

Metal and Oxidant Free Direct C(sp³)-H Arylation of N-Heterocycles

A Dissertation

*Submitted in partial fulfilment of the
Requirements for the Degree of
Doctor of Philosophy*

By

Surajit Haldar



Department of Chemistry

Indian Institute of Technology Guwahati

Guwahati-781039

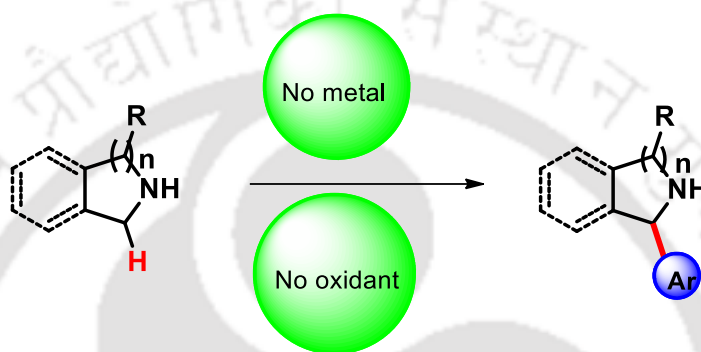
India

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STATEMENT

The work contained in this thesis entitled “**Metal and Oxidant Free Direct C(sp^3)-H Arylation of N-Heterocycles**” is the outcome of the research work carried out by me under the supervision of Dr. C. 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.

September, 2018

Surajit Haldar
(Roll No: 126122007)
Department of Chemistry
IIT Guwahati
Guwahati, Assam, India-781039





INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled “**Metal and Oxidant Free Direct C(sp³)-H Arylation of N-Heterocycles**” which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Surajit Halder (Roll No: 126122007) was carried out by him under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati

Dr. Chandan K. Jana
(Thesis supervisor)



Dedicated to my parents and family members





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List of Publications, Patent, and Presentations

1. **Halдар, S.**; Mahato, S.; Jana, C. K. "Metal and Oxidant Free Direct sp^3 C-H Arylation of Pyrrolidine". *Asian J. Org. Chem.* **2014**, 3, 44 – 47. (*This was listed as one of the top 20 Most Read articles from ChemPubSoc Europe, ACES, and GDCh journals in the month of December, 2013 and the work was highlighted in ChemistryViews*).
2. Mahato, S.; **Halдар, S.**; Jana, C. K. "Diastereoselective α -C-H Functionalization of Aliphatic N-heterocycles: An Efficient Route to Ring Fused Oxazines". *Chem. Commun.* **2014**, 50, 332 – 334. (*The work is highlighted in Synfacts 2014, 10, 399*)
3. **Halдар, S.**; Roy, S.K.; Maity, B.; Koley, D.; Jana, C. K. "Regio-, Diastereoselective 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*)
4. **Halдар, S.**; Saha, S.; Mandal, S.; Jana, C. K. "C-H Functionalization Enabled Stereo selective Ugi-azide reaction to α -tetrazoyl Alicyclic Amines." *Green. Chem.* **2018**, 20, 3463–3467.
5. **Halдар, S.**; Jana, C. K. "Direct (Het)Arylation of Tetrahydroisoquinoline via a Metal and Oxidant Free C(sp^3)-H Functionalization Enabled Three Component Reaction" *Org. Biomol. Chem.* **2018**, DOI: 10.1039/C8OB02309C. (*An invited article for the issue New Talent*).

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3. Presented a poster in **Research conclave-2017** held at Department of chemistry Guwahati, India.
4. Presented a poster in **National Symposium on Natural Products: Prospects and perspectives- 2016** held at NEIST, Jorhat, India.
5. Presented a poster in **Fics-2014** held at Department of chemistry, IIT Guwahati, Guwahati, India



Members of Doctoral committee

Dr. Chandan K. Jana (Thesis supervisor)

Prof. Gopal Das (Chairman)

Dr. Subhas Chandra Pan (Member)

Dr. Debapratim Das (Member)



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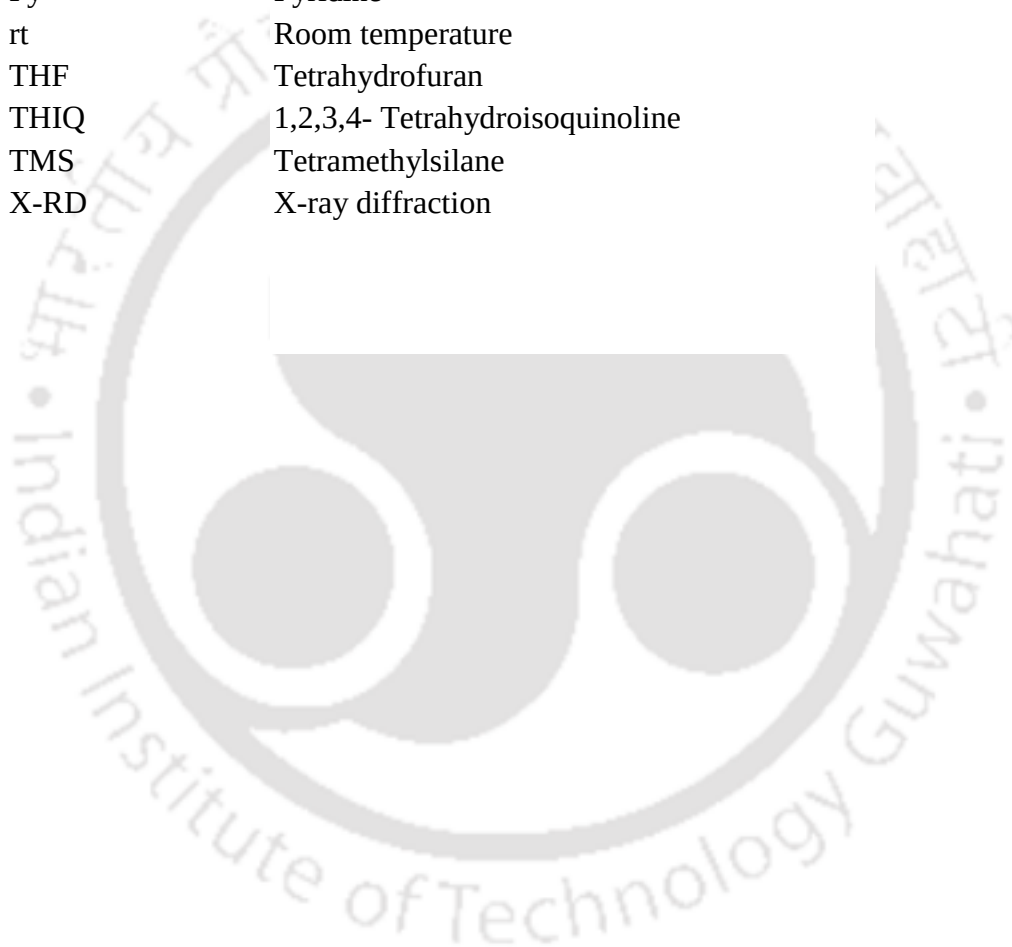




Abbreviation

APCI	Atmospheric pressure chemical ionization
Å	Angstrom
Ar	Argon
br.	Broad
Bn	Benzyl
Bu	Butyl
Boc	<i>tert</i> -butoxycarbonyl
1,4 BQ	Benzoquinone
ⁿ Bu	<i>n</i> -Butyl
Cat.	Catalytic/Catalyst
Cbz	Carboxybenzyl
CDCl ₃	Chloroform- <i>d</i>
CAN	Ceric ammonium nitrate
CDC	Cross Dehydrogenative Coupling
CH ₃ CN	Acetonitrile
CCDC	Cambridge crystallographic data centre
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
°C	Degree Celsius
Cu	Copper
d	Doublet or day
δ	Chemical shift or delta
DCM	Dichloromethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
<i>dr</i>	Diastereomeric ratio
EtOAc	Ethyl acetate
<i>ee</i>	Enantiomeric excess
equiv.	Equivalent
ESI	Electrospray ionization
Fl	Fluorenone
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
<i>p</i> TSA	<i>p</i> -Toluenesulfonic acid
Py	Pyridine
rt	Room temperature
THF	Tetrahydrofuran
THIQ	1,2,3,4- Tetrahydroisoquinoline
TMS	Tetramethylsilane
X-RD	X-ray diffraction



Abstract

The contents of the thesis entitled “**Metal and Oxidant Free Direct C(sp³)-H Arylation of N-heterocycles**” have been divided into six chapters based on the results of experimental works performed during the complete course of the research period. Carbon–hydrogen bonds are abundant in most organic molecules. Methods for their direct and selective functionalization are attractive as an efficient means to access more complex molecular structure. The first chapter of the thesis presents a review on different aspects of C-H arylation of secondary amines. Chapters 2-4 describes the studies on the metal and oxidant free direct C(sp³)-H arylation of *N*-heterocycles (e.g. pyrrolidine, substituted pyrrolidines, 1,2,3,4-tetrahydroisoquinoline and β -carboline). Chapter 2 describes metal and oxidant free route to direct C(sp³)-H arylation of pyrrolidine. In Chapter 3, a regio-, diastereo and enantiospecific metal free C(sp³)-H arylation of 2-substituted pyrrolidines has been described. The method was found to be efficient for the synthesis of optically active 5-aryl-2,5-disubstituted pyrrolidine. Chapter 4 describes direct C-H arylation of 1,2,3,4-tetrahydroisoquinoline and β -carboline under metal, oxidant, and solvent free conditions. C-H functionalization enabled stereoselective Ugi-azide reaction of *N*-heterocycles to α -tetrazolyl alicyclic amines has been described in chapter 5. Finally, Chapter 6 contain the copies of ¹H, ¹³C NMR spectra, and HPLC chromatogram, of selected new compounds respectively.

Chapter 1: C(sp³)-H Arylation of Secondary Amines

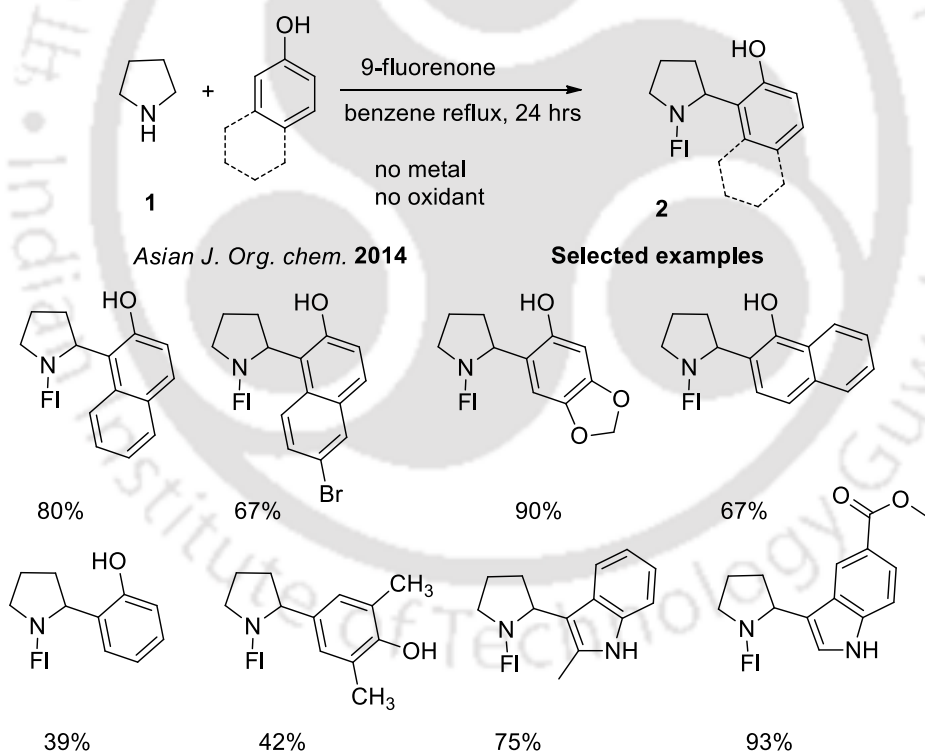
An aryl group at the α -position of an amine is frequently observed in drug molecules, natural products and auxiliaries/or catalyst for asymmetric transformations. This chapter summarizes the known strategies for the synthesis of arylated *N*-heterocycles. Sometimes, *N*-cycloalkylation strategies involving chiral amines were adopted for the synthesis of arylated *N*-heterocycles. α -deprotonation of *N*-Boc-protected pyrrolidine with a strong base followed by transmetallation and subsequent coupling with arene based substrates has been widely used for the preparation of α -arylated pyrrolidine. One of the approaches involves transition metal catalyzed directed arylation of *N*-heterocycles. Metal and photo catalyzed Cross-Dehydrogenative- Coupling (CDC) reaction of arene and *N*-heterocycles have been popular for the synthesis of arylated *N*-heterocycles. Arylated *N*-heterocycles were also synthesised from pre-functionalized and pre-oxidized *N*-heterocycles. However the practical applications of these are limited due to involvement of toxic and expensive metal catalyst, oxidants and harsh reaction

conditions. Therefore the main aim of the thesis is to develop of novel synthetic methodologies, which are environment friendly and free from the aforementioned difficulties.

Chapter 2: Metal and Oxidant Free Direct C(sp³)-H Arylation of Pyrrolidine

All of the known protocol for direct arylation of saturated *N*-heterocycles generally involve the use of organometallic reactants either in stoichiometric and/or catalytic amount in the presence of toxic oxidants. In another approach preoxidized starting materials were used for the arylation with or without metal-based reagents. Therefore, all of these known processes produce toxic chemical wastes, which are a burden to the environment.

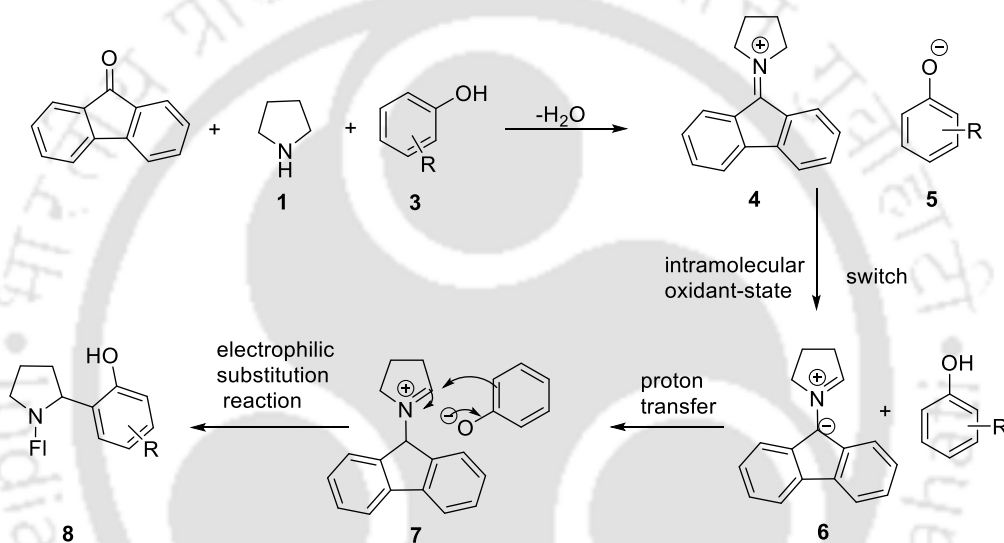
A metal-free, oxidant-free, atom-economic and operationally simple method for direct α -C-H arylation of pyrrolidine via a three component reaction, without any additional aid has been developed. Arylated pyrrolidines were formed from the reaction of pyrrolidine and electron rich arene in the presence of 9-fluorenone under reflux in benzene with excellent yield. The method is highly regioselective and very efficient even on a gram scale.



Scheme 1: Direct C-H arylation of pyrrolidine by electron rich nucleophiles, phenols naphthols and indoles.

Based on the experimental findings a mechanistic proposal for the metal- and oxidant-free atom-economic α -C-H arylation of pyrrolidine is presented in Scheme 2. Pyrrolidine condenses with 9-fluorenone with the assistance of the phenolic OH group (3 as a proton source) to form the corresponding iminium cation 4, which is accompanied by phenolate

anion **5**. Base-(pyrrolidine or phenolate) aided isomerization of parent iminium ion **4** occurs to produce the azomethine ylide **6**, which has a fluorenyl anion moiety that is stabilized by its aromaticity. A secondary iminium ion **7** is probably formed through protonation of azomethine ylide **6**. The oxidation state switch from the fluorenone carbon in **4** to the C2 position of pyrrolidine in **7** eliminates the possibility of Mannich or Betti product formation. Then, the secondary iminium ion **7** reacts with the phenolic compound by an aromatic electrophilic substitution reaction to provide the α -arylated product **8**. The close association (as shown in Scheme 2) of the electrophilic iminium ion **7** with the nucleophilic phenolate anion probably directs the reaction entirely through the *ortho* position and consequently brings the exclusive regioselectivity.

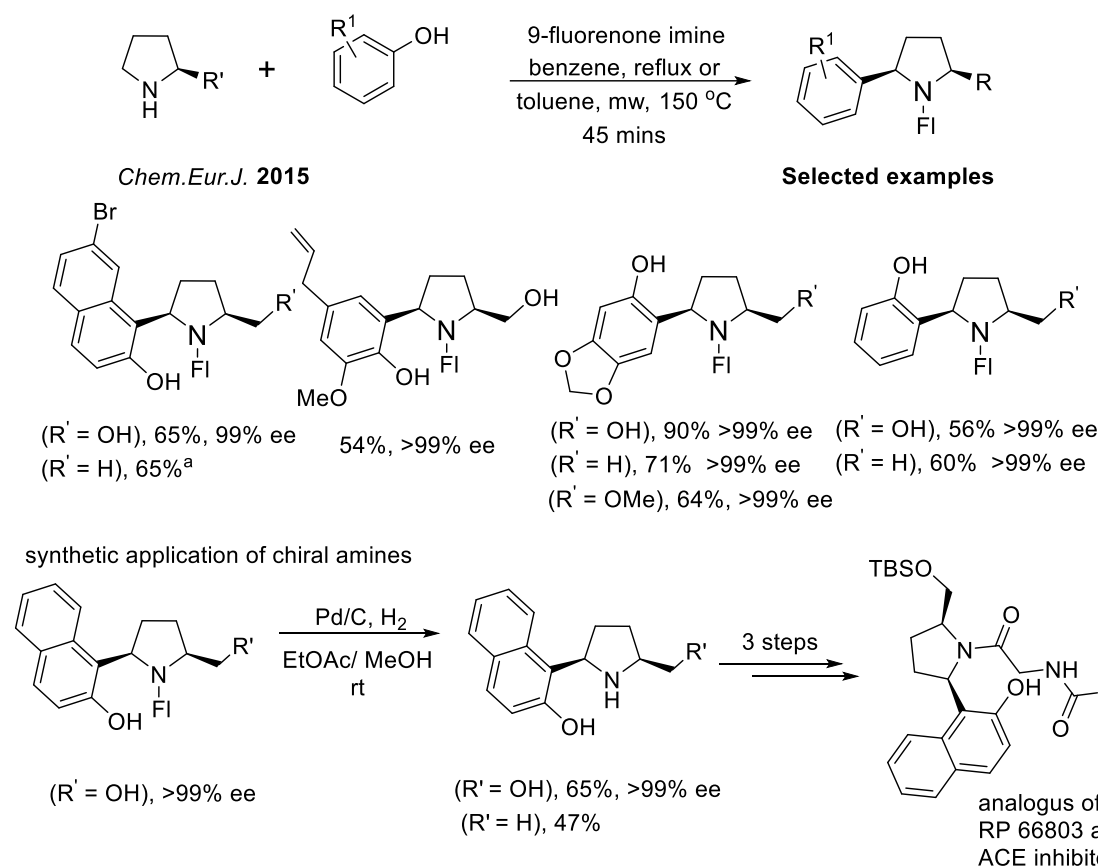


Scheme 2: Proposed reaction mechanism for metal free arylation of pyrrolidine.

Chapter 3: Regio-, Diastereo-selective and Enantiospecific Metal Free C(sp³)-H Arylation: A Facile Access To Optically Active 5-aryl 2,5-Disubstituted Pyrrolidine

Optically active 5-aryl-2,5-disubstituted pyrrolidines are the principal structural moieties of many bioactive compounds including natural products and catalysts for asymmetric synthesis. Various methods have been reported for the synthesis of the arylated pyrrolidines. However, strategies for syntheses of these molecules in enantiomerically pure form are limited. A highly regio- and diastereo-selective and enantiospecific method for direct α -CH arylation of substituted pyrrolidine has been developed under metal and oxidant free conditions. Structurally diverse enantiopure arylated pyrrolidines were synthesized from commercially available starting materials, through a single-step three-component reaction under metal- and oxidant-free

conditions. Optically active arylated pyrrolidine was shown to be useful for the easy and efficient synthesis of structural analogues of RP 66803 and ACE inhibitors. Furthermore, DFT studies were performed to explore the mechanistic route for the selective C-H arylation reaction.

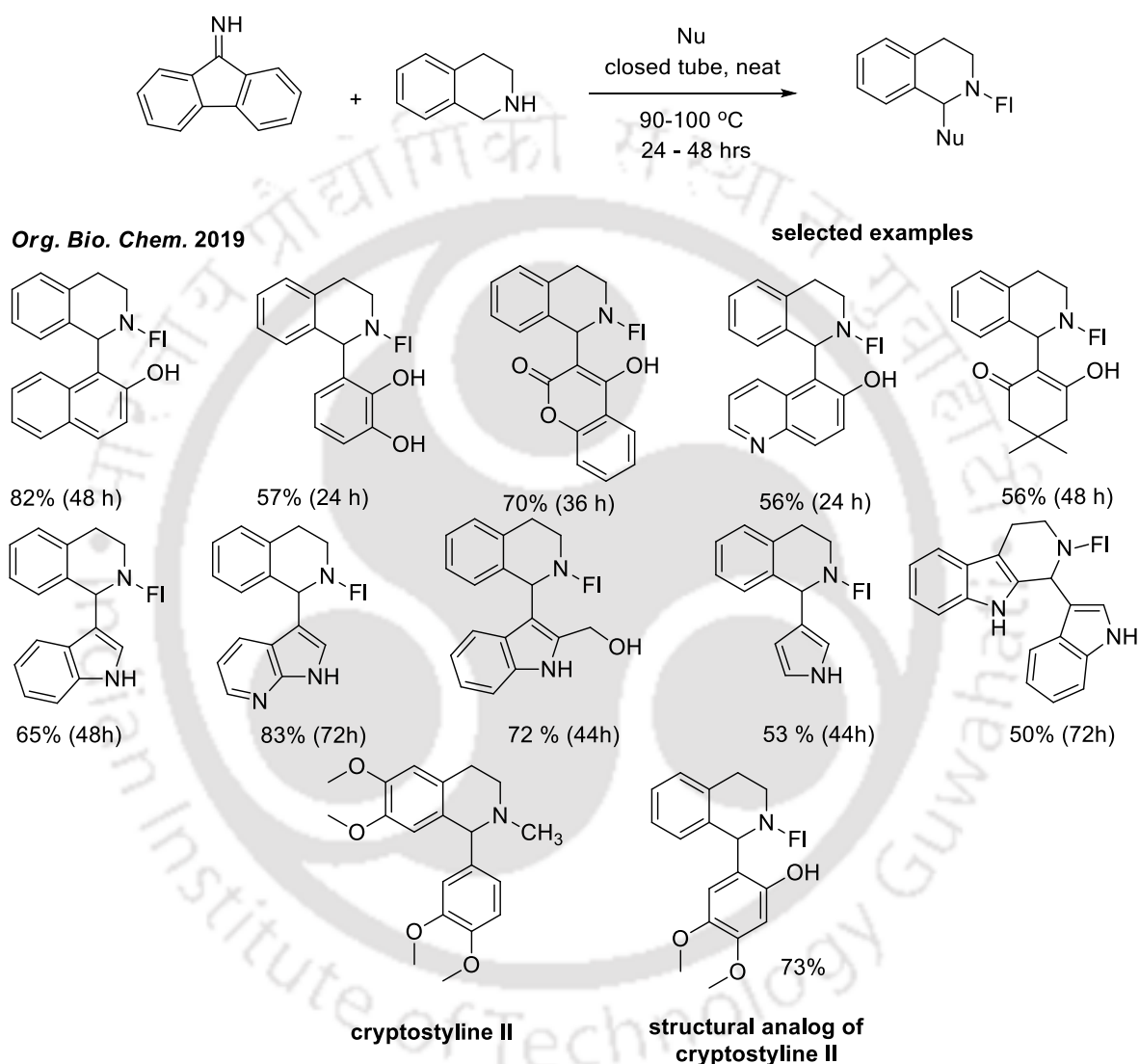


Scheme 3: Direct stereoselective C-H arylation of substituted pyrrolidines and synthetic application of chiral amines. ^a The reaction were carried out with racemic amine.

Chapter 4: Metal, Oxidant and Solvent Free Direct C(sp³)-H Arylation of 1,2,3,4-Tetrahydroisoquinolines and β -Carbolines

Tetrahydroisoquinoline is a privileged heterocyclic skeleton and a variety of its natural and unnatural derivatives exhibit wide range of biological activities. Therefore, a number of methodologies for the efficient preparation of such compounds have been developed. Pictet–Spengler condensation and the Bischler–Napieralski cyclization/reduction sequence were mostly used. α -C–H arylation of THIQs presents a novel synthetic strategy for direct access to this molecules. Toxic and expensive transition metal catalysts, oxidants and harsh conditions, which limit their practical application, were mainly used in most of the known strategies. An operationally simple, highly atom economic three component reaction for

efficient and high yielding $C(sp^3)$ -H bond functionalization of 1,2,3,4-tetrahydroisoquinolines and β -carbolines have been developed under metal, oxidant and solvent free condition. The method also allowed the synthesis of the structural analogues of cryptostyline II.

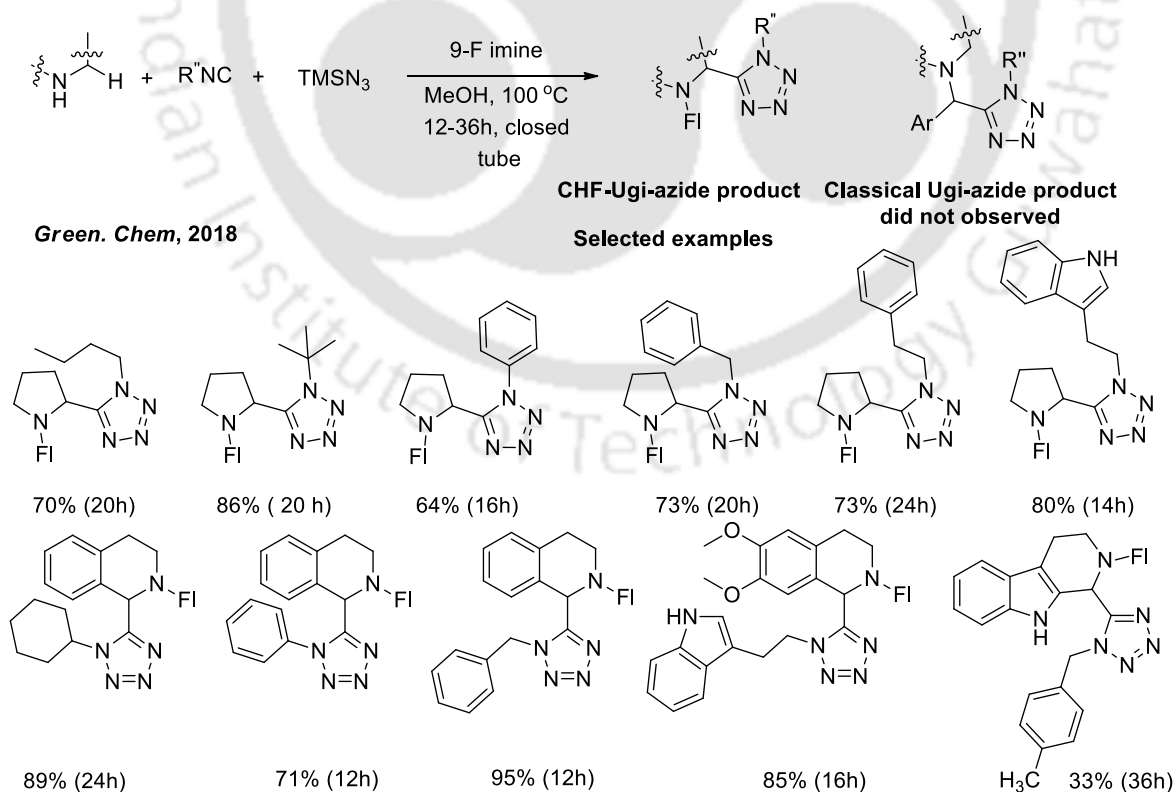


Scheme 4: Direct C-H Arylation of 1,2,3,4-tetrahydroisoquinoline and β - carboline.

Chapter 5: C-H Functionalization Enabled Stereoselective Ugi-azide reaction to α -tetrazoyl Alicyclic Amines

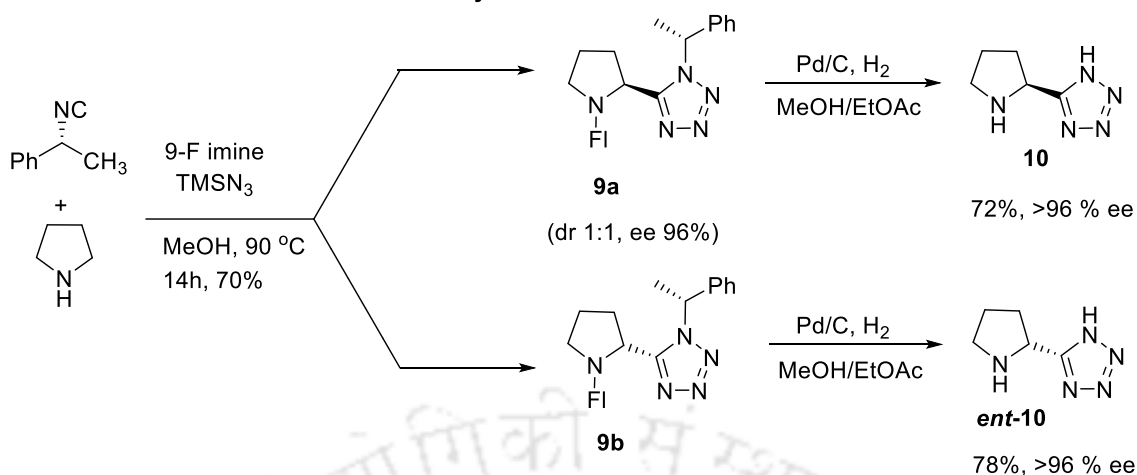
In recent years multicomponent reactions are one of the most powerful synthetic tools for the chemist to produce simple organic molecules to diverse complex molecules. As large variety of C-H bonds are present in organic molecules, the integration of C-H functionalization into multicomponent reaction would provide an opportunity to greatly expand the scope and

product diversity. Among these multicomponent reactions, isocyanides based four component (Ugi-4CR) Ugi-azide reactions is well-known for its efficiency in preparation of tetrazole derivative. Tetrazoles are important class of compounds because of their wide range of application as the medicinal drug, ligand for metal ion, imaging agent precursors for metal-organic frame work and highly energetic compounds. In particular, α -tetrazoyl amines, which are tetrazole analogs of amino acids, have been recognized as the interesting scaffolds in peptidomimetics and medicinal chemistry. Additionally, enantiopure α -tetrazoyl pyrrolidine is widely used as organocatalyst in asymmetric organic synthesis. Related tetrazoyl pyrrolidine derivative also utilized for the synthesis of aza-sugar containing nucleoside analogs. The known synthesis of aza-sugar containing nucleoside analogs required multistep reaction sequences. The first example of a metal and oxidant free C-H functionalization enabled azido-Ugi reaction (CHF-Ugi-azide) is developed (scheme 5). The reaction enables direct conversion of *N*-heterocycles to α -terazoyl *N*-heterocycles instead of tetrazoyl methyl amines that generally are formed through calassical Ugi-azide reactions. Importantly, the stereoselective reaction involving chiral amines or chiral isocyanides allowed the expeditious syntheses of aza-sugar containing nucleoside analogs and α -tetrazoyl pyrrolidine in enantiopure form.

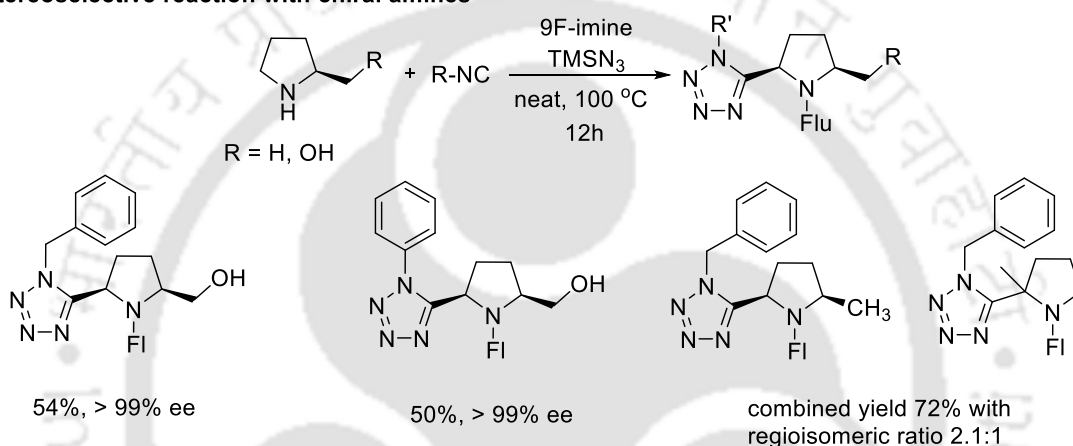


Scheme 5: C-H functionalization of enabled via Ugi-azide reaction.

stereoselective reaction with chiral isocyanide

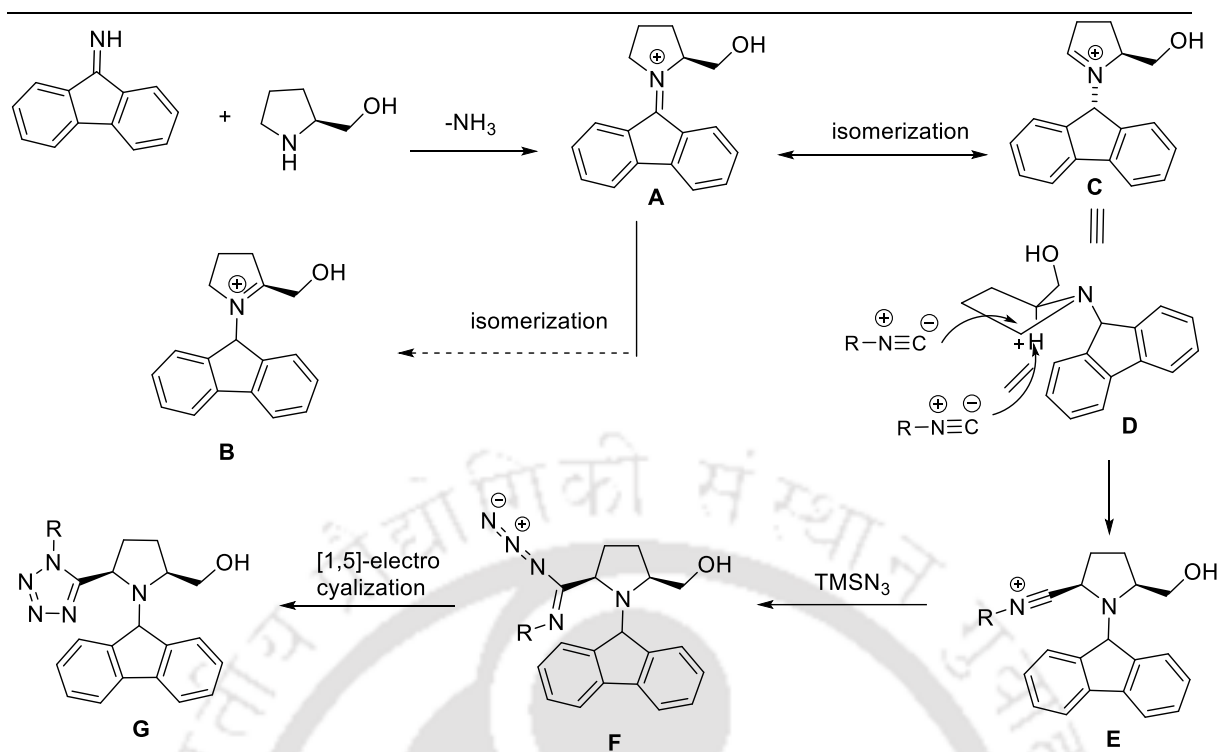


stereoselective reaction with chiral amines

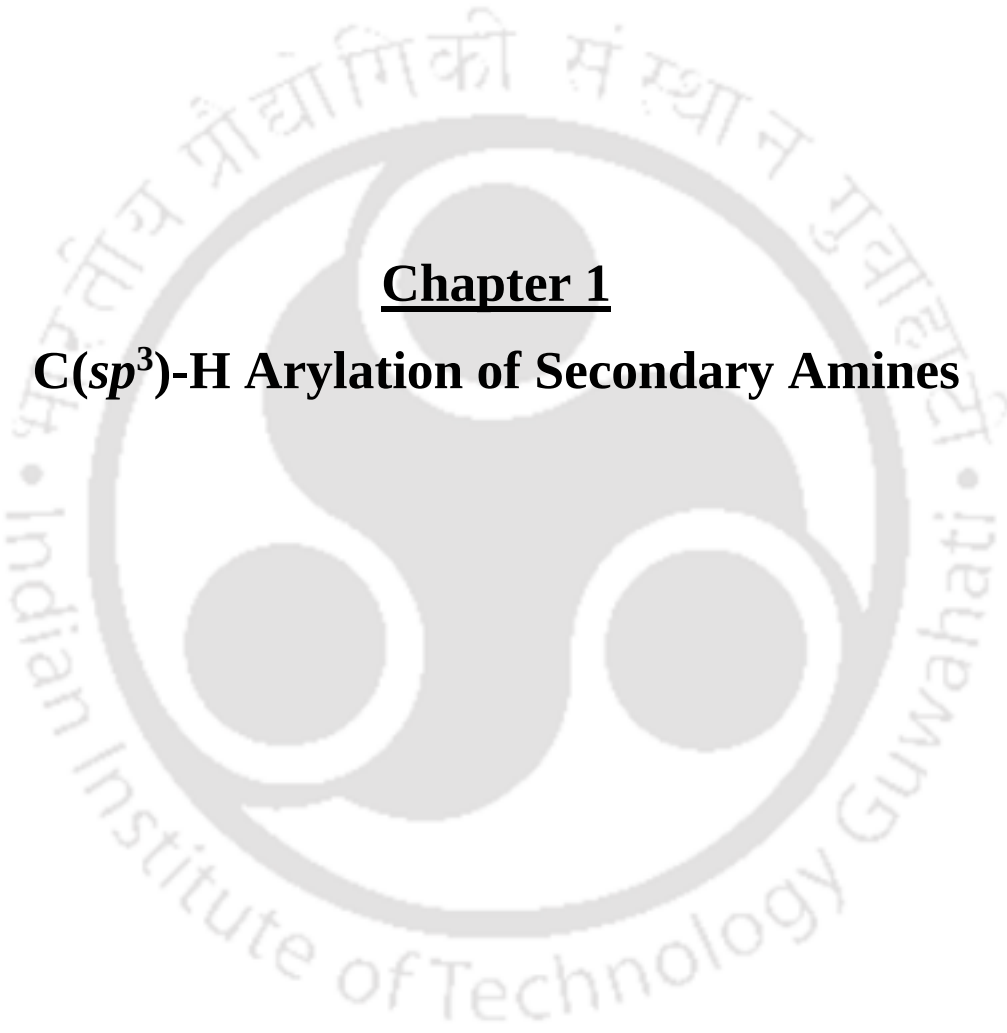


Scheme 6: Stereoselective CHF-Ugi-azide reaction with chiral isocyanides and chiral amines.

A plausible reaction mechanism has been proposed for the CHF-Ugi-azide reaction (**scheme 7**). Activator (9F-imine) reacts with prolinol to produce iminium ion **A**. Isomerization of the initially formed iminium ion **A** could be preferentially drawn towards **C** probably due to the unfavourable allylic strain in its regioisomer **B**. Then, the isocyanide approached from the less hindered side of **D** where the fluorenyl group prefers to remain in the opposite side of –CH₂OH group to avoid the steric interaction. The nitrilium ion **E** with *syn* geometry reacted with TMSN₃ to give the corresponding adduct **F**. Finally, [1, 5] electrocyclization of **F** provided the desired product **G** with observed *syn* stereochemistry.



Scheme 7: Plausible reaction mechanism for the synthesis of tetrazole substituted cyclic amines.



Chapter 1

C(sp³)-H Arylation of Secondary Amines



1.1. Introduction:

Alkaloids are one of the important classes of natural products exhibiting potent biological activities.¹ In many cases, α -arylated *N*-heterocycles constitute the key structural moiety of alkaloids.² For example nicotine,³ having α -arylated pyrrolidine unit is a potent parasympathomimetic stimulant. Similarly, 2-azapodophyllotoxin⁴, which possess an arylated *N*-heterocycle as the key structural motif, has potent antitumor activity. Marketed drug molecules such as, AMG-8735 and aprepitant also contain α -arylated *N*-heterocycles as the key unit.⁵ In addition to natural products and drugs, biologically or pharmacologically active molecules such as CERC 501 κ -opioid receptor antagonist⁶ and L-733,060 NK1 receptor antagonist⁷ have α -arylated *N*-heterocycles as key structural moiety. Apart from biological and medicinal applications, enantioenriched arylated *N*-heterocycles have been widely used as organocatalysts and chiral ligands in asymmetric synthesis (**Figure 1**).⁸

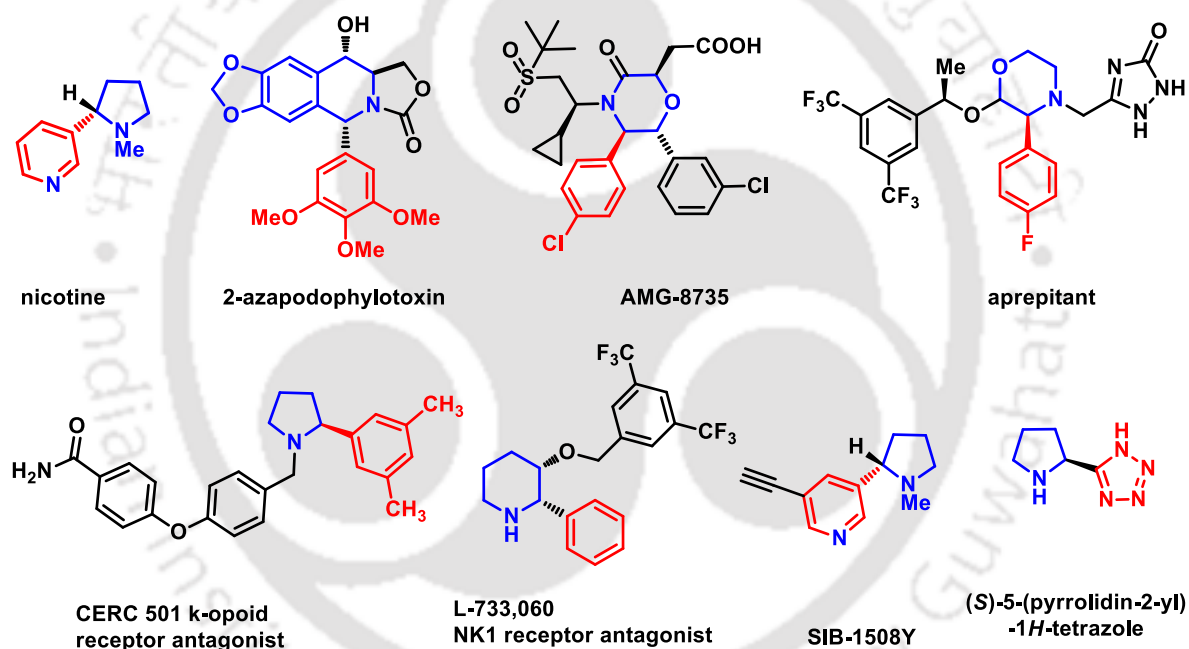


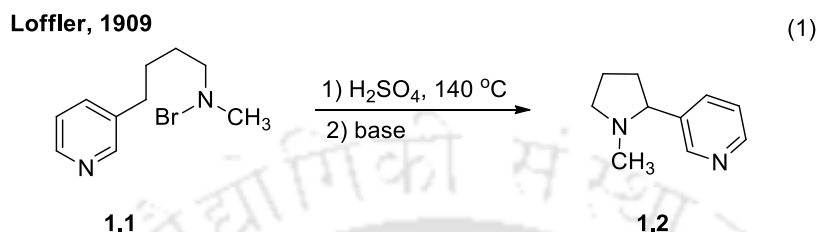
Figure 1: α -Arylated *N*-heterocycles in natural products, bioactive compounds and organocatalyst.

1.2 Approaches to arylated *N*-heterocycles:

Owing to the widespread potential applications of α -arylated *N*-heterocycles in biology and chemistry, there has been long-lasting interest in their synthesis. Therefore, various unique synthetic strategies have been developed for the synthesis of α -arylated *N*-heterocycles both in racemic or enantioenriched form.

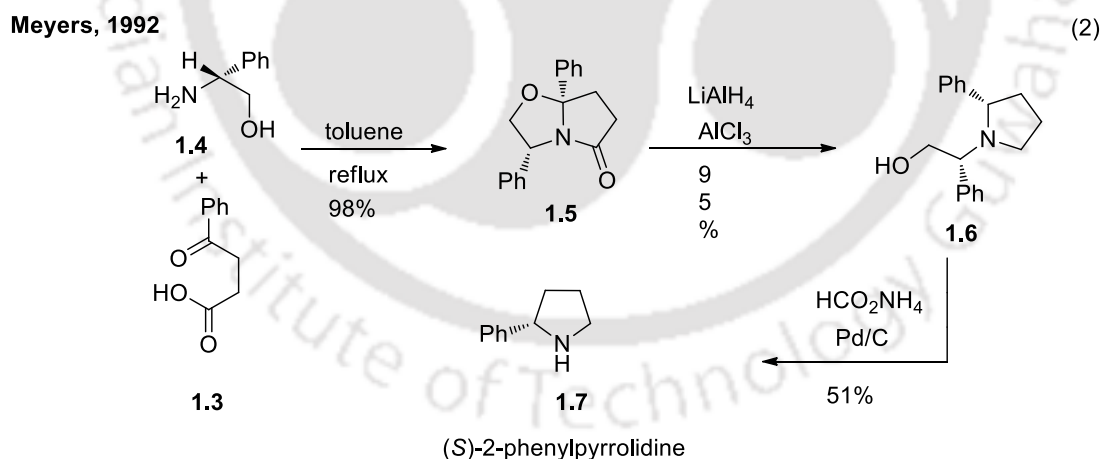
1.3 Synthesis of α -Arylated *N*-Heterocycles via *N*-Cycloalkylation Strategy:

Multisteps *N*-cycloalkylation strategy is often used for the synthesis of α -arylated *N*-heterocycles. In 1909, K. Löffler and C. Freytag reported the synthesis of nicotine **1.2** from *N*-bromo-*N*-methyl-4-(pyridin-3-yl)butan-1-amine **1.1** by using *N*-cycloalkylation strategy (**Scheme 1**, eq. 1).⁹



Scheme 1: Early approach for nicotine synthesis.

In 1992, Meyers and co-workers reported an efficient synthetic procedure for the preparation of the 2-aryl substituted pyrrolidines with high enantiomeric purity starting from 3-benzoylpropionic acids **1.3** and (*R*)-phenylglycinol **1.4**. Stereoselective reduction of chiral bicyclic lactams **1.5**, which was prepared from the corresponding γ -keto acid **1.3** and (*R*)-phenylglycinol **1.4**, using alane provided the *N*-substituted pyrrolidines **1.6**. Subsequent cleavage of the phenylglycinol derivatives provided 2-phenyl pyrrolidine **1.7** (**Scheme 2**, eq. 2).¹⁰

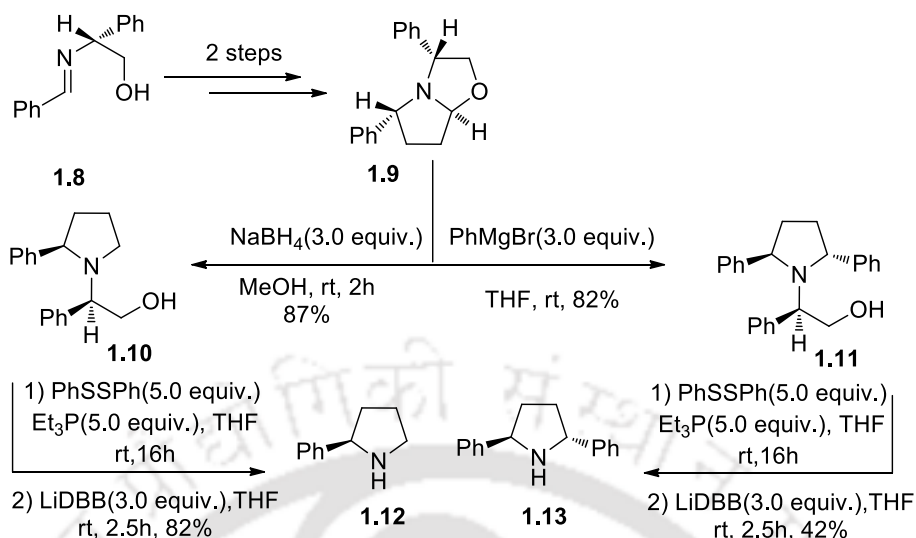


Scheme 2: Synthesis of (*S*)-2-phenylpyrrolidine.

In 1994, Higashiyama and co-workers reported the asymmetric syntheses of (*R*)-2-phenylpyrrolidine **1.12** and (*R,R*)-2,5-bis(aryl)pyrrolidine **1.13** from 1,3-oxazolidine **1.9** which was prepared from chiral aromatic imine **1.8**. Diastereoselective addition of Grignard reagent was the key reaction (**Scheme 3**, eq. 3).¹¹

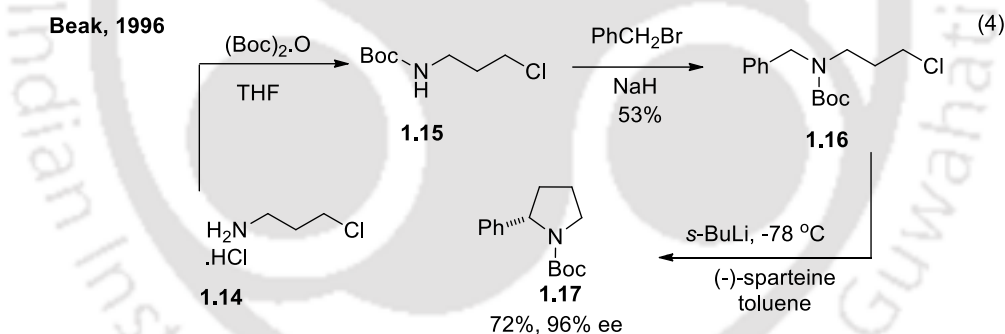
Higashiyama, 1994

(3)



Scheme 3: Syntheses of (*R*)-2-aryl- and (*R,R*)-2,5-bis(aryl)pyrrolidines.

In 1996, Beak and co-workers reported the synthesis of enantioenriched (*S*)-2-phenyl-Boc-pyrrolidine **1.17** by *N*-cycloalkylation reaction of the corresponding *tert*-butyl benzyl (3-chloropropyl) carbamate **1.16** with *s*-BuLi in the presence of (-)-sparteine as a chiral ligand (**Scheme 4**, eq. 4).¹²

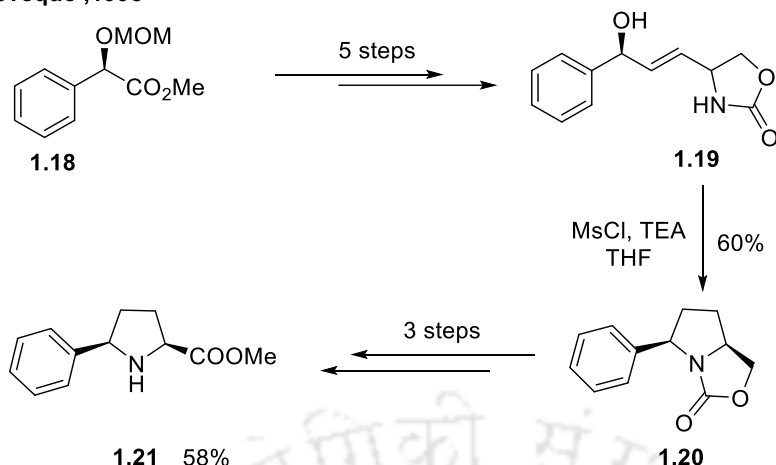


Scheme 4: Enantioselective lithiation-cyclizations strategy for (*S*)-2-phenyl *N*-Boc pyrrolidine.

The synthesis of the structural precursor of RP 66803, (2*S*,5*R*)-methyl 5-phenylpyrrolidine-2-carboxylate **1.21** has been demonstrated by Larcheveque and co-workers in 1998. In this synthesis, the corresponding arylated compound **1.21** was prepared by a linear 9-step synthetic sequence starting from MOM protected ester of (*R*)-mandelic acid derivative **1.18** with 58% yield (**Scheme 5**, eq. 5).¹³

Larcheveque, 1998

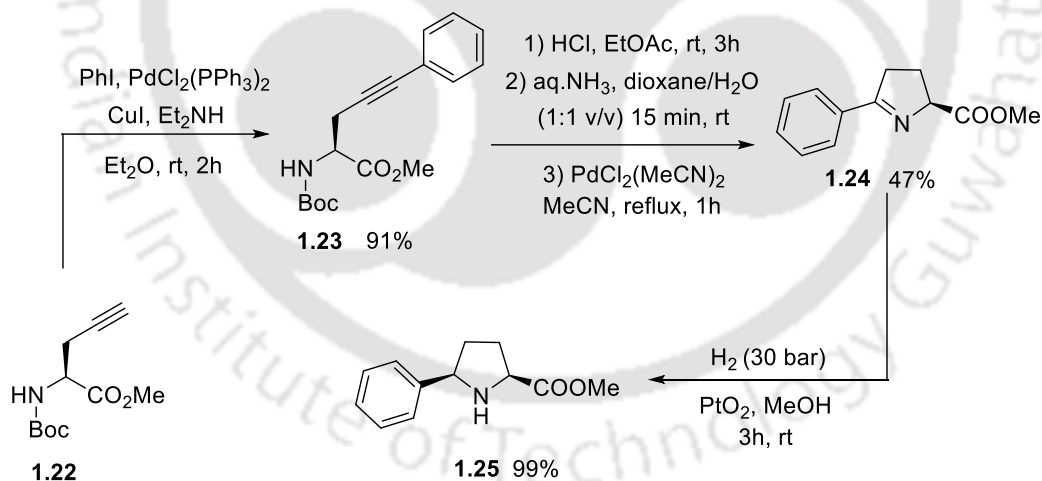
(5)



Scheme 5: Enantioselective synthesis of (2*S*,5*R*)-methyl 5-phenylpyrrolidine-2-carboxylate. In 2004, Rutjes and co-worker reported a novel approach for the synthesis of 5-substituted proline analogues. They have shown that the synthesis of 2,5-disubstituted pyrrolines **1.24** can be achieved via a mild Pd catalyzed 5-endo-dig cyclization of propargylglycine derivatives **1.23**. Finally, they also demonstrated that the obtained pyrroline can be easily converted into the corresponding 5-substituted proline **1.25** analogues by hydrogenation reaction with 99% yield in enantioenriched form (**Scheme 6**, eq. 6).¹⁴

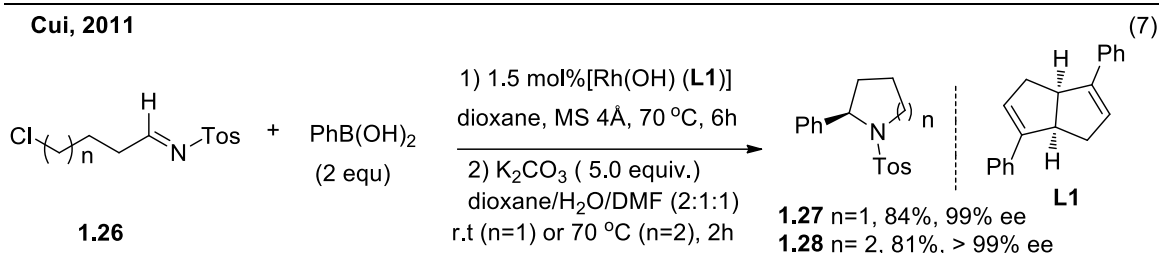
Rutjes, 2004

(6)



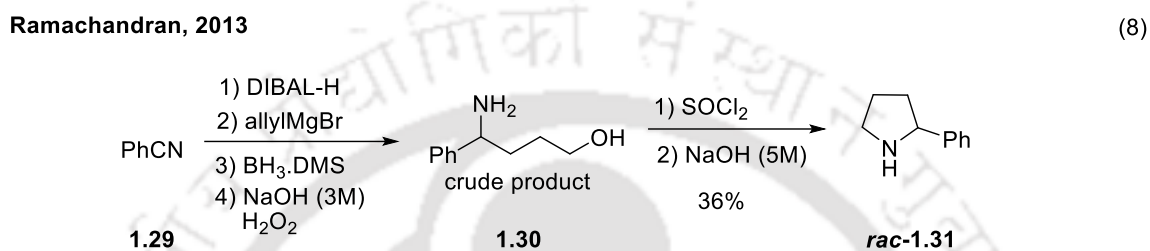
Scheme 6: Synthesis of 5-substituted proline derivatives using a palladium-catalyzed cyclization.

In 2011, Cui and co-workers reported a one-pot methodology for the enantioselective synthesis of chiral 2-phenylpyrrolidine **1.27** and 2-phenylpiperidine **1.28**. Under neutral reaction conditions, rhodium hydroxide based complex catalyzed arylation of aliphatic *N*-tosylaldimines **1.26**. The resulting α -aryl amine underwent *N*-cycloalkylation to provide chiral 2-phenylpyrrolidine **1.27** and 2-phenylpiperidine **1.28** (**Scheme 7**, eq. 7).¹⁵



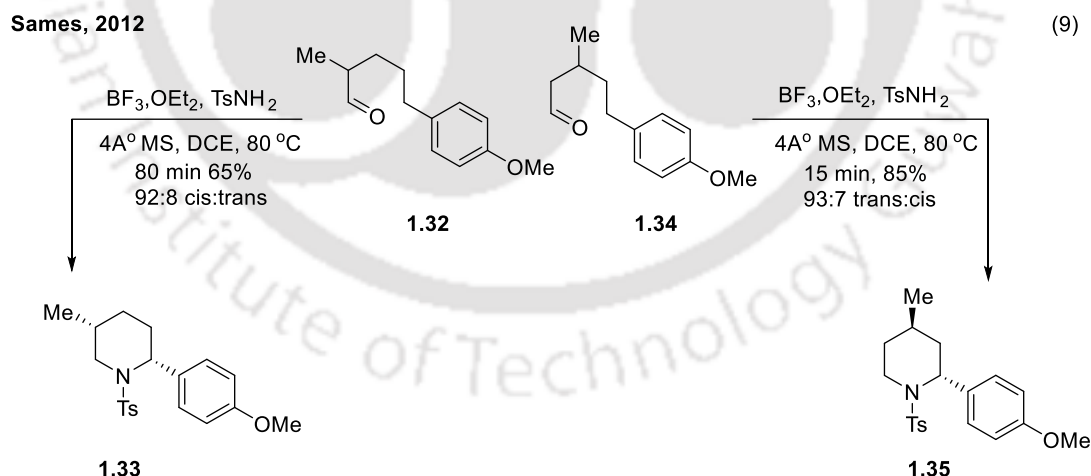
Scheme 7: Synthesis of chiral pyrrolidine and piperidine.

In 2013, Ramachandran and co-workers reported the preparation of production of 2-substituted pyrrolidine **rac-1.31** from commercially available nitrile **1.29** (Scheme 8, eq.8).¹⁶



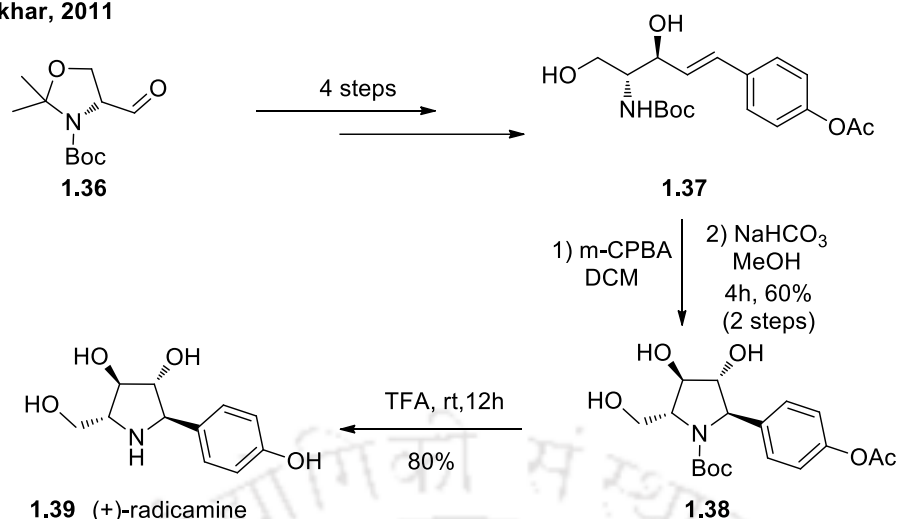
Scheme 8: One pot *N*-cycloalkylation strategy for preparation 2-substituted pyrrolidine.

In 2012, Sames and co-workers reported an intramolecular amination method of $\text{C}(\text{sp}^3)\text{-H}$ bond via the hydride transfer followed by cyclization of *N*-tosylamines. In this particular reaction, 2-substituted aldehyde **1.32** yielded *cis*-2,5-disubstituted piperidine **1.33**, while 3-substituted aldehyde **1.34** afforded *trans*-2,4-disubstituted piperidine **1.35** (Scheme 9, eq. 9).¹⁷



Scheme 9: Stereoselective intramolecular hydrogen transfer amination.

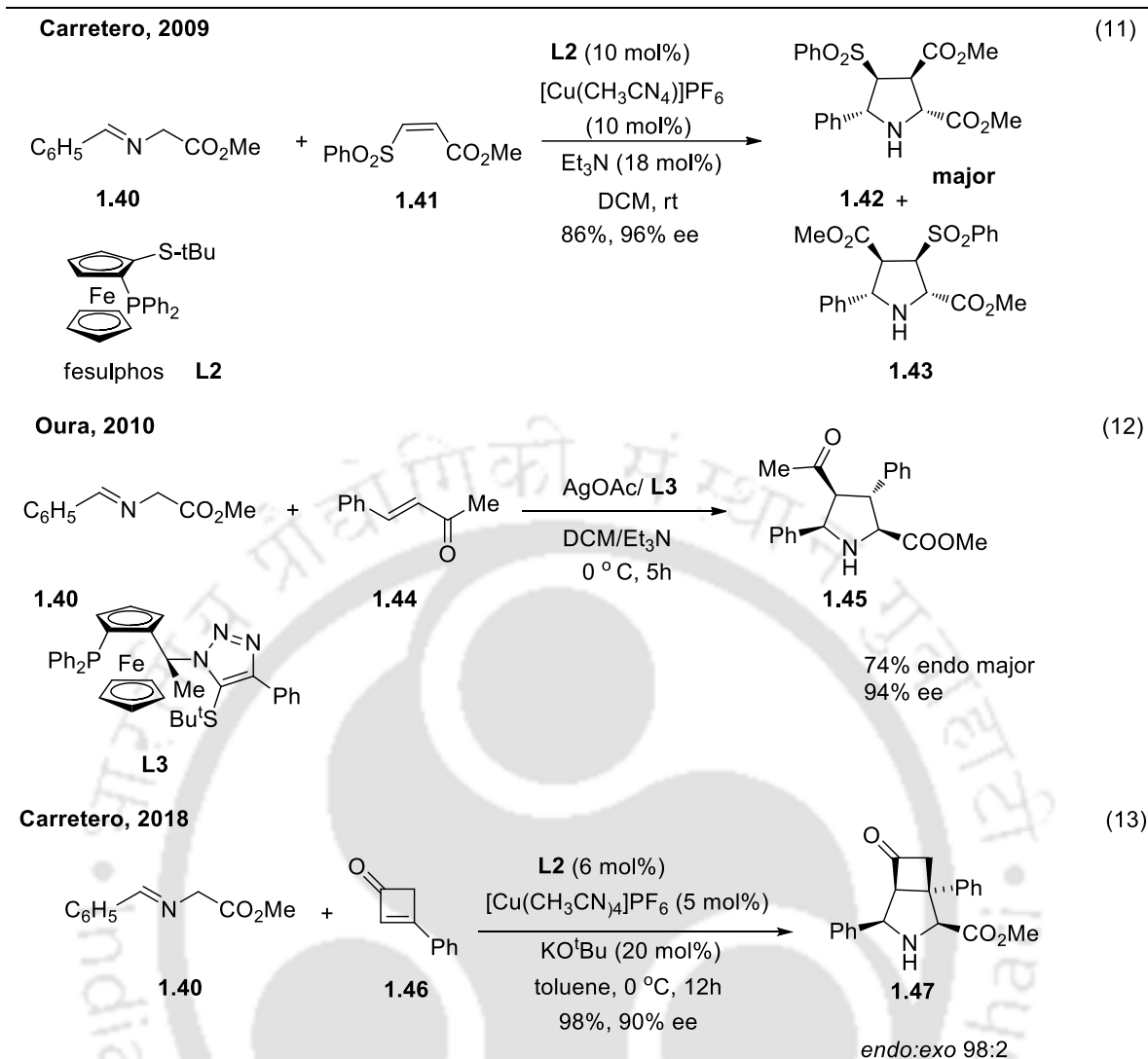
N-Cycloalkylation strategy has proven its synthetic usefulness for the synthesis of many polyhydroxylated alkaloids natural products such as (-)-codonopsinine, radicamines A and B. Chandrasekhar and co-workers achieved the synthesis of (+) radicamine B **1.39** in 8 steps starting from (*R*)-(+)-Garner aldehyde **1.36** (Scheme 10, eq. 10).¹⁸



Scheme 10: Total synthesis of (+)-radicamine B by Chandrasekhar's approach.

1.4. Azomethine ylide based cycloaddition reactions for synthesis of arylated *N*-heterocycles:

Cycloaddition reactions are one of the most important classes of reactions in synthetic chemistry. Particularly, the 1,3-dipolar cycloaddition reaction has found extensive use as a high-yielding and efficient, regio- and stereoselective method for the synthesis of many different heterocyclic compounds. The reaction sequence consisting of aldehyde + amine $\rightarrow$ imine $\rightarrow$ azomethine ylide + dipolarophile $\rightarrow$ pyrrolidine was first reported by Grigg.¹⁹ Recently, examples of catalytic asymmetric cascade [3+2] cycloadditions of azomethine ylides have also been reported for the synthesis of highly substituted pyrrolidine derivatives.²⁰ For example, in 2009, Carretero and co-workers reported the catalytic asymmetric 1,3-dipolar cycloaddition of (*Z*)-sulfonyl acrylates **1.41** with azomethine ylides **1.40** to provide tetra substituted pyrrolidine **1.42** (**Scheme 11**, eq. 11).²¹ Oura and co-workers reported a silver(I) catalyzed highly *endo*-selective asymmetric 1,3-dipolar cycloaddition reaction of methyl *N*-benzylideneglycinate as a source of azomethine ylide with (*E*)-acyclic enone **1.44** to give highly functionalized *endo*-4-acyl pyrrolidine **1.45** in good yields with high enantioselectivity (**Scheme 11**, eq. 12).²² In 2018, Carretero and co-workers have been reported a catalytic asymmetric 1,3-dipolar cycloaddition of cyclobutenone **1.46** with azomethine anion precursor **1.40** to access highly substituted 3-azabicyclo[3.2.0]heptane **1.47** (**Scheme 11**, eq. 13).²³



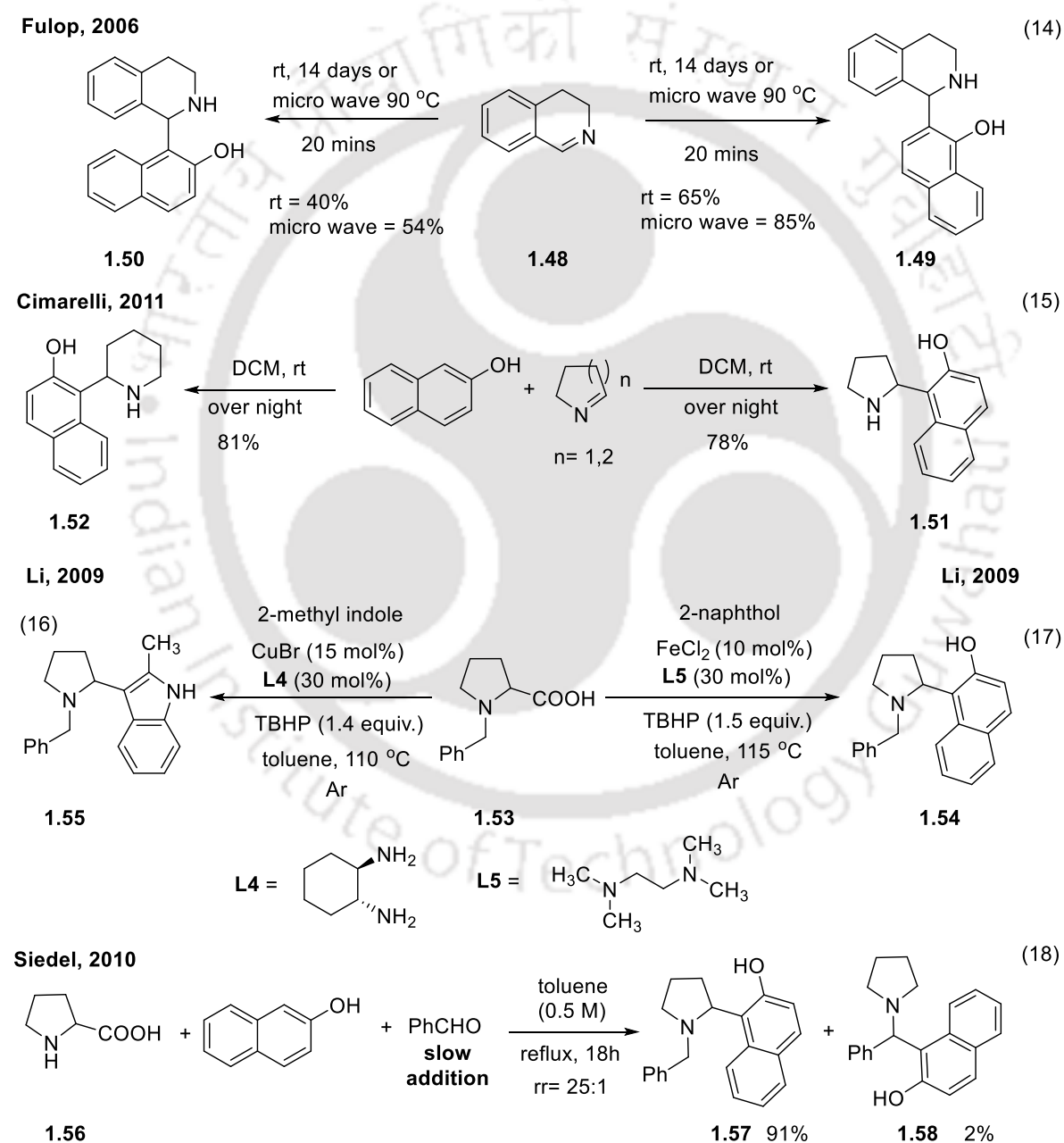
Scheme 11: Synthesis of highly substituted pyrrolidine via 1,3 dipolar cycloaddition reaction.

1.5. Synthesis of arylated *N*-heterocycles from pre-oxidized or prefunctionalized starting materials:

Sometimes pre-oxidized or pre-functionalized *N*-heterocycles were used for the synthesis of arylated *N*-heterocycles with or without the help of metal-based reagents. In this context, 2006 Fulop and co-workers synthesized 1-(hydroxynaphthyl)-1,2,3,4 tetrahydroisoquinolines **1.49** & **1.50** using the Mannich or Betti reaction. They have synthesized the arylated THIQ from the reaction between 3,4-dihydroisoquinoline and naphthols derivatives under room temperature or microwave reaction conditions (**Scheme 12**, eq. 14).²⁴ Similarly, Cimarelli group has reported a synthetic method for the preparation of aminocycloalkylphenols and -naphthols from the reaction between activated phenols and naphthols with five or six-membered cyclic imines (**Scheme 12**, eq. 15).²⁵ The previous two examples are for the synthesis of arylated *N*-heterocycles from pre-oxidized starting materials without using any external metal-based reagents. There are the example of some synthetic methods where

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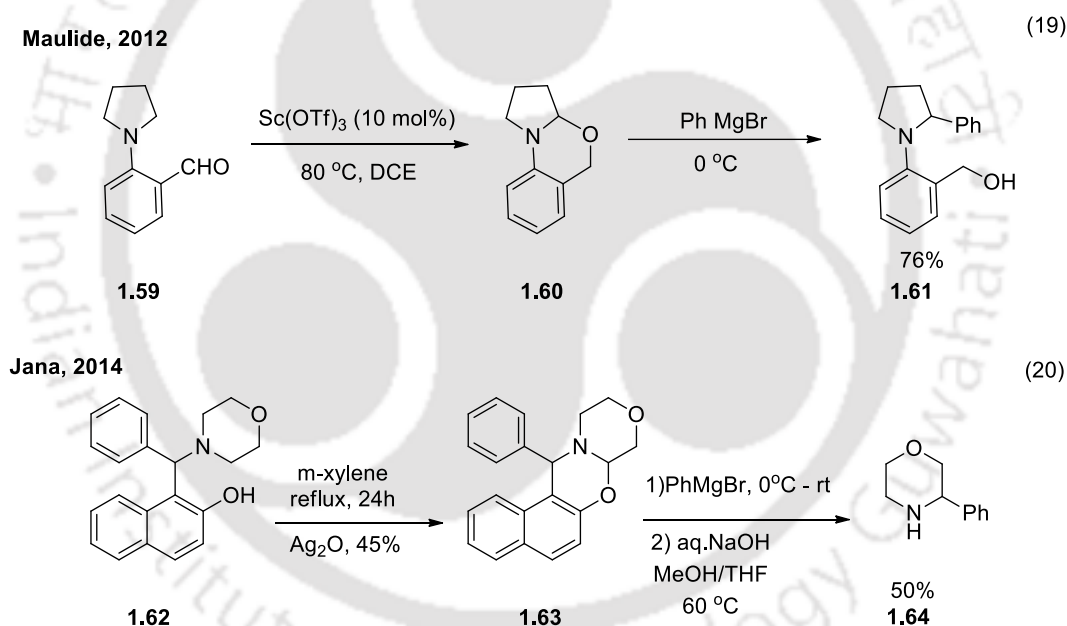
synthesis of arylated *N*-heterocycles could be possible from pre-functionalized starting materials with the help of an external metal based reagents. In 2009, Li and co-workers reported a method for the synthesis of α -arylated *N*-heterocycles from amino acid derivatives by using external metal catalyst (CuBr) and oxidant (TBHP) with different nucleophiles (**Scheme 12**, eq. 16).²⁶ In 2009, Li and co-workers developed a Fe-catalyzed intermolecular decarboxylative $Csp^3 - Csp^2$ coupling reaction between proline derivatives and different electron rich nucleophiles. By using this synthetic method they have synthesized α -arylated *N*-heterocycles (**Scheme 12**, eq. 17).²⁷



Scheme 12: Synthesis of α -arylated *N*-heterocycles from pre-oxidized and prefuctionalized starting materials.

In 2010, Siedel and co-workers reported a three-component decarboxylative reaction among amino acids, aldehyde, and nucleophiles to produce arylated *N*-heterocycles. In this reaction, α -arylated *N*-heterocycles are obtained with less amount of corresponding regioisomeric products. During this reaction, the addition of the corresponding aldehyde should be slow otherwise a complex mixture of products will be obtained along with the desired product (**Scheme 12**, eq. 18).²⁸

In 2012, Maulide and co-workers have reported a method for functionalization of amine through oxazine formation (**Scheme 13**, eq. 19).²⁹ In 2014, Jana and co-workers have developed a novel method for direct C–H functionalization of saturated *N*-heterocycles to form corresponding ring fused oxazine.³⁰ The reaction of phenylmagnesium bromide with the ring-fused oxazine **1.63** provided the corresponding 3-phenylated morpholine derivative, which after mild base mediated removal of the hydroxy-naphthyl group at nitrogen produced alpha-phenylated morpholine **1.64** (**Scheme 13**, eq. 20).



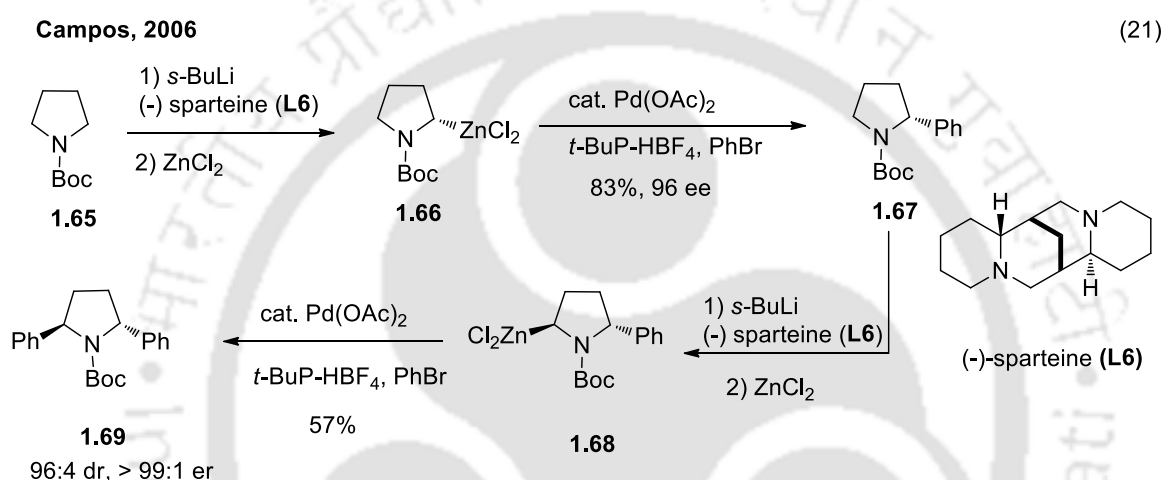
Scheme 13: Synthesis of α -arylated *N*-heterocycles through oxazine formation.

1.6. Direct methods for the synthesis of α -arylated *N*-heterocycles:

Although these methods via *N*-cycloalkylation strategy are efficient for the synthesis of arylated *N*-heterocycles, it required long synthetic route and suffers from the low step and atom economy. As compared to the multistep synthetic strategies for the synthesis of α -arylated *N*-heterocycles direct synthetic methods via C–H functionalization are more attractive in the context of step and atom economy. The selected approaches for direct methods for the synthesis of α -arylated *N*-heterocycles are discussed.

1.7. C(sp³)-H Arylation Through α -Deprotonation of *N*-Heterocycles:

In this field, since the pioneering work developed by Beak and Hoppe, extensive efforts have focused on the low temperature, alkyllithium/chiral diamine mediated deprotonation of *N*-protected pyrrolidines to obtain α -functionalized pyrrolidine derivatives.³¹ Campos and co-workers, successfully demonstrated that α -deprotonation of *N*-Boc-pyrrolidine **1.65** with strong base *s*-BuLi and (-)-sparteine (**L6**) followed by the trans-metallation with ZnCl₂ **1.66** and subsequent coupling with phenyl bromide under Negishi conditions gave *N*-protected α -aryl pyrrolidine derivative **1.67**. This strategy is also applicable to the synthesis of 2,5-di-substituted pyrrolidine **1.69** (Scheme 14, eq. 21).³²

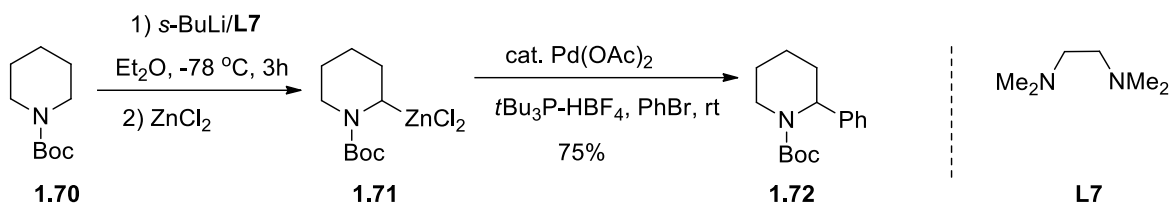


Scheme 14: Arylation via α -deprotonation of *N*-Boc pyrrolidine.

Although this methodology is successfully applied for preparation of enantioenriched α -arylated pyrrolidine, arylation of piperidine could not be achieved. In this regard, Coldham and Leonori further extended the scope of the Pd-catalyzed α -arylation methodology to prepare racemic *N*-substituted 2-aryl piperidine **1.72** from racemic *N*-Boc piperidine **1.70**. In this method first racemic *N*-Boc piperidine **1.70** was deprotonated with *s*-BuLi in the presence of TMEDA (**L7**) at -78 °C. Transmetalation with ZnCl₂ followed by Negishi coupling with phenyl bromide yielded α -arylated racemic piperidine **1.72** (Scheme 15, eq. 22).³³ Similarly, Beng and Gawley have synthesized enantioenriched 2-aryl *N*-Boc piperidines **1.75** in the presence of chiral ligand **L8** (Scheme 15, eq.23).³⁴

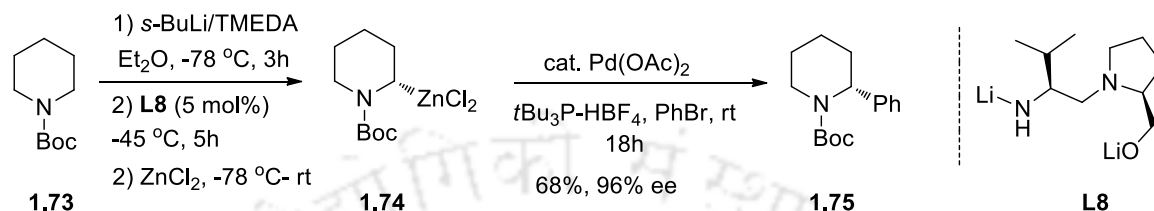
Coldham, 2008

(22)

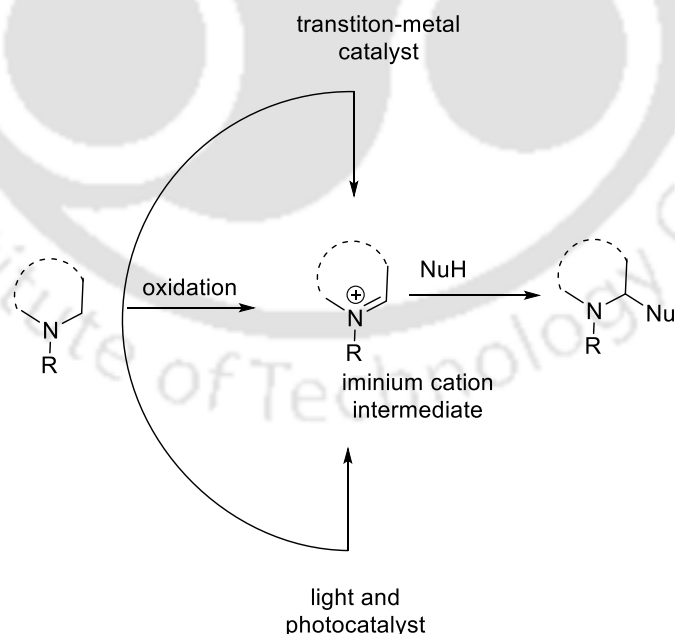


Beng, 2011

(23)

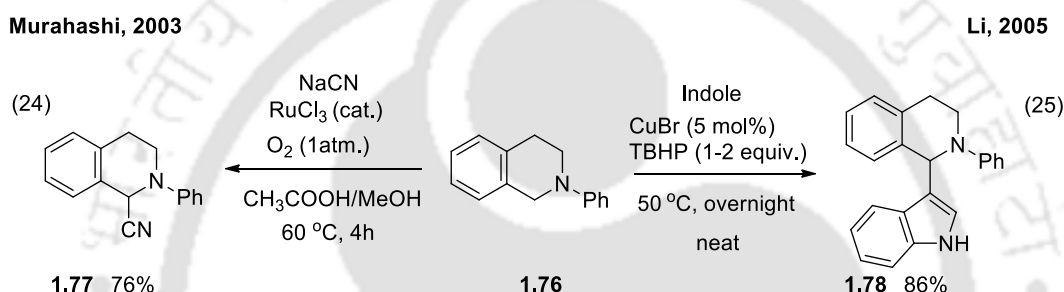
**Scheme 15:** Arylation via deprotonation of *N*-Boc piperidine.**1.8. Arylation of Amines through Cross-Dehydrogenative Coupling (CDC):**

Cross-dehydrogenative couplings (CDCs) have become one of the most straightforward protocols in the C–H bond functionalizations of tertiary amines. The main principle in CDCs approach involves the generation of an iminium ion intermediate from a given amine to form an electrophilic species that can be coupled with a nucleophilic partner. The different reported strategies for the generation of iminium intermediate for the arylation of amines have been summarized below (**Scheme 16**).

**Scheme 16:** Different reported strategies for formation of iminium ions.

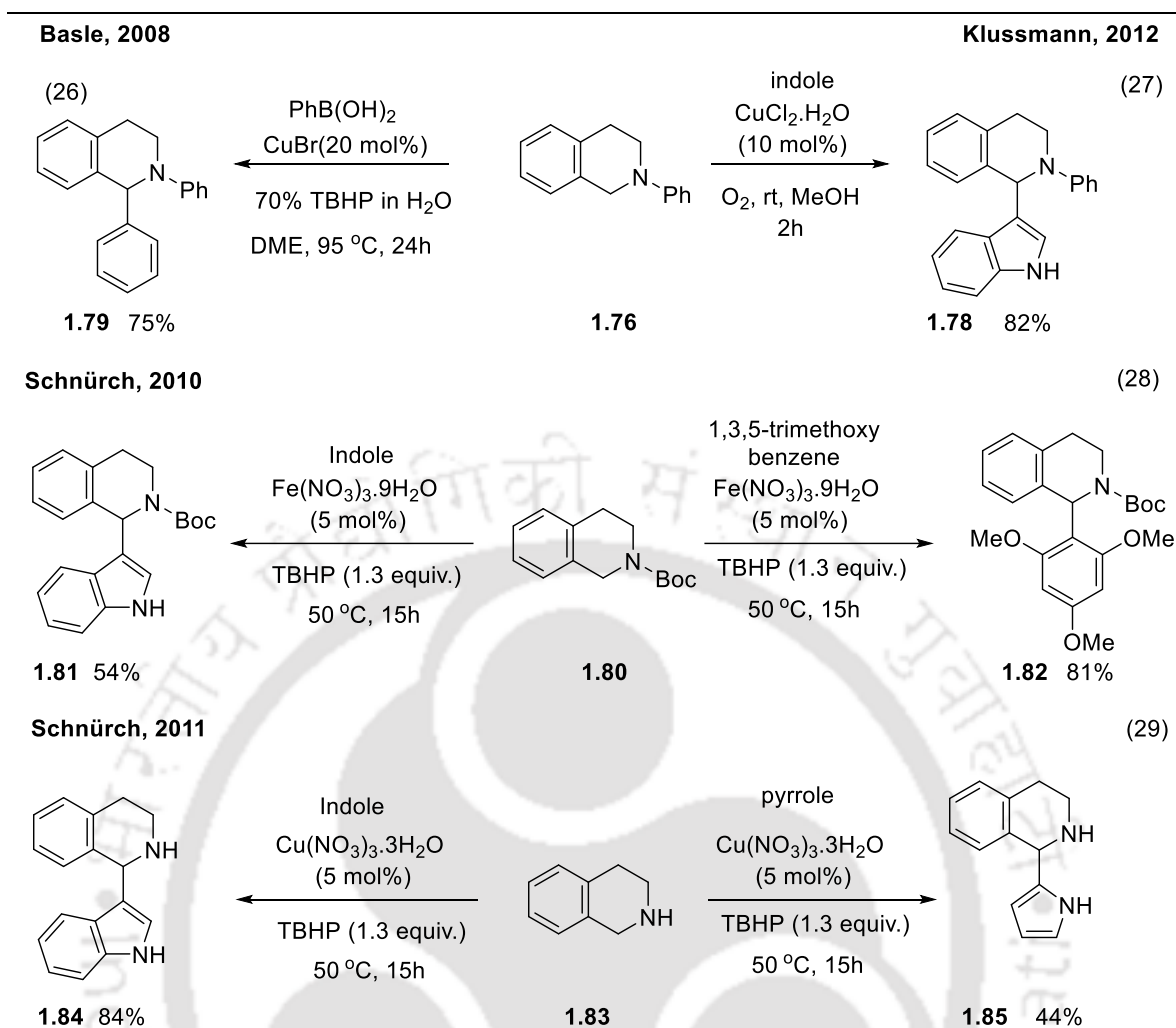
1.9. CDC Approaches using Transition Metal Catalyst:

In CDC approaches for arylation of cyclic tertiary amines the majority of reported methodologies involve the use of transition metal catalyst with a variety of “classical” chemical oxidants (e.g. TBHP, O₂). In 2003, Murahashi and co-workers reported an oxidative cyanation of tertiary amines which employed RuCl₃.nH₂O as the catalyst and oxygen as the stoichiometric oxidant under mild conditions (**Scheme 17** eq. 24).³⁵ In 2005, Li and co-workers developed the direct method of indolation of tetrahydroisoquinoline using CuBr as the catalyst and TBHP as an oxidant (**Scheme 17** eq. 25).³⁶ Following the pioneering works of Murahashi and Li, a number of reports on the oxidative α -functionalization of cyclic tertiary amines have developed with a wide range of appropriate nucleophilic coupling partners.

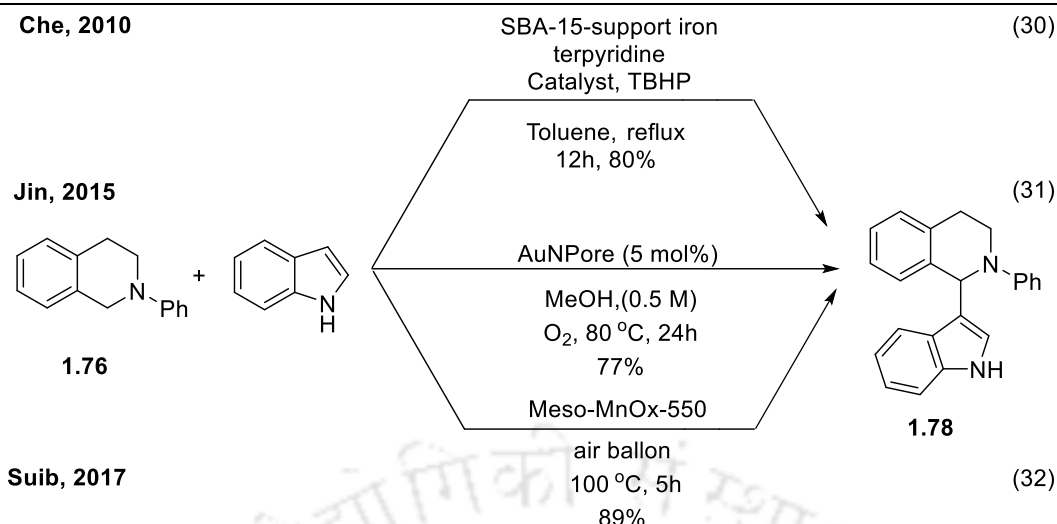


Scheme 17: Pioneering works of Murahashi and Li for α arylation via CDC approaches.

Here we will focus only on the reactions where aromatic compounds were used as potential nucleophiles. Li and Basle used arylboronic acids as nucleophilic coupling partner for the oxidative Cu-catalyzed α -arylation of cyclic tertiary amines. They reported that a variety of α -arylated *N*-aryltetrahydroisoquinoline **1.79** derivatives can be obtained from the oxidative Cu-catalyzed reaction of *N*-aryltetrahydroisoquinolines **1.76** and arylboronic acids using aqueous TBHP (**Scheme 18**, eq. 26).³⁷ In 2012, Klusmann and co-workers reported Cu catalyzed oxidative coupling reaction of *N*-phenyltetrahydroisoquinolines **1.76** with different nucleophiles in the presence of molecular oxygen as the oxidant (**Scheme 18**, eq. 27).³⁸ This method is not limited to copper catalysis but several methods have also been developed using Fe catalysis. Schnürch and colleagues have described an efficient solvent and ligand-free Fe-catalyzed direct C1 indolation and methoxyphenylation of *N*-Boc protected tetrahydroisoquinolines **1.80** (**Scheme 18**, eq. 28).³⁹ The same group have also reported a complementary Cu-based method for the indolation of *N*-Boc-tetrahydroisoquinoline **1.80**. This Cu-catalyzed protocol has been demonstrated to be efficiently applicable for functionalization of unprotected tetrahydroisoquinoline **1.83** with a variety of indoles and pyrroles (**Scheme 18**, eq. 29).⁴⁰



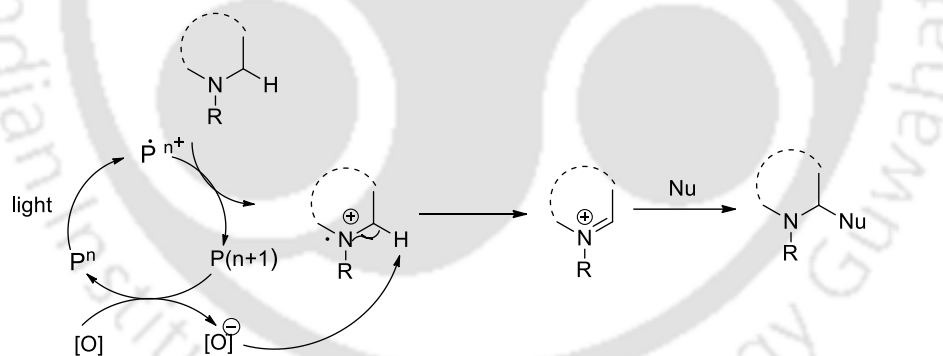
Scheme 18: Arylation of *N*-heterocycles via CDC approaches with transition metal catalyst. In the previous section, CDC approaches for the synthesis of α -arylated *N*-heterocycles in the presence of homogenous transition metal catalyst with different oxidants have been discussed. However, the use of recoverable and reusable heterogeneous catalysts for $C(sp^3)$ –H arylation of *N*-heterocycles would be more desirable in the context of green and sustainable chemistry.⁴¹ In this regard, 2010 Che and co-workers developed SBA-15-supported iron terpyridine catalyzed direct indolation of *N*-aryl tetrahydroisoquinoline. (**Scheme 19**, eq. 30).⁴² Later in 2015, Jin and co-workers have demonstrated that the zero-valent AuNPore can be used as a highly efficient and reusable heterogeneous catalyst for the $C(sp^3)$ –H arylation of tertiary amines in the presence of molecular oxygen or TBHP as an oxidant under mild conditions (**Scheme 19** eq. 31).⁴³ Recently in 2017, Suib and co-workers have reported a heterogeneous catalytic approach for selective coupling of C1 of *N*-aryl tetrahydroisoquinolines with C3 of indoles in the presence of mesoporous manganese oxides (**Scheme 19**, eq.32).⁴⁴



Scheme 19: CDC approaches using heterogeneous transition metal catalyst.

1.10. Visible-light-induced Photocatalytic Oxidation for Arylation of *N*-heterocycles:

The photocatalyzed reaction is activated in the presence of light. The activated catalyst oxidizes the amine to an amino radical cation. Then an external oxidant regenerates the photocatalyst, while itself becoming a radical species which can abstract the α -hydrogen of the amino radical cation. The resulting iminium ion is subsequently trapped by the nucleophilic coupling partner (**Scheme 20**).

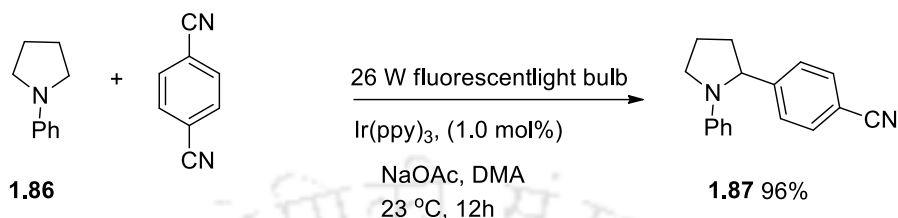


Scheme 20: General mechanism for photo catalytic amine functionalization.

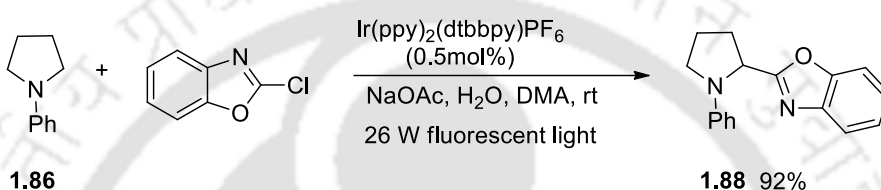
In 2011, MacMillan and co-workers reported a light-mediated iridium-catalyzed C(sp^3)-H arylation of benzocyclic amines with electron poor cyano arenes (**Scheme 21**, eq. 33).⁴⁵ In 2014, the same group reported a method for α -amino arylation of secondary amines by using chloro-polyheteroarenes as arylating agents instead of cyano arenes with the help Ir(ppy)₂(dtbbpy)PF₆ as a photocatalyst (**Scheme 21**, eq. 34).⁴⁶ Recently, in 2016, Wang group developed a direct and oxidant free method for the arylation of *N*-acyl-protected tetrahydroisoquinolines with electron deficient arenes (**Scheme 21**, eq.35).⁴⁷ Organo

photocatalysts are also useful for the preparation of α -arylated *N*-heterocycles. In 2013, Li and co-workers reported a light-induced cross-coupling hydrogen evaluation reaction (CCHE) using the cheaper and less toxic eosin Y as the photocatalyst to achieve the C(sp³)-H arylation of THIQs (**Scheme 21**, eq. 36).⁴⁸

Macmillan, 2011 (33)



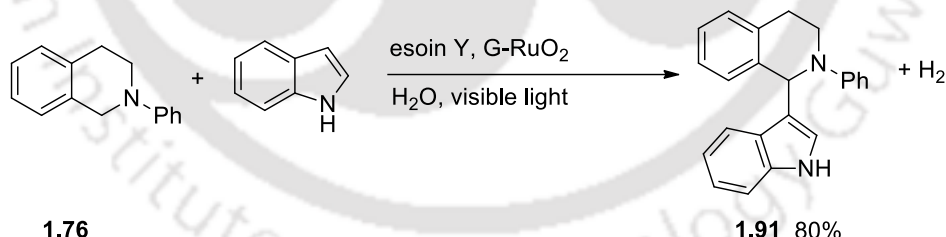
Macmillan, 2014 (34)



Wang, 2016 (35)



Wu, 2013 (36)

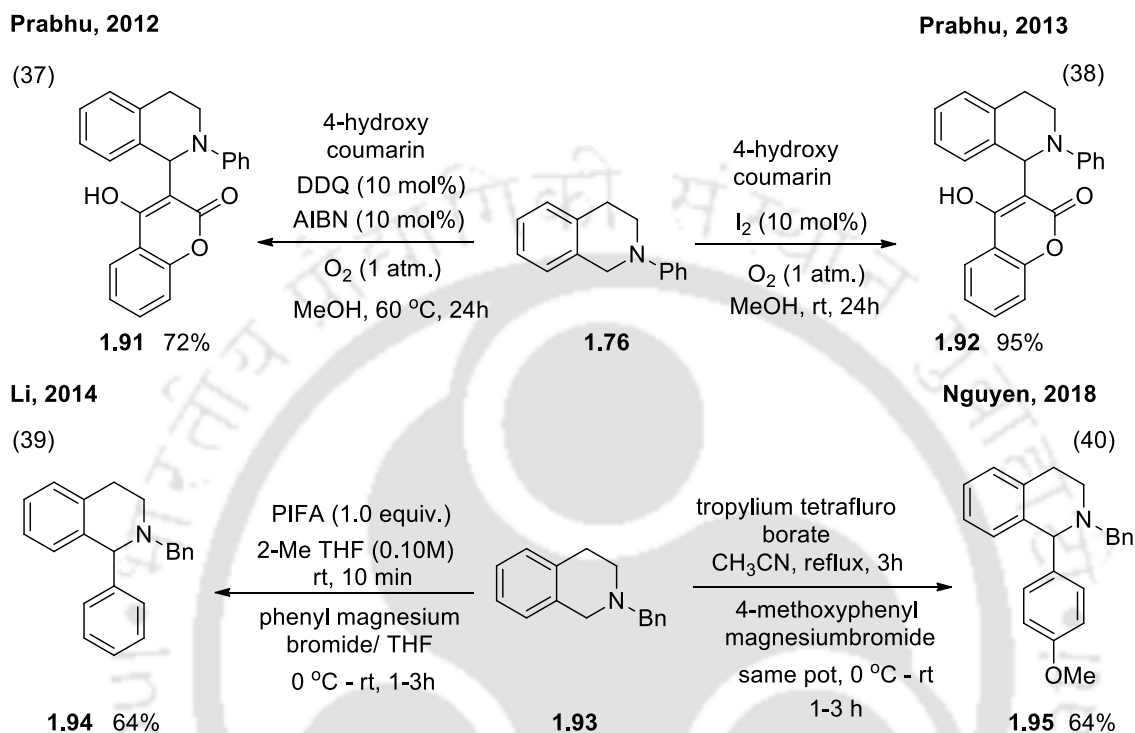


Scheme 21: Photo catalytic arylation of *N*-heterocycles.

1.11. CDC Approaches via Chemical Oxidation:

Several methods for the α -arylation of cyclic tertiary amines, which used a catalytic or stoichiometric amount of oxidant rather than an oxidant in combination with a transition-metal catalyst, have been reported. In 2012, Prabhu and co-workers reported a metal-free DDQ catalyzed C(sp³)-H arylation of tetrahydroisoquinoline under an oxygen atmosphere (**Scheme 22**, eq. 37).⁴⁹ Later in 2013, the same group developed a method for arylation on *N*-protected tetrahydroisoquinoline using molecular iodine as a catalyst.⁵⁰ In this method, they showed that a catalytic amount of molecular iodine was sufficient to bring the α -arylated

product under oxygen atmosphere (**Scheme 22**, eq. 38). In 2014, Li and co-workers reported one step method for C(sp³)–H arylation at the C-1 position of THIQ derivatives mediated by PIFA in the presence of Grignard reagents under mild conditions (**Scheme 22**, eq. 39).⁵¹ Recently in 2018, Nguyen and co-workers reported a related method for arylation of THIQ derivatives by using tropylium salt instead of PIFA (**Scheme 22**, eq. 40).⁵²



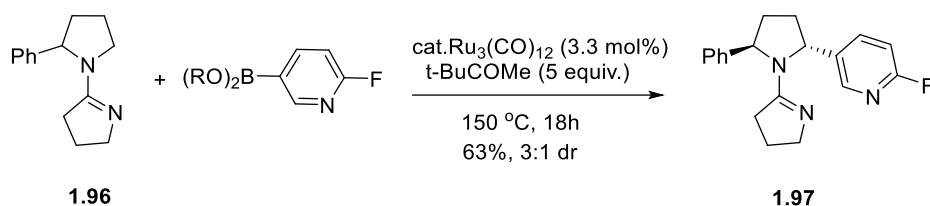
Scheme 22: Synthesis of *N*-heterocycles by chemical oxidant.

1.12. Direct C(sp³)–H Arylation using Transition-Metal-Catalysts:

Numerous methods reported for direct arylation of cyclic amines through α -deprotonation and iminium ion formation have been reported. However, transition metal catalyzed direct C(sp³)–H arylation of *N*-heterocycles remains limited, probably because of the reactivity and selectivity problems associated with C(sp³)–H arylation of cyclic amines. In 2006, Sames and co-workers first reported the direct Ru catalyzed α -arylation of pyrrolidines using aryl boronate. An amidine moiety acts as a directing group. The use of excess ketone in the reaction was necessary to allow transmetallation step in the proposed catalytic cycle. The directing pyrroline group could subsequently be removed by reaction with hydrazine and acid (**Scheme. 23**, eq. 41).⁵³

Sames, 2006

(41)

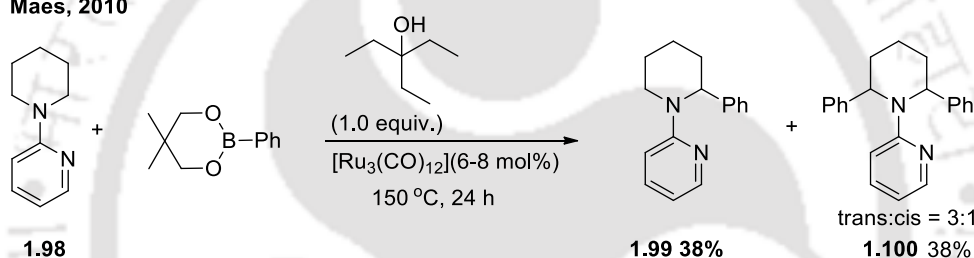


Scheme 23: Ruthenium metal catalyzed arylation of pyrrolidine using pyrroline as directing group.

Later in 2010, Maes and co-workers reported a new and general methodology for the synthesis of arylated *N*-substituted piperidines **1.99**, through a directing group assisted transition metal catalyzed reaction. In this case, pyridine was chosen as an effective directing group. Along with mono arylated product **1.99**, di-arylated product **1.100** was also obtained with inseparable trans/cis isomers. (**Scheme. 24, eq. 42**).⁵⁴

Maes, 2010

(42)

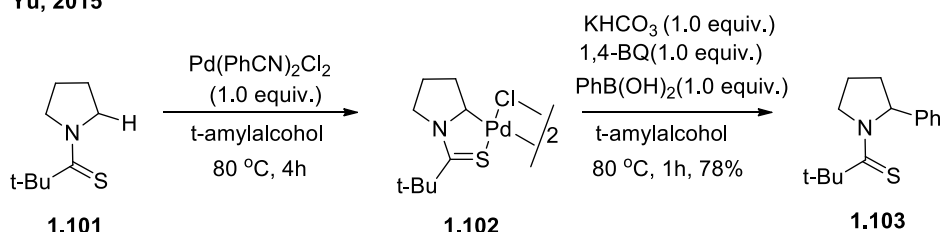


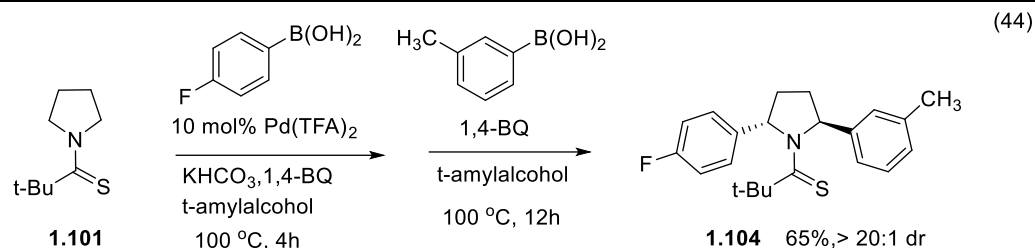
Scheme 24: Ruthenium catalyzed α -arylation of piperidine using pyridine as the directing group.

Beside pyrroline and pyridine the thioamide group, has been also used as an efficient directing group for α -C(*sp*³)-H arylation of secondary amines. In 2015, Yu and co-workers reported a Pd catalyzed α -C(*sp*³)-H arylation of secondary amines with aryl boronic acids (**Scheme. 25, eq. 43**). In this transformation pyrrolidines, piperidines, azepanes, and *N*-methylamine have been arylated with a wide range of boronic acid including heteroatomic boronic acids. This reaction is also applicable for diastereoselective one-pot hetero-diarylation of pyrrolidines (**Scheme 25, eq. 44**).⁵⁵

Yu, 2015

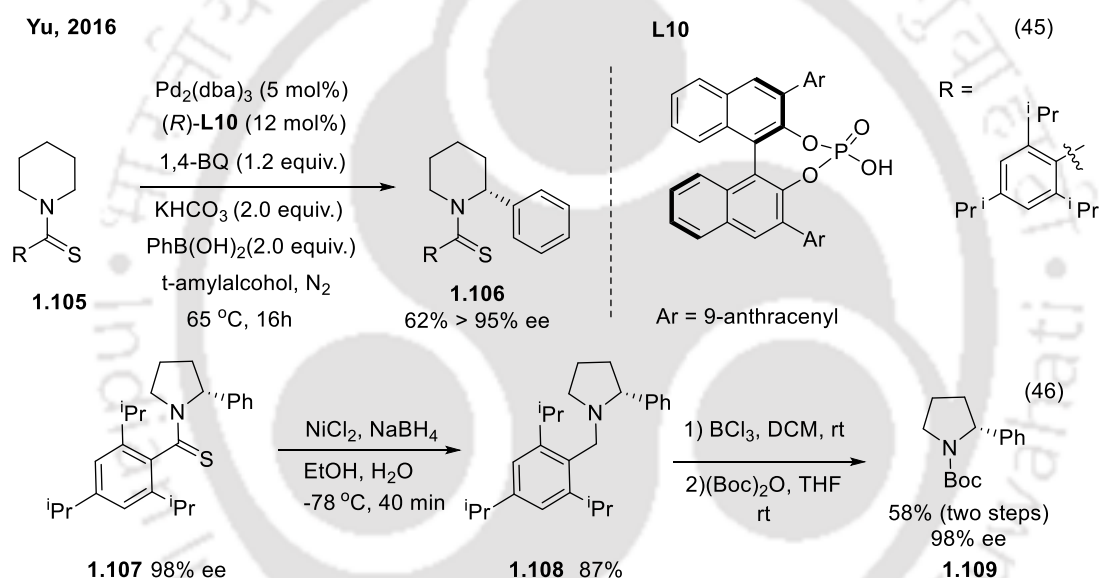
(43)





Scheme. 25: Palladium catalyzed arylation of pyrrolidine.

Recently in 2016, the same group reported a palladium catalyzed enantioselective α -arylation of thioamides **1.105** with boronic acids in the presence of chiral phosphate ligand **L10**. This reaction showed an efficient way to prepare highly privileged enantioenriched motif **1.106** with moderate to good yield and enantioselectivity (**Scheme 26**, eq. 45). A two steps sequence was required for removal of thioamide directing group (**Scheme 26**, eq. 46).⁵⁶



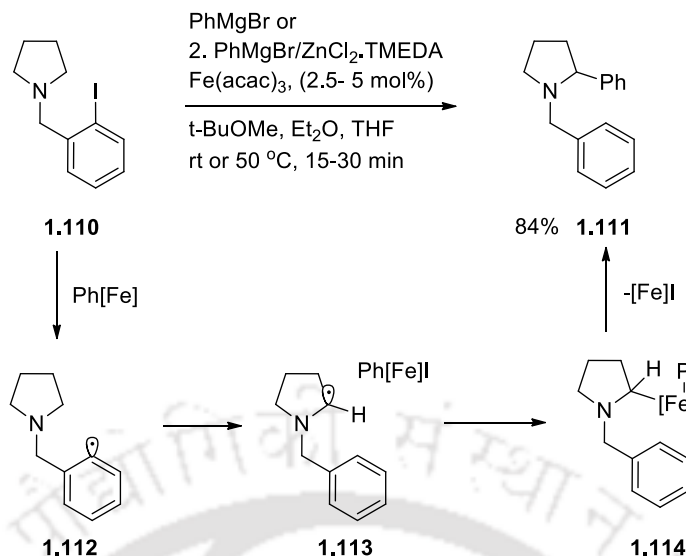
Scheme 26: Enantioselective arylation of *N*-heterocycles.

1.13. Intramolecular or intermolecular hydrogen transfer to synthesis of α -arylated amines:

Intramolecular or intermolecular hydrogen transfer reactions were used for synthesis of α -arylated amines. In 2010, Nakamura and co-workers reported an iron-catalyzed C(sp³)-H arylation reaction of an aliphatic amine **1.110** with a Grignard reagent to produce an α -substituted product **1.111**. The reaction proceeds through proposed intermediates such as **1.112**, **1.113**, and **1.114** to form the desired product **1.111** (**Scheme 27**, eq. 47).⁵⁷

Nakamura, 2010

(47)

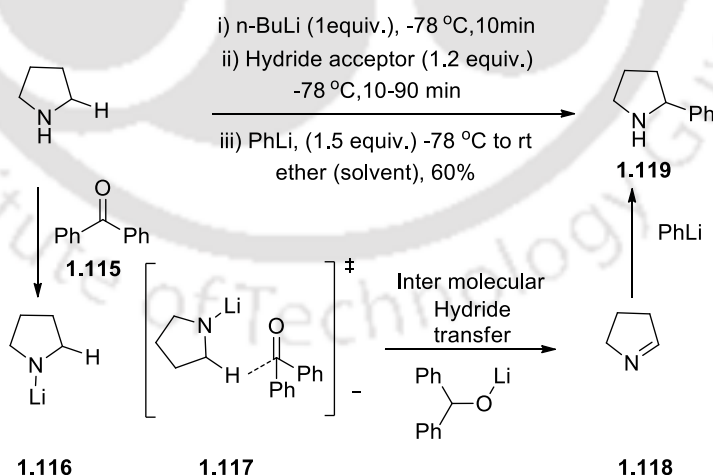


Scheme 27: Iron-catalyzed α -arylation of aliphatic amines via 1,5 hydride transfer.

Recently in 2018, Siedel and co-workers reported a method based on a one pot three steps reaction for α -C–H bond functionalization of cyclic amines. In this reaction, first pyrrolidine was reacted with *n*-BuLi to obtain lithitated pyrrolidine **1.116**. A sacrificial hydride acceptor **1.115**, which accept hydride to provide cyclic imine **1.118** via the proposed transition state **1.117**. Finally, the cyclic amine **1.118** reacts with the organolithium reagent to obtain the α -arylated cyclic amine **1.119** (Scheme 28, eq. 48).⁵⁸

Siedel, 2018

(48)



Scheme 28: α -Arylation of secondary amine via inter molecular hydride transfer.

Though aforementioned numerous examples for the synthesis of arylated *N*-heterocycles have been reported in the literature, many challenges still remain. For example, although there has been an increasing number of reports on *N*-cycloalkylation strategies and the approaches that

use pre-oxidized or pre-functionalized amines for the synthesis of arylated *N*-heterocycles, most of them involve a multi-step synthetic procedure including hazardous metal and oxidant which harmful are for the environment. Besides these indirect methods, various direct methods for the synthesis of arylated *N*-heterocycles were also reported. The α -deprotonation strategy involves the use of a strong base, a hazardous metal catalyst with the expensive ligand. On the other hand, CDC approaches are a break-through in the field of amine functionalization. But uses of sophisticated and valuable transition metal or organocatalyst and external oxidant reduces its practical utility. Transition metal catalyzed directed arylation of *N*-heterocycles suffered from poor selectivity and reactivity.

Therefore, the primary focus of the thesis is to develop novel environmentally friendly strategies for the synthesis of α -arylated *N*-heterocycles without uses of any external metal, oxidant and pre-oxidized or pre-functionalized starting materials.

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Chapter 2
**Metal and Oxidant Free Direct C(sp³)-H Arylation
of Pyrrolidine**



2.1 Introduction:

The dependence of human society on functional molecules (serving as advanced material and medicine) is increasing tremendously with time. Accordingly, huge progress has been made for the development of novel methods and strategies to synthesize those functional molecules. During the synthesis of those functional molecules excess atomic units (in the form of reactants, reagents, solvents or catalysts) required to achieve chemical selectivity and molecular complexity, are eliminated as the chemical waste, which becomes a major problem for the environment. Enormous effort is on-going to modify known methods and /or to develop a new methodology for minimizing the production of the chemical wastes. Various concepts like atom economy,¹ redox economy,² and step economy³ were introduced and accepted by the synthetic chemistry community, as some of the important parameters for evaluating the practicability of synthetic methods.⁴ In this respect, the reaction via simple addition of reactants, without any other aid (e.g. metal based catalyst, oxidant etc.), providing desired product would be better suited. A very few reactions of such kind (e.g. Diels-Alder,⁵ Mannich,⁶ Betti reaction⁷ etc.), in comparison to the pool of known chemical processes, are preceded in literature. Therefore, innovative design for the development of new reactions or reformatting the known ones to minimize the waste, keeping the essential features intact (selectivity, yields etc.), is intensely needed.

In view of such development, evolutionary efforts are continuing in the context of direct C-H-arylation of saturated *N*-heterocycles, as α -arylated heterocycles, like arylated pyrrolidine have a wide range of application in chemistry as well as in medicine (**Figure 1**).^{8,9}

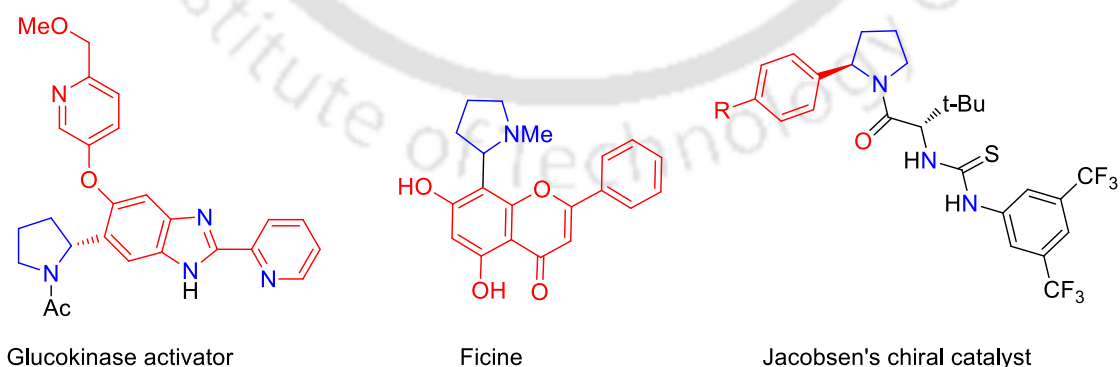
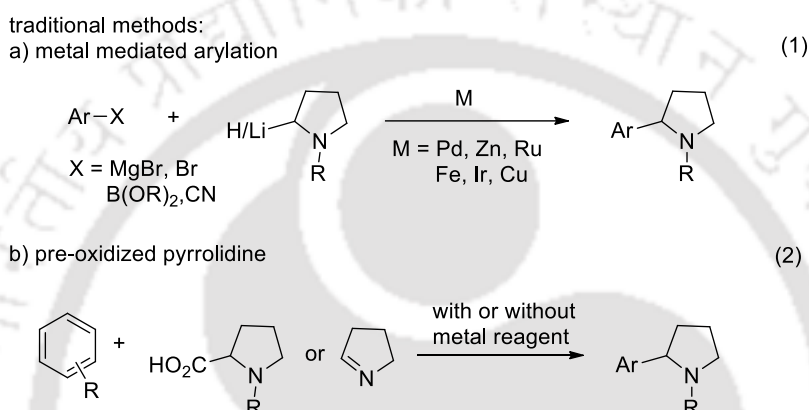


Figure 1: Arylated pyrrolidine containing important molecules in chemistry as well as medicine.

In chapter 1, various methods for the synthesis of α -arylated *N*-heterocycles including arylated pyrrolidine have been described. It was observed that, all of the known protocols for

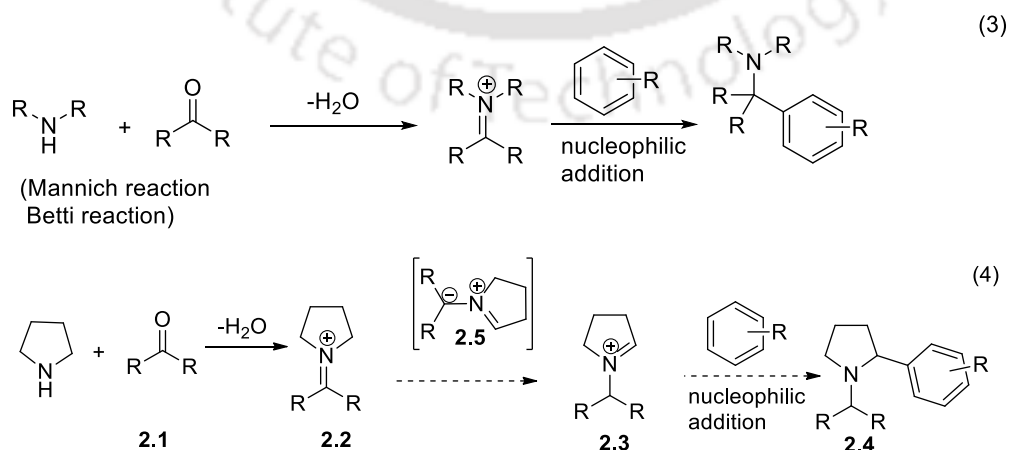
efficient direct arylation of saturated *N*-heterocycles generally involve the use of organometallic reactants either in stoichiometric and/or catalytic amount (**Scheme 1**, eq. 1).^{10, 11} The metal mediated reactions are highly efficient in terms of selectivity and reactivity in producing a wide variety of C-H arylated valuable heterocyclic compounds. However, considerable interests are shown in recent years for developing metal free transformations to exclude the traces of toxic metal contamination in pharmaceutically important compounds as well as to avoid the unwanted metal-based chemical wastes.¹² In an another approach, pre-oxidized starting materials were used for the arylation with or without metal-based reagents (**Scheme 1**, eq. 2).¹³



Scheme 1: Traditional methods for arylation of pyrrolidine.

Therefore, all of these known processes produce toxic chemical wastes which are a burden to the environment. In addition, not easily achievable reaction conditions (such as moisture free, air free etc.) in metal-based reaction creates difficulty, especially in industrial scale production. Therefore, the primary aim was to develop a metal-free, oxidant-free, atom economic and operationally simple method for direct α -C-H arylation of pyrrolidine.

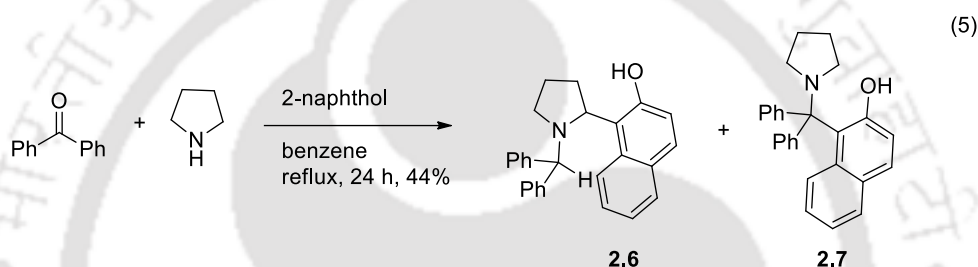
2.2. Hypothesis for direct C(sp³)-H arylation of *N*-heterocycles:



Scheme 2. Two different modes of iminium ion reactivities.

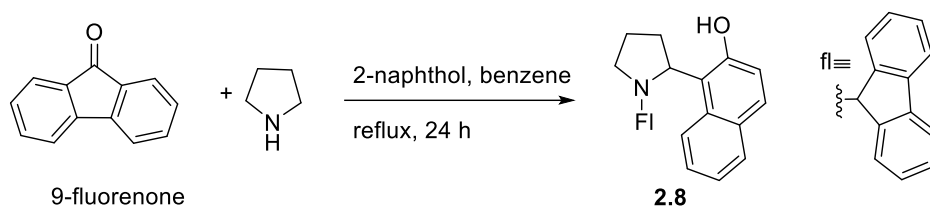
Alkylation or arylation of aldehyde and ketone via nucleophilic addition to the corresponding iminium ions (Mannich reaction, **Scheme 2**, eq.3) is a very efficient carbon-carbon bond forming reaction. Thus the reaction was extensively applied in organic synthesis producing various functional molecules.⁶ In the context of alpha C-H arylation of amines, it was anticipated that by the judicious design of a carbonyl compound **2.1**, one could isomerize the initial iminium ion **2.2** to **2.3** that will react subsequently with nucleophilic aromatic compound to give the arylated product **2.4**. The azomethine ylide **2.5** may be involved in mediating this isomerization.¹⁴ A perfect design of the carbonyl compound would stabilize the negative charge of the zwitterion **2.5**.

2.3. First reaction for direct C-H Arylation:



In this context, benzophenone, which is cheap and commercially available, was elected as the carbonyl partner to test the mechanistic hypothesis. The choice was based on the perception that the initial iminium ion (**2.2**, R = Ph) will be sterically hindered for nucleophilic attack, and the anion in the corresponding azomethine ylide (**2.5**, R = Ph) will be stable due to the possibility of its delocalization through two phenyl groups present. Accordingly, the first reaction of benzophenone with pyrrolidine in the presence of 2-naphthol as a nucleophile was carried out in benzene under reflux condition. Indeed, the desired α -arylated pyrrolidine **2.6** was isolated with 44% yield (eq. 5). The product was formed as a sole regioisomer without producing Betti or Mannich adduct **2.7**. Encouraged by this initial result, the same reaction was performed at an elevated temperature (150 °C for 48 h) to increase the yield of the reaction. However, the desired compound was isolated with a reduced yield (18%).

2.4. Table 1: Optimization of the reaction condition:



Entry ^a	Solvent	Temp.	Time	Yield ^b (%)
1	benzene	reflux	24h	80
2	benzene	rt	24h	27
3	toluene	reflux	24h	32
4	DCM	40 °C	24h	16
5	THF	reflux	24h	39
6	EtOAc	reflux	24h	23

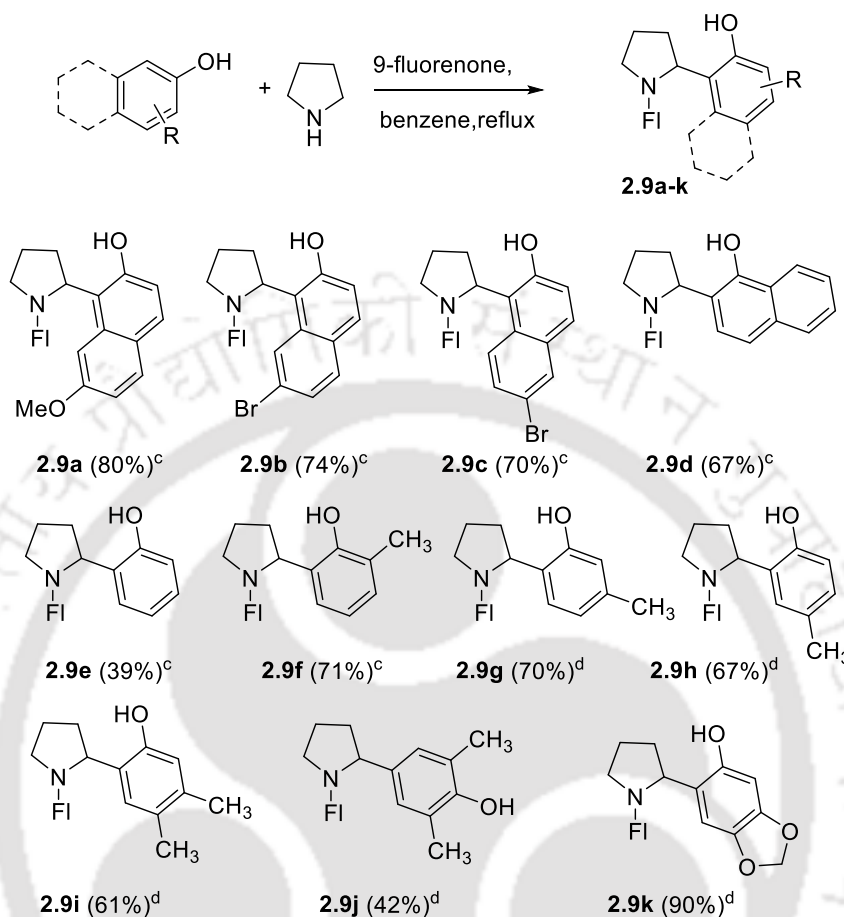
^a Reactions were carried out with 0.7 mmol of 2-naphthol, 1.2 eq. of pyrrolidine and 1.2 eq. of 9-fluorenone. ^b Isolated yields.

At that point, we had turn to our attention to search for a different carbonyl compound that can serve to provide both high yield as well as exclusive regio-selectivity. Ready availability of that carbonyl compound was also considered during our planning. Accordingly, 9-fluorenone was selected as a suitable carbonyl partner keeping in mind that extra benefit may be obtained due to the aromatic nature of the anion in corresponding azomethine yield. The reactivity of 9-fluorenone was tested by allowing it to react with pyrrolidine in refluxing benzene in the presence of 2-naphthol. As expected, the arylated pyrrolidine **2.8** was isolated as a single regioisomer with a very good yield of 80% (Table 1, entry 1). Different reaction conditions, by varying reaction temperatures and solvents, were examined for further improvement in the yield of the desired product. Although other solvents like toluene, THF, DCM, etc. are suitable for the reaction, benzene was found to be the most suited solvent under reflux condition.

2.5. Substrate scope of the reaction:

The scope of this new reaction was then investigated employing the optimized reaction conditions (**Scheme 3**). At first, different commercially available naphthol derivatives were examined as potential nucleophiles. Methoxy and bromo substituted 2-naphthols gave the desired products **2.9a** (80%), **2.9b** (74%), and **2.9c** (70%), respectively, with very good yields. Similar reactivity was observed in the case of 1-naphthol providing the α -naphthylated

pyrrolidine derivative **2.9d**. In every case, only C-H arylated compound was formed without producing Betti product (**Scheme 3**).



Scheme 3: Arylation of pyrrolidine using naphthol and phenol derivatives. ^c yield after 24h; ^d yield after 36h.

Next, phenol and its derivatives were considered as the potential nucleophilic substrates. Phenol derivatives can react through both *ortho* as well as *para*-position. Thus, this creates the possibility of producing at least two regioisomeric products. Surprisingly, a single regioisomer was formed from the reaction of phenol and its derivatives. The regiochemistry of representative compounds were confirmed from their X-ray crystal structures (**Figure 2**). Phenol reacted exclusively through *ortho*-position and the product **2.9e** was isolated in moderate yield. On the other hand, a very good yield (71% of **2.9f**) and exclusive regioselectivity was obtained for *ortho*-cresol. Similar reactivity was observed for both *meta*-cresol and *para*-cresol furnishing the desired products **2.9g** (70%) and **2.9h** (67%), respectively. Slightly lower yields of the desired product **2.9i** (61%) obtained for 3, 4-dimethylphenol. The reaction was forced to occur through *para*-position of 2,6-dimethyl phenol as both of its *ortho*-positions were blocked. However, the *para*-product **2.9j** was isolated with slightly

lower yield. The highly oxygenated phenol derivative sesamol also reacted very efficiently. The desired product **2.9k** was isolated with the highest yield (90%) in this series. Expectedly, electron deficient *meta*-bromo phenol provided the desired product in trace amounts. On the other hand, no desired product was formed for *para*-nitro phenol.

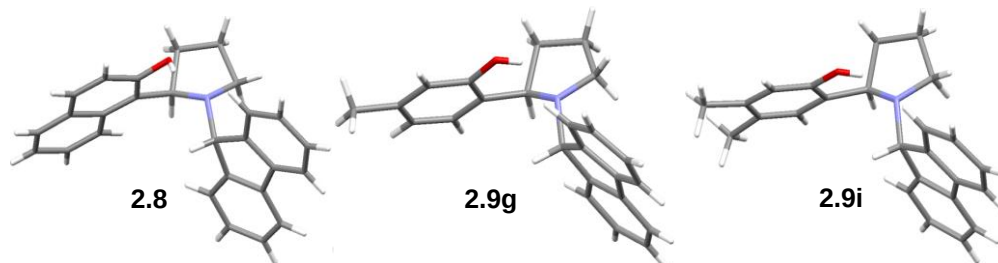
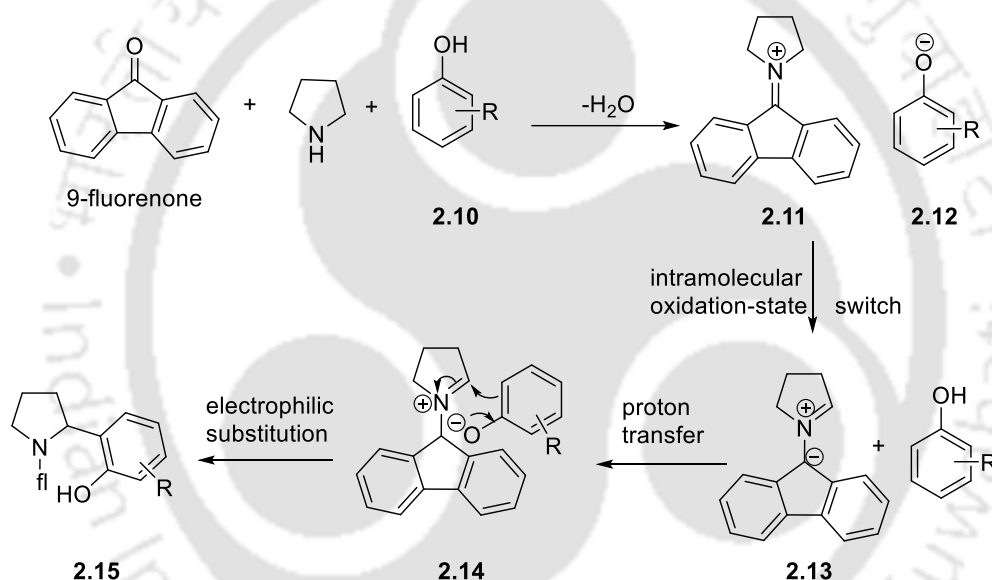


Figure. 2: X-ray crystal structure of **2.8**, **2.9g** & **2.9i**

2.6. Proposed reaction mechanism:

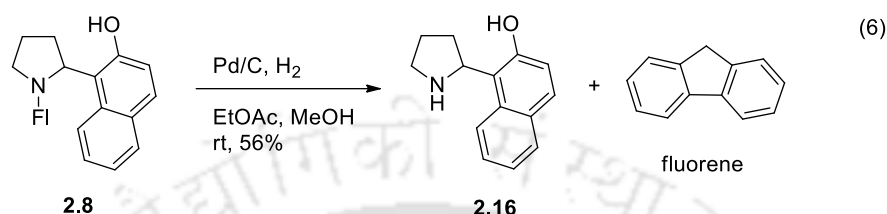


Scheme 4: Proposed mechanism of metal free arylation of pyrrolidine.

A mechanistic proposal for the newly developed, metal-free, oxidant-free and atom economic alpha C-H arylation of pyrrolidine is presented in the Scheme 4. Pyrrolidine condensed with 9-fluorenone with the assistance of phenolic-OH (**2.10** as a proton source) forming the corresponding iminium cation **2.11** which is accompanied with phenolate anion **2.12**. Base (pyrrolidine or phenolate) aided isomerization of parent iminium ion **2.11** occurred, producing the azomethine ylide **2.13**, that has a fluorenyl anion moiety which is stabilized due to its aromaticity. A secondary iminium ion **2.14**, probably formed through protonation of azomethine ylide **2.13**, leading to an oxidation state switch from fluorenone carbon (in **2.11**) to C2 of pyrrolidine in **2.14**, eliminated the possibility of Mannich or Betti product formation.¹⁵ Then, the secondary iminium ion **2.14** reacted with phenolic compound, via

aromatic electrophilic substitution reaction, providing the α -arylated product **2.15**. The close association (as shown in **Scheme 4**) of the electrophilic iminium ion **2.14** with the nucleophilic phenolate anion probably directs the reaction entirely through *ortho*-position and consequently brings the exclusive regio-selectivity.^{13d}

2.7. Cleavage of *N*-fluorenyl moiety:



The cleavage of the *N*-fluorenyl moiety of arylated pyrrolidine was investigated next. Accordingly, compound **2.8**, when reacted under standard hydrogenolysis conditions for 24 h, provided desired 2-naphthyl pyrrolidine **2.16** with 56% yield along with 34% of unreacted starting material (eq. 6). Therefore, fluorenyl moiety which is installed in the C-H arylation process can serve as the protecting group similar to benzyl protecting group for amine. Further, fluorene produced via reductive cleavage can be oxidized and reused.

2.8. Arylation of pyrrolidine with indole derivatives:

Indolyl *N*-heterocycles is found as important core in many biologically active molecule and natural products. Therefore, the direct arylation reaction using indole as the nucleophile was investigated next. Accordingly, a reaction of 9-fluorenone with pyrrolidine in the presence of indole as nucleophile was performed in refluxing benzene. After, 24 hours the desired product was not formed. The same reaction was performed by increasing the reaction time, at that moment the desired α -arylated product **2.17** obtained with 21% after 72 hours (Table 2, entry 1). This result encouraged us to investigate the reaction further to improve the yield. The yield was further improved by using 9-fluorenone imine as an activator instead of 9-fluorenone. (Table 2, entry 2). Next, we had turned our attention to decrease the reaction time. In this context, a reaction was carried out at 150 °C in toluene under microwave irradiation. At this moment, 43% chemical yield was observed after 40 minutes. The best result was obtained when the reaction was performed with 9-fluorenone imine, pyrrolidine and indole in toluene under microwave irradiation for 60 minutes.

2.9. Table 2: Optimization of the reaction condition:

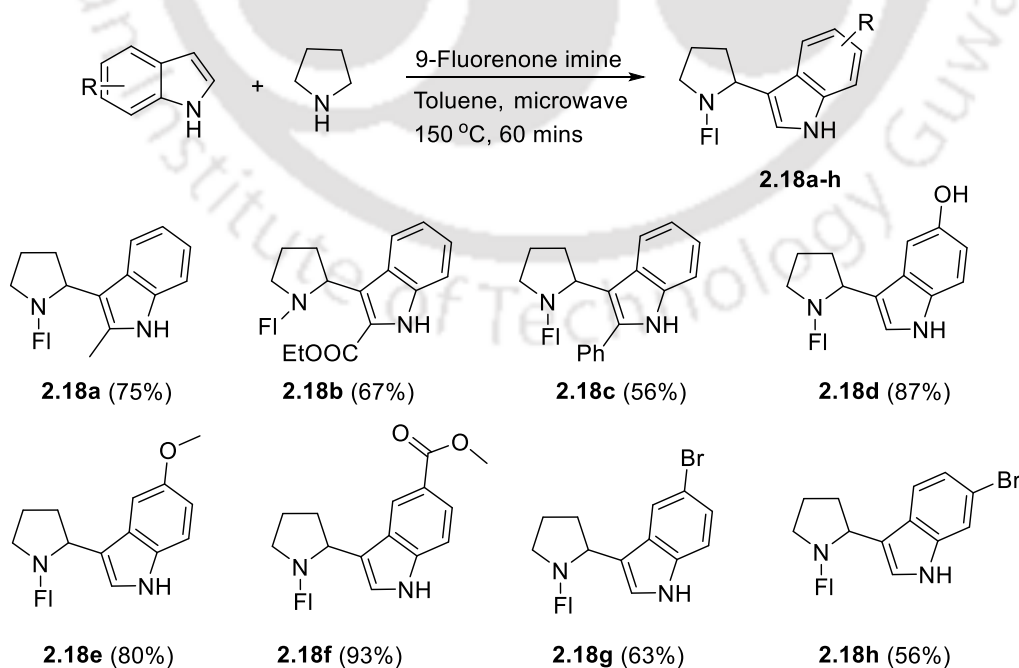
different conditions
9-fluorenone
or 9-fluorenone imine
(9-F imine)

2.17

Entry ^e	Activator	solvent	Temperature	Time	Yield ^f
1	9-fluorenone	benzene	reflux	72h	21 %
2	9-F imine	benzene	reflux	72 h	33 %
3	9- F imine	neat	100 °C	66 h	-
4	9-fluorenone	toluene, μ w	150 °C	45 min	43 %
5	9-F imine	toluene, μ w	150 °C	60 min	60 %
6	9-F imine	xylene, μ w	170 °C	60 min	51 %
7	9-F imine	CH ₃ CN, μ w	100 °C	60 min	trace
8	9-F imine	MeOH, μ w	60 °C	60 min	46 %
9	9-F imine	ETOH, μ w	100 °C	60 min	34%
10	9-F imine	Benzene, μ w	100 °C	60 min	23 %

^e Reactions were carried out with 0.25 mmol of indole, 3.0 equiv. of pyrrolidine, 1.2 equiv. of 9-fluorenone imine and reaction was performed under microwave condition. ^f isolated yield.

2.10. Substrate scope of the reaction:



Scheme 8: Arylation of pyrrolidine with indole.

The scope of the reaction was investigated using an optimized reaction condition. At first, different commercially available indole derivatives were used as potential nucleophiles. Substituted indoles such as 2-methyl indole and ethyl indole 2-carboxylate derivatives participated as potential nucleophiles to provide the desired products **2.18a** (75%), and **2.18b** (67%) respectively, with good yields. The, slightly lower yield was obtained for highly sterically hindered 2- phenyl indole **2.18c** (56%). Next, electron donating indole derivatives at 5-position were tested for arylation reaction. In this context, 5-hydroxy, 5-methoxy and methyl 1H-indole-5-carboxylate indoles derivatives gave the desired product **2.18d** (87%), **2.18e** (80%), and **2.18f** (93%) with good to excellent yield respectively. Halogen substituted 5-bromo and 6-bromo indole also gave the desired arylated product with slightly lower yield **2.18g** (63%) and **2.18h** (56%) respectively.

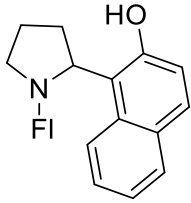
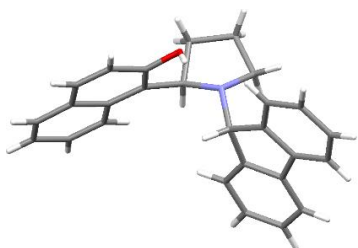
2.11. Summary:

In summary, the first example of a metal, oxidant and other additive-free method for direct sp^3 C-H arylation of pyrrolidine via an operationally simple, and highly atom economic three component reaction has been developed. Importantly, a new approach for direct C-H arylation based on a novel reactivity of iminium ion, differing from the traditional reactivity in Mannich or Betti reaction, is presented. As an alternative to the metal-mediated reaction, the method is highly stereo-selective and efficient even in multi-gram scale reaction. Therefore the method will be highly compatible for industrial scale synthesis of valuable arylated pyrrolidines for practical application. Soon after our publication Siedel and co-workers reported as similar arylation reaction employing 2,6-dichlorobenzaldehyde as an activator (carbonyl partner) in place of a 9-fluorenone.¹⁶

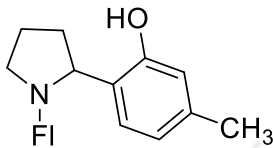
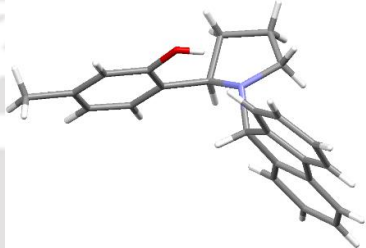
2.12. Experimental Section:

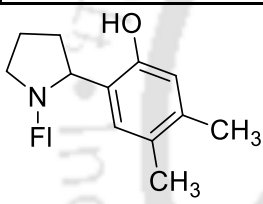
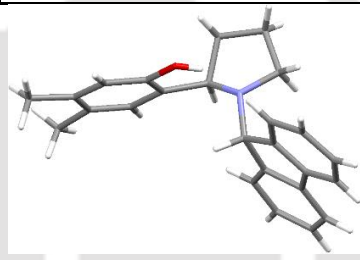
General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. THF and Diethylether (Et₂O) were freshly distilled from Sodium under argon. Dichloromethane (CH₂Cl₂) was freshly distilled from phosphorus(V)oxide (P₂O₅). Triethylamine (Et₃N) was distilled from CaH₂ and stored under argon. Commercial grade xylene, benzene and toluene were distilled 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, ¹³C NMR spectroscopy: *Varian Mercury plus 400 MHz* (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS ($\delta(^1\text{H})$ 0.0 ppm, $\delta(^{13}\text{C})$ 0.0 ppm) which was used as the inner reference. otherwise the solvents residual proton resonance and carbon resonance (CHCl₃, $\delta(^1\text{H})$ 7.26 ppm, $\delta(^{13}\text{C})$ 77.0 ppm; CD₃OD, (¹H) 3.31 ppm, $\delta(^{13}\text{C})$ 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 a Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak). X-ray crystallographic data were collected using a Bruker SMART APEX-II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube Mo-K α radiation (λ = 0.71073 Å) at 296(2) K, with increasing ω (width of 0.3° per frame) at a scan speed of 3 s/frame. Structures were solved by direct methods using SHELXS-97 and refined with fullmatrix least squares on F^2 using SHELXL-97. Using Olex2¹⁷, structure was solved with the Superflip¹⁸ structure solution program using Charge Flipping and refined with the olex2.refine¹⁹ refinement package using Gauss-Newton minimisation. All the non-hydrogen atoms were refined anisotropically.

Crystal Structures:Crystal data for **2.8**:

	
Crystal data and structure refinement for 2.8 CCDC NO-955427	
Empirical formula Formula weight Crystal habit, colour Crystal size, mm ³ Temperature, <i>T</i> Wavelength, λ (Å) Crystal system Space group Unit cell dimensions Volume, $V(\text{\AA}^3)$ <i>Z</i> Calculated density, Mg·m ⁻³ Absorption coefficient, $\mu(\text{mm}^{-1})$ <i>F</i> (000) θ range for data collection Limiting indices Reflection collected / unique Completeness to θ	C ₂₇ H ₂₃ N O 377.46 needle / colorless 20*25*30 296(2) K 0.71073 triclinic 'P-1' $a = 10.9272(16)\text{\AA}$ $b = 19.193(3)\text{\AA}$ $c = 19.223(3)\text{\AA}$ $\alpha = 89.892(12)^\circ$, $\gamma = 87.325(11)^\circ$, $\beta = 89.805(11)^\circ$ 4027.0(11) 8 1.245 0.075 1600 1.06° to 25.00° $-12 \leq h \leq 12$, $-22 \leq k \leq 22$, $-22 \leq l \leq 22$ 39369 / 3843 [<i>R</i> (int) = 0.1741] 96.8% ($\theta = 25.00^\circ$)

Chapter 2

Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	3843 / 0 / 1049
Goodness-of-fit on F^2	0.990
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0775$, $wR2 = 0.1768$
R indices (all data)	$R1 = 0.2793$, $wR2 = 0.2730$
Largest diff. peak and hole	0.328 and $-0.423 \text{ e} \cdot \text{\AA}^{-3}$
 	
Crystal data and structure refinement for 2.9g CCDC NO-955429	
Empirical formula	$\text{C}_{24} \text{H}_{23} \text{N O}$
Formula weight	341.43
Crystal habit, colour	needle / colorless
Crystal size, mm^3	15*20*25
Temperature, T	296(2) K
Wavelength, $\lambda(\text{\AA})$	0.71073
Crystal system	orthorhombic
Space group	' $P-1$ '
Unit cell dimensions	$a = 13.6446(2) \text{\AA}$ $b = 12.7242(2) \text{\AA}$ $c = 21.6300(3) \text{\AA}$ $\alpha = 90.00^\circ$, $\gamma = 90.00^\circ$, $\beta = 90.00^\circ$
Volume, $V(\text{\AA}^3)$	3755.33(10)
Z	8
Calculated density, $\text{Mg} \cdot \text{m}^{-3}$	1.208
Absorption coefficient, $\mu(\text{mm}^{-1})$	0.073

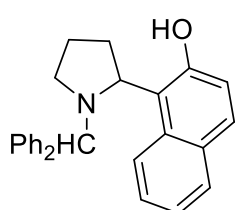
$F(000)$	1456
θ range for data collection	1.88° to 28.58°
Limiting indices	$-12 \leq h \leq 12, -22 \leq k \leq 22, -22 \leq l \leq 22$
Reflection collected / unique	47887 / 2572 [$R(\text{int}) = 0.1778$]
Completeness to θ	99.7% ($\theta = 28.58^\circ$)
Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	2572 / 0 / 237
Goodness-of-fit on F^2	1.079
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0727, wR2 = 0.1877$
R indices (all data)	$R1 = 0.1150, wR2 = 0.2028$
Largest diff. peak and hole	0.392 and $-0.288 \text{ e} \cdot \text{\AA}^{-3}$
	
Crystal data and structure refinement for 2.9i CCDC NO-955428	
Empirical formula	$\text{C}_{25} \text{H}_{25} \text{N O}$
Formula weight	355.46
Crystal habit, colour	needle / colorless
Crystal size, mm^3	17*20*25
Temperature, T	296(2) K
Wavelength, $\lambda(\text{\AA})$	0.71073
Crystal system	triclinic
Space group	' $P1$ '
Unit cell dimensions	$a = 9.5351(8) \text{\AA}$ $b = 12.1609(10) \text{\AA}$

Chapter 2

	$c = 17.2642(15)\text{\AA}$
	$\alpha = 90.159(4)^\circ, \gamma = 94.762(4)^\circ, \beta = 90.134(4)^\circ$
Volume, $V(\text{\AA}^3)$	1995.0(3)
Z	4
Calculated density, $\text{Mg}\cdot\text{m}^{-3}$	1.183
Absorption coefficient, $\mu(\text{mm}^{-1})$	0.071
$F(000)$	760
θ range for data collection	1.18° to 24.00°
Limiting indices	$-10 \leq h \leq 10, -13 \leq k \leq 13, -19 \leq l \leq 19$
Reflection collected / unique	19547 / 7213 [$R(\text{int}) = 0.0863$]
Completeness to θ	92.0% ($\theta = 24.00^\circ$)
Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	7213 / 0 / 985
Goodness-of-fit on F^2	0.981
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0619, wR2 = 0.1657$
R indices (all data)	$R1 = 0.0778, wR2 = 0.1844$
Largest diff. peak and hole	0.333 and $-0.301\text{e}\cdot\text{\AA}^{-3}$

Experimental procedure:

1-(1-benzhydrylpyrrolidin-2-yl)naphthalen-2-ol (2.6): Benzophenone (0.23 g, 1.25 mmol),



pyrrolidine (0.10 mL, 1.25 mmol), 2-naphthol (0.15 g, 1.04 mmol) in 3 mL benzene under reflux for 24 h and SiO_2 column chromatography (hexane: ethyl acetate 100:1) gave **2.6** as light yellow solid (0.18 g, 44 %).

FTIR (KBr): $\tilde{\nu} = 3451, 2972, 1899, 1620, 1596, 1581, 1520, 1492, 1453, 1415, 1334, 1315, 1240, 1167, 1157, 1139, 1071, 1029, 1001, 975, 954, 929, 899, 769, 749, 733, 713, 631, 602, 562, 527, 507, 479, 465\text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 13.32$ (s, 1H), 7.63 (d, $J = 8.0\text{ Hz}$, 1H), 7.58 (d, $J = 8.4\text{ Hz}$, 1H), 7.53 (d, $J = 8.8\text{ Hz}$, 1H), 7.34 – 7.17 (m, 9H), 7.03 – 6.87 (m, 4H), 4.97 (s, 1H), 4.52 (t, $J = 8.4\text{ Hz}$, 1H), 3.40 – 3.35 (m, 1H), 2.51 – 2.45 (m, 1H), 2.67 – 2.2 (m, 1H), 2.03 – 1.74 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 156.1, 140.5, 138.7, 132.1, 129.7, 128.8, 128.5, 128.4, 128.0, 127.9, 127.7, 126.9, 126.1,$

122.2, 121.0, 119.6, 116.0, 70.3, 62.0, 50.0, 32.0, 23.4 ppm. HRMS (ESI) exact mass calculated for $C_{27}H_{26}NO^+$ ($[M+H]^+$): 380.2009, found: 380.2012.

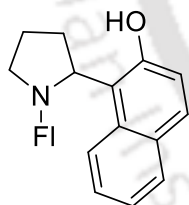
General procedure I for C-H arylation:

Phenol or naphthol derivative (0.5 mmol, 1.0 eq.) was added to a solution of pyrrolidine (1.2 eq.) and 9-fluorenone (1.2 eq.) in benzene (2 mL) at room temperature. Then the reaction mixture was stirred under the reflux conditions for 24h or 36h depending on the substrate. Then the mixture was cooled to room temperature, the organic solvents were removed under vacuum and the crude product was purified by column chromatography providing analytically pure 2-aryl pyrrolidines. Some of the compounds (like **2.8**, **2.9b**, **2.9c**) crystallized from the reaction mixture, thus did not require column chromatographic purification.

General procedure II, for CH arylation under microwave irradiation:

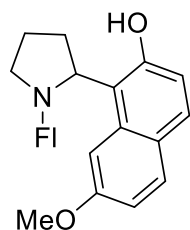
Indole derivative (0.25 mmol, 1.0 equiv.) was added to a solution of pyrrolidine (3.0 equiv.) and 9-fluorenone or 9-fluorenone imine (1.2 equiv.) in toluene (1 mL) at room temperature. Then the reaction mixture was heated under the microwave irradiation (200 watt) for 60 min at 150 °C. Then the mixture was cooled to room temperature, the organic solvents were removed under vacuum and the crude product was purified by column chromatography providing analytically pure arylated pyrrolidine.

1-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)naphthalen-2-ol (2.8): According to general



procedure I: 9-fluorenone (1.5 g, 8.33 mmol), pyrrolidine (0.68 mL, 8.33 mmol), 2-naphthol (1.00 g, 6.94 mmol) in 8 mL benzene under reflux for 24 h gave **2.8** as light brown solid (appeared on cooling the reaction mixture, 2.05 g, 80%). FTIR (KBr): $\tilde{\nu}$ = 3444, 3050, 2964, 2942, 2848, 2609, 1918, 1815, 1619, 1597, 1581, 1520, 1467, 1450, 1414, 1307, 1269, 1239, 1166, 1135, 1090, 1076, 955, 936, 905, 857, 816, 736, 673, 638, 622 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ = 13.32 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.83 – 7.74 (m, 3H), 7.66 – 7.55 (m, 4H), 7.37 – 7.32 (m, 4H), 7.25 – 7.722 (m, 2H) 5.36 (t, J = 8.4 Hz, 1H), 4.94 (s, 1H), 2.64 – 2.58 (m, 1H), 2.42 – 2.35 (m, 1H), 2.08 – 1.99 (m, 2H), 1.89 – 1.82 (m, 1H), 1.74 – 1.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.6, 144.2, 142.4, 140.8, 140.3, 133.2, 129.6, 129.3, 128.8, 128.7, 128.5, 128.0, 127.0, 126.9, 126.7, 125.5, 122.6, 120.8, 120.2, 120.0, 119.8, 114.2, 62.6, 61.9, 44.7, 31.5, 22.4 ppm. HRMS (ESI) exact mass calculated for $C_{27}H_{24}NO$ ($[M+H]^+$): 378.1852, Found: 378.1856.

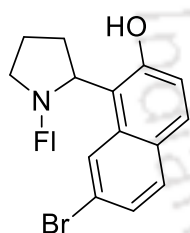
1-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-7-methoxynaphthalen-2-ol (2.9a): According to



general procedure I : 9-fluorenone (77 mg, 0.34 mmol), pyrrolidine (35 μ L, 0.34 mmol), 7-methoxy-2-naphthol (50 mg, 0.29 mmol) in 2 mL benzene under reflux for 24 h, and SiO₂ column chromatography (hexane: ethyl acetate 100:1) gave **2.9a** as light brown solid (94 mg, 80 %). FTIR (KBr): $\tilde{\nu}$ = 3432, 3048, 2955, 2823, 1719, 1618, 1516, 1465, 1385, 1318, 1264,

1224, 1132, 1085, 1033, 915, 823, 737, 677, 638, 605 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 13.23 (s, 1H), 7.78 – 7.77 (m, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.59 – 7.57 (m, 1H), 7.50 – 7.45 (m, 2H), 7.39 – 7.20 (m, 4H), 7.08 (d, J = 8.8 Hz, 1H), 7.04 (dd, J = 8.8, 2.4 Hz, 1H), 5.21 (m, 1H), 4.94 (s, 1H), 4.02 (s, 3H), 2.64 – 2.58 (m, 1H), 2.43 – 2.35 (m, 1H), 2.10 – 2.00 (m, 2H), 1.92 – 1.81 (m, 1H), 1.76 – 1.66 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 158.8, 157.2, 144.3, 142.6, 140.7, 140.4, 134.4, 130.9, 129.4, 128.8, 128.6, 128.1, 126.9, 126.8, 125.6, 124.3, 120.3, 119.9, 117.5, 114.1, 113.2, 100.9, 62.6, 61.9, 55.6, 44.7, 31.1, 22.3 ppm. HRMS (ESI) exact mass calculated for C₂₈H₂₆NO₂ ([M+H]⁺): 408.1958, Found: 408.1961.

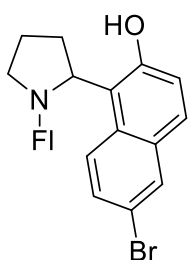
1-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-7-bromonaphthalen-2-ol (2.9b): According to



general procedure I : 9-fluorenone (58 mg, 0.32 mmol), pyrrolidine (26 μ L, 0.32 mmol), 7-bromo-2-naphthol (60 mg, 0.27 mmol) in 2 mL benzene under reflux for 24, white solid appeared on cooling the reaction mixture. The solid compound was washed with mixture of ethyl acetate and hexane 1:20 to obtain **2.9b** as white solid (91 mg, 74%). FTIR (KBR): $\tilde{\nu}$ = 3439,

3056, 2967, 2828, 1613, 1580, 1505, 1446, 1370, 1305, 1257, 1231, 1200, 1079, 970, 938, 850, 735, 674, 641, 547 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 13.49 (s, 1H), 8.11 (s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.75 – 7.60 (m, 4H), 7.53 (d, J = 7.2 Hz, 1H), 7.42 – 7.35 (m, 4H), 7.33 – 7.20 (m, 2H), 5.22 – 5.12 (m, 1H), 4.89 (s, 1H), 2.63 – 2.60 (m, 1H), 2.40 – 2.38 (m, 1H), 2.07 – 1.98 (m, 2H), 1.88 – 1.84 (m, 1H), 1.75 – 1.70 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 157.6, 144.0, 142.4, 140.6, 140.4, 134.5, 130.9, 129.5, 128.9, 128.7, 128.1, 127.3, 127.2, 126.6, 125.9, 125.5, 123.2, 121.6, 120.5, 120.3, 119.9, 113.6, 62.7, 61.9, 44.9, 31.6, 22.5 ppm. HRMS (ESI) exact mass calculated for C₂₇H₂₃BrNO⁺ ([M+H]⁺): 456.0958, Found: 456.0969.

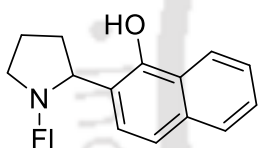
1-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-6-bromonaphthalen-2-ol (2.9c): According to



general procedure I : 9-fluorenone (87 mg, 0.49 mmol), pyrrolidine (40 μ L, 0.49 mmol), 6-bromo-2-naphthol (90 mg, 0.41 mmol), in 2 mL benzene under reflux for 24 h and SiO₂ column chromatography gave **2.9c** as white solid (0.13 g, 70 %). FTIR (KBr): $\tilde{\nu}$ = 3443, 3053, 2958, 2849, 1581, 1505, 1447, 1398, 1314, 1260, 1235, 1164, 1081, 1030, 947, 886, 810, 737, 675,

616 cm^{-1} . ¹H NMR (400 MHz, CDCl₃) δ = 13.39 (s, 1H), 7.95-7.947 (m, 1H), 7.87 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 7.2 Hz, 1H), 7.65-7.60 (m, 5H), 7.52 – 7.48 (m, 2H), 7.39 – 7.21 (m, 3H), 5.29 – 5.25 (m, 1H), 4.91 (s, 1H), 2.64 – 2.59 (m, 1H), 2.37 – 2.34 (m, 1H), 2.04 – 1.97 (m, 2H), 1.85 – 1.64 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 157.0, 144.1, 142.6, 140.7, 140.4, 131.7, 131.2, 130.1, 128.9, 128.7, 128.2, 127.2, 126.7, 125.6, 122.6, 121.2, 120.4, 119.9, 116.1, 114.6, 62.8, 61.9, 44.9, 31.6, 22.5 ppm. HRMS (ESI) exact mass calculated for C₂₇H₂₃BrNO⁺ ([M+H]⁺): 456.0958, found: 456.0973.

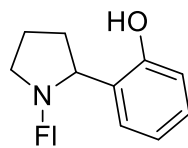
2-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)naphthalen-1-ol (2.9d): According to general



procedure I : 9-fluorenone (0.12 g, 0.66 mmol), pyrrolidine (54 μ L, 0.66 mmol), 1-naphthol (80 mg, 0.55 mmol) in 2 mL benzene under reflux for 24 h and SiO₂ column chromatography (hexane: ethyl acetate, 100:1) gave **2.9d** as white solid (0.14 g, 67 %). FTIR (KBr):

$\tilde{\nu}$ = 3451, 3047, 2959, 2873, 2850, 1634, 1599, 1573, 1450, 1392, 1325, 1305, 1198, 1185, 1130, 1091, 1024, 907, 807, 739, 675 cm^{-1} . ¹H NMR (400 MHz, CDCl₃) δ = 12.65 (s, 1H), 8.40 (d, J = 7.6 Hz, 1H), 7.80 – 7.78 (m, 2H), 7.65 – 7.59 (m, 3H), 7.52 – 7.40 (m, 2H), 7.45 – 7.21 (m, 6H), 4.97 (s, 1H), 4.68 – 4.63 (m, 1H), 2.58 – 2.56 (m, 1H), 2.25 – 2.23 (m, 1H), 2.15 – 1.99 (m, 2H), 1.82 – 1.63 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 153.6, 144.3, 142.3, 141.4, 140.2, 134.2, 128.6, 128.4, 127.9, 127.5, 127.1, 126.9, 126.5, 126.2, 125.7, 125.4, 125.0, 122.4, 120.1, 119.7, 118.6, 116.9, 67.3, 62.2, 44.7, 32.6, 22.3. HRMS (ESI) exact mass calculated for C₂₇H₂₄NO⁺ ([M+H]⁺): 378.1852, Found: 378.1864.

2-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)phenol (2.9e): According to general procedure I: 9-

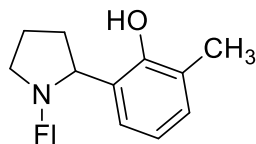


fluorenone (0.34 g, 1.91 mmol), pyrrolidine (0.16 mL, 1.91 mmol), phenol (0.14 mL, 1.59 mmol), in 2 mL benzene under reflux for 24 h, and SiO₂ column chromatography (hexane: ethyl acetate, 150:1) gave **2.9e** as yellow

gummy solid (0.20 g, 39 %). FTIR (KBr): $\tilde{\nu}$ = 3448, 2923, 2852, 1662, 1641, 1467, 1450, 1259, 1197, 1136, 1123, 1097, 1021, 801, 739, 656, 600 cm^{-1} . ¹H NMR (300 MHz, CDCl₃) δ

= 11.77 (s, 1H), 7.73 – 7.63 (m, 4H), 7.51 – 7.21 (m, 6H), 6.98 (d, J = 8.5 Hz, 1H), 6.90 (t, J = 7.3 Hz, 1H), 4.99 (s, 1H), 4.57 – 4.52 (m, 1H), 2.60 – 2.51 (m, 1H), 2.21 – 1.97 (m, 4H), 1.88 – 1.75 (m, 1H). HRMS (ESI) exact mass calculated for $C_{23}H_{22}NO^+$ ($[M+H]^+$): 328.1696, Found: 328.1704.

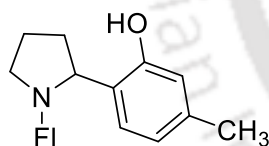
2-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-6-methylphenol (2.9f): According to general



procedure I: 9-fluorenone (0.12 g, 0.67 mmol), pyrrolidine (54 μ L, 0.67 mmol) 2-methylphenol (57 μ L, 0.56 mmol) in 2 mL benzene under reflux for 24 h, and SiO_2 column chromatography (hexane: ethyl

acetate, 100:1) gave **2.9f** as light yellow solid (0.14 g, 71 %). FTIR(KBr): $\tilde{\nu}$ = 3039, 2962, 2866, 1902, 1610, 1595, 1470, 1449, 1371, 1397, 1324, 1309, 1254, 1235, 1202, 1180, 1157, 1139, 1075, 1032, 1004, 980, 940, 915, 880, 834, 744, 735, 730, 701, 674, 643, 619 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ = 11.81 (s, 1H), 7.72 – 7.60 (m, 4H), 7.39 – 7.23 (m, 4H), 7.12 – 7.07 (m, 2H), 6.79 (t, J = 7.6 Hz, 1H), 4.94 (s, 1H), 4.51 (dd, J = 9.6, 7.2, Hz, 1H), 2.56–2.49 (m, 1H), 2.33 (s, 3H), 2.20–1.95 (m, 3H), 1.84 – 1.74 (m, 1H), 1.67 – 1.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.9, 144.4, 142.3, 141.6, 140.2, 130.3, 128.7, 128.4, 127.9, 126.9, 126.7, 125.5, 125.8, 123.4, 120.2, 119.8, 118.9, 67.2, 62.3, 44.7, 32.3, 22.2, 15.9 ppm. HRMS (ESI) exact mass calculated for $C_{24}H_{24}NO$ ($[M+H]^+$): 342.1852, found: 342.1854.

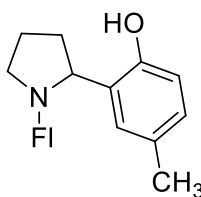
2-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-5-methylphenol (2.9g): According to general



procedure I: 9-fluorenone (0.12 g, 0.67 mmol), pyrrolidine (54 μ L, 0.67 mmol), 3-methylphenol (58 μ L, 0.56 mmol) in 2 mL benzene under reflux for 36 h and SiO_2 column chromatography (hexane: ethyl

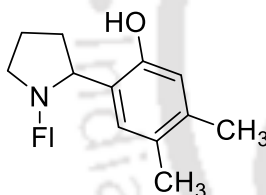
acetate, 100:1) gave **2.9g** as light yellow solid (0.13 g, 70%). FTIR (KBr): $\tilde{\nu}$ = 3444, 3020, 2929, 2868, 2689, 1948, 1886, 1712, 1618, 1580, 1511, 1448, 1379, 1344, 1277, 1195, 1149, 1122, 1087, 1023, 950, 905, 849, 805, 738, 673, 594, 555, 490 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ = 11.56 (s, 1H), 7.68 – 7.58 (m, 4H), 7.44 – 7.20 (m, 4H), 7.11 (d, J = 7.6 Hz, 1H), 6.8 (s, 1H), 6.17 – 6.69 (m, 1H), 4.94 (s, 1H), 4.51 – 4.46 (m, 1H), 2.52 – 2.46 (m, 1H), 2.33 (s, 3H), 2.18–1.91 (m, 3H), 1.79 – 1.72 (m, 1H), 1.64 – 1.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.6, 144.5, 142.4, 141.6, 140.3, 139.2, 129.1, 128.7, 128.5, 127.9, 126.9, 126.7, 125.5, 121.3, 120.3, 120.2, 119.8, 117.7, 67.0, 62.3, 44.6, 32.4, 22.1, 21.4 ppm. HRMS (ESI) exact mass calculated for $C_{24}H_{24}NO^+$ ($[M+H]^+$): 342.1852, found: 342.1843.

2-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-4-methylphenol (2.9h): According to general



procedure I: 9-fluorenone (60 mg, 0.56 mmol), pyrrolidine (54 μ L, 0.67 mmol), 4-methylphenol (58 μ L, 0.56 mmol) in 2 mL benzene under reflux for 36 h and SiO₂ column chromatography (hexane: ethyl acetate, 100:1) gave **2.9h** as light yellow solid (0.12 g, 67%). FTIR (KBr): $\tilde{\nu}$ = 3052, 3034, 2956, 2977, 2940, 2914, 2870, 2854, 1602, 1599, 1498, 1476, 1448, 1405, 1355, 1330, 1306, 1254, 1208, 1149, 1133, 1092, 1077, 1022, 1003, 927, 912, 866, 849, 818, 737, 674, 659, 643, 622, 488, 456 cm^{-1} . ¹H NMR (400 MHz, CDCl₃) δ = 11.44 (s, 1H), 7.71 – 7.62 (m, 3H), 7.41 – 7.24 (m, 5H), 7.05 – 7.03 (m, 2H), 6.86 (d, J = 9.2 Hz, 1H), 4.98 (s, 1H), 4.5 – 4.46 (m, 1H), 2.52 – 2.50 (m, 1H), 2.32 (s, 3H), 2.18 – 2.16 (m, 1H), 2.08 – 1.95 (m, 2H), 1.81 – 1.77 (m, 1H), 1.64 – 1.60 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 155.4, 144.4, 142.3, 141.6, 140.2, 129.8, 129.5, 128.7, 128.4, 127.9, 126.9, 126.7, 125.4, 124.0, 120.2, 119.7, 116.8, 67.2, 62.3, 44.7, 32.3, 22.2, 20.7 ppm. HRMS (ESI) exact mass calculated for C₂₄H₂₄NO⁺ ([M+H]⁺): 342.1852, found: 342.1844.

2-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-4,5-dimethylphenol (2.9i): According to general



procedure I: 9-fluorenone (89 mg, 0.49 mmol), pyrrolidine (41 μ L, 0.49 mmol), 3,4-dimethylphenol (50 mg, 0.41 mmol) in 2 mL benzene under reflux for 36 h and SiO₂ column chromatography (hexane: ethyl acetate, 100:1) gave **2.9i** as light brown gum (89 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 3459, 3038, 3005, 2954, 2858, 2827, 1951, 1762, 1717, 1631, 1586, 1505, 1468, 1586, 1505, 1468, 1449, 1389, 1328, 1307, 1291, 1275, 1246, 1200, 1183, 1159, 1138, 1108, 1076, 1023, 1000, 939, 909, 875, 860, 831, 764, 735, 674, 621, 581, 524, 493, 488. cm^{-1} . ¹H NMR (400 MHz, CDCl₃) δ = 11.36 (s, 1H), 7.72 – 7.64 (m, 4H), 7.42 – 7.25 (m, 4H), 7.01 (s, 1H), 6.8 (s, 1H), 5.01 (s, 1H), 4.51 – 4.46 (m, 1H), 2.54 – 2.49 (m, 1H), 2.26 (s, 3H), 2.25 (s, 3H), 2.11 – 1.94 (m, 3H), 1.81 – 1.78 (m, 1H), 1.67 – 1.59 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 155.5, 144.6, 142.4, 141.7, 140.3, 137.4, 130.3, 128.9, 128.5, 128.0, 127.2, 126.9, 126.8, 125.5, 121.5, 120.2, 119.8, 118.3, 67.0, 62.3, 44.6, 32.5, 22.2, 19.8, 19.0 ppm. HRMS (ESI) exact mass calculated for C₂₅H₂₆NO⁺ ([M+H]⁺): 356.2009, Found: 356.2006.

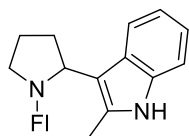
4-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-2,6-dimethylphenol (2.9j): According to general procedure I: 9-fluorenone (0.14 g, 0.79 mmol), pyrrolidine (63 μ L, 0.79 mmol), 2,6-dimethylphenol (80 mg, 0.65 mmol), in 2 mL benzene under reflux for 36 h and SiO₂ column chromatography (hexane: ethyl acetate, 25:1) gave **2.9j** as light yellow solid (97 mg, 42 %). FTIR (KBr): $\tilde{\nu}$ = 3582, 3062, 3035, 2963, 2936, 2847, 2803, 1604, 1483, 1448, 1377, 1358, 1300, 1258, 1233, 1185, 1149, 1112, 1018, 938, 867, 735, 672, 621, 564, 487 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 7.66 – 7.61 (m, 4H), 7.33 – 7.17 (m, 6H), 4.86 (s, 1H), 4.26 – 4.23 (m, 1H), 2.53 – 2.49 (m, 1H), 2.28 (s, 6H), 2.14 – 2.06 (m, 2H), 1.75 – 1.66 (m, 2H), 1.61 – 1.56 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 151.5, 146.5, 144.7, 141.8, 140.1, 135.1, 128.1, 127.9, 127.4, 126.6, 126.5, 125.4, 123.2, 120.0, 119.5, 65.9, 62.7, 45.3, 35.9, 22.4, 16.3 ppm. HRMS (ESI) exact mass calculated for C₂₅H₂₆NO⁺ ([M+H]⁺): 356.2009, found: 356.2009.

6-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)benzo[d][1,3]dioxol-5-ol (2.9k): According to general procedure I: 9-fluorenone (0.16 g, 0.87 mmol), pyrrolidine (71 μ L, 0.87 mmol), sesamol (0.10 g, 0.72 mmol) in 2 mL benzene under reflux for 36 h and SiO₂-column chromatography (hexane: ethyl acetate, 100:1) gave **9k** as white solid (0.24 g, 90 %). FTIR (KBr): $\tilde{\nu}$ = 3450, 2970, 2867, 1632, 1500, 1478, 1450, 1416, 1307, 1255, 1185, 1150, 1091, 1035, 936, 914, 862, 838, 745, 738, 686, 666, 616, 520 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ = 11.63 (s, 1H), 7.88 – 7.57 (m, 4H), 7.41 – 7.21 (m, 4H), 6.74 (s, 1H), 6.60 (s, 1H), 5.92 (s, 2H), 4.95 (s, 1H), 4.42 – 4.37 (m, 1H), 2.62 – 2.44 (m, 1H), 2.29 – 1.90 (m, 3H), 1.90 – 1.50 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ = 153.0, 148.0, 144.4, 142.4, 141.5, 140.4, 140.3, 128.7, 128.5, 128.0, 127.0, 126.6, 125.4, 120.2, 119.8, 115.3, 108.6, 101.0, 99.5, 67.1, 62.1, 44.6, 32.2, 22.0 ppm. HRMS (ESI) exact mass calculated for C₂₄H₂₂NO₃⁺ ([M+H]⁺): 372.1594, Found: 372.1606.

1-(pyrrolidin-2-yl)naphthalen-2-ol (2.16): A solution of compound **2.8** (50 mg, 0.133 mmol) in 4.5 mL of EtOAc-MeOH-CH₂Cl₂ (3:1:0.5) was degassed under vacuum and successively purged with hydrogen gas from balloon. Then 10% Pd/C (15 mg, 0.13 μ mol) was added to the mixture and the reaction mixture was stirred at room temperature for 24 h under hydrogen atmosphere. The reaction mixture was filtered through a pad of celite and the celite cake was washed with ethyl acetate (3 X 5 mL). The filtrate was concentrated and the crude product was purified via neutral alumina column chromatography (first with 100% dichloromethane and then 1:100 methanol : dichloromethane) to afford naphthyl pyrrolidine **2.16**²⁰ as light brown oil (16 mg,

75 μ mol, 56%), **2.8** (17 mg, 45 μ mol, 34%) and fluorene (12 mg, 72 μ mol, 55%). ^1H -NMR(600 MHz, CDCl_3): 7.80 – 7.68 (m, 2H), 7.60 – 7.47 (m, 1H) 7.46 – 7.39 (m, 1H), 7.33 – 7.23 (m, 1H) 7.16 – 7.02 (m, 1H), 5.15 – 5.06 (m, 1H) 3.37 – 3.28 (m, 1H), 3.20 – 3.11 (m, 1H), 2.55 – 2.44 (m, 1H), 2.09 – 1.79 (m, 3H). HRMS (ESI) exact mass calculated for $\text{C}_{14}\text{H}_{16}\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 214.1226, Found: 214.1231.

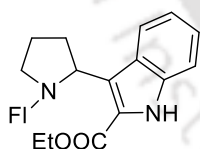
3-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-2-methyl-1H-indole (2.18a): According to general



procedure II: 9-fluorenone imine (54 mg, 0.30 mmol), pyrrolidine (61 μ L, 0.75 mmol), and 2-methylindole (33 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}\text{C}$ for 60 minutes and SiO_2 column

chromatography (hexane: ethyl acetate; 6:1) gave **2.18a** as yellow solid (68 mg, 75%). FTIR (KBr): $\tilde{\nu}$ = 3421, 2921, 2963, 1713, 1600, 1583, 1420, 1280, 1106, 798, 768, 732 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 8.16 (d, J = 7.2 Hz, 1H), 7.78 (s, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.56 – 7.54 (m, 1H), 7.34 – 7.28 (m, 3H), 7.24 – 7.15 (m, 4H), 4.89 (s, 1H), 4.63 – 4.60 (m, 1H), 2.60 (s, 3H), 2.58 – 2.53 (m, 1H), 2.21 – 2.10 (m, 3H), 1.94 – 1.84 (m, 1H), 1.73 – 1.63 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 146.7, 144.9, 141.7, 135.9, 135.4, 133.9, 128.5, 128.1, 127.8, 127.5, 126.6, 126.0, 125.9, 125.8, 125.8, 121.4, 120.3, 119.5, 119.2, 110.3, 68.1, 65.4, 59.3, 44.1, 30.9, 12.7 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{26}\text{H}_{25}\text{N}_2^+$ ($[\text{M}+\text{H}]^+$): 365.2012, found :365.2030.

Ethyl 3-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1H-indole-2-carboxylate (2.18b): According

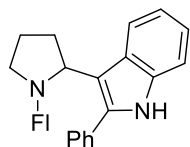


to general procedure II: 9-fluorenone imine (54 mg, 0.30 mmol), pyrrolidine (61 μ L, 0.75 mmol), and ethyl 1H-indole-2-carboxylate (47 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}\text{C}$ for

60 minutes and SiO_2 column chromatography (hexane: ethyl acetate; 6:1) gave **2.18b** as light brown solid (71 mg, 67%). FTIR (KBr): $\tilde{\nu}$ = 3339, 3036, 2971, 2804, 1675, 1541, 1251, 1190, 1092, 748 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 8.81 (s, 1H), 8.63 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.43 – 7.21 (m, 1H), 7.39 – 7.36 (m, 1H), 7.35 – 7.31 (m, 1H), 7.30 – 7.27 (m, 1H), 7.24 – 7.23 (m, 2H), 5.53 (t, J = 8.4 Hz, 1H), 4.80 (m, 1H), 4.55 – 4.48 (m, 2H), 2.60 – 2.57 (m, 1H), 2.23 – 2.21 (m, 3H), 1.96 – 1.91 (m, 1H), 1.74 – 1.68 (m, 1H), 1.50 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ = 162.5, 146.6, 144.0, 141.8, 140.1, 136.7, 127.7, 127.3, 126.9, 126.8, 126.6, 125.9, 125.8, 125.5, 124.6, 124.5, 119.9, 119.9, 119.4, 112.0, 63.3, 61.3,

58.3, 45.4, 32.5, 22.8, 14.7. HRMS (ESI) exact mass calculated for $C_{28}H_{27}O_2N_2^+$ ($[M+H]^+$): 423.2067, found : 423.2084.

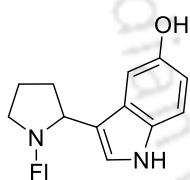
3-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-2-phenyl-1H-indole (2.18c): According to general



procedure II: 9-fluorenone imine (54 mg, 0.30 mmol), pyrrolidine (61 μ L, 0.75 mmol), and 2-phenylindole (48 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C for 60 minutes and SiO_2 column

chromatography (hexane: ethyl acetate; 15:1) gave **2.18c** as gray solid (60 mg, 56%). FTIR (KBr): $\tilde{\nu}$ = 3409, 3059, 2962, 2924, 1709, 1610, 1448, 1261, 1098, 1026, 800, 741 cm^{-1} . 1H NMR (600 MHz, $CDCl_3$) δ = 8.43 – 8.41 (m, 1H), 8.08 (s, 1H), 7.59 – 7.57 (m, 3H), 7.56 – 7.51 (m, 3H), 7.49 – 7.47 (m, 2H), 7.41 – 7.39 (m, 1H), 7.27 – 7.24 (m, 2H), 7.22 – 7.17 (m, 2H), 6.81 – 6.78 (m, 1H), 6.60 (d, J = 7.8 Hz, 1H), 4.70 (s, 1H), 4.65 – 4.63 (m, 1H), 2.50 – 2.40 (m, 2H), 2.24 – 2.20 (m, 1H), 1.97 – 1.87 (m, 2H), 1.71 – 1.65 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 146.8, 143.8, 141.8, 140.0, 137.1, 136.8, 133.3, 129.2, 129.0, 128.3, 127.9, 127.6, 127.5, 127.3, 126.3, 126.2, 125.8, 122.6, 122.2, 119.8, 119.6, 119.3, 113.4, 111.1, 62.7, 58.7, 45.1, 32.0, 22.4 ppm. HRMS (ESI) exact mass calculated for $C_{31}H_{27}N_2^+$ ($[M+H]^+$): 427.2169, found : 427.2189

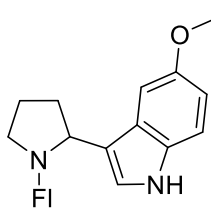
3-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1H-indol-5-ol (2.18d): According to general



procedure II: 9-fluorenone imine (54 mg, 0.30 mmol), pyrrolidine (61 μ L, 0.75 mmol), and 5-hydroxyindole (33 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C for 60 minutes and SiO_2 column chromatography (hexane: ethyl acetate; 5:1) gave **2.18d** as brown solid

(80 mg, 87%). FTIR (KBr): $\tilde{\nu}$ = 3289, 3033, 3057, 2950, 2877, 2877, 1697, 1597, 1449, 1323, 1241, 1090, 787, 740, 731, 673 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ = 11.49 (s, 1H), 8.12 (s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.71 – 7.65 (m, 3H), 7.40 – 7.33 (m, 3H), 7.29 – 7.28 (m, 2H), 6.91 (d, J = 8.8 Hz, 1H), 6.64 (s, 1H), 5.05 (s, 1H), 5.02 – 4.98 (m, 1H), 2.60 – 2.54 (m, 1H), 2.34 – 2.28 (m, 1H), 2.16 – 2.06 (m, 1H), 2.02 – 1.98 (m, 1H), 1.90 – 1.82 (m, 1H), 1.73 – 1.70 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 149.2, 143.2, 140.7, 139.8, 138.9, 129.4, 127.3, 127.2, 126.8, 126.5, 125.8, 125.5, 124.3, 123.9, 118.9, 118.6, 111.1, 110.8, 110.1, 97.0, 61.9, 61.1, 43.1, 29.8, 20.7. HRMS (ESI) exact mass calculated for $C_{25}H_{23}N_2O^+$ ($[M+H]^+$): 367.1805, found : 367.1821

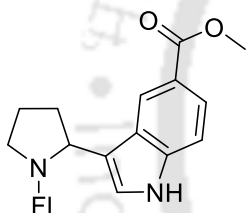
3-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-5-methoxy-1H-indole (2.18e): According to general



procedure II: 9-fluorenone imine (54 mg, 0.30 mmol), pyrrolidine (61 μ L, 0.75 mmol), and 5-methoxyindole (37 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C for 60 minutes and SiO₂ column chromatography (hexane: ethyl acetate; 5:1) gave **2.18e** as brown solid (76 mg, 80%). FTIR (KBr): $\tilde{\nu}$ = 3200, 2921, 2804, 1617, 1251, m1190, 735

676 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.95 (s, 1H), 7.69 – 7.67 (m, 1H), 7.65 – 7.62 (m, 1H), 7.61 – 7.59 (m, 2H), 7.38 – 7.32 (m, 3H), 7.29 – 7.23 (m, 4H), 6.92 – 6.89 (m, 1H), 5.00 (s, 1H), 4.65 – 4.61 (m, 1H), 3.97 (s, 3H), 2.57 – 2.52 (m, 1H), 2.17 – 2.05 (m, 3H), 1.88 – 1.81 (m, 1H), 1.70 – 1.63 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 153.8, 146.7, 144.5, 141.9, 140.2, 132.6, 127.8, 127.7, 127.3, 127.2, 126.6, 126.5, 125.6, 123.8, 120.0, 119.5, 117.4, 112.4, 112.1, 103.0, 62.9, 59.8, 56.3, 45.3, 32.9, 22.4. HRMS (ESI) exact mass calculated for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}^+$ ($[\text{M}+\text{H}]^+$): 381.1961, found : 381.1974.

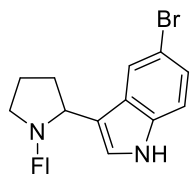
Methyl 3-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1H-indole-5-carboxylate (2.18f): According



to general procedure II: 9-fluorenone imine (54 mg, 0.30 mmol), pyrrolidine (61 μ L, 0.75 mmol), and methyl 1H-indole-3-carboxylate (44 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150

$^{\circ}$ C for 60 minutes and SiO₂ column chromatography (hexane: ethyl acetate; 5:1) gave **2.18f** as yellow solid (95 mg, 93%). FTIR (KBr): $\tilde{\nu}$ = 3410, 3333, 2815, 2954, 1704, 1616, 1436, 1295, 1259, 1109, 741, 672, 596, 555 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 8.92 (s, 1H), 8.35 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.63 – 7.60 (m, 2H), 7.41 (s, 1H), 7.38 – 7.36 (m, 1H), 7.31 – 7.24 (m, 3H), 7.20 – 7.18 (m, 1H), 4.96 (s, 1H), 4.70 – 4.66 (m, 1H), 4.01 (s, 3H), 2.62 – 2.57 (m, 1H), 2.20 – 2.04 (m, 3H), 1.94 – 1.84 (m, 1H), 1.68 – 1.59 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 168.6, 146.4, 144.4, 141.8, 140.2, 139.9, 127.9, 127.8, 127.5, 126.5, 126.5, 126.3, 125.7, 124.0, 124.0, 123.8, 121.6, 120.0, 119.5, 111.1, 63.0, 59.5, 52.1, 45.4, 33.8, 22.4. HRMS (ESI) exact mass calculated for $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 408.1838, found : 409.1932.

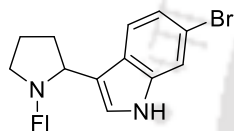
3-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-5-bromo-1H-indole (2.18g): According to general procedure II: 9-fluorenone imine (54 mg, 0.30 mmol), pyrrolidine (29 μ L, 0.75 mmol), and



5-bromoindole (49 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C for 60 minutes and SiO₂ column chromatography (hexane: ethyl acetate; 5:1) gave **2.18g** as brown solid (68 mg, 63%). FTIR (KBr): $\tilde{\nu}$ = 3421, 3062, 2924, 1709, 1610, 1448, 1093, 794, 735, 670 cm^{-1} . ¹H NMR

(600 MHz, CDCl₃) δ = 8.30 (s, 1H), 8.07 (s, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.35 (s, 1H), 7.34 – 7.30 (m, 4H), 7.24 – 7.20 (m, 2H), 4.93 (s, 1H), 4.61 – 4.58 (m, 1H), 2.59 – 2.56 (m, 1H), 2.17 – 2.06 (m, 3H), 1.89 – 1.83 (m, 1H), 1.68 – 1.64 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 146.4, 144.4, 141.9, 140.2, 136.0, 128.4, 127.9, 127.9, 127.5, 126.5, 126.5, 125.7, 125.2, 124.1, 123.6, 120.0, 119.5, 112.9, 112.7, 62.9, 59.5, 45.4, 33.3, 22.4. HRMS (ESI) exact mass calculated for C₂₅H₂₂BrN₂⁺ ([M+H]⁺): 429.0961, found : 429.0972.

3-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-6-bromo-1H-indole (2.18h): According to general



procedure II: 9-fluorenone imine (54 mg, 0.30 mmol), pyrrolidine (29 μ L, 0.75 mmol), and 6-bromoindole (49 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C for 60 minutes and SiO₂ column

chromatography (hexane: ethyl acetate; 5:1) gave **2.18h** as brown solid (57 mg, 56%). FTIR(KBr): $\tilde{\nu}$ = 3421, 3062, 2924, 1709, 1610, 1448, 1093, 794, 735, 670 cm^{-1} . ¹H NMR (600 MHz, CDCl₃) δ = 8.04 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.55 – 7.50 (m, 2H), 7.34 – 7.30 (m, 4H), 7.27 – 7.24 (m, 1H), 7.23 – 7.21 (m, 1H), 4.92 (s, 1H), 4.62 (t, J = 7.8 Hz, 1H), 2.57 – 2.54 (m, 1H), 2.17 – 2.08 (m, 3H), 1.89 – 1.82 (m, 1H), 1.69 – 1.64 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 146.5, 144.4, 141.9, 140.1, 138.2, 127.9, 127.8, 127.4, 126.5, 126.5, 125.6, 125.6, 123.5, 122.8, 122.2, 120.1, 119.5, 118.1, 115.9, 114.4, 62.8, 59.6, 45.4, 33.1, 22.4. HRMS (ESI) exact mass calculated for C₂₅H₂₂BrN₂⁺ ([M+H]⁺): 429.0961, found : 429.0964.

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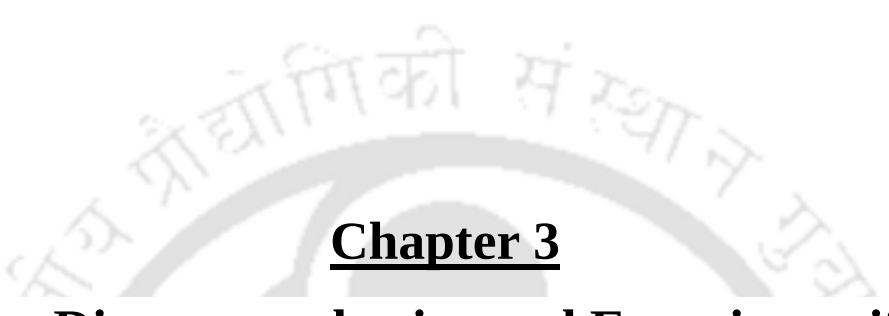
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Chapter 3

Regio-, Diastereo-selective and Enantiospecific Metal Free C(sp^3)-H Arylation: A Facile Access To Optically Active 5-aryl 2,5-Disubstituted Pyrrolidine



3.1. Introduction:

5-Aryl-2,5-disubstituted pyrrolidine serves as the key structural motif of many natural as well as synthetic functional molecules.¹ For some relevant examples, they are present in different bioactive natural products like prolinalin B,^{1d} (-)-codonopsinine,^{1e} and radicamine B^{1f, g} (**Figure 1**). Moreover, many medicinally important synthetic molecules are built on arylated pyrrolidine. The enantiopure 5-arylproline derivative is the core unit of CCK antagonist (RP 66803),^{1h} angiotensin-converting enzyme (ACE) inhibitor^{1i, j} and Schramm's C-azanucleoside^{1k} having potential trypanosomal activity. Other than pharmacological applications, enantioenriched arylated pyrrolidine based molecules have important value in organic synthesis. They are either used directly or in the presence of a metal catalyst to promote asymmetric reactions.² The obvious widespread function of enantioenriched arylated pyrrolidine derivatives, in both medicinal chemistry and organic synthesis, demands the development of novel and applicable method for their preparation.

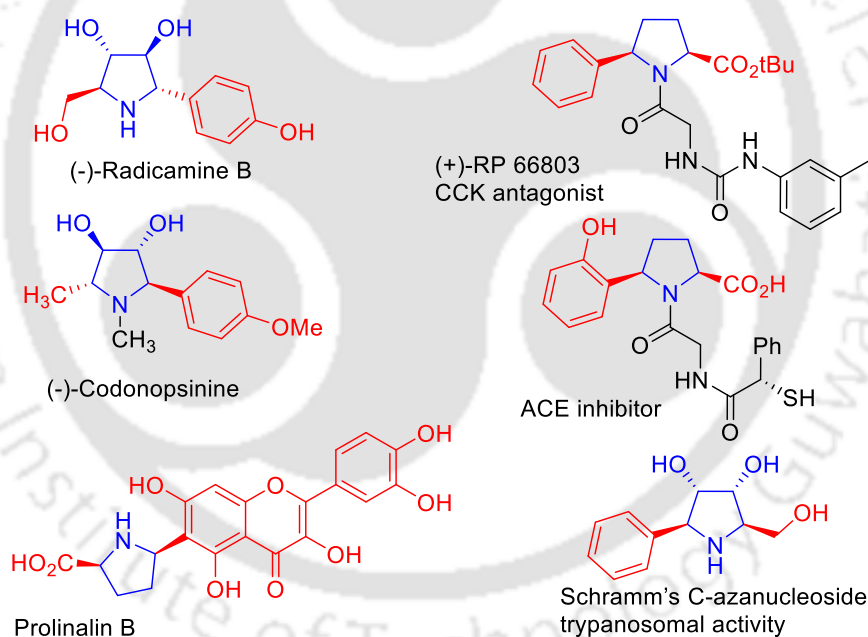


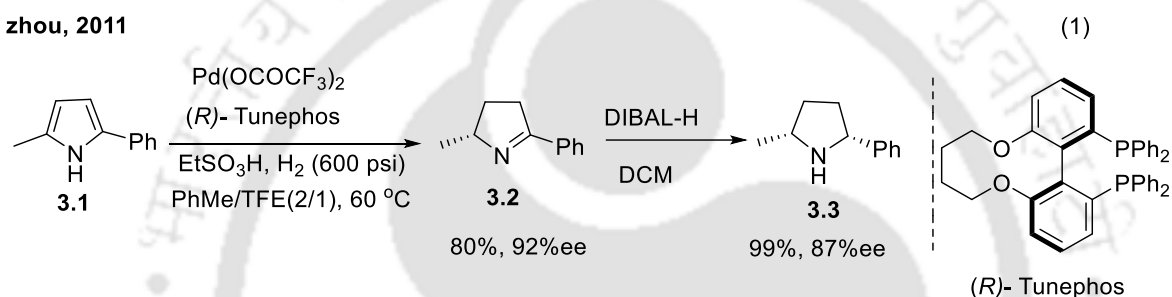
Figure 1: 5-aryl-2,5-disubstituted pyrrolidines in bioactive molecules.

3.2. Background:

Various methods for the synthesis of the arylated pyrrolidine were documented in the literature.^{3, 4, 5} However, strategies for the syntheses of these molecules in enantiomerically pure form are limited. Chiral auxiliary based strategy was mainly relied in this regard.⁶ In addition, only some enantioselective strategies were also applied.⁷ However, primarily multistep *N*-cycloalkylation strategies involving chiral amines were adopted for syntheses of enantioenriched 5-aryl-2,5-disubstituted pyrrolidines.^{8, 2e} A diastereoselective carboxylation⁹

involving the stoichiometric amount of chiral reagent and a diastereoselective Heck arylation¹⁰ were developed to obtain the 2,5-disubstituted pyrrolidine, however, with moderate yield and selectivity. These synthetic strategies already have been discussed in chapter 1. Apart from these strategies for the synthesis of 5-aryl-2,5-disubstituted pyrrolidines, an asymmetric hydrogenation strategy was also employed for reduction of substituted pyrroles under high pressure of hydrogen. In 2010, Zhou and co-workers have been reported enantioselective Pd-catalyzed partial hydrogenation of simple 2,5-disubstituted pyrroles **3.1** in the presence of a brønsted acid as an activator for the preparation of chiral 2,5-disubstituted 1-pyrrolines **3.2**. Furthermore, they have also demonstrated that chiral 2,5-disubstituted 1-pyrrolines can be reduced with DIBAL-H to afford *cis*-2,5-substituted pyrrolidines **3.3** (Scheme 1, eq. 1).¹¹

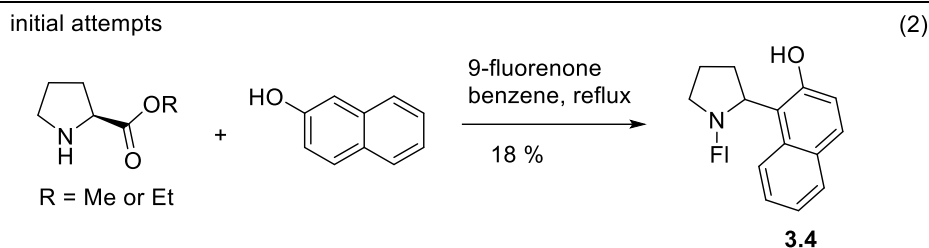
zhou, 2011



Scheme 1: Asymmetric hydrogenation of 2,5-disubstituted pyrroles.

3.3. Motivation and aim of our work:

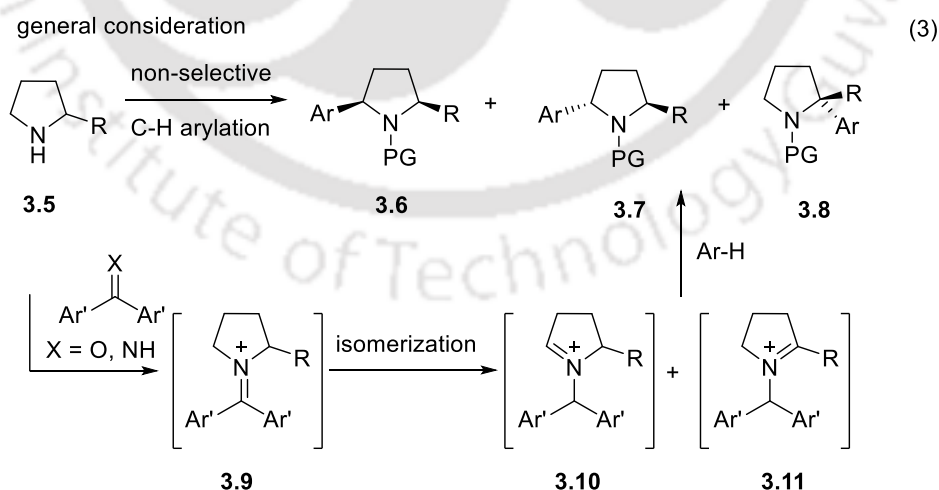
The main drawback of known protocols, to be considered for the practical application, originates from the multistep reaction sequence often with moderate diastereoselectivities. Apart from the aforementioned problems sometimes hazardous metal and oxidant are required for the synthesis of 5-aryl-2,5-disubstituted pyrrolidines. During our ongoing interest on direct functionalization of an aliphatic amine,¹² we have developed a method for direct C-H arylation of pyrrolidine via a simple three component reaction under metal and oxidant free condition.⁵¹ However, no report on stereoselective C-H arylation of substituted pyrrolidine accessing enantiopure 2,5-disubstituted pyrrolidine was known. Opportunity to obtain enantioenriched 2,5-disubstituted pyrrolidine via direct C-H functionalization of commercially available starting material will be of particular interest in the context of finding new bioactive compound and chiral scaffold for asymmetric catalysis. Readily available enantiopure proline loses its chirality due to decarboxylation during arylation reaction.^{5h-j} It was thought that ester derivative of proline may be used to avoid decarboxylation during the direct C-H arylation reaction. However, decarboxylation was found even in a reaction of *L*-proline methyl or ethyl ester providing arylated pyrrolidine **3.4** (Scheme 2. eq. 2).



Scheme 2: Arylation reaction of *L*-proline ester.

3.4. General notes on direct C-H arylation reaction:

Generally, during direct C-H arylation of substituted *N*-heterocycle **3.5**, the reaction should overcome regio- and diastereoselectivity issues to avoid the mixture of diastereoisomers **3.6**, **3.7** & **3.8** (scheme 3, eq.3). The use of enantiopure starting material, aiming for the enantioenriched product, put further challenges due to the possibility of racemization that may allow forming a mixture of six isomers. Preferences for the formation of less substituted enamine, to avoid the allylic strain that exists in its more substituted isomer, were well documented in the literature.¹³ Therefore, we anticipated that the isomerization of initially formed iminium ion **3.9** could be preferentially drawn towards **3.10** due to the presence of unfavorable allylic strain in its regioisomer **3.11**. Thus the selective formation of **3.10** will solve the regioselectivity issue as well as racemization problem. The remaining facial selectivity can be controlled by tuning the nature of Ar, R and CHAr'Ar' (PG) to afford one isomer selectively.¹⁴



Scheme 3: Challenges and opportunity of direct C-H Arylation of substituted pyrrolidines.

3.5. Table 1: Optimization of the reaction condition:

(4)

3.12 + 2-naphthol $\xrightarrow[\text{activators}]{\text{conditions}}$ 3.18a

3.13 3.14 3.15 3.16 3.17

^a Entry	Activator	Solvent, Temp.	Time	Yield ^b
1	3.13	THF, reflux	48 h	37
2	3.13	THF, reflux	78 h	65
3 ^c	3.13	benzene, reflux	66 h	59
4	3.13	toluene, μ w, 150 °C	40 min	46
5	3.14	THF, reflux	66 h	56
6	3.14	benzene, reflux	72 h	71
7	3.14	toluene, μ w, 150 °C	30 min	53
8	3.14	toluene, μ w, 150 °C	40 min	65
9	3.14	xylene, μ w, 170 °C	40 min	31
10	3.14	CH ₃ CN, μ w, 100 °C	40 min	20
11	3.14	DCM, μ w, 60 °C	40 min	trace
12	3.14	EtOH, μ w, 100 °C	40 min	trace
13	3.14	benzene, μ w, 100 °C	40 min	12
14	3.15	toluene, μ w, 150 °C	40 min	-
15	3.16	toluene, μ w, 150 °C	40 min	-
16	3.17	toluene, μ w, 150 °C	40 min	-

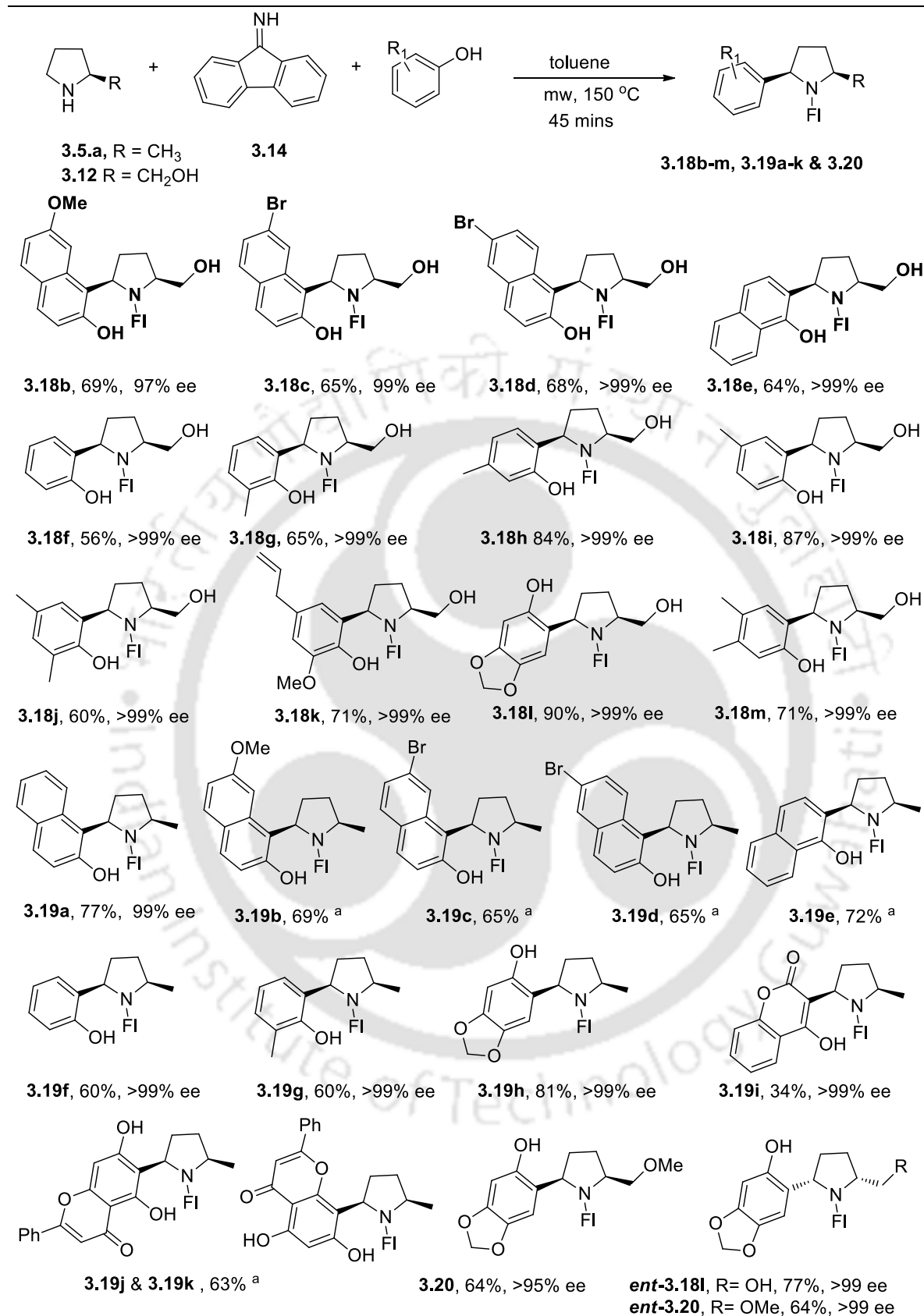
^aReactions were carried out with 0.3 mmol of prolinol (3.12), 0.25 mmol of 2-naphthol and 0.3 mmol of 9-fluorenone (3.13) or its imine derivative (3.14). ^b isolated percent yields. ^cprolinol (3.0 equiv.) was used in excess.

We started our investigation with the attempt to functionalize commercially available enantiomerically pure (S)-prolinol (3.12). To start with, enantioenriched prolinol was reacted with 9-fluorenone (3.13) in tetrahydrofuran under reflux condition in the presence of 2-naphthol as a potential nucleophile. After 48 hours, the desired product 3.18a was isolated with 37 % yield as the single diastereomer (table 1). The relative *syn*-stereochemistry was assigned in analogy of the stereochemistry observed from the single crystal X-ray structures of 3.18f, 3.18g, and 3.18l (figure 2). To our delight, we also found that the chiral center of starting prolinol (3.12) was retained to provide 3.18a with >99 % enantiomeric excess. This encouraging finding led us to investigate the reaction further to improve the yield. Higher

reaction time (78 h) increases the chemical yield to 65 %. Efforts were then continued to decrease the reaction time. We anticipated that the reaction time can be reduced by promoting the reaction of a secondary amine and carbonyl compound. Therefore, we employed 9-fluorenone imine (**3.14**) instead of 9-fluorenone to facilitate the reaction more effectively. Maximum yield of 71 % of the desired product was obtained after 72 h. On the other hand, 53 % yield was obtained in 30 min when the reaction was carried out at 150 °C in toluene under microwave irradiation. At the same time, the reaction was highly stereoselective to provide **3.18a** as the sole isomer with unaltered enantiopurity. The yield was further increased to 65 % by increasing the reaction time to 40 min. Different other reaction conditions varying solvents, temperatures and carbonyl compounds (activator) were examined. A trace amount of the product was obtained using protic and low boiling solvents. Other activators like benzophenone, anthrone, and anthraquinone, which are analogous to 9-fluorenone, failed to produce corresponding C-H arylated compounds. Thus the reactions using 9-fluorenone imine in benzene under reflux and in toluene at 150 °C for 40 min under microwave irradiation were found to be superior for this C-H arylation process.

3.6. Substrates scope of the direct C-H arylation reaction:

Optimized reaction condition was then utilized to investigate the substrate scope. Different electron rich aromatic compounds were used for the direct C-H functionalization of prolinol and 2-methylpyrrolidine (**scheme 4**). Naphthols and their derivatives were reacted smoothly providing different 2,5-disubstituted pyrrolidine derivatives (**3.18b-e** and **3.19a-e**) with very good yields and excellent stereoselectivity. Apart from naphthols, phenol derivatives and 4-hydroxycoumarin were also employed as the effective nucleophiles producing C-H functionalized derivatives (**3.18f-m**, **3.20** & **3.19f-3.19k**). Functional groups, which are sensitive towards transition metal- and oxidant-mediated reaction, were well tolerated in this reaction. Two regioisomeric products **3.19j** & **3.19k** were isolated using chrysin as nucleophile. The best yield (90 %) of arylated pyrrolidine derivative **3.18l** was obtained employing a highly oxygenated phenol derivative, sesamol, as the nucleophile. Similarly, arylated amine **3.20** with 64 % yield and >95 % ee was obtained through arylation of 2-methoxymethyl pyrrolidine. For all the cases, the products were isolated as the single diastereomer. The relative *syn*-orientation of aryl group and alkyl group in **3.18f**, **3.18g**, **3.18l** & **3.19a** were confirmed from their corresponding molecular structures obtained via the single crystal X-ray diffraction analysis (**Figure 2**).



Scheme 4: Substrate scope of arylation reaction. ^areactions were carried out with racemic amine.

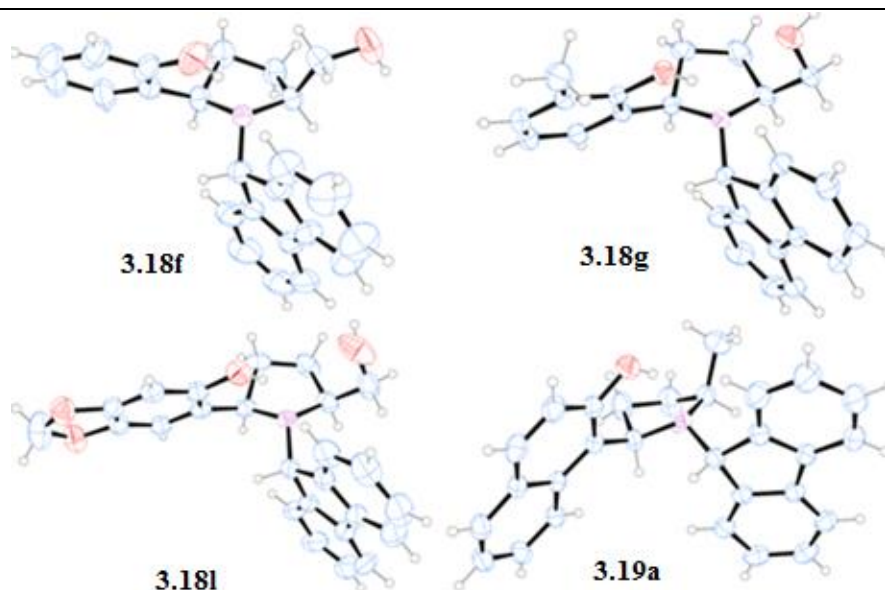


Figure 2. ORTEP (30 % probability) of representative compounds **3.18f**, **3.18g**, **3.18l** and **3.19a** showing relative *syn* stereochemistry.

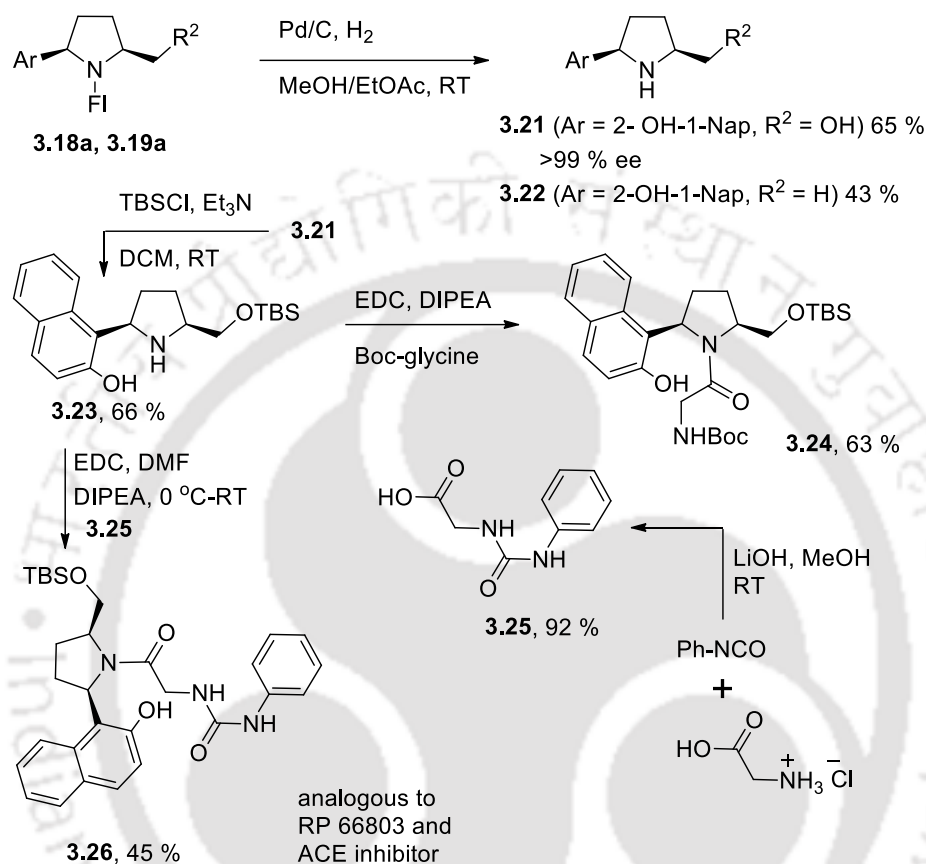
During the C-H arylation of enantiopure (*S*)-pyrrolidine methanol and its derivatives, arylated compounds were found to have excellent enantiopurity from HPLC analysis. Optically pure arylated compounds (**ent-3.18l** & **ent-3.20**) were also obtained from (*R*)-pyrrolidine methanol and its *O*-methylated derivatives. Analogous retention of chiral center occurred during the arylation of enantioenriched (*R*)-2-methylpyrrolidine providing 5-aryl 2-methylpyrrolidines with excellent enantiopurity (>99 %). On the other hand, indole derivatives, the most widely used nucleophilic aromatic substrates, were unable to provide an acceptable yield of corresponding C-H arylated compounds under this condition. This indicates that the phenolic OH plays an important role in the reaction.

3.7. Syntheses and derivatization of chiral amines:

Enantiopure *N*-fluorenyl 2,5-disubstituted pyrrolidine derivatives, which were obtained from this method, can be directly used as the chiral ligand in metal catalyzed asymmetric reaction.

² Further modification to form free amine would open an important avenue in finding new bioactive compound and chiral scaffold for asymmetric catalysis. For *N*-defluorenylation, the pyrrolidine derivative **3.18a** was reacted under hydrogenolysis condition to produce the 5-aryl prolinol **3.21** with 65 % yield and with retention of enantiomeric excess (>99 %, scheme 4). Similarly, compound **3.18a** provided the corresponding secondary amine **3.22**. The corresponding phenyl derivative of **3.21** was prepared via a linear 10 step synthetic sequence in the context of the synthesis of RP 66803.^{8e} The primary hydroxy group was selectively

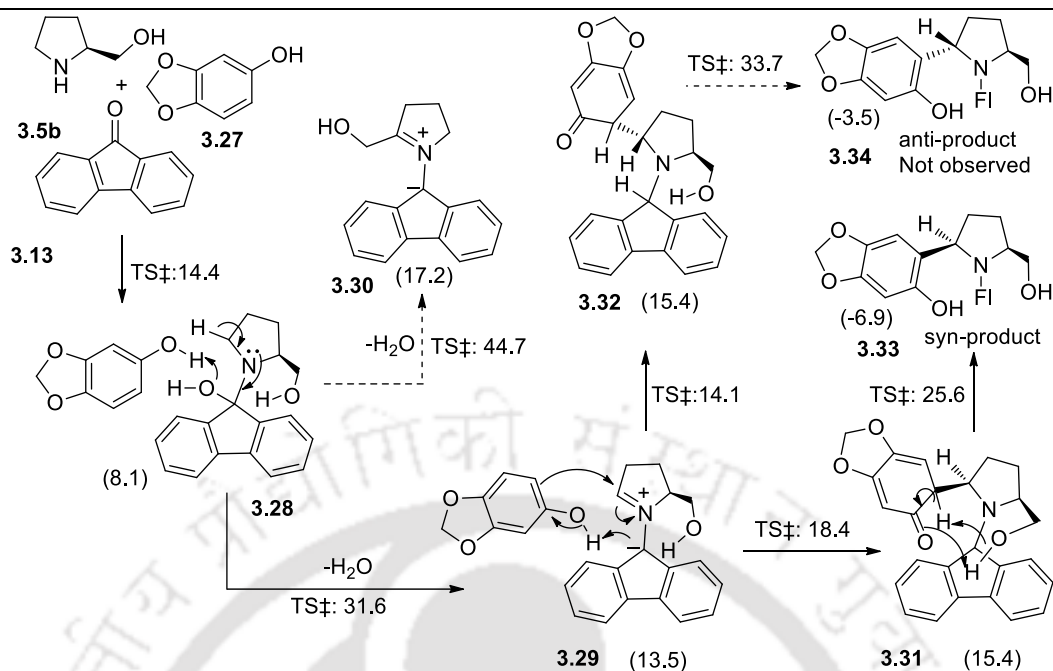
silylated under standard condition providing silyl ether **3.23** (66 %). Then the enantioenriched 5-arylated prolinol **3.23** was reacted efficiently with Boc-protected glycine to afford the dipeptide **3.24** (63 %). Similarly, urea derivative **3.25**, prepared from glycine with 92% yield, was coupled with **3.23** to provide amide **3.26** that structurally resembles with the biologically important dipeptides like RP 66803 and ACE inhibitors.



Scheme 5: Synthesis of chiral amines and their synthetic application.

3.8. Mechanism of the reaction:

To better understand the mechanism of the reaction DFT calculations were carried.¹⁵ The DFT studies revealed that prolinol **3.5b** condensed with 9-fluorenone **3.13** in the presence of sesamol **3.27** to provide the aminal **3.28**. The aminal **3.28** then underwent dehydration to give the less substituted zwitterionic intermediate **3.29**. However, the formation of more substituted zwitterionic intermediate **3.30** involved higher energy transition state. Protonation followed by nucleophilic attack of less substituted zwitterionic intermediate **3.29** occurred to provide both *syn* and *anti*-adduct **3.31** & **3.32**, respectively. However, subsequent aromatization reaction was found to be determining to provide the product with observed *syn*-stereoisomer **3.33**.



Scheme 6. Proposed mechanism of the overall reaction. The respective energy terms (in kcal/mol) below the arrows and in parenthesis are activation barrier ($\Delta^\ddagger G_L^S$) and relative free energy (ΔG_L^S) with respect to the starting materials at M06-2X/TZVPP/SMD//M06-2X/6-31+G(d,p) level.

3.9. Summary:

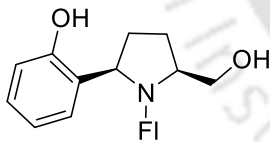
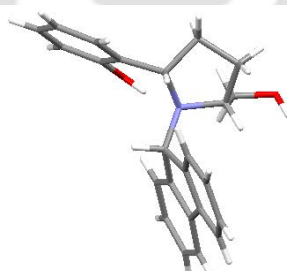
In summary, highly regio-, stereo-selective and enantiospecific direct C-H arylation of substituted pyrrolidine was achieved under metal and oxidant free reaction condition producing a variety of *syn* -2,5- disubstituted pyrrolidines with excellent enantiomeric excess. In the reaction, facial-selectivity, regioselectivity, and racemization were controlled to provide one out of six possible isomers. Optically active arylated pyrrolidine was showed to be useful for the easy and efficient synthesis of structural analogue of RP66803 and ACE-inhibitors. Furthermore, DFT calculations were performed to explore the mechanistic route for the selective C-H arylation reaction correlating strongly with the experimental results.

3.10. 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). Triethylamine (Et_3N) was distilled from CaH_2 and stored under argon. Commercial grade xylene, benzene and toluene were distilled before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. Microwave reactions were performed on CEM, Discover system. ^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 (^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 a Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in m/z (% of basis peak). HPLC: Waters analytical HPLC, water 2489 UV/visible detector. Polarimetry: Rudolph research analytical auto plot II.

Crystal Data:

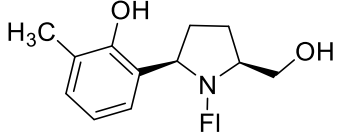
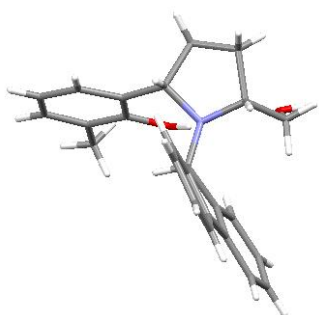
Crystallographic data for **3.18f**

 	
Crystallographic data and structure refinement for 3.18f CCDC NO- 1062485	
Empirical formula	C ₂₄ H ₂₃ N O ₂
Formula weight	357.43
Crystal habit, colour	needle / colorless
Crystal size, mm ³	0.42 * 0.20 * 0.18
Temperature, T	296(2)K
Wavelength, λ (Å)	0.71073

Crystal system	'monoclinic '
Space group	'P 1 21 1'
Unit cell dimensions	$a = 9.5174(6)\text{\AA}$ $b = 18.2290(12)\text{\AA}$ $c = 11.2975(8)\text{\AA}$ $\alpha = 90.00^\circ, \gamma = 90.00^\circ, \beta = 100.264(4)^\circ$
Volume, $V (\text{\AA}^3)$	1928.7(2)
Z	4
Calculated density, $\text{Mg}\cdot\text{m}^{-3}$	1.231
Absorption coefficient, $\mu (\text{mm}^{-1})$	0.078
$F(000)$	760
θ range for data collection	1.83 to 25.00°
Limiting indices	$-11 \leq h \leq 10, -21 \leq k \leq 21, -13 \leq l \leq 12$
Reflection collected/unique	14252/3424 [$R(\text{int}) = 0.0264$]
Completeness to θ	95.6% ($\theta = 25.00^\circ$)
Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	5900/1/ 491
Goodness-of-fit on F^2	1.049
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0531, wR2 = 0.0829$
R indices (all data)	$R1 = 0.1321, wR2 = 0.1487$
Largest diff. peak and hole	0.102 and $-0.167 \text{ e}\cdot\text{\AA}^{-3}$

Chapter 3

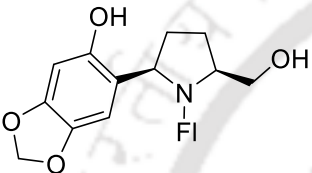
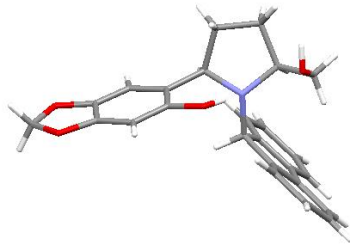
Crystallographic data for **3.18g**

	
Crystallographic data and structure refinement for 3.18g CCDC NO- 1062553	
Empirical formula Formula weight Crystal habit, colour Crystal size, mm ³ Temperature, <i>T</i> Wavelength, λ (Å) Crystal system Space group Unit cell dimensions	C ₂₅ H ₂₅ N O ₂ 371.46 needle / colorless 0.42 *0.20*0.18 296(2)K 0.71073 'monoclinic ' 'P 1 21 1' <i>a</i> = 19.084(3)Å <i>b</i> = 7.3765(9)Å <i>c</i> = 14.3524(16)Å $\alpha = 90.00^\circ, \gamma = 90.00^\circ, \beta = 98.465(14)^\circ$
Volume, <i>V</i> (Å ³) <i>Z</i> Calculated density, Mg·m ⁻³ Absorption coefficient, μ (mm ⁻¹) <i>F</i> (000)	1998.4(4) 4 1.235 0.078 792
θ range for data collection Limiting indices Reflection collected/unique Completeness to θ	2.16 to 28.44 ° -25 ≤ <i>h</i> ≤ 25, -9 ≤ <i>k</i> ≤ 9, -19 ≤ <i>l</i> ≤ 19 14252/3424 [<i>R</i> (int) = 0.0264] 98.8 % ($\theta = 28.44^\circ$)

Regio-, Diastereo-selective and Enantiospecific Metal Free C(sp³)-H Arylation: A Facile Access to Optically Active 5-aryl 2,5-disubstituted Pyrrolidine

Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	4449/1/ 256
Goodness-of-fit on F^2	1.071
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0387$, $wR2 = 0.0509$
R indices (all data)	$R1 = 0.0886$, $wR2 = 0.0943$
Largest diff. peak and hole	0.102 and -0.167 e $\cdot\text{\AA}^{-3}$

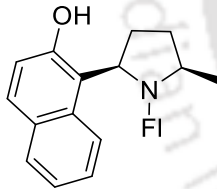
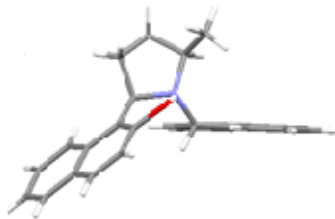
Crystallographic data for **3.18l**

 	
Crystallographic data and structure refinement for 3.18l CCDC NO- 1059663	
Empirical formula	C ₂₅ H ₂₃ NO ₄
Formula weight	401.44
Crystal habit, colour	needle / colorless
Crystal size, mm ³	30*25*22
Temperature, T	296(2) K
Wavelength, λ (Å)	0.71073
Crystal system	'Monoclinic'
Space group	'P2(1) '
Unit cell dimensions	$a = 7.3209(3) \text{ \AA}$ $b = 9.7276(4) \text{ \AA}$ $c = 14.2738(6) \text{ \AA}$ $\alpha = 90.00^\circ(2)$, $\gamma = 90.00^\circ(2)$, $\beta = 91.087(2)^\circ$,
Volume, V (Å ³)	1016.32(7)
Z	2

Chapter 3

Calculated density, $\text{Mg} \cdot \text{m}^{-3}$	1.312
Absorption coefficient, μ (mm^{-1})	0.089
$F(000)$	424
θ range for data collection	2.53 to 25.00°
Limiting indices	$-8 \leq h \leq 8, -11 \leq k \leq 11, -16 \leq l \leq 16$
Reflection collected/unique	14252/3424 [$R(\text{int}) = 0.0264$]
Completeness to θ	99.4% ($\theta = 25.00^\circ$)
Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	3424/1/273
Goodness-of-fit on F^2	1.006
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0436, wR2 = 0.0982$
R indices (all data)	$R1 = 0.0675, wR2 = 0.1086$
Largest diff. peak and hole	0.102 and $-0.167 \text{ e} \cdot \text{\AA}^{-3}$

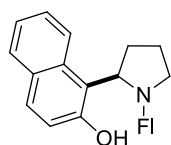
Crystallographic data for **3.19a**

 	
Crystallographic data and structure refinement for 3.19a CCDC NO- 1059394	
Empirical formula	$\text{C}_{28}\text{H}_{25}\text{NO}$
Formula weight	391.49
Crystal habit, colour	needle / colorless
Crystal size, mm^3	22*25*27
Temperature, T	296(2) K
Wavelength, λ ($\text{\AA}$)	0.71073
Crystal system	'Triclinic'

Space group	'P1'
Unit cell dimensions	$a = 11.2125(4) \text{ \AA}$ $b = 12.8478(5) \text{ \AA}$ $c = 15.5617(6) \text{ \AA}$ $\alpha = 87.237^\circ(2), \gamma = 82.833^\circ(2), \beta = 73.031(2)^\circ,$
Volume, $V(\text{\AA}^3)$	2124.83(14)
Z	4
Calculated density, $\text{Mg}\cdot\text{m}^{-3}$	1.224
Absorption coefficient, $\mu (\text{mm}^{-1})$	0.073
$F(000)$	832
θ range for data collection	1.37 to 25.00°
Limiting indices	$-13 \leq h \leq 13, -15 \leq k \leq 14, -18 \leq l \leq 18$
Reflection collected/unique	25533/7152 [$R(\text{int}) = 0.0254$]
Completeness to θ	95.2% ($\theta = 25.00^\circ$)
Max. and min. transmission	0.848 / 0.781
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	7152/0/545
Goodness-of-fit on F^2	1.057
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0448, wR2 = 0.1220$
R indices (all data)	$R1 = 0.0783, wR2 = 0.1316$
Largest diff. peak and hole	0.147 and $-0.138 \text{ e}\cdot\text{\AA}^{-3}$

Experimental procedure:

rac-1-((R)-1-(9H-fluoren-9-yl)pyrrolidin-2-yl)naphthalen-2-ol (3.4): 2-naphthol derivative



(36 mg, 0.25 mmol) was added to a solution of *L*-Methyl proline hydrochloride (0.16 g, 0.75 mmol), 9-fluorenone (54 mg, 0.30 mmol) and triethylamine (0.10 mL, 0.75 mmol) in benzene (2 mL) at room temperature.

Then the reaction mixture was refluxed for 36 h. Then the mixture was cooled to room temperature, the organic solvents were removed under vacuum and the crude product was purified by SiO₂ column chromatography (hexane: ethyl acetate, 100:1) gave **3.4** as brown solid (17 mg, 0.05 mmol, 18 %). FTIR (KBr): $\bar{\nu}$ = 3438, 3049, 2954, 2921, 2853, 1619, 1597, 1582, 1520, 1467, 1450, 1330, 1182, 1166, 1090, 1027, 955, 905, 816, 736, 673, 638, 559 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 13.32 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.81 (t, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.59 – 7.56 (m, 1H), 7.39 – 7.34 (m, 4H), 7.28 – 7.25 (m, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 5.39 – 5.36 (m, 1H), 4.99 (s, 1H), 2.65 – 2.61 (m, 1H), 2.43 – 2.37 (m, 1H), 2.08 – 2.02 (m, 2H), 1.91 – 1.84 (m, 1H), 1.75 – 1.69 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 156.6, 144.3, 142.5, 140.8, 140.4, 133.2, 129.6, 129.3, 128.8, 128.8, 128.6, 128.1, 127.1, 127.0, 126.8, 125.6, 122.7, 120.8, 120.3, 120.0, 119.9, 114.2, 62.7, 61.9, 44.7, 31.5, 22.5 ppm. HRMS (ESI) exact mass calculated for C₂₇H₂₄NO⁺ ([M+H]⁺): 378.1852, found: 378.1856.

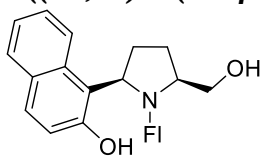
General procedure A, reaction under microwave irradiation:

Phenol or naphthol derivative (0.25 mmol, 1.0 eq) was added to a solution of 2-substituted pyrrolidine (1.2 eq) and 9-fluorenone or 9-fluorenone imine (1.2 eq) in toluene (1 mL) at room temperature. Then the reaction mixture was heated under the microwave irradiation (200 watt) for 45 min at 150 °C. Then the mixture was cooled to room temperature, the organic solvents were removed under vacuum and the crude product was purified by column chromatography providing analytically pure aryl pyrrolidines in enantiopure form.

General procedure B, reaction under reflux condition:

Phenol or naphthol derivative (0.25 mmol, 1.0 eq) was added to a solution of 2-substituted pyrrolidine (3.0 eq) and 9-fluorenone or 9-fluorenone imine (1.2 eq) in benzene (2 mL) at room temperature. Then the reaction mixture was refluxed for 66 h. Then the mixture was cooled to room temperature, the organic solvents were removed under vacuum and the crude product was purified by column chromatography providing analytically pure aryl pyrrolidines in enantiopure form.

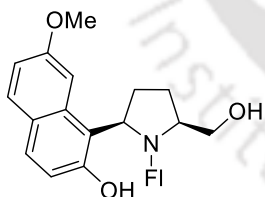
1-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)naphthalen-2-ol



(3.18a): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (29 μ L, 0.30 mmol), and 2-naphthol (36 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C

for 45 minutes and SiO₂ column chromatography (hexane: ethyl acetate; 4:1) gave **3.18a** as brown solid (66 mg, 0.16 mmol, 65 %). $[\alpha]_D^{25} = +152.5$ (c = 0.16, MeOH). FTIR (KBr): $\bar{\nu}$ = 3414, 3060, 2925, 2872, 1912, 1621, 1599, 1519, 1467, 1449, 1268, 1239, 1201, 11555, 1043, 963, 944, 815, 742, 717, 674 cm^{-1} . ¹H NMR (600 MHz, CDCl₃) δ = 12.99 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.83 – 7.79 (m, 2H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.64 (dd, *J* = 18.9, 7.3 Hz, 2H), 7.54 – 7.52 (m, 1H), 7.39 – 7.36 (m, 2H), 7.35 – 7.30 (m, 3H), 7.22 (d, *J* = 8.8 Hz, 1H), 5.72 (dd, *J* = 10.6, 6.5 Hz, 1H), 5.01 (s, 1H), 3.12 – 3.09 (m, 1H), 3.00 – 2.97 (m, 1H), 2.78 – 2.70 (m, 1H), 2.36 – 2.31 (m, 1H), 2.17 – 2.1 (m, 1H), 1.95 – 1.90 (m, 2H). ¹³C-NMR (100 MHz, CDCl₃) δ = 156.5, 144.3, 142.2, 141.9, 140.2, 133.3, 129.6, 129.3, 128.9, 128.86, 128.8, 128.1, 127.4, 126.9, 126.2, 126.1, 122.7, 120.8, 120.4, 120.1, 120.1, 114.3, 65.4, 65.1, 63.7, 59.8, 30.5, 28.0 ppm. HRMS (ESI) exact mass calculated for C₂₈H₂₆NO₂⁺ ([M+H]⁺): 408.1958, found : 408.1962. The enantiomeric excess (97 %) was determined by HPLC column: chiralpak IA; solvent: 2-propanol: hexane (1:4); light: 220 nm; flow: 1 mL /min; major enantiomer *t*_r = 9.9 min, minor enantiomer *t*_r = 13.5 min.

1-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)-7-methoxynaphthalen-2-ol (3.18b):

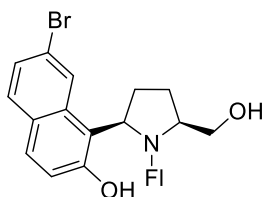


According to general procedure A: 9-fluorenone imine (0.11 g, 0.60 mmol), S-prolinol (58 μ L, 0.60 mmol), and 7-methoxy-2-naphthol (87 mg, 0.50 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C for 45 minutes and SiO₂ column chromatography (hexane: ethyl acetate; 4:1) gave **3.18b** as brown solid (0.15 g, 0.34 mmol, 69 %). $[\alpha]_D^{25} =$

+45.6 (c = 0.25, MeOH). FTIR (KBr): $\bar{\nu}$ = 3578, 3063, 3035, 2927, 1624, 1581, 1518, 1448, 1385, 1331, 1275, 1233, 1198, 1032, 987, 842, 737, 729, 648 cm^{-1} . ¹H NMR (400 MHz, CDCl₃) δ = 12.96 (s, 1H), 7.87 (d, *J* = 7.1 Hz, 1H), 7.79 (d, *J* = 7.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.31 (m, 3H), 7.27 – 7.25 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 5.58 – 5.54 (m, 1H), 4.96 (s, 1H), 3.98 (s, 3H), 3.13 – 3.09 (m, 1H), 3.01 – 2.97 (m, 1H), 2.79 – 2.70 (m, 1H), 2.36 – 2.28 (m, 1H), 2.16 – 2.06 (m, 1H), 1.94 – 1.89 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 158.6, 157.1, 144.3, 142.2, 142.0, 140.3, 134.5, 130.8, 129.4, 128.9, 128.9, 128.1, 127.3, 126.1,

124.3, 120.4, 120.1, 117.7, 113.6, 113.4, 101.4, 65.4, 65.0, 63.8, 59.9, 55.6, 30.1, 28.0 ppm. HRMS (ESI) exact mass calculated for $C_{29}H_{28}BrNO_3^+([M+H]^+)$: 438.2064, found: 438.2060. The enantiomeric excess (>99 %) was determined by HPLC column: chiral pak IA; solvent: 2-propanol: hexane (1:4); light: 220 nm; flow: 1 mL/min; major enantiomer t_r = 9.9 min, minor enantiomer t_r = 13.4 min.

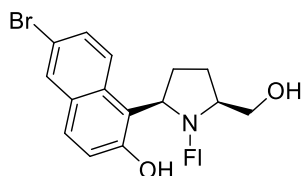
1-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)-7-bromonaphthalen-2-



ol (3.18c): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (29 μ L, 0.30 mmol), and 7-bromo-2-naphthol (55 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C for 45 minutes and SiO_2 column chromatography (hexane: ethyl acetate; 4:1) gave **3.18c** as brown solid (82 mg, 0.17

mmol, 68 %). $[a]_D^{25} = +32.8$ ($c = 0.25$, MeOH). FTIR (KBr): $\bar{\nu} = 3413, 3061, 2924, 2872, 1615, 1581, 1504, 1448, 1396, 1353, 1233, 1200, 1158, 1080, 1026, 973\text{ cm}^{-1}$. 1H NMR (400 MHz, $CDCl_3$) $\delta = 13.04$ (s, 1H), 8.01 (s, 1H), 7.90 (d, $J = 7.4$ Hz, 1H), 7.80 (d, $J = 7.4$ Hz, 1H), 7.68 – 7.63 (m, 4H), 7.42 – 7.31 (m, 5H), 7.19 (d, $J = 8.8$ Hz, 1H), 5.55 – 5.51 (m, 1H), 5.02 (s, 1H), 3.19 – 3.16 (m, 1H), 3.06 – 3.02 (m, 1H), 2.86 – 2.81 (m, 1H), 2.37 – 2.28 (m, 1H), 2.17 – 2.07 (m, 1H), 2.00 – 1.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 157.3, 144.0, 142.0, 141.8, 140.4, 134.5, 130.8, 129.5, 129.0, 128.9, 128.1, 127.5, 127.2, 126.1, 125.9, 123.2, 121.4, 120.6, 120.4, 120.1, 113.8, 65.1, 65.0, 63.8, 60.1, 30.6, 28.0$ ppm. HRMS (ESI) exact mass calculated for $C_{28}H_{25}BrNO_2^+([M+H]^+)$: 488.1063, found :488.1053. The enantiomeric excess (99 %) was determined by HPLC column: chiralpak IA; solvent: 2-propanol: hexane (1:4); light: 220 nm; flow: 1 mL /min; major enantiomer t_r = 11.4 min, minor enantiomer t_r = 9.8 min .

1-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)-6-bromonaphthalen-2-

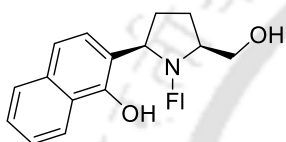


ol (3.18d): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (29 μ L, 0.30 mmol), and 6-bromo-2-naphthol (55 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C for 45 minutes and SiO_2 column chromatography

(hexane: ethyl acetate; 4:1) gave **3.18d** as brown solid (83 mg, 0.17 mmol, 68 %). $[a]_D^{25} = +159.1$ ($c = 0.17$, MeOH). FTIR (KBr): $\bar{\nu} = 3413, 3061, 2924, 2872, 1615, 1581, 1504, 1448, 1396, 1353, 1233, 1200, 1158, 1080, 1026, 973\text{ cm}^{-1}$. 1H NMR (600 MHz, $CDCl_3$) $\delta = 12.99$ (s, 1H), 7.94 – 7.89 (m, 2H), 7.82 – 7.79 (m, 2H), 7.66 (dd, $J = 12.6, 7.5$ Hz, 2H), 7.63 (d, J

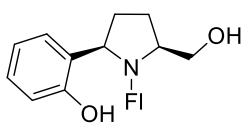
= 8.9 Hz, 1H), 7.57 – 7.56 (m, 1H), 7.41 – 7.38 (m, 2H), 7.37 – 7.34 (m, 1H), 7.32 – 7.3 (m, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 5.64 – 5.61 (m, 1H), 5.03 (s, 1H), 3.17 – 3.14 (m, 1H), 3.03 – 3.01 (m, 1H), 2.81 – 2.77 (m, 1H), 2.33 – 2.27 (m, 1H), 2.17 – 2.09 (m, 1H), 1.96 – 1.92 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ = 156.7, 144.1, 142.1, 141.8, 140.3, 131.8, 131.1, 130.0, 129.9, 129.0, 128.9, 128.7, 128.1, 127.4, 126.1, 126.1, 122.6, 121.3, 120.4, 120.1, 116.1, 114.7, 65.1, 65.0, 63.8, 60.02, 30.6, 28.0 ppm. HRMS (ESI) exact mass calculated for C₂₈H₂₅BrNO₂⁺ ([M+H]⁺): 488.1063, found : 488.1060. The enantiomeric excess (>99 %) was determined by HPLC column : chiralpak IA; solvent : 2-propanol: hexane (1:4); light: 220 nm; flow: 1 mL/min; major enantiomer *t_r* = 53.1 min, minor enantiomer *t_r* = 30.4 min .

2-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)naphthalen-1-ol



(3.18e): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (29 μ L, 0.30 mmol), and 1-naphthol (36 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 °C for 45 minutes and SiO₂ column chromatography (hexane: ethyl acetate; 4:1) gave **3.18e** as brown solid (65 mg, 0.16 mmol, 64 %). [α]_D²⁵ = +182.5 (c = 0.25, MeOH). FTIR (KBr): $\bar{\nu}$ = 3429, 3052, 2924, 2875, 1598, 1574, 1509, 1450, 1393, 1299, 1263, 1194, 1026, 805, 743, 674, 574 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.42 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 6.7 Hz, 1H), 7.80 – 7.76 (m, 2H), 7.67 – 7.60 (m, 2H), 7.51 – 7.45 (m, 2H), 7.39 – 7.32 (m, 4H), 7.29 – 7.24 (m, 2H), 5.06 (s, 1H), 4.99 – 4.94 (m, 1H), 3.11 – 3.08 (m, 1H), 2.98 – 2.94 (m, 1H), 2.77 – 2.69 (m, 1H), 2.23 – 2.18 (m, 2H), 1.88 – 1.85 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 153.3, 144.6, 142.5, 142.1, 140.2, 134.2, 128.8, 128.8, 128.1, 127.5, 127.3, 126.3, 126.1, 126.1, 125.8, 125.1, 122.5, 120.4, 120.0, 118.7, 117.2, 71.3, 65.1, 63.7, 59.9, 31.8, 28.1 ppm. HRMS (ESI) exact mass calculated for C₂₈H₂₆NO₂⁺ ([M+H]⁺): 408.1958, found: 408.1960. The enantiomeric excess (>99 %) was determined by HPLC column: chiralpak IA; solvent : 2-propanol: hexane (1:4); light: 220 nm; flow :1 mL /min; major enantiomer *t_r* = 8.3 min, minor enantiomer *t_r* = 12.4 min .

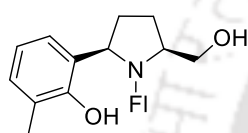
2-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)phenol **(3.18f):**



According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (73 μ L, 0.75 mmol), and phenol (23 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 °C for 45 minutes and SiO₂ column chromatography (hexane: ethyl acetate, 5:1) gave **3.18f** as grey solid (51 mg, 0.14 mmol, 56 %). [α]_D²⁵ = +156.0 (c = 0.10, MeOH). FTIR (KBr): $\bar{\nu}$ = 3452, 3061, 2928,

2873, 1613, 1588, 1488, 1476, 1449, 1257, 1033, 740, 675, 621 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 11.28 (s, 1H), 7.81 (d, J = 7.1 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.66 (d, J = 7.1 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.35 – 7.30 (m, 2H), 7.28 – 7.16 (m, 2H), 6.96 (d, J = 7.9 Hz, 1H), 6.86 – 6.822 (m, 1H), 5.06 (s, 1H), 4.86 – 4.82 (m, 1H), 3.07 – 3.03 (m, 1H), 2.90 – 2.86 (m, 1H), 2.74 – 2.71 (m, 1H), 2.21 – 2.1 (m, 2H), 1.91 – 1.85 (m, 2H). ^{13}C -NMR (101 MHz, CDCl_3) δ = 157.5, 144.7, 142.6, 142.1, 140.1, 129.5, 129.2, 128.8, 128.7, 128.1, 127.3, 126.1, 125.9, 124.8, 120.4, 120.1, 119.4, 110.2, 71.1, 64.9, 63.5, 59.9, 31.5, 28.0 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{24}\text{H}_{24}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$): 358.1802, found: 358.1802. The enantiomeric excess (>99 %) was determined by HPLC column: chiral pak IA; solvent: 2-propanol: hexane (3:97); light: 220 nm; flow: 1 ml/min; major enantiomer t_r = 30.7 min, minor enantiomer t_r = 35.5 min.

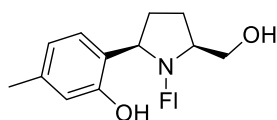
2-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)-6-methylphenol



(3.18g): According to general procedure B: 9-fluorenone imine (54 mg, 0.30 mmol), *S*-prolinol (73 μL , 0.75 mmol), and *ortho*-cresol (26 μL , 0.25 mmol), in 2 mL benzene under reflux for 60 hours and SiO_2

column chromatography (hexane: ethyl acetate, 5:1) gave **3.18g** as yellow solid (60 mg, 0.16 mmol, 65 %). $[\alpha]_D^{25} = +141.6$ (c = 0.25, MeOH). FTIR (KBr): $\bar{\nu}$ = 3437, 2922, 2854, 1630, 1448, 1469, 1382, 1255, 1165, 1116, 1029, 743, 670 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 11.35 (s, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.38 (dt, J = 14.8, 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 6.77 – 6.73 (m, 1H), 5.04 (s, 1H), 4.82 – 4.80 (m, 1H), 3.05 – 3.04 (m, 1H), 2.90 – 2.88 (m, 1H), 2.74 – 2.72 (m, 1H), 2.34 (s, 3H), 2.22 – 2.15 (m, 1H), 2.12 – 2.08 (m, 1H), 1.89 – 1.85 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.7, 144.8, 142.6, 142.1, 140.2, 130.4, 128.8, 128.7, 128.1, 127.3, 127.1, 126.2, 126.0, 125.9, 123.8, 120.4, 120.1, 119.0, 71.2, 65.0, 63.4, 59.9, 31.3, 27.9, 16.1 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{25}\text{H}_{26}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$): 372.1958, found: 372.1968. The enantiomeric excess (>99 %) was determined by HPLC column: chiral pak IA; solvent: 2-propanol: hexane (10:90); light: 220 nm; flow: 1 mL/min; major enantiomer t_r = 8.1 min, minor enantiomer t_r = 9.2 min.

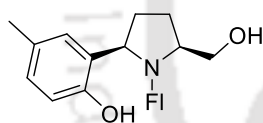
2-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)-5-methylphenol



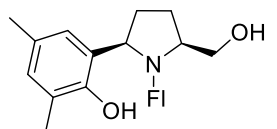
(3.18h): According to general procedure B: 9-fluorenone imine (54 mg, 0.30 mmol), *S*-prolinol (73 μL , 0.75 mmol), and *meta*-cresol (26 μL , 0.25 mmol), in 2 mL benzene under reflux for 60 hours and

SiO₂ column chromatography (hexane: ethylacetate, 5:1) gave **3.18h** as white solid (78 mg, 0.21 mmol, 84 %). $[\alpha]_D^{25} = +183.5$ (c = 0.17, MeOH). FTIR (KBr): $\bar{\nu} = 3497, 3063, 3037, 3007, 2923, 2870, 1581, 1514, 1467, 1450, 1370, 1266, 1184, 1153, 1114, 1089, 1024, 963, 861, 807, 738, 622, 595, 547 \text{ cm}^{-1}$. ¹H NMR (600 MHz, CDCl₃) $\delta = 11.14$ (s, 1H), 7.80 (d, $J = 7.5$ Hz, 1H), 7.75 (d, $J = 7.3$ Hz, 1H), 7.70 (d, $J = 7.5$ Hz, 1H), 7.65 (d, $J = 7.4$ Hz, 1H), 7.41 – 7.35 (m, 2H), 7.33 – 7.28 (m, 2H), 7.06 (d, $J = 6$ Hz, 1H), 6.79 (s, 1H), 6.66 (d, $J = 7.5$ Hz, 1H), 5.06 (s, 1H), 4.83 – 4.80 (m, 1H), 3.03 – 3.00 (m, 1H), 2.87 – 2.84 (m, 1H), 2.71 – 2.67 (m, 1H), 2.32 (s, 3H), 2.19 – 2.06 (m, 2H), 1.87 – 1.83 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) $\delta = 157.4, 144.9, 142.7, 142.1, 140.1, 139.3, 129.4, 128.8, 128.7, 128.1, 127.3, 126.1, 125.9, 121.7, 120.4, 120.3, 120.0, 117.9, 80.0, 65, 63.4, 59.8, 31.6, 28.0, 21.4$ ppm. HRMS (ESI) exact mass calculated for C₂₅H₂₆NO₂⁺ ([M+H]⁺): 372.1958, found : 372.1962. The enantiomeric excess (>99 %) was determined by HPLC column: chiralpak IA; solvent: 2-propanol: hexane (10:90); light: 220 nm; flow: 1 mL/min; major enantiomer $t_r = 18.5$ min, minor enantiomer $t_r = 13.8$ min.

2-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)-6-methylphenol (3.18i):

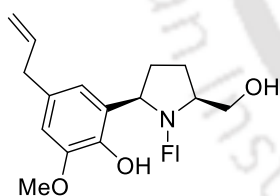


According to general procedure B: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (73 μ L, 0.75 mmol), and *para*-cresol (26 μ L, 0.25 mmol), in 2 mL benzene under reflux for 60 hours and SiO₂ column chromatography (hexane: ethyl acetate, 5:1) gave **3.18i** as white solid (81 mg, 0.22 mmol, 87 %). $[\alpha]_D^{25} = +125.3$ (c = 0.15, MeOH). FTIR (KBr): $\bar{\nu} = 3572, 3436, 2950, 2927, 2855, 1600, 1498, 1448, 1396, 1361, 1259, 1149, 1090, 1058, 1021, 958, 887, 802, 738, 619, 580, 491 \text{ cm}^{-1}$. ¹H NMR (600 MHz, CDCl₃) $\delta = 10.97$ (s, 1H), 7.80 (d, $J = 7.5$ Hz, 1H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.71 (d, $J = 7.5$ Hz, 1H), 7.65 (d, $J = 7.4$ Hz, 1H), 7.42 – 7.39 (m, 1H), 7.38 – 7.35 (m, 1H), 7.33 – 7.29 (m, 2H), 7.03 – 7.01 (m, 1H), 6.99 – 6.97 (m, 1H), 6.86 (d, $J = 8.1$ Hz, 1H), 5.06 (s, 1H), 4.81 – 4.78 (m, 1H), 3.04 – 3.01 (m, 1H), 2.87 – 2.85 (m, 1H), 2.73 – 2.69 (m, 1H), 2.28 (s, 3H), 2.22 – 2.14 (m, 1H), 2.13 – 2.08 (m, 1H), 1.89 – 1.84 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) $\delta = 155.2, 144.9, 142.7, 142.1, 140.1, 130.0, 129.7, 128.8, 128.7, 128.5, 128.1, 127.3, 126.2, 125.9, 124.4, 120.5, 120.0, 117.1, 71.3, 65.0, 63.5, 59.8, 31.5, 28.0, 20.7$ ppm. HRMS (ESI) exact mass calculated for C₂₅H₂₆NO₂⁺ ([M+H]⁺): 372.1958, found : 372.1961. The enantiomeric excess (>99 %) was determined by HPLC column : chiralpak IA ; solvent : 2-propanol : hexane (10:90); light: 220 nm; flow :1 mL /min; major enantiomer $t_r = 12.7$ min, minor enantiomer $t_r = 14.9$ min.

2-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)-4, 6-dimethylphenol (3.18j):


(**3.18j**): According to general procedure B: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (73 μ L, 0.75 mmol), and 2,4-dimethylphenol (35 μ L, 0.25 mmol), in 2 mL benzene under reflux for 60

hours and SiO₂ column chromatography (hexane: ethyl acetate, 5:1) gave **3.18j** as brown solid (57 mg, 0.15 mmol, 60 %). $[\alpha]_D^{25} = +151.8$ (c = 0.17, MeOH). FTIR (KBr): $\bar{\nu} = 3568, 3455, 2961, 2928, 2869, 1609, 1484, 1448, 1378, 1340, 1249, 1195, 1155, 1052, 1037, 854, 764, 741, 731, 707, 673, 622, 577, 465$ cm⁻¹. ¹H NMR (600 MHz, CDCl₃) $\delta = 11.07$ (s, 1H), 7.81 (d, $J = 7.5$ Hz, 1H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.70 (d, $J = 7.5$ Hz, 1H), 7.65 (d, $J = 7.4$ Hz, 1H), 7.41 – 7.35 (m, 2H), 7.34 – 7.28 (m, 2H), 6.91 (s, 1H), 6.83 (s, 1H), 5.04 (s, 1H), 4.79 – 4.76 (m, 1H), 3.03 – 3.01 (m, 1H), 2.88 – 2.85 (m, 1H), 2.72 – 2.69 (m, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.19 – 2.14 (m, 1H), 2.11 – 2.07 (m, 1H), 1.89 – 1.84 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) $\delta = 153.2, 144.9, 142.7, 142.1, 140.1, 131.1, 128.8, 128.7, 128.1, 127.9, 127.6, 127.3, 126.2, 125.9, 125.8, 123.5, 120.4, 120.0, 71.3, 64.9, 63.4, 59.8, 31.3, 27.9, 20.7, 16.1$ ppm. HRMS (ESI) exact mass calculated for C₂₆H₂₈NO₂⁺ ([M+H]⁺): 386.2115, found: 386.2122. The enantiomeric excess (>99 %) was determined by HPLC column: chiralpak IA; solvent: 2-propanol: hexane (5:95); light: 220 nm; flow: 1mL /min; major enantiomer $t_r = 10.1$ min, minor enantiomer $t_r = 13.7$ min.

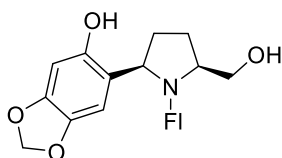
2-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)-4-allyl-6-methoxyphenol (3.18k):


methoxyphenol (3.18k): According to general procedure B: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (73 μ L, 0.75 mmol), and eugenol (35 μ L, 0.25 mmol), in 2 mL benzene under reflux for 60 hours and SiO₂ column chromatography (hexane: ethyl

acetate, 5:1) gave **3.18k** as brown solid (58 mg, 0.14 mmol, 54 %). $[\alpha]_D^{25} = +159.1$ (c = 0.21, MeOH). FTIR (KBr): $\bar{\nu} = 3447, 3063, 2926, 2874, 1637, 1598, 1494, 1449, 1402, 1365, 1260, 1246, 1152, 1082, 1030, 912, 846, 797, 743, 680, 622$ cm⁻¹. ¹H NMR (600 MHz, CDCl₃) $\delta = 10.87$ (s, 1H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.69 (d, $J = 7.5$ Hz, 1H), 7.64 (d, $J = 7.5$ Hz, 1H), 7.40 – 7.34 (m, 2H), 7.31 – 7.27 (m, 2H), 6.67 (s, 1H), 6.62 (s, 1H), 6.00 – 5.94 (m, 1H), 5.12 – 5.09 (m, 1H), 5.09 – 5.06 (m, 2H), 4.85 – 4.80 (m, 1H), 3.92 (s, 3H), 3.31 (d, $J = 6.0$ Hz, 2H), 3.06 – 3.02 (m, 1H), 2.92 – 2.89 (m, 1H), 2.74 – 2.69 (m, 1H), 2.21 – 2.07 (m, 2H), 1.87 – 1.83 (m, 2H). ¹³C- NMR (151 MHz, CDCl₃) $\delta = 148.4, 144.8, 144.7, 142.9, 142.1, 140.1, 138.0, 130.7, 128.8, 128.7, 128.1, 127.2, 126.1, 126.1, 125.0, 121.1, 120.4, 120.0, 115.8, 111.6, 70.5, 65.1, 63.7, 60.0, 56.2, 40.1, 31.7, 28.2$ ppm. HRMS

(ESI) exact mass calculated for C₂₈H₃₀NO₃⁺ ([M+H]⁺): 428.2220, found: 428.2222. The enantiomeric excess (>99 %) was determined by HPLC column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (20:80); light: 220 nm; flow: 1mL/min; major enantiomer t_r = 9.5 min, minor enantiomer t_r = 7.7 min.

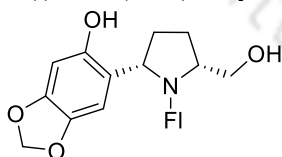
6-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)benzo[d][1,3]dioxol-5-ol



(3.18I): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (29 µL, 0.30 mmol), and sesamol (34 mg, 0.25 mmol), in 1mL toluene under microwave heating at 150 °C for

45 minutes and SiO₂ column chromatography (hexane: ethyl acetate; 4:1) gave **3.18I** as white solid (90 mg, 0.22 mmol, 90 %). $[\alpha]_D^{25} = +148.1$ (c = 0.27, MeOH). FTIR (KBr): $\bar{\nu}$ = 3578, 3056, 2960, 2877, 1500, 1481, 1447, 1404, 1389, 1209, 1182, 1148, 929, 864, 847, 744, 734, 684 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 11.09 (s, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.73 – 7.70 (m, 2H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.33 – 7.28 (m, 2H), 6.63 (s, 1H), 6.53 (s, 1H), 5.89 – 5.86 (m, 2H), 5.08 (s, 1H), 4.70 – 4.67 (m, 1H), 3.04 – 3.02 (m, 1H), 2.88 – 2.85 (m, 1H), 2.73 – 2.70 (m, 1H), 2.18 – 2.06 (m, 2H), 1.87 – 1.83 (m, 2H). ¹³C-NMR (CDCl₃, 100 MHz) δ = 152.7, 148.0, 144.7, 142.5, 142.0, 140.5, 140.2, 128.9, 128.8, 128.1, 127.3, 126.1, 126.0, 120.4, 120.0, 115.8, 108.8, 101.1, 99.6, 71.1, 65.0, 63.4, 59.8, 31.4, 27.8. HRMS (ESI) exact mass calculated for C₂₅H₂₄NO₄⁺ ([M+H]⁺): 402.1700, found: 402.1701. The enantiomeric excess (>99 %) was determined by HPLC column: chiralpak IA; solvent: 2-propanol: hexane (1:4); light: 220 nm; flow: 1 mL /min; major enantiomer t_r = 15.5 min, minor enantiomer t_r = 21.4 min .

6-((2S,5R)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)benzo[d][1,3]dioxol-5-ol

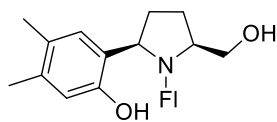


(ent-3.18I): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), R-prolinol (29 µL, 0.30 mmol), and sesamol (34 mg, 0.25 mmol), in 1mL toluene under microwave heating at 150 °C

for 45 minutes and SiO₂ column chromatography (hexane: ethyl acetate; 4:1) gave **ent-3.18I** as white solid (77 mg, 0.19 mmol, 77%). $[\alpha]_D^{25} = -145.3$ (c = 0.22, MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 11.11 (s, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.72 (t, *J* = 7.3 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.29 (m, 4H), 6.63 (s, 1H), 6.53 (s, 1H), 5.88 (d, *J* = 4.3 Hz, 2H), 5.08 (s, 1H), 4.71 – 4.67 (m, 1H), 3.08 – 3.00 (m, 1H), 2.88 – 2.85 (m, 1H), 2.75 – 2.68 (m, 1H), 2.18 – 2.06 (m, 2H), 1.86 – 1.83 (m, 2H) ppm. HRMS (ESI) exact mass calculated for C₂₅H₂₄NO₄⁺ ([M+H]⁺): 402.1700, found: 402.11696. The enantiomeric excess (>99 %) was

determined by HPLC column: chiralpak IA; solvent: 2-propanol: hexane (1:4); light: 220 nm; flow: 1 mL /min; major enantiomer t_r = 16.7 min, minor enantiomer t_r = 13.2 min .

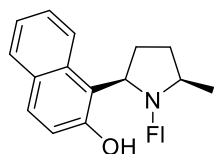
2-((2R,5S)-1-(9H-fluoren-9-yl)-5-(hydroxymethyl)pyrrolidin-2-yl)-4,5-dimethylphenol



(3.18m) : According to general procedure B: 9-fluorenone imine (54 mg, 0.30 mmol), S-prolinol (73 μ L, 0.75 mmol), and 3,4-dimethylphenol (30 mg, 0.25 mmol), in 2 mL benzene under reflux for 66

hours and SiO₂ column chromatography (hexane : ethyl acetate, 5:1) gave **3.18m** as yellow solid (68 mg, 0.18 mmol, 71 %). $[\alpha]_D^{25} = +77.3$ ($c = 0.12$, MeOH). FTIR (KBr): $\bar{\nu} = 3430$, 3063, 3006, 2922, 2856, 1730, 1628, 1582, 1504, 1449, 1384, 1263, 1194, 1105, 1025, 876, 742, 621, 580 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 10.85 (s, 1H), 7.80 – 7.76 (m, 2H), 7.70 (d, $J = 7.5$ Hz, 1H), 7.64 (d, $J = 7.4$ Hz, 1H), 7.41 – 7.39 (m, 1H), 7.37 – 7.34 (m, 1H), 7.31 – 7.28 (m, 2H), 6.94 (s, 1H), 6.78 (s, 1H), 5.06 (s, 1H), 4.79 (dd, $J = 10.6, 6.4$ Hz, 1H), 3.01 – 2.99 (m, 1H), 2.85 – 2.83 (m, 1H), 2.69 – 2.66 (m, 1H), 2.23 (s, 3H), 2.19 (s, 3H), 2.16 – 2.06 (m, 2H), 1.88 – 1.83 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.3, 145.0, 142.8, 142.1, 140.1, 137.5, 130.6, 128.8, 128.7, 128.1, 127.3, 127.2, 126.2, 125.9, 121.8, 120.4, 120.0, 118.5, 71.0, 65.0, 63.4, 59.7, 31.6, 28.0, 19.8, 19.0 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{26}\text{H}_{28}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$): 386.2115, found: 386.2129. The enantiomeric excess (>99 %) was determined by HPLC column: chiralpak IA; solvent: 2-propanol: hexane (10:90); light: 220 nm; flow: 1 mL/min; major enantiomer t_r = 16.7 min, minor enantiomer t_r = 13.9 min.

1-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)naphthalen-2-ol **(3.19a):**

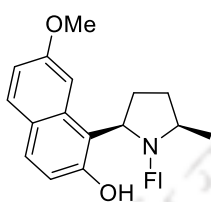


According to general procedure B: 9-fluorenone imine (54 mg, 0.30 mmol), R-2-methylpyrrolidine (31 μ L, 0.30 mmol), and 2-naphthol (36 mg, 0.25 mmol), in 2 mL benzene under reflux for 48 hours and SiO₂ column

chromatography (hexane: ethyl acetate, 100:1) gave **3.19a** as brown solid (75 mg, 0.19 mmol, 77 %). $[\alpha]_D^{25} = +96.0$ ($c = 0.2$, MeOH). FTIR (KBr): $\bar{\nu} = 3421$, 3054, 2956, 2869, 1621, 1598, 1520, 1449, 1374, 1348, 1273, 1241, 1196, 784, 735, 672 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 13.60 (s, 1H), 7.93 (d, $J = 7.6$ Hz, 2H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.79 (d, $J = 7.7$ Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.64 (d, $J = 6.9$ Hz, 1H), 7.53 – 7.50 (m, 1H), 7.40 – 7.29 (m, 5H), 7.21 (d, $J = 8.8$ Hz, 1H), 5.66 – 5.63 (m, 1H), 5.04 (s, 1H), 2.87 – 2.81 (m, 1H), 2.39 – 2.34 (m, 1H), 2.14 – 2.09 (m, 1H), 2.01 – 1.95 (m, 1H), 1.59 – 1.56 (m, 1H), 0.75 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 156.7, 144.5,

142.3, 142.1, 140.3, 133.2, 129.5, 129.3, 128.8, 128.8, 128.6, 127.9, 127.2, 126.8, 126.7, 126.3, 122.5, 120.8, 120.3, 120.2, 119.8, 114.8, 65.1, 63.7, 54.9, 33.0, 30.4, 23.0 ppm. HRMS (ESI) exact mass calculated for C₂₈H₂₆NO⁺ ([M+H]⁺): 392.2009, found: 392.2009. The enantiomeric excess (>99 %) was determined by HPLC column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (1:99); light: 220 nm; flow: 1mL /min; major enantiomer t_r = 12.9 min, minor enantiomer t_r = 8.5 min.

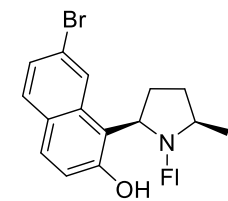
rac-1-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)-7-methoxynaphthalen-2-ol



(3.19b): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), 2-methylpyrrolidine (31 μL, 0.30 mmol), and 7-methoxy-2-naphthol (44 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 °C for 45 minutes and SiO₂ column chromatography (hexane: ethyl

acetate, 50:1) gave **3.19b** as brown solid (72 mg, 0.17 mmol, 69 %). FTIR (KBr): $\bar{\nu}$ = 3433, 2958, 2924, 2853, 1621, 1587, 1518, 1477, 1463, 1449, 1378, 1262, 1224, 1206, 1098, 1031, 835, 802, 738, 673 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 13.53 (s, 1H), 7.91 (d, *J* = 7.1 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.67 – 7.60 (m, 3H), 7.38 – 7.31 (m, 2H), 7.28 – 7.20 (m, 2H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.03 – 7.00 (m, 1H), 5.49 (dd, *J* = 9.4, 7.3 Hz, 1H), 4.99 (s, 1H), 3.99 (s, 3H), 2.88 – 2.80 (m, 1H), 2.39 – 2.32 (m, 1H), 2.15 – 2.05 (m, 1H), 2.02 – 1.93 (m, 1H), 1.62 – 1.54 (m, 1H), 0.75 (d, *J* = 6.3 Hz, 3H). ¹³C-NMR (101 MHz, CDCl₃) δ = 158.5, 157.2, 144.5, 142.2, 142.1, 140.3, 134.3, 130.8, 129.2, 128.7, 128.5, 127.8, 127.1, 126.9, 126.1, 124.1, 120.3, 119.8, 117.7, 113.9, 113.5, 101.4, , 65.1, 63.6, 55.6, 54.9, 32.9, 30.1, 22.9 ppm. HRMS (ESI) exact mass calculated for C₂₉H₂₈NO₂⁺ ([M+H]⁺): 422.2115, found : 422.2105.

rac-1-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)-7-bromonaphthalen-2-ol

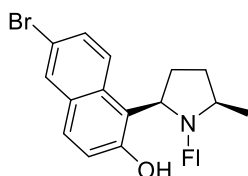


(3.19c): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), 2-methylpyrrolidine (31 μL, 0.30 mmol), and 7-bromo-2-naphthol (55 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 °C for 45 minutes and SiO₂ column chromatography (hexane: ethyl acetate, 50:1) gave **3.19c** as brown solid (76 mg, 0.16 mmol, 65 %). FTIR (KBr): $\bar{\nu}$ =

3426, 3050, 2962, 2870, 2604, 1916, 1598, 1574, 1510, 1449, 1395, 1375, 1321, 1194, 1086, 1024, 917, 804, 729, 734, 673, 649, 574 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 13.65 (s, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 6.9 Hz, 1H), 7.68 (d, *J* = 7.1 Hz, 1H), 7.61 – 7.52 (m, 4H), 7.33 – 7.20 (m, 5H), 7.11 (d, *J* = 8.8 Hz, 1H), 5.37 – 5.33 (m, 1H), 4.89 (s, 1H), 2.88 – 2.79 (m, 1H),

2.32 – 2.23 (m, 1H), 2.06 – 1.89 (m, 2H), 1.57 – 1.48 (m, 1H), 0.75 (d, $J = 6.0$ Hz, 3H) ^{13}C -NMR (101 MHz, CDCl_3) $\delta = 157.5, 144.1, 142.0, 141.9, 140.4, 134.4, 130.8, 129.4, 128.8, 128.7, 127.8, 127.3, 127.1, 126.6, 126.1, 125.8, 123.2, 121.3, 120.6, 120.2, 119.9, 114.4, 64.7, 63.7, 55.3, 32.9, 30.5, 22.8$ ppm. HRMS (ESI) exact mass calculated for $\text{C}_{28}\text{H}_{25}\text{BrNO}^+$ ($[\text{M}+\text{H}]^+$): 470.1114, found: 470.1116.

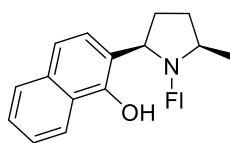
rac-1-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)-6-bromonaphthalen-2-ol



(3.19d): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), 2-methylpyrrolidine (31 μL , 0.30 mmol), and 6-bromo-2-naphthol (55 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}\text{C}$ for 45 minutes and SiO_2 column

chromatography (hexane: ethyl acetate, 50:1) gave **3.19d** as brown solid (76 mg, 0.16 mmol, 65 %). FTIR (KBr): $\bar{\nu} = 3436, 3065, 2958, 2869, 1614, 1588, 1506, 1464, 1449, 1397, 1374, 1331, 1238, 1199, 1097, 1077, 951, 944, 884, 817, 781, 741, 673, 501$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3) $\delta = 13.59$ (s, 1H), 7.82 (d, $J = 8.3$ Hz, 2H), 7.70 – 7.65 (m, 2H), 7.59 – 7.52 (m, 3H), 7.47 (d, $J = 10.3$ Hz, 1H), 7.33 – 7.24 (m, 3H), 7.19 (d, $J = 5.7$ Hz, 1H), 7.12 (d, $J = 8.9$ Hz, 1H), 5.46 – 5.42 (m, 1H), 4.93 (s, 1H), 2.86 – 2.74 (m, 1H), 2.29 – 2.19 (m, 1H), 2.04 – 1.85 (m, 2H), 1.52 – 1.47 (m, 1H), 0.71 (d, $J = 6.3$ Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3) $\delta = 156.9, 144.2, 142.2, 141.9, 140.4, 131.6, 131.0, 130.0, 129.9, 128.9, 128.7, 128.6, 127.9, 127.2, 126.7, 126.1, 122.6, 121.3, 120.3, 119.9, 115.9, 115.3, 64.8, 63.7, 55.2, 33.0, 30.6, 22.9$ ppm. HRMS (ESI) exact mass calculated for $\text{C}_{28}\text{H}_{25}\text{BrNO}^+$ ($[\text{M}+\text{H}]^+$): 470.1114, found: 470.1113.

rac-2-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)naphthalen-1-ol **(3.19e):**

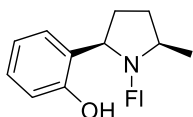


According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), 2-methylpyrrolidine (31 μL , 0.30 mmol), and 1-naphthol (36 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}\text{C}$

for 45 minutes and SiO_2 column chromatography (hexane: ethyl acetate, 50:1) gave **3.19e** as brown solid (70 mg, 0.18 mmol, 72 %). FTIR (KBr): $\bar{\nu} = 3426, 3050, 2962, 2870, 1916, 1598, 1574, 1510, 1449, 1395, 1375, 1347, 1321, 1299, 1194, 1086, 1024, 917, 804, 786, 729, 734, 673, 649, 574$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3) $\delta = 12.85$ (s, 1H), 8.33 (d, $J = 8.8$ Hz, 1H), 7.83 (d, $J = 7.2$ Hz, 1H), 7.71 – 7.69 (m, 2H), 7.61 (d, $J = 7.5$ Hz, 1H), 7.57 – 7.55 (m, 1H), 7.45 – 7.37 (m, 2H), 7.32 – 7.23 (m, 4H), 7.20 – 7.13 (m, 2H), 5.00 (s, 1H), 4.86 – 4.81 (m, 1H), 2.77 – 2.7 (m, 1H), 2.18 – 2.04 (m, 2H), 1.9 – 1.8 (m, 1H), 1.51 – 1.42 (m, 1H), 0.66 (d, $J = 6.3$ Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3) $\delta = 153.6, 144.8, 142.6, 142.2,$

140.2, 134.2, 128.7, 128.5, 127.8, 127.5, 127.1, 127.1, 126.7, 126.2, 126.2, 125.8, 125.0, 122.5, 120.3, 119.8, 118.5, 117.7, 70.7, 63.5, 55.0, 33.0, 31.6, 23.2 ppm. HRMS (ESI) exact mass calculated for C₂₈H₂₆NO⁺ ([M+H]⁺): 392.2009, found : 392.2008.

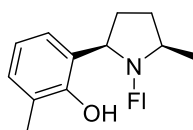
2-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)phenol (3.19f): According to



general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), *R*-2-methylpyrrolidine (51 μ L, 0.50 mmol), and phenol (23 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}$ C for 45 minutes and SiO₂ column

chromatography (hexane: ethyl acetate, 50:1) gave **3.19f** as white solid (51 mg, 0.15 mmol, 60 %). $[\alpha]_D^{25} = +142.3$ ($c = 0.17$, MeOH). FTIR (KBr): $\bar{\nu} = 3436, 3047, 2958, 2925, 1612, 1593, 1492, 1476, 1447, 1337, 1294, 1260, 1202, 1187, 1078, 1016, 848, 637, 754, 733, 741, 673$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃) $\delta = 11.91$ (s, 1H), 7.81 (d, $J = 7.4$ Hz, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.65 (d, $J = 7.4$ Hz, 1H), 7.41 – 7.34 (m, 2H), 7.33 – 7.27 (m, 2H), 7.22 – 7.18 (m, 1H), 7.12 – 7.10 (m, 1H), 6.93 (d, $J = 8.1$ Hz, 1H), 6.81 (t, $J = 7.0$ Hz, 1H), 5.05 (s, 1H), 4.76 (t, $J = 8.5$ Hz, 1H), 2.83–2.75 (m, 1H), 2.16 – 2.10 (m, 2H), 1.96 – 1.86 (m, 1H), 1.54 – 1.46 (m, 1H), 0.66 (d, $J = 6.3$ Hz, 3H). ¹³C-NMR (101 MHz, CDCl₃) $\delta = 157.5, 144.7, 142.6, 142.1, 140.1, 129.5, 129.2, 128.8, 128.7, 128.1, 127.3, 126.1, 125.9, 124.8, 120.4, 120.1, 119.4, 110.2, 71.1, 64.9, 63.5, 59.9, 31.5, 28.0$ ppm. HRMS (ESI) exact mass calculated for C₂₄H₂₄NO⁺ ([M+H]⁺): 342.1852, found: 342.1858. The enantiomeric excess (>99 %) was determined by HPLC column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (1:99); light: 254 nm; flow: 1 mL /min; major enantiomer $t_r = 10.9$ min, minor enantiomer $t_r = 13.4$ min.

2-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)-6-methylphenol (3.19g):

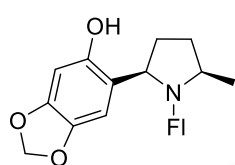


According to general procedure B: 9-fluorenone imine (21 mg, 0.12 mmol), *R*-2-methylpyrrolidine (31 μ L, 0.30 mmol), and *ortho*-cresol (10 μ L, 0.10 mmol), in 2 mL benzene under reflux for 48 hours and SiO₂ column

chromatography (hexane: ethyl acetate, 50:1) gave **3.19g** as brown solid (23 mg, 0.07 mmol, 65 %). $[\alpha]_D^{25} = +96.4$ ($c = 0.14$, MeOH). FTIR (KBr): $\bar{\nu} = 3433, 2957, 2924, 1596, 1460, 1371, 1471, 1448, 1376, 1258, 1192, 1096, 1081, 1031, 803, 785, 737, 710, 618$ cm⁻¹. ¹H NMR (600 MHz, CDCl₃) $\delta = 11.96$ (s, 1H), 7.83 (d, $J = 7.4$ Hz, 1H), 7.74 (d, $J = 7.5$ Hz, 1H), 7.70 (d, $J = 7.3$ Hz, 1H), 7.65 (d, $J = 7.2$ Hz, 1H), 7.40 – 7.35 (m, 2H), 7.34 – 7.31 (m, 1H), 7.29 – 7.27 (m, 1H), 7.08 (d, $J = 7.4$ Hz, 1H), 6.96 (d, $J = 7.4$ Hz, 1H), 6.75 – 6.71 (m, 1H), 5.04 (s, 1H), 4.75 – 4.72 (m, 1H), 2.82 – 2.76 (m, 1H), 2.34 (s, 3H), 2.16 – 2.11 (m, 2H), 1.95

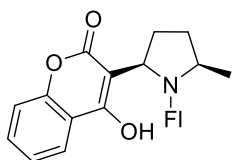
– 1.89 (m, 1H), 1.53 – 1.46 (m, 1H), 0.66 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) $\delta = 155.9, 144.9, 142.6, 142.1, 140.2, 130.2, 128.6, 128.4, 127.8, 127.0, 126.8, 126.6, 125.8, 124.4, 120.3, 119.8, 118.8, 70.6, 63.2, 54.9, 32.8, 31.1, 23.1, 16.0$ ppm. HRMS (ESI) exact mass calculated for $\text{C}_{25}\text{H}_{26}\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 356.2009, found: 356.2020 The enantiomeric excess (>99 %) was determined by HPLC column: phenomenex lux 5u cellulose -1; solvent : 2-propanol: hexane (1:99); light: 220 nm; flow: 1mL /min; major enantiomer $t_r = 7.8$ min, minor enantiomer $t_r = 6.9$ min.

6-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)benzo[d][1,3]dioxol-5-ol (3.19h):



According to general procedure A: 9-fluorenone imine (27 mg, 0.15 mmol), *R*-2-methylpyrrolidine (15 μL , 0.15 mmol), and sesamol (17 mg, 0.12 mmol), in 1 mL toluene under microwave heating at 150 $^\circ\text{C}$ for 45 minutes and SiO_2 column chromatography (hexane: ethyl acetate, 50:1) gave **3.19h** as brown solid (40 mg, 0.10 mmol, 83 %). $[\alpha]_D^{25} = +127.5$ ($c = 0.25$, MeOH) FTIR (KBr): $\bar{\nu} = 3435, 3052, 2961, 2925, 2880, 1631, 1500, 1482, 1413, 1375, 1292, 1250, 1202, 1183, 1150, 1096, 1033, 930, 861, 843, 791, 764, 734, 684, 664, 622, 521$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3) $\delta = 11.74$ (s, 1H), 7.77 (d, $J = 7.4$ Hz, 1H), 7.70 (d, $J = 7.6$ Hz, 2H), 7.65 (d, $J = 7.3$ Hz, 1H), 7.41 – 7.34 (m, 2H), 7.32 – 7.25 (m, 2H), 6.57 (s, 1H), 6.51 (s, 1H), 5.86 (d, $J = 5.1$ Hz, 2H), 5.05 (s, 1H), 4.62 – 4.58 (m, 1H), 2.81 – 2.73 (m, 1H), 2.13 – 2.05 (m, 2H), 1.93 – 1.84 (m, 1H), 1.51 – 1.44 (m, 1H), 0.64 (d, $J = 6.2$ Hz, 3H) ^{13}C - NMR (101 MHz, CDCl_3) $\delta = 152.9, 147.9, 144.8, 142.5, 142.1, 140.3, 140.2, 128.7, 128.4, 127.8, 127.1, 126.5, 126.1, 120.3, 119.8, 116.3, 108.5, 101.0, 99.5, 70.4, 63.2, 54.8, 32.7, 31.1, 23.0$ ppm. HRMS (ESI) exact mass calculated for $\text{C}_{25}\text{H}_{24}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$): 386.1751, found: 386.1752. The enantiomeric excess (>99 %) was determined by HPLC column : phenomenex lux 5u cellulose -1 ; solvent :2-propanol: hexane (1:99); light: 220 nm; flow:1 mL /min; major enantiomer $t_r = 18.7$ min, minor enantiomer $t_r = 13.2$ min.

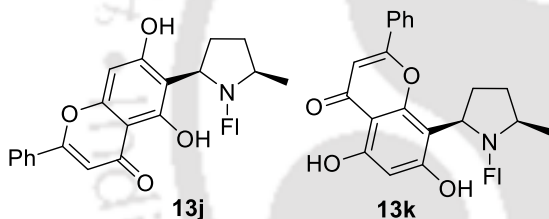
3-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)-4-hydroxy-2H-chromen-2-one



(3.19i): According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), *R*-2-methylpyrrolidine (31 μL , 0.30 mmol), and 4-hydroxy coumarin (40 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 $^\circ\text{C}$ for 45 minutes and SiO_2 column chromatography (hexane: ethyl acetate, 1:1) gave **3.19i** as brown solid (34 mg, 0.08 mmol, 33 %). $[\alpha]_D^{25} = +60.0$ ($c = 0.15$, MeOH). FTIR (KBr): $\bar{\nu} = 3441, 3064, 299, 2850, 1670, 1601, 1535, 1451, 1432, 1273, 1189,$

1048, 769, 745, 737, 571 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 15.22 (s, 1H), 8.10-8.09 (m, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.75 – 7.69 (m, 2H), 7.53 – 7.49 (m, 2H), 7.47 – 7.45 (m, 1H), 7.39 – 7.35 (m, 2H), 7.32 – 7.28 (m, 2H), 5.32 – 5.29 (m, 1H), 5.20 (s, 1H), 2.92 – 2.87 (m, 1H), 2.48 – 2.43 (m, 1H), 2.27 – 2.11 (m, 1H), 1.92 – 1.85 (m, 1H), 1.60 – 1.56 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 174.5, 164.9, 154.4, 142.8, 140.8, 139.7, 136.7, 131.7, 130.6, 130.3, 128.6, 128.3, 127.2, 126.6, 124.2, 123.4, 120.9, 120.8, 120.6, 116.9, 110.2, 68.1, 62.4, 56.2, 32.1, 28.9, 21.5. HRMS (ESI) exact mass calculated for C₂₇H₂₄NO₃⁺ ([M+H]⁺): 410.1751, found: 410.1762. The enantiomeric excess (>99 %) was determined by HPLC column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (30:70); light: 220 nm; flow: 1 mL /min; major enantiomer t_r = 10.4 min, minor enantiomer t_r = 8.3 min.

***rac*-6-((2*R*,5*R*)-1-(9*H*-fluoren-9-yl)-5-methylpyrrolidin-2-yl)-5,7-dihydroxy-2-phenyl-4*H*-chromen-4-one (3.19j) and *rac*-8-((2*R*,5*R*)-1-(9*H*-fluoren-9-yl)-5-methylpyrrolidin-2-yl)-5,7-dihydroxy-2-phenyl-4*H*-chromen-4-one (3.19k):** According to general procedure A: 9-fluorenone imine (54 mg, 0.30 mmol), 2-methyl pyrrolidine (31 μL, 0.30 mmol), and chrysin (63 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 °C for 45 minutes and SiO₂ column chromatography (hexane: ethyl acetate, 50:1) gave one isomer (of **3.19j** and **3.19k**) as brown solid (55 mg, 0.11 mmol, 44 %) and other isomer brown solid (23 mg, 0.05 mmol, 18.4 %).

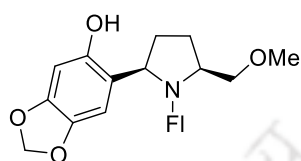


fluorenone imine (54 mg, 0.30 mmol), 2-methyl pyrrolidine (31 μL, 0.30 mmol), and chrysin (63 mg, 0.25 mmol), in 1 mL toluene under microwave heating at 150 °C for 45 minutes and SiO₂ column chromatography (hexane: ethyl acetate, 50:1) gave one isomer (of **3.19j** and **3.19k**) as brown solid (55 mg, 0.11 mmol, 44 %) and other isomer brown solid (23 mg, 0.05 mmol, 18.4 %).

FTIR (KBr): $\bar{\nu}$ = 3435, 3063, 2958, 2924, 1651, 1621, 1586, 1484, 1484, 1448, 1371, 1300, 1103, 1276, 1167, 844, 767, 738, 686, 578 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 13.18 (s, 1H), 7.82 – 7.79 (m, 3H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.44 – 7.42 (m, 3H), 7.36 – 7.22 (m, 4H), 6.56 (s, 1H), 6.45 (s, 1H), 5.30 (dd, *J* = 9.6, 6.9 Hz, 1H), 4.91 (s, 1H), 2.65 – 2.61 (m, 1H), 2.26 – 2.19 (m, 1H), 1.96 – 1.86 (m, 1H), 1.85 – 1.76 (m, 1H), 1.43 – 1.36 (m, 1H), 0.64 (d, *J* = 6.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 182.6, 166.7, 163.8, 159.8, 157.5, 143.8, 142.3, 141.5, 140.5, 131.8, 131.8, 129.2, 129.0, 128.8, 127.8, 127.5, 126.7, 126.5, 120.3, 120.0, 107.5, 105.8, 104.4, 95.3, 63.5, 62.3, 54.6, 32.9, 29.8, 23.0 ppm. HRMS (ESI) exact mass calculated for C₃₃H₂₈NO₄⁺ ([M+H]⁺): 502.2013, found : 502.2015. Other isomer: FTIR (KBr): $\bar{\nu}$ = 3433, 2966, 2926, 1653, 1623, 1585, 1492, 1450, 1423, 1362, 1290, 1270, 1169, 1113, 1079, 843, 816, 748, 683, 662, 647, 560, 544 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 12.61 (s, 1H), 7.79

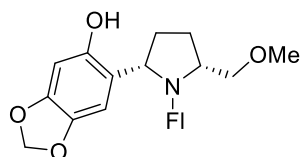
– 7.74 (m, 3H), 7.71 – 7.69 (m, 1H), 7.61 – 7.55 (m, 4H), 7.35 – 7.31 (m, 3H), 7.14 (t, $J = 8$ Hz, 1H), 6.63 (s, 1H), 6.33 (s, 1H), 5.23 (t, $J = 8$ Hz, 1H), 5.10 (s, 1H), 3.09 – 3.03 (m, 1H), 2.30 – 2.23 (m, 1H), 2.03 – 1.96 (m, 2H), 1.67 – 1.60 (m, 2H), 0.89 (d, $J = 8$ Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3) $\delta = 182.5, 165.9, 163.0, 161.6, 154.6, 143.2, 141.7, 140.9, 131.9, 129.4, 129.0, 128.9, 127.8, 127.2, 126.5, 126.2, 125.91, 120.2, 120.1, 105.9, 104.8, 103.6, 101.0, 101.0, 63.5, 60.9, 56.0, 32.9, 30.9, 22.2$. HRMS (ESI) exact mass calculated for $\text{C}_{33}\text{H}_{28}\text{NO}_4^+$ ($[\text{M}+\text{H}]^+$): 502.2013, found: 502.2029.

6-((2*R*,5*S*)-1-(9*H*-fluoren-9-yl)-5-(methoxymethyl)pyrrolidin-2-yl)benzo[d][1,3]dioxol-5-



ol (3.20): According to general procedure A: 9-fluorenone imine (27 mg, 0.15 mmol), *S*-2-(methoxymethyl)pyrrolidine (18 μL , 0.15 mmol), and sesamol (17 mg, 0.12 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}\text{C}$ for 45 minutes and SiO_2 column chromatography (hexane: ethyl acetate, 4:1) gave **3.20** as white solid (33 mg, 0.08 mmol, 64 %). $[\alpha]_D^{25} = +90.0$ ($c = 0.10$, MeOH). FTIR (KBr): $\bar{\nu} = 3435, 3237, 2890, 1627, 1501, 1481, 1449, 1385, 1179, 1145, 1038, 932, 868, 855, 796, 767, 743, 621, 518 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 10.67$ (s, 1H), 7.67 – 7.60 (m, 3H), 7.56 (d, $J = 7.4$ Hz, 1H), 7.29 – 7.27 (m, 2H), 7.24 – 7.18 (m, 2H), 6.54 (s, 1H), 6.46 (s, 1H), 5.82 – 5.77 (m, 2H), 4.98 (s, 1H), 4.58 – 4.54 (m, 1H), 2.99 (s, 3H), 2.71 – 2.63 (m, 2H), 2.51 – 2.43 (m, 1H), 2.14 – 2.04 (m, 1H), 1.97 – 1.90 (m, 1H), 1.83 – 1.68 (m, 2H). ^{13}C -NMR (101 MHz, CDCl_3) $\delta = 152.7, 148.0, 144.9, 143.1, 142.1, 140.3, 140.1, 128.7, 128.5, 127.7, 127.2, 126.4, 126.0, 120.3, 119.8, 116.0, 108.9, 101.0, 99.6, 75.3, 70.9, 63.4, 58.7, 57.7, 31.3, 28.8$. HRMS (ESI) exact mass calculated for $\text{C}_{25}\text{H}_{26}\text{NO}_4^+$ ($[\text{M}+\text{H}]^+$): 416.1856, found: 416.1856. The enantiomeric excess (95 %) was determined by HPLC column: phenomenex lux 5u cellulose-1; solvent: 2-propanol: hexane (1:4); light: 220 nm; flow: 1 mL/min; major enantiomer $t_r = 10.3$ min, minor enantiomer $t_r = 12.4$ min.

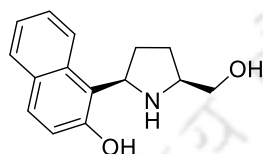
6-((2*S*,5*R*)-1-(9*H*-fluoren-9-yl)-5-(methoxymethyl)pyrrolidin-2-yl)benzo[d][1,3]dioxol-5-



ol (ent-20): According to general procedure A: 9-fluorenone imine (27 mg, 0.15 mmol), *R*-2-(methoxymethyl)pyrrolidine (18 μL , 0.15 mmol), and sesamol (17 mg, 0.12 mmol), in 1 mL toluene under microwave heating at 150 $^{\circ}\text{C}$ for 45 minutes and SiO_2 column chromatography (hexane: ethyl acetate, 4:1) gave **ent-3.20** as white solid (33 mg, 0.08 mmol, 64 %). $[\alpha]_D^{25} = -98.4$ ($c = 0.25$, MeOH). ^1H NMR (400 MHz, CDCl_3) $\delta = 10.68$ (s, 1H), 7.68 – 7.61 (m, 3H), 7.57 (d, $J = 7.4$

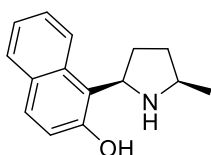
Hz, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.18 (m, 2H), 6.54 (s, 1H), 6.47 (s, 1H), 5.80 (d, $J = 3.8$ Hz, 2H), 4.99 (s, 1H), 4.59 – 4.55 (m, 1H), 2.99 (s, 3H), 2.71 – 2.66 (m, 2H), 2.49 – 2.45 (m, 1H), 2.13 – 2.04 (m, 1H), 1.94 – 1.90 (m, 1H), 1.83 – 1.68 (m, 2H) ppm. HRMS (ESI) exact mass calculated for C₂₅H₂₆NO₄⁺ ([M+H]⁺): 416.1856, found: 416.1856. The enantiomeric excess (99 %) was determined by HPLC column: phenomenex lux 5u cellulose-1; solvent: 2-propanol: hexane (1:4); light: 220 nm; flow: 1 mL/min; major enantiomer $t_r = 14.9$ min, minor enantiomer $t_r = 10.4$ min.

1-((2R,5S)-5-(hydroxymethyl)pyrrolidin-2-yl)naphthalen-2-ol (3.21): Compound **3.18a**



(51 mg, 0.12 mmol) was dissolved in ethyl acetate and methanol (3:1, v/v) and Pd/C (13 mg, 10%) was added to it. Then the flask was degassed 3 times to create hydrogen atmosphere. The reaction mixture was shaken at 20 PSI of hydrogen for three and half hours at room temperature. Then the reaction mixture was filtered through a pad of celite and was washed with ethyl acetate (3X10 mL). The filtrate was concentrated and the crude product was purified (preparative TLC; 100% ethyl acetate) to afford desired product **3.21** as brown solid (20 mg, 0.08 mmol, 65 %). $[\alpha]_D^{25} = +65.3$ ($c = 0.25$, MeOH). FTIR (KBr): $\bar{\nu} = 3426, 3069, 3051, 2953, 2849, 2789, 1617, 1593, 1559, 1505, 1460, 1430, 1373, 1293, 1270, 1249, 1160, 1079, 1056, 947, 818, 746, 717, 637, 573, 507$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.70$ (t, $J = 7.1$ Hz, 2H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.41 (t, $J = 7.7$ Hz, 1H), 7.26 (t, $J = 7.3$ Hz, 1H), 6.99 (s, 1H), 5.15 (t, $J = 8.2$ Hz, 1H), 3.82–3.78 (m, 1H), 3.74 – 3.67 (m, 1H), 3.64 – 3.56 (m, 1H), 2.42 – 2.35 (m, 1H), 2.1 – 2.01 (m, 1H), 1.99 – 1.92 (m, 1H), 1.8 – 1.76 (m, 1H). ¹³C-NMR (101 MHz, CDCl₃) $\delta = 156.0, 132.4, 129.4, 129.0, 128.5, 126.7, 122.6, 121.1, 120.1, 114.7, 65.8, 59.9, 59.0, 31.9, 27.1$ ppm. HRMS (ESI) exact mass calculated for C₁₅H₁₈NO₂⁺ ([M+H]⁺): 244.1332, found: 244.1336. The enantiomeric excess (>99 %) was determined by HPLC column: chiralCel OD-H; solvent: 2-propanol: hexane (1:4); light: 220 nm; flow: 1 mL/min; major enantiomer $t_r = 28.4$ min, minor enantiomer $t_r = 22.4$ min.

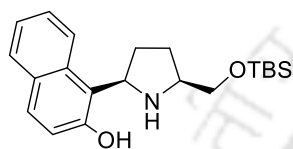
1-((2R,5R)-5-methylpyrrolidin-2-yl)naphthalen-2-ol (3.22): Compound **3.19a** (60 mg, 0.15



mmol) was dissolved ethyl acetate and methanol (3:1, v/v) and 10% palladium on charcoal (16 mg) was added to it. Then the flask was degassed 3 times to create hydrogen atmosphere. The reaction mixture was kept shaking at 20 PSI of hydrogen for four and half hours. Then the reaction mixture was filtered through a pad of celite and the celite cake was washed with ethyl acetate (3X10

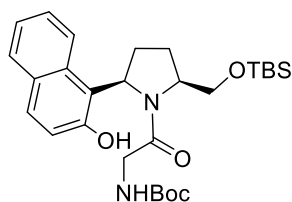
mL). The filtrate was concentrated and the crude product was purified (preparative TLC, ethyl acetate) to afford desired product **3.22** as brown gum (15 mg, 0.07 mmol, 43 %). FTIR (KBr): $\bar{\nu}$ = 3429, 3055, 2961, 2924, 2850, 1622, 1600, 1512, 1458, 1377, 1269, 1241, 1169, 1208, 814, 745, 638, 472 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.76 – 7.72 (m, 2H), 7.63 (d, J = 8.8 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.28 – 7.25 (m, 2H), 7.05 (d, J = 8.8 Hz, 1H), 5.18 – 5.15 (m, 1H), 3.54 – 3.48 (m, 1H), 2.48 – 2.42 (m, 1H), 2.15 – 2.09 (m, 1H), 1.99 – 1.94 (m, 1H), 1.72 – 1.66 (m, 2H), 1.36 (d, J = 6.2 Hz, 3H). ^1H NMR (400 MHz, CDCl_3) δ = 156.5, 132.3, 129.0, 128.5, 126.5, 122.4, 121.3, 120.5, 116.1, 58.8, 54.3, 32.8, 32.7, 21.9. HRMS (ESI) exact mass calculated for $\text{C}_{15}\text{H}_{18}\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 228.1383, found: 228.1390.

1-((2R,5S)-5-((tert-butyldimethylsilyloxy)methyl)pyrrolidin-2-yl)naphthalen-2-ol (3.23): A



solution of *tert*-butyldimethylsilyl chloride (0.27 g, 1.8 mmol) in dichloromethane (1 mL) was added dropwise to a solution of **3.21** (0.20 g, 0.82 mmol) and Et_3N (0.29 mL, 2.12 mmol) in dry dichloromethane (1.5 mL). The reaction mixture was stirred for 12 h under argon atmosphere. After completion of the reaction, the reaction mixture was washed with brine and extracted with dichloromethane (3×25 mL) and the organic layers were dried over Na_2SO_4 , concentrated under reduced pressure and the crude was purified via neutral alumina column chromatography (ethyl acetate: hexane 1:20) to afford **3.23** as a solid (0.19 g, 0.54 mmol, 66 %). $[\alpha]_D^{25} = +32.7$ ($c = 0.11$, MeOH). FTIR (KBr): $\bar{\nu}$ = 3436, 3305, 3053, 2956, 2927, 2854, 1622, 1600, 1521, 1473, 1461, 1258, 1242, 1093, 839, 819, 774, 746 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.75 (dd, J = 12.5, 8.3 Hz, 2H), 7.64 (d, J = 8.9 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.28 – 7.25 (m, 1H), 7.06 (d, J = 8.8 Hz, 1H), 5.15 (t, J = 8.1 Hz, 1H), 3.80–3.76 (m, 1H), 3.69–3.65 (m, 1H), 3.55 – 3.49 (m, 1H), 2.46 – 2.38 (m, 1H), 2.07 – 1.98 (m, 1H), 1.95 – 1.85 (m, 1H), 1.77 – 1.70 (m, 1H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (151 MHz, CDCl_3) δ = 156.5, 132.4, 129.1, 129.0, 128.5, 126.5, 122.4, 121.2, 120.4, 115.7, 67.4, 60.3, 58.6, 32.0, 27.1, 26.2, 18.6, -5.1, -5.1. HRMS (ESI) calculated for $\text{C}_{21}\text{H}_{32}\text{NO}_2\text{Si}^+$ $[\text{M}+\text{H}]^+$: 358.2197, found 358.2196.

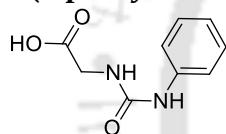
***tert*-butyl 2-((2S,5R)-2-((tert-butyldimethylsilyloxy)methyl)-5-(2-hydroxynaphthalen-1-yl)pyrrolidin-1-yl)-2-oxoethylcarbamate (3.24):** BOC-Glycine



(29 mg, 0.17 mmol), **3.23** (50 mg, 0.14 mmol), EDC.HCl (26 mg, 0.17 mmol) and *N,N*-diisopropylethylamine (60 μL , 0.35 mmol) were dissolved in dichloromethane (1 mL). After stirred for 5 min at 0 $^\circ\text{C}$ then the reaction mixture was stirred for 18 h at room temperature. After completion

of the reaction the reaction mixture was washed with NaHCO₃ solution (15mL) and extracted by dichloromethane (3 × 10 mL). Then the combined organic layers were dried over Na₂SO₄, concentrated under vacuum and the crude was purified by column chromatography via neutral alumina (ethyl acetate: hexane = 1:4) to afford **3.24** (45 mg, 0.09 mmol, 63%). FTIR (KBr): $\bar{\nu}$ = 3413, 2955, 2930, 2883, 2857, 1714, 1645, 1624, 1517, 1471, 1439, 1390, 1366, 1256, 1170, 1092, 1049, 838, 780, 745 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 8.01 (bs, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.49 – 7.46 (m, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 5.68– 5.66 (m, 1H), 5.12 – 5.01 (m, 1H), 4.47 – 4.38 (m, 2H), 3.78–3.69 (m, 2H), 3.21 (bs, 1H), 2.52 – 2.48 (m, 1H), 2.37 – 2.28 (m, 1H), 2.23 – 2.16 (m, 1H), 2.02 – 1.99 (m, 1H), 1.34 (s, 9H), 0.93 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ = 172.1, 156.0, 152.4, 132.0, 130.1, 129.4, 129.3, 127.2, 123.3, 121.3, 121.0, 115.3, 79.5, 66.1, 61.5, 58.8, 43.0, 28.5, 27.6, 26.2, 18.8, -5.2, -5.3. HRMS (ESI) calculated for C₂₈H₄₃N₂O₅Si⁺ [M+H⁺]: 515.2936, found: 515.2939.

2-(3-phenylureido)acetic acid (3.25): Glycine (0.50 g, 6.7 mmol) and LiOH (0.16 g, 6.7

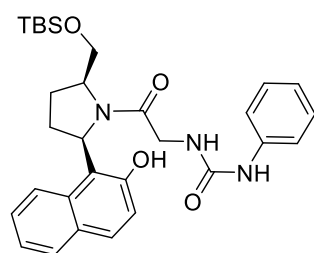


mmol) were dissolved in dry MeOH (15 mL) and the solution was cooled to 0 °C. After 5 min phenylisocyanate (0.61 mL, 5.6 mmol) was added dropwise to the reaction mixture. Then the reaction mixture was stirred

for 12h at room temperature and the solvent was evaporated, the solid compound was washed with 1N HCl (25 mL) to give white solid **3.25** (1.0 g, 5.2 mmol, 92 %). FTIR (KBr) : $\bar{\nu}$ = 3373, 3329, 2939, 1633, 1599, 1572, 1559, 1498, 1439, 1418, 1334, 1314, 1300, 1273, 1233, 726, 695, 637, 598, 510 cm⁻¹. ¹H NMR (600 MHz, DMSO-*d*₆) δ = 10.45 (s, 1H), 7.67 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 7.7 Hz, 2H), 6.80 (t, *J* = 7.2 Hz, 1H), 3.62 (d, *J* = 3.2 Hz, 2H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ = 173.4, 155.6, 141.9, 128.3, 120.1, 117.7, 45.00. HRMS (ESI) calculated for C₉H₁₁N₂O₃⁺ [M+H⁺]: 195.0764, found 195.0772

1-(2-((2*S*,5*R*)-2-((*tert*-butyldimethylsilyloxy)methyl)-5-(2-hydroxynaphthalen-1-

yl)pyrrolidin-1-yl)-2-oxoethyl)-3-phenylurea (3.26): 2-(3-phenylureido)acetic acid **3.25** (25



mg, 0.13 mmol), **3.23** (38 mg, 0.11 mmol), EDC.HCl (20 mg, 0.13 mmol) and *N,N*-diisopropylethylamine (46 μ L, 0.26 mmol) were dissolved in 0.5 mL DMF. After stirred for 5 min at 0 °C, the reaction mixture was stirred for 60 h at room temperature. Then the solvents were evaporated and the reaction mixture was diluted

with NaHCO₃ solution (10 mL) and extracted with dichloromethane (3 X 10 mL). Then the

combined organic layers were dried over Na₂SO₄, concentrated under vacuum and the crude product was purified by column chromatography via neutral alumina (ethyl acetate: hexane = 1:3) to afford **3.26** (26 mg, 0.05 mmol, 45 %). $[\alpha]_D^{25} = -90.0$ (c = 0.2, MeOH). FTIR (KBr): $\bar{\nu} = 3371, 2961, 2926, 2854, 1621, 1556, 1499, 1440, 1313, 1259, 1100, 1019, 839, 814, 753 \text{ cm}^{-1}$. ¹H NMR (600 MHz, CDCl₃) $\delta = 8.07$ (bs, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.34 – 7.32 (m, 1H), 7.19 (bs, 1H), 7.11 – 7.08 (m, 5H), 6.90 – 6.89 (m, 1H), 5.83 – 5.78 (m, 2H), 4.45–4.31 (m, 2H), 3.92 (d, *J* = 12.1 Hz, 1H), 3.73 (d, *J* = 9.9 Hz, 1H), 2.55 – 2.51 (m, 1H), 2.36 – 2.31 (m, 1H), 2.25 – 2.17 (m, 1H), 2.05 – 1.97 (m, 1H), 0.91 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) $\delta = 173.5, 155.9, 152.3, 138.9, 132.1, 130.2, 129.5, 129.2, 129.0, 127.4, 123.5, 123.3, 121.4, 121.1, 120.6, 115.6, 66.2, 61.6, 58.9, 42.7, 29.9, 27.7, 26.2, 18.9, -5.2, -5.3$. HRMS (ESI) calculated for C₃₀H₄₀N₃O₄Si⁺ [M+H⁺]: 534.2783, found 534.2798.

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Chapter 4
**Metal, Oxidant and Solvent Free Direct C(sp³)-H
Arylation of 1,2,3,4-Tetrahydroisoquinolines and β -
Carbolines**



4.1 Introduction:

Functionalized 1,2,3,4-tetrahydroisoquinolines (THIQs) are the important structural motif of numerous natural products and in pharmaceutical drugs.¹ Moreover, 1-substituted tetrahydroisoquinolines analogues are potential neuroprotective agents² and act as an anti-HIV agent *in vitro*.³ For example, (+)-cryptostyline II,⁴ (+)-cryptostyline III⁵ and solifenacin⁶ are built on arylated THIQ. 1-(indol-3-yl)-THIQ derivatives is also found as the core unit of Rad51 inhibitor that act as anticancer agents (**Figure. 1**).⁷ Furthermore, 1-(indol-3-yl)-THIQ was investigated as agents against neurodegenerative diseases.⁸ Apart from THIQ, aromatic β -carboline scaffolds are also observed in diverse natural products⁹ and bioactive molecules showing a broad range of biological activities such as neuroprotection,¹⁰ antiviral,¹¹ antitumor,¹² anti-HIV,¹³ antimalarial¹⁴ etc. The versatile biological properties of THIQ and β -carboline derivatives make them synthetically important molecules. Therefore, enormous efforts have been devoted to their synthesis.¹⁵

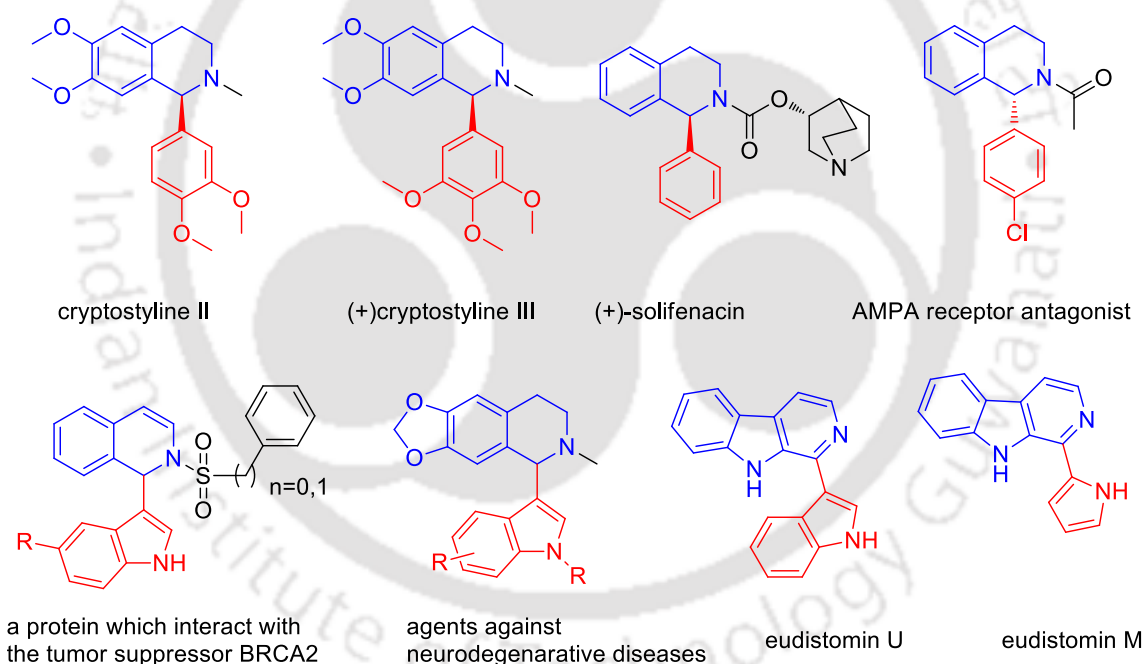
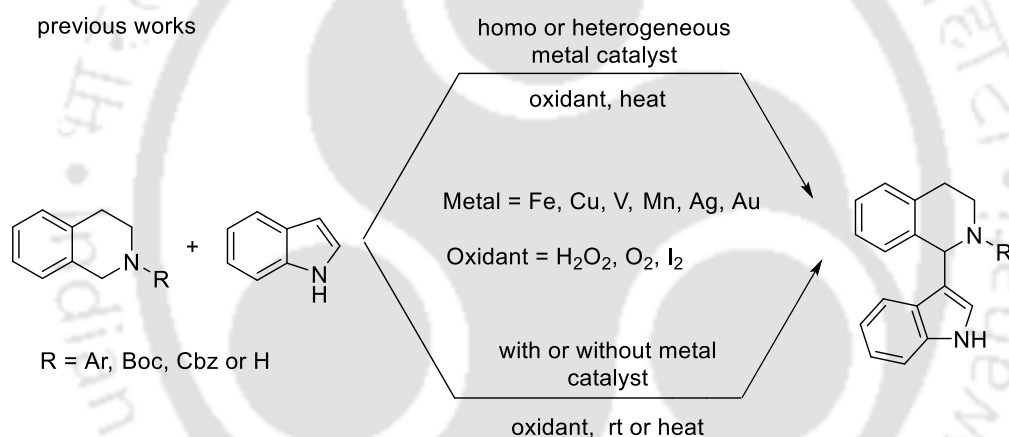


Figure 1: THIQ and β -carboline containing natural products and drug molecules.

4.2. Background:

Historically, the two mostly used traditional approaches for the synthesis of C1-substituted *N*-heterocycles are Pictet–Spengler condensation and the Bischler–Napieralski cyclization/reduction sequence. Recently, lots of efforts have been given for the development of alternatives to these two traditional methods for preparation of α -substituted *N*-heterocycles.¹⁶ Because in these two process harsh acidic reaction condition and external dehydrating agents were required for the synthesis of desired product. Since the pioneering works of Murahashi and Li, group

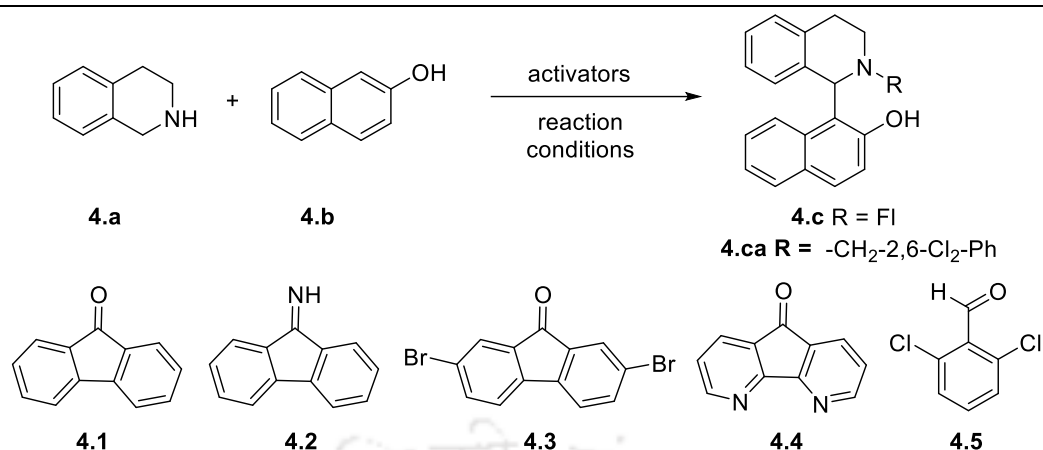
much progress has been made to develop for cross-dehydrogenative-coupling (CDC) reaction on *N*-substituted heterocycles with different metal catalysts, oxidants, and nucleophiles (**Scheme 4.1**).¹⁷ A summary of these methods in the context of the synthesis of arylated *N*-heterocycles has been provided in chapter 1. However, the main drawbacks associated with these methods are the use of toxic and expensive transition metal catalysts, external oxidants, harsh reaction conditions or multi-step syntheses of pre-functionalized precursors. Moreover, in many cases, the *N*-protecting group which is difficult to remove is essential. Thus, developing environmentally benign synthetic methods for the synthesis of C1-substituted *N*-heterocycles derivatives is highly desirable. Particularly, in the chemical industry, large quantities of solvents are used which not only produce hazardous toxic waste for the environment but also have an impact on cost, safety and health issues. From the synthetic viewpoint, the solvent-free approach is one of the most promising strategies for the development of environmentally friendly reaction conditions.



Scheme 1: Direct C-H arylation of 1,2,3,4-tetrahydroisoquinoline.

4.3. Table 1: Optimization of the reaction conditions:

We have already developed a method for direct C-H arylation of pyrrolidine via a simple three component reaction under metal and oxidant free condition.¹⁸ Thus, we wanted to use the same strategy for the arylation of THIQ. Accordingly, 1,2,3,4-tetrahydroisoquinoline **4.a**, 2-naphthol **4.b** and 9-fluorenone **4.1** were reacted in refluxing benzene (Table 1, entry 1). In this reaction condition, the desired product **4.c** was not obtained. The variation of reaction time and solvent also did not provide the desired product **4.c** (Table 1, entries 2-10). Reaction under microwave irradiation was also unsuccessful to produce the α -substituted tetrahydroisoquinoline derivative (Table 1, entry 5). In the previous studies, we have seen that 9-fluorenone imine **4.2** act as an effective activator as compared to 9-fluorenone **4.1**. Therefore, 9-fluorenone imine **4.2**, has been selected as an activator for this transformation.

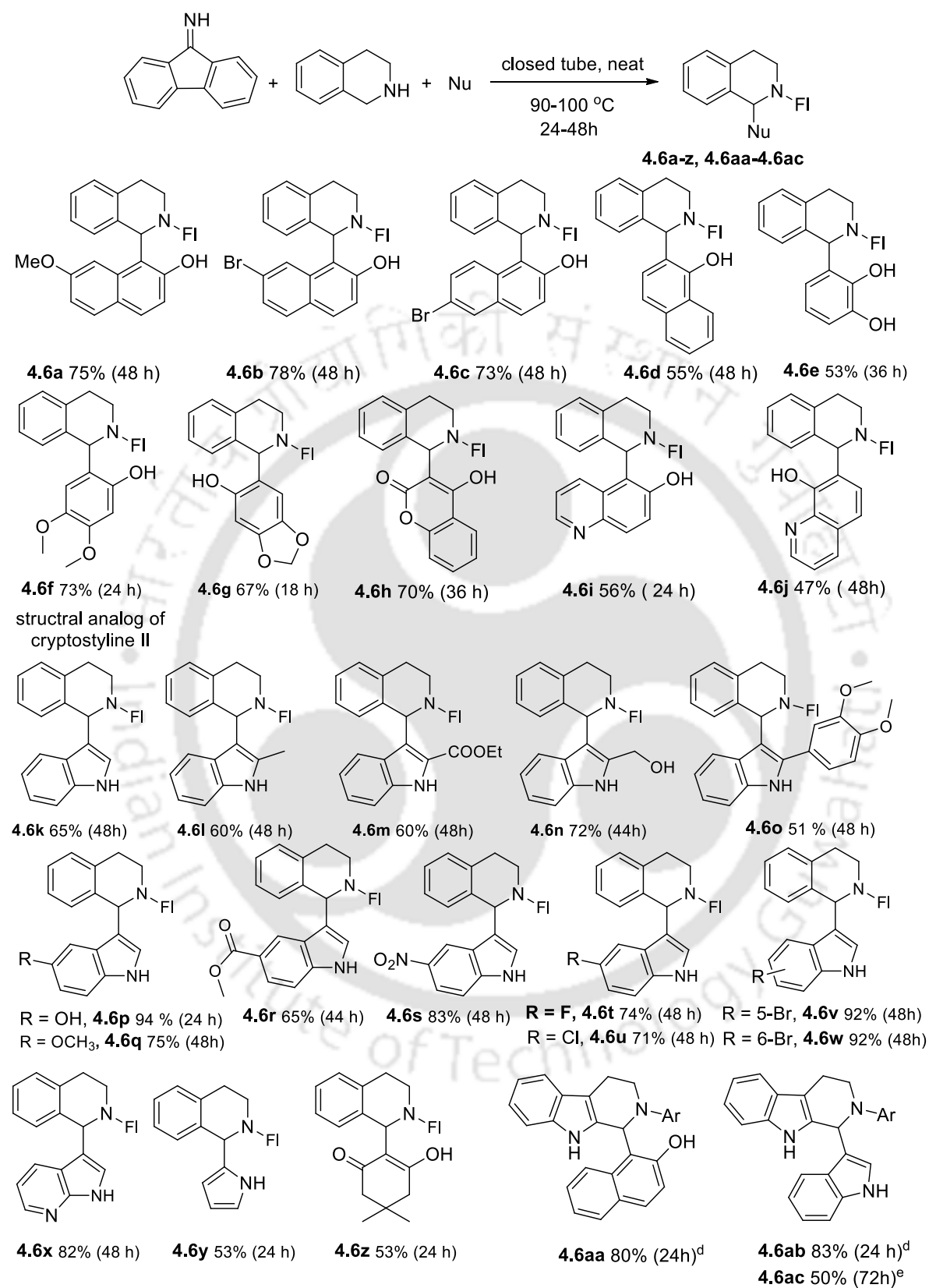


^a Entry	Activator	Solvent, Temp.	Time	Yield ^b
1	4.1	benzene, reflux	24 h	-
2	4.1	benzene, reflux	36 h	-
3	4.1	benzene, reflux	48 h	-
4	4.1	toluene, reflux	48 h	-
5	4.1	toluene, μ w, 150 °C	45 min	-
6	4.2	benzene, reflux	48 h	-
7	4.2	toluene, reflux	48 h	-
8 ^c	4.2	toluene, reflux	48 h	-
9	4.2	toluene, μ w, 150 °C	45 min	-
10 ^c	4.2	toluene, μ w, 150 °C	45 min	-
11	4.1	neat, 60-70 °C	24 h	29 %
12	4.1	neat, 60-70 °C	48 h	56 %
13	4.2	neat, 60-70 °C	48 h	70 %
14	4.2	neat, 100 °C	48 h	82 %
15	4.3	neat, 100 °C	48 h	trace
16	4.4	neat, 100 °C	48 h	-
17	4.5	neat, 100 °C	48 h	60 %

^aReactions were carried out with 0.75 mmol of THIQ (**3.9**), 0.25 mmol of 2-naphthol and 0.3 mmol of carbonyl derivatives (**4.1-4.5**).^b isolated percent yields. ^c reactions were carried out in presence of 20 mol% Sc(OTf)₃

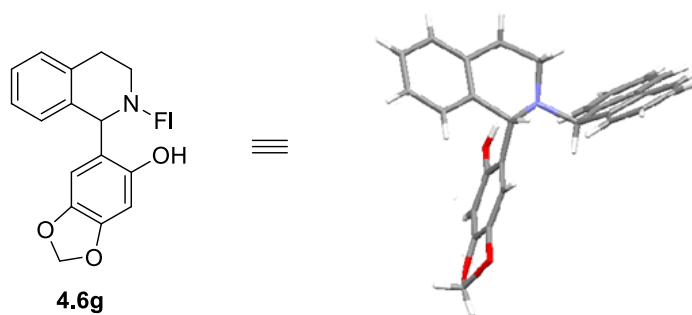
However the arylated product **4.c** was isolated in 29% when the reaction was carried out under a solvent free condition at 70 °C for 24h (Table 1, entry 11). Inspired by this initial result, a number of reactions by varying reaction time, temperature and activators have been performed to increase the yield of the desired product. The maximum yield (82%) of the desired product was obtained from the reaction which was carried out with **4.2** under solvent free condition at 100 °C for 48 h (Table 1, entry 14). On the other hand, 2,7-dibromo fluorenone (**4.3**) and 5H-cyclopenta[1,2-b:5,4-b']dipyridin-5-one (**4.4**) failed to produce the desired arylated product (Table 1, entries 15-16). However, other than ketone and imine derivatives, 2, 6-dichlorobenzaldehyde gave the desired arylated product **4.ca** with 60% yield.

4.4. Substrate scope:

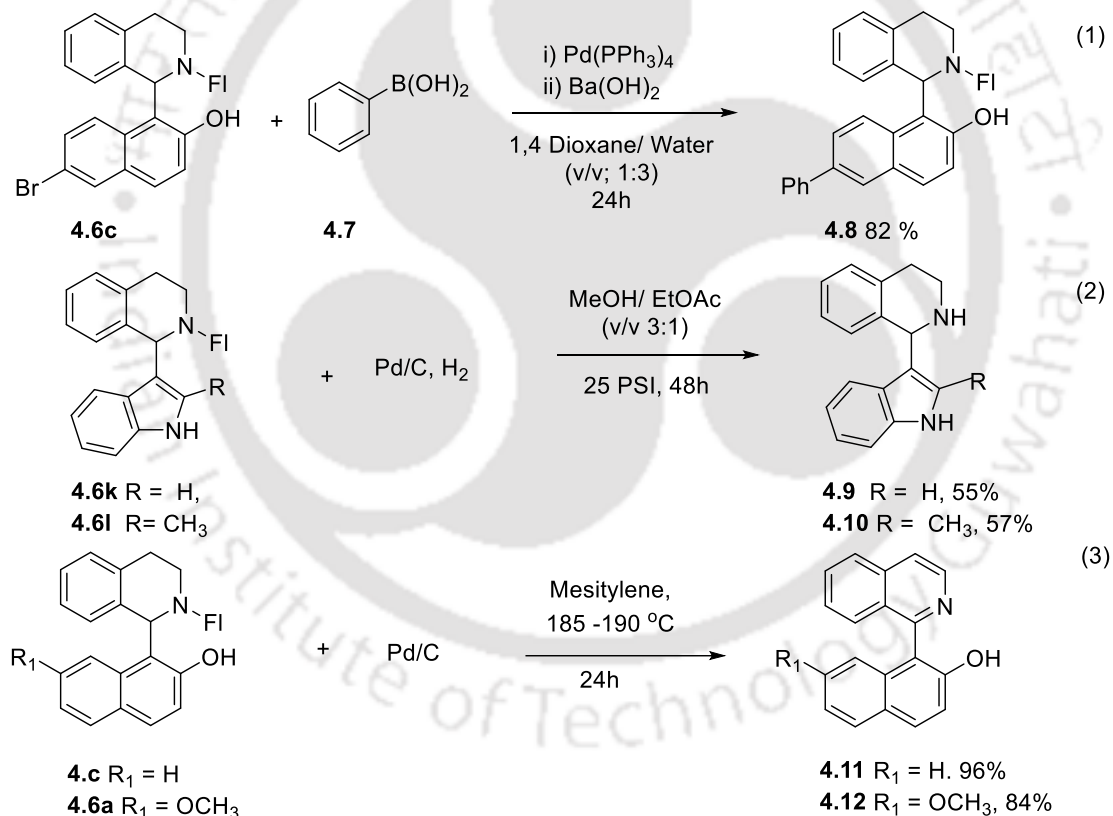


Scheme 2: Arylation of THIQ and tetrahydro- β -carbolines; ^dreaction was carried out with 4.5 as an activator; ^e reaction was carried out in presence of methanol and 4.2 as an activator.

Next, the substrate scope of the reaction was investigated using the optimized reaction condition. At first, different commercially available naphthol derivatives were used as potential nucleophiles. 7-Methoxy, 7-bromo, and 6-bromo-2-naphthols, provided the desired arylated products **4.6a** (75%), **4.6b** (78%) and **4.6c** (73%), respectively, with very good yields. In addition to 2-naphthols, 1-naphthol also gave α -arylated product **4.6d** (55%) with good yield. Then, phenol and its derivatives were tested as potential nucleophiles. Unfortunately, simple phenol did not take part in the arylation reaction but its derivatives catechol and 3,4-dimethoxyphenol produced the desired products with moderate to good yields **4.6e** (53%) and **4.6f** (73%), respectively, with exclusive regioselectivity. Other than phenol derivatives, sesamol, 4-hydroxy coumarin and 6 and 8-hydroxyquinolines also participated in this reaction to provide the desired products **4.6g-4.6j** with moderate to good yields. Then, we have turned our attention to indole derivatives which can serve as potential nucleophiles for the arylation reaction of THIQ. Accordingly, a reaction of THIQ and indole was carried out under standard condition to obtain the desired product **4.6k** with good yield (65%). Interestingly, 2-substituted indoles derivatives such as 2-methylindole, ethyl indole-2-carboxylate and (1*H*-indol-2-yl)methanol derivatives acted as the effective nucleophiles to produce corresponding arylated products **4.6l - 4.6n** (60 -72 %) with very good yields. Highly sterically hindered substrate, 2-(3,4-dimethoxyphenyl)-1*H*-indole, also gave the desired product **4.6o** (51%), however with moderate yield. Both electron-rich and electron-poor indoles derivatives also produced the desired arylated product. 5-Fluoro, 5-chloro, 5-bromo, and 6-bromoindole derivatives gave the desired α -arylated products **4.6t** (74%), **4.6u** (71%), **4.6v** (92%), and **4.6w** (91%) respectively, with good to excellent yields. Hetero atom containing, 7-aza indole also participated in the arylation reaction to provide the desired product **4.6x** with very good yield (82%). Unfortunately, 1-methyl and 3-methyl indoles did not produce the desired products. Beside the indole derivatives, pyrroles and dimedone have successfully used as a nucleophiles. Other than the THIQ, 2, 3, 4, 9-tetrahydro-1*H*-pyrido[3,4-*b*]indole, also reacted with 2-naphthol and indole to produce the corresponding α -arylated products **4.6aa** (80%), **4.6ab** (83%), and **4.6ac** (50%) respectively.

**Figure 2:** Crystal structure of **4.6g****4.5. Synthetic applications:**

To establish the synthetic utility of our methodology, arylated compounds were further derivatized using selected reactions. The 6-bromo functionality of **4.6c** was utilized for Suzuki coupling reaction with phenylboronic acid **4.7** to obtain the corresponding phenyl substituted arylated THIQ derivative **4.8** with an excellent yield (82%) (**Scheme 3**, eq. 1).

**Scheme 3:** Synthetic transformations of arylated THIQ derivatives.

Removal of *N*-fluorenyl group of arylated compounds can be achieved using standard hydrogenolysis conditions. Accordingly, secondary amines **4.9** (55%) and **4.10** (57%) were formed from **4.6k** and **4.6l** respectively (**Scheme 3**, eq. 2). Next, the compounds **4.6c** and **4.6a** were aromatized under dehydrogenation condition to obtain the 1-(isoquinolin-1-

yl)naphthalen-2-ol derivatives **4.11** (96%) and **4.12** (84%) (**Scheme 4.3**, eq. 3). Removal *N*-fluorenyl group and aromatization occurred in the same step.

4.6. Summary:

In summary, an environmentally friendly method for the synthesis of α -arylated THIQs and β -carbolines directly starts from corresponding free amines without the involvement of metallic reagents/oxidant and pre-functionalized steps has been developed. The method is highly atom-economic and also it is applicable to a wide range of nucleophiles such as naphthols, indoles, and pyrroles to provide the desired product with good to excellent yields.

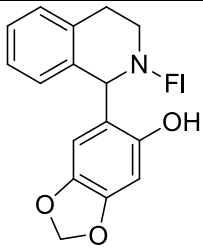
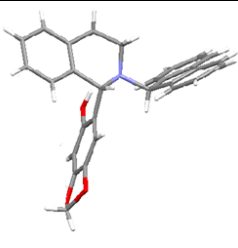


4.7. Experimental section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. THF and diethylether (Et₂O) were freshly distilled from Sodium under argon. Dichloromethane (CH₂Cl₂) was freshly distilled from phosphorus (V)oxide (P₂O₅). Triethylamine (Et₃N) was distilled from CaH₂ and stored under argon. Commercial grade xylene, benzene and toluene were distilled 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, ¹³C NMR spectroscopy: Varian Mercury plus 400 MHz (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS ($\delta(^1\text{H})$ 0.0 ppm, $\delta(^{13}\text{C})$ 0.0 ppm) which was used as the inner reference. Otherwise the solvents residual proton resonance and carbon resonance (CHCl₃, $\delta(^1\text{H})$ 7.26 ppm, $\delta(^{13}\text{C})$ 77.0 ppm; CD₃OD, (¹H) 3.31 ppm, $\delta(^{13}\text{C})$ 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 recorded on a Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak). X-ray crystallographic data were collected using a Bruker SMART APEX-II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube Mo-K α radiation (λ = 0.71073 Å) at 296(2) K, with increasing ω (width of 0.3° per frame) at a scan speed of 3 s/frame. Structures were solved by direct methods using SHELXS-97 and refined with fullmatrix least squares on F^2 using SHELXL-97. Using Olex2¹⁹, structure was solved with the Superflip²⁰ structure solution program using Charge Flipping and refined with the olex2.refine²¹ refinement package using Gauss-Newton minimisation. All the non-hydrogen atoms were refined anisotropically.

Crystal Structures:

Crystal data and structure refinement for **4.6g**

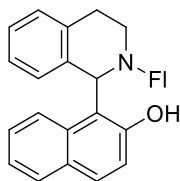
	
Crystal data and structure refinement for 4.6g	

Metal, Oxidant and Solvent Free Direct C(sp³)-H Arylation of 1,2,3,4 Tetrahydroisoquinoline and β Carbolines

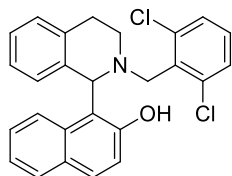
Empirical formula	C ₂₉ H ₂₃ N O ₃
Formula weight	433.48
Crystal habit, colour	needle / colorless
Crystal size, mm ³	0.24* 0.17* 0.15
Temperature, T	293(2) K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	'P2 ₁ /n'
Unit cell dimensions	$a = 15.1652(8)\text{Å}$ $15.1364(13)\text{Å}$ $c = 19.9955(13)\text{Å}$ $\alpha = 90.00^\circ, \gamma = 90.00^\circ, \beta = 106.480(6)^\circ$
Volume, V(Å ³)	4401.3(5)
Z	8
Calculated density, Mg·m ⁻³	1.308
Absorption coefficient, μ (mm ⁻¹)	0.085
F(000)	1824
θ range for data collection	3.00 ° to 25.00°
Limiting indices	$-18 \leq h \leq 18, -16 \leq k \leq 18, -23 \leq l \leq 23$
Reflection collected / unique	16211 / 3089 [$R(\text{int}) = 0.1058$]
Completeness to θ	98.7% ($\theta = 25.00^\circ$)
Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	7645 / 0 / 597
Goodness-of-fit on F^2	0.885
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0840, wR2 = 0.1888$
R indices (all data)	$R1 = 0.3467, wR2 = 0.2036$
Largest diff. peak and hole	0.574 and -0.650 Å ⁻³

General procedure I:

In a reaction tube, nucleophile (0.25 mmol, 1.0 equiv) was added to the mixture of aldehyde or ketone or imine (0.30 mmol, 1.2 equiv.) and 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv.). The tube was closed and the mixture was stirred at 100 °C (oil bath temperature) for 18 - 48h. After completion of the reaction, the product was purified either via precipitation or column chromatography (Ethyl acetate: hexane) to obtain an analytically pure product.

1-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-2-ol (4.c):

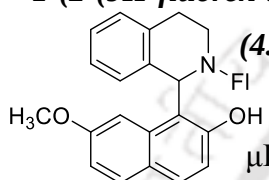
According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 2-naphthol (0.25 mmol, 1.0 equiv, 36 mg) were reacted for 48 h. Then the reaction mixture was dissolved in methanol and the solid product was precipitated from reaction mixture. The solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product **4.c** (70 mg) as light brown solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:20) to give an additional amount (20 mg) of the product. The combined yield is (90 mg, 82%). FTIR (KBr): $\tilde{\nu}$ = 3056, 3033, 2838, 1619, 1462, 1448, 1268, 1227, 811, 741, 531 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 11.77 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.83 – 7.79 (m, 3H), 7.7 – 7.65 (m, 2H), 7.63- 7.61 (m, 1H), 7.42 – 7.38 (m, 1H), 7.38 – 7.33 (m, 3H), 7.27 – 7.20 (m, 2H), 7.1 – 7.03 (m, 2H), 6.94 – 6.90 (m, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.65 (s, 1H), 4.98 (s, 1H), 3.13 – 3.02 (m, 1H), 2.64 – 2.51 (m, 2H), 2.48 – 2.44 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 155.8, 144.0, 142.1, 141.4, 141.2, 136.6, 134.4, 134.3, 130.3, 129.5, 129.0, 128.7, 128.66, 128.56, 128.2, 127.9, 127.7, 127.1, 126.8, 126.6, 126.4, 125.9, 123.0, 121.5, 120.5, 120.1, 119.6, 118.0, 65.2, 60.7, 43.2, 29.9 ppm. HRMS (ESI) exact mass calculated for C₃₂H₂₆NO⁺ ([M+H]⁺): 440.2009, found: 440.2001.

1-(2-(2,6-dichlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-2-ol (4.ca):

According to general procedure I, 2,6 di-chlorobenzaldehyde (0.3 mmol, 1.2 equiv, 52 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 2-naphthol (0.25 mmol, 1.0 equiv, 36 mg), in neat condition were reacted for 48 h. After completion of the reaction, the reaction mixture was dissolved in methanol and the solvent mixture was evaporated under reduce pressure and residue was purified by SiO₂ column chromatography (ethyl acetate: hexane;

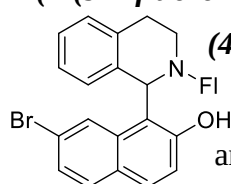
1:20) to obtain **4.ca** as brown solid (65 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 3067, 2959, 2904, 2818, 1620, 1596, 1561, 1464, 1262, 1239, 747 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 10.55 (s, 1H), 8.26 (d, J = 9.2 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.73 – 7.72 (m, 1H), 7.59 – 7.55 (m, 1H), 7.39 – 7.35 (m, 1H), 7.30 – 7.23 (m, 2H), 7.15 – 7.13 (m, 1H), 7.08 – 7.03 (m, 3H), 6.90 – 6.86 (m, 1H), 6.64 – 6.62 (m, 1H), 5.71 (s, 1H), 4.22 – 4.19 (m, 1H), 3.91 – 3.88 (m, 1H), 3.22 – 3.17 (m, 2H), 2.96 – 2.82 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ = 155.6, 137.7, 136.8, 134.4, 134.0, 132.5, 129.9, 129.7, 129.2, 128.9, 128.7, 128.1, 127.3, 127.2, 126.6, 126.5, 122.8, 121.5, 120.2, 119.4, 64.0, 55.5, 49.0, 29.9 ppm. HRMS (ESI) exact mass calculated for C₂₆H₂₂Cl₂NO⁺ ([M+H]⁺): 434.1073, found, 434.1073.

1-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-7-methoxynaphthalen-2-ol



(4.6a): According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 7-methoxy-2-naphthol (0.25 mmol, 1.0 equiv, 43.5 mg), in neat condition were reacted for 48 h. Then the reaction mixture was dissolved in methanol and the solid product was precipitated from reaction mixture. The solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product **4.6a** (65 mg) as light brown solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column SiO₂ chromatography (Ethyl acetate: hexane; 1:20) to give an additional amount (23 mg) of the product. The combined yield is (88 mg, 75%). FTIR (KBr): $\tilde{\nu}$ = 3412, 3023, 2962, 2809, 1446, 1262, 742 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 11.67 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.67 – 7.66 (m, 2H), 7.62 (d, J = 7.2 Hz, 1H), 7.39 – 7.34 (m, 3H), 7.23 – 7.21 (m, 1H), 7.11 – 7.05 (m, 4H), 6.97 – 6.94 (m, 1H), 6.87 – 6.85 (m, 1H), 6.57 (s, 1H), 5.00 (s, 1H), 4.05 (s, 3H), 3.09 – 3.00 (m, 1H), 2.64 – 2.61 (m, 1H), 2.57 – 2.43 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ = 159.5, 156.4, 144.0, 142.1, 141.5, 141.1, 136.7, 135.6, 134.3, 131.0, 130.1, 128.7, 128.67, 128.61, 128.3, 127.8, 126.9, 126.8, 126.6, 126.3, 125.9, 124.4, 120.64, 119.6, 117.6, 117.3, 115.1, 100.9, 65.2, 60.9, 55.6, 43.2, 29.9 ppm. HRMS (ESI) exact mass calculated for C₃₃H₂₈NO₂⁺ ([M+H]⁺): 470.2115, found 470.2118.

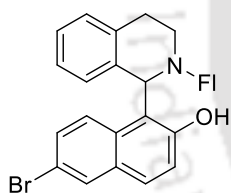
1-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-7-bromonaphthalen-2-ol



(4.6b): According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 7-bromo-2-naphthol (0.25 mmol, 1.0 equiv, 56 mg), in neat condition

were reacted for 48 h. Then the reaction mixture was dissolved in methanol and the solid product was precipitated from reaction mixture. The solid was filtered and washed with (3×5 mL) methanol to obtain the desired product **4.6b** (74 mg) as light brownish solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:20) to give an additional amount (27 mg) of the product. The combined yield is (101 mg, 78%). FTIR (KBr): $\tilde{\nu}$ = 3431, 2842, 1589, 1449, 1260, 925, 742 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 11.88 (s, 1H), 8.52 (s, 1H), 7.78 – 7.71 (m, 4H), 7.65 – 7.60 (m, 2H), 7.48 – 7.47 (m, 1H), 7.38 – 7.30 (m, 4H), 7.23 – 7.20 (m, 1H), 7.10 – 7.05 (m, 2H), 6.97 – 6.94 (m, 1H), 6.77 – 6.75 (m, 1H), 6.51 (s, 1H), 4.92 (s, 1H), 3.10 – 3.00 (m, 1H), 2.67 – 2.59 (m, 1H), 2.54 – 2.50 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ = 156.7, 143.7, 142.0, 141.2, 141.1, 136.1, 135.6, 134.3, 131.0, 130.3, 128.8, 128.76, 128.7, 128.2, 127.8, 127.34, 127.29, 127.0, 126.7, 126.4, 126.3, 125.8, 123.9, 122.3, 120.6, 119.7, 117.4, 65.2, 60.7, 43.2, 29.8 ppm. (Total count of ¹³C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for C₃₂H₂₅BrNO⁺ ([M+H]⁺): 518.1114, found, 518.1120.

1-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-6-bromonaphthalen-2-ol

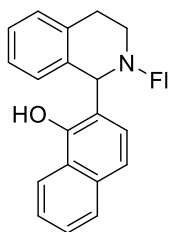


(4.6c): According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 6-bromo-2-naphthol (0.25 mmol, 1.0 equiv, 56 mg) were reacted for 48 h. Then, the reaction mixture was dissolved in methanol

and the solid product was precipitated from reaction mixture. The solid was filtered and washed with (3×5 mL) methanol to obtain the desired product **4.6c** (68 mg) as light brown solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:20) to give an additional amount (29 mg) of the product. The combined yield is (97mg, 75%). FTIR (KBr): $\tilde{\nu}$ = 3057, 2842, 1612, 1589, 1507, 1448, 1260, 925, 742 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 11.87 (s, 1H), 8.26 – 8.23 (m, 1H), 8.01 (s, 1H), 7.83 – 7.81 (m, 1H), 7.79 – 7.70 (m, 4H), 7.67 – 7.68 (m, 1H), 7.42 – 7.35 (m, 3H), 7.30 – 7.28 (m, 1H), 7.23 – 7.21 (m, 1H), 7.12 – 7.05 (m, 2H), 6.96 – 6.92 (m, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 1H), 4.97 (s, 1H), 3.11 – 3.02 (m, 1H), 2.63 – 2.61 (m, 1H), 2.56 – 2.49 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 156.1, 143.7, 142.0, 141.2, 141.1, 136.1, 134.3, 132.9, 131.3, 130.8, 130.2, 129.4, 128.83, 128.77, 128.7, 128.3, 127.7, 127.2, 127.0, 126.6, 126.2, 125.9, 123.3, 121.3, 120.7, 119.7, 118.3, 116.5, 65.2, 60.7, 43.2, 29.9 ppm. (Total count of ¹³C is less than expected due to the merging of signals in the

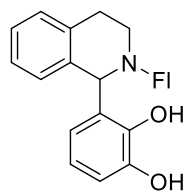
aromatic region). HRMS (ESI) exact mass calculated for C₃₂H₂₅BrNO⁺ ([M+H]⁺): 518.1114, found, 518.1107.

2-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol (4.6d):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 1-naphthol (0.25 mmol, 1.0 equiv, 36 mg) were reacted for 48 h. Then, the reaction mixture was dissolved in methanol and the solid product was precipitated from reaction mixture. The solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product **4.6d** (48 mg) as light brown solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:20) to give an additional amount (12 mg) of the product. The combined yield is (60 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 3956, 2838, 1619, 1462, 1448, 1258, 811, 741 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 11.32 (s, 1H), 8.31 – 8.30 (m, 1H), 7.81 (d, *J* = 7.2 Hz, 3H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.40 – 7.34 (m, 3H), 7.29 – 7.27 (m, 1H), 7.10 – 7.04 (m, 2H), 7.00 – 7.04 (m, 1H), 6.96 – 6.95 (m, 1H), 5.90 (s, 1H), 5.15 (s, 1H), 3.10 – 3.04 (m, 1H), 2.61 – 2.59 (m, 1H), 2.51 – 2.44 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ = 152.8, 144.0, 142.1, 142.0, 141.2, 136.8, 134.5, 134.2, 128.6, 128.3, 127.6, 127.5, 126.7, 126.5, 126.4, 125.9, 125.8, 125.3, 125.1, 122.6, 122.7, 120.7, 120.5, 119.7, 119.7, 119.6, 119.1, 119.0, 67.3, 65.2, 42.9, 30.0 ppm. (Total count of ¹³C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for C₃₂H₂₆NO⁺ ([M+H]⁺): 440.2009, 440.2020.

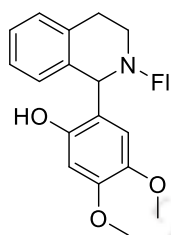
3-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)benzene-1,2-diol (4.6e):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and pyrocatechol (0.25 mmol, 1.0 equiv, 27.5 mg) were reacted for 36h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:10) to obtain **4.6e** as brown solid (56 mg, 53%). FTIR (KBr): $\tilde{\nu}$ = 3501, 2923, 1602, 1479, 1450, 1259, 1180, 745, 737 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 10.85 (s, 1H), 7.74 – 7.72 (m, 2H), 7.68 – 7.67 (m, 2H), 7.41 – 7.38 (m, 2H), 7.36 – 7.33 (m, 1H), 7.29 – 7.24 (m, 1H), 7.13 – 7.11 (m, 2H),

7.08 (d, $J = 7.2$ Hz, 1H), 7.06 – 7.04 (m, 1H), 6.99 (d, $J = 7.8$ Hz, 1H), 6.96 – 6.94 (m, 1H), 6.92 – 6.89 (m, 1H), 5.75 (s, 1H), 5.60 (s, 1H), 5.09 (s, 1H), 3.01 – 2.95 (m, 1H), 2.59 – 2.56 (m, 1H), 2.43 – 2.41 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) $\delta = 145.8, 143.8, 143.4, 142.0, 141.8, 141.3, 136.0, 134.1, 128.83, 128.77, 128.6, 128.2, 127.1, 126.9, 126.7, 126.5, 125.5, 122.0, 120.6, 120.2, 119.8, 115.1, 66.9, 65.1, 42.7, 29.9$ ppm. (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for $\text{C}_{24}\text{H}_{28}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 406.1802, found: 406.1803.

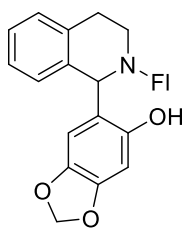
2-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-4,5-dimethoxyphenol (4.6f):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μL) and 3,4-dimethoxyphenol (0.25 mmol, 1.0 equiv, 38 mg) were reacted for 24 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solvent mixture was evaporated under reduce pressure and

residue was purified by SiO_2 column chromatography (Ethyl acetate: hexane; 1:10) to obtain **4.6f** as brown solid (82 mg, 73%). FTIR (KBr): $\tilde{\nu} = 2922, 2845, 1504, 1449, 1191, 1113, 740$ cm^{-1} . ^1H NMR (600 MHz, CDCl_3) $\delta = 10.07$ (s, 1H), 7.76 – 7.74 (s, 3H), 7.69 – 7.65 (m, 1H), 7.42 – 7.31 (m, 3H), 7.29 – 7.24 (m, 1H), 7.13 – 7.05 (m, 3H), 7.03 (s, 1H), 6.98 (s, 1H), 6.54 (s, 1H), 5.64 (s, 1H), 5.18 (s, 1H), 3.96 (s, 3H), 3.84 (s, 3H), 3.01 – 2.91 (m, 1H), 2.58 – 2.52 (m, 1H), 2.48 – 2.35 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) $\delta = 151.2, 150.4, 144.1, 142.3, 142.2, 142.0, 141.1, 136.7, 134.2, 128.7, 128.64, 128.62, 128.2, 128.0, 127.0, 126.8, 126.4, 126.3, 125.7, 120.6, 119.7, 117.2, 115.0, 102.4, 67.0, 65.0, 57.5, 56.0, 43.0, 29.9$ ppm. HRMS (ESI) exact mass calculated for $\text{C}_{30}\text{H}_{28}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$): 450.2064, found, 450.2062.

6-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)benzo[d][1,3]dioxol-5-ol (4.6g):



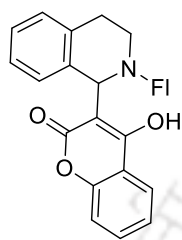
According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μL) and sesamol (0.25 mmol, 1.0 equiv, 34.5 mg) were reacted for 18 h. After completion of the reaction, the reaction mixture was dissolved in methanol and the solvent mixture was evaporated under reduce pressure and residue

was purified by SiO_2 column chromatography (Ethyl acetate: hexane: 1:10) to obtain **4.6g** as brown solid (73 mg, 67%). FTIR (KBr): $\tilde{\nu} = 2890, 2830, 1479, 1450, 1181, 1033, 743$ cm^{-1} . ^1H NMR (600 MHz, CDCl_3) $\delta = 10.30$ (s, 1H), 7.73 – 7.70 (m, 3H), 7.67 (d, $J = 7.2$ Hz, 1H), 7.40 – 7.38 (m, 2H), 7.36 – 7.33 (m, 1H), 7.27 – 7.24 (m, 1H), 7.12 – 7.07 (m, 2H), 7.02 – 7.01 (m, 3H), 6.51 (s, 1H), 5.95 (d, $J = 1.2$ Hz, 1H), 5.90 (d, $J = 1.2$ Hz, 1H), 5.61 (s, 1H),

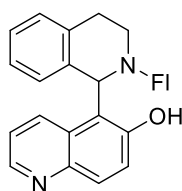
5.17 (s, 1H), 2.98 – 2.92 (m, 1H), 2.55 – 2.52 (m, 1H), 2.43 – 2.36 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ = 152.1, 148.5, 144.0, 142.0, 141.1, 140.7, 136.5, 134.3, 128.7, 128.6, 128.2, 127.9, 127.1, 126.8, 126.4, 126.3, 125.7, 120.6, 119.7, 117.9, 110.17, 101.3, 100.1, 67.1, 64.9, 42.9, 29.9 ppm. (Total count of ¹³C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for C₂₉H₂₄NO₃⁺ ([M+H]⁺): 434.1751, found, 434.1759.

3-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-4-hydroxy-2H-chromen-2-one

(4.6h): According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 4-hydroxy coumarin (0.25 mmol, 1.0 equiv, 36 mg) were reacted for 48h. Then, the reaction mixture was dissolved in methanol and the solid product was precipitated from reaction mixture. The solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product **4.6h** (70 mg) as light yellow solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:20) to give an additional amount (10 mg) of the product. The combined yield is (80 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 2925, 1671, 1604, 1130, 748, 615 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.00 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.51 – 7.51 (m, 2H), 7.46 – 7.36 (m, 3H), 7.34 – 7.24 (m, 3H), 7.19 – 7.10 (m, 2H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.40 (s, 1H), 5.27 (s, 1H), 3.15 – 3.07 (m, 1H), 2.63 – 2.58 (m, 2H), 2.54 – 2.46 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 165.5, 154.4, 142.1, 141.6, 139.5, 136.6, 134.8, 134.7, 132.1, 131.7, 130.3, 130.1, 129.2, 128.8, 128.4, 127.9, 127.8, 127.5, 127.4, 127.4, 125.6, 124.4, 124.20, 123.6, 120.4, 120.2, 116.9, 64.1, 61.6, 42.3, 28.1 ppm. HRMS (ESI) exact mass calculated for C₃₁H₂₄NO₃⁺ ([M+H]⁺): 458.1751, found, 458.1766.



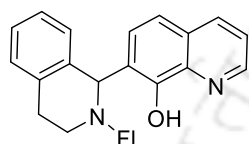
5-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)quinolin-6-ol (4.6i): According



to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 6-hydroxyquinol (0.25 mmol, 1.0 equiv, 36 mg) were reacted for 24 h. After, the completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane) to obtain **4.6i** as brown solid (62 mg, 56%). FTIR (KBr): $\tilde{\nu}$ = 2915, 2841, 1610, 1447, 1249, 1128, 828, 742, 728 cm⁻¹. ¹H

NMR (400 MHz, CDCl₃) δ = 11.83 (s, 1H), 8.85 (d, J = 3.8 Hz, 1H), 8.68 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 6.8 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.65 (d, J = 7.2 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.45 – 7.42 (m, 1H), 7.40 – 7.37 (m, 3H), 7.29 – 7.27 (m, 1H), 7.14 – 7.06 (m, 2H), 6.96 – 6.92 (m, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.58 (s, 1H), 4.98 (s, 1H), 3.14 – 3.02 (m, 1H), 2.70 – 2.62 (m, 1H), 2.60 – 2.45 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ = 156.0, 147.3, 144.2, 143.6, 142.1, 141.3, 141.1, 136.1, 134.4, 131.7, 129.6, 129.2, 128.9, 128.8, 128.7, 128.4, 127.7, 127.2, 127.1, 126.7, 126.0, 125.9, 123.7, 122.3, 120.7, 119.7, 117.6, 65.3, 60.3, 43.3, 29.9 ppm. HRMS (ESI) exact mass calculated for C₃₁H₂₅N₂ O⁺ ([M+H]⁺): 441.1961, found, 441.1962.

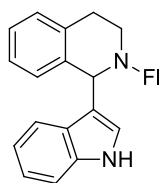
7-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)quinolin-8-ol (4.6j): According



to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 8-hydroxyquinol (0.25 mmol, 1.0 equiv, 36 mg) were reacted for 24 h.

After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:6) to obtain **4.6j** as brown solid (58 mg, 53%). FTIR (KBr): $\tilde{\nu}$ = 2923, 1629, 1449, 1375, 1090, 742 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 9.57 (s, 1H), 8.82 (s, 1H), 8.11 (d, J = 7.3 Hz, 1H), 8.05 (s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.64 (s, 2H), 7.40 (d, J = 7.4 Hz, 2H), 7.38 – 7.31 (m, 2H), 7.28 (s, 2H), 7.24 (s, 1H), 7.06 (s, 2H), 6.99 (s, 1H), 6.93 (s, 1H), 6.40 (s, 1H), 4.93 (s, 1H), 3.08 – 3.03 (m, 1H), 2.58 – 2.51 (m, 2H), 2.40 – 2.31 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 151.7, 148.5, 145.4, 143.6, 141.7, 140.9, 139.0, 138.4, 136.1, 135.4, 129.2, 128.7, 128.69, 128.4, 128.3, 128.2, 127.7, 127.0, 126.8, 126.2, 126.0, 125.5, 125.41, 121.9, 120.3, 119.4, 118.5, 65.3, 61.4, 43.0, 30.5 ppm. HRMS (ESI) exact mass calculated for C₃₁H₂₅N₂ O⁺ ([M+H]⁺): 441.1961, found, 441.1961.

2-(9H-fluoren-9-yl)-1-(1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (4.6k): According to

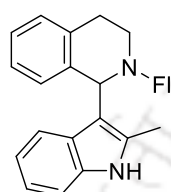


general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and indole (0.25 mmol, 1.0 equiv, 29 mg) were reacted for 48 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution

mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:15) to obtain **4.6k** as brown solid (67 mg, 65%). FTIR (KBr): $\tilde{\nu}$ = 3328, 2955, 1687, 1274, 117, 742 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ =

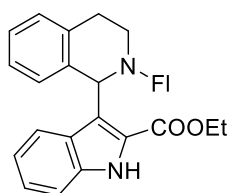
8.23 (s, 1H), 7.80 – 7.75 (m, 2H), 7.69 – 7.68 (m, 1H), 7.61 – 7.6 (m, 1H), 7.50 (s, 1H), 7.40 (d, J = 7.2 Hz, 1H), 7.35 – 7.33 (m, 2H), 7.28 – 7.26 (m, 1H), 7.24 – 7.23 (m, 2H), 7.20 – 7.14 (m, 2H), 7.07 – 7.04 (m, 3H), 6.94 – 6.93 (m, 2H), 5.92 (s, 1H), 5.07 (s, 1H), 3.12 – 3.03 (m, 1H), 2.59 – 2.53 (m, 2H), 2.37 – 2.34 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 146.5, 144.8, 141.7, 140.6, 139.4, 137.4, 135.8, 128.6, 128.2, 127.8, 127.8, 127.5, 126.5, 126.5, 126.2, 125.9, 125.8, 125.8, 124.9, 122.5, 121.67, 120.3, 119.6, 119.2, 118.4, 111.3, 65.2, 60.9, 43.8, 30.8 ppm. HRMS (ESI) exact mass calculated for C₃₀H₂₅N₂⁺ ([M+H]⁺): 413.2012, found, 413.2017.

2-(9H-fluoren-9-yl)-1-(2-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (4.6l):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 2-methylindole (0.25 mmol, 1.0 equiv, 33 mg) were reacted for 48 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:15) to obtain **4.6l** as brown solid (64 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 3409, 1601, 1449, 1286, 1217, 742 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.83 (d, J = 7.2 Hz, 1H), 7.80 (s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.34 – 7.32 (m, 1H), 7.29 – 7.22 (m, 3H), 7.19 – 7.16 (m, 1H), 7.09 – 7.07 (m, 1H), 7.05 – 7.03 (m, 3H), 6.95 – 6.92 (m, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.00 (s, 1H), 5.03 (s, 1H), 3.11 – 3.05 (m, 1H), 2.63 – 2.61 (m, 1H), 2.60 (s, 3H), 2.58 – 2.55 (m, 1H), 2.33 – 2.31 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 146.7, 144.9, 141.7, 140.5, 139.6, 135.8, 135.4, 133.9, 128.5, 128.1, 127.79, 127.77, 127.5, 126.6, 126.0, 125.9, 125.9, 125.8, 121.4, 120.4, 119.5, 119.2, 113.9, 110.3, 65.4, 59.3, 44.1, 30.9, 12.7 ppm. (Total count of ¹³C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for C₃₁H₂₇N₂⁺ ([M+H]⁺): 427.2169, found, 427.2166.

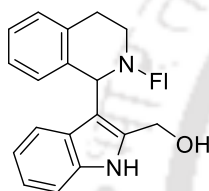
Ethyl 3-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1H-indole-2-carboxylate (4.6m):



(4.6m): According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and ethyl 1H-indole-2-carboxylate (0.25 mmol, 1.0 equiv, 47 mg) were reacted for 48 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate:

hexane; 1:20) to obtain **4.6m** as brown solid (72 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 3339, 3036, 2971, 2804, 1675, 1541, 1251, 1190, 1092, 748, 735 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 8.87 (s, 1H), 8.08 – 8.03 (m, 2H), 7.70 – 7.69 (m, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.38 – 7.35 (m, 2H), 7.28 – 7.25 (m, 3H), 7.17 – 7.15 (m, 1H), 7.10 – 7.08 (m, 2H), 7.06 – 7.04 (m, 1H), 6.97 – 6.94 (m, 1H), 6.91 – 6.90 (m, 2H), 4.86 (s, 1H), 4.60 – 4.51 (m, 2H), 3.19 – 3.13 (m, 1H), 2.63 – 2.57 (m, 2H), 2.35 – 2.70 (m, 1H), 1.50 (t, J = 6.6 Hz, 3H). ^{13}C NMR (151 MHz,) δ = 162.5, 146.3, 144.3, 141.7, 140.7, 138.5, 136.8, 135.1, 128.7, 128.1, 127.9, 127.4, 126.6, 126.57, 126.1, 126.07, 126.01, 125.9, 124.7, 120.2, 119.2, 111.8, 65.9, 61.5, 58.8, 43.4, 30.9, 14.7 ppm. (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for $\text{C}_{33}\text{H}_{29}\text{N}_2\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 485.2224, found, 485.2230.

(3-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1H-indol-2-yl)methanol

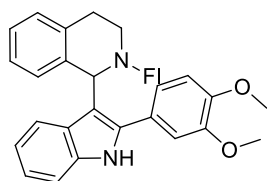


(4.6n): According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μL) and (1H-indol-2-yl)methanol (0.25 mmol, 1.0 equiv, 37 mg) were reacted for 44 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO_2 column chromatography (Ethyl acetate: hexane; 1:1) to obtain **4.6n** as yellow solid (80 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 3178, 3108, 1448, 1286, 1042, 744, 742 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 8.41 (s, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.94 – 7.92 (m, 1H), 7.70 – 7.68 (m, 2H), 7.60 (d, J = 7.2 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.32 – 7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 7.10 – 7.04 (m, 2H), 6.98 – 6.94 (m, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.25 (s, 1H), 5.10 (s, 1H), 4.68 (d, J = 13.6 Hz, 1H) 4.68 (d, J = 14.0 Hz, 1H), 3.15 – 3.07 (m, 1H), 2.65 – 2.61 (m, 1H), 2.58 – 2.53 (m, 1H), 2.41 – 2.37 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ = 145.0, 143.3, 141.9, 140.9, 138.8, 137.3, 135.1, 134.9, 134.9, 129.3, 128.53, 128.35, 128.3, 127.9, 126.9, 126.4, 126.3, 126.1, 125.7, 124.5, 122.2, 120.42, 120.39, 119.4, 115.1, 111.4, 65.4, 58.4, 58.2, 44.0, 30.1 ppm. (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic and aliphatic region). HRMS (ESI) exact mass calculated for $\text{C}_{31}\text{H}_{27}\text{N}_2\text{O}^+$ ($[\text{M}+\text{H}]^+$): 443.2118, found, 443.2128.

1-(2-(3,4-dimethoxyphenyl)-1H-indol-3-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-

tetrahydroisoquinoline (4.6o): According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μL) and 2(3,4-dimethoxyphenyl)-1H-indole (0.25 mmol, 1.0 equiv, 63 mg) were reacted for 48 h.

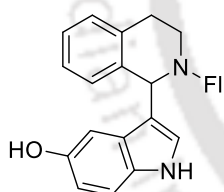
Then, the reaction mixture was dissolved in methanol and the solid product was precipitated



from reaction mixture. The solid was filtered and washed with (3×5 mL) methanol to obtain the desired product **4.6o** (60 mg) as light yellow solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography

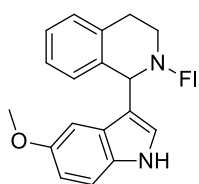
(Ethyl acetate: hexane; 1:3) to give an additional amount (10 mg) of the product. The combined yield is (70 mg, 51%). FTIR (KBr): $\tilde{\nu}$ = 3421, 3349, 1510, 1450, 1260, 1242, 1136, 1023, 746 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.12 (s, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.24 – 7.22 (m, 3H), 7.20 – 7.18 (m, 2H), 7.16 – 7.14 (m, 2H), 7.11 – 7.10 (m, 4H), 7.04 – 7.00 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.85 (s, 1H), 5.99 (s, 1H), 4.83 (s, 1H), 3.95 (s, 3H), 3.70 (s, 3H), 3.12 – 3.00 (m, 1H), 2.57 – 2.53 (m, 1H), 2.46 – 2.4 (m, 1H), 2.25 – 2.21 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 149.7, 149.5, 146.6, 144.1, 141.5, 140.6, 139.7, 138.2, 136.5, 135.7, 128.8, 127.8, 127.7, 127.5, 127.4, 126.3, 126.2, 126.1, 126.0, 125.9, 125.88, 122.6, 121.8, 120.0, 119.9, 119.1, 114.2, 112.6, 111.7, 110.8, 65.2, 59.7, 56.3, 56.2, 44.0, 30.7 ppm. HRMS (ESI) exact mass calculated for C₃₈H₃₃N₂O₂⁺ ([M+H]⁺): 549.2537 found, 549.2569.

3-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1H-indol-5-ol (**4.6p**):

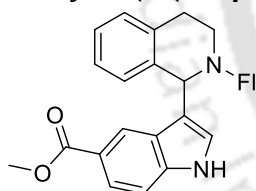


According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 5-hydroxyindole (0.25 mmol, 1.0 equiv, 33 mg) were reacted for 44 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure

and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:4) to obtain **4.6p** as brown solid (103 mg, 96%). FTIR (KBr): $\tilde{\nu}$ = 3328, 2923, 1687, 1615, 1247, 1237, 739 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 8.01 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.35 – 7.33 (m, 1H), 7.30 – 7.27 (m, 1H), 7.24 – 7.17 (m, 3H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 2H), 6.97 – 6.95 (m, 2H), 6.74 – 6.73 (m, 1H), 5.86 (s, 1H), 5.07 (s, 1H), 3.09 – 3.03 (m, 1H), 2.56 – 2.53 (m, 2H), 2.36 – 2.34 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 149.2, 146.4, 144.7, 141.6, 140.5, 139.2, 135.3, 132.6, 128.5, 128.0, 127.74, 127.72, 127.5, 127.2, 127.0, 126.4, 126.1, 125.9, 125.88, 125.7, 120.2, 119.2, 117.5, 112.3, 111.8, 106.0, 65.1, 60.8, 43.7, 30.7 ppm. HRMS (ESI) exact mass calculated for C₃₀H₂₅N₂O⁺ ([M+H]⁺): 429.1961 found, 429.1962.

2-(9H-fluoren-9-yl)-1-(5-methoxy-1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (4.6q):

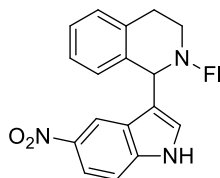
According to the general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 5-methoxyindole (0.25 mmol, 1.0 equiv, 36 mg) were reacted for 48 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:5) to obtain **4.6q** as brown solid (83 mg, 75%). FTIR (KBr): $\tilde{\nu}$ = 3421, 2924, 1581, 1448, 1201, 741 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 8.06 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.45 (s, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.35 – 7.32 (m, 1H), 7.30 – 7.27 (m, 1H), 7.23 – 7.21 (m, 3H), 7.20 – 7.17 (m, 2H), 7.06 (s, 2H), 6.96 – 6.95 (m, 2H), 6.83 – 6.82 (m, 1H), 5.89 (s, 1H), 5.10 (s, 1H), 3.78 (s, 3H), 3.09 – 3.03 (m, 1H), 2.57 – 2.54 (m, 2H), 2.37 – 2.35 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 153.7, 146.5, 144.8, 141.6, 140.7, 139.2, 135.4, 132.6, 128.5, 128.2, 127.8, 127.8, 127.4, 127.0, 126.5, 126.2, 125.9, 125.8, 125.76, 125.6, 120.3, 119.3, 118.1, 112.5, 111.9, 103.6, 65.2, 60.8, 56.0, 43.8, 30.9 ppm. HRMS (ESI) exact mass calculated for C₃₁H₂₇N₂O⁺ ([M+H]⁺): 443.2118, found, 443.2126.

Methyl-3-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1H-indole-5-carboxylate (4.6r):

According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and methyl 1H-indole-5-carboxylate (0.25 mmol, 1.0 equiv, 44 mg) were reacted for 44 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:4) to obtain **4.6r** as brown solid (104 mg, 88%). FTIR (KBr): $\tilde{\nu}$ = 339, 3058, 2911, 1713, 1445, 1211, 1090, 738 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.66 (s, 1H), 8.44 (s, 1H), 7.87 – 7.85 (m, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.48 (m, 2H), 7.34 – 7.29 (m, 3H), 7.22 – 7.18 (m, 2H), 7.07 – 7.05 (m, 2H), 6.96 – 6.90 (m, 2H), 5.94 (s, 1H), 5.02 (s, 1H), 3.92 (s, 1H), 3.17 – 3.09 (m, 1H), 2.60 – 2.54 (m, 2H), 2.43 – 2.39 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 168.4, 146.1, 144.6, 141.6, 140.6, 140.0, 138.9, 135.4, 128.9, 127.9, 127.6, 126.6, 126.14, 126.12, 126.07, 125.9, 125.74, 125.72, 125.26, 124.7, 124.0, 121.8, 120.3, 120.2, 119.9, 119.3, 111.1, 65.4,

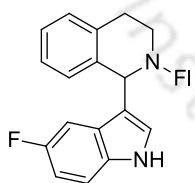
60.6, 52.1, 43.9, 30.7 ppm. HRMS (ESI) exact mass calculated for C₃₂H₂₇N₂O₂⁺ ([M+H]⁺): 471.2067, found, 471.2060.

2-(9H-fluoren-9-yl)-1-(5-nitro-1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (4.6s):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 5-nitroindole (0.25 mmol, 1.0 equiv, 40 mg), in neat condition were reacted for 48h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:2) to obtain **4.6s** as yellow solid (95 mg, 83%). FTIR (KBr): $\tilde{\nu}$ = 3429, 2923, 1610, 1584, 1489, 1450, 1360, 1258, 1235, 1211, 1149 743, 728 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.79 (s, 1H), 8.45 (s, 1H), 8.10 – 8.07 (m, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.62 (m, 2H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.35 – 7.30 (m, 2H), 7.24 – 7.19 (m, 2H), 7.14 – 7.08 (m, 2H), 6.99 – 6.95 (m, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 1H), 4.98 (s, 1H), 3.25 – 3.17 (m, 1H), 2.68 – 2.61 (m, 2H), 2.52 – 2.48 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 145.6, 144.3, 141.7, 141.6, 140.6, 140.3, 138.1, 135.4, 129.1, 128.1, 128.0, 127.8, 127.7, 127.5, 126.6, 126.4, 126.0, 125.8, 125.6, 125.5, 121.2, 120.4, 119.5, 119.1, 118.4, 111.4, 65.6, 60.4, 44.1, 30.7 ppm. HRMS (ESI) exact mass calculated for C₃₀H₂₄N₃O₂⁺ ([M+H]⁺): 458.1863, found, 458.1879.

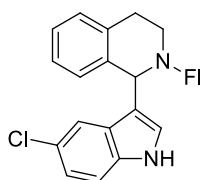
2-(9H-fluoren-9-yl)-1-(5-fluoro-1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (4.6t):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 5-fluoroindole (0.25 mmol, 1.0 equiv, 34 mg) were reacted for 48 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:5) to obtain **4.6t** as yellow solid (80 mg, 74%). FTIR (KBr): $\tilde{\nu}$ = 3432, 2922, 1484, 1448, 1581, 1168, 746, 738 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 8.20 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.51 – 7.50 (m, 1H), 7.40 – 7.39 (m, 2H), 7.35 – 7.33 (m, 1H), 7.31 – 7.28 (m, 1H), 7.24 – 7.20 (m, 3H), 7.09 – 7.07 (m, 2H), 6.98 (m, 1H), 6.91 – 6.87 (m, 2H), 5.87 (s, 1H), 5.02 (s, 1H), 3.12 – 3.05 (m, 1H), 2.57 – 2.54 (m, 2H), 2.38 – 2.35 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 158.3, 156.8, 146.2, 144.6, 141.7, 140.6, 138.8, 135.4, 133.9,

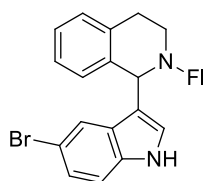
128.7, 128.0, 127.9, 127.6, 126.6, 126.5, 126.14, 126.08, 125.8, 125.7, 120.4, 119.3, 118.4, 111.9, 111.86, 111.1, 110.9, 106.5, 106.4, 65.2, 60.8, 43.8, 30.7 ppm. HRMS (ESI) exact mass calculated for $C_{30}H_{24}FN_2^+$ ($[M+H]^+$): 431.1918, found, 431.1920.

1-(5-chloro-1H-indol-3-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinoline (4.6u):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 5-chloroindole (0.25 mmol, 1.0 equiv, 38 mg) were reacted for 48h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO_2 column chromatography (Ethyl acetate: hexane; 1:5) to obtain **4.6u** as brown solid (79 mg, 71%). FTIR (KBr): $\tilde{\nu}$ = 3441, 2924, 17112, 1609, 1446, 1297, 1261, 1095, 739 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ = 8.17 (s, 1H), 7.75 – 7.74 (m, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.47 – 7.46 (m, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 7.10 – 7.06 (m, 3H), 7.00 – 6.93 (m, 1H), 6.90 – 6.88 (m, 1H), 5.85 (s, 1H), 4.99 (s, 1H), 3.12 – 3.04 (m, 1H), 2.57 – 2.52 (m, 2H), 2.40 – 2.36 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.1, 144.6, 141.6, 140.7, 138.8, 135.8, 135.4, 128.8, 127.93, 127.91, 127.7, 127.4, 126.6, 126.14, 126.12, 125.8, 125.7, 125.2, 122.9, 121.1, 120.3, 119.3, 118.2, 112.3, 65.3, 60.7, 43.9, 30.7 ppm. (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for $C_{30}H_{24}ClN_2^+$ ($[M+H]^+$): 447.1623, found, 447.1620.

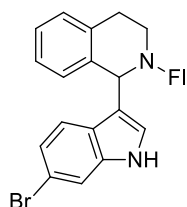
1-(5-bromo-1H-indol-3-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinoline (4.6v):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 5-bromoindole (0.25 mmol, 1.0 equiv, 48.5 mg) were reacted for 48 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO_2 column chromatography (Ethyl acetate: hexane; 1:5) to obtain **4.6v** as yellow brown solid (113 mg, 92%). FTIR (KBr): $\tilde{\nu}$ = 3442, 3027, 3058, 2911, 1713, 1445, 1090, 1041, 881, 822, 796, 738 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ = 8.08 (s, 1H), 7.95 – 7.94 (m, 1H), 7.73 – 7.68 (m, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.27 – 7.25 (m, 1H), 7.24 – 7.22 (m, 2H), 7.20 – 7.17 (m, 1H), 7.09 – 7.08 (m, 2H), 6.98 – 6.94 (m, 1H), 6.91 – 6.89 (m, 1H), 5.87 (s, 1H), 4.99 (s, 1H), 3.13 – 3.05 (m, 1H), 2.58 – 2.51 (m, 2H), 2.41 – 2.37 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 144.5, 141.6,

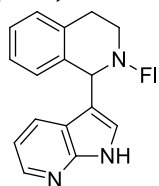
140.7, 138.7, 136.0, 135.3, 128.8, 128.0, 127.94, 127.91, 127.7, 126.6, 126.2, 126.1, 125.9, 125.8, 125.8, 125.7, 125.5, 124.3, 120.3, 119.4, 118.2, 112.9, 112.8, 65.3, 60.7, 43.9, 30.7 ppm. HRMS (ESI) exact mass calculated for C₃₀H₂₄BrN₂⁺ ([M+H]⁺): 493.1097, found, 493.1129.

1-(5-bromo-1H-indol-3-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinoline (4.6w):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 6-bromoindole (0.25 mmol, 1.0 equiv, 48.5 mg) were reacted for 48h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:5) to obtain **4.6w** as yellow brown solid (112 mg, 91%). FTIR (KBr): $\tilde{\nu}$ = 3442, 2951, 1713, 1445, 1417, 1211, 1041, 738 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.15 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.63 – 7.59 (m, 2H), 7.51 – 7.49 (s, 2H), 7.36 – 7.32 (m, 2H), 7.31 – 7.29 (m, 1H), 7.25 – 7.19 (m, 2H), 7.17 – 7.14 (m, 1H), 7.08 – 7.07 (m, 2H), 6.98 – 6.94 (m, 1H), 6.90 – 6.88 (m, 1H), 5.89 (s, 1H), 5.02 (s, 1H), 3.11 – 3.03 (m, 1H), 2.59 – 2.50 (m, 2H), 2.38 – 2.34 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 146.2, 144.6, 141.7, 140.6, 138.9, 138.3, 135.4, 128.7, 128.0, 127.92, 127.91, 127.6, 126.6, 126.12, 126.10, 125.8, 125.7, 125.4, 125.2, 123.0, 122.9, 120.4, 120.6, 119.3, 118.7, 116.2, 114.3, 65.2, 60.7, 43.8, 30.8 ppm. HRMS (ESI) exact mass calculated for C₃₀H₂₄BrN₂⁺ ([M+H]⁺): 491.1117, found, 491.1121.

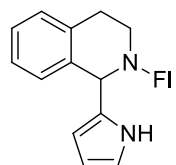
2-(9H-fluoren-9-yl)-1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (4.6x):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and 7-azaindole (0.25 mmol, 1.0 equiv, 29.5 mg) were reacted for 48 h. After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:2) to obtain **4.6x** as yellow solid (90 mg, 82%). FTIR (KBr): $\tilde{\nu}$ = 2895, 2814, 1582, 1446, 1418, 1120, 773, 741 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.31 (d, *J* = 4.8 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.70 – 7.68 (m, 2H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.25 – 7.17 (m, 3H), 7.09 – 7.08 (m, 2H), 7.06 – 7.02 (m, 1H), 7.00 – 6.92 (m, 2H), 5.90 (s, 1H), 5.05 (s, 1H), 3.12 – 3.03 (m, 1H), 2.62 – 2.57 (m, 2H), 2.41 – 2.37 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ =

150.0, 146.1, 144.6, 143.4, 141.6, 140.7, 138.8, 135.4, 130.2, 128.7, 128.2, 128.0, 127.9, 127.5, 126.6, 126.2, 126.1, 125.8, 125.5, 125.3, 120.4, 119.4, 119.0, 117.1, 116.0, 65.3, 61.0, 43.9, 30.8 ppm. HRMS (ESI) exact mass calculated for $C_{29}H_{24}N_3^+$ ($[M+H]^+$): 414.1965, found, 414.1964.

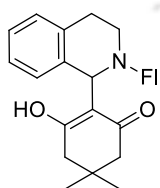
2-(9H-fluoren-9-yl)-1-(1H-pyrrol-3-yl)-1,2,3,4-tetrahydroisoquinoline (4.6y): According



to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and pyrrole (0.25 mmol, 1.0 equiv, 18 μ L), in neat condition were reacted for 24 h. After completion of the reaction, the reaction mixture was dissolved in methanol

and solution mixture was evaporated under reduced pressure and residue was purified by SiO_2 column chromatography (Ethyl acetate: hexane; 1:20) to obtain **4.6y** as yellow solid (48 mg, 53%). FTIR (KBr): $\tilde{\nu}$ = 3398, 3060, 1713, 1428, 1287, 1110, 772, 748 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ = 8.39 (s, 1H), 7.77 – 7.70 (m, 2H), 7.69 – 7.65 (m, 1H), 7.46 – 7.44 (m, 1H), 7.35 – 7.33 (m, 2H), 7.29 – 7.28 (m, 1H), 7.24 – 7.23 (m, 1H), 7.13 – 7.03 (m, 3H), 6.98 – 6.96 (m, 1H), 6.80 (s, 1H), 6.56 (s, 1H), 6.18 (s, 1H), 5.75 (s, 1H), 4.96 (s, 1H), 2.94 – 2.85 (m, 1H), 2.51 – 2.45 (m, 2H), 2.32 – 2.28 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.8, 144.2, 141.6, 140.9, 137.9, 135.2, 132.4, 128.8, 128.4, 128.1, 128.0, 127.5, 126.8, 126.5, 126.4, 126.0, 125.0, 120.4, 119.6, 118.6, 110.5, 107.7, 65.3, 61.2, 43.3, 30.3 ppm. HRMS (ESI) exact mass calculated for $C_{26}H_{23}N_2^+$ ($[M+H]^+$): 363.1856, found, 363.1857.

2-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-hydroxy-5,5-



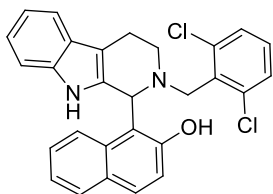
dimethylcyclohex-2-enone (4.6z): According to general procedure II: 9-

fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μ L) and dimedone (0.25 mmol, 1.0 equiv, 35 mg) were reacted for 44 h. After completion of the

reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO_2 column chromatography (Ethyl acetate: hexane; 1:4) to obtain **4.6z** as brown solid (60 mg, 56%). FTIR (KBr): $\tilde{\nu}$ = 3495, 2925, 1672, 1120, 748 cm^{-1} . 1H NMR (600 MHz, $CDCl_3$) δ = 7.93 (d, J = 7.2 Hz, 1H), 7.74 – 7.70 (m, 3H), 7.47 – 7.41 (m, 2H), 7.40 – 7.37 (m, 1H), 7.33 – 7.30 (m, 1H), 7.25 – 7.23 (m, 1H), 7.17 – 7.15 (m, 1H), 7.12 – 7.10 (m, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.30 (s, 1H), 5.25 (s, 1H), 3.01 – 2.96 (m, 1H), 2.55 – 2.51 (m, 1H), 2.48 – 2.45 (m, 2H), 2.44 – 2.36 (m, 4H), 1.10 (s, 6H). HRMS (ESI) exact mass calculated for $C_{30}H_{30}NO_2^+$ ($[M+H]^+$): 436.2271, found, 436.2260.

1-(2-(2,6-dichlorobenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)naphthalen-2-ol

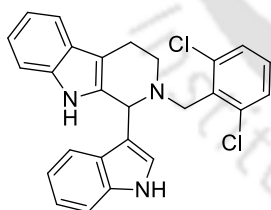
(4.6aa): 2,6-di-chlorobenzaldehyde (0.3 mmol, 1.2 equiv, 52 mg), 2,3,4,9-tetrahydro-1H-



pyrido[3,4-b]indole (0.3 mmol, 1.2 equiv, 52 mg) and 2-naphthol (0.13 mmol, 1.0 equiv, 29 mg) were reacted for 24 h. Then reaction mixture was dissolved in methanol and the solid product was precipitated from reaction mixture. Then, the solid was filtered and

washed with (3×5 mL) methanol to obtain the desired product **4.6aa** (70 mg) as light brown solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (Ethyl acetate: hexane; 1:20) to give an additional amount (20 mg) of the product. The combined yield is (90 mg, 82%). FTIR (KBr): $\tilde{\nu}$ = 3351, 2920, 2853, 1622, 1468, 1435, 1434, 1314, 1245, 778, 741, 636 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 10.98 (s, 1H), 8.24 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.61 – 7.59 (m, 1H), 7.47 – 7.46 (m, 1H), 7.42 – 7.49 (m, 1H), 7.23 – 7.21 (m, 2H), 7.14 (s, 1H), 7.11 – 7.10 (m, 1H), 7.06 – 7.03 (m, 3H), 6.96 (d, J = 9.0 Hz, 1H), 5.83 (s, 1H), 4.33 (d, J = 13.2 Hz, 1H), 4.05 (d, J = 13.2 Hz, 1H), 3.41 – 3.36 (m, 1H), 3.09 – 3.01 (m, 2H), 2.93 – 2.89 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 156.6, 137.6, 136.4, 133.4, 132.5, 132.4, 130.3, 129.7, 129.5, 128.9, 128.6, 127.5, 126.7, 123.0, 121.9, 120.7, 120.0, 119.6, 118.4, 114.4, 111.1, 109.1, 61.0, 55.7, 50.7, 21.9. 6 ppm. HRMS (ESI) exact mass calculated for C₂₈H₂₃Cl₂N₂O⁺ ([M+H]⁺): 473.1182, found, 473.1205.

2-(2-(2,6-dichlorobenzyl)-1-(1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole

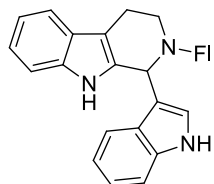


(4.6ab): According to general procedure I, 2,6-dichloro benzaldehyde (0.3 mmol, 1.2 equiv, 52 mg), 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (0.3 mmol, 1.2 equiv, 52 mg) and indole (0.25 mmol, 1.0 equiv, 29 mg), in neat condition were reacted for 24 h.

After completion of the reaction, the reaction mixture was dissolved in methanol and solution mixture was evaporated under reduced pressure and residue was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:4) to obtain **4.6ab** as brown solid (92 mg, 83%) desired product. FTIR (KBr): $\tilde{\nu}$ = 3401, 2922, 1560, 1454, 1434, 1091, 767, 741 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 7.94 (s, 1H), 7.59 – 7.53 (m, 1H), 7.51 (s, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.23 (s, 1H), 7.20 – 7.16 (m, 1H), 7.14 (d, J = 3.5 Hz, 2H), 7.12 – 7.08 (m, 3H), 6.94 – 6.90 (m, 1H), 6.82 – 6.81 (m, 1H), 5.12 (s, 1H), 4.15 (d, J = 12.4 Hz, 1H), 3.87 (d, J = 12.4 Hz, 1H), 3.24 – 3.18 (m, 1H), 2.99 – 2.90 (m, 2H), 2.83 – 2.76 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 137.4, 136.5, 136.1, 135.6, 134.7, 128.9, 128.5, 127.5,

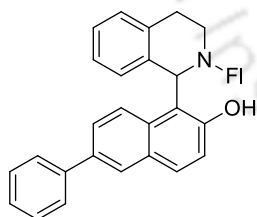
127.2, 124.9, 122.3, 121.5, 120.0, 119.8, 119.3, 118.4, 116.0, 111.2, 111.1, 109.0, 55.6, 52.7, 47.1, 20.2 ppm. HRMS (ESI) exact mass calculated for $C_{26}H_{22}Cl_2N_3^+$ ($[M+H]^+$): 446.1185, found, 446.1185.

2-(9H-fluoren-9-yl)-1-(1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (4.6ac):



According to general procedure I, 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (0.3 mmol, 1.2 equiv, 52mg) and indole (0.25 mmol, 1.0 equiv, 33 mg), in 2 ml methanol were reacted for 72 h. After completion of the reaction, solution mixture was evaporated under reduced pressure and residue was purified by SiO_2 column chromatography (Ethyl acetate: hexane; 1:4) to obtain **4.6ac** as brown solid (52 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 3401, 2922, 1560, 1454, 1434, 1091, 767, 741 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$) δ = 8.23 (s, 1H), 7.82 – 7.77 (m, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.55 – 7.54 (m, 1H), 7.49 – 7.46 (m, 1H), 7.45 – 7.43 (m, 2H), 7.39 – 7.36 (m, 2H), 7.35 – 7.27 (m, 2H), 7.23 – 7.20 (m, 3H), 7.14 – 7.11 (m, 1H), 7.06 – 7.04 (m, 3H), 6.01 (s, 1H), 5.09 (s, 1H), 2.91 – 2.82 (m, 1H), 2.73 – 2.66 (m, 1H), 2.61 – 2.57 (m, 1H), 2.51 – 2.47 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 146.5, 144.8, 141.7, 140.6, 137.3, 136.2, 135.9, 127.9, 127.9, 127.7, 127.5, 126.6, 126.2, 125.8, 124.9, 122.9, 121.8, 121.4, 121.3, 120.4, 120.2, 119.3, 119.3, 118.3, 115.1, 111.4, 111.0, 109.1, 64.8, 56.9, 44.7, 22.6 ppm. HRMS (ESI) exact mass calculated for $C_{32}H_{26}N_3^+$ ($[M+H]^+$): 452.2121, found, 452.2116.

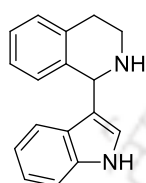
1-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-6-phenylnaphthalen-2-ol (4.8):



phenylboronic acid (0.26 mmol, 1.5 equiv, 31 mg), $Ba(OH)_2 \cdot 8H_2O$ (0.23 mmol, 1.2 equiv, 40mg), $Pd(PPh_3)_4$ (0.01 mmol, 0.019 equiv, 11 mg), 1,4-dioxane (1.3 mL), H_2O (0.4 mL) and 1-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-6-bromonaphthalen-2-ol, **4.6c** (0.193 mmol, 1equiv, 100 mg) were refluxed for 24 h under inert atmosphere. After completion of the reaction 1,4-dioxane was evaporated under reduce pressure. The resulting mass was diluted with DCM (30 mL) and the mixture was washed with 1M HCl (3×20 mL) and then with brine (2×20 mL). Combined organic layers were dried over sodium sulfate and concentrated under vacuum to give crude product which was further purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:2) to afford desired product **4.8** as light yellow solid (82 mg, 82%). FTIR (KBr): $\tilde{\nu}$ = 2959, 2924, 1493, 1448, 1261, 1079, 812, 739 cm^{-1} . 1H NMR (600 MHz, $CDCl_3$) δ = 11.78 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 1.2 Hz, 1H), 7.97 – 7.95 (m, 1H), 7.86 – 7.83 (m, 3H), 7.77 – 7.76 (m,

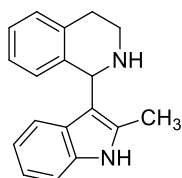
2H), 7.68 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 6.6 Hz, 1H), 7.51 – 7.48 (m, 2H), 7.40 – 7.35 (m, 4H), 7.29 – 7.27 (m, 1H), 7.23 (s, 1H), 7.11 – 7.09 (m, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.95 – 6.94 (m, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.68 (s, 1H), 5.03 (s, 1H), 3.10 – 3.05 (m, 1H), 2.65 – 2.62 (m, 1H), 2.59 – 2.55 (m, 1H), 2.49 – 2.47 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 155.9, 143.9, 142.1, 141.5, 141.1, 141.0, 136.5, 135.7, 134.3, 133.6, 130.6, 129.3, 129.1, 128.8, 128.7, 128.6, 128.3, 127.9, 127.37, 127.36, 127.29, 127.27, 127.18, 126.9, 126.6, 126.4, 125.9, 122.1, 120.60, 120.59, 119.7, 118.0, 65.3, 60.8, 43.2, 29.9 ppm. HRMS (ESI) exact mass calculated for C₃₈H₃₀NO⁺ ([M+H]⁺): 516.2322, found, 516.2322.

1-(2-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (4.9): 2-(9H-fluoren-9-yl)-1-



(1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline, (**4.6k**) (0.18 mmol, 1 equiv, 75 mg) was dissolved in ethyl acetate and methanol (3:1, v/v). Palladium (10%) on charcoal (0.18 mmol, 1 equiv, 20 mg) was added to it. Then the flask was evacuated and re-filled with hydrogen. The process was repeated three times. Then, the reaction mixture was kept on shaking at 25 PSI of hydrogen for 48 hours. After the completion of the reaction, the reaction mixture was filtered through a pad of celite, and the celite pad was washed successively with methanol (3×5 mL) and ethyl acetate (3×5 mL). The filtrate was concentrated and the crude product was purified (preparative TLC, ethyl acetate: hexane; 2:1) to afford desired product **4.9** as brown gum (25 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 2923, 2855, 1622, 1452, 1263, 1099, 742 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 8.19 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.20 – 7.13 (m, 2H), 7.07 – 7.05 (m, 1H), 7.04 – 7.01 (m, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.93 – 6.92 (m, 1H), 5.51 (s, 1H), 3.29 – 3.25 (m, 1H), 3.12 – 3.08 (m, 1H), 3.03 – 2.98 (m, 1H), 2.92 – 2.88 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 138.1, 136.7, 135.1, 129.1, 128.1, 126.5, 125.9, 124.3, 122.3, 119.9, 119.6, 119.2, 111.5, 53.9, 41.8, 29.7 ppm. HRMS (ESI) exact mass calculated for C₁₇H₁₇N₂⁺ ([M+H]⁺): 249.1386, found, 249.1387.

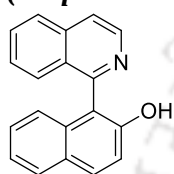
1-(2-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (4.10): 2-(9H-fluoren-9-yl)-1-



(2-methyl-1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline **4.6l** (0.23 mmol, 1 equiv, 100 mg) was dissolved in ethyl acetate and methanol (3:1, v/v). Palladium (10%) on charcoal (0.23 mmol, 1 equiv, 25 mg) was added to it. Then the flask was evacuated and re-filled with hydrogen. The process was repeated three times. Then, the reaction mixture was kept on shaking at 25 PSI of hydrogen for 48 h. After the completion of the reaction, the reaction mixture was filtered

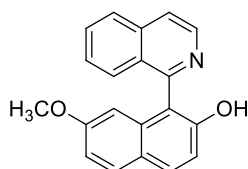
through a pad of celite, and the celite pad was washed successively with methanol (3×5 mL) and ethyl acetate (3×5 mL). The filtrate was concentrated and the crude product was purified (preparative TLC, ethyl acetate: hexane; 2:1) to afford desired product **4.10** as brown gum (35 mg, 57%). FTIR (KBr): $\tilde{\nu}$ = 3604, 3298, 3228, 2922, 1622, 1460, 1428, 1261, 738 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.97 (s, 1H), 7.25 – 7.23 (m, 1H), 7.17 – 7.16 (m, 1H), 7.13 – 7.09 (m, 2H), 7.06 – 7.03 (m, 1H), 6.99 – 6.96 (m, 1H), 6.93 – 6.89 (m, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.42 (s, 1H), 3.40 – 3.37 (m, 1H), 3.20 – 3.11 (m, 2H), 2.88 – 2.85 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ = 139.0, 135.5, 135.3, 133.2, 129.0, 127.6, 126.2, 126.1, 121.1, 119.5, 119.2, 114.4, 110.4, 53.9, 43.8, 30.3, 12.3 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{18}\text{H}_{19}\text{N}_2^+$ ($[\text{M}+\text{H}]^+$): 263.1543, found, 263.1543.

1-(isoquinolin-1-yl)naphthalen-2-ol(4.11):



1-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-2-ol, (4.c) (0.17 mmol, 1 equiv, 75 mg) was dissolved in 3 mL mesitylene. Palladium (10%) on charcoal (0.34 mmol, 2 equiv, 36 mg) was added to it. Then, the reaction mixture was and reflux temperature for 24 h. After the completion of the reaction, the reaction mixture was filtered through a pad of celite, and the celite pad was washed successively with methanol (3×5 mL) and ethyl acetate (3×5 mL). The filtrate was concentrated and the crude product was purified SiO_2 column chromatography (ethyl acetate: hexane; 1:2) to afford desired product **4.11** as brown solid (44 mg, 96%). FTIR (KBr): $\tilde{\nu}$ = 3050, 1620, 1582, 1558, 1434, 1350, 1276, 823, 747 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 8.59 (d, J = 5.6 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.84 – 7.82 (m, 1H), 7.78 – 7.76 (m, 2H), 7.71 – 7.69 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.33 – 7.29 (m, 1H), 7.21 – 7.18 (m, 2H), 7.08 (d, J = 8.8 Hz, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 157.6, 153.6, 141.8, 137.3, 133.3, 131.2, 131.0, 129.0, 128.4, 128.4, 128.0, 127.7, 127.3, 126.6, 125.1, 123.4, 121.1, 119.4, 117.5 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{19}\text{H}_{14}\text{NO}^+$ ($[\text{M}+\text{H}]^+$): 272.1070, found, 272.1097.

1-(isoquinolin-1-yl)-7-methoxynaphthalen-2-ol (4.12):



1-(2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-7-methoxynaphthalen-2-ol, (4.6a) (0.16 mmol, 1 equiv, 75 mg) was dissolved in 3 ml mesitylene. Palladium (10%) on charcoal (0.32 mmol, 2 equiv, 34 mg) was added to it. Then, the reaction mixture was and refluxed for 24 h. After the completion of the reaction, the reaction mixture was filtered through a pad of celite, and the celite pad was washed successively with methanol (3×5 mL) and ethyl acetate (3×5 mL). The filtrate was concentrated and the crude product was purified SiO_2 column chromatography (ethyl acetate:

hexane; 1:2) to afford desired product **4.12** as brown solid (41 mg, 84%). FTIR (KBr): $\tilde{\nu}$ = 2952, 1623, 1588, 1348, 1223, 827 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 8.67 (d, *J* = 6.0 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.79 – 7.77 (m, 2H), 7.74 – 7.70 (m, 2H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.44 – 7.41 (m, 1H), 7.17 (d, *J* = 9.0 Hz, 1H), 6.98 (dd, *J* = 9.0, 3.6 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 3.42 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ = 158.3, 157.7, 154.4, 141.9, 137.3, 134.4, 131.0, 131.0, 129.9, 128.6, 128.0, 127.5, 127.3, 124.4, 121.0, 116.8, 116.7, 115.5, 104.6, 55.1 ppm. HRMS (ESI) exact mass calculated for C₂₀H₁₆NO₂⁺ ([M+H]⁺): 302.1176, found, 302.1179.

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Chapter 5
**C-H Functionalization Enabled Stereoselective Ugi-
azide reaction to α -tetrazoyl Alicyclic Amines**



5.1. Introduction:

The multicomponent reaction is one of the best approaches for reaching the standing challenges in designing a reaction that provides the products with desired complexity and structural diversity starting from simple and readily available substrates in a single operation. Despite the development of various synthetic strategies, the structural diversity of the products of the MCR is still limited because this strategy relies mainly on the reactivity of classical functional groups, such as carbonyl, nitrile, isocyanides, etc.¹ As a large variety of C–H bonds are present in organic molecules, the integration of C–H functionalization into a multicomponent reaction would provide an opportunity to greatly expand the scope and the product diversity.

Tetrazoles are an important class of compounds because of their wide range of application as medicinal drugs, ligands for metal ions, imaging agents, precursors for metal–organic frameworks and highly energetic compounds.² In particular, α -tetrazolyl amines, which are tetrazole analogs of amino acids, have been recognized as interesting scaffolds in peptidomimetics and medicinal chemistry.³ Additionally, enantiopure α -tetrazolyl pyrrolidine is widely used as an organocatalyst in asymmetric organic synthesis.⁴ Related tetrazolyl pyrrolidine derivatives are also utilized for the synthesis of nucleoside analogs⁵ (**Figure 1**).

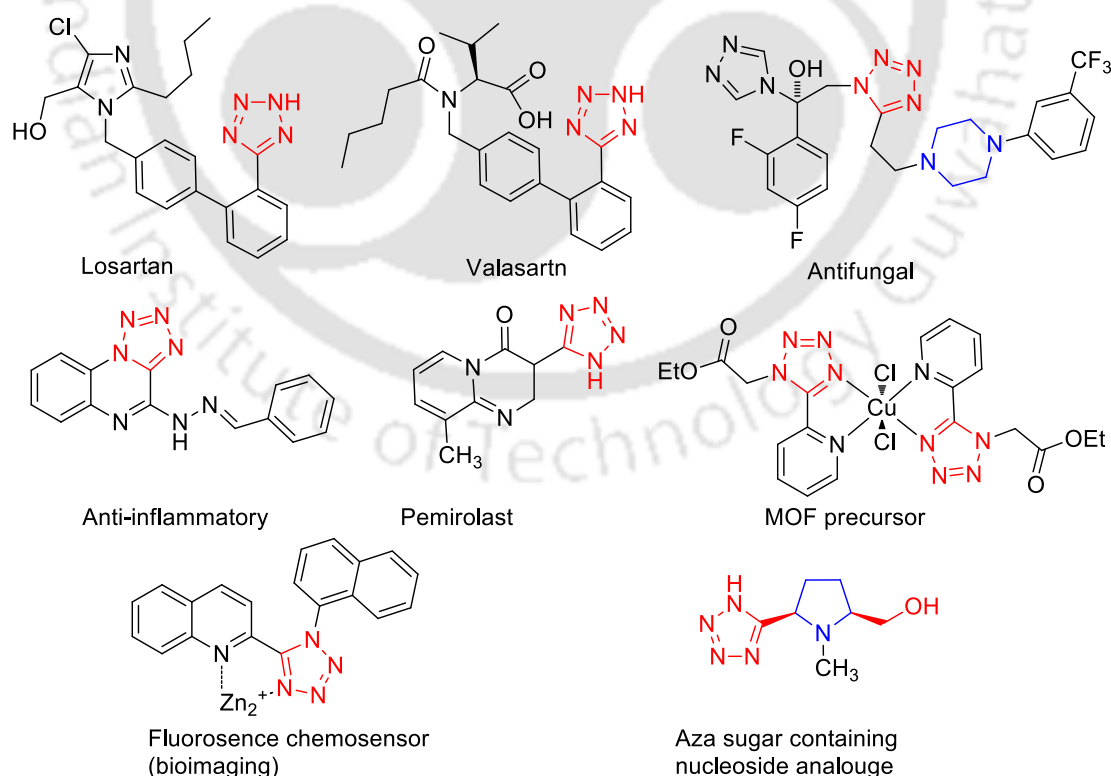


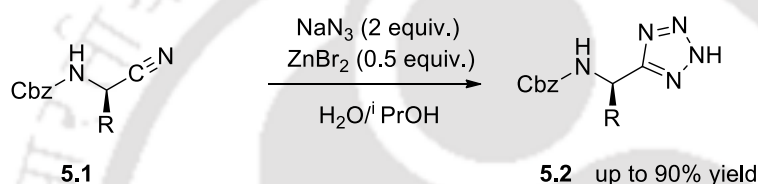
Figure 1: N-Heterocycles and tetrazoles containing some important molecules.

5.2. Background:

Tetrazoles are prepared mainly either via azide addition to cyanide and amide or through a multicomponent Ugi-azide reaction. However, the isocyanide based Ugi-azide reaction dominated the field.⁶ A large number of reports are known for the syntheses of tetrazolyl methylamines.⁷ Selected recent examples of the synthesis of tetrazolyl methyl amine in shown in scheme 1. In 2002, Sharpless and co-workers reported a method, for the transformation of α -aminonitriles **5.1** to the tetrazole derivative **5.2**. The reaction was carried out in the presence of sodium azide and a catalytic amount of zinc bromide in water/2-propanol at 80 °C (**Scheme 1**, eq.1).^{7c} In 2016, Domling group utilized β - cyanoethyl isocyanide in the Ugi-azide reaction. By this method 1-substituted 1*H*-tetrazole **5.4** containing pyrrolidine scaffold was obtained (**Scheme 1**, eq.2).^{7e}

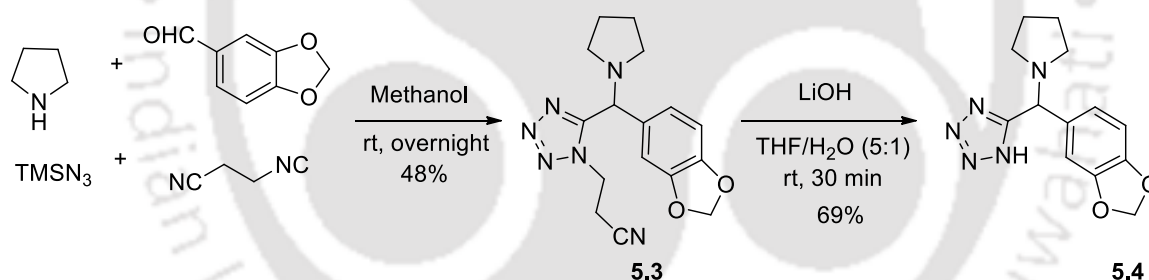
Sharpless, 2002

(1)



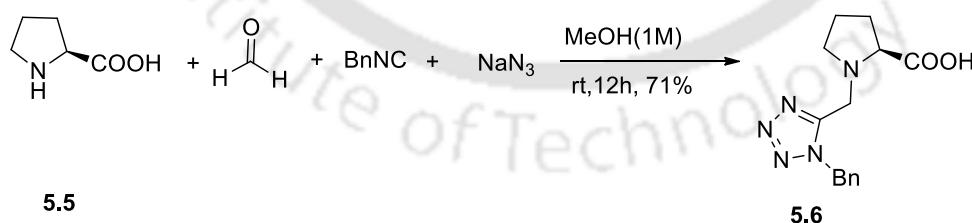
Domling, 2016

only classical Ugi product (2)



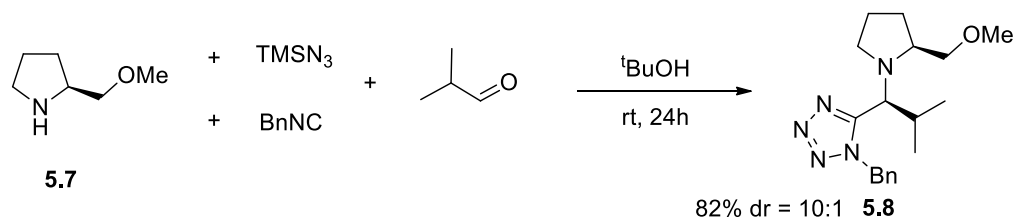
Domling, 2017

only classical Ugi product (3)



Nenajdenko, 2017

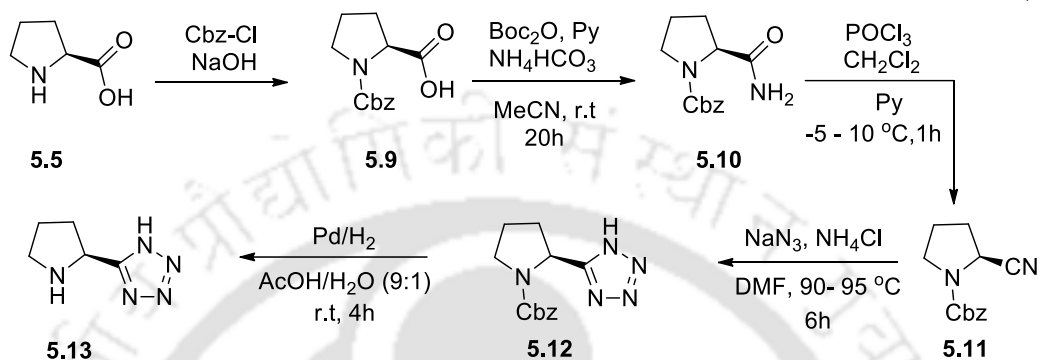
only classical Ugi product (4)



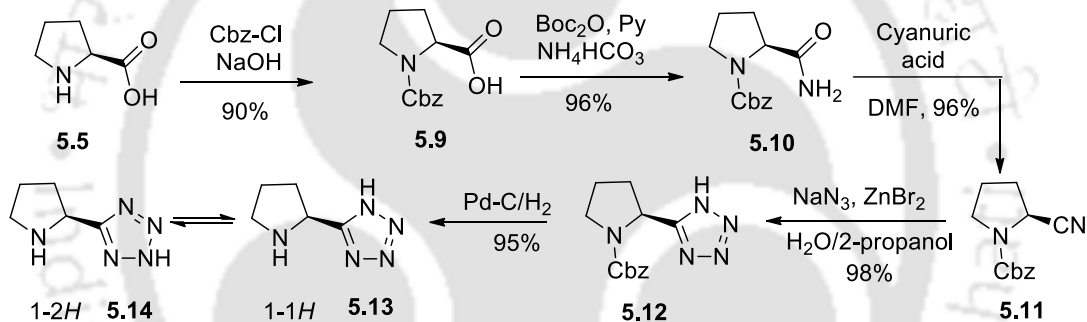
Scheme 1: Synthesis of tetrazolyl methylamines.

In 2017, the same group developed the direct usage of unprotected amino acid **5.5** in Ugi-azide reactions to produce a novel class of tetrazole **5.6** containing acid group (**Scheme 1**, eq.3).^{7f} In 2017, Nenajdenko and co-workers reported the diastereoselective azido-Ugi reaction of cyclic amines for the synthesis tetrazolyl methyl amine **5.8** with good yield and diastereoselectivity under mild conditions (**Scheme 1**, eq.4).^{7g}

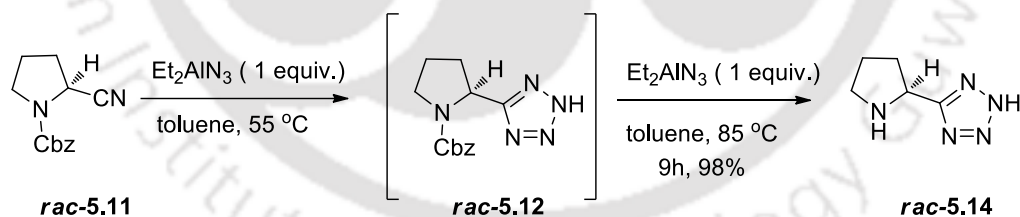
Yamamoto, 2004 (5)



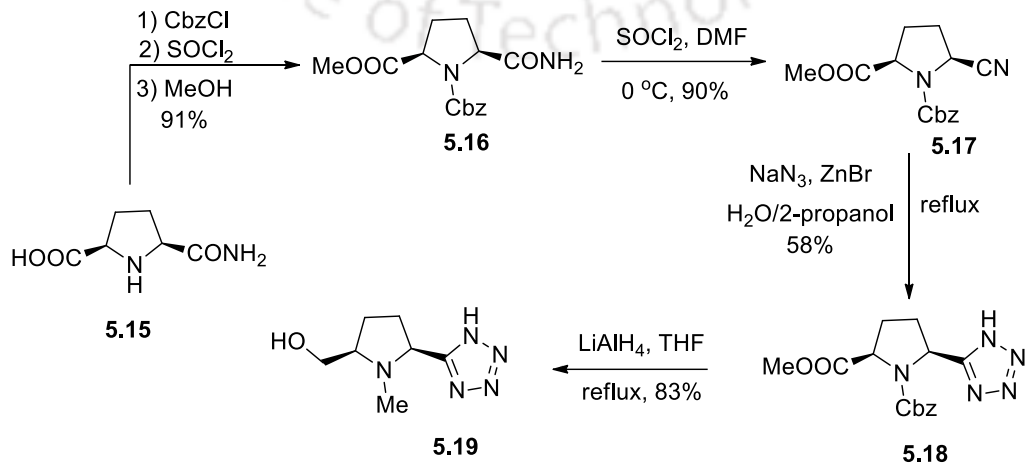
Arvidsson, 2004 (6)



Sedelmeier, 2007 (7)

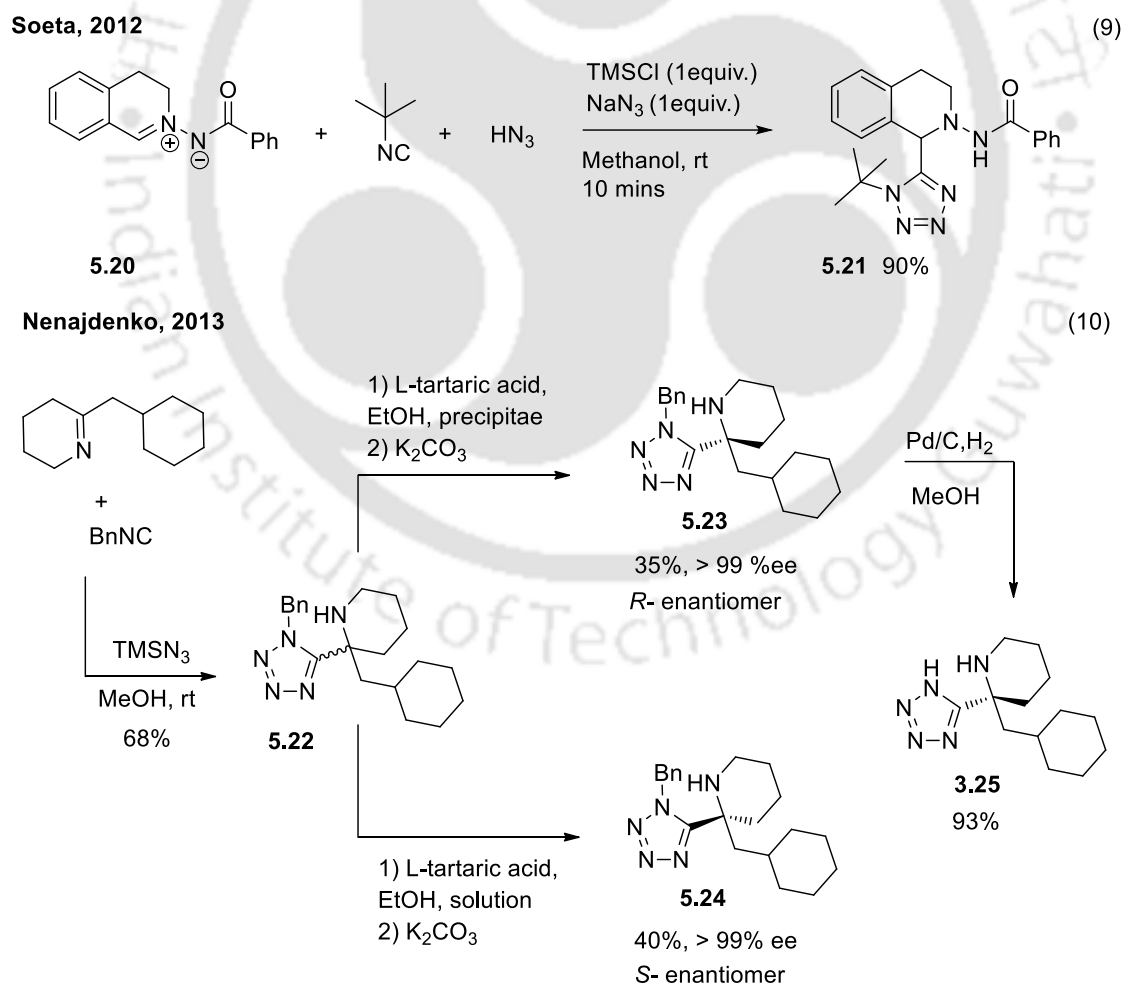


Wang, 2012 (8)



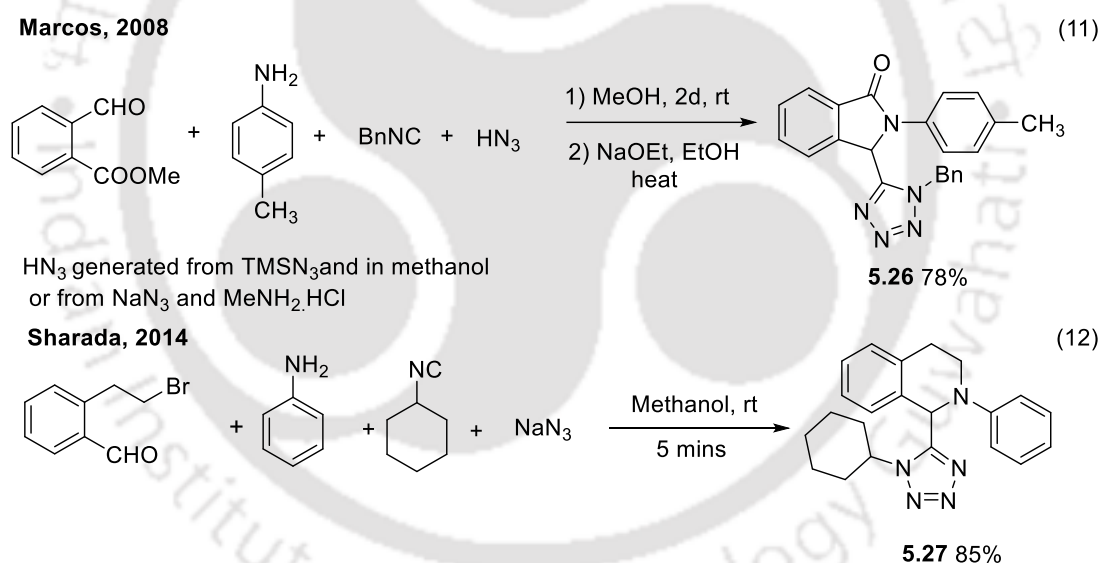
Scheme 2: Metal mediated synthesis of α -tetrazolyl *N*-heterocycles.

Although numerous number of methods have existed for the synthesis of tetrazolyl methyl amines through classical Ugi-azide reaction, only a few examples are known for the synthesis of α -tetrazolyl *N*-heterocycles. For the synthesis of α -tetrazolyl *N*-heterocycles metal-mediated azide addition to α -cyanopyrrolidine, a prefunctionalized *N*-heterocycle was mainly utilized.^{4,8} In this context 1975, Almquist and co-workers reported the synthesis of 5-pyrrolidin-2-yltetrazole.^{8a} In 2004, Yamamoto and Arvidsson groups individually have reported a metal-mediated multistep synthetic procedure for the preparation of proline based tetrazole **5.13** starting from simple *L*-proline **5.5** (Scheme 2, eq.5 & eq. 6). Later in 2007, Sedelmeier and co-workers reported a modified reaction procedure for the preparation of 2*H*-tetrazol-5-yl pyrrolidine **5.13** starting from *N*-protected proline by using diethylaluminum azide as a metal catalyst (Scheme 2, eq.7). In 2012, Wang group reported a method for the synthesis of aza-sugar containing nucleoside analogue **5.19** starting from (2*R*,5*S*)-5-carbamoylpyrrolidine-2-carboxylic acid **5.15** (Scheme 2, eq.8).

**Scheme 3:** Synthesis of α -tetrazolyl *N*-heterocycles from pre-oxidized starting materials.

Similarly, pre-oxidized *N*-heterocycles were reacted to obtain the desired tetrazole derivatives.⁹ In 2012, Soeta and co-workers developed multicomponent reaction of isocyanides and C, N-cyclic *N*'-acyl azomethine imine **5.20** in the presence of TMSCl and NaN₃ leads to the tetrazole derivative **5.21** (Scheme 3, eq.9).^{9a} In 2013, Nenajdenko and co-workers developed a new route to tetrazole derived cyclic amine using cyclic imine as the starting materials (Scheme 3, eq.10).^{9b, 9c}

Formation of tetrazole via a classical Ugi-azide reaction followed by *N*-cycloalkylation was also employed for the synthesis of α -tetrazolyl tetrahydroisoquinolines.¹⁰ In 2008, Marcos and co-workers developed a four-component condensation reaction of methyl o-formylbenzoates, anilines, isocyanides, and TMSN₃ to afford the tetrazole which was upon treatment with sodium ethoxide in ethanol to provide tetrazolyl-isoindolinone **5.26** (Scheme 4, eq.11).^{10a} In 2014, Sharada and co-workers developed one-pot, four-component Ugi-azide reaction followed by intramolecular cyclization for the synthesis of tetrazolyl-tetrahydroisoquinoline derivatives (Scheme 4, eq.12).^{10c}



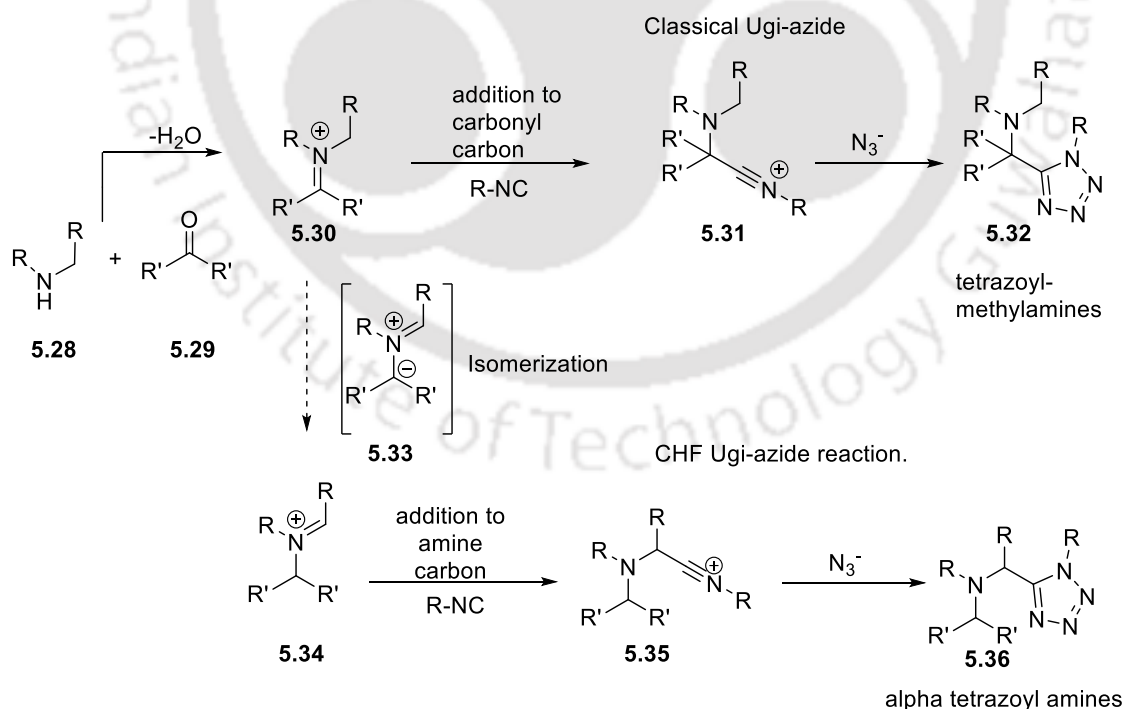
Scheme 4: Synthesis of α -tetrazolyl *N*-heterocycles via *N*-cycloalkylation strategy.

5.3. Motivation and Aim of the work:

Evidently, the known protocols suffer from significant drawbacks because of the involvement of a multistep synthetic sequence, hazardous metallic reagents and oxidants. Therefore, in the context of practical application, synthesis of α -tetrazolyl *N*-heterocycles directly from corresponding *N*-heterocycles would be advantageous as compared to the known methods. Despite the different known strategies for amine functionalization,^{11,12} no report was known for the synthesis of α -tetrazolyl *N*-heterocycles directly from the corresponding amines.

5.4. Classical Ugi-azide vs C-H functionalization enabled Ugi-azide (CHF Ugi-azide) reaction

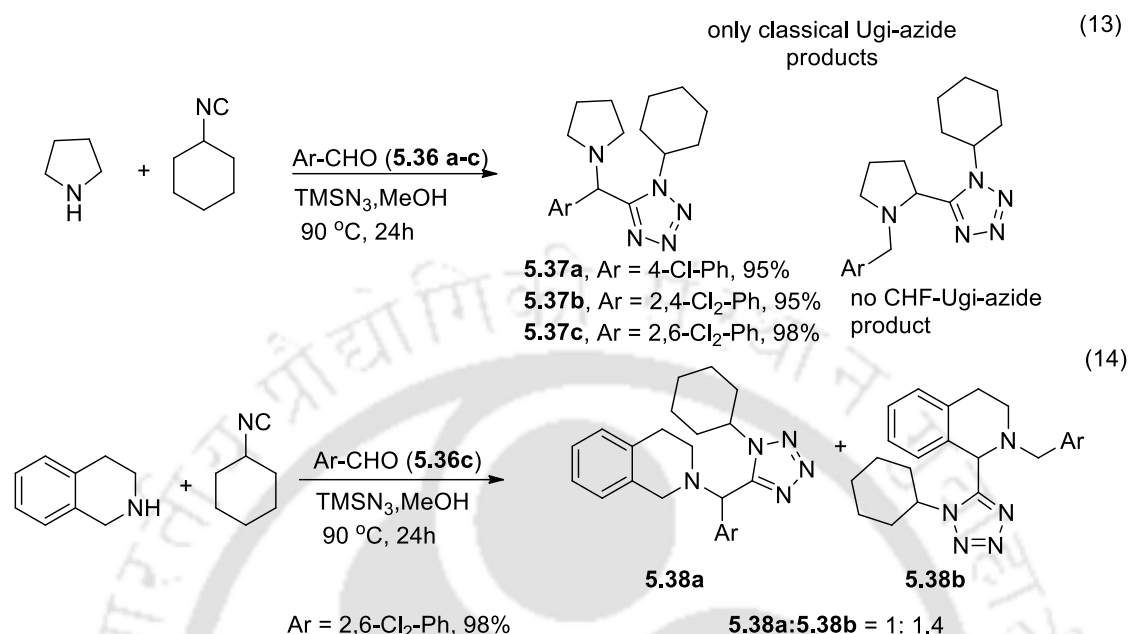
In the classical azido-Ugi reaction, amine **5.28** and carbonyl compound **5.29** undergo condensation to form the imine or iminium ion **5.30** (Scheme 5). Subsequent nucleophilic addition of isocyanide to imine-carbon followed by reaction of the resulting nitrilium ion **5.31** with azide furnishes the tetrazolyl methylamines **5.32**. It was anticipated that an isomerization of iminium ion **5.30** via the zwitterionic intermediate **5.33** would lead to the corresponding regioisomeric ion **5.34**. Subsequent reaction of the isomerized iminium ion **5.34** with isocyanide would provide the nitrilium ion **5.35**. Then the reaction of azide and **5.35** would install the tetrazole moiety at the α -carbon of the aliphatic amine (as in **5.36**) instead at the carbonyl carbon (as in **5.32**). In this way, integration of a C–H functionalization step in the multicomponent Ugi azide reaction would bring the opportunity to obtain α -tetrazolyl *N*-heterocycles directly from corresponding amines without involving metallic reagents and pre-functionalization/pre-oxidation steps. The extent of isomerization will depend on the stability of the carbanion of the zwitterionic intermediate **5.33**. Therefore, the nature of the carbonyl compound **5.29** will decide the extent of isomerization and thus the choice of the carbonyl compound is crucial to determine the viability of this C–H functionalization enabled Ugi-azide (CH-Ugi-azide) reaction.



Scheme 5: Classical Ugi-azide vs C-H functionalization enabled Ugi-azide (CHF Ugi-azide) reaction.

5.5. Initial results:

The studies commenced with the examination of the suitability of different aldehydes for the proposed CH-Ugi-azide reactions.



Scheme 6: Initial reactions for synthesis of α -tetrazolyl *N*-heterocycles.

Interestingly, aldehydes **5.36a–c** including 2,6-dichloro- and 4-chlorobenzaldehyde, which were found to be efficient for corresponding Ugi and other amine functionalization reactions by Seidel *et al.*,^{11d,12} provided only the classical Ugi-azide product **5.37a–c** (**Scheme 7**). However, the reaction of THIQ in the presence of 2,6-dichlorobenzaldehyde **5.36c** provided a 1: 1.4 mixture of the classical Ugi-azide product **5.38a** and desired α -tetrazolyl tetrahydroisoquinoline **5.38b**.

5.6. Table 1: Optimization of reaction conditions:

Next, the feasibility of the CH-Ugi-azide reaction in the presence of different ketones was tested. Accordingly, a reaction of pyrrolidine with 9-fluorenone **5.39a** in the presence of cyclohexyl isocyanide and TMS-azide in methanol was performed (table 1). Pleasingly, the desired product **5.40a** was isolated with 85% yield after 12 hours of reaction in a closed vessel at 90–100 °C (table 1, entry 1). The yield of the desired product **5.40a** was further increased to 98% with the increase in the reaction time (entry 2). However, a lower yield was obtained from the reaction, which was carried out at room temperature. Dibromo-9-fluorenone **5.39c** provided only 31% of the desired product, while the reaction with benzophenone (**3.39d**) and anthrone (**5.39e**) could not offer the desired product. 9-Fluorenone imine **5.39b** produced the desired tetrazole **5.40a** with the best yield (>99%, **Table 1**, eq. 15).

Table 1: Optimization of the reaction conditions:

(15)

Cy= Cyclohexyl

5.40a

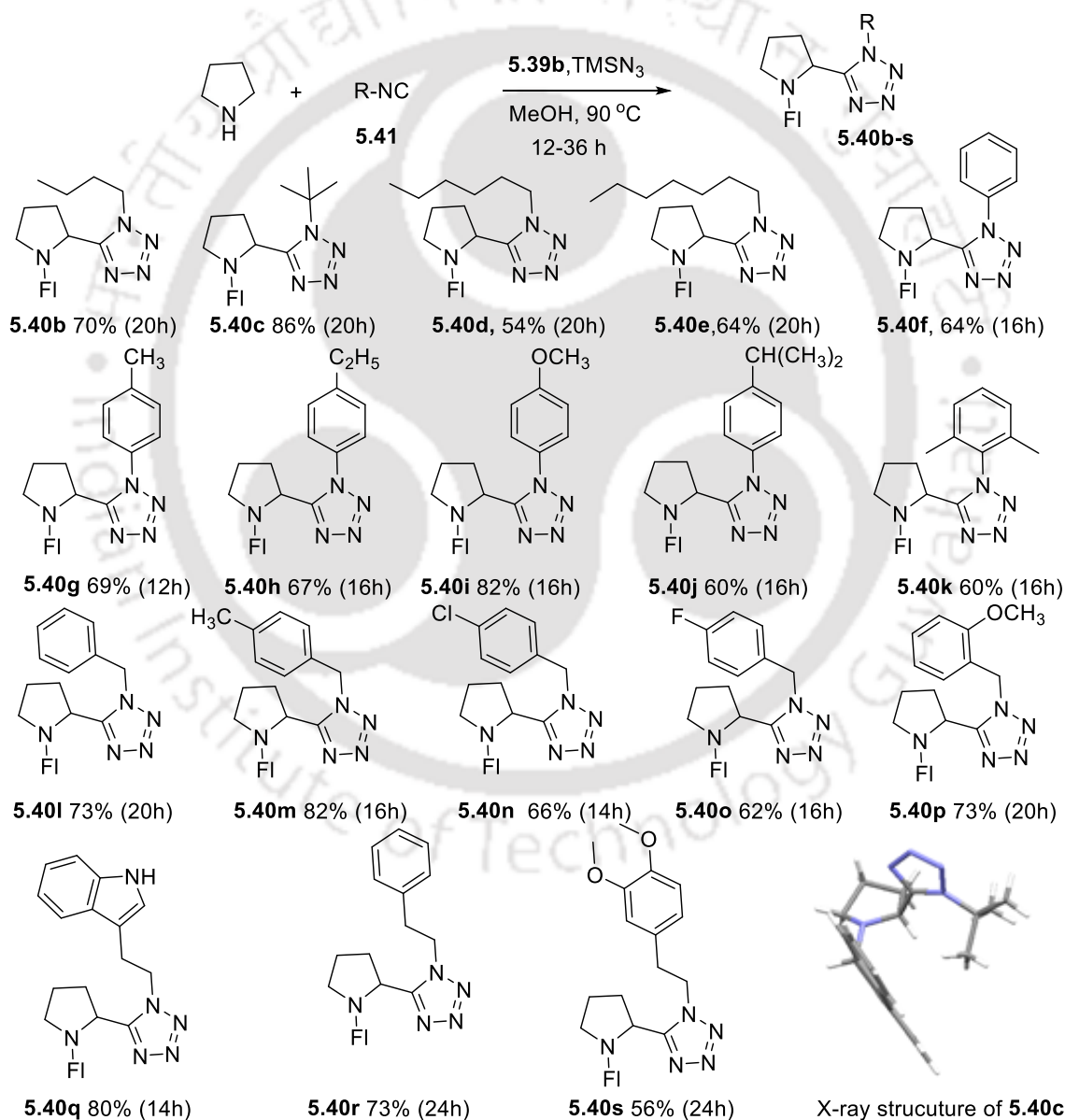
5.39a **5.39b** **5.39c** **5.39d** **5.39e**

^a Entry	activators	conditions ^b	yield ^c (%)
1	5.39a	TMSN ₃ , MeOH, 90 °C, 12 h	85
2	5.39a	TMSN ₃ , MeOH, 90 °C, 24 h	98
3	5.39a	TMSN ₃ , MeOH, rt, 24 h	44
4	5.39b	TMSN ₃ , MeOH, 90 °C, 24 h	99
5 ^d	5.39b	TMSN ₃ , MeOH, 90 °C, 24 h	97
6	5.39b	TMSN ₃ , CH ₃ CN, 90 °C, 24 h	52
7	5.39b	TMSN ₃ , H ₂ O, 90 °C, 24 h	-
8	5.39b	TMSN ₃ , benzene, 90 °C, 24 h	31
9	5.39b	TMSN ₃ , toluene, 90 °C, 24 h	32
10	5.39b	TMSN ₃ , xylene, 90 °C, 24 h	39
11	5.39b	NaN ₃ , MeOH, 90 °C, 24 h	32
12	5.39b	DIPA, MeOH, 90 °C, 24 h	87
13	5.39c	TMSN ₃ , MeOH, 90 °C, 24 h	31 ^e
14	5.39a	TMSN ₃ , neat, 100 °C, 24 h	42
15	5.39a	TMSN ₃ , EtOH, 100 °C, 24 h	21
16	5.39a	TMSN ₃ , H ₂ O, 100 °C, 24 h	-
17	5.39b	TMSN ₃ , EtOH, 100 °C, 24h	54
18	5.39a	TMSN ₃ , H ₂ O, 100 °C, 24h	-
19	5.39b	TMSN ₃ , MeOH:H ₂ O (1:1), 100 °C, 24h	30
21	5.39c	TMSN ₃ , MeOH, 100 °C, 24h	-
22	5.39d	TMSN ₃ , MeOH, 100 °C, 12h	-
23	5.39e	TMSN ₃ , MeOH, 100 °C, 24h	-

^aReactions were performed in a closed vessel with isocyanide (0.13 mmol, 1 equiv.), azide (1 equiv), **5.39** (1.2 equiv.) and pyrrolidine (3 equiv.). ^bOil bath temperature is mentioned. ^c isolated yields. ^dreaction was carried out in round bottom flask under conventional heating.

Reactions in aprotic solvents such as acetonitrile, benzene, toluene, and xylene provided the desired product with poor yields. However, methanol was found to be the best solvent whereas the reaction in water did not produce the desired product. In addition to TMSN₃, other azide sources, such as sodium azide and DIPA, were also suitable for the CH-Ugi-azide reaction.

5.7. Substrate scope of the reaction with pyrrolidine:



Scheme 7: Scope in synthesis of tetrazolyl pyrrolidine.

The optimized reaction conditions were then used to evaluate the scope of the isocyanides in CHF-Ugi-azide reaction (**Scheme 7**). The reactions of pyrrolidine with aliphatic, aromatic and benzyl isocyanides **5.41** went smoothly to produce the desired tetrazoles **5.40b-s** with good to excellent yields. Isocyanides with linear aliphatic hydrocarbon as well as the highly branched *tert*-butyl group provided corresponding 1-alkyl tetrazoles **5.40b-e** with very good yields. In addition, 1-alkyl tetrazoles having indole and methoxyphenyl groups (**5.40q-s**) were obtained from the reaction of isocyanides derived from neurotransmitter tryptamine, phenethylamine and 3,4- dimethoxyphenethylamine, respectively. A series of phenyl and benzyl isocyanides with various *ortho* and *para* substituents were reacted with pyrrolidine to afford structurally diverse substituted tetrazole derivatives **5.40f-p** with good to excellent yield.

5.8. Substrate scope of the reaction with Tetrahydroisoquinoline (THIQ) and substituted THIQ:

Tetrahydroisoquinoline (THIQ) and substituted THIQ are frequently observed in natural products and biologically active molecules including marketed drugs. Therefore, we were interested to investigate the scope of THIQ and its derivatives **5.42** in the CH-Ugi-azide reaction (**Scheme 9**). Excellent yields of a series of structurally diverse α -tetrazolyl THIQ **5.43a-q** and substituted THIQ **5.43r-x** were obtained from the CH-Ugi-azide reaction of the corresponding THIQ or its derivatives in the presence of various isocyanides. Like in the case of pyrrolidine, THIQ or its derivatives reacted smoothly with alkyl, benzyl and aryl isocyanides. However, relatively higher yields of α -tetrazolyl THIQ as compared to corresponding pyrrolidine derivatives were obtained. The higher yields are probably due to easiness in the isomerization of the iminium ion (**5.30** to **5.34**, **Scheme 5**) in case of THIQ and its derivatives as compared to pyrrolidine. The challenging substrate, 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole, also reacted with 1-(isocyanomethyl)-4-methylbenzene under standard conditions. However, the desired product **5.43y** was isolated with moderate yield (33%).

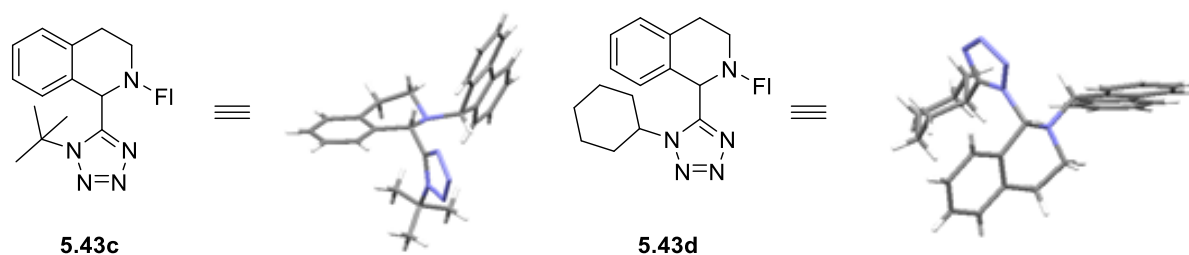
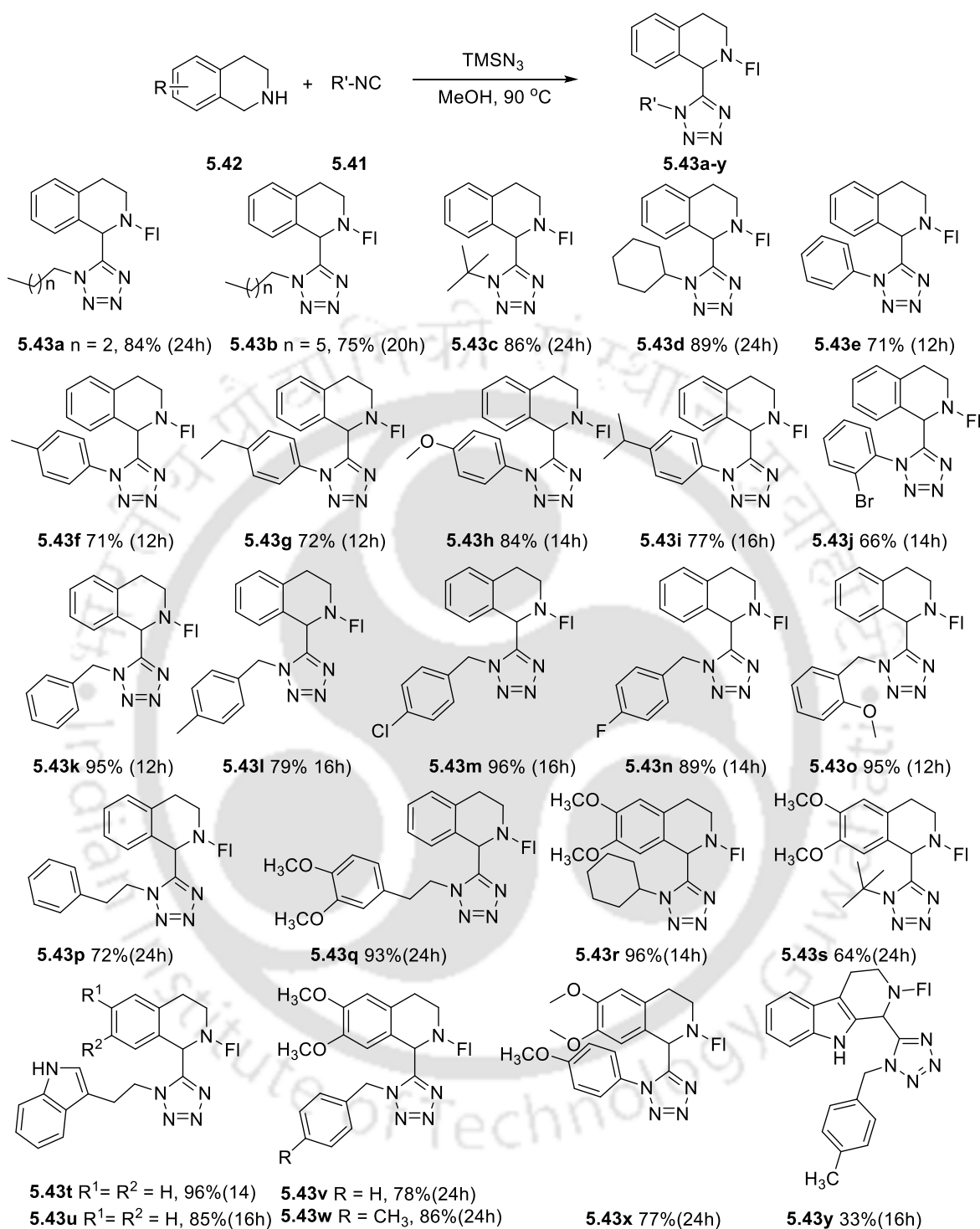


Figure 2: Crystal structure of **5.43c** and **5.43d**.

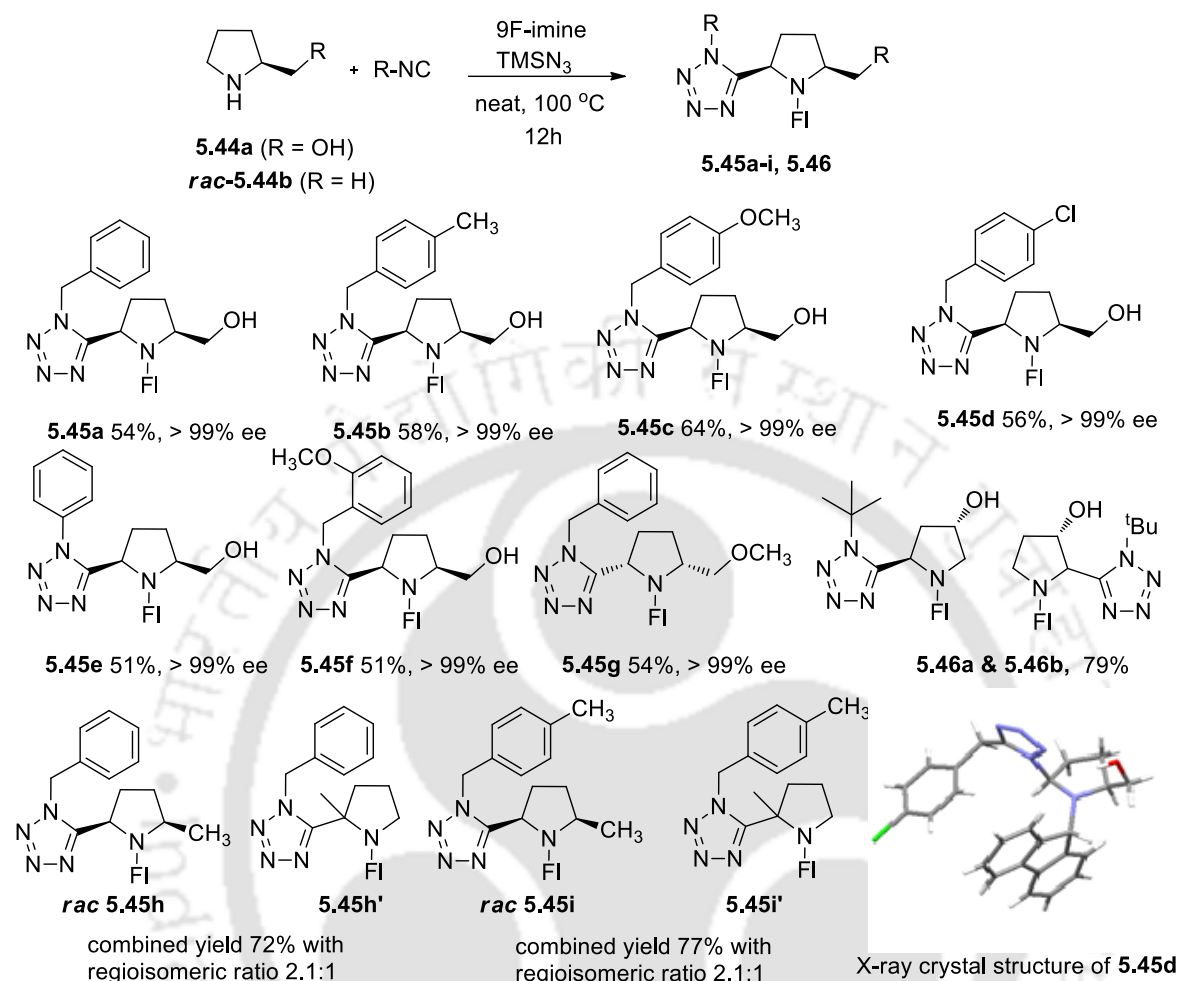


Scheme 8: Reactions of THIQ and substituted THIQ

5.9. Substrate scope of the reaction with chiral amines:

Diastereoselective reactions using chiral amines and chiral isocyanides were investigated next (**Schemes 9, 10 & 11**). Accordingly, enantioenriched prolinol **5.44a** was reacted with different isocyanides at 100 °C under solvent free condition (**Scheme 9**). Interestingly, the

desired tetrazole derivatives **5.45a–i** were isolated with good to moderate yields and excellent enantiopurity (>99%).



Scheme 9. Stereoselective reactions with chiral amines: syntheses of nucleoside analogs.

However, regioisomeric products **5.45h**, **5.45i**, and **5.45h'**, **5.45i'** were isolated from the reaction of racemic 2-methylpyrrolidine (**rac-5.44b**) with a 2:1 ratio. Therefore, in this way, nucleoside analogs **5.45a–g**, the known synthesis of which required a multistep reaction sequence,⁵ were prepared in a single step from commercially available starting material. On the other hand, a mixture of both regioisomeric and diastereoisomeric products **5.46a** and **5.46b** were isolated with 79% combined yield from the reaction of 3-hydroxy pyrrolidine. The relative *syn*-stereochemistry was determined through X-ray analysis and NOE experiments.

5.10. NOE analysis of compound **5.45a** & **rac-3.45h**:

The peaks at 3.58 ppm and 3.70 ppm region corresponds to the protons H_b and H_c, respectively. On the other hand, the signal at 4.01 ppm corresponds to the protons H_a and H_d. During 1D-NOE experiments, H_b (3.58 ppm) has been selectively irradiated. The

enhancement of peak Ha in the region 4.01 ppm was observed. This result indicated the relative *syn*-stereochemistry of the compound **5.45a**.

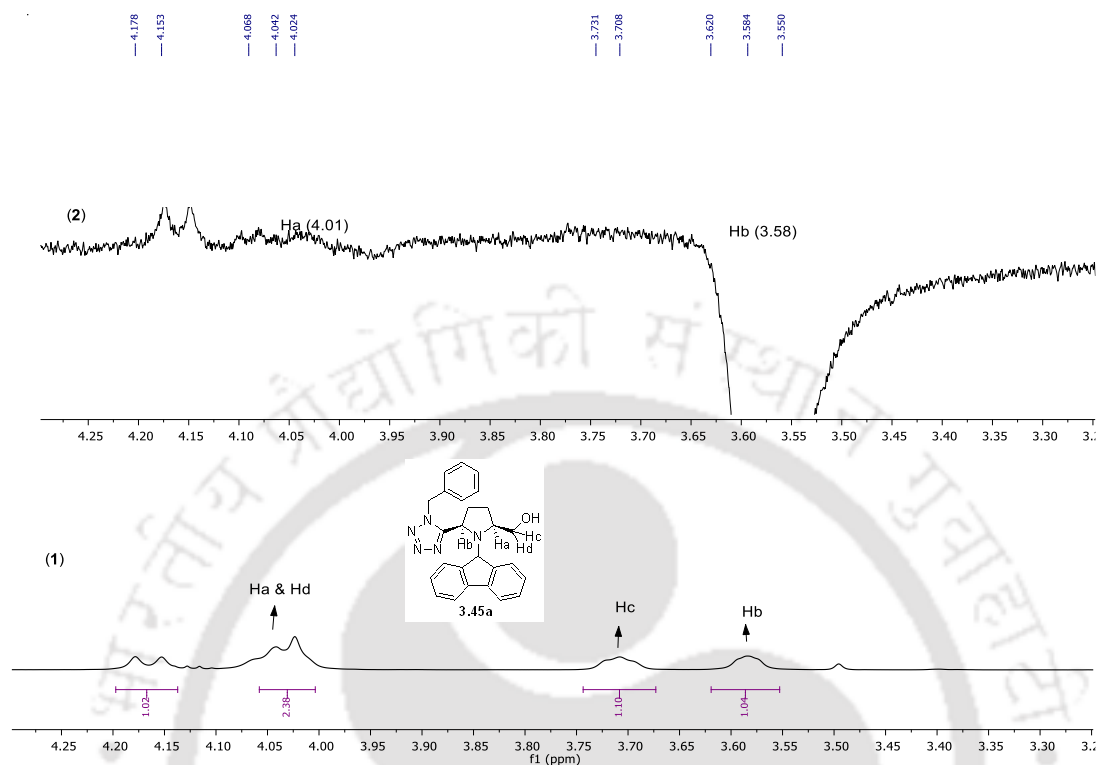


Figure 2: 1-D NOE spectra of compound **5.45a**.

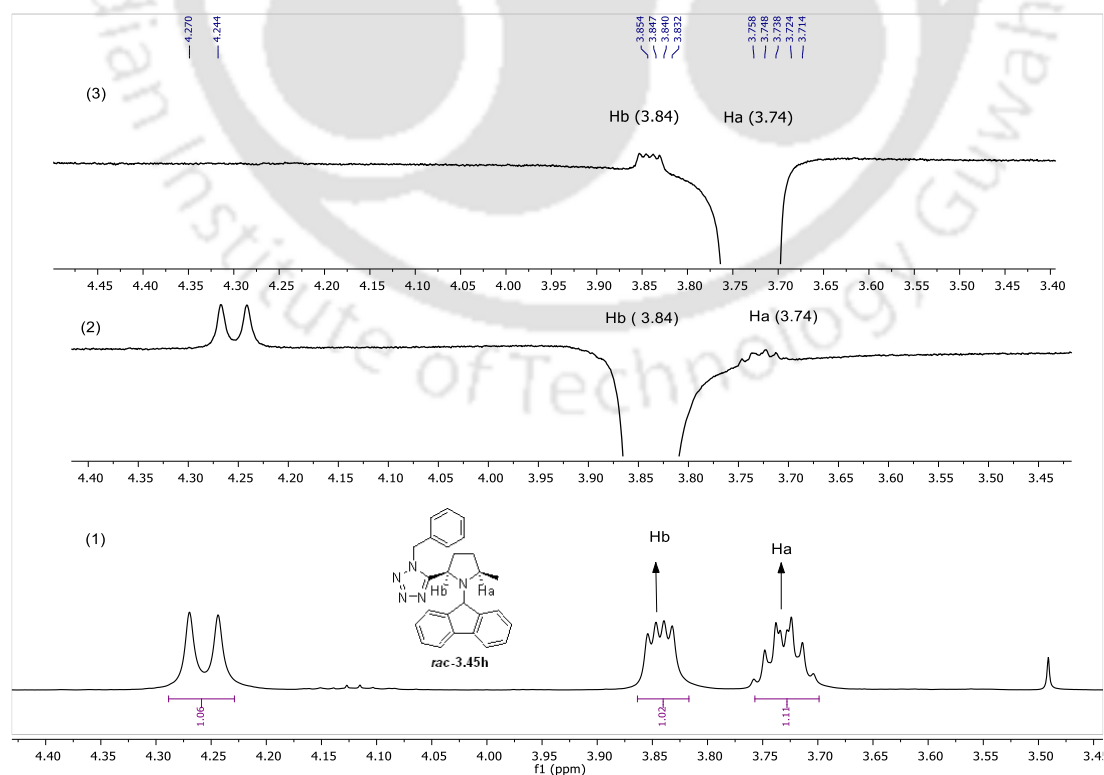
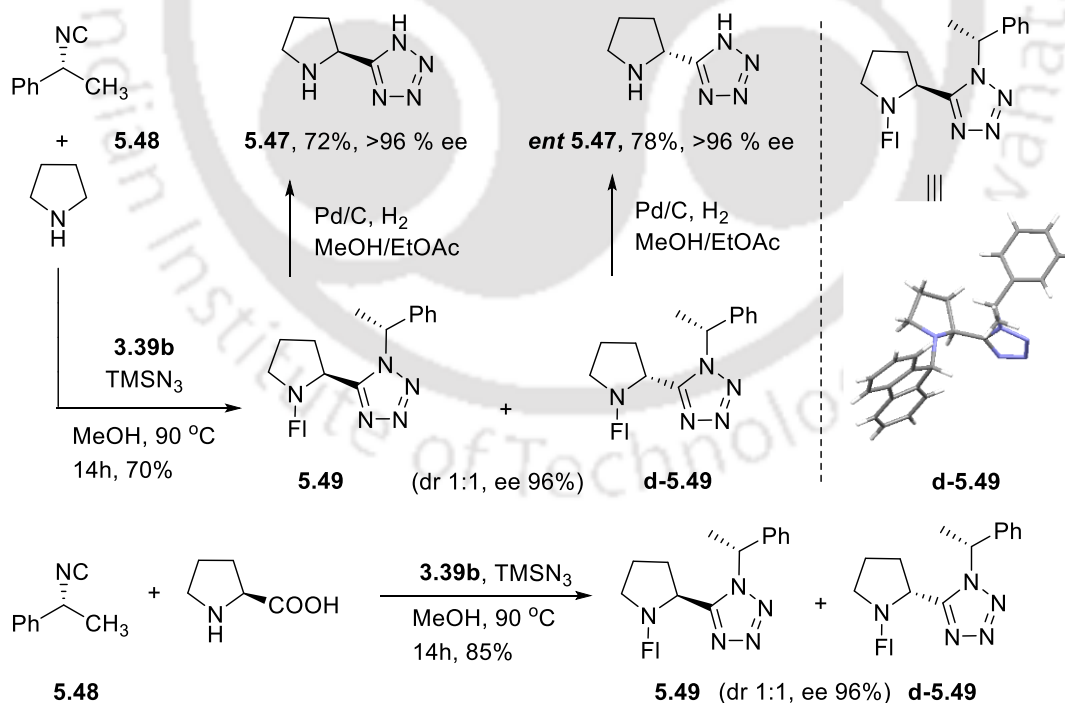


Figure 3: 1-D NOE spectra of compound **rac-3.45h**.

The selective irradiation of Ha (3.74 ppm) in 1D-NOE experiments resulted in enhancement of signal of Hb (3.84 ppm). Similarly, irradiation of Hb (3.84 ppm) resulted in enhancement of Ha (3.74 ppm). So, this result indicated the relative *syn*-stereochemistry of **rac-3.45h**.

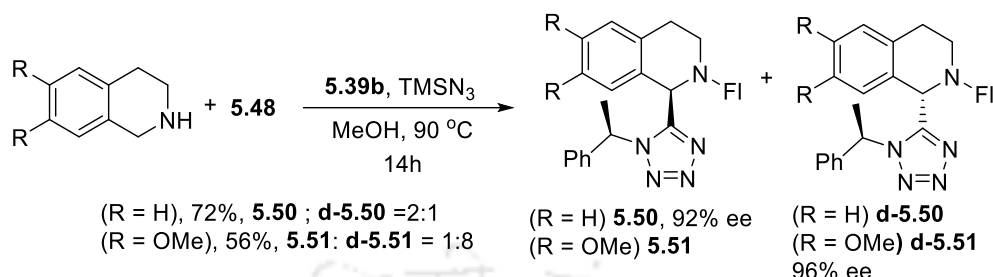
5.11. Chiral isocyanide in Ugi-azide reaction:

Enantiopure α -tetrazolyl pyrrolidine **5.47** is an excellent organocatalyst, which has been found to have wide applications in various asymmetric reactions, such as Mannich, aldol, nitroaldol, amination, nitroso aldol, *etc.*⁴ It showed superior catalytic activity due to its higher solubility in organic solvents as compared to proline. The known synthesis of this molecule in the enantiomerically pure form required a multistep synthetic sequence involving pre-functionalization/peroxidation steps.⁸ This inspired us to apply our CH-Ugi-azide reaction for an elegant synthesis of enantioenriched α -tetrazolyl pyrrolidine from pyrrolidine (**Scheme 10**). Enantioenriched 1-((*R*)-1-isocyanoethyl)benzene **5.48**, which is also commercially available, derived from α -methylbenzylamine was reacted with pyrrolidine under standard reaction conditions to obtain the corresponding enantioenriched tetrazoles **5.49** (34%, 96% ee) and **d-5.49** (35%, 96% ee). A better combined yield of **5.49** (85%) was obtained when *L*-proline was used in place of pyrrolidine. The relative and the absolute stereochemistry of **d-5.49** was confirmed from the single crystal X-ray structure.



Scheme 10: Diastereoselective reactions with chiral isocyanides: syntheses of (*R*)- and (*S*)- α -tetrazolyl pyrrolidines.

Both benzyl and fluorenyl groups of **5.49** and **d-5.49** were removed under standard hydrogenolysis conditions to afford (*S*)-2-tetrazolyl pyrrolidine and (*R*)-2-tetrazolyl pyrrolidine, respectively, with excellent yields and enantiopurities.



Scheme 11: Diastereoselective reactions with chiral isocyanides and THIQ.

Diastereoselective reactions of THIQ and its derivative with **5.48** provided the desired enantioenriched tetrazoles **5.50** and **5.51** with very good yields. Enantioenriched tetrazoles **5.50** and **d-5.50** were isolated with a 2:1 ratio whereas a higher ratio of 1:8 was observed for **5.51** and **d-5.51**. The relative stereochemistries of **5.50** and **d-5.51** were confirmed from X-ray crystal structures (**Scheme 11**).

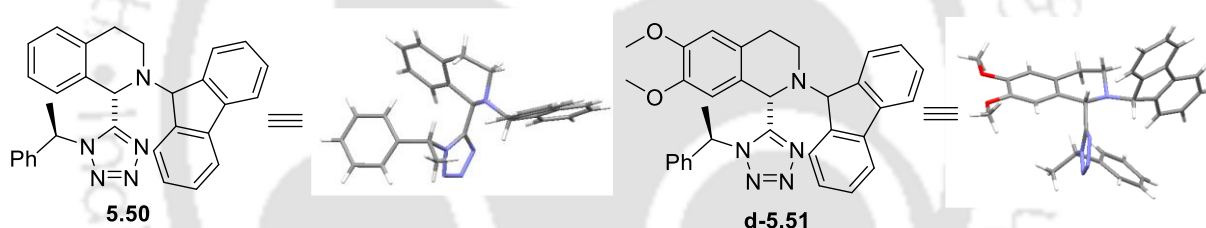


Figure 4: Crystal structure of **5.50** and **d-5.51**

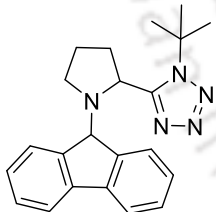
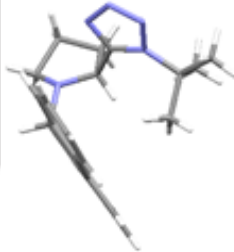
5.12. Summary:

In summary, we have reported the first examples of a C–H functionalization enabled azido-Ugi (CH-Ugi-azide) reaction to access α -tetrazolyl alicyclic amines directly from the corresponding *N*-heterocycles under metal and oxidant free conditions. The reaction is operationally simple and highly efficient to functionalize a wide range of *N*-heterocycles producing structurally diverse α -tetrazolyl alicyclic amines (60 examples, 50–99%) either in enantioenriched or in racemic form. Importantly, the diastereoselective reactions involving enantioenriched amines provided direct access to nucleoside analogs whereas the reaction of enantioenriched isocyanide provided access to (+)- or (–)- α -tetrazolyl pyrrolidine, which is a widely used organocatalyst, in enantioenriched form just in two steps starting from pyrrolidine.

5.13. 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). Triethylamine (Et_3N) was distilled from CaH_2 and stored under argon. Commercial grade xylene, benzene and toluene were distilled 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 400, 600 MHz (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS (^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). HPLC: Waters analytical HPLC, thermo scientific ultimate 3000 /visible detector. Polarimetry: Rudolph research analytical auto plot II.

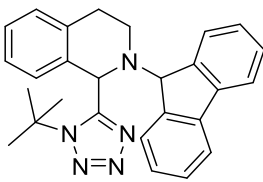
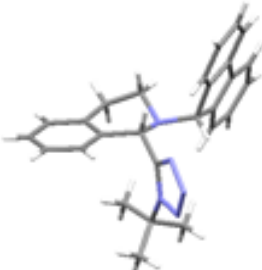
Crystal structures:Crystal data for **5.40c**:

 	
Crystal data and structure refinement for 5.40c CCDC NO 1829737	
Empirical formula	C ₂₂ H ₂₅ N ₅
Formula weight	359.47
Crystal habit, colour	block / colorless
Crystal size, mm ³	0.32* 0.29* 0.25
Temperature, T	296(2)K
Wavelength, λ (Å)	0.71073

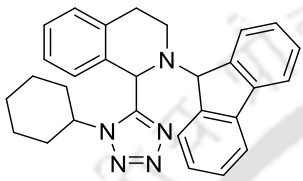
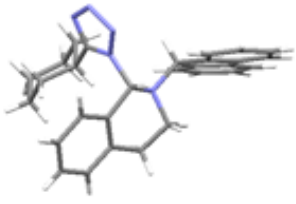
*C-H Functionalization Enabled Stereoselective Ugi-azide Reaction to
α-tetrazolyl Alicyclic Amines*

Crystal system	triclinic
Space group	'P -1'
Unit cell dimensions	$a = 8.1540(14) \text{ \AA}$ $b = 14.767(2) \text{ \AA}$ $c = 16.628(3) \text{ \AA}$ $\alpha = 90.056(11)^\circ, \gamma = 90.188(11)^\circ, \beta = 100.409(11)^\circ$
Volume, $V(\text{\AA}^3)$	1969.2(6)
Z	4
Calculated density, $\text{Mg} \cdot \text{m}^{-3}$	1.212
Absorption coefficient, $\mu(\text{mm}^{-1})$	0.074
$F(000)$	768
θ range for data collection	1.25 ° to 25.00 °
Limiting indices	$-9 \leq h \leq 8, -17 \leq k \leq 17, -19 \leq l \leq 19$
Reflection collected / unique	26548 / 3049 [R(int) = 0.4404]
Completeness to θ	98.0% ($\theta = 25.00^\circ$)
Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	6797 / 0 / 493
Goodness-of-fit on F^2	0.931
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.1109, wR2 = 0.1677$
R indices (all data)	$R1 = 0.3007, wR2 = 0.2542$
Largest diff. peak and hole	0.094 and $-0.515 \text{ e} \cdot \text{\AA}^{-3}$

Chapter 5

Crystal data for 5.43c :	
	
Crystal data and structure refinement for 5.43c CCDC NO 1829738	
Empirical formula	C ₂₇ H ₂₇ N ₅
Formula weight	421.54
Crystal habit, colour	block / colorless
Crystal size, mm ³	0.35 * 0.32 * 0.30
Temperature, <i>T</i>	296(2)K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	'P 21/n'
Unit cell dimensions	$a = 11.3769(3) \text{ \AA}$ $b = 17.6453(5) \text{ \AA}$ $c = 11.4216(3) \text{ \AA}$ $\alpha = 90.00^\circ \gamma = 90.00^\circ \beta = 96.532(2)^\circ$
Volume, <i>V</i> (Å ³)	2277.99(11)
<i>Z</i>	4
Calculated density, Mg·m ⁻³	1.229
Absorption coefficient, μ(mm ⁻¹)	0.075
<i>F</i> (000)	896
θ range for data collection	2.13° to 25.25°
Limiting indices	-13 ≤ <i>h</i> ≤ 13, -21 ≤ <i>k</i> ≤ 21, -13 ≤ <i>l</i> ≤ 13
Reflection collected / unique	31002 / 4096 [<i>R</i> (int) = 0.1741]
Completeness to θ	99.4% (θ = 25.25°)

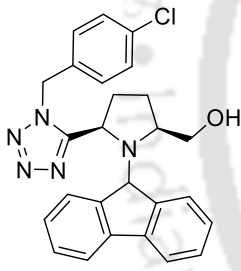
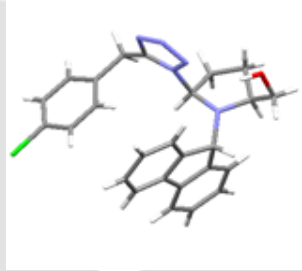
*C-H Functionalization Enabled Stereoselective Ugi-azide Reaction to
α-tetrazolyl Alicyclic Amines*

Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	4096 / 0 / 293
Goodness-of-fit on F^2	1.442
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0492$, $wR2 = 0.0622$
R indices (all data)	$R1 = 0.1581$, $wR2 = 0.1694$
Largest diff. peak and hole	0.038 and $-0.218 \text{ e} \cdot \text{\AA}^{-3}$
 	
Crystal data and structure refinement for 5.43d CCDC NO 1829735	
Empirical formula	C ₂₉ H ₂₉ N ₅
Formula weight	447.57
Crystal habit, colour	block / colorless
Crystal size, mm ³	0.35 * 0.30 * 0.25
Temperature, T	296(2)K
Wavelength, $\lambda(\text{\AA})$	0.71073
Crystal system	triclinic
Space group	'P-1'
Unit cell dimensions	$a = 9.7181(5) \text{ \AA}$ $b = 11.6016(7) \text{ \AA}$ $c = 12.0845(7) \text{ \AA}$ $\alpha = 69.980(4)^\circ$ $\gamma = 71.223(4)^\circ$ $\beta = 78.308(4)^\circ$
Volume, $V(\text{\AA}^3)$	1205.45(12)
Z	2
Calculated density, $\text{Mg} \cdot \text{m}^{-3}$	1.233
Absorption coefficient, $\mu(\text{mm}^{-1})$	0.075

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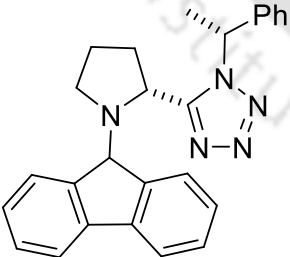
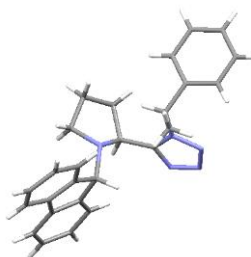
$F(000)$	476
θ range for data collection	1.94 ° to 25.25 °
Limiting indices	$-11 \leq h \leq 11, -13 \leq k \leq 13, -13 \leq l \leq 14$
Reflection collected / unique	17100 / 2854 [$R(\text{int}) = 0.0360$]
Completeness to θ	97.7% ($\theta = 25.25^\circ$)
Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	4265 / 0 / 307
Goodness-of-fit on F^2	0.978
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0599, wR2 = 0.0888$
R indices (all data)	$R1 = 0.1354, wR2 = 0.1544$
Largest diff. peak and hole	0.040 and $-0.369 \text{ e} \cdot \text{\AA}^{-3}$

Crystal data for **5.45d**:

 	
Crystal data and structure refinement for 5.45d CCDC NO 1829745	
Empirical formula	C ₂₆ H ₂₄ Cl N ₅ O
Formula weight	457.95
Crystal habit, colour	block / colorless
Crystal size, mm ³	0.31* 0.22* 0.18
Temperature, T	293(2)K
Wavelength, $\lambda(\text{\AA})$	0.71073
Crystal system	monoclinic
Space group	' $P 21$ '
Unit cell dimensions	$a = 9.5211(10) \text{ \AA}$ $b = 11.9295(7) \text{ \AA}$

	$c = 20.9205(17) \text{ \AA}$
	$\alpha = 90.00^\circ, \gamma = 90.00^\circ, \beta = 100.110(8)^\circ$
Volume, $V(\text{\AA}^3)$	2339.3(3)
Z	4
Calculated density, $\text{Mg} \cdot \text{m}^{-3}$	1.300
Absorption coefficient, $\mu(\text{mm}^{-1})$	0.192
$F(000)$	960
θ range for data collection	2.97° to 25.00°
Limiting indices	$-11 \leq h \leq 11, -14 \leq k \leq 8, -24 \leq l \leq 23$
Reflection collected / unique	9851 / 2769 [$R(\text{int}) = 0.0643$]
Completeness to θ	99.8% ($\theta = 25.00^\circ$)
Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	6254 / 1 / 597
Goodness-of-fit on F^2	0.961
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0723, wR2 = 0.1657$
R indices (all data)	$R1 = 0.0854, wR2 = 0.1806$
Largest diff. peak and hole	0.040 and $-0.369 \cdot \text{\AA}^{-3}$

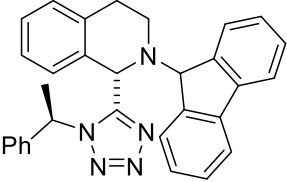
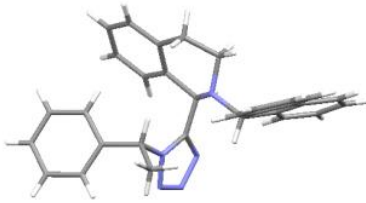
Crystal data for **d-5.49** :

 	
Crystal data and structure refinement for d-5.49 CCDC NO 1829746	
Empirical formula	C ₂₆ H ₂₅ N ₅
Formula weight	407.51
Crystal habit, colour	needle / colorless

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Crystal size, mm ³	0.35* 0.28* 0.21
Temperature, T	293(2)K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	'P 21/c'
Unit cell dimensions	$a = 13.8953(7)\text{Å}$ $b = 9.4127(5)\text{Å}$ $c = 16.8510(8)\text{Å}$ $\alpha = 90.00^\circ, \gamma = 97.186(4)^\circ, \beta = 90.00^\circ$
Volume, V(Å ³)	2186.67(19)
Z	4
Calculated density, Mg·m ⁻³	1.238
Absorption coefficient, μ (mm ⁻¹)	0.075
F(000)	864
θ range for data collection	2.96 ° to 25.00°
Limiting indices	$-16 \leq h \leq 15, -11 \leq k \leq 10, -20 \leq l \leq 19$
Reflection collected / unique	8225 / 2827 [R(int) = 0.0234]
Completeness to θ	99.8% ($\theta = 25.00^\circ$)
Max. and min. transmission	
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	3836 / 0 / 281
Goodness-of-fit on F^2	0.979
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0786, wR2 = 0.1018
R indices (all data)	R1 = 0.2368, wR2 = 0.2200
Largest diff. peak and hole	0.053 and -0.172 e·Å ⁻³
Crystal data for 5.50:	

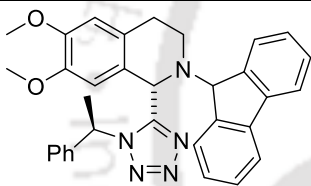
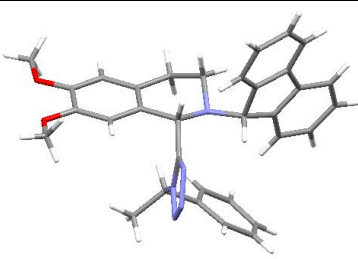
*C-H Functionalization Enabled Stereoselective Ugi-azide Reaction to
α-tetrazolyl Alicyclic Amines*

	
Crystal data and structure refinement for 5.50 CCDC NO	
Empirical formula Formula weight Crystal habit, colour Crystal size, mm³ Temperature, <i>T</i> Wavelength, λ(Å) Crystal system Space group Unit cell dimensions Volume, <i>V</i>(Å³) <i>Z</i> Calculated density, Mg·m⁻³ Absorption coefficient, μ(mm⁻¹) <i>F</i>(000) θ range for data collection Limiting indices Reflection collected / unique Completeness to θ Max. and min. transmission Refinement method	C31 H27 N5 469.58 block / colorless 0.35* 0.27* 0.22 296(2) K 0.71073 monoclinic 'P21/n' <i>a</i> = 13.3835(8)Å <i>b</i> = 10.5702(7) Å <i>c</i> = 17.9182(12) Å α = 90.00 °, γ = 90.00 °, β = 106.349(4)° 2432.3(3) 72 1.329 0.094 1008 1.69 ° to 18.72 ° -12 ≤ <i>h</i> ≤ 12, -9 ≤ <i>k</i> ≤ 9, -15 ≤ <i>l</i> ≤ 16 17176 / 1254 [<i>R</i>(int) 0.3836] 98.5% (θ = 18.7200°) 'SHELXL-97 (Sheldrick, 1997)'

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Data / restraints / parameters	1856 / 0 / 326
Goodness-of-fit on F^2	0.930
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0748$, $wR2 = 0.0992$
R indices (all data)	$R1 = 0.1507$, $wR2 = 0.1731$
Largest diff. peak and hole	0.048 and $-0.235 \text{ \AA}^{-3}$

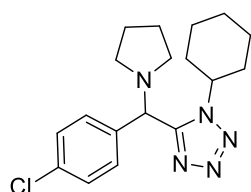
Crystal data for **d-5.51**:

 	
Crystal data and structure refinement for d-5.51 CCDC NO 1829751	
Empirical formula	C ₃₃ H ₃₁ N ₅ O ₂
Formula weight	529.63
Crystal habit, colour	block / colorless
Crystal size, mm ³	0.40* 0.34* 0.25
Temperature, T	296(2) K
Wavelength, $\lambda(\text{\AA})$	0.71073
Crystal system	orthorhombic
Space group	$P 21 21 21'$
Unit cell dimensions	$a = 9.5012(10) \text{ \AA}$ $b = 15.8064(15) \text{ \AA}$

	$c = 18.7456(17) \text{ \AA}$
	$\alpha = 90.00^\circ, \gamma = 90.00^\circ, \beta = 90.00^\circ$
Volume, $V(\text{\AA}^3)$	2815.2(5)
Z	4
Calculated density, $\text{Mg} \cdot \text{m}^{-3}$	1.250
Absorption coefficient, $\mu(\text{mm}^{-1})$	0.080
$F(000)$	1120
θ range for data collection	1.69 ° to 25.00°
Limiting indices	$-11 \leq h \leq 11, -18 \leq k \leq 17, -22 \leq l \leq 22$
Reflection collected / unique	29404 / 3377 [$R(\text{int}) = 0.0490$]
Completeness to θ	100.0% ($\theta = 25.00^\circ$)
Max. and min. transmission	1.69/ 25.00
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	4964 / 0 / 364
Goodness-of-fit on F^2	0.950
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0434, wR2 = 0.0670$
R indices (all data)	$R1 0.0880, wR2 = 0.0972$
Largest diff. peak and hole	0.036 and $-0.161 \text{ e} \cdot \text{\AA}^{-3}$

General procedure I: Isocyanide derivative (0.13 mmol, 1 equiv) and trimethylsilyl azide (0.13 mmol, 1 equiv) were added to the solution of aldehyde or ketone or imine (0.15 mmol, 1.2 equiv) and *N*-heterocycle (0.38 mmol, 3 equiv) in methanol (2 mL) and the mixture was stirred at 100 °C (oil bath temperature) for 10 - 24 hours. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography to obtain analytically pure α-tetrazolyl *N*-heterocycle.

5-((4-chlorophenyl)(pyrrolidin-1-yl)methyl)-1-cyclohexyl-1H-tetrazole(5.37a): According

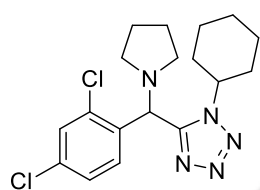


to the general procedure I : *para*-chlorobenzaldehyde (0.15 mmol, 1.2 equiv, 21 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and cyclohexyl isocyanide (0.13 mmol, 1 equiv, 16μL) in 2 mL methanol were reacted for 12 hours.

The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:10) to obtain **5.37a** as white solid (46 mg, 95%). FTIR (KBr): $\tilde{\nu} = 3423, 3096, 2935, 2861, 2789,$

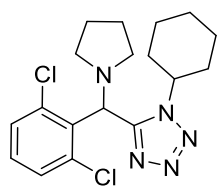
1564, 1586, 1468, 1262, 1093, 859, 825, 803, 749 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.43 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.96 (s, 1H), 4.63 – 4.55 (m, 1H), 2.65 – 2.60 (m, 2H), 2.43 – 2.38 (m, 2H), 2.01 – 1.92 (m, 2H), 1.84 – 1.80 (m, 5H), 1.77 – 1.70 (m, 2H), 1.47 – 1.44 (m, 1H), 1.38 – 1.22 (m, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ = 154.1, 135.9, 134.4, 129.6, 129.1, 64.0, 58.2, 53.1, 33.1, 32.9, 25.7, 25.5, 25.0, 23.7 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{18}\text{H}_{25}\text{ClN}_5^+([\text{M}+\text{H}]^+)$: 346.1793, found: 346.1794.

1-cyclohexyl-5-((2,4-dichlorophenyl)(pyrrolidin-1-yl)methyl)-1H-tetrazole(5.37b):



According to the general procedure I : 2,4-dichlorobenzaldehyde (0.15 mmol, 1.2 equiv, 26 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and cyclohexyl isocyanide (0.13 mmol, 1 equiv, 16 μL) in 2 mL methanol were reacted for 14 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:10) to obtain **5.37b** as white solid (46 mg, 94%). FTIR (KBr): $\tilde{\nu}$ = 3423, 3096, 3063, 1564, 1586, 1468, 1450, 1262, 1093, 825, 803, 749, 695 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.81 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.31 – 7.30 (m, 1H), 5.37 (s, 1H), 4.44 – 4.39 (m, 1H), 2.56 – 2.51 (m, 4H), 2.02 – 1.93 (m, 2H), 1.91 – 1.87 (m, 3H), 1.86 – 1.79 (m, 4H), 1.76 – 1.74 (m, 1H), 1.63 – 1.59 (m, 1H), 1.46 – 1.25 (m, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 154.8, 136.0, 134.8, 134.5, 133.2, 130.5, 129.3, 59.7, 59.2, 53.6, 34.1, 26.6, 25.9, 24.5 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{18}\text{H}_{24}\text{Cl}_2\text{N}_5^+([\text{M}+\text{H}]^+)$: 380.1403, found: 380.1410.

1-cyclohexyl-5-((2,6-dichlorophenyl)(pyrrolidin-1-yl)methyl)-1H-tetrazole (5.37c):

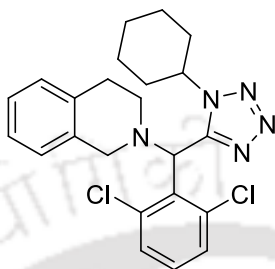
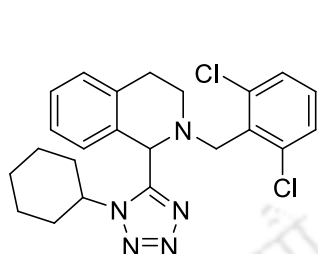


According to the general procedure I : 2,6-dichlorobenzaldehyde (0.15 mmol, 1.2 equiv, 26 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and cyclohexyl isocyanide (0.13 mmol, 1 equiv, 16 μL) in 2 mL methanol were reacted for 14 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:10) to obtain **5.37c** as white solid (46 mg, 94%). FTIR (KBr): $\tilde{\nu}$ = 3448, 3117, 3062, 2982, 2951, 2939, 2810, 1572, 1557, 1429, 1415, 1185, 1165, 880, 795, 746, 675, 425 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.39 – 7.37 (m, 2H), 7.28 – 7.27 (m, 1H), 5.83 (s, 1H), 3.84 – 3.79 (m, 1H), 3.01 – 2.98 (m, 2H), 2.74 – 2.71 (m, 2H), 2.01 – 1.97 (m, 2H), 1.92 – 1.83 (m, 4H), 1.77 – 1.73 (m, 2H), 1.69 – 1.62 (m, 2H), 1.32 – 1.20 (m, 2H), 1.14 – 1.10 (m, 1H), 0.92 – 0.84 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 153.4, 136.7, 132.2, 130.6, 129.9, 59.5,

58.2, 52.1, 33.1, 32.6, 25.7, 25.5, 24.9, 23.7 ppm. HRMS (ESI) exact mass calculated for $C_{18}H_{24}Cl_2N_5^+([M+H]^+)$: 380.1403, found: 380.1393.

2-((1-cyclohexyl-1H-tetrazol-5-yl)(2,6-dichlorophenyl)methyl)-

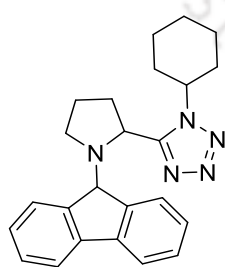
1,2,3,4-tetrahydroisoquinoline and 1-(1-cyclohexyl-1H-tetrazol-5-yl)-2-(2,6-dichlorobenzyl)-1,2,3,4-tetrahydroisoquinoline (5.38a and 5.38b): According to the general



procedure I : 2,6-dichlorobenzaldehyde (0.15 mmol, 1.2 equiv, 26 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and cyclohexyl

isocyanide (0.13 mmol, 1 equiv, 17 μ L) in 2 mL methanol were reacted for 14 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:6) to obtain an inseparable mixture of **5.38a** and **5.38b** as white solid (57 mg, 99%). Characteristic signals of both the isomer are mentioned 1H NMR (600 MHz, $CDCl_3$) δ = 5.98 (s, 1.4H), 5.44 (s, 1H), 4.15 (d, J = 15.0 Hz, 1H), 4.09 – 4.08 (m, 1H), 4.06 (d, J = 9.1 Hz, 1H), 3.94 (d, J = 12.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 155.1, 152.9, 137.3, 136.9, 135.0, 134.6, 134.3, 133.5, 132.3, 131.6, 130.8, 130.1, 129.6, 129.1, 128.8, 128.7, 128.2, 127.8, 126.9, 126.7, 126.2, 125.7, 61.1, 58.9, 58.4, 58.1, 54.2, 52.8, 48.5, 47.6, 33.2, 32.6, 32.4, 29.7, 28.3, 25.7, 25.6, 25.50, 25.46, 25.0, 24.9 ppm. HRMS (ESI) exact mass calculated for $C_{23}H_{26}Cl_2N_5^+([M+H]^+)$: 442.1560, found: 442.1549.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-cyclohexyl-1H-tetrazole (5.40a): According to the

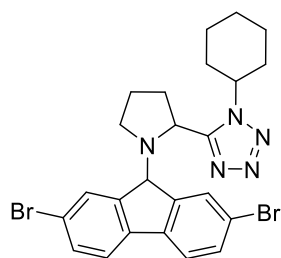


general procedure I : 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and cyclohexyl isocyanide (0.13 mmol, 1 equiv, 16 μ L) in 2 mL methanol were reacted for 24 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:5) to obtain **5.40a** as light yellow solid (50 mg, 99.9%). FTIR (KBr): $\tilde{\nu}$ = 3064,

2947, 2853, 2807, 1450, 1442, 1302, 1263, 1181, 1158, 1137, 1101, 1075, 1006, 899, 789, 747, 676, 620 cm^{-1} . 1H NMR (600 MHz, $CDCl_3$) δ = 7.68 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 7.8 Hz, 2H), 7.51 (d, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.22 – 7.19 (m, 1H), 4.75 (s, 1H), 4.70 (t, J = 7.8 Hz, 1H), 4.60 – 4.55 (m, 1H), 2.93 – 2.89 (m, 1H), 2.47 – 2.43 (m, 1H), 2.28 – 2.22 (m, 1H), 2.06 – 1.98 (m, 6H), 1.94 – 1.90 (m, 1H), 1.84 – 1.83

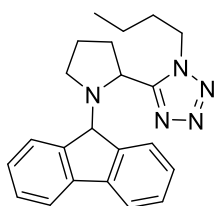
(m, 1H), 1.81 – 1.78 (m, 2H), 1.49 – 1.44 (m, 1H), 1.39 – 1.33 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.1, 144.3, 142.2, 141.1, 140.9, 128.64, 128.61, 127.6, 127.4, 127.0, 125.1, 120.1, 119.9, 64.1, 58.0, 54.7, 48.0, 33.8, 33.1, 32.0, 25.6, 25.1, 23.1 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{24}\text{H}_{28}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 386.2339, found: 386.2336.

1-cyclohexyl-5-(1-(2,7-dibromo-9H-fluoren-9-yl)pyrrolidin-2-yl)-1H-tetrazole (5.40ca):



According to the general procedure I: 2,7-dibromo-9-fluorenone (0.15 mmol, 1.2 equiv, 50 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and cyclohexyl isocyanide (0.13 mmol, 1 equiv, 16 μL) in 2 mL methanol were reacted for 36 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:4) to obtain **5.40ca** as light yellow solid (22 mg, 31%). FTIR (KBr): $\tilde{\nu}$ = 3448, 2853, 1560, 1450, 1442, 1263, 1158, 899, 789, 676 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.81 (s, 1H), 7.59 (s, 1H), 7.51 – 7.50 (m, 4H), 4.86 – 4.83 (m, 1H), 4.77 – 4.73 (m, 1H), 4.68 (s, 1H), 2.78 – 2.77 (m, 1H), 2.39 – 2.28 (m, 2H), 2.23 – 2.17 (m, 1H), 2.11 – 1.93 (m, 8H), 1.85 – 1.84 (m, 2H), 1.59 – 1.55 (m, 1H), 1.47 – 1.39 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ = 154.4, 146.2, 144.1, 139.4, 138.6, 132.1, 132.0, 129.9, 128.4, 122.0, 121.8, 121.49, 121.48, 63.6, 58.4, 55.6, 47.2, 33.8, 33.6, 31.6, 25.8, 25.7, 25.1, 23.0. HRMS (ESI) exact mass calculated for $\text{C}_{24}\text{H}_{26}\text{Br}_2\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 542.0549, found: 542.0550.

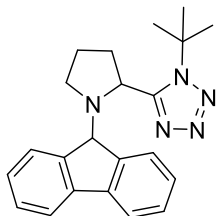
5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-butyl-1H-tetrazole(5.40b):



According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and *n*-butyl isocyanide (0.13 mmol, 1 equiv, 16 μL) in 2 mL methanol were reacted for 20 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:3) to obtain **5.40b** as white solid (33 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 2958, 2871, 1966, 1438, 1301, 1200, 1159, 946, 830, 748, 677 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.69 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.41 – 7.39 (m, 1H), 7.32 – 7.30 (m, 2H), 7.17 – 7.14 (m, 1H), 4.85 (s, 1H), 4.51 – 4.48 (m, 1H), 4.33 – 4.28 (m, 1H), 4.10 – 4.05 (m, 1H), 3.12 – 3.08 (m, 1H), 2.76 – 2.72 (m, 1H), 2.26 – 2.20 (m, 1H), 2.10 – 2.05 (m, 1H), 1.95 – 1.92 (m, 1H), 1.88 – 1.85 (m, 1H), 1.83 – 1.78 (m, 2H), 1.37 – 1.34 (m, 2H), 0.94 (t, J =

7.4 Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 156.4, 144.1, 142.6, 141.1, 140.9, 128.7, 128.6, 127.6, 127.4, 126.6, 125.5, 120.1, 119.9, 64.5, 53.8, 49.3, 47.2, 32.2, 32.0, 23.7, 20.1, 13.7 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{22}\text{H}_{26}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 360.2183, found: 360.2182.

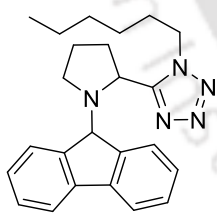
5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(tert-butyl)-1H-tetrazole(5.40c): According to the



general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and *tert*-butyl isocyanide (0.13 mmol, 1 equiv, 16 μL) in 2 mL methanol were reacted for 20 hours. The crude product was purified

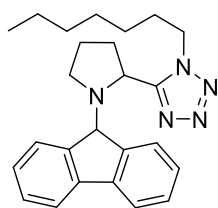
by SiO_2 column chromatography (ethyl acetate: hexane; 1:3) to obtain **5.40c** as light yellow solid (40 mg, 86%). FTIR (KBr): $\tilde{\nu}$ = ^1H NMR (600 MHz, CDCl_3) δ = 7.81 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.23 – 7.21 (t, J = 7.4 Hz, 1H), 7.10 – 7.03 (m, 1H), 5.14 (s, 1H), 4.24 – 4.22 (m, 1H), 3.63 – 3.61 (m, 1H), 3.43 – 3.38 (m, 1H), 2.34 – 2.28 (m, 1H), 2.15 – 2.11 (m, 1H), 1.96 – 1.93 (m, 1H), 1.73 – 1.7 (m, 1H), 1.29 (s, 9H). ^{13}C NMR (151 MHz, CDCl_3) δ = 159.7, 144.7, 143.8, 141.2, 140.4, 128.6, 128.3, 127.5, 127.2, 126.7, 126.2, 119.9, 119.7, 65.6, 60.4, 54.2, 52.0, 34.6, 29.8, 24.3 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{22}\text{H}_{26}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 360.2183, found: 360.2175.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-hexyl-1H-tetrazole(5.40d): According to the



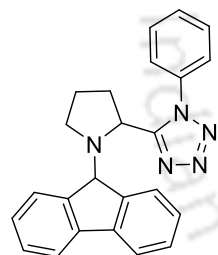
general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and *n*-hexyl isocyanide (0.13 mmol, 1 equiv, 14 mg) in 2 mL methanol were reacted for 14 hours. The crude product was purified

by SiO_2 column chromatography (ethyl acetate: hexane; 1:4) to obtain **5.40d** as brown solid (27 mg, 64 %). ^1H NMR (600 MHz, CDCl_3) δ = 7.70 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.33 – 7.30 (m, 2H), 7.17 – 7.14 (m, 1H), 4.86 (s, 1H), 4.51 – 4.49 (m, 1H), 4.31 – 4.27 (m, 1H), 4.09 – 4.04 (m, 1H), 3.13 – 3.08 (m, 1H), 2.77 – 2.72 (m, 1H), 2.26 – 2.22 (m, 1H), 2.12 – 2.04 (m, 1H), 1.95 – 1.91 (m, 1H), 1.89 – 1.82 (m, 3H), 1.33 – 1.28 (m, 6H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 156.4, 144.1, 142.6, 141.1, 140.9, 128.7, 128.6, 127.6, 127.4, 126.6, 125.6, 120.1, 119.9, 64.5, 53.8, 49.3, 47.5, 32.2, 31.3, 30.0, 26.5, 23.7, 22.6, 14.2. HRMS (ESI) exact mass calculated for $\text{C}_{24}\text{H}_{30}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 388.2496, found: 388.2500.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-heptyl-1H-tetrazole (5.40e):

general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and *n*-heptyl isocyanide (0.13 mmol, 1 equiv, 16 mg) in 2 mL methanol were reacted for 14 hours. The crude product was purified

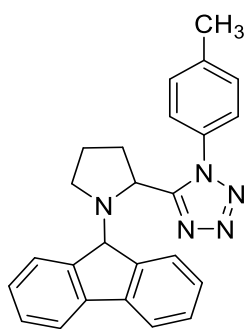
by SiO₂ column chromatography (ethyl acetate: hexane; 1:4) to obtain **5.40e** as brown solid. (34 mg, 64 %) FTIR (KBr): $\tilde{\nu}$ = 3065, 2951, 2927, 2860, 1449, 1301, 736, 673, 621 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.69 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.41 – 7.39 (m, 1H), 7.32 – 7.30 (m, 2H), 7.17 – 7.14 (m, 1H), 4.84 (s, 1H), 4.52 – 4.49 (m, 1H), 4.32 – 4.27 (m, 1H), 4.10 – 4.05 (m, 1H), 3.12 – 3.07 (m, 1H), 2.75 – 2.71 (m, 1H), 2.26 – 2.20 (m, 1H), 2.10 – 2.04 (m, 1H), 1.95 – 1.91 (m, 1H), 1.87 – 1.81 (m, 3H), 1.34 – 1.25 (m, 8H), 0.88 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 156.3, 144.1, 142.6, 141.0, 140.9, 128.7, 128.6, 127.5, 127.4, 126.5, 125.5, 120.1, 119.9, 64.5, 53.9, 49.2, 47.5, 32.1, 31.7, 30.0, 28.8, 26.8, 23.7, 22.7, 14.2 ppm. HRMS (ESI) exact mass calculated for C₂₅H₃₂N₅⁺ ([M+H]⁺): 402.2652, found: 402.2646.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-phenyl-1H-tetrazole(5.40f):

general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and phenyl isocyanide (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 14 hours 16 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) to

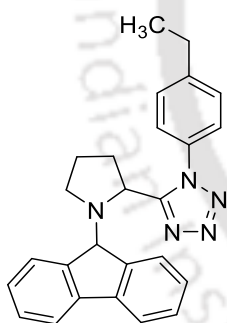
obtain **5.40f** as brown solid (32 mg, 64 %). FTIR (KBr): $\tilde{\nu}$ = ¹H NMR (400 MHz, CDCl₃) δ = 7.58 – 7.53 (m, 2H), 7.50 – 7.42 (m, 4H), 7.34 – 7.27 (m, 3H), 7.23 – 7.19 (m, 3H), 7.12 – 7.08 (m, 1H), 4.94 (s, 1H), 4.35 – 4.32 (m, 1H), 3.23 – 3.17 (m, 1H), 2.89 – 2.83 (m, 1H), 2.14 – 2.03 (m, 2H), 1.99 – 1.95 (m, 1H), 1.84 – 1.82 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 158.2, 144.1, 143.2, 140.85, 140.82, 134.0, 130.4, 129.6, 128.45, 128.43, 127.4, 127.2, 126.3, 125.7, 125.6, 119.9, 119.8, 64.9, 53.2, 50.2, 32.5, 24.1 (one aromatic carbon is merging in aromatic region) ppm. HRMS (ESI) exact mass calculated for C₂₄H₂₂N₅⁺ ([M+H]⁺): 380.1870, found: 380.1859.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(p-tolyl)-1H-tetrazole(5.40g): According to the

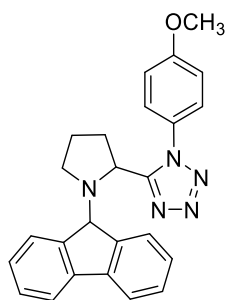


general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and *p*-methylphenyl isocyanide (0.13 mmol, 1 equiv, 15 mg) in 2 mL methanol were reacted for 12 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) to obtain **5.40g** as brown solid (35 mg, 69 %). FTIR (KBr): $\tilde{\nu}$ = 2924, 2853, 1644, 1516, 1448, 1384, 1124, 1098, 822, 745, 669 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.59 (d, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.33 – 7.28 (m, 3H), 7.24 – 7.21 (m, 3H), 7.11 – 7.07 (m, 3H), 4.93 (s, 1H), 4.36 – 4.34 (m, 1H), 3.16 – 3.13 (m, 1H), 2.83 – 2.79 (m, 1H), 2.43 (s, 3H), 2.12 – 2.02 (m, 2H), 1.97 – 1.93 (m, 1H), 1.82 – 1.77 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 158.1, 144.2, 143.2, 140.9, 140.8, 140.7, 131.5, 130.1, 128.4, 128.3, 127.4, 127.2, 126.4, 125.7, 125.4, 119.9, 119.8, 64.8, 53.4, 49.9, 32.4, 24.1, 21.4. HRMS (ESI) exact mass calculated for C₂₅H₂₄N₅⁺ ([M+H]⁺): 394.2026, found: 394.2027.

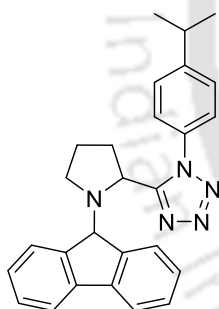
5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(4-ethylphenyl)-1H-tetrazole (5.40h): According



to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and *p*-ethylphenyl isocyanide (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 12 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) to obtain **5.40h** as brown solid (36 mg, 68 %). FTIR (KBr): $\tilde{\nu}$ = 3036, 2963, 2848, 1959, 1518, 1448, 1369, 1320, 1237, 1151, 1100, 1073, 841, 746, 729, 612, 565 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.57 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.29 (m, 3H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.11 – 7.08 (m, 3H), 4.91 (s, 1H), 4.37 – 4.35 (m, 1H), 3.16 – 3.13 (m, 1H), 2.82 – 2.78 (m, 1H), 2.74 – 2.70 (m, 2H), 2.15 – 2.01 (m, 2H), 2.00 – 1.96 (m, 1H), 1.83 – 1.79 (m, 1H), 1.29 (t, *J* = 7.8 Hz, 3H). ¹³C NMR (151 MHz, CDCl₃) δ = 158.0, 146.9, 144.3, 143.2, 140.9, 140.8, 131.7, 128.9, 128.4, 127.4, 127.2, 126.4, 125.7, 125.5, 119.9, 119.8, 64.8, 53.4, 49.8, 32.5, 28.8, 24.0, 15.6 ppm. (Total count of ¹³C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for C₂₆H₂₆N₅⁺ ([M+H]⁺): 408.2183, found: 408.2184.

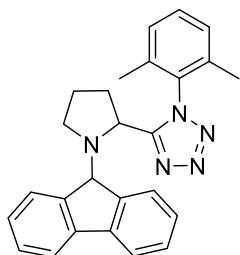
5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(4-methoxyphenyl)-1H-tetrazole (5.40i):

According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and *p*-methoxyphenyl isocyanide (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 16 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) gave **5.40i** as light yellow solid (42 mg, 82 %). FTIR (KBr): $\tilde{\nu}$ = 3401, 2924, 2853, 1609, 1444, 1256, 1023, 823, 743 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.53 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.26 (m, 1H), 7.25 – 7.22 (d, *J* = 8.1 Hz, 2H), 7.18 – 7.16 (m, 1H), 7.06 – 7.03 (m, 3H), 6.86 – 6.85 (m, 2H), 4.88 (s, 1H), 4.27 – 4.25 (m, 1H), 3.80 (s, 3H), 3.11 – 3.08 (m, 1H), 2.78 – 2.74 (m, 1H), 2.05 – 1.94 (m, 2H), 1.90 – 1.86 (m, 1H), 1.76 – 1.71 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 160.9, 158.2, 144.2, 143.2, 140.9, 140.8, 128.4, 127.5, 127.2, 127.0, 126.7, 126.4, 125.8, 119.9, 119.8, 114.6, 6.83, 55.9, 53.3, 49.9, 32.3, 24.1. HRMS (ESI) exact mass calculated for C₂₅H₂₄N₅O⁺ ([M+H]⁺): 410.1975, found: 410.1978.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(4-isopropylphenyl)-1H-tetrazole (5.40j):

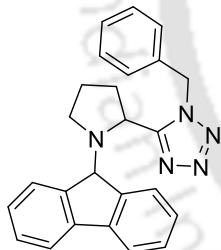
According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and *para*-isopropyl phenyl isocyanide (0.13 mmol, 1 equiv, 19 mg) in 2 mL methanol were reacted for 16 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:4) to obtain **5.40j** as brown solid (33 mg, 60 %). FTIR (KBr): $\tilde{\nu}$ = 3061, 3035, 2961, 2926, 2847, 1956, 1913, 1585, 1514, 1445, 1364, 1206, 1128, 1099, 840, 746, 668, 574 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 7.57 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.27 (m, 5H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.10 – 7.07 (m, 3H), 4.91 (s, 1H), 4.33 – 4.29 (m, 1H), 3.20 – 3.16 (m, 1H), 3.02 – 2.95 (m, 1H), 2.87 – 2.80 (m, 1H), 2.17 – 2.05 (m, 2H), 2.03 – 1.98 (m, 1H), 1.86 – 1.81 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 6H). ¹³C NMR (151 MHz, CDCl₃) δ = 158.1, 151.5, 144.2, 143.1, 140.83, 140.78, 131.6, 128.4, 127.5, 127.4, 127.2, 126.3, 125.7, 125.5, 119.9, 119.7, 64.7, 53.2, 50.0, 34.2, 32.6, 24.1, 24.1, 24.0 ppm. (Total count of ¹³C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for C₂₇H₂₈N₅⁺ ([M+H]⁺): 422.2339, found: 422.2340.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(2,6-dimethylphenyl)-1H-tetrazole (5.40k):

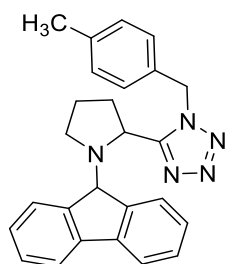


According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 2,6-dimethylphenyl isocyanide (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 16 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) to obtain **5.40k** as white solid (30 mg, 57 %). FTIR (KBr): $\tilde{\nu}$ = 3069, 2918, 2815, 1471, 1449, 1100, 748, 622 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.68 – 7.66 (m, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.31 – 7.29 (m, 1H), 7.28 – 7.27 (m, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.16 – 7.14 (m, 1H), 7.12 – 7.1 (m, 1H), 4.80 (s, 1H), 4.54 – 4.51 (m, 1H), 2.72 – 2.69 (m, 1H), 2.22 – 2.18 (m, 1H), 2.14 – 2.09 (m, 2H), 2.05 (s, 3H), 1.99 – 1.92 (m, 1H), 1.88 (s, 3H), 1.66 – 1.62 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 159.0, 144.8, 143.5, 141.9, 139.9, 136.1, 136.0, 132.4, 131.2, 129.2, 129.1, 128.5, 128.4, 127.8, 126.9, 126.1, 125.7, 120.3, 119.6, 64.7, 55.6, 46.8, 32.2, 23.9, 17.9, 17.7. HRMS (ESI) exact mass calculated for C₂₆H₂₆N₅⁺ ([M+H]⁺): 408.2183, found: 408.2184.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-benzyl-1H-tetrazole (5.40l):

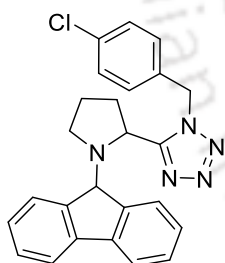


According to general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and benzyl isocyanide (0.13 mmol, 1 equiv, 15 mg) in 2 mL methanol heating at methanol were reacted for 20 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) to obtain **5.40l** as brown solid (37 mg, 73 %). FTIR (KBr): $\tilde{\nu}$ = 3399, 2959, 2925, 1654, 1406, 1248, 1181, 747, 620 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.73 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.32 – 7.30 (m, 2H), 7.29 – 7.27 (m, 3H), 7.16 – 7.13 (m, 1H), 7.00 – 6.99 (m, 2H), 5.71 (d, J = 15.0 Hz, 1H), 5.11 (d, J = 15.0 Hz, 1H), 4.89 (s, 1H), 4.41 – 4.36 (m, 1H), 3.15 – 3.12 (m, 1H), 2.79 – 2.75 (m, 1H), 1.99 – 1.89 (m, 2H), 1.76 – 1.72 (m, 1H), 1.64 – 1.58 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 157.0, 144.1, 142.7, 141.1, 140.8, 134.4, 129.2, 128.8, 128.7, 128.6, 127.6, 127.5, 127.3, 126.5, 125.7, 120.2, 119.9, 64.7, 53.6, 50.8, 49.8, 31.8, 23.7. HRMS (ESI) exact mass calculated for C₂₅H₂₄N₅⁺ ([M+H]⁺): 394.2026, found: 394.2019.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(4-methylbenzyl)-1H-tetrazole (5.40m):

According to general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 1-(isocyanomethyl)-4-methylbenzene (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 16 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) to obtain **5.40m** as brown solid (43 mg, 82 %).

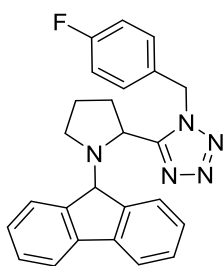
FTIR (KBr): $\tilde{\nu}$ = 3064, 2924, 2854, 1730, 1654, 1447, 1299, 1249, 1182, 1022, 813, 734, 673, 620, 475 cm^{-1} . ¹H NMR (400 MHz, CDCl₃) δ = 7.72 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.33 – 7.30 (m, 2H), 7.15 – 7.12 (m, 1H), 7.08 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 5.64 (d, J = 15.6 Hz, 1H), 5.08 (d, J = 15.6 Hz, 1H), 4.89 (s, 1H), 4.41 – 4.37 (m, 1H), 3.15 – 3.10 (m, 1H), 2.79 – 2.72 (m, 1H), 2.29 (s, 3H), 2.01 – 1.87 (m, 2H), 1.77 – 1.71 (m, 1H), 1.66 – 1.59 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 156.9, 144.1, 142.7, 141.1, 140.8, 138.6, 131.3, 129.8, 128.7, 128.6, 127.6, 127.4, 127.3, 126.5, 125.7, 120.1, 119.9, 64.6, 53.7, 50.6, 49.7, 31.8, 23.6, 21.3 ppm. HRMS (ESI) exact mass calculated for C₂₆H₂₆N₅⁺ ([M+H]⁺): 408.2183, found: 408.2180.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(4-chlorobenzyl)-1H-tetrazole (5.40n):

to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 1-chloro-4-(isocyanomethyl)benzene (0.13 mmol, 1 equiv, 20 mg) in 2 ml methanol were reacted for 14 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:4) to obtain **5.40n** as brown solid (37 mg, 66 %).

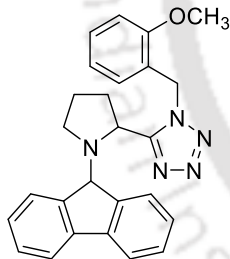
FTIR (KBr): $\tilde{\nu}$ = 3063, 2953, 2924, 2853, 1493, 1449, 1411, 1113, 1017, 771, 735, 498 cm^{-1} . ¹H NMR (600 MHz, CDCl₃) δ = 7.73 (d, J = 7.2 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.44 – 7.42 (m, 2H), 7.33 – 7.30 (m, 2H), 7.27 – 7.25 (m, 2H), 7.16 – 7.13 (m, 1H), 6.93 (d, J = 8.4 Hz, 2H), 5.66 (d, J = 15.6 Hz, 1H), 5.07 (d, J = 15.0 Hz, 1H), 4.90 (s, 1H), 4.36 – 4.34 (m, 1H), 3.18 – 3.15 (m, 1H), 2.83 – 2.79 (m, 1H), 2.00 – 1.93 (m, 2H), 1.80 – 1.76 (m, 1H), 1.64 – 1.57 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 157.0, 143.9, 142.6, 141.1, 140.8, 134.8, 132.8, 129.4, 128.9, 128.8, 128.7, 127.7, 127.5, 126.5, 125.7, 120.2, 120.0, 64.7, 53.5, 50.1, 50.0, 31.9, 23.7 ppm. HRMS (ESI) exact mass calculated for C₂₅H₂₃ClN₅⁺ ([M+H]⁺): 428.1636, found: 428.1637.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(4-fluorobenzyl)-1H-tetrazole (5.40o): According

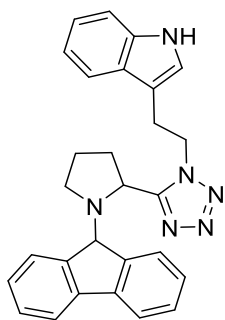


to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 1-fluoro-4-(isocyanomethyl)benzene (0.13 mmol, 1 equiv, 18 mg) in 2 mL methanol were reacted for 14 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) to obtain **5.40o** as brown solid (33 mg, 62 %). FTIR (KBr): $\tilde{\nu}$ = 3067, 2957, 2926, 2877, 2818, 1606, 1510, 1449, 1224, 1165, 832, 776, 533, 495 cm^{-1} . ¹H NMR (600 MHz, CDCl₃) δ = 7.74 (d, J = 7.2 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.33 – 7.31 (m, 2H), 7.15 (t, J = 7.2 Hz, 1H), 7.01 – 6.96 (m, 4H), 5.65 (d, J = 15.6 Hz, 1H), 5.05 (d, J = 15.6 Hz, 1H), 4.90 (s, 1H), 4.36 – 4.34 (m, 1H), 3.21 – 3.15 (m, 1H), 2.84 – 2.80 (m, 1H), 2.01 – 1.90 (m, 2H), 1.81 – 1.76 (m, 1H), 1.63 – 1.58 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 164.1, 161.63, 156.9, 144.0, 142.7, 141.2, 140.8, 129.4, 129.3, 128.8, 128.7, 127.6, 127.5, 126.5, 125.7, 120.2, 119.9, 116.3, 116.1, 64.8, 53.6, 50.1, 50.0, 32.0, 23.7. HRMS (ESI) exact mass calculated for C₂₅H₂₃FN₅⁺ ([M+H]⁺): 412.1932, found: 412.1940.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(2-methoxybenzyl)-1H-tetrazole (5.40p):

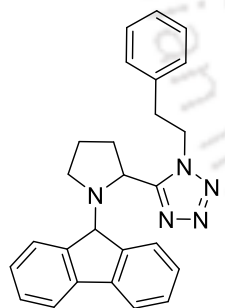


According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 1-(isocyanomethyl)-2-methoxybenzene (0.13 mmol, 1 equiv, 19 mg) in 2 mL methanol were reacted for 14 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:4) to obtain **5.40p** as brown solid (36 mg, 65 %). FTIR (KBr): $\tilde{\nu}$ = 3065, 2951, 2927, 2860, 1449, 1301, 736, 673, 621 cm^{-1} . ¹H NMR (600 MHz, CDCl₃) δ = 7.71 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.44 – 7.41 (m, 1H), 7.40 (d, J = 7.2 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.27 – 7.24 (m, 1H), 7.16 – 7.13 (m, 1H), 6.86 – 6.81 (m, 3H), 5.56 (d, J = 15.6 Hz, 1H), 5.18 (d, J = 15.6 Hz, 1H), 4.93 (s, 1H), 4.45 – 4.48 (m, 1H), 3.70 (s, 3H), 3.14 – 3.11 (m, 1H), 2.78 – 2.74 (m, 1H), 2.01 – 1.97 (m, 2H), 1.77 – 1.73 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 157.2, 156.7, 144.5, 143.0, 141.1, 141.0, 130.1, 129.1, 128.62, 128.58, 127.5, 127.4, 126.5, 125.9, 122.8, 121.2, 120.1, 119.9, 110.8, 64.8, 55.5, 53.8, 49.5, 46.0, 32.0, 23.8 ppm. HRMS (ESI) exact mass calculated for C₂₆H₂₆N₅O⁺ ([M+H]⁺): 424.2132, found 424.2134.

3-(2-(5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1H-tetrazol-1-yl)ethyl)-1H-indole (5.40q):

According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 3-(2-isocyanoethyl)-1H-indole (0.13 mmol, 1 equiv, 22 mg) in 2 mL methanol were reacted for 14 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:4) to obtain **5.40q** as brown solid (46 mg, 80 %). FTIR (KBr): $\tilde{\nu}$ = 3229, 3057, 2919, 2860, 1620, 1451, 1361, 1103, 742, 621 cm⁻¹.

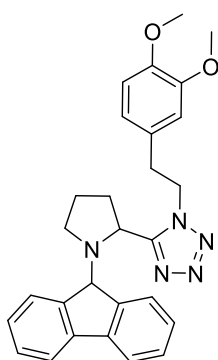
¹H NMR (400 MHz, CDCl₃) δ = 8.32 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.33 – 7.27 (m, 3H), 7.19 – 7.15 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.58 (s, 1H), 4.82 (s, 1H), 4.32 – 4.25 (m, 1H), 3.92 – 3.84 (m, 1H), 3.61 – 3.58 (m, 1H), 3.20 – 3.13 (m, 3H), 2.90 – 2.83 (m, 1H), 1.92 – 1.84 (m, 1H), 1.60 – 1.52 (m, 1H), 1.23 – 1.09 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 158.0, 144.1, 143.1, 141.0, 140.4, 136.5, 128.7, 128.5, 127.6, 127.4, 126.6, 126.2, 125.9, 123.0, 122.4, 120.0, 119.9, 119.7, 118.0, 111.6, 110.2, 64.9, 52.0, 50.9, 47.0, 31.7, 26.4, 24.0 ppm. HRMS (ESI) exact mass calculated for C₂₈H₂₇N₆⁺ ([M+H]⁺): 447.2292, found: 447.2299.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-phenethyl-1H-tetrazole (5.40r):

According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and (2-isocyanoethyl)benzene (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 24 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) to obtain **5.40r** as light yellow solid (39 mg, 73 %). FTIR (KBr): $\tilde{\nu}$ = 3065, 2923, 1695, 1403, 1104, 743, 668 cm⁻¹.

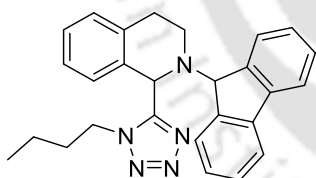
¹H NMR (400 MHz, CDCl₃) δ = 7.72 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.36 – 7.33 (m, 1H), 7.32 – 7.30 (m, 2H), 7.21 – 7.20 (m, 3H), 7.13 – 7.10 (m, 1H), 6.89 – 6.87 (m, 2H), 4.84 (s, 1H), 4.44 – 4.39 (m, 1H), 4.01 – 3.95 (m, 2H), 3.19 – 3.15 (m, 1H), 3.10 – 3.01 (m, 2H), 2.87 – 2.83 (m, 1H), 2.06 – 1.98 (m, 1H), 1.78 – 1.74 (m, 2H), 1.45 – 1.39 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 157.3, 144.1, 142.9, 141.1, 140.6, 136.8, 129.1, 128.8, 128.7, 128.6, 127.5, 127.45, 127.34, 126.3, 125.7, 120.1, 119.9, 64.8, 52.8, 50.4, 48.4, 36.3, 32.0, 24.0 ppm. HRMS (ESI) exact mass calculated for C₂₆H₂₆N₅⁺ ([M+H]⁺): 408.2183, found: 408.2176.

5-(1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-(3,4-dimethoxyphenethyl)-1H-tetrazole (5.40s):



According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.38 mmol, 3 equiv, 31 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (0.123 mmol, 1equiv, 25 mg) in 2 mL methanol were reacted for 24 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:3) gave **5.40s** as light yellow solid (39 mg, 64 %). FTIR (KBr): $\tilde{\nu}$ = 2962, 2927, 1649, 1418, 1261, 1030, 802, 742, 674, cm^{-1} . ¹H NMR (600 MHz, CDCl₃) δ = 7.71 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.31 – 7.29 (m, 2H), 7.13 – 7.11 (m, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.41 – 6.40 (m, 1H), 6.31 (s, 1H), 4.81 (s, 1H), 4.41 – 4.37 (m, 1H), 4.01 – 3.98 (m, 1H), 3.97 – 3.92 (m, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.16 – 3.13 (m, 1H), 3.06 – 2.97 (m, 2H), 2.85 – 2.81 (m, 1H), 2.03 – 1.99 (m, 1H), 1.78 – 1.73 (m, 2H), 1.42 – 1.39 (m, 1H). ¹³C NMR (50 MHz, CDCl₃) δ = 157.4, 149.3, 148.3, 144.1, 142.9, 141.0, 140.6, 129.2, 128.7, 128.6, 127.5, 126.3, 125.7, 120.8, 120.1, 119.9, 111.8, 111.7, 64.7, 56.1, 56.0, 52.9, 50.2, 48.6, 35.9, 31.9, 24.0 ppm. (Total count of ¹³C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for C₂₈H₃₀N₅O₂⁺ ([M+H]⁺): 468.2394, found: 468.2399.

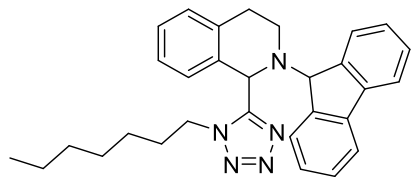
1-(1-butyl-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinoline(5.43a):



According to general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and *n*-butyl isocyanide (0.13 mmol, 1 equiv, 16 μ L) in 2 mL methanol were reacted for 24 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:15) to obtain **5.43a** as white solid (46 mg, 84%). FTIR (KBr): $\tilde{\nu}$ = 3064, 2962, 2926, 2872, 1961, 1449, 1126, 1087, 1043, 941, 777, 747, 680 cm^{-1} . ¹H NMR (600 MHz, CDCl₃) δ = 7.92 (d, J = 7.2 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.40 – 7.36 (m, 2H), 7.35 – 7.33 (m, 1H), 7.30 – 7.26 (m, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 7.2 Hz, 1H), 7.11 – 7.08 (m, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.46 (s, 1H), 4.56 – 4.53 (m, 1H), 4.52 (s, 1H), 4.36 – 4.31 (m, 1H), 2.97 – 2.92 (m, 1H), 2.61 – 2.58 (m, 1H), 2.51 – 2.49 (m, 2H), 1.54 – 1.48 (m, 1H), 1.14 – 1.04 (m, 3H), 0.73 (t, J = 7.2 Hz, 3H). ¹³C NMR (151 MHz, CDCl₃) δ = 155.7, 143.8, 142.1, 141.4, 141.29, 135.2, 133.1, 129.4, 128.8, 128.7, 127.73, 127.68, 127.5,

127.3, 126.8, 126.7, 124.9, 120.4, 120.0, 66.0, 57.5, 48.1, 43.1, 30.7, 30.0, 19.9, 13.5 ppm. HRMS (ESI) exact mass calculated for $C_{27}H_{28}N_5^+$ ($[M+H]^+$): 422.2339, found: 422.2376.

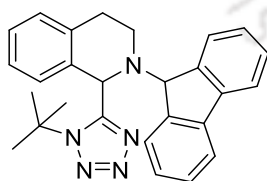
2-(9H-fluoren-9-yl)-1-(1-heptyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (5.43b):



According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and *n*-

heptyl isocyanide (0.13 mmol, 1 equiv, 16 mg) in 2 mL methanol were reacted for 17 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:20) to obtain **5.43b** as white solid (45 mg, 75%). FTIR (KBr): $\tilde{\nu}$ = 3443, 2956, 2926, 2856, 2827, 1469, 1449, 1290, 1127, 1086, 750, 737, 724, 677 cm^{-1} . 1H NMR (600 MHz, $CDCl_3$) δ = 7.91 (d, J = 7.8 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.39 – 7.37 (m, 2H), 7.34 (d, J = 7.2 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.20 – 7.18 (m, 1H), 7.13 (d, J = 7.2 Hz, 1H), 7.11 – 7.07 (m, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.47 (s, 1H), 4.56 – 4.52 (m, 1H), 4.51 (s, 1H), 4.36 – 4.31 (m, 1H), 2.97 – 2.92 (m, 1H), 2.61 – 2.58 (m, 1H), 2.51 – 2.49 (m, 2H), 1.56 – 1.50 (m, 1H), 1.25 – 1.21 (m, 3H), 1.12 – 1.08 (m, 3H), 1.08 – 1.05 (m, 3H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 155.7, 143.8, 142.1, 141.4, 141.3, 135.2, 133.1, 129.4, 128.8, 128.7, 127.7, 127.6, 127.5, 127.3, 126.8, 126.7, 124.8, 120.4, 119.9, 66.0, 57.5, 48.4, 43.0, 31.6, 29.9, 28.8, 28.7, 26.6, 22.6, 14.2 ppm. HRMS (ESI) exact mass calculated for $C_{30}H_{34}N_5^+$ ($[M+H]^+$): 464.2809, found: 464.2821.

1-(1-(tert-butyl)-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinoline (5.43c):

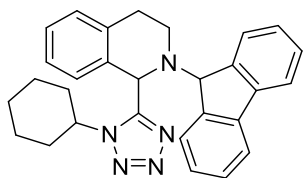


(**5.43c**): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and *tert*-butyl isocyanide (0.13 mmol, 1 equiv, 16 μ L) in 2 mL

methanol were reacted for 24 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:15) to obtain **5.43c** as white solid (47 mg, 86%). FTIR (KBr): $\tilde{\nu}$ = 3061, 3021, 2977, 2942, 1476, 1450, 1405, 1369, 1301, 1239, 1122, 739, 726, 678, 424 cm^{-1} . 1H NMR (600 MHz, $CDCl_3$) δ = 8.20 (s, 1H), 7.68 (t, J = 8.4 Hz, 2H), 7.54 (d, J = 7.2 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.30 (t, J = 7.2 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H), 7.09 – 7.06 (m, 2H), 6.70 (s, 1H), 6.53 (d, J = 7.8 Hz, 1H), 4.52 (s, 1H), 2.92 – 2.88 (m, 1H), 2.53 – 2.48 (m, 2H), 2.41 – 2.38 (m, 1H), 1.67 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.9, 143.9, 141.7, 141.4, 135.4, 135.1, 129.3, 128.7, 128.6, 127.7, 127.5, 127.4, 126.5,

126.3, 124.9, 120.2, 119.9, 66.0, 63.8, 59.8, 43.0, 30.7, 29.1 ppm. (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for $\text{C}_{27}\text{H}_{28}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 422.2339, found: 422.2318.

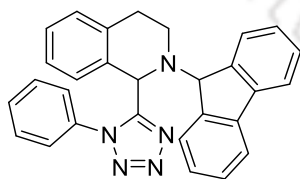
1-(1-cyclohexyl-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinoline



(5.43d): According to general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and cyclohexyl isocyanide (0.13 mmol, 1 equiv, 16

μL) in 2 mL methanol were reacted for 24 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:3) to obtain **5.43d** as white solid (52 mg, 89%). FTIR (KBr): $\tilde{\nu}$ = 3060, 2938, 1948, 1450, 1434, 742, 724, 622 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 8.02 (d, J = 7.8 Hz, 1H), 7.71 – 7.67 (m, 2H), 7.40 – 7.38 (m, 2H), 7.35 – 7.34 (m, 1H), 7.31 – 7.27 (m, 2H), 7.19 – 7.17 (m, 1H), 7.13 – 7.12 (m, 1H), 7.10 – 7.08 (m, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 4.76 – 4.71 (m, 1H), 4.57 (s, 1H), 3.00 – 2.93 (m, 1H), 2.60 – 2.57 (m, 1H), 2.47 – 2.38 (m, 2H), 2.25 – 2.21 (m, 2H), 2.08 – 2.06 (m, 1H), 1.68 – 1.67 (m, 1H), 1.59 (d, J = 16.2 Hz, 1H), 1.48 – 1.41 (m, 2H), 1.28 – 1.25 (m, 1H), 0.88 – 0.82 (m, 1H), 0.72 – 0.70 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.0, 144.0, 142.1, 141.5, 141.4, 135.3, 133.4, 129.3, 128.8, 128.7, 127.7, 127.5, 127.4, 127.1, 126.7, 124.4, 120.4, 120.0, 65.8, 58.6, 57.7, 42.6, 32.9, 32.3, 30.1, 25.9, 25.6, 25.1 ppm (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for $\text{C}_{29}\text{H}_{30}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 448.2496, found: 448.2484.

2-(9H-fluoren-9-yl)-1-(1-phenyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (5.43e):

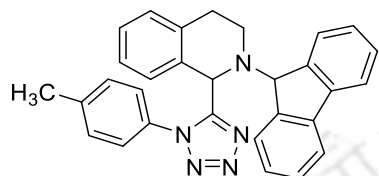


According to general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and phenyl isocyanide (0.13 mmol, 1 equiv, 14 mg) in 2 mL methanol

were reacted for 12 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:20) to obtain **5.43e** as white solid (41 mg, 71%). FTIR (KBr): $\tilde{\nu}$ = 3062, 2969, 2895, 2847, 1595, 1493, 1450, 1264, 1080, 756, 742, 686, 534 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.89 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.47 – 7.45 (m, 1H), 7.37 – 7.35 (m, 3H), 7.33 – 7.31 (m, 1H), 7.27 – 7.24 (m, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.15 – 7.13 (m, 2H), 7.11 – 7.08 (m, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.86

(d, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 7.8$ Hz, 1H), 6.57 (s, 1H), 4.61 (s, 1H), 2.56 – 2.50 (m, 1H), 2.38 – 2.37 (m, 3H). ^{13}C NMR (151 MHz, CDCl_3) $\delta = 156.1, 143.7, 142.2, 141.5, 141.1, 135.7, 135.0, 133.5, 130.1, 129.3, 129.0, 128.7, 128.6, 127.7, 127.5, 127.3, 127.0, 126.8, 126.6, 125.7, 125.0, 120.4, 119.7, 65.9, 57.8, 42.7, 29.4$ ppm. HRMS (ESI) exact mass calculated for $\text{C}_{29}\text{H}_{24}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 442.2026, found: 442.2020.

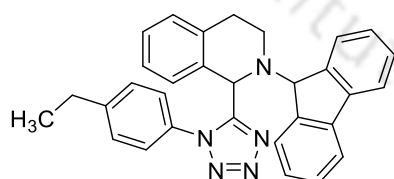
2-(9H-fluoren-9-yl)-1-(1-(p-tolyl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (5.43f):



According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and *p*-methyl

phenyl isocyanide (0.13 mmol, 1 equiv, 15 mg) in 2 mL methanol were reacted for 14 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:20) to obtain **5.43f** as white solid (41 mg, 70%). FTIR (KBr): $\tilde{\nu} = 3066, 2929, 2848, 1904, 1650, 1450, 1433, 1384, 1260, 1073, 823, 738, 723, 535$ cm^{-1} . ^1H NMR (600 MHz, CDCl_3) $\delta = 7.87$ (d, $J = 7.8$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.37 – 7.32 (m, 2H), 7.27 – 7.24 (m, 1H), 7.17 – 7.14 (m, 4H), 7.11 – 7.07 (m, 3H), 7.01 (d, $J = 7.2$ Hz, 1H), 6.86 (d, $J = 7.8$ Hz, 1H), 6.77 (d, $J = 7.2$ Hz, 1H), 6.54 (s, 1H), 4.61 (s, 1H), 2.59 – 2.53 (m, 1H), 2.42 (s, 3H), 2.41 – 2.39 (m, 3H). ^{13}C NMR (151 MHz, CDCl_3) $\delta = 156.2, 143.8, 142.4, 141.5, 141.1, 140.3, 135.8, 133.7, 132.5, 129.5, 129.3, 128.6, 128.6, 127.6, 127.5, 127.3, 127.0, 126.8, 126.6, 125.5, 125.1, 120.4, 119.7, 66.1, 57.7, 42.8, 29.5, 21.4$ ppm. HRMS (ESI) exact mass calculated for $\text{C}_{30}\text{H}_{26}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 456.2183, found: 456.2181.

1-(1-(4-ethylphenyl)-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-

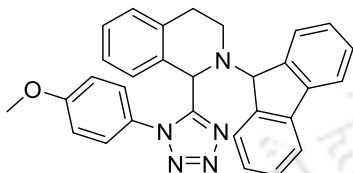


tetrahydroisoquinoline(5.43g): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and *p*-

ethylphenyl isocyanide (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 12 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:20) to obtain **5.43g** as white solid (44 mg, 72%). FTIR (KBr): $\tilde{\nu} = 3062, 2960, 2835, 1517, 1449, 1259, 839, 751, 739, 552$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3) $\delta = 7.86$ (d, $J = 7.2$ Hz, 1H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.37 – 7.29 (m, 2H), 7.25 – 7.22 (m, 1H), 7.19 – 7.15 (m, 2H), 7.19 – 7.08 (m, 5H), 7.00 (d, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 7.6$ Hz, 1H), 6.68 (d, $J = 7.6$ Hz, 1H), 6.55 (s, 1H), 4.58 (s, 1H), 2.73 – 2.68 (m, 2H), 2.60 –

2.52 (m, 1H), 2.41 – 2.37 (m, 3H), 1.28 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) $\delta = 156.1, 146.7, 143.8, 142.3, 141.4, 141.0, 135.7, 133.7, 132.6, 129.3, 128.6, 128.5, 128.4, 127.6, 127.5, 127.3, 127.0, 126.8, 126.6, 125.6, 125.1, 120.3, 119.7, 65.9, 57.8, 42.7, 29.4, 28.8, 16.0$. HRMS (ESI) exact mass calculated for $\text{C}_{31}\text{H}_{28}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 470.2339, found: 470.2342.

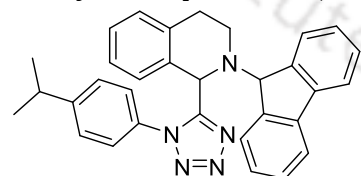
2-(9H-fluoren-9-yl)-1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)-1,2,3,4-



tetrahydroisoquinoline (5.43h): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and *p*-methoxyphenyl isocyanide (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for

14 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:6) to obtain **5.43h** as white solid (51 mg, 84%). FTIR (KBr): $\tilde{\nu} = 3064, 3010, 2909, 2841, 1607, 1517, 1449, 1301, 1253, 1082, 1024, 834, 741, 726, 620, 539\text{ cm}^{-1}$. ^1H NMR (600 MHz, CDCl_3) $\delta = 7.88$ (d, $J = 7.8$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 7.2$ Hz, 1H), 7.38 – 7.32 (m, 2H), 7.27 – 7.24 (m, 1H), 7.18 – 7.13 (m, 2H), 7.11 – 7.08 (m, 3H), 7.00 (d, $J = 7.2$ Hz, 1H), 6.88 – 6.83 (m, 4H), 6.53 (s, 1H), 4.63 (s, 1H), 3.85 (s, 3H), 2.57 – 2.51 (m, 1H), 2.41 – 2.36 (m, 3H). ^{13}C NMR (151 MHz, CDCl_3) $\delta = 160.7, 156.3, 143.8, 142.3, 141.5, 141.1, 135.8, 133.6, 129.3, 128.64, 128.58, 127.8, 127.6, 127.5, 127.3, 127.1, 127.0, 126.8, 126.6, 125.1, 120.4, 119.8, 114.1, 66.0, 57.6, 55.9, 42.7, 29.5\text{ ppm}$. HRMS (ESI) exact mass calculated for $\text{C}_{30}\text{H}_{26}\text{N}_5\text{O}^+$ ($[\text{M}+\text{H}]^+$): 472.2131, found: 472.2134.

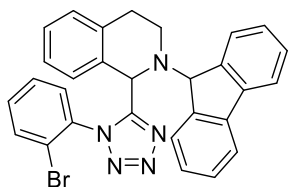
2-(9H-fluoren-9-yl)-1-(1-(4-isopropylphenyl)-1H-tetrazol-5-yl)-1,2,3,4-



tetrahydroisoquinoline (5.43i): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and *p*-isopropylphenyl isocyanide (0.13 mmol, 1 equiv, 19 mg) in 2 mL methanol were reacted for 16 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:20) to obtain **5.43i** as grey solid (48 mg, 77%). FTIR (KBr): $\tilde{\nu} = 3059, 3037, 2961, 2926, 2850, 1821, 1518, 1449, 1421, 1266, 1137, 1075, 835, 747, 725, 556\text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.85$ (d, $J = 7.6$ Hz, 1H), 7.67 (d, $J = 7.2$ Hz, 1H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.37 – 7.29 (m, 2H), 7.24 – 7.20 (m, 2H), 7.17 – 7.09 (m, 5H), 7.01 (d, $J = 7.6$ Hz, 1H), 6.89 (d, $J = 7.2$ Hz, 1H), 6.60 – 6.54 (m,

2H), 4.56 (s, 1H), 3.01 – 2.94 (m, 1H), 2.61 – 2.53 (m, 1H), 2.41 – 2.35 (m, 3H), 1.29 (d, J = 6.4 Hz, 6H). ^{13}C NMR (151 MHz, CDCl_3) δ = 156.0, 151.3, 143.7, 142.2, 141.4, 141.0, 135.6, 133.7, 132.6, 129.3, 128.6, 128.5, 127.6, 127.4, 127.3, 127.0, 126.9, 126.8, 126.6, 125.6, 125.0, 120.3, 119.7, 65.9, 57.9, 42.7, 42.2, 34.2, 29.4, 24.2, 24.1 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{32}\text{H}_{30}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 484.2496, found: 484.2497.

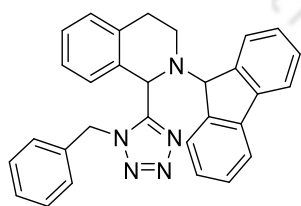
1-(1-(2-bromophenyl)-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-



tetrahydroisoquinoline (5.43j): According to the general procedure

I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and *o*-bromophenyl isocyanide (0.13 mmol, 1 equiv, 24 mg) in 2 mL methanol were reacted for 14 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:20) to obtain **5.43j** as brown gummy compound (44 mg, 65%). FTIR (KBr): $\tilde{\nu}$ = 3062, 2969, 2895, 2847, 1595, 1493, 1450, 1264, 1080, 756, 742, 686 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.91 (d, J = 7.2 Hz, 1H), 7.73 – 2.79 (m, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.39 – 7.34 (m, 3H), 7.28 – 7.24 (m, 2H), 7.22 – 7.18 (m, 2H), 7.16 – 7.13 (m, 2H), 7.07 (d, J = 7.6 Hz, 1H), 6.94 – 6.92 (m, 2H), 6.51 (s, 1H), 4.89 (s, 1H), 2.40 – 2.22 (m, 4H). ^{13}C NMR (101 MHz, CDCl_3) δ = 156.9, 143.8, 142.4, 141.6, 141.2, 136.0, 134.1, 134.0, 133.4, 132.0, 129.1, 129.0, 128.7, 128.6, 127.72, 127.70, 127.5, 127.4, 127.3, 127.0, 126.8, 125.4, 121.6, 120.3, 119.8, 66.4, 57.6, 42.3, 29.3. HRMS (ESI) exact mass calculated for $\text{C}_{29}\text{H}_{23}\text{BrN}_5^+$ ($[\text{M}+\text{H}]^+$): 520.1133, found: 520.1123.

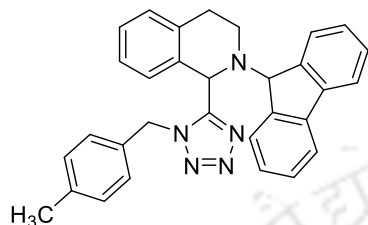
1-(1-benzyl-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-tetrahydroisoquinoline (5.43k):



According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and benzyl isocyanide (0.13 mmol, 1 equiv, 15 mg) in 2 mL methanol were reacted for 12 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:20) to obtain **5.43k** as white solid (56 mg, 95%). FTIR (KBr): $\tilde{\nu}$ = 3063, 2933, 2899, 1497, 1449, 1132, 1157, 1084, 773, 743, 725, 692, 678, 621 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.90 (d, J = 7.6 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.40 – 7.35 (m, 2H), 7.28 – 7.17 (m, 4H), 7.14 – 7.10 (m, 4H), 6.90 – 6.86 (m, 1H), 6.75 (d, J = 7.6 Hz, 2H), 6.47 (d, J = 7.6 Hz, 1H), 6.40 (s, 1H), 5.74 (d, J = 14.8 Hz, 1H), 5.41 (d, J = 14.8 Hz, 1H), 4.54 (s, 1H), 3.05 – 2.97 (m, 1H), 2.65 – 2.52 (m, 3H). ^{13}C NMR (151 MHz,

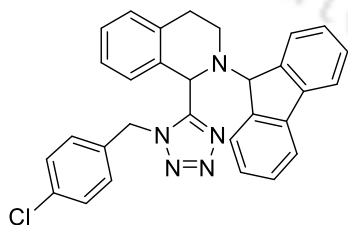
CDCl₃) δ = 155.8, 143.6, 142.1, 141.4, 141.3, 135.0, 133.3, 132.9, 129.4, 128.84, 128.82, 128.77, 128.5, 128.2, 127.8, 127.7, 127.5, 127.4, 126.81, 126.77, 125.1, 120.4, 119.9, 66.3, 57.1, 51.6, 43.4, 29.9 ppm. HRMS (ESI) exact mass calculated for C₃₀H₂₆N₅⁺ ([M+H]⁺): 456.2183, found: 456.2187.

2-(9H-fluoren-9-yl)-1-(1-(4-methylbenzyl)-1H-tetrazol-5-yl)-1,2,3,4-



tetrahydroisoquinoline (5.43l): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 1-(isocyanomethyl)-4-methylbenzene (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 16 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:20) to obtain **5.43l** as white solid (48 mg, 79%). FTIR (KBr): $\tilde{\nu}$ = 3054, 2960, 2919, 2815, 1447, 1287, 1126, 1041, 741, 725, 622, 476 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.91 (d, *J* = 7.2 Hz, 1H), 7.71 – 7.68 (m, 2H), 7.41 – 7.37 (m, 2H), 7.28 – 7.23 (m, 2H), 7.19 – 7.16 (m, 1H), 7.14 – 7.11 (m, 2H), 6.95 – 6.92 (m, 3H), 6.64 (d, *J* = 7.8 Hz, 2H), 6.49 (d, *J* = 7.2 Hz, 1H), 6.41 (s, 1H), 5.68 (d, *J* = 14.4 Hz, 1H), 5.34 (d, *J* = 14.4 Hz, 1H), 4.56 (s, 1H), 3.04 – 3.00 (m, 1H), 2.66 – 2.63 (m, 2H), 2.58 – 2.56 (m, 1H), 2.27 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ = 155.7, 143.7, 142.2, 141.4, 141.3, 138.4, 135.1, 133.1, 130.4, 129.5, 129.4, 128.8, 128.7, 128.4, 127.7, 127.5, 127.4, 126.8, 125.2, 120.4, 119.9, 66.3, 57.2, 51.6, 43.4, 30.0, 21.3 ppm (Total count of ¹³C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for C₃₁H₂₈N₅⁺ ([M+H]⁺): 470.2339, found: 470.2341.

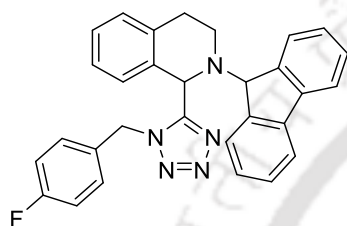
1-(1-(4-chlorobenzyl)-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-



tetrahydroisoquinoline (5.43m): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 1-chloro-4-(isocyanomethyl)benzene (0.13 mmol, 1 equiv, 20 mg) in 2 mL methanol were reacted for 16 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:20) to obtain **5.43m** as white solid (61 mg, 96%). FTIR (KBr): $\tilde{\nu}$ = 3101, 3031, 2961, 2816, 1590, 1493, 1448, 1126, 740, 725, 511, 442 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.90 (d, *J* = 7.2 Hz, 1H), 7.70 – 7.67 (m, 2H), 7.40 –

7.37 (m, 2H), 7.28 – 7.25 (m, 2H), 7.21 – 7.20 (m, 1H), 7.15 – 7.12 (m, 1H), 7.10 – 7.07 (m, 3H), 7.21 – 7.20 (m, 1H), 6.91 – 6.87 (m, 2H), 6.50 (d, $J = 8.4$ Hz, 1H), 6.44 (s, 1H), 5.78 (d, $J = 15.0$ Hz, 1H), 5.45 (d, $J = 15.0$ Hz, 1H), 4.51 (s, 1H), 3.02 – 2.96 (m, 1H), 2.63 – 2.62 (m, 1H), 2.55 – 2.53 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) $\delta = 155.8, 143.5, 141.9, 141.4, 141.3, 134.9, 134.5, 132.8, 131.7, 129.6, 129.5, 128.9, 128.8, 127.8, 127.7, 127.5, 127.4, 126.9, 126.7, 124.9, 120.5, 120.0, 66.1, 57.3, 50.9, 43.2, 29.9$ ppm. (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for $\text{C}_{30}\text{H}_{25}\text{ClN}_5^+$ ($[\text{M}+\text{H}]^+$): 490.1793, found: 490.1792.

2-(9H-fluoren-9-yl)-1-(1-(4-fluorobenzyl)-1H-tetrazol-5-yl)-1,2,3,4-



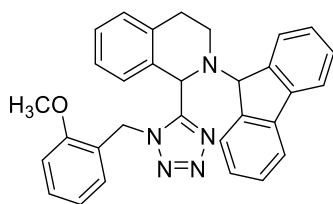
tetrahydroisoquinoline (5.43n): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and 1-fluoro-

4-(isocyanomethyl)benzene (0.13 mmol, 1 equiv, 18 mg) in 2 mL methanol were reacted for 14 hours. After completion of the reaction, the solid product was precipitated from the reaction mixture. Then, the solid product was filtered and washed with (3 $\times$ 5 mL) methanol to get the desired product (48 mg) as white solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column chromatography (Ethyl acetate: hexane; 1:10) to give an additional amount (7 mg) of the product. The combined yield is (55 mg, 89%). FTIR (KBr): $\tilde{\nu} = 3065, 2926, 2836, 1605, 1510, 1450, 1225, 1158, 745, 773, 677, 538$ cm^{-1} . ^1H NMR (600 MHz, CDCl_3) $\delta = 7.90$ (d, $J = 7.8$ Hz, 1H), 7.70 – 7.67 (m, 2H), 7.40 – 7.36 (m, 2H), 7.28 – 7.25 (m, 4H), 7.14 – 7.10 (m, 2H), 6.93 – 6.88 (m, 1H), 6.80 – 6.77 (m, 2H), 6.71 – 6.85 (m, 2H), 6.49 (d, $J = 7.8$ Hz, 1H), 6.43 (s, 1H), 5.77 (d, $J = 15.0$ Hz, 1H), 5.45 (d, $J = 14.4$ Hz, 1H), 4.52 (s, 1H), 3.04 – 2.98 (m, 1H), 2.66 – 2.63 (m, 1H), 2.58 – 2.55 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) $\delta = 155.7, 143.6, 142.0, 141.4, 141.3, 135.0, 133.0, 130.3, 130.2, 129.5, 129.1, 128.9, 128.8, 127.8, 127.7, 127.6, 127.4, 126.9, 126.7, 125.0, 120.5, 120.0, 115.8, 115.6, 66.3, 57.3, 50.9, 43.4, 30.0$ ppm. HRMS (ESI) exact mass calculated for $\text{C}_{30}\text{H}_{25}\text{FN}_5^+$ ($[\text{M}+\text{H}]^+$): 474.2089, found: 474.2088.

2-(9H-fluoren-9-yl)-1-(1-(2-methoxybenzyl)-1H-tetrazol-5-yl)-1,2,3,4-

tetrahydroisoquinoline (5.43o): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and 1-(isocyanomethyl)-2-methoxybenzene (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 14 hours.

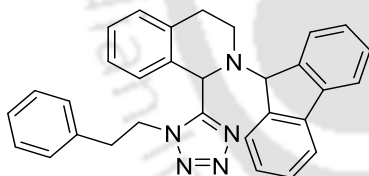
After completion of the reaction, the solid product was precipitated from the reaction



mixture. Then, the solid product was washed with (3×5 mL) methanol to get the desired product (53 mg) as white solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column chromatography (Ethyl acetate:

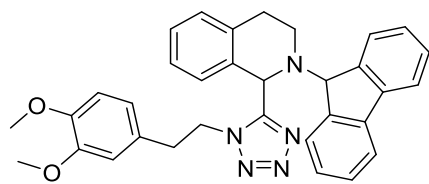
hexane; 1:10) to give an additional amount (7 mg) of the product. The combined yield is (60 mg, 95%). FTIR (KBr): $\tilde{\nu}$ = 3067, 2957, 2926, 1606, 1510, 1449, 1224, 1165, 1111, 832, 733, 533, 495 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ 7.92 (d, J = 7.2 Hz, 1H), 7.73 – 7.70 (m, 2H), 7.42 – 7.38 (m, 2H), 7.32 – 7.31 (m, 1H), 7.29 – 7.27 (m, 2H), 7.22 – 7.20 (m, 1H), 7.06 – 7.01 (m, 2H), 6.92 – 6.90 (m, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.74 – 6.71 (m, 1H), 6.55 (d, J = 7.2 Hz, 2H), 6.41 (s, 1H), 5.63 – 5.60 (m, 1H), 5.55 – 5.53 (m, 1H), 4.66 (s, 1H), 3.70 (s, 3H), 3.00 – 2.95 (m, 1H), 2.70 – 2.51 (m, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 156.6, 155.9, 143.8, 142.3, 141.4, 141.3, 135.3, 132.6, 129.7, 129.1, 128.75, 128.7, 127.7, 127.5, 127.4, 127.3, 126.8, 126.5, 125.3, 121.7, 120.7, 120.4, 119.9, 110.4, 66.5, 56.9, 55.4, 46.5, 43.3, 29.8 ppm (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for $\text{C}_{31}\text{H}_{28}\text{N}_5\text{O}^+$ ($[\text{M}+\text{H}]^+$): 486.2288, found: 486.2285.

2-(9H-fluoren-9-yl)-1-(1-phenethyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline



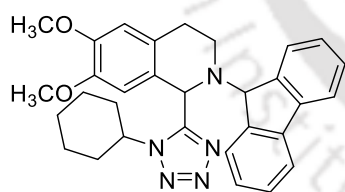
(5.43p): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and (2-

isocyanoethyl)benzene (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 24 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:3) to obtain **5.43p** as (52 mg, 89%) white solid. FTIR (KBr): $\tilde{\nu}$ = 3062, 2961, 2820, 1494, 1138, 753, 742, 696 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.90 (d, J = 7.6 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.39 – 7.34 (m, 2H), 7.28 – 7.22 (m, 8H), 7.16 – 7.12 (m, 1H), 6.89 (d, J = 7.2 Hz, 2H), 6.78 (d, J = 8.0 Hz, 1H), 6.47 (s, 1H), 4.81 – 4.74 (m, 1H), 4.57 – 4.85 (m, 2H), 3.01 – 2.88 (m, 2H), 2.66 – 2.62 (m, 1H), 2.57 – 2.48 (m, 2H), 2.10 – 2.02 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.8, 143.5, 142.0, 141.4, 141.2, 136.7, 135.3, 133.2, 129.6, 129.0, 128.9, 128.80, 128.76, 128.0, 127.72, 127.66, 127.3, 127.2, 127.1, 126.6, 125.0, 120.4, 119.9, 66.1, 57.3, 49.4, 43.3, 35.5, 30.0 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{31}\text{H}_{28}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 470.2339, found: 470.2333.

1-(1-(3,4-dimethoxyphenethyl)-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-


tetrahydroisoquinoline (5.43q): According to the general

procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (0.13 mmol, 1 equiv, 25 mg) in 2 mL methanol were reacted for 24 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:3) to obtain **5.43q** as white solid (64 mg, 93%). FTIR (KBr): $\tilde{\nu}$ = 3414, 2962, 2927, 1649, 1418, 1261, 1030, 802, 742, 674 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.90 (d, J = 7.2 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.28 – 7.24 (m, 3H), 7.23 – 7.21 (m, 2H), 7.15 – 7.13 (m, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.48 – 6.46 (m, 2H), 6.37 – 6.36 (m, 1H), 4.77 – 4.73 (m, 1H), 4.52 – 4.47 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.00 – 2.94 (m, 1H), 2.90 – 2.85 (m, 1H), 2.65 (d, J = 16.2 Hz, 1H), 2.56 – 2.48 (m, 2H), 2.05 – 2.01 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 155.8, 149.2, 148.2, 143.5, 142.0, 141.5, 141.3, 135.3, 133.3, 129.4, 129.2, 128.85, 128.78, 128.0, 127.7, 127.4, 127.1, 126.6, 125.0, 121.0, 120.5, 120.0, 112.0, 111.6, 66.1, 57.3, 56.1, 49.7, 43.3, 35.1, 30.0, 29.9 ppm (Total count of ¹³C is less than expected due to the merging of signals in the aromatic region). HRMS (ESI) exact mass calculated for C₃₃H₃₂N₅O₂⁺ ([M+H]⁺): 530.2551, found: 530.2553.

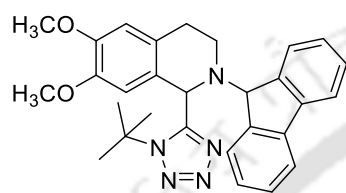
1-(1-(cyclohexyl-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-6,7-dimethoxy-1,2,3,4-


tetrahydroisoquinoline (5.43r): According to the general

procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.38 mmol, 3 equiv, 87 mg), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and triethylamine (0.19 mmol, 1.5 equiv, 26 μ L) and Cyclohexyl isocyanide (0.13 mmol, 1 equiv, 16 μ L) in 2 mL methanol were reacted for 20 hours. After completion of the reaction, the solid product was precipitated from the reaction mixture. Then, the solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product **5.43r** (47 mg) as white solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column chromatography (Ethyl acetate: hexane; 1:6) to give an additional amount (16 mg) of the product. The combined yield is (63 mg, 96%). FTIR (KBr): $\tilde{\nu}$ = 3400, 2937, 1609, 1517, 1444, 1248, 1221, 1128, 1010, 747 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.00 (d, J = 7.6 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.41 – 7.38 (m, 2H), 7.36 – 7.34 (m, 1H), 7.31 –

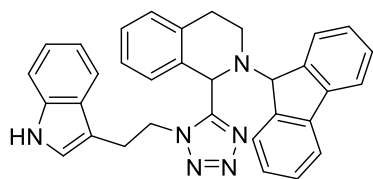
7.29 (m, 2H), 6.60 (s, 1H), 6.48 (s, 1H), 6.16 (s, 1H), 4.87 – 4.80 (m, 1H), 4.58 (s, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 2.94 – 2.85 (m, 1H), 2.51 – 2.37 (m, 3H), 2.29 – 2.23 (m, 2H), 2.10 – 2.07 (m, 1H), 1.72 – 1.64 (m, 2H), 1.53 – 1.42 (m, 2H), 1.32 – 1.21 (m, 1H), 0.96 – 0.78 (m, 2H) ppm. ^{13}C NMR (151 MHz, CDCl_3) δ = 155.0, 148.7, 148.2, 144.0, 142.2, 141.5, 141.4, 128.8, 128.7, 127.7, 127.6, 127.4, 127.0, 125.1, 124.5, 120.4, 112.0, 111.5, 109.8, 65.9, 58.6, 57.4, 56.22, 56.17, 42.8, 32.9, 32.6, 29.7, 25.9, 25.7, 25.1 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{31}\text{H}_{34}\text{N}_5\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 508.2707, found: 508.2709.

1-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-2-(9*H*-fluoren-9-yl)-6,7-dimethoxy-1,2,3,4-



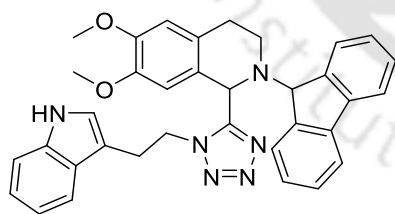
tetrahydroisoquinoline(5.43s): According to general procedure

I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.38 mmol, 3 equiv, 87 mg), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and triethyl amine (0.19 mmol, 1.5 equiv, 26 μL) and *tert*-butyl isocyanide (0.13 mmol, 1 equiv, 16 μL) in 2 mL methanol were reacted for 24 hours. After completion of the reaction, the solid product was precipitated from the reaction mixture. Then, the solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product **5.43s** (26 mg) as white solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column chromatography (Ethyl acetate: hexane; 1:5) to give an additional amount (16 mg) of the product. The combined yield is (42 mg, 67%). FTIR (KBr): $\tilde{\nu}$ = 2997, 2835, 1611, 1524, 1471, 1449, 1357, 1260, 1236, 1017, 739, 777 cm^{-1} . ^1H NMR (600 MHz, CDCl_3 at 298 K) δ = 8.19 (s, 1H), 7.71 – 7.68 (m, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.32 – 7.29 (m, 2H), 6.65 (s, 1H), 6.55 (s, 1H), 5.97 (s, 1H), 4.52 (s, 1H), 3.84 (s, 3H), 3.63 (s, 3H), 2.84 – 2.80 (m, 1H), 2.51 – 2.36 (m, 3H), 1.70 (s, 9H). ^1H NMR (400 MHz, CDCl_3 at 328 K) δ 8.19 (d, J = 6.7 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.57 (d, J = 7.4 Hz, 1H), 7.41 (q, J = 7.0 Hz, 2H), 7.33 (d, J = 7.4 Hz, 2H), 6.65 (s, 1H), 6.58 (s, 1H), 6.03 (s, 1H), 4.59 (s, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 2.97 – 2.78 (m, 1H), 2.68 – 2.53 (m, 1H), 2.51 – 2.32 (m, 2H), 1.73 (s, 9H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.1, 148.4, 147.9, 144.0, 141.5, 128.7, 128.6, 127.7, 127.5, 127.4, 126.9, 124.9, 120.2, 119.9, 111.6, 109.0, 66.1, 63.9, 59.5, 56.1, 56.0, 43.1, 30.7, 28.7 ppm. (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region.) HRMS (ESI) exact mass calculated for $\text{C}_{29}\text{H}_{32}\text{N}_5\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 482.2551, found: 482.2551.

1-(1-(2-(1H-indol-3-yl)ethyl)-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-1,2,3,4-


tetrahydroisoquinoline (5.43t): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.38 mmol, 3 equiv, 48 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 3-

(2-isocyanoethyl)-1H-indole (0.13 mmol, 1 equiv, 22 mg) in 2 mL methanol were reacted for 24 hours. After completion of the reaction, the solid product was precipitated from the reaction mixture. Then, the solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product **5.43t** (51 mg) as white solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column chromatography (Ethyl acetate: hexane; 1:10) to give an additional amount (12 mg) of the product. The combined yield is (63 mg, 96%). FTIR (KBr): $\tilde{\nu}$ = 3229, 2919, 2860, 1620, 1451, 1361, 1103, 742, 621 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 8.23 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.38 – 7.31 (m, 4H), 7.27 – 7.19 (m, 5H), 7.15 – 7.09 (m, 3H), 6.78 (s, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.45 (s, 1H), 4.80 – 4.73 (m, 1H), 4.66 – 4.59 (m, 1H), 4.50 (s, 1H), 3.21 – 3.13 (m, 1H), 2.95 – 2.89 (m, 1H), 2.61 – 2.57 (m, 1H), 2.53 – 2.39 (m, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.7, 143.4, 141.9, 141.3, 141.0, 136.2, 135.1, 133.0, 129.4, 128.6, 127.8, 127.6, 127.3, 127.1, 126.9, 126.8, 126.5, 124.9, 122.6, 122.3, 120.4, 120.3, 119.7, 119.6, 118.4, 111.4, 110.9, 66.0, 57.2, 48.7, 43.0, 29.7, 25.0 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{33}\text{H}_{29}\text{N}_6^+$ ($[\text{M}+\text{H}]^+$): 509.2448, found: 509.2448.

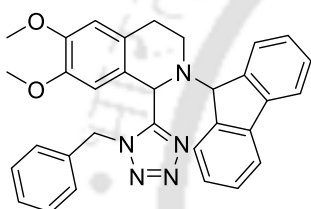
1-(1-(2-(1H-indol-3-yl)ethyl)-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-6,7-dimethoxy-1,2,3,4-


tetrahydroisoquinoline (5.43u): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.38 mmol, 3 equiv, 87 mg), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and triethylamine (0.19

mmol, 1.5 equiv, 26 μ L) and 3-(2-isocyanoethyl)-1H-indole (0.13 mmol, 1 equiv, 22 mg) in 2 mL methanol were reacted for 16 hours. After completion of the reaction, the solid product was precipitated from the reaction mixture. Then, the solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product **5.43u** (51 mg) as white solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column chromatography (Ethyl acetate: hexane; 1:4) to give an additional amount (12 mg) of the product. The combined yield is (63 mg, 85%). FTIR (KBr): $\tilde{\nu}$ = 3412, 3069, 2959, 2824, 1958, 1603, 1655,

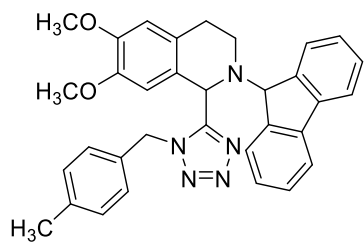
1589, 1521, 1447, 1294, 1247, 1124, 1084, 1024, 746, 520 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 8.06 (s, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.40 – 7.37 (m, 4H), 7.28 – 7.19 (m, 2H), 7.17 – 7.15 (m, 1H), 7.11 – 7.10 (m, 1H), 6.83 (d, J = 1.8 Hz, 1H), 6.59 (s, 1H), 6.40 (s, 1H), 6.17 (s, 1H), 4.89 – 4.83 (m, 1H), 4.72 – 4.66 (m, 1H), 4.54 (s, 1H), 3.82 (s, 3H), 3.63 (s, 3H), 3.25 – 3.18 (m, 1H), 2.89 – 2.84 (m, 1H), 2.72 – 2.66 (m, 1H), 2.49 – 2.46 (m, 3H). ^{13}C NMR (50 MHz, CDCl_3) δ = 156.0, 148.8, 148.2, 143.6, 142.1, 141.5, 141.2, 136.3, 128.7, 127.7, 127.5, 127.3, 127.1, 126.6, 125.0, 124.6, 122.5, 120.4, 119.9, 119.7, 118.5, 111.6, 111.2, 109.7, 66.2, 57.1, 56.2, 56.1, 48.9, 43.3, 29.5, 25.1 ppm. (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region.) HRMS (ESI) exact mass calculated for $\text{C}_{35}\text{H}_{33}\text{N}_6\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 569.2660, found: 569.2660.

1-(1-benzyl-1H-tetrazol-5-yl)-2-(9H-fluoren-9-yl)-6,7-dimethoxy-1,2,3,4-



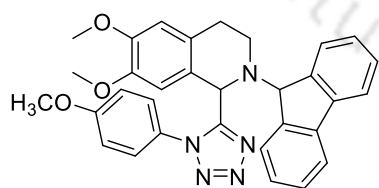
tetrahydroisoquinoline (5.43v): According to the general

procedure I: 9-fluorenone imine (0.24 mmol, 1.2 equiv, 43 mg), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.6 mmol, 3 equiv, 137 mg), trimethylsilyl azide (0.2 mmol, 1 equiv, 26 μL) and triethylamine (0.3 mmol, 1.5 equiv, 41 μL) and benzyl isocyanide (0.2 mmol, 1 equiv, 24 mg) in 2 mL methanol were reacted for 24 hours. After completion of the reaction, the solid product was precipitated from the reaction mixture. Then, the solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product (70 mg) as white solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column chromatography (Ethyl acetate: hexane; 1:5) to give an additional amount (10 mg) of the product. The combined yield is (80 mg, 78%). FTIR (KBr): $\tilde{\nu}$ = 3420, 2875, 1609, 1519, 1450, 1255, 1213, 1133, 847, 736, 721, 702 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.87 (d, J = 6.0 Hz, 1H), 7.72 – 7.69 (m, 2H), 7.42 – 7.37 (m, 2H), 7.29 – 7.25 (m, 3H), 7.21 – 7.18 (m, 1H), 7.13 – 7.11 (m, 2H), 6.79 – 6.77 (m, 2H), 6.49 (s, 1H), 6.30 (s, 1H), 5.81 – 5.79 (m, 2H), 5.52 – 5.49 (m, 1H), 4.59 (s, 1H), 3.80 (s, 3H), 3.38 (s, 3H), 2.96 – 2.91 (m, 1H), 2.67 – 2.54 (m, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.9, 148.7, 147.9, 143.7, 142.2, 141.4, 141.3, 133.3, 128.9, 128.8, 128.6, 128.4, 127.73, 127.70, 127.4, 127.1, 126.7, 125.1, 124.4, 120.4, 120.0, 111.5, 109.6, 66.5, 56.6, 56.0, 55.8, 51.4, 43.6, 29.6 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{32}\text{H}_{30}\text{N}_5\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 516.2394, found: 516.2393.

2-(9H-fluoren-9-yl)-6,7-dimethoxy-1-(1-(4-methylbenzyl)-1H-tetrazol-5-yl)-1,2,3,4-

tetrahydroisoquinoline (5.43w): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.38 mmol, 3 equiv, 87 mg), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and triethylamine (0.19

mmol, 1.5 equiv, 26 μ L) and 1-(isocyanomethyl)-4-methylbenzene (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 24 hours. After completion of the reaction, the solid product was precipitated from the reaction mixture. Then, the solid was filtered and washed with (3 $\times$ 5 mL) methanol to obtain the desired product **5.43w** (47 mg) as white solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column chromatography (Ethyl acetate: hexane; 1:6) to obtain an additional amount (16 mg) of the product. The combined yield is (63 mg, 96%). FTIR (KBr): $\tilde{\nu}$ = 3024, 2938, 2917, 2830, 1614, 1520, 1450, 1252, 1219, 1129, 1015, 786, 747, 674, 476 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.85 (d, J = 6.6 Hz, 1H), 7.70 – 7.67 (m, 2H), 7.40 – 7.35 (m, 2H), 7.28 – 7.24 (m, 3H), 6.93 (d, J = 7.8 Hz, 2H), 6.66 (d, J = 7.8 Hz, 2H), 6.51 (s, 1H), 6.27 (s, 1H), 5.81 (s, 1H), 5.72 (d, J = 15.0 Hz, 1H), 5.41 – 5.39 (m, 1H), 4.57 (s, 1H), 3.81 (s, 3H), 3.40 (s, 3H), 2.94 – 2.90 (m, 1H), 2.65 – 2.54 (m, 3H), 2.26 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.8, 148.7, 148.0, 143.6, 142.2, 141.3, 141.2, 138.2, 130.4, 129.3, 128.8, 128.7, 127.8, 127.6, 127.3, 127.1, 126.6, 125.1, 124.5, 120.4, 119.9, 111.5, 109.7, 66.5, 56.6, 56.0, 55.8, 51.3, 43.7, 29.5, 21.2 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{33}\text{H}_{32}\text{N}_5\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 530.2551, found: 530.2551.

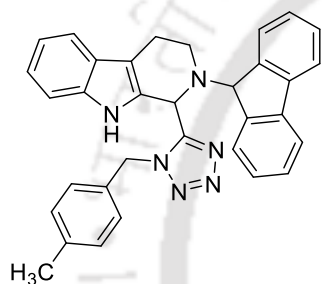
2-(9H-fluoren-9-yl)-6,7-dimethoxy-1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)-1,2,3,4-

tetrahydroisoquinoline (5.43x): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.38 mmol, 3 equiv, 87 mg), triethyl amine

(0.19 mmol, 1.5 equiv, 26 μ L) and *p*-methoxyphenyl isocyanide (0.13 mmol, 1 equiv, 17 mg) in 2 mL methanol were reacted for 24 hours. After completion of the reaction, the solid product was precipitated from the reaction mixture. Then, the solid was filtered and washed with (3 $\times$ 5 mL) methanol to get the desired product **5.43x** (42 mg) as white solid. Next, mother liquor was evaporated under reduced pressure and residue was purified by column chromatography (Ethyl acetate: hexane; 1:6) to give an additional amount (11 mg) of the

product. The combined yield is (53 mg, 77%). FTIR (KBr): $\tilde{\nu}$ = 3059, 3006, 2939, 2913, 2840, 1878, 1609, 1590, 1404, 1300, 1220, 1198, 1011, 980, 846, 734, 621, 535 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.88 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.27 – 7.24 (m, 1H), 7.17 – 7.15 (m, 3H), 6.87 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 7.2 Hz, 1H), 6.49 (s, 1H), 6.47 (s, 1H), 6.31 (s, 1H), 4.62 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 2.49 – 2.44 (m, 1H), 2.38 – 2.36 (m, 2H), 2.30 – 2.27 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 160.7, 156.2, 148.5, 148.0, 143.8, 142.3, 141.4, 141.0, 128.6, 128.5, 128.1, 127.9, 127.5, 127.3, 127.0, 126.8, 125.14, 125.07, 120.3, 119.7, 114.0, 111.4, 109.3, 66.0, 57.4, 56.2, 56.1, 55.9, 42.8, 29.1 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{32}\text{H}_{30}\text{N}_5\text{O}_3^+$ ($[\text{M}+\text{H}]^+$): 532.2343, found: 532.2338.

2-(9H-fluoren-9-yl)-1-(1-(4-methylbenzyl)-1H-tetrazol-5-yl)-2,3,4,9-tetrahydro-1H-



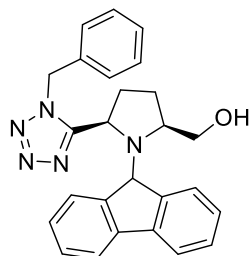
pyrido[3,4-*b*]indole (5.43y): According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (0.38 mmol, 3 equiv, 22 mg), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and 1-(isocyanomethyl)-4-methylbenzene (0.13 mmol, 1 equiv, 18 mg) in 2 mL methanol were reacted for 36 hours. The crude product

was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:6) to obtain **5.43y** as brown solid (22 mg, 33%). FTIR (KBr): $\tilde{\nu}$ = 2997, 2835, 1611, 1524, 1471, 1449, 1357, 1260, 1236, 1017, 739, 777 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ 7.81 (d, J = 7.2 Hz, 1H), 7.71 – 7.70 (m, 2H), 7.53 – 7.49 (m, 1H), 7.44 – 7.32 (m, 2H), 7.40 – 7.36 (m, 1H), 7.29 – 7.28 (m, 2H), 7.25 – 7.22 (m, 1H), 7.11 – 7.06 (m, 2H), 7.01 (d, J = 7.8 Hz, 1H), 6.66 (d, J = 7.8 Hz, 2H), 6.56 (d, J = 7.8 Hz, 2H), 6.39 (s, 1H), 5.86 (d, J = 14.4 Hz, 1H), 5.41 – 5.39 (m, 1H), 4.69 (s, 1H), 2.85 – 2.83 (m, 3H), 2.71 – 2.69 (m, 1H), 2.10 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 154.0, 143.7, 142.3, 141.3, 141.2, 138.4, 136.7, 130.0, 129.2, 128.9, 128.8, 128.7, 127.7, 127.7, 127.4, 126.5, 126.5, 125.3, 122.6, 120.5, 120.0, 119.9, 118.6, 111.5, 111.0, 66.5, 51.6, 44.7, 29.9, 22.2, 21.2 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{33}\text{H}_{29}\text{N}_6^+$ ($[\text{M}+\text{H}]^+$): 509.2448, found: 509.2442.

General procedure II: Isocyanides derivative (0.13 mmol, 1 equiv), trimethylsilyl azide (0.13 mmol, 1 equiv), imine (0.15 mmol, 1.2 equiv), *N*-heterocycle (0.38 mmol, 3 equiv) and acetic acid (0.13 mmol, 1 equiv) were taken in closed tube in neat condition and the mixture

was stirred at 100 °C (oil bath temperature) for 12 hours. The residue was purified by column chromatography to obtain analytically pure α -tetrazoyl-*N*-heterocycle.

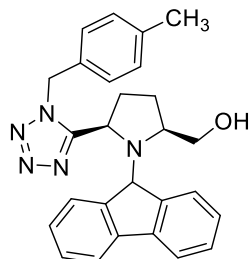
((2*S*,5*R*)-5-(1-benzyl-1*H*-tetrazol-5-yl)-1-(9*H*-fluoren-9-yl)pyrrolidin-2-yl)methanol



(5.45a): According to the general procedure II : 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), (*S*)-pyrrolidin-2-ylmethanol (0.38 mmol, 3 equiv, 37 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and benzyl isocyanide (0.13 mmol, 1 equiv, 15 mg) and acetic acid (0.13 mmol, 1 equiv, 7 μ L) were reacted for 12 hours. The crude

product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:1) to obtain **5.45a** as a brown solid (30 mg, 54%). FTIR (KBr): $\tilde{\nu}$ = 3062, 2925, 1650, 1631, 1449, 1403, 1086, 1008, 743 cm⁻¹. $[\alpha]_D^{25}$ = -23.33 (*c* = 0.12, MeOH). ¹H NMR (600 MHz, CDCl₃) δ = 7.79 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.51 – 7.47 (m, 1H), 7.37 – 7.34 (m, 1H), 7.29 – 7.28 (m, 1H), 7.21 – 7.18 (m, 1H), 7.16 – 7.13 (m, 3H), 7.06 – 7.04 (m, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.12 (s, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.17 (d, *J* = 15.0 Hz, 1H), 4.04 – 4.02 (m, 2H), 3.73 – 3.68 (m, 1H), 3.61 – 3.57 (m, 1H), 2.33 – 2.27 (m, 1H), 2.01 – 1.96 (m, 1H), 1.63 – 1.55 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ = 159.8, 143.9, 143.7, 141.7, 139.7, 133.4, 129.2, 129.1, 128.8, 128.7, 127.8, 127.3, 126.2, 125.6, 120.4, 119.7, 65.2, 65.0, 63.2, 52.4, 50.2, 32.5, 27.2 ppm. HRMS (ESI) exact mass calculated for C₂₆H₂₆N₅O⁺ ([M+H]⁺): 424.2132, found: 424.2134. The enantiomeric excess (>99 %) was determined by HPLC analysis; column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (12:88); uv light: 254 nm; flow: 1 mL /min; major enantiomer *t_r* = 42.26 min, minor enantiomer *t_r* = 38.82 min.

((2*S*,5*R*)-1-(9*H*-fluoren-9-yl)-5-(1-(4-methylbenzyl)-1*H*-tetrazol-5-yl)pyrrolidin-2-yl)methanol (5.45b)

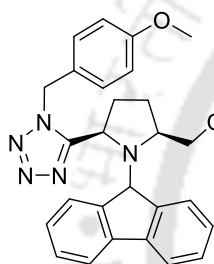


(5.45b): According to the general procedure II : 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), (*S*)-pyrrolidin-2-ylmethanol (0.38 mmol, 3 equiv, 37 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 1-(isocyanomethyl)-4-methylbenzene (0.13 mmol, 1 equiv, 17 mg) and acetic acid (0.13 mmol, 1 equiv, 7 μ L) were

reacted for 12 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:1) to obtain **5.45b** as a brown solid (34 mg, 60%) FTIR (KBr): $\tilde{\nu}$ = 3419, 2924, 2874, 1446, 1433, 1080, 745 cm⁻¹. $[\alpha]_D^{25}$ = -11.82 (*c* = 0.22, MeOH). ¹H NMR (600 MHz, CDCl₃) δ = 7.78 (d, *J* = 7.2 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.50 – 7.48 (m, 1H), 7.36 –

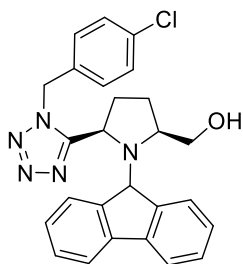
7.34 (m, 1H), 7.28 – 7.25 (m, 1H), 7.15 – 7.14 (m, 1H), 7.05 – 7.02 (m, 1H), 6.92 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 7.8 Hz, 2H), 5.10 (s, 1H), 4.99 (d, J = 15.6 Hz, 1H), 4.17 (d, J = 15.0 Hz, 1H), 4.01 – 4.00 (m, 2H), 3.70 – 3.68 (m, 1H), 3.64 – 3.60 (m, 1H), 2.32 – 2.27 (m, 1H), 2.25 (s, 3H), 2.02 – 1.96 (m, 1H), 1.66 – 1.55 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ = 159.7, 144.0, 143.8, 141.7, 139.7, 138.7, 130.4, 129.8, 129.0, 128.6, 127.8, 127.7, 127.3, 126.2, 125.6, 120.3, 119.7, 65.1, 65.0, 63.3, 52.6, 50.1, 32.5, 27.2, 21.3 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{27}\text{H}_{28}\text{N}_5\text{O}^+$ ($[\text{M}+\text{H}]^+$): 438.2288, found: 438.2293 The enantiomeric excess (>96 %) was determined by HPLC analysis; column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (15:85); UV light: 254 nm; flow: 1 mL /min; major enantiomer t_r = 28.58 min, minor enantiomer t_r = 25.46 min.

((2S,5R)-1-(9H-fluoren-9-yl)-5-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)pyrrolidin-2-



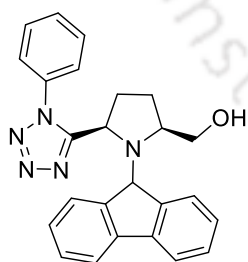
yl)methanol (5.45c): According to the general procedure II : 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), (S)-pyrrolidin-2-ylmethanol (0.38 mmol, 3 equiv, 37 μL), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μL) and 1-(isocyanomethyl)-4-methoxybenzene (0.13 mmol, 1 equiv, 19 mg) and acetic acid (0.13 mmol, 1 equiv, 7 μL) in neat condition were reacted for 12 hours. The crude product was

purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:1) to obtain **5.45c** as a brown solid (38 mg, 64%). FTIR (KBr): $\tilde{\nu}$ = 2923, 2852, 1638, 1452, 1260, 1025, 804, 749 cm^{-1} . $[\alpha]_D^{25}$ = -18.52 (c = 0.27, MeOH). ^1H NMR (600 MHz, CDCl_3) δ = 7.78 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.37 – 7.34 (m, 1H), 7.28 – 7.27 (m, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.05 – 7.03 (m, 1H), 6.63 – 6.62 (m, 2H), 6.55 (m, 2H), 5.11 (s, 1H), 4.96 (d, J = 15.0 Hz, 1H), 4.16 (d, J = 15.0 Hz, 1H), 4.05 – 4.02 (m, 2H), 3.73 (s, 3H), 3.71 – 3.70 (m, 1H), 3.64 – 3.56 (m, 1H), 2.34 – 2.28 (m, 1H), 2.03 – 1.96 (m, 1H), 1.67 – 1.63 (m, 1H), 1.58 – 1.55 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 159.8, 159.7, 144.0, 143.8, 141.7, 139.6, 129.0, 128.9, 128.7, 127.8, 126.3, 125.6, 125.3, 120.3, 119.7, 114.5, 65.2, 64.9, 63.1, 55.4, 52.5, 49.9, 32.5, 27.1 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{27}\text{H}_{28}\text{N}_5\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 454.2238, found: 454.2243. (Total count of ^{13}C is less than expected due to the merging of signals in the aromatic region). HPLC analysis: column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (20:80); UV light: 291 nm; flow: 1 mL /min; major enantiomer t_r = 27.85 min, minor enantiomer t_r = 22.17 min.

((2S,5R)-5-(1-(4-chlorobenzyl)-1H-tetrazol-5-yl)-1-(9H-fluoren-9-yl)pyrrolidin-2-yl)methanol (5.45d):

yl)methanol (5.45d): According to the general procedure II : 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), (S)-pyrrolidin-2-ylmethanol (0.38 mmol, 3 equiv, 37 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 1-chloro-4-(isocyanomethyl)benzene (0.13 mmol, 1 equiv, 20 mg) and acetic acid (0.13 mmol, 1 equiv, 7 μ L) in neat condition were reacted for 12 hours. The crude product was

purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:1) to obtain **5.45d** as a brown solid (32 mg, 54%). FTIR (KBr): $\tilde{\nu}$ = 2922, 2853, 1638, 1492, 1448, 1410, 1083, 1014, 802, 747 cm⁻¹. $[\alpha]_D^{25}$ = - 81.33 (c = 0.15, MeOH) ¹H NMR (600 MHz, CDCl₃) δ = 7.77 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.36 – 7.34 (m, 1H), 7.29 – 7.24 (m, 1H), 7.19 – 7.17 (m, 1H), 7.09 – 7.08 (m, 2H), 7.04 – 7.02 (m, 1H), 6.52 (d, *J* = 8.4 Hz, 2H), 5.12 (s, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.35 (d, *J* = 15.6 Hz, 1H), 4.08 – 4.07 (m, 2H), 3.74 (d, *J* = 9.6 Hz, 1H), 3.56 – 3.49 (m, 1H), 2.35 – 2.29 (m, 1H), 2.06 – 2.02 (m, 1H), 1.77 – 1.75 (m, 1H), 1.65 – 1.60 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 159.7, 143.8, 143.7, 141.7, 139.5, 134.8, 131.7, 129.5, 129.1, 128.64, 128.61, 127.8, 126.3, 125.5, 120.4, 119.7, 65.4, 64.9, 62.9, 52.3, 49.5, 32.6, 26.9. HRMS (ESI) exact mass calculated for C₂₆H₂₅ClN₅O⁺ ([M+H]⁺): 458.1742, found: 458.1753. HPLC analysis: column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (25:75); UV light: 254 nm; flow: 1 mL /min; major enantiomer *t_r* = 31.30 min, minor enantiomer *t_r* = 15.48 min.

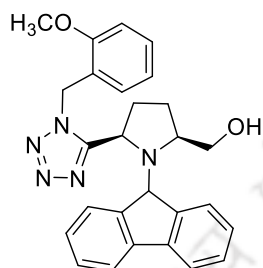
((2S,5R)-1-(9H-fluoren-9-yl)-5-(1-phenyl-1H-tetrazol-5-yl)pyrrolidin-2-yl)methanol (5.45e):

(5.45e): According to the general procedure II : 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), (S)-pyrrolidin-2-ylmethanol (0.38 mmol, 3 equiv, 37 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and phenyl isocyanide (0.13 mmol, 1 equiv, 13 mg) and acetic acid (0.13 mmol, 1 equiv, 7 μ L) in neat condition were reacted for 12

hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:1) to obtain **5.45e** as a brown oil (27 mg, 51%) FTIR (KBr): $\tilde{\nu}$ = 2923, 2852, 1742, 1450, 1261, 1084, 744 cm⁻¹. $[\alpha]_D^{25}$ = - 5.26 (c = 0.38, MeOH) ¹H NMR (600 MHz, CDCl₃) δ = 7.61 (d, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.40 – 7.38 (m, 1H), 7.34 – 7.31 (m, 3H), 7.25 – 7.21 (m, 2H), 7.08 – 7.06 (m, 1H), 6.55 (d, *J* = 7.2 Hz, 2H), 5.12 (s, 1H), 4.12 – 4.09 (m, 2H), 3.78 – 3.76 (m, 1H), 3.68 – 3.67 (m, 1H), 2.54 – 2.48 (m, 1H), 2.12 – 2.08 (m, 1H), 2.00 – 1.96 (m, 1H), 1.84 – 1.79 (m, 1H). ¹³C NMR (151 MHz,

CDCl₃) δ = 160.5, 143.8, 143.7, 141.5, 140.0, 132.9, 130.4, 129.5, 128.8, 128.6, 127.7, 127.6, 126.3, 125.4, 125.1, 120.0, 119.7, 65.2, 64.6, 62.7, 52.6, 33.3, 26.9 ppm. HRMS (ESI) exact mass calculated for C₂₅H₂₄N₅O⁺ ([M+H]⁺): 410.1975, found: 410.1995. HPLC analysis: column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (1:5); UVlight: 291 nm; flow: 1 mL /min; major enantiomer t_r = 24.02 min, minor enantiomer t_r = 20.25 min.

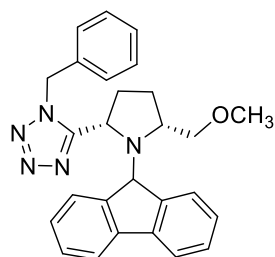
((2S,5R)-1-(9H-fluoren-9-yl)-5-(1-(2-methoxybenzyl)-1H-tetrazol-5-yl)pyrrolidin-2-



yl)methanol (5.45f): According to the general procedure II : 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), (S)-pyrrolidin-2-ylmethanol (0.38 mmol, 3 equiv, 37 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and 1-(isocyanomethyl)-2-methoxybenzene (0.13 mmol, 1 equiv, 19 mg) and acetic acid (0.13 mmol, 1 equiv, 7 μ L)

in neat condition were reacted for 12 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:1) to obtain **5.45f** as a brown solid (30 mg, 51%). FTIR (KBr): $\tilde{\nu}$ = 2923, 2853, 1637, 1495, 1449, 1251, 1082, 1025, 745 cm⁻¹. $[\alpha]_D^{25}$ = - 6.00 (c = 0.50) ¹H NMR (400 MHz, CDCl₃) δ = 7.76 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.36 – 7.32 (m, 1H), 7.29 – 7.27 (m, 1H), 7.20 – 7.13 (m, 2H), 7.04 – 7.02 (m, 1H), 6.73 – 6.63 (m, 3H), 5.12 (s, 1H), 4.83 (d, *J* = 15.2 Hz, 1H), 4.45 (d, *J* = 15.2 Hz, 1H), 4.04 – 4.02 (m, 2H), 3.80 – 3.75 (m, 1H), 3.71 – 3.69 (m, 1H), 3.46 (s, 3H), 2.39 – 2.29 (m, 1H), 2.04 – 1.96 (m, 1H), 1.79 – 1.71 (m, 1H), 1.59 – 1.56 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ = 159.9, 156.4, 144.3, 143.8, 141.8, 139.8, 130.4, 129.8, 128.9, 128.6, 127.7, 127.6, 126.2, 125.6, 121.5, 121.0, 120.4, 119.8, 110.6, 65.0, 64.9, 63.0, 55.2, 44.8, 32.5, 27.1 ppm. HRMS (ESI) exact mass calculated for C₂₇H₂₈N₅O₂⁺ ([M+H]⁺): 454.2238, found: 454.2272. HPLC column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (7:93); UV light: 291 nm; flow: 1 mL /min; major enantiomer t_r = 94.49 min, minor enantiomer t_r = 86.82 min.

5-((2R,5S)-1-(9H-fluoren-9-yl)-5-(methoxymethyl)pyrrolidin-2-yl)-1-benzyl-1H-

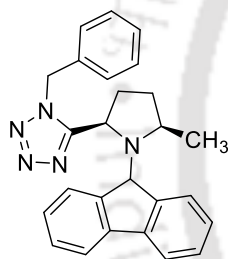


tetrazole(5.45g): According to the general procedure II : 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), (R)-2-(methoxymethyl)pyrrolidine (0.38 mmol, 3 equiv, 47 μ L), trimethylsilyl azide (0.13 mmol, 1 equiv, 17 μ L) and benzyl isocyanide (0.13 mmol, 1 equiv, 15 mg) and acetic acid (0.13 mmol,

1 equiv, 7 μ L) in neat condition were reacted for 12 hours. The crude product was purified by

SiO₂ column chromatography (ethyl acetate: hexane; 1:1) to obtain **5.45g** as a brown solid (35 mg, 53%) FTIR (KBr): $\tilde{\nu}$ = 2925, 2853, 1452, 1261, 1091, 1025, 804, 749, 720 cm⁻¹. $[\alpha]_D^{25}$ = - 40.00 (c= 0.28, MeOH). ¹H NMR (400 MHz, CDCl₃) δ = 7.80 (d, *J* = 7.6 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.50 – 7.46 (m, 1H), 7.36 – 7.28 (m, 3H), 7.20 – 7.14 (m, 3H), 7.11 – 7.07 (m, 1H), 6.70 (d, *J* = 6.8 Hz, 2H), 5.34 (d, *J* = 15.6 Hz, 1H), 5.26 (s, 1H), 4.22 (d, *J* = 15.6 Hz, 1H), 3.93 – 3.84 (m, 2H), 3.66 – 3.63 (m, 1H), 3.55 – 3.51 (m, 1H), 3.41 (s, 3H), 2.08 – 2.02 (m, 2H), 1.74 – 1.67 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ = 158.1, 144.3, 144.2, 141.5, 139.8, 134.3, 129.1, 128.9, 128.7, 128.5, 127.7, 127.6, 127.2, 126.0, 125.9, 120.4, 119.8, 77.6, 66.0, 63.0, 59.4, 53.3, 50.0, 31.7, 28.9. HRMS (ESI) exact mass calculated for C₂₇H₂₈N₅O⁺ ([M+H]⁺): 438.2288, found: 438.2293. HPLC column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (1:5); UV light: 291 nm; flow: 1 mL /min; major enantiomer *t_r* = 11.23 min, minor enantiomer *t_r* = 20.29 min.

5-((2*R*,5*R*)-1-(9*H*-fluoren-9-yl)-5-methylpyrrolidin-2-yl)-1-benzyl-1*H*-tetrazole (rac-5.45h) 5-(1-(9*H*-fluoren-9-yl)-2-methylpyrrolidin-2-yl)-1-benzyl-1*H*-tetrazole (5.45h')

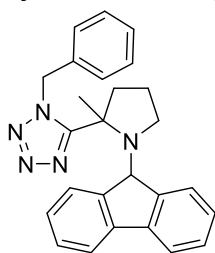


5.45h) According to the general procedure II: 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), *rac* 2-methyl pyrrolidine (0.75 mmol, 3 equiv, 78 μ L), trimethylsilyl azide (0.25 mmol, 1 equiv, 33 μ L) and benzyl isocyanide (0.25 mmol, 1 equiv, 30 mg) and acetic acid (0.25 mmol, 1 equiv, 15 μ L) in neat condition

were reacted for 12 hours. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:1) to obtain **rac-5.45h** as brown solid (49 mg, 48%) and **5.45h'** (24 mg, 24%) as a brown solid. The regioisomeric ratio of **rac-5.45h** and **5.45h'** is (2.1:1).

Analytical data for (**rac-5.45h**): FTIR (KBr): $\tilde{\nu}$ = 3046, 2963, 1607, 1452, 1383, 1128, 1075, 745, 722 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 7.81 (d, *J* = 7.2 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.50 – 7.47 (m, 1H), 7.35 – 7.33 (m, 1H), 7.29 – 7.28 (m, 1H), 7.22 – 7.15 (m, 4H), 7.08 – 7.05 (m, 1H), 6.69 (d, *J* = 7.2 Hz, 2H), 5.28 (d, *J* = 15.6 Hz, 1H), 5.10 (s, 1H), 4.26 (d, *J* = 15.6 Hz, 1H), 3.85 – 3.83 (m, 1H), 3.76 – 3.71 (m, 1H), 2.02 – 1.97 (m, 1H), 1.92 – 1.88 (m, 1H), 1.66 – 1.64 (m, 1H), 1.54 – 1.49 (m, 1H), 1.41 (d, *J* = 6.0 Hz, 3H). ¹³C NMR (151 MHz, CDCl₃) δ = 158.5, 144.2, 144.1, 141.7, 139.7, 134.3, 129.1, 128.9, 128.6, 128.5, 127.6, 127.4, 127.1, 126.2, 126.0, 120.4, 119.7, 63.6, 59.1, 52.3, 50.0, 33.0, 30.9, 20.9 ppm. HRMS (ESI) exact mass calculated for C₂₆H₂₆N₅⁺ ([M+H]⁺): 408.2183, found: 408.2188.

Analytical data for (**5.45h'**): FTIR (KBr): $\tilde{\nu}$ = 3063, 2926, 1649, 1452, 1108, 1068, 744, 736,

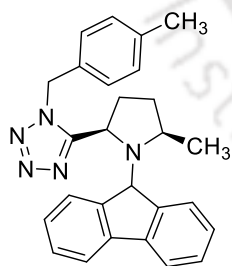


702 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.78 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.53–7.50 (m, 1H), 7.47–7.45 (m, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.24–7.22 (m, 1H), 7.19–7.15 (m, 3H), 7.10–7.07 (m, 1H), 6.57 (d, J = 6.6 Hz, 2H), 5.18 (s, 1H), 4.98 (d, J = 15.0 Hz, 1H), 4.31–4.10 (m, 1H), 3.73 (s, 1H), 2.59

–2.53 (m, 1H), 1.97–1.91 (m, 1H), 1.59–1.56 (m, 1H), 1.54–1.50 (m, 1H), 1.41 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 157.1, 144.4, 144.3, 140.8, 139.0, 134.4, 129.0, 128.9, 128.6, 128.1, 127.7, 127.6, 127.0, 126.6, 125.8, 120.2, 119.7, 60.9, 54.5, 50.0, 49.9, 32.0, 29.5, 19.8. HRMS (ESI) exact mass calculated for $\text{C}_{26}\text{H}_{26}\text{N}_5^+([\text{M}+\text{H}]^+)$: 408.2183, found: 408.2173.

5-((2R,5R)-1-(9H-fluoren-9-yl)-5-methylpyrrolidin-2-yl)-1-(4-methylbenzyl)-1H-tetrazole (rac-19i) and 5-(1-(9H-fluoren-9-yl)-2-methylpyrrolidin-2-yl)-1-(4-methylbenzyl)-1H-tetrazole (rac-19i'): According to the general procedure II : 9-fluorenone imine (0.30 mmol, 1.2 equiv, 54 mg), *rac*-2-methylpyrrolidine (0.75 mmol, 3 equiv, 78 μL), trimethylsilyl azide (0.25 mmol, 1 equiv, 33 μL) and 1-(isocyanomethyl)-4-methylbenzene (0.25 mmol, 1 equiv, 34 mg) and acetic acid (0.13 mmol, 1 equiv, 15 μL) in neat condition were reacted for 12 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane;1:1) to obtain **rac-5.45i** as brown solid (55 mg, 52%) and **5.45i'** (26 ,25%) as brown solid. The region-isomeric ratio of **rac-5.45i** and **5.45i'** is 2.1:1.

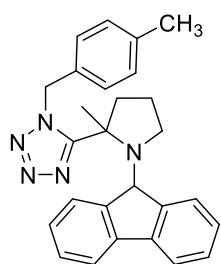
Analytical data for (**rac-5.45i**): FTIR (KBr): $\tilde{\nu}$ = 2961, 2924, 1630, 1449, 1261, 1101, 1020,



800, 745 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ = 7.80 (d, J = 7.2 Hz, 1H), 7.66–7.63 (m, 2H), 7.50–7.47 (m, 1H), 7.35–7.33 (m, 1H), 7.29–7.27 (m, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.07–7.05 (m, 1H), 6.97–6.96 (m, 2H), 6.59–6.57 (m, 2H), 5.23 (d, J = 15.6 Hz, 1H), 5.10 (s, 1H), 4.24 (d, J = 15.6 Hz, 1H), 3.88–3.85 (m, 1H), 3.75–3.70 (m, 1H), 2.25 (s,

3H), 2.02–1.97 (m, 1H), 1.94–1.89 (m, 1H), 1.71–1.66 (m, 1H), 1.56–1.51 (m, 1H), 1.40 (d, J = 6.0 Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 158.4, 144.2, 144.1, 141.7, 139.7, 138.4, 131.3, 129.7, 128.8, 128.6, 127.6, 127.4, 127.1, 126.2, 126.0, 120.4, 119.7, 63.6, 59.1, 52.3, 49.9, 33.0, 30.9, 29.9, 21.3, 20.9. ppm. ^{13}C NMR (151 MHz, CDCl_3) δ = 157.1, 144.4, 144.3, 140.8, 139.0, 138.4, 131.4, 129.7, 128.8, 128.1, 127.7, 127.6, 127.0, 126.6, 125.8, 120.2, 119.7, 60.9, 54.5, 50.0, 49.8, 32.1, 29.5, 21.2, 19.9 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{27}\text{H}_{28}\text{N}_5^+([\text{M}+\text{H}]^+)$: 422.2339, found: 422.2329.

Analytical data for (**5.45 i'**): FTIR (KBr): $\tilde{\nu}$ = 2957, 2924, 2855, 1630, 1450, 1261, 1076, 742,



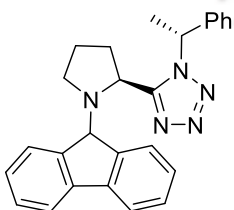
732 cm^{-1} . ^1H NMR (600 MHz, Chloroform-*d*) δ 7.77 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.52–7.49 (m, 1H), 7.46–7.44 (m, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.24–7.21 (m, 1H), 7.09–7.07 (m, 1H), 6.95 (d, J = 7.8 Hz, 2H), 6.47–6.44 (m, 2H), 5.16 (s, 1H), 4.94 (d, J = 15.0 Hz, 1H), 4.31–4.24 (m, 1H), 4.15–4.08 (m, 1H), 3.76–3.63

(s, 1H), 2.59–2.53 (m, 1H), 2.23 (s, 3H), 1.98–1.92 (m, 1H), 1.55–1.50 (m, 1H), 1.40 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 158.5, 144.2, 144.1, 141.7, 139.7, 134.3, 129.1, 128.9, 128.6, 128.5, 127.6, 127.4, 127.1, 126.2, 126.0, 120.4, 119.7, 63.6, 59.1, 52.3, 50.0, 33.0, 30.9, 20.9 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{27}\text{H}_{28}\text{N}_5^+([\text{M}+\text{H}]^+)$: 422.2339, found: 422.2396.

5-((*S*)-1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-((*R*)-1-phenylethyl)-1H-tetrazole (5.49**) and 5-((*R*)-1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-((*R*)-1-phenylethyl)-1H-tetrazole (**d-5.49**):**

According to the general procedure I: 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), pyrrolidine (0.75 mmol, 3 equiv, 62 μL), trimethylsilyl azide (0.25 mmol, 1 equiv, 34 μL) and (*R*)-(1-isocyanoethyl)benzene (0.25 mmol, 1 equiv, 33mg) in 4 mL methanol were reacted for 14 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:6) to obtain 5-((*R*)-1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-((*S*)-1-phenylethyl)-1H-tetrazole (**5.49**) as brown solid (35 mg, 34%) and 5-((*S*)-1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-1-((*R*)-1-phenylethyl)-1H-tetrazole (36 mg, 35%) (**d-5.49**) solid.

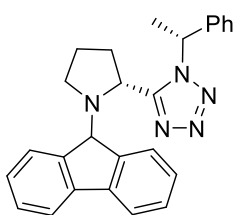
Analytical data for (**5.49**): FTIR (KBr): $\tilde{\nu}$ = 3065, 2810, 1493, 1448, 1301, 1140, 742, 624



cm^{-1} . $[\alpha]_D^{25} = +24.24$ (c = 0.85, MeOH). ^1H NMR (400 MHz, CDCl_3) δ = 7.79 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.50–7.43 (m, 2H), 7.32–7.27 (m, 3H), 7.18–7.17 (m, 3H), 7.10–7.06 (m, 1H), 6.68–6.67 (m, 2H), 5.05 (s, 1H), 4.60–4.55 (m, 1H), 3.85–3.82 (m, 1H), 3.51–

3.46 (m, 1H), 3.24–3.17 (m, 1H), 2.25–2.13 (m, 1H), 1.87–1.77 (m, 1H), 1.65 (d, J = 6.4 Hz, 3H), 1.62–1.57 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ = 158.0, 144.0, 143.5, 141.3, 140.6, 140.0, 128.8, 128.5, 128.3, 127.6, 126.7, 126.2, 125.7, 120.0, 119.5, 65.4, 57.9, 52.2, 51.5, 32.6, 24.3, 22.4 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{26}\text{H}_{26}\text{N}_5^+([\text{M}+\text{H}]^+)$: 408.2183, found: 408.2171. The enantiomeric excess (>96 %) was determined by HPLC analysis: column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (1:9); UV light: 291 nm; flow: 1 mL /min; major enantiomer t_r = 14.62 min, minor enantiomer t_r = 11.28 min.

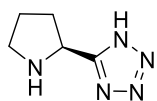
Analytical data for **(d-5.49)**: FTIR (KBr): $\tilde{\nu}$ = 3065, 2810, 1493, 1448, 1301, 1140, 742, 624



cm^{-1} . $[\alpha]_D^{25} = +162.16$ ($c = 0.37$, MeOH). ^1H NMR (400 MHz, CDCl_3) δ = 7.69 – 7.67 (m, 2H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.42 – 7.33 (m, 8H), 7.24 – 7.20 (m, 1H), 6.69 (q, $J = 7.1$ Hz, 1H), 4.97 – 4.93 (m, 1H), 4.69 (s, 1H), 2.73 – 2.68 (m, 1H), 2.22 – 2.17 (m, 1H), 2.13 (d, $J = 7.1$ Hz, 3H), 2.06 – 1.99 (m, 1H), 1.75 – 1.76 (m, 1H), 1.66 – 1.60 (m, 1H), 1.55 – 1.49 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.1, 144.3, 141.8, 141.6, 140.8, 140.4, 129.3, 128.7, 128.7, 128.6, 127.7, 127.3, 126.8, 126.3, 124.9, 120.2, 120.1, 63.7, 58.6, 56.1, 46.7, 30.5, 24.0, 22.7 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{26}\text{H}_{26}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 408.2183, found: 408.2191. The enantiomeric excess (>96 %) was determined by HPLC analysis; column: phenomenex lux 5u cellulose -1; solvent: 2-propanol: hexane (1:5); light: 291 nm; flow: 1 mL /min; major enantiomer $t_r = 14.88$ min, minor enantiomer $t_r = 7.05$ min.

Reaction of *L*-proline with 9-fluorenone imine : According to the general procedure I: 9-fluorenone imine (0.3 mmol, 1.2 equiv, 54 mg), *L*-proline (0.75 mmol, 3 equiv, 87 mg), trimethylsilyl azide (0.25 mmol, 1 equiv, 34 μL) and (*R*)-(1-isocyanoethyl)benzene (0.25 mmol, 1 equiv, 33mg) in 4 mL methanol were reacted for 14 hours. The crude product was purified by SiO_2 column chromatography (ethyl acetate: hexane; 1:6) to obtain 5-((*R*)-1-(9*H*-fluoren-9-yl)pyrrolidin-2-yl)-1-((*S*)-1-phenylethyl)-1*H*-tetrazole (**5.49**) as brown solid (44 mg, 44 %) and 5-((*S*)-1-(9*H*-fluoren-9-yl)pyrrolidin-2-yl)-1-((*R*)-1-phenylethyl)-1*H*-tetrazole (42 mg, 42 %) (**d-5.49**) solid.

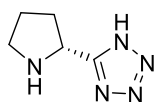
(*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (5.47): 5-((*S*)-1-(9*H*-fluoren-9-yl)pyrrolidin-2-yl)-1-



((*R*)-1-phenylethyl)-1*H*-tetrazole (**5.49**) (0.28 mmol, 1 equiv, 115 mg) was dissolved in ethyl acetate and methanol (3:1, v/v). Palladium (10%) on charcoal (0.49 mmol, 2 equiv, 56 mg) was added to it. Then the flask was evacuated and re-filled with hydrogen. The process was repeated three times. Then, the reaction mixture was kept on shaking at 40 PSI of hydrogen for 72 hours. After the completion of the reaction, the reaction mixture was filtered through a pad of celite, and the celite pad was washed successively with methanol (5×5 mL) and ethyl acetate (2× 5 mL). The filtrate was concentrated under reduced pressure to obtain brown gummy compound which was washed with distilled hexane (3×10 mL) and chloroform (10×3 mL) successively. Finally, the residual solvent was removed under reduced pressure to obtain the analytically pure compound **5.47** as brown solid (28 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = . $[\alpha]_D^{25} = -8.75$ (MeOH, $c = 0.80$) (reported

value: $[\alpha]_D^{26} = -8.57$ (MeOH, $c = 0.63$).¹ ^1H NMR (600 MHz, MeOD) $\delta = 3.48 - 3.43$ (m, 2H), 2.55 – 2.50 (m, 1H), 2.37 – 2.33 (m, 1H), 2.29 – 2.26 (m, 1H), 2.22 – 2.16 (m, 1H). HRMS (ESI) exact mass calculated for $\text{C}_5\text{H}_{10}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 140.0931, found: 140.0933.

(R)-5-(pyrrolidin-2-yl)-1H-tetrazole (ent-5.47): 5-((R)-1-(9H-fluoren-9-yl)pyrrolidin-2-yl)-



1-((R)-1-phenylethyl)-1H-tetrazole (**d-5.49**) (0.25 mmol, 1 equiv, 100 mg)

was dissolved in ethyl acetate and methanol (3:1, v/v). Palladium (10%) on charcoal (0.5 mmol, 2 equiv, 53 mg) was added to it. Then the flask was evacuated and re-filled with hydrogen. The process was repeated three times. Then, the reaction mixture was kept on shaking at 40 PSI of hydrogen for 72 hours. After the completion of the reaction, the reaction mixture was filtered through a pad of celite, and the celite pad was washed successively with methanol (5×5 mL) and ethyl acetate (2× 5 mL). The filtrate was concentrated under reduce pressure to obtain a brown gummy compound which was washed with distilled hexane (3×10 mL) and chloroform (10×3 mL) successively. Finally, the residual solvent was removed under reduced pressure to obtain the analytically pure compound **ent-5.47** as grey solid (27 mg, 78%). FTIR (KBr): $\tilde{\nu} = 2960, 1651, 1634, 1428, 1409, 1009, 831$ cm^{-1} $[\alpha]_D^{25} = +8.0$ ($c = 0.80$ MeOH). ^1H NMR (400 MHz, DMSO) $\delta = 4.81 - 4.77$ (m, 1H), 3.32 – 3.26 (m, 2H), 2.40 – 2.32 (m, 1H), 2.21 – 2.13 (m, 1H), 2.10 – 1.98 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO) $\delta = 157.9, 55.1, 44.7, 30.0, 23.3$. HRMS (ESI) exact mass calculated for $\text{C}_5\text{H}_{10}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 140.0931, found: 140.0935.

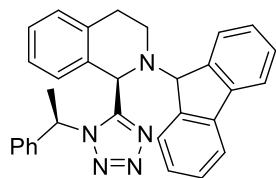
(R)-2-(9H-fluoren-9-yl)-1-(1-((R)-1-phenylethyl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline: (5.50) and (S)-2-(9H-fluoren-9-yl)-1-(1-((R)-1-phenylethyl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline: (d-5.50).

According to the general procedure II : 9-fluorenone imine (0.15 mmol, 1.2 equiv, 27 mg), 1,2,3,4-tetrahydroisoquinoline (0.75 mmol, 3 equiv, 96 μL), trimethylsilyl azide (0.25 mmol, 1 equiv, 34 μL) and (R)-(1-isocyanoethyl)benzene (0.25 mmol, 1 equiv, 33mg) in 4 mL methanol were reacted for 24 hours. After the completion of the reaction, the solid product was precipitated from the reaction mixture. Then the solid product was washed with (3×5 mL) methanol to obtain (**5.50**) as white solid (40 mg). Next, mother liquor was evaporated under reduced pressure. The crude product was purified by SiO_2 column chromatography

¹ N. Momiyama, H. Torii, S. Satio, H. Yamamoto, *Proc. Nat. Acad. Sci. U. S. A.* **2004**, *101*, 5374.

(ethyl acetate: hexane; 1:20) to obtain additional amount (**5.50**) (10 mg) and (**d-5.50**) (26 mg, 22%). The combined yield of (**5.50**) is (50 mg, 43%).

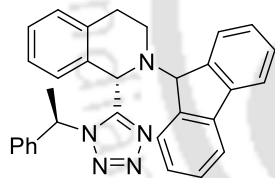
Analytical data for (**5.50**): FTIR (KBr): $\tilde{\nu}$ = 3035, 3020, 2923, 1650, 1450, 1433, 1377, 1240,



736, 722 cm^{-1} . $[\alpha]_D^{25} = +210.77$ ($c = 0.26$, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ = 8.03 (d, $J = 7.2$ Hz, 1H), 7.71 (t, $J = 7.6$ Hz, 2H), 7.52 (d, $J = 7.2$ Hz, 1H), 7.41 (q, $J = 7.73$ Hz, 2H), 7.36 – 7.28 (m, 2H), 7.10 – 7.03 (m, 2H), 7.02 – 6.95 (m, 3H), 6.71 (d, $J = 7.6$ Hz,

2H), 6.58 (t, $J = 7.6$ Hz, 1H), 6.52 (s, 1H), 6.30 – 6.25 (m, 2H), 4.51 (s, 1H), 3.08 – 3.00 (m, 1H), 2.61 – 2.57 (m, 1H), 2.51 – 2.47 (m, 1H), 2.43 – 2.36 (m, 1H), 2.11 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 154.8, 143.8, 141.8, 141.5, 141.4, 138.5, 134.6, 132.6, 129.1, 128.9, 128.8, 128.5, 127.8, 127.6, 127.5, 127.2, 126.6, 126.5, 124.5, 120.4, 120.0, 65.8, 58.9, 58.0, 42.9, 29.9, 24.0 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{31}\text{H}_{28}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 470.2339, found: 470.2345. The enantiomeric excess (>92%) was determined by HPLC column: chiralpak IA; solvent: 2-propanol: hexane (3:97); light: 291 nm; flow: 1 mL/min; major enantiomer $t_r = 12.81$ min, minor enantiomer $t_r = 10.81$ min.

Analytical data for (**d-5.50**): FTIR (KBr): $\tilde{\nu}$ = 3063, 2925, 1715, 1652, 1450, 1263, 744 cm^{-1}

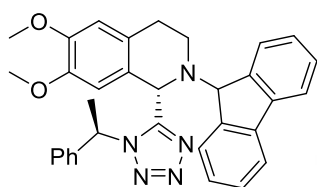


$[\alpha]_D^{25} = -192.31$ ($c = 0.26$, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ = 7.89 (d, $J = 6.4$ Hz, 1H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.41 – 7.29 (m, 5H), 7.27 – 7.20 (m, 6H), 7.04 (s, 1H), 6.95 – 6.91 (m, 1H), 6.35 – 6.15 (m, 3H), 5.28 (s, 1H), 4.58 (s, 1H), 3.04

– 2.96 (m, 1H), 2.73 – 2.56 (m, 3H), 1.39 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ = 155.9, 143.3, 142.4, 141.2, 140.9, 140.2, 135.5, 133.3, 129.6, 129.3, 128.6, 128.5, 128.4, 127.8, 127.5, 127.3, 127.0, 126.9, 126.8, 126.7, 125.4, 120.3, 119.5, 66.4, 59.0, 56.1, 43.3, 30.0, 23.1 ppm. HRMS (ESI) exact mass calculated for $\text{C}_{31}\text{H}_{28}\text{N}_5^+$ ($[\text{M}+\text{H}]^+$): 470.2339, found: 470.2339. The enantiomeric excess (>96%) was determined by HPLC column: chiralpak IA; solvent: 2-propanol: hexane (4:96); light: 291 nm; flow: 1 mL/min; major enantiomer $t_r = 9.54$ min, minor enantiomer $t_r = 15.7$ min.

(S)-2-(9H-fluoren-9-yl)-6,7-dimethoxy-1-((R)-1-phenylethyl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydroisoquinoline (d-5.51): According to the general procedure I: 9-fluorenone imine (0.6 mmol, 1.2 equiv, 54 mg), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1.5 mmol, 3 equiv, 344 mg), trimethylsilyl azide (0.5 mmol, 1 equiv, 68 μL) and (R)-(1-isocyanoethyl)benzene (0.5 mmol, 1 equiv, 66 mg) in 6 mL methanol were reacted for 24

hours. After the completion of the reaction, the solid product was precipitated from the reaction mixture. Then the solid product was washed with (3×5 mL) methanol to obtain (**d-5.51**) as white solid (48 mg). Next, mother liquor was evaporated under reduced pressure. The crude product was purified by SiO₂ column chromatography (ethyl acetate: hexane; 1:5) to obtain additional amount (**d-5.51**) (100 mg) compound. The combined yield of (**d-5.51**) is (148 mg, 56 %).



FTIR (KBr): $\tilde{\nu}$ = 3065, 2927, 2817, 1609, 1520, 1448, 1254, 1007, 748, 768 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ = 8.01 (d, J = 7.2 Hz, 1H), 7.74 – 7.71 (m, 2H), 7.50 (d, J = 7.2 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.36 – 7.34 (m, 1H), 7.31 – 7.29 (m, 1H), 7.13 – 7.11 (m, 1H), 7.03 – 7.01 (m, 2H), 6.75 (d, J = 7.2 Hz, 2H), 6.46 (s, 1H), 6.42 (s, 1H), 6.31 (q, J = 7.2 Hz, 1H), 5.55 (s, 1H), 4.51 (s, 1H), 3.80 (s, 3H), 3.16 (s, 3H), 2.98 – 2.90 (m, 1H), 2.51 – 2.40 (m, 3H), 2.12 (d, J = 7.2 Hz, 3H). ¹³C NMR (151 MHz, CDCl₃) δ = 155.1, 148.5, 147.6, 144.0, 141.9, 141.5, 141.4, 138.9, 128.9, 128.8, 128.2, 127.9, 127.8, 127.5, 127.1, 126.7, 126.1, 124.6, 124.3, 120.5, 120.0, 111.2, 109.5, 65.9, 59.1, 57.6, 66.0, 55.4, 43.1, 29.5, 24.1 ppm. ¹³C NMR (151 MHz, CDCl₃) δ = 155.9, 148.6, 148.0, 143.3, 142.7, 141.1, 140.9, 140.2, 129.4, 128.5, 128.5, 128.4, 127.8, 127.5, 127.4, 126.8, 125.5, 124.8, 120.3, 119.5, 111.6, 109.0, 66.8, 58.8, 60.6, 56.1, 56.0, 43.6, 29.6, 23.5 ppm. HRMS (ESI) exact mass calculated for C₃₃H₃₂N₅O₂⁺ ([M+H]⁺): 530.2551, found: 530.2549.

5.13. References:

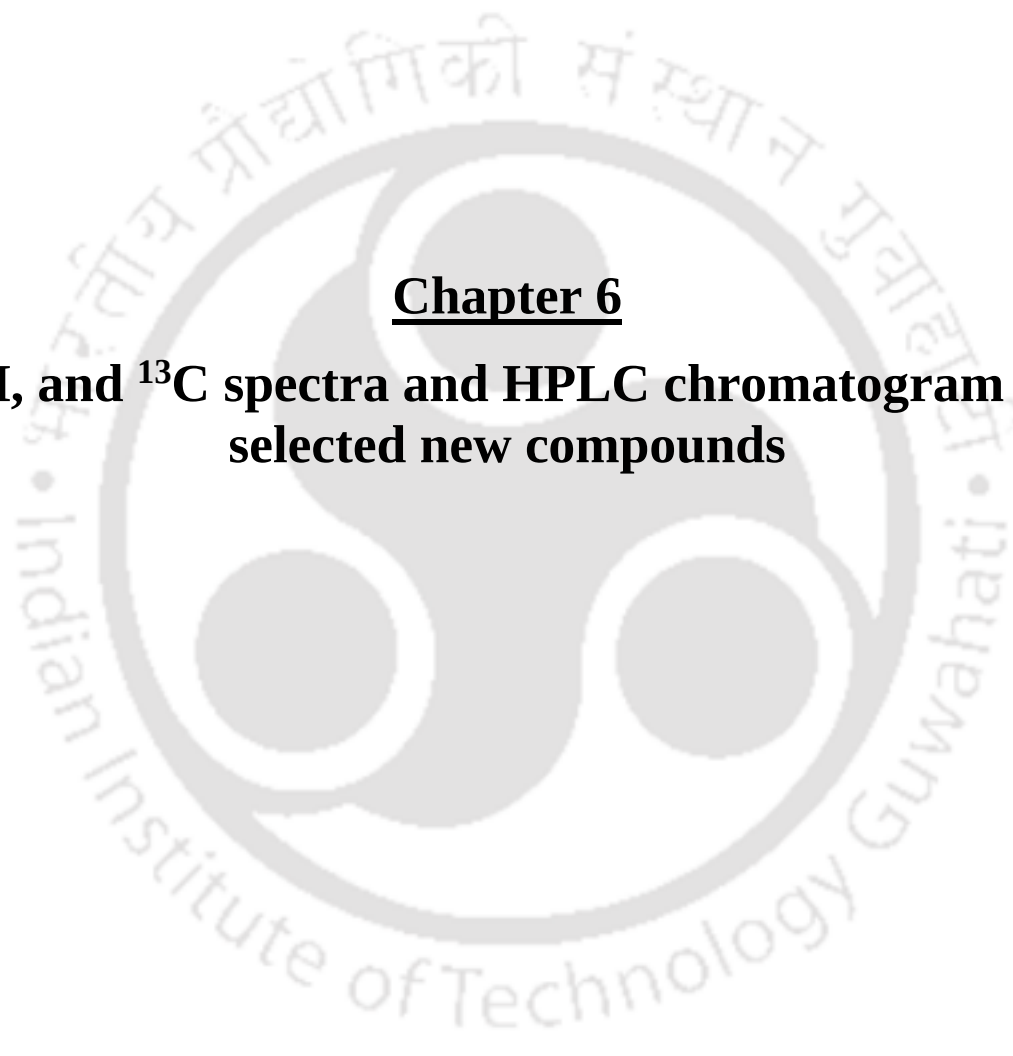
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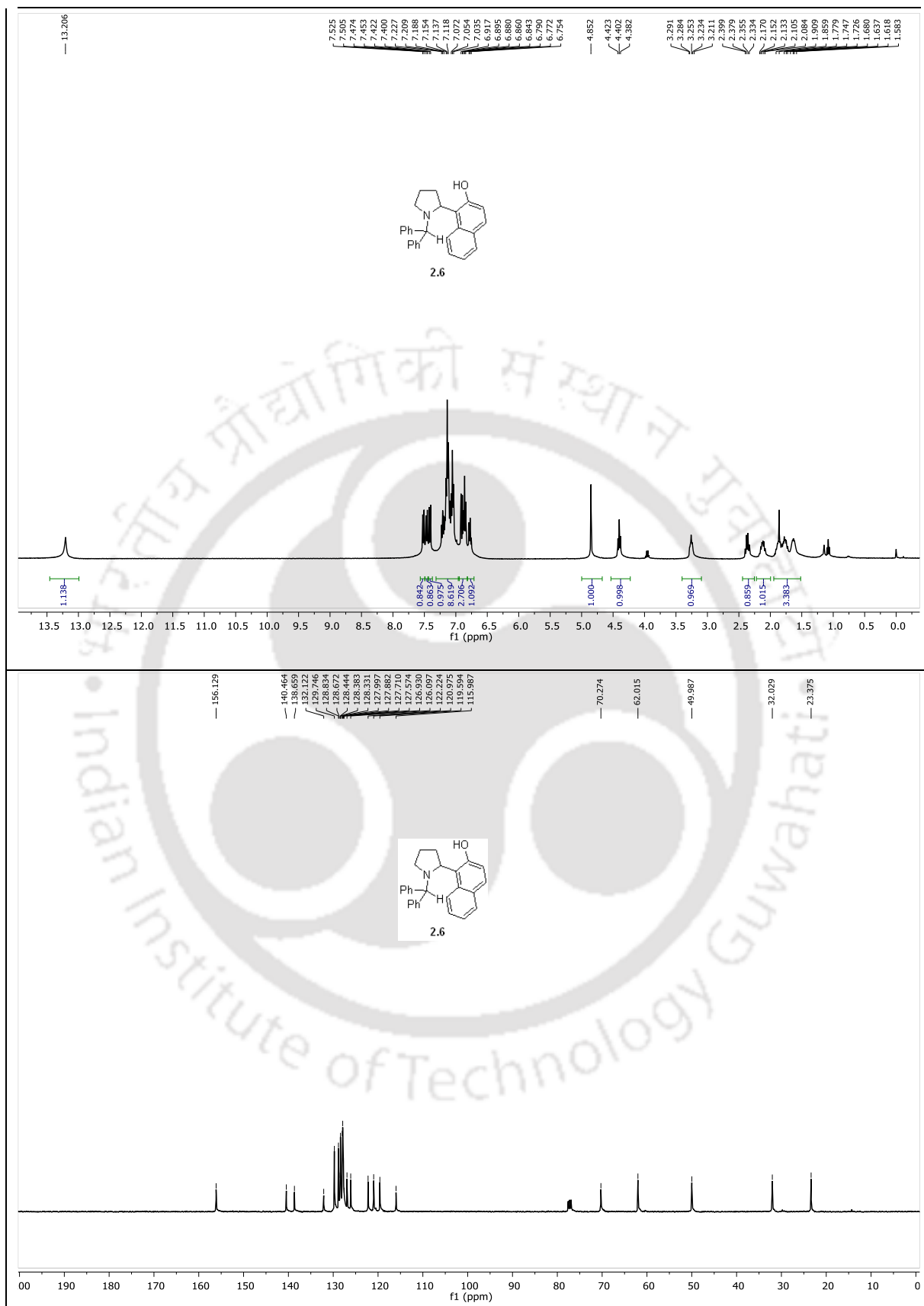


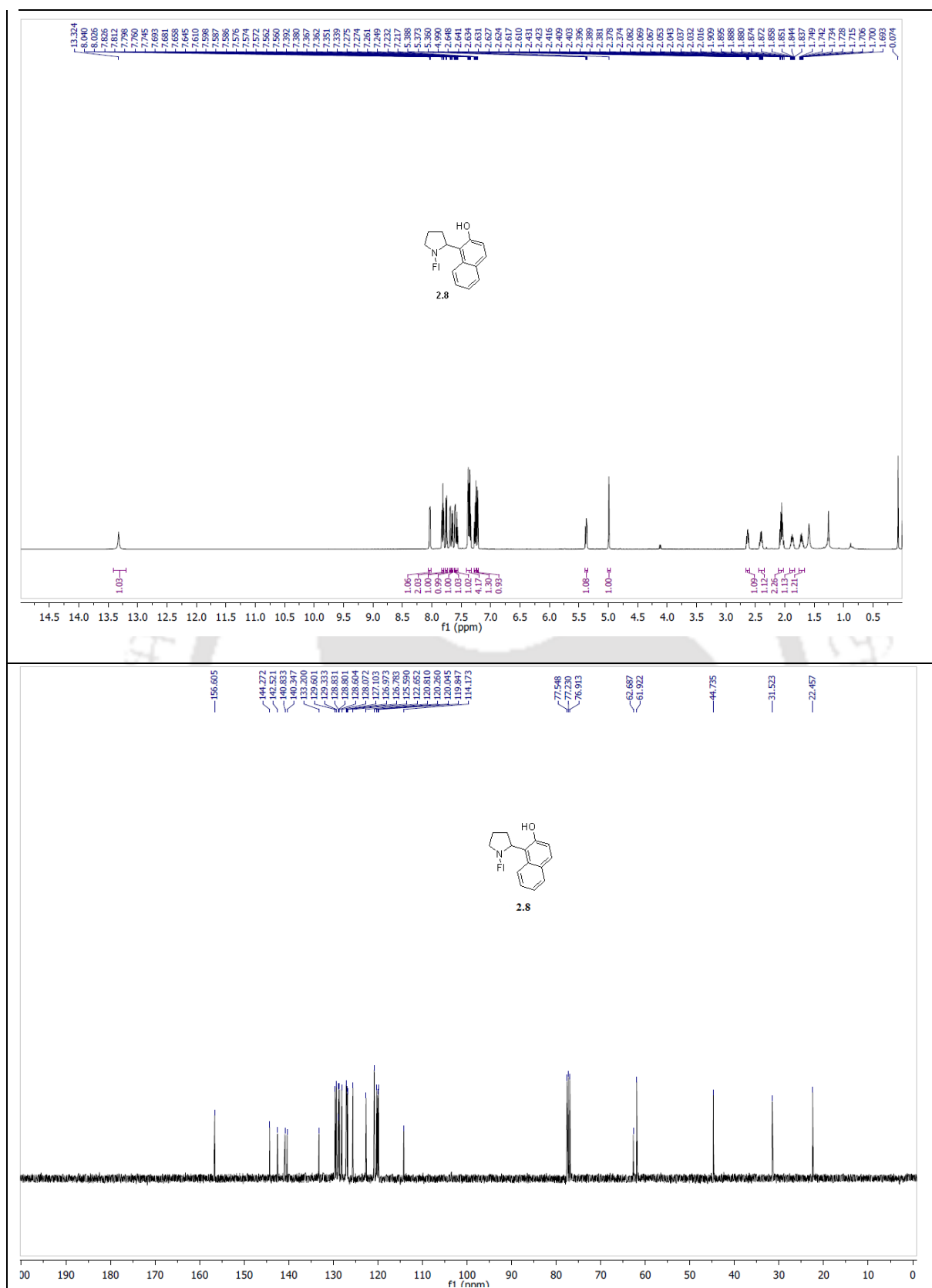
Chapter 6

^1H , and ^{13}C spectra and HPLC chromatogram of selected new compounds

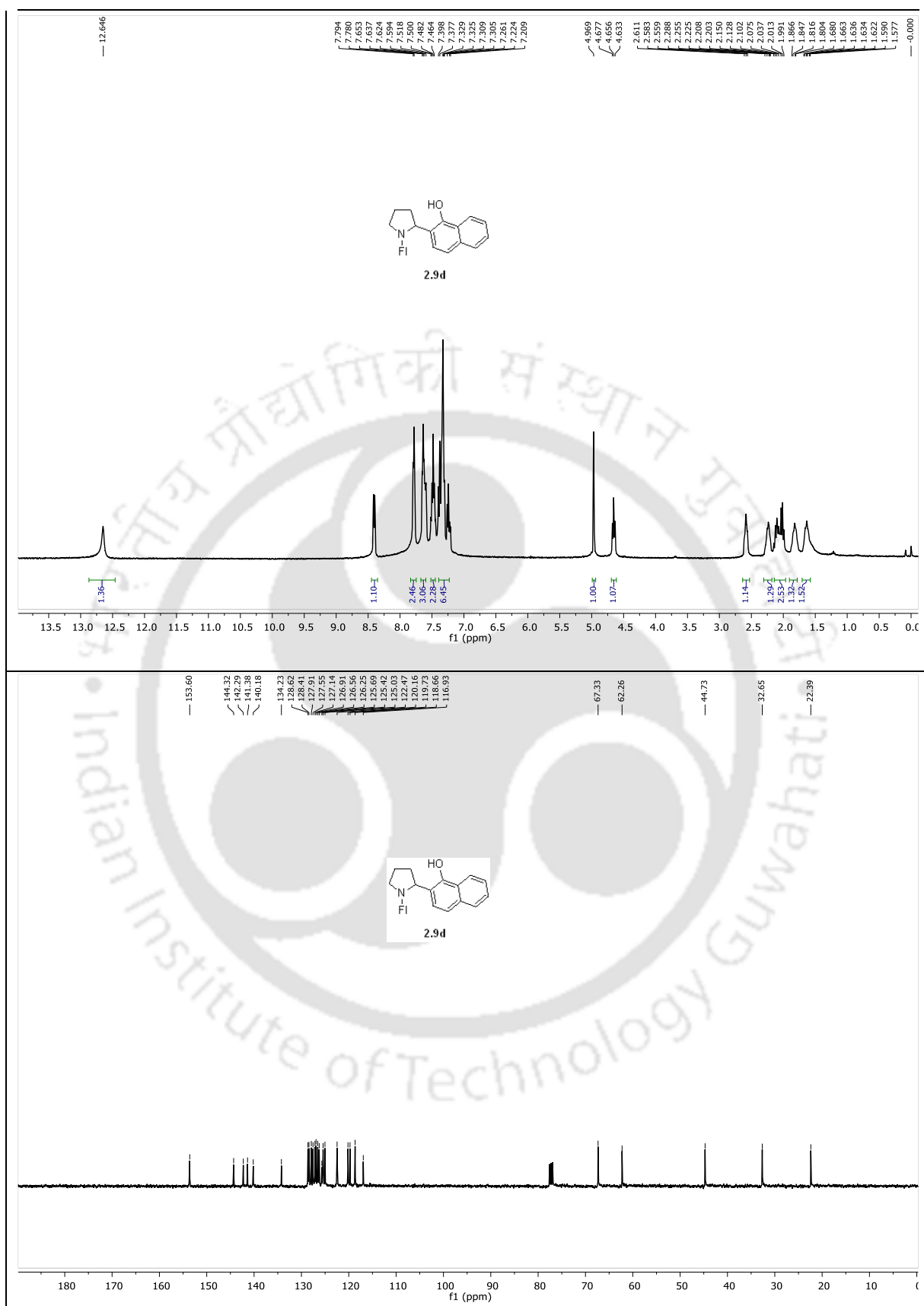


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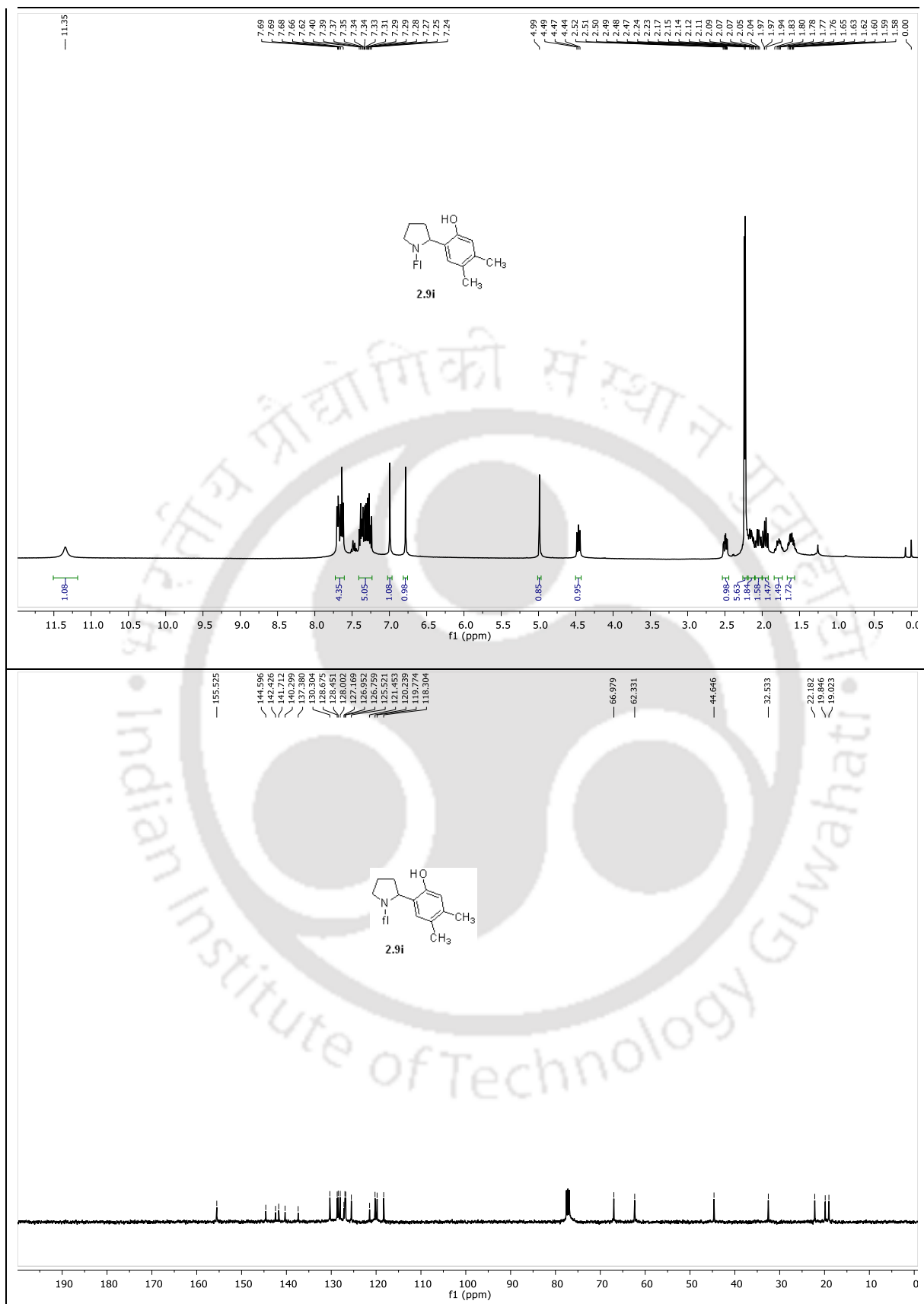




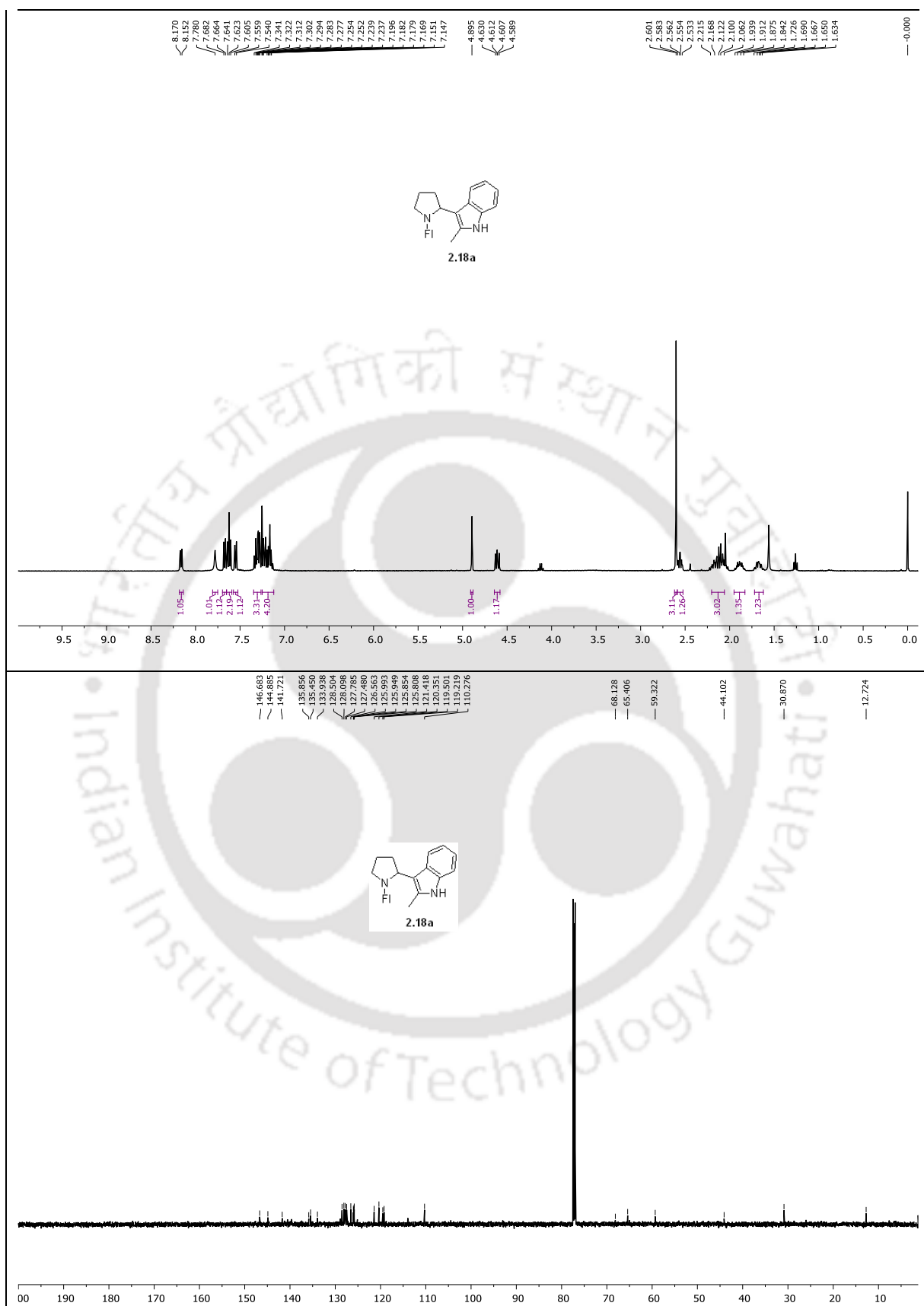
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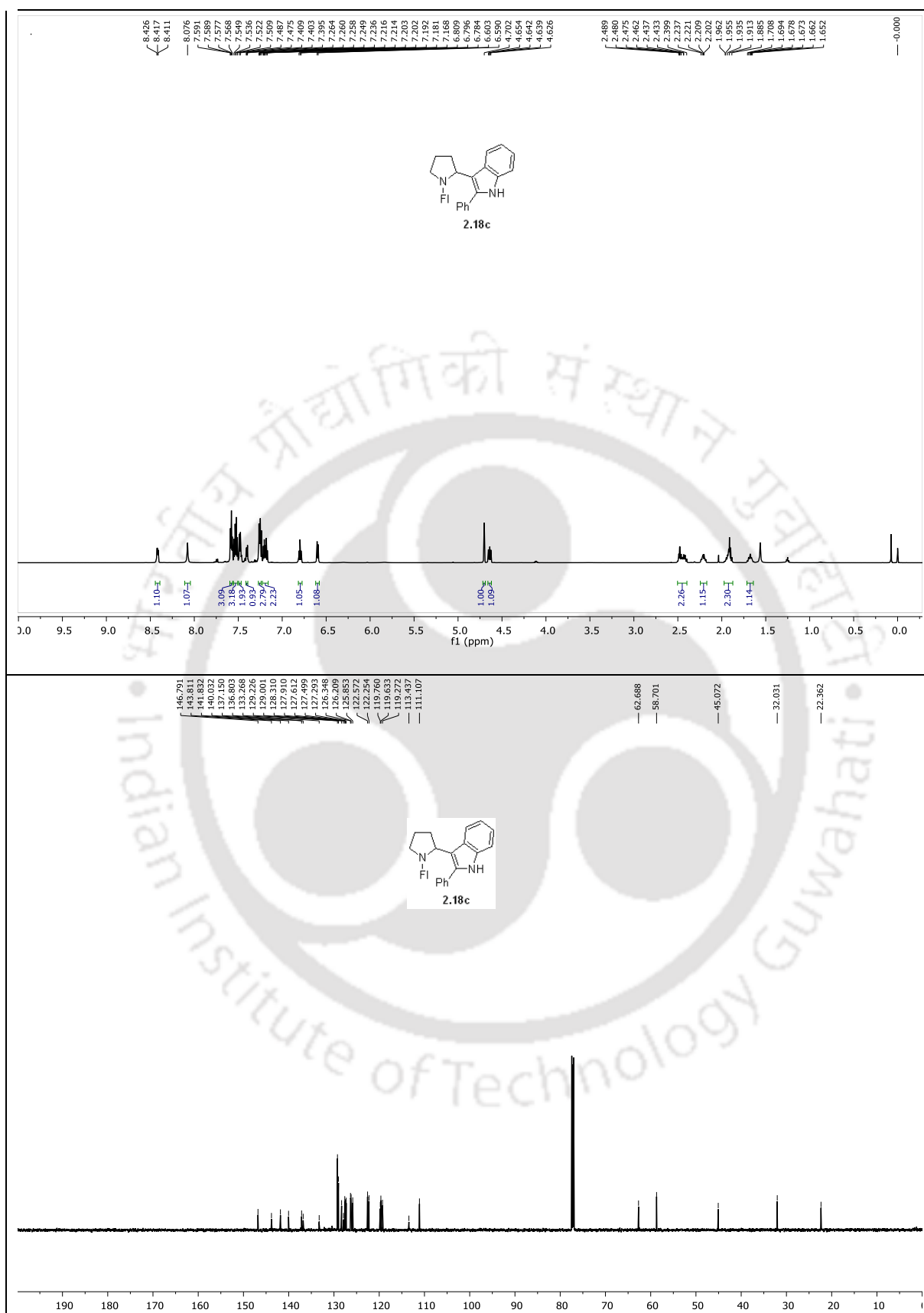


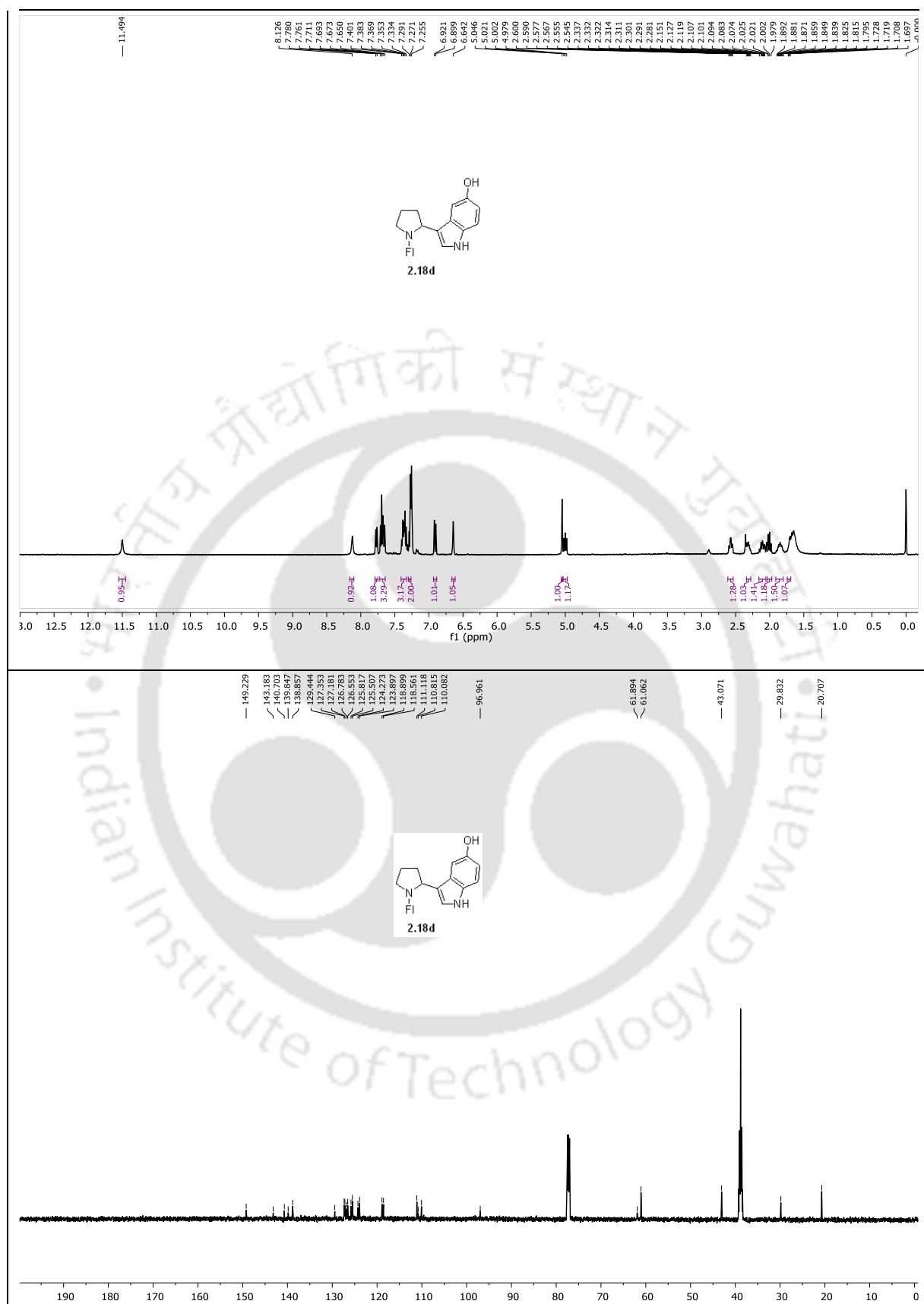
Chapter 6



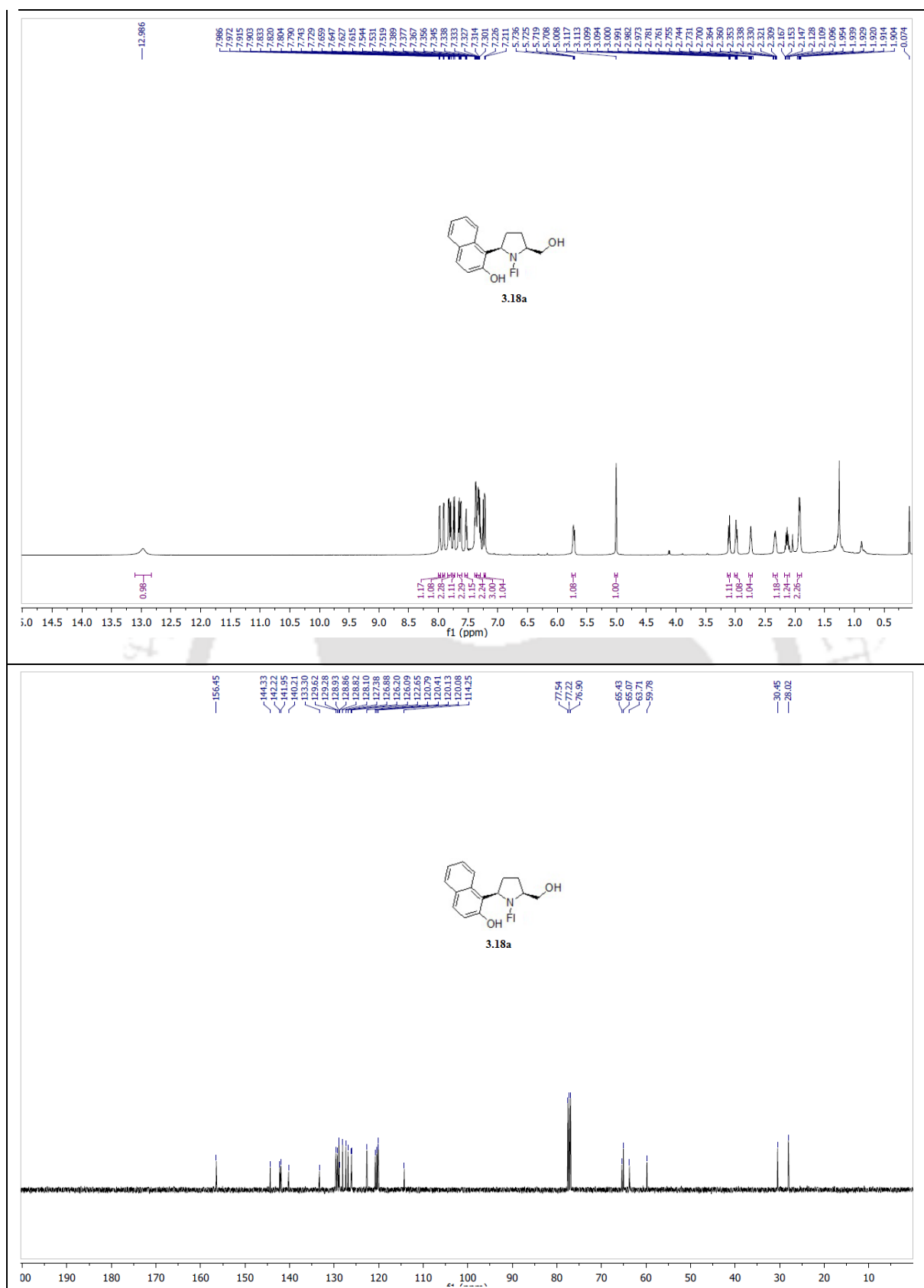
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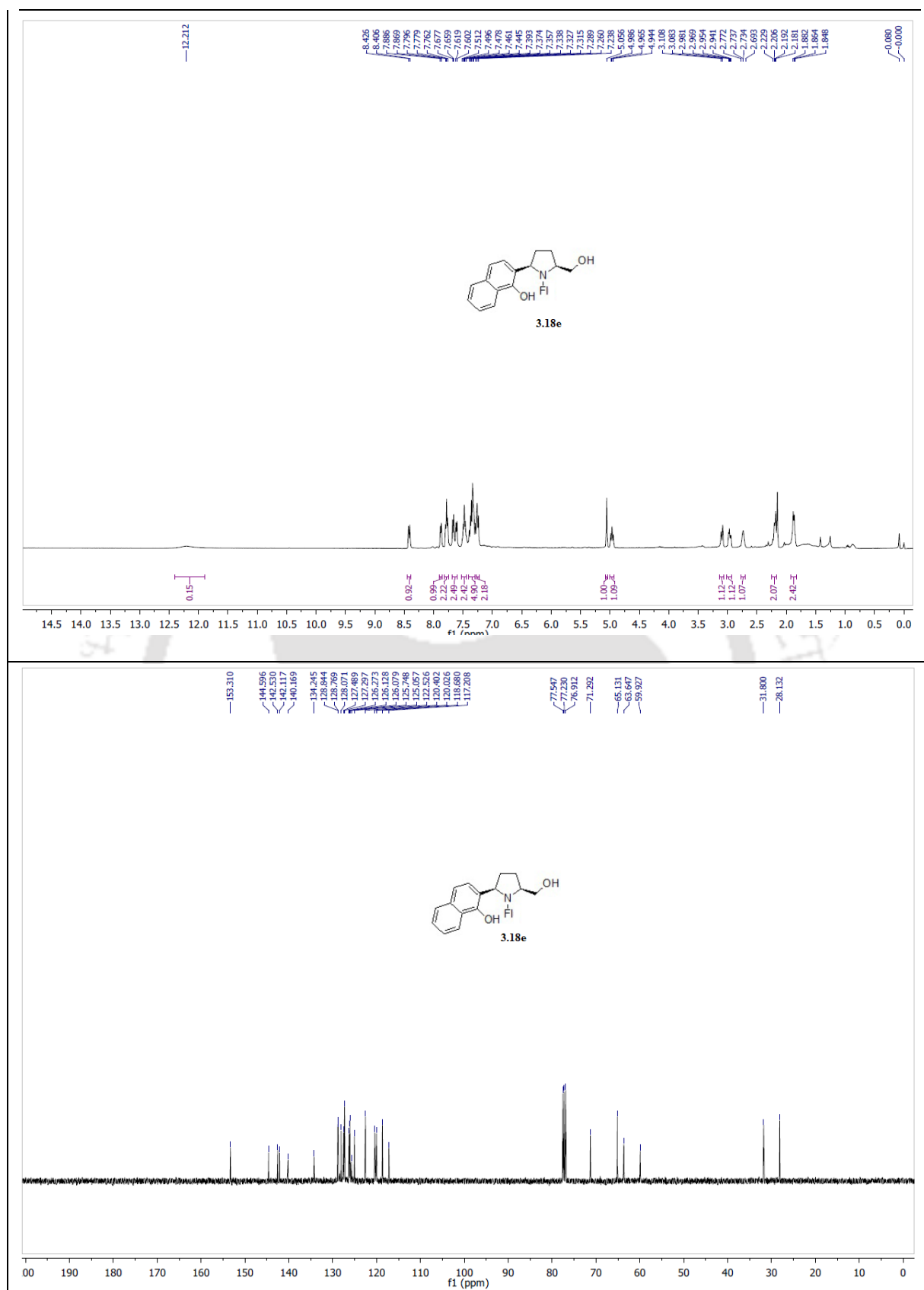


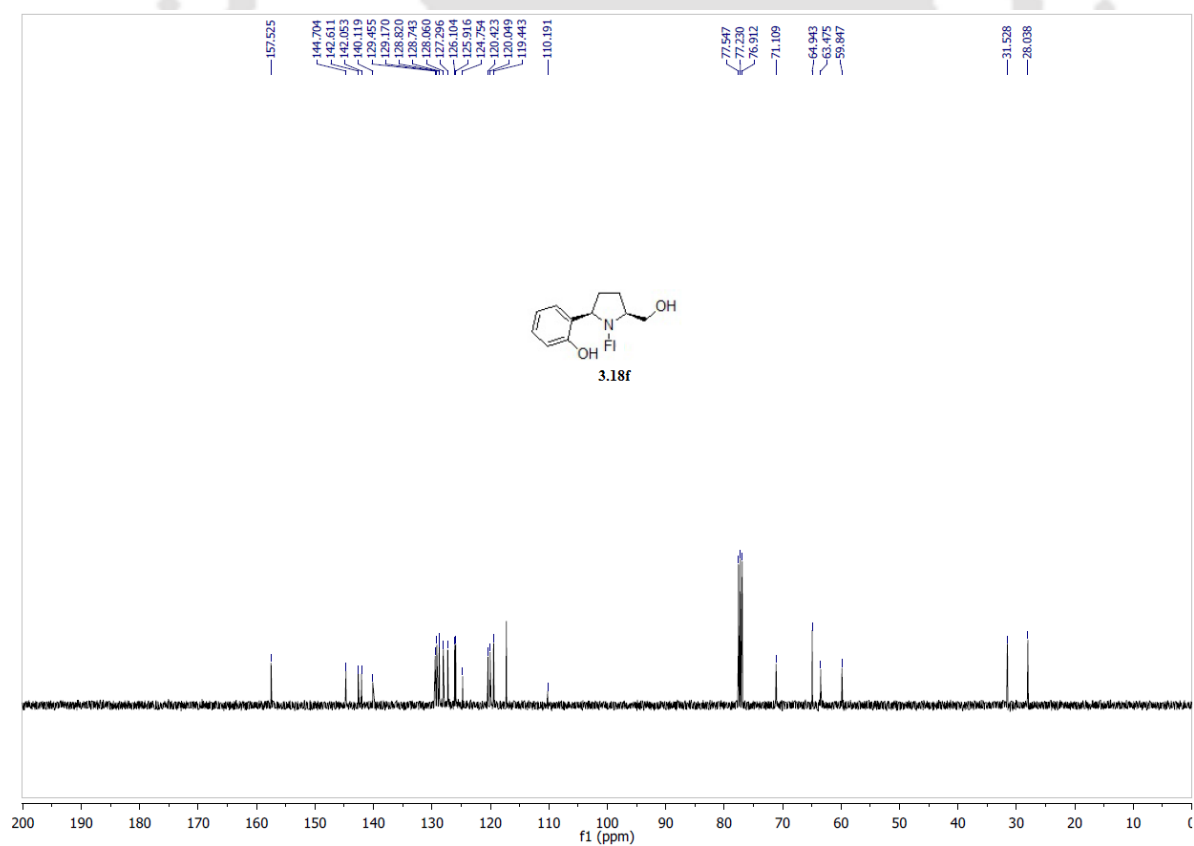
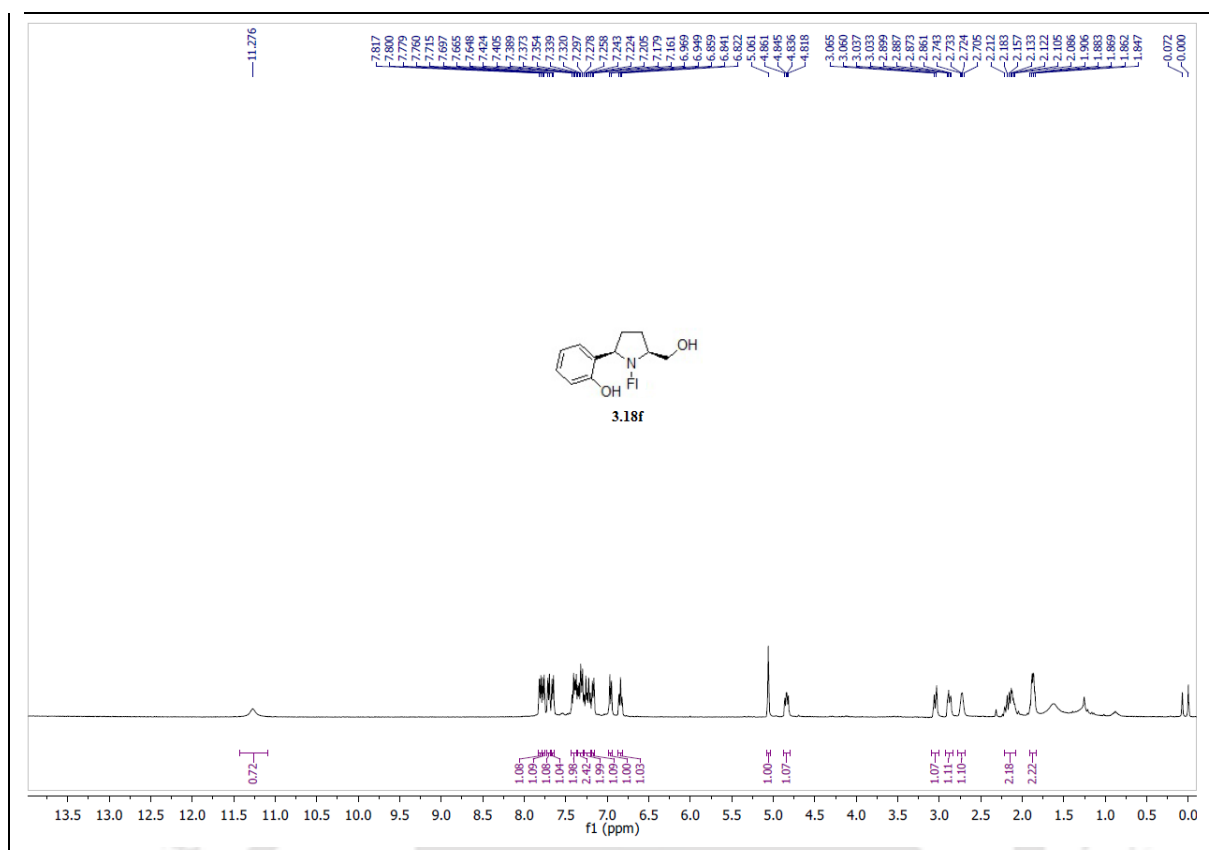


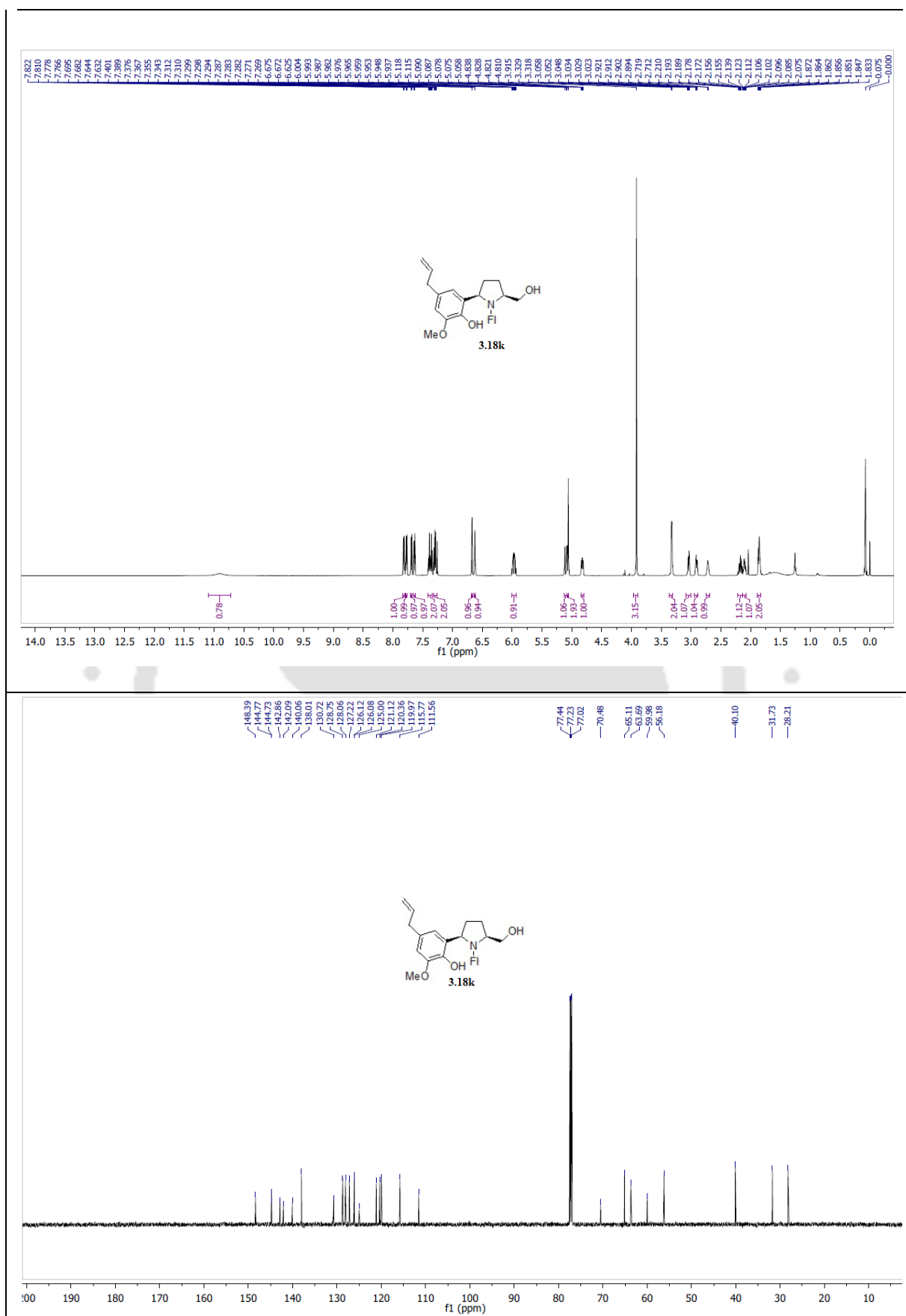
Chapter 6

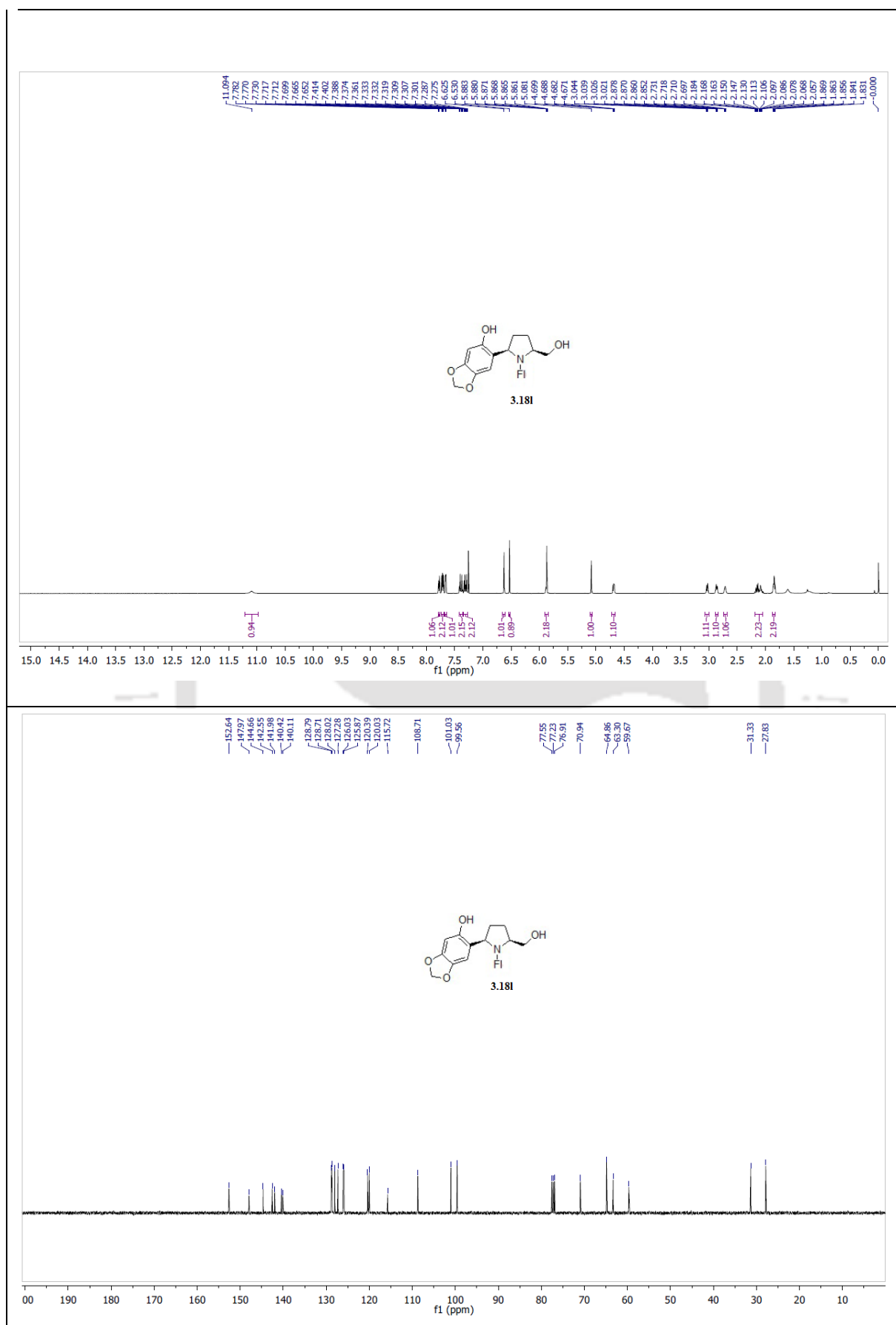


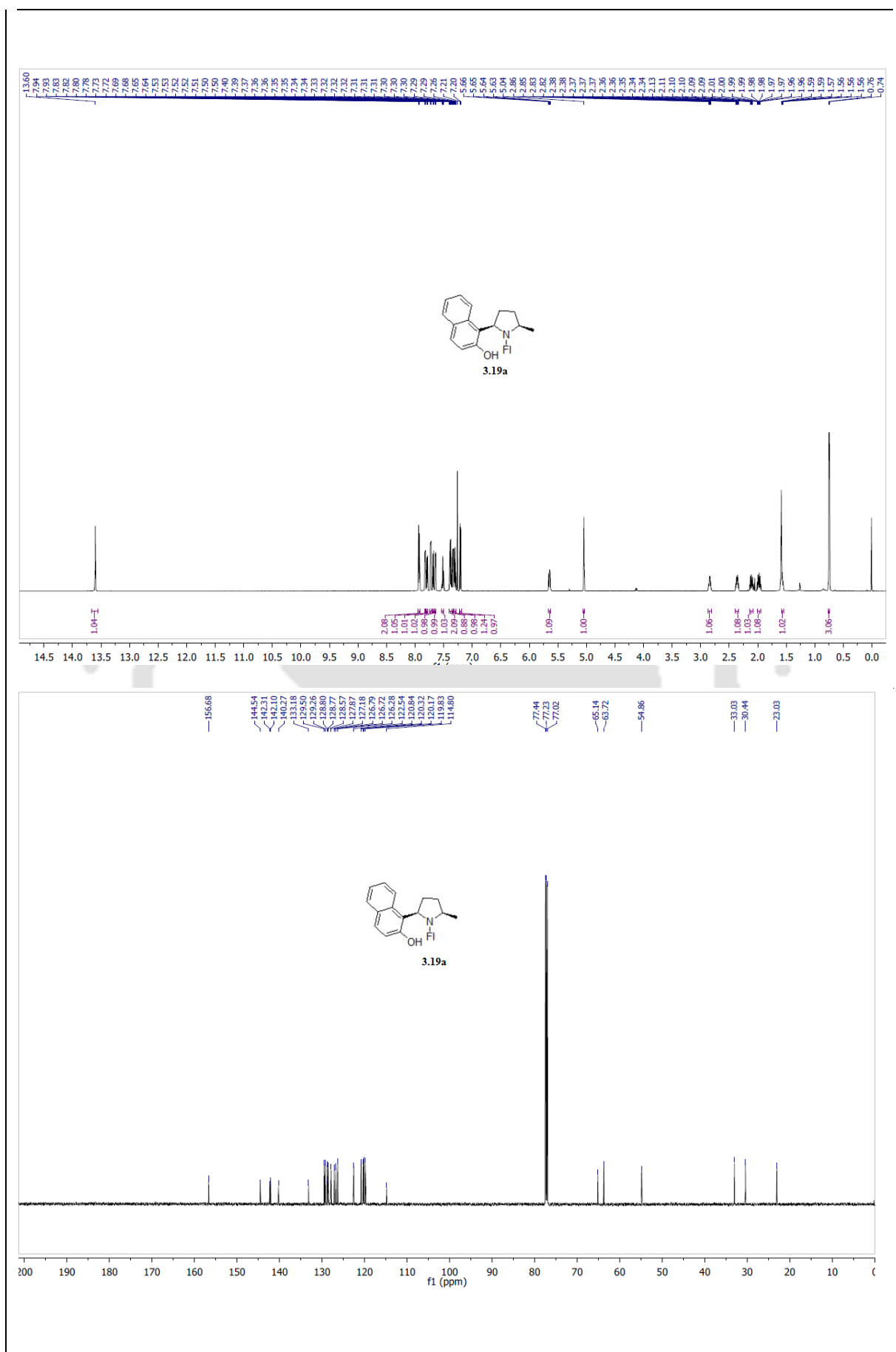
^1H , & ^{13}C spectra & HPLC chromatogram of selected new compounds



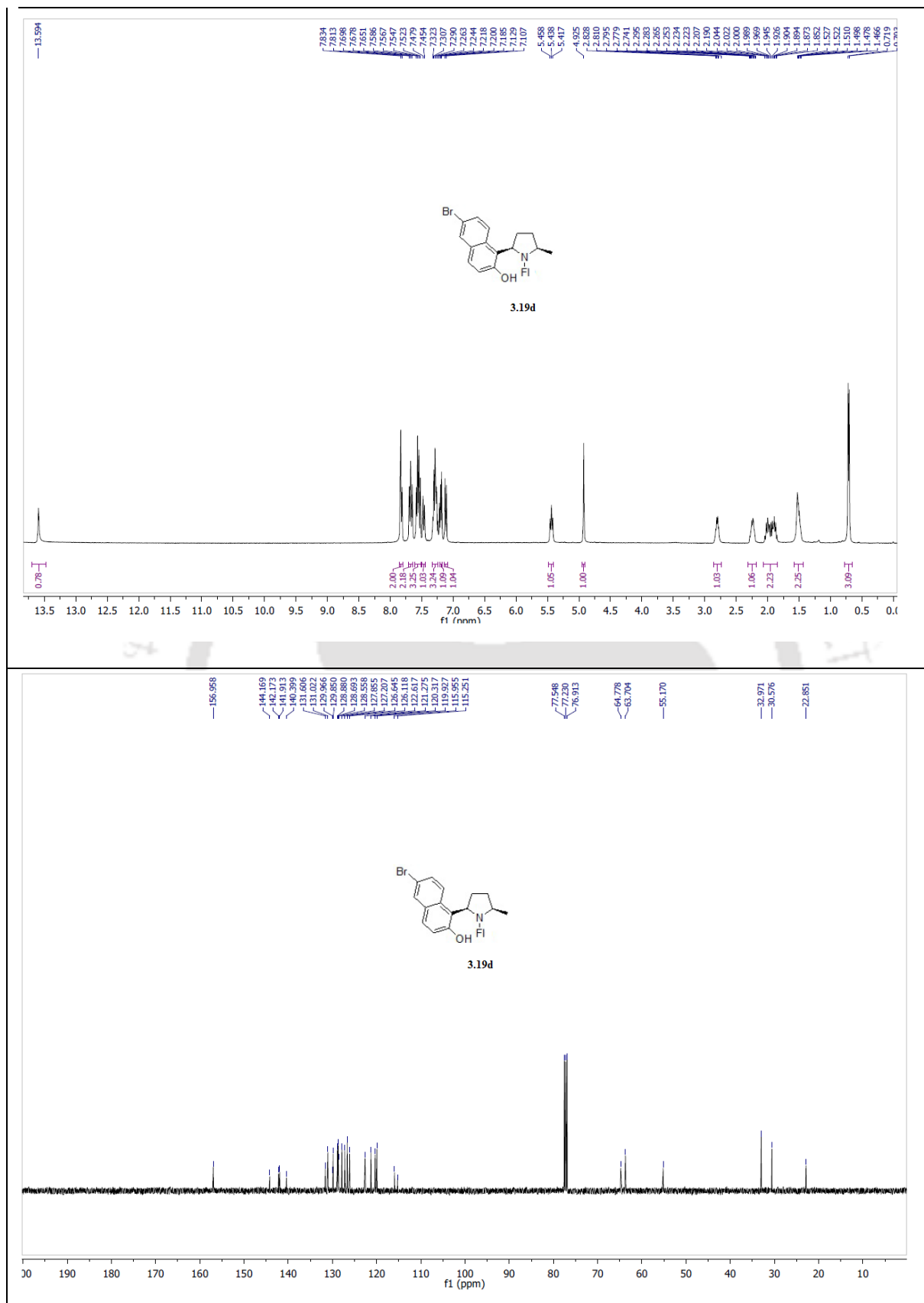




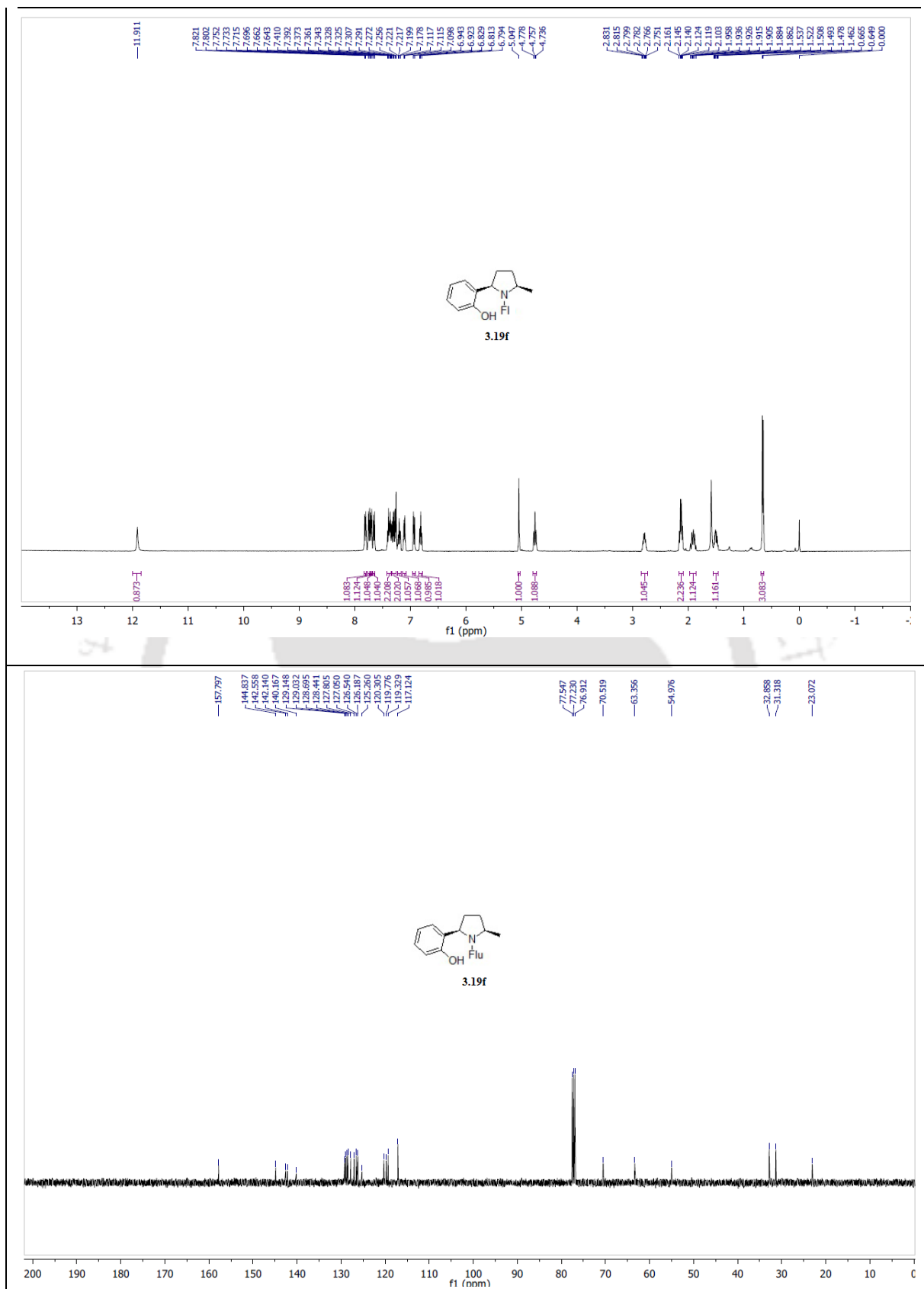




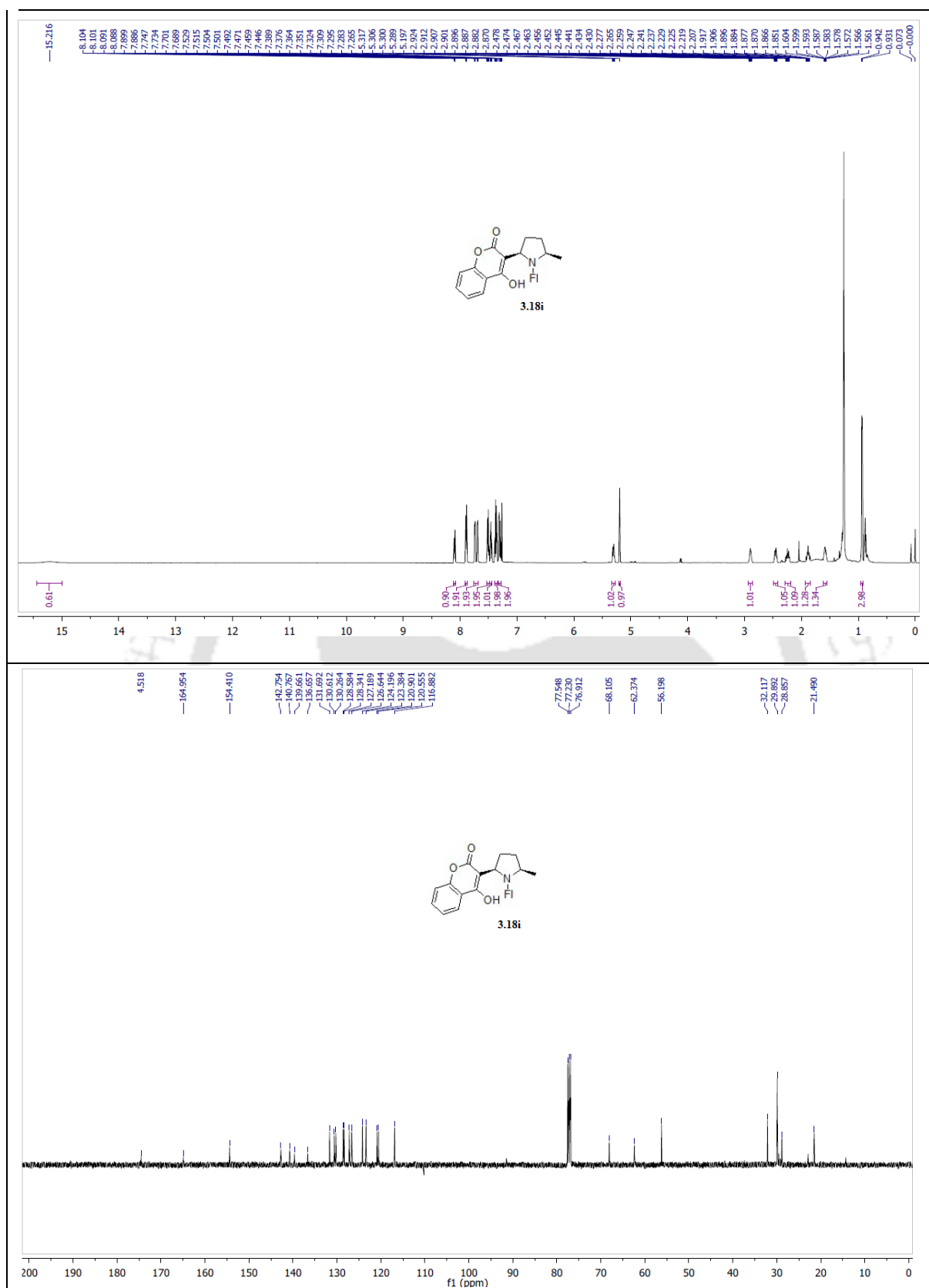
Chapter 6



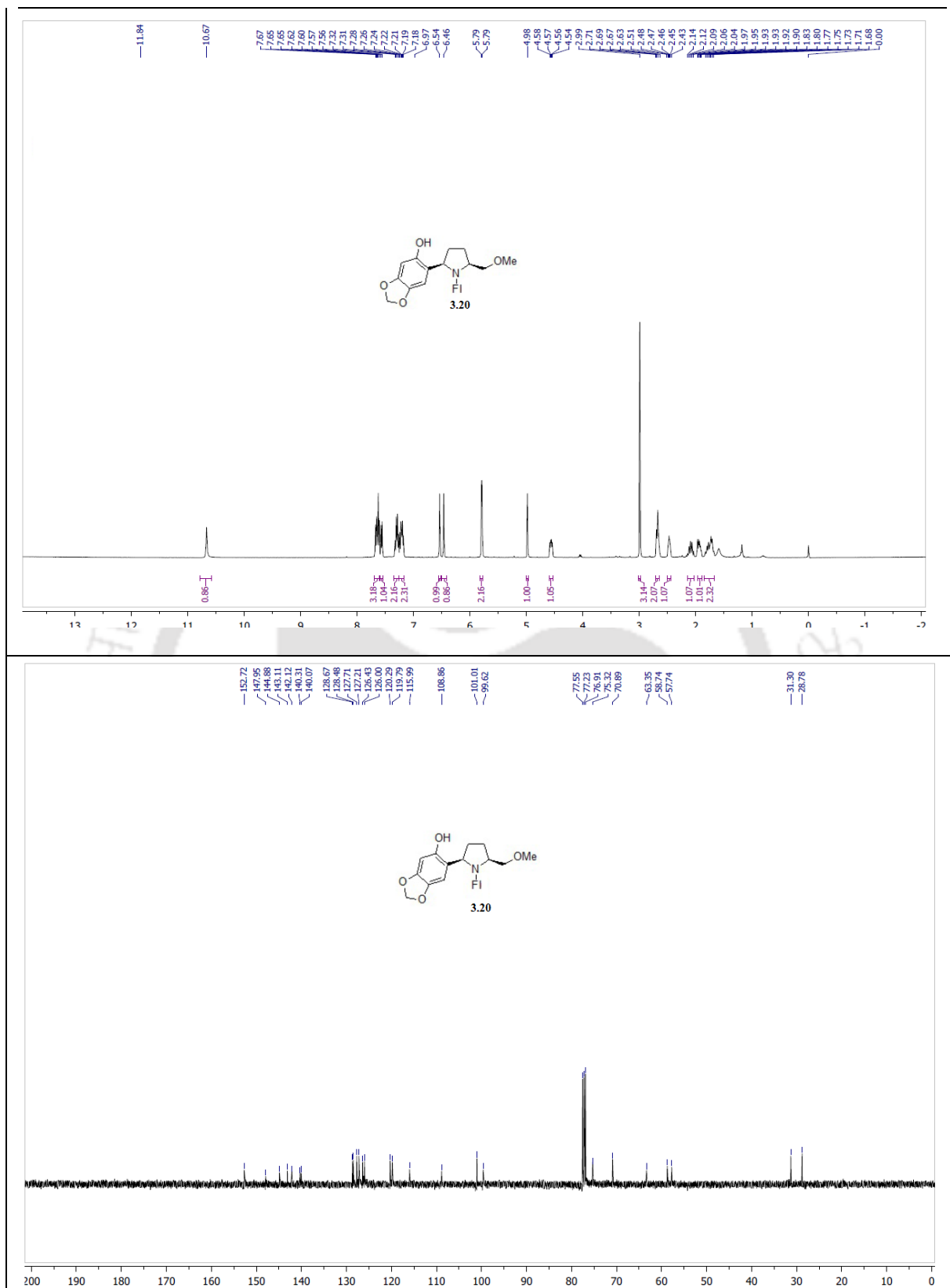
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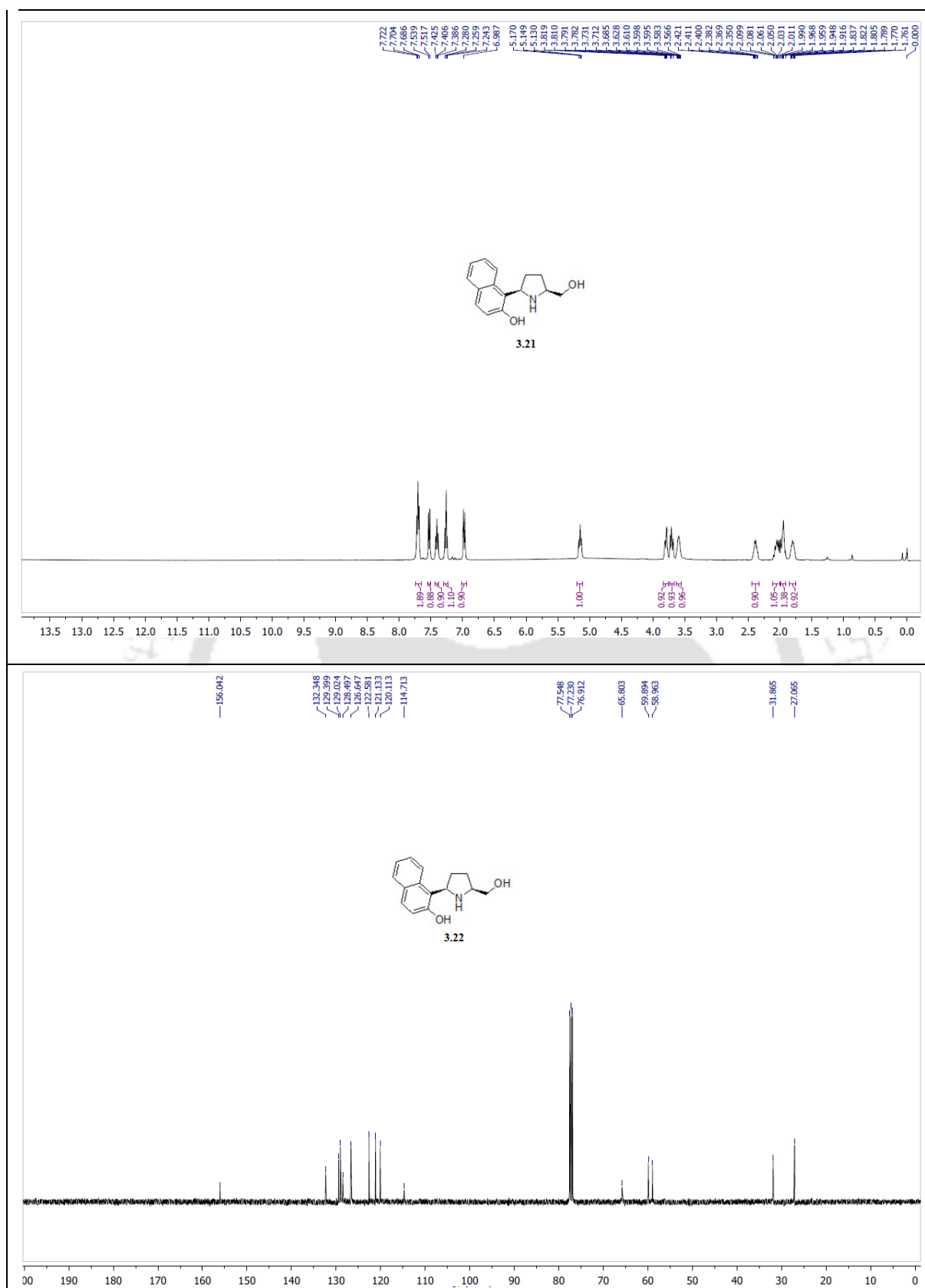


Chapter 6

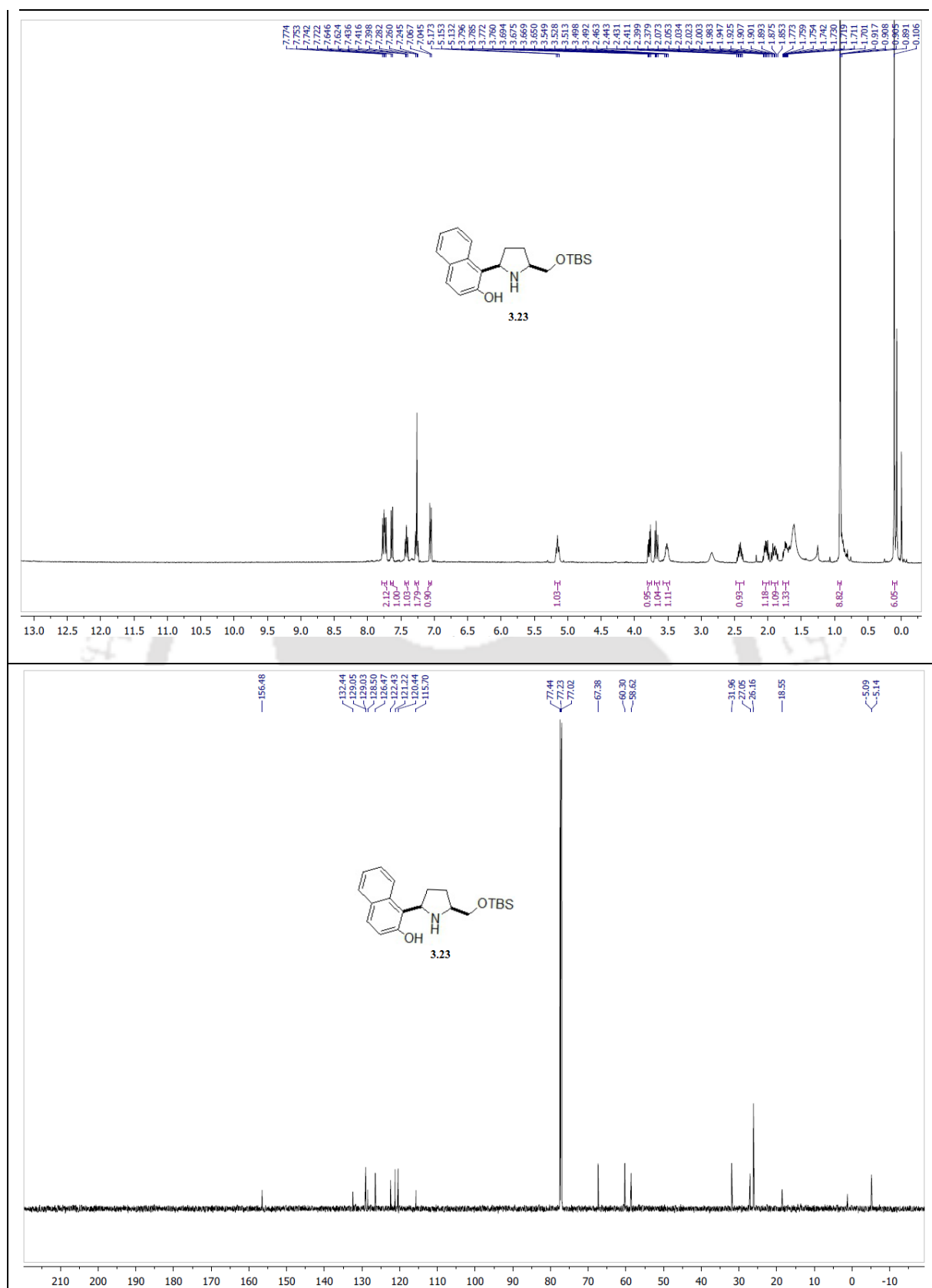


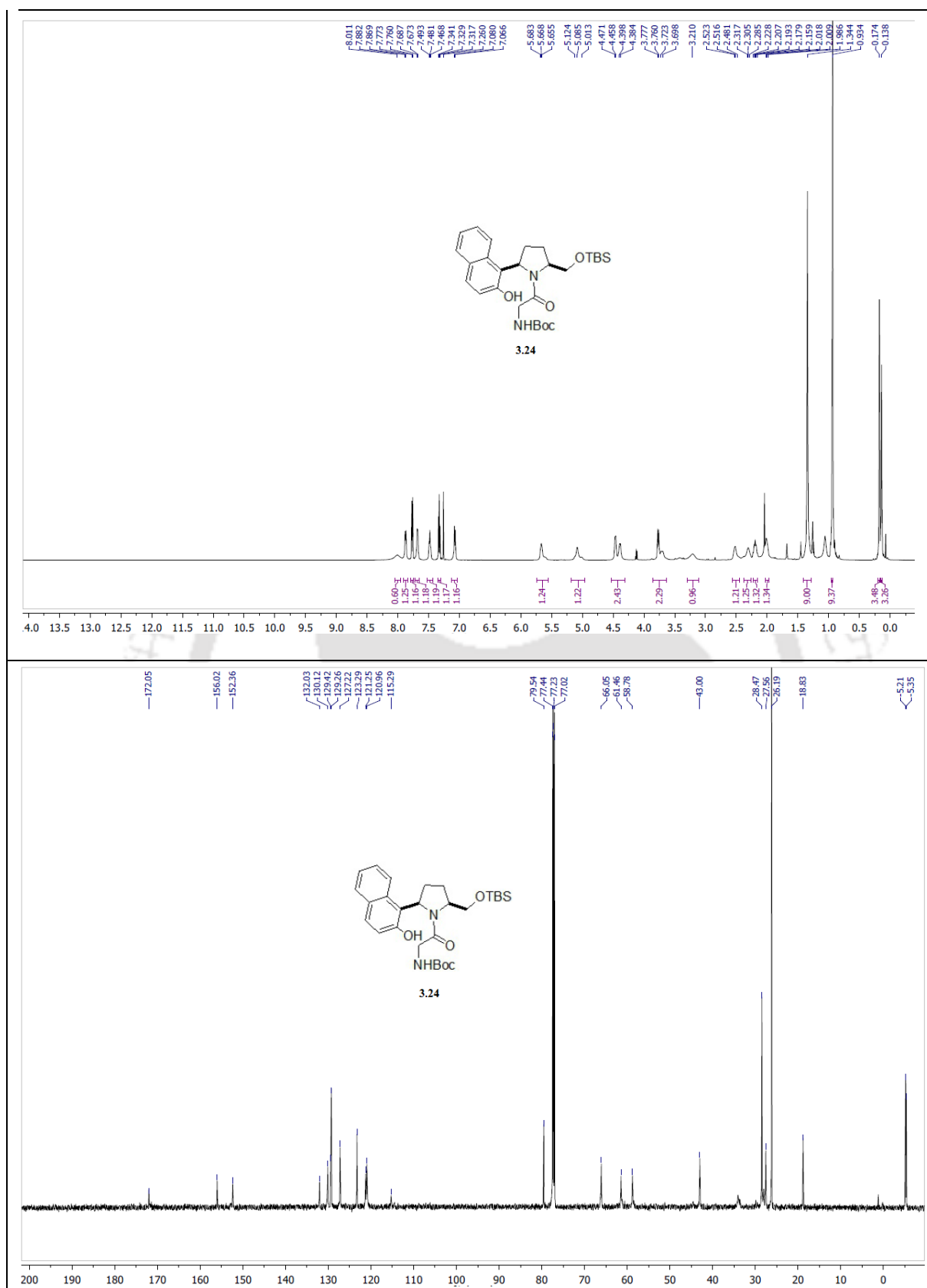
^1H , & ^{13}C spectra & HPLC chromatogram of selected new compounds



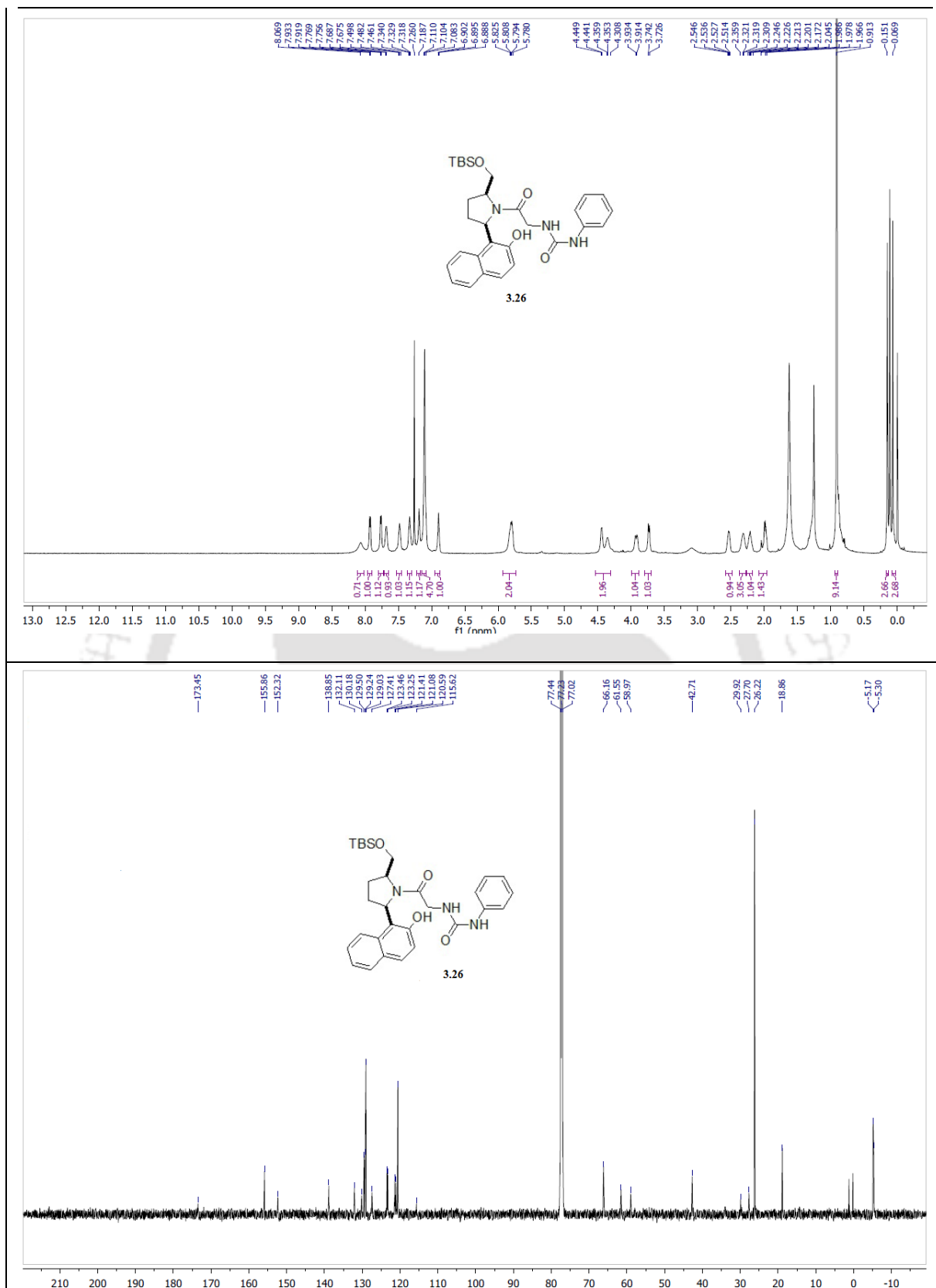


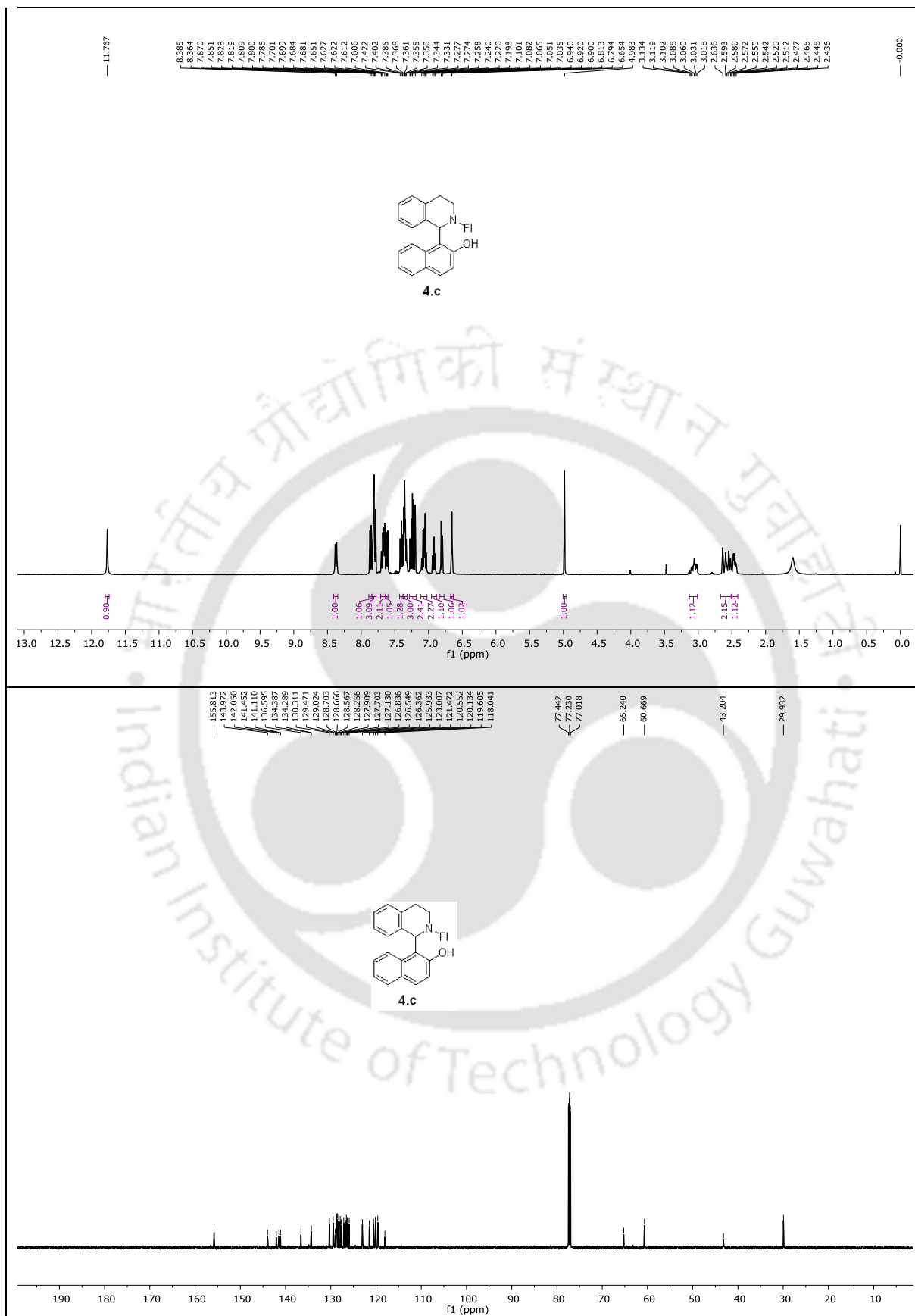
^1H , & ^{13}C spectra & HPLC chromatogram of selected new compounds



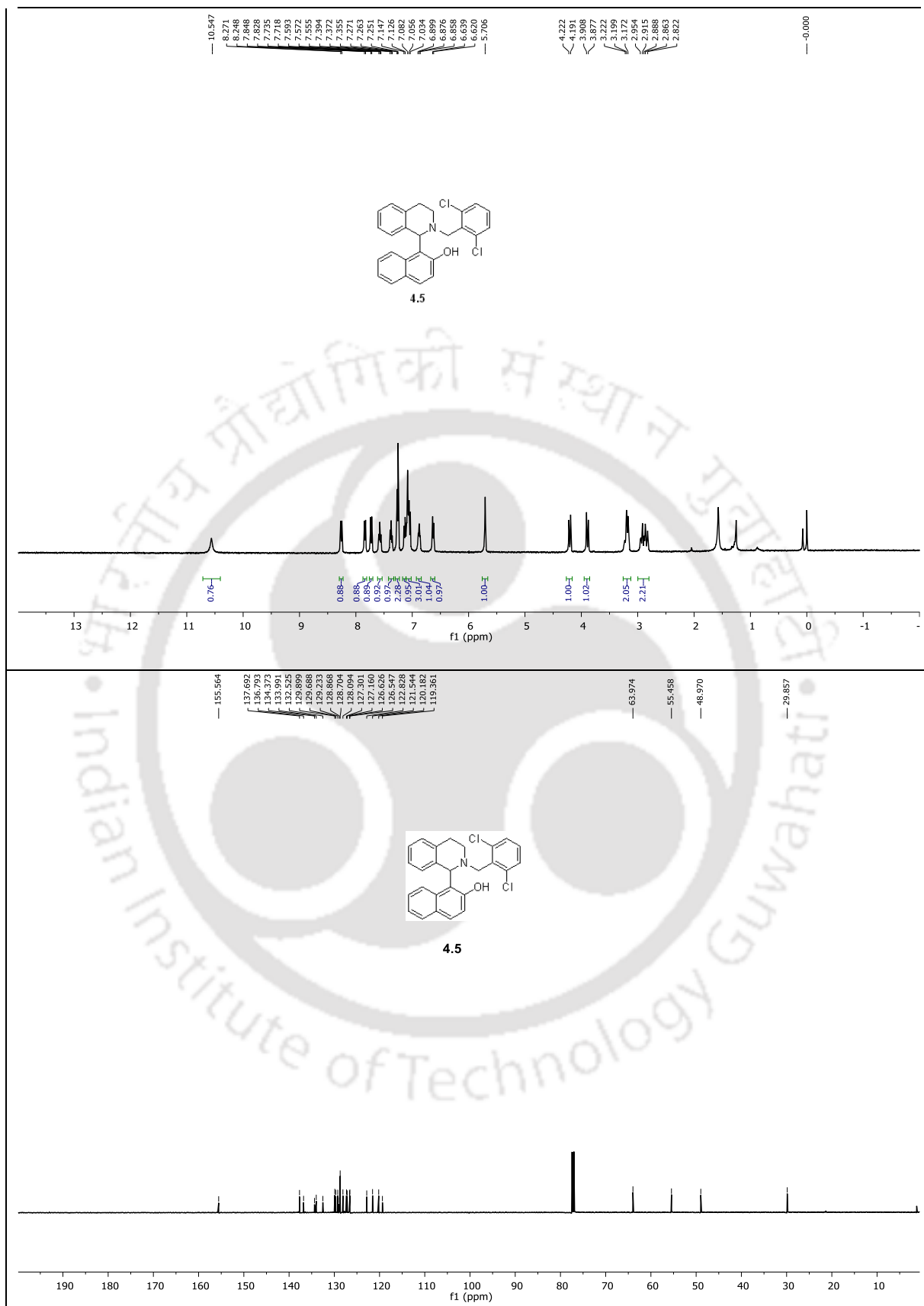


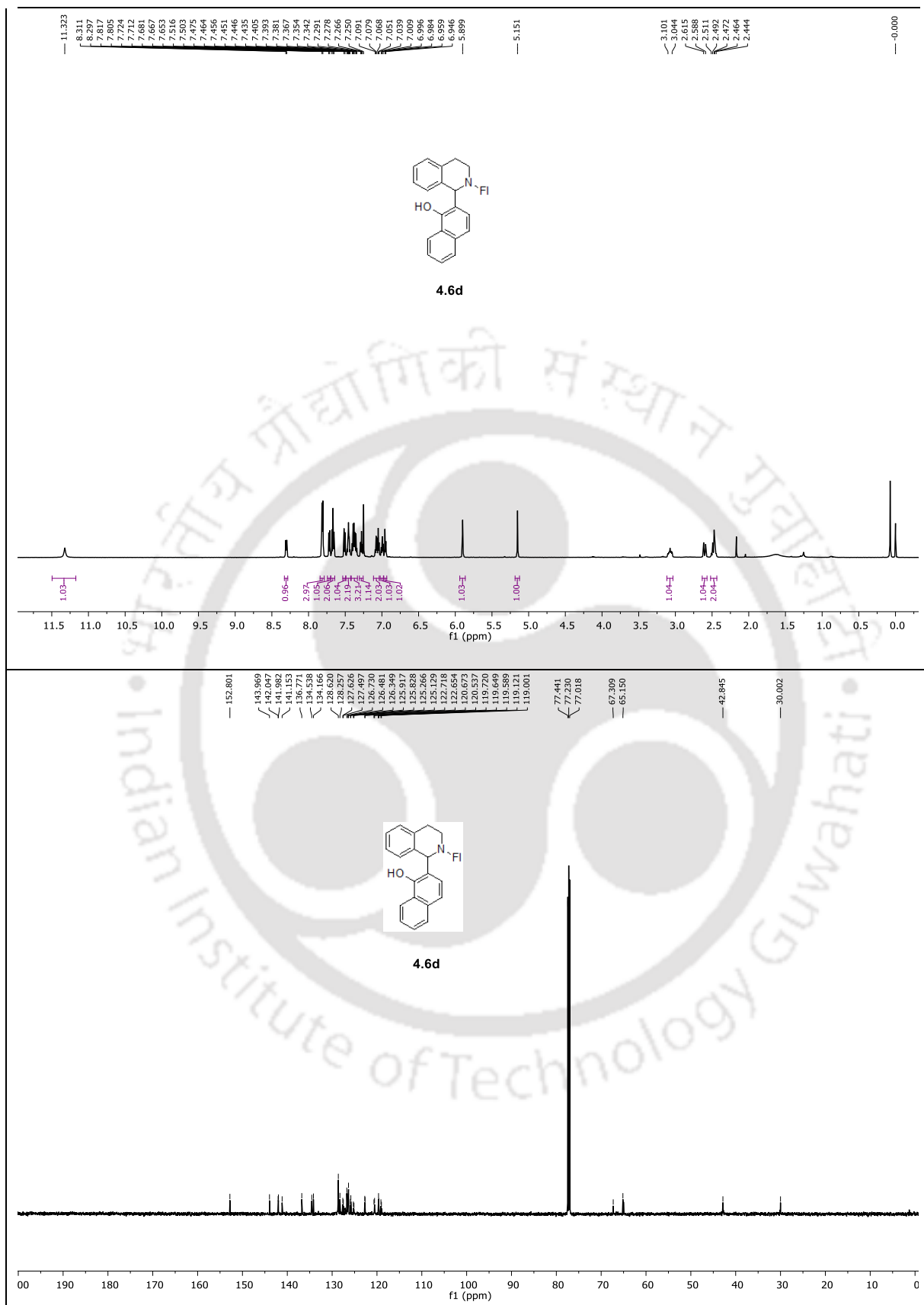
^1H , & ^{13}C spectra & HPLC chromatogram of selected new compounds

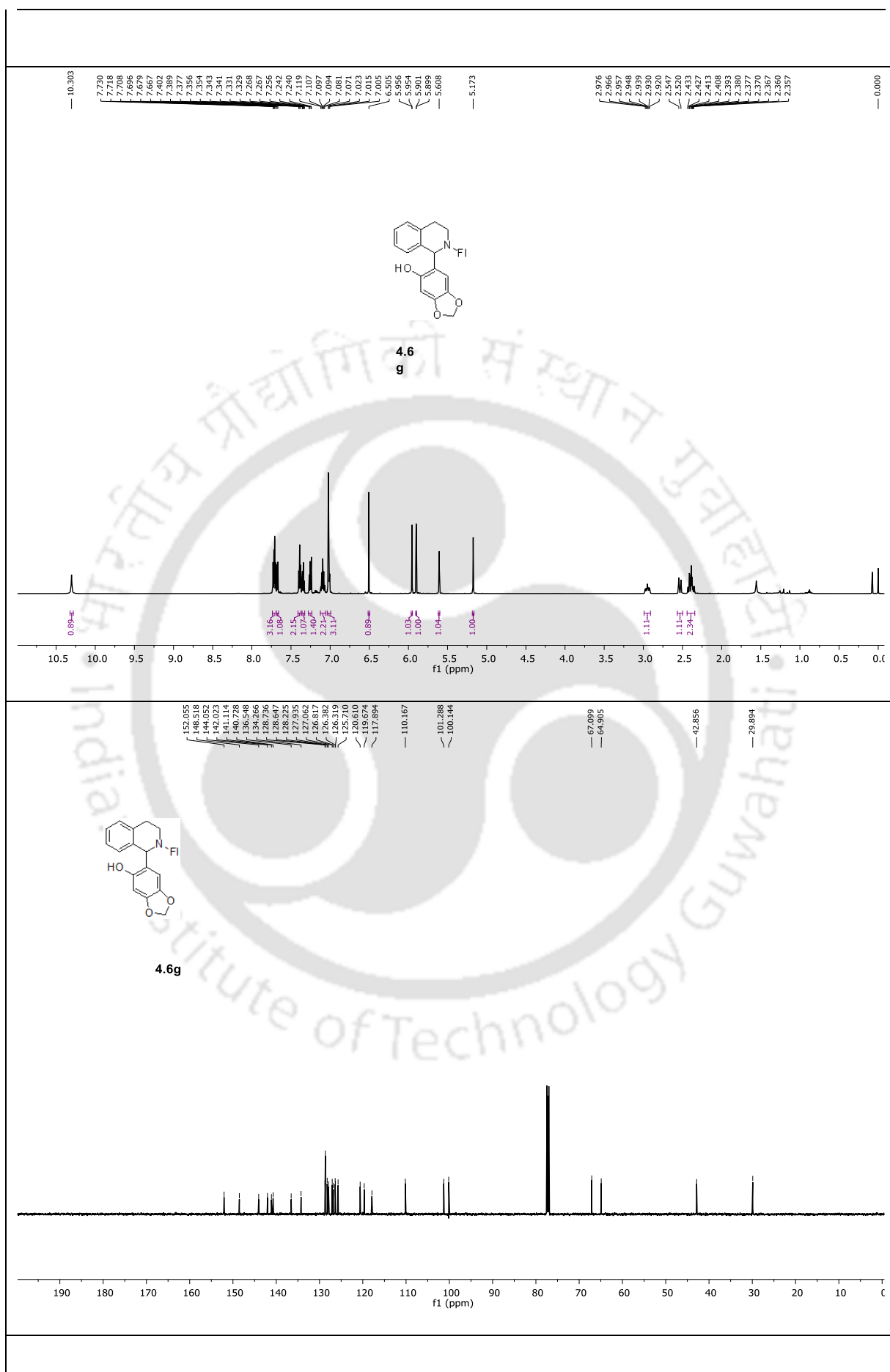


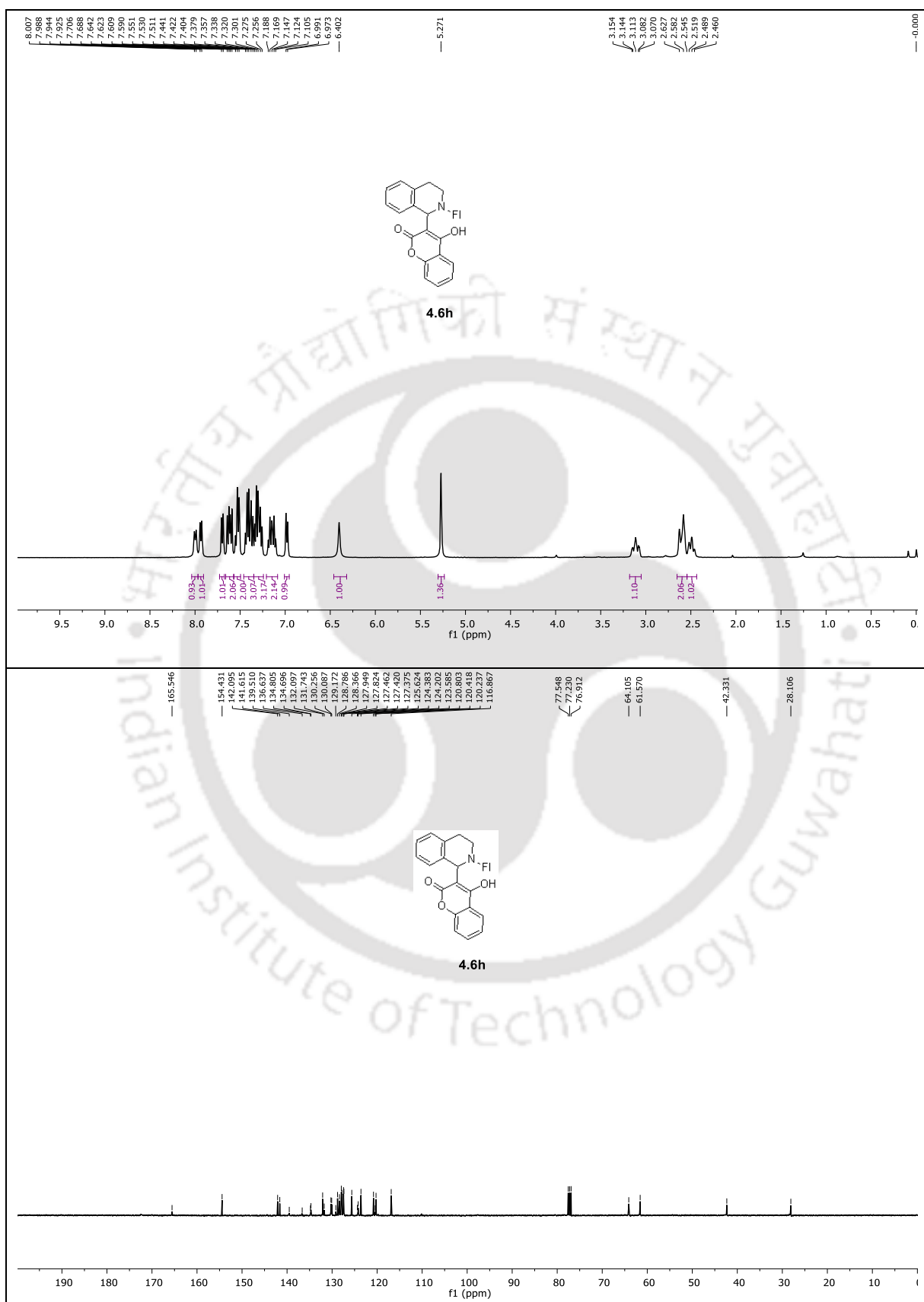


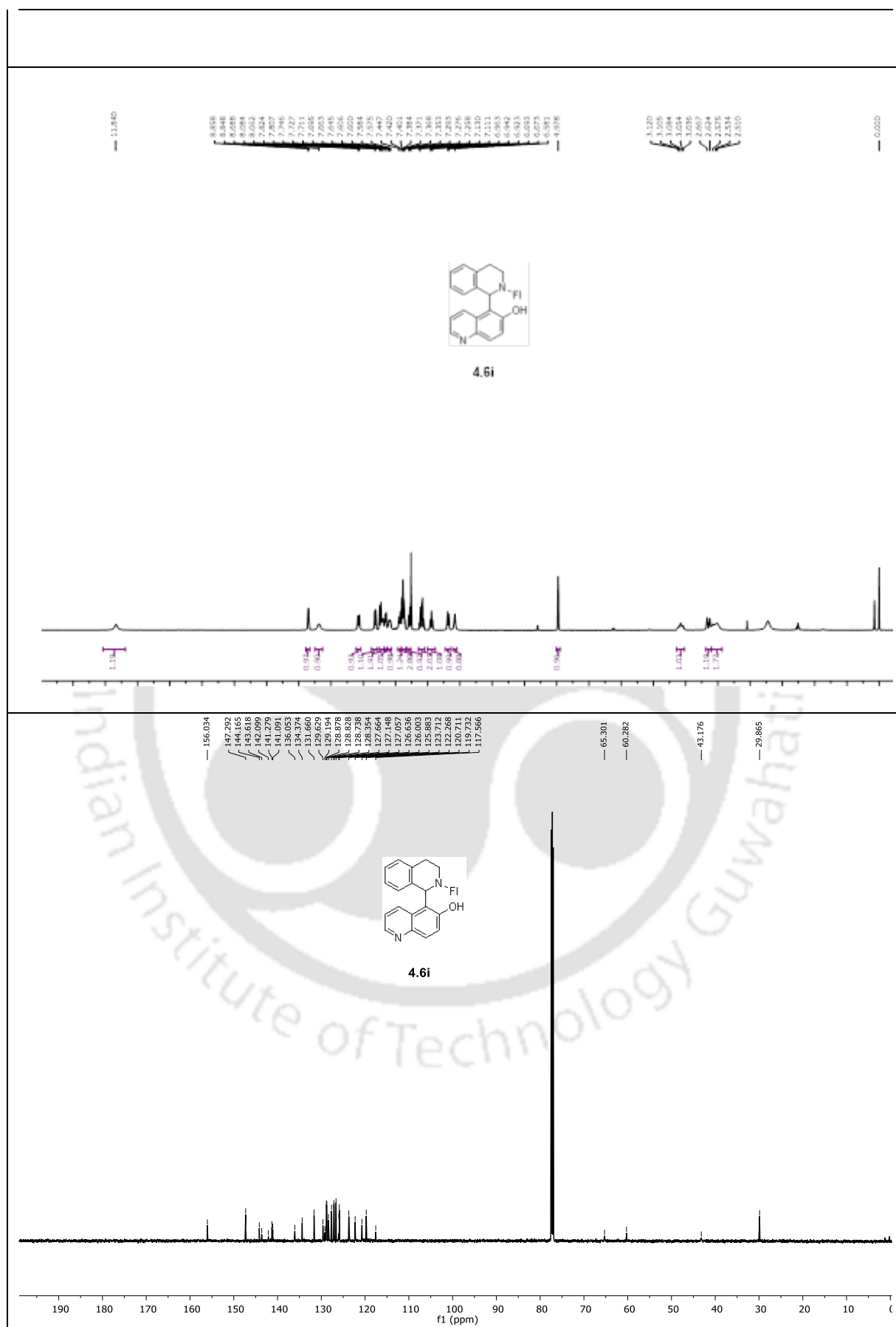
^1H , & ^{13}C spectra & HPLC chromatogram of selected new compounds

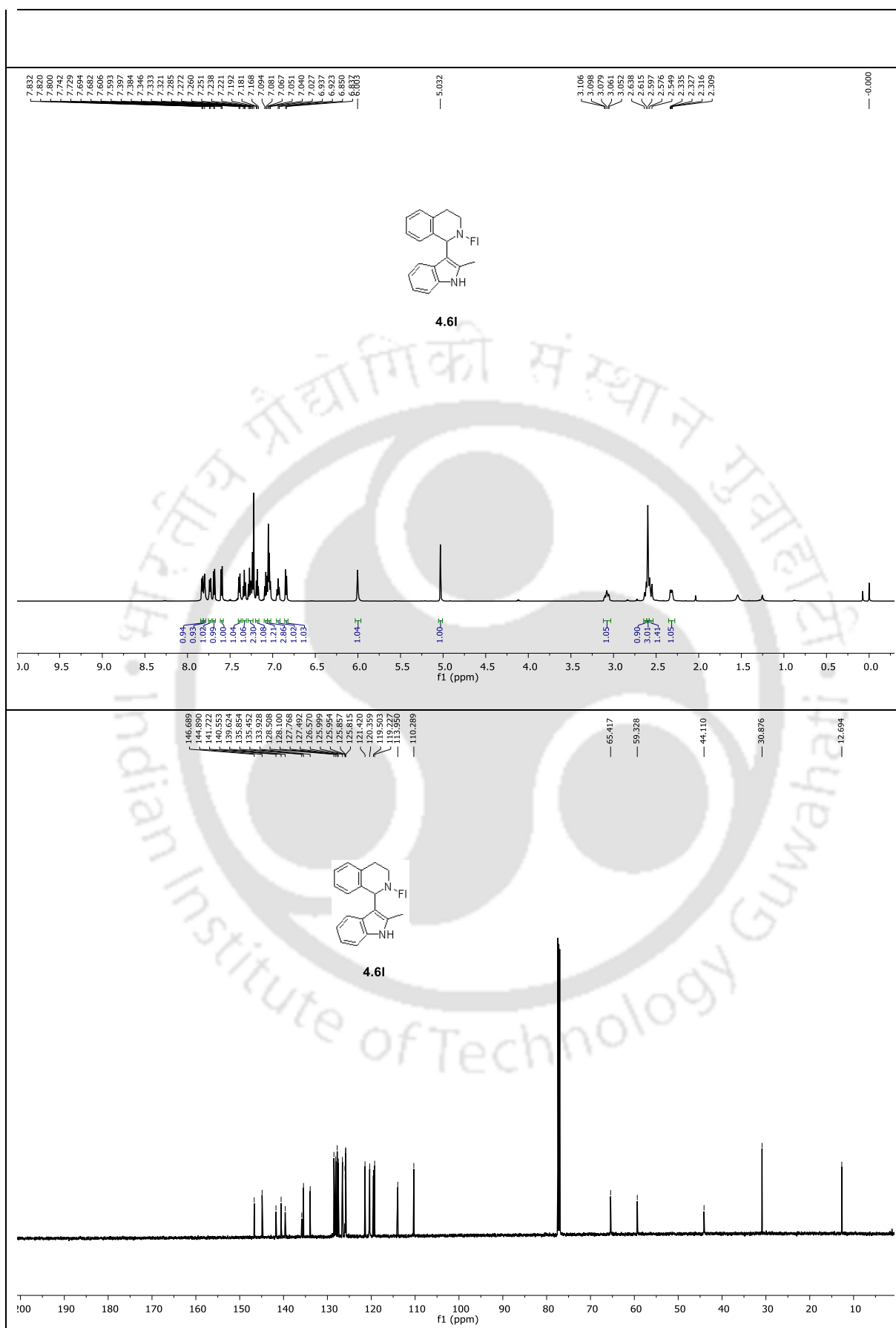


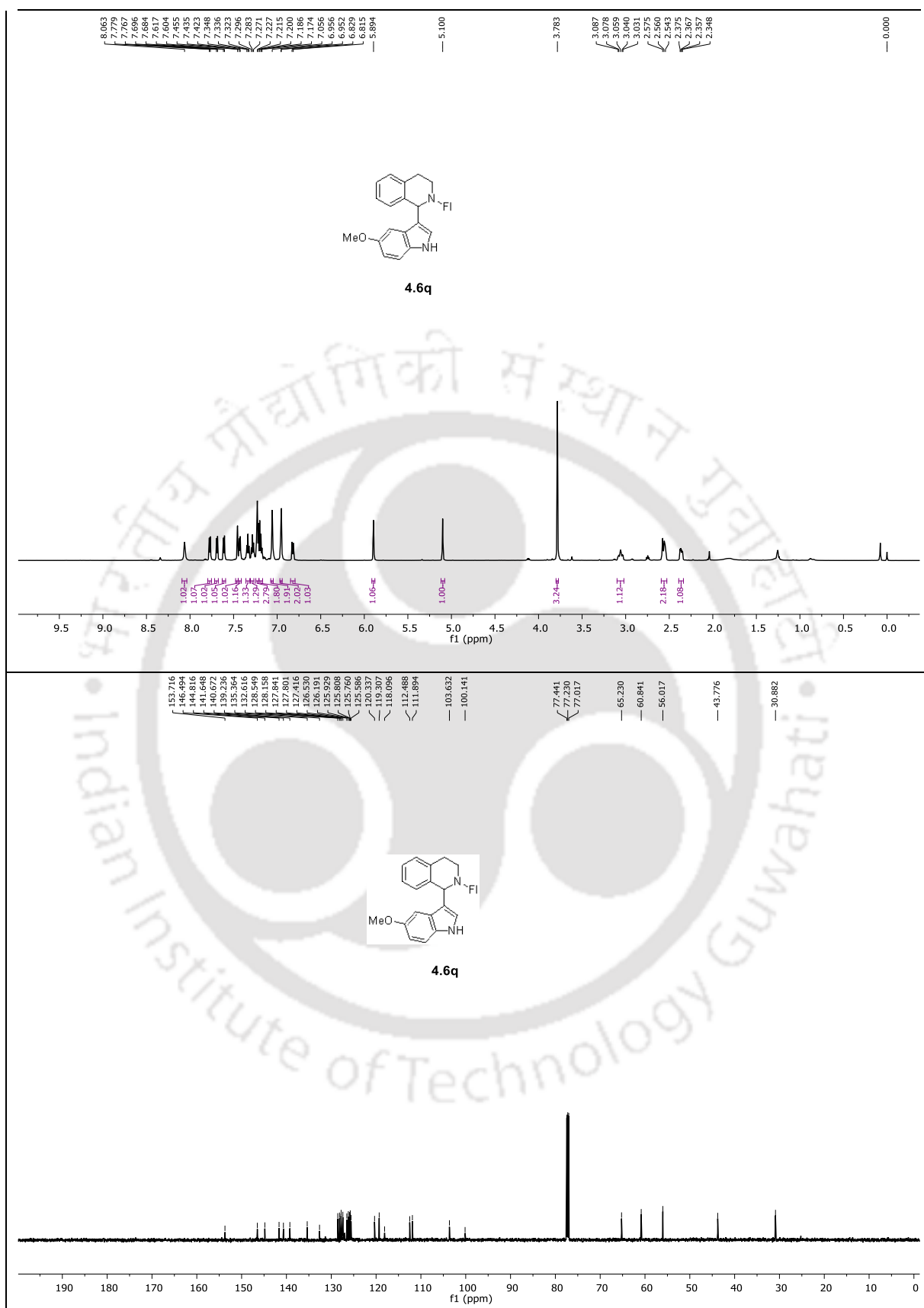


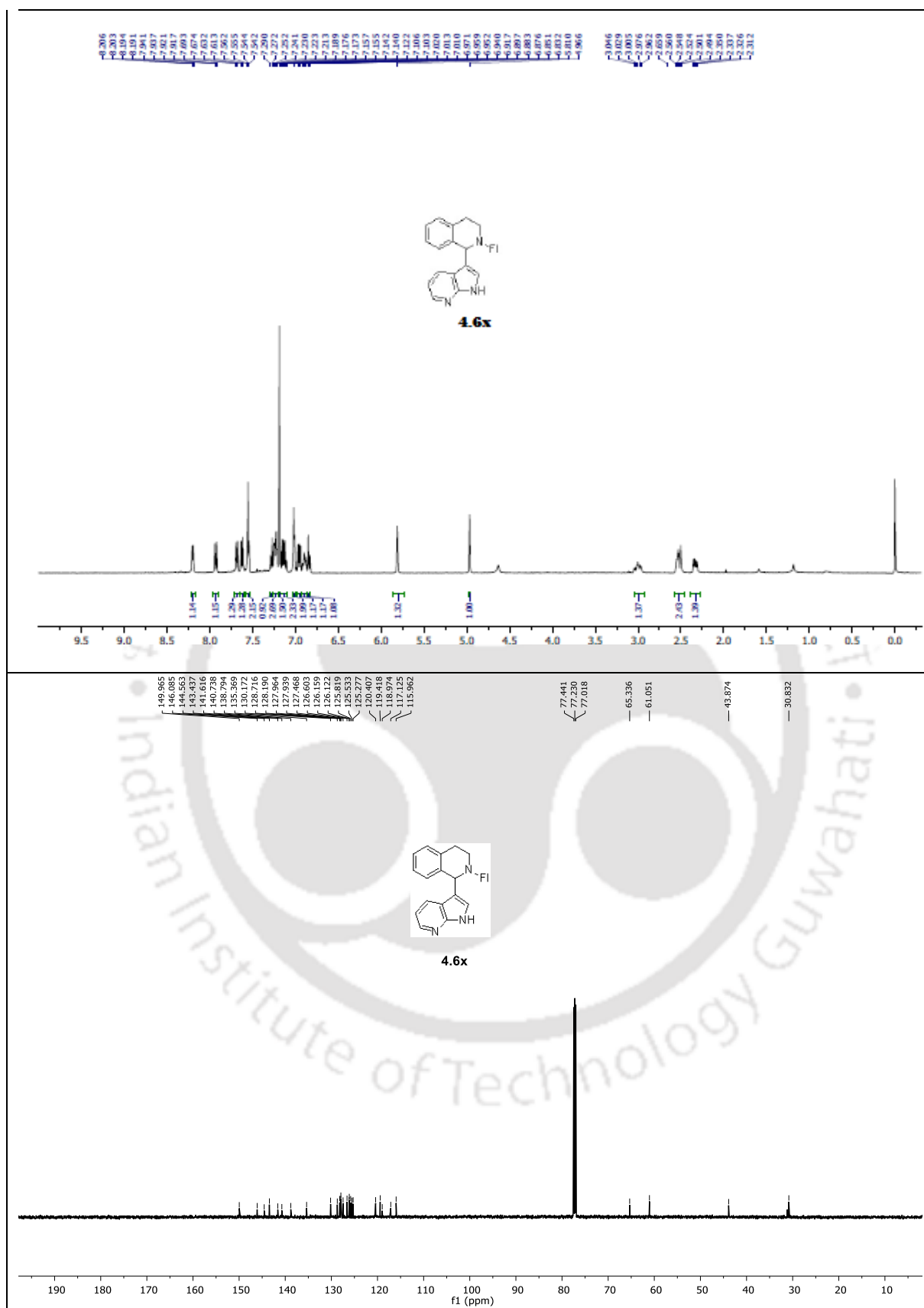


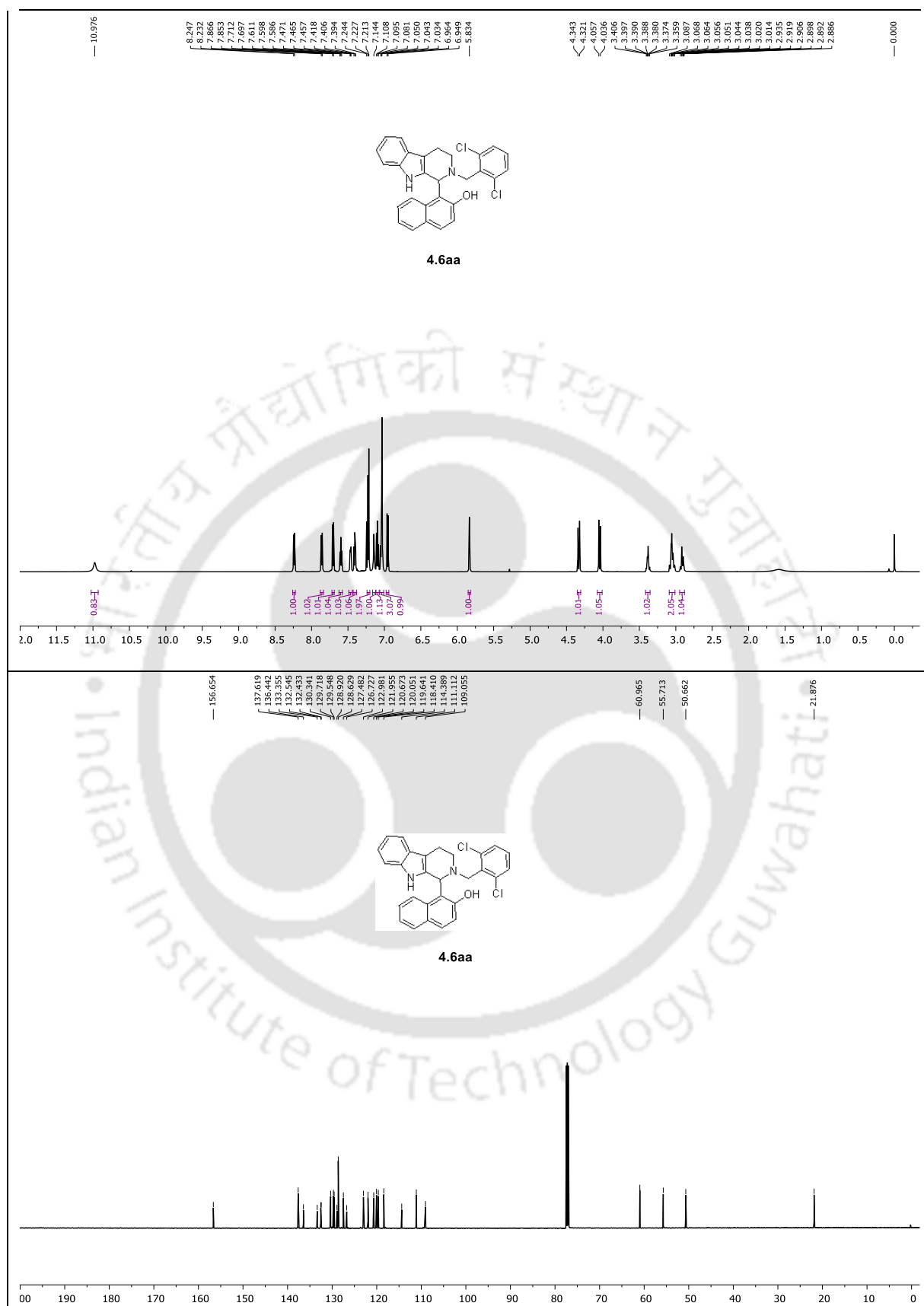


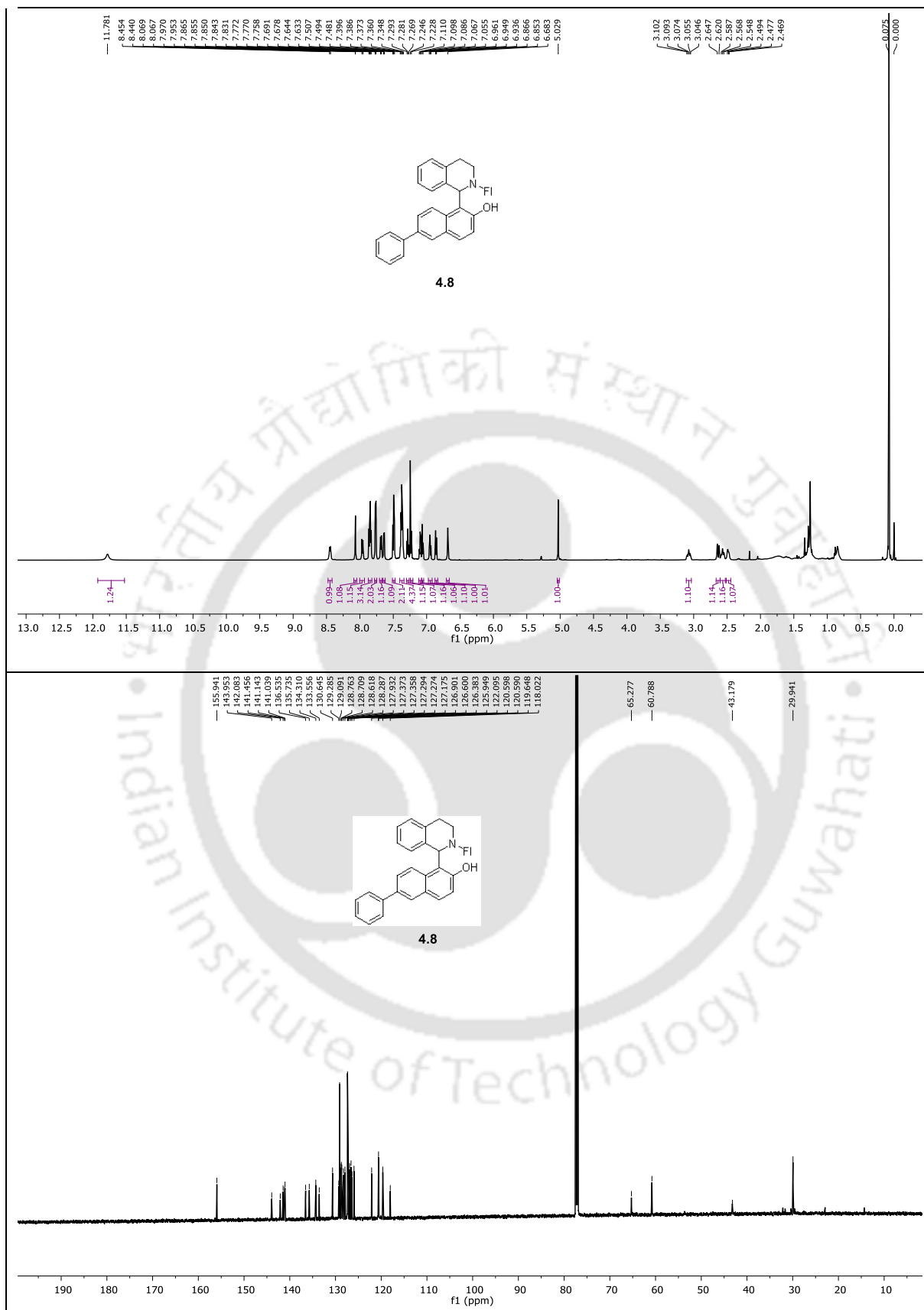


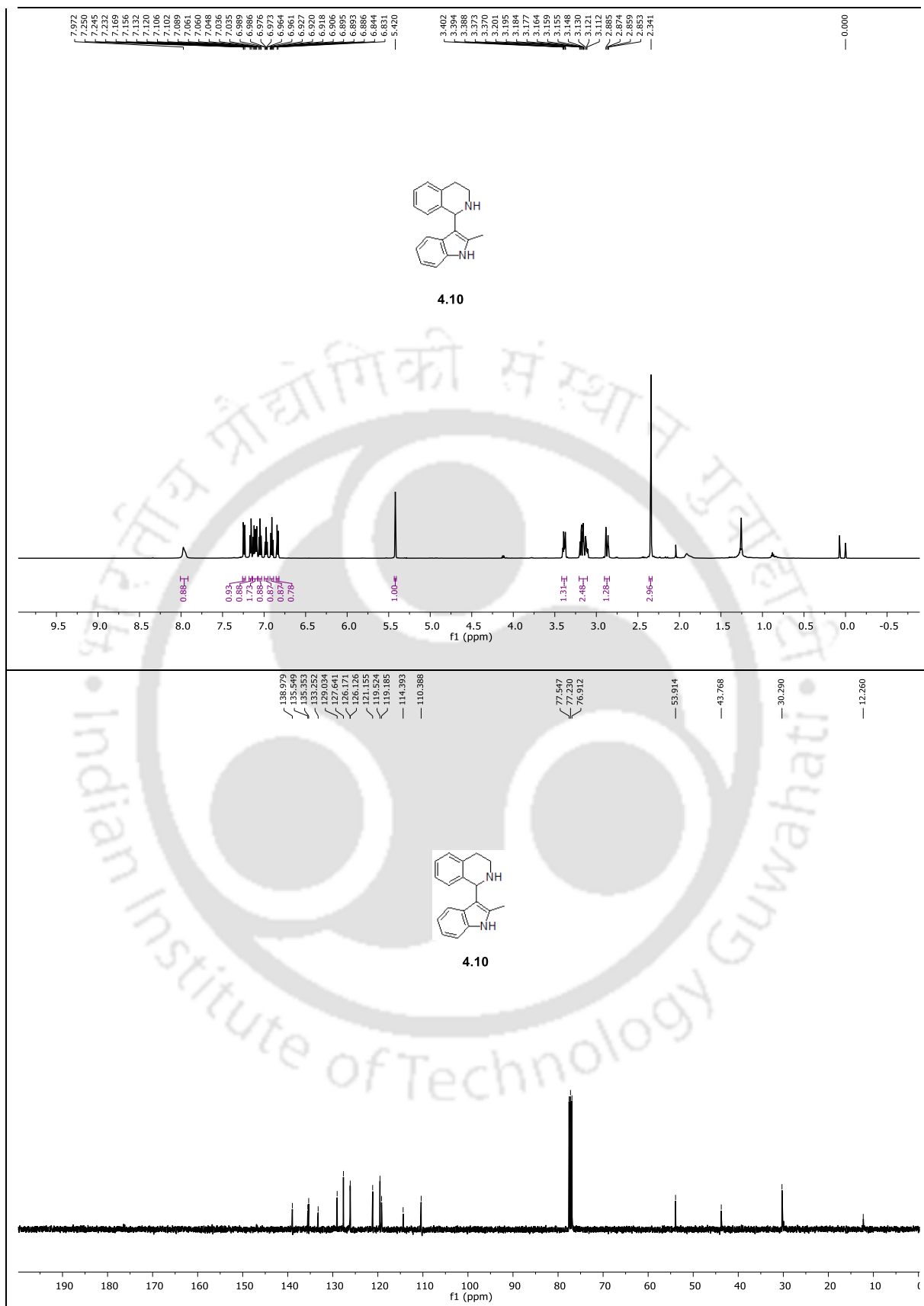


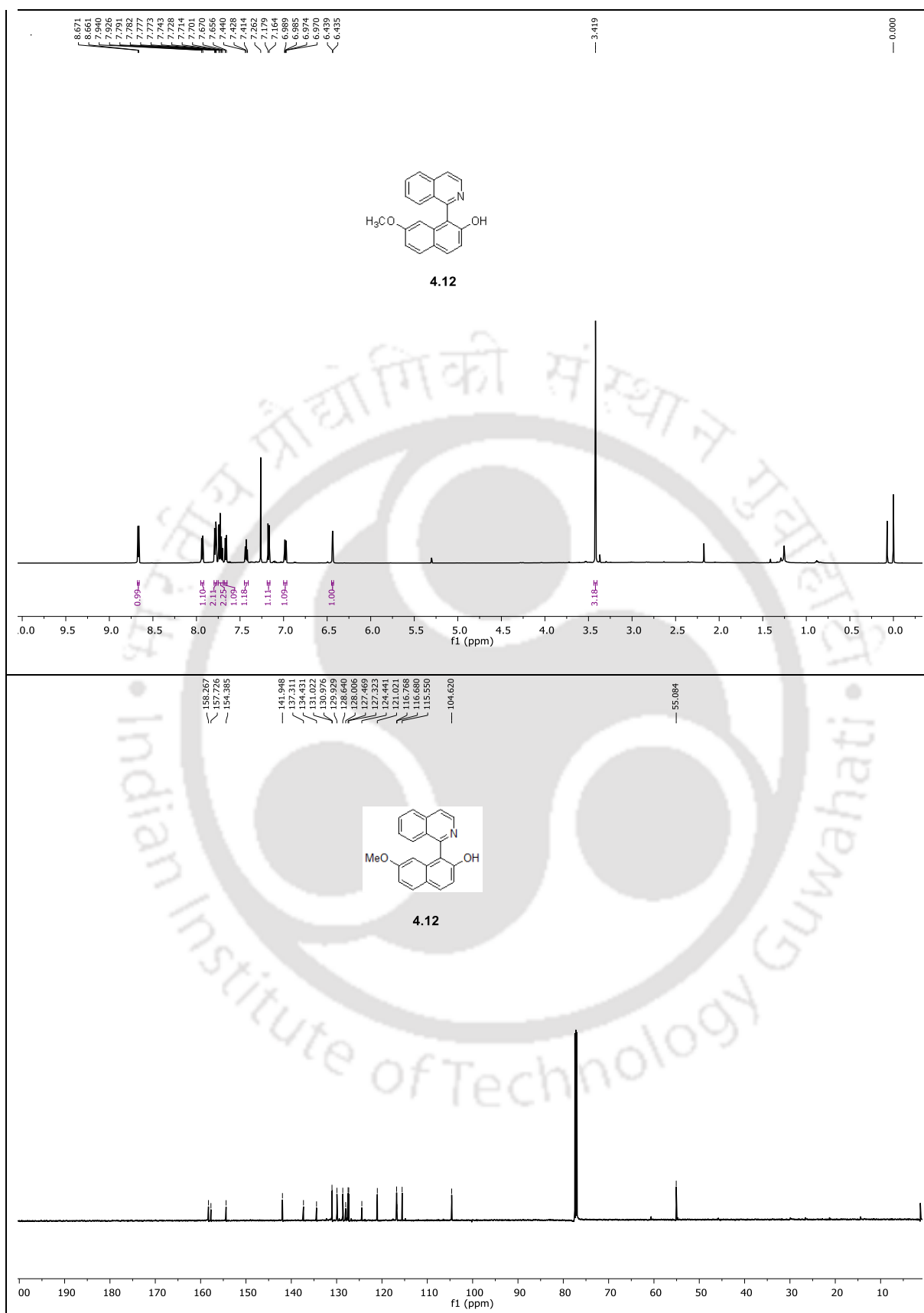


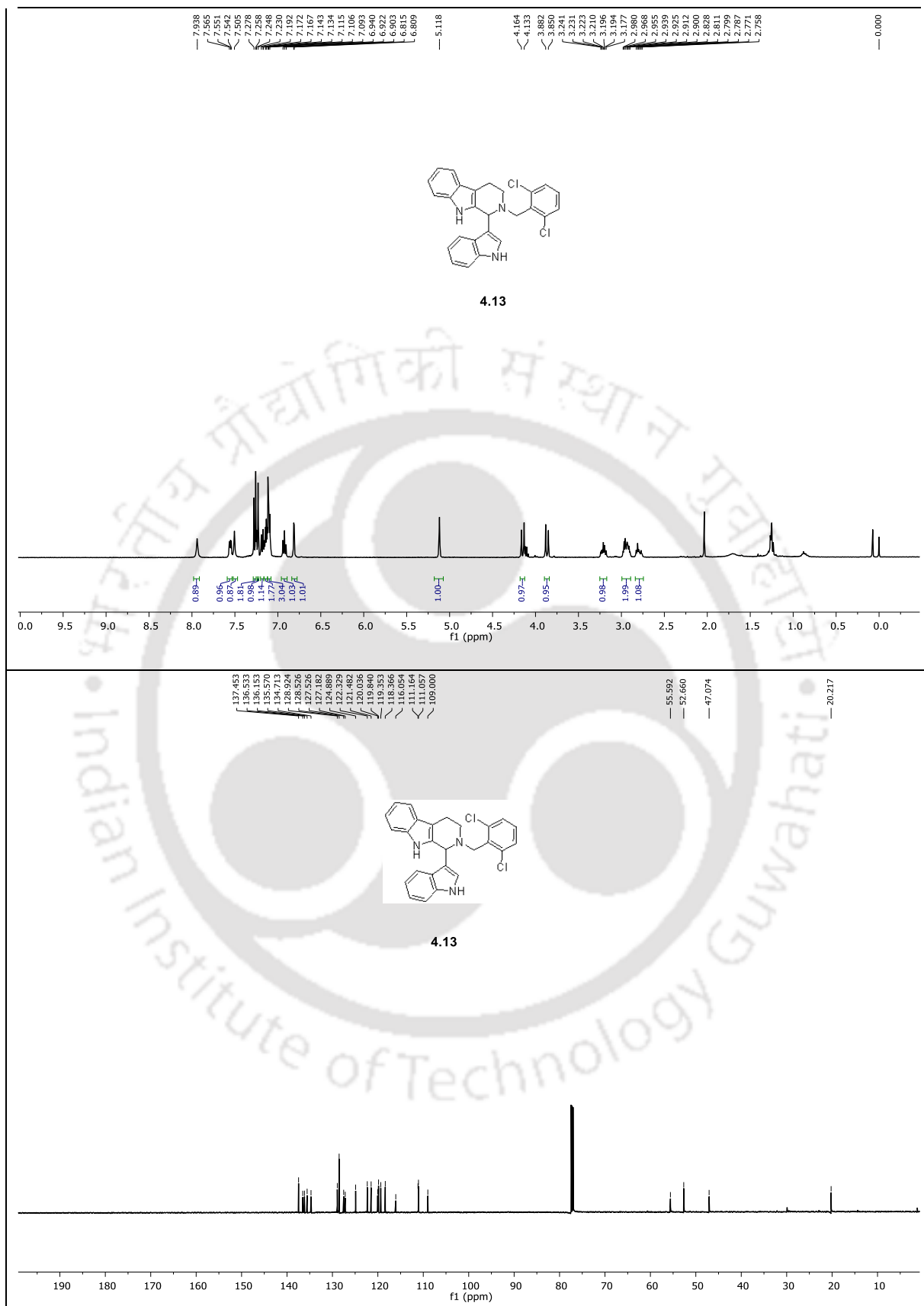


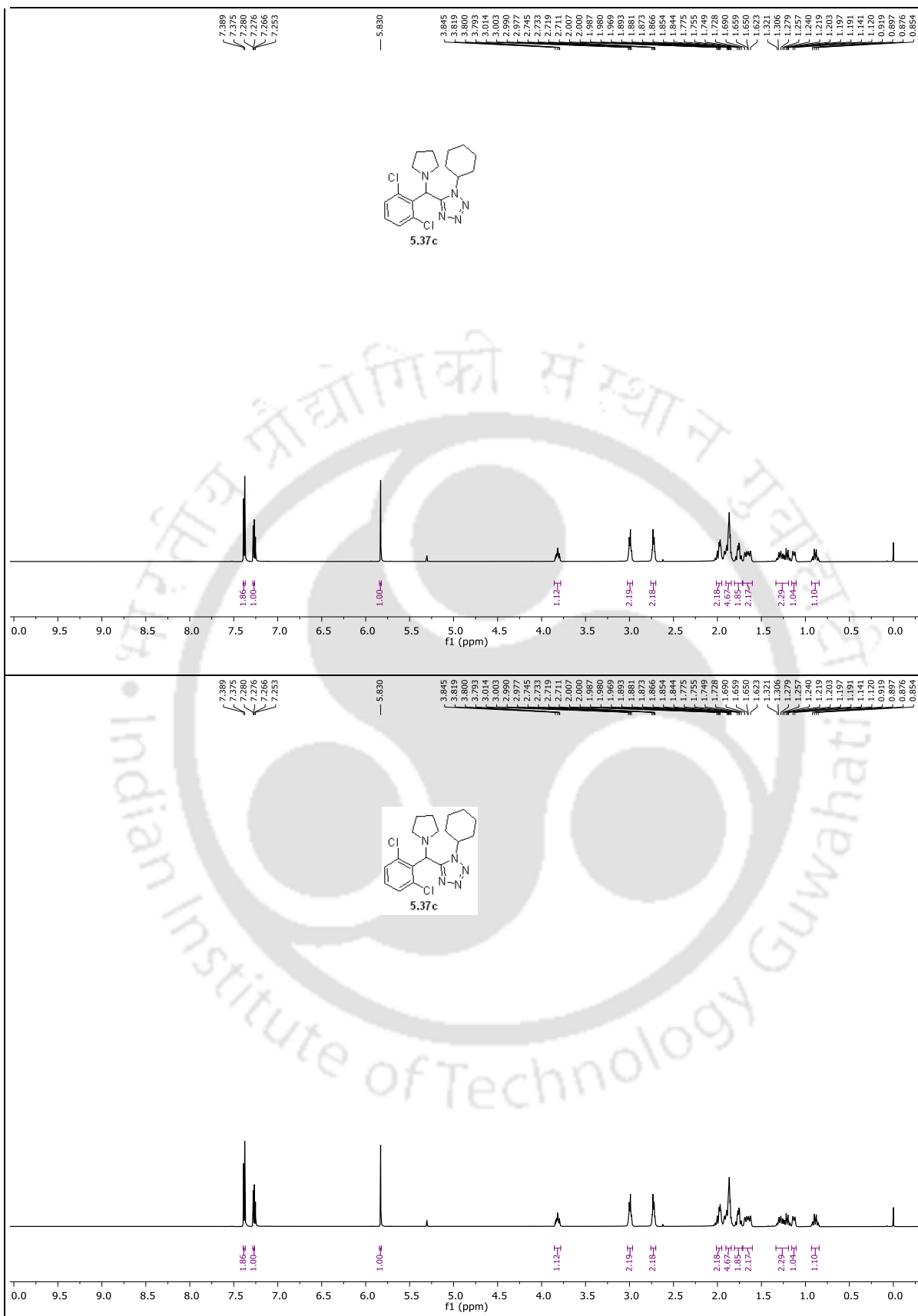


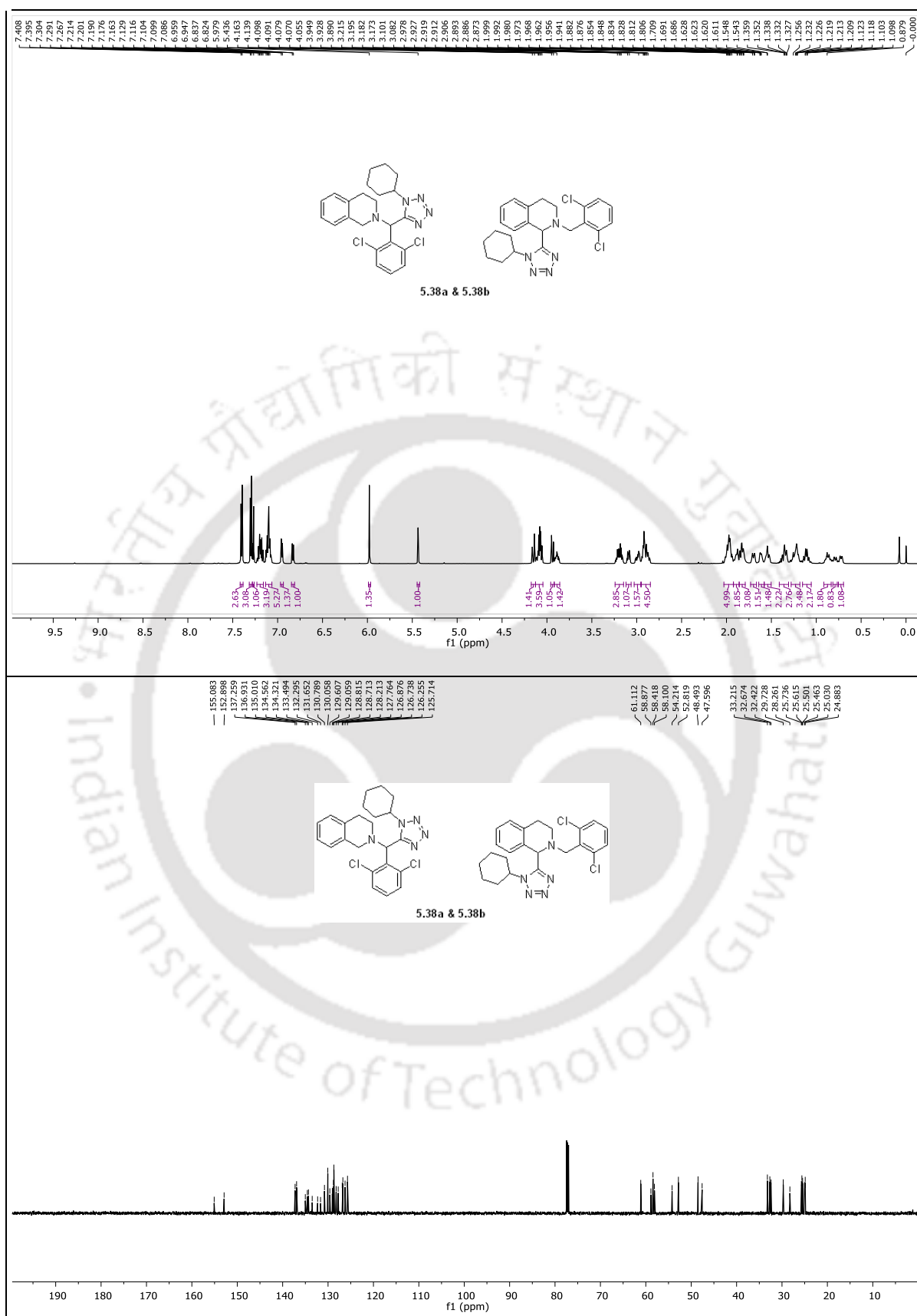




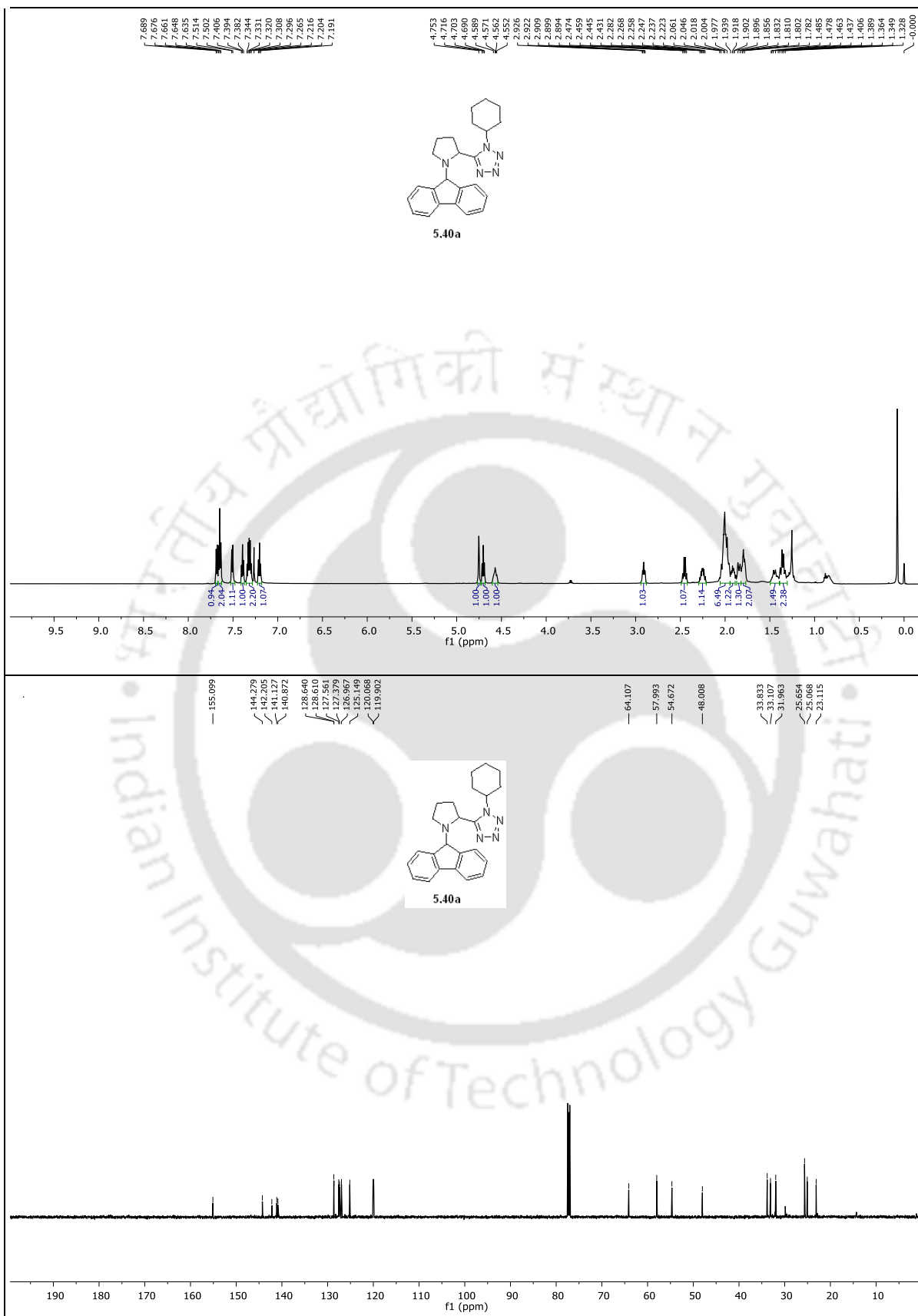


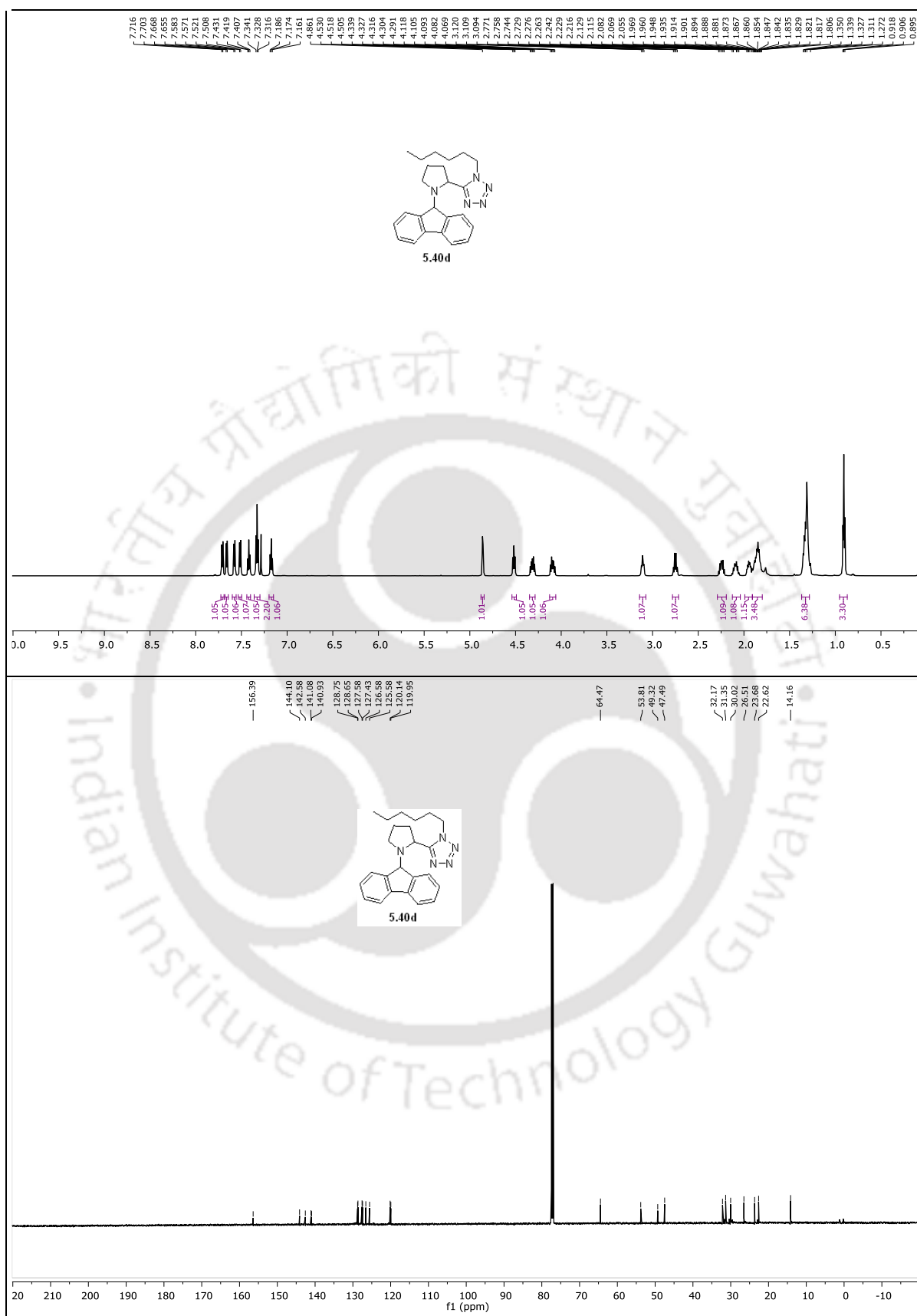


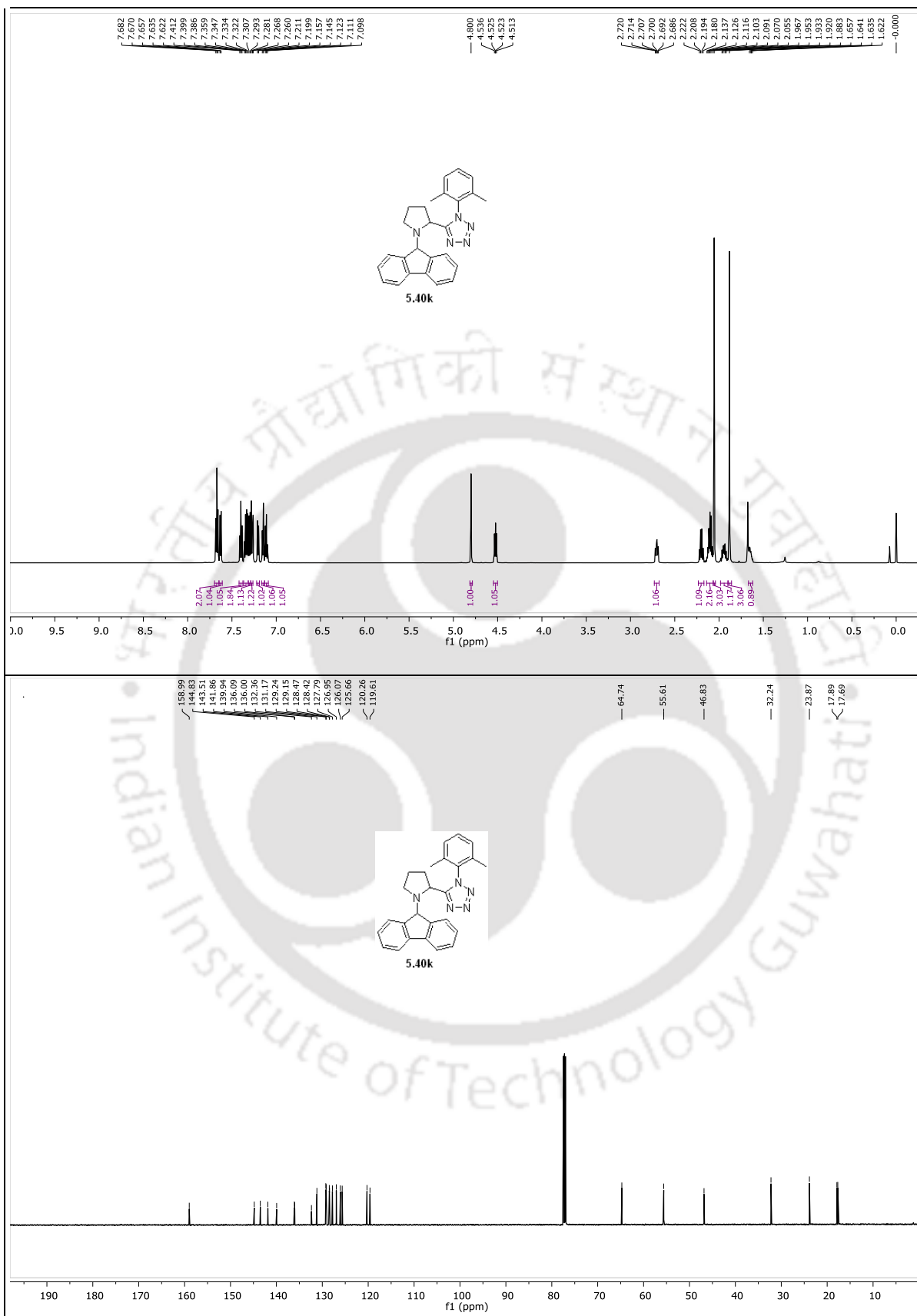


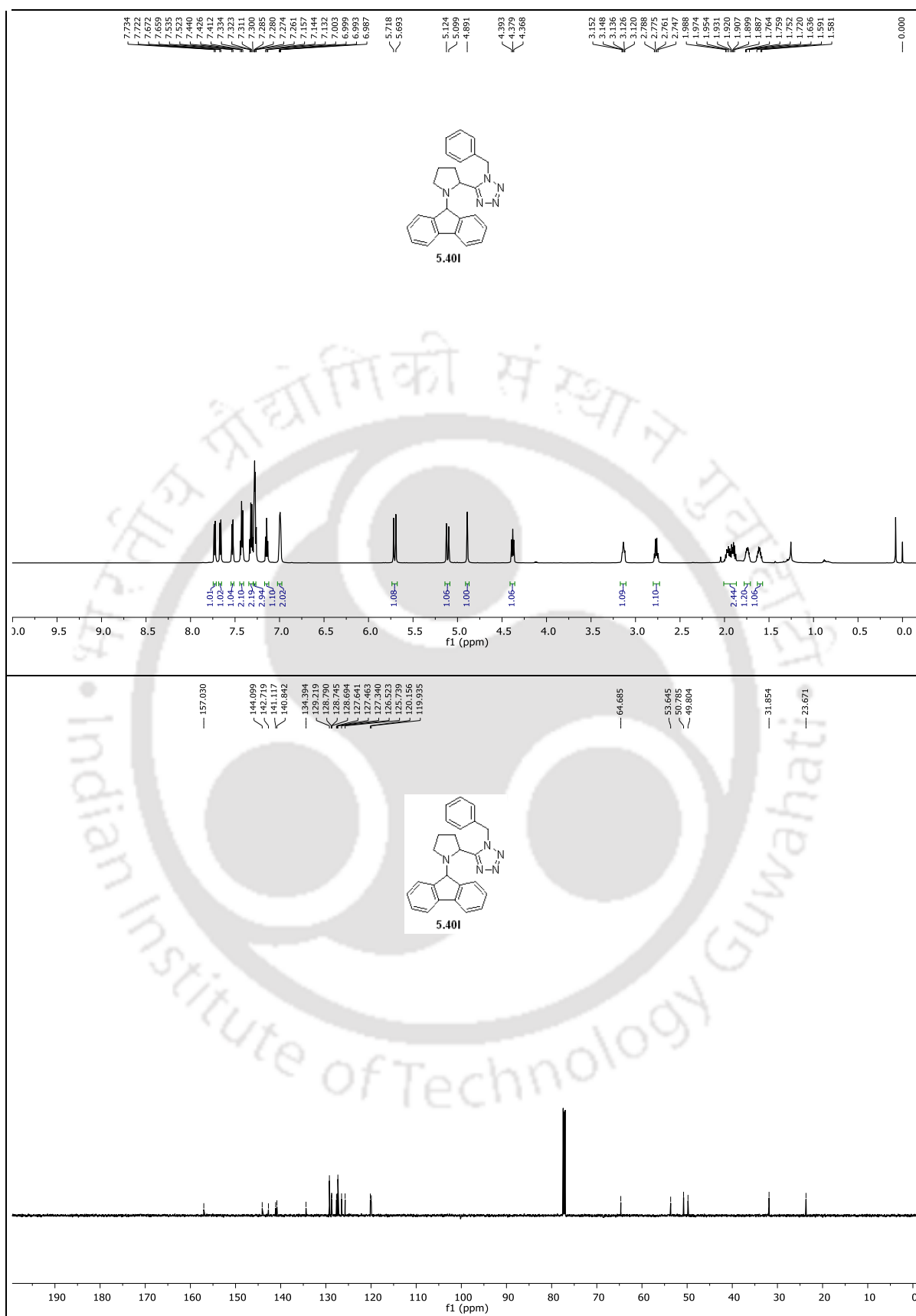


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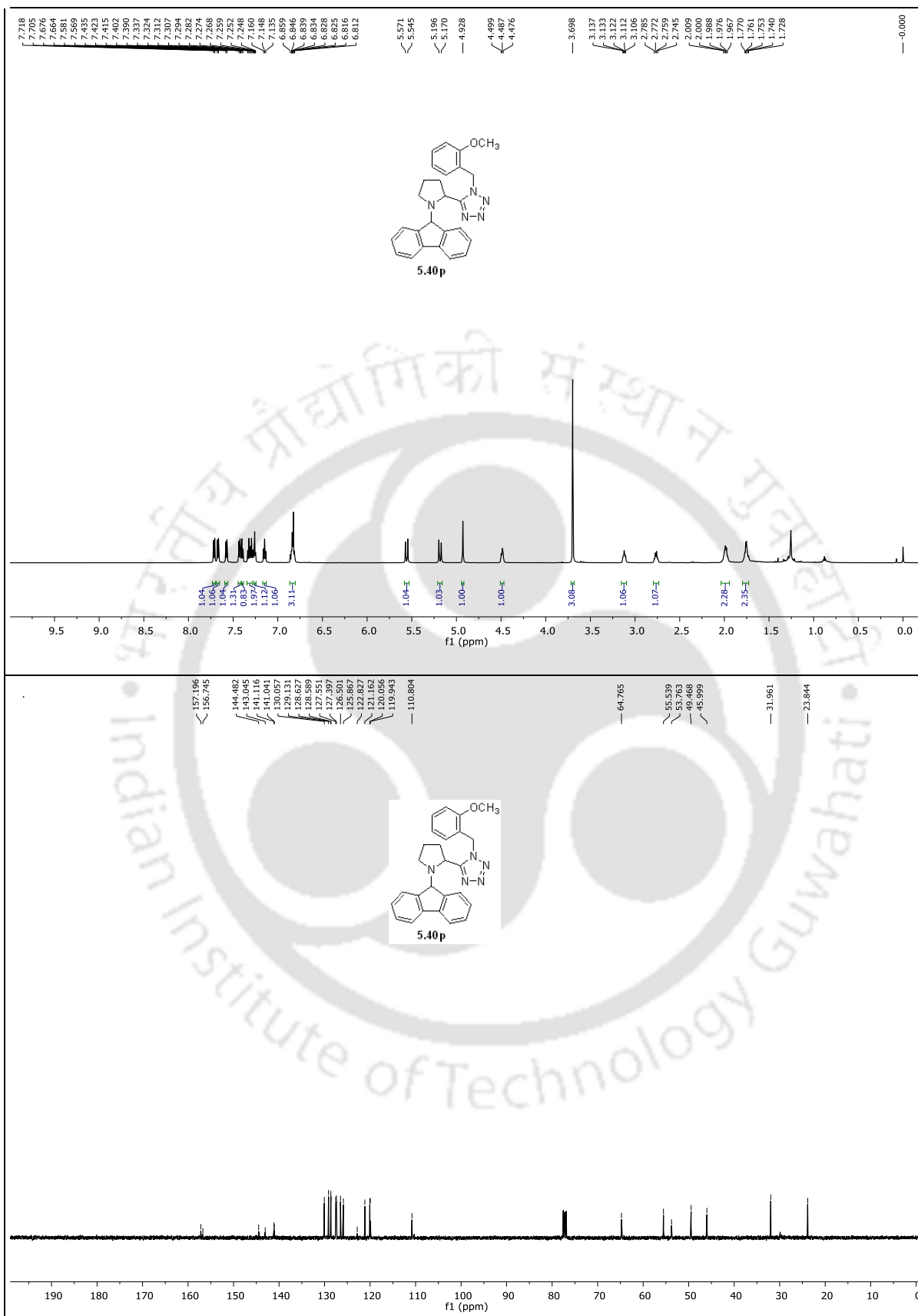


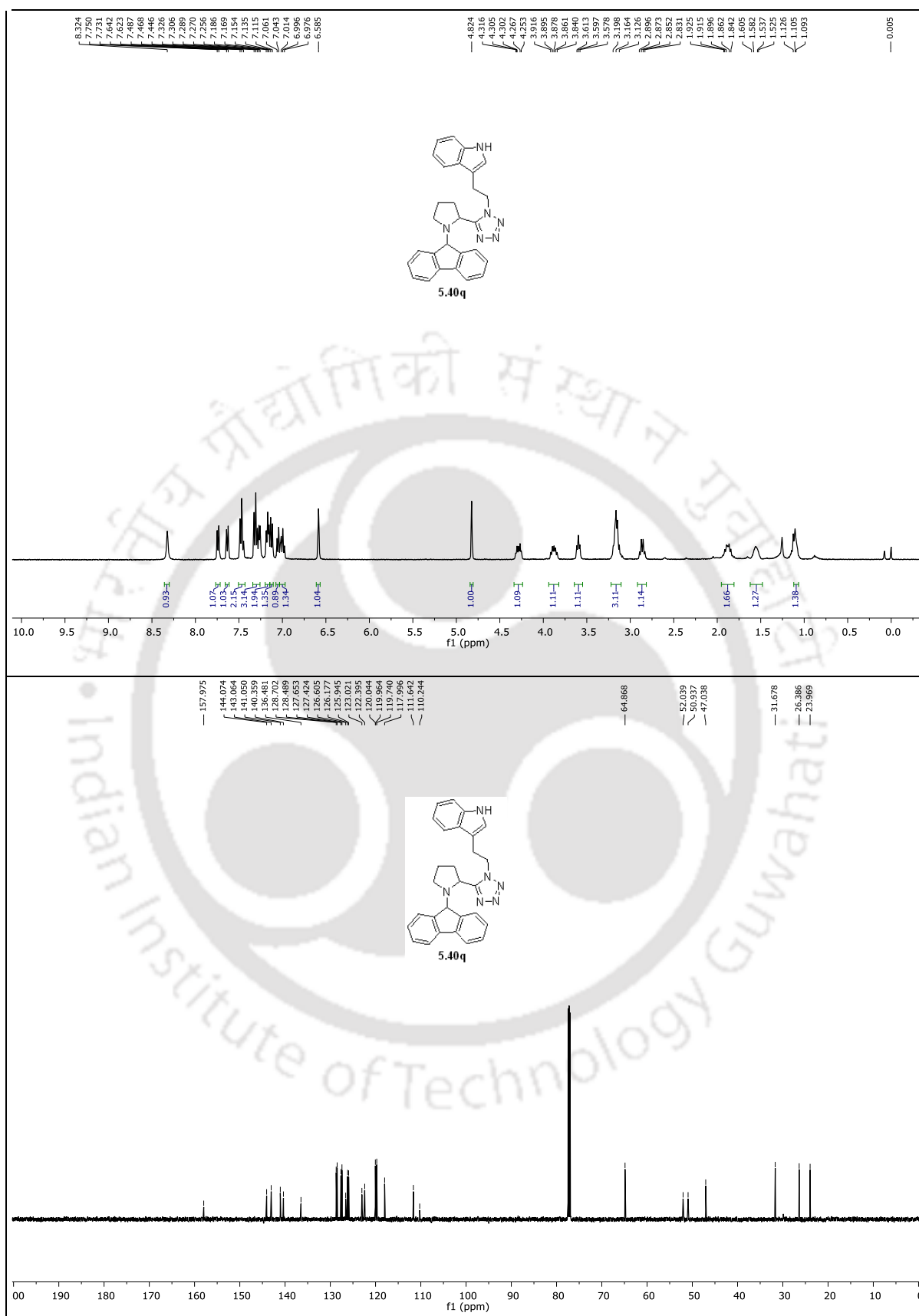




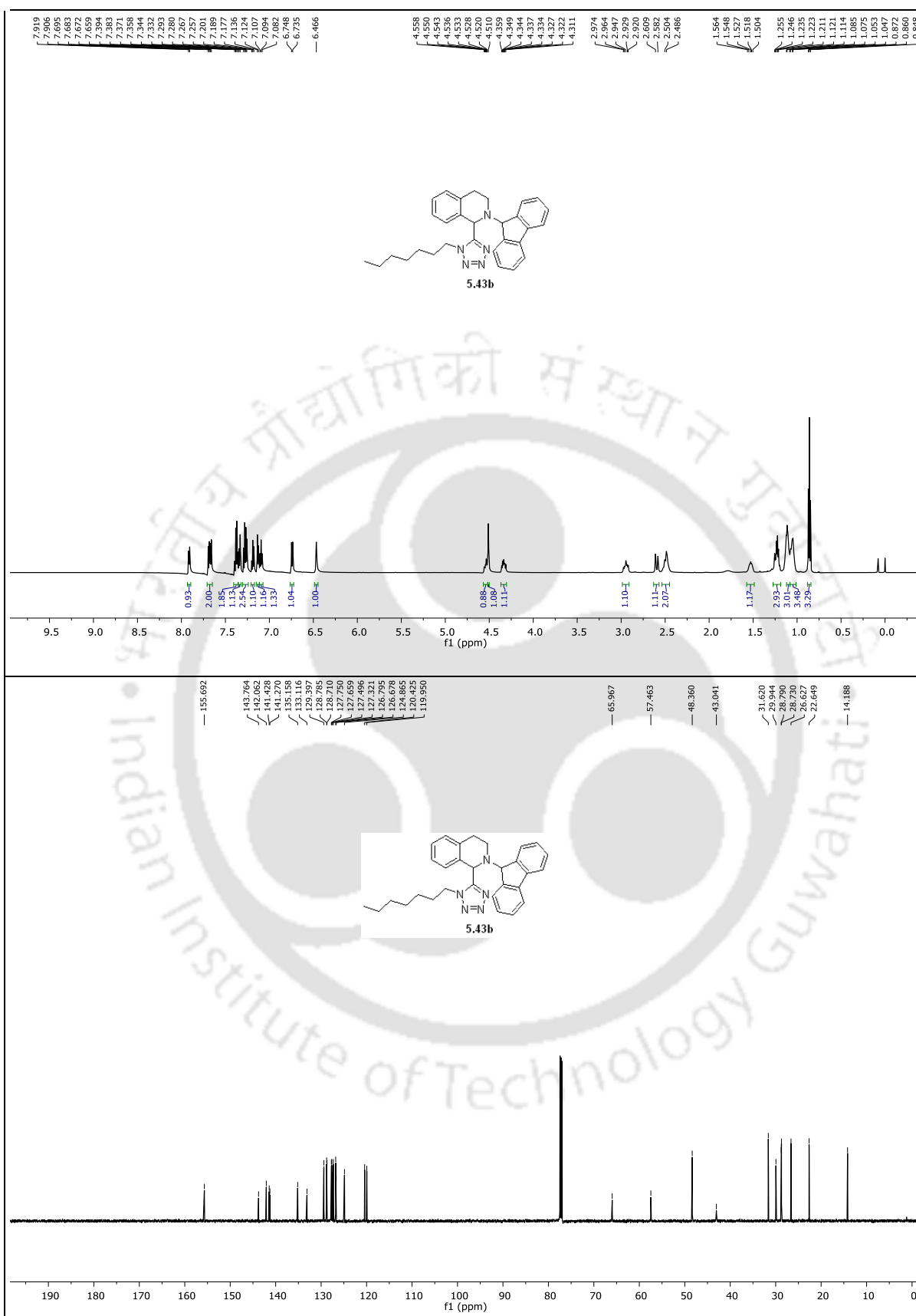


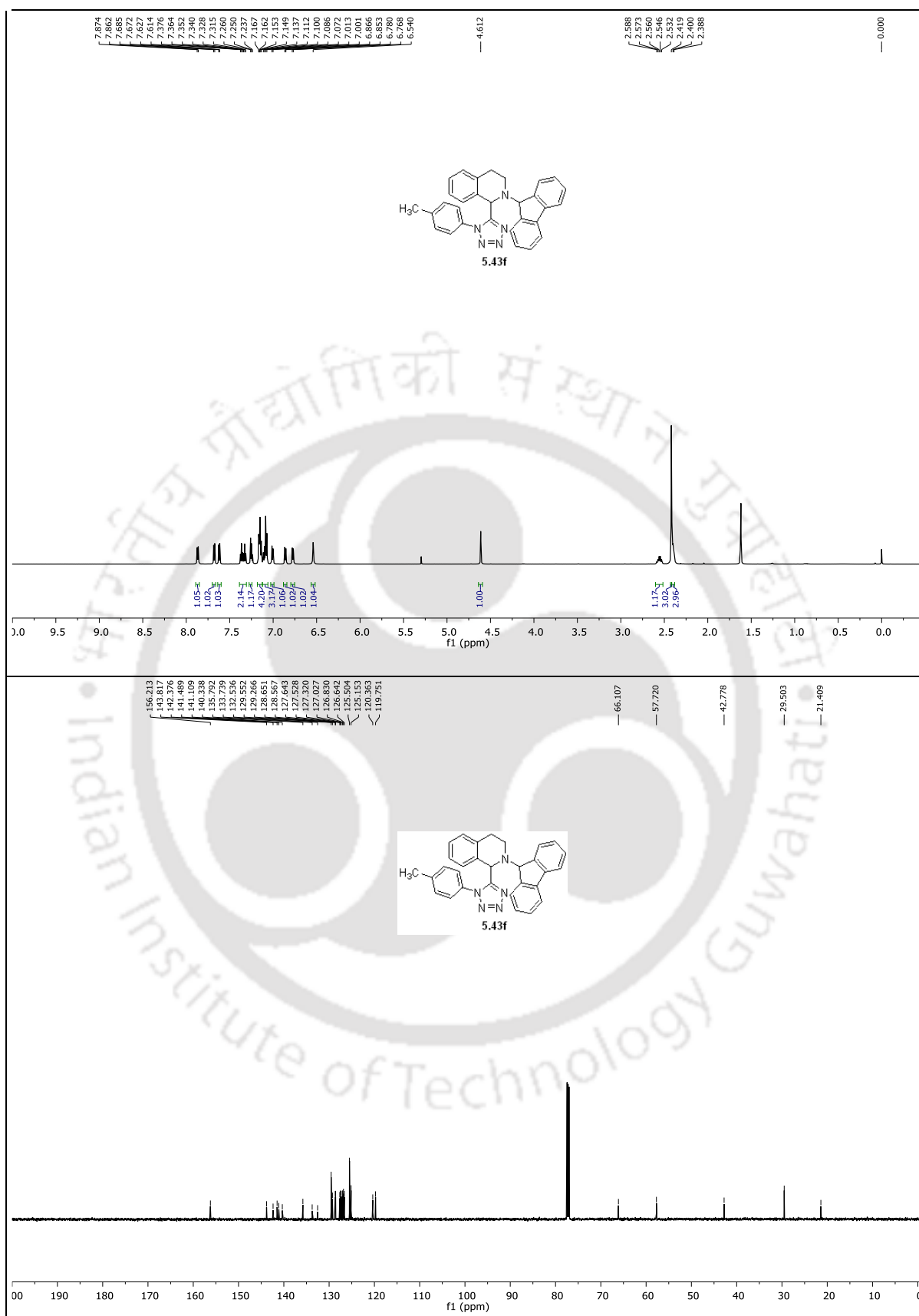
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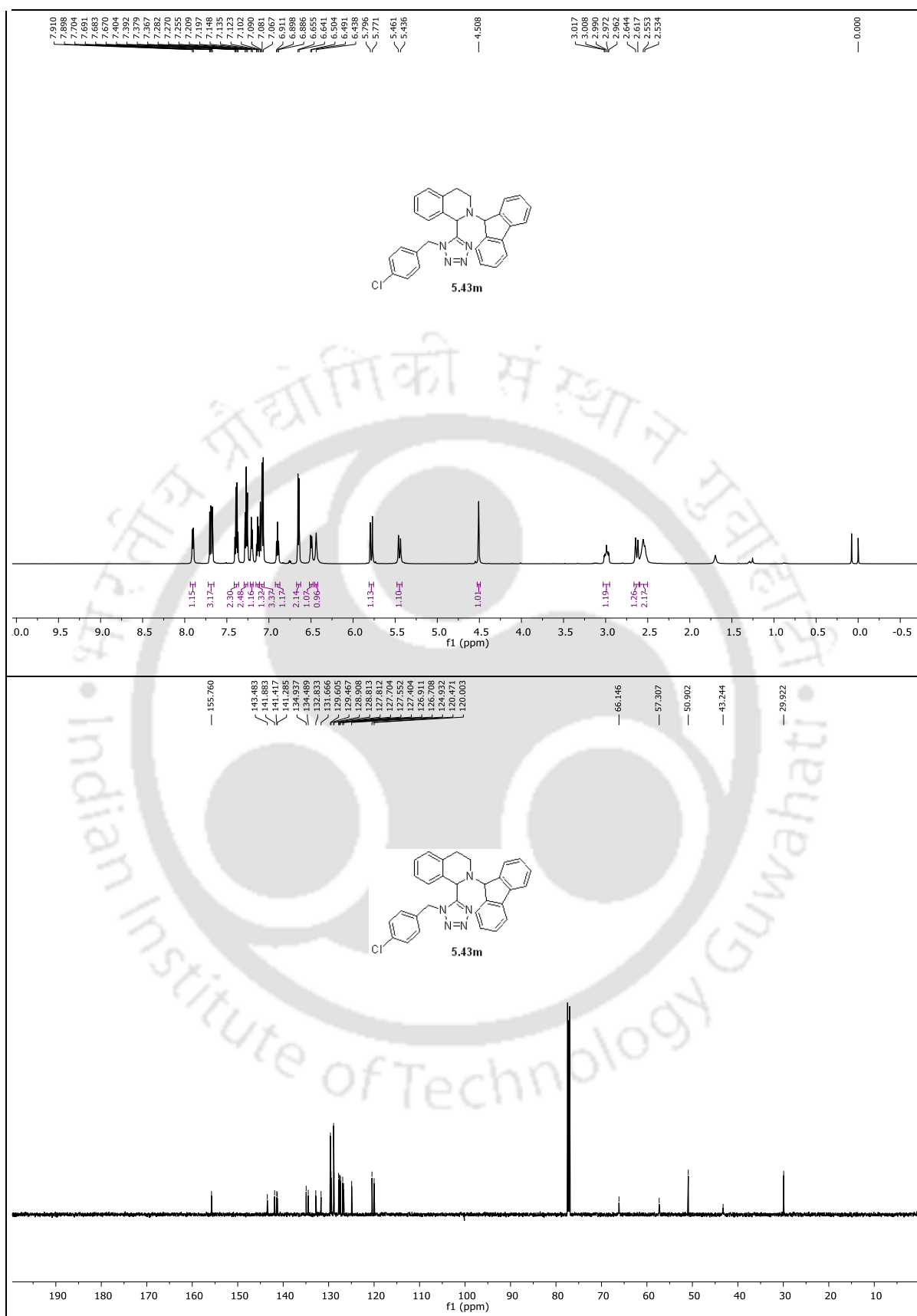


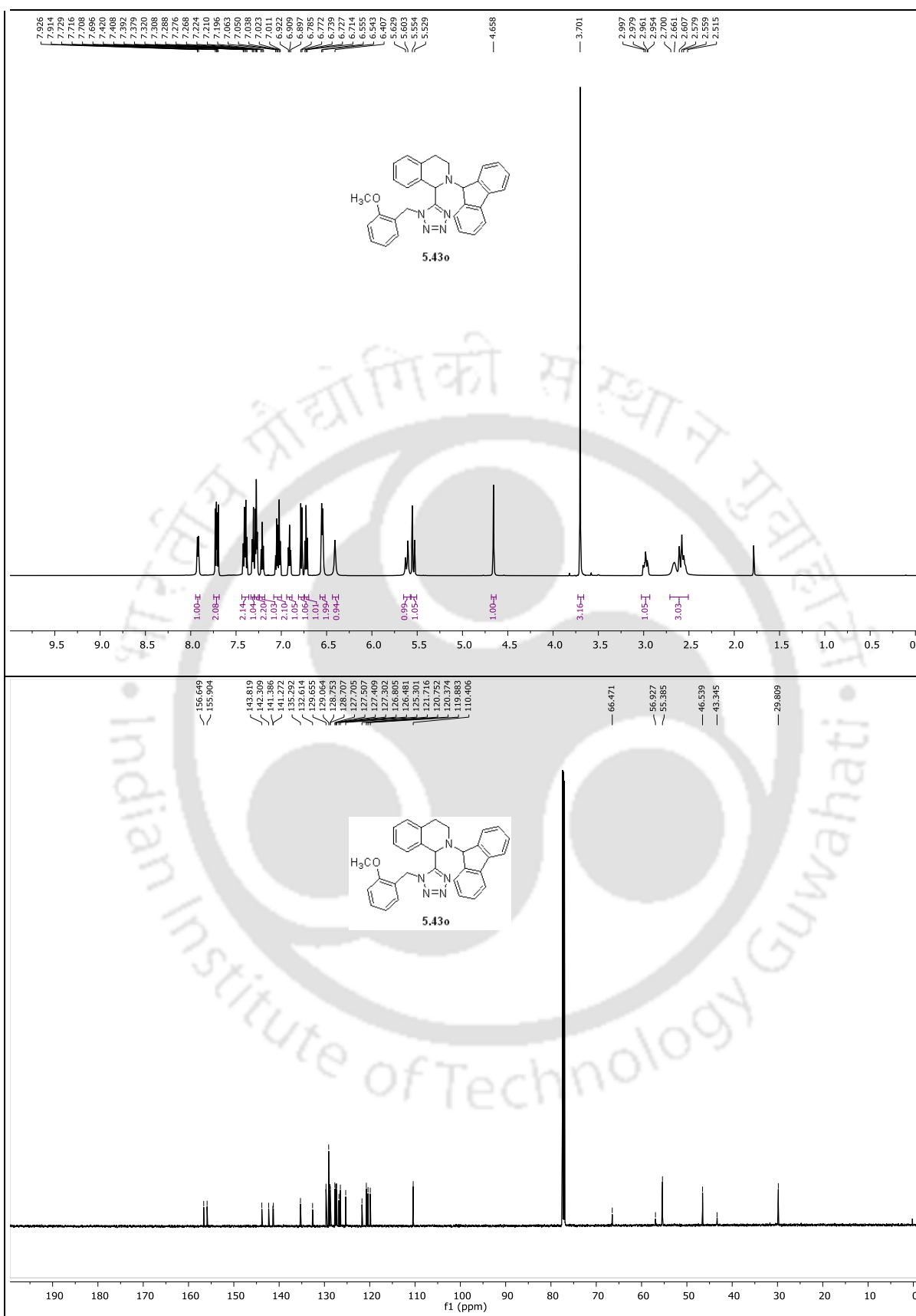


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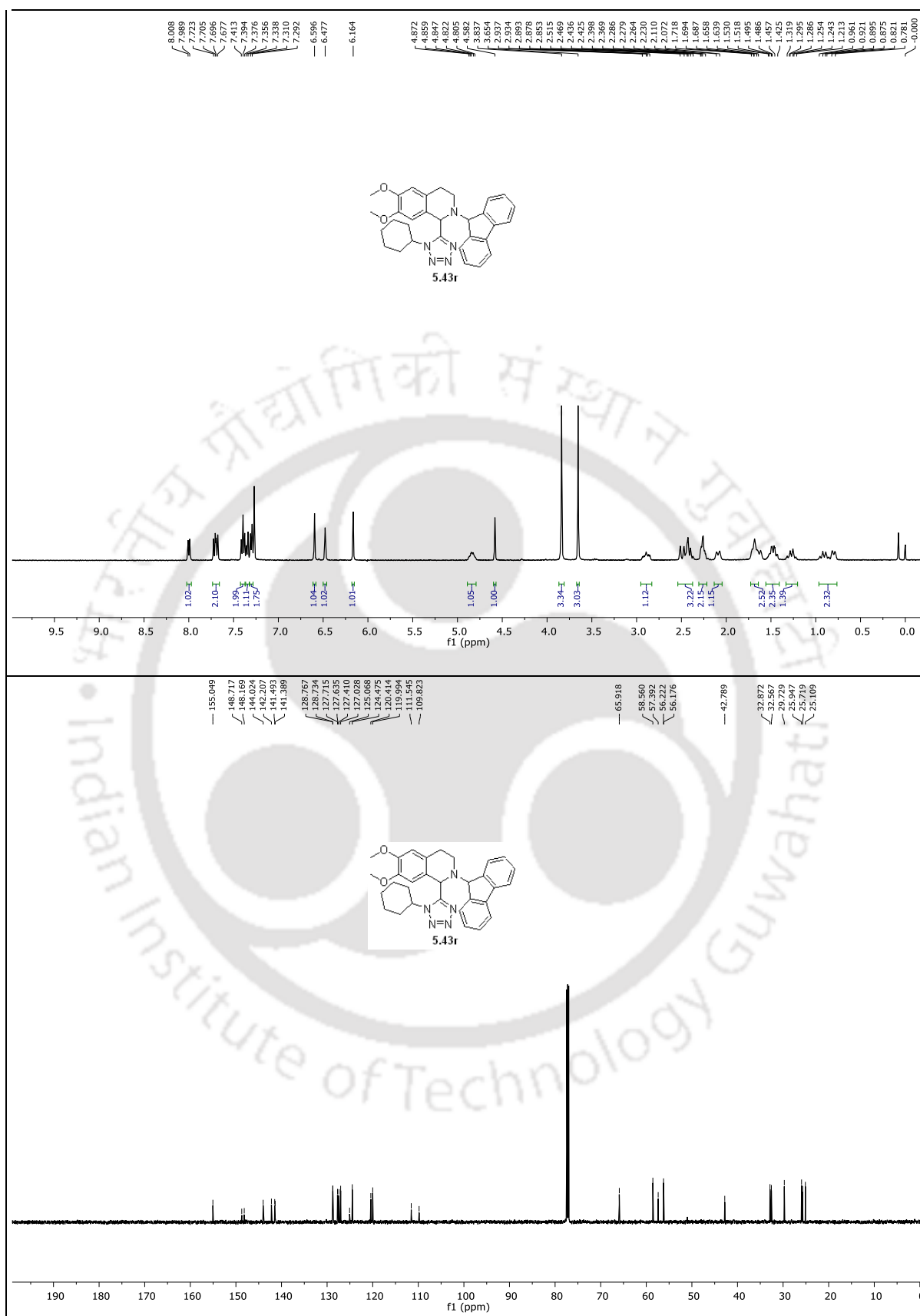


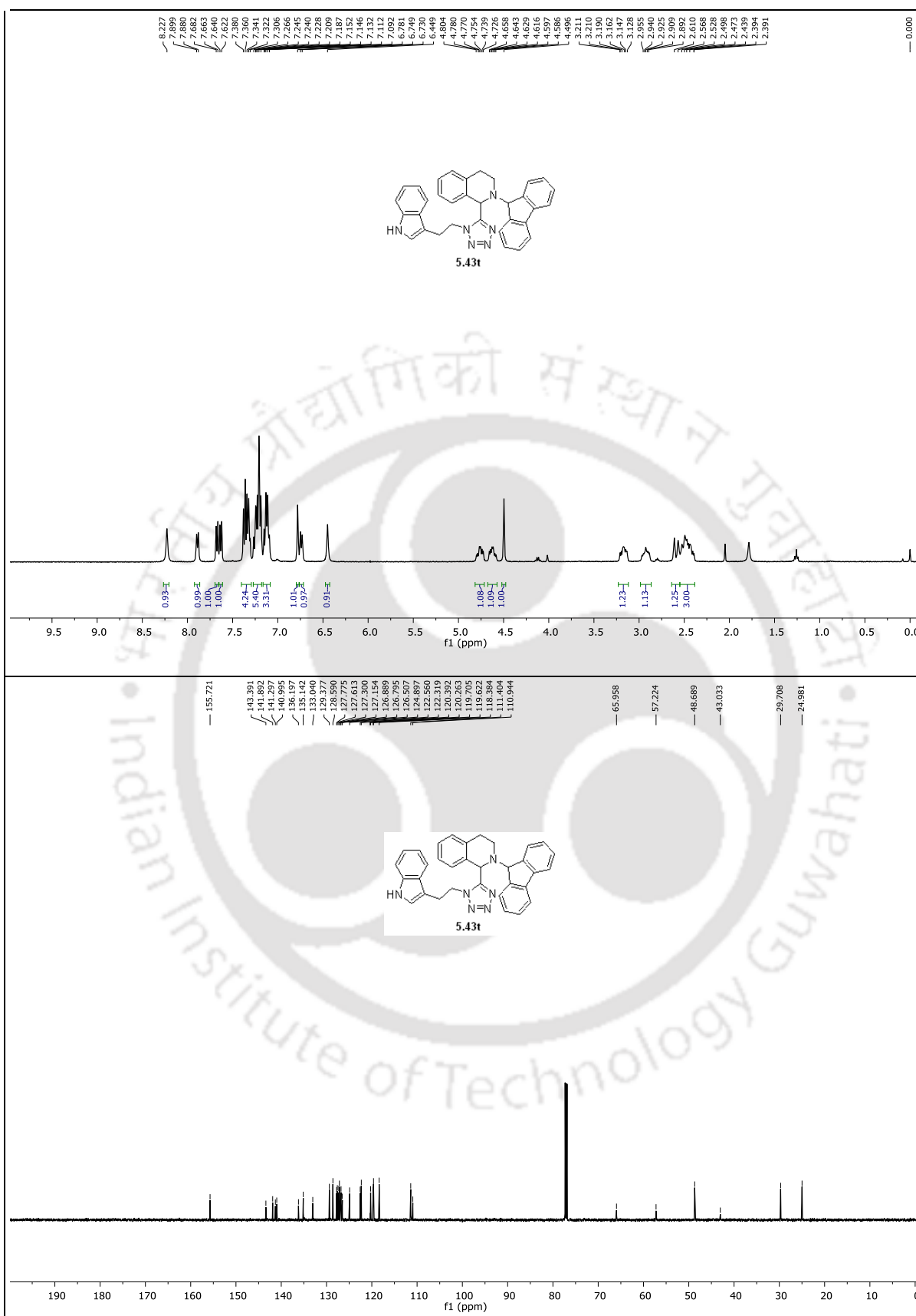


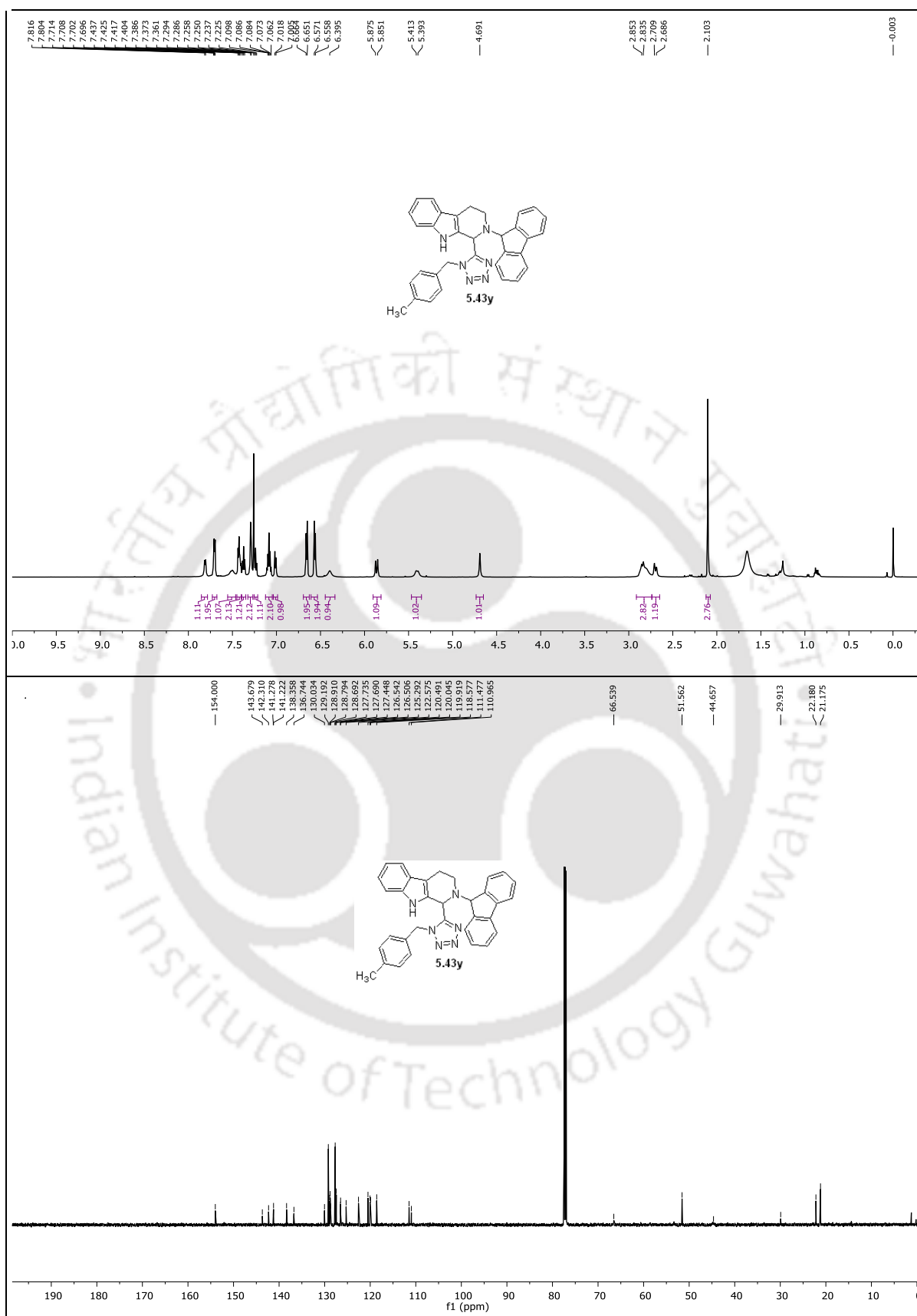


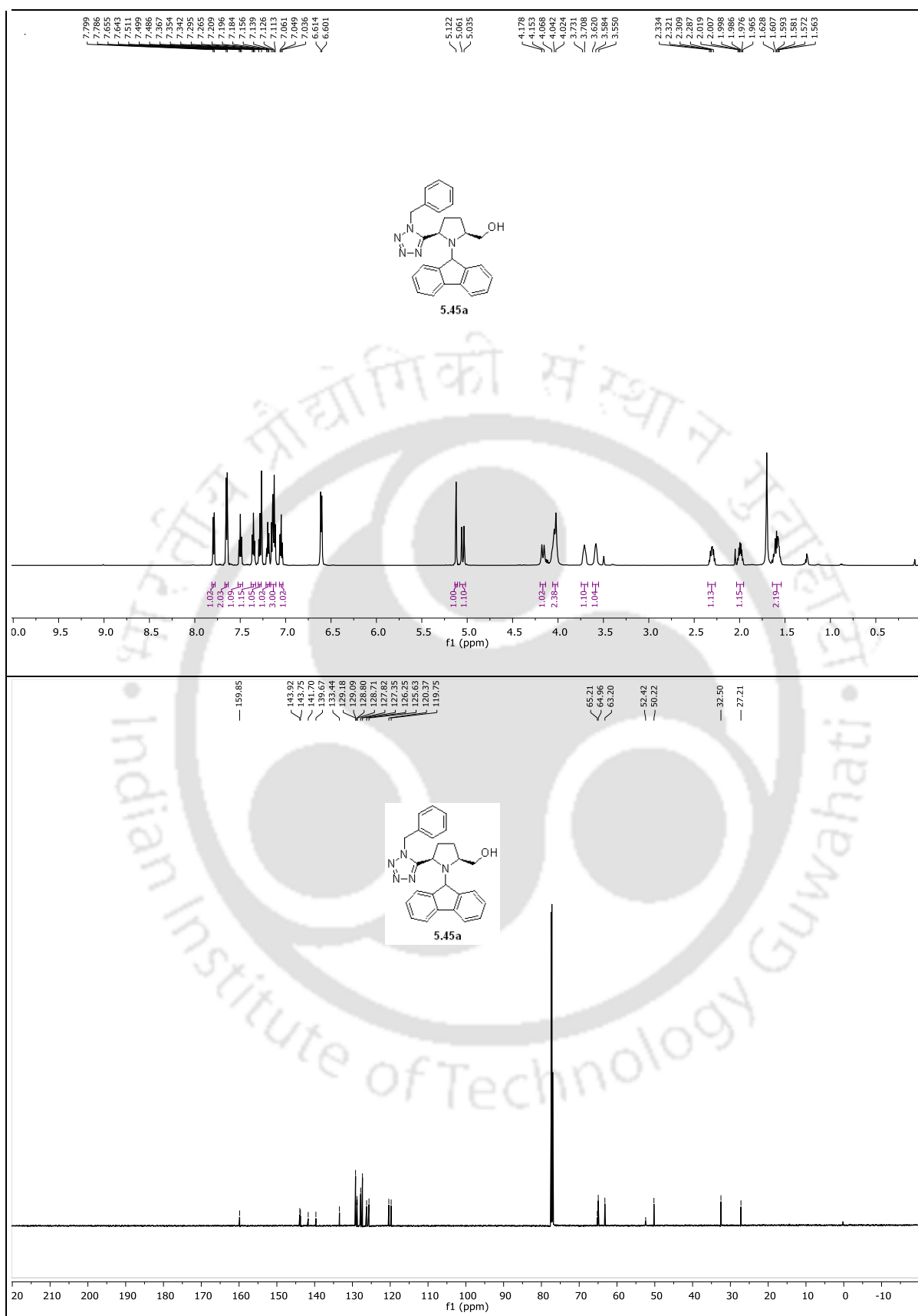


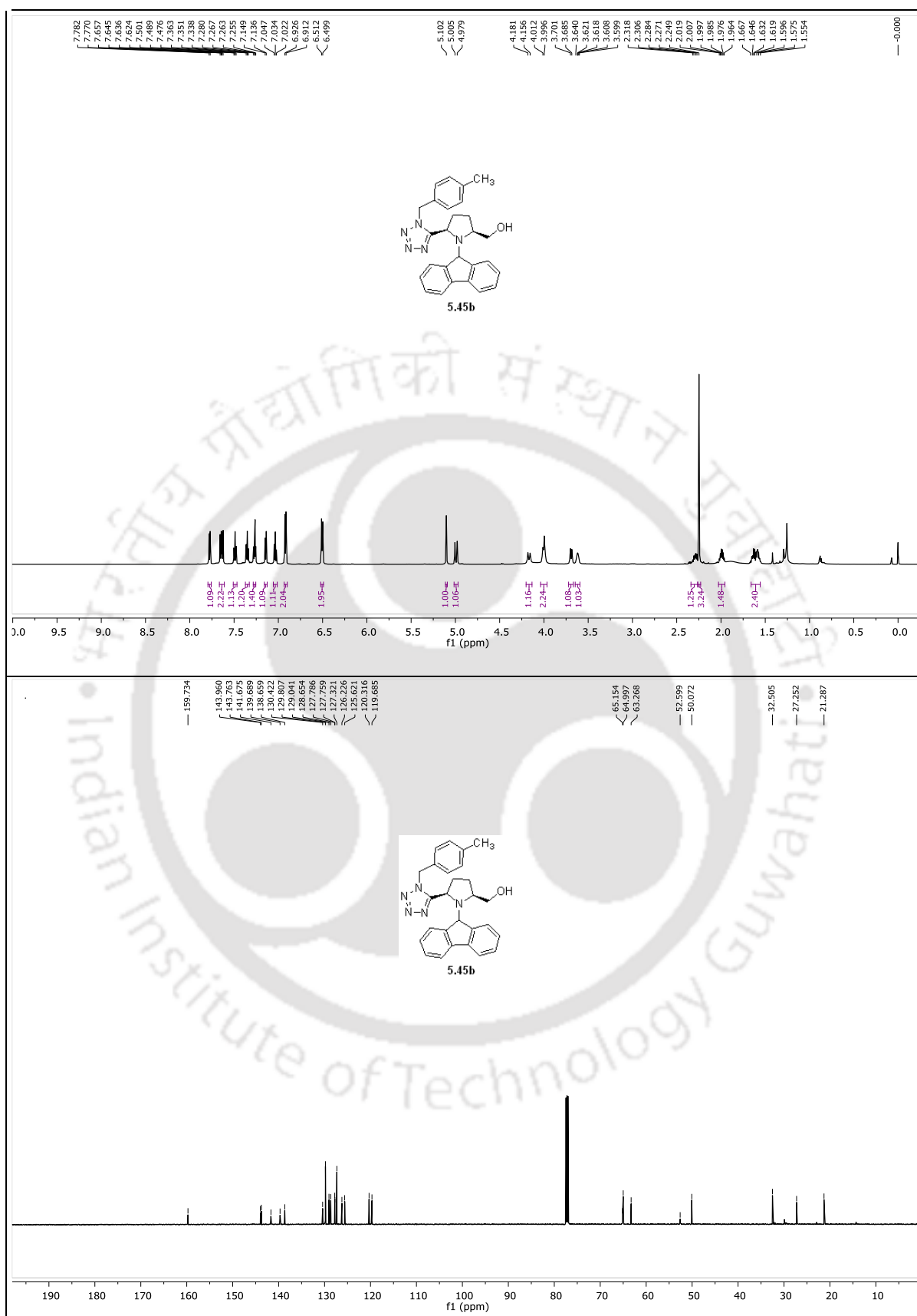
^1H , & ^{13}C spectra & HPLC chromatogram of selected new compounds

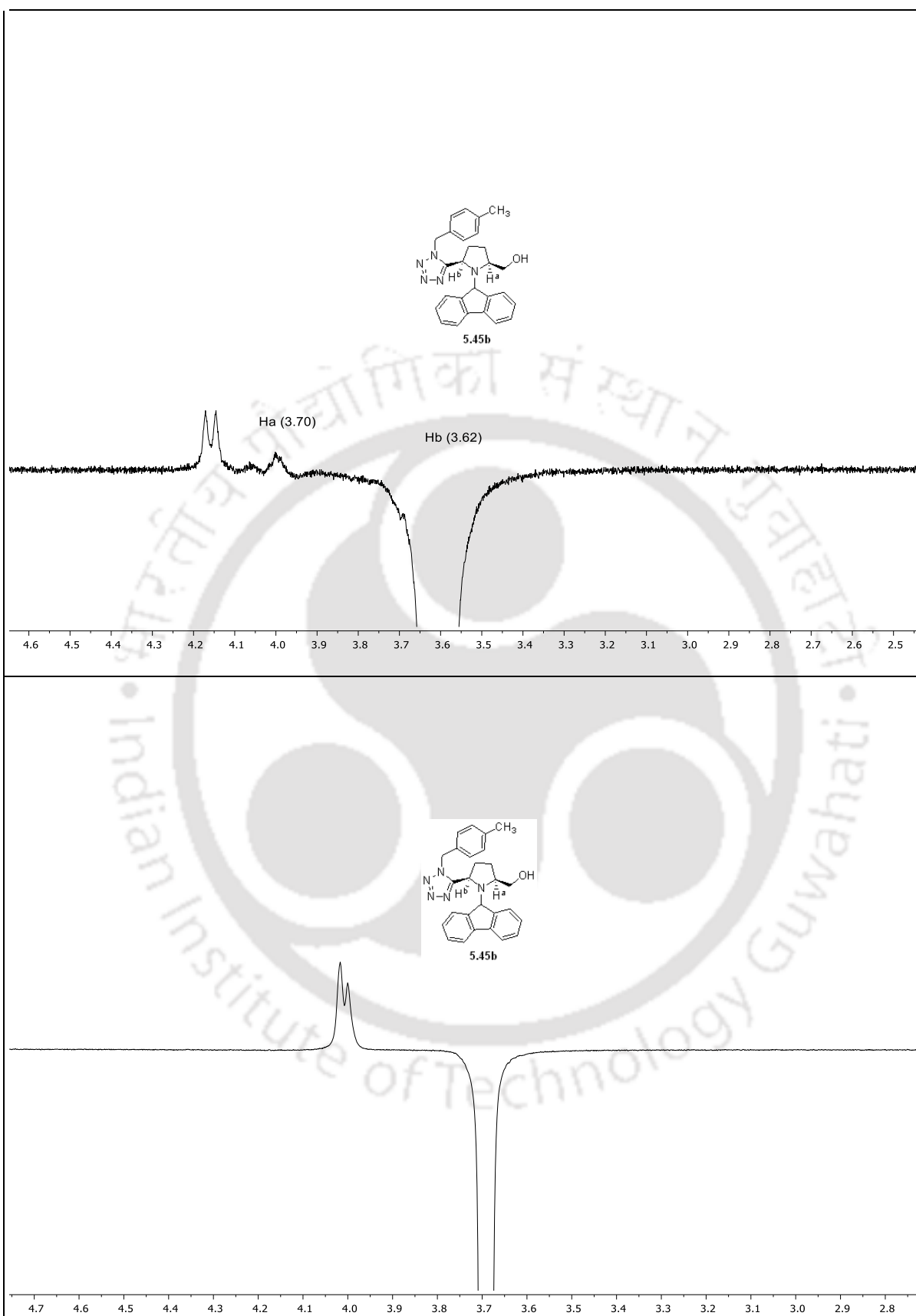


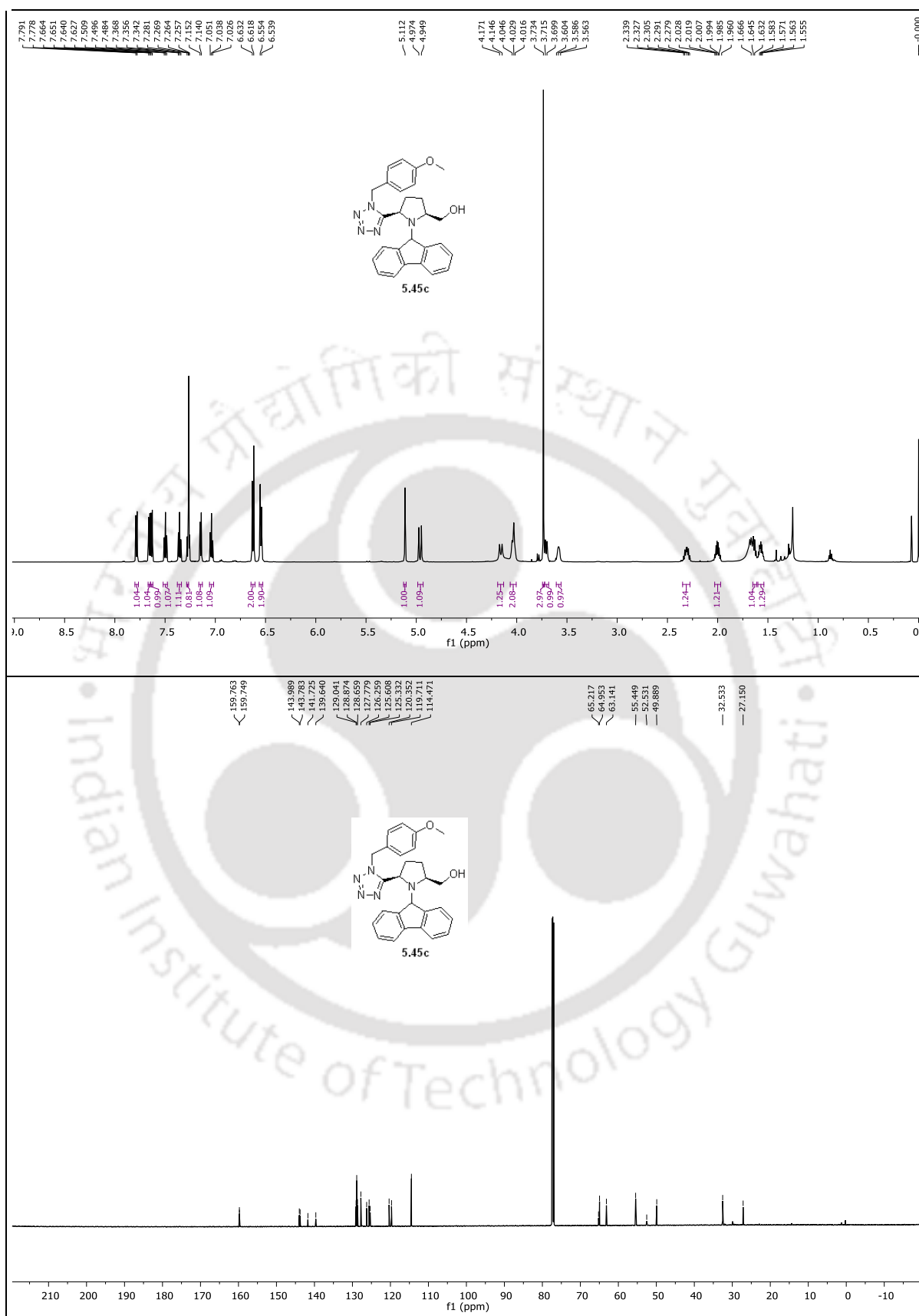




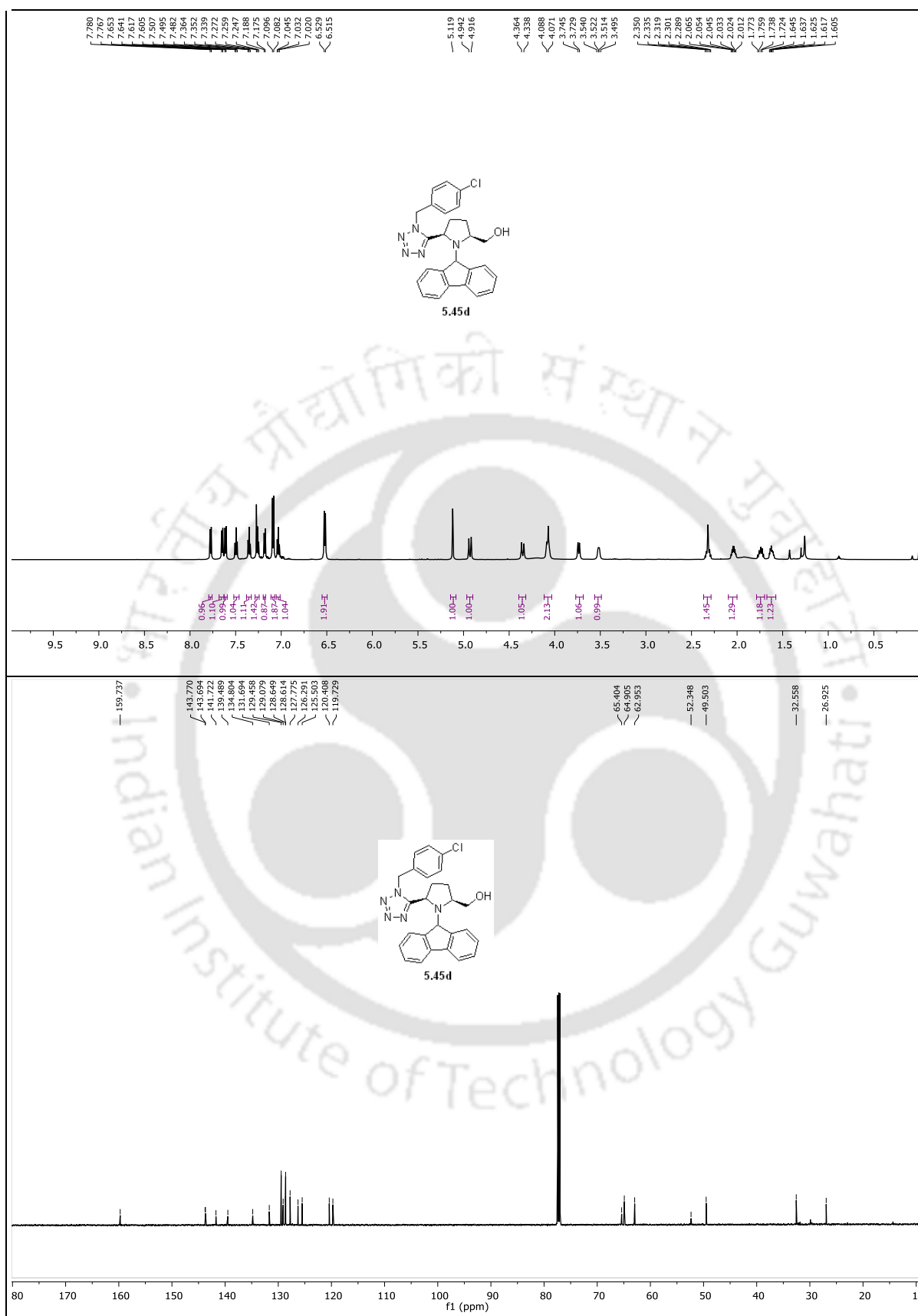




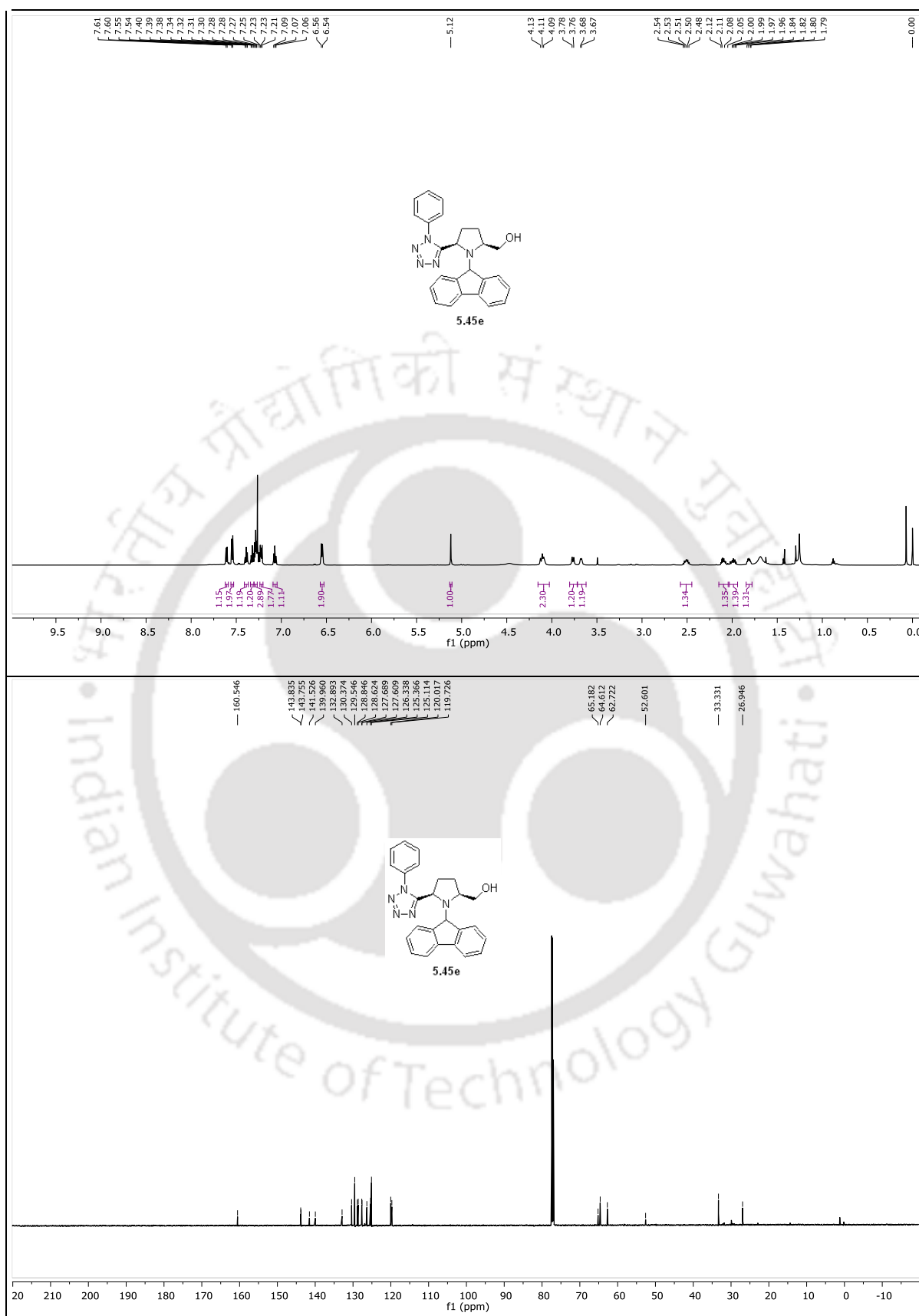


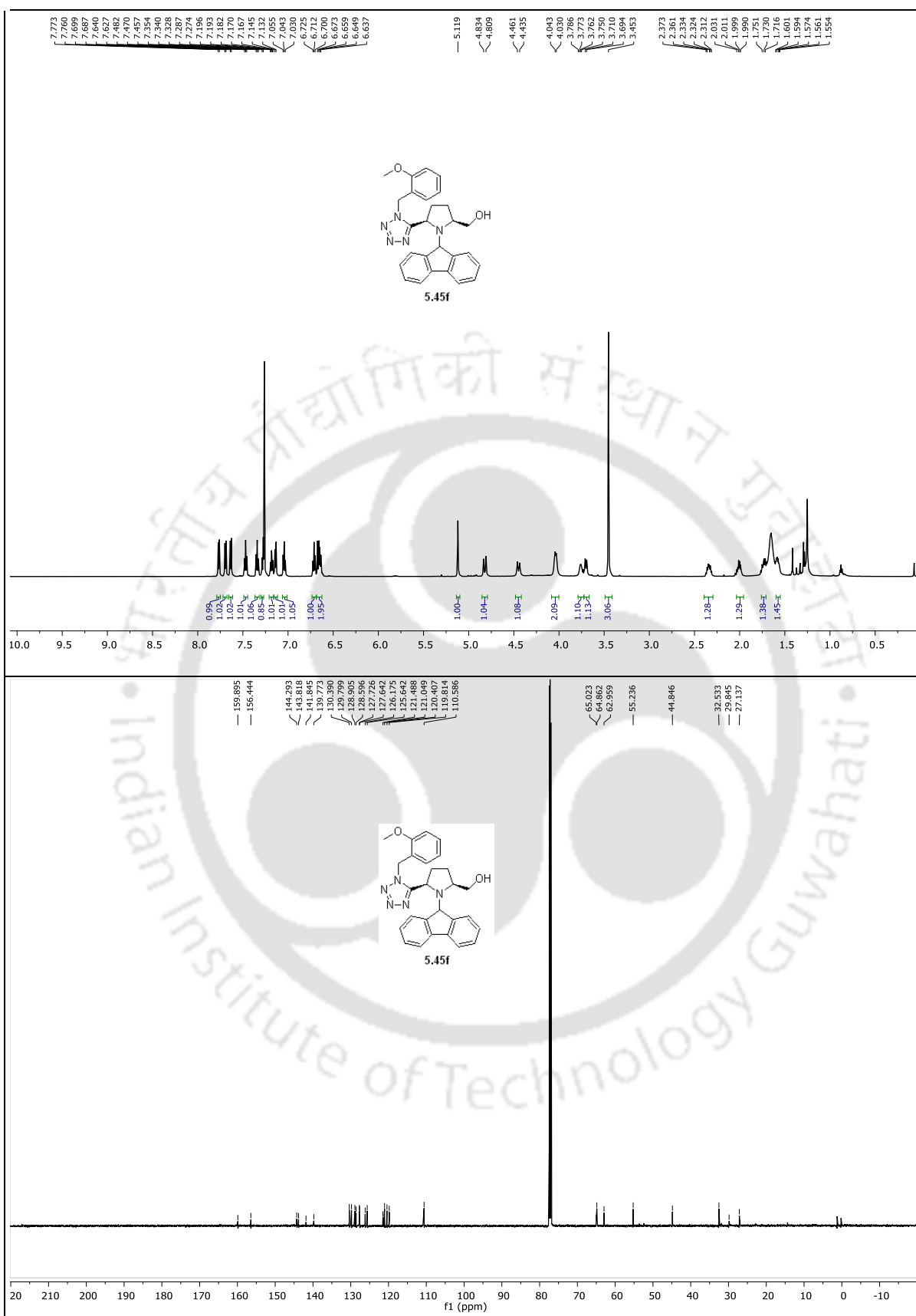


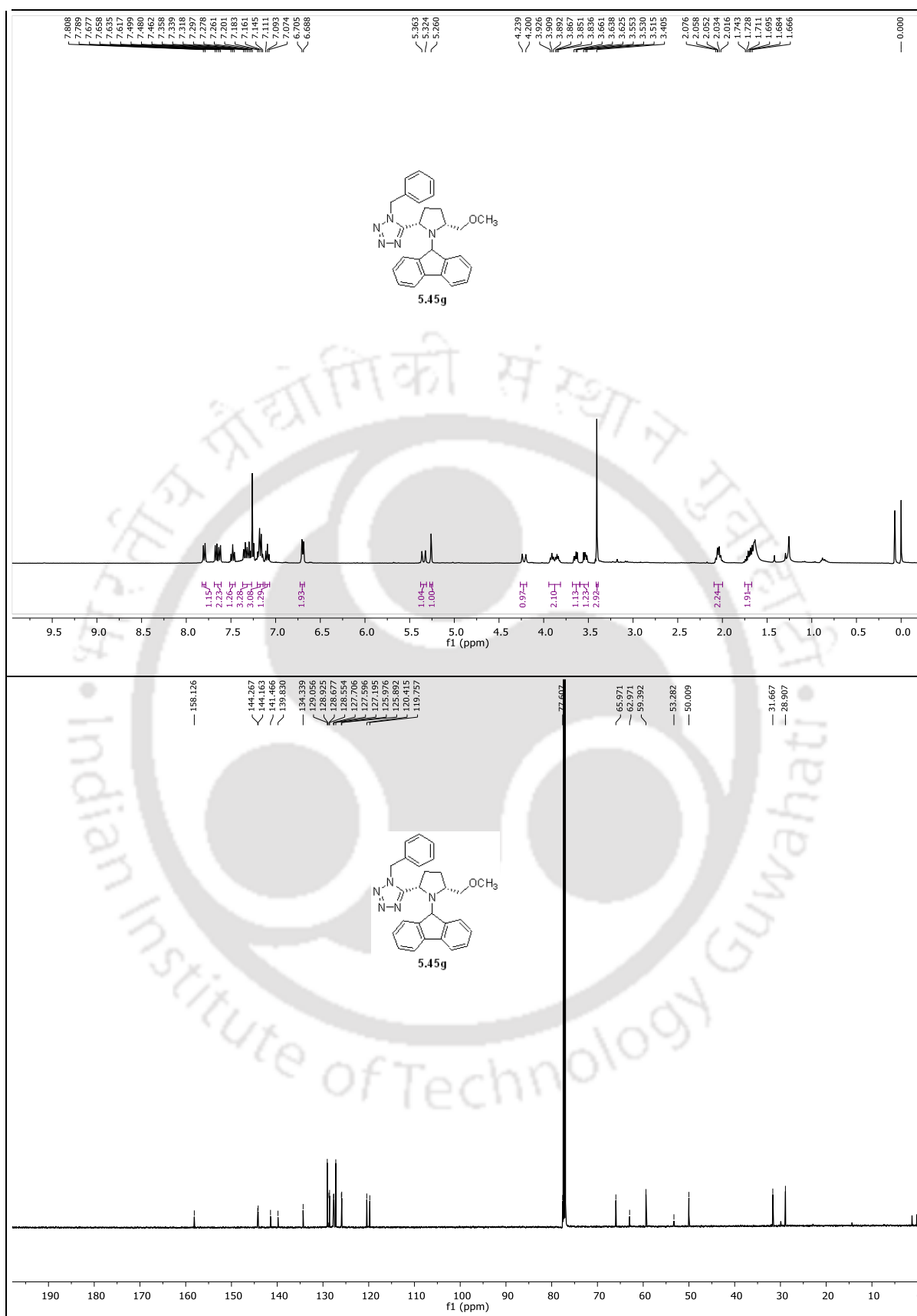
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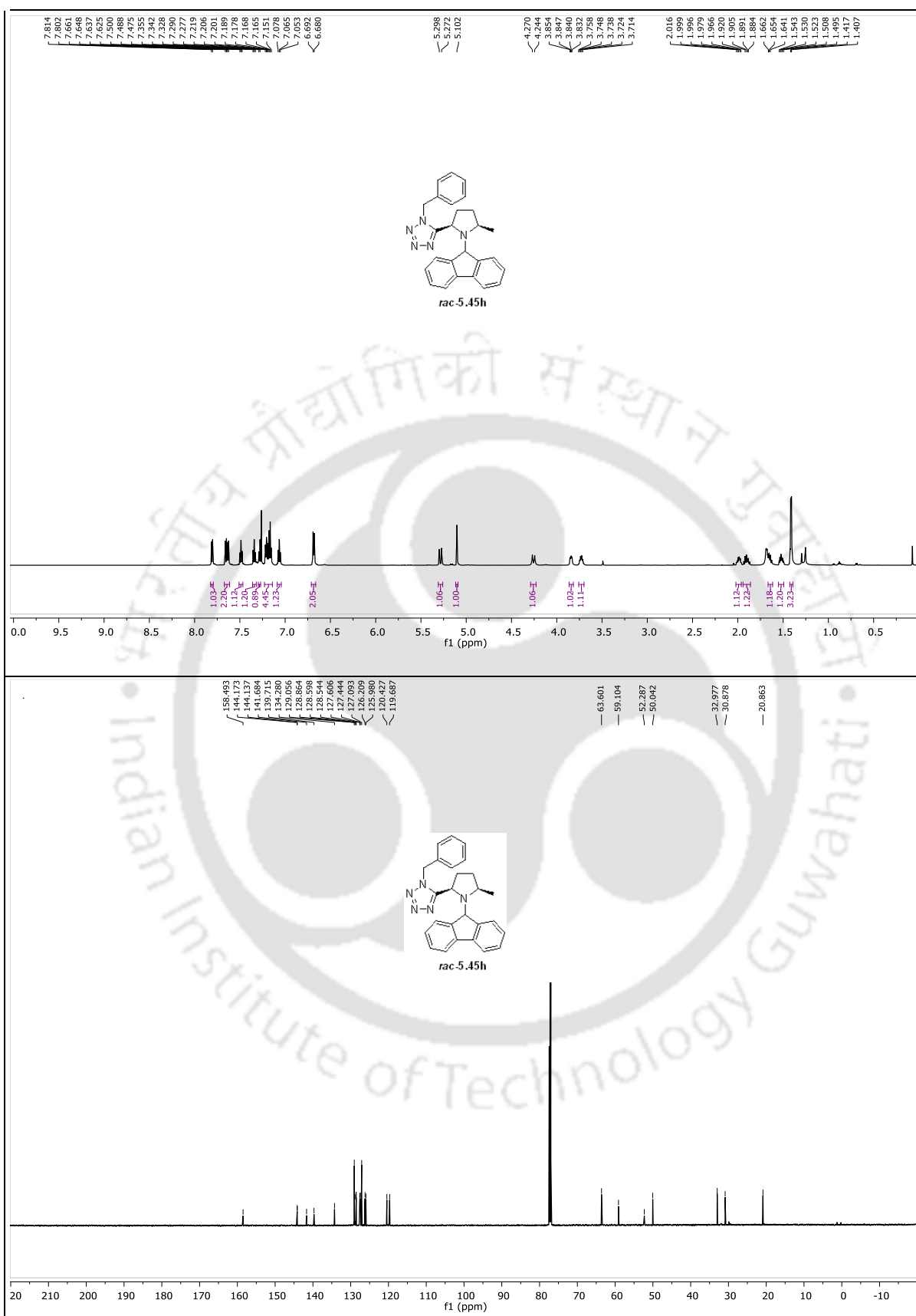


^1H , & ^{13}C spectra & HPLC chromatogram of selected new compounds

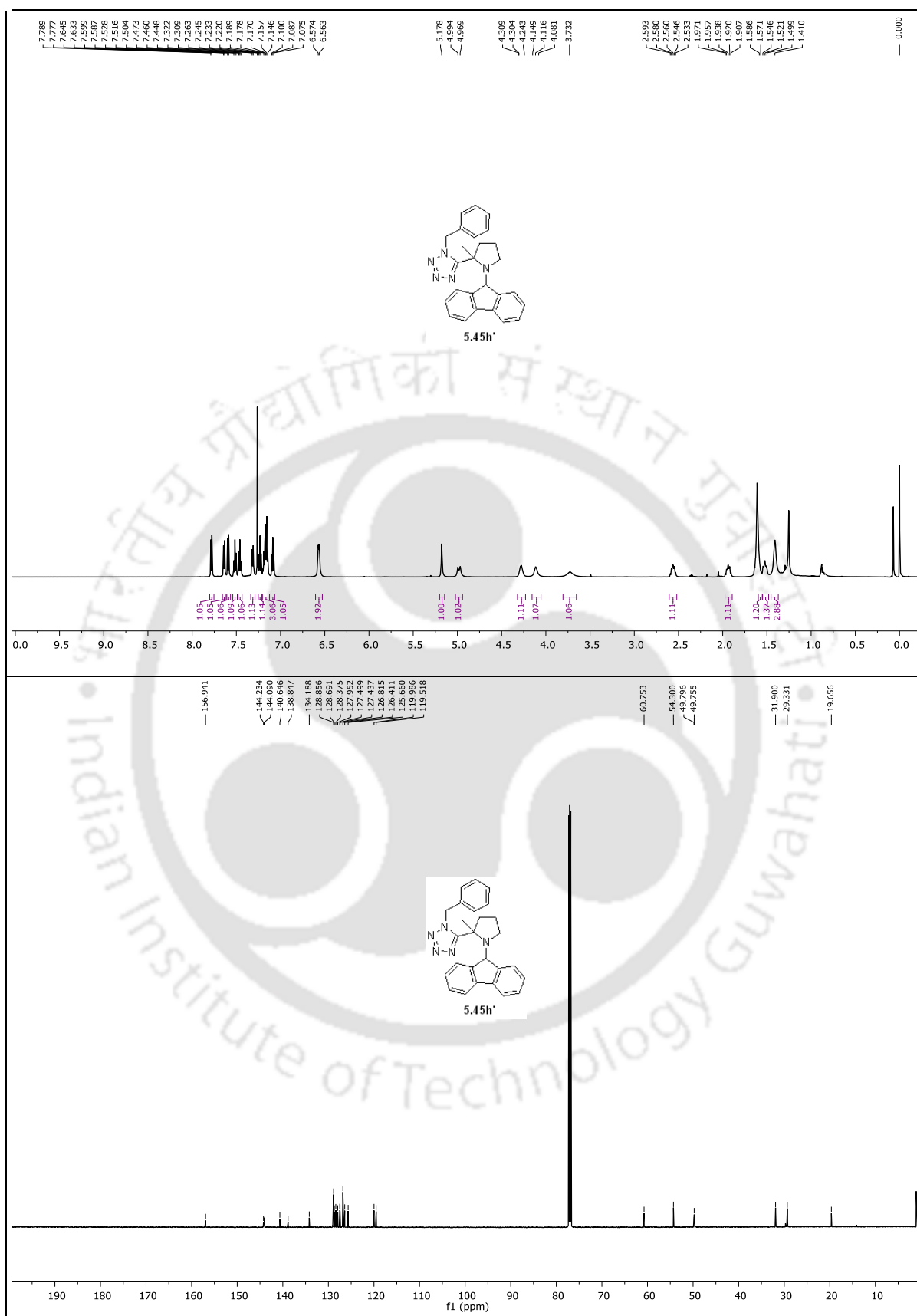


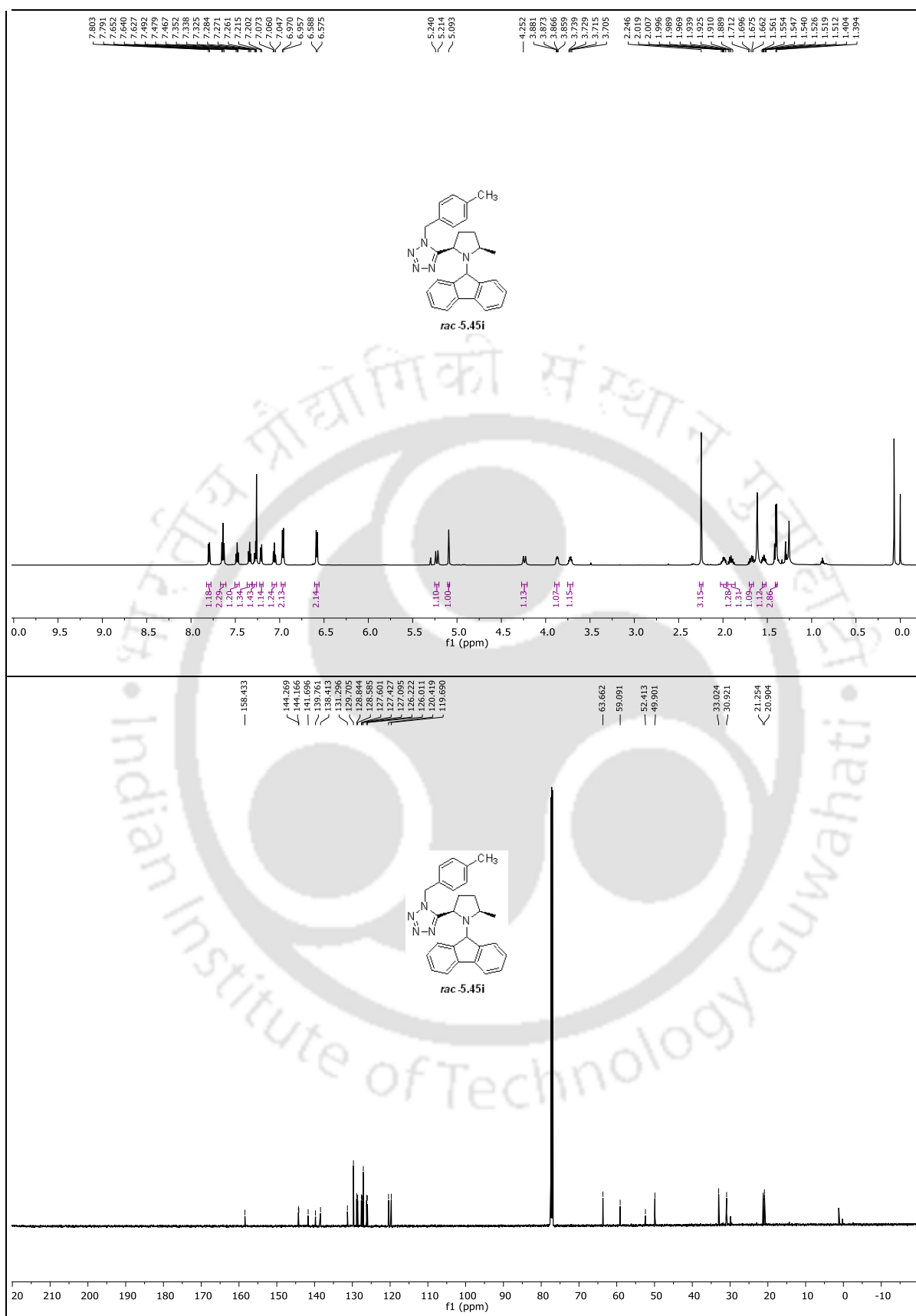


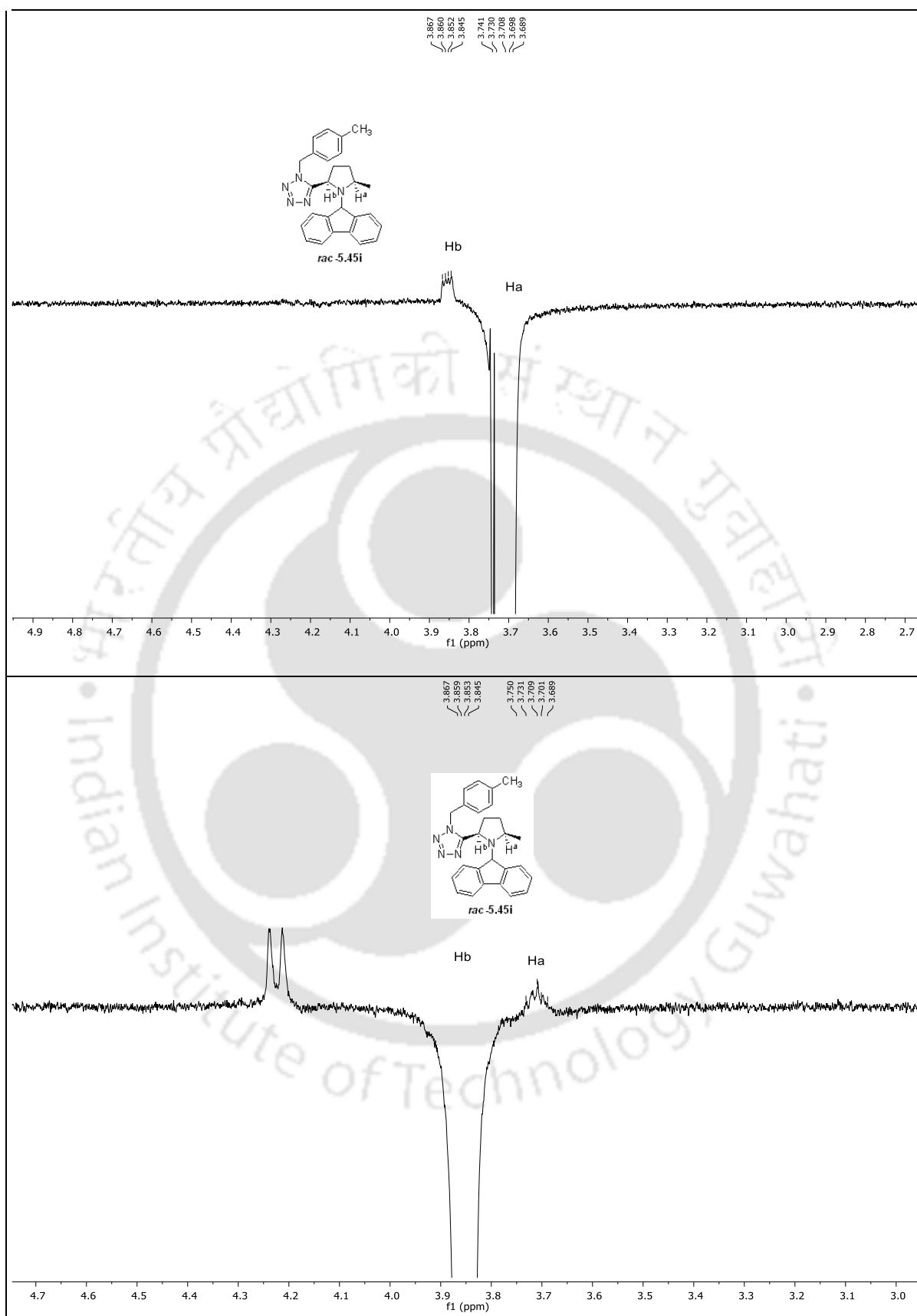


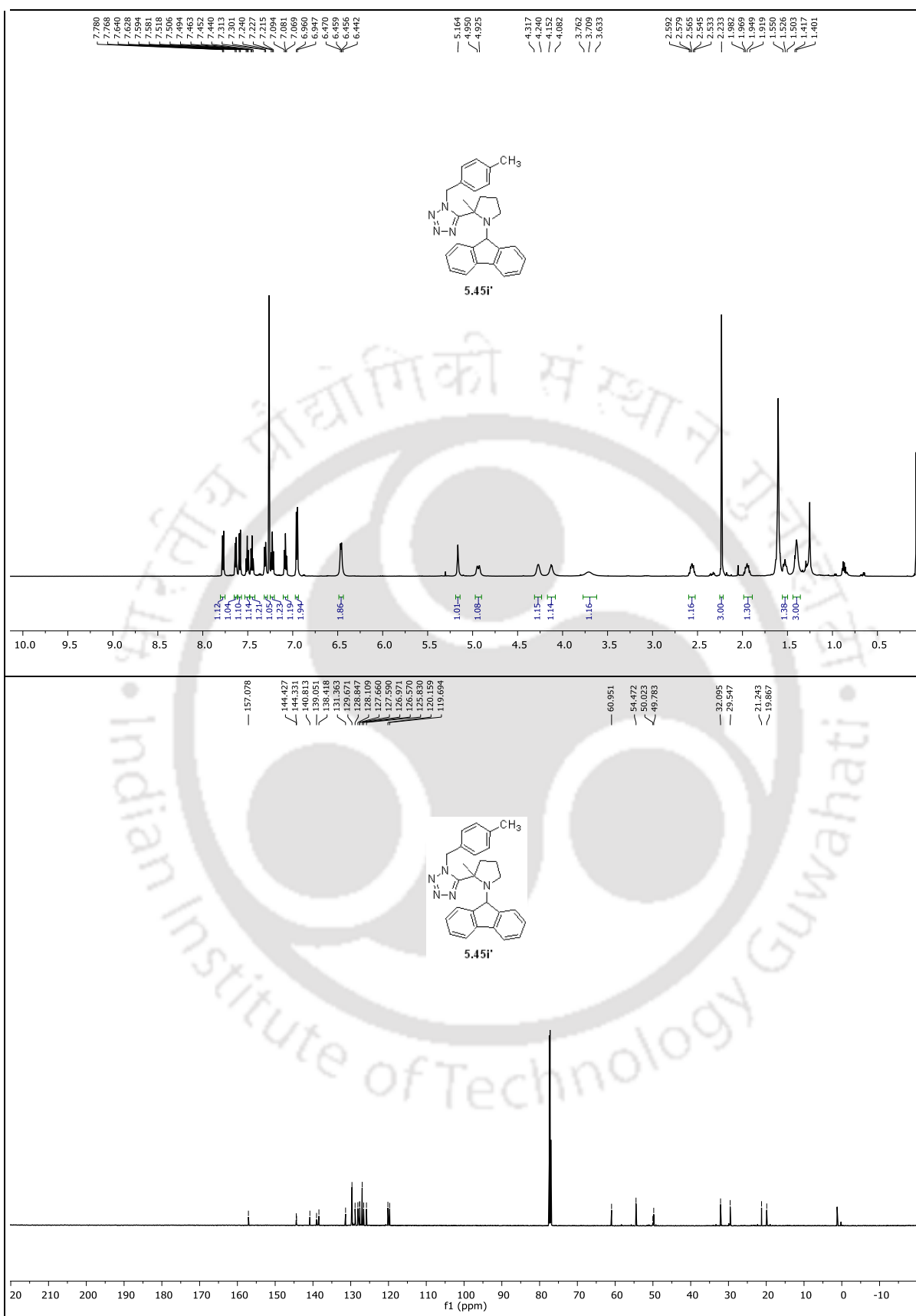


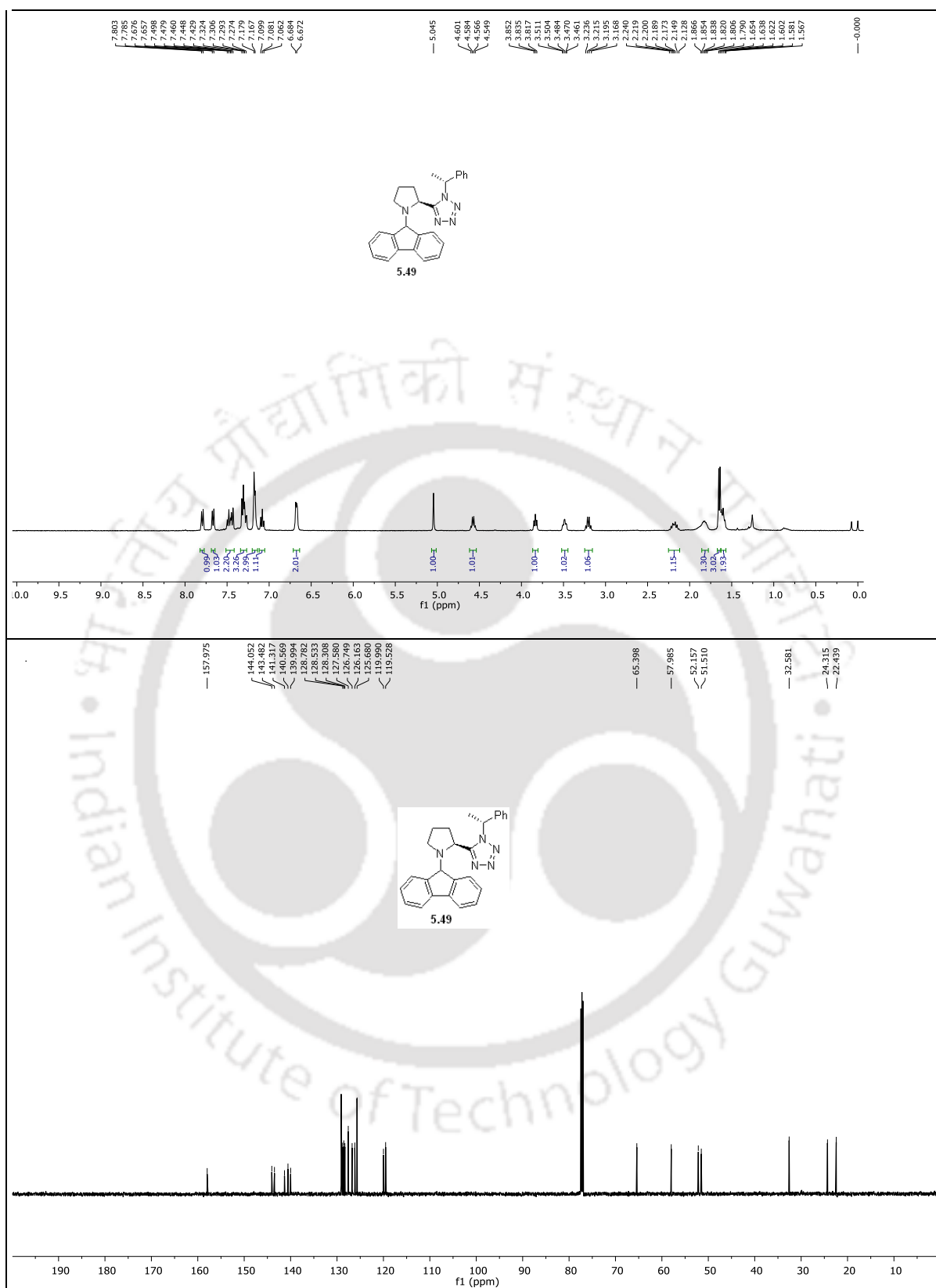
^1H , & ^{13}C spectra & HPLC chromatogram of selected new compounds

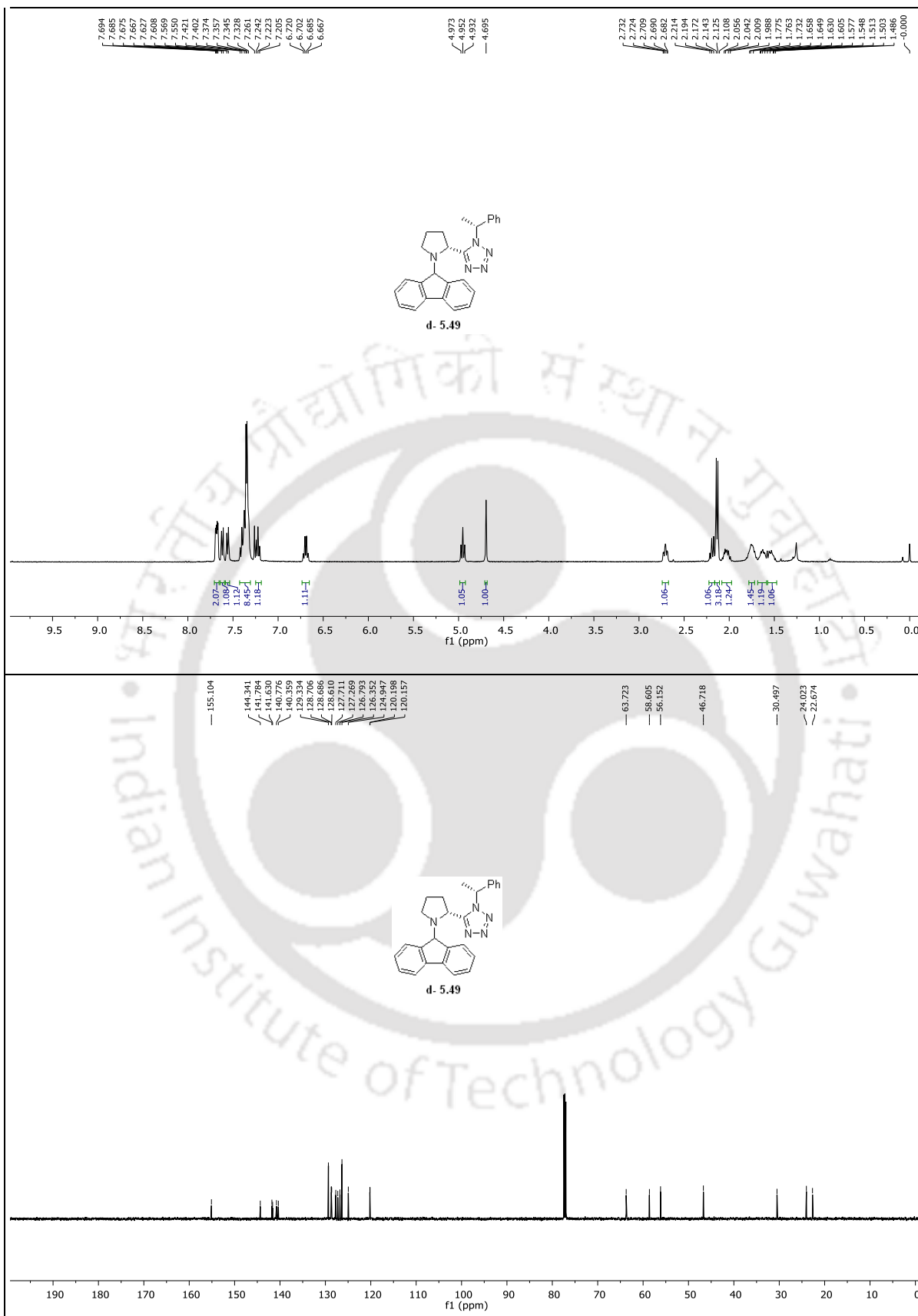


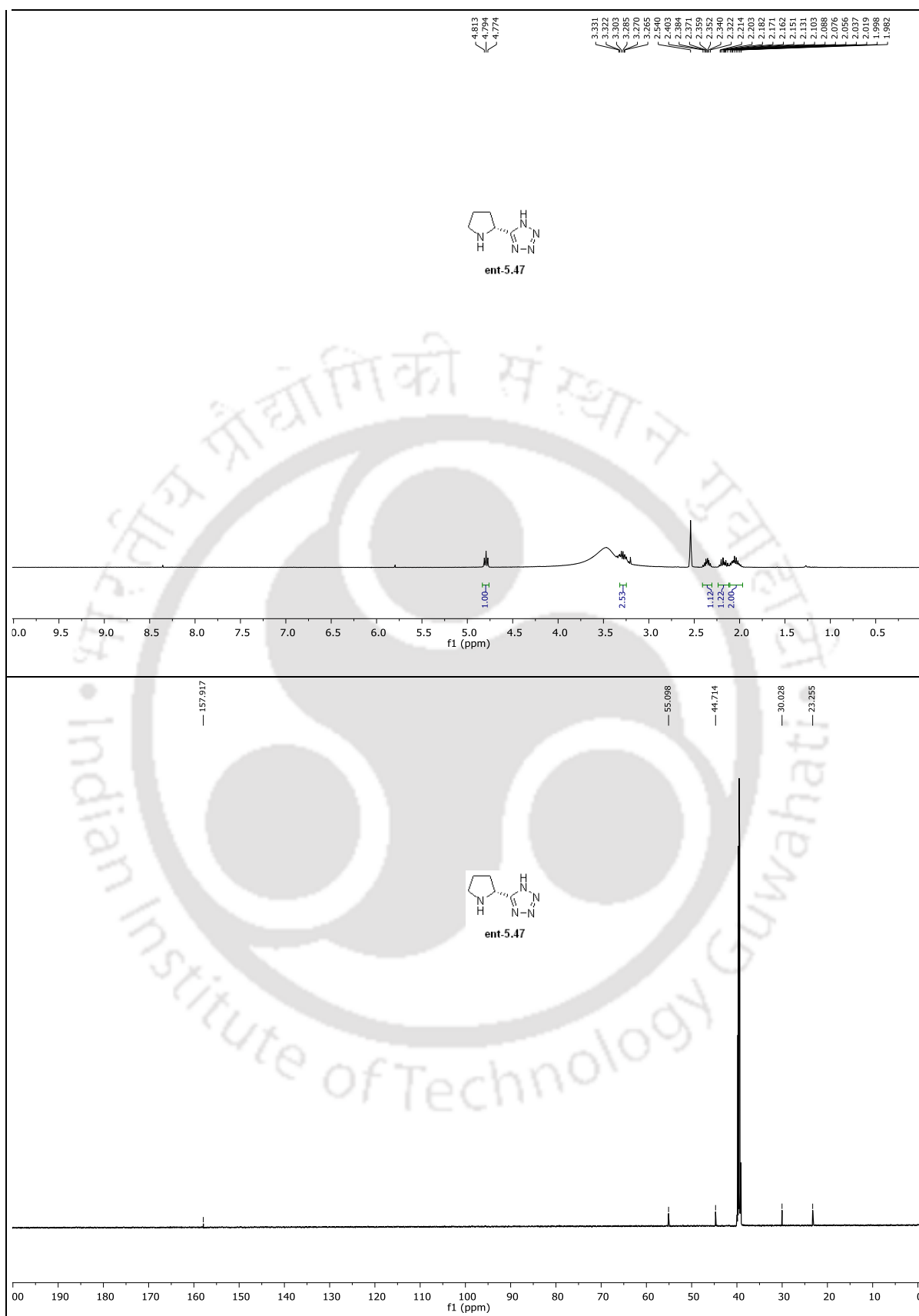


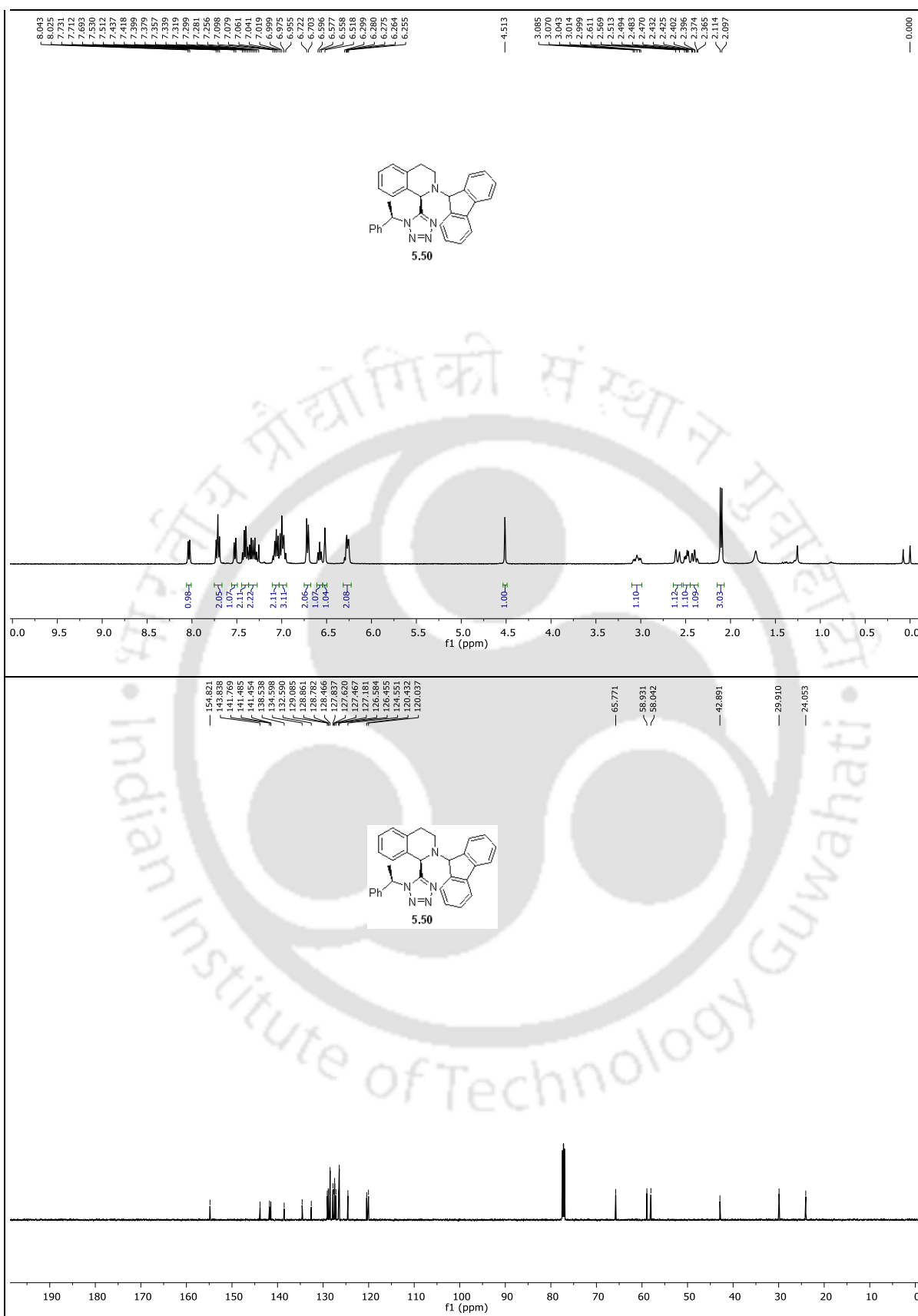




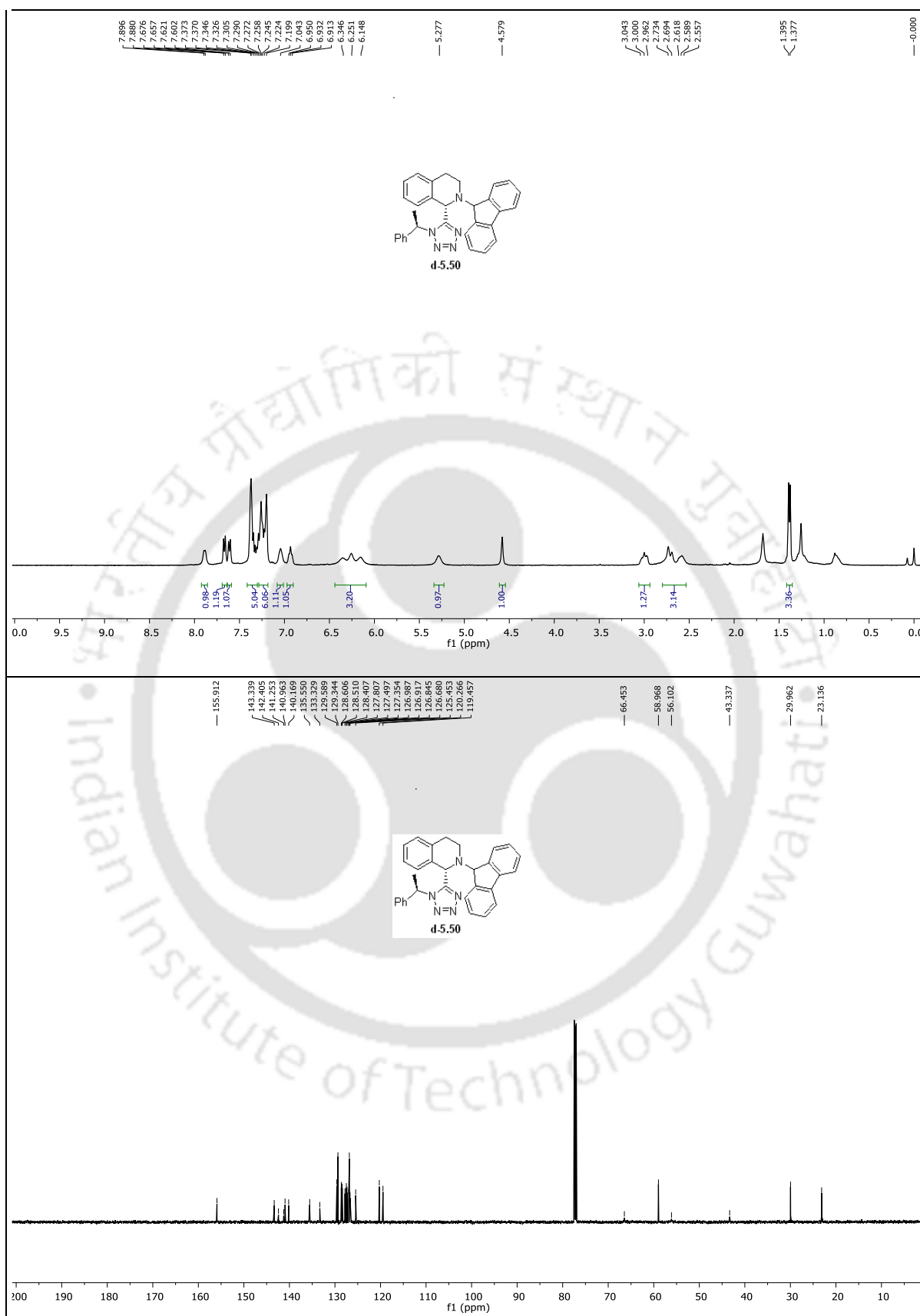




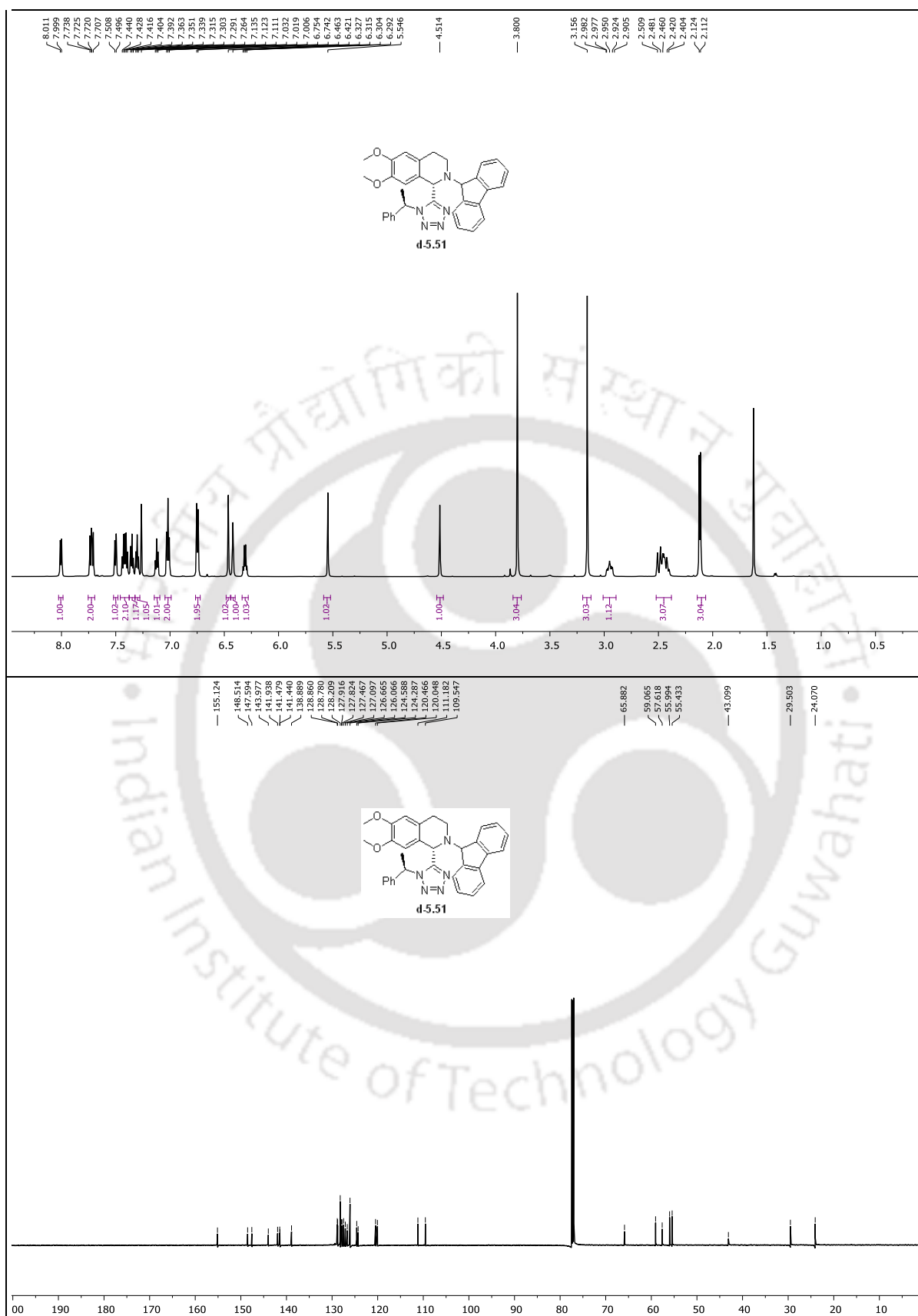


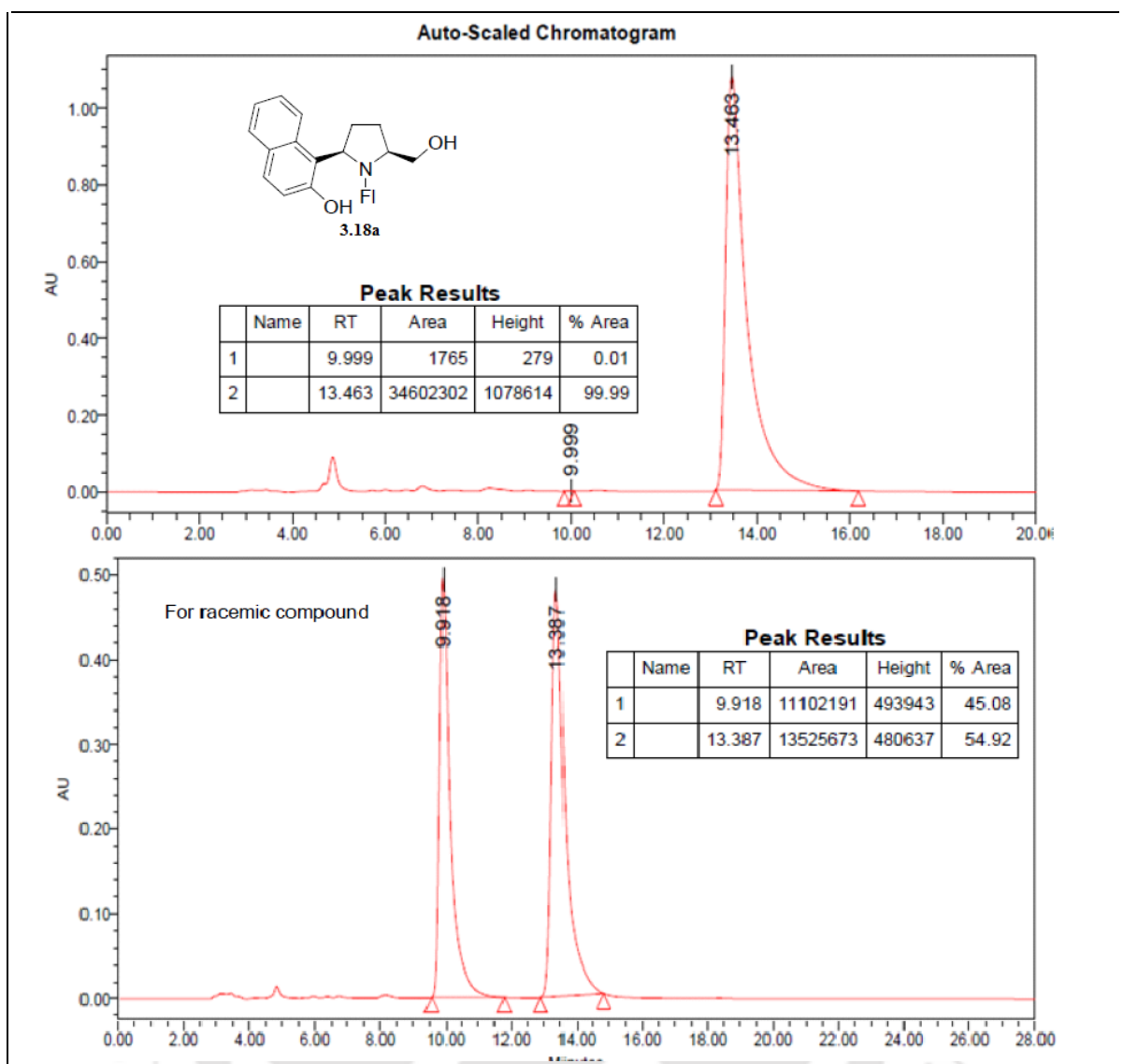


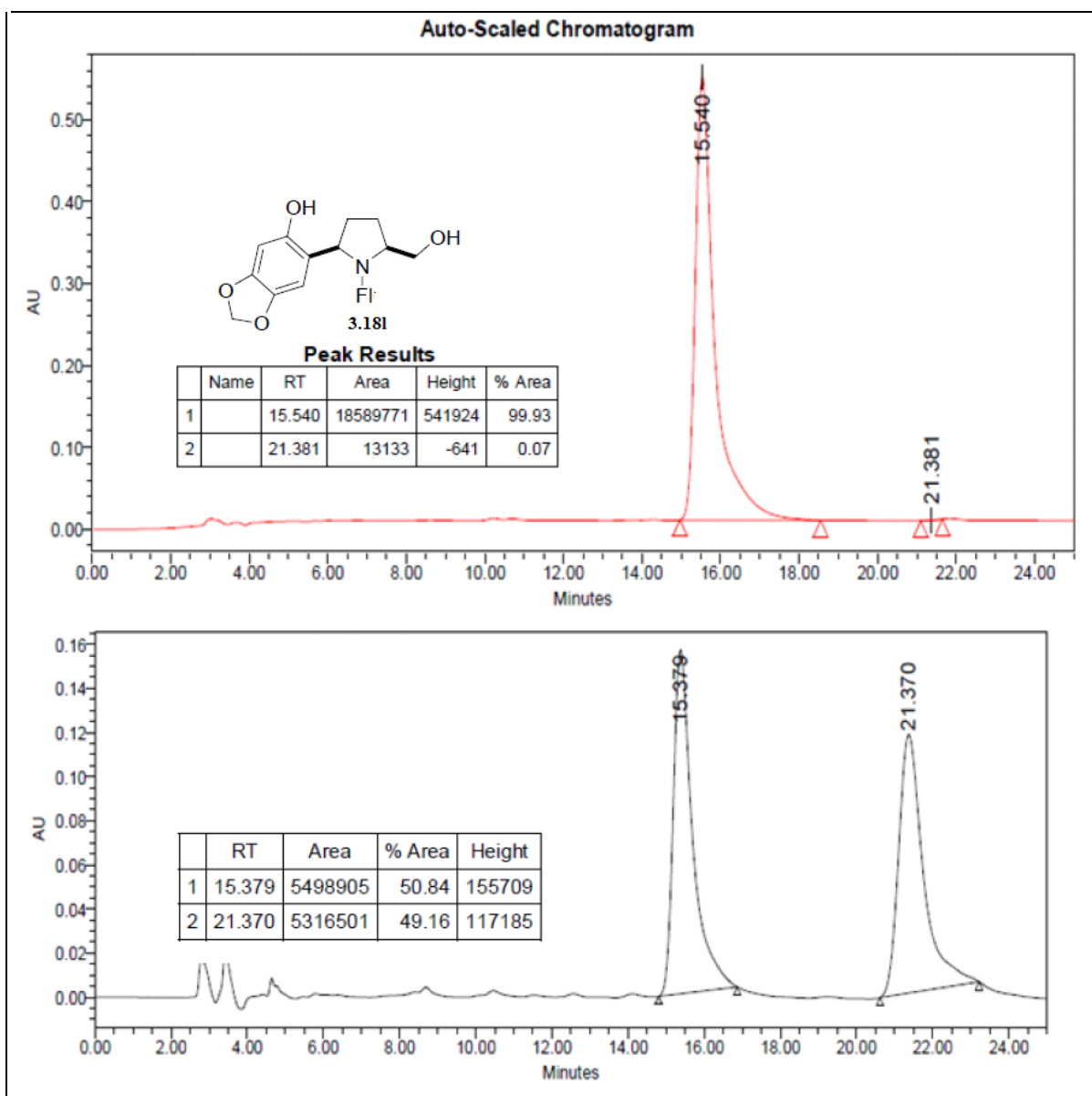
^1H , & ^{13}C spectra & HPLC chromatogram of selected new compounds

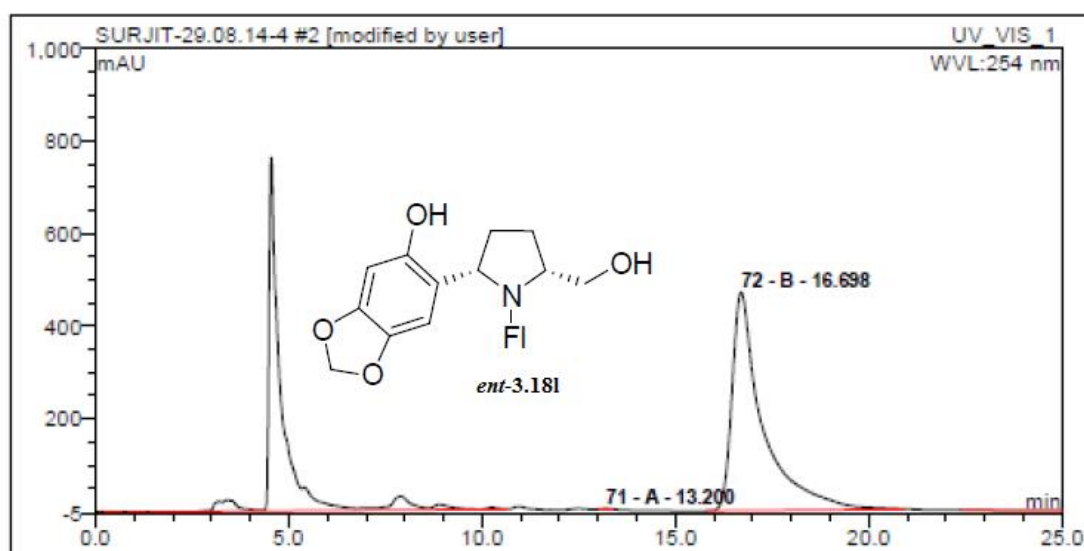


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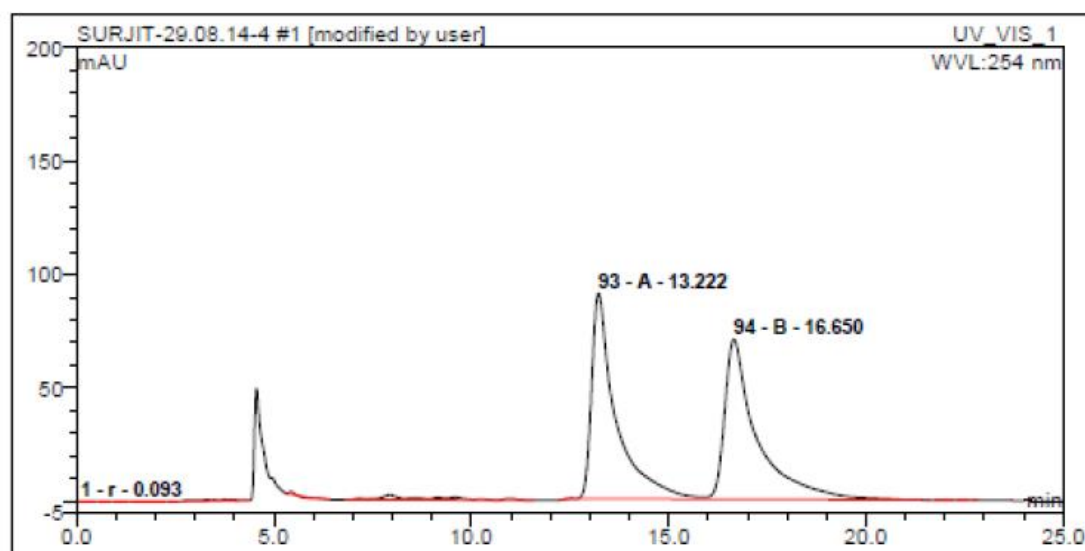




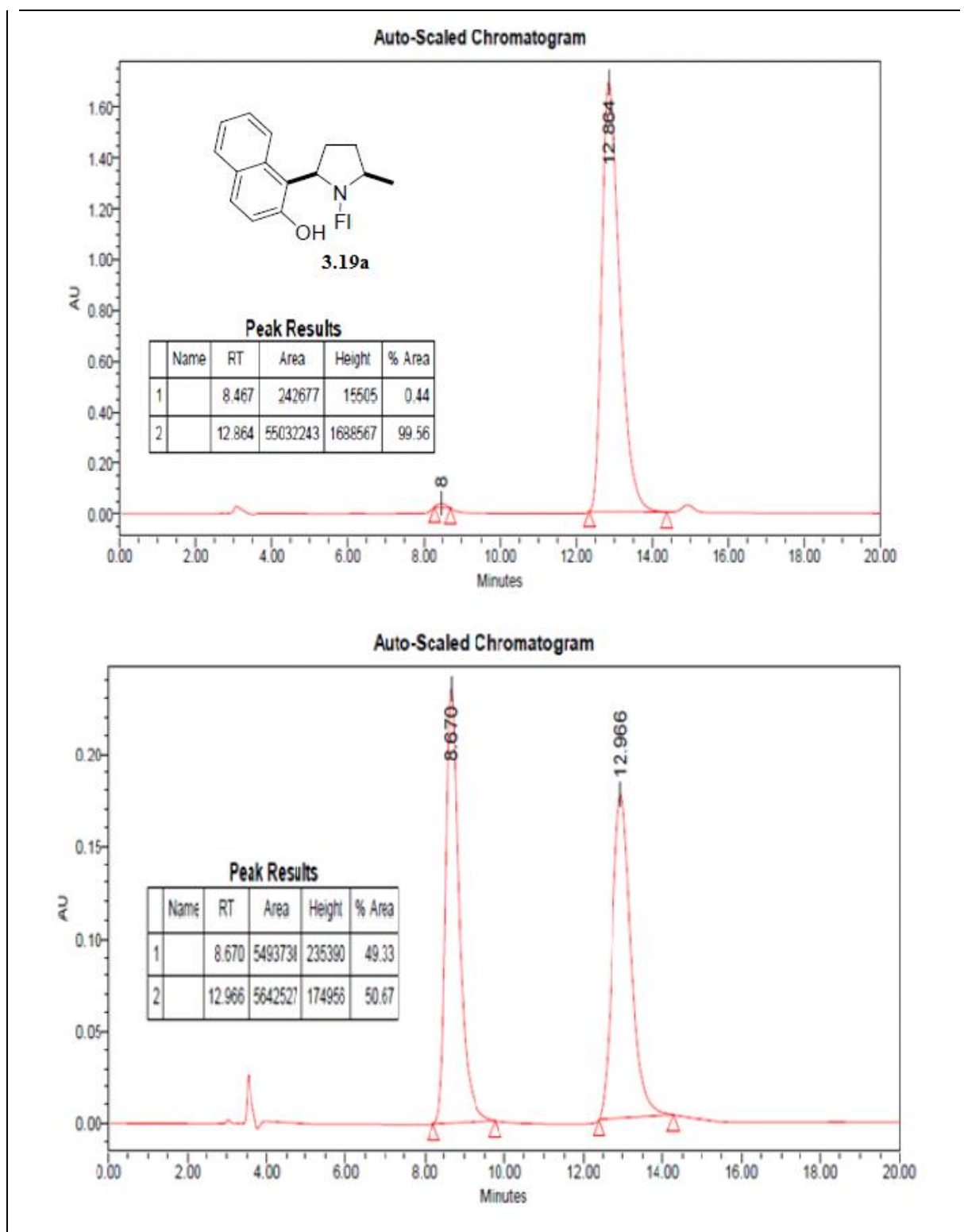


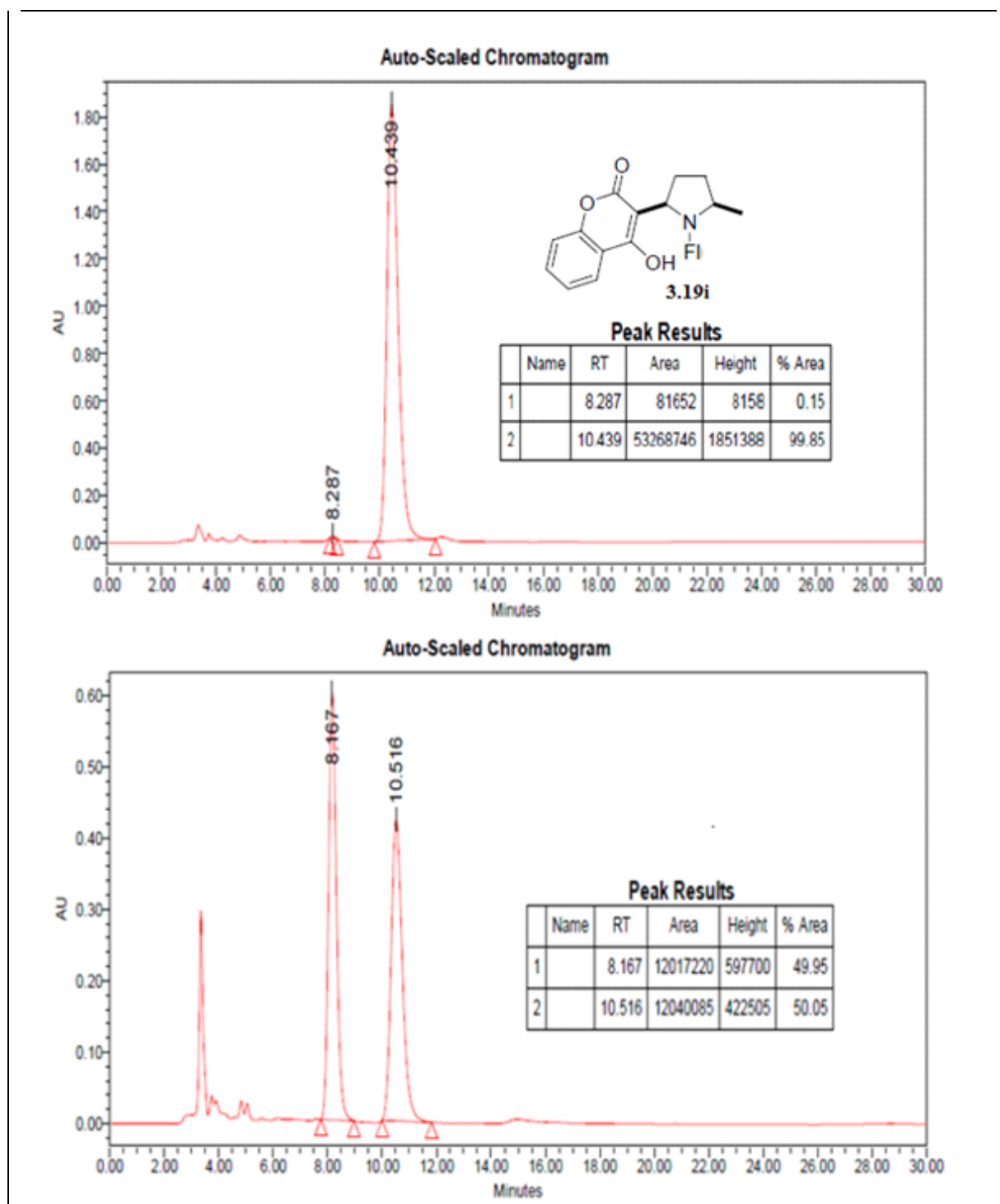


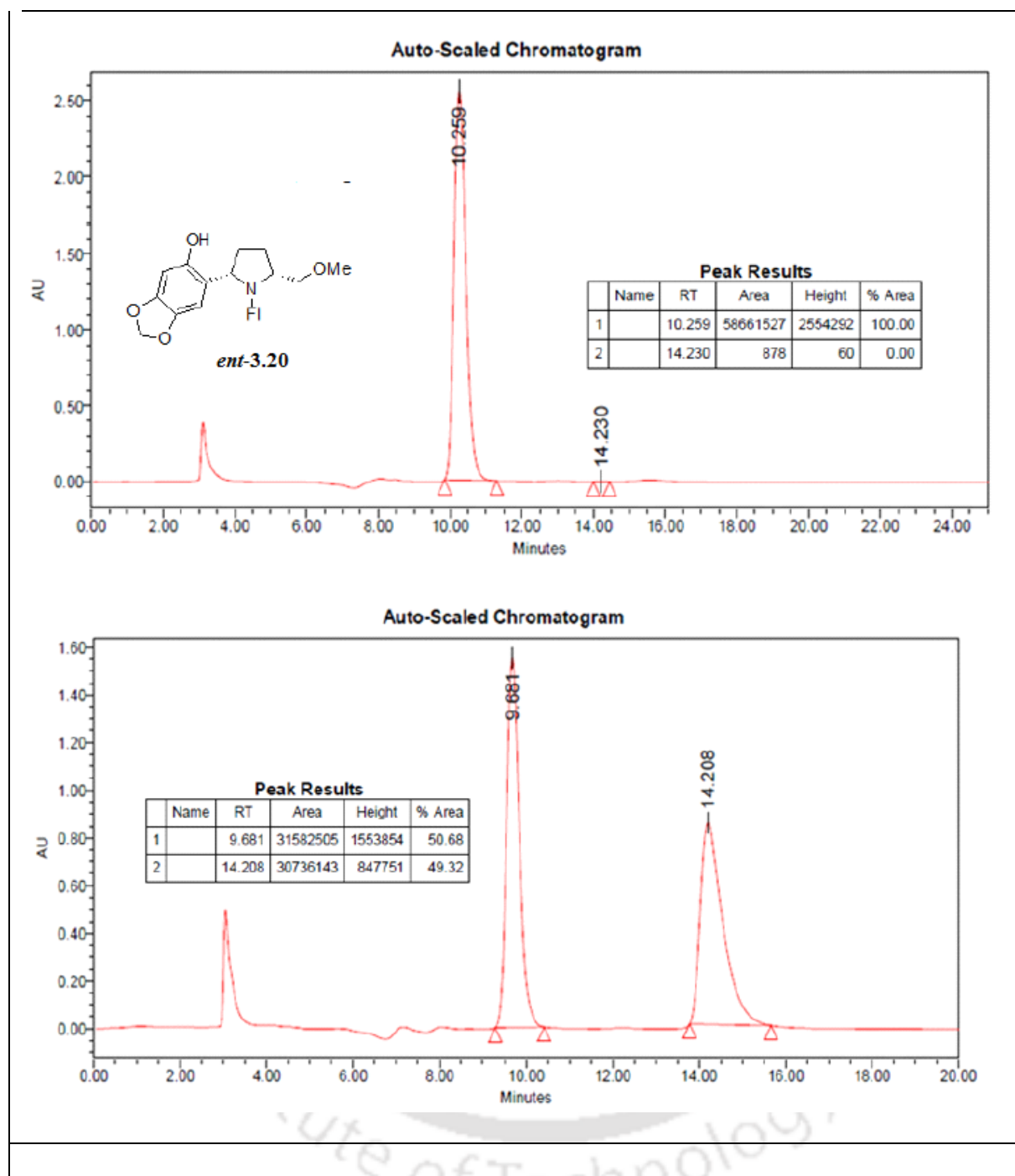
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
71 A		13.2	0.288298	0.06663969315	1.23207	n.a.
72 B		16.70	432.334	99.93	471.736	n.a.

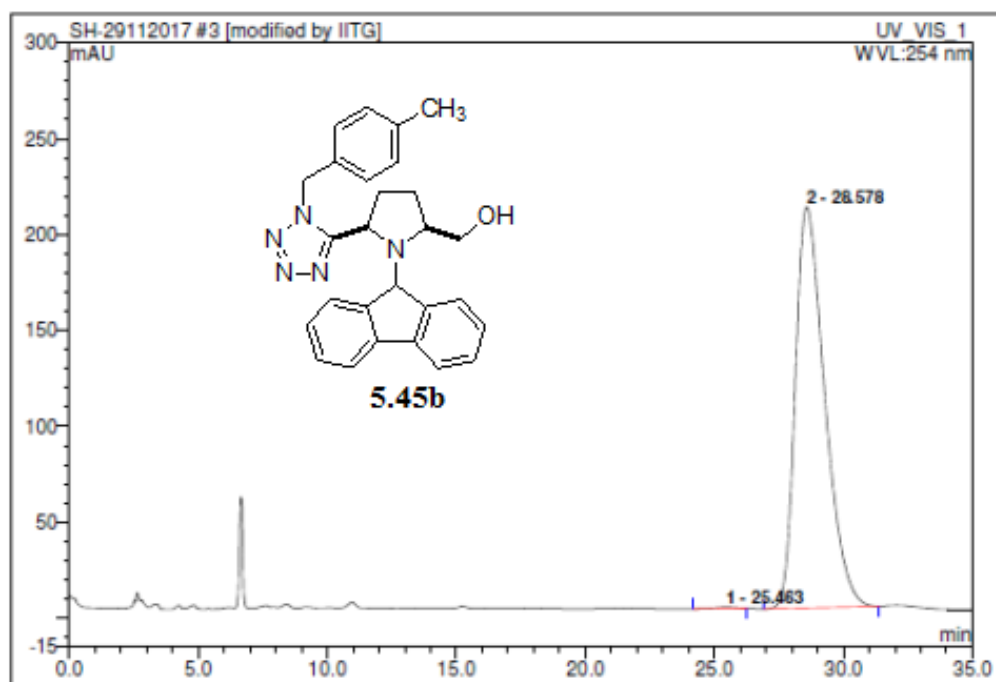


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
93 A		13.22166667	64.22772	49.10212905	90.52649	n.a.
94 B		16.65	66.577	50.90	70.389	n.a.

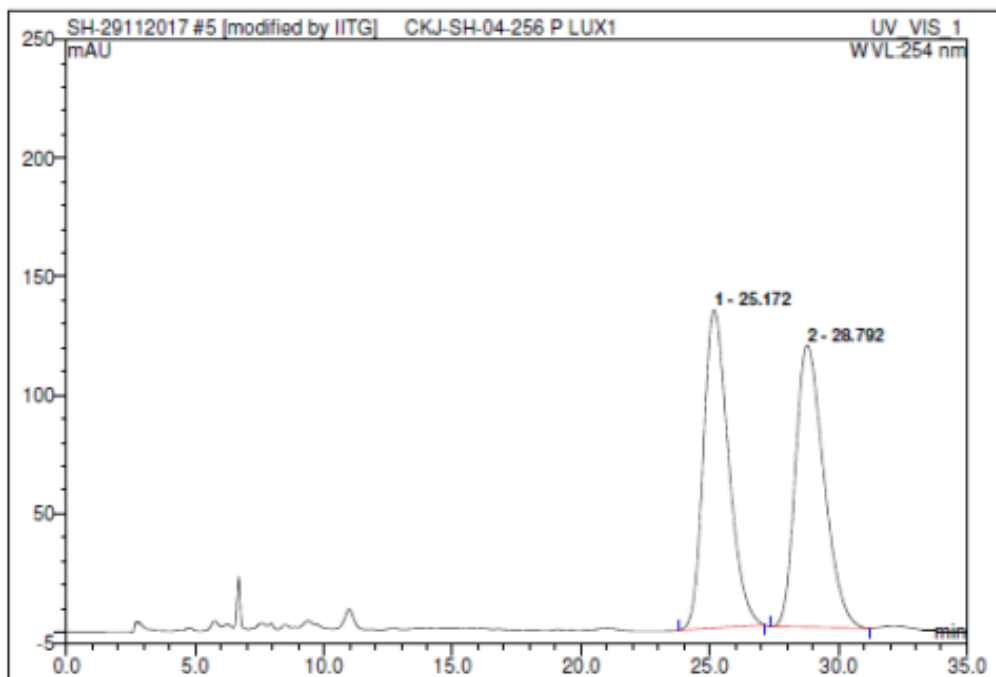




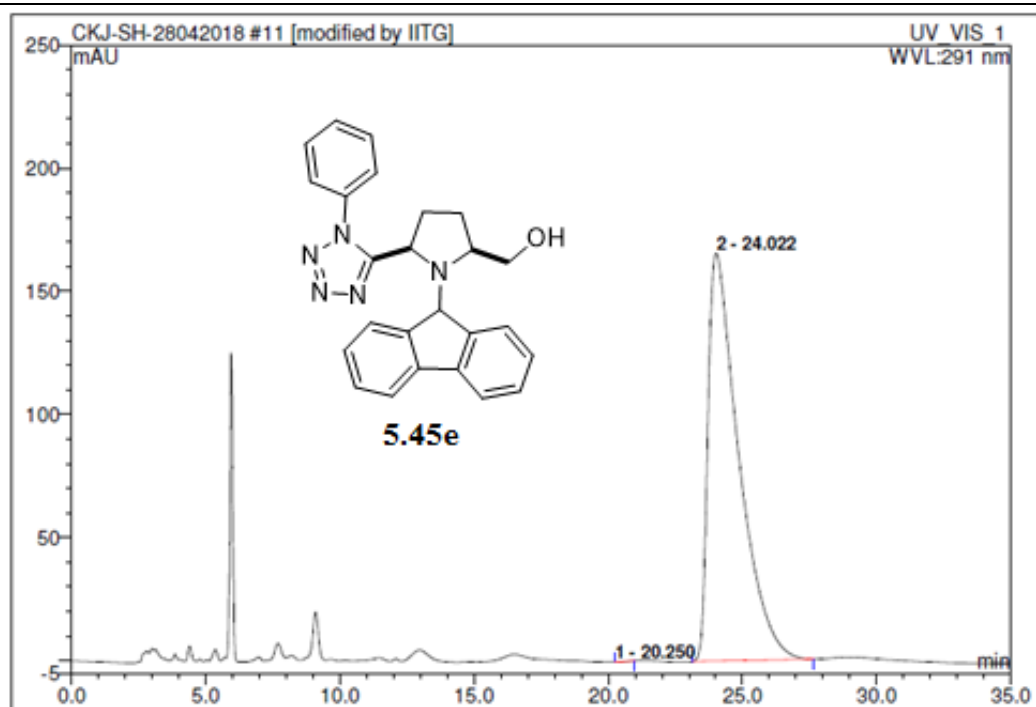




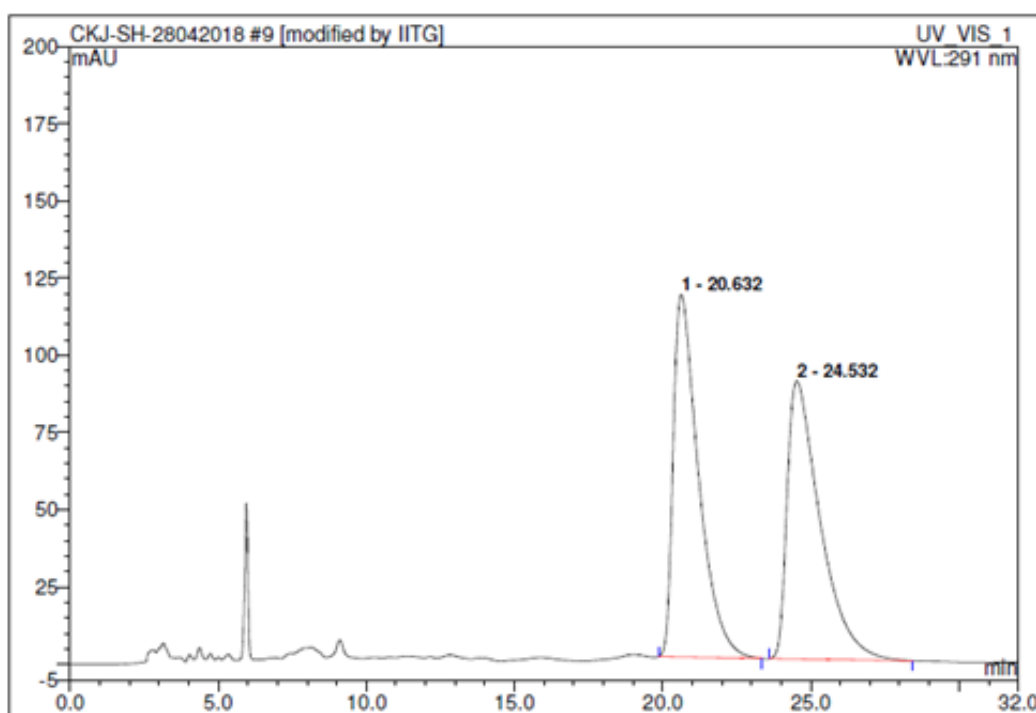
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.46	n.a.	0.834	0.802	0.29	n.a.	BMB*
2	28.58	n.a.	209.103	275.447	99.71	n.a.	BMB*
Total:			209.937	276.248	100.00	0.000	



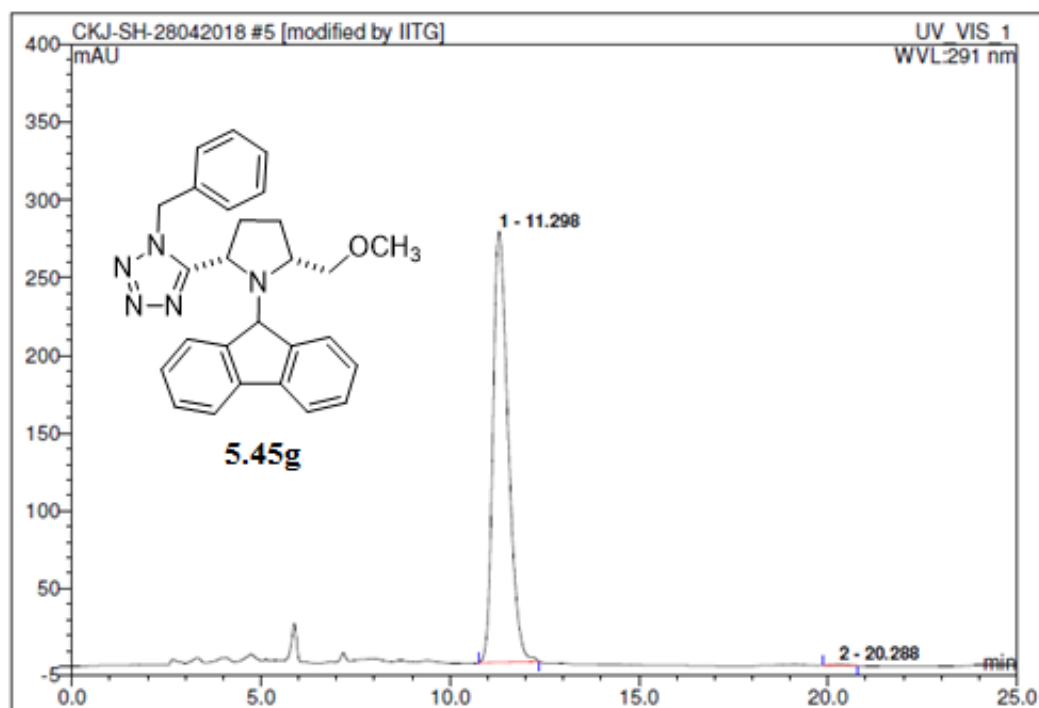
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.17	n.a.	134.287	152.041	49.97	n.a.	BMB*
2	28.79	n.a.	118.998	152.248	50.03	n.a.	BMB
Total:			253.284	304.289	100.00	0.000	



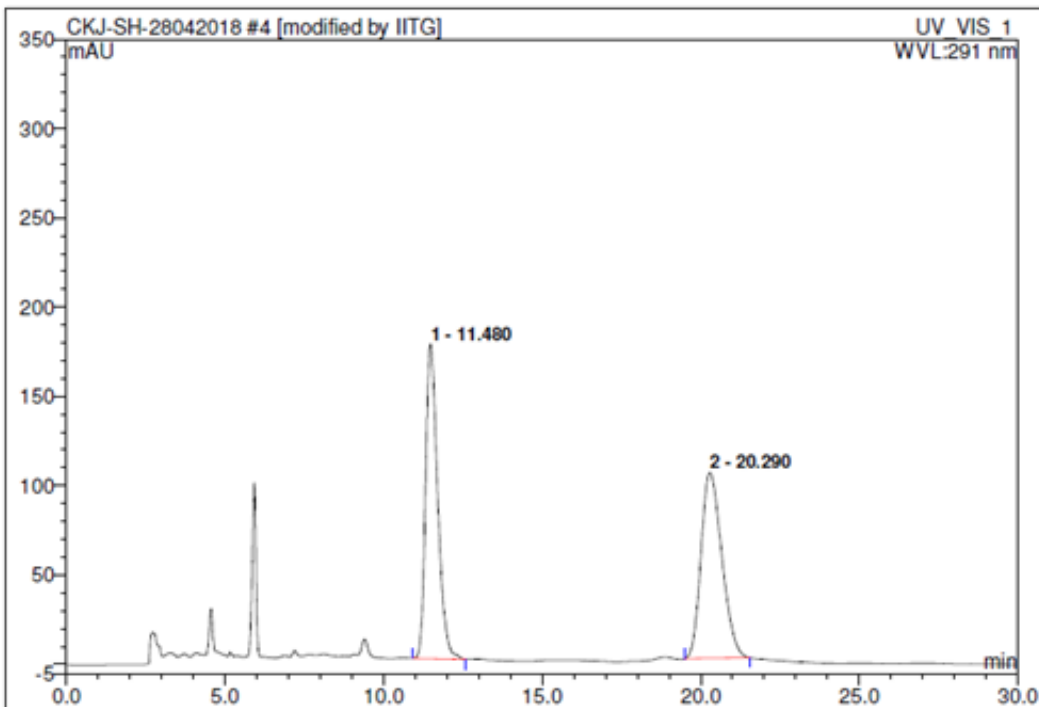
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.25	n.a.	0.008	0.036	0.02	n.a.	BMB*
2	24.02	n.a.	165.603	218.953	99.98	n.a.	BMB*
Total:			165.611	218.990	100.00	0.000	



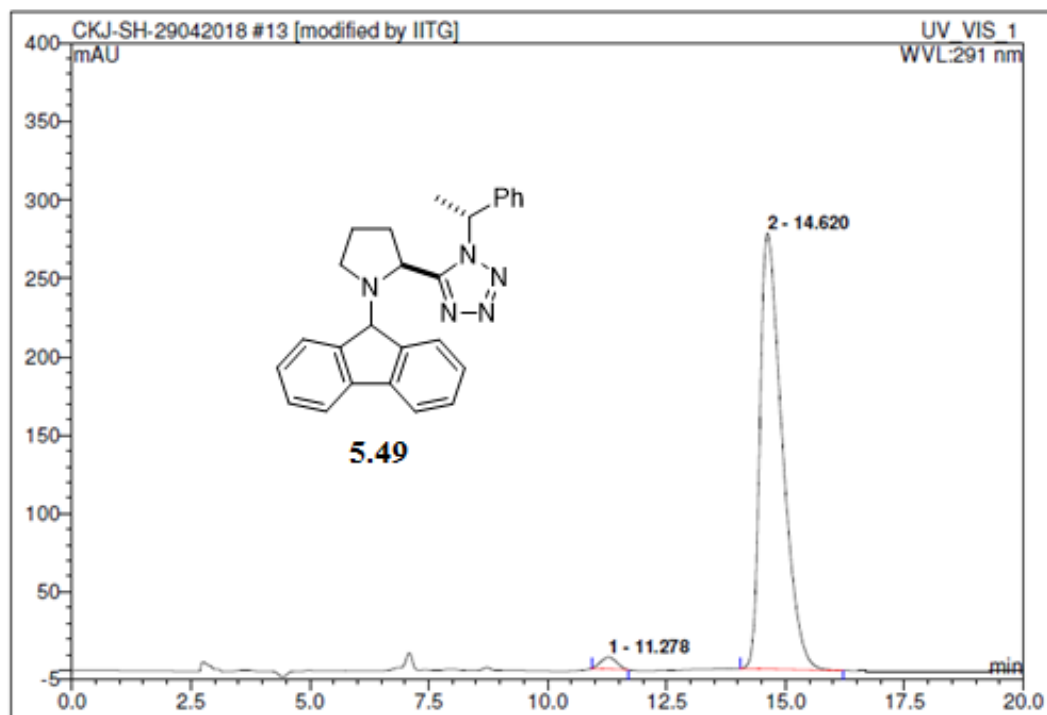
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.63	n.a.	117.378	116.269	50.08	n.a.	BMB*
2	24.53	n.a.	90.031	115.885	49.92	n.a.	BMB*
Total:			207.409	232.154	100.00	0.000	



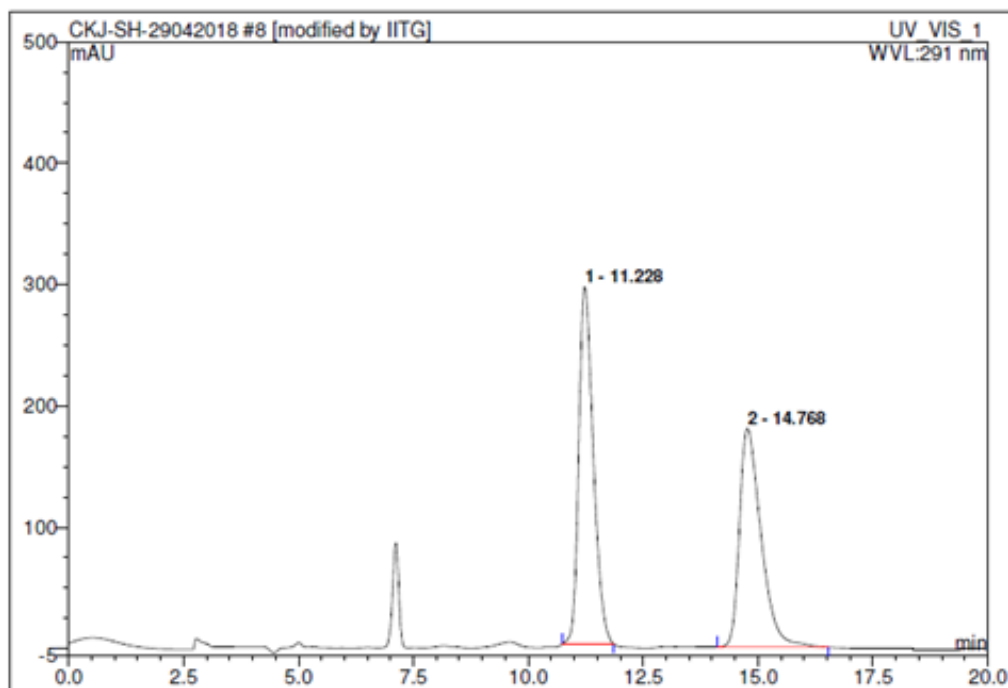
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.30	n.a.	277.213	129.207	99.69	n.a.	BMB*
2	20.29	n.a.	0.751	0.406	0.31	n.a.	BMB*
Total:			277.964	129.613	100.00	0.000	



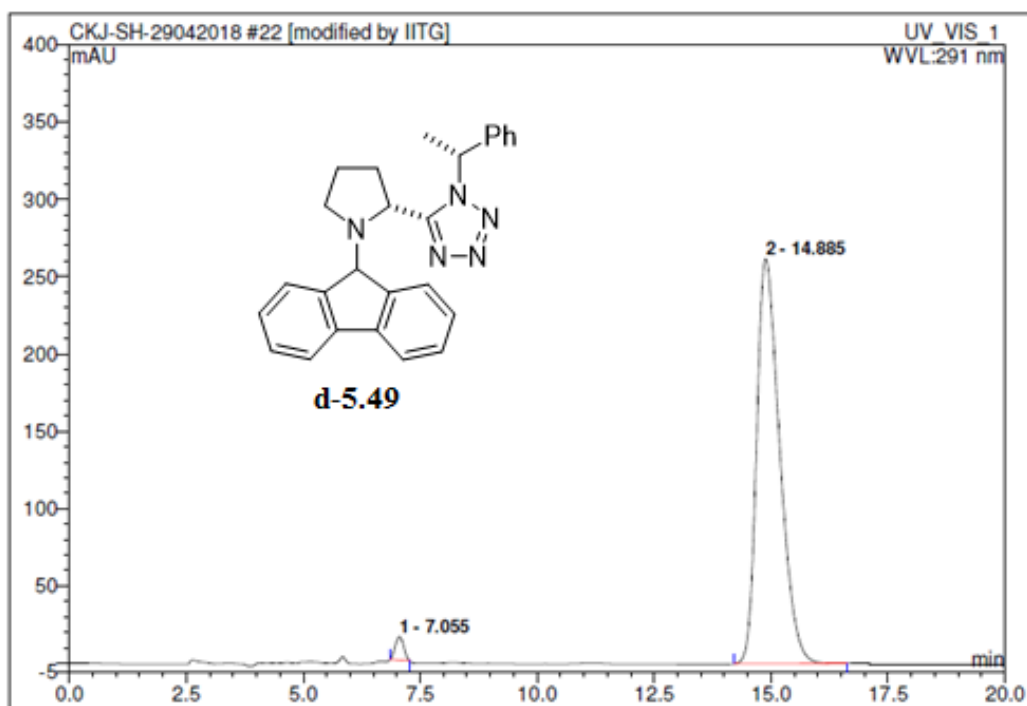
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.48	n.a.	176.127	77.607	49.53	n.a.	BMB*
2	20.29	n.a.	103.920	79.087	50.47	n.a.	BMB*
Total:			280.047	156.694	100.00	0.000	



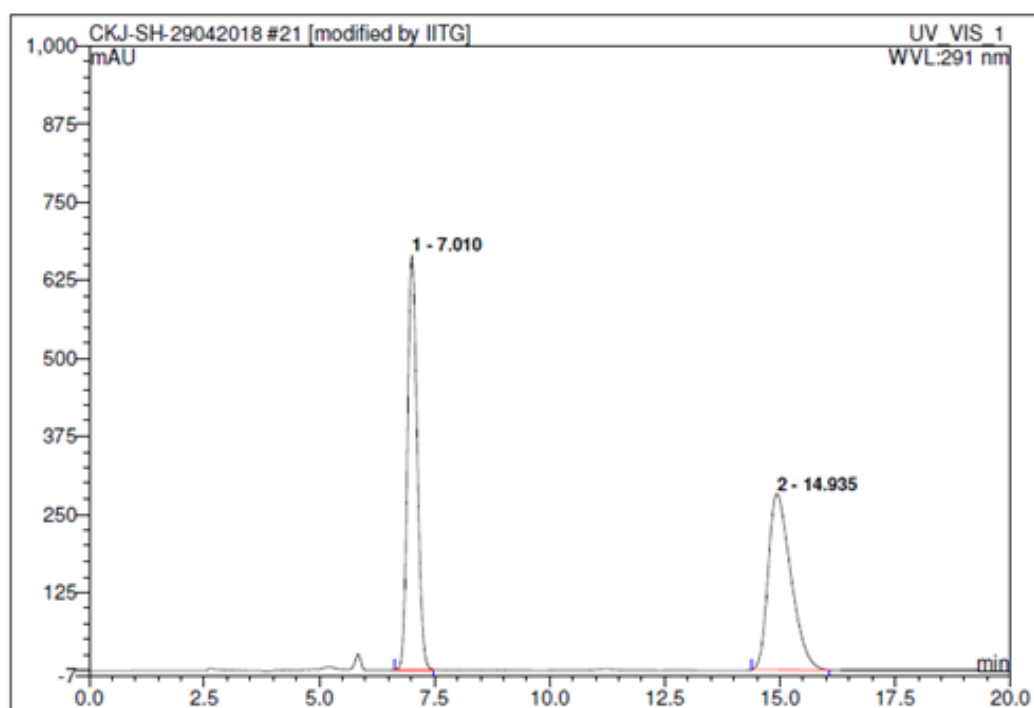
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.28	n.a.	7.534	2.925	1.91	n.a.	BMB*
2	14.62	n.a.	277.879	150.407	98.09	n.a.	BMB*
Total:			285.413	153.331	100.00	0.000	



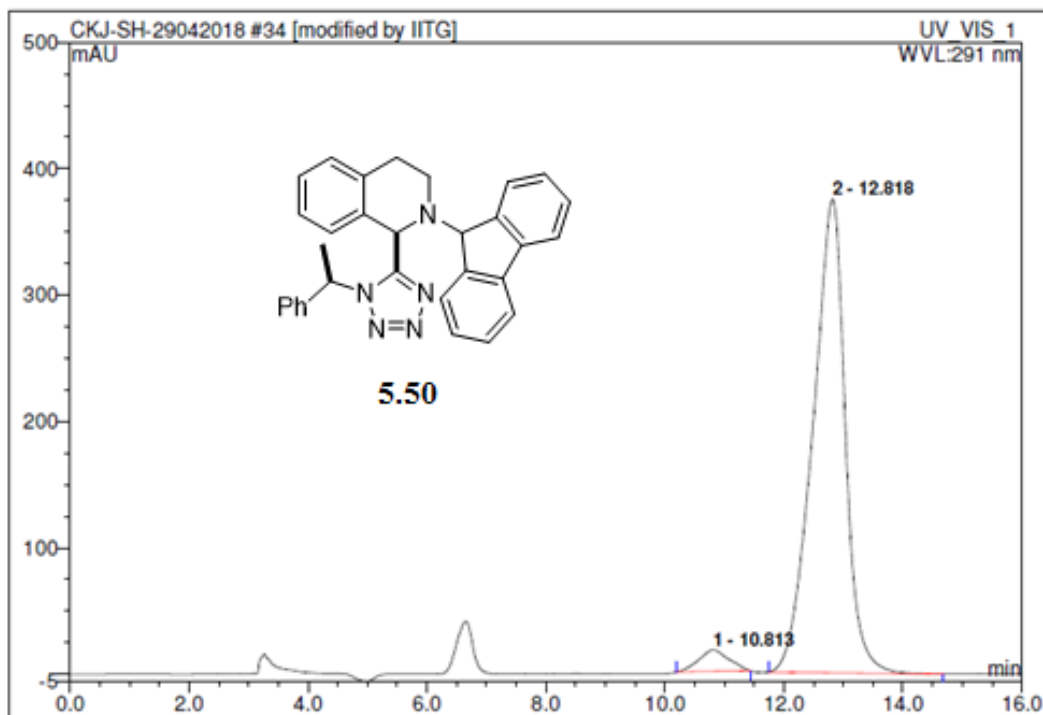
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.23	n.a.	294.102	107.333	52.23	n.a.	BMB*
2	14.77	n.a.	180.115	98.150	47.77	n.a.	BMB*
Total:			474.217	205.483	100.00	0.000	



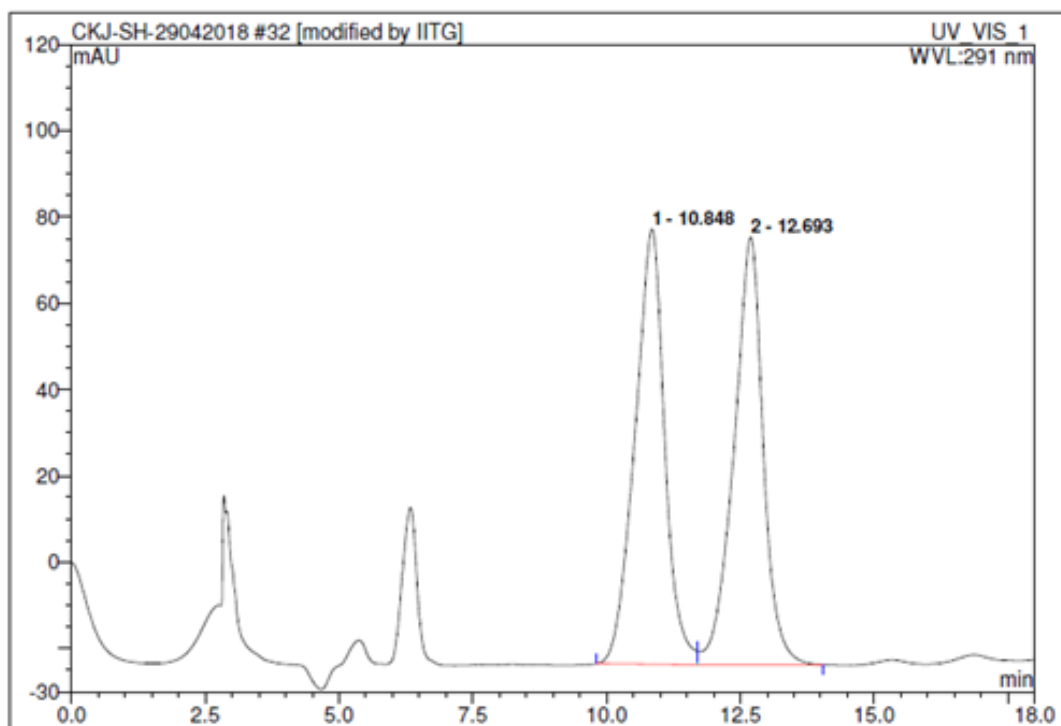
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.06	n.a.	15.079	3.157	2.07	n.a.	BMB*
2	14.89	n.a.	261.580	149.046	97.93	n.a.	BMB*
Total:			276.659	152.203	100.00	0.000	



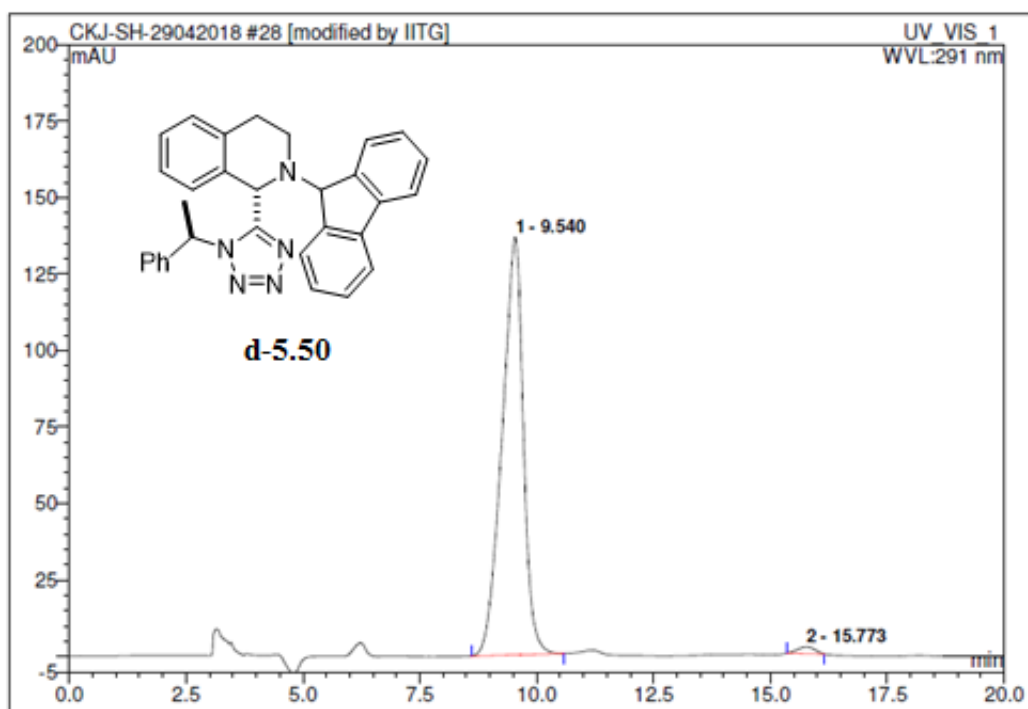
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.01	n.a.	663.686	160.704	49.97	n.a.	BMB*
2	14.94	n.a.	281.285	160.885	50.03	n.a.	BMB*
Total:			944.971	321.589	100.00	0.000	



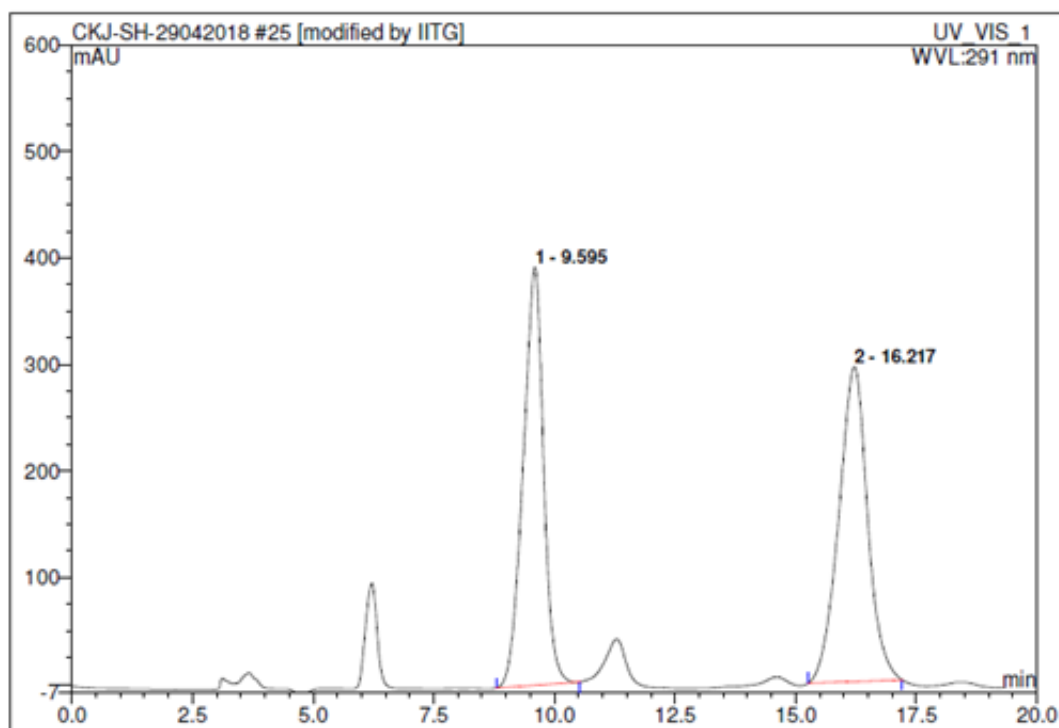
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.81	n.a.	16.970	9.964	4.05	n.a.	BMB*
2	12.82	n.a.	374.773	236.049	95.95	n.a.	BMB*
Total:			391.743	246.014	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.85	n.a.	100.906	65.002	50.72	n.a.	BM *
2	12.69	n.a.	99.098	63.145	49.28	n.a.	MB*
Total:			200.004	128.148	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.54	n.a.	136.610	71.806	98.68	n.a.	BMB*
2	15.77	n.a.	2.221	0.962	1.32	n.a.	BMB*
Total:			138.831	72.768	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.60	n.a.	392.325	191.855	48.42	n.a.	BMB*
2	16.22	n.a.	295.443	204.403	51.58	n.a.	BMB*
Total:			687.768	396.258	100.00	0.000	