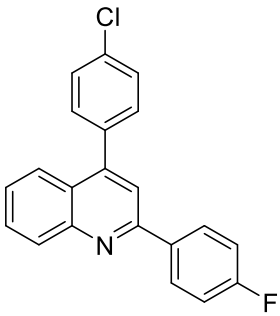
4-(4-(*tert*-butyl)phenyl)-2-(*p*-tolyl)quinoline (5.43m):[29] According to GP II: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-N-(4-methylbenzyl)-1-(p-tolyl)methanimine (94 mg, 0.42 mmol) were reacted for 12 h, 4-tertbutylstyrene (90 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43m** as yellow gum (38 mg, 39%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.37 (d, *J* = 7.5 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.82 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.53 – 7.47 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 1.43 (s, 9H) ppm. HRMS: Exact mass calculated for $C_{26}H_{26}N$ ($[M+H]^+$): 352.2060, Found: 352.2066.



4-(4-(*tert*-butyl)phenyl)-2-phenylquinoline (5.43n):[26] According to GP II: Nitrosobenzene (30 mg, 0.28mmol), (*E*)-N-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, 4-*tert*butylstyrene (90 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were reacted further 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:50) gave **5.43n** as yellow gum (40 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 7.5 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.84 (s, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.55 – 7.46 (m, 6H), 1.43 (s, 9H) ppm. HRMS: Exact mass calculated for $C_{25}H_{24}N$ ($[M+H]^+$): 338.1903, Found: 338.1907.

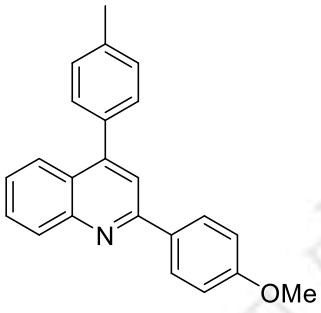


4-(4-chlorophenyl)-2-(4-fluorophenyl)quinoline (5.43o): According to GP II: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-(4-fluorobenzyl)-1-(4-fluorophenyl)methanimine (97 mg, 0.42 mmol) were reacted for 12 h, 4-chlorostyrene (78 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.43o** as colorless gum (33 mg, 37%). FT-IR ($\tilde{\nu}$) = 2962, 2925, 2854, 1598, 1496, 1357, 1156, 1015, 830, 763, 584 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.24 (d, *J* = 8.4 Hz, 1H), 8.20 – 8.18 (m, 2H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.77 – 7.74 (m,



2H), 7.55 – 7.49 (m, 5H), 7.22 (t, *J* = 8.4 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.2 (d, *J* = 250.1 Hz), 155.8, 148.6 (d, *J* = 35.9 Hz), 136.7, 135.3, 135.1, 131.0, 130.3, 130.0, 129.8 (d, *J* = 8.2 Hz), 127.0, 125.64, 125.55, 119.2, 116.1 (d, *J* = 21.6 Hz) ppm. HRMS: Exact mass calculated for $C_{21}H_{14}NClF$ ($[M+H]^+$): 334.0793, Found: 334.0792.

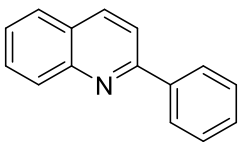
2-(4-methoxyphenyl)-4-(*p*-tolyl)quinoline (5.43p):[29] According to GP II: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-(4-methoxybenzyl)-1-(4-methoxyphenyl)methanimine (0.11 g, 0.42 mmol) were reacted for 12 h, 4-methylstyrene (66 mg, 0.56 mmol), $Yb(OTf)_3$ (26 mg, 0.042 mmol) were reacted further 48 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:20) gave **5.43p** as white gum (32 mg, 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.26 (d, *J* = 6.0 Hz, 1H), 8.17 (d, *J* = 7.2 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H), 7.73 – 7.71 (m, 1H), 7.47 – 7.44 (m, 3H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 3.89 (s, 3H), 2.49 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{23}H_{20}NO$($[M+H]^+$): 326.1539, Found: 326.1536.



General procedure for the synthesis of quinolines(III):

Nitrosoarene (1 eq.) was added to a solution of azomethine (1.5 eq.) in xylene (3mL). The mixture was heated at 120-130 ^{o}C for 12 h under argon atmosphere. After that, the reaction mixture was cooled down to room temperature. Ethylvinylether (2 eq.) and $Cu(OTf)_2$ (20 mol%) were added to the reaction mixture. Then the reaction mixture was heated at 120-130 ^{o}C for another 24 under argon atmosphere. Then the solvent was evaporated under reduced pressure. Then the reaction mixture was diluted with water (1x20 mL) and extracted with DCM (3x20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to column chromatography (neutral alumina) to afford analytically pure products.

2-phenylquinoline (5.35a):[30] According to GP III: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35a** as colorless gum (36 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (t, *J* = 8.4 Hz, 2H), 8.18 – 8.16 (m, 2H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.56 – 7.52 (m, 3H), 7.49 –



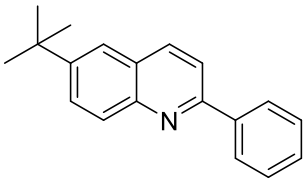
7.46 (m, 1H) ppm. HRMS: Exact mass calculated for $C_{15}H_{12}N$ ($[M+H]^+$): 206.0964, Found: 206.0974.

6-methyl-2-phenylquinoline (5.35b):[15] According to GP III: 1-methyl-4-nitrosobenzene (34 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35b** as colorless gum (35 mg, 57%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.16 – 8.10 (m, 4H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.54 – 7.52 m, 2H), 7.47 – 7.45 (m, 1H), 2.55 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{16}H_{14}N$ ($[M+H]^+$): 220.1121, Found: 220.1121.

3. 6-ethyl-2-phenylquinoline (5.35c):[31] According to GP III: 1-ethyl-4-nitrosobenzene (38 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35c** as colorless gum (35 mg, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.18 – 8.16 (m, 4H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.62 – 7.60 (m, 2H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.0 Hz, 1H), 2.88 – 2.84 (m, 2H), 1.36 (t, *J* = 7.5 Hz, 3H) ppm. HRMS: Exact mass calculated for $C_{17}H_{16}N$ ($[M+H]^+$): 234.1277, Found: 234.1272.

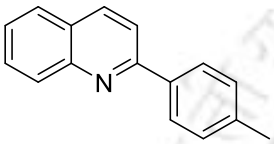
6-isopropyl-2-phenylquinoline (5.35d):[32] According to GP III: 1-isopropyl-4-nitrosobenzene (38 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35d** as colorless gum (42 mg, 60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 4.8 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.64 (s, 1H), 7.55 – 7.53 (m, 2H), 7.48 (d, *J* = 7.2 Hz, 1H), 3.15 – 3.10 (m, 1H), 1.37 (d, *J* = 6.6 Hz, 6H) ppm. HRMS: Exact mass calculated for $C_{18}H_{18}N$ ($[M+H]^+$): 248.1434, Found: 248.1434.

6-*tert*butyl-2-phenylquinoline (5.35e):[33] According to GP III: 1-*tert*butyl-4-nitrosobenzene



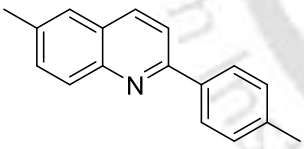
(42 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35e** as white gum (45 mg, 61%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.25 – 8.21 (m, 2H), 8.16 (d, *J* = 7.2 Hz, 2H), 7.86 – 7.84 (m, 2H), 7.76 (s, 1H), 7.55 – 7.52 (m, 2H), 7.48 – 7.46 (m, 1H), 1.45 (s, 9H) ppm. HRMS: Exact mass calculated for $C_{19}H_{20}N$ ($[M+H]^+$): 262.1590, Found: 262.1599.

2-(p-tolyl)quinoline (5.35f):[15] According to GP II: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-



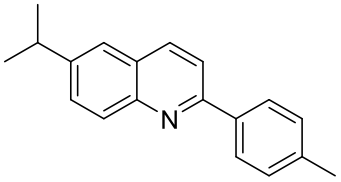
N-(4-methylbenzyl)-1-(p-tolyl)methanimine (94 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35f** as colorless gum (33 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.34 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 7.89 – 7.83 (m, 2H), 7.77 – 7.74 (m, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{16}H_{14}N$ ($[M+H]^+$): 220.1121, Found: 220.1123.

6-methyl-2-(*p*-tolyl)lquinoline (5.35g):[34] According to GP III: Nitrosobenzene (30 mg, 0.28



mmol), (*E*)-N-(4-methylbenzyl)-1-(p-tolyl)methanimine (94 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35g** as colorless gum (36 mg, 55%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 8.4 Hz, 1H), 8.11 – 8.07 (m, 3H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 2.57 (s, 3H), 2.46 (s, 3H) ppm. HRMS: Exact mass calculated for $C_{17}H_{16}N$ ($[M+H]^+$): 234.1277, Found: 234.1281.

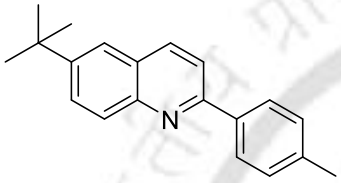
6-isopropyl-2-(*p*-tolyl)lquinoline (5.35h): According to GP III: Nitrosobenzene (30 mg,



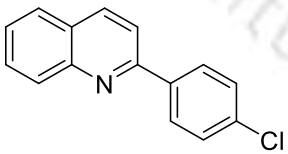
0.28 mmol), (*E*)-N-(4-methylbenzyl)-1-(p-tolyl)methanimine (94 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude

product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35h** as colorless gum (37 mg, 50%). FT-IR ($\tilde{\nu}$) = 2960, 2925, 2872, 1596, 1494, 1459, 1189, 891, 784 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 - 812 (m, 2H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.15 – 3.08 (m, 1H), 2.43 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.6, 147.4, 139.9, 137.3, 130.2, 129.8, 129.1, 127.8, 127.4, 123.8, 119.2, 34.3, 24.1, 21.6 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{19}H_{20}N$ ($[M+H]^+$): 262.1590, Found: 262.1596.

6-*tert*butyl-2-(*p*-tolyl)lquinoline (5.35i): According to GP III: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-N-(4-methylbenzyl)-1-(p-tolyl)methanimine (94 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc:hexane, 1:40) gave **5.35i** as colorless gum (39 mg, 51%). FT-IR ($\tilde{\nu}$)= 2955, 2920, 2862, 1595,1491, 1361, 1261, 1182, 910, 610 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.19 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.74 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 1.44 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.7, 149.7, 140.0, 137.8, 129.9, 129.3, 128.6, 127.9, 127.1, 122.7, 119.2, 35.2, 31.4, 21.6 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{20}H_{22}N$ ($[M+H]^+$): 276.1747, Found: 276.1740.



2-(4-chlorophenyl)quinoline (5.35j):[15] According to GP II: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-N-(4-chlorobenzyl)-1-(4-chlorophenyl)methanimine (0.11 g, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35j** as colorless gum (22 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.38 (d, *J* = 6.5 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H) ppm. HRMS: Exact mass calculated for $C_{15}H_{11}NCl$ ($[M+H]^+$): 240.0575, Found: 240.0580.



2-(4-fluorophenyl)quinoline (5.35k):[15] According to GP II: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-(4-fluorobenzyl)-1-(4-fluorophenyl)methanimine (97 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35k** as colorless gum (23 mg, 37%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.26 – 8.17 (m, 4H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.76 – 7.73 (m, 1H), 7.56 – 7.53 (m, 1H), 7.22 (t, *J* = 8.0 Hz, 2H) ppm. HRMS: Exact mass calculated for $C_{15}H_{11}NF$ ($[M+H]^+$): 224.0870, Found: 224.0877.

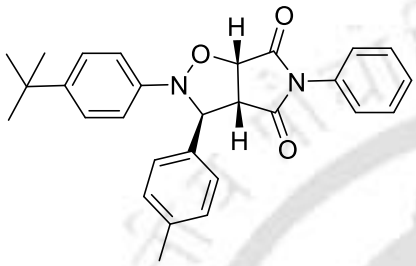
6-chloro-2-phenylquinoline (5.35l):[15] According to GP III: 1-methyl-4-nitrosobenzene (34 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) were reacted for 12 h, ethylvinyl ether (40 mg, 0.56 mmol), $Cu(OTf)_2$ (20 mg, 0.056 mmol) were added and reacted further for 24 h and column chromatography of crude product (neutral alumina; EtOAc : hexane, 1:40) gave **5.35l** as colorless gum (26 mg, 39%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 7.5 Hz, 1H), 8.21 – 8.17 (m, 3H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.84 (s, 1H), 7.70 (d, *J* = 7.0 Hz, 1H), 7.57 – 7.50 (m, 3H) ppm. HRMS: Exact mass calculated for $C_{15}H_{11}NCl$ ($[M+H]^+$): 240.0575, Found: 240.0576.

General procedure for the synthesis of isoxazolidine(IV):

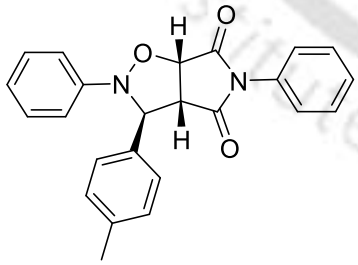
Nitrosoarene (1 eq.) was added to a solution of imine derivative (1.5 eq.) in xylene (3mL) followed by the addition of N-phenyl maleimide (1 eq.). The mixture was heated at 120 -130 ^{o}C for 12 h under argon atmosphere. After that, the reaction mixture was cooled down to room temperature. Then the solvent was evaporated under reduced pressure. The crude mixture was subjected to flash chromatography (silica gel) to afford analytically pure products.

(3S,3aR,6aS)-2,3,5-triphenyltetrahydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5*H*)-dione (5.61a): According to GP IV: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-benzyl-1-phenylmethanimine (82 mg, 0.42 mmol) and *N*-phenyl maleimide (48 mg, 0.28 mmol) were reacted for 12 h, flash chromatography of crude product (silica gel; EtOAc : hexane, 1:3) gave **5.61a** as white solid (64 mg, 62%). M.p. – 152 – 155 ^{o}C. FT-IR ($\tilde{\nu}$) = 3068, 3036, 2986, 1713, 1595, 1493, 1381, 1265, 1197, 1029, 730, 575 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 7.2 Hz, 2H), 7.45 (t,

J = 7.8 Hz, 2H), 7.39 – 7.34 (m, 4H), 7.29 – 7.27 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.64 – 6.62 (m, 2H), 5.79 (s, 1H), 5.11 (d, *J* = 7.8 Hz, 1H), 4.02 (d, *J* = 7.8 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.3, 172.8, 149.0, 138.8, 131.1, 129.6, 129.2, 129.1, 128.3, 126.7, 126.3, 123.1, 114.5, 77.5, 70.1, 57.5 ppm. Total count of 13C is less than expected due to the merging of signals in the aromatic region. HRMS: Exact mass calculated for $C_{23}H_{19}N_2O_3$ ([M+H]$^+$): 371.1390, Found: 371.1381.

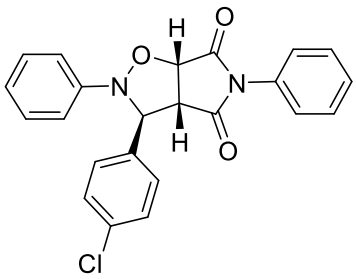
(3S,3aR,6aS)-2-(4-(*tert*-butyl)phenyl)-5-phenyl-3-(*p*-tolyl)tetrahydro-4H-pyrrolo[3,4-d]isoxazole-4,6(5*H*)-dione (5.61b): 

According to GP IV: 1-*tert*butyl-4-nitrosobenzene (46 mg, 0.28 mmol), (*E*)-*N*-(4-methylbenzyl)-1-(*p*-tolyl)methanimine (94 mg, 0.42 mmol) and *N*-phenyl maleimide (48 mg, 0.28 mmol) were reacted for 12 h, flash chromatography of crude product (silica gel; EtOAc : hexane, 1:3) gave **5.61b** as colorless gum (71 mg, 58%). FT-IR ($\tilde{\nu}$) = 3061, 3033, 2987, 1715, 1602, 1498, 1375, 1210, 1155, 1021, 722, 578 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 7.8 Hz, 2H), 7.34 – 7.26 (m, 7H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.51 (d, *J* = 6.6 Hz, 2H), 5.82 (s, 1H), 5.09 (d, *J* = 7.8 Hz, 1H), 4.03 (d, *J* = 7.8 Hz, 1H), 2.41 (s, 3H), 1.31 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.5, 173.0, 146.8, 146.0, 138.0, 136.1, 131.0, 129.8, 129.19, 129.16, 126.50, 126.47, 126.4, 114.0, 77.7, 69.6, 57.5, 34.4, 31.6, 21.3 ppm. HRMS: Exact mass calculated for $C_{28}H_{29}N_2O_3$ ([M+H]$^+$): 441.2173, Found: 441.2174.

(3S,3aR,6aS)-2,5-diphenyl-3-(*p*-tolyl)tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (5.61c): 

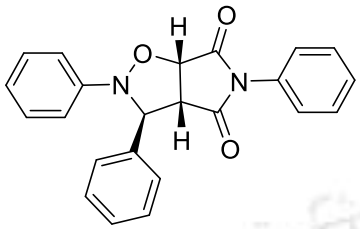
According to GP IV: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-N-(4-methylbenzyl)-1-(p-tolyl)methanimine (94 mg, 0.42 mmol) and *N*-phenyl maleimide (48 mg, 0.28 mmol) were reacted for 12 h, flash chromatography of crude product (silica gel; EtOAc : hexane, 1:3) gave **5.61c** as white gum (59 mg, 55%). FT-IR ($\tilde{\nu}$) = 2960, 2925, 2857, 1714, 1595, 1489, 1380, 1265, 1020, 801, 757, 508 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.47 (d, *J* = 7.8 Hz, 2H), 7.36 – 7.35 (m, 3H), 7.28 – 7.24 (m, 4H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.69 – 6.65 (m, 2H), 5.75 (s, 1H), 5.14 (d, *J* = 7.8 Hz, 1H), 4.03 (d, *J* = 7.8 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.4, 172.9, 149.1, 138.2, 135.8, 131.1, 129.8, 129.6, 129.21,

129.19, 126.7, 126.4, 123.1, 114.6, 77.5, 70.0, 57.5, 21.3 ppm. HRMS: Exact mass calculated for $C_{24}H_{21}N_2O_3$ ($[M+H]^+$): 385.1547, Found: 385.1544.

(3S,3aR,6aS)-3-(4-chlorophenyl)-2,5-diphenyltetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-dione (5.61d): 

According to GP IV: Nitrosobenzene (30 mg, 0.28 mmol), (*E*)-*N*-(4-chlorobenzyl)-1-(4-chlorophenyl)methanimine (0.11 g, 0.42 mmol) and *N*-phenyl maleimide (48 mg, 0.28 mmol) were reacted for 12 h, flash chromatography of crude product (silica gel; EtOAc : hexane, 1:3) gave **5.61d** as white solid (52 mg, 46%). M.p. – 202 - 204 ^oC. FT-IR ($\tilde{\nu}$) = 3065, 3036, 1717, 1595, 1455, 1384, 1199, 1090, 827, 692 cm^{-1}. ^1H NMR (600 MHz, CDCl3) δ = 7.51 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.32 (m, 3H), 7.27 – 7.24 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.01 – 7.00 (m, 1H), 6.63 – 6.61 (m, 2H), 5.72 (s, 1H), 5.09 (d, *J* = 7.2 Hz, 1H), 3.96 (d, *J* = 7.8 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 174.1, 172.6, 148.7, 137.3, 134.3, 131.0, 129.7, 129.32, 129.26, 129.2, 128.2, 126.3, 123.3, 114.6, 77.4, 69.5, 57.5 ppm. HRMS: Exact mass calculated for $C_{23}H_{18}ClN_2O_3$ ($[M+H]^+$): 405.1000, Found: 405.1003.

Crystallographic data of 5.61a:

	
Empirical formula	$C_{23}H_{18}N_2O_3$
Formula weight	370.39
Crystal size (mm^3), color	0.28 x 0.23 x 0.18, colorless
Crystal system	orthorhombic
Space group	P 21 21 21
a (Å)	6.840(10)
b (Å)	11.120(16)
c (Å)	24.67(4)
α (deg)	90
β (deg)	90
γ (deg)	90
V ($Å^3$)	1876(5)
Z	4
ρ_{calc} (g cm^{-3})	1.311
μ (M_0 Kα) (mm^{-1})	0.088
F (000)	776.0
T(K)	296(2)
Range of indices (h; k; l)	-8, 8; -13, 13; -29, 29
Number of reflections collected	41325
Unique reflection	3279
Completeness to 2θ	99.9
R_{int}	0.5508
Refinement method	SHELXL-2018/3 (Sheldrick, 2018)
Data / restraints / parameters	3279/0/254
goodness-of-fit	0.904
$R_1[I \geq 2\sigma(I)]$	0.0776
$wR_2[I \geq 2\sigma(I)]$	0.1597
R_1 (all data)	0.2613
wR_2 (all data)	0.2428
Δ_r (max, min) e $Å^{-3}$	0.204/-0.233

5.24 References:

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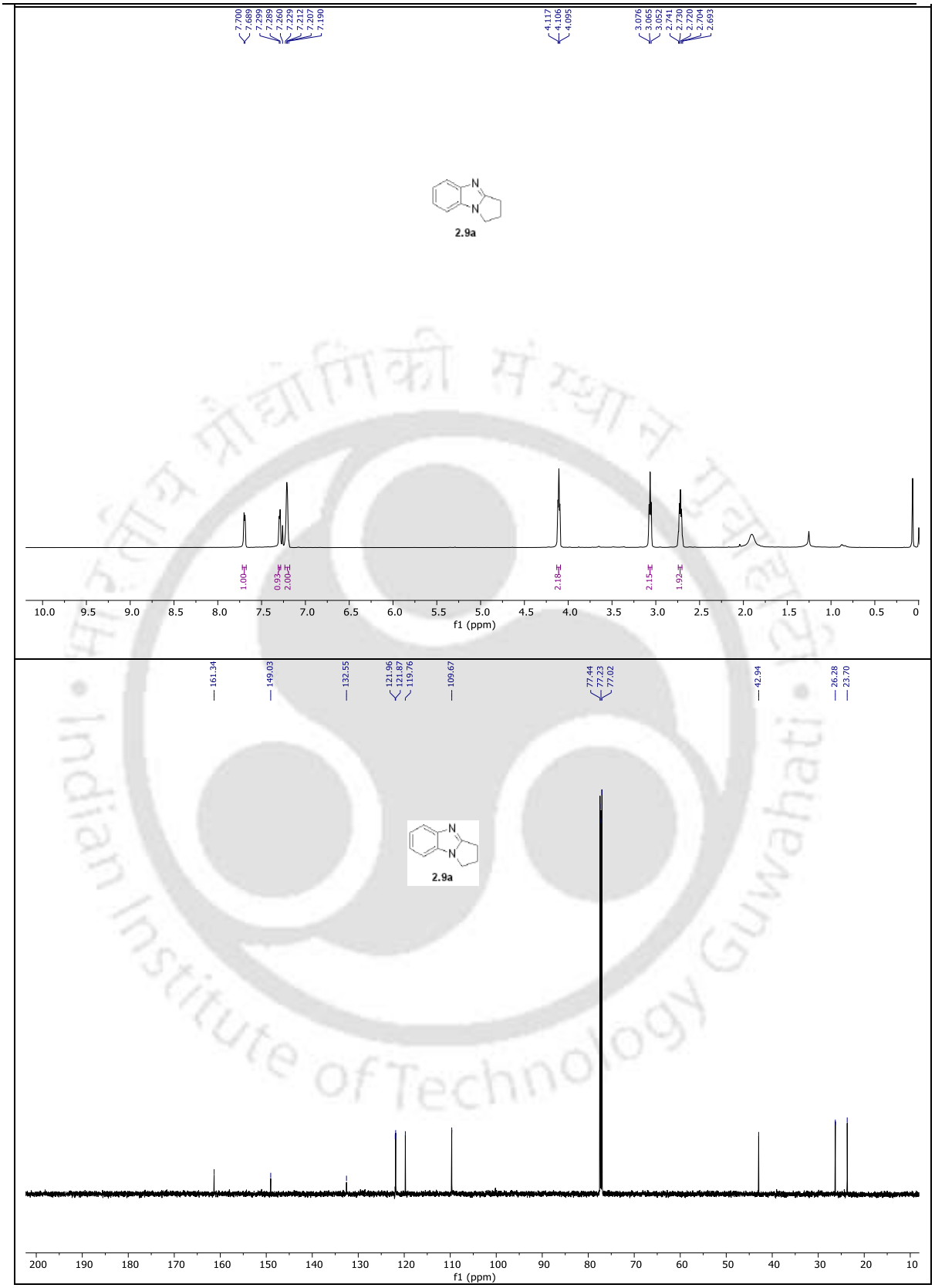
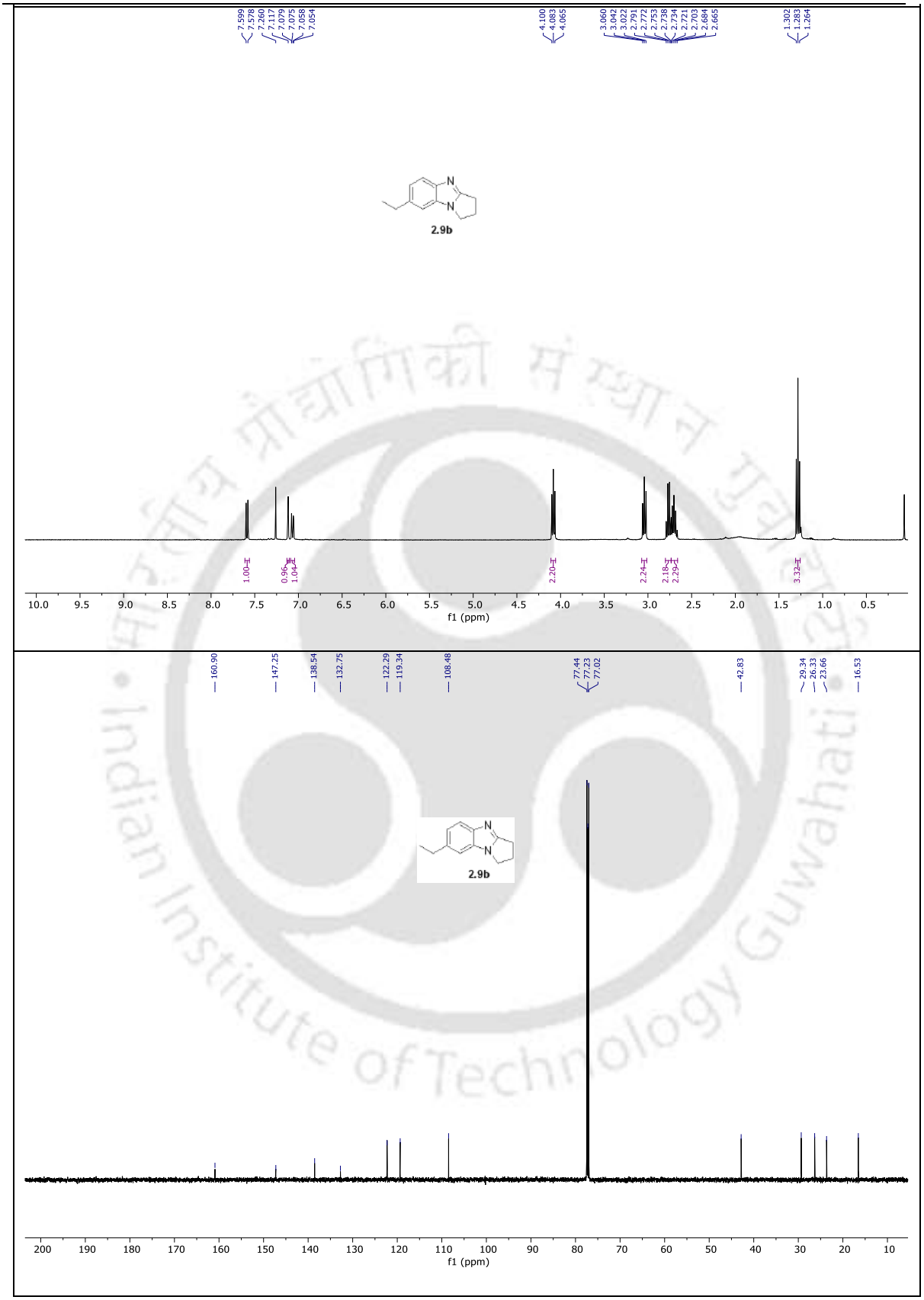
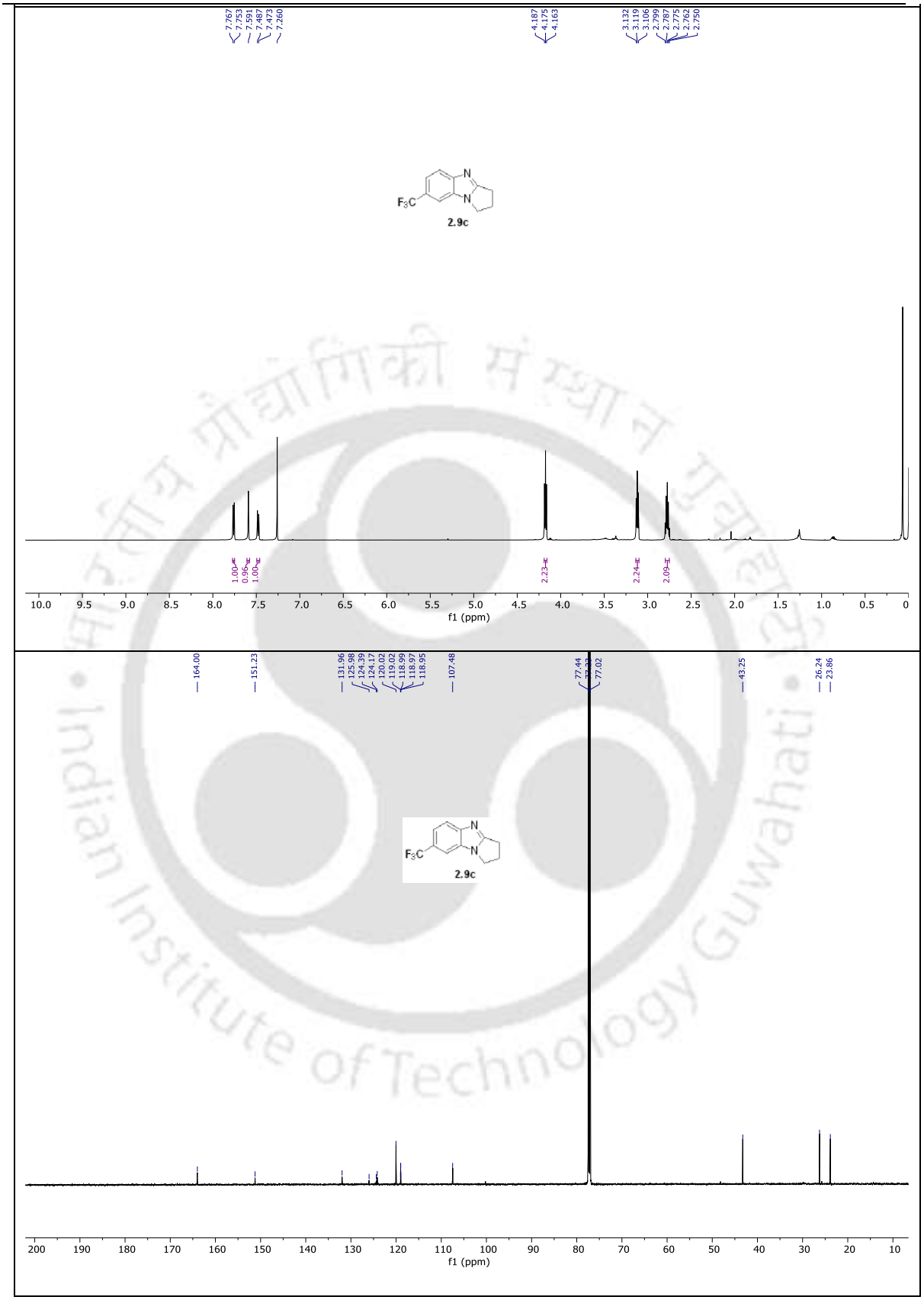
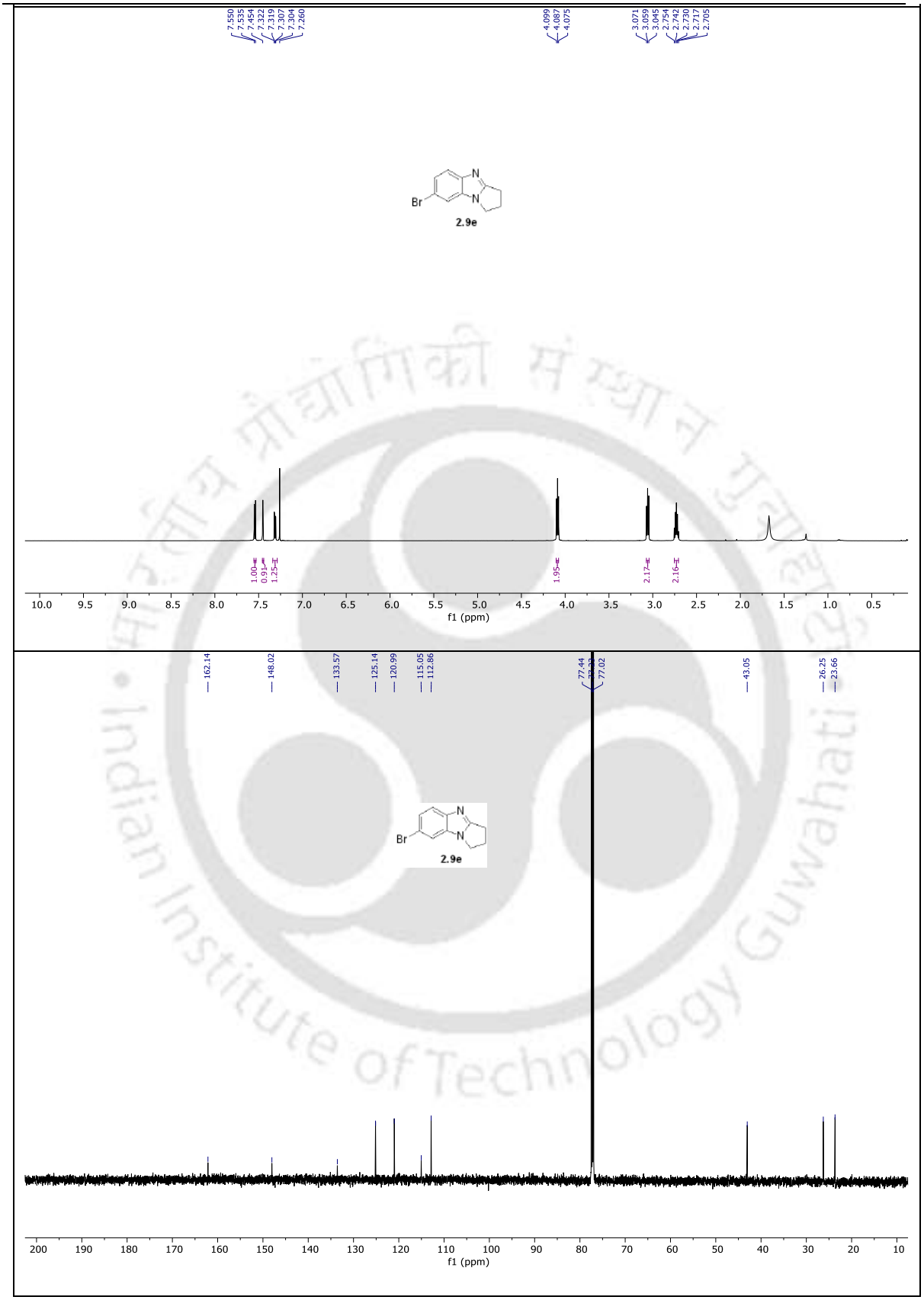
CHAPTER - 6

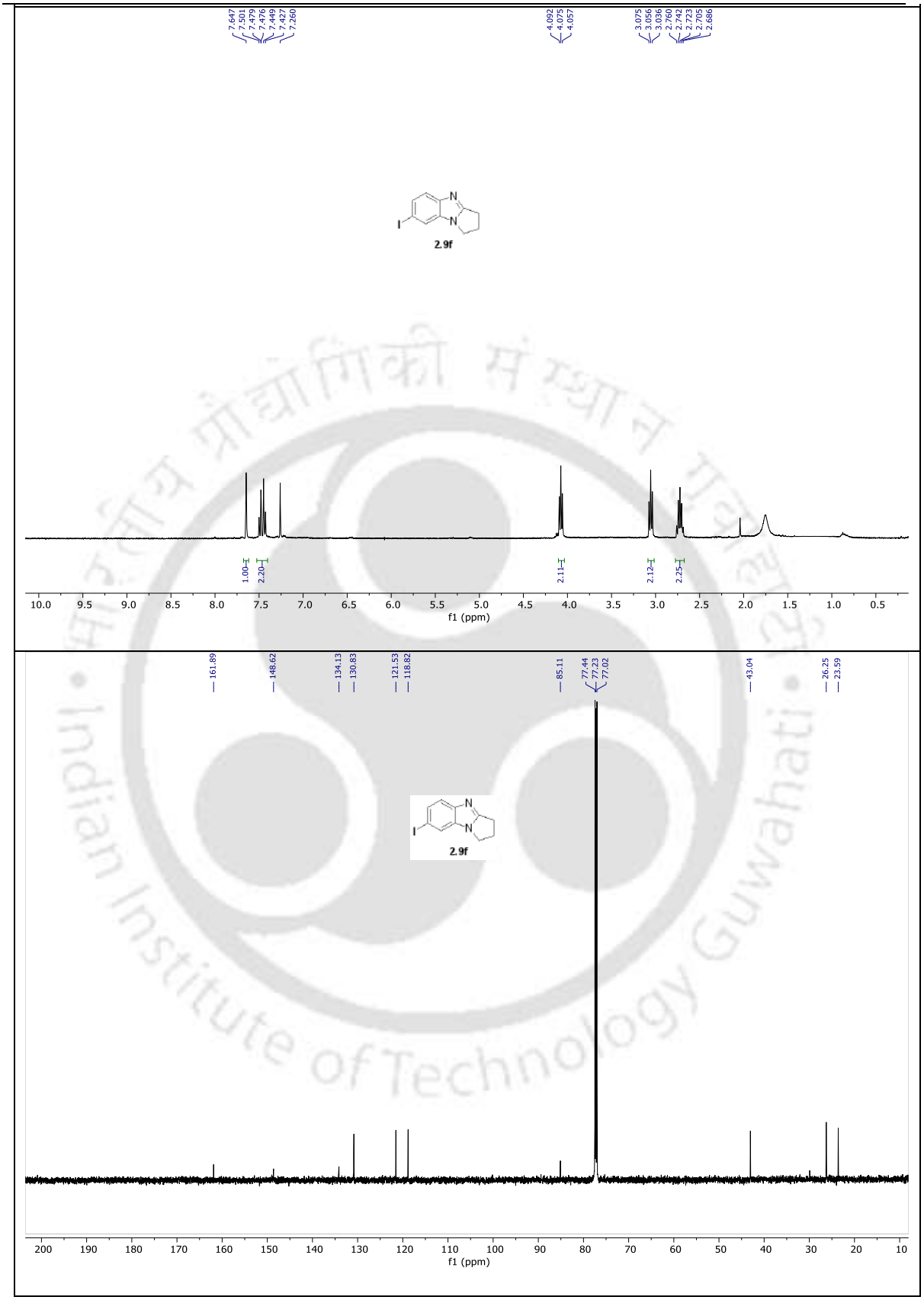
^{1}H, ^{13}C NMR Spectra of Selected Compounds

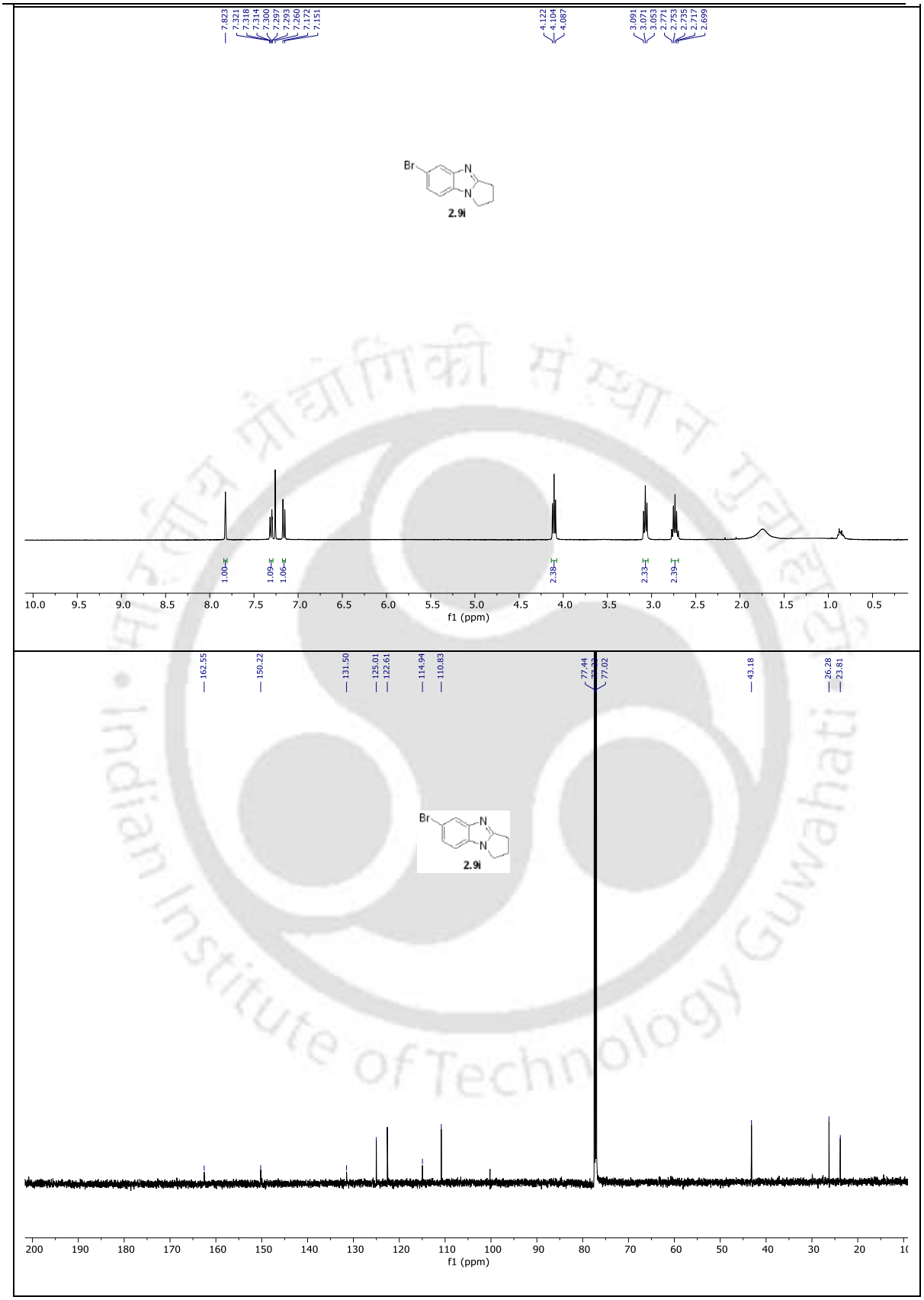


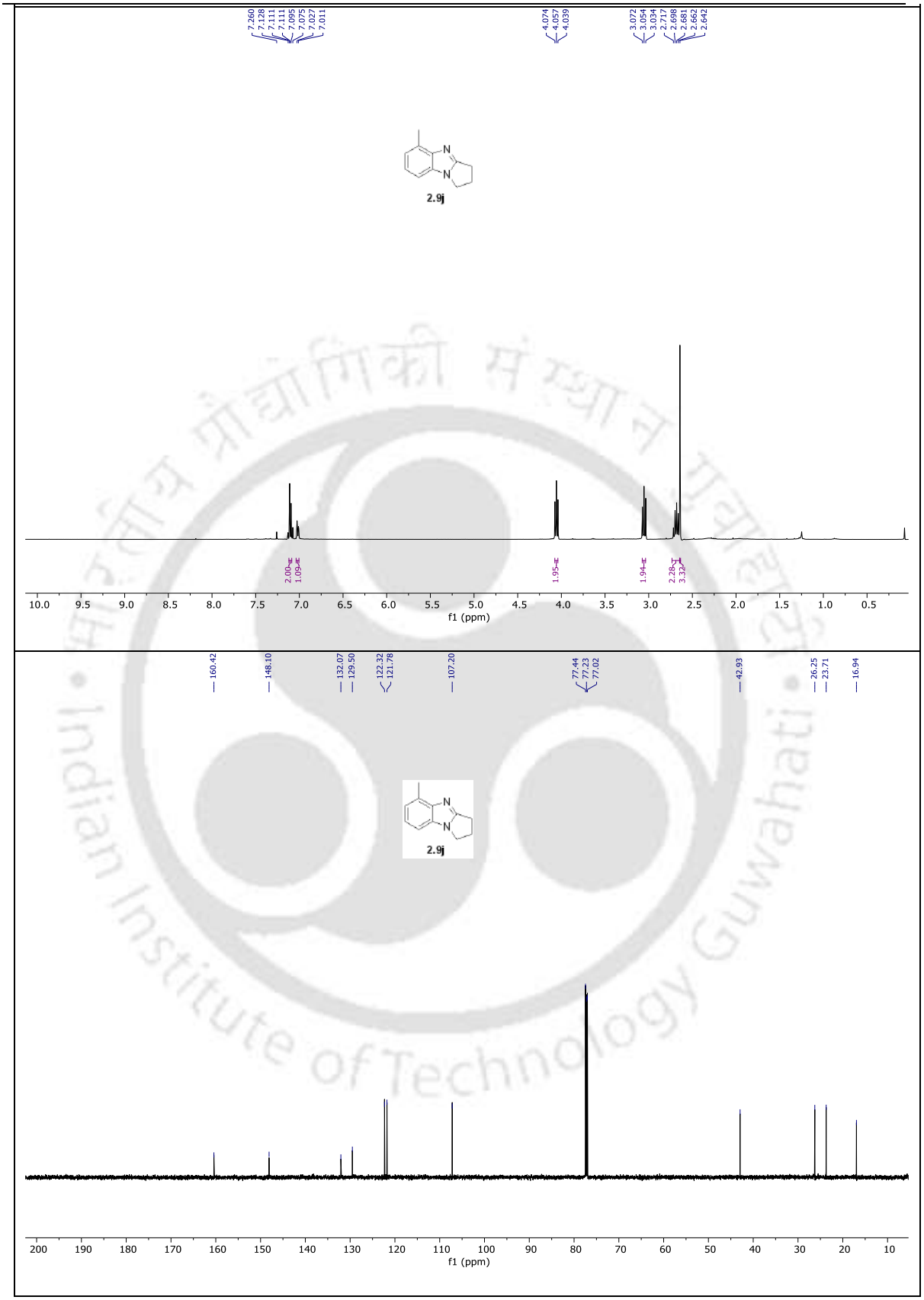


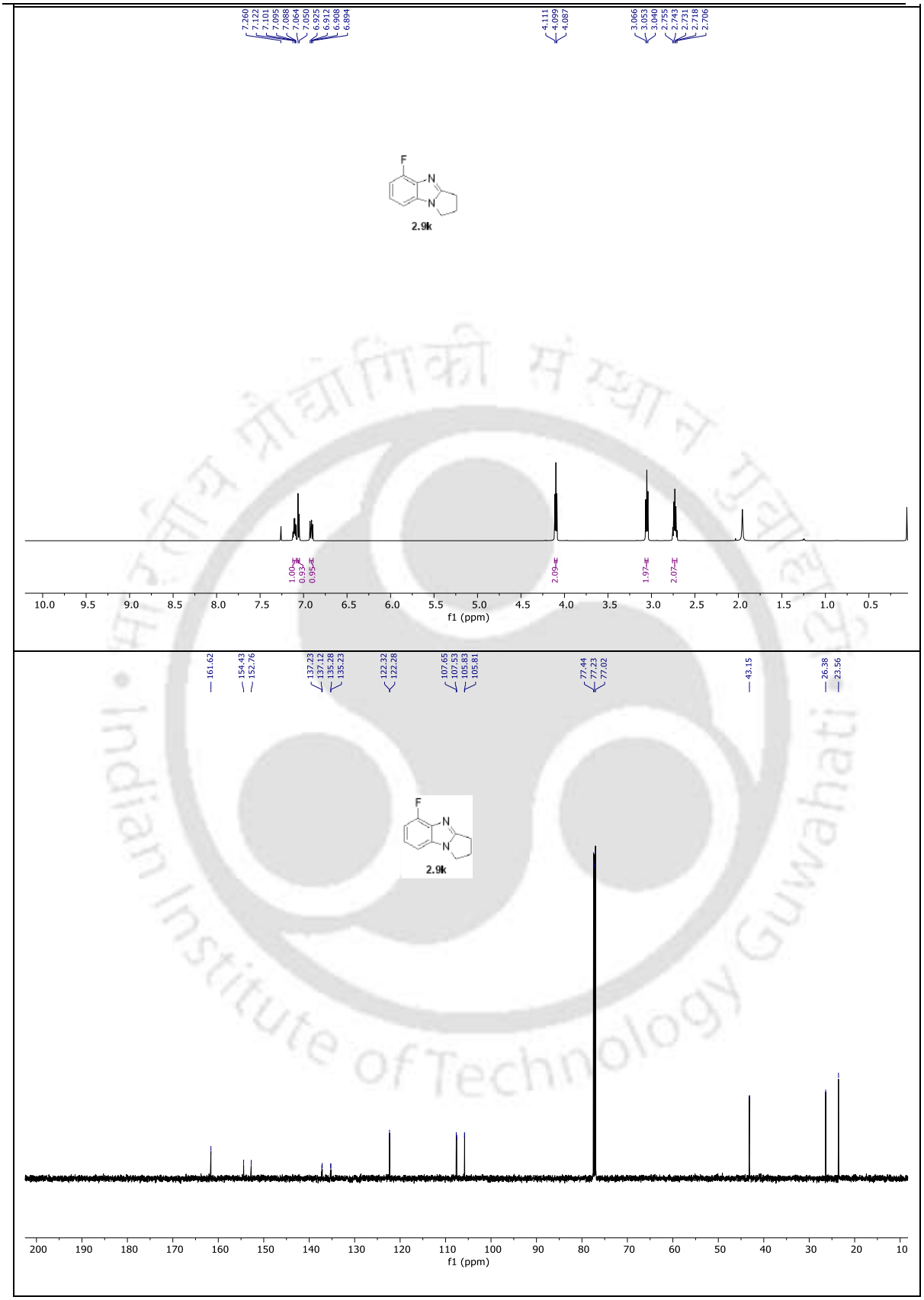


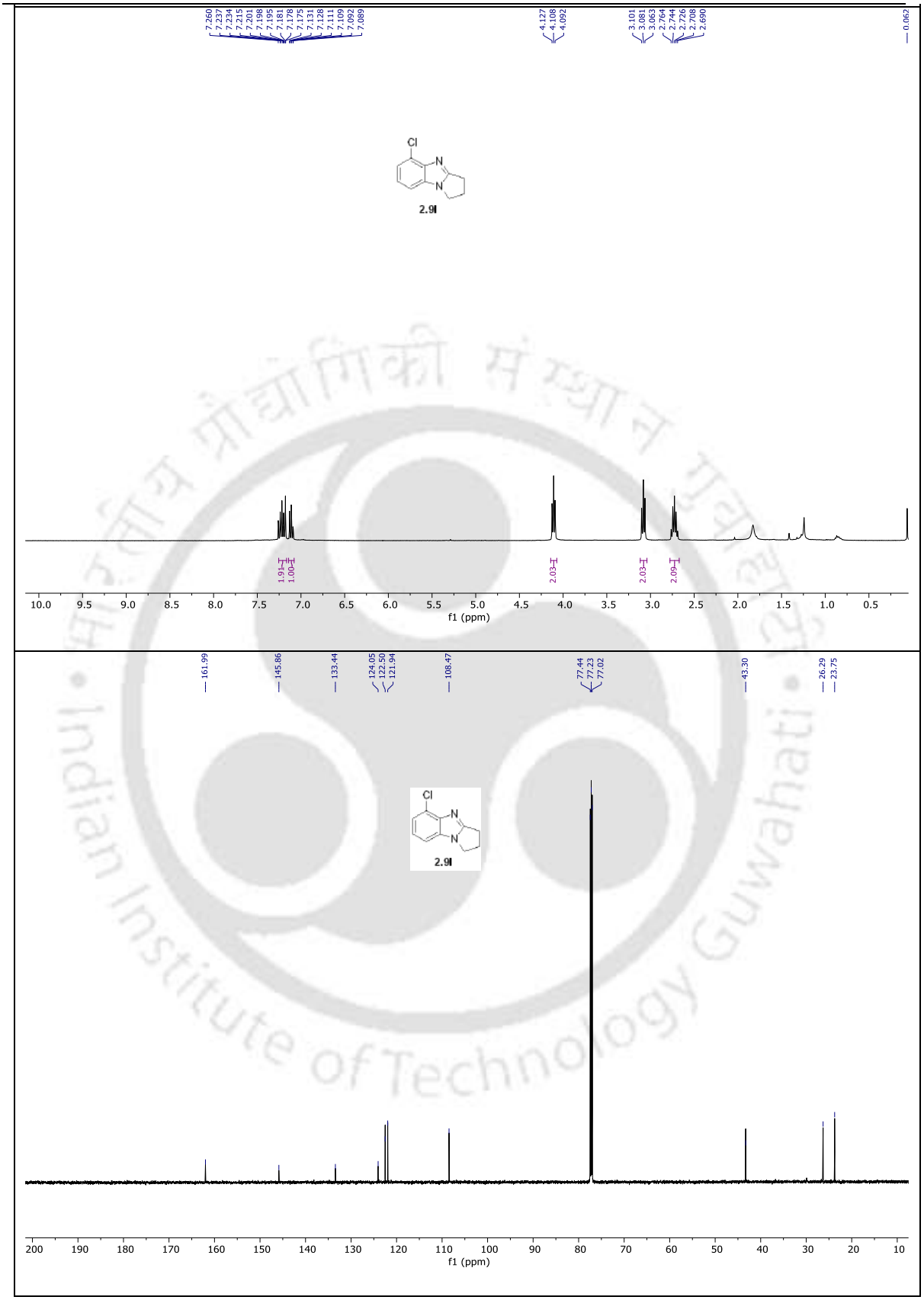


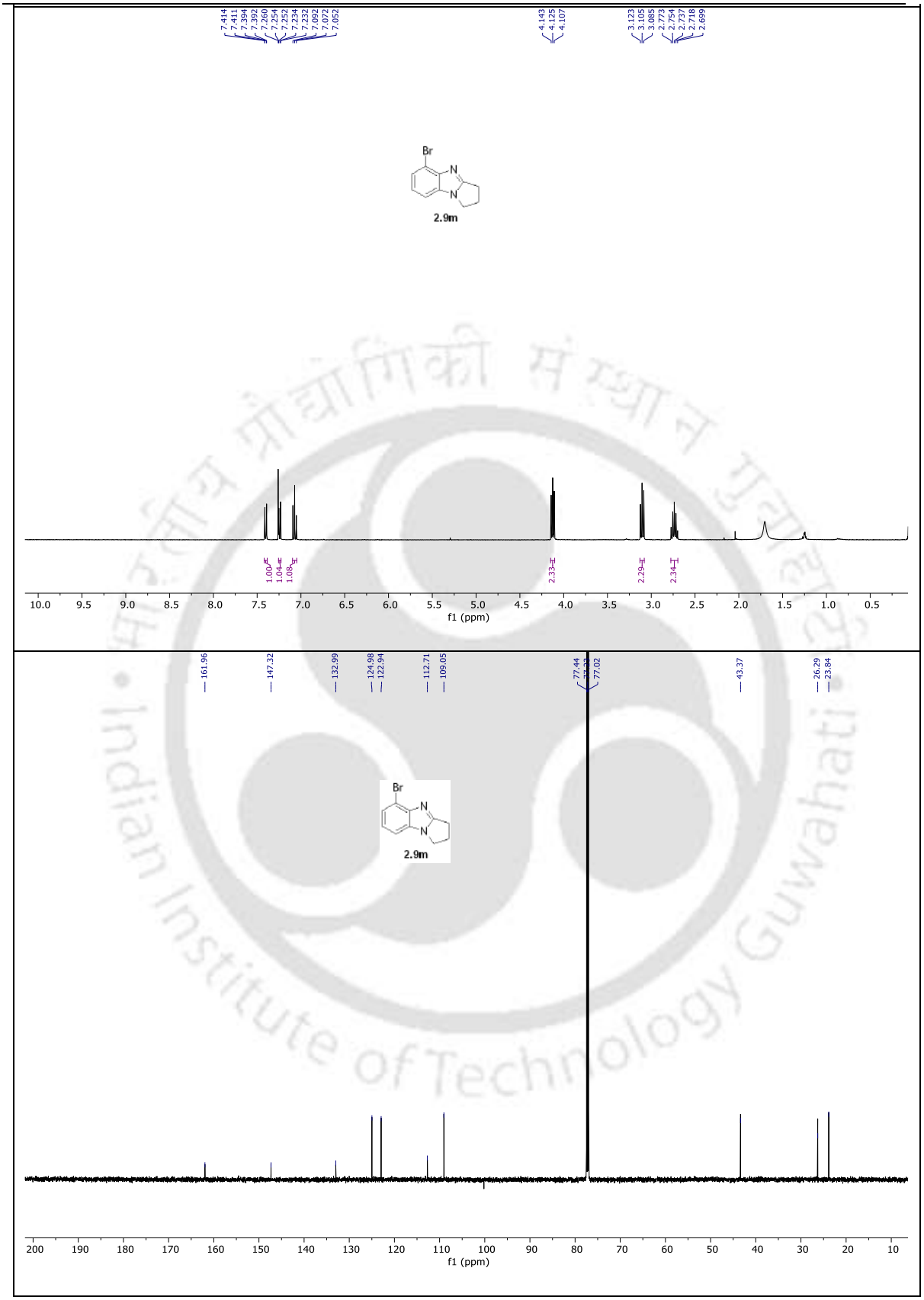


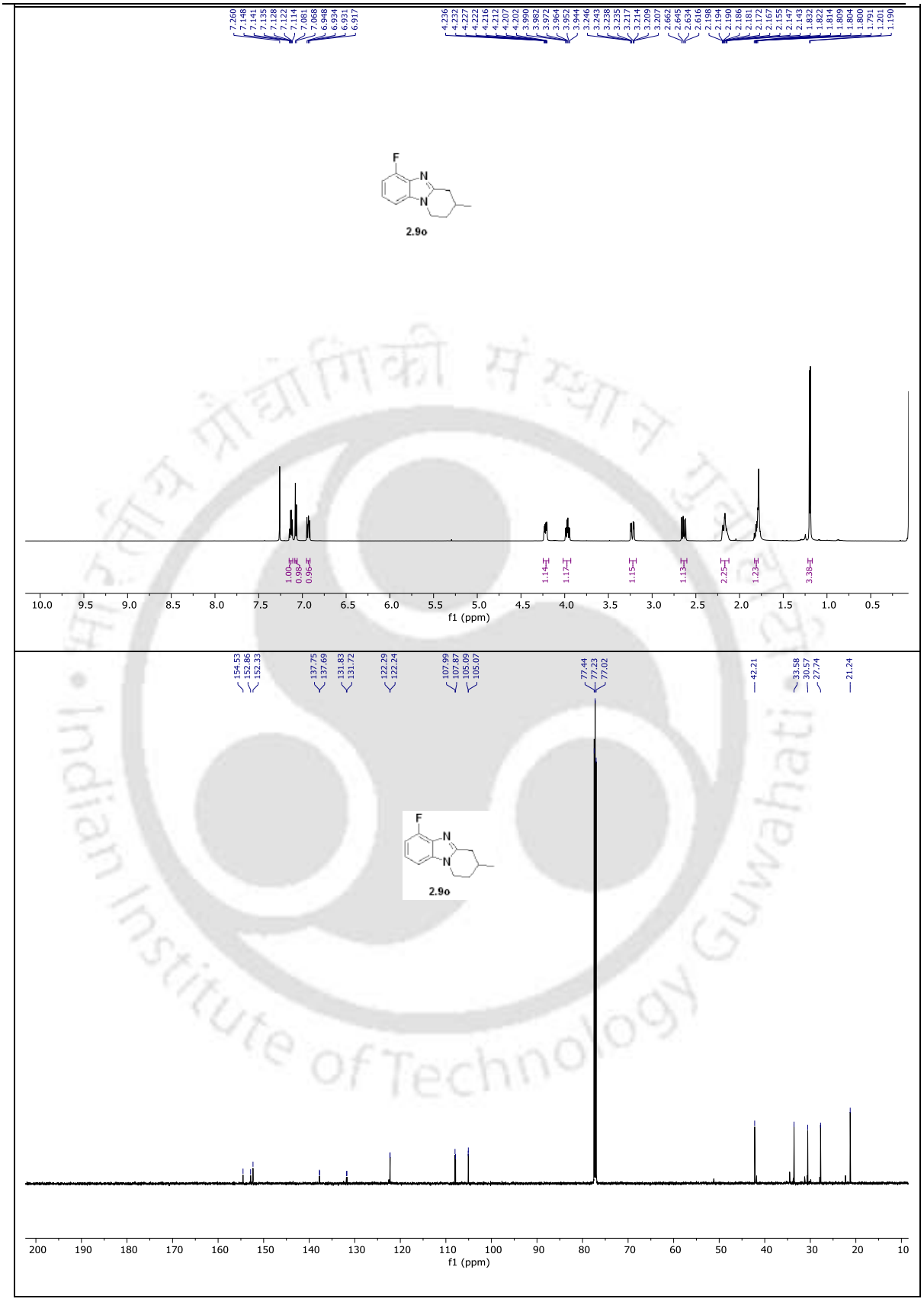


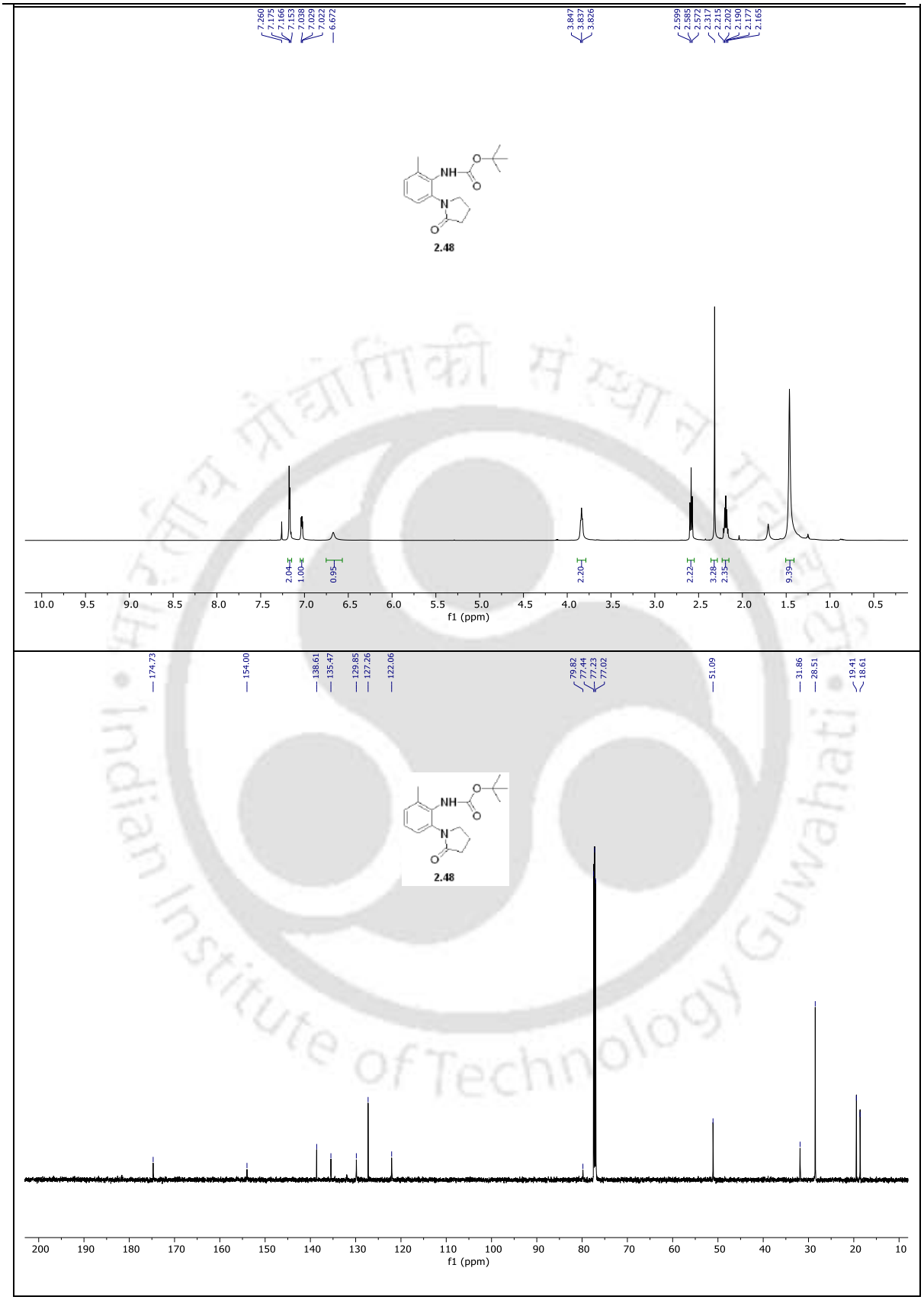


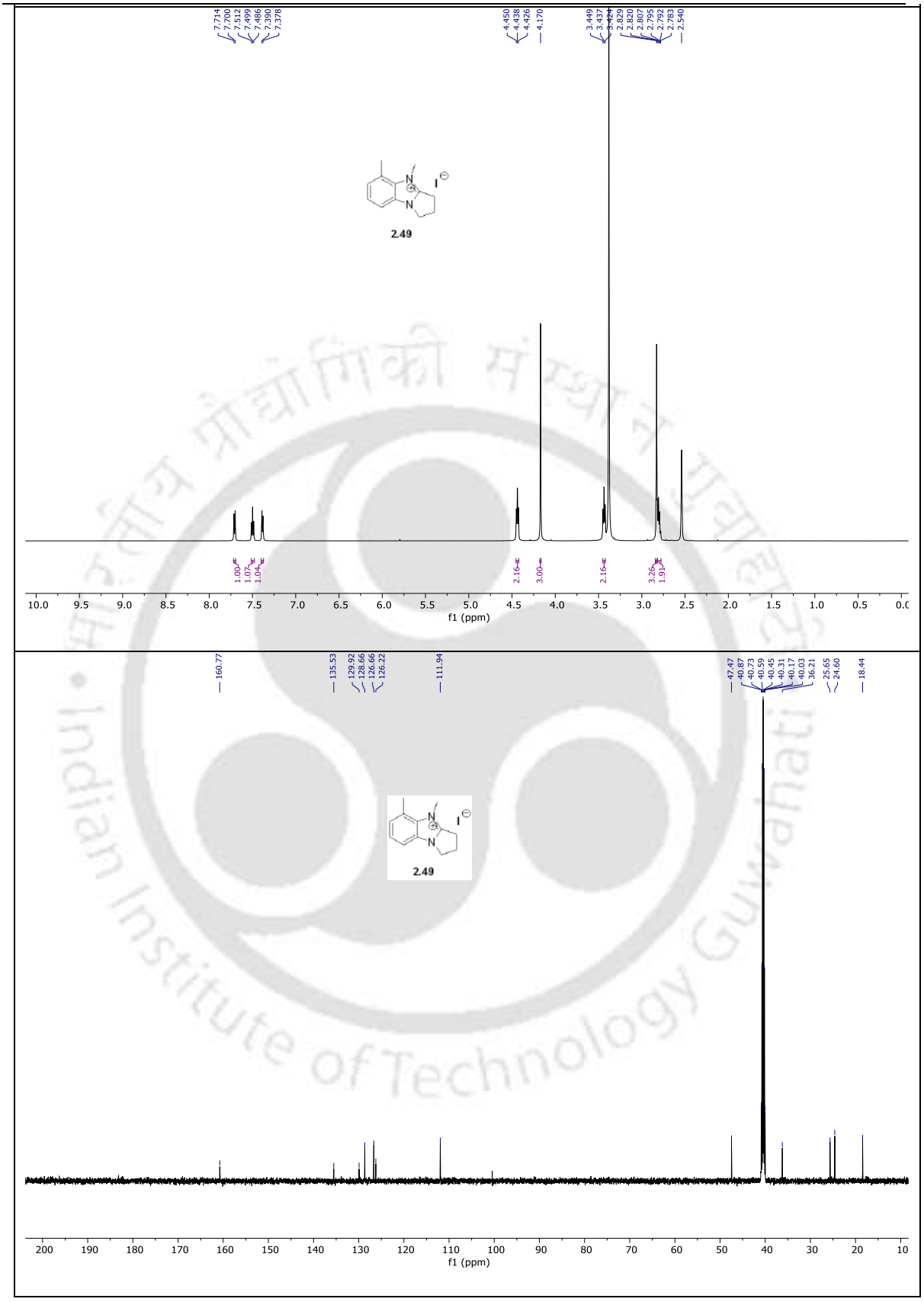


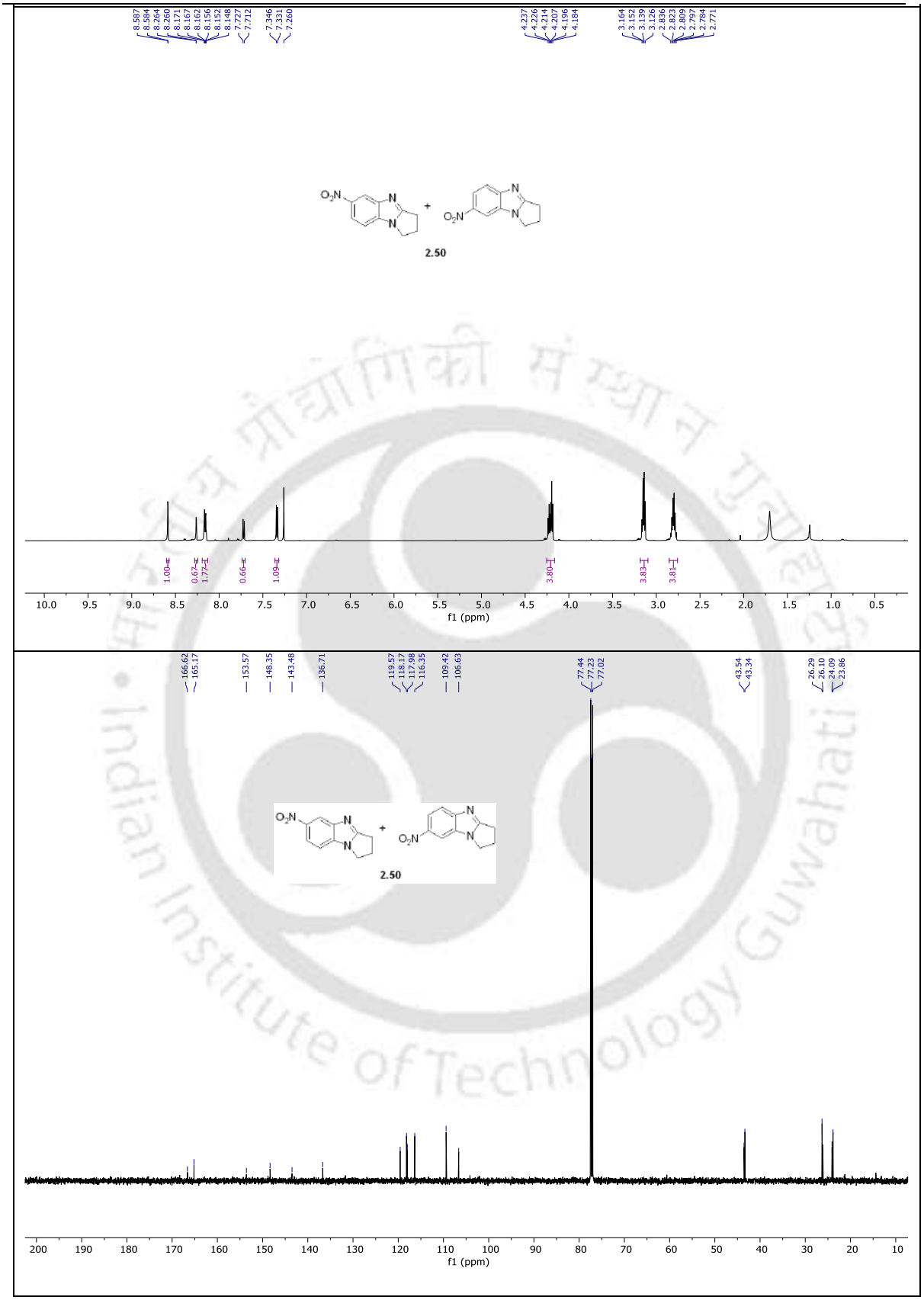


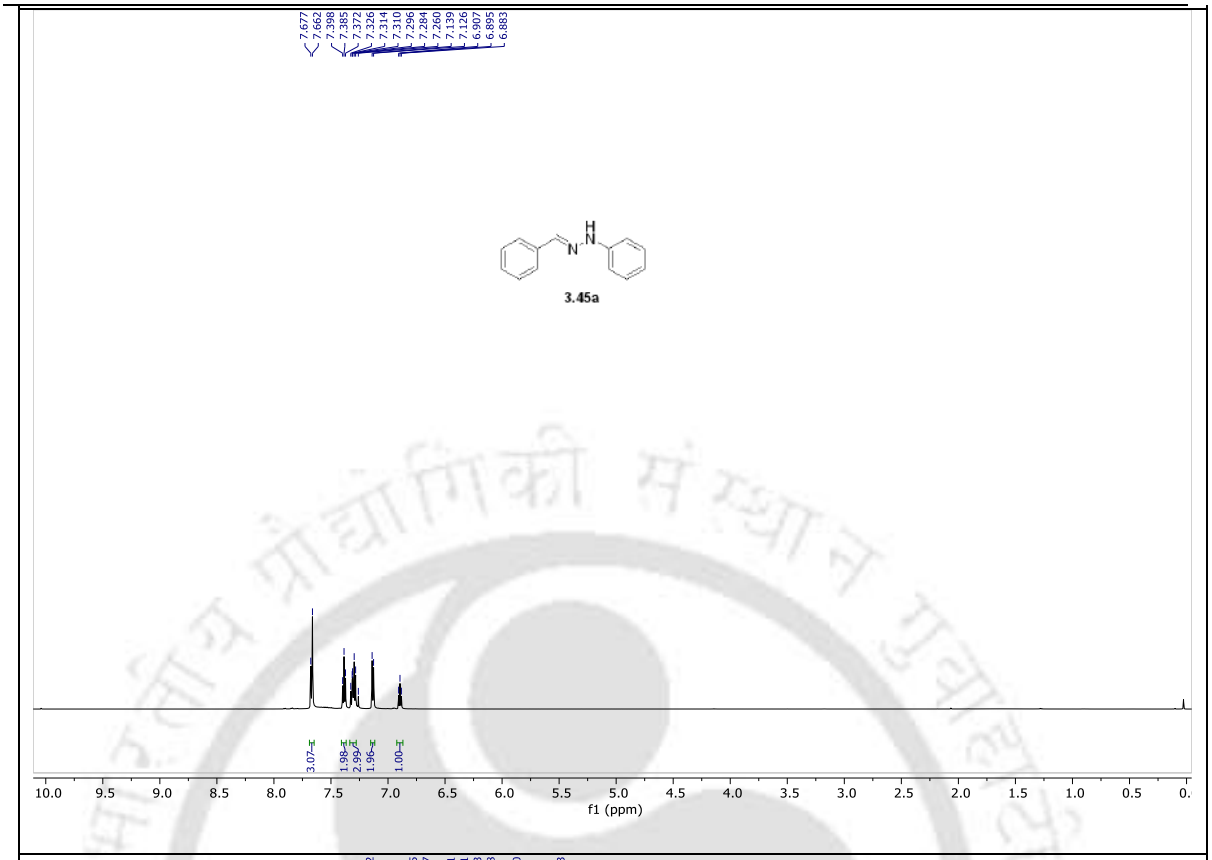


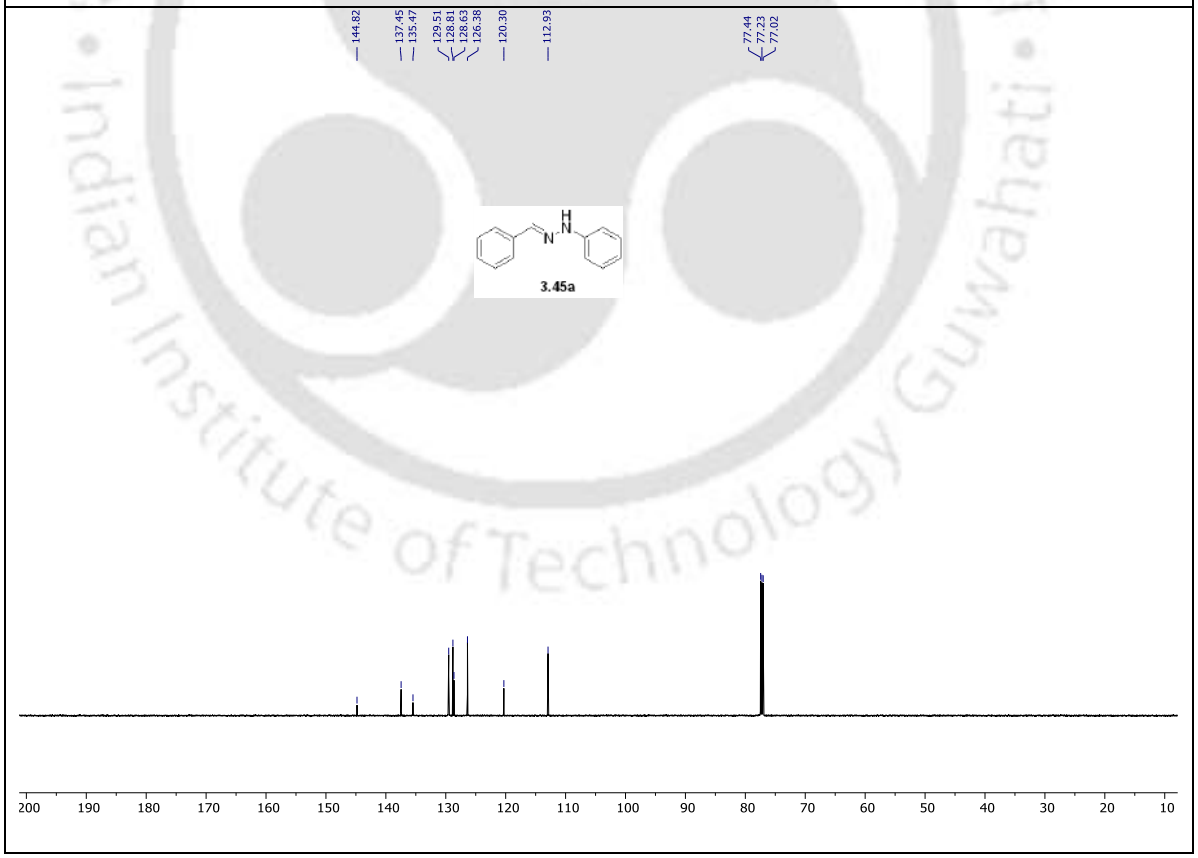


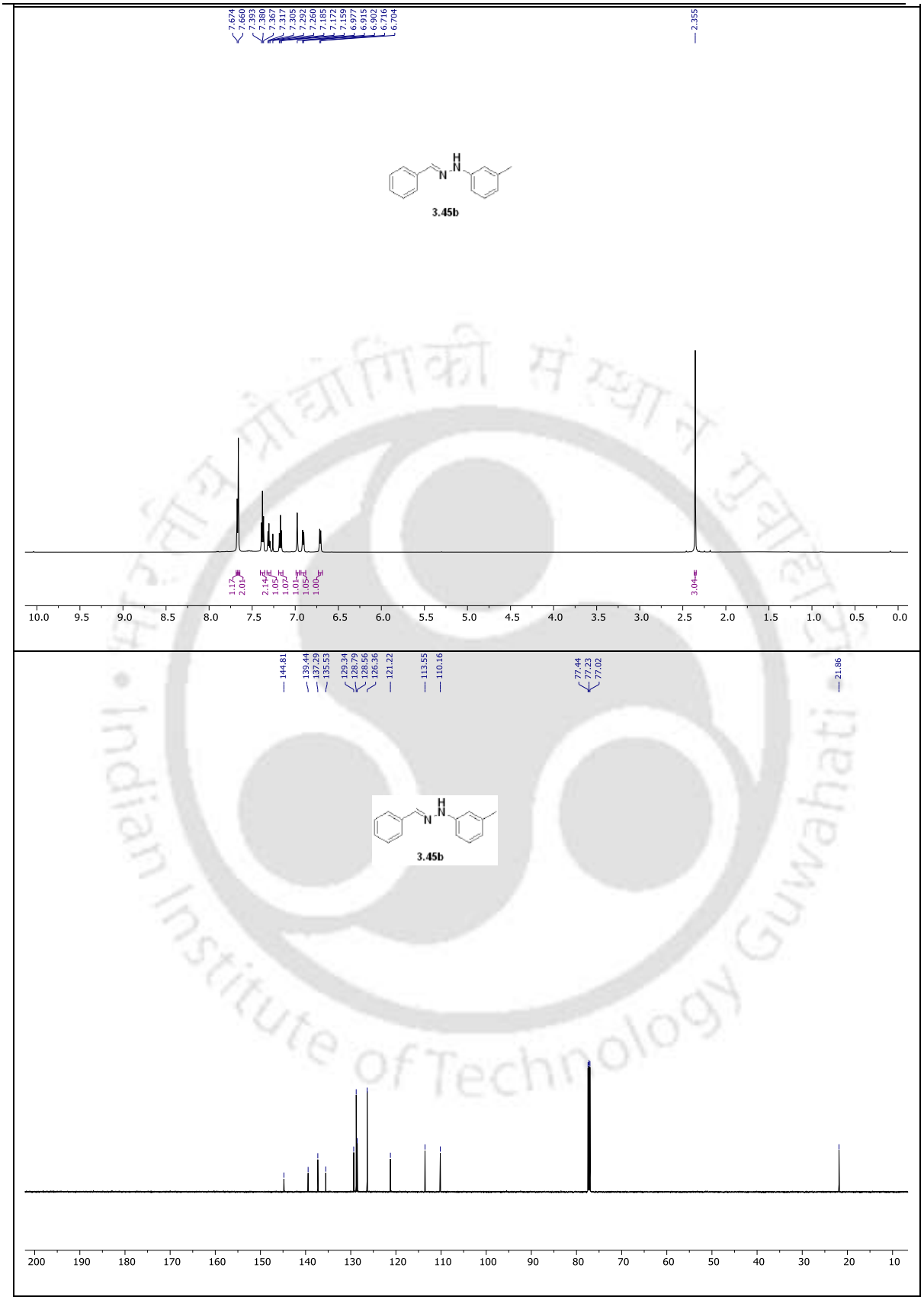


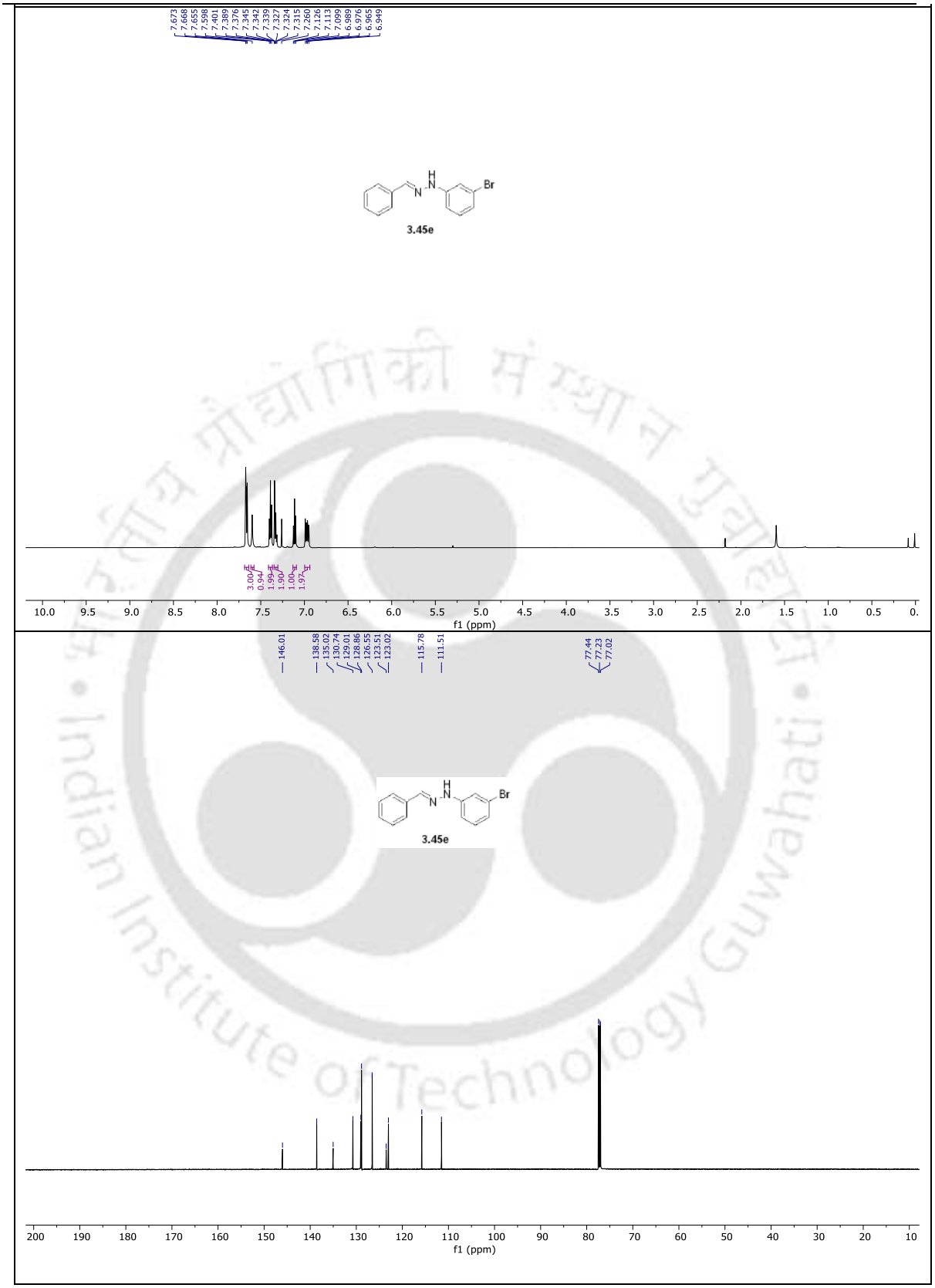


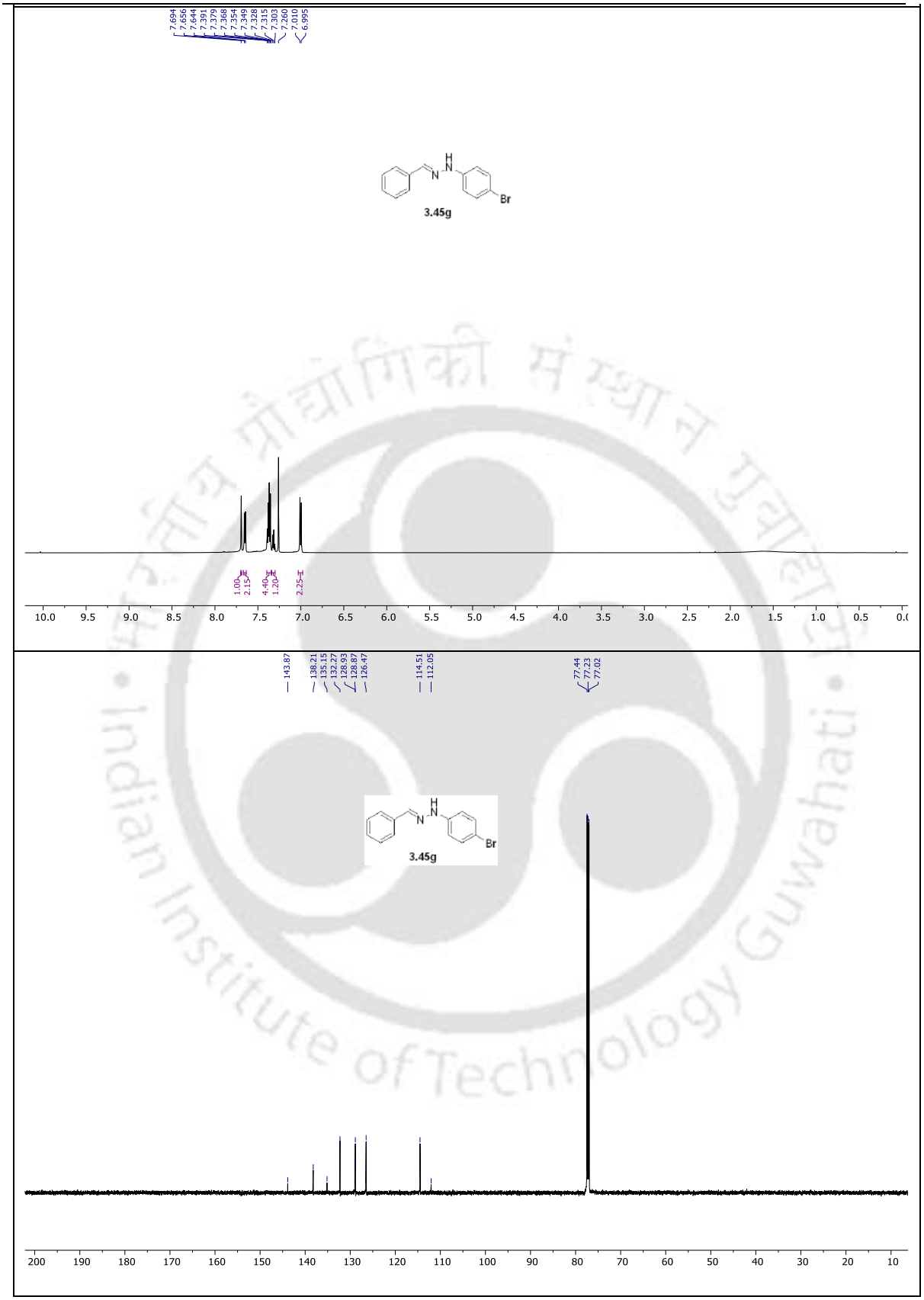


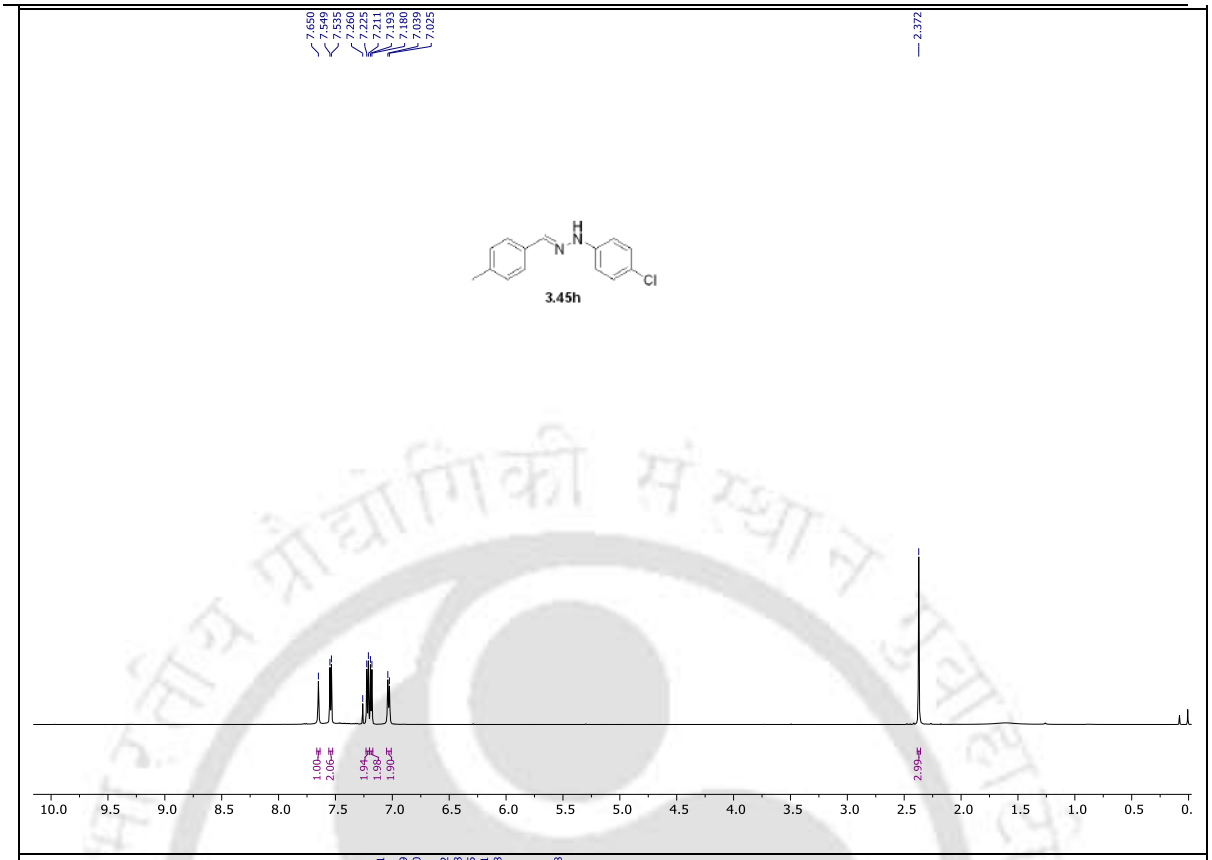


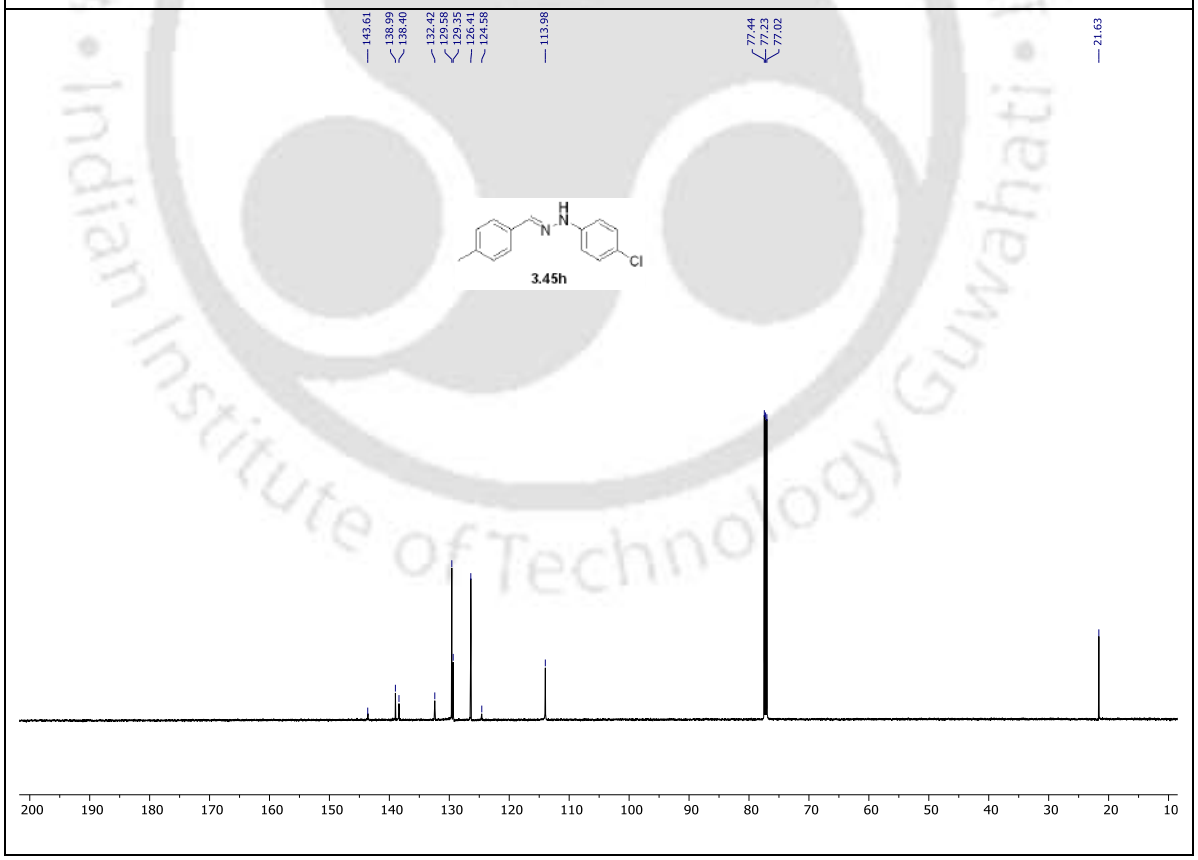


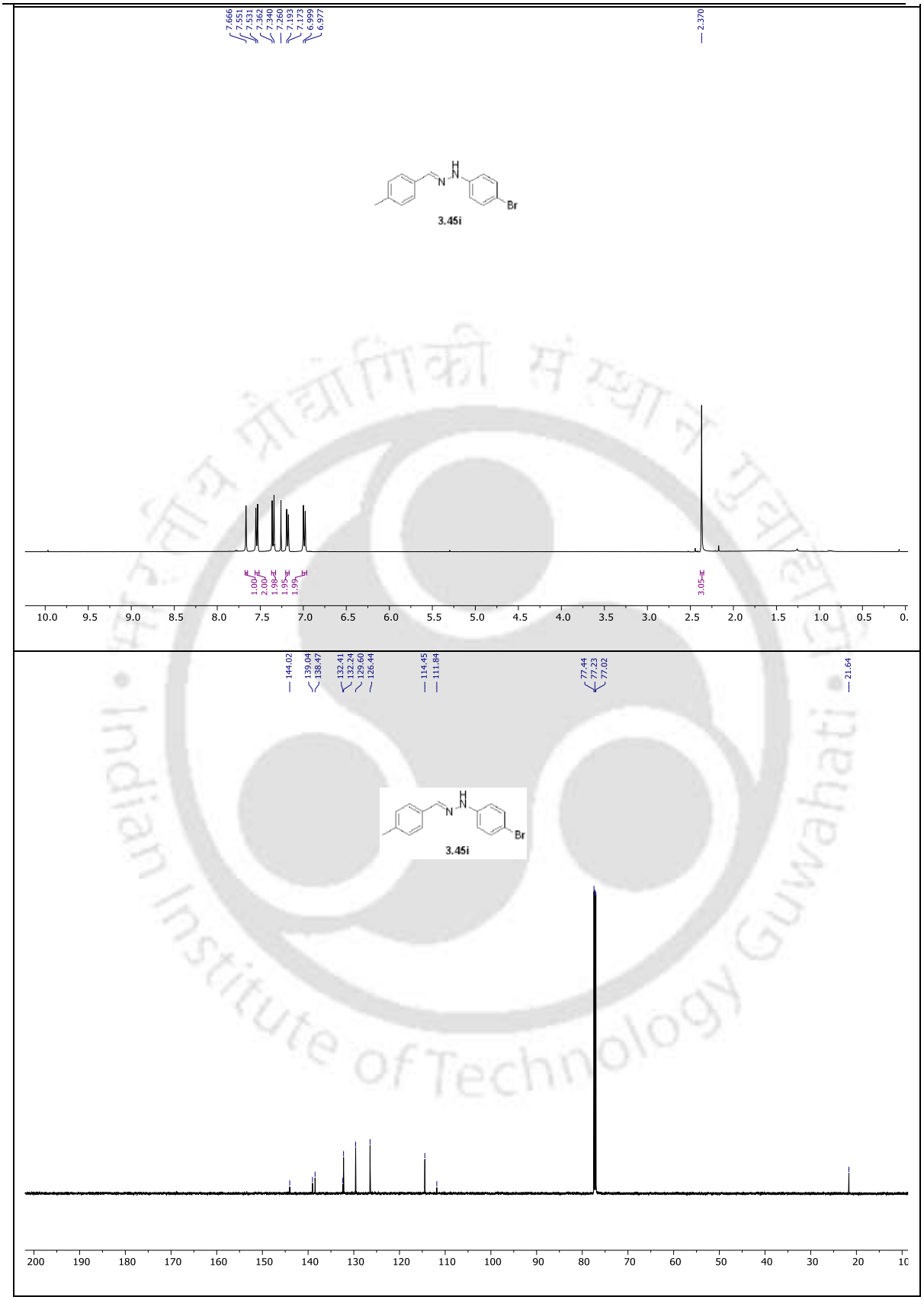


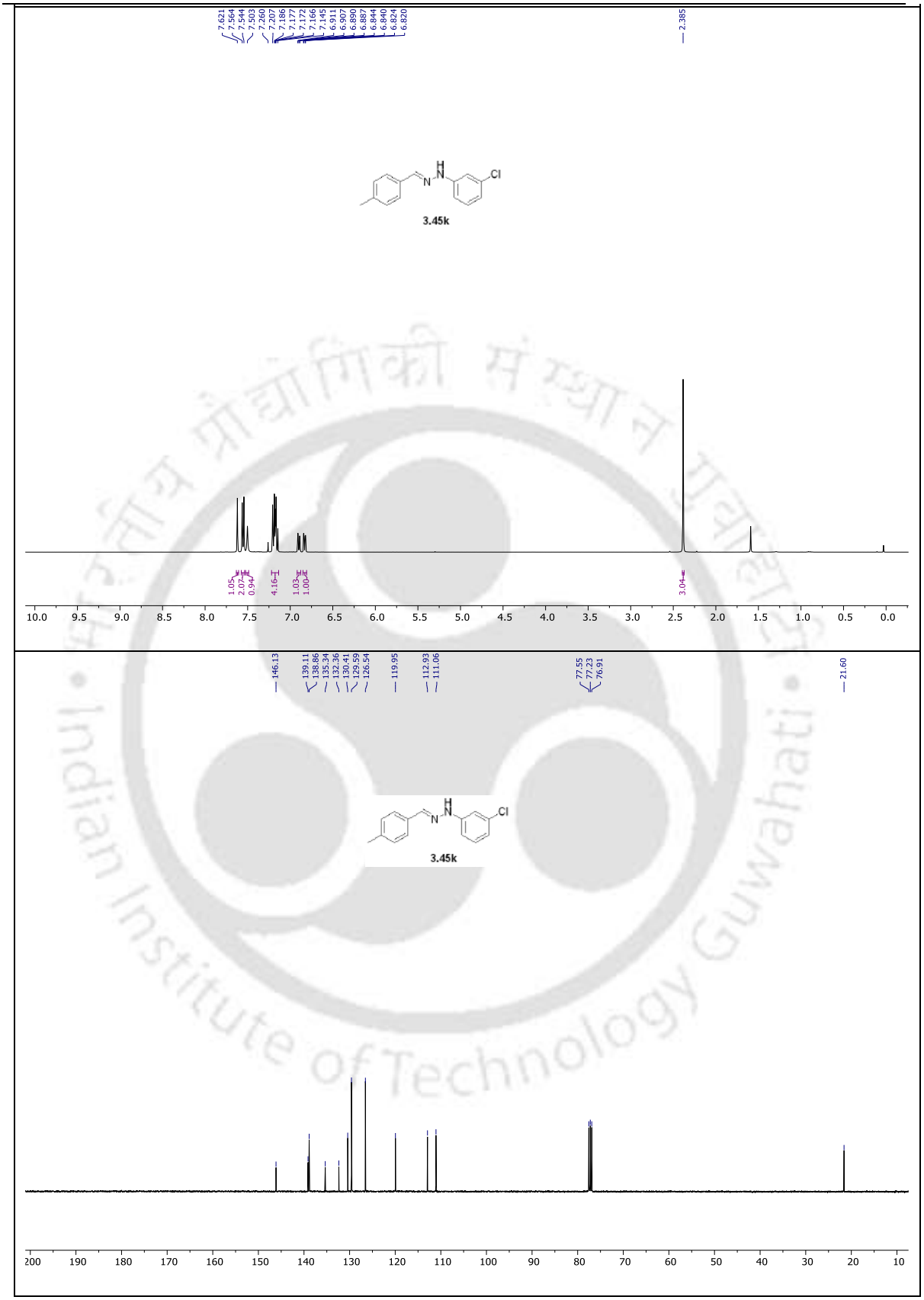


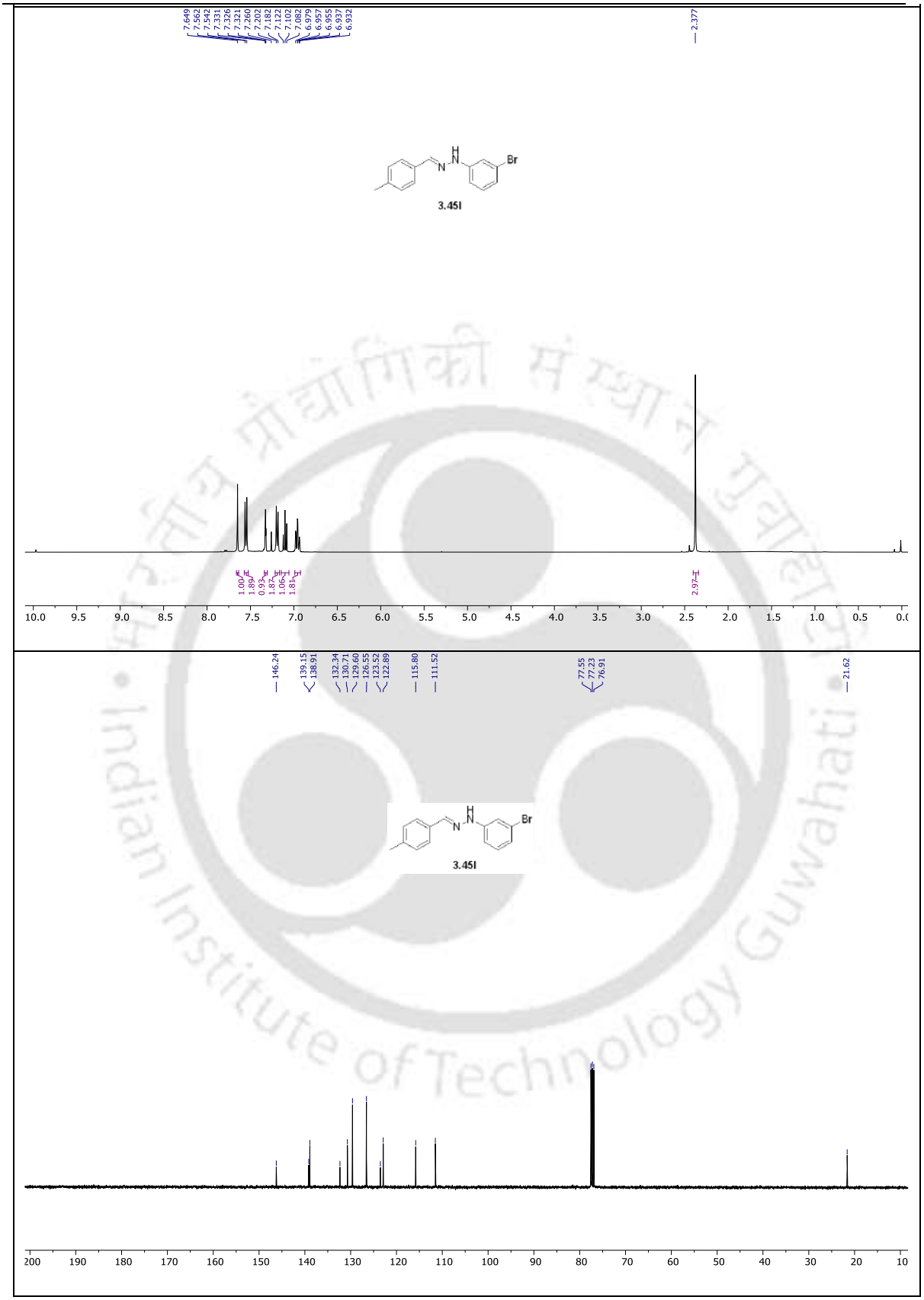


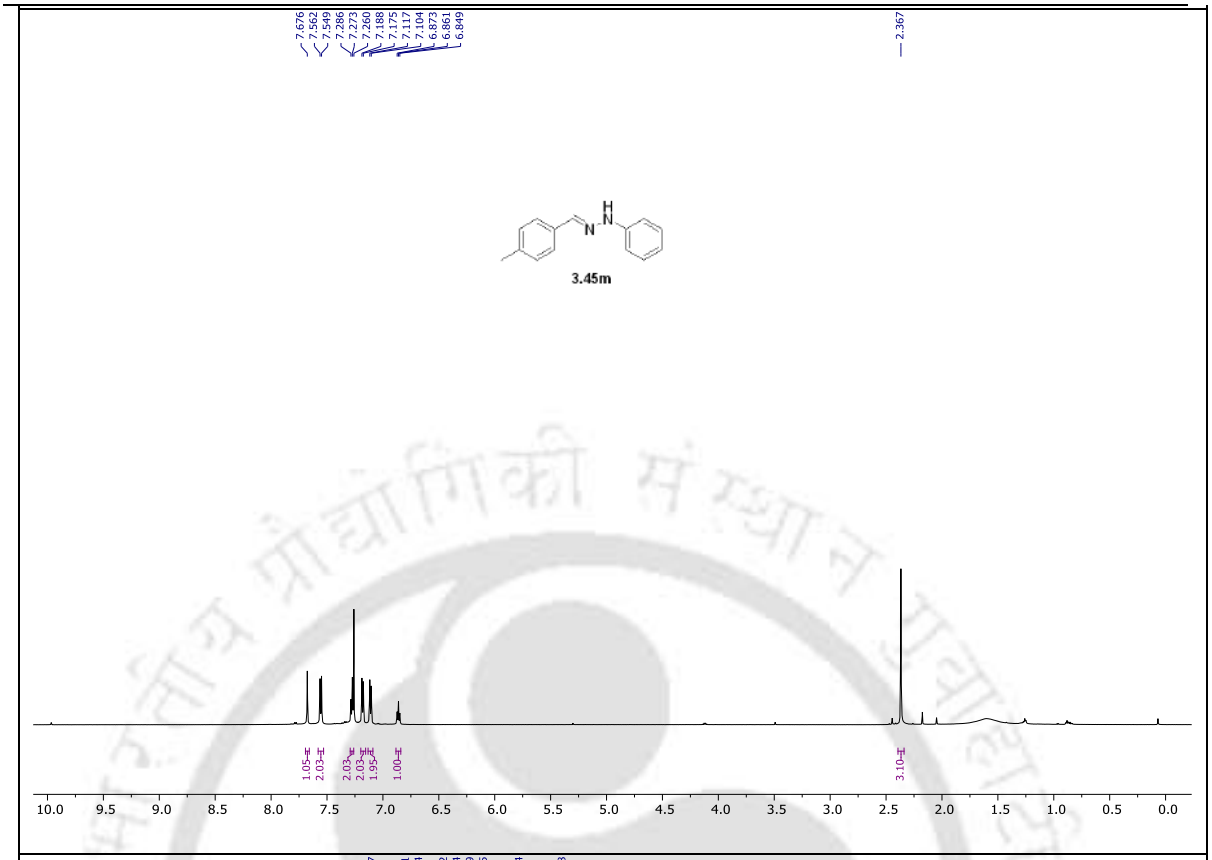


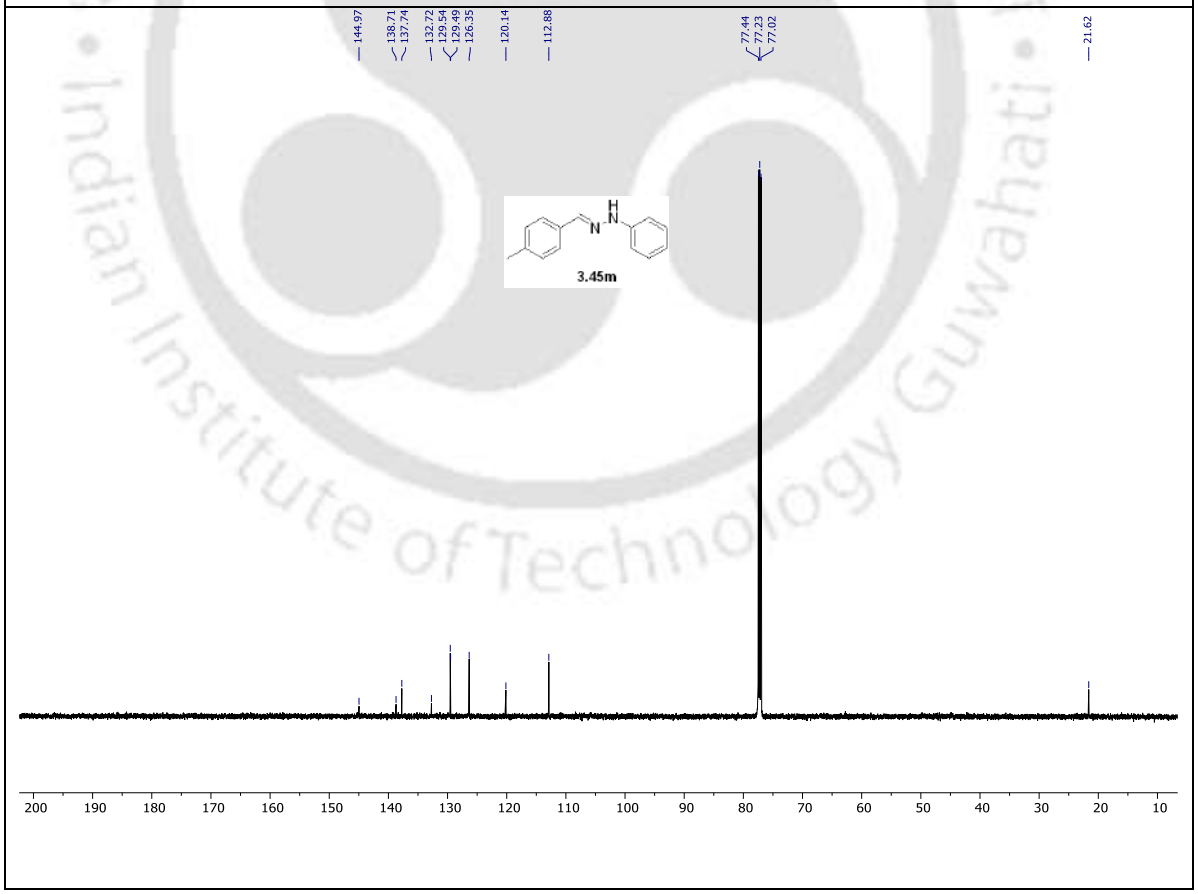


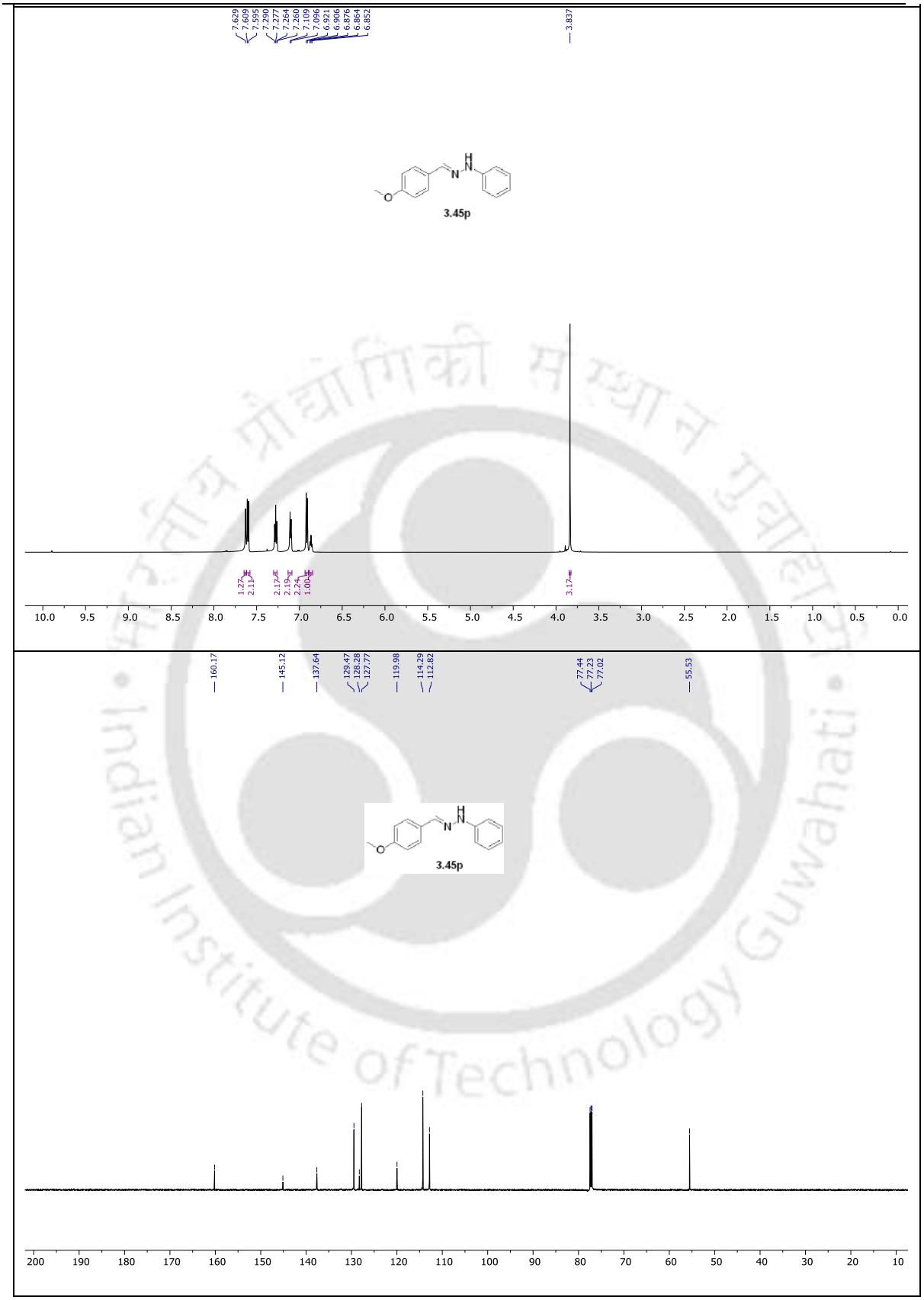


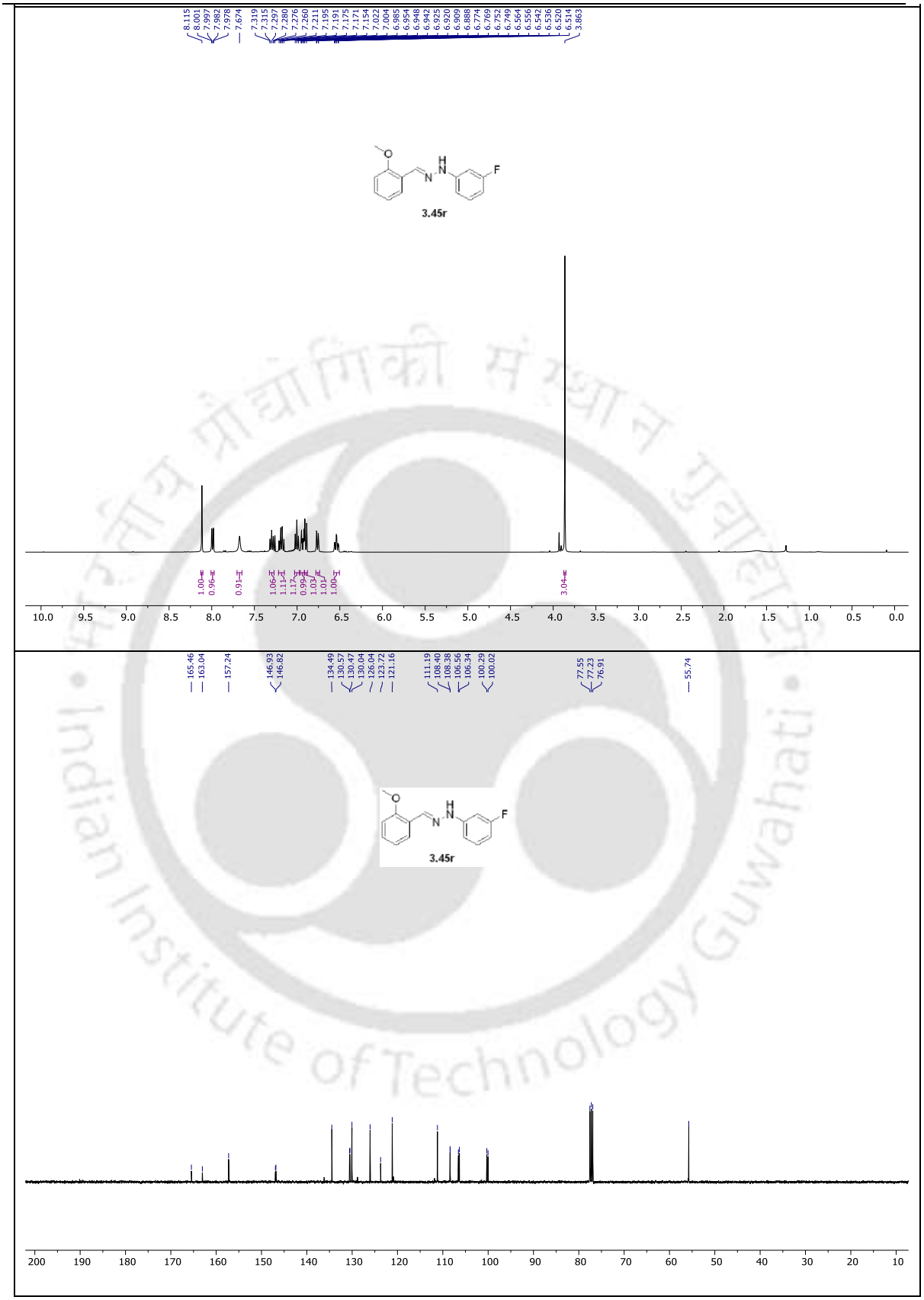


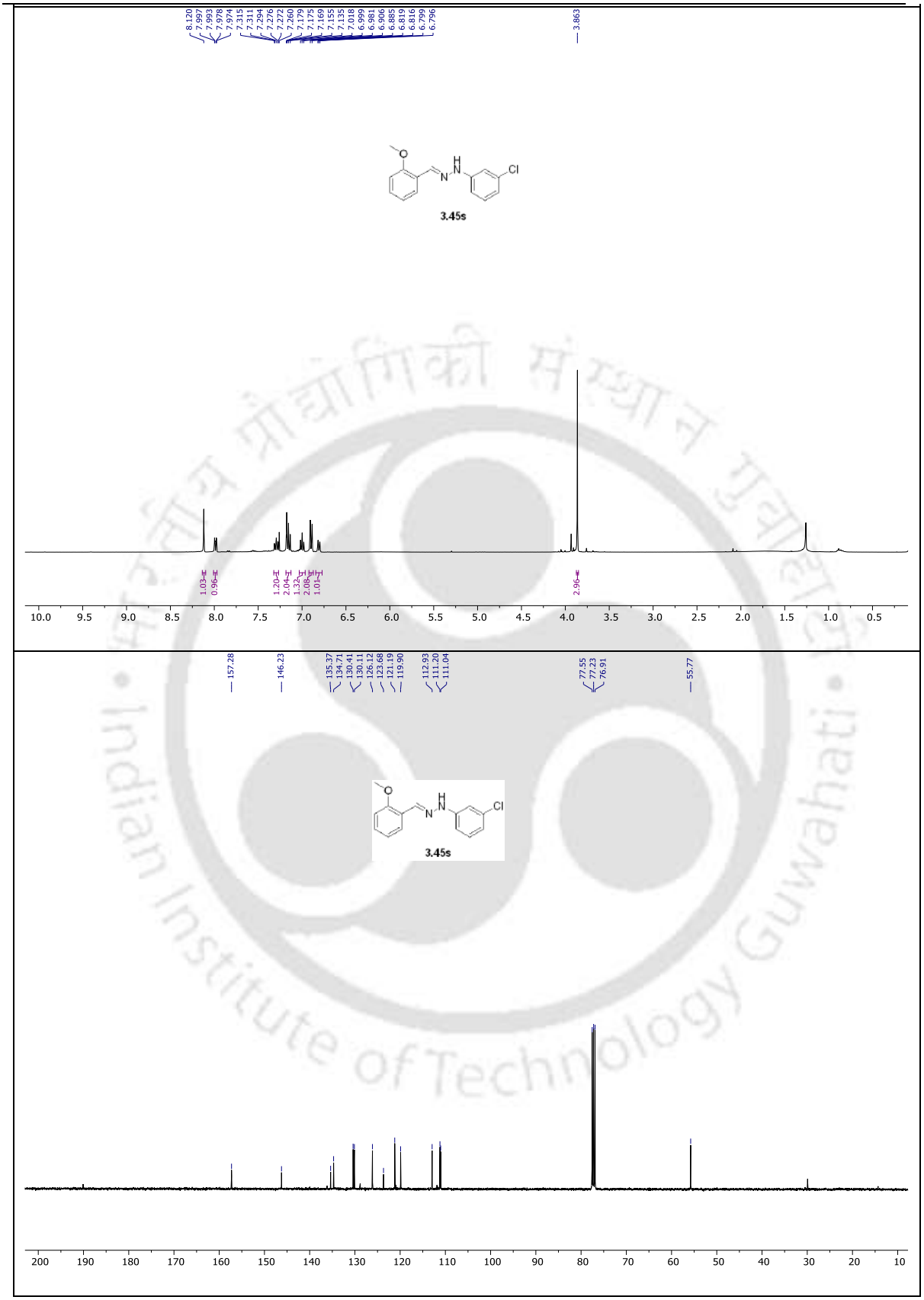


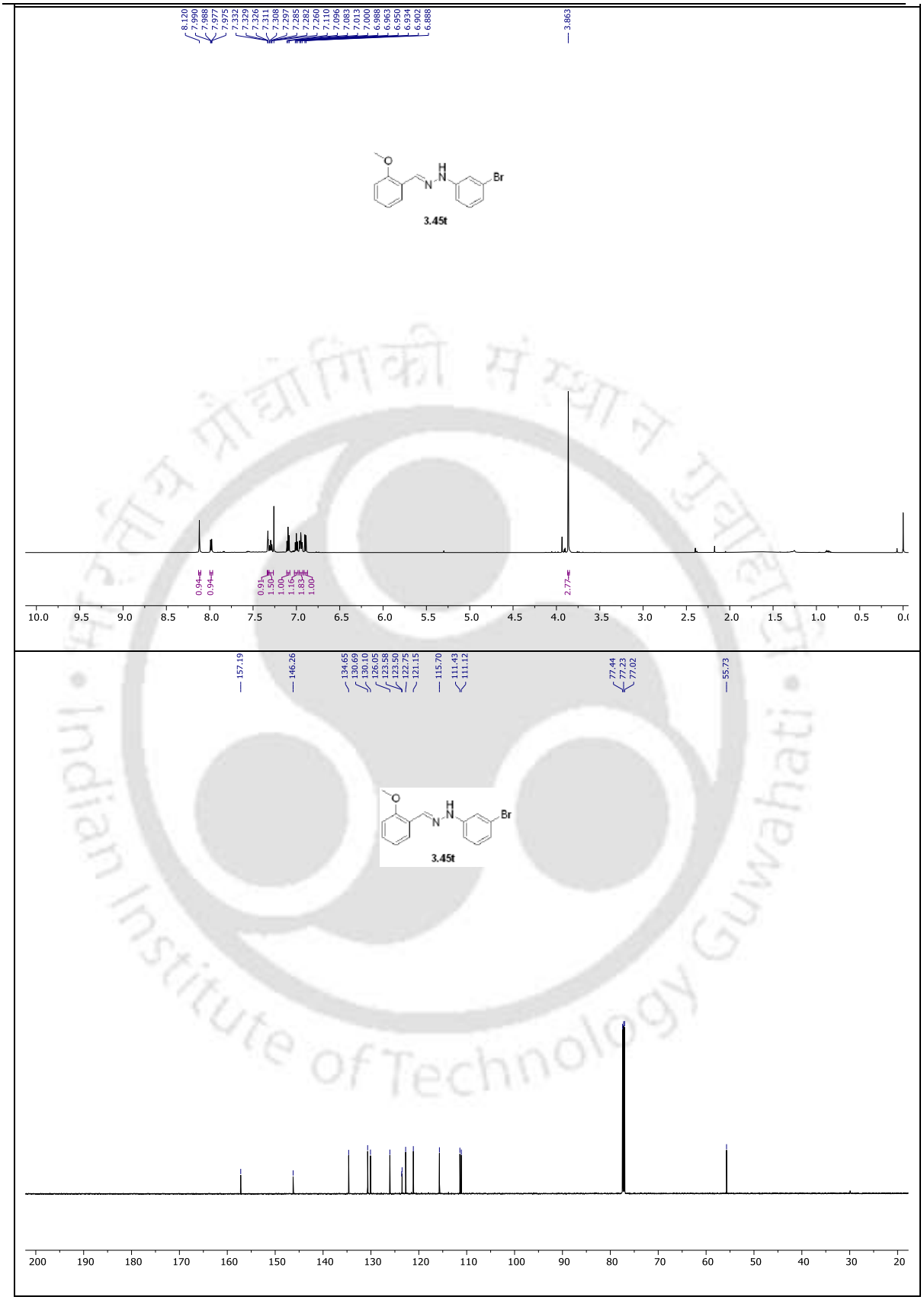


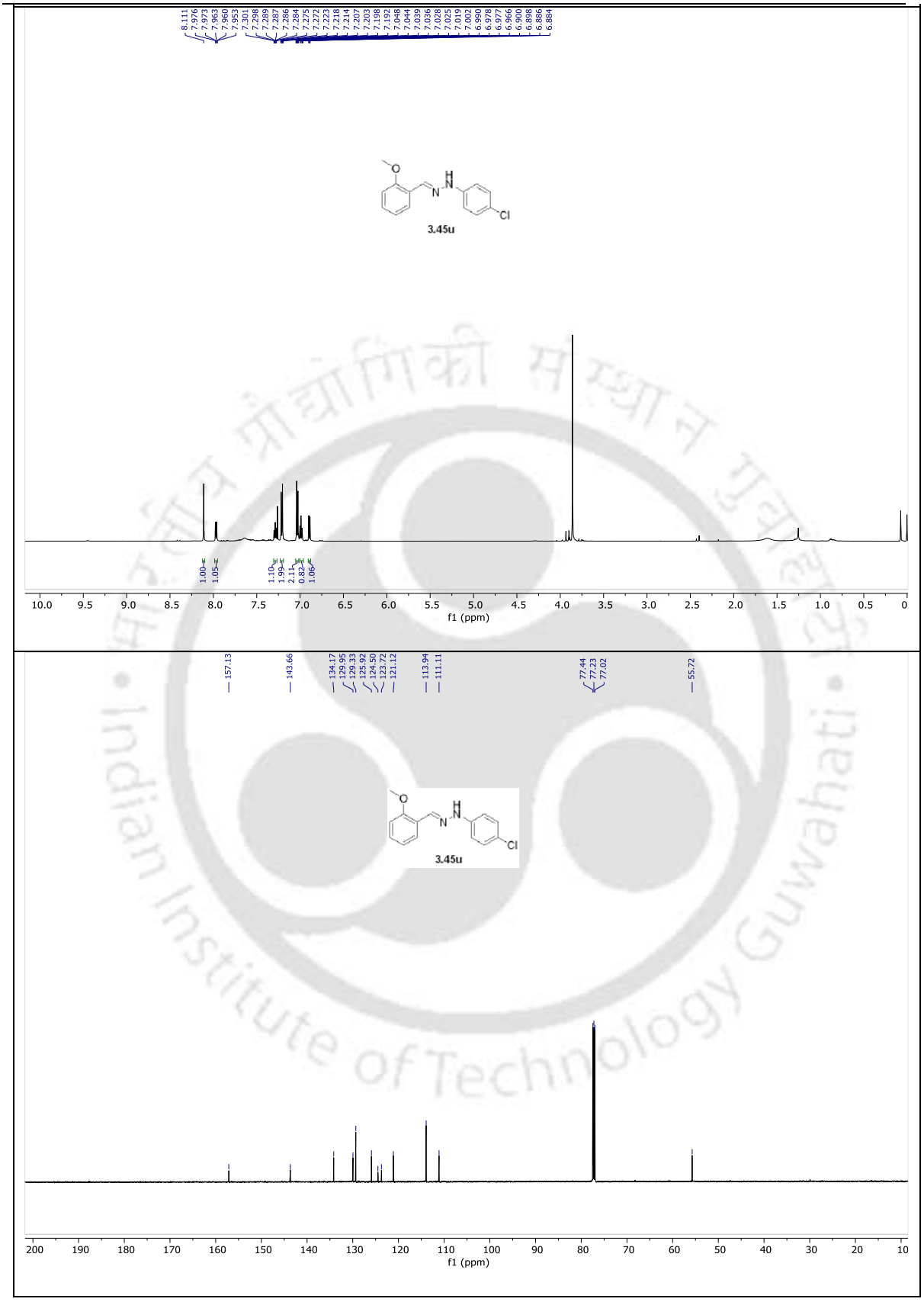


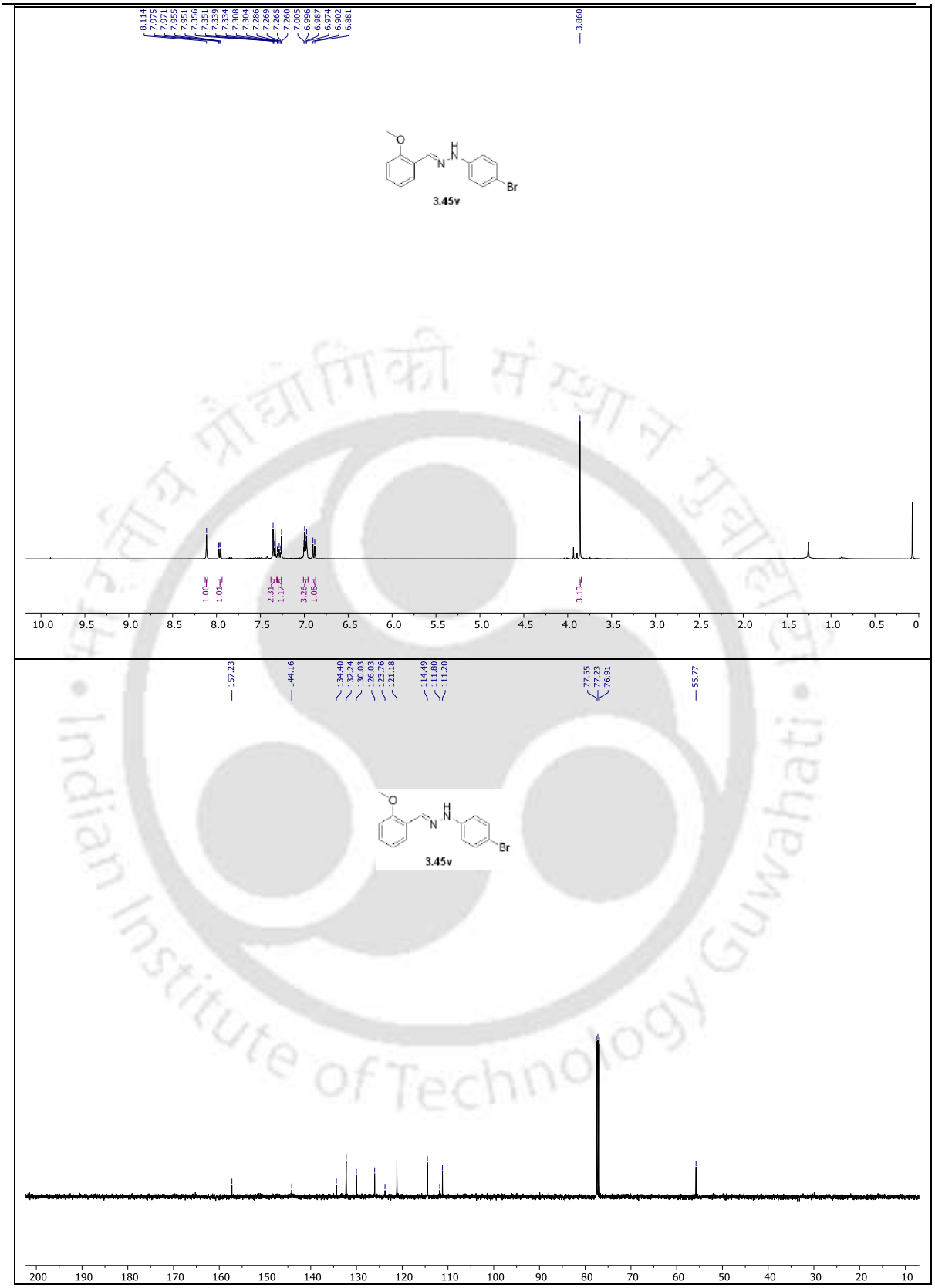


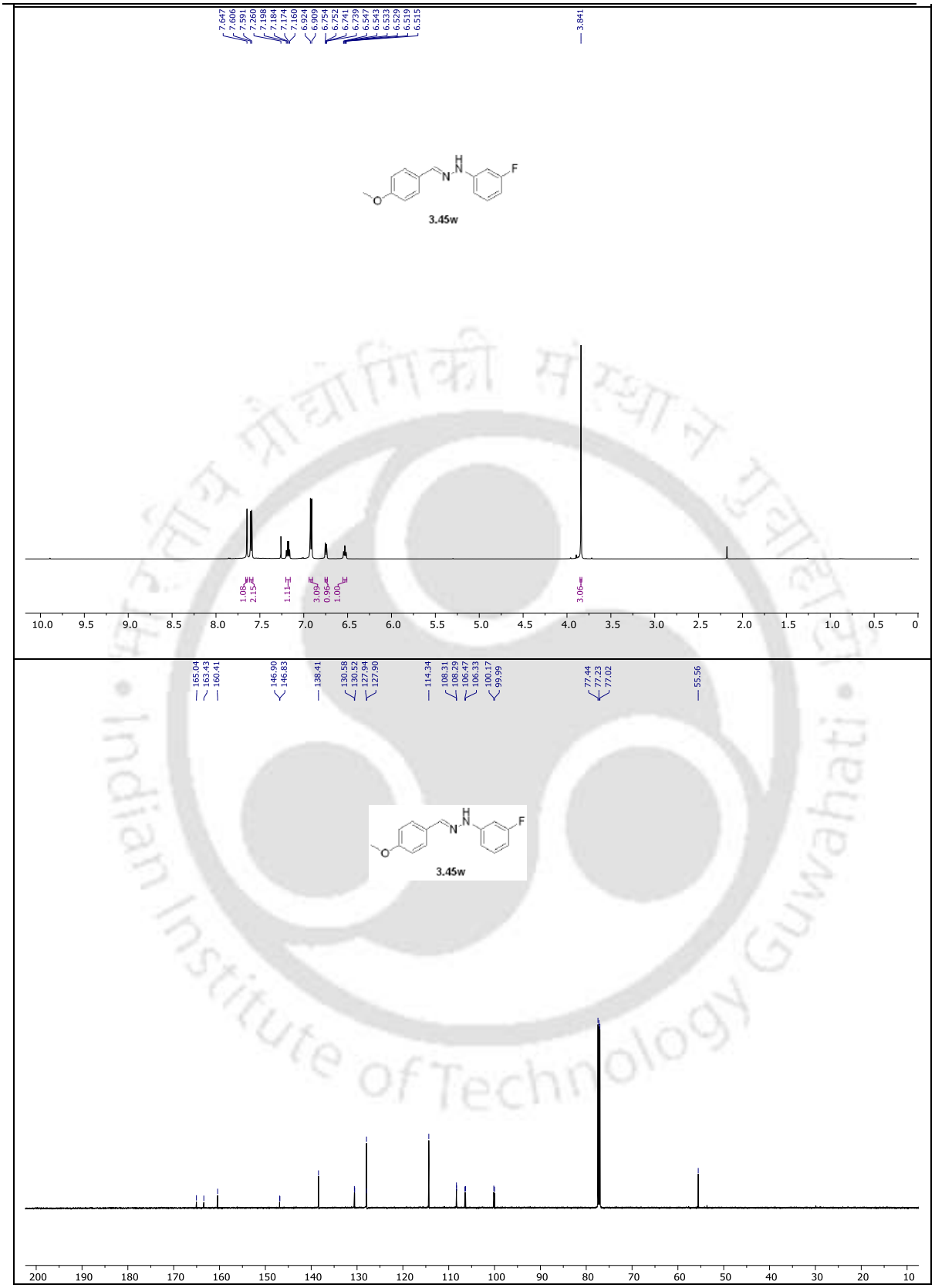


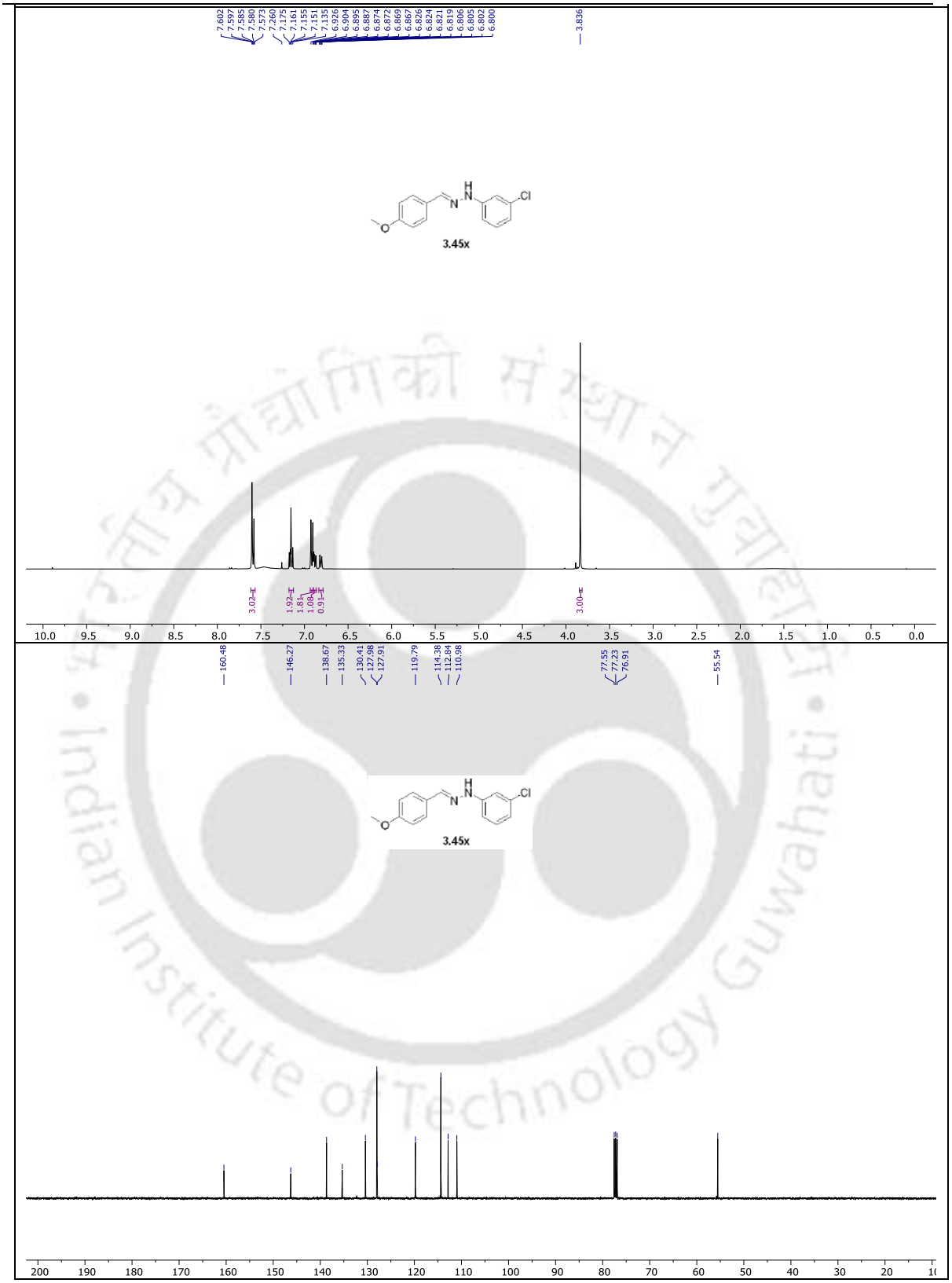


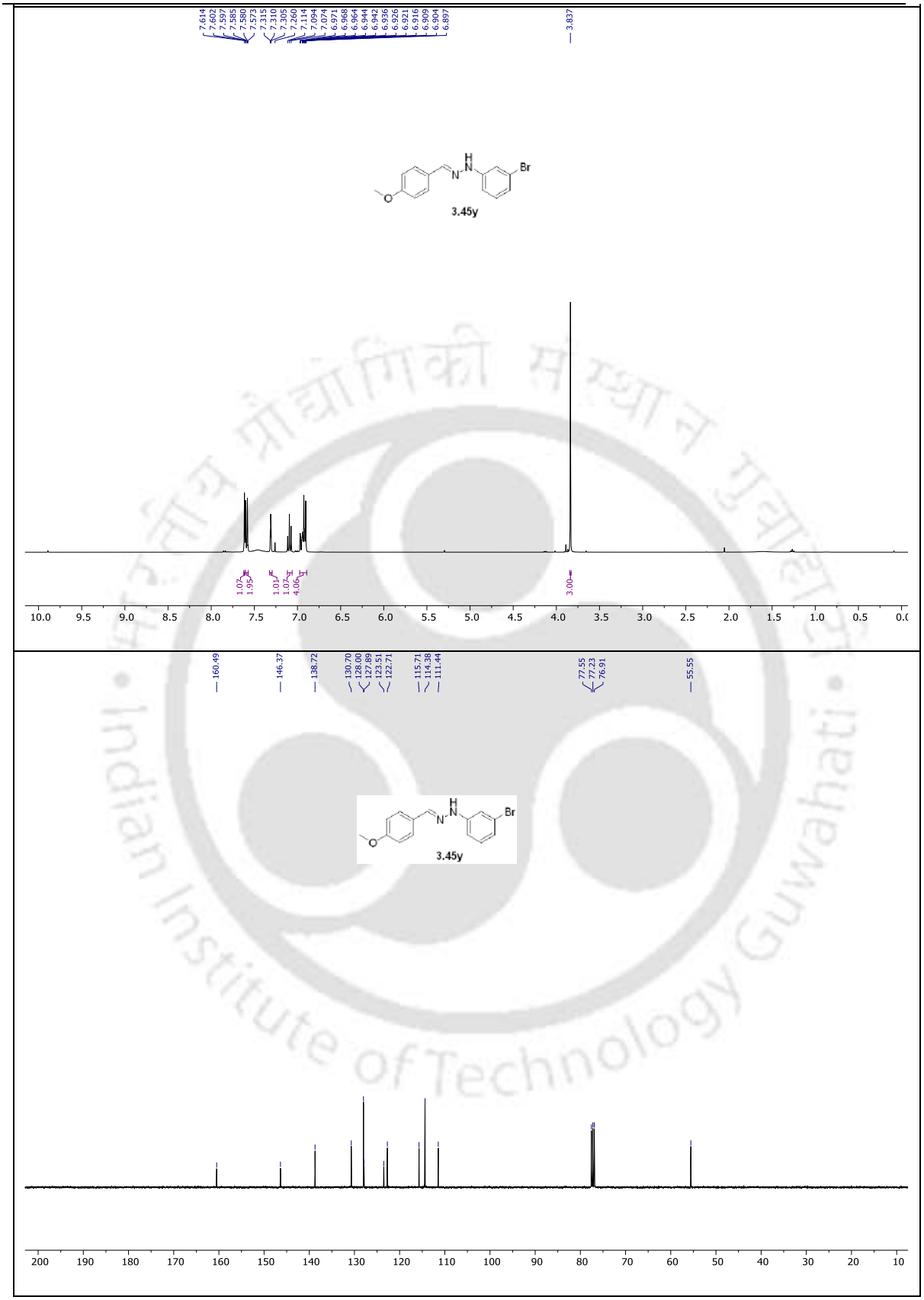


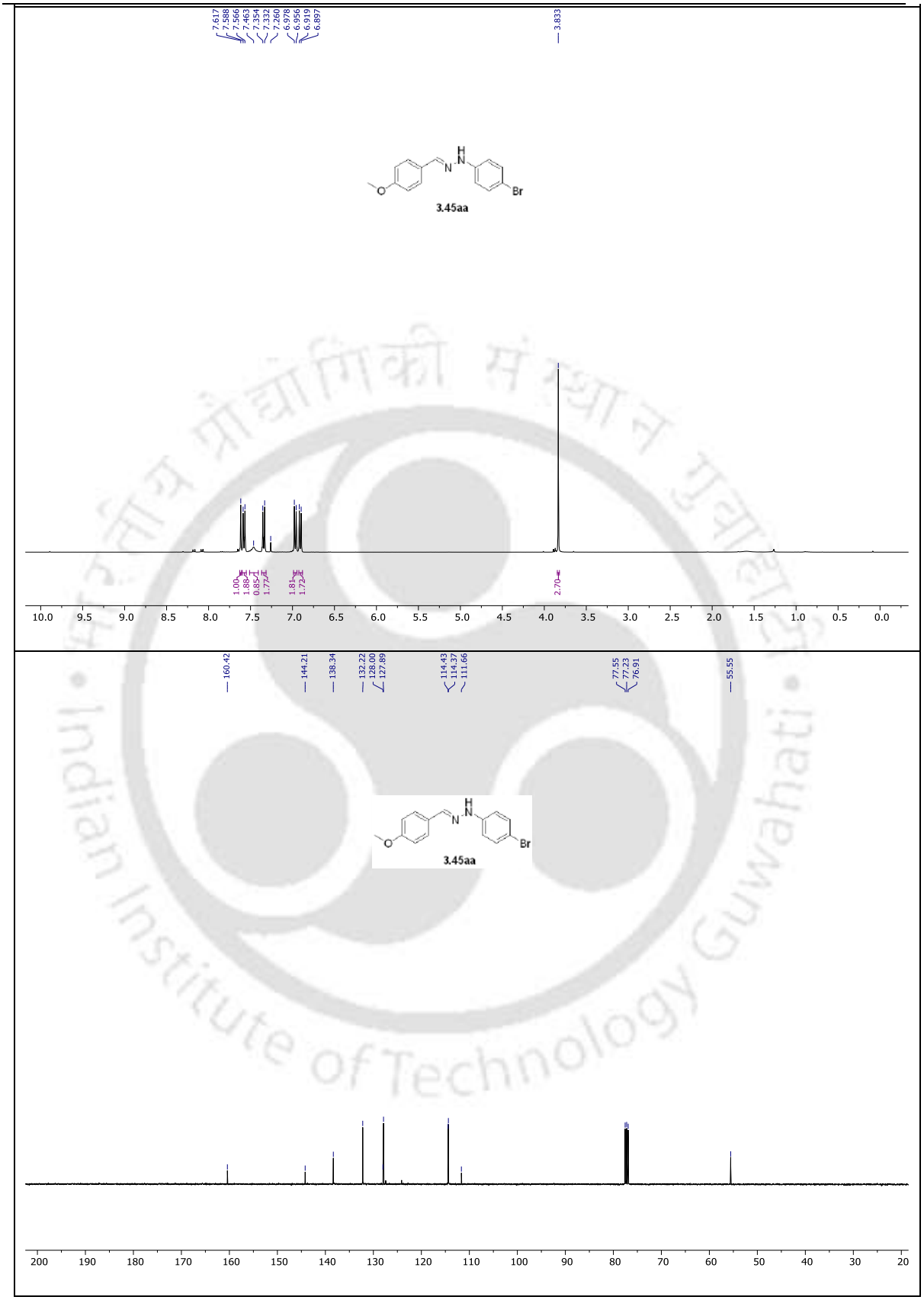


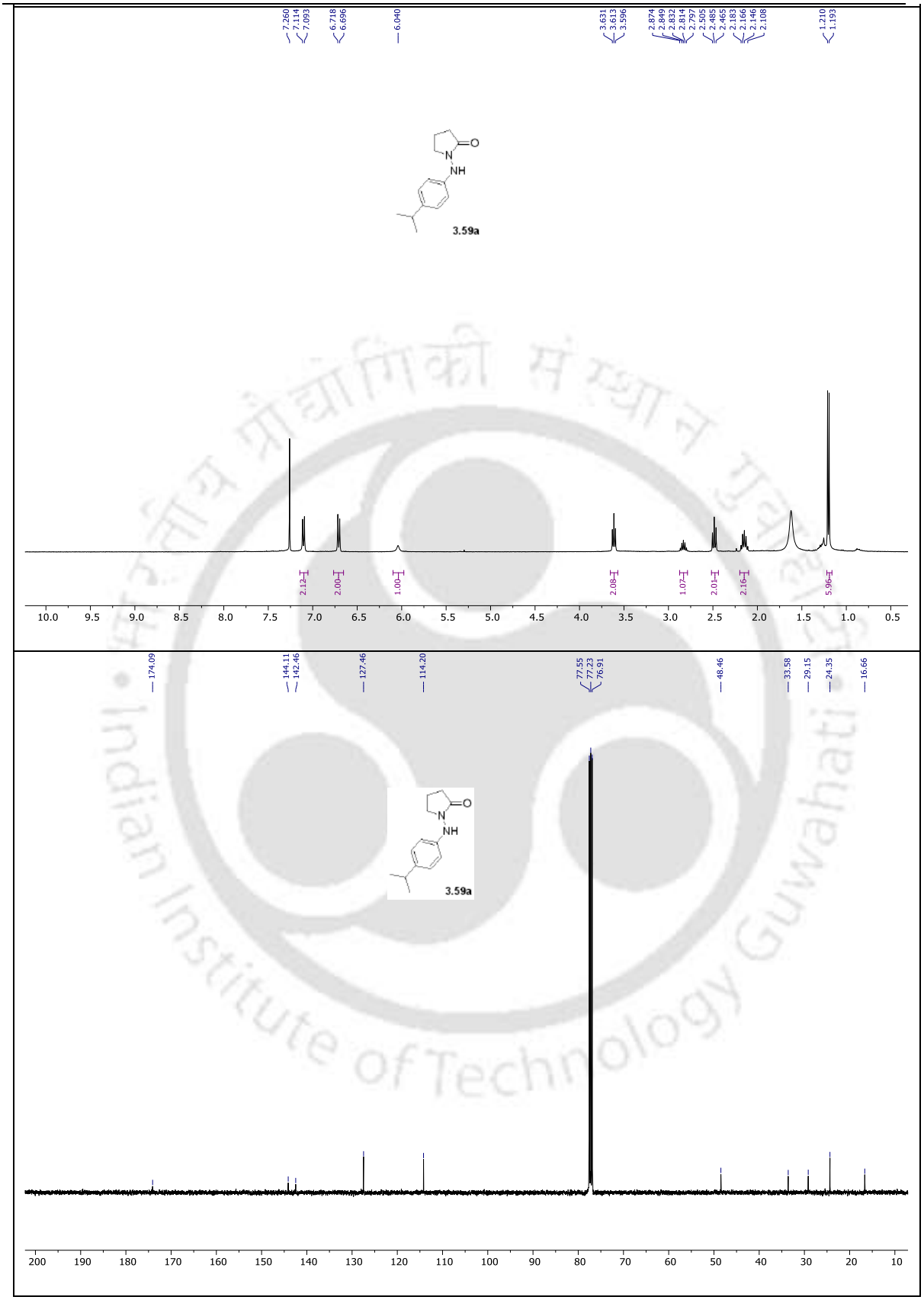


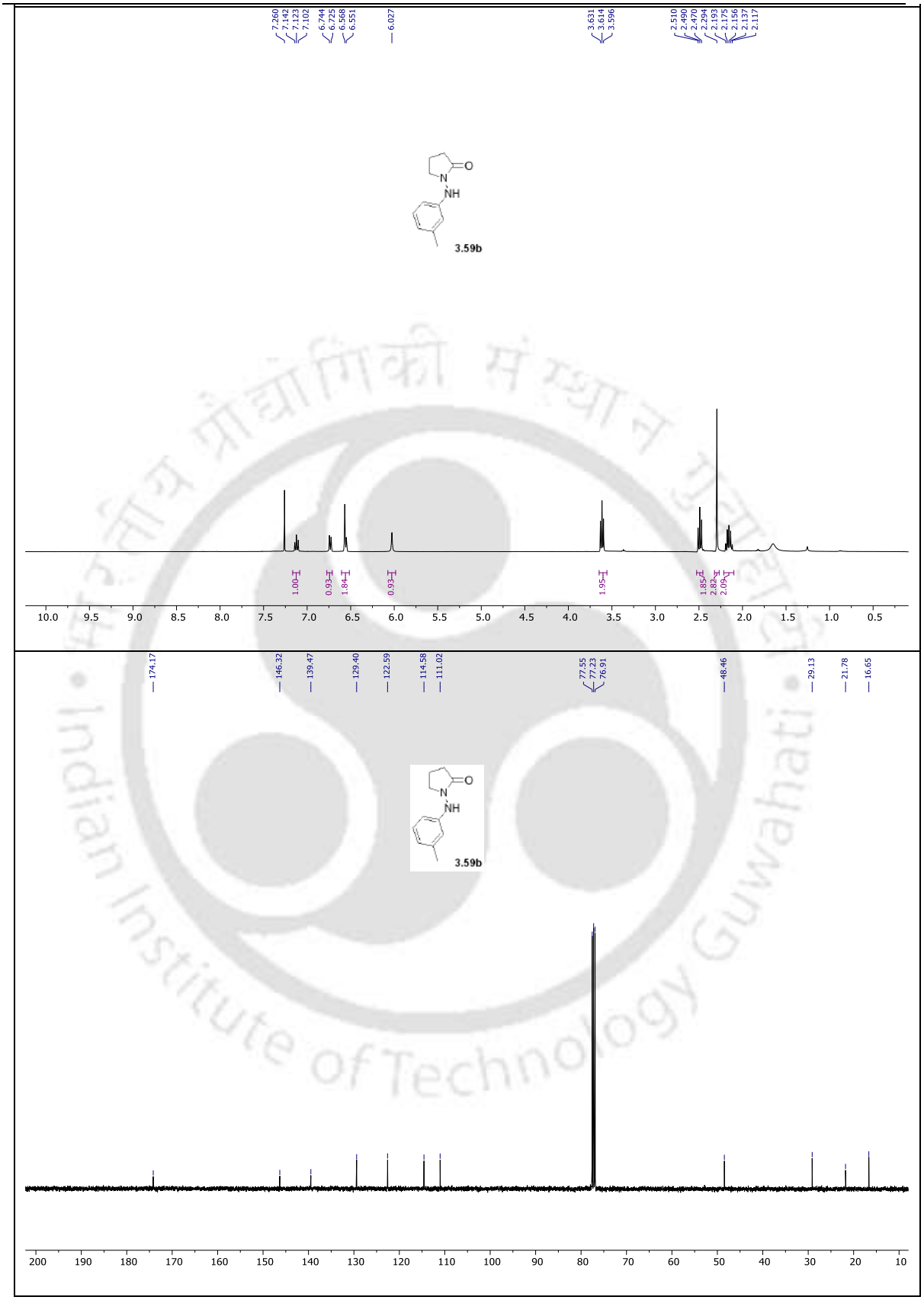


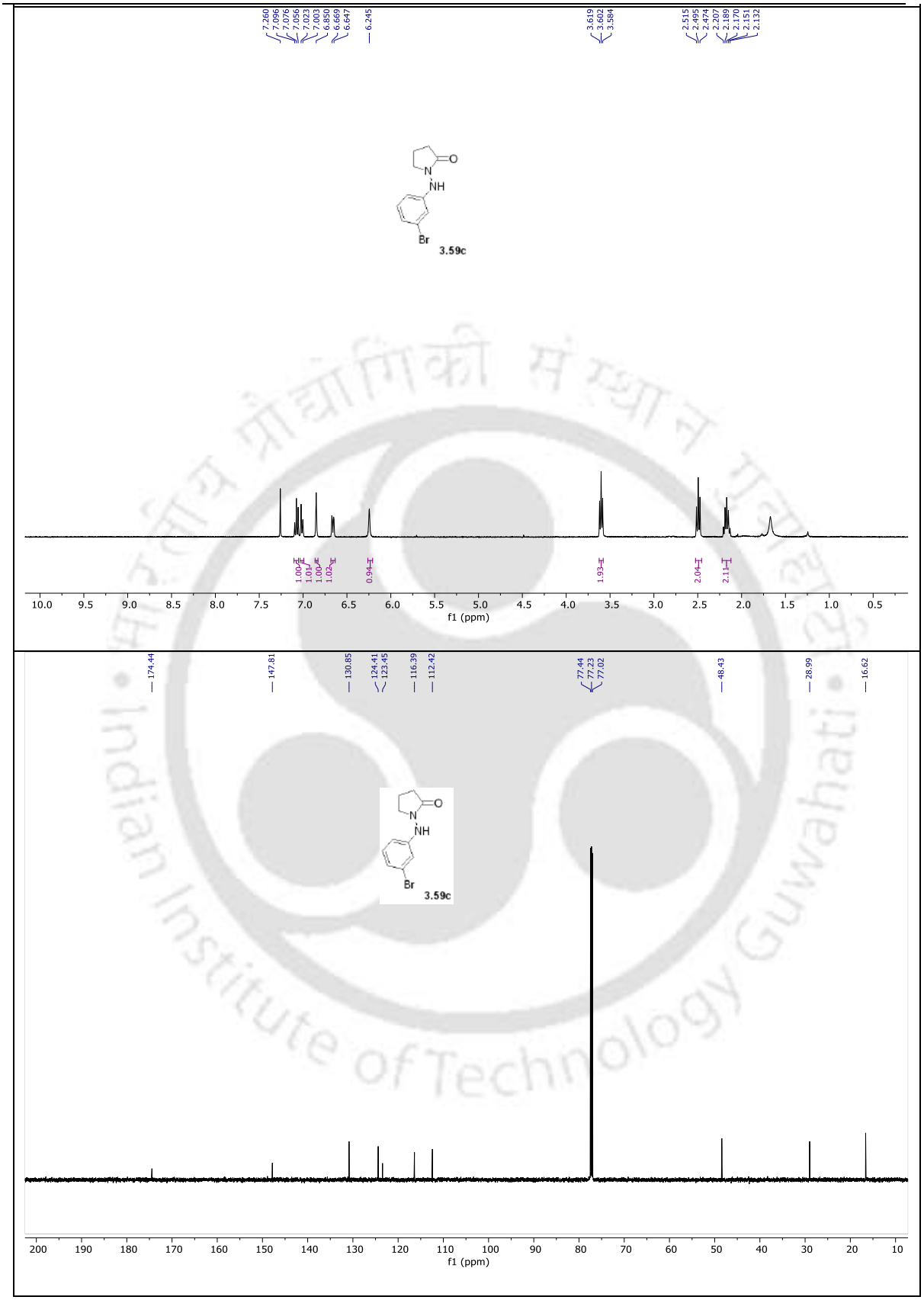


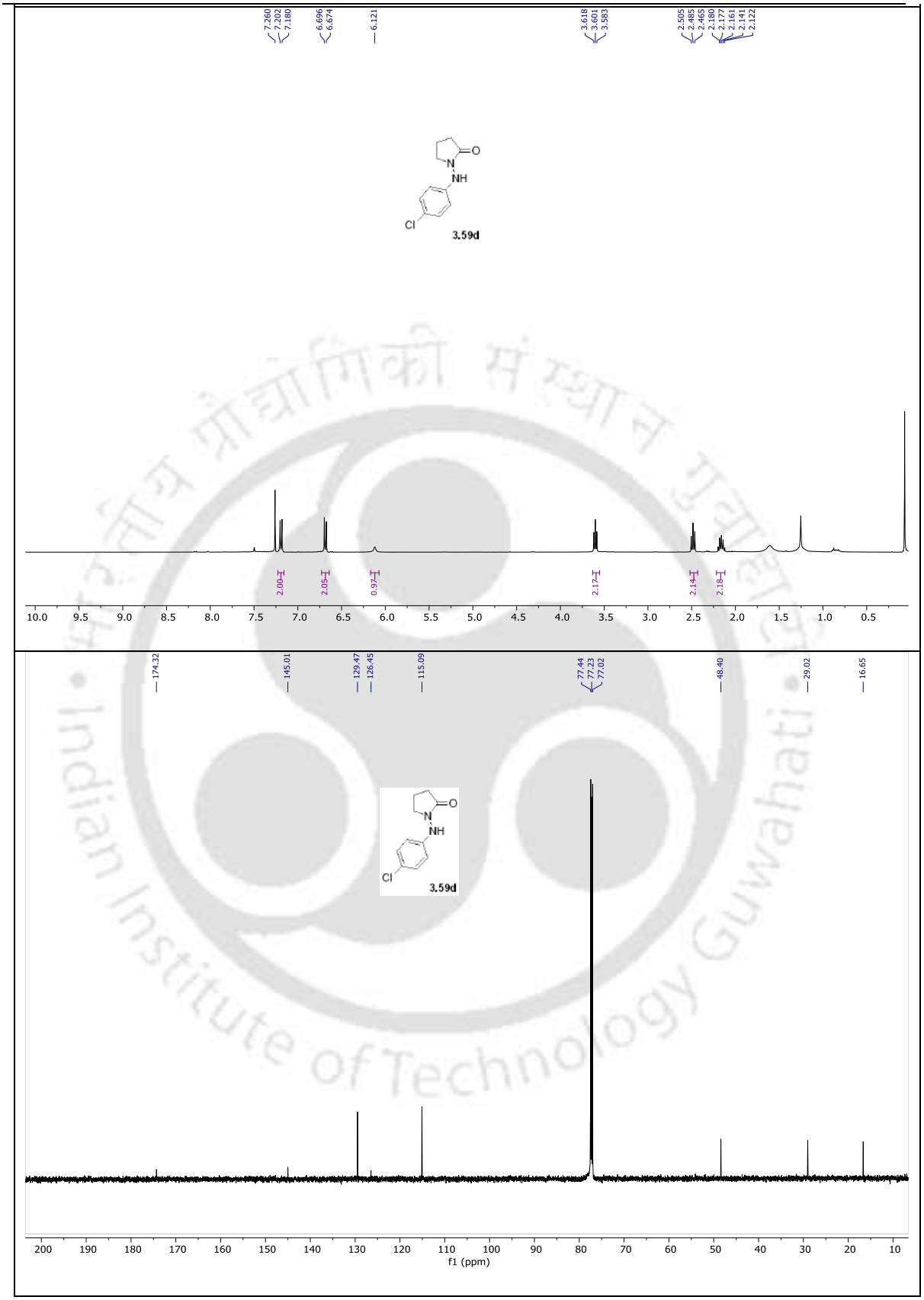


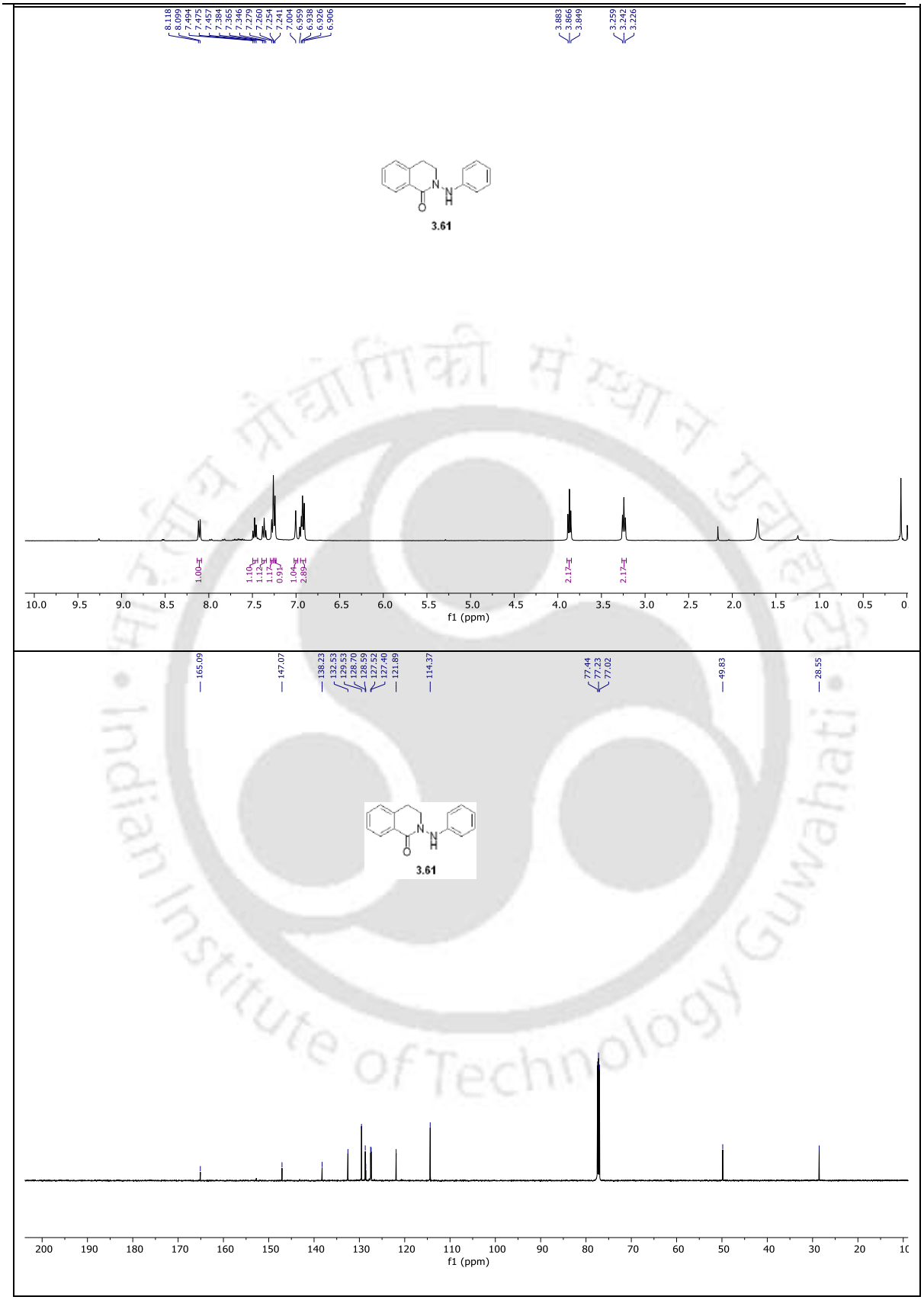


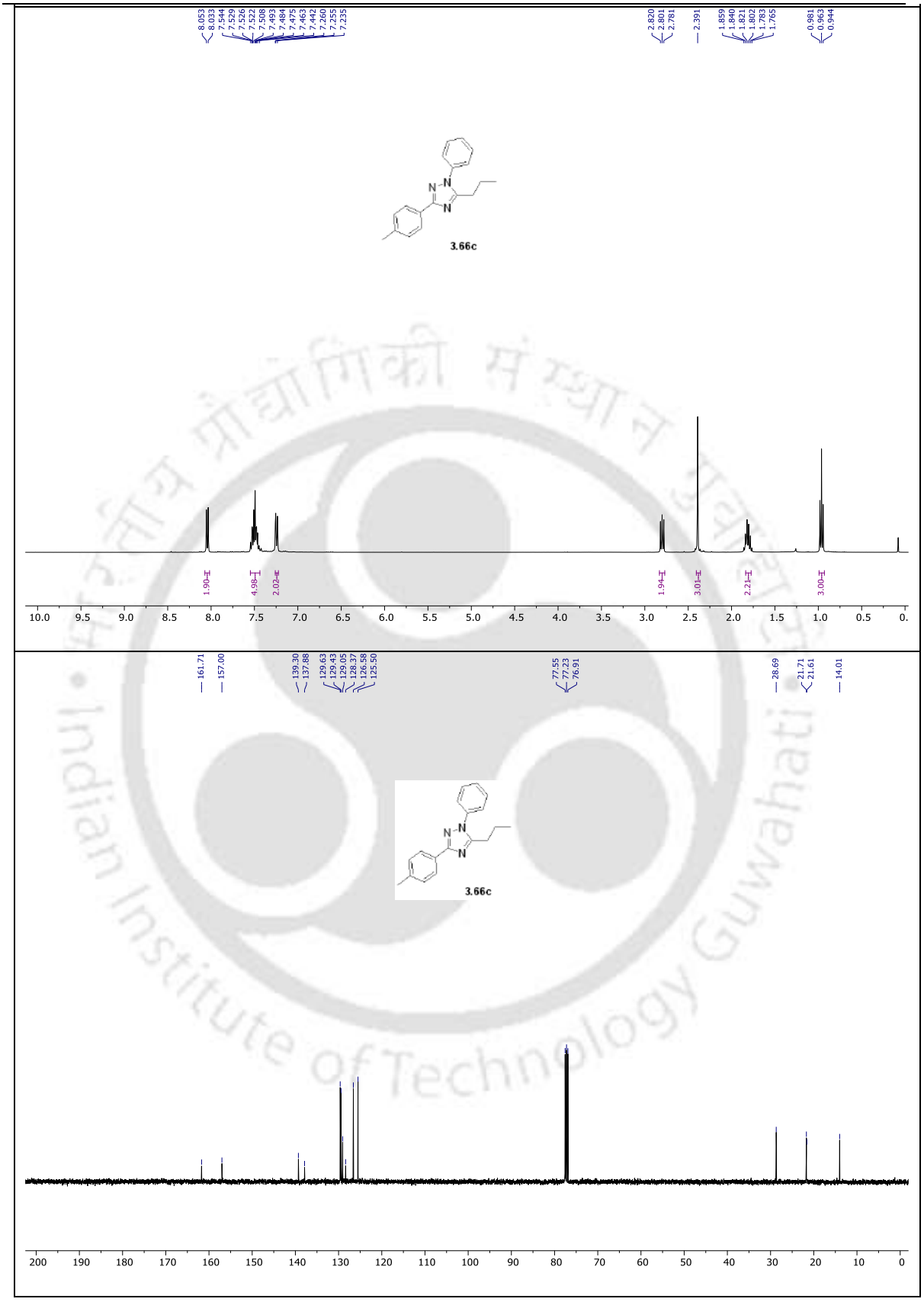


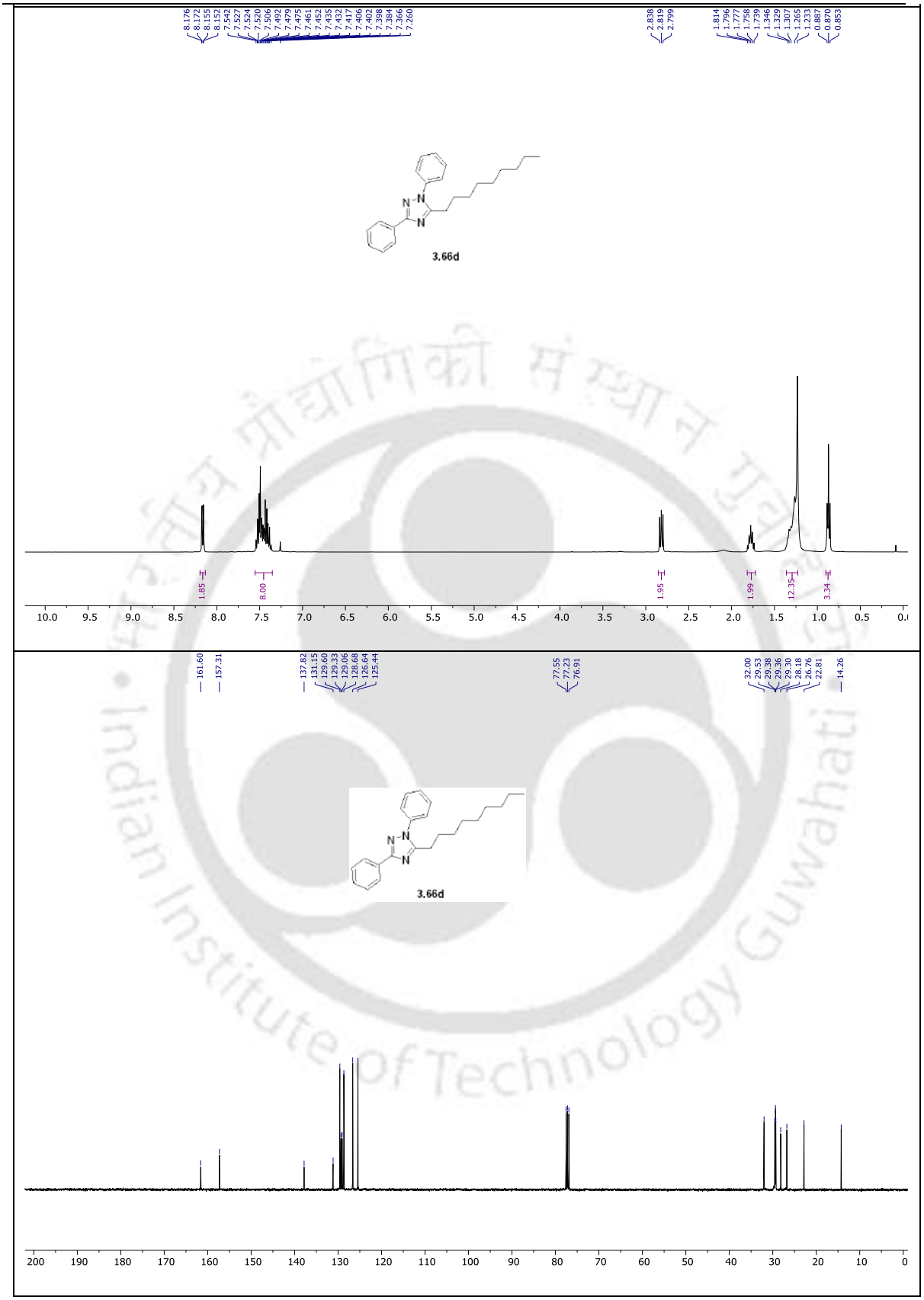


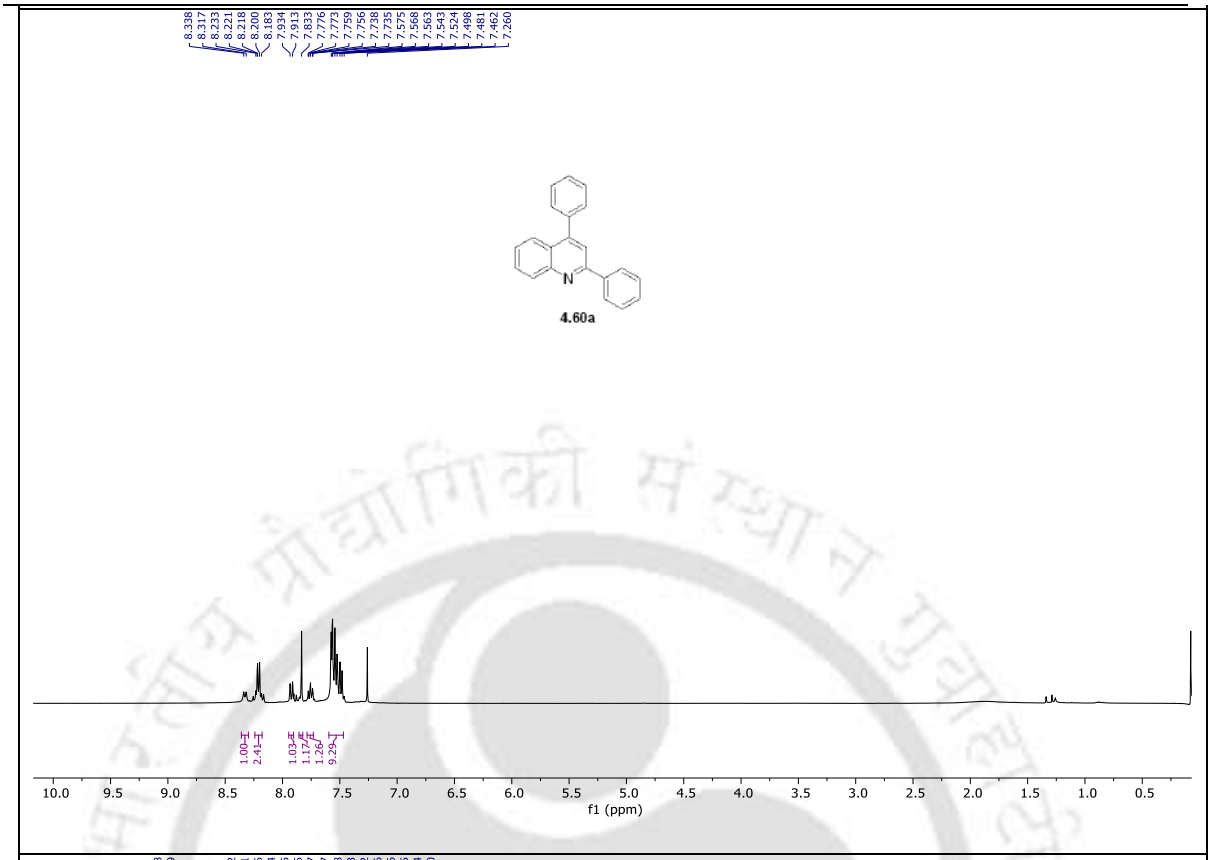


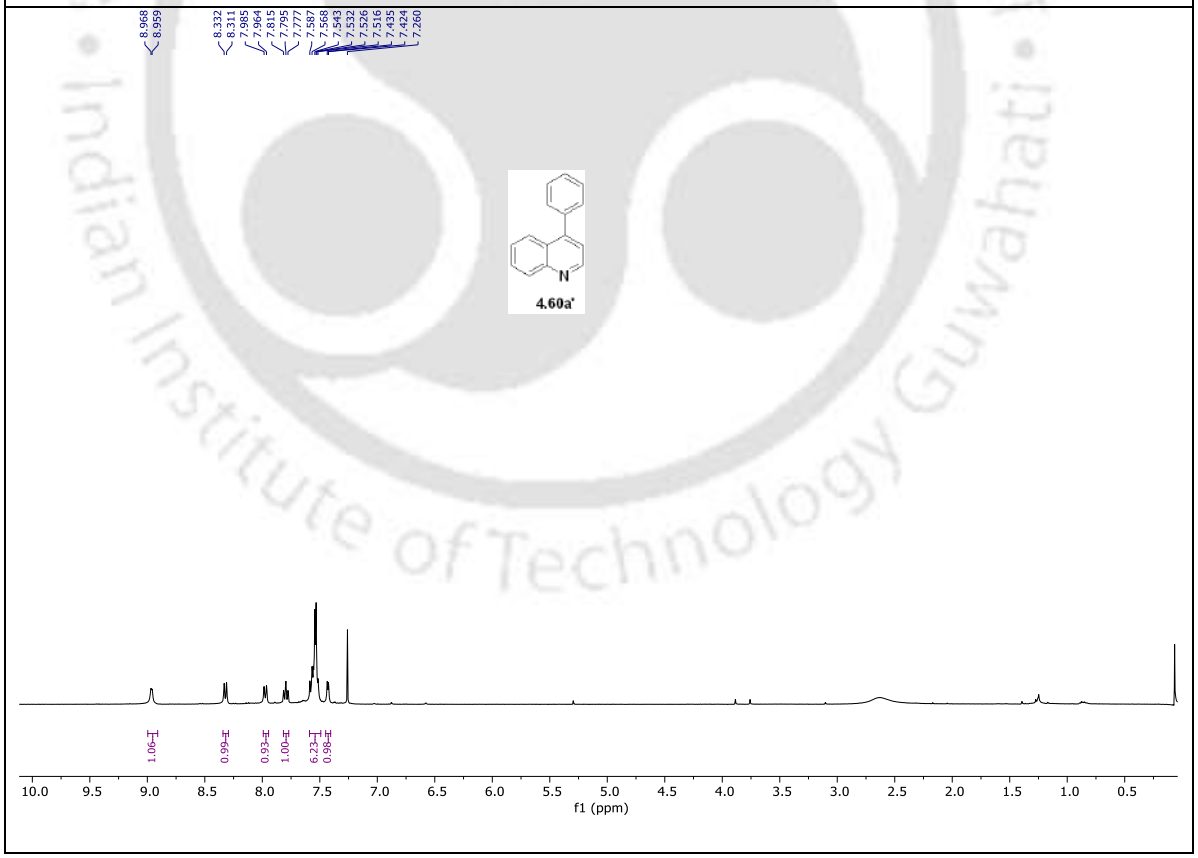


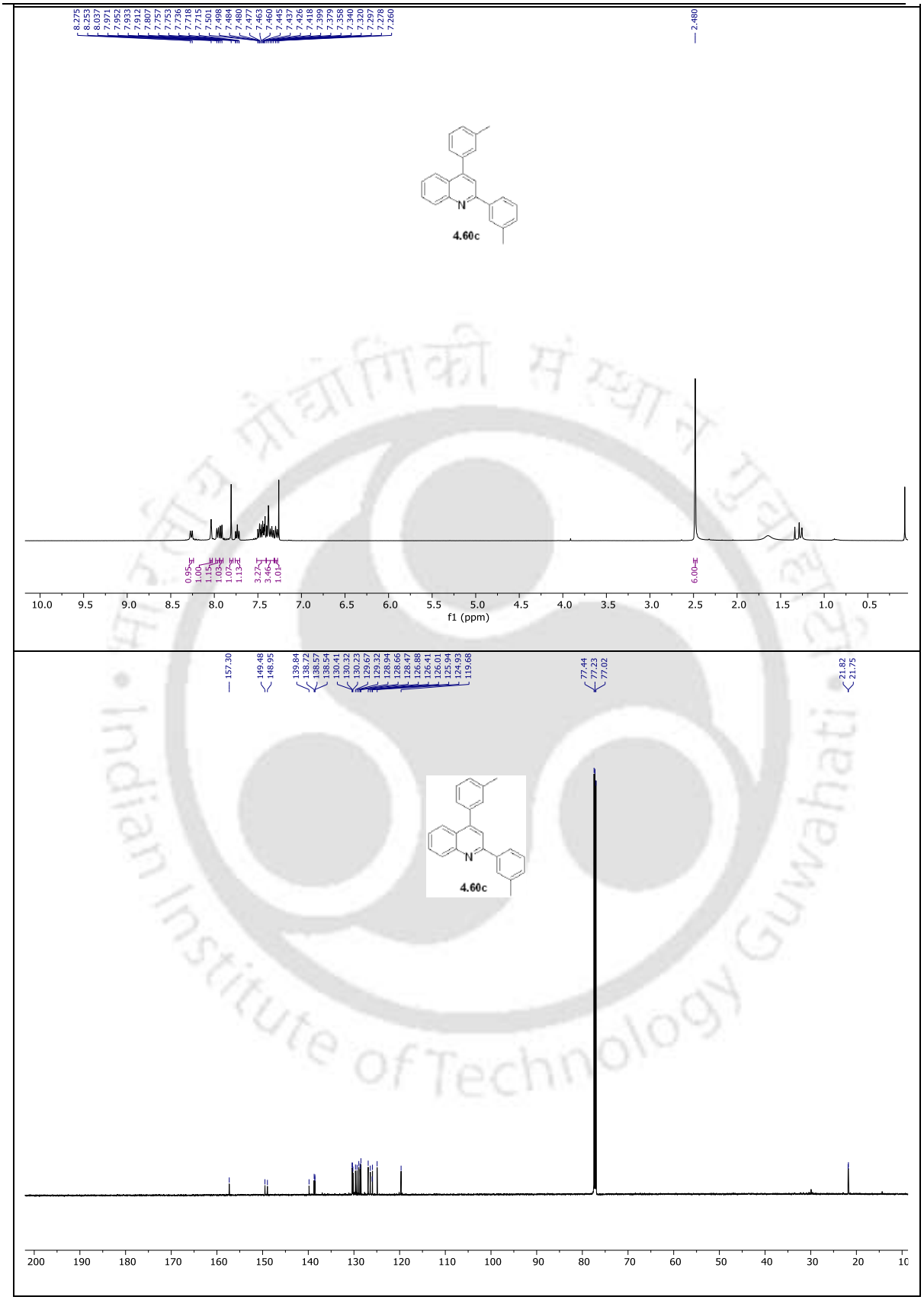


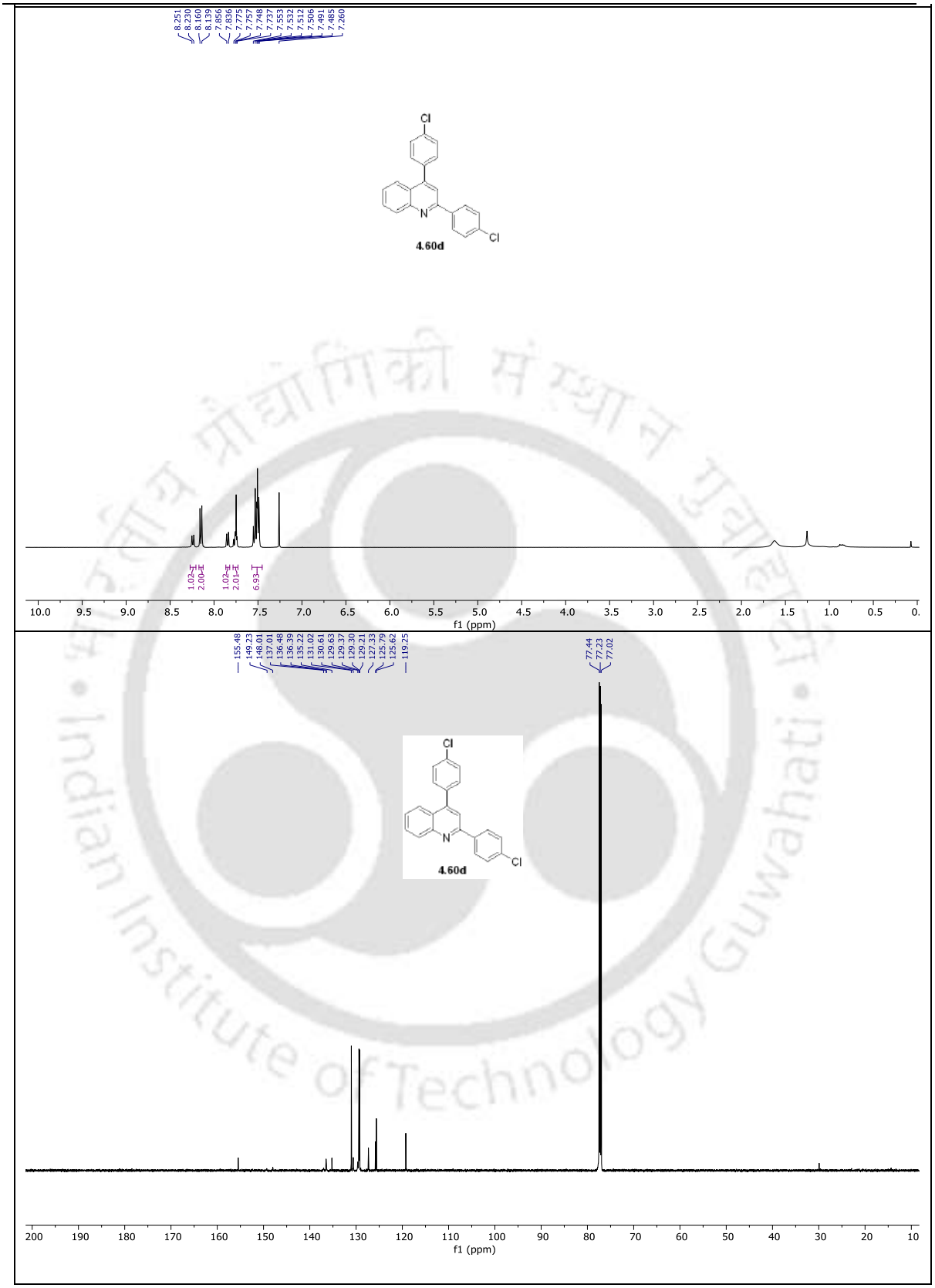


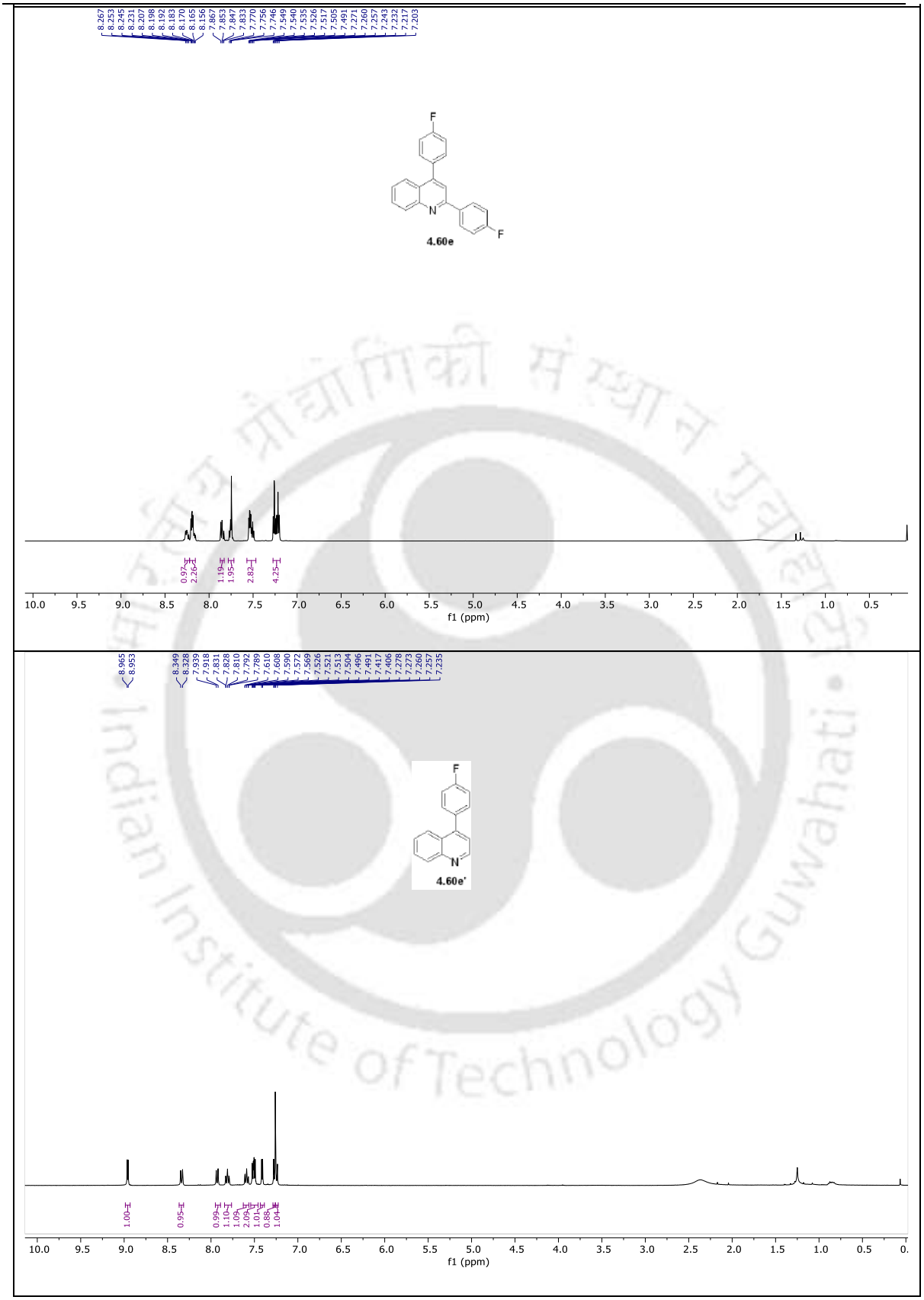


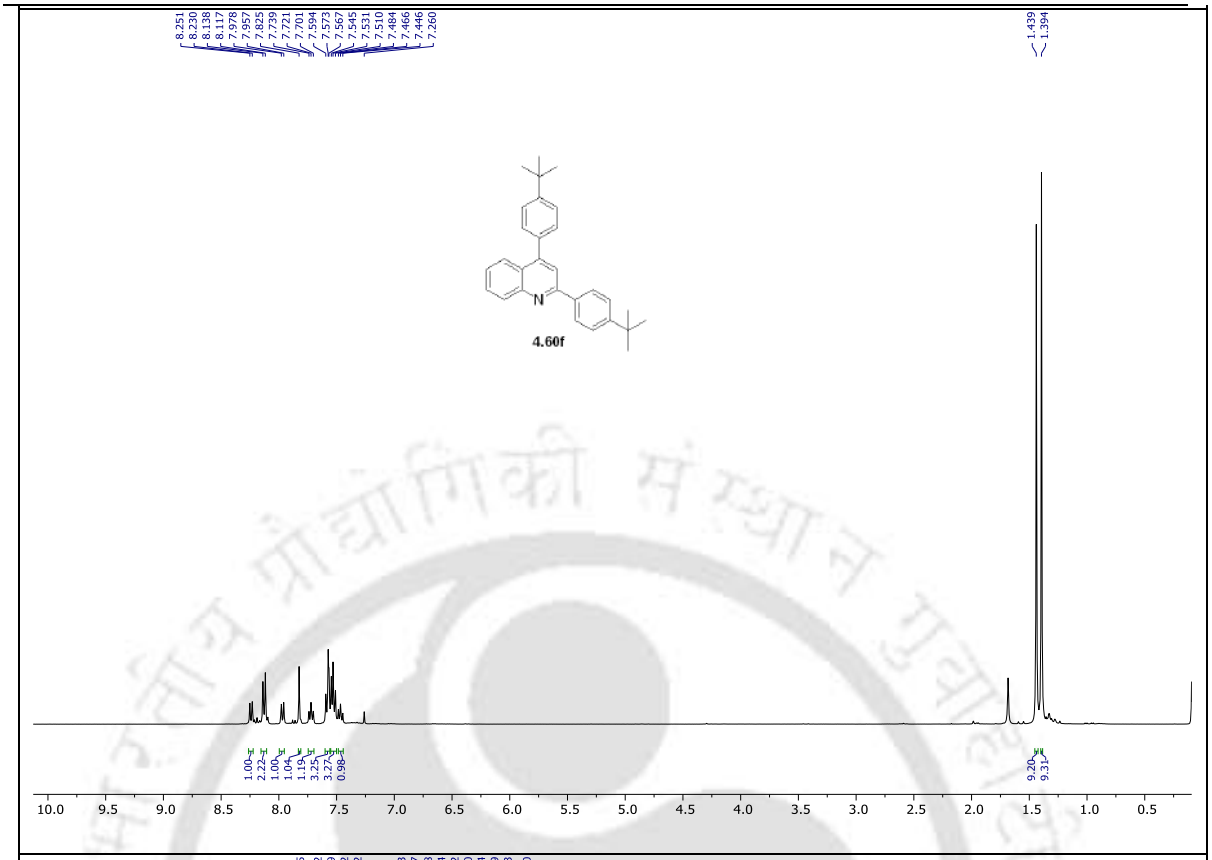


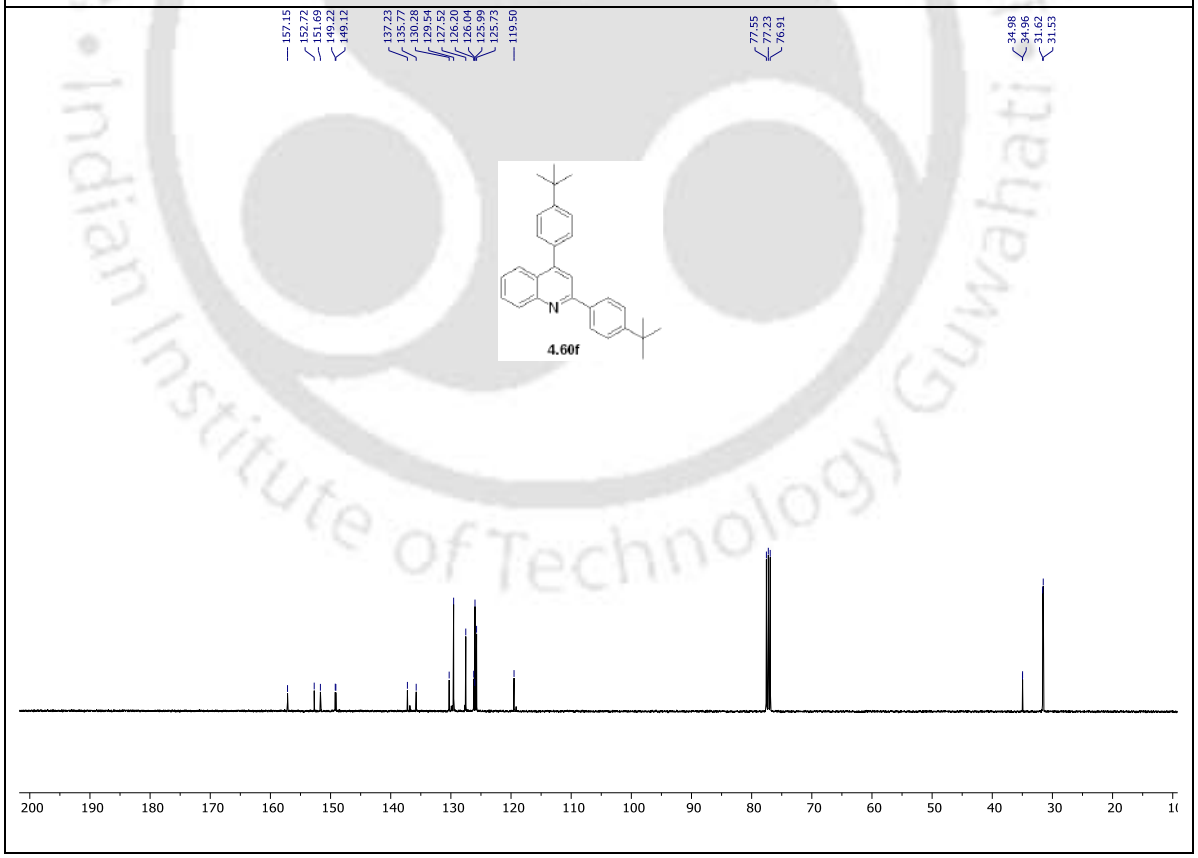


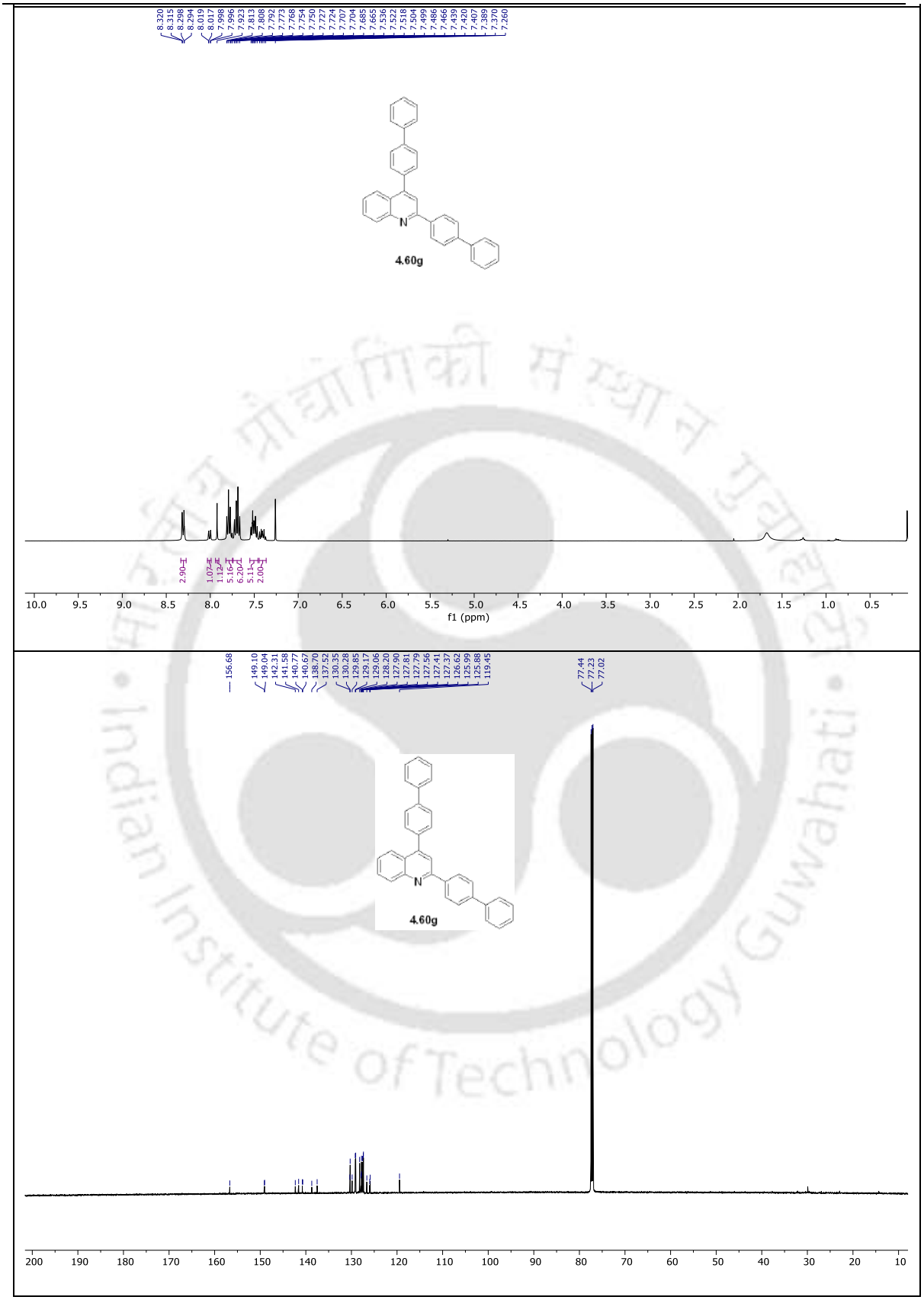


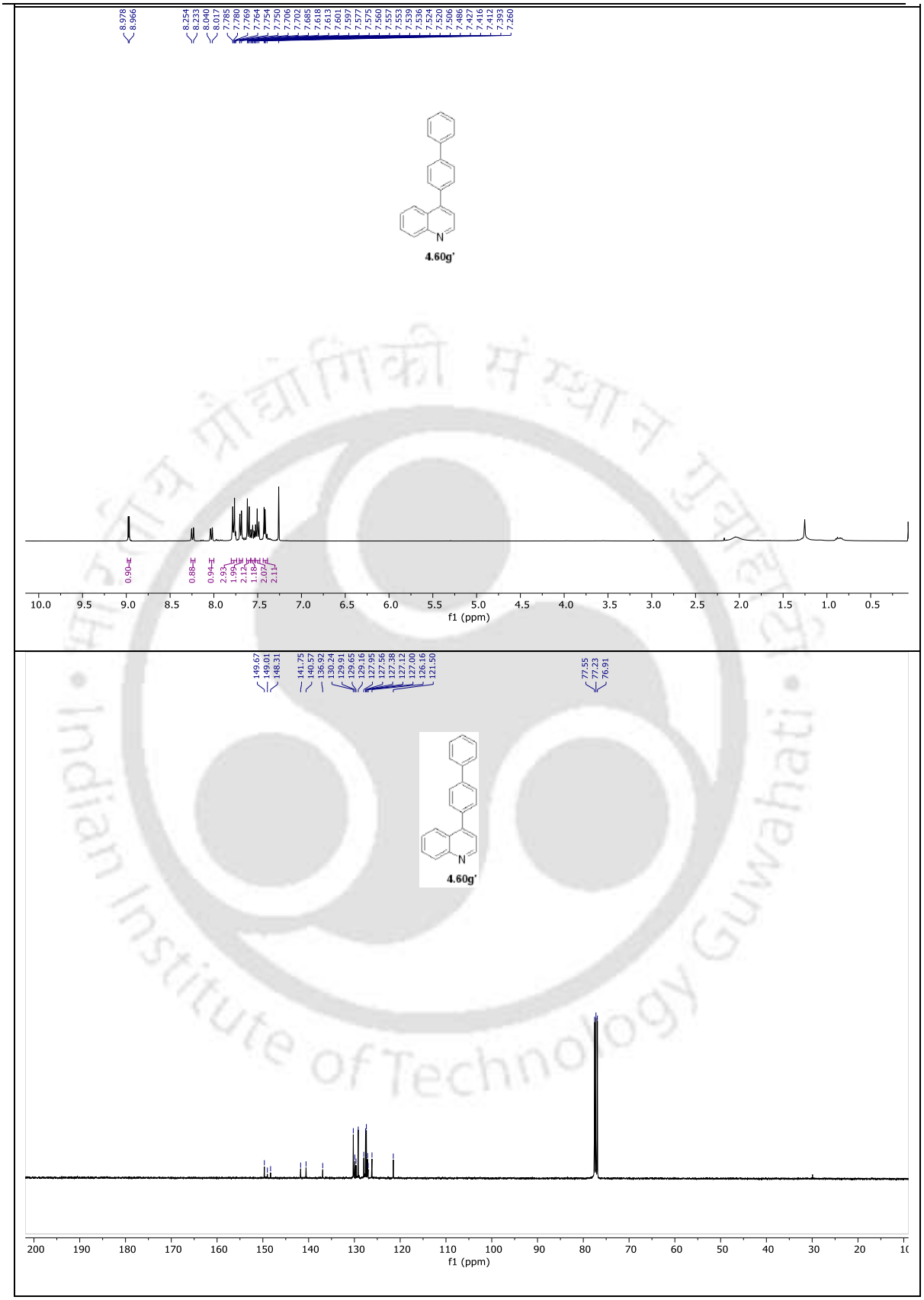


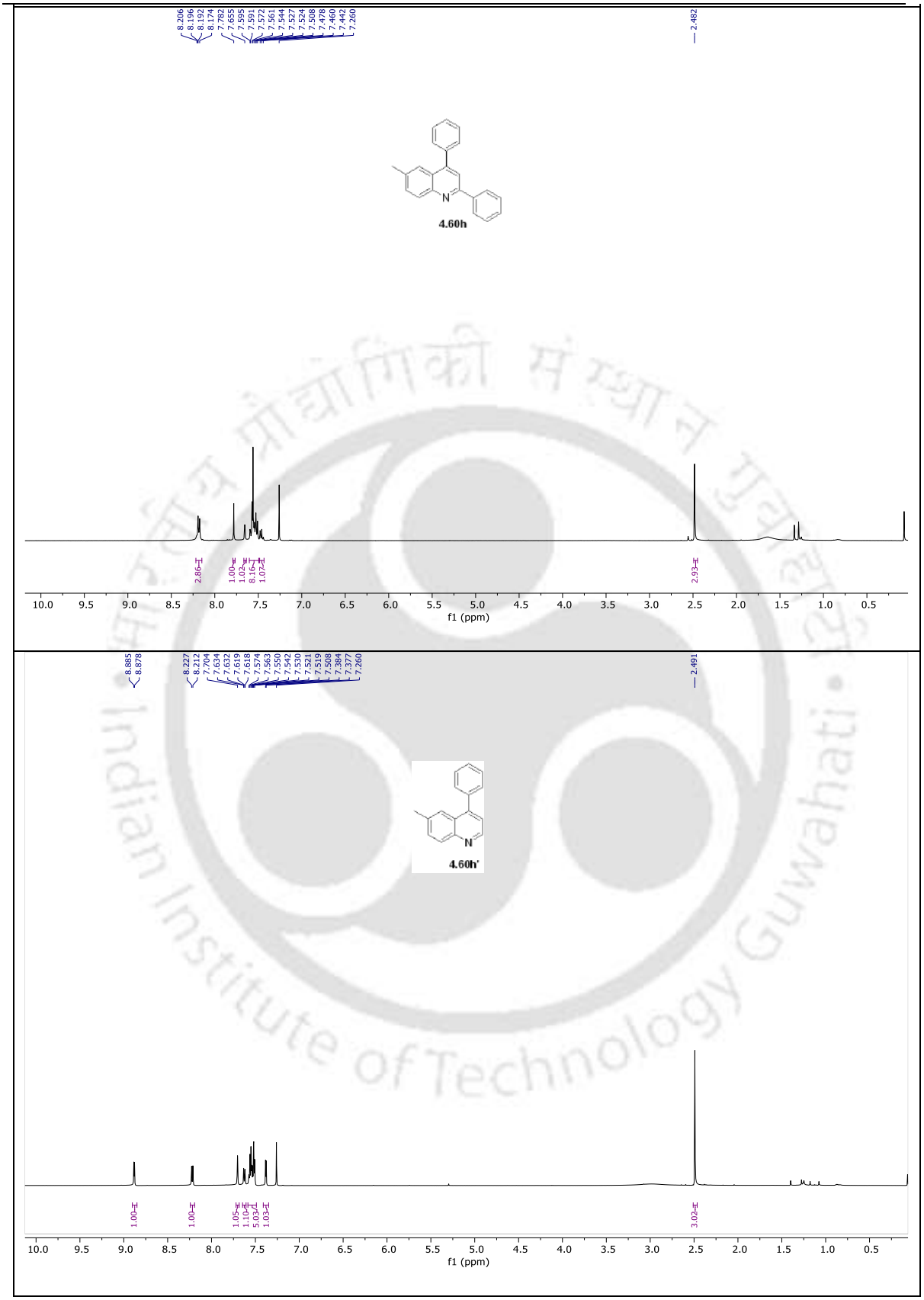


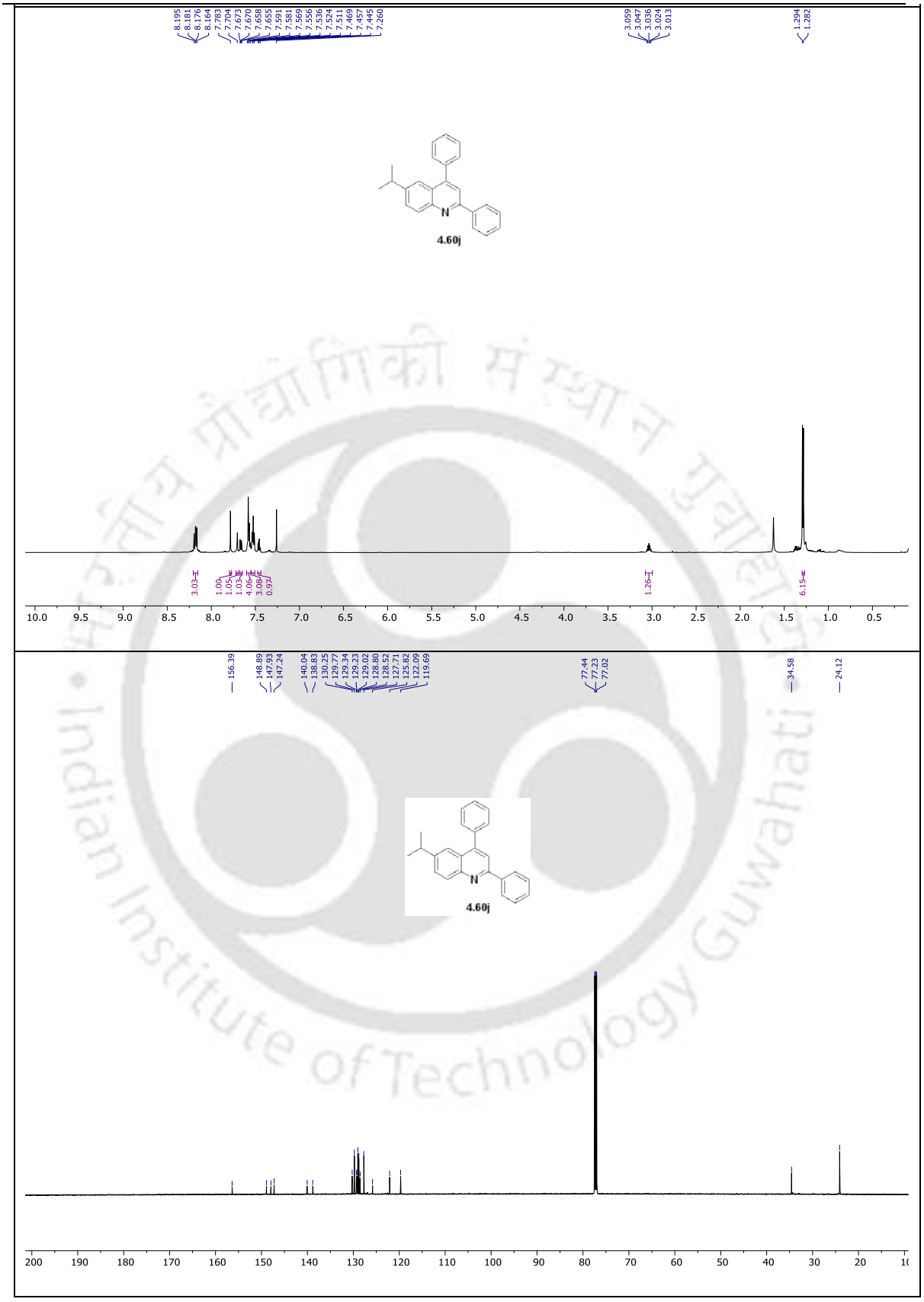


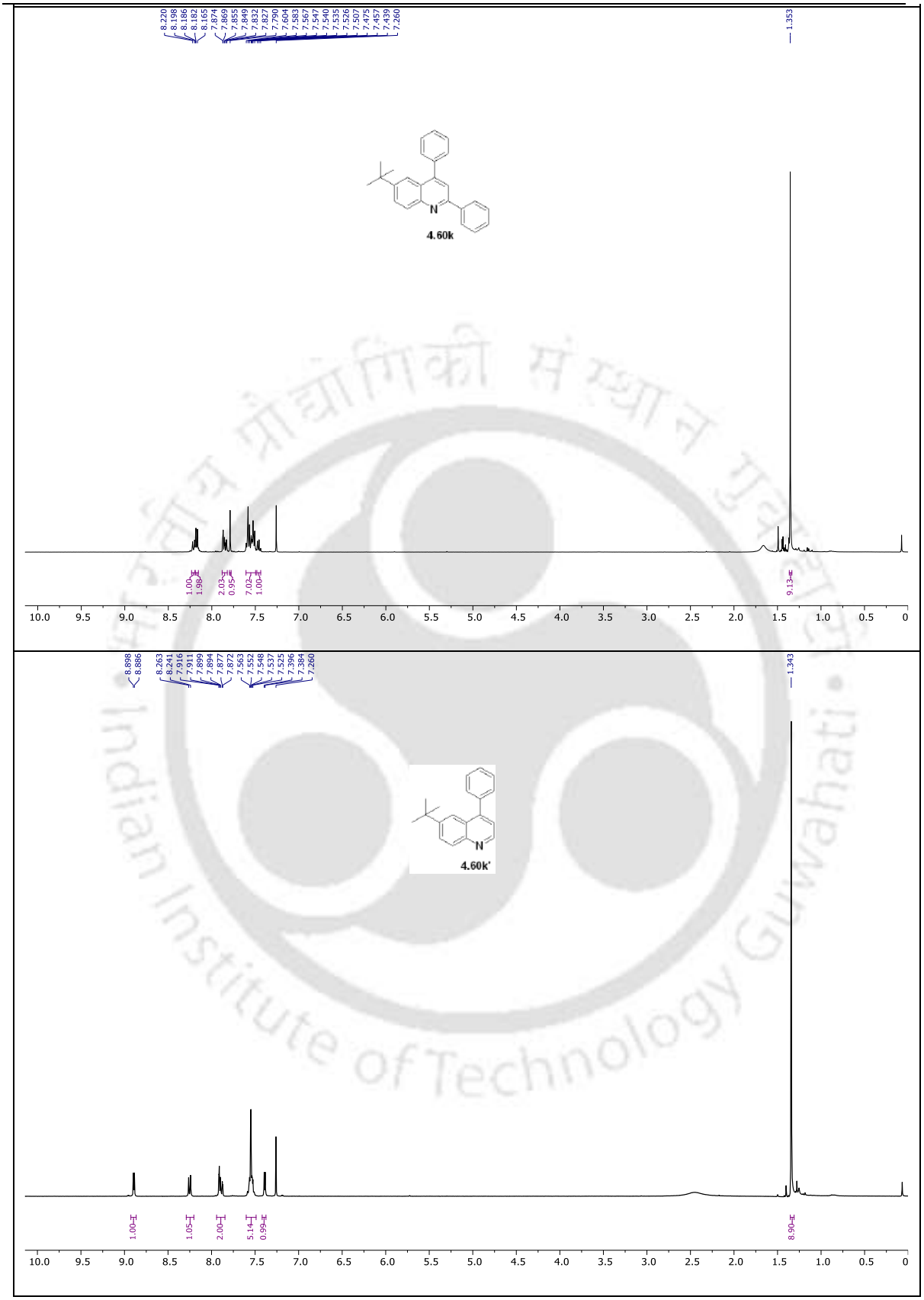


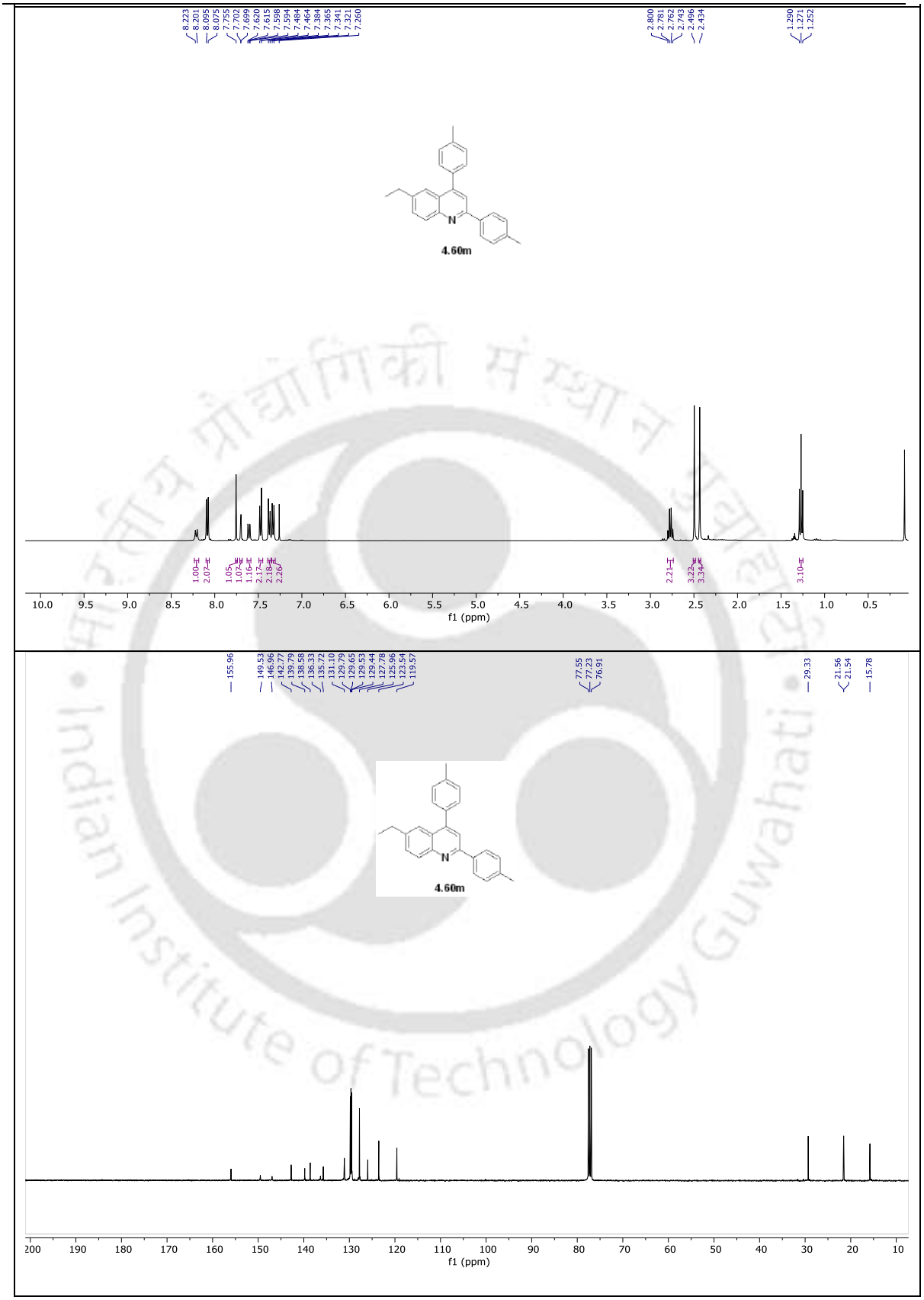


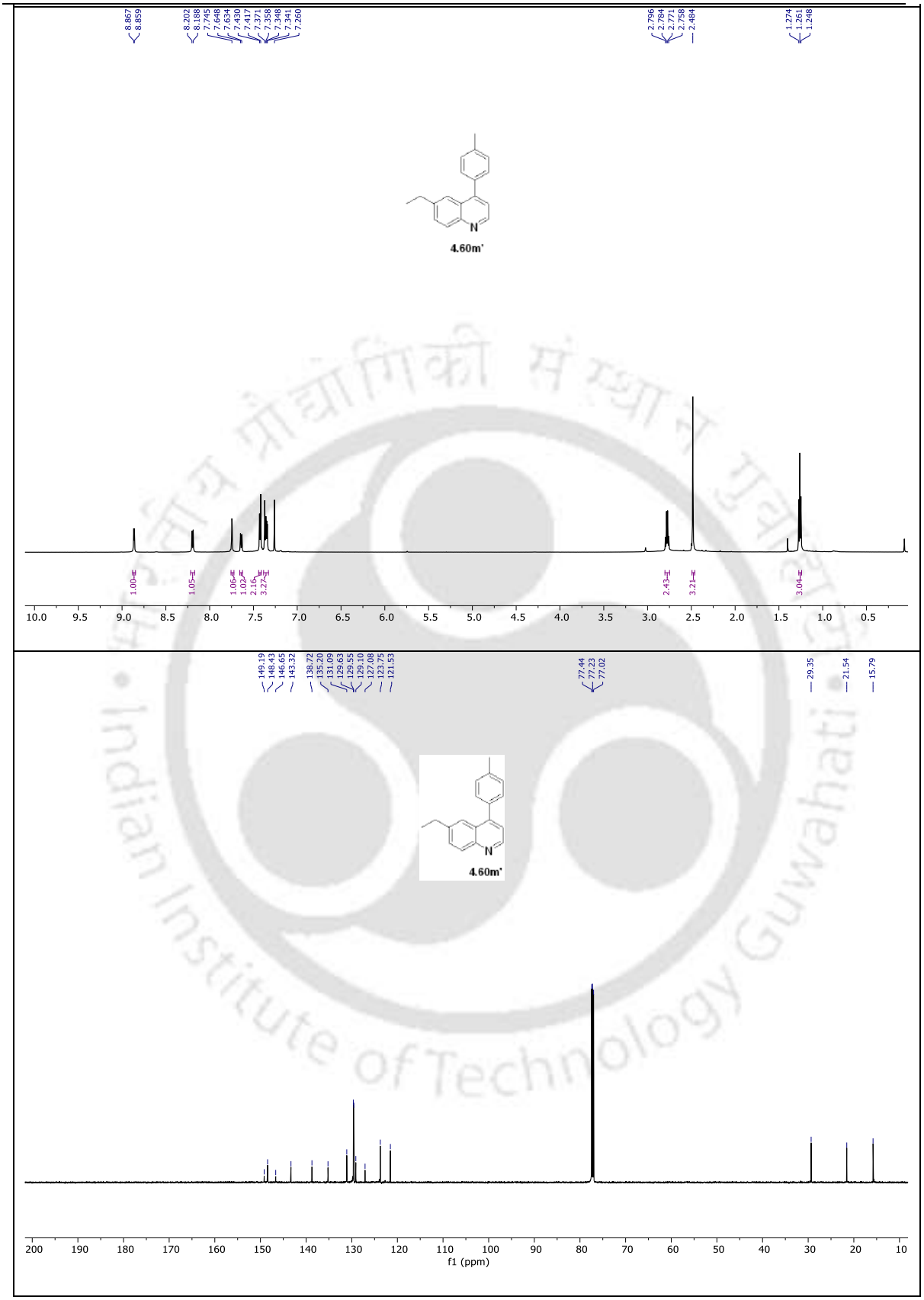


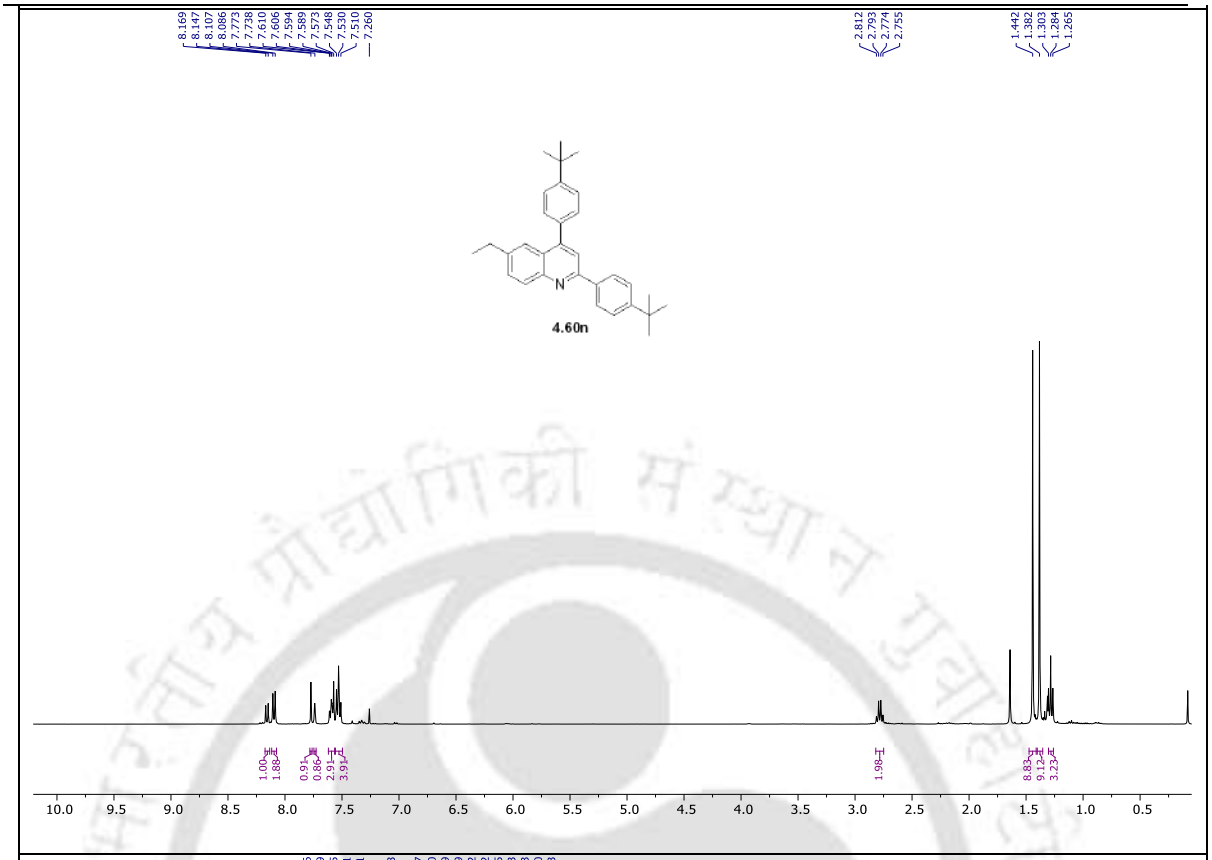


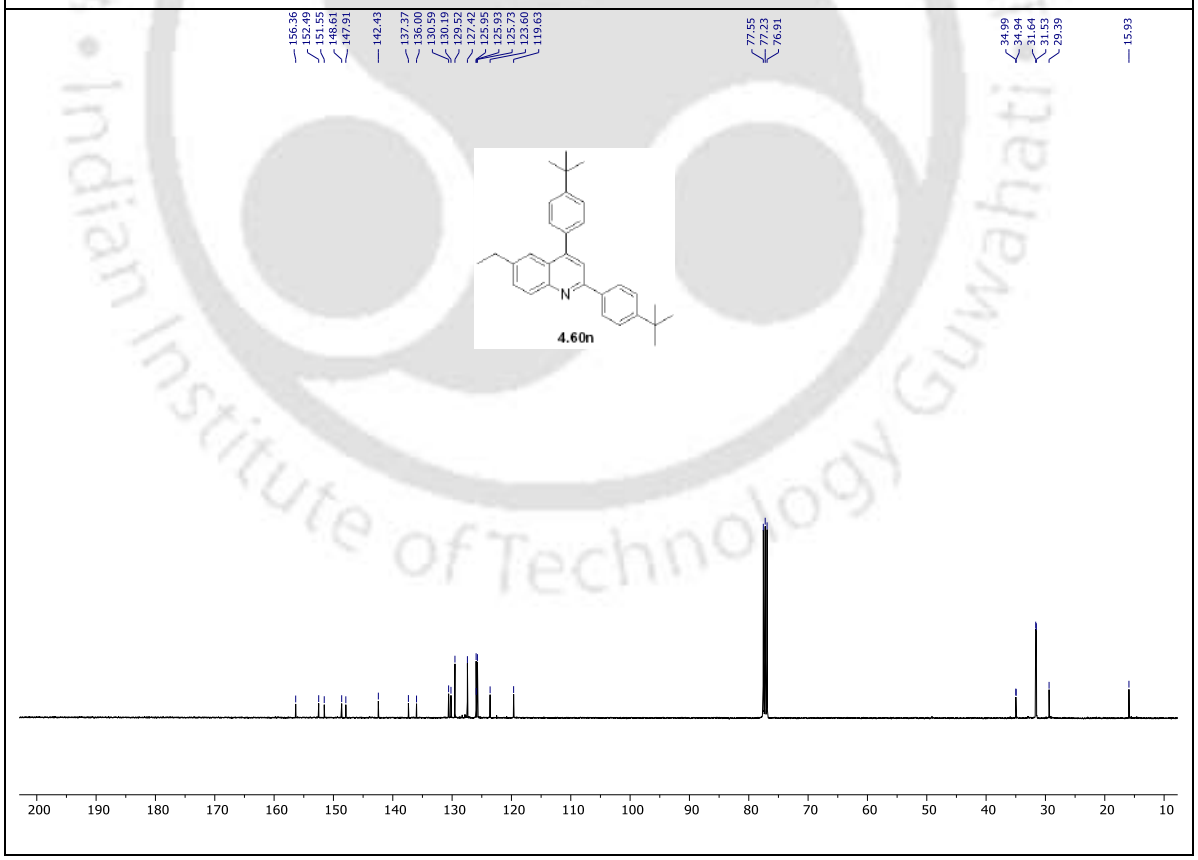


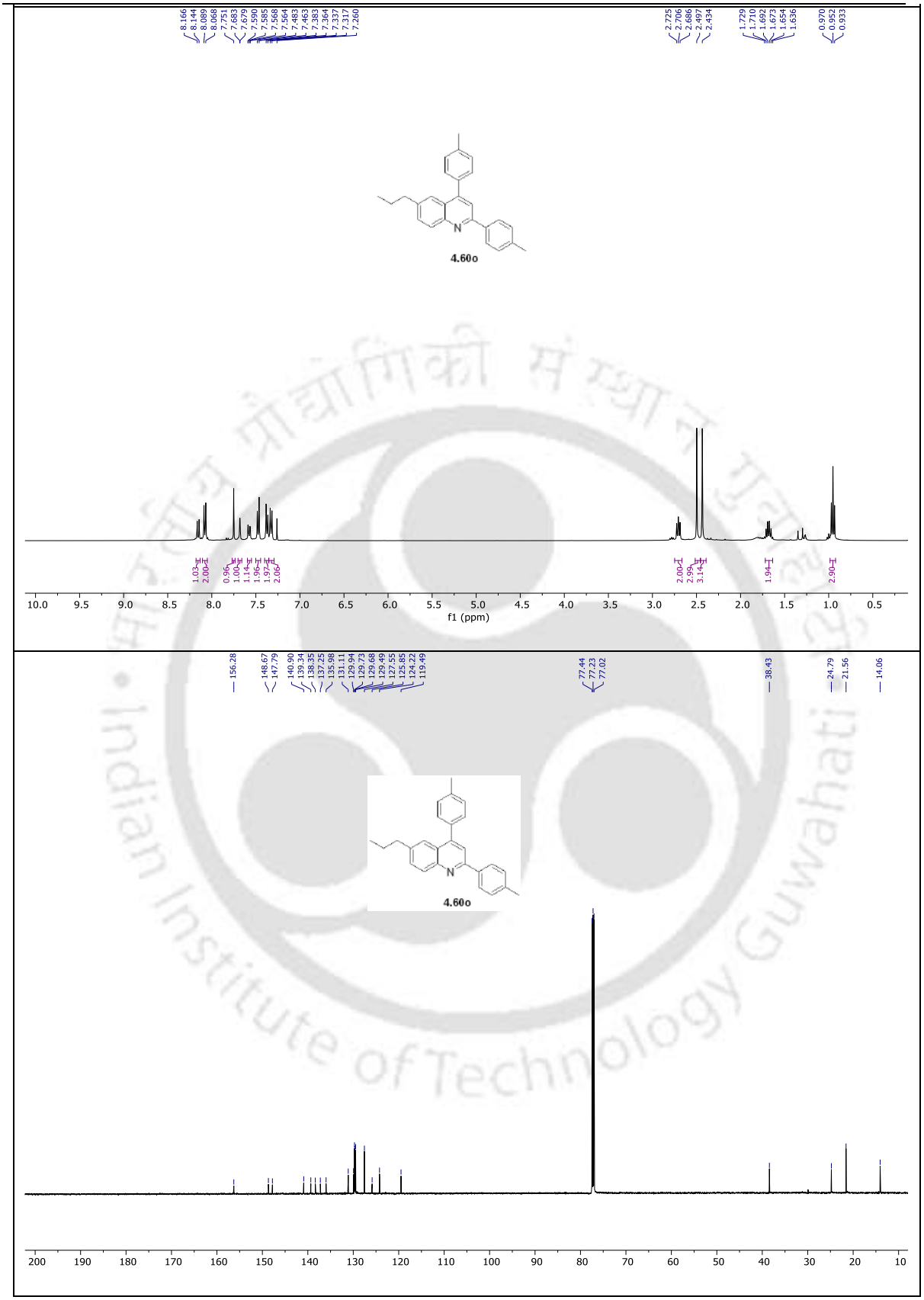


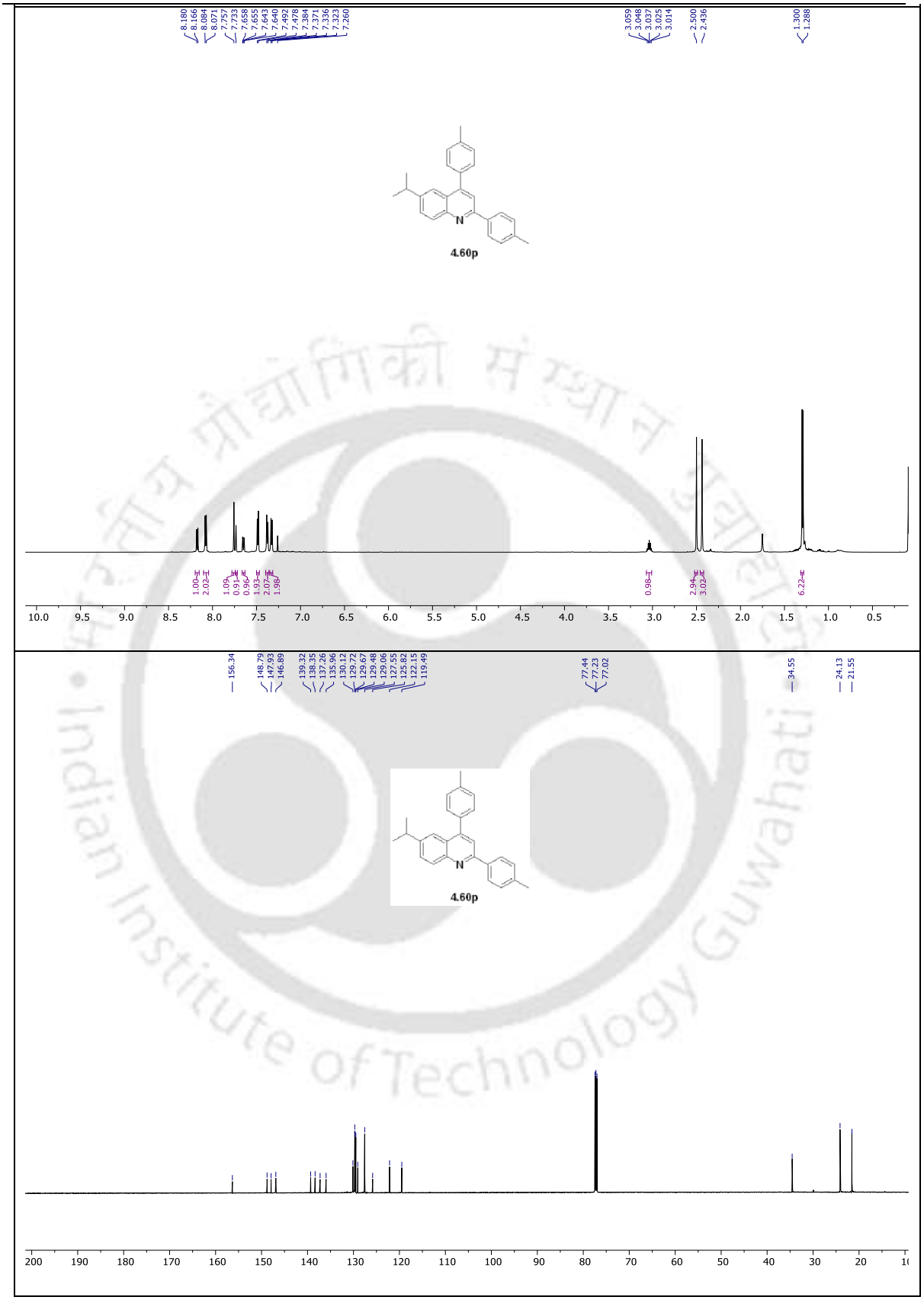


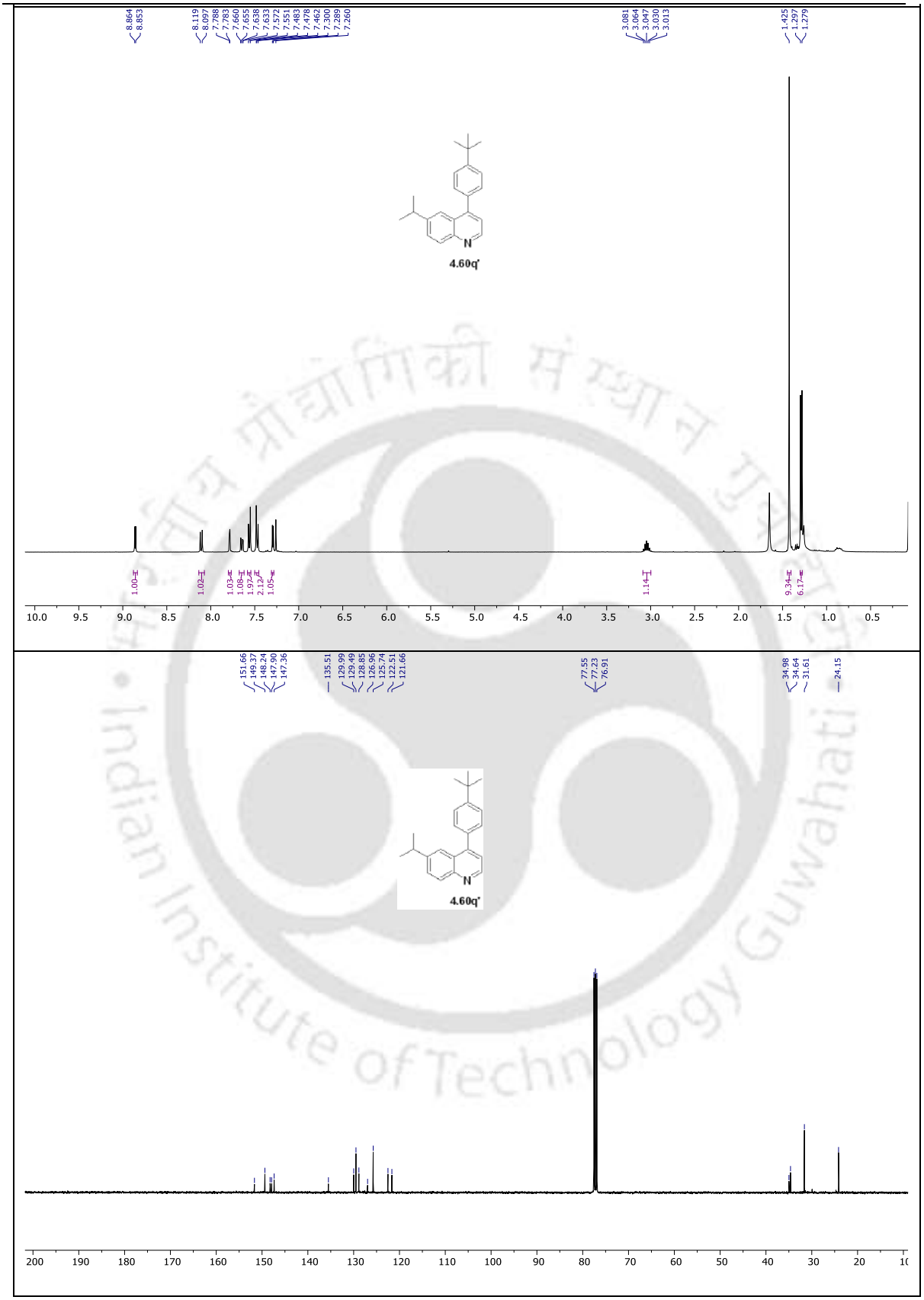


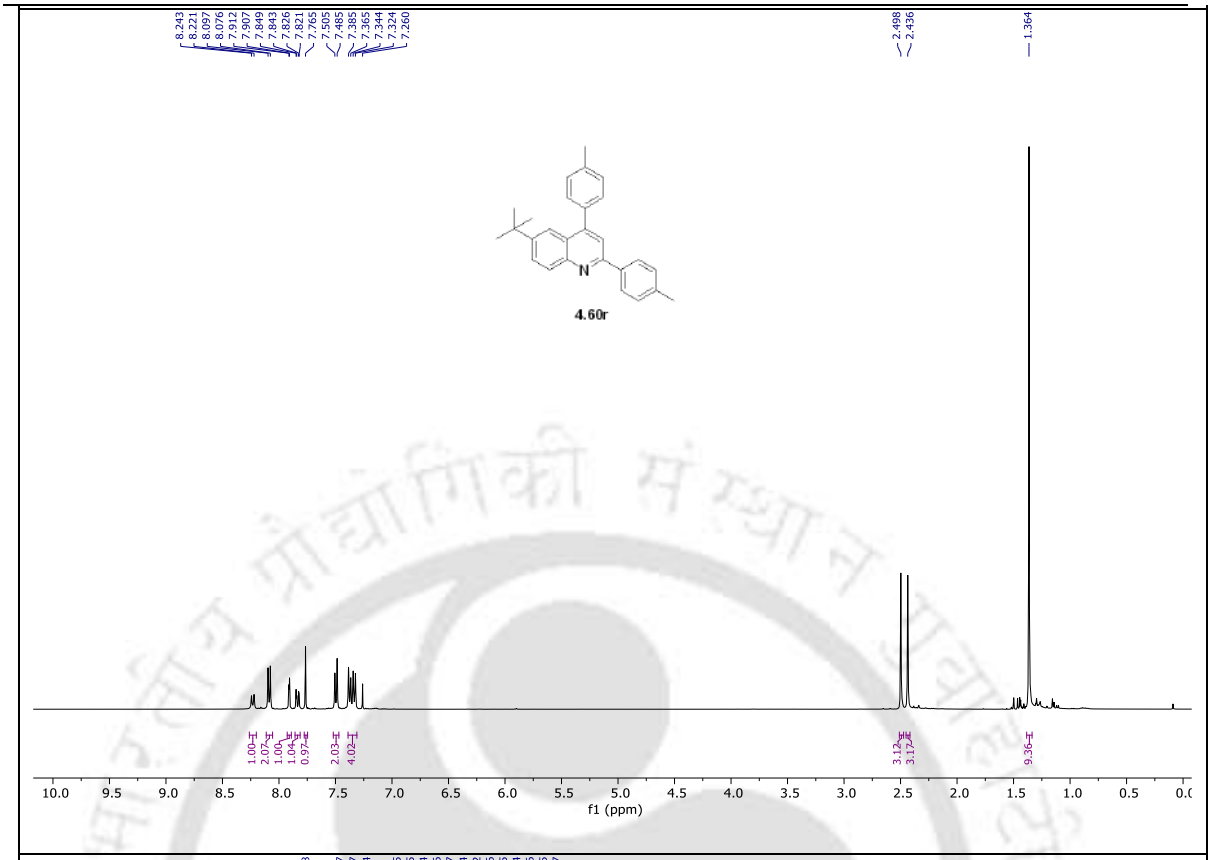


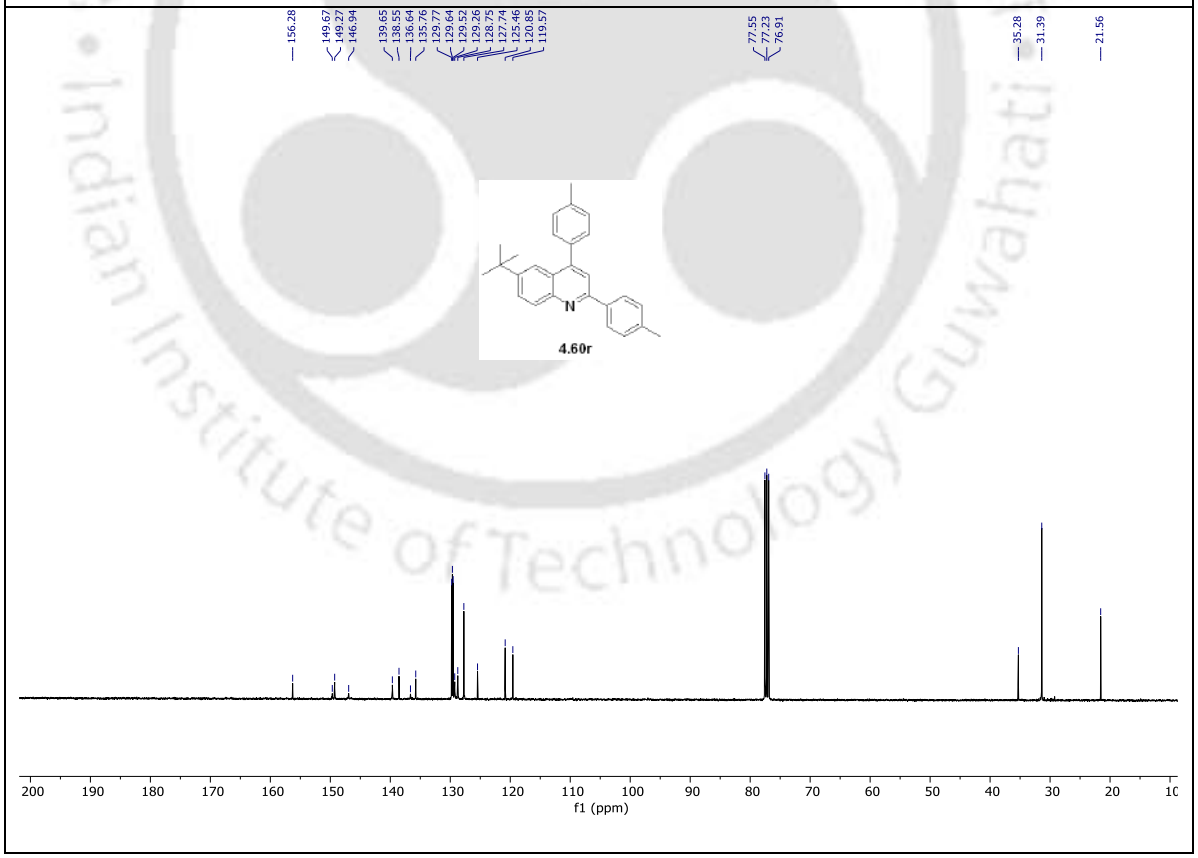


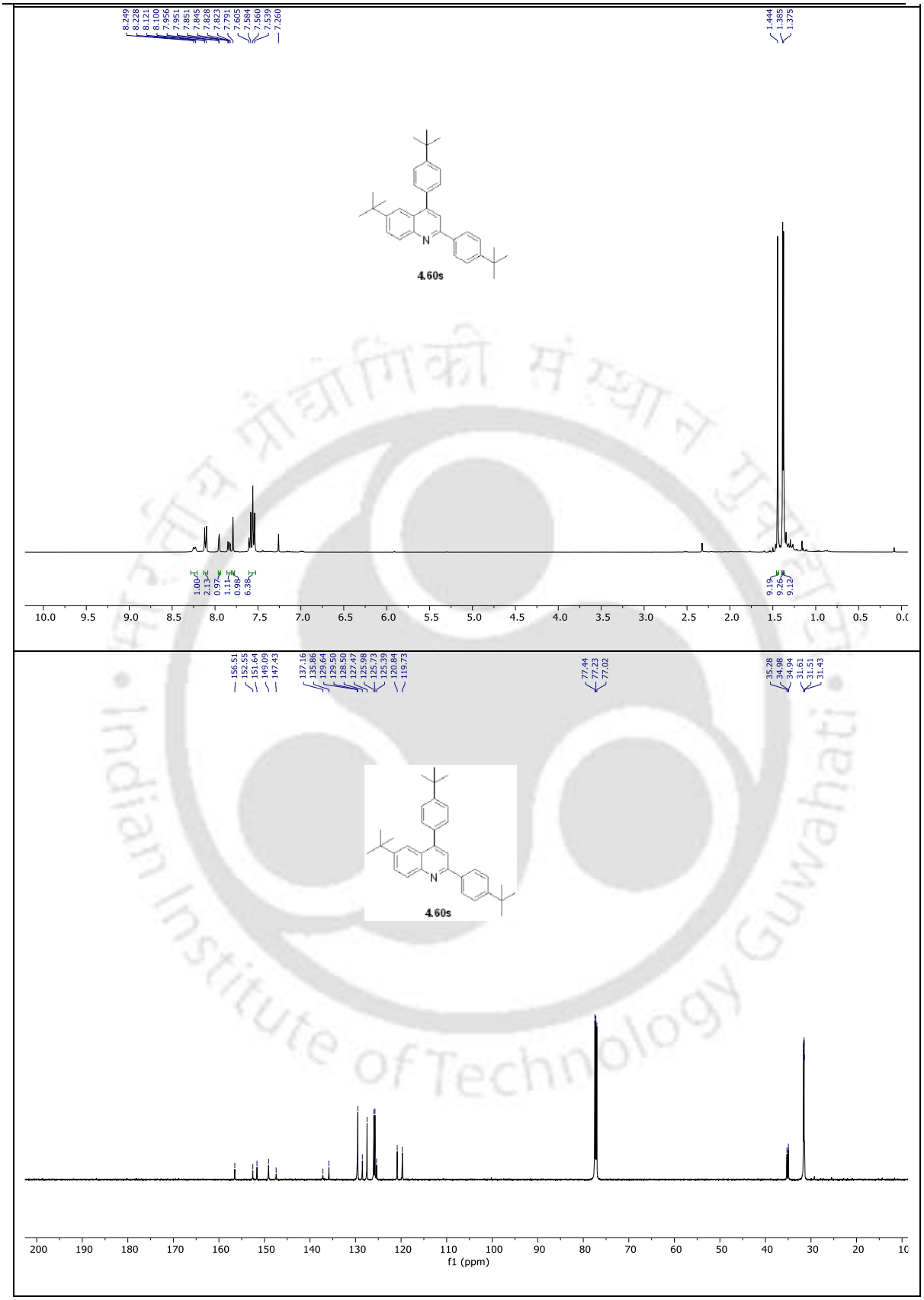


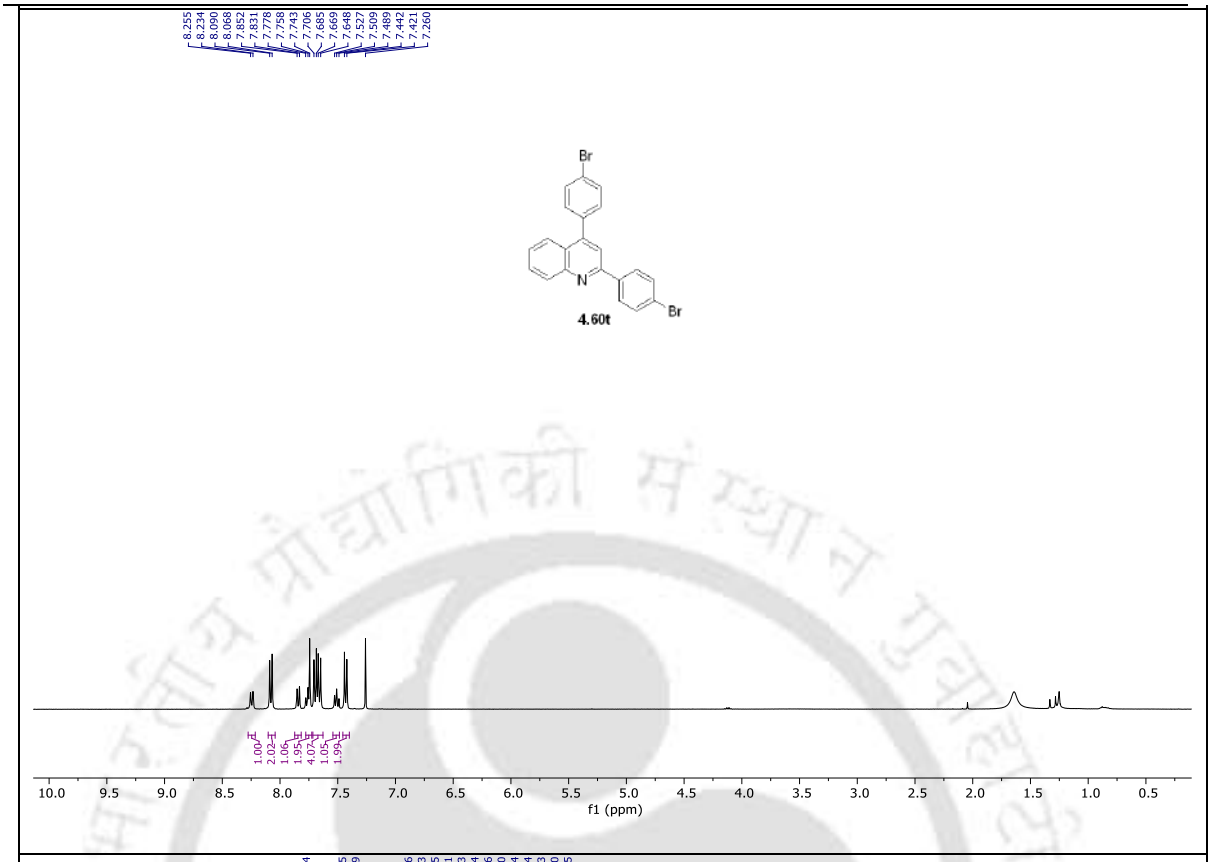


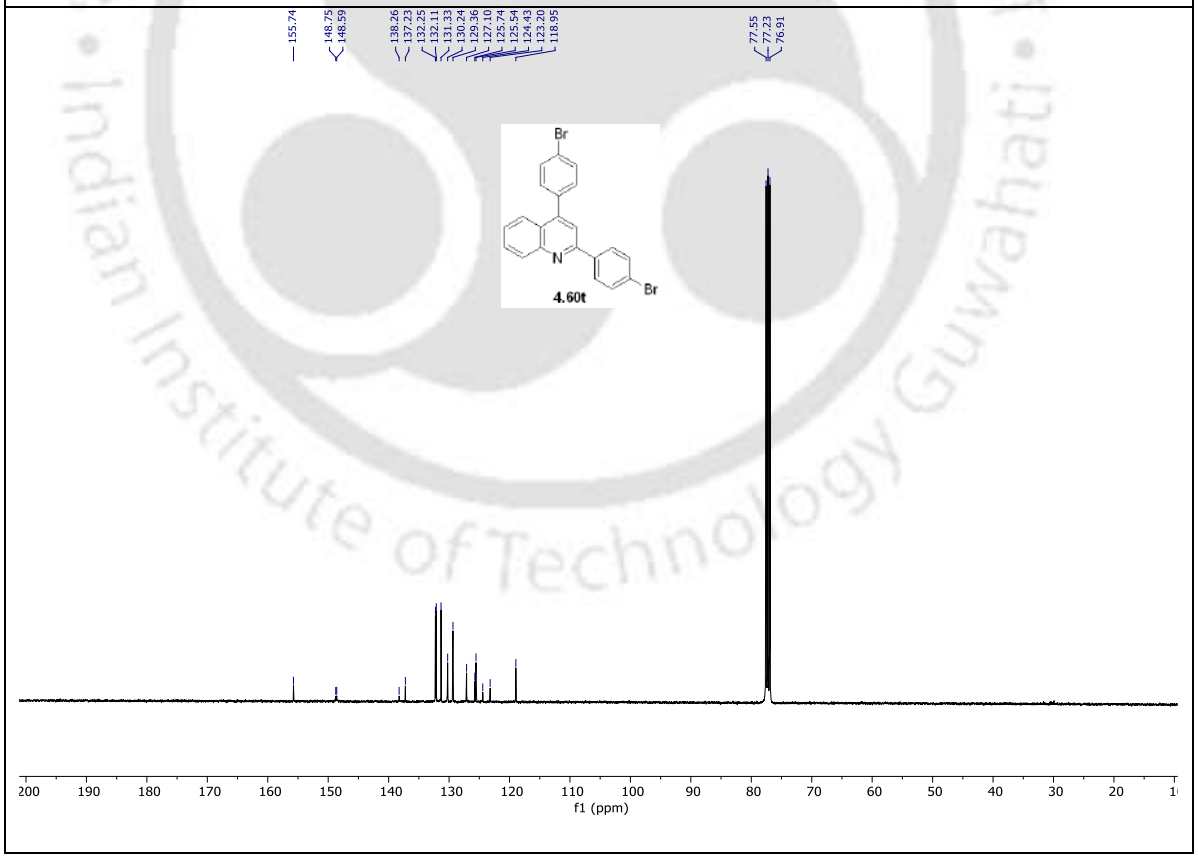


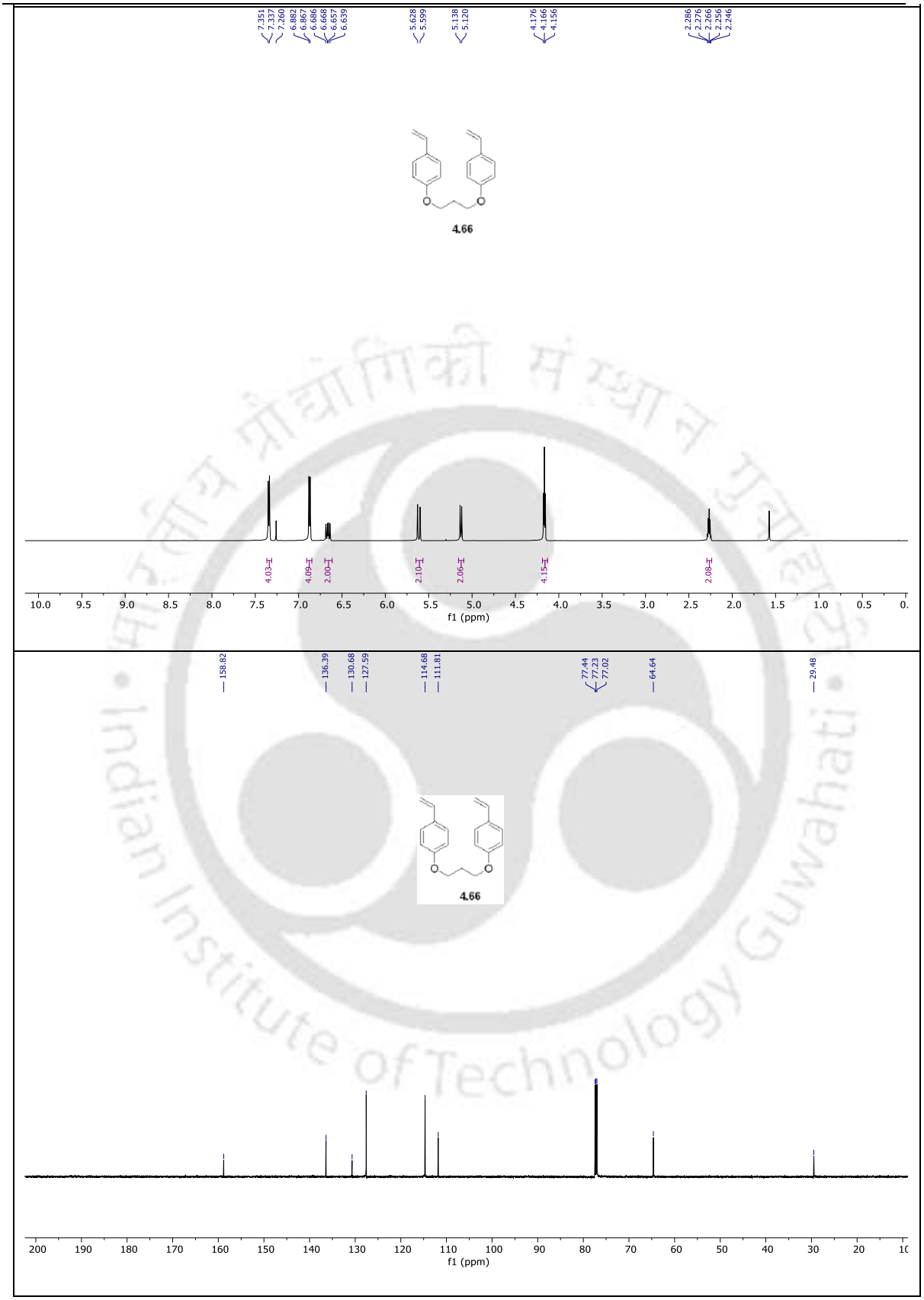


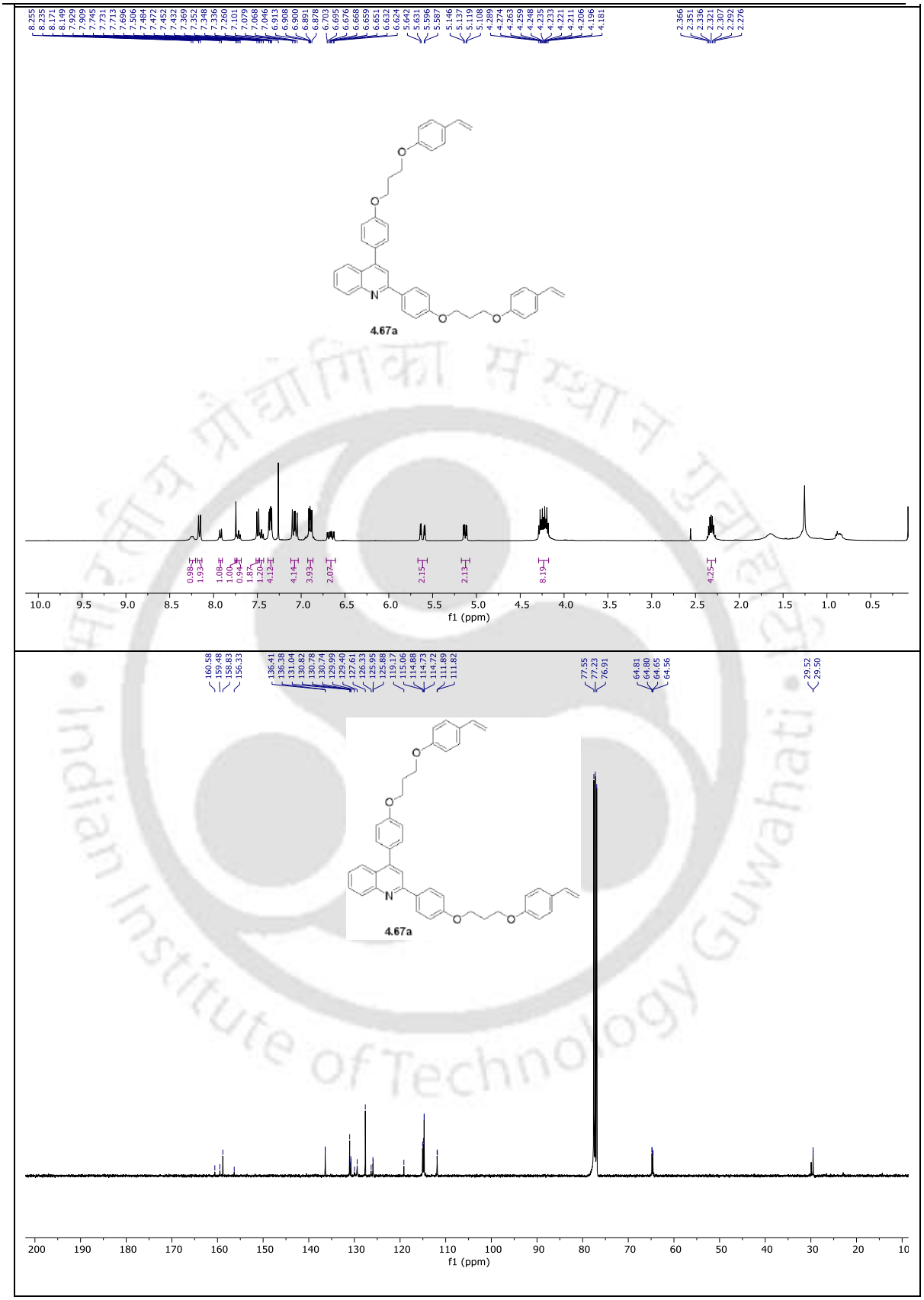








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f1 (ppm)
4.67a
f1 (ppm)