C-H Aminations and Syntheses of Heterocycles Using Nitrosoarene

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

By

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July, 2019

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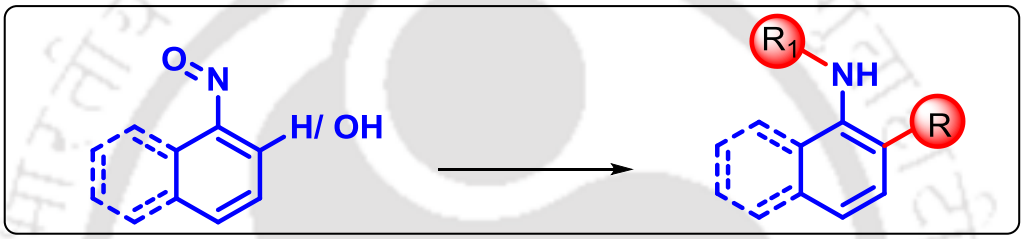

Department of Chemistry

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INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

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STATEMENT

The work contained in this thesis entitled "**C-H Aminations and Syntheses of Heterocycles Using Nitrosoarene"** is the outcome of the research work carried out by me under the supervision of Dr. Chandan K. Jana, Department of Chemistry, Indian Institute of Technology Guwahati, India. In the present thesis the general practice of the scientific observations are reported and whenever needed, the work on the findings of other investigators are described and thus due acknowledgements have been made.

26th July, 2019

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***C-H Aminations and Syntheses of Heterocycles Using Nitrosoarene***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Subhra Kanti Roy (Roll No: 136122018) was carried out by him under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati
26th July, 2019

Dr. Chandan K. Jana
(Thesis supervisor)

Dedicated to my parents and family members

~Acknowledgements~

As I approach towards the end of my doctoral research journey, there are so many wonderful people to whom I owe a debt of gratitude, for their contribution, support and guidance towards my Ph.D. dissertation.

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List of Publications and Presentations:

1. S. Haldar, S. K. Roy, B. Maity, D. Koley and C. K. Jana, "Regio-, Diastereo-selective and Enantiospecific Metal Free C(sp^3)-H Arylation: A Facile Access to Optically Active 2,5-disubstituted Pyrrolidine." *Chem. -Eur. J.*, 2015, **21**, 15290–15298. (The work is highlighted in Organic Chemistry Portal).

2. A. Purkait,‡ S. K. Roy,‡ H. K. Srivastava and C. 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. (‡contributed equally).
3. S. K. Roy, A. Tiwari, Md. Saleem and C. K. Jana, "Metal free direct C(sp^2)–H arylaminations using nitrosoarenes to 2-hydroxy-di(het)aryl amines as multifunctional Aβ-aggregation modulators". *Chem. Commun.*, 2018, **54**, 14081- 14084.

4. S. K. Roy, A. Purkait, Sk Md T. Aziz and C. K. Jana, 'Acid Mediated Coupling of Aliphatic Amines and Nitrosoarenes to Indoles." (*manuscript under revision*).

5. S. K. Roy, R. Shome, S. S. Ghosh and C. K. Jana, "Selective *N*-terminal proline modification of peptides via aminooxazole synthesis and application in cell imaging." (*manuscript under preparation*).

Conferences Attended:

1. Presented a poster in **FICS-2018**, held at IIT Guwahati, Guwahati, India.
2. Presented a poster in **CRSI-2017**, held at Department of Chemistry, Gauhati University, Guwahati, India.
3. Presented a poster in **Research Conclave-2017**, held at Department of Chemistry, IIT Guwahati, Guwahati, India.
4. Presented a poster in **International Conference on Emerging Trends in Chemical Sciences-2018**, held at Department of Chemistry, Dibrugarh University, India.

Members of Doctoral committee

Dr. Chandan K. Jana (Thesis supervisor)

Dr. Lal Mohan Kundu (Chairman)

Dr. Subhas Chandra Pan (Member)

Dr. Kingsuk Mahata (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

Selective transformation of ubiquitous but inert C-H bonds into C-C, C-N, C-O, C-X is the central interest to modern organic chemistry. Direct transformation of C-H bond into C-N bond has been emerged as a high impact area of research, because it allows the preparation of nitrogen-containing cyclic and acyclic compounds which are biologically active or which can act as synthetic scaffolds for pharmaceuticals. The contents of this thesis entitled "***C-H Aminations and Syntheses of Heterocycles Using Nitrosoarene***" have been divided into six chapters. The first chapter of the thesis provides a review on different aspects of C-H amination with various aminating agents. All the other chapters describe the C-N bond forming reactions of nitrosoarenes. Chapter 2 describes C(sp^2)-H arylamination of 2-hydroxyarene to provide 2-hydroxy-di(het)aryl amines. Chapter 3 illustrates C(sp^3)-H functionalization enabled annulation of nitrosoarenes and *N*-heterocycles to ring-fused imidazoles. Selective *N*-terminal proline modification of peptides via amino-oxazole synthesis and application of modified peptides in cell imaging have been described in chapter 4. Chapter 5 demonstrates indole synthesis via C(sp^2)-H functionalization of nitrosoarene and β-C(sp^3)-H functionalization of secondary amines. Finally, chapter 6 contains copies of ^{1}H and ^{13}C NMR spectra.

Chapter 1: Introduction on C-H Aminations:

This chapter describes the brief history of C-H amination reactions. Various strategies for C-H amination, different aminating agents, challenges for direct C-H amination, development of new methodologies to address those challenges and advantages of direct C-H amination over classical approaches in organic synthesis have been discussed. Different aminating agents utilized for C-H amination has been shown in **Figure 1**.

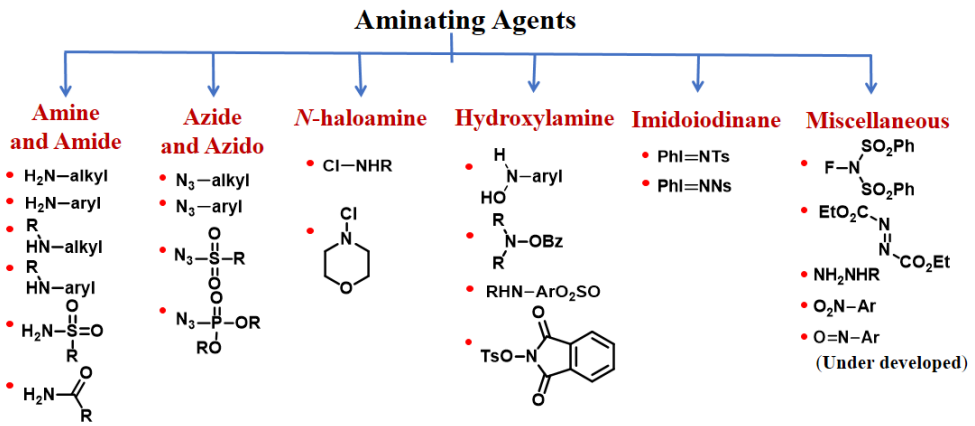


Figure 1: Various aminating agents.

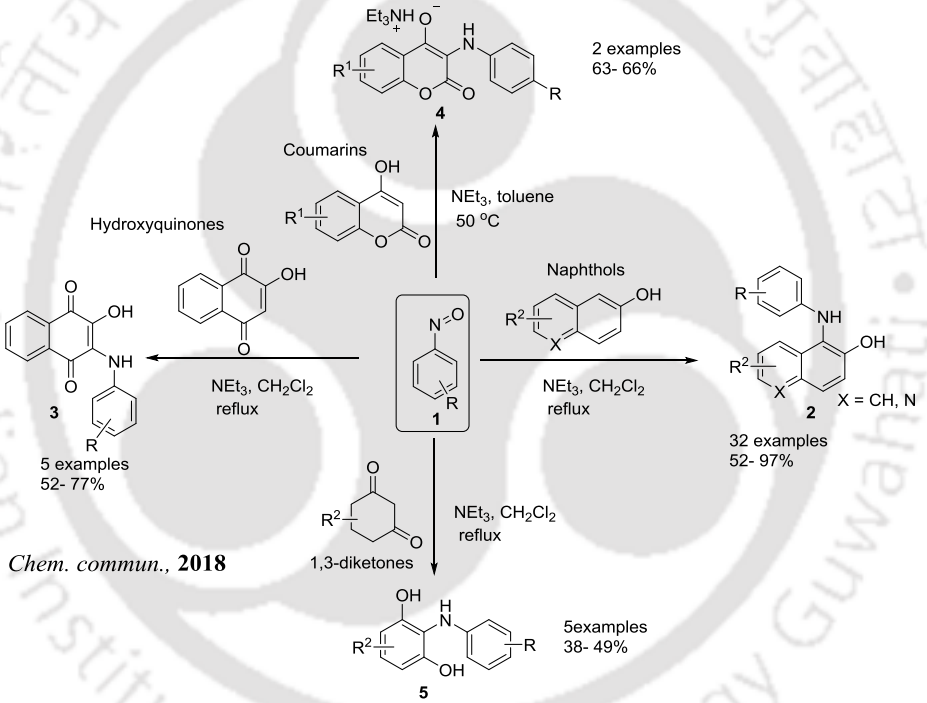
Classical arylamination via Copper catalyzed Ullmann-Goldberg coupling, Chan-Lam coupling and palladium catalyzed Migita-Kosugi reaction and the Buchwald-Hartwig amination have been widely used. Apart from the classical approaches of amination, such as reductive carbonyl amination, nucleophilic displacement of a leaving group and imine alkylation, the development of novel transition metal catalyzed C-H amination and C-H arylamination have been tremendously progressed over the years. On the other hand, photo-redox catalyzed C-H amination indubitably was an important discover Amination using aminating agents like azide, *N*-haloamines, hydroxyl amine and nitroarene have also been made remarkable progress in this field. However, in spite of the advancement in the field of amination reactions, the previous strategies have some limitations. For example, the Buchwald-Hartwig amination involved preactivated electrophiles (aryl halides) and amines in the presence of Pd catalyst. Thus the scope of these reactions are somewhat limited because aryl halides which sometimes are not readily available. The main drawbacks of metal catalyzed arylamination reactions are the use of expensive metal, synthesis of aryl halides or pseudohalides, undesired byproducts. Moreover, amination using other aminating agents like azide, *N*-haloamines, hydroxyl amine, nitroarene and nitrosoarene suffer from limitations related to the use of harsh reaction condition, functional group incompatible and general applicability. Nitrosoarenes are readily available. Due to high polarizability of N=O bond it can react easily with nucleophiles and proved to be an important synthetic building block in synthetic organic chemistry to install amine functionality in molecules. However, very few reports on C-H amination using nitrosoarene are known. Therefore, the aim of this thesis is to develop novel synthetic methodologies for C-N bond formation using nitrosoarene under operationally simple conditions without using metallic reagents/ catalyst.

Chapter 2: Metal Free Direct C(sp^2)-H Arylaminations Using Nitrosoarenes to 2-hydroxy-di(het)aryl Amines as Potent Multifunctional Aβ-aggregation Modulators:

Diarylamines and their derivatives are ubiquitous structural motifs of natural products, active pharmaceuticals, antioxidants, dyes, and agrochemical agents. Direct amination of inert carbon-hydrogen (C-H) bonds is one of the most versatile approaches for the construction C-N bond. Transition metal catalyzed cross-coupling reaction, metal and photoredox catalyzed direct amination of C-H bonds, amination reactions involving varieties of electrophilic amine sources are the main approaches

for diarylamine synthesis. However, the involvement of metallic reagents and stoichiometric metal-based or organic reductants, functional group incompatibility are the major drawbacks of these previous reports.

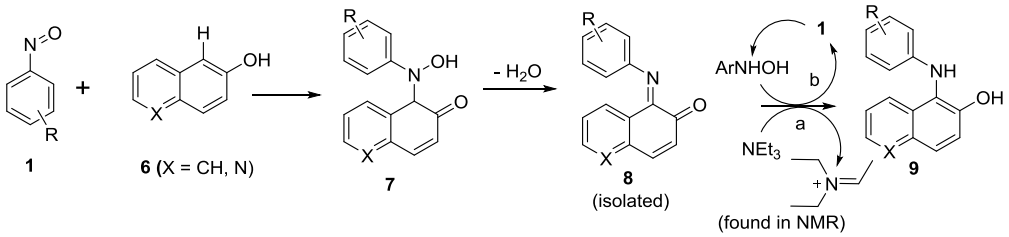
This chapter reports a metal free direct C(sp^2)-H arylamination reaction using nitrosoarenes as amine source to provide 2-hydroxy-di(het)aryl amines. The direct arylamination of a broad range of substrates, such as naphthols, hydroxyquinolines, hydroxyquinones, coumarins and 1,3-cyclohexadinones were achieved under operationally simple and mild conditions without the aid of additional reagents/steps for the N-O bond reduction. The optimized reaction conditions were employed to obtain structurally diverse 2-hydroxy-di(het)aryl amines with good to excellent yields.



Scheme 1: Scope of arylamination reactions using nitrosoarenes.

Based on the experimental results, a plausible reaction mechanism for this metal-free reductive arylamination reaction has been depicted in Scheme 2. Naphthol derivatives reacted with nitrosoarene to provide corresponding iminoquinone **8** probably through the corresponding hydroxylamine derivative **7**. The reduction of the iminoquinone **8** occurred via two possible pathways. In the major pathway, NEt_3 reduced iminoquinone **8** either via electron transfer mechanism or via ionic mechanism to produce desired aminated product **9**. Consequently, triethylamine was oxidized to the corresponding iminium ion which was detected by ^{1}H-NMR. Additionally, arylhydroxylamine formed from the nitrosoarene during the auto-

oxidation-reduction process could also be involved for the reduction of **8** to the desired product in the minor pathway.



Scheme 2: Proposed mechanism.

Interestingly, the novel 2-hydroxydiaryl amines were found to be highly potential Aβ- aggregation inhibitors. The potential of **2a** and **2b** in inhibiting the Aβ-

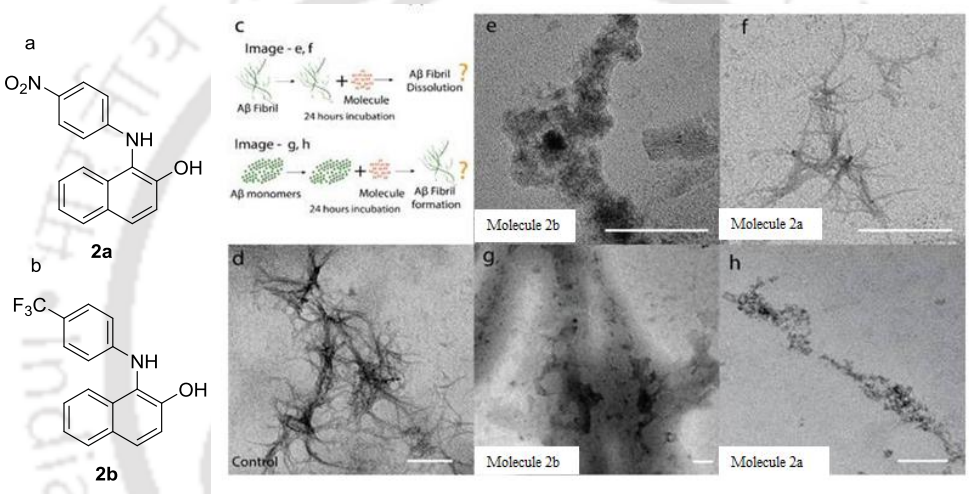


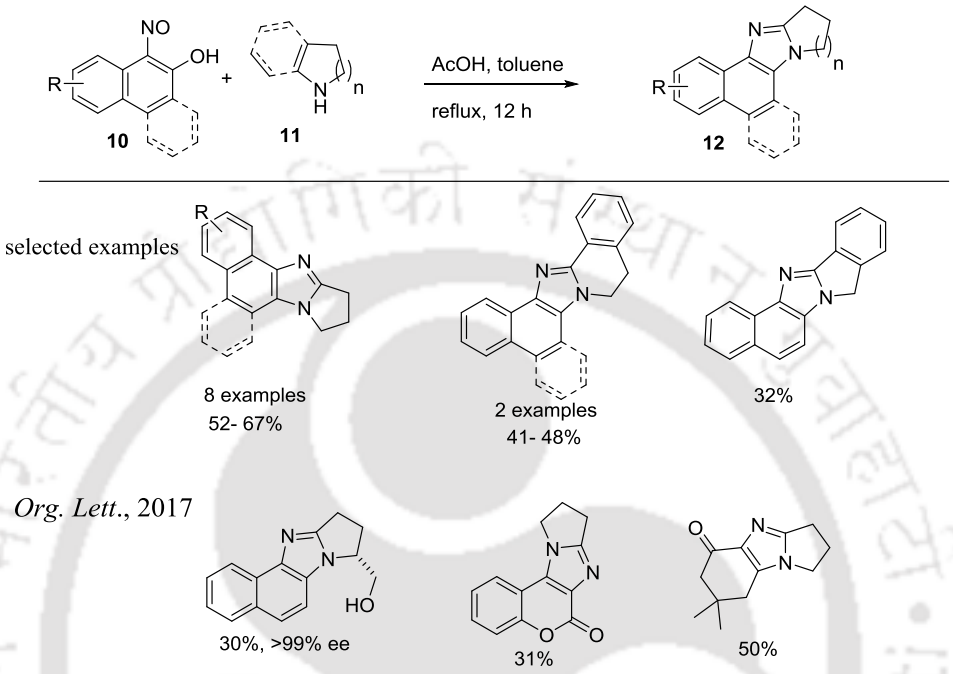
Figure 2: (a) & (b) molecular structure of **2a** & **2b** respectively. (c) Illustration of the experimental design. (d) Control image of untreated Aβ-40. (e) & (f) TEM micrographs of pre-formed Aβ-40 fibril incubated with molecule **2b** and **2a** for 24 hours, respectively. (g) & (h) TEM micrograph of molecule **2b** & **2a**, respectively, incubated with Aβ-40 monomers for 24 hours. (Scale bars, 100 nm)

aggregation was confirmed by the changes in the fibrillary morphology observed by transmission electron microscopy (**Figure 2**). Furthermore, the dissolution of the pre-formed Aβ-40 fibril was observed with the treatment with **2b** (**Figure 2e**).

Chapter 3: Metal Free C(sp^3)-H Functionalization Enabled Annulation of Nitrosoarenes and *N*-heterocycles to Ring-fused Imidazoles

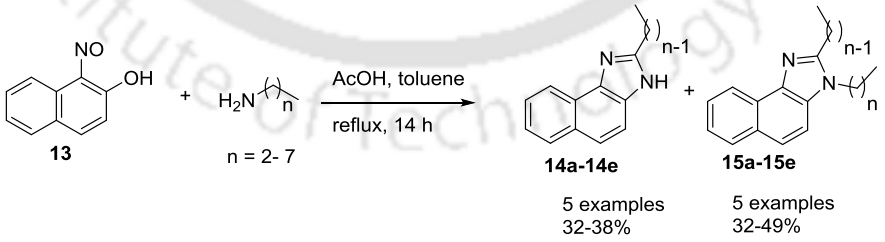
Imidazoles are privileged moiety which are present in many bioactive molecules including natural products. Particularly, ring-fused benzimidazole derivatives were identified as the important pharmacophore for anticancer activity. Syntheses of this valuable scaffolds

mainly relied on the multistep reaction sequences. A metal-free C(sp^3)-H functionalization enabled annulation of nitrosoarenes and *N*-heterocycles for the synthesis of ring-fused imidazoles has been developed. Structurally diverse novel polycyclic imidazoles were prepared readily from the reaction of 2-hydroxy-C-nitroso compounds and secondary cyclic amines in the presence of acetic acid in refluxing toluene.



Scheme 3: Scope of metal free C(sp^3)-H functionalization enabled annulation of nitrosoarenes and *N*-heterocycles.

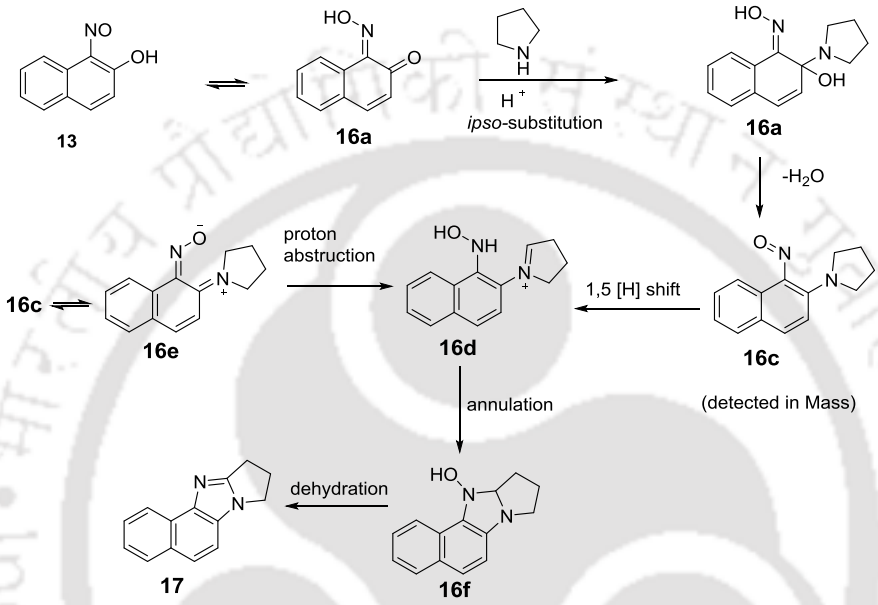
Moreover, aliphatic primary amines with varied chain length also participated in annulation reaction with the 2-nitrosonaphthol under the standard reaction conditions. The desired naphtho-imidazoles along with corresponding *N*-alkylated derivatives were isolated with very good to excellent combined yields.



Scheme 4: Scope of metal free C(sp^3)-H functionalization enabled annulation of nitrosoarenes with acyclic amines.

Based on the experimental evidence, a plausible mechanism for the annulations reaction has been depicted in **Scheme 5**. Nitrosonaphthalene derivative **16c** could be formed from the nucleophilic *ipso*-substitution reaction of nitrosonaphthol **13** or its keto-oxime tautomer **16a** with pyrrolidine through intermediate **16b**. Amino nitroso derivative **16c** then readily

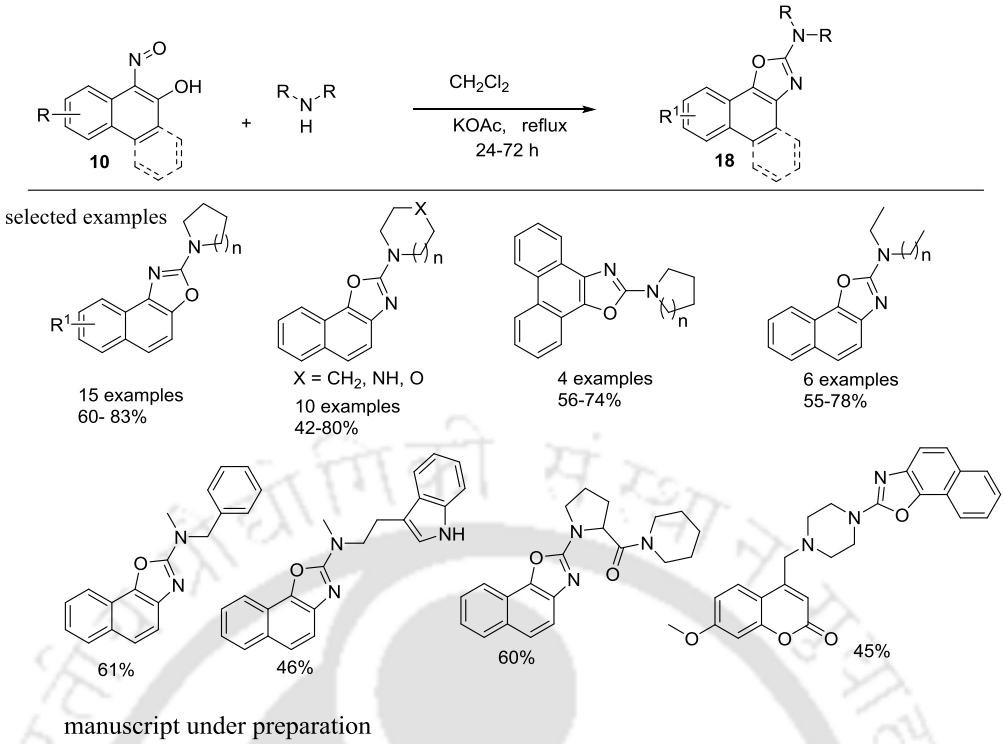
undertook a 1, 5-hydride shift to provide the iminium ion **16d**. Alternatively, the iminium ion **16d** could also be produced through deprotonation of iminium ion **16e** which was produced from isomerisation/ mesomerization of **16c**. Annulation of **16d** followed by acid mediated dehydration of resulting *N*-hydroxy derivative **16f** provided the desired imidazole **17**. **16c** was detected in mass the spectrometry, this supports the intermediacy of **16.3** in the reaction.



Scheme 5: Proposed mechanism for metal free annulation of nitrosoarene and *N*-heterocycles.

Chapter 4: Selective *N*-terminal proline modification of peptides via aminooxazole synthesis and application in cell imaging

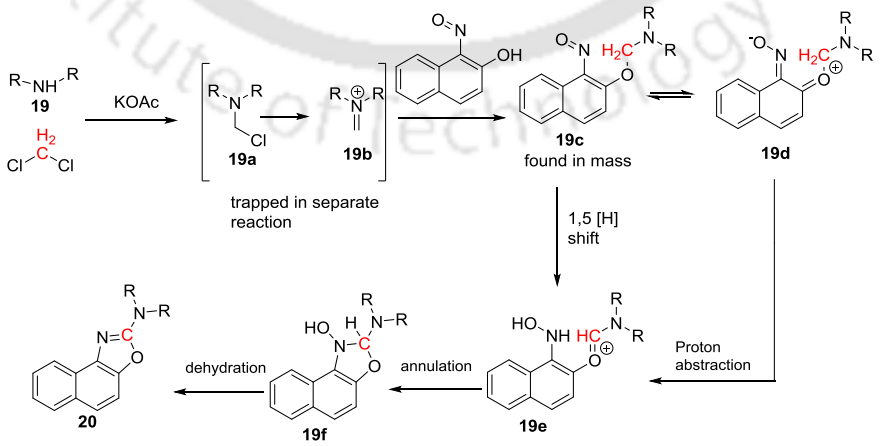
2-aminooxazoles is one of the most promising pharmacologically interesting class of heterocycles. However, the known methods for the synthesis of aminooxazole have their own limitations due to the involvement of vigorous reaction conditions, multiple numbers of reaction steps and production of adverse by-products. Thus the previously reported synthetic methods to obtain 2-aminooxazoles mostly suffer from the requirement of multiple reaction steps, metals, strong oxidants, harsh reaction conditions, and undesirable by-products. In this chapter, a novel method for the synthesis of 2-amino-oxazole derivatives has been developed under simple and mild reaction condition where dichloromethane was used as the C2 source of 2-aminooxazole. 2-hydroxy-C-nitroso compounds on reaction with amines and dichloromethane in presence of base afforded corresponding 2-amiooxazoles derivative. The reaction is operationally simple, very



Scheme 6: Scope of 2-aminooxazole synthesis.

general and highly efficient in *N*-functionalizing both cyclic and acyclic amines. The generality of this method has been proven by the use of a wide range of saturated amine based substrates.

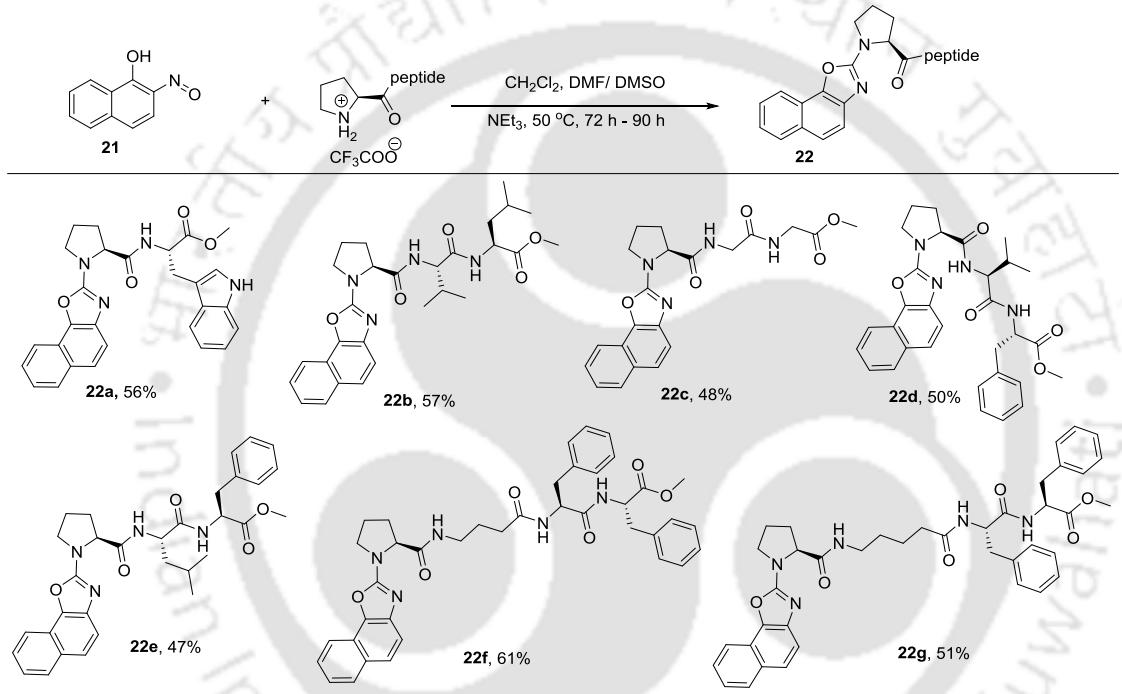
Based on the results of controlled experiments a plausible mechanism for this oxidative cyclization reaction is presented in **Scheme 7**. Amine **19** reacted with dichloromethane in presence of the base to generate the imminium ion **19b** which on reaction with 1-nitroso-2-naphthol afforded **19c**. Then **19c** readily undertook a 1,5-hydride shift to provide the.



Scheme 7: Proposed mechanism for the synthesis of 2-aminonaphthaoxazole.

iminium ion **19e** which also could be obtained by the isomerisation of **19d**. Annulation of **19e** followed by dehydration of resulting *N*-hydroxy derivative **19f** provided the desired 2-aminooxazole **20.**

Utilizing this developed method for synthesis of aminooxazole derivatives, spacer free *N*-terminal modification of peptides has been achieved to afford fluorescent peptides. 2-hydroxy-C-nitroso on reaction with various peptides afforded corresponding 2-amiooxazoles derivative



Scheme 8: *N*-terminal peptide modification.

The modified peptides have been successfully used for imaging of HeLa cells and found to be used as excellent luminescent probes for rapid staining of cell cytoplasm.

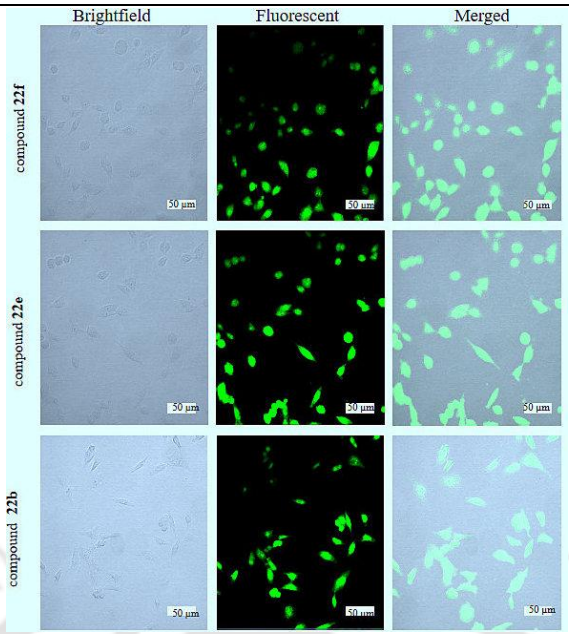
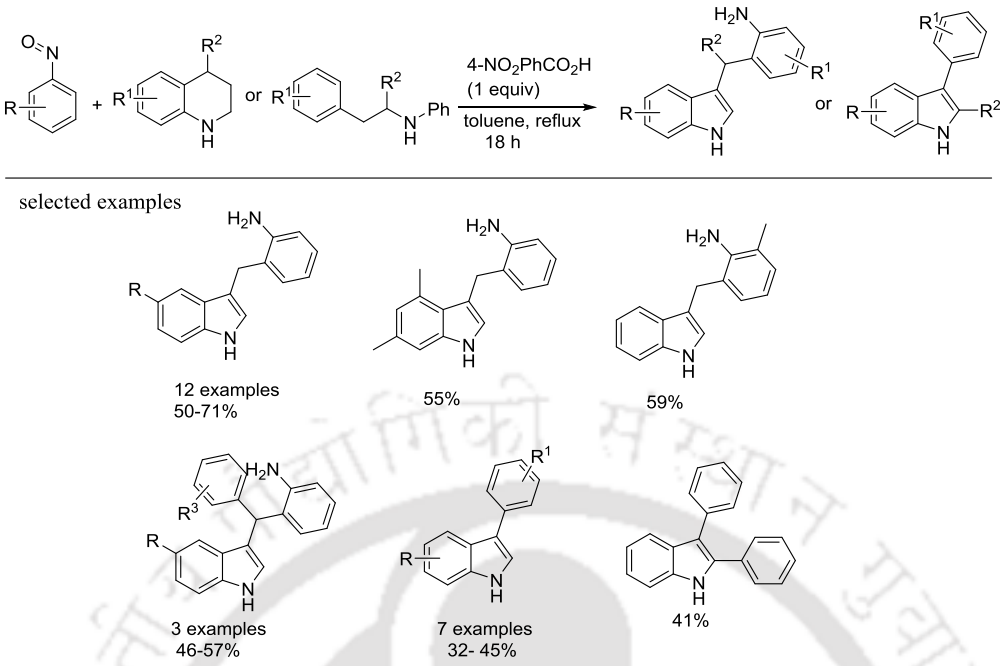


Figure 3: Confocal laser scanning microscopy images of HeLa cells stained with **22f**, **22e** and **22b** respectively. Cells were incubated with 40 µM of the compounds for 20 min. Excitation: 458 nm Emission range: 480-605 nm. Scale bar: 50 µm.

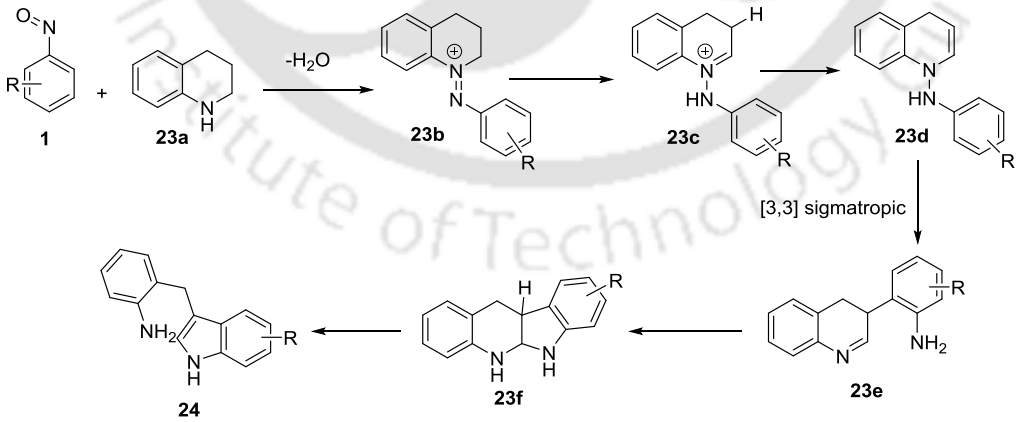
Chapter 5: Direct C(sp^2)-H functionalization of nitrosoarene and *β*-C(sp^3)-H functionalization of secondary amines to Indoles

Functionalized indoles are ubiquitous in biologically active natural products, pharmaceuticals, and agro-chemicals. The indole alkaloids are the structural analog of endogenous amines and neurotransmitters. Over the past decades, several pioneering methods have been developed for the synthesis of indole derivatives. Most of the previous methods require prefunctionalized precursors thereby lengthening the synthetic path. Therefore, the availability and synthesis of the suitably substituted precursors limit the scope of these reactions. A metal-free unprecedented method for the synthesis of indole derivatives via C(sp^2)-H functionalization of nitrosoarene and *α, β*-C(sp^3)-H functionalization of aliphatic amines has been developed. Diversely substituted indoles were prepared by the reaction of various nitrosoarenes and various amines in the presence of 4-NO_2-benzoic acid in refluxing toluene.



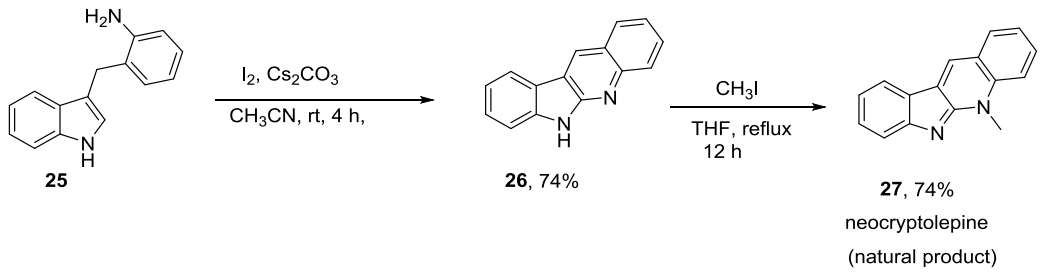
Scheme 9: Selected examples of 3-benzyl- and 3-aryl indoles.

Based on the experimental results a plausible mechanism has been depicted in **Scheme 10**. Tetrahydroquinoline reacted with nitrosoarene to afford imminium ion **23b** which isomerizes to **23c**. Further isomerization of **23c** gave rise to ene-hydrazine **23d** which underwent [3, 3] sigmatropic rearrangement to provide **23e**. Annulation to **23e** followed by ring opening of **23f** afforded indole **24**.



Scheme 10: Plausible mechanism for the synthesis of 3-benzylindoles.

Cyclization reaction of indole **25** was successfully achieved by using molecular iodine and Cs_2CO_3 to provide biologically important norneocryptolepine. Further *N*-methylation of **26** with CH_3I provided natural product neocryptolepine **27** (**Scheme 11**).



Scheme 11: Synthesis of neocryptolepine.

Summary:

In summary, the thesis describes the C-N bond forming reaction of nitrosoarenes and heterocycles syntheses. Synthesis of 2-hydroxy-di(het)aryl amines was achieved by C(sp^2)-H arylamination of using nitrosoarene. Synthesis of biologically privileged moiety ring-fused imidazole was achieved via C(sp^3)-H functionalization of nitrosoarenes and *N*-heterocycles. The selective *N*-terminal proline modification of peptides via aminooxazole synthesis was developed and application of these modified peptides in cell imaging has been studied. Indole synthesis via C(sp^2)-H functionalization of nitrosoarenes and β-C(sp^3)-H functionalization of secondary amines were also established. In future, the focus will be to investigate and explore the functionalization of acyclic amines with nitrosoarenes. Also, the possibility of functionalization of other aliphatic cyclic amines with nitrosoarenes to afford heterocycles such as indole, quinoxaline, quinoline will be studied in the near future.

Chapter 1

Introduction on C-H Aminations

1.1 Introduction:

C-H bonds are present in a plethora of molecules.[1,2,3] The selective transformation of ubiquitous but inert C-H bonds into C-C, C-N, C-O, C-X is the central interest to modern organic chemistry, as it directly escalates the molecular complexity of much simpler molecules.[4,5,6,7,8] Despite being recognized as an inert scaffold in functional group chemistry, C-H bond modification is considered to be one of the key steps for the future development of organic synthesis. The majority of conventional methodologies used for C-H functionalization, usually involve the use of pre-existing functional groups that may introduce new functionality in the molecule and eventually this process leads towards intensified molecular complexity.

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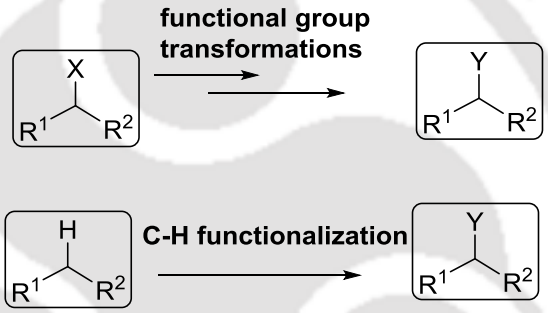


Scheme 1: Functional group transformation approach *vs*. direct C-H functionalization.

However, this type of approach often demands the introduction of sensitive functional groups at the very early stages of chemical synthesis. This ultimately results in need of concurrent additional steps such as change of oxidation state and/or protecting group sequences, which often translates into poor selectivities (**Scheme 1**). From the last few decades, a wave of novel reaction technologies has been unveiled aiming at the selective modification of aliphatic and aromatic C–H bonds.[9] In this context, the use of transition metal catalysts has represented a tremendous step forward to directly functionalize sp^3, sp^2 and sp hybridized C-H bonds. The functionalization of C–H bonds have been emerged as a highly sought methodology because of its ability to rapidly convert simple starting materials into highly functionalized organic compounds. In addition to that, this approach structurally manipulates the molecules by eliminating the involvement of functional group and thus results in the minimization of synthetic wastes. Therefore, the interest of the organic

chemists in developing these sustainable methodologies is rapidly increasing for both environmental and economic reasons.

Till date, several noteworthy methods for selective functionalization of C–H bond have been developed, such as arylation, alkylation and carbonylation of an C–H bond adjacent to a heteroatom, the borylation and silylation of a C–H bond with hydroboranes and hydrosilanes, the introduction of a heteroatom at an C–H bond, and so on.[10]

Nitrogen, one of the fundamental atoms in nature, is ubiquitous in numerous biologically active natural products and synthetic pharmaceuticals (**Figure 1**). Nitrogen functionality, especially amines, are of great importance to the organic chemists because of their abundance in biologically active molecules, pharmaceuticals ingredients, synthetic drugs and agrochemicals involved.[11] Moreover, the presence of nitrogen in the structures of polymers can have a profound effect on their physical, electronic or surface properties.

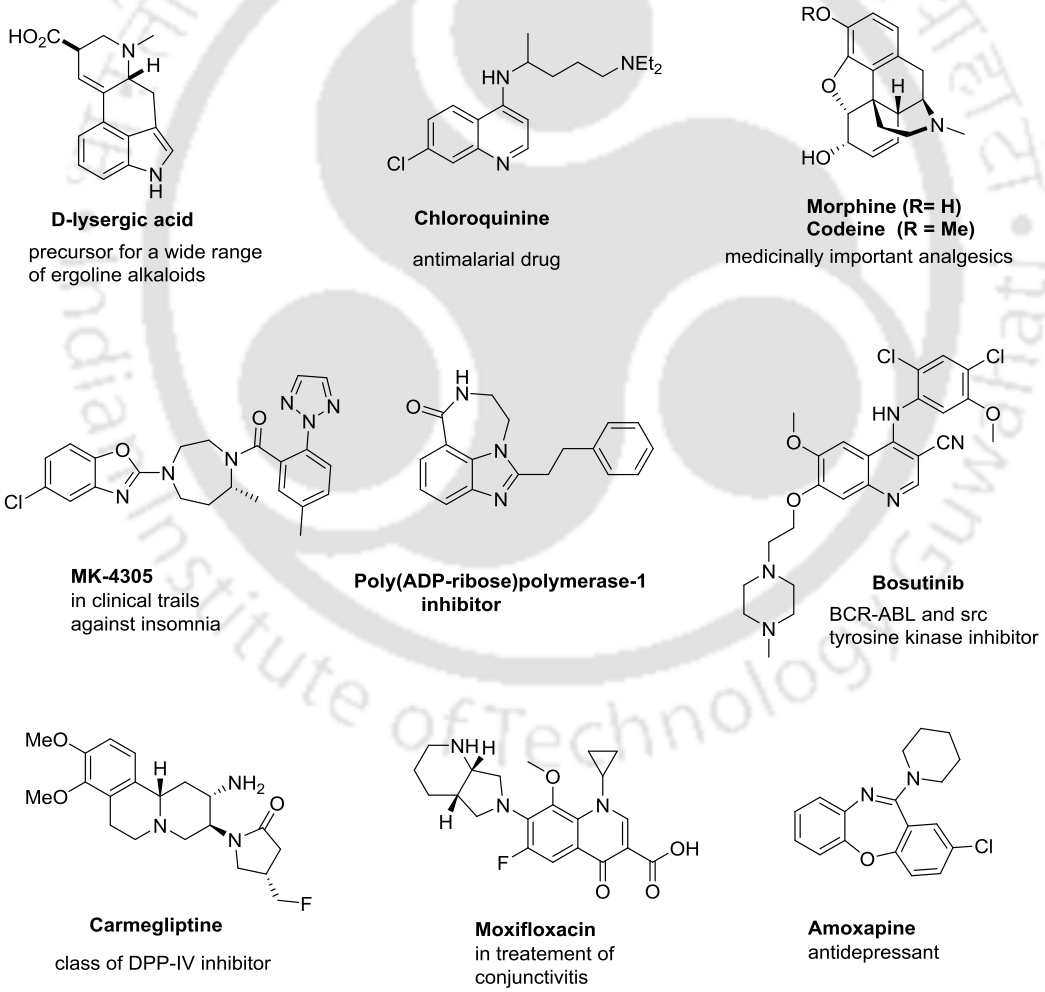
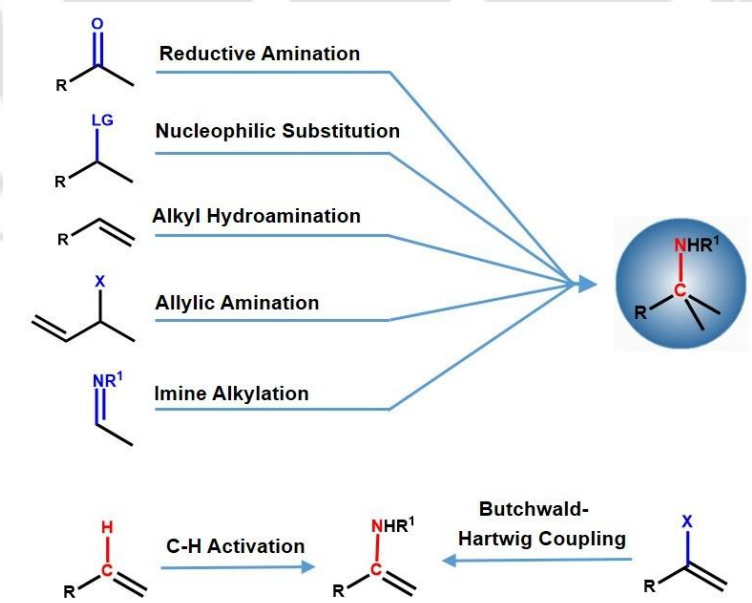


Figure 1: Structures of biologically active molecules containing functionalized *N*-heterocycles.

Thus, from the perspective of an organic chemist, the development of novel C-N bond forming methodologies is an intensively investigated field of the utmost importance. Along the same line, the direct transformation of C-H bond into C-N bond has emerged as a high impact area of research because it allows the preparation of nitrogen-containing compounds that are biologically active or can act as the scaffolds for synthetic pharmaceuticals. However, there are three fundamental challenges majorly associated with the direct amination of C-H bonds: 1) Activating an inert C-H bond so that it permits the barrier of chemical attack; 2) Selectively targeting a specific C-H bond among the other available C-H bonds in the molecule; 3) for multistep reaction it is challenging to carry through synthetic sequences as highly reactive nitrogen can react with other functional groups present in the molecule. Therefore, to overcome these limitations, the development of new and advanced methodologies for C-H amination needs special attention. Besides, precise one step conversion of C-H bonds to C-N without disrupting the other functionality is highly desirable.

The classical approaches of amination include 1) reductive amination of carbonyl compounds, 2) nucleophilic substitution reaction, 3) alkyl hydroamination, 4) allylic amination, 5) imine alkylation, 6) Buchwald-Hartwig coupling and 7) via direct C-H activation (**Scheme 2**). Along with direct approaches, different aminating agents have been



Scheme 2: Different approaches to C-H amination.

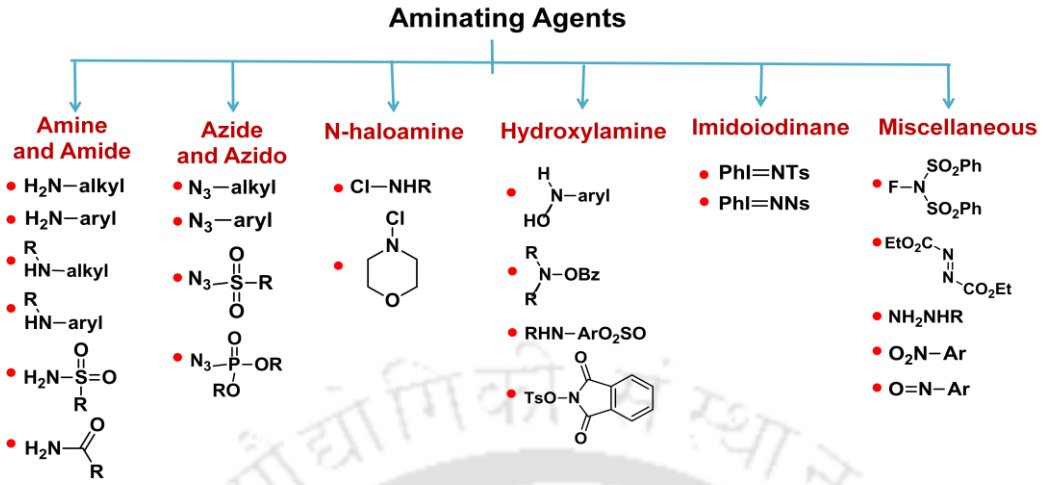


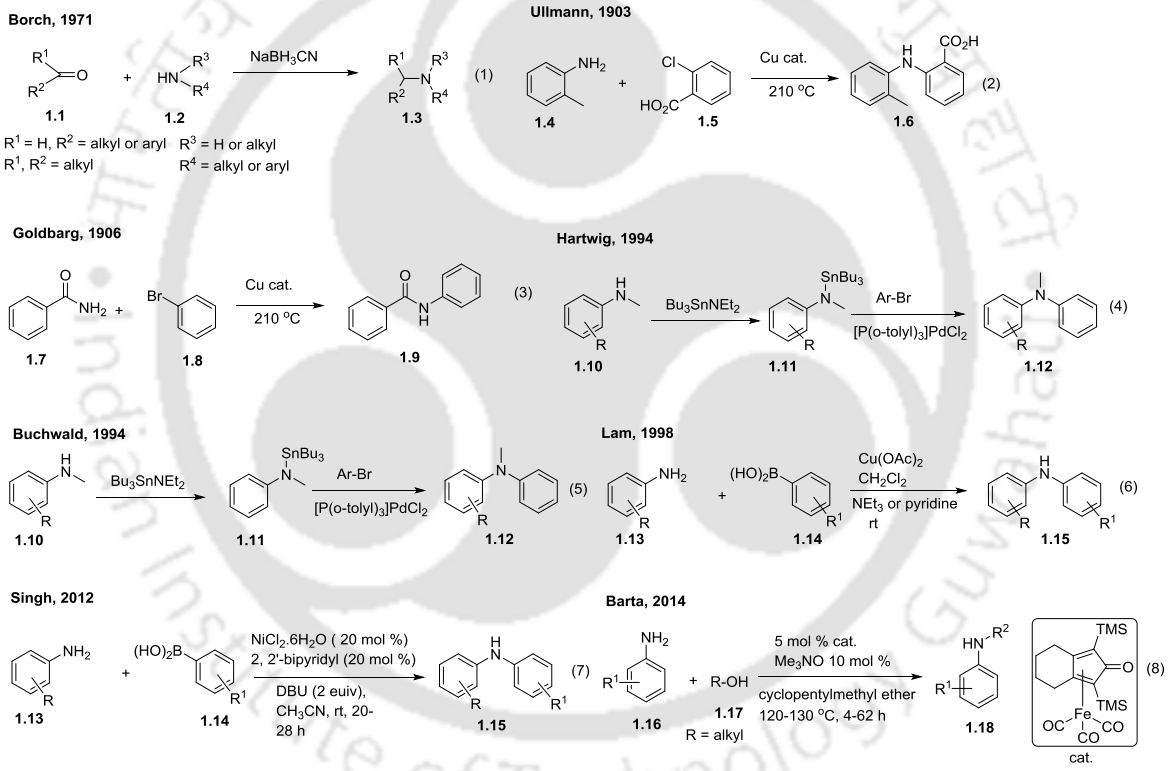
Figure 2: Different aminating agents for C-H amination.

1.2 Amination using amines and amides:

The nitrogen atom primarily found in amines and amides which are generally considered as the principle source of nitrogen without presynthesis. In these sources, the nitrogen atoms present are mostly nucleophilic in character. In the modern era, the reductive amination reaction remains as one of the most powerful, versatile and widely used transformations in chemical synthesis of amines and related functional compounds. It has long been known that ammonia and amine (primary or secondary) reacts with aldehydes or ketones in the presence of a reducing agent to afford primary, secondary or tertiary amines, respectively. The reaction mechanism is believed to involve the initial formation of an addition product as an aminal intermediate or carbinol amine, which under the suitable reaction conditions gets dehydrated to form an imine. The imine undergoes protonation to form an iminium ion, that subsequently on reduction results in the corresponding alkylated amine. Various reducing agents have been used so far for the reduction of *in situ* generated imines.[12] The 1970s saw the first practical hydride procedure for direct reductive amination, as reported by Borch and coworker. They used the more selective sodium cyanoborohydride ($NaBH_3CN$) as the reducing agent for reduction of *in situ* generated imine from the reaction of carbonyl group and amine to afford aminated product **1.3** (**Scheme 3**, eq. 1).[13]

The majority of synthetic advances for the construction of diaryl amines over the century have been accomplished mainly through aromatic amines (aniline derivatives). The classical metal-catalyzed coupling reactions such as copper-catalyzed Ullmann−Goldberg condensation (**Scheme 3**, eq. 2, eq. 3)[14,15] and Chan−Lam coupling (**Scheme 3**, eq. 6),[16,17] as

well as palladium-catalyzed Migita−Kosugi reaction[10] and Buchwald−Hartwig amination[18,19] have been tremendously utilized since last two decades for amination. Palladium-catalyzed amination reaction was first introduced through Buchwald−Hartwig reaction, that demonstrates the reaction between pre-activated electrophiles (aryl halides) and amines in the presence of catalyst and base (**Scheme 3**, eq. 4, eq. 5).[18,19] Apart from copper and palladium, other metals had also been widely used for amination reaction with aromatic amines. Among them, Singh and his group are worth mentioning because of their first time report on nickel-catalyzed C-N bond formation reaction, employing a range of *N*-nucleophiles **1.13** and arylboronic acids **1.14** (**Scheme 3**, eq. 7).[20] In 2014 Barta's group were able to show a very effective synthetic protocol of iron-catalyzed, direct alkylation of amines **1.16** with alcohols **1.17** (**Scheme 3**, eq. 8).[21]

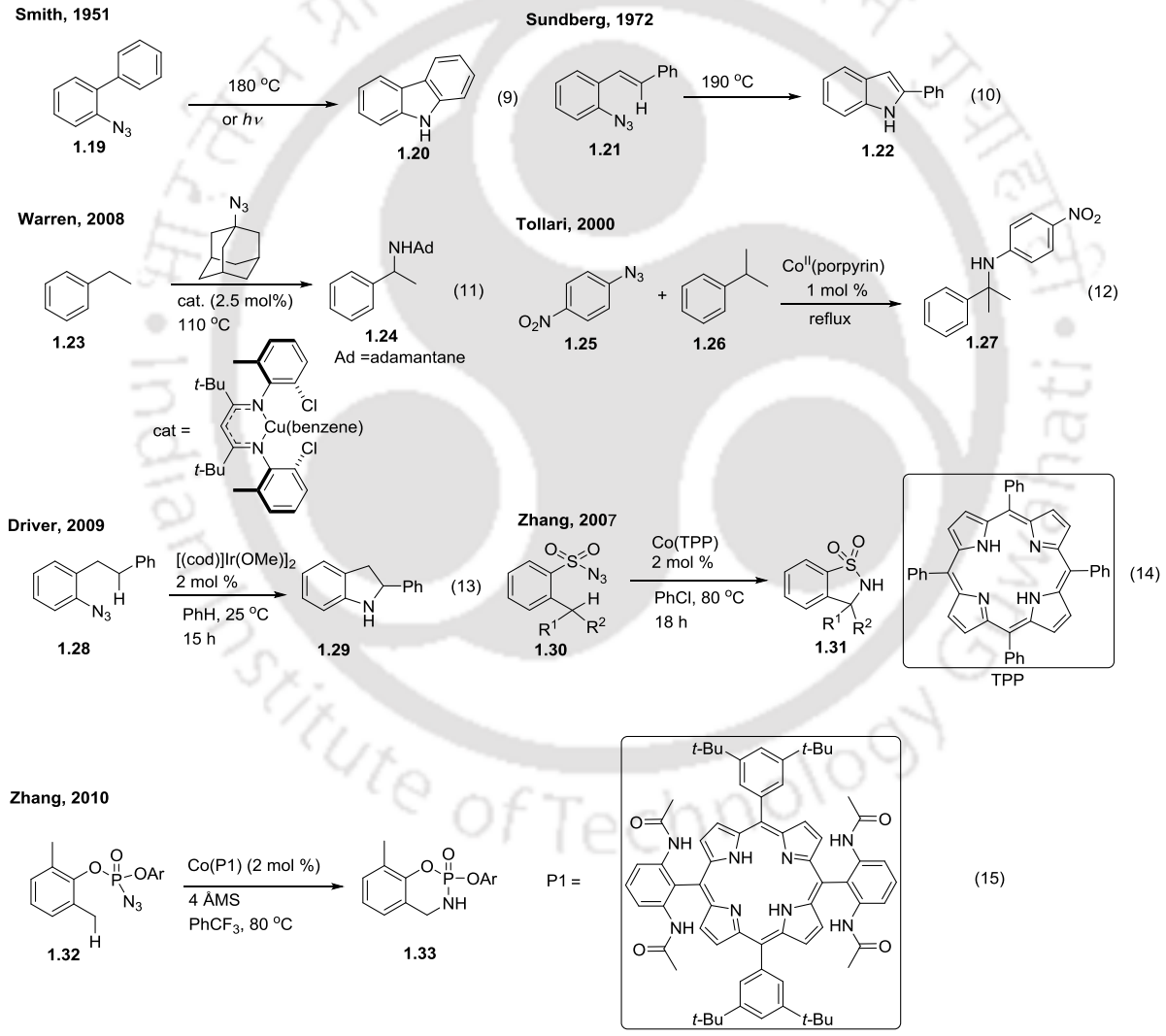


Scheme 3: Amination using amines and amides.

1.3 C-H amination using azides and azido compounds:

Since the discovery of phenyl azides by Peter Grieb in 1864,[22] azide derivatives have emerged and been widely applied in organic synthesis. For the construction of new C-N bond, azides have attained immense interest to the research community. From the last two decades, reaction of azides for C-H amination have experienced remarkable progress. Long back in 1951, Smith and co-workers reported thermolysis and photolysis of biaryl azides to

afford substituted carbazoles.[23] *o*-azidobiphenyl **1.19** under the influence of heat or ultraviolet light afforded carbazoles **1.20** (**Scheme 4**, eq. 9). Later, Sundberg and Hemetsberger disclosed an extension to include styryl azides and vinyl azides respectively.[24,25] Styryl azide **1.21** was heated up to 190 ^{o}C to form corresponding indole derivative **1.22** (**Scheme 4**, eq. 10). In continuation, a variety of indole has also been employed in C(sp^3)-H amination reaction. Warren group have developed copper ketiminate complex catalyzed C(sp^3)-H amination using simple hydrocarbon to afford various benzylamine derivatives (**Scheme 4**, eq. 11).[26] Tollari and his research group also demonstrated a cobalt(II) porphyrins catalyzed C(sp^3)-H amination reaction of hydrocarbon



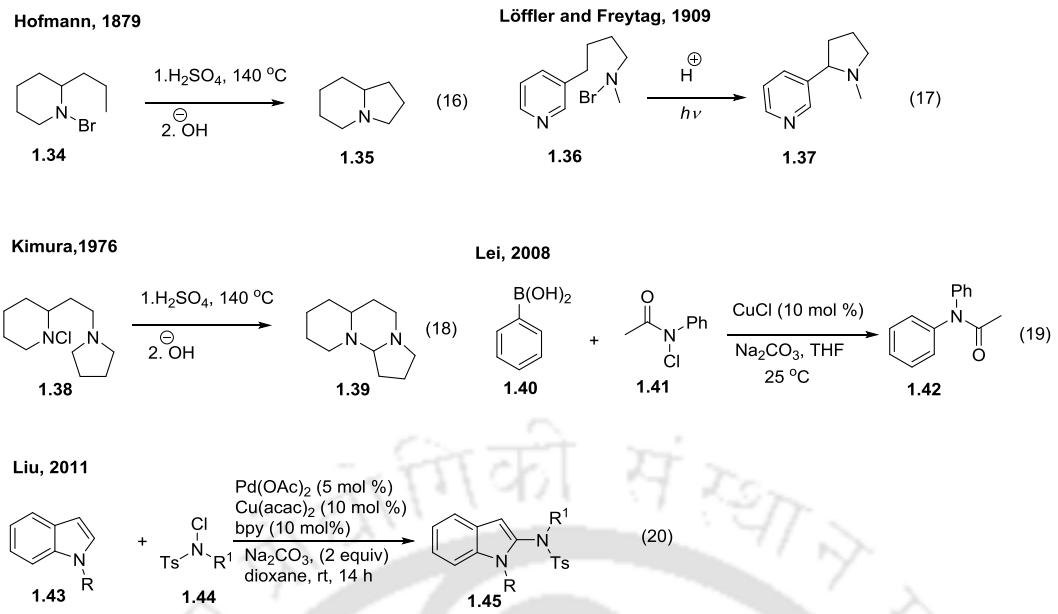
Scheme 4: C-H amination using azides and azido compounds.

(**Scheme 4**, eq. 12).[27] Driver and his co-workers have reported an Iridium(I) catalyzed intramolecular benzylic C-H bond amination of *ortho*-homobenzyl-substituted aryl azides

1.28 to yield indolines **1.29** (**Scheme 4**, eq. 13).[28] Apart from aryl azides, sulfonyl-, and phosphoryl azides also participated in numerous selective intramolecular aminative cyclization reactions. In 2007, Zhang and co-workers reported cobalt(II) tetraphenylporphyrin complexes, Co(TPP), as an effective catalyst for intramolecular amination reaction of benzylic C–H bonds using arylsulfonylazides to synthesize corresponding benzosultam (**Scheme 4**, eq. 14), which are mostly present in various important natural products.[29] Later, Zhang group also reported an intramolecular benzylic C–H bond amination from aryl phosphoryl azides (**Scheme 4**, eq. 15).[30] In the case of phosphoryl azide, the cobalt tetraphenylporphyrin was found to be inactive and Co-**P1** was the more efficient catalyst to afford phosphoramidite **1.33**.

1.4 C-H amination using *N*-haloamines:

The classical example of C–H amination reaction using *N*-haloamines was first discovered by Hofmann in 1880. Later the reaction was named as The Hofmann–Löffler–Freytag reaction. This was probably the very first example of the C–H amination chemistry.[31] Thermal or photochemical decomposition of protonated *N*-haloamine leads to *N*-radical which abstract H-atom to form C-radical. Chlorination of the C-radicals and subsequent intramolecular substitution reactions result in the C–N bond formation. The Hofmann−Löffler−Freytag (HLF) reaction is particularly important for the synthesis of five-membered tertiary amines using *N*-halogenated amines (**Scheme 5**, eq. 16). Almost 25 years after Hofmann's discovery in 1909, K. Löffler and C. Freytag extended the scope of this reaction and demonstrated the synthetic utility to synthesize nicotine **1.37** (**Scheme 5**, eq. 17).[32] Thereafter, *N*-haloamines has been widely used for C-H amination reactions. Several modifications of the Hofmann–Löffler–Freytag reaction were introduced due to the incompatibility of the sensitive functional group present in the starting materials with strongly acidic reaction conditions. Kimura and co-workers developed a photochemical and base mediated H-atom abstraction and cyclization protocol (**Scheme 5**, eq. 18).[33] From the last two decades, in addition to *N*-chloroamines, *N*-chloroamides have been utilized in metal-catalyzed electrophilic amination and chloroamination reactions because of the ease of their preparation and the high reactivities of the N-Cl bond. Lie and co-workers have developed a copper-catalyzed electrophilic amination of arylboronic acids with *N*-chloroamides **1.41** to produce diarylamides **1.42** (**Scheme 5**, eq. 19).[34] Later, Liu and co-workers utilized *N*-chloro-*N*-alkyl−benzenesulfonamide **1.44** for the direct 2-amination of *N*-methylindole in the presence of $Pd(OAc)_2$ and $Cu(acac)_2$ (**Scheme 5**, eq. 20).[35]

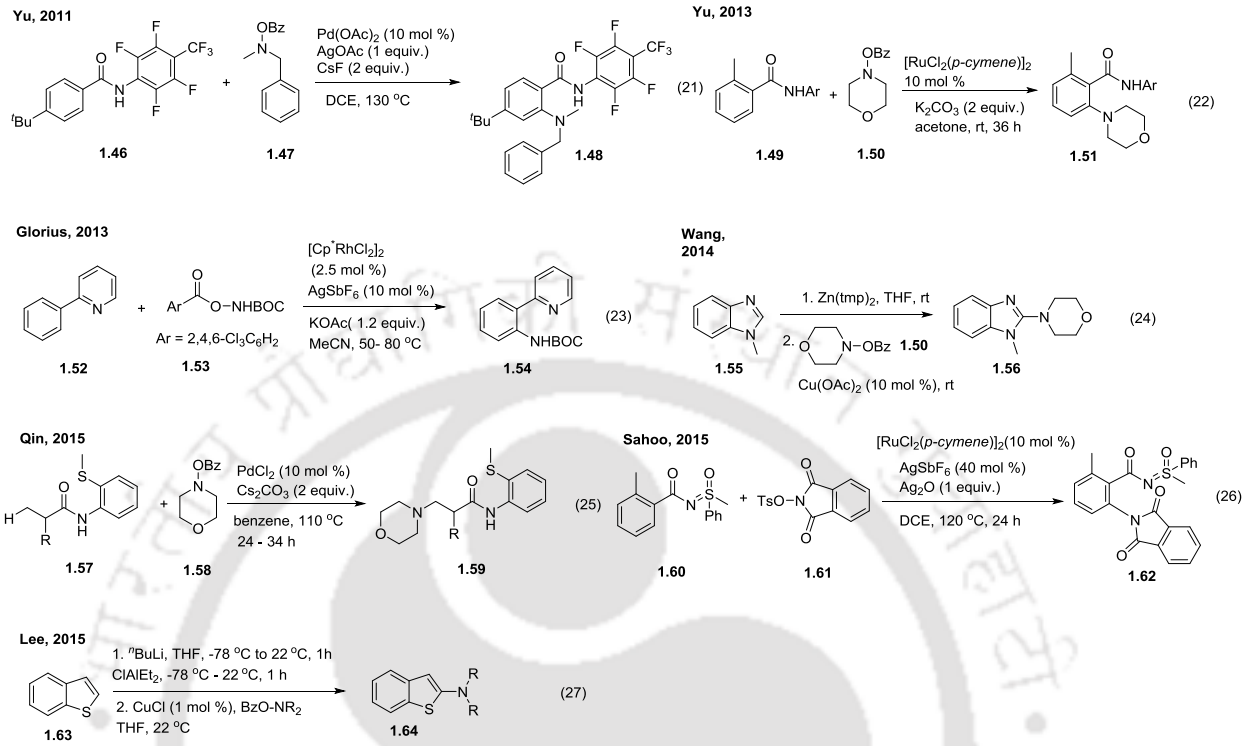


Scheme 5: C-H amination using *N*-haloamines.

1.5 C-H amination using hydroxylamine derivatives:

Over the last 10 years, hydroxylamine derivatives were also envisioned to be an effective source of amino group. Specially *N*-substituted *O*-benzoyl hydroxylamines and *N*,*N*-disubstituted *O*-benzoyl hydroxylamines have been vastly used in the synthesis of secondary and tertiary amines. Yu and co-workers reported amide-directed C-N bond formation by using catalytic amount of $Pd(OAc)_2$, stoichiometric amount of AgOAc, and benzoyl hydroxylamine **1.47 (Scheme 6**, eq. 21).[36] Later, the same group developed a ruthenium-catalyzed $C(sp^2)$-H amination of benzamides **1.49** using *O*-benzoylhydroxylamine **1.50** (**Scheme 6**, eq. 22).[37] Utilizing *O*-(2,4,6-trichlorobenzoyl) hydroxylamines, Glorius and co-workers showed that C-H amination can be achieved for both aryl and alkenyl $C(sp^2)$-H bonds (**Scheme 6**, eq. 23).[38] Wang and co-worker have disclosed a copper-catalyzed direct amination reaction of arenes and heteroarenes **1.55** to afford **1.56** (**Scheme 6**, eq. 24).[39] Qin and co-workers have extended Yu's intermolecular amination reaction and developed amination reaction of unactivated $C(sp^3)$-H bonds using bidentate directing group, a 2-aminothioether **1.58**, to afford aminated product **1.59 (Scheme 6**, eq. 25).[40] Later, Sahoo and co-workers discovered that (*N*-OTs)phthalimide **1.61** can act as an effective amino group source in the reaction of benzamides bearing a methyl phenylsulfoximine **1.60** directing group (**Scheme 6**, eq. 26).[41] Lee and co-workers reported a Cu catalyzed one pot electrophilic C-H amination of heteroarenes **1.63** using *O*-

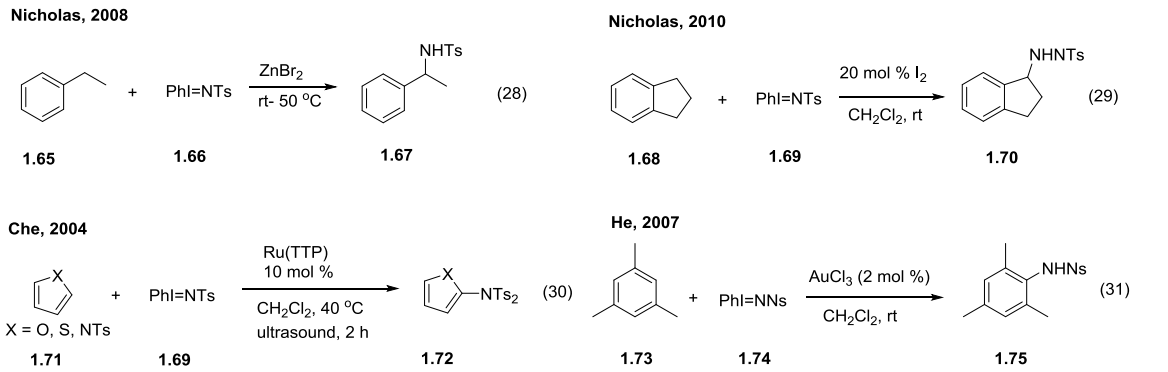
benzoyl hydroxylamines. The direct C−H lithiation/transalumination of heteroarenes **1.63** and catalytic amination sequence afforded **1.64** (**Scheme 6**, eq. 27).[42]



Scheme 6: C-H amination using hydroxylamine derivatives.

1.6 C-H amination using imidoiodinanes:

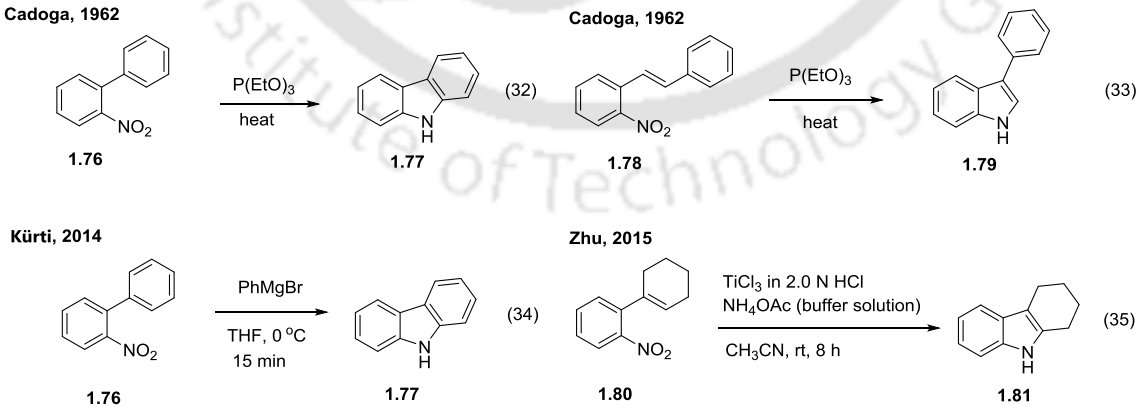
In 1975 Okawara, have discovered a protocol for preparation of *N*-tosyliminophenyliodinane, since then it has been used as an aminating agent.[43] Nicholas and co-worker have disclosed a C(sp^3)-H amination reaction of benzylic and allylic hydrocarbons by a $ZnBr_2$ catalyzed reaction with PhI=NTs to afford corresponding sulfonamides **1.67** (**Scheme 7**, eq. 28).[44] Later the same group reported I_2 catalyzed amination of benzylic, aliphatic saturated and unsaturated hydrocarbons by reaction with imidoiodinanes (**Scheme 7,** eq. 29).[45] Direct C(sp^2)-H amination of a simple hydrocarbon was the most desirable but challenging task. Che and co-workers have developed selective amination of aromatic heterocycles using iminoiodinanes as the aminating agents. (**Scheme 7**, eq. 30).[46] In 2007, He and co-workers developed a gold-catalyzed direct C-H amidation of arene (**Scheme 7**, eq. 31).[47]



Scheme 7: C-H amination using imidoiodinanes.

1.7 C-H amination using nitro compounds:

Nitroarenes, due to their general availability and easy synthesis,[48] are attractive starting materials for the synthesis of bioactive *N*-heterocycles and diarylamines. Almost 55 years ago, Cadogan and co-workers, during the course of their investigations on the chemistry of triethyl phosphate, discovered that some aromatic nitroarenes on reaction with triethyl phosphate undergo deoxygenation to form a heterocyclic ring. They found that carbazole **1.77** was formed when *o*-nitrobiphenyl **1.76** was heated with triethyl phosphate (**Scheme 8**, eq. 32).[49] In the same work, they also reported the formation of 2-phenylindole from the reaction of triethyl phosphite with both *trans*- and *cis*-*o*-nitrostilbene (**Scheme 8**, eq. 33).[49] This has lead to the great interest to the several research groups to explore the chemistry of nitroarenes to synthesize *N*-heterocycles. Later, in 2014, Kürti and co-workers have disclosed a simple protocol for the synthesis of fused *N*-heterocycles from 2-nitrobiaryls

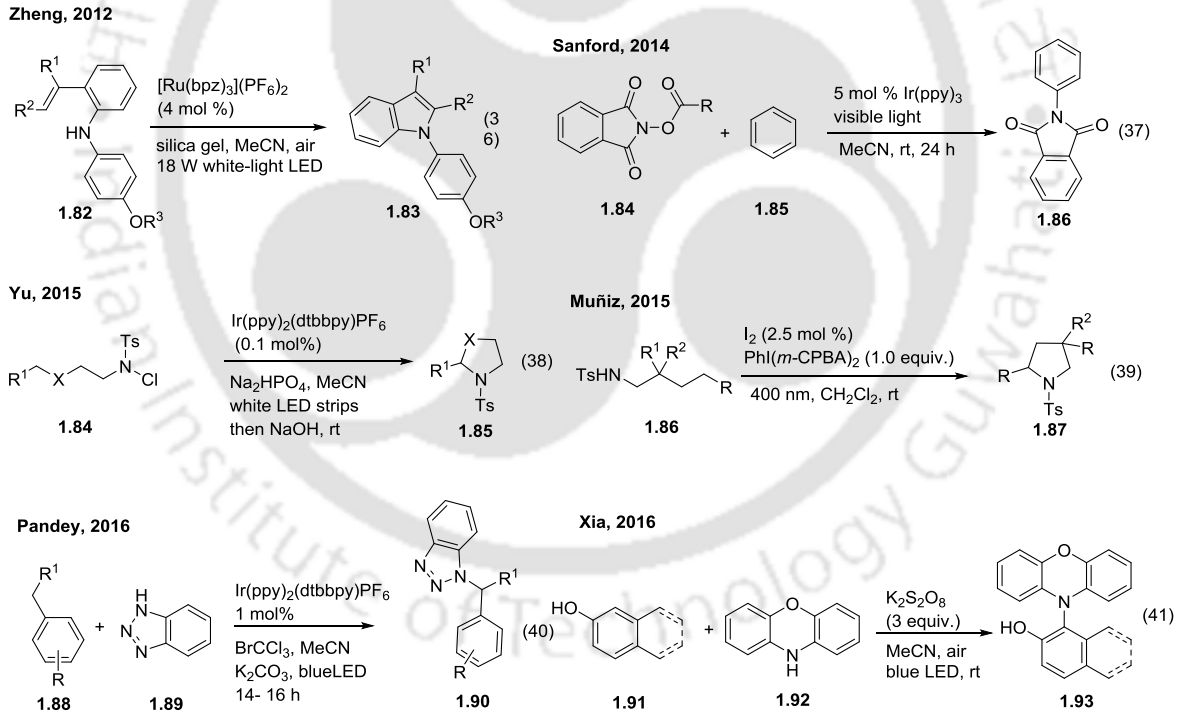


Scheme 8: C-H amination using nitroarenes.

and PhMgBr (**Scheme 8**, eq. 34).[50]Zhu and coworker have reported a formal reductive C(sp^2)-H amination process by using *o*-nitrostyrenes **1.80** with aqueous solution of $TiCl_3$ to afford indoles **1.81** (**Scheme 8**, eq. 35).[51]

1.8 C-H amination via photoredox reaction:

Recently, visible-light photocatalyzed reactions have made great advancement. Several interesting visible-light photocatalyzed and radical amination reactions have also been developed, especially, in the last five years.[52] Under mild redox-neutral conditions, via a single-electron transfer (SET) process, *N*-centered radical or radical cation species is generally generated from *N*-centered radical precursors (N-X, X = O, Cl, Br, N, etc.) in the presence of photocatalysts. In 2012, Zheng and coworkers reported a photoredox reaction for the direct intramolecular C-N bond formation to afford *N*-arylindoles from styryl diarylamines (**Scheme 9**, eq. 36).[53] Later, Sanford and co-workers developed a visible-light photocatalyzed direct C-H amination of (hetero)arenes in the presence of an Ir(III) catalyst



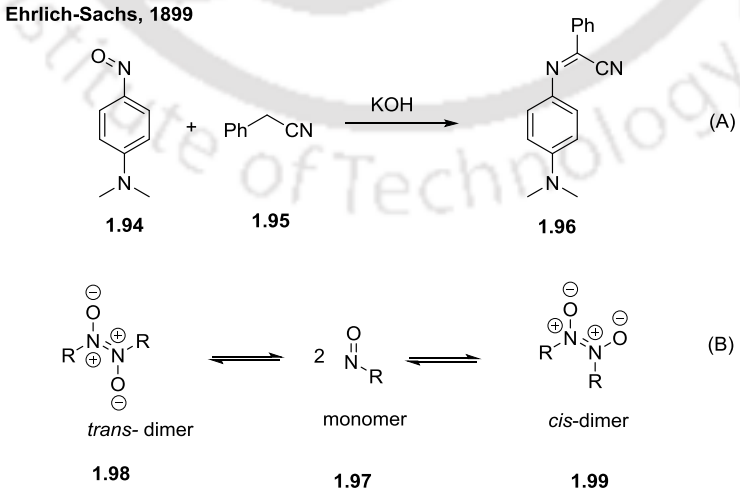
Scheme 9: C-H amination via photoredox reaction.

using *N*-acyloxyphthalimides as a precursor for nitrogen-based radicals (**Scheme 9**, eq. 37).[54] Yu and co-workers developed a visible-light-promoted C(sp^3)-H amination of *N*-chlorosulfonamides **1.84** using 0.1 mol% photocatalyst, Ir(ppy)$_{2(}$dtbbpy)PF_6, to afford nitrogen-containing heterocycles **1.85** (**Scheme 9**, eq. 38).[55] Muñiz and co-workers in 2015,

reported a visible-light initiated iodine-catalyzed intramolecular C–H amination reaction to obtain pyrrolidine derivatives **1.87** (**Scheme 9**, eq. 39).[56] Pandey and co-workers described a visible-light-mediated intermolecular benzylic C(sp^3)-H bond amination using imidazole, benzotriazole, benzimidazole, and tetrazole as the amine source (**Scheme 9**, eq. 40).[57] In the same year, Xia's group developed a visible-light-mediated amination of phenols using phenothiazines **1.92** as amine source and $K_2S_2O_8$ as the external oxidant to afford *ortho*-aminated phenols **1.93** (**Scheme 9**, eq. 41).[58]

1.9 C-H amination using nitrosoarene:

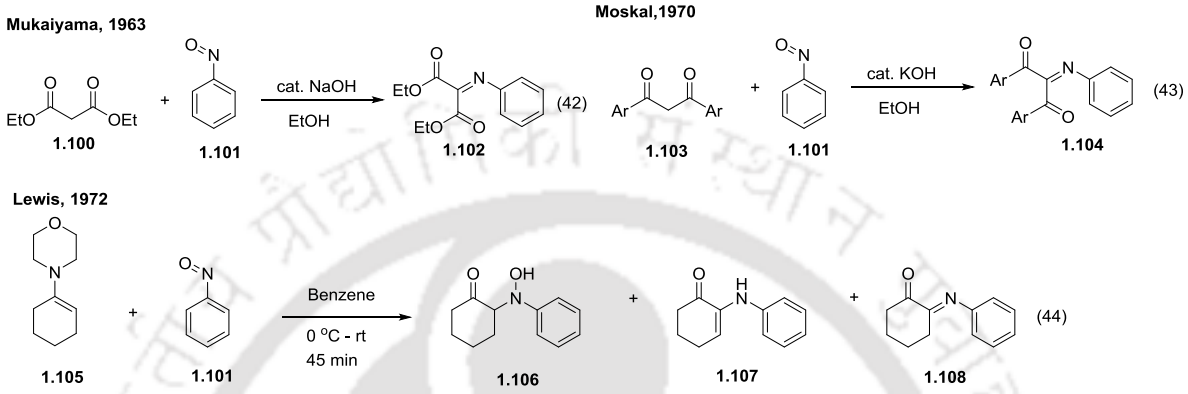
In 1874, Adolf Baeyer first reported the preparation of nitrosobenzene,[59] since then nitrosoarenes have been extensively used to incorporate nitrogen as well as oxygen functionality in the molecules.[60] In due course, nitrosoarenes proved to be an important synthetic building block in synthetic organic chemistry. The high reactivity of nitrosoarenes due to the polarization of N=O bond and its ready/easy availability as starting materials are the significant aspects, which makes it a versatile electrophile for the construction of bioactive molecules and natural products.[2] Ehrlich and Sachs, in 1899, reported the reaction of *p*-nitrosodimethylaniline with active methylene compounds to afford azomethine derivatives.[61] Since then, many examples of Diels–Alder reactions,[62] ene reactions[63] and the addition of carbanion enolates[64] using nitrosoarene have been reported. However, the major difficulty in nitroso chemistry, particularly with regard to the yield of the desired product, is the equilibrium between the monomer and azodioxy dimer. In fact "*the careful control of this equilibrium is an essential prerequisite for use of nitroso compounds in organic synthesis*."[60a]



Scheme 10: **A)** First nucleophilic addition reaction on nitrosoarene; **B)** Equilibrium between the monomer and azodioxy dimer of nitrosoarene.

1.10 C-H amination via nitroso aldol reaction:

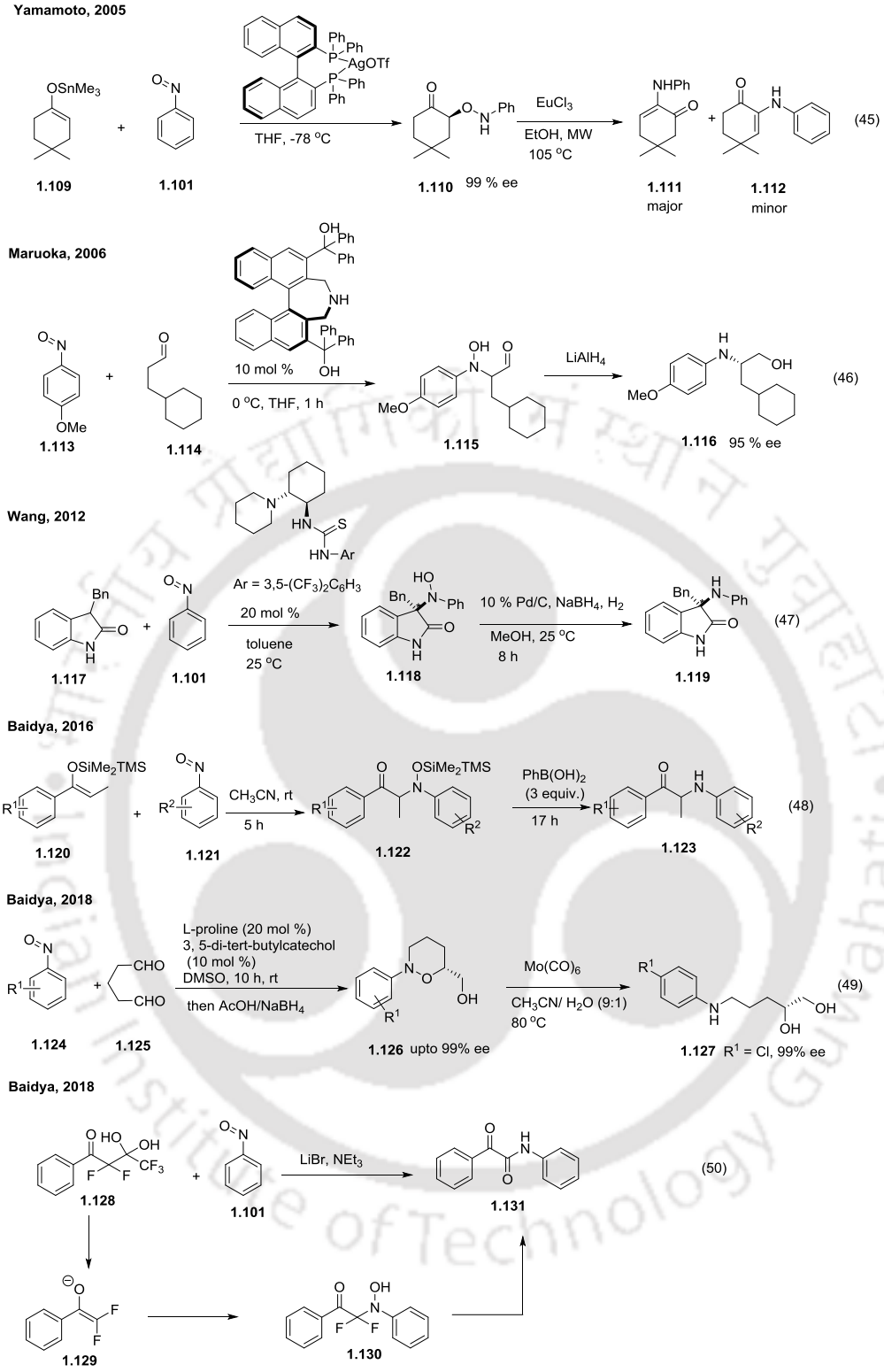
After Ehrlich and Sachs's report, Mukaiyama and co-workers reported addition of enolates to nitrosobenzene to access azomethine derivatives **1.102** (**Scheme 11**, eq. 42).[65] Subsequent studies by Moskal and co-workers developed a similar condensation of 1,3-diaronlymethanes with nitrosobenzene (**Scheme 11**, eq. 43).[66]



Scheme 11: Early report on amination via nitroso aldol reaction.

Lewis and co-worker in 1972, reported the synthesis of *α*-hydroxyamino ketones **1.106** using nitrosobenzene. The reaction was performed in benzene at 0 ^{o}C to room temperature with 1-morpholino-1-cyclohexene **1.105** (**Scheme 11**, eq. 44).[67] Along with the *α*-hydroxyaminoketone, the corresponding aniline derivative **1.107** have also been isolated from the reaction.

These previous results prompted the development of new methods for carbon-nitrogen bond formation by exploring the potential of *N*-nitrosoaldol 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. Yamamoto group has extensively studied *N*-nitroso aldol reactions to produce *α*-aminooxy carbonyl derivatives.[68] In 2005, they developed a method to achieve the synthesis of *α*-aminooxy carbonyl derivatives **1.110** and *α*-amino enone derivatives **1.111** and **1.112** by a lewis acid catalyzed ($EuCl_3$) 1,2-rearrangement of **1.110** (**Scheme 12**, eq. 45).[69] Maruoka group, in 2006, have developed a hydroxyl amination reaction with nitrosoarene and aldehyde to afford *α*-*N*-hydroxylamino aldehyde **1.115**. Reduction of **1.115** with $LiAlH_4$ afforded amino alcohol **1.116** (**Scheme 12**, eq. 46).[70] Wang group applied chiral bifunctional tertiary amine thiourea to achieve the asymmetric hydroxyamination of 3-substituted oxindole **1.117** with nitrosobenzene. The corresponding hydroxylamine derivative **1.118** was further reduced to



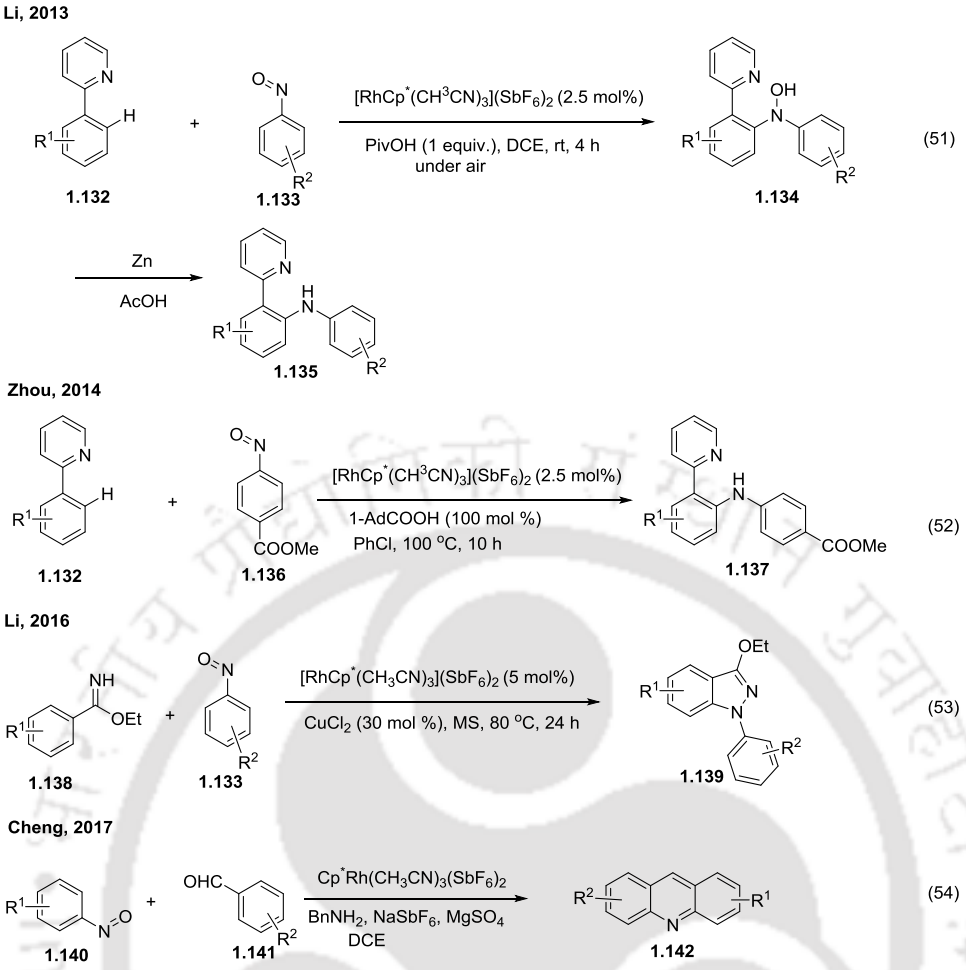
Scheme 12: Amination via nitroso aldol reactions.

give enantiopure 3-amino-2-oxindoles **1.119** (**Scheme 12**, eq. 47).[71] The major concern of nitroso aldol reaction is the cleavage of N-O bond to produce direct aminated product. Although many researchers have developed the direct method for synthesis of aminated

product by nitroso aldol reaction over the past years, Baidya group have developed a one-pot synthesis of *α*-amino ketones **1.123** via a nitroso aldol reaction between aromatic nitroso compounds **1.121** and silyl enol ethers **1.120**. The *in situ* cleavage of N-O bond of **1.122** was achieved by using brønsted acid to directly get *α*-amination of ketones (**Scheme 12**, eq. 48).[72] Very recently, the same group has developed asymmetric nitroso aldol reaction of distal dialdehydes with nitrosoarene to access N-O bond containing chiral heterocycles. The cleavage of N-O bond was carried out by $Mo(CO)_6$ to access amino alcohol **1.127** with excellent enantioselectivites (**Scheme 12**, eq. 49).[73] Baidya group have also demonstrated electrophilic amination reactions of *gem*-difluoro-enolates **1.129**, which was generated *in situ* from difluorinated *gem*-diols **1.128**, in the presence of LiBr and NEt_3. *N*-selective nitroso aldol reaction with electrophilic nitrosoarenes **1.101** followed by a cascade rearrangement of **1.130** provided *α*-ketoamides **1.131** (**Scheme 12**, eq. 50).[74]

1.11 Metal-catalyzed C(sp^2)-H amination using nitrosoarene:

Reports on C(sp^2)-H amination involving nitrosoarene are limited. Li and co-workers have developed an unprecedented rhodium-catalyzed aryl C-H amination using nitrosobenzenes to afford synthetically important *N*-arylhydroxylamines **1.134**. Reduction of **1.134** with Zn/AcOH gave the valuable diarylamine **1.135** (**Scheme 13**, eq. 51).[75] Later the same group, in their extension of the previous work, have developed a protocol of aryl C-H amination followed by *in situ* cleavage of the resulting hydroxylamines to afford versatile diarylamines **1.137** (**Scheme 13**, 52).[76] Due to the versatile reactivity of N=O bond of nitrosoarene it has also been used for the synthesis of bioactive core moiety like indazole derivatives. Li and co-workers have reported a rhodium and copper catalyzed efficient synthesis of 1*H*-indazoles **1.139** via C-H activation and C-N/N-N bond formation (**Scheme 13**, eq. 53).[77] Cheng group have demonstrated a Rh(III)-catalyzed C-H functionalization and cyclization of aromatic aldehydes **1.141** and nitrosoarene **1.140** to access acridine analogs **1.142**. An imino transient directing group was used for a sequential C-H amination, cyclization, and aromatization to lead to the formation of **1.142** (**Scheme 13**, eq.54).[78]



Scheme 13: Metal catalyzed C(sp^2)-H amination.

In recent years, amination reactions using different aminating reagents are gradually developing and different ways of amination reactions have its own potential. Classical arylamination via Copper catalyzed Ullmann-Goldberg coupling, Chan-Lam coupling and palladium catalyzed Migita-Kosugi reaction and the Buchwald-Hartwig amination have been widely used. Apart from the other classical approaches of amination, such as reductive carbonyl amination, nucleophilic displacement of a leaving group and imine alkylation, the development of novel transition metal catalyzed C-H amination and C-H arylamination have been tremendously progressed over the years. On the other hand, photo-redox catalyzed C-H amination indubitably was an important discovery. Amination using aminating agents like azides, *N*-haloamines, hydroxylamines and nitroarenes have also been made remarkable progress in this field. However, in spite of the advancement in the field of amination reactions, the previous strategies have some limitations. For example, the Buchwald-Hartwig amination involved preactivated electrophiles (aryl halides) and amines in the presence of Pd catalyst. Thus, the scope of these reactions are somewhat limited

because of aryl halides, which sometimes are not readily available. The main drawbacks of metal catalyzed arylamination reactions are the use of expensive metal, synthesis of aryl halides or pseudohalides, undesired byproducts. Moreover, amination using other aminating agents like azides, *N*-haloamines, hydroxylamines and nitroarenes suffer from limitations related to the use of harsh reaction condition, functional group incompatibility and general applicability. Nitrosoarenes are readily available. Due to high polarizability of N=O bond it can react easily with nucleophiles and proved to be an important synthetic building block in synthetic organic chemistry to install amine functionality in molecules. However, very few reports on C-H amination using nitrosoarene are known till date. Therefore, the aim of this thesis is to develop novel synthetic methodologies for C-N bond formation using nitrosoarene under operationally simple conditions without using metallic reagents/ catalyst.

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Chapter 2

Metal Free Direct C(sp^2)-H Arylaminations Using Nitrosoarenes to 2-hydroxy-di(het)aryl Amines as Potent Multifunctional Aβ-aggregation Modulators

2.1 Introduction:

Diarylamines and their derivatives are ubiquitous structural motifs of natural products, active pharmaceuticals, antioxidants, dyes, and agrochemical agents.[1] Selected examples are shown in **Figure 1**. Norsegoline,[2] a marine alkaloid containing diarylamine moiety, exhibits antileukemic properties. Bosutinib,[3] which contains arylaminoquinoline moiety, is a BCR-ABL and src tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukemia. Popolohuanone,[4] an amioquinone derivative, is a naturally occurring anticancer agent. Arylaminocoumarin derivative novobiocin[5] exhibits antibiotic properties. This widespread application has promoted the development of novel and efficient methodologies for the synthesis of diarylamines and their derivatives.

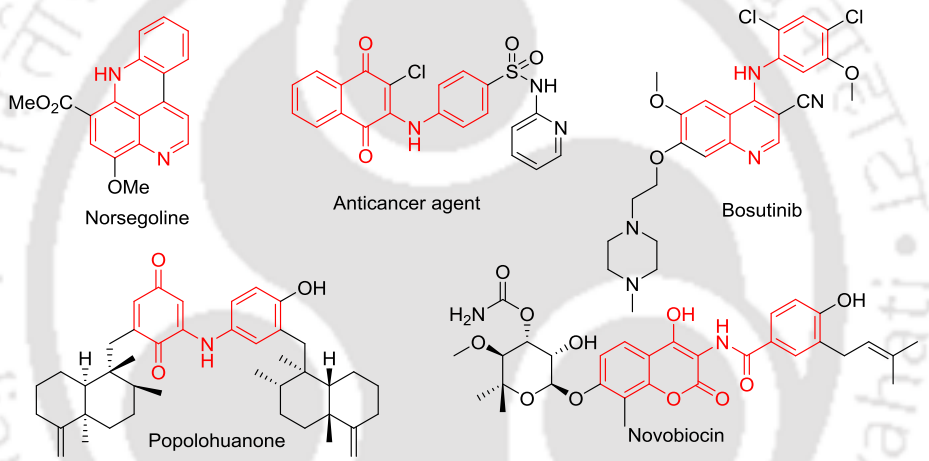
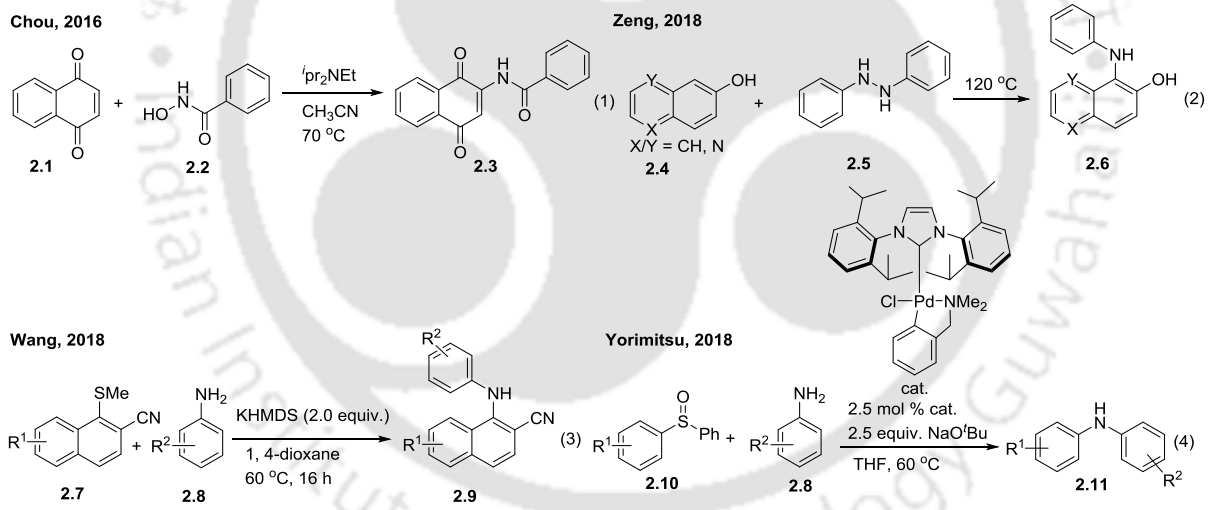


Figure 1: Relevant examples of important diarylamines.

2.2 Known methods for the synthesis of diarylamines:

Numerous synthetic strategies have been reported in the literature for the synthesis of diarylamine. In this context, transition metal-based catalyzed cross-coupling reaction between suitably functionalized arene and arylamine substrates works efficiently for the synthesis of diarylamines.[6] In **Chapter 1** (**1.2**, **Scheme 3**), various methods for the synthesis of diarylamines using transition metal catalyst have been described. Apart from transition metal-catalyzed amination, visible-light photocatalyzed syntheses of diarylamines have emerged recently as a powerful alternative. Different approaches to diarylamines using various photocatalysts have also been mentioned in **Chapter 1** (**1.8, Scheme 9).** Other main

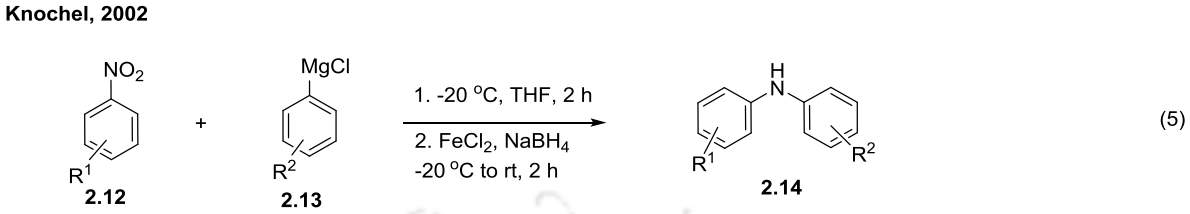
approaches to synthesize diarylamines via amination reactions involving varieties of electrophilic amine sources, such as azides, *N*-halo amines, hydroxylamine derivatives and nucleophilic arene derivatives have also been discussed in **Chapter 1** (**1.3**, **Scheme 4**, **1.4 Scheme 5**, **1.5 Scheme 6**). Besides all these methods, hydroxamic acid, hydrazine, aryl alkyl thioether and aryl sulphoxide have also been used for the synthesis of biologically important diarylamines. In 2016, Chou and co-workers have reported an operationally simple protocol for the synthesis of amidoquinone **2.3** using naphthoquinones **2.1** and hydroxamic acid derivative **2.2** under basic conditions (**Scheme 1**, eq. 1).[7] Zeng and co-workers in 2018, developed an *ortho*-selective amination reaction of 2-naphthol **2.4** with substituted hydrazines **2.5** (**Scheme 1**, eq. 2).[8] In the same year, Wang and co-workers disclosed a transition metal-free protocol for the synthesis of diarylated aniline derivatives. Aniline **2.8** on reaction with aryl alkyl thioether **2.7** under basic condition afforded desired diarylated amine via C(sp^2)-S bond cleavage (**Scheme 1**, eq. 3).[9] Later, Yorimitsu and co-workers developed a palladium/*N*-heterocyclic carbene (NHC) catalyzed amination of diaryl sulfoxides **2.10** using anilines **2.8** (**Scheme 1**, eq. 4).[10]



Scheme 1: Selected methods for the synthesis of diarylamines.

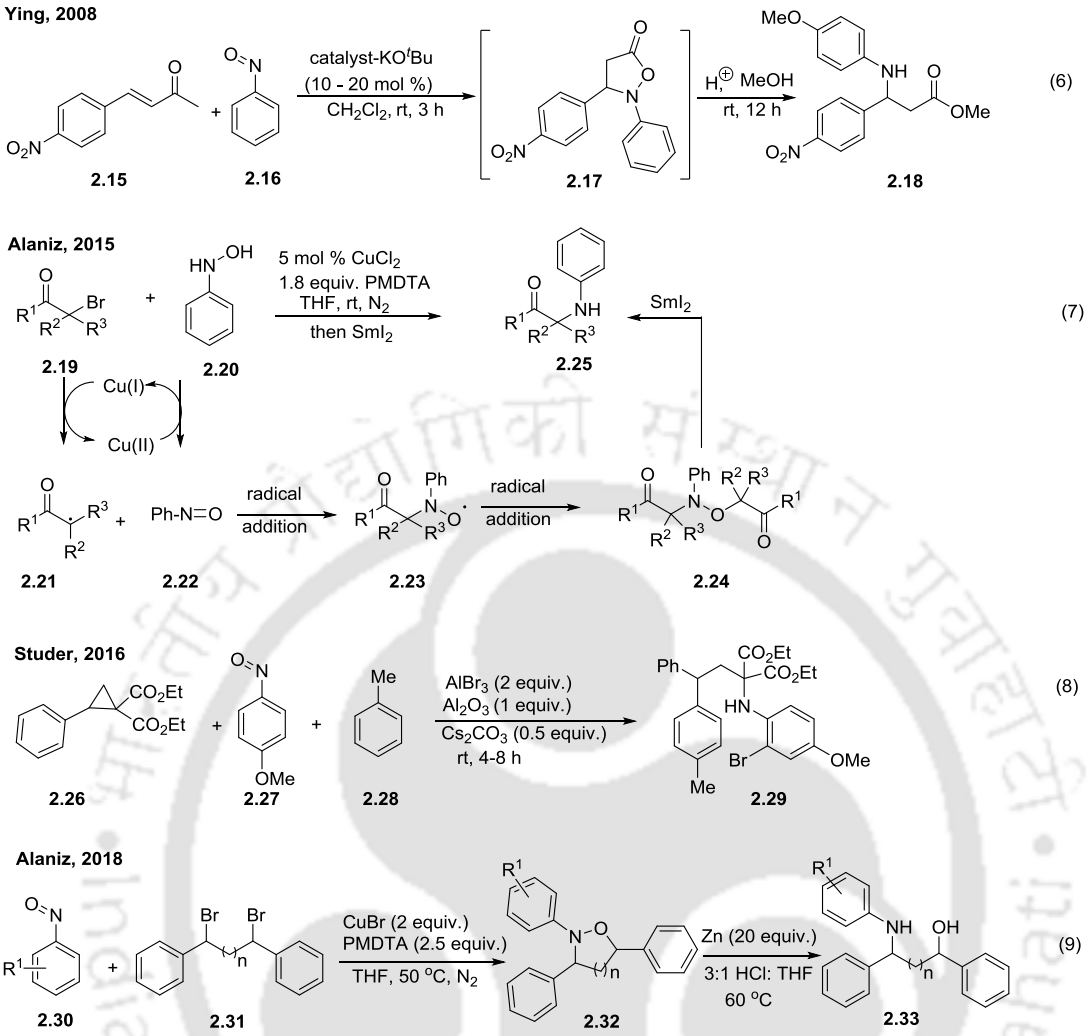
Nitroarenes have been widely used as electrophilic aminating agents for the synthesis of diarylamines/ alkyl arylamines because of their easy availability. In 2002, Knochel and coworkers have developed a one-pot synthesis of diarylamines **2.14** by the addition of arylmagnesium compounds **2.13** to nitroarenes **2.12** (**Scheme 2**, eq. 5).[11] $FeCl_2$ and $NaBH_4$ were used to reduce *in situ* generated diarylhydroxylamine. In addition to the synthesis of

diarylamine, there are reports on the use of nitroarenes for the synthesis of aryl alkyl amines.[12,13,14]



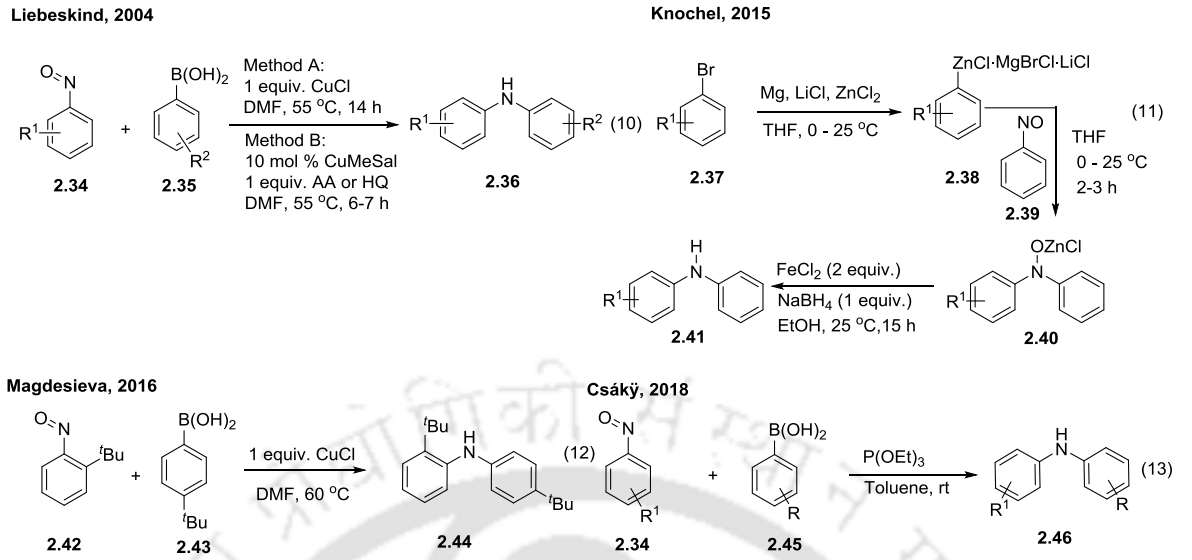
Scheme 2: Synthesis of diaryl amines using nitroarenes.

Nitrosoarenes, which are reactive and readily available, are also widely used as the amine source for the synthesis of aliphatic amines.[15] Nitrosoarenes participated in various reactions, such as Diels-Alder, ene, nitroso aldol reaction to install amine functionality in the molecules. However, only a few reports on the use of nitrosoarene for the synthesis of diarylamines are known. Metal catalyzed C(sp^2)-H aminations using nitrosoarene have been discussed in **Chapter 1** (**1.95**, **Scheme 16**). Additionally, in 2008, Ying and coworker have reported an *N*-heterocyclic carbene (NHC)-catalyzed reaction of *α*, *β*- unsaturated aldehyde **2.15** with nitrosoarene **2.16**. In a one-pot reaction, acid-catalyzed esterification of the intermediate *N*-phenylisoxazolidin-5-ones **2.17** and Bamberger-like rearrangement afforded *β*-amino acid esters **2.18** (**Scheme 3**, eq. 6).[16] In a very unique approach, Alaniz and co-workers have developed a method for the synthesis of hindered *α*-amino carbonyl derivatives **2.25.** Copper-catalyzed radical addition to the *in situ* generated nitrosobenzene **2.22** from phenylhydroxylamine **2.20** followed by reduction with SmI_2 afforded amino carbonyl derivative **2.25** (**Scheme 3**, eq. 7).[17] In 2016, Studer and co-workers developed a reaction of donor-acceptor cyclopropanes **2.26** and nitrosoarene **2.27** for the synthesis of **2.29** (**Scheme 3**, eq. 8).[18] Very recently, Alaniz and co-workers have developed a copper(II)bromide catalyzed method for the direct installation of arylamine and hydroxyl functionality using nitrosoarene **2.30** and dibromo alkane **2.31**. Subsequent reductive cleavage of N-O bond of **2.32** by Zn metal gave corresponding amino alcohol **2.33** (**Scheme 3**, eq. 9).[19]



Scheme 3: Selected amination reactions using nitrosoarene.

Addition of metal-based arene nucleophile to the nitroso group has been proven to be one of the major routes for the direct synthesis of diaryl amines. In 2004, Liebeskind and co-workers reported two methods for amination of arylboronic acids **2.35** with nitrosoarene **2.34** to give the diarylamine **2.36** (**Scheme 4**, eq. 10).[20] A stoichiometric amount of CuCl, ascorbic acid (AA) or hydroquinone (HQ) was used as reducing agents. Magdesieva and co-workers reported amination of arylboronic acids **2.43** with sterically hindered nitrosoarene **2.42** using a stoichiometric amount of CuCl or $Cu(OAc)_2$ to afford diarylamine **2.44** (**Scheme 4**, eq. 12).[21]



Scheme 4: Diarylamine synthesis involving metal based arene neucleophiles.

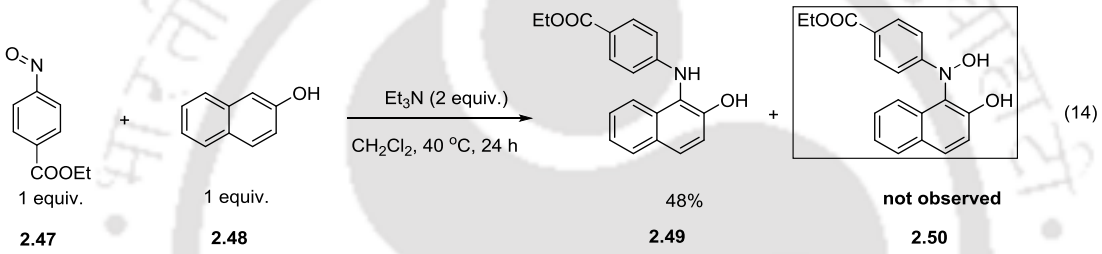
Apart from boron, zinc-based reagents also had been used for amination reaction using nitrosoarene. In the year of 2015, Knochel and co-workers have developed an aryl zinc reagent addition reaction to nitrosoarene to access zinc salt of the corresponding hydroxylamine derivative **2.40**. Then the hydroxylamine derivative **2.40** was reduced by $FeCl_2$ and $NaBH_4$ in ethanol to the corresponding polyfunctional secondary amine **2.41** (**Scheme 4**, eq. 11).[22] Recently, in 2018, Csákÿ and co-workers have reported a direct cross-coupling reaction between nitrosoarene **2.34** and arylboronic acid **2.45**. A stoichiometric amount of triethylphosphate $P(OEt)_3$ was used for *in situ* formation of nitrene intermediate which adds to the arylboronic acid to provide diarylamie amine **2.46** (**Scheme 4**, eq. 13).[23]

The majority of the diarylamine synthesis depends on coupling reaction between functionalized arene and arylamine substrates using expensive metal and sophisticated photocatalyst. The scope of these reactions is somewhat limited because these reactions involve the use of functionalized arenes, which sometimes are not readily available. The reported methods for the synthesis of diarylamine using nitrosoarene and organometallic reagents,- are incompatible with the substrates having -OH or -NH groups. Moreover, the synthesis of diarylamines using nitrosoarene required an additional step for N-O bond cleavage with metallic or organic reducing agents. Therefore, development of a novel method for a metal-free direct C(sp^2)-H arylaminations of arene using nitrosoarenes without the aid of additional reagents or steps for the N-O bond cleavage would be advantageous. Additionally, to the best of our knowledge, no method for direct C-H arylamination reaction

of naphthol or phenol using nitrosoarene was reported in the literature. Therefore, the interest was to investigate the possibility of direct C-H arylamination of naphthol/ phenol using nitrosoarenes as an aminating agent.

2.3 Results and Discussions:

The studies commenced with the reaction of ethyl 4-nitrosobenzoate and 2-naphthol as a nucleophile in the presence of triethylamine (NEt_3). Pleasingly, the reaction of 1 equiv. of **2.47** with 2-naphthol **2.48** in the presence of 2 equiv. of triethylamine in dichloromethane at 40 ^oC for 24 h provided arylaminonaphthol **2.49** with 48% yield instead of corresponding hydroxylamine derivative **2.50** which generally formed in the nucleophilic addition reaction of nitrosoarene (**Scheme 5**, eq. 14).



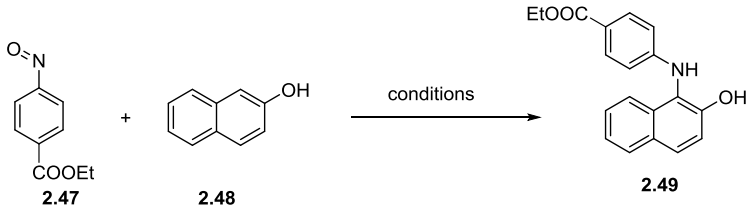
Scheme 5: Initial result.

2.4 Optimization of reaction condition:

Encouraged by the initial result, different conditions were examined to increase the yield of the desired arylaminonaphthol **2.49**.

The increase in the yield of the desired arylaminonaphthol was observed with an increase in the relative stoichiometry of the nitrosoarene (**Table 1**, entry 2, 3). Dichloromethane was found to be the best among the other solvents such as toluene, methanol, ethanol which were screened. The reaction in the absence of base provided **2.49** with a reduced yield of 46% (**Table 1**, entry 9). A similar reduction of the yield was observed when the inorganic base, such as KO^{t}Bu and K_2CO_3 were used. The best yield (85%) was obtained from the reaction of nitrosoarene **2.47** (1.85 equiv.) with 2-naphthol **2.48** (1 equiv.) in the presence of Et_3N (2 equiv.) in refluxing dichloromethane for 24 h (**Table 1**, entry 4).

Table 1: Optimization of reaction conditions



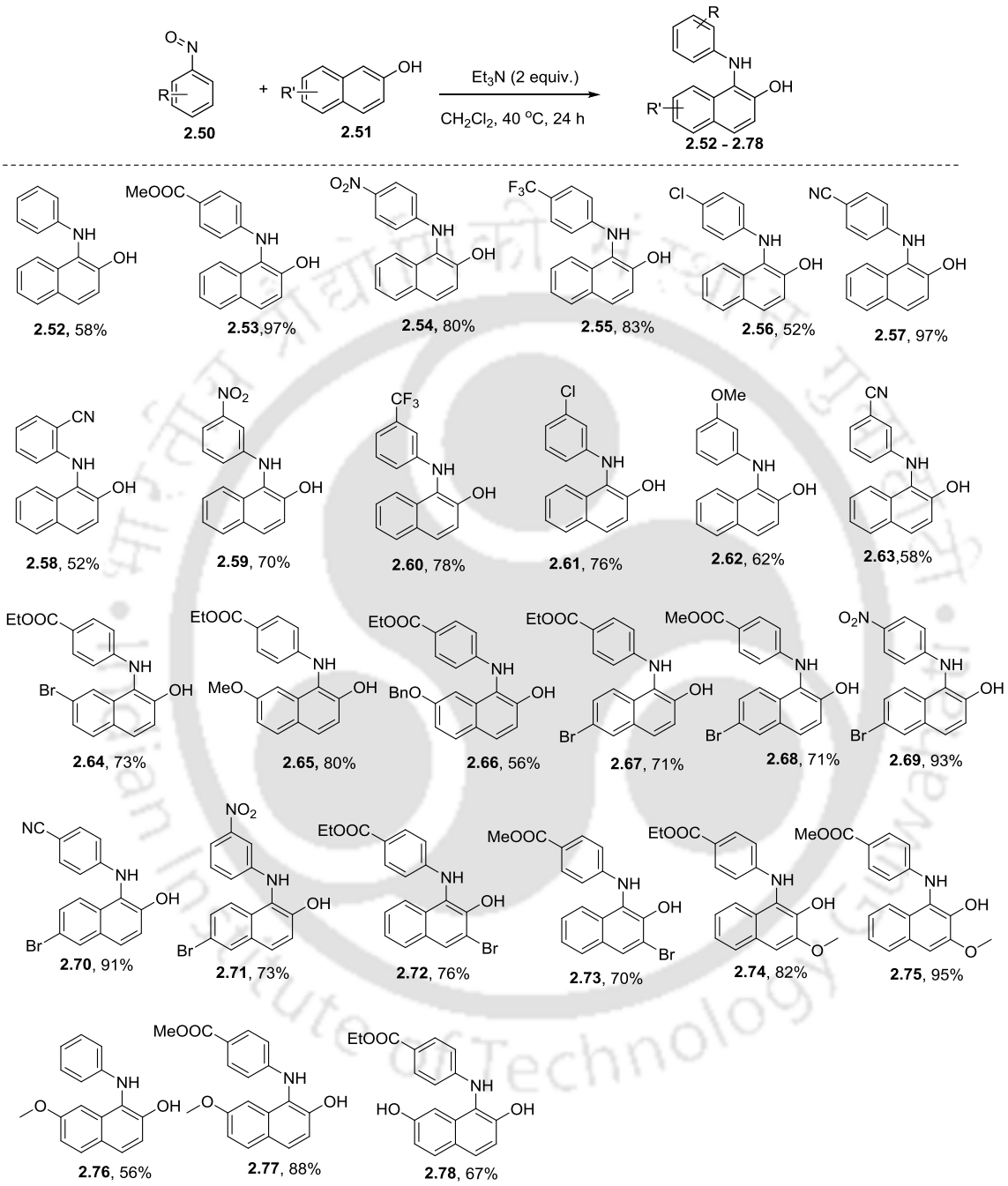
Entry	Conditions (equiv.)	Isolated yield (%)
1[b]	NEt_3(2), DCM, 40 °C	48
2[c]	NEt_3(2), DCM, 40 °C	64
3[d]	NEt_3(2), DCM, 40 °C	76
4	NEt_3(2), DCM, 40 °C	85
5	NEt_3(0.2), DCM, 40 °C	50
6	NEt_3(0.5), DCM, 40 °C	55
7	NEt_3(1), DCM, 40 °C	71
8	NEt_3(2), DCM, rt	75
9	DCM, 40 °C	46
10	K^{t}OBu, DCM, 40 °C	30
11	NEt_3(2), Toluene, 40 °C	79
12	^{i}pr$_2$NEt (2), DCM, 40 °C	64
13	NEt_3 (2), DCE, 80 °C	53
14	K_2CO_3 (2), DCM, 40 °C	36
15	NEt_3 (2), MeOH, 40 °C	69
16	NEt_3 (2), EtOH, 40 °C	45
17	THIQ, DCM, 40 °C	22

[a]All reactions were performed with 2-naphthol (0.17 mmol), nitrosobenzene (0.31 mmol) in solvent (4 mL) for 24 h. [b]1 equiv. , [c]1.25 equiv. and [d]1.5 equiv. of nitrosobenzene was used.

2.5 Scope of arylaminations of naphthols:

Optimized reaction conditions were used to explore the substrate scope of the coupling reaction of 2-naphthol with various nitrosoarenes. Nitrosoarenes with both electron-donating and electron-withdrawing groups reacted smoothly to provide the desired aminoaryl- naphthols **2.52-2.78** with good to excellent yields (**Scheme 6**). Electron-withdrawing substituents, such as COOMe, NO_2, and CF_3 at the *p*-position of nitrosoarene

gave the withdrawing substituents, such as COOMe, NO_2, and CF_3 at the *p*-position of nitrosoarene gave the corresponding aminonaphthol **2.53** (97%)**, 2.54** (80%), and **2.55** (83%) with excellent yield. However, slightly lower yields of aminonaphthols **2.52** (58%)

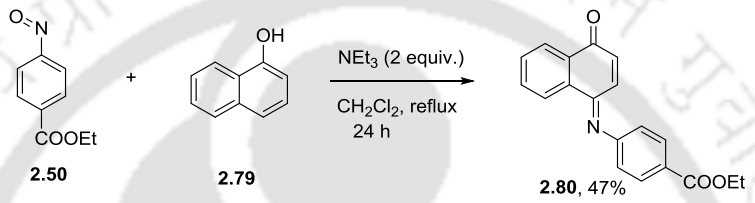


Scheme 6: Scope of arylaminations of naphthols.

and **2.62** (62%) were obtained from the reaction of nitrosobenzene and *m*-methoxy nitrosobenzene, respectively. The coupling reactions of diversely substituted naphthols with different nitrosoarenes were investigated next to further expand the

scope of this novel arylamination reaction. All the substituted naphthols reacted efficiently to form the corresponding aminonaphthols with very good to excellent yields (**Scheme 6**). Nevertheless, 7-benzyloxy 2-naphthol gave the desired products **2.66** with lower yield probably due to the steric hindrance exerted by the benzyl group. Interestingly, selective mono-arylamination occurred in the reaction of 2,7-dihydroxynaphthalene providing **2.78** with good yield.

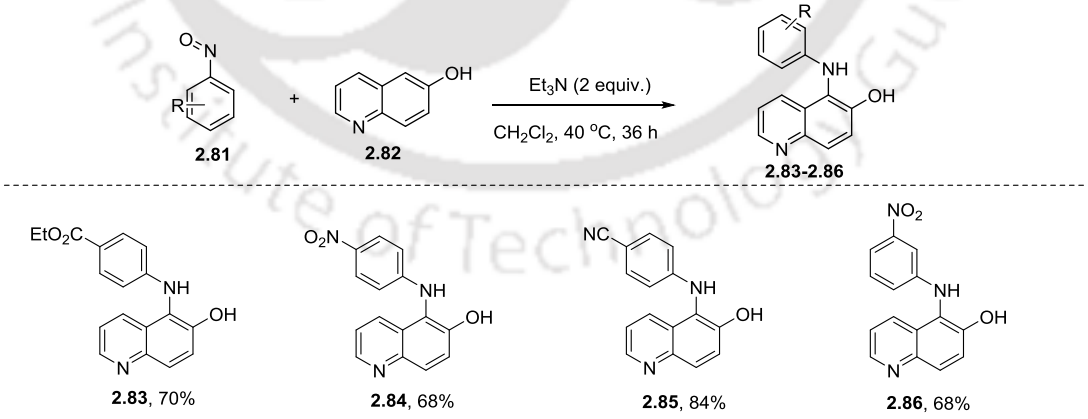
Interestingly, the reaction of 1-naphthol and nitrosoarene **2.50**, afforded *para*-iminoquinone derivative **2.80** with 47% yield (**Scheme 7**).



Scheme 7: Reaction with 1-naphthol.

2.6 Scope of arylaminations of hydroxyquinoline:

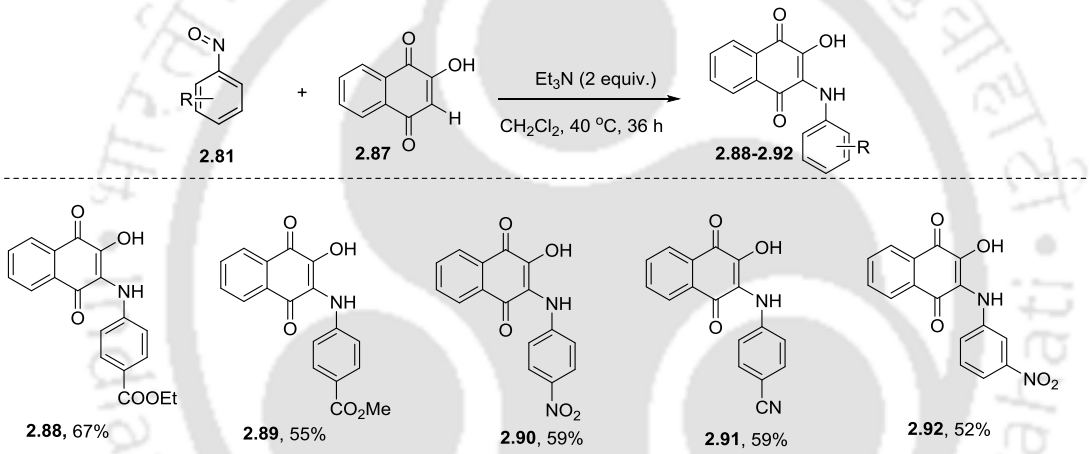
Other than the naphthols, hydroxyquinolines were also participated in the amination reaction to provide the corresponding diarylamines **2.83**-**2.86** with very good yields (**Scheme 8**).



Scheme 8: Scope of arylaminations of hydroxyquinoline.

2.7 Scope of arylaminations of hydroxyquinones:

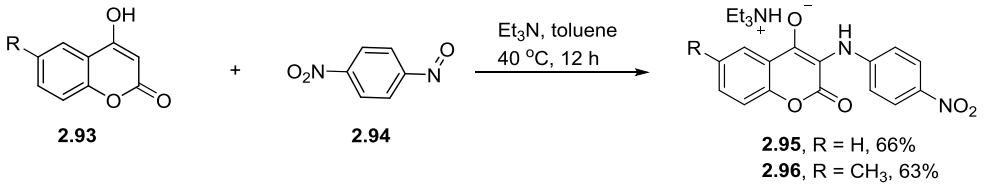
Arylanimo-naphthoquinones are found as the key structural element of many bioactive molecules and natural products.[24] In general, the arylamino group in the naphthoquinones are installed via either metal-mediated cross-coupling reactions or via a nucleophilic substitution reaction of corresponding vinylogous acid chloride.[25] Therefore, the scope of this coupling reaction for the direct C-H arylamination of naphthoquinone derivative without involving metallic reagents and pre-derivatization/activation steps was investigated. Accordingly, hydroxynaphthoquinone was reacted with various nitrosoarenes under standard reaction conditions and the expected arylamino-naphthoquinones **2.88-2.92** were isolated with moderate to good yields (**Scheme 9**).



Scheme 9: Scope of arylaminations of hydroxyquinones.

2.8 Scope of arylaminations of coumarins:

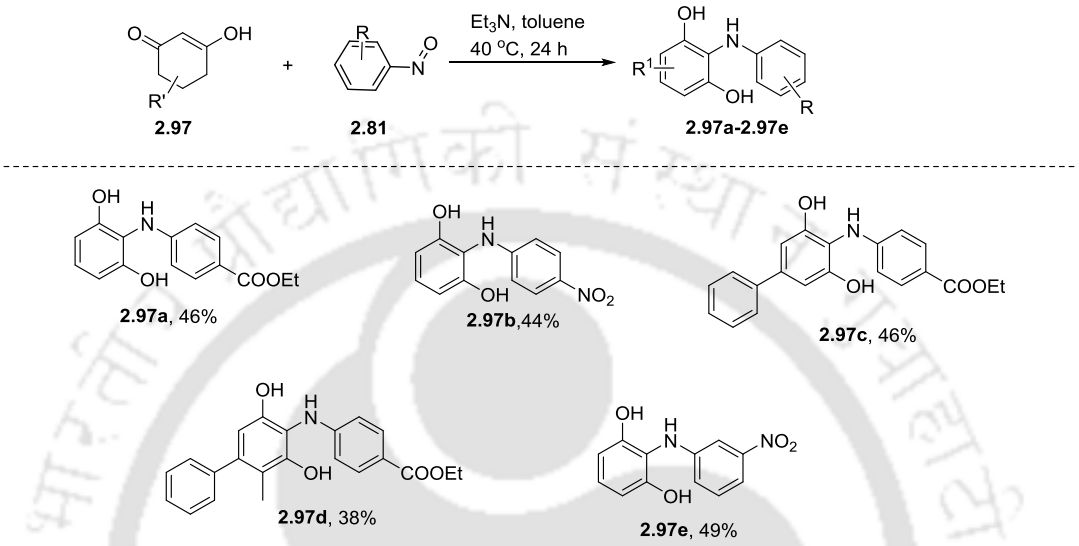
Next, the scope of this amination reaction with *β*-hydroxyenones was investigated. Interestingly, the reaction of 4-hydroxycoumarin derivatives **2.93** with nitrosoarene provided the corresponding arylaminocoumarins **2.95-2.96** with 66% and 63% yields, respectively (**Scheme 10**).



Scheme 10: Scope of arylaminations of coumarins.

2.9 Scope of arylaminations of 1,3-diketones:

The scope of the reaction then tested using 1,3-cyclohexanedione derivatives. Interestingly, 2-arylamino resorcinol derivatives **2.97a-2.97e** were isolated with slightly lower yields from the reaction with nitrosoarenes and 1,3-cyclohexanediones (**Scheme 11**).

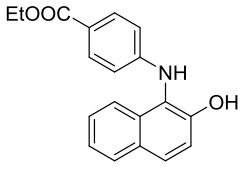
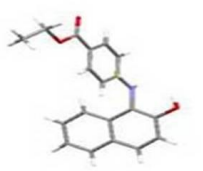
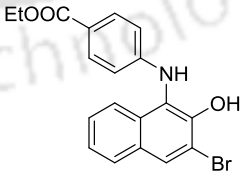
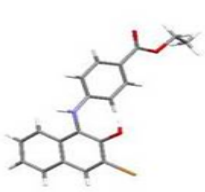
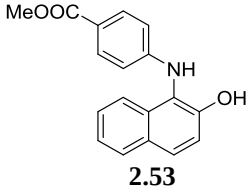
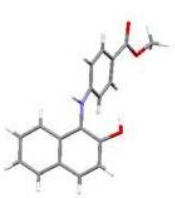
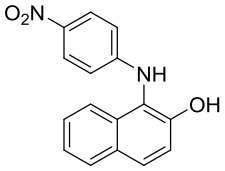
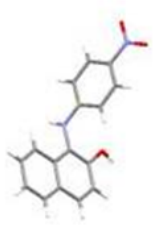


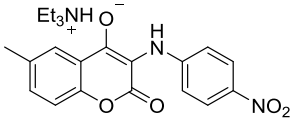
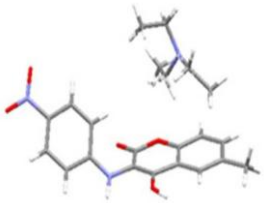
Scheme 11: Scope of arylaminations of 1,3-diketones.

2.10 Crystal structures of diarylamines:

The structures of the arylnaphthyl amines and arylaminocoumarin were confirmed by their crystal structures (**Table 2**).

Table 2: Crystal structures of synthesized diarylamines.

Compound	Crystal structure	Compound	Crystal structure
 **2.49**		 **2.72**	
 **2.53**		 **2.54**	

Compound	Crystal structure
 **2.96**	

2.11 Investigation of the mechanism of the arylamination reaction:

The reaction was closely monitored using NMR-spectroscopy in order to understand the mechanism of this novel reductive coupling reaction of nitrosoarene, which proceeded without the aid of any additional reducing agent. After 10 min of the reaction, a signal at 179.2 ppm in ^{13}C-NMR of the reaction mixture was observed (**Figure 2**). After 10 min of the reaction at room temperature, the intermediate was isolated with 52% yield and that was identified to be the corresponding iminoquinone **2.98** (**Scheme 12**, eq. 15). Interestingly, the desired aminonaphthol **2.67** was isolated with 61% from a reaction of iminoquinone with only triethylamine under standard conditions (**Scheme 12** eq. 16).

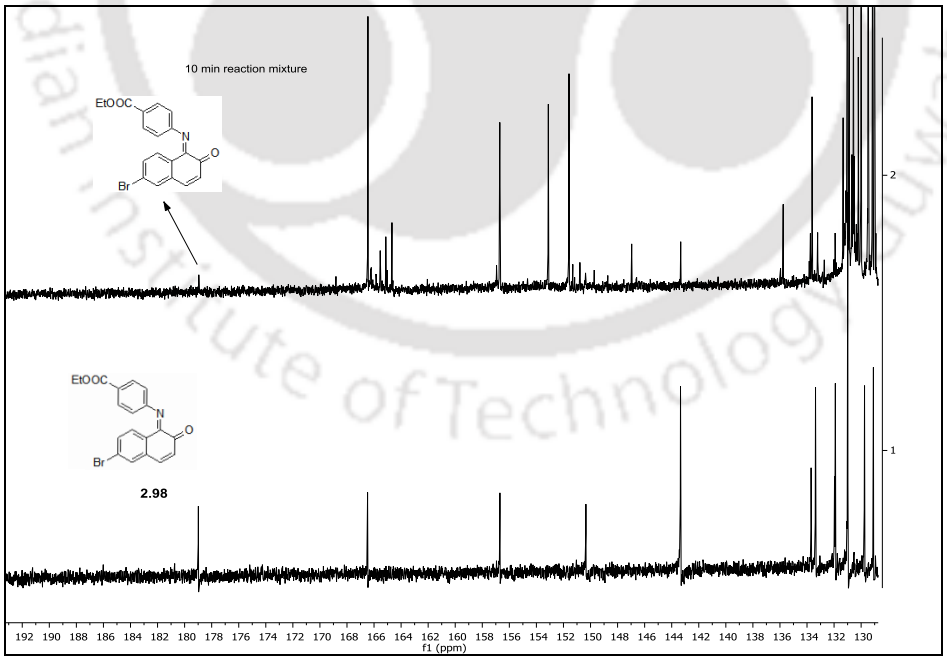
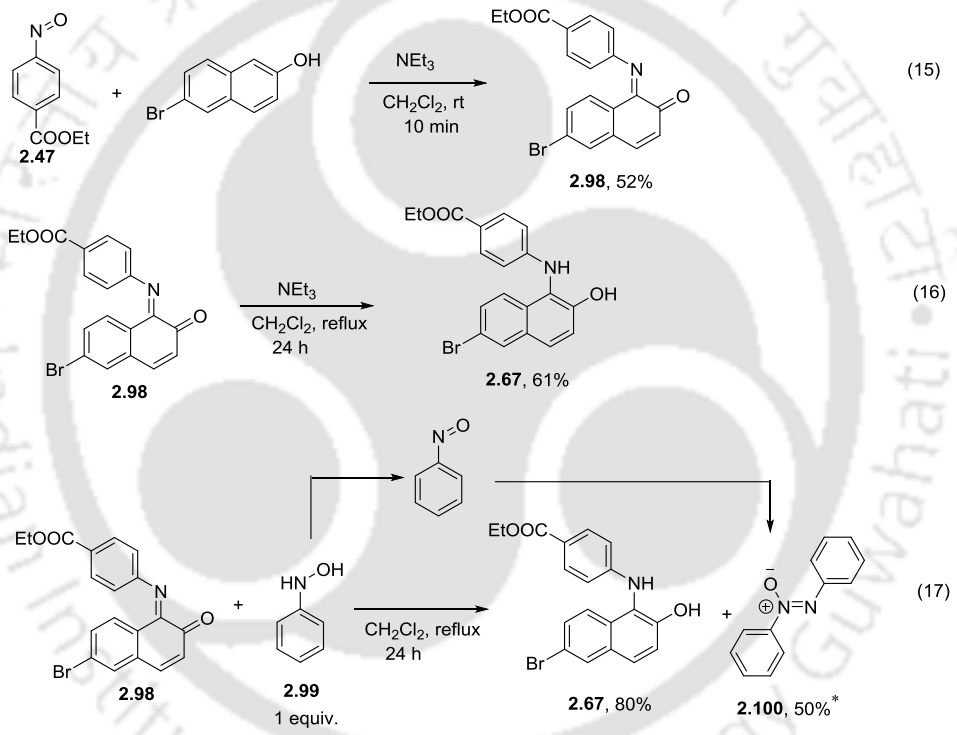


Figure 2: (1) ^{13}C-NMR of isolated iminoquinone **2.98**. (2) ^{13}C-NMR of the reaction mixture of 6-bromo-2-naphthol and ethyl 4-nitrosobenzoate in presence of NEt_3 in CD_2Cl_2 after 10 min.

It was anticipated that the arylhydroxylamine generated *in situ* from the nitrosoarene (during auto-oxidation reduction process) can act as the potential reducing agent. To investigate this possibility, iminoquinone **2.98** was reacted in the presence of phenylhydroxyl amine. Interestingly, the reduction of **2.98** occurred rapidly to provide the desired product **2.67** with 80% yield. Azoxybenzene **2.100** was also isolated from the reaction indicating that phenylhydroxylamine is oxidized to corresponding nitrosobenzene (**Scheme 12**, eq.17). These results suggest that nitrosoarene may also be indirectly involved in the reduction process.

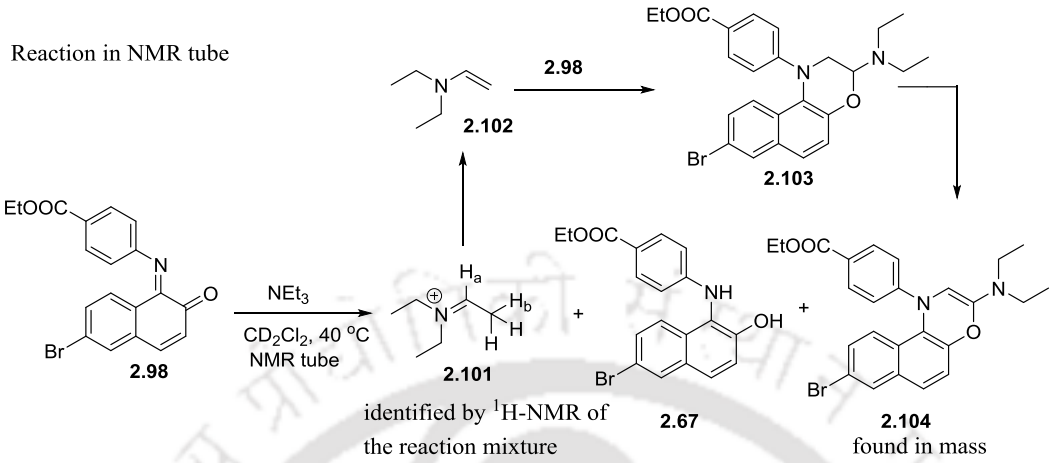


*****yield was calculated with respect to phenylhydroxyl amine.

Scheme 12: Controlled experiments.

To better understand the role of NEt_3 in reduction of the iminoquinone **2.98,** a reaction of iminoquinone **2.98** and NEt_3 in CD_2Cl_2 was monitored using ^{1}H-NMR spectroscopy and mass spectrometry. After 3 h of the reaction, one peak at 9.73 (q, J = 2.8 Hz, 1H) ppm and another peak at 2.13 (d, J = 2.8 Hz, 3H) ppm were found in ^{1}H-NMR spectrum indicating the formation of iminium ion **2.101** (**Figure 3**). In addition, a cycloaddition adduct **2.103** of **2.98** and enamine **2.102**, which is formed from **2.98**, has been detected in the mass spectrum (**Scheme 13**). The related inverse electron demand Diels-Alder (IEDDA) reaction is known

in the literature.[26] This observation clearly indicates that triethylamine acts as the reducing agent and is oxidized to its corresponding iminium ion **2.101**.



Scheme 13: Reaction of iminoquinone **2.98** with NEt_3 in CD_2Cl_2 in NMR tube.

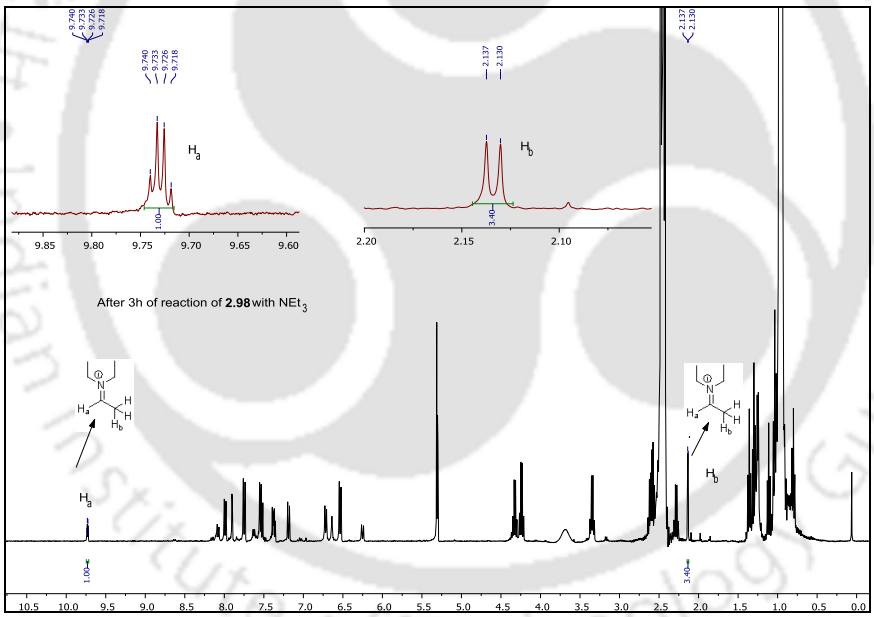
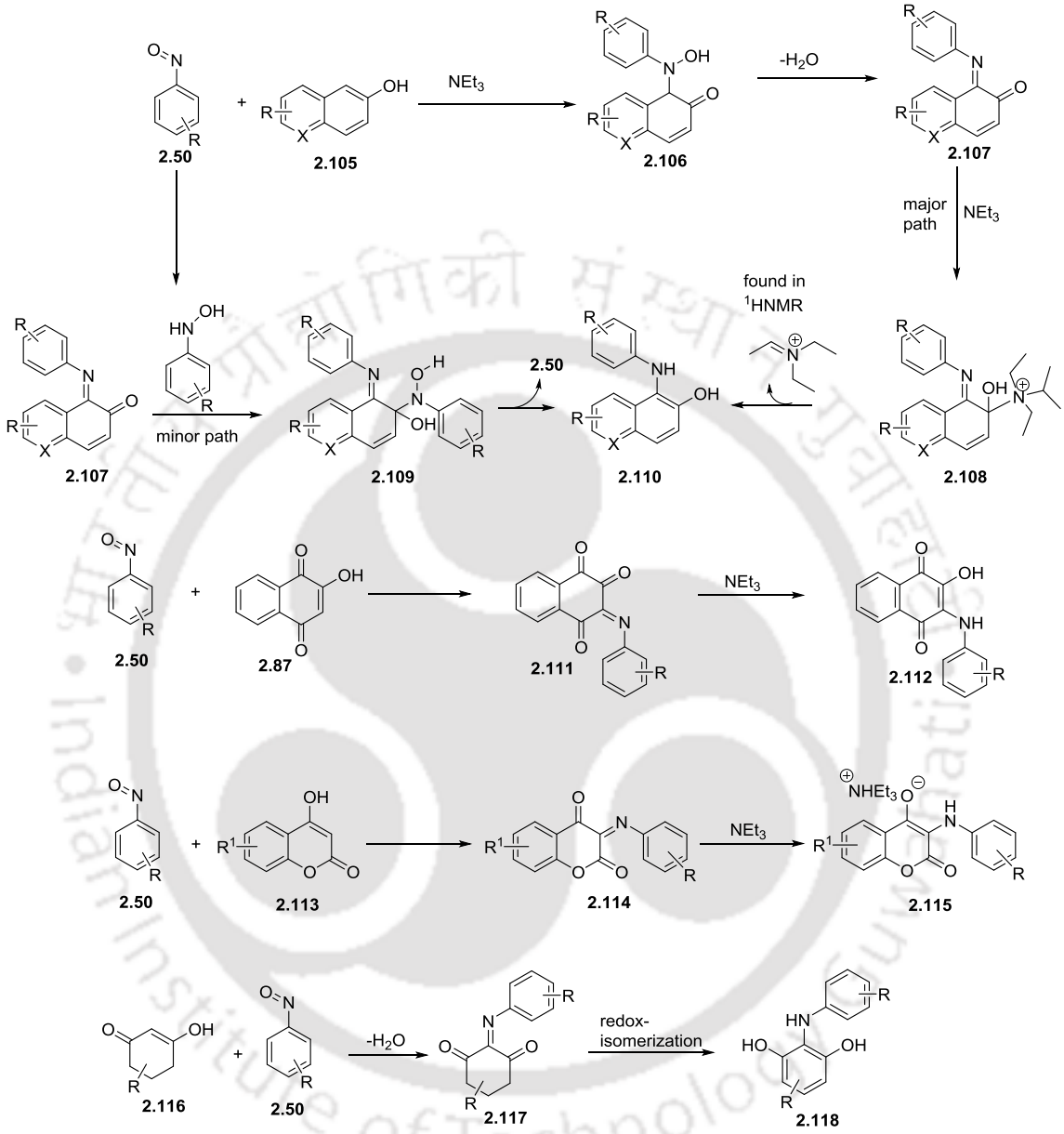


Figure 3: ^{1}H-NMR spectra of the reaction mixture of **2.98** and NEt_3 after 3 h.

Based on these experimental results, a plausible reaction mechanism for this metal-free reductive arylamination reaction has been depicted in **Scheme 14**. Naphthol derivatives reacted with nitrosoarene to provide corresponding iminoquinone **2.107** probably through the corresponding hydroxylamine derivative **2.106**. The reduction of the iminoquinone **2.107** occurred via two possible pathways. In the major pathway, NEt_3 reduced iminoquinone **2.107** either via electron transfer mechanism or via ionic mechanism (via **2.108**)[27] to produce desired aminated product **2.110**.[28]

Consequently, triethylamine was oxidized to corresponding iminium ion which was detected by ^{1}H-NMR. Additionally, arylhydroxylamine formed from the nitrosoarene



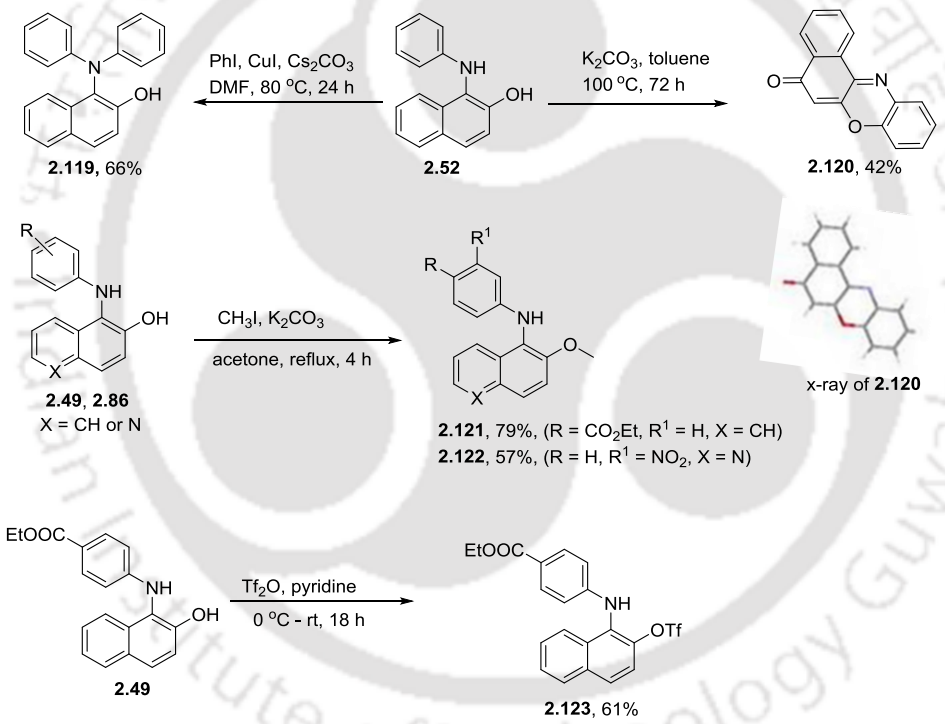
Scheme 14: Proposed mechanism.

during auto-oxidation-reduction process could also be involved for the reduction of **2.107** (via **2.109**) to the desired product in the minor pathway.[29] Similarly, arylamination of naphthoquinones and hydroxycoumarins is proposed to occur via the corresponding iminoquinone intermediate **2.111** and **2.114** respectively. On the other hand, iminoquinone **2.117** produced from the condensation of 1,3-cyclohexadinone **2.116** and nitrosoarene **2.50** underwent aromatization driven redox-

isomerization to furnish the observed 2-amino resorcinol derivatives **2.118 (Scheme 14**).

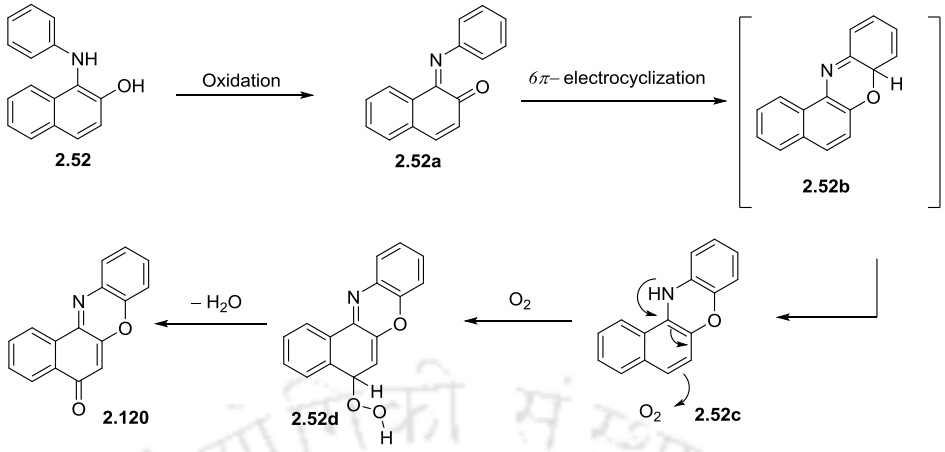
2.12 Synthetic application:

Cu-catalyzed Ullmann coupling of **2.52** with PhI occurred smoothly to provide triarylamine **2.119**. Interestingly, a tetracyclic iminonaphthoquinone derivative **2.120** was formed when a solution of the aminonaphthol **2.52** was heated in the presence of K_2CO_3 for 72 h. Selective *O*-methylation and *O*-trifluoromethanesulfonylation of aminonaphthols **2.49** and aminoquinoline **2.86** were achieved by reacting with CH_3I and triflic anhydride, respectively (**Scheme 15**).



Scheme 15: Further synthetic elaboration.

The possible mechanism for the formation of **2.120** has been depicted in **Scheme 16**. A reaction sequence of oxidation-electrocyclization-oxidation of **2.52** (via intermediate **2.52a-2.52d**) probably resulted in the tetracyclic framework of **2.120**.



Scheme 14: Possible mechanism for the formation of **2.120**.

2.13 Application as Multifunctional Aβ-aggregation Modulators:

Looking at the structural features, we realized that the synthesized 2-hydroxy-di(het)aryl amines having planar conjugated hydrophobic rings, H-bond donors and acceptors, and metal ions chelating sites, can act as a multifunctional competitive modulator of undesired hydrophobic interaction, H-bonding and metal chelation which drive protein misfolding and aggregation.[30] Therefore, to test this anticipation, we screened selected molecules for their inhibiting propensity of Amyloid Beta 40 (Aβ-40) aggregation by ThT Assay (**Figure 4**). Amongst the ten molecules tested for their fibrillation inhibitory effect, some of the molecules indeed had a significant effect on slowing/arresting the Aβ-40 aggregation kinetics. **Figure 5** depicts the screening of growth rates of Aβ-40 in the presence of synthesized molecules. Interestingly, while molecules named **2.54**, **2.55**, **2.73** seem to have retarded the growth rate most strongly, however, the Aβ-40 seem to have attained the fibrillary phase eventually, as reflected in the ThT fluorescence intensity (**Figure 4**). Later, an additional pool of monomers of the peptide was added and this solution was allowed to aggregate for 24 h in the absence of ThT. Finally, the detection of the mature fibrils was done at the end of the kinetics by adding excess ThT to the solution. In this study, we have employed the use of real-time monitoring of the Aβ-40 aggregation growth kinetics in the presence of small molecules, where, the molecules were added directly to the initial, mostly low-to-high oligomeric pool of Aβ-40. One possible reason for the decrease in the growth rate of Aβ-40 in the presence of these molecules could be due to the decrease in the number of nuclei that are formed and which leads to a decreased growth rate. Alternatively, it could

be also possible that even after the formation of sufficient number of nuclei the subsequent addition of monomeric Aβ-40 is competitively being inhibited by these molecules to certain degree owing to screening of hydrophobic patches on growing Aβ-40.

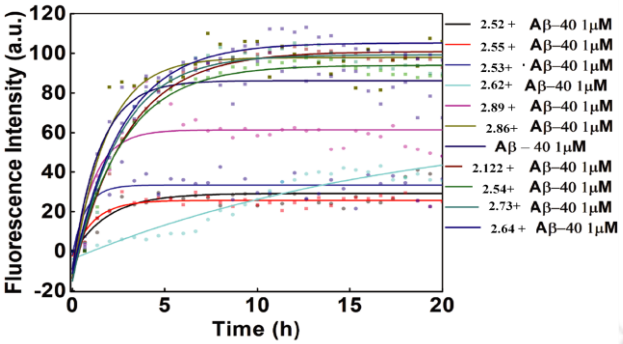


Figure 4: ThT assay based screening of molecules for their potency to inhibit the fibrillation kinetics of Aβ-40.

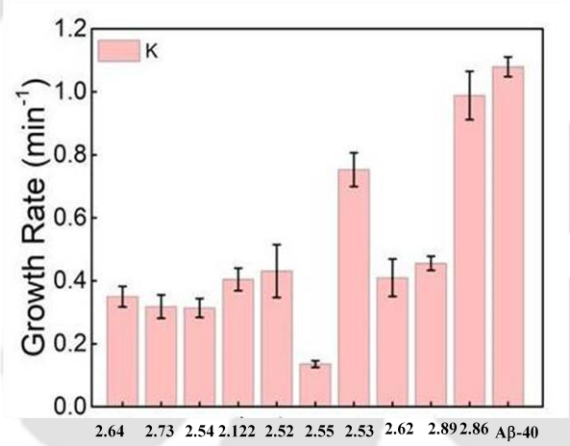


Figure 5: ThT assay derived growth rate plot for the different molecules.

Aβ species are known to aggregate and form fibrils and amyloid plaques that are part of the pathophysiology of Alzheimer's Disease. Interestingly, molecule **2.54** and **2.55** showed a potency of modulating/inhibiting the fibrillation kinetics of Aβ-40 as confirmed by the striking reduction in the growth rate. This was confirmed by the changes in the fibrillary morphology observed by electron microscopy (**Figure 6**, 1h). Further, the potency of these two molecules in terms of their capability to dissolve the preformed Aβ-40 fibril was also tested (**Figure 6**). Dissolution of the pre-formed fibrils was observed with the treatment with **2.55** (**Figure 6**, e).[29] However, compound **2.74** could not alter the fibrillated morphology (**Figure 6**, f).

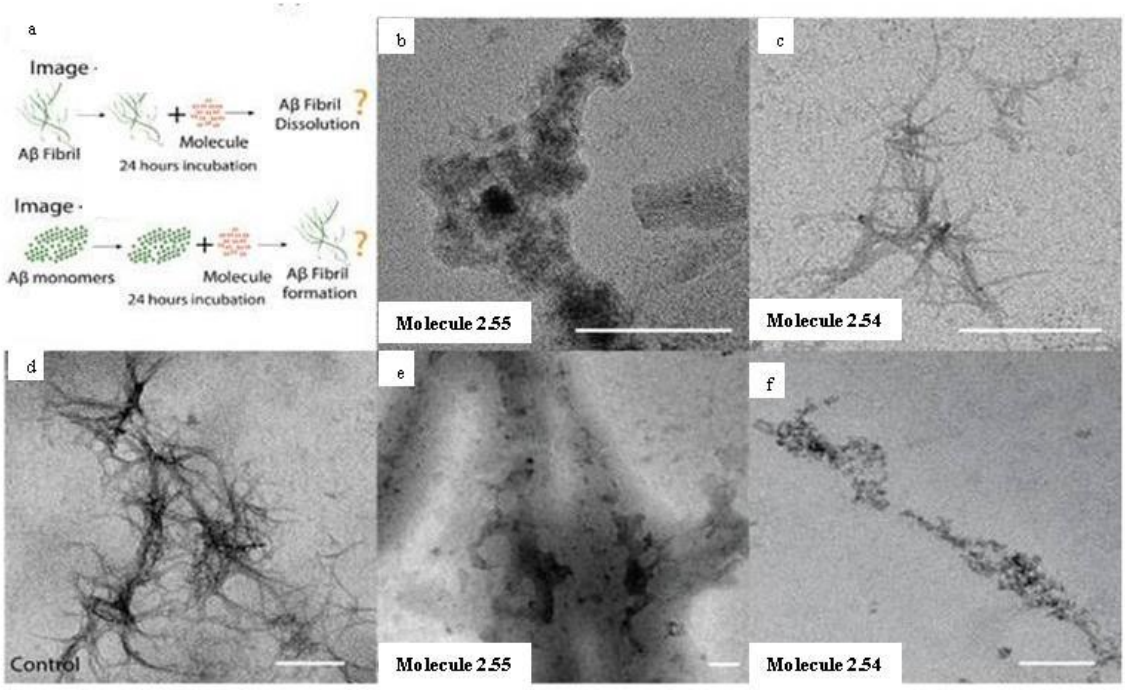


Figure. 6: **a.** Illustration of the experimental design. **d.** Control image of untreated Aβ-40. **b**. & **c** TEM micrographs of pre-formed Aβ-40 fibril incubated with molecule **2.55** and **2.54** for 24 h, respectively. **e** & **f** TEM micrograph of molecule **2.55** & **2.54**, respectively, incubated with Aβ-40 monomers for 24 h.(Scale bars, 100 nm)

2.14 Conclusion:

In summary, we have developed an unprecedented method for C(sp^2)-H arylamination of hydroxyarenes to provide structurally diverse 2-hydroxy-di(het)aryl amines with good to excellent yields. The direct coupling of nitrosoarenes with hydroxyarenes was achieved under metal free mild condition without aid of any additional reagents/steps for N-O bond cleavage. Mechanistic investigation suggested the arylamination proceeds through the iminoquinone intermediate. Moreover, biological evaluation revealed the potential of 2-hydroxy-di(het)aryl amines as potent Amyloid Beta aggregation inhibitors.

2.15. 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). FETEM measurements of the samples were carried out in a JEOL (JEM 2100F) microscope with an operating voltage of 200 kV. Nitrosoarene derivatives[31] and 4-methyl-5-phenylcyclohexane-1,3-dione[32] were synthesized by literature procedures.

ThT Assay for fibrillation kinetics:

Stock solution of Amyloid β-40 was prepared in de-ionised water, aliquots of this solution were then lyophilized and stored at -20°C. For each experiment Amyloid β- 40 (Aβ-40) peptide concentrations were normalized to 1μM by further dilution using 20 mM Phosphate buffer saline (PBS) and a final concentration of 20 μM Thioflavin T (ThT) was added in a NEST 96-well plate along with 50 μM of the respective molecules in each well. This plate was then sealed using an opti-seal to prevent evaporation. The fibrillation kinetics were followed using a BioTek Synergy H1 fluorescence plate reader at an excitation wavelength of 440 nm and an emission wavelength of 490 nm. Readings were recorded in triplicate every 40 min for a period of 20 h. The amyloid fibrillation growth rates were calculated by fitting the initial portion of the aggregation kinetics using the equation y = A + B*exp(- *k*x).

Transmission Electron Microscopy:

10 µL of sample solution was added on to a carbon coated copper grid and this was left for 2 minutes, it was later wicked off with a filter paper. The grid was then rinsed with deionized water and a 5 µL 4% uranyl acetate replacement (EMS) droplet was placed on to the grid. After a minute this solution was wicked off and the grid was air dried. The imaging was performed on JEOL (JEM 2100F) microscope with an operating voltage of 200 kV.

Pre-formed Aβ-40 treated with molecule **2.55** and incubated for 24 hours showed no fibril like structures where as in case of **2.54** showed fibril like structures although less in comparison to the control Aβ-40 (**Figure 7**, a-c**)**. However when the monomeric Aβ-40 treated with molecule **2.55** and **2.54** and incubated for 24 hours no fibril like structures was observed in both the cases (**Figure 7**, d-e)**.**

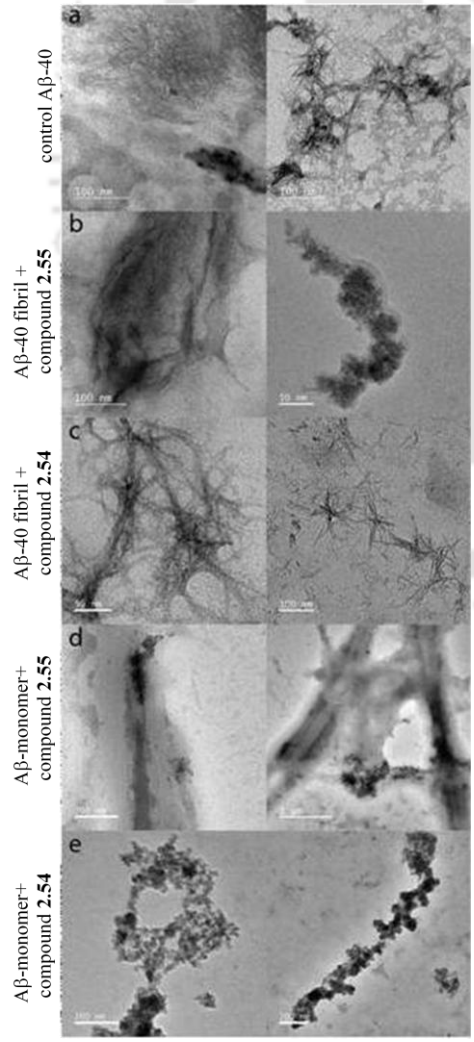
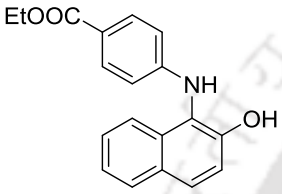


Figure 7: Changes in fibril morphology triggered by the molecule interaction observed by Transmission Electron Microscopy. **a.** Representative TEM micrographs for control Aβ-40 (untreated) **b.** Representative TEM micrographs of pre-formed Aβ-40 treated with molecule **2.55** and incubated for 24 hours showed no fibril like structures. **c.** Representative TEM micrographs of pre-formed Aβ-40 treated with molecule **2.54** and incubated for 24 hours showed fibril like structures albeit the networking between them was visibly less in comparison to the control **d.** Representative TEM micrographs of monomeric Aβ-40 treated with molecule **2.55** and incubated for 24 hours were devoid of fibril like structures **e.** Representative TEM micrographs of monomeric Aβ-40 treated with molecule **2.54** and incubated for 24 hours were devoid of fibril like structures.

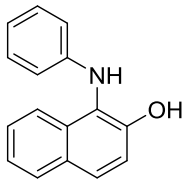
General procedure for the synthesis of aminated derivatives (GP-1):

Nitrosoarene (1.85 equiv) was added to a solution of naphthol/cyclohexadione/4-hydroxycumarine derivatives (0.14 – 0.34 mmol) and triethylamine (2 – 4 equiv) in dry dichloromethane or dry toluene (3 – 5 mL) and the reaction mixture was refluxed for 12 – 36 h under argon atmosphere. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under vacuum to obtain brown gummy residue which was further purified by column chromatography to afford analytically pure products.

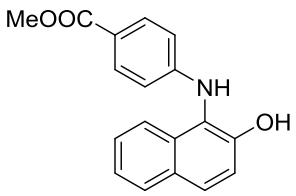
Ethyl 4-(2-hydroxynaphthalen-1-ylamino)benzoate (2.49): According to GP-1: 2-naphthol (25 mg, 0.17 mmol), ethyl 4-nitrosobenzoate (57 mg, 0.31 mmol) and NEt_3 (48 µL, 0.34 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.49** as a brown solid (45 mg, 85%). FTIR (KBr): $\tilde{\nu}$ = 3299, 2983, 1670, 1603, 1516, 1391, 1286, 1172, 769, 754 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.87 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.36 – 7.33 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 2H), 6.32 (s, 1H), 5.59 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.7, 152.0, 151.0, 132.0, 131.9, 129.82, 129.77, 128.9, 127.4, 123.9, 121.7, 121.5, 117.5, 117.3, 113.5, 60.7, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{19}H_{18}NO_3^+$ ($[M + H]^+$): 308.1281; Found: 308.1278.



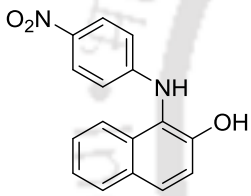
1-(phenylamino)naphthalen-2-ol (2.52): According to GP-1: 2-naphthol (30 mg, 0.21 mmol), nitrosobenzene (41 mg, 0.32 mmol) and NEt_3 (58 µL, 0.42 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **2.52** as a white solid (29 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 3426, 1626, 1601, 1496, 1388, 1208, 749 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.82 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.35 – 7.32 (m, 2H), 7.21 – 7.17 (m, 2H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 2H), 6.54 (s, 1H), 5.23 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.3, 146.8, 132.2, 129.80, 129.77, 129.3, 128.8, 127.2, 123.6, 121.6, 119.9, 118.7, 117.0, 114.4 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{14}NO^+$ ($[M + H]^+$): 236.1070 ; Found: 236.1073.



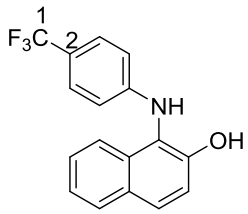
Methyl 4-(2-hydroxynaphthalen-1-ylamino)benzoate (2.53): According to GP-1: 2-naphthol (25 mg, 0.17 mmol), methyl 4-nitrosobenzoate (57 mg, 0.31 mmol) and NEt_3 (48 µL, 0.34 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.53** as a brown solid (49 mg, 97%). FTIR (KBr): $\tilde{\nu}$ = 3385, 1695, 1606, 1518, 1282, 1172, 832, 768 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.87 – 7.82 (m, 3H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 9.0 Hz, 1H), 6.63 – 6.60 (m, 2H), 6.42 (s, 1H), 5.64 (s, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.3, 151.9, 151.1, 132.0, 131.9, 131.8, 129.7, 128.8, 127.4, 123.9, 121.5, 117.5, 117.4, 114.0, 113.5, 52.0 ppm. HRMS (ESI) exact mass calculated for $C_{18}H_{16}NO_3^+$ ($[M + H]^+$): 294.1125; Found: 294.1127.



1-(4-nitrophenylamino)naphthalen-2-ol (2.54): According to GP-1: 2-naphthol (35 mg, 0.24 mmol), 1-nitro-4-nitrosobenzene (68 mg, 0.45 mmol) and NEt_3 (68 µL, 0.49 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:3) of the crude gave **2.54** as a yellow solid (54 mg, 80%). FTIR (KBr): $\tilde{\nu}$ = 3445, 2962, 2924, 2854, 1624, 1525, 1477, 1349, 1263, 1209, 812, 736 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.08 (d, *J* = 9.0 Hz, 2H), 7.86 – 7.87 (m, 2H), 7.59(d, *J* = 8.4 Hz, 1H), 7.45 – 7.43 (m, 1H), 7.39 – 7.37 (m, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 2H), 6.10 (s, 1H), 5.90 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.7, 151.7, 140.4, 131.7, 130.3, 129.8, 129.0, 127.8, 126.6, 124.2, 121.3, 117.6, 116.7, 113.4 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{13}N_2O_3$ ($[M + H]^+$): 281.0921; Found: 281.0921.



1-(4-(trifluoromethyl)phenylamino)naphthalen-2-ol (2.55): According to GP-1: 2-naphthol (35 mg, 0.24 mmol), 1-(trifluoromethyl)-4-nitrosobenzene (79 mg, 0.45 mmol) and NEt_3 (68 µL, 0.49 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **2.55** as yellow solid (61 mg, 83%). FTIR (KBr): $\tilde{\nu}$ = 3466, 3343, 2924, 1615, 1392, 1261, 1105, 816, 753 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.43 – 7.41 (m, 3H), 7.37 – 7.36 (m, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.30 (s, 1H), 5.49 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$)



δ = 152.06, 149.72, 131.95, 129.87, 129.83, 128.93, 127.5, 127.2 (C2), 127.2 (C2), 127.2 (C2), 127.1 (C2), 125.68, 123.95, 123.89, 122.1 (C1), 121.9 (C1), 121.7 (C1), 121.5 (C1), 121.41, 117.57, 117.27, 113.87. ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{13}F_3NO^+$ ($[M + H]^+$): 304.0944; Found: 304.0949.

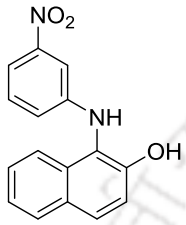
1-(4-chlorophenylamino)naphthalen-2-ol (2.56): According to GP-1: 2-naphthol (25 mg, 0.17 mmol), 1-chloro-4-nitrosobenzene (45 mg, 0.32 mmol), NEt_3 (48 µL, 0.35 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **2.56** as a brown gum (24 mg, 52%). FTIR (KBr): $\tilde{\nu}$ = 3438, 1632, 1262, 1092, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.81 (dd, *J* = 13.6, 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.42– 7.40 (m, 1H), 7.38 – 7.30 (m, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 6.44 (s, 1H), 5.26 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.2, 145.5, 132.0, 129.8, 129.7, 129.6, 128.9, 127.4, 124.7, 123.8, 121.4, 118.34, 117.1, 115.6 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{13}ClNO^+$ ($[M + H]^+$): 270.0680; Found: 270.0681.

4-(2-hydroxynaphthalen-1-ylamino)benzonitrile (2.57): According to GP-1: 2-naphthol (35 mg, 0.24 mmol), 4-nitrosobenzonitrile (59 mg, 0.45 mmol) and NEt_3 (68 µL, 0.49 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.57** as a brown solid (61 mg, 97%). FTIR (KBr): $\tilde{\nu}$ = 3378, 2220, 1606, 1511, 1471, 1388, 1318, 1135, 835, 822, 754 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.84 – 7.80 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.40 (m, 3H), 7.39 – 7.35 (m, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.4 Hz, 3H), 6.28 (s, 1H), 5.74 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 151.7, 150.5, 134.1, 131.6, 123.0, 129.6, 128.8, 127.5, 123.9, 121.1, 119.7, 117.2, 116.6, 114.1, 101.9 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{13}N_2O^+$ ($[M + H]^+$): 261.1022 ; Found: 261.1024.

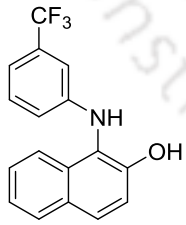
2-(2-hydroxynaphthalen-1-ylamino)benzonitrile (2.58): According to GP-1: 2-naphthol (30 mg, 0.21 mmol), 2-nitrosobenzonitrile (51 mg, 0.38 mmol) and NEt_3 (58 µL, 0.42 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **2.58** as a brown gum (28 mg, 52%). FTIR (KBr): $\tilde{\nu}$ = 3435, 2216, 1626, 1603, 1500, 1290, 1290, 1143, 816, 749 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.85 –

7.82 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.56 (dd, *J* = 7.8 Hz,1.2 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.38 – 7.35 (m, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.85 – 6.83 (m, 1H), 6.28 (d, *J* = 8.4 Hz, 1H), 6.26 (s, 1H), 6.07 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.0, 149.7, 134.8, 133.0, 131.7, 130.3, 129.8, 128.9, 127.7, 124.1, 121.2, 119.5, 117.7, 117.4, 116.5, 113.6, 97.4 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{13}N_2O^+$ ($[M + H]^+$): 261.1022; Found: 261.1031.

1-(3-nitrophenylamino)naphthalen-2-ol (2.59): According to GP-1: 2-naphthol (35 mg, 0.24 mmol), 1-nitro-3-nitrosobenzene (68 mg, 0.45 mmol) and NEt_3 (68 µL, 0.49 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:4) of the crude gave **2.59** as a yellow gum (48 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 3448, 1620, 1525, 1349, 1208, 814, 735, cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.86 – 7.83(m, 2H), 7.67 – 7.65 (m, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 1.8 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.37 – 7.35 (m, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 7.29 (t, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 9.6 Hz, 1H), 6.34 (s, 1H), 5.59 (s, 1H).ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.1, 149.7, 148.1, 131.5, 130.5, 130.2, 129.9, 129.1, 127.6, 124.0, 121.2, 120.0, 117.35, 117.26, 114.7, 108.9 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{13}N_2O^+$ ($[M + H]^+$): 281.0921; Found: 281.0920.



1-(3-(trifluoromethyl)phenylamino)naphthalen-2-ol (2.60): According to GP-1: 2-naphthol (25 mg, 0.17 mmol), 1-nitroso-3-(trifluoromethyl)benzene (56 mg, 0.32 mmol) and NEt_3 (48 µL, 0.31 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:6) of the crude gave **2.60** as a white solid (41 mg, 78%). FTIR (KBr): $\tilde{\nu}$ = 3493, 1614, 1522, 1470, 1330, 1105, 816, 754 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.85 – 7.81 (m, 2H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.37 – 7.33 (m, 2H), 7.27 – 7.23 (m, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.95 (s, 1H), 6.70 (s, 1H), 6.35 (s, 1H), 5.43 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.2, 147.3, 132.2, 132.0, 131.9, 130.4, 129.8, 129.0, 127.5, 123.9, 121.3, 117.7, 117.21, 117.17, 116.6, 116.6, 116.5, 116.5, 111.09, 111.06, 111.04, 111.01 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{13}F_3NO^+$ ($[M + H]^+$): 304.0944; Found: 304.0950.



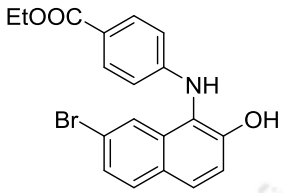
1-(3-chlorophenylamino)naphthalen-2-ol (2.61): According to GP-1: 2-naphthol (25 mg, 0.17 mmol), 1-chloro-3-nitrosobenzene (45 mg, 0.32 mmol) and NEt_3 (48 µL, 0.35 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:15) of the crude gave **2.61** as a brown gum (36 mg, 76%). FTIR (KBr): $\tilde{\nu}$ = 3372, 2963, 1625, 1598, 1479, 1396, 1264, 1143, 1095, 816, 748, 681 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.36 – 7.34 (m, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.81 – 6.80 (m, 1H), 6.62 – 6.61 (m, 1H), 6.53 – 6.51 (m, 1H), 6.42 (s, 1H), 5.28 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.2, 148.2, 135.6, 132.0, 130.8, 129.8, 129.7, 128.9, 127.4, 123.8, 121.4, 120.0, 117.9, 117.1, 114.3, 112.6 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{13}ClNO^+$ ($[M + H]^+$): 270.0680; Found: 270.0679.

1-(3-methoxyphenylamino)naphthalen-2-ol (2.62): According to GP-1: 2-naphthol (30 mg, 0.21 mmol), 1-methoxy-3-nitrosobenzene (53 mg, 0.38 mmol) and NEt_3 (58 µL, 0.42 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **2.62** as a brown gum (34 mg, 62%). FTIR (KBr): $\tilde{\nu}$ = 3442, 1619, 1601, 1487, 1392, 1206, 818 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.34 – 7.29 (m, 2H), 7.11 – 7.07 (m, 1H), 6.52 (s, 1H), 6.41 – 6.38 (m, 1H), 6.28 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.19 – 6.18(m, 1H), 5.26 (s, 1H), 3.70 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.2, 152.2, 148.3, 132.2, 130.6, 129.7, 129.3, 128.8, 127.2, 123.6, 121.6, 118.6, 117.1, 107.3, 104.9, 100.7, 55.3 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{16}NO_2^+$ ($[M + H]^+$): 266.1176; Found: 266.1185.

3-((2-hydroxynaphthalen-1-yl)amino)benzonitrile (2.63): According to GP-1: 2-naphthol (35 mg, 0.24 mmol), 3-nitrosobenzonitrile (59 mg, 0.45 mmol) and NEt_3 (68 µL, 0.49 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:6) of the crude gave **2.63** as a brown gum (36 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 3438, 2924, 2854, 2229, 1633, 1603, 1463, 1263, 680 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.84 (dd, *J* = 12.6, 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.43 –7.41 (m, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.84 (s, 1H), 5.49 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 151.9, 147.3,

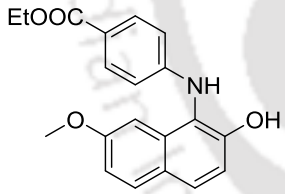
131.6, 130.4, 129.9, 129.7, 128.9, 127.4, 123.8, 123.3, 121.0, 118.9, 118.6, 117.1, 117.0, 116.9, 113.4 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{13}N_2O^+$ ([M + H]$^+$): 261.1022 ; Found: 261.1030.

Ethyl 4-(2-bromo-7-hydroxynaphthalen-8-ylamino)benzoate (2.64): According to GP-1:



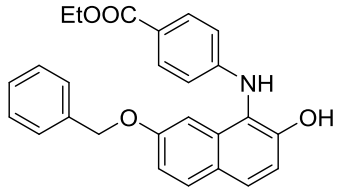
7-bromo-2-naphthol (30 mg, 0.14 mmol), ethyl 4-nitrosobenzoate (57 mg, 0.25 mmol) and NEt_3 (38 µL, 0.27 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.64** as an off white solid (39 mg, 73%). FTIR (KBr): $\tilde{\nu}$ = 3421, 2924, 1662, 1604, 1442, 1262, 1107, 768 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.87 (d, *J* = 9.0 Hz, 2H), 7.78 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.41 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.31 (d, *J* = 9.0 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 2H), 5.61 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.8, 152.8, 150.4, 133.5, 132.0, 130.5, 129.7, 128.2, 127.4, 123.8, 122.2, 121.9, 117.9, 116.9, 113.4, 60.8, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{19}H_{17}BrNO_3^+$ ([M + H]$^+$): 386.0386; Found: 386.0386.

Ethyl 4-(2-hydroxy-7-methoxynaphthalen-1-ylamino)benzoate (2.65): According to GP-1:



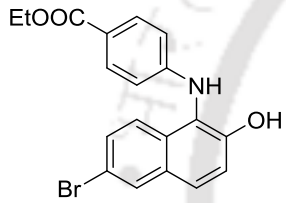
7-methoxy-2-naphthol (30 mg, 0.17 mmol), ethyl 4-nitrosobenzoate (57 mg, 0.31 mmol) and NEt_3 (48 µL, 0.34 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.65** as a white solid (47 mg, 80%). FTIR (KBr): $\tilde{\nu}$ = 3436, 2925, 1628, 1605, 1513, 1263, 1021, 830, 769 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 4.8 Hz, 1H), 7.70 (d, *J* = 4.8 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 11.4 Hz, 1H), 6.84 (s, 1H), 6.60 (d, *J* = 7.8 Hz, 2H), 5.58 (s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.68 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.8, 159.0, 152.6, 150.9, 133.4, 131.9, 130.5, 129.4, 125.0, 121.5, 116.9, 115.9, 114.6, 113.4, 100.7, 60.7, 55.3, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{20}H_{20}NO_4^+$ ([M + H]$^+$): 338.1387; Found: 338.1398.

Ethyl 4-(2-(benzyloxy)-7-hydroxynaphthalen-8-ylamino)benzoate (2.66): According to GP-1: 7-(benzyloxy)-2-naphthol (40 mg, 0.16 mmol), ethyl 4-nitrosobenzoate (53 mg, 0.30 mmol) and NEt_3 (45 µL, 0.32 mmol) were reacted for 24 h in dry DCM (4 mL). Column



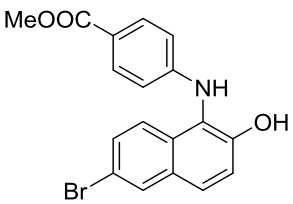
chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.66** as a white solid (37 mg, 56%). FTIR (KBr): $\tilde{\nu}$ = 3354, 2979, 1689, 1607, 1517, 1283, 1263, 1105, 1018, 804, 767 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 9.0 Hz, 2H), 7.72 – 7.69 (m, 2H), 7.30 – 7.29 (m, 4H), 7.28 – 7.26 (m, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 7.06 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.92 (s, 1H), 6.58 (d, *J* = 8.4 Hz, 2H), 5.46 (s, 1H), 4.95 (s, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.8, 158.2, 152.6, 150.9, 136.8, 133.4, 131.9, 130.5, 129.5, 128.7, 128.2, 127.6, 125.1, 121.6, 116.9, 116.5, 114.7, 113.4, 102.2, 70.1, 60.7, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{26}H_{24}NO_4^+$ ($[M + H]^+$): 414.1700 ; Found: 414.1695.

Ethyl 4-(2-bromo-6-hydroxynaphthalen-5-ylamino)benzoate (2.67): According to GP-1:



6-bromo-2-naphthol (30 mg, 0.135 mmol), ethyl 4-nitrosobenzoate (45 mg, 0.25 mmol) and NEt_3 (38 µL, 0.27 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.67** as a brown solid (37 mg, 71%). FTIR (KBr): $\tilde{\nu}$ = 3345, 2985, 1685, 1633, 1600, 1515, 1281, 1173, 772 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.97 (s, 1H), 7.86 (d, *J* = 9.0 Hz, 2H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.44 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 2H), 6.41 (s, 1H), 5.61 (s, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.7, 152.3, 150.6, 131.9, 130.9, 130.8, 130.6, 128.8, 123.5, 121.9, 118.6, 117.8, 117.7, 113.5, 60.7, 14.6 ppm. Total count of ^{13}C is less than expected due to the merging of signal in the aromatic region. HRMS (ESI) exact mass calculated for $C_{19}H_{17}BrN_3O^+$ ($[M + H]^+$): 386.0386; Found: 386.0388.

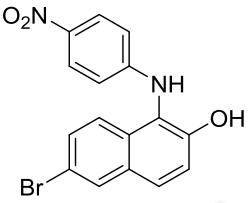
Methyl 4-(2-bromo-6-hydroxynaphthalen-5-ylamino)benzoate (2.68): According to GP-



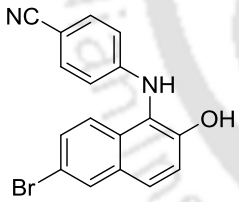
1: 6-bromo-2-naphthol (35 mg, 0.16 mmol), methyl 4-nitrosobenzoate (48 mg, 0.29 mmol) and NEt_3 (44 µL, 0.31 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.68** as a brown solid (42 mg, 71%). FTIR (KBr): $\tilde{\nu}$ = 3334, 1712, 1693, 1605, 1518, 1434, 1282, 1173, 1108, 768 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.97 (s, 1H), 7.84 (d, *J* = 9.0 Hz, 2H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.44 (d, *J* = 10.8 Hz, 1H), 7.33

(d, *J* = 9.0 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 2H), 6.43 (s, 1H), 5.63 (s, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.2, 152.2, 150.7, 132.0, 130.9, 130.8, 130.6, 130.6, 128.8, 123.5, 121.5, 118.7, 117.8, 117.7, 113.5, 52.0 ppm. HRMS (ESI) exact mass calculated for $C_{18}H_{15}BrNO_3^+$ ([M + H]$^+$): 372.0230; Found: 372.0231.

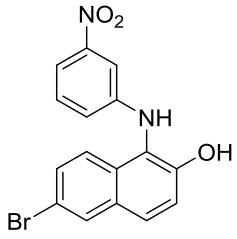
1-(4-nitrophenylamino)-6-bromonaphthalen-2-ol (2.69): According to GP-1: 6-bromo- 2-naphthol (40 mg, 0.18 mmol), 1-nitro-4-nitrosobenzene (51 mg, 0.34 mmol) and NEt_3 (50 µL, 0.36 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:3) of the crude gave **2.69** as a light yellow solid (60 mg, 93%). FTIR (KBr): $\tilde{\nu}$ = 3370, 1594, 1499, 1466, 1264, 1111, 840 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 9.0 Hz, 2H), 8.00 (s, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 9.0 Hz, 2H), 5.92 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.3, 152.0, 140.6, 131.0, 130.9, 130.4, 129.4, 126.6, 123.2, 118.9, 118.0, 117.0, 113.6, 113.4 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{12}BrN_2O_3^+$ ([M + H]$^+$): 359.0026; Found: 359.0027.



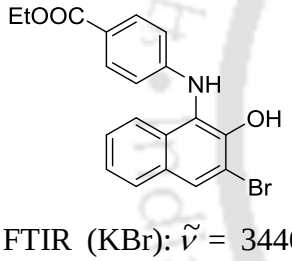
4-(2-bromo-6-hydroxynaphthalen-5-ylamino)benzonitrile (2.70): According to GP-1: 6-bromo-2-naphthol (35 mg, 0.16 mmol), 4-nitrosobenzonitrile (38 mg, 0.29 mmol) and NEt_3 (44 µL, 0.31 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.70** as a brown solid (49 mg, 91%). FTIR (KBr): $\tilde{\nu}$ = 3436, 2213, 1607, 1515, 1361, 1172, 819 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.99 (s, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.47 – 7.46 (m, 2H), 7.43 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 9.0 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 2H), 5.73 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.2, 150.4, 134.3, 130.9, 130.8, 130.4, 129.2, 123.3, 119.8, 118.7, 117.9, 117.1, 114.3, 102.3 ppm Total count of ^{13}C is less than expected due to the merging of signal in the aromatic region. HRMS (ESI) exact mass calculated for $C_{17}H_{12}BrN_2O^+$ ([M + H]$^+$): 339.0128; Found: 339.0124.



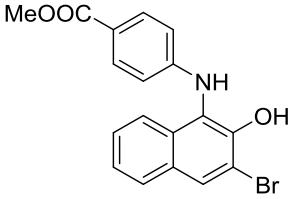
1-(3-nitrophenylamino)-6-bromonaphthalen-2-ol (2.71): According to GP-1: 6-bromo-2-naphthol (35 mg, 0.16 mmol), 1-nitro-3-nitrosobenzene (44 mg, 0.29 mmol) and NEt_3 (44 µL, 0.32 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc: Hexane, 1:4) of the crude gave **2.71** as a yellow solid (41 mg, 73%). FTIR (KBr): $\tilde{\nu}$ = 3437, 1620, 1600, 1472, 1349, 735 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.99 (s, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.67 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.47 – 7.46 (m, 3H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.31 – 7.29 (m, 1H), 6.85 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.38 (s, 1H), 5.58 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.4, 149.7, 147.8, 131.0, 130.9, 130.6, 130.4, 129.2, 123.2, 119.9, 118.7, 117.8, 117.6, 114.9, 108.9 ppm. Total count of ^{13}C is less than expected due to the merging of signal in the aromatic region. HRMS (ESI) exact mass calculated for $C_{16}H_{12}BrN_2O_3^+$ ($[M + H]^+$): 359.0026; Found: 359.0026.



Ethyl 4-(2-bromo-3-hydroxynaphthalen-4-ylamino)benzoate (2.72): According to GP-1: 3-bromo-2-naphthol (40 mg, 0.18 mmol), ethyl 4-nitrosobenzoate (60 mg, 0.34mmol) and NEt_3 (50 µL, 0.36 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.72** as a brown solid (53 mg, 76%). FTIR (KBr): $\tilde{\nu}$ = 3446, 1629, 1604, 1310, 1276, 1172, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.07 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.43 – 7.35 (m, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.40 (s, 1H), 5.81 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.7, 150.5, 147.9, 131.8, 131.2, 131.1, 129.8, 127.9, 127.6, 125.0, 122.4, 122.1, 119.8, 113.9, 111.4, 60.7, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{19}H_{17}BrN_3O^+$ ($[M + H]^+$): 386.0386; Found: 386.0392.

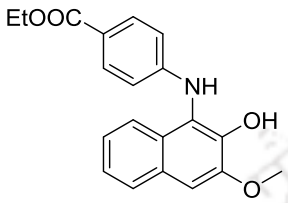


Methyl 4-(2-bromo-3-hydroxynaphthalen-4-ylamino)benzoate (2.73): According to GP-1: 3-bromo-2-naphthol (35 mg, 0.16 mmol), methyl 4-nitrosobenzoate (48 mg, 0.29 mmol) and NEt_3 (44 µL, 0.31 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc: Hexane, 1:4) of the crude gave **2.73** as a yellow solid (41 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 3355, 1681, 1603, 1582, 1457, 1432, 1175, 1134, 768, 755 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ = 8.37 (s, 1H), 8.21 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4

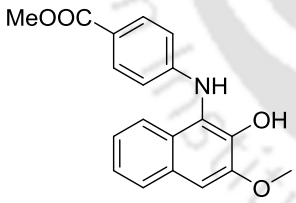


Hz, 1H), 7.43 – 7.40 (m, 1H), 7.35 – 7.32 (m, 1H), 6.51 – 6.45 (m, 2H), 3.73 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 166.4, 152.0, 148.9, 131.2, 131.0, 130.5, 128.9, 127.5, 127.0, 124.2, 122.3, 120.1, 117.8, 113.1, 112.7, 51.5 ppm. HRMS (ESI) exact mass calculated for $C_{18}H_{15}BrNO_3^+$ ([M + H]$^+$): 372.0230; Found: 372.0230.

Ethyl 4-(2-hydroxy-3-methoxynaphthalen-1-ylamino)benzoate (2.74): According to GP-1: 3-methoxy-2-naphthol (35 mg, 0.20 mmol), ethyl 4-nitrosobenzoate (66 mg, 0.37 mmol) and NEt_3 (56 µL, 0.40 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.74** as a brown solid (55 mg, 82%). FTIR (KBr): $\tilde{\nu}$ = 3377, 2978, 1697, 1605, 1518, 1478, 1277, 1173, 1107, 770 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.13 (s, 1H), 6.60 (d, *J* = 8.4 Hz, 2H), 6.25 (s, 1H), 5.90 (s, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.03 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.9, 150.9, 147.7, 142.1, 131.5, 128.8, 127.3, 127.0, 124.8, 124.6, 122.4, 120.8, 119.3, 113.7, 105.1, 60.5, 56.2, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{20}H_{20}NO_4^+$ ([M + H]$^+$): 338.1387; Found: 338.1389.



Methyl 4-(2-hydroxy-3-methoxynaphthalen-1-ylamino)benzoate (2.75): According to GP-1: 3-methoxy-2-naphthol (35 mg, 0.20 mmol), methyl 4-nitrosobenzoate (61 mg, 0.37 mmol) and NEt_3 (56 µL, 0.40 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:4) of the crude gave **2.75** as a orange yellow solid (61 mg, 95%). FTIR (KBr): $\tilde{\nu}$ = 3360, 1683, 1604, 1517, 1287, 1174, 1115, 770 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 9.0 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.37 – 7.35 (m, 1H), 7.32 – 7.30 (m, 1H), 7.14 (s, 1H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.21 (s, 1H), 5.89 (s, 1H), 4.05 (s, 3H), 3.83 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.4, 151.0, 147.7, 142.1, 131.6, 128.8, 127.3, 127.0, 124.9, 124.6, 122.4, 120.5, 119.2, 113.7, 105.1, 56.3, 51.8 ppm. HRMS (ESI) exact mass calculated for $C_{19}H_{18}NO_4^+$ ([M + H]$^+$): 324.1230; Found: 324.1229.



7-methoxy-1-(phenylamino)naphthalen-2-ol (2.76): According to GP-1: 7-methoxy-2-naphthol (30 mg, 0.17 mmol), nitrosobenzene (34 mg, 0.32 mmol) and NEt_3 (48 µL, 0.34 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **2.76** as a white solid (26 mg, 56%). FTIR (KBr): $\tilde{\nu}$ = 3443, 1632, 1496, 1266, 1224, 749 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.72 – 7.69 (m, 2H), 7.19 – 7.15 (m, 3H), 6.97 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.92 (s, 1H), 6.83 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 2H), 6.57 (s, 1H), 5.16 (s, 1H), 3.71 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.9, 152.9, 146.7, 133.6, 130.4, 129.8, 129.0, 125.0, 119.9, 118.1, 115.7, 114.4, 114.3, 100.8, 55.3 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{16}NO_2^+$ ($[M + H]^+$): 266.1176 ; Found: 266.1178.

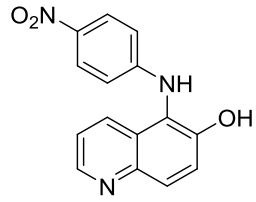
Methyl 4-(2-hydroxy-7-methoxynaphthalen-1-ylamino)benzoate (2.77): According to GP-1: 7-methoxy-2-naphthol (35 mg, 0.20 mmol), methyl 4-nitrosobenzoate (61 mg, 0.37 mmol) and NEt_3 (56 µL, 0.40 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.77** as a brown solid (57 mg, 88%). FTIR (KBr): $\tilde{\nu}$ = 3373, 1681, 1603, 1514, 1287, 1142, 808, 768 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 9.0 Hz, 2H), 7.72 (d, *J* = 3.6 Hz, 1H), 7.70 (d, *J* = 3.6 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.99 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.84 (s, 1H), 6.61 (d, *J* = 8.4 Hz, 2H), 5.56 (s, 1H), 3.84 (s, 3H), 3.69 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.2, 159.1, 152.6, 150.9, 133.4, 131.9, 130.5, 129.5, 125.0, 121.3, 116.8, 116.0, 114.6, 113.5, 100.7, 55.4, 52.0 ppm. HRMS (ESI) exact mass calculated for $C_{19}H_{18}NO_4^+$ ($[M + H]^+$): 324.123; Found: 324.1222.

Ethyl 4-(2,7-dihydroxynaphthalen-8-ylamino)benzoate (2.78): According to GP-1: 7-hydroxy-2-naphthol (40 mg, 0.25 mmol), ethyl 4-nitrosobenzoate (83 mg, 0.46 mmol) and NEt_3 (69 µL, 0.50 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:2) of the crude gave **2.78** as a brown solid (54 mg, 67%). FTIR (KBr): $\tilde{\nu}$ = 3368, 2980, 1686, 1605, 1510, 1282, 1178, 1109, 830, 769 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ = 7.75 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.86 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ = 168.9, 157.3, 154.1, 153.2, 135.5, 132.2, 131.0, 129.0, 125.6, 119.3, 118.5, 116.3, 116.0,

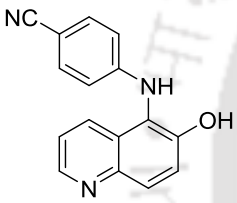
113.7, 105.2, 61.3, 14.7 ppm. HRMS (ESI) exact mass calculated for $C_{19}H_{18}NO_4^+$ ([M + H]$^+$): 324.1230; Found: 324.1236.

Ethyl (*E*)-4-((4-oxonaphthalen-1(4*H*)-ylidene)amino)benzoate (2.80): According to GP-1: 7- 1-naphthol (20 mg, 0.14 mmol), ethyl 4-nitrosobenzoate (46 mg, 0.26 mmol) and NEt_3 (38 µL, 0.28 mmol) were reacted for 24 h in dry DCM (3 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **2.80** as a orange solid (20 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$ δ= 8.44 (d, *J* = 8.9 Hz, 1H), 8.17 (d, *J* = 6.4 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 2H), 7.79 – 7.67 (m, 2H), 7.12 (d, *J* = 10.4 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 10.4 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.45, 166.39, 155.45, 154.09, 134.84, 134.57, 133.47, 131.85, 131.69, 130.94, 130.29, 127.28, 126.45, 125.77, 120.03, 61.22, 14.59. HRMS (ESI) exact mass calculated for $C_{19}H_{16}NO_3^+$ ([M + H]$^+$): 306.1125; Found: 306.1222.

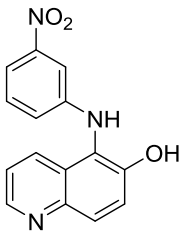
Ethyl 4-(6-hydroxyquinolin-5-ylamino)benzoate (2.83): According to GP-1: 6-hydroxy-quinoline (35 mg, 0.21 mmol), ethyl 4-nitrosobenzoate (68 mg, 0.38 mmol) and NEt_3 (59 µL, 0.41 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:1) of the crude gave **2.83** as a brown solid (45 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 3403, 2965, 1904, 1689, 1606, 1479, 1369, 1204, 1134, 838, 807, 763 cm^{-1}. ^{1}H NMR (600 MHz, CD_3OD) δ = 8.64 (dd, *J* = 4.2, 1.2 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.40 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ = 168.6, 153.5, 153.4, 148.0, 144.6, 133.0, 132.3, 129.1, 128.8, 123.6, 122.5, 120.1, 119.9, 113.8, 61.4, 14.7 ppm. HRMS (ESI) exact mass calculated for $C_{18}H_{17}N_2O_3^+$ ([M + H]$^+$): 309.1234; Found: 309.1236.



5-(4-nitrophenylamino)quinolin-6-ol (2.84): According to GP-1: 6-hydroxyquinoline (30 mg, 0.21 mmol), 1-nitro-4-nitrosobenzene (58 mg, 0.38 mmol) and NEt_3 (57 µL, 0.41 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:1) of the crude gave **2.84** as a brown solid (39 mg, 68%). FTIR (KBr): $\tilde{\nu}$ = 3366, 2962, 2206, 1605, 1513, 1469, 1261, 1081, 818, 805 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ = 10.31 (s, 1H), 9.00 (s, 1H), 8.72 (d, *J* = 5.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 2H), 7.92 (d, *J* = 9.6 Hz, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.63 – 6.45 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 153.8, 151.3, 147.5, 143.5, 137.0, 130.2, 129.1, 126.9, 126.1, 122.3, 121.8, 117.0, 112.4 ppm. HRMS (ESI) exact mass calculated for $C_{15}H_{12}N_3O_3^+$ ($[M + H]^+$): 282.0873; Found: 282.0884.



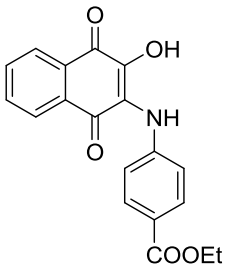
4-(6-hydroxyquinolin-5-ylamino)benzonitrile (2.85): According to GP-1: 6-hydroxyquinoline (30 mg, 0.21 mmol), 4-aminobenzonitrile (50 mg, 0.38 mmol) and NEt_3 (57 µL, 0.41 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:1) of the crude gave **2.85** as a brown solid (45 mg, 84%). FTIR (KBr): $\tilde{\nu}$ = 3366, 2962, 2206, 1605, 1513, 1469, 1261, 1081, 818, 805 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ = 8.65 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 9.6 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.42 – 7.39 (m, 3H), 6.59 (d, *J* = 8.4 Hz, 2H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ = 153.4, 153.1, 148.1, 144.5, 134.6, 132.7, 129.10, 129.08, 123.6, 122.7, 121.2, 119.2, 114.7, 99.9 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{12}N_3O^+$ ($[M + H]^+$): 262.0975; Found: 262.0975.



5-(3-nitrophenylamino)quinolin-6-ol (2.86): According to GP-1: 6-hydroxy-quinoline (50 mg, 0.34 mmol), 1-nitro-3-nitrosobenzene (96 mg, 0.63 mmol) and NEt_3 (95 µL, 0.68 mmol) were reacted for 36 h in dry DCM (5 mL). Column chromatography (silica; EtOAc : Hexane, 1:1) of the crude gave **2.86** as a brown solid (65 mg, 68%). FTIR (KBr): $\tilde{\nu}$ = 3403, 2964, 1689, 1606, 1515, 1282, 1262, 1174, 807, 763 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ = 10.24 (s, 1H), 8.70 (d, *J* = 5.4 Hz, 1H), 8.33 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 9.6 Hz, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.24 (s, 1H), 6.90 (d, *J* = 7.8 Hz, 1H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 151.2, 148.84, 148.79, 147.6, 143.6, 130.6, 130.2, 128.5, 127.1, 122.4, 121.7, 119.8,

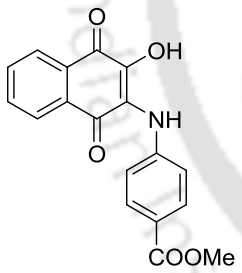
118.3, 111.5, 106.9 ppm. HRMS (ESI) exact mass calculated for $C_{15}H_{12}N_3O_3^+$ ($[M + H]^+$): 282.0873; Found: 282.0876.

Ethyl 4-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-ylamino)benzoate (2.88):

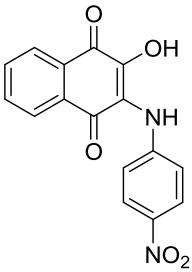


According to GP-1: 2-hydroxy-1,4-naphthoquinone (35 mg, 0.20 mmol), ethyl 4-nitrosobenzoate (67 mg, 0.37 mmol) and NEt_3 (56 µL, 0.40 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 2:1) of the crude gave **2.88** as a light violet solid (46 mg, 67%). FTIR (KBr): $\tilde{\nu}$ = 3304, 2987, 1709, 1645, 1606, 1267, 1178, 1063, 765, 717 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ = 8.46 (s, 1H), 7.98 (t, *J* = 7.8 Hz, 2H), 7.80 – 7.78 (m, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 181.8, 178.0, 165.7, 146.7, 145.0, 134.0, 133.7, 131.0, 130.5, 129.5, 125.8, 125.6, 124.0, 120.1, 117.3, 60.0, 14.4 ppm. HRMS (ESI) exact mass calculated for $C_{19}H_{16}NO_5^+$ ($[M + H]^+$): 338.1023; Found: 338.1026.

Methyl 4-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-ylamino)benzoate (2.89):

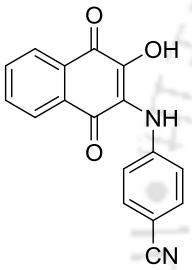


According to GP-1: 2-hydroxy-1,4-naphthoquinone (35 mg, 0.20 mmol), methyl 4-nitrosobenzoate (61 mg, 0.37 mmol) and NEt_3 (56 µL, 0.40 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 2:1) of the crude gave **2.89** as a light violet solid (36 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 3307, 2963, 1721, 1713, 1646, 1625, 1262, 1097, 1020, 800, 764 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ = 8.43 (s, 1H), 7.99 – 7.96 (m, 2H), 7.80 – 7.78 (m, 2H), 7.74 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 5.74 (s, 1H), 3.77 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 181.9, 180.0, 166.3, 146.8, 145.1, 134.0, 133.8, 131.1, 130.5, 129.6, 125.9, 125.6, 124.0, 119.8, 117.3, 51.6 ppm. HRMS (ESI) exact mass calculated for $C_{18}H_{12}NO_4^-$ ($[M – H]^-$): 322.0721; Found: 322.0726.



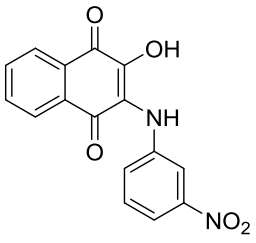
2-(4-nitrophenylamino)-3-hydroxynaphthalene-1,4-dione (2.90): According to GP-1: 2-hydroxy-1,4-naphthoquinone (35 mg, 0.20 mmol), 1-nitro-4-nitrosobenzene (57 mg, 0.37 mmol) and NEt_3 (56 µL, 0.40 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:1) of the crude gave **2.90** as a light violet foam (37 mg, 59%). FTIR (KBr): $\tilde{\nu}$ = 3302, 2924, 1675, 1645, 1587, 1487, 1337, 1272, 1112, 1059, 719 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.88 (s, 1H), 8.04 (d, J = 9.2 Hz, 2H), 8.02 – 7.99 (m, 2H), 7.83 – 7.81(m, 2H), 6.87 (d, J = 9.2 Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 181.9, 180.8, 149.9, 148.0, 138.9, 134.7, 134.1, 131.6, 130.8, 126.3, 126.1, 125.1, 123.1, 116.8 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{11}N_2O_5^+$ ($[M + H]^+$): 311.0662; Found: 311.0663.

4-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-ylamino)benzonitrile (2.91):

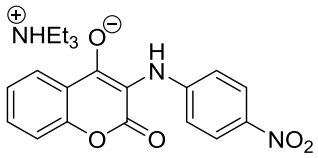


According to GP-1: 2-hydroxy-1,4-naphthoquinone (40 mg, 0.23 mmol), 4-nitrosobenzonitrile (56 mg, 42 mmol) and NEt_3 (64 µL, 0.46 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:1) of the crude gave **2.91** as a violet solid (51 mg, 77%). FTIR (KBr): $\tilde{\nu}$ = 3301, 2220, 1645, 1604, 1579, 1326, 1267, 1237, 718 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ = 8.57 (s, 1H), 8.00 – 7.97 (m, 2H), 7.80 – 7.79 (m, 2H), 7.56 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 181.7, 180.2, 146.7, 146.2, 134.1, 133.7, 132.3, 131.2, 130.5, 125.8, 125.6, 123.3, 120.1, 117.7, 99.8 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_9N_2O_3^-$($[M – H]^-$): 289.0619; Found: 289.0629.

2-(3-nitrophenylamino)-3-hydroxynaphthalene-1,4-dione (2.92): According to GP-1: 2-hydroxy-1,4-naphthoquinone (35 mg, 0.20 mmol), 1-nitro-3-nitrosobenzene (57 mg, 0.37 mmol) and NEt_3 (56 µL, 0.40 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:1) of the crude gave **2.92** as a purple solid (32 mg, 52%). FTIR (KBr): $\tilde{\nu}$ = 3300, 1649, 1625, 1533, 1350, 1331, 1263, 1232, 1097, 801, 718 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ = 8.50 (s, 1H), 8.00 – 7.97 (m, 2H), 7.80 – 7.79 (m, 2H), 7.64 – 7.63 (m, 2H), 7.44 – 7.41 (m, 1H), 7.24 (d, J = 9.0 Hz, 1H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 181.8, 180.0, 147.8, 144.1, 143.2, 133.9, 133.7, 131.0, 130.5, 128.9, 125.8, 125.6, 124.7, 124.2, 114.0, 112.4 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{11}N_2O_5^+$ ($[M + H]^+$): 311.0662; Found: 311.0660.

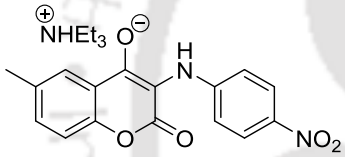


Triethylammonium 3-((4-nitrophenyl)amino)-2-oxo-2H-chromen-4-olate (2.95):



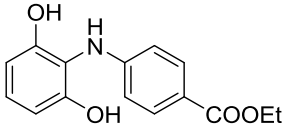
According to GP-1: 4-hydroxycumarine (40 mg, 0.25 mmol), 1-nitro-4-nitrosobenzene (75 mg, 0.45 mmol) and NEt_3 (0.14 mL, 0.98 mmol) were reacted at 50 °C for 12 h in dry toluene (4 mL) and orange precipitate was obtained. The precipitate was filtered and washed with ethylacetate-hexane (1:2) to give **2.95** as orange solid (65 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 3254, 1655, 1599, 1524, 1326, 1498, 1117, 1076, 759 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ = 8.01 – 8.00 (m, 3H), 7.53 – 7.50 (m, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 3.19 (q, *J* = 7.2 Hz, 6H), 1.29 (t, *J* = 7.2 Hz, 9H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ = 173.3, 166.8, 155.9, 154.2, 138.2, 132.0, 126.8, 125.9, 124.3, 123.7, 117.2, 113.4, 102.9, 47.9, 9.2 ppm. HRMS (ESI) exact mass calculated for $C_{15}H_{11}N_2O_5^+$ ($[M + H]^+$): 299.0662; Found: 299.0667.

Triethylammonium 6-methyl-3-((4-nitrophenyl)amino)-2-oxo-2H-chromen-4-olate (2.96):



According to GP-1: 6-methyl-4-hydroxycumarine (40 mg, 0.23 mmol), 1-nitro-4-nitrosobenzene (64 mg, 0.42 mmol) and NEt_3 (0.13 mL, 0.98 mmol) were reacted at 50 °C for 12 h in dry toluene (4 mL) and orange precipitate was obtained. The precipitate was filtered and washed with ethyl acetate-hexane (1:2) to give **2.96** as orange solid (60 mg, 63%). FTIR (KBr): $\tilde{\nu}$ = 3386, 1632, 1600, 1515, 1478, 1343, 1261, 1107, 804 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ = 8.00 (d, *J* = 9.0 Hz, 2H), 7.80 (s, 1H), 7.34 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 2H), 3.16 (q, *J* = 7.2 Hz, 6H), 2.41 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 9H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ = 173.4, 166.9, 155.9, 152.3, 138.1, 134.1, 133.0, 126.8, 125.6, 123.4, 117.1, 113.4, 102.9, 47.8, 21.0, 9.2 ppm. HRMS (APCI) exact mass calculated for $C_{16}H_{13}N_2O_5^+$ ($[M + H]^+$): 313.0819; Found: 313.0821.

Ethyl 4-(2,6-dihydroxyphenylamino)benzoate (2.97a): According to GP-1: cyclohexane-1,3-dione (35 mg, 0.31 mmol), ethyl 4-nitrosobenzoate (0.10 g, 0.58 mmol) and NEt_3 (86 µL, 0.62 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (neutral alumina; EtOAc: Hexane, 1:1) of the crude gave **2.97a** as a colorless gum (39 mg, 46%). FTIR (KBr): $\tilde{\nu}$ = 3448, 1675, 1604, 1518, 1466, 1283, 1174, 1017, 770 cm^{-1}. ^1H NMR (600 MHz,



$CDCl_3$) δ = 7.83 (d, *J* = 9.0 Hz, 2H), 7.11 – 7.08 (m, 1H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 2H), 5.41 (s, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.2, 154.2, 150.4, 131.8, 129.1, 121.7, 113.9, 113.6, 107.8, 60.9, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{15}H_{16}NO_4^+$ ($[M + H]^+$): 274.1074; Found: 274.1075.

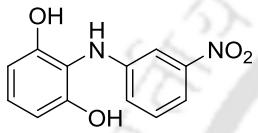
2-(4-nitrophenylamino)benzene-1,3-diol (2.97b): According to GP-1: cyclohexane-1,3-dione (30 mg, 0.27 mmol), 1-nitro-4-nitrosobenzene (75 mg, 0.49 mmol) and NEt_3 (74 µL, 0.53 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (neutral alumina; EtOAc : Hexane, 1:1) of the crude gave **2.97b** as a light yellow gum (29 mg, 44%). FTIR (KBr): $\tilde{\nu}$ = 3403, 2924, 1596, 1498, 1480, 1306, 1260, 1113, 1013, 776 cm^{-1}. ^{1}H NMR (600 MHz, CD_3OD) δ = 8.02 (d, *J* = 9.0 Hz, 2H), 6.97 – 6.94 (m, 1H), 6.61 (d, *J* = 9.6 Hz, 2H), 6.43 (d, *J* = 8.4 Hz, 2H), 5.50 (s, 1H), 4.64 (s, 1H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ = 155.7, 155.3, 139.0, 128.5, 126.6, 115.5, 113.8, 108.1 ppm. HRMS (ESI) exact mass calculated for $C_{12}H_{11}N_2O_4^+$ ($[M + H]^+$): 247.0713; Found: 247.0718.

Ethyl 4-((3,5-dihydroxy-[1,1'-biphenyl]-4-yl)amino)benzoate (2.97c): According to GP-1: 5-phenyl-1,3-cyclohexanedione (35 mg, 0.18 mmol), ethyl 4-nitrosobenzoate (62 mg, 0.34 mmol) and NEt_3 (52 µL, 0.37 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (neutral alumina; EtOAc : Hexane, 1:2) of the crude gave **2.97c** as a colourless gum (30 mg, 46%). FTIR (KBr): $\tilde{\nu}$ = 3435, 2961, 2925, 1676, 1604, 1279, 1173, 1106, 1048, 800, 767 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.43 – 7.41 (m, 2H), 7.36 – 7.39 (m, 1H), 6.83 (s, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 5.44 (s, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.1, 154.2, 150.3, 142.3, 140.4, 131.8, 129.0, 127.9, 127.1, 121.8, 113.6, 113.1, 106.7, 60.9, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{21}H_{20}NO_4^+$ ($[M + H]^+$): 350.1387; Found: 350.1391.

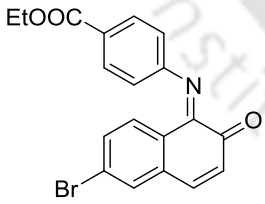
Ethyl 4-((3,5-dihydroxy-2-methyl-[1,1'-biphenyl]-4-yl)amino)benzoate (2.97d): According to GP-1: 4-Methyl-5-phenyl-1,3-cyclohexanedione[2] (35 mg, 0.17 mmol), ethyl 4-nitrosobenzoate (57 mg, 0.32 mmol) and NEt_3 (48 µL, 0.35

mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (neutral alumina; EtOAc : Hexane, 1:1) of the crude gave **2.97d** as a colourless gum (26 mg, 38%). FTIR (KBr): $\tilde{\nu}$ = 3448, 2924, 2854, 1637, 1461, 1275, 1258, 750 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ = 7.80 (d, *J* = 8.8 Hz, 2H), 7.42 –7.38 (t, *J* = 7.2 Hz, 2H), 7.33 – 7.29 (m, 3H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.35 (s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.04 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). ppm. ^{13}C NMR (101 MHz, CD_3OD) δ = 168.9, 154.1, 153.7, 152.8, 143.5, 142.9, 132.0, 130.2, 129.0, 127.8, 120.1, 115.0, 114.6, 114.2, 109.4, 61.4, 14.7, 13.4 ppm**.** HRMS (ESI) exact mass calculated for $C_{22}H_{22}NO_4^+$ ($[M + H]^+$): 364.1543; Found: 364.1544.

2-(3-nitrophenylamino)benzene-1,3-diol (2.97e): According to GP-1: cyclohexane-1,3-dione (30 mg, 0.27 mmol), 1-nitro-3-nitrosobenzene (75 mg, 0.49 mmol) and NEt_3 (74 µL, 0.53 mmol) were reacted for 24 h in dry DCM (4 mL). Column chromatography (neutral alumina; EtOAc : Hexane, 1:3) of the crude gave **2.97e** as a light yellow gum (32 mg, 49%). FTIR (KBr): $\tilde{\nu}$ = 3402, 2924, 1595, 1480, 1331, 1317, 1013, 839, 751 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ = 7.29 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.18 – 7.17 (m, 1H), 7.08 – 7.06 (m, 1H), 6.78 – 6.77 (m, 1H), 6.75 – 6.72 (m, 1H), 6.24 (d, *J* = 8.4 Hz, 2H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ = 155.5, 150.5, 150.2, 130.2, 127.9, 121.2, 116.6, 112.9, 109.0, 108.1 ppm. HRMS (ESI) exact mass calculated for $C_{12}H_{11}N_2O_4^+$ ($[M + H]^+$): 247.0713; Found: 247.0719.

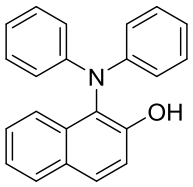


(4E)-ethyl 4-(6-bromo-2-oxonaphthalen-1(2H)-ylideneamino)benzoate (2.98): Ethyl 4-nitrosobenzoate (30 mg, 0.17 mmol) was added to a solution of 6-bromo-2-naphthol (20 mg, 0.09 mmol) and triethylamine (25 µL, 0.18 mmol) in dry dichloromethane (3 mL). The reaction mixture was stirred at room temperature under argon atmosphere. After 10 mins the solvent was immediately evaporated under vacuum at 30 ^oC to obtain green gum residue which was immediately purified by preparative TLC (ethyl acetate: hexane, 1:5) to afford **2.98** as green gum (18 mg, 52%). FTIR (KBr): $\tilde{\nu}$ = 2924, 1634, 1605, 1517, 1280, 1104, 767 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.13 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.66 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.56 (s, 1H), 7.40 (d, *J* = 9.6 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.31 (d, *J* = 10.2 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 179.2, 166.7, 156.9, 150.5, 143.5, 133.9, 133.6,



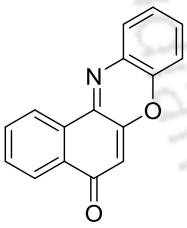
132.2, 132.1, 131.2, 129.9, 129.3, 127.3, 125.6, 115.5, 60.9, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{19}H_{15}BrNO_3^+$ ([M + H]$^+$): 384.0230; Found: 384.0246.

1-(diphenylamino)naphthalen-2-ol (2.119): Iodobenzene (38 µL, 0.34 mmol) was added



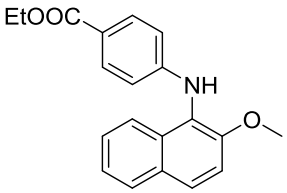
to a solution of **2.52** (40 mg, 017 mmol), Cs_2CO_3 (111 mg, 0.34 mmol) and CuI (6 mg, 0.034 mmol) in dry DMF (2 mL) under argon atmosphere. The mixture was stirred at 110 ^{o}C for 24 h. After completion of the reaction the solvent was removed under reduced pressure and the resulting mixture was extracted with dichloromethane (3×20 mL) and washed with $NaHCO_3$ (3×15 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (silica, EtOAc: hexane, 1:20) to give **2.119** as a brown solid (35 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 3449, 2961, 2921, 2851, 1632, 1492, 1467, 1261, 1023, 798, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 –7.79 (m, 2H), 7.72 – 7.70 (m, 1H), 7.35 – 7.28 (m, 3H), 7.23 – 7.19 (m, 4H), 7.12 – 7.10 (m, 4H), 6.96 – 6.93 (m, 2H), 5.88 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.0, 146.1, 132.7, 130.4, 129.8, 129.7, 128.7, 127.4, 124.0, 123.9, 122.8, 122.4, 120.4, 118.2 ppm. HRMS (ESI) exact mass calculated for $C_{22}H_{18}NO^+$ ([M + H]$^+$): 312.1400; Found: 312.1409.

12,12a-dihydrobenzo[a]phenoxazin-5-one (2.120): K_2CO_3 (47 mg, 0.34 mmol) was added



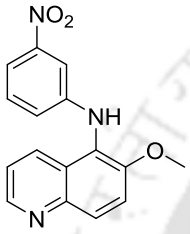
to a solution of **2.52** (40 mg, 0.17 mmol) in toluene (3 mL) and the mixture was stirred at 100 ^{o}C for 72 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica; EtOAc: Hexane, 1:10) gave **2.120** as light yellow solid (18 mg, 42%). FTIR (KBr): $\tilde{\nu}$ = 2959, 2923, 2853, 1736, 1637, 1596, 1457, 1306, 1261, 1102, 1024, 855, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.63 (d, *J* = 8.0 Hz, 1H), 8.21 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 9.2 Hz, 1H), 6.34 (s, 1H) ppm.^{13}C NMR (151 MHz, $CDCl_3$) δ = 184.2, 151.5, 147.6, 144.3, 133.0, 132.4, 132.3, 132.1, 131.8, 131.5, 130.1, 126.1, 125.5, 124.9, 116.1, 107.6 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{10}NO_2^+$ ([M + H]$^+$): 248.0700; Found: 248.0708.

Ethyl 4-(2-methoxynaphthalen-1-ylamino)benzoate (2.121): Methyl iodide (24 µL, 0.39 mmol) was added to solution of **2.49** (40 mg, 0.13 mmol) and K_2CO_3 (90 mg, 0.65 mmol) in acetone (3 mL) and the mixture was stirred at 60 ^{o}C for 4 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica; EtOAc: Hexane, 1:5) gave **2.121** as a brown solid (33 mg, 79%). FTIR (KBr): $\tilde{\nu}$ = 3322,

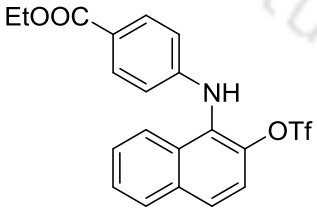


2979, 1687, 1600, 1580, 1365, 1287, 1169, 1097, 802, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) = 7.86 – 7.83 (m, 3H), 7.81 – 7.78 (m, 2H), 7.43 – 7.34 (m, 3H), 6.59 (d, *J* = 8.8 Hz, 2H), 6.10 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.9, 151.7, 151.2, 131.3, 131.0, 129.4, 128.4, 127.4, 126.8, 124.1, 123.3, 122.3, 120.5, 113.9, 113.5, 60.4, 56.6, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{20}H_{20}NO_3^+$ ($[M + H]^+$): 322.1438; Found: 322.1433.

6-methoxy-*N*-(3-nitrophenyl)quinolin-5-amine (2.122): Methyl iodide (33 µL, 0.53 mmol) was added to solution of **2.86** (50 mg, 0.18 mmol) and K_2CO_3 (0.12 g, 0.89 mmol) in acetone (4 mL) and the mixture was stirred at 60 ^oC for 4 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica; EtOAc: Hexane, 1:2) gave **2.122** as a brown solid (30 mg, 57%). FTIR (KBr): $\tilde{\nu}$ = 3399, 3376, 2924, 2852, 1618, 1590, 1526, 1356, 1319, 1264, 1097, 1060, 807, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.83 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.12 – 8.09 (m, 2H), 7.64 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.60 (d, *J* = 9.2 Hz, 1H), 7.43 – 7.42 (m, 1H), 7.33 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.28 – 7.24 (m, 1H), 6.85 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.07 (s, 1H), 3.97 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.7, 149.5, 148.9, 148.1, 144.2, 131.4, 130.0, 129.0, 126.1, 121.8, 121.7, 120.5, 116.6, 114.2, 109.4, 56.7 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{14}N_3O_3^+$ ($[M + H]^+$): 296.1030; Found: 296.1033.

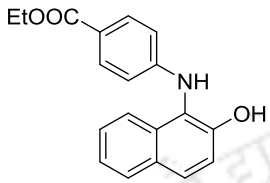
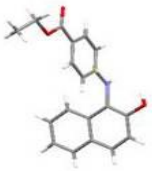


1-(4-(ethoxycarbonyl)phenylamino)naphthalen-2-yl trifluoromethanesulfonate (2.123): Trifluoromethanesulfonic anhydride (26 µL, 0.16 mmol) was added to a solution of **2.49** (40 mg, 0.13 mmol) in pyridine (0.5 mL) at 0 ^oC and the reaction mixture was stirred for 18 h at room temperature. Aq. NH_4OH solution (10 mL) and 2 N HCl (0.2 mL) were added to the reaction mixture and extracted with dichloromethane (3×15 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (silica, EtOAc: hexane, 1:5) to give **2.123** as a colorless solid (35 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 3307, 1688, 1606, 1583, 1510, 1466, 1423, 1290, 1259, 1142, 829, 753 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.96 – 7.94 (m, 2H), 7.89 – 7.87 (m, 3H), 7.61 – 7.58 (m, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.16 (s, 1H), 4.32 (q, *J* = 7.2 Hz,

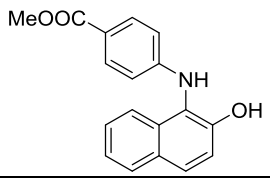
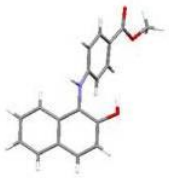


2H), 1.35 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.7, 149.4, 143.0, 133.7, 131.5, 131.3, 128.9, 128.8, 128.7, 128.0, 127.7, 124.4, 121.8, 120.0, 119.8, 117.7, 113.9, 60.7, 14.6 ppm. HRMS (ESI) exact mass calculated for $C_{20}H_{17}F_3NO_5S^+$ ($[M + H]^+$): 440.0774; Found: 440.0774.

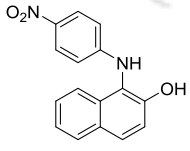
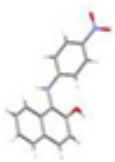
Crystal of **2.49** (CCDC 1866324):

	
Empirical formula	$C_{19}\ H_{17}\ N\ O_3$
Formula weight	61.47
Crystal habit, colour	Block, Brown
Crystal size, mm^3	0.38X 0.33X 0.31
Temperature, T	296(2)
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*P 21/c*
Unit cell dimensions	a = 11.7960(11)Å b = 11.9194(12)Å c = 11.1919(10) α = 90°, β = 90.881(6)°, γ = 90°,
Volume, V(Å^3)	1573.4(3)
Z	20
Calculated density, $Mg{\cdot}m^{-3}$	1.297
Absorption coefficient, $\mu(mm^{-1})$	0.088
F(000)	648
θ range for data collection	1.727° to 25.046°
Limiting indices	$-14 \le h \le 13$, $-14 \le k \le 13$, $-13 \le l \le 13$
Reflection collected / unique	16900/ 1943 [R(int) = 0.0361]
Completeness to θ	97.6% (θ = 25.242°)
Refinement method	SHELXL-2013 (Sheldrick, 2013)
Data / restraints / parameters	1943/ 0 / 214
Goodness–of–fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0500, wR2 = 0.1290
R indices (all data)	R1 = 0.0721, wR2 = 0.1432
Largest diff. peak and hole	0.287 and -0.221e·Å^{-3}

Crystal of **2.53** (CCDC 1866321):

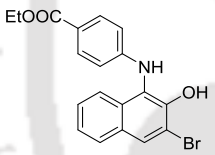
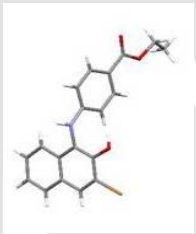
	
Empirical formula	$C_{18}H_{15}NO_3$
Formula weight	40.46
Crystal habit, colour	Needle, Brown
Crystal size, mm^3	0.31 X 0.26 X 0.21
Temperature, *T*	296(2)
Wavelength, λ(Å)	0.71073
Crystal system	orthorhombic
Space group	*P b c a*
Unit cell dimensions	*a* = 13.692(3) Å *b* = 9.810(2) Å *c* = 21.438(5) Å $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$,
Volume, *V*($Å^3$)	2879.4(11)
Z	58
Calculated density, $Mg \cdot m^{-3}$	1.353
Absorption coefficient, $\mu(mm^{-1})$	0.093
F(000)	1232
θ range for data collection	1.90 ° to 25.05 °
Limiting indices	$-14 \leq h \leq 16$, $-11 \leq k \leq 11$, $-25 \leq l \leq 20$
Reflection collected / unique	17752/ 1819 [*R*(int) = 0.0476]
Completeness to θ	97.4% (θ = 25.242°)
Refinement method	SHELXL-2013 (Sheldrick, 2013)
Data / restraints / parameters	1819 / 0 / 205
Goodness−of−fit on F^2	1.053
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0463, *wR*2 = 0.1193
R indices (all data)	*R*1 = 0.0661, *wR*2 = 0.1312
Largest diff. peak and hole	0.209 and -0.184e·$Å^{-3}$

Crystal of **2.54** (CCDC 1866312):

	
Empirical formula	$C_{16}H_{12}N_2O_3$
Formula weight	280.0848
Crystal habit, colour	Needle, yellow
Crystal size, mm^3	0.35 X 0.28X 0.23
Temperature, *T*	293(2)
Wavelength, λ(Å)	0.71073

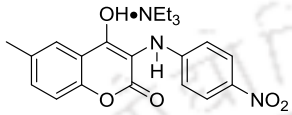
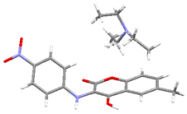
Crystal system	monoclinic
Space group	*P 21/c*
Unit cell dimensions	*a* = 5.4752(8) Å *b* = 17.649(2)Å *c* = 13.8907(17) Å *α* = 90°, *β* = 94.311(15) °, *γ* = 90°,
Volume, *V*(Å^3)	1338.5(3)
Z	4
Calculated density, Mg·m^{-3}	1.391
Absorption coefficient, *μ*(mm^{-1})	0.098
F(000)	584
θ range for data collection	2.94 ° to 25.00°
Limiting indices	$-3 \le h \le 6$, $-20 \le k \le 18$, $-16 \le l \le 16$
Reflection collected / unique	4555 / 1208 [*R*(int) = 0.0412]
Completeness to *θ*	97.8% (*θ* = 25.00 °)
Refinement method	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	1208 / 0 / 196
Goodness–of–fit on F^2	0.963
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0775, *wR*2 = 0.1733
R indices (all data)	*R*1 = 0.1361, *wR*2 = 0.2356
Largest diff. peak and hole	0.242 and –0.225e·Å^{-3}

Crystal of **2.72** (CCDC 1866323):

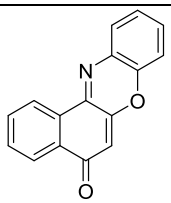
	
Empirical formula	$C_{19}H_{16}BrNO_3$
Formula weight	386.24
Crystal habit, colour	Block, Brown
Crystal size, mm^3	0.41 X 0.36 X 0.31
Temperature, *T*	293(2)
Wavelength, *λ*(Å)	0.71073
Crystal system	monoclinic
Space group	*P 21/c*
Unit cell dimensions	*a* = 11.6484(7)Å *b* = 13.0417(5) Å *c* = 11.0000(6) Å *α* = 90°, *β* = 91.035(5) °, *γ* = 90°,
Volume, *V*(Å^3)	1670.79(15)
Z	4
Calculated density, Mg·m^{-3}	1.535
Absorption coefficient, *μ*(mm^{-1})	2.477
F(000)	784
θ range for data collection	2.97 ° to 25.00°
Limiting indices	$-12 \le h \le 13$, $-15 \le k \le 15$, $-13 \le l \le 12$
Reflection collected / unique	6195/ 2030 [*R*(int) = 0.0423]
Completeness to *θ*	98.5% (*θ* = 25.00°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)

Data / restraints / parameters	2030 / 0 / 223
Goodness–of–fit on F^2	1.060
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0501, *wR*2 = 0.1238
R indices (all data)	*R*1 = 0.0819, *wR*2 = 0.1489
Largest diff. peak and hole	0.302 and –0.622·Å^{-3}

Crystal of **2.96** (CCDC 1866300):

	
Empirical formula	$C_{22}H_{27}N_3O_5$
Formula weight	413.47
Crystal habit, colour	Needle, Orange
Crystal size, mm^3	0.28 X 0.25 X 0.22
Temperature, *T*	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*P 21/c*
Unit cell dimensions	*a* = 19.306(3)Å *b* = 10.033(2)Å *c* = 11.1506(14)Å α = 90°, β = 93.091(13)°, γ = 90°,
Volume, *V*(Å^3)	2156.7(6)
Z	4
Calculated density, Mg·m^{-3}	1.273
Absorption coefficient, μ(mm^{-1})	0.091
F(000)	880
θ range for data collection	2.89° to 25.00 °
Limiting indices	$-22 \le h \le 22, -11 \le k \le 11, -12 \le l \le 13$
Reflection collected / unique	15558 / 2079 [*R*(int) = 0.1142]
Completeness to θ	99.3% (θ = 25.00°)
Refinement method	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	2070/ 0 / 276
Goodness–of–fit on F^2	1.795
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.2241, *wR*2 = 0.5229
R indices (all data)	*R*1 = 0.2791, *wR*2 = 0.5529
Largest diff. peak and hole	1.048 and – 0.522 Å^{-3}

Crystal of **2.120** (CCDC 1866319):

	
Empirical formula	C_{16} H_9 N O_2
Formula weight	247.24
Crystal habit, colour	Needle, yellow
Crystal size, mm^3	0.36 X 0.34X 0.32
Temperature, *T*	296(2)
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*P 21/n*
Unit cell dimensions	*a* = 3.9089(13) Å *b* = 23.323(8) Å *c* = 12.350(4) Å α = 90°, β = 94.388(4)°, γ = 90°,
Volume, *V*($Å^3$)	1122.6(6)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.463
Absorption coefficient, $\mu(mm^{-1})$	0.098
F(000)	512
θ range for data collection	1.746° to 24.997°
Limiting indices	$-4 \le h \le 4$, $-27 \le k \le 27$, $-14 \le l \le 14$
Reflection collected / unique	25762/ 1531 [*R*(int) = 0.0584]
Completeness to θ	97.5% (θ = 25.242°)
Refinement method	SHELXL-2013 (Sheldrick, 2013)
Data / restraints / parameters	1531 / 0 / 172
Goodness−of−fit on F^2	1.051
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0416, *wR*2 = 0.0972
R indices (all data)	*R*1 = 0.0587, *wR*2 = 0.1112
Largest diff. peak and hole	0.146 and $-0.164 \cdot Å^{-3}$

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Chapter 3

Metal Free C(sp^3)-H Functionalization Enabled Annulation of Nitrosoarenes and *N*-heterocycles to Ring-fused Imidazoles

3.1 Introduction:

Imidazoles are privileged moieties which are present in many bioactive molecules including natural products.[1] Imidazole derivatives exhibit a wide range of pharmacological activities including anti-cancer,[2] anti-bacterial,[3] anti-fungal,[4] and anti-viral[5] activities. Particularly, ring-fused benzimidazole derivatives were identified as one of the most important pharmacophores due to their diverse biological activities.[6,7]

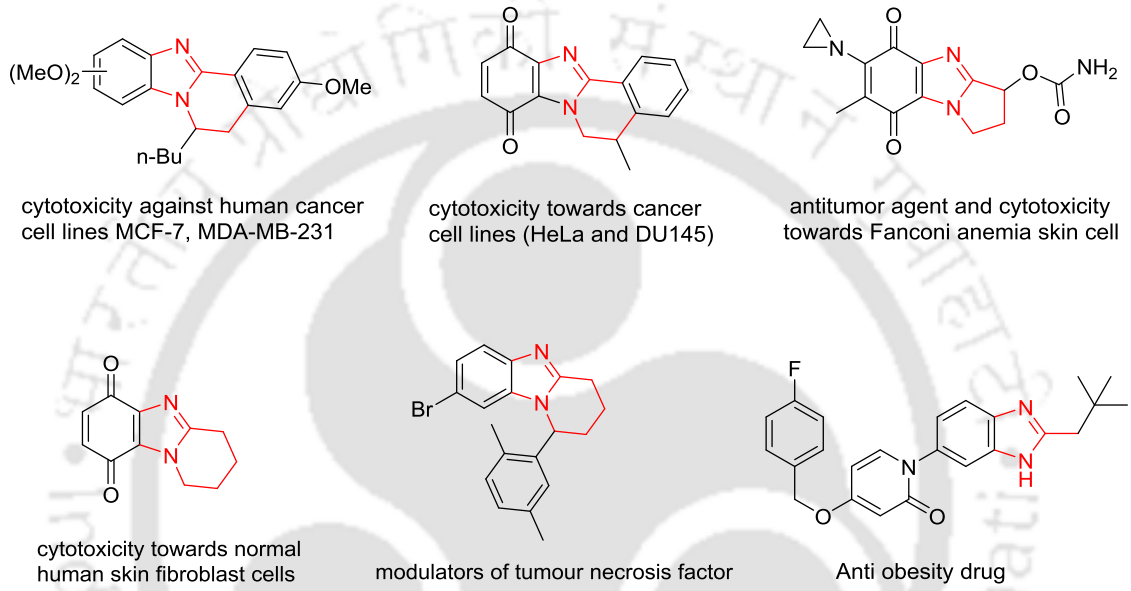
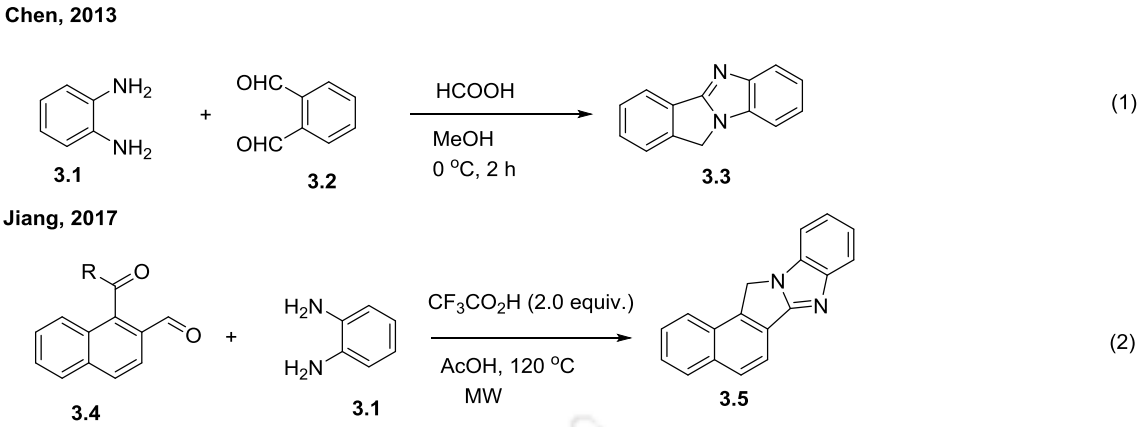


Figure 1: Biologically active ring fused imidazoles.

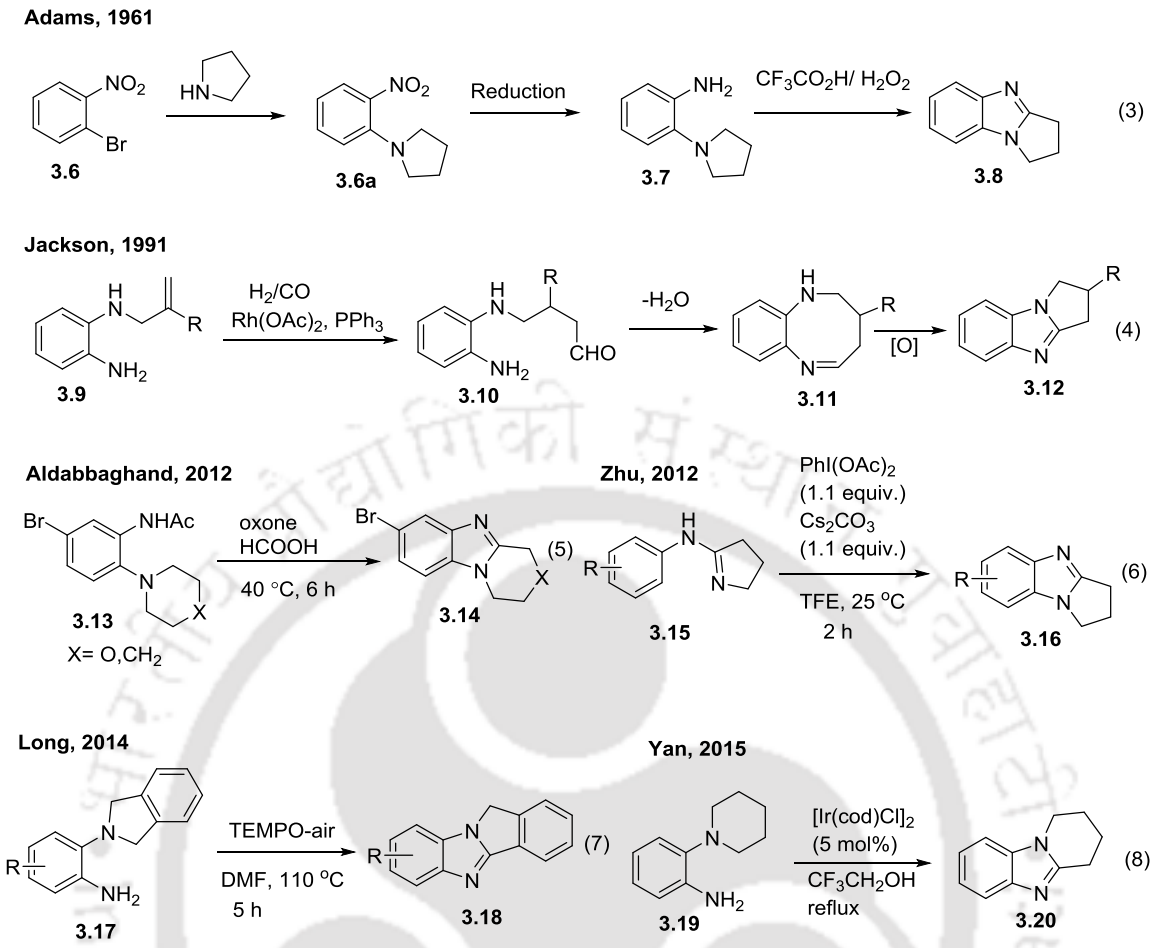
3.2 Known methods for the synthesis of ring fused imidazoles:

The widespread application of fused imidazole derivatives has promoted the development of novel and efficient methodologies for their synthesis. Several synthetic methodologies have been reported in the literature for the synthesis of this important scaffold. The classical approach to synthesize fused imidazole is the redox condensation between *o*-phenylenediamines and 1,4-dialdehydes. In 2013, Chen and co-workers have developed a metal-free acid-promoted coupling reaction between dialdehyde **3.2** and *o*-diaminobenzene **3.1** to synthesize benzo[4,5]imidazo[2,1-*a*]isoindole **3.3** (**Scheme 1**, eq. 1).[8] Later in 2017, Jiang and co-workers reported an acid-mediated condensation reaction of 1,4-dicarbonyl **3.4** and *o*-diaminobenzene **3.1** to afford benzo[*e*]benzo[4,5]imidazo[2,1-*a*]isoindoles **3.5** (**Scheme 1**, eq. 2).[9]



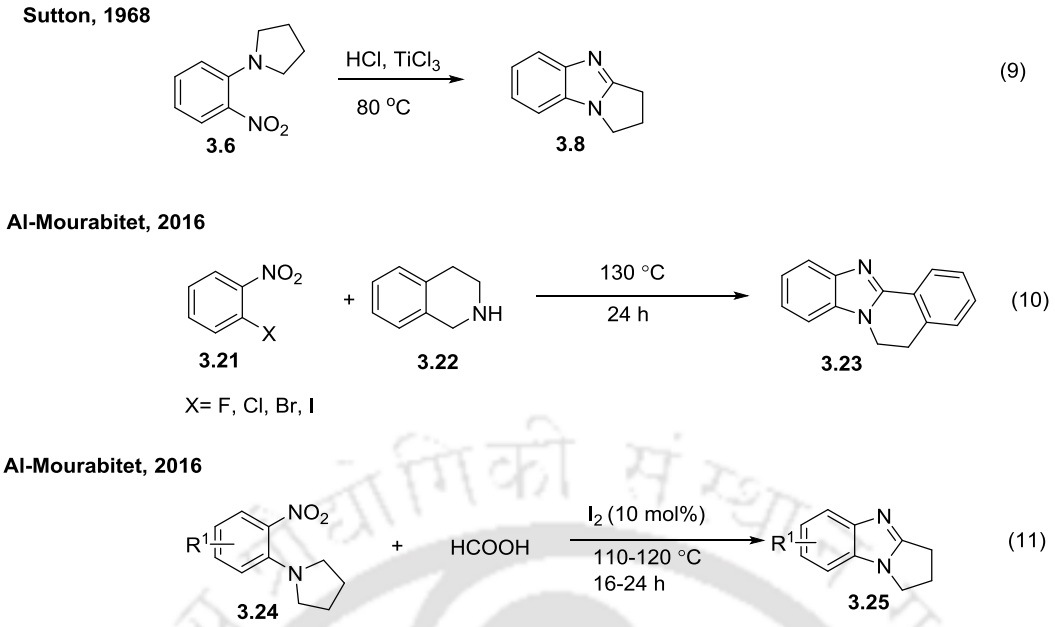
Scheme 1: Synthesis of fused imidazoles via redox condensations.

The other strategies for the synthesis of ring fused imidazoles mainly relied on different oxidative and dehydrogenative cyclizations. In 1961, Adam and co-workers have developed a multistep strategy for the synthesis of piperidino-, pyrrolidino-, morpholino- and hexahydroazepitio-benzimidazoles.[10] Substitution reaction of *o*-nitrobromobenzene **3.6** with various heterocyclic secondary amines afforded the corresponding substitution products **3.6a** which was reduced further to the corresponding aromatic amine **3.7**. Oxidative cyclization of the aromatic amine **3.7** by peroxytrifluoroacetic acid afforded fused imidazole ring **3.8** (**Scheme 2**, eq. 3). A Rhodium catalyzed reaction for the synthesis of fused benzimidazoles has been developed by Jackson and co-workers in 1991. *N*-alkenyl-1,2-diaminobenzenes **3.9** on reaction with hydrogen and carbon monoxide in the presence of $[Rh(OAc)_2]$, PPh_3 afforded **3.10**. Condensation followed by cyclization and oxidation afforded the fused benzimidazole **3.12** (**Scheme 2**, eq. 4).[11] In 2012, Aldabbaghand and co-workers reported an oxidative cyclization of *o-tert*-aminoacetanilides **3.13** using oxone in 90% formic acid to access ring-fused benzimidazole **3.14** (**Scheme 2**, eq. 5).[12] Zhu and co-workers have disclosed a $PhI(OAc)_2$-mediated intramolecular oxidative imidation reaction of aromatic C-H of *N*-arylamidines **3.15** to afford fused benzimidazole **3.16** (**Scheme 2**, eq. 6).[13] Later in 2014, Long and co-workers discovered 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 **3.17** afforded **3.18** (**Scheme 2**, eq. 7).[14] Iridium-catalyzed intramolecular dehydrogenative coupling of tertiary amines **3.19** to afford **3.20** has been developed by Yan and co-workers (**Scheme 2**, eq. 8).[15]



Scheme 2: Fused imidazoles via oxidative and dehydrogenative cyclization.

Earlier in 1968, Sutton and co-workers have developed a $TiCl_3$ mediated reductive cyclization reaction of *N*-2-nitrophenyl-heterocycles **3.6** to access fused benzimidazole **3.8** using (**Scheme 3**, eq. 9).[16] In 2016, Al-Mourabit and co-workers reported a protocol for the synthesis of fused imidazoles via redox condensation of *o*-halonitrobenzene **3.21** with 1,2,3,4-tetrahydroisoquinoline **3.22** under solvent-free conditions (**Scheme 3**, eq. 10).[17] Later, the same group has developed a molecular iodine catalyzed approach for the synthesis of fused benzimidazoles via reductive redox cyclization of *o*-nitro-*tert*-anilines **3.24** using formic acid as the hydrogen source (**Scheme 3**, eq. 11).[18]

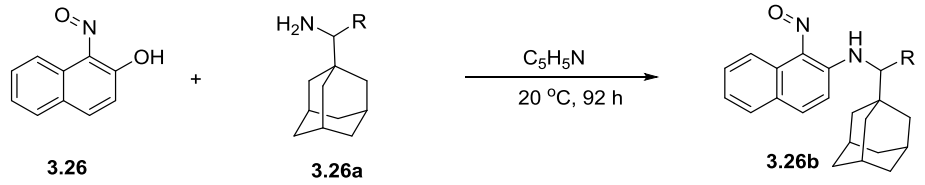


Scheme 3: Ring fused imidazoles via reductive redox cyclization.

The redox condensation reaction of *o*-phenylenediamines with dialdehydes does not involve metal, external reductant or oxidant. However, this strategy usually requires several steps to obtain the starting materials, thus limits the substrate scope and also harsh reaction conditions were applied. Among the reported strategies for the synthesis of fused imidazoles, most of the strategies need an external reductant or oxidant to promote the desired cyclization step. The *o*-NH_2-*tert*-anilines, which were used as the starting material for oxidative cyclization using different oxidants (H_2O_2, oxone, TEMPO), were obtained by reduction of the corresponding parent nitroanilines. Also, dehydrogenative cyclization strategy involves metallic reagents. The use of hazardous organic or metallic oxidants, reductants, harsh reaction conditions and involvement of multistep reaction sequences are the significant drawbacks of these reported strategies. In this context, the development of an alternative step economy, metal and hazardous reagents free protocol would be advantageous as compared to the known methods.

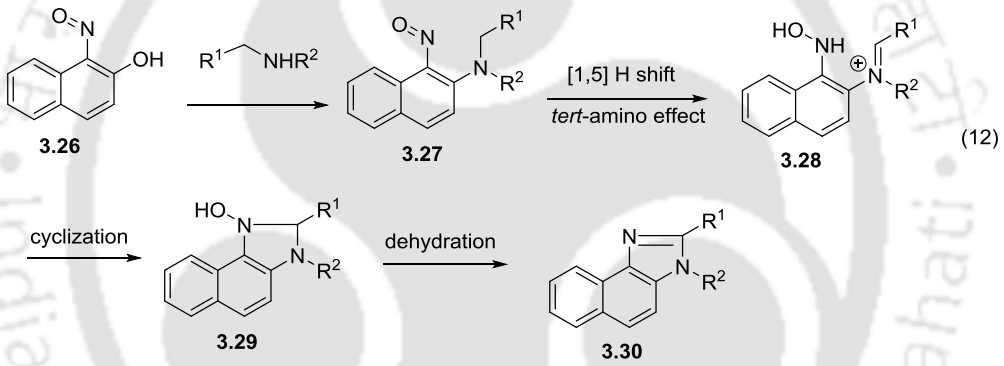
Nitrosoarenes are frequently used in the various synthetic application for incorporating nitrogen and oxygen functionality in the molecule. In particularly, nitrosoarene is used widely for the C(sp^3)-H amination mainly via *N*-nitroso aldol reaction as discussed in **Chapter 1** (**1.96**, **Scheme 17**). Nitrosonaphthols are readily available and can be easily prepared. It can participate in *ipso* substitution of -OH group to provide *o*-nitroso tertiary amine. Suboch and co-workers have reported an *ipso*-substitution reaction of the -OH group

of nitrosonaphthol **3.26** with primary amine to afford *o*-nitroso tertiary amine **3.26a** (**Scheme 4**).[19]



Scheme 4: *Ipso*-substitution reaction of nitrosonaphthol with primary amine.

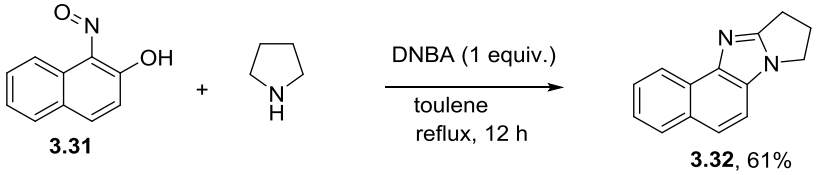
It was anticipated that the reaction of nitrosonaphthol **3.26** with secondary amine can provide *o*-nitroso tertiary amine **3.27** which can undergo 1,5-hydride shift due to tertiary amino effect followed by cyclization to provide the desired ring-fused imidazole derivative **3.30** (**Scheme 5**, eq. 12).



Scheme 5: Hypothesis for ring-fused imidazole formation.

3.3. Results and Discussions:

To test the hypothesis, 1-nitroso-2-naphthol was reacted with pyrrolidine in presence of 3,5-dinitrobenzoic acid (DNBA) in refluxing toluene. As expected, ring-fused naphtho-imidazole **3.32** was formed with 61% yield **(Scheme 6**).

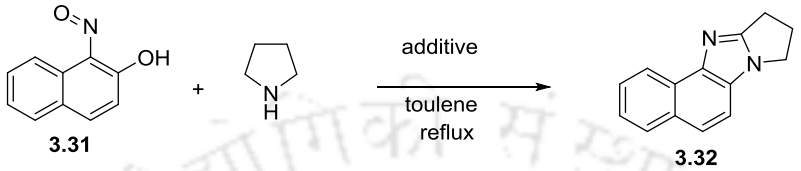


Scheme 6: Initial result.

3.4 Optimization of reaction conditions:

Encouraged by the initial result, various reaction conditions were screened to optimize the reaction condition for the better yield of the naphthoimidazole **3.32**.

Table 1: Optimization of the reaction conditions



Entry	Acids (equiv.)	Equiv. of pyrrolidine	Time	Yield (%)
1	DNBA (1)	2	12 h	61
2	DNBA (0.5)	2	12 h	51
3	DNBA (1)	4	12 h	63
4	DNBA (1)	6	12 h	33
5	TFA (1)	4	12 h	35
6	TfOH (1)	4	12 h	33
7	CSA (0.1)	4	12 h	ND
8	PhCOOH (1)	4	12 h	50
9	4-NO_2-PhCOOH (1)	4	12 h	45
10	85% H_3PO_4 (1)	4	12 h	65
11	AcOH (1)	4	12 h	67
12	AcOH (2)	4	12 h	35

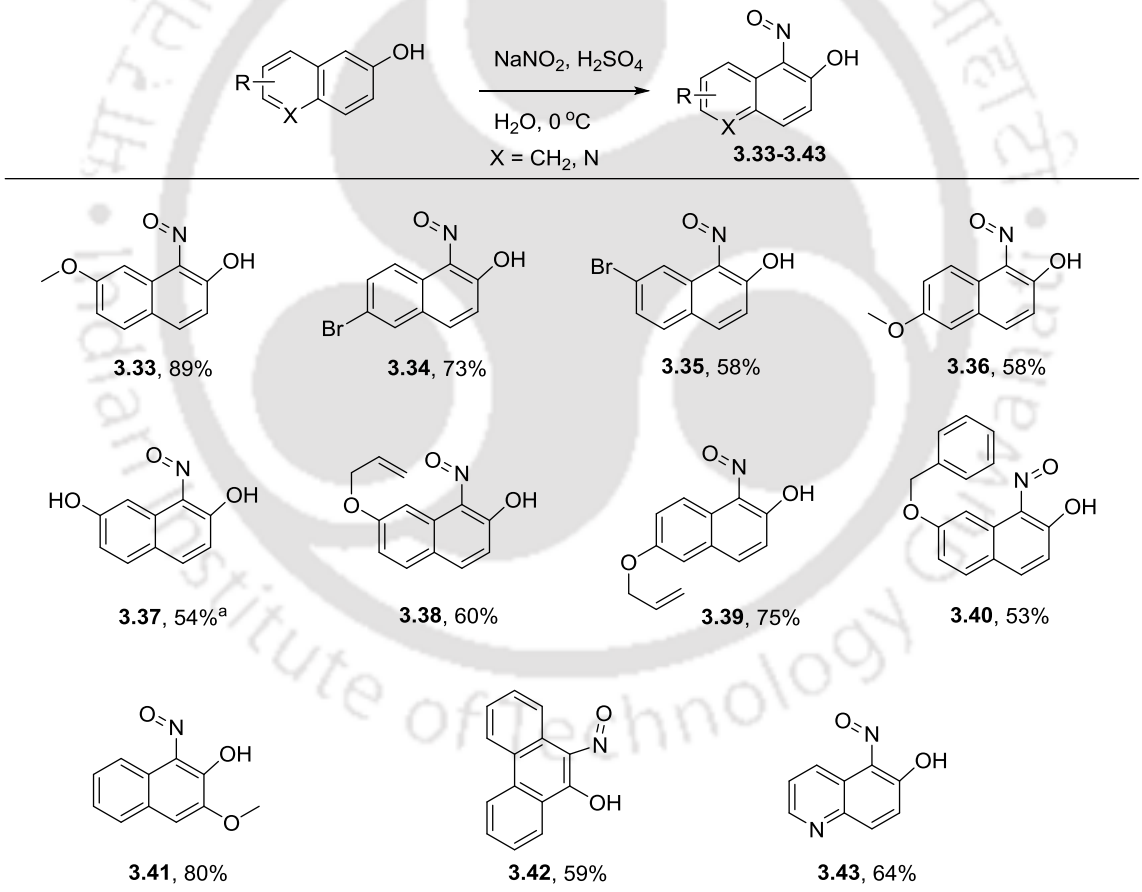
All the reactions were carried with 0.57 mmol of nitrosonaphthol in toluene (5 mL). DNBA = 3,5-dinitrobenzoic acid.

On decreasing the amount of 3,5-DNBA to 0.5 equiv., the yield of the reaction was observed to decrease to 51% (**Table 1**, entry 2). On the other hand, increasing the equivalency of pyrrolidine to 4 equiv. led to little improvement of the yield (63%) (**Table 1**, entry 3). However, a further increase in the equivalency of pyrrolidine (6 equiv.) did not improve in the yield of the reaction (**Table 1**, entry 4). Toluene was proved to be the best solvent among the solvents used in the optimization process. Use of various acids like TFA, TfOH, CSA, benzoic acid, 4-nitrobenzoic acid did not provide better yields (**Table 1**, entry 5-9 respectively). However, an enhancement of the yield to 65% was observed by using 1

equiv. of 85% H_3PO_4 (**Table 1**, entry 10). The best yield (67%) was found from the reaction of 4 equiv. of pyrrolidine with 1 equiv. of 1-nitroso-2-naphthol in the presence of 1 equiv. of AcOH in refluxing toluene (**Table 1**, entry 11). A further increase in the amount of acetic acid resulted in a lower yield (**Table 1**, entry 12).

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

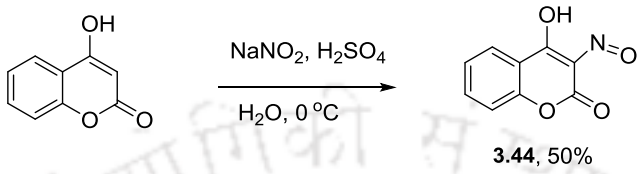
To investigate the scope of the reaction, varieties of 2-hydroxy-C-nitroso compounds were readily prepared by the reaction of corresponding hydroxyl derivative with $NaNO_2$ in the presence H_2SO_4 at 0 ^oC (**Scheme 7**, eq. 21).



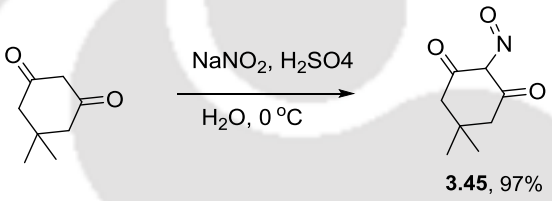
[a.] reaction was carried out at 60 ^oC.

Scheme 7: Preparation of 2-hydroxy-C-nitroso compounds.

Different 2-naphthol, phenanthrene, quinoline derivatives were treated with $NaNO_2$ in the presence of H_2SO_4 to afford corresponding 2-hydroxy-C-nitroso compounds **3.33-3.43** with good to moderate yields (**Scheme 5**). Similarly, 2-hydroxy-C-nitroso compounds derived from, coumarin and dimedone derivatives, **3.44**, **3.45** respectively, were prepared (**Scheme 8, Scheme 9** respectively).

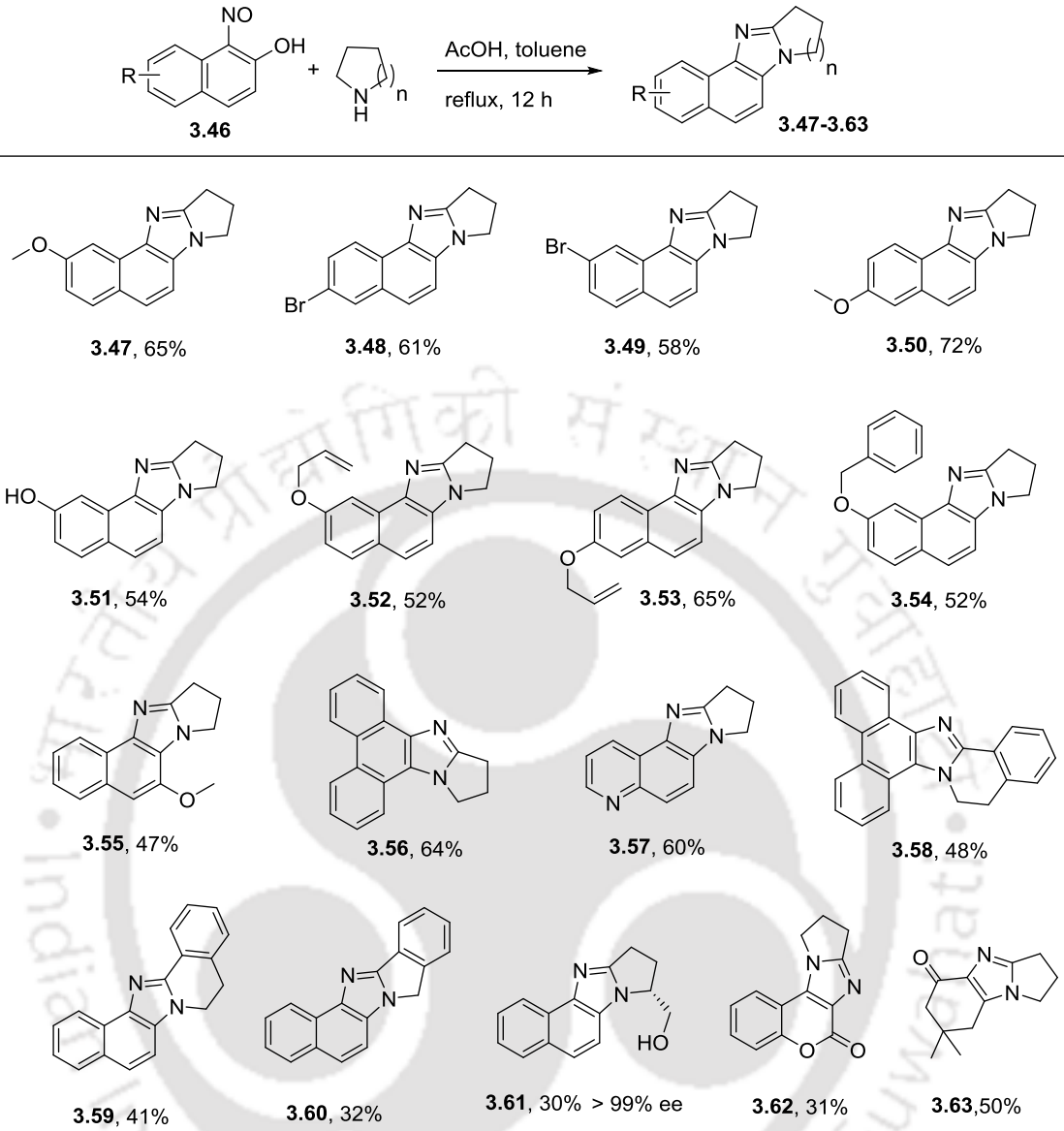


Scheme 8: Preparation of 2-hydroxy-C-nitroso compounds from 4-OH coumarin.



Scheme 9: Preparation of 2-hydroxy-C-nitroso compounds from dimedone.

Diversely substituted nitrosonaphthols (**3.33-3.41**) were reacted with pyrrolidine to obtain the novel class of ring fused imidazole derivatives **3.47-3.55**, **3.59-3.61** with good yields (**Scheme 10**). Hydroxy, alkoxy and bromo -substituted nitrosonaphthols reacted smoothly to provide the corresponding naphtho-imidazole derivatives. However, a slightly lower yield of imidazole **3.55** (47%) as compared to **3.47** and **3.50** was obtained from sterically hindered 3-methoxy nitrosonaphthol relative to its 6-methoxy and 7-methoxy derivatives. Phenanthroline and quinoline derivatives **3.56** (60%) and **3.57** (64%) were also obtained from corresponding *o*-hydroxy-nitroso compounds **3.42** and **3.43** respectively. Other relatively bulky *N*-heterocycles, such as tetrahydroisoquioline and indoline also provided the desired imidazoles (**3.58-3.60**), however, with lower yields. *R*-prolinol provided corresponding imidazole **3.61** with excellent enantiopurity (> 99%). We also examined the reactivity of a non-aromatic α-hydroxy-nitroso/keto-oxime (**3.44** & **3.45**) in the presence of pyrrolidine under optimized conditions. Corresponding imidazole derivatives **3.62** and **3.63** were formed with satisfactory yields.

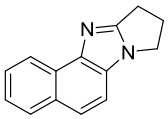
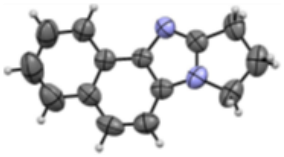
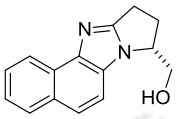
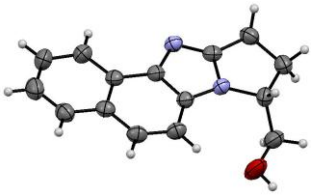
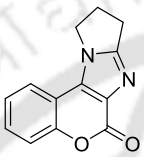
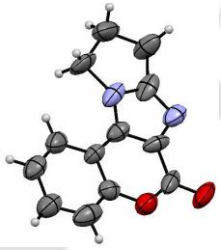


Scheme 10: Scope of successive C(sp^2)-OH and C(sp^3)-H amination.

3.6 Crystal structures of ring fused imidazoles:

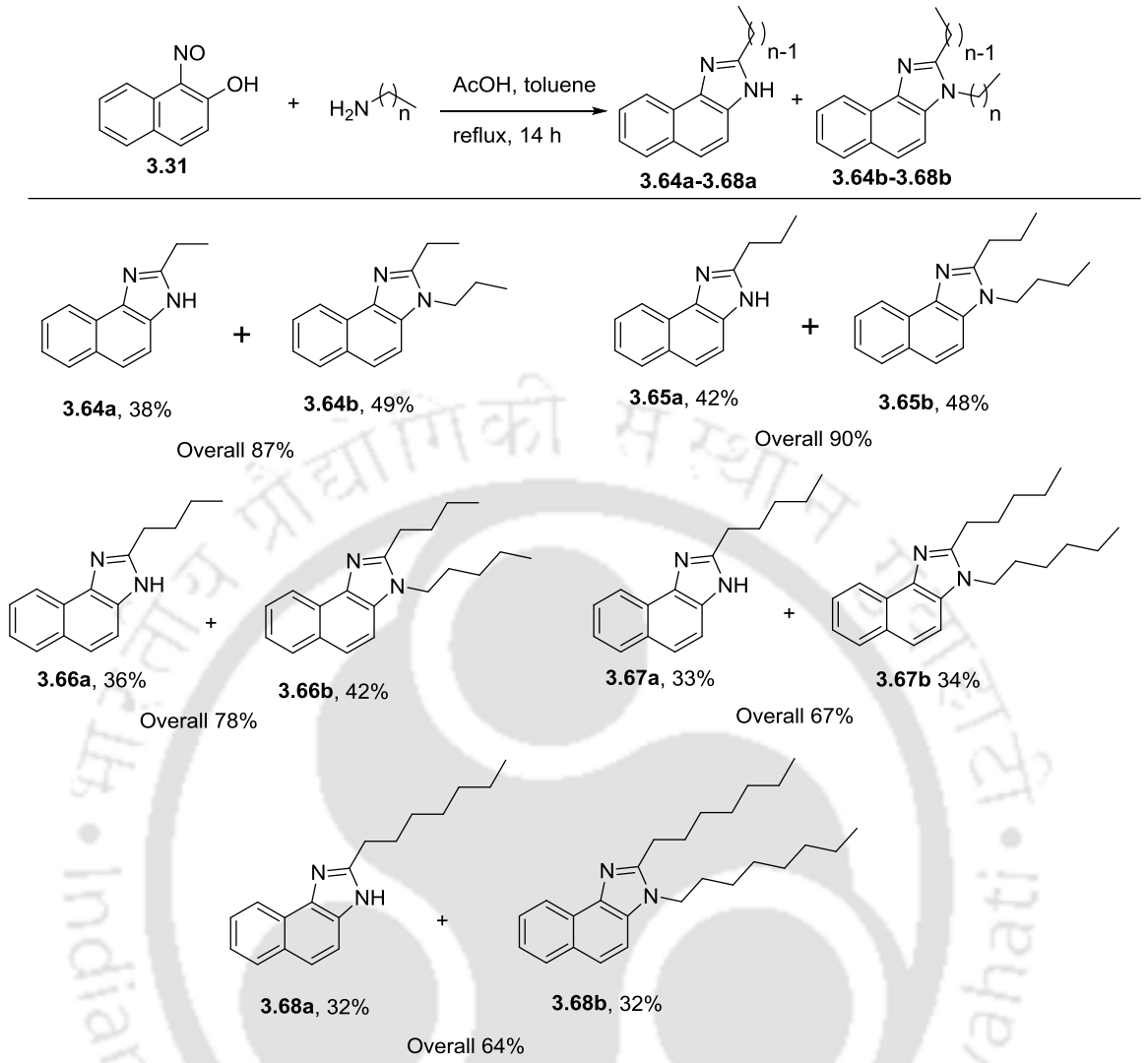
The structures of the imidazole derivatives **3.32**, **3.61** and **3.62** were confirmed by X-ray crystallographic analysis. The structures of compounds have been shown below (**Table 2**).

Table 2: Selected ring fused imidazoles and their X-ray crystal structures.

Compound	Crystal structure
 **3.32**	
 **3.61**	
 **3.62**	

3.7 Scope of the reaction with primary aliphatic amines:

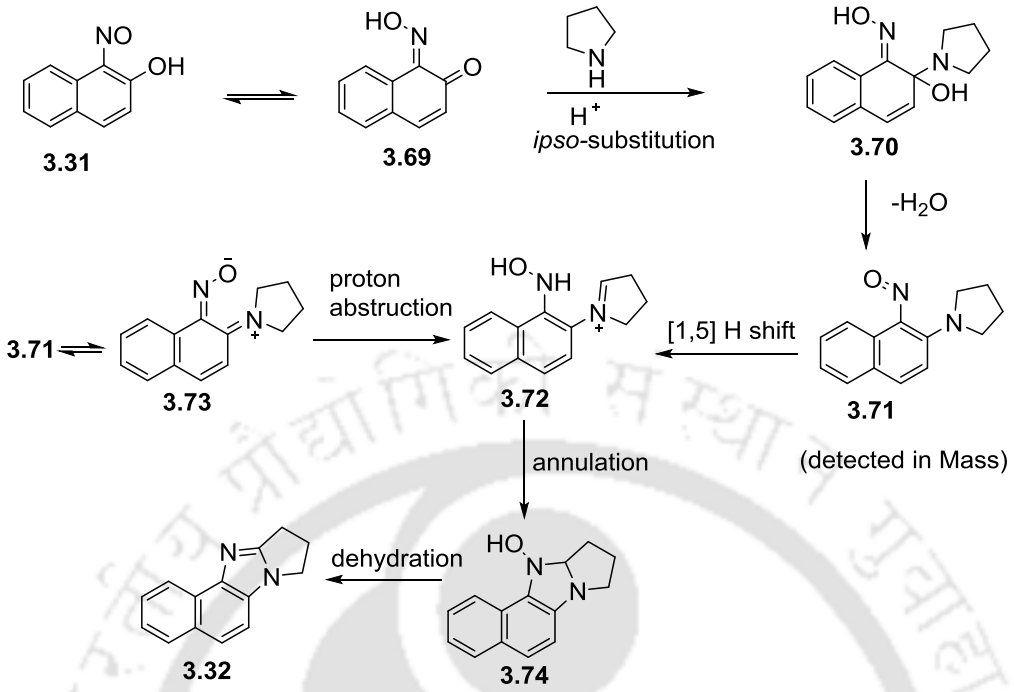
After having success in C(sp^3)-H amination reaction involving secondary cyclic amines, the scope of this reaction with aliphatic primary amines was investigated. Aliphatic primary amines with varied chain length were then reacted with 1-nitroso-2-naphthol under the standard reaction conditions. Interestingly, when *n*-propyl amine reacted with 1-nitroso-2-naphthol in presence of acetic acid in refluxing toluene for 14 h, the desired naphtho-imidazoles **3.64a** was isolated along with the corresponding *N*-alkylated derivatives **3.64b** with very good combined yield (87%). *n*-butyl amine also gave the naphtho-imidazole **3.65a** and *N*-alkylated derivative **3.65b** with excellent combined yield. Similarly, *n*-pentyl-, *n*-hexyl- and *n*-octyl-amines were tested under this reaction conditions and afforded the naphtho-imidazoles **3.66a-3.68a** and the corresponding *N*-alkylated derivatives **3.66b-3.68b** with very good to excellent combined yields (**Scheme 11**).



Scheme 11: Scope of the reaction with primary aliphatic amines.

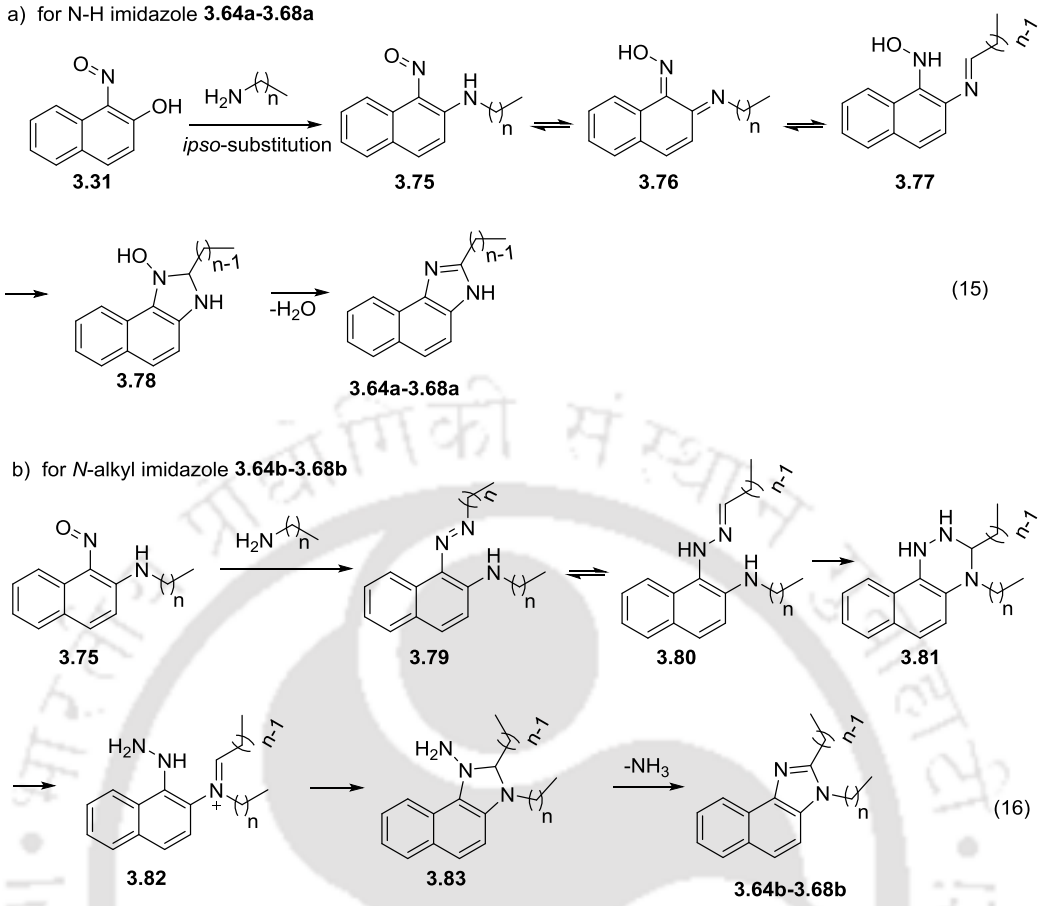
3.8 Plausible mechanism:

A plausible mechanism for unprecedented domino C(sp^3)-H amination/ annulation reaction is presented in **Scheme 12**. Nitrosonaphthalene derivative **3.71** could be formed from the nucleophilic *ipso*-substitution reaction of nitrosonaphthol **3.31** or its keto-oxime tautomer **3.69** with pyrrolidine through intermediate **3.70**. Amino nitroso derivative **3.71** then readily undertook a 1,5-hydride shift to provide the iminium ion **3.72**. Alternatively, the iminium ion **3.72** could also be formed through deprotonation of iminium ion **3.73** which was produced from isomerization/ mesomerization of **3.71**. Annulation of **3.72** followed by acid-mediated dehydration of resulting *N*-hydroxy derivative **3.74** provided the desired imidazole **3.32**. Nitrosoarene **3.71** was detected in mass spectrometry. This support the intermediacy of **3.71** in the reaction.



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

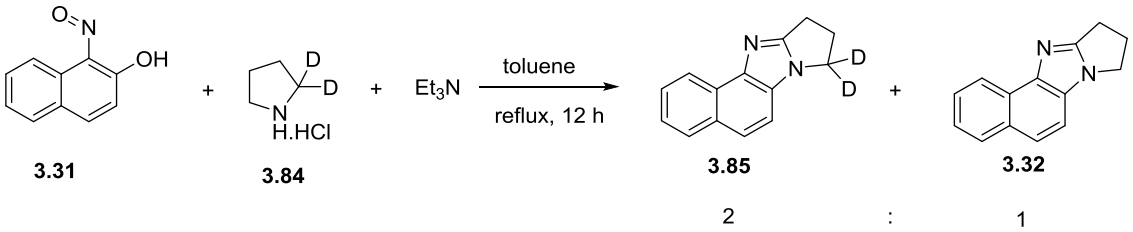
In case of reaction with primary amines, a plausible mechanism has been depicted in **Scheme 13**. The formation of naphtho-imidazoles **3.64a-3.68a** follows the similar mechanism as in case of secondary amines. *Ipso* substitution of nitrosonaphthol **3.31** provided **3.76** which readily tautomerizes to provide **3.77**. Then annulations followed by dehydration afforded **3.64a-3.68a** (**Scheme 13**, eq. 15). For the formation of *N*-alkylated naphtho-imidazoles derivatives, *N*-amination of **3.75** by primary amine afforded azo compound **3.79** which underwent isomerization to provide **3.80**. Annulation of **3.80** produced **3.81**. Ring-opening of **3.81** could occur to provide **3.82**. Annulation of **3.82** followed by elimination of ammonia provided *N*-alkylated naphtho-imidazole **3.64b -3.68b** (**Scheme 13**, eq. 16).



Scheme 13: Proposed mechanism for metal free annulation of nitrosoarene and aliphatic primary amines.

3.9 Labelling Experiment:

To further understand the reaction mechanism C(sp^3)-H amination/ annulation reaction, a labelling experiment has been performed by reacting hydrochloride salt of pyrrolidine-2,2-d_2 with 1-nitroso-2-naphthol in the presence of Et_3N in refluxing toluene. Deuterium incorporated product **3.85** and deuterium exclusion product **3.32** were separated in 2:1 ratio as an inseparable mixture (**Figure 2**). This result suggests that C-H bond cleavage might occur in the rate-determining step (**Scheme 14**). Similar isotope effect was observed for the related reaction.[20]



Scheme 14: Labelling experiment.

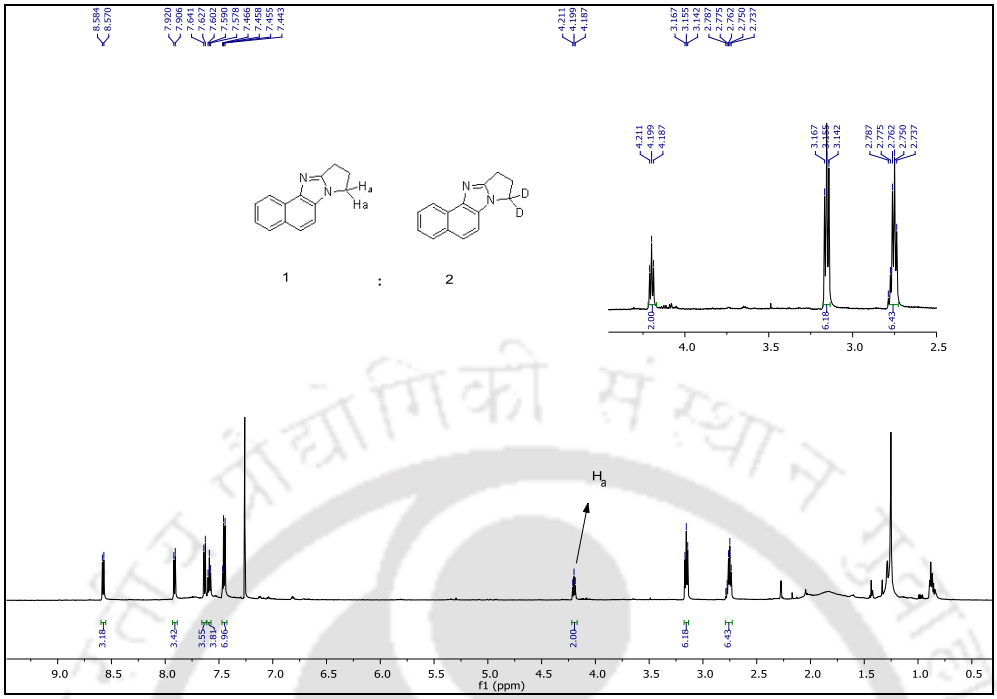
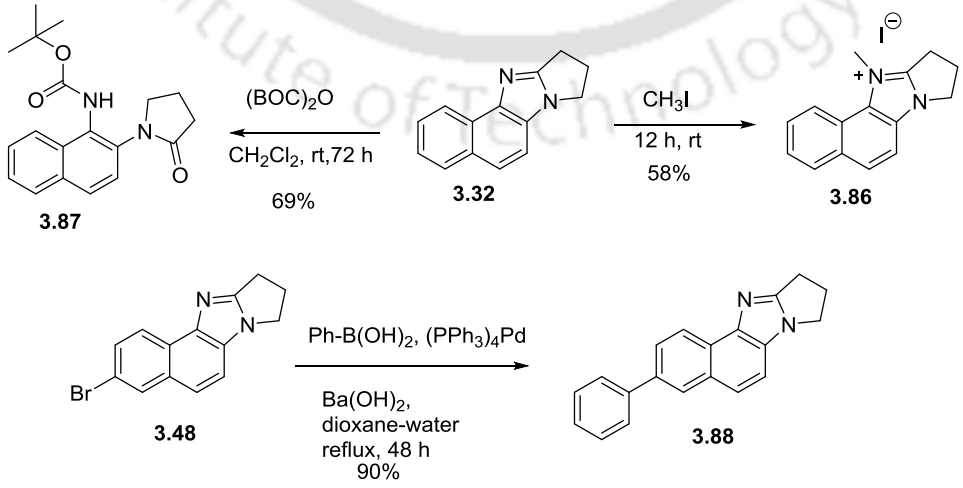


Figure 2: ^{1}H-NMR of mixture **3.32** and **3.85**.

3.10 Synthetic application:

N-methylation of imidazole **3.32** with CH_3I occurred readily to provide imidazolium iodide **3.86**. *N*-acylation of **3.32** in the presence of di-*tert*-butyl dicarbonate followed by hydrolysis of resulting imidazolium salt leads to the cleavage of imidazole ring to provide corresponding *o*-diamino arenes **3.87** with very good yield. Bromo functionality of **3.48** was utilized for Suzuki coupling with phenylboronic acid to obtain the corresponding phenyl substituted imidazole **3.88** with 90% yield. (**Scheme 15**).



Scheme 15: Synthetic application of imidazole derivatives.

3.11 Conclusion:

In summary, a novel annulation reaction of nitrosoarene and aliphatic amine via an unprecedented sequential C(sp^2)-OH amination of nitrosoarene and α-C(sp^3)-H amination of aliphatic amines without the aid of metallic reagent/catalyst and external oxidant has been developed. Novel polycyclic imidazole were prepared readily from the reaction of 2-hydroxy-C-nitroso compounds. Moreover, the synthesis of *N*-alkylated fused naphtho-imidazole derivatives was achieved by this methodology from the reaction of aliphatic acyclic primary amines. Various secondary amines, as well as primary amines, were successfully functionalized using this operationally simple protocol.

3.12 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). 7-(allyloxy)naphthalen-2-ol,[21] 7-(benzyloxy)naphthalen-2-ol[22], 6-(allyloxy)naphthalen-2-ol,[21] compounds were synthesized according to reported procedures.

General procedure for the preparation of nitroso compounds: GP-1

Various substituted naphthols (0.44 mmol – 7.18 mmol) were dissolved in a warm solution of sodium hydroxide (1 equiv.) in water (1.6 mL – 15 mL). The solution was cooled to 0° C and solid sodium nitrite (1 equiv.) was added into it. Concentrated H_2SO_4 was added drop-wise into the reaction mixture while maintaining the temperature 0° C and stirring continued for additional 1 h at the same temperature. Solid precipitate obtained was filtered and washed 5-6 times with water (10-20 mL). The crude solid was loaded directly onto silica gel column and purified to afford pure nitroso compounds.

7-methoxy-1-nitrosonaphthalen-2-ol (3.33):[23] According to GP-1: 7-methoxy-2-naphthol (1.25 g, 7.18 mmol), NaOH (0.29 g, 7.18 mmol) in water (15 mL), $NaNO_2$ (0.5 g, 7.18 mmol), H_2SO_4 (0.5 mL, 9.3 mmol) were stirred at 0 ºC for 1h. Reddish brown precipitate obtained, drying in vacuum gave **3.33** a reddish brown solid (1.29 g, 89%). FTIR (KBr): $\tilde{\nu}$ = 3075, 2925, 2846, 1623, 1612, 1554, 1525, 1231, 1177, 883, 808 cm $^{-1}$. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.80 (s, 1H), 7.62 (d, *J* = 9.6 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.41 (d, *J* =

9.6 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 183.0, 162.2, 148.3, 145.0, 133.1, 131.6, 122.8, 122.6, 117.7, 106.5, 55.9. HRMS (ESI) exact mass calculated for $C_{11}H_{10}NO_3$ ($[M + H]^+$): 204.0655; Found: 204.0657.

6-bromo-1-nitrosonaphthalen-2-ol (3.34): According to GP-1: 6-bromo-2-naphthol (0.50 g, 2.24 mmol), NaOH (90 mg, 2.24 mmol) in water (10 mL), $NaNO_2$ (0.16 g, 2.24 mmol), H_2SO_4 (0.16 mL, 2.91 mmol) were reacted at 0 ºC for 1 h. Solid precipitate obtained and column chromatography (SiO_2; EtOAc : Hexane, 1:20) gave product **3.34** as a yellow solid (0.41 g, 73%). FTIR (KBr): $\tilde{\nu}$ = 3059, 2961, 2922, 2851, 1622, 1580, 1517, 1259, 1065, 964, 802, cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.61 (m, 3H), 6.62 (d, *J* = 9.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 182.5, 146.4, 144.6, 134.0, 132.2, 130.1, 129.6, 127.3, 124.9, 123.9 HRMS (ESI) exact mass calculated for $C_{10}H_7BrNO_2$ ($[M + H]^+$): 251.9655; Found: 251.9657.

7-bromo-1-nitrosonaphthalen-2-ol (3.35): According to GP-1: 7-bromo-2-naphthol (0.10 g, 0.44 mmol), NaOH (18 mg, 0.44 mmol) in water (1.6 mL), $NaNO_2$ (31 mg, 0.44 mmol), H_2SO_4 (0.48 mL, 0.96 mmol) were stirred at 0 ºC for 1.5 h. Solid precipitate obtained and column chromatography (SiO_2; EtOAc : hexane, 1:20) gave pure product **3.35** as a yellow solid (64 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 2958, 29323, 2853, 1628, 1458, 1384, 1160, 1080, 846 cm $^{-1}$. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.49 (s, 1H), 7.66 (d, *J* = 9.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 6.61 (d, *J* = 10.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 182.3, 146.9, 144.3, 133.0, 132.5, 131.1, 127.5, 126.4, 126.35, 126.32. HRMS (ESI) exact mass calculated for $C_{10}H_7BrNO_2$ ($[M + H]^+$): 251.9655; Found: 251.9660.

6-methoxy-1-nitrosonaphthalen-2-ol (3.36): [24] According to GP-1: 6-methoxy-2-naphthol (0.12 g, 0.69 mmol), NaOH (28 mg, 0.69 mmol) in water (3 mL), $NaNO_2$ (48 mg, 0.69 mmol), H_2SO_4 (48 µL, 0.89 mmol) were reacted at 0 º C for 1h. Solid crude precipitate obtained and column chromatography (SiO_2; EtOAc : Hexane, 1:10) gave **3.36** as a reddish brown solid (82 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 3052, 2959, 2934, 2832, 2093, 1693, 1595, 1611, 1512, 1294, 1062, 1037, 755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 10.0 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.56 (d, *J* = 10.0 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 183.2, 160.9,

147.8, 144.7, 130.1, 126.6, 125.1, 123.8, 118.0, 113.5, 55.8. HRMS (ESI) exact mass calculated for for $C_{11}H_{10}NO_3$ ($[M + H]^+$): 204.0655; Found: 204.0657.

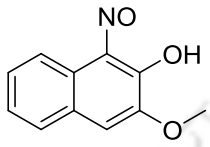
7-(allyloxy)-1-nitrosonaphthalen-2-ol (3.38): According to GP-1: 7-(allyloxy)naphthalen-2-ol (0.28 g, 1.4 mmol), NaOH (56 mg, 1.4 mmol) in water (4 mL), $NaNO_2$ (97 mg, 1.4 mmol), H_2SO_4 (97 µL, 1.82 mmol) were stirred at 0 ºC for 1h. Solid precipitate obtained and column chromatography (SiO_2; EtOAc: Hexane, 1:15) gave pure product **3.38** as a reddish brown solid (0.19 g, 60 %). FTIR (KBr): $\tilde{\nu}$ = 3417, 2920, 2850, 1628, 1553, 1407, 1273, 1075, 1018, 839, 817 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.76 (s, 1H), 7.59 (d, *J* = 10.2 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.02 – 7.00 (m, 1H), 6.38 (d, *J* = 9.6 Hz, 1H), 6.08 – 6.02 (m, 1H), 5.44 (d, *J* = 16.2 Hz, 1H), 5.32 (d, *J* = 11.4 Hz, 1H), 4.62 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 182.9, 161.1, 148.2, 144.9, 133.1, 132.5, 131.6, 122.8, 122.6, 118.5, 118.1, 107.3, 69.2. HRMS (ESI) exact mass calculated for $C_{13}H_{12}NO_3$ ($[M + H]^+$): 230.0812; Found: 230.0803.

6-(allyloxy)-1-nitrosonaphthalen-2-ol (3.39): According to GP-1: 6-(allyloxy)naphthalen-2-ol (0.10 g, 0.51 mmol), NaOH (21 mg, 0.51 mmol) in water (1.5 mL), $NaNO_2$ (35 mg, 0.51 mmol), H_2SO_4 (35 µL, 0.66 mmol) were stirred at 0 ºC for 1h. Solid precipitate obtained and column chromatography (SiO_2; EtOAc : Hexane, 1:10) gave pure product **3.39** as a reddish brown solid (89 mg, 75 %). FTIR (KBr): $\tilde{\nu}$ = 2967, 2925, 2856, 1665, 1605, 1513, 1307, 1261, 1238, 1016, 839, 803 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 10.2 Hz, 1H), 7.11– 7.09 (m, 1H), 6.95 (d, *J* = 3.0 Hz, 1H), 6.56 (d, *J* = 10.2 Hz, 1H), 6.09 – 6.04 (m, 1H), 5.45 (d, *J* = 18.6 Hz, 1H), 5.34 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 5.4 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 183.2, 159.9, 147.8, 144.7, 132.6, 130.0, 126.6, 125.1, 123.9, 118.6, 118.5, 114.4, 69.2. HRMS (ESI) exact mass calculated $C_{13}H_{12}NO_3$ ($[M + H]^+$): 230.0812; Found: 230.0802.

7-(benzyloxy)-1-nitrosonaphthalen-2-ol (3.40): According to GP-1: 7-(benzyloxy)naphthalen-2-ol (0.22 g, 0.88 mmol), NaOH (36 mg, 0.88 mmol) in water (3.6 mL), $NaNO_2$ (61 mg, 0.88 mmol), H_2SO_4 (61 µL, 1.14 mmol) were stirred at 0 ºC for 1 h. Solid precipitate obtained and column chromatography (SiO_2; EtOAc : Hexane, 1:15) gave pure product **3.40** as a red solid (0.18 g, 53 %). FTIR (KBr): $\tilde{\nu}$ = 3026, 3033,

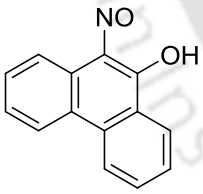
2938, 2918, 1614, 1553, 1379, 1068, 870, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.85 (s, 1H), 7.57 – 7.54 (m, 1H), 7.45 – 7.43 (m, 2H), 7.41 – 7.37 (m, 2H), 7.35 – 7.32 (m, 2H), 7.06 – 7.04 (m, 1H), 6.36 (d, *J* = 9.6 Hz, 1H), 5.12 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 182.8, 161.2, 148.1, 144.9, 136.1, 133.1, 131.6, 128.8, 128.4, 127.7, 122.9, 122.7, 118.1, 107.4, 70.4. HRMS (ESI) exact mass calculated for $C_{17}H_{14}NO_2$ ($[M + H]^+$): 280.0968; Found: 280.0967.

3-methoxy-1-nitrosonaphthalen-2-ol (3.41): According to GP-1: 3-methoxy-2-naphthol



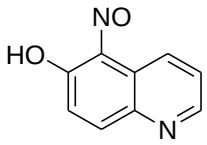
(0.35 g, 2.02 mmol), NaOH (81 mg, 2.02 mmol) in water (7 mL), $NaNO_2$ (0.14 g, 2.02 mmol), H_2SO_4 (0.14 mL, 2.62 mmol) were stirred at 0 ºC for 1 h. Solid precipitate obtained and column chromatography (SiO_2; EtOAc : Hexane, 1:10) gave pure product **3.41** as a red solid (0.33 g, 80%). FTIR (KBr): $\tilde{\nu}$ = 3076, 3050, 2964, 2918, 2854, 1700, 1610, 1595, 1522, 1462, 1294, 1143, 1062, 865, 755,636 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.35 – 7.28 (m, 2H), 6.77 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 177.3, 150.5, 145.0, 130.1, 128.7, 128.4, 128.3, 126.8, 123.0, 118.9, 56.1.HRMS (ESI) exact mass calculated for $C_{11}H_{10}NO_3$ ($[M + H]^+$): 204.0655; Found: 204.0654.

10-nitrosophenanthren-9-ol (3.42):[25] Hydroxylamine hydrochloride (0.51 g, 7.4 mmol)

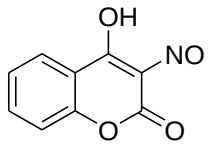


was added to a solution of 9, 10 Phenanthrenequinone (0.52 g, 1.85 mmol) in chloroform (25 mL) and ethanol (12 mL) and the solution was refluxed for 5 h. After completion of reaction, the mixture was cooled to room temperature, diluted with chloroform (10 mL) and the organic phases were washed with water (4 x 100 mL), dried over sodium sulfate and concentrated under vacuum to give crude mixture which was purified by column chromatography (SiO_2; EtOAc : Hexane, 1:30) and afforded pure product **3.42** as a light yellow solid (0.24 g, 59%). FTIR (KBr): $\tilde{\nu}$ = 2961, 2923, 2859, 1680, 1623, 1598, 1448, 1280, 1164, 1091, 755 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.37 (d, *J* = 7.8 Hz, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.53 – 7.48 (m, 2H), 7.45 – 7.42 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 182.5, 144.2, 137.7, 136.4, 130.2, 129.6, 129.4, 129.3, 129.1, 128.5, 128.4, 124.1, 123.6, 123.5. HRMS (ESI) exact mass calculated for $C_{14}H_{10}NO_2$ ($[M + H]^+$): 224.0706; Found: 224.0707.

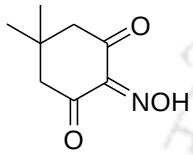
5-nitrosoquinolin-6-ol (3.43):[26] ^{1}H NMR (600 MHz, DMSO-d_6) δ = 9.05 (s, 1H), 8.66 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.51 – 7.50 (m, 1H), 6.63 (d, J = 9 Hz, 1H). HRMS (ESI) exact mass calculated for $C_9H_7N_2O_2$ ([M + H]$^+$): 175.0502, found: 175.0502



4-hydroxy-3-nitroso-2*H*-chromen-2-one (3.44):[27] ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.93 (d, J = 7.2 Hz, 1H), 7.76 – 7.73 (m, 1H), 7.33 (t, J = 6.6 Hz, 1H), 7.29 – 7.25 (m, 1H). HRMS (ESI) exact mass calculated for $C_9H_6NO_4$ ([M + H]$^+$): 192.0291, found: 192.0294.

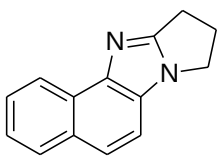


2-(hydroxyimino)-5,5-dimethylcyclohexane-1,3-dione (3.45):[28] Sodium nitrite (0.25 g, 3.57 mmol) was added to a suspension of 5,5-Dimethyl-1,3-cyclohexanedione (0.50 g, 3.57 mmol) in a solution of potassium hydroxide (0.20 g in 12 mL of water) and the reaction mixture was cooled to 0 ºC. H_2SO_4 (0.25 mL) was added drop-wise into the reaction mixture maintaining the temperature (0° C). After 30 min the precipitate was filtered off and dried under reduced pressure to afford **3.45** (0.21 g, 97 %) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.68 (s, 2H), 2.64 (s, 2H), 1.09 (s, 6H). ^{13}C NMR (151 MHz $CDCl_3$) δ = 198.9, 191.8, 145.9, 52.7, 30.5, 28.6. HRMS (ESI) exact mass calculated for $C_8H_{12}NO_3$ ([M + H]$^+$): 170.0812, found: 170.0818.



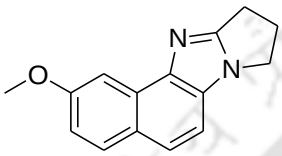
General procedure for the synthesis of fused naphtho-imidazole derivatives (GP-2): Acetic acid (1 equiv.) and secondary amine (2– 4 equiv.) were added to a solution of nitroso compounds (0.2 – 0.57 mmol) in dry toluene (2.5 – 5 mL) and the reaction mixture was refluxed for 10 – 24 h under argon atmosphere. The reaction mixture was allowed to cool to room temperature and saturated $NaHCO_3$ (15 mL) solution was added to the mixture. The mixture was extracted with dichloromethane (3 x 15 mL) and the combined organic layers were dried over sodium sulfate and concentrated under vacuum to obtain brown gummy residue which was further purified by column chromatography to afford analytically pure fused naphtho-imidazole derivatives.

9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.32): According to GP-2: 1-nitroso-2-naphthol (0.10 g, 0.57 mmol), pyrrolidine (0.19 mL, 2.30 mmol), AcOH (33 µL, 0.57 mmol) were reacted for 12 h in dry toluene (5 mL) and column chromatography (neutral alumina; EtOAc : Hexane, 1:1) gave **3.32** as white solid (80 mg, 67%). FTIR (KBr): $\tilde{\nu}$ = 3058,



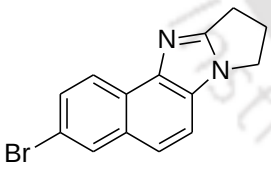
2951, 2917, 1700, 1627, 1535, 1378, 1370, 1302, 1081, 1046, 1015, 1015, 809, 738, 698 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.59 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.45 –7.43 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 4.0 – 3.96 (m, 2H), 3.04 – 3.02 (m, 2H), 2.62 – 2.57 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.8, 143.8, 130.0, 128.5, 128.2, 127.2, 126.3, 124.1, 122.6, 121.7, 110.6, 43.0, 26.2, 23.6. HRMS (ESI) exact mass calculated for $C_{14}H_{13}N_2$ ($[M + H]^+$): 209.1073; Found: 209.1073.

2-methoxy-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.47): According



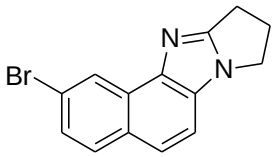
GP-2: **3.33** (55 mg, 0.27 mmol), pyrrolidine (89 µL, 1.08 mmol), AcOH (16 µL, 0.27 mmol) were reacted for 12 h in dry toluene (2.5 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:2) gave **3.47** as white solid (41 mg, 65%). FTIR (KBr): $\tilde{\nu}$ = 2981, 2939, 2903, 2831, 1700, 1628, 1572, 1534, 1476, 1461, 1389, 1376, 1224, 1134, 1037, 826, 717 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.90 (s, 1H), 7.81 – 7.79 (m, 1H), 7.57 – 7.55 (m, 1H), 7.30 – 7.28 (m, 1H), 7.11 – 7.08 (m, 1H), 4.19 – 4.14 (m, 2H), 4.00 (s, 3H), 3.16 – 3.12 (m, 2H), 2.77 – 2.73 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.6, 158.5, 143.2, 130.2, 128.8, 128.4, 125.2, 122.7, 116.8, 108.1, 100.3, 55.7, 43.2, 26.4, 23.8. HRMS (ESI) exact mass calculated for $C_{15}H_{15}N_2O$ ($[M + H]^+$): 239.1179; Found: 239.1179.

3-bromo-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.48): According

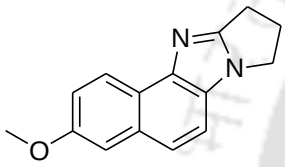


GP-2: **3.34** (65 mg, 0.26 mmol), pyrrolidine (85 µL, 1.04 mmol), AcOH (15 µL, 0.26 mmol) were reacted for 12 h in dry toluene (2.5 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:2) gave **3.48** as white solid (46 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 2961, 2924, 2850, 1629, 1591, 1521, 1464, 1427, 1384, 1083, 879, 797 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.45 (d, *J* = 8.8 Hz, 1H), 8.05 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.52 –7.50 (m, 1H), 7.46 – 7.44 (m, 1H), 4.18 (t, *J* = 7.2 Hz, 2H), 3.14 (t, *J* = 7.6 Hz, 2H), 2.80 – 2.72 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 159.4, 143.9, 131.4, 130.5, 129.6, 128.6, 125.8, 123.7, 121.8, 118.0, 111.8, 43.4, 26.5, 23.8. HRMS (ESI) exact mass calculated for $C_{14}H_{12}BrN_2$ ($[M + H]^+$): 287.0178; Found: 278.0181.

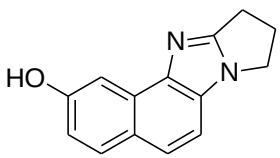
2-bromo-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.49): According to GP-2: **3.35** (50 mg, 0.2 mmol), pyrrolidine (66 µL, 0.8 mmol), AcOH (12 µL, 0.2 mmol) were reacted for 12 h in dry toluene (2.5 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:2) gave **3.49** as white solid (33 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2918, 2857, 1698, 1658, 1629, 1481, 1440, 1384, 1083, 824 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.75 (s, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.52 – 7.51 (m, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 4.22 – 4.19 (m, 2H), 3.16 – 3.14 (m, 2H), 2.8.0 – 2.75 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 159.4, 143.1, 130.2, 129.0, 128.5, 128.4, 127.6, 124.4, 122.6, 120.8, 111.1, 43.4, 26.5, 23.8. HRMS (ESI) exact mass calculated for $C_{14}H_{12}BrN_2$ ($[M + H]^+$): 287.0178; Found: 287.0178.



3-methoxy-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.50): According to GP-2: **3.36** (44 mg, 0.21 mmol), pyrrolidine (48 µL, 0.84 mmol), AcOH (13 µL, 0.21 mmol) were reacted for 12 h in dry toluene (2.5 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:2) gave **3.50** as brown solid (37 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 2961, 2922, 2852, 1640, 1631, 1543, 1383, 1157, 801, 613 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.49 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.26 (m, 2H), 4.21 – 4.19 (m, 2H), 3.94 (s, 3H), 3.17 – 3.14 (m, 2H), 2.80 – 2.77 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.9, 156.7, 144.3, 131.3, 127.3, 123.4, 122.5, 121.8, 118.3, 111.1, 107.6, 55.6, 43.3, 26.5, 23.9. HRMS (ESI) exact mass calculated for $C_{15}H_{15}N_2O$ ($[M + H]^+$): 239.1179; Found: 239.1178.



9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazol-2-ol (3.51): According to to GP-2: 1-nitrosonaphthalene-2,7-diol,[29] (50 mg, 0.26 mmol), pyrrolidine (44 µL, 0.52 mmol), AcOH (15 µL, 0.26 mmol) were reacted for 12 h in dry toluene (2.5 mL) and column chromatography (neutral alumina, EtOAc : DCM, 10:1) gave **3.51** as white solid (32 mg, 54%). FTIR (KBr): $\tilde{\nu}$ = 3437, 2961, 2924, 2854, 1636, 1570, 1460, 1419, 1384, 1259, 1103, 875, 801, 674 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$ + CD_3OD) δ = 7.67 (d, *J* = 9.0 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 1H), 6.95 – 6.93 (m, 1H), 4.14 – 4.09 (m, 2H), 3.02 – 3.0 (m, 2H), 2.69 – 2.67 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$ + CD_3OD) δ = 158.0, 155.7, 141.7, 130.3, 128.3, 128.0, 124.8, 123.2, 116.2, 107.5,

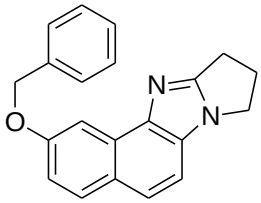


103.4, 43.2, 26.1, 23.4. HRMS (ESI) exact mass calculated for $C_{14}H_{13}N_2O$ ($[M + H]^+$): 225.1022 ; Found: 225.1022.

2-(allyloxy)-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.52): According to GP-2: **3.38** (60 mg, 0.26 mmol), pyrrolidine (86 µL, 1.04 mmol), AcOH (16 µL, 0.26 mmol) were reacted for 12 h in dry toluene (2.5 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:3) gave **3.52** as brown solid (36 mg, 52%). FTIR (KBr): $\tilde{\nu}$ = 2850, 1699, 1635, 1446, 1565, 1377, 1224, 1135, 1202, 1021, 824 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 1.8 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.18 – 6.12 (m, 1H), 5.48 (d, *J* = 18.6 Hz, 1H), 5.31 (d, *J* = 10.8 Hz, 1H), 4.73 (d, *J* = 5.4 Hz, 2H), 4.19 – 4.16 (m, 2H), 3.16 – 3.13 (m, 2H), 2.76 – 2.73 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.6, 157.4, 143.4, 133.5, 130.2, 128.9, 128.4, 125.3, 122.7, 117.8, 117.1, 108.2, 101.4, 69.1, 43.3, 26.5, 23.8. HRMS (ESI) exact mass calculated for $C_{17}H_{17}N_2O$ ($[M + H]^+$): 265.1335; Found: 265.1335.

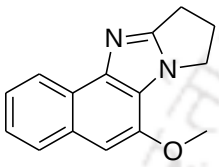
3-(allyloxy)-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.53): According to GP-2: **3.39** (55 mg, 0.24 mmol), pyrrolidine (79 µL, 0.96 mmol), AcOH (14 µL, 0.24 mmol) were reacted for 12 h in dry toluene (2.5 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:3) gave **3.53** as brown solid (42 mg, 65%). FTIR (KBr): $\tilde{\nu}$ = 3121, 2961, 2925, 2851, 1700, 1627, 1645, 1596, 1525, 1367, 1268, 1063, 1087, 869, 796 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.49 (d, *J* = 9.0 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.28 (m, 2H), 6.18 - 6.11 (m, 1H), 5.48 (d, *J* = 17.4 Hz, 1H), 5.32 (d, *J* = 10.2 Hz, 1H), 4.67 (d, *J* = 5.4 Hz, 2H), 4.20 – 4.18 (m, 2H), 3.16 – 3.13 (m, 2H), 2.78 – 2.74 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.9, 155.7, 144.3, 133.7, 131.2, 127.3, 123.4, 122.6, 121.8, 118.6, 117.8, 111.1, 108.9, 69.2, 43.3, 26.5, 23.9. HRMS (ESI) exact mass calculated for $C_{17}H_{17}N_2O$ ($[M + H]^+$): 265.1335; Found: 265.1333.

2-(benzyloxy)-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.54): According to to GP-2: **3.40** (90 mg, 0.32 mmol), pyrrolidine (0.11 mL, 1.28 mmol), AcOH (18 µL, 0.32 mmol) were reacted for 12 h in dry toluene (4 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:4) gave **3.54** as white solid (53 mg,



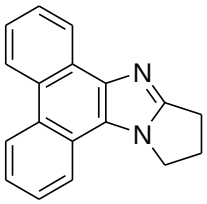
52%). FTIR (KBr): $\tilde{\nu}$ = 3016, 2922, 3027, 2849, 1491, 1630, 1567, 1449, 1221, 1027, 932, 835, 733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 2.4 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.36 – 7.31 (m, 2H), 7.20 – 7.18 (m, 1H), 5.27 (s, 2H), 4.20 (t, *J* = 6.8 Hz, 2H), 3.18 – 3.15 (m, 2H), 2.81 – 2.73 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.6, 157.7, 143.4, 137.3, 130.3, 128.9, 128.7, 128.5, 128.1, 127.9, 125.4, 122.7, 117.2, 108.2, 101.5, 70.3, 43.3, 26.5, 23.9. HRMS (ESI) exact mass calculated for $C_{21}H_{19}N_2O$ ($[M + H]^+$): 315.1492; Found: 315.1494.

6-methoxy-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.55): According to to GP-2: **3.41** (65 mg, 0.32 mmol), pyrrolidine (0.11 mL, 1.28 mmol), AcOH (18 µL, 0.32 mmol) were reacted for 12 h in dry toluene (4 mL) under argon atmosphere and column chromatography (neutral alumina, EtOAc : Hexane, 1:2) gave **3.55** as white solid (36 mg, 47%).

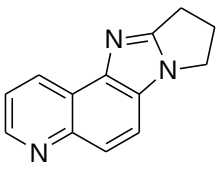


FTIR (KBr): $\tilde{\nu}$ = 2961, 2925, 2853, 1699, 1651, 1632, 1457, 1141, 1274, 1263, 1096, 785, 755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.39 (m, 2H), 6.88 (s, 1H), 4.40 – 4.37 (m, 2H), 4.02 (s, 3H), 3.14 – 3.10 (m, 2H), 2.76 – 2.71 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.8, 147.0, 145.3, 131.3, 127.3, 124.8, 124.1, 123.6, 121.7, 121.5, 99.7, 55.6, 45.6, 26.8, 23.6. HRMS (ESI) exact mass calculated for $C_{15}H_{15}N_2O$ ($[M + H]^+$): 239.1179; Found: 239.1180.

11,12-dihydro-10*H*-phenanthro[9,10-*d*]pyrrolo[1,2-*a*]imidazole (3.56): According to to GP-2: **3.42** (52 mg, 0.23 mmol), pyrrolidine (77 µL, 0.93 mmol), AcOH (13 µL, 0.23 mmol) were reacted for 12 h in dry toluene (3 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:4) gave **3.56** as orange yellow solid (38 mg, 64%). FTIR (KBr): $\tilde{\nu}$ = 2965, 2922, 2852, 1660, 1631, 1453, 1384, 1103, 874, 802 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.76 (d, *J* = 7.8 Hz, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 8.63 (d, *J* = 7.8 Hz, 1H), 8.11 – 8.10 (m, 1H), 7.70 – 7.67 (m, 1H), 7.64 – 7.57 (m, 3H), 4.60 – 4.58 (m, 2H), 3.19 – 3.67 (m, 2H), 2.88 – 2.83 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.4, 142.0, 128.2, 128.0, 127.9, 127.4, 126.8, 125.2, 124.9, 124.7, 124.3, 123.4, 123.2, 122.4, 120.5, 46.1, 26.9, 23.4. HRMS (ESI) exact mass calculated for $C_{18}H_{15}N_2$ ($[M + H]^+$): 259.1230; Found: 259.1234.

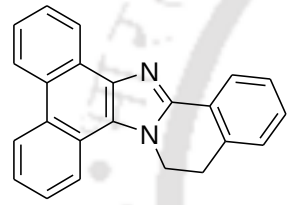


9,10-dihydro-8*H*-pyrrolo[1,2:1,2]imidazo[4,5-*f*]quinolone (3.57): According to GP-2:



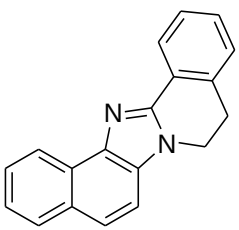
3.43 (50 mg, 0.28 mmol), pyrrolidine (48 µL, 0.57 mmol), AcOH (16 µL, 0.28 mmol) were reacted for 10 h in dry toluene (2.5 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:2) gave **3.57** as brown solid (36 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 2961, 2923, 2853, 1729, 1640, 1628, 1463, 1451, 1418, 1384, 871, 810 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.90 – 8.89 (m, 2H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.52 – 7.49 (m, 1H), 4.27 – 4.25 (m, 2H), 3.20 – 3.18 (m, 2H), 2.83 – 2.79 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 160.1, 148.4, 145.8, 143.3, 130.3, 128.5, 124.1, 122.6, 121.3, 113.9, 43.5, 26.5, 23.9. HRMS (ESI) exact mass calculated for $C_{13}H_{12}N_3$ ($[M + H]^+$): 210.1026; Found: 210.1028.

5,6-dihydrophenanthro[9,10:4,5]imidazo[2,1-*a*]isoquinoline (3.58): According to to GP-2:



3.42 (0.15 g, 0.67 mmol), tetrahydroisiquinoline (0.17 mL, 1.34 mmol), AcOH (39 µL, 0.26 mmol) were reacted for 9.5 h in dry toluene (7.5 mL) and column chromatography (SiO_2, EtOAc : Hexane, 1:15) gave **3.58** as white solid (0.10 g, 48 %). FTIR (KBr): $\tilde{\nu}$ = 2960, 2924, 2857, 1636, 1458, 1384, 1160, 1106, 799, 721 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.80 – 8.79 (m, 2H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.36 – 8.32 (m, 2H), 7.70 – 7.68 (m, 1H), 7.64 – 7.60 (m, 3H), 7.43 – 7.40 (m, 1H), 7.38 – 7.36 (m, 1H), 7.32 – 7.30 (m, 1H), 4.92 – 4.89 (m, 2H), 3.35 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 147.2, 138.4, 132.7, 129.5, 129.3, 128.1, 127.9, 127.6, 127.5, 127.4, 127.3, 126.7, 126.1, 125.6, 125.5, 124.9, 124.6, 123.5, 123.2, 122.9, 121.1, 43.8, 28.7. HRMS (ESI) exact mass calculated for $C_{14}H_{13}N_2O$ ($[M + H]^+$): 321.1386 ; Found: 321.1389.

8,9-dihydronaphtho[1',2':4,5]imidazo[2,1-*a*]isoquinoline (3.59): According to GP-2: 1-



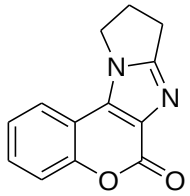
nitroso 2-naphthol (70 mg, 0.4 mmol), tetrahydroisoquinoline (0.1 mL, 0.8 mmol), AcOH (21 µL, 0.4 mmol) were reacted for 10 h in dry toluene (3 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 1:4) gave **3.59** as white solid (45 mg, 41%). FTIR (KBr): $\tilde{\nu}$ = 2921, 2953, 2854, 1652, 1636, 1558, 1454, 1383, 1106, 748 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.75 (d, *J* = 7.8 Hz, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.33 – 7.32 (m, 1H), 4.43 (t, *J* = 6.6, 2H), 3.34 – 3.32

(m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 147.5, 139.5, 133.8, 130.9, 130.7, 129.9, 128.7, 128.2, 128.0, 127.2, 127.1, 126.7, 125.6, 124.8, 124.1, 122.3, 109.9, 41.0, 28.6. HRMS (ESI) exact mass calculated for $C_{19}H_{15}N_2$ ([M + H]$^+$): 271.1230; Found: 271.1226.

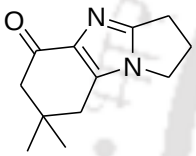
8*H*-naphtho[1',2':4,5]imidazo[2,1-*a*]isoindole (3.60): According to GP-2: 1-nitroso 2-naphthol (60 mg, 0.34 mmol), isoindoline (79 µL, 0.69 mmol), AcOH (16 µL, 0.34 mmol) were reacted for 10 h in dry toluene (3 mL) under argon atmosphere and column chromatography (neutral alumina, EtOAc : Hexane, 1:10) gave **3.60** as brown solid (28 mg, 32%). FTIR (KBr): $\tilde{\nu}$ = 2965, 2923, 2852, 1629, 1452, 1384, 1260, 1101, 874, 801 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.73 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.59 – 7.57 (m, 2H), 7.55 – 7.52 (m, 1H), 7.51 – 7.45 (m, 2H), 5.12 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.7, 143.5, 143.1, 130.4, 129.9, 129.2, 129.04, 129.0, 128.8, 127.8, 126.8, 124.7, 124.1, 124.0, 122.2, 122.0, 110.4, 47.7. HRMS (ESI) exact mass calculated for $C_{18}H_{13}N_2$ ([M + H]$^+$): 257.1073; Found: 257.1081.

(9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazol-8-yl)methanol (3.61): According to to GP-2: 1- nitroso-2-naphthol (60 mg, 0.34 mmol), (*R*)-prolinol (0.13 mL, 1.38 mmol), AcOH (20 µL, 0.34 mmol) were reacted for 10 h in dry toluene (3 mL) and column chromatography (neutral alumina, EtOAc : DCM 10:1) gave **3.61** as brown solid (25 mg, 30%). $[\alpha]_D^{25}$ = -0.05 (c = 0.125). FTIR (KBr): $\tilde{\nu}$ = 3447, 2961, 2923, 2852, 1660, 1637, 1566, 1417, 1405, 1384, 1263, 1161, 1104, 1026, 752, 616 cm^{-1}. ^{1}H NMR (600 MHz, CD_3OD) δ = 8.43 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.56 -7.54 (m, 1H), 7.45 - 7.42 (m, 1H), 4.74 – 4.72 (m, 1H), 4.07 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.83 (dd, *J* = 11.8, 5.5 Hz, 1H), 3.23 - 3.18 (m, 1H), 3.09 – 3.05 (m, 1H), 2.93 – 2.86 (m, 1H), 2.60 – 2.57 (m, 1H). ^{13}C NMR (151 MHz, CD_3OD) δ = 160.9, 144.2, 132.0, 129.9, 129.8, 128.2, 127.4, 125.5, 124.2, 122.6, 113.3, 64.9, 60.5, 30.5, 24.4. HRMS (ESI) exact mass calculated for $C_{15}H_{15}N_2O$ ([M + H]$^+$): 239.1179; Found: 239.1172. The enantiomeric excess (>99 %) was determined by HPLC column: phenomenex lux 5u cellulose -1; solvent: 2-propanol : hexane (1:3); wavelength of UV: 291 nm; flow: 1mL /min; major enantiomer t_r = 16.5 min, minor enantiomer t_r = 13.5 min.

9,10-dihydro-6*H*,8*H*-chromeno[3,4-*d*]pyrrolo[1,2-*a*]imidazol-6-one (3.62): According to to GP-2: **3.44** (80 mg, 0.45 mmol), pyrrolidine (74 µL, 0.9 mmol), H_3PO_4 (23 µL, 0.45 mmol) were reacted for 12 h in dry toluene (4 mL) and column chromatography (neutral alumina, EtOAc) gave **3.62** as white solid (32 mg, 31%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2924, 2859, 1747, 1724, 1620, 1592, 1537, 1499, 1446, 1384, 1261, 1099, 1033, 800, 762, 702 cm $^{-1}$. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 7.2 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.33 – 7.30 (m, 1H), 4.42 (t, *J* = 7.2 Hz, 2H), 3.08 – 3.05 (m, 2H), 2.88 – 2.83 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 160.0, 157.1, 152.1, 134.2, 130.6, 129.6, 124.4, 120.6, 118.2, 113.3, 45.3, 26.9, 22.9. HRMS (ESI) exact mass calculated for $C_{13}H_{11}N_2O_2$ ($[M + H]^+$): 227.0810; Found: 227.0811.



7,7-dimethyl-1,2,3,6,7,8-hexahydro-5*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-5-one (3.63): According to to GP-2: C-Nitroso compound **3.45** (45 mg, 0.26 mmol), pyrrolidine (87 µL, 1.06 mmol), AcOH (15 µL, 0.26 mmol) were reacted for 12 h in dry toluene (2.5 mL) and column chromatography (neutral alumina, EtOAc : Hexane, 2:1) gave **3.63** as white solid (27 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 2953, 2922, 2854, 1659, 1551, 1448, 1384, 1260, 1104, 764, 750 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.88 (t, *J* = 7.0 Hz, 2H), 2.89 – 2.86 (m, 2H), 2.66 – 2.60 (m, 4H), 2.38 (s, 2H), 1.13 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 190.8, 156.4, 139.8, 139.7, 52.3, 43.0, 36.0, 35.5, 28.9 (2C), 26.4, 22.9. HRMS (ESI) exact mass calculated for $C_{12}H_{17}N_2O$ ($[M + H]^+$): 205.1230; Found: 205.1230.

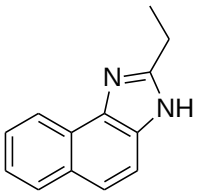


General procedure for the preparation of *N*-H and *N*-Alkyl naphthoimidazole derivatives (primary amine) GP-3: Acetic acid (1 equiv.) and primary amine (4 equiv.) were added to solution of 1-nitroso 2-naphthol (0.34 mmol) in dry toluene (5 mL) and the reaction mixture was refluxed for 14 h under argon atmosphere. The reaction mixture was allowed to cool to room temperature and the solvent was removed under vacuum to give brown gummy residue which was further purified by column chromatography to afford analytically pure *N*-H and *N*-Alkyl naphtho-imidazole derivatives.

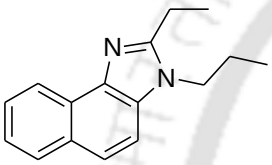
2-ethyl-3*H*-naphtho[2,1-*d*]imidazole (3.64a) and **2-ethyl-3-propyl-3*H*-naphtho[2,1-*d*]imidazole (3.64b):** According to GP-3: 2- nitroso-1-napthol (60 mg, 0.34 mmol), *n*-propylamine (0.11 mL, 1.38 mmol), AcOH (20 µL, 0.34 mmol) were reacted for 14 h in dry

toluene (5 mL) and column chromatography (SiO_2; EtOAc : Hexane, 1:1) gave **3.64a** as yellow gum (26 mg, 38%) and column chromatography (EtOAc : Hexane, 1:3) gave **3.64b** as yellow gum (39 mg, 49 %).

(3.64a): FTIR (KBr): $\tilde{\nu}$ = 2962, 2928, 2875, 1636, 1547, 1562, 1413, 1384, 1260, 1094, 1022, 804, 698, 565 cm $^{-1}$. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.40 – 8.38 (m, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.52 – 7.49 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 3.08 – 3.04 (m, 2H), 1.44 (t, *J* = 7.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.8, 134.8, 134.1, 130.5, 128.9, 126.4, 124.4, 124.3, 123.4, 121.5, 115.2, 22.9, 13.1. HRMS (ESI) exact mass calculated for $C_{13}H_{13}N_2$ ($[M + H]^+$): 197.1073; Found: 197.1070.

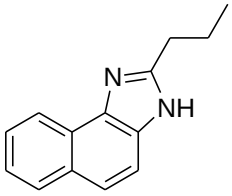


(3.64b): FTIR (KBr): $\tilde{\nu}$ = 2922, 2850, 1633, 1430, 1382, 1163, 1112, 1059, 615 cm $^{-1}$. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.47 – 7.44 (m, 2H), 4.19 – 4.16 (m, 2H), 3.02 (q, *J* = 7.8 Hz, 2H), 1.92 – 1.88 (m, 2H), 1.51 (t, *J* = 7.8 Hz, 3H), 1.0 (t, *J* = 7.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.0, 134.8, 131.1, 130.4, 128.5, 126.9, 126.5, 124.5, 123.2, 122.1, 110.4, 45.7, 23.9, 21.1, 13.1, 11.6. HRMS (ESI) exact mass calculated for $C_{16}H_{19}N_2$ ($[M + H]^+$): 239.1543; Found: 239.1547.

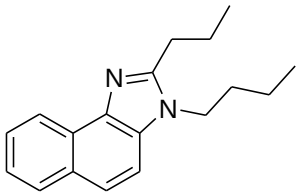


2-propyl-3*H*-naphtho[2,1-*d*]imidazole (3.65a) and **3-butyl-2-propyl-3*H*-naphtho[2,1-*d*]imidazole (3.65b):** According to GP-3: 1-nitroso 2-naphthol (60 mg, 0.34 mmol), *n*-butylamine (0.14 mL, 1.38 mmol), AcOH (20 µL, 0.34 mmol) were reacted for 14 h in dry toluene (5 mL) and column chromatography (SiO_2; EtOAc : Hexane, 1:5) gave **3.65a** as yellow gum (30 mg, 42 %) and column chromatography (SiO_2; EtOAc : Hexane, 1:10) gave **3.65b** (49 mg, 48%) as yellow gum.

(3.65a): FTIR (KBr): $\tilde{\nu}$ = 2958, 2924, 2853, 1655, 1613, 1456, 1384, 1430, 1105, 805, 748 cm $^{-1}$. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.41– 8.40 (m, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.49 – 7.46 (m, 1H), 7.44 – 7.42 (m, 1H), 2.98 (t, *J* = 7.8 Hz, 2H), 1.89 – 1.85 (m, 2H), 0.93 – 0.92 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 153.5, 134.5, 134.2, 130.5, 128.9, 126.3, 124.5, 124.4, 123.4, 121.5, 115.0, 31.4, 22.2, 14.01. HRMS (ESI) exact mass calculated for $C_{14}H_{15}N_2$ ($[M + H]^+$): 211.1230; Found 211.1230.



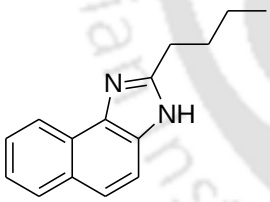
(3.65b): FTIR (KBr): $\tilde{\nu}$ = 3059, 2961, 2875, 1687, 1636, 1595, 1377, 1096, 801, 746 cm $^{-1}$.



^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.64 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.60 – 7.58 (m,1H), 7.46 – 7.44 (m, 2H), 4.2 – 4.17 (m, 2H), 2.95 – 2.93 (m, 2H), 1.97 – 1.93 (m, 2H), 1.83 – 1.81 (m, 2H), 1.45 – 1.38 (m, 2H), 1.10 – 1.08 (m,, 3H), 0.98 – 0.96 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.9, 138.1, 131.1, 130.3, 128.4, 127.0, 126.4, 124.3, 122.9, 122.0, 110.5, 43.9, 32.7, 29.8, 22.3, 20.4, 14.3, 13.9. HRMS (ESI) exact mass calculated for $C_{18}H_{23}N_2$ ($[M + H]^+$): 267.1856; Found 267.1853.

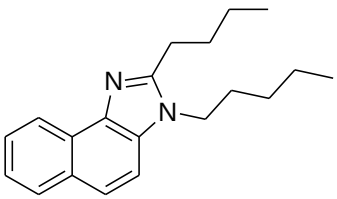
2-butyl-3*H*-naphtho[2,1-*d*]imidazole (3.66a) and **2-butyl-3-pentyl-3*H*-naphtho[2,1-*d*]imidazole (3.66b):** According to GP-3: 1-nitroso 2 naphthol (60 mg, 0.34 mmol), *n*-pentylamine (0.16 mL, 1.38 mmol), AcOH (20 µL, 0.34 mmol) were reacted for 14 h in dry toluene (5 mL) and column chromatography (SiO_2; EtOAc : Hexane, 1:5) gave **3.66a** (28 mg, 36 %) as yellow gum and column chromatography (SiO_2; EtOAc : Hexane, 1:5) and **3.66b** (42 mg, 42%) as yellow gum.

(3.66a): FTIR (KBr): $\tilde{\nu}$ = 2955, 2924, 2853, 1640, 1618, 1384, 1108, 1054, 1032, 1016, 678 cm $^{-1}$.



^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.39 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.52 – 7.50 (m, 1H), 7.46 – 7.43 (m, 1H), 3.01 (t, *J* = 7.8 Hz, 2H), 1.84 (p, *J* = 7.8 Hz, 2H), 1.39 – 1.36 (m, 2H), 0.85 (t, *J* = 7.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 153.5, 134.4, 130.4, 128.9, 126.3, 124.4, 123.3, 121.4, 114.9, 31.0, 29.3, 22.7, 13.9, (2C overlap in aromatic region). HRMS (ESI) exact mass calculated for $C_{15}H_{17}N_2$ ($[M + H]^+$): 225.1386; Found 225.1388.

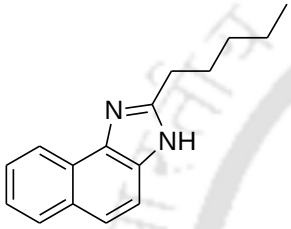
(3.66b): FTIR (KBr): $\tilde{\nu}$ = 2962, 2924, 2853, 1631, 1458, 1384, 1160, 1105, 874, 801 cm $^{-1}$.



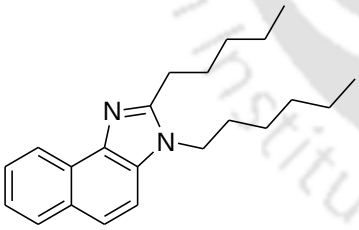
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.63 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.47 – 7.43 (m, 2H), 4.20 – 4.17 (m, 2H), 2.98 – 2.94 (m, 2H), 1.91 – 1.83 (m, 4H), 1.54 – 1.48 (m, 2H), 1.38 – 1.36 (m, 4H), 1.02 – 0.98 (m, 3H), 0.92 – 0.89 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 153.1, 138.1, 131.0, 130.2, 128.5, 126.9, 126.4, 124.3, 122.9, 122.0, 110.5, 44.1, 31.1,

30.3, 29.2, 27.7, 23.0, 22.6, 14.12, 14.10. HRMS (ESI) exact mass calculated for $C_{20}H_{27}N_2$ ($[M + H]^+$): 295.2169; Found 295.2170.

2-pentyl-3*H*-naphtho[2,1-*d*]imidazole(3.67a) and **3-hexyl-2-pentyl-3*H*-naphtho[2,1-*d*]imidazole (3.67b):** According to GP-3: 1-nitroso 2 naphthol (60 mg, 0.34 mmol), *n*-hexylamine (0.18 mL, 1.38 mmol), AcOH (20 µL, 0.34 mmol) were reacted for 14 h in dry toluene (5 mL) and column chromatography (SiO_2; EtOAc : Hexane, 1:5) gave **3.67a** (27 mg, 33 %) as yellow gum and column chromatography **3.67b** (37 mg, 34%) (SiO_2; EtOAc : hexane, 1:20) as yellow gum.



(3.67a): FTIR (KBr): $\tilde{\nu}$ = 2958, 2925, 2855, 1628, 1454, 1384, 1152, 1105, 805 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.40 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.52 – 7.49 (m, 1H), 7.46 – 7.43 (m, 1H), 3.03 (t, *J* = 7.8 Hz, 2H), 1.88 – 1.83 (m, 2H), 1.32 (dt, *J* = 15.0, 7.2 Hz, 2H), 1.28 – 1.21 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 153.6, 134.1, 130.4, 128.8, 126.3, 124.3, 123.3, 121.5, 114.9, 31.7, 29.6, 28.7, 22.5, 14.1, (2C overlap in aromatic region). HRMS (ESI) exact mass calculated for $C_{16}H_{19}N_2$ ($[M + H]^+$): 239.1543; Found 239.1546.

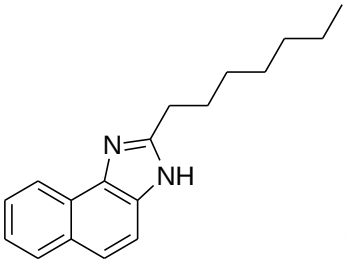


(3.67b):FTIR (KBr): $\tilde{\nu}$ = 3059, 2955, 2926, 2856, 1630, 1530, 1500, 1465, 1383, 1100, 799 cm^{-1}. ^1H NMR (600 MHz $CDCl_3$) δ = 8.63 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.46 – 7.43 (m, 2H), 4.19 – 4.17 (m, 2H), 2.97 – 2.94 (m, 2H), 1.93 – 1.88 (m, 2H), 1.86 – 1.81 (m, 2H), 1.48 – 1.45 (m, 2H), 1.42 – 1.36 (m, 4H), 1.33 – 1.29 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 153.1, 138.0, 131.0, 130.2, 128.4, 126.9, 126.4, 124.3, 122.9, 122.0, 110.5, 44.2, 32.0, 31.6, 30.6, 28.7, 27.9, 26.8, 22.71, 22.69, 14.23, 14.18. HRMS (ESI) exact mass calculated for $C_{22}H_{31}N_2$ ($[M + H]^+$): 323.2482; Found 323.2484.

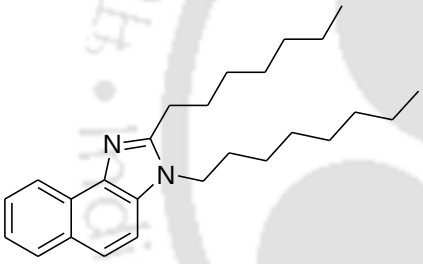
2-heptyl-3*H*-naphtho[2,1-*d*]imidazole (**3.68a**) and **2-heptyl-3-octyl-3*H*-naphtho[2,1-*d*]imidazole (3.68b)**: According to GP-3: 1-nitroso 2 naphthol (60 mg, 0.34 mmol), *n*-octylamine (0.23 mL, 1.38 mmol), AcOH (20 µL, 0.34 mmol) were reacted for 14 h in dry toluene (5 mL) and column chromatography (SiO_2; EtOAc : Hexane, 1:5) gave **3.68a** (29

mg, 32 %) as yellow oil and **3.68b** (41 mg, 32%) (SiO_2; EtOAc : hexane, 1:20) as yellow oil .

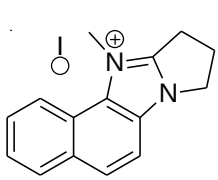
(**3.68a):** FTIR (KBr): $\tilde{\nu}$ = 3052, 2959, 2924, 2853, 1634, 1544, 1457, 1384, 1096, 806, 746 cm $^{-1}$. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.40 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.50 – 7.48 (m, 1H), 7.44 – 7.42 (m, 1H), 2.98 (t, *J* = 8.4 Hz, 2H), 1.85 – 1.80 (m, 2H), 1.29 – 1.25 (m, 2H), 1.17 – 1.11 (m, 6H), 0.78 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 153.3, 133.9, 130.2, 128.6, 126.1, 124.2, 123.2, 121.2, 114.7, 31.6, 29.3, 28.9, 28.7, 22.5, 14.0, (2C overlap in aromatic region). HRMS (ESI) exact mass calculated for $C_{18}H_{23}N_2$ ($[M + H]^+$): 267.1856; Found 267.1855.



(3.68b): FTIR (KBr): $\tilde{\nu}$ = 2958, 2923, 2853, 1697, 1629, 1464, 1383, 1104, 798, 743 cm $^{-1}$. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.63 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.46 – 7.43 (m, 2H), 4.20 – 4.17 (m, 2H), 2.96 – 2.94 (m, 2H), 1.93 – 1.89 (m, 2H), 1.86 – 1.81 (m, 2H), 1.50 – 1.45 (m, 2H), 1.39 – 1.37 (m, 4H), 1.33 – 1.25 (m, 12H), 0.9 – 0.86 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 153.1, 138.1, 131.1, 130.2, 128.4, 126.9, 126.3, 124.3, 122.9, 122.0, 110.5, 44.1, 31.9, 30.6, 29.9, 29.4, 29.3, 29.29, 29.0, 28.0, 27.2, 22.8, 22.8, 14.3, 14.3 (1C overlap in the aliphatic region). HRMS (ESI) exact mass calculated for $C_{26}H_{39}N_2$ ($[M + H]^+$): 379.3108; Found 379.3104.



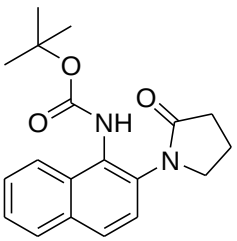
11-methyl-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazol-11-ium iodide



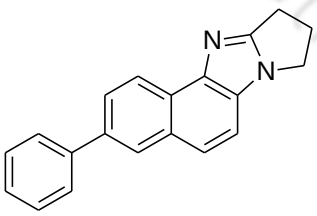
(3.86): Compound **3.32** (62 mg, 0.3 mmol) was dissolved in methyl iodide (0.46 mL, 1.2 mmol) and the solution was stirred at room temperature for 12 hours. Upon addition of diethyl ether (2.5 mL) into the reaction mixture white precipitate was obtained. The precipitate was filtered and washed with ethyl acetate (10 mL). The ion **3.86** was obtained as white solid (61 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 2978, 2911, 1700, 1588, 1564, 1534, 1457, 1441, 1393, 1365, 1127, 812, 788 cm^{-1}. ^{1}H NMR (500 MHz, DMSO) δ = 8.63 – 8.61 (m, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 11.0 Hz, 1H), 7.84 – 7.81 (m,

1H), 7.75 – 7.72 (m, 1H), 4.53 (t, *J* = 7 Hz, 2H), 4.37 (s, 3H), 3.49 – 3.46 (m, 2H), 2.86 – 2.80 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 157.9, 131.3, 130.2, 129.8, 128.4, 127.6, 126.54, 126.50, 121.7, 120.9, 112.2, 47.1, 36.8, 25.1, 23.9. HRMS (ESI) exact mass calculated for $C_{15}H_{15}N_2$ ([M + H]$^+$): 223.1230; Found: 223.1231.

***tert*-butyl 2-(2-oxopyrrolidin-1-yl)naphthalen-1-ylcarbamate (3.87):** Di-*tert*-butyl dicarbonate [$(BOC)_2O$] (0.17 g, 0.77 mmol) was added to a solution of imidazole **3.32** (40 mg, 0.19 mmol) in dichloromethane (1.8 mL) and the reaction mixture was stirred at room temperature. After 72 h the reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (neutral alumina, EtOAc : Hexane, 1:5) to obtain **3.87** as a white solid (43 mg, 69%). FTIR (KBr): $\tilde{\nu}$ = 3351, 3059, 3002, 2972, 2928, 2889, 1720, 1677, 1594, 1485, 1457, 1317, 1301, 1239, 1165, 1018, 1046, 1018, 913, 875, 640 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 8.5 Hz, 1H), 7.81 – 7.77 (m, 2H), 7.56 – 7.53 (m, 1H), 7.50 – 7.47 (m, 1H), 7.31 (d, *J* = 9.0 Hz, 1H), 6.94 (bs, 1H), 3.96 – 3.93 (m, 2H), 2.63 (t, *J* = 8.0 Hz, 2H), 2.26 – 2.20 (m, 2H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 174.4, 154.6, 133.2, 132.2, 132.0, 129.0, 128.3, 128.0, 127.0, 126.4, 124.3, 122.0, 80.1, 50.6, 31.8, 28.5, 19.5. HRMS (ESI) exact mass calculated for $C_{19}H_{23}N_2O_3$ ([M + H]$^+$): 327.1703; Found: 327.1705.

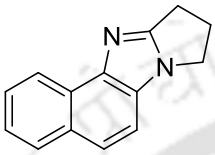
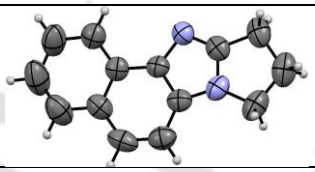


3-phenyl-9,10-dihydro-8*H*-naphtho[1,2-*d*]pyrrolo[1,2-*a*]imidazole (3.88): Phenylboronic acid (32 mg, 0.26 mmol), $Ba(OH)_2$, $8H_2O$ (0.10 g, 0.31 mmol), $Pd(PPh_3)_4$ (8 mg, 3.3 mol%), 1,4-dioxane (1.4 mL), H_2O (0.5 mL), and **3.48** (50 mg, 0.17 mmol) were refluxed for 48 h under argon. After completion of reaction 1,4-dioxane was removed under reduced pressure. The resulting mass was diluted with CH_2Cl_2 (30 mL), amd the mixture was washed with 1 M HCl (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulfate and concentrated under vacuum to give crude product which was further purified by column chromatography (SiO_2; EtOAc : Hexane, 1:1) to afford pure **3.88 (**45 mg, 90%). FTIR (KBr): $\tilde{\nu}$ = 2923, 2892, 1700, 1587, 1532, 1423, 1372, 1359, 1299, 1033, 888, 753, 710, 695 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 8.4 Hz, 1H), 8.12 (s, 1H), 7.88 (d, *J* = 6.6 Hz, 1H), 7.75

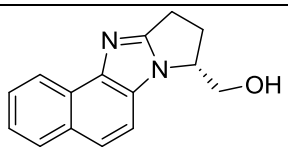
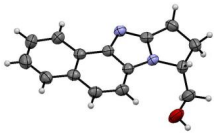


(d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.45 – 7.42 (m, 1H), 7.37 – 7.34 (m, 1H), 4.16 – 4.12 (m, 2H), 3.13 – 3.11 (m, 2H), 2.73 – 2.70 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 159.8, 143.8, 141.6, 137.0, 130.4, 129.0, 128.5, 127.5, 127.2, 126.6, 126.4, 126.0, 123.1, 122.4, 111.1, 43.3, 26.4, 23.8. HRMS (ESI) exact mass calculated for $C_{20}H_{17}N_2$ ($[M + H]^+$): 285.1386; Found: 285.1381.

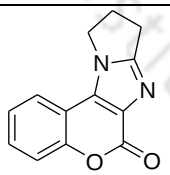
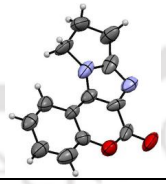
Crystal of **3.32 (**CCDC 1536912):

	
Empirical formula	$C_{14}H_{12}N_2$, H_2O
Formula weight	226.27
Crystal habit, colour	Needle, colorless
Crystal size, mm^3	0.28 X 0.22 X 0.19
Temperature, *T*	298(2)
Wavelength, λ(Å)	0.71073
Crystal system	trigonal
Space group	*R -3 :H*
Unit cell dimensions	*a* = 28.764 (4)Å *b* = 28.764 (4)Å *c* = 7.4790 (11)Å α = 90°, β = 90°, γ = 120°,
Volume, *V*($Å^3$)	5358.9(17)
Z	18
Calculated density, $Mg·m^{-3}$	1.262
Absorption coefficient, μ(mm^{-1})	0.081
F(000)	2160.0
θ range for data collection	1.416° to 25.250°
Limiting indices	$-30 \le h \le 34$, $-34 \le k \le 32$, $-8 \le l \le 8$
Reflection collected / unique	13057/ 699 [*R*(int) = 0.1300]
Completeness to θ	99.7% (θ = 25.242°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)
Data / restraints / parameters	699 / 0 / 162
Goodness–of–fit on F^2	1.084
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0585, *wR*2 = 0.0717
R indices (all data)	*R*1 = 0.2253, *wR*2 = 0.0929
Largest diff. peak and hole	0.141 and –0.193e·$Å^{-3}$

Crystal of **3.61 (**CCDC 1536910):

	
Empirical formula	$C_{15}\ H_{14}\ N_2\ O$
Formula weight	238.28
Crystal habit, colour	needle / colorless
Crystal size, mm^3	0.42 X 0.22 X 0.13
Temperature, *T*	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*P2(1)*
Unit cell dimensions	*a* = 7.8696(4) Å *b* = 7.7941(4) Å *c* = 19.1879(9) Å $\alpha = 90.00°$, $\gamma = 90.00°$, $\beta = 97.029(3)°$
Volume, *V*($Å^3$)	1168.07(10)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.355
Absorption coefficient, $\mu(mm^{-1})$	0.087
F(000)	504
θ range for data collection	2.1° to 25.0°
Limiting indices	$-9 \le h \le 9, -9 \le k \le 9, -22 \le l \le 22$
Reflection collected / unique	16335/ 3585 [*R*(int) = 0.0293]
Completeness to θ	99.5% (θ = 25.00°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	3585 / 0 / 327
Goodness–of–fit on F^2	0.911
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0353, *wR*2 = 0.1167
R indices (all data)	*R*1 = 0.0412, *wR*2 = 0.1791
Largest diff. peak and hole	0.151and –0. 0.170e·$Å^{-3}$

Crystal of **3.62 (**CCDC 1536911):

	
Empirical formula	$C_{13}\ H_{12}\ N_2\ O_3$
Formula weight	244.25
Crystal habit, colour	needle / colorless
Crystal size, mm^3	0.4 X 0.2 X 0.1
Temperature, *T*	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*' P 1 21/c 1 '*
Unit cell dimensions	*a* = 9.894(4) Å *b* = 16.029(7) Å *c* = 7.065(3) Å $\alpha = 90.00°$, $\gamma = 90.00°$, $\beta = 92.05(4)°$
Volume, *V*($Å^3$)	1119.8(8)
Z	4

Calculated density, $Mg \cdot m^{-3}$	1.449
Absorption coefficient, $\mu(mm^{-1})$	0.105
$F(000)$	512
θ range for data collection	3.15° to 24.50°
Limiting indices	$-11 \le h \le 9, -18 \le k \le 6, -8 \le l \le 7$
Reflection collected / unique	3653 / 567 [R(int) = 0.0867]
Completeness to θ	99.8% (θ = 24.50 °)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	567 / 0 / 166
Goodness–of–fit on F^2	1.283
Final R indices [I>2sigma(I)]	$R1$ = 0.1270, $wR2$ = 0.2331
R indices (all data)	$R1$ = 0.2688, $wR2$ = 0.3011
Largest diff. peak and hole	0.388 and -0.426 $\cdot Å^{-3}$

3.13 References:

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Chapter 4

Selective *N*-terminal proline modification of peptides via aminooxazole synthesis and application in cell imaging

4.1 Introduction:

Functionalized oxazoles are key structural motifs of in various biologically active molecules with a wide range of biological activities.[1] In particular, 2-aminooxazoles is one of the most promising pharmacologically interesting class of heterocycles.[2] 2-aminooxazole skeleton has emerged as a basic structural motif which is found in several biologically important molecules and targeted drugs such as nAChR antagonist,2 MK-4305 (used in clinical trial against insomnia),[3] PPAR antagonist (**Figure 1**).[4] Moreover, this moiety has high activity as partial antagonists for 5-HT receptors (5-HT = 5-hydroxy-tryptamine, serotonin) for the treatment of Alzheimer's disease and schizophrenia.[5]

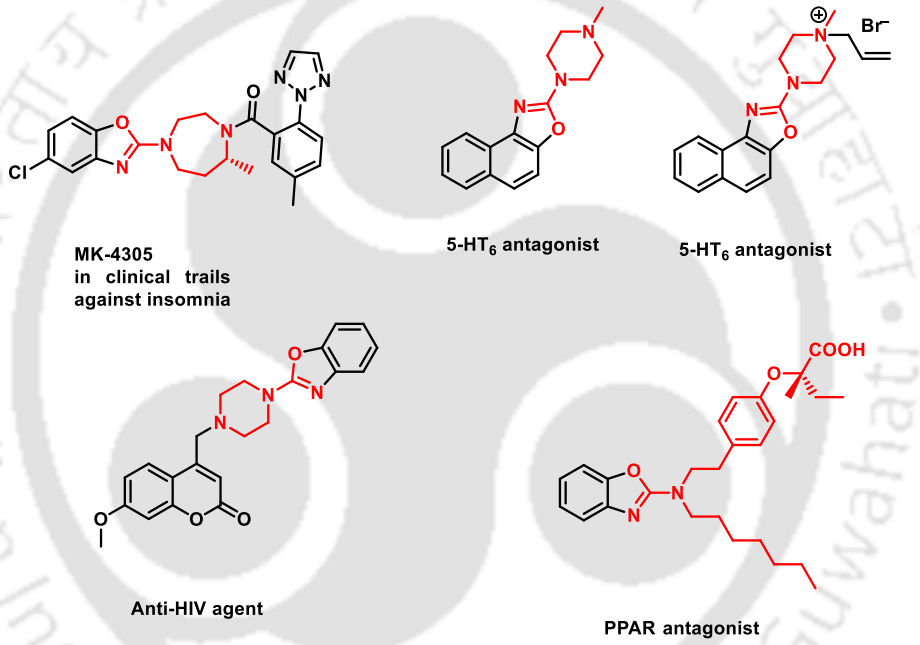


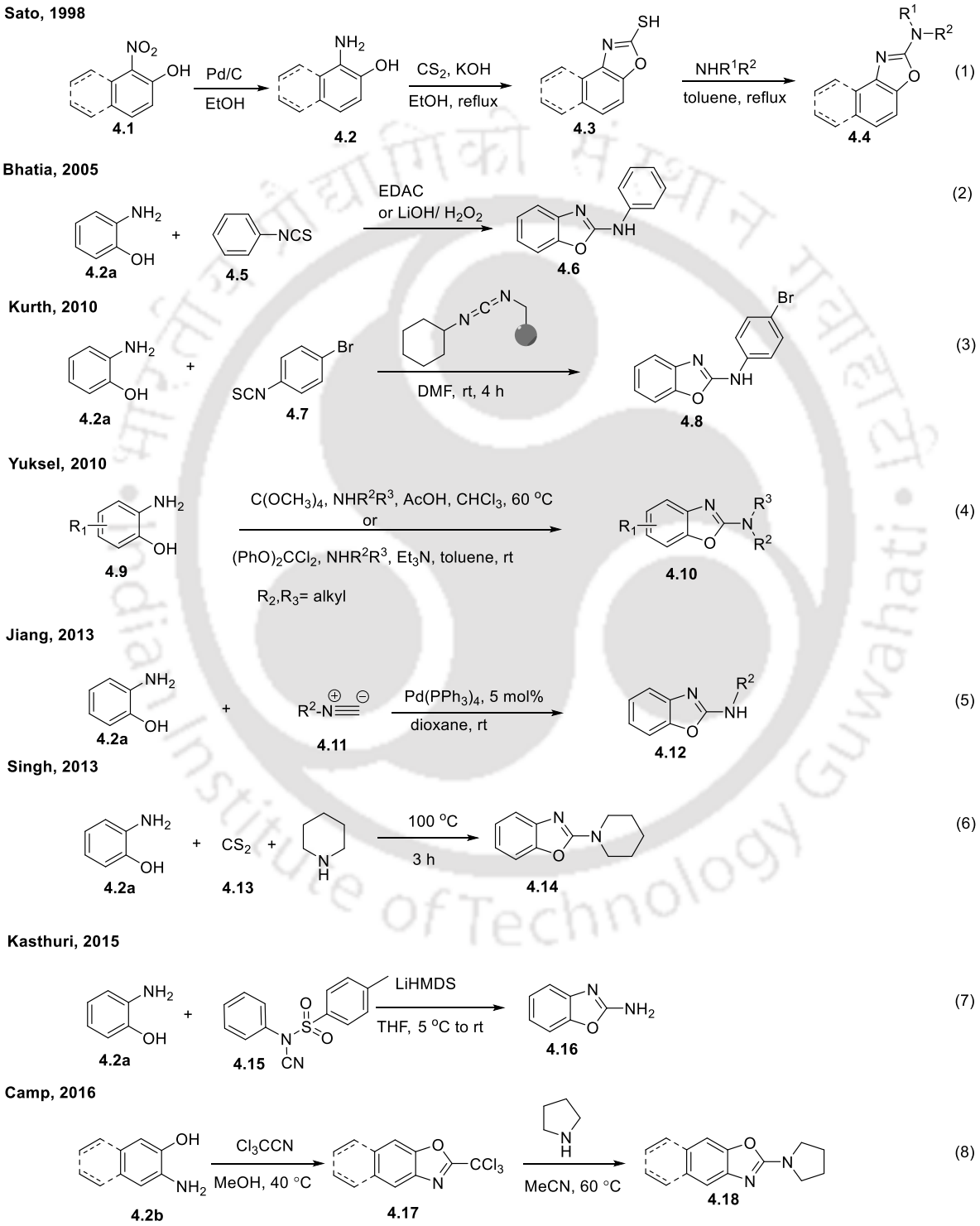
Figure 1: Selected biologically active 2-amino-oxazole derivatives.

4.2 Known methods for amiooxazole synthesis:

Fascinated by the potential medicinal values of 2-aminooxazoles, significant efforts have been made to develop new synthetic methods for the preparation of these compounds. The main strategies developed for the synthesis of 2-aminooxazole derivatives are prepared mainly by *via* (a) cyclization of 2-aminophenols, (b) nucleophilic *ipso* substitution, (c) metal-free direct amination of benzoxazoles and (d) metal-catalyzed direct amination of benzoxazoles.

4.2.1 Aminooxazole via Cyclization of 2-aminophenols:

In 1998, Sato and co-workers have reported a multistep process to synthesis 2-aminobenzoxazole derivatives. Nitro phenol **4.1** was reduced to corresponding aminophenol **4.2**. Thiol compound **4.3** underwent substitution reaction to afford the desired aminooxazole

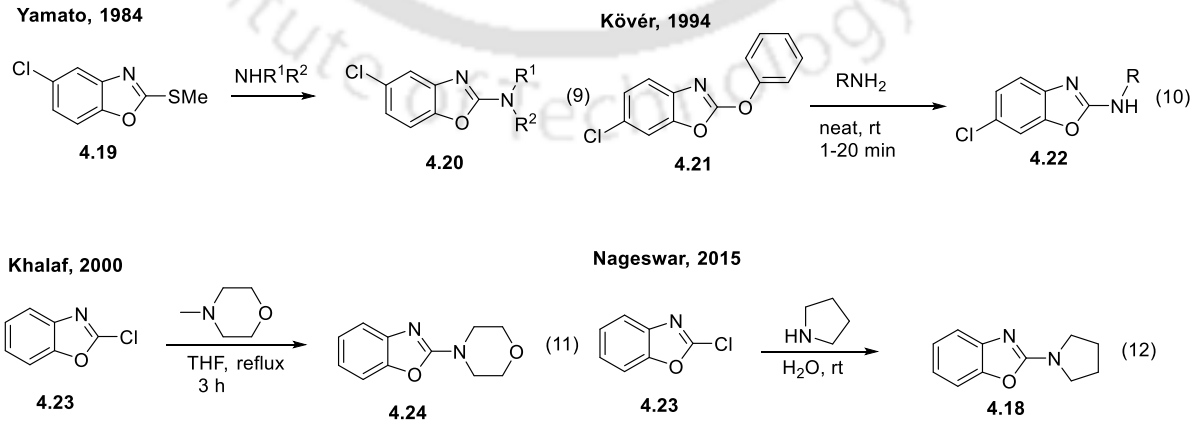


Scheme 1: Synthesis of 2-aminooxazole from 2-aminophenol.

4.4 (**Scheme 1**, eq. 1).[6,29]In 2005, Bhatia and co-workers reported a method of synthesis of 2-aminobenzoxazole **4.6** derivative *via* cyclodesulfurization method starting from 2-aminophenol **4.2a** and arylisothiocyanate **4.5** (**Scheme 1**, eq. 2).[7] Kurth and co-workers have developed a reaction of aryl isothiocyanates **4.7** with 2-aminophenol **4.2a** in the presence of a carbodiimide-functionalized resin to afford benzoxazole **4.8** (**Scheme 1**, eq. 3).[8] In 2010, Yuksel and co-workers have reported two methods for the synthesis of 2-aminobenzoxazoles **4.10** using tetramethylorthocarbonate or 1,1-dichlorodiphenoxymethane and secondary amine (**Scheme 1,** eq. 4).[9] Later, in 2013, Jiang and co-workers have reported a palladium-catalyzed synthesis of 2-aminobenzoxazoles using 2-aminophenols **4.2** and isocyanides **4.11** (**Scheme 1**, eq. 5).[10] In the same year, Singh and co-workers disclosed a reaction of aliphatic amine, carbon disulfide and 2-aminophenol to afford 2-aminobenzoxazoles **4.14** (**Scheme 1**, eq. 6).[11] In 2015, Kasthuri and co-workers have reported a facile synthesis of 2-aminobenzoxazole utilizing *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide **4.15** and various substituted 2-aminophenols derivatives **4.2** in the presence of lithium hexamethyldisilazide (LiHMDS) (**Scheme 1**, eq. 7).[12] Recently, Camp and co-workers have reported a substitution reaction of 2-trichloromethylbenzoxazoles **4.17** by amines to synthesize benzoxazoles. Trichloromethylbenzoxazole **4.17** has been prepared from the corresponding 2-aminophenol **4.2a** and Cl_3CCN (**Scheme 1**, eq. 8).[13]

4.2.2 Aminooxazole *via* Nucleophilic *ipso* substitution:

Long back in 1984, Yamato and co-workers reported a reaction of 2-(methylthio)-benzoxazole **4.19** with secondary amines to prepare 2-aminobenzole derivative **4.20** (**Scheme 2**, eq. 9).[14] Later in 1994, Kövér and co-workers have developed a substitution

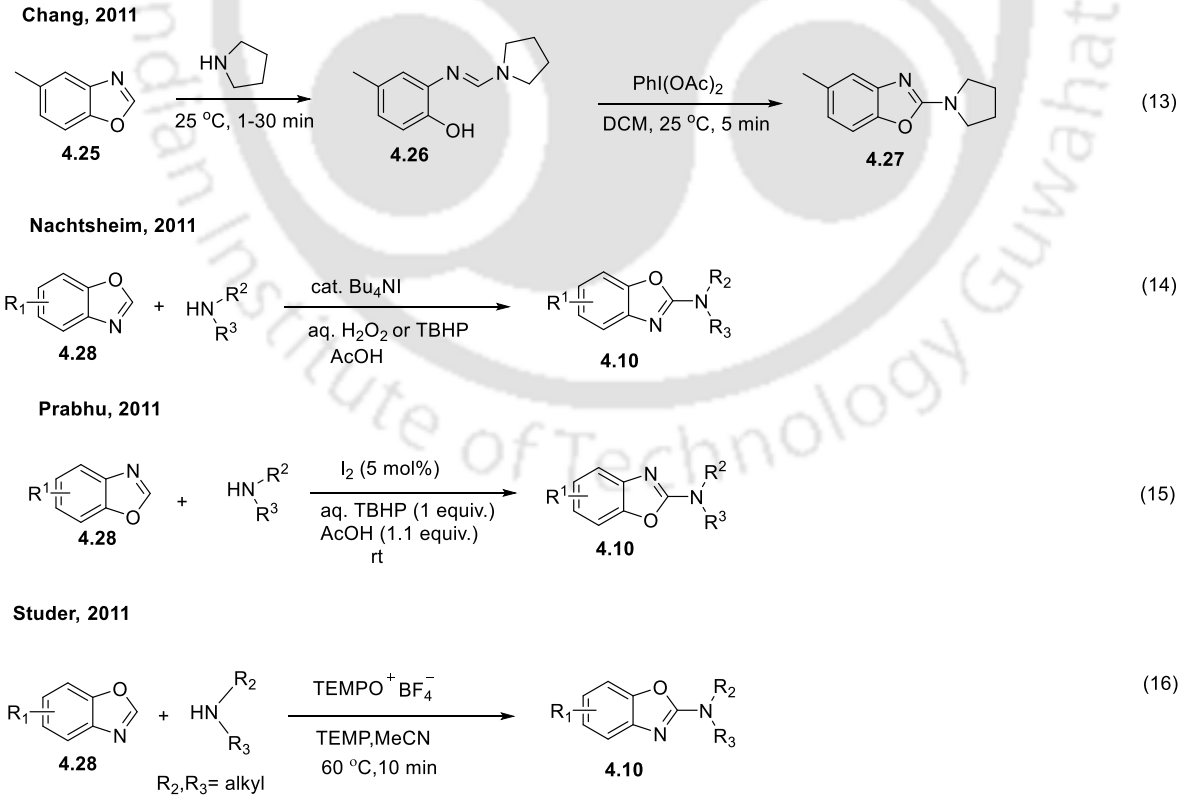


Scheme 2: Synthesis of 2-aminooxazole from 2-substituted benzoxazoles.

reaction of 6-chloro-2-phenoxybenzoxazole **4.21** by using primary amines to afford 2-aminobenzole derivative **4.22** (**Scheme 2**, eq. 10).[15] Khalaf and co-workers have developed a nucleophilic substitution reaction of 2-chlorobenzoxazole **4.23** with *N*-alkyl tertiary amines to synthesize 2-aminobenzoxazoles **4.24** *via* dealkylation of the amine (**Scheme 2**, eq. 11).[16] In 2016, Nageswar and co-workers have reported a green approach for the preparation of 2-aminooxazole s **4.18** by reacting 2-chlorobenzoxazole **4.23** with various amines in water (**Scheme 2**, 12).[17]

4.2.3 Metal-free direct amination of benzoxazoles:

In recent years, aminations of benzoxazole derivatives have been proven to be a powerful route for the preparation of 2-amino-oxazoles. In 2011, Chang and co-workers have developed a metal-free amination reaction of benzoxazole **4.25** with amines. A ring-opening reaction of **4.25** gave **4.26** which underwent cyclization followed by oxidation provides **4.**27 (**Scheme 3**, eq. 13).[18] Nachtsheim and co-workers have reported a direct amination of benzoxazole **4.28** using catalytic amounts of tetrabutylammoniumiodide and aqueous solutions of H_2O_2 or TBHP as co-oxidant to afford **4.10** (**Scheme 3**, eq. 14).[19] Later, Prabhu

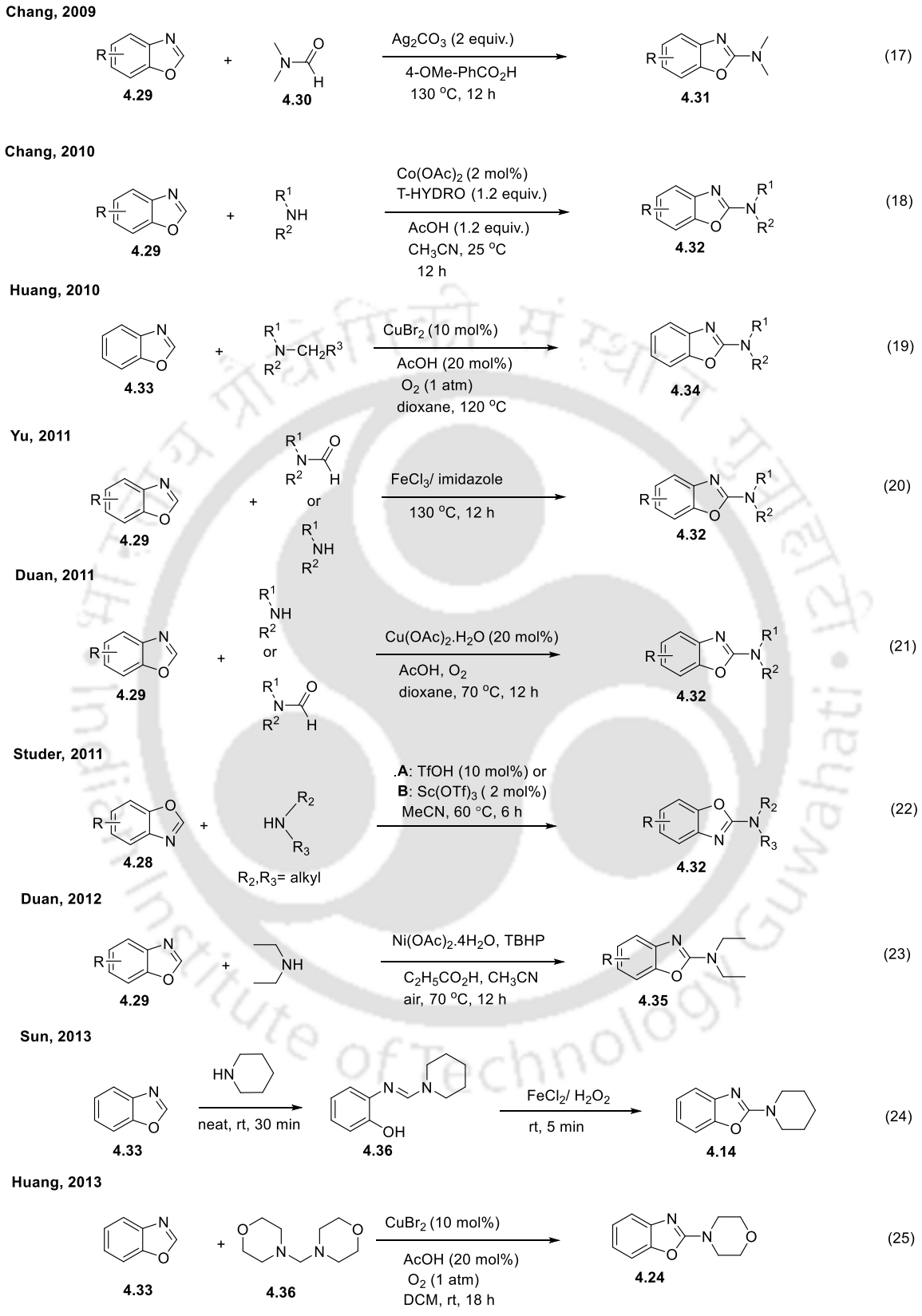


Scheme 3: Metal-free direct C-H amination of benzoxazole to 2-amino-benzoxazole.

and co-workers reported a iodine catalyzed oxidative amination of benzoxazole **4.28** with secondary and primary amine in aqueous *tert*-butyl hydroperoxide at room temperature to afford 2-benzoxazole derivatives **4.10** (**Scheme 3**, eq. 15).[20] Studer and co-workers have developed a protocol for amination of benzoxazole. 2,2,6,6-tetramethyl piperidine-*N*-oxoammonium tetrafluoroborate ($TEMPO^+BF_4^-$) used as an oxidant to afford **4.10** from amine and **4.28**. (**Scheme 3**, eq. 16).[21]

4.2.4 Metal catalyzed direct C-H amination of benzoxazoles:

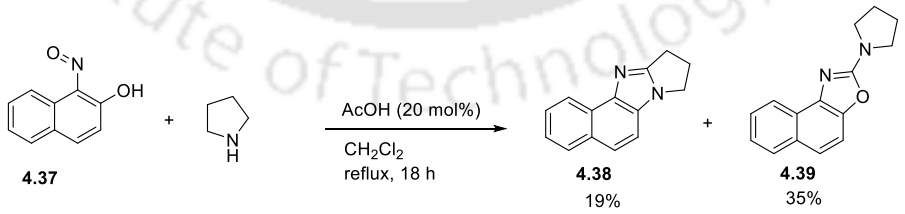
Development of metal catalyzed direct C-H amination of benzoxazole has been enormously progressed over the last two decades. Ag_2CO_3 mediated direct amination of benzoxazole **4.29** utilizing formamides **4.30** as the amino source have been disclosed by Chang and co-workers in 2009 (**Scheme 4**, eq. 17). In the next year, the same group have developed a cobalt catalyzed direct amination of benzoxazole **4.29** in the presence of peroxide and acetic acid (**Scheme 4**, eq. 18).[22] Huang and co-workers developed a copper-catalyzed oxidative amination of benzoxazole **4.33** with tertiary amines using atmospheric oxygen as oxidant to prepare **4.34** (**Scheme 4**, eq. 19).[23] In 2011, Yu and co-workers have reported iron-catalyzed amination reaction of benzoxazole using formamides or amines as nitrogen sources (**Scheme 4**, eq. 20).[24] Duan and co-workers have developed a copper-catalyzed direct C-H amination of benzoxazoles **4.29** using formamides or secondary amines as amino source in the presence of atmospheric oxygen as oxidant to afford 2-aminobenzoxazoles **4.32** (**Scheme 4**, eq. 21).[25] The same group in 2012, reported nickel-catalyzed C-H amination reaction for the synthesis of 2-aminobenzoxazole derivative **4.35** using benzoxazole **4.29** and secondary amines (**Scheme 4**, eq. 23).[26] Studer and co-workers have developed a lewis acid $Sc(OTf)_3$ promoted amination of benzoxazole (**Scheme 4**, eq. 22).[21] In 2013, Sun and co-workers have developed an iron-catalyzed ring opening of benzoxazoles with secondary amines to provide **4.36**. Cyclization and subsequent oxidation of **4.36** in presence of aqueous H_2O_2 as an oxidant provided 2-aminobenzoxazole **4.14** (**Scheme 4**, eq. 24).[27] Huang and co-workers have disclosed a copper catalyzed oxidative C-H amination of benzoxazoles **4.33** using aminal **4.36** as amine source to prepare 2-aminobenzoxazole derivative **4.24** (**Scheme 4**, eq. 25).[28]



Scheme 4: Metal catalyzed direct C-H amination of benzoxazole to 2-aminobenzoxazole.

Evidently, from the last few decades, the synthesis of aminooxazole has made remarkable progress. The most common methods for the synthesis of 2-aminobenzoxazoles directly from 2-aminophenols often requires multiple steps for the preparation of amine surrogates prior to ring cyclization. In addition, the methods necessitate the use of activated and sensitive reagents (such as CS_2, R-NCS, CO etc) as the carbon source of C2 of oxazoles. The methods are associated with cyclodesulfurization of an intermediary thiourea under harsh reaction conditions. On the other hand, the methods involving oxidative cyclization, usually use toxic heavy-metal oxide or strong oxidants which produces undesirable by-products. The classical approach of direct oxidative C-H amination of benzoxazoles towards the construction of 2-aminobenzoxazoles has also been extensively studied. However, this strategy required the use of preformed oxazole as the substrate. Thus the previously reported synthetic methods to generate 2-aminooxazoles mostly suffer from the requirement of multiple reaction steps, metallic reagents, strong oxidant harsh reaction conditions, and undesirable by-products. Therefore, development of novel and environment-friendly method devoid of any type of toxic metallic reagents and oxidant could be beneficial in the field of synthesis of bioactive aminooxazole s. A large number of report of 2-aminobenzoxazole is known in the literature. Interestingly, reports for the synthesis of corresponding 2-aminonaphthoxazole is very limited.

During the study of C(sp^3)-H functionalization of *N*-heterocycles to synthesize ring-fused imidazoles (see **Chapter 3**), 1-nitroso-2-naphthol was reacted with 4 equiv. of pyrrolidine in presence of 20 mol% of acetic acid in refluxing dichloromethane, in addition to the formation of the ring-fused imidazole, 2-aminonaphthoxazole was isolated with 35% yield (**Scheme 5**).



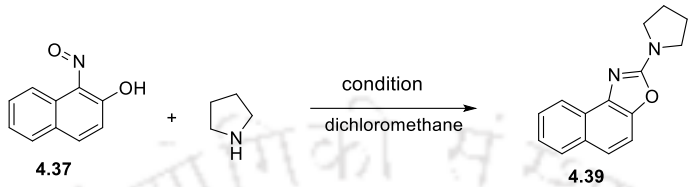
Scheme 5: Initial result.

4.3 Results and Discussions:

It was realized that the reaction could provide the opportunity to achieve the direct synthesis of 2-amino-oxazole derivatives under simple reaction conditions without using metal- or

oxidant-based reagents or catalysts. Furthermore, the method will have the potential to provide privileged structures in a single step without using any activated reagents as the C-2 carbon of oxazole. Therefore, various reaction conditions were screened to optimize the reaction condition for the better yield of the 2-aminonaphthoxazole **4.39**.

Table 1: Variation of reagents and reaction conditions to obtain the best yields of the desired product.



4.37 4.39

Entry	Additive	Temperature	Time	%Yield
1	-	reflux	14 h	40
2	AcOH (20 mol%)	reflux	12 h	35
3	NEt_3 1 equiv.	reflux	14h	41
4	KOAc 1 equiv.	reflux	14 h	42
5	KOAc 1 equiv.	reflux	24 h	54
6	KOAc 2 equiv.	rt	24 h	20
7	KOAc 2 equiv.	reflux	24 h	66
8	K_2CO_3 2 equiv.	reflux	24h	43
9	Et_3N 2 equiv.	reflux	24 h	50
10	DBU 2 equiv.	reflux	24 h	60
11	KOAc 2 equiv.	reflux	36/ 48 h	70
12	KOAc 1 equiv.	reflux	36 h	55
13	NaOH 2 equiv.	reflux	24 h	ND

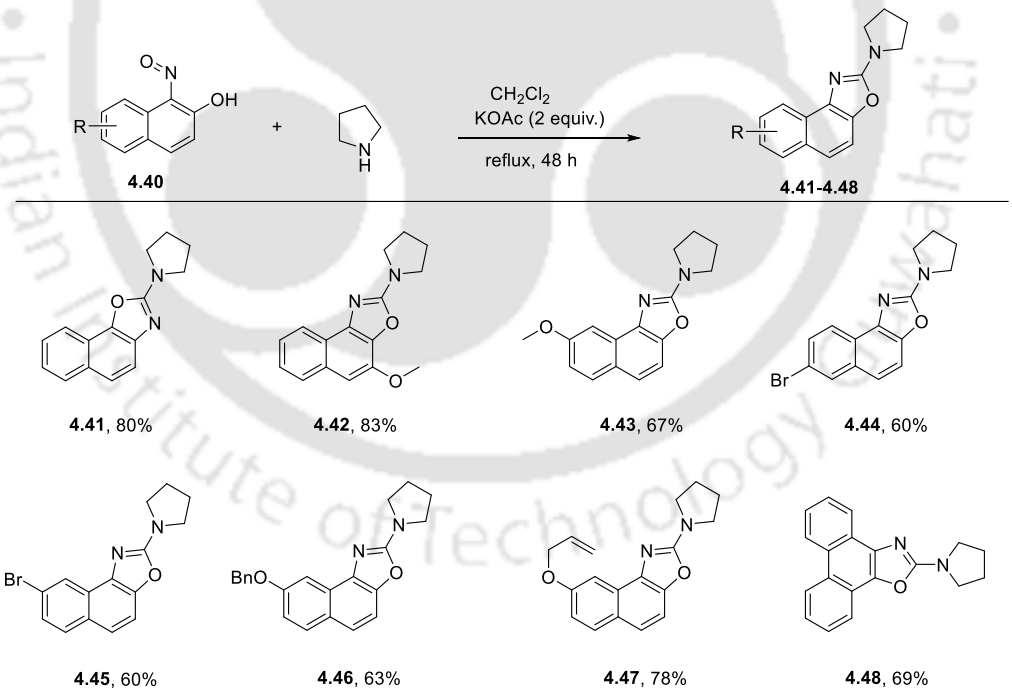
[a]All the reactions were carried out using 0.23 mmol of **1**, 0.94 mmol of pyrrolidie, 0.46 mmol of KOAc and 4ml dichloromethane.

The reaction in the absence of acid provided a better yield (**Table 1**, entry 1). The additive was changed from acid to base to optimize the reaction conditions. When 1equiv. of Et_3N, 4 equiv. of pyrrolidine were used under refluxing dichloromethane (DCM), the yield of **4.39** was increased to 41% (**Table 1**, entry 3). In the presence of 1 equiv. of KOAc the yield of **4.39** was found to 42% (**Table 1**, entry 4). With increasing time up to 24 h the yield was found to increase to 54% (**Table 1**, entry 5). However, no significant increment of the yield was observed on using K_2CO_3 (43%, **Table 1**, entry 8). On the contrary, a considerable

increase in yield was observed when DBU was used (58%, **Table 1**, entry 10). On changing the base to KOAc (2 equiv.) an increment of yield was observed (66%, **Table 1**, entry 12). It was found that with increasing time of the reaction, the yield was increased. The best result was obtained using 4 equiv. of pyrrolidine, 2 equiv. of KOAc and 1 equiv. of 1-nitroso-2-naphthol were under refluxing dichloromethane for 36 h to afford **2a** with 70% yield (**Table 1**, entry 13).

4.4 Substrate scope with various nitrosoarenes:

To investigate the scope of the reaction, the reaction of a variety of 1-nitroso-2-naphthol and 2-nitroso-1-naphthol with pyrrolidine has been studied using optimized condition (**Scheme 6**). 2-nitroso-1-naphthol on reaction with pyrrolidine afforded desired 2-amino-naphtholoxazole derivatives **4.41** with very good yield (80%). Similarly, 3-OMe substitution on nitrosoarene gave the desired aminonaphthoxazole **4.42** with 83% yield. 7-OMe, 6-Br, 7-Br, O-benzyl, O-allyl, substituted nitrosonaphthols also reacted smoothly with pyrrolidine to provide corresponding aminooxazole derivatives **4.43**, **4.44**, **4.45**, **4.46**,

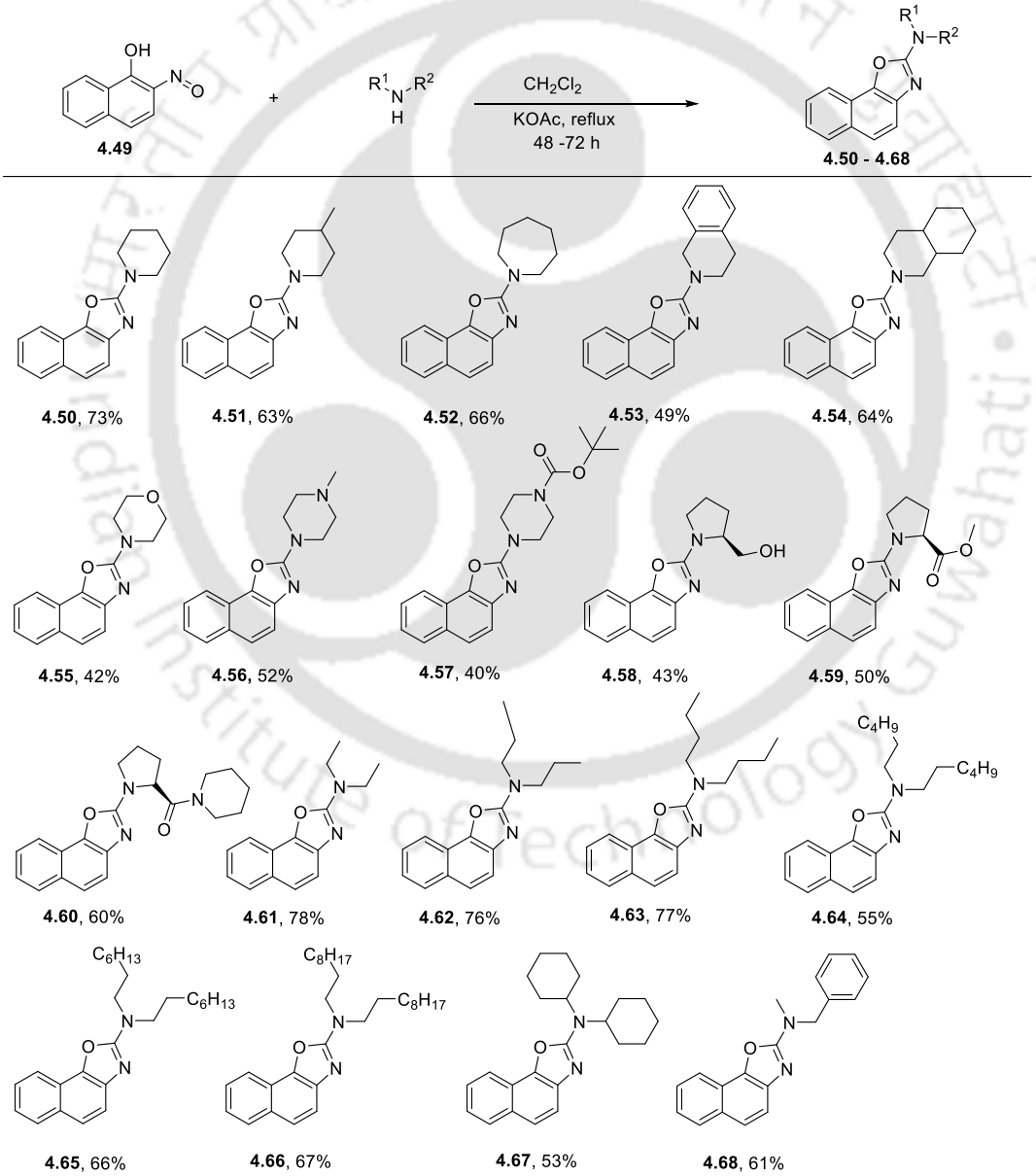


Scheme 6: Scope of the reaction with pyrrolidine and various nitrosonaphthols.

4.47 respectively, with good to very good yields. Phenanthroline derivative **4.48** (69%) was also obtained from the reaction of corresponding *o*-hydroxy-nitroso compounds with pyrrolidine.

4.5 Substrate scope with 2-nitroso 1-naphthol and various secondary amines:

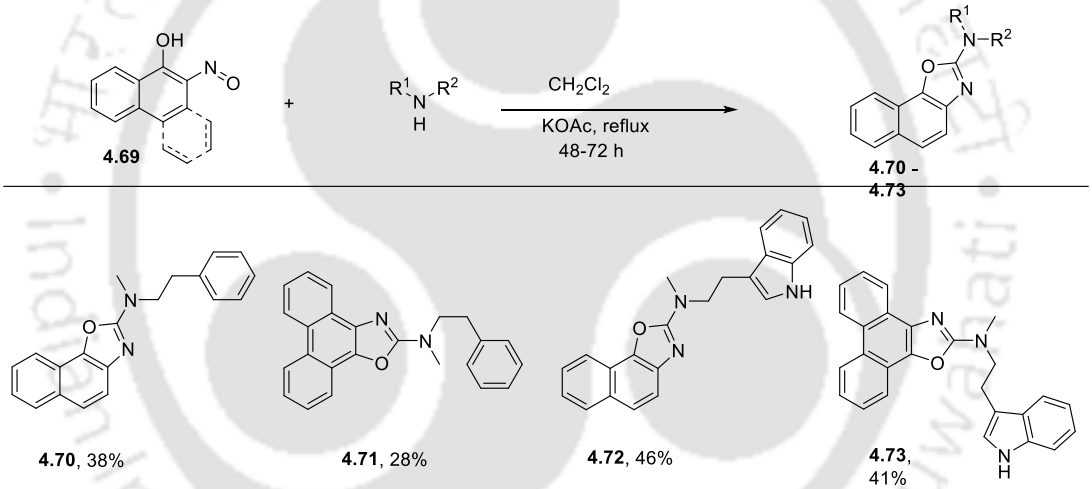
The scope of the reaction with different secondary amines was investigated next. A variety of cyclic and acyclic secondary amines were reacted with 2-nitroso 1-naphthol and dichloromethane to obtain 2-aminonaphthoxazole derivatives **4.50-4.68** with moderate to very good yield. Apart from pyrrolidine, other cyclic amines piperidine, 4-methyl-piperidine piperidine, azepane also worked well to provide the corresponding 2-



Scheme 7: Scope of the reaction with 2-nitroso-1-naphthol and various secondary amines.

aminonaphthoxazole **4.50** (73%), **4.51** (63%), **4.52** (66%) respectively with good yields. Similar reactivities were observed in the case of tetrahydroisoquinoline, perhydroisoquinoline, morpholine to provide the desired products **4.53**, **4.51**, **4.55** respectively with moderate to good yields. The reaction of *N*-methylpiperazine, *N*-Boc-piperazine and proline derivatives also resulted in the production of the corresponding naphthaoxazole **4.56**-**4.60** with slightly lower yields. In addition to that, acyclic amines also smoothly participated in the reaction to furnish 2-aminonaphthoxazole derivatives **4.61**-**4.68** with good to very good yields (**Scheme 7**).

Biogenic secondary amines were then tested as the potential substrate for this reaction. *N*-methylphenethylamine was proved to be effective to provide corresponding 2-aminooxazole derivatives **4.70** and **4.71**. Similarly, *N*-methyl-tryptamine reacted with 2-nitroso-1-naphthol and 10-nitrosophenanthren-9-ol to provide **4.72** and **4.73** respectively (**Scheme 8**).

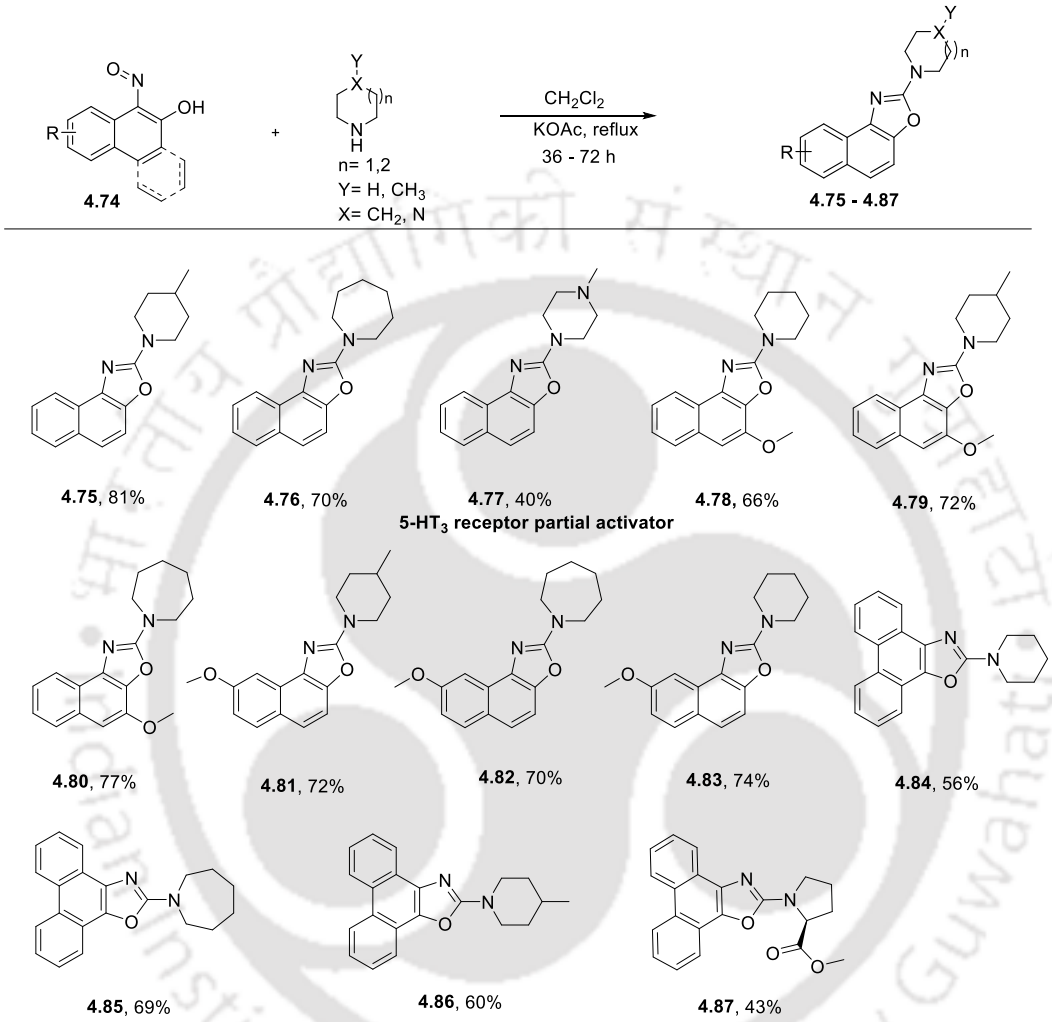


Scheme 8: Scope of the reaction with biogenic secondary amines.

4.6 Substrate scope with different nitrosoarenes and different amines:

After investigating the substrate scope of 2-aminonaphthoxazole with different nitrosonaphthol and various amines, further the scope of the reaction was tested with piperidine, azepane, 4-methyl piperidine, *N*-methyl piperazine as the amines counterpart and various nitrosonaphthols (**Scheme 9**). The reaction of 1-nitroso-2-naphthol with 4-methyl piperidine and azepane afforded **4.75** and **4.76** with very good yields. Furthermore, 2-(*N*-methylpiperazyl)naphthoxazole **4.77**, which is a serotonin $5HT_3$ receptor partial activator,[29] has been synthesized easily in a single step starting from 1-nitroso-2-naphthol and *N*-methylpiperazine. Similarly, 3-methoxy-2-nitroso-1-naphthol and 7-methoxy-2-nitroso-1-naphthol also reacted well with piperidine, 4-methyl piperidine, azepane, to afford

the desired 2-aminonaphthoxazole **4.78 - 4.83**, respectively, with very good yields. 10-nitrosophenanthren-9-ol on reaction with piperidine, 4-methyl piperidine, azepane gave **4.84**, **4.85** and **4.86**, respectively, with very good yields. However, methylester of proline gave the desired product **4.87** with lower yields (**Scheme 9**).

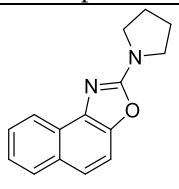
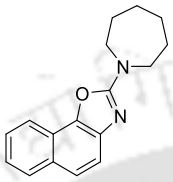
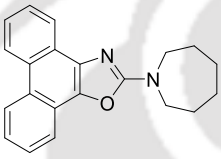


Scheme 9: Scope of the reaction different nitrosoarenes with different amines.

4.7 Crystal structures of the 2-amino-oxazole derivatives:

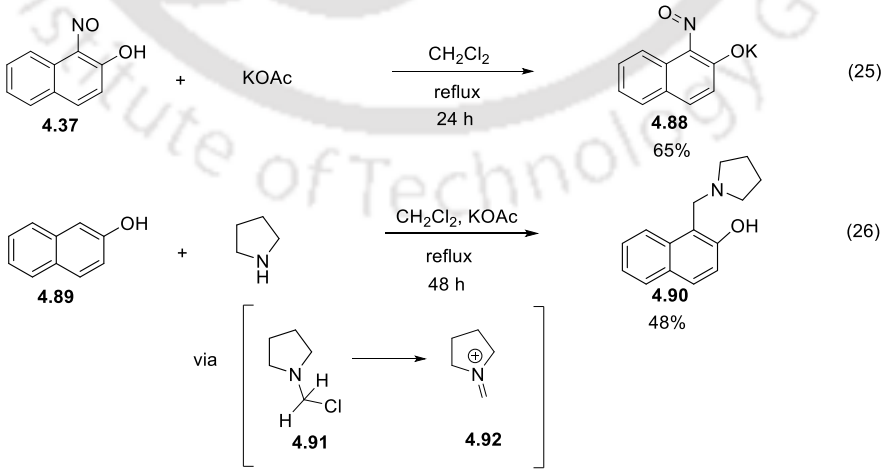
The structure of the 2-amino-oxazole derivatives **4.39**, **4.52** and **4.85** were confirmed by X-ray crystallographic analysis. The structures of compounds have been shown in **Table 2**.

Table 2: Selected 2-amino-oxazoles and their X-ray crystal structures.

Compound	Crystal structure
 **4.39**	
 **4.52**	
 **4.85**	

4.8 Controlled experiments:

To investigate the mechanistic path of the reaction, some controlled experiments have been performed (**Scheme 10**). When1-nitroso-2-naphthol was reacted with KOAc in dichloromethane at reflux temperature, only potassium salt of 1-nitroso2-naphthol was isolated (**Scheme 10**, eq. 25). These results demonstrates that dichloromethane did not react

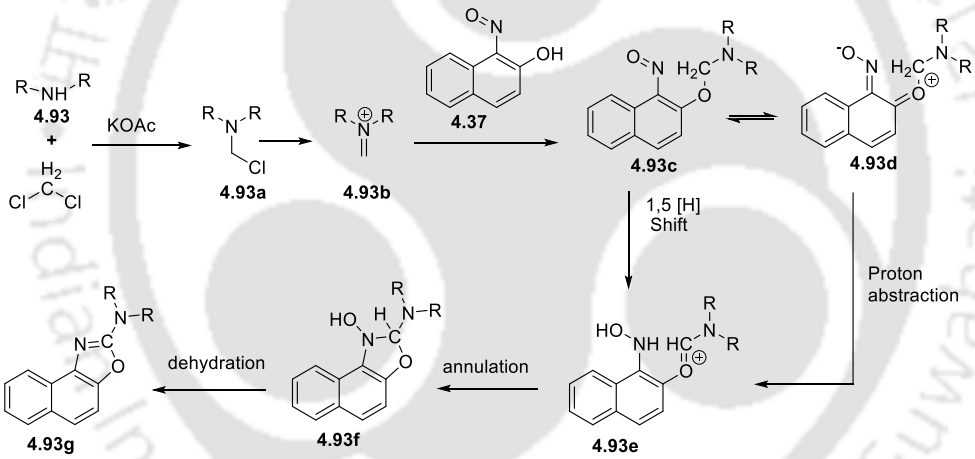


Scheme 10: Controlled experiments.

with 1-nitroso-2-naphthol. Furthermore, 2-naphthol on reaction with pyrrolidine and dichloromethane afforded corresponding Betti product **4.90** with 48% yield (**Scheme 10**, eq. 26). This indicates that the reaction may proceed via iminium ion **4.92** or its derivative **4.91**.

4.9 Proposed mechanism:

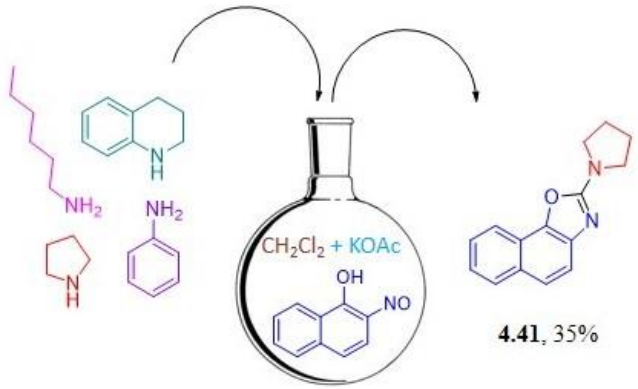
Based on the results of controlled experiments a plausible mechanism for this annulation reaction is presented in **Scheme 11**. Amine **4.93** reacted with dichloromethane in the presence of base to generate the iminium ion **4.93b** via *α*-cholroamine **4.93a**. The reaction of **4.93a** or **4.93b** with 1-nitroso2-naphthol afforded *O*-alkylated derivative **4.93c**. Then **4.93c** readily undertook a 1,5-hydride shift to provide the iminium ion **4.93e** which also could be obtained by the isomerization via **4.93d.** Annulation of **4.93e** followed by dehydration of resulting *N*-hydroxy derivative **4.93f** provided the desired aminooxazole **4.93g**.



Scheme 11: Proposed mechanism for the synthesis of 2-aminonaphthaoxazole.

4.10 Chemoselectivity of the reaction:

Next, the chemoselectivity of the reaction has been investigated. Accordingly, a mixture of primary non-aromatic (*n*-hexylamine), non-conjugated secondary amine (pyrrolidine), conjugated primary aromatic amine (aniline) and conjugated secondary aromatic amine (tetrahydroquinoline) were reacted with 2-nitroso-1-naphthol in one pot under standard reactions. Interestingly, it was observed that pyrrolidine took part in the reaction selectively to afford **4.41** with 35% yield and unreacted 2-nitroso-1-naphthol (**Scheme 12**). This result showed the excellent chemoselectivity of the reaction towards non-conjugated secondary amines.



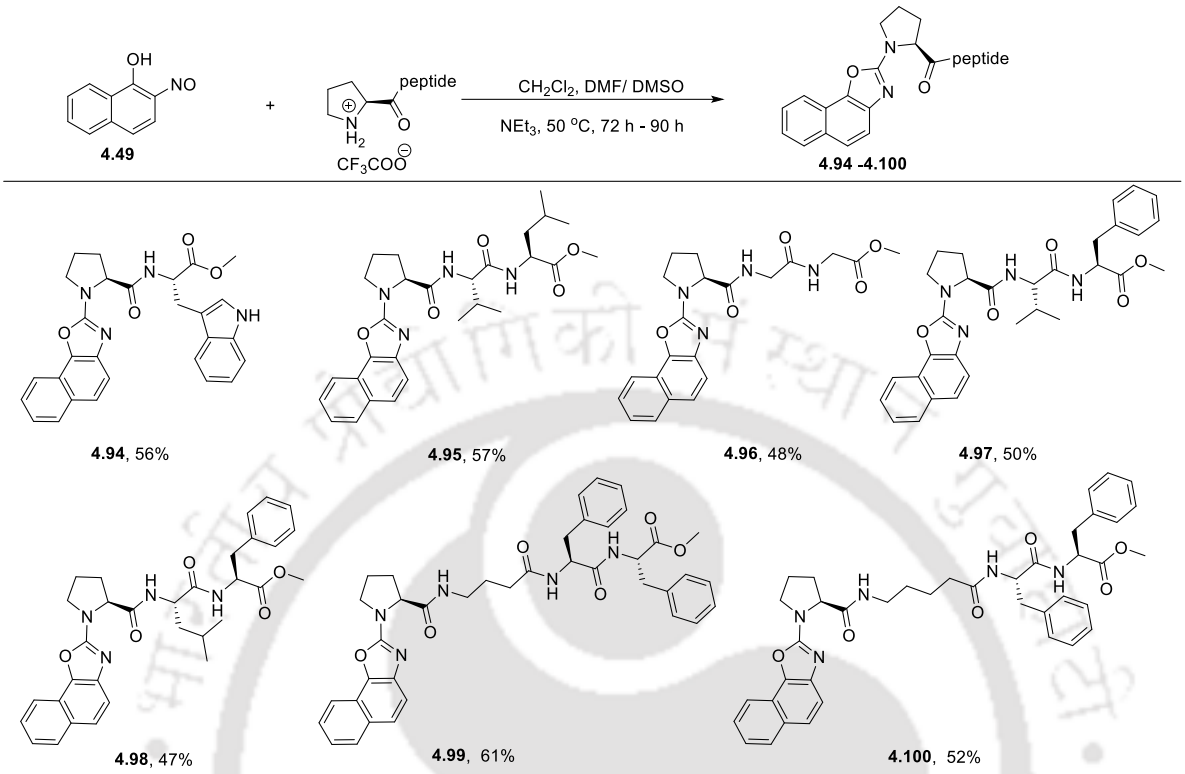
Scheme 12: Chemoselectivity towards non-conjugated secondary amine.

4.11 Site selective *N*-terminal modification of peptides:

N-terminal modification of peptides has emerged as an important tool for study biological process and development of new biotherapeutics.[30] Introduction of fluorescent tags via *N*-terminal peptides have been used for the imaging of biological systems and analysis of biological mechanism.[31,32,33,34] Moreover, in drug discovery, modified peptide often used as an alternate of parent small molecule drugs due to its higher target specificity.[35,36] Also, binding affinity, cell permeability and stability of the peptides can be significantly improved by *N*-terminal modification.[37]

Next, *N*-terminal modification of peptides applying this chemoselective annulations reaction has been investigated. As the reaction is selective towards non-conjugated secondary amines, various di-, tri- or tetra-peptides were prepared keeping (L)-proline as the *N*-terminal. These di-, tri- and tetra-peptides containing *N*-terminal proline were reacted with 2-nitroso-1-naphthol and dichloromethane in the presence of NEt_3 to provide the desired *N*-terminal modified peptides with good unoptimized yields (**Scheme 10**). Di-peptide (L)-Pro-(L)-Trp-OMe on reaction with 2-nitroso-1-naphthol and dichloromethane afforded *N*-terminal modified peptide **4.94** with 56% yield. Afterward, tri-peptides were employed for *N*-terminal modification. (L)-Pro-(L)-Val-(L)-Lue-OMe, (L)-Pro-(L)-Ala-(L)-Ala-OMe gave the corresponding *N*-terminal modified peptides **4.95** and **4.96**. Similarly, (L)-Pro-(L)-Val-(L)-Phe-OMe, (L)-Pro-(L)-Leu-(L)-Phe-OMe afforded corresponding *N*-terminal modified peptides **4.97** and **4.98** with moderate yields. Further, on moving to tetra-peptides

(L)-Pro-GABA-(L)-Phe-(L)-Phe-OMe, (L)-Pro-DAVA-(L)-Phe-(L)-Phe-OMe also provided desired peptides **4.99** and **4.100** respectively.



Scheme 10: *N*-terminal peptide modification.

4.12 Photophysical properties of the aminooxazole derivatives and *N*-terminal modified peptides:

The photophysical properties of the synthesized compounds **4.41** and **4.60** have been studied in a micromolar solution in DMSO. The absorption spectra of these two compounds exhibited absorption bands at 266 nm, 305 nm and 345 nm (**Figure 2, c**). Emission spectra at absorption 305 nm showed high-intensity band in the range 389−425 nm (**Figure 2, b**). Next, the photophysical properties of the *N*-terminal modified peptides **4.94-4.100** were explored by studying the absorption and emission profile of a micromolar solution in DMSO (**Figure 3, a**). The absorption spectra of all these peptides were well structure and exhibited two absorption bands at 266 nm, 305 nm and 345 nm. Emission spectra of these compounds **4.94-4.100** at absorption 305 nm showed high-intensity band in the range 389−429 nm (**Figure 3, b**).

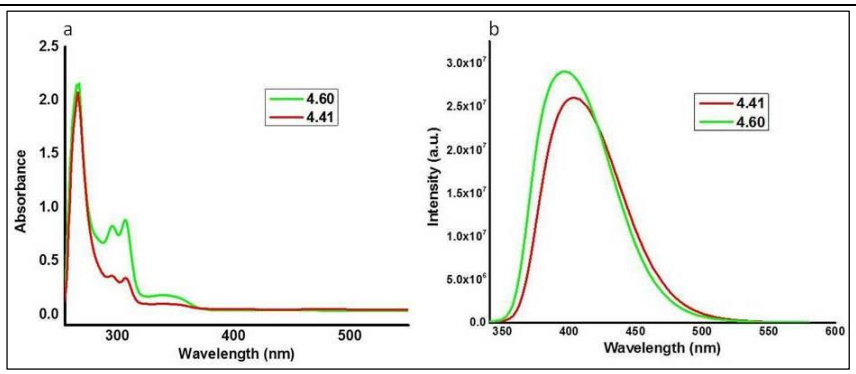


Figure 2: (a) absorption spectra and (b) emission spectra (at λ= 305 nm) in a micromolar DMSO solution of **4.41** and **4.60**.

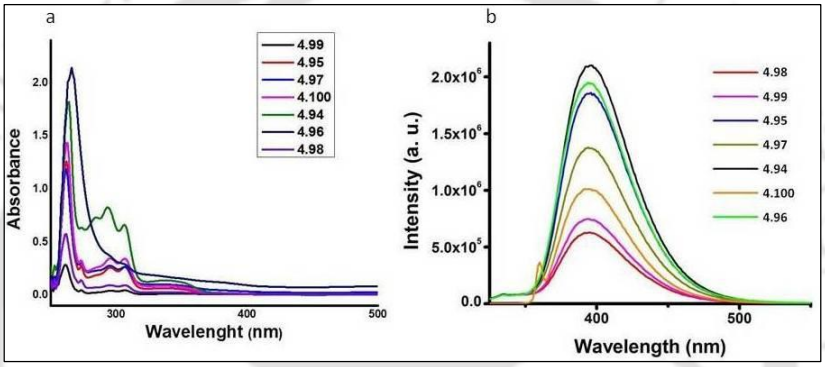


Figure 3: (a) absorption spectra and (b) emission spectra (at λ= 305 nm) in a micromolar DMSO solution of the peptides **4.94**-**4.100**.

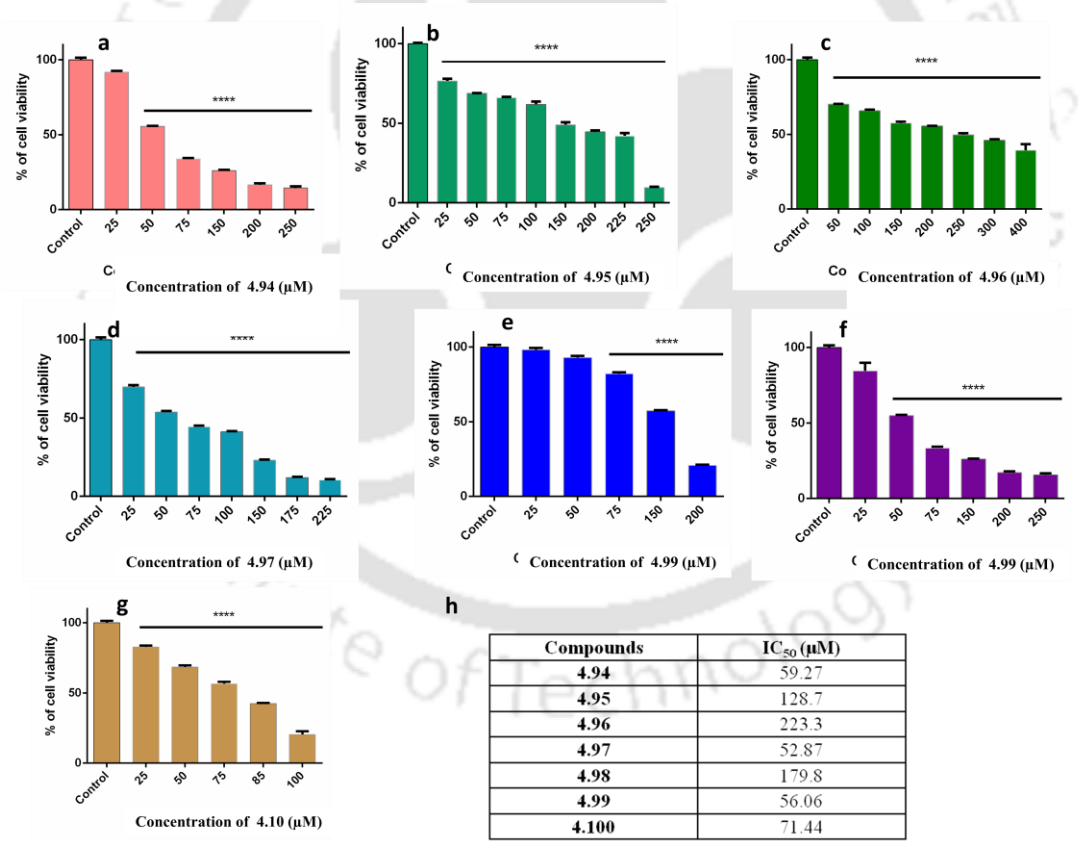
Relative fluorescence quantum yields of the modified peptides were measured with respect to quinine sulfate (0.1 M H_2SO_4 solution, Q_f = 0.54). The quantum yields of the compounds **4.94**, **4.95**, **4.96**, **4.97**, **4.98**, **4.99** and **4.100** are 0.18, 0.36, 0.12, 0.49, 0.30, 0.28 and 0.27 respectively.

4.13 Biocompatibility of the *N*-terminal modified peptides on HeLa cells:

Fluorescent peptides are ideal for *in vitro* imaging, enzyme activity assays, the study of a variety of biological process, interactions in cells and applications in disease diagnostics.[38] Applications for fluorescent peptides range from the study of peptide-protein interactions, or development of novel disease models. Fluorescent dyes are covalently bonded to the *N*-terminal of the peptides during their synthesis, or can be linked/ modified site-specifically to a pre-existing peptide. Amino group or thio group in the side-chains of the peptide have been also used for the labelling. Also, peptides can be labelled *in situ* using fluorescent

conjugates. Fluorescent peptides are also used in monitoring protease activity.[39] The main drawback of these strategies is the requirement of fluorescent dye to couple at the specific site of the peptides.

To understand the biocompatibility of the synthesized *N*-naphthoxazoles containing peptides cell viability assay was performed using alamarBlue. Through this assay, cytotoxicity was evaluated, as cytotoxicity is a potential side effect of the fluorophores that must be controlled when dealing with living cells, tissues, or animals. As depicted in **Figure 4- (b**, **c**, **e)** a significant decrease in cell viability was not observed even at concentration up to 100 µM for compound **4.95**, **4.96**, **4.98**. Compounds **4.94**, **4.97**, **4.99**, **4.100** did not show any significant anti-proliferative activity up to a concentration of 40 µM, demonstrating negligible cytotoxicity and superior biocompatibility of the compounds (**Figure 4- a, d, f, g**). The calculated IC_{50} values for these compounds have been mentioned in **Figure 4- h**.



h

Compounds	IC_{50} (µM)
4.94	59.27
4.95	128.7
4.96	223.3
4.97	52.87
4.98	179.8
4.99	56.06
4.100	71.44

Figure 4: (a), (b), (c), (d), (e), (f) and (g) Effect of compounds **4.94**, **4.95**, **4.96**, **4.97**, **4.98**, **4.99** and **4.100** respectively in terms of reduction in percentage of viable cells as demonstrated by alamerBlue assay. Statistical significance has been determined by one-way .ANOVA, where *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.(h) IC_{50} values of the respective compounds.

4.14 Bio-imaging for uptake studies on HeLa cells:

Fluorescent labelled peptides are versatile and precious tools for medical and biological research. Therefore, the potential of the synthesized fluorescent peptides as cell imaging has been investigated. For biological analysis and clinical diagnostic *in vitro* cellular imaging using fluorescent bioimaging techniques are elegant and non-invasive analytical tools. In these studies, analysis of the uptake of the compounds **4.94- 4.100** into HeLa cells were

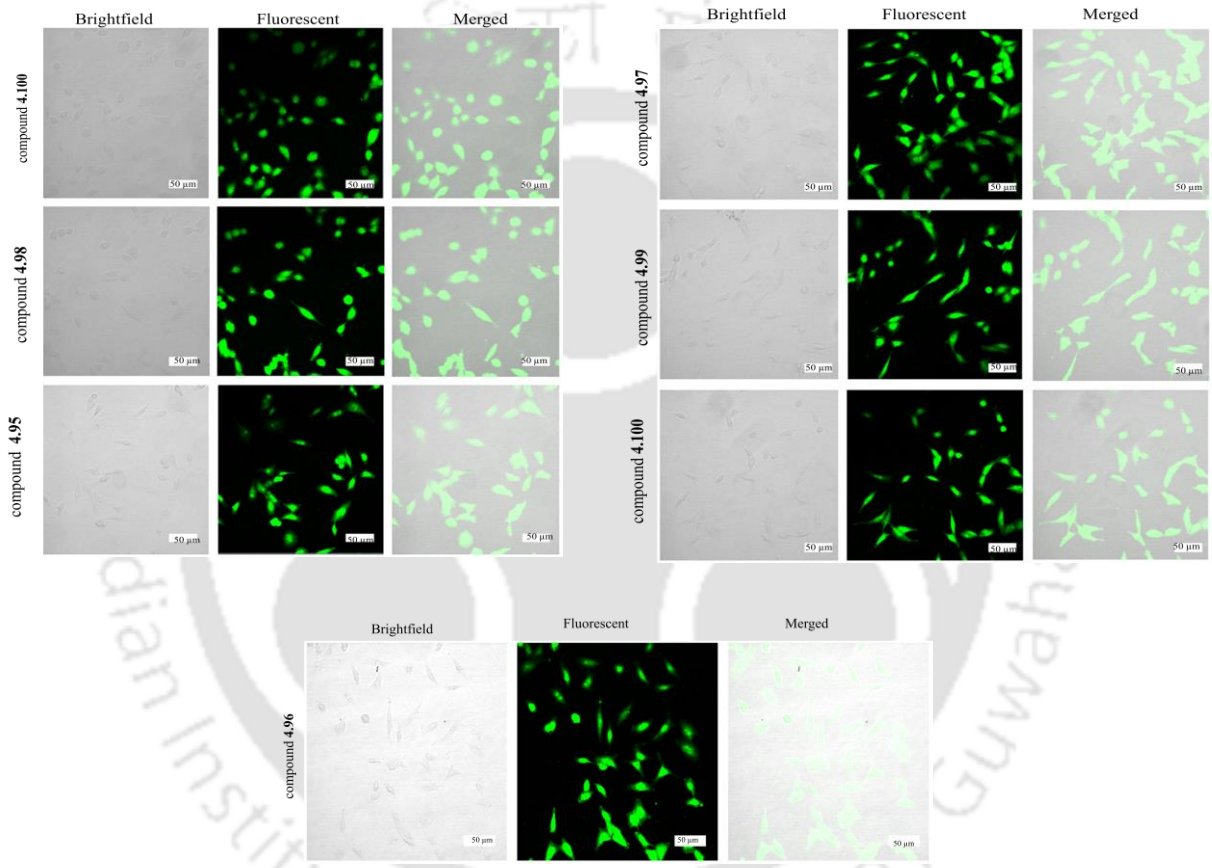


Figure 5: Confocal laser scanning microscopy images of HeLa cells stained with **4.100**, **4.98**, **4.95**, **4.97**, **4.99**, **4.94** and **4.96** respectively. Cells were incubated with 40 µM of the compounds for 20 min. Excitation: 458 nm; Emission range: 480-605 nm; Scale bar: 50 µm.

compounds is clearly indicated by Z stack analysis of the treated cells **(Figure 6)**. Similarly, bright luminescence was observed on HeLa cells following treatment of compounds **4.97**, **4.99**, **4.94** and **4.96** (**Figure 6**). Shorter incubation time suggests their superior penetrability to the cell membrane. From CLSM images, it is apparent that the fluorescence signals are abundant in cell cytoplasm and to a lower extent even in the nucleus. Thus, it is evident that these compounds could be used as excellent luminescent probe for rapid staining of the cell

cytoplasm. These molecules can be used instead of commonly used staining agents such as eosin, malachite green, acridine orange which are not easy to prepare.

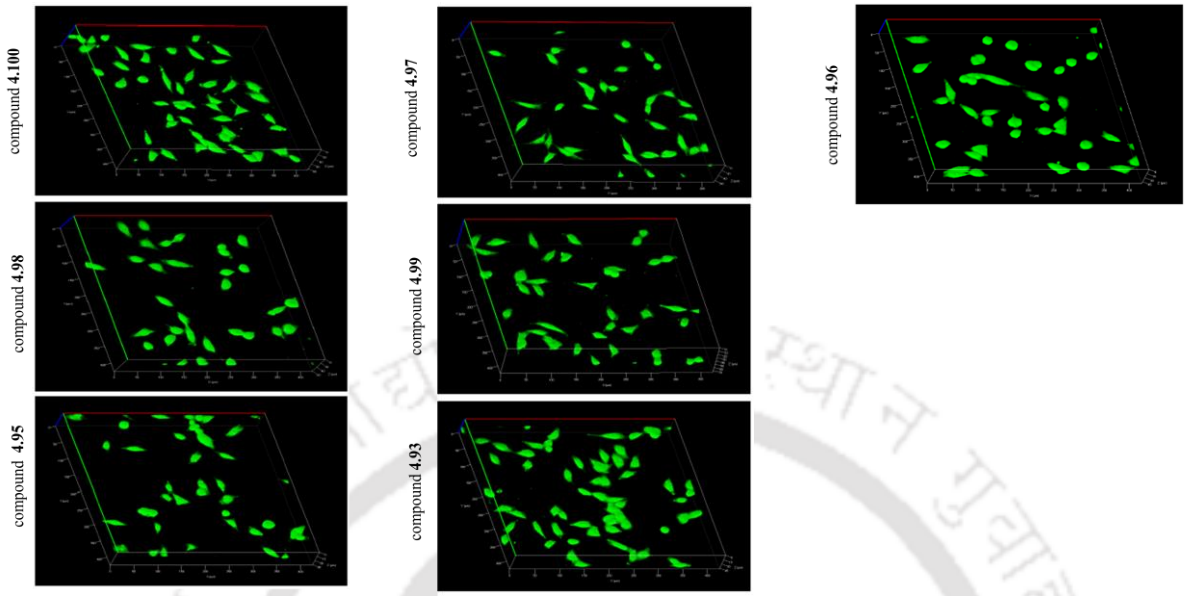


Figure 6: 3D Confocal laser scanning microscopy images of HeLa cells obtained by Z-stacking. Cells were treated with compounds **4.100**, **4.98**, **4.95**, **4.97**, **4.99**, **4.94** and **4.96** respectively, at a concentration of 40 µM for 20 min. Excitation: 458 nm; Emission range: 480-605nm.

4.15 Cell cycle studies:

To delineate the impact of compounds on HeLa cells, flow-cytometer based analysis of cell cycle progression was performed. It was observed that the following treatment with the compounds **4.100**, **4.98**, **4.95**, **4.97**, **4.99**, **4.94** and **4.96** the number of cells in G1/S phase

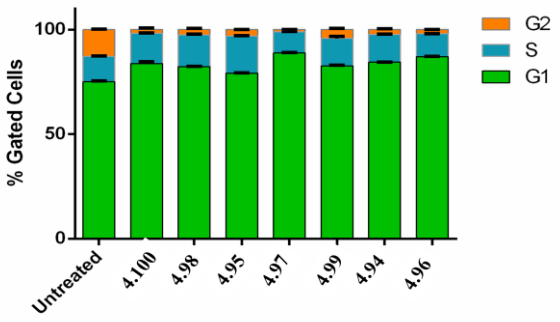
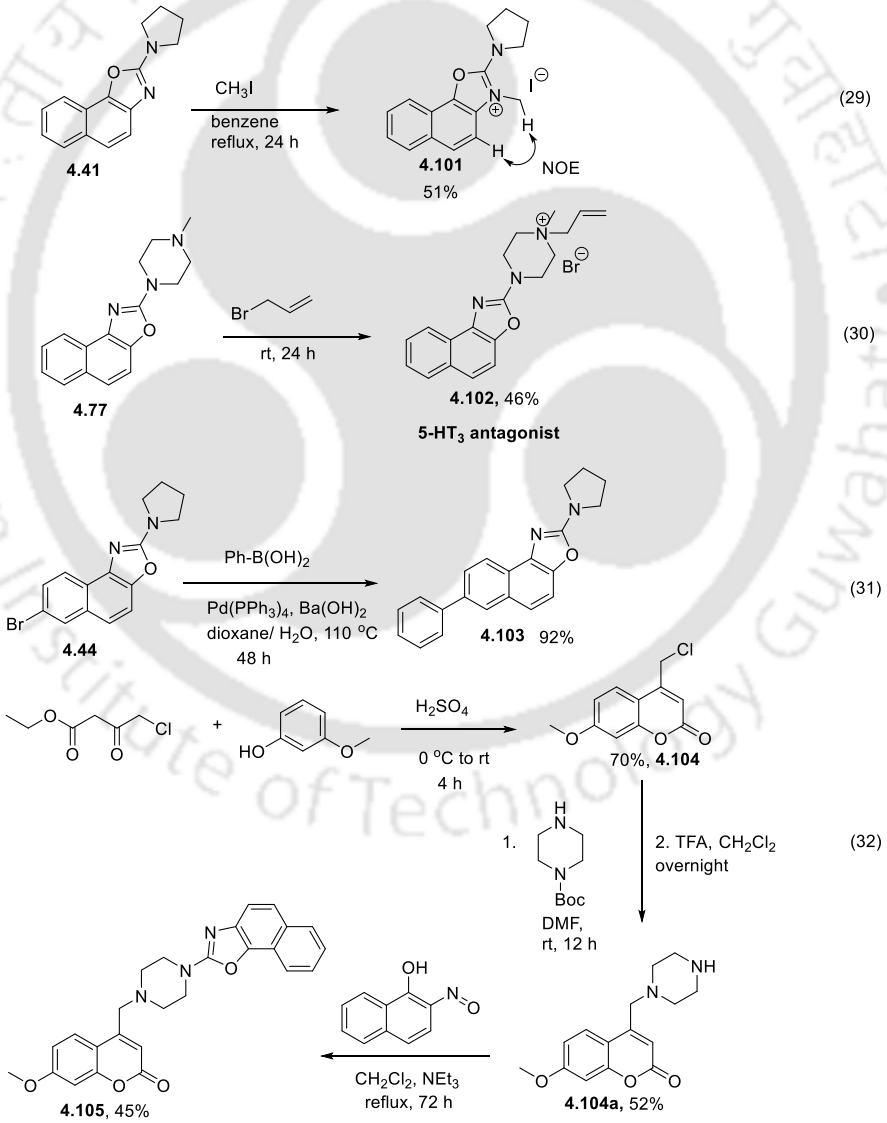


Figure 7: Flow cytometry based analysis of cell cycle of HeLa cells treated with compound **4.100**, **4.98**, **4.95**, **4.97**, **4.99**, **4.94** and **4.96** which showing significant reduction of G2 phase.

increased substantially as compared to untreated cells (**Figure 7**). This study surmises that a higher concentration of the compounds induced cell growth inhibition via cell cycle arrest, which correlates with the results observed in alamarBlue assays and morphology studies.

4.16 Synthetic application:

N-methylation of **4.41** with CH_3I occurred readily to provide corresponding iodide salt **4.101** (**Scheme 13**, eq. 29). The reaction of **4.77** with allylbromide provided bromide salt **4.102**, which is 5-HT_3 antagonist, with 46% yield (**Scheme 13**, eq. 30). Bromo functionality of **4.44** was utilized for Suzuki coupling with phenylboronic acid to obtain the corresponding phenyl substituted oxazole **4.103** with 92% yield (**Scheme 13**, eq. 31).



Scheme 13: Synthetic application of aminonaphthoxazole derivatives.

Anti-HIV analogue **4.105** was synthesized by the reaction of 2-nitroso-1-naphthol and coumarin based amine **4.104a** which was prepared in 3 steps (**Scheme 13**, eq. 32). Compound **4.103** shows absorption band at 266 nm and 345 nm (**Figure 8a**). Emission spectra of **4.103** at 345 nm showed high-intensity band in the range 430- 460 nm (**Figure 8b**)

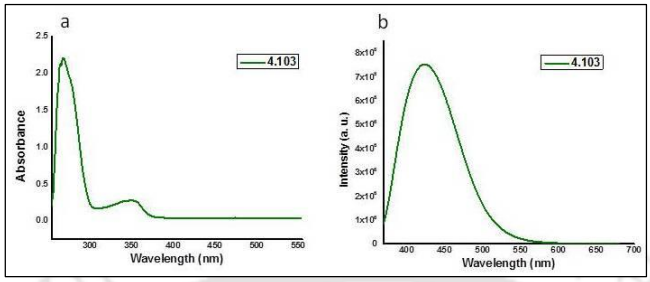


Figure 8: (a) absorption spectra and (b) emission spectra (at λ= 345) nm in a micromolar DMSO solution of **4.103**.

Relative fluorescence quantum yields of the compound **4.103** was measured with respect to quinine sulfate (0.1 M H_2SO_4 solution, Q_f = 0.54). The quantum yields of the compounds of **4.103** is 0.18.

4.17 Conclusion:

A novel method for the synthesis of 2-amino-oxazole derivatives has been developed under simple and mild reaction condition where dichloromethane was used as the C2 source of 2-amino-oxazole. Structurally diverse 2-aminooxazole derivatives have been prepared by using a variety of secondary amines and different nitrosoarenes. Applying this developed method bioactive compounds and their derivatives have been synthesized successfully. The versatility of the protocol has been further proven by efficient spacer free *N*-terminal modification of peptides to afford fluorescent peptides. The modified peptides showed high IC_{50} values and have been successfully used for imaging of HeLa cells and could be used as excellent luminescent probes for rapid staining of cell cytoplasm.

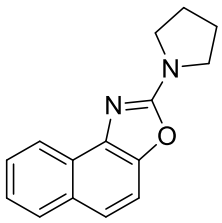
4.18 Experimental Section:

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). Nitrosoarene derivatives were synthesized by literature procedures.[40]

General procedure for the synthesis of 2-aminooxazole derivatives (GP-1):

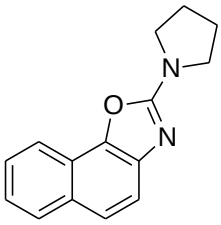
Nitrosoarene (0.23 – 0.40 mmol) was added to a mixture of secondary amine (2 – 4 equiv.) and potassium acetate (2 equiv) in dry dichloromethane (4 – 6 mL) and the reaction mixture was refluxed for 36 – 72 h under argon atmosphere. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under vacuum to obtain brown gummy residue which was purified by column chromatography to afford analytically pure 2-aminooxazole derivatives.

2-(pyrrolidin-1-yl)naphtho[1,2-*d*]oxazole (4.39): According to GP-1: 1-nitroso-2-naphthol (40 mg, 0.23 mmol), pyrrolidine (76 µL, 0.92 mmol) and KOAc (46 mg, 0.46 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **4.39** as a brown solid (40 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 2964, 2927, 2874, 1649, 1618, 1571, 1481, 1345, 1261, 1086, 1025, 796, 726 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.39 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 15.2 Hz, 3H), 7.44 – 7.42 (m, 1H), 3.75 – 3.72 (m, 4H), 2.08 – 2.05 (m,

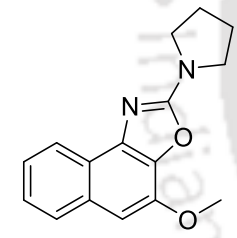


4H). ^{13}C NMR (151 MHz, CDCl3) δ = 161.0, 144.9, 138.3, 131.1, 128.3, 125.6, 124.8, 124.5, 122.4, 120.4, 109.7, 47.7, 25.7.HRMS (ESI) exact mass calculated for $C_{15}H_{15}N_2O^+$ ($[M + H]^+$): 239.1179; Found: 239.1184.

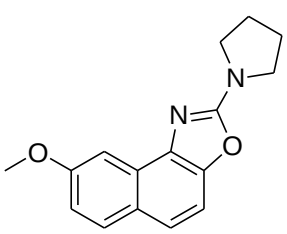
2-(pyrrolidin-1-yl)naphtho[2,1-*d*]oxazole (4.41): According to GP-1: 2-nitroso-1-naphthol (40 mg, 0.23 mmol), pyrrolidine (76 µL, 0.92 mmol) and KOAc (45 mg, 0.46 mmol) were reacted for 36 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **4.41** as a brown solid (44 mg, 80%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2927, 2874, 1649, 1618, 1571, 1406, 1261, 1086, 1024, 797, 726 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.35 – 7.33 (m, 1H), 3.73 – 3.71 (m, 4H), 2.08 – 2.05 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.2, 143.2, 140.1, 129.4, 128.8, 126.4, 124.4, 123.4, 119.9, 118.9, 117.1, 47.7, 25.8. HRMS (ESI) exact mass calculated for $C_{15}H_{15}N_2O^+$ ($[M + H]^+$): 239.1179; Found: 239.1183.



4-methoxy-2-(pyrrolidin-1-yl)naphtho[1,2-*d*]oxazole (4.42): According to GP-1: 3-methoxy-1-nitrosonaphthalen-2-ol (52 mg, 0.25 mmol), pyrrolidine (83 µL, 1.0 mmol) and KOAc (49 mg, 0.50 mmol) were reacted for 48 h in dry DCM (5 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.42** as a brown solid (56 mg, 83%). FTIR (KBr): $\tilde{\nu}$ = 2964, 2882, 2839, 1737, 1653, 1625, 1596, 1467, 1433, 1372, 1231, 1028, 825, 726 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.29 – 8.27 (m, 1H), 7.77 – 7.76 (m, 1H), 7.41 – 7.39 (m, 2H), 6.89 (s, 1H), 4.06 (s, 3H), 3.75 – 3.73 (m, 4H), 2.06 – 2.04 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.4, 144.5, 140.6, 136.1, 132.1, 127.3, 125.3, 123.5, 122.4, 121.1, 99.8, 56.0, 47.9, 25.8. HRMS (ESI) exact mass calculated for $C_{16}H_{17}BrN_2O_2^+$ ($[M + H]^+$): 269.1285; Found: 269.1284.



8-methoxy-2-(pyrrolidin-1-yl)naphtho[1,2-*d*]oxazole (4.43): According to GP-1: 7-methoxy-1-nitrosonaphthalen-2-ol (60 mg, 0.29 mmol), pyrrolidine (96 µL, 1.18 mmol) and KOAc (68 mg, 0.59 mmol) were reacted for 36 h in dry DCM (5 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.43** as a brown gum (53 mg, 67%). FTIR (KBr): $\tilde{\nu}$ = 2958, 2925, 2854, 1651, 1621, 1574, 1461, 1261, 1381, 1161, 1142, 805, 725 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 9.0 Hz, 1H), 7.62 – 7.61 (m,

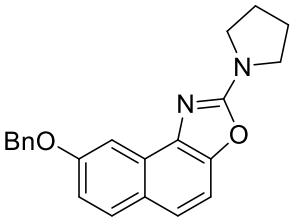


1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.98 (s, 3H), 3.73 – 3.71 (m, 4H), 2.07 – 2.05 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.2, 158.0, 145.7, 138.0, 130.1, 126.7, 126.2, 120.5, 117.6, 107.4, 100.7, 55.8, 47.8, 25.9. HRMS (ESI) exact mass calculated for $C_{16}H_{17}N_2O_2^+$ ($[M + H]^+$): 269.1285; Found: 269.1292.

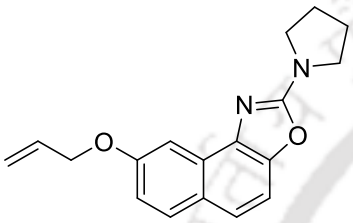
7-bromo-2-(pyrrolidin-1-yl)naphtho[1,2-*d*]oxazole (4.44): According to GP-1: 6-bromo-1-nitrosonaphthalen-2-ol (0.10 g, 0.40 mmol), pyrrolidine (0.13 mL, 1.6 mmol) and KOAc (78 mg, 0.8 mmol) were reacted for 48 h in dry DCM (10 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.44** as a brown solid (76 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 2964, 2923, 2869, 1649, 1613, 1420, 1385, 1339, 1086, 904, 798 cm^{-1}. 1H NMR (600 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.4 Hz, 1H), 8.02 (s, 1H), 7.58 – 7.56 (m, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 3.72 – 3.70 (m, 4H), 2.07 – 2.05 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.5, 145.4, 139.2, 132.4 130.4, 128.8, 124.4, 123.4, 119.3, 118.5, 110.9, 47.8, 25.8. HRMS (ESI) exact mass calculated for $C_{15}H_{14}BrN_2O^+$ ($[M + H]^+$): 317.0284; Found: 317.0288.

8-bromo-2-(pyrrolidin-1-yl)naphtho[1,2-*d*]oxazole (4.45): According to GP-1: 7-bromo-1-nitrosonaphthalen-2-ol (50 mg, 0.20 mmol), pyrrolidine (66 µL, 0.8 mmol) and KOAc (39 mg, 0.40 mmol) were reacted for 48 h in dry DCM (5 mL). Column chromatography (silica; EtOAc : Hexane, 1:15) of the crude gave **4.45** as a colorless solid (38 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2927, 2872, 1649, 1614, 1566, 1434, 1325, 1089, 881, 823, 771 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.45 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.36 – 7.35 (m, 1H), 3.65 – 3.62 (m, 4H), 2.01 – 1.97 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.4, 145.7, 138.3, 130.2, 129.6, 128.0, 125.9, 124.8, 120.2, 120.0, 110.2, 47.8, 25.9. HRMS (ESI) exact mass calculated for $C_{15}H_{14}BrN_2O^+$ ($[M + H]^+$): 317.0284; Found: 317.0284.

8-(benzyloxy)-2-(pyrrolidin-1-yl)naphtho[1,2-*d*]oxazole (4.46): According to GP-1: 7-(benzyloxy)-1-nitrosonaphthalen-2-ol (54 mg, 0.19 mmol), pyrrolidine (63 µL, 0.77 mmol) and KOAc (38 mg, 0.39 mmol) were reacted for 60 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.46** as a brown yellow

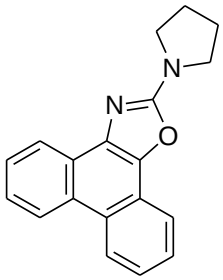


gum (42 mg, 63%). FTIR (KBr): $\tilde{\nu}$ = 2962, 2923, 2853, 1647, 1624, 1596, 1579, 1457, 1261, 1022, 800, 729 cm^{-1}. ^{1}H NMR (400 MHz) δ = 7.79 (d, *J* = 8.8 Hz, 1H), 7.76 – 7.75 (m, 1H), 7.52 – 7.50 (m, 2H), 7.45 – 7.34 (m, 5H), 7.17 (dd, *J* = 9.2, 2.4 Hz, 1H), 5.24 (s, 2H), 3.75 – 3.72 (m, 4H), 2.09 – 2.05 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.2, 157.3, 145.8, 138.1, 137.3, 130.2, 128.8, 128.1, 128.0, 126.8, 126.2, 120.5, 118.0, 107.5, 101.9, 70.4, 47.8, 25.9. . HRMS (ESI) exact mass calculated for $C_{22}H_{21}N_2O_2^+$ ($[M + H]^+$): 345.1598; Found: 345.1607.



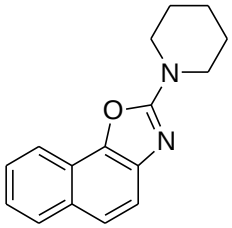
8-(allyloxy)-2-(pyrrolidin-1-yl)naphtho[1,2-*d*]oxazole (4.47): According to GP-1: 7-(allyloxy)-1-nitrosonaphthalen-2-ol (45 mg, 0.19 mmol), pyrrolidine (64 µL, 0.78 mmol) and KOAc (38 mg, 0.39 mmol) were reacted for 72 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **4.47** as a brown gum (45 mg, 78%). FTIR (KBr): $\tilde{\nu}$ = 2924, 2853, 1647, 1624, 1556, 1263, 1021, 822, 741 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 9.0 Hz, 1H), 7.65 – 6.64 (m, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.12 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.18 – 6.13 (m, 1H), 5.51 – 5.48 (m, 1H), 5.33 – 5.31 (m, 1H), 4.74 – 4.73 (m, 2H), 3.74 – 3.72 (m, 4H), 2.08 – 2.06 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.6, 157.0, 145.4, 136.8, 133.4, 130.2, 126.7, 125.7, 120.9, 118.1, 117.9, 107.4, 101.8, 69.2, 48.0, 25.8. HRMS (ESI) exact mass calculated for $C_{18}H_{19}N_2O_2^+$ ($[M + H]^+$): 295.1441; Found: 295.1443.

2-(pyrrolidin-1-yl)phenanthro[9,10-*d*]oxazole (4.48): According to GP-1: 10-nitrosophenanthren-9-ol (60 mg, 0.27 mmol), pyrrolidine (89 µL, 1.08 mmol) and KOAc (53 mg, 0.54 mmol) were reacted for 72 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.48** as a colorless solid (54 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 3056, 2955, 2942, 1646, 1609, 1355, 1261, 1097, 1028, 963, 899, 803, 752, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72 – 8.70 (m, 2H), 8.46 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.60 (m, 3H), 7.55 –7.51 (m, 1H), 3.78 – 3.75 (m, 4H), 2.08 – 2.06 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.3, 140.7, 136.2, 128.6, 127.0, 126.9, 125.9, 125.4, 124.1, 123.7, 123.4, 123.0, 121.2, 119.3, 47.8, 25.9. Total count of ^{13}C is less than expected due to the merging of signal in the

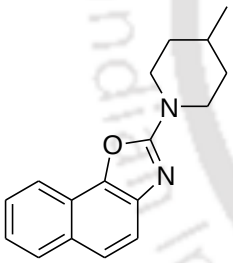


aromatic region. HRMS (ESI) exact mass calculated for $C_{19}H_{17}N_2O^+$ ([M + H]$^+$): 289.1335; Found: 289.1338.

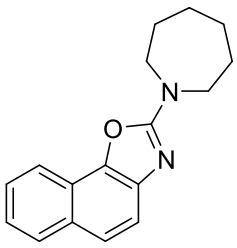
2-(piperidin-1-yl)naphtho[2,1-*d*]oxazole (4.50): According to GP-1: 2-nitroso-1-naphthol (70 mg, 0.40 mmol), piperidine (0.16 mL, 1.62 mmol) and KOAc (79 mg, 0.81 mmol) were reacted for 36 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.50** as a colorless solid (75 mg, 74%). FTIR (KBr): $\tilde{\nu}$ = 3059, 2984, 2936, 2857, 1940, 1633, 1562, 1520, 1451, 1289, 1253, 1024, 859, 806, 748, 683, 422 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.51 – 7.49 (m, 1H), 7.36 – 7.33 (m, 1H), 3.73 – 3.72 (m, 4H), 1.74 – 1.69 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.6, 142.8, 139.7, 129.5, 128.8, 126.4, 124.4, 123.5, 119.8, 118.8, 117.0, 46.9, 25.4, 24.2. HRMS (ESI) exact mass calculated for $C_{16}H_{17}N_2O^+$ ([M + H]$^+$): 253.1335; Found: 253.1334.



2-(4-methylpiperidin-1-yl)naphtho[2,1-*d*]oxazole (4.51): According to GP-1: 2-nitroso-1-naphthol (70 mg, 0.40 mmol), 4-methylpiperidine (0.19 mL, 1.62 mmol) and KOAc (79 mg, 0.81 mmol) were reacted for 36 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.51** as a colorless solid (68 mg, 63%). FTIR (KBr): $\tilde{\nu}$ = 2955, 2923, 2850, 1625, 1563, 1455, 1369, 1290, 1260, 1086, 806 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.50 (m, 1H), 7.36 – 7.34 (m, 1H), 4.38 – 4.35 (m, 2H), 3.14 – 3.10 (m, 2H), 1.80 – 1.78 (m, 2H), 1.67 – 1.64 (m, 1H), 1.37 – 1.32 (m, 2H), 1.01 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.7, 142.9, 139.8, 129.5, 128.8, 126.5, 124.5, 123.5, 119.8, 118.9, 117.1, 46.4, 33.6, 30.8, 22.1. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2O^+$ ([M + H]$^+$): 267.1492; Found: 267.1489.

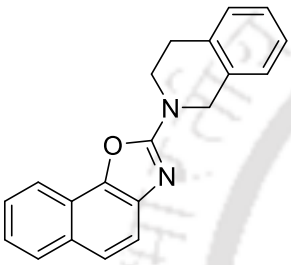


2-(azepan-1-yl)naphtho[2,1-*d*]oxazole (4.52): According to GP-1: 2-nitroso-1-naphthol (70 mg, 0.40 mmol), azepane (0.18 mL, 1.62 mmol) and KOAc (79 mg, 0.81 mmol) were reacted for 36 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.52** as a colorless solid (71 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 2963,



2925, 2851, 1627, 1564, 1289, 1260, 1095, 1024, 804, 724 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.34 – 7.32 (m, 1H), 3.78 – 3.74 (m, 4H), 1.90 – 1.87 (m, 4H), 1.63 – 1.62 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.8, 143.0, 140.2, 129.3, 128.8, 126.4, 124.3, 123.3, 119.8, 118.8, 117.0, 48.3, 28.5, 27.7. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2O^+$ ($[M + H]^+$): 267.1492; Found: 267.1492.

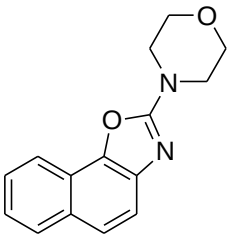
2-(3,4-dihydroisoquinolin-2(1H)-yl)naphtho[2,1-*d*]oxazole (4.53): According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), tetrahydroisoquinoline (0.17 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 60 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.53** as a colorless solid (51 mg, 49%). FTIR (KBr): $\tilde{\nu}$ = 2958, 2922, 2852, 1627, 1564, 1457, 1261, 1087, 749 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.66 (m, 1H), 7.61 – 7.60 (m, 1H), 7.53 – 7.51 (m, 1H), 7.37 – 7.35 (m, 1H), 7.24 – 7.18 (m, 4H), 4.92 (s, 2H), 4.03 – 4.01 (m, 2H), 3.04 (t, *J* = 6.0 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.1, 143.1, 139.6, 134.2, 132.5, 129.6, 129.0, 128.8, 127.0, 126.7, 126.57, 126.56, 124.6, 123.6, 119.8, 118.9, 117.1, 47.4, 43.4, 28.7. HRMS (ESI) exact mass calculated for $C_{20}H_{17}N_2O^+$ ($[M + H]^+$): 301.1335; Found: 301.1336.



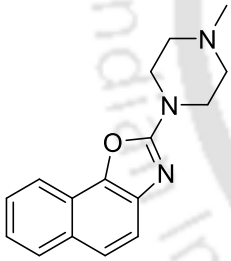
2-(octahydroisoquinolin-2(1*H*)-yl)naphtho[2,1-*d*]oxazole (4.54): According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), perhydroisoquinoline (0.20 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 72 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:20) of the crude gave **4.54** as a colorless solid (68 mg, 64%). FTIR (KBr): $\tilde{\nu}$ = 2924, 2851, 1646, 1565, 1297, 1248, 1210, 1153, 814, 746 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.66 –7.64 (m, 1H), 7.59 – 7.58 (m, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.35 – 7.33 (m, 1H), 4.42 – 4.39 (m, 1H), 4.25 – 4.23 (m, 1H), 3.10 –3.06 (m, 1H), 2.72 – 2.68 (m, 1H), 1.78 – 1.75 (m, 2H), 1.70 – 1.66 (m, 3H), 1.43 – 1.36 (m, 1H), 1.32 – 1.29 (m, 3H), 1.16 – 1.15 (m, 1H), 1.05 – 0.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.4, 142.8, 139.7, 129.4, 128.6, 126.2, 124.2, 123.2, 119.7,

118.7, 116.9, 52.0, 46.7, 41.5, 41.4, 32.9, 32.3, 29.9, 26.2, 25.8. HRMS (ESI) exact mass calculated for $C_{20}H_{23}N_2O^+$ ([M + H]$^+$): 307.1805; Found: 307.1803

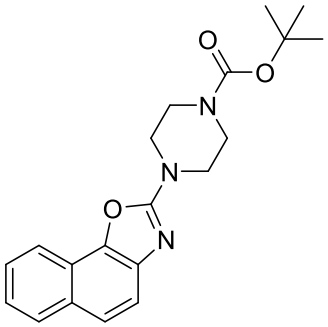
2-morpholinonaphtho[2,1-*d*]oxazole (4.55): According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), morpholine (0.12 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 72 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:4) of the crude gave **4.55** as a brown gum (37 mg, 42%). FTIR (KBr): $\tilde{\nu}$ = 2962, 2920, 2863, 1610, 1562, 1287, 1245, 1118, 894, 812, 736 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.69 – 7.68 (m, 1H), 7.60 – 7.58 (m, 1H), 7.54 – 7.52 (m, 1H), 7.40 – 7.37 (m, 1H), 3.88 – 3.87 (m, 4H), 3.78 – 3.76 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.3, 143.2, 139.2, 129.8, 128.9, 126.7, 124.8, 123.9, 119.9, 118.9, 117.22, 66.4, 46.1. HRMS (ESI) exact mass calculated for $C_{15}H_{15}N_2O_2^+$ ([M + H]$^+$): 255.1128; Found: 255.1124.



2-(4-methylpiperazin-1-yl)naphtho[2,1-d]oxazole (4.56): According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), 1-methylpiperazine (0.15 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 72 h in dry DCM (6 mL). Column chromatography (silica; MeOH : DCM, 1:20) of the crude gave **4.56** as a brown gum (48 mg, 52%). FTIR (KBr): $\tilde{\nu}$ = 2960, 2922, 2849, 1644, 1619, 1471, 1366, 1262, 1026, 799, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.39 – 7.35 (m, 1H), 3.82 – 3.79 (m, 4H), 2.59 – 2.57 (m, 4H), 2.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.4, 143.1, 139.5, 129.7, 128.9, 126.6, 124.7, 123.8, 119.9, 118.9, 117.2, 54.4, 46.5, 45.9. HRMS (ESI) exact mass calculated for $C_{16}H_{18}N_3O^+$ ([M + H]$^+$): 268.1444; Found: 268.1445.

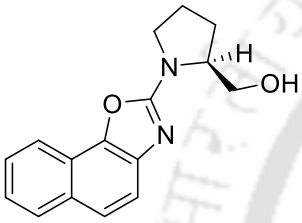


***tert*-butyl 4-(naphtho[2,1-*d*]oxazol-2-yl)piperazine-1-carboxylate (4.57)**: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), 1-Boc-piperazine (0.26 g, 0.94 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 72 h in dry DCM (4 mL). Column chromatography (neutral allumina; EtOAc : Hexane, 1:4) of the crude gave **4.57** as a brown solid (43 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 3054, 2970, 2923, 2854, 1697, 1628, 1565, 1364, 1167, 747 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* =



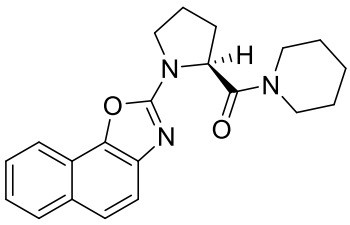
8.5 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.55 – 7.52 (t, *J* = 8.0 Hz, 1H), 7.40 – 7.37 (m, 1H), 3.76 – 3.74 (m, 4H), 3.63 – 3.61 (m, 4H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.2, 154.8, 143.2, 139.3, 129.8, 128.9, 126.7, 124.8, 123.9, 119.9, 118.9, 117.2, 80.7, 45.9, 43.3, 28.6. HRMS (ESI) exact mass calculated for $C_{20}H_{24}N_3O_3^+$ ([M + H]$^+$): 354.1812; Found: 354.1818.

(*S*)-(1-(naphtho[2,1-*d*]oxazol-2-yl)pyrrolidin-2-yl)methanol (4.58): According to GP-1: 2-nitroso-1-naphthol (50 mg, 0.29 mmol), (*S*)-prolinol (0.11 mL, 1.2 mmol) and KOAc (57 mg, 0.58 mmol) were reacted for 72 h in dry DCM (5 mL). Column chromatography (silica; EtOAc : Hexane: DCM, 10:10:1) of the crude gave **4.58** as a colorless solid (34 mg, 44%). (KBr): $\tilde{\nu}$ = 3.63, 2952, 2924, 2854, 1628, 1566, 1457, 1288, 1258, 1050, 808, 728 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.98 – 7.96 (m, 1H), 7.90 – 7.88 (m, 1H), 7.70 – 7.67 (m, 1H), 7.54 – 7.48 (m, 2H), 7.38 – 7.34 (m, 1H), 4.21 – 4.18 (m, 1H), 3.84 – 3.67 (m, 4H), 2.25 – 2.09 (m, 3H), 2.07 – 2.02 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ = 162.5, 143.8, 139.9, 130.9, 129.7, 127.7, 125.7, 124.7, 120.9, 119.5, 117.1, 63.6, 62.4, 49.8, 29.4, 24.9. HRMS (ESI) exact mass calculated for $C_{16}H_{17}N_2O_2^+$ ([M + H]$^+$): 269.1285; Found: 269.1287.



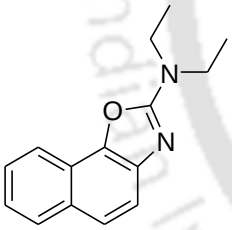
methyl naphtho[2,1-*d*]oxazol-2-ylprolinate (4.59): 2-nitroso-1-naphthol (50 mg, 0.29 mmol), L-proline methyl ester hydrochloride (0.19 g, 1.16 mmol) and Et_3N (0.20 mL, 1.44 mmol) were reacted for 72 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:1) of the crude gave **4.59** as a colorless solid (43 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 2921, 2853, 1741, 1627, 1567, 1513, 1450, 1097, 810, 743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.38 – 7.34 (m, 1H), 4.75 – 4.72 (m, 1H), 4.00 – 3.95 (m, 1H), 3.87 – 3.78 (m, 1H), 3.78 (s, 3H), 2.45 – 2.40 (m, 1H), 2.27 – 2.21 (m, 1H), 2.18 – 2.10 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.1, 160.5, 143.5, 139.8, 129.6, 128.8, 126.5, 124.6, 123.7, 119.9, 119.0, 117.4, 60.6, 52.7, 48.4, 31.1, 24.3. HRMS (ESI) exact mass calculated for $C_{17}H_{17}N_2O_3^+$ ([M + H]$^+$): 297.1234; Found: 297.1239.

(1-(naphtho[2,1-*d*]oxazol-2-yl)pyrrolidin-2-yl)(piperidin-1-yl)methanone (4.60):

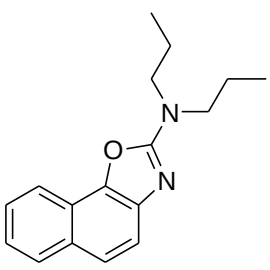


According to GP-1: 2-nitroso-1-naphthol (30 mg, 0.17 mmol), (*S*)-1-prolylpiperidine (63 mg, 0.35 mmol) and KOAc (34 mg, 0.35 mmol) were reacted for 72 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:1) of the crude gave **4.60** as a brown solid (37 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 2924, 2849, 1760, 1634, 1563, 1448, 1101, 1021, 806, 750 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.35 – 7.31 (m, 1H), 5.02 (dd, *J* = 8.0, 3.0 Hz, 1H), 4.04 – 4.00 (m, 1H), 3.89 – 3.84 (m, 1H), 3.68 – 3.61 (m, 2H), 3.56 – 3.52 (m, 2H), 2.39 – 2.33 (m, 1H), 2.26 – 2.20 (m, 1H), 2.12 – 2.04 (m, 2H), 1.86 – 1.81 (m, 2H), 1.77 – 1.72 (m, 2H), 1.68 – 1.62 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.0, 160.7, 143.3, 140.1, 129.5, 128.8, 126.3, 124.3, 123.3, 119.9, 118.8, 117.4, 58.60, 58.57, 48.5, 46.8, 43.7, 30.8, 26.8, 25.8, 24.8, 24.1. HRMS (ESI) exact mass calculated for $C_{21}H_{24}N_3O_2^+$ ($[M + H]^+$): 350.1863; Found: 350.1864.

***N,N*-diethylnaphtho[2,1-*d*]oxazol-2-amine (4.61)**: According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), diethylamine (0.14 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 60 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:15) of the crude gave **4.61** as a yellow gum (65 mg, 78%). FTIR (KBr): $\tilde{\nu}$ = 3063, 2958, 2927, 2858, 1629, 1566, 1522, 1408, 1373, 1290, 1259, 808, 748 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.65 (m, 1H), 7.60 – 7.59 (m, 1H), 7.52 – 7.49 (m, 1H), 7.35 – 7.33 (m, 1H), 3.67 (q, *J* = 7.2 Hz, 4H), 1.34 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.4, 143.0, 140.1, 129.3, 128.8, 126.4, 124.3, 123.3, 119.8, 118.8, 117.0, 43.2, 13.6. HRMS (ESI) exact mass calculated for $C_{15}H_{17}N_2O^+$ ($[M + H]^+$): 241.1335; Found: 241.1335.

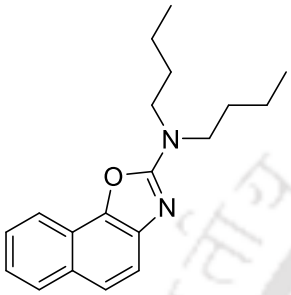


***N,N*-dipropylnaphtho[2,1-*d*]oxazol-2-amine (4.62):** According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), dipropylamine (0.19 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 48 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:30) of the crude gave **4.62** as a brown gum (71 mg, 76%). FTIR (KBr): $\tilde{\nu}$ = 3060, 2963, 2929, 2873, 1628, 1566,

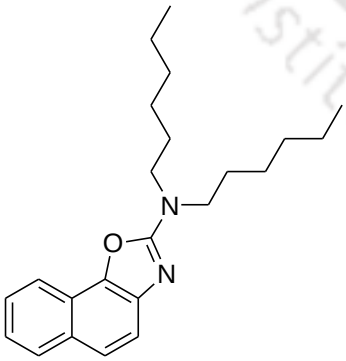


1522, 1291, 1244, 1150, 809, 747 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.64 (m, 1H), 7.61 – 7.59 (m, 1H), 7.52 – 7.49 (m, 1H), 7.35 – 7.32 (m, 1H), 3.57 – 3.55 (m, 4H), 1.81 – 1.74 (m, 4H), 1.01 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.8, 142.8, 140.1, 129.3, 128.8, 126.4, 124.3, 123.3, 119.8, 118.8, 117.0, 50.7, 21.4, 11.5. HRMS (ESI) exact mass calculated for $C_{17}H_{21}N_2O^+$ ($[M + H]^+$): 269.1648; Found: 269.1641.

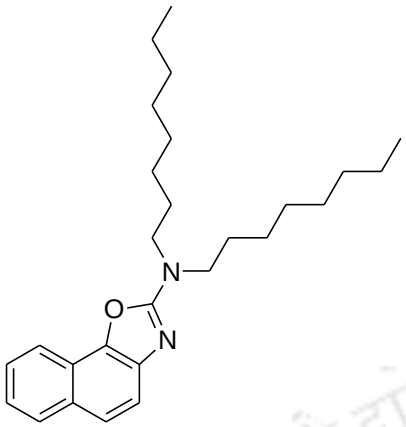
***N*, *N*-dibutylnaphtho[2,1-*d*]oxazol-2-amine (4.63)**: According to GP-1: 2-nitroso-1-naphthol (70 mg, 0.40 mmol), di-butylamine (0.27 mL, 1.62 mmol) and KOAc (79 mg, 0.81 mmol) were reacted for 72 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:15) of the crude gave **4.63** as a colorless solid (92 mg, 77%). FTIR (KBr): $\tilde{\nu}$ = 3061, 2959, 2931, 2870, 1628, 1565, 1522, 1371, 1257, 1109, 809, 747, 728 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.60 – 7.59 (m, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.35 – 7.33 (m, 1H), 3.56 (t, *J* = 7.8 Hz,, 4H), 1.75 –1.70 (m, 4H), 1.47 – 1.40 (m, 4H), 1.00 (t, *J* = 7.8 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.8, 142.8, 140.2, 129.3, 128.8, 126.4, 124.3, 123.3, 119.8, 118.8, 117.1, 48.6, 30.3, 20.3, 14.1. HRMS (ESI) exact mass calculated for $C_{19}H_{25}N_2O^+$ ($[M + H]^+$): 297.1961; Found: 297.1964.



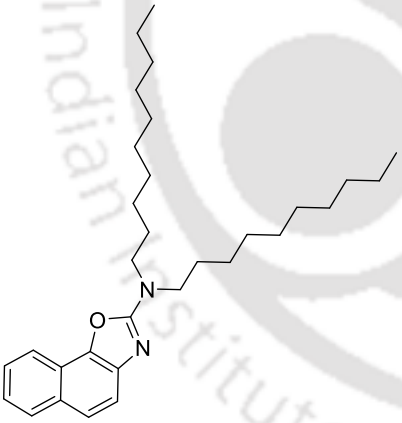
***N*,*N*-dihexylnaphtho[2,1-*d*]oxazol-2-amine (4.64):** According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), dihexylamine (0.32 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 60 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:15) of the crude gave **4.64** as a yellow oil (67 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 2951, 2924, 2854, 1647, 1628, 1573, 1459, 1103, 877, 747 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.64 (m, 1H), 7.61 – 7.59 (m, 1H), 7.52 – 7.49 (m, 1H), 7.35 – 7.33 (t, *J* = 7.8 Hz, 1H), 3.60 – 3.57 (m, 4H), 1.76 – 1.71 (m, 4H), 1.41 – 1.34 (m, 12H), 0.93 – 0.90 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.8, 142.9, 140.2, 129.3, 128.8, 126.4, 124.3, 123.3, 119.8, 118.8, 117.1, 49.0, 31.8, 28.2, 26.7, 22.8, 14.2. HRMS (ESI) exact mass calculated for $C_{23}H_{33}N_2O^+$ ($[M + H]^+$): 353.2587; Found: 353.2581.

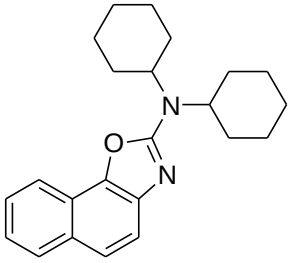


***N,N*-dioctylnaphtho[2,1-*d*]oxazol-2-amine (4.65):** According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), dioctylamine (0.42 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 72 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:25) of the crude gave **4.65** as a brown gum (68 mg, 64%). FTIR (KBr): $\tilde{\nu}$ = 3062, 2955, 2926, 2855, 1628, 1566, 1455, 1291, 1258, 1113, 808, 727 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.0 (d, *J* = 8.4 Hz,, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.66 – 7.65(m, 1H), 7.62 – 7.60 (m, 1H), 7.52 – 7.49 (m, 1H), 7.35 – 7.33 (m, 1H), 3.60 – 3.57 (m, 4H), 1.75 – 1.71 (m, 4H), 1.40 – 1.36 (m, 8H), 1.31 – 1.29 (m, 12H), 0.89 (t, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.8, 142.9, 140.2, 129.3, 128.8, 126.3, 124.2, 123.2, 119.8, 118.8, 117.1, 48.9, 32.0, 29.6, 29.4, 28.2, 27.0, 22.8, 14.2. HRMS (ESI) exact mass calculated for $C_{27}H_{41}N_2O^+$ ($[M + H]^+$): 409.3213; Found: 409.3213.



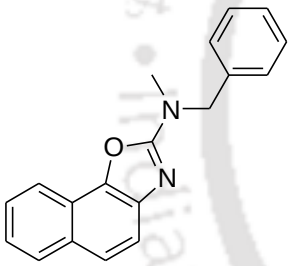
***N,N*-didecylnaphtho[2,1-*d*]oxazol-2-amine (4.66):** According to GP-1: 2-nitroso-1-naphthol (50 mg, 0.29 mmol), didecylamine (0.43 mL, 1.2 mmol) and KOAc (57 mg, 0.58 mmol) were reacted for 72 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:40) of the crude gave **4.66** as a yellow oil (90 mg, 67%). FTIR (KBr): $\tilde{\nu}$ = 3062, 2955, 2925, 2854, 1628, 1566, 1455, 1374, 1290, 1003, 808, 726 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.64 (m, 1H), 7.60 – 7.58 (m, 1H), 7.52 – 7.48 (m, 1H), 7.36 – 7.32 (m, 1H), 3.60 – 3.56 (m, 4H), 1.75 – 1.72 (m, 4H), 1.38 – 1.37 (m, 7H), 1.28 – 1.26 (m, 21H), 0.88 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.9, 142.9, 140.2, 129.3, 128.8, 126.4, 124.3, 123.3, 119.9, 118.8, 117.1, 49.0, 32.1, 29.81, 29.79, 29.6, 29.5, 28.2, 27.1, 22.9, 14.3. HRMS (ESI) exact mass calculated for $C_{31}H_{49}N_2O^+$ ($[M + H]^+$): 465.3839; Found: 465.3839.



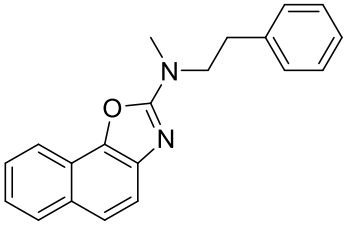


***N*,*N*-dicyclohexylnaphtho[2,1-*d*]oxazol-2-amine (4.67):** According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), dicyclohexylamine (0.27 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 72 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:20) of the crude gave **4.67** as a colorless solid (64 mg, 53%). FTIR (KBr): $\tilde{\nu}$ = 2962, 2924, 2852, 1649, 1582, 1566, 1434, 1262, 1090, 1018, 821, 771, 724 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.53 – 7.49 (m, 1H), 7.36 – 7.32 (m, 1H), 3.86 – 3.80 (m, 2H), 2.06 – 1.94 (m, 4H), 1.91 – 1.81 (m, 8H), 1.75 – 1.72 (m, 2H), 1.50 – 1.41 (m, 4H), 1.31 – 1.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.5, 142.6, 138.9, 129.3, 128.9, 126.5, 124.3, 123.4, 119.7, 118.8, 116.8, 57.3, 31.4, 26.4, 25.8. HRMS (ESI) exact mass calculated for $C_{23}H_{29}N_2O^+$ ($[M + H]^+$): 349.2274; Found: 349.2271.

***N*-benzyl-*N*-methylnaphtho[2,1-*d*]oxazol-2-amine (4.68):** According to GP-1: 2-nitroso-1-naphthol (60 mg, 0.35 mmol), *N*-benzylmethylamine (0.18 mL, 1.4 mmol) and KOAc (68 mg, 0.69 mmol) were reacted for 60 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:15) of the crude gave **4.68** as a violet solid (61 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 3026, 2961, 2924, 2853, 1631, 1565, 1453, 1409, 1261, 1094, 818, 723, 690 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.69 (m, 1H), 7.64 – 7.62 (m, 1H), 7.54 – 7.51 (m, 1H), 7.38 – 7.35 (m, 5H), 7.33 – 7.31 (m, 1H), 4.85 (s, 2H), 3.21 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 163.1, 143.2, 140.0, 136.7, 129.6, 129.0, 128.8, 128.0, 126.6, 124.6, 123.6, 119.9, 118.9, 117.2, 54.3, 35.5. Total count of ^{13}C is less than expected due to the merging of signal in the aromatic region. HRMS (ESI) exact mass calculated for $C_{19}H_{17}N_2O^+$ ($[M + H]^+$): 289.1335; Found: 289.1340.

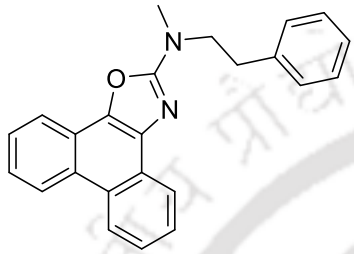


***N*-methyl-*N*-phenethylnaphtho[2,1-*d*]oxazol-2-amine (4.70):** According to GP-1: 2-nitroso-1-naphthol (45 mg, 0.26 mmol), *N*-methyl-phenylethylamine (0.14 g, 1.04 mmol) and KOAc (51 mg, 0.52 mmol) were reacted for 72 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:8) of the crude gave **4.70** as a brown solid (30 mg, 38%). FTIR (KBr): $\tilde{\nu}$ = ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz,

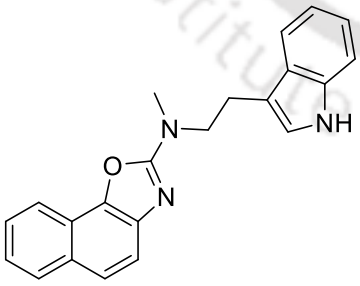


1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.31 – 7.28 (m, 4H), 7.22 – 7.20 (m, 1H), 3.87 – 3.85 (m, 2H), 3.19 (s, 3H), 3.07 – 3.04 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.7, 143.2, 140.0, 138.9, 129.5, 129.1, 128.9, 128.8, 126.7, 126.5, 124.5, 123.5, 119.9, 118.9, 117.2, 52.7, 36.7, 34.4. HRMS (ESI) exact mass calculated for $C_{20}H_{19}N_2O^+$ ($[M + H]^+$): 303.1492; Found: 303.1491.

***N*-methyl-*N*-phenethylphenanthro[9,10-*d*]oxazol-2-amine (4.71)**: According to GP-110-nitrosophenanthren-9-ol (40 mg, 0.17 mmol), *N*-methyl-phenylethylamine (90 mg, 0.67 mmol) and KOAc (33 mg, 0.52 mmol) were reacted for 90 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:3) of the crude gave **4.71** as a yellow solid (17 mg, 28%). FTIR (KBr): $\tilde{\nu}$ = 2974, 2926, 2855, 1697, 1512, 1365, 1250, 1168, 699 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.72 (d, *J* = 8.4 Hz, 2H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.66 – 7.63 (m, 2H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.32 – 7.31 (m, 4H), 7.22 – 7.20 (m, 1H), 3.92 (t, *J* = 7.2 Hz, 2H), 3.28 (s, 3H), 3.10 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.5, 140.7, 138.9, 129.1, 128.85, 128.79, 128.7, 127.1, 127.0, 127.0, 126.7, 125.6, 124.3, 123.8, 123.5, 123.1, 121.1, 119.3, 52.8, 36.8, 34.3. Total count of ^{13}C is less than expected due to the merging of signal in the aromatic region. HRMS (ESI) exact mass calculated for $C_{24}H_{21}N_2O^+$ ($[M + H]^+$): 353.1648; Found: 353.1686.

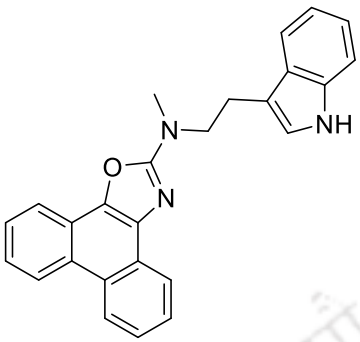


***N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-methylnaphtho[2,1-*d*]oxazol-2-amine (4.72)**: According to GP-1: 2-nitroso-1-naphthol (40 mg, 0.23 mmol), *N*-methyltryptamine (0.16 g, 1.62 mmol) and KOAc (79 mg, 0.92 mmol) were reacted for 96 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:3) of the crude gave **4.72** as a colorless solid (36 mg, 46%). FTIR (KBr): $\tilde{\nu}$ = 3243, 2854, 2256, 1636, 1457, 1367, 1100, 1010, 746, 700 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.90 – 7.86 (m, 2H), 7.75 – 7.74 (m, 1H), 7.67 – 7.65 (m, 1H), 7.61 – 7.58 (m, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.23 – 7.17 (m, 2H), 7.05 (s, 1H), 3.97 – 3.93 (m, 2H), 3.23 (s, 3H), 3.22 – 3.19 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.7, 143.1, 139.8, 136.5, 129.4, 128.7, 127.5, 126.4, 124.4, 123.4, 122.3, 122.2, 119.8, 119.6, 118.8, 118.7, 117.0, 112.9,



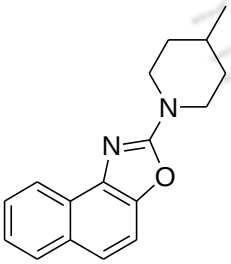
111.4, 51.4, 36.5, 23.9. HRMS (ESI) exact mass calculated for $C_{22}H_{20}N_3O^+$ ([M + H]$^+$): 342.1601; Found: 342.1602.

***N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-methylphenanthro[9,10-*d*]oxazol-2-amine (4.73)**:



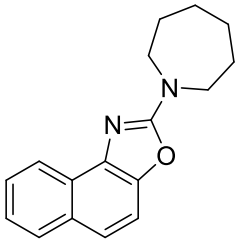
According to GP-1: According to GP-1: 10-nitrosophenanthren-9-ol (40 mg, 0.17 mmol), *N*-methyltryptamine (0.12 g, 0.67 mmol) and KOAc (33 mg, 0.34 mmol) were reacted for 96 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **4.73** as a red solid (24 mg, 36%). FTIR (KBr): $\tilde{\nu}$ = 2964, 2929, 2083, 1636, 1261, 1093, 1022, 800, 746 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.72 (dd, *J* = 8.5, 4.0 Hz, 2H), 8.47 – 8.45 (m, 1H), 8.00 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.83 – 7.82 (m, 1H), 7.70 – 7.67 (m, 1H), 7.65 – 7.60 (m, 2H), 7.56 – 7.52 (m, 1H), 7.36 – 7.34 (m, 1H), 7.23 – 7.21 (m, 2H), 7.08 (s, 1H), 4.00 (t, *J* = 7.5 Hz, 2H), 3.31 (s, 3H), 3.25 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.9, 140.7, 136.6, 136.3, 128.7, 127.7, 127.1, 126.9, 126.0, 125.5, 124.2, 123.8, 123.5, 123.1, 122.4, 122.3, 121.2, 119.7, 119.4, 119.0, 113.2, 111.5, 51.5, 36.6, 23.9. Total count of ^{13}C is less than expected due to the merging of signal in the aromatic region. HRMS (ESI) exact mass calculated for $C_{26}H_{22}N_3O^+$ ([M + H]$^+$): 392.1757; Found: 392.1758.

2-(4-methylpiperidin-1-yl)naphtho[1,2-*d*]oxazole (4.75): According to GP-1: 1-nitroso-2-naphthol (70 mg, 0.40 mmol), 4-methylpiperidine (0.19 mL, 1.62 mmol) and KOAc (79 mg, 0.81 mmol) were reacted for 48 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:20) of the crude gave **4.75** as a brown solid (88 mg, 82%). FTIR (KBr): $\tilde{\nu}$ = 2948, 2925, 2836, 2811, 1636, 1598, 1571, 1453, 1413, 1347, 1259, 878, 767, 731 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.54 – 7.52 (m, 1H), 7.50 – 7.48 (mz, 2H), 7.44 –7.42 (m, 1H), 4.39 – 4.37 (m, 2H), 3.13 – 3.09 (m, 2H), 1.80 – 1.78 (m, 2H), 1.67 – 1.62 (m, 1H), 1.37 – 1.29 (m, 2H), 1.01 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.8, 144.9, 138.6, 131.3, 128.5, 125.8, 125.1, 124.6, 122.4, 120.7, 109.9, 46.4, 33.7, 30.8, 22.1. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2O^+$ ([M + H]$^+$): 267.1492; Found: 267.1497.

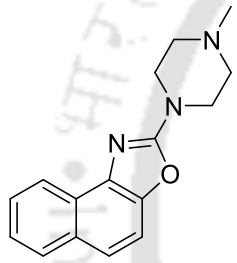


2-(azepan-1-yl)naphtho[1,2-*d*]oxazole (4.76): According to GP-1: 1-nitroso-2-naphthol (70 mg, 0.40 mmol), azepane (0.18 mL, 1.62 mmol) and KOAc (79 mg, 0.81 mmol) were

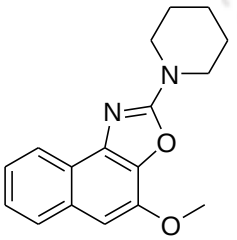
reacted for 36 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:20) of the crude gave **4.76** as a brown solid (76 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 2922, 2849, 1644, 1611, 1568, 1443, 1407, 1365, 1273, 998, 802, 722 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.37 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.44 – 7.42 (m, 1H), 3.78 (t, *J* = 6.0 Hz, 4H), 1.90 – 1.86 (m, 4H), 1.64 – 1.63 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.9, 145.0, 139.0, 131.3, 128.5, 125.6, 125.0, 124.6, 122.6, 120.1, 109.8, 48.3, 28.6, 27.8. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2O^+$ ($[M + H]^+$): 267.1492; Found: 267.1494.



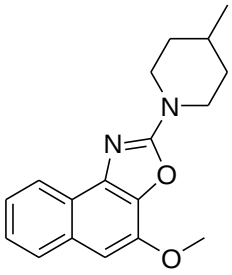
2-(4-methylpiperazin-1-yl)naphtho[1,2-*d*]oxazole (4.77): According to GP-1: 1-nitrosonaphthalen-2-ol (50 mg, 0.29 mmol), *N*-methyl-pipirazine (0.13 mL, 1.2 mmol) and KOAc (50 mg, 0.58 mmol) were reacted for 72 h in dry DCM (5 mL). Column chromatography (silica; EtOAc : MeOH, 10:1) of the crude gave **4.77** as a brown gum (27 mg, 40%). FTIR (KBr): $\tilde{\nu}$ = 2962, 2925, 2853, 1643, 1452, 1406, 1366, 1262, 1022, 798, 746 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.32 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.49 (m, 3H), 7.45 – 7.43 (m, 1H), 3.81 – 3.79 (m, 4H), 2.58 – 2.57 (m, 4H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.5, 145.1, 138.4, 131.3, 128.6, 125.9, 125.3, 124.8, 122.4, 121.1, 109.9, 54.5, 46.5, 45.9. HRMS (ESI) exact mass calculated for $C_{16}H_{18}N_3O^+$ ($[M + H]^+$): 268.1444; Found: 268.1444.



4-methoxy-2-(piperidin-1-yl)naphtho[1,2-*d*]oxazole (4.78): According to GP-1: 3-methoxy-1-nitrosonaphthalen-2-ol (50 mg, 0.25 mmol), piperidine (0.10 mL, 0.98 mmol) and KOAc (48 mg, 0.49 mmol) were reacted for 48 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:15) of the crude gave **4.78** as a colorless solid (46 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 2960, 2924, 2854, 1647, 1614, 1572, 1387, 1261, 1097, 1020, 804, 726 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.25 – 8.24 (m, 1H), 7.77 – 7.76 (m, 1H), 7.41 – 7.39 (m, 2H), 6.90 (s, 1H), 4.06 (s, 3H), 3.74 – 3.74 (m, 4H), 1.72 – 1.71 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.8, 144.5, 140.3, 135.8, 132.1, 127.3, 125.3, 123.6, 122.4, 121.2, 100.0, 56.0, 47.0, 25.5, 24.5. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2O_2^+$ ($[M + H]^+$): 283.1441; Found: 283.1443.

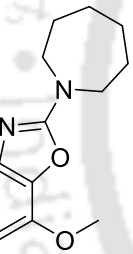


4-methoxy-2-(4-methylpiperidin-1-yl)naphtho[1,2-*d*]oxazole (4.79): According to GP-1:

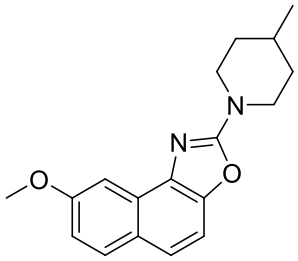


3-methoxy-1-nitrosonaphthalen-2-ol (50 mg, 0.25 mmol), 4-methylpiperidine (0.12 mL, 1.0 mmol) and KOAc (48 mg, 0.49 mmol) were reacted for 48 h in dry DCM (5 mL). Column chromatography (silica; EtOAc : Hexane, 1:15) of the crude gave **4.79** as a colorless solid (51 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 3066, 3012, 2919, 2848, 1887, 1668, 1643, 1581, 1472, 1374, 1256, 1026, 819, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 – 8.2 (m, 1H), 7.78 – 7.76 (m, 1H), 7.41 – 7.39 (m, 2H), 6.89 (s, 1H), 4.41 – 4.38 (m, 2H), 4.05 (s, 3H) 3.14 – 3.07 (m, 2H), 1.79 – 1.76 (m, 2H), 1.68 – 1.59 (m, 1H), 1.37 – 1.27 (m, 2H), 1.00 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.7, 144.4, 140.2, 135.8, 132.1, 127.3, 125.3, 123.6, 122.3, 121.1, 99.9, 56.0, 46.4, 33.7, 30.8, 22.1. HRMS (ESI) exact mass calculated for $C_{18}H_{21}N_2O_2^+$ ($[M + H]^+$): 297.1598; Found: 297.1597.

2-(azepan-1-yl)-4-methoxynaphtho[1,2-*d*]oxazole (4.80): According to GP-1: 3-methoxy-1-nitrosonaphthalen-2-ol (50 mg, 0.24 mmol), azepane (0.11 mL, 0.98 mmol) and KOAc (48 mg, 0.49 mmol) were reacted for 36 h in dry DCM (5 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.80** as a brown gum (56 mg, 77%). FTIR (KBr): $\tilde{\nu}$ = 3045, 2961, 2932, 2879, 1651, 1621, 1573, 1480, 1381, 1163, 805, 728 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.27 – 8.25 (m, 1H), 7.77 – 7.76 (m, 1H), 7.40 – 7.38 (m, 2H), 6.88 (s, 1H), 4.06 (s, 3H), 3.81 – 3.80 (m, 4H), 1.90 – 1.87 (m, 4H), 1.65 –1.63 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.9, 144.4, 140.6, 135.8, 132.0, 127.3, 125.2, 123.5, 122.5, 121.0, 99.6, 56.0, 48.3, 28.5, 27.8. HRMS (ESI) exact mass calculated for $C_{18}H_{21}N_2O_2^+$ ($[M + H]^+$): 297.1598; Found: 297.1593.



8-methoxy-2-(4-methylpiperidin-1-yl)naphtho[1,2-*d*]oxazole (4.81):According to GP-1:



7-methoxy-1-nitrosonaphthalen-2-ol (70 mg, 0.34 mmol), 4-methylpiperidine (0.16 mL, 1.37 mmol) and KOAc (67 mg, 0.69 mmol) were reacted for 36 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.81** as a brown gum (73 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 3016, 2949, 2926, 2848, 1643, 1595, 1579, 1468, 1432, 1363, 1345, 1276, 1026, 876, 828 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 9.0 Hz, 1H), 7.60 – 7.59 (m, 1H), 7.44 – 7.42 (m, 1H), 7.34 – 7.33 (m, 1H), 7.08 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.38 – 4.34

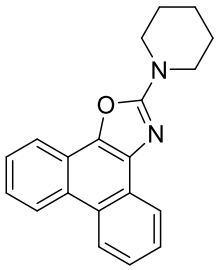
(m, 2H), 3.99 (s, 3H), 3.13 – 3.08 (m, 2H), 1.81 – 1.77 (m, 2H), 1.67 - 1.62 (m, 1H), 1.36 – 1.30 (m, 2H), 1.01 (d, *J* = 6.6 Hz, 3H). 13C NMR (151 MHz, $CDCl_3$) δ = 162.5, 158.0, 145.4, 137.7, 130.1, 126.6, 126.2, 120.7, 117.6, 107.4, 100.5, 55.7, 46.3, 33.7, 30.8, 22.1. HRMS (ESI) exact mass calculated for $C_{18}H_{21}N_2O_2^+$ ([M + H]$^+$): 297.1598; Found: 297.1604.

2-(azepan-1-yl)-8-methoxynaphtho[1,2-*d*]oxazole (4.82): According to GP-1: 7-methoxy-1-nitrosonaphthalen-2-ol (70 mg, 0.34 mmol), azepane (0.16 mL, 1.37 mmol) and KOAc (67 mg, 0.69 mmol) were reacted for 36 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.82** as a brown solid (71 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 2920, 2580, 1644, 1620, 1581, 1472, 1374, 1279, 1027, 819, 875, 741, 725 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 9.0 Hz, 1H), 7.65 – 7.64 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.09 – 7.07 (m, 1H), 4.00 (s, 3H), 3.77 (t, *J* = 6.0, 4H), 1.89 – 1.86 (m, 4H), 1.64 – 1.62 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.6, 157.9, 145.4, 138.0, 130.1, 126.6, 126.0, 120.1, 117.5, 107.3, 100.6, 55.9, 48.2, 28.6, 27.8. HRMS (ESI) exact mass calculated for $C_{18}H_{21}N_2O_2^+$ ([M + H]$^+$): 297.1598; Found: 297.1598.

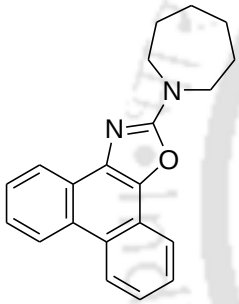
8-methoxy-2-(piperidin-1-yl)naphtho[1,2-*d*]oxazole (4.83): According to GP-1: 7-methoxy-1-nitrosonaphthalen-2-ol (70 mg, 0.34 mmol), piperidine (0.15 mL, 1.37 mmol) and KOAc (67 mg, 0.69 mmol) were reacted for 48 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:10) of the crude gave **4.83** as a brown gum (72 mg, 74%). FTIR (KBr): $\tilde{\nu}$ = 3061, 2962, 2921, 2849, 1641, 1610, 1496, 1450, 1414, 1351, 1264, 1084, 1005, 745 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 9.0 Hz, 1H), 7.61– 7.60 (m, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.09 – 7.07 (m, 1H), 3.99 (s, 3H), 3.73 – 3.72 (m, 4H), 1.74 – 1.70 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.5, 158.0, 145.4, 137.7, 130.2, 126.6, 126.2, 120.7, 117.6, 107.3, 100.5, 55.7, 46.9, 25.5, 24.3. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2O_2^+$ ([M + H]$^+$): 283.1441; Found: 283.1447.

2-(piperidin-1-yl)phenanthro[9,10-*d*]oxazole (4.84): According to GP-1: 10-nitrosophenanthren-9-ol (50 mg, 0.22 mmol), piperidine (88 µL, 0.9 mmol) and KOAc (44

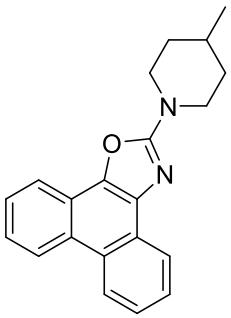
mg, 0.45 mmol) were reacted for 72 h in dry DCM (5 mL). Column chromatography (silica; EtOAc : Hexane, 1:40) of the crude gave **4.84** as a yellow gum (38 mg, 56%). FTIR (KBr): $\tilde{\nu}$ = 2960, 2923, 2852, 1673, 1646, 1624, 1609, 1451, 1356, 1261, 1096, 753, 726 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.72 (d, *J* = 8.4 Hz, 2H), 8.42 (d, *J* = 9.0 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.65 – 6.61 (m, 2H), 7.55 – 7.52 (m, 1H), 3.80 – 3.79 (m, 4H), 1.79 – 1.77 (m, 4H), 1.76 – 1.72 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 162.8, 140.5, 136.1, 128.7, 127.1, 127.1, 126.9, 126.0, 125.5, 124.2, 123.8, 123.5, 123.0, 121.3, 119.4, 47.1, 25.5, 24.3. HRMS (ESI) exact mass calculated for $C_{20}H_{19}N_2O^+$ ($[M + H]^+$): 303.1492; Found: 303.1493.



2-(azepan-1-yl)phenanthro[9,10-*d*]oxazole (4.85): According to GP-1: 10-nitrosophenanthren-9-ol (60 mg, 0.27 mmol), azepane (0.12 mL, 1.08 mmol) and KOAc (53 mg, 0.54 mmol) were reacted for 72 h in dry DCM (6 mL). Column chromatography (silica; EtOAc : Hexane, 1:20) of the crude gave **4.85** as a colorless solid (59 mg, 69%). FTIR (KBr): $\tilde{\nu}$ = 2922, 2877, 2847, 1643, 1604, 1562, 1356, 1332, 876, 752, 724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72 –8.70 (m, 2H), 8.45 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.60 (m, 3H), 7.55 –7.51 (m, 1H), 3.86 – 3.83 (m, 4H), 1.95 – 1.90 (m, 4H), 1.68 – 1.64 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.9, 140.4, 136.4, 128.6, 127.0, 126.83, 126.77, 125.9, 125.4, 124.0, 123.8, 123.4, 123.0, 121.2, 119.2, 48.3, 28.6, 27.9. HRMS (ESI) exact mass calculated for $C_{22}H_{21}N_2O^+$ ($[M + H]^+$): 317.1648; Found: 317.1649.

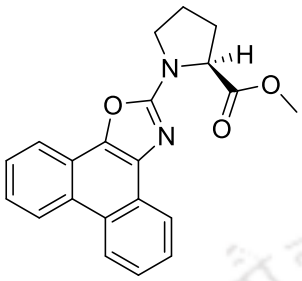


2-(4-methylpiperidin-1-yl)phenanthro[9,10-*d*]oxazole (4.86): According to GP-1: According to GP-1: 10-nitrosophenanthren-9-ol (50 mg, 0.21 mmol), 4-methylpiperidine (0.11 mL, 0.84 mmol) and KOAc (44 mg, 0.42 mmol) were reacted for 72 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:20) of the crude gave **4.86** as a colorless solid (40 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 2924, 2853, 1630, 1565, 1455, 1290, 726 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.72 (d, *J* = 8.4 Hz, 2H), 8.42 (d, *J* = 9.0 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.69 – 6.66 (m, 1H), 7.65 – 7.62 (m, 2H), 7.55 – 7.53 (m, 1H), 4.45 – 4.43 (m, 2H), 3.19 – 3.14 (m, 2H), 1.84 – 1.82 (m, 2H), 1.69 – 1.67 (m, 1H), 1.42 – 1.35 (m, 2H), 1.03 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.8, 140.5, 136.0, 128.7, 127.0, 127.0, 126.9, 125.9, 125.4, 124.2,



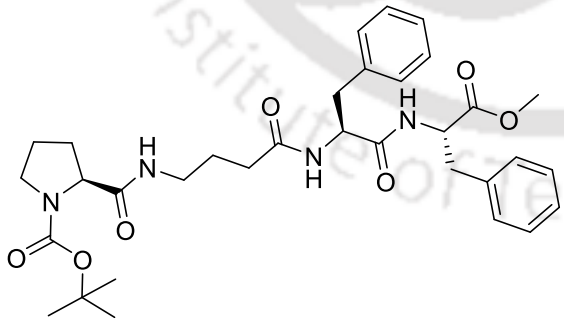
123.7, 123.4, 122.9, 121.2, 119.3, 46.4, 33.7, 30.8, 22.0. HRMS (ESI) exact mass calculated for $C_{20}H_{24}N_3O_3^+$ ([M + H]$^+$): 317.1648; Found: 317.1652.

methyl phenanthro[9,10-*d*]oxazol-2-ylprolinate (4.87): 10-nitrosophenanthren-9-ol (30 mg, 0.13 mmol), L-proline methyl ester hydrochloride (84 mg, 0.50 mmol) and Et_3N (88 µL, 0.50 mmol) were reacted for 80 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **4.87** as a colorless solid (19 mg, 43%). FTIR (KBr): $\tilde{\nu}$ = 3056, 2927, 1741, 1632, 1566, 1453, 1017, 821, 744 cm $^{-1}$. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.71 (d, *J* = 8.4 Hz, 2H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.68 – 7.66 (m, 1H), 7.65 – 7.61 (m, 2H), 7.56 – 7.53 (m, 1H), 4.80 – 4.78 (m, 1H), 4.05 – 4.01 (m, 1H), 3.92 – 3.89 (m, 1H), 3.80 (s, 3H), 2.48 – 2.42 (m, 1H), 2.28 – 2.24 (m, 1H), 2.22 – 2.16 (m, 1H), 2.15 – 2.11 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.4, 160.5, 141.1, 136.1, 128.7, 127.2, 127.1, 126.9, 126.0, 125.6, 124.4, 123.8, 123.5, 123.2, 121.2, 119.4, 60.8, 52.7, 48.5, 31.1, 24.4. HRMS (ESI) exact mass calculated for $C_{21}H_{19}N_2O_3^+$ ([M + H]$^+$): 347.1390; Found: 347.1386.



Synthesis of *N*-terminal proline peptides:

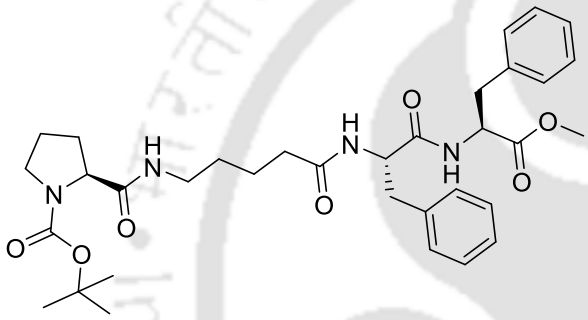
***tert-butyl* (*R*)-2-((4-(((*S*)-1-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobutyl)carbamoyl)pyrrolidine-1-carboxylate (4.99a):**



(L)-Phe-(L)-Phe-methyl ester (0.14 g, 0.42 mmol), Boc-(L)-Pro-GABA (0.12 g, 0.42 mmol), *N*,*N*-diisopropylethylamine (0.28 mL, 1.67 mmol), EDC.HCl (79 mg, 0.42 mmol) and 1-hydroxybenzotriazole (56 mg, 0.42 mmol) were dissolved in a mixture of dichloromethane (4 mL) and DMF (1 mL)). After stirred for 5min at 0 ºC then the reaction mixture was stirred for 72 h at room temperature. After completion of the reaction the solvent was evaporated in vacuo. The residue was neutralized with 0.1 N HCl solution and $NaHCO_3$ solution (15 mL) and extracted with ethylacetate (3x15 mL). Then the combined organic layers were dried over Na_2SO_4,concentrated under vacuum and the crude was purified by column chromatography

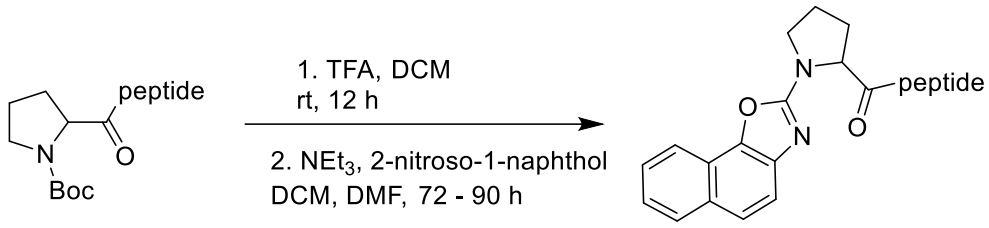
via neutral alumina (ethylacetate : hexane = 1:3) to afford Boc-(L)-Pro-GABA-(L)-Phe-(L)-Phe-OMe **4.99a** (0.16 g, 62%). FTIR (KBr): $\tilde{\nu}$ = 3428, 3085, 2926, 2924, 2247, 1952, 1748, 1632, 1449, 1384, 1164, 913, 746 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 – 741 (m, 1H), 7.29 – 7.20 (m, 8H), 7.13 – 7.11 (m, 2H), 6.89 – 6.37 (m, 1H), 4.82 – 4.78 (m, 1H), 4.67 – 4.62 (m, 1H), 4.23 – 4.22 (m, 1H), 3.67 (s, 3H), 3.52 – 6.41 (m, 3H), 3.21 – 2.96 (m, 6H), 2.20 – 2.05 (m, 4H), 1.88 – 1.81 (m, 3H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.6, 173.5, 171.8, 171.7, 155.5, 137.0, 136.1, 129.5, 129.4, 128.7, 128.7, 127.2, 127.0, 80.8, 60.4, 58.6, 55.1, 53.7, 52.4, 47.4, 38.04, 37.96, 32.3, 29.4, 28.6, 24.9. HRMS (ESI) exact mass calculated for $C_{33}H_{45}N_4O_7^+$ ($[M + H]^+$): 609.3283; Found: 609.3286.

***tert-butyl* (*S*)-2-((5-(((*S*)-1-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-5-oxopentyl)carbamoyl)pyrrolidine-1-carboxylate (4.100a)**:



(L)-Phe-(L)-Phe-methyl ester (0.22 g, 0.67 mmol), Boc-(L)-Pro-DAVA (0.21 g, 0.67 mmol), *N*,*N*-diisopropylethylamine (0.45 mL, 2.67 mmol), EDC.HCl (127 mg, 0.67 mmol) and 1-hydroxybenzotriazole (90 mg, 0.67 mmol) were dissolved in a mixture of dichloromethane (4 mL) and DMF (1 mL)). After stirred for 5 min at 0 ºC then the reaction mixture was stirred for 72 h at room temperature. After completion of the reaction the solvent was evaporated in vacuo. The residue was neutralized with 0.1 N HCl solution and $NaHCO_3$ solution (15 mL) and extracted with ethylacetate (3x15 mL). Then the combined organic layers were dried over Na_2SO_4,concentrated under vacuum and the crude was purified by column chromatography via neutral alumina (ethylacetate : hexane = 1:3) to afford Boc-(L)-Pro-DAVA-(L)-Phe-(L)-Phe-OMe **4.100a** (0.21 g, 50%). FTIR (KBr): $\tilde{\nu}$ = 3437, 2972, 2930, 2861, 1742, 1647, 1548, 1445, 1384, 1259, 1163, 749 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.28 – 7.16 (m, 8H), 7.05 –7.04 (m, 2H), 6.85 – 6.84 (m, 1H), 6.61 – 6.54 (m, 1H), 4.74 – 4.67 (m, 2H), 4.24 – 4.18 (m, 1H), 3.64 (s, 3H), 3.46 – 3.18 (m, 4H), 3.08 – 3.03 (m, 2H), 3.00 – 2.94 (m, 2H), 2.60 – 2.57 (m, 2H), 2.17 – 2.12 (m, 3H), 1.96 – 1.83 (m, 3H), 1.56 – 1.55 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.3, 173.0, 172.7, 171.6, 155.5, 136.8, 135.9, 129.4, 129.3, 128.6, 128.6, 127.1, 126.92, 61.5, 60.1, 54.4, 53.7, 52.3, 47.2, 38.8, 38.0, 37.9, 35.3, 31.3, 28.5, 24.6, 22.8. HRMS (ESI) exact mass calculated for $C_{34}H_{47}N_4O_7^+$ ($[M + H]^+$): 623.3439; Found: 623.3447.

Synthesis of *N*- terminal modified peptides: General Procedure 2 (GP-2):



TFA (0.6 –1.5 mL) was added drop-wise to the solution of peptide in DCM. The reaction mixture was allowed to stir at room temperature for 12 h. The reaction mixture was diluted with methanol and the solvent was removed in vacuo. The residue was washed with diethylether and dried in vacuo to give the trifluroacetate salt of the peptide. Triethylamine (5 equiv.) was added to the solution of the residue either in mixture of DCM-DMF (4:1) or DCM-DMSO (4:1). After 5 min 2-nitroso-1-naphthol was added to the solution and the reaction mixture was heated at 50 ^{o}C for 72 h to 90 h. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under vacuum to obtain gummy residue which was purified by column chromatography to afford analytically pure products.

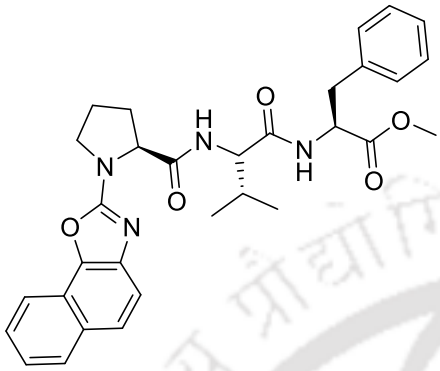
methyl naphtho[2,1-*d*]oxazol-2-yl-L-prolyl-L-tryptophanate (4.94): According to GP-2: 2-nitroso-1-naphthol (47 mg, 0.36 mmol), trifluroacetate salt of (L)-Pro-(L)-Trp-OMe[41] (78 mg, 0.18 mmol) and NEt_3 (0.12 mL, 0.90 mmol) were reacted for 72 h in dry DCM (4 mL)/DMF (1 mL) . Column chromatography (silica; EtOAc : Hexane, 2:1) of the crude gave **4.94** as a brown solid (44 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 2958, 2925, 2851, 2078, 1637, 1654, 1347, 744, 684 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.67 – 7.66 (m, 2H), 7.53 – 7.50 (m, 3H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.05 – 7.00 (m, 3H), 6.83 – 6.82 (m, 1H), 4.97 – 4.94 (m, 1H), 4.57 – 4.56 (m, 1H), 3.65 (s, 3H), 3.61 – 3.57 (m, 2H), 3.36 – 3.33 (m, 1H), 3.26 – 3.22 (m, 1H), 2.41 – 2.37 (m, 1H), 2.10 – 2.04 (m, 1H), 1.97 – 1.94 (m, 1H), 1.90 – 1.86 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 172.1, 171.0, 161.0, 143.3, 138.9, 135.8, 129.5, 128.6, 127.5, 126.5, 124.5, 123.7, 122.6, 122.0, 119.7, 119.5, 118.9, 118.2, 116.9, 111.1, 109.9, 62.2, 53.1, 52.4, 48.6, 29.3, 27.3, 24.4. HRMS (ESI) exact mass calculated for $C_{28}H_{27}N_4O_4^+$ ([M + H]$^+$): 483.2027; Found: 483.2035.

methyl naphtho[2,1-*d*]oxazol-2-yl-L-prolyl-L-valyl-L-leucinate (4.95): According to GP-2: 2-nitroso-1-naphthol (38 mg, 0.22 mmol), trifluroacetate salt of (L)-Pro-(L)-Val-(L)-Leu-OMe[43] (50 mg, 0.11 mmol) and NEt_3 (76 µL, 0.55 mmol) were reacted for 72 h in dry DCM (4 mL)/ DMF (1 mL) . Column chromatography (silica; EtOAc : Hexane, 2:1) of the crude gave **4.95** as a violet solid (32 mg, 57%). FTIR (KBr): $\tilde{\nu}$ = 3062, 2958, 2920, 2853, 1743, 1644, 1470, 1435, 1258, 1224, 1025, 818 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.65 (br.s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.52 (m, 1H), 7.39 – 7.37 (m, 1H), 6.49 (d, *J* = 7.2 Hz, 1H), 4.66 – 4.65 (m, 1H), 4.59 – 4.55 (m, 1H), 4.30 – 4.28 (m, 1H), 3.95 – 3.92 (m, 1H), 3.81 – 3.77 (m, 1H), 3.71 (s, 3H), 2.49 – 2.45 (m, 1H), 2.25 – 2.17 (m, 3H), 2.14 – 2.11 (m, 1H), 1.63 – 1.58 (m, 2H), 1.51 – 1.48 (m, 1H), 0.89 – 0.86 (m, 6H), 0.85 – 0.84 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.3, 171.8, 171.0, 161.4, 143.6, 139.0, 129.8, 128.8, 126.7, 125.0, 124.0, 119.9, 119.0, 117.1, 62.8, 59.1, 52.5, 50.5, 49.1, 41.5, 30.7, 29.8, 25.03, 25.00, 22.9, 22.0, 19.4, 17.9. HRMS (ESI) exact mass calculated for $C_{28}H_{37}N_4O_5^+$ ($[M + H]^+$): 509.2758; Found: 509.2755.

methyl naphtho[2,1-d]oxazol-2-yl-L-prolylglycylglycinate (4.96): According to GP-2: 1-nitroso-2-naphthol (73 mg, 0.42 mmol), trifluroacetate salt of (L)-Pro-(L)-Ala-(L)-Ala-OMe[42] (0.10 g, 0.28 mmol) and NEt_3 (0.19 mL, 1.4 mmol) were reacted for 90 h in dry DCM (4 mL)/DMF (1 mL). Column chromatography (silica; EtOAc : Hexane, 2:1) of the crude gave **4.96** as a violet solid (53 mg, 46%). FTIR (KBr): $\tilde{\nu}$ = 3062, 2955, 2923, 1747, 1628, 1565, 1522, 1453, 1260, 1209, 811, 727 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.65 – 7.63 (m, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.51 – 7.49 (m, 1H), 7.46 – 7.45 (m, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 7.38 – 7.35 (m, 1H), 4.56 – 4.54 (m, 1H), 4.11 (dd, *J* = 17.4, 6.6 Hz, 1H), 3.99 – 3.94 (m, 3H), 3.89 (dd, *J* = 18.0, 5.4 Hz, 1H), 3.83 – 3.78 (m, 1H), 3.52 (s, 3H), 2.35 – 2.31 (m, 2H), 2.21 – 2.16 (m, 1H), 2.10 – 2.06 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 172.5, 170.5, 169.8, 161.2, 143.5, 138.8, 129.8, 128.8, 126.9, 124.9, 124.1, 119.9, 119.0, 116.5, 63.0, 52.4, 49.1, 43.2, 41.1, 30.7, 24.9.

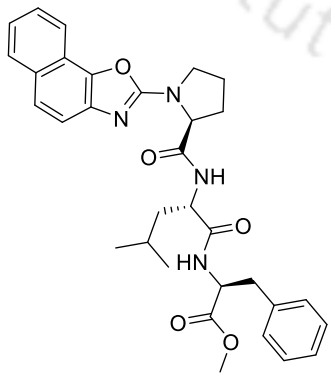
HRMS (ESI) exact mass calculated for $C_{23}H_{27}N_4O_5^+$ ([M + H]$^+$): 411.1663; Found: 411.1664.

methyl naphtho[2,1-*d*]oxazol-2-yl-L-prolyl-L-valyl-L-phenylalaninate (4.97):



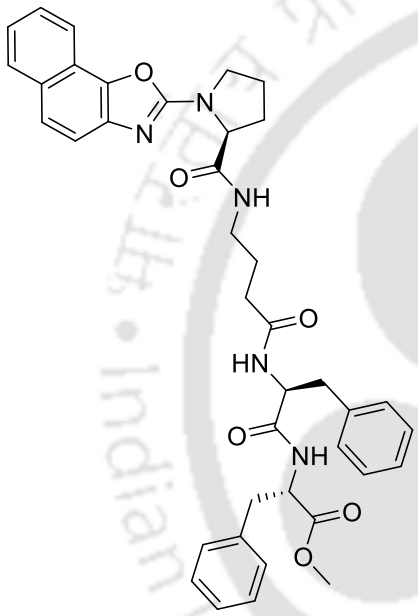
According to GP-2: 2-nitroso-1-naphthol (35 mg, 0.20 mmol), trifluroacetate salt of (L)-Pro-(L)-Val-(L)-Phe-OMe[43] (50 mg, 0.10 mmol) and NEt_3 (69 µL mg, 0.50 mmol) were reacted for 72 h in dry DCM (4 mL)/DMF (1 mL) . Column chromatography (silica; EtOAc : Hexane, 2:1) of the crude gave **4.97** as a violet solid (27 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 3064, 2958, 2926, 2853, 1742, 1628, 1566, 1369, 1284, 1211, 1097, 1023, 811, 737 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.39 – 7.36 (m, 1H), 7.27 – 7.20 (m, 3H), 7.21 – 7.20 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.54 – 6.52 (m, 1H), 4.85 – 4.82 (m, 1H), 4.63 – 4.62 (m, 1H), 4.27 – 4.25 (m, 1H), 3.94 – 3.91 (m, 1H), 3.82 – 3.75 (m, 1H), 3.70 (s, 3H), 3.10 – 3.07 (m, 1H), 3.00 – 2.95 (m, 1H), 2.49 – 2.46 (m, 1H), 2.20 – 2.12 (m, 4H), 0.82 (d, *J* = 7.2 Hz, 3H), 0.77 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.9, 171.7, 170.8, 161.5, 143.6, 139.0, 136.0, 129.8, 129.4, 128.9, 128.8, 127.3, 126.8, 125.0, 124.0, 119.9, 119.0, 117.1, 62.8, 59.0, 53.3, 52.5, 49.1, 38.1, 30.5, 29.6, 25.0, 19.4, 17.7. HRMS (ESI) exact mass calculated for $C_{31}H_{35}N_4O_5^+$ ([M + H]$^+$): 543.2602; Found: 543.2606.

methyl naphtho[2,1-*d*]oxazol-2-yl-L-prolyl-L-leucyl-L-phenylalaninate (4.98):

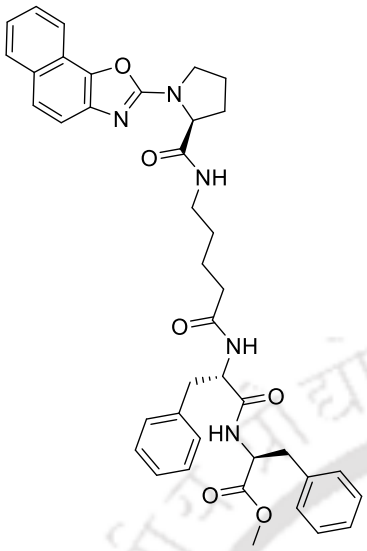


According to GP-2: 1-nitroso-2-naphthol (40 mg, 0.23 mmol), trifluroacetate salt of (L)-Pro-(L)- Leu-(L)-Phe-OMe[44] (54 mg, 0.14 mmol) and NEt_3 (54 mg, 0.46 mmol) were reacted for 72 h in dry DCM (4 mL)/DMF (1 mL) . Column chromatography (silica; EtOAc : Hexane, 2:1) of the crude gave **4.98** as a violet solid (39 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 3299, 3062, 2951, 2871, 1752, 1650, 1627, 1565, 1593, 1280, 1208, 1105, 809, 700 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.99 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.54 – 7.49 (m, 3H), 7.39 – 7.37 (m, 1H), 7.27 – 7.24 (m, 2H), 7.21 – 7.19 (m, 1H), 7.08 (d, J = 7.2 Hz, 2H), 6.77 (d, J = 7.8 Hz, 1H), 4.83

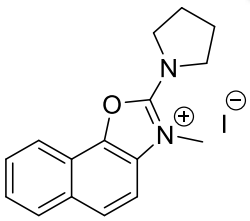
– 4.79 (m, 1H), 4.59 (d, *J* = 8.4 Hz, 1H), 4.42 – 4.38 (m, 1H), 3.93 – 3.90 (m, 1H), 3.80 – 3.75 (m, 1H), 3.70 (s, 3H), 3.12 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.01 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.44 – 2.40 (m, 1H), 2.22 – 2.09 (m, 3H), 1.66 – 1.61 (m, 1H), 1.55 – 1.47 (m, 2H), 0.77 (d, *J* = 4.2 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.9, 171.6, 161.3, 143.5, 136.1, 129.8, 129.5, 128.8, 128.7, 127.2, 126.8, 125.0, 124.1, 119.9, 119.0, 117.0, 62.6, 53.4, 52.5, 52.3, 49.1, 40.6, 38.0, 29.7, 25.0, 23.0, 21.9. Total count of ^{13}C is less than expected due to the merging of signal in the aromatic region HRMS (ESI) exact mass calculated for $C_{32}H_{37}N_4O_5^+$ ($[M + H]^+$): 557.2758; Found: 557.2753.

methyl (4-((*R*)-1-(naphtho[2,1-*d*]oxazol-2-yl)pyrrolidine-2-carboxamido)butanoyl)-*L*-phenylalanyl-*L*-phenylalaninate (4.99): 

According to GP-2: 2-nitroso-1-naphthol (33 mg, 0.19 mmol), trifluroacetate salt of (L)-Pro-GABA-(L)-Phe-(L)-Phe-OMe (60 mg, 0.10 mmol) and NEt_3 (76 µL, 0.48 mmol) were reacted for 72 h in dry DCM (4 mL)/DMF (1 mL) . Column chromatography (silica; EtOAc : Hexane, 2:1) of the crude gave **4.99** as a violet solid (40 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 3062, 2958, 2926, 2853, 1740, 1644, 1564, 1452, 1371, 1260, 1091, 802, 700 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.54 - 7.51 (m, 2H), 7.48 (br.d, *J* = 6.9 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.25 – 7.24 (m, 2H), 7.21 – 7.20 (m, 1H), 7.17 – 7.16 (m, 3H), 7.09 – 7.07 (m, 4H), 6.61 (d, *J* = 7.8 Hz, 1H), 4.77 – 4.74 (m, 1H), 4.60 – 4.56 (m, 2H), 4.00 – 3.97 (m, 1H), 3.85 – 3.79 (m, 1H), 3.64 (s, 3H), 3.26 – 3.22 (m, 1H), 3.14 – 3.08 (m, 2H), 3.02 – 2.95 (m, 2H), 2.92 – 2.89 (m, 1H), 2.39 – 2.232 (m, 3H), 2.23 – 2.17 (m, 1H), 2.13 – 2.10 (m, 2H), 1.84 – 1.80 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.7, 172.6, 171.7, 171.5, 161.0, 143.4, 139.1, 136.7, 136.0, 129.7, 129.5, 129.3, 128.9, 128.75, 128.74, 127.3, 127.1, 126.8, 124.9, 124.0, 119.9, 119.0, 116.7, 62.6, 55.0, 53.7, 52.5, 49.2, 38.4, 38.1, 37.8, 32.5, 30.8, 24.8, 24.6. HRMS (ESI) exact mass calculated for $C_{39}H_{42}N_5O_6^+$ ($[M + H]^+$): 676.3130; Found: 676.3110.

methyl (5-((R)-1-(naphtho[2,1-*d*]oxazol-2-yl)pyrrolidine-2-carboxamido)pentanoyl)-L-phenylalanyl-L-phenylalaninate (4.100): 

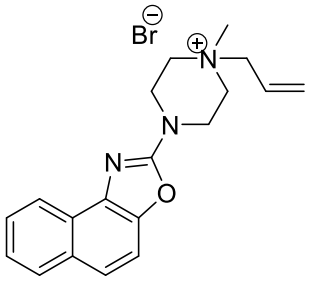
According to GP-2: 1-nitroso-2-naphthol (40 mg, 0.23 mmol), trifluroacetate salt of (L)-Pro-DAVA-(L)-Phe-(L)-Phe-OMe (0.16 g, 0.25 mmol) and NEt_3 (0.17 mL, 1.2 mmol) were reacted for 72 h in dry DCM (4 mL)/DMF (1 mL). Column chromatography (silica; EtOAc : Hexane, 2:1) of the crude gave **4.100** as a brown solid (40 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 3290, 3062, 3030, 2927, 1742, 1665, 1639, 1542, 1286, 1257, 1108, 1029, 726, 699 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.52 – 7.50 (m, 1H), 7.46 (d, *J* = 5.4 Hz, 1H), 7.44 – 7.43 (m, 1H), 7.38 – 7.35 (m, 1H), 7.30 (bs, 1H), 7.24 – 7.19 (m, 3H), 7.09 – 7.08 (m, 3H), 7.05 – 7.04 (m, 2H), 6.98 – 6.97 (m, 2H), 6.68 – 6.67 (m, 1H), 4.74 – 4.71 (m, 1H), 4.64 – 4.58 (m, 2H), 3.99 – 3.95 (m, 1H), 3.80 – 3.75 (m, 1H), 3.66 (s, 3H), 3.38 – 3.33 (m, 1H), 3.12 – 3.07 (m, 2H), 3.02 – 2.98 (m, 1H), 2.95 – 2.85 (m, 2H), 2.37 – 2.25 (m, 3H), 2.21 – 2.16 (m, 1H), 2.13 – 2.06 (m, 2H), 1.68 – 1.64 (m, 1H), 1.58 – 1.54 (m, 1H), 1.51 – 1.47 (m, 1H), 1.34 – 1.31 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.5, 172.2, 171.7, 171.5, 161.0, 143.4, 139.0, 136.6, 135.9, 129.6, 129.4, 129.2, 128.8, 128.7, 128.6, 127.2, 127.0, 126.7, 124.8, 123.9, 119.9, 119.0, 116.7, 62.4, 54.6, 53.8, 52.4, 49.1, 39.2, 38.0, 37.8, 34.8, 30.8, 27.6, 24.7, 22.9. HRMS (ESI) exact mass calculated for $C_{40}H_{44}N_5O_6^+$ ($[M + H]^+$): 690.3286; Found: 690.3285.

1-methyl-1-(naphtho[2,1-*d*]oxazol-2-yl)pyrrolidin-1-ium iodide (4.101): 

Methyl iodide (0.13 mL, 2.1 mmol) was added to a solution of **4.41** (50 mg, 0.21 mmol) in toluene (2.0 mL) and the solution was stirred at 80 °C for 18 h. The precipitate was filtered and washed with ethyl acetate (10 mL). The ion **4.101** was obtained as white solid (40 mg, 51%). FTIR (KBr): $\tilde{\nu}$ = 2917, 2857, 2256, 2129, 1762, 1646, 1046, 1025, 826, 765 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ = 8.16 – 8.11 (m, 3H), 7.92 – 7.90 (m, 1H), 7.78 – 7.76 (m, 1H), 7.64 – 7.62 (m, 1H), 4.06 – 4.02 (m, 4H), 3.99 (s, 3H), 2.07 – 2.047 (d, *J* = 6.4 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 155.1, 138.2, 130.3, 128.9, 128.7,

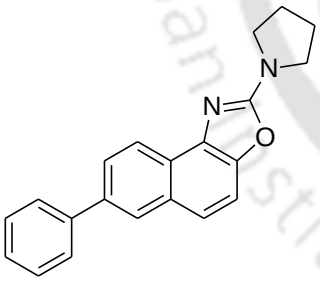
128.6, 126.8, 126.1, 118.3, 118.1, 110.4, 49.9, 31.9, 24.9. HRMS (ESI) exact mass calculated for $C_{16}H_{17}N_2O^+$ ([M + H]$^+$): 253.1335; Found: 253.1332.

1-allyl-1-methyl-4-(naphtho[2,1-*d*]oxazol-2-yl)piperazin-1-ium bromide (4.102):



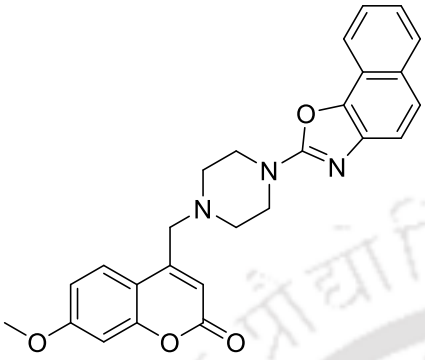
Allybromide (0.170 mL, 2.0 mmol) was added to a solution of **4.77** (27 mg, 0.10 mmol) in DMF (1 mL) and the solution was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and reaction mixture was diluted with ethylacetate. The precipitate was filtered and washed with ethyl acetate (5 mL). The ion **4.102** was obtained as brown solid (23 mg, 59%). FTIR (KBr): $\tilde{\nu}$ = 2783, 2433, 2094, 1643, 1616, 1468, 1571, 1427, 1368, 1283, 974 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD-d_4) δ = δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.46 – 7.44 (m, 1H), 7.38 – 7.35 (m, 1H), 6.14 – 6.04 (m, 1H), 5.77 – 5.71 (m, 2H), 4.17 (d, *J* = 7.4 Hz, 4H), 3.63 (s, 4H), 3.20 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ = 161.1, 145.1, 136.8, 131.3, 129.0, 128.3, 125.9, 124.9, 124.6, 123.9, 122.1, 121.3, 109.6, 66.2, 58.3, 39.5, 34.1. HRMS (ESI) exact mass calculated for $C_{19}H_{22}N_3O^+$ ([M + H]$^+$): 308.1757; Found: 308.1768.

7-phenyl-2-(pyrrolidin-1-yl)naphtho[1,2-*d*]oxazole (4.103): Phenylboronic acid (23 mg, 0.19 mmol), $Ba(OH)_2$, $8H_2O$ (86 mg, 0.27 mmol), $Pd(PPh_3)_4$ (6 mg, 3.3 mol%), 1,4-dioxane (1.4 mL), H_2O (0.5 mL), and **4.44** (46 mg, 0.15 mmol) were refluxed for 48 h under argon atmosphere. After completion of reaction 1,4-dioxane was removed under reduced pressure. The resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 M HCl (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulfate and concentrated under vacuum to give crude product which was purified by column chromatography (SiO_2; EtOAc : Hexane, 1:1) to afford pure **4.103 (**42 mg, 92%). FTIR (KBr): $\tilde{\nu}$ = 3054, 2967, 2924, 2858, 1647, 1617, 1418, 1264, 1087, 994, 757, 695 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.44 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H), 7.82 – 7.80 (m, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.56 – 7.52 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 3.75 – 3.73 (m, 4H), 2.08 – 2.05 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 161.4, 145.4, 141.6, 138.9, 137.3, 131.5, 129.0, 127.6, 127.3, 126.5, 125.4, 124.1,



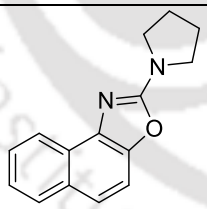
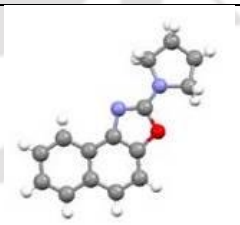
123.1, 120.7, 110.3, 47.8, 25.9. HRMS (ESI) exact mass calculated for $C_{21}H_{19}N_2O^+$ ([M + H]$^+$): 315.1492; Found: 315.1489.

7-methoxy-4-((4-(naphtho[2,1-*d*]oxazol-2-yl)piperazin-1-yl)methyl)-2H-chromen-2-one



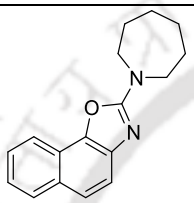
(4.105): According to GP-1: 2-nitroso-1-naphthol (40 mg, 0.23 mmol), **4.104**[45] (0.13 g, 0.46 mmol) and NEt_3 (65 µL, 0.46 mmol) were reacted for 60 h in dry DCM (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:3) of the crude gave **4.105** as a colorless solid (46 mg, 45%). FTIR (KBr): $\tilde{\nu}$ = 2953, 2924, 2854, 1719, 1616, 1454, 1287, 1144, 1066, 811, 743 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.38 – 7.36 (m, 1H), 6.86 – 6.83 (m, 2H), 6.41 (s, 1H), 3.87 (s, 3H), 3.82 – 3.80 (m, 4H), 3.66 (s, 2H), 2.71 – 2.69 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.9, 162.1, 161.5, 155.9, 151.7, 143.1, 139.4, 129.7, 128.8, 126.6, 125.9, 124.7, 123.8, 119.8, 118.9, 117.1, 112.5, 112.4, 112.2, 101.1, 59.3, 55.9, 52.8, 45.9. HRMS (ESI) exact mass calculated for $C_{22}H_{20}N_3O^+$ ([M + H]$^+$): 442.1761; Found: 442.1754.

Crystal of **4.39:**

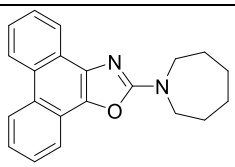
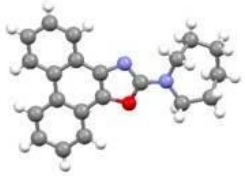
	
Empirical formula	$C_{15}H_{14}N_2O$
Formula weight	238.28
Crystal habit, colour	Block, colorless
Crystal size, mm^3	0.40X 0.38 X 0.35
Temperature, *T*	293(2)
Wavelength, *λ*(Å)	0.71073
Crystal system	monoclinic
Space group	*P 21/c*
Unit cell dimensions	*a* = 6.3429(12)Å *b* = 15.1467(18)Å *c* = 12.9960(16)Å *α* = 90°, *β* = 103.927(17)°, *γ* = 90°,
Volume, *V*(Å^3)	1211.9(3)
Z	4
Calculated density, Mg·m^{-3}	1.306
Absorption coefficient, *μ*(mm^{-1})	0.083

F(000)	504
θ range for data collection	3.230° to 24.997°
Limiting indices	$-7 \leq h \leq 4$, $-18 \leq k \leq 10$, $-15 \leq l \leq 15$
Reflection collected / unique	3001/ 1284 [*R*(int) = 0.0317]
Completeness to θ	84.5% (θ = 25.242°)
Refinement method	SHELXL-2013
Data / restraints / parameters	1284 / 0 / 163
Goodness–of–fit on F^2	1.096
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0746, *wR*2 = 0.1996
R indices (all data)	*R*1 = 0.0969, *wR*2 = 0.2267
Largest diff. peak and hole	0.240 and – 0.239 $Å^{-3}$

Crystal of **4.52:**

	
Empirical formula	$C_{17}H_{18}N_2O$
Formula weight	266.33
Crystal habit, colour	Needle, colorless
Crystal size, mm^3	0.38 X 0.36X 0.32
Temperature, *T*	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*P 21/c*
Unit cell dimensions	*a* = 5.3217(4)Å *b* = 26.6790(17) Å *c* = 10.0784(6) Å α = 90°, β = 102.466(4) °, γ = 90°,
Volume, *V*($Å^3$)	1397.17(16)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.266
Absorption coefficient, μ(mm^{-1})	0.080
F(000)	568
θ range for data collection	1.53° to 25.00°
Limiting indices	$-6 \leq h \leq 6$, $-31 \leq k \leq 31$, $-11 \leq l \leq 11$
Reflection collected / unique	15172/ 1826 [*R*(int) = 0.0373]
Completeness to θ	100% (θ = 25.00 °)
Refinement method	SHELXL-97
Data / restraints / parameters	15172/ 0 / 183
Goodness–of–fit on F^2	1.020
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0852, *wR*2 = 0.1828
R indices (all data)	*R*1 = 0.1020, *wR*2 = 0.1975
Largest diff. peak and hole	0.284 and – 0.315 $Å^{-3}$

Crystal of **4.85:**

	
Empirical formula	C_{21} H_{20} N_2 O
Formula weight	316.39
Crystal habit, colour	Needle, yellow
Crystal size, mm^3	0.35X 0.32X 0.30
Temperature, *T*	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*P 21*
Unit cell dimensions	*a* = 11.6978(6)Å *b* = 5.1772(2)Å *c* = 14.0219(7)Å α = 90°, β = 107.748(6)°, γ = 90°,
Volume, *V*($Å^3$)	808.78(7)
Z	2
Calculated density, $Mg \cdot m^{-3}$	1.299
Absorption coefficient, μ(mm^{-1})	0.081
F(000)	336
θ range for data collection	3.04° to 25.00°
Limiting indices	$-13 \leq h \leq 8$, $-6 \leq k \leq 5$, $-13 \leq l \leq 16$
Reflection collected / unique	2991/ 1986 [*R*(int) = 0.0115]
Completeness to θ	99.7% (θ = 25.00 °)
Refinement method	'SHELXL–97 (Sheldrick, 1997)
Data / restraints / parameters	1986 / 1 / 218
Goodness–of–fit on F^2	1.199
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0428, *wR*2 = 0.1148
R indices (all data)	*R*1 = 0.0491, *wR*2 = 0.1205
Largest diff. peak and hole	0.206 and $-0.141 e \cdot Å^{-3}$

4.18 References:

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Chapter 5

Direct C(sp^2)-H functionalization of nitrosoarene and β-C(sp^3)-H functionalization of secondary amines to Indoles

5.1 Introduction:

Indoles and their derivatives are ubiquitous in biologically active natural products, pharmaceuticals, and agro-chemicals.[1] The indole alkaloids are the structural analogue of endogenous amines and neurotransmitters. In particular, 3-substituted indoles have attracted considerable interest due to their importance in bio-significant applications and drug discovery. They possess diverse biological effects, such as anticancer, anti-inflammatory, analgesic, antitumor, antidepressant activities (**Figure 1**).[2] Moreover, several indole-based drugs, triptans, which are used for the treatment of migraine,[3] are currently marketed.

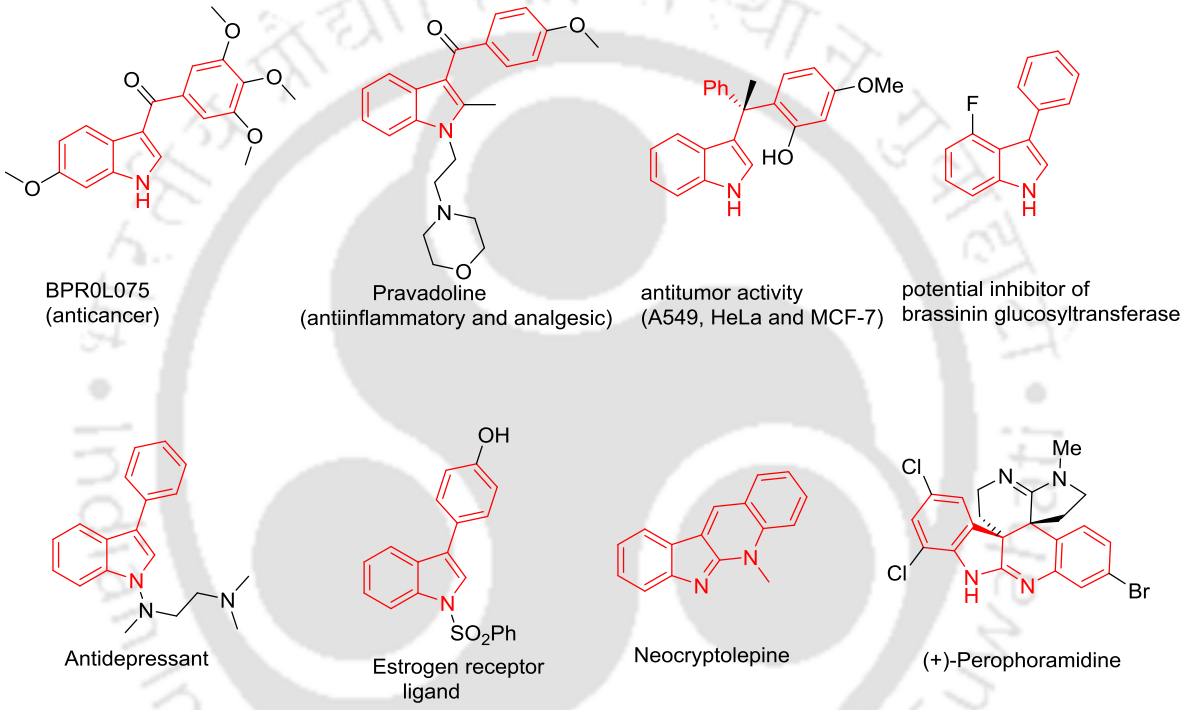
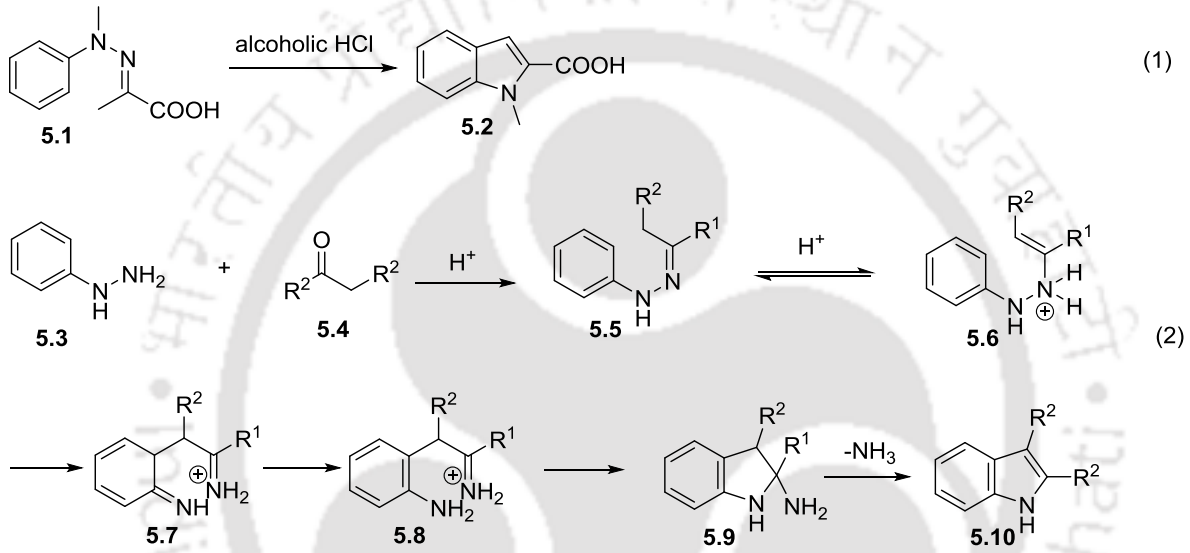


Figure 1: Selected examples of bioactive indole derivatives.

5.2 Known methods for indole synthesis:

Due to the biological importance of this heterocyclic compound, over the past decades, several pioneering methods have been developed for the synthesis of indole ring.[4] In this context, the Fischer indole synthesis stands as one of the most widely used protocols for the synthesis of indole using aryl hydrazine derivatives. The Fischer reaction provides indole ring from enolizable *N*-arylhydrazones (**Scheme 1**). In 1883, Fischer and Jourdan reported a reaction of pyruvicacid-1-methylphenylhydrazone **5.1** with alcoholic HCl.[5] However, later the product was identified by Fischer and Hess as 1-methylindole-2-carboxylic acid **5.2** (**Scheme 1**, eq. 1).[6] Since the discovery of this reaction, this method has been extensively used for indole synthesis. Later, several modifications have been done to synthesize indole

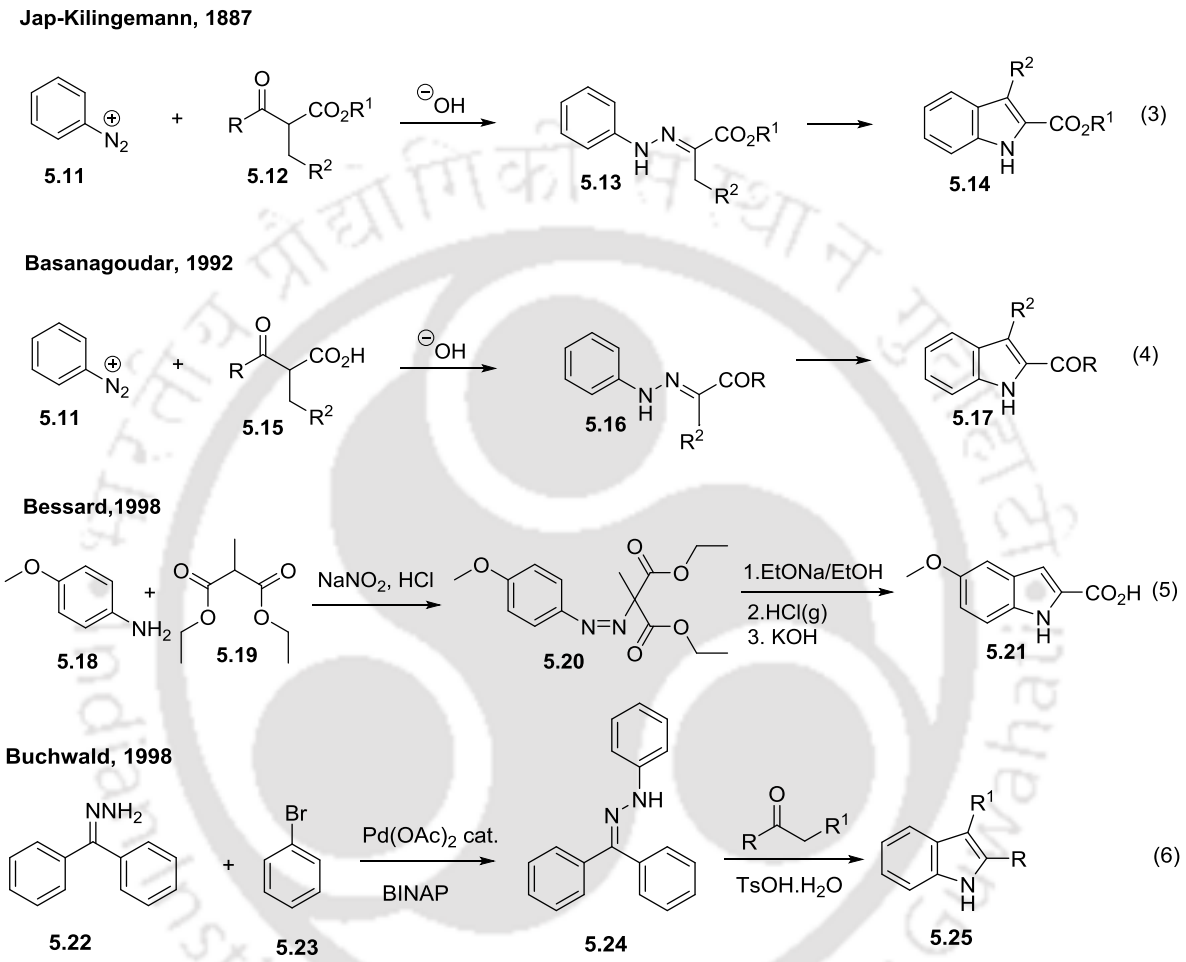
based on Fischer indolization chemistry. Ketone/aldehyde **5.4** and the arylhydrazine **5.3** reacts in presence of acid involving a [3,3]-sigmatropic rearrangement followed by annulation provides indole ring. The Fischer indole reaction provides a simple, efficient method for the transformation of *N*-arylhydrazones into indoles. Often, the indole formation is carried out by simple heating the ketone or aldehyde and the arylhydrazine in the presence of acid catalyst, without the isolation of hydrazone intermediate. Also, the *N*-arylhydrazones are easily prepared via condensation of an arylhydrazine with ketone. The main advantages of the Fischer indole synthesis are functional group compatibility and the formation of the new C-C and C-N bonds without requiring any prefunctionalization.



Scheme 1: Fischer indole synthesis.

Indolization using aryldiazonium salt has been used as an alternative route to Fischer indole reaction. In 1992, Japp-Kilingemann and co-workers reported indolization reaction of aryldiazonium salts and *β*-ketoesters. When aryldiazonium salt **5.11** was treated with *β*-ketoesters derivative **5.12** in the presence of a base, aryl hydrazone **5.13** was formed via deacylation of **5.12**. [3, 3] sigmatropic rearrangement followed by annulation provide the indole **5.14** (**Scheme 2**, eq. 3).[7] Similarly, Basanagoudar and co-workers reported preparation of 2-acylindole **5.17** by using a *β*–ketoacid **5.15** and aryldiazonium salt **5.11**. Decarboxylation followed by annulation afforded indole **5.17** (**Scheme 2**, eq. 4).[8] In 1998, Bessard and co-workers developed a one-pot reaction to prepare indole derivative. Diazotization of *p*-anisidine **5.18** in presence of $NaNO_2$, HCl gave the diazonium salt, which was *in situ* treated with dimethyl 2-methylmalonate **5.19** to afford **5.20**. Catalytic

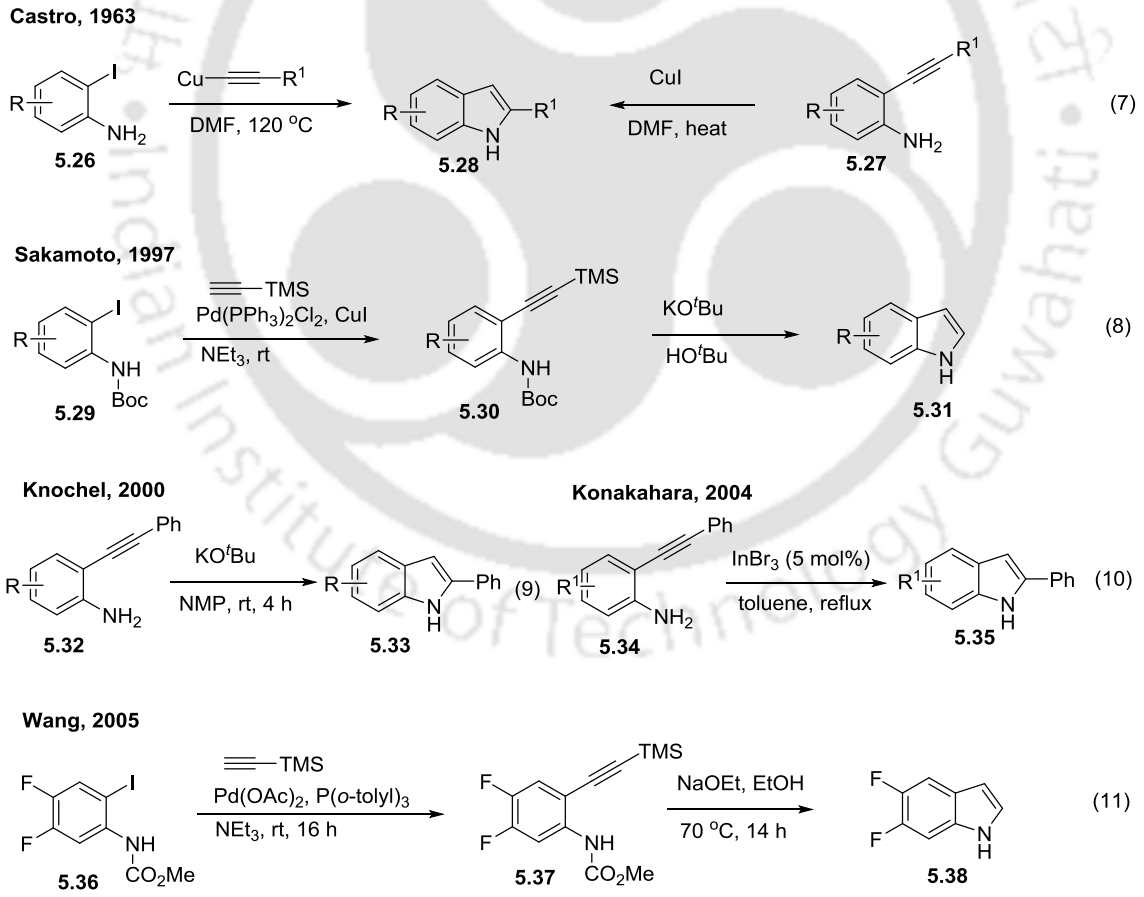
sodium ethoxide in ethanol was used to get the corresponding hydrazone. Then cyclization was achieved by using gaseous HCl to provide indole-2-carboxylic acid derivative (**Scheme 2**, eq. 5).[9] Buchwald and co-workers have used a Pd catalyzed coupling of **5.22** and **5.23** for indole synthesis. The reaction of the intermediate *N*-aryl benzophenone hydrozone **5.24** with a ketone provided the indole derivative **5.25** (**Scheme 2,** eq. 6).[10]



Scheme 2: Selected examples of indolization using aryldiazonium salt and hydrazone derivatives.

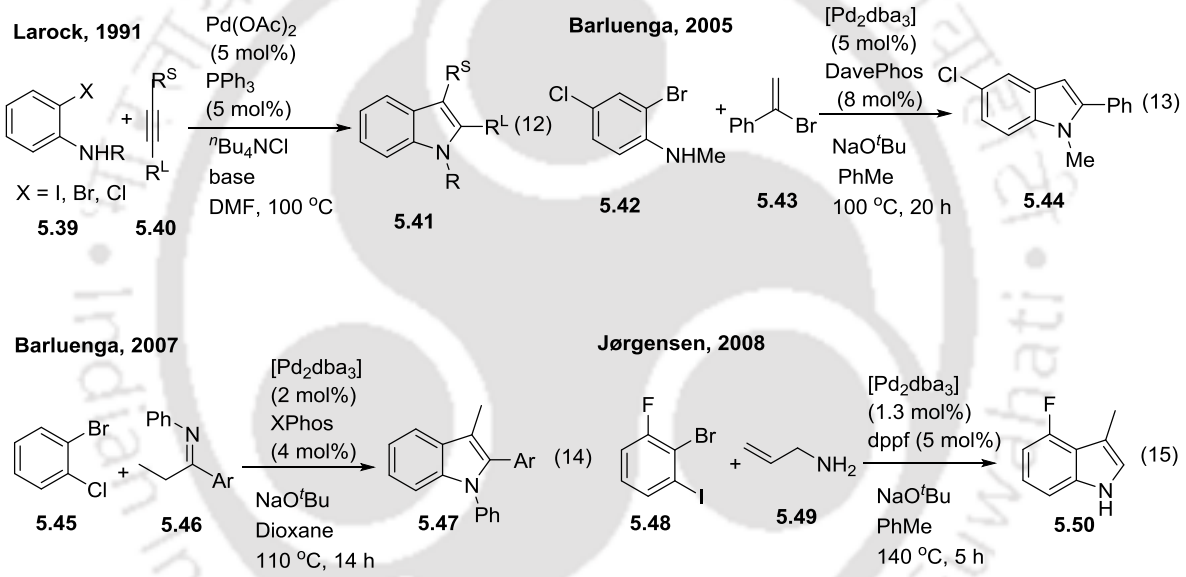
During the last two decades, *o*-alkynylaniline derivatives have been extensively used for indole ring synthesis. The overall reaction sequence involves a two-step process: (1) Sonogashira cross-coupling of *o*-haloanilines with alkyne and (2) cyclization of 2-alkynylanilines gives the corresponding indole. In 1963, Castro and co-workers disclosed a protocol for the synthesis of indole derivative **5.28** involving cyclization of *o*-iodoaniline derivatives **5.26** with cuprous acetylides. Indole derivative **5.28** was also formed from the reaction of 2-alkynylaniline **5.27** with copper(I)iodide (**Scheme 3**, eq. 7).[11] Since then copper(I)iodide promoted indolization via cyclizations of 2-alkynylanilines have received a

great amount of attention as an alternative protocol for the construction of indoles. Later in 1997, Sakamoto and co-workers have demonstrated an alkoxide-mediated cyclization protocol of 2-alkynylaniline for indole synthesis. $Pd(PPh)_2Cl_2$ and copper(I) iodide mediated Sonogashira cross-coupling of (trimethylsilyl)acetylene and iodoanilides **5.29** in the presence of triethylamine afforded the (trimethylsilyl)ethynyl phenylcarbamates **5.30** which underwent cyclization in the presence of KO^{t}Bu to provide indole **5.31** (**Scheme 3**, eq. 8).[12] Knochel and co-workers reported KO^{t}Bu mediated cyclization of 2-alkynylaniline **5.32** to indole **5.33** (**Scheme 3**, eq. 9).[13] In 2004, Konakahara and co-workers reported indium tribromide catalyzed intramolecular cyclization of 2-alkynylaniline **5.34** to afford indole **5.35** (**Scheme 3**, eq. 10).[14] Wang and co-workers have developed a NaOEt mediated cyclization of 2-alkynylanilines for the synthesis of indole derivatives. Palladium-catalyzed coupling of carbamate **5.36** and trimethylsilylacetylene in the presence of NEt_3 afforded acetylenide **5.37** which on treatment with NaOEt in EtOH underwent cyclization, desilylation, and deacylation to provide indole **5.38** (**Scheme 3**, eq. 11).[15]



Scheme 3: Indole synthesis from *o*-alkynylanilines derivatives.

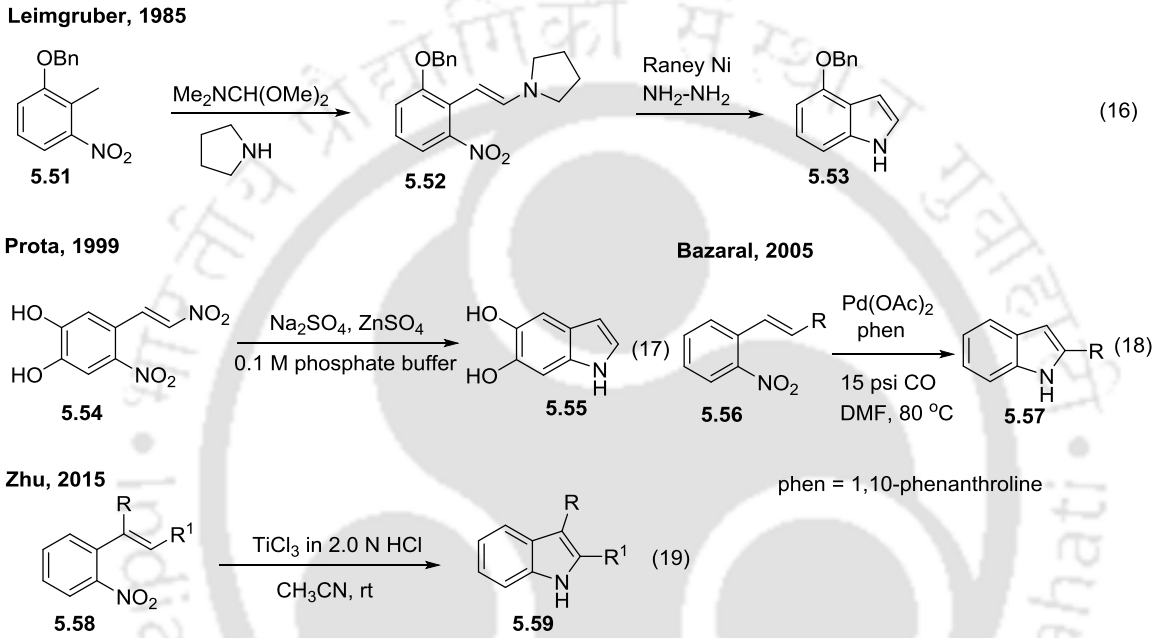
In 1991, Larock and co-workers disclosed a method of 2,3-disubstituted indoles synthesis. Palladium-catalyzed heteroannulation of *N*-protected *o*-iodoaniline **5.39** and alkynes **5.40** afforded 2,3-disubstituted indole **5.41** (**Scheme 4**, eq. 12).[16] Barluenga and co-workers described a $Pd_2(dba)_3$ catalyzed method to access 2-substituted indole **5.44** from *o*-haloanilines **5.42** and *α*-bromostyrene **5.43** (**Scheme 4**, eq. 13).[17] Later, the same group has developed a route to 2,3-disubstituted indole using *o*-dihaloarenes **5.45** and imines **5.46** (**Scheme 4,** eq. 14).[18] In 2008, Jørgensen and co-workers developed an elegant protocol for indole synthesis using *o*-dihaloarene **5.48** and allylamine **5.49**. Pd_2dba_3-dppf catalyzed *N*-arylation, Heck-coupling and an isomerization reaction sequence lead to the indole **5.50** (**Scheme 4**, eq. 15).[19]



Scheme 4: Indole synthesis from *o*-halolanilines and *o*-dihaloarenes.

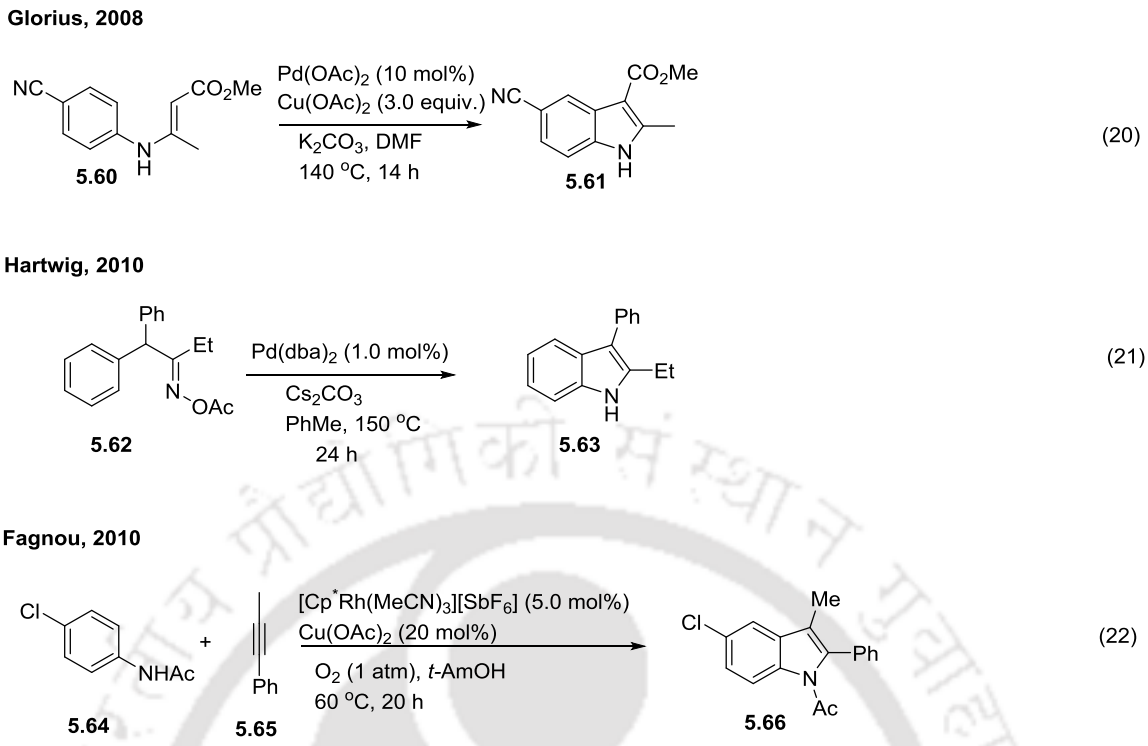
The reductive cyclization of aromatic nitro compounds is another prevalent method for the construction of the indole ring. Due to commercial availability and readily accessibile *o*-nitrotoluene derivatives, they have been widely used in synthesis of indoles via reductive cyclization process. One of the most commonly used methods for the construction of 2,3-unsubstituted indoles is the Leimgruber-Batcho indole synthesis. In 1985, Leimgruber and co-workers reported condensation reaction of *o*-nitrotoluene **5.51** and dimethylformamide dimethyl acetal to afford *β*-(dimethylamino)-2-nitrostyrene **5.52** which on reductive cyclization provided indole derivative **5.53** (**Scheme 5**, eq. 16).[20] The reductive cyclization of *ortho*-*β*-nitrostyrenes is one of the important and effective methods for the indole

synthesis, where other protocols have failed. Prota and co-workers developed a method for synthesis of 5,6-dihydroxyindole **5.55** from **5.54**. The reaction does not require any protecting groups for hydroxyl functionality (**Scheme 5**, eq. 17).[21] In 2005, Bazaral and co-workers developed a reductive cyclization reaction of **5.56** to afford corresponding indole derivative **5.57** (**Scheme 5**, eq. 17).[22] In 2015, Zhu and co-workers have reported a $TiCl_3$ promoted cyclization reaction of *o*-nitrostyrene **5.58** to prepare indole **5.59** via reductive C(sp^2)-H amination process (**Scheme 5**, eq. 19).[23]



Scheme 5: Selected examples of indole synthesis via reductive cyclization of nitroarenes.

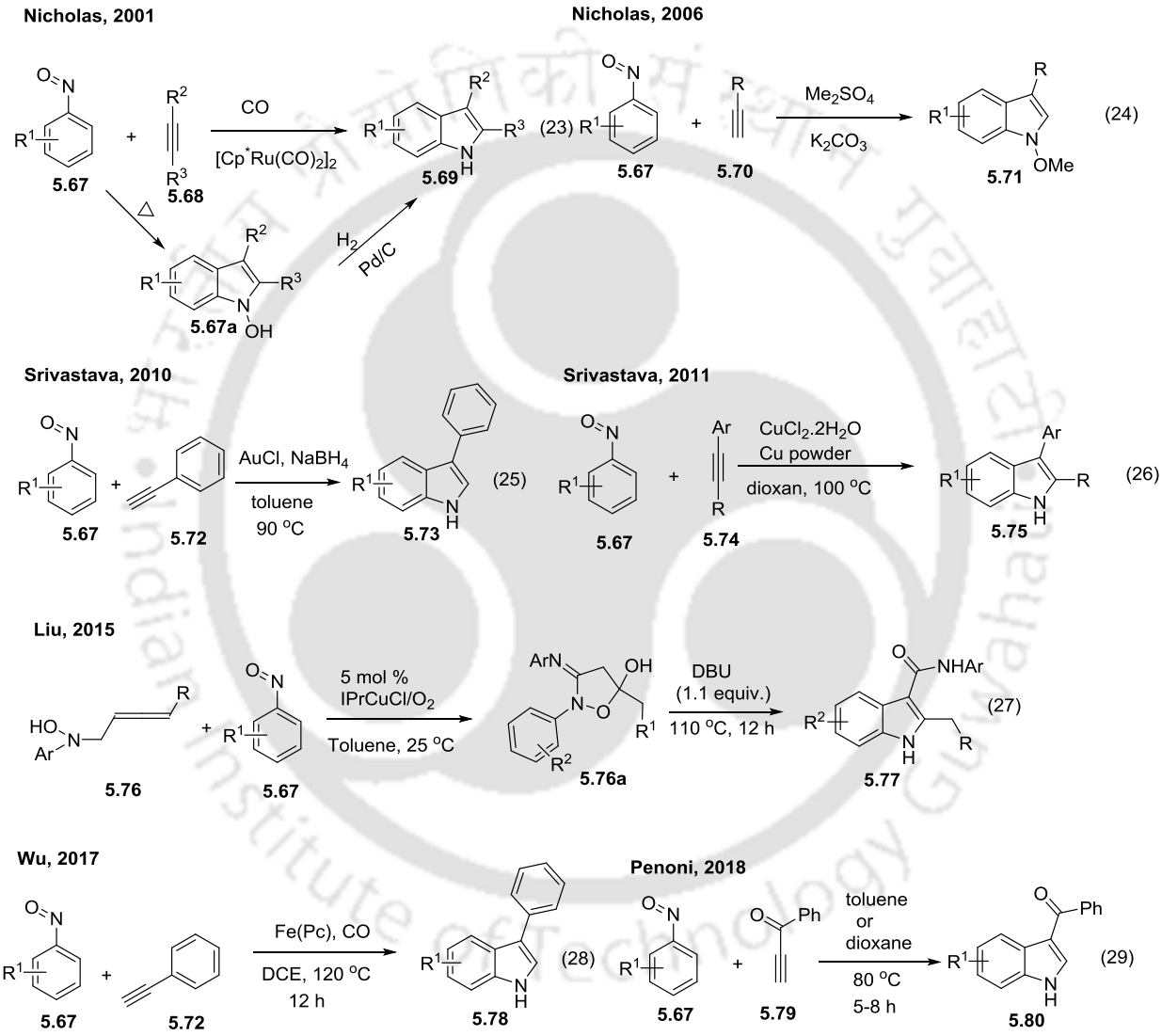
Since last decades, transition metal-catalyzed C-H-bond functionalization has emerged as an important strategy for indole syntheses. In 2008, Glorius and co-workers have developed a Pd catalyzed intramolecular oxidative cyclization through C-H functionalization of *N*-aryl enamine **5.60** to afford indole derivative **5.61** (**Scheme 6**, eq. 20).[24] Hartwig and co-workers have developed a palladium-catalyzed intramolecular amination of an aromatic C-H-bond of *β*-aryl oxime ester derivative **5.62** to access indole derivative **5.63** (**Scheme 6**, eq. 21).[25] Fagnou and co-workers reported a rhodium-catalyzed cyclization of protected aniline derivative **5.64** with alkyne **5.65** to afford 2, 3-disubstituted indole **5.66** (**Scheme 6**, eq. 22).[26]



Scheme 6: Selected examples of indole synthesis through C-H-bond functionalizations.

Recently, nitrosoarene has been employed for the construction of indole ring due to its high reactivity and easy availability. In 2001, Nicholas group reported an annulation reaction of nitrosoarene and alkynes. $[Cp^*Ru(CO)_2]^{2-}$catalyzed reaction of nitrosoareane **5.67** with alkyne **5.68** in the presence of carbon monoxide afforded indole **5.69**.[27] They also discovered that simple heating a mixture of **5.67** and **5.70** without using Ru catalyst provided *N*-hydroxy indole **5.67a**. The reduction of the intermediate *N*-hydroxyindoles **5.67a** afforded indole derivative **5.69** (**Scheme 7**, eq. 23).[28] Later, the same group has developed a synthesis of *N*-methoxyindoles **5.71** from the reaction between nitrosoarenes **5.67** and alkynes **5.72** in the presence of $K_2CO_3/(CH_3)_2SO_4$ (**Scheme 7**, eq. 25).[29] Srivastava and co-workers have developed an Au-catalyzed annulations reaction of nitrosoarene **5.67** and phenylacetylene **5.70** to form 3-arylindole **5.71** (**Scheme 7**, eq. 24).[30] The intermediate hydroxyindole was reduced to the corresponding indole derivatives by using $NaBH_4$. They have also developed a two-step method for the preparation of indole derivative using nitrosoarenes and alkynes in the presence of a mixture of $CuCl_2$–Cu powder (**Scheme 7**, eq. 26).[31] Liu and his group reported a [3 + 2]-annulation reactions of *N*-hydroxy allenylamines **5.76** with nitrosoarene **5.67** to form isoxazolidin-*5*-ol **5.78** using $IPrCuCl/O_2$ as a radical initiator. Isoxazolidin-*5*- ol **5.76a** undergo skeletal rearrangement on heating in the presence

of DBU to afford indole derivative **5.75** (**Scheme 7**, eq. 27).[32] In 2017, Wu and co-workers have reported a method for 3-aryl indole synthesis by using nitrosoarene and phenylacetylene in the presence of iron(II) phthalocyanine (Pc) catalyst and CO as the reductant (**Scheme 7**, eq. 28).[33] In 2018, Penoni and co-workers have developed an annulation reaction of nitrosoarene with conjugated terminal alkynones to synthesize 3-arylindoles (**Scheme 7**, eq. 29).[34]

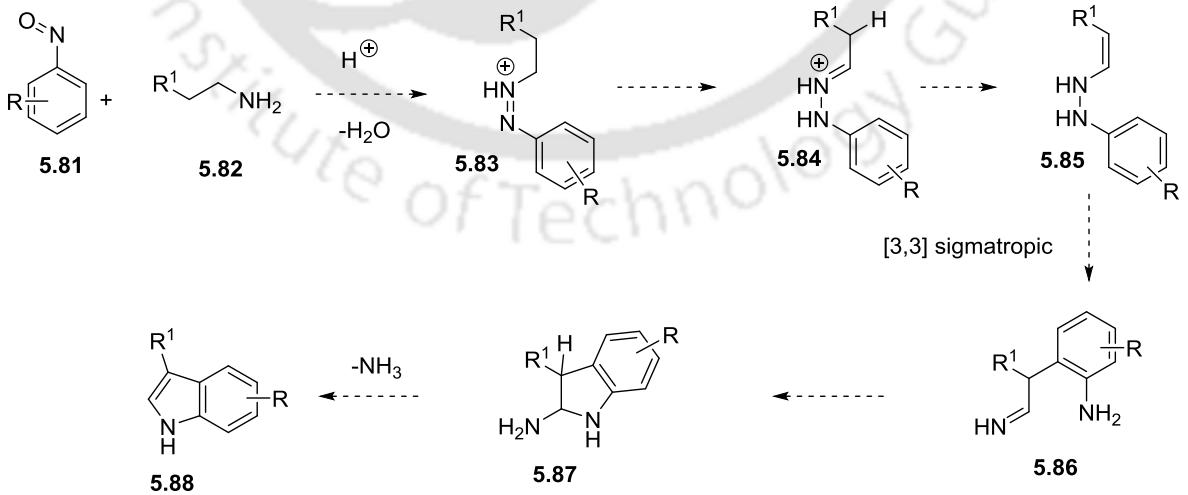


Scheme 7: Indole synthesis using nitrosoarene.

In spite of the huge progress in the field of indole synthesis, the previous methods have their own advantages and disadvantages. The Fischer indole and related synthesis, which employs hydrazines and ketones, suffers from few drawbacks. The lack of availability of all aryl hydrazines which usually are prepared by reduction of corresponding aryl diazonium salts using toxic metal mediate reagents (e.g, tin) is the major drawback. Moreover, in case

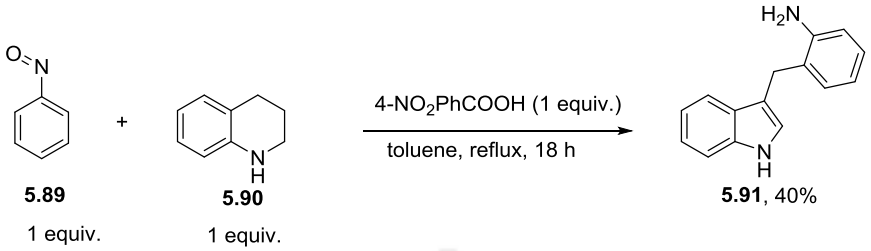
of unsymmetrical ketones having more than one enolizable proton results in two regioisomeric indoles. Transition-metal-catalyzed transformation using *o*-halogenated anilines strategies require pre-functionalized precursors thereby lengthening the synthetic path. During the last two decade, indole synthesis from *o*-alkynylaniline became a very useful tool, however, this often requires multiple steps to synthesize the *o*-alkynylaniline, thus restricting their application to some extent. Reductive cyclization of 2-nitro aryl, *o*-nitrostyrenes and *o*-*β*-nitrostyrenes compounds is another convenient route to indole scaffold. Availability and synthesis of the suitably substituted precursors limit the scope of these reactions. Reductive annulations or cycloaddition of nitrosoarene with an alkynes are well established by Nicholas group and Srivastava group. However, these methods entail expensive metals, an additional reducing agent or high-pressure CO to reduced hydroxy indoles *in situ*. While the majority of the indole synthesis using nitrosoarene involved alkynes derivatives. Therefore, the development of a metal-free and direct method to access indoles using nitrosoarene as simple and readily available starting material is desirable.

Generally, the addition of amines to the nitroso group of nitrosoarene results in the formation of azo compounds.[35] It was anticipated that azo compound **5.83** formed from the reaction of nitrosoarene **5.81** and amine **5.82** can undergo isomerization to afford **5.84.** Further isomerisation of **5.85** can give rise to hydrazine analogue **5.85** which can undergo [3, 3] sigmatropic rearrangement to provide **5.86**. Then cyclization followed by aromatization can afford the desired indole derivative **5.88** (**Scheme 8**).



Scheme 8: Hypothesis for the indole synthesis via direct condensation of amines and nitrosoarenes.

According to the anticipation, nitrosobenzene **5.89** was reacted with 1 equiv. of tetrahydroquinoline (THQ) **5.90** in presence of 1 equiv. of 4-NO_2-benzoic acid in refluxing toluene. To our delight, after 18 h 3-substituted indole **5.91** was isolated with 40%.

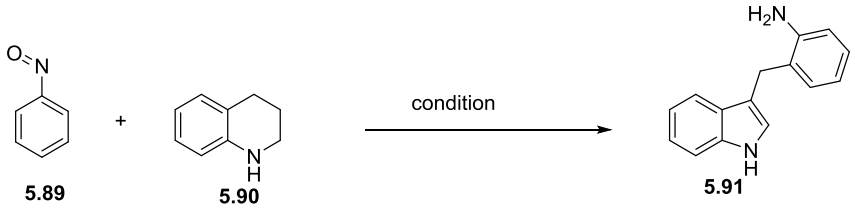


Scheme 9: Initial result.

5.3 Results and Discussions:

Encouraged by the initial result, different reaction conditions were screened to increase the yield of the indole derivative **5.91**. The relative stoichiometry of nitrosobenzene was increased to 1.5 equiv. and reacted with 1 equiv. of THQ to afford **5.91** with 51% yield (**Table 1**, entry 3). The yield of **5.91** was found to increase to 58% on further increase in the amount of nitrosobenzene to 2 equiv. (**Table 1**, entry 4). However, further increase in the equivalence of nitrosobenzene leads to a decrease in the yield of **5.91** (**Table 1**, entry 5). Toluene was found to be the best among the other solvents, such as dichloroethane (DCE), benzene, toluene, DMF, DMSO (**Table 1**, entry 6-10). When benzoic acid was used as acid source, the yield of **5.91** decreased to 42% (**Table 1**, entry 11). Similar decrease of the yields of the reaction were observed on using different organic and inorganic acids such as 3, 5-di-NO_2-benzoic acid, 2, 5-di-Cl-benzoic acid, 4-Cl-benzoic acid, CF_3CO_2H and acetic acid etc (**Table 1**, entry 12-18). It was realized that the formation of azoxybenzene leads to decrease in the formation of desired **5.91**. To avoid the formation of undesired azoxybenzene, the reaction was performed with slow addition of nitrosobenzene. When a solution of nitrosobenzene in toluene was added to a solution of THQ and 4-NO_2-benzoic acid using syringe pump over 2 h, provided **5.91** with 68% yield (**Table 1**, entry 21). The best result was found when 1 equiv. of THQ was reacted with 2 equiv. of nitrosobenzene (added portion-wise over a period of 2 h) in the presence of 1 equiv. of 4-NO_2-benzoic acid in refluxing toluene (70%, **Table 1**, entry 20).

Table 1: Variation of reagents and reaction conditions to obtained the best yields of the desired product.



5.89 5.90 5.91

Variation of equivalence of nitrosobenzene.

Entry	Acids (equiv.)	Equiv. of PhNO	Solvent (reflux)	Yield (%)
1	4-NO_2PhCO_2H (1.0)	1	toluene	40
2 [a]	4-NO_2PhCO_2H (1.0)	1	toluene	54
3	4-NO_2PhCO_2H (1.0)	1.5	toluene	51
4	4-NO_2PhCO_2H (1.0)	2	toluene	58
5	4-NO_2PhCO_2H (1.0)	2.5	toluene	49

Screening of the solvent of the reaction.

Entry	Acids (equiv.)	Equiv. of PhNO	Solvent (reflux)	Yield (%)
6	4-NO_2-PhCOOH (1)	2	DCE	45
7	4-NO_2-PhCOOH (1)	2	benzene	46
8	4-NO_2-PhCOOH (1)	2	xylene	40
9	4-NO_2-PhCOOH (1)	2	DMSO	31
10	4-NO_2-PhCOOH (1)	2	DMF	24

Variation of acid source.

Entry	Acids (equiv.)	Equiv. of PhNO	Solvent (reflux)	Yield (%)
11	$PhCO_2H$ (1.0)	2	toluene	42
12	4-Cl-$PhCO_2H$ (1.0)	2	toluene	40
13	3, 5-di-NO_2PhCO_2H (1.0)	2	toluene	40
14	2, 5-di-Cl-$PhCO_2H$ (1.0)	2	toluene	37
15	CF_3CO_2H (1.0)	2	toluene	ND
16	1-NO_2PhCO_2H (1.0)	2	toluene	28
17	AcOH (1.0)	2	toluene	ND
18	PTSA(1.0)	2	toluene	ND
19	No acid	2	toluene	trace

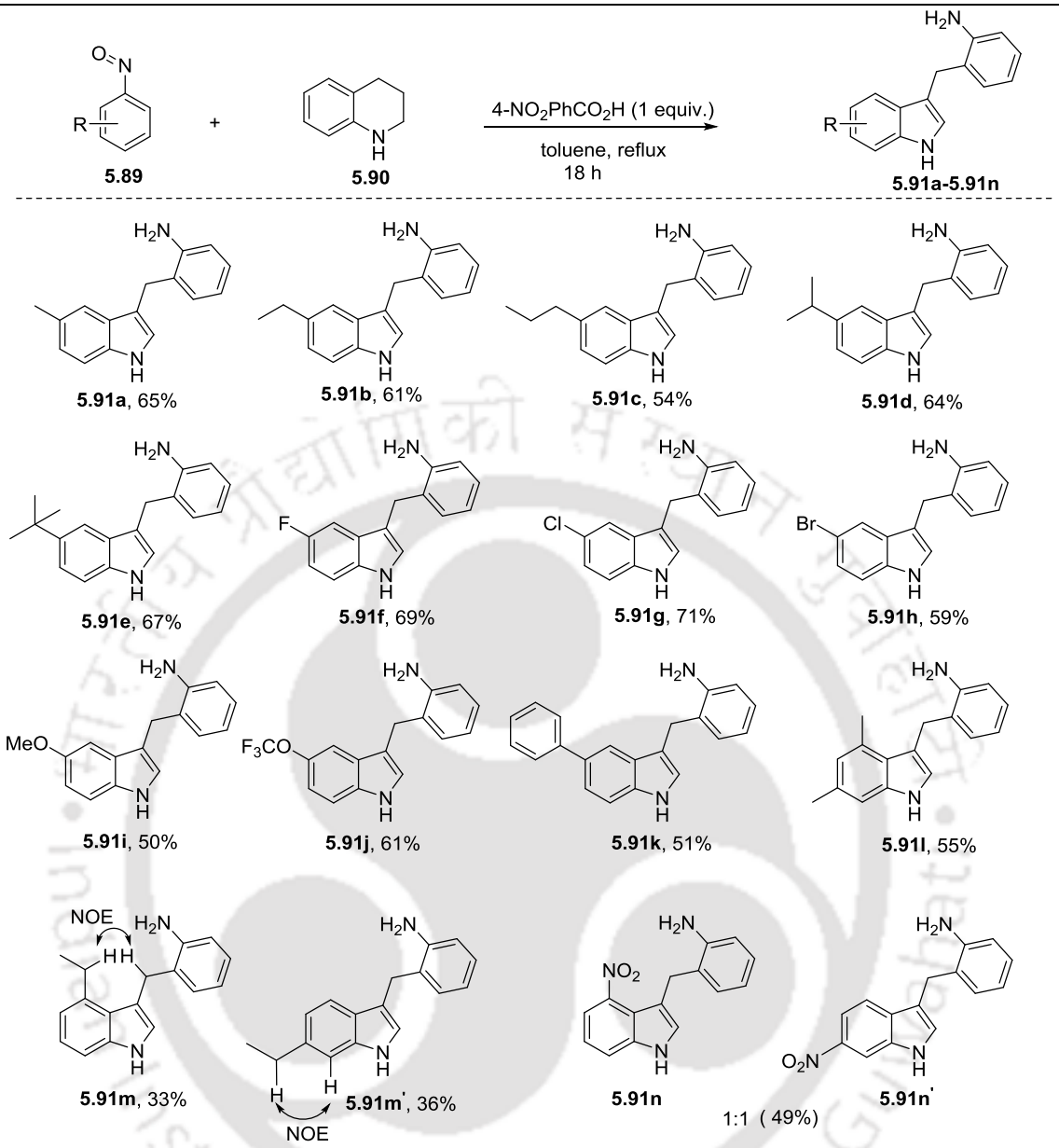
Addition of nitrosobenzene.

Entry	Acids (equiv.)	Equiv. of PhNO	Solvent (reflux)	Yield (%)
20[b]	4-NO_2-PhCOOH (1)	2	toluene	70
21[c]	4-NO_2-PhCOOH (1)	2	toluene	68
22[b]	4-NO_2PhCO_2H (0.2)	2	toluene	54
23[b]	4-NO_2PhCO_2H (0.5)	2	toluene	60
24[b]	4-NO_2PhCO_2H (2)	2	toluene	41
25[d]	4-NO_2PhCO_2H (1)	2	toluene	66

All reactions were performed with of THQ (0.30 mmol), nitrosobenzene (0.60 mmol) in solvent (4 mL) for 18 h. [a]1.5 equiv. of THQ was used, [b] addition of nitrosobenzene over 2 h and [c]addition of nitrosobenzene in toluene was carried out over 2 h by syringe pump. [d]addition of nitrosobenzene over 3 h.

5.4 Scope of the reaction with nitrosoarenes:

Optimized reaction conditions were used to explore the substrate scope of the reaction of indole synthesis with various nitrosoarenes and THQ. Nitrosoarene containing different *para*-substituents were reacted with THQ to obtain the corresponding 3-substituted indoles (**Scheme 10**). Alkyl group (Me, Et, *n*-propyl, ^{i}pr, ^{t}Bu) substituted nitrosarenes reacted well with THQ to give corresponding indoles (**5.91a-5.91e**) with good yields. *para*-fluoro substituted nitrosoarene provides corresponding indoles **5.91f** with 69% yield. Similarly, *para*-chloro and –bromo nitrosoarenes provided indole **5.91g** and **5.91h** with good yields. 4-substituted nitrosoarenes (4-OCH_3,-OCF_3, -Ph) gave the corresponding indole **5.91i-5.91k** with good to moderate yield. 3, 5-dimethylnitrosobenzene also reacted smoothly to afford **5.91l** with a moderate yield. However, regioisomeric products were obtained from the reaction of *m*-substituted nitrosobenzene. **5.91m** (33%) and **5.91m'** (36%) were isolated from the reaction of 3-ethylnitrosobenzene. However, 3-nitro-nitrosobenzene provided an inseparable mixture of **5.91n** and **5.91n'** with 1:1 ratio (49%) (**Scheme 10**).

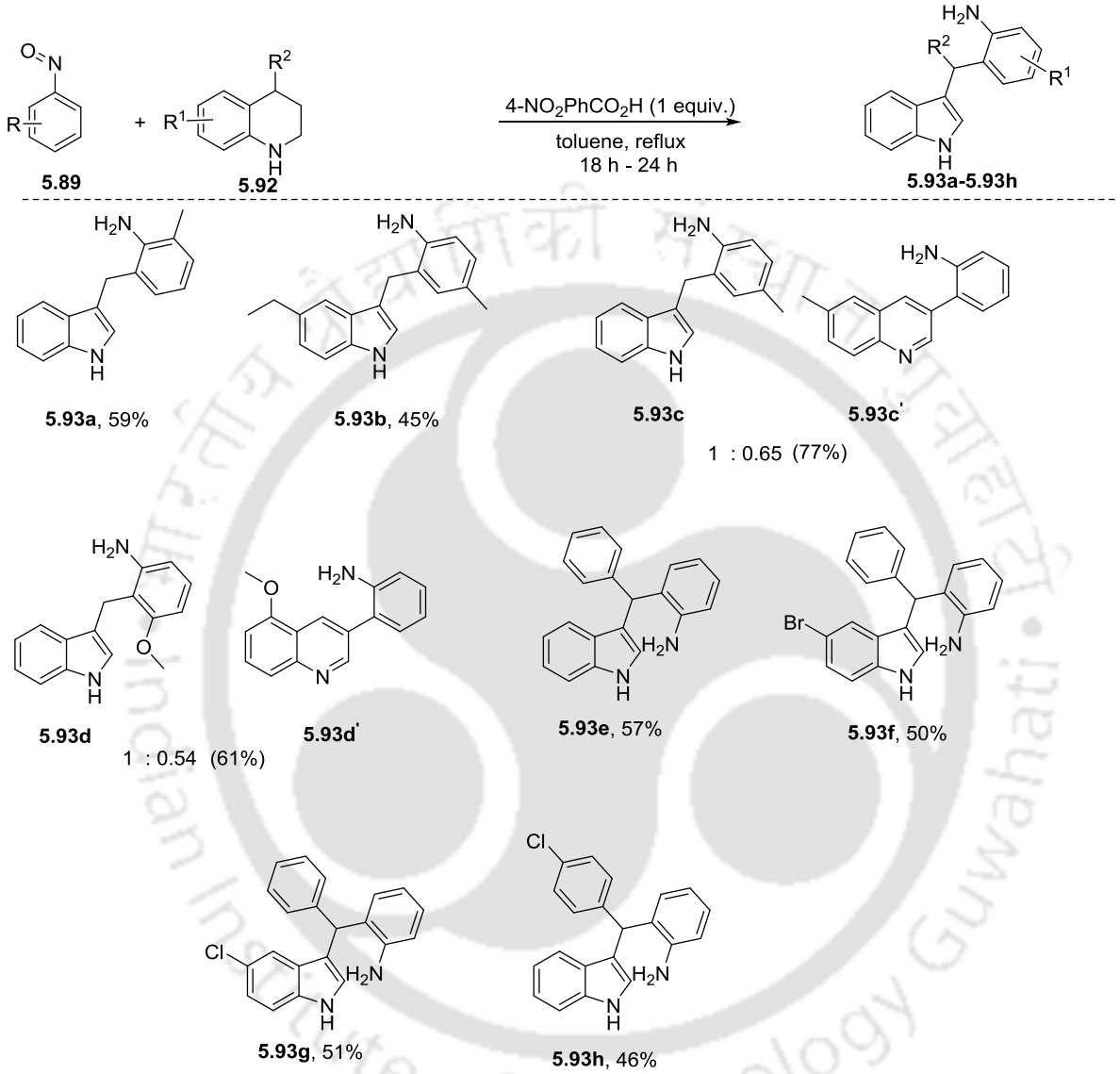


Scheme 10: Scope of the reaction with nitrosoarenes.

5.5 Scope of the reaction with tetrahydroquinoline derivatives:

Next, the reaction of substituted THQ derivative with different nitrosoarenes was investigated to further expand the scope of this novel indole synthesis reaction. 8-methyltetrahydroquinoline afforded corresponding indole **5.93a** with 59% yield. 6-methyltetrahydroquinoline on reaction with 4-ethylnitrosobenzene provided indole **5.93b** with 47% yield. Interestingly, the presence of electron donating group such as -Me, -OMe in THQ on reaction with unsubstituted nitrosoarene gave rise to corresponding 3-aryltedquinoline derivatives along with the desired indoles. 6-methyltetrahydroquinoline

afforded desired **5.93c** with 47% yield along with **5.93c'** with 30% yield. Similarly, 5-methoxytetrahydroquinoline produced **5.93d** and **5.93d'** with 45% and 26% respectively. 4-aryl substituted THQ derivatives on reaction with different nitrosoarenes also gave the corresponding indoles **5.93e-5.93h** with good to moderate yields (**Scheme 11**).

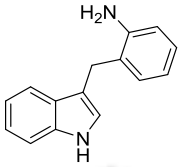
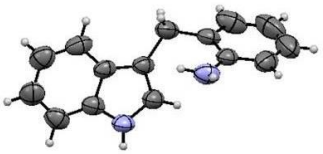
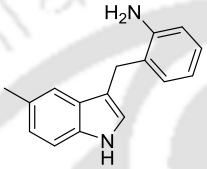
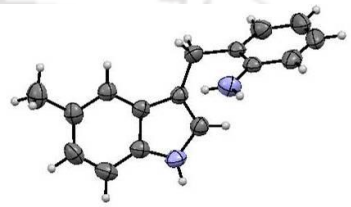
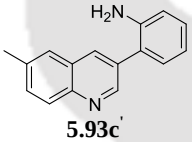
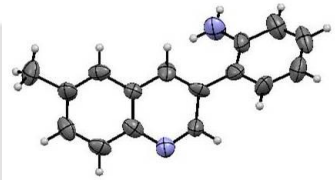


Scheme 11: Scope of the reaction with THQ derivatives.

5.6 Crystal structures of the 3-benzylindole derivatives and 3-arylquinoline derivative:

The structures of the 3-benzylindole **5.91**, **5.91a** and 3-arylquinoline **5.93c'** were confirmed by X-ray crystallographic analysis. The structures of compounds have been shown below (**Table 5**).

Table 5: Selected 3-benzylindole derivatives and 3-arylquinoline derivative and their X-ray crystal structures.

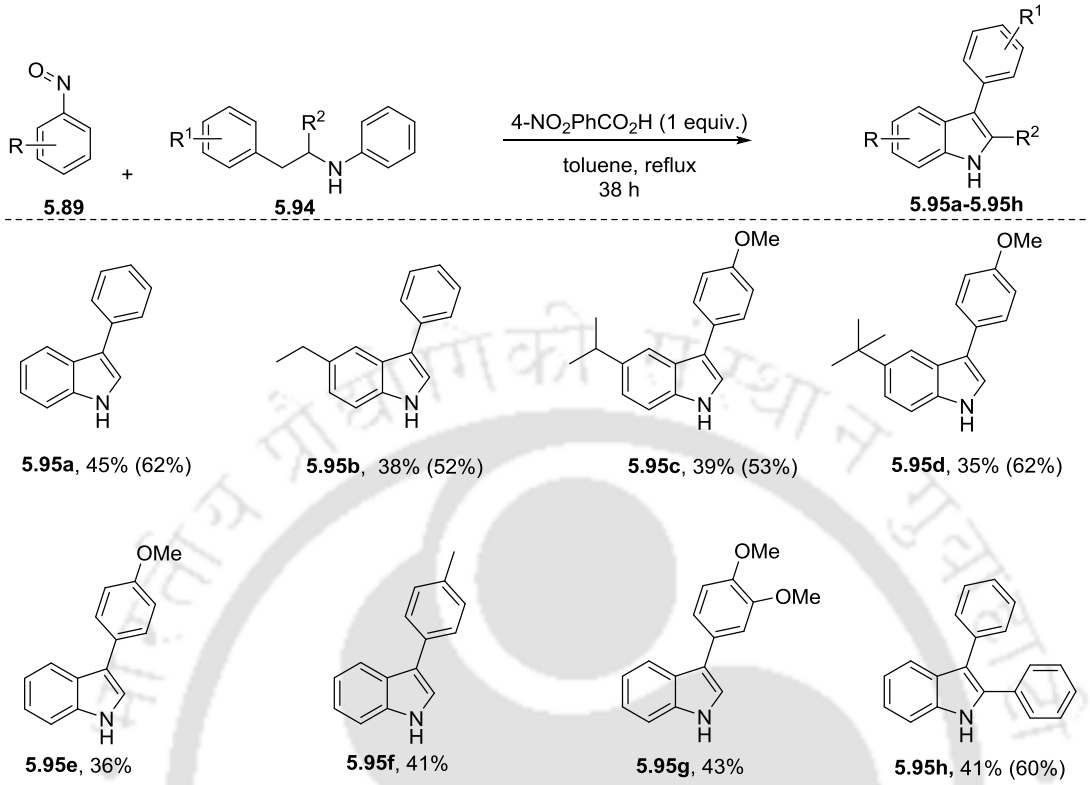
Compound	Crystal structure
 **5.91**	
 **5.91a**	
 **5.93c**	

5.7 Scope of the indole synthesis with acyclic amines:

Functionalization of acyclic secondary amine is extremely challenging without using any metallic reagent or photocatalyst.[36,37] After having success in C(sp^3)-H amination reaction involving cyclic amines THQ, the scope of this reaction with acyclic secondary amines was investigated. When *N*-phenylphenethyl amine was reacted with nitrosobenzene in the presence of 4-NO_2PhCOOH in refluxing toluene, after 38 h, desired 3-phenylidole **5.95a** was isolated with 45% yield. However, with respect to the recovered starting phenethyl-phenyl-amine, the yield of the reaction was found to be 62%.

Then various nitrosoarenes and various phenethyl-phenyl-amine derivatives were reacted to further increase the scope of the reaction. *para*-substituted nitrosobenzenes were reacted with *N*-phenylphenethyl amine derivatives to afford different 3-arylindoles **5.95b-5.95d** with lower yields (38%, 39% and 35% respectively). Different substituted *N*-phenylphenethyl amines were also reacted with nitrosobenzene to afford the corresponding

3-arylindoles **5.95e-5.95g**. 2-substituted *N*-phenylphenethyl amines also afforded indole **5.95h** with 41% yield (**Scheme 12**).

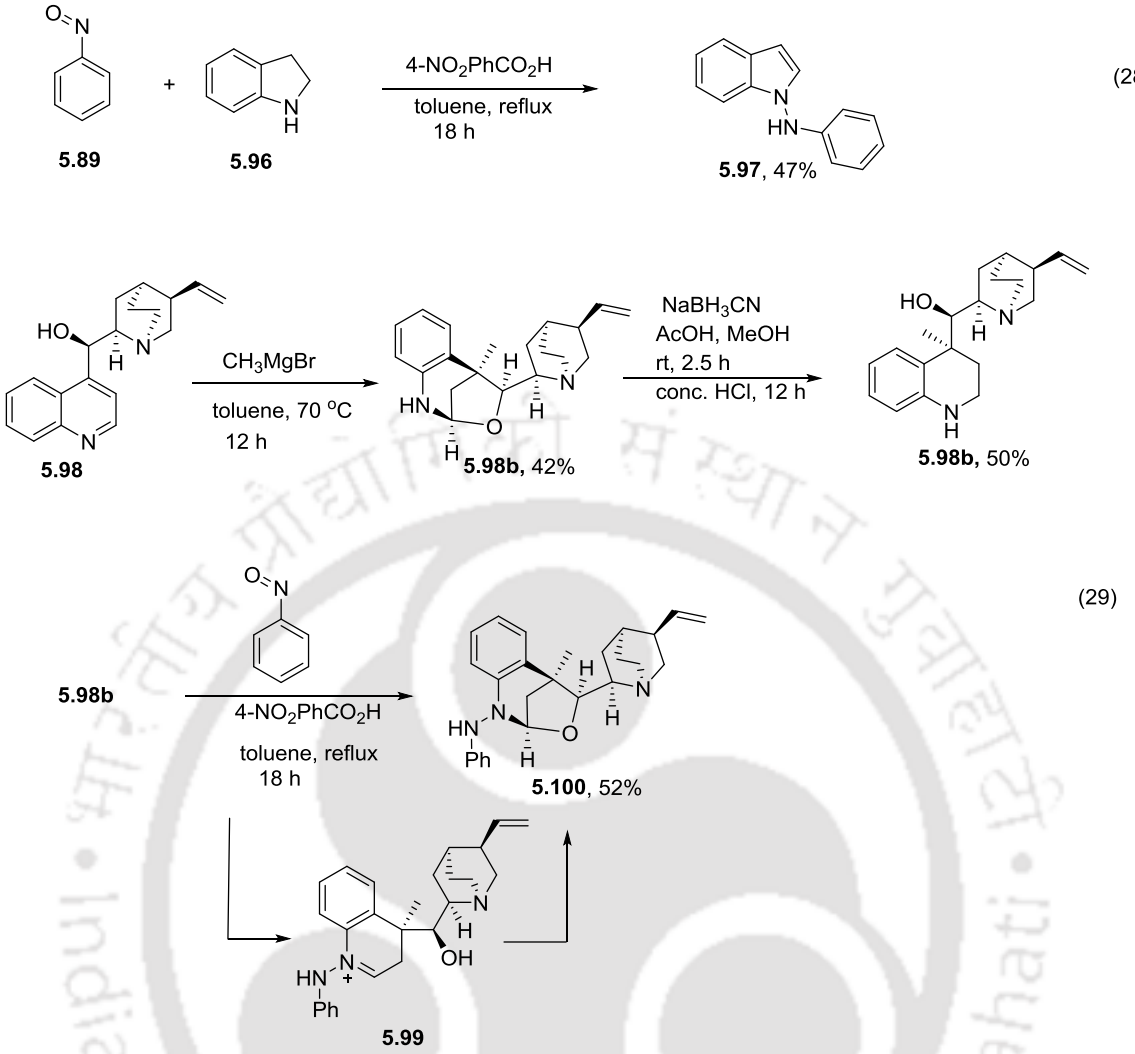


Scheme 12: Scope of the indole synthesis with acyclic amines.

Yields with respect to the recovered starting material are in the in parentheses.

5.8 Controlled experiments:

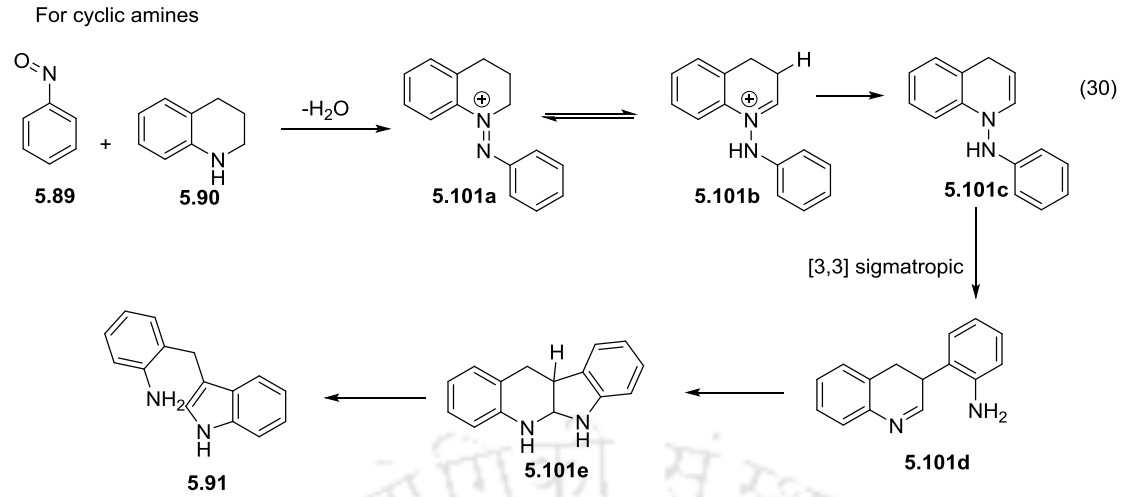
To understand the mechanism of this indole formation reaction, controlled experiments were performed. When indoline **5.96** was reacted with nitrosobenzene under standard reaction conditions, *N*-phenylindole **5.97** was isolated with 47% (**Scheme 13**, eq. 28). The reaction of nitrosobenzene with cinchonine derivative **5.98a** provided *N*-aminated oxazine **5.100** with 51% yield (**Scheme 13**, eq. 29). These results suggest that the reaction is going via iminium ion intermediate **5.99** and the reaction is going via *N*-amination of nitrosoarene.



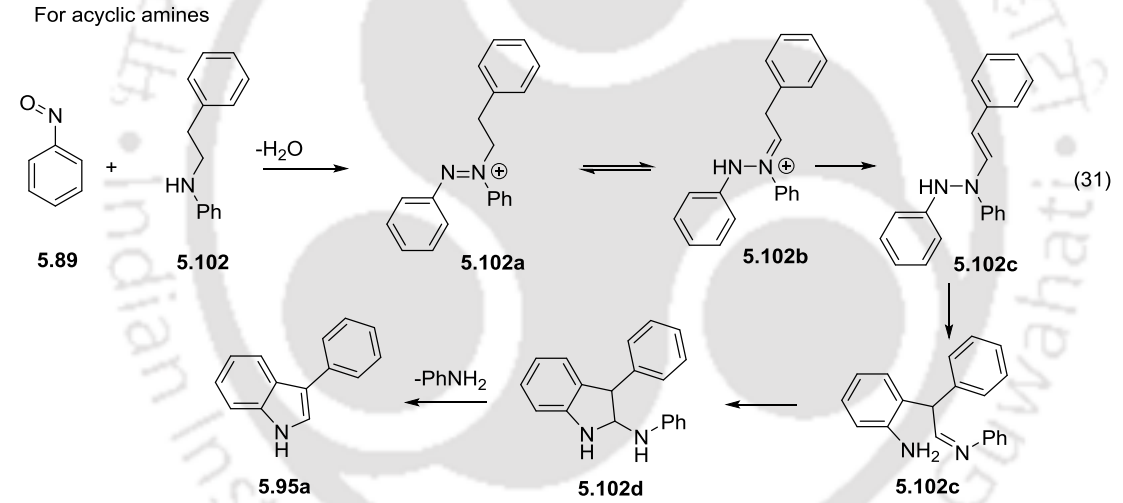
Scheme 13: Controlled experiments.

5.9 Plausible mechanism for indole synthesis:

Based on the experimental results, a plausible mechanism has been depicted in **Scheme 14**. Tetrahydroquinoline reacted with nitrosoarene to afford iminium ion **5.101a** which isomerizes to **5.101b**. Further deprotonation of the *β*-hydrogen gave rise to hydrazine **5.10c** which underwent [3, 3]-sigmatropic rearrangement to provide **5.101d**. Annulation followed by ring-opening of **5.101e** afforded indole **5.91**.



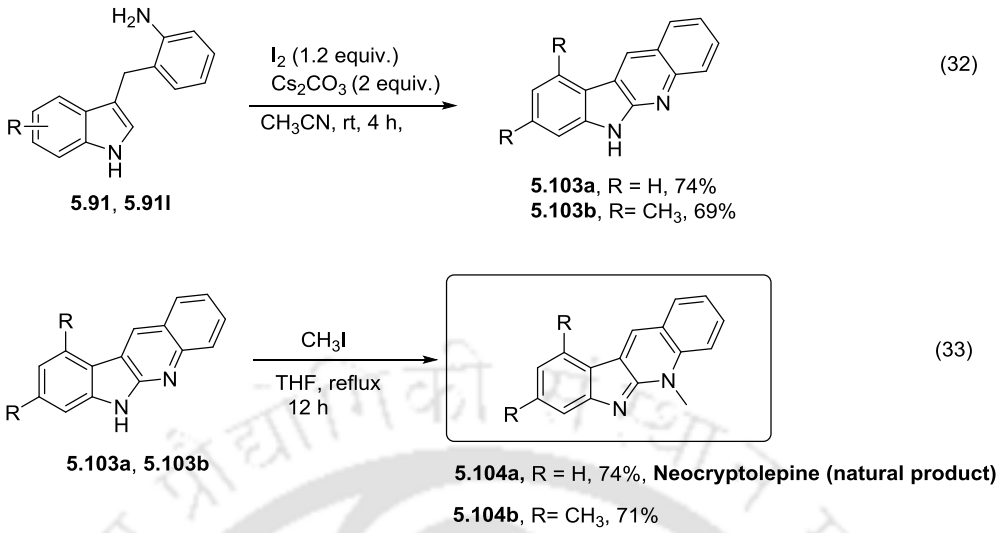
In case of acyclic amines, similar mechanistic path involving *N*-amination, isomerization, deprotonation, [3, 3]-sigmatropic rearrangement and annulations has been followed to afford **5.102d**. Elimination of $PhNH_2$ from **5.120d** provided 3-arylindole **5.95a** (**Scheme 14**).



Scheme 14: Plausible mechanism for the indole synthesis.

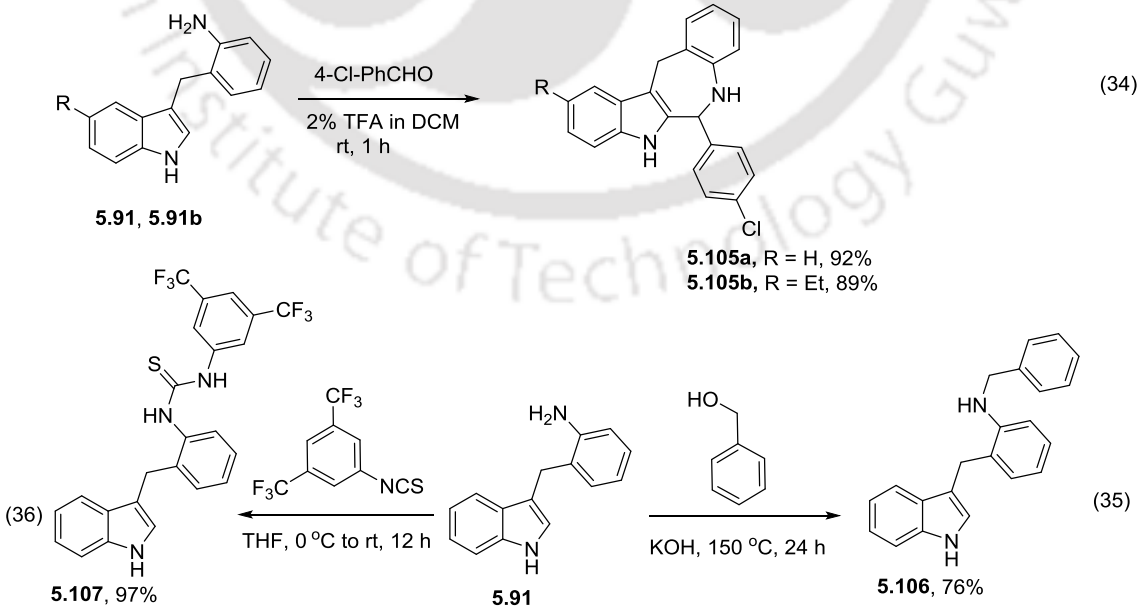
5.10 Synthesis of Neocryptolepine and synthetic applications of 3-benzyl indoles:

Utilizing the advantage of the presence of free -NH_2 group in the benzyl substitution of indole compounds, selected indoles were derivatized under different reaction conditions. Cyclization of indoles **5.91** and **5.103l** was successfully achieved by using molecular iodine and Cs_2CO_3 to provide biologically important norneocryptolepine[38] derivatives **5.103a** and **5.103b** with very good yields (**Scheme 15**, eq. 32). Further *N*-methylation of **5.103a** with CH3I provided natural product neocryptolepine **5.104a** with 74% yield. Similarly, neocryptolepine derivative **5.104b** was prepared from **5.103b** (**Scheme 15**, eq. 33).



Scheme 15: Synthesis of Neocryptolepine.

The azepinoindole derivatives have been found in the marine sponge metabolite hymenialdisine which exhibits several bioactivities such as anti-proliferative, anti-inflammatory etc.[39, 40] Reaction of 4-Cl-benzaldehyde with indole **5.91** and **5.91b** using 2% TFA in dichloromethane in room temperature afforded corresponding benzazepin-indole derivatives **5.105a** and **5.105b** with 92% and 89% yields, respectively (**Scheme 16**, eq. 34). Selective benzylation of -NH_2 was successfully achieved by using benzyl alcohol in the presence of KOH to afford **5.106** with 76% yield (**Scheme 16**, eq. 35). Thiourea formation was carried out by using thiocyanate to afford **5.107** with 97% yield (**Scheme 16**, eq. 36).



Scheme 16: Synthetic applications.

5.11 Conclusion:

In summary, a novel synthetic method for synthesis of indole via C(sp^2)-H functionalization of nitrosoarenes and β-C(sp^3)-H functionalization secondary amines has been developed. Diversely substituted indoles were prepared by the reaction of nitrosoarenes and tetrahydroquinoline. Moreover, β-functionalization of acyclic amines was achieved to provide various 3-arylindoles. Mechanistic studies suggested that the reaction proceeds via *N*-amination of amines and [3, 3]-sigmatropic rearrangement. Additionally, neocryptolepine and its derivatives and other important molecules were prepared by using this novel methodology.

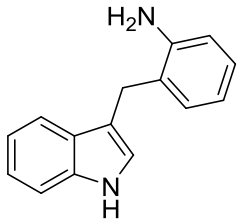
5.12 Experimental Section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Toluene was freshly distilled from phosphorus(V) oxide (P_2O_5). Commercial grade xylene and benzene 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). Nitrosoarene derivatives were synthesized by literature procedures.[41]

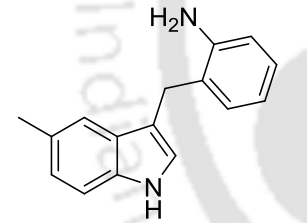
General procedure for the synthesis of 3-benzyl indole derivatives (GP-1): Nitrosoarene (1 equiv.) and 4-nitrobenzoic acid (1 equiv.) were added to a solution of tetrahydroquinoline derivative (0.19 – 0.48 mmol) in dry toluene (4 – 5 mL). After 1 h, additional 1 equiv. of nitrosoarene was added portion wise over a period of 2 h. Then the reaction mixture was refluxed for another 15 h under argon atmosphere. The reaction mixture was allowed to cool to room temperature. Saturated $NaHCO_3$ solution (15 – 20 mL) was added to reaction mixture and extracted with DCM (3 ×15 mL). Organic layer was dried over Na_2SO_4 and the

which was purified by column chromatography to afford analytically pure 3-benzyl indole derivatives.

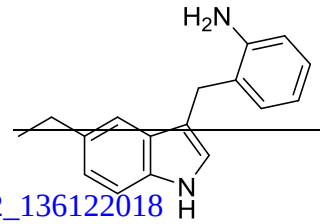
2-((1*H*-indol-3-yl)methyl)aniline (5.91): According to GP-1: nitrosobenzene (64 mg, 0.60 mmol), 1,2,3,4-tetrahydroquinoline (38 µL, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91** as a colorless solid (47 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 3429, 3344, 2962, 2922, 1700, 1611, 1493, 1456, 1262, 1051, 802, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.99 (br.s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.13 – 7.09 (m, 2H), 6.83 – 6.82 (m, 1H), 6.81 – 6.77 (m, 1H), 6.72 – 6.70 (m, 1H), 4.03 (s, 2H), 3.35 (br.s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 145.0, 136.7, 130.6, 127.6, 127.5, 125.4, 122.5, 122.4, 119.7, 119.3, 118.9, 116.0, 113.9, 111.3, 28.4 ppm. HRMS (ESI) exact mass calculated for $C_{15}H_{15}N_2$+ ([M + H]+): 223.1230; Found: 223.1238.



2-((5-methyl-1*H*-indol-3-yl)methyl)aniline (5.91a): According to GP-1: 1-methyl-4-nitrosobenzene (73 mg, 0.60 mmol), 1,2,3,4-tetrahydroquinoline (38 µL, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91a** as a colorless solid (42 mg, 59%). FTIR (KBr): $\tilde{\nu}$ = 3416, 3333, 3218, 3218, 2917, 2851, 1614, 1582, 1493, 1455, 1442, 1317, 1264, 1095, 1034, 802, 752, 715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.88 (br.s, 1H), 7.37 – 7.36 (m, 1H), 7.24 (s, 1H), 7.16 – 7.14 (m, 1H), 7.11 – 7.06 (m, 1H), 7.03 – 7.01 (m, 1H), 6.78 – 6.74 (m, 2H), 6.69 – 6.67 (m, 1H), 3.97 (s, 2H), 3.19 (br.s, 1H), (2.43 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.0, 135.1, 130.6, 128.9, 127.8, 127.5, 125.6, 124.0, 122.6, 118.9, 118.9, 116.0, 113.4, 111.0, 28.3, 21.7 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{17}N_2^+$ ([M + H]+): 237.1386 ; Found: 237.1390.

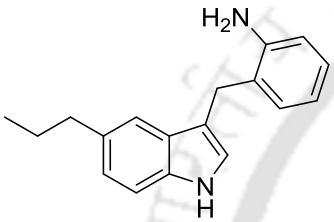


2-((5-ethyl-1H-indol-3-yl)methyl)aniline (5.91b): According to GP-1: 1-ethyl-4-nitrosobenzene (81 mg, 0.60 mmol), 1,2,3,4-tetrahydroquinoline (38 µL, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol)

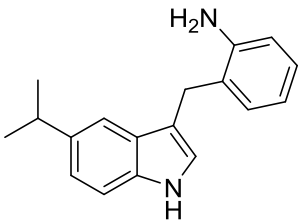


were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91b** as a brown solid (46 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 3428, 2962, 2925, 2854, 1623, 1523, 1341, 1317, 1262, 1102, 1014, 800, 753, 723 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.25 – 7.23 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.02 – 6.98 (m, 1H), 6.96 – 6.94 (m, 1H), 6.86 (s, 1H), 6.74 – 6.72 (m, 1H), 6.70 – 6.64 (m, 1H), 3.95 (s, 2H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ = 146.7, 137.4, 136.1, 131.5, 129.4, 128.5, 128.3, 124.5, 123.5, 120.2, 118.6, 117.8, 113.93, 112.5, 30.6, 29.3, 17.6 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2$+ ([M + H]+): 251.1543 ; Found: 251.1543.

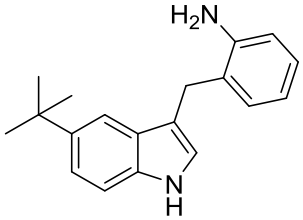
2-((5-propyl-1*H*-indol-3-yl)methyl)aniline (5.91c): According to GP-1: 1-nitroso-4-propylbenzene (67 mg, 0.45 mmol), 1,2,3,4-tetrahydroquinoline (28 µL, 0.23 mmol) and 4-nitrobenzoic acid (38 mg, 0.23 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91c** as a colorless solid (43 mg, 54%). FTIR (KBr): $\tilde{\nu}$ = 3442, 3387, 3311, 3210, 3036, 2960, 2922, 2857, 1615, 1589, 1492, 1458, 1260, 1097, 1023, 865, 798, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (br.s, 1H), 7.37 (s, 1H), 7.24 (s, 1H), 7.16 – 7.14 (m, 1H), 7.10 – 7.06 (m, 1H), 7.05 – 7.02 (m, 1H), 6.77 – 6.74 (m, 2H), 6.69 – 6.66 (m, 1H), 3.98 (s, 2H), 2.68 – 2.64 (m, 2H), 1.69 – 1.63 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.0, 135.3, 134.1, 130.6, 127.7, 127.5, 125.6, 123.5, 122.6, 118.9, 118.3, 116.0, 113.6, 111.0, 38.5, 28.3, 25.6, 14.2 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2^+$ ($[M + H]^+$): 265.1699; Found: 265.1700.



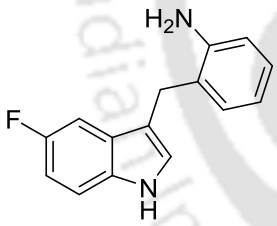
2-((5-isopropyl-1*H*-indol-3-yl)methyl)aniline (5.91d): According to GP-1: 1-isopropyl-4-nitrosobenzene (89 mg, 0.60 mmol), 1,2,3,4-tetrahydroquinoline (38 µL, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91d** as a brown solid (51 mg, 64%). FTIR (KBr): $\tilde{\nu}$ = 3383, 3307, 3188, 3036, 2958, 2925, 2870, 1616, 1586, 1491, 1458, 1353, 1256, 1228, 1100, 799, 753, 726, 653 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (br.s, 1H), 7.44 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.20 – 7.18 (m, 1H), 7.13 – 7.08 (m, 2H), 6.80 – 6.76 (m, 2H), 6.71 – 6.69 (m, 1H), 4.01 (s, 2H), 3.01 (sept, *J* = 6.8 Mz, 1H), 1.31 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.0, 140.4, 135.4, 130.7, 127.7, 127.6, 125.6, 122.6, 121.6, 118.9,



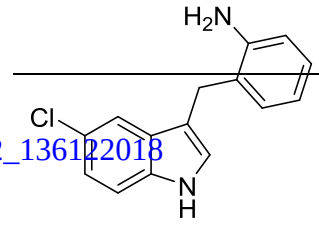
116.1, 116.0, 113.7, 111.1, 34.4, 28.4, 24.9 ppm. HRMS (ESI) exact mass calculated for $C_{18}H_{21}N_2$+ ([M + H]+): 265.1699; Found: 265.1697.



2-((5-(tert-butyl)-1*H*-indol-3-yl)methyl)aniline (5.91e): According to GP-1: 1-(*tert*-butyl)-4-nitrosobenzene (73 mg, 0.45 mmol), 1,2,3,4-tetrahydroquinoline (28 µL, 0.23 mmol) and 4-nitrobenzoic acid (38 mg, 0.23 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91e** as a brown solid (42 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 3386, 3315, 2959, 2858, 1615, 1490, 1458, 1259, 1226, 1101, 1021, 802, 757 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (br.s, 1H), 7.56 (s, 1H), 7.29 – 7.28 (m, 2H), 7.20 – 7.19 (m, 1H), 7.11 – 7.07 (m, 1H), 6.79 – 6.74 (m, 2H), 6.69 – 6.67 (m, 1H), 4.01 (s, 2H), 3.52 (br.s, 1H), (1.37 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.1, 142.6, 135.0, 130.8, 127.6, 127.3, 125.6, 122.5, 120.7, 118.9, 116.0, 115.0, 113.9, 110.8, 34.8, 32.2, 28.5 ppm. HRMS (ESI) exact mass calculated for $C_{19}H_{23}N_2$+ ([M + H]+): 279.1856; Found: 279.1856.



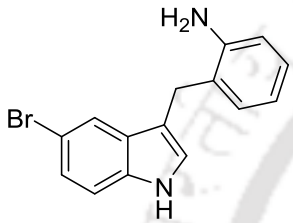
2-((5-fluoro-1*H*-indol-3-yl)methyl)aniline (5.91f): According to GP-1: 1-fluoro-4-nitrosobenzene (75 mg, 0.60 mmol), 1,2,3,4-tetrahydroquinoline (38 µL, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91f** as a brown solid (50 mg, 69%). FTIR (KBr): $\tilde{\nu}$ = 3474, 3397, 3018, 2961, 2920, 2852, 1618, 1578, 1487, 1452, 1312, 1262, 1159, 1091, 1029, 932, 857, 790, 754 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (br.s, 1H), 7.16 – 7.08 (m, 2H), 7.07 – 7.05 (m, 1H), 7.03 – 6.99 (m, 1H), 6.87 – 6.82 (m, 1H), 6.78 – 6.77 (m, 1H), 6.71 – 6.67 (m, 1H), 6.61 – 6.59 (m, 1H), 3.86 (s, 2H), 3.12 (br.s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.9 (d, *J* = 235.5 Hz), 144.9, 133.2, 130.6, 128.0, 127.9 (d, *J* = 9.8 Hz), 125.1, 124.3, 119.1, 116.1, 114.1 (d, *J* = 4.8 Hz), 111.9 (d, *J* = 9.7 Hz), 110.9 (d, *J* = 26.5 Hz), 104.2 (d, *J* = 23.5), 28.3 ppm. HRMS (ESI) exact mass calculated for $C_{15}H_{14}FN_2$+ ([M + H]+): 241.1136 ; Found: 241.1138.



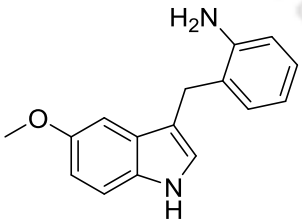
2-((5-chloro-1*H*-indol-3-yl)methyl)aniline (5.91g): According to GP-1: 1-chloro-4-nitrosobenzene (85 mg, 0.60 mmol), 1,2,3,4-tetrahydroquinoline

(38 µL, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91g** as a light green solid (55 mg, 71%). FTIR (KBr): $\tilde{\nu}$ = 3392, 2929, 1629, 1493, 1459, 1315, 1096, 795, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (br.s, 1H), 7.56 – 7.55 (m, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.16 – 7.11 (m, 3H), 6.82 – 6.81 (m, 1H), 6.79 – 7.77 (m, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 3.95 (s, 2H), 3.48 (br.s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.8, 135.0, 130.5, 128.6, 127.7, 125.4, 125.0, 123.9, 122.7, 119.1, 118.7, 116.1, 113.7, 112.4, 28.0 ppm. HRMS (ESI) exact mass calculated for $C_{15}H_{14}ClN_2$+ ([M + H]+): 257.0840; Found: 257.0846.

2-((5-bromo-1*H*-indol-3-yl)methyl)aniline (5.91h): According to GP-1: 1-bromo-4-nitrosobenzene (0.10 g, 0.60 mmol), 1,2,3,4-tetrahydroquinoline (38 µL, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91h** as a brown solid (53 mg, 64%). FTIR (KBr): $\tilde{\nu}$ = 3421, 3027, 2964, 2922, 2855, 1618, 1587, 1492, 1457, 1275, 1262, 1244, 1093, 881, 751 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.06 (br.s, 1H), 7.71 (s, 1H), 7.28 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 1H), 7.14 – 7.113 (m, 2H), 6.81 – 6.78 (m, 2H), 6.72 – 6.72 (m, 1H), 3.94 (s, 2H), 3.49 (br.s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.8, 135.3, 130.5, 129.3, 127.8, 125.2, 125.0, 123.7, 121.8, 119.1, 116.1, 113.6, 112.9, 112.8, 28.0 ppm. HRMS (ESI) exact mass calculated for $C_{15}H_{14}BrN_2$+ ([M + H]+): 301.0335; Found: 301.0341.



2-((5-methoxy-1*H*-indol-3-yl)methyl)aniline (**5.91i)**: According to GP-1: 1-methoxy-4-nitrosobenzene (0.10 g, 0.75 mmol), 1,2,3,4-tetrahydroquinoline (44 µL, 0.37 mmol) and 4-nitrobenzoic acid (63 mg, 0.37 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91i** colorless solid (47 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 3386, 3308, 3162, 3040, 2992, 2899, 2825, 1617, 1585, 1489, 1458, 1253, 1214, 1047, 760 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.93 (br.s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.19 – 7.18 (m, 1H), 7.12 – 7.09 (m, 1H), 6.99 – 6.98 (s, 1H), 6.86 – 6.85 (m, 1H), 6.81 – 6.79 (m, 2H), 6.75 – 6.74 (m, 1H), 4.00 (s, 2H), 3.81 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.1, 144.1, 131.8, 130.6, 127.9, 127.6, 126.0, 123.3, 119.5, 116.5, 113.4, 112.6, 112.1, 100.9,



56.0, 28.4 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{17}N_2O^+$ ([M + H]+): 253.1335; Found: 253.1331.

2-((5-(trifluoromethoxy)-1*H*-indol-3-yl)methyl)aniline (5.91j): According to GP-1: 1-nitroso-4-(trifluoromethoxy)benzene (0.12 g, 0.60 mmol), 1,2,3,4-tetrahydroquinoline (38 µL, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91j** as a colorless solid (55 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 3426, 3344, 3220, 2923, 2853, 1603, 1521, 1460, 1346, 1257, 1216, 1177, 1096, 887, 753, 722 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.08 (br.s, 1H), 7.42 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.15 – 7.07 (m, 3H), 6.91– 6.90 (m, 1H), 6.80 – 6.76 (m, 1H), 6.72 – 6.70 (m, 1H), 3.98 (s, 2H), 3.57 (br.s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.8, 143.07, 143.05, 143.03, 143.01, 135.0, 130.6, 127.8, 127.8, 124.8, 124.4, 122.8, 122.3, 119.7, 119.1, 116.4, 116.2, 114.5, 111.9, 111.8, 28.1.HRMS (ESI) exact mass calculated for $C_{16}H_{14}F_3N_2O^+$ ([M + H]+): 307.1053; Found: 307.1054.

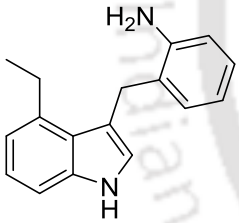
2-((5-phenyl-1*H*-indol-3-yl)methyl)aniline (5.91k): According to GP-1: 4-nitroso-1,1'-biphenyl (69 mg, 0.38 mmol), 1,2,3,4-tetrahydroquinoline (24 µL, 0.19 mmol) and 4-nitrobenzoic acid (32 mg, 0.19 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91k** as a colorless solid (28 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 3436, 2962, 2924, 2852, 1635, 1271, 1260, 1097, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.02 (br.s, 1H), 7.80 (s, 1H), 7.64 – 7.62 (m, 2H), 7.49 – 7.42 (m, 4H), 7.33 – 7.29 (m, 1H), 7.20 – 7.18 (m, 1H), 7.12 – 7.09 (m, 1H), 6.87 – 6.86 (s, 1H), 6.80 – 6.76 (m, 1H), 6.72 – 6.70 (m, 1H), 4.05 (s, 2H), 3.64 (br.s, 1H). ^{13}C NMR (101 MHz, CDCl3) δ = 144.9, 142.7, 136.3, 133.3, 130.7, 128.8, 128.1, 127.7, 127.6, 126.5, 125.4, 123.2, 122.3, 119.0, 117.8, 116.1, 114.4, 111.6, 28.3. HRMS (ESI) exact mass calculated for $C_{21}H_{19}N_2^+$ ([M + H]+): 299.1543; Found: 299.1550.

2-((4,6-dimethyl-1*H*-indol-3-yl)methyl)aniline (5.91l): According to GP-1: 1,3-dimethyl-5-nitrosobenzene (0.10 g, 0.75 mmol), 1,2,3,4-tetrahydroquinoline (47 µL, 0.37 mmol) and 4-nitrobenzoic acid (63 mg, 0.37 mmol)

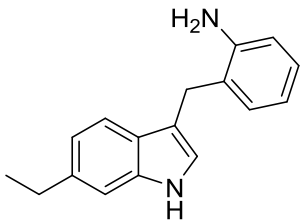
were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.91l** as a colorless solid (52 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 3389, 3311, 3225, 2917, 2853, 1614, 1588, 1494, 1456, 1257, 1112, 804, 751, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (br.s, 1H), 7.14 – 7.10 (m, 1H), 7.06 – 7.04 (m, 1H), 6.98 (s, 1H), 6.78 – 6.73 (m, 3H), 6.57 – 6.56 (m, 1H), 4.17 (s, 2H), 3.43 (br.s, 2H), 2.65 (s, 3H), 2.43 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.6, 137.8, 132.3, 131.0, 130.4, 127.4, 126.3, 124.1, 123.1, 122.2, 119.0, 115.8, 114.4, 109.1, 30.1, 21.6, 20.3 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2^+$ ([M + H]+): 251.1543; Found: 251.1549.

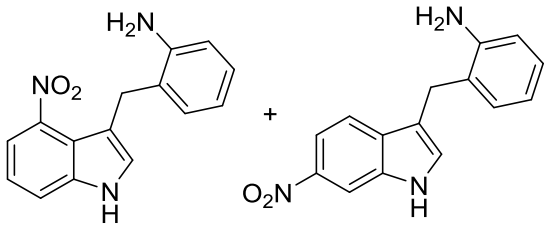
2-((4-ethyl-1*H*-indol-3-yl)methyl)aniline and **2-((6-ethyl-1*H*-indol-3-yl)methyl)aniline (5.91m** and **5.91m')**: According to GP-1: 1-ethyl-3-nitrosobenzene (0.12 g, 0.90 mmol), 1,2,3,4-tetrahydroquinoline (57 µL, 0.45 mmol) and 4-nitrobenzoic acid (75 mg, 0.45 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:6) of the crude gave **5.91m** as a light yellow solid (37 mg, 33%) and **5.91m'** as a colorless solid (41 mg, 36%).

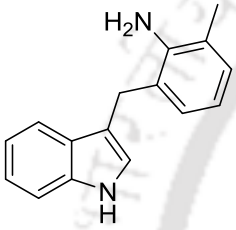
5.91m: FTIR (KBr): $\tilde{\nu}$ = 3384, 3308, 3208, 3186, 2963, 2920, 1616, 1585, 1491, 1455, 1255, 1229, 1050, 855, 813, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (br.s, 1H), 7.21 – 7.19 (m, 1H), 7.15 – 7.09 (m, 2H), 7.08 – 7.04 (m, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 6.83 – 6.77 (m, 2H), 6.61 (s, 1H), 4.20 (s, 2H), 3.05 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.9, 137.9, 137.6, 130.7, 127.6, 126.6, 125.4, 123.0, 122.6, 119.7, 119.4, 116.4, 114.1, 109.3, 30.4, 26.6, 16.6 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2^+$ ([M + H]+): 251.1543; Found: 251.1549.

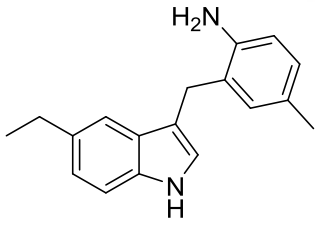


5.91m': FTIR (KBr): $\tilde{\nu}$ = 3435, 2957, 2925, 2869, 1624, 1457, 1377, 1155, 812, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (bs, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.18 - 7.16 (m, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 9.2 Hz, 1H), 6.79 (s, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 3.99 (s, 2H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.36 (bs, 2H), 1.28 (t, *J* = 7.6 Hz, 3H).. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.0, 138.9, 137.2, 130.6, 127.5, 125.7, 125.6, 121.9, 120.4, 119.0, 118.9, 116.0, 113.8, 110.0, 29.3, 28.5, 16.4 ppm. HRMS (ESI) exact mass calculated for $C_{17}H_{19}N_2^+$ ([M + H]+): 251.1543; Found: 251.1544.



2-((4-nitro-1*H*-indol-3-yl)methyl)aniline and **2-((6-nitro-1*H*-indol-3-yl)methyl)aniline (5.91n** and **5.91n'**:  According to GP-1: 1-nitro-3-nitrosobenzene (91mg, 0.60 mmol), 1,2,3,4-tetrahydroquinoline (38 µL, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave 1:1 inseparable mixture of **5.91n** and **5.91n'** as a as a yellow gum (39 mg, 49%). HRMS (ESI) exact mass calculated for $C_{15}H_{14}N_3O_2^+$ ([M + H]+): 268.1081 ; Found: 268.1083.

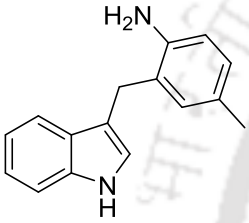
2-((1*H*-indol-3-yl)methyl)-6-methylaniline (5.93a):  According to GP-1: nitrosobenzene (87 mg, 0.82 mmol), 8-methyl-1,2,3,4-tetrahydroquinoline (56 µL, 0.41 mmol) and 4-nitrobenzoic acid (68 mg, 0.41 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.93a** as a brown solid (58 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 3354, 2987, 1676, 1602, 1569, 1514, 1482, 1456, 1384, 1283, 1173, 1119, 769, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.99 (br.s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.13 – 7.09 (m, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.84 – 6.83 (m, 1H), 6.71 (t, *J* = 7.8 Hz, 1H), 4.03 (s, 2H), 2.18 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 142.9, 136.8, 128.9, 128.6, 127.7, 125.0, 122.7, 122.6, 122.4, 119.7, 119.3, 118.5, 114.1, 111.3, 28.6, 17.8 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{17}N_2$+ ([M + H]+): 237.1386 ; Found: 237.1387.

2-((5-ethyl-1*H*-indol-3-yl)methyl)-4-methylaniline (5.93b):  According to GP-1: 1-ethyl-4-nitrosobenzene (55 mg, 0.40 mmol), 6-methyl-1,2,3,4-tetrahydroquinoline (30 mg, 0.20 mmol) and 4-nitrobenzoic acid (34 mg, 0.20 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.93b** as a colorless solid (24 mg, 45%). FTIR (KBr): $\tilde{\nu}$ = 3354, 2987, 1675, 1602, 1569, 1514, 1482, 1457, 1384, 1309, 1283, 1173, 1119, 1105, 769, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 (br.s, 1H), 7.42 (s, 1H), 7.28 – 7.26 (m, 1H), 7.08 – 7.06 (m, 1H), 7.009 – 7.005 (m, 1H), 6.92 – 6.90 (m, 1H), 6.77 – 6.76 (m, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 3.97 (s, 2H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.26 (s, 3H), 1.29

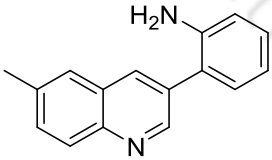
(t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.4, 135.6, 135.3, 131.3, 128.1, 128.0, 127.8, 125.7, 123.0, 122.6, 117.6, 116.2, 113.8, 111.1, 29.2, 28.3, 20.7, 16.7 ppm. HRMS (ESI) exact mass calculated for $C_{18}H_{21}N_2^+$ ([M + H]+): 265.1699; Found: 265.1702.

2-((1*H*-indol-3-yl)methyl)-4-methylaniline and **2-((1*H*-indol-3-yl)methyl)-4-methylaniline (5.93c** and **5.93c')** : According to GP-1: nitrosobenzene (58 mg, 0.54 mmol), 6-methyl-1,2,3,4-tetrahydroquinoline (40 mg, 0.27 mmol) and 4-nitrobenzoic acid (45 mg, 0.54 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:5) of the crude gave **5.93c** as a colorless solid (30 mg, 47%) and **5.93c'** as a colorless solid (19 mg, 30%).

5.93c: FTIR (KBr): $\tilde{\nu}$ = 3401, 3192, 2962, 2922, 2851, 1691, 1607, 1518, 1492, 1450, 1344, 1261, 1097, 1033, 876, 794, 749, 713 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (br.s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.16 – 7.13 (m, 1H), 7.04 (s, 1H), 6.96 – 6.94 (m, 1H), 6.80 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 4.01 (s, 2H), 3.37 (br.s, 2H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.3, 136.7, 131.3, 128.1, 128.0, 127.5, 125.6, 122.5, 122.3, 119.6, 119.2, 116.2, 114.0, 111.3, 28.3, 20.7. HRMS (ESI) exact mass calculated for $C_{16}H_{17}N_2^+$ ([M + H]+): 237.1386; Found: 237.1388.



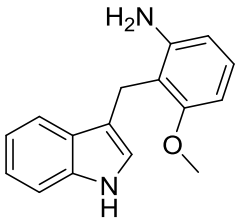
5.93c': FTIR (KBr): $\tilde{\nu}$ = 3426, 3298, 3199, 1632, 1494, 1463, 1447, 1342, 1300, 1132, 1028, 823, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.87 (d, *J* = 2.4 Hz, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 7.51 (s, 1H), 7.50 – 7.48 (m, 1H), 7.17 – 7.12 (m, 2H), 6.84 – 6.80 (m, 1H), 6.76 – 6.74 (m, 1H), 3.60 (br.s, 2H), 2.48 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.7, 145.8, 144.2, 137.2, 135.1, 132.6, 132.1, 131.0, 129.5, 129.0, 128.2, 126.8, 124.1, 119.2, 116.1 21.8 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{15}N_2^+$ ([M + H]+): 235.1230; Found: 235.1236.



2-((1*H*-indol-3-yl)methyl)-3-methoxyaniline and **2-(5-methoxyquinolin-3-yl)aniline** (**5.93d** and **5.93d'**): According to GP-1: nitrosobenzene (64 mg, 0.60 mmol), 5-methoxy-1,2,3,4-tetrahydroquinoline (49 mg, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 18 h in dry toluene (4 mL). Column chromatography (silica; EtOAc

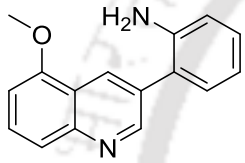
: Hexane, 1:5) of the crude gave **5.93d** as a colorless solid (34 mg, 45%) and **5.93d'** as brown solid (18 mg, 24%).

5.93d: FTIR (KBr): $\tilde{\nu}$ = 3423, 2958, 2926, 2854, 1627, 1468, 1121, 795, 742 cm^{-1}. ^1H NMR



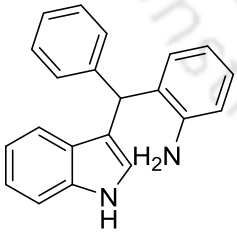
(400 MHz, $CDCl_3$) δ = 7.91 (br.s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.21– 7.18 (m, 1H), 7.14 – 7.11 (m, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.78 –6.77 (m, 1H), 6.46 – 6.44 (m, 1H), 6.37 – 6.35 (m, 1H), 4.10 (s, 2H), 3.84 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) = 158.3, 146.3, 136.6, 127.5, 127.3, 122.1, 121.7, 119.3, 119.1, 114.0, 113.7, 111.1, 109.2, 101.4, 55.8, 19.8 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{17}N_2O^+$ ([M + H]+): 253.1335; Found: 253.1343.

5.93d': FTIR (KBr): $\tilde{\nu}$ = 3381, 3305, 3178, 2920, 2882, 1618, 1504, 1454, 1259, 1224, 821, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.01 (d, *J* = 2.4 Hz, 1H),

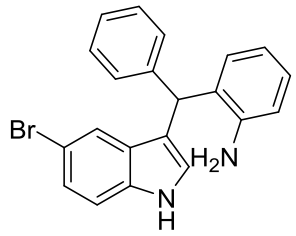


8.70 (d, *J* = 2.8 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.62 (m, 1H), 7.24 – 7.21 (m, 2H), 6.91 – 6.87 (m, 2H), 6.84 – 6.82 (m, 1H), 4.01 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.4, 151.7, 147.9, 144.2, 131.8, 131.1, 130.8, 129.8, 129.5, 124.3, 121.3, 120.7, 119.2, 116.1, 104.9, 56.0 ppm. HRMS (ESI) exact mass calculated for $C_{16}H_{15}N_2O^+$ ([M + H]+): 251.1179; Found: 251.1180.

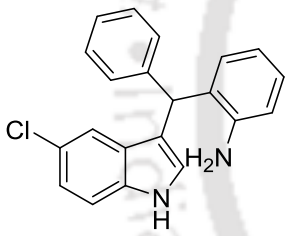
2-((1*H*-indol-3-yl)(phenyl)methyl)aniline (5.93e): According to GP-1: nitrosobenzene (48 mg, 0.45 mmol), 4-phenyl-1,2,3,4-tetrahydroquinoline (47 mg, 0.22 mmol) and 4-nitrobenzoic acid (37 mg, 0.22 mmol) were reacted for 18 h in dry toluene (4 mL) under argon atmosphere. Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.93e** as a brown gum (38 mg, 57%). FTIR (KBr): $\tilde{\nu}$ = 3437, 2957, 2925, 2869, 1623, 1599, 1488, 1455, 1089, 1015, 823, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.01 (br.s, 1H), 7.38 – 7.36 (m, 1H), 7.31 – 7.28 (m, 3H), 7.26 – 7.24 (m, 3H), 7.20 – 7.16 (m, 1H), 7.10 – 7.06 (m, 1H), 7.03 – 6.99 (m, 1H), 6.81 – 6.79 (m, 1H), 6.73 – 6.67 (m, 2H), 6.63 – 6.62 (m, 1H), 5.67 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.0, 142.5, 136.8, 129.6, 129.2, 129.1, 128.5, 127.3, 127.1, 126.5, 124.0, 122.3, 119.9, 119.6, 118.8, 118.1, 116.3, 111.1, 43.8 ppm. HRMS (ESI) exact mass calculated for $C_{21}H_{19}N_2^+$ ([M + H]+): 299.1543; Found: 299.1536.



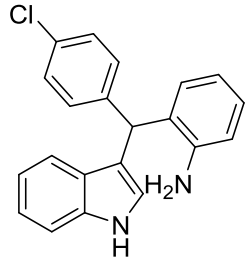
2-((5-bromo-1*H*-indol-3-yl)(phenyl)methyl)aniline (5.93f): According to GP-1: 1-bromo-4-nitrosobenzene (89 mg, 0.48 mmol), 4-phenyl-1,2,3,4-tetrahydroquinoline (50 mg, 0.24 mmol) and 4-nitrobenzoic acid (40 mg, 0.24 mmol) were reacted for 18 h in dry toluene (4 mL) under argon atmosphere. Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.93f** as a brown gum (45 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 3445, 2956, 2925, 2869, 1620, 1598, 1584, 1488, 1389, 1089, 1015, 834, 765, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (br.s, 1H), 7.36 –7.35 (m, 1H), 7.25 – 7.21 (m 2H), 7.20 – 7.13 (m, 5H), 7.03 – 6.99 (m, 1H), 6.69 – 6.67 (m, 1H), 6.64 – 6.59 (m, 2H), 6.55 –6.54 (s, 1H), 5.50 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.4, 142.4, 135.6, 129.6, 129.2, 129.0, 128.8, 128.7, 127.7, 126.9, 125.5, 125.4, 122.4, 118.9, 118.1, 116.5, 113.1, 112.8, 43.8 ppm. HRMS (ESI) exact mass calculated for $C_{21}H_{18}BrN_2^+$ ([M + H]+): 377.0648; Found: 377.0641.



2-((5-chloro-1*H*-indol-3-yl)(phenyl)methyl)aniline (5.93g): According to GP-1: 1-chloro-4-nitrosobenzene (94 mg, 0.67 mmol), 4-phenyl-1,2,3,4-tetrahydroquinoline (70 mg, 0.33 mmol) and 4-nitrobenzoic acid (56 mg, 0.33 mmol) were reacted for 24 h in dry toluene (4 mL) under argon atmosphere. Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.93g** as a brown gum (49 mg, 51%). FTIR (KBr): $\tilde{\nu}$ = 3412, 2963, 2925, 2853, 1634, 1491, 1451, 1261, 1095, 795, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (br.s, 1H), 7.25 – 7.17 (m, 5H), 7.15 – 7.12 (d, *J* = 8.4 Hz, 2H), 7.05 – 6.99 (m, 2H), 6.70 – 6.60 (m, 3H), 6.55 (s, 1H), 5.52 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.0, 142.3, 135.3, 129.6, 129.3, 128.9, 128.8, 128.3, 127.7, 126.9, 125.6, 125.5, 122.8, 119.4, 119.2, 118.1, 116.7, 112.3, 43.8 ppm. HRMS (ESI) exact mass calculated for $C_{21}H_{18}ClN_2^+$ ([M + H]+): 333.1153; Found: 333.1145.



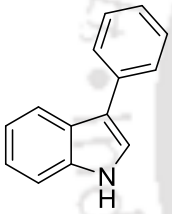
2-((4-chlorophenyl)(1*H*-indol-3-yl)methyl)aniline (5.93h): According to GP-1: nitrosobenzene (66 mg, 0.60 mmol), 4-(4-chlorophenyl)-1,2,3,4-tetrahydroquinoline (75 mg, 0.31 mmol) and 4-nitrobenzoic acid (51 mg, 0.31 mmol) were reacted for 24 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:6) of the crude gave **5.93h** as a brown gum (47 mg, 46%). FTIR (KBr): $\tilde{\nu}$ = 3415, 3331, 3053, 2961, 2924, 2868, 1591, 1476, 1451, 1240, 1013, 850, 811, 756, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (br.s, 1H), 7.28 – 7.26 (m, 1H),



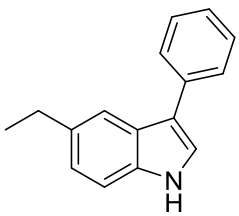
7.18 – 7.16 (m, 3H), 7.11 – 7.06 (m, 3H), 7.11 – 6.99 (m, 1H), 6.92 – 6.89 (m, 1H), 6.69 – 6.62 (m, 3H), 6.51 (s, 1H), 5.59 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.2, 141.1, 136.8, 132.3, 130.6, 129.5, 129.1, 128.6, 127.5, 126.9, 124.0, 122.4, 119.7, 119.7, 119.5, 117.3, 116.9, 111.2, 43.1 ppm. HRMS (ESI) exact mass calculated for $C_{21}H_{18}ClN_2^+$ ([M + H]+): 333.1153; Found: 333.1160.

General procedure for the synthesis of 3-aryl indoles and 2, 3 diaryl indole (GP-2): Nitrosoarene (2 equiv.) and 4-nitrobenzoic acid (1 equiv.) were added to a solution of *N*-phenethylaniline derivative (0.25 – 0.37 mmol) in dry toluene (4 – 5 mL) and reflux for 14 h. Another 1 equiv. of nitrosoarene was added and further the reaction was refluxed for 24 h. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure to obtain brown gummy residue which was purified by column chromatography to afford analytically pure indole derivatives.

3-phenyl-1*H*-indole (5.95a): According to GP-2: nitrosobenzene (97 mg, 0.91 mmol), *N*-phenethylaniline (60 mg, 0.30 mmol) and 4-nitrobenzoic acid (50 mg, 0.30 mmol) were reacted for 38 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.95a** as a colorless gum (27 mg, 45%, 62% brsm). FTIR (KBr): $\tilde{\nu}$ = 2956, 2923, 2853, 1629, 1597, 1455, 1379, 1355, 746, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 (br.s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.60 (m, 2H), 7.40 – 7.35 (m, 3H), 7.30 – 7.29 (m, 1H), 7.24 – 7.18 (m, 2H), 7.16 – 7.11 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.8, 135.7, 129.0, 127.7, 126.2, 126.0, 122.6, 121.9, 120.5, 120.0, 118.6, 111.6 ppm. HRMS (ESI) exact mass calculated for $C_{14}H_{12}N^+$ ([M + H]+): 194.0964; Found: 194.0967.

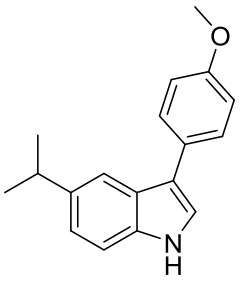


5-ethyl-3-phenyl-1*H*-indole (5.95b): According to GP-2: 1-ethyl-4-nitrosobenzene (0.10 g, 0.75 mmol), *N*-phenethylaniline (50 mg, 0.25 mmol) and 4-nitrobenzoic acid (42 mg, 0.25 mmol) were reacted for 38 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.95b** as a colorless gum (21 mg, 37%, 52% brsm). FTIR (KBr): $\tilde{\nu}$ = 3053, 2960, 2921, 2852, 1636, 1600, 1539, 1275, 748, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (br.s, 1H), 7.75 (s, 1H), 7.69 – 7.68 (m, 2H), 7.48 – 7.44 (m, 2H), 7.37 – 7.34 (m, 2H), 7.31 – 7.27 (m, 1H), 7.13 – 7.11 (m, 1H), 2.81 – 2.74 (m, 2H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.6,

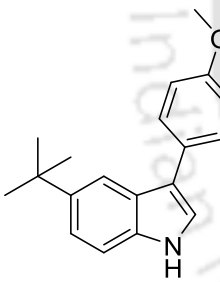


136.0, 135.3, 128.9, 127.7, 126.2, 126.1, 123.2, 122.1, 118.4, 118.3, 111.4, 29.4, 16.9. HRMS (ESI) exact mass calculated for $C_{16}H_{16}N^+$ ([M + H]+): 222.1277; Found: 222.1282.

5-isopropyl-3-(4-methoxyphenyl)-1*H*-indole (5.95c): According to GP-2: 1-isopropyl-4-nitrosobenzene (0.12 g, 0.81 mmol), *N*-(4-methoxyphenethyl)aniline (60 mg, 0.27 mmol) and 4-nitrobenzoic acid (45 mg, 0.27 mmol) were reacted for 38 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.95c** as a brown gum (28 mg, 39%, 53% brsm). FTIR (KBr): $\tilde{\nu}$ = 2961, 2924, 2854, 1637, 1493, 1452, 1261, 747, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.05 (s, 1H), 7.64 (s, 1H), 7.53 – 7.50 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.19 – 7.18 (m, 1H), 7.07 (d, *J* = 9.6 Hz, 1H), 6.96 – 6.94 (m, 2H), 3.80 (s, 3H), 2.97 (sept, *J* = 6.8 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.2, 141.1, 135.3, 128.9, 128.5, 126.2, 121.7, 121.6, 118.0, 116.8, 114.4, 111.3, 55.6, 34.6, 24.9. HRMS (ESI) exact mass calculated for $C_{18}H_{20}NO^+$ ([M + H]+): 266.1539; Found: 266.1539.



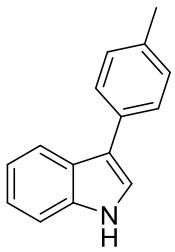
5-(tert-butyl)-3-(4-methoxyphenyl)-1*H*-indole (5.95d): According to GP-2: 1-(*tert*-butyl)-4-nitrosobenzene (0.15 g, 0.92 mmol), *N*-(4-methoxyphenethyl)aniline (70 mg, 0.31 mmol) and 4-nitrobenzoic acid (51 mg, 0.31 mmol) were reacted for 38 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.95d** as a brown gum (30 mg, 35%, 62% brsm). FTIR (KBr): $\tilde{\nu}$ = 2963, 2924, 2853, 1637, 1495, 1260, 797, 745, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.11 (br.s, 1H), 7.87 (s, 1H), 7.60 – 7.57 (m, 2H), 7.38 – 7.32 (m, 2H), 7.27 (s, 1H), 7.03 – 7.01 (m, 2H), 3.87 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 158.2, 143.3, 134.9, 128.9, 128.5, 125.8, 121.6, 120.8, 118.3, 115.5, 114.5, 111.0, 55.6, 34.9, 32.2. HRMS (ESI) exact mass calculated for $C_{19}H_{22}NO^+$ ([M + H]+): 280.1696; Found: 280.1695.



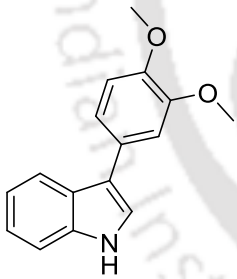
3-(4-methoxyphenyl)-1*H*-indole (5.95e): According to GP-2: Nitrosobenzene (86 mg, 0.81 mmol), *N*-(4-methoxyphenethyl)aniline (60 mg, 0.27 mmol) and 4-nitrobenzoic acid (45 mg, 0.27 mmol) were reacted for 38 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.95e** as a brown gum (28 mg, 39%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2924, 2853, 1637, 1545, 1495, 1450, 1260, 745, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.21 (br.s, 1H), 7.90 (d, *J* = 8.0 Hz,

1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.44 – 7.42 (m, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.24 – 7.16 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.3, 136.8, 128.8, 128.3, 126.1, 122.5, 121.3, 120.3, 119.9, 118.3, 114.4, 111.5, 55.6. HRMS (ESI) exact mass calculated for $C_{15}H_{14}NO^+$ ([M + H]+): 224.1070; Found: 224.1079.

3-(p-tolyl)-1*H*-indole (5.95f): According to GP-2: nitrosobenzene (0.10 g, 1.0 mmol), N-(4-methylphenethyl)aniline (70 mg, 0.33 mmol) and 4-nitrobenzoic acid (55 mg, 0.33 mmol) were reacted for 38 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:6) of the crude gave **5.95f** as a colorless gum (25 mg, 36%). FTIR (KBr): $\tilde{\nu}$ = 2922, 2853, 1638, 1660, 1543, 1493, 1450, 1260, 1175, 1099, 805, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (br.s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.34 (m, 1H), 7.28 – 7.25 (m, 3H), 7.23 – 7.17 (m, 1H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.8, 135.8, 132.8, 129.7, 127.6, 126.1, 122.5, 121.7, 120.4, 120.1, 118.5, 111.5, 21.4. HRMS (ESI) exact mass calculated for $C_{15}H_{14}N^+$ ([M + H]+): 208.1121; Found: 208.1124.



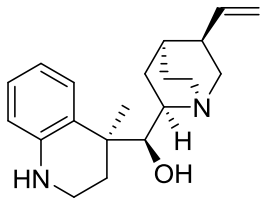
3-(3,4-dimethoxyphenyl)-1*H*-indole (5.95g): According to GP-2: Nitrosobenzene (62 mg, 0.58 mmol), *N*-(3,4-dimethoxyphenethyl)aniline (50 mg, 0.19 mmol) and 4-nitrobenzoic acid (32 mg, 0.19 mmol) were reacted for 38 h in dry toluene (4 mL). Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.95g** as a brown gum (21 mg, 43%). FTIR (KBr): $\tilde{\nu}$ = 2923, 2853, 1637, 1456, 1261, 1098, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.33 - 7.32 (m, 1H), 7.27 - 7.23 (m, 2H), 7.22 - 7.17 (m, 3H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.2, 147.6, 136.6, 128.5, 125.9, 122.4, 121.2, 120.2, 119.8, 119.7, 118.3, 111.7, 111.4, 111.2, 56.0, 55.9. HRMS (ESI) exact mass calculated for $C_{16}H_{16}NO_2^+$ ([M + H]+): 254.1176; Found: 254.1178.



2,3-diphenyl-1*H*-indole (5.95h): According to GP-2: nitrosobenzene (0.12 g, 1.1 mmol), *N*-(1,2-diphenylethyl)aniline (0.10 g, 0.37 mmol) and 4-nitrobenzoic acid (62 mg, 0.37 mmol) were reacted for 38 h in dry toluene (5 mL). Column chromatography (silica; EtOAc : Hexane, 1:7) of the crude gave **5.95h** as a colorless gum (41mg, 41%, 60% brsm). FTIR (KBr): $\tilde{\nu}$ = 3062, 3027, 2923, 2853, 1955, 1894, 1670, 1600, 1478, 1323, 1274, 1072, 762, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.19 (br.s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.35 (m, 4H), 7.32 – 7.27 (m, 3H), 7.26 – 7.21 (m, 4H), 7.17 – 7.16 (m, 1H), 7.10 – 7.06 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.1, 135.3, 134.3, 132.9, 130.4, 129.0, 128.9, 128.7, 128.4, 127.9, 126.4, 122.9, 120.6, 119.9, 115.3, 111.1. HRMS (ESI) exact mass calculated for $C_{20}H_{16}N^+$ ([M + H]+): 270.1277; Found: 270.1287.

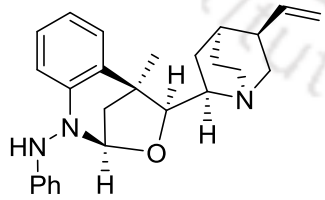
5-methyl-4-(5-vinylquinuclidin-2-yl)-1,2,4,5-tetrahydro 2,5methanobenzo[d][1,3]oxazepine (5.98a): Methylmagnesium bromide (4.69 mL, 3.0 M in diethylether, 14.1 mmol) was added to a solution of cinchonine (1.2 g, 4.08 mmol) in dry toluene (15 mL). The reaction mixture was stirred for overnight at 70 ^oC and then cooled to 0 ^oC. The mixture was diluted with diethylether and the reaction was quenched by addition of saturated solution of aq. NH_4Cl (30 mL). The organic layer was separated and dried over Na_2SO_4 and evaporated under reduced pressure to give white solid residue which was purified by column chromatography (silica; EtOAc: MeOH: NEt_3, 50:1:1) to give **5.98a** as colorless gum (0.53 g, 42%). FTIR (KBr): $\tilde{\nu}$ = 2962, 2935, 2871, 1637, 1608, 1489, 1454, 1307, 1011, 749 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.03 (d, *J* = 7.8 Hz, 1H), 6.99 – 6.71 (m, 1H), 6.70 – 6.67 (m, 1H), 6.44 – 6.42 (m, 1H), 5.96 – 5.91 (m, 1H), 5.07 – 5.06 (m, 1H), 4.97 – 4.94 (m, 2H), 4.91 – 4.87 (m, 1H), 3.91 (d, *J* = 6.0 Hz, 1H), 2.81 – 2.77 (m, 1H), 2.64 – 2.58 (m, 2H), 2.57 – 2.51 (m, 1H), 2.31 – 2.72 (m, 1H), 2.20 (d, *J* = 10.8 Hz, 1H), 2.17 – 2.09 (m, 2H), 1.59 – 1.56 (m, 1H), 1.50 (s, 3H), 1.49 – 1.47 (m, 1H) 1.35 – 1.31 (m, 2H), 0.86 – 0.81 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.9, 141.1, 129.3, 127.4, 125.7, 118.4, 114.5, 114.0, 95.3, 83.0, 56.6, 48.8, 48.7, 43.5, 40.7, 40.4, 27.5, 26.7, 24.0, 19.2. HRMS (ESI) exact mass calculated for $C_{20}H_{27}N_2O^+$ ([M + H]+): 311.2118; Found: 311.2110.

(4-methyl-1,2,3,4-tetrahydroquinolin-4-yl)(5-vinylquinuclidin-2-yl)methanol (5.98b):



$NaBH_3CN$ (0.11 g, 1.68 mmol) was added to a solution of **5.98a** (0.26 g, 0.84 mmol) in AcOH (0.25 mL) and methanol (2 mL) at 0 ^oC. The reaction mixture was stirred at room temperature. After 2.5 h, concentrated HCl (0.6 mL) was added to the reaction mixture and stirred for additional 12 h at room temperature. The reaction was quenched by the addition of 2 M sodium hydroxide until pH >9. The reaction mixture was extracted with ethyl acetate (3x 15 mL). The combine organic layers were washed with brine (3x 10 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified by column chromatography (silica; EtOAc: MeOH: NEt_3, 50:1:1) to give **5.98b** as colorless oil (0.13 g, 50%). FTIR (KBr): $\tilde{\nu}$ = 2968, 2935, 2869, 1636, 1604, 1500, 1452, 1345, 746, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.06 (d, *J* = 8.0 Hz, 1H), 6.92 – 6.88 (m, 1H), 6.54 (t, *J* = 7.6 Hz, 1H), 6.39 (d, *J* = 8.0 Hz, 1H), 5.97 – 5.89 (m, 1H), 5.00 – 4.87 (m, 2H), 3.92 (d, *J* = 3.6 Hz, 1H), 3.85 (br.s, 1H), 3.36 – 3.29 (m, 1H), 3.20 – 3.15 (m, 1H), 2.91 – 2.86 (m, 1H), 2.80 – 2.61 (m, 4H), 2.13 – 2.03 (m, 2H), 1.97 – 1.90 (m, 1H), 1.66 – 1.59 (m, 2H), 1.50 – 1.45 (m, 2H), 1.31 – 1.27 (m, 1H), 1.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.2, 141.2, 127.8, 127.5, 126.4, 116.6, 114.4, 114.2, 77.1, 56.5, 49.2, 49.2, 40.4, 40.2, 38.5, 31.4, 28.3, 27.0, 23.7, 23.3. HRMS (ESI) exact mass calculated for $C_{20}H_{29}N_2O^+$ ([M + H]+): 313.2274; Found: 313.2276.

5-methyl-*N*-phenyl-4-(5-vinylquinuclidin-2-yl)-4,5-dihydro 2,5methanobenzo[*d*][1,3] oxazepin-1(2*H*)-amine (5.100): According to GP-1: nitrosobenzene (21 mg, 0.19 mmol), **5.98b** (30 mg, 0.10 mmol) and 4-nitrobenzoic acid (16 mg, 0.10 mmol) were reacted for 36 h in dry toluene (4 mL). Column chromatography (silica; EtOAc: MeOH: NEt_3, 40:1:1) of the crude gave **5.100** as a colorless gum (20 mg, 52%). FTIR (KBr): $\tilde{\nu}$ = 3376, 3019, 2958, 2925, 2867, 1650, 1611, 1499, 1474, 1380, 1257, 1160, 811, 647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.26 –7.22 (m, 3H), 7.10 – 7.06 (m, 1H), 7.03 – 7.01 (m, 1H), 6.94 – 6.82 (m, 4H), 6.03 (s, 1H), 5.98 – 5.90 (m, 1H), 5.15 – 5.08 (m, 3H), 4.27 – 4.20 (m, 1H), 2.94 (d, *J* = 9.2 Hz, 2H), 2.78 – 2.74 (m, 2H), 2.49 (d, *J* = 11.2 Hz, 2H), 2.30 – 2.25 (m, 2H), 1.66 – 1.63 (m, 1H), 1.56 (s, 3H), 1.55 – 1.51 (m, 3H) 0.68 – 0.62 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.8, 144.9, 138.0, 128.4, 128.2, 127.4, 123.4, 120.1, 119.1, 114.7, 114.5, 111.6, 91.5, 89.0, 56.3,



47.2, 46.6, 42.9, 40.7, 37.0, 26.0, 24.0, 20.2, 17.7. HRMS (ESI) exact mass calculated for $C_{26}H_{32}N_3O^+$ ([M + H]+): 402.2540; Found: 402.2542.

6H-indolo[2,3-*b*]quinoline (5.103a): A mixture of **5.91** (30 mg, 0.13 mmol), iodine (41 mg, 0.16 mmol), Cs_2CO_3 (88 mg, 0.27 mmol) in dry CH_3CN (2 mL) was heated at 60 ^oC for 4 h under argon atmosphere. The solvent was removed under vacuum and the reaction mixture was diluted with aq. $Na_2S_2O_3$ solution (10 mL) and the reaction mixture was extracted with dichloromethane (3x10 mL). The combined organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuum to give brown gum which was purified by column chromatography (silica; EtOAc : Hexane, 1:3) to give **5.103a** as a colorless solid (22 mg, 74%). FTIR (KBr): $\tilde{\nu}$ = 3144, 3055, 2956, 2922, 2851, 1659, 1613, 1580, 1479, 1459, 1406, 1255, 1230, 1123, 908, 737 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 11.70 (s, 1H), 9.04 (s, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.55 – 7.46 (m, 3H), 7.28 – 7.24 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ = 153.0, 146.4, 141.5, 128.8, 128.8, 128.3, 127.7, 127.1, 123.8, 122.9, 121.9, 120.4, 119.8, 118.0, 111.0. The ^1H NMR and ^{13}C NMR data matched with the literature.[42] HRMS (ESI) exact mass calculated for $C_{15}H_{11}N_2^+$ ([M + H]+): 219.0917; Found: 219.0913.

8,10-dimethyl-6*H*-indolo[2,3-*b*]quinoline (5.103b): A mixture of **5.91l** (40 mg, 0.16 mmol), Iodine (48 mg, 0.19 mmol), Cs_2CO_3 (0.10 g, 0.32 mmol) in dry CH_3CN (3 mL) was heated at 60 ^oC for 4 h under argon atmosphere. The solvent was removed under vacuum and the reaction mixture was diluted with aq. $Na_2S_2O_3$ solution (10 mL) and the reaction mixture was extracted with dichloromethane (3x10 mL). The combined organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuum to give brown gum which was purified by column chromatography (silica; EtOAc : Hexane, 1:3) to give **5.103b** as a colorless solid (27 mg, 69%). FTIR (KBr): $\tilde{\nu}$ =2922, 2851, 1675, 1606, 1480, 1260, 795, 745 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ =11.62 (s, 1H), 8.90 (s, 1H), 8.16 – 8.14 (m, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.48 – 7.45 (m, 1H), 7.14 (s, 1H), 6.89 (s, 1H), 2.82 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ = 153.4, 145.9, 142.3, 138.4, 134.4, 129.2, 128.8, 128.8, 127.2, 124.3, 122.9, 118.9, 116.9, 109.1, 22.2, 20.6 ppm. Total count of ^{13}C is less because of overlap in the aromatic region. HRMS (ESI) exact mass calculated for $C_{17}H_{15}N_2^+$ ([M + H]+): 247.1230; Found: 247.1232.

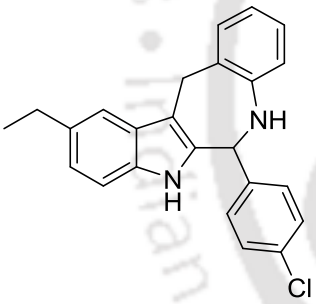
Neocryptolepine (5.104a): CH_3I (0.11 mL, 1.80 mmol) was added drop-wise to a solution of **5.103a** (40 mg, 0.18 mmol) in dry THF (2 mL) and the reaction mixture was reflux for 12 h. The reaction mixture was neutralized with aq. NH_3 solution and the mixture was extracted with dichloromethane (3x15 mL). The combined organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuum to give yellow residue which was purified by column chromatography (silica; EtOAc : Hexane, 1:3) to give **5.104a** as a light orange solid (31 mg, 74%). FTIR (KBr): $\tilde{\nu}$ = 2962, 2924, 2853, 1646, 1615, 1576, 1496, 1452, 1299, 1100, 799, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.55 (s, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.75 (m, 3H), 7.58 – 7.54 (m, 1H), 7.48 – 7.44 (m, 1H), 7.26 – 7.23 (m, 1H), 4.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.2, 155.2, 137.1, 130.7, 130.2, 129.6, 128.5, 128.2, 124.0, 122.2, 121.2, 121.1, 120.2, 117.8, 114.4, 33.4. The ^1H NMR and ^{13}C NMR data matched with the literature.[42] HRMS (ESI) exact mass calculated for $C_{16}H_{13}N_2^+$ ([M + H]+): 233.1073; Found: 233.1075.

5,8,10-trimethyl-5*H*-indolo[2,3-*b*]quinoline (5.104b): CH_3I (0.10 mL, 1.62 mmol) was added dropwise to a solution of **5.103b** (40 mg, 0.16 mmol) in dry THF (2 mL) and the reaction mixture was reflux for 12 h. The reaction mixture was neutralized with NH_3 solution and the mixture was extracted with dichloromethane (3x15 mL). The combined organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuum to give yellow gum residue which was purified by column chromatography (silica; EtOAc : Hexane, 1:3) to give **5.104b** as a light orange solid (30 mg, 71%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2925, 2852, 1634, 1261, 1096, 1021, 864, 748, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.43 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.75 – 7.74 (m, 2H), 7.45 – 7.42 (m, 2H), 6.87 (s, 1H), 4.36 (s, 3H), 2.79 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.4, 155.5, 139.8, 136.4, 133.9, 130.2, 130.1, 129.1, 128.8, 123.3, 122.0, 121.4, 120.1, 116.0, 114.2, 33.3, 22.5, 20.4. HRMS (ESI) exact mass calculated for $C_{18}H_{17}N_2^+$ ([M + H]+): 261.1386; Found: 261.1393.

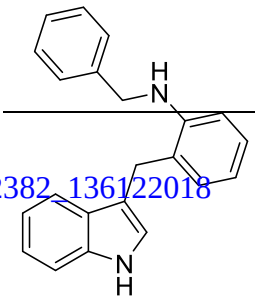
6-(4-chlorophenyl)-5,6,7,12-tetrahydrobenzo[6,7]azepino[3,4-*b*]indole (5.105a): TFA (40 µL) was added dropwise to a solution of **5.91** (30 mg, 0.13 mmol) and 4-chlorobenzaldehyde (23 mg, 0.16 mmol) in dry

dichloromethane (2 mL) and the reaction mixture was stirred at room temperature. After 1 h the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and the reaction mixture was extracted with dichloromethane (3x10 mL). The combined organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give brown gum residue which was purified by column chromatography (silica; EtOAc : Hexane, 1:7) to give **5.105a** as a yellow solid (43 mg, 92%). FTIR (KBr): $\tilde{\nu}$ = 2961, 1593, 1477, 1453, 1323, 1240, 1013, 811, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.71 – 7.69 (m, 1H), 7.31 – 7.29 (m, 4H), 7.21 – 7.19 (m, 2H), 7.16 – 7.12 (m, 3H), 7.10 – 7.06 (m, 1H), 7.03 – 6.99 (m, 1H), 6.73 – 6.72 (m, 1H), 5.49 (s, 1H), 4.32 (d, *J* = 15.2 Hz, 1H), 4.12 (d, *J* = 15.2 Hz, 1H) ppm.^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.6, 140.7, 138.0, 135.6, 134.3, 134.1, 133.9, 129.8, 129.1, 129.0, 127.8, 127.2, 123.9, 123.7, 122.6, 116.8, 111.0, 110.5, 61.7, 29.3, 28.9, 16.8 ppm. HRMS (ESI) exact mass calculated for $C_{22}H_{18}ClN_2^+$ ([M + H]+): 345.1153; Found: 345.1164.

6-(4-chlorophenyl)-2-ethyl-5,6,7,12-tetrahydrobenzo[6,7]azepino[3,4-*b*]indole (5.105b):



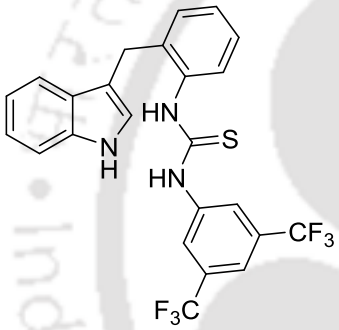
TFA (40 µL) was added drop-wise to a solution of **5.91b** (30 mg, 0.12 mmol) and 4-chlorobenzaldehyde (20 mg, 0.14 mmol) in dry dichloromethane (2 mL) and the reaction was stirred at room temperature. After 1 h the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and the reaction mixture was extracted with dichloromethane (3x10 mL). The combined organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give brown gum which was purified by column chromatography (silica; EtOAc : Hexane, 1:7) to give **5.105b** as a yellow solid (40 mg, 89%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2929, 1636, 1486, 1261, 1095, 1023, 801, 656 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$) δ = 7.50 (s, 1H), 7.32 – 7.27 (m, 3H), 7.22 (br.s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.09 – 7.05 (m, 2H), 7.04 – 6.97 (m, 2H), 6.73 – 6.71 (m, 1H), 5.50 (s, 1H), 4.29 (d, *J* = 15.5 Hz, 1H), 4.13 (d, *J* = 15.6 Hz, 1H), 2.79 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.6, 140.7, 138.0, 135.6, 134.3, 134.1, 133.9, 129.8, 129.1, 129.0, 127.8, 127.2, 123.9, 123.7, 122.6, 116.8, 111.0, 110.5, 61.7, 29.3, 28.9, 16.8 ppm. HRMS (ESI) exact mass calculated for $C_{24}H_{22}ClN_2^+$ ([M + H]+): 373.1466; Found: 373.1475.



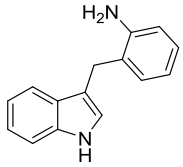
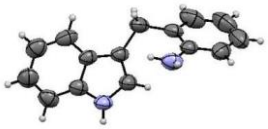
2-((1*H*-indol-3-yl)methyl)-N-benzylaniline (5.106): A mixture of compound **5.91**(25 mg, 0.11 mmol), benzyl alcohol (36 µL, 0.34

mmol) and KOH (18 mg, 0.34 mmol) in toluene (1.5 mL) were heated at 150 ^oC for 24 h. After the reaction the brown residue was purified by column chromatography (silica; EtOAc : Hexane, 1:7) to give **5.106** as a colorless gum (27 mg, 77%). FTIR (KBr): $\tilde{\nu}$ = 2958, 2923, 2853, 1628, 1604, 1510, 1453, 1330, 1261, 1090, 800, 742 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.98 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.24 –7.19 (m, 5H), 7.15 – 7.12 (m, 3H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.85 (s, 1H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 4.27 (s, 2H), 4.04 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 146.2, 139.5, 136.8, 130.3, 128.7, 127.7, 127.6, 127.4, 127.2, 125.1, 122.5, 122.4, 119.7, 119.4, 117.6, 113.8, 111.3, 111.2, 48.2, 28.6. HRMS (ESI) exact mass calculated for $C_{22}H_{21}N_2^+$ ([M + H]+): 313.1699; Found: 313.1709.

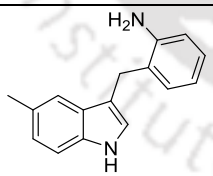
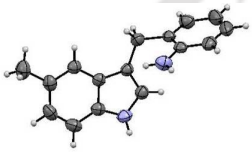
1-(2-((1*H*-indol-3-yl)methyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (5.107): 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (25 µL, 0.13 mmol5, 7) was added to a solution of **5.91** (30 mg, 0. 13 mmol) in dry THF (2 mL) under argon atmosphere. The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated in vacuum to give brown solid which was purified by column chromatography (silica; EtOAc : Hexane, 1:5) to give **5.107** as a yellow solid (65 mg, 97%). FTIR (KBr): $\tilde{\nu}$ = 3433, 2925, 2854, 1631, 1487, 1455, 1381, 1343, 1277, 1176, 1133, 1095, 850, 794, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.35 (s, 1H), 7.89 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.45 (s, 1H), 7.36 – 7.33(m, 3H), 7.31 – 7.24 (m, 2H), 7.19 – 7.16 (m, 1H), 7.14 – 7.12 (m, 1H), 7.04 – 7.03 (m, 2H), 6.93 – 6.89 (m, 1H), 6.86 (br.s, 1H), 4.09 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.1, 139.6, 139.1, 136.5, 134.4, 132.2, 131.8, 131.5, 131.2, 129.6, 128.8, 128.5, 127.2, 126.8, 124.4, 124.1, 124.1, 123.0, 122.6, 121.7, 119.8, 119.08, 119.01, 119.01, 119.0, 118.9, 118.8, 113.0, 111.7, 29.7. HRMS (ESI) exact mass calculated for $C_{24}H_{18}F_6N_3S^+$ ([M + H]+): 494.1120; Found: 494.1119.



Crystal of **5.91:**

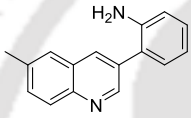
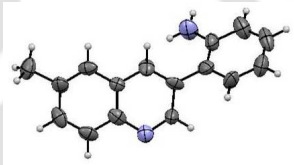
	
Empirical formula	$C_{15}H_{14}N_2$
Formula weight	222.28
Crystal habit, colour	Block, colorless
Crystal size, mm^3	0.38X 0.33X 0.31
Temperature, *T*	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	orthorhombic
Space group	*P c c n*
Unit cell dimensions	*a* = 20.3252(11)Å *b* = 17.4919(13)Å *c* = 7.6118(3)Å $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$,
Volume, *V*($Å^3$)	2706.2(3)
Z	8
Calculated density, $Mg \cdot m^{-3}$	1.091
Absorption coefficient, $\mu(mm^{-1})$	0.065
F(000)	944
θ range for data collection	3.09 ° to 24.99°
Limiting indices	$-24 \le h \le 22$, $-20 \le k \le 13$, $-8 \le l \le 9$
Reflection collected / unique	7088/ 1387 [*R*(int) = 0.0286]
Completeness to θ	99.8% (θ = 24.99°)
Refinement method	SHELXL–97
Data / restraints / parameters	1387 / 0 / 155
Goodness–of–fit on F^2	1.346
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.1227, *wR*2 = 0.3538
R indices (all data)	*R*1 = 0.1657, *wR*2 = 0.3975
Largest diff. peak and hole	0.956 and –0. 0.335 $eÅ^{-3}$

Crystal of **5.91a**:

	
Empirical formula	$C_{16}H_{16}N_2$
Formula weight	236.31
Crystal habit, colour	Block, colorless
Crystal size, mm^3	0.39X 0.37X 0.35
Temperature, *T*	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*C 2/c*
Unit cell dimensions	*a* = 20.126(4)Å *b* = 7.6043(4)Å *c* = 19.1043(19)Å $\alpha = 90°$, $\beta = 114.182(10)°$, $\gamma = 90°$,
Volume, *V*($Å^3$)	2667.2(6)
Z	8
Calculated density, $Mg \cdot m^{-3}$	1.177

Absorption coefficient, μ(mm^{-1})	0.070
F(000)	1008
θ range for data collection	2.34 ° to 25.00°
Limiting indices	$-23 \leq h \leq 23$, $-9 \leq k \leq 8$, $-13 \leq l \leq 22$
Reflection collected / unique	4654 / 1614 [*R*(int) = 0.0262]
Completeness to θ	99.9% (θ = 25.00 °)
Refinement method	'SHELXL–97
Data / restraints / parameters	1614 / 0 / 165
Goodness–of–fit on F^2	1.076
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0559, *wR*2 = 0.1357
R indices (all data)	*R*1 = 0.0861, *wR*2 = 0.1603
Largest diff. peak and hole	0.190 and –0.305·Å^{-3}

Crystal of **5.93c'**:

	
Empirical formula	$C_{16}H_{14}N_2$
Formula weight	234.29
Crystal habit, colour	Needle, brown
Crystal size, mm^3	0.38X 0.35 X 0.33
Temperature, *T*	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*P 1 21/c 1*
Unit cell dimensions	*a* = 13.081(6) Å *b* = 13.044(4)Å *c* = 7.296(3)Å α = 90°, β = 99.38(5)°, γ = 120°,
Volume, *V*(Å^3)	1228.2(8)
Z	4
Calculated density, Mg·m^{-3}	1.267
Absorption coefficient, μ(mm^{-1})	0.076
F(000)	496
θ range for data collection	2.22 ° to 24.99°
Limiting indices	$-15 \leq h \leq 10$, $-14 \leq k \leq 15$, $-8 \leq l \leq 8$
Reflection collected / unique	4154/ 341 [*R*(int) = 0.2801]
Completeness to θ	99.7% (θ = 24.99°)
Refinement method	'SHELXL–97
Data / restraints / parameters	341 / 0 / 166
Goodness–of–fit on F^2	0.841
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.1228, *wR*2 = 0.3430
R indices (all data)	*R*1 = 0.4372, *wR*2 = 0.2001
Largest diff. peak and hole	0.275 and – 0.254 ·Å^{-3}

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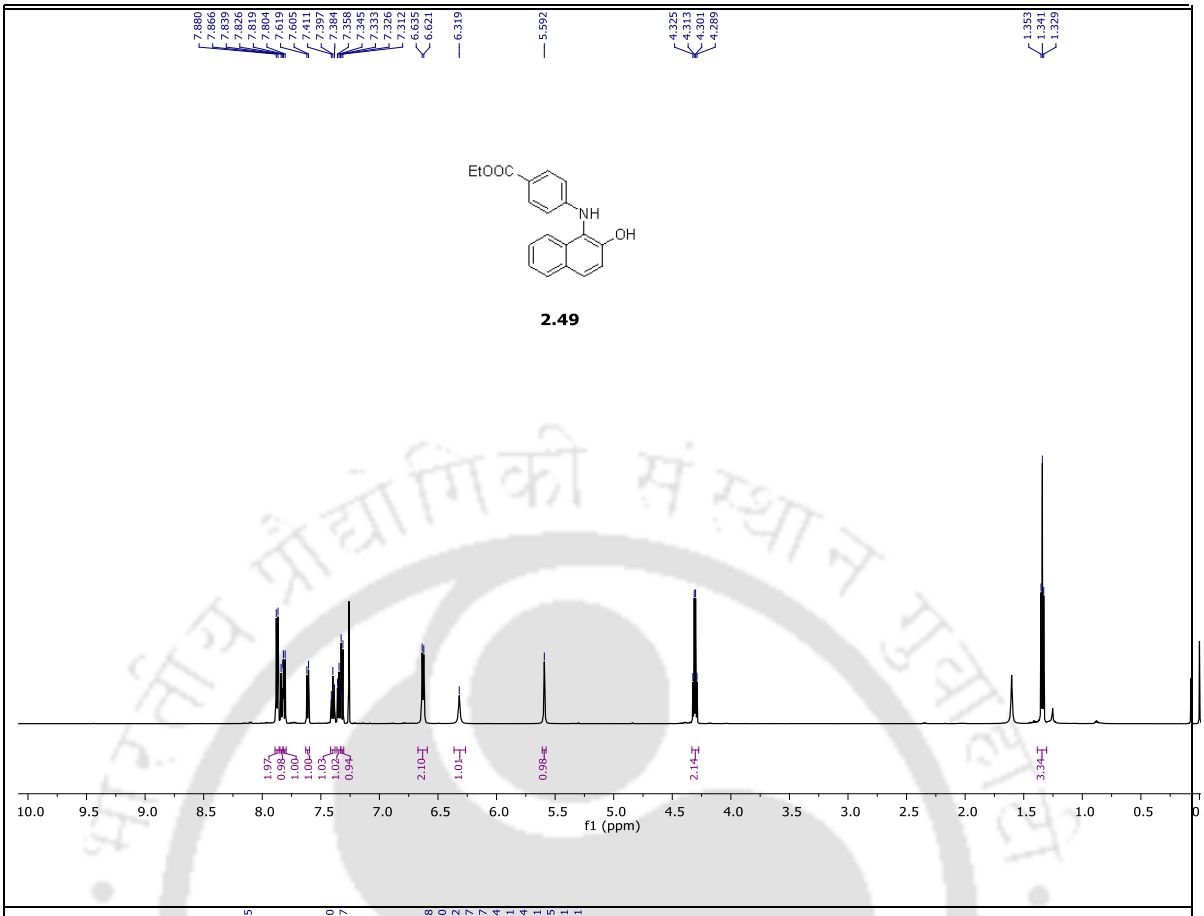
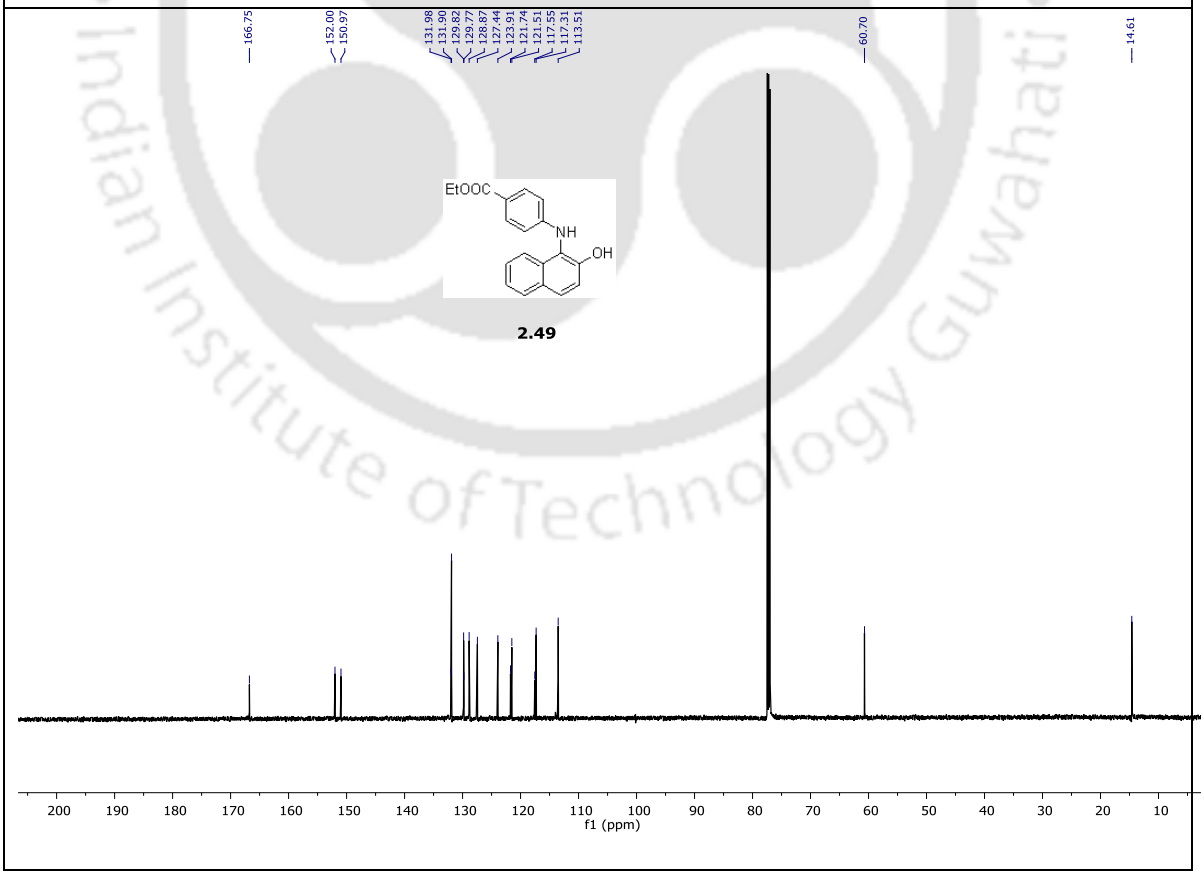
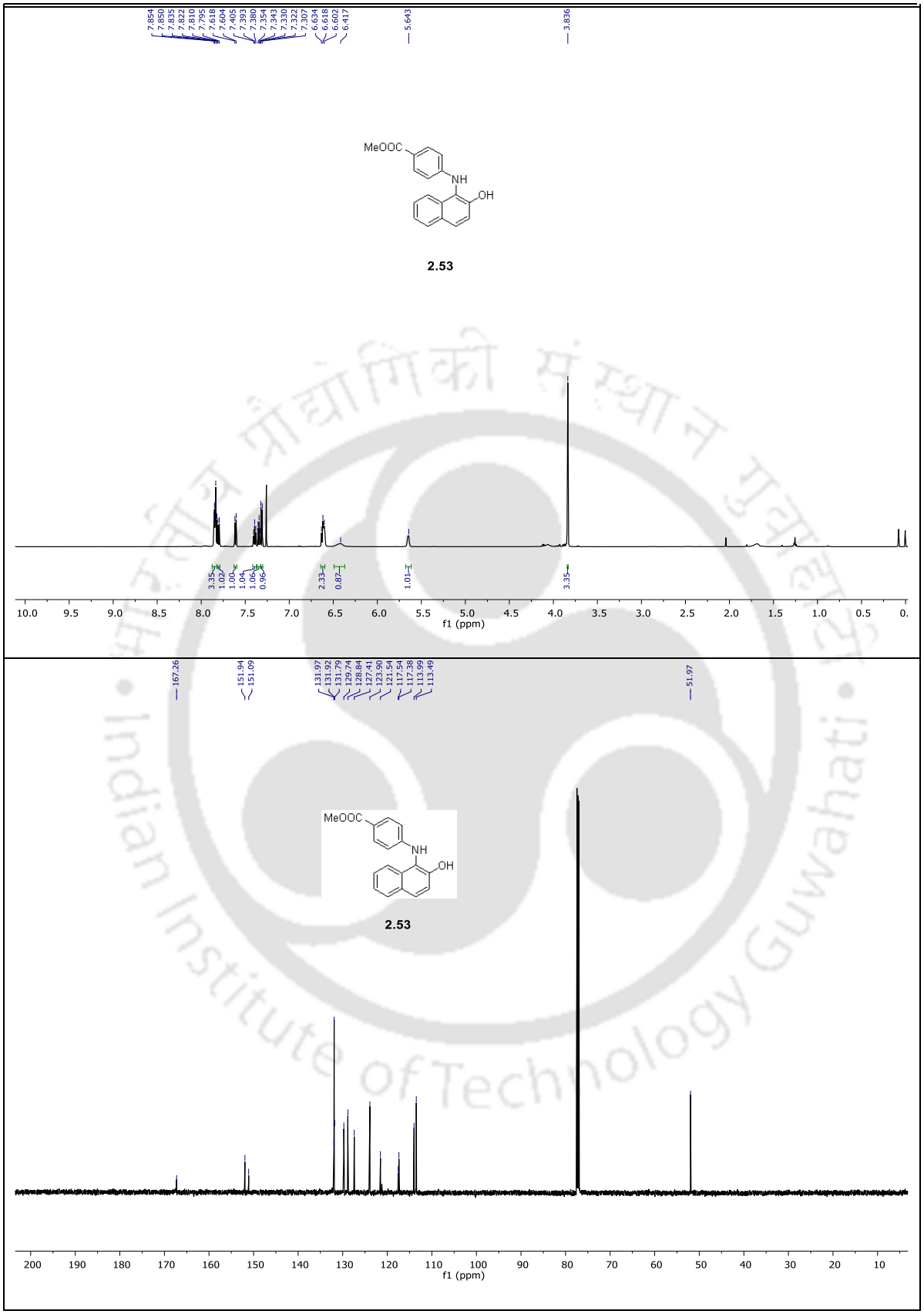
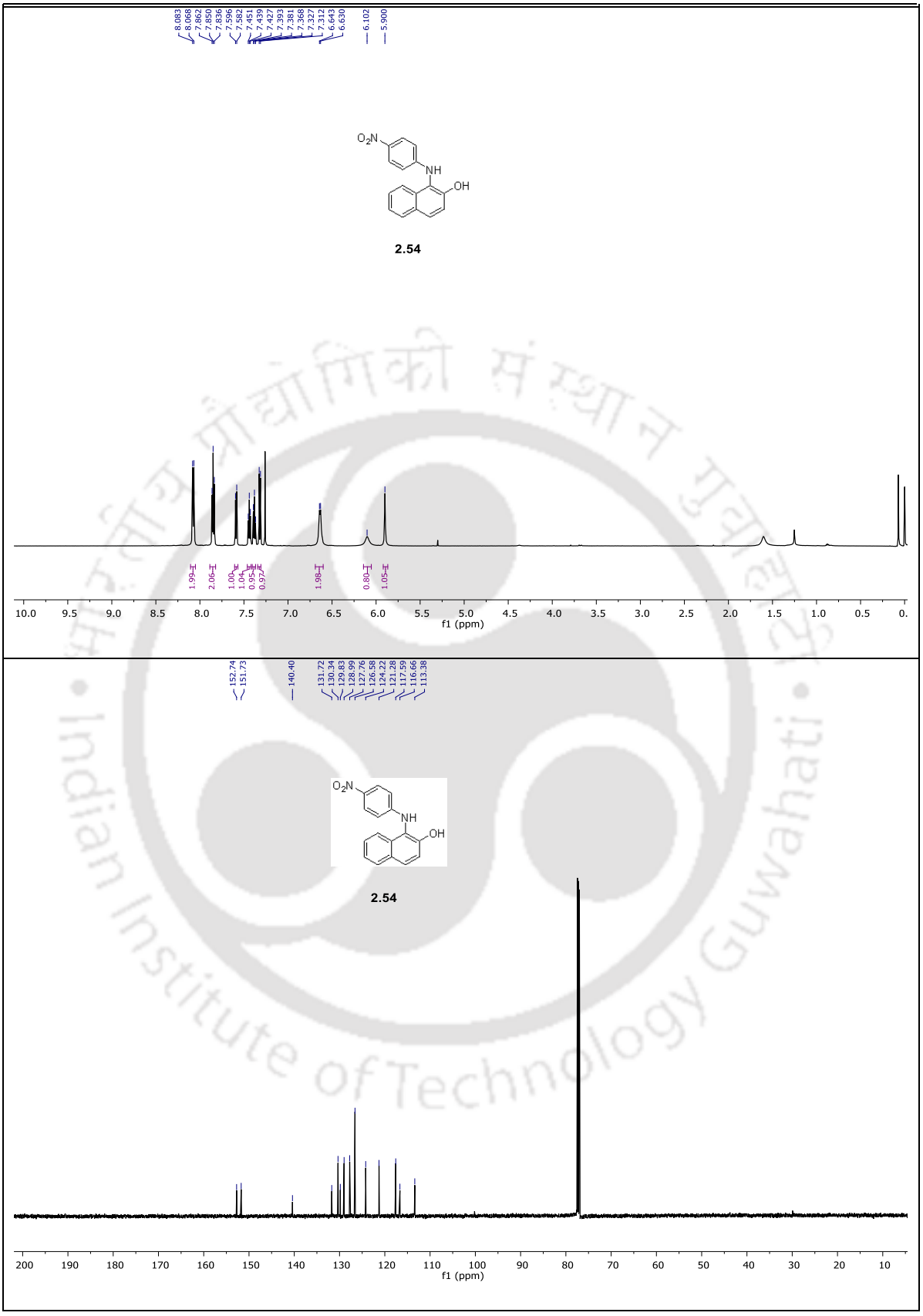
Chapter 6

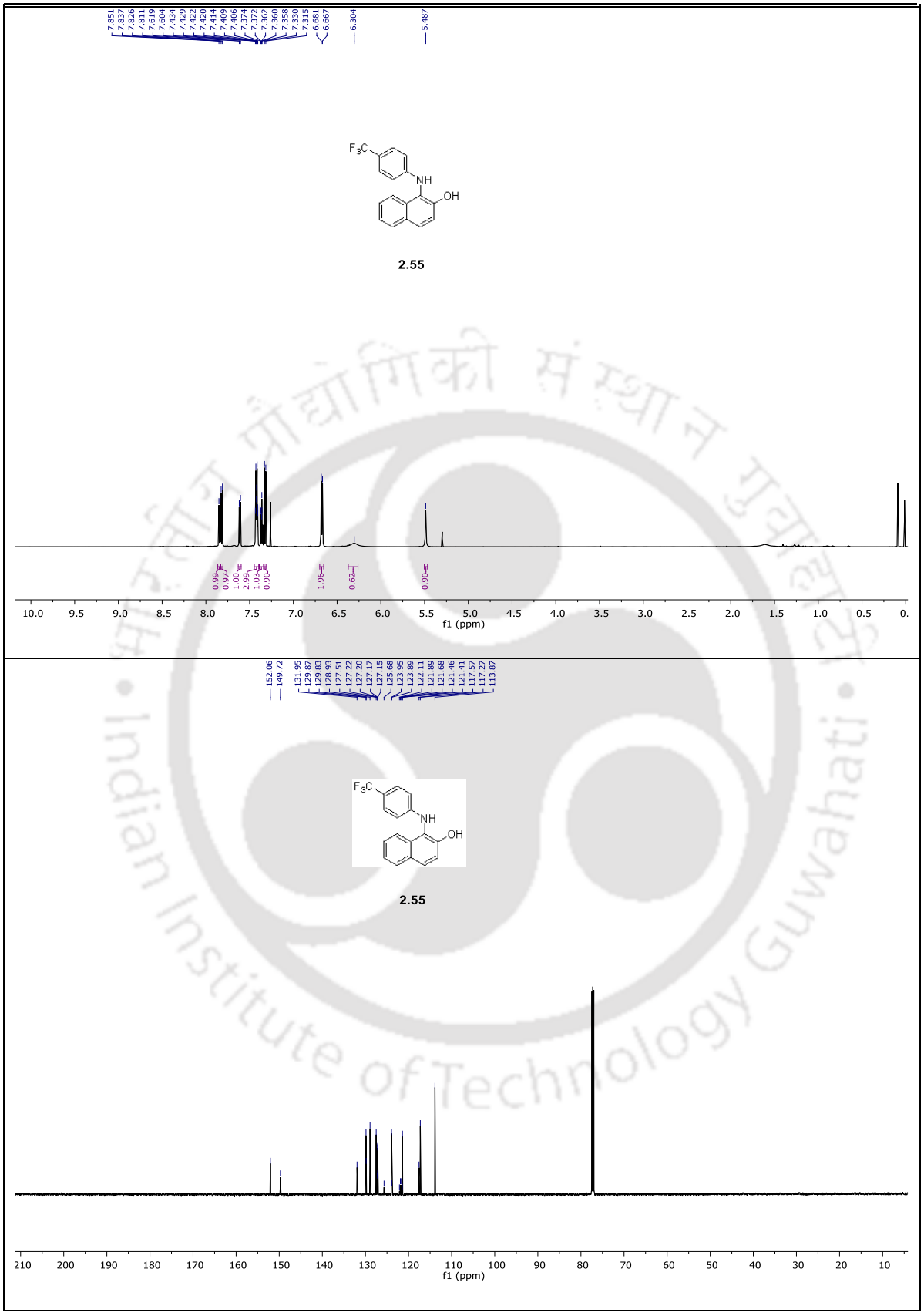
^{1}H and ^{13}C Spectra of Selected New Compounds

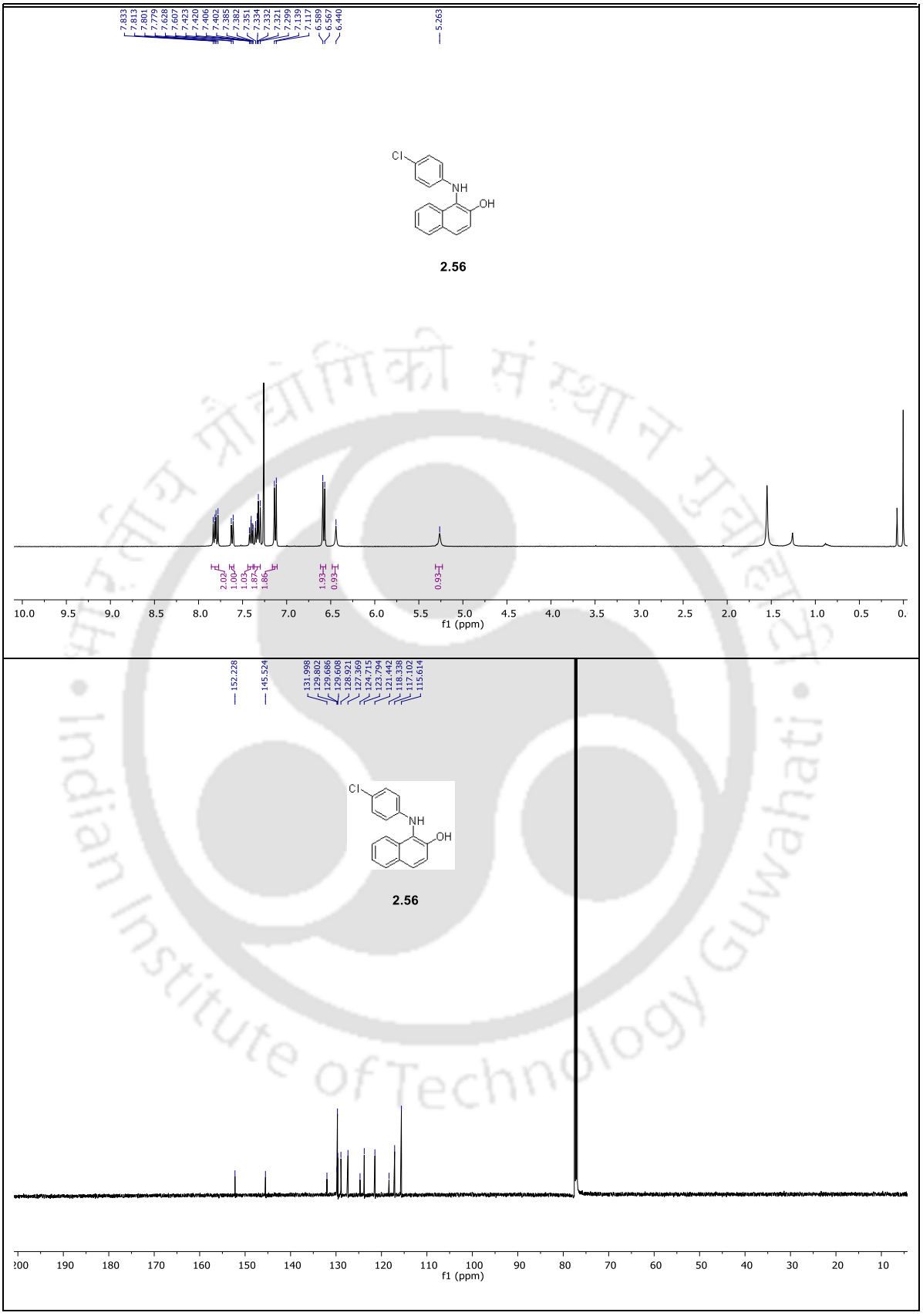


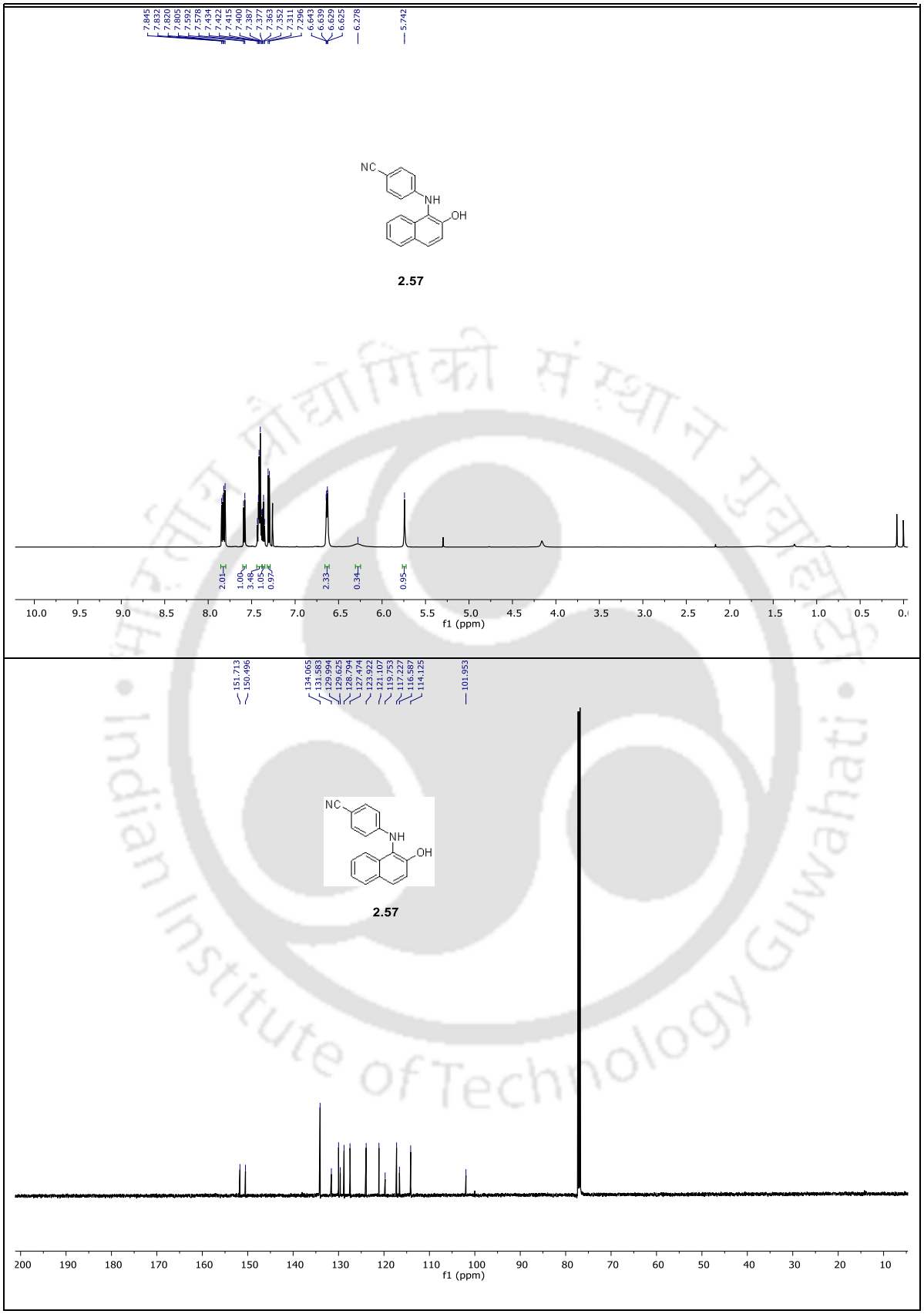


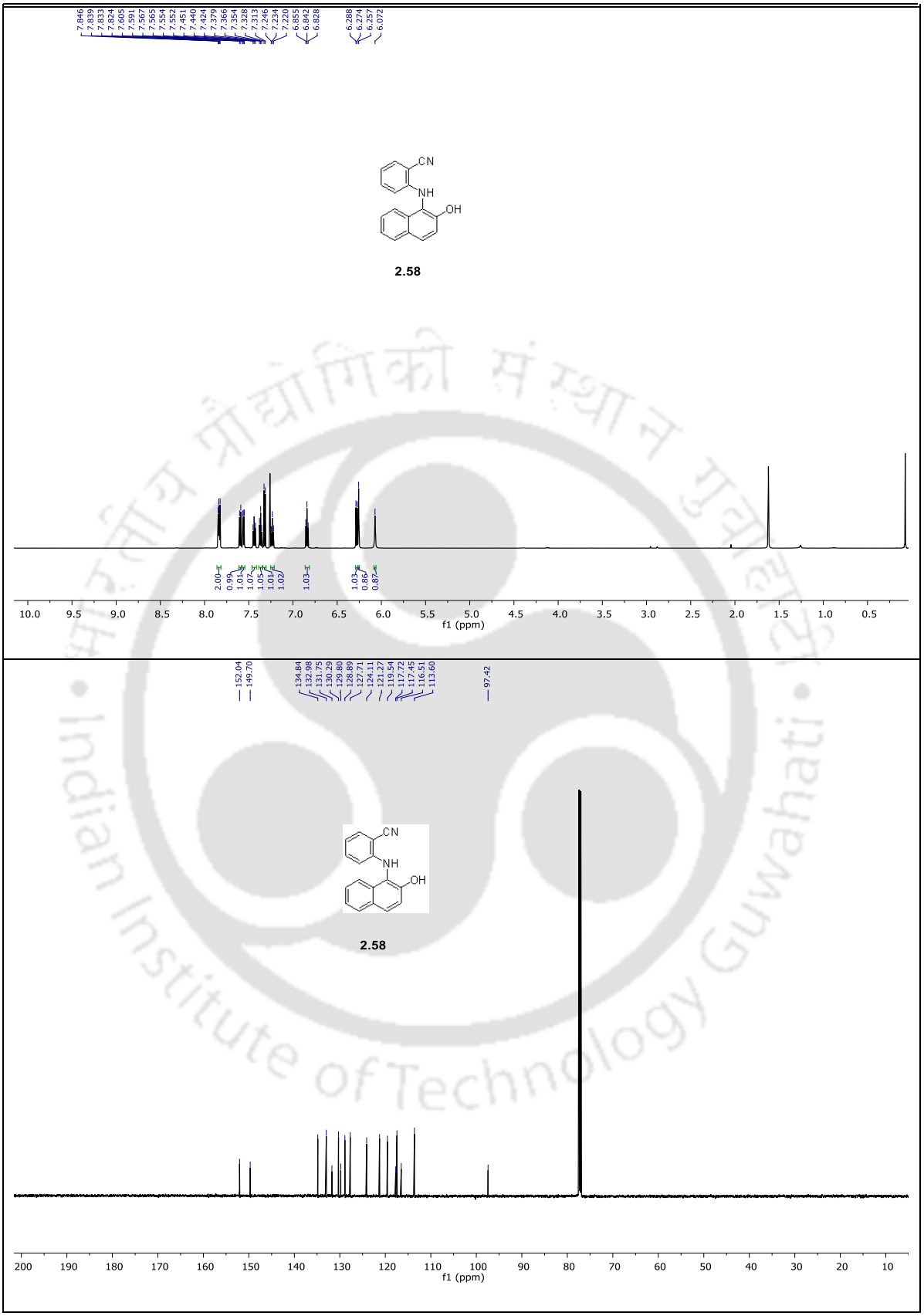


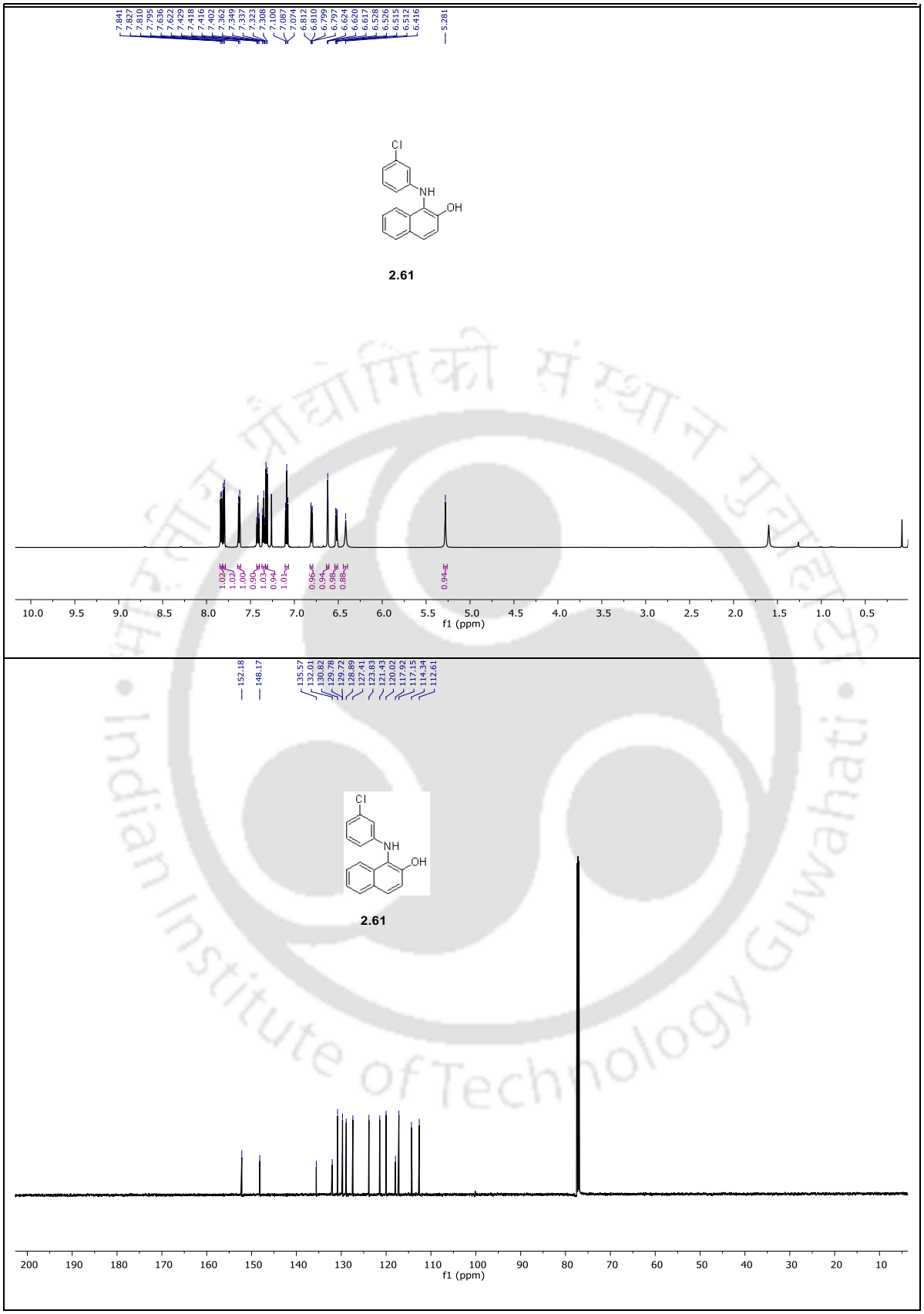


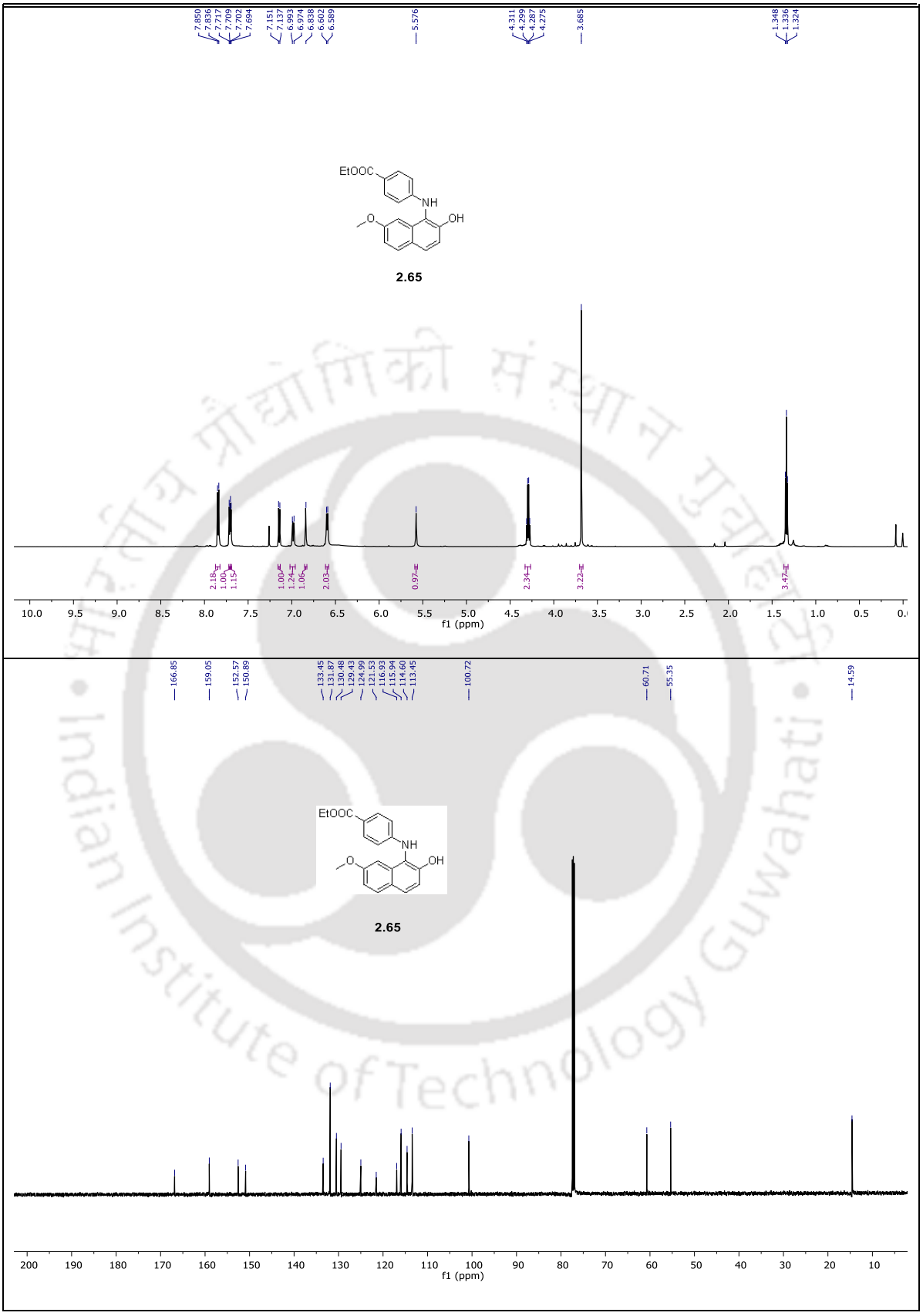


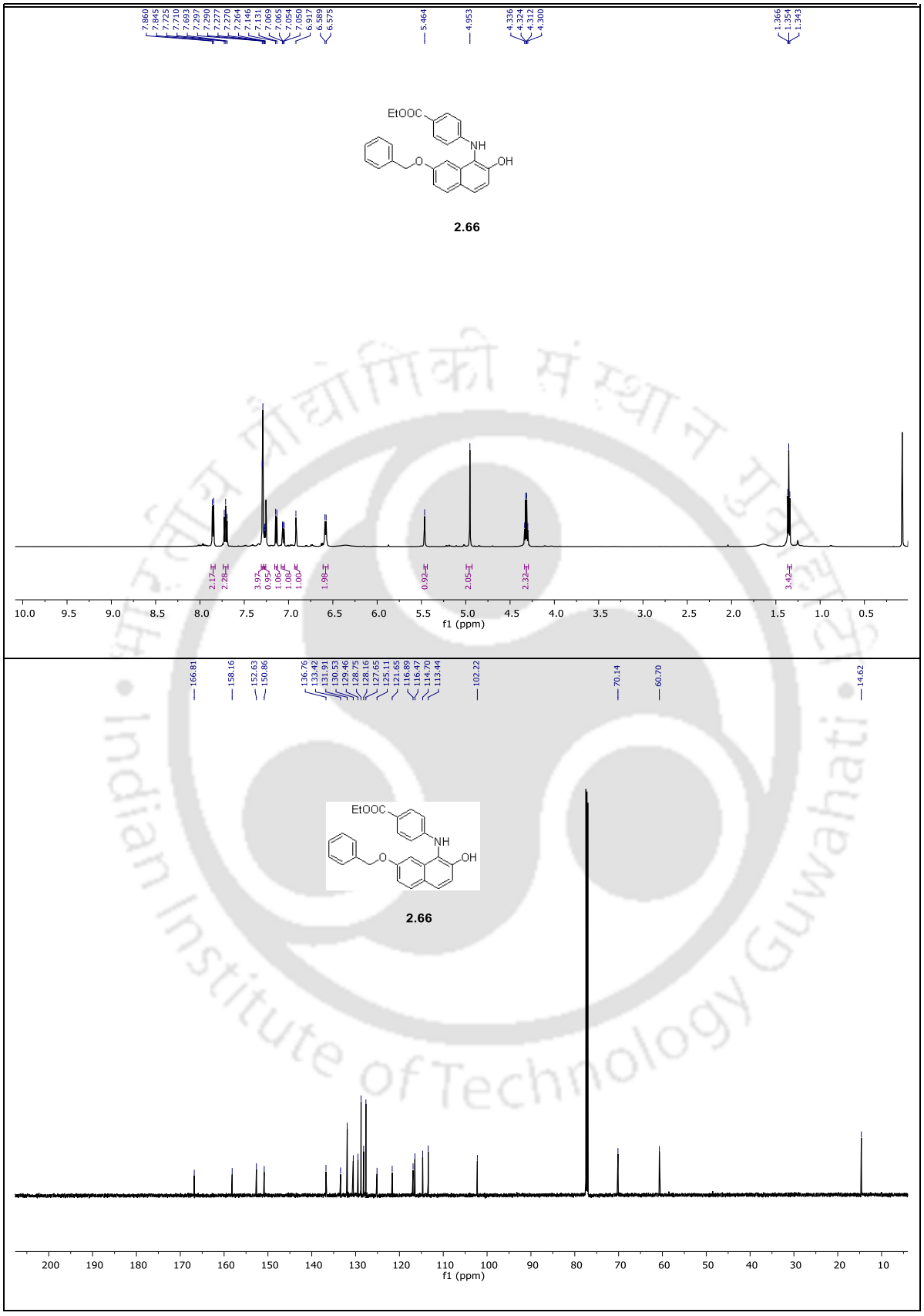


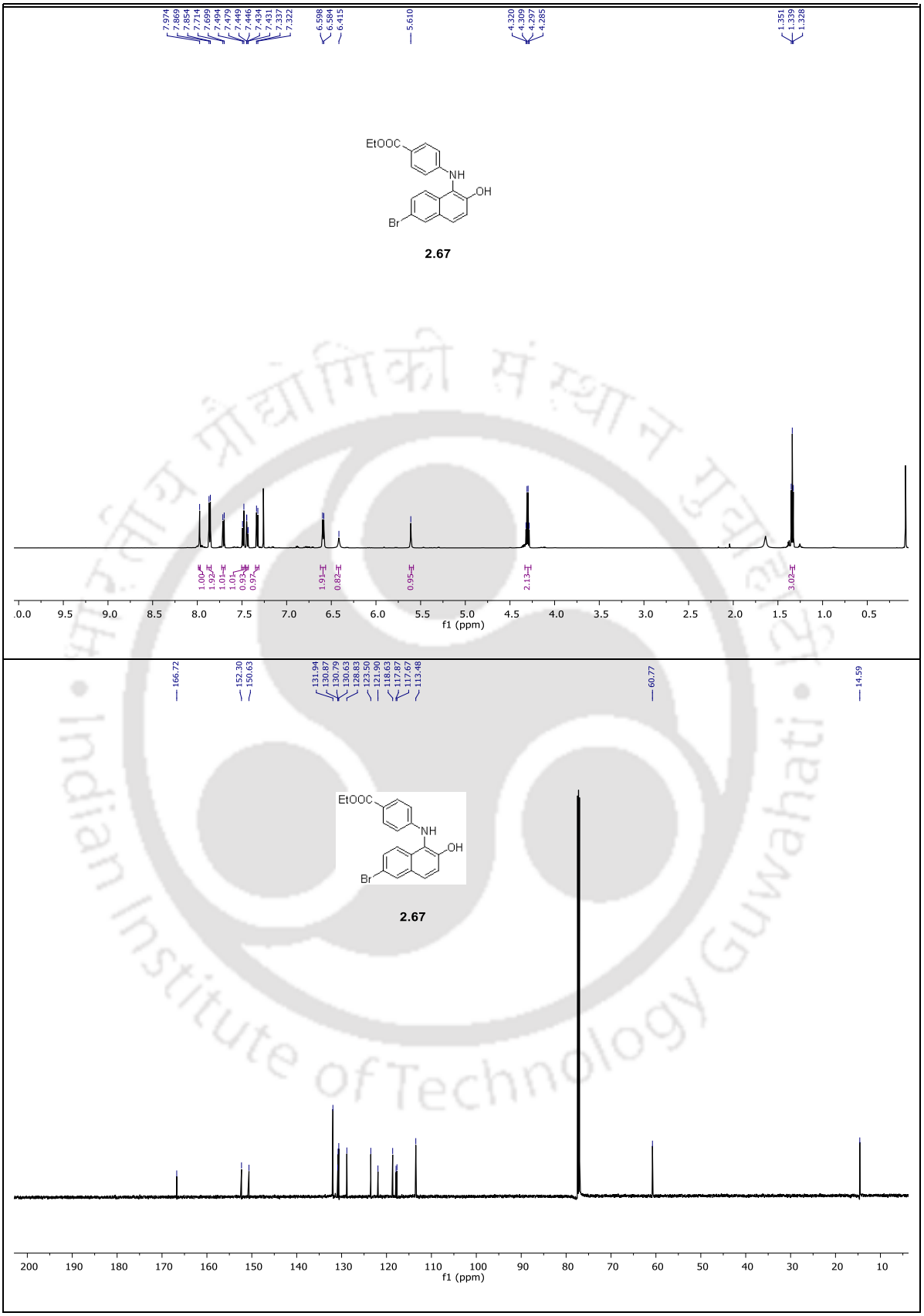


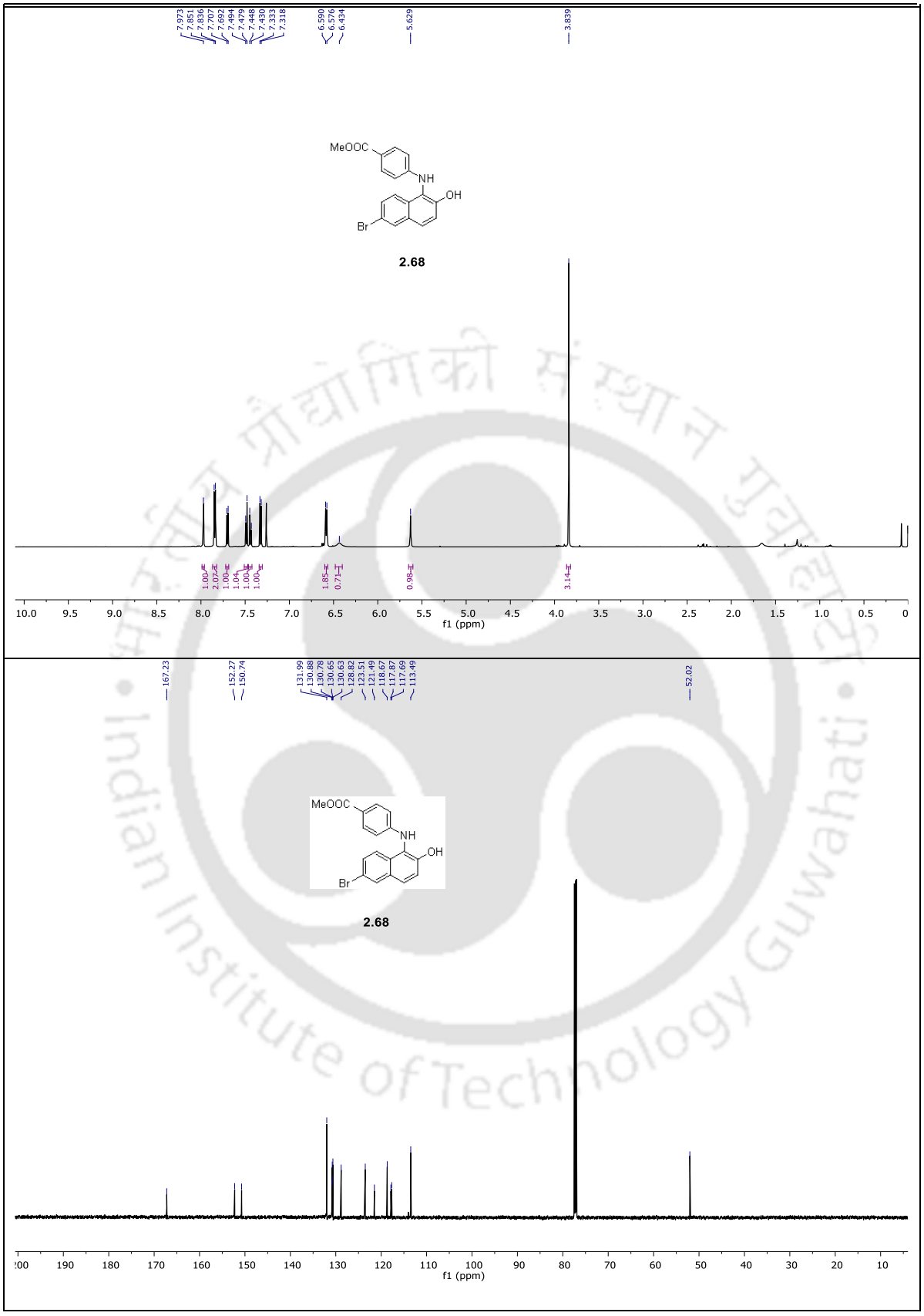


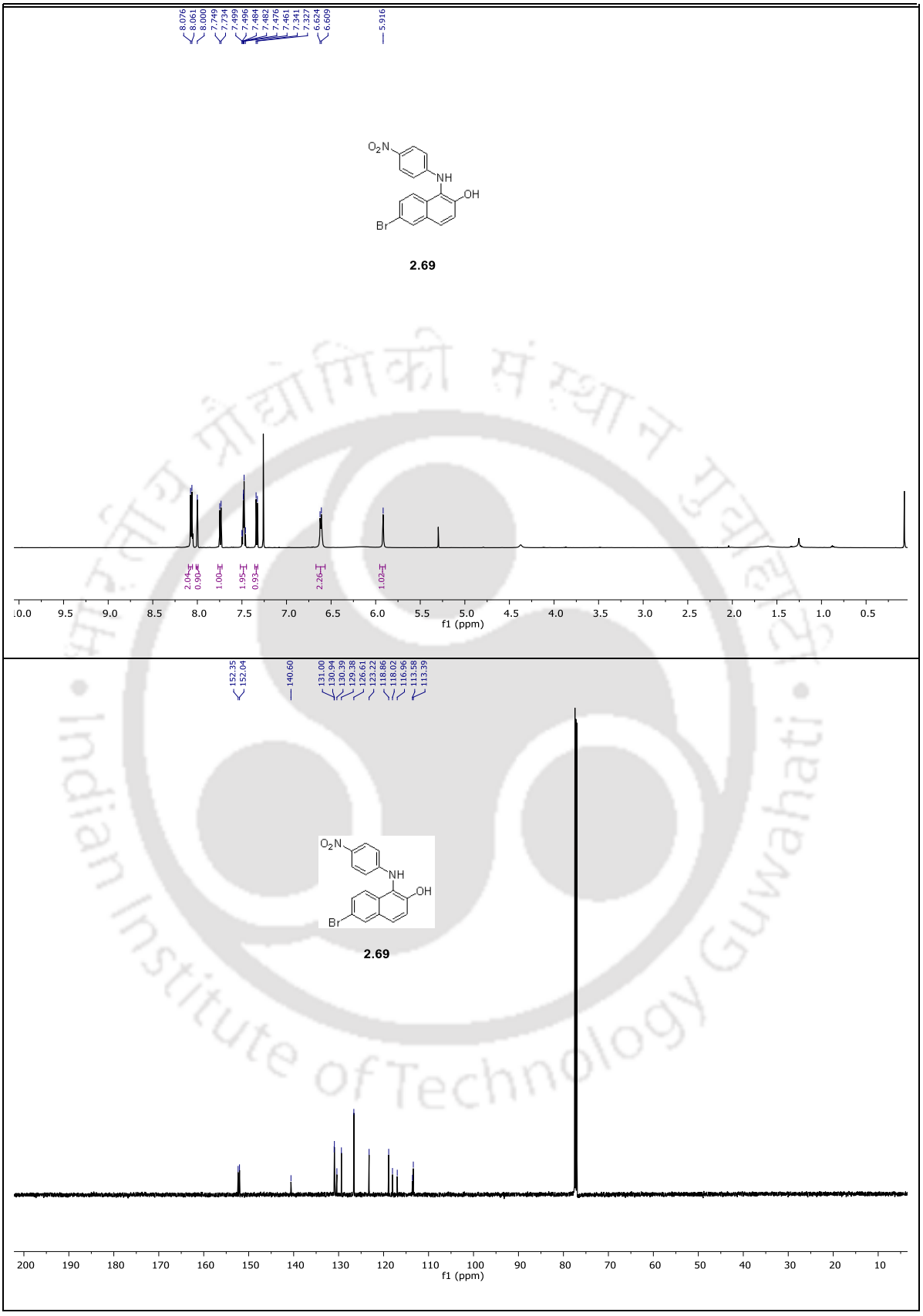


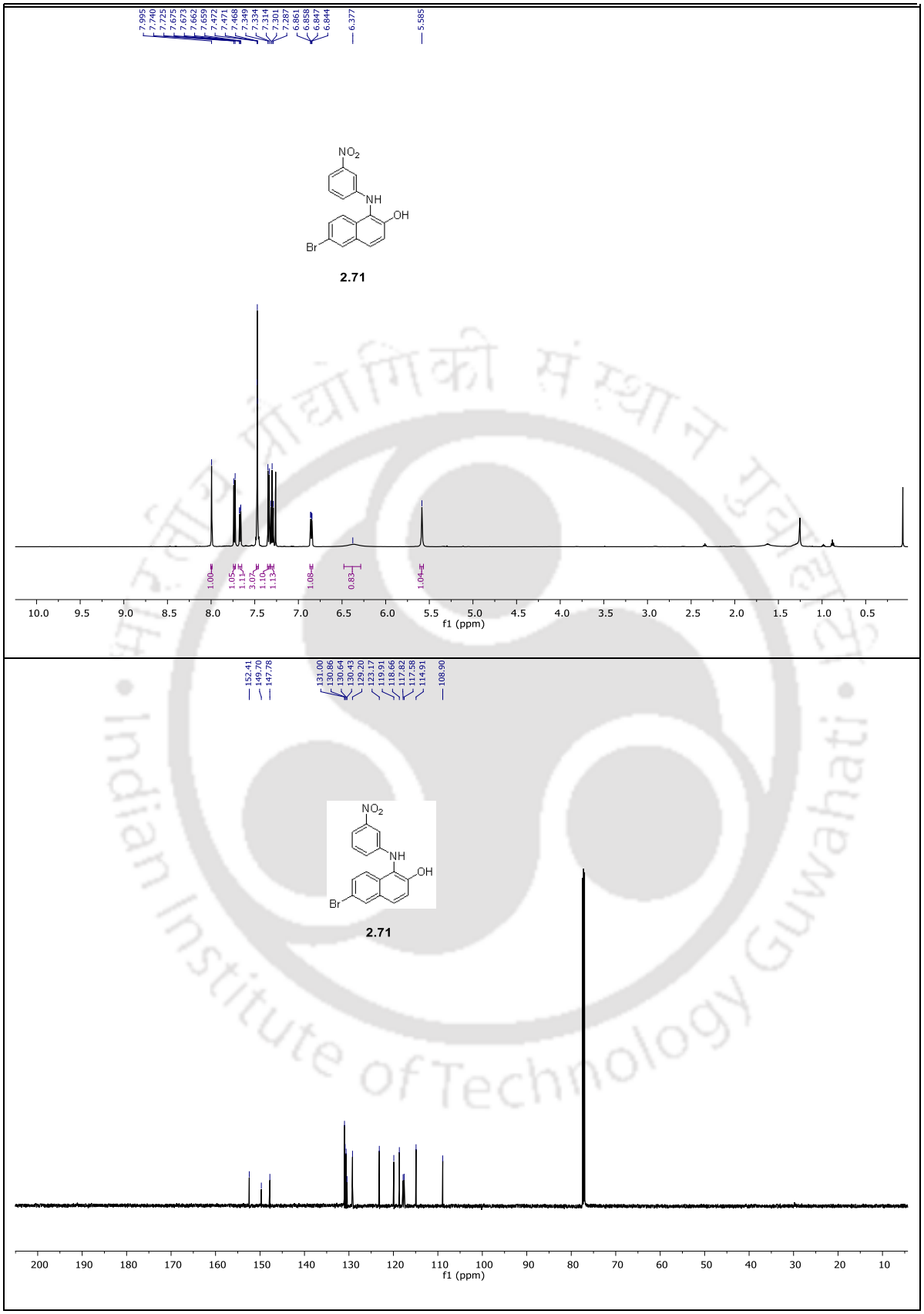


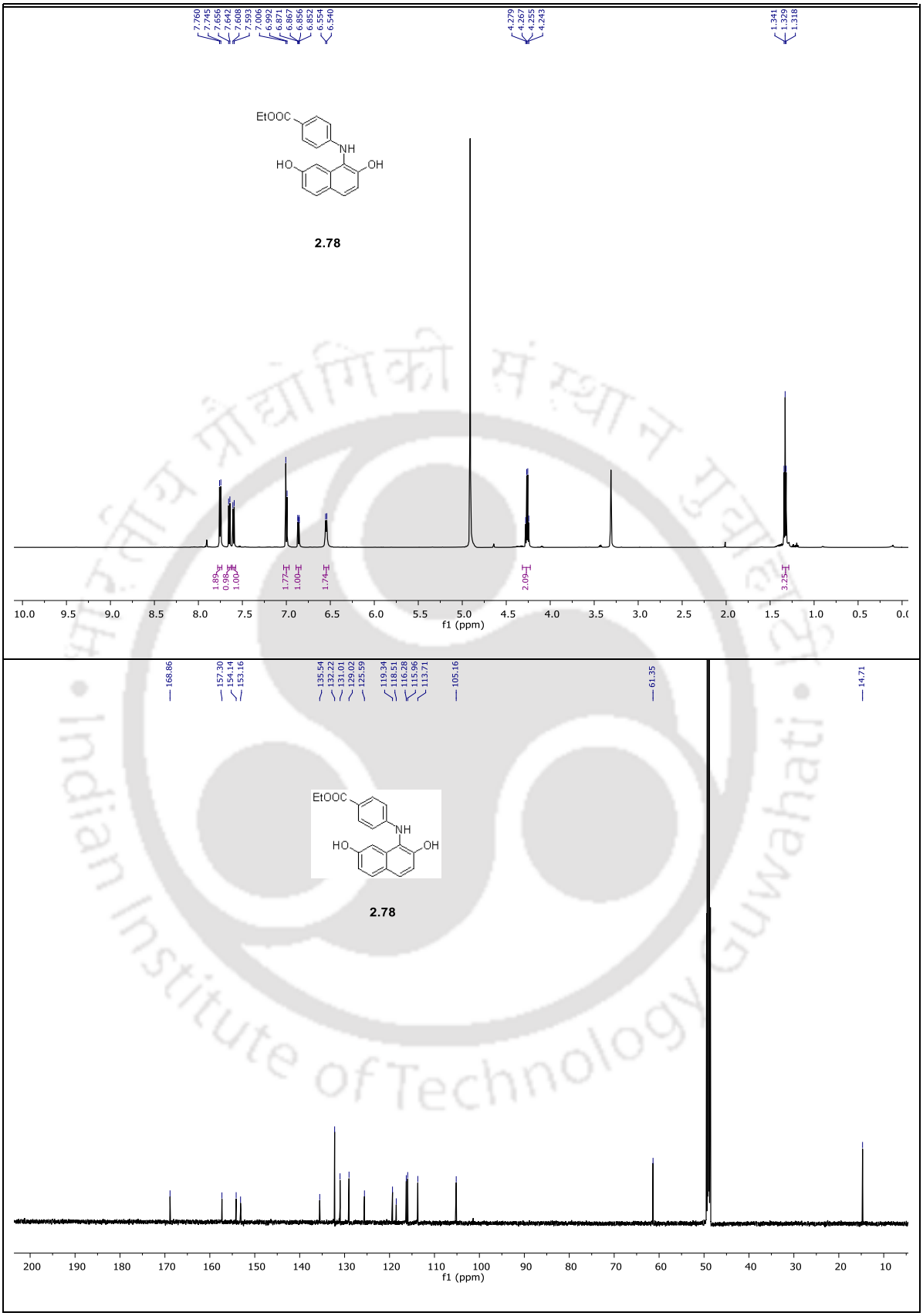


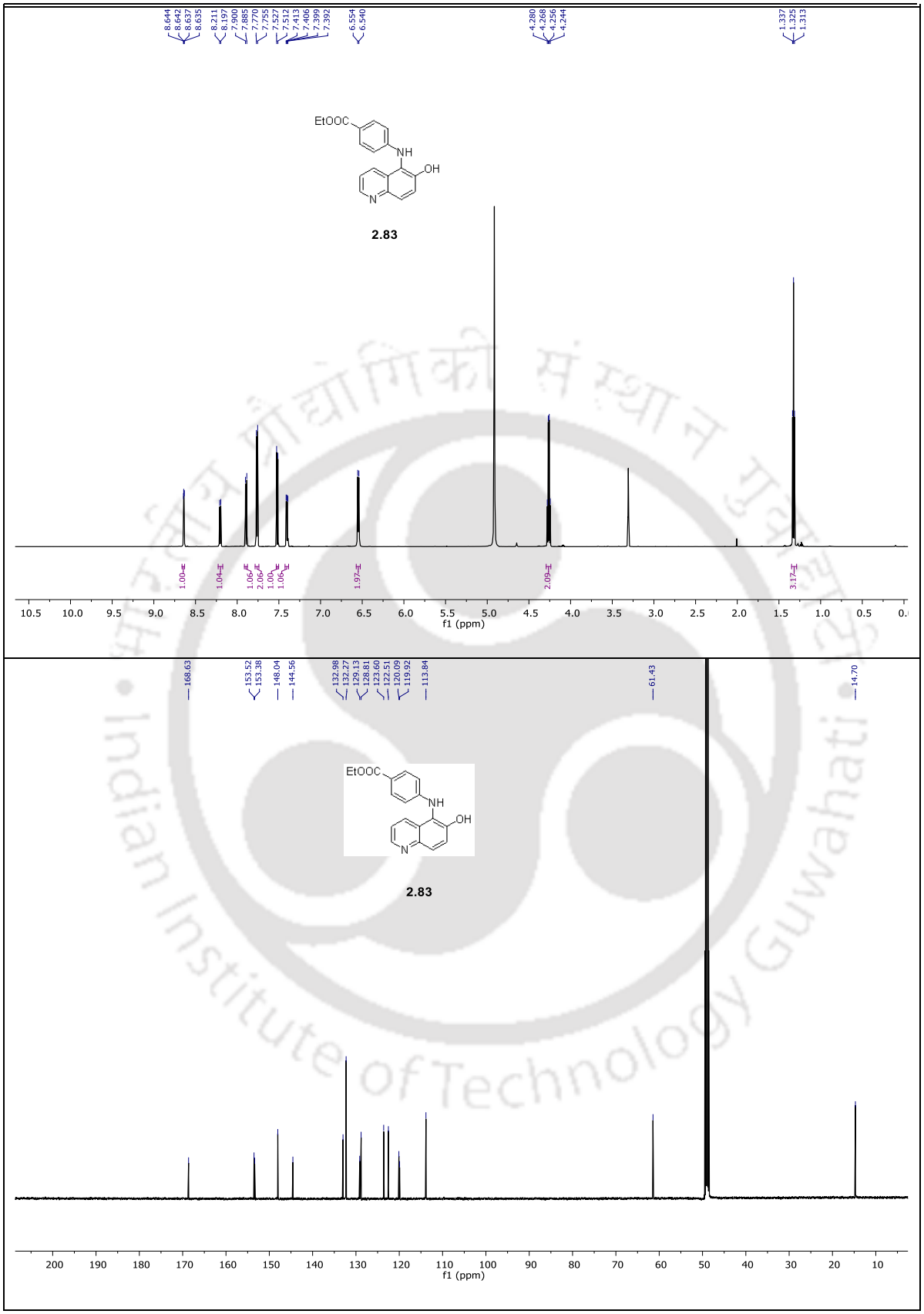


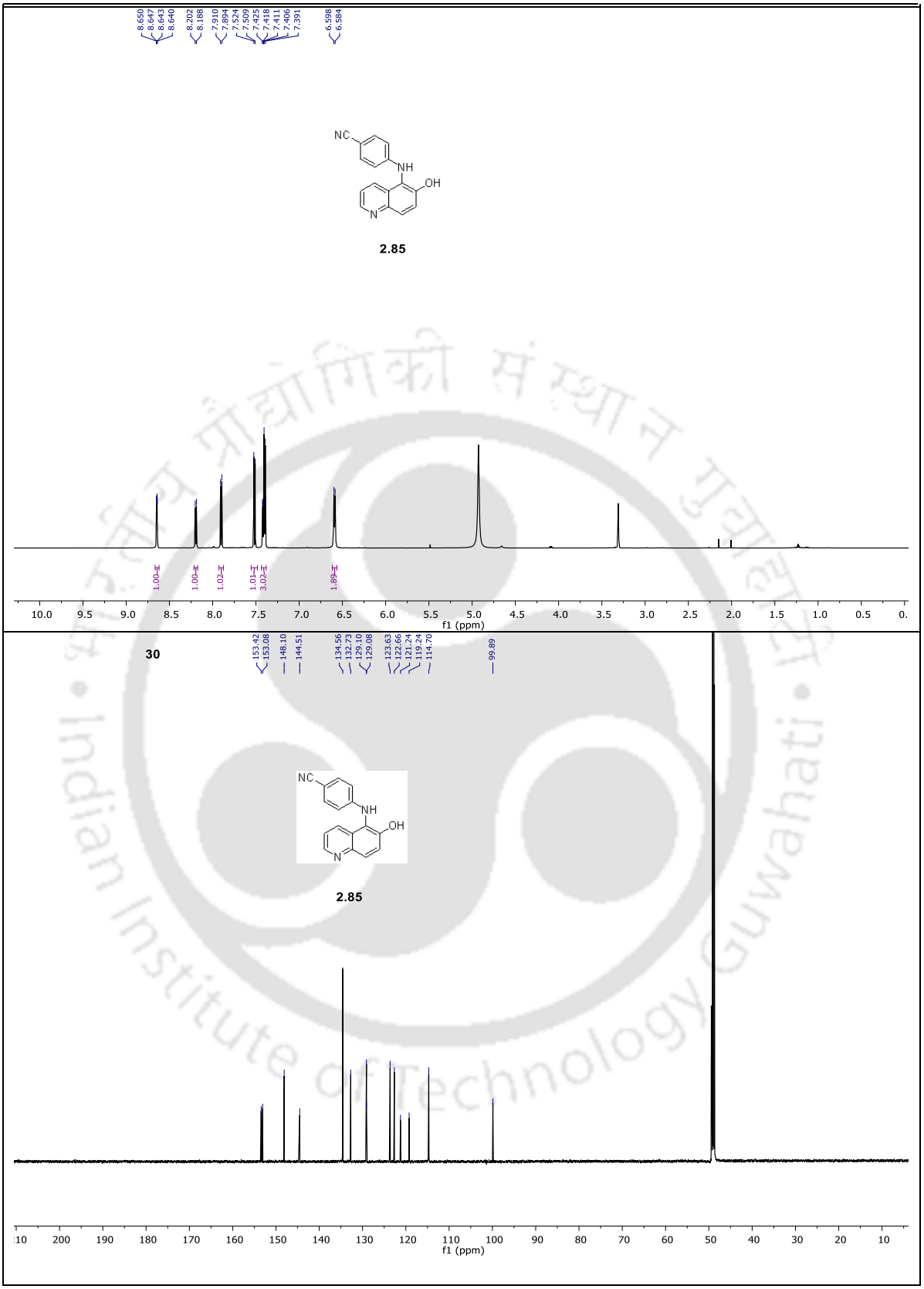


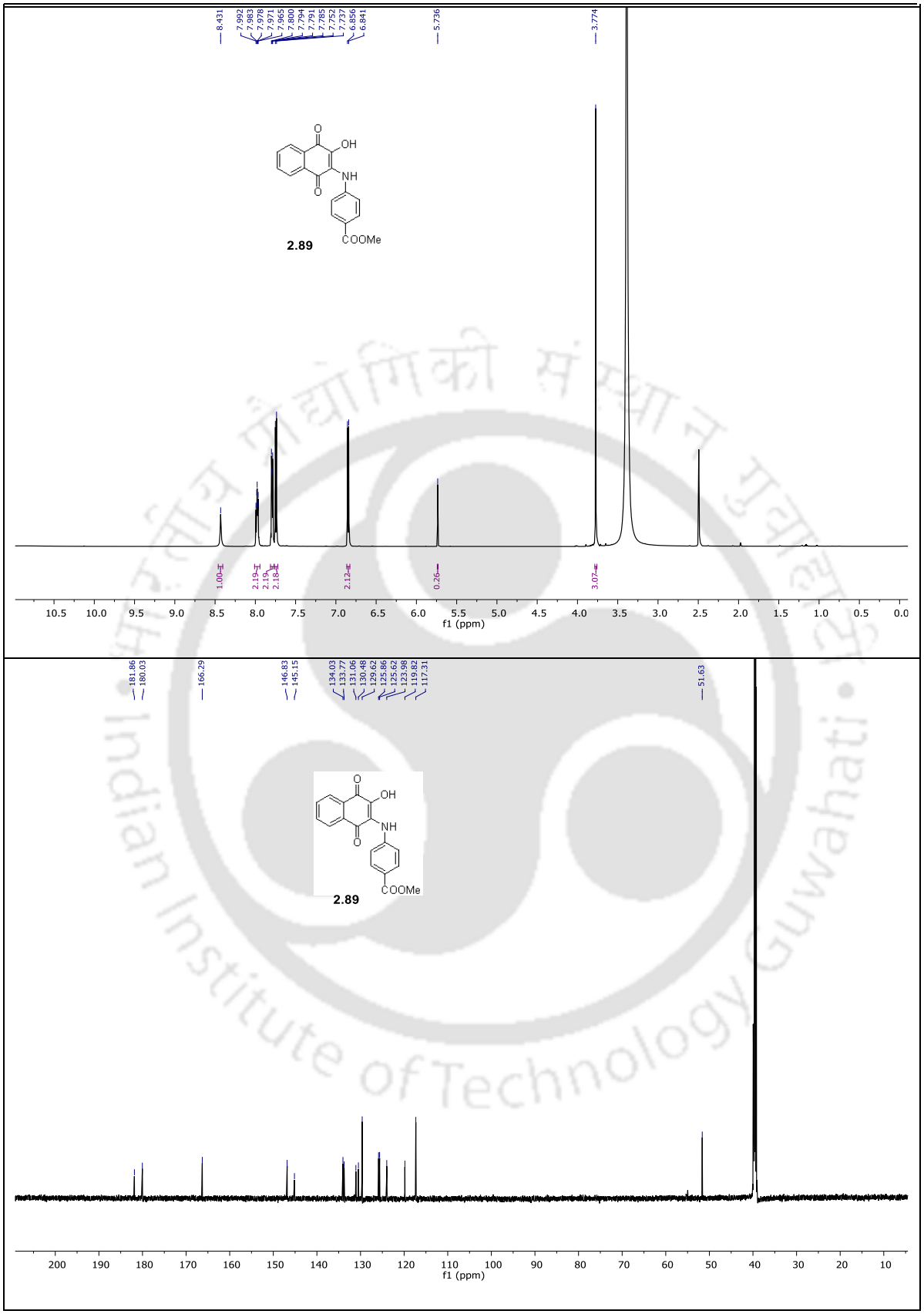


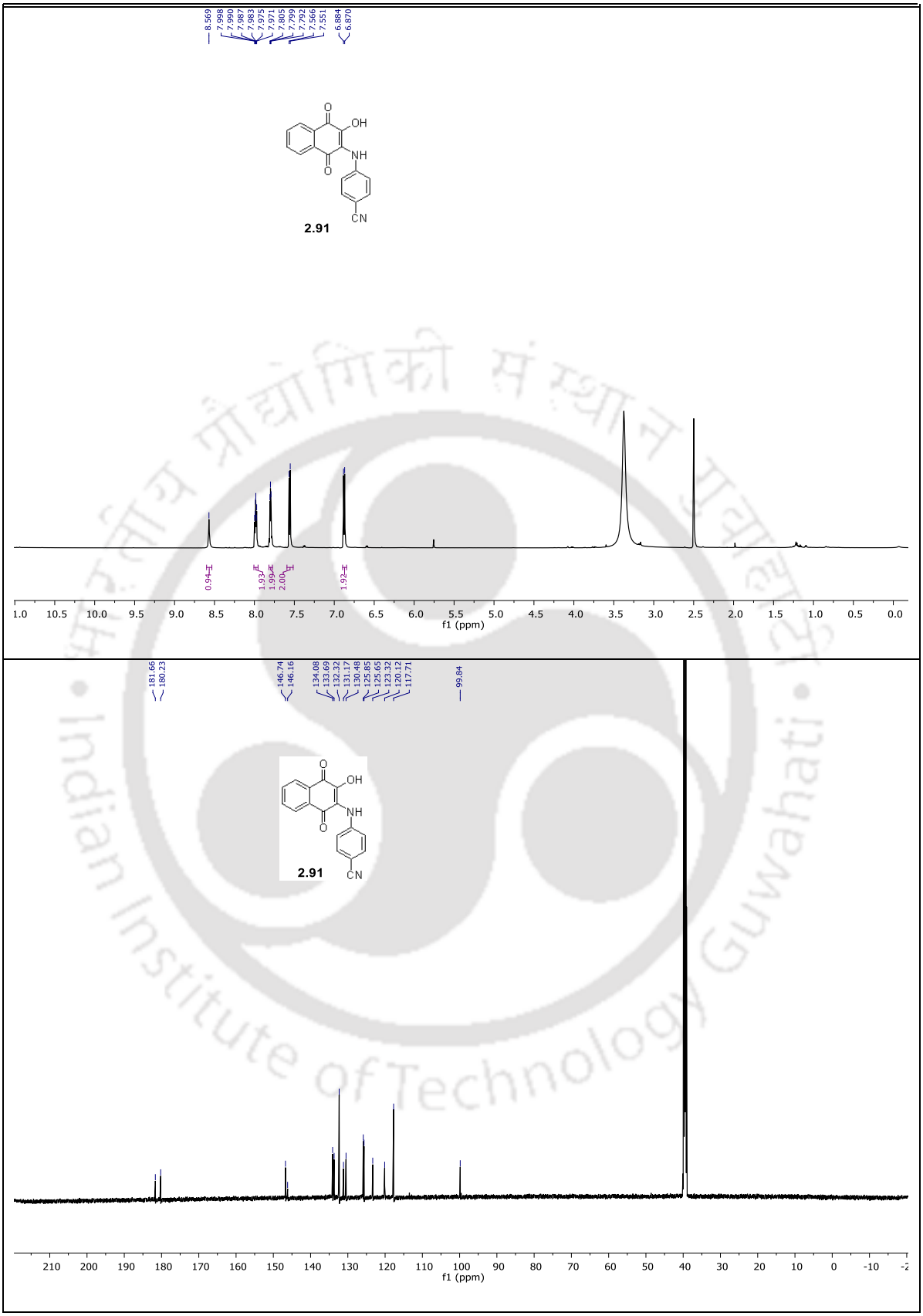


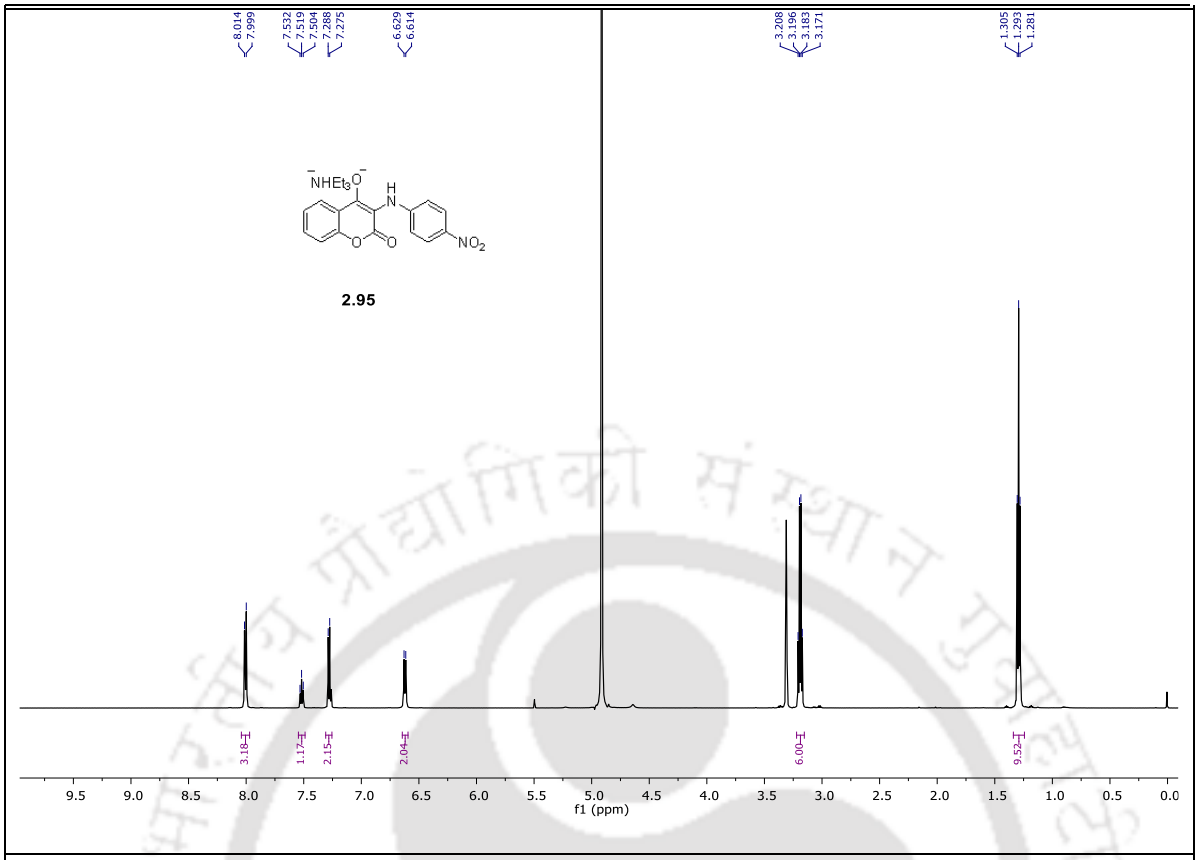


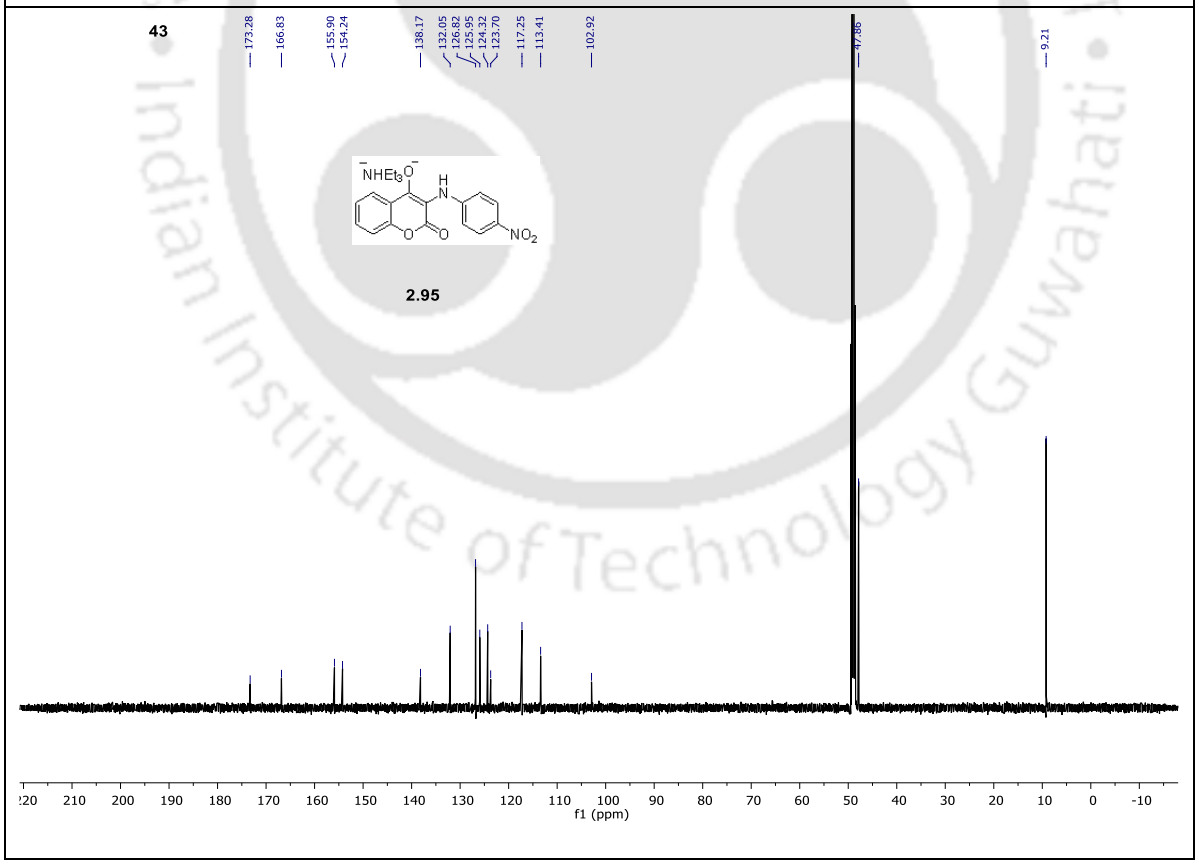


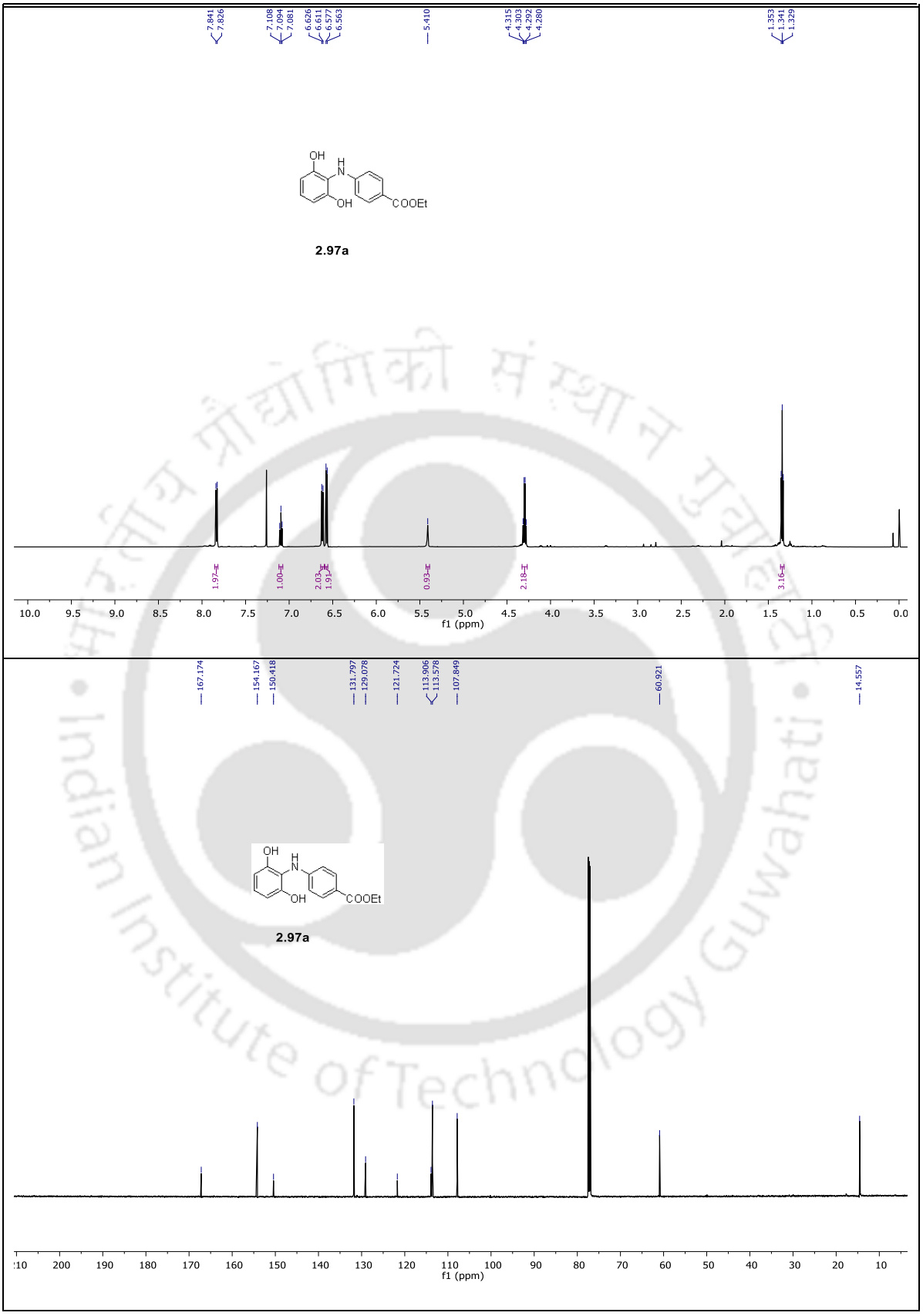


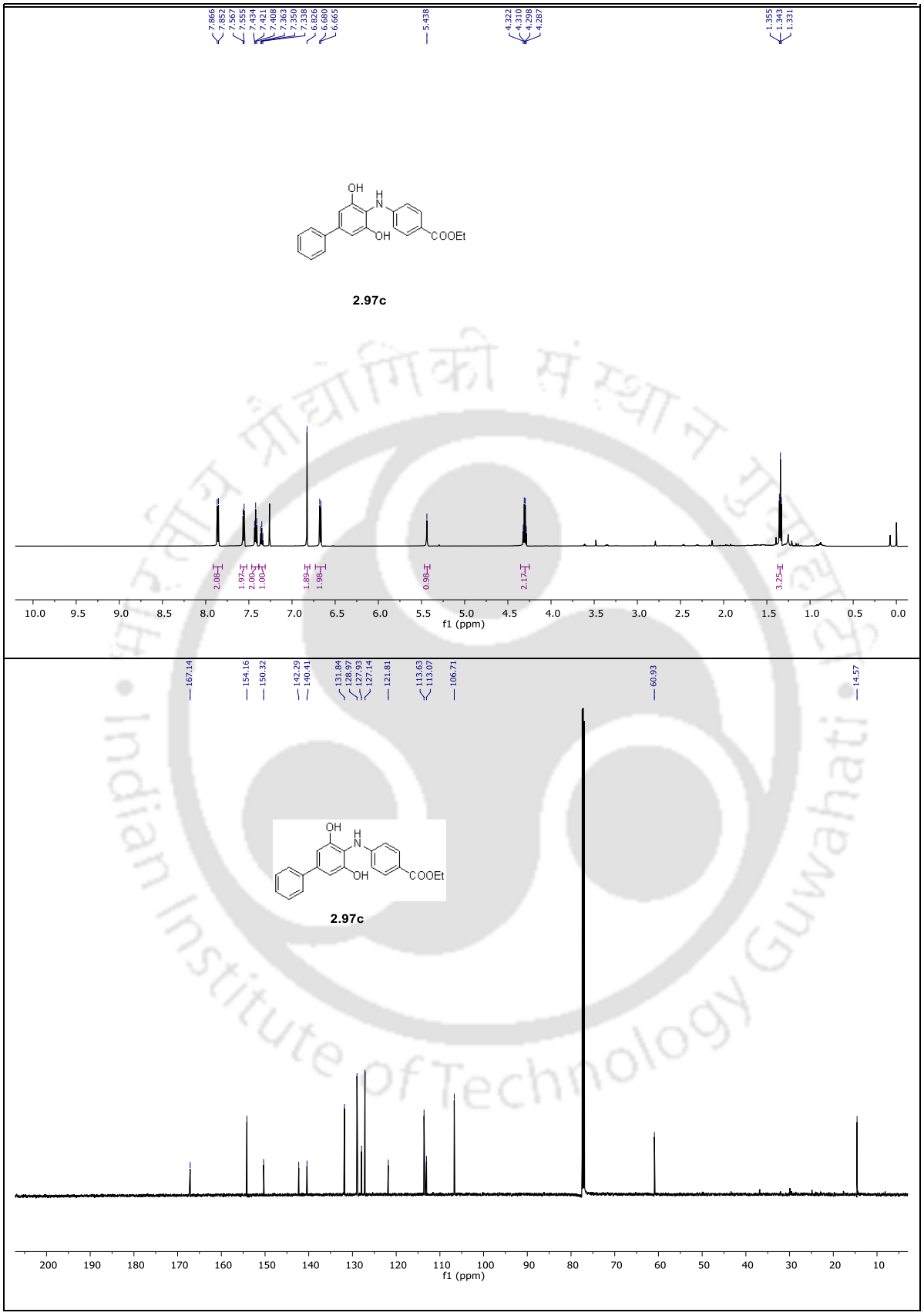


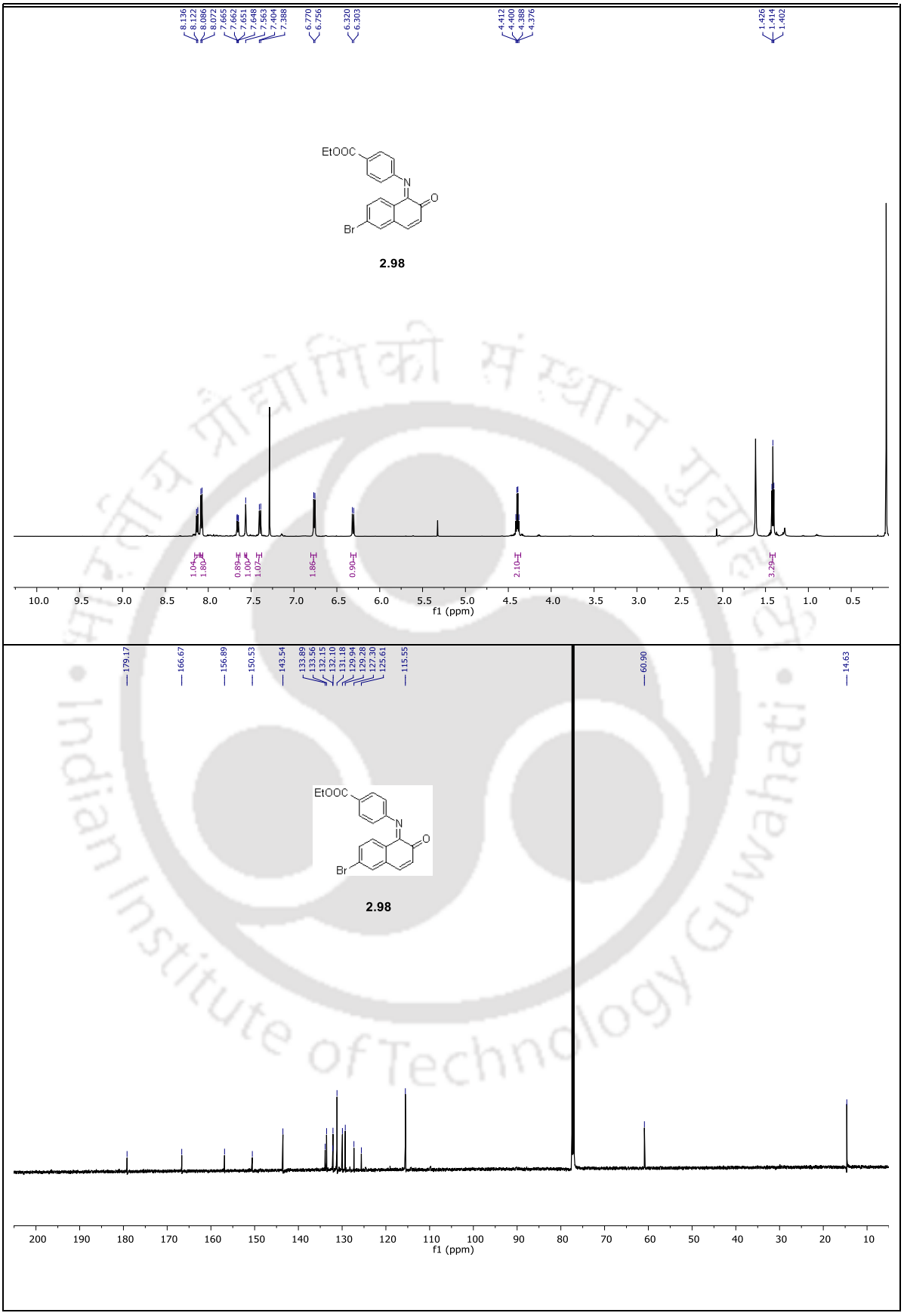


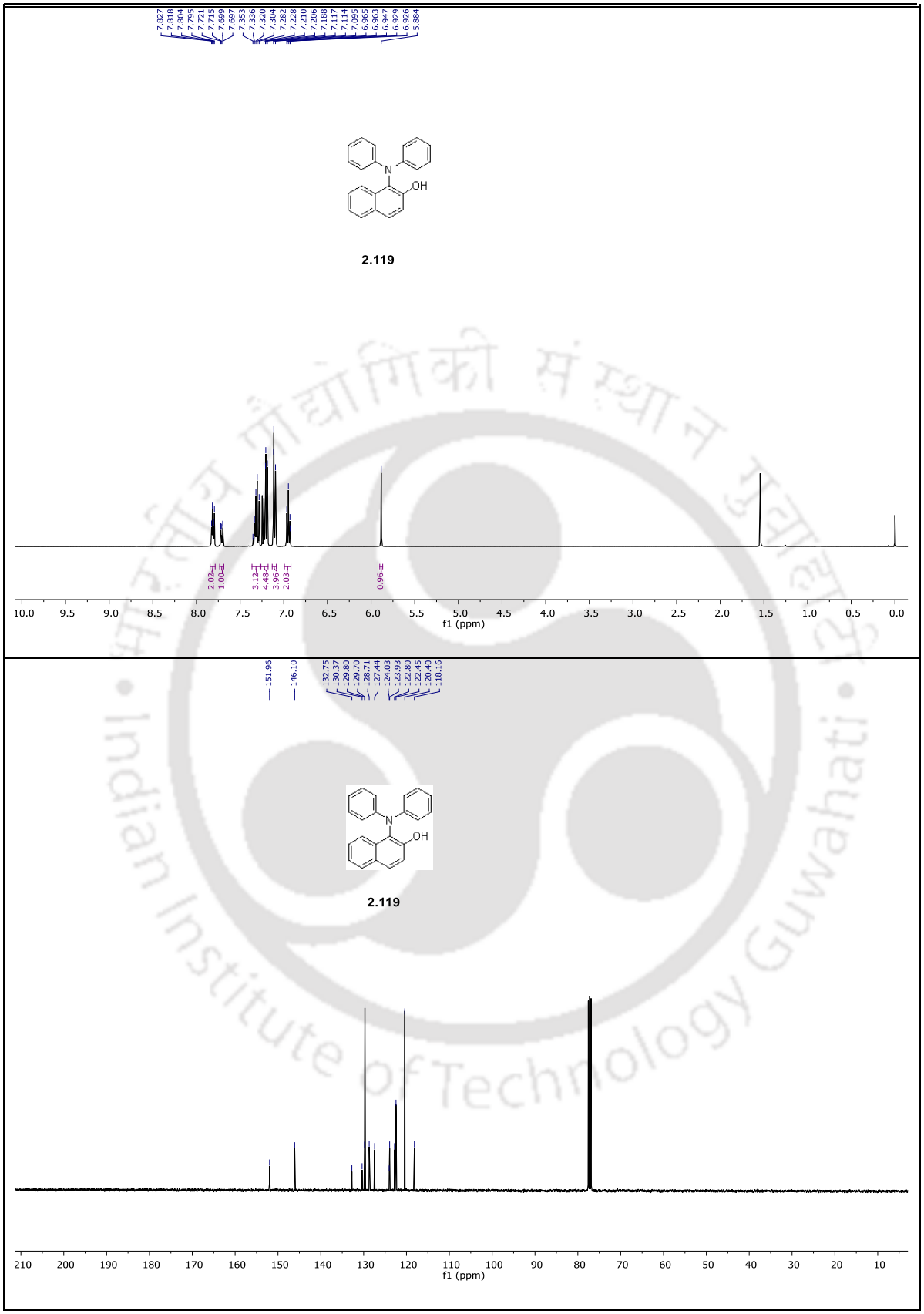


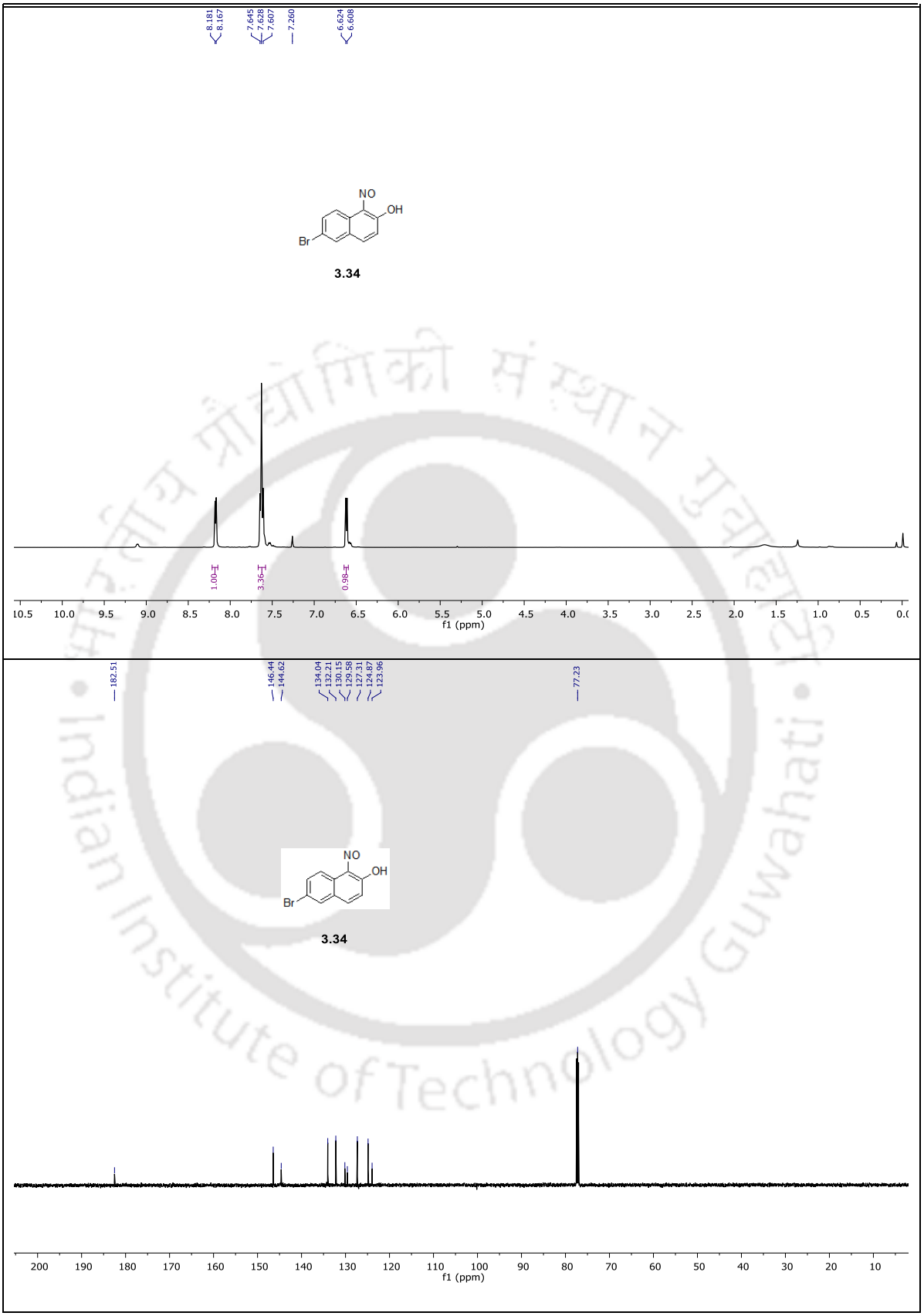


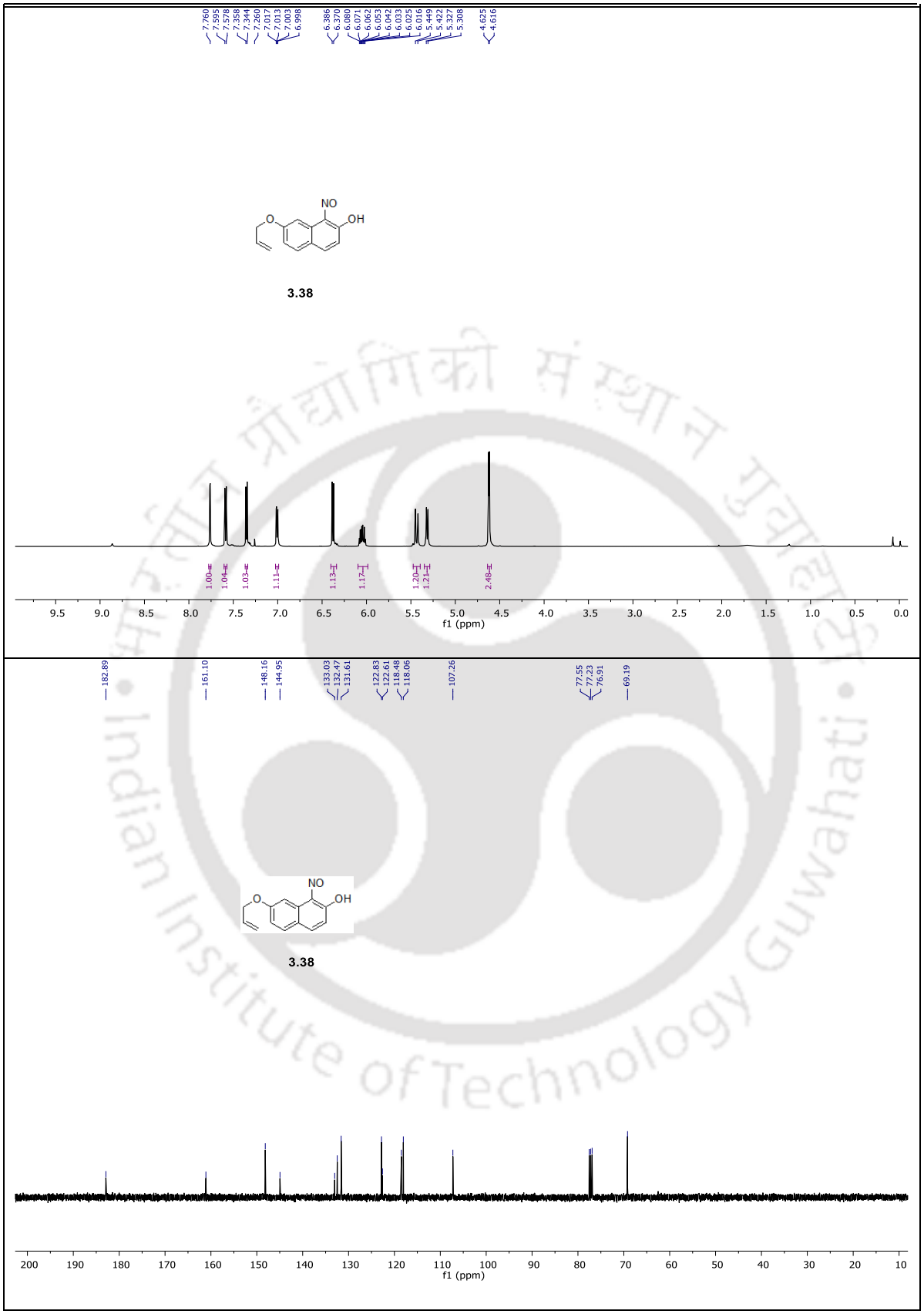


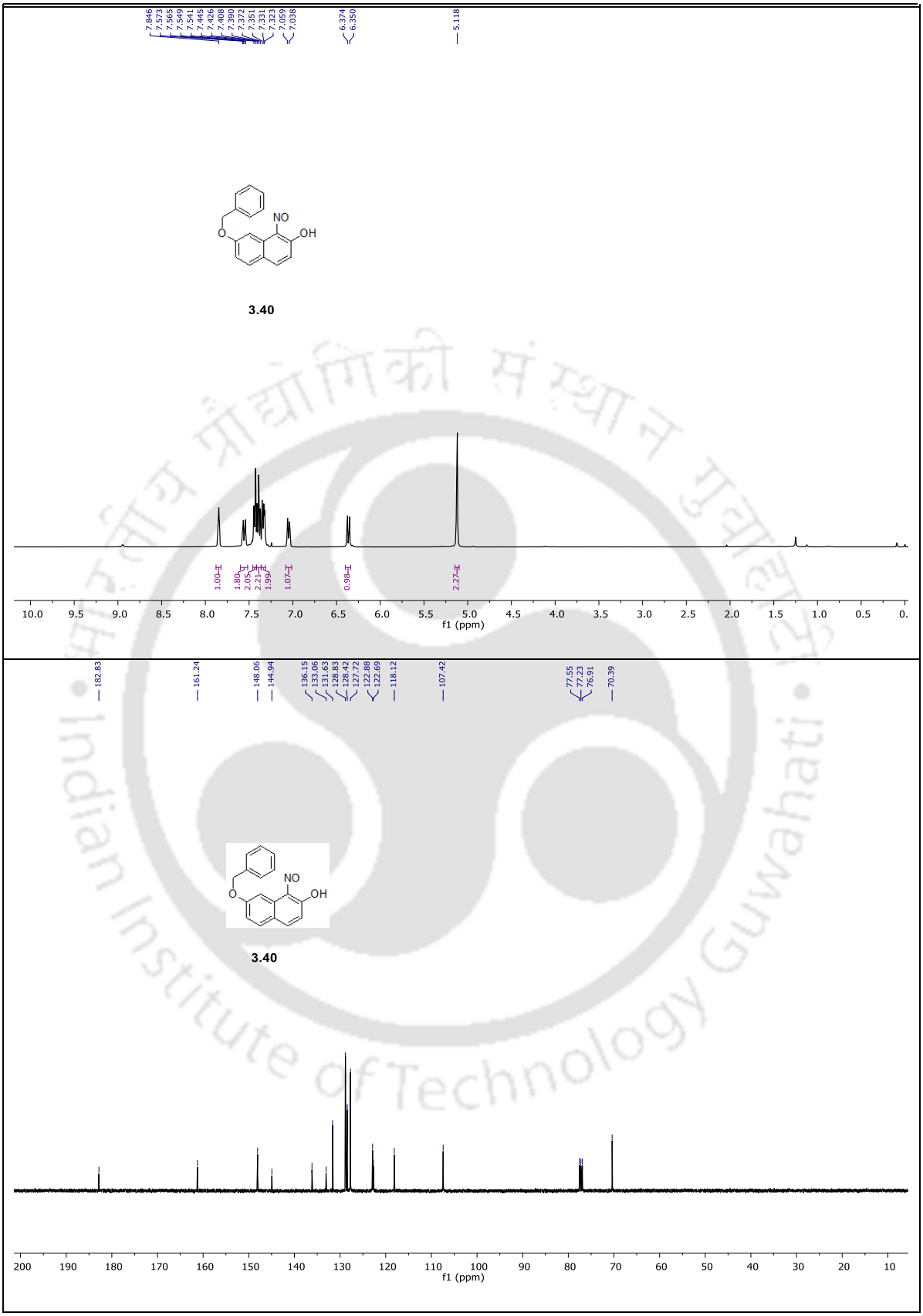


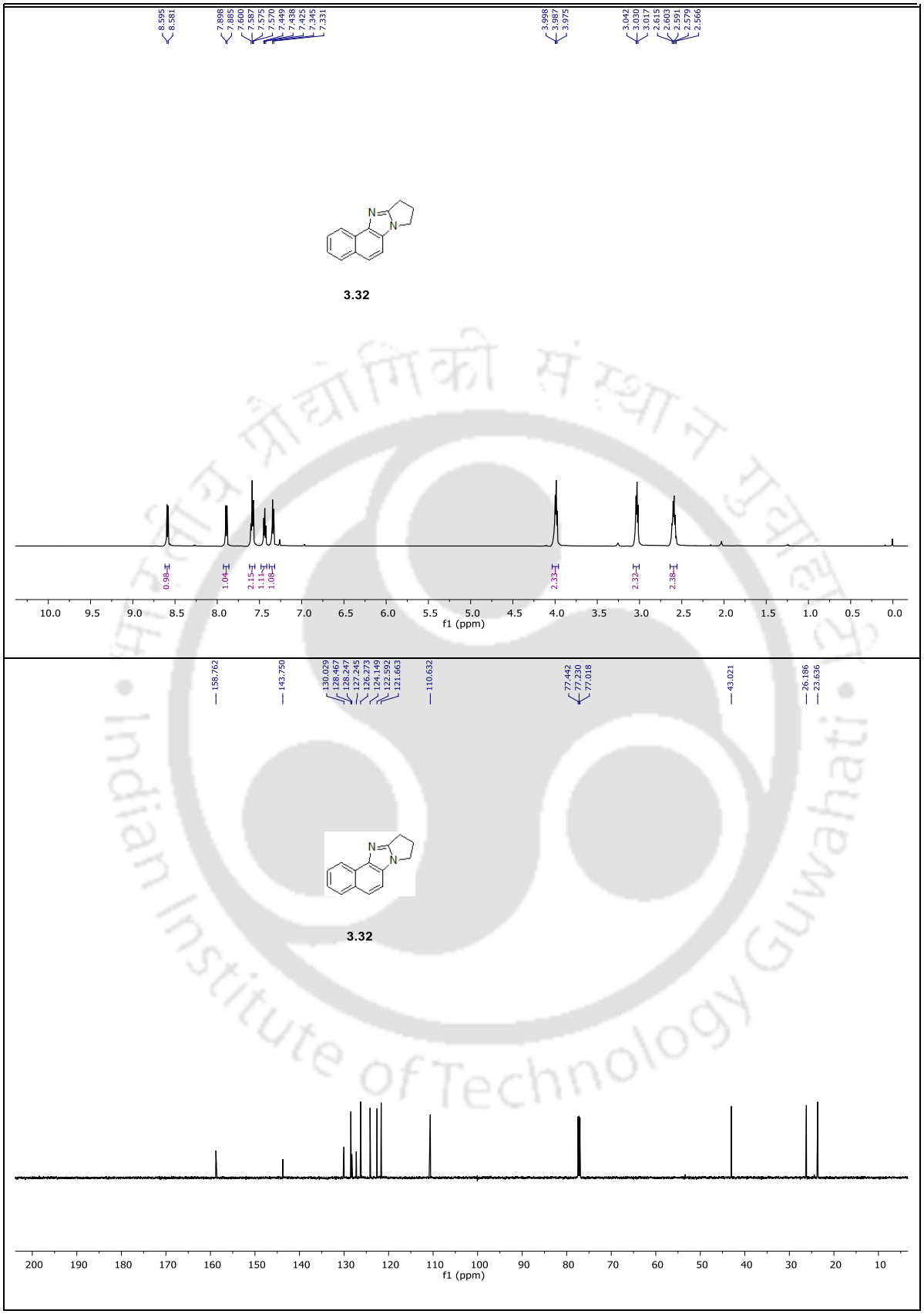


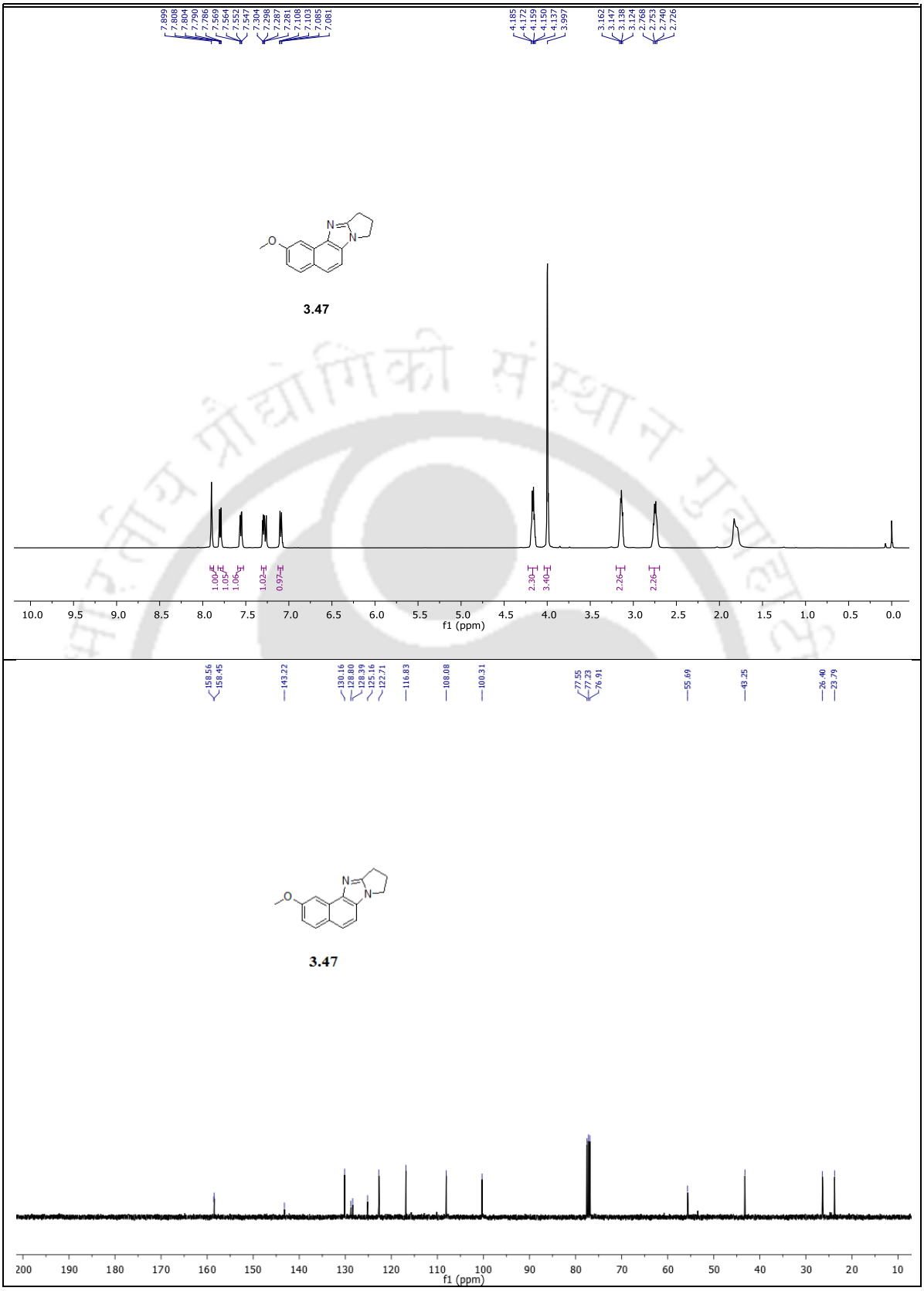


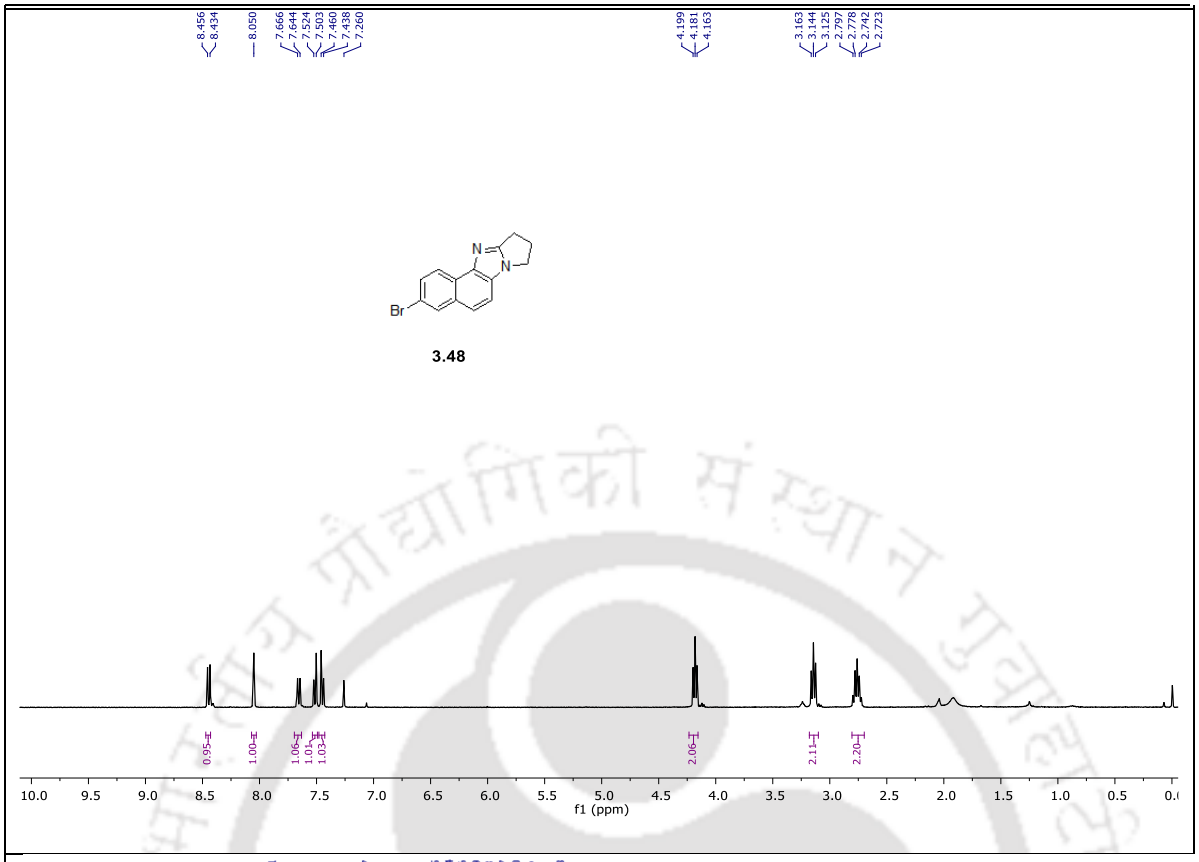


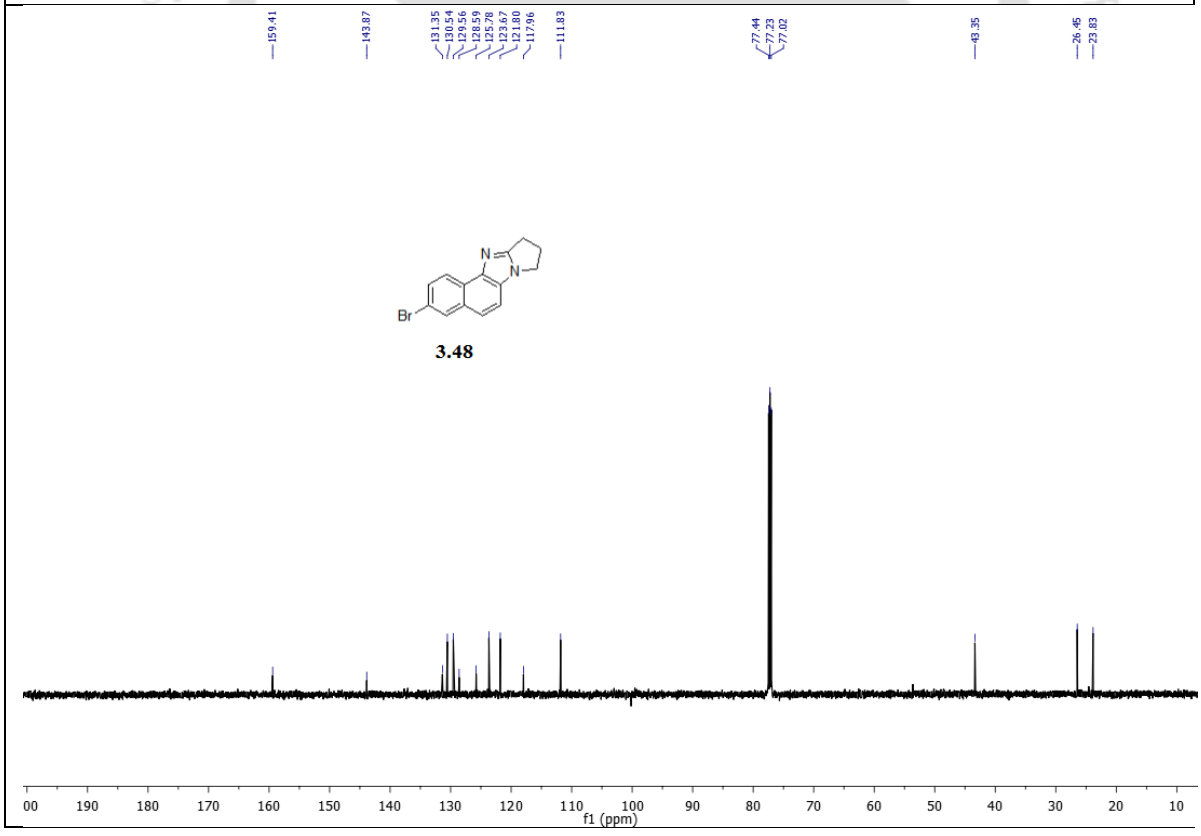


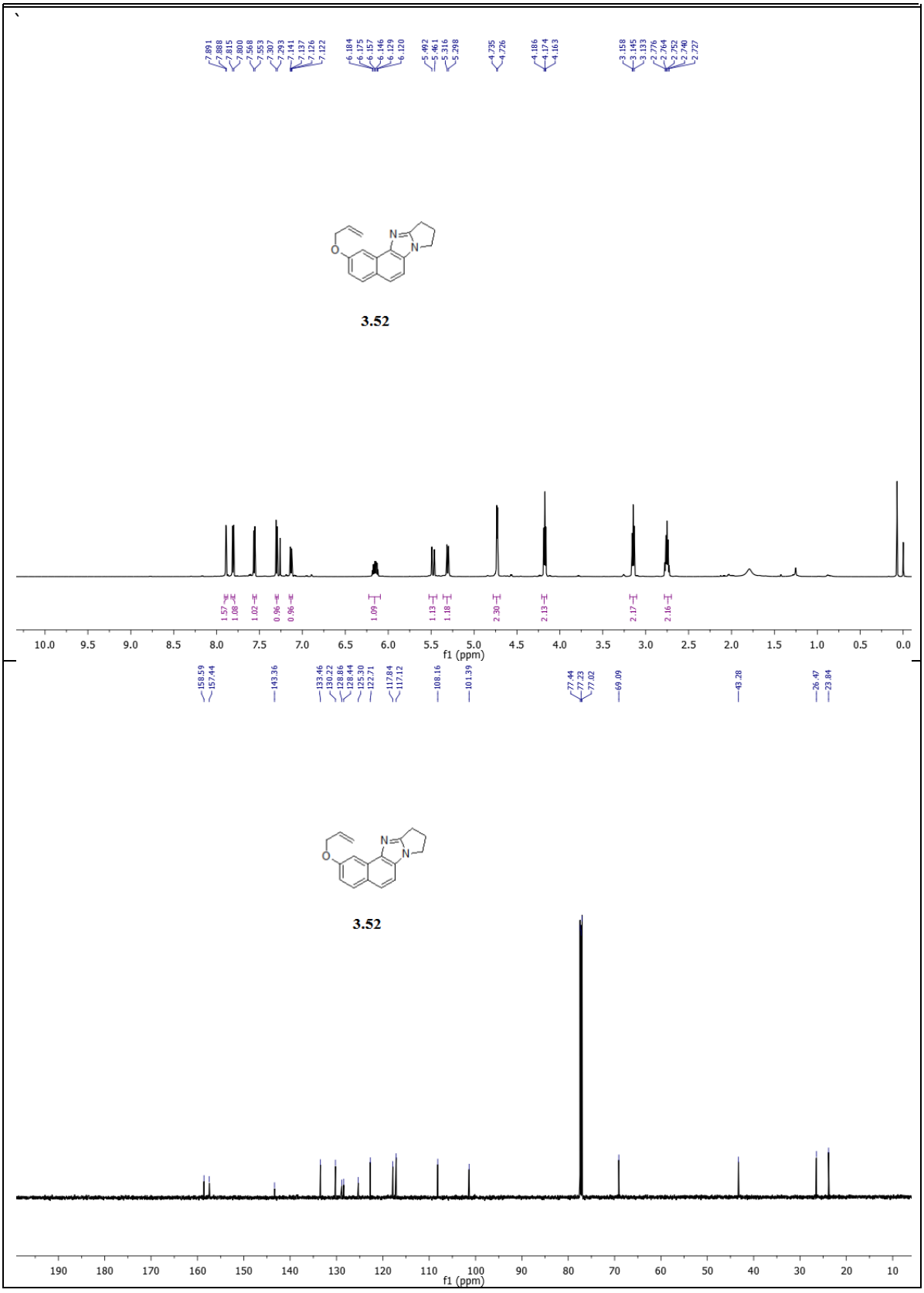








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1.02
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0.96
1.09
1.13
1.18
2.30
2.13
2.17
2.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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157.44
143.36
133.46
130.22
128.86
128.44
125.30
122.71
117.84
117.12
108.16
101.39
77.44
77.23
77.02
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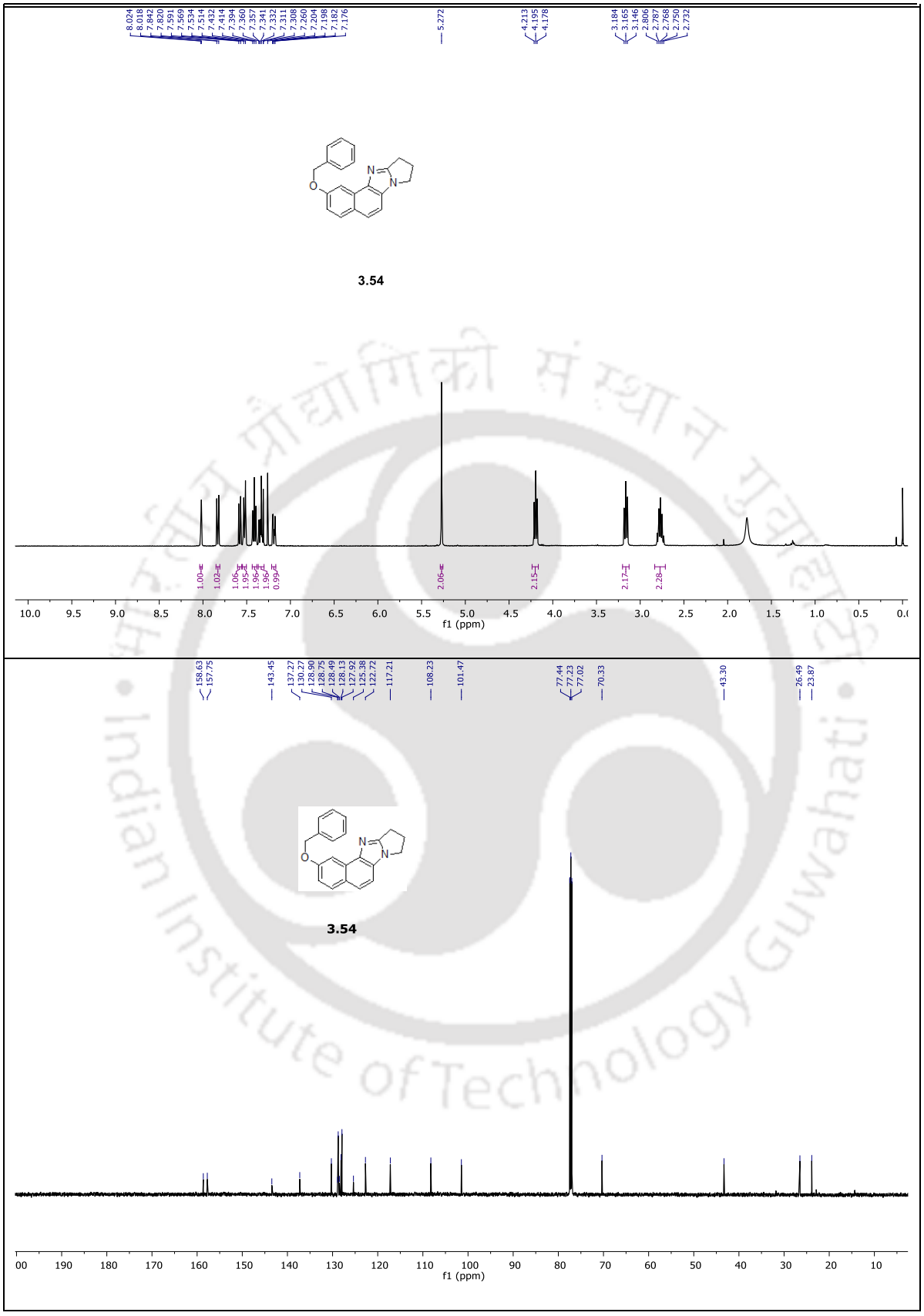
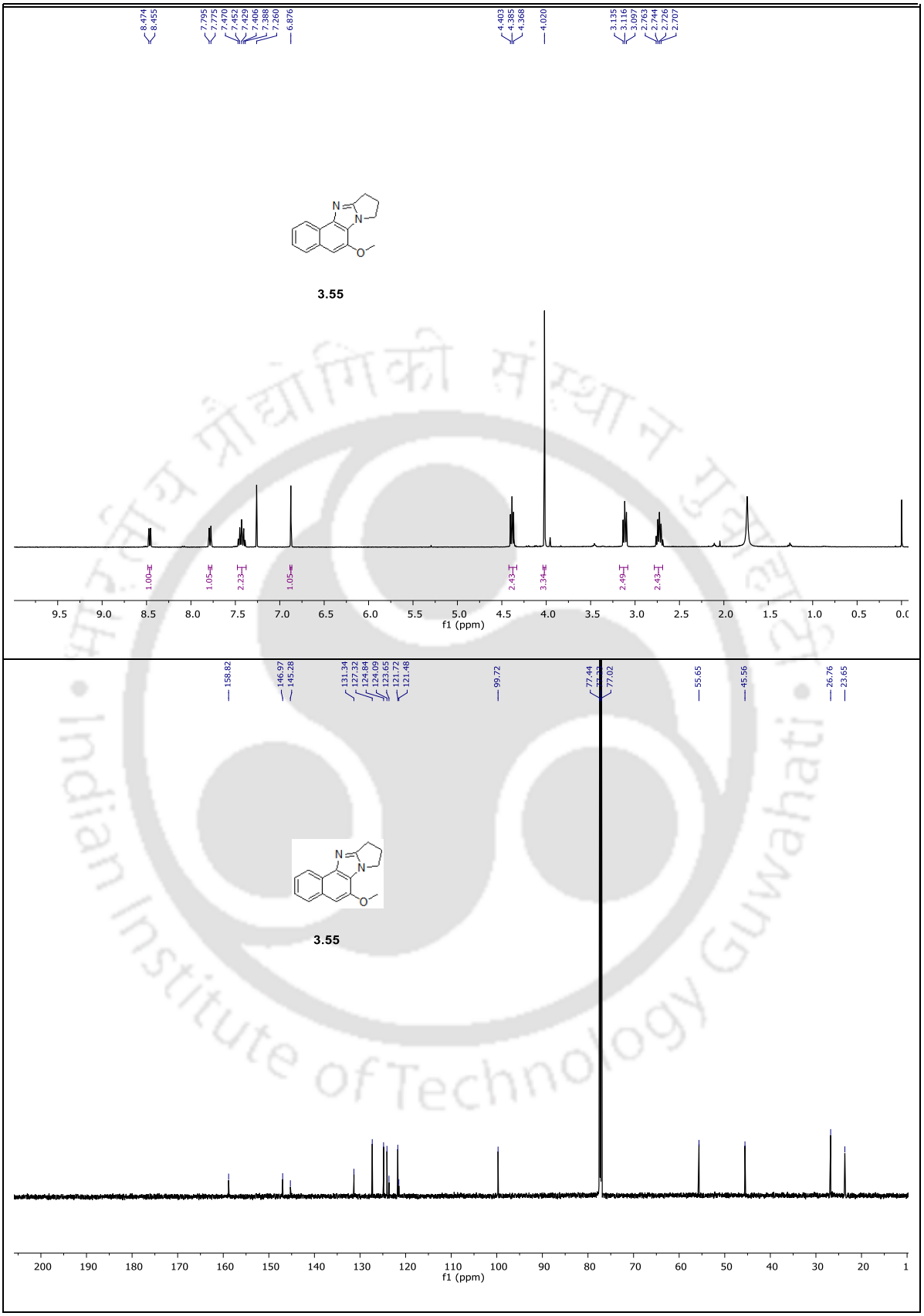
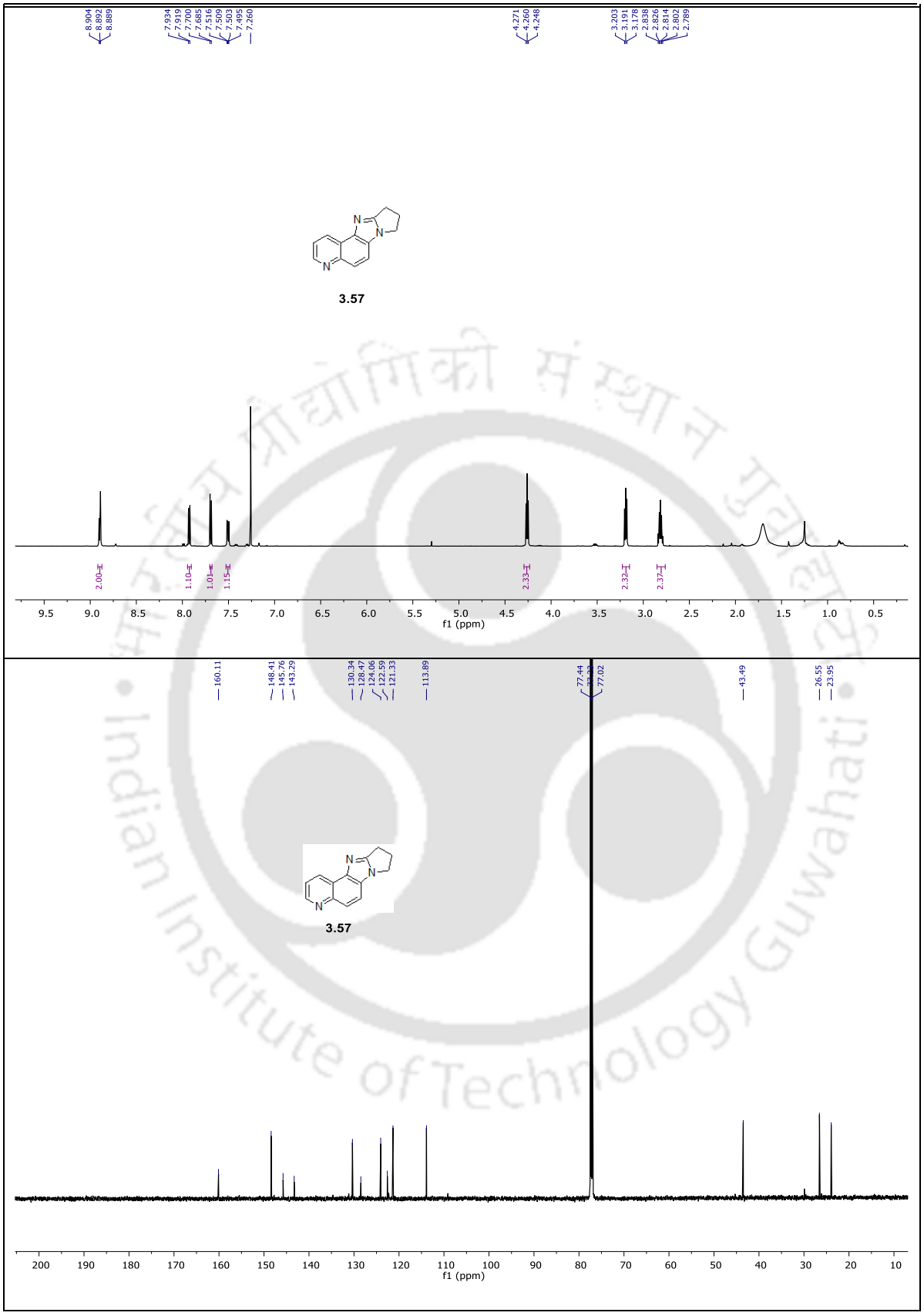
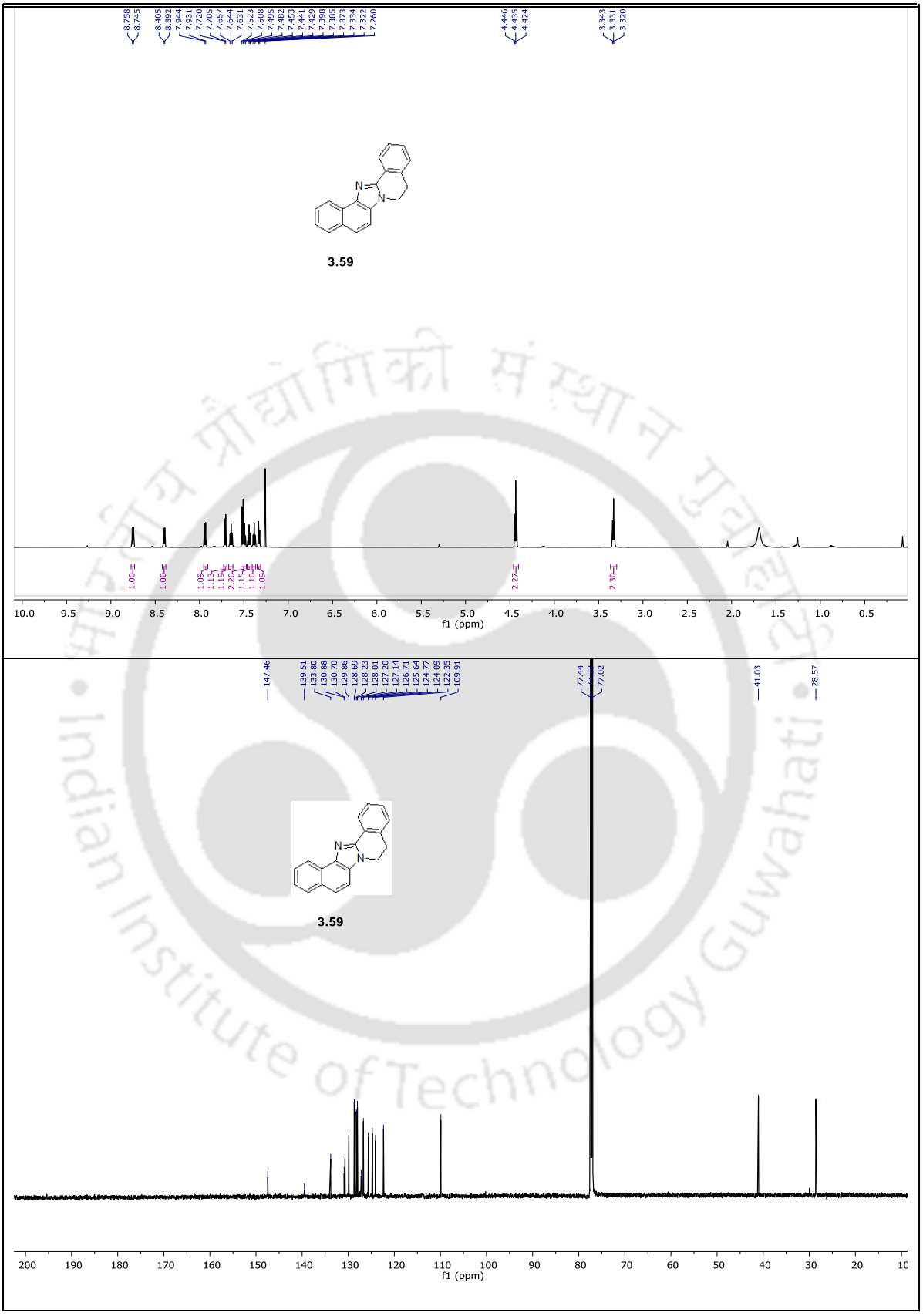
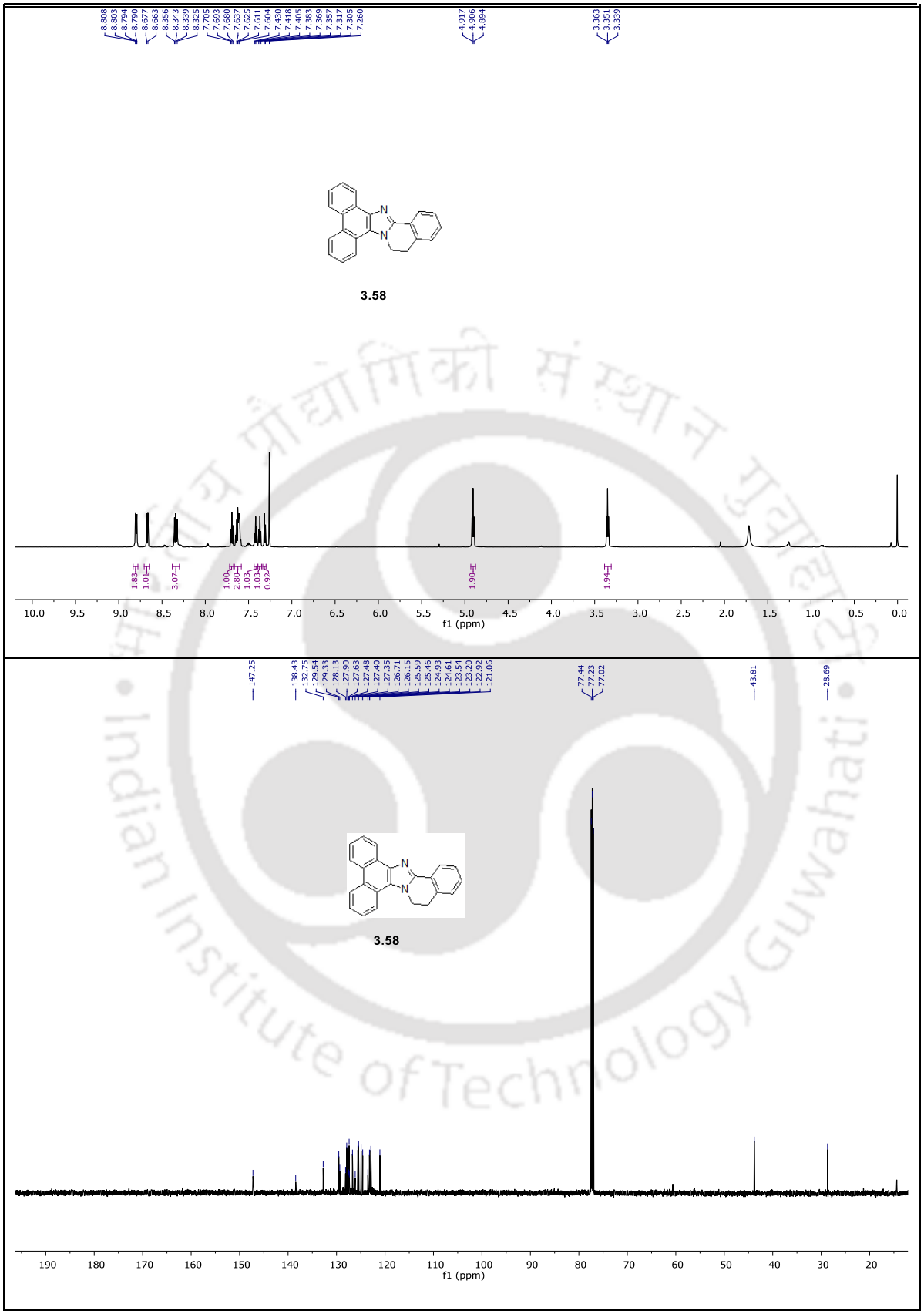
f1 (ppm)

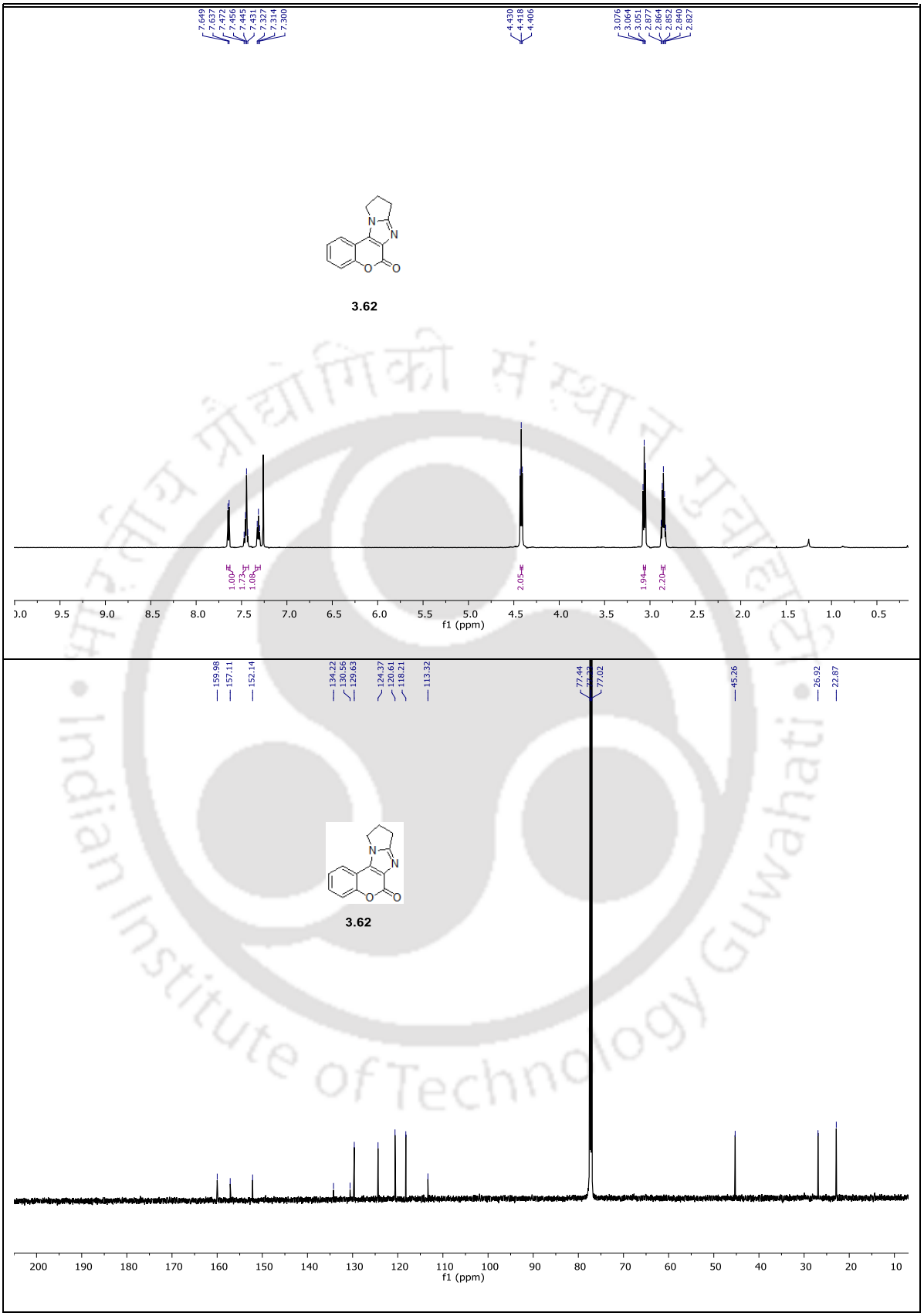


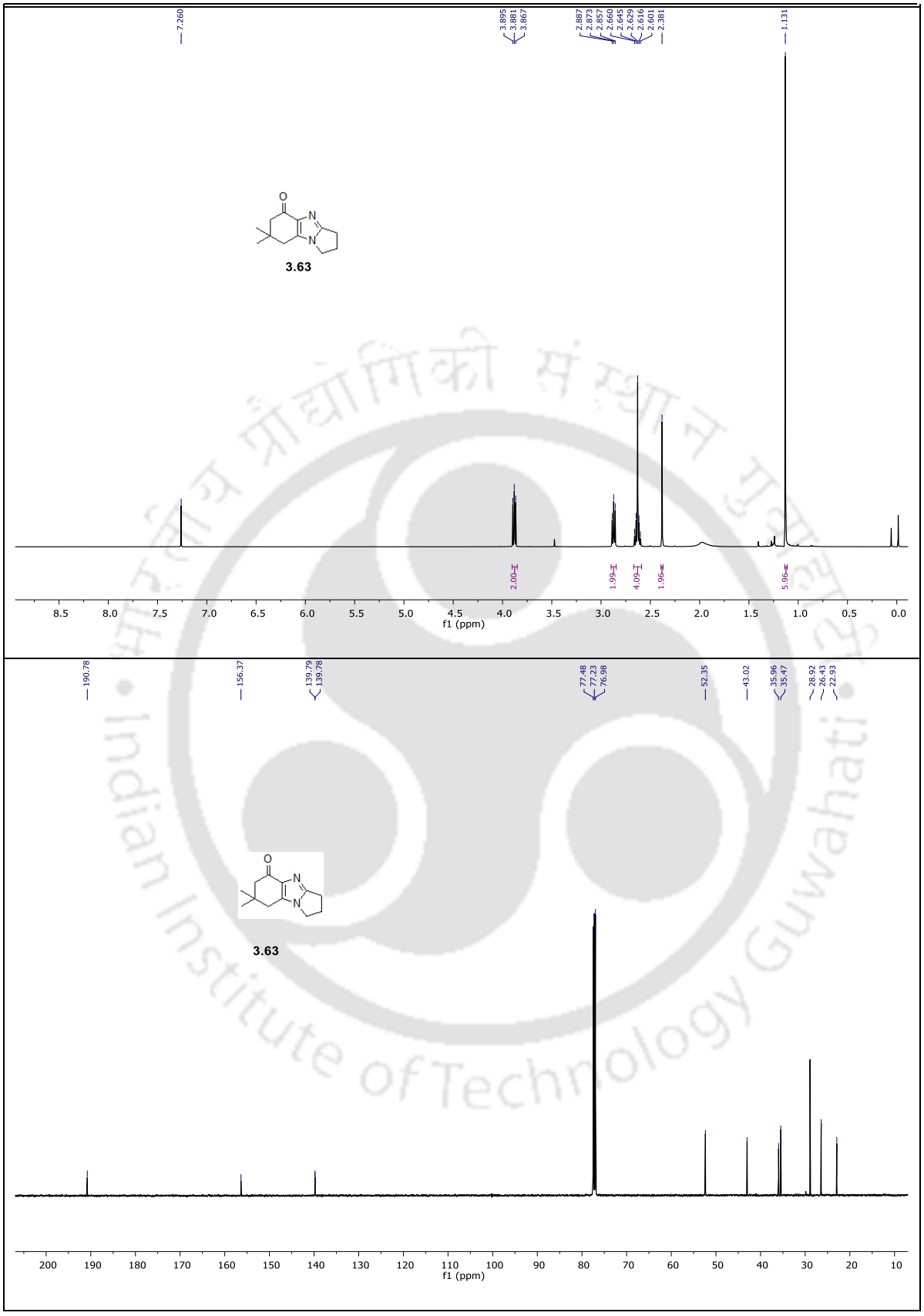


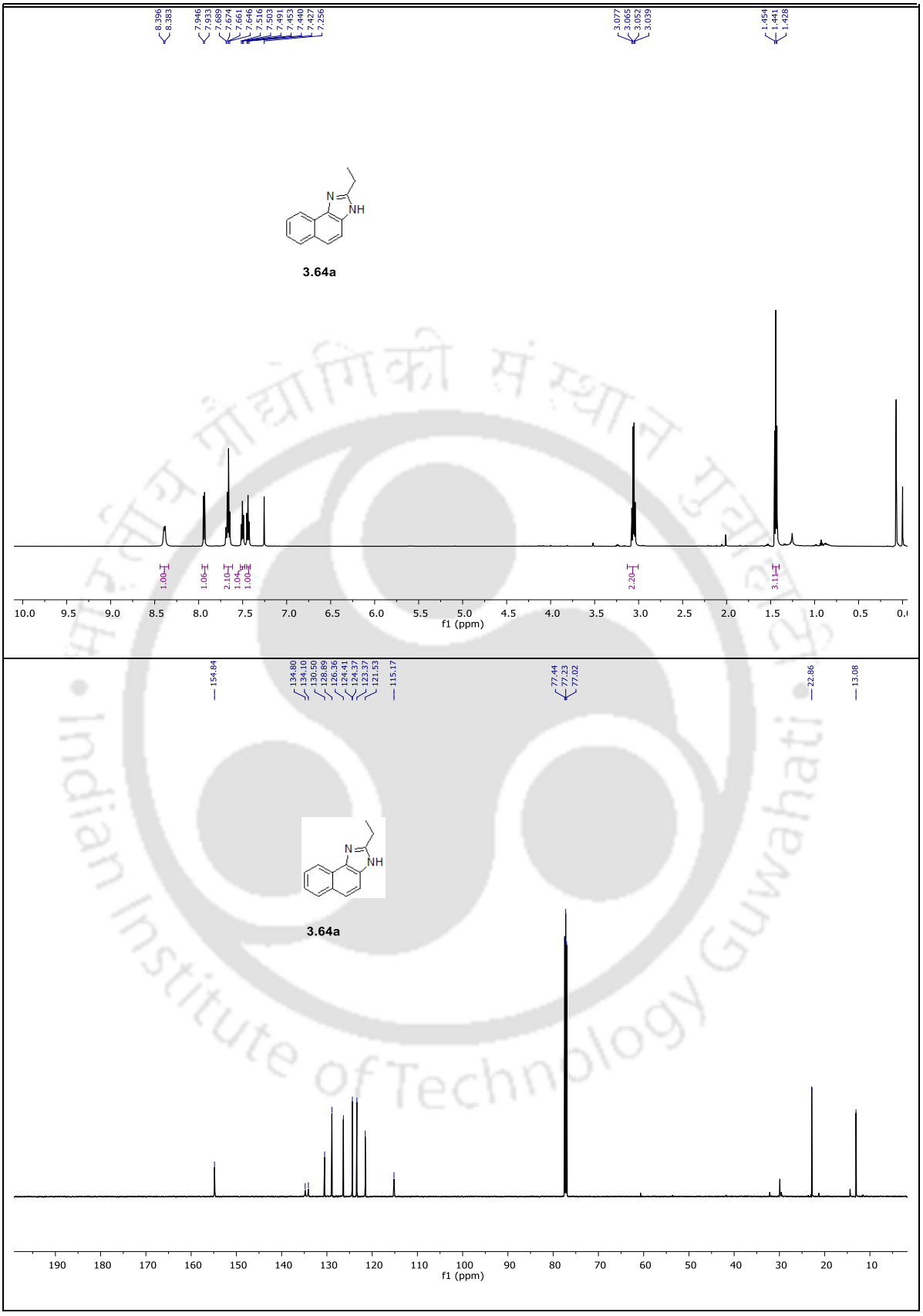


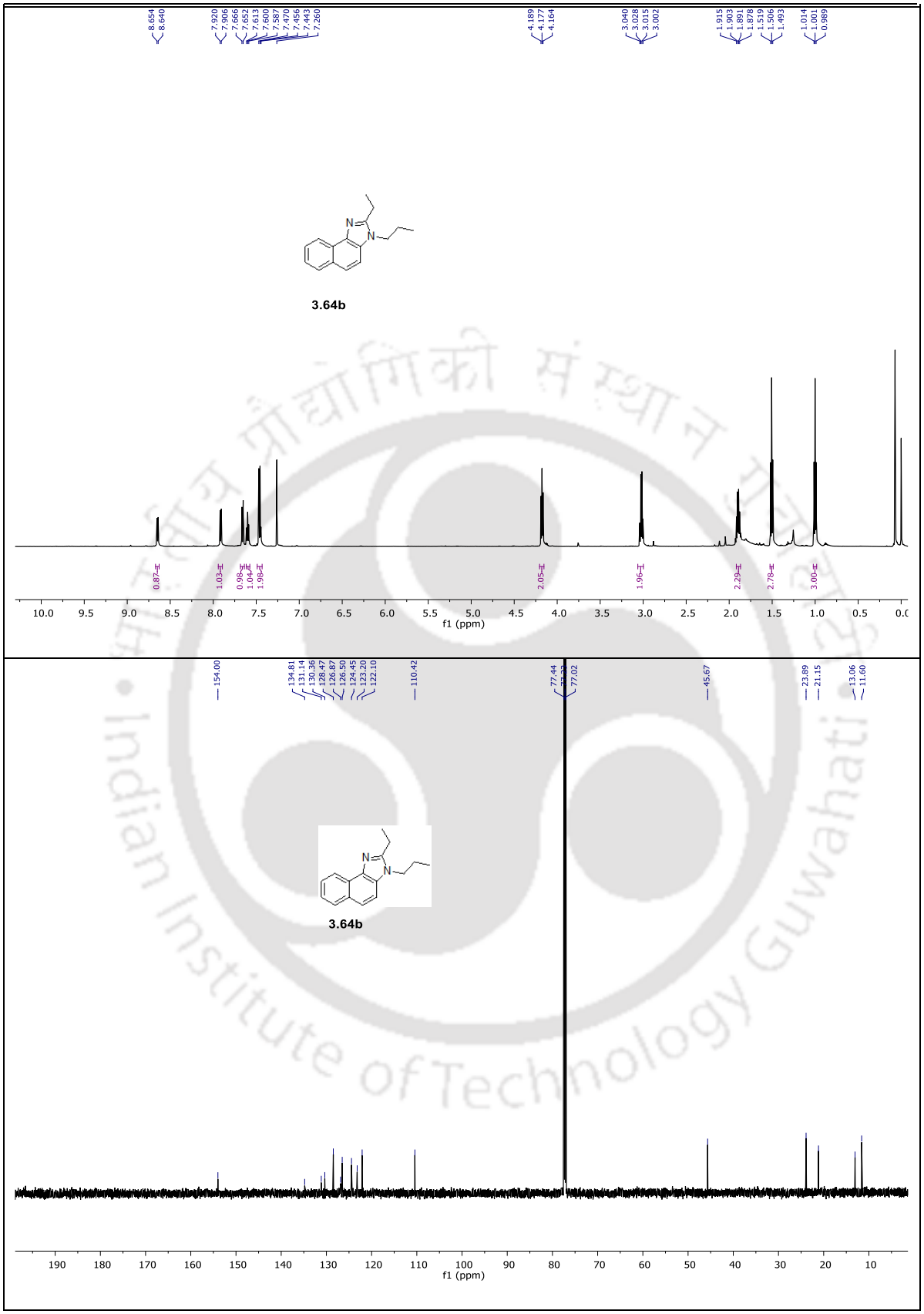


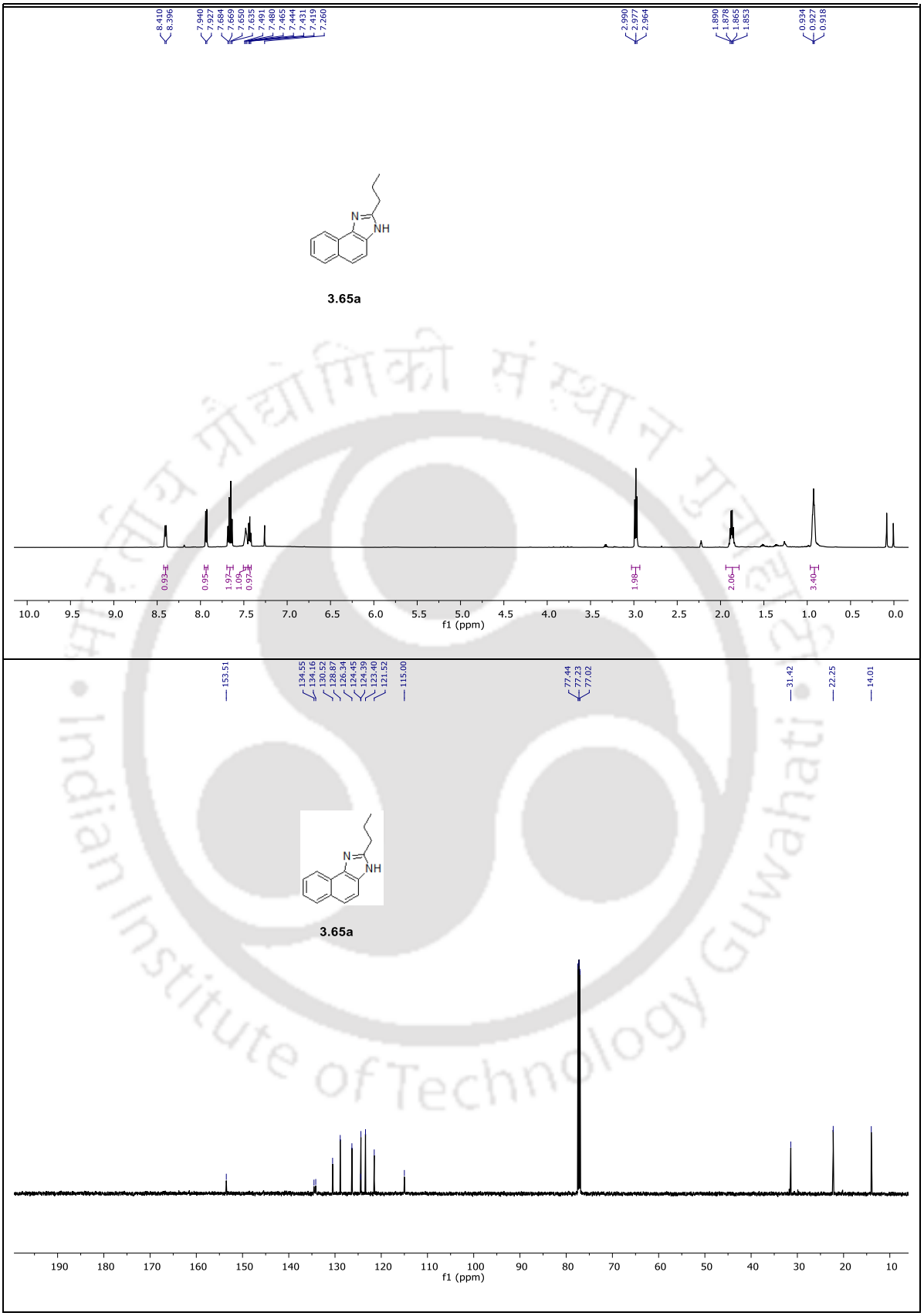


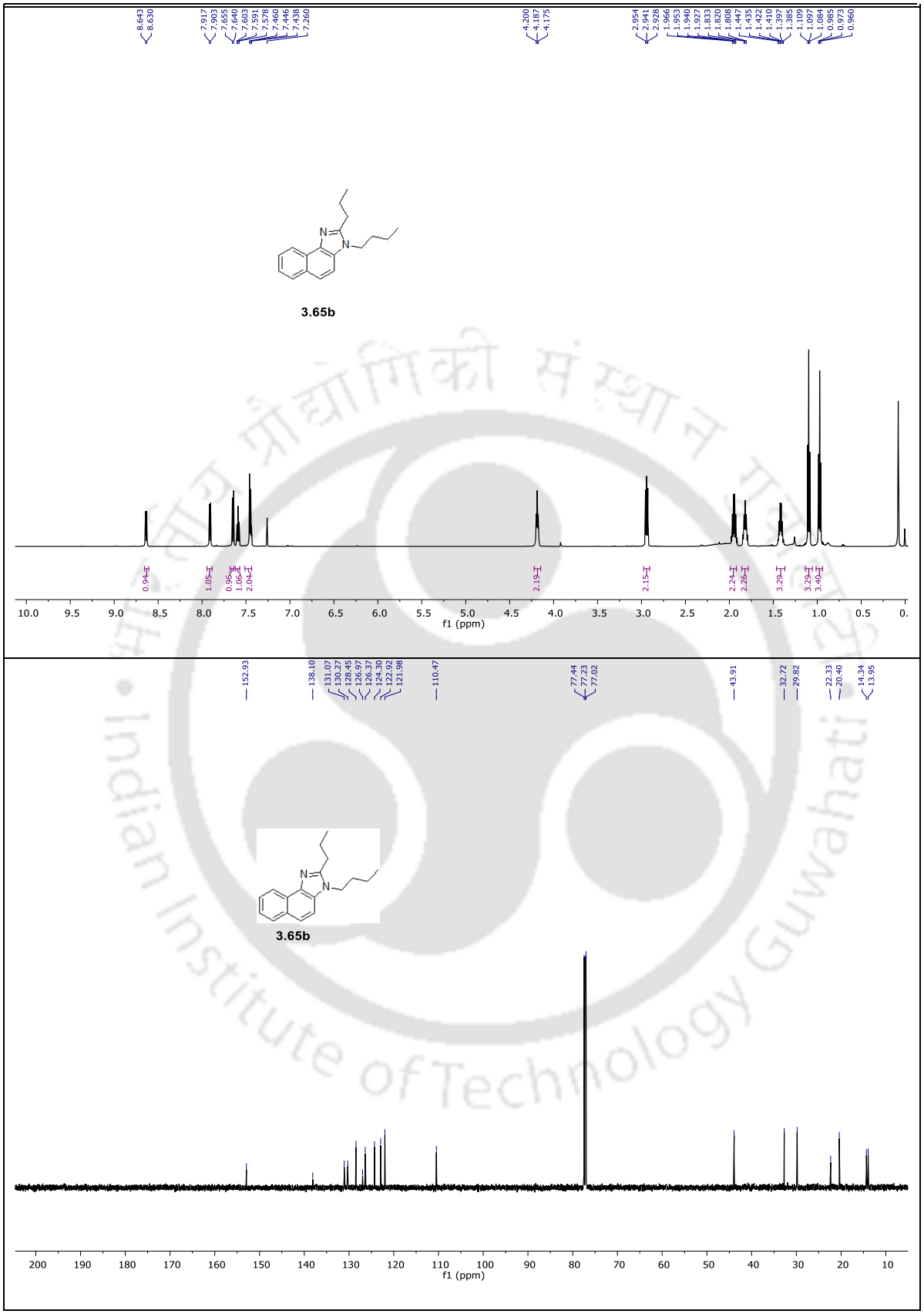


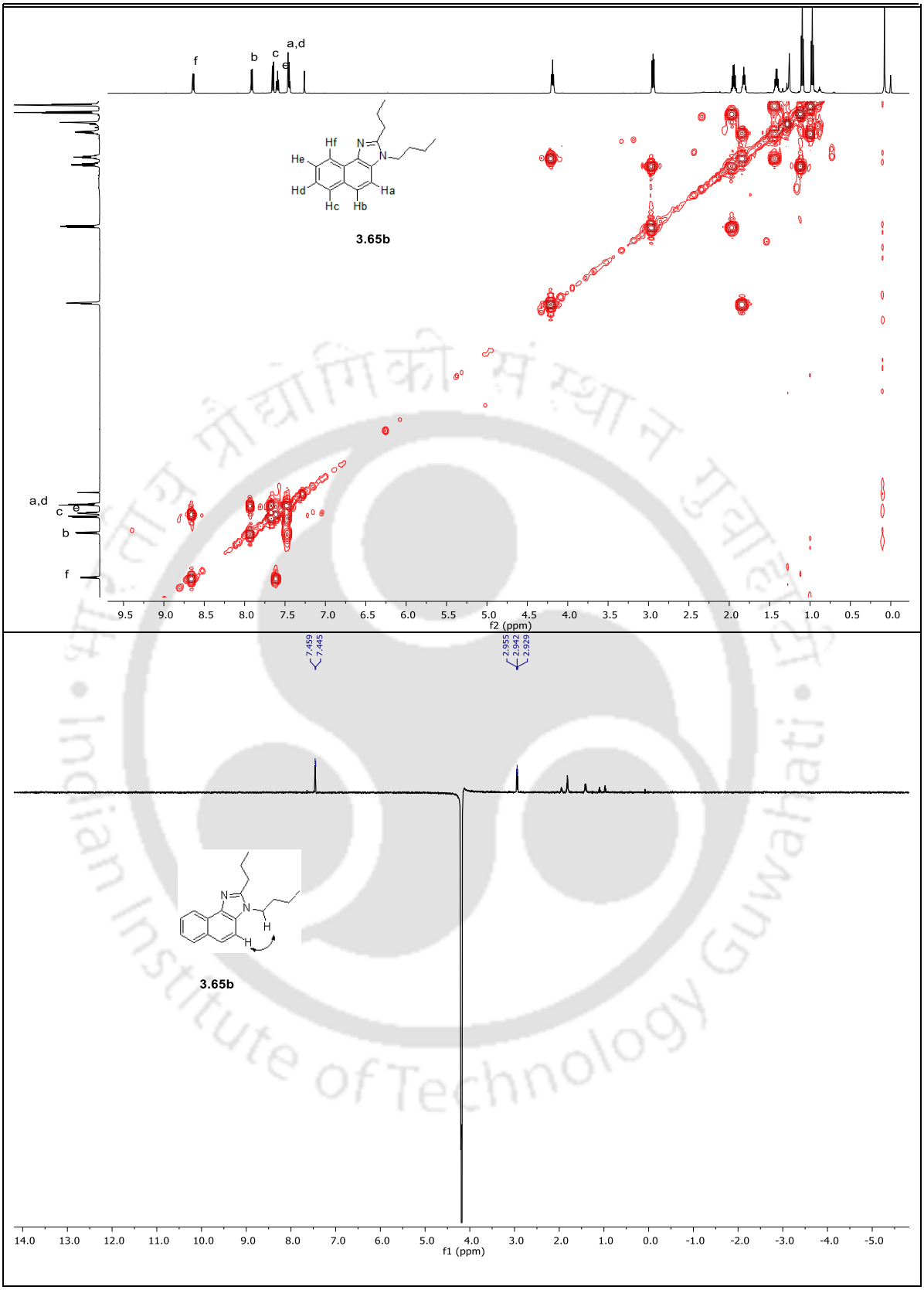


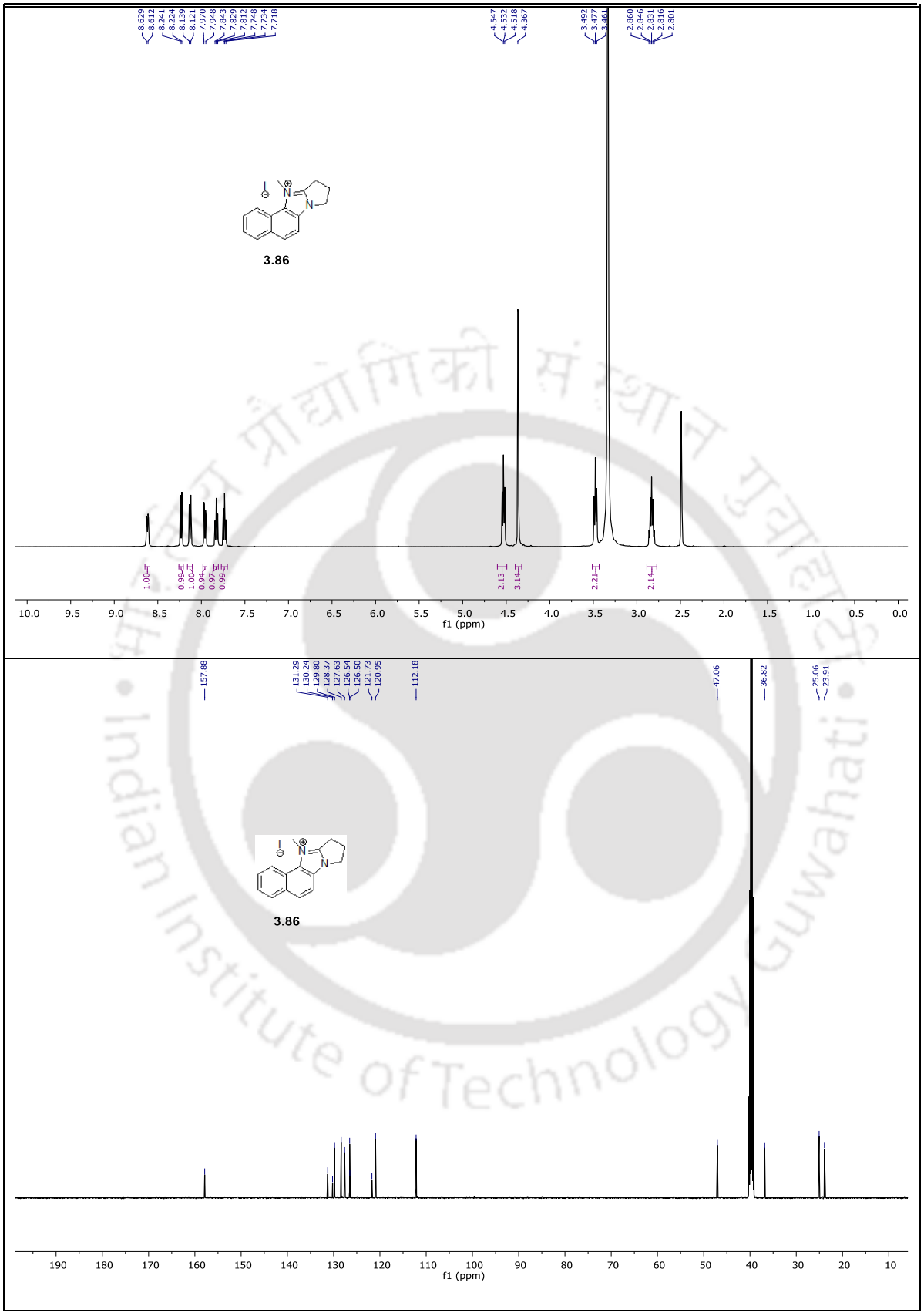


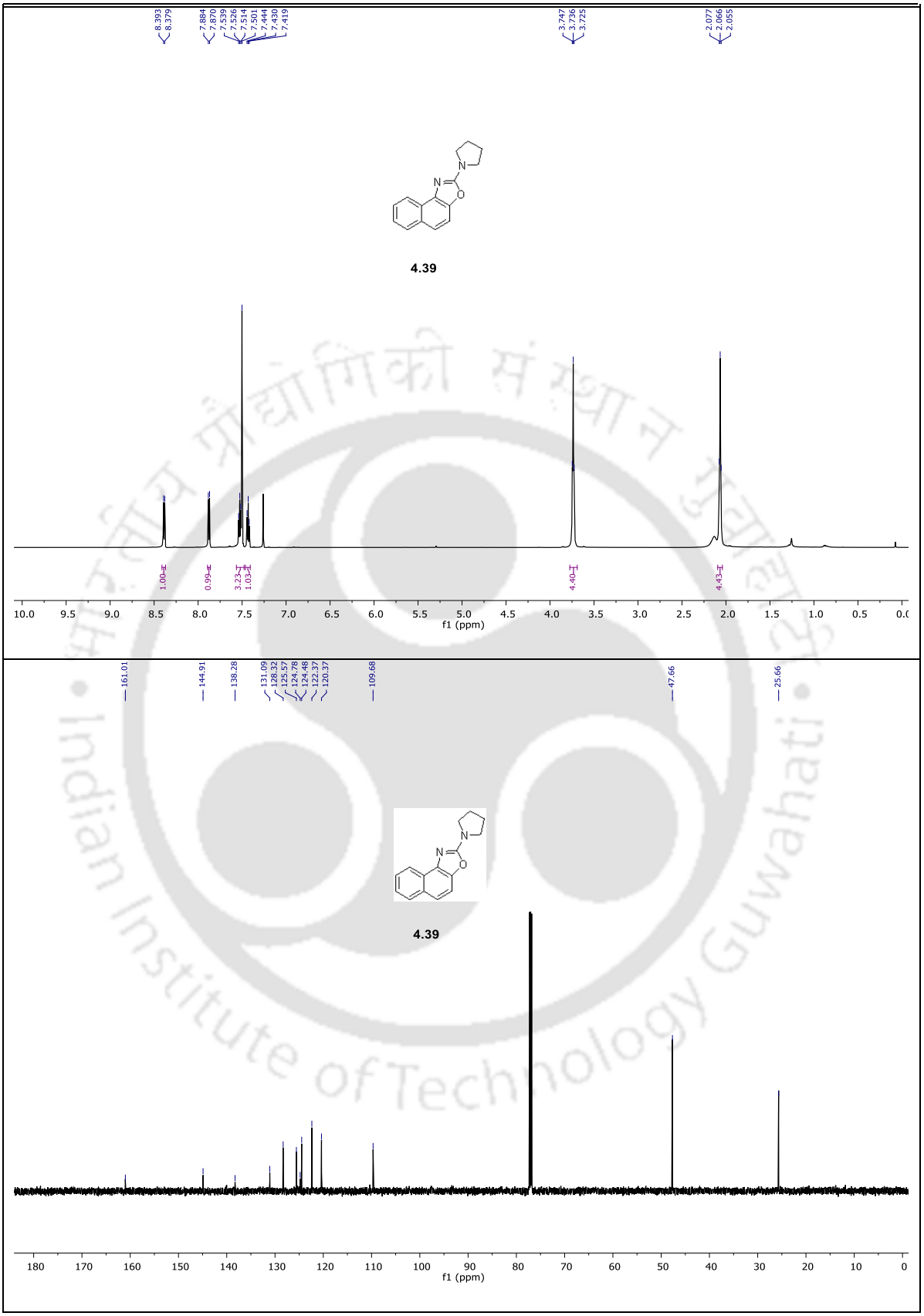


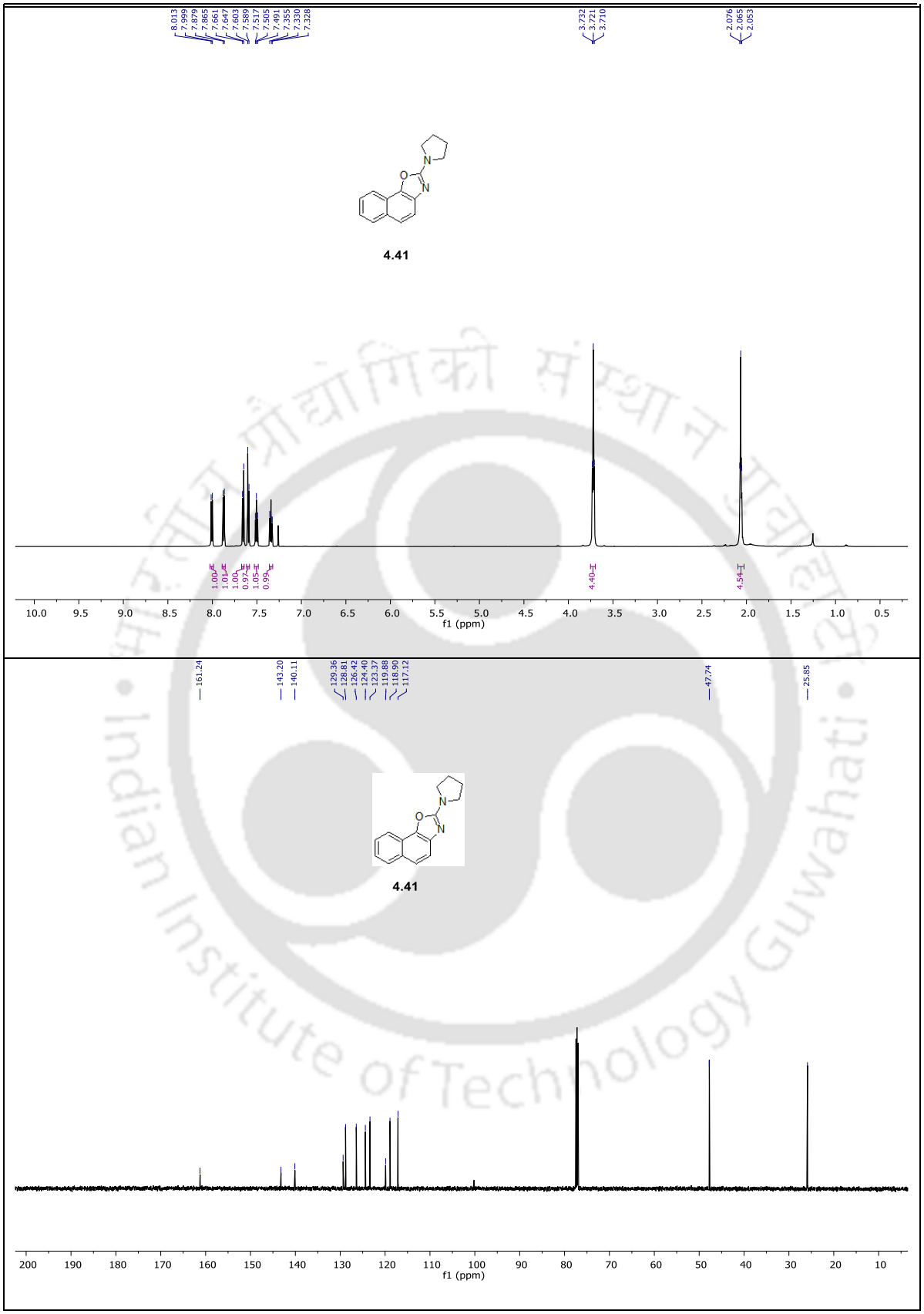


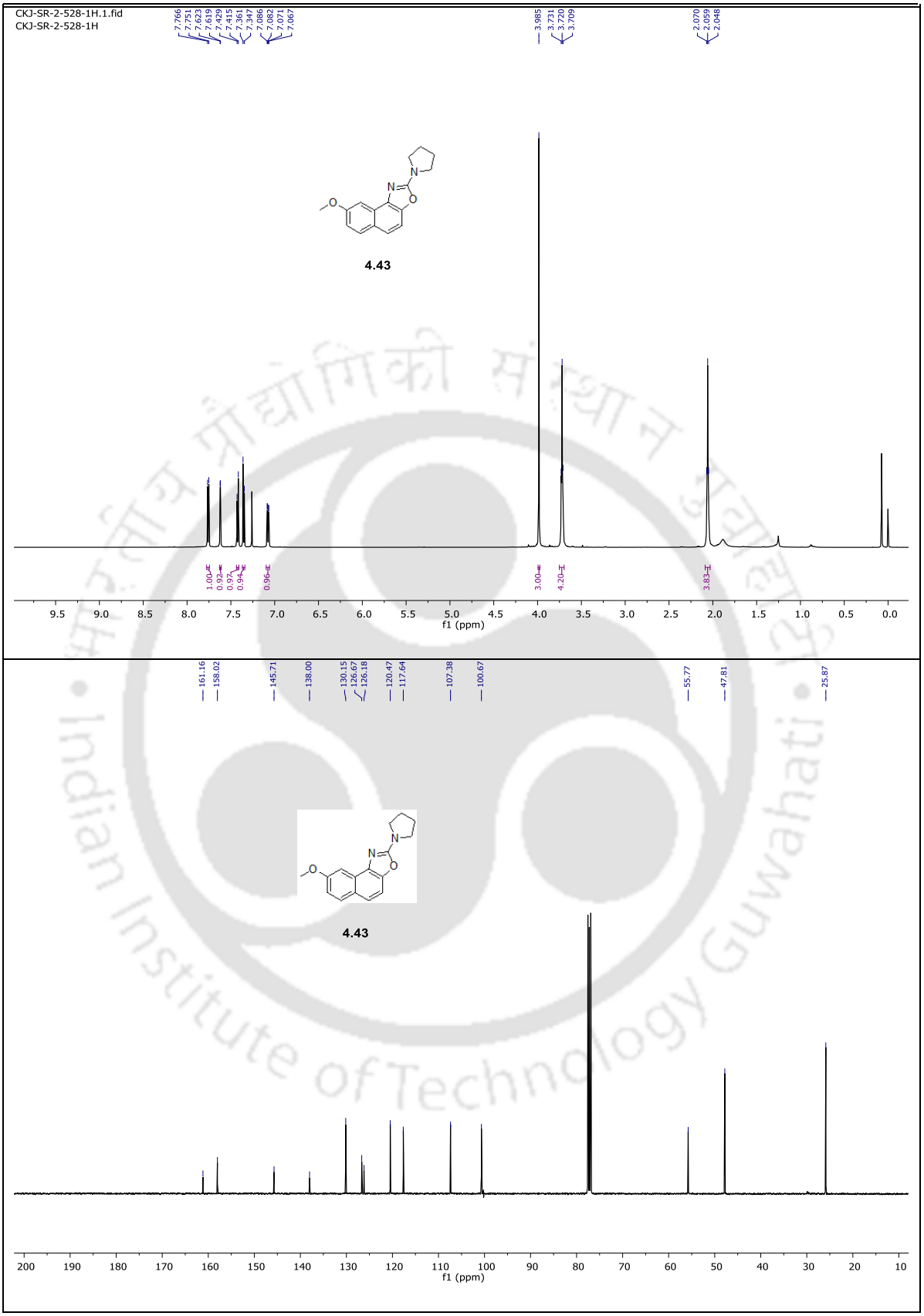


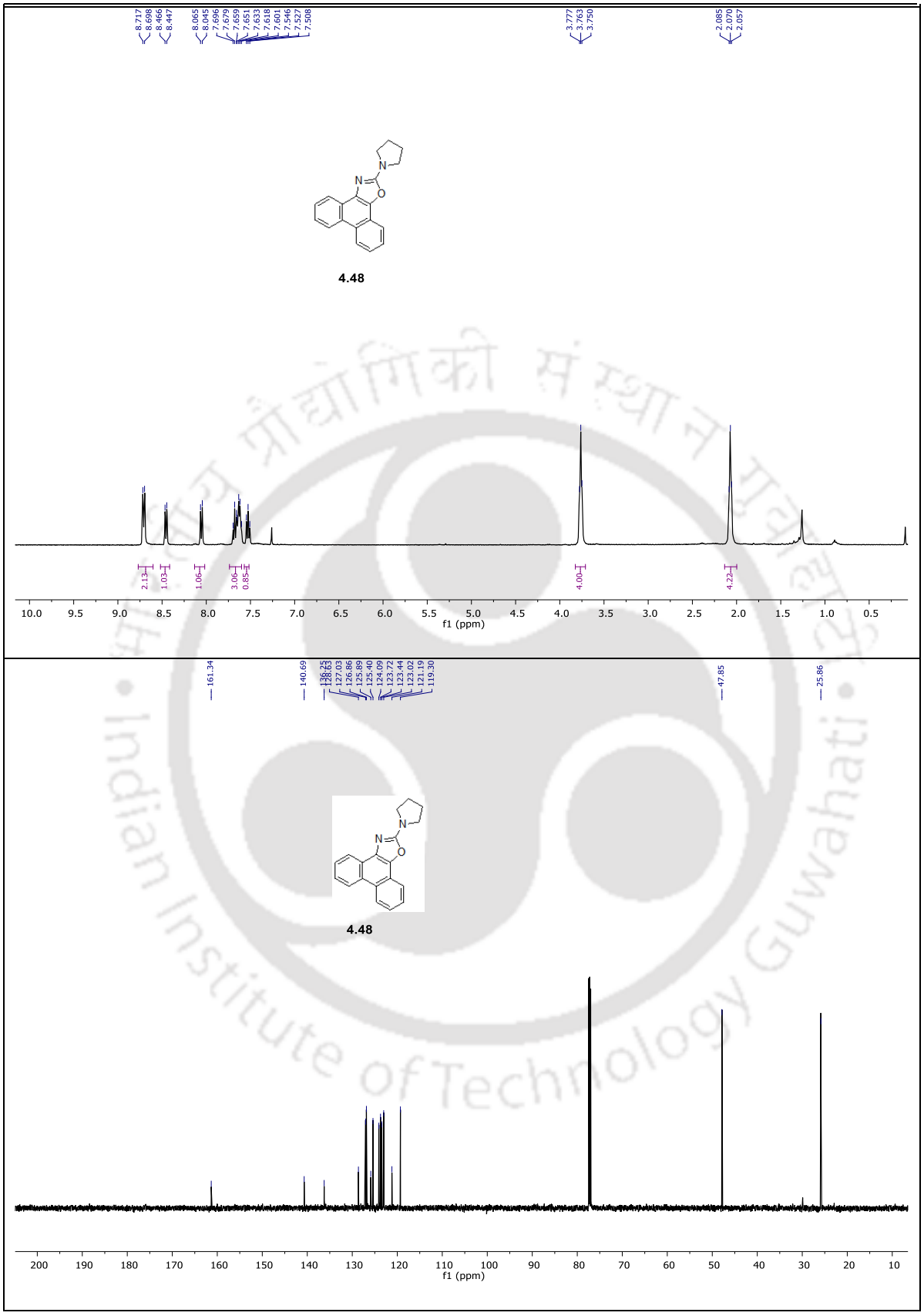


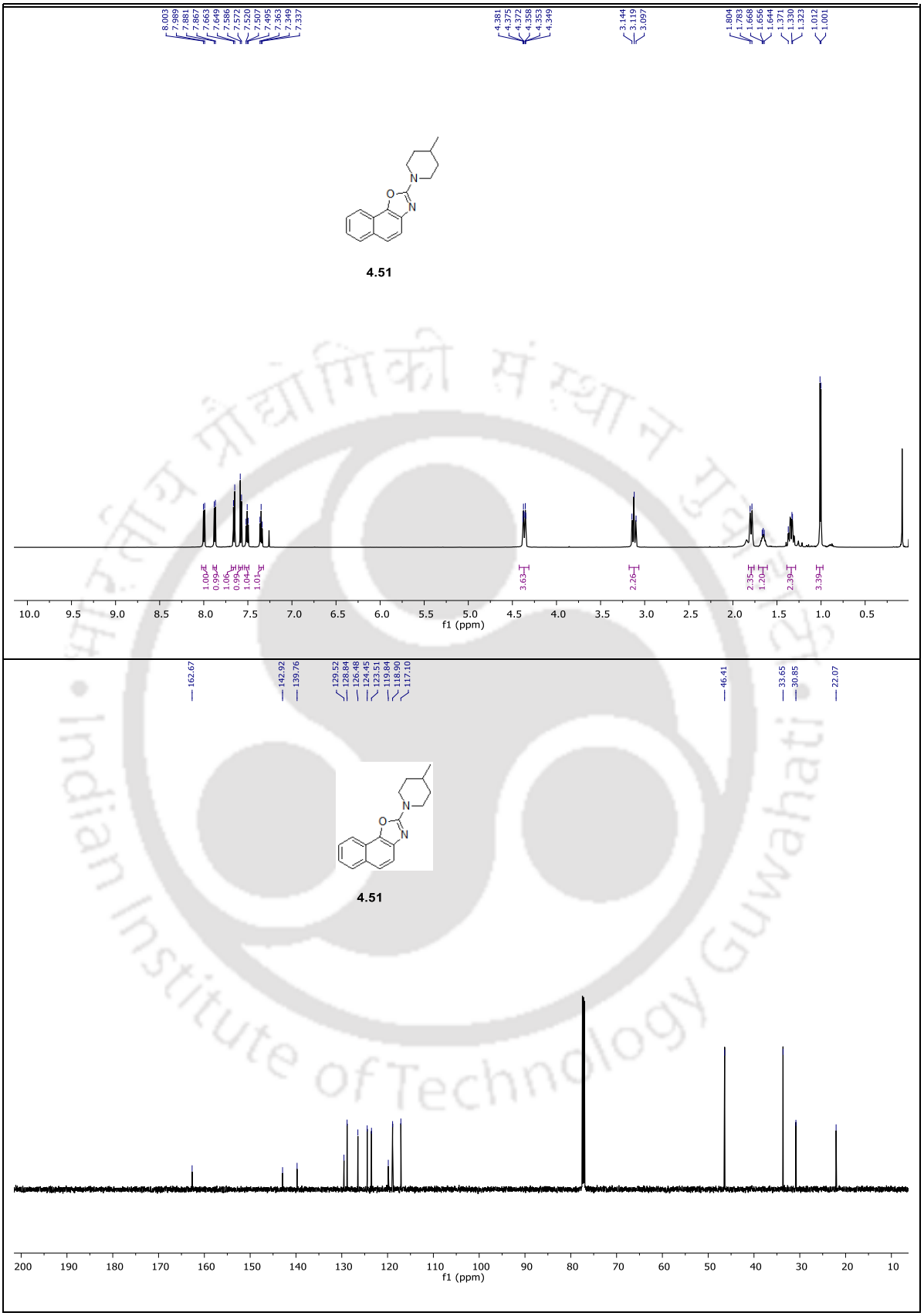


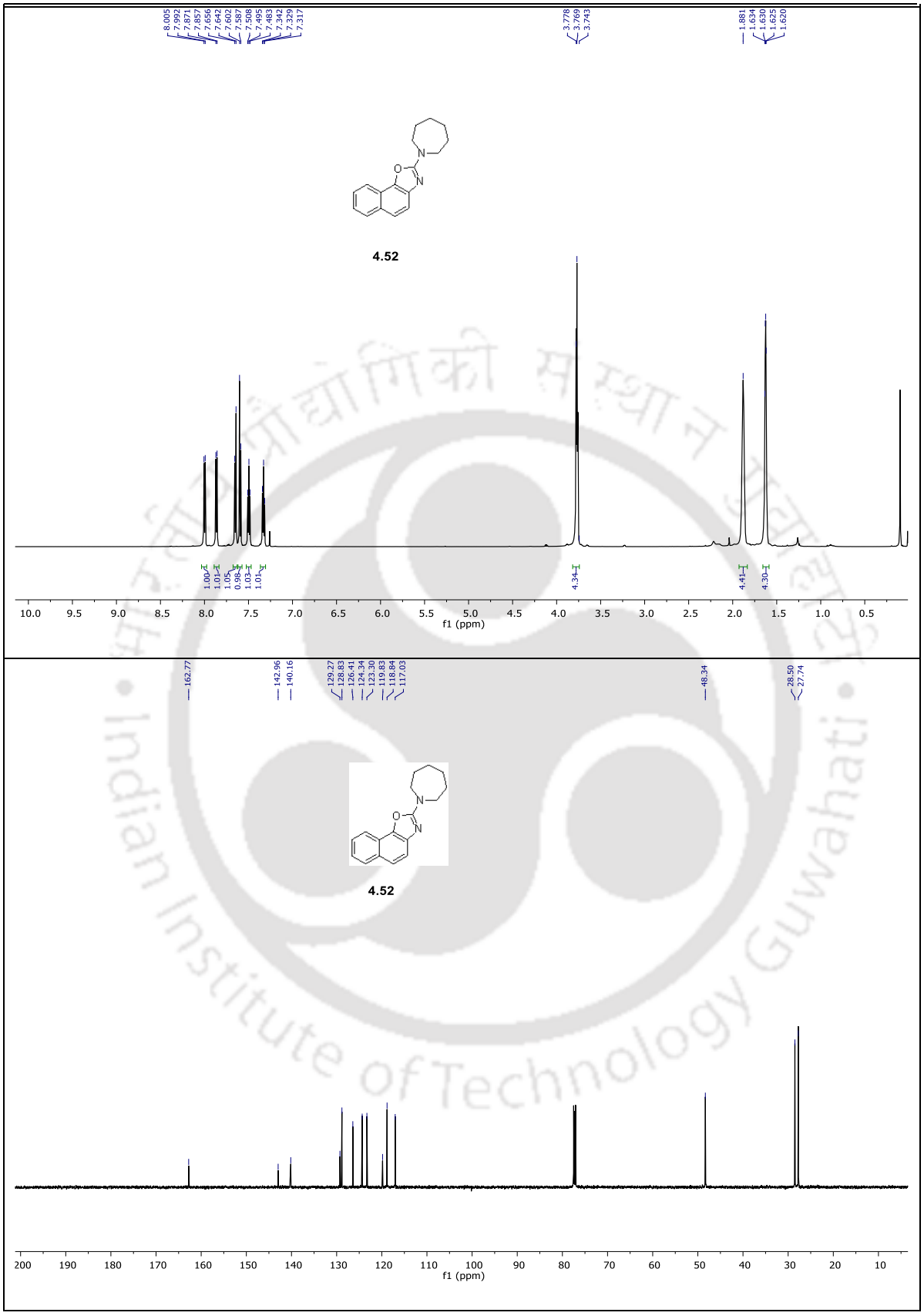


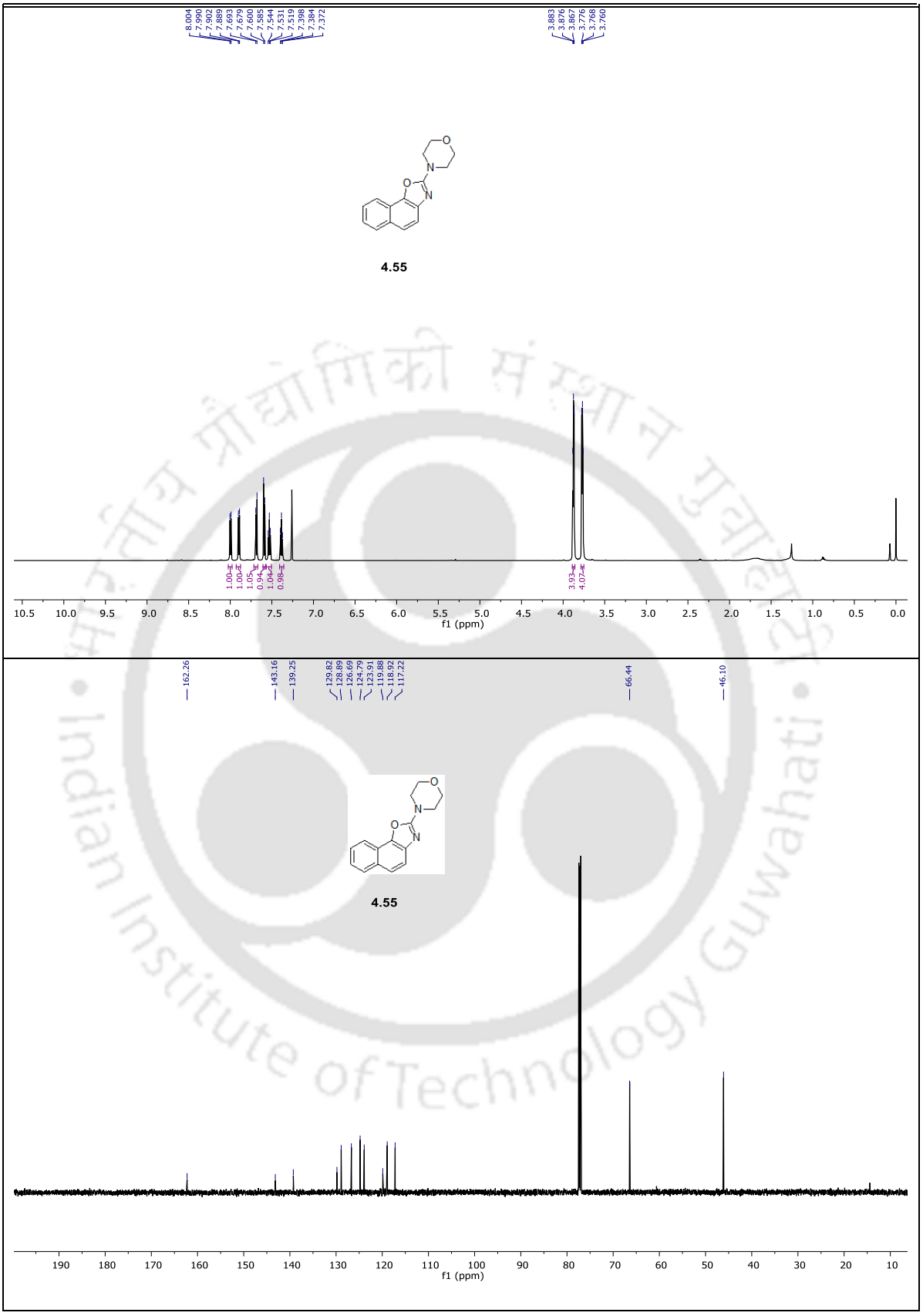


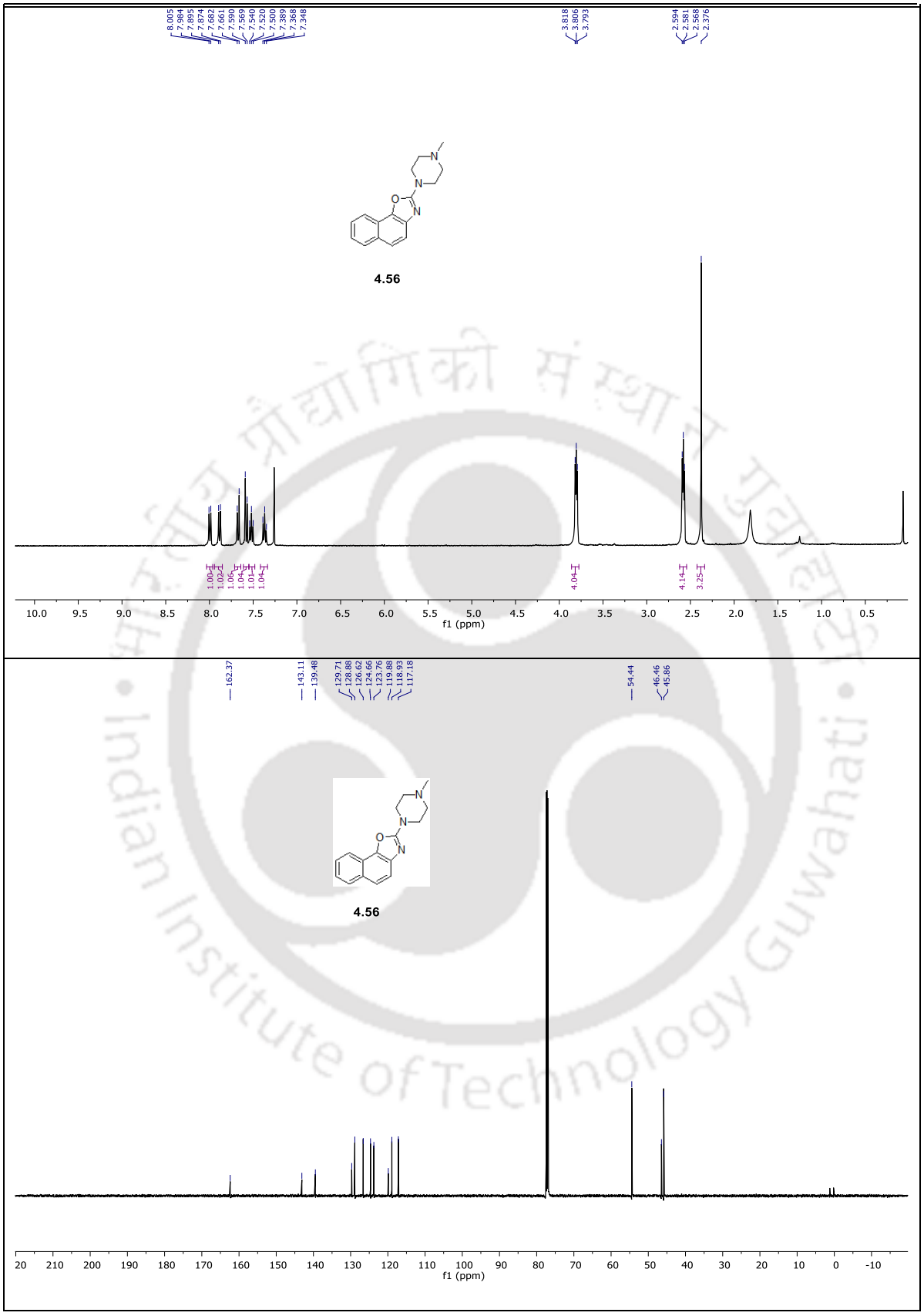


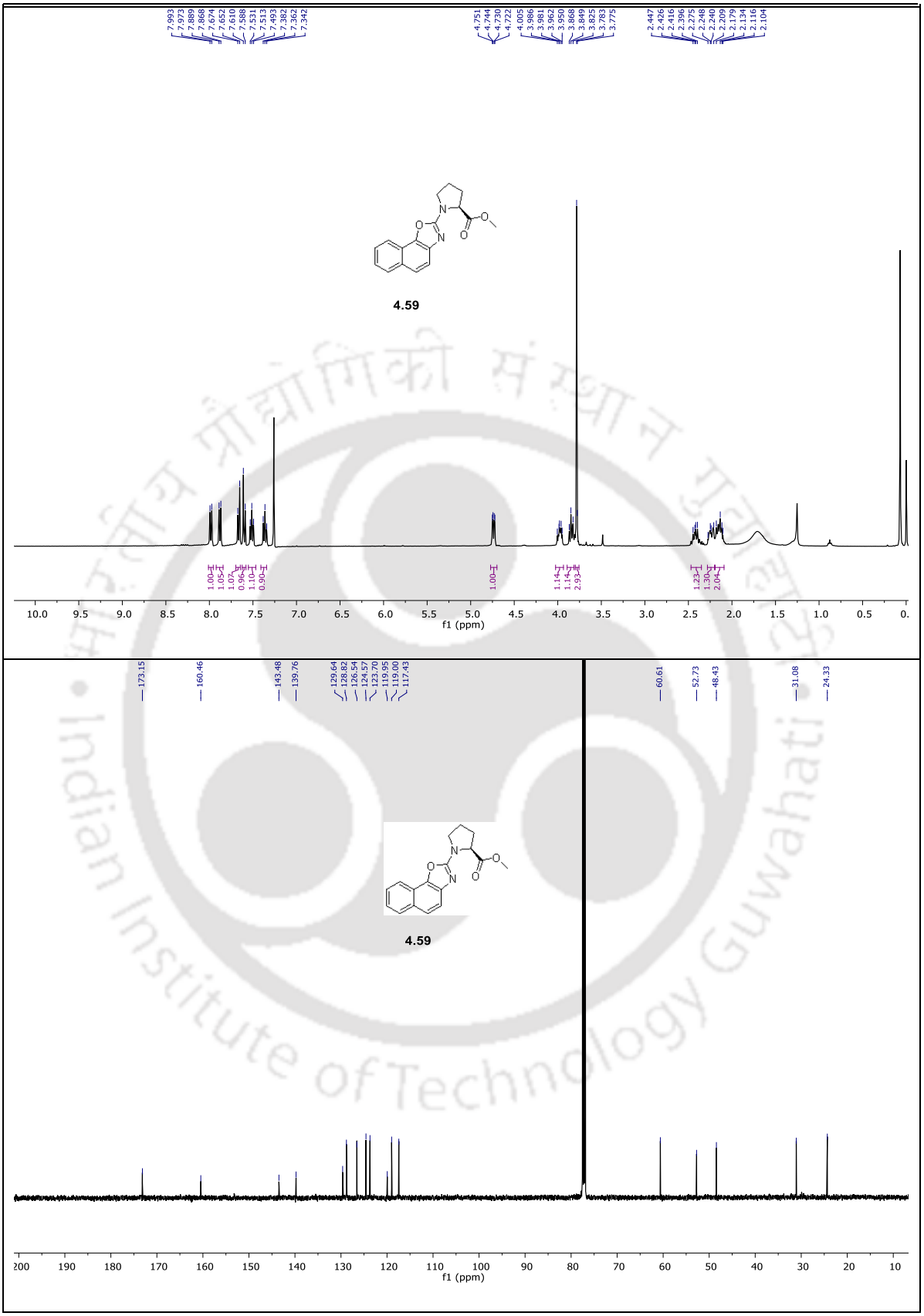


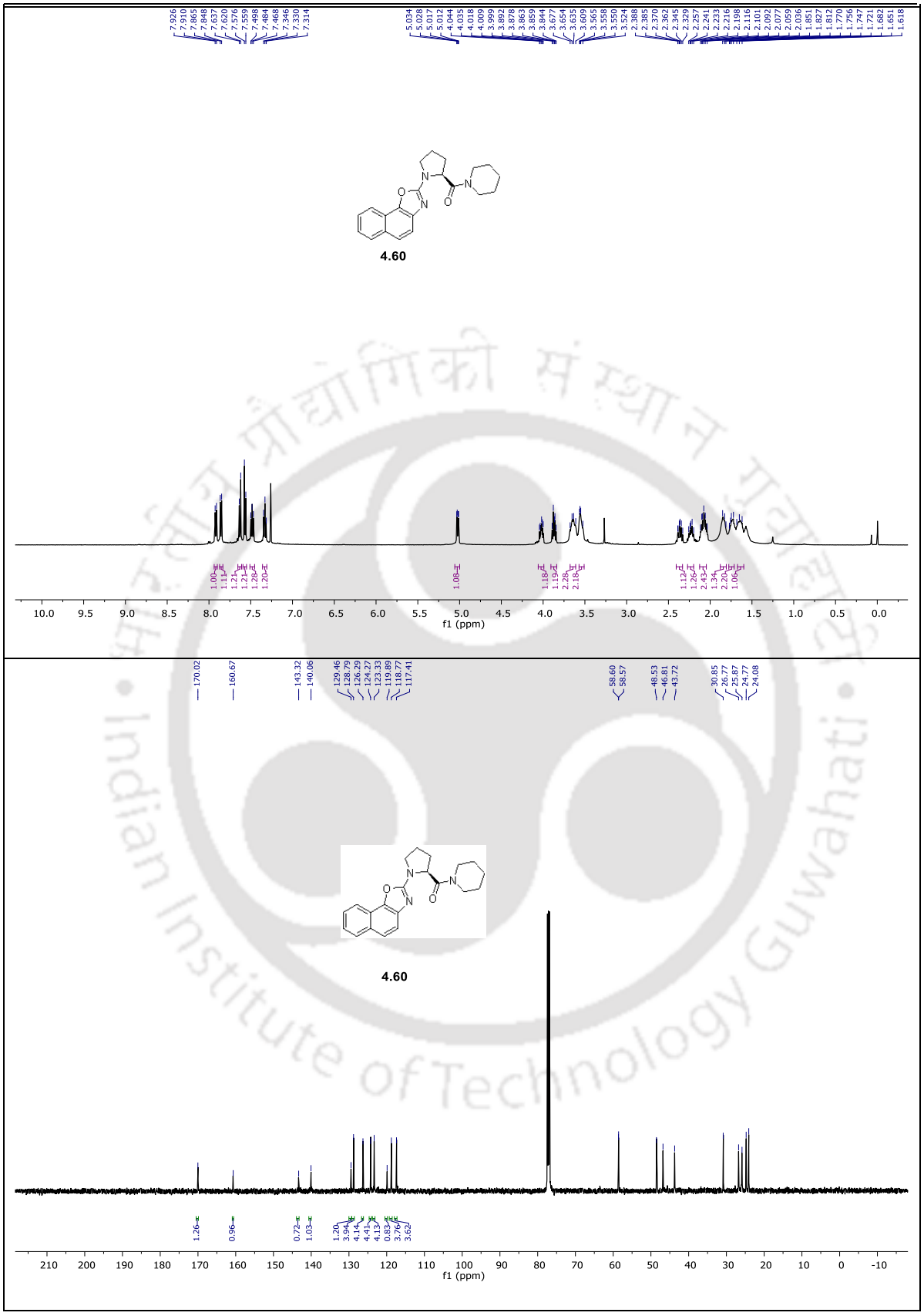


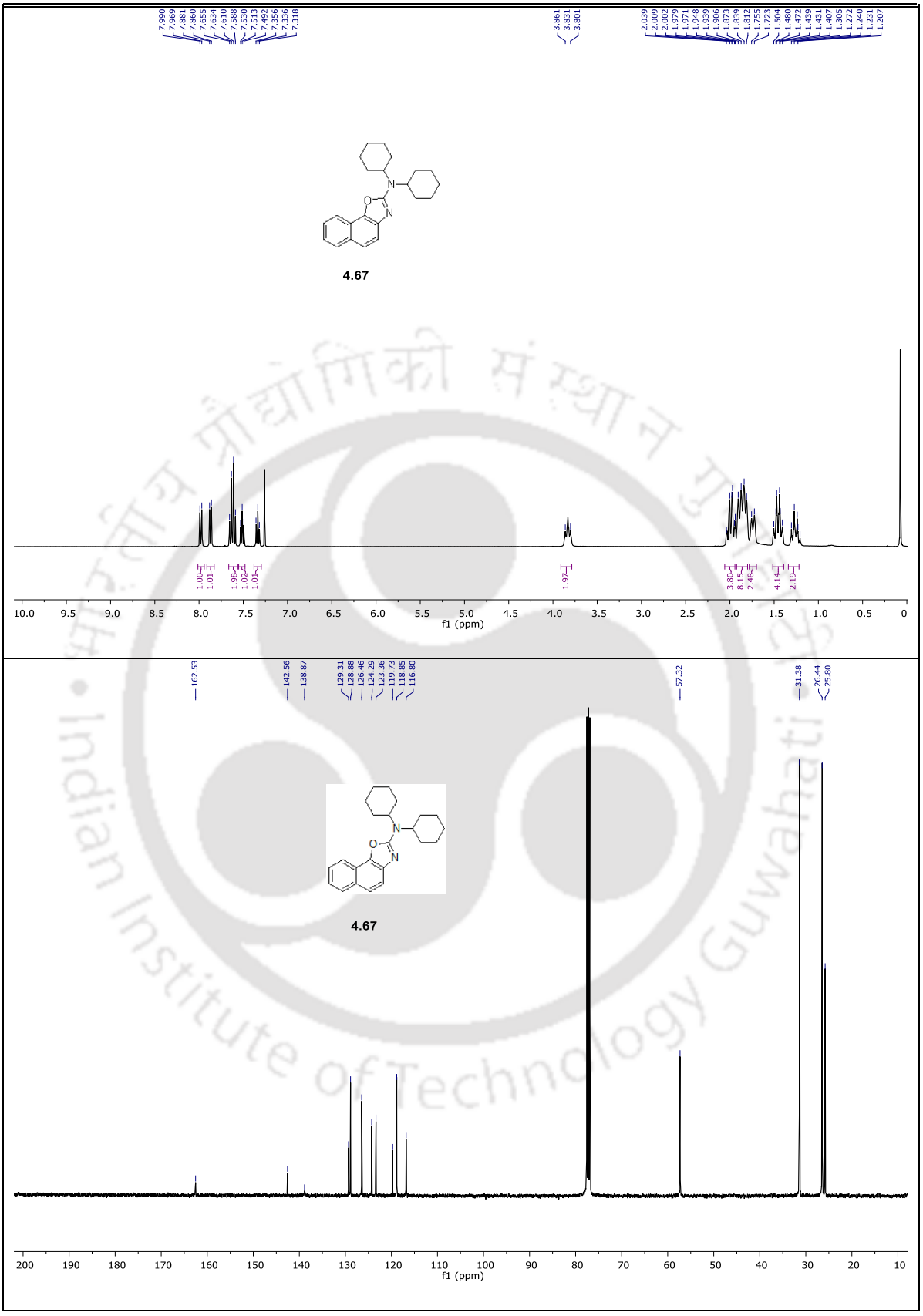


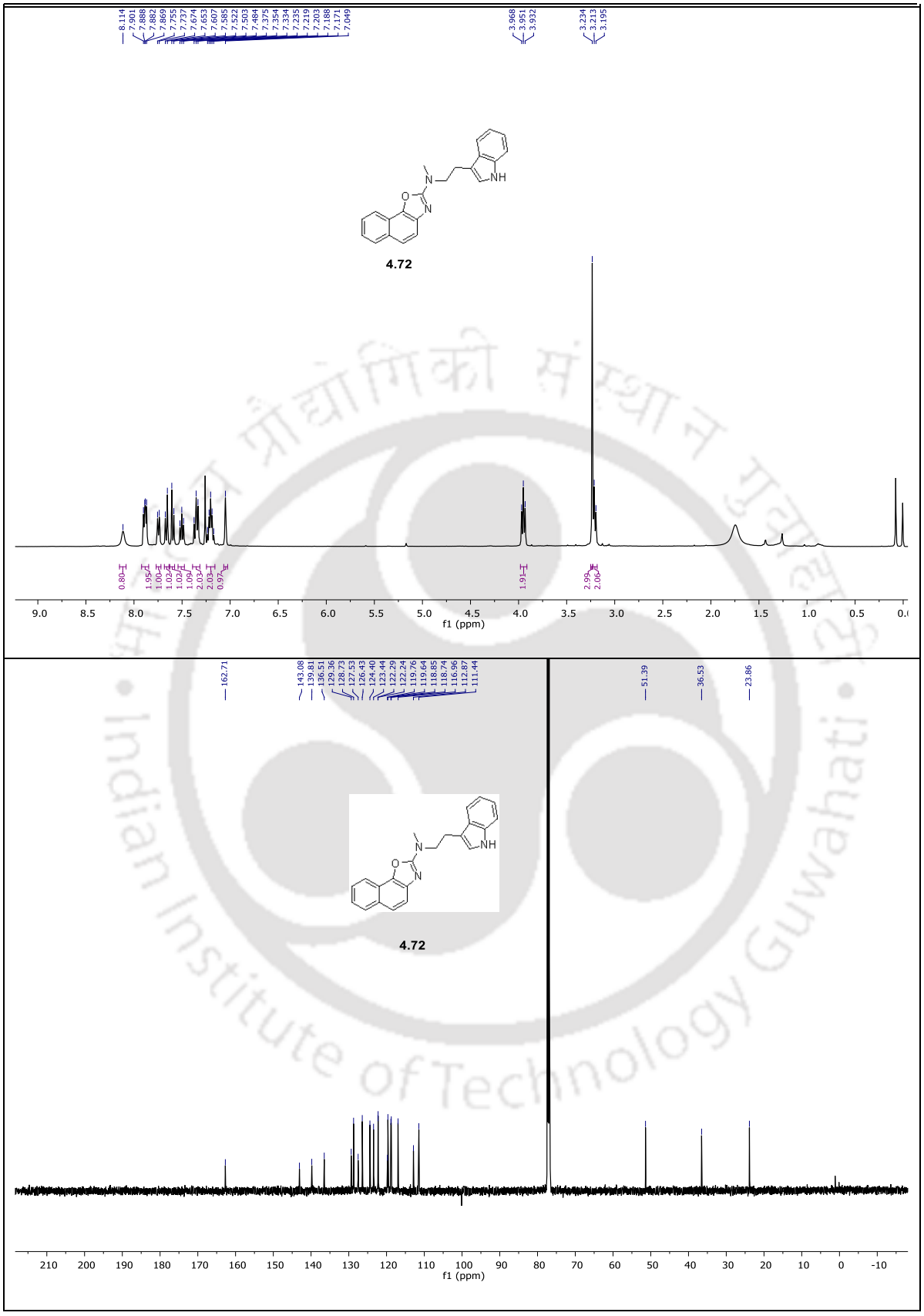


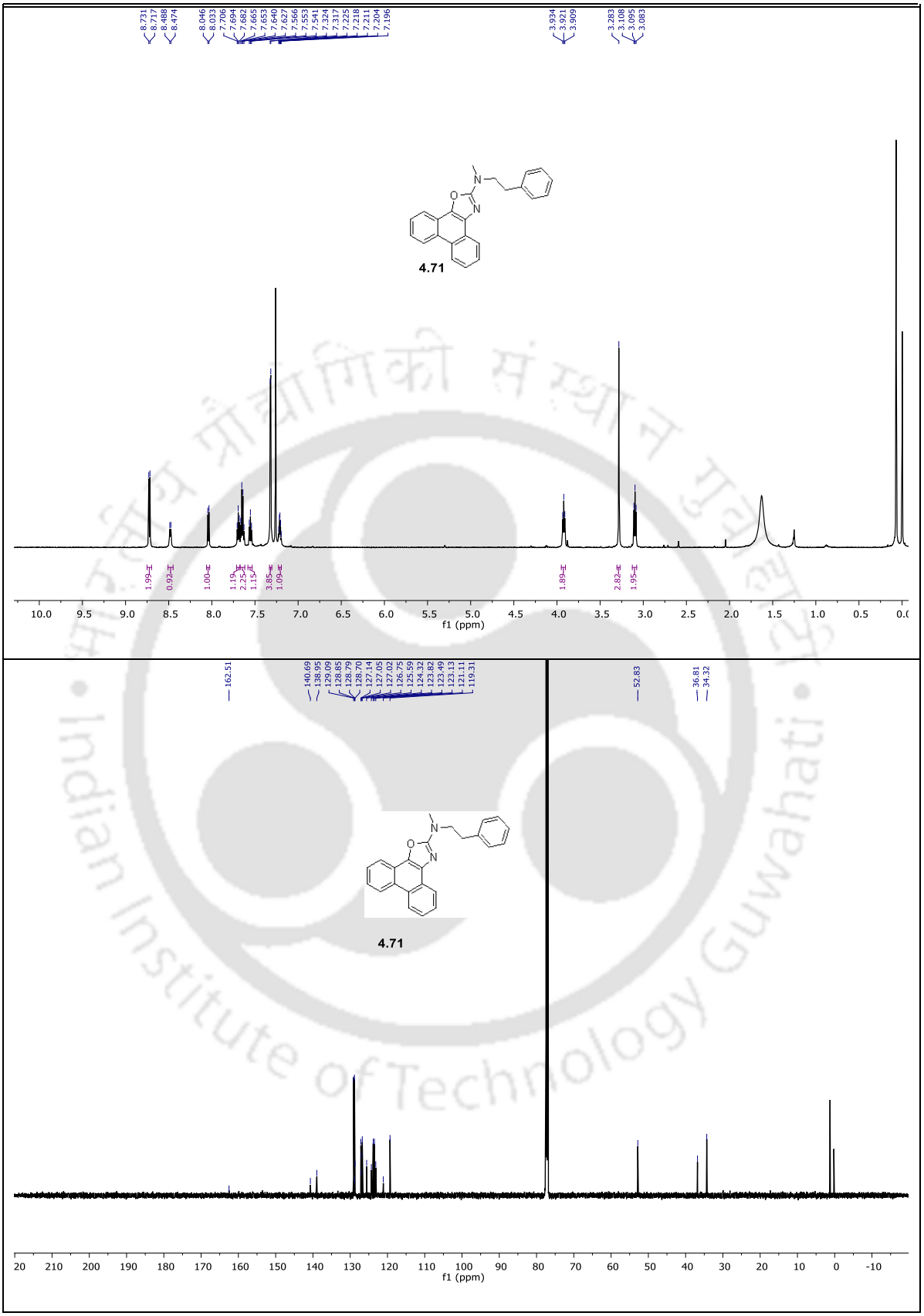


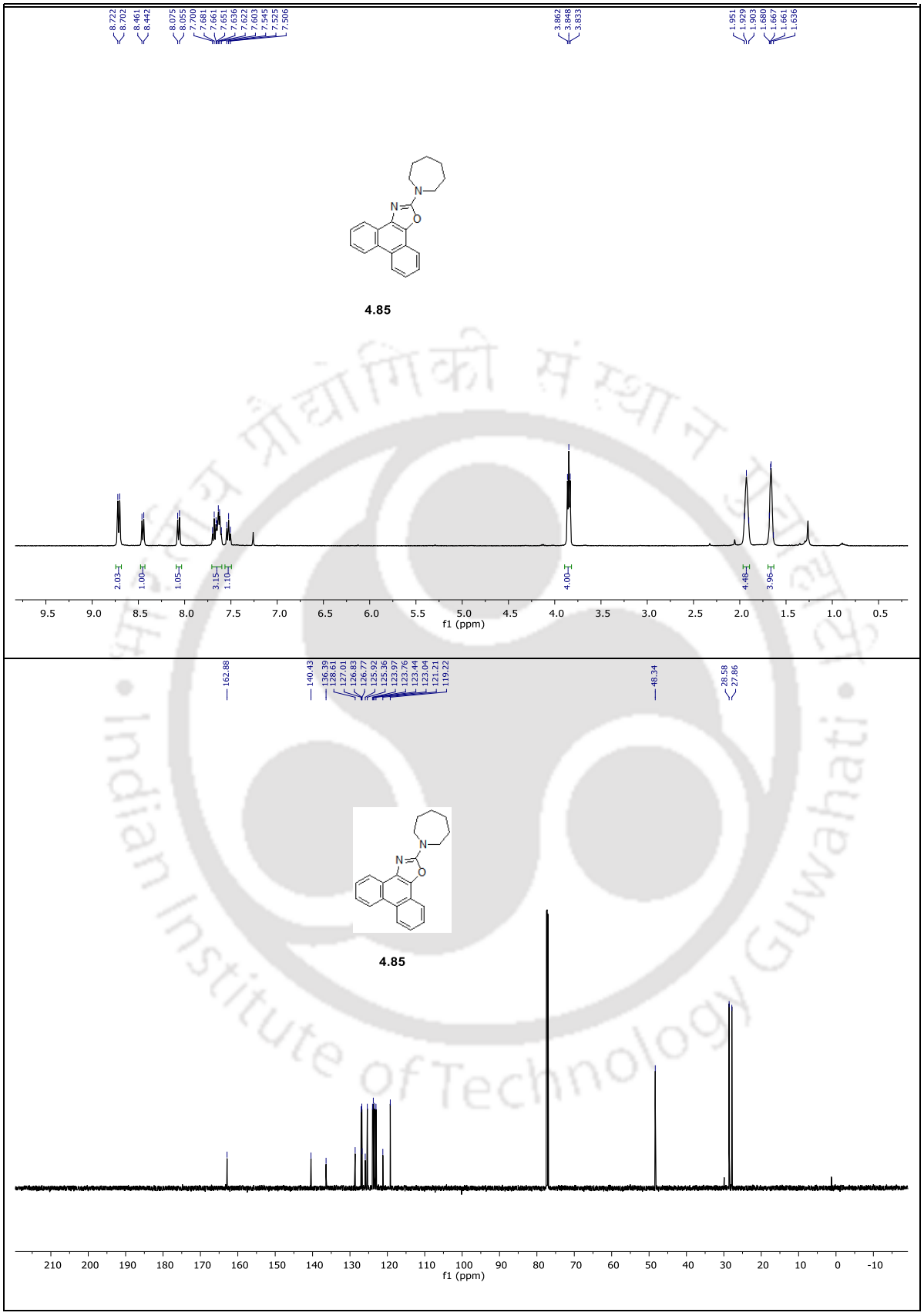


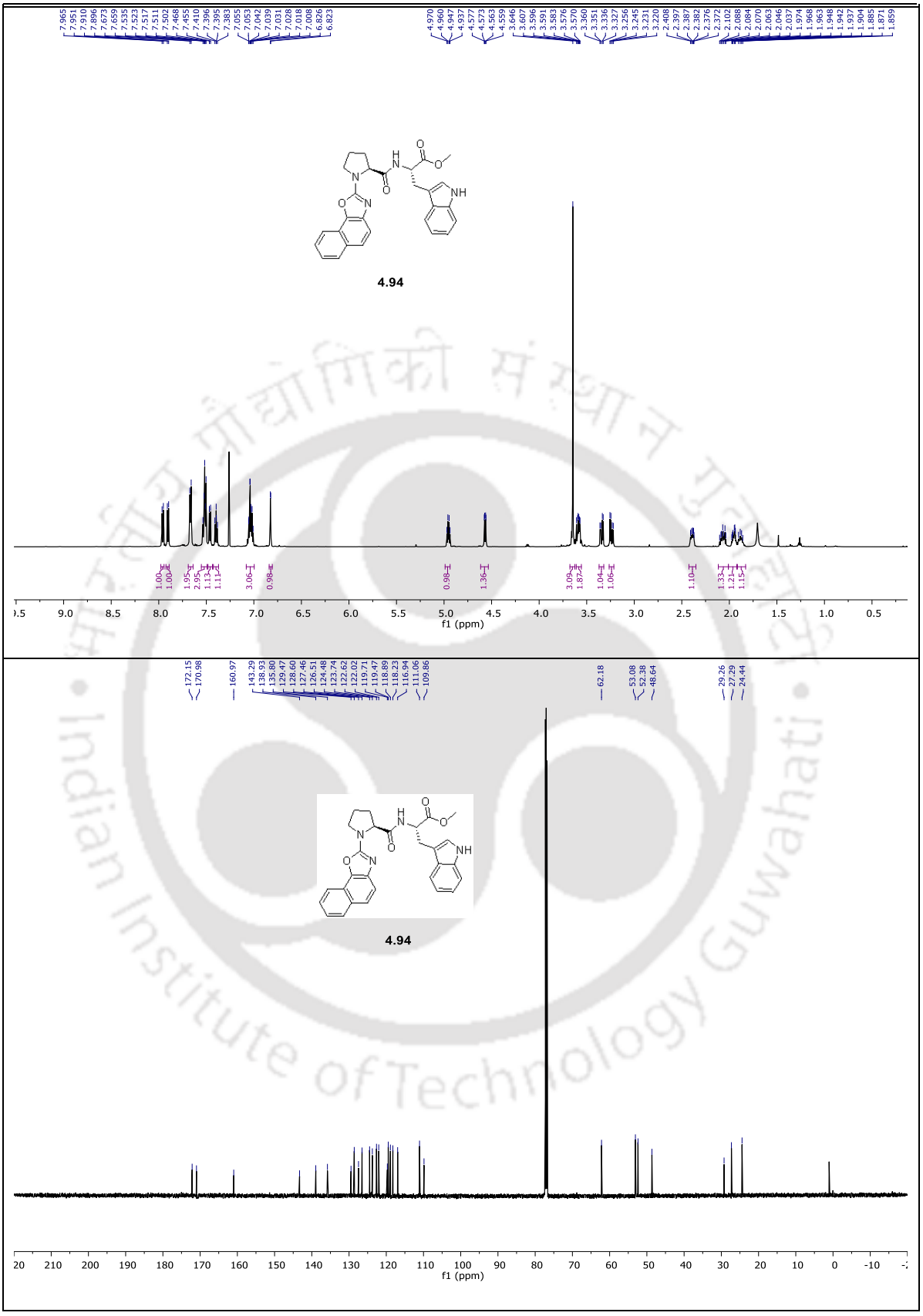


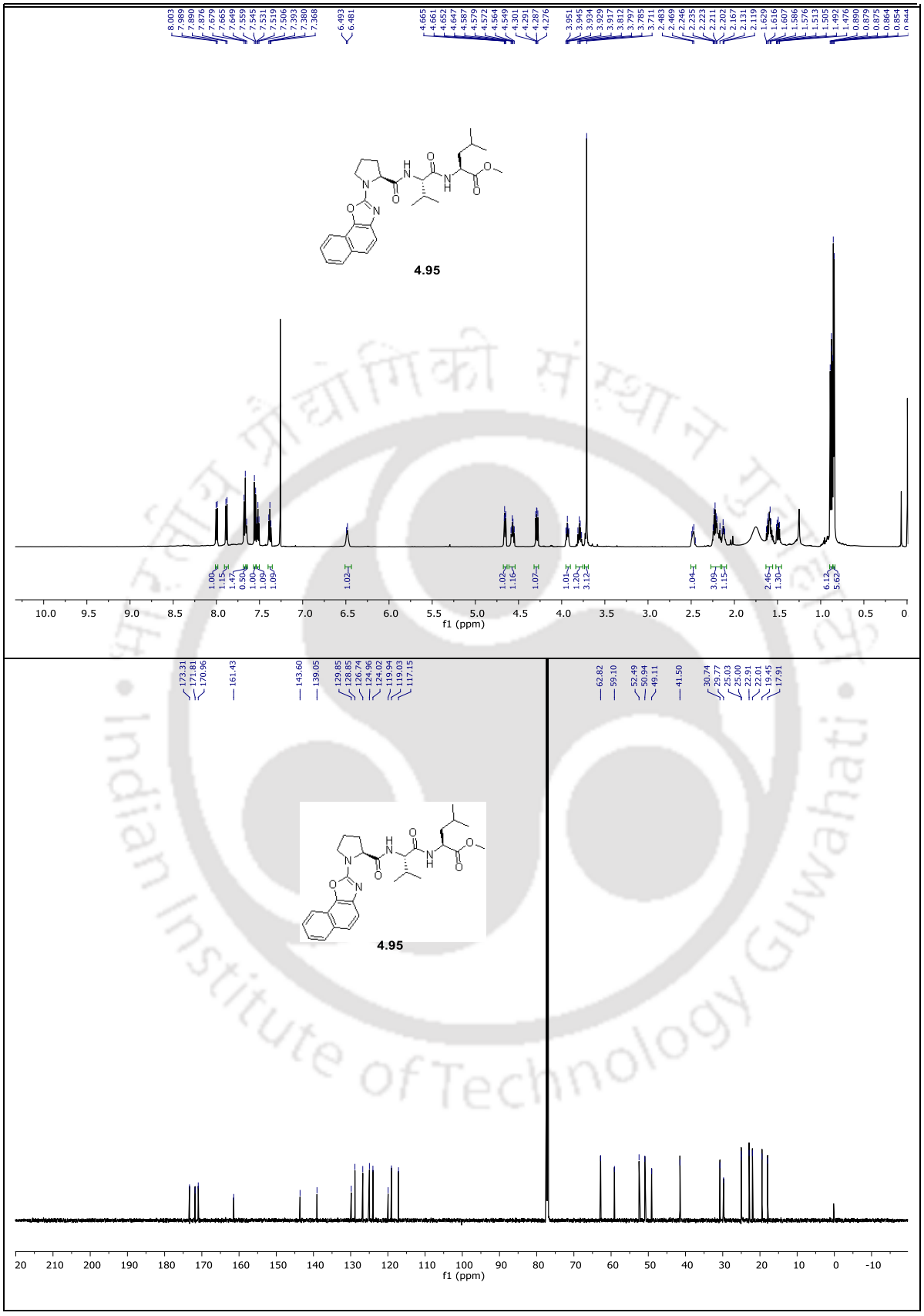


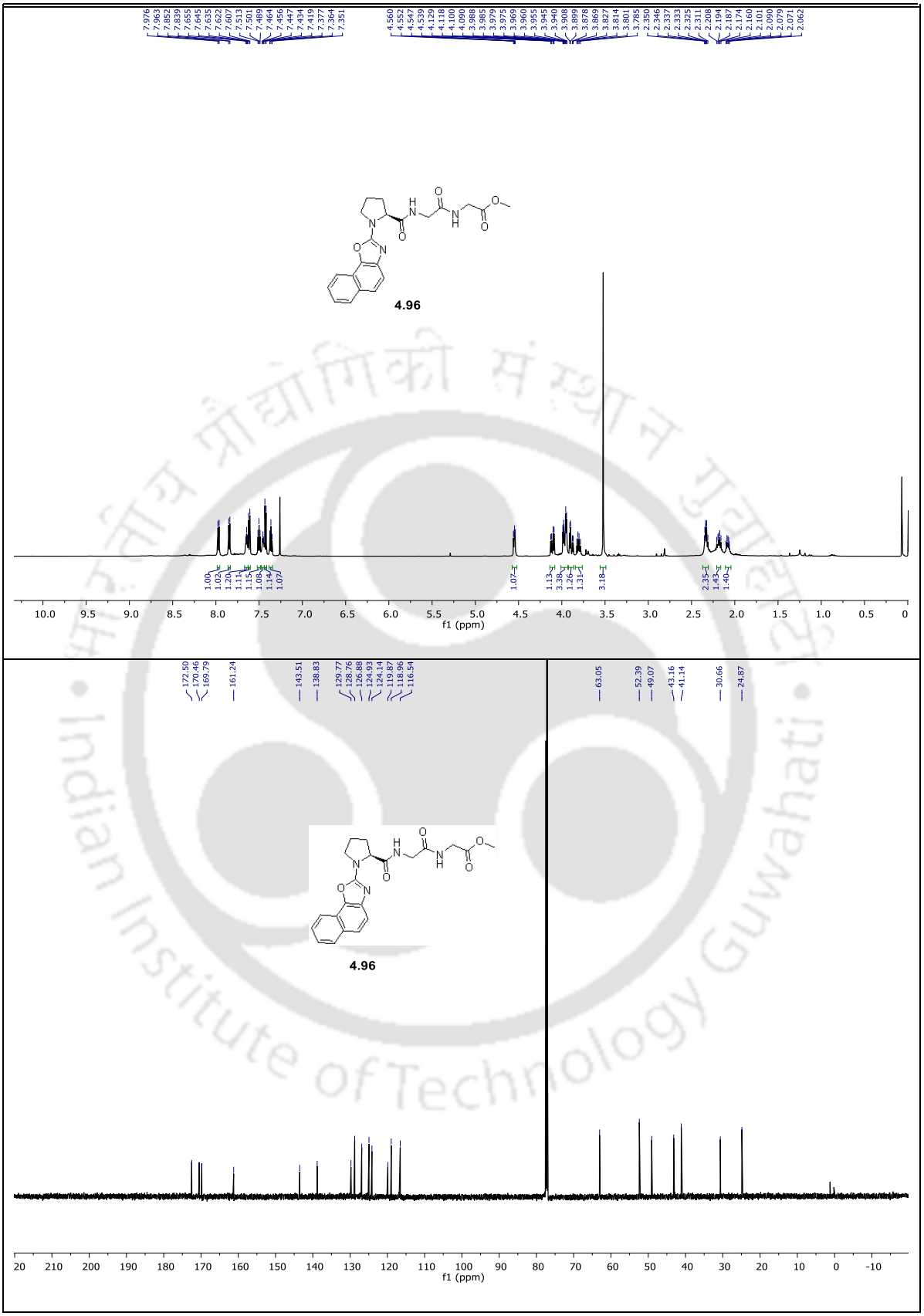








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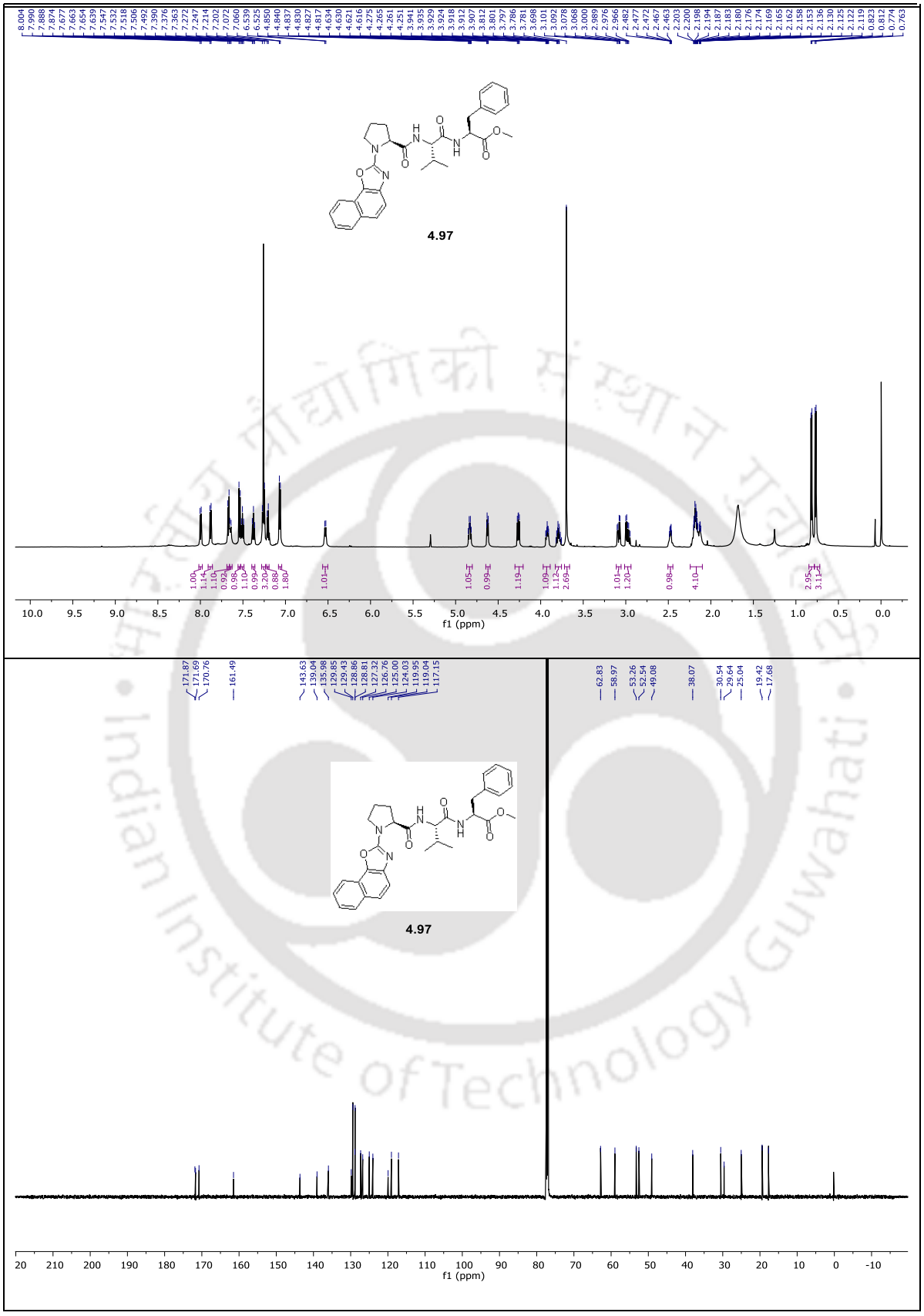
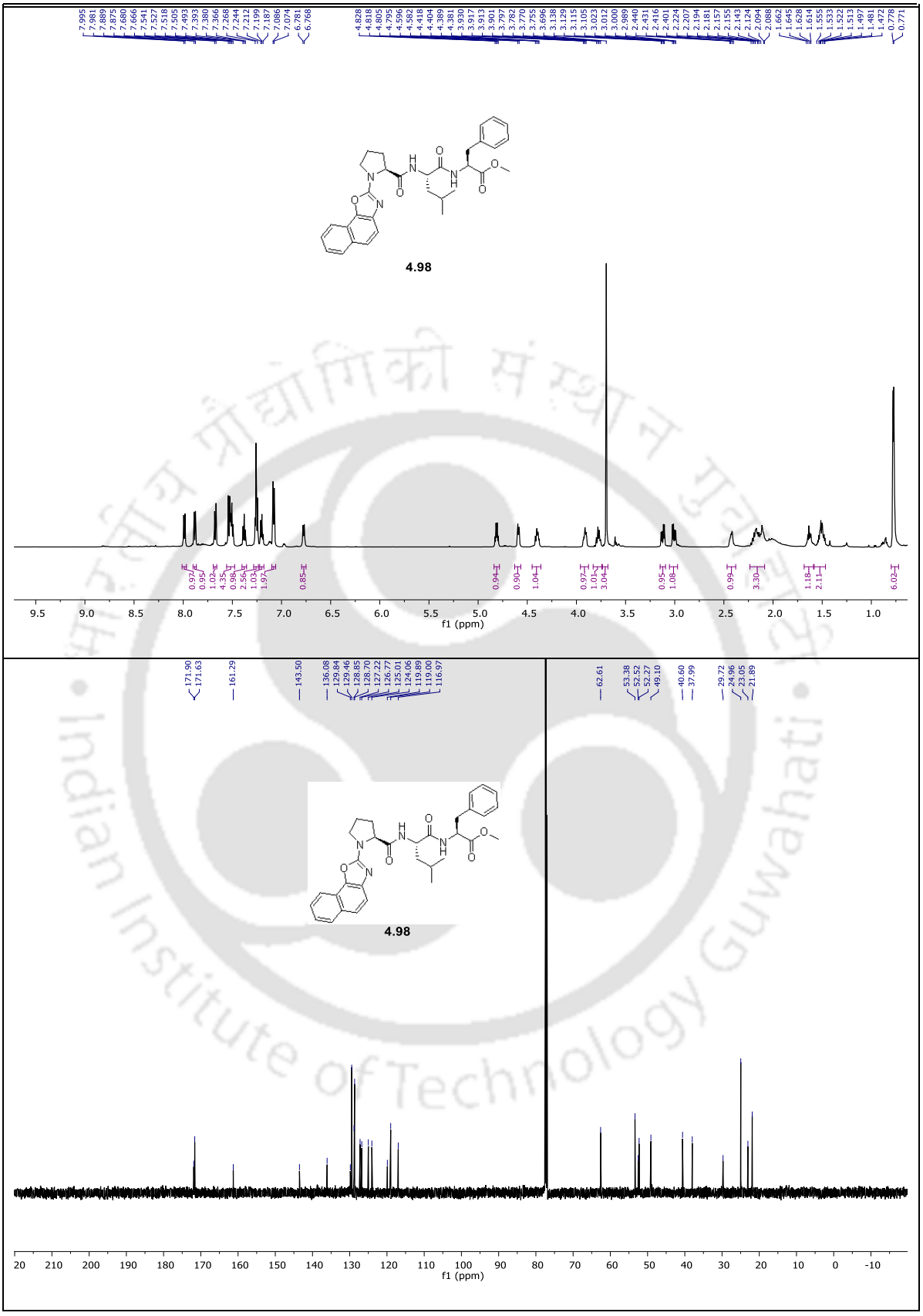
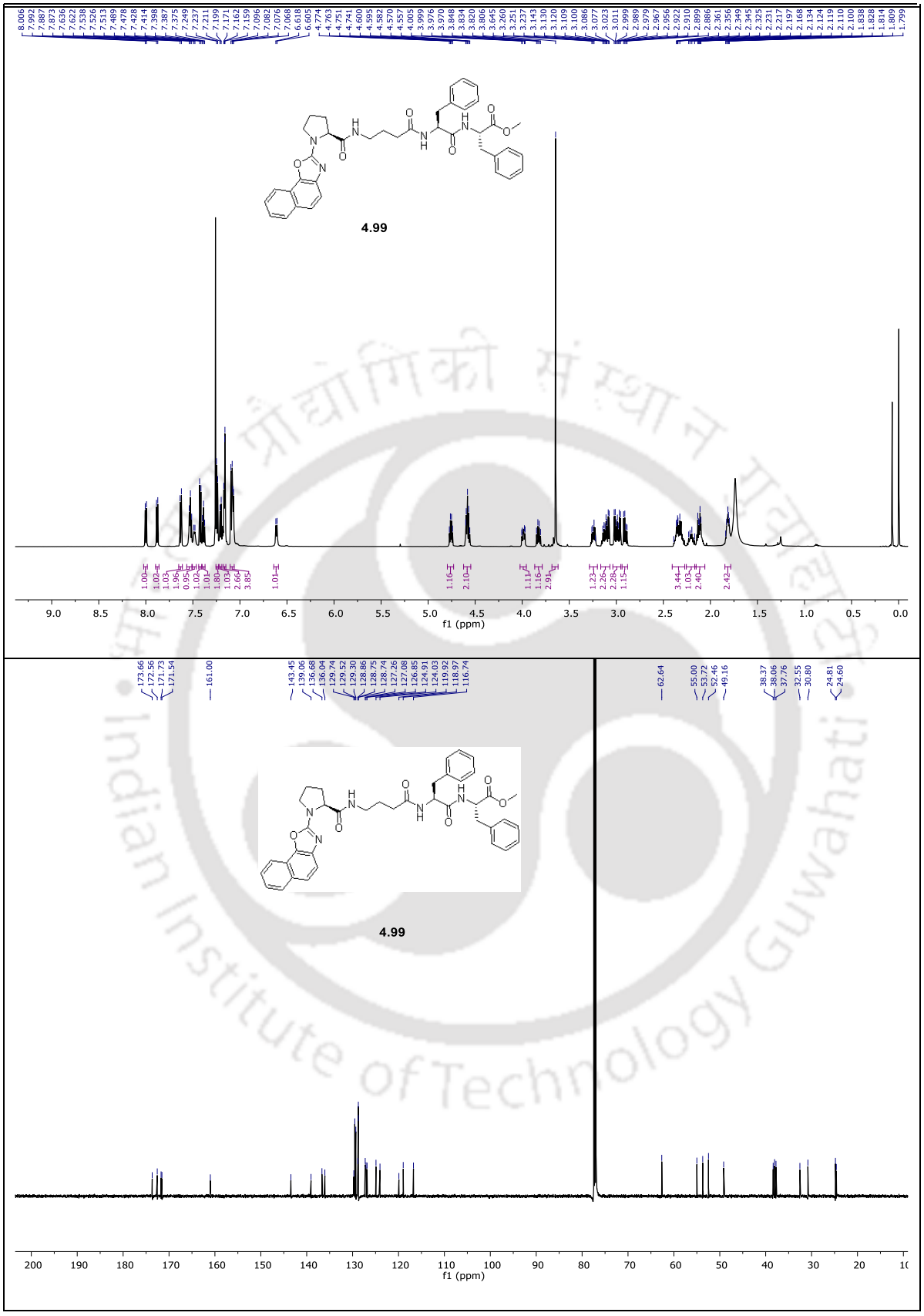
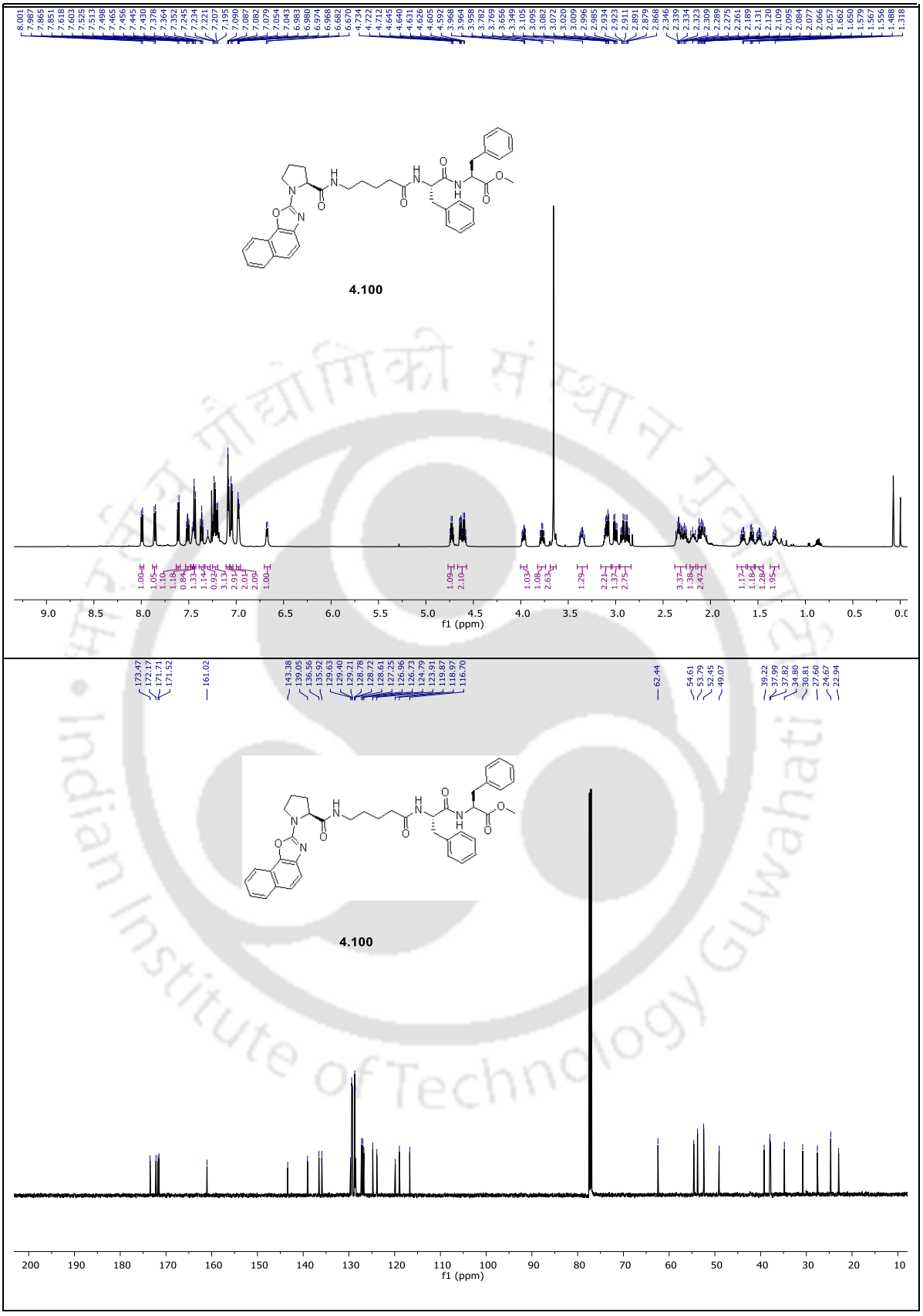
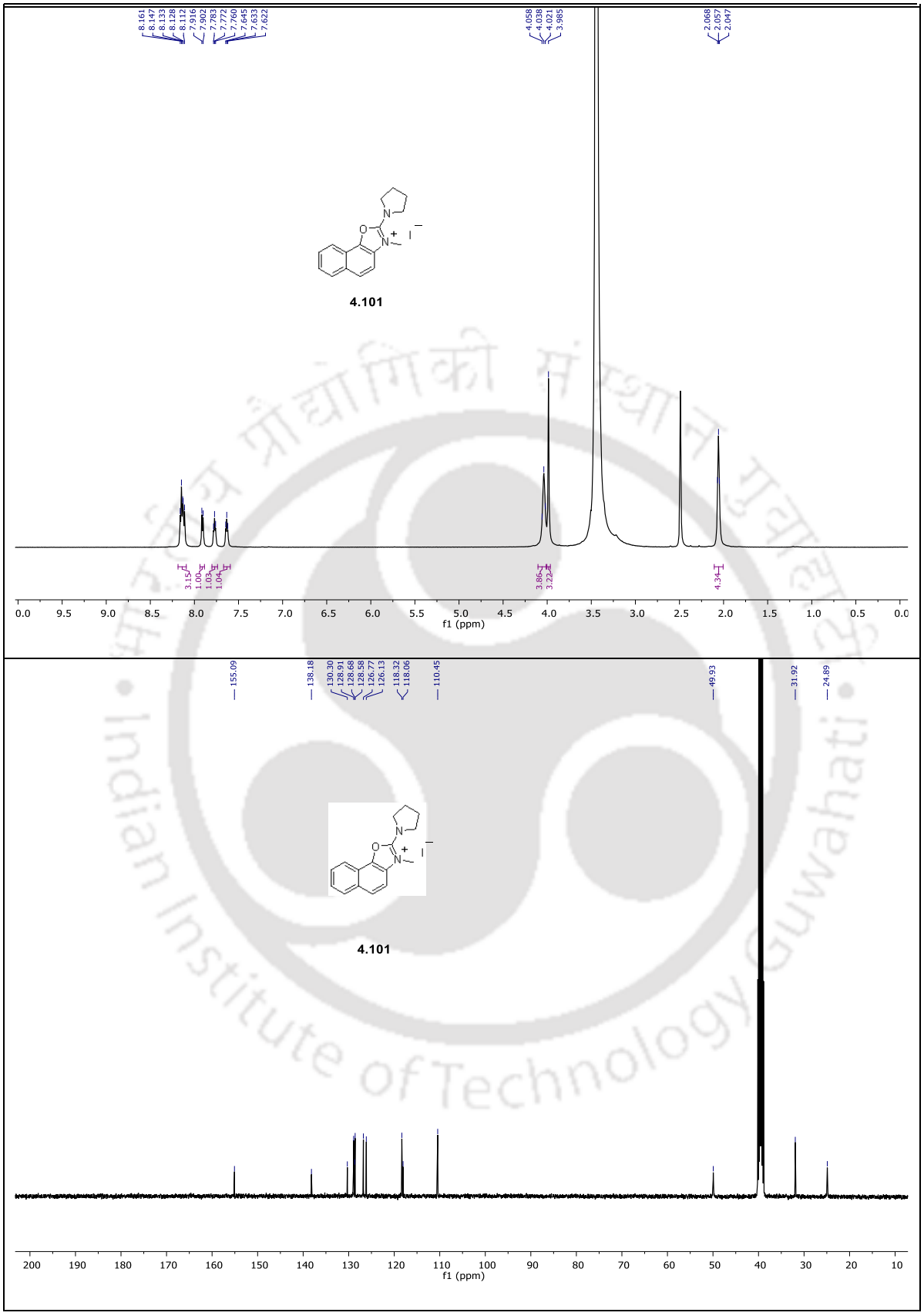
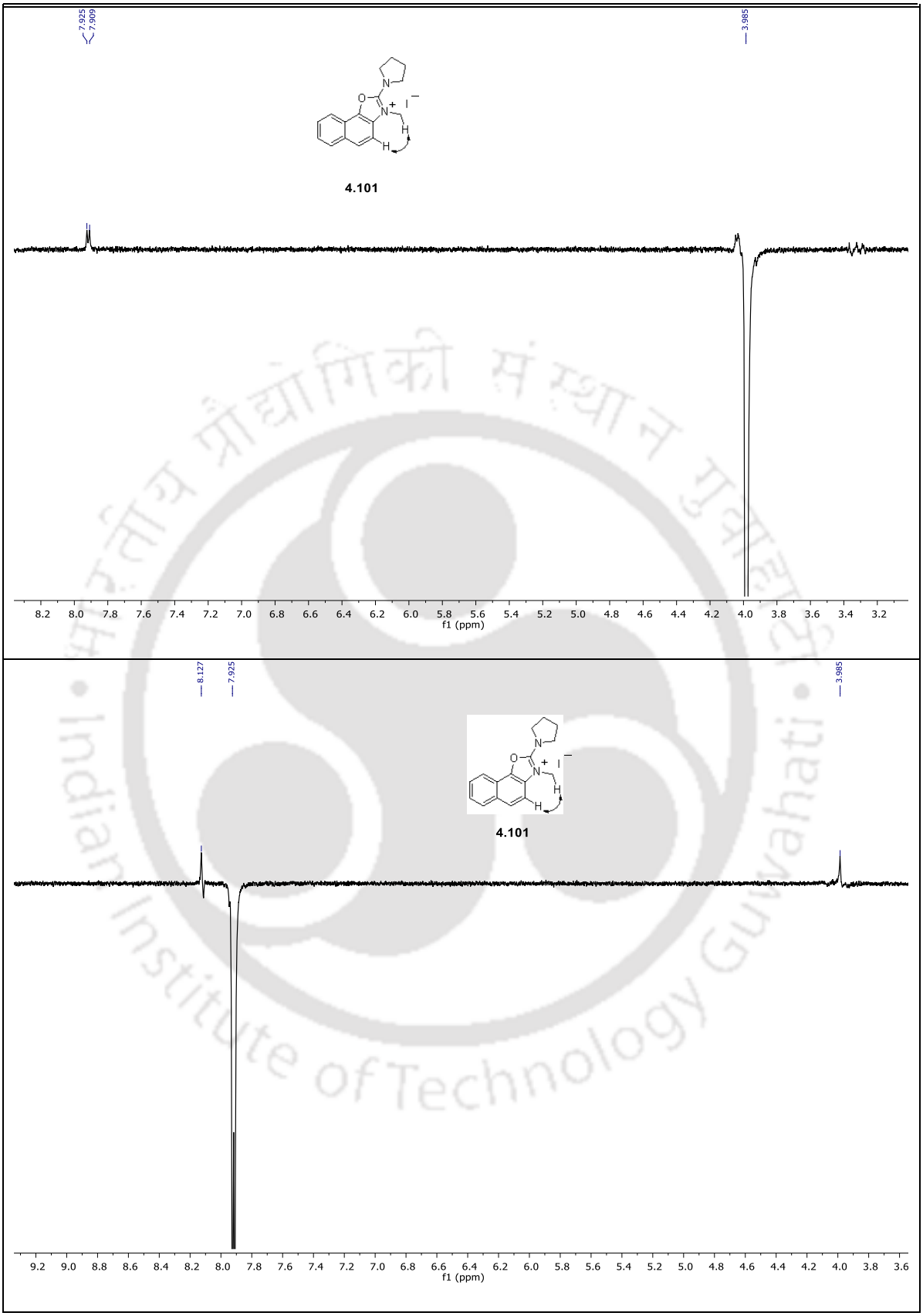


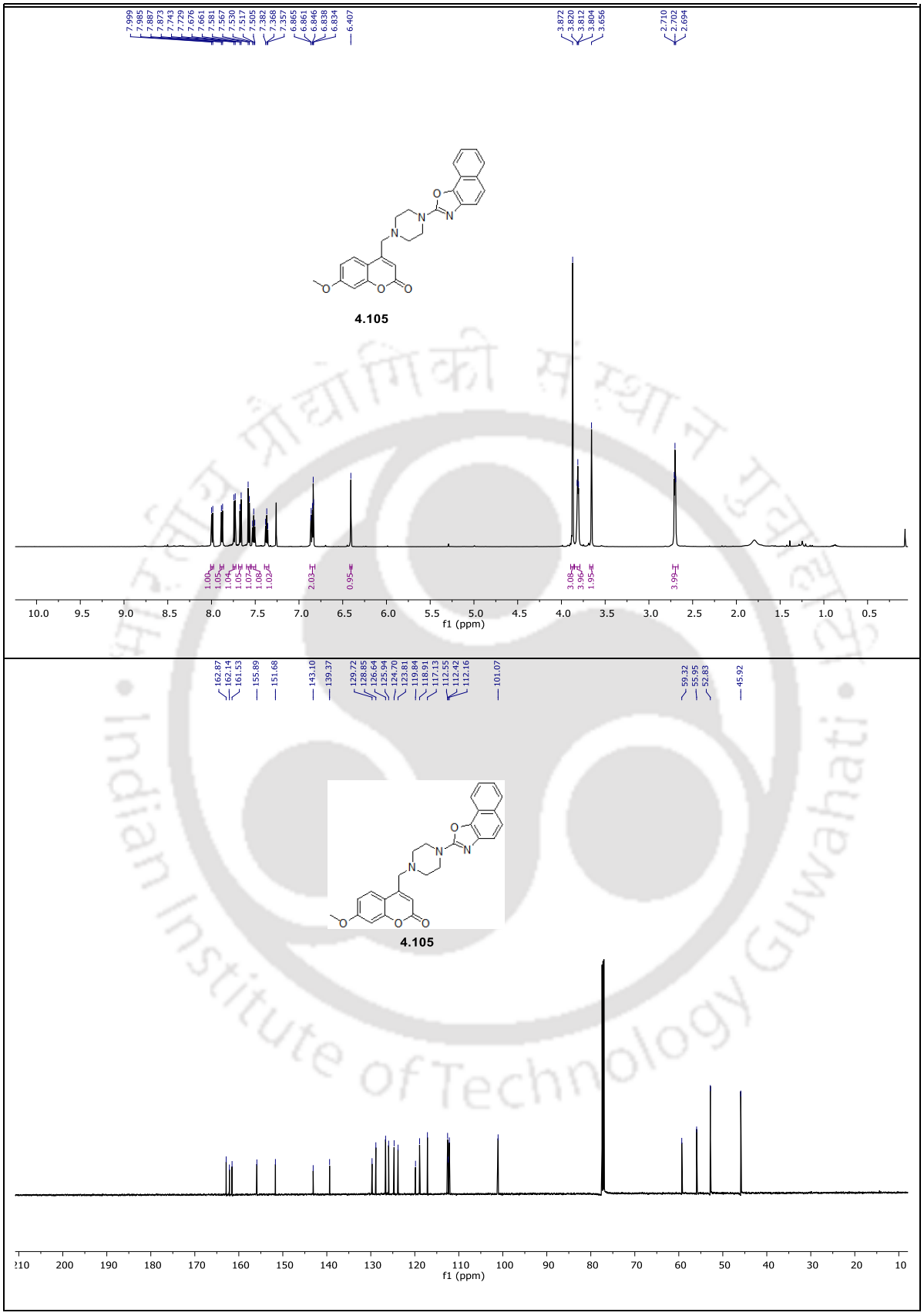


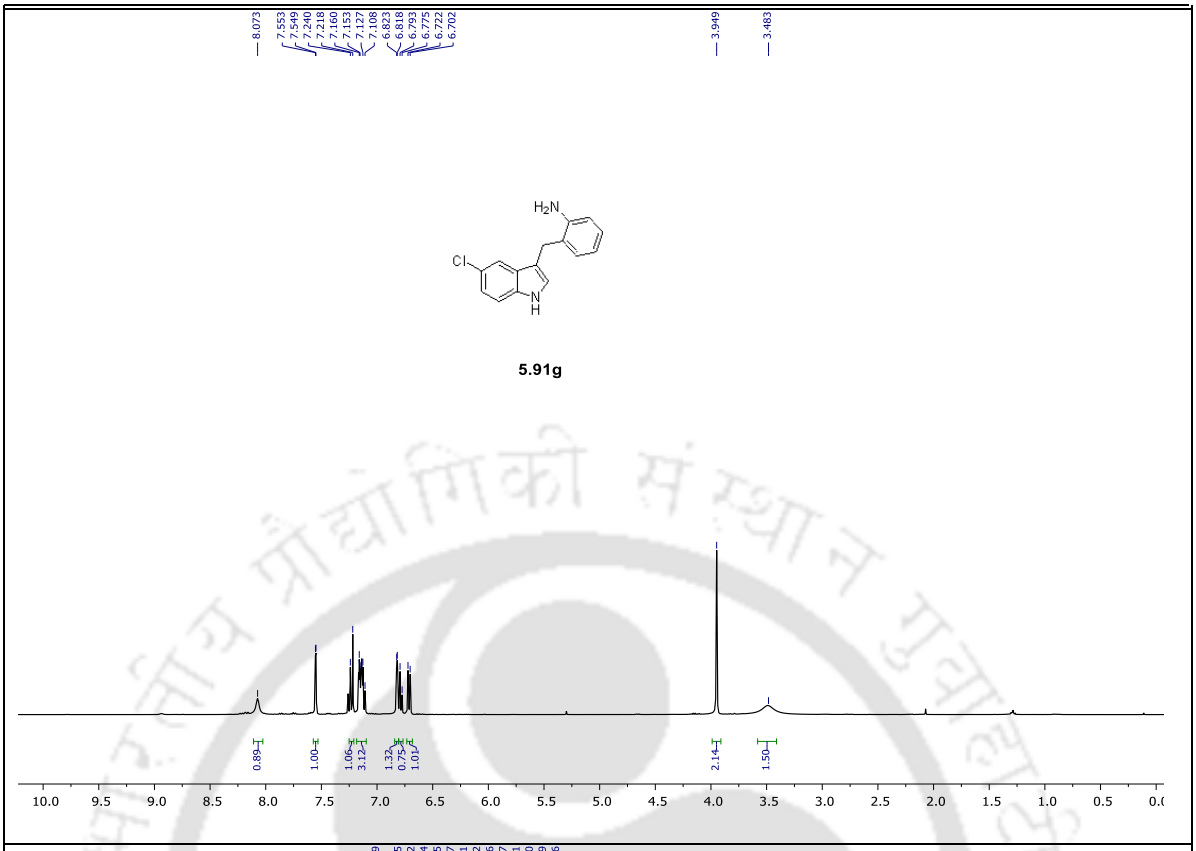


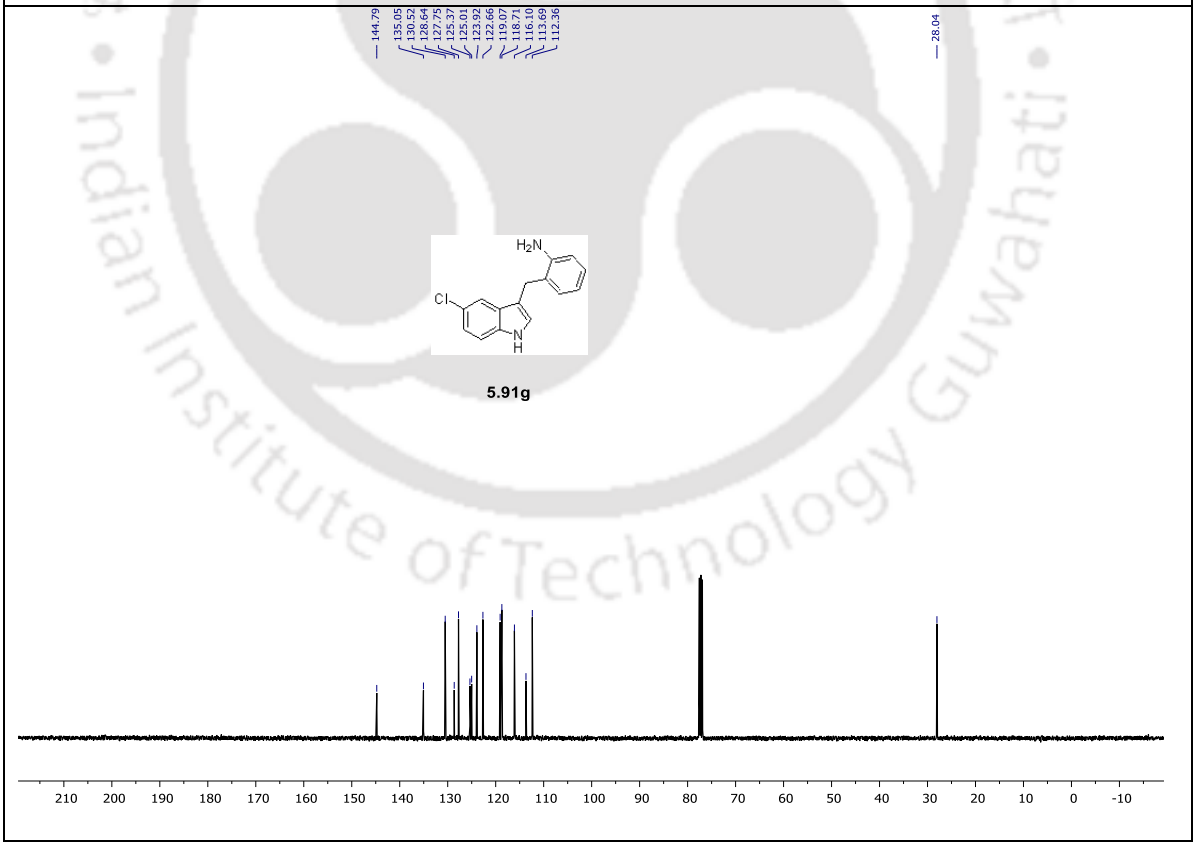


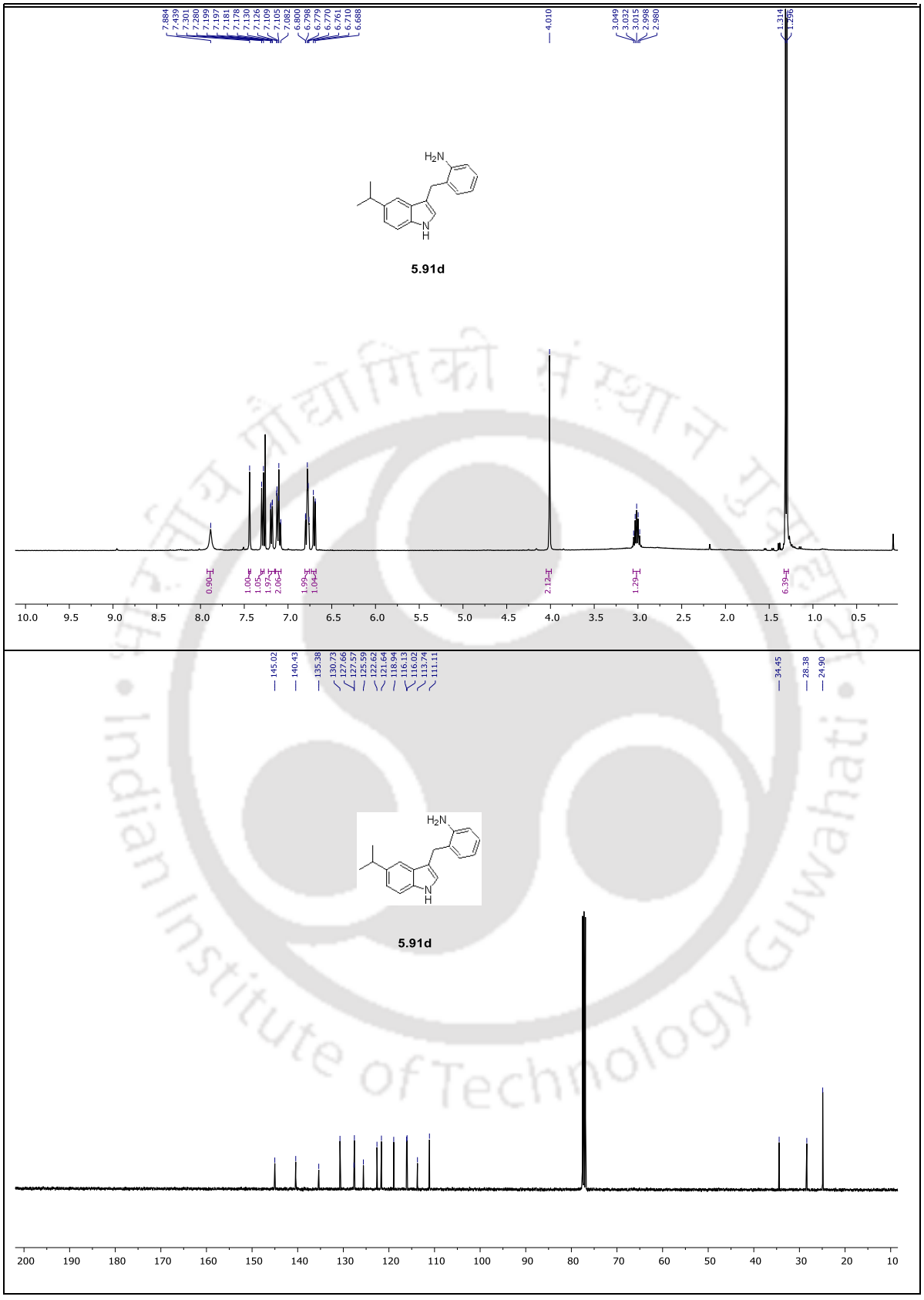


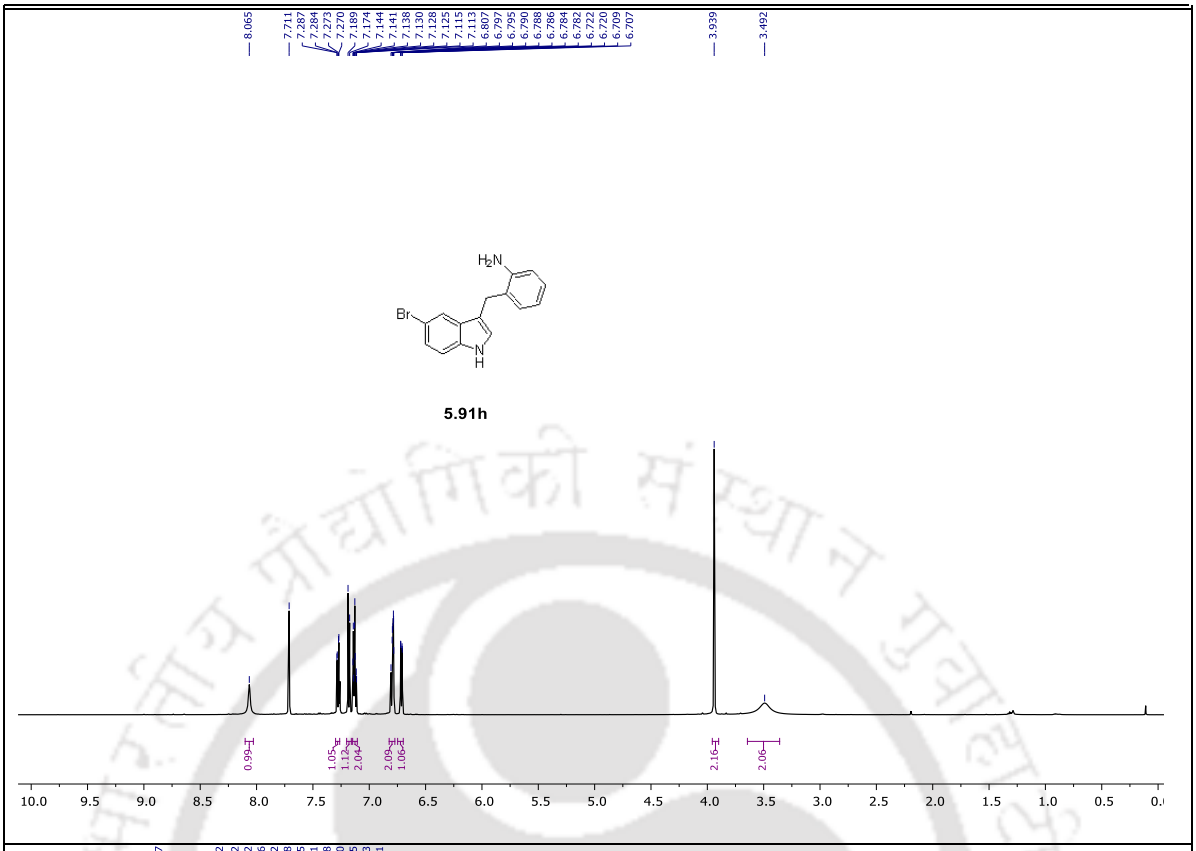


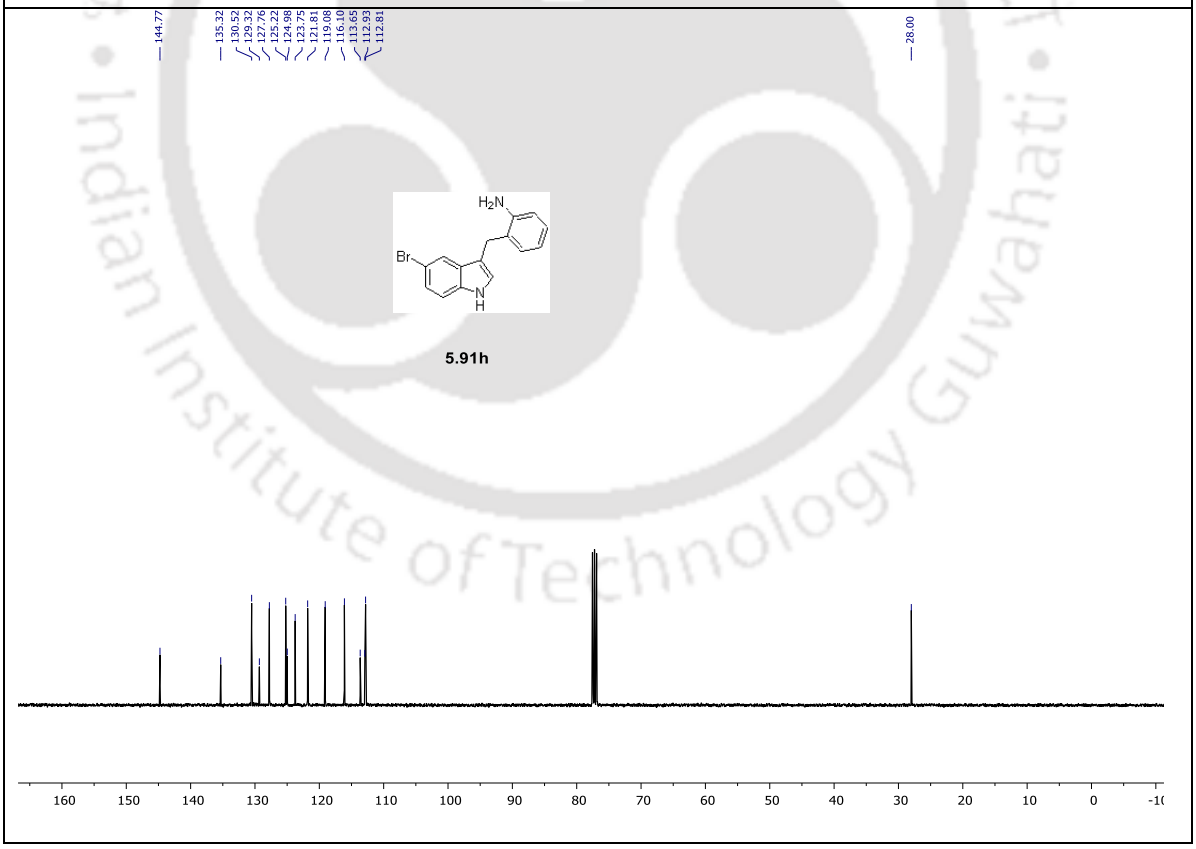


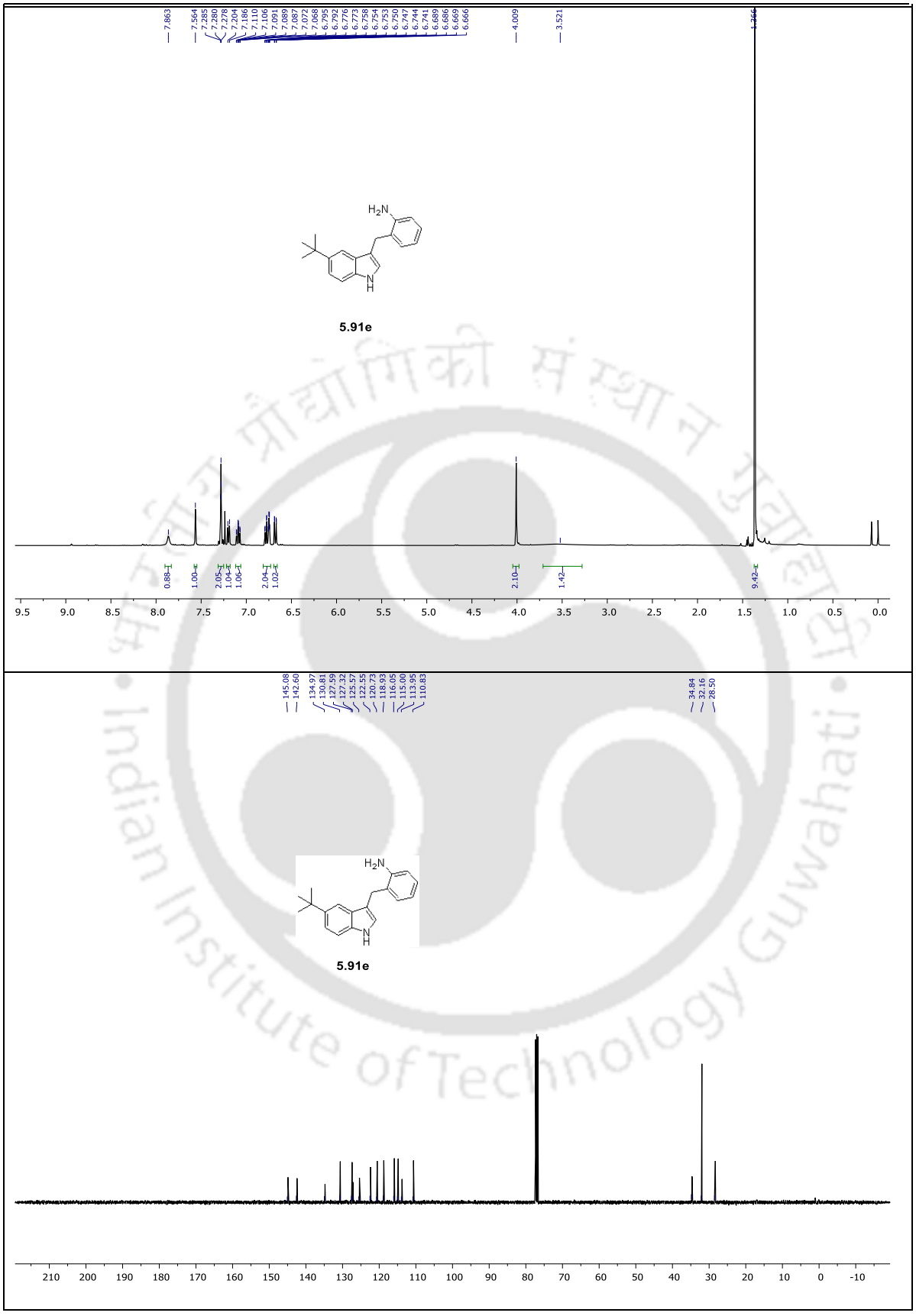


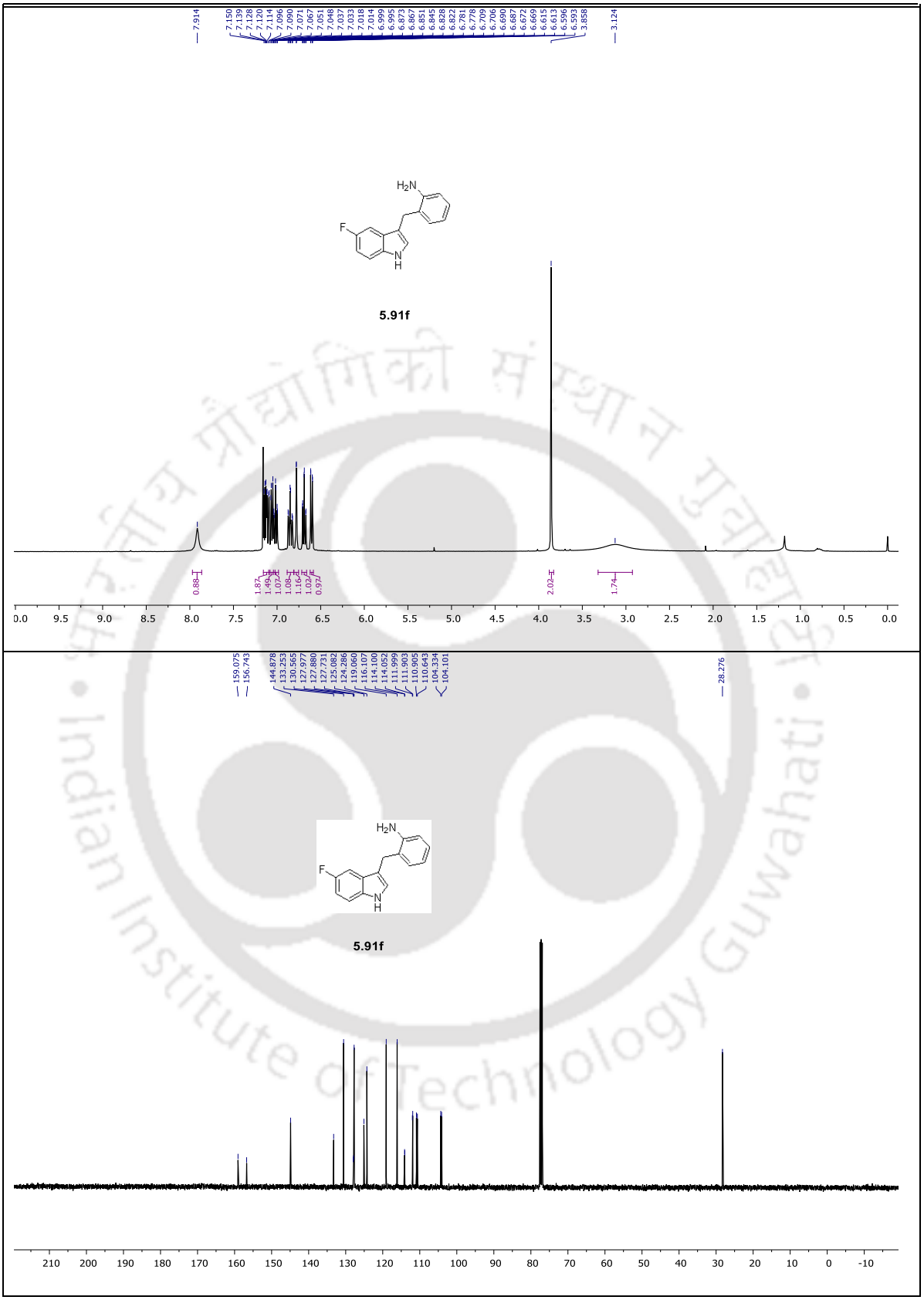


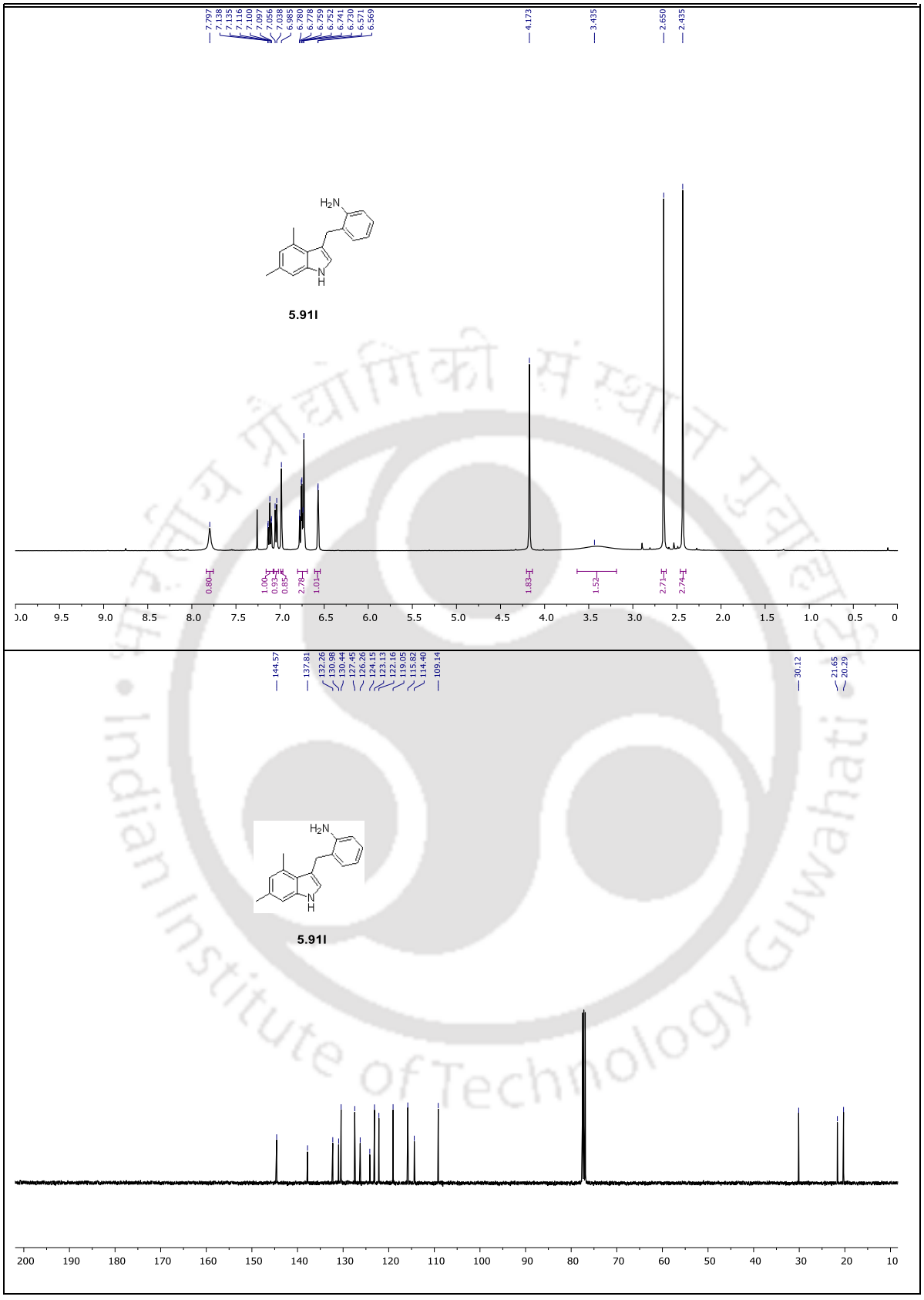


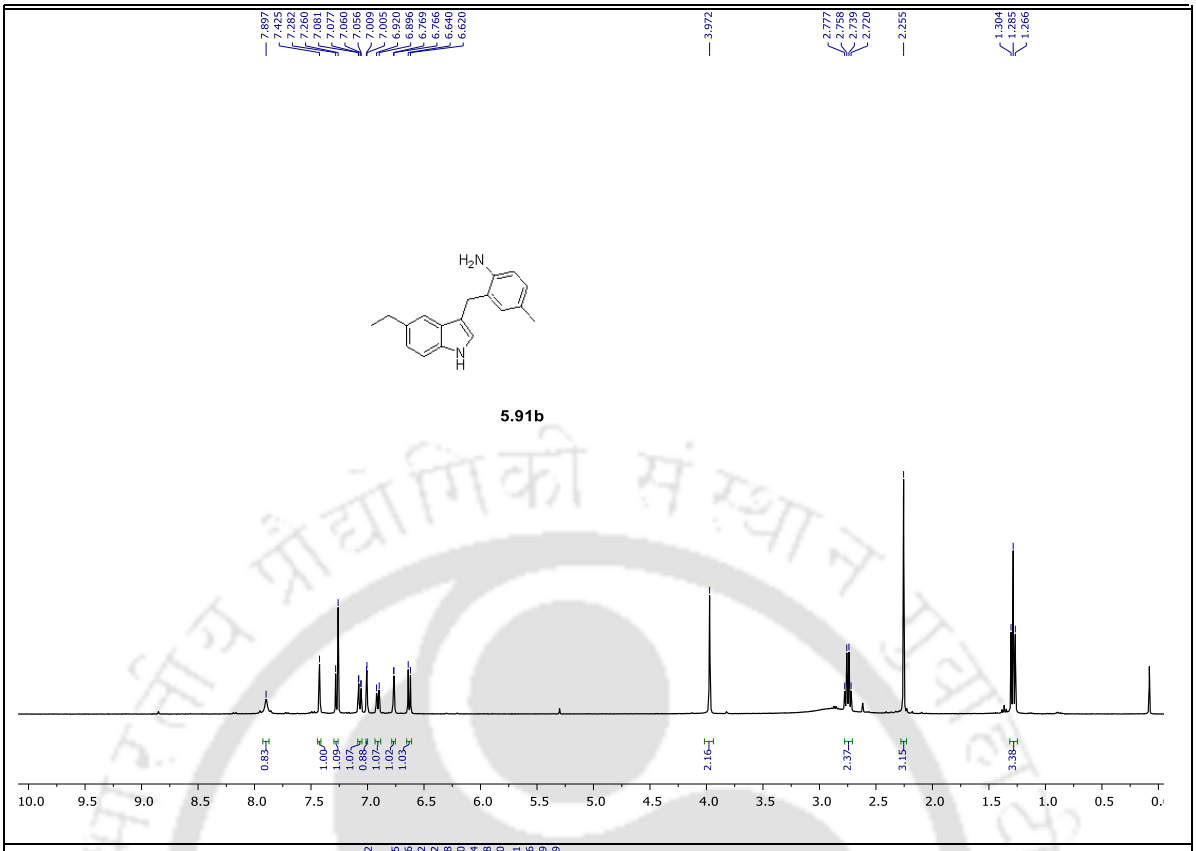


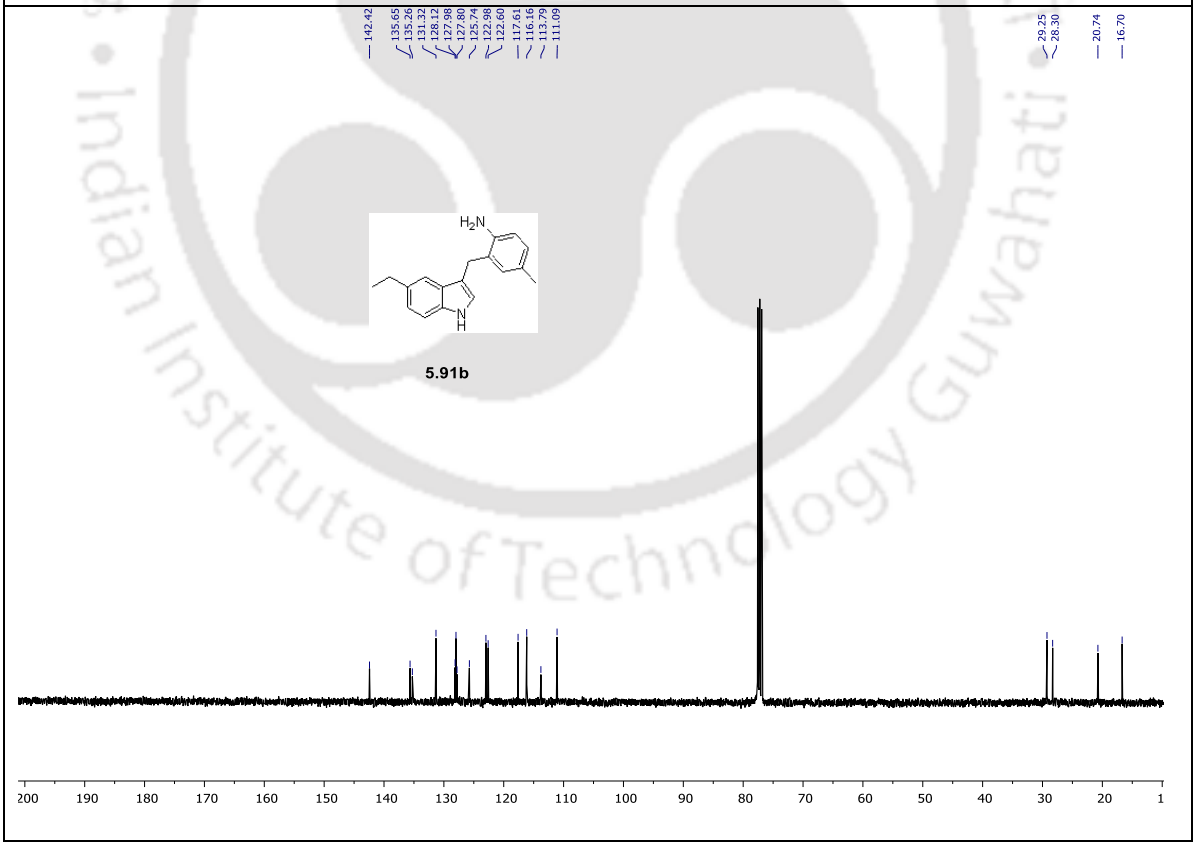


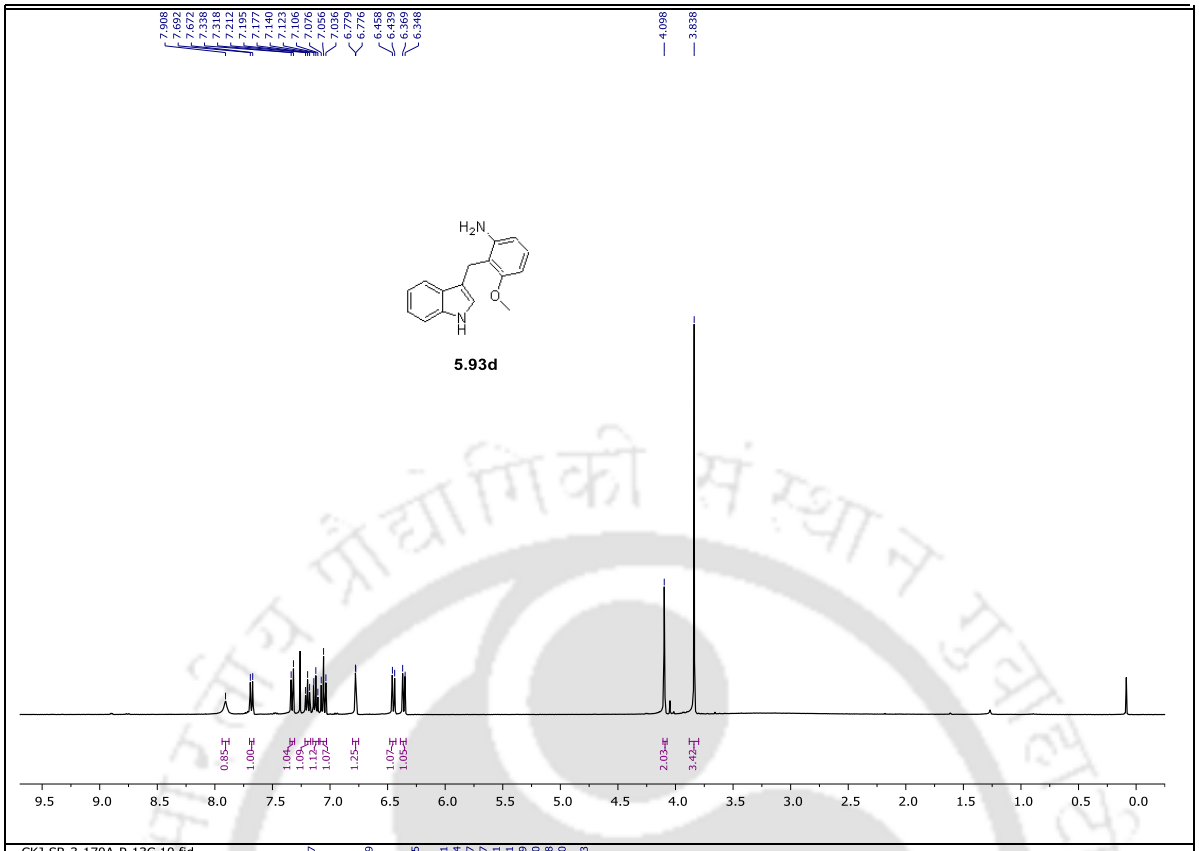


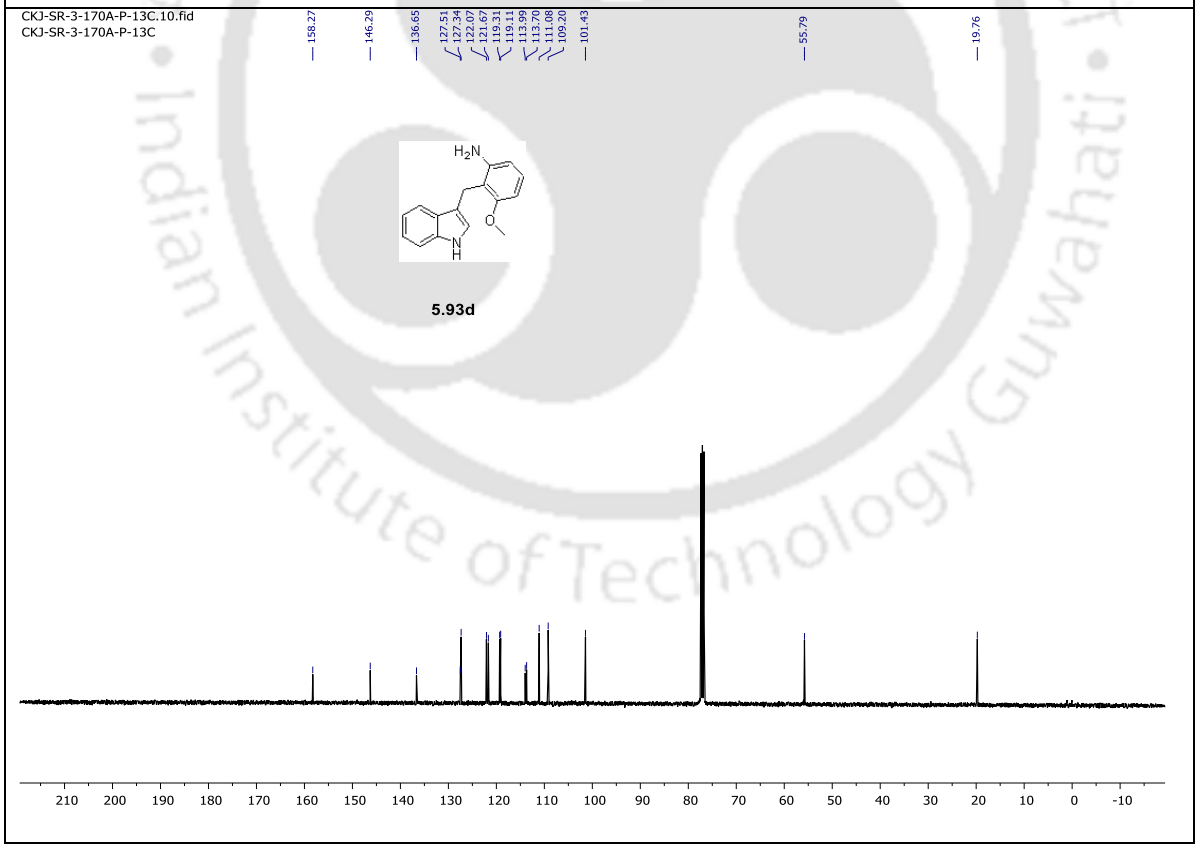


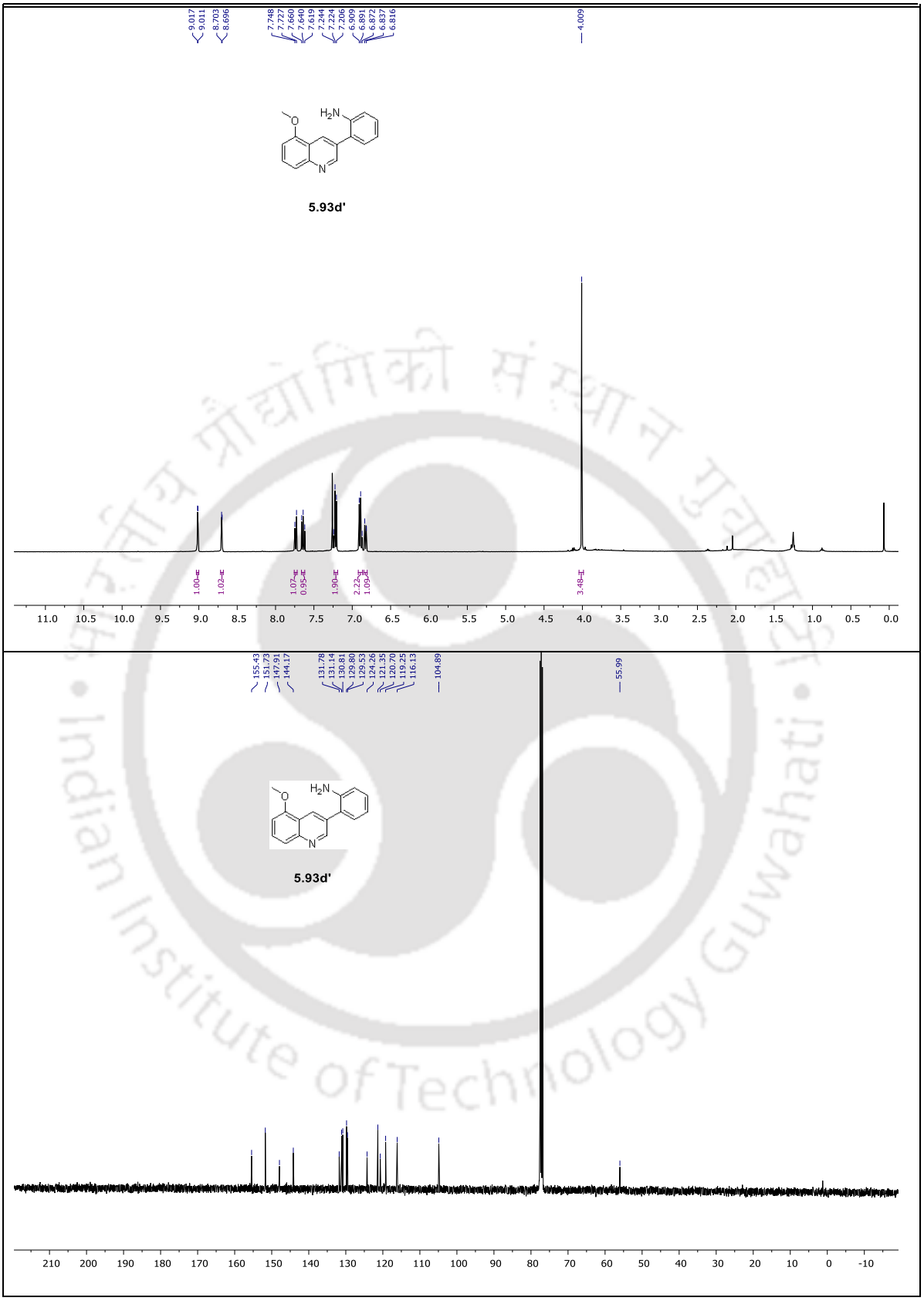


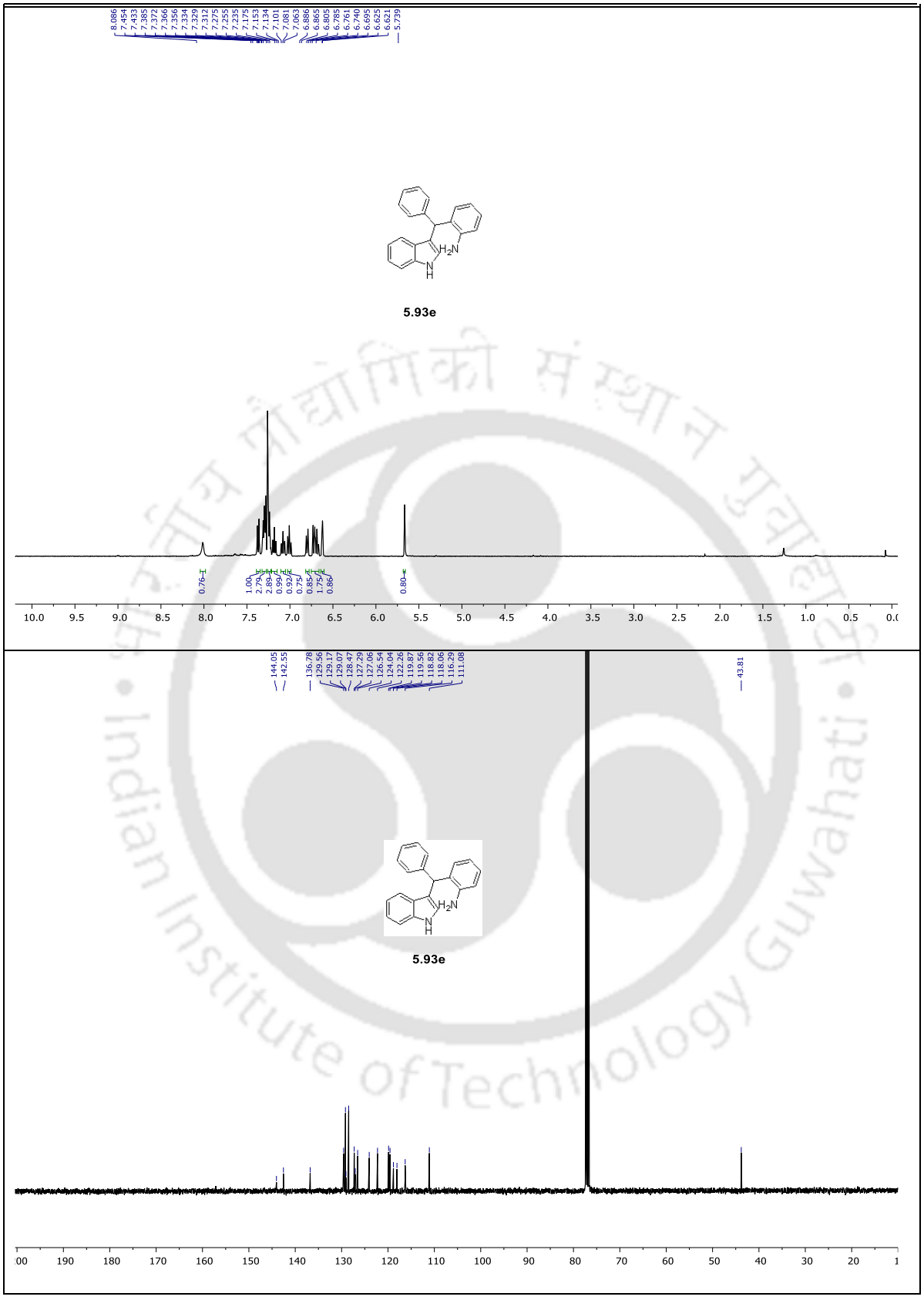


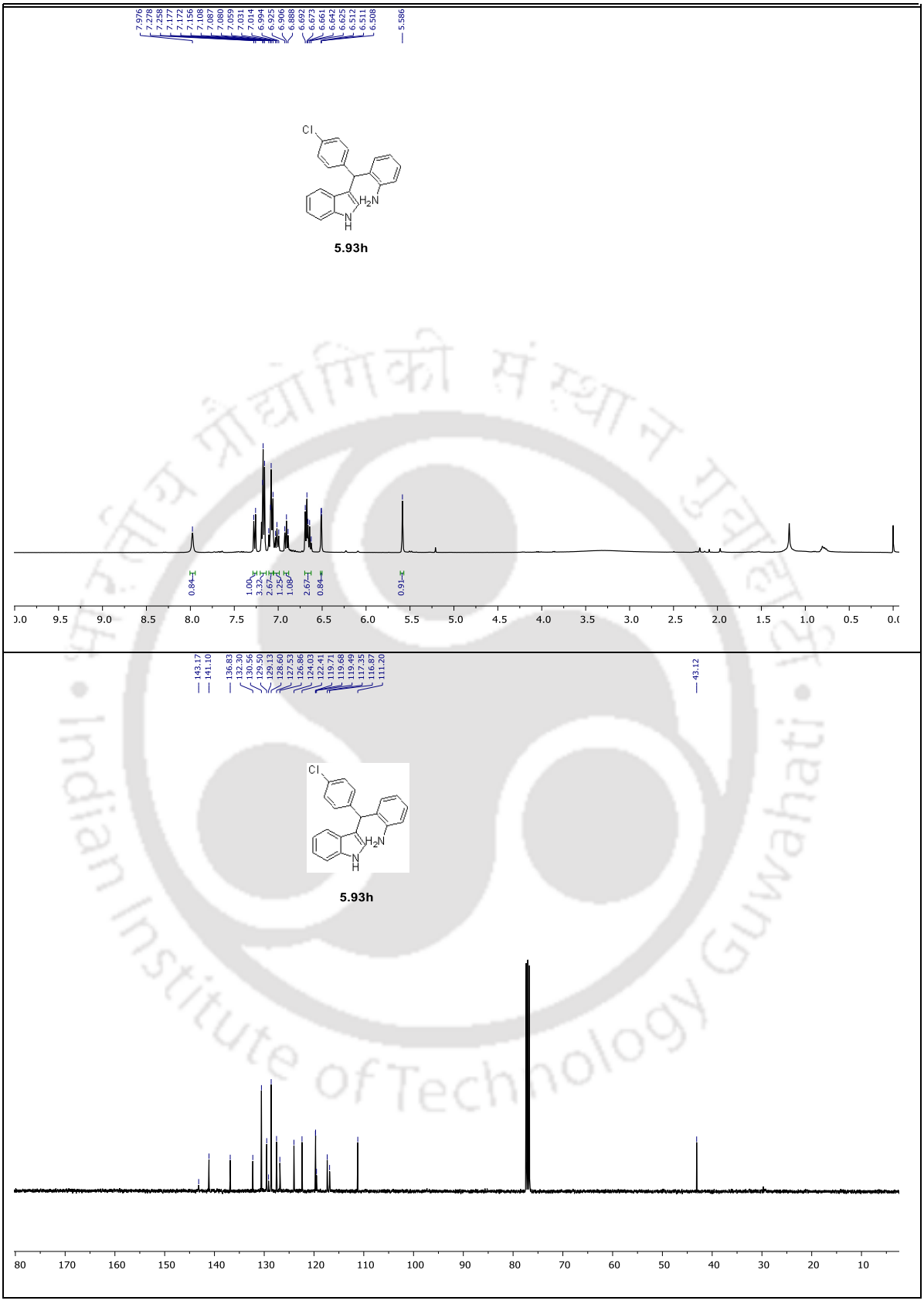


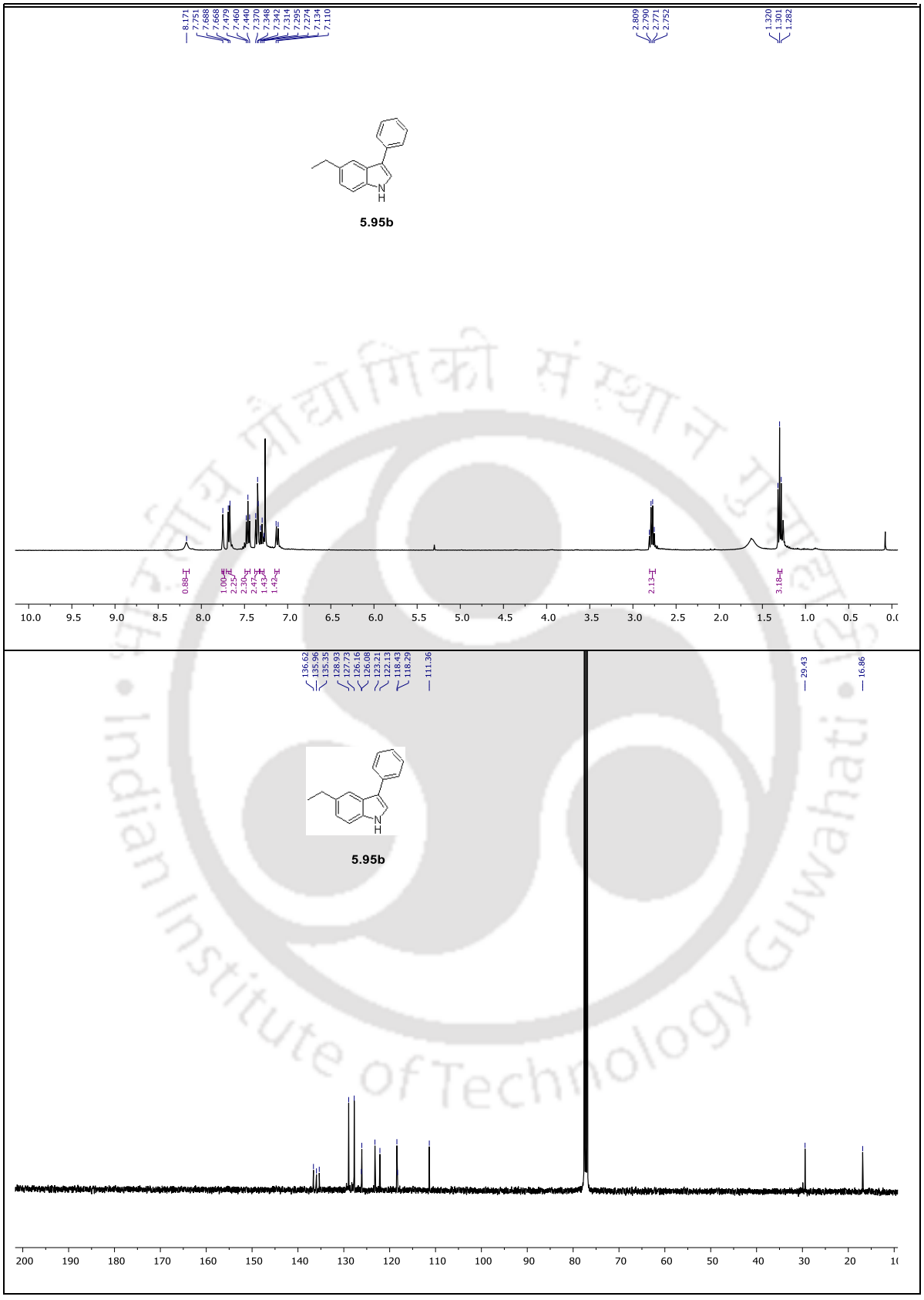


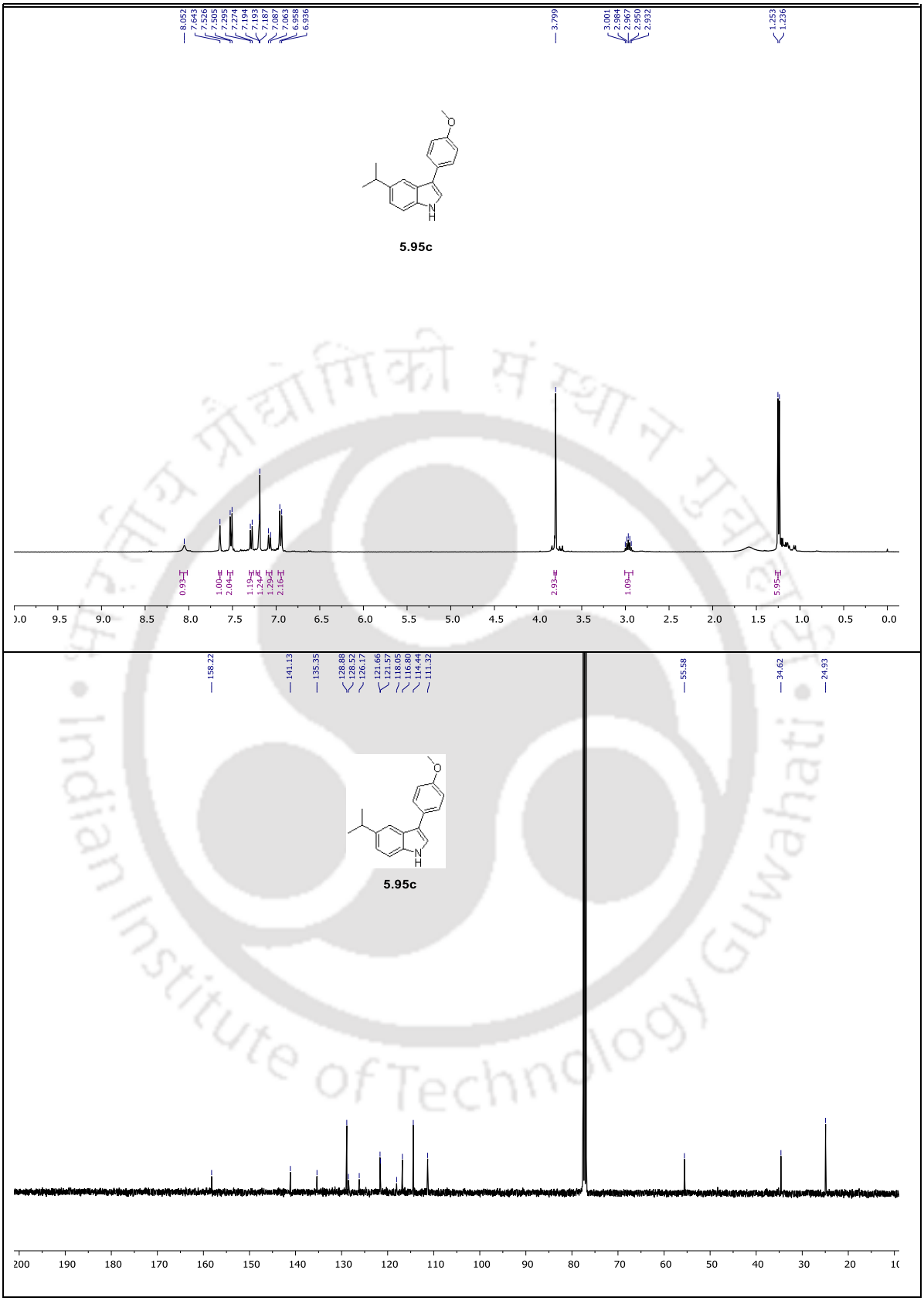


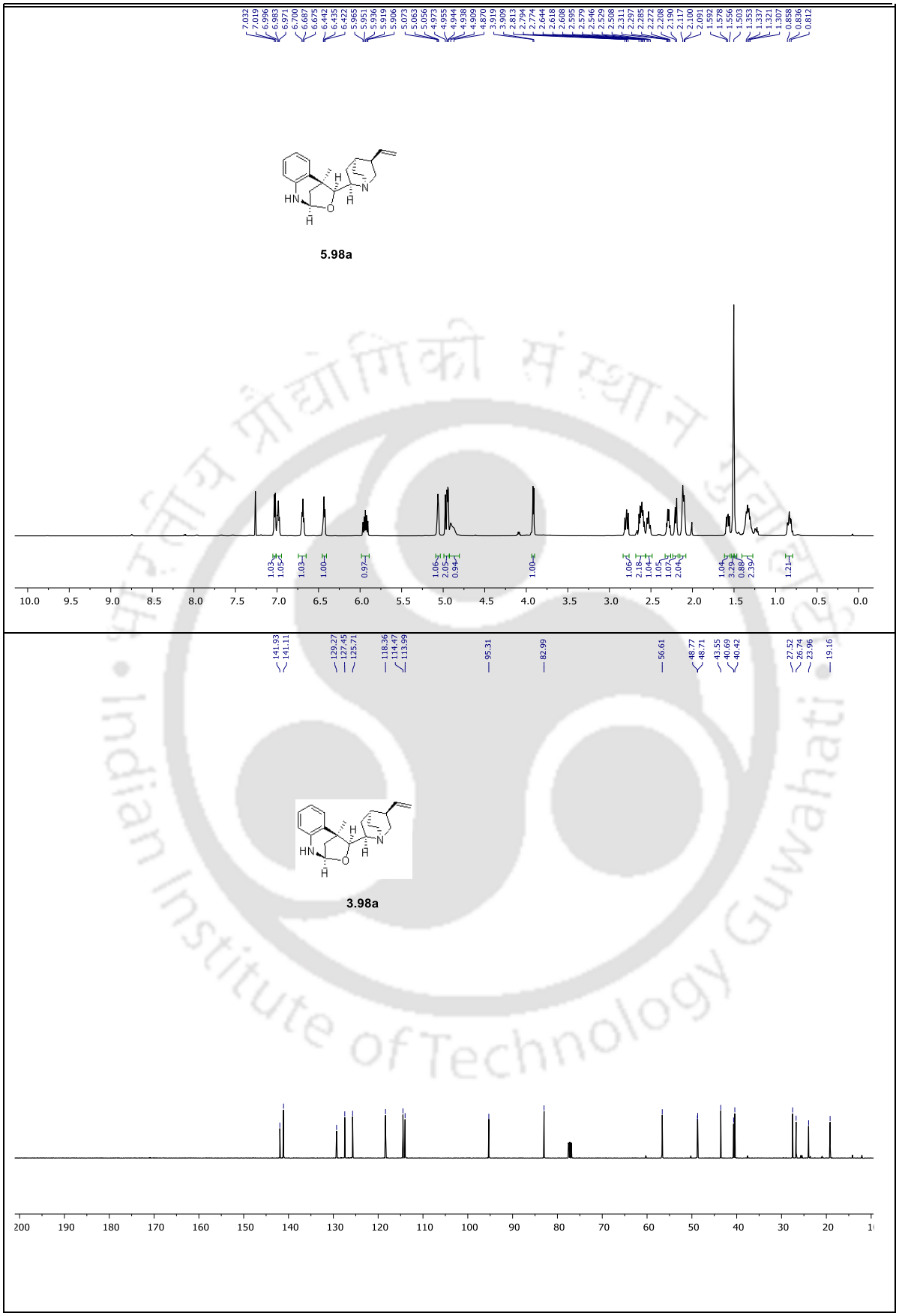


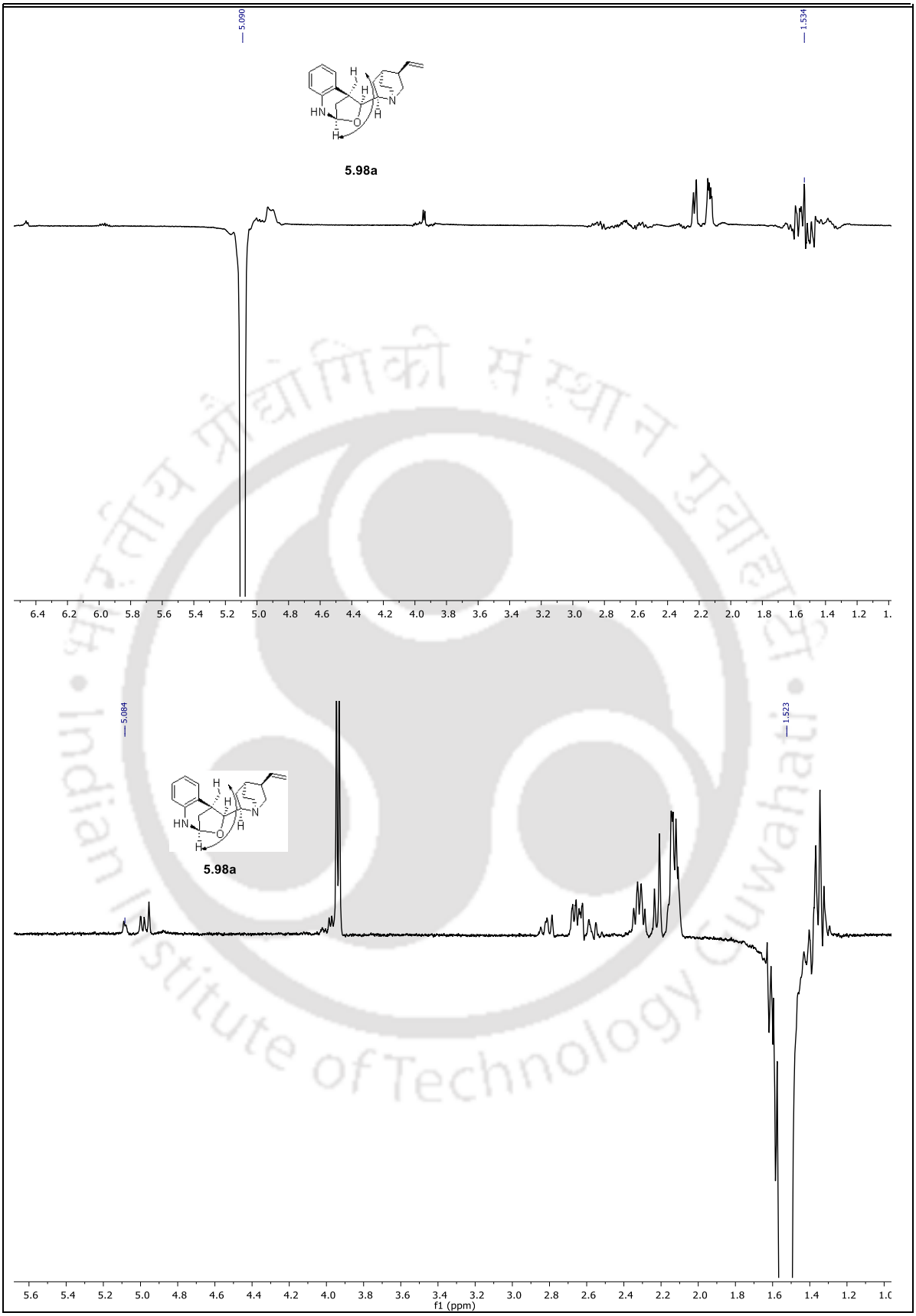


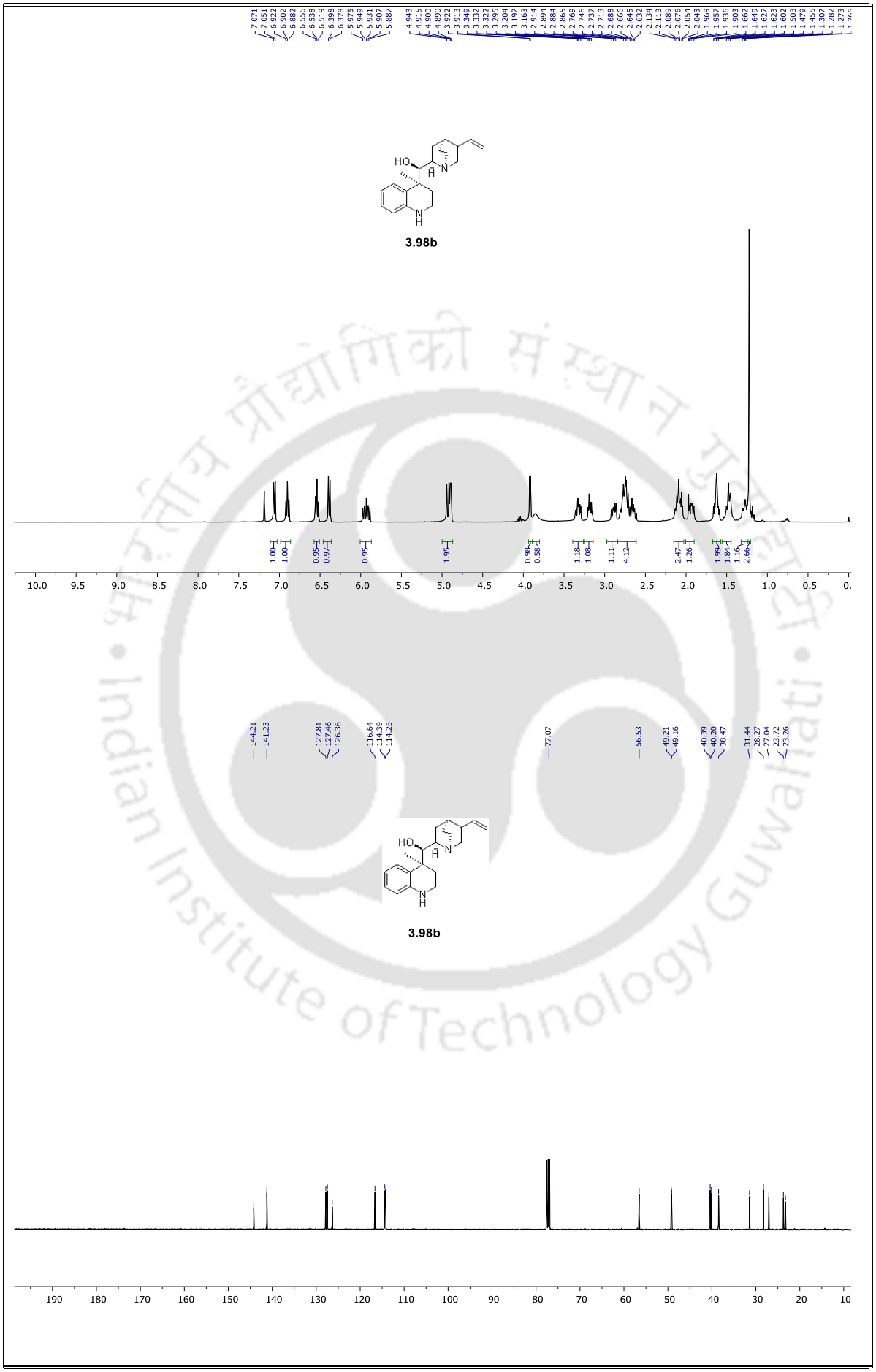


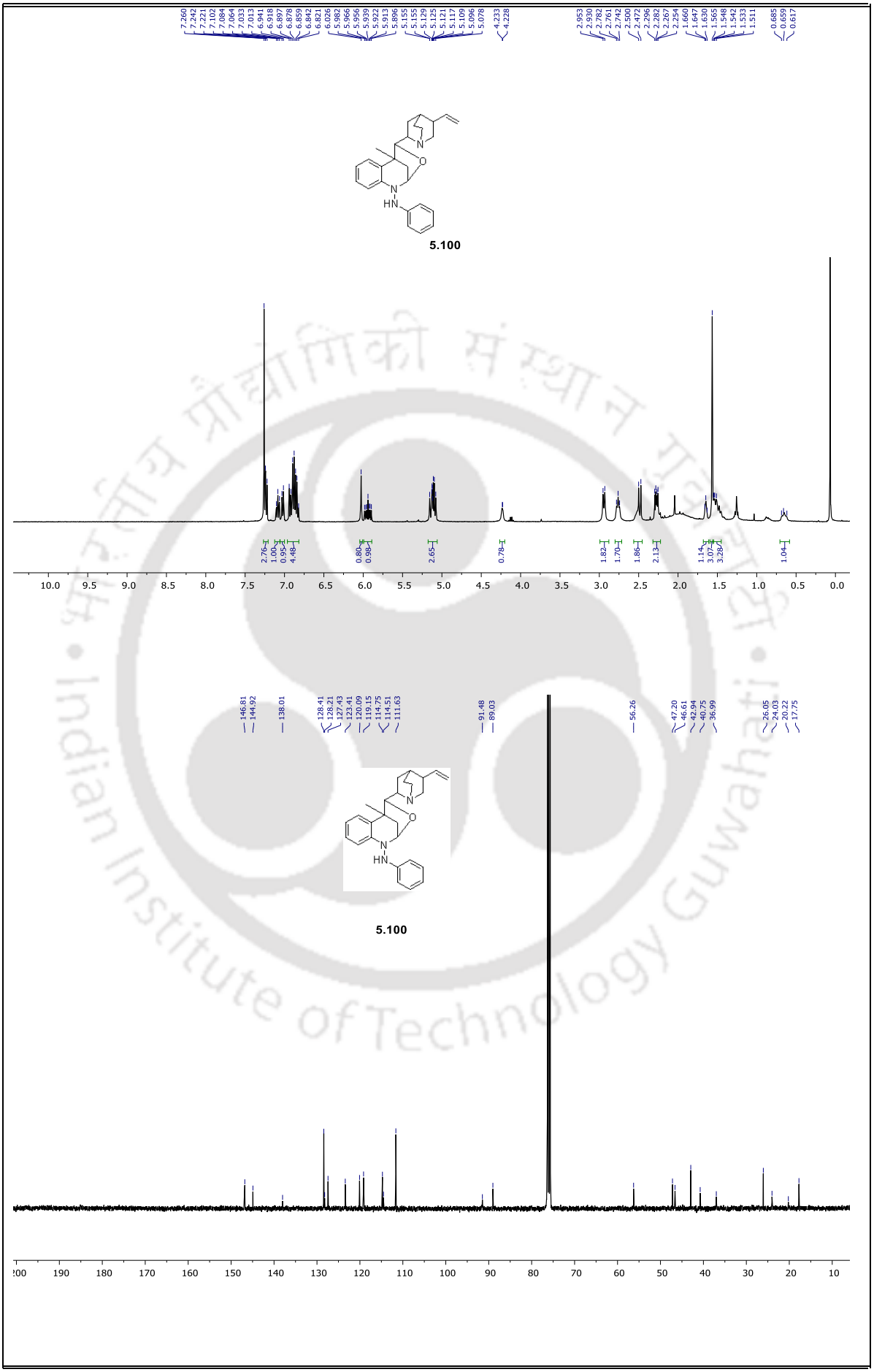


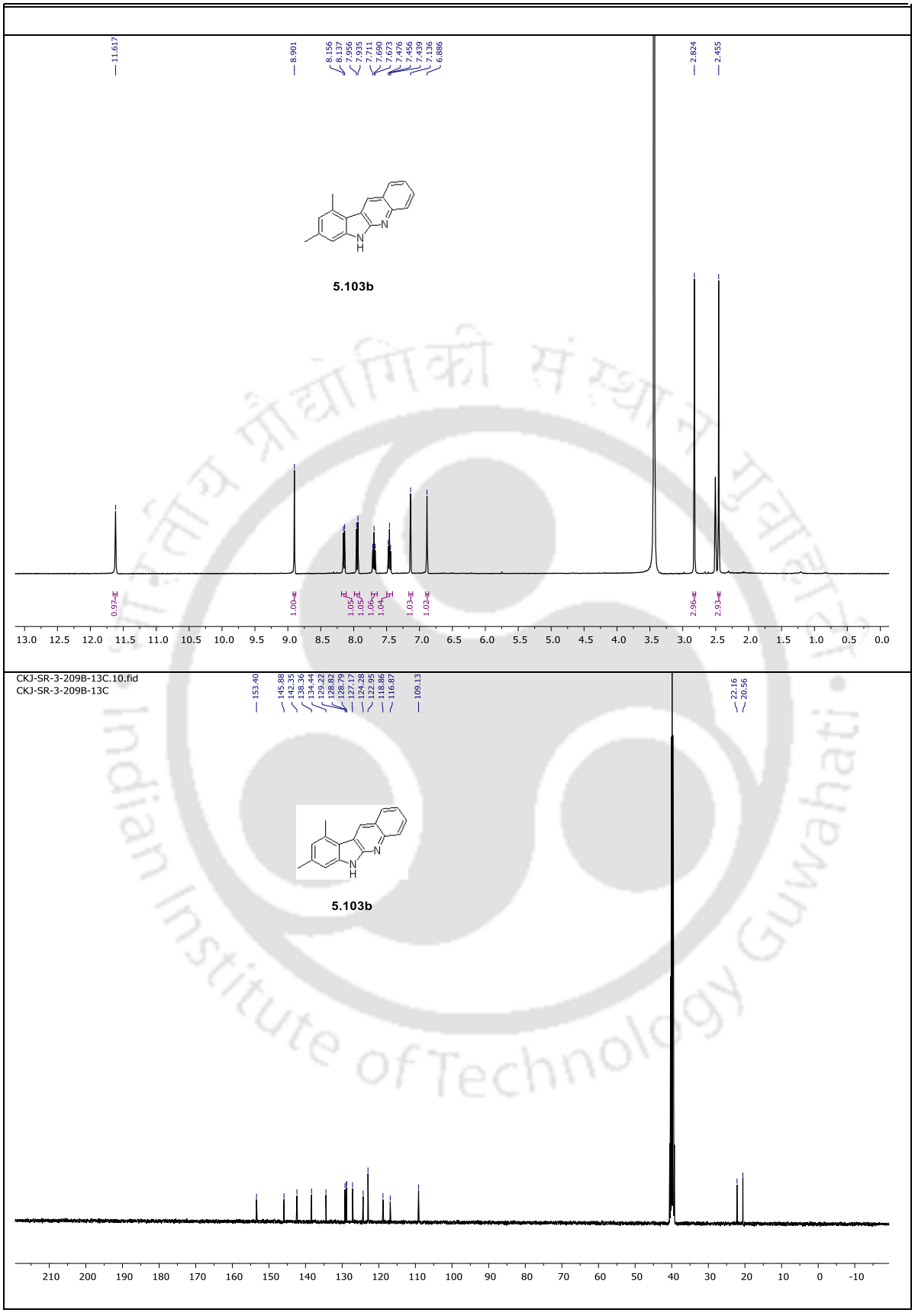


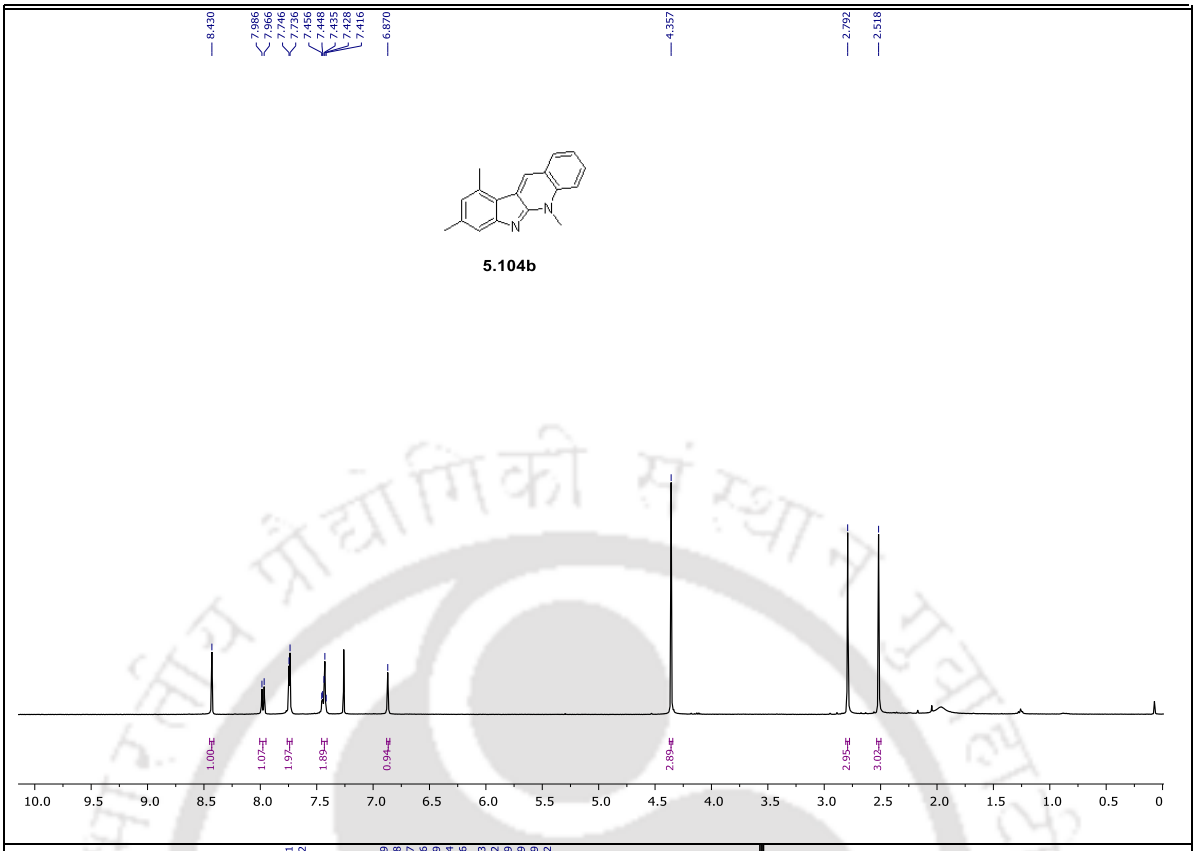


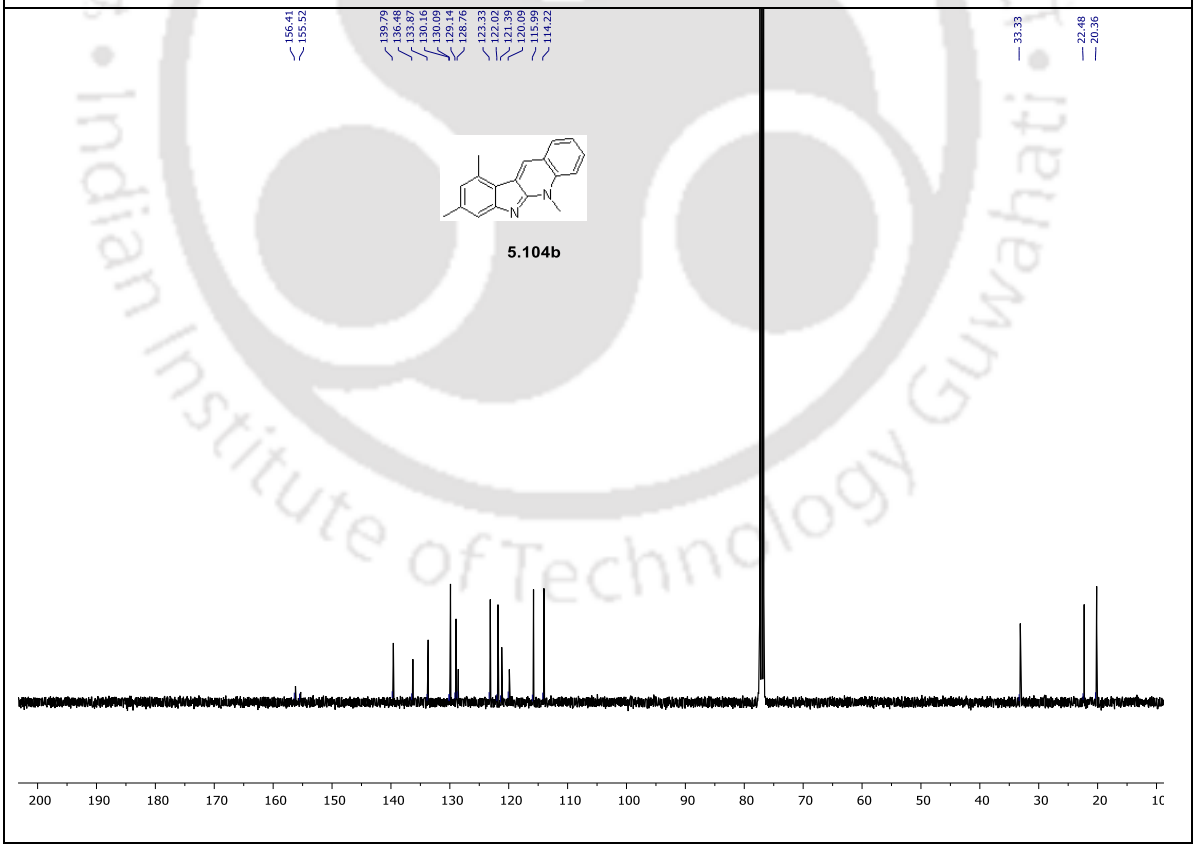


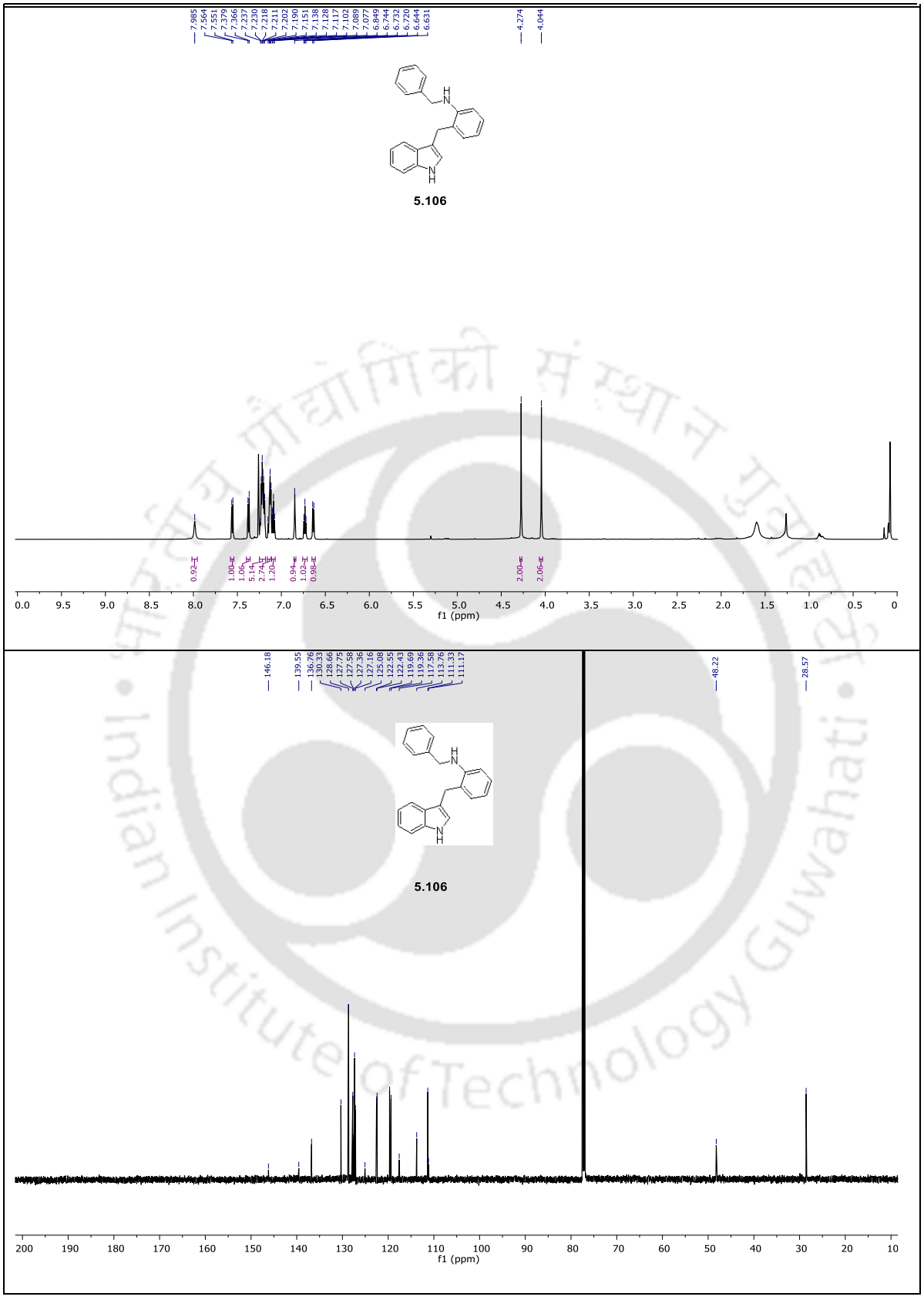


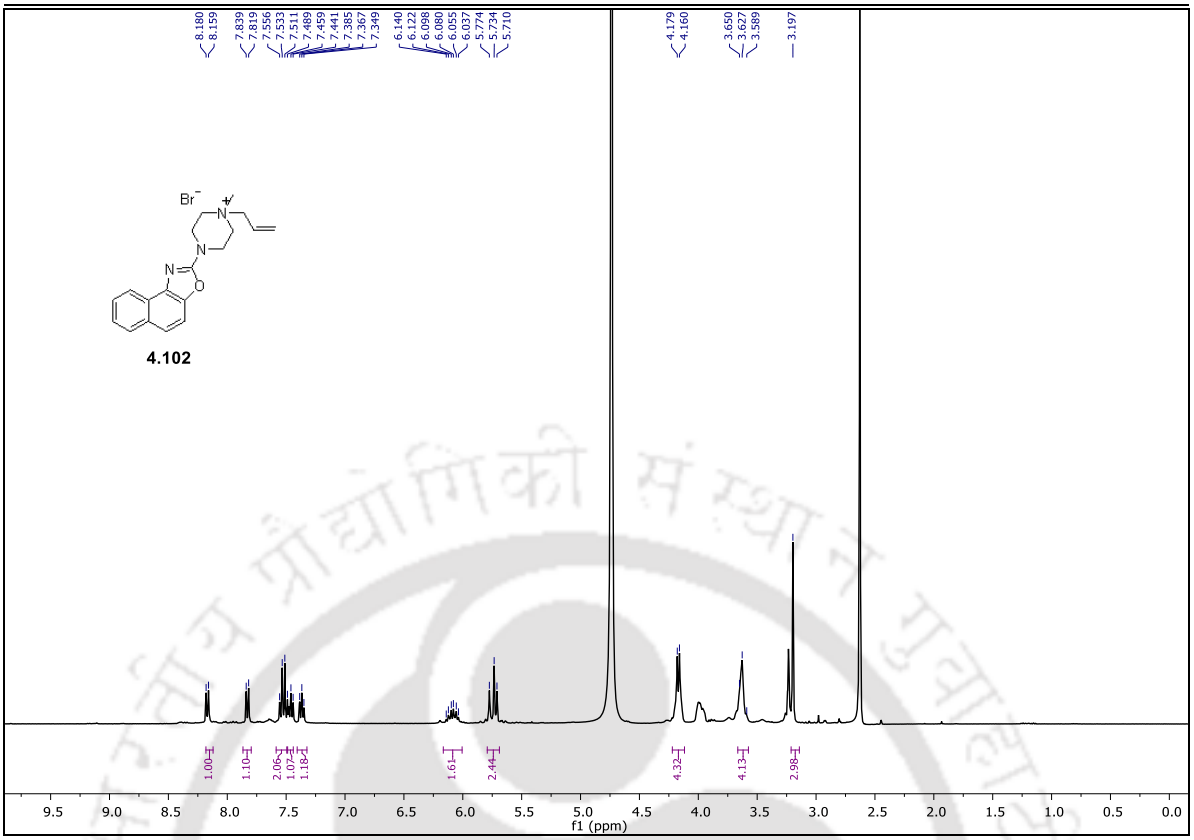


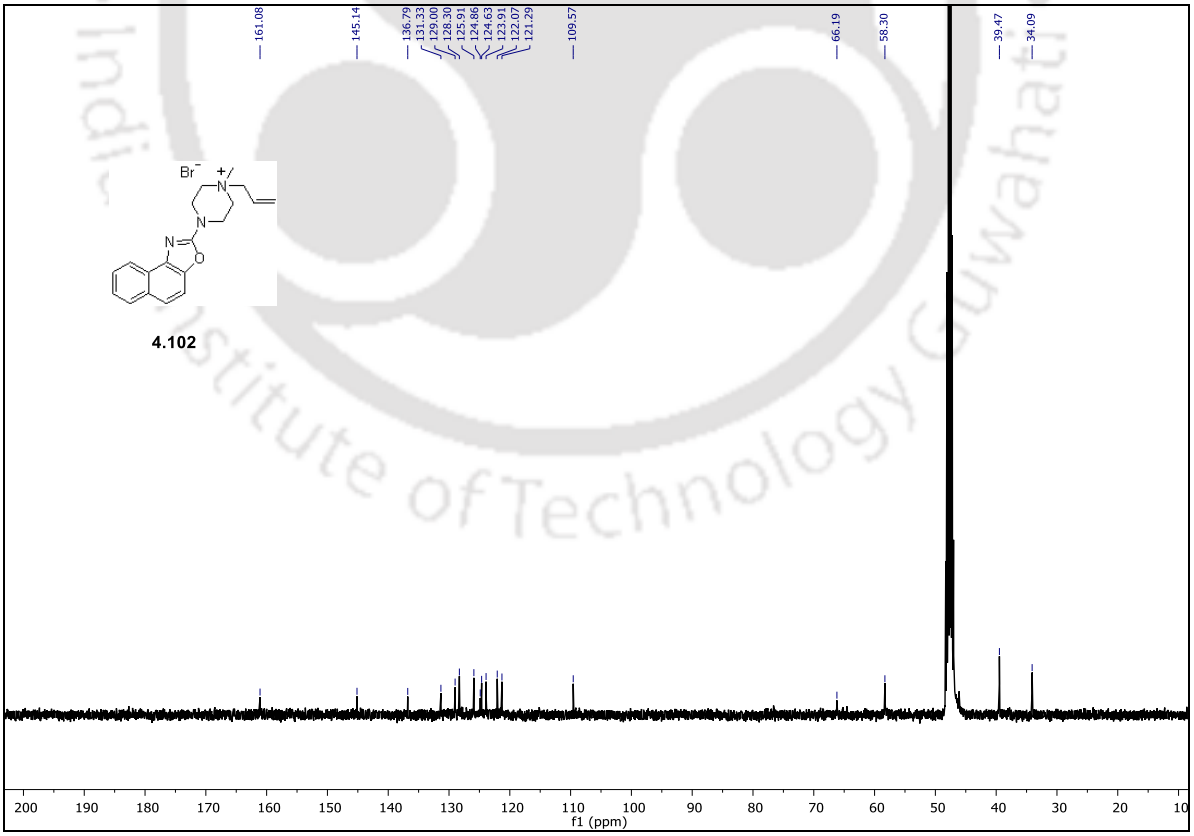




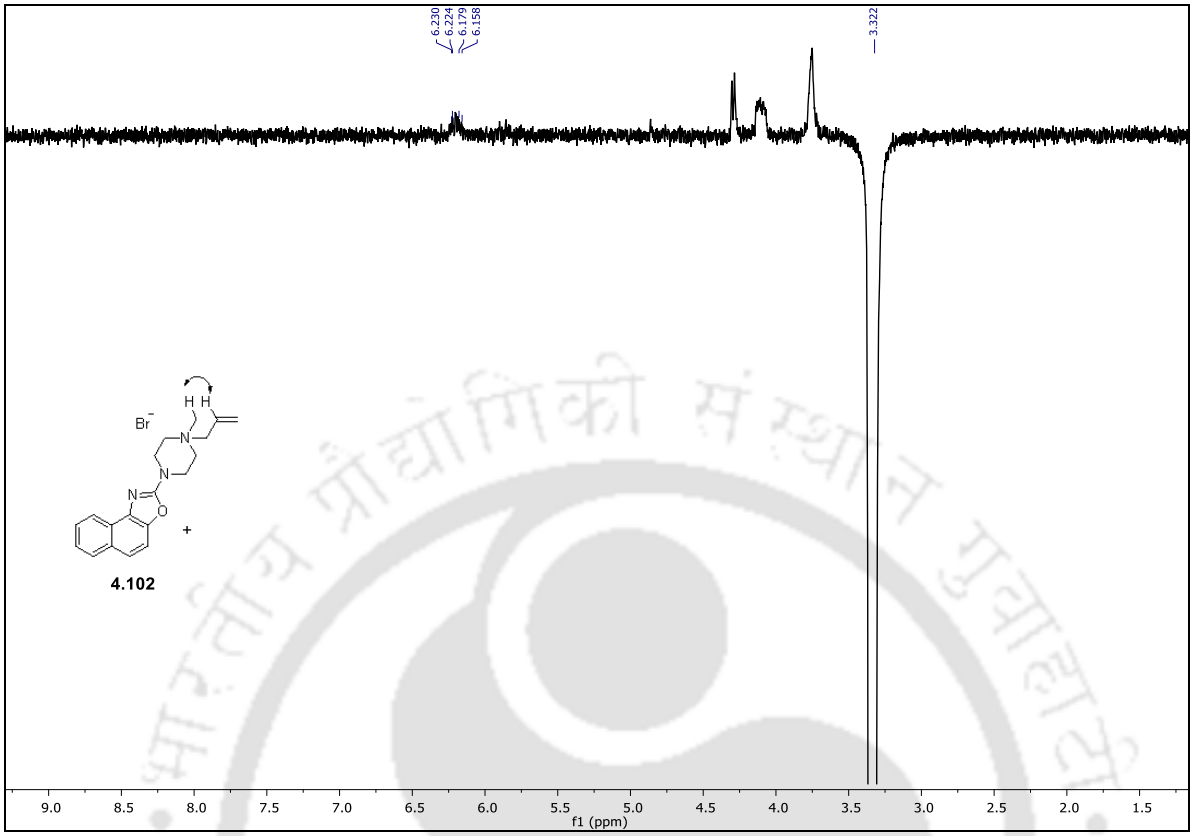


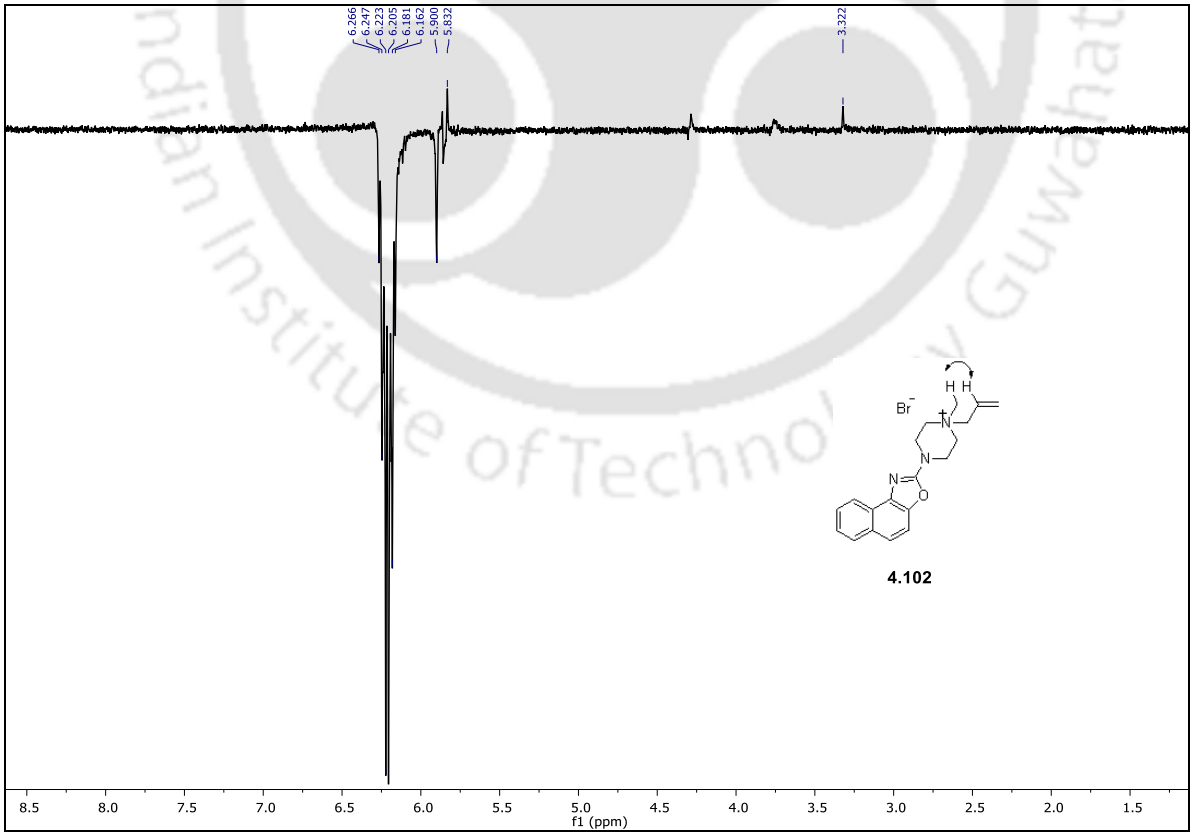






1D-NOE Spectra of **4.102**





Melting points of the solid compounds:

Compound	Melting point (^{o}C)	Compound	Melting point (^{o}C)
4.39	118-123	**4.42**	69-74
4.43	82-87	**4.44**	119-124
4.45	69-74	**4.48**	83-88
4.50	84-89	**4.51**	97-102
4.52	70-75	**4.54**	130-135
4.55	94-99	**4.56**	210-215
4.57	115-120	**4.58**	102-107
4.60	90-95	**4.66**	122-127
4.67	133-138	**4.68**	105-110
4.75	96-101	**4.76**	83-88
4.82	72-77	**4.83**	90-95
4.85	126-131	**4.94**	161-166
4.95	192-197	**4.96**	126-131
4.97	160-165	**4.98**	200-205
4.99	190-195	**4.100**	161-166
4.105	220-225	**5.91a**	118-123
5.91c	103-108	**5.91d**	93-98
5.91f	123-128	**5.91g**	158-163
5.91i	112-117	**5.91j**	114-119
5.91l	163-168	**5.91m**	110-115
5.91m'	135-140	**5.103a**	213-218
5.105a	146-151		