C-C and C-O Bond Formation through Umpolung Reactivity of Imine and Synthesis of Amide and Lactam using Meldrum's Acid

A Dissertation

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By

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STATEMENT

The work contained in this thesis entitled "**C-C and C-O Bond Formation through Umpolung Reactivity of Imine and Synthesis of Amide and Lactam using Meldrum's Acid"** is the outcome of the research work carried out by me under the supervision of Prof. 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.

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**C-C and C-O Bond Formation through Umpolung Reactivity of Imine and Synthesis of Amide and Lactam using Meldrum's Acid"** which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Santanu Ghosh (Roll No: 146122013) 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

Prof. Chandan K. Jana

(Thesis supervisor)

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Dedicated to my parents and family members

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Santanu Ghosh

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List of Publications, Patent, and Presentations

Publications:

1. **S. Ghosh**, C. K. Jana, Aminofluorene-Mediated Biomimetic Domino Amination−Oxygenation of Aldehydes to Amides. *Org. Lett.* **2016**, *18*, 5788.
2. **S. Ghosh**, C. K. Jana, Metal-Free Thermal Activation of Molecular Oxygen Enabled Direct α-CH_2-Oxygenation of Free Amines. *J. Org. Chem.* **2018**, *83*, 260.
3. **S. Ghosh**, C. K. Jana, Rapid Access to Cinnamamides and Piper Amides via Three Component Coupling of Arylaldehyde, Amines, and Meldrum's Acid. *Green Chem.*, **2019**, *21*, 5803.
4. **S. Ghosh**, C. K. Jana, Metal Free Biomimetic Dehydrogenative Direct C-C Coupling of Unprotected Primary Amines with Active Methylenes. *Org. Biomol. Chem.*, **2019**, *17*, 10153.
5. **S. Ghosh**, A. Purkait, C. K. Jana, Environmentally benign decarboxylative N-, O-, and S-acetylations and acylations, *Green Chem.*, **2020**, *22*, 8721.
6. A. Purkait, S. Saha, **S. Ghosh**, C. K. Jana, Lewis Acid Catalyzed Reactivity Switch: Pseudo Three-Component Annulation of Nitrosoarenes and (Epoxy)styrenes, *Chem. Commun.* **2020**, *56*, 15032**.**
7. **S. Ghosh**, C. K. Jana, Stereoselective single pot multistep reaction to densely functionalized Spiro cyclic ene-lactam. (Manuscript under preparation).

Patent:

1. C. K. Jana, **S. Ghosh**, "TITLE: A ONE STEP PROCESS FOR SYNTHESIS OF CINNAMAMIDES AND PIPER AMIDES."(**Application No-201931038052, Filled on-20.09.2019**).

Conferences Attended:

1. Presented a poster in **JNOST-2019** held at Delhi University, Delhi, India.
2. Presented an oral presentation in **FICS-2018** held at IIT Guwahati, Guwahati, India.
3. Presented a poster in **CRSI-2017** held at Gauhati University, Guwahati, India.
4. Presented a poster in **CFOS-2017** held at IIT Roorkee, Roorkee, India.
5. Presented a poster in **Research conclave-2017** held at IIT Guwahati, Guwahati, India.
6. Presented a poster in **FICS-2016** held at IIT Guwahati, Guwahati, India.

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Content

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Abbreviation

9-F	9-Fluorenone
APCI	Atmospheric pressure chemical ionization
Å	Angstrom
Ar	Argon
br.	Broad
Bn	Benzyl
Bu	Butyl
Boc	*tert*-butoxycarbonyl
1,4 BQ	Benzoquinone
^{n}Bu	*n*-Butyl
Cat.	Catalytic/Catalyst
Cbz	Carboxybenzyl
$CDCl_3$	Chloroform-*d*
CAN	Ceric ammonium nitrate
CDC	Cross Dehydrogenative Coupling
CH3CN	Acetonitrile
CCDC	Cambridge crystallographic data centre
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
^{o}C	Degree Celsius
Cu	Copper
d	Doublet or day
δ	Chemical shift or delta
DCM	Dichloromethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
EtOAc	Ethyl acetate
ee	Enantiomeric excess
equiv.	Equivalent
ESI	Electrospray ionization
Fl	Fluorenone

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FTIR	Fourier transform infrared spectroscopy
g	Grams
γ	Gamma
h	Hours
HFIP	Hexafluoroisopropanol
HPLC	High performance liquid chromatography

Abstract

The contents of the thesis entitled "**C-C and C-O bond formation through umpolung reactivity of imine and synthesis of amide and lactam using Meldrum's acid**" have been divided into 8 chapters based on the results of experimental works performed during the complete course of the research period. C-C and C-O bonds are abundant in most organic molecules. Therefore development of new methods for C-O and C-C bond formations is an important aspect of organic synthesis. The first chapter of the thesis presents a review on different aspects of umpolung reactivity of imine. **Chapters 2-4** describe the studies on C-O and C-C bond formation using umpolung reactivity of imine. **Chapter 2** describes a metal and oxidant free route to direct oxygenation of aldehyde to amide. In **Chapter 3**, metal free direct α-CH_2-oxygenation of free amines has been described. The method was found to be efficient for the synthesis of important drugs and their anlogs. Dehydrogenative direct C-C coupling of unprotected primary amines with active methylenes has been described in **Chapter 4**. In **Chapters 5-7** described the amides and lactams synthesis by using Meldrum's acid. Three component coupling of arylaldehyde, amines, and Meldrum's acid towards the synthesis of cinnamamides and piper amides has been described in **Chapter 5**. **Chapter 6** describes decarboxylative N-, O-, and S-acetylation and acylation by using Meldrum's acid. Diasteroselective ene-lactam synthesis *via* one pot sequential reactions has been described in **Chapter 7**. Finally, **Chapter 8** contains the copies of ^{1}H and ^{13}C NMR spectra of selected new compounds.

Chapter 1: Introduction

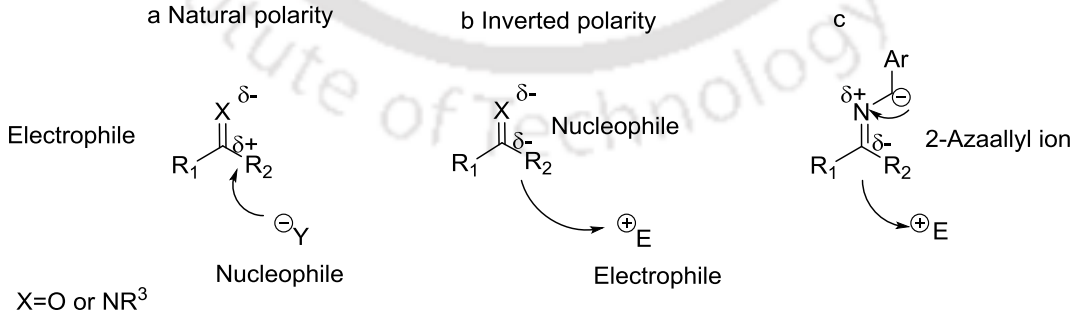

Figure 1: Explanation of umpolung

This chapter gives a brief account on umpolung reaction of imine. Umpolung describes the inversion of natural polarization in molecules.[1,2] The concept was introduced by D. Seebach (hence the German word umpolung for reversed polarity) and E.J. Corey.[3] In natural

polarization of ketones (in which X = O) and imines (X = NR_3) places partial positive charge (δ^+) on the carbon atom and partial negative charge (δ^-) on X. These compounds are therefore electrophilic and reacted with nucleophilic molecules (Y^-). Ketones and imines are thus prone to attack by nucleophiles. In umpolung reaction, ketones and imines will react with electrophiles (E^+) **(figure 1).**

The development of synthetic strategies based on umpolung is very useful for the synthesis of many biologically active molecules.[1] The successful development of numerous C–C bond-forming umpolung reactions with carbonyls as acyl anion equivalents has greatly expanded the repertoire of organic synthesis.[2a, 2b] However, umpolung reactions of imine are under developed. Mostly studied imine umpolung involved reaction of proton as the electrophile producing amines or amino acids via transamination.[2b]

There are few reactions with limited substrates on imine umpolung were developed where carbon based electrophile instead of proton were used.[3c] Electrophiles like aldehyde, enone and allyl bromide were used in the presence of metal based reagents or catalysts.[3d] However, the uses of hetero atom based electrophiles were not known.

The aim of the thesis is to develop a new synthetic pathway for C-C and C-O bond formation by direct functionalization of amines using umpolung strategy.

Chapter 2: Aminofluorene Mediated Biomimetic Domino Amination-Oxygenation of Aldehydes to Amides

Amide is a ubiquitous functionality of organic molecules and forms essential part of many natural products, medicinal drugs and functional materials.[4] Direct oxidative amidation of aldehyde is one of the elegant methods for amide synthesis. However, practicability of this methods for amide synthesis was reduced due to the involvement of metallic reagents and hazardous oxidants (e.g. hypervalent iodine, KMnO4, etc.).[6] In addition, most often the methods necessitate sensitive reaction conditions. Molecular oxygen has been used as a viable alternative to hazardous oxidants, however, this worked only in the presence of metallic reagents/ catalyst.[7] A mechanistically different metal free approach for direct amidation of aldehydes via biomimetic domino amination-oxygenation reactions based on umpolung reactivity of imine has been developed. Molecular oxygen has been used as the oxidant. In the presence of $^{18}O_2$, ^{18}O-amide was formed with excellent (95%) isotopic purity. Different aryl, heteroaryl, and alkenyl aldehydes were reacted smoothly to produce corresponding primary and secondary carboxamides with good to excellent yields. Reaction condition and selected examples were given in **Scheme 1.**

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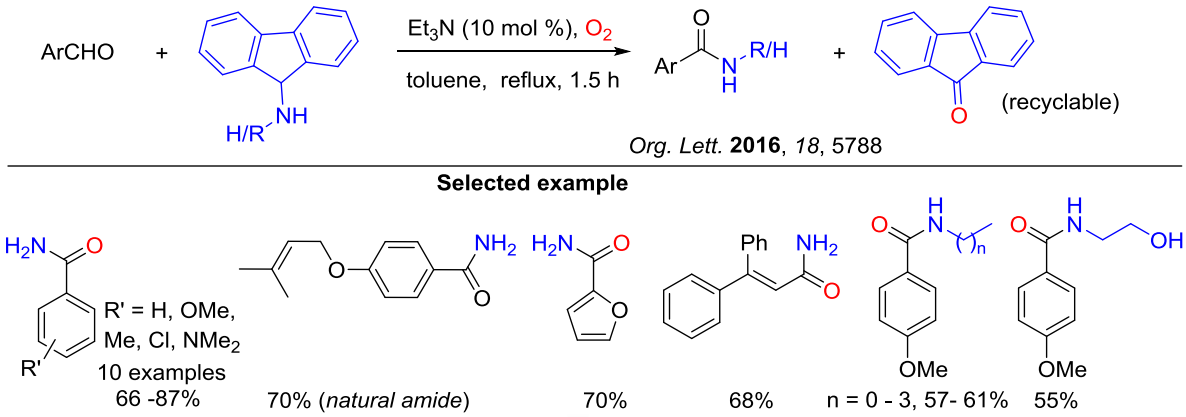
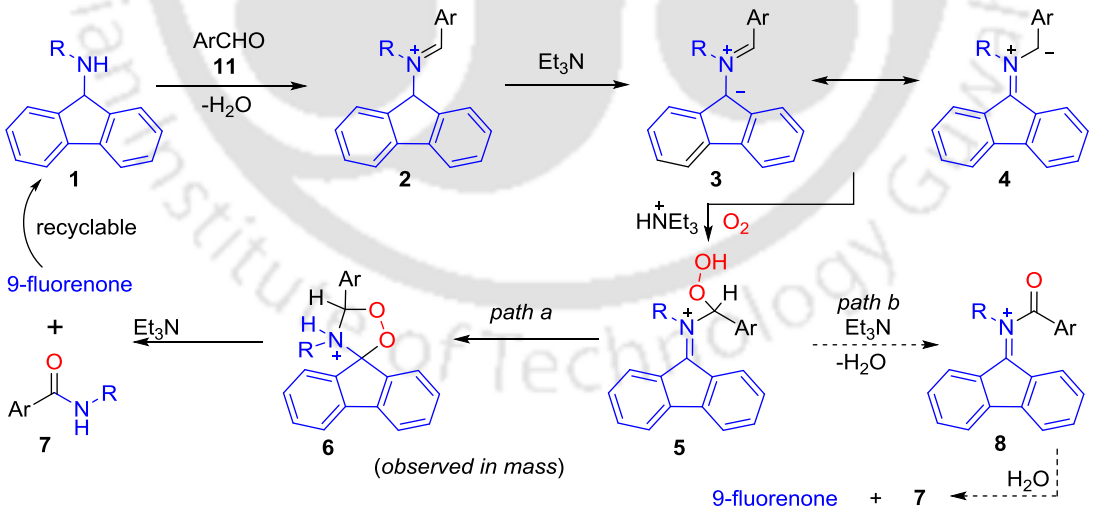


Scheme 1: Scope in NH_2/NHR-transfer-oxygenation reaction

Condensation of benzaldehyde and 9-aminofluorenyl derivatives 1 occurred to provide corresponding aldimine 2 (**Scheme 2**). Triethylamine promoted deprotonation of 2 and furnished stabilized azomethine anion 3. Anion 3 or mesomer 4 reacted with molecular oxygen to provide hydroperoxide 5 or its regioisomer. Hydroperoxide 5 could react further to furnish corresponding dioxazolidine 6, which on subsequent thermal decomposition would provide desired amide 7 and 9-fluorenone (path a). However, the base mediated O-O bond cleavage of hydroperoxide 5 followed by hydrolysis of resulting imine 8 could also provide the desired products (path b). In the presence 18O2, formation of amide and 9-fluorenone both with high level of 18O indicated that the reactions proceed via dioxazolidine 6 (path a).



Scheme 2. Proposed reaction mechanism.

Chapter 3: Metal Free Thermal Activation of Molecular Oxygen Enabled Direct α-CH_2-Oxygenation of Free Amines

Conventional methods for the amide synthesis utilize coupling reaction of carboxylic acids or its activated derivatives with amines in the presence of expensive coupling reagents which produce a stoichiometric amount of byproducts.[9] To avoid this drawback, amidation reactions using catalytic amounts of coupling reagents have been developed.[10] Additionally, conversions of alcohol and aldehyde,[11,12] oximes and nitrile,[13] α-keto acids, and α-bromo nitroalkanes[14] to amides were developed as alternative direct methods. However, relatively less number of examples was known for the direct oxidation of α-methylene group of free amines to corresponding amides because of the higher reactivity of the amine moiety. The known examples primarily involve metal-based reagents/catalysts or hazardous inorganic and organic oxidants [15,16]. Molecular oxygen would be a viable substitute of hazardous inorganic or organic oxidants. However, photochemical or metal mediated activation is generally required to activate kinetically inert oxygen before its reaction with other organic molecules.[17] Therefore, in some cases, molecular oxygen acts as the viable oxidant only in the presence of sophisticated metallic reagents/ catalysts.[16] Importantly, α-oxygenation of free amines to amides is generally hard to achieve due to the associated side reactions producing corresponding imines and nitriles, and thus protection of amine moiety is required before oxidation reaction.[18] Therefore, the development of novel methodology for direct oxygenation of amines that work under the conditions free of metallic reagents/catalysts and hazardous oxidants avoiding undesired side reaction would be of particular importance. The first example of one-step, metal free and operationally simple direct oxygenation of free aliphatic amines to amides and lactams using molecular oxygen as the source of amide oxygen has been developed. Arylmethylamines having electron donating as well as electron withdrawing groups at different positions of aryl moiety provided the desired benzamides with good to moderate yields. Oxidation of cyclic and acyclic aliphatic secondary amines occurred smoothly to yield corresponding lactams and secondary benzamides respectively. Reaction condition and selected examples were represented in **Scheme 4.**

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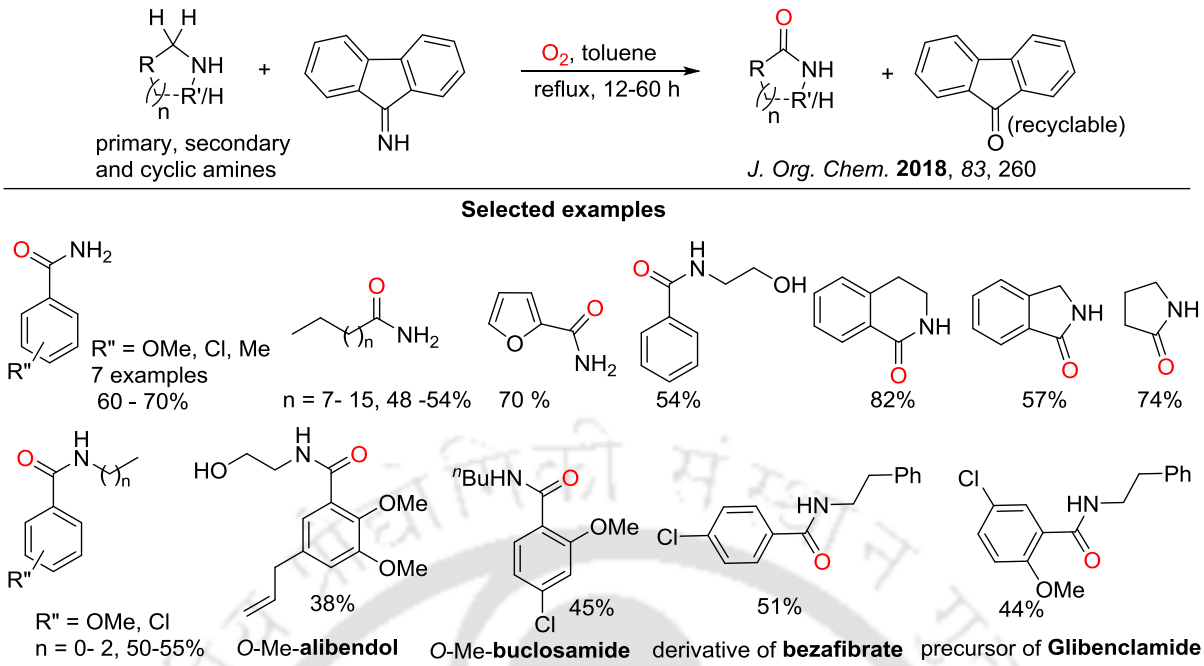
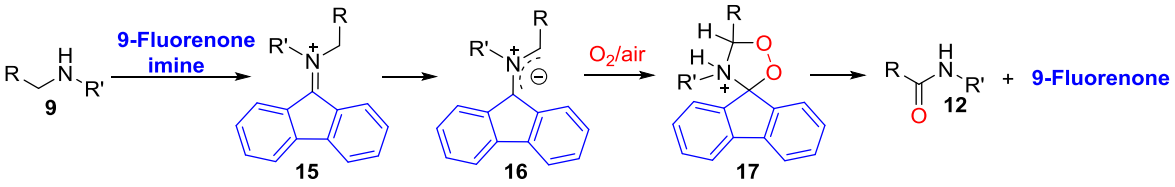


Scheme 4: Scope of oxygenation of aromatic and aliphatic amines.

Based on experimental evidence a possible mechanistic pathway has been drawn in **Scheme 5**. The reaction proceeded through the imine/iminum ion **15** which could be formed from the condensation of amine **1** and 9H-fluoren-9-imine. Amine assisted deprotonation of **15** to form the azomethine anion/ylide **16** which subsequently reacted with molecular oxygen to provide the peroxide intermediate **17**. Thermal disintegration of peroxide **17** provided the desired amide/lactam **12** and 9-fluorenone.



Scheme 5: Proposed Reaction Mechanism.

Chapter 4: Metal Free Biomimetic Dehydrogenative Direct C-C Coupling of Unprotected Primary Amines with Active Methylenes

The amines functionality is frequently found to be converted to corresponding imine, nitrile or aldehyde.[19-22] In some cases, the imine formed was subsequently reacted with heteronucleophiles to produce the corresponding imidazole, oxazole, thiazole or quinoxaline.[23] However, the reaction of the imine generated *in situ* via dehydrogenation of an

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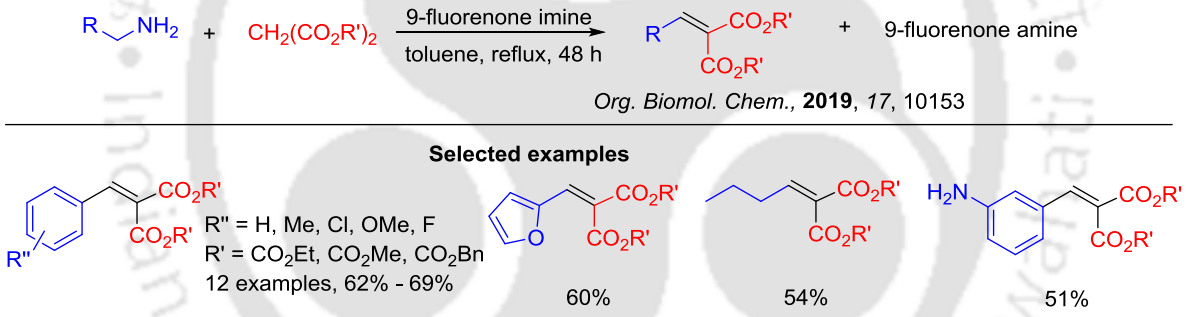
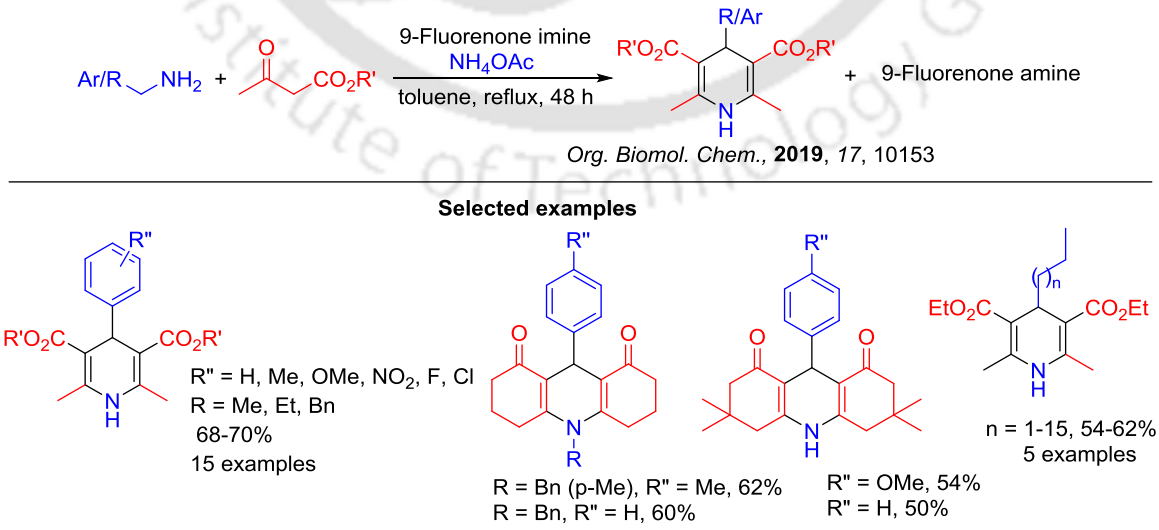
amine with the carbon-based nucleophile like active methylene compound is uncommon.[24] Moreover, to the best of our knowledge, no report on the direct coupling of unprotected primary amines with active methylenes producing alkenes and dihydropyridines is known in the literature. This is probably because the active methylenes are susceptible towards oxidation/decomposition under strong oxidizing conditions.[25] Moreover, propensity to over-oxidation of amines to nitriles and high nucleophilicity of free primary amines put further challenges for the success of C-C coupling of free primary amines and active methylenes. Therefore, development of a method that can operate under the mild conditions without the aid of strong oxidants and metallic reagents would allow the subsequent one-pot reaction of imine with suitable nucleophile like active methylene compound. A biomimetic dehydrogenative coupling of primary amines with active methylene compounds to alkene and dihydropyridine has been developed. A simple imine derivative has been used as the FAD mimic to produce imine from amine under the conditions free of strong oxidizing agents and metallic reagents. A wide range of primary amines was reacted with different active methylenes to provide structurally diverse trisubstituted alkenes and dihydropyridines.[27]



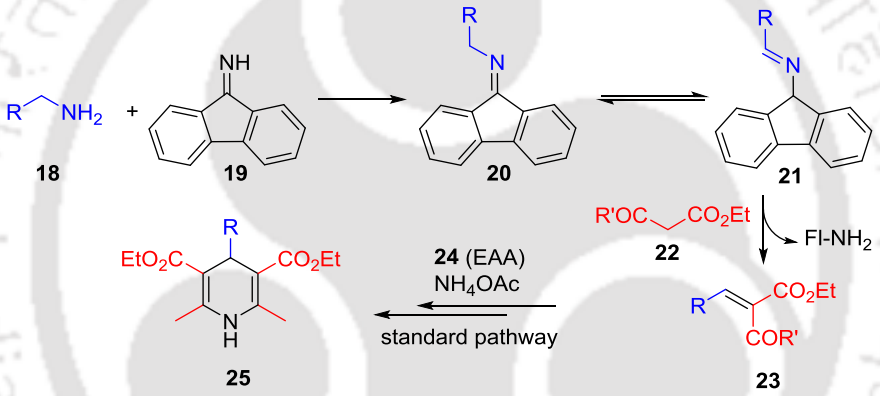
Scheme 6: Scope for the olefins syntheses.



Scheme 7: Scope for the Synthesis of dihydropyridines.

Various functional groups (e.g., OR, F, Cl) in the aromatic ring of arylmethyl amines were tolerated under this reaction conditions. Substrates having both electron-donating (e.g., Me, OMe) and electron-withdrawing (e.g., NO_2, F, Cl) groups were efficiently reacted to produce the desired products. Kinetic study revealed an activation barrier of 6.8 kcal/ mol for the key step of the reaction. Selected examples for the formation of alkene and dihydropyridines were given in **Scheme 6** and **Scheme 7** respectively.

Condensation of amine **18** and 9-fluorenone imine **19** occurred to provide corresponding ketimine **20 (Scheme 8)**. Isomerization of **20** furnished the regioisomeric aldimine **21** which on subsequent reaction with active methylenes **22** provided the corresponding alkene **23**. In the reaction with acetoacetate, the corresponding alkene reacted further with ammonia, which was either generated during condensation of **18** and **19** or from NH_4OAc, and another equivalent of acetoacetate **24** to provide the dihydropyridines **25** following standard pathway.



Scheme 8: Proposed mechanism of C-C coupling of amines and active methylenes.

Chapter 5: Rapid Access to Cinnamamides and Piper Amides via Three Component Coupling of Arylaldehyde, Amines, and Meldrum's Acid

Cinnamamides is an important class of compounds having a wide spectrum of bioactivity, such as anticancer,[28] anti-malarial,[29] anti-trypanosomal,[30] anti-oxidant,[31] anti-diabetic,[32] anti-microbial activity,[33] etc.[34] In addition, cinnamamides were found as the key structural unit of many natural products including piper amides.[35] A large number of cinnamamides with wide structural diversity have been synthesized to investigate the structure activity relationship studies in the field of medicinal chemistry.[34] The synthesis of cinnamamides and piper amides mainly rely on the coupling reaction of cinnamic acid derivatives which are prepared from the Knoevenagel condensation of aromatic aldehyde and malonic acid .[36] Oxidative amidation of cinnamaldehydes is another approach for the synthesis of cinnamamides .[37] Wittig or Horner-Wadsworth-Emmons reactions were also used for the synthesis of

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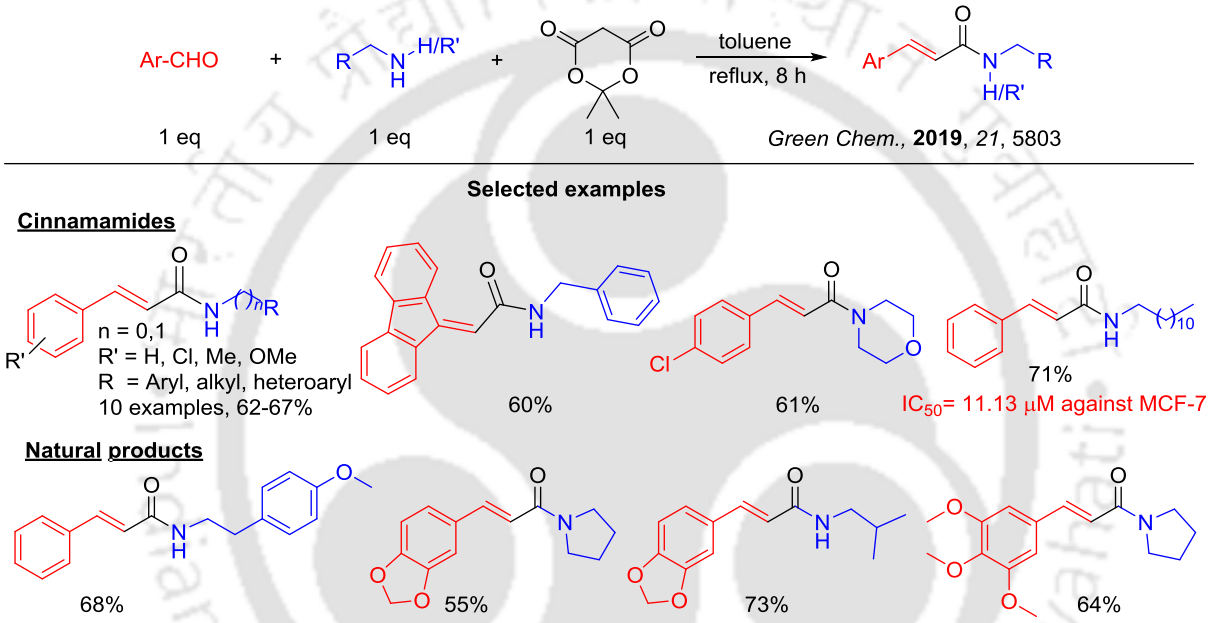
cinnamamides starting from aromatic aldehyde.[38] However, most of the methods rely on the multistep process and involve the formation of unwanted by-products originated from coupling agents, oxidants, phosphine based reagents, etc. Therefore, development of an operationally simple method without using additional catalysts, reagents, or additives that produce hazardous chemical wastes is desirable. A one-step process for the preparation of cinnamamides and piper amides *via* an unprecedented three component reaction of aryl aldehyde, amine and Meldrum's acid has been developed. The reaction proceeds without aid of any additional catalysts, reagents or additives.



Scheme 9: Scope in synthesis of Cinnamamides and piper amides.

A wide variety of aromatic aldehydes and amines were reacted with Meldrum's acid to provide the corresponding cinnamamides with very good yields. Accordingly, optimized reaction conditions were used to prepare structurally diverse piper amides with good to very good yields. Reaction condition and selected examples of cinnamamides and piper amides were presented in **Scheme 9**.

Based on the experimental evidence, a plausible mechanism for the three component coupling reaction is shown in **Scheme 10**. The reaction of the amine **26** with Meldrum's acid **27** provided monoamides of malonic acid **28** and acetone. Observed cinnamamide **30** can be formed *via* two possible pathways. Aldol reaction of **28** and aromatic aldehyde can provide beta-hydroxy acid **29**. In the second possibility, Knoevenagel condensation of **28** and aldehyde could occur to provided benzylidene derivative **31** *via* corresponding alcohol **29**.

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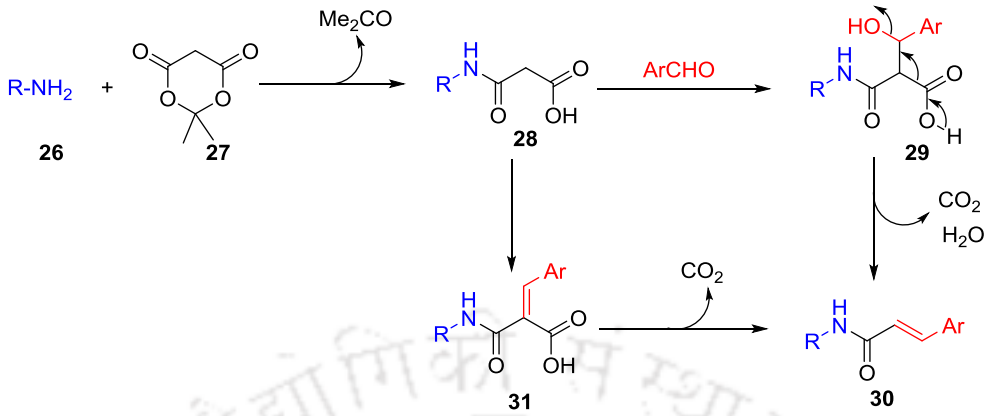
Decarboxylation of **31** and/or decarboxylation assisted dehydration of alcohol **29** gave the thermodynamically more stable trans-cinnamamides **30.**



Scheme 10: Proposed mechanism of three component reaction.

Chapter 6: Environmentally Benign Decarboxylative N-, O-, and S-Acetylations and acylation by Meldrum's Acid

Acetylation is one of the most important reactions used in chemistry and biology.[39] The wide application of acetyl group prompted the development of different methods/ reagents/strategies for the acetylation reaction. The majority of acetylation reactions are carried out using acid anhydrides in the presence of an acid, a base or metal catalyst.[40] Other commonly used methodologies involves the use of acetic acid and its derivatives, such as acetyl chloride, ethyl acetate, vinyl acetate, ammonium acetate or with other acetyl sources.[41] Various metal based catalysts like zinc(II) chloride, scandium(III) triflate, bismuth(III) triflate, ruthenium(III) acetylacetonate were for employed acetylation reactions.[42] The commonly used acetylating reagents are low boiling, toxic, corrosive and thus are hazardous, particularly, in the industrial scale synthesis. In addition, most of the acetylation reaction releases acids which might affect any acid-sensitive functionality present in the substrates. Therefore, development of a more environmentally benign method for the acetylation reaction which operates under base or acid free conditions is essential.

Recently, Huang and co-worker have developed a method for the amidation of aniline derivative using Meldrum's acid derivatives.[44] Acetylation of *N*-alkyl/aryl aniline derivative using Meldrum's acid is known. However, acetylation of primary amine such as alkylamine, benzylamine, aliphatic secondary amine, phenol, alcohol using Meldrum's acid were not known. Moreover, acylation of other major functional group such as phenol, alcohols using Meldrum's acid were not known. Therefore, the development of a method that works for

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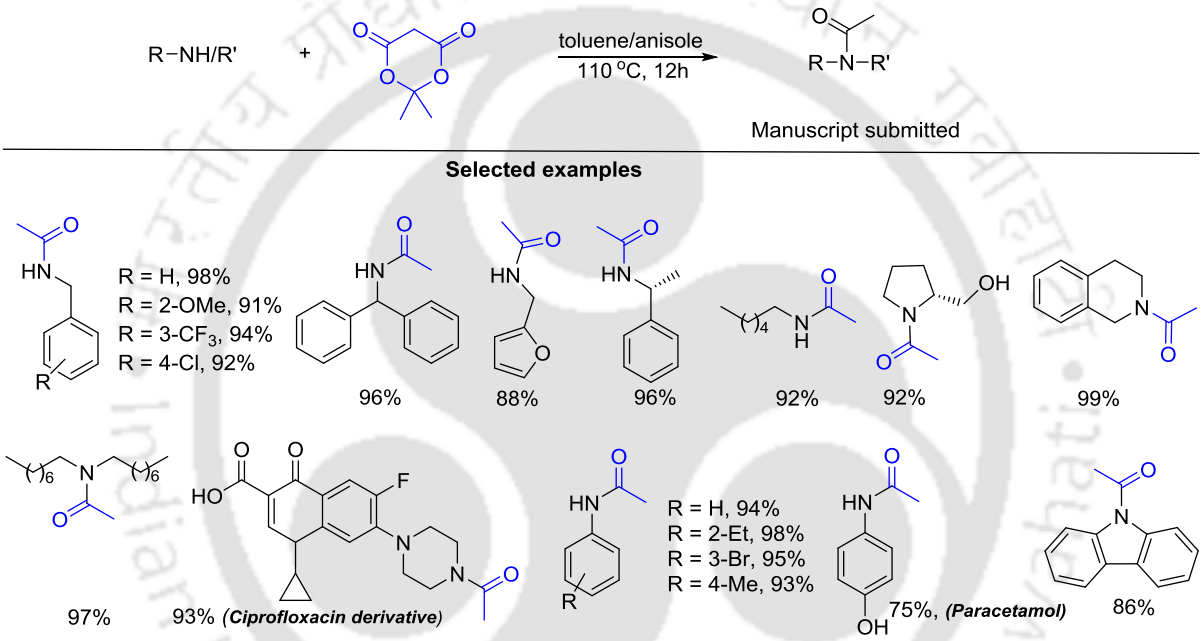
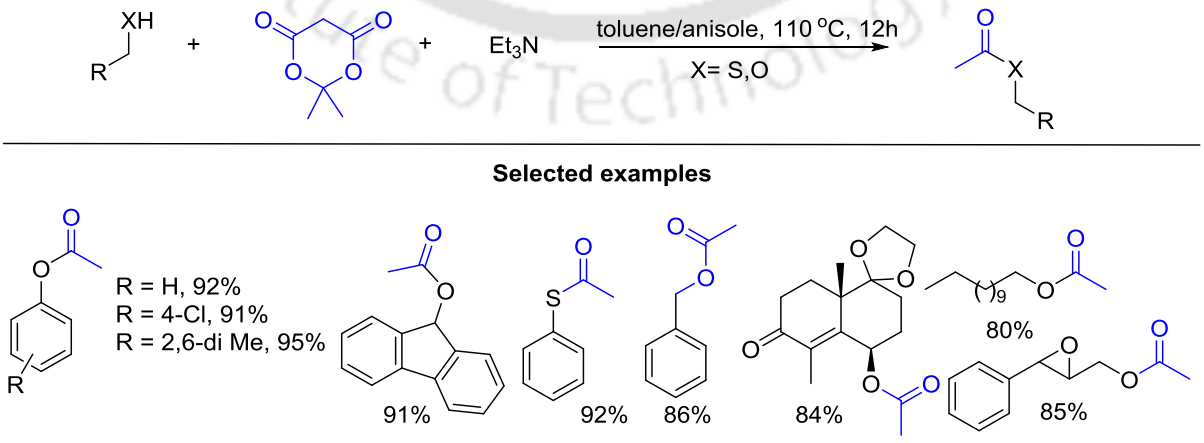
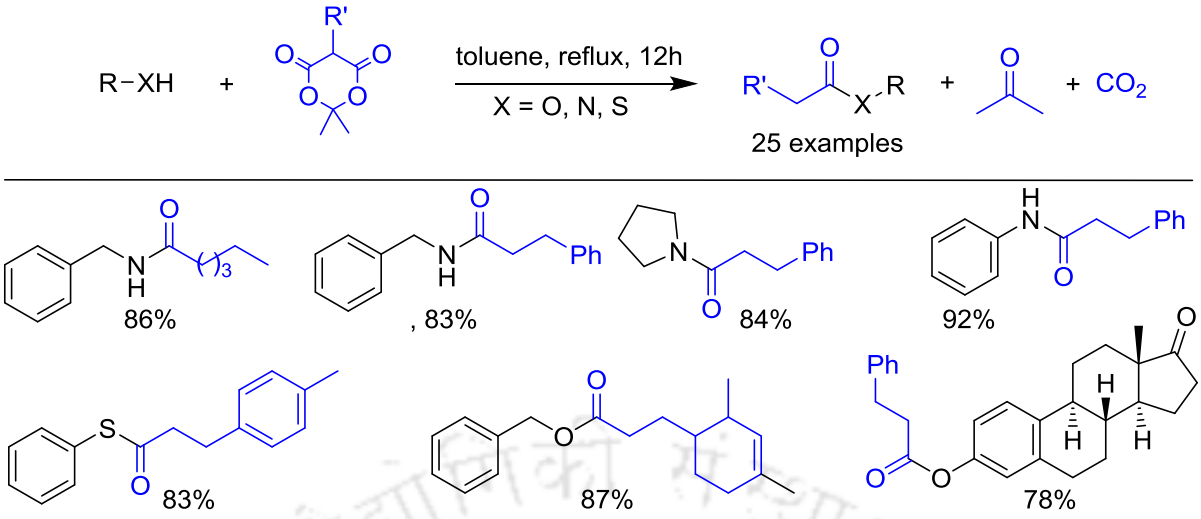
acetylation of large classes of functional groups would be advantageous. A general method for acetylation reaction that is capable of acetylating major substrate class, such as aromatic and aliphatic amines, aromatic and aliphatic alcohols, thiols and hydrazones has been developed. Different primary and secondary amines were reacted with Meldrum's acid under the optimized reaction conditions to afford the corresponding *N*-acylated product with excellent yields. Phenol, benzyl alcohol, saturated aliphatic alcohols, such as dodecanol also reacted smoothly to afford the desired acetates with excellent yield. Substrates bearing both electron-rich and electron-deficient groups were acetylated and acylated efficiently (which was summarised in **Scheme 11, Scheme 12** and **scheme 13**).



Scheme 11: Scope for the acetylation of amine

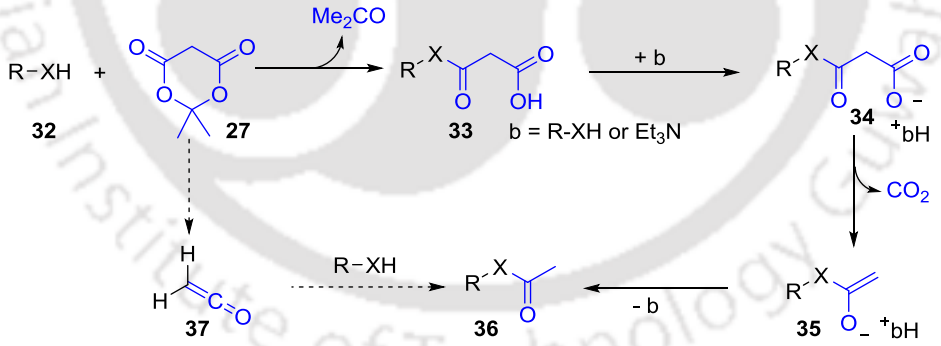


Scheme 12: Scope for the acetylation of phenols, alcohols and thiol



Scheme 13: Scope for the acylation of amine, alcohol and thiol

A plausible mechanism for the acetylation reaction is shown in **Scheme 14**. The acetylation reaction is believed to proceed via malonic acid derivatives **33** which was formed through the reaction of nucleophilic substrates and the Meldrum's acid. Thermal decarboxylation of **34** followed by protonation of resulting enolate provided the acetyl derivative **36**. The possibility of the reaction via ketene, which is formed by thermal decomposition of Meldrum acid, can be eliminated as the simple reaction of alcohol and Meldrum's acid failed to provide the acetates. Moreover, thermal decomposition of Meldrum's acid to corresponding ketene required the temperature which is higher than the current reaction temperature.



Scheme 14: Proposed Reaction Mechanism

Chapter 7: Stereoselective single pot multistep reaction to densely functionalized Spiro cyclic ene-lactam

Lactams are cyclic amides of varying ring sizes, such as alpha, beta, and gamma lactams.[45] Lactam ring derivatives exhibit additional pharmacological effects. Ene-lactams are highly versatile intermediates for the synthesis of piperidine and hydroquinoline ring systems and useful intermediates for the preparations of alkaloids, piperidinones, and many other

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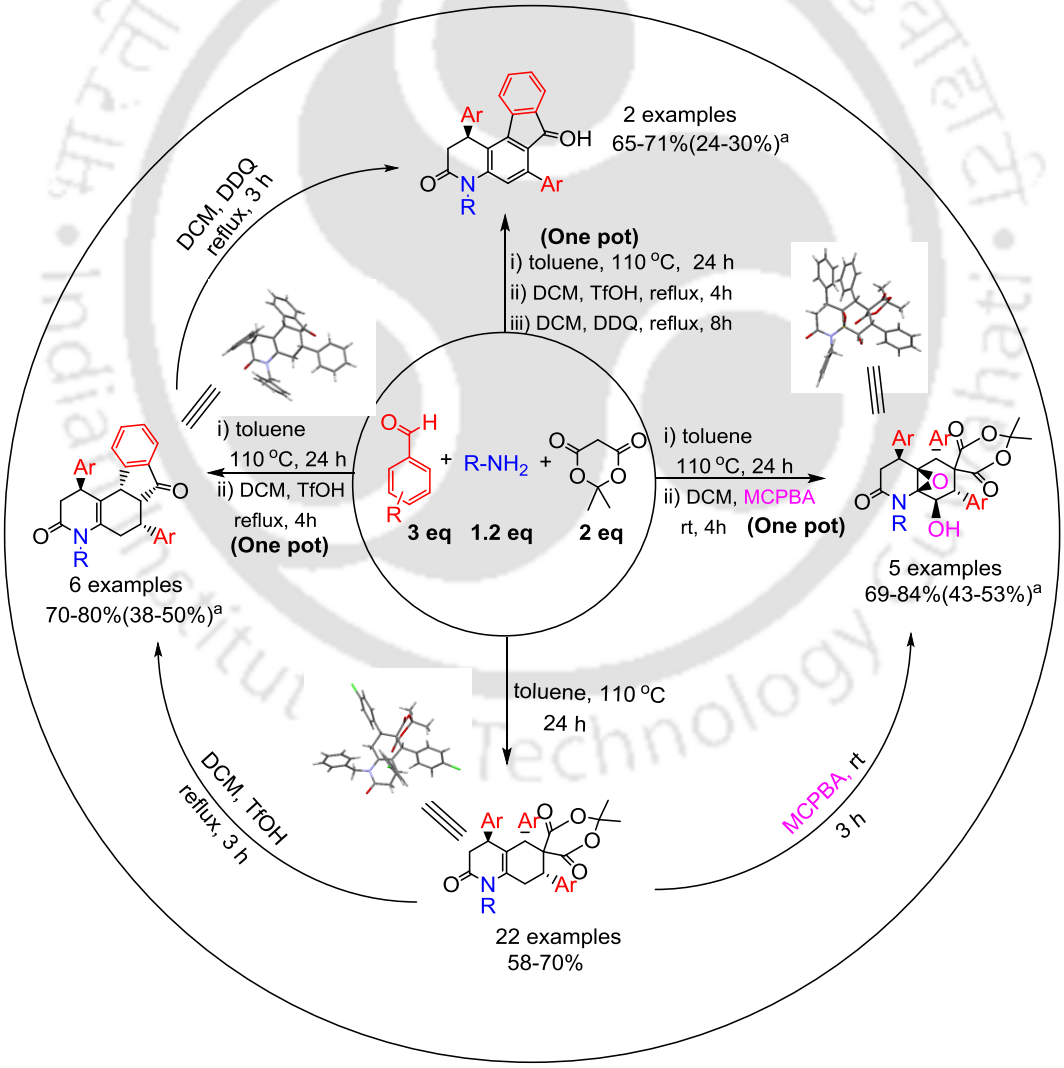
biologically active heterocycles.[46] However, there were only limited reports on the general preparation of this type of compound. Many required high temperatures above 180 ^{o}C or elevated pressure, in which more reaction conditions delicate starting materials may not survive. Synthetic procedures for the synthesis of bicyclic ene-lactams are rare.[46] Generally, multistep synthetic procedures are needed to achieve the bicyclic ene-lactams.

By observing the importance of spiro compound[47], a new method for the synthesis of byclic ene-lactam having spirocycles in a single step without using metal catalyst or other additives has been developed. Simultaneous epoxidation and hydroxylation occurred when spiro cyclic ene-lactam was treated with MCPBA. Tetracyclic ene-lactam was formed by reacting spirocyclic ene-lactam with triflic acid. Aromatized product (9-fluorenone derivative) of tetracyclic ene-lactam was synthesized *via* DDQ oxidation.



Scheme 15: Synthesis of tricyclic ene-lactam. [a]Yields from one-pot reaction.

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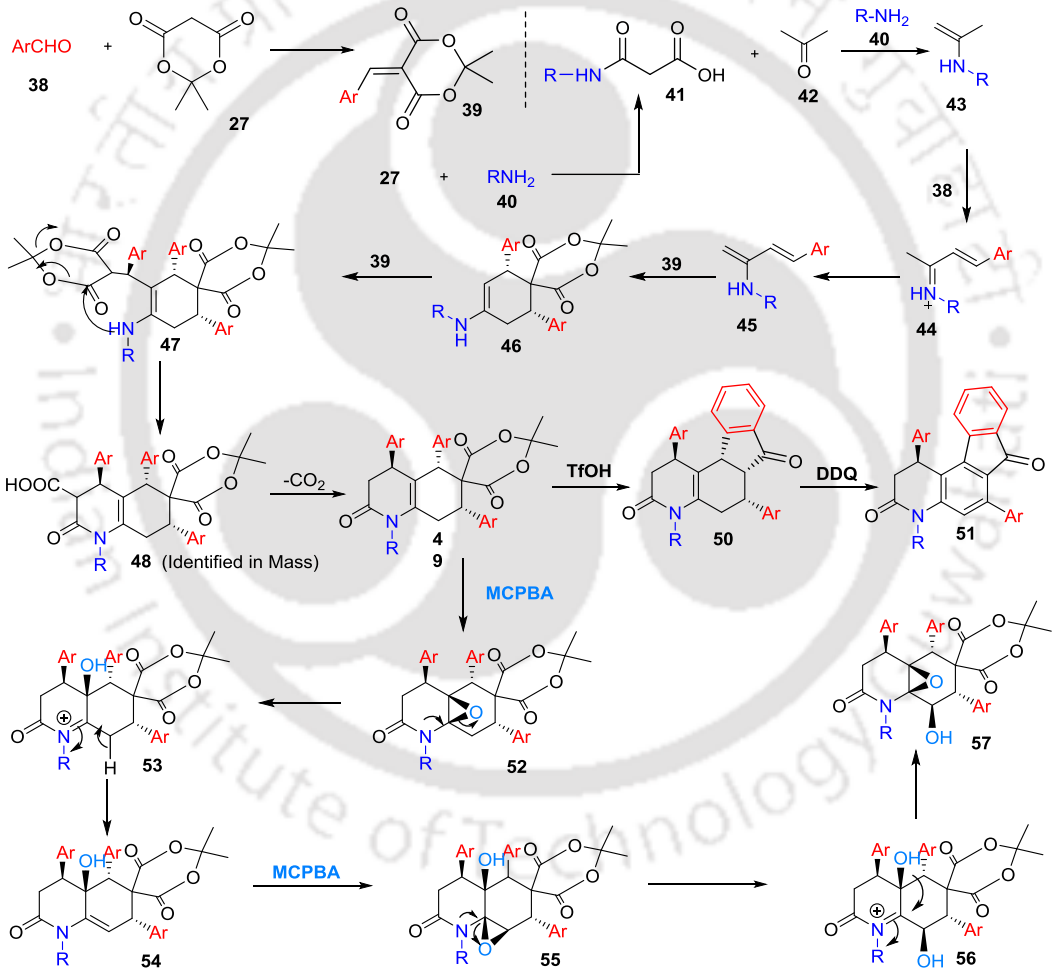
On the basis of controlled reaction, a plausible mechanism for the one pot ene-lactam formation is shown in **Scheme 16**. The reaction is believed to proceeds via spiro derivative **46** which is formed through the reaction of aldehyde, amine and Meldrum's acid. Diastereoselective reaction of **46** with **39** to avoid steric interaction between two Ar groups, gave derivative **47**. On cyclization of **47**, a carboxylic acid derivative **48** was formed. Decarboxylation of **48** gave the desired ene-lactam **49**. In the presence of acid, spiro compound **49** cyclized (decarboxylation) to form tetracyclic derivative **50,** which after aromatization by DDQ produced fluorenone derivative **51.** Spiro ene-lactam **49** was reacted with MCPBA to produce epoxide derivative **57** *via* **52**. MCPBA approached from the site opposite to the two Ar groups of B-ring of ene-lactam.



Scheme 16: Proposed Mechanism.

Summary: The thesis describes new synthetic methodologies for the synthesis of amides, lactams, alkenes and dihydropyridines. The umpolung reactivity of imine was applied for the C-C and C-O bond formation to provide amides including some medicinal drugs and natural

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products and alkenes in the absence of metallic reagent or hazardous oxidant. Amides were prepared either from aldehyde (described in Chapter 2) or from directly from amine (described in Chapter 3) through C-O bond formation. C-C bond formation strategy was applied for the synthesis of alkenes and dihydropyridines directly from amines (described in Chapter 4). Synthesis of cinnamamide and piper amide was obtained directly from amine, aldehyde and Meldrum's acid through a single step procedure without using any coupling agent or catalyst (described in Chapter 5). A general acetylation acylation method has been developed using Meldrum's acid (described in Chapter 6). A synthetic route for diastereoselective one pot synthesis of ene-lactam derivatives has been developed using aldehyde, amine and Meldrum's acid (described in Chapter 7).

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CHAPTER 1

Introduction: C-C and C-O Bond Formation through Umpolung Reactivity of Imine

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Introduction: C-C and C-O Bond Formation through Umpolung Reactivity of Imine

1.1 Introduction:

Umpolung or polarity inversion in organic chemistry is the chemical modification of a functional group reversing the polarity of that group.[1] In natural polarization of ketones (in which X = O) and imines (X = NR) places partial positive charge (δ^+) on the carbon atom and partial negative charge (δ^-) on X. These compounds are, therefore, electrophilic and react with nucleophilic molecules (Nu^-). The application of umpolung to ketones and imines would make them nucleophilic and prone to attack by electrophiles (E^+) (**figure 1**). The concept was introduced by D. Seebach (hence the German word umpolung for reversed polarity) and E.J. Corey[3a]. The umpolung of an imine or of a carbonyl-containing compound, such as a ketone, would place partial negative charge at the carbon atom, rendering the atom nucleophilic **(figure 1)**. The development of synthetic strategies based on umpolung is very useful for the synthesis of many biologically active molecules[2]. The successful development of numerous C-C bond-forming umpolung reactions with carbonyls as acyl anion equivalents has greatly expanded the repertoire of organic synthesis[4]. However, umpolung reactions of imine are underdeveloped. Mostly studied imine umpolung involved the reaction of a proton as the electrophile producing amines or amino acids via transamination[1b].

Figure 1: Natural and inverted polarity

1.2 Literature review:

1.2.1 Umpolung reactivity of carbonyl compound:

Corey - Seebach umpolung: Corey Seabach's reaction is the classic example of umpolung reaction. It allows the reversal of the normal reactivity of acyl carbon atoms, which combine only with electrophiles (**Scheme 1**)[3c]. Dithiane intermediate **1.2** was used as the masked acyl anion.

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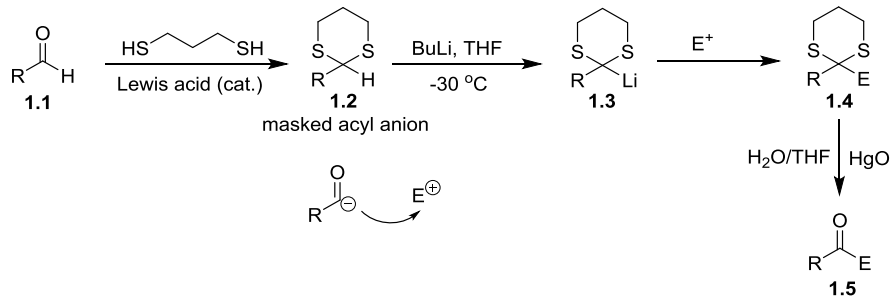
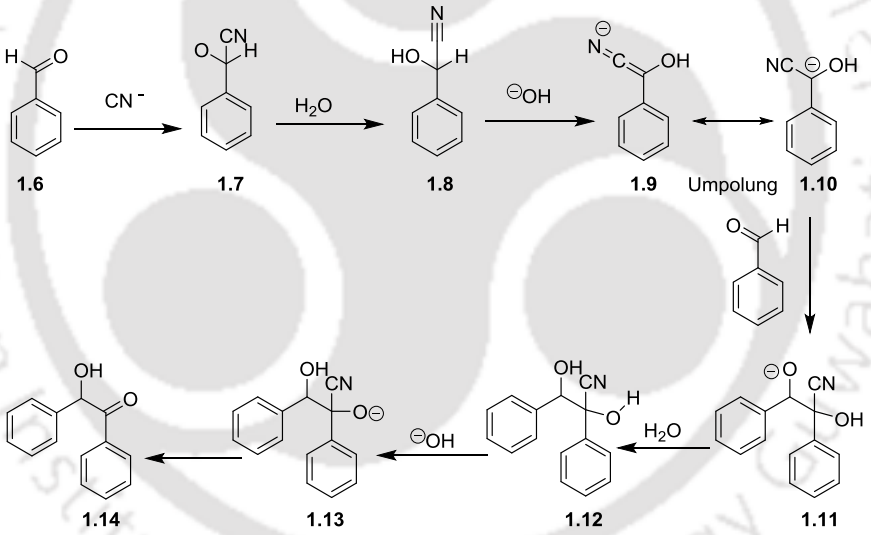


Scheme 1: Umpolung of carbonyl compound *via* masked acyl anion

1.2.2 Cyanide mediated umpolung:

Another classic example of polarity inversion was found in the benzoin condensation reaction. Cyanide is a key catalyst that helps in reversing the polarity (**Scheme 2**)[3f]. Addition of the cyanide ion to create a cyanohydrin **1.8** affects a umpolung of the normal carbonyl charge affinity, and the electrophilic aldehyde carbon becomes nucleophilic after deprotonation (as shown in **1.10**)



Scheme 2: Benzoin condensation via umpolung of carbonyl

1.2.3 Carbene catalyzed umpolung reaction:

N-heterocyclic carbene or NHCs, are similar to cyanide in reactivity. Like cyanide, NHCs have an unusual chemical ambivalence, which allows it to trigger umpolung reactions. The carbene has six electrons - two each in the carbon-nitrogen single bonds, two in its sp^2-hybridized orbital, and an empty p-orbital. The sp^2 lone pair acts as an electron donor, whereas the empty p-orbital is capable of acting as an electron acceptor (**Scheme 3**)[3g].

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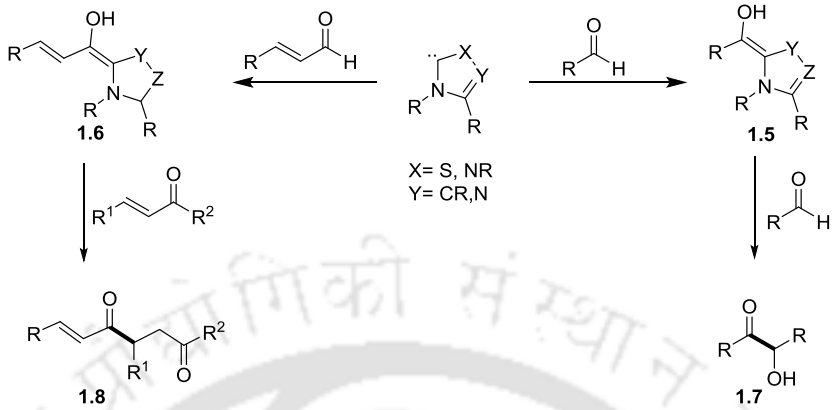
The reaction of carbene with aldehydes provides the umpoled intermediates **1.5** and **1.6,** which then can react with the suitable electrophile to form the expected products **1.7** and **1.8,** respectively.



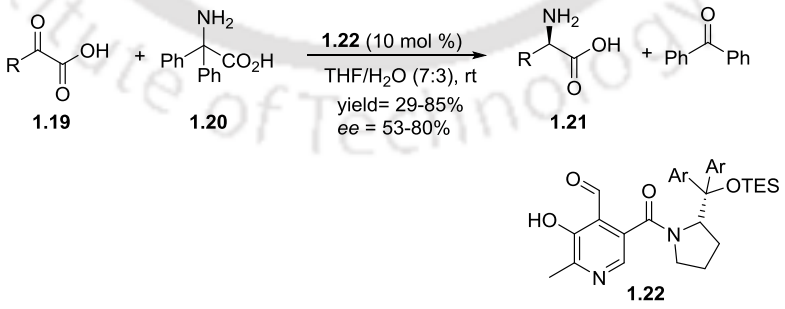
Scheme 3: Umpolung of carbonyl using NHCs

1.2.4 Umpolung of imine:

(a) Transamination reaction by using proton as the electrophile:

Carbonyl umpolung reactivity was used in transamination reactions producing a large variety of amines and amino acids[1b]. In the transamination reaction, H^+ was used as the electrophile.

Zhao *et al.* have developed a series of chiral pyridoxals (like **1.22)** from commercially available pyridoxine and (S)-α,α-diarylprolinols. The pyridoxals exhibited good catalytic activity in an asymmetric transamination of α-keto acids **1.19** with 2,2-diphenylglycine **1.20** as the amine source to give various α-amino acids **1.21** in 29−85% yields with 53-80% *ee*'s (**Scheme 4**)[4c].



Scheme 4: Biomimetic transamination of α-keto acids *via* umpolung

Similarly, Chruma and coworkers developed condensation reaction between the tetrabutylammonium salt of 2,2-diphenylglycine **1.23** and aldehydes **1.24** for a

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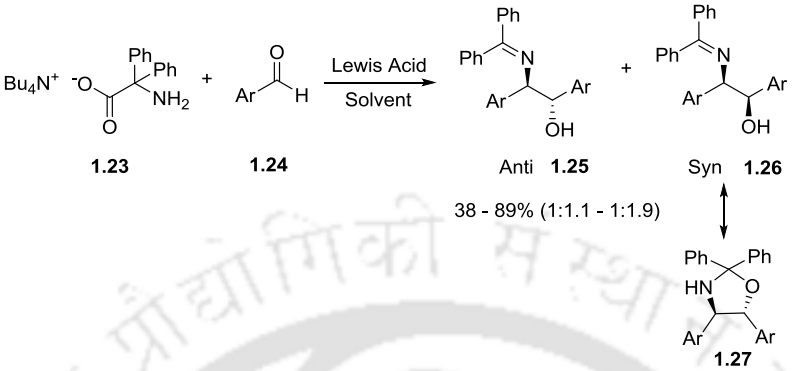
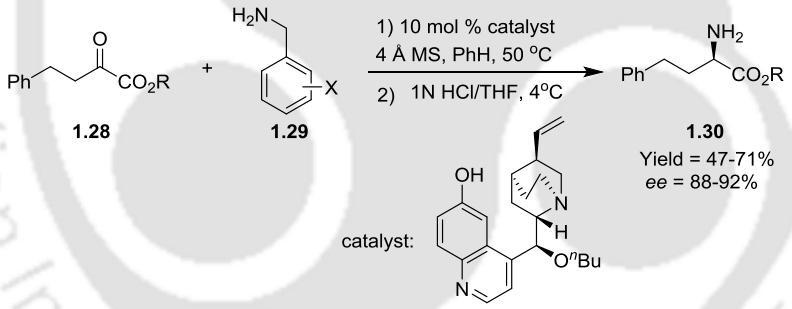
decarboxylative Erlenmeyer reaction, affording 1,2-diaryl-2-iminoalcohols as a mixture of diastereomers **1.25** and **1.26** . The diastereomeric ratio shifts over time, with the anti diastereomer **1.25** and the syn oxazolidine tautomer **1.27** serving as the kinetic and thermodynamic products, respectively (**Scheme 5**)[4a].



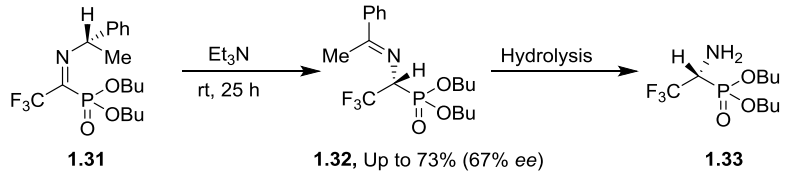
Scheme 5: Synthesis of 2-iminoalcohols *via* umpolung

Shi and coworkers described an effective chiral base catalyzed biomimetic transamination of α-keto esters using simple benzyl amine derivatives **1.29**. A wide variety of α-amino esters **1.30** containing various functional groups can be synthesized in high enantioselectivity and reasonable yield (**Scheme 6**)[4j].



Scheme 6: Synthesis α-keto esters to optically active α-amino acid derivative

Yuan and coworkers reported the synthesis of 1-amino-2,2,2-trifluoroethanephosphonic acid **1.33** from ketimine **1.31** *via* a base-catalyzed transamination and subsequent hydrolysis (**Scheme 7)** [5p].



Scheme 7: Isomerization of 1-imino-2,2,2-trifluoroethanephosphonate

Soloshonok and coworkers disclosed a practical asymmetric entry to the family of

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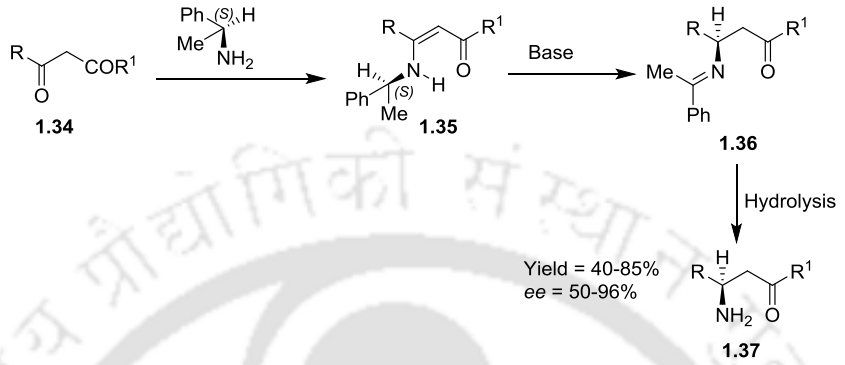
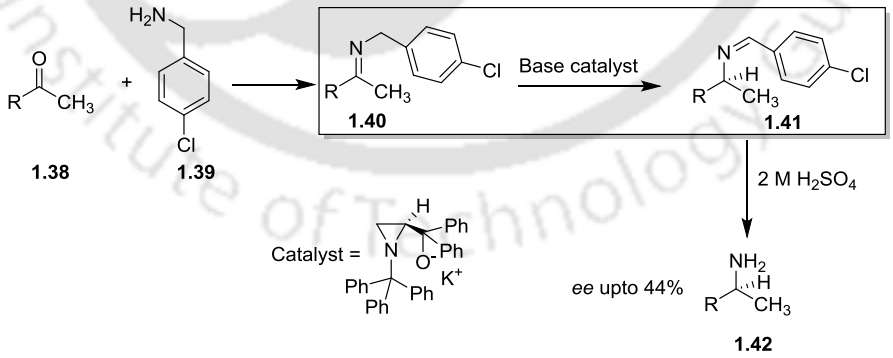
biomedically important chiral amino acid (**Scheme 8**)[4o]. The enamine **1.35** derived from ketones and (*S*)-R-phenylethylamine under certain reaction conditions could be isomerized to the corresponding *N*-(R-phenylethylidene) derivatives **1.36**. *N*-(R-phenylethylidene) **1.36** then hydrolysed to the corresponding amine with the enantioselectivity ranging from 50 to 96% ee.



1.34 **1.35** **1.36** **1.37**

Scheme 8: Biomimetic transamination of α-Keto carboxylic acid

Zwanenburg and coworkers described an asymmetric catalytic synthesis of chiral amines using a chiral base-catalyzed [1,3]-proton shift reaction of imines. The isomerization reaction of *N*-benzylimines **1.40** derived from prochiral ketones **1.38** (benzylacetone, acetophenone) and p-substituted benzylamines **1.39**, is catalyzed by a chiral base and gives enantiomerically enriched (up to 44% e.e.) *N*-benzylidene derivatives **1.41**. The resulting products are readily hydrolyzed to their corresponding amines **1.42** (**Scheme 9**)[4v].



1.38 **1.39** **1.40** **1.41** **1.42**

Scheme 9: Enantioselective synthesis of chiral amines

(b) Transamination involving carbon-based electrophile:

Zhao and coworkers developed a novel strategy for the generation of α-amino anions **1.45,**

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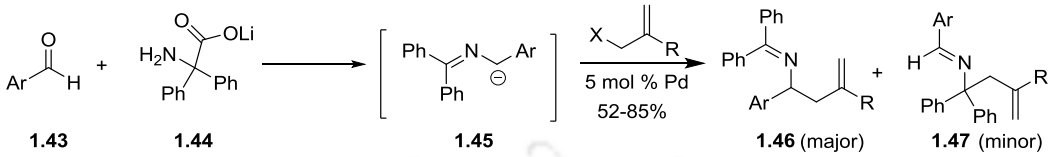
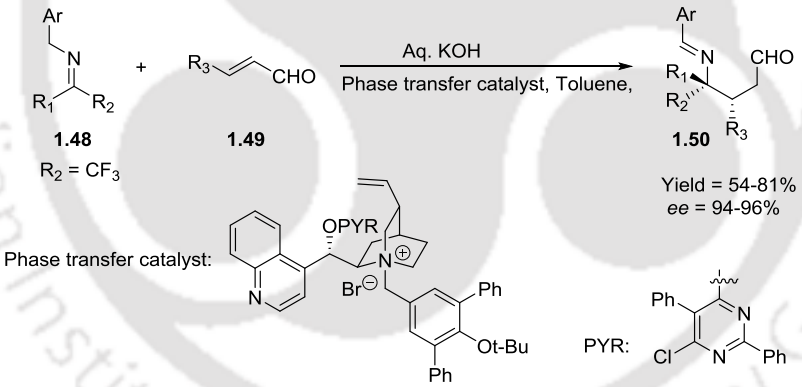
from aldehydes **1.43**. Aromatic aldehyde **1.43** was converted to α-amino anion **1.45** *via* reaction with 2,2-diphenylglycine **1.44** and subsequent decarboxylation. The in situ generated α-imino anions **1.45** were highly reactive for Pd-catalyzed allylation reaction forming the corresponding homoallylic amines **1.46** with excellent regioselectivity (**Scheme 10**)[4b].



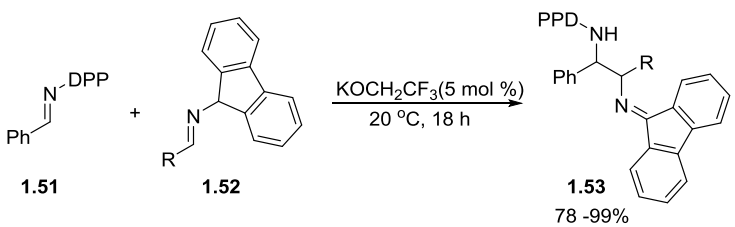
Scheme 10: Aminative umpolung by Pd catalyst

Deng and colleagues reported an asymmetric carbon-carbon bond-forming reaction between imines **1.48** and α,β-unsaturated aldehydes **1.49**. The reaction depends on a umpolung reactivity of the imine, which occurred in the presence of a phase-transfer catalyst. The catalyst helped to transfer a base (potassium hydroxide) from an aqueous solution to toluene (the solvent in which the reaction occurs), and also promoted asymmetric induction to form the product **1.50** with high enantiomeric excess (**Scheme 11**)[4h].



Scheme 11: Catalytic enantioselective of umpolung reactions

Kobayashi *et al.* reported an efficient catalytic imine–imine cross-coupling reactions based on a umpolung strategy. An imine **1.52** bearing a 9-fluorenyl moiety on its nitrogen atom acted as a nucleophile, reacted with another imine **1.51** to afford an imine–imine cross-coupling product **1.53** (**Scheme 12**)[4g].



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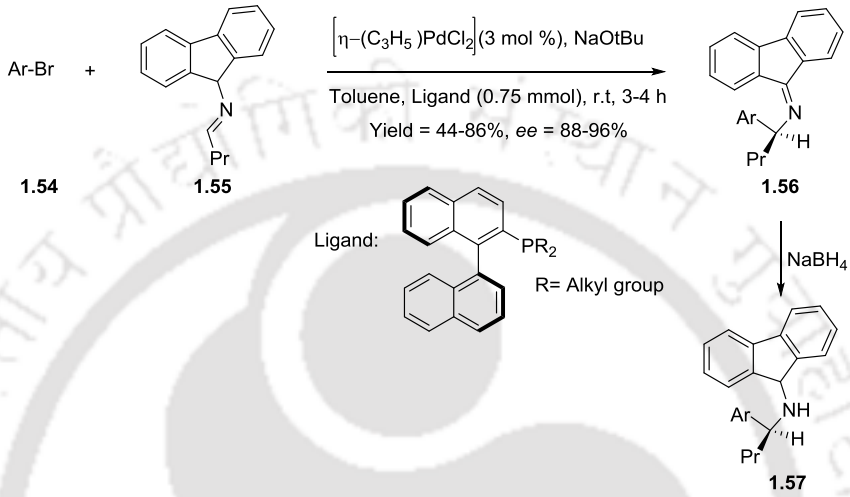
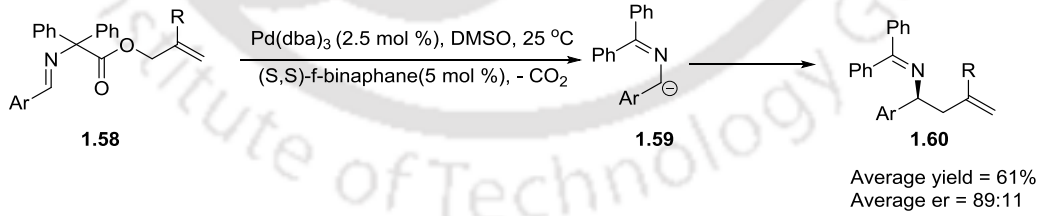
Scheme 12: Imine-imine cross-coupling reactions based on an umpolung strategy

Buchwald and coworkers reported palladium-catalyzed asymmetric arylation of 9-aminofluorene-derived imines **1.55** using a chiral dialkylbiaryl phosphine as the supporting ligand. A diverse range of α-branched benzylamines **1.57** were prepared with high enantioselectivity. In contrast, the related diphenylmethanamine-derived imine did not participate in the reaction under the same conditions (**Scheme 13**)[4e].



Scheme 13: Palladium-catalyzed asymmetric arylation

Chruma et al. developed palladium-catalyzed asymmetric decarboxylative allylic alkylation of allyl 2,2-diphenylglycinate imines **1.58** using (*S,S*)-f-binaphane as a chiral supporting ligand. This transformation allows enantioselective allylation of nonenolate α- imino (2-azaallyl anions) to afford α-aryl homoallylic imines **1.60** (**Scheme 14**)[4f].



Scheme 14: Decarboxylative asymmetric allylation

Zhou and coworkers reported palladium-catalyzed asymmetric umpolung allylation reaction of imines **1.61** with allylic alcohols **1.62**. In the presence of chiral spiro phosphoramidite ligand **1.64**, the allylated derivative **1.63** was formed with high yields and good enantioselectivities. The use of highly stable and easily available allylic alcohols instead of allylic metal reagents facilitated the preparation of chiral homoallylic amine (**Scheme 15**) [4i].

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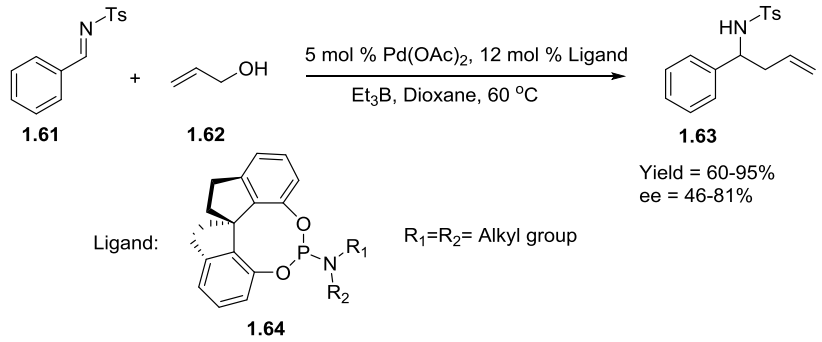

Scheme 15: Asymmetric umpolung allylation of imines with allylic alcohols

1.3 Summary aim of the thesis:

Many examples of carbonyl umpolung reactions were known, but umpolung reactions of imine were underdeveloped. Imine umpolung involving the reaction of a proton as the electrophile producing amines or amino acids *via* transamination is mostly studied. Few reactions with limited substrates on imine umpolung were developed where carbon-based electrophiles instead of protons were used. Electrophiles like aldehyde, enone, allyl bromide were used in the presence of metal-based reagents or catalysts. Strong bases, a hazardous metal-based reagent with the expensive ligand, were employed to promote the C-C bond formation involving aldehyde and imine. However, the reactions with hetero atom-based electrophiles were not investigated. The aim of the thesis was to develop a new synthetic pathway for C-C and C-heteroatom bond formation by direct functionalization of amines using umpolung strategy.

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CHAPTER 2

Aminofluorene Mediated Biomimetic Domino Amination-Oxygenation of Aldehydes to Amides

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2.1 Introduction:

Amide is a ubiquitous functionality of organic molecules and forms an essential part of many natural products, medicinal drugs, and functional materials.[1] Proteins and important plastics like Nylons, Kevlar are polymers whose units are connected by amide groups (polyamides). Amides are also key moiety of many other important biological compounds, as well as many drugs like paracetamol, penicillin, and LSD.

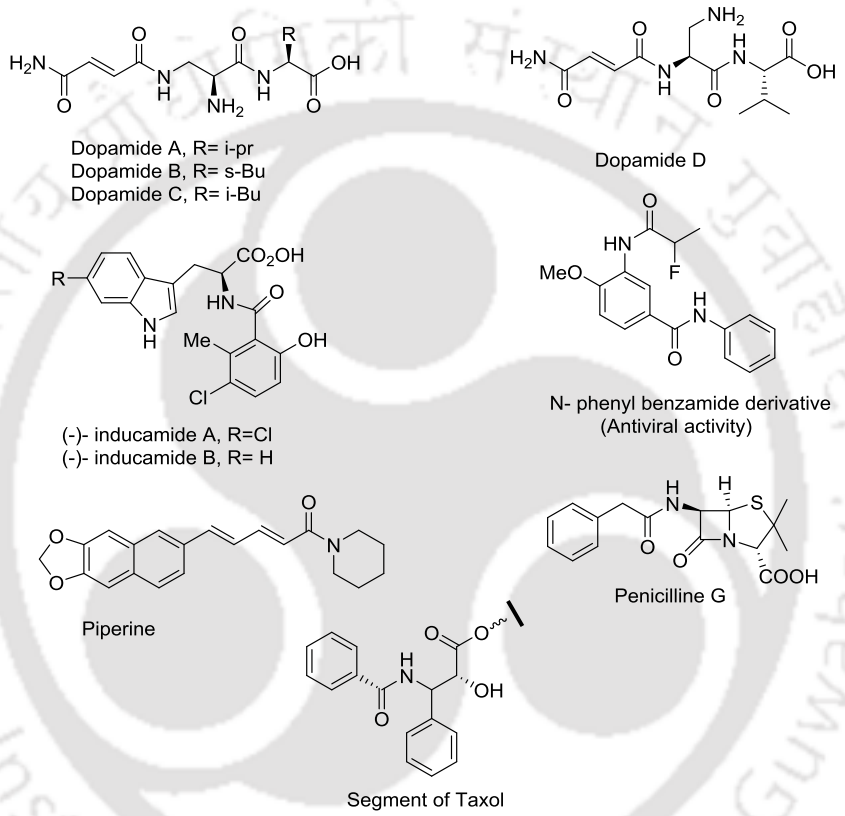

Figure 1: Important medicinal compound containing amide moiety

The primary way to form an amide bond is the classical condensation of a carboxylic acid with an amine. The reactions are promoted by coupling reagents, which produce the super-stoichiometric amount of wastes.[2] To circumvent this, different methods using a catalytic amount of coupling reagents, which are primarily based on boron and other metal based complexes, have been developed.[3] Alternatively, oxidative coupling of an aldehyde/alcohol with an amine is one of the elegant approaches that are developed as the direct methods for amide synthesis.[4,5] Other direct alternatives include amidation involving α-keto acids,[6] α-bromo nitroalkanes,[7] and Staudinger ligation.[8,9] However, the practicability of these

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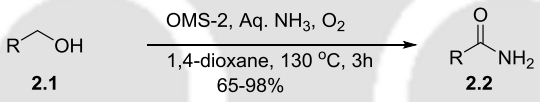
methods was reduced due to the involvement of metallic reagents and hazardous oxidants (e.g. hypervalent iodine, $KMnO_4$, etc.). In addition, most often these methods necessitate sensitive reaction conditions. Molecular oxygen has been used as a viable alternative to hazardous oxidants, however, this worked only in the presence of metallic reagents/ catalyst.[4h,i] On the other hand, carbene catalyzed direct amidation of aldehydes was achieved under metal free conditions.[10] However, pre-functionalized aldehydes, stoichiometric organic oxidants (e.g. nitroxides and quinones) or electrochemical oxidation were essential for the reactions.

2.2 Selected Known methods for aldehyde to amides

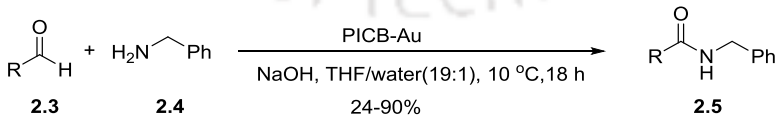
2.2.1. Amide Synthesis using a metal catalyst

Mizuno and coworkers demonstrated the direct synthesis of primary amides **2.2** from primary alcohols **2.1** and aqueous ammonia in the presence of manganese oxide-based octahedral molecular sieves (KMn_8O_{16}; OMS-2). This transformation was achieved by the triple catalytic functions of OMS-2: 1) dehydrogenation of alcohols to aldehydes, 2) dehydrogenation of NH aldimines to nitriles, and 3) hydration of nitriles (**Scheme 1**).[4d/4f]



Scheme 1: Synthesis of primary amides directly from primary alcohols

Kobayashi and coworkers reported the use of Au-NPs for amide formation from aldehydes and amines. A wide range of substrate combinations was applicable. This is the first report of a highly selective amide **2.5** syntheses from aldehydes **2.3** and primary amines **2.4** under aerobic oxidative conditions (**Scheme 2**).[4i]



Scheme 2: Amide synthesis from aldehyde using gold nanoparticle

Chakraborty and co-workers developed a simple, efficient, chemoselective, and inexpensive $FeCl_3$ catalyzed method for the conversion of aldehydes **2.6** into primary amides **2.8**. A variety of aromatic, aliphatic, and conjugated aldehydes were converted directly into the

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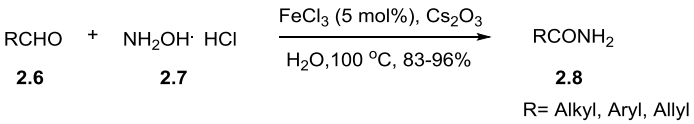
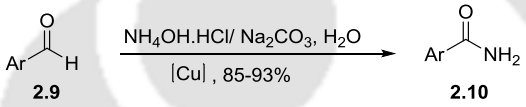
amide with stoichiometric amounts of hydroxylamine hydrochloride **2.7** in the presence of Cs_2CO_3 and catalytic quantities of $FeCl_3$ (**Scheme 3**).[4b]



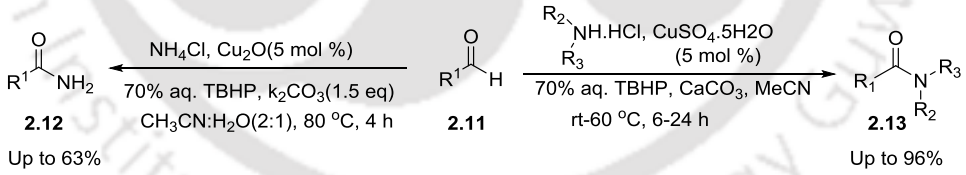
Scheme 3: Fe^{III}-catalyzed synthesis of primary amides from aldehydes

Luque and co-workers reported preparation of an efficient heterogeneous Cu-containing catalyst for conversion of aldehydes **2.9** into primary amides **2.10** under the mild aqueous conditions. (**Scheme 4**).[4]



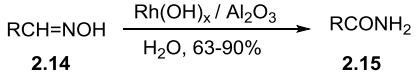
Scheme 4: Conversion of aldehydes to amides using copper-grafted nanoporous silica

Chen and coworkers developed a practical method for the amidation of aldehydes **2.11** with economic ammonium chloride or amine hydrochloride salt. They reported a wide variety of amides (**2.12** or **2.13**) by using inexpensive copper sulfate or copper (I) oxide as a catalyst and aqueous *tert*-butyl hydroperoxide as an oxidant. **(Scheme 5**).[4]



Scheme 5: Copper-catalyzed oxidative amidation of aldehydes

Mizuno and coworkers reported a one-pot synthesis of primary amides **2.15** from various kinds of aldoximes **2.14** in water using rhodium hydroxide ($Rh(OH)_x/Al_2O_3$) as an effective heterogeneous catalyst (**Scheme 6**).[4d/4f]



Scheme 6: Synthesis of primary amides from aldoximes

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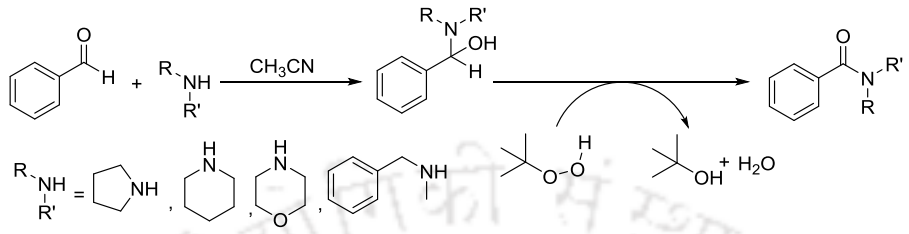
2.2.2 Selected methods for amide synthesis using an oxidizing agent

Wolf and coworkers reported convenient access to amides **2.20** *via* metal-free oxidative amination of aromatic aldehydes **2.17** in the presence of TBHP. This method avoided free carboxylic acid intermediates. Proline-derived amides could be prepared in excellent yields without noticeable racemization (**Scheme 7**).[5a]

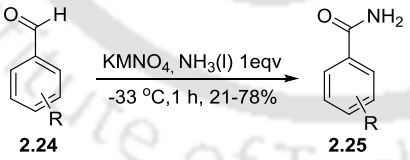


Scheme 7: Metal-free one-pot oxidative amination of aldehydes to amides

Singh and co-workers developed an efficient and green methodology for the synthesis of amides **2.21** using *N*-chloroamines as aminating agents **2.22** under metal- and base-free conditions (**Scheme 8**).[5e]

Scheme 8: AIBN-initiated metal-free amidation of aldehydes using *N*-chloroamines

Mąkosza and coworkers described a simple and practical synthetic procedure by which aromatic aldehydes **2.24** could be directly converted into benzamides **2.25**. The scope of the reaction is somewhat limited by the concurrent formation of carboxylic acids. (**Scheme 9**).[5d]



Scheme 9: Conversion of aromatic aldehydes into benzamides

Xiao and coworkers reported the green and atom-economical synthesis of primary amides **2.27** from primary alcohols **2.26** and ammonia using MnO_2 uniformly attached on both sides of GO (Graphene oxide) sheets (MnO_2/GO) as an efficient heterogeneous catalyst. Analytically pure crystals of product could be isolated by simply cooling in ice (**Scheme 10**).[5c]

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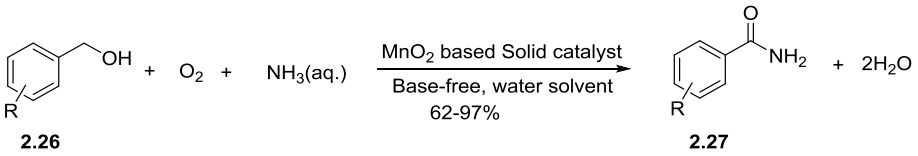
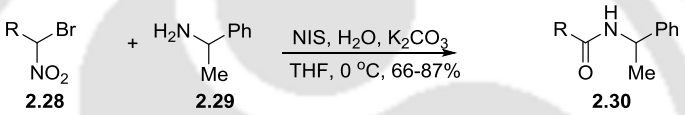


Scheme 10: Amide synthesis from alcohols and ammonia in aqueous media using MnO_2/graphene oxide

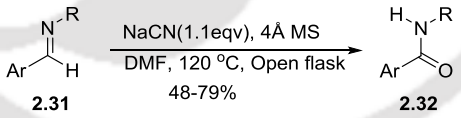
2.2.3 Selected other methods for amide synthesis:

Johnston *et.al* showed that the coupling of amines **2.29** and nitroalkanes **2.28** in the presence of electrophilic iodine source could lead directly to amide products **2.30**. The use of nitroalkanes as acyl anion equivalents provides a conceptually innovative approach to amide and peptide synthesis (**Scheme 11**).[7a]



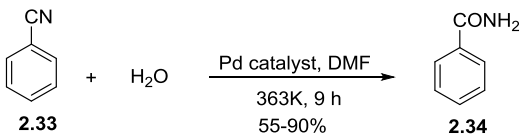
Scheme-11: Amide and peptide synthesis by NIS

Cheon and coworkers developed a new protocol for the direct formation of amides **2.32** from imines **2.31** derived from aromatic aldehydes *via* metal-free aerobic oxidation in the presence of cyanide. This protocol was applicable to various aldimines, and the desired amides were obtained in moderate to good yields (**Scheme 12**).[6]



Scheme 12: Formation of amides from imines by NaCN

Mizuno and coworkers reported that mixture of $Pd(OAc)_2$ and $TBA_4[\gamma\text{-}SiW_{10}O_{34}(H_2O)_2]$ (TBA-SiW_{10}, TBA = $[(n\text{-}C_4H_9)_4N]^+$ showed high catalytic activities for hydration of various kinds of structurally diverse nitriles **2.33** for the synthesis of amide **2.34** (**Scheme 13**).[9a]



Scheme 13: Hydration of nitriles to amide

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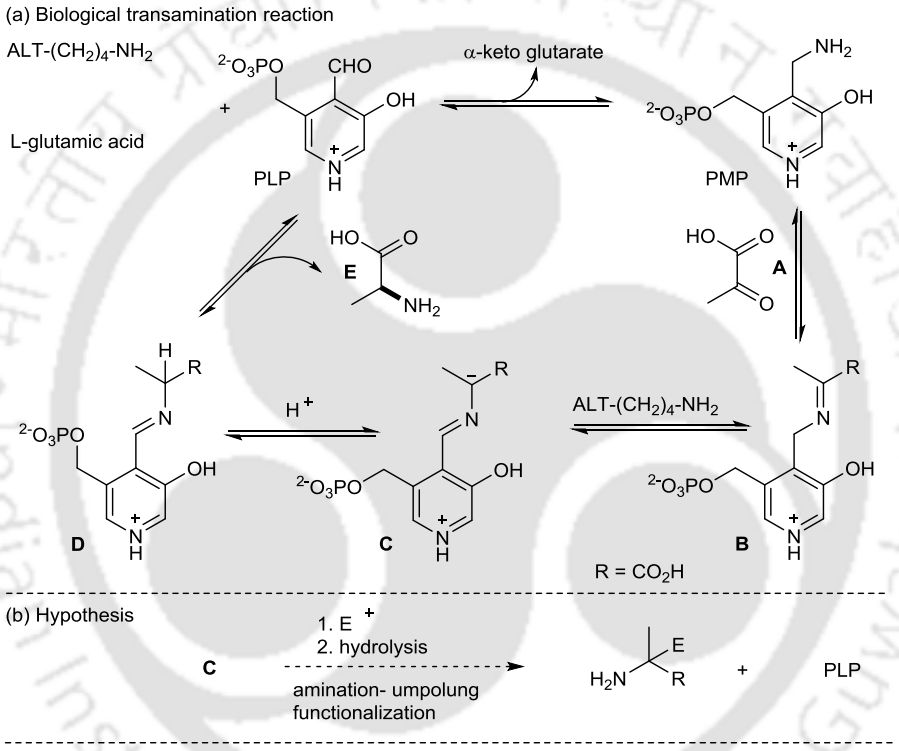
2.3 Hypothesis of present work:

In aminotransferase catalyzed transamination, coenzyme pyridoxyl-5'-phosphate (PLP) is aminated producing pyridoxamine-5'-phosphate (PMP), which subsequently transfers the amine group to keto acid **A** to provide amino acid E (**Scheme 14a**).[11] Ketamine **B**, which is formed in a reaction of PMP with the keto acid, undergoes deprotonative isomerization to anion **C**. Protonation of **C** produces corresponding aldimine **D**, which after hydrolysis provides alanine (**E**) and PLP.



Scheme 14 (a) Alanine aminotransferase (ALT) catalyzed transamination; (b) Our hypothesis for biomimetic amination-umpolung-functionalization of carbonyls

Various suitable amines, which mimic the activity of PMP, were developed for the transamination reactions producing chiral or achiral amines and amino acids.[12] Currently, our group is working on the development of metal and hazardous oxidant free organic transformations.[13] Along that line, it was thought that the reaction of the anion in C with any other electrophile except proton would lead to the amination-umpolung-functionalization of carbonyl carbon of A **(Scheme 14b)**.[14] Therefore, it was anticipated that molecular oxygen would be a suitable electrophile to test the hypothesis because oxygen was found to oxidize the related azomethine anion in Lucifarase catalyzed biological reactions.[15] Commercially

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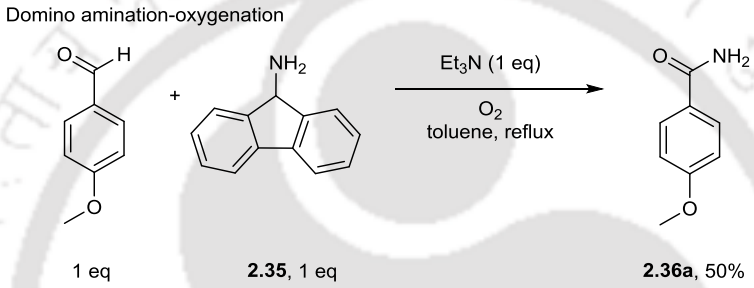
available 9-aminofluorene (**2.35**) was employed as the PMP-analogue to ease the deprotonative isomerization through a stabilized aromatic anion (**2.46**, in **Scheme 21**).[13] Surprisingly, 9-aminofluorene was not known as a transaminating agent despite of its potential.

2.4 Preliminary Results

According to the hypothesis, a reaction of 4-methoxybenzaldehyde and 9-aminofluorene in the presence of triethylamine under the oxygen atmosphere was anticipated. The desired 4-methoxybenzamide (**2.36a**) was produced with a 50% isolated yield.



Scheme 15: Preliminary result

2.5 Optimization of the reaction condition:

Different reaction conditions, such as varying solvents, temperatures, reactant-stoichiometry, etc. were evaluated to optimize the reaction (**Table 1**). The best result (83% of **2.36a** in 1.5 h) was obtained in a triethylamine catalyzed reaction of **2.35** and aldehyde in refluxing toluene under an oxygen atmosphere. The use of benzylamine and 4-flurobenzylamine, replacing 9-aminofulorene, did not yield the desired amide under the same conditions. However, a trace amount of **2.36a** was identified using diphenylmethylamine (**table 1, entry 10**).

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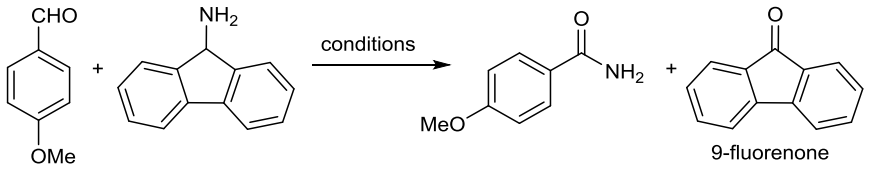
Table 1: Optimization



2.35 **2.36a** **2.37**

entry	conditions	Et_3N	Yield of **2.36a** (%)[b]
1[c]	O_2, toluene, reflux, 12 h	1 eq.	50
2	O_2, toluene, reflux, 2h	1 eq.	75
4	O_2, toluene, rt, 48 h	1 eq.	42
3	O_2, THF, reflux, 2 h	1 eq.	55
5	O_2, toluene, reflux, 12 h	-	50
7[c]	toluene, reflux, 12 h	1 eq.	40
6	O_2, methanol, reflux, 12 h	1 eq.	0
8	O_2, toluene, reflux, 1.5 h	10 mol %	83
9	O_2, xylene, reflux, 1.5 h	10 mol %	76
10[d]	O_2, toluene, reflux, 12h	1 eq.	trace
11[e]	O_2, toluene, reflux, 1.5 h	10 mol %	64
12[f]	O_2, toluene, reflux, 1.5 h	10 mol %	59

[a]Aldehyde (0.37 mmol) was reacted with amine **2.35** (0.55 mmol) in air or oxygen atmosphere. [b]Isolated yields. [c]1eq. of 9-aminofluorene used. [d]Diphenylmethylamine was used in place of 9-aminofluorene. [e]2,7-dibromo-9-aminofluorene was used. [f]2-amino-9-aminofluorene was used.

2.6 Substrate scope:

The scope of the metal free and biomimetic amidation of aldehydes using oxygen as the ecologically viable oxidant was tested next. Different aryl, heteroaryl, and alkenyl aldehydes were reacted smoothly to produce corresponding primary carboxamides **2.36a - 2.36w** with good to excellent yields **(Scheme 16).**

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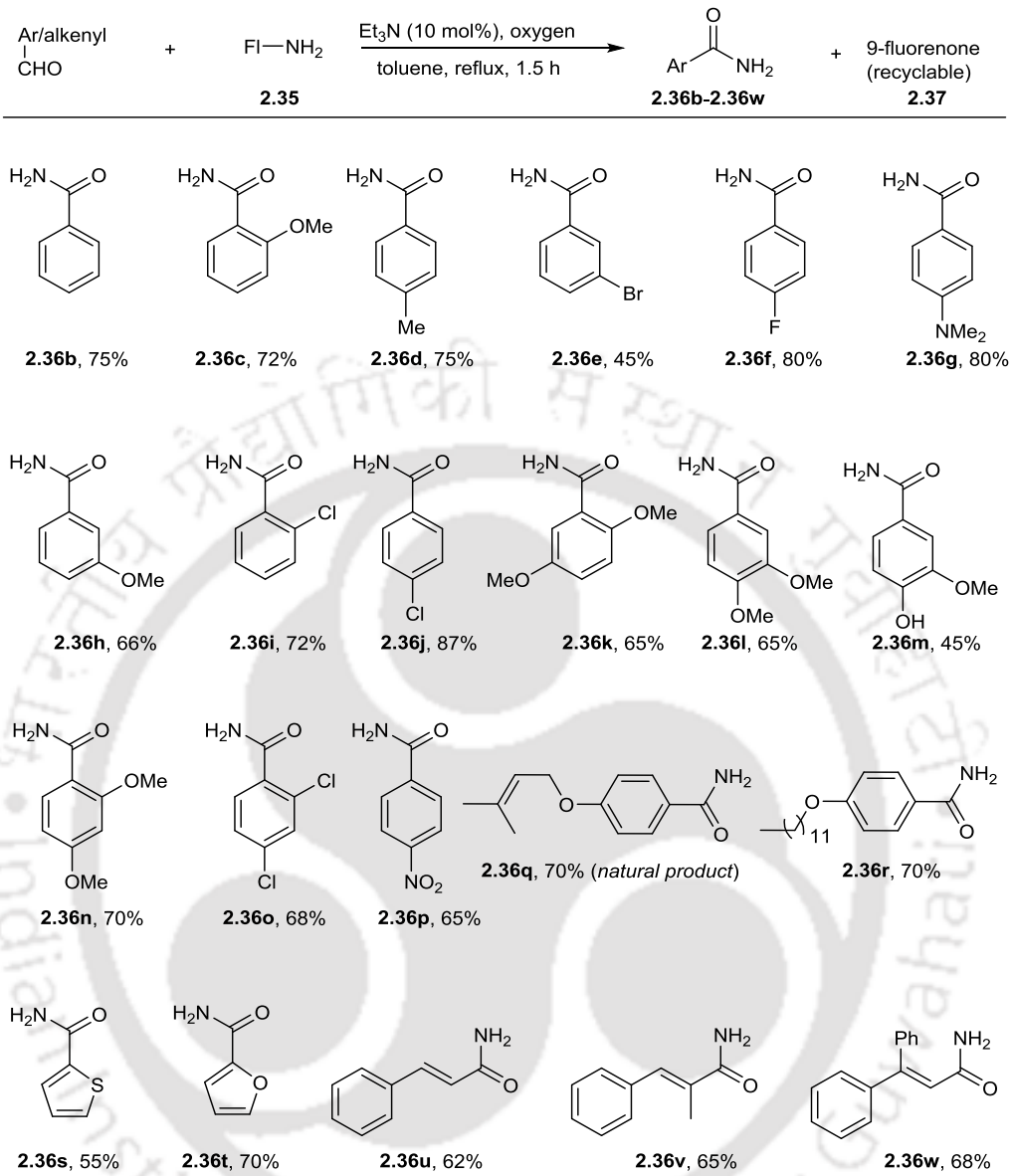

Scheme 16. Scope in NH_2-transfer-oxygenation forming primary carboxamides.

Various functional groups were tolerated under the reaction conditions. The functional groups (e.g. -OR, -NR_2, -OH, Ar-Br, -alkene), which are sensitive to oxidizing agent and transition metal mediated reaction, were found to be well accepted in this reaction. Substrates having both electron donating (e.g. -OH, -OMe, -NMe_2) and electron withdrawing (e.g. -NO_2, -F, -Cl) groups were efficiently reacted to produce the desired amides. Oxidizable heteroaromatic thiophene ring also remained intact during the reaction to yield **2.36s**.

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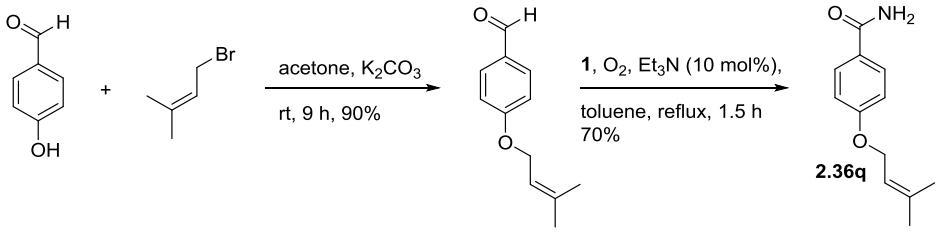
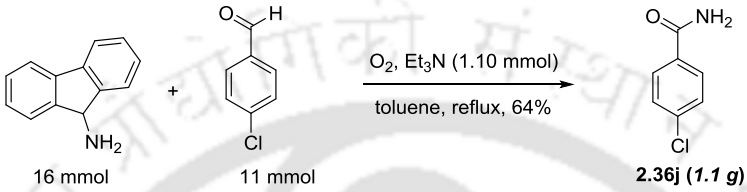


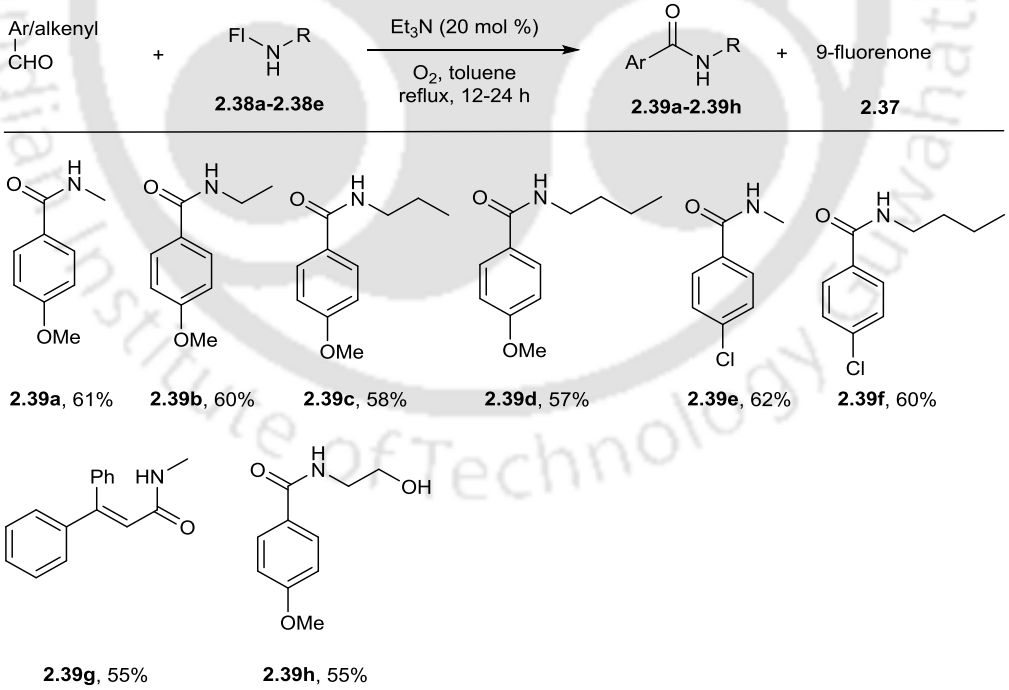
Scheme 17: Synthesis of natural amide **2.36q**

The amination-oxygenation reaction was also applied for the synthesis of natural amide **2.36q** (**Scheme 17).**



Scheme 18: Gram scale synthesis of primary amide

Additionally, the reaction was found to be effective in gram scale synthesis, which indicated its potential for practical application (**Scheme 18**). Moreover, the byproduct 9-fluorenone can be recycled after been converted to corresponding 9-aminofluorene derivative.



Scheme 19: Scope in RNH-transfer-oxygenation

Although there were several reports on the transamination (NH_2-transfer) using primary amine[12,] there was no example where RNH was transferred involving secondary amine. Therefore, investigation for the possibility of RNH- transfer involving secondary amines to

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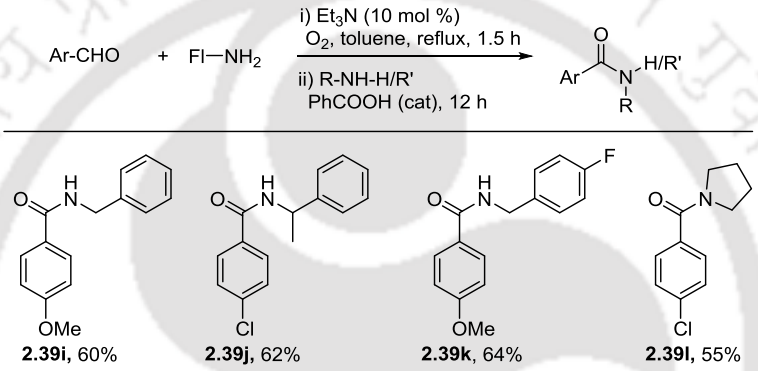
obtain the corresponding secondary amides would be very interesting. Accordingly, different secondary amines **2.38a-2.38e** were reacted with various aldehyde to afford secondary amides **2.39a-2.39h** with good yields **(Scheme 19)**.[16]

Under these conditions, 9-*N*-benzylaminofluorene was unable to provide corresponding amide **2.39i** with isolable yields. However, the desired benzyl amides **2.39i-j** along with tertiary amides **2.39l** were also obtained directly from corresponding aldehydes *via* a one-pot current amidation to a primary amide and its subsequent transamidation[17] reaction with suitable primary and secondary amines (**Scheme 20**).



Scheme 20: Amides prepared by one-pot amidation-transamidation

2.7 Additional Reaction:

Several additional experiments were carried out to better understand the mechanism and chemoselectivity of the amine-transfer-oxygenation reaction (**Scheme 21**).[16] Reaction of benzoic acid and 9-aminofuorene under standard reaction conditions did not yield the desired benzamide (eq. 1). This ruled out the possibility of amide formation via thermal condensation of amine with carboxylic acid that can be formed *in situ* by oxidation of aldehyde. On the other hand, desired benzamide **2.36a** (60%) was isolated from the reaction of preformed aldimine **2.40** (eq. 2). This observation suggested azomethine **2.40** or its derivative **2.46** (**Scheme 22**) as a possible intermediate of the reaction. The reduced yield of benzamide obtained from the reaction, which was carried out without oxygen balloon, indicated the necessity of molecular oxygen for the reaction (Table 1, entry 7). A competition experiment was performed to investigate the relative reactivity of primary and secondary amines (eq. 3).

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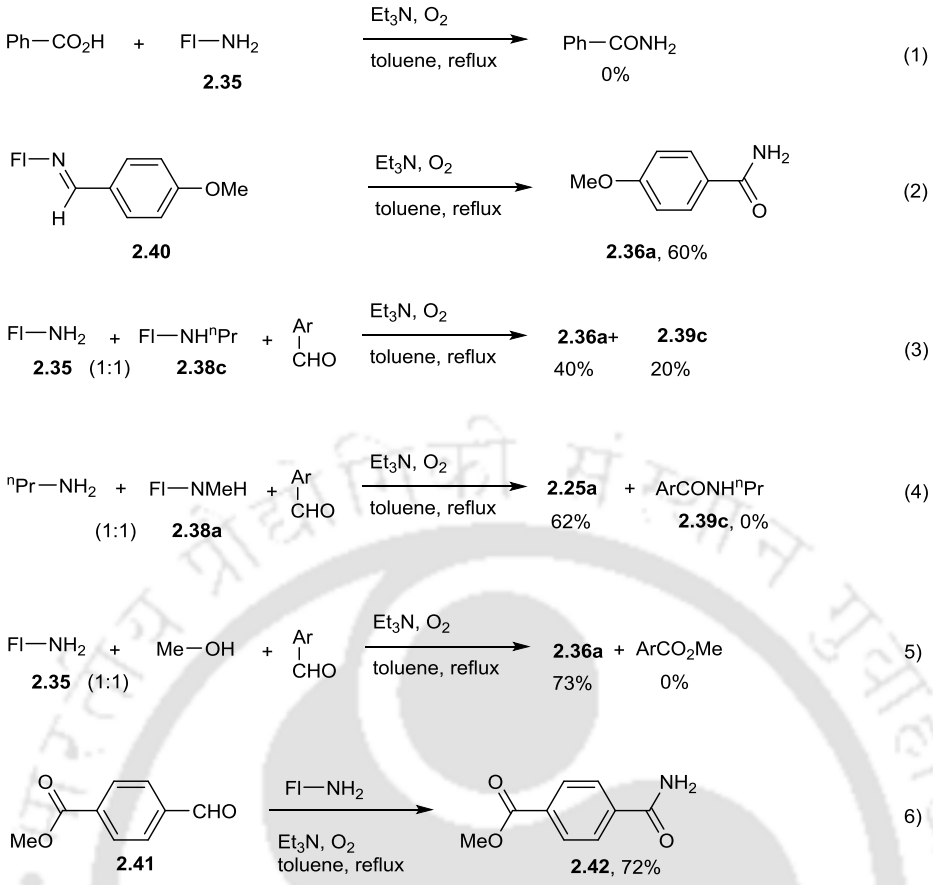

Scheme 21: Controlled reactions

Expectedly, lower yield (20%) of secondary amide **2.39c** (vs 40% of primary amide **2.36a**) was obtained due to the reduced reactivity of corresponding bulky secondary amine **2.38c** as compared to primary amine 1. Different other experiments were carried out to test the chemoselectivity of the reaction (eq. 4 - 6). The amides **2.39a** and **2.36a** were isolated from the reactions shown in eq. 4 and 5 respectively. Amide **2.39c** and methyl ($ArCO_2Me$) ester were not formed. Thus the results demonstrated the excellent chemoselectivity of this coupling reaction in the presence of other potential coupling partner like alcohol (eq. 5) and amine (eq. 4). Similarly, the aldehyde functionality in **2.41** reacted selectively in the presence of ester moiety to obtain corresponding amide **2.42** with very good yield (72%, eq. 6). Further, the results from the reactions shown in eq. 2.4 and 2.5 suggested that amines, which are attached with fluorenyl moiety, were specifically transferred to form corresponding amides.

2.8 Proposed reaction mechanism

Based on the experimental evidence, a plausible mechanism for the base catalyzed metal free biomimetic amine transfer and subsequent molecular oxygen mediated oxidation of

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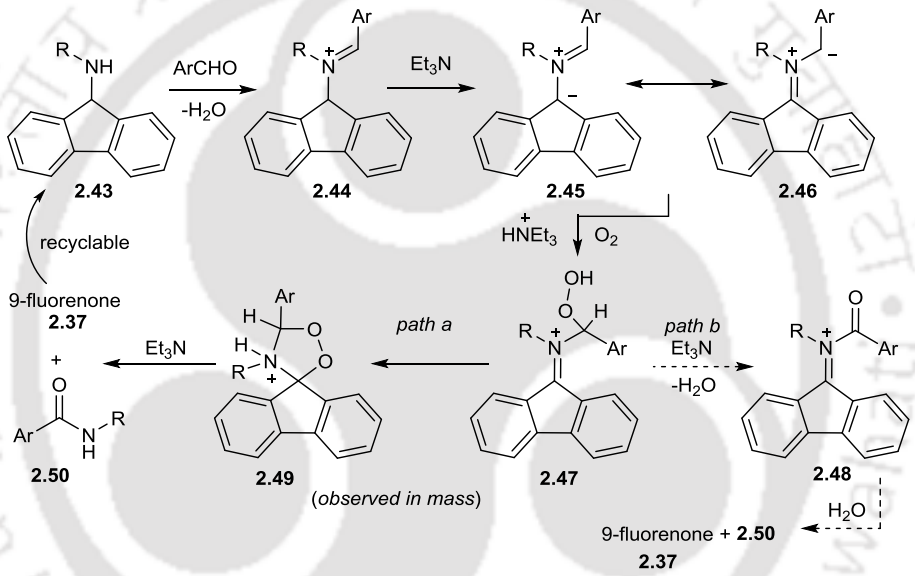
aldehydes to amides is proposed in **Scheme 22**. Condensation of aldehyde and 9-aminofluorenyl derivatives **2.43** occurred to provide corresponding aldimine **2.10**. Triethylamine promoted deprotonation of **2.44** and furnished stabilized azomethine anion **2.45**. Anion **2.45** or its mesomer **2.46** reacted with molecular oxygen to provide hydroperoxide **2.47** or its regioisomer. Hydroperoxide **2.47** could react further to furnish corresponding dioxazolidine **2.49**, which on subsequent thermal decomposition would provide desired amide **2.50** and 9-fluorenone (path a). However, the base mediated O-O bond cleavage of hydroperoxide **2.47** followed by hydrolysis of resulting imine **2.48** could also provide the desired products (path b).



Scheme 22: Proposed reaction mechanism.

Mass spectrometric analysis of the reaction mixture identified peroxide derivatives **2.47** or **2.49** (R = H, Ar = 4-ClPh or 4-MeOPh). This observation suggested that the reaction occurs through the peroxide intermediate **2.47** or **2.49**. However, the mass corresponding to compound **2.48** was not observed.

2.9 Labelling Experiment.

The reaction was also performed in the presence of $^{18}O_2$ to get further insights into the mechanism (**Scheme 23b**). Amide **2.36a**-^{18}O was formed having 95% of ^{18}O incorporation, which was observed from mass spectrometric analysis (**Scheme 23a III**). At the same time, incorporation of 62% of ^{18}O was observed in 9-fluorenone (**Scheme 23a IV**).[18] However,

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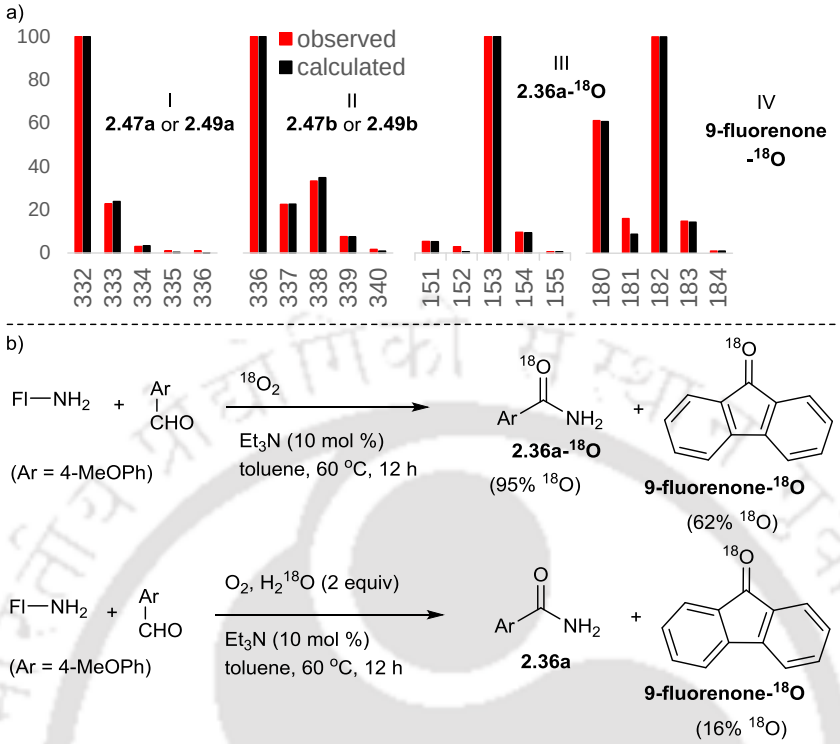
incorporation of ^{18}O did not occur in amide **2.36a** when the reaction was carried out in the presence of $H_2{}^{18}O$ **(Scheme 23b)**.



Scheme 23: a) Observed and calculated mass with isotopic pattern for compound **2.47a** or **2.49a** (I) (Ar = 4-MeOPh), **2.47b** or **2.49b** (II) (Ar = 4-ClPh), 2-^{18}O with 95% ^{18}O (III), and 9-fluoreneo-^{18}O with 62% ^{18}O (IV). b) Amination-oxygenation reaction in the presence of $^{18}O_2$ (preparation of ^{18}O-amide) and $H_2{}^{18}O$.

In contrast, 9-fluorenone formed in the reaction was found to have 16% of ^{18}O.[18] Therefore, in the presence $^{18}O_2$, formation of amide **2.36a** and 9-fluorenone both with high level of ^{18}O indicated that the reactions proceed via dioxazolidine **2.49** (path a). Importantly, the observations also revealed that the ^{18}O-labeled amides with excellent isotopic purity can be prepared by this method just performing the reaction in the presence of $^{18}O_2$.

Decrease of ^{18}O level from expected 95% to observed 62% in 9-fluorenone occurred due to mixing of unlabeled 9-fluorenone formed from the hydrolysis corresponding imine by H_2O. The imine was formed from the aerial oxidation of 9-aminofluorene during the reaction. Similarly, reaction performed in the presence of $H_2{}^{18}O$ allowed the incorporation of 16% ^{18}O into 9-fluorenone. This observation was further supported by the formation of ^{18}O-9-fluorenone from the reaction of imine and $H_2{}^{18}O$.

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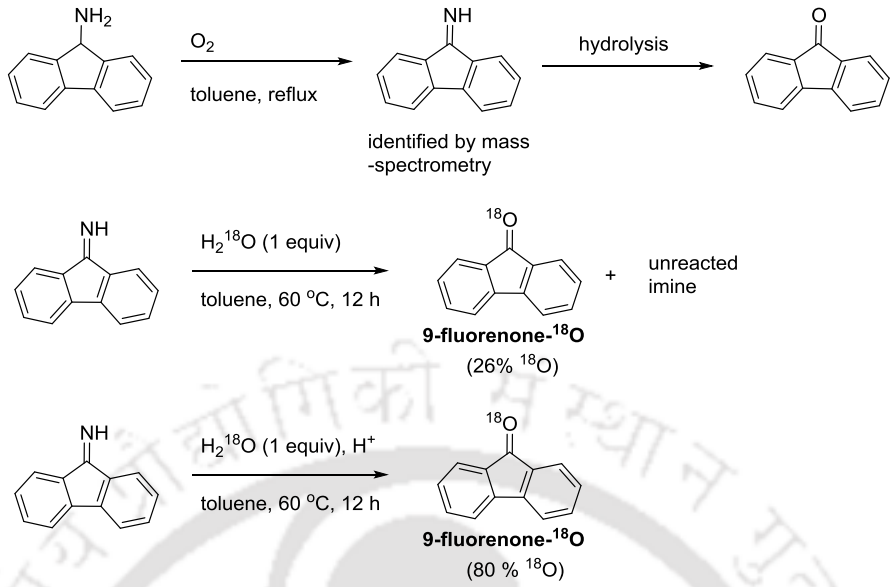

Scheme 24: Side reaction producing 9-fluorenone

2.10 Summary: An unprecedented approach for chemoselective direct amidation of aldehydes based on a biomimetic amination-oxygenation was disclosed. This environmentally benign method used triplet molecular oxygen as the oxidant without the aid of metallic reagents and other hazardous oxidants. In addition to facile synthesis of primary amides *via* NH_2-transfer, RNH- transfer involving secondary amine was also achieved for the first time providing corresponding secondary amides. Mass spectrometric and isotope labelling studies revealed that the oxygenation of azomethine ylide occurred through the dioxazolidine intermediate.^{18}O-amides can be prepared easily by performing this reaction in the presence of $^{18}O_2$. The proposed amination-umpolung functionalization strategy can also be applied for direct derivatization of carbonyl compounds employing other (e.g. carbon based) electrophiles.

2.11 Experimental section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Commercial grade dichloromethane (CH_2Cl_2), xylene, benzene and toluene were distilled over CaH_2 before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ^{1}H, ^{13}C NMR spectroscopy: *Varian Mercury plus 400 MHz, Bruker 600 MHz* (at 298 K). Chemical shifts, δ (in ppm), are

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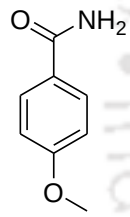
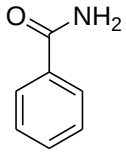
reported relative to TMS δ (^{1}H) 0.0 ppm, δ (^{13}C) 0.0 ppm) which was used as the inner reference. Otherwise, the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.2 ppm; CD_3OD, (^{1}H) 3.31 ppm, δ (^{13}C) 49.0 ppm) were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity. MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

General procedure for the synthesis of primary amide (GP I): Aldehyde (1 eq.) was added to a solution of amine **2.35** (1.5 eq.) in toluene (2 mL) and the mixture was stirred at room temperature for 30 min. Triethylamine (10-20 mol %) was then added to the mixture and the reaction mixture was refluxed for 1.5 h under oxygen atmosphere (placing oxygen balloon). After disappearance of starting materials (indicated by TLC) solvent was evaporated under reduced pressure. The crude mixture was subjected to column chromatography (silica) to afford analytically pure products.

4-Methoxybenzamide (2.36a): According to GP I: 4-Methoxybenzaldehyde (45 µL, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel; EtOAc:hexane, 1:1) gave **2.36a** as white solid (46 mg, 83%). ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.86 – 7.84 (m, 3H), 7.20 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 3.78 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 167.8, 161.7, 129.5, 126.5, 113.5, 55.4 ppm. HRMS: Exact mass calculated for $C_8H_9NO_2$ ($[M+H]^+$): 152.0706, Found: 152.0708.



Benzamide (2.36b): According to GP I: Benzaldehyde (37 µL, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (slica gel; EtOAc: hexane, 1:1) gave **2.36b** as white solid (34 mg, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 6.47 (s, 1H), 6.40 (s, 1H).^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.1, 133.5, 132.1, 128.8, 127.5 ppm. HRMS: Exact mass calculated for C_7H_7NO ($[M+H]^+$): 122.0606, Found:122.0609.



2-Methoxybenzamide (2.36c): According to GP I: 2-Methoxybenzaldehyde (35 µL, 0.39 mmol), amine **2.35** (80 mg, 0.44 mmol) and triethylamine (4 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel; EtOAc:hexane, 1:1) gave **3.36c** as white

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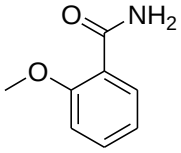
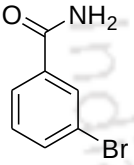


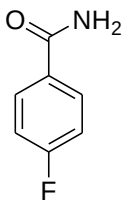
solid (32 mg, 72%) .^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 – 8.17 (m, 1H), 7.74 (s, 1H), 7.48 – 7.43 (m, 1H), 7.06 – 7.03 (m, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.44 (s, 1H), 3.94 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.3, 157.8, 133.4, 132.4, 121.2, 120.7, 111.3, 55.9 ppm. HRMS: Exact mass calculated for $C_8H_9NO_2$ ($[M+H]^+$): 152.0706, Found: 152.0704.

4-Methylbenzamide (2.36d): According to GP I: 4-Methylbenzaldehyde (43 µL, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (Silica gel, EtOAc:hexane, 1:1) gave **2.36d** as white solid (37 mg, 75%). ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.89 (s, 1H), 7.77 (d, *J* = 7.8 Hz, 2H), 7.26 – 7.23 (m, 3H), 2.34 (s, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 167.8, 141.1, 131.5, 128.8, 127.5, 21.0 ppm. HRMS: Exact mass calculated for C_8H_9NO ($[M+H]^+$): 136.0757, Found: 136.0755.



3-Bromobenzamide (2.36e): According to GP I: 3-Bromobenzaldehyde (43 µL, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36e** as off white solid (33 mg, 45%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.96 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.12 (s, 1H), 5.93 (s, 1H) ppm. ^{13}C NMR (151 MHz $CDCl_3$) δ = 168.0, 135.4, 135.2, 130.8, 130.4, 126.1, 123.0 ppm. HRMS: Exact mass calculated for C_7H_6BrNO ($[M+H]^+$): 199.9706, Found: 199.9702.

4-Fluorobenzamide (2.36f): According to GP I: 4-Fluorobenzaldehyde (39 µL, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed



for 1.5 h and column chromatography (silica gel, EtOAc:hex, 1:1) gave **2.36f** as white solid (41 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.83 (dd, *J* = 8.7, 5.2 Hz, 2H), 7.12 (t, *J* = 8.4 Hz, 2H), 6.10 (br. s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.6, 166.1, 164.4, 130.0, 129.9, 129.7, 116.0, 115.8 ppm. HRMS: Exact mass calculated for C_7H_6FNO ($[M+H]^+$): 140.0506, Found: 140.0504.

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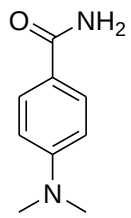
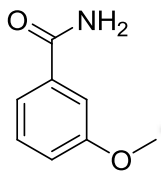
4-(dimethylamino)benzamide (2.36g): According to GP I: 4-



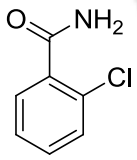
(dimethylamino)benzaldehyde (53 mg, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36g** as off white solid (51 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 7.8 Hz, 2H), 5.76 (br. s, 2H), 3.02 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.0, 152.3, 128.6, 128.5, 119.4, 110.5, 110.4, 39.7, 39.6 ppm. HRMS: Exact mass calculated for $C_9H_{12}N_2O$ ($[M+H]^+$): 165.1022, Found: 165.0190.

3-Methoxybenzamide (2.36h): According to GP I : 3-Methoxybenzaldehyde (43 µL, 0.36



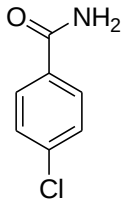
mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36h** as white solid (36 mg, 66%) . ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.40 (s, 1H), 7.35 – 7.31 (m, 2H), 7.07 – 7.06 (m, 1H), 6.18 (s, 1H), 6.05 (s, 1H), 3.85 (s, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.6, 160.0, 135.0, 129.8, 119.3, 118.5, 112.7, 55.6. HRMS: Exact mass calculated for $C_8H_9NO_2$ ($[M+H]^+$): 152.0706, Found: 152.0695.

2-Chlorobenzamide (2.36i): According to GP I: 2-Chlorobenzaldehyde (40 µL, 0.36



mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36i** as white solid (40 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.53 (s, 1H), 6.40 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.5, 134.0, 132.0, 131.0, 130.8, 130.6, 127.3 ppm. HRMS: Exact mass calculated for C_7H_6ClNO ($[M+H]^+$): 156.0211, Found: 156.0214.

4-Chlorobenzamide (2.36j): According to GP I: 4-Chlorobenzaldehyde (51 mg, 0.36



mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol), was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36j** as white solid (49 mg , 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 – 7.74 (m, 2H), 7.44 – 7.42 (m, 2H), 6.10 (s, 1H), 5.97 (s, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.9, 136.1, 133.0, 131.2, 129.4, 128.7, 128.3 ppm. HRMS: Exact mass calculated for C_7H_6ClNO ($[M+H]^+$): 156.0211, Found: 156.0216.

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2,5-Dimethoxybenzamide (2.36k): According to GP I: 2,5-Dimethoxybenzaldehyde (60 mg, 036 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36k** as white solid (43 mg, 65%) . ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.85 (s, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.34 (s, 1H), 3.91 (s, 3H), 3.81 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.1, 153.9, 152.3, 121.4, 120.2, 115.7, 113.1, 56.6, 56.0 ppm. HRMS: Exact mass calculated for $C_9H_{11}NO_3$ ($[M+H]^+$): 182.0812 Found: 182.0808.

3,4-Dimethoxybenzamide (2.36l): According to GP I: 3,4-Dimethylbenzaldehyde (60 mg, 036 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36l** as white solid (43 mg, 65 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.45 (s, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 1H), 5.98 (s, 1H), 3.92 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.3, 152.3, 149.2, 126.1, 120.3, 111.0, 110.4, 56.2 (2C) ppm. HRMS: Exact mass calculated for $C_9H_{11}NO_3$ ($[M+H]^+$): 182.0812, Found: 182.0810.

4-Hydroxy-3-methoxybenzamide (2.36m): According to GP I: 4-Hydroxy-3-methoxybenzaldehyde (56 mg, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36m** as off white solid (29 mg, 45%). FTIR (KBr): $\tilde{\nu}$ = 3445, 2923, 1647, 1520, 1384, 1116, 615 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 – 7.49 (m, 1H), 7.26 – 7.23 (m, 1H), 6.94 – 6.92 (m, 1H), 6.04 (s, 1H), 5.61(s, 1H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 149.8, 146.9, 125.7, 120.8, 114.2, 111.0, 56.5 ppm. HRMS: Exact mass calculated for $C_8H_9NO_2$ ($[M+H]^+$): 168.0655, Found: 168.0657.

2,4-Dimethoxybenzamide (2.36n): According to GP I: 2,4-Dimethoxybenzaldehyde (60 mg, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1), gave **2.36n** as white

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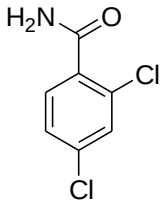
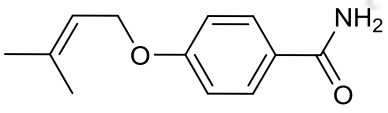
solid (47 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 8.8 Hz, 1H), 7.61 (s, 1H), 6.56 (d, *J* = 8.8 Hz, 1H), 6.46 (s, 1H), 6.31 (s, 1H), 3.90 (s, 3H), 3.82 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 163.9, 159.3, 134.2, 113.9, 105.4, 98.6, 56.0, 55.6 ppm. HRMS: Exact mass calculated for $C_9H_{11}NO_3$ ($[M+H]^+$): 182.0812, Found: 182.0804.

2,4-Dichlorobenzamide (2.36o): According to GP I: 2,4-Dichlorobenzaldehyde (64 mg, 0.36 mmol) amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36o** as white solid (50 mg, 68%) . ^{1}H NMR (600 MHz, DMSO-d_6) δ = 7.91 (s, 1H), 7.65 - 7.64 (m, 2H), 7.46 - 7.45 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 167.2, 136.0, 134.2, 130.9, 130.0, 129.1, 127.2 ppm. HRMS: Exact mass calculated for $C_7H_5Cl_2NO$ ($[M+H]^+$): 189.9821, Found: 189.9823.



4-Nitrobenzamide (2.36p): According to GP I: 4-Nitrobenzaldehyde (55 mg, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36p** as light yellow solid (40 mg, 65%). FTIR (KBr): $\tilde{\nu}$ = 3417, 3386, 3314, 3110, 2564, 2425, 2387, 1645, 1603, 1515, 1413, 1392, 1321, 1115, 1104, 870, 861, 783, 697, 497 cm^{-1}. ^{1}H NMR (600 MHz, CD_3OD) δ = 8.28 (d, *J* = 7.8 Hz, 2H), 8.05 (d, *J* = 7.8 Hz, 2H) ppm.^{13}C NMR (151 MHz, CD_3OD) δ = 168.9, 150.0, 139.6, 128.8, 123.4 ppm. HRMS: Exact mass calculated for $C_7H_6N_2O_3$ ($[M+H]^+$): 167.0451 Found: 167.0450.

4-(3-methylbut-2-enyloxy)benzamide (2.36q): According to GP I: 4-(3-methylbut-2-enyloxy)benzaldehyde (70 mg, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36q** as white solid (53 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 3381, 3167, 1647, 1617, 1604, 1570, 1512, 1423, 1395, 1304, 1247, 1180, 1145, 1117, 841, 804, 624, 492 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.09 (br. s, 2H), 5.49 - 5.45 (m, 1H), 4.55 (d, *J* = 6.6 Hz, 2H), 1.80 (s, 3H), 1.75 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 161.6, 138.6, 129.0, 125.1, 118.6, 114.2,



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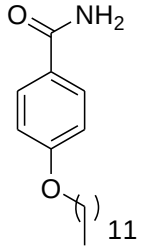
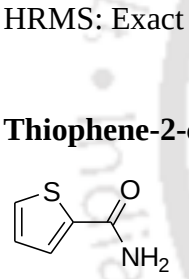
64.7, 25.6, 18.0 ppm. HRMS: Exact mass calculated for $C_{12}H1_5NO_2$ ($[M+H]^+$): 206.1176, Found: 206.1174.

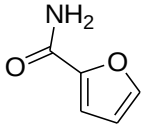
4-(dodecyloxy)benzamide (2.36r): According to GP I: 4-(dodecyloxy)benzaldehyde (0.10 g, 0.34 mmol), amine **2.35** (93 mg, 0.51 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36r** as white solid (74 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 3385, 3175, 2921, 2852, 1647, 1608, 1573, 1516, 1473, 1419, 1399, 1393, 1308, 1258, 1174, 1145, 1120, 1018, 842, 802, 621 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.13 (s, 1H), 5.84 (s, 1H), 3.98 (t, *J* = 6.6 Hz, 2H), 1.81 – 1.76 (m, 2H), 1.47 - 1.42 (m, 2H), 1.33 – 1.24 (m, 16H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.2, 162.4, 129.4, 125.4, 114.4, 68.4, 32.1, 29.9, 29.8, 29.8, 29.8, 29.5, 29.3, 26.1, 22.9, 14.3 ppm. HRMS: Exact mass calculated for $C_{19}H_{31}NO_2$ ($[M+H]^+$): 306.2428, Found: 306.2435.



Thiophene-2-carboxamide (2.36s): According to GP I: Thiophene-2-carbaldehyde (34 µL, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36s** as white solid (26 mg, 55%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.55 – 7.52 (m, 2H), 7.12 – 7.09 (m, 1H), 5.90 (br. s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.5, 130.8, 130.7, 129.1, 127.6 ppm. HRMS: Exact mass calculated for C_5H_5NOS ($[M+H]^+$): 128.0165, Found: 128.0165.



Furan-2-carboxamide (2.36t): According to GP I: Furan-2-carbaldehyde (30 µL, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL , 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36t** as white solid (29 mg,70%) . ^1H NMR (400 MHz, $CDCl_3$) δ = 7.46 – 7.45 (m, 1H), 7.14 (d, *J* = 3.6 Hz, 1H), 6.50 – 6.49 (m, 1H), 6.46 (s, 1H), 6.37 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 160.3, 147.5, 144.6, 115.5, 112.5 ppm. HRMS: Exact mass calculated for $C_5H_5NO_2$ ($[M+H]^+$): 112.0393, Found: 112.0399.



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Cinnamamide (2.36u):GP: According to GP I: Cinnamaldehyde (46 µL, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36u** as white solid (34 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 15.7 Hz, 1H), 7.52-7.50 (m, 2H), 7.38 - 7.36 (m, 3H), 6.46 (d, *J* = 15.7 Hz, 1H), 5.65 (br. s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.0, 142.8, 134.7, 130.2, 129.1, 128.1, 119.6 ppm. HRMS: Exact mass calculated for C_9H_9NO ($[M+H]^+$):148.0757, Found: 148.0759.

2-Methyl-3-phenylacrylamide (2.36v): According to GP I: 2-Methyl-3-phenylacrylaldehyde (51 µL, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36v** as white solid (39 mg , 65%). FTIR (KBr): $\tilde{\nu}$ = 3377, 3197, 2923, 1650, 1600, 1447, 1381, 1287, 1115, 923, 837, 755, 693, 674, 646, 520 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 - 7.31 (m, 6H), 6.01 (br. s, 2H), 2.12 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.0, 136.0, 135.5, 131.0, 129.6, 128.6, 128.2, 14.5 ppm. HRMS: Exact mass calculated for $C_{10}H_{11}NO$ ($[M+H]^+$): 162.0913, Found: 162.0914.

3,3-Diphenylacrylamide (2.36w) : According to GP I : 3,3-Diphenylacrylaldehyde (76 mg, 0.36 mmol), amine **2.35** (0.10 g, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36w** as white solid (56 mg, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.38 – 7.35 (m, 3H), 7.28 – 7.24 (m, 3H), 7.22 – 7.21 (m, 2H), 7.20 - 7.18 (m, 2H), 6.30 (s, 1H), 5.75 (s, 1H), 5.06 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.9, 151.2, 140.7, 138.3, 129.4, 129.3, 129.0, 129.0, 128.6, 128.2, 121.9 ppm. HRMS: Exact mass calculated for $C_{15}H_{13}NO$ ($[M+H]^+$): 224.1070, Found: 224.1065.

4-chlorobenzamide (**2.36j**): According to GP I: 4-Chlorobenzaldehyde (1.54 g, 11.05 mmol), amine **2.35** (3 g, 16 mmol) and triethylamine (154 µL, 1.10 mmol), were refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.36j** as white solid (1.1 g, 64%).

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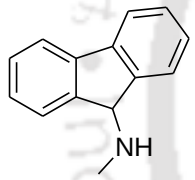
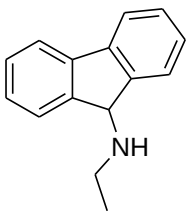
General procedure for the syntheses of secondary amines (GP II): A mixture of 9*H*-Fluoren-9-imine (1 eq.) and alkylamine (1 eq.) in DCM (2-3 mL) was stirred at room temperature for overnight. After completion of the reaction (checked by TLC), the reaction mixture was concentrated in vacuo. The residue was dissolved in diethyl ether and the organic layer was washed with H_2O (3 X 20 mL), dried (anhydrous Na_2SO_4) and concentrated in vacuo to obtain the desired imine. Without further purification, the imine was dissolved in MeOH. Sodium cyanoborohydride (2 eq.) and acetic acid were then added to the solution. The reaction mixture was heated at 40 ^oC for 1 h. After evaporation of MeOH, aq. NaOH (2M, 2 mL) was added into the crude mixture. The mixture was extracted with ethyl acetate (3 X 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vaccua and the crude product was subjected to SiO_2-column chromatography to obtain the analytically pure compounds.

***N*-Methyl-9*H*-fluoren-9-amine (2.38a)**: According to GP II: 9*H*-Fluoren-9-imine (0.01 g, 0.55 mmol) and methyl amine hydrochcloride (37 mg, 0.55 mmol) were dissolved in DCM (2 mL) to get the corresponding imine. Reduction of imine by sodium cyanoborohydride (130.6 mg, 2.1 mmol) in presence of acetic acid (100 µL) and column chromatography (silica gel, EtOAc:hexane, 1:1) gave secondary amine **2.38a** as colourless oil (180 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 2H), 4.63 (s, 1H), 1.96 (s, 3H), 1.91 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.0, 140.7, 127.9, 127.0, 124.6, 119.7, 64.1, 30.8 ppm. HRMS: Exact mass calculated for $C_{14}H_{13}N$ ($[M+H]^+$): 196.1121, Found: 196.1127.



***N*-Ethyl-9*H*-fluoren-9-amine (2.38b):** A mixture of amine **1** (0.10 g, 0.55 mmol) and acetaldehyde (20 µL, 0.36 mmol) in DCM (2 mL) was stirred overnight at rt. Then the reaction mixture was concentrated under vacuum, extracted with Et_2O and the combined organic layers were concentrated in vaccuo to get the corresponding imine. According to GP II, reduction of imine by sodium cyanoborohydride (60.8 mg, 0.96 mmol) in presence of acetic acid (100 µL) and column chromatography (silica gel, EtOAc:hexane, 1:1) gave secondary amine **2.38b** as colourless oil (90 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.23 – 7.19 (m, 2H), 7.18 – 7.14 (m, 2H),



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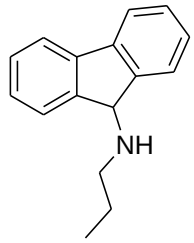
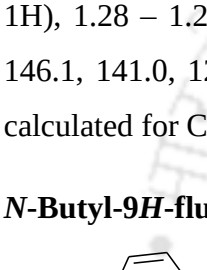
4.76 (s, 1H), 2.33 (q, *J* = 7.2 Hz, 2H), 1.85 (s, 1H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.2, 140.2, 127.5, 126.7, 124.2, 119.33, 62.9, 38.4, 15.3 ppm. HRMS: Exact mass calculated for $C_{15}H_{15}N$ ($[M+H]^+$): 210.1277, Found: 210.1272.

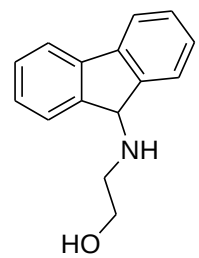
***N*-Propyl-9*H*-fluoren-9-amine (2.38c):** According to to GP II: 9*H*-Fluoren-9-imine (200 mg, 1.12 mmol) and *n*-propyl amine (92 µL, 1.1 mmol) were dissolve in DCM (3 mL) to get the corresponding imine. Reduction of imine by sodium cyanoborohydride (99 mg, 1.58 mmol) in the presence of acetic acid (100 µL) and column chromatography (silica gel, EtOAc:hexane, 1:1) gave secondary amine **2.38c** as colourless oil (150 mg, 84%) by. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 7.2 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 2H), 4.71 (s, 1H), 2.19 (t, *J* = 7.2 Hz, 2H), 1.82 (s, 1H), 1.28 – 1.24 (m, 2H), 0.67 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 146.1, 141.0, 128.2, 127.5, 125.0, 120.1, 63.8, 46.7, 24.1, 12.1 ppm. HRMS: Exact mass calculated for $C_{16}H_{17}N$ ($[M+H]^+$): 224.1434, Found: 224.1432.



***N*-Butyl-9*H*-fluoren-9-amine (2.38d):** According to GP II: 9*H*-Fluoren-9-imine (200 mg, 1.11 mmol) and normal butylamine (110 µL, 1.11 mmol) were dissolve in DCM (3 mL) to get the corresponding imine. Reduction of imine by sodium cyanoborohydride (120 mg, 1.91 mmol) in presence of acetic acid (100 µL) and column chromatography (silica gel, EtOAc:hexane, 1:1) gave secondary amine **2.38d** as colourless oil (200 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 7.1 Hz, 2H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.21– 7.17 (t, 2H), 4.78 (s, 1H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.84 (s, 1H), 1.36 – 1.23 (m, 2H), 1.24 – 1.08 (m, 2H), 0.80 – 0.64 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.7, 140.6, 127.8, 127.0, 124.6, 119.7, 63.4, 44.0, 32.7, 20.2, 13.9 ppm. HRMS: Exact mass calculated for $C_{17}H_{19}N$ ($[M+H]^+$): 238.1590, Found: 238.1589.



2-(9*H*-fluoren-9-ylamino)ethanol (2.38e): According to to GP II: 9*H*-Fluoren-9-imine (200 mg, 1.11 mmol) and 2-aminoethanol (67 µL, 1.11 mmol) were dissolve in DCM (3 mL) to get the corresponding imine. Reduction of imine by sodium cyanoborohydride (113 mg, 1.79 mmol) in the presence of acetic acid (100 µL) and column chromatography(silica gel; EtOAc:hexane, 1:1) gave secondary amine **2.38e** as white solid (190 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 7.4 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H),



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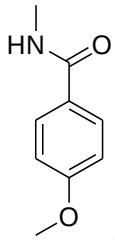
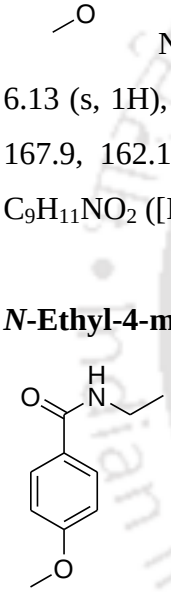
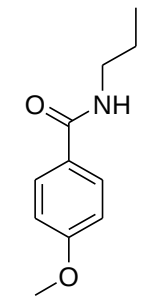
7.39 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 4.95 (s, 1H), 3.53 – 3.50 (m, 2H), 2.59 – 2.56 (m, 2H), 1.26 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.6, 140.3, 127.8, 126.9, 124.3, 119.5, 62.6, 61.1, 45.5 ppm. HRMS: Exact mass calculated for $C_{15}H_{15}NO$ ($[M+H]^+$): 226.1226, Found: 226.1226.

4-Methoxy-*N*-methylbenzamide (3.39a): According to GP I: 4-Methoxybenzaldehyde (18 µL, 0.15 mmol), amine **2.38a** (45 mg, 0.23 mmol) and triethylamine (4 µL, 0.03 mmol) was refluxed for 12 h and column chromatography (Silica gel, EtOAc:hexane; 1:1) gave **2.39a** as white solid (16 mg, 61%). FTIR (KBr): $\tilde{\nu}$ = 3442, 1628, 1606, 1554, 1506, 1408, 1255, 1182, 1031, 845, 769, 607 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.13 (s, 1H), 3.84 (s, 3H), 2.99 (d, *J* = 5.4 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.9, 162.1, 128.7, 126.8, 113.8, 55.6, 27.0 ppm. HRMS: Exact mass calculated for $C_9H_{11}NO_2$ ($[M+H]^+$): 166.0863, Found: 166.0872.



***N*-Ethyl-4-methoxybenzamide (2.39b)**: According to GP I: 4-Methoxybenzaldehyde (31 µL, 0.25 mmol), amine **2.38b** (80 mg, 0.38 mmol) and triethylamine (7 µL, 0.05 mmol) was refluxed for 15 h and column chromatography (silica gel, EtOAc:hexane, 1:2) gave **2.39b** as white solid (27 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 3442, 1633, 1547, 1505, 1304, 1255, 1180, 1028, 844, 768, 607 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.21 (s, 1H), 3.83 (s, 3H), 3.49-3.43 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.0, 162.0, 128.6, 127.0, 113.6, 55.4, 34.9, 14.9 ppm. HRMS: Exact mass calculated for $C_{10}H_{13}NO_2$ ($[M+H]^+$): 180.1019, Found: 180.1014.





4-Methoxy-*N*-propylbenzamide (2.39c): According to GPI: 4-Methoxybenzaldehyde (54 µL, 0.45 mmol), amine **2.38c** (150 mg, 0.67 mmol) and triethylamine (12 µL, 0.08 mmol) was refluxed for 24h and column chromatography (silica gel, EtOAc:hexane, 1:3) gave **2.39c** as colourless oil (50 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 3434, 2962, 2925, 1633, 1546, 1505, 1302, 1256, 1179, 1108, 1030, 845, 769, 608 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.15 (s, 1H), 3.84 (s, 3H), 3.42 – 3.37 (m,

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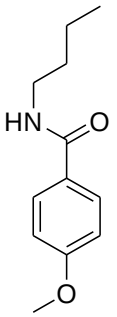
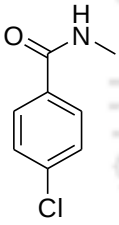
2H), 1.67 – 1.57 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.6, 161.5, 128.1, 126.5, 113.2, 54.9, 41.2, 22.5, 11.0 ppm. HRMS: Exact mass calculated for$C_{11}H_{15}NO_2$ ($[M+H]^+$): 194.1176, Found: 194.1179

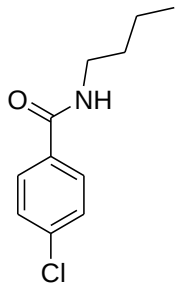
***N*-Butyl-4-methoxybenzamide (2.39d)**: According to GP I: 4-Methoxybenzaldehyde (34 µL, 0.28 mmol), amine **2.38d** (100 mg, 0.42 mmol) and triethylamine (7 µL, 0.05 mmol) was refluxed for 28 h and column chromatography (silica gel, EtOAc:hexane, 1:4) gave **2.39d** as colourless oil (33 mg, 57%). FTIR (KBr): $\tilde{\nu}$ = 3420, 2256, 2129, 1649, 1439, 1286, 1112, 1047, 1030, 1025, 998, 926, 865, 750, 686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.72 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.10 (s, 1H), 3.84 (s, 3H), 3.45 – 3.40 (m, 2H), 1.62 – 1.55 (m, 2H), 1.45 – 1.35 (m, 2H), 0.94 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.1, 162.0, 128.6, 127.0, 113.7, 55.4, 39.7, 31.8, 20.2, 13.8 ppm. HRMS: Exact mass calculated for $C_{12}H1_7NO2$ ($[M+H]^+$): 208.1332, Found: 208.1334



4-Chloro-*N*-methylbenzamide (2.39e): According to GP I: 4-Chlorobenzaldehyde (24 mg, 0.17 mmol), amine **2.38a** (50 mg, 0.25 mmol) and triethylamine (4 µL, 0.03 mmol) was refluxed for 12 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.39e** as white solid (18 mg, 62%). FTIR (KBr): $\tilde{\nu}$ = 3339, 1638, 1601, 1552, 1488, 1405, 1323, 1300, 1164, 1091, 1020, 840, 752, 623, 521 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 6.30 (s, 1H), 2.99 (d, *J* = 4.8 Hz 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.0, 137.4, 132.7, 128.6, 128.1, 26.7 ppm. HRMS: Exact mass calculated for C_8H_8ClNO ($[M+H]^+$): 170.0367, Found: 170.0362.



***N*-Butyl-4-chlorobenzamide (2.39f)**: According to GP I : 4-Chlorobenzaldehyde (18 mg, 0.12 mmol), amine **2.38d** (46 mg, 0.19 mmol) and triethylamine (3 µL, 0.02 mmol) was refluxed for 28 h and column chromatography (silica gel, EtOAc:hexane, 1:4) gave **2.39f** as colourless oil (17 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 3415, 2256, 2129, 1649, 1439, 1286, 1112, 1047, 1025, 998, 826, 765, 686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 3.46 – 3.41 (m, 2H), 1.63 –



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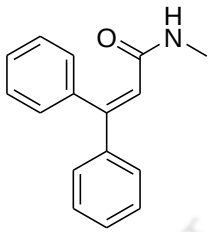
1.55 (m, 2H), 1.45 – 1.35 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.6, 137.7, 133.4, 129.0, 128.5, 40.11, 31.9, 20.3, 14.0 ppm. HRMS: Exact mass calculated for $C_{11}H_{14}ClNO$ ($[M+H]^+$): 212.0837, Found: 212.0837.

***N*-Methyl-3,3-diphenylacrylamide (2.39g)**: According to GP I: 3,3-Diphenylacrylaldehyde (71 mg, 0.34 mmol), amine **2.38a** (100 mg, 0.51 mmol) and triethylamine (9 µL, 0.07 mmol), was refluxed for 15 h and column chromatography (silica gel, EtOAc:hexane, 1:2) gave **2.39g** as colourless oil (42 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 3453, 2924, 1642, 1446, 1102, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 – 7.45 (m, 3H), 7.38 – 7.34 (m, 4H), 7.32 – 7.30 (m, 3H), 6.41 (s, 1H), 5.24 (s, 1H), 2.67 (d, *J* = 5.2 Hz 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.4, 149.6, 140.6, 138.8, 129.9, 129.3, 128.9, 128.6, 128.4, 128.0, 122.4, 26.2 ppm. HRMS: Exact mass calculated for $C_{16}H15NO$ ($[M+H]^+$): 238.1226, Found: 238.1225.



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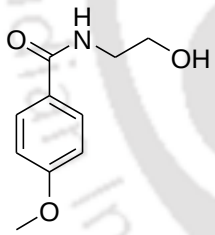
***N*-(2-hydroxyethyl)-4-methoxybenzamide (2.39h):** According to GP I: 4-Methoxybenzaldehyde (36 µL, 0.29 mmol), amine **2.38e** (100 mg, 0.29 mmol) and triethylamine (8 µL, 0.05 mmol), was refluxed for 40 h and column chromatography (silica gel, EtOAc: hexane, 1:3) gave **2.39h** as colourless liquid (32 mg, 55%). FTIR (KBr): $\tilde{\nu}$ = 3436, 2926, 1712, 1645, 1607, 1512, 1450,1256, 1170, 1075, 1028, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.40 (t, *J* = 9.6 Hz, 2H), 4.03 (t, *J* = 9.6 Hz, 2H), 3.84 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.5, 162.00, 129.9, 120.1, 113.7, 67.5, 55.3, 54.7 ppm. HRMS: Exact mass calculated for $C_{10}H_{13}NO_3$ ($[M+H]^+$): 196.0968 , Found: 196.0792.



General procedure for *in situ* transamidation (GP III): According to GP I: Aryl aldehyde (0.36 mmol), amine **2.35** (100 mg, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h. After disappearance of the starting materials (checked by TLC) solvent was evaporated and reaction mixture was transferred to a closed tube. Amine (3 eq.) and benzoic acid (10 mol %) were added into the reaction mixture. Reaction mixture

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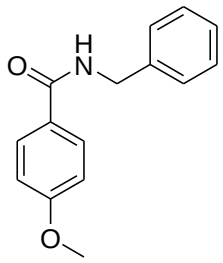
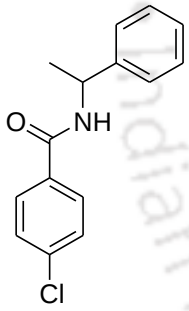
heated at 130 ^{o}C for 30 h. Then crude mixture was purified by column chromatography (silica gel).

***N*-Benzyl-4-methoxybenzamide (2.39i)**: According to GP III: 4-Methoxybenzaldehyde (45 µL, 0.36 mmol), amine **2.35** (100 mg, 0.55 mmol), and triethylamine (5 µL, 0.03 mmol)



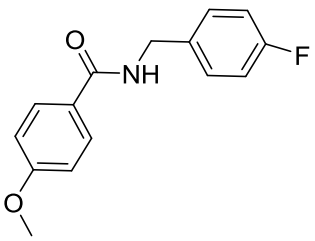
was refluxed for 1.5 h followed by addition of benzylamine (120 µL, 1.1 mmol) and benzoic acid (5 mg, 0.03 mmol) and heated for 30h and column chromatography (silica gel, EtOAc:hexane, 1:3) gave **2.39i** as white solid (54 mg, 60%). FTIR (KBr): $\tilde{\nu}$ = 3266, 3057, 2956, 2837, 1632, 1607, 1558, 1508, 1449, 1441, 1419, 1408, 1268, 1254, 1179, 1119, 1055, 1030, 842, 723, 696, 686, 632, 592, 530 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.8 Hz, 2H), 7.34 – 7.27 (m, 5H), 6.90 (d, *J* = 8.9 Hz, 2H), 6.48 (br. s, 1H) 4.61 (d, *J* = 5.6 Hz, 2H), 3.83 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.0, 162.4, 138.6, 128.94, 128.91, 128.1, 127.7, 126.8, 113.9, 55.6, 44.2 ppm. HRMS: Exact mass calculated for $C_{15}H_{15}NO_2$ ($[M+H]^+$): 242.1176, Found: 242.1174.

4-Chloro-*N*-(1-phenylethyl)benzamide (2.39j): According to GP III: 4-



Chlorobenzaldehyde (51 mg, 0.36 mmol), amine **2.35** (100 mg, 0.55 mmol) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h followed by addition of 1-phenylethanamine (140 µL, 1.10 mmol) and benzoic acid (5 mg, 0.03 mmol) and heated for 30 h and column chromatography (silica gel, EtOAc:hexane, 1:3) gave **2.39j** as white solid (58 mg, 62%). FTIR (KBr): $\tilde{\nu}$ = 3256, 3047, 2956, 2838, 1632, 1607, 1590, 1508, 1449, 1442, 1419, 1408, 1268, 1254, 1212, 1179, 1119, 1055, 1030, 842, 770, 723, 696 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 5.2 Hz, 2H), 7.39 – 7.26 (m, 7H), 6.32 (s, 1H), 5.34 – 5.30 (m, 1H), 1.62 (d, *J* = 5.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.7, 143.1, 143.1, 137.9, 133.1, 129.0, 128.6, 127.8, 126.4, 49.6, 21.8 ppm. HRMS: Exact mass calculated for $C_{15}H_{14}ClNO$ ($[M+H]^+$): 260.0837, Found: 260.0850

***N*-(4-fluorobenzyl)-4-methoxybenzamide (2.39k)**: According to GP III: 4-



methoxybenzaldehyde (45 µL, 0.36 mmol), amine **2.35** (100 mg, 0.55 mmol), and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h followed by addition of (4-fluorophenyl) methanamine (126 µL, 1.10 mmol) and benzoic acid (5 mg, 0.03 mmol) and heated for 30 h and column chromatography (silica gel,

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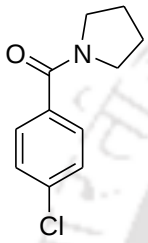
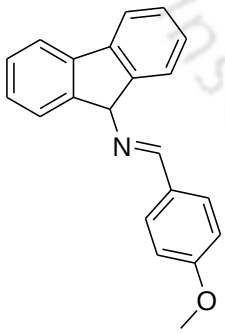
EtOAc:hexane, 1:3) gave **2.39k** as white solid (60 mg, 64%). FTIR (KBr): $\tilde{\nu}$ = 3272, 2969, 2842, 1631, 1607, 1560, 1511, 1423, 1330, 1258, 1178, 1157, 1027, 990, 842, 812, 776, 683, 499 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8.8 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.02 -6.98 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.56 (d, *J* = 5.6 Hz, 2H), 3.83 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.6, 163.0, 161.9, 160.6, 133.9, 133.9, 129.2, 129.1, 128.4, 126.1, 115.3, 115.1, 113.4, 55.1, 42.9 ppm. HRMS: Exact mass calculated for $C_{15}H_{14}FNO_2$ ($[M+H]^+$): 260.1081, Found: 260.1081.

(4-chlorophenyl)(pyrrolidin-1-yl)methanone (2.39l): According to GP III: 4-chlorobenzaldehyde (51 mg, 0.36 mmol), Amine **2.35** (100 mg, 0.55 mmol), and trimethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h followed by addition of pyrrolidine (90 µL, 1.1 mmol) and benzoic acid (5 mg, 0.03 mmol) and heated for 30 h and column chromatography (silica gel, EtOAc : hexane, 1:3) gave **2.39l** as white solid (42 mg, 55%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.58 (t, *J* = 5.5 Hz, 2H), 3.37 (t, *J* = 5.3 Hz, 2H), 1.92 – 1.81 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.4, 135.6, 135.3, 128.5, 128.3, 49.5, 46.1, 26.2, 24.2 ppm. HRMS: Exact mass calculated for $C_{11}H_{12}ClNO$ ($[M+H]^+$): 210.0680, Found: 210.0681.



***N*-(4-methoxybenzylidene)-9*H*-fluoren-9-amine (2.40)**: 4-methoxybenzaldehyde (169 µL, 1.39 mmol) and amine **2.35** (230 mg, 1.27 mmol) were dissolved in toluene (3 mL) and stirred at rt in presence of MS 4A° (200 mg). After 1 h, reaction mixture was filtered and toluene was evaporated to get white solid. Crude product was purified by washing with DCM-hexane (1:50) to give analytically pure **2.40** as white solid (300 mg, 72%)**.** ^1H NMR (600 MHz, $CDCl_3$) δ = 8.74 (s, 1H), 7.80 -7.79 (m, 4H), 7.45 – 7.43 (m, 4H), 7.34 (d, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 7.2 Hz, 2H), 5.41 (s, 1H), 3.85 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.3, 159.1, 142.2, 138.1, 127.3, 126.2, 125.6, 124.7, 122.5, 117.3, 111.2, 72.0, 52.6 ppm. HRMS: Exact mass calculated for $C_{21}H_{17}NO$ ($[M+H]^+$): 300.1383, Found: 300.1384.



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Methyl-4-carbamoylbenzoate (2.42): According to GP I: Methyl-4-formylbenzoate (60 mg, 0.36 mmol), amine **2.35** (100 mg, 0.55) and triethylamine (5 µL, 0.03 mmol) was refluxed for 1.5 h and column chromatography (silica gel, EtOAc:hexane, 1:1) gave **2.42** as white solid (48 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 3407, 3194, 3018, 2963, 1725, 1659, 1623, 1572, 1506, 1435, 1420, 1281, 1196, 1114, 1017, 961, 869, 774, 732, 714 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 2H), 6.17 (s, 1H) 5.91 (s, 1H), 3.95 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.0, 165.8, 132.1, 129.0 (2C), 127.4, 51.9 ppm. HRMS: Exact mass calculated for $C_9H_{10}NO_3$ ($[M+H]^+$): 180.0655, Found: 180.0655.

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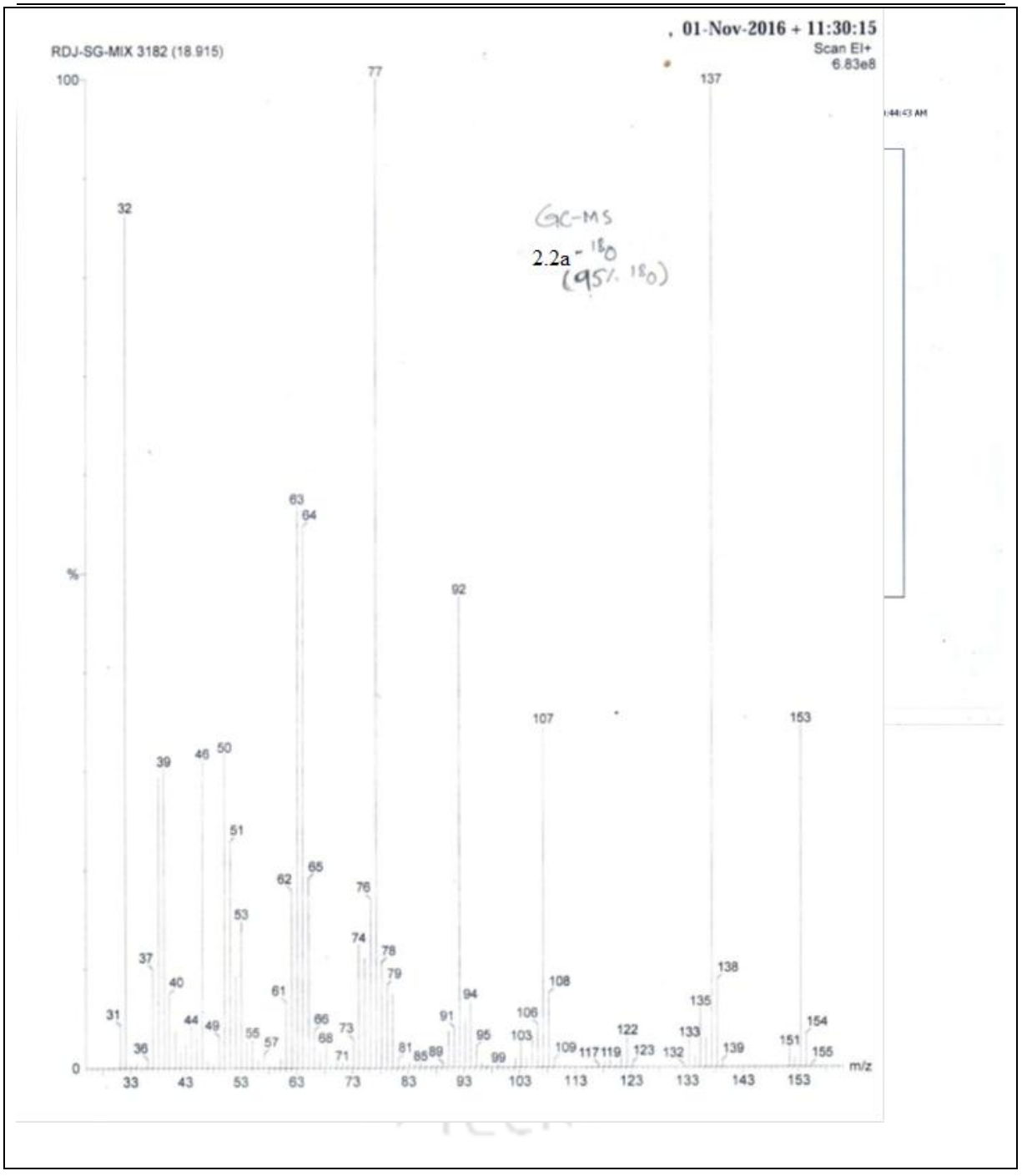
RDJ-SG-MIX 3182 (18.915)
01-Nov-2016 + 11:30:15
Scan EI+
6.83e8
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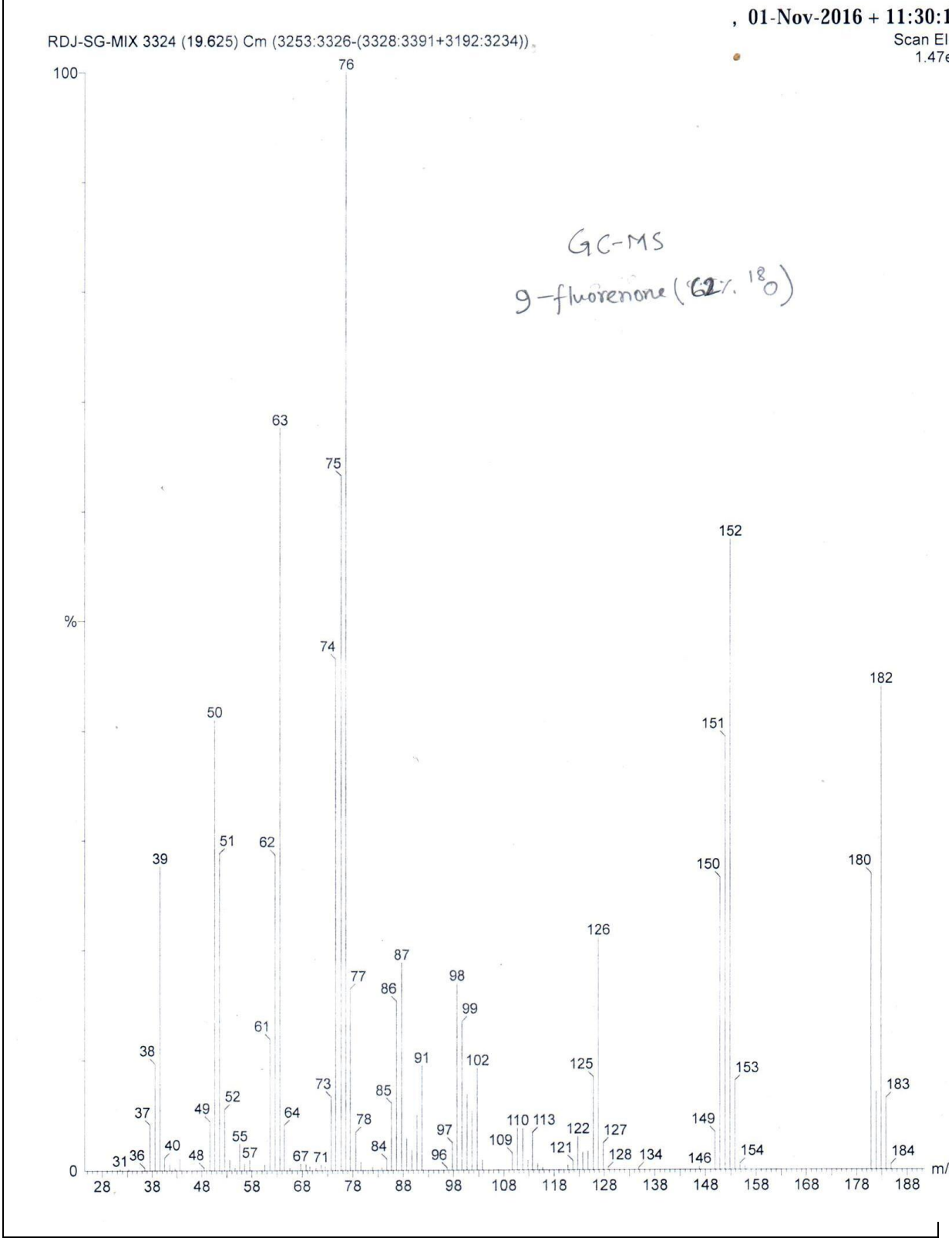

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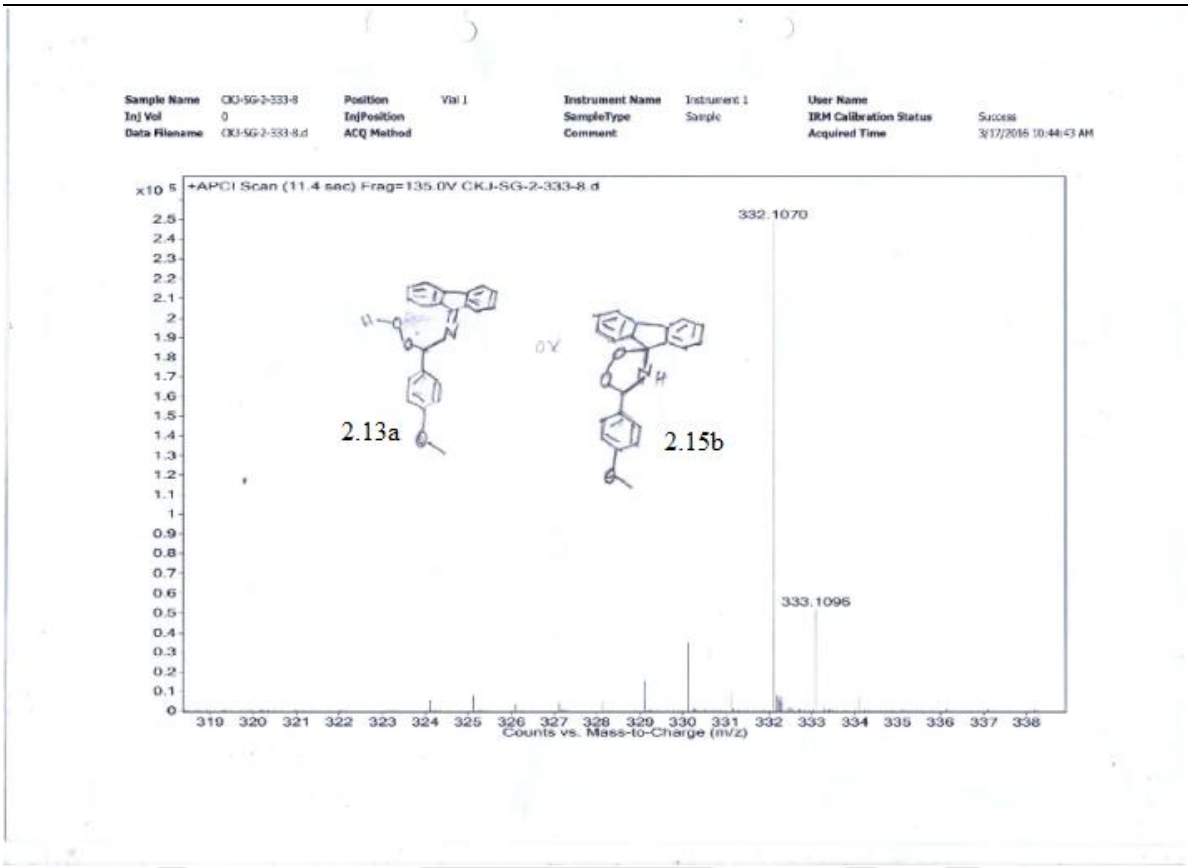

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CHAPTER 3

Metal Free Thermal Activation of Molecular Oxygen Enabled Direct α-CH_2-Oxygenation of Free Amines

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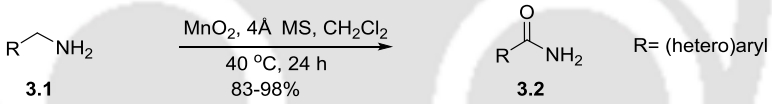
3.1 Introduction:

Amides and lactams are ubiquitously found as the core structural unit of both natural and synthetic molecules which are relevant to advanced materials and medicines.[1] Conventional methods for the amide synthesis utilize coupling reaction of carboxylic acids or its activated derivatives with amines in the presence of coupling reagents which produce a stoichiometric amount of byproducts.[2] To avoid this drawback, amidation reactions using catalytic amounts of coupling reagents have been developed.[3] Additionally, conversions of alcohol and aldehyde,[4,5] oximes and nitrile,[6] α-keto acids, and α-bromo nitroalkanes[7] to amides were developed as alternative direct methods. However, a relatively fewer number of examples were known for the direct oxidation of the α-methylene group of free amines to corresponding amides because of the higher reactivity of the amine moiety.

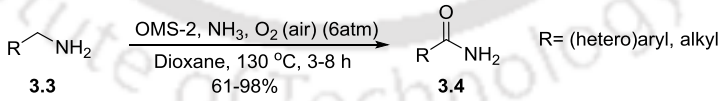
3.2 Known reported methods for amide synthesis from amine:

Mountford and coworkers reported a manganese dioxide mediated oxidation of benzylamines **3.1** to the corresponding amides **3.2** under mild reaction conditions. (**Scheme1**)[8f].



Scheme1: Conversion of benzylamines to benzamide

Mizuno *et al.* reported manganese oxide-catalyzed transformation of primary amines **3.3** to primary amides **3.4** through the sequence of oxidative dehydrogenation and successive hydration (**Scheme 2**) [6b].



Scheme 2: Synthesis of primary amides from primary amines

Nishinga *et al.* reported a novel synthetic route to amides **3.7** from arylmethylamines **3.5** *via* Schiff bases derived from amines **3.5** and 2,6-di-*t*-butyl-p-benzoquinone **3.6**. Condensation of the arylmethylamines and 2, 6-di-*t*-butyl-*p* -benzoquinone gives the 4-(*N*-arylmethyleneamino)- 2,6-di-t-butylphenols which on base-catalyzed oxygenation leads to the formation of the amides (**Scheme 3**) [9e].

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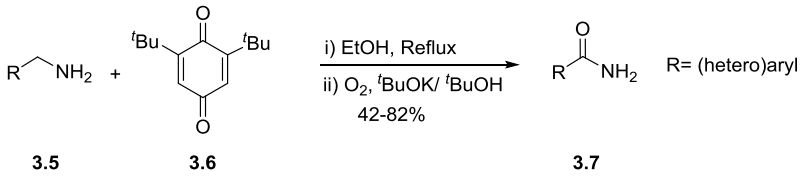
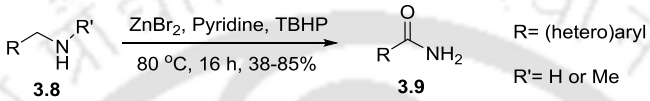


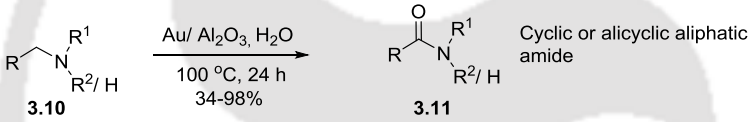
Scheme 3: Synthesis of benzamide from benzylamine

Beller and coworkers reported a novel Lewis acid-catalyzed oxidation of benzylamine derivatives **3.8** to the corresponding amides **3.9**. Using 10 mol % of $ZnBr_2$ or $FeCl_3$ as the catalyst and TBHP as the oxidant, amides were produced under mild conditions (**Scheme 4**)[8c].



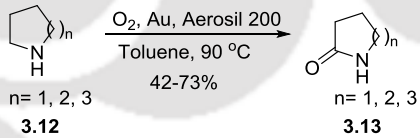
Scheme 4: Synthesis of benzylamine to amide by Beller *et al.*

Mizuno and coworkers reported the use of gold nanoparticles for efficient α-oxygenation of secondary and tertiary amines **3.10** into amides **3.11**. (**Scheme** 5)[9d].



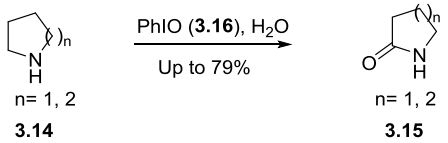
Scheme 5: Alpha-oxygenation of secondary and tertiary amines into amides

Woo and coworkers reported gold nanoparticles catalyzed conversion of cyclic amines **3.12** to lactams **3.13** by (**Scheme 6**) [9a].



Scheme 6: Conversions of cyclic amines to lactams

Moriartoy and coworkers reported the oxidation of cyclic amines **3.14** [pyrrolidine and piperidine] by iodosobenzene (**3.16**) in water led to lactams **3.15** [2-pyrrolidinone and valerolactam respectively] (**Scheme** 7)[8a].



Scheme 7: Synthesis of cyclic amides from cyclic amines

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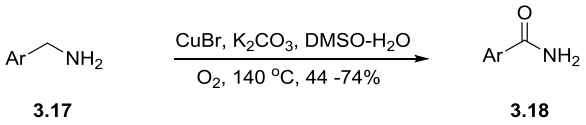
Fu and co-workers developed a copper-catalyzed aerobic oxidative method for the synthesis of primary aryl amides **3.18** from (aryl)methanamines **3.17** by molecular oxygen. (Scheme-8).[9b]

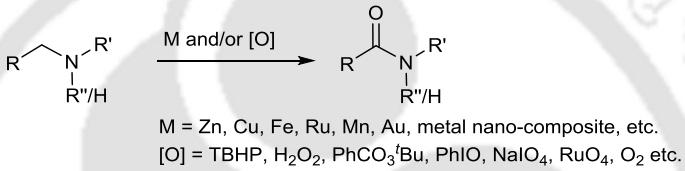


3.17 **3.18**

Scheme 8: Copper-catalyzed aerobic oxidative amide synthesis

3.3 Summary of known methods for amine oxidation

The known examples primarily involve metal-based reagents/catalysts or hazardous inorganic and organic oxidants.[8,9]



Scheme 9. Synthesis of amides and lactams from amines.

Molecular oxygen would be a viable substitute for hazardous inorganic or organic oxidants. However, photochemical or metal-mediated activation is generally required to activate kinetically inert oxygen before its reaction with other organic molecules.[10] Therefore, in some cases, molecular oxygen acts as the viable oxidant only in the presence of sophisticated metallic reagents/ catalysts.[9] Importantly, *α*-oxygenation of free amines to amides is generally hard to achieve due to the associated side reactions producing corresponding imines and nitriles, and thus protection of amine moiety is required before oxidation reaction.[11] Therefore, the development of novel methodology for direct oxygenation of amines that work under the conditions free of metallic reagents/catalysts and hazardous oxidants avoiding undesired side reaction would be of particular importance.

3.4 Background for the present work:

A biomimetic domino amination-oxygenation strategy for direct conversion of aldehydes to amides has been developed recently by our group (eq 1)[5]. An azomethine ylide related to **3.19a**,[5,12] which was formed from aldehyde and fluorenyl amine, reacted with molecular oxygen/air to provide the corresponding amide. We anticipated the formation of an iminium ion **3.19b**/zwitterion **3.19c** from the reaction of an aliphatic amine with the suitable ketone or its derivatives (eq 2).[12] Subsequent reaction of intermediate zwitterion **3.19c** with

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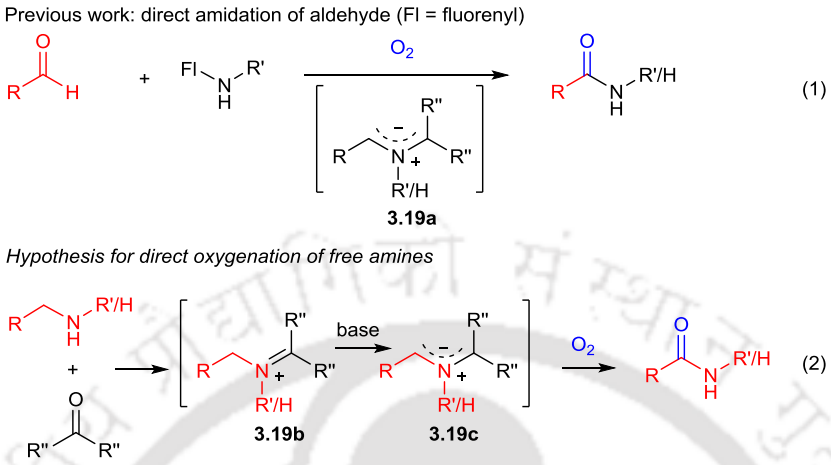
molecular oxygen could furnish desired amides. In this way, direct α-oxygenation of free amines to amides can be achieved under metal and oxidant free conditions without forming undesired side products, such as imines and nitriles.



Scheme 10: Previous work and hypothesis of present work

3.5 Initial result and optimization of reaction condition:

The investigation started with a reaction of benzylamine and 9-fluorenone (**3.20a**) in the presence of molecular oxygen (Table 1). However, the expected benzamide (**3.21a**) was not formed (entry 1). Similarly, the reactions in the presence of various other carbonyl compounds were also found to be unsuccessful in providing the desired benzamide. Interestingly, benzylamine reacted with 9-fluorenone in the presence of Bronsted acid and molecular oxygen to provide the desired amide with a maximum 40% isolated yield (entry 2). This indicated that the initial imine formation from the amine and carbonyl compound is crucial in achieving the α-oxygenation of amines. Then it was decided to use 9*H*-fluoren-9-imine (**3.20b**) instead of 9-fluorenone (**3.20a**) to facilitate the imine formation via transimination reaction with benzylamine. Expectedly, the desired benzamide (**3.21a**) was isolated with 62% yield from the reaction of benzylamine with 9*H*-fluoren-9-imine in refluxing toluene for 4 h under oxygen environment (entry 3). An increase in the yield to 70% was observed upon an increase in the reaction time to 12 h (entries 4, 5, 7). Further improvement of the yield was not observed employing other reaction conditions using different solvents, temperatures, etc. The slightly lower yield was obtained from the reaction in the presence of air as compared to the reaction carried out in the presence of oxygen (entry 13).

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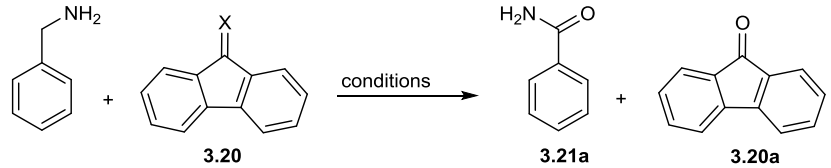
Table 1: Screening of reaction conditions.[a]



3.20 **3.21a** **3.20a**

3.20a: X = O and **3.20b**: X = NH

entry	conditions	Isolated yield (%)
1	**3.20a**, oxygen, toluene, RT, 24 h	0
2[b]	**3.20a**, oxygen, amberlyst-15, toluene, reflux, 24 h	40
3	**3.20b**, oxygen, toluene, reflux, 4 h	62
4	**3.20b**, oxygen, toluene, reflux, 8 h	67
5	**3.20b**, oxygen, toluene, reflux, 12 h	70
6	**3.20b**, oxygen, toluene, 80 ^{o}C, 24 h	65
7	**3.20b, oxygen, toluene, reflux, 24 h**	**70**
8[c]	**3.20b**, oxygen, toluene, reflux, 24 h	25
9	**3.20b**, oxygen, benzene, reflux, 24 h	65
10[d]	**3.20b**, oxygen, Et_3N, toluene, reflux, 12 h	70
11	**3.20b**, oxygen, xylene, reflux, 12 h	70
12	**3.20b**, oxygen, xylene, 110 ^{o}C, 12 h	69
13[e]	**3.20b**, toluene 110 ^{o}C, 12 h	57
14[d, e]	**3.2b**, toluene 110 ^{o}C, Et_3N, 12 h	48
15	**3.20b**, oxygen, ^{t}BuOK, toluene, reflux, 12 h	72
16	**3.20b**, oxygen, DCM, reflux, 24 h	15
17	**3.20b**, oxygen, toluene, RT, 24 h	5

[a]Amine (0.56 mmol) was reacted with **3.20** (0.56 mmol) in air or oxygen atmosphere. [b]Use of 50 mol% of the 2a provided only 35% yield. [c]Catalytic (20 mol%) amount of 2b was used. [d]Reactions were carried out in the presence of 20 mol% of triethylamine. [e]Reactions were performed in the presence of an air balloon.

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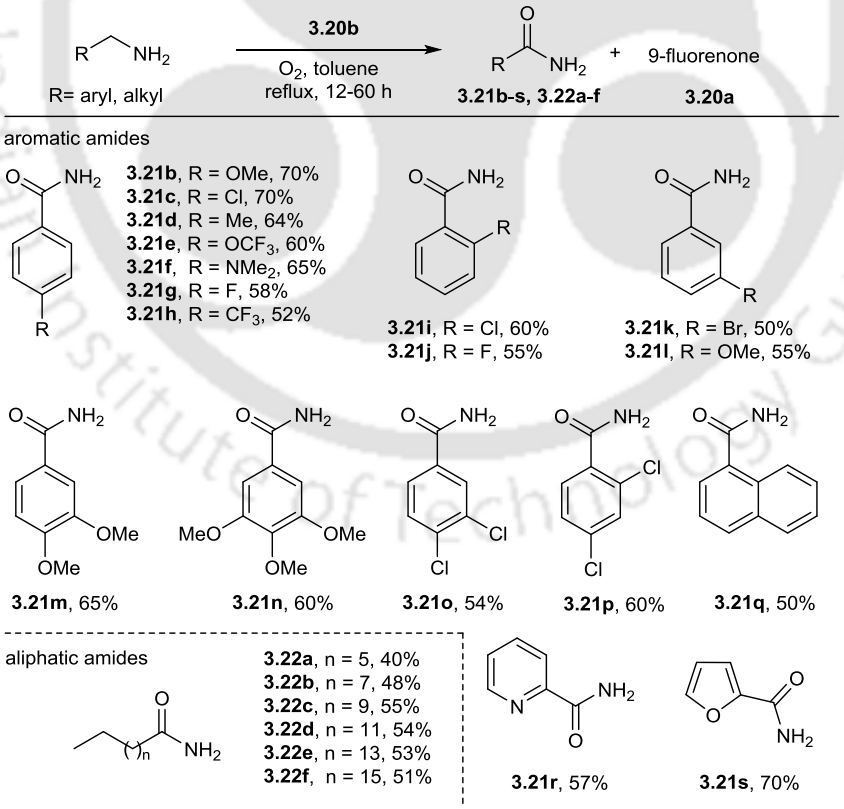
3.6 Substrate scope for primary amide:

Next, the best conditions were used to investigate the substrate scope of this novel amidation reaction (**Scheme 11**). Arylmethylamines having electron-donating as well as electron-withdrawing groups at different positions of aryl moiety provided the desired benzamides **3.21b-q** with good to moderate yields. Amines containing heteroaryl groups like picolylamine or 2-amino furan also reacted smoothly to afford corresponding amides **3.21r** and **3.21s**, respectively. Importantly, selective α-oxygenation of amines occurred to provide the corresponding amides while other reactive hetero-functional groups (e.g., –OR, -Br, -F, -Cl, -NMe_2) remained unreacted.

The scope of direct C-H oxygenation of unactivated aliphatic primary amines was tested next. Accordingly, the long-chain aliphatic primary amines with varying chain lengths were reacted to obtain corresponding amides **3.22a-f**. Higher reaction time (60 h) was required to obtain the amides with moderate to good yields.



Scheme 11. Scope of oxygenation of primary aromatic and aliphatic amines.

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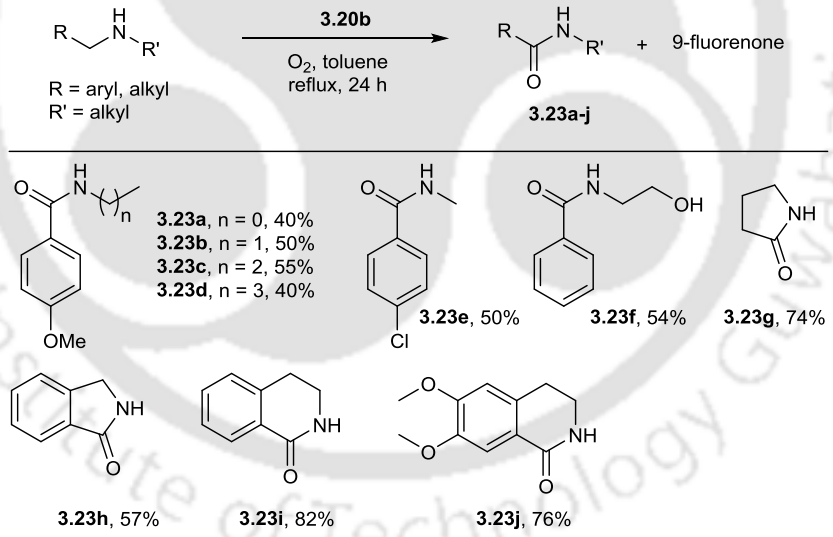
3.7 Substrate scope for secondary amine:

With success in oxygenation of primary amines, reactions using secondary amines were carried out to examine the generality of this method (Scheme 12). Oxidation of cyclic and acyclic aliphatic secondary amines occurred smoothly to yield corresponding secondary benzamides **3.23a-f** and lactams **3.23g-j**, respectively. A longer reaction time (24 h) of secondary amines as compared to that of primary benzylamines was necessary for good conversion due to the reduced reactivity of sterically demanding secondary amines. However, N-substituted benzamides **3.23a-f** were isolated with slightly lower yields as compared to lactams. Interestingly, *α*-C-H oxygenation of pyrrolidine was achieved using 9-fluorenone to obtain γ-lactam with 60% isolated yield. However, better yields of the lactams were obtained using 9*H*-fluoren-9-imine (**3.20b**). Tetrahydroisoquinoline gave the highest yield (82%) of the desired lactam.



Scheme 12. Scope in the oxidation of secondary acyclic and cyclic amines.

To demonstrate the synthetic utility of this method, a reaction of benzylamine was carried out in gram scale (1.8 g) under optimized conditions to afford the desired benzamides (**3.21a)** in grams quantity (1.1 g). 9-fluorenone, which was produced (with 88%) as the only by product, can be easily separated *via* simple washing and recycled after its conversion to 9*H*-fluoren-9-imine **3.20b**.

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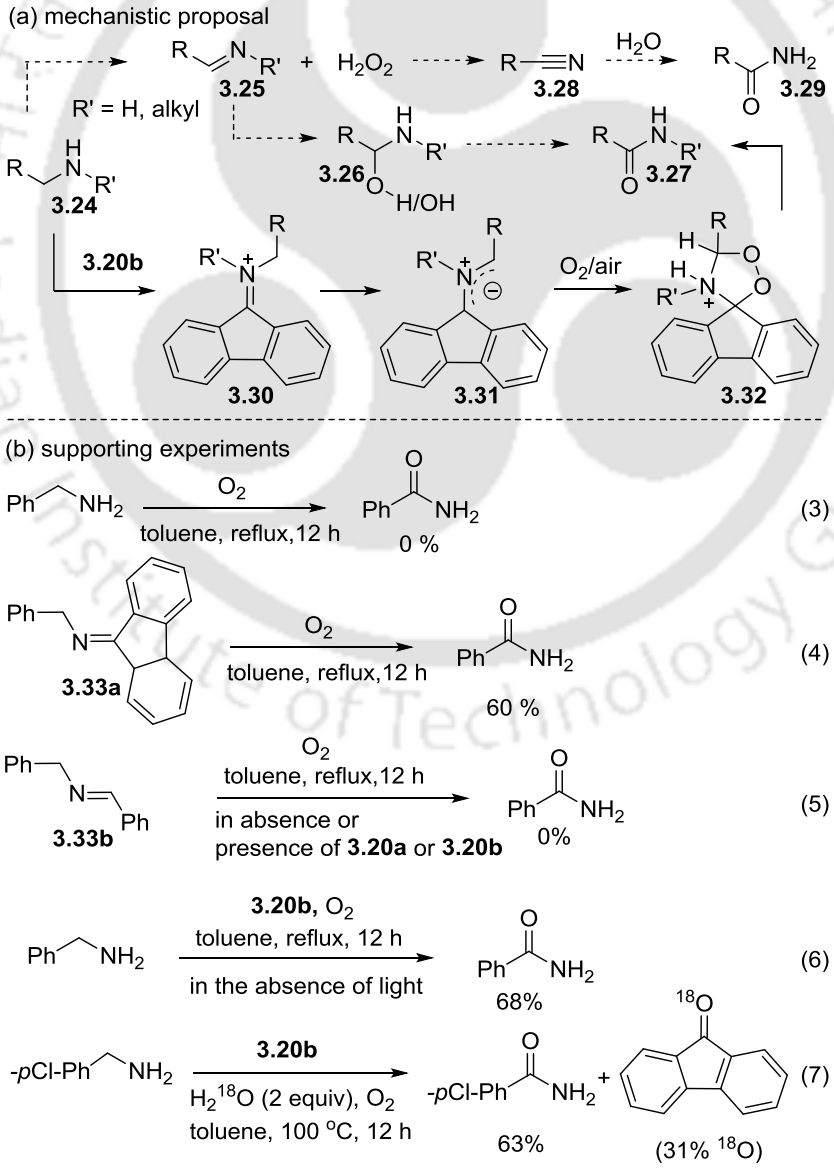
3.8 Controlled reaction and proposed mechanism:

Different mechanistic possibilities, which are shown in **Scheme 13a**, may be operative for the direct conversion of amines to corresponding amides and lactams. Direct oxidation of amines **3.24** by molecular oxygen followed by reaction of resulting imines **3.26** (*via* **3.27**) under oxidizing conditions may lead to corresponding amides **3.27**.[13] Conversion of imines **3.25** to corresponding nitriles **3.28** and its subsequent hydrolysis could also be another pathway for the formation of amide **3.29**. These mechanistic possibilities can be eliminated as the reaction of the only benzylamine under optimized conditions did not produce the desired amide (**Scheme 13b,** eq 3). On the other hand, the reaction of preformed imine **3.33a** under the same reaction conditions provided the desired benzamide with 60% yield (eq 4).



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Scheme 13. (a) Proposed mechanism. (b) Controlled and labelling experiments.

However, the yield of benzamide increased to 72% when the reaction was carried out in the presence of a catalytic amount of triethylamine. Therefore, the reaction proceeded through the imine/iminum ion **3.33**, which could be formed from the condensation of amine **3.26** and 9*H*-fluoren-9-imine (**3.20b**). Amine assisted deprotonation of **3.30** to form the azomethine anion/ylide **3.31** which subsequently reacted with molecular oxygen to provide the peroxide intermediate **3.32**.[12g] Related 1,2,4-dioxazolidine were known to be prepared from the reaction of *α*-hydroperoxy-amine with carbonyl compounds and from the reaction of carbonyl oxide with imine.[14] Thermal disintegration of peroxide **3.32** provided the desired amide/lactam and 9-fluorenone.[5, 14] Interestingly, imine **3.33b** derived from benzaldehyde and benzylamine did not provide the desired amides under the standard conditions (eq 5). Therefore, the easy formation of azomethine anion/ylide **3.31** and its enhanced stability due to the aromatic nature of fluorenyl anion turned out to be crucial for this transformation.

Alternatively, imine/iminum ion **3.30** or its regioisomer could participate in an Alder-ene reaction with singlet oxygen[15] to produce corresponding hydroperoxides, which could subsequently react directly or through the formation of **3.32** to provide the desired amide. However, the reaction of imine **3.33b** in the presence of either **3.20a** or **3.20b** did not produce the desired amide under standard reaction condition (eq 5). Moreover, the desired amide was formed with 68% from a reaction which was carried out without exposing the reaction mixture to the light (eq 6). Therefore, these observations are unsupportive to the singlet-oxygen-ene reaction pathway.

p-Chlorobenzylamine and **3.20b** were reacted under standard reaction conditions in the presence of H_2O^{18} to identify the source of amide oxygen (eq 7). Expectedly, the formation of ^{18}O-amide was not observed, which supported our proposed mechanism that the amide oxygen has been incorporated from molecular O_2 and not from H_2O. Incorporation of 31% ^{18}O into 9-fluorenone occurred through the partial hydrolysis of 9*H*-fluoren-9-imine in the presence of $H_2{}^{18}O$.

3.9 Application in syntheses of medicinal drugs and their derivatives:

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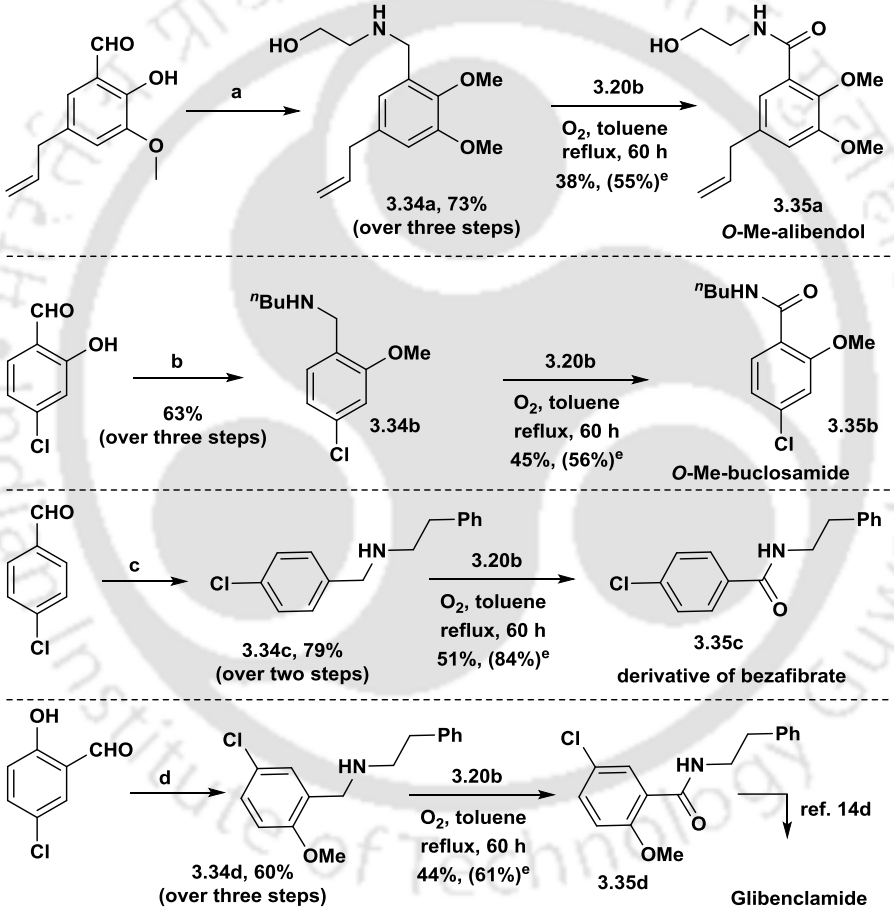
Amide functionality in medicinal drugs is generally installed via condensation of the corresponding carboxylic acid derivatives with the amines. The overall synthetic sequence involves the use of toxic oxidants and coupling reagents.[16] We applied this novel strategy for the direct conversion of amines to amides under metal and toxic oxidant free conditions for the synthesis of the analogs of amide containing medicinal drugs (**Scheme 14**). O-Me-alibendol **3.35a** and –buclosamide **3.35b** were obtained readily from the reaction of respective secondary amines **3.34a** and **3.34b**, which were prepared from commercially available aldehydes. Similarly, a derivative of bezafibrate **3.35c** and synthetic precursor **3.35d** for glibenclamide were prepared from benzyl amines **3.34**c and **3.34**d, respectively.



Scheme 14: Application in syntheses of medicinal drugs and their derivatives. (a) (i) Me_2SO_4, K_2CO_3, acetone, reflux, 12 h, 90%, (ii) 2-aminoethanol, 4 Å MS, DCM, rt, 12 h, 85%, (iii) $NaCNBH_3$, MeOH, 40 ^oC, 4 h, 95%; (b) (i) Me_2SO_4, K_2CO_3, acetone, reflux, 12 h, 80%, (ii) n-butylamine, 4 Å MS, DCM, rt, 12 h, 88%, (iii) $NaCNBH_3$, MeOH, 40 ^oC, 4 h, 90%; (c) (i) 2-phenylethanamine, 4 Å MS, DCM, rt, 12 h, 88%; (ii) $NaCNBH_3$, MeOH, 40 ^oC, 4 h, 90%; (d) (i) Me_2SO_4, K_2CO_3, acetone, reflux, 12 h, 78%; (ii) 2-

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phenylethanamine, 4 Å MS, DCM, rt, 12 h, 85%, (iii) $NaCNBH_3$, MeOH, 40 ^oC, 4 h, 90%. [e]Yields based on recovered starting materials.

3.10 Summary:

A conceptually novel method for direct *α*-oxidation of free aliphatic amines to amides and lactams without the aid of metallic reagents and toxic oxidants was developed. *α*-C(sp^3)-H oxygenation was achieved through a metal-free thermal activation of molecular oxygen. The reaction is operationally simple, efficient and applicable to a broad class of primary amines (activated benzyl or unactivated alkyl amines), cyclic and acyclic secondary amines. The elegant syntheses of highly functionalized *N*-alkyl benzamide moieties of medicinal drugs using this method showed its synthetic potential.

3.11 Experimental Section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Commercial grade dichloromethane (CH_2Cl_2), xylene, benzene and toluene were distilled over CaH_2 before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ^1H, ^{13}C NMR spectroscopy: *Varian Mercury plus 400 MHz, Bruker 600 MHz* (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS δ (^1H) 0.0 ppm, δ (^{13}C) 0.0 ppm) which was used as the inner reference. Otherwise, the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.2 ppm; CD_3OD, (^1H) 3.31 ppm, δ (^{13}C) 49.0 ppm) were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity. MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

General procedure for the synthesis of aryl amides from primary benzylamines (I):

Primary amine (0.56 mmol) was added to a solution of 9*H*-fluoren-9-imine **3.20b** (1 equiv) in toluene (2 mL) and the mixture was refluxed for 12 h. After the disappearance of the starting material indicated from TLC, solvent was evaporated in vacuum and crude product was subjected to silica gel chromatography (EtOAc: hexane, 1:1) to afford the analytically pure amides.

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Benzamide[4d] **(3.21a):** White solid (47 mg, 70%). **4-Methoxybenzamide** [5] **(3.21b):** White solid (60 mg, 70%). **4-Chlorobenzamide**[4d] **(3.21c):** White solid (61 mg, 70%). **4-Methylbenzamide**[4d] **(3.21d):** White solid (49 mg, 65%). **4-(trifluoromethoxy)benzamide**[4c] **(3.21e):** White solid (69 mg, 60%). **4-(dimethylamino)benzamide**[5] **(3.21f):** White solid (60 mg, 65%). **4-Fluorobenzamide**[8c] **(3.21g):** White solid (45 mg, 58%). **4-(trifluoromethyl)benzamide**[8f] **(3.21h):** White solid (53 mg, 50%). **2-Chlorobenzamide**[5] **(3.21i):** White solid (52 mg, 60%). **2-Fluorobenzamide**[6g] **(3.21j):** White solid (43 mg, 55%). **3-Bromobenzamide**[5] **(3.21k):** White solid (56 mg, 50%). **3-Methoxybenzamide**[8c] **(3.21l):** White solid (47 mg, 55%). **3,4-Dimethoxybenzamide**[5] **(3.21m):** White solid (66 mg, 65%). **3,4,5-Trimethoxybenzamide**[5] **(3.21n):** White solid (72 mg, 60%). **3,4-Dichlorobenzamide**[17c] **(3.21o):** White solid (68 mg, 54%). **2,4-Dichlorobenzamide**[5] **(3.21p):** White solid (67 mg, 63%). **1-Naphthamide**[4d] **(3.21q):** White solid (48 mg, 50%). **Picolinamide**[4d] **(3.21r):** White solid (38 mg, 56%). **Furan-2-carboxamide**[5] **(3.21s):** White solid (44 mg, 70%).

General procedure for the synthesis of primary aliphatic amides from primary amines (GP II): Primary amine (0.56 mmol) was added to a solution of 9*H*-fluoren-9-imine **3.20b** (1 equiv) in toluene (2 mL) and the mixture was refluxed for 60 h. After the disappearance of the starting material indicated from TLC, solvent was evaporated in vacuum and crude product was subjected to silica gel chromatography (EtOAc: hexane, 1:1) to afford the analytically pure amides.

Octanamide[11c] **(3.22a):** White solid (32 mg, 40%). **Decanamide**[17e] **(3.22b):** White solid (46 mg, 48%). **Dodecanamide**[11c] **(3.22c):** White solid (62 mg, 55%). **Tetradecanamide**[17a] **(3.22d):** White solid (69 mg, 54%).

Palmitamide (3.22e): According to general procedure II, hexadecylamine (0.14 mL, 0.56 mmol) and 9*H*-fluoren-9-imine **3.20b** (0.10 g, 0.56 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography (silica gel; EtOAc: hexane, 1:1) of the crude product gave **3.22e** as white solid (76 mg, 53%). Mp: 103-104 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.48 (s, 1H), 5.42 (s, 1H), 2.21 (t, J = 7.8 Hz, 2H), 1.65 – 1.60 (m, 2H), 1.33 – 1.24 (m, 24H), 0.87 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.8, 36.2, 32.1, 29.89, 29.87, 29.85, 29.80, 29.7, 29.6, 29.5, 29.4, 25.7, 22.9, 14.3 ppm. (Reduced numbers of ^{13}C signals is observed due to overlapping). HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{16}H_{34}NO$ 256.2635; Found 256.2638.

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Stearamide (3.22f): According to general procedure II, octadecylamine (0.15 mL, 0.56 mmol) and 9*H*-fluoren-9-imine **3.20b** (0.10 g, 0.56 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography (silica gel; EtOAc: hexane, 1:1) of crude gave **3.22f** as white solid (82 mg, 51%). Mp 106-107 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.51 (s, 1H), 5.42 (s, 1H), 2.21 (t, *J* = 7.8 Hz, 2H), 1.65 – 1.60 (m, 2H), 1.34 – 1.22 (s, 28H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.8, 36.1, 32.1, 29.9, 29.83, 29.78, 29.65, 29.5, 29.4, 25.7, 22.9, 14.3 ppm. (Reduced numbers of ^{13}C signals is observed due to overlapping). HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{18}H_{38}NO$ 284.2948; Found 284.2946.

General procedure for the synthesis of Secondary Amides or lactams from secondary acyclic or cyclic amines (III):

Secondary acyclic or cyclic amine (0.56 mmol) was added to a solution of 9*H*-fluoren-9-imine **3.20b** (0.56 mmol) in toluene (2 mL) and the mixture was refluxed for 24 h. After the disappearance of the starting material indicated from TLC, solvent was evaporated in vacuum and crude product was subjected to silica gel chromatography (silica gel; EtOAc: hexane, 1:1) to afford the analytically pure amides and lactams.

4-Methoxy-*N*-methylbenzamide[5] **(3.23a):** White solid (37 mg, 40%).

***N*-ethyl-4-methoxybenzamide**[5] **(3.23b):** Column chromatography (silica gel; EtOAc: hexane, 1:2) gave **3.23b** as colorless oil (50 mg, 50%).

4-Methoxy-*N*-propylbenzamide[5] **(3.23c):** Column chromatography (silica gel; EtOAc: hexane, 1:3) gave **3.24c** as an oil (60 mg, 55%).

***N*-butyl-4-methoxybenzamide**[5] **(3.23d):** Column chromatography (silica gel; EtOAc: hexane, 1:3) gave **3.23d** as an oil (50 mg, 40%).

4-Chloro-*N*-methylbenzamide[5] **(3.23e):** White solid (48 mg, 50%).

***N*-(2-hydroxyethyl)benzamide**[17f] **(3.23f): C**olumn chromatography (silica gel; EtOAc: hexane, 2:1) gave **3.23f** as an oil (50 mg, 54%).

Pyrrolidin-2-one[8a] **(3.23g):** Oil (36 mg, 75%).

Isoindolin-1-one[17b] **(3.23h):** White solid (43 mg, 57%).

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3,4-Dihydroisoquinolin-1(2H)-one[9d] **(3.23i):** Oil (71 mg, 82%).

3,4-Dihydro-6,7-dimethoxyisoquinolin-1(2H)-one[17d] **(3.23j):** Column chromatography (silica gel; EtOAc: hexane, 2:1) gave **3.23j** as white solid (88 mg, 76%).

2-(5-allyl-2,3-dimethoxybenzylamino)ethanol (3.34a): 5-allyl-2-hydroxy-3-methoxybenzaldehyde (0.28 g, 1.43 mmol), dimethyl sulphate (0.54 g, 4.30 mmol) and potassium carbonate (0.59 g, 4.30 mmol) in acetone (5 mL) were refluxed for 12 h. After completetion of the starting materials (indicated from TLC), solvent was evaporated and residue was purified by coloum chromatography (silica gel; EtOAc: hexane, 1:20) to afford 5-allyl-2,3-dimethoxybenzaldehyde as an oil (0.27 g, 90%). Then 5-allyl-2,3-dimethoxybenzaldehyde (0.10 g, 0.49 mmol) and ethanolamine (30 mg, 0.49 mmol) were dissolved in dichloromethane (3 mL) and the mixture was stirred at room temperature for 12 h in the presence of 4Å MS (0.1 g). After consumption of starting material, molecular sieves were filtered out and the solvent was evaporated to give 2-(5-allyl-2,3-dimethoxybenzylideneamino)ethanol (0.10 g, 85%). 2-(5-allyl-2,3-dimethoxybenzylideneamino)ethanol (0.10 g, 0.40 mmol) was treated with sodium cyanoborohydride (51 mg, 0.80 mmol) in MeOH (3 mL) at 40 °C for 4 h. MeOH was then evaporated and residue was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (20 mL of brine and 20 mL of water), dried (Na_2SO4) and concentrated in vaccua. Colum chromatography (silica gel; EtOAc: hexane, 1:3) of the residue gave **3.34a** as an oil (94 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.77 (s, 1H), 6.64 (s, 1H), 5.94 – 5.89 (m, 1H), 5.10 – 5.05 (m, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.62 – 3.57 (m, 4H), 3.32 (d, *J* = 6.5 Hz, 2H), 2.63 – 2.60 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.5, 146.1, 137.4, 135.6, 132.4, 122.5, 115.8, 111.6, 60.7, 58.9, 55.7, 54.9, 52.3, 40.1 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{14}H_{22}NO_3$ 252.1594; Found 252.1594.

5-Allyl-*N*-(2-hydroxyethyl)-2,3-dimethoxybenzamide (3.35a): According to general procedure III, 2-(5-allyl-2,3-dimethoxybenzylamino)ethanol (**3.34a**) (75 mg, 0.30 mmol) and 9*H*-fluoren-9-imine, **3.20b** (80 mg, 0.45 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography (silica gel; EtOAc: hexane, 2:1) of the crude product gave **3.35a** as an oil (30 mg, 38%) along with starting material **3.34a** (23 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.45 (s, 1H), 7.52 (s, 1H), 6.87 (s, 1H), 6.01 – 5.88 (m, 1H), 5.12 – 5.07 (m, 2H), 3.88 (s, 6H), 3.84 – 3.81 (m, 2H), 3.65 – 3.61 (m, 2H), 3.37 (d, *J* = 6.8 Hz,

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2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.7, 152.5, 145.9, 136.8, 136.6, 125.8, 122.4, 116.4, 115.9, 62.9, 61.4, 56.1, 42.9, 40.0 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{14}H_{20}NO_4$ 266.1387; Found 266.1398.

***N*-(4-chloro-2-methoxybenzyl)butan-1-amine (3.34b):** 4-chloro-2-hydroxybenzaldehyde (0.25 g, 1.61 mmol), dimethyl sulphate (0.61 g, 4.84 mmol) and potassium carbonate (0.67 g, 4.84 mmol) in acetone (5 mL) were refluxed for 12 h. After completetion of the starting materials (indicated from TLC), solvent was evaporated and the residue was purified by coloum chromatography (silica gel; EtOAc: hexane, 1:20) to afford 4-chloro-2-methoxybenzaldehyde as a white solid (0.22 g, 80%). Then 4-chloro-2-methoxybenzaldehyde (0.1 g, 0.59 mmol) and n-butylamine (43 mg, 0.59 mmol) were dissolved in dichloromethane (3 mL) and the mixture was stirred at room temperature for 12 h in the presence of 4Å MS (0.1 g). After consumption of starting material, molecular sieves were filtered out and the solvent was evaporated to give *N*-(4-chloro-2-methoxybenzylidene)butan-1-amine (0.12 g, 88%). *N*-(4-chloro-2-methoxybenzylidene)butan-1-amine (0.1 g, 0.44 mmol) was treated with sodium cyanoborohydride (56 mg, 0.89 mmol) in MeOH (3 mL) at 40 °C for 4 h . MeOH was evaporated and residue was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (20 mL of brine and 20 mL of water), dried (Na_2SO4) and concentrated in vaccua. Colum chromatography (silica gel; EtOAc: hexane, 1:1) of the residue gave **3.34b** as an oil (91 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 2.8 Hz, 1H), 7.16 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 2H), 2.59 – 2.55 (m, 2H), 1.51 – 1.44 (m, 2H), 1.37 – 1.30 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.2, 130.4, 129.5, 127.6, 125.3, 111.3, 55.6, 49.0, 48.8, 32.2, 20.5, 14.0 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{12}H_{19}ClNO$ 228.1150; Found 228.1155.

***N*-butyl-4-chloro-2-methoxybenzamide** (**3.35b**): According to general procedure III: (E)-N-(4-chloro-2-methoxybenzylidene)butan-1-amine (**3.34b**) (68 mg, 0.30 mmol) and 9*H*-fluoren-9-imine, **3.20b** (80 mg, 0.45 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography (silica gel; EtOAc: hexane, 2:1) of the crude product gave **3.35b** as an oil (32 mg, 45%) along with starting material **3.34a** (14 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 2.8 Hz, 1H), 7.79 (s, 1H), 7.37 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 3.95 (s, 3H), 3.48 – 3.43 (m, 2H), 1.63 – 1.56 (m, 2H), 1.44 – 1.38 (m, 2H),

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0.96 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.0, 156.0, 132.2, 132.1, 126.9, 123.3, 112.9, 56.4, 39.7, 31.7, 20.3, 13.9 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{12}H_{17}ClNO_2$ 242.0942; Found 242.0950.

***N*-(4-chlorobenzyl)-2-phenylethanamine (3.34c):** 4-chlorobenzaldehyde (0.20 g, 1.43 mmol) and 2-phenylethanamine (0.17 g, 1.43 mmol) were dissolved in dichloromethane (3 mL) and the mixture was stirred at room temperature for 12 h in the presence of 4Å MS (0.20 g). After consumption of starting material, molecular sieves were filtered out and the solvent was evaporated to obtain the imine *N*-(4-chlorobenzylidene)-2-phenylethanamine (0.30 g, 88%). *N*-(4-chlorobenzylidene)-2-phenylethanamine (0.10 g, 0.41 mmol) was treated with sodium cyanoborohydride (52 mg, 0.82 mmol) in MeOH (3 mL) at 40 °C for 4 h. MeOH was evaporated and residue was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (20 mL of brine and 20 mL of water), dried (Na_2SO4) and concentrated in vaccua. Colum chromatography (silica gel; EtOAc: hexane, 1:3) of the residue gave **3.34c** as an oil, (91 mg, 90%).^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.37 – 7.32 (m, 4H), 7.29 – 7.26 (m, 5H), 3.81 (s, 2H), 2.96 – 293 (m, 2H), 2.89 – 2.87 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 140.0, 138.9, 132.6, 129.5, 128.8, 128.6, 128.5, 126.3, 53.1, 50.5, 36.4 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{15}H_{17}ClN$ 246.1044; Found 246.1038.

4-Chloro-*N*-phenethylbenzamide (**3.35c**): According to general procedure III, *N*-(4-chlorobenzyl)-2-phenylethanamine (**3.34c**) (73 mg, 0.30 mmol) and 9*H*-fluoren-9-imine, **3.20b** (80 mg, 0.45 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography (silica gel; EtOAc: hexane, 2:1) of the crude product gave **3.35c** as an oil (39 mg, 51%) along with starting material **3.34c** (29 mg 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 – 7.60 (m, 2H), 7.39 – 7.31 (m, 4H), 7.27 – 7.22 (m, 3H), 6.14 (s, 1H), 3.71 (q, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.5, 138.8, 137.7, 133.1, 128.9, 128.9, 128.9, 128.3, 126.8, 41.3, 35.7 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{15}H_{15}ClNO$ 260.0837; Found 260.0836.

***N*-(5-chloro-2-methoxybenzyl)-2-phenylethanamine (3.34d):** 5-chloro-2-hydroxybenzaldehyde (0.28 g, 1.77 mmol), dimethyl sulphate (0.67 g, 5.32 mmol) and potassium carbonate (0.73 g, 5.32 mmol) in acetone (5 mL) were refluxed for 12 h. After completetion of the starting materials (indicated from TLC), solvent was evaporated and residue was purified by coloum chromatography (silica gel; EtOAc: hexane, 1:20) to afford 5-chloro-2-methoxybenzaldehyde as white solid (0.23 g, 78%). Then 5-chloro-2-

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methoxybenzaldehyde (0.12 mg, 0.71 mmol) and pnenylethanamine (85 mg, 0.71 mmol) were dissolved in dichloromethane (3 mL) and stirred at room temperature for 12 h in the presence of 4Å MS (0.12 g). After consumption of starting material, molecular sieves were filtered out and the solvent was evaporated to obtain the imine, *N*-(5-chloro-2-methoxybenzylidene)-2-phenylethanamine (0.16 g, 85%). *N*-(5-chloro-2-methoxybenzylidene)-2-phenylethanamine (0.15 g, 0.55 mmol) was treated with sodium cyanoborohydride (69 mg, 1.10 mmol) in MeOH (3 mL) at 40 °C for 4 h. MeOH was evaporated and residue was diluted with EtOAc (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (20 mL of brine and 20 mL of water), dried (Na_2SO4) and concentrated in vaccua. Colum chromatography (silica gel; EtOAc: hexane, 1:2) of the residue gave **3.34d** as an oil (0.14 g, 90%).^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.27 (m, 2H), 7.22 – 7.15 (m, 5H), 6.73 (d, *J* = 8.8 Hz, 1H), 3.76 (s, 2H), 3.70 (s, 3H), 2.88 – 2.80 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.1, 139.8, 129.63, 129.58, 128.7, 128.5, 127.8, 126.2, 125.3, 111.3, 55.4, 50.1, 48.7, 36.1 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{16}H_{19}ClNO$ 276.1150; Found 276.1157.

5-Chloro-2-methoxy-*N*-phenethylbenzamide(**3.35d**): According to general procedure III, *N*-(5-chloro-2-methoxybenzyl)-2-phenylethanamine (**3.34d**) (82 mg, 0.30 mmol) and 9*H*-fluoren-9-imine, **3.20b** (80 mg, 0.45 mmol) in toluene (2 mL) were refluxed for 60 h and column chromatography of crude product (silica gel; EtOAc: hexane, 2:1) gave **3.35d** as an oil (38 mg, 44%) along with starting material **3.34d** (23 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 2.8 Hz, 1H), 7.83 (s, 1H), 7.36 – 7.32 (m, 3H), 7.27 – 7.24 (m, 3H), 6.84 (d, *J* = 8.8 Hz, 1H), 3.78 – 3.75 (m, 2H), 3.73 (s, 3H), 2.92 (t, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 163.9, 155.9, 139.2, 132.2, 132.0, 128.9, 128.6, 126.7, 126.5, 122.9, 112.7, 56.0, 40.9, 35.5 ppm. HRMS (ESI-TOF) m/z: ($[M+H]^+$) calculated for $C_{16}H_{17}ClNO_2$ 290.0942; Found 290.0949.

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CHAPTER 4

Metal Free Biomimetic Dehydrogenative Direct C-C Coupling of Unprotected Primary Amines with Active Methylenes

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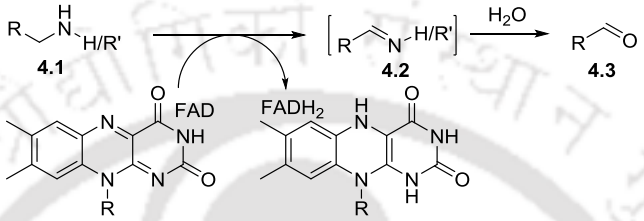
4.1 Introduction:

Monoamine oxidase (MAO) oxidizes a variety of primary and secondary amines, polyamines, and amino acids in the biological system. The flavin adenine dinucleotide (FAD) acts as the coenzyme for this deamination reactions. In the first step, an amine **4.1** is dehydrogenated to form the imine **4.2** while FAD is reduced to $FADH_2$. The imine is hydrolyzed subsequently to produce the corresponding carbonyl compounds **4.3** (**Scheme 1**).[1]



Scheme 1: Imine (FAD) mediated biological deaminations

A large number of methods have been developed for the transformation of amine to an imine. The reported methods for the conversion of amines to the corresponding imines employed stoichiometric/catalytic amounts of oxidants[2] (e.g. IBX, DDQ, iminoquinone, etc.) and metallic reagents or catalysts[3] (e.g. Ru, Pt, Rh, Au, etc.) in the presence or absence of oxidants. Molecular oxygen or air was also used as oxidants for the amine to imine oxidation in the presence of metallic reagents.[4] Aerobic photooxidation of primary benzylamines using catalytic amounts of hindered acridinium salts, $BiVO_4$ or Ru-based complex were also reported.[5] These methods are efficient, but often require harsh reaction conditions, strong oxidants, metallic reagents, and other additives.

4.2 Known methods for dehydrogenation of amine:

4.2.1 Selected methods for dehydrogenation of amine by using metallic reagent with or without oxidant:

Kobayashi and coworkers discovered a class of cooperative catalytic system consisting of heterogeneous polymer-immobilized bimetallic Pt/Ir alloyed nanoclusters (NCs) and 4-*tert*-butylcatechol for the aerobic oxidation of amines **4.4** to imines **4.5** under ambient conditions (**Scheme 2)**.[4e]

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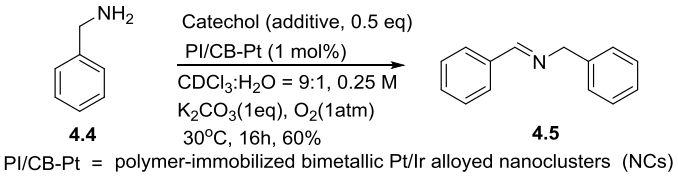
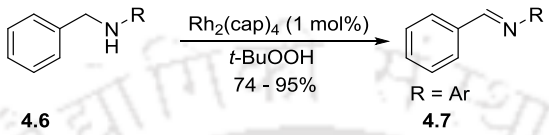


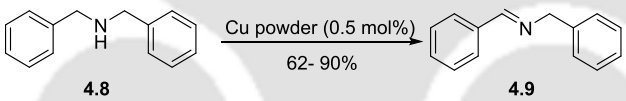
Scheme 2: Metal nanoclusters for the aerobic oxidation of amines b

Doyle and coworkers developed a $Rh_2(cap)_4$ catalyzed mild, efficient, and selective oxidation of secondary amines **4.6** to imines **4.7** using TBHP. (**Scheme 3)**.[3c]



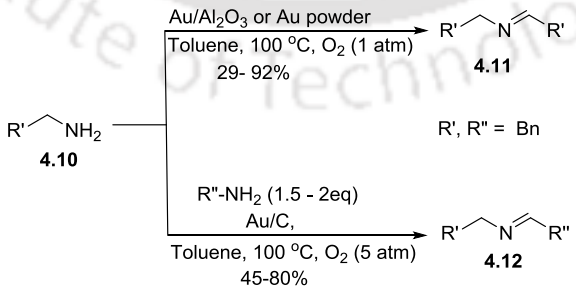
Scheme 3: Rhodium catalyzed oxidation of secondary amines

Adimurthy and coworkers described copper(0)-catalyzed direct synthesis of imines **4.9** from amines **4.8** under solvent-free aerobic. The method is applicable for the synthesis of various imines from corresponding amines such as benzylic, aliphatic, cyclic secondary and heteroaromatic amines. (**Scheme 4)**.[4c]



Scheme 4: Cu-catalyzed aerobic oxidation of amines to imines

Lageron and coworkers developed a method for selective aerobic oxidation of benzylamine **4.10** to *N*-benzylidene-benzylamine (**4.11** and **4.12**) using nanogold catalysts supported on alumina/graphite (**Scheme 5)**.[6d]



Scheme 5: Au catalyzed oxidation of primary amines to imines

Mizuno and coworkers developed a new method for the oxidation of non-activated, as well as activated amines **4.13** to the corresponding nitriles or imines **4.14** by using Ru/Al_2O_3 as

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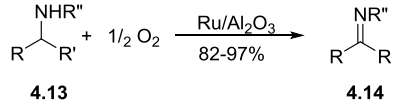
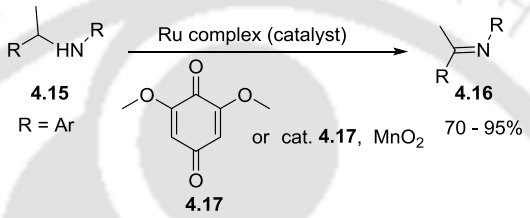
an efficient heterogeneous catalyst in the presence of 1 atm of dioxygen or air. (**Scheme 6)**.[4f]



Scheme 6: Aerobic oxidation of amines

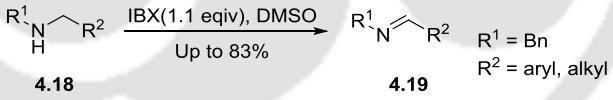
Backvall and coworkers developed a ruthenium-catalyzed efficient method for dehydrogenation of amines **4.15** to imines **4.16** under mild conditions using 2,6-dimethoxy benzoquinone or catalytic amount of 2,6-dimethoxy benzoquinone /MnO_2 as oxidant. **(Scheme 7)**.[3d]



Scheme 7: Dehydrogenation of aromatic amines to imines

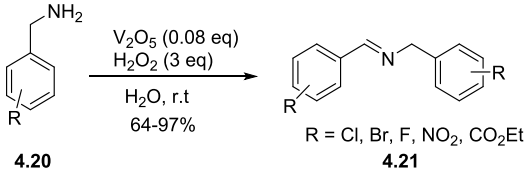
4.2.2 Selected methods on metal-free dehydrogenation of amine by using an oxidizing agent:

Montagnon and co-workers developed an efficient method for the oxidation of amine **4.18** to imine **4.19** by *o*-Iodoxybenzoic acid (IBX) (**Scheme 8)**.[2b]



Scheme 8: IBX-mediated oxidation of amine

Li and coworkers reported a V_2O_5 catalyzed method for the syntheses of imines **4.21** from benzylamines **4.20** by using H_2O_2 in water at room temperature. (**Scheme 9)**.[3a]



Scheme 9: V_2O_5 catalyzed synthesis of imines from primary benzylamines

Stahl and co-workers developed a method for the biomimetic aerobic oxidation of primary benzylic amines **4.22** to imines (**4.23** and **4.24**) by using a quinone as the catalyst. Excellent

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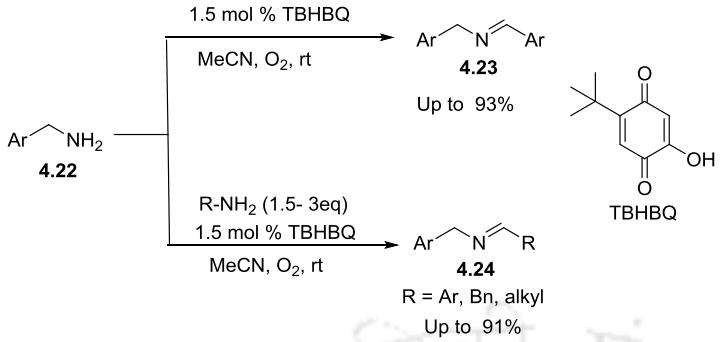
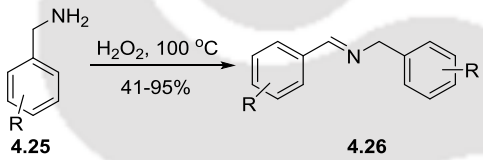
selectivity is observed for primary, unbranched benzylic amines relative to secondary/tertiary amines, branched benzylic amines, and aliphatic amines (**Scheme 10)**.[2c]



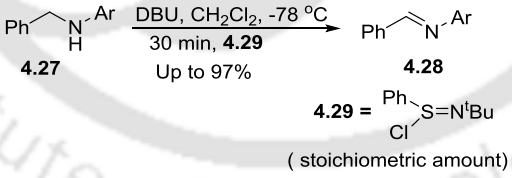
Scheme 10: Quinone catalyzed oxidation of amine to imine

A convenient procedure for the oxidation of benzyl amines **4.25** to the corresponding imines **4.26** has been developed by Langer and co-workers. Various imines were produced in good to excellent yields. Notably, no catalyst and no solvent was needed, and H_2O_2 was used as the oxidant. (**Scheme 11)**.[2d]



Scheme 11: Metal-free oxidation of benzyl amines to imines

Secondary amines **4.27** was dehydrogenated to imines **4.28** at −78 °C by using *N-tert*-Butyl benzene sulfinimidoyl Chloride **4.29** and DBU (**Scheme 12)**.[2i]



Scheme 12: Oxidation of amines to imine

4.2.3 Selected methods on dehydrogenation of amine by using Photocatalyst:

Li and co-workers found that $BiVO_4$ acted as an efficient photocatalyst under visible light irradiation for the oxidation of a series of amines **4.30**, forming the corresponding imines **4.31** using O_2 as an oxidant. (**Scheme 13)**.[5b]

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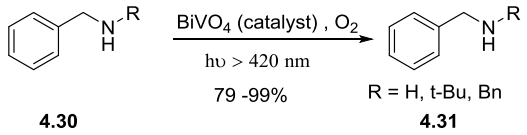
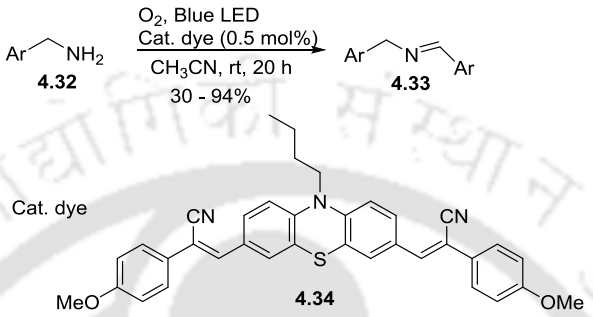


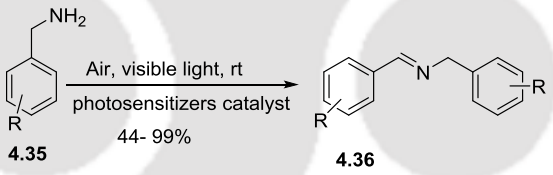
Scheme 13: $BiVO_4$ catalyzed photo-oxidation of amines to imines

Son and co-workers developed photocatalytic oxidation of primary amines **4.32** to imines **4.33** by using phenothiazine dyes in the presence of visible light (**Scheme 14)**.[5c]



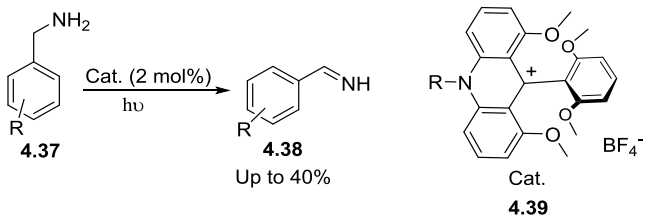
Scheme 14: Visible-Light-driven oxidation of primary amines

Ma and co-workers developed a method for aerobic oxidation of amines **4.35** to imine **4.36** by using bodipy derivatives as an organic triplet photosensitizers (**Scheme 15)**.[5e]



Scheme 15: Formation of imine from amine developed

Lacour and coworkers developed an acridinium salt **4.39** catalyzed aerobic photo-oxidation of primary benzyl amines **4.37** to benzylimines **4.38**. (**Scheme 16)**.[5a]



Scheme 16: Catalytic aerobic photo-oxidation of primary benzylic amines using hindered acridinium salts

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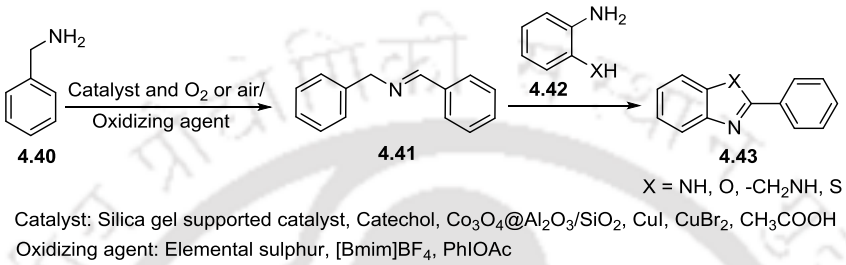
4.3 Dehydrogenative coupling of amines with other nucleophiles:

4.3.1 Dehydrogenative coupling of amines with heteroatom-based (N, O, S) nucleophiles:

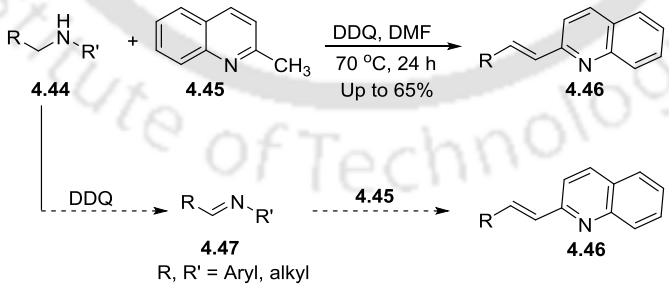
Amine **4.40** was oxidized to the corresponding imine **4.41** by using a catalyst and/ oxidizing agent. Imine **4.41** was then reacted with different types of hetero nucleophiles to form the corresponding coupling product **4.43** (imidazole, oxazole, thiazole or quinoxaline) (Scheme 17).



Scheme 17: Coupling of amines with heteronucleophiles

4.3.2 Dehydrogenative coupling of amines with carbon-based nucleophiles:

Tian and coworkers reported an unprecedented olefination reaction of secondary amines **4.44** with carbon nucleophiles **4.45** through C–N/ C–H functionalization under metal-free oxidative conditions. A stoichiometric amount of 2, 3-dichloro- 5, 6-dicyano-1, 4-benzoquinone (DDQ) was used as an oxidant. Preliminary mechanistic studies revealed that the oxidative olefination reaction proceeds through amine oxidation to form imine **4.47** followed by its reaction with **4.45** to form **4.46** (**Scheme 18)**.[7a]



Scheme 18: Olefination reaction of secondary amines with carbon-based nucleophiles in the presence of a stoichiometric amount of DDQ

Seeberger and coworkers prepared tri- or tetrasubstituted alpha-cyanoepoxides **4.51** from unactivated amines **4.48** and malononitrile **4.50**. During this reaction, olefin **4.52** was also

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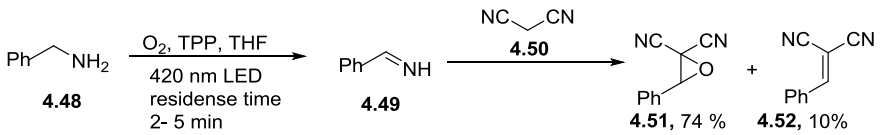
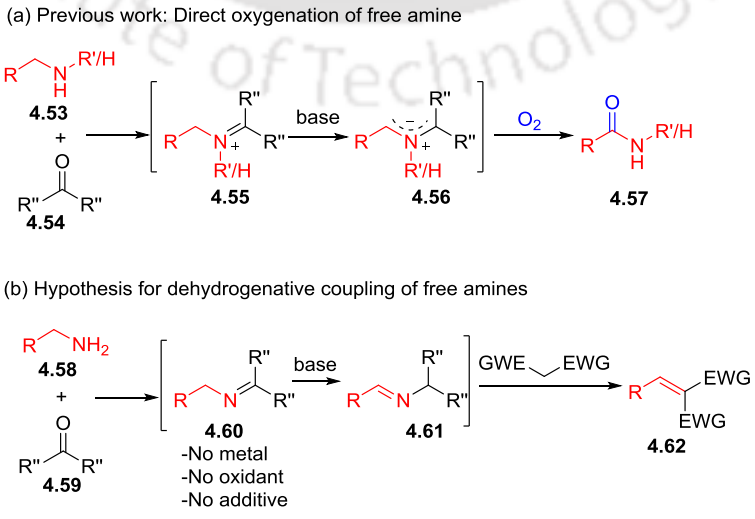
formed as a minor byproduct. In-situ generated peroxide oxidize the amines **4.48** to imine **4.49** which reacted with malononitrile **4.50** to produce olefin **4.52** (**Scheme 19)**.[7b]



Scheme 19: Synthesis of Knoevenagel type olefin as the side product directly from amine

In most of the aforementioned methods, the amines functionality was converted to corresponding imine, nitrile or aldehyde.[2-5] In some cases, the imine formed was subsequently reacted with heteronucleophiles to produce the corresponding imidazole, oxazole, thiazole or quinoxaline (**Scheme 17**).[6] However, the reaction of the imine generated in situ via dehydrogenation of an amine with the carbon-based nucleophile like active methylene compound is uncommon.[7] Moreover, to the best of our knowledge, no report on the direct coupling of unprotected primary amines with active methylenes producing alkenes and dihydropyridines is known in the literature. This is probably because the active methylenes are susceptible to oxidation/decomposition under strongly oxidizing conditions.[8] Moreover, the propensity to over-oxidation of amines to nitriles and high nucleophilicity of free primary amines put further challenges for the success of C-C coupling of free primary amines and active methylenes. Therefore, the development of a method that can operate under mild conditions without the aid of strong oxidants and metallic reagents would allow the subsequent one-pot reaction of the imine with suitable nucleophiles like active methylene compound.

4.4 Hypothesis for the present work:



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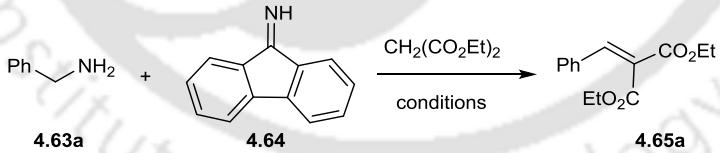
Scheme 20: Dehydrogenation of amines and subsequent coupling reactions

Based on the previous findings (**Scheme 20a)**, a Schiff base **4.60** could be generated from 9-fluorenone and benzylamine. The Schiff base **4.60** can be isomerimerized to **4.61,** which then can react with the active methylene compounds to provide olefin 4.62. In this way, olefin **4.62** could be formed from amine without any oxidizing agent or catalyst (**Scheme 20b**).

4.5 Optimization of the reaction condition for olefin synthesis:

According to the hypothesis, a reaction of benzylamine (**4.63a**), 9-fluorenone imine (**4.64**), and diethyl malonate was performed in refluxing toluene under argon atmosphere. The desired alkene **4.65a** was isolated with a 35% yield after 12 h of reaction (**Table 1**). The yield of the product increased to 68% when the reaction was carried out for a longer time (48 h). However, the same reaction performed at room temperature did not provide the desired product. Different reaction conditions, such as solvents, temperatures, reactant stoichiometry, reaction time, etc., were evaluated to increase the yield of the alkene. Solvents with the low boiling points provided the lower yields as compared to toluene and xylene. The addition of inorganic/organic bases with either catalytic or stoichiometric amounts did not improve the yield of the product. Interestingly, the use of 9-fluorenone, replacing 9-fluorenone imine, did not yield the desired alkene under the same conditions.

Table 1: Optimization of biomimetic deaminative direct coupling reaction of benzyl amine.[a]



4.63a 4.64 4.65a

entry	Conditions (Ar balloon)	yield (%)[b]
1	toluene, reflux, 12 h	35
2	toluene, reflux, 48 h	68
3[c]	toluene, reflux, 48 h	70
4	toluene, reflux, 60 h	69
5	toluene, rt, 12 h	0
6	xylene, reflux, 48 h	68

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7	DCE, reflux, 48 h	40
8	MeOH, reflux, 48 h	20
9	DMF, reflux, 48 h	55
10	benzene, reflux, 48 h	50
11	DCM, reflux, 48 h	15
12	toluene, reflux, 48 h, Et_3N (1 eq)	69
13	toluene, reflux, 48 h, DBU (1eq)	65
14	toluene, reflux, 48 h, KOH (1eq)	30
15	DMF, reflux, 48 h, K_2CO_3 (1eq)	64
16	toluene, reflux, 48 h, NaH (1eq)	40
17	THF, reflux, 48 h	50

[a]1eq (0.56 mmol) of benzyl amine, 1eq of 9-fluorenone imine (0.56 mmol) and 1 eq of diethyl malonate were (0.56 mmol) reacted. [b]Isolated yield. [c]1.2 eq. of 9-fluorenone imine was used.

4.6 Substrate scope for the synthesis of olefin:

The scope of the metal-free dehydrogenative coupling of amine was tested next. Different aryl and heteroaryl amines reacted smoothly to produce the corresponding trisubstituted alkenes **4.65b-r** with good yields (Table 2). Various functional groups (e.g., OR, NR_2, F, Cl) in the aromatic ring of arylmethylamines were tolerated under these reaction conditions. Substrates having both electron-donating (e.g., Me, OMe) and electron-withdrawing (e.g., NO_2, F, Cl) groups were efficiently reacted to produce the desired products. Heteroarylmethyl amines also participated in the reaction to produce the desired compound **4.65p** with good yield under the optimized reaction conditions. In addition to the symmetrically substituted malonates, unsymmetrical malonates such as ethyl acetoacetate reacted smoothly to produce the desired products **4.65q** (1.3:1) and **4.65r** (1.5:1) as the mixture of *E*- and *Z*-isomers. Interestingly, the reaction with malonic acid afforded cinnamic acid derivatives **4.65s-t** with good yields. Additionally, the reaction was found to be effective in gram-scale synthesis, which indicated its potential for practical application (**Scheme 22).**

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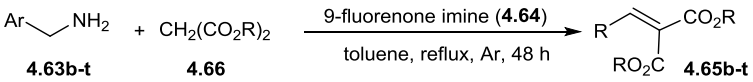
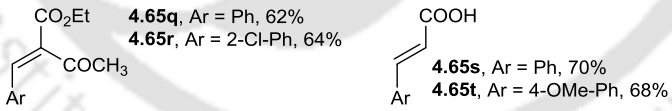
Table 2: Scope for the olefins syntheses.



entry	Ar	R	alkene	yield (%)
1	4-Me-Ph	Et	**4.65b**	67
2	4-OMe-Ph	Et	**4.65c**	64
3	4-Cl-Ph	Et	**4.65d**	69
4	4-OCF_3-Ph	Et	**4.65e**	68
5	4-F-Ph	Et	**4.65f**	68
6	2-F-Ph	Et	**4.65g**	60
7	2-Cl-Ph	Et	**4.65h**	65
8	2-OMe-Ph	Et	**4.65i**	70
9	3,4-Cl-Ph	Et	**4.65j**	65
10	3-OMe-Ph	Et	**4.65k**	64
11	Ph	Me	**4.65l**	62
12	2-OMe-Ph	Me	**4.65m**	63
13	Ph	Bn	**4.65n**	64
14	2-OMe-Ph	Bn	**4.65o**	72
15	2-furyl	Et	**4.65p**	60



Direct coupling of amino benzylamine with diethyl malonate followed by mild acid hydrolysis gave the alkene **4.67** having amine functionality with good yield (**Scheme 21).** The use of a classical reaction of aminoaldehyde, which is not readily available, could be problematic because of their propensity towards polymerization. Therefore, incorporation of the amino group to the dihydropyridine and alkene necessities the reduction of corresponding nitro compounds using harsh conditions (Zn-AcOH or Sn-HCl).[11] Thus, the present method can be applied as an advantageous alternative to the classical condensation of an aldehyde with the active methylene compounds.

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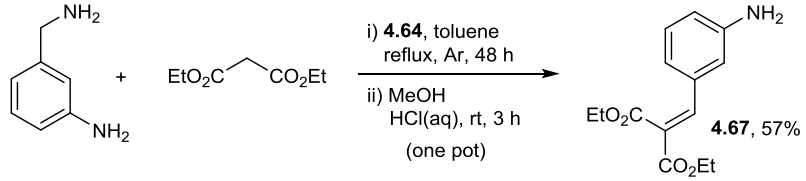
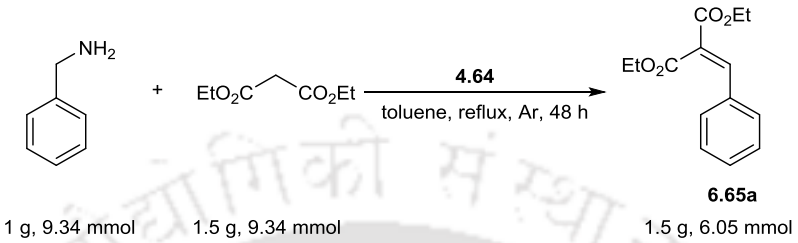


Scheme 21: Scope for the Synthesis of 3-amino olefin derivative.



Scheme 22: Preparative scale Synthesis of olefin derivative.

4.7 Dihydropyridine synthesis:

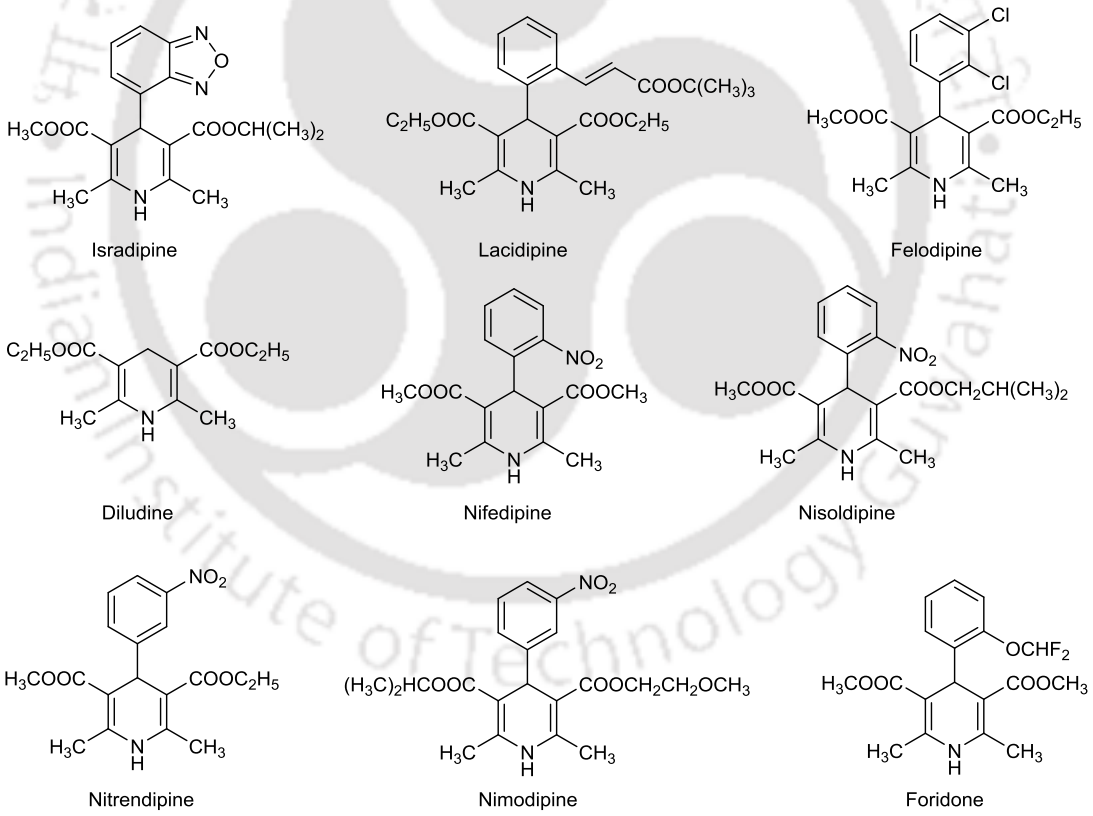


Figure 1: Examples of some selective medicinal drugs of 1, 4-DHP

The 1, 4-DHP scaffolds have served as a nucleus for several blockbuster drugs such as nifedipine and amlodipine. 4-Substituted 1, 4-dihydropyridines (1, 4-DHPs) are analogs of NADH coenzymes and an important class of drugs. The classical Hantzsch dihydropyridines synthesis involve the pseudo-four-component condensation reaction of an

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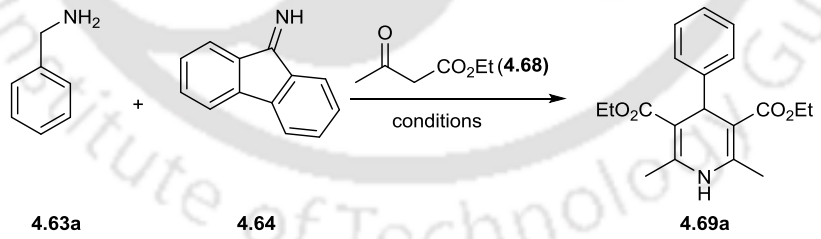
aldehyde, acetoacetic ester, and ammonia or amines.[10] The alkene formed from the initial condensation of acetoacetic ester and aldehyde acts as the key intermediate in the reaction. As this novel deaminative coupling reaction produces the related alkene (e.g. **4.65q**), the scope of this method for the synthesis of 1,4-dihydropyridines was investigated next (**Table 3**). The coupling reaction in the presence of 9-fluorenone imine releases one equivalent of ammonia. Therefore, employing our deaminative coupling reaction, the dihydropyridines can be synthesized without using additional ammonia source. As expected, the reaction of benzylamine, ethyl acetoacetate (and 9-fluorenone imine (**4.64**) in the absence of additional ammonia source provided the desired dihydropyridine **4.69a** with a maximum yield of 51% (**Table 3, entry 6**). Various reaction conditions like solvent, temperature, reaction time etc were screened to increase the yield of the dihydropyridines. When the reaction was conducted in rt, desire product did not form (Table 3, entry 1). Toluene, xylene, DCM, DCE, MeOH, THF were used but it was found that toluene was the best solvent. Without solvent also it is working with less yield (**Table 3, entry 22**). Then we optimized the reaction time and it was found that yield is increasing when the time increased from 12h to 48h (**Table 3, entry 9, 13, 14**). Amount of the external ammonia source also optimized and it was observed that 2 eq NH_4OAc afforded the best result (**Table 3, entry 9**). Reaction was also done under microwave irradiation but yield did not increase (**Table 3, entry 24, 25**). Highest yield was observed when reaction was done in tolune (reflux) for 48h by using 2 eq NH_4OAc under argon atmosphere.

Table 3: Optimization for the synthesis of dihydropyridines.



4.63a **4.64** **4.69a**

entry	Conditions (Ar balloon)	yield[b]
1	toluene, rt, 12 h	0
2	toluene, reflux, 12 h	10
3	toluene, reflux, 24 h	12
4	toluene, reflux, 48 h	13

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5	toluene, close tube, 48 h	45
6	neat, close tube, 48 h	51
7	neat, close tube, 60 h	50
8	toluene, reflux, 48 h, NH_4OAc (1 eq)	63
9	**toluene, reflux, 48 h, NH_4OAc (2 eq)**	**68**
10	toluene, reflux, 48 h, NH_4OAc (3 eq)	67
11	toluene, reflux, 60 h, NH_4OAc (2 eq)	69
12	toluene, reflux, 36 h, NH_4OAc (2 eq)	53
13	toluene, reflux, 24 h, NH_4OAc (2 eq)	45
14	toluene, reflux, 12 h, NH_4OAc (2 eq)	35
15	xylene, reflux, 48 h, NH_4OAc (2 eq)	68
16	xylene, reflux, 24 h, NH_4OAc (2 eq)	48
17	DCE, reflux, 48 h, NH_4OAc (2 eq)	40
18	MeOH, reflux, 48 h, NH_4OAc (2 eq)	25
19	DMF, reflux, 48 h, NH_4OAc (2 eq)	50
20	benzene, reflux, 48 h, NH_4OAc (2 eq)	48
21	DCM, reflux, 48 h, NH_4OAc (2 eq)	12
22	neat, 130 ^oC, 48 h, NH_4OAc (2 eq)	67
23	neat, 130 ^oC, 48 h, NH_4OAc (1 eq)	64
24	neat, MW, 120 ^oC, 45 min, NH_4OAc (2 eq)	60
25	toluene, MW, 120 ^oC, 45 min, NH_4OAc (2 eq)	58
26	THF, reflux, 48 h, NH_4OAc (2 eq)	35

[a]1eq (0.56 mmol) benzyl amine, 1eq 9-fluorenone imine (0.56 mmol), and 2 eq ethylacetoacetate (1.12 mmol) were reacted in 2 mL solvent under argon environment. [b]Isolated yield.

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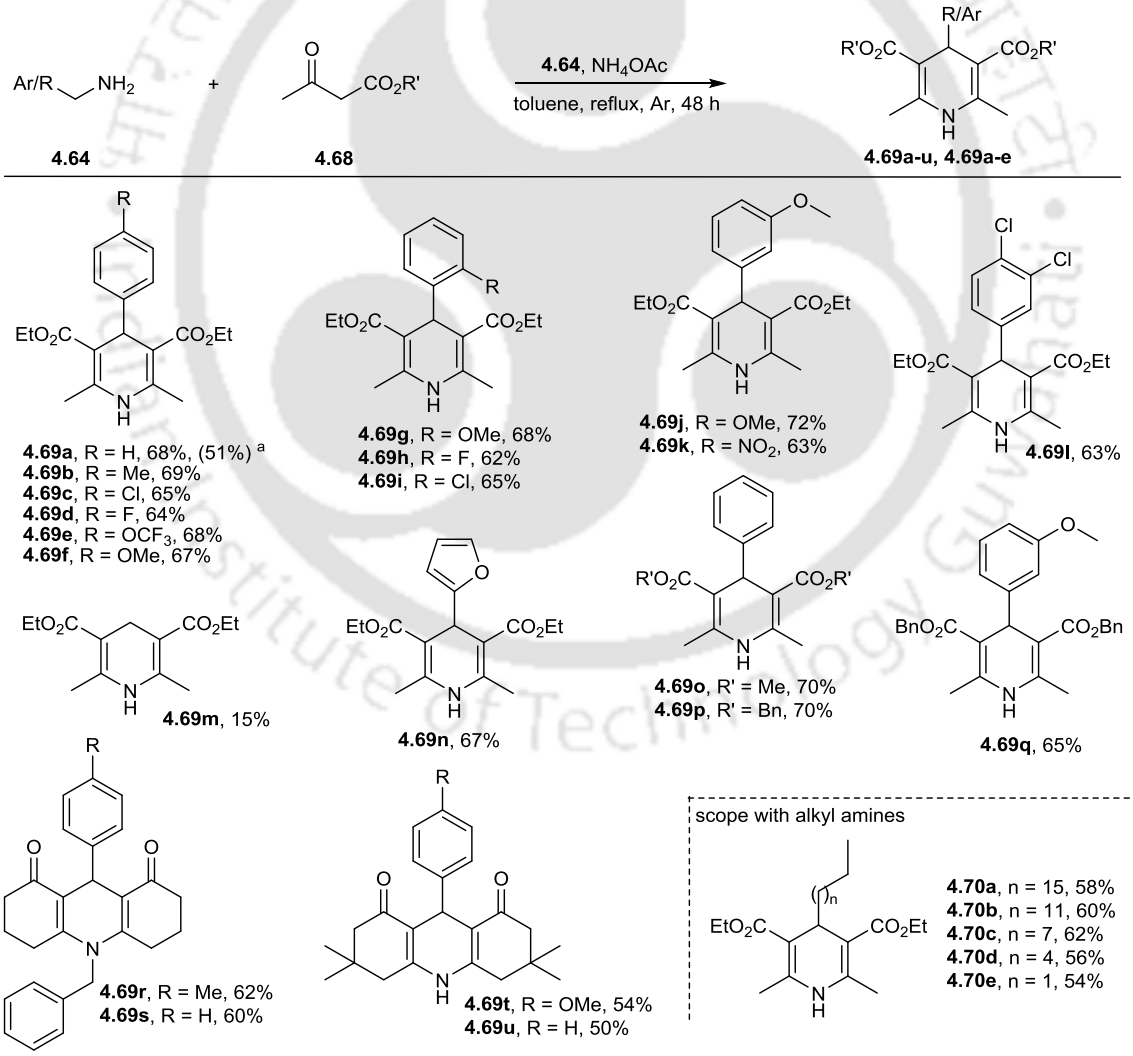
4.8 Substrate scope for the dihydropyridine synthesis:

Large varieties of benzylamines containing both electron-withdrawing and electron-donating groups in the aryl moiety reacted efficiently to provide the desired 1,4-dihydropyridines **4.69a-u** with good yields (**Scheme 23**). Other than ethyl acetoacetate, methyl and benzyl acetoacetate also reacted smoothly to produce corresponding dihydropyridines **4.69o-q**. The reaction with dimedone provided the expected tricyclic dihydropyridines **4.69t-u**. Interestingly, simple 1, 3-cyclohexadienone gave the *N*-benzylated dihydropyridines **4.69r-**s with good yields. In addition to the benzylamines, alkyl amines with varying chain lengths participated in the reaction to produce the corresponding dihydropyridines **8.70a-e** with good yields. Interestingly, simple methyl amine acted as the substitute of formaldehyde to afford the desired dihydropyridine **4.69m**, however, with poor yield.



[a]Reaction was carried out in the absence of NH_4OAc (see Table 3).

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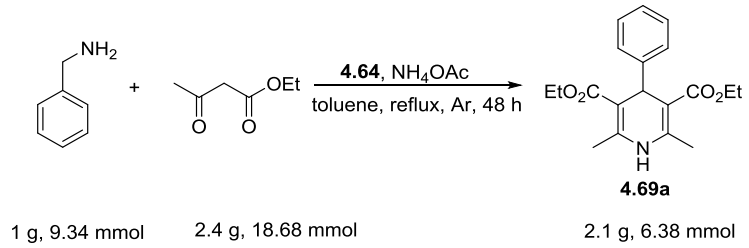
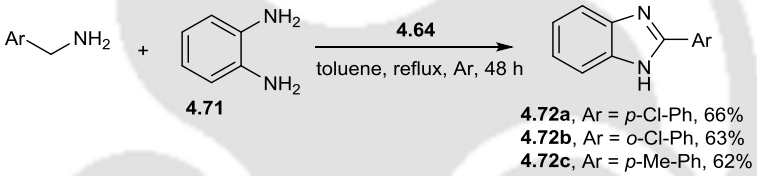
Scheme 23: Scope for the Synthesis of dihydropyridines.



Scheme 24: Preparative scale synthesis of dihydropyridine

4.9 Substrate scope for the benzimidazole synthesis:

After the success in direct coupling of the amine with carbon-based nucleophile, the possibility of the reaction with hetero-dinucleophiles was investigated. Accordingly, benzimidazole derivatives **4.72a-c** were formed, when 2-amino aniline was reacted with amine and **4.64** under the same reaction condition (**Scheme 25**).



Scheme 25: Scope for the Synthesis of Imidazole derivatives.

4.10 Controlled experiments and probable mechanism:

Additional reactions were conducted to understand the possible reaction pathway (**Scheme 26a**). The reaction in the absence of 9-flurenone imine (eq 1) did not provide the desired coupling product. In addition, pre-formed imine provided the desired products **4.65a** and **4.69a** from the separate reactions under standard conditions (eq 2 and 3). These results indicate that the 9-flurenone imine is essential for the reaction, and the reaction proceeds *via* imine intermediate **4.73.**

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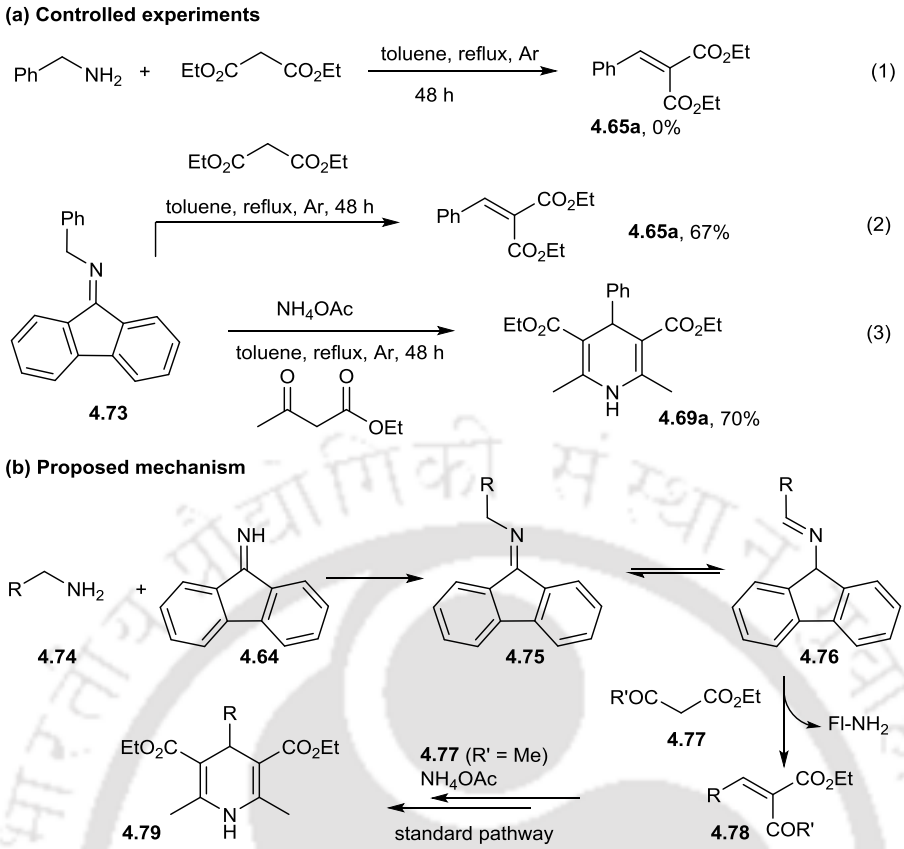

Scheme 26: (a) Controlled experiments. (b) Proposed mechanism of C-C coupling of amines and active methylenes.

On the basis of the experimental evidence, a plausible mechanism for the metal-free dehydrogenative direct coupling of a primary amine with active methylenes is proposed in **Scheme 26b**. Condensation of amine **4.74** and 9-flurenone imine (**4.64**) occurred to provide corresponding ketimine **4.75.** Isomerization of **4.76** furnished the regioisomeric aldimine **4.77**, which on subsequent reaction with active methylenes **4.78** provided the corresponding alkene **4.79**. In the reaction with acetoacetate, the corresponding alkene reacted further with ammonia, which was either generated during condensation of **4.74** and **4.64** or from NH_4OAc, and another equivalent of acetoacetate to provide the dihydropyridines following standard pathway.

4.11 Kinetic experiment:

In a NMR tube, benzylamine **4.63a** (30 mg, 0.28 mmol) was added to a solution of 9-fluorenone imine **4.64** (50 mg, 0.28 mmol) and triphenylmethane (13.8 mg, 0.056 mmol) in benzene-d_6 (0.75 mL) and the solution was kept 12 h in room temperature (**Scheme 27**). The yield of the imine **4.80** was calculated to be 80-90% form the ^{1}H NMR experiment

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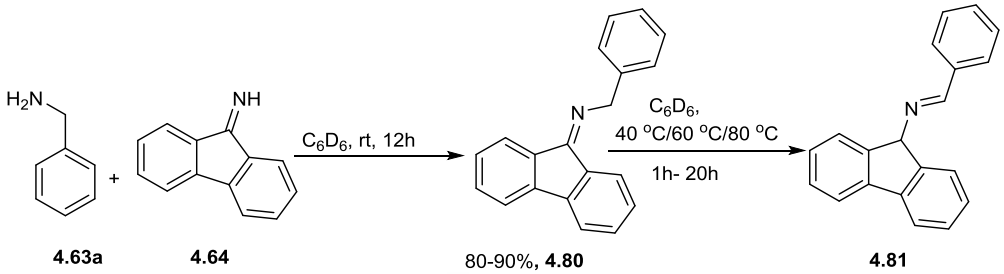
(**figure 3).** Then the mixture was heated and the time dependent concentrations of **4.80** were calculated using ^{1}H-NMR experiments.



Scheme 27: NMR tube reaction

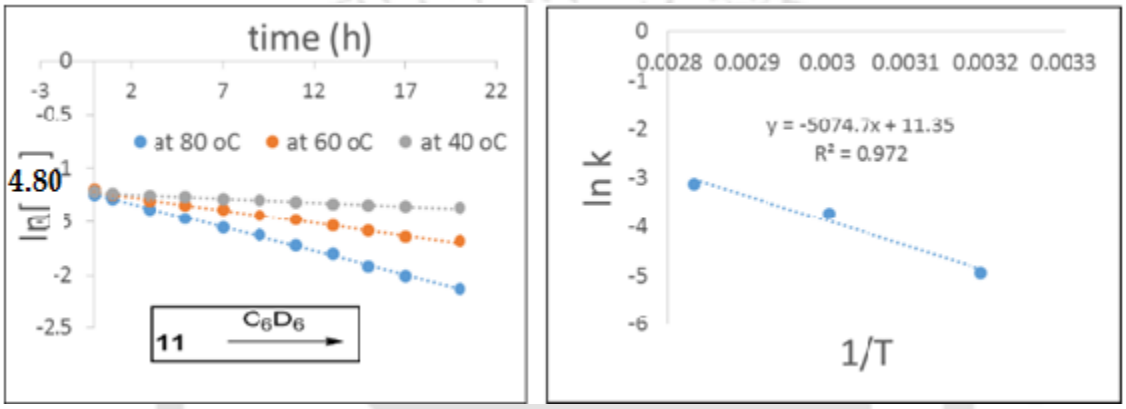


Figure 2: The rate of the conversion of ketamine **4.80.** The concentration of **4.80** was determined using triphenyl methane as the internal standard

The kinetics of the conversion of key intermediate **4.80** of the reaction was investigated with the help of ^{1}H-NMR spectroscopy (**Figure 2**). It was observed that the rate of the conversion of imine **4.80** follows a first order kinetics with the rate constant of 4.4 x 10^{-2} h^{-1} at 80 ^{o}C. The rate decreases with the decrease in the reaction temperature. The activation energy for this conversion reaction (10.1 kcal/mol) was found from the slope of Arrhenius plot.

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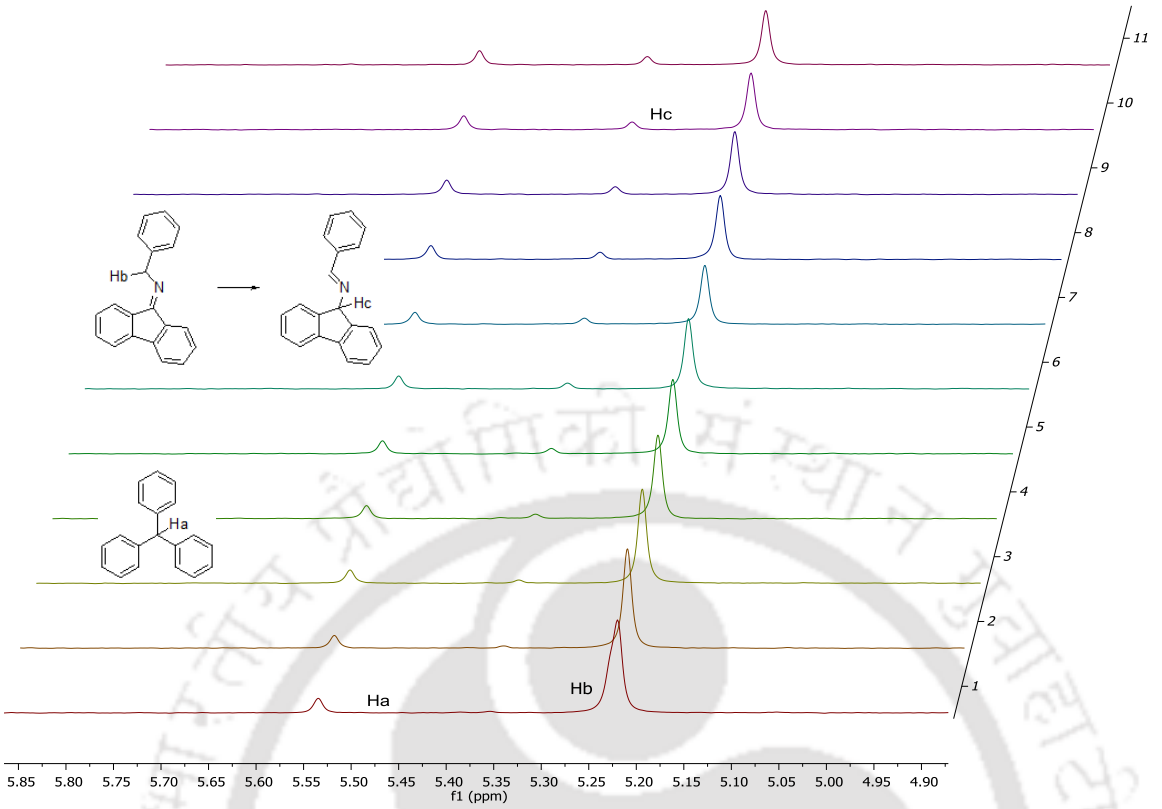

Figure 3: NMR study for thee rate of the isomerization of ketamine

4.12 Summary:

We have developed a non-classical method for direct C-C coupling of primary amines with the active methylenes to obtain alkene and dihydropyridines which are traditionally accessed from the reaction of an aldehyde and active methylenes. Biomimetic dehydrogenation of primary amine under mild conditions, which is free of metallic reagents or catalysts and strong oxidizing agents, allowed subsequent reaction of resulted imines with the activated methylene compounds. The ketamine to aldimine isomerization, the key step of the reaction, followed a first order kinetics with an activation barrier of 10.1 kcal/mol. This non-classical approach for the synthesis of alkenes and dihydropyridines starting from primary amines would bring the diversity in synthetic planning.

4.13 Experimental section:

General procedure for the synthesis of olefin (GP I): Amine (0.56 mmol) was added to a solution of 9-fluorenone imine (0.56 mmol) in toluene (2 mL) and the mixture was stirred at room temperature for 1 h. Active methylene compound (0.56 mmol) was then added to the mixture and the reaction mixture was refluxed for 48 h under argon atmosphere (placing argon balloon). After disappearance of starting materials (indicated by TLC) solvent was

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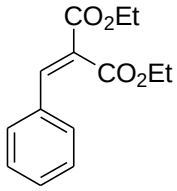
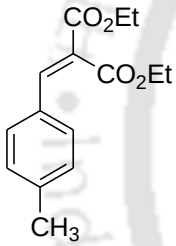
evaporated under reduced pressure. The crude mixture was subjected to column chromatography (silica) to afford analytically pure products.

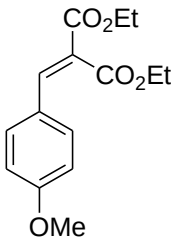
Diethyl 2-benzylidenemalonate (4.65a)[12b]: According to GP I, benzylamine (60 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65a** as a colourless oil (94 mg, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.73 (s, 1H), 7.45 - 744 (m, 2H), 7.39 - 7.34 (m, 3H), 4.35 - 4.28 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.9, 164.3, 142.3, 133.1, 130.7, 129.6, 129.0, 126.5, 61.9, 61.8, 14.3, 14.1 ppm.



Diethyl 2-(4-methylbenzylidene)malonate (4.65b)[12b]: According to GP I, 4-methylbenzylamine (68 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65b** as a colourless oil (99 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.37 - 4.27 (m, 4H), 2.36 (s, 3H), 1.34 - 1.29 (m, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.2, 164.5, 142.4, 141.4, 130.3, 129.8, 129.8, 125.4, 61.9, 61.6, 21.7, 14.4, 14.1 ppm.



Diethyl 2-(4-methoxybenzylidene)malonate (4.65c)[12b]: According to GP I, 4-methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65c** as a colourless oil (0.10 g, 64%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.68 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.34 - 1.31 (m, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.4, 164.6, 161.7, 141.9, 131.7, 125.5, 123.7, 114.4, 61.8, 61.6, 55.5, 14.3, 14.1 ppm.



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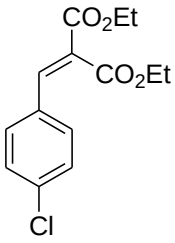
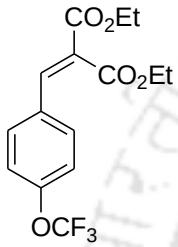
Diethyl 2-(4-chlorobenzylidene)malonate (4.65d)[12b]: According to GP I, 4-



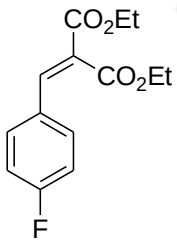
chlorobenzylamine (79 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65d** as a colourless oil (0.11 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 7.40 - 7.34 (m, , 4H), 4.36 - 4.28 (m, 4H), 1.35 - 1.28 (m, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.6, 164.1, 140.9, 136.8, 131.6, 130.8, 129.3, 127.1, 62.1, 62.0, 14.3, 14.1 ppm.

Diethyl 2-(4-(trifluoromethoxy)benzylidene)malonate (4.65e): According to GP I, 4-



trifluoromethoxybenzylamine (0.11 g, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65e** as a colourless oil (0.13 g, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.70 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.36 - 4.29 (m, 4H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.5, 164.1, 150.7, 140.5, 131.7, 131.2, 127.4, 121.1, 62.1, 62.1, 14.3, 14.1 ppm. HRMS: Exact mass calculated for $C_{15}H_{15}F_3O_5$ ($[M+H]^+$): 333.0944, Found: 333.0961.

Diethyl 2-(4-fluorobenzylidene)malonate (4.65f) [12b]: According to GP I, 4-



Fluorobenzylamine (70 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.03 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65f** as a colourless oil (0.10 g, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.68 (s, 1H), 7.47 - 7.44 (m, 2H), 7.06 (t, *J* = 8.4 Hz, 2H), 4.35 - 4.28 (m, 4H), 1.34 - 1.28 (m, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.8, 164.9, 164.2, 163.2, 141.0, 131.8, 131.6, 129.6, 129.3, 129.3, 129.0, 126.3, 126.3, 116.3, 116.3, 116.1, 62.0, 61.9, 14.3, 14.1 ppm.

Diethyl 2-(2-fluorobenzylidene)malonate (4.65g)[12c]: According to GP I, 2-fluorobenzylamine (70 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65g** as a colourless oil (89 mg,

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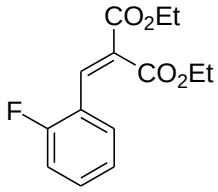
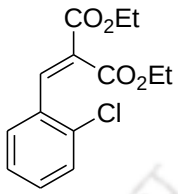
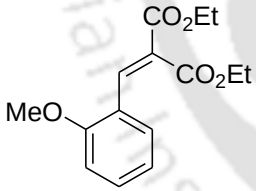


60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.89 (s, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.39 - 7.34 (m, 1H), 7.13 - 7.06 (m, 2H), 4.33 - 4.26 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.1, 163.8, 162.1, 159.6, 134.8, 134.7, 132.3, 132.2, 129.4, 129.4, 128.2, 124.3, 124.2, 121.4, 121.3, 116.0, 115.8, 61.8, 61.7, 14.1, 13.8 ppm.

Diethyl 2-(2-chlorobenzylidene)malonate (4.65h)[12c]: According to GP I, 2-chlorobenzylamine (79 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65h** as a colourless oil (0.10 g, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.03 (s, 1H), 7.44 - 7.42 (m, 2H), 7.33 - 7.30 (m, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.1, 163.9, 139.5, 134.9, 132.2, 131.4, 130.1, 129.5, 129.0, 127.0, 62.1, 61.9, 14.3, 14.0 ppm.



Diethyl 2-(2-methoxybenzylidene)malonate (4.65i)[12f]: According to GP I, 2-methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65i** as a colourless oil (0.11 g, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.07 (s, 1H), 7.38 - 7.33 (m, 2H), 6.90 - 6.87 (m, 2H), 4.30 - 4.24 (m, 4H), 3.83 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.9, 164.5, 158.1, 138.4, 132.1, 129.3, 126.3, 122.4, 120.6, 110.9, 61.6, 61.5, 55.6, 14.3, 14.0 ppm.



Diethyl 2-(3,4-dichlorobenzylidene)malonate (4.65j)[12d]: According to GP I, 3,4-dichlorobenzylamine (98 mg, 0.56 mmol), 9-fluorenone imine **4.65** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65j** as a colourless oil (0.12 g, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.28 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.38 - 4.29 (m, 4H), 1.33 (q, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR

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(151 MHz, $CDCl_3$) δ = 166.2, 163.8, 139.4, 134.9, 133.4, 133.1, 131.2, 131.0, 128.6, 128.3, 62.2, 62.2, 14.3, 14.2 ppm.

Diethyl 2-(3-methoxybenzylidene)malonate (4.65k)[12f]: According to GP I, 3-methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65k** as a colourless oil (0.1 g, 64%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.73 (s, 1H), 7.32 - 7.29 (m, 1H), 7.08 - 7.06 (m, 1H), 7.02 - 7.01 (m, 1H), 6.97-6.96 (m, 1H), 4.38 - 4.31 (m, 4H), 3.82 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.9, 164.3, 159.9, 142.2, 134.4, 130.0, 126.8, 122.2, 116.7, 114.5, 61.9, 61.9, 55.5, 14.4, 14.1 ppm.

Dimethyl 2-benzylidenemalonate (4.65l)[12e]: According to GP I, benzylamine (60 mg, 0.36 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and dimethylmalonate (64 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:15) of crude product gave **4.65l** as a colourless oil (77 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.43 - 7.37 (m, 5H), 3.84 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.4, 164.7, 143.2, 132.9, 130.9, 129.6, 129.1, 125.6, 53.0, 52.9 ppm.

Dimethyl 2-(2-methoxybenzylidene)malonate (4.65m)[12g]: According to GP I, 2-methoxybenzylamine (77, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and dimethylmalonate (64 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:15) of crude product gave **4.65m** as a colourless oil (88 mg, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.38 - 7.32 (m, 2H), 6.93 - 6.89 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.4, 164.9, 158.2, 139.3, 132.4, 129.2, 125.4, 122.3, 120.7, 111.1, 55.7, 52.7, 52.6 ppm.

Dibenzyl 2-benzylidenemalonate (4.65n)[12c]: According to GP I, benzylamine (60 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and dibenzylmalonate (0.14 mL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:10) of crude product gave **4.65n** as a colourless oil (0.13 g, 64%). ^{1}H NMR (600 MHz,

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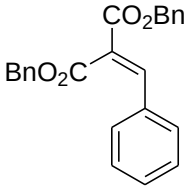
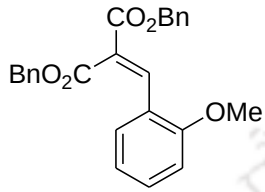
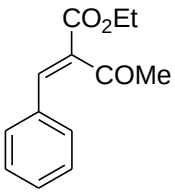


$CDCl_3$) δ = 7.82 (s, 1H), 7.39 - 7.28 (m, 15H), 5.313 (s, 2H), 5.309 (s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.5, 164.1, 143.4, 135.7, 135.0, 132.8, 130.8, 129.7, 129.0, 128.97, 128.78, 128.73, 128.65, 128.48,128.22, 125.8, 67.8, 67.4 ppm.

Dibenzyl 2-(2-methoxybenzylidene)malonate (4.65o): According to GP I, 2-methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and dibenzylmalonate (0.14 mL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:10) of crude product gave **4.65o** as a colourless oil (0.16 g, 72%). ^1H NMR (600 MHz, $CDCl_3$) δ = 8.17 (s, 1H), 7.37 - 7.23 (m, 12H), 6.89 - 6.75 (m, 2H), 5.29 (s, 2H), 5.24 (s, 2H), 3.82 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.6, 164.3, 158.2, 139.7, 135.8, 135.2, 132.3, 129.4, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 125.6, 122.2, 120.7, 111.0, 67.5, 67.2, 55.6 ppm. HRMS: Exact mass calculated for $C_{25}H_{22}O_2$ ($[M+H]^+$): 403.1540, Found: 403.1555.



Diethyl 2-((furan-2-yl)methylene)malonate (4.65p)[12a]: According to GP I, furfurylamine (54 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and diethylmalonate (85 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave **4.65p** as a colourless oil (80 mg, 60%). ^1H NMR (600 MHz, $CDCl_3$) δ = 7.46 (d, *J* = 1.9 Hz, 1H), 7.39 (s, 1H), 6.71 (d, *J* = 3.6 Hz, 1H), 6.44 - 6.43 (m, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.3, 164.2, 149.03, 146.2, 127.5, 122.0, 118.0, 112.7, 61.7, 61.6, 14.2, 14.1 ppm.



***(E/Z)*-ethyl 2-benzylidene-3-oxobutanoate (4.65q)[12j]:** According to GP I, benzylamine (60 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol)) and Ethyl acetoacetate (71 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave a mixture of E/Z (1.3:1) isomer of **4.65q** as a colourless oil (76 mg, 62%). ^1H NMR (600 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 7.57 (s, 1H), 7.46 - 7.44 (m, 1H), 7.41 - 7.37 (m, 8H), 4.35 - 4.28 (m, 4H), 2.43 (s, 2H), 2.35 (s, 3H), 1.33 (t, *J* = 7.2 Hz,

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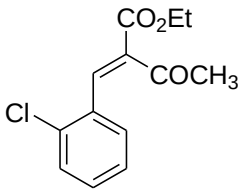
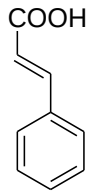
3H), 1.27 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 203.8, 194.9, 168.0, 164.6, 141.5, 140.7, 134.8, 134.2, 133.1, 133.06, 130.9, 130.6, 129.9, 129.7, 129.1, 129.1, 62.0, 61.8, 31.5, 26.8, 14.4, 14.1 ppm.

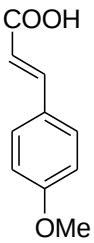
***(E/Z)*-ethyl 2-(2-chlorobenzylidene)-3-oxobutanoate (4.65r):** According to GP I, 2-Chlorobenzylamine (79 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and Ethyl acetoacetate (71 µL, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:20) of crude product gave a mixture of E/Z (1.5:1) isomer of **4.65r** as a colourless oil (91 mg, 64%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.85 (s, 1H), 7.78 (s, 1H), 7.36 - 7.32 (m, 4H), 7.25 - 7.20 (m, 3H), 7.17 - 7.11 (m, 2H), 4.25 - 4.19 (m, 2H), 4.16 - 4.11 (m, 2H), 2.36 (s, 2H), 2.14 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 4H), 1.07 (t, *J* = 7.2 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.0, 194.6, 166.8, 164.1, 138.3, 137.5, 136.8, 136.5, 134.7, 134.4, 132.1, 131.9, 131.4, 131.2, 130.2, 129.9, 129.9, 129.3, 127.1, 127.0, 61.8, 6.7, 31.3, 26.8, 14.2, 13.9 ppm.



Cinnamic acid (4.65s)[12h]: According to GP I: Benzylamine (60 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and malonic acid (58 mg, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:1) of crude product gave **4.65s** as a white solid (58 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 16.0 Hz, 1H), 7.58 - 7.56 (m, 2H), 7.42 - 7.41 (m, 3H), 6.47 (d, *J* = 16.0 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 172.9, 147.3, 134.2, 131.0, 129.2, 128.6, 117.5 ppm.



***(E)*-3-(4-methoxyphenyl)acrylic acid (4.65t)[12i]:** According to GP I: 4-Methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and malonic acid (58 mg, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:1) of crude product gave **4.65t** as a white solid (68 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 15.9 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.32 (d, *J* = 15.9 Hz, 1H), 3.85 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 162.0, 146.9, 130.3, 127.1, 114.8, 114.6, 55.6 ppm.



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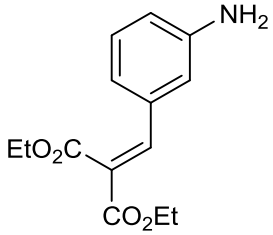
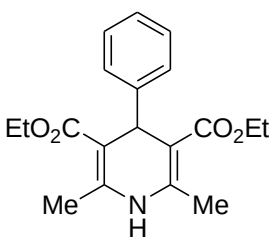
Diethyl 2-(3-aminobenzylidene) malonate (4.67): According to GP I, 2-aminobenzylamine (0.10 g, 0.82 mmol), 9-fluorenone imine **4.64** (0.22 g, 1.23 mmol) and diethylmalonate (0.13 mL, 0.82 mmol) were reacted for 48 h and solvent was evaporated after cooling down the reaction mixture. Then crude mixture was dissolved in methanol and 1 (N) aq HCl was added to it. After 3 h stirring at rt, solvent was evaporated and reaction mixture was diluted by NaHCO3 (10 mL) and the mixture was extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed successively with water (20 mL) and brine (10 mL). The organic layer was dired over sodium sulphate and the solvents were evaporated to get the crude reaction mixture which was subjected to column chromatography (silica gel; EtOAc: hexane, 1:4) to obtain analytically pure product (**4.67**) as a pale yellow oil (0.12 g, 54%). 1H NMR (400 MHz, CDCl3) δ = 7.64 (s, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.85 – 6.84 (m, 1H), 6.82 – 6.79 (m, 1H), 4.35 – 4.27 (m, 4H), 2.52 (s, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm. 13C NMR (151 MHz, CDCl3) δ = 167.0, 164.3, 144.6, 142.3, 134.2, 123.0, 126.6, 121.4, 118.6, 116.9, 62.0, 61.9, 14.4, 14.1 ppm.



General procedure for the synthesis of dihydropyridine (GP II): Amine (0.56 mmol) was added to a solution of 9-fluorenone imine (0.56 mmol) in toluene (2 mL) and the mixture was stirred at room temperature for 1 h. Active methylene compound (1.12 mmol) and ammonium acetate (1.12 mmol) was then added to the mixture and the reaction mixture was refluxed for 48 h under argon atmosphere (placing argon balloon). After disappearance of starting materials (indicated by TLC) solvent was evaporated under reduced pressure. The crude mixture was subjected to column chromatography (silica) to afford analytically pure products.

Diethyl-1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (4.69a)[(13a)]: According to GP II, benzylamine (60 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69a** as a yellow gum (0.13 g, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.29 - 7.26 (m, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.2



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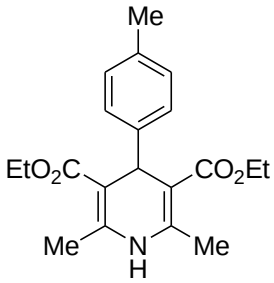
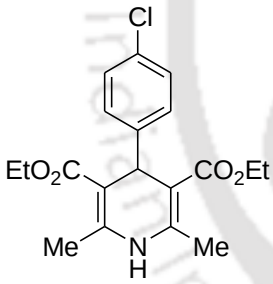
Hz, 2H), 7.11 (t, *J* = 7.2 Hz, 1H), 5.96 (s, 1H), 4.99 (s, 1H), 4.14 - 4.02 (m, 4H), 2.30 (s, 6H), 1.22 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.7, 147.8, 144.1, 128.0, 127.8, 126.1, 104.0, 59.7, 39.7, 19.5, 14.3 ppm.

Diethyl-1,4-dihydro-2,6-dimethyl-4-p-tolylpyridine-3,5-dicarboxylate (4.69b)[13c]:



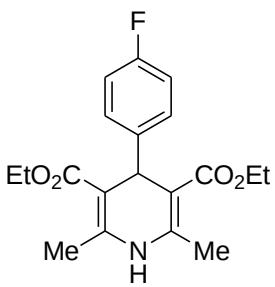
According to GP II, 4-methylbenzylamine (68 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69b** as a yellow gum (0.13 g, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.17 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 5.73 (s, 1H), 4.94 (s, 1H), 4.11 - 4.05 (m, 4H), 2.31 (s, 6H), 2.27 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.9, 145.1, 144.0, 135.7, 128.7, 128.0, 104.4, 59.9, 39.3, 21.3, 19.8, 14.5 ppm.

Diethyl-4-(4-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4.69c)[13a]:



According to GP II, 4-chlorobenzylamine (79 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69c** as a yellow gum (0.13 g, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.22 - 7.20 (m, 2H), 7.17 - 7.15 (m, 2H), 5.66 (s, 1H), 4.95 (s, 1H), 4.123 - 4.04 (m, 4H), 2.32 (s, 6H), 1.21 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.6, 146.5, 144.2, 131.9, 129.6, 128.1, 104.1, 60.0, 39.5, 19.8, 14.5 ppm.

Diethyl-4-(4-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4.69d)[13c]: According to GP II, 4-fluorobenzylamine (0.70 g, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69d** as a yellow gum (0.12 g, 64%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.24 - 7.22 (m, 2H), 6.90 - 6.86 (m, 2H),



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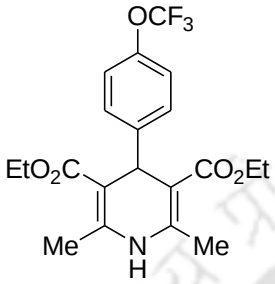
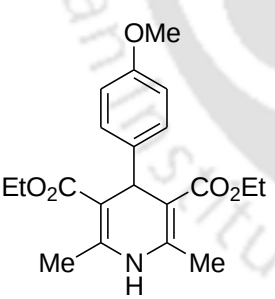
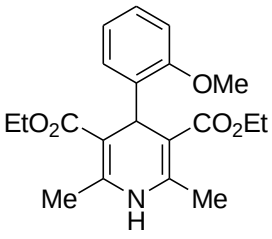
5.67 (s, 1H), 4.95 (s, 1H), 4.14 - 4.03 (m, 4H), 2.32 (s, 6H), 1.21 (t, *J* = 7.2 Hz, 6H). ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.7, 162.3, 160.7, 144.0, 143.9, 143.8, 129.7, 129.6, 114.8, 114.6, 104.4, 60.0, 39.2, 19.8, 14.5 ppm.

Diethyl-1,4-dihydro-2,6-dimethyl-4-(4-(trifluoromethoxy)phenyl)pyridine-3,5dicarboxylate (4.69e): According to GP II, 4-trifluoromethoxybenzylamine (107 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69e** as a yellow gum (0.16 g, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 5.82 (s, 1H), 4.99 (s, 1H), 4.13 - 4.03 (m, 4H), 2.32 (s, 6H), 1.20 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.7, 147.6, 146.7, 144.3, 129.5, 120.5, 104.0, 60.1, 39.4, 19.8, 14.4 ppm. HRMS: Exact mass calculated for $C_{20}H_{22}F_3NO_5$ ($[M+H]^+$): 414.1523, Found: 414.1514.



Diethyl-1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4.69f)[13b]: According to GP II, 4-methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69f** as a yellow gum (0.14 g, 67%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 5.79 (s, 1H), 4.92 (s, 1H), 4.12 - 4.04 (m, 4H), 3.74 (s, 3H), 2.30 (s, 6H), 1.22 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.9, 158.0, 143.9, 140.5, 129.1, 113.3, 104.5, 59.9, 55.3, 38.9, 19.7, 14.5 ppm.





Diethyl-1,4-dihydro-4-(2-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4.69g)[13d]: According to GP II, 2-methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12

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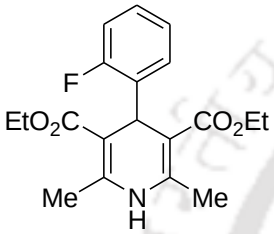
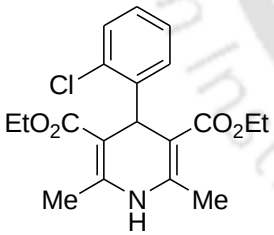
mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69g** as a yellow gum (0.14 g, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.21 (dd, *J* = 7.58, 1.8 Hz, 1H), 7.10 (td, *J* = 7.8, 1.8 Hz, 1H), 6.82 - 6.77 (m, 2H), 5.62 (s, 1H), 5.26 (s, 1H), 4.04 (q, *J* = 7.2 Hz, 4H), 3.77 (s, 3H), 2.28 (s, 6H), 1.19 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.3, 157.3, 143.9, 135.5, 130.8, 127.5, 120.2, 110.8, 103.3, 59.7, 55.5, 35.5, 19.7, 14.4 ppm.

Diethyl-4-(2-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4.69h)[13b]: According to GP II, 2-fluorobenzylamine (70 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69h** as a yellow gum (0.12 g, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.31 - 7.28 (m, 1H), 7.10 - 7.07 (m, 1H), 7.00 - 6.97 (m, 1H), 6.91 - 6.88 (m, 1H), 5.77 (s, 1H), 5.23 (s, 1H), 4.09 - 4.00 (m, 4H), 2.30 (s, 6H), 1.19 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.8, 160.8, 159.1, 144.5, 135.2, 135.1, 131.3, 131.3, 127.90, 127.9, 123.8, 123.8, 115.2, 115.0, 103.2, 59.9, 34.3, 19.7, 14.2 ppm.



Diethyl-4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4.69i)[13c]: According to GP II, 2-chlorobenzylamine (79 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69i** as a yellow gum (0.13 g, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.36 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.21 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.10 (td, *J* = 7.6, 1.4 Hz, 1H), 7.01 (td, *J* = 7.6, 1.7 Hz, 1H), 6.25 (s, 1H), 5.38 (s, 1H), 4.08-4.04 (m, 4H), 2.24 (s, 6H), 1.18 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.0, 145.8, 144.5, 132.5, 131.7, 129.4, 127.4, 126.8, 103.7, 59.9, 37.6, 19.4, 14.4 ppm.



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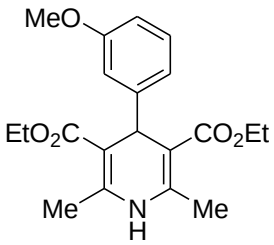
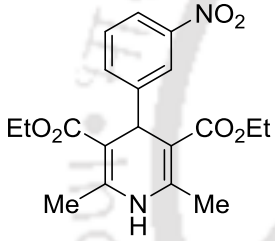
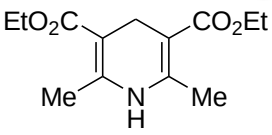
Diethyl-1,4-dihydro-4-(3-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4.69j)[13h]: According to GP II, 3-methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mm ol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69j** as a yellow gum (0.14 g, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.12 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.85 - 6.84 (m, 1H), 6.68 - 6.67 (m, 1H), 5.70 (s, 1H), 4.98 (s, 1H), 4.12 - 4.06 (m, 4H), 3.76 (s, 3H), 2.32 (s, 6H), 1.23 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.8, 159.4, 149.5, 144.2, 128.9, 120.7, 114.4, 111.0, 104.2, 60.0, 55.3, 39.7, 19.8, 14.5 ppm.



Diethyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (4.69k)[13d]: According to GP II: 3-Nitrobenzylamine (85 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69k** as a yellow gum (0.13 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (s, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 8 Hz, 1H), 5.69 (s, 1H), 5.02 (s, 1H), 4.025-3.97 (m, 4H), 2.29 (s, 6H), 1.15 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.3, 150.1, 148.3, 144.9, 134.7, 128.8, 123.3, 121.5, 103.6, 60.2, 40.2, 19.9, 14.4 ppm.



Diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4.69l)[13c]: According to GP II, methylamine hydrochloride (38 mg, 0.56 mmol), 9-fluorenone imine **4.60** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:2) of crude product gave **4.69l** as a yellow solid (22 mg, 15%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.40 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 4H), 3.24 (s, 2H), 2.17 (s, 6H), 1.26 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.3, 145.2, 99.6, 59.9, 25.0, 19.3, 14.7 ppm.



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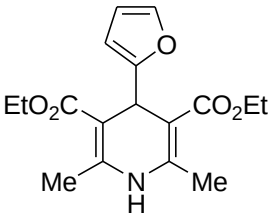
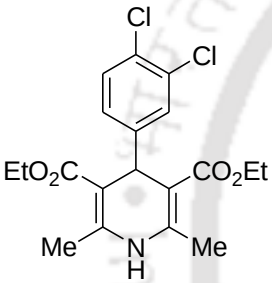
Diethyl 4-(furan-2-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4.69m)[13a]:



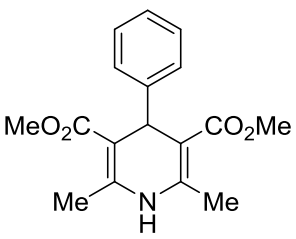
According to GP II, furfurylamine (54 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69m** as a yellow gum (0.12 g, 67%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.20 (s, 1H), 6.20 - 6.19 (m, 1H), 6.01 (s, 1H), 5.93 (d, *J* = 3.0 Hz, 1H), 5.19 (s, 1H), 4.20 - 4.09 (m, 4H), 2.31 (s, 6H), 1.25 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.7, 158.8, 145.4, 141.0, 110.2, 104.6, 100.8, 60.0, 33.5, 19.7, 14.5 ppm.

Diethyl-4-(3,4-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4.69n)[13f]:



According to GP II, 3,4-dichlorobenzylamine (98 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69n** as a yellow gum (0.14 g, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 1.8 Hz, 1H), 7.25 (d, *J* = 3.6 Hz, 1H), 7.11 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.70 (s, 1H), 4.92 (s, 1H), 4.14 - 4.03 (m, 4H), 2.32 (s, 6H), 1.23 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.4, 148.2, 144.5, 131.8, 130.3, 130.0, 129.9, 127.8, 103.6, 60.2, 39.5, 19.9, 14.5 ppm.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (4.69o)[13a]: According to GP II, benzylamine (60 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), methyl acetoacetate (1.2 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69o** as a yellow gum (0.12 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 - 7.17 (m, 2H), 7.16 - 7.12 (m, 2H), 7.08-7.04 (m, 1H), 5.60 (s, 1H), 4.93 (s, 1H), 3.57 (s, 6H), 2.27 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.2, 147.6, 144.4, 128.2, 127.8, 126.4, 104.1, 51.2, 39.4, 19.9 ppm.



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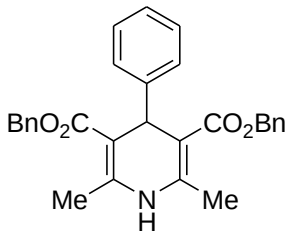
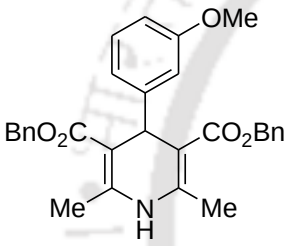
Dibenzyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (4.69p)[13g]:



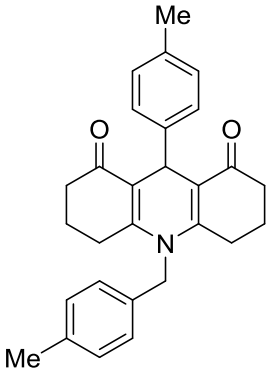
According to GP II, benzylamine (60 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), benzyl acetoacetate (1.9 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69p** as a yellow gum (0.18 g, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.29 - 7.28 (m, 5H), 7.20 - 7.19 (m, 6H), 7.17 - 7.11 (m, 4H), 5.77 (s, 1H), 5.11 - 5.04 (m, 5H), 2.33 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 167.5, 147.6, 144.6, 144.6, 136.7, 128.5, 128.3, 128.2, 128.0, 127.9, 126.4, 104.1, 65.8, 39.7, 19.9 ppm.

Dibenzyl 1,4-dihydro-4-(3-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate



(4.69q): According to GP I: According to GP II, 3-methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), benzyl acetoacetate (1.9 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.69q** as a yellow gum (0.18 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 - 7.20 (m, 10H), 7.07 (t, *J* = 8 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.76 - 6.75 (m, 1H), 6.68 - 6.65 (m, 1H), 5.73 (s, 1H), 5.12 - 5.04 (m, 5H), 3.57 (s, 3H), 2.32 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.5, 159.5, 149.2, 144.8, 136.7, 129.0, 128.5, 128.0, 127.9, 120.7, 114.1, 111.7, 103.9, 65.8, 55.1, 39.7, 19.8 ppm. HRMS: Exact mass calculated for $C_{30}H_{29}NO_5$ ($[M+H]^+$): 484.2118, Found: 484.2130.

10-(4-Methylbenzyl)-9-(p-tolyl)decahydroacridine-1,8(*2H,5H*)-dione (4.69r)[13e]:



According to GP I, 4-methylbenzylamine (0.135 g, 1.12 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and 1,2-cyclohexanedione (0.13 g, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:1) of crude product gave **4.69r** as a white solid (0.14 g, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.20 - 7.18 (m, 4H), 7.04 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 5.35 (s, 1H), 4.89 (s, 2H), 2.68 - 2.64 (m,

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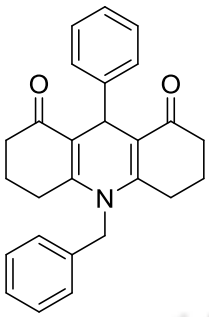
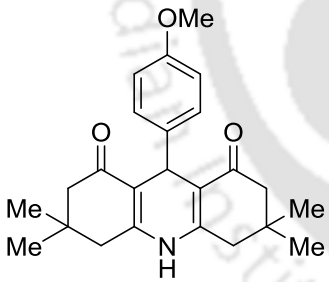
2H), 2.50 – 2.45 (m, 2H), 2.37 (s, 3H), 2.37 - 2.34 (m, 2H), 2.31 - 2.28 (m, 2H), 2.26 (s, 3H), 1.98 - 1.94 (m, 2H), 1.91 - 1.87 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 196.12, 152.43, 143.50, 137.84, 135.49, 133.99, 130.09, 128.92, 127.88, 125.41, 116.49, 48.83, 36.68, 31.48, 26.87, 21.64, 21.27, 21.25 ppm.

10-Benzyl-decahydro-9-phenylacridine-1,8(*5H,8aH*)-dione(4.69s)[13e]: According to GP



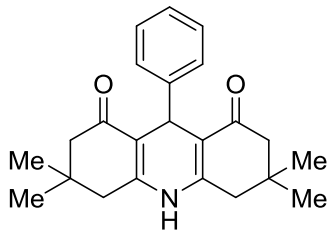
I, benzylamine (0.12 g, 1.12 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and cyclohexanedione (0.13 g, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:1) of crude product gave **4.69s** as a white solid (0.13 g, 60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.40 (t, J = 7.4 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.31 - 7.30 (m, 2H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 2H), 7.14 - 7.11 (m, 1H), 5.44 (s, 1H), 4.96 (s, 2H), 2.72 - 2.67 (m, 2H), 2.53-2.48 (m, 2H), 2.44 - 2.40 (m, 2H), 2.35 - 2.30 (m, 2H), 2.03 - 1.98 (m, 2H), 1.96 - 1.89 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 196.1, 152.5, 146.3, 137.1, 129.5, 128.3, 128.1, 128.0, 126.2, 125.5, 116.5, 49.1, 36.7, 31.8, 26.9, 21.7 ppm.

Decahydro-9-(4-methoxyphenyl)-3,3,6,6-tetramethylacridine-1,8(*5H,8aH*)-



dione(4.69t)[13e]: According to GP I, 4-methoxybenzylamine (77 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (0.16 g, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:1) of crude product gave **4.69t** as a white solid (0.115 g, 54%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.85 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 5.02 (s, 1H), 3.63 (s, 3H), 2.24 - 2.09 (m, 8H), 1.03 (s, 6H), 0.92 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 196.5, 157.7, 150.2, 139.4, 129.0, 113.3, 113.1, 55.1, 51.0, 40.4, 32.9, 32.7, 29.7, 27.1 ppm.

Decahydro-3,3,6,6-tetramethyl-9-phenylacridine-1,8(*5H,8aH*)-dione (4.69u)[13e]:



According to GP I, benzylamine (60 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (0.16 g, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:1) of crude product gave **4.69u** as a white solid (97 mg,

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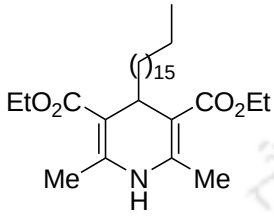
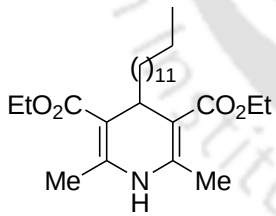
50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.66 (s, 1H), 7.34 (d, *J* = 6.8 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 5.10 (s, 1H), 2.28 - 2.11 (m, 8H), 1.05 (s, 6H), 0.94 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 195.5, 147.5, 146.5, 128.3, 128.2, 126.2, 114.1, 50.9, 41.5, 33.8, 32.9, 29.7, 27.4 ppm.

Diethyl-4-heptadecyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4.70a):



According to GP II, octadecylamine (0.151 g, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:5) of crude product gave **4.70a** as a yellow gum (0.16 g, 58%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.54 (s, 1H), 4.23 - 4.11 (m, 4H), 3.91 (t, *J* = 6 Hz, 1H), 2.27 (s, 6H), 1.30 - 1.21 (m, 38H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.4, 144.8, 103.6, 59.8, 37.1, 33.1, 32.1, 30.2, 30.0, 29.97, 29.93, 29.88, 29.58, 25.1, 22.9, 19.7, 14.6, 14.4 ppm (Less no carbon observed due to overlapping in aliphatic region). HRMS: Exact mass calculated for $C_{30}H_{53}NO_4$ ($[M+H]^+$): 492.4047, Found: 492.4031.

Diethyl-1,4-dihydro-2,6-dimethyl-4-tridecylpyridine-3,5-dicarboxylate (4.70b):



According to GP II, tetradecylamine (0.119 g, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:5) of crude product gave **4.70b** as a yellow gum (0.15 g, 60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.51 (s, 1H), 4.24 - 4.12 (m, 4H), 3.91 (t, *J* = 6 Hz, 1H), 2.28 (s, 6H), 1.30 - 1.18 (m, 30H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.4, 144.7, 103.6, 59.8, 37.1, 33.1, 32.1, 30.2, 30.01, 29.96, 29.93, 29.92, 29.88, 29.58, 25.1, 22.9, 19.7, 14.6, 14.4 ppm (Less no carbon observed due to overlapping in aliphatic region). HRMS: Exact mass calculated for $C_{26}H_{45}NO_4$ ($[M+H]^+$): 436.3421, Found: 436.3434.

Diethyl-1,4-dihydro-2,6-dimethyl-4-nonylpyridine-3,5-dicarboxylate (4.70c)[2i]:

According to GP II, decylamine (88 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56

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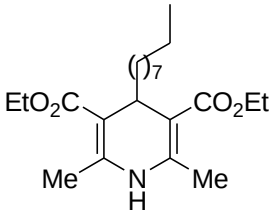
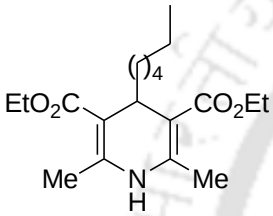
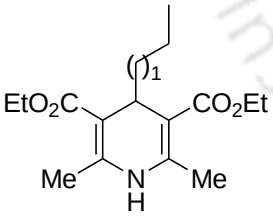
mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:5) of crude product gave **4.70c** as a yellow gum (0.131 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.51 (s, 1H), 4.25 - 4.12 (m, 4H), 3.92 (t, *J* = 5.8 Hz, 1H), 2.27 (s, 6H), 1.31 - 1.20 (m, 22H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.4, 144.8, 103.6, 59.8, 37.1, 33.1, 32.1, 30.2, 30.0, 29.9, 29.6, 25.1, 22.9, 19.7, 14.6, 14.3 ppm.



Diethyl-4-hexyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4.70d)[13j]: According to GP II, heptylamine (64 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.70d** as a yellow gum (0.116 g, 56%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.51 (s, 1H), 4.24 - 4.11 (m, 4H), 3.91 (t, *J* = 6.0 Hz, 1H), 2.28 (s, 6H), 1.30 - 1.19 (m, 16H), 0.85 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.4, 144.8, 103.6, 59.8, 37.1, 33.1, 32.2, 29.8, 25.1, 23.0, 19.7, 14.6, 14.4 ppm.



Diethyl-1,4-dihydro-2,6-dimethyl-4-propylpyridine-3,5-dicarboxylate (4.70e)[13k]: According to GP II, butylamine (41 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol), ethyl acetoacetate (1.4 mL, 1.12 mmol) and ammonium acetate (86 mg, 1.12 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:4) of crude product gave **4.70e** as a yellow gum (89 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.50 (s, 1H), 4.23 - 4.12 (m, 4H), 3.93 (t, *J* = 5.6 Hz, 1H), 2.28 (s, 6H), 1.30 - 1.18 (m, 10H), 0.84 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.4, 144.8, 103.6, 59.8, 39.4, 32.9, 19.7, 18.2, 14.6, 14.5 ppm.



General procedure for the synthesis of benzimidazole (GP III): Amine (0.56 mmol) was added to a solution of 9-fluorenone imine (0.56 mmol) in toluene (2 mL) and the mixture was stirred at room temperature for 1 h. o-Phenylenediamine (1.12 mmol) then added to the mixture and the reaction mixture was refluxed for 48 h under argon atmosphere (placing

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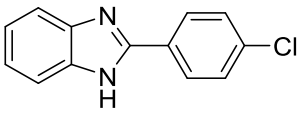
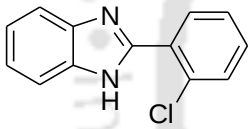
argon balloon). After disappearance of starting materials (indicated by TLC) solvent was evaporated under reduced pressure. The crude mixture was subjected to column chromatography (silica) to afford analytically pure products.

2-(4-methylphenyl)-*1H*-benzo*[d]*imidazole (4.72a)[14a]: According to GP III, 4-



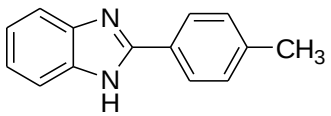
Chloroenzylamine (79 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and o-phenylenediamine (60 mg, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:3) of crude product gave **4.72a** as a pale yellow solid (84 mg, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.03 (s, 1H), 8.23 (d, *J* = 8.6 Hz, 2H), 7.70 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.57 (s, 1H), 7.26 - 7.21 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ = 150.3, 143.9, 135.2, 134.6, 129.1, 128.2, 122.8, 121.9, 119.0, 111.5, 99.6 ppm.

2-(2-chlorophenyl)-*1H*-benzo*[d]*imidazole (4.72b)[14a]: According to GP III, 2-



chloroenzylamine (79 mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and o-phenylenediamine (60 mg, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:3) of crude product gave **4.72c** as a white solid (80 mg, 63%). ^{1}H NMR (400 MHz, DMSO-D_6) δ = 12.78 (s, 1H), 7.93 - 7.90 (m, 1H), 7.72 (s, 1H), 7.67 - 7.65 (m, 1H), 7.64 - 7.51 (m, 3H), 7.28 - 7.25 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-D_6) δ = 149.6, 143.6, 135.1, 132.5, 132.1, 131.7, 130.8, 130.3, 127.9, 123.3, 122.2, 119.5, 112.2 ppm.

2-p-tolyl-*1H*-benzo*[d]*imidazole (4.72c)[14a]: According to GP III, 4-methylenzylamine (68



mg, 0.56 mmol), 9-fluorenone imine **4.64** (0.10 g, 0.56 mmol) and o-phenylenediamine (60 mg, 0.56 mmol) were reacted for 48 h and column chromatography (silica gel; EtOAc:hexane, 1:3) of crude product gave **4.72c** as a white solid (72 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.88 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 2H), 7.66 (s, 1H), 7.66 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 4.4 Hz, 2H), 2.38 (s, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ = 150.3, 143.9, 135.2, 134.6, 129.1, 128.2, 122.8, 121.9, 119.0, 111.5, 99.6 ppm.

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4.14 References

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CHAPTER 5

Rapid Access to Cinnamamides and Piper Amides via Three Component Coupling of Arylaldehyde, Amines, and Meldrum's Acid

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5.1 Introduction:

Cinnamamides is an important class of compounds having a wide spectrum of bioactivity, such as anticancer,[1] anti-malarial,[2] anti-trypanosomal,[3] anti-oxidant,[4] anti-diabetic,[5] anti-microbial activity,[6] etc. (**Figure 1**). In addition, cinnamamides were found as the key structural unit of many natural products including piper amides.[8]

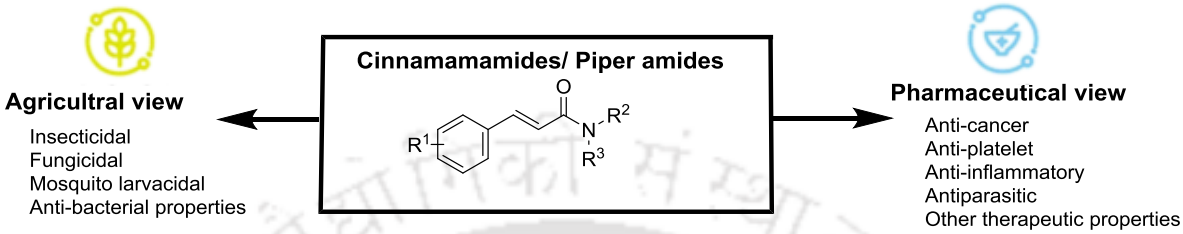


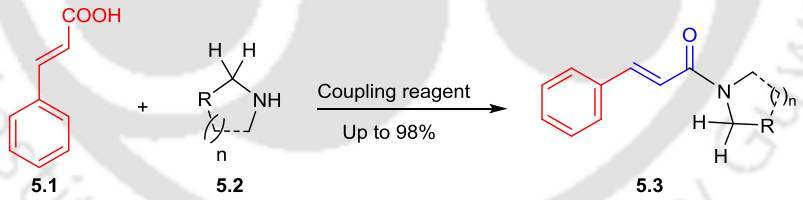
Figure 1: Agricultural and pharmaceutical importance of cinnamamides and piper amides

A large number of cinnamamides with wide structural diversity have been synthesized to investigate the structure-activity relationship studies in the field of medicinal chemistry[7].

5.2 Selected known methods for the synthesis of cinnamamide:

5.2.1 Conventional procedure:

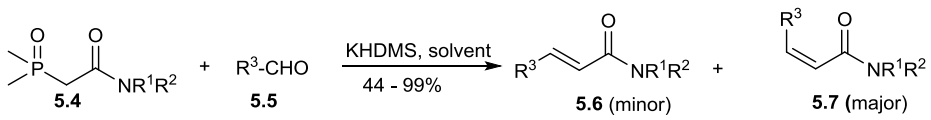
The conventional method relies on the conversion of acids **5.1** to their corresponding active species like acid chlorides by using reagents such as $SOCl_2$ or $POCl_3$ or by using other coupling reagents, followed by condensation with amines **5.2** in the presence of bases such as triethylamine or pyridine (**Scheme 1**).



Scheme 1: Cinnamamide synthesis from cinnamic acid

5.2.2 Selected examples for the synthesis of cinnamamide from benzaldehyde:

Ohba *et al*. have developed the *Horner–Wadsworth–Emmons* reaction of *N*,*N* dibenzyl(diphenylphosphono)- acetamides **5.4** with aromatic aldehydes **5.5** to provide unsaturated amides **5.6** and **5.7** with high *Z*-selectivities. (**Scheme 2**).[11]



Scheme 2: Cinnamamide synthesis by KHDMS

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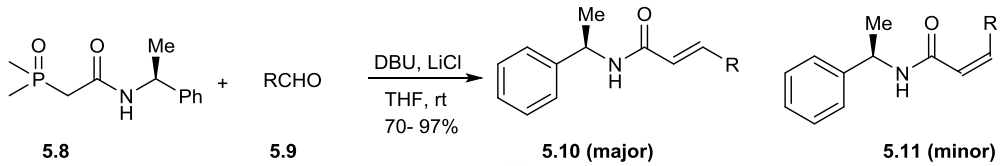
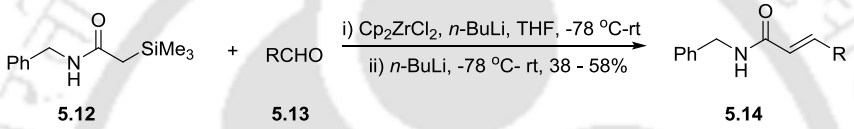
Ordóñez *et al.* developed a highly stereoselective synthesis of (*E*)-α,β-unsaturated amides **5.10** bearing (*S*)-α-methylbenzylamine from 2-phosphonamide derivatives **5.8** *via* Horner–Wadsworth–Emmons reaction. The starting phosphonamides are prepared in two steps **(Scheme 3)**.[12]



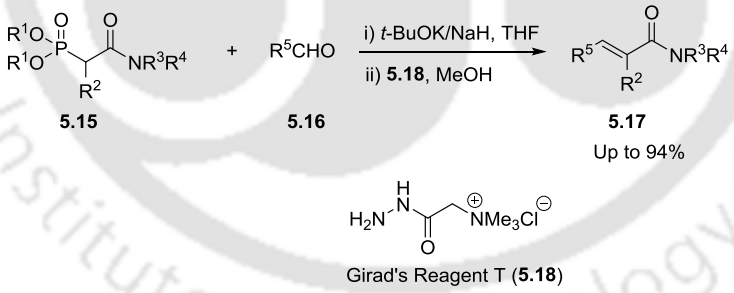
Scheme 3: Cinnamamide synthesis by LiCl

Szymoniak and co-workers developed one-pot procedure for the transformation of compound **5.12** to a α,β-unsaturated secondary amides **5.14 (Scheme 4)**.[11b]



Scheme 4: Zr-mediated cinnamamide synthesis

Kim and co-workers achieved an efficient solution-phase parallel synthesis of a library of natural piper-amide-like compounds **5.17** from the bifunctional β-phosphono-*N*-hydroxysuccinimidyl ester **5.15** intermediate **(Scheme 5)**.[11a]



Scheme 5: Natural-piper amide like compound synthesis

5.2.3 Selected examples for the synthesis of cinnamamide from cinnamaldehyde:

Yamamoto *et al.* developed oxidative amide formation using *N*-hydroxysuccinimide and hypervalent iodine reagents. The method enables cinnmaldehyde **5.19** and amine **5.20** to be coupled under mild reaction conditions providing amide **5.21** in good to excellent yield (**Scheme 6)**. [10e]

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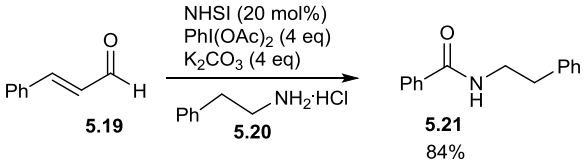
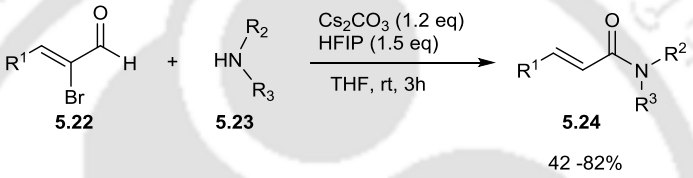


NHSI: *N*-hydroxysuccinimide

Scheme 6: Cinnamamide synthesis from cinnamaldehyde catalyzed by NHSI

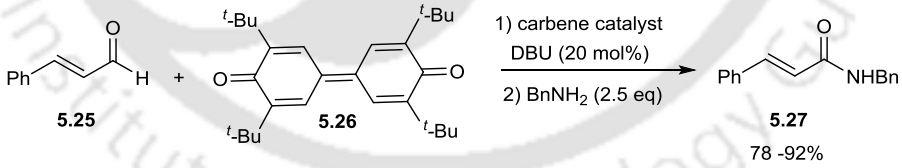
Jiao *et al.* reported a simple and efficient procedure for NHC-catalyzed transformations of bromoenal or α,β -dibromoenal **5.16** into α,β-unsaturated amides **5.18** with high stereoselectivity through C–N bond formation (**Scheme 7**).[10f]



HFIP: hexafluoroisopropanol, NHC catalyst used.

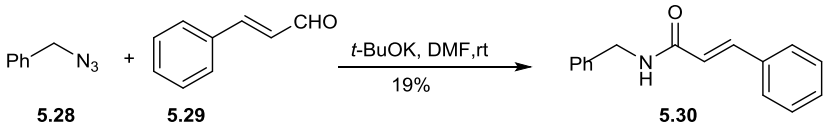
Scheme 7 Cinnamamide synthesis by Cs_2CO_3

Studer and co-workers described *N*-Heterocyclic carbene catalyzed oxidative amidations of cinamaldehyde **5.25** and benzylamine to the corresponding cinnamamide **5.27** by using the readily available quinone based oxidant **5.26** (**Scheme 8**). [10h]



Scheme 8: Cinnamamide synthesis

Manetsch *et al.* developed a practical and efficient amidation reaction involving cinnamaldehyde **5.29** and various azides **5.28** under mild conditions to form cinnamamides **5.30** (**Scheme 9**).[10a]



Scheme 9: Cinnamamide synthesis from azide

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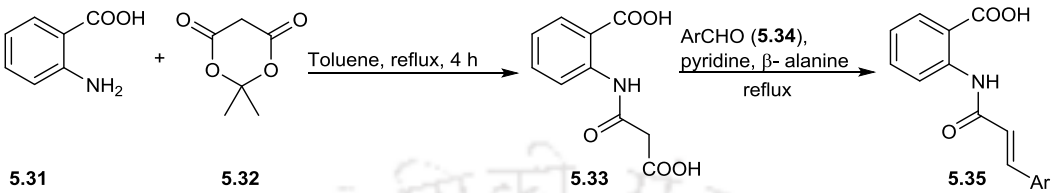
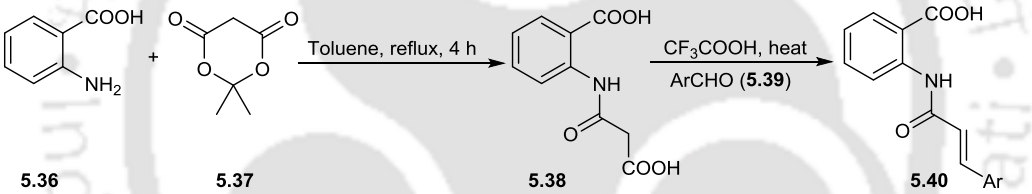
5.2.4 Two-step synthesis of cinnamamides from anthranilic acid by Meldrum's acid:

Parab and co-workers reported a two-step method for the synthesis of cinnamamide derivatives **5.35** from antharanilic acid **5.31**, Meldrum's acid **5.32** and aryl aldehyde **5.34** (**Scheme 10**).[15a]



Scheme 10: Cinnamamide synthesis by Meldrum's acid in pyridine

Jure and co-workers reported a method for the synthesis of cinnamamides **5.40** from the monoanilides of malonic acid **5.38,** Which was formed from anthranilic acid **5.36** and Meldrum's acid **5.37,** and aromatic aldehydes **5.39** (**Scheme 11**).[15b]



Scheme 11: Cinnamamide synthesis trifluoroacetic acid

5.3 Summary of known methods for the synthesis of cinnamamides:

The synthesis of cinnamamides and piper amides mainly relies on the coupling reaction of cinnamic acid derivatives which are prepared from the Knoevenagel condensation of aromatic aldehyde and malonic acid (**Scheme 12a**).[9] Oxidative amidation of cinnamaldehydes is another approach for the synthesis of cinnamamides (**Scheme 12b**).[10] Wittig or Horner-Wadsworth-Emmons reactions were also used for the synthesis of cinnamamides starting from aromatic aldehyde (**Scheme 12c**).[11] However, most of the methods rely on the multistep process and involve the formation of unwanted by-products originated from coupling agents, oxidants, phosphine based reagents, etc. Therefore, development of an operationally simple method without using additional catalysts, reagents, or additives that produce hazardous chemical wastes is desirable.

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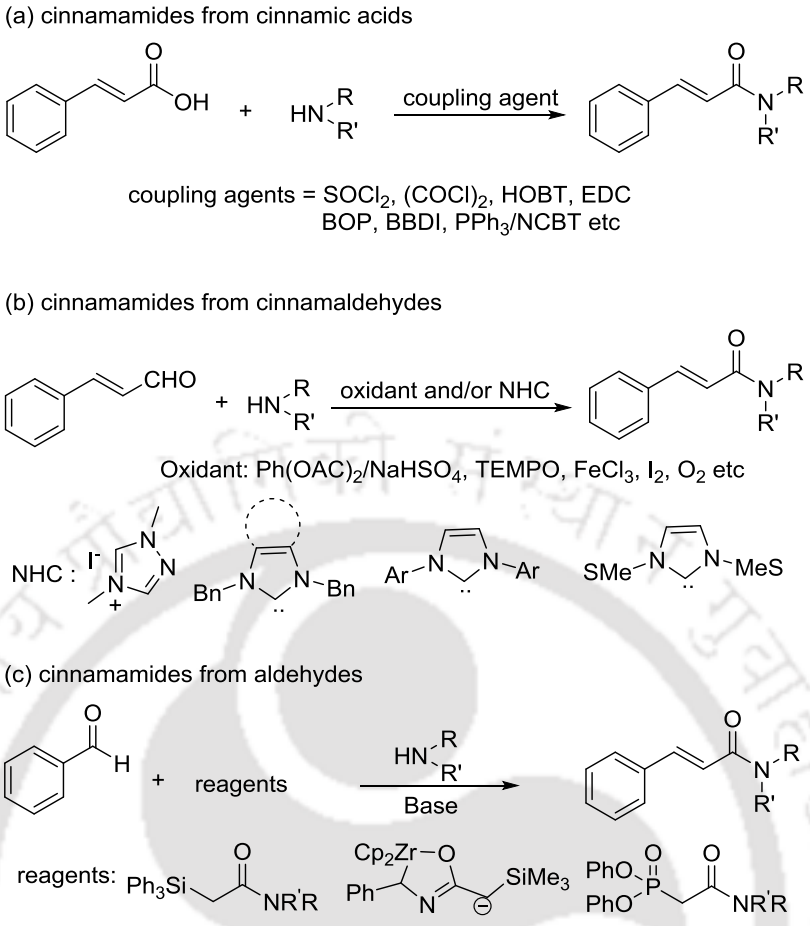
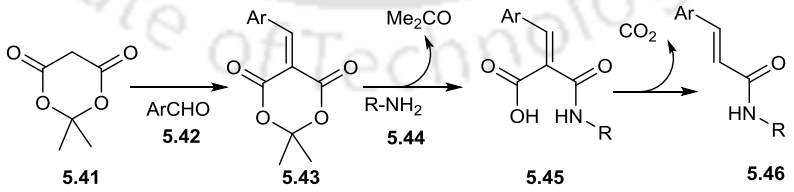


Scheme12. Known strategies for the **s**ynthesis of cinnamamides

5.4 Hypothesis for the present work:

It was anticipated that Knoevenagel condensation of Meldrum's acid (**5.41**) with aldehyde **5.42** would provide the enone **5.43** (**Scheme 13**).[12] The enone can react with amine **5.44** to produce corresponding amide **5.45** which can undergo decarboxylation to give the desired cinnamamide



Scheme 13: Hypothesis for one-step synthesis of cinnamamides.

5.5 Reaction Optimization:

According to the hypothesis, the investigation started with a reaction of benzylamine and 4-chlorobenzaldehyde in the presence of Meldrum's acid (**5.41**) at room temperature (Table 1, entry 1). However, the desired cinnamamide **5.46a** was not

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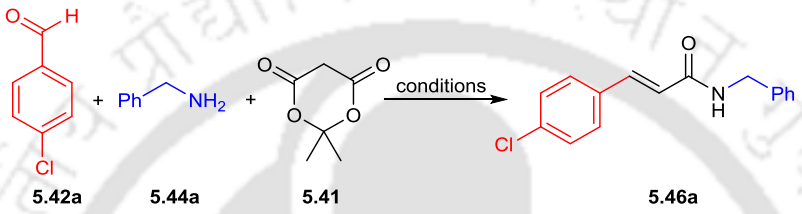
formed. Pleasingly, the desired cinnamamide **5.46a** was isolated with a 67% yield from the reaction which was carried out in refluxing toluene for 12 h (Table 1, entry 2,). Different reaction conditions, such as solvents, temperatures, reactant stoichiometry, etc. were evaluated to maximize the yield of the desired product **5.46a** (Table 1). The best yield of **5.46a** (68%, Table 1, entry 4) was obtained from the reaction of a mixture of Meldrum's acid (**5.41**), 4-chlorobenzaldehyde and benzylamine in refluxing toluene without any other catalysts, reagents or additives.

Table 1. Optimization of reaction conditions[a]



5.42a **5.44a** **5.41** **5.46a**

entry	Conditions	Yield (%)[b]
1	toluene, rt, 12 h	0
2	toluene, reflux, 12 h	67
3	toluene, reflux, 24 h	64
4	**toluene, 110 ^{o}C, 8 h**	**68**
5	toluene, 110 ^{o}C, 2 h	56
6	DMF, 140 ^{o}C, 5 h	25
7	DCM, 40 ^{o}C, 5 h	5
8	m-xylene, 140 ^{o}C, 5 h	66
9	toluene, MW, 120 ^{o}C, 30 min	50
10	methanol, 80 ^{o}C, 5 h	10
11	neat, 120 ^{o}C, 12 h	60
12[c]	toluene, 110 ^{o}C, 5 h	69
13[d]	toluene, 110 ^{o}C, 5 h	67

[a] All reactions were carried out with 4-chlorobenzaldehyde (1.42 mmol), benzyl amine (1 eq, 1.42 mmol), and Meldrum's acid (**5.41**) (1 eq, 1.42 mmol) in 3 mL of solvent. [b]Isolated yield. [C] reaction was performed by using 1.2 eq of benzylamine**.** [d]reaction was performed by using 1.2 eq of Meldrum's acid (**5.41**).

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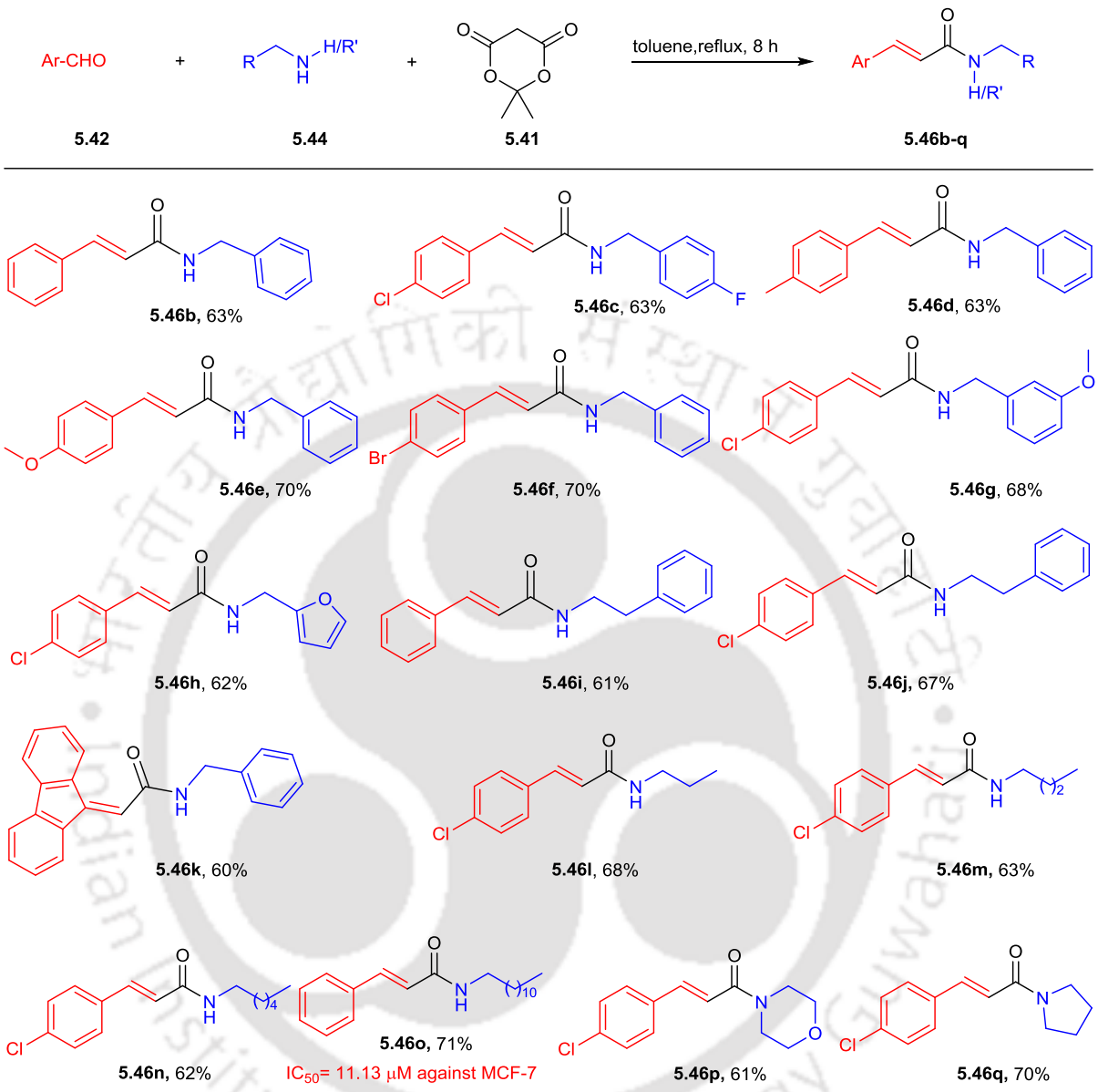
5.6 Substrate scope for Cinnamamides:



Scheme 14: Scope in synthesis of cinnamamides.

Next, the optimized conditions were used to test the substrates scope of this three component reaction (**Scheme 14**). A wide variety of aromatic aldehydes **5.42** and amines **5.44** were reacted with Meldrum's acid to provide the corresponding cinnamamides **5.46b-q** with very good yields (Scheme 3). Substrates (aldehydes and amines) having both electron-donating (e.g. Me, OMe) and electron-withdrawing (e.g. F, Cl) groups were efficiently reacted to provide the desired cinnamamides. Unsaturated amides **5.46h** containing heteroaromatic group were also prepared in

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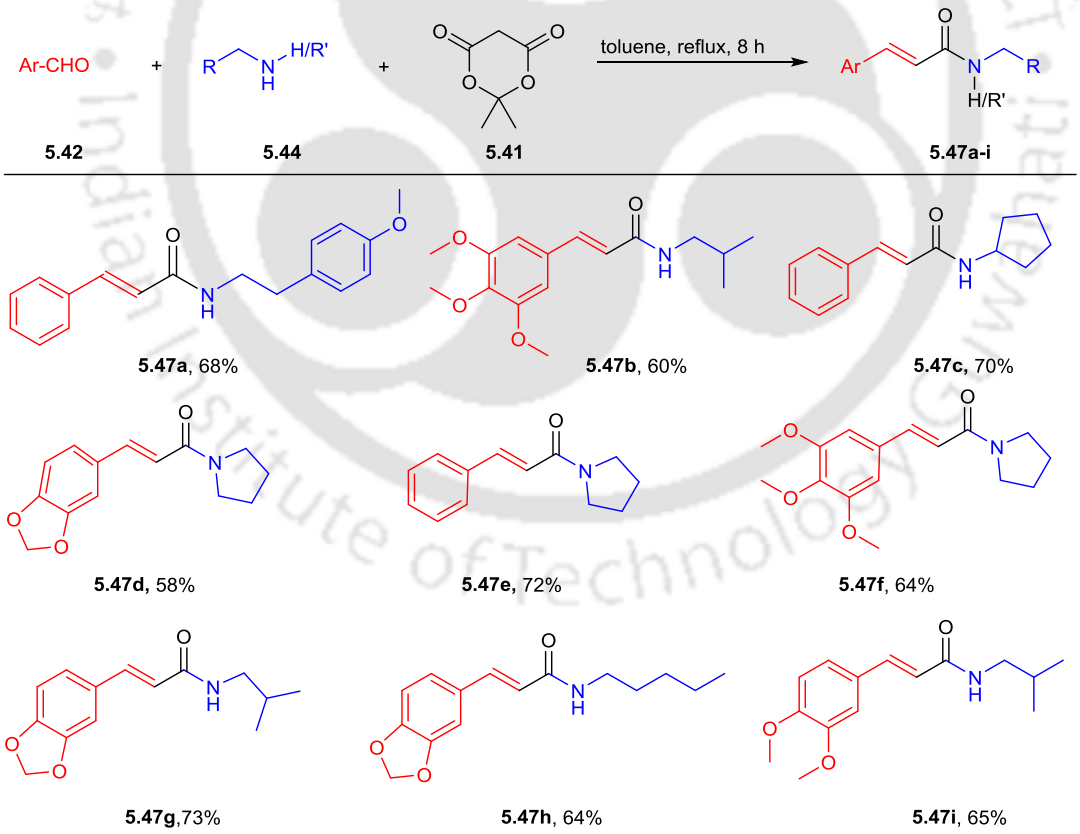
very good yields using this reaction. 9-Fluorenone also reacted with benzylamine and Meldrum's acid under the optimized reaction condition to form the desire amide **5.46k** with a 60% yield. Acyclic primary and secondary amines reacted smoothly to produce the desire cinnamamides. Importantly, a potent molecule, *N*-dodecylcinnamamide **5.46o**, which was synthesized in two steps starting from cinnamic acid involving hazardous reagents like $SOCl_2$,[13] was prepared in a single step using our method. Aliphatic *N*-heterocycles and diheterocycles also participated in the reaction.

5.7 Substrate scope for Piper amides:

A large number of bioactive cinnamamides have been isolated from Piper *species*.[8] We were interested in applying our methods for the synthesis of natural cinnamamides (piper amides). Accordingly, optimized reaction conditions were used to prepare structurally diverse piper amides **5.47a-i** with good to very good yields (**Scheme 15**).



Scheme 15: Scope in the synthesis of piper amides.

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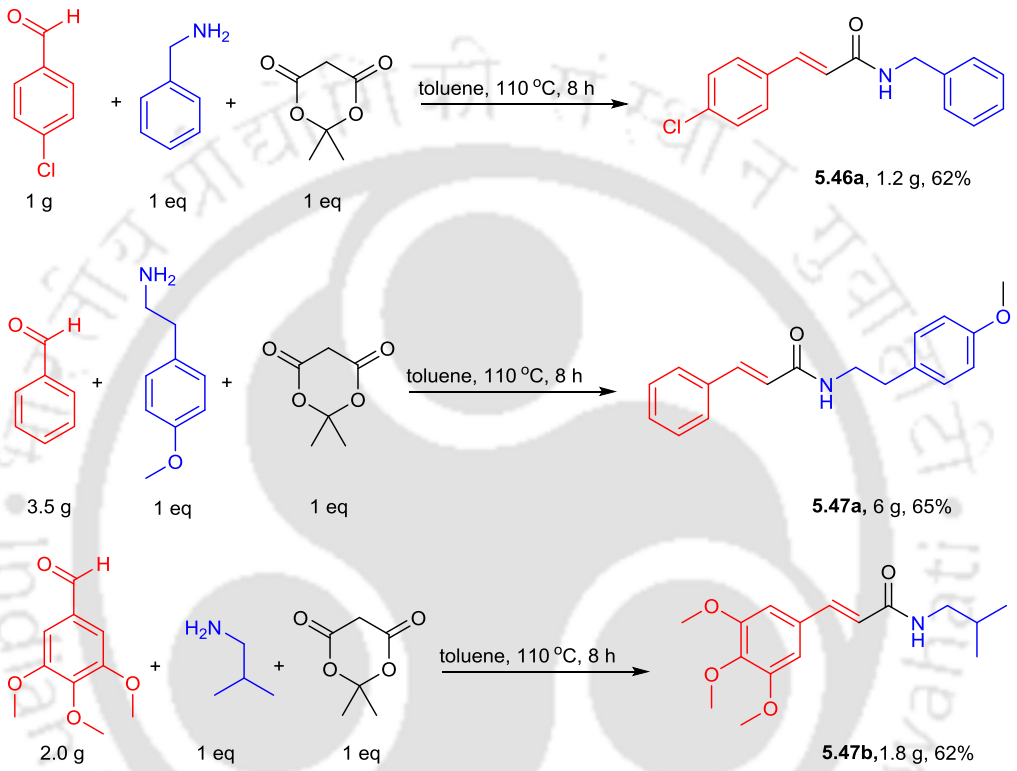
The yield of this one-step reaction was observed to be higher or comparable with the known methods. However, the present method is superior to all the known methods in the context of atom economy, step economy, and reduction of undesired chemical waste.

5.8 Gram scale synthesis:



Scheme 16: Preparative scale synthesis of selected unnatural and natural cinnamamides

The reaction was found to be effective in gram-scale synthesis, which indicated its potential for its practical application **(Scheme 16)**. Cinnamamide **5.46a** and the natural cinnamamides **5.47a** and **5.47b** were synthesized in 1.2 -6.0 grams quantity using this methodology.

5.9 Controlled reaction:

Additional reactions were performed to understand the reaction mechanism of this three component coupling reaction (**Scheme 17**). The reaction of benzylamine with Meldrum's acid (**5.41**) at room temperature gave monoamides of malonic acid **5.48**

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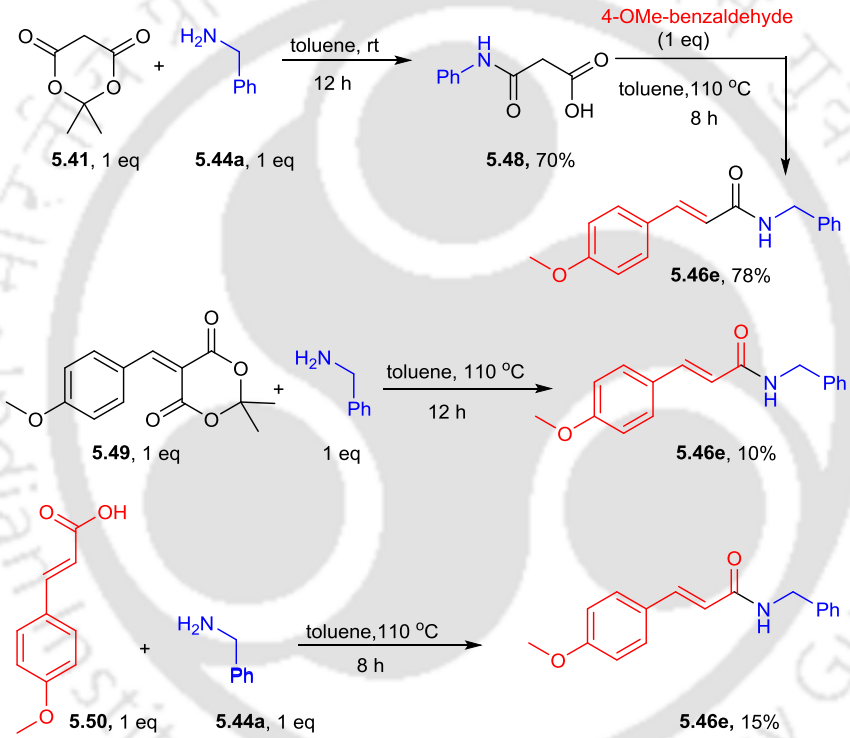
with good yield (70%). Desired cinnamamide **5.46e** was formed with very good yield (78%) when the acid **5.48** was reacted with 4-methoxybenzaldehyde under standard conditions. This observation indicates that the reaction proceeds via malonic acid derivative **5.48**. However, the reaction of benzylidene **5.49** with amines under standard reaction conditions provided the desired product 5.4**6e** with 10% yield. In addition, direct condensation of 4-OMe-cinnamic acid **5.50**, which can be formed *in situ*,[14] and amines gave the corresponding cinnamamides 5.4**6e** with poor yield (15%). These studies indicate that the reactions via benzylidene **5.49** and cinnamic acid **5.50** deliver a minor contribution to the total yield of cinnamamide.



Scheme 17: Controlled experiments

5.10 Proposed mechanism:

Based on the experimental evidence, a plausible mechanism for the three component coupling reaction is shown in **Scheme 18**. The reaction of the amine **5.44** with Meldrum's acid **5.41** provided monoamides of malonic acid **5.51** and acetone. Observed cinnamamide **5.54** can be formed via two possible pathways. Aldol reaction of **5.51** and aromatic aldehyde can provide beta-hydroxy acid **5.52**. In the second possibility, Knoevenagel condensation of **5.51** and aldehyde could occur to

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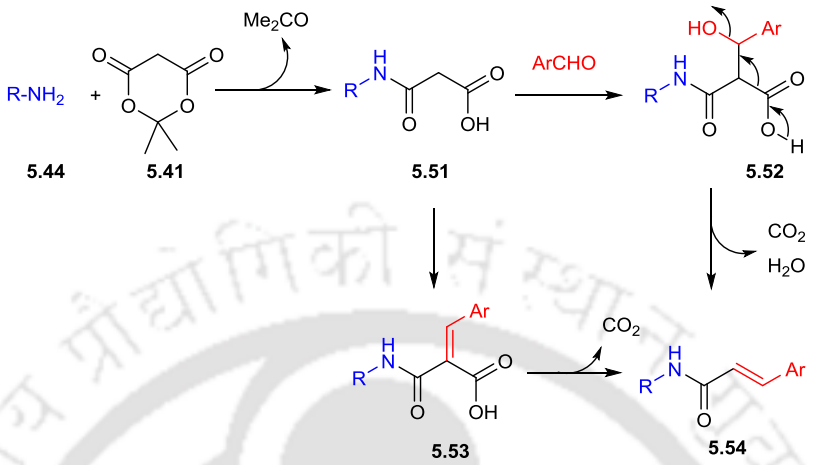
provided benzylidene derivative **5.53** *via* corresponding alcohol **5.52**. Decarboxylation of **5.53** and/or decarboxylation assisted dehydration of alcohol **5.52** gave the thermodynamically more stable *trans*-cinnamamides **5.54**.



Scheme 18: Proposed mechanism of three component reaction.

5.11 Summary:

We have developed an original three-component reaction of aldehyde, amines and Meldrum's acid to provide a wide variety of cinnamamides and piper amides with very good yields which are superior than most of the known methods. The reaction enables the synthesis of cinnamamide without using coupling reagents, oxidants or catalysts that produce undesired chemical wastes. The reaction is highly atom economic producing CO_2 and acetone as the by-product. We believe that this method will find wide application for the rapid synthesis of a library of medicinally important cinnamamides/piper amides to facilitate the identification of the most potent molecule.

5.12 Experimental section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus(V)oxide (P_2O_5). Commercial grade xylene, benzene and toluene were distilled over CaH_2 before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ^1H, ^{13}C NMR spectroscopy: *Bruker 600 MHz* (at 298 K), *Bruker*

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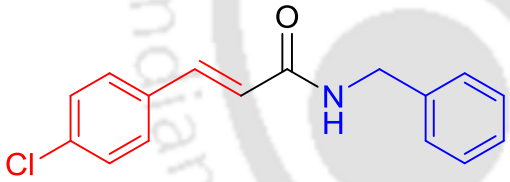
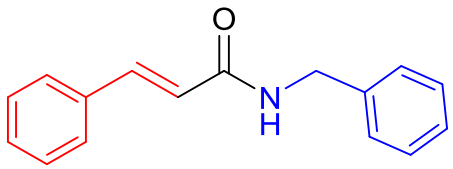
400 MHz (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS δ (^{1}H) 0.0 ppm, δ (^{13}C) 0.0 ppm) which was used as the inner reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.2 ppm; CD_3OD, (^{1}H) 3.31 ppm, δ (^{13}C) 49.0 ppm) were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity. 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). IR: IR spectra were recorded on a PerkinElmer diamond tip IR.

General procedure for the synthesis of cinnamamide (GP I): Arylaldehyde (0.94 – 0.56 mmol) was added to a solution of amine (0.94 – 0.56 mmol) and Meldrum's acid (0.94 – 0.56 mmol) in toluene (2 – 4 mL) and the mixture was refluxed (110 ^{o}C) for 8 h. After disappearance of starting materials (indicated by TLC), solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography to get analytically pure product.

(*E*)-*N*-benzyl-3-(4-chlorophenyl)acrylamide (5.46a)[6]: According to GP I, 4-chlorobenzaldehyde (0.10 g, 0.71 mmol), benzylamine (76 mg, 0.71 mmol) and Meldrum's acid (0.10 g, 0.71 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.46a** as white solid (0.14 g, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 15.6 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 3H), 7.39 – 7.29 (m, 6H), 6.41 (d, *J* = 15.6 Hz, 1H), 6.07 (br. s, 1H), 4.59 (d, *J* = 5.8 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.5, 140.1, 138.1, 135.6, 133.2, 129.1, 129.0, 128.8, 127.9, 127.7, 120.9, 43.9 ppm.



(*E*)-*N*-benzylcinnamamide (5.46b)[1,6]: According to GP I, benzaldehyde (0.1 g, 0.94 mmol), benzylamine (0.1 g, 0.94 mmol) and Meldrum's acid (0.14 g, 0.94 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.46b** as white solid (0.14 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ =



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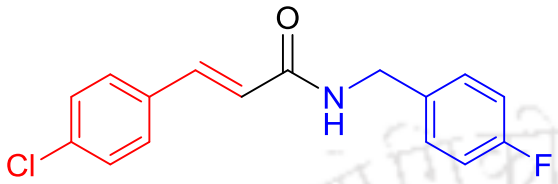
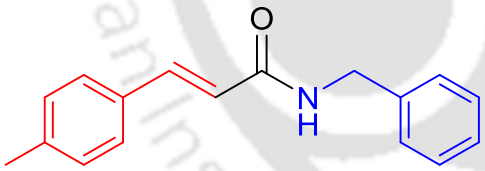
7.56 (d, *J* = 15.6 Hz, 1H), 7.37 – 7.35 (m, 2H), 7.26 – 7.13 (m, 8H), 6.38 (d, *J* = 15.6 Hz, 1H), 6.36 (br. s, 1H), 4.43 (d, *J* = 5.8 Hz, 2H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.0, 141.3, 138.3, 134.8, 129.7, 128.8, 128.7, 127.9, 127.8, 127.5, 120.7, 43.82 ppm.

(*E*)-*N*-(4-fluorobenzyl)-3-(4-chlorophenyl)acrylamide (5.46c): According to GP I, 4-chlorobenzaldehyde (0.10 g, 0.71 mmol), 4-fluorobenzylamine (89 mg, 0.71 mmol) and



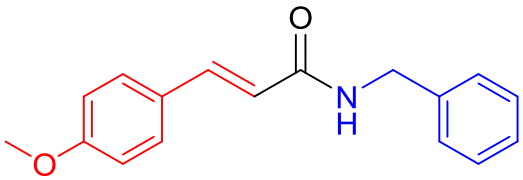
Meldrum's acid (0.10 g, 0.71 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.46c** as colouerless gum (0.13 g, 63%). FTIR: $\tilde{\nu}$ = 3288, 1654, 1622, 1510, 1224, 1091, 821 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, *J* = 15.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.20 (m, 4H), 6.96 (t, *J* = 8.4 Hz, 2H), 6.30 (d, *J* = 15.6 Hz, 1H), 5.84 (br. s, 1H), 4.48 (d, *J* = 5.7 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.4, 139.4, 134.7, 132.9, 132.1, 128.6, 128.6, 128.1, 128.0, 119.7, 114.7, 114.5, 42.2 ppm. (Increased number of ^{13}C signal is observed due to F-coupling). HRMS: Exact mass calculated for $C_{16}H_{13}ClFNO$ ([M+H]$^+$): 290.0742, Found: 290.0742.

(*E*)-*N*-benzyl-3-*p*-tolylacrylamide (5.46d)[7]: According to GP I, 4-methylbenzaldehyde (0.10 g, 0.82 mmol), benzylamine (88 mg, 0.82 mmol) and Meldrum's acid (1.20 g, 0.82



mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.46d** as white solid (0.13 g, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 15.6 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.37 – 7.31 (m, 4H), 7.31 – 7.26 (m, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.29 (br. s, 1H), 4.56 (d, *J* = 5.6 Hz, 2H), 2.37 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.1, 141.3, 140.0, 138.3, 132.1, 129.5, 128.7, 127.9, 127.8, 127.5, 119.5, 43.2, 21.4 ppm.

(*E*)-*N*-benzyl-3-(4-methoxyphenyl)acrylamide (5.46e)[6]: According to GP I, 4-methoxy benzaldehyde (0.10 g, 0.94 mmol), benzylamine (0.10 g, 0.94 mmol) and Meldrum's acid



(0.14 g, 0.94 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane,

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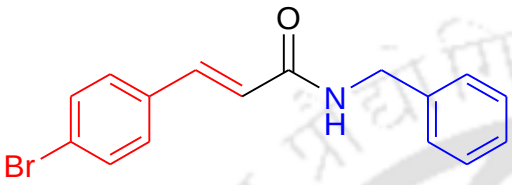
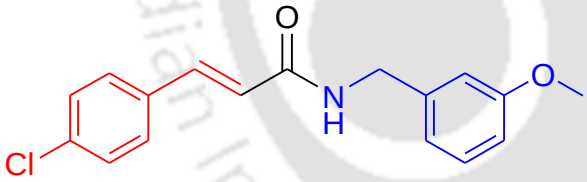
1:3) to get analytically pure product **5.46e** as white solid (0.18 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 15.6 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.16 (m, 5H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.23 (d, *J* = 15.6 Hz, 1H), 6.10 (br. s, 1H), 4.46 (d, *J* = 5.8 Hz, 2H), 3.73 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2, 160.9, 140.9, 138.4, 129.4, 128.7, 127.9, 127.54, 127.48, 118.2, 114.3, 55.3, 43.8 ppm.

(*E*)-*N*-benzyl-3-(4-bromophenyl)acrylamide (5.46f)[6]: According to GP I, 4-bromo benzaldehyde (0.10 g, 0.54 mmol), benzylamine (58 mg, 0.54 mmol) and Meldrum's acid (78 mg, 0.54 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.46f** as white solid (0.12 g, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 15.6 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.26 (m, 7H), 6.40 (d, *J* = 15.6 Hz, 1H), 6.06 (br. s, 1H), 4.56 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.4, 140.2, 138.1, 133.7, 132.1, 129.2, 128.8, 127.9, 127.7, 123.9, 121.1, 43.9 ppm.



(*E*)-*N*-(4-methoxybenzyl)-3-(4-chlorophenyl)acrylamide (5.46g): According to GP I, 4-chloro benzaldehyde (0.10 g, 0.71 mmol), 3-methoxylbenzylamine (98 mg, 0.71 mmol) and Meldrum's acid (0.1 g, 0.71 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.46g** as colouerless gum (0.15 g, 68%). FTIR: $\tilde{\nu}$ = 2917, 2850, 1735, 1656, 1619, 1491, 1465, 1243, 1091, 1027, 821, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 15.6 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.31 – 7.28 (m, 4H), 6.96 – 6.87 (m, 2H), 6.35 (d, *J* = 15.6 Hz, 1H), 6.12 (br. s, 1H), 4.57 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.3, 157.6, 139.6, 135.4, 133.4, 130.0, 129.0, 128.9, 126.1, 121.4, 120.8, 110.3, 55.4, 39.7 ppm. (Reduced number of ^{13}C signal is observed due to overlapping in aromatic region). HRMS: Exact mass calculated for $C_{17}H_{16}ClNO_2$ ($[M+H]^+$): 302.0942, Found: 302.0947.



(*E*)-3-(4-chlorophenyl)-*N*-((furan-2-yl)methyl)acrylamide (5.46h): According to GP I, 4-chlorobenzaldehyde (0.10 g, 0.71 mmol), furfurylamine (70 mg, 0.71 mmol) and Meldrum's acid (0.1 g, 0.71 mmol) was reacted for 8 h and the crude mixture was purified

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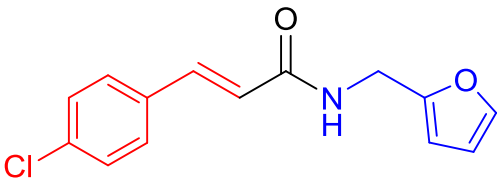
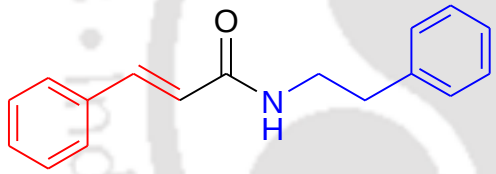
by coloum chromatography (Silica gel; EtOAc: Hexane, 1:3) to get analytically pure product **5.46h** as colourless gum (0.12 g, 62%).



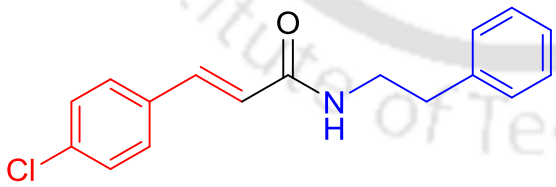
FTIR: $\tilde{\nu}$ = 3287, 1655, 1625, 1551, 1491, 1405, 1328, 1225, 1149, 1090, 975, 820, 737 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 15.6 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.33 (m, 3H), 6.36 (d, *J* = 15.6 Hz, 1H), 6.34 – 6.33 (m, 1H), 6.29 – 6.27 (m, 1H), 5.95 (br. s, 1H), 4.57 (d, *J* = 5.4 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.3, 151.0, 142.3, 140.3, 135.6, 133.2, 129.1, 129.0, 120.7, 110.6, 107.7, 36.7 ppm. HRMS: Exact mass calculated for $C_{14}H_{12}ClNO_2$ ($[M+H]^+$): 262.0629, Found: 262.0624.

(*E*)-*N*-phenethylcinnamamide (5.46i)[9]: According to GP I, benzaldehyde (0.1 g, 0.94 mmol), phenethylamine (0.10 g, 0.94 mmol) and Meldrum's acid (0.14 g, 0.94 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:5) to get analytically pure product **5.46i** as colouerless liquid (0.14 g, 61%).



1H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 15.6 Hz, 1H), 7.42 – 7.52 (m, 2H), 7.30 – 7.23 (m, 5H), 7.19 – 7.14 (m, 3H), 6.25 (d, *J* = 15.6 Hz, 1H), 5.64 (br. s, 1H), 3.61 – 3.56 (m, 2H), 2.84 – 2.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.9, 141.1, 138.9, 134.8, 129.7, 128.8, 128.8, 128.7, 127.8, 126.6, 120.6, 40.8, 35.7 ppm.

(*E*)-3-(4-chlorophenyl)-*N*-phenethylacrylamide (5.46j)[8]: According to GP I, 4-chloro benzaldehyde (0.1 g, 0.71 mmol), phenethylamine (86 mg, 0.71 mmol) and Meldrum's acid (0.1 g, 0.71 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:5) to get analytically pure product **5.46j** as colouerless liquid (0.13 g, 67%).



^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 15.6 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.24 (m, 4H), 7.19 – 7.16 (m, 3H), 6.21 (d, *J* = 15.6 Hz, 1H), 5.56 (br. s, 1H), 3.62 – 3.57 (m, 2H), 2.82 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.5, 139.8, 138.8, 135.5, 133.3, 129.1, 128.9, 128.8, 128.7, 126.6, 121.1, 40.8, 35.6 ppm.

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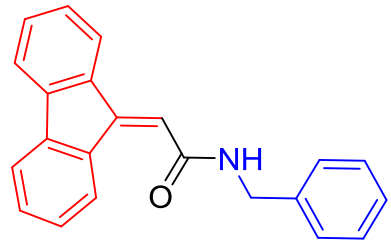
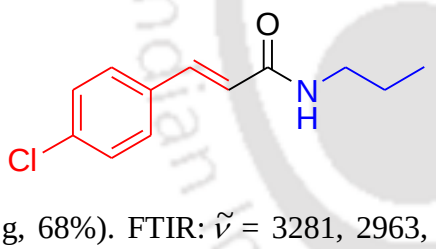
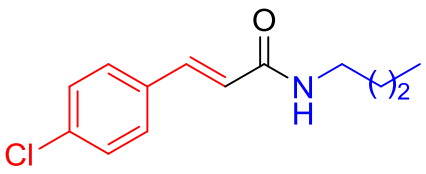
(*E*)-N-benzyl-3-(9*H*-fluoren-9-yl)acrylamide (5.46k): According to GP I, 9-fluorenone (0.10 g, 0.56 mmol), benzylamine (59.0 mg, 0.56 mmol) and Meldrum's acid (80 mg, 0.56 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.46k** as yellow solid (0.11 g, 60%). Mp: 167 – 169 °C. FTIR: $\tilde{\nu}$ = 3295, 2918, 2850, 1644, 1628, 1529, 1441, 1247, 1232, 780, 727, 698 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 8.56 (d, *J* = 7.8 Hz, 1H), 7.67 - 7.64 (m, 2H), 7.41 - 7.37 (m, 6H), 7.35 – 7.34 (m, 1H), 7.28 - 7.24 (m, 3H), 6.76 (s, 1H), 6.29 (br. s, 1H), 4.66 (d, *J* = 5.6 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.1, 143.6, 141.9, 140.4, 138.6, 137.7, 135.3, 130.2, 129.9, 128.9, 128.2, 127.9, 127.79, 127.77, 127.3, 120.7, 119.8, 119.6, 117.1, 44.0 ppm. HRMS: Exact mass calculated for $C_{22}H_{17}NO$ ($[M+H]^+$): 312.1383, Found: 312.1388.



(*E*)-3-(4-chlorophenyl)-*N*-propylacrylamide (5.46l): According to GP I, 4-chlorobenzaldehyde (0.10 g, 0.71 mmol), n-propylamine (42 mg, 0.71 mmol) and Meldrum's acid **5.41** (0.10 g, 0.71 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.46l** as colourless gum (0.10 g, 68%). FTIR: $\tilde{\nu}$ = 3281, 2963, 2927, 1656, 1618, 1551, 1510, 1491, 1406, 1337, 1222, 1092, 1013, 979, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 15.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.29 (d, *J* = 15.6 Hz, 1H), 5.57 (br. s, 1H), 3.32 – 3.27 (m, 2H), 1.56 – 1.50 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.6, 139.7, 135.5, 133.4, 129.1, 128.9, 121.2, 41.6, 22.9, 11.4 ppm. HRMS: Exact mass calculated for $C_{12}H_{14}ClNO$ ($[M+H]^+$): 224.0837, Found: 224.0837.



(*E*)-*N*-butyl-3-(4-chlorophenyl)acrylamide (5.46m)[2]: According to GP I, 4-cholorobenzaldehyde (0.10 g, 0.71 mmol), n-butylamine (52 mg, 0.71 mmol) and Meldrum's acid **5.41** (0.10 g, 0.71 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.46m** as colourless gum (0.10 g,



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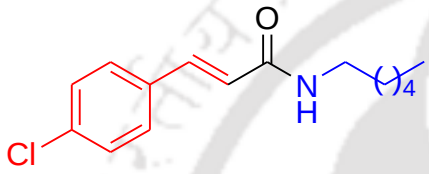
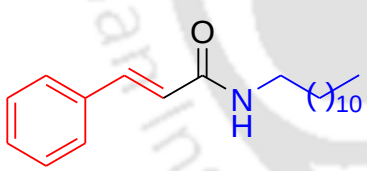
63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 15.6 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.36 (d, *J* = 15.6 Hz, 1H), 5.60 (br. s, 1H), 3.44 – 3.39 (m, 2H), 1.62 – 1.54 (m, 2H), 1.46 – 1.39 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.5, 149.7, 139.6, 136.8, 129.1, 128.9, 121.3, 39.6, 31.7, 20.1, 13.8 ppm.

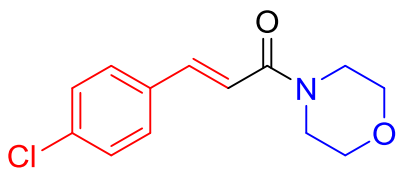
(*E*)-3-(4-chlorophenyl)-*N*-hexylacrylamide (5.46n): According to GP I, 4-chlorobenzaldehyde (0.1g, 0.71 mmol), n-hexylamine (72 mg, 0.71 mmol) and Meldrum's acid **5.41** (0.1 g, 0.71 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:5) to get analytically pure product **5.46n** as white solid (0.12 g, 62%). Mp: 113 – 115°C. FTIR: $\tilde{\nu}$ = 3286, 2927, 2857, 1654, 1619, 1545, 1491, 1339, 1221, 1094, 972, 820 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 15.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.27 (d, *J* = 15.4 Hz, 1H), 5.52 (br. s, 1H), 3.34 – 2.29 (m, 2H), 1.42 – 1.05 (m, 8H), 0.84 – 0.81 (m, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.5, 139.5, 135.4, 133.4, 129.1, 128.9, 121.3, 39.85, 31.48, 29.6, 26.6, 22.6, 14.0 ppm. HRMS: Exact mass calculated for $C_{15}H_{20}ClNO$ ($[M+H]^+$): 266.1306, Found: 266.1304.



(*E*)-*N*-decylcinnamamide (5.46o)[12]: According to GP I, benzaldehyde (0.10 g, 0.94 mmol), n-dodecylamine (0.18 g, 0.94 mmol) and Meldrum's acid **5.41** (0.14 g, 0.94 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:5) to get analytically pure product **5.46o** as white solid (0.19 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 15.6 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.40 – 7.31 (m, 3H), 6.39 (d, *J* = 15.6 Hz, 1H), 5.59 (br. s, 1H), 3.41 – 3.36 (m, 2H), 1.60 – 1.53 (m, 7H), 1.33 – 1.26 (m, 13H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.8, 140.8, 134.9, 129.6, 128.8, 127.7, 120.8, 39.8, 31.9, 29.7, 29.64, 29.62, 29.58, 29.54, 29.3, 29.3, 26.0, 22.7, 14.1 ppm.



(*E*)-3-(4-chlorophenyl)-1-morpholinoprop-2-en-1-one (5.46p)[4]: According to GP I, 4-chlorobenzaldehyde (0.1 g, 0.71 mmol), morpholine (62 mg, 0.71 mmol) and Meldrum's acid **5.41** (0.10 g, 0.71 mmol) was reacted for 8 h and the crude mixture was



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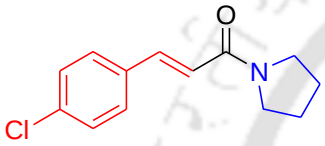
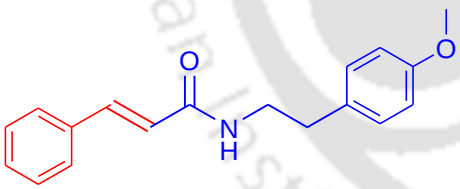
purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:2) to get analytically pure product **5.46p** as white solid (0.11 g, 61%). Mp: 142 – 143°C. FTIR: $\tilde{\nu}$ = 2966, 2917, 2851, 1648, 1610, 1494, 1430, 1405, 1230, 1112, 1048, 1011, 820 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 15.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 15.4 Hz, 1H), 3.76 – 3.62 (m, 8H). ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.3, 141.9, 135.6, 133.6, 129.1, 129.0, 117.0, 66.8, 46.3, 42.5 ppm. HRMS: Exact mass calculated for $C_{13}H_{14}ClNO_2$ ($[M+H]^+$): 252.0786, Found: 252.0789.

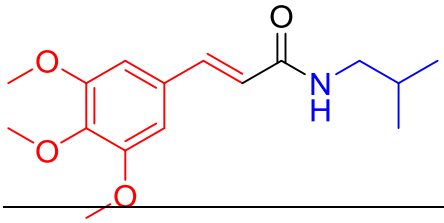
(*E*)-3-(4-chlorophenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (5.46q)[3]: According to GP I, 4-chlorobenzaldehyde (0.10 g, 0.71 mmol), pyrrolidine (51 mg, 0.71 mmol) and Meldrum's acid **5.41** (0.10 g, 0.71 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:2) to get analytically pure product **5.46q** as white solid (0.12 g, 70%). ^1H NMR (400 MHz, DCl_3) δ = 7.62 (d, *J* = 15.6 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 15.6 Hz, 1H), 3.62 – 3.55 (m, 4H), 2.02 – 1.97 (m, 2H), 1.91 – 1.85 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.4, 140.3, 135.3, 133.9, 129.00, 119.4, 46.6, 46.1, 26.1, 24.3 ppm.



(*E*)-*N*-(4-methoxyphenethyl)cinnamamide (5.47a)[7]: According to GP I, benzaldehyde (0.1 g, 0.94 mmol), 4-methoxyphenethylamine (0.14 g, 0.94 mmol) and Meldrum's acid **5.41** (0.14 g, 0.94 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.47a** as colourless gum (0.18 g, 68%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 15.4 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.36 – 7.34 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.33 (d, *J* = 15.4 Hz, 1H), 5.70 (br. s, 1H), 3.80 (s, 3H), 3.65 – 3.60 (m, 2H), 2.85 – 2.81 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.9, 158.3, 141.1, 134.8, 130.8, 129.8, 129.7, 128.8, 127.8, 120.5, 114.1, 55.3, 41.0, 34.7 ppm.



(*E*)-*N*-isobutyl-3-(3,4,5-trimethoxyphenyl)acrylamide (5.47b): According to GP I, 3,4,5-trimethoxybenzaldehyde (0.10 g, 0.51 mmol), isobutylamine (37 mg, 0.51 mmol) and Meldrum's acid **5.41** (73 mg, 0.51 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography



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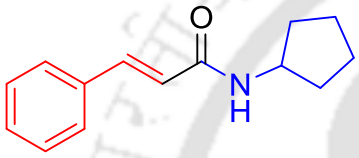
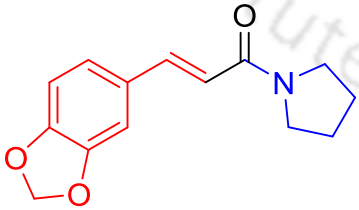
(Silica gel; EtOAc: Hexane, 1:3) to get analytically pure product **5.47b** as white solid (90 mg, 60%). Mp: 145 – 146°C. FTIR: $\tilde{\nu}$ = 3302, 2917, 2850, 1736, 1655, 1619, 1581, 1546, 1508, 1467, 1417, 1323, 1281, 1241, 1210, 993, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, *J* = 15.4 Hz, 1H), 6.66 (s, 2H), 6.27 (d, *J* = 15.4 Hz, 1H), 5.70 (br. s, 1H), 3.81 (s, 6H), 3.80 (s, 3H), 3.18 – 3.14 (m, 2H), 1.81 – 1.75 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.9, 153.4, 141.0, 139.5, 130.4, 120.0, 104.9, 61.0, 56.1, 47.1, 28.6, 20.2 ppm. HRMS: Exact mass calculated for $C_{16}H_{23}NO_4$ ($[M+H]^+$): 294.1700, Found: 294.1700.

(*E*)-*N*-cyclopentylcinnamamide (5.47c)[12]: According to GP I, benzaldehyde (0.10 g, 0.94 mmol), cyclopentylamine (82 mg, 0.94 mmol) and Meldrum's acid **5.41** (0.14 g, 0.94 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.47c** as white solid (0.14 g, 70%). Mp: 144 – 145°C. FTIR: $\tilde{\nu}$ = 3256, 2959, 2870, 1655, 1615, 1543, 1449, 1338, 1225, 978, 765, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 15.6 Hz, 1H), 7.50 – 7.48 (m, 2H), 7.36 – 7.34 (m, 3H), 6.36 (d, *J* = 15.6 Hz, 1H), 5.63 (br. s, 1H), 4.37 – 4.32 (m, 1H), 2.10 – 2.02 (m, 2H), 1.72 – 1.61 (m, 4H), 1.47 – 1.41 (m, 2H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.5, 140.8, 134.9, 129.6, 128.8, 127.7, 120.9, 51.5, 33.3, 23.8 ppm. HRMS: Exact mass calculated for $C_{14}H_{17}NO$ ($[M+H]^+$): 216.1383, Found: 216.1389.



(*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (5.47d)[7]: According to GP I, piperonyl aldehyde (0.10 g, 0.66 mmol), pyrrolidine (47 mg, 0.66 mmol) and Meldrum's acid **5.41** (96 mg, 0.66 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:1) to get analytically pure product **5.47d** as white solid (98 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 15.4 Hz, 1H), 7.03 – 6.95 (m, 2H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 15.4 Hz, 1H), 5.95 (s, 2H), 3.60 – 3.54 (m, 4H), 2.00 – 1.95 (m, 2H), 1.90 – 1.83 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.8, 148.9, 148.2, 141.4, 129.8, 123.8, 116.9, 108.5, 106.4, 101.4, 46.5, 46.0, 26.1, 24.3 ppm.



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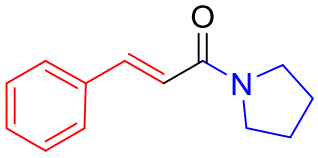
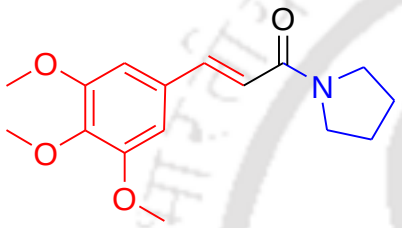
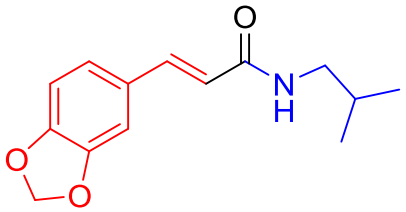
(*E*)-3-phenyl-1-(pyrrolidin-1-yl)prop-2-en-1-one (5.47e)[6,7]: According to GP I, benzaldehyde (0.10 g, 0.94 mmol), pyrrolidine (67 mg, 0.94 mmol) and Meldrum's acid **5.41** (0.14 g, 0.94 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:1) to get analytically pure product **5.47e** as white solid (0.13 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 15.6 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.35 – 7.23 (m, 3H), 6.66 (d, *J* = 15.6 Hz, 1H), 3.64 – 3.57 (m, 4H), 2.03 – 1.97 (m, 2H), 1.93 – 1.88 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.7, 141.7, 135.4, 129.5, 128.8, 127.8, 118.9, 46.6, 46.1, 26.2, 24.4 ppm.



(*E*)-3-(3,4,5-trimethoxyphenyl)-1-(pyrrolidin-1-yl)prop-2-en-1-one (5.47f)[5]: According to GP I, 3,4,5-trimethoxybenzaldehyde (0.10 g, 0.51 mmol), pyrrolidine (36 mg, 0.51 mmol) and Meldrum's acid **5.41** (73 mg, 0.51 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:1) to get analytically pure product **5.47f** as white solid (91 mg, 64%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 15.4 Hz, 1H), 6.73 (s, 2H), 6.60 (d, *J* = 15.4 Hz, 1H), 3.87 (s, 6H), 3.85 (s, 3H), 3.64 – 3.62 (m, 2H), 3.59 – 3.56 (m, 2H), 2.02 – 1.96 (m, 3H), 1.92 – 1.85 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.7, 153.4, 141.8, 139.6, 130.9, 118.1, 105.1, 60.9, 56.2, 46.6, 46.1, 26.1, 24.3 ppm.



(*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)-*N*-isobutylacrylamide (5.47g)[7]: According to GP I, piperonyl aldehyde (0.10 g, 0.66 mmol), isobutylamine (50 mg, 0.66 mmol) and Meldrum's acid **5.41** (96 mg, 0.66 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:2) to get analytically pure product **5.47g** as white solid (0.12 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 15.5 Hz, 1H), 7.00 – 6.97 (m, 2H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.24 (d, *J* = 15.5 Hz, 1H), 5.99 (s, 2H), 5.73 (br. s, 1H), 3.23 – 3.20 (m, 2H), 1.87 – 1.81 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 6H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2, 149.0, 148.2, 140.9, 129.2, 123.9, 118.6, 108.5, 106.3, 101.4, 47.2, 28.6, 20.2 ppm.



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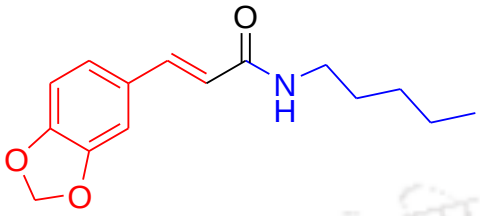
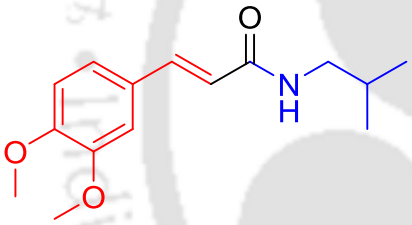
(*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)-*N*-pentylacrylamide (5.47h)[11]: According to GP I, piperonyl aldehyde (0.10 g, 0.66 mmol), amylamine (58 mg, 0.66 mmol) and Meldrum's acid **5.41** (96 mg, 0.66 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.47h** as white solid (0.11 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 15.6 Hz, 1H), 7.01 – 6.95 (m, 2H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.20 (d, *J* = 15.6 Hz, 1H), 5.98 (s, 2H), 5.59 (br. s, 1H), 3.39 – 3.34(m, 2H), 1.60 – 1.53 (m, 2H), 1.35 – 1.33 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.0, 149.0, 148.2, 140.5, 129.3, 123.8, 118.9, 108.5, 106.3, 101.4, 39.8, 29.4, 29.1, 22.4, 14.0 ppm.



(*E*)-*N*-isobutyl-3-(3,4-dimethoxyphenyl)acrylamide (5.47i)[7]: According to GP I, 3,4-dimethoxybenzaldehyde (0.10 g, 0.60 mmol), isobutylamine (44 mg, 0.60 mmol) and Meldrum's acid **5.41** (87 mg, 0.60 mmol) was reacted for 8 h and the crude mixture was purified by coloum chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **5.47i** as white solid (0.10 g, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 15.6Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.27 (d, *J* = 15.6 Hz, 1H), 5.59 (br. s, 1H), 3.912 (s, 3H), 3.907 (s, 3H), 3.23 – 3.21 (m, 2H), 1.86 – 1.82 (m, 1H), 0.96 (d, *J* = 7.2 Hz, 6H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2, 150.5, 149.1, 140.9, 127.8, 121.9, 118.6, 111.1, 109.6, 56.0, 55.9, 47.1, 28.7, 20.2 ppm.



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CHAPTER 6

Environmentally Benign Decarboxylative N-, O-, and S-Acetylations acylation by Meldrum's Acid

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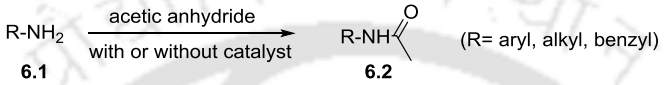
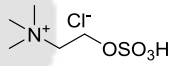
6.1 Introduction

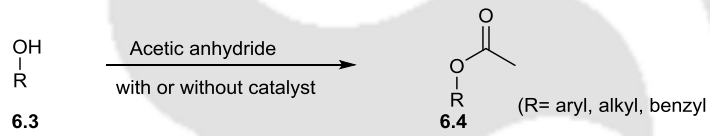
Acetylation is one of the most important reactions used in chemistry and biology.[1] Acetyl moiety, which is frequently found in bioactive molecules, natural products, medicinal drugs etc., is installed *via* acetylation reaction during their chemical synthesis. In addition, acetyl functionality is frequently used as the protecting group of the reactive functional group, such as amines, alcohols, thiols, etc. The wide application of the acetyl group prompted the development of different methods/ reagents/strategies for the acetylation reaction. The majority of acetylation reactions are carried out using acid anhydrides in the presence of an acid, a base or metal catalyst (**Scheme 1** and **2**).[2]



Catalyst: $Cp_2(OSO_2C_8F_{17})_2$, $Cp_2Zr(OPf)_2$,Ag(OTf), Zirconyl triflate, Nickel-zirconium phosphate nanoparticles, SiO_2/PDA-SO_3H, Glycerol based carbon-SO_3H catalyst, Fe_3O_4-NPs (PDA-SO_3H), Pentafluorophenyl ammonium triflate(PFPAT), Ric Husk,

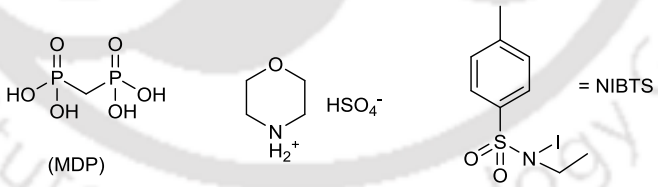


Scheme 1: Acetylation of amine using acetic anhydride



Metalic reagent/ catalyst: Li, Mg, Au, Co, Ti, Cu, Sn, Na, V, Al, Zn, Zr, Gd etc

Other catalyst: Lewis acid catalyst such as: SO_3H based catalyst, $GaCl_3$, ZSM-5-SO_3H, FeAlP solid acid catalyst, SiO_2/PDA-SO_3H, DMAP.HCl, Pentafluoroammonium triflate, Binuclear Hafnocene perfluorooctanesulfonate comlex as lewis acid, Yttrium triflate $Y(OTf)_3$, Zirconyl triflate, $Cu(CH_3CN)_4$, OTf, Rice Husk Ash catalyst, SiO_2/PDA-SO_3H, $SbCl_3$, Succinimide -N-sulfonic acid, Sodium acetate, DMPA-MONNS(DMPAP-microporous organic nanotube networks), CSC-star(amorphous, carbon -silicacomposite sulfonic acid), Preyssler heteropolyacid, Poly(N-vinylimidazole)



Scheme 2: Acetylation of alcohol using acetic anhydride

Other commonly used methodologies involve the use of acetic acid and its derivatives, such as acetyl chloride, ethyl acetate, vinyl acetate, ammonium acetate or with other acetyl sources (**Scheme 3** and **4**).[3]

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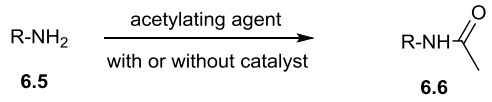
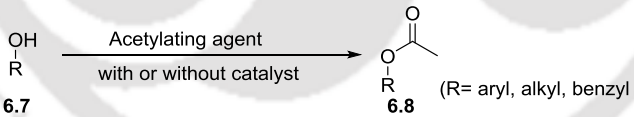


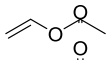
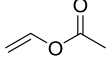
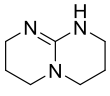
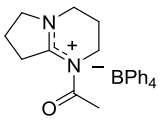
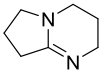
6.5 **6.6**

Acetylating agent	Catalyst
Tetra Acetoxymethyl Glycoluril	No catalyst
Ethyl Acetate	distannoxane(Sn)
Acetic acid	nano-MgO
Acetic acid	natural ferrous chamosite
Acetic acid	coupling agent
Acetic acid chloride	Et_3N
Acetamide	Ru-NHC
Acetamide	nanosized zeolite beta
Ester	Graphene Oxide Supported Base Metal Nanocatalyst
Acetic acid	diatomite earth@IL/ZrCl4
Amides	Hydroxylamine
aminium carboxylates	N-(p-toluenesulfonyl) imidazole
Isopropenyl acetate	No catalyst
Amides	Chitosan
carboxylic acids	Silica gel (MW)
Ethyl acetate	Acetic acid
Acetic acid	AgNPs@m-MgO
CH_2O, AcSH	No catalyst
Amine hydrochloride salts and Orthoesters	No Catalyst
Amides	silica nanoparticles
Acetic acid	Montmorillonite-K10
Acetic acid	Polyaniline (mPANI/Ag) nanocomposite
AcSH	Fe_3O_4@GAA]Cu(II) nanoparticles
Acetic acid chloride	No catalyst (MW)
Ethyl acetate	Lanthanum(III) Triflate
Acetamide	Sulfated tungstate
Acetamide	Zeolite
N-Methylacetamide	$AlCl_3$
Acetamide	Lanthanide Alkoxide
Alcohol	Gold Nanoparticles
Acetamide	Imidazolium Chloride

Scheme 3: Acetylation of amine by different acylating agent



6.7 **6.8**

Acylating agent	Catalyst
i) CH_3COCl	CF_3SO_3H
ii) 2-acyl-4,5-dichloropyridazinones	No catalyst
iii) vinyl acetate	lipase Amano PS
iv) acylimidazolium acetate	Acylimidazolium acetate
v) vinyl acetate	DABCO
vi) Acyl maleic hydrazides	No catalyst
vii) alkenyl Carboxylates	Na_2CO_3
viii) Alkyl Esters	Nanocrystalline Beta
ix) 2-Acyl-4,5-dichloropyridazinones	$AlCl_3$
x) Acetic acid	Natural ferrous chamosite
xi) 	$[Bu_4N][Fe(CO)_3(NO)]$
xii) 	
xiii) 	

Scheme 4: Acetylation of alcohol by different acylating agent

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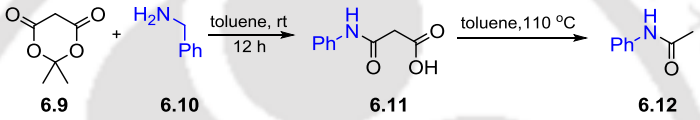
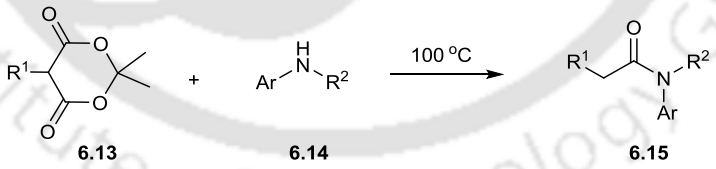
Various metal-based catalysts like zinc(II) chloride, scandium(III) triflate, bismuth(III) triflate, ruthenium(III) acetylacetonate were for employed acetylation reactions.[4] The use of CO_2 for the acetylation reaction, which generally requires metal-based catalyst/reagent and high-pressure of CO_2, is another important strategy.[5] The commonly used acetylating reagents are low boiling, toxic, corrosive and thus are hazardous, particularly in the industrial-scale synthesis. In addition, most of the acetylation reaction releases acids, which might affect any acid-sensitive functionality present in the substrates. Therefore, the development of a more environmentally benign method for the acetylation reaction, which operates under base or acid-free conditions, is essential. During the mechanistic studies on the synthesis of cinnamamide and piper amide, an acylation of amines **6.12** was observed from a reaction of Meldrum's acid **6.9** and benzylamine **6.10** (**Scheme 5**).



Scheme 5: First observation of acetylation of amines using Meldrum's acid

Realizing the potential of Meldrum's acid as an environmentally benign acylating agent, a seminal report was found on the synthesis of acetanilide **6.15** on heating a mixture of aniline **6.14** and Meldrum's acid **6.13**.[6] Recently, Huang and co-worker have also developed a method for the amidation of aniline derivative using Meldrum's acid derivatives (**Scheme 6**).[7]



Scheme 6: Acylation of aniline by Meldrum's acid

The method works efficiently with the limited *N*-alkyl/aryl aniline derivative to provide the corresponding tertiary amides. However, the method did not work for the acylation of primary amines such as alkylamine, benzylamines, and aliphatic secondary amines. Moreover, acylation of other major functional groups such as phenol, alcohol using Meldrum's acid was not known.[8] Thus the scope of the acylation reaction was severely

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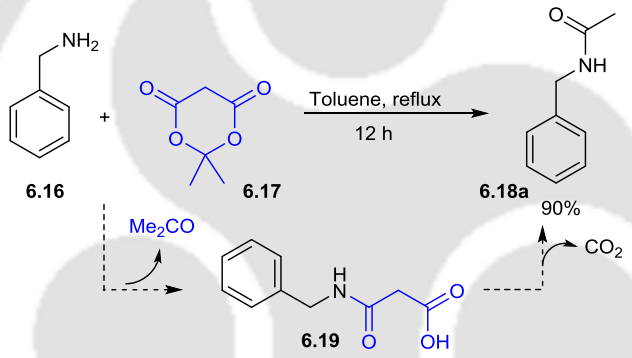
limited. Therefore, the development of a method that works for the acetylation of large classes of functional groups would be advantageous.

6.2 Preliminary result:

Meldrum's acid **6.17** and amines are generally reacted to form the corresponding monoamides of malonic acid.[9] However, to the best of our knowledge, there is no report known for the acetylation of aliphatic amines using Meldrum's acid **6.17**. Therefore, initial investigations focused on finding appropriate reaction conditions for the acetylation reaction of benzylamine using Meldrum's acid (2,2-Dimethyl-1,3-dioxane-4,6-dione) **6.17**. Accordingly, a reaction of benzylamine and Meldrum's acid **6.17** was performed in refluxing toluene for 12 h. pleasingly; analytically pure *N*-benzylacetamide (**6.18a**) was isolated as a liquid gum with 90% yield without requiring any column purification (**Scheme 7**).



Scheme 7: Acetylation of benzylamine

6.3 Solvent optimization for the acetylation:

Then the reactions were carried out in different other solvents in order to find a better alternative of toluene (**Table 1**). The studies revealed that the reaction proceeded efficiently in anisole (**Table 1, entry 5**), which is categorized as "recommended" according to the solvent selection guide.[10] In addition, to minimize the quantity of solvent, the acetylation reactions with reduced amounts of solvent have also been investigated(**Table 1, entry 10, 11, 12**). No significant decrease in the yield of the acetylation reaction was found when the reaction was carried out with high concentration (~4 M). Moreover, it was shown that the solvent could be recycled easily.

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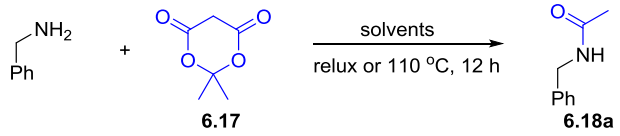
Table 1: Solvent screening for acetylation reaction.[a]



6.17 6.18a

entry	solvents	Yield (%)[f]
1	**Toluene, reflux**	**90**
2	Xylene, 110 °C	89
3	MIBK, 110 °C	93
4	Cyclohexanone, 110 °C	82
5	Anisole, 110 °C	**98**
6	EtOAC, reflx	25
7	Water, reflux	10
8[b]	Water, reflux	45
9	no solvent	0
10[c]	**Anisole, 110 °C**	**95**
11[d]	Anisole, 110 °C	93
12[e]	Anisole, 110 °C	94

[a]1 eq (0.93 mmol) of benzylamine was reacted with 1eq of Meldrum's acid (0.93 mmol) in 2 mL (0.47 M) solvent. [b]TBAB (20 mol %) was used. Reaction was performed in [c]1 mL (0.93 M), [d]0.5 mL (1.87 mM) and [e] 0.25 mL (3.72 M) of anisole. [f]Isolated yield.

6.4 Substrate scope for aliphatic amine:

Then we became interested to investigate the substrate scope of this acetylation reaction as the desired acetylation could be achieved without aid of any additional reagents/catalyst or additives. Moreover, the volatile byproducts acetone and carbon dioxide can be separated easily. Thus no further purification is essential to obtain the pure product. Various functional groups, such as OMe, CF_3, Ar-Cl, Ar-F etc were tolerated under the reaction conditions. The wide range of functional groups (e.g. OMe, CF_3, Cl, F etc) were found to be well accepted in this reaction. Substrates having both electron donating (e.g. OMe) and electron withdrawing (e.g. F, Cl) groups were efficiently reacted to produce the desired acylated product. Acid sensitive heteroaromatic furan ring also remained intact during the reaction to yield **6.3f** with very good yields. With success in the acetylation of benzylamines, we also

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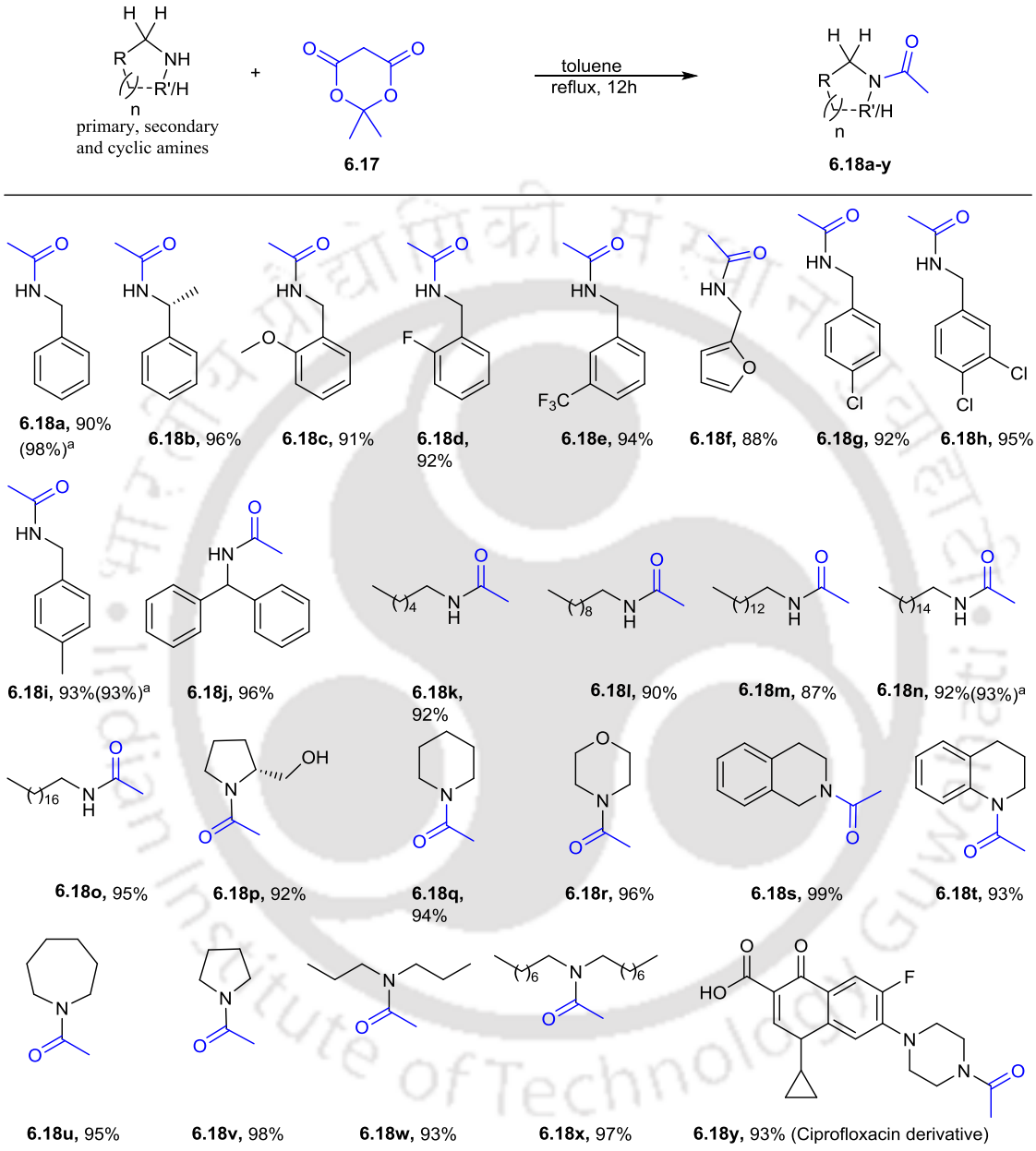
explored acetylation of aliphatic primary amines. Different amines with variable chain lengths were reacted with Meldrum's acid **6.17** to obtain corresponding acetamides **6.18k-o** with excellent yields.



Scheme 8: Scope for the acetylation of aliphatic amine. [a]anisole was used as the solvent (at 110 ^{o}C).

After success in the acetylation of primary amines, the acetylation reaction of secondary aliphatic amines was investigated. Accordingly, different secondary amines were reacted with Meldrum's acid **6.17** under the optimized reaction conditions to afford the

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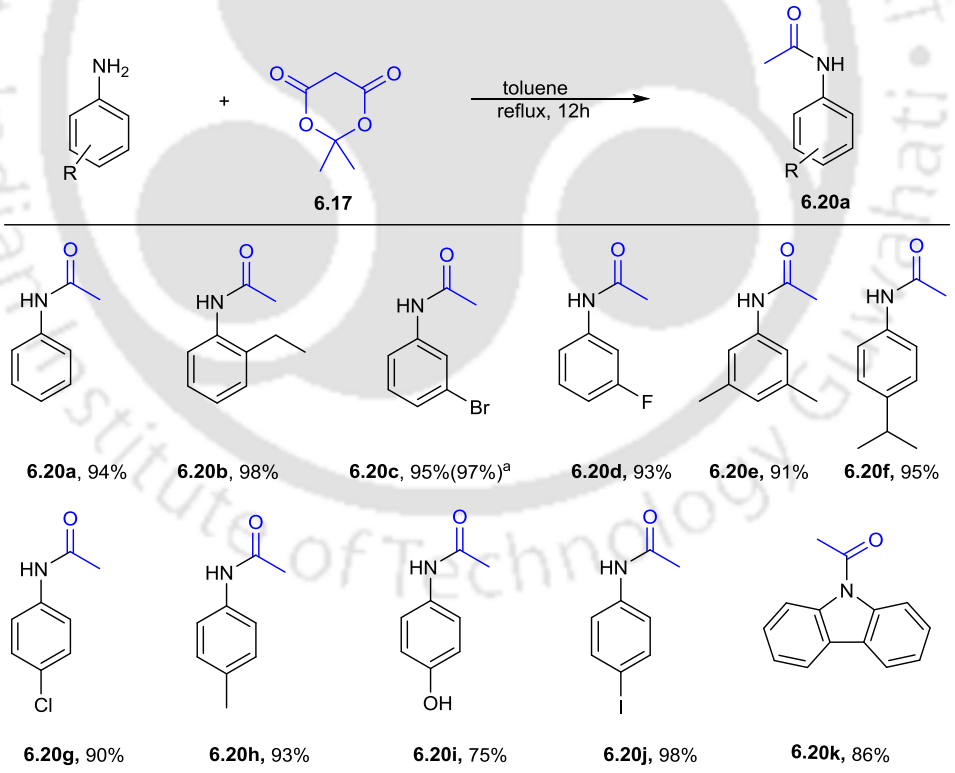
corresponding *N*-acylated product **6.18p-y** with excellent yields (**Scheme 8**). *N*-heterocycles with varied ring sizes and substituents were acetylated efficiently to obtain the desired *N*-acetylated heterocycles. Ciprofloxacin, a well-known medicinal drug, was also acetylated selectively by using the standard condition to provide the *N*-acetyl Ciprofloxacin (**6.18y**) with 93% yield. The selective *N*-acetylation of (*s*)-prolinol provided the desired amide (**6.18p**) with a very good yield. Apart from the *N*-heterocycles, aliphatic acyclic secondary amines also reacted smoothly with Meldrum's acid **6.17** to produce the acetylated product with high yield (**6.18w** and **6.18x)**.

6.5 Substrate scope for aniline:

With the success acetylation of aliphatic amines, reactions using anilines were carried out to examine the generality of this method (**Scheme 9**). Acetylation of various anilines was done by reacting with Meldrum's acid **6.17** under optimized conditions to obtain the acetanilide with excellent yield (**6.20a-k**). The precipitated products were separated via simple filtration of the reaction mixture.



Scheme 9: Scope for the acetylation of anilines. [a]anisole was used as solvent (110 ^{o}C).

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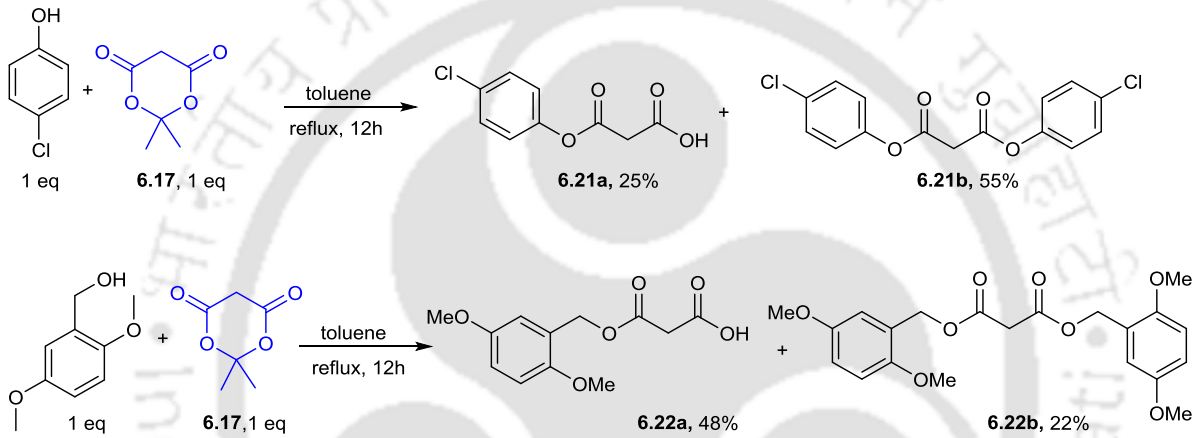
6.6 Acetylation of alcohol:

Alcohols are another potential class of substrates for acetylation. The reaction of alcohols with Meldrum's acid **6.17** is known to provide either the mono-ester of malonic acid depending on the reaction conditions.[11] We were then interested to study the scope of this acetylation reaction using alcohols as the substrates.

6.6.1 Optimization for the acetylation of alcohol:

The initial attempt by reacting para-chlorophenol and Meldrum's acid **6.17** in refluxing toluene failed to provide the corresponding acetates **6.23b** (**Table 1, entry 1**). However, as reported previously, a mixture of mono **(6.21a and 6.22aa**) and di-ester (**6.21b and 6.22b**) of malonic acid were formed in the reaction (**Scheme 9**).



Scheme 9: Attempts for acetylation of alcohols

The reactions with increased reaction time and performing in a closed tube at 120 ^{o}C did not provide the desired product (**Table 1, entry 2, 3**). Then we decided to carry out the reaction in the presence of a base to facilitate decarboxylation. As anticipated, the reaction of para-chlorophenol and Meldrum's acid **6.17** in the presence of triethylamine provided the desired acetate with a 62% yield (Table 1, entry 4). Further increase in the yield of 92% was observed when the relative stoichiometry of Meldrum's acid **6.17** was increased (**Table 1, entry 6**). The use of the catalytic amount of base was able to provide the desired acetylation with excellent yield (92%) (**Table 1, entry 7**). The reaction was performed by using anisole as the green solvent, and then yield was increased up to 95% (**Table 1, entry 9**).

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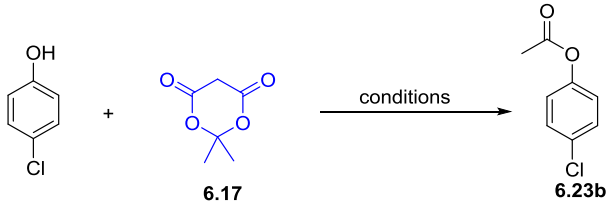
Table 2: Optimization for the acetylation of alcohol.[a]



6.17 6.23b

entry	conditions	yield (%)[b]
1	toluene, reflux, 12 h	0
2	toluene, reflux, 48 h	0
3	toluene, closed tube at 110 ^{o}C, 12 h	0
4	toluene, reflux, 12 h, Et_3N (1 eq)	62
5[c]	toluene, reflux, 24 h, Et_3N (1 eq)	73
6[d]	toluene, reflux, 12 h, Et_3N (1 eq)	92
7[d]	toluene, reflux, 12 h, Et_3N (20 mol%)	92
8[d]	toluene, reflux, 12 h, DMAP (20 mol%)	72
9[d]	Anisole, 110 ^{o}C, 12 h, Et_3N (20 mol%)	95
10	anisole, 110 ^{o}C, 12 h, Et_3N (20 mol%)	74
11	anisole, 110 ^{o}C, 12 h, DIPEA (20 mol%)	76
12[e]	anisole, 110 ^{o}C, 12 h, Et_3N (5 mol%)	79
13[e]	anisole, 110 ^{o}C, 12 h, DIPEA (5 mol%)	80

[a]1 eq (0.78 mmol) of 4-chlorophenol, 1eq of Meldrum's acid (0.78 mmol), and solvent (2mL) were reacted. [b]Isolated yield. [c]1.2 eq Meldrum's acid used. [d]1.5 eq Meldrum's acid used. [e]0.25 mL of anisole was used.

6.6.2 Substrate scope for alcohol:

Phenol, benzyl alcohol, saturated aliphatic alcohols, such as dodecanol, reacted smoothly to afford the desired acetates with excellent yield (**Scheme 11**). Substrates bearing both electron-rich (such as 2, 6-dimethylphenol, Thymol, and Carvacol) and electron-deficient (4-chlorophenol) groups were acetylated efficiently. Cinnamyl alcohol also produced the corresponding acetylated derivatives **6.23m** with an 85% yield. Acid labile groups such as ketal (in **6.23l**) and epoxy functionality (in **6.8n**) were unaffected under these reaction conditions. The double acetylation of resorcinol was also achieved under the same reaction

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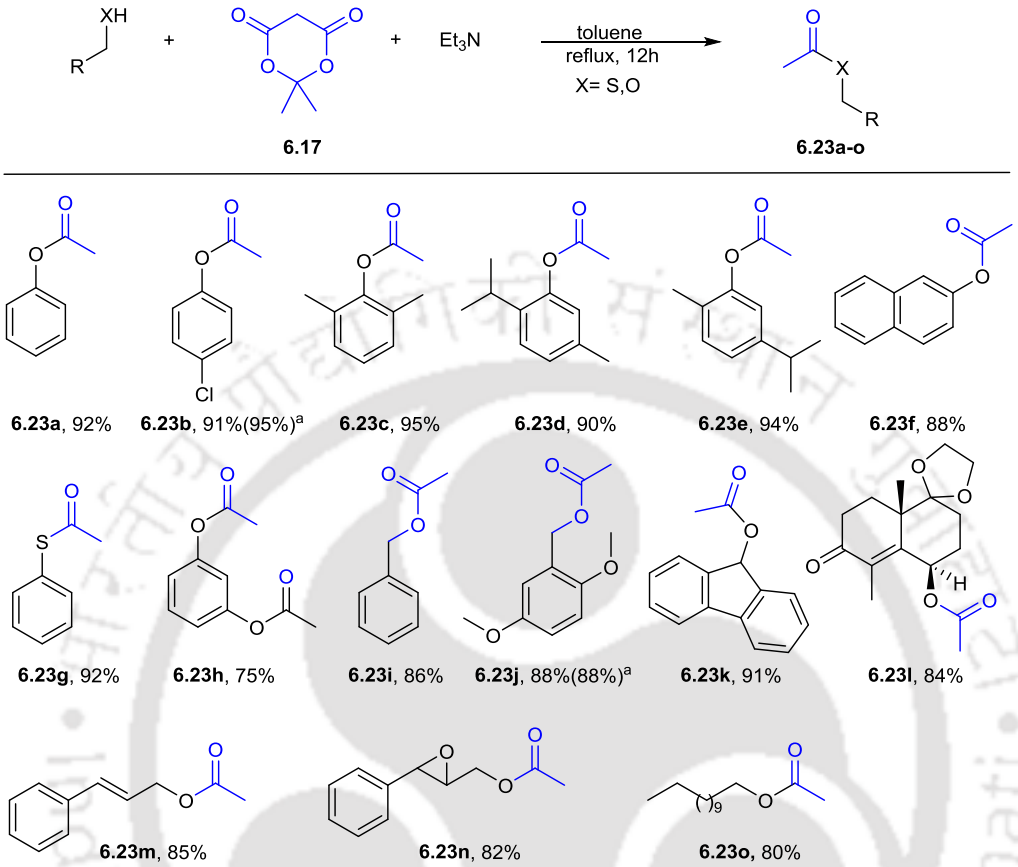
conditions (**6.23h**). Thiophenol was also found to be excellent substrates for this acetylation (**6.23g**) reaction that is employed for amines and alcohols.



Scheme 11: Scope for the acetylation of phenols and alcohols and thiol. [a]anisole was used as the solvent (at 110 ^{o}C).

6.7 Substrate scope for hydrazones:

N-acetylation of hydrazone was then attempted. The reaction of hydrazone **6.24** and Meldrum's acid **6.17** under standard conditions provided the desired *N*-acetyl derivative **6.25a** with very good yield (**Scheme 12a**). Then decided to perform the hydrazone formation and the *N*-acetylation of hydrazone in a single operation (**Scheme 12b**). Accordingly, arylaldehyde, hydrazine and Meldrum's acid **6.17** was reacted under standard conditions. As expected, *N*-acetylhydrazones **6.25a-e** was formed with very good yields (**Scheme 12b**).

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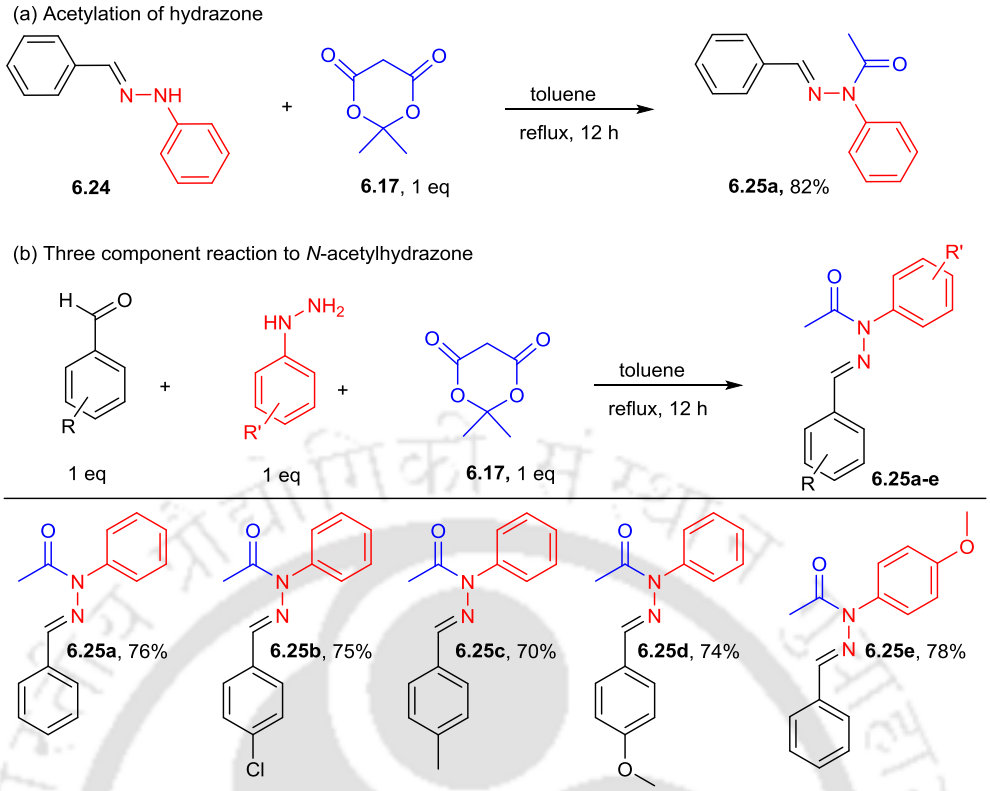
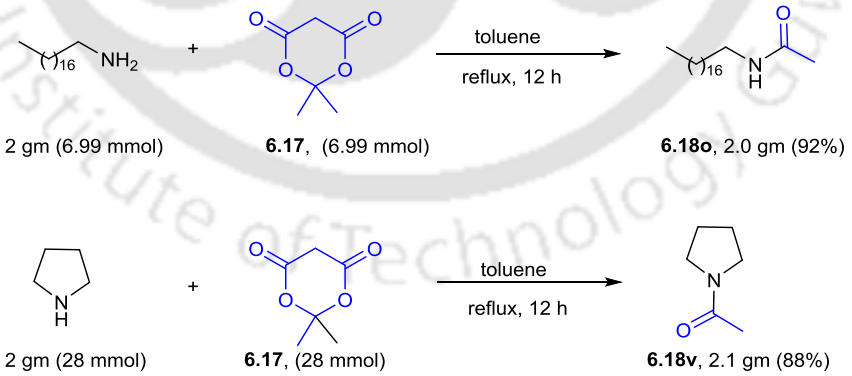


Scheme 12: Acetylation of hydrazones to *N*-acetylhydrazones.

6.8 Gram scale synthesis:

Additionally, the reaction was found to be effective in gram-scale synthesis, which indicated its potential for practical application (**Scheme 13**). The analytically pure products (**6.18o** and **6.18v**) were obtained just after the evaporation of the solvents without involving standard work-up and column chromatography.



Scheme 13: Preparative scale synthesis.

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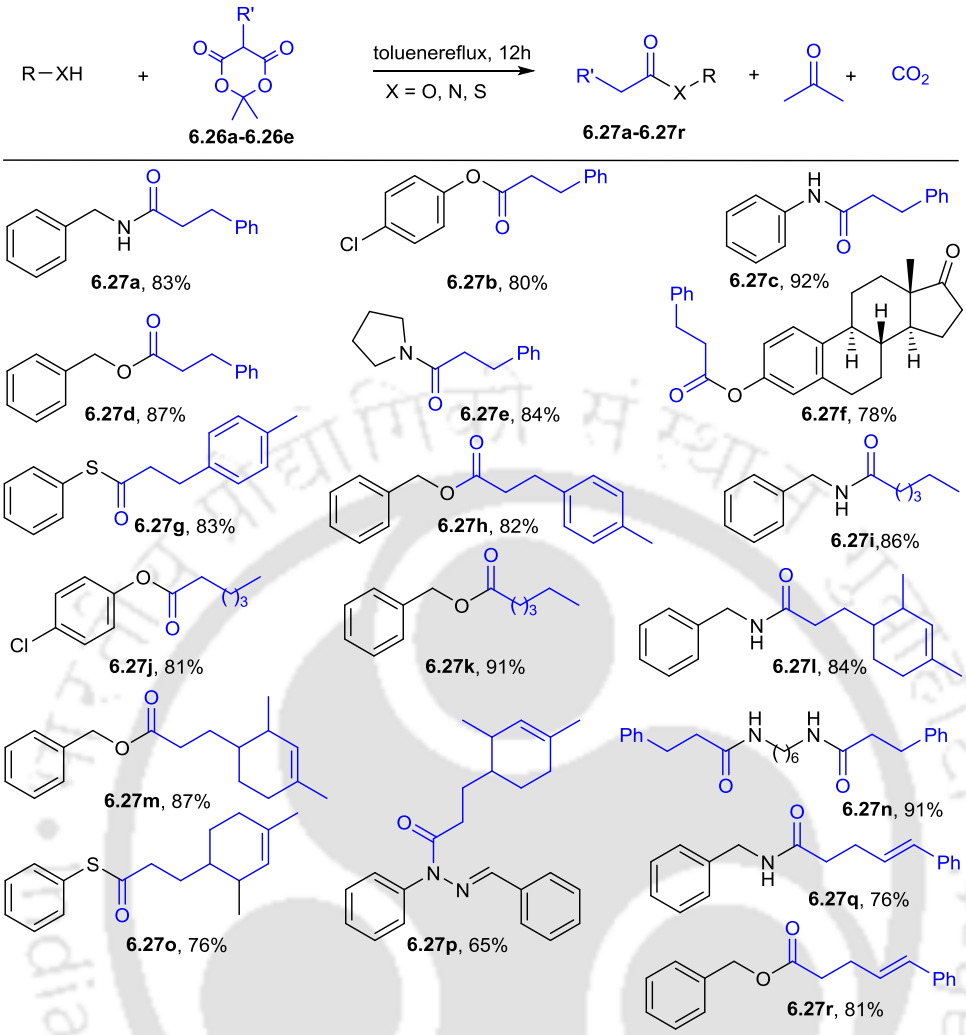
6.9 Substrate scope for acylation:



Scheme 14: Acylation of alcohols, amines and thiols.

Then it was decided to study N-, O-, and S- acylation reactions using Meldrum's acid derivatives. Accordingly, various Meldrum's acid derivatives **6.26a-6.26e** were prepared through a straight forward reductive coupling of Meldrum's acid and structurally diverse aldehyde, such as aromatic aldehyde, aliphatic aldehyde, and vinylic aldehydes. As like acetylation reaction, acylation of a broad range of amines (aliphatic and aromatic), alcohols (aliphatic and aromatic), thiols and hydrazines participated in acylation reaction with Meldrum's acid derivatives **6.26a-6.26e** to provide structurally diverse acylated products **6.27a-6.27r** with very good to excellent yields (**scheme 14**). Acylation of estrone gave the corresponding acylated estrone **6.27f** with very good yield. Interestingly, bis-acylation of hexyldiamine went smoothly to provide the corresponding bisamide **6.27n** with excellent yield.

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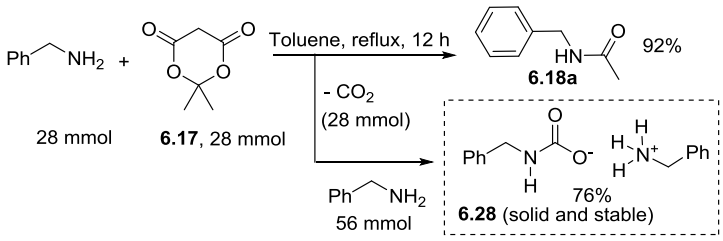
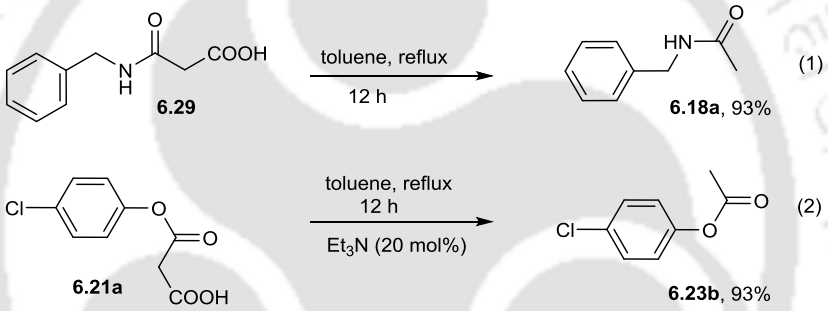
6.10 Carbon di oxide capturing:



Scheme 15: Utilization of released carbon di oxide

Carbon dioxide which was produced during the decarboxylation of **6.17** was arrested efficiently as a bench-stable amine carbamate ammonium salt **6.28** (**Scheme 15**). This salt can be used as reagents and catalyst in different organic reaction.[13]

6.11 Controlled reaction:



Scheme 16: Controlled reaction.

The controlled experiments were performed by reacting mono-acid **6.29** and **6.6a** separately. Under standard reaction conditions (reflux in toluene for 12 h) the desired acetylated products **6.18a** (eq 1) and **6.23b** (eq 2) were isolated with excellent yields (**Scheme 16**). This indicates that the reaction proceeded *via* intermediate **6.29**.

6.12 Proposed Mechanism:

A plausible mechanism for the acetylation reaction is shown in **Scheme 17**. The acetylation reaction is believed to proceed *via* malonic acid derivatives **6.31,** which is formed through the reaction of nucleophilic substrates **6.30** and the Meldrum's acid. Thermal decarboxylation of **6.32** followed by protonation of resulting enolate **6.33** provided the acetyl derivative **6.35**. The possibility of the reaction *via* ketene **6.34**, which is formed by thermal decomposition of Meldrum acid, can be eliminated as the simple reaction of alcohol

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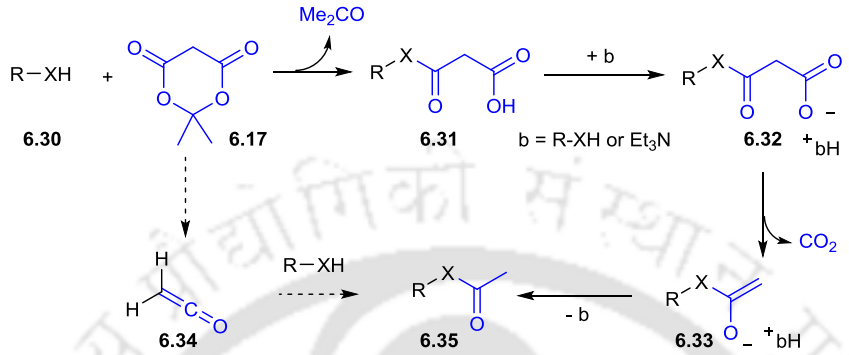
and Meldrum's acid failed to provide the acetates. Moreover, thermal decomposition of Meldrum's acid to corresponding ketene required the temperature which is higher than the current reaction temperature.[12] The isolation and identification of mono and di-ester (**6.21a, 6.22a and 6.21b, 6.22b**) provides further support for the reaction mechanism which proceed *via* **6.31**.



Scheme 17: Plausible mechanism for acetylation reaction.

6.13 Summary:

A general and unprecedented method for the acetylation of amines, alcohols, thiols and hydrazones using Meldrum's acid, which is cheap, commercially available, and non-hazardous, has been developed. The byproducts (CO_2 and acetone) of the reaction can be easily separated from the acetylated product without workup and column chromatography. Operational simplicity and lack of requirement of the use of additional catalyst/reagents/acid/base are the other important advantages of the present acetylation protocol.

6.14 Experimental section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus (V)oxide (P_2O_5). Commercial grade xylene, benzene and toluene were distilled over CaH_2 before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ^1H, ^{13}C NMR spectroscopy: *Bruker 400 MHz, Bruker 600 MHz* (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS δ (^1H) 0.0 ppm, δ (^{13}C) 0.0 ppm) which was used as the inner reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.2 ppm; CD_3OD, (^1H) 3.31 ppm, δ (^{13}C) 49.0 ppm) were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity.. MS (ESI-HRMS): Mass spectra were

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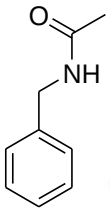
recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

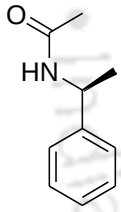
General procedure for the acetylation of amine (GP I): Meldrum's acid **6.17** (1 eq.) was added to a solution of amine (1 eq) in toluene (2 - 4 mL) and the mixture was refluxed for 12 h. After disappearance of starting materials (indicated by TLC) solvent was evaporated under reduced pressure to obtain the analytically pure product.

***N*-benzylacetamide (6.18a)[12]:** According to GP I, benzylamine (0.2 g, 1.86 mmol) and



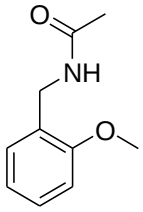
Meldrum's acid **6.17** (0.27 g, 1.86 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18a** as pale yellow liquid (0.25 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 (br. s, 1H), 7.17 - 7.07 (m, 5H), 4.16 (d, *J* = 5.8 Hz, 2H), 1.75 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.7, 138.5, 128.5, 127.6, 127.6, 127.2, 43.4, 22.9 ppm.

***N*-((S)-1-phenylethyl)acetamide (6.18b)[9]:** According to GP I, (S)-(-)-α-



methylbenzylamine (0.20 g, 1.65 mmol) and Meldrum's acid **6.17** (0.24 g, 1.65 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18b** as pale yellow liquid (0.26 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.37 - 7.33 (m, 4H), 7.30 - 7.27 (m, 1H), 6.21 (br. s, 1H), 5.15 - 5.10 (m, 1H), 2.01 (s, 3H), 1.51 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.5, 143.0, 128.7, 127.5, 126.2, 49.0, 23.2, 21.7 ppm.

***N*-benzylacetamide (6.18c)[12]:** According to GP I, 2-methoxybenzylamine (0.20 g, 1.46



mmol) and Meldrum's acid **6.17** (0.21 g, 1.46 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18c** as pale yellow liquid (0.24 g, 91%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.21 - 7.17 (m, 2H), 6.86 - 6.83 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 2H, one NH is there, not distinguishable), 4.34 (d, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 1.89 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.3, 157.3, 129.2, 128.6, 126.3, 120.5, 110.2, 55.2, 39.0, 23.0 ppm.

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***N*-(2-fluorobenzyl)acetamide (6.18d)[7]:** According to GP I, 2-fluorobenzylamine (0.20 g, 1.60 mmol) and Meldrum's acid **6.17** (0.23 g, 1.60 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18d** as pale yellow liquid (0.25 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.24 - 7.21 (m, 1H), 7.18 - 7.15 (m, 1H), 7.02 - 6.99 (m, 2H, one NH is there, not distinguishable), 6.96 - 6.93 (m, 1H), 4.36 (d, *J* = 5.4 Hz, 2H), 1.91 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.7, 161.6, 160.0, 129.96, 129.94, 129.1, 129.0, 125.35, 125.25, 124.17, 124.15, 115.3, 115.1, 37.29, 37.26, 22.83, 22.81 ppm.

***N*-(3-(trifluoromethyl)benzyl)acetamide (6.18e)[12]:** According to GP I, 3-(trifluoromethyl) benzylamine (0.20 g, 1.14 mmol) and Meldrum's acid **6.17** (0.16 g, 1.14 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18e** as white solid (0.23 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 - 7.36 (m, 2H), 7.32 - 7.28 (m, 2H), 6.97 (br. s, 1H), 4.16 (d, *J* = 5.8 Hz, 2H), 1.75 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.8, 139.5, 131.0, 130.9, 130.9, 130.6, 129.1, 129.0, 124.9, 124.2 (CF_3), 124.15 (CF_3), 124.12 (CF_3), 124.09 (CF_3), 124.06 (CF_3), 124.04 (CF_3), 123.1, 42.9, 42.9, 22.8 ppm.

***N*-((furan-2-yl)methyl)acetamide (6.18f)[11]:** According to GP I, furfurylamine (0.20 g, 2.05 mmol) and Meldrum's acid **6.17** (0.30 g, 2.05 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18f** as pale yellow liquid (0.25 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 - 7.29 (m, 1H), 6.85 (br. s, 1H), 6.27 - 6.26 (m, 1H), 6.17 - 6.16 (m, 1H), 4.34 (d, *J* = 5.4 Hz, 2H), 1.94 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.5, 151.4, 142.0, 110.4, 107.3, 36.5, 22.9 ppm.

***N*-(4-chlorobenzyl)acetamide (6.18g)[12]:** According to GP I, 4-chlorobenzylamine (0.20 g, 1.42 mmol) and Meldrum's acid **6.17** (0.20 g, 1.42 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18g** as pale yellow liquid (0.24 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.10 (br. s, 1H), 4.36 (d, *J* = 5.8 Hz, 2H), 2.01 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.2, 136.7, 133.3, 129.2, 128.8, 43.0, 23.2 ppm.

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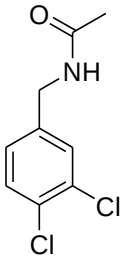
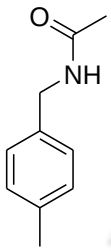
***N*-(3,4-dichlorobenzyl)acetamide (6.18h)[20]:** According to GP I, 3,4-dichlorobenzylamine



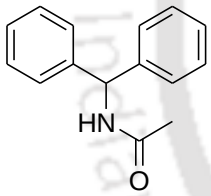
(0.20 g, 1.14 mmol) and Meldrum's acid **6.17** (0.16 g, 1.14 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18h** as white solid (0.24 mg, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 1.8 Hz, 1H), 7.32 (dd, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H), 6.57 (br. s, 1H), 4.31 (d, *J* = 6.0 Hz, 2H), 2.00 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.5, 138.6, 132.6, 131.4, 130.6, 129.5, 127.0, 42.5, 23.1 ppm.

***N*-(4-methylbenzyl)acetamide (6.18i)[12]:** According to GP I, 4-methylbenzylamine (0.20 g,



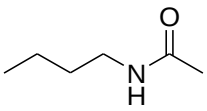
1.46 mmol) and Meldrum's acid **6.17** (0.21 g, 1.46 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18i** as pale yellow liquid (0.24 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.15 - 7.11 (m, 4H), 6.21 (br. s, 1H), 4.33 (d, *J* = 5.4 Hz, 2H), 2.32 (s, 3H), 1.97 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.7, 138.5, 128.5, 127.6, 127.2, 43.4, 22.9 ppm.

***N*-benzhydrylacetamide (6.18j)[2]:** According to GP I, benzhydrylamine (0.20 g, 1.09



mmol) and Meldrum's acid **6.17** (0.16 g, 1.09 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18j** as white solid (0.24 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.36 - 7.33 (m, 4H), 7.30 - 7.28 (m, 2H), 7.26 - 7.23 (m, 4H), 6.49 (br. s, 1H), 6.25 (d, *J* = 8.4 Hz, 1H), 2.06 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.5, 141.4, 128.7, 127.5, 127.4, 57.2, 23.2 ppm.

***N*-butylacetamide (6.18k)[5]:** According to GP I, butylamine (0.1 g, 01.36 mmol) and



Meldrum's acid **6.17** (0.20 g, 1.36 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18k** as pale yellow liquid (0.14 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.52 (br. s, 1H), 3.14 - 3.11 (m, 2H), 1.89 (s, 3H), 1.42 - 1.35 (m, 2H), 1.28 - 1.22 (m, 2H), 0.82 (t, *J* = 7.8 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.5, 39.3, 31.5, 23.0, 20.0, 13.7 ppm.

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***N*-decylacetamide (6.18l)[25]:** According to GP I, decylamine (0.20 g, 1.08 mmol) and Meldrum's acid **6.17** (0.16 g, 1.08 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product 6.18**l** as pale yellow gum (0.19 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.28 (br. s, 1H), 3.17 - 3.12 (m, 2H), 1.91 (s, 3H), 1.44 - 1.41 (m, 2H), 1.25 - 1.19 (m, 14H), 0.80 (t, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.2, 39.7, 31.8, 29.5, 29.3, 29.3, 26.9, 23.1, 22.6, 14.1 ppm. Total count of ^{13}C is less than expected due to the merging of signal in the aliphatic region.

***N*-tetradecylacetamide (6.18m)[25]:** According to GP I, tetradecylamine (0.20 g, 0.94 mmol) and Meldrum's acid **6.17** (0.14 g, 0.94 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18m** as white solid (0.21 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85 (br. s, 1H), 3.22 - 3.17 (m, 2H), 1.96 (s, 3H), 1.50 - 1.44 (m, 2H), 1.27 - 1.21 (m, 22H), 0.85 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.2, 39.8, 31.9, 29.7, 29.7, 29.64, 29.58, 29.56, 29.54, 29.34, 29.30, 26.9, 23.2, 22.7, 14.1 ppm. Total count of ^{13}C is less than expected due to the merging of signal in the aliphatic region.

***N*-hexadecylacetamide (6.18n)[26]:** According to GP I, hexadecylamine (0.20 g, 0.83 mmol) and Meldrum's acid **6.17** (0.12 g, 0.83 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18n** as white solid (0.22 mg, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.90 (br. s, 1H), 3.21 - 3.18 (m, 2H), 1.96 (s, 3H), 1.49 - 1.44 (m, 2H), 1.28 - 1.21 (m, 26H), 0.85 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.22, 39.76, 31.93, 29.71, 29.69, 29.67, 29.61, 29.56, 29.38, 29.33, 26.95, 23.24, 22.70, 14.14 ppm. Total count of ^{13}C is less than expected due to the merging of signal in the aliphatic region.

***N*-octadecylacetamide (6.18o)[27]:** According to GP I, octadecylamine (0.30 g, 1.12 mmol) and Meldrum's acid **6.17** (0.16 g, 1.12 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18o** as white solid (0.33 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.89 (br. s, 1H), 3.20 - 3.17 (m, 2H), 1.95 (s, 3H), 1.48 - 1.45 (m, 2H), 1.29 - 1.22 (s, 30H), 0.85 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.2, 39.7, 31.9, 29.69, 29.67, 29.65, 29.59, 29.56, 29.55, 29.35,

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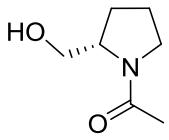
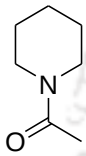
29.31, 26.9, 23.2, 22.7, 14.1 ppm. Total count of ^{13}C is less than expected due to the merging of signal in the aliphatic region.

((S)-1-acetylpyrrolidin-2-yl)methyl acetate (6.18p)[14]: According to GP I, (S)-prolinol



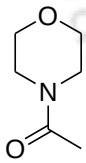
(0.20 g, 0.99 mmol) and Meldrum's acid **6.17** (0.14 g, 0.99 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18p** as liquid oil (0.13 g, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ = 4.23 (br. s, 1H), 4.15 - 4.09 (m, 1H), 3.60 - 3.50 (m, 2H), 3.46 - 3.42 (m, 2H), 2.04 (s, 3H), 2.00 - 1.82 (m, 3H), , 1.63 - 1.55 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.3, 67.4, 61.3, 49.2, 28.6, 24.5, 23.1 ppm.

1-(piperidin-1-yl)ethanone (6.18q)[11]: According to GP I, piperidine (0.10 g, 1.18 mmol) and Meldrum's acid **6.17** (0.17 g, 1.18 mmol) was reacted for 12 h and evaporation of the



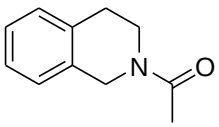
solvent gave analytically pure product **6.18q** as pale yellow oil (0.14 g, 94%). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.31 - 3.29 (m, 2H), 3.18 - 3.16 (m, 2H), 1.84 (s, 3H), 1.42 - 1.39 (m, 2H), 1.36 - 1.34 (m, 2H), 1.31 - 1.28 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.5, 47.2, 42.2, 26.2, 25.3, 24.3, 21.3 ppm.

1-Morpholinoethanone (6.18r)[11]: According to GP I, morpholine (0.1 g, 1.15 mmol) and



Meldrum's acid **6.17** (0.17 g, 1.15 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18r** as pale yellow oil (0.14 g, 96%). ^1H NMR (600 MHz, $CDCl_3$) δ = 3.57 - 3.52 (m, 4H), 3.48 - 3.46 (m, 2H), 3.54 - 3.33 (m, 2H), 1.86 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.1, 66.7, 66.5, 46.5, 41.6, 21.0 ppm.

1-(3,4-dihydroisoquinolin-2(*1H*)-yl)ethanone (6.18r)[15]: According to GP I,



tetrahydroisoquinilone (0.20 g, 1.50 mmol) and Meldrum's acid **6.17** (0.22 g, 1.50 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18s** as colourless oil with a mixture (1.3:1) of two rotamers (0.26 mg, 99%). ^1H NMR (600 MHz, $CDCl_3$) δ = 7.12 - 7.08 (m, 2H), 7.07 - 7.03 (m, 2H), 4.63 (s, 2H, major), 4.51 (s, 1H, minor), 3.71 (t, *J* = 6.0 Hz, 1H, minor), 3.56 (t, *J* = 5.9 Hz, 2H, major), 2.80 (t, *J* = 5.9 Hz, 2H, major), 2.74 (t, *J* = 5.9 Hz,

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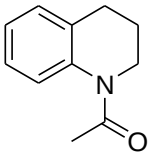
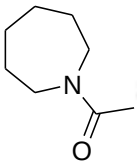
1H, minor), 2.09 (s, 2H, minor), 2.08(s, 3H, major) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.5, 169.4, 135.0, 134.0, 133.4, 132.6, 128.9, 128.3, 126.9, 126.6, 126.5, 126.5, 126.3, 126.0, 48.0, 44.0, 43.9, 39.4, 29.4, 28.5, 22.0, 21.7 ppm.

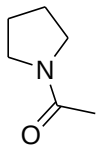
1-(3,4-dihydroquinolin-1(*2H*)-yl)ethanone (6.18t)[16]: According to GP I, tetraqhydroquinoline (0.10 g, 0.75 mmol) and Meldrum's acid **6.17** (0.11 g, 0.75 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.18t** as colourless oil (0.12 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.17 - 7.08 (m, 4H), 3.80 - 3.73 (m, 2H), 2.71 - 2.68 (m, 2H), 2.20 (s, 3H), 1.95 - 1.91 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.1, 139.3, 133.6, 128.4, 126.1, 125.2, 124.6, 42.8, 26.9, 24.1, 23.2 ppm.



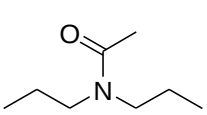
1-(azepan-1-yl)ethanone (6.18u)[24]: According to GP I, azepane (0.1 g, 1.01 mmol) and Meldrum's acid **6.17** (1.5 g, 1.01 mmol) was reacted for 12 h and evaporation the solvent gave analytically pure product **6.18u** as pale yellow oil (0.14 mg, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.41 - 3.39 (m, 2H), 3.32 - 3.30 (m, 2H), 1.98 (s, 3H), 1.62 - 1.59 (m, 4H), 1.45 - 1.44 (m, 4H). ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.3, 48.6, 45.7, 28.9, 27.5, 27.0, 26.8, 21.5 ppm.



1-(pyrrolidin-1-yl)ethanone (6.18v)[11]: According to GP I, pyrrolidine (0.20 g, 2.82 mmol) and Meldrum's acid **6.17** (0.41 g, 2.82 mmol) was reacted for 12 h and evaporation of the solvent gave get analytically pure product **6.18v** as pale yellow oil (0.28 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.42 - 3.36(m, 4H), 2.01 (s, 3H), 1.93 - 1.88 (m, 2H), 1.85 - 1.80 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 47.4, 45.6, 26.1, 24.6, 22.4 ppm.



***N,N*-dipropylacetamide (6.18w)[28]:** According to GP I, dipropylaminee (0.10 g, 0.99 mmol) and Meldrum's acid **6.17** (0.14 g, 0.99 mmol) was reacted for 12 h and evaporation the solvent gave analytically pure product **6.18w** as pale yellow liquid (0.13 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.20 (t, *J* = 8.0 Hz, 2H), 3.12 (t, *J* = 7.6 Hz, 2H), 2.01 (s, 3H), 1.55 - 1.45 (m, 4H), 0.87 - 0.79 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.1, 50.4, 47.3, 22.0, 21.5, 20.8, 11.3, 11.1 ppm.



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***N,N*-dioctylacetamide (6.18x)[29]:** According to GP I, dioctylamine (0.20 g, 1.55 mmol) and Meldrum's acid **6.17** (0.22 g, 1.55 mmol) was reacted for 12 h and evaporation the solvent gave analytically pure product **6.18x** as pale yellow liquid (0.26 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 3.21 - 3.18 (m, 2H), 3.13 - 3.10 (m, 2H), 2.44 - 2.42 (m, 1H), 1.99 (s, 3H), 1.65 - 1.62 (m, 1H), 1.50 - 1.40 (m, 4H), 1.22 - 1.16 (m, 18H), 0.80 - 0.76 (m, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.2, 48.8, 45.8, 31.8, 31.7, 29.3, 29.3, 29.18, 29.15, 28.8, 27.7, 27.03, 26.97, 26.8, 26.6, 22.6, 21.4, 14.0 ppm.

7-(4-acetylpiperazin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (6.18y)[33]: According to GP I, ciprofloxacin (0.20 g, 0.60 mmol) and Meldrum's acid **6.17** (87 mg, 0.60 mmol) was reacted for 12 h and after evaporation of the solvent and washing with ethyl acetate gave analytically pure product **6.18y** as white solid (0.21 g, 93%). ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.61 (s, 1H), 7.82 (d, *J* = 13.2 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 3.79 - 3.78 (m, 1H), 3.68 - 3.66 (m, 4H), 3.36 - 3.34 (m, 2H), 3.29 - 3.27 (m, 2H), 2.07 (s, 3H), 1.33 - 1.32 (m, 2H), 1.18 - 1.17 (m, 2H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 176.7, 169.0, 166.4, 154.2, 152.5, 148.4, 145.3, 139.4, 119.1, 119.1, 111.4, 111.3, 107.1, 106.9, 50.0, 49.6, 45.8, 40.9, 36.3, 21.6, 8.0 ppm. HRMS: Exact mass calculated for $C_{19}H_{20}FN_3O_4$ ($[M+H]^+$): 374.1516, Found:374.1540.

General procedure for the acetylation of aniline (GP II): Meldrum's acid **6.17** (1eq.) was added to a solution of aniline (1eq) in toluene (2 - 4 mL) and the mixture was refluxed for 12 h. After cooling the reaction mixture, solid product was filtered and washed to get analytically pure product.

***N*-phenylacetamide (6.20a)[1]:** According to GP II, aniline (0.20 g, 2.15 mmol) and Meldrum's acid **6.17** (0.31 g, 2.15mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20a** as white solid (0.27 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (br. s, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.21 - 7.16 (m, 2H), 7.01 - 6.98 (m, 1H), 2.05 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.4, 138.1, 128.9, 124.3, 120.3, 24.4 ppm.

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***N*-(2-ethylphenyl)acetamide (6.20b)[23]:** According to GP II, 2-ethylaniline (0.20 g, 1.65 mmol) and Meldrum's acid **6.17** (0.24 g, 1.65 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20b** as white solid (0.26 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 - 7.54 (m, 1H), 7.28 (br. s, 1H), 7.19 - 7.10 (m, 3H), 2.48 (q, *J* = 7.6 Hz, 2H), 2.05 (s, 3H), 1.10 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.2, 136.3, 134.9, 128.5, 126.5, 126.0, 124.9, 24.2, 23.9, 14.0 ppm.

***N*-(3-bromophenyl)acetamide (6.20c)[8]:** According to GP II, 3-bromoaniline (0.20 g, 1.16 mmol) and Meldrum's acid **6.17** (0.17 g, 1.16 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20c** as white solid (0.24 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (br. s, 1H), 7.78 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 2.16 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.6, 139.3, 130.2, 127.3, 123.2, 122.5, 118.7, 24.4 ppm.

***N*-(3-fluorophenyl)acetamide (6.20d)[1]:** According to GP II, 3-fluoroaniline (0.20 g, 1.80 mmol) and Meldrum's acid **6.17** (0.26 g, 1.80 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20d** as white solid (0.26 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.96 (br. s, 1H), 7.51 - 7.47 (m, 1H), 7.22 - 7.17 (m, 2H), 6.78 - 6.75 (m, 1H), 2.16 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.8, 169.8, 163.7, 162.1, 139.7, 139.6, 130.02, 129.96, 115.6, 111.0, 110.9, 107.7, 107.6, 24.3 ppm.

***N*-(3,5-dimethylphenyl)acetamide (6.20e)[21]:** According to GP II, 3,5-dimethylaniline (0.20 g, 1.66 mmol) and Meldrum's acid **6.17** (0.24 g, 1.65 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20e** as white solid (0.25 g, 91%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.64 (br. s, 1H), 7.13 (s, 2H), 6.74 (s, 1H), 2.26 (s, 6H), 2.14 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.7, 138.6, 137.8, 126.1, 117.8, 24.5, 21.4 ppm.

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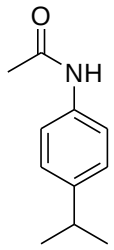
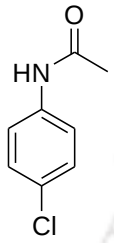
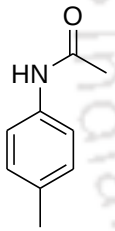
***N*-(4-isopropylphenyl)acetamide (6.20f)[21]:** According to GP II, 4-isopropylaniline (0.20 g, 1.48 mmol) and Meldrum's acid **6.17** (0.14 g, 1.48 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20f** as white solid (0.25 g, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.15 (br. s, 1H), 7.44 - 7.41 (m, 2H), 7.16 - 7.12 (m, 2H), 2.88 - 2.84 (m, 1H), 2.12 (s, 3H), 1.22 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.2, 145.0, 135.8, 126.8, 120.5, 33.6, 24.3, 24.1 ppm.



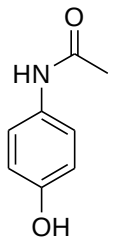
***N*-(4-chlorophenyl)acetamide (6.20g)[1]:** According to GP II, 4-chloroaniline (0.2 g, 1.57 mmol) and Meldrum's acid **2** (0.23 g, 1.57 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20g** as white solid (0.24 g, 90%). ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.09 (br. s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 2.04 (s, 3H). ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 168.9, 138.7, 129.0, 126.0, 120.9, 24.4 ppm.



***N*-*p*-tolylacetamide (6.20h)[1]:** According to GP II, 4-methylaniline (0.30 g, 2.80 mmol) and Meldrum's acid **6.17** (0.40 g, 2.80 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20h** as white solid (0.39 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (br. s, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 2.30 (s, 3H), 2.14 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.8, 135.4, 134.0, 129.4, 120.3, 24.3, 20.9 ppm.



***N*-(4-hydroxyphenyl)acetamide (6.20i)[1]:** According to GP II, 4-hydroxyaniline (0.3 g, 2.75 mmol) and Meldrum's acid **2** (0.40 g, 2.75 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:3) gave **6.20i** as white solid (0.31 g, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.42 (br. s, 1H), 8.95 (br. s, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 8.8 Hz, 2H), 1.72 (s, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.2, 153.6, 131.4, 121.4, 115.5, 24.1 ppm.



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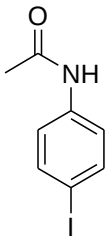
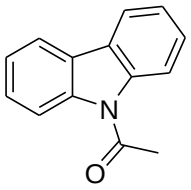
***N*-(4-iodophenyl)acetamide (6.20j)[22]:** According to GP II, 4-iodoaniline (0.2 g, 0.91 mmol) and Meldrum's acid **6.17** (1.3 g, 0.91 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20j** as white solid (0.23 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 8.8 Hz, 2H), 7.53 (br. s, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 2.17 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.6, 137.9, 137.6, 121.8, 87.6, 24.6 ppm.

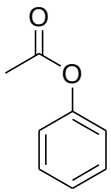


1-(acridin-10(*9H*)-yl)ethanone (6.20k)[6]: According to GP II, carbazole (0.20 g, 1.20 mmol) and Meldrum's acid **6.17** (0.17 g, 1.20 mmol) was reacted for 12 h and filtration and washing (EtOAc : hexane, 1:5) gave **6.20k** as white solid (0.22 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.87 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.21 - 7.16 (m, 2H), 7.11 - 7.07 (m, 2H), 2.87 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.2, 138.6, 127.4, 126.4, 123.7, 119.9, 116.3, 27.8 ppm.

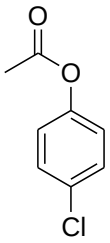


General procedure for the acetylation of alcohol (GP III): Triethylamine (20 mol%) was added to a solution of alcohol/thiol (1 eq.) and Meldrum's acid **6.17** (1.5 eq.) in toluene (2 - 4 mL) and the mixture was refluxed for 12 h. After disappearance of the starting materials (indicated by TLC) solvent was evaporated under reduced pressure. The crude mixture was subjected to column chromatography (silica) to afford analytically pure products.

Phenyl acetate (6.23a)[13]: According to GP III, phenol (0.20 g, 2.13 mmol), Meldrum's acid **6.17** (0.31 g, 3.19 mmol) and triethylamine (43 mg, 0.43 mmol) was reacted for 12 h and column chromatography (silica gel; EtOAc: hexane, 1:20) gave **6.23a** as colourless liquid (0.27 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 - 7.23 (m, 2H), 7.12 - 7.11 (m, 1H), 6.99 - 6.96 (m, 2H), 2.15 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.5, 150.8, 129.5, 125.9, 121.6, 21.1 ppm.



4-chlorophenyl acetate (6.23b)[13]: According to GP III, 4-clorophenol (0.1 g, 0.78 mmol), Meldrum's acid **6.17** (0.17 g, 1.18mmol), and triethylamine (16 mg, 0.16 mmol) was reacted for 12 h and column chromatography (silica gel; EtOAc: hexane, 1:20) gave **6.23b** as colourless liquid (1.2 g, 91%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 9.0 Hz, 2H), 7.06 (d, *J* = 9.0 Hz, 2H), 2.31 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.3, 149.1, 131.2, 129.5, 123.0, 21.1 ppm.



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2,6-dimethylphenyl acetate (6.23c)[19]**:** According to GP III, 2,6-dimethylphenol (0.1 g, 0.82 mmol), Meldrum's acid **6.17** (0.18 g, 1.23 mmol) and triethylamine (17 mg, 0.16 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.23c** as colourless liquid (0.13 g, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.15 - 7.12 (m, 3H), 2.40 (s, 3H), 2.23 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.9, 148.3, 130.1, 128.6, 125.9, 20.5, 16.4 ppm.

2-isopropyl-5-methylphenyl acetate (6.23d)[18]**:** According to GP III, thymol (0.1 g, 0.67 mmol), Meldrum's acid **6.17** (0.14 g, 0.10 mmol) and triethylamine (14 mg, 0.13 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.23d** as colourless liquid (0.12 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.10 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.72 (s, 1H), 2.92 - 2.85 (m, 1H), 2.22 (s, 3H), 2.21 (s, 3H), 1.10 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.8, 147.9, 137.0, 136.6, 127.2, 126.5, 122.8, 27.2, 23.1, 21.0, 20.9 ppm.

5-isopropyl-2-methylphenyl acetate (6.23e)[31]**:** According to GP III, carvacol (0.1 g, 0.67 mmol), Meldrum's acid **6.17** (0.14 g, 1.0 mmol) and triethylamine (14 mg, 0.13 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave 6.**23e** as colourless liquid (0.12 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 7.6 Hz, 1H), 7.06 (d *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 2.96 - 2.89 (m, 1H), 2.34 (s, 3H), 2.19 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.3, 149.4, 148.1, 130.9, 127.2, 124.2, 119.8, 33.6, 23.9, 20.8, 15.8 ppm.

Naphthalen-6-yl acetate (6.23f)[13]**:** According to GP III, 2-napthol (0.1 g, 0.69 mmol), Meldrum's acid **2** (0.15 g, 1.04 mmol)and triethylamine (14 mg, 0.14 mmol) was reacted for 12 h and column chromatography

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(slica gel; EtOAc: hexane, 1:15) gave **6.23f** as colourless liquid (0.11 g, 88%). ^{1}H NMR (400 MHz, CDCl3) δ = 7.69 - 7.62 (m, 3H), 7.41 (s, 1H), 7.34 - 7.27 (m, 2H), 7.10 - 7.07 (m, 1H), 2.17 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.7, 148.5, 133.9, 131.6, 129.5, 127.9, 127.7, 126.7, 125.8, 121.3, 118.6, 21.2 ppm.

S-phenyl ethanethioate (6.23g)[19]: According to GP III, thiophenol (0.1 g, 0.91 mmol), Meldrum's acid **6.17** (0.20 g, 1.36 mmol) and triethylamine (18 mg, 0.18 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:30) gave **6.23g** as colourless liquid (0.15 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 - 7.41 (m, 5H), 2.42 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 193.1, 133.4, 128.4, 128.2, 126.9, 29.2 ppm.

1,3-phenylene diacetate (6.23h)[13]: According to GP III, resorcinol (0.1 g, 0.91 mmol), Meldrum's acid **6.17** (0.39 g, 2.72 mmol) and triethylamine (18 mg, 0.18 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.23h** as colourless liquid (0.13 g, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.39 - 7.36 (m, 1H), 7.00 - 6.98 (m, 2H), 6.94 - 6.92 (m, 1H), 2.28 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.0, 151.1, 129.7, 119.0, 115.5, 21.1 ppm.

Benzyl acetate (6.23i)[4]: According to GP III, benzyl alcohol (0.1 g, 0.92 mmol), Meldrum's acid **6.17** (0.2 g, 1.38 mmol) and triethylamine (18 mg, 0.18 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:30) gave **6.23i** as colourless liquid (0.12 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 - 7.22 (m, 5H), 5.01 (s, 2H), 2.00 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.8, 136.0, 128.6, 128.3, 128.2, 66.3, 21.0 ppm.

2,5-dimethoxybenzyl acetate (6.23j)[30]: According to GP III, 2,5-dimethoxy benzylalcohol (0.1 g, 0.59 mmol), Meldrum's acid **6.17** (0.13 g, 0.89 mmol) and triethylamine (12 mg, 0.12 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:10) gave **6.23j** as colourless liquid (0.10 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.91 (s, 1H), 6.82 - 6.81 (m, 2H), 5.13 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 2.10 (s, 3H) ppm.

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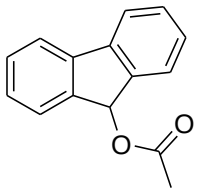
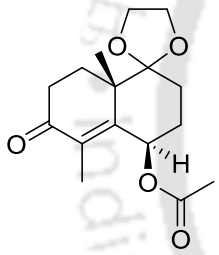
^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.0, 153.4, 151.6, 125.2, 115.7, 113.7, 111.5, 61.6, 56.0, 55.7, 21.1 ppm.

9*H*-fluoren-9-yl acetate (6.23k)[3]: According to GP III, 9*H*-fluoren-9-ol (0.1 g, 0.55 mmol),

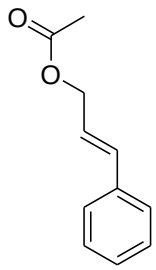


Meldrum's acid **6.17** (0.12 g, 0.82 mmol) and triethylamine (11 mg, 0.11 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:10) gave **6.23k** as colourless liquid (0.10 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 7.4 Hz, 2H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 2H), 6.67 (s, 1H), 2.05 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.8, 142.1, 141.1, 129.5, 127.9, 125.9, 120.1, 75.2, 21.3 ppm.

(4*R*,8a*S*)-5,8a-dimethyl-6-oxo-3,4,6,7,8,8a-hexahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolan]-4-yl acetate (6.23l): According to GP III, (4*R*,8a*S*)-4-hydroxy-5,8a-dimethyl-3,4,8,8a-tetrahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolan]-6(7H)-one (0.1 g, 0.42 mmol), Meldrum's acid **6.17** (91 mg, 0.63 mmol) and triethylamine (8 mg, 0.08 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:5) gave **6.23l** as colourless liquid (99 mg, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.97 - 5.96 (m, 1H), 3.97 - 3.89 (m, 4H), 2.45 - 2.44 (m, 2H), 2.26 - 2.19 (m, 1H), 2.13 - 2.07 (m, 1H), 2.01 (s, 3H), 1.91 - 1.89 (m, 2H), 1.81 (s, 3H), 1.66 - 1.62 (m, 1H), 1.58 - 1.55 (m, 1H), 1.41 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 199.4, 169.7, 153.0, 135.0, 112.0, 68.3, 65.4, 65.1, 44.6, 33.6, 27.4, 27.2, 25.2, 21.5, 21.3, 11.5 ppm. HRMS: Exact mass calculated for $C_{16}H_{22}O_5$ ([M+Na]+): 317.1359, Found:317.1366.



Cinnamyl acetate (6.23m)[4]: According to GP III, cinnamyl alcohol (0.1 g, 0.75 mmol),



Meldrum's acid **6.17** (0.16 g, 1.12 mmol) and triethylamine (15 mg, 0.15 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:10) gave **6.23m** as colourless liquid (0.10 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.43 - 7.41 (m, 2H), 7.37 - 7.34 (m, 2H), 7.30 - 7.28 (m, 1H), 6.68 (d, *J* = 16.2 Hz, 1H), 6.34 - 6.30 (m, 1H), 4.76 (d, *J* = 6.6 Hz, 2H),

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2.13 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.9, 136.2, 134.2, 128.6, 128.1, 126.6, 123.2, 65.1, 21.0 ppm.

(3-phenyloxiran-2-yl)methyl acetate (6.23n)[34]: According to GP III, (3-phenyloxiran-2-yl)methanol (0.1 g, 0.67 mmol), Meldrum's acid **6.17** (0.14 g, 0.99 mmol) and triethylamine (14 mg, 0.13 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:5) gave **6.23n** as colourless liquid (0.11 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 - 7.23 (m, 3H), 7.29 - 7.27 (m, 2H), 4.49 (dd, *J* = 12.4, 3.2 Hz, 1H), 4.09 (dd, *J* = 12.4, 6.0 Hz, 1H), 3.82 (d, *J* = 2.0 Hz, 1H), 3.29 - 3.26 (m, 1H), 2.12 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.7, 136.3, 128.6, 128.5, 125.7, 64.2, 59.3, 56.4, 20.8 ppm.

dodecyl acetate: (6.23o)[32]: According to GP III, dodecyl alcohol (0.2 g, 1.07 mmol), Meldrum's acid **6.17** (2.30 g, 1.61 mmol) and triethylamine (22 mg, 0.21 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:10) gave **6.23o** as colourless liquid (0.25 g, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.04 (t, *J* = 6.8 Hz, 2H), 2.03 (s, 3H), 1.64 -1.57 (m, 2H), 1.32 - 1.23 (m, 18H), 0.87 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.5, 64.9, 31.1, 29.9, 29.83, 29.77, 29.72, 29.55, 29.46, 28.8, 26.1, 22.9, 21.2, 14.3 ppm.

(*E*)-*N*'-benzylidene-*N*-phenylacetohydrazide (6.25a): According to GP II, (*E*)-1-benzylidene-2-phenylhydrazine **6.24** (0.1 g, 0.51 mmol) and Meldrum's acid **6.17** (73 mg, 0.51 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:5) gave **6.25a** as colourless gum (0.1 g, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.60 - 7.56 (m, 4H), 7.50 - 7.48 (m, 1H), 7.37 - 7.36 (m, 3H), 7.23 (s, 1H), 7.19 (d, *J* = 7.4 Hz, 2H), 2.64 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.0, 141.5, 135.9, 134.3, 130.3, 129.9, 129.4, 129.3, 128.7, 127.2, 22.3 ppm.

(*E*)-*N*'-benzylidene-*N*-phenylacetohydrazide (6.25a): According to GP II, phenylhydrazine (0.1 g, 0.93 mmol), benzaldehyde (98 mg, 0.93 mmol) and Meldrum's acid **6.17** (0.13 g, 0.93 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane,

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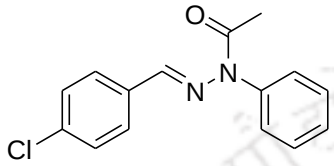
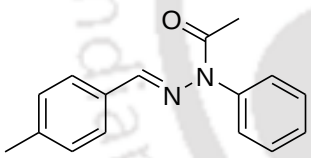
1:5) gave **6.25a** as colourless gum (0.17 g, 76 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.60 - 7.55 (m, 4H), 7.50 - 7.48 (m, 1H), 7.38 - 7.36 (m, 3H), 7.22 (s, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 2.64 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.0, 141.5, 135.9, 134.3, 130.3, 129.9, 129.4, 129.3, 128.7, 127.2, 22.3 ppm.

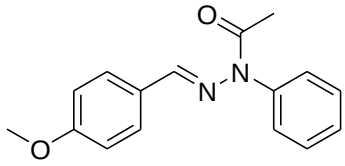
(*E*)-*N*'-(4-chlorobenzylidene)-*N*-phenylacetohydrazide (6.25b): According to GP II, phenylhydrazine (77 mg, 0.71 mmol), 4-chlorobenzaldehyde (0.1 g, 0.71 mmol) and Meldrum's acid **6.17** (0.10 g, 0.71 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:5) gave **6.25b** as colourless gum (0.15 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 - 7.46 (m, 5H), 7.35 - 7.32 (m, 2H), 7.18 - 7.16 (m, 3H), 2.61 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.9, 140.2, 135.8, 135.6, 132.8, 130.3, 129.5, 129.2, 129.0, 128.3, 22.20 ppm. HRMS: Exact mass calculated for $C_{19}H_{20}FN_3O_4$ ($[M+H]^+$): 273.0789, Found:273.10796.



(*E*)-*N*'-(4-methylbenzylidene-*N*-phenylacetohydrazide (6.25c): According to GP II: phenylhydrazine (0.1 g, 0.93 mmol), 4-methylbenzaldehyde (0.11 g, 0.93 mmol) and Meldrum's acid **6.17** (0.13 g, 0.93 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:5) gave **6.25c** as colourless gum (0.16 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 - 7.54 (m, 2H), 7.50 - 7.47 (m, 3H), 7.21 - 7.17 (m, 5H), 2.63 (s, 3H), 2.37 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.9, 141.7, 140.1, 136.1, 131.6, 130.2, 129.4, 129.31, 129.28, 127.1, 22.3, 21.5 ppm.



(*E*)-*N*'-(4-methoxybenzylidene)-*N*-phenylacetohydrazide(6.25d): According to GP II, phenylhydrazine (80 mg, 0.74 mmol), 4-methoxybenzaldehyde (0.1 g, 0.74 mmol) and Meldrum's acid **6.17** (0.11 g, 0.74 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:5) gave **6.25d** as colourless gum (0.15 g, 74%). 1H NMR (400 MHz, $CDCl_3$) δ = 7.45 - 7.41 (m, 4H), 7.37 - 7.34 (m, 1H), 7.08 - 7.06 (m, 3H), 6.77 (d, *J* = 8.8 Hz, 2H), 3.69 (s, 3H), 2.51 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.7, 160.0, 140.4, 135.1, 129.1, 128.3, 128.2, 127.6, 125.9, 113.1,



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54.3, 21.2 ppm. HRMS: Exact mass calculated for $C_{19}H_{20}FN_3O_4$ ($[M+H]^+$): 269.1285, Found:269.1286.

(*E*)-*N'*-benzylidene-*N*-(4-methoxyphenyl)acetohydrazide (6.25e): According to GP II, 4-methoxyphenylhydrazine (0.1 g, 0.72 mmol), benzaldehyde (77 mg, 0.72 mmol) and Meldrum's acid **6.17** (0.10 g, 0.72 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:5) gave **6.25e** as colourless gum (0.15 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 - 7.61 (m, 2H), 7.42 - 7.38 (m, 3H), 7.29 (s, 1H), 7.13 - 7.07 (m, 4H), 3.89 (s, 3H), 2.65 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.2, 160.0, 141.4, 134.4, 130.3, 129.8, 128.7, 128.2, 127.2, 115.5, 55.5, 22.2 ppm.

5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**6.26a**)[7a]: Compound **6.26a** was prepared by following the exactly same procdure mentioned in the reference 7a. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.10 (m, 5H), 3.70 (t, *J* = 5.0 Hz, 1H), 3.42 (d, *J* = 5.0 Hz, 2H), 1.66 (s, 3H), 1.42 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.34, 137.3, 129.8, 128.7, 127.2, 105.3, 48.2, 32.2, 28.5, 27.3 ppm.

2,2-dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione (**6.26b**)[7a]: Compound was prepared by following the procdure mentioned in the reference 7a. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.75 (t, *J* = 5.0 Hz, 1H), 3.44 (d, *J* = 4.9 Hz, 2H), 2.30 (s, 3H), 1.73 (s, 3H), 1.50 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.7, 132.1, 129.4, 124.9, 124.5, 100.5, 43.5, 27.0, 23.7, 22.5, 16.3 ppm.

5-butyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**6.26c**)[7a]: Compound was prepared by following the exactly same procdure mentioned in the reference 7a. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.58 – 3.41 (m, 1H), 2.20 – 1.99 (m, 2H), 1.75 (d, *J* = 12.0 Hz, 6H), 1.43 – 1.32 (m, 4H), 0.91 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.7, 104.8, 46.1, 28.6, 28.4, 26.9, 26.4, 22.6, 13.7 ppm.

5-((2,4-dimethylcyclohex-3-en-1-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6.26d**): In a round-bottom flask, 2,4-dimethylcyclohex-3-ene-1-carbaldehyde (1.3 g, 10 mmol) were

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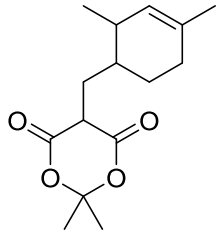
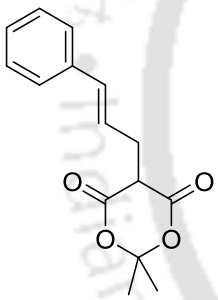
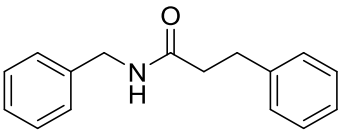


dissolved in TEAF solution (10 mL) prepared by mixing triethylamine and aqueous formic acid (85%) (5:2 mol/mol). After addition of Meldrum's acid (1.4 g, 10 mmol), the mixture was stirred at 45 ^{o}C (oil bath), and the reaction was monitored by TLC analysis (for around 6 hours). Then, the mixture was cooled to room temperature, and poured into ice water (pH = 2-3), leading to the precipitation of 5-alkyl Meldrum's acid **6.26d** as white solid (1.8 g, 68%). FTIR: ϑ = 2959, 2915, 2868, 1785, 1745, 1448, 1394, 1382, 1300, 1203, 1062, 1006, 983, 856 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.13 – 5.11 (m, 1H), 3.44 – 3.41 (1, 1H), 2.22 – 2.16 (m, 1H), 1.93 – 1.89 (m, 1H), 1.89 – 1.78 (m, 3H), 1.75 (s, 3H), 1.70 (s, 3H), 1.58 (s, 3H), 1.51 – 1.45 (m, 1H), 1.28 – 1.22 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2, 166.0, 132.8, 126.8, 104.9, 44.2, 37.9, 35.9, 30.7, 28.9, 28.7, 26.8, 26.2, 23.5, 20.6 ppm.

5-cinnamyl-2,2-dimethyl-1,3-dioxane-4,6-dione (6.26e)[46]: In a round-bottom flask, cinnamaldehydes (1.3 g, 10 mmol) were dissolved in TEAF solution (10 mL) prepared by mixing triethylamine and aqueous formic acid (85%) (5:2 mol/mol). After addition of Meldrum's acid (1.4 g, 10 mmol), the mixture was stirred at 45 ^{o}C (oil bath), and the reaction was monitored by TLC analysis (for around 6 hours). Then, the mixture was cooled to room temperature, and then poured into ice water (pH = 2-3), leading to the precipitation of 5-alkyl Meldrum's acid derivative **6.26e** as white solid (1.7 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 7.2 Hz, 2H), 7.25 – 7.18 (m, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 15.8 Hz, 1H), 6.23 – 6.13 (m, 1H), 3.59 (t, *J* = 5.0 Hz, 1H), 2.97 – 2.94 (m, 2H), 1.71 (s, 3H), 1.67 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.0, 136.8, 134.7, 128.5, 127.6, 126.4, 123.9, 105.1, 46.7, 29.6, 28.4, 27.0. ppm.



***N*-benzyl-3-phenylpropanamide (6.27a)**[38]**:** According to GP I: benzylamine (80 mg, 0.34 mmol) and 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26a** (37 mg, 0.34 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.27a** as colorless gum (68 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 – 7.15 (m, 5H), 7.14 – 7.06 (m, 3H), 7.02 – 7.00 (m, 2H), 6.08 (s, 1H), 4.24 (d, *J* = 6.0 Hz, 2H), 2.85 (t, *J* = 7.6 Hz, 2H),



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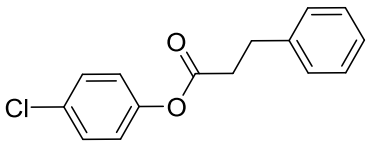
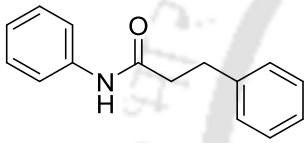
2.38 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.2, 140.8, 138.2, 128.63, 128.56, 128.4, 127.7, 127.4, 126.3, 43.5, 38.4, 31.8 ppm.

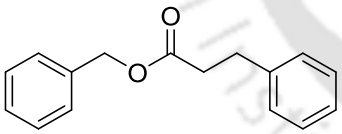
4-chlorophenyl 3-phenylpropanoate (6.27b)[40]**:** According to GP III: 4-chloro phenol (37 mg, 0.28 mmol), 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26a** (0.1 g, 0.43 mmol) and triethylamine (6 mg, 0.06 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.27b** as colorless liquid (60 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 – 7.17 (m, 4H), 7.16 – 7.10 (m, 3H), 6.83 (d, *J* = 8.8 Hz, 2H), 2.95 (t, *J* = 7.8 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.1, 148.0, 138.9, 130.1, 128.4, 127.6, 127.3, 125.5, 121.9, 34.8, 29.8 ppm.



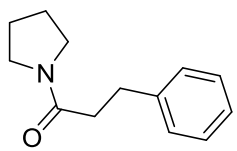
***N*,3-diphenylpropanamide (6.27c)**[7a]**:** According to GP II: aniline (40 mg, 0.43 mmol) and 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26a** (0.1 g, 0.43 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:1) gave **6.27c** as colourless gum (89 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 7.8 Hz, 2H), 7.24 – 7.21 (m, 3H), 7.19 – 7.15 (m, 3H), 7.07 – 6.97 (m, 2H), 2.98 (t, *J* = 7.2 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.6, 140.6, 137.7, 129.0, 128.7, 128.4, 126.4, 124.3, 120.0, 39.4, 31.6 ppm.



benzyl 3-phenylpropanoate (6.27d)[39]**:** According to GP III: benzyl alcohol (80 mg, 0.34 mmol), 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26a** (0.2 g, 0.85 mmol) and triethylamine (12 mg, 0.11 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product gave **6.27d** as colourless liquid (0.12 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.14 (m, 7H), 7.14 – 7.07 (m, 3H), 5.02 (s, 2H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.8, 140.5, 136.0, 128.59, 128.55, 128.4, 128.3, 126.3, 66.3, 35.9, 31.0 ppm.



3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (6.27e)[38]**:** According to GP I: pyrrolidine (30 mg, 0.43 mmol) and 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26a** (0.1 g, 0.34 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.27e** as colorless gum (73 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 – 7.17 (m, 2H), 7.16 – 7.07 (m, 3H), 3.37 (t, *J* = 6.7 Hz, 2H), 3.18 (t, *J* = 6.6 Hz, 2H), 2.94 – 2.83 (m, 2H), 2.52 – 2.40 (m, 2H), 1.82 –



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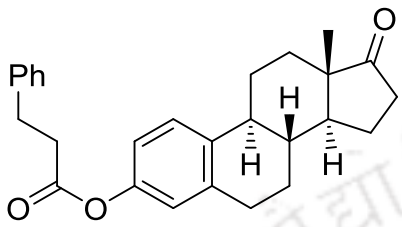
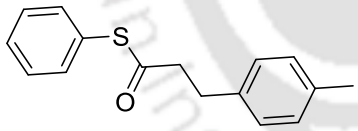
1.69 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.9, 141.4, 128.4, 126.1, 46.6, 45.7, 36.7, 31.2, 26.0, 24.4 ppm (Less number of ^{13}C observed due to overlap in the aromatic region).

(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 3-phenylpropanoate (6.26f): According to GP III: estrone (77 mg, 0.28 mmol), 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26a** (0.1 g, 0.43 mmol) and triethylamine (6 mg, 0.06 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.27f** as colorless liquid (90 mg, 78%). FTIR: ῡ = 3030, 2931, 2861, 1738, 1493, 1453, 1221, 1208, 1150, 1127, 1077, 1052, 1007, 733, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 – 7.21 (m, 2H), 7.21 – 7.13 (m, 4H), 6.72 – 6.69 (m, 1H), 6.66 (s, 1H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.84 – 2.77 (m, 4H), 2.45 – 2.39 (m, 1H), 2.35 – 2.29 (m, 1H), 2.34 – 2.29 (m, 1H), 2.11 – 2.04 (m, 1H), 2.02 – 1.86 (m, 3H), 1.58 – 1.33 (m, 6H), 0.83 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 220.8, 171.7, 148.5, 140.2, 138.0, 137.4, 128.6, 128.4, 126.44, 126.39, 121.6, 118.7, 50.4, 48.0, 44.2, 38.0, 36.0, 35.9, 31.6, 31.0, 29.4, 26.4, 25.8, 21.6, 13.9 ppm.



S-phenyl 3-(p-tolyl)propanethioate (6.27g): According to GP III: thiophenol (44 mg, 0.40 mmol), 2,2-dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione **6.26b** (0.1 g, 0.40 mmol) and triethylamine (8 mg, 0.08 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.27g** as colorless liquid (86 mg, 83%). FTIR: ῡ = 3025, 2923, 2861, 1704, 1515, 1477, 1440, 1042, 1023, 961, 744, 688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (s, 5H) (multiplet but looks like singlet), 7.00 (s, 4H) (multiplet but looks like singlet), 2.91 – 2.81 (m, 4H), 2.22 (s, 3H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.8, 136.9, 136.0, 134.6, 129.4, 129.31, 129.25, 128.3, 127.8, 45.4, 31.1, 21.1 ppm.



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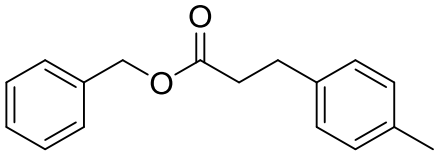
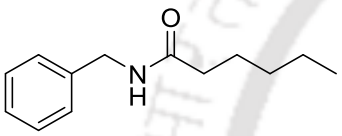
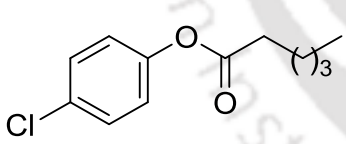
benzyl (*E*)-5-phenylpent-4-enoate (6.27h): According to GP III: benzyl alcohol (43 mg, 0.38 mmol), 2,2-dimethyl-5-(4-methylbenzyl)-1,3-dioxane-4,6-dione **6.26b** (0.1 g, 0.40 mmol) and triethylamine (8 mg, 0.08 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.27h** as colorless liquid (83 mg, 82%). FTIR: ῡ = 3035, 2923, 2861, 1732, 1515, 1464, 1380, 1352, 1288, 1212, 1147, 811, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.31 (m, 5H), 7.10 (s, 4H) (multiplet but looks like singlet), 5.13 (s, 2H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.69 (t, *J* = 7.8 Hz, 2H), 2.34 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.8, 137.4, 136.0, 135.8, 129.2, 128.6, 128.3, 128.22, 128.21, 66.3, 36.1, 30.6, 21.1 ppm.



***N*-benzylhexanamide (6.27i)[38]:** According to GP I: benzylamine (54 mg, 0.5 mmol) and 5-butyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26c** (0.1 g, 0.34 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.27i** as colorless gum (88 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.23 (m, 2H), 7.22 – 7.18 (m, 3H), 5.84 (s, 1H), 4.35 (d, *J* = 5.6 Hz, 2H), 2.17 – 2.08 (m, 2H), 1.62 – 1.54 (m, 2H), 1.25 – 1.22 (m, 4H), 0.82 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.1, 138.4, 128.7, 127.8, 127.5, 43.6, 36.8, 31.5, 25.5, 22.4, 14.0 ppm.



4-chlorophenyl hexanoate (6.27j)[44]: According to GP III: 4-chloro phenol (43 mg, 0.33 mmol), 5-butyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26c** (0.1 g, 0.5 mmol) and triethylamine (7 mg, 0.07 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.27j** as colorless liquid (47 mg, 91%).^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.24 (m, 2H), 6.97 – 6.92 (m, 2H), 2.47 (t, *J* = 7.6 Hz, 2H), 1.71- 1.64 (m, 2H), 1.34 – 1.28 (m, 4H), 0.86 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 149.2, 131.1, 129.4, 123.0, 34.3, 31.3, 24.6, 22.3, 13.9 ppm.



***N*-benzyl-3-phenylpropanamide (6.27k)[45]:** benzyl alcohol (54 mg, 0.34 mmol), 5-butyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26c** (0.1 g, 0.5 mmol) and triethylamine (5 mg, 0.05 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.27k** as colorless liquid (47 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.18 (m, 5H), 5.03 (s, 2H), 2.27 (t, *J* = 7.6 Hz, 2H), 1.60 – 1.53 (m, 2H), 1.26 –

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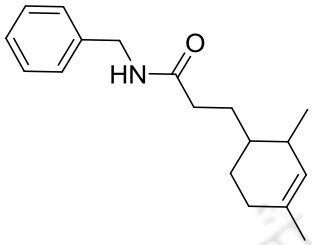
1.18 (m, 4H), 0.80 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.7, 136.2, 128.6, 128.18, 128.16, 66.1, 34.3, 31.3, 24.7, 22.3, 13.9 ppm.

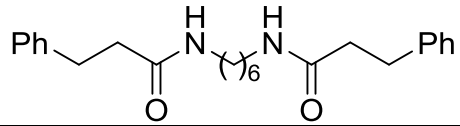
***N*-benzyl-3-(2,4-dimethylcyclohex-3-en-1-yl)propanamide (6.27l):** According to GP I:



benzylamine (41 mg, 0.38 mmol) and 5-((2,4-dimethylcyclohex-3-en-1-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26d** (0.1 g, 0.38 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:2) gave **6.27l** as colorless liquid (88 mg, 84%). FTIR: ῡ = 3282, 2957, 2923, 2868, 1643, 1539, 1453, 1260, 1080, 1028, 802, 730, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.25 (m, 2H), 7.24 – 7.19 (m, 3H), 5.68 (s, 1H), 5.10 – 5.09 (m, 1H), 4.37 (d, *J* = 5.6 Hz, 2H), 2.29 – 2.22 (m, 1H), 2.14 – 2.06 (m, 1H), 1.88 – 1.79 (m, 2H), 1.78 – 1.75 (m, 1H), 1.72 – 1.65 (m, 3H), 1.56 (s, 3H), 1.45 – 1.34 (m, 1H), 1.08 – 1.01 (m, 1H), 0.90 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.2, 138.4, 132.9, 128.7, 127.9, 127.5, 127.2, 43.7, 39.9, 35.4, 34.4, 29.3, 29.2, 26.5, 23.5, 20.7 ppm.

benzyl 3-(2,4-dimethylcyclohex-3-en-1-yl)propanoate (6.27m): benzyl alcohol (28 mg, 0.26 mmol), 5-((2,4-dimethylcyclohex-3-en-1-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26d** (0.1 g, 0.38 mmol) and triethylamine (5 mg, 0.05 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.27m** as colorless liquid (61 mg, 87%). FTIR: ῡ = 2956, 2925, 2869, 1734, 1454, 1379, 1257, 1150, 966, 748, 734, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.27 (m, 5H), 5.09 – 5.08 (m, 1H), 5.04 (s, 2H), 2.41 – 2.34 (m, 1H), 2.30 – 2.22 (m, 1H), 1.86 – 1.78 (m, 3H), 1.77 – 1.72 (m, 1H), 1.70 – 1.64 (m, 1H), 1.55 (s, 3H), 1.43 – 1.34 (m, 1H), 1.21 – 1.12 (m, 1H), 1.05 – 0.97 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.9, 136.1, 132.9, 128.6, 128.2, 128.2, 127.2, 66.2, 39.8, 35.4, 32.1, 29.3, 28.5, 26.5, 23.5, 20.6 ppm.

***N*,*N'*-(hexane-1,6-diyl)bis(3-phenylpropanamide) (6.27n)[43]:** According to GP I:



hexamethylene diamine (25 mg, 0.21 mmol) and 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26a** (0.1

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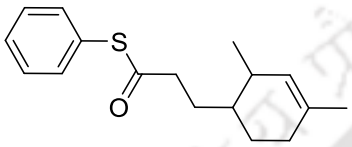
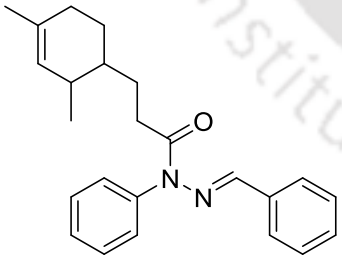
g, 0.43 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **26.27n** as yellow gum (74 mg, 91%). FTIR: ῡ = 3006, 2935, 2857, 1635, 1537, 1496, 1371, 1236, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 – 7.18 (m, 4H), 7.13 – 7.09 (m, 6H), 5.56 (s, 2H), 3.13 – 3.08 (m, 4H), 2.88 (t, *J* = 7.7 Hz, 4H), 2.40 (d, *J* = 7.6 Hz, 4H), 1.35 – 1.29 (m, 4H), 1.16 – 1.12 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.2, 140.9, 128.5, 128.4, 126.2, 39.0, 38.5, 31.8, 29.3, 25.8 ppm.

S-phenyl 3-(2,4-dimethylcyclohex-3-en-1-yl)propanethioate (6.27o): According to GP III: thiophenol (42 mg, 0.38 mmol), 5-((2,4-dimethylcyclohex-3-en-1-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26d** (0.1 g, 0.38 mmol) and triethylamine (8 mg, 0.08 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:20) gave **6.27o** as colorless liquid (78 mg, 76%). FTIR: ῡ = 2956, 2923, 2868, 1706, 1477, 1440, 1036, 1023, 965, 742, 704, 694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.31 (m, 5H), 5.10 – 5.09 (m, 1H), 2.71 – 2.63 (m, 1H), 2.60 – 2.52 (m, 1H), 1.94 – 1.87 (m, 1H), 1.86 – 1.81 (m, 2H), 1.80 – 1.68 (m, 2H), 1.57 (s, 3H), 1.51 – 1.41 (m, 1H), 1.24 – 1.17 (m, 1H), 1.12 – 1.03 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.8, 134.5, 132.9, 129.3, 129.2, 128.0, 127.1, 41.5, 39.7, 35.4, 29.2, 29.1, 26.5, 23.5, 20.6 ppm.



(*E*)-*N*'-benzylidene-3-(2,4-dimethylcyclohex-3-en-1-yl)-*N*-phenylpropanehydrazide (6.27p): According to GP I: phenylhydrazine (21 mg, 0.19 mmol), benzaldehyde (20 mg, 0.19 mmol) and 5-((2,4-dimethylcyclohex-3-en-1-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26d** (50 mg, 0.19 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:4) gave **6.27p** as colorless gum (44 mg, 65%). FTIR: ῡ = 2965, 2927, 2872, 1600, 1489, 1448, 1392, 1230, 1178, 1165, 938, 754, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 – 7.44 (m, 4H), 7.40 – 7.36 (m, 1H), 7.31 – 7.25 (m, 3H), 7.15 (s, 1H), 7.09 – 7.07 (m, 2H), 5.13 – 5.12 (m, 1H), 3.08 – 2.87 (m, 2H), 2.00 – 1.98 (m, 1H), 1.89 – 1.82 (m, 5H), 1.57 (s, 3H), 1.33 – 1.26 (m, 1H), 1.21 – 1.14 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.8, 141.4, 136.2, 134.4, 133.0, 130.2, 129.8, 129.29, 129.25, 128.7, 127.4, 127.2, 40.3, 35.6, 32.1, 29.5, 29.0, 26.9, 23.6, 20.8 ppm.



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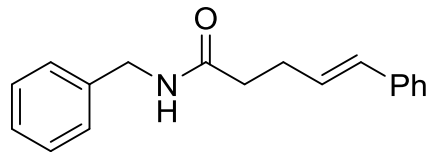
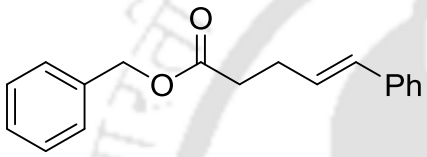
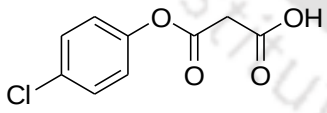
(E)-N-benzyl-5-phenylpent-4-enamide (6.27q)[42]: According to GP I: benzylamine (41 mg, 0.38 mmol) and 5-cinnamyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26e** (0.1 g, 0.38 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.27q** as colorless gum (78 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 – 7.18 (m, 4H), 7.15 – 7.09 (m, 6H), 6.31 (d, *J* = 15.6 Hz, 1H), 6.19 – 6.17 (m, 1H), 6.11 – 6.03 (m, 1H), 4.29 (d, *J* = 5.6 Hz, 2H), 2.47 – 2.41 (m, 2H), 2.25 (t, *J* = 7.4 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.3, 138.3, 137.3, 131.1, 128.7, 128.6, 127.7, 127.4, 127.2, 126.1, 43.6, 36.3, 29.1 ppm (Less number of ^{13}C observed due to overlap in the aromatic region).



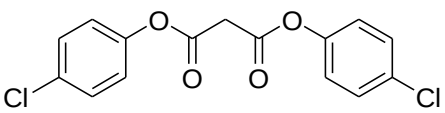
benzyl (E)-5-phenylpent-4-enoate (6.27r)[41]: According to GP III: benzyl alcohol (42 mg, 0.38 mmol), 5-cinnamyl-2,2-dimethyl-1,3-dioxane-4,6-dione **6.26e** (0.1 g, 0.38 mmol) and triethylamine (8 mg, 0.08 mmol) was reacted for 12 h and evaporation of the solvent gave analytically pure product **6.27r** as colorless liquid (83 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.24 (m, 5H), 7.22 – 7.18 (m, 4H), 7.14 – 7.10 (m, 1H), 6.33 (d, *J* = 15.6 Hz, 1H), 6.15 – 6.07 (m, 1H), 5.05 (s, 2H), 2.49 – 2.44 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.8, 137.3, 136.0, 131.1, 128.6, 128.5, 128.3, 128.3, 128.3, 127.2, 126.1, 66.3, 34.1, 28.3 ppm.



2-((4-chlorophenoxy)carbonyl)acetic acid (6.21a)[35]: 4-Chlorophenol (0.2 g, 1.56 mmol) and Meldrum's acid **6.17** (0.23 g, 1.56 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:1) gave **6.21a** as white solid (0.18 g, 55%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 10.70 (br. s, 1H), 7.42 - 7.34 (m, 2H), 7.18 - 7.03 (m, 2H), 3.71 (s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 172.1, 164.6, 148.7, 131.8, 129.7, 122.7, 41.1 ppm.



bis(4-chlorophenyl) malonate (6.21b)[36]: 4-Chlorophenol (0.2 g, 1.56 mmol) and Meldrum's acid **6.17** (0.23 g, 1.56 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:10) gave **6.21b** as colourless gum



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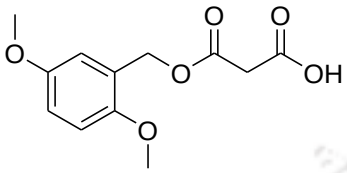
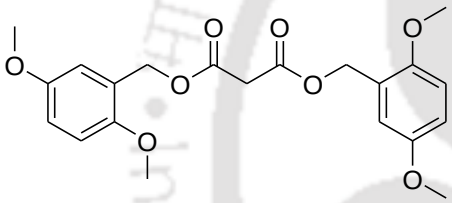
(0.13 g, 25%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 9.0 Hz, 4H), 7.10 (d, *J* = 8.4 Hz, 4H), 3.85 (s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 164.4, 148.7, 131.9, 129.7, 122.7, 41.5 ppm.

2-((2,5-dimethoxybenzyloxy)carbonyl)acetic acid (6.22a): 2,5-Dimethoxy benzyl alcohol (0.2 g, 1.18 mmol) and Meldrum's acid **6.17** (0.17 g, 1.18 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:1) gave **6.22a** as colourless gum (0.14 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.45 (br. s, 1H), 6.92 - 6.91 (m, 1H), 6.85 - 6.78 (m, 2H), 5.22 (s, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.48 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.2, 166.7, 153.4, 151.6, 124.3, 115.6, 114.3, 111.7, 63.0, 56.0, 55.8, 40.9 ppm.



bis(2,5-dimethoxybenzyl) malonate (6.22b): 2,5-Dimethoxy benzyl alcohol (0.2 g, 1.18 mmol) and Meldrum's acid **6.17** (0.17 g, 1.18 mmol) was reacted for 12 h and column chromatography (slica gel; EtOAc: hexane, 1:10) gave **6.22b** as colourless gum (0.10 g, 22%). ^{1}H NMR (600 MHz, CDC_3) δ = 6.92 - 6.91 (m, 2H), 6.83 - 6.79 (m, 4H), 5.22 (s, 4H), 3.78 (s, 6H), 3.75 (s, 6H), 3.50 (s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 166.4, 153.5, 151.5, 124.6, 115.4, 114.1, 111.6, 62.6, 56.0, 55.8, 41.6 ppm.



Phenylmethanaminium benzylcarbamate (6.28)[37]**:** Meldrum's acid **6.17** (28 mmol) was added to a solution of benzylamine (28 mmol) in toluene (30 mL) in a 50 mL round bottom flask and round bottom flask was connected with a condenser. Open mouth of the condenser was closed with septum and one cannula was connected the condenser (through septum) and another closed round bottom flask containing benzylamine (56 mmol). The reaction mixture for acetylation containing Meldrum's acid (28 mmol), amine (28 mmol) in toluene, was heated at 120 ^{o}C and released carbon dioxide was allowed to pass through cannula to the benzylamine at room temperature. Carbamate salt **6.26** was formed as the white solid with 76% yield (5.5 g, yield was calculated w.r.t carbon dioxide (28 mmol) released). ^{1}H NMR (400 MHz, MeOH-d_4) δ = 7.40 – 7.27 (m, 10H), 4.29 (s, 1H), 3.88 (s, 4H) ppm. ^{13}C NMR (101 MHz, MeOH-d_4) δ = 164.0, 160.1, 141.1, 136.7, 128.5, 128.0, 127.9, 126.7, 126.2, 45.1, 43.8 ppm.

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CHAPTER 7

Stereoselective Single Pot Multistep Reaction to Densely Functionalized Spirocyclic Ene-lactam

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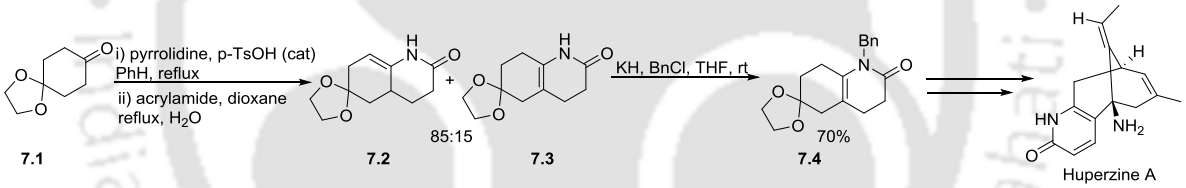
7.1 Introduction:

Lactams are cyclic amides of varying ring sizes, such as alpha, beta, and gamma lactams.[1] Lactam ring derivatives serve as pharmacophores in antibiotics, antipsychotics, and other drug candidates.[2] Moreover, they can be used as the monomers for synthesis of versatile synthetic polymers, such as poly(1-vinylpyrrolidin-2-one) derivatives.[3] Conventional synthetic methods for lactam include the intramolecular condensation of amino acid derivatives under extremely harsh conditions. Moreover, the intramolecular cyclization of haloamides with Brønsted bases affords lactams.[4,5,6] Ene-lactams are highly versatile intermediates for the synthesis of piperidine[7] and hydroquinoline[8] ring systems. They are also useful intermediates for the preparations of alkaloids, piperidinones, and many other biologically active heterocycles.[9,10]

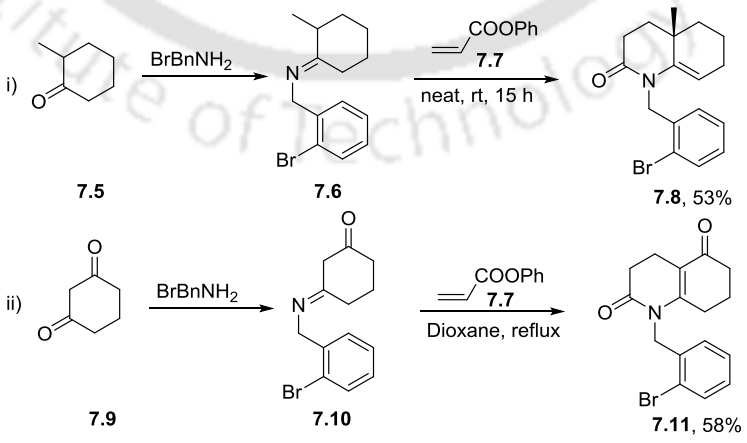
7.2 Reports on the synthesis of ene-lactam:

Kozikowski *et al.* reported the total synthesis of the alkaloid "huperzine A" *via* ene-lactam intermediate. Ene-lactam **7.4** was formed from ketone **7.1** and acrylamide and then benzylation by benzyl chloride (**Scheme 1)**.[11d]



Scheme 1: *N*-benzylated ene-lactam synthesis in two steps

Jabin *et al.* developed a method for the synthesis of ene-lactam **7.8** and **7.11** using Michael reaction of enamine derived from imine (**7.6** and **7.10**) and olefin derivative **7.7** (**Scheme 2)**.[10b]



Scheme 2: Two-step synthesis of ene-lactam

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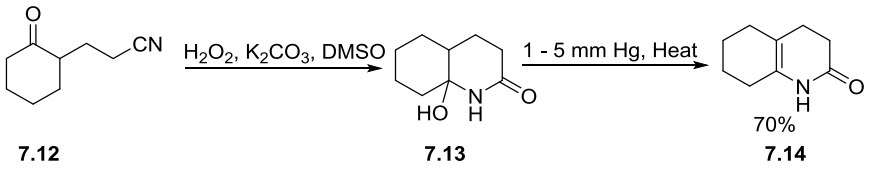
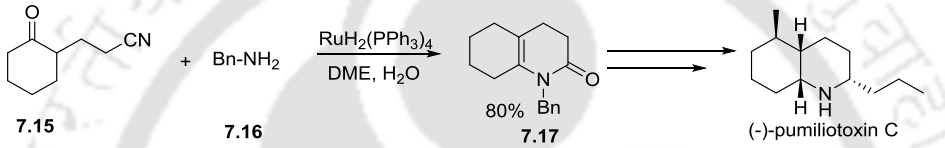
Citterio *et al.* reported a procedure for the synthesis of 3,4-dihydro-2-pyridones (ene-lactams) **7.14** from cyanoethylated ketones **7.12** (**Scheme 3).**[11c]



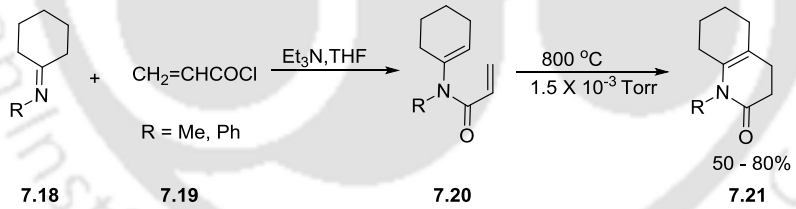
Scheme 3: Two-step synthesis of ene-lactam from cyanoethylated ketones

Murahashi *et al.* developed a $RuH_2(PPh_3)_4$ catalyzed method for the conversion of δ-ketonitriles **7.15** into the corresponding ene-lactams **7.17**. The efficiency of the reaction is demonstrated by the short-step synthesis of (-)-pumiliotoxin C (**Scheme 4)**.[11a]



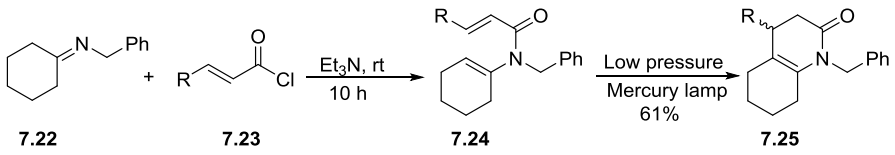
Scheme 4: Ene-lactams synthesis using Ru catalyst

Lesniak *et al.* presented an and effective method for the transformation of enamides **7.20** to tetrahydro-2-pyridones **7.21** using flash vacuum thermolysis (**Scheme 5)**.[11e]



Scheme 5: Tetrahydro-2-pyridones using flash vacuum thermolysis

Ninomiya *et al.* developed a photocyclization reaction of α,β -unsaturated enamides **7.24** to provide ene-lactam derivatives **7.25** (**Scheme 6)**.[11i]



Scheme 6: Synthesis of 3,4-dihydrocarbostyril derivatives

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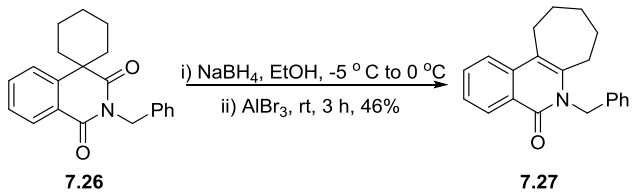
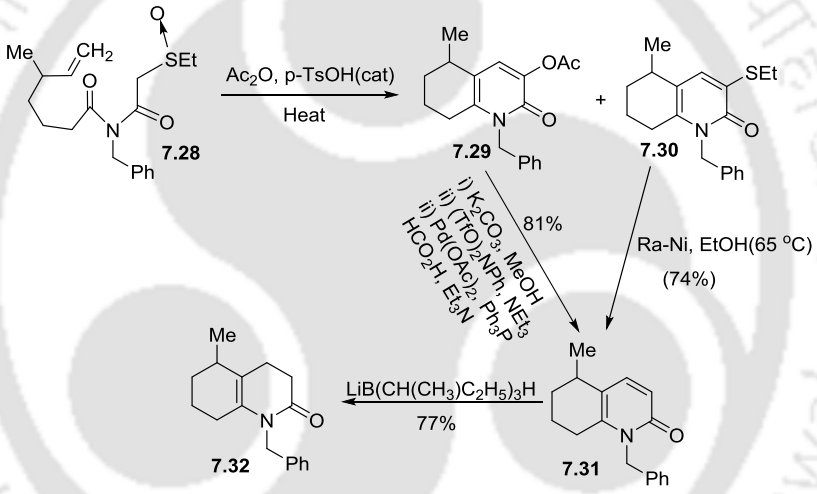
Heaney *et al.* developed a method for the synthesis of ene-lactam derivatives **7.27** from 1-benzylpiperidine-2,6-dione derivatives **7.26** (**Scheme 7**).[11j]



Scheme 7: Synthesis of tetrahedrophenanthridinones and isoquinolones

Padwa, *et al.* developed a route for the synthesis of ene-lactam derivatives **7.32** using the Pummerer cyclization-deprotonation-cycloaddition cascade of imidosulfoxides **7.28** (**Scheme 8**).[11f]



Scheme 8: Synthesis of ene-lactam from imidosulfoxides

7.3 Limitation of the above methods and importance of spirocyclic compound:

Most of the aforesaid methods suffer from lack of selectivity leading to a mixture of products. Ene-lactams were synthesized *via* a multistep process. The overall yield of the ene-lactam is not very good. Metal catalyst and/ hazardous chemicals were used for the synthesis of ene-lactam, which produced stoichiometric or catalytic amount of waste.

Moreover, spirocyclic compounds are attractive intermediates in the synthesis of natural products and in medicinal chemistry[12]. They are the starting materials for the synthesis of interesting amino acids used to modify the physical properties and biological activities of peptides, peptidomimetics, and proteins.[13] Some of these have been

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identified as new anticancer agents and chemical probes to study signaling networks in neoplastic cells, and have shown HIV-1 integrase inhibitory as well as interesting antiproliferative activities.[14] Therefore, the synthesis of a new highly substituted spiro ring system of Meldrum's acid with the skeleton of ene-lactam may be of potential biological interest.

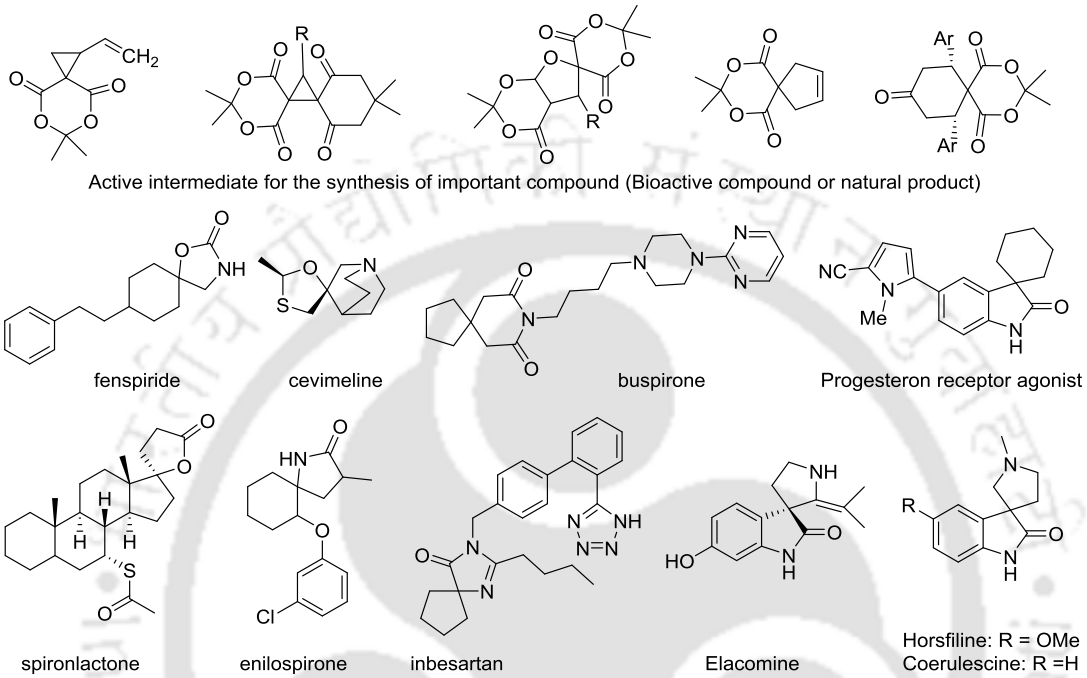
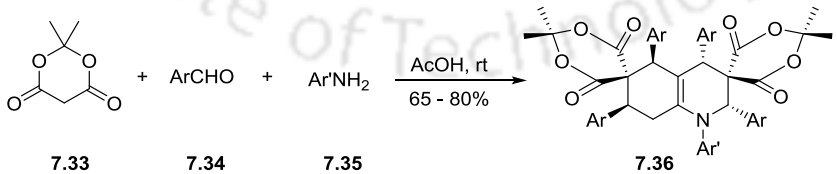


Figure 1: Important spirocyclic compounds

Torre-Fernández *et al.* developed a novel Route for the diastereoselective synthesis of dispiro [tetrahydroquinoline-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)] derivatives **7.36** *via* a one-pot domino multicomponent reaction of arylamines **7.35**, aromatic aldehydes **7.34**, and Meldrum's acid **7.33** (**Scheme 9).**[12c]



Scheme 9: Synthesis of di piro derivative

Barbas III *et al.* developed organocatalytic multicomponent reactions through combinations of Aldol, Wittig, Knoevenagel, Michael, Diels-Al der and Huisgen cycloaddition reactions for the diastereospecific and enantioselective construction of highly substituted

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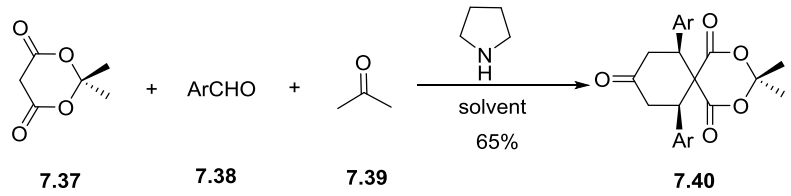
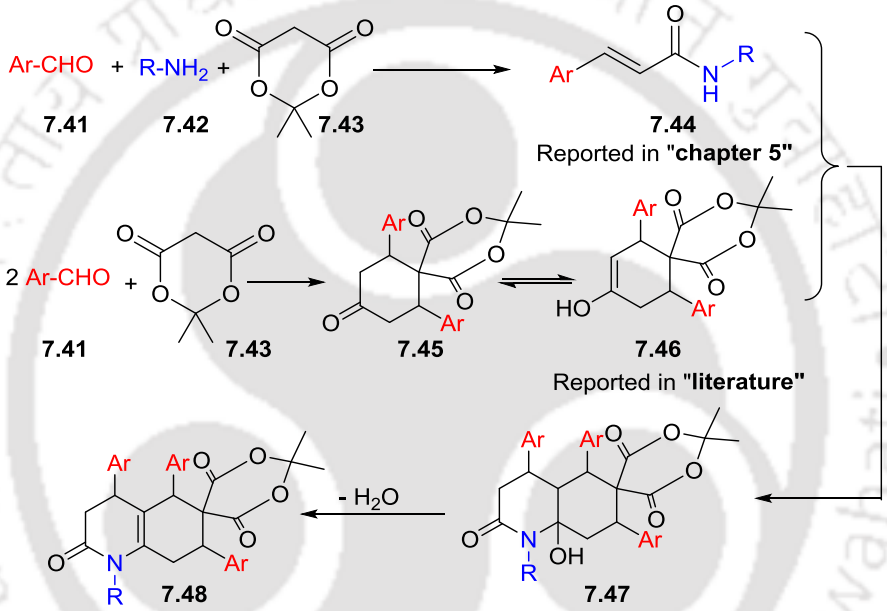
spiro[5,5]undecane-1,5,9-triones **7.40** from aldehyde **7.38**, Meldrum's acid **7.37** and acetone **7.39** (**Scheme 10**).[13d]



Scheme 10: Synthesis of spiro[5,5]undecane-1,5,9-triones

7.4 Hypothesis for the present method:



Scheme-11: Hypothesis for the present work

A method for the synthesis of cinnamamide **7.44** from aryl aldehyde **7.41**, amine **7.42** and Meldrum's acid **7.43** has been developed (**chapter 5)**. The synthesis of spirocyclic ketone **7.46** from aryl aldehyde **7.50** and Meldrum's acid **7.52** is known in the literature. A reaction with an excess amount of aryl aldehyde, amine, and Meldrum's acid was performed to form cinnamamide **7.44** and spiro compound **7.46** in the same reaction mixture. After that cinnamamide **7.44** and spiro compound, **7.46** may react to produce the desire spirocyclic ene-lactam **7.48 (Scheme 11)**.

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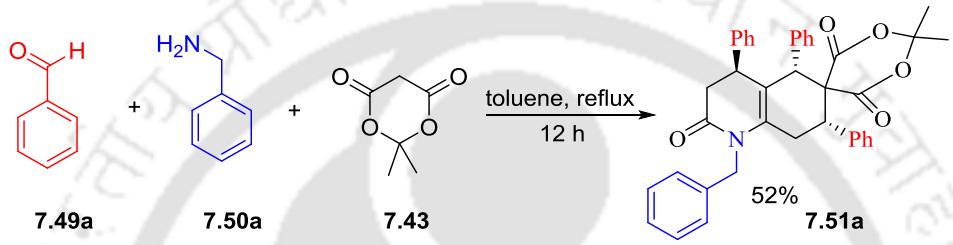
7.5 Preliminary result:

According to the hypothesis, a reaction of benzaldehyde (3eq), benzylamine (1eq) and Meldrum's acid (2eq) at room temperature was anticipated to form (4S,5S,7S)-1-benzyl-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (**7.51a**).Unfortunately, the desired product did not form at room temperature**.** However, the desired product was formed with a 52% yield from the reaction in refluxing toluene for 12 h (**Scheme 12**). The relative stereochemistry of the product **7.51a** was confirmed from the x-ray single-crystal structure. The relative stereochemistry of other derivatives is assigned in analogy.



Scheme 12: Initial reaction performed

7.6 Optimization of the reaction condition:

To further increase the yield of the desired product, reaction conditions were screened by changing solvent, reaction time, and molar ratios of the reactants. Increasing the reaction time from 12 h to 24 h in refluxing toluene, the yield of the desired product increased from 52% to 58% (**Table 1, entry 3**). Not much improvement of the yield (59%) was noticed when reaction time extended to 48 h (**Table 1, entry 4**). The reaction performed in a reaction tube at 110 ^{o}C in toluene for 24 h gave a 61% yield (**Table 1, entry 5**). The best result 68% yield was obtained by increasing the molar ratio of benzylamine from 1 eq to 1.2 eq (**Table 1, entry 6**). Further increment of the molar ratio of benzylamine did not improve the yield (**Table 1, entry 7**). Solvents like DCM, m-xylene, methanol, DMF were also screened (**Table 1, entry 9, 10, 12, 14**). A yield of 60% was obtained when the reaction was performed under solvent-free condition (**Table 1, entry 13**). The yield of the desired product was decreased (55%) when the reaction was performed under microwave irradiation at 120 ^{o}C for 30 mins (**Table 1, entry 7**). Addition of 1 eq of acetone to the reaction mixture did not lead to improvement of the yield of the desired product (**Table 1, entry 15**)

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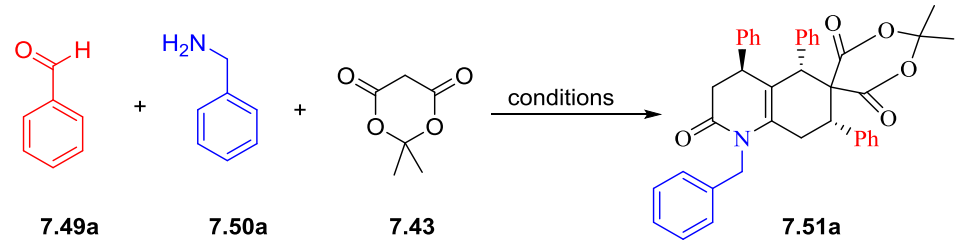
Table 1: Optimization for the synthesis of ene-lactam



7.49a 7.50a 7.43 7.51a

entry	Conditions	Yield (%)[b]
1	toluene, rt, 12 h	0
2	toluene, reflux, 12 h	52
3	toluene, reflux, 24 h	58
4	toluene, reflux, 48 h	59
5	toluene, closed tube, 110 ^{o}C, 24 h	61
6[c]	**toluene, closed tube, 110 ^{o}C, 24 h**	**68**
7[d]	toluene, closed tube, 110 ^{o}C, 24 h	68
8[c]	toluene, closed tube, 110 ^{o}C, 48 h	67
9[c]	DCM, closed tube, 40 ^{o}C, 24 h	10
10[c]	m-xylene, closed tube,140 ^{o}C, 24 h	66
11[c]	toluene, MW, 120 ^{o}C, 30 min	55
12[c]	methanol, closed tube, 80 ^{o}C, 5 h	15
13[c]	neat, 120 ^{o}C, 12 h	60
14[c]	DMF, closed tube, 140 ^{o}C, 24 h	58
15[c,e]	toluene, closed tube, 110 ^{o}C, 24 h	61

[a]3 eq (1.89 mmol) benzaldehyde **1**, 1eq (0.63 mmol) benzylamine, and 2 eq (1.26 mmol) Meldrum's acid **3** were reacted in 3 mL solvent. [b]Isolated yield. [c]reaction performed by using 1.2 eq of benzylamine **2.** [d]reaction performed by using 1.5 eq of Meldrum's acid. [e] reaction performed by adding 1 eq of acetone.

7.7 Substrate scope for spirocyclic ene-lactam:

Next, the scope of the reaction was investigated by varying the aryl aldehyde and amine (**Scheme 13)**. Benzaldehyde having both electron-donating (e.g -Me) and electron-

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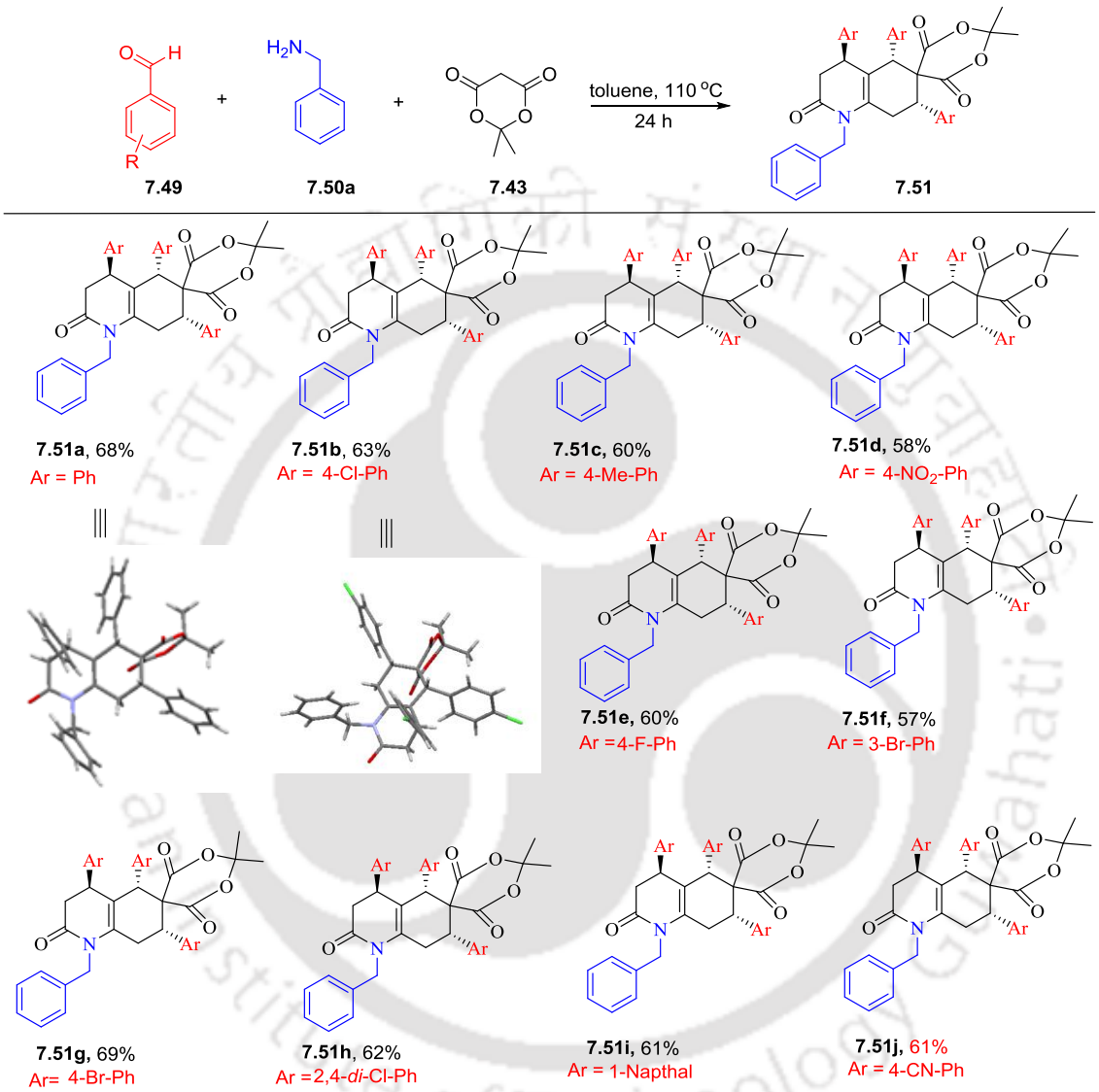
withdrawing (e.g -Cl, -F) benzaldehyde afforded the desired product with very good yield. Disubstistuted benzaldehyde (2,4-dichloro benzaldehyde) also reacted smoothly to give the desired product **7.51h**. Bulky aryl aldehyde like napthaldehyde also provides the desired sterically hindered product **7.51j** with a 61% yield.



Scheme 13: Variation of aldehydes

Then we decided to synthesize ene-lactam derivative by varying the primary amine moiety (**Scheme 14).** Alkyl amine and benzylamine were successfully employed for the synthesis of structurally diverse highly substituted lactams **7.52a-l**. Both the electron-withdrawing (-Cl, -F, -CF_3) and electron-donating (-Me, -OMe) group containing benzylamine effectively reacted to form the desired compound. Hetero-aromatic amine also reacted smoothly to give

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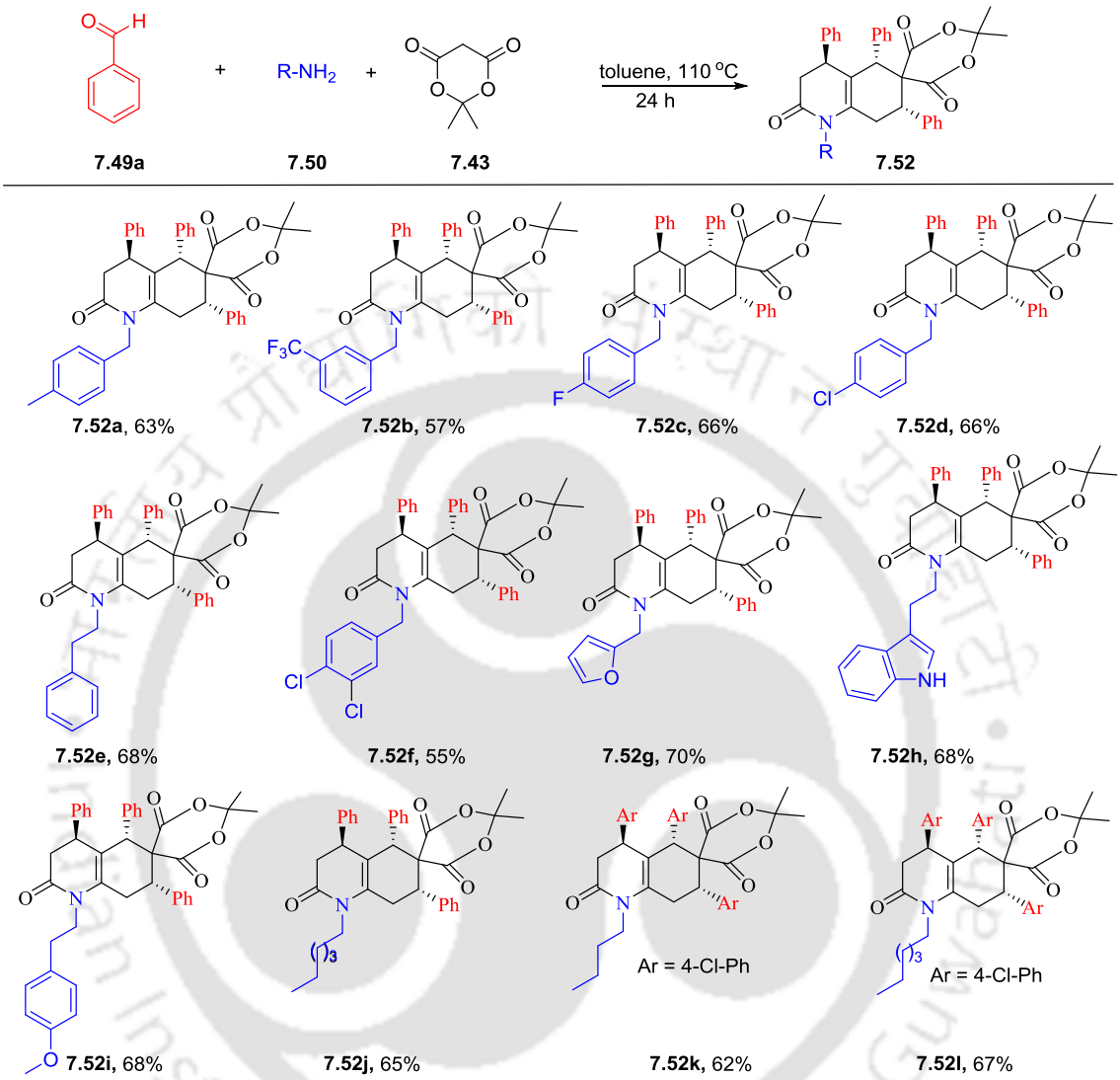
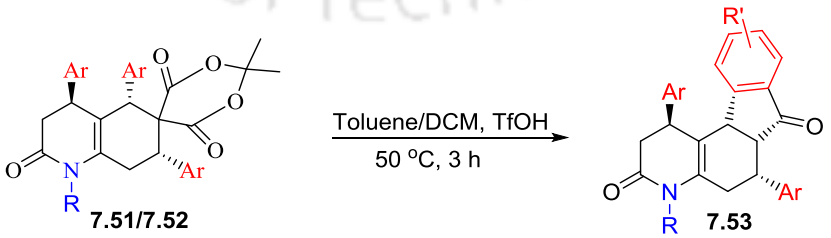
the desired product **7.52g** and **7.52h.** Alkyl amine of various chain lengths also reacted sucessfully to afford the desired product **7.52j-l**.



Scheme 14: Variation of amines

7.8 Cyclization of spiro compound to indanone derivatives:



Scheme 15: Intramolecular cyclization to indanone

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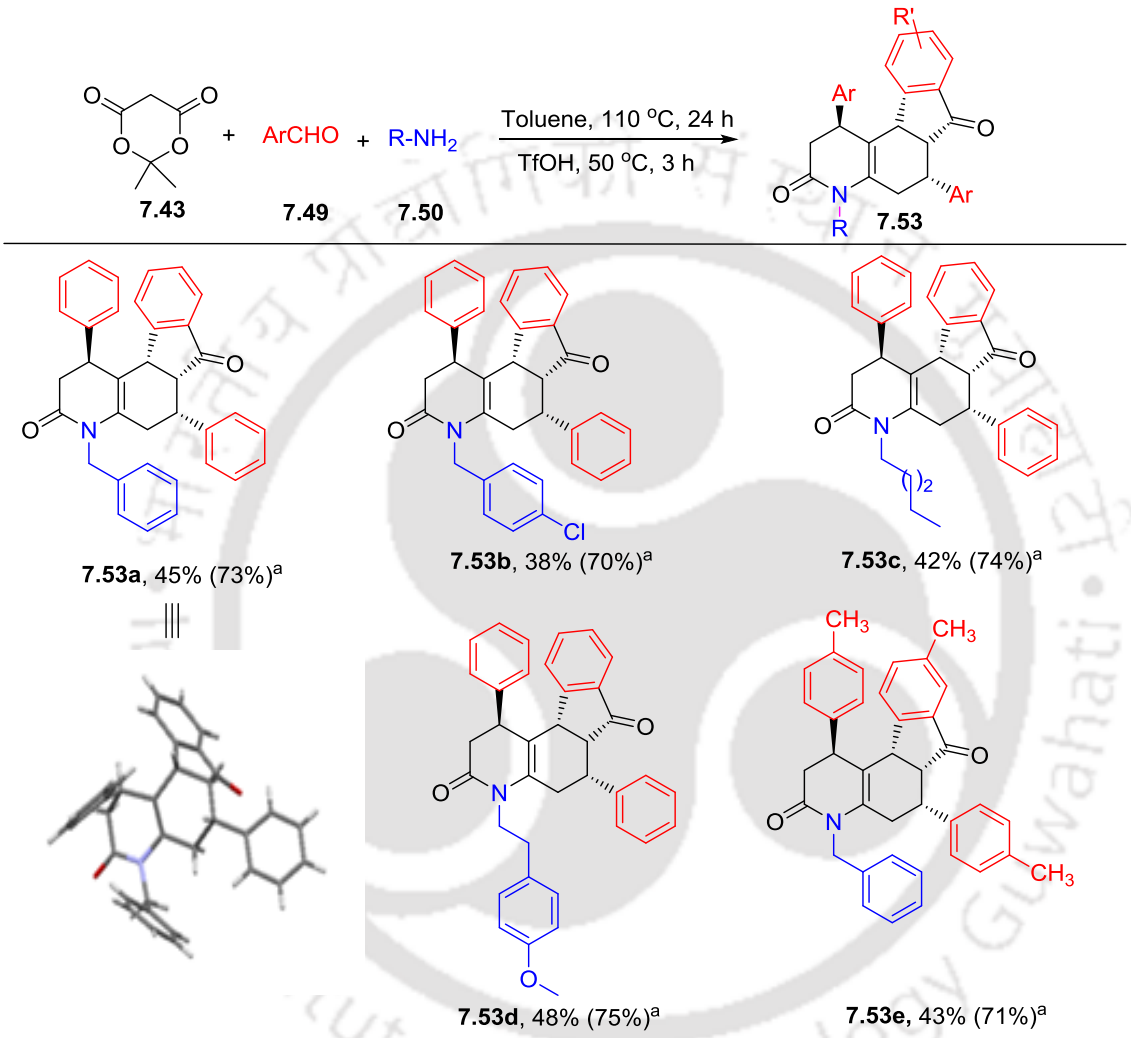
The intramolecular Friedel-Craft reaction of **7.51**/**7.52** with TfOH provided indanone **7.53** with very good (75%) yield (**Scheme 15**).

This methodology was then applied for the single-step synthesis of tetracyclic product directly from aldehyde, amine, and Meldrum's acid. A list of synthesized ketone derivatives **7.53a-e** was given in **Scheme 16**.



Scheme 16: Synthesis of indanone derivatives. [a]Yield from pure spirocyclic ene-lactam.

The substrate was prepared by varying both the aldehyde and amine moiety. Both electron-withdrawing and electron-donating substituted amines reacted efficiently to produce the desired product. Aliphatic alkyl amine also reacted efficiently to form the desired lactams **7.53c**. However, aldehyde having an electron-withdrawing group did not provide the desired product. Stereochemistry of the product was confirmed from x-ray single-crystal structure.

7.9 Aromatization of Indanone derivatives:

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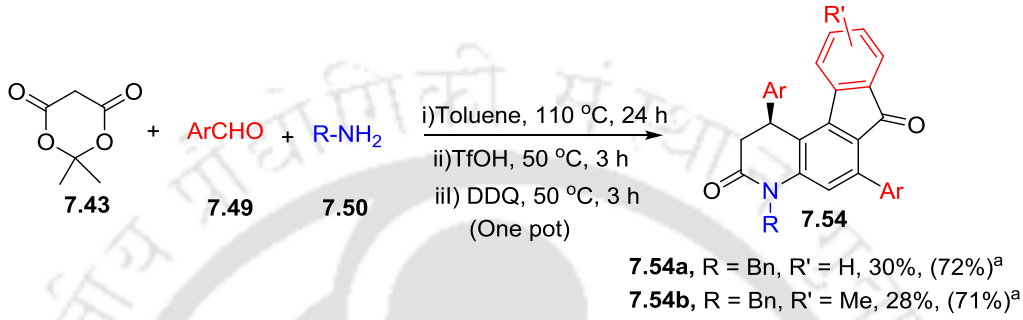
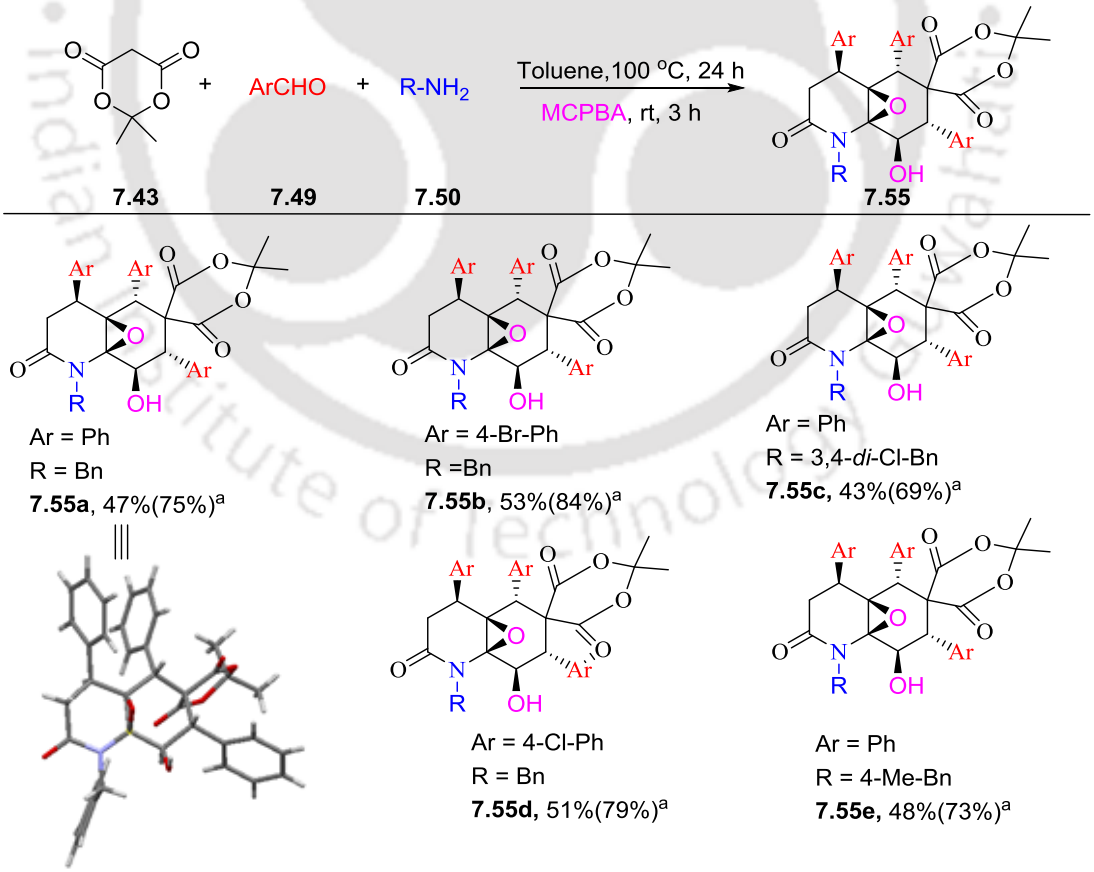
The indanone derivative **7.53** could be oxidized easily by DDQ in refluxing DCM to provide 9-fluorenone derivative **7.54**. Highly substituted 9-Fluorenone derivatives **7.54a-b** were prepared with excellent yield. 9-Fluorenone derivatives were synthesized in one pot single-step reaction directly from the spiro bicyclic compound **7.51** (**Scheme 17).** The significant importance[15] of the use of 9-fluorenone derivative in organic synthesis led us to explore the substrate scope by varying both the amine and aldehyde.



Scheme 17: Synthesis of 9-fluorenone derivatives. [a]Yield from pure spirocyclic ene-lactam.

7.10 Epoxidation and hydroxylation of ene-lactam:



Scheme 18: Substrate scope. [a]Yield from pure spirocyclic ene-lactam.

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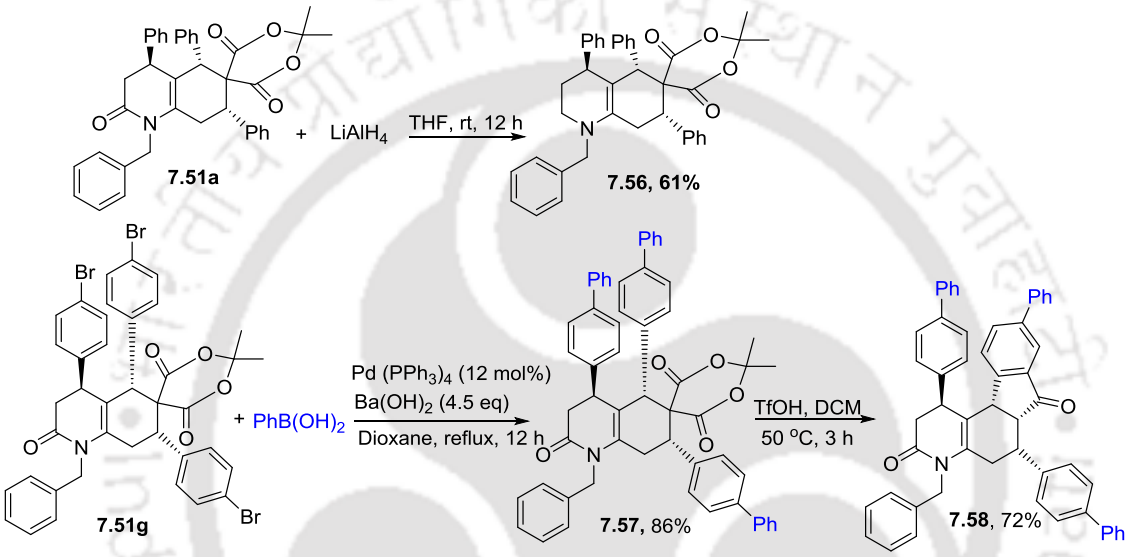
Then a one-pot epoxidation of ene-lactam was planned. Accordingly, benzaldehyde, amine, and Meldrum's acid were heated at 110 ^{o}C in toluene for 24 h, and then MCPBA was added to the same reaction mixture. Unexpectedly, instead of epoxide, hydroxy epoxide was formed. Substrates (**7.55a-e**) were prepared by changing both the benzaldehyde and amine moiety with good yield (**Scheme 18**). Hydroxy epoxide was also prepared from pure ene-lactam (**7.51/7.52**) with excellent yield. Stereochemistry of the product was confirmed from x-ray single-crystal structure.

7.11 Additional reaction:



Scheme 19: Additional reaction

Amide carbonyl of ene-lactam **7.51a** was selectively reduced with $LiAlH_4$ to the perhydro quinoline derivative **7.56**. The ene-lactam **7.51g** derived from 4-bromo benzaldehyde was coupled with phenylboronic acid in the presence of Pd catalyst to produce **7.57** with excellent yield (**Scheme 19**). Bulky and highly substituted cyclic ketone **7.58** was also prepared from **7.57** by applying the optimized conditions, which was mentioned in the previous section.

7.12 Controlled reaction:

Few controlled reactions were conducted to clarify the reaction mechanism (**Scheme 22).** According to the hypothesis, the reactions were performed by using the spirocyclic ketone derivative **7.59** and cinnamamide **7.60** in refluxing toluene in the absence (**Scheme 22, eq. 1**) and presence of benzylamine (**Scheme 22, eq. 2**). However, the desired product **7.51a**

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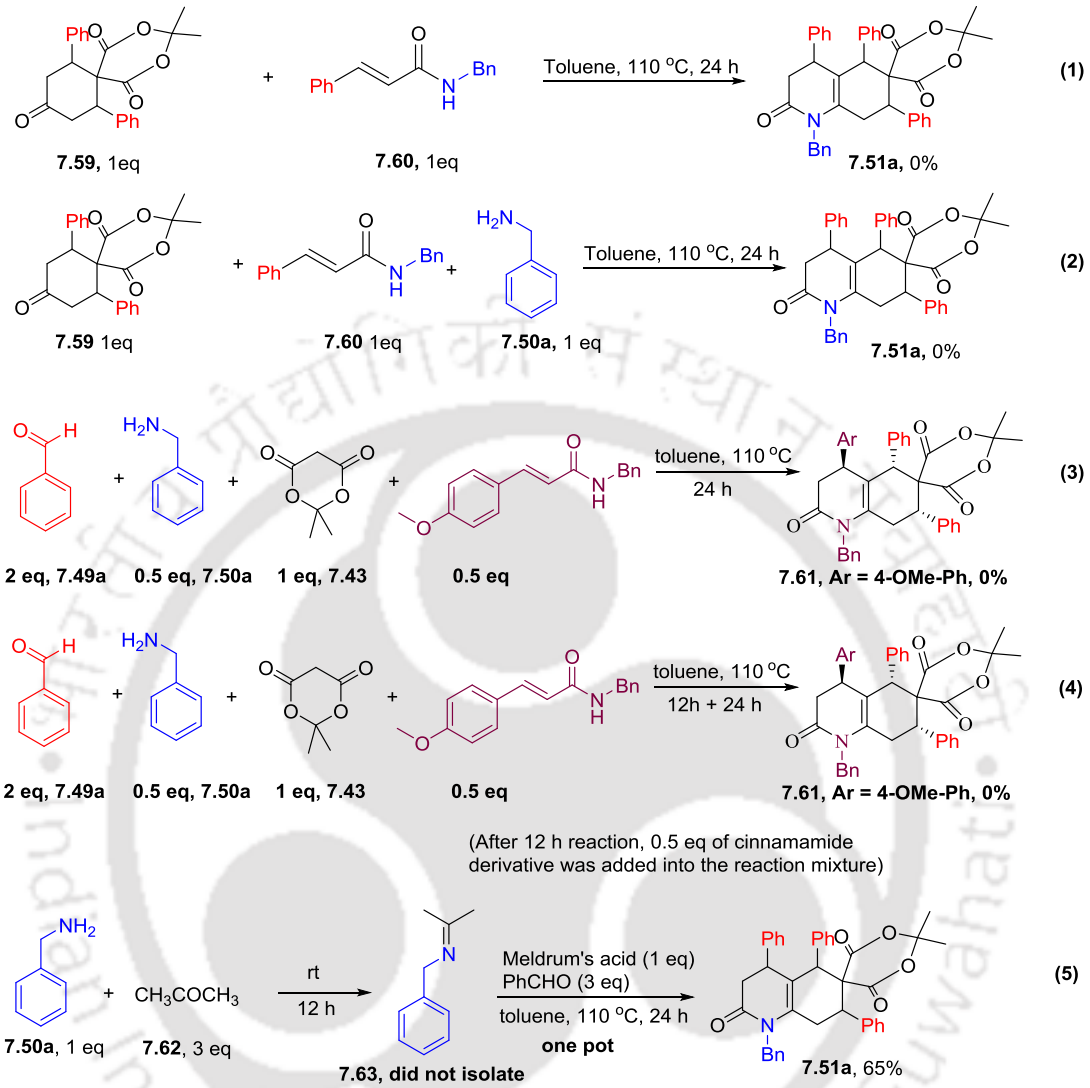
did not form in both cases. These finding discarded the possibility of reaction proceeds through cinnamamide and ketone.



Scheme 22: Controlled experiments

When the reactions were performed after in situ addition of different cinnamamide derivative, no cross product **7.61** did not observe (**Scheme 22, eq. 3, and eq. 4**). These two reactions also confirmed that reaction is not proceeding through cinnamamide derivative. An imine intermediate **7.63** prepared from amine and acetone,[16] which then treated with benzaldehyde and Meldrum's acid under optimized reaction condition (**eq. 5**). It was observed that, in this reaction, the desired product **7.51a** was formed with a 65% yield, which supports the proposed reaction mechanism *via* intermediate **7.69** (**Scheme 22**).

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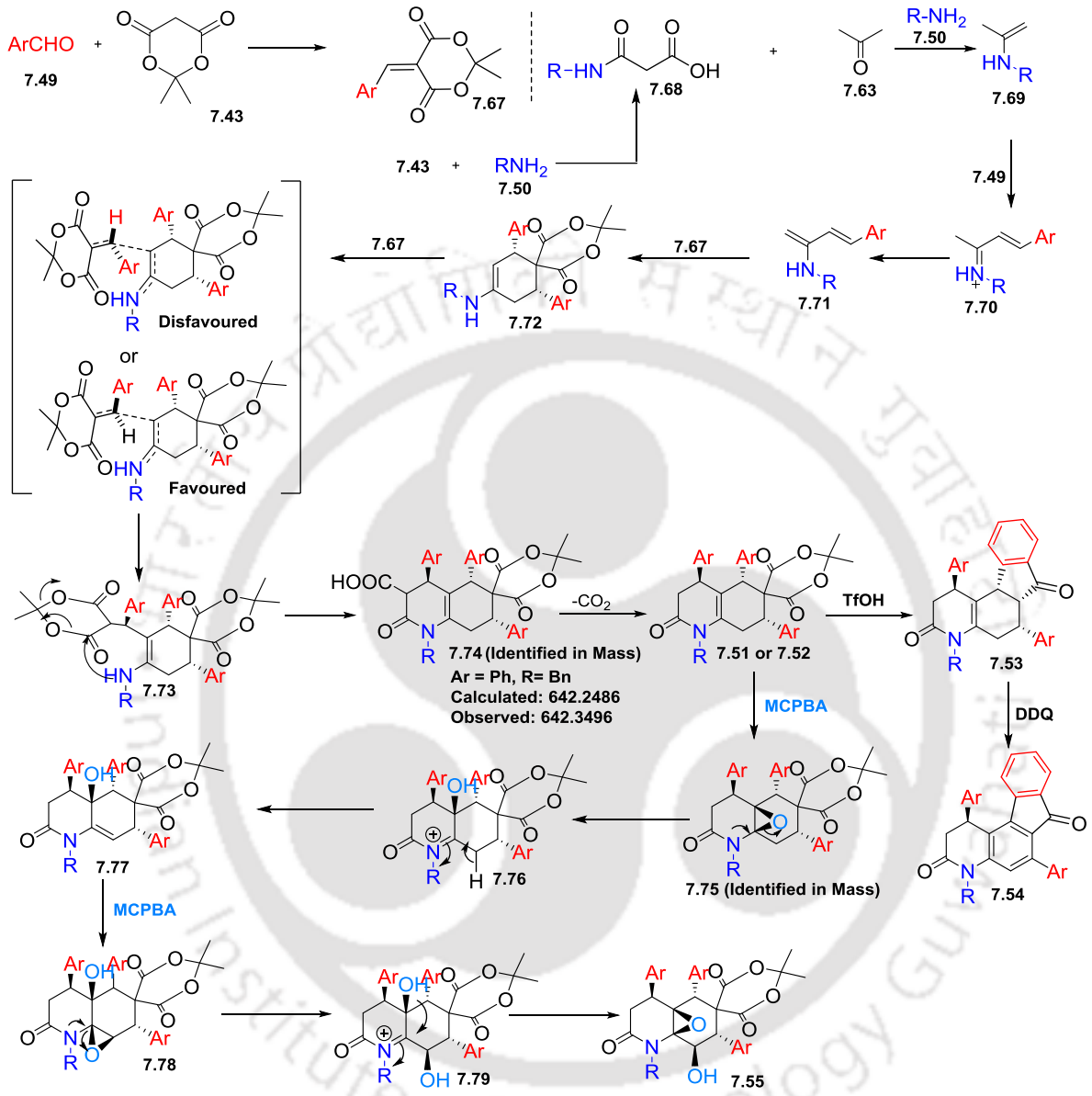
7.13 Reaction mechanism:



Scheme 21: Proposed Mechanism.

On the basis of controlled reactions and literature study[12], a plausible mechanism for the one-pot ene-lactam formation is shown in **Scheme 21**. The reaction is believed to proceeds *via* spiro derivative **7.72,** which is formed through the reaction of aldehyde, amine and Meldrum's acid. At first, amine-catalyzed Knoevenagel condensation of aldehyde with Meldrum's acid provides the benzelidene derivative of Meldrum's acid **7.67**. Acetone, which is formed from Meldrum's acid, reacted with amine to form enamine **7.69**. Aldol reaction of **7.69** with benzaldehyde provide enamine **7.71**. The reaction of **7.71** and **7.67** *via*

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Diels-Alder reaction or Michael-Michael sequence provided thermodynamically more stable spirocycle **7.72** with cis configaration.[12a,12b,13d] The diastereoselective reaction of **7.72** with **7.67** to avoid steric interaction between two Ar groups, gave derivative **7.73**. A carboxylic acid derivative **7.74** was formed via intramolecular cyclization of **7.73**. Decarboxylation of **7.74** gave the desired ene-lactam **7.51** or **7.52** In the presence of acid, spirocyclic ene-lactam **7.51** or **7.52** underwent decarboxylative cyclization to form tetracyclic derivative **7.53,** which after aromatization by DDQ produced fluorenone derivative **7.54.** When spirocyclic ene-lactam **7.51** or **7.52** is treated with MCPBA, epoxide derivative **7.75** formed. Then epoxide ring-opening of **7.75** followed by second epoxidation provided **7.78**. The final epoxy alcohol **7.55** was formed from the Payne-type rearrangement of **7.78**. MCPBA approached from the site opposite to the two Ar groups of B-ring of ene-lactam.

7.14 Summary:

An unprecedented method for the stereoselective synthesis of densely functionalized ene-lactam in a single step reaction has been developed. A single isomer of ene-lactam containing three stereocenters was formed selectively. Stereochemistry of the compound was confirmed from x-ray single-crystal structure. The reaction is operationally simple, efficient and applicable to a broad class of aldehyde and amine (activated benzyl or unactivated alkyl amines). This environmentally benign method used easily available and cheap starting material for the synthesis of ene-lactam without the aid of metallic reagents, oxidants and other additives. In addition to facile synthesis of spirocyclic ene-lactam, indanone and 9-fluorenone derivative was also achieved through a single step one pot reaction.

7.15 Experimental section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus (V) oxide (P_2O_5). Commercial grade xylene, benzene and toluene were distilled over CaH_2 before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros, Merck and Spectrochem. ^1H, ^{13}C NMR spectroscopy: *Bruker 600 MHz* (at 298 K), *Bruker 400 MHz* (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS δ (^1H) 0.0

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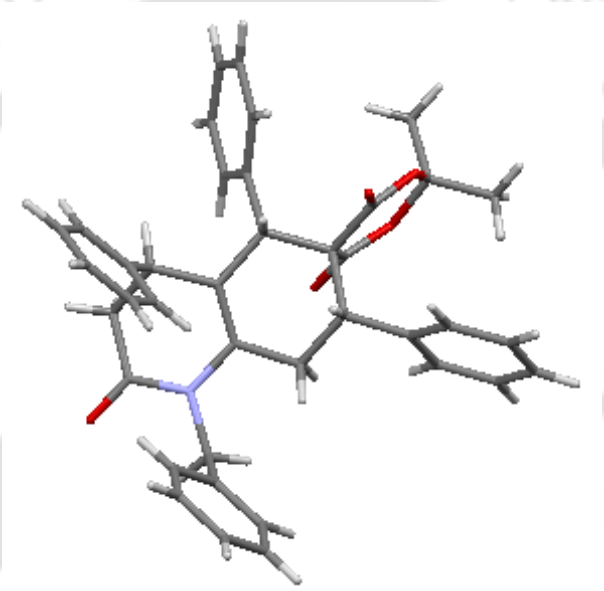
ppm, δ (^{13}C) 0.0 ppm) which was used as the inner reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.2 ppm; CD_3OD, (^{1}H) 3.31 ppm, δ (^{13}C) 49.0 ppm) were used for calibration. Column chromatography: Merck or Spectrochem silica gel 60-120 under gravity. 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). X-ray single crystal was measured by *Bruker APEX-II CCD* and *SuperNova, Single source at offset/far, Eos diffractometer*.

Crystal data for 7.51a:



Empirical formula	$C_{39}H_{35}NO_5$
Formula weight	597.7110
Crystal habit, colour	Block, colourless
Crystal size, mm^3	0.30 × 0.26 × 0.22
Temperature, *T*	293 K
Wavelength, *λ*(Å)	0.71073
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	*a* = 1.2207(6) Å
	b = 11.7527(6) Å
	c = 15.2227(9) Å

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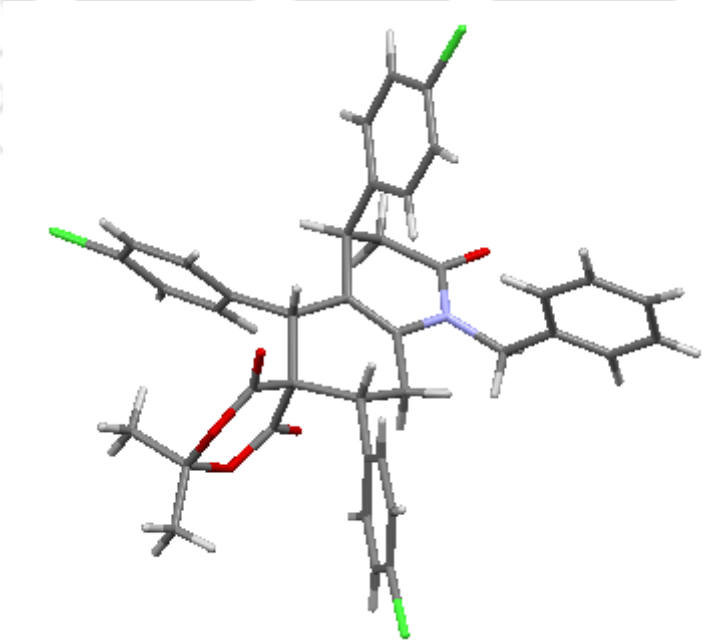
	α = 72.625°, β = 88.642°, γ = 65.743°,
Volume, V(Å^3)	1735.38(16)
Z	2
Calculated density, Mg·m^{-3}	1.306
Absorption coefficient, μ(mm^{-1})	0.233
F(000)	716.0
θ range for data collection	4.64° to 50°
Limiting indices	-13 ≤ h ≤ 13, -13 ≤ k ≤ 13, -12 ≤ l ≤ 18
Reflection collected / unique	11750/6105 [R(int) = 0.0261]
Completeness to θ	99.8% (θ = 25.000°)
Refinement method	Gauss-Newton minimisation. (Puschmann)
Data / restraints / parameters	6105/0/435
Goodness–of–fit on F^2	1.051
Final R indices [I>2sigma(I)]	*R1 = 0.0924, wR2 = 0.2540*
R indices (all data)	*R1 = 0.1255, wR2 = 0.2903*
Largest diff. peak and hole	0.59 and -0.68 Å^{-3}

Crystal data for 7.51b:



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Empirical formula	$C_{39}H_{32}Cl_3NO_5$
Formula weight	701.01
Crystal habit, colour	Block, colourless
Crystal size, mm^3	0.25 × 0.21 × 0.18
Temperature, *T*	293 K
Wavelength, λ(Å)	0.71073
Crystal system	orthorhombic
Space group	Pbcn
Unit cell dimensions	*a* = 24.593(10) Å
	b = 13.168(5) Å
	c = 21.489(8) Å
	$\alpha = 90°$, $\beta = 90^o$, $\gamma = 90°$,
Volume, *V*($Å^3$)	6959(5)
Z	8
Calculated density, $Mg \cdot m^{-3}$	1.338
Absorption coefficient, $\mu(mm^{-1})$	0.309
F(000)	2912.0
θ range for data collection	3.32^o to 50^o
Limiting indices	$-29 \leq h \leq 29$, $-15 \leq k \leq 15$, $-25 \leq l \leq 25$
Reflection collected / unique	176345 / 6127 [*R*(int) = 0.2267]
Completeness to θ	100% (θ = 25°)
Refinement method	Gauss-Newton minimisation (Puschmann)
Data / restraints / parameters	6127/0/467
Goodness–of–fit on F^2	1.089
Final *R* indices [*I*>2sigma(*I*)]	*R1 = 0.0702, wR2 = 0.1712*
R indices (all data)	*R1 = 0.1528, wR2 = 0.2285*
Largest diff. peak and hole	0.19 and –0.41 $Å^{-3}$

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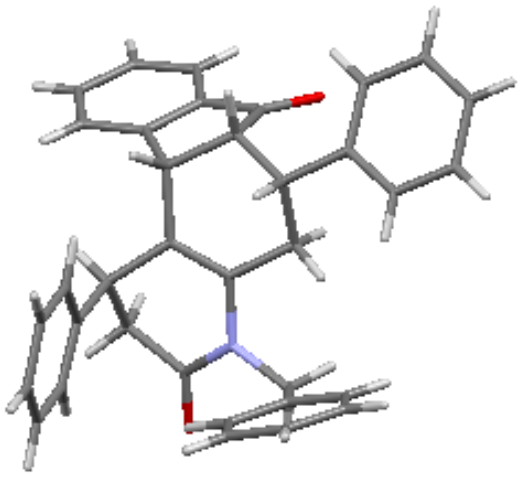
Crystal data for 7.53a:



Empirical formula	$C_{35}H_{29}NO_2$
Formula weight	495.59
Crystal habit, colour	Block, colourless
Crystal size, mm^3	0.30 × 0.27 × 0.24
Temperature, *T*	296K
Wavelength, λ(Å)	0.71073
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	*a* = 9.2997(15) Å
	b = 10.5640(18) Å
	c = 13.949(2) Å
	α = 73.924°, β = 85.964°, γ = 77.565°
Volume, *V*($Å^3$)	1285.8(4)
Z	2
Calculated density, $Mg \cdot m^{-3}$	1.280
Absorption coefficient, μ(mm^{-1})	0.079

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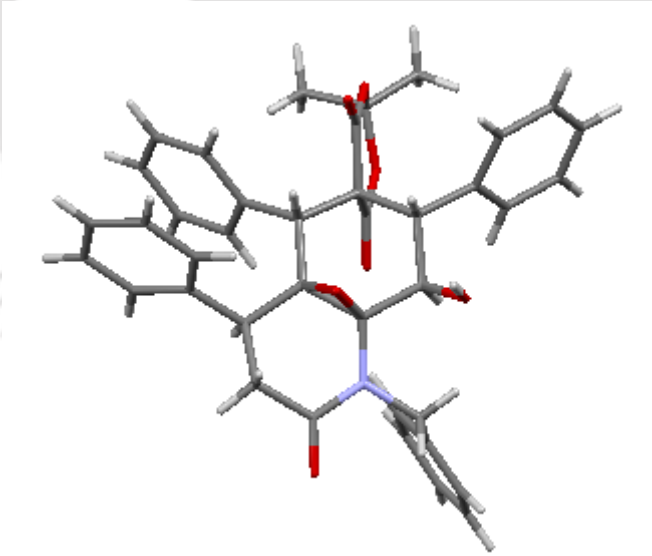
F(000)	524.0
θ range for data collection	2.806^{o} to 55.788^{o}
Limiting indices	-11≤ h ≤ 11, -12 ≤ k ≤ 12, -16≤ l ≤ 16
Reflection collected / unique	130724/ 7510 [*R*(int) = 0.1477]
Completeness to θ	100% (θ = 25.000°)
Refinement method	ShelXL-2015 (Sheldrick, 2015)
Data / restraints / parameters	4531/0/343
Goodness–of–fit on F^2	1.015
Final *R* indices [*I*>2sigma(*I*)]	*R1 = 0.0654, wR2 = 0.1532*
R indices (all data)	*R1 = 0.1360, wR2 = 0.1922*
Largest diff. peak and hole	0.17 and –0.22 Å^{-3}

Crystal data for 7.55a:



Empirical formula	$C_{39}H_{35}NO_7$
Formula weight	629.68
Crystal habit, colour	Block, colourless
Crystal size, mm^3	0.23 × 0.18 × 0.18
Temperature, *T*	296.15 K
Wavelength, λ(Å)	0.71073

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Crystal system	Monoclinic
Space group	*P21/n*
Unit cell dimensions	a = 16.6756(9) Å
	b = 10.4042(5) Å
	c = 19.313(1) Å
	α = 90°, β = 109.277°, γ = 90°,
Volume, V(Å^3)	3162.9(3)
Z	1
Calculated density, Mg·m^{-3}	1.322
Absorption coefficient, μ(mm^{-1})	0.091
F(000)	1328.0
θ range for data collection	2.806° to 55.788°
Limiting indices	-21 ≤ h ≤ 21, -13 ≤ k ≤ 13, -25 ≤ l ≤ 25
Reflection collected / unique	130724/ 7510 [R(int) = 0.1477]
Completeness to θ	99.4% (θ = 27.894°)
Refinement method	ShelXL-2015 (Sheldrick, 2015)
Data / restraints / parameters	7510/0/427
Goodness–of–fit on F^2	1.017
Final R indices [I>2sigma(I)]	*R1 = 0.0654, wR2 = 0.1532*
R indices (all data)	*R1 = 0.1360, wR2 = 0.1922*
Largest diff. peak and hole	0.17 and –0.22 Å^{-3}

General procedure for the synthesis of lactam (7.51a – 7.51j and 7.52a – 7.52l) (GP I): Arylaldehyde (0.94 – 0.54 mmol) was added to a solution of amine (0.38 – 0.22 mmol) and Meldrum's acid (0.63 – 0.36 mmol) in toluene (2 – 3 mL) and the mixture was refluxed (110 °C) for 24 h. After disappearance of starting materials (indicated by TLC), solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography to get analytically pure product.

Rac-(*4S,5S,7S*)-1-benzyl-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.51a): According to GP I, benzaldehyde (0.30 g, 2.83 mmol), benzylamine (121 mg, 1.13 mmol) and Meldrum's acid (272 mg, 1.89 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by

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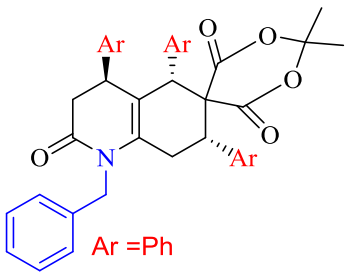
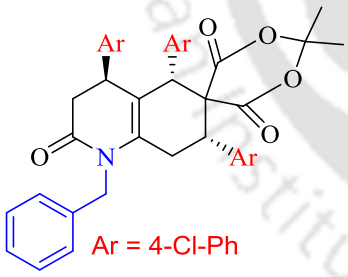


column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.51a** as white solid (0.38 g, 68%). Mp 221-223 °C. FTIR: ῡ = 3063, 3031, 2939, 1728, 1672, 1494, 1454, 1389, 1359, 1290, 1267, 1241, 1191, 1099, 1052, 973, 732, 698, 553 $cm^{-1.}$ ^1H NMR (600 MHz, $CDCl_3$) δ = 7.39 (t, *J* = 7.8 Hz, 1H), 7.32 – 7.23 (m, 8H), 7.21 – 7.17 (m, 5H), 7.17 – 7.12 (m, 3H), 6.98 – 6.97 (m, 2H), 6.84 (d, *J* = 7.2, 1H), 5.35 (d, *J* = 16.2 Hz, 1H), 4.78 (d, *J* = 16.2 Hz, 1H), 4.64 (s, 1H), 3.79 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.46 (t, *J* = 5.6 Hz, 1H), 3.41 (t, *J* = 14.8 Hz, 1H), 3.06 – 3.03 (m, 1H), 2.91 – 2.87 (m, 1H), 2.80 (dd, *J* = 17.0, 5.0 Hz, 1H), 0.59 (s, 3H), 0.49 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.18, 169.17, 163.9, 140.7, 137.8, 137.54, 137.48, 134.7, 131.4, 129.3, 129.1, 129.0, 128.8, 128.7, 128.6, 128.5, 128.2, 127.3, 127.1, 126.83, 126.79, 113.4, 105.8, 60.8, 53.3, 47.1, 44.6, 39.2, 38.7, 30.1, 28.5, 28.3 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{36}NO_5$ 598.2588; Found 598.2589.

Rac-(*4S,5S,7S*)-1-benzyl-4,5,7-tris(4-chlorophenyl)-2',2'-dimethyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.51b): According to GP I, 4-chloro benzaldehyde (0.10 g, 0.71 mmol), benzylamine (30 mg, 0.28 mmol) and Meldrum's acid (68 g, 0.47 mmol) in toluene (2 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.51b** as white solid (0.11 g, 63%). FTIR: ῡ = 3060, 3000, 2943, 1730, 1674, 1489, 1285, 1265, 1091, 1014, 830, 733, 702, 520 $cm^{-1.}$ ^1H NMR (600 MHz, $CDCl_3$) δ = 7.40 – 7.38 (m, 1H), 7.33 – 7.28 (m, 5H), 7.21 – 7.15 (m, 6H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 2H), 6.73 – 6.71 (m, 1H), 5.30 (d, *J* = 16.2 Hz, 1H), 4.78 (d, *J* = 16.2 Hz, 1H), 4.50 (s, 1H), 3.73 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.37 – 3.29 (m, 2H), 2.99 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.85 – 2.75 (m, 2H), 0.70 (s, 3H), 0.61 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.9, 168.7, 163.7, 138.9, 137.6, 135.7, 135.6, 135.2, 134.7, 134.4, 132.8, 132.5, 130.3, 130.1, 129.7, 129.3, 129.1, 128.9, 128.7, 128.6, 127.4, 126.8, 112.5, 106.1, 60.4, 52.4, 46.6, 44.7, 39.3, 38.5, 30.1, 28.7, 28.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{33}Cl_3NO_5$ 700.1419; Found 700.1429.



Rac-(*4S,5S,7S*)-1-benzyl-2',2'-dimethyl-4,5,7-tri-p-tolyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.51c): According to GP I, 4-

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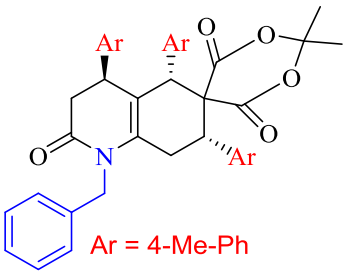
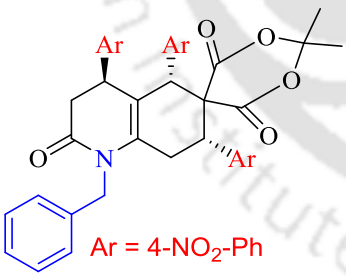
methylbenzaldehyde (0.10 g, 0.83 mmol), benzylamine (36 mg, 0.33 mmol) and Meldrum's acid (80 g, 0.56 mmol) in toluene (2 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.51c** as white solid (0.11 g, 60%). FTIR: ῡ = 3030, 2921, 2858, 1764, 1674, 1513, 1390, 1277, 1192, 1097, 1054, 819, 749, 701 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 – 7.20 (m, 3H), 7.19 – 7.14 (m, 2H), 7.11 – 7.08 (m, 4H), 7.06 – 6.96 (m, 5H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.35 (d, *J* = 16.4 Hz, 1H), 4.70 (d, *J* = 16.4 Hz, 1H), 4.56 (s, 1H), 3.72 – 3.67 (m, 1H), 3.38 – 3.30 (m, 2H), 3.06 – 3.00 (m, 1H), 2.87 – 2.82 (m, 1H), 2.76 – 2.70 (m, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H), 0.59 (s, 3H), 0.50 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.4, 169.3, 164.1, 138.2, 137.9, 137.8, 137.7, 136.3, 134.64, 134.55, 134.2, 131.3, 130.1, 129.6, 129.44, 129.35, 128.8, 128.7, 128.6, 127.1, 127.1, 126.8, 113.9, 105.7, 60.9, 53.0, 46.8, 44.6, 39.0, 38.0, 30.2, 28.5, 28.3, 21.07, 21.05, 21.02 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{42}H_{42}NO_5$ 640.3057; Found 640.3084.



Rac-(*4S,5S,7S*)-1-benzyl-2',2'-dimethyl-4,5,7-tris(4-nitrophenyl)-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.51d): According to GP I, 4-nitrobenzaldehyde (0.10 g, 0.66 mmol), benzylamine (28 mg, 0.26 mmol) and Meldrum's acid (64 mg, 0.44 mmol) in toluene (2 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:3) to get analytically pure product **7.51d** as pale yellow solid (93 mg, 58%). Mp 260-262 ^{o}C. FTIR: ῡ = 3075, 2931, 2856, 1731, 1676, 1604, 1520, 1347, 1294, 1199, 1108, 858, 733, 701 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 – 8.26 (m, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 8.02 – 7.99 (m, 1H), 7.50 – 7.47 (m, 1H), 7.36 – 7.29 (m, 5H), 7.16 – 7.14 (m, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.95 – 6.93 (m, 1H), 5.25 (d, *J* = 16.0 Hz, 1H), 4.85 (d, *J* = 16.0 Hz, 1H), 4.66 (s, 1H), 3.91 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.46 – 3.37 (m, 2H), 3.08 – 3.02 (dd, *J* = 16.2, 6.8 Hz, 1H), 2.91 – 2.83 (m, 2H), 0.63 (s, 3H), 0.54 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.12, 167.8, 163.2, 148.1, 147.9, 147.5, 147.2, 144.0, 143.8, 137.2, 136.6, 132.1, 130.3, 130.0, 128.9, 128.2, 127.8, 126.8, 124.6, 124.3, 124.2, 124.1,



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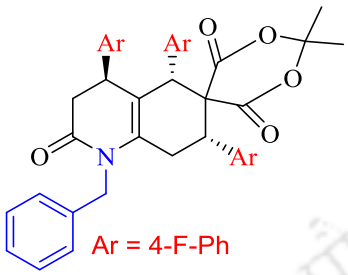
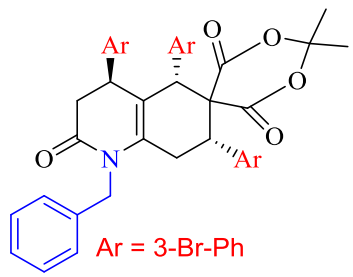
110.43, 106.4, 59.8, 52.7, 47.1, 44.9, 39.5, 39.1, 30.0, 29.0, 28.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{33}N_4O_{11}$ 733.2140; Found 733.2106.

Rac-(*4S,5S,7S*)-1-benzyl-4,5,7-tris(4-fluorophenyl)-2',2'-dimethyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.51e): According to GP I, 4-fluorobenzaldehyde (0.30 g, 2.41 mmol), benzylamine (0.10 g, 0.97 mmol) and Meldrum's acid (0.23 g, 1.61 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.51e** as white solid (0.32 g, 60%). Mp 219-221 °C. FTIR: ῡ = 3065, 3030, 2923, 1729, 1673, 1604, 1507, 1390, 1293, 1224, 1203, 1160, 1103, 1053, 838, 734, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.23 – 7.13 (m, 4H), 7.09 – 7.04 (m, 4H), 7.03 – 6.98 (m, 1H), 6.91 (t, *J* = 8.6 Hz, 2H), 6.80 – 6.78 (m, 4H), 6.75 – 6.72 (m, 1H), 6.65 – 6.61 (m, 1H), 5.17 (d, *J* = 16.4 Hz, 1H), 4.73 (d, *J* = 16.4 Hz, 1H), 4.44 (s, 1H), 3.67 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.32 – 3.20 (m, 2H), 2.91 – 2.85 (m, 1H), 2.76 – 2.66 (m, 2H), 0.59 (s, 3H), 0.50 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.1, 168.8, 163.89 (carbon attached with F), 163.86, 163.7 (carbon attached with F), 163.0 (carbon attached with F), 161.4, 161.2, 160.5, 137.7, 136.2, 136.1, 135.0, 133.2, 133.1, 133.0, 133.0, 132.9, 132.8, 130.8, 130.7, 130.5, 130.4, 128.79, 128.75, 128.71, 128.67, 127.3, 127.0, 126.8, 116.7, 116.5, 116.2, 116.0, 115.8, 115.7, 115.6, 115.5, 113.1, 106.0, 60.7, 52.3, 46.4, 44.7, 39.6, 38.5, 30.3, 28.7, 28.4 ppm. (Increased number of ^{13}C signal in aromatic region is observed due to F-coupling). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{33}F_3NO_5$ 652.2305; Found 652.2304.



Rac-(*4S,5S,7S*)-1-benzyl-4,5,7-tris(3-bromophenyl)-2',2'-dimethyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.51f): According to GP I, 3-bromobenzaldehyde (0.30 g, 1.62 mmol), benzylamine (70 mg, 0.65 mmol) and Meldrum's acid (0.16 g, 1.08 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.51f** as white solid (0.26 g, 57%). Mp 243-245 °C. FTIR: ῡ = 3066, 2946, 1765, 1731, 1676, 1590, 1567, 1437, 1429, 1389, 1288, 1193, 1074, 1053, 789, 734, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.44 – 7.26 (m, 8H), 7.22 – 7.13 (m, 4H), 7.12 – 7.05



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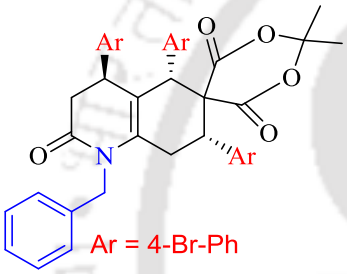
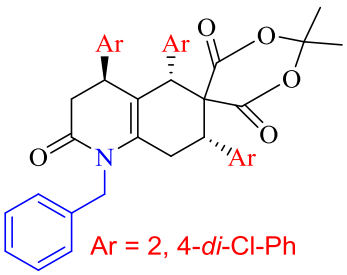
(m, 2H), 7.03 – 6.99 (m, 1H), 6.93 – 6.87 (m, 1H), 6.79 – 6.64 (m, 1H), 5.30 – 5.21 (m, 1H), 4.84 – 4.77 (m, 1H), 4.45 (d, *J* = 17.6 Hz, 1H), 3.73 – 3.67 (m, 1H), 3.39 – 3.29 (m, 2H), 3.02 – 2.91 (m, 1H), 2.86 – 2.72 (m, 2H), 0.71 (s, 3H), 0.60 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.53, 168.50, 163.6, 142.9, 142.6, 139.6, 139.2, 137.6, 135.6, 133.8, 132.1, 131.9, 131.6, 130.8, 129.8, 128.91, 128.88, 127.6, 127.3, 126.7, 125.80, 125.7, 123.4, 123.2, 122.9, 112.1, 111.9, 106.1, 60.2, 52.6, 46.8, 44.8, 39.5, 39.4, 30.2, 28.5, 28.4 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{33}Br_3NO_5$ 833.9883; Found 833.9881.

Rac-(*4S,5S,7S*)-1-benzyl-4,5,7-tris(4-bromophenyl)-2',2'-dimethyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.51g): According to GP I, 4-bromobenzaldehyde (0.30 g, 1.62 mmol), benzylamine (70 mg, 0.65 mmol) and Meldrum's acid (0.16 g, 1.08 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.51g** as white solid (0.31 g, 69%). Mp 259-261 °C. FTIR: ῡ = 3065, 3030, 2943, 1765, 1730, 1675, 1486, 1387, 1284, 1201, 1074, 1053, 1010, 826, 733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.44 (m, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.25 – 7.18 (m, 6H), 7.07 – 7.04 (m, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.58 – 6.56 (m, 1H), 5.19 (d, *J* = 16.0 Hz, 1H), 4.69 (d, *J* = 16.4 Hz, 1H), 4.39 (s, 1H), 3.64 – 3.60 (m, 1H), 3.26 – 3.18 (m, 2H), 2.92 – 2.87 (m, 1H), 2.76 – 2.65 (m, 2H), 0.61 (s, 3H), 0.52 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.8, 168.6, 163.7, 139.4, 137.6, 136.2, 136.1, 135.3, 132.8, 132.6, 132.3, 132.1, 131.9, 130.7, 130.4, 129.0, 128.7, 127.4, 126.8, 122.8, 122.5, 120.9, 112.3, 106.1, 60.3, 52.6, 46.7, 44.7, 39.2, 38.6, 30.0, 28.7, 28.4 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{33}Br_3NO_5$ 833.9888; Found 833.9888.



Rac-(*4S,5S,7S*)-1-benzyl-4,5,7-tris(2,4-dichlorophenyl)-2',2'-dimethyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.51h): According to GP I, 2,4-dichlorobenzaldehyde (0.10 g, 0.57 mmol), benzylamine (25 mg, 0.23 mmol) and Meldrum's acid (55 mg, 0.38 mmol) in toluene (2 mL) was reacted for 24 h and the crude mixture was purified by



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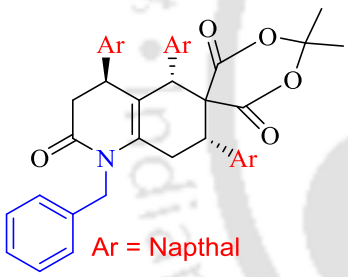
column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.51h** as white solid (95 mg, 62%). FTIR: ῡ = 3068, 3000, 2943, 1773, 1737, 1679, 1586, 1471, 1382, 1277, 1200, 1145, 1105, 833, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.33 (m, 3H), 7.31 – 7.23 (m, 7H), 7.19 – 7.14 (m, 3H), 6.99 (d, *J* = 8.4 Hz, 1H), 5.06 (d, *J* = 15.6 Hz, 1H), 4.97 (s, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.55 – 4.51 (m, 1H), 3.72 – 3.69 (m, 1H), 3.27 – 3.20 (m, 1H), 2.81 – 2.79 (m, 3H), 1.05 (s, 3H), 0.78 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.8, 166.6, 164.7, 137.4, 137.1, 137.0, 135.9, 135.5, 135.1, 134.9, 134.6, 134.4, 133.7, 132.9, 132.4, 130.7, 130.00, 129.8, 129.6, 129.1, 128.8, 128.1, 128.0, 127.60, 127.6, 127.1, 112.6, 106.1, 56.4, 47.7, 44.8, 42.5, 38.0, 36.7, 31.6, 29.3, 28.6 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{33}Cl_5NO_5$ 804.0220; Found 804.0270.

Rac-(*4S,5S,7S*)-1-benzyl-2',2'-dimethyl-4,5,7-tri(naphthalen-1-yl)-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.51i): According to GP I, napthaldehyde (0.10 g, 0.64 mmol), benzylamine (27 mg, 0.26 mmol) and Meldrum's acid (61 g, 0.43 mmol) in toluene (2 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.51i** as brown solid (98 mg, 61%). Mp 202-204 °C. FTIR: ῡ = 3032, 2928, 2872, 1729, 1671, 1596, 1511, 1389, 1268, 1202, 1055, 1013, 970, 798, 776, 731, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.47 (d, *J* = 8.8 Hz, 1H), 7.92 (dd, *J* = 18.0, 8.0 Hz, 2H), 7.80 – 7.44 (m, 17H), 7.40 – 7.37 (m, 1H), 7.33 – 7.25 (m, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 5.76 (s, 1H), 5.23 (s, 2H), 5.18 – 5.14 (m, 1H), 4.48 (t, *J* = 8.8 Hz, 1H), 3.82 (t, *J* = 12.8 Hz, 1H), 3.31 – 3.25 (m, 1H), 3.15 – 3.09 (m, 2H), 0.71 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.1, 168.7, 164.9, 138.0, 136.6, 136.0, 134.9, 134.1, 134.0, 133.4, 132.9, 131.7, 131.5, 130.8, 129.1, 128.8, 128.7, 128.4, 127.9, 127.6, 127.3, 127.2, 126.7, 126.2, 126.0, 125.63, 125.55, 125.4, 125.3, 125.24, 125.21, 125.1, 125.0, 123.4, 122.6, 122.4, 115.9, 105.6, 58.9, 47.1, 44.9, 41.1, 39.7, 37.1, 32.9, 28.7, 27.7 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{51}H_{42}NO_5$ 748.3057; Found 748.3091.



Rac-4,4',4''-((*4S,5S,7S*)-1-benzyl-2',2'-dimethyl-2,4',6'-trioxo-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-4,5,7-triyl)tribenzonitrile (7.51j): According to GP I, 4-cyanobenzaldehyde (0.10 g, 0.76 mmol), benzylamine (33 mg, 0.31 mmol) and Meldrum's acid (73 g, 0.51 mmol) in toluene (2 mL) was reacted for 24 h and the crude

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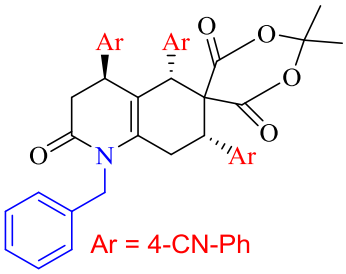
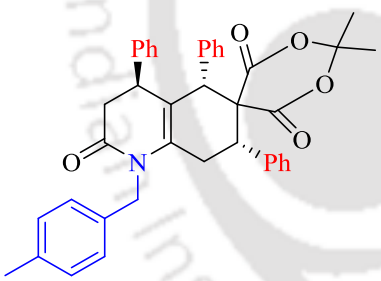
mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.51j** as white solid (0.11 g, 61%). FTIR: ῡ = 3063, 2961, 2926, 2229, 1765, 1730, 1674, 1607, 1504, 1392, 1291, 1200, 1054, 841, 700, 564 $cm^{-1.}$ ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.74 – 7.73 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.46 (m, 1H), 7.41 – 7.39 (m, 1H), 7.35 – 7.32 (m, 2H), 7.31 – 7.28 (m, 3H), 7.17 – 7.16 (m, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.85 – 6.84 (m, 1H), 5.26 (d, *J* = 16.2 Hz, 1H), 4.84 (d, *J* = 16.2 Hz, 1H), 4.58 (s, 1H), 3.84 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.42 – 3.35 (m, 2H), 3.03 – 3.00 (m, 1H), 2.87 – 2.82 (m, 2H), 0.65 (s, 3H), 0.55 (s, 3H). ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 168.2, 167.9, 163.2, 145.5, 142.0, 141.9, 137.2, 136.4, 133.1, 133.0, 132.8, 132.7, 131.8, 130.0, 129.7, 128.9, 128.1, 127.7, 126.8, 118.3, 117.8, 117.7, 113.1, 112.8, 111.3, 110.6, 106.4, 59.8, 52.9, 47.1, 44.9, 39.7, 39.2, 29.8, 28.9, 28.4 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{42}H_{33}N_4O_5$ 673.2445; Found 673.2438.



Rac-(*4S,5S,7S*)-2',2'-dimethyl-1-(4-methylbenzyl)-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52a): According to GP I, benzaldehyde (0.30 g, 2.83 mmol), 4-methylbenzylamine (0.14 g, 1.13 mmol) and Meldrum's acid (0.27 g, 1.89 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52a** as white solid (0.37 g, 63%). FTIR: ῡ = 3063, 3033, 2924, 1765, 1730, 1674, 1493, 1454, 1389, 1292, 1194, 1099, 1053, 764, 749, 703 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 (t, *J* = 7.2 Hz, 1H), 7.32 – 7.26 (m, 5H), 7.22 – 7.12 (m, 6H), 7.07 – 7.00 (m, 4H), 6.96 – 6.94 (m, 2H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.34 (d, *J* = 16.2 Hz, 1H), 4.66 (d, *J* = 16.2 Hz, 1H) 4.60 (s, 1H), 3.78 – 3.74 (m, 1H), 3.43 – 3.36 (m, 2H), 3.05 – 3.00 (m, 1H), 2.88 – 2.77 (m, 2H), 2.31 (s, 3H), 0.57 (s, 3H), 0.48 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.2, 169.1, 164.0, 140.7, 137.6, 137.5, 136.6, 134.8, 134.7, 131.4, 129.3, 129.1, 129.03, 128.98, 128.8, 128.7, 128.5, 128.1, 127.3, 126.80, 126.77, 113.3, 105.8, 60.8, 53.4, 47.1, 44.4, 39.2, 38.7, 30.1, 28.4, 28.3, 21.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{40}H_{38}NO_5$ 612.2744; Found 612.2780.



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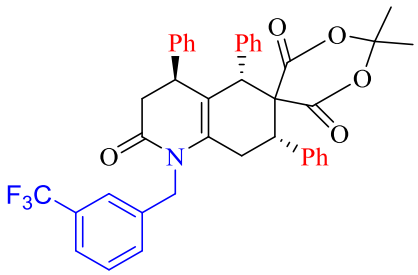
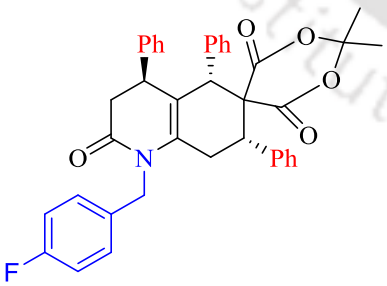
Rac-(*4S,5S,7S*)-2',2'-dimethyl-4,5,7-triphenyl-1-(3-(trifluoromethyl)benzyl)-1,3,4,5,7,8-hexahydro-2*H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52b): According to



GP I, benzaldehyde (0.10 g, 0.94 mmol), (3-(trifluoromethyl)phenyl)methanamine (66 mg, 0.38 mmol) and Meldrum's acid (91 g, 0.63 mmol) in toluene (2 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52b** as white solid (0.12 g, 57%). Mp 184-186 °C. FTIR: ῡ = 3065, 3033, 2926, 1766, 1729, 1676, 1494, 1454, 1389, 1328, 1293, 1275, 1164, 1124, 1074, 764, 749, 701 $cm^{-1.}$ ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.46 – 7.43 (m, 2H), 7.36 – 7.31 (m, 1H), 7.29 – 7.27 (m, 2H), 7.24 – 7.16 (m, 5H), 7.13 – 7.08 (m, 5H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.84 – 6.82 (m, 2H), 6.65 (d, *J* = 7.6 Hz, 1H), 5.12 (d, *J* = 16.4 Hz, 1H), 4.92 (d, *J* = 16.4 Hz, 1H), 4.53 (s, 1H), 3.72 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.40 (t, *J* = 6.6 Hz, 1H), 3.33 – 3.23 (m, 1H), 2.95 – 2.89 (m, 1H), 2.83 – 2.78 (m, 1H), 2.65 – 2.59 (m, 1H), 0.50 (s, 3H), 0.40 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.3, 169.1, 163.9, 140.6, 139.0, 137.4, 137.1, 134.3, 131.3, 130.1, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.1, 127.1, 126.8, 124.2, 124.2, 124.1, 124.1, 123.5, 123.5, 123.5, 123.4, 114.3, 105.8, 60.7, 53.3, 47.1, 44.3, 39.3, 39.1, 30.4, 28.4, 28.3 ppm. (Increased number of ^{13}C signal in aromatic region is observed due to F-coupling). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{40}H_{35}F_3NO_5$ 666.2462; Found 666.2460.

Rac-(4S,5S,7S)-1-(4-fluorobenzyl)-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-2*H*- spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52c): According to



GP I, benzaldehyde (0.30 g, 2.83 mmol), 4-fluorobenzylamine (0.14 g , 1.13 mmol) and Meldrum's acid (0.27 g, 1.89 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52c** as white solid (0.38 g, 66%). Mp 271-273 °C. FTIR: ῡ = 3060, 3028, 29418, 1766, 1727, 1672, 1509, 1494, 1388, 1290, 1222, 1192, 1098, 1052, 762, 733, 701 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.38 (m, 1H), 7.35 – 7.28 (m, 5H), 7.26 – 7.20 (m, 5H), 7.17 – 7.11 (m, 3H), 6.99 – 6.94 (m, 4H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.27 (d, *J* = 16.4 Hz, 1H), 4.77 (d, *J* = 16.0 Hz, 1H), 4.64 (s, 1H), 3.80 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.48 – 3.36 (m, 2H), 3.06 – 3.00 (m, 1H), 2.91 –

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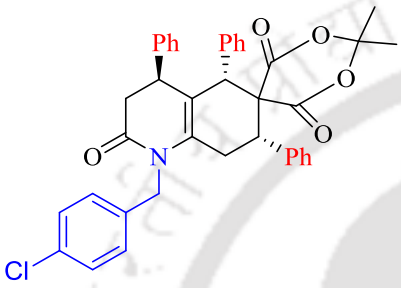
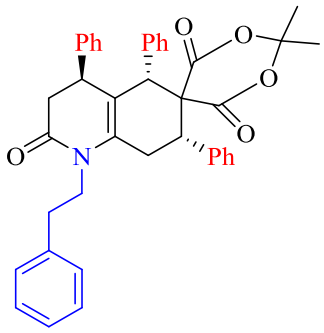
2.86 (m, 1H), 2.80 – 2.74 (m, 1H), 0.61 (s, 3H), 0.50 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 169.1, 164.0, 163.2, 160.7, 140.6, 137.5, 137.4, 134.5, 133.5, 131.4, 129.3, 129.1, 129.00, 128.95, 128.8, 128.7, 128.6, 128.5, 128.2, 127.2, 126.8, 115.6, 115.4, 113.9, 105.8, 60.7, 53.4, 47.1, 43.9, 39.2, 38.7, 30.3, 28.4, 28.3 ppm. (Increased number of ^{13}C signal in aromatic region is observed due to F-coupling). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{35}FNO_5$ 616.2494; Found 616.2482.

Rac-(*4S,5S,7S*)-1-(4-chlorobenzyl)-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52d): According to GP I, benzaldehyde (0.30 g, 2.83 mmol), 4-chlorobenzylamine (0.16 g, 1.13 mmol) and Meldrum's acid (0.27 g, 1.89 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52d** as white solid (0.39 g, 65%). Mp 248-250 °C. FTIR: ῡ = 3063, 3030, 2946, 1764, 1728, 1674, 1492, 1454, 1388, 1291, 1193, 1098, 1053, 974, 763, 735, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 – 7.28 (m, 1H), 7.24 – 7.21 (m, 4H), 7.13 – 7.09 (m, 8H), 7.09 – 7.03 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.89 – 6.85 (m, 2H), 6.74 (d, *J* = 7.6 Hz, 1H), 5.18 (d, *J* = 16.4 Hz, 1H), 4.64 (d, *J* = 16.4 Hz, 1H), 4.55 (s, 1H), 3.70 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.37 – 3.26 (m, 2H), 2.96 – 2.90 (m, 1H), 2.82 – 2.76 (m, 1H), 2.66 – 2.61 (m, 1H), 0.51 (s, 3H), 0.40 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 169.1, 164.0, 140.6, 137.5, 137.4, 136.4, 134.4, 132.9, 131.4, 129.3, 129.1, 129.02, 128.95, 128.80, 128.76, 128.7, 128.6, 128.2, 128.2, 127.2, 126.9, 113.9, 105.9, 60.7, 53.4, 47.1, 44.0, 39.1, 38.6, 30.3, 28.4, 28.3 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{35}ClNO_5$ 632.2198; Found 632.2193.

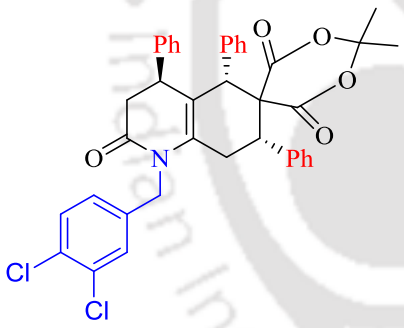


Rac-(*4S,5S,7S*)-2',2'-dimethyl-1-phenethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52e): According to GP I, benzaldehyde (0.30 g, 2.83 mmol), phenethylamine (0.14 mg, 0.38 mmol) and Meldrum's acid (0.27 g, 1.89 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52e** as white solid (0.39 g, 68%). FTIR: ῡ = 3063,



3030, 2926, 1736, 1728, 1671, 1494, 1454, 1391, 1291, 1268, 1242, 1153, 1053, 736, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.21 (m, 5H), 7.19 – 7.12 (m, 8H), 7.11 – 7.07 (m, 3H), 7.02 – 6.98 (m, 1H), 6.83 – 6.80 (m, 2H), 6.63 (d, *J* = 7.6 Hz, 1H), 4.51 (s, 1H), 3.92 (t, *J* = 7.8 Hz, 2H), 3.70 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.32 – 3.24 (m, 2H), 2.94 – 2.79 (m, 2H), 2.76 (d , *J* = 6.4 Hz, 1H), 2.68 (d , *J* = 6.8 Hz, 1H), 2.65 – 2.56 (m, 1H), 0.55 (s, 3H), 0.41 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 168.8, 164.1, 141.0, 138.7, 137.7, 137.3, 134.3, 131.3, 129.12, 129.10, 129.08, 129.0, 128.9, 128.8, 128.61, 128.55, 128.5, 128.01, 127.2, 126.7, 126.5, 114.3, 105.8, 60.8, 53.3, 47.3, 42.7, 39.6, 39.3, 35.5, 30.2, 28.4, 28.3 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{40}H_{38}NO_5$ 612.2744; Found 612.2741.

Rac-(*4S,5S,7S*)-1-(4,4-dichlorobenzyl)-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52f): According to GP I, benzaldehyde (0.30 g, 2.83 mmol), 3,4-dichlorobenzylamine (0.20 g, 1.13 mmol) and Meldrum's acid (0.27 g, 1.89 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52f** as white solid (0.35 g, 55%). Mp 228-230 °C. FTIR: ῡ = 3063, 2995, 2948, 1771, 1736, 1676, 1586, 1471, 1382, 1271, 1200, 1105, 1045, 869, 788, 734, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39 (t, *J* = 7.4 Hz, 1H), 7.34 – 7.28 (m, 6H), 7.25 – 7.21 (m, 6H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.00 – 6.94 (m, 3H), 6.80 (d, *J* = 7.6 Hz, 1H), 5.22 (d, *J* = 16.4 Hz, 1H), 4.76 (d, *J* = 16.8 Hz, 1H), 4.65 (s, 1H), 3.82 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.48 (t, *J* = 6.6 Hz, 1H), 3.43 – 3.36 (m, 1H), 3.04 – 2.98 (m, 1H), 2.92 – 2.86 (m, 1H), 2.72 – 2.66 (m, 1H), 0.60 (s, 3H), 0.50 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.3, 169.0, 164.0, 140.4, 138.2, 137.4, 137.2, 134.2, 132.8, 131.4, 131.2, 130.6, 129.3, 129.1, 129.01, 128.95, 128.84, 128.81, 128.7, 128.6, 128.2, 127.1, 126.9, 126.2, 114.3, 105.9, 60.7, 53.3, 47.1, 43.6, 39.2, 38.8, 30.3, 28.5, 28.3 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{34}Cl_2NO_5$ 666.1809; Found 666.1810.



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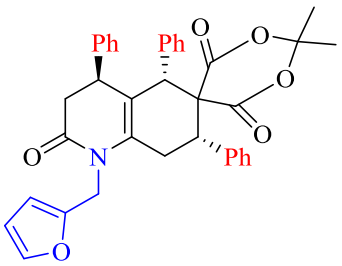
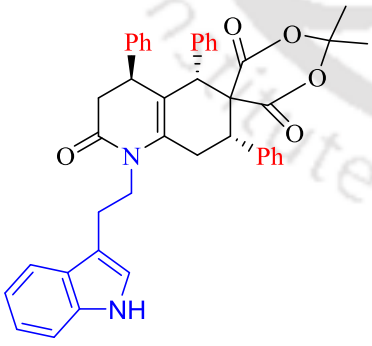
Rac-(*4S,5S,7S*)-1-(furan-2-ylmethyl)-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52g): According to GP I, benzaldehyde (0.30 g, 2.83 mmol), furfurylamine (0.11 g, 1.13 mmol) and Meldrum's acid (0.27 g, 1.89 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52g** as colourless gum (0.39 g, 70%). FTIR: ῡ = 3058, 3035, 2926, 1727, 1676, 1494, 1454, 1391, 1379, 1283, 1266, 1203, 1052, 763, 733, 700 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.34 (m, 4H), 7.33 – 7.25 (m, 5H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.13 – 7.09 (m, 3H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.80 – 6.78 (m, 2H), 6.34 – 6.33 (m, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 5.37 (d, *J* = 16.2 Hz, 1H), 4.66 (d, *J* = 16.2 Hz, 1H), 4.58 (s, 1H), 3.89 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.50 – 3.43 (m, 1H), 3.34 (t, *J* = 5.6 Hz, 1H), 3.17 – 3.12 (m, 1H), 3.03 – 2.97 (m, 1H), 2.75 – 2.70 (m, 1H), 0.62 (s, 3H), 0.50 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 168.6, 164.0, 151.02, 141.9, 140.8, 137.7, 137.6, 134.0, 131.4, 129.3, 129.1, 129.02, 129.00, 128.9, 128.7, 128.6, 128.2, 127.0, 126.8, 113.8, 110.5, 108.2, 105.8, 60.8, 53.1, 47.2, 39.2, 39.0, 37.7, 29.9, 28.5, 28.3 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{37}H_{34}NO_6$ 588.2381; Found 588.2376.



Rac-(*4S,5S,7S*)-1-(2-(2H-isoindol-1-yl)ethyl)-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52h): According to GP I, benzaldehyde (0.30 g, 2.83 mmol), tryptamine (0.18 g, 1.13 mmol) and Meldrum's acid (0.27 g, 1.89 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52h** as white solid (0.14 g, 68%). FTIR: ῡ = 3060, 2926, 2853, 1726, 1646, 1492, 1455, 1391, 1291, 1267, 1240, 1053, 764, 736, 700 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (br. s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.29 – 7.20 (m, 5H), 7.18 (s, 1H), 7.16 – 7.06 (m, 7H), 7.05 – 7.00 (m, 2H), 6.95 – 6.92 (m, 1H), 6.88 – 6.81 (m, 2H), 6.65 (d, *J* = 7.6 Hz, 1H), 4.51 (s, 1H), 4.10 – 3.99 (m, 1H), 4.00 – 3.89 (m, 1H), 3.69 – 3.65 (m, 1H), 3.32 – 3.23 (m, 1H), 3.12 – 3.04 (m, 1H), 3.00 – 2.91 (m, 1H), 2.87 – 2.81 (m, 1H), 2.72 – 2.66 (m, 1H), 0.84 – 0.76 (m, 2H), 0.53 (s, 3H), 0.41 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.3, 168.9,



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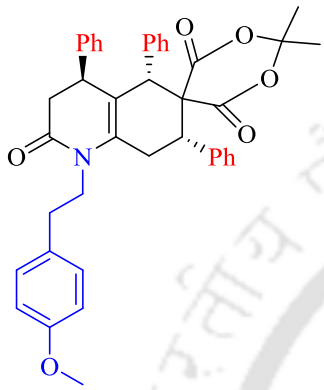
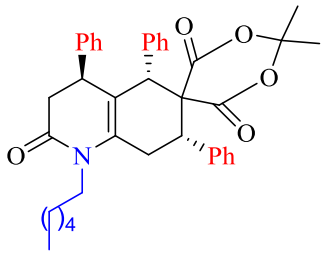
164.0, 141.1, 137.6, 137.4, 136.2, 134.4, 131.3, 129.2, 129.11, 129.06, 128.9, 128.8, 128.6, 128.5, 128.0, 127.4, 127.2, 126.7, 122.2, 122.0, 119.4, 118.9, 113.9, 112.8, 111.1, 105.8, 60.8, 53.2, 47.3, 42.1, 39.6, 39.3, 30.1, 28.5, 28.3, 25.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{42}H_{39}N_2O_5$ 651.2853; Found 651.2858.

Rac-(*4S,5S,7S*)-1-(4-methoxyphenethyl)-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52i): According to GP I, benzaldehyde (0.30 g, 2.83 mmol), 4-methoxyphenethylamine (0.17 g, 1.13 mmol) and Meldrum's acid (0.27 g, 1.89 mmol) in toluene (3 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52i** as white solid (0.35 g, 58%). FTIR: ῡ = 3030, 2938, 2838, 1763, 1674, 1728, 1670, 1646, 1511, 1455, 1391, 1290, 1243, 1178, 1156, 1052, 1033, 822, 765, 735, 701 $cm^{-1.}$ ^1H NMR (600 MHz, $CDCl_3$) δ = 7.40 – 7.35 (m, 3H), 7.33 – 7.31 (m, 1H), 7.28 – 7.24 (m, 4H), 7.22 – 7.17 (m, 3H), 7.13 – 7.09 (m, 3H), 6.92 (d, *J* = 6.6 Hz, 2H), 6.81 (d, *J* = 5.6 Hz, 2H), 6.74 (d, *J* = 7.8 Hz, 1H), 4.61 (s, 1H), 4.04 – 3.99 (m, 1H), 3.96 – 3.91 (m, 1H), 3.80 (s, 3H), 3.78 – 3.75 (m, 1H), 3.39 – 3.32 (m, 2H), 2.95 – 2.82 (m, 3H), 2.78 – 2.74 (m, 1H), 2.67 – 2.63 (m, 1H) 0.64 (s, 3H), 0.50 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.2, 168.9, 164.1, 158.2, 141.0, 137.6, 137.3, 134.3, 131.3, 130.7, 129.0, 129.2, 129.11, 129.07, 128.9, 128.8, 128.6, 128.6, 128.0, 127.2, 126.7, 114.2, 113.9, 105.8, 60.8, 55.2, 53.2, 47.3, 42.9, 39.5, 39.2, 34.6, 30.2, 28.5, 28.3 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{41}H_{40}NO_6$ 642.2850; Found 642.2854.



Rac-(*4S,5S,7S*)-1-hexyl-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52j): According to GP I, benzaldehyde (0.30 g, 2.83 mmol), hexylamine (0.11 g, 1.13 mmol) and Meldrum's acid (0.27 g, 1.89 mmol) in toluene (2 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52j** as colourless gum (0.34 g, 62%). Mp 168-170 °C. FTIR: ῡ = 2956, 2923, 2853, 1729, 1668, 1454, 1390, 1290, 1241, 1183, 1099, 1031, 764, 734, 699 $cm^{-1.}$ ^1H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.32 (m, 3H), 7.31 – 7.28 (m, 3H), 7.25 – 7.21 (m, 2H), 7.19 – 7.14 (m, 3H), 7.09



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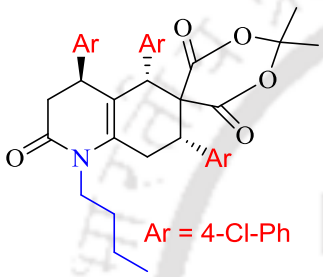
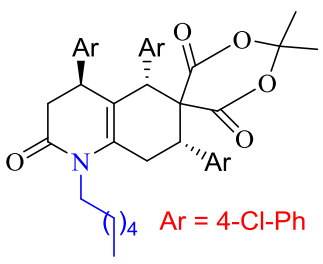
(t, *J* = 7.6 Hz, 1H), 6.89 – 6.87 (m, 2H), 6.73 (d, *J* = 7.6 Hz, 1H), 4.58 (s, 1H), 3.90 – 3.81 (m, 2H), 3.68 – 3.61 (m, 1H), 3.45 – 3.34 (m, 2H), 2.90 – 2.84 (m, 1H), 2.80 – 2.67 (m, 2H), 1.62 – 1.56 (m, 2H), 1.35 – 1.24 (m, 6H), 0.87 (t, *J* = 6.6 Hz, 3H), 0.62 (s, 3H), 0.49 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.2, 168.6, 164.0, 141.0, 137.8, 137.4, 134.4, 131.3, 129.12, 129.05, 128.9, 128.8, 128.6, 128.0, 127.2, 126.7, 114.0, 105.8, 60.8, 53.2, 47.3, 41.2, 39.7, 39.3, 31.6, 30.1, 29.4, 28.4, 28.3, 26.6, 22.6, 14.0 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{38}H_{42}NO_5$ 592.3057; Found 592.3060.

Rac-(*4S,5S,7S*)-1-butyl-4,5,7-tris(4-chlorophenyl)-2',2'-dimethyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52k): According to GP I, 4-chlorobenzaldehyde (0.10 g, 0.71 mmol), butylamine (21 mg, 0.28 mmol) and Meldrum's acid (68 mg, 0.47 mmol) in toluene (2 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52k** as white solid (0.34 g, 62%). Mp 271-273 °C. FTIR: ῡ = 2959, 2931, 2876, 1765, 1731, 1673, 1490, 1391, 1286, 1201, 1092, 1014, 831, 725 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.33 (m, 3H), 7.21 – 7.19 (m, 2H), 7.16 – 7.13 (m, 3H), 7.10 – 7.08 (m, 1H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.63 – 6.60 (m, 1H), 4.47 (s, 1H), 3.85 – 3.75 (m, 2H), 3.70 – 3.63 (m, 1H), 3.36 – 3.27 (m, 2H), 2.84 – 2.78 (m, 1H), 2.75 – 2.69 (m, 1H), 2.67 – 2.61 (m, 1H), 1.62 – 1.52 (m, 2H), 1.36 – 1.30 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.72 (s, 3H), 0.59 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.9, 168.1, 163.8, 139.2, 135.9, 135.6, 135.0, 134.8, 134.3, 132.7, 132.4, 130.4, 130.2, 129.6, 129.4, 128.9, 128.8, 128.5, 113.0, 106.1, 60.44, 52.38, 46.8, 41.0, 39.7, 39.1, 31.5, 30.0, 28.7, 28.5, 20.2, 13.9 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{35}Cl_3NO_5$ 666.1575; Found 666.1578.



Rac-(*4S,5S,7S*)-4,5,7-tris(4-chlorophenyl)-1-hexyl-2',2'-dimethyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.52l): According to GP I, 4-chlorobenzaldehyde (0. 10 g, 0.71 mmol), hexylamine (29 mg, 0.28 mmol) and Meldrum's acid (68 mg, 0.47 mmol) in toluene (2 mL) was reacted for 24 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.52l** as white solid (0.34 g, 62%). FTIR: ῡ = 2958, 2931, 2858, 1765, 1730, 1671, 1489, 1390, 1284,



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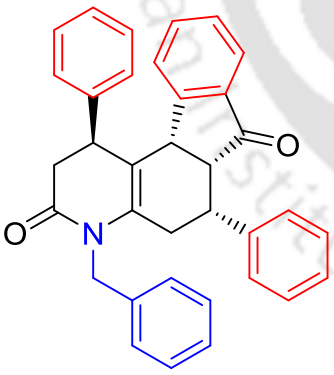
1091, 1014, 830, 726 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 8.4 Hz, 3H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.9 – 7.06 (m, 3H), 7.04 – 7.01 (m, 1H), 6.72 (d, *J* = 8.4 Hz, 2H), 6.56 – 6.53 (m, 1H), 4.41 (s, 1H), 3.78 – 3.58 (m, 3H), 3.30 – 3.21 (m, 2H), 2.77 – 2.55 (m, 3H), 1.54 – 1.49 (m, 2H), 1.23 – 1.17 (m, 6H), 0.81 (t, *J* = 6.6 Hz, 3H), 0.66 (s, 3H), 0.54 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.9, 168.1, 163.8, 139.2, 135.9, 135.6, 135.1, 134.8, 134.3, 132.7, 132.4, 130.4, 130.2, 129.5, 129.3, 128.9, 128.8, 128.5, 113.1, 106.1, 60.5, 52.4, 46.8, 41.2, 39.7, 39.1, 31.5, 30.0, 29.4, 28.7, 28.5, 26.6, 22.6, 14.0 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{38}H_{39}Cl_3NO_5$ 694.1888; Found 694.1862.

General procedure for the synthesis of indanone derivatives from ene lactam (7.53a – 7.53e) (GP IIA): Spirocyclic ene-lactam was dissolved in toluene/DCM (1 - 2 mL) and TfOH was added to the reaction mixture. Then the reaction mixture was stirred for 3 h at 50 ^{o}C. After consumption of the ene lactam (indicated by TLC), toluene was removed under reduced pressure. The resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 M $NaHCO_3$ (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulphate and concentrated under vacuum. The crude mixture was purified by column chromatography to get analytically pure product.

Rac-(*1R,6R,6aR,11bS*)-4-benzyl-1,6-diphenyl-1,4,5,6,6a,11b-hexahydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.53a): According to GP IIA, spirocyclic ene-lactam 6a (60 mg, 0.10 mmol) and TfOH (75 mg, 0.50 mmol) in toluene (2 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53a** as white solid (36 mg, 72%). Mp 146-148 ^{o}C. FTIR: ϑ = 3063, 3028, 2928, 1712, 1670, 1602, 1495, 1453, 1386, 1290, 1180, 1030, 755, 733, 699 $cm^{-1.}$ ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.61 (m, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.42 (m, 3H), 7.39 – 7.35 (m, 4H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.24 – 7.19 (m, 3H), 7.06 – 7.01 (m, 2H), 5.17 (d, *J* = 16.2 Hz, 1H), 4.73 (d, *J* = 16.2 Hz, 1H), 4.23 (*J* = 6.6 Hz, 1H), 4.02 (t, *J* = 5.6 Hz, 1H), 3.42 (t, *J* = 5.4 Hz, 1H), 3.36 – 3.33 (m, 1H), 2.90 – 2.87 (m, 1H), 2.82 – 2.68 (m, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 204.7, 168.6, 155.0, 141.1, 140.9, 137.7, 137.1, 135.8, 134.4, 129.2, 128.6, 128.2, 127.8, 127.7, 127.4, 127.2, 126.7, 126.6, 126.0, 124.0, 116.9, 53.0, 44.8, 44.0, 40.7, 39.9, 39.0, 27.8 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{35}H_{30}NO_2$ 496.2271; Found 496.2275.



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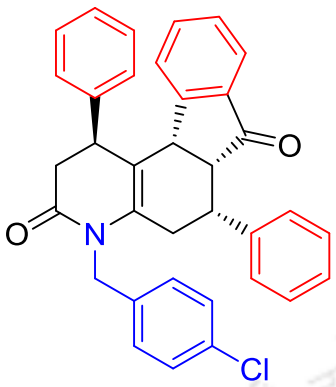
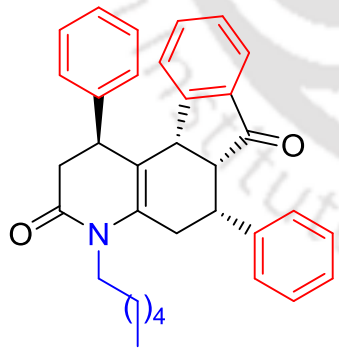
Rac-(*1R,6R,6aR,11bS*)-4-(4-chlorobenzyl)-1,6-diphenyl-1,4,5,6,6a,11b-hexahydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.53b): According to GP IIA, spirocyclic ene-lactam **6a** (40 mg, 0.06 mmol) and TfOH (48 mg, 0.32 mmol) in toluene (1 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53b** as white solid (23 mg, 69%). FTIR: ϑ = 3030, 2958, 2925, 2856, 1712, 1673, 1487, 1388, 1179, 1007, 839, 762, 697 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 – 7.54 (m, 1H), 7.52 – 7.50 (m, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.36 – 7.33 (m, 3H), 7.30 – 7.24 (m, 6H), 7.21 – 7.17 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.56 (d, *J* = 16.4 Hz, 1H), 4.15 (d, *J* = 6.8 Hz, 1H), 3.91 (t, *J* = 6.0 Hz, 1H), 3.35 – 3.32 (m, 1H), 3.28 – 3.23 (m, 1H), 2.81 – 2.76 (m, 1H), 2.65 – 2.59 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 204.6, 168.6, 154.9, 141.0, 140.7, 137.1, 136.2, 135.5, 134.4, 133.0, 129.2, 128.8, 128.3, 128.1, 127.8, 127.7, 127.5, 126.7, 125.9, 124.1, 117.6, 53.0, 44.1, 44.1, 40.7, 39.7, 38.8, 27.9 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{35}H_{29}ClNO_2$ 530.1881; Found 530.1902.



Rac-(*1R,6R,6aR,11bS*)-4-hexyl-1,6-diphenyl-1,4,5,6,6a,11b-hexahydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.53c): According to GP IIA, spirocyclic ene-lactam **6a** (50 mg, 0.09 mmol) and TfOH (65 mg, 0.43 mmol) in toluene (1 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53c** as colourless gum (30 mg, 71%). FTIR: ϑ = 2954, 2927, 2856, 1711, 1670, 1665, 1496, 1454, 1392, 1275, 1260, 1180, 1030, 755, 698 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 7.6 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.36 – 7.31 (m, 4H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 4.14 (d, *J* = 6.8 Hz, 1H), 3.90 – 3.82 (m, 2H), 3.76 – 3.69 (m, 2H), 3.59 – 3.47 (m, 1H), 3.45 – 3.31 (m, 3H), 3.19 – 3.10 (m, 1H), 2.87 – 2.82 (m, 1H), 2.74 – 2.69 (m, 2H), 2.65 – 2.49 (m, 2H), 1.29 – 1.07 (m, 3H), 0.80 (t, *J* = 6.4, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 204.8, 167.91, 155.1, 141.3, 141.2, 137.1, 135.5, 134.4, 129.2, 128.3, 128.0, 127.7, 127.3, 126.8, 126.7, 125.9, 124.0, 116.8, 53.1, 44.0, 41.3, 41.2, 40.0, 39.3, 31.5, 29.4,



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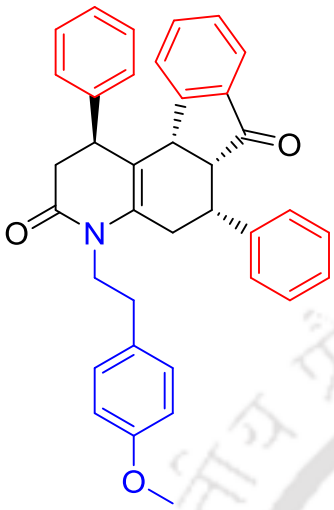
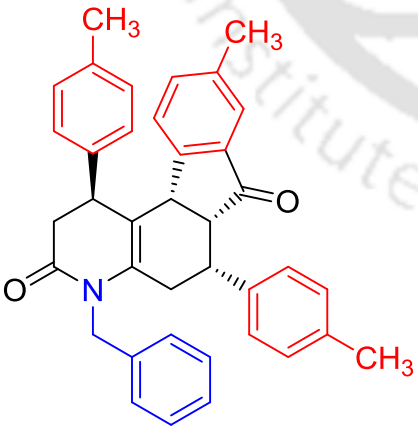
27.4, 26.5, 22.5, 14.0 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{34}H_{35}NO_2$ 490.2741; Found 490.2747.

Rac-(*1S,6R,6aR,11bS*)-4-(4-methoxyphenethyl)-1,6-diphenyl-1,4,5,6,6a,11b-hexahydro-3H-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.53d): 

According to GP IIA, spirocyclic ene-lactam **6a** (30 mg, 0.05 mmol) and TfOH (35 mg, 0.24 mmol) in toluene (1 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53d** as colourless gum (19 mg, 75%). FTIR: ῡ = 3028, 2963, 2933, 1708, 1603, 1512, 1456, 1247, 1177, 1079, 1031, 797, 751, 700 $cm^{-1.}$ ^1H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 7.6 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.26 (m, 9H), 7.24 – 7.19 m, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 4.16 (d, *J* = 6.8 Hz, 1H), 3.86 – 3.77 (m, 2H), 3.73 – 3.68 (m, 1H), 3.65 (s, 3H), 3.33 – 3.24 (m, 2H), 2.68 – 2.52 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.7, 167.0, 157.2, 154.1, 140.4, 140.2, 136.1, 134.5, 133.3, 129.4, 128.8, 128.2, 127.2, 127.1, 126.9, 126.8, 126.4, 125.6, 124.9, 123.0, 115.8, 112.9, 54.2, 52.0, 42.9, 42.1, 40.1, 39.2, 38.5, 33.7, 26.7 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{37}H_{34}NO3$ 540.2533; Found 540.2554.

Rac-(*1R,6R,6aR,11bS*)-4-benzyl-9-methyl-1,6-di-p-tolyl-1,4,5,6,6a,11b-hexahydro-3*H*-indeno[1,2-f]quinoline-3,7(2*H*)-dione (7.53e): 

According to GP IIA, spirocyclic ene-lactam **6a** (50 mg, 0.08 mmol) and TfOH (59 mg, 0.39 mmol) in toluene (1 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53e** as colourless gum (34 mg, 81%). FTIR: ῡ = 3030, 2921, 2863, 1707, 1669, 1602, 1488, 1385, 1282, 1263, 1155, 813, 733, 700 $cm^{-1.}$ ^1H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.31 (m, 3H), 7.19 – 7.06 (m, 11H), 6.94 – 6.92 (m, 2H), 5.05 (d, *J* = 16.2 Hz, 1H), 4.61 (d, *J* = 16.2 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.86 (t, *J* = 5.6 Hz, 1H), 3.27 – 3.25 (m, 1H), 3.21 – 3.16 (m, 1H), 2.78 – 2.72 (m, 1H), 2.68 – 2.55 (m, 3H), 2.32 (s, 6H), 2.27 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 204.9, 168.7, 152.5, 138.22, 138.15, 137.9, 137.8,

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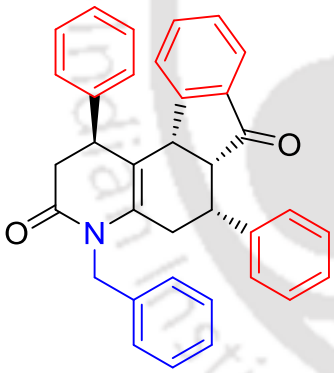
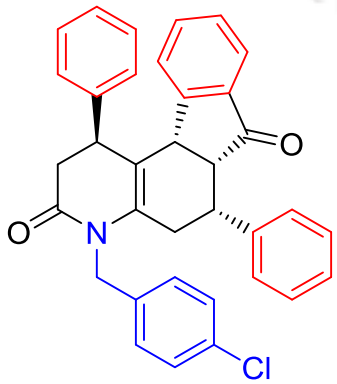
137.3, 137.0, 136.0, 135.5, 135.4, 129.8, 128.9, 128.6, 127.7, 127.6, 127.1, 126.7, 125.7, 123.9, 117.4, 53.3, 44.8, 43.7, 40.6, 39.9, 38.7, 27.9, 21.12, 21.11, 21.07 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{38}H_{36}NO_2$ 538.2741; Found 538.2738.

General procedure for the one pot synthesis of indanone derivatives (7.53a – 7.53e) (GP IIB): Arylaldehyde (0.94 – 0.54 mmol) was added to a solution of amine (0.38 – 0.22 mmol) and Meldrum's acid (0.63 – 0.36 mmol) in toluene (2 - 3 mL) and the mixture was refluxed (110 ^oC) for 24 h. After disappearance of amine (indicated by TLC), TfOH was added to the reaction mixture and the mixture was stirred for 4 h at 50 ^oC. After consumption of the intermediate spirocyclic ene lactam (indicated by TLC), toluene was removed under reduced pressure. The resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 M $NaHCO_3$ (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulphate and concentrated under vacuum. The crude mixture was purified by column chromatography to get analytically pure product.

Rac-(*1R,6R,6aR,11bS*)-4-benzyl-1,6-diphenyl-1,4,5,6,6a,11b-hexahydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.53a): 

According to GP IIB, benzaldehyde (0.10 g, 0.94 mmol), benzylamine (40 mg, 0.38 mmol), Meldrum's acid (91 mg, 0.63 mmol) and TfOH (0.24 g, 1.57 mmol) in toluene (2 mL) was reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53a** as white solid (70 mg, 45%).

Rac-(*1R,6R,6aR,11bS*)-4-(4-chlorobenzyl)-1,6-diphenyl-1,4,5,6,6a,11b-hexahydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.53b): 

According to GP IIB, benzaldehyde (0.10 g, 0.94 mmol), benzylamine (54 mg, 0.38 mmol), Meldrum's acid (91mg, 0.63 mmol) and TfOH (0.24 g, 1.57 mmol) in toluene (2 mL) was reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53b** as white solid (64 mg, 38%).

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Rac-(*1R,6R,6aR,11bS*)-4-hexyl-1,6-diphenyl-1,4,5,6,6a,11b-hexahydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.53c): According to GP IIB, benzaldehyde (0.10 g, 0.94 mmol), hexylamine (38 mg, 0.38 mmol), Meldrum's acid (91 mg, 0.63 mmol) and TfOH (0.24 g, 1.57 mmol) in toluene (2 mL) was reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53c** as colourless gum (66 mg, 43%).

Rac-(*1S,6R,6aR,11bS*)-4-(4-methoxyphenethyl)-1,6-diphenyl-1,4,5,6,6a,11b-hexahydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.53d): According to GP IIB, benzaldehyde (0.10 g, 0.94 mmol), 2-(4-methoxyphenyl)ethan-1-amine (57 mg, 0.38 mmol), Meldrum's acid (91 mg, 0.63 mmol) and TfOH (0.24 g, 1.57 mmol) in toluene (2 mL) was reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53d** as colourless gum (82 mg, 48%).

Rac-(*1R,6R,6aR,11bS*)-4-benzyl-9-methyl-1,6-di-p-tolyl-1,4,5,6,6a,11b-hexahydro-3*H*-indeno[1,2-f]quinoline-3,7(2*H*)-dione (7.53e): According to GP IIB, 4-methylbenzaldehyde (0.10 g, 0.83 mmol), benzylamine (35 mg, 0.33 mmol), Meldrum's acid (79 mg, 0.55 mmol) and TfOH (0.21 g, 1.38 mmol) in toluene (2 mL) was reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.53e** as colourless gum (77 mg, 52%).

General procedure for the synthesis of 9-fluorenone derivatives from ene lactam (7.54a – 7.54b) (GP IIIA): TfOH and DDQ was added successively to a solution spirocyclic ene-lactam in toluene/DCM. Then the reaction mixture was heated for 12 h at 50 ^{o}C. After consumption of spirocyclic ene-lactam (indicated by TLC), toluene was removed under

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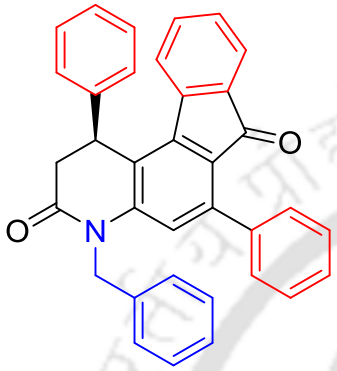
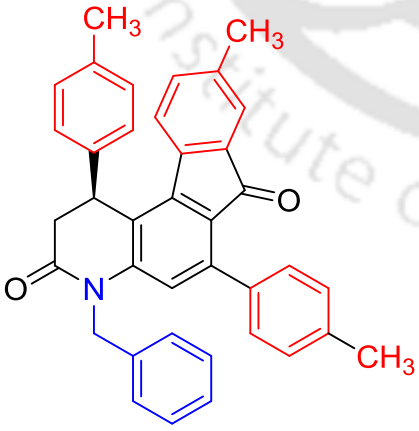
reduced pressure. The resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 M $NaHCO_3$ (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulphate and concentrated under vacuum. The crude mixture was purified by column chromatography to get analytically pure product

Rac-(*S*)-4-benzyl-1,6-diphenyl-1,4-dihydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.54a): According to GP IIIA, spirocyclic ene-lactam 6a (50 mg, 0.08 mmol), TfOH (63 mg, 0.42 mmol) and DDQ (57 mg, 0.25 mmol) in toluene (2 mL) was reacted for 12 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.54a** as yellow solid (30 mg, 73%). Mp 148-150 °C. FTIR: ῡ = 3063, 3028, 2926, 1663, 1604, 1495, 1453, 1400, 1312, 1189, 1152, 962, 736, 697 $cm^{-1.}$ ^1H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 7.2 Hz, 1H), 7.35 (m, 3H), 7.31 – 7.27 (m, 2H), 7.26 – 7.22 (m, 5H), 7.19 – 7.14 (m, 4H), 7.10 (d, *J* = 6.6 Hz, 2H), 7.01 – 6.99 (m, 2H), 6.85 – 6.80 (m, 1H), 5.32 (d, *J* = 16.0 Hz, 1H), 4.97 – 4.88 (m, 2H), 3.27 – 3.12 (m, 2H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.4, 168.6, 144.8, 144.0, 142.3, 142.2, 138.5, 137.2, 136.1, 135.7, 134.4, 129.2, 129.0, 128.7, 128.5, 128.0, 127.7, 127.6, 127.4, 125.3, 124.0, 123.5, 123.4, 118.9, 45.9, 38.9, 37.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{35}H_{26}NO_2$ 492.1958; Found 492.1974.



Rac-(*S*)-4-benzyl-9-methyl-1,6-di-p-tolyl-1,4-dihydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.54b): According to GP IIIA, spirocyclic ene-lactam 6a (0.10 g, 0.16 mmol), TfOH (0.12 g, 0.782 mmol) and DDQ (0.11 g, 0.47 mmol) in toluene (2 mL) was reacted for 12 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.54b** as yellow gum (60 mg, 71%). FTIR: ῡ = 2961, 2923, 2856, 1683, 1599, 1491, 1453, 1393, 1364, 1184, 1152, 1021, 820, 797, 731, 699 $cm^{-1.}$ ^1H NMR (600 MHz, $CDCl_3$) δ = 7.42 – 7.39 (m, 1H), 7.32 – 7.25 (m, 9H), 7.15 – 7.13 (m, 3H), 7.11 – 7.08 (m, 3H), 6.87 (s, 1H), 5.38 (d, *J* = 16.0 Hz, 1H), 5.05 (d, *J* = 16.0 Hz, 1H), 4.95 (d, *J* = 5.4 Hz, 1H), 3.33 – 3.30 (m, 1H), 3.25 – 3.21 (m, 1H), 2.45 (s, 3H), 2.35 (s, 3H), 2.32 (s,



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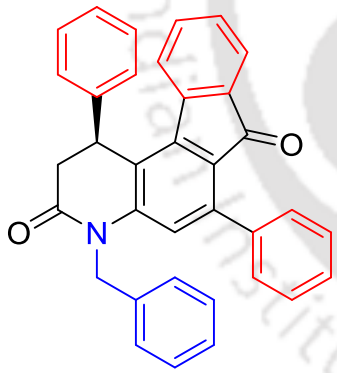
3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 191.8, 168.8, 144.7, 144.2, 142.1, 139.7, 139.4, 138.3, 137.2, 136.2, 136.0, 135.5, 134.9, 134.4, 129.9, 129.0, 128.70, 128.65, 127.5, 127.3, 127.3, 125.4, 124.6, 123.3, 123.0, 118.4, 46.0, 38.9, 36.8, 21.4, 21.3, 21.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{38}H_{32}NO_2$ 534.2428; Found 534.2419.

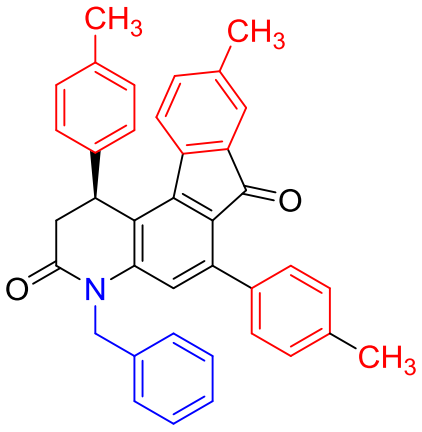
General procedure for the one pot synthesis of 9-fluorenone derivatives (7.54a – 7.54b) (GP IIIB): Arylaldehyde (0.94 – 0.54 mmol) was added to a solution of amine (0.38 – 0.22 mmol) and Meldrum's acid (0.63 – 0.36 mmol) in toluene (2 – 3 mL) and the mixture was refluxed (110 ^oC) for 24 h. After disappearance of amine (indicated by TLC), TfOH and DDQ were added successively to the reaction mixture and the mixture was stirred for another 12 h at 50 ^oC. After consumption of the intermediate spirocyclic ene lactam (indicated by TLC), toluene was removed under reduced pressure. The resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 M $NaHCO_3$ (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulphate and concentrated under vacuum. The crude mixture was purified by column chromatography to get analytically pure product

Rac-(*S*)-4-benzyl-1,6-diphenyl-1,4-dihydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione



(7.54a): According to GP IIIB, benzaldehyde (0.10 g, 0.94 mmol), benzylamine (40 mg, 0.38 mmol), Meldrum's acid (91 mg, 0.63 mmol), TfOH (0.24 g, 1.57 mmol) and DDQ (71 mg, 0.31 mmol) in toluene (2 mL) was reacted for 36 h (24 h + 12 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.54a** as yellow solid (46 mg, 30%).

Rac-(*S*)-4-benzyl-9-methyl-1,6-di-p-tolyl-1,4-dihydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione



(7.54b): According to GP IIIB, benzaldehyde (0.10 g, 0.83 mmol), benzylamine (36mg, 0.36 mmol), Meldrum's acid (80 mg, 0.56 mmol), TfOH (0.21 g, 1.39 mmol) and DDQ (0.19 g, 0.83 mmol) in toluene (2 mL) was reacted for 36 h (24 h + 12 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.54b** as yellow gum (42 mg,

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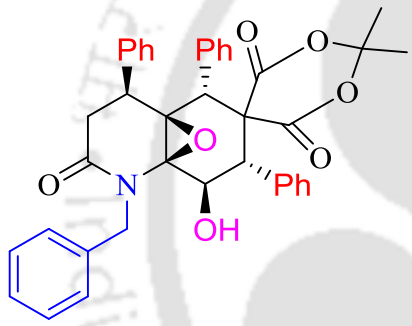
28%).

General procedure for synthesis of epoxy alcohols from ene lactams (7.55a – 7.55e) (GP IVA): mCPBA (0.22 - 0.42 mmol) was added to a solution of spirocyclic ene lactam (0.09 - 0.17 mmol) in toluene/DCM and reacted for 3 h at room temperature. After consumption spirocyclic ene lactam (indicated by TLC), toluene was removed under reduced pressure. The resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 M $NaHCO_3$ (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulphate and concentrated under vacuum. The crude mixture was purified by column chromatography to get analytically pure product.

Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-1'-benzyl-8'-hydroxy-2,2-dimethyl-4',5',7'-triphenyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55a): 

According to GP IVA, spirocyclic ene-lactam 6a (0.10 g, 0.17 mmol) and mCPBA (72 mg, 0.42 mmol) in toluene (2 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.55a** as white solid (80 mg, 75%). Mp 198-200 ^{o}C. FTIR: ῡ = 3065, 3035, 2963, 1766, 1726, 1646, 1291, 1264, 1101, 1059, 1029, 951, 763, 731, 697 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 – 7.44 (m, 4H), 7.36 – 7.26 (m, 6H), 7.10 – 7.07 (m, 3H), 7.02 – 6.97 (m, 3H), 6.83 – 6.81 (m, 2H), 6.77 – 6.73 (m, 1H), 6.18 (d, *J* = 8.0 Hz, 1H), 5.52 (d, *J* = 16.4 Hz, 1H), 5.21 (d, *J* = 16.4 Hz, 1H), 5.15 (d, *J* = 9.6 Hz, 1H), 4.05 (s, 1H), 3.66 – 3.60 (m, 2H), 2.82 – 2.75 (m, 1H), 2.63 – 2.57 (m, 1H), 0.57 (s, 3H), 0.28 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.8, 166.9, 165.8, 140.2, 138.8, 135.1, 134.5, 133.1, 129.4, 128.9, 128.8, 128.6, 128.5, 128.5, 127.8, 127.3, 127.0, 126.8, 126.2, 106.6, 76.2, 71.0, 69.3, 61.7, 53.3, 52.6, 46.4, 41.5, 39.8, 28.3, 27.9 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{36}NO_7$ 630.2486; Found 630.2471.

Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-1'-benzyl-4',5',7'-tris(4-bromophenyl)-8'-hydroxy-2,2-dimethyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55b): According to GP IVA, spirocyclic ene-lactam 6a (75 mg, 0.09 mmol) and mCPBA (39 mg, 0.22 mmol) in toluene (2 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get

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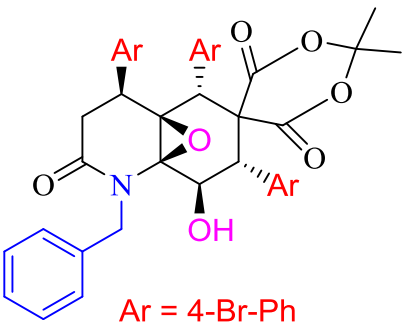
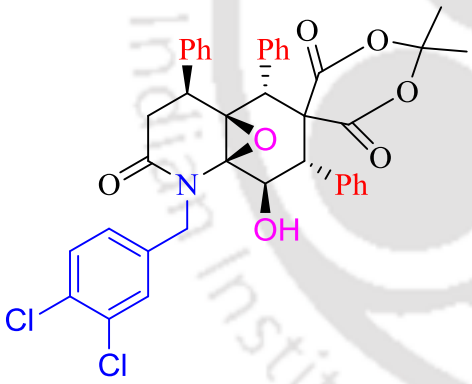
analytically pure product **7.55b** as white solid (66 mg, 84%). FTIR: ῡ = 3028, 2926, 2858, 1766, 1726, 1650, 1488, 1392, 1302, 1288, 1075, 1010, 824, 735, 699 $cm^{-1.}$ ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.45 – 7.43 (m, 8H), 7.38 – 7.33 (m, 2H), 7.20 – 7.17 (m, 3H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 2H), 6.09 (d, *J* = 7.8 Hz, 1H), 5.51 (d, *J* = 16.8 Hz, 1H), 5.14 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 9.6 Hz, 1H), 3.94 (s, 1H), 3.53– 3.49 (m, 2H), 2.72 – 2.68 (m, 1H), 2.59 – 2.55 (m, 1H), 0.68 (s, 3H), 0.42 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.3, 166.5, 165.6, 139.0, 138.4, 134.7, 133.8, 133.4, 132.5, 132.0, 131.8, 131.7, 130.7, 128.9, 128.6, 127.2, 126.8, 123.2, 122.7, 120.6, 106.9, 76.2, 70.5, 69.0, 61.1, 52.7, 52.1, 46.3, 41.1, 39.5, 28.7, 28.0 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{33}Br_3NO_7$ 865.9781; Found 865.9785.



Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-1'-(3,4-dichlorobenzyl)-8'-hydroxy-2,2-dimethyl-4',5',7'-triphenyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55c): According to GP IVA, spirocyclic ene-lactam 6a (0.10 g, 0.15 mmol) and mCPBA (65 mg, 0.38 mmol) in toluene (2 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.55c** as white solid (72 mg, 69%). FTIR: ῡ = 3030, 2928, 2856, 1766, 1725, 1651, 1455, 1365, 1292, 1270, 1203, 1030, 733, 700 $cm^{-1.}$ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.42 (m, 2H), 7.28 – 7.19 (m, 6H), 7.03 – 6.99 (m, 3H), 6.94 – 6.89 (m, 3H), 6.73 – 6.66 (m, 3H), 6.09 (d, *J* = 7.6 Hz, 1H), 5.29 (d, *J* = 16.8 Hz, 1H), 5.07 (d, *J* = 16.8 Hz, 1H), 5.04 (d, *J* = 9.6, 1H), 3.96 (s, 1H), 3.57 – 3.51 (m, 2H), 2.71 – 2.64 (m, 1H), 2.53 – 2.47 (m, 1H), 0.52 (s, 3H), 0.21 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.8, 166.8, 165.9, 139.9, 139.3, 134.9, 134.2, 133.1, 132.4, 130.8, 130.5, 129.5, 129.3, 129.1, 128.90, 128.88, 128.6, 128.5, 128.0, 127.2, 126.4, 126.23, 106.8, 76.1, 71.1, 69.6, 61.6, 53.2, 52.5, 45.6, 41.4, 39.7, 28.3, 27.9 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{34}Cl_2NO_7$ 698.1707; Found 698.1703.



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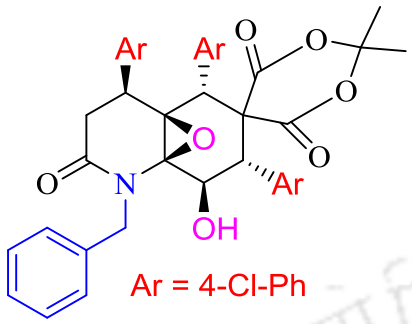
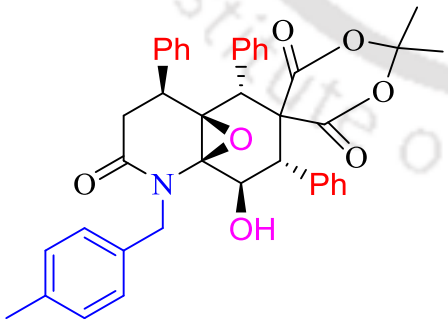
Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-1'-benzyl-4',5',7'-tris(4-chlorophenyl)-8'-hydroxy-2,2-dimethyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55d): According to GP IVA, spirocyclic ene-lactam 6a (0.10 g, 0.14 mmol) and mCPBA (62 mg, 0.36 mmol) in toluene (2 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.55d** as white solid (82 mg, 78%). FTIR: ῡ = 2956, 2927, 2856, 1765, 1728, 1650, 1415, 1392, 1290, 1192, 1094, 1015, 953, 752, 708 $cm^{-1.}$ ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.34 (m, 4H), 7.29 – 7.25 (m, 1H), 7.21 – 7.14 (m, 4H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.91 – 6.79 (s, 2H), 6.76 – 6.73 (m, 1H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.09 – 6.06 (m, 1H), 5.42 (d, *J* = 16.4 Hz, 1H), 5.05 (d, *J* = 16.4 Hz, 1H), 4.93 (d, *J* = 10.0 Hz, 1H), 3.88 (s, 1H), 3.46 – 341 (s, 2H), 2.65 – 258 (m, 1H), 2.50 – 2.48 (m, 1H), 0.59 (s, 3H), 0.33 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.3, 166.6, 165.6, 138.47, 138.45, 135.1, 134.6, 134.5, 133.3, 132.9, 132.6, 130.4, 129.6, 129.0, 128.9, 128.8, 128.6, 128.5, 127.2, 126.8, 106.9, 76.2, 70.6, 69.1, 61.3, 52.5, 52.0, 46.3, 41.0, 39.6, 28.8, 28.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{33}Cl_3NO_7$ 732.1317; Found 732.1322.



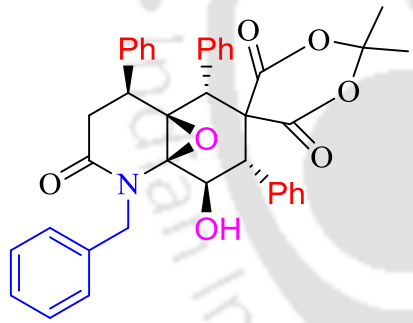
Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-8'-hydroxy-2,2-dimethyl-1'-(4-methylbenzyl)-4',5',7'-triphenyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55e): According to GP IVA, spirocyclic ene-lactam 6a (0.10 g, 0.16 mmol) and mCPBA (71 mg, 0.41 mmol) in toluene (2 mL) was reacted for 3 h and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.55e** as white solid (86 mg, 82%). FTIR: ῡ = 3030, 2928, 2858, 1727, 1650, 1455, 1364, 1291, 12868, 1181, 1062, 1031, 918, 763, 750, 700 $cm^{-1.}$ ^1H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.26 (m, 3H), 7.23 – 7.15 (m, 6H), 7.01 – 6.98 (m, 3H), 6.93 – 6.88 (m, 3H), 6.73 – 6.71 (m, 2H), 6.66 (t, *J* = 7.6 Hz, 1H), 6.09 (d, *J* = 7.8 Hz, 1H), 5.32 - 5.28 (m, 1H), 5.14 – 5.10 (m, 2H), 3.97 (s, 1H), 3.57 – 3.51 (m, 2H), 2.73 – 2.65 (m, 1H), 2.53 – 2.48 (m, 1H), 2.31 (s, 3H), 0.50 (s, 3H), 0.20 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.7, 166.9, 165.9, 140.2, 136.4, 135.6, 135.1, 134.5, 133.1, 129.40, 129.36, 129.2, 128.9,



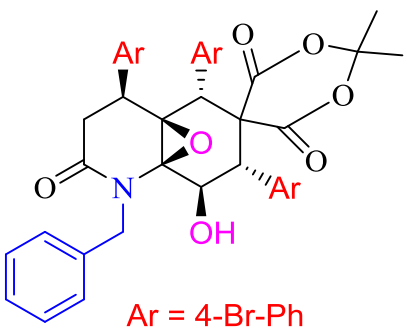
128.8, 128.6, 128.5, 127.8, 127.3, 126.6, 126.2, 106.6, 76.3, 71.0, 69.5, 61.7, 53.3, 52.6, 46.3, 41.5, 39.9, 28.4, 27.9, 21.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{40}H_{38}NO_7$ 644.2643; Found 644.2644.

General procedure for the one pot synthesis of epoxy alcohols (7.55a – 7.55e) (GP IVB): Arylaldehyde (0.94 - 0.54 mmol) was added to a solution of amine (0.38 - 0.22 mmol) and Meldrum's acid (0.63 - 0.36 mmol) in toluene and the mixture was refluxed (110 ^oC) for 24 h. After disappearance of amine (indicated by TLC), mCPBA was added to the reaction and the mixture was stirred for 4 h at rt. After consumption of intermediate spirocyclic ene lactam (indicated by TLC), toluene was removed under reduced pressure. The resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 M $NaHCO_3$ (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulphate and concentrated under vacuum. The crude mixture was purified by column chromatography to get analytically pure product

Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-1'-benzyl-8'-hydroxy-2,2-dimethyl-4',5',7'-triphenyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55a): According to GP IVB, benzaldehyde (0.10 g, 0.94 mmol), benzylamine (40 mg, 0.38 mmol), Meldrum's acid (91 mg, 0.63 mmol) and mCPBA (0.14 g, 0.79 mmol) in toluene (2 mL) was reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.55a** as white solid (93 mg, 47%).



Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-1'-benzyl-4',5',7'-tris(4-bromophenyl)-8'-hydroxy-2,2-dimethyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55b): According to GP IVB, p-bromobenzaldehyde (0.10 g, 0.54 mmol), benzylamine (23 mg, 0.22 mmol), Meldrum's acid (52 mg, 0.36 mmol) and MCPBA (78 mg, 0.45 mmol) in toluene (2 mL) was reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.55b** as white solid (83 mg, 53%).



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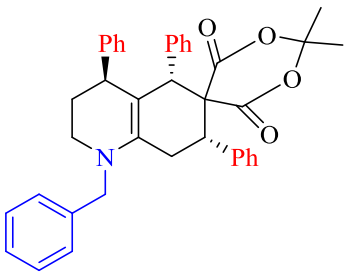
Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-1'-(3,4-dichlorobenzyl)-8'-hydroxy-2,2-dimethyl-4',5',7'-triphenyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55c): According to GP IVB, benzaldehyde (0.10 g, 0.94 mmol), benzylamine (66 mg, 0.38 mmol), Meldrum's acid (91 mg, 0.63 mmol) and MCPBA (0.14 g, 0.79 mmol) in toluene (2 mL) was reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.55c** as white solid (95 mg, 43%).

Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-1'-benzyl-4',5',7'-tris(4-chlorophenyl)-8'-hydroxy-2,2-dimethyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55d): According to GP IVB, 4-chlorobenzaldehyde (0.10 g, 0.71 mmol), benzylamine (31 mg, 0.29 mmol), Meldrum's acid (69 mg, 0.48 mmol) and mCPBA (0.10 g, 0.60 mmol) in toluene (2 mL) was reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.55d** as white solid (88 mg, 51%).

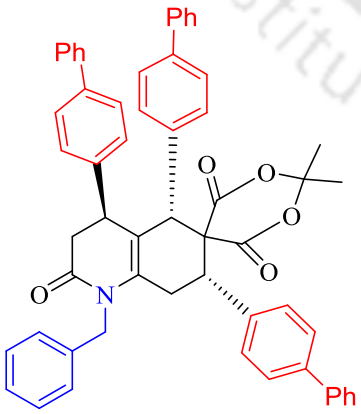
Rac-(*4'S,4a'S,5'R,7'S,8'R,8a'R*)-8'-hydroxy-2,2-dimethyl-1'-(4-methylbenzyl)-4',5',7'-triphenyltetrahydro-*5'H*-spiro[[1,3]dioxane-5,6'-[4a,8a]epoxyquinoline]-2',4,6(*1'H*)-trione (7.55e): According to GP IVB, benzaldehyde (0.10 g, 0.94 mmol), 4-methylbenzylamine (46 mg, 0.38 mmol), Meldrum's acid (91 mg, 0.63 mmol) and mCPBA (0.14 g, 0.79 mmol) was in toluene (2 mL) reacted for 28 h (24 h + 4 h) and the crude mixture was purified by column chromatography (Silica gel; EtOAc: Hexane, 1:4) to get analytically pure product **7.55e** as white solid (0.11 g, 54%).

Rac-(*4S,5S,7S*)-1-benzyl-2',2'-dimethyl-4,5,7-triphenyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-4',6'-dione (7.56): Compound 6a (50 mg, 0.08 mmol) was



treated with $LiAlH_4$ (13 mg, 0.34 mmol) in 2 mL THF at r.t for 12 h. After completion of reaction THF was evaporated and resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 (N) HCl (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulphate and concentrated under vacuum to give crude product which was further purified by column chromatography (SiO_2; EtOAc : Hexane, 1:3) to afford **7.56** as colourless gum (30 mg, 61%). FTIR: ῡ = 3058, 3026, 2993, 1560, 1494, 1447, 1386, 1257, 1202, 1113, 1030, 747, 732, 699 $cm^{-1.}$ ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, *J* = 7.4 Hz, 2H), 7.35 – 7.29 (m, 3H), 7.26 – 7.18 (m, 7H), 7.10 – 7.00 (m, 4H), 6.86 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 6.4 Hz, 2H), 6.27 (d, *J* = 7.6 Hz, 1H), 4.39 – 4.21 (m, 3H), 3.85 (dd, *J* = 12.4, 5.2 Hz, 1H), 3.42 – 3.35 (m, 1H), 3.17 (t, *J* = 6.6 Hz, 1H), 2.99 – 2.97 (m, 2H), 2.69 (dd, *J* = 16.4, 5.2 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.69 – 1.62 (m, 1H), 0.52 (s, 3H), 0.39 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.8, 164.4, 145.1, 140.3, 139.8, 139.0, 138.1, 131.7, 130.0, 129.0, 128.9, 128.5, 128.3, 128.2, 128.1, 127.5, 127.3, 126.9, 125.8, 105.3, 102.9, 60.4, 54.2, 53.9, 47.3, 46.4, 41.9, 32.7, 30.9, 28.46, 28.3 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{38}NO_4$ 584.2795; Found 584.2781. (Structure was further confirmed by DEPT-135 as one $–CH_2$ carbon increased)

Rac-((*4S,5S,7S*)-4,5,7-tri([1,1'-biphenyl]-4-yl)-1-benzyl-2',2'-dimethyl-1,3,4,5,7,8-hexahydro-*2H*-spiro[quinoline-6,5'-[1,3]dioxane]-2,4',6'-trione (7.57): Phenylboronic



acid (32 mg, 0.26 mmol), $Ba(OH)_2$, $8H_2O$ (0.10 g, 0.31 mmol), $Pd(PPh_3)_4$ (8 mg, 3.3 mol%), H_2O (0.5 mL), and 6a (50 mg, 0.059 mmol) in 1,4-dioxane (1.4 mL), were refluxed for 48 h under inert atmosphere. After completion of reaction 1,4-dioxane was removed under reduced pressure. The resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 M HCl (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulphate and concentrated under vacuum to give crude product which was further purified by column chromatography (SiO_2; EtOAc : Hexane, 1:3) to afford **7.57** as white solid (42 mg, 86%). FTIR: ῡ = 3063, 3028, 22923, 1766, 1728, 1672,

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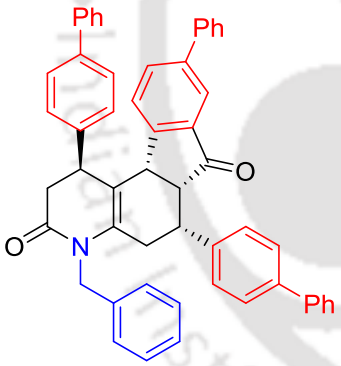
1486, 1389, 1276, 1194, 1073, 1009, 829, 734, 697 $cm^{-1.}$ ^1H NMR (600 MHz, $CDCl_3$) δ = 7.69 – 7.68 (m, 1H), 7.62 – 7.54 (m, 8H), 7.51 – 7.44 (m, 8H), 7.43 – 7.37 (m, 4H), 7.32 – 7.27 (m, 6H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 6.6 Hz, 1H), 5.42 (d, *J* = 16.2 Hz, 1H), 4.82 (d, *J* = 16.2 Hz, 1H), 4.76 (s, 1H), 3.91 – 3.88 (m, 1H), 3.59 (t, *J* = 5.6 Hz, 1H), 3.54 – 3.40 (m, 1H), 3.16 – 3.12 (m, 1H), 3.00 – 2.97 (m, 1H), 2.90 – 2.86 (m, 1H), 0.65 (s, 3H), 0.57 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.3, 169.2, 164.0, 141.4, 141.1, 140.8, 140.11, 140.09, 139.9, 139.7, 137.8, 136.5, 136.4, 134.8, 131.8, 129.4, 129.2, 128.90, 128.89, 128.79, 128.65, 128.0, 127.71, 127.68, 127.65, 127.4, 127.24, 127.18, 127.0, 126.92, 126.90, 126.8, 113.5, 106.0, 60.8, 53.1, 46.9, 44.7, 39.2, 38.5, 30.2, 28.5, 28.4 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{57}H_{48}NO_5$ 826.3527; Found 826.3577. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{57}H_{48}NO_5$ 826.3527; Found 826.3529.

Rac-(*1S,6R,6aR,11bS*)-1,6-di([1,1'-biphenyl]-4-yl)-4-benzyl-9-phenyl-1,4,5,6,6a,11b-hexahydro-*3H*-indeno[1,2-f]quinoline-3,7(*2H*)-dione (7.58): Compound 6a (50 mg, 0.06 mmol) was refluxed with TfOH (45 mg, 0.30 mmol) in 2 mL DCM for 3 h. After completion of reaction resulting mass was diluted with CH_2Cl_2 (30 mL), and the mixture was washed with 1 (N) NaOH (3 × 20 mL) and then with brine solution (2 × 20 mL). Combined organic layers were dried over sodium sulphate and concentrated under vacuum to give crude product which was further purified by column chromatography (SiO_2; EtOAc : Hexane, 1:3) to afford **7.58** as colourless gum (26 mg, 72%).



FTIR: ῡ = 3030, 2958, 2925, 1711, 1673, 1601, 1487, 1453, 1389, 1261, 1180, 1076, 839, 762, 697 $cm^{-1.}$ ^1H NMR (400 MHz, $CDCl_3$) δ = 7.86 – 7.85 (m, 2H), 7.69 – 7.62 (m, 5H), 7.60 – 7.58 (m, 5H), 7.53 – 7.38 (m, 12H), 7.37 – 7.32 (m, 2H), 7.21 – 7.19 (m, 3H), 7.06 – 7.04 (m, 2H), 5.20 (d, *J* = 16.2 Hz, 1H), 4.74 (d, *J* = 16.2 Hz, 1H), 4.32 (d, *J* = 6.6 Hz, 1H), 4.10 – 4.07 (m, 1H), 3.55 (d, *J* = 5.2 Hz, 1H), 3.53 – 3.49 (m, 1H), 3.45 – 3.36 (m, 1H), 2.97 – 2.87 (m, 1H), 2.84 – 2.71 (m, 2H). ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 204.7, 168.6, 153.8, 141.5, 140.9, 140.7, 140.5, 140.2, 139.8, 139.7, 139.5, 137.7, 137.7, 135.9, 133.4, 129.0, 128.9, 128.73, 128.67, 128.22, 128.19, 128.0, 127.5, 127.22, 127.15, 127.13, 127.12, 127.08, 126.9, 126.7, 126.3, 122.2, 117.0, 65.34, 53.3, 40.5, 30.1, 29.1, 23.3, 23.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{53}H_{42}NO_2$ 724.3210; Found 724.3215.

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CHAPTER 8

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

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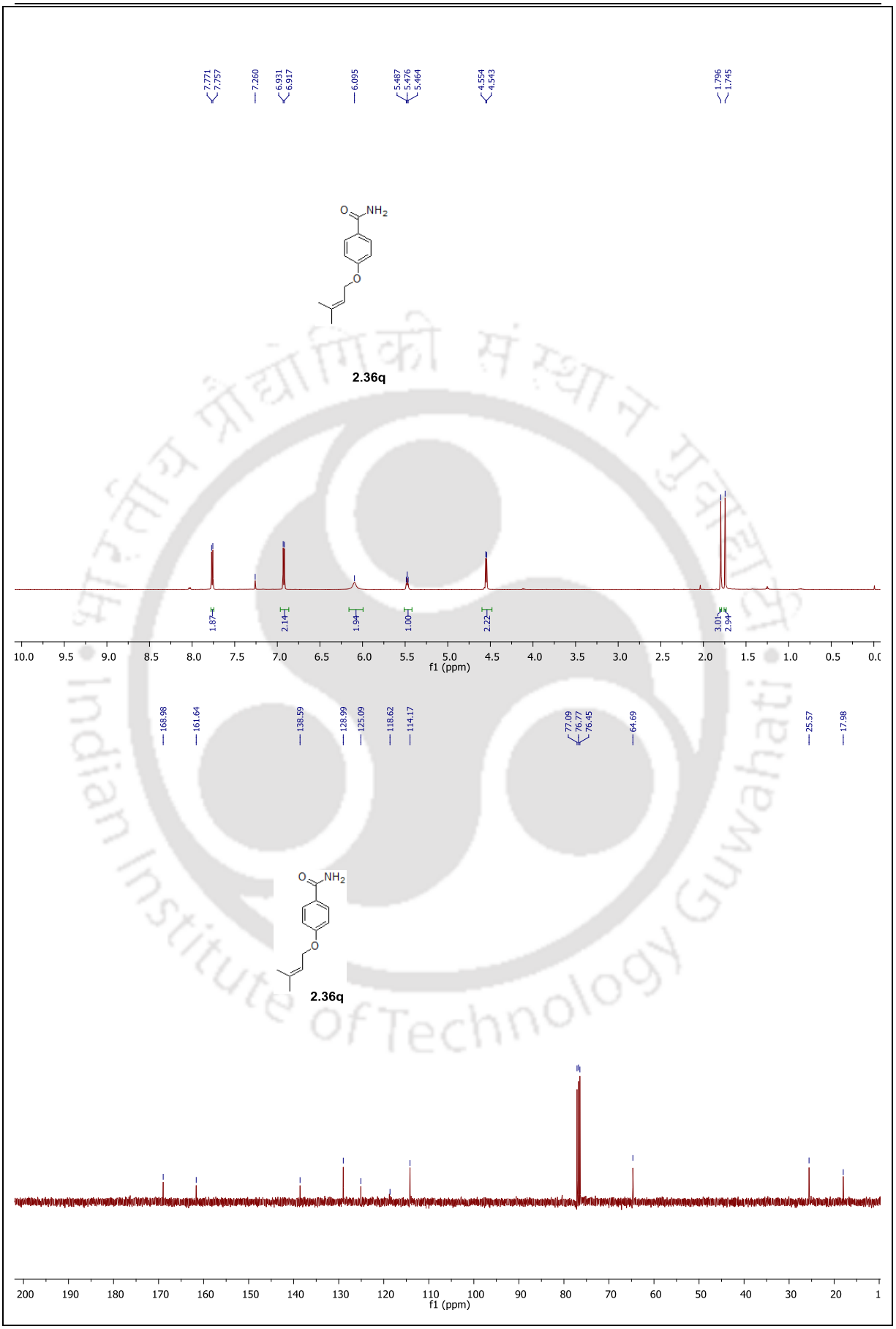

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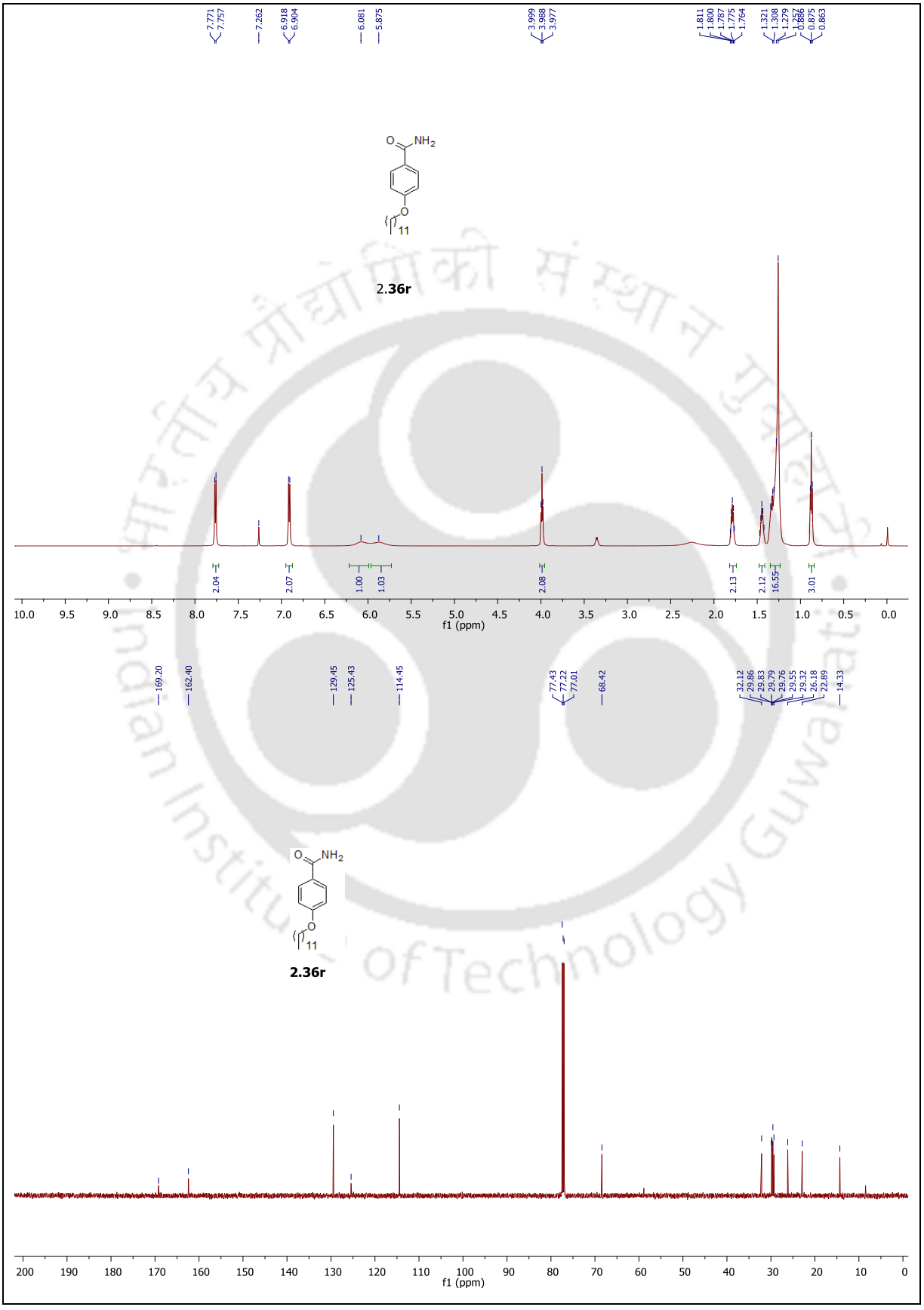

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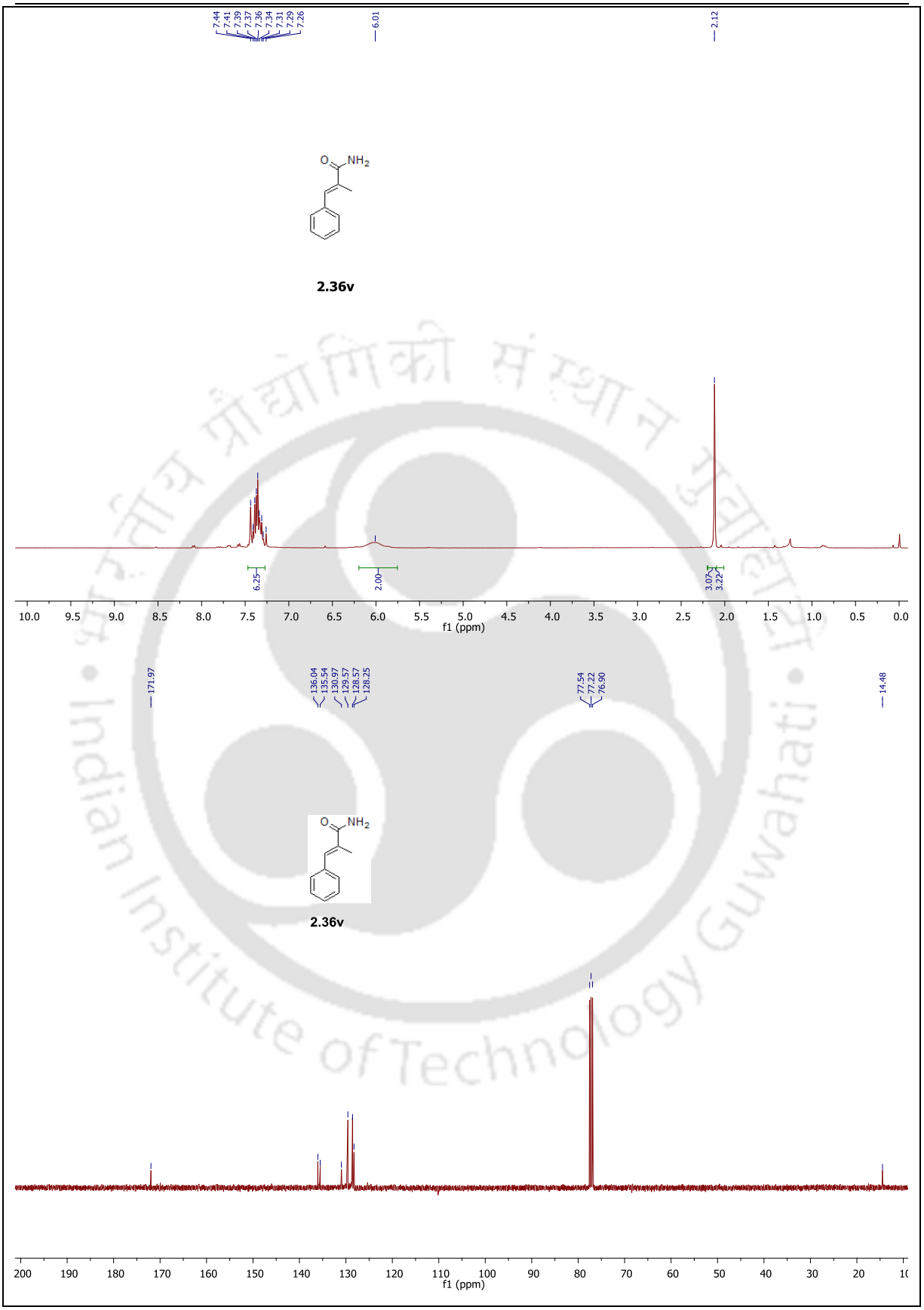

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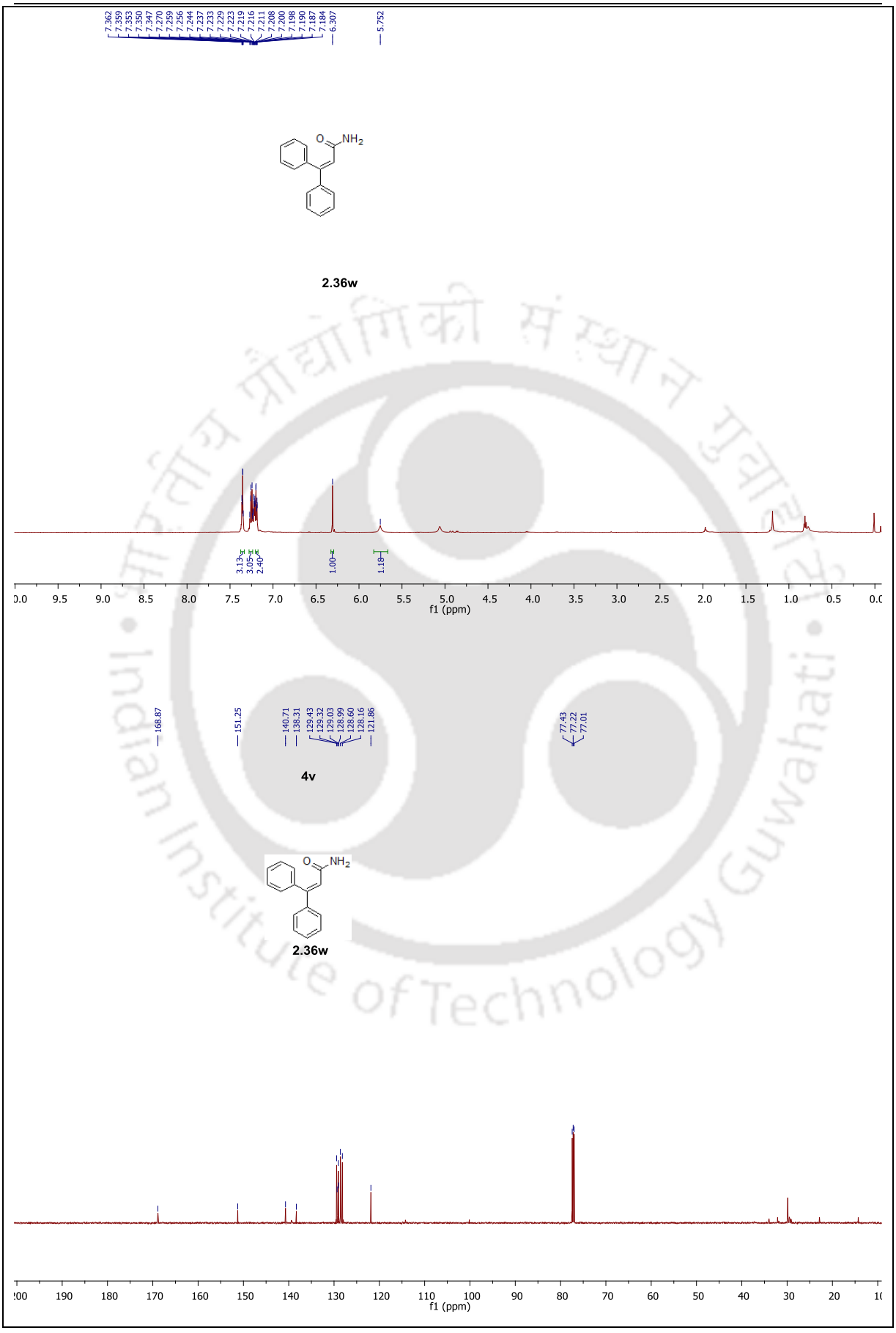

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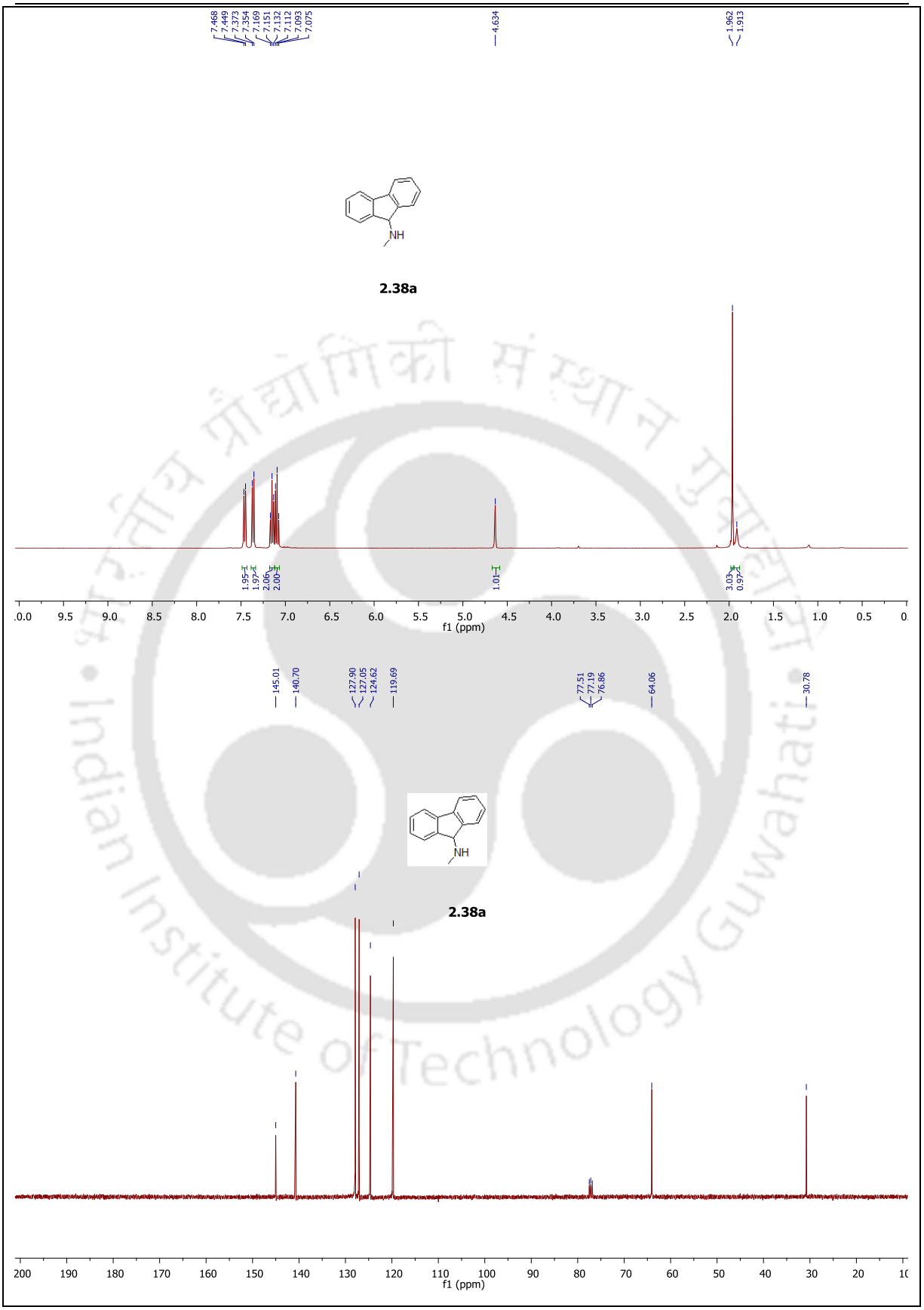

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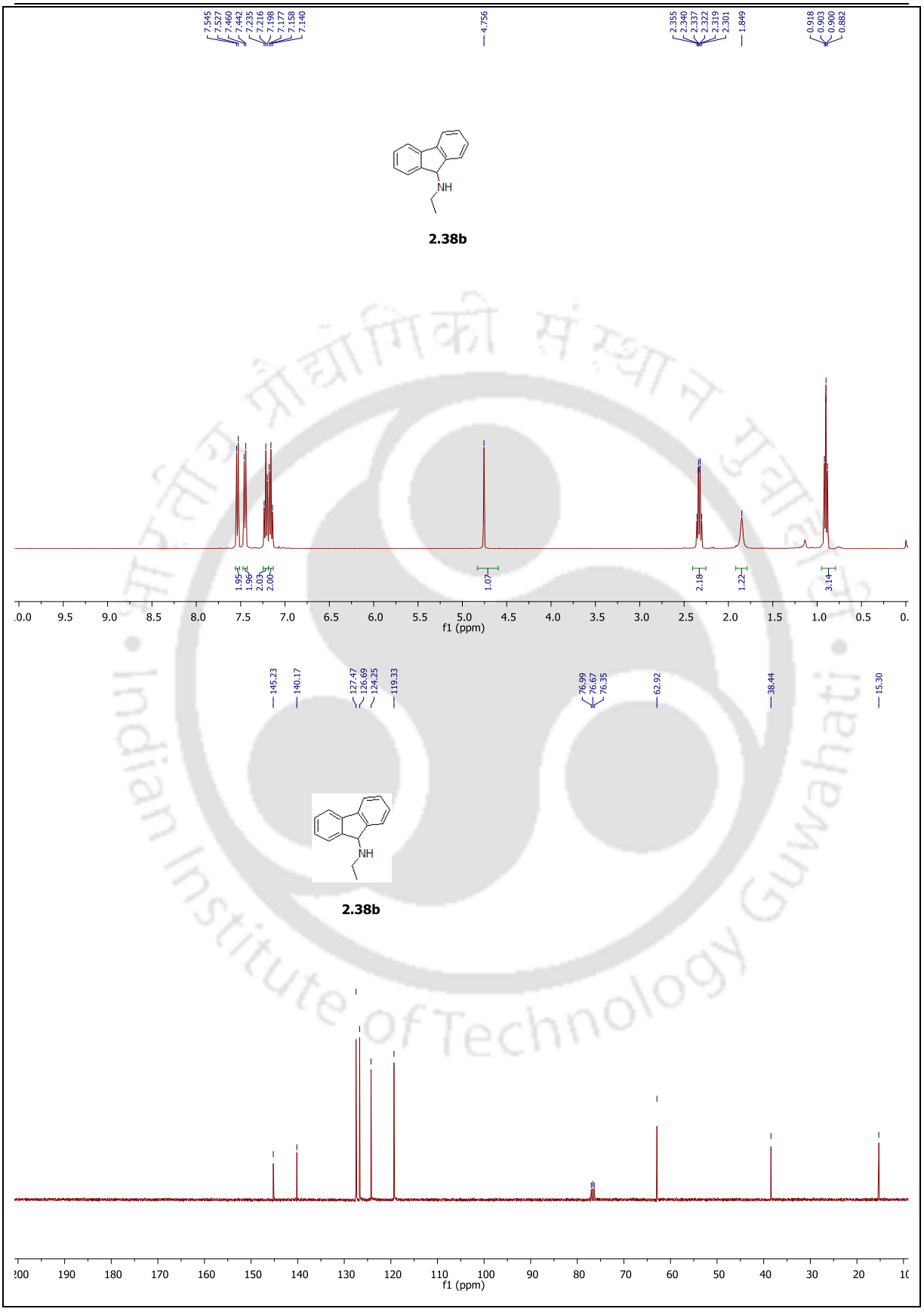

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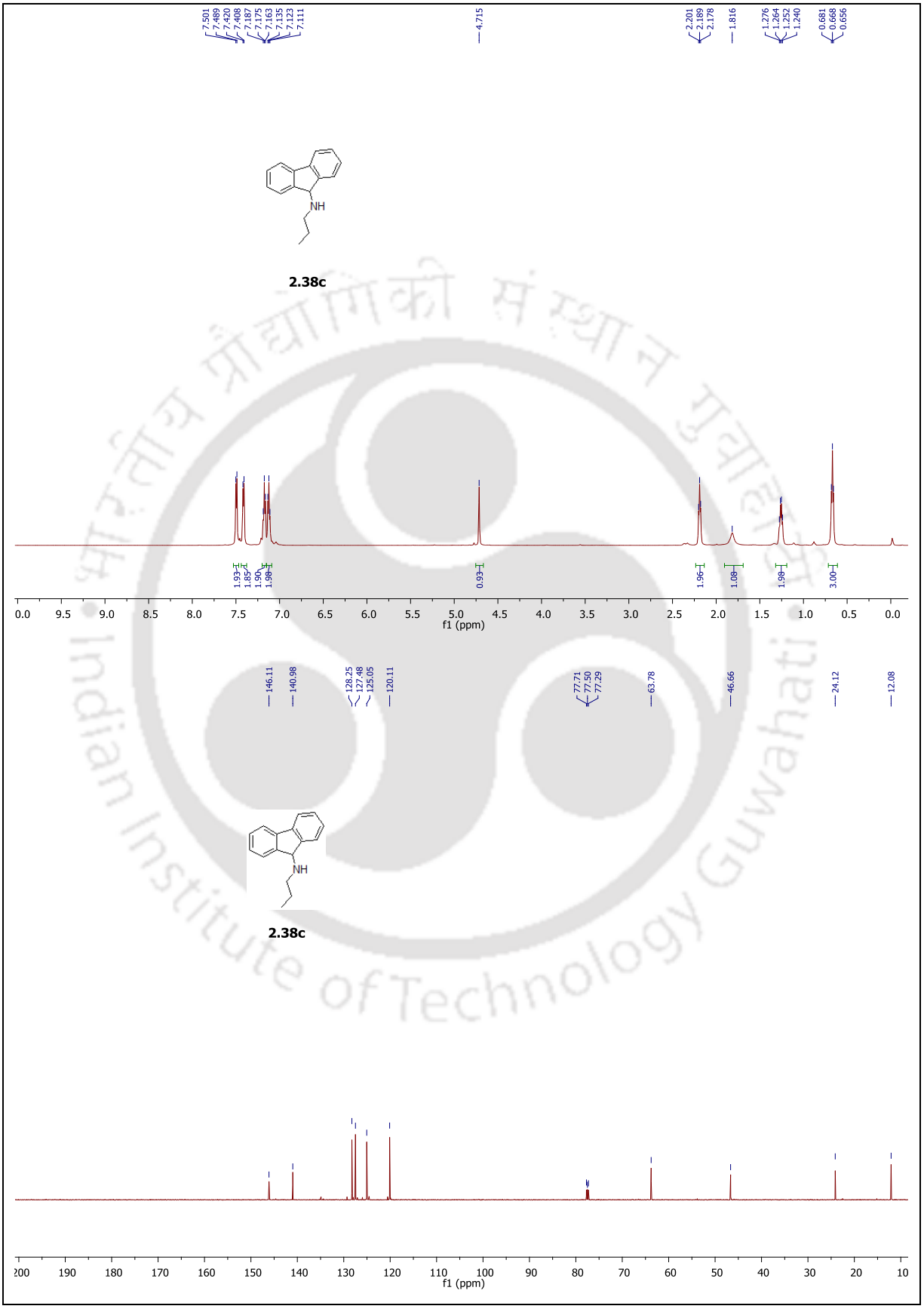

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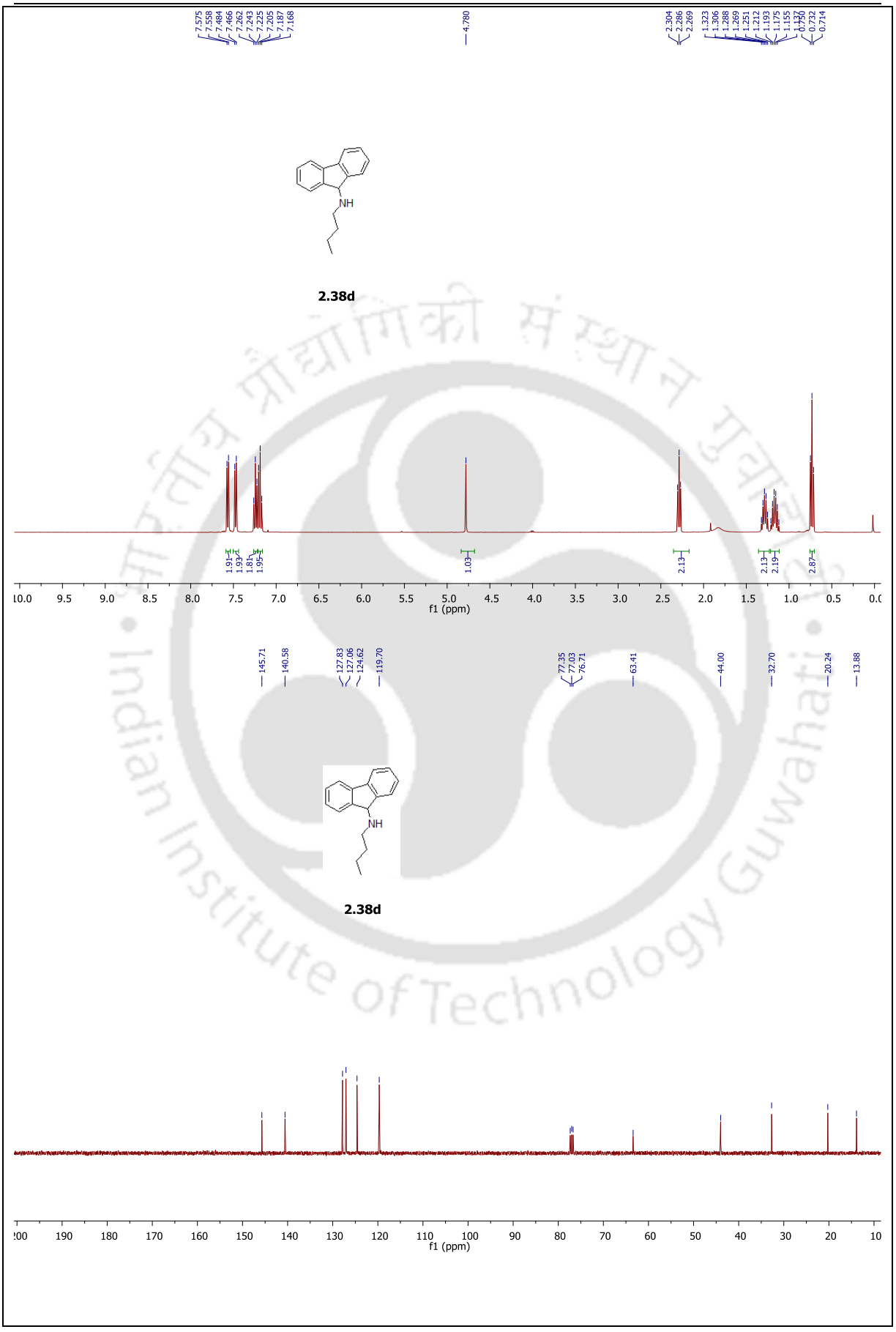

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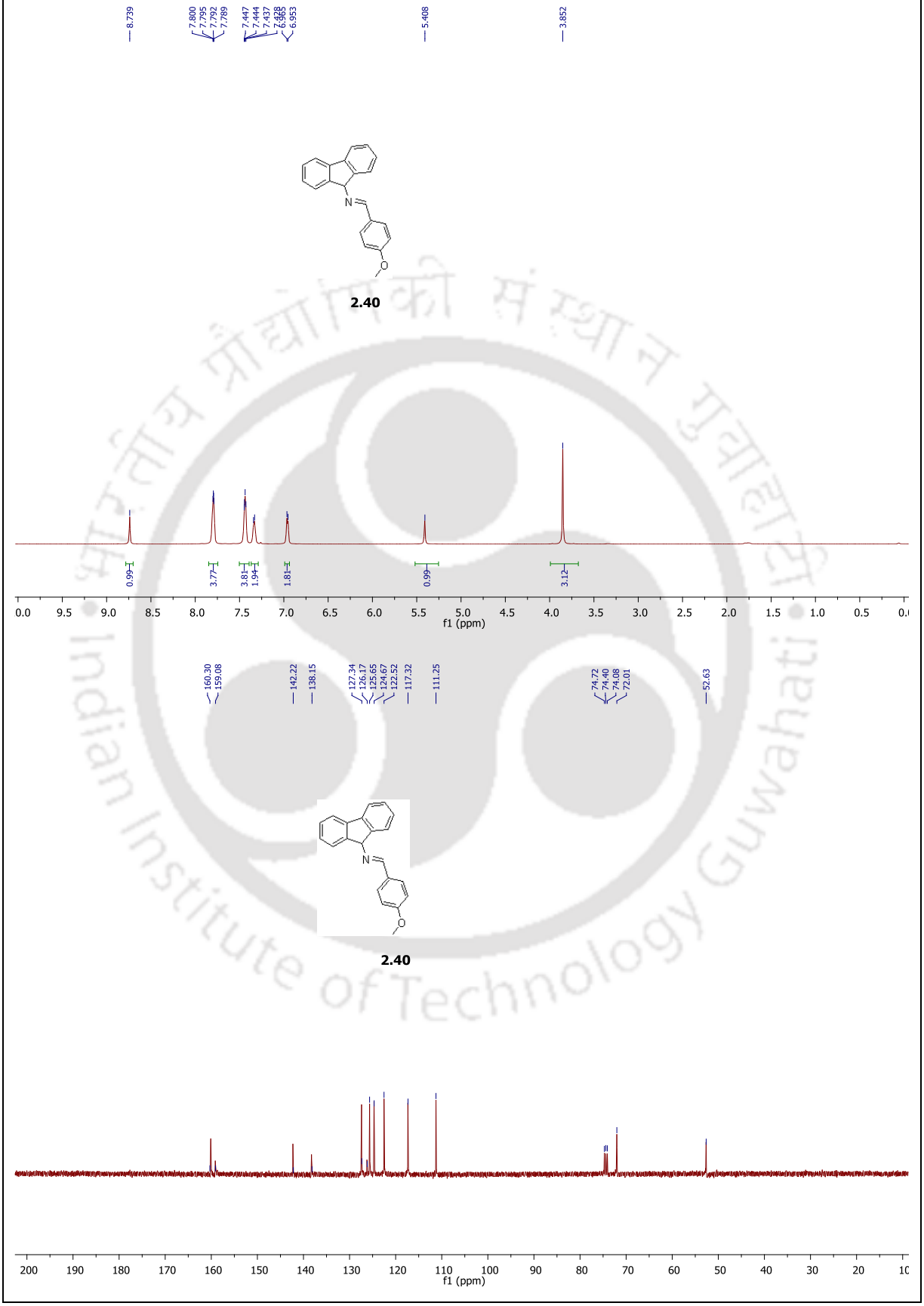

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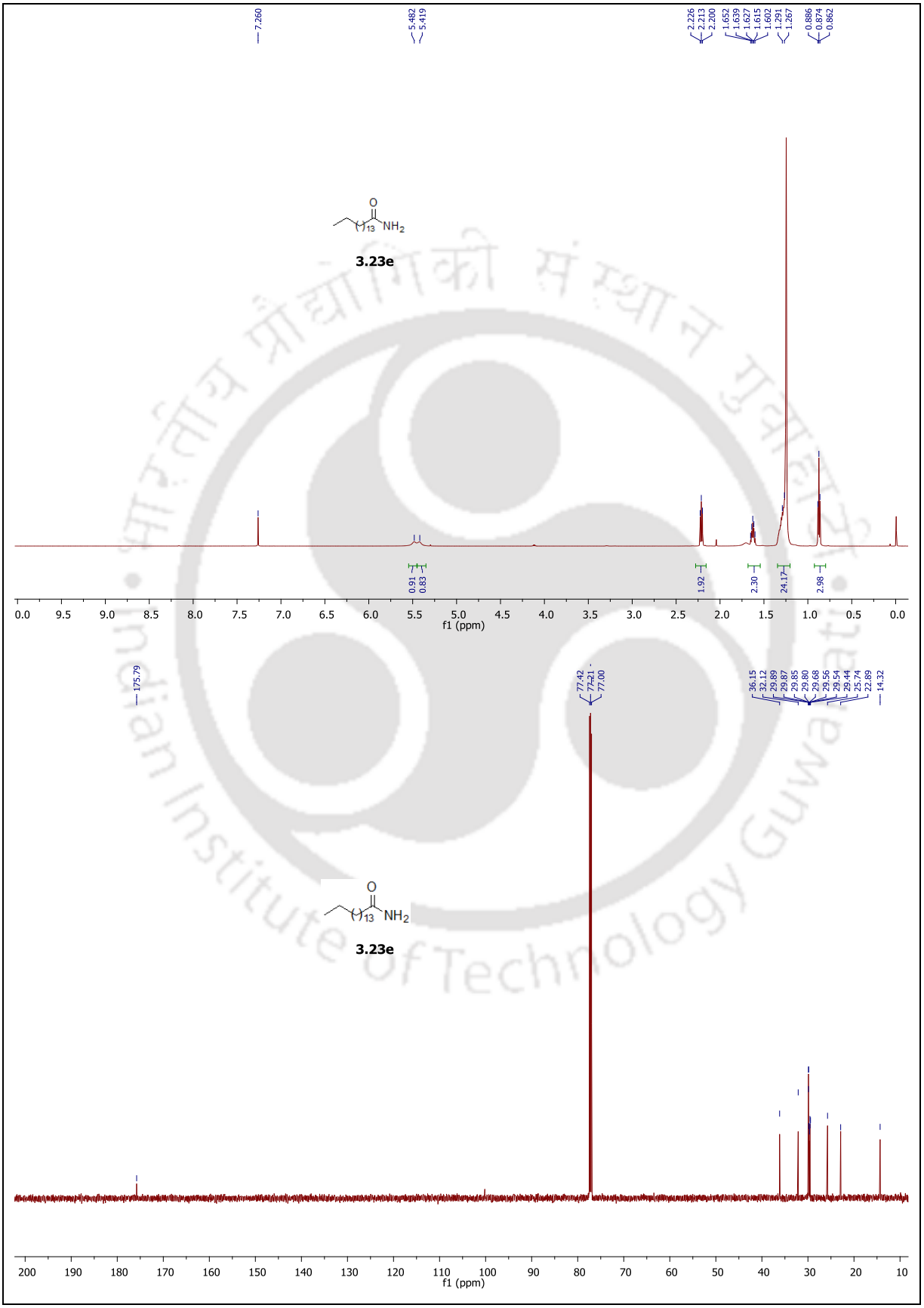

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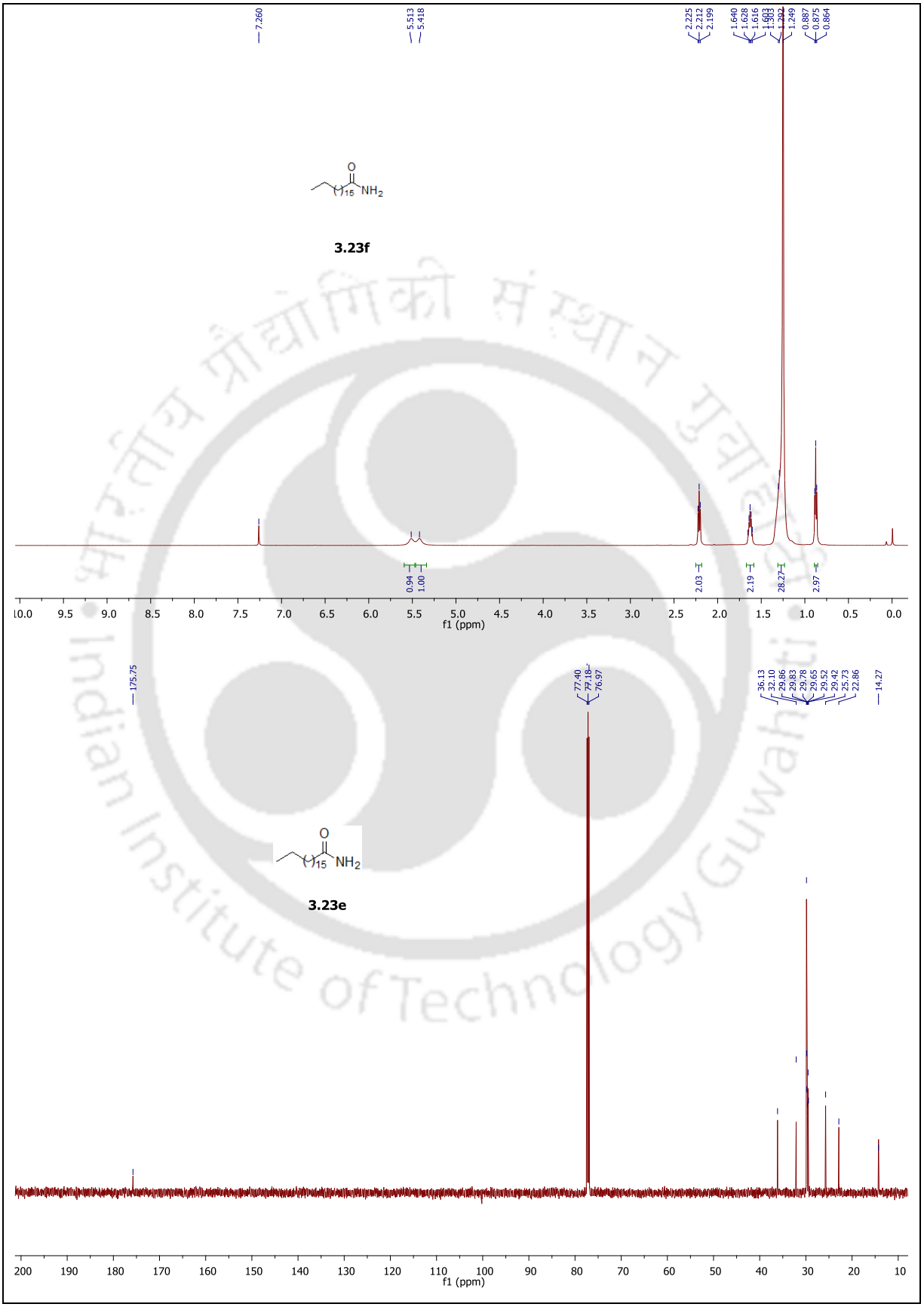

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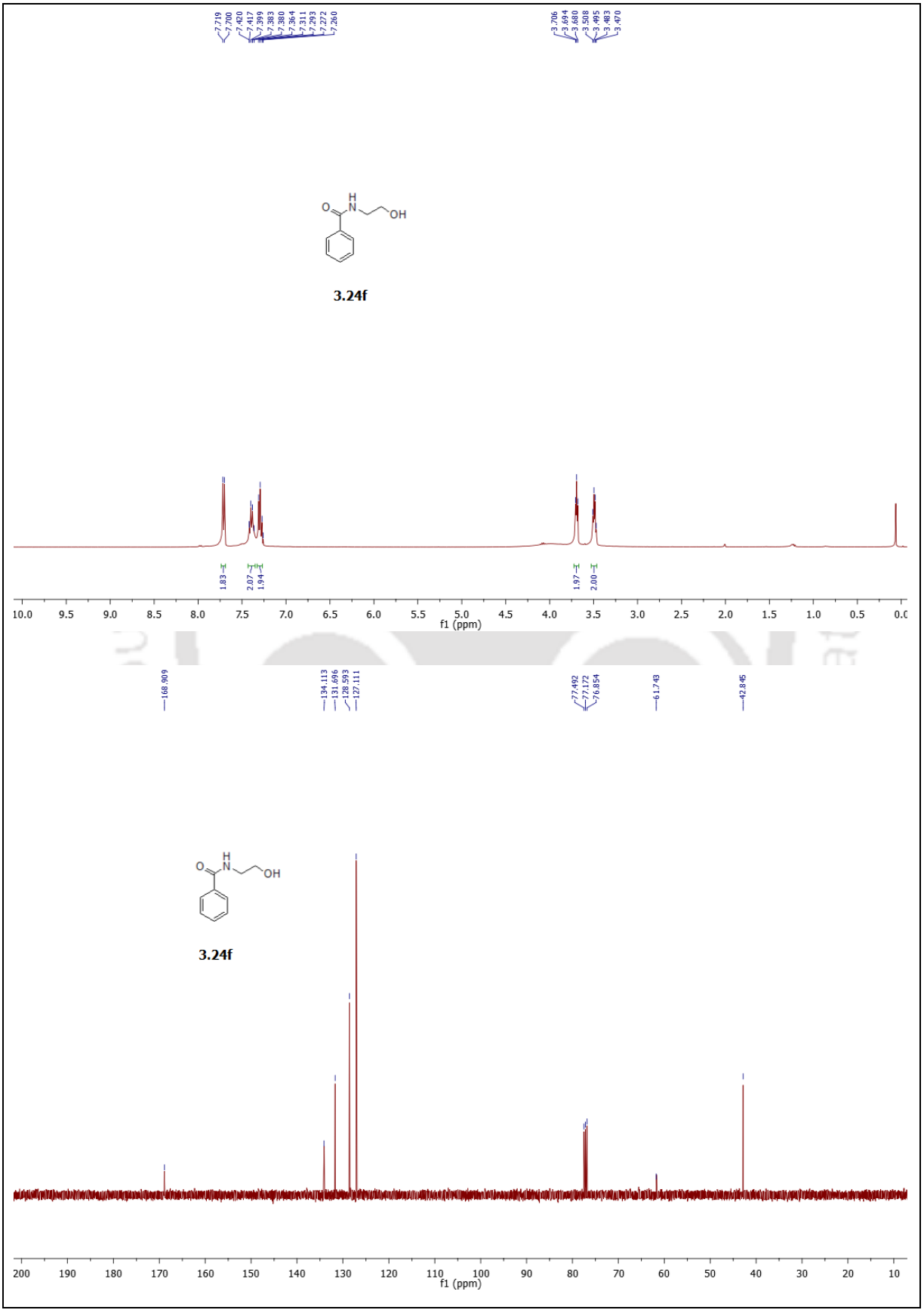

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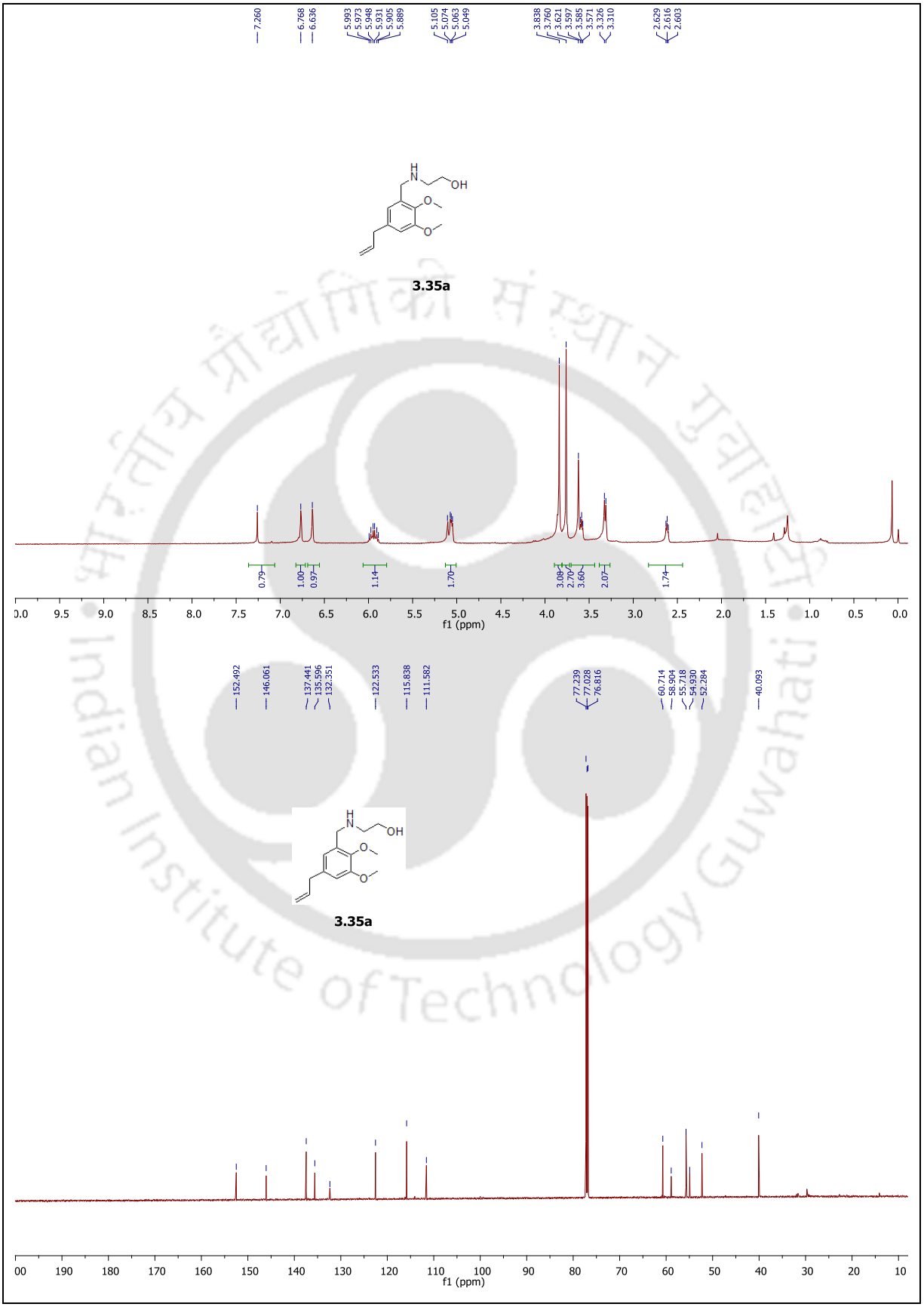

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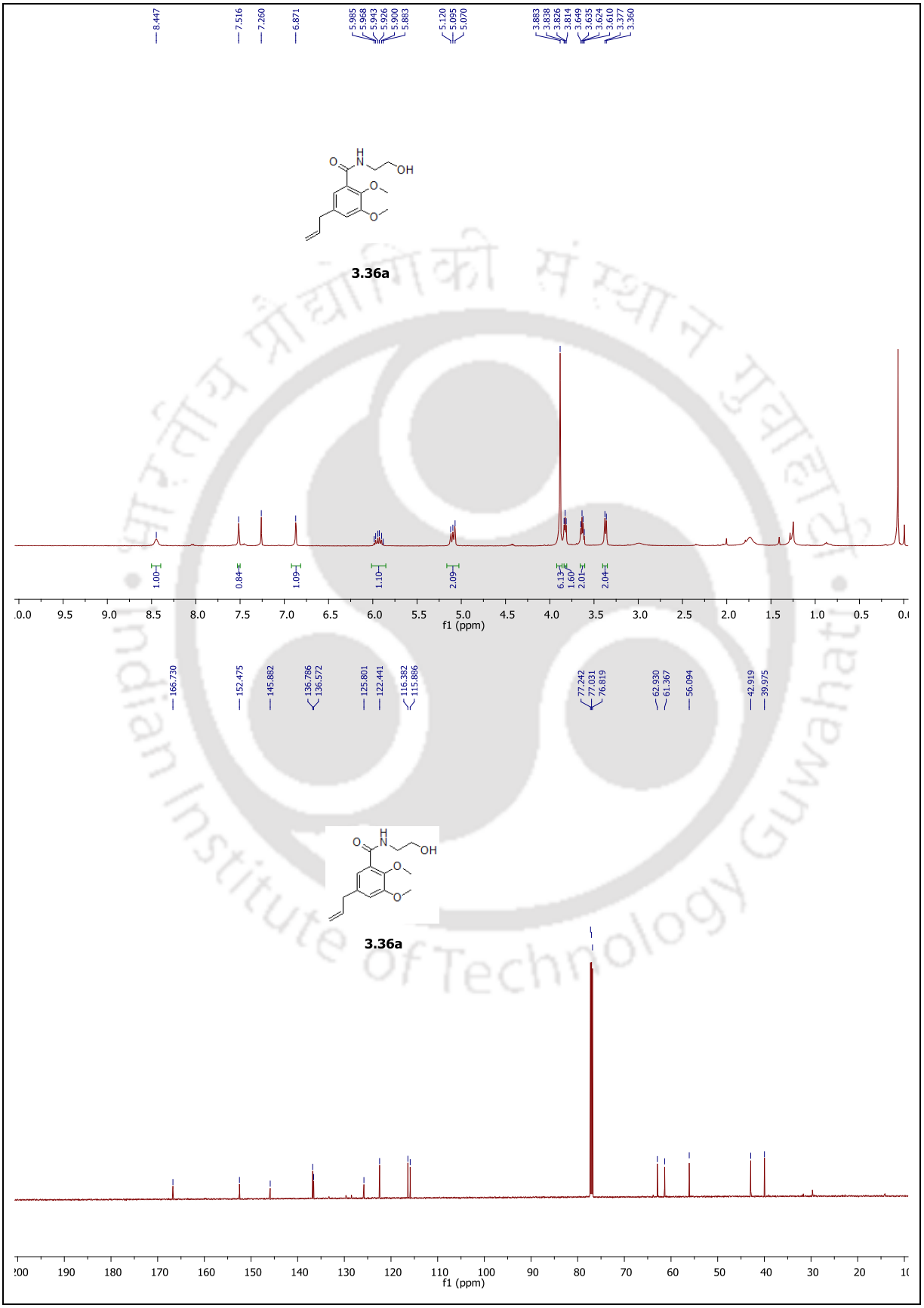

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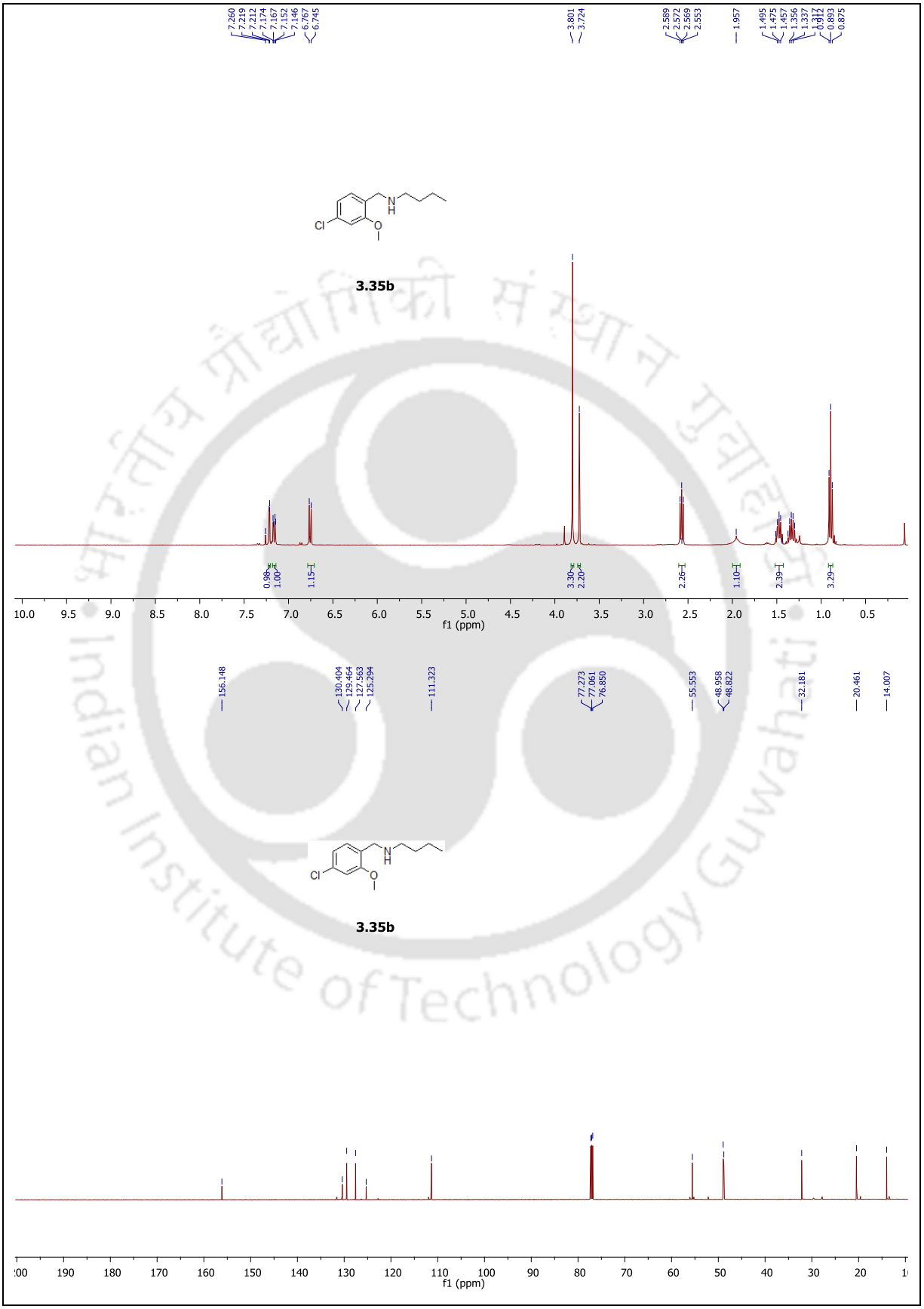

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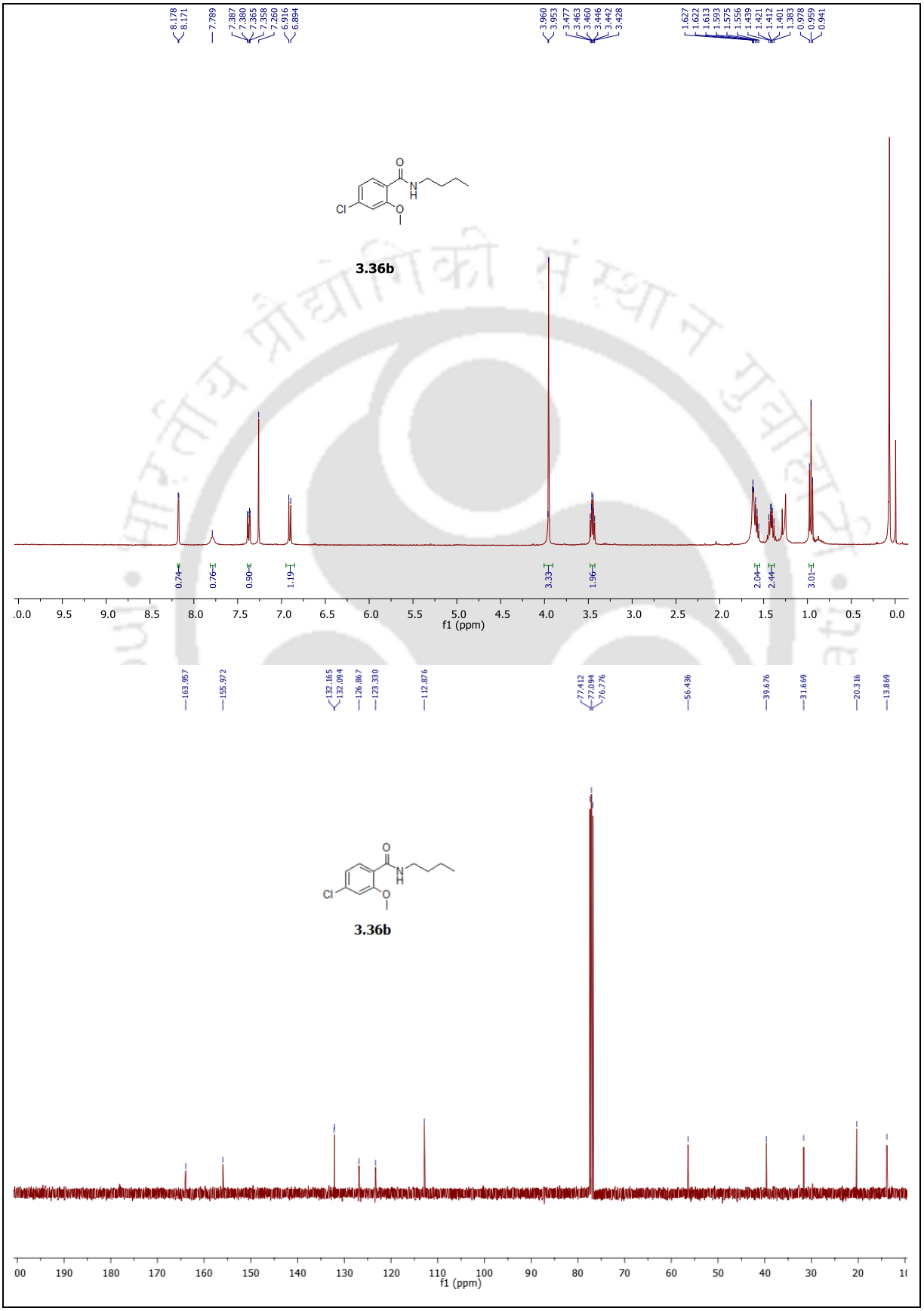

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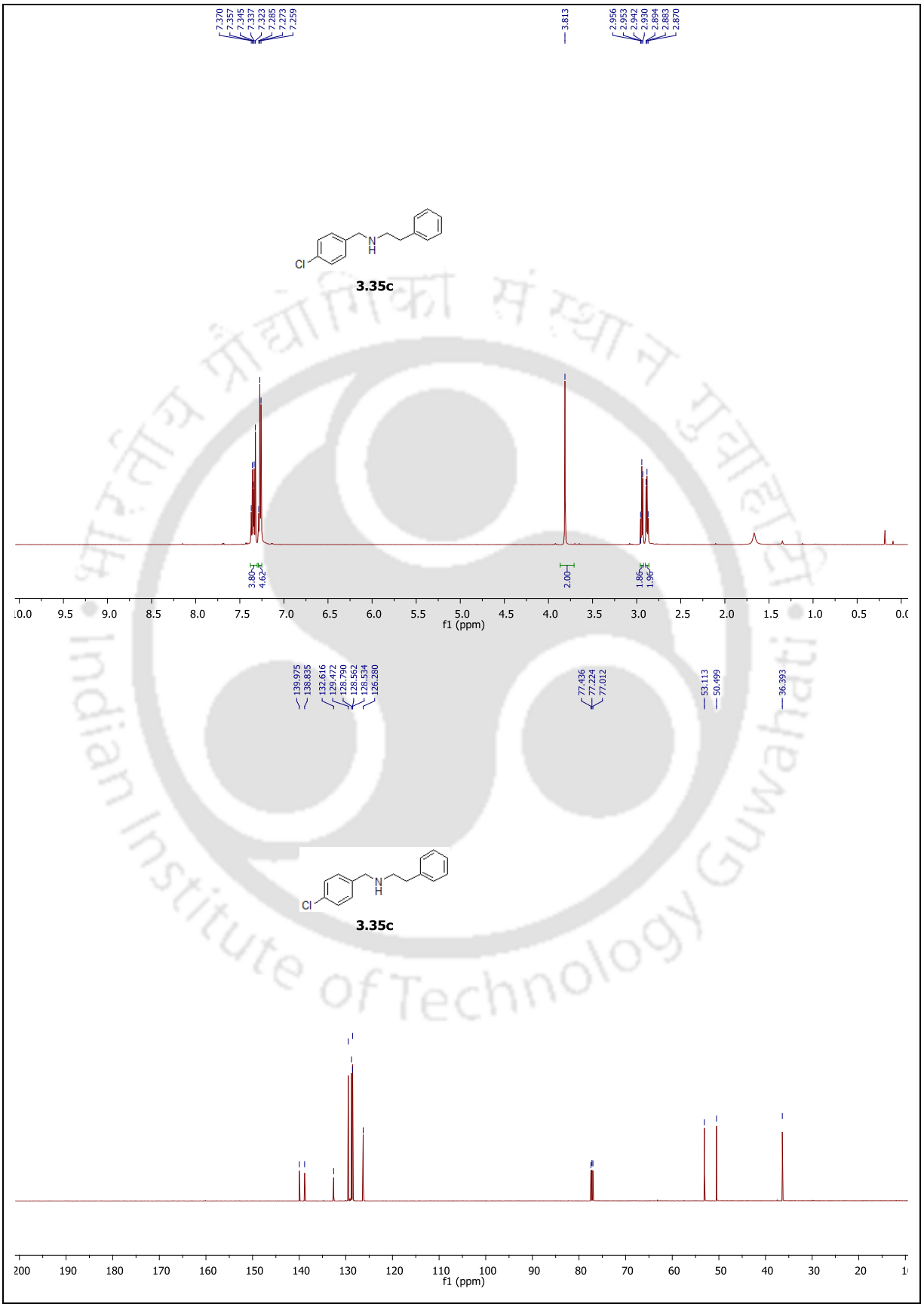

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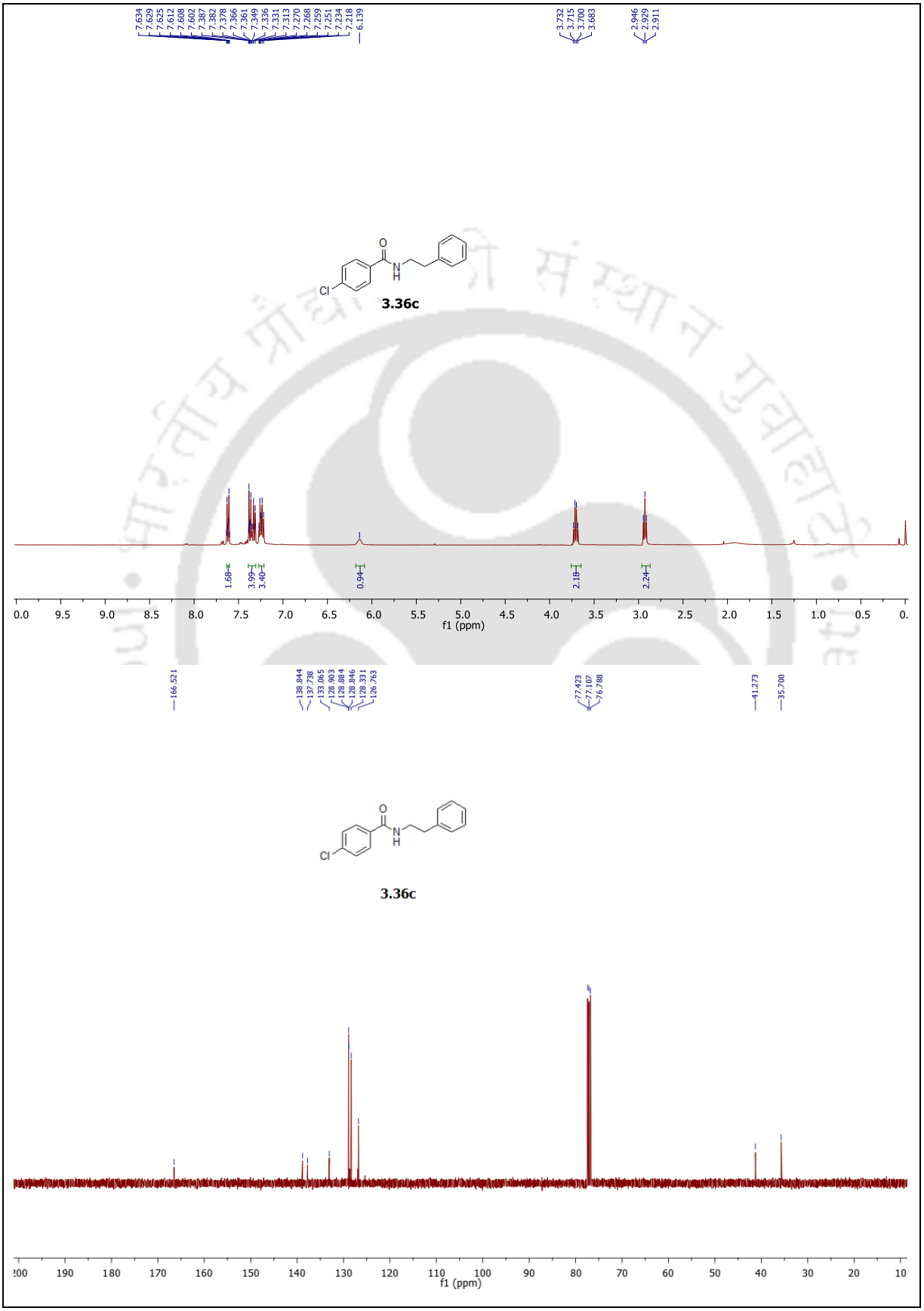

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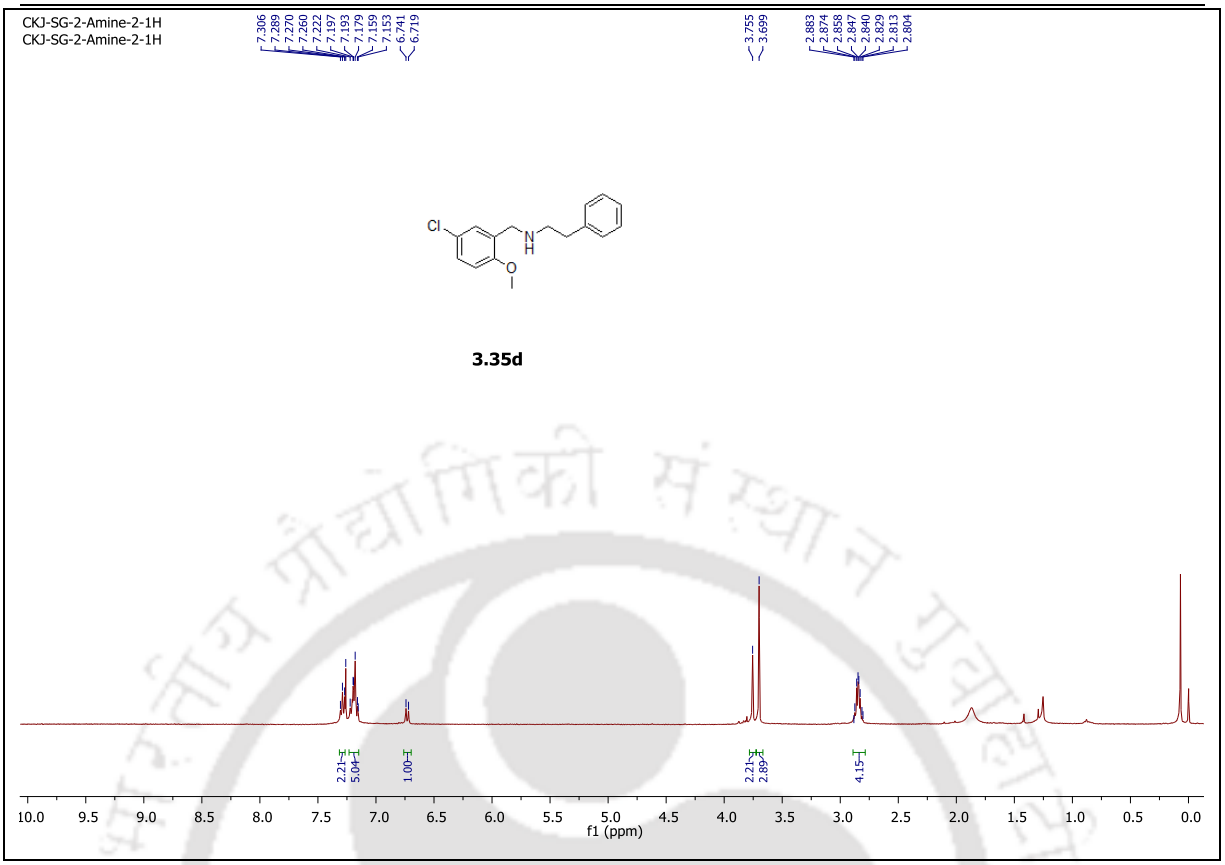

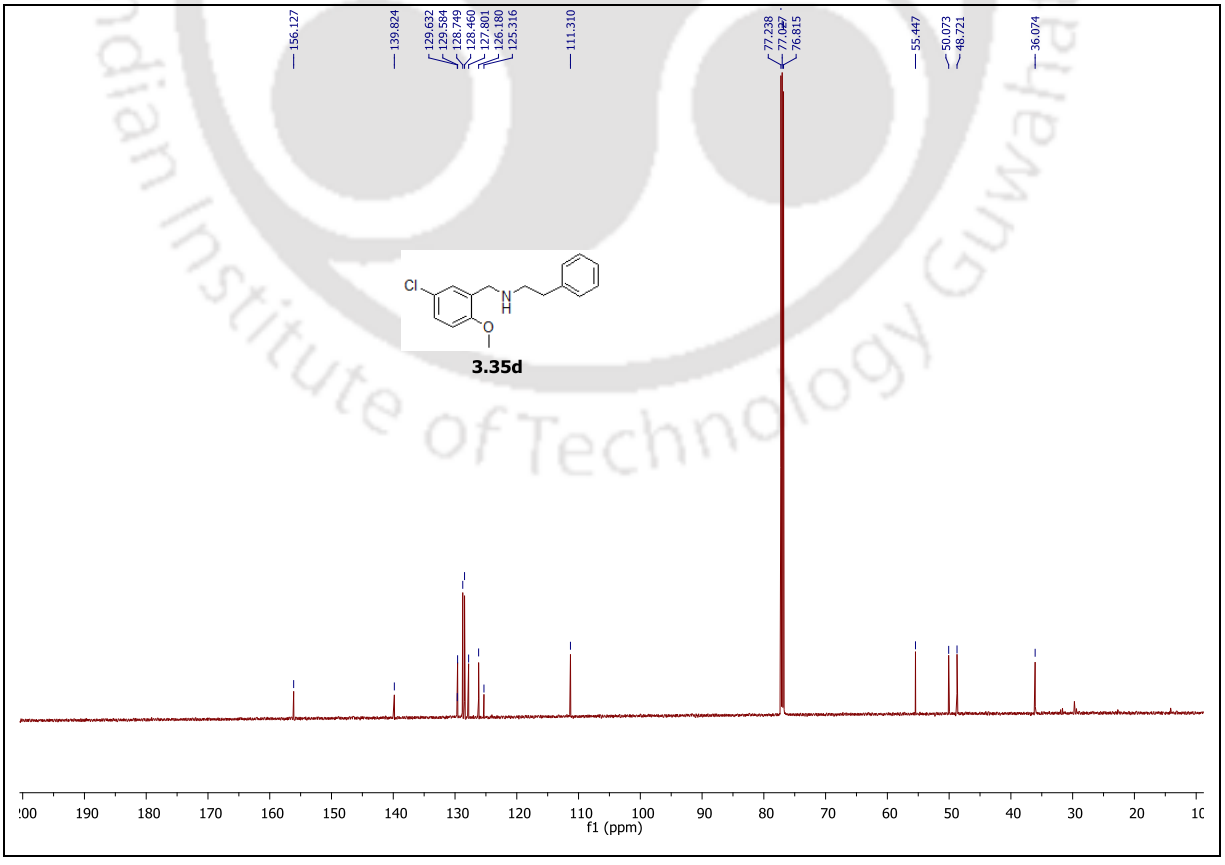

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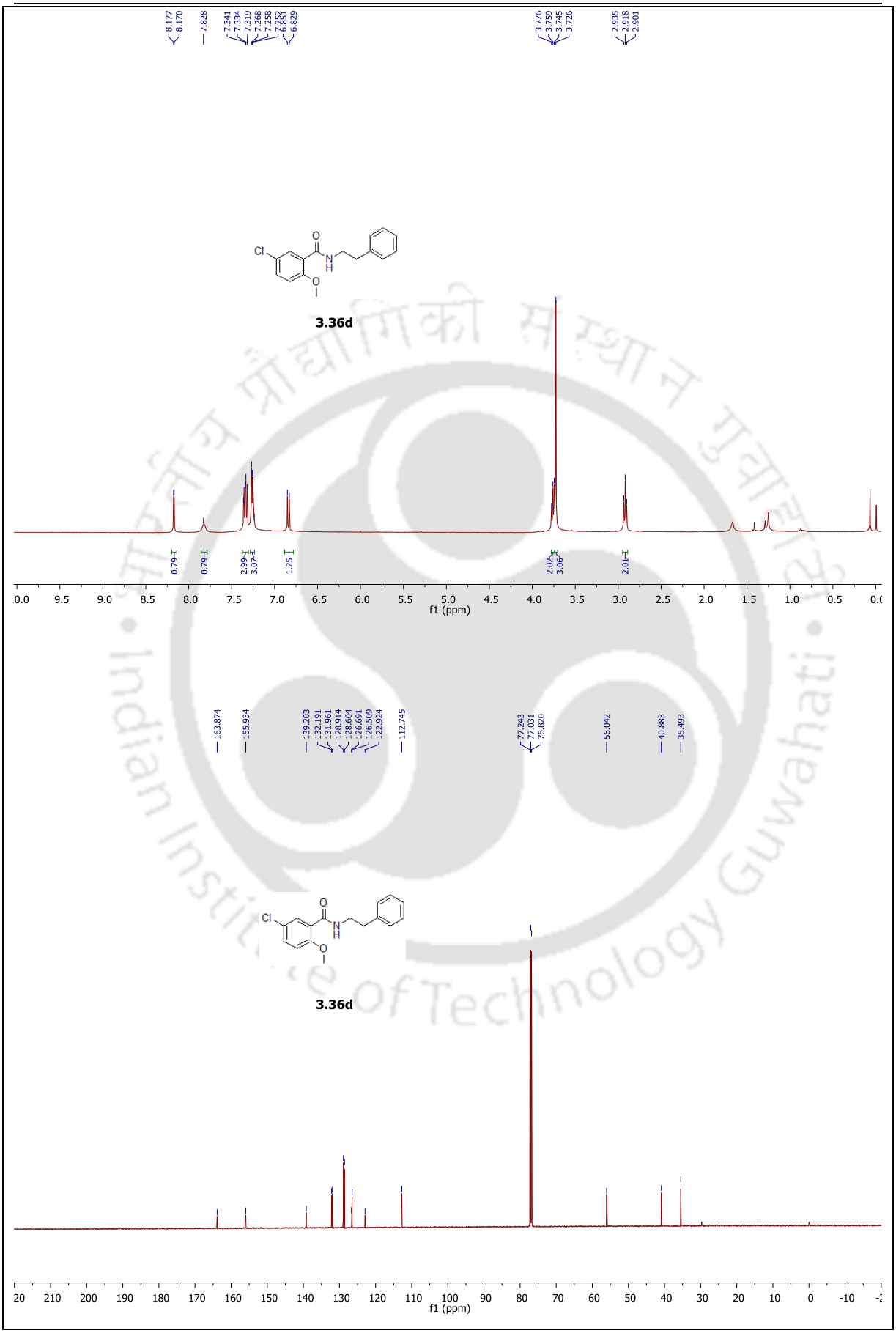

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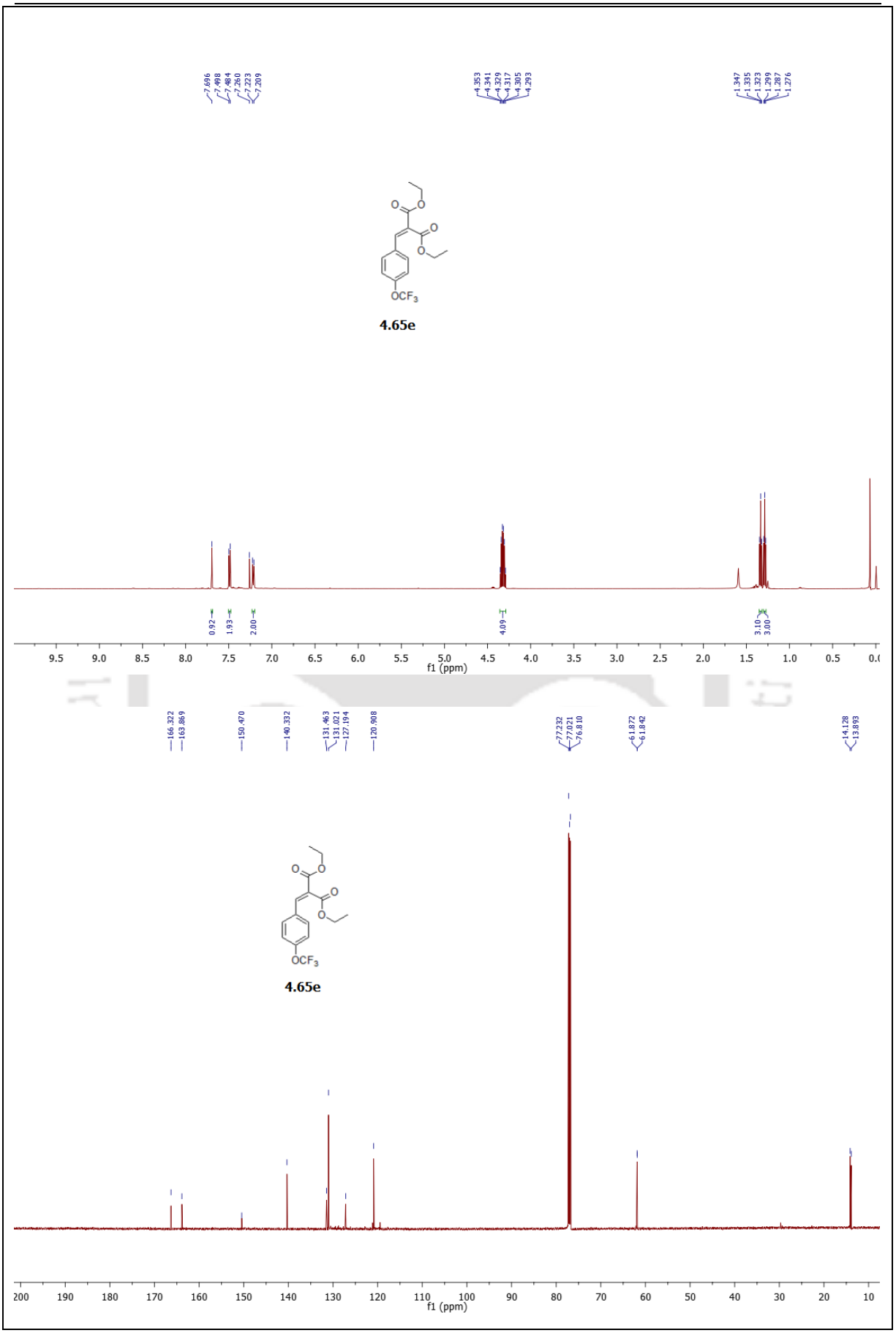

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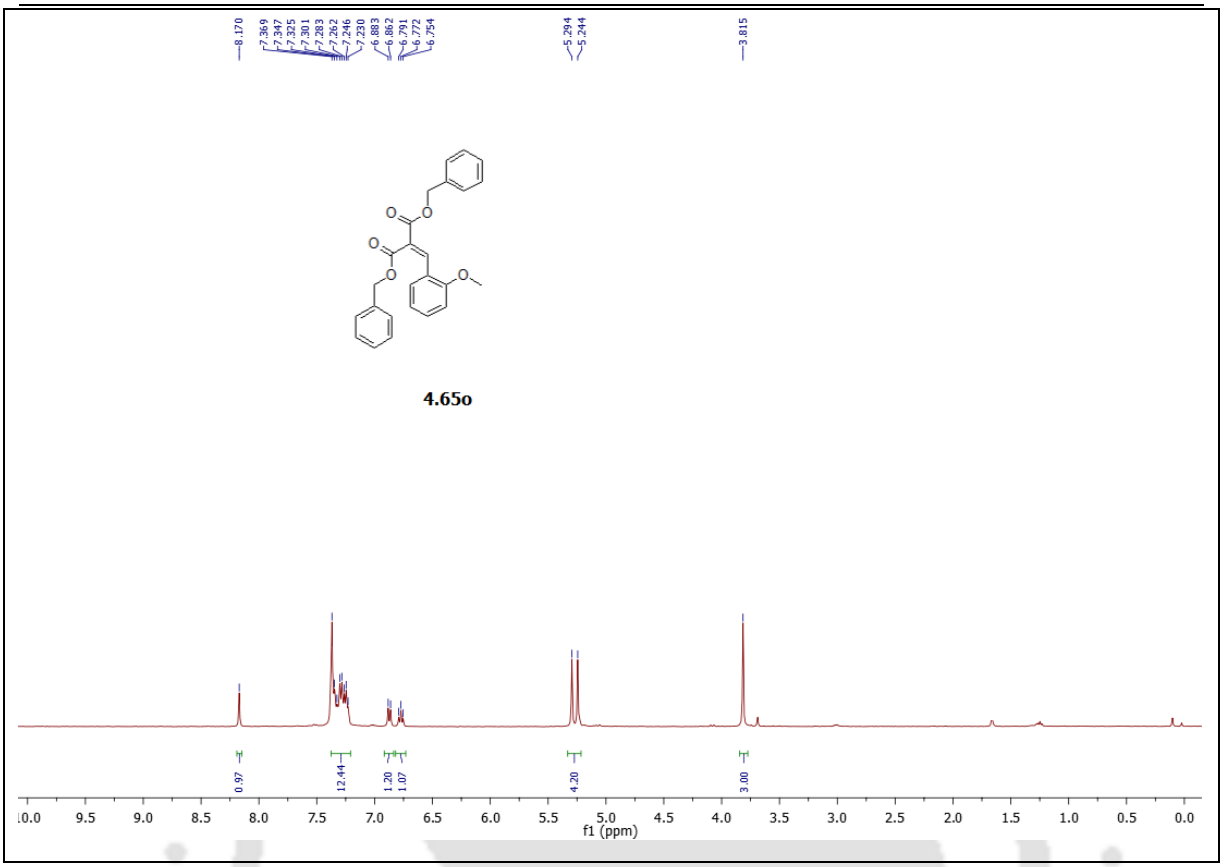

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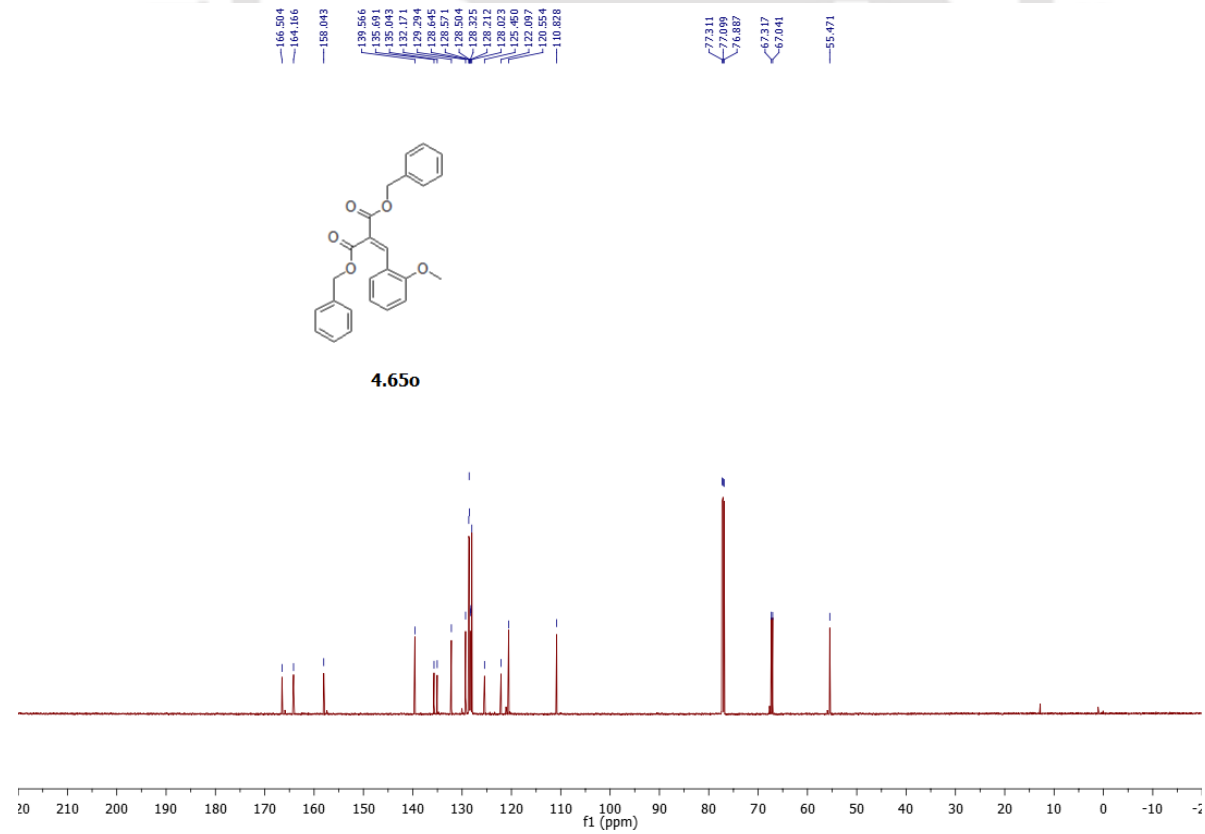

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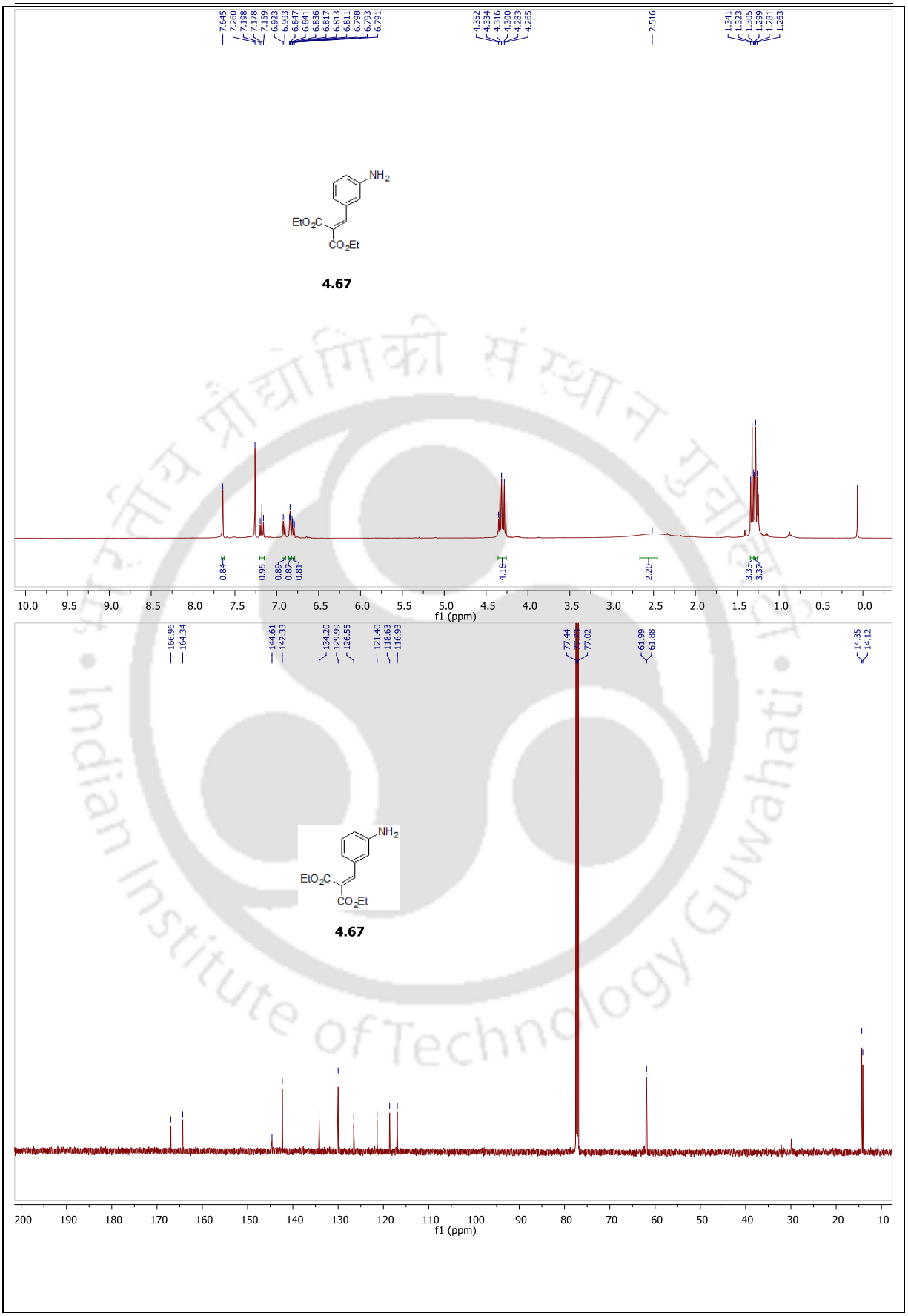

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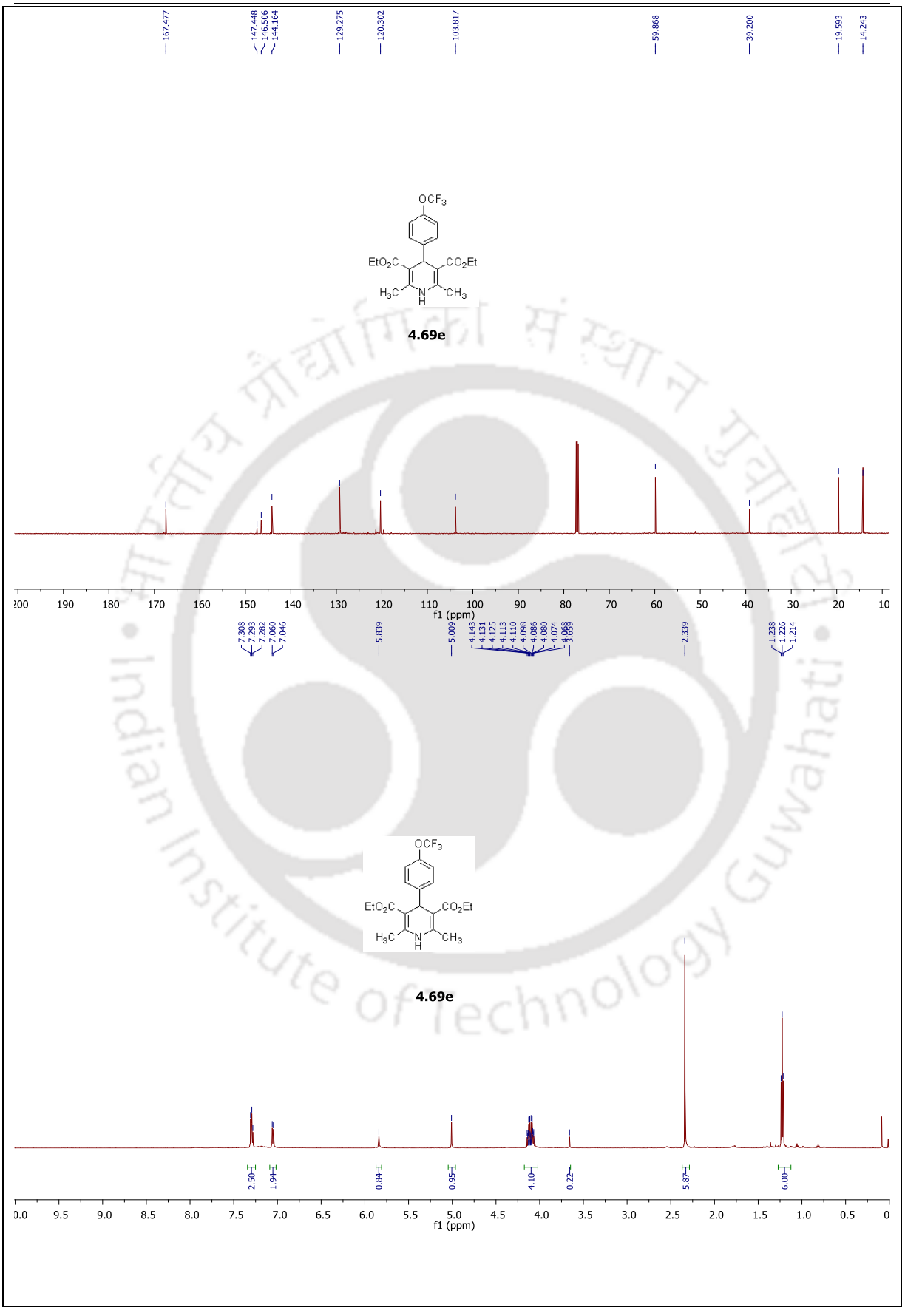

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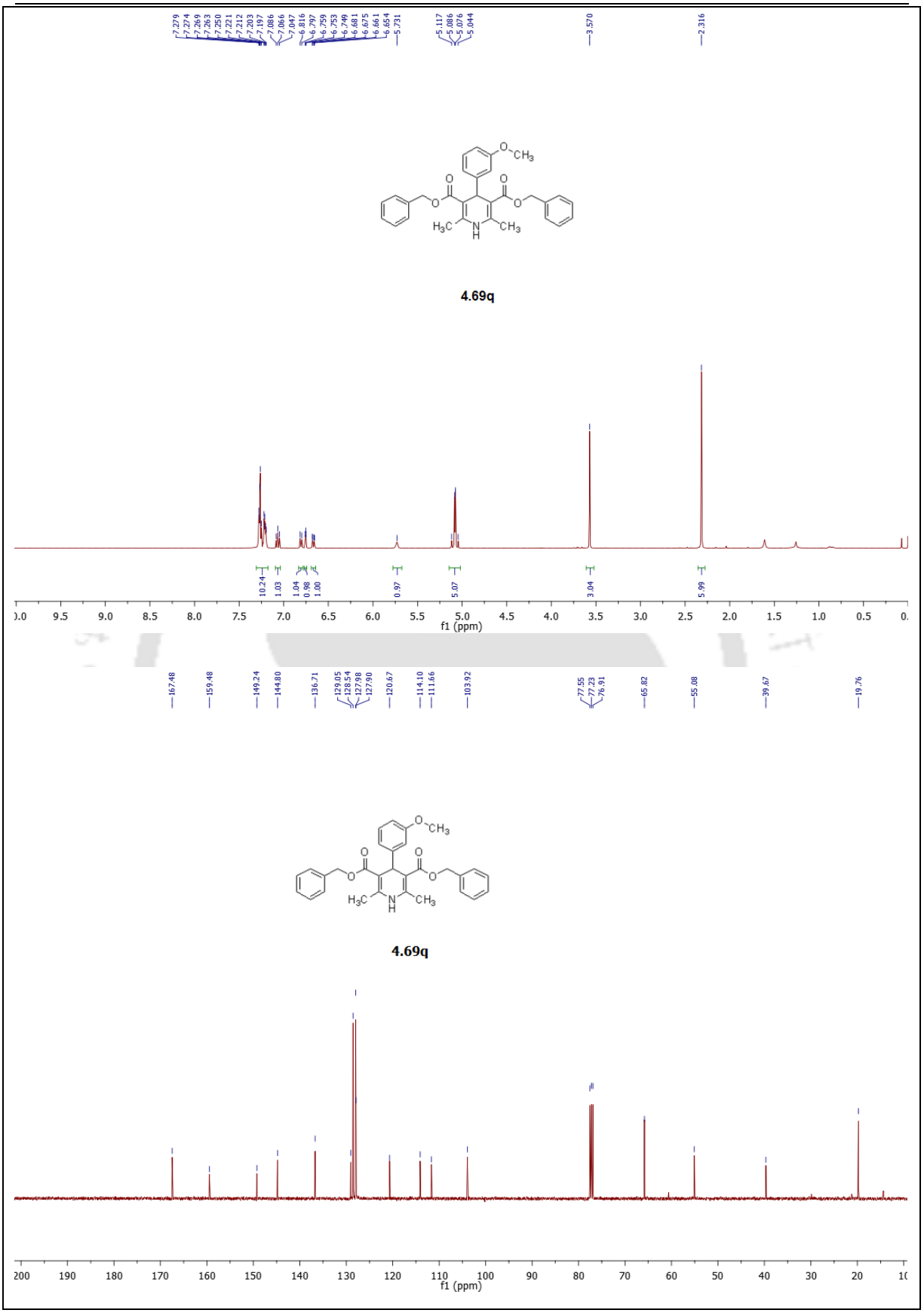

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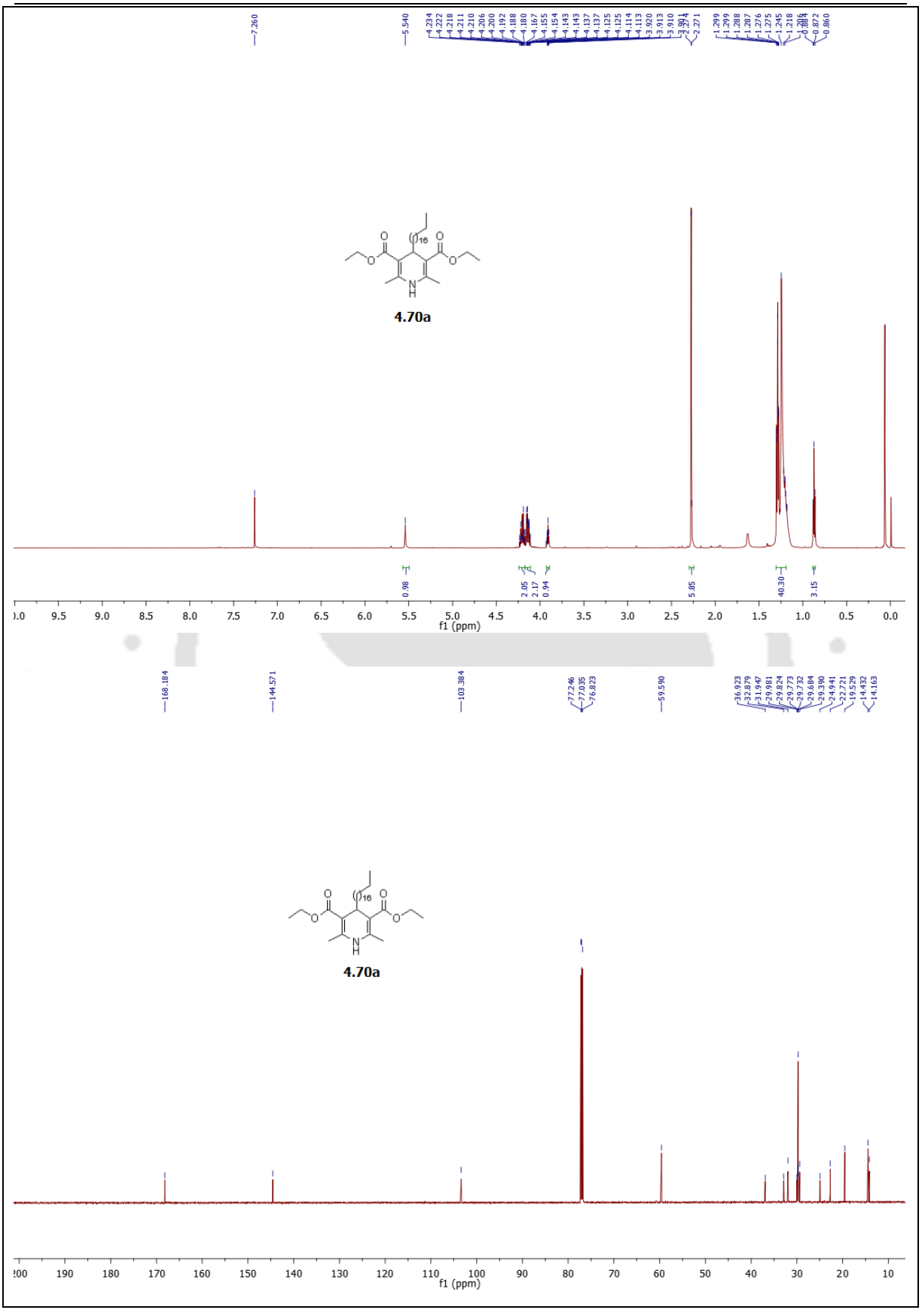

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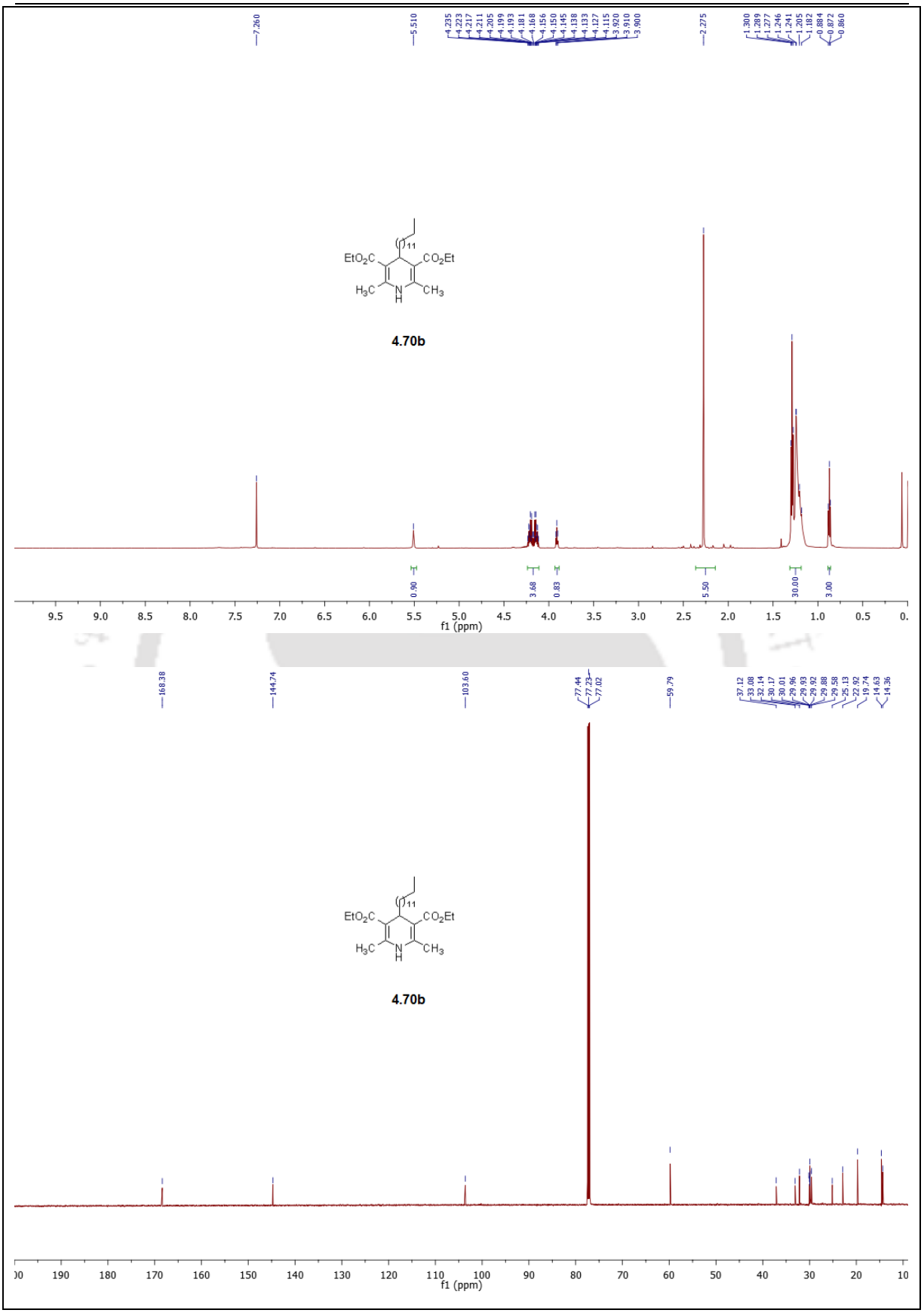

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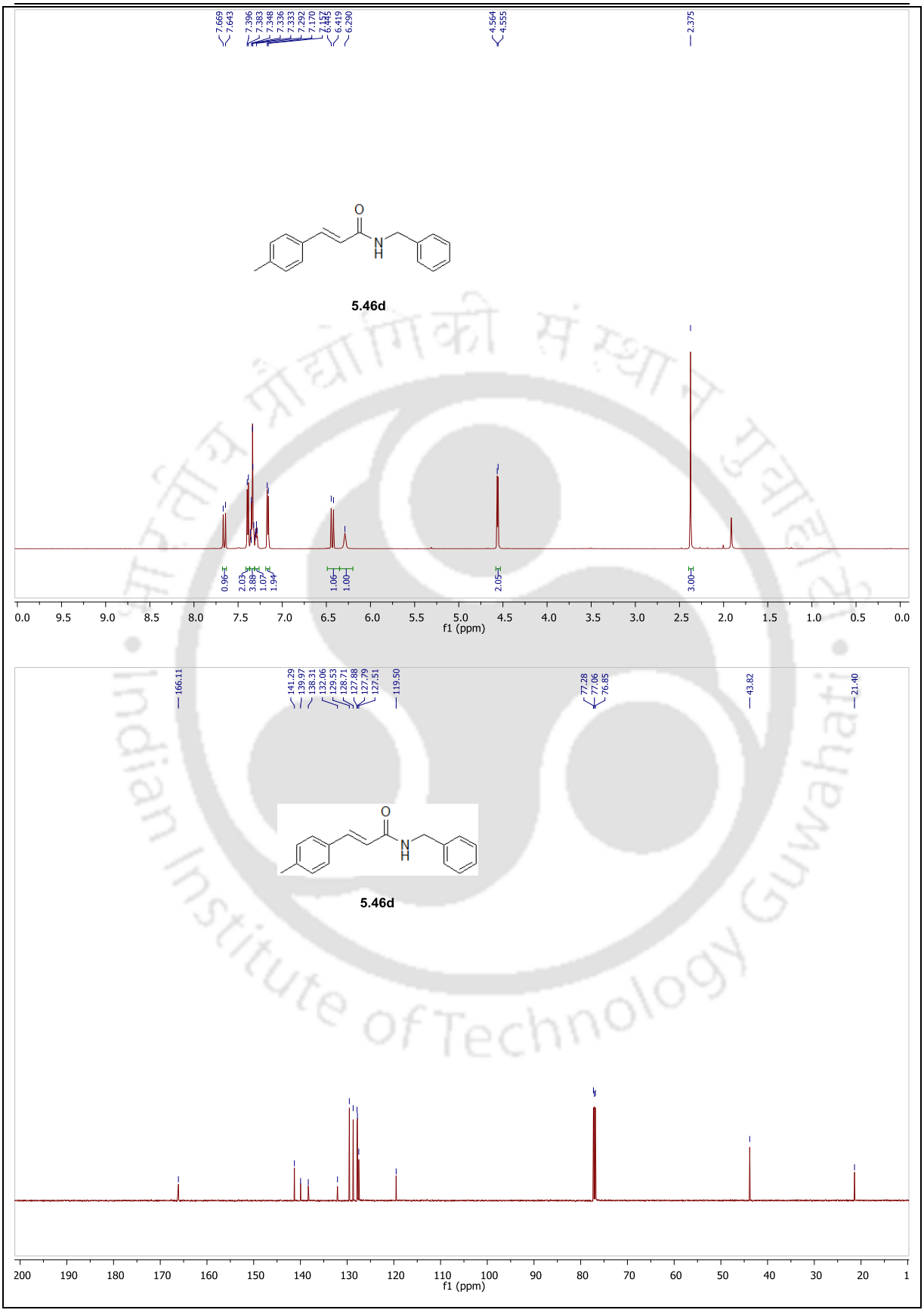

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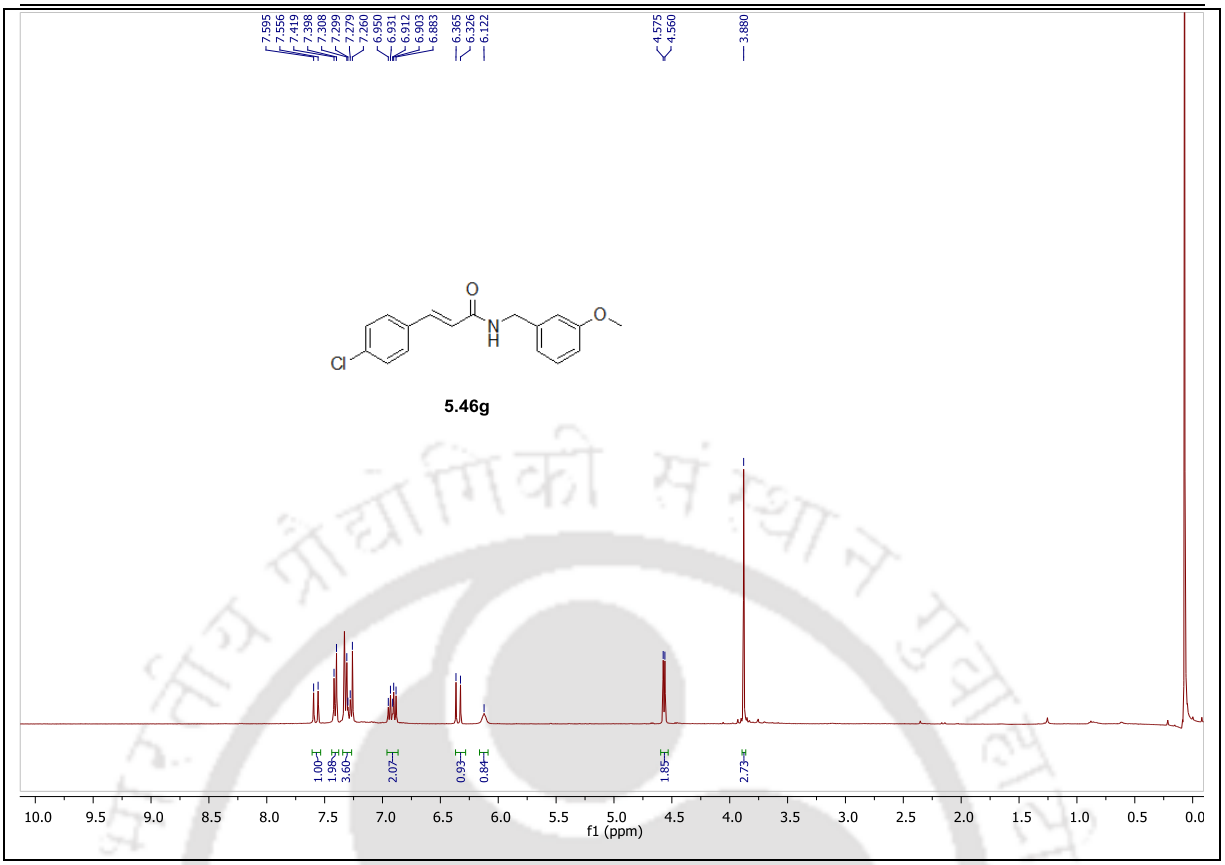

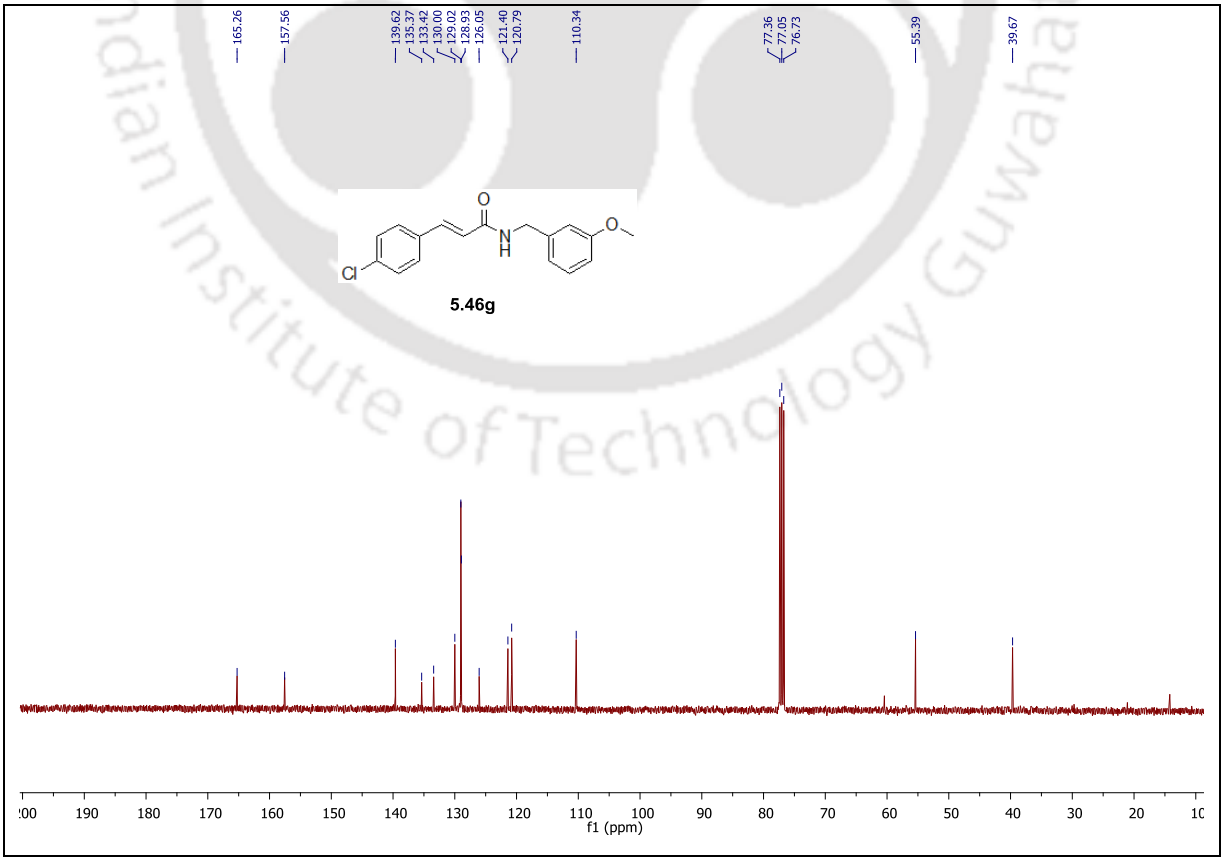

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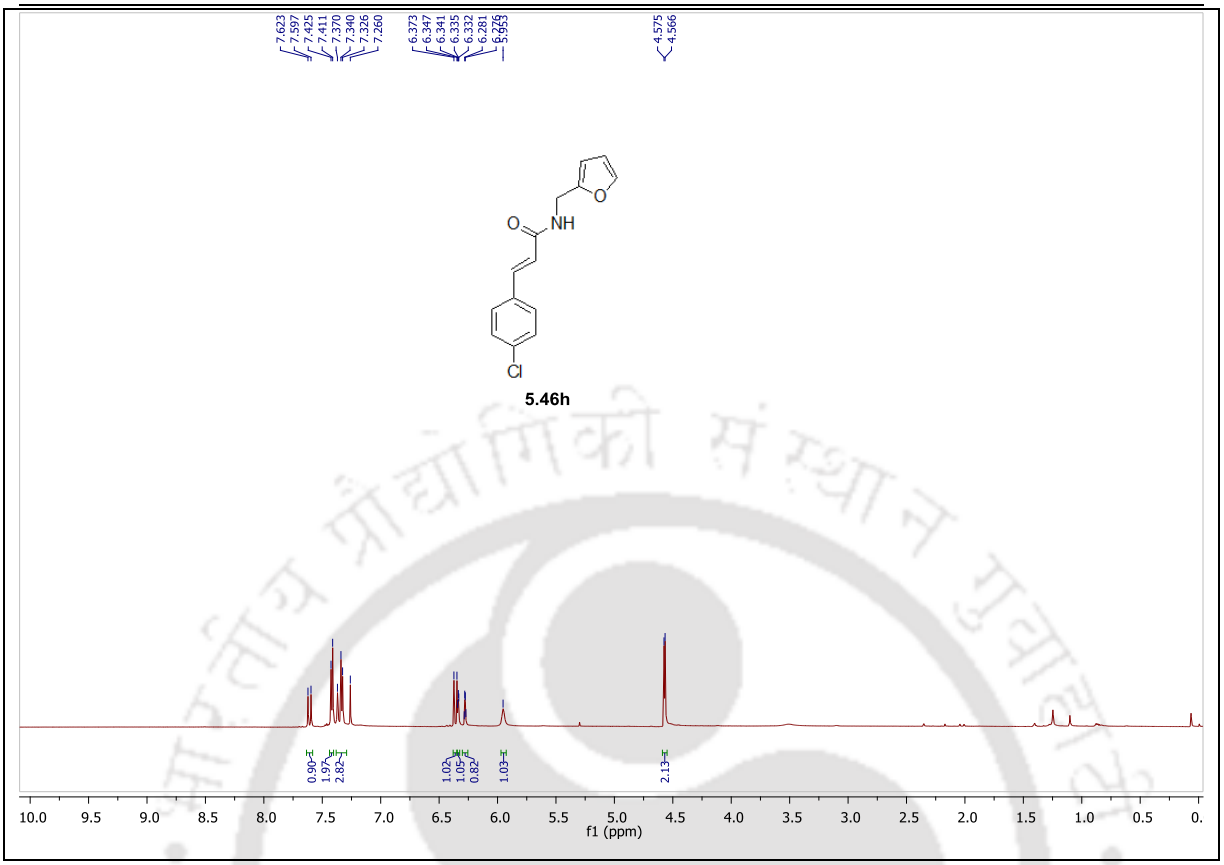

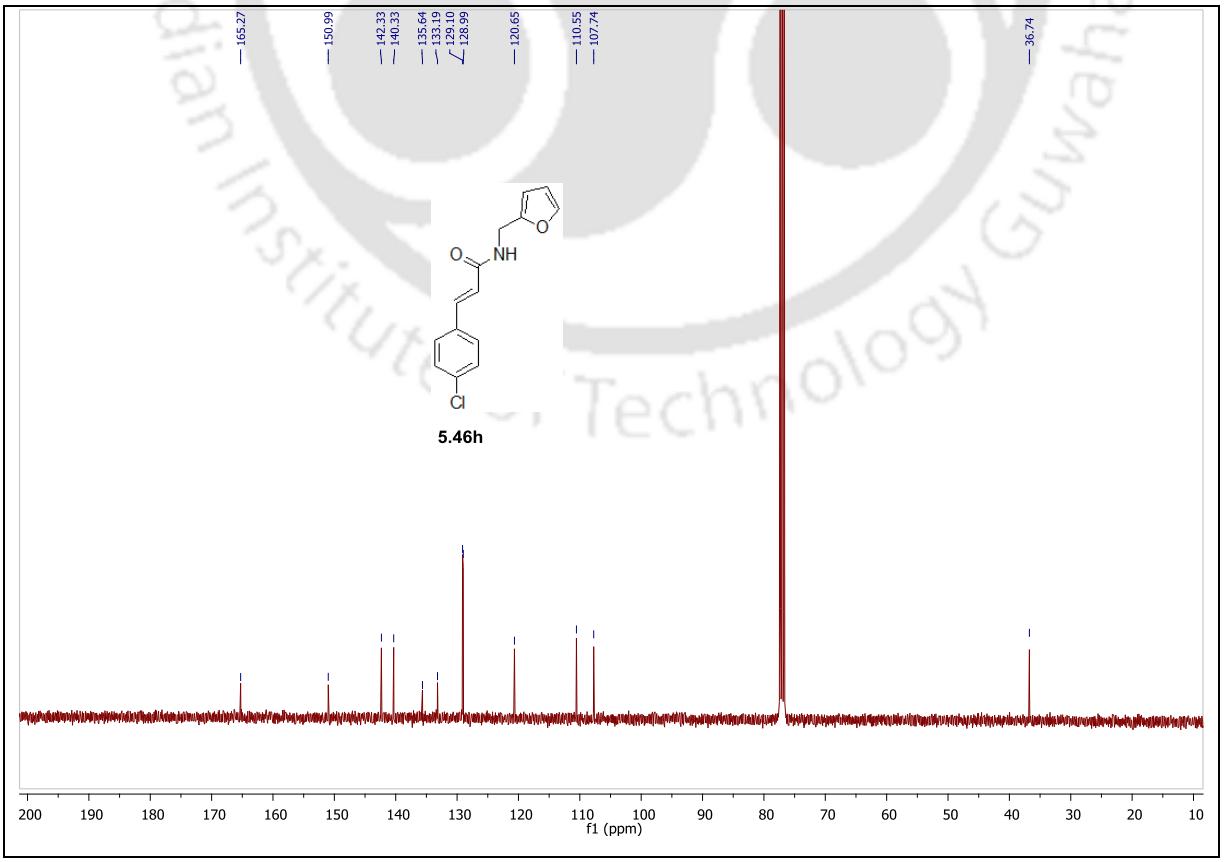

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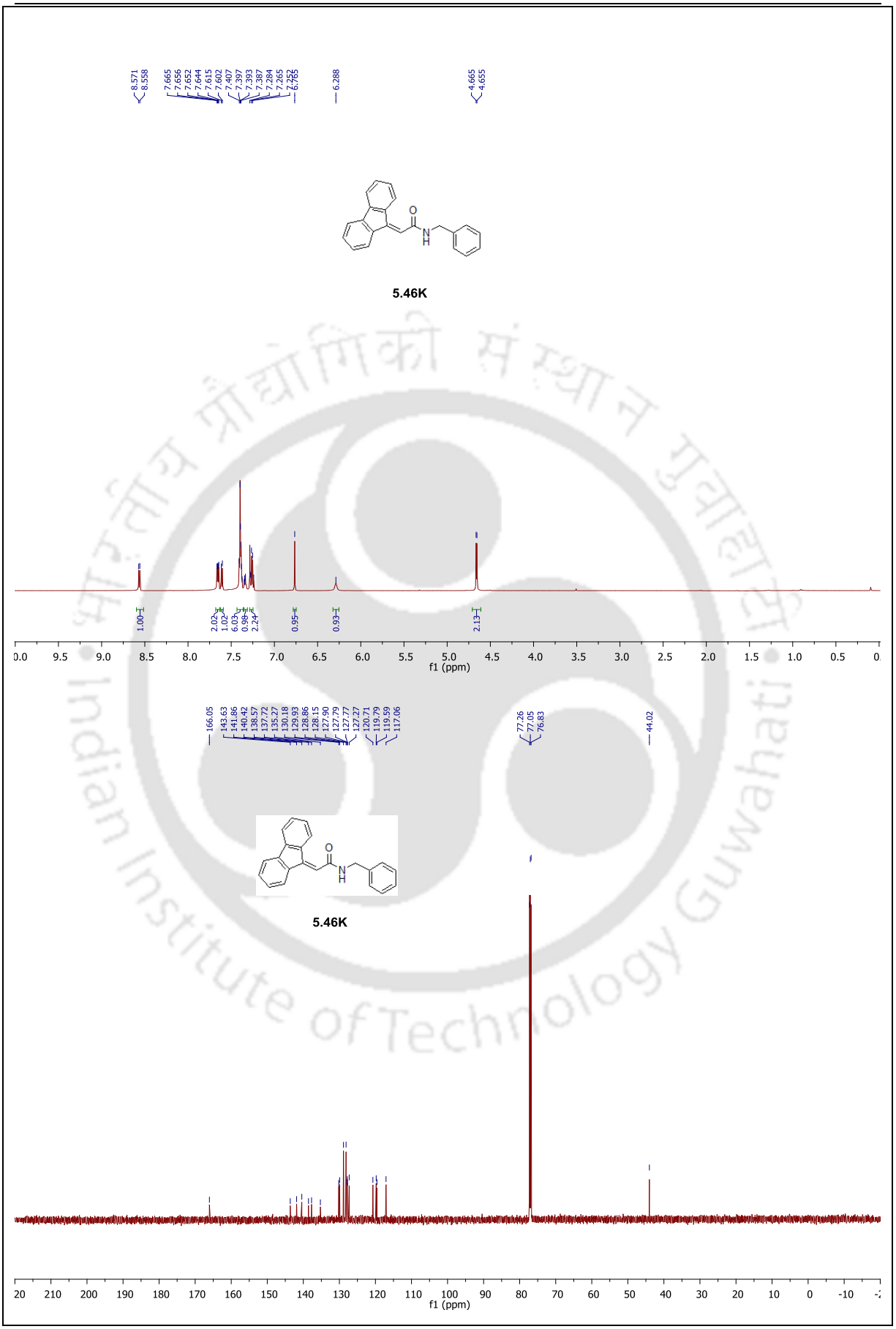

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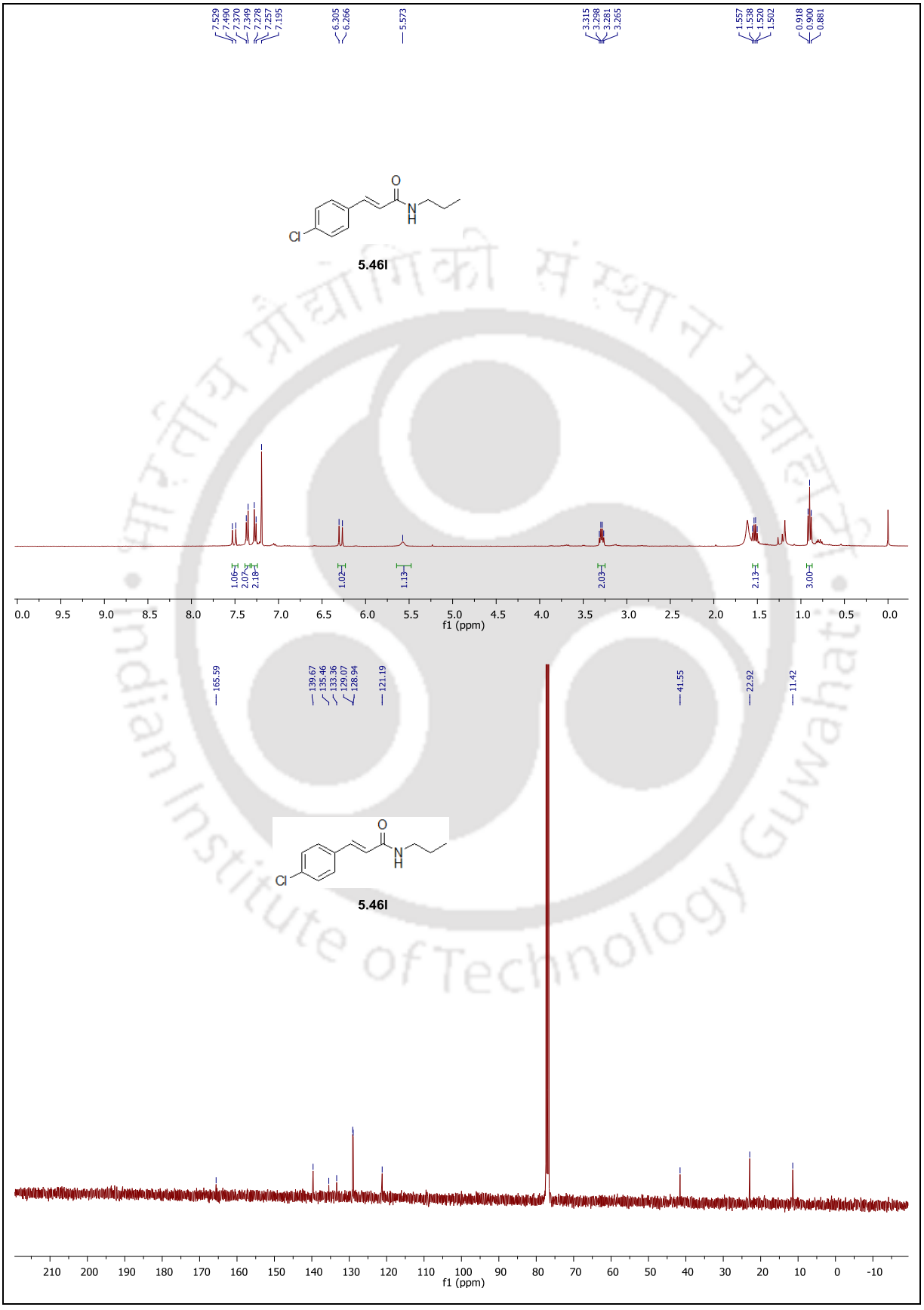

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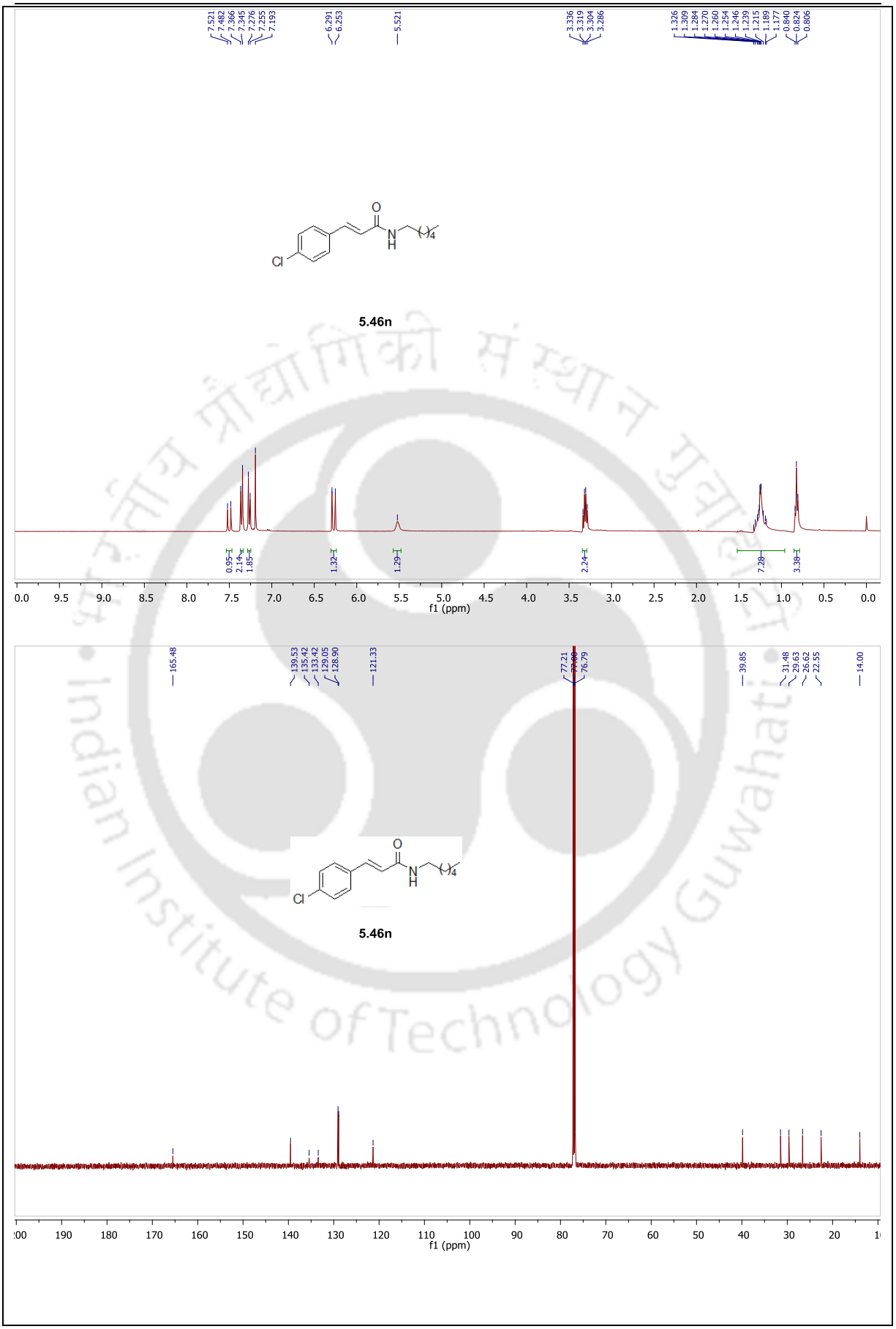

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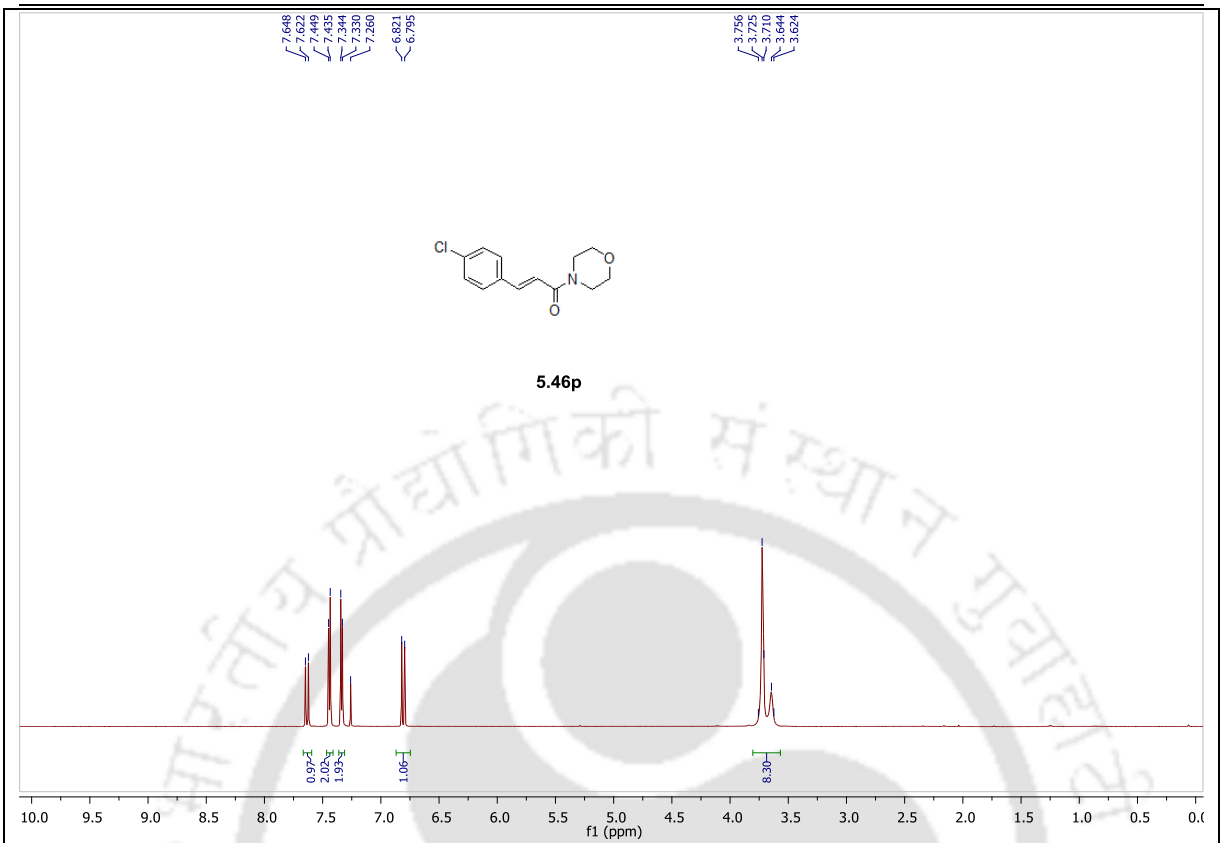

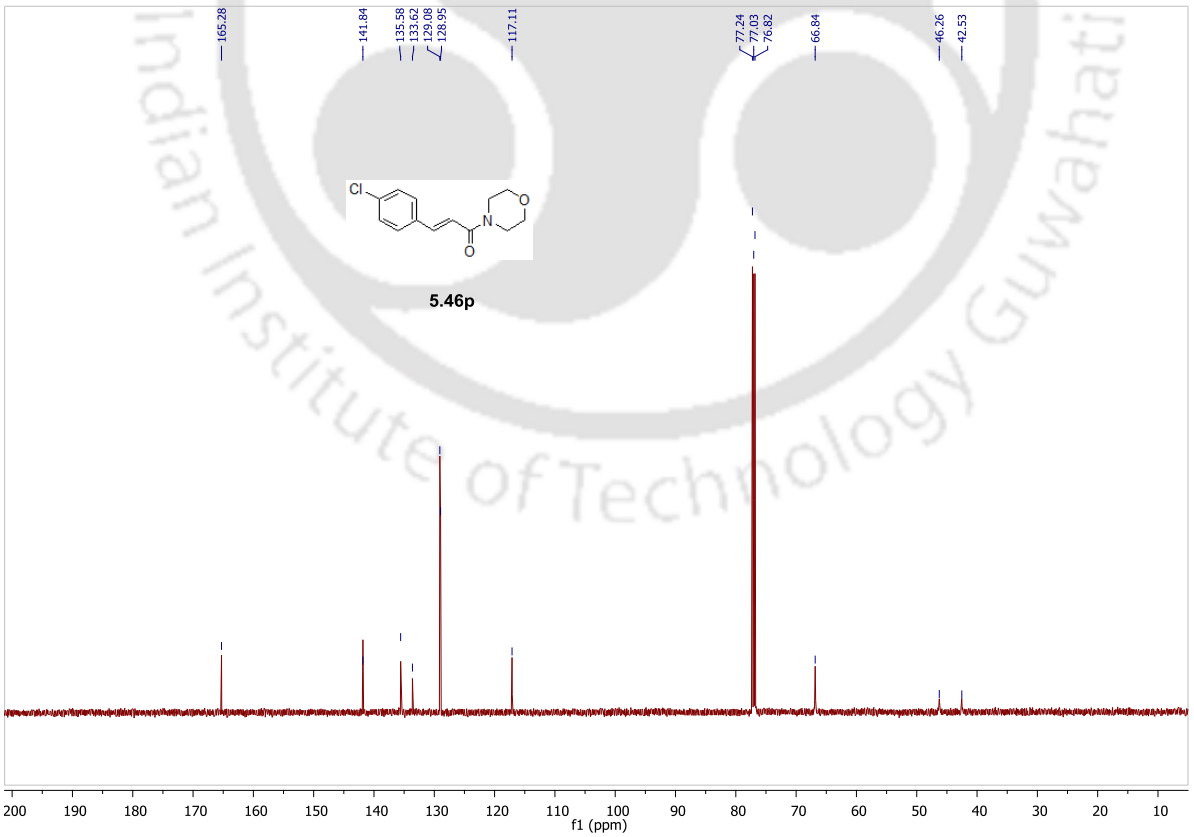

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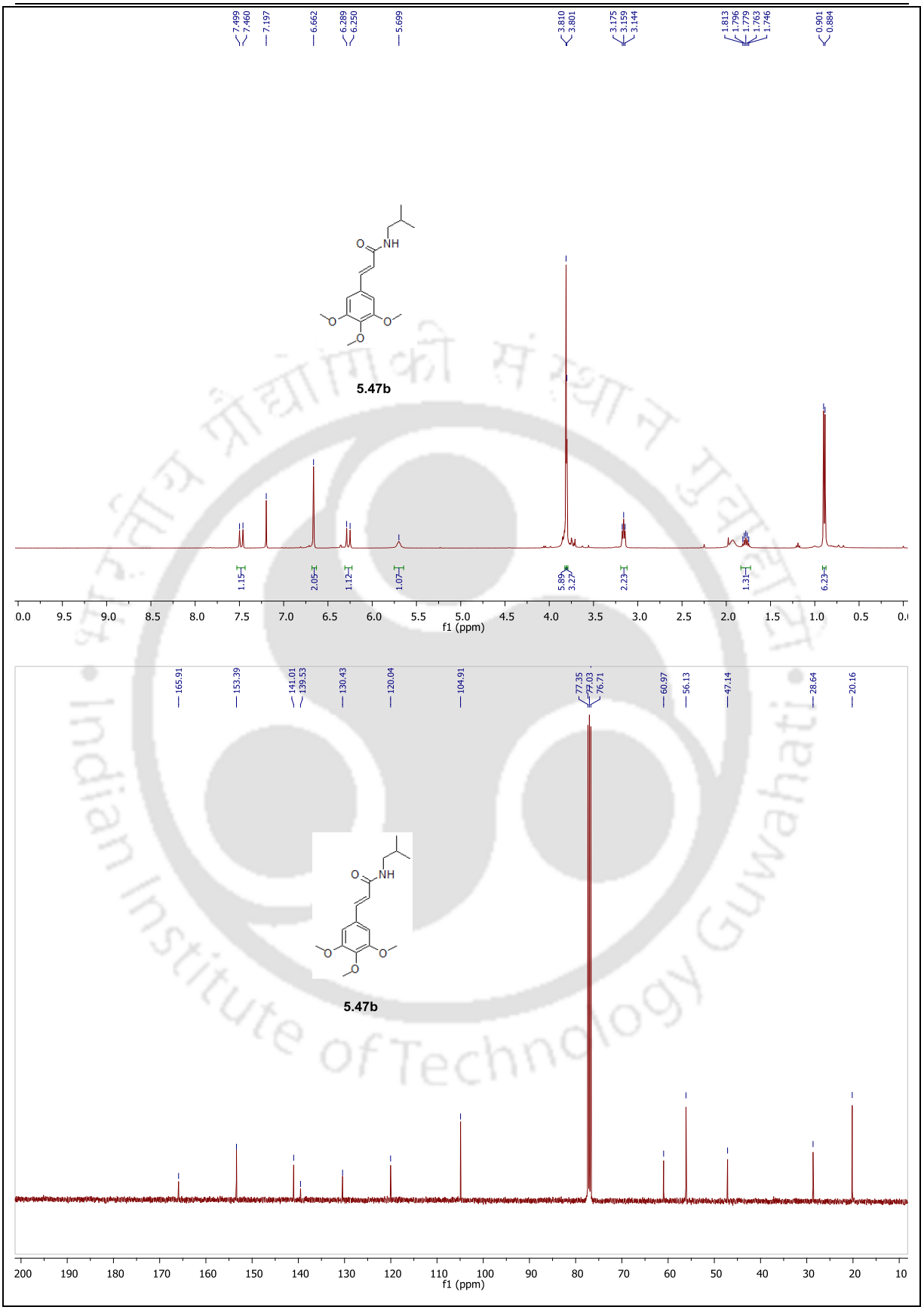

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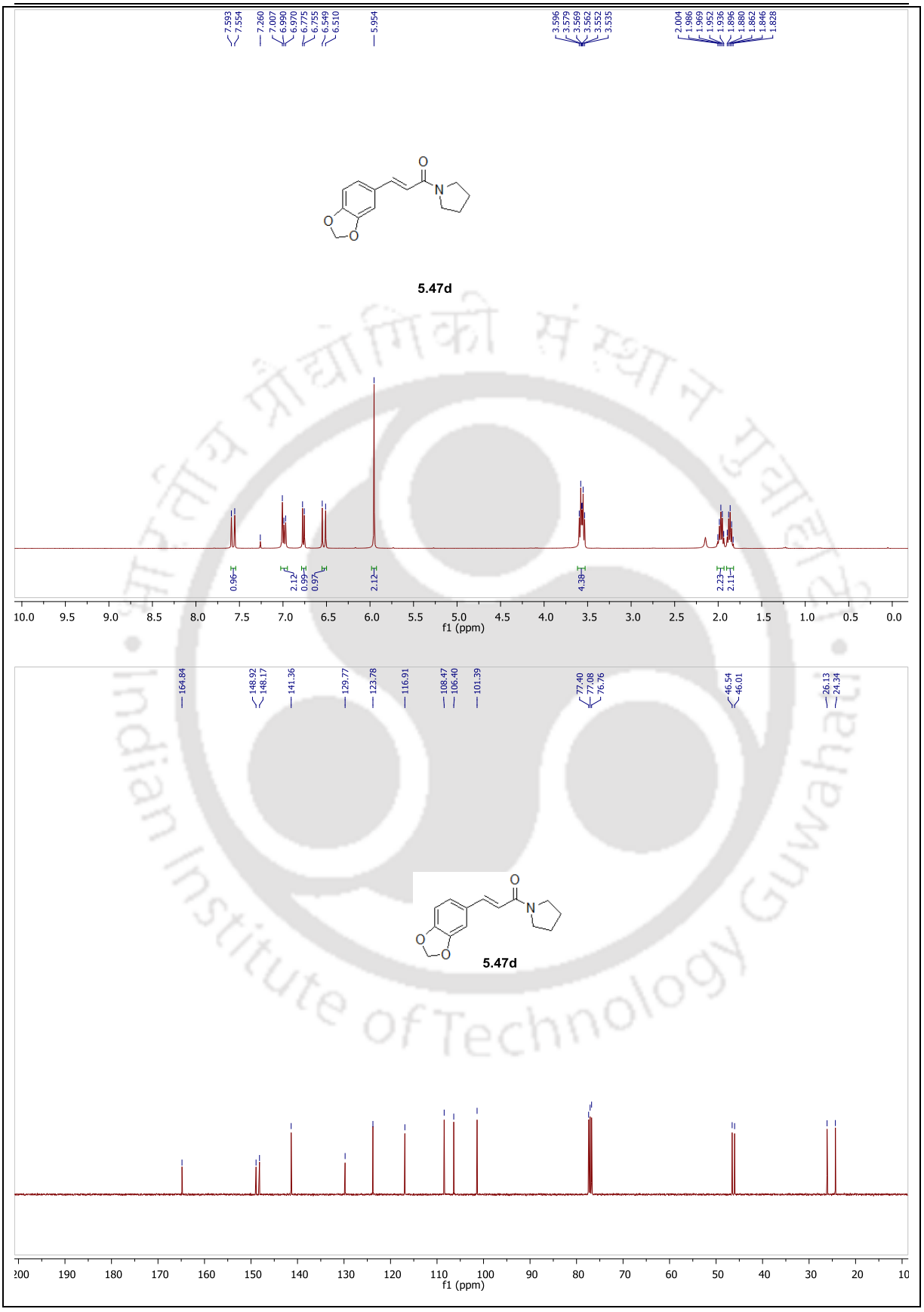

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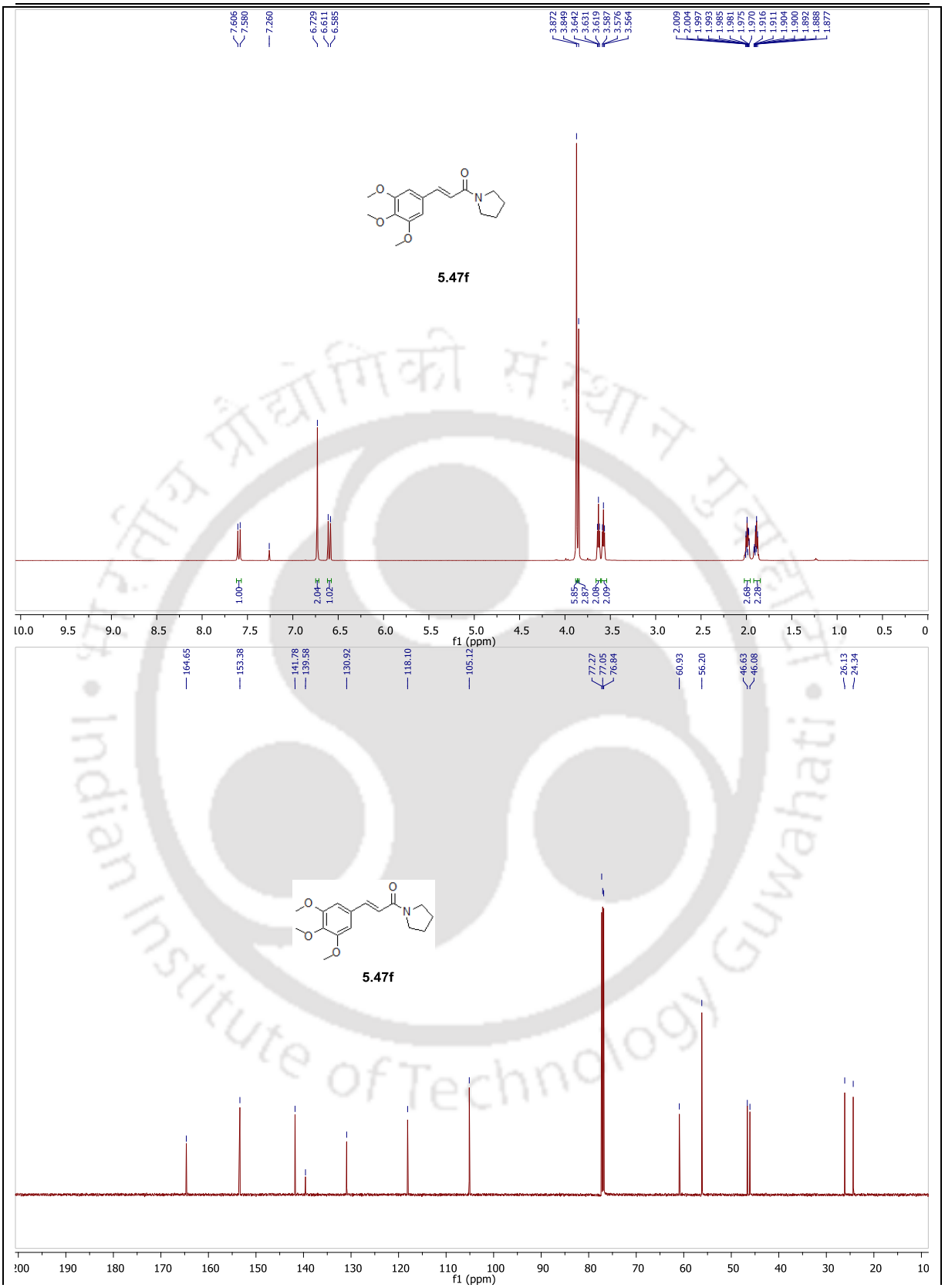

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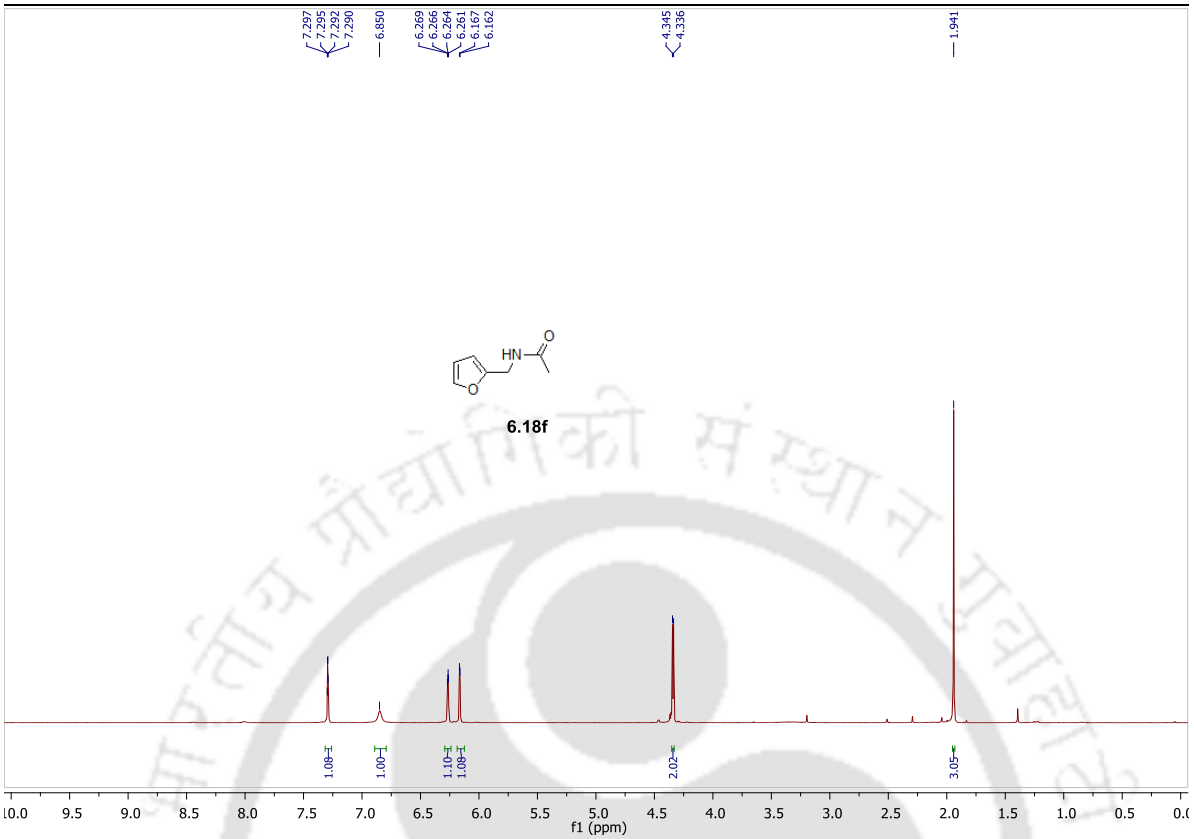

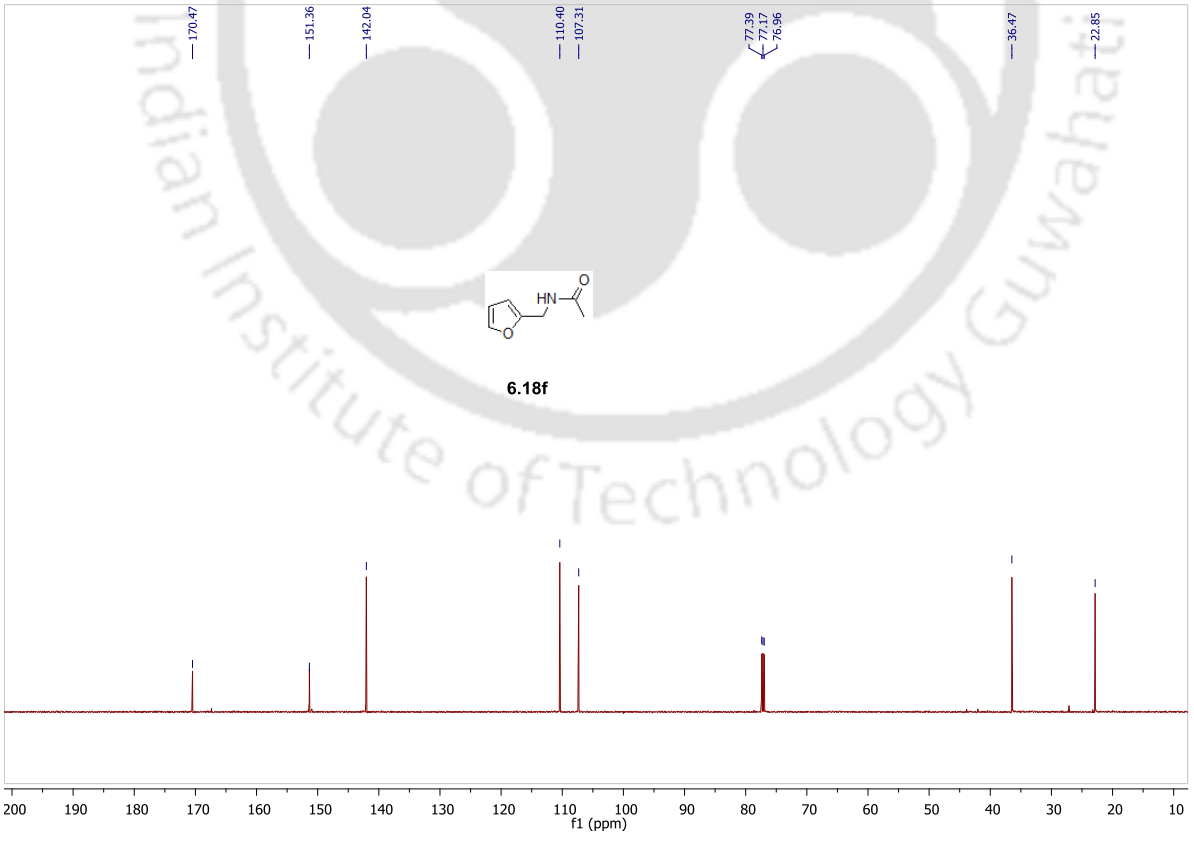

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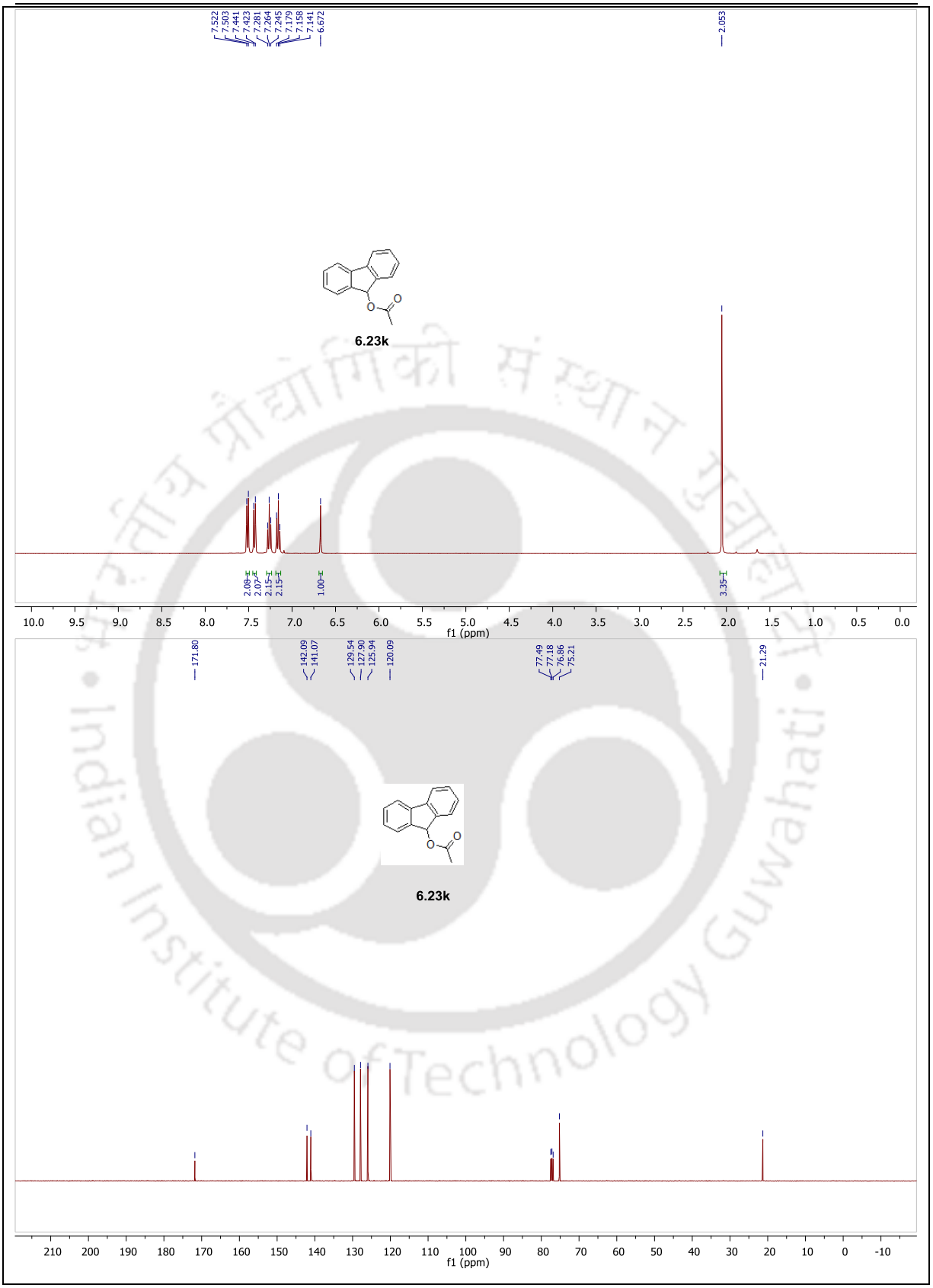

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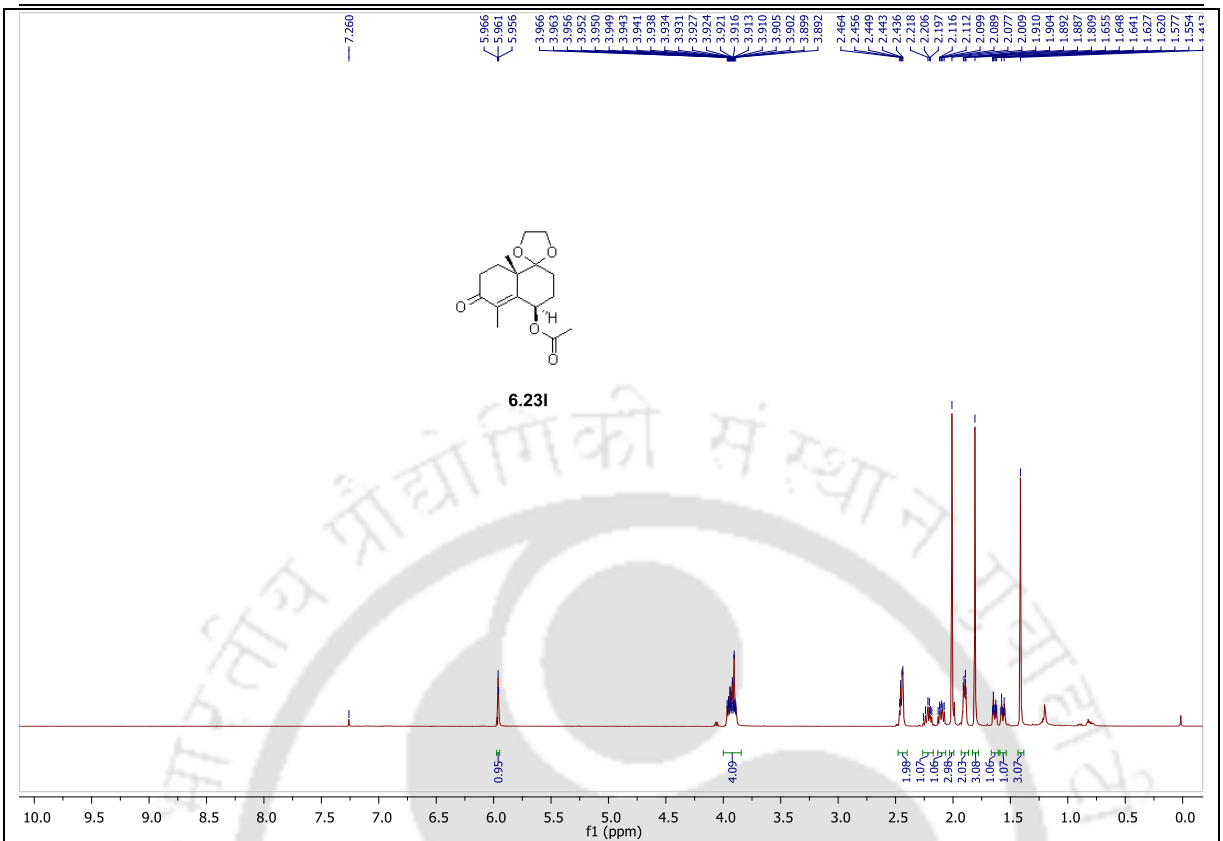

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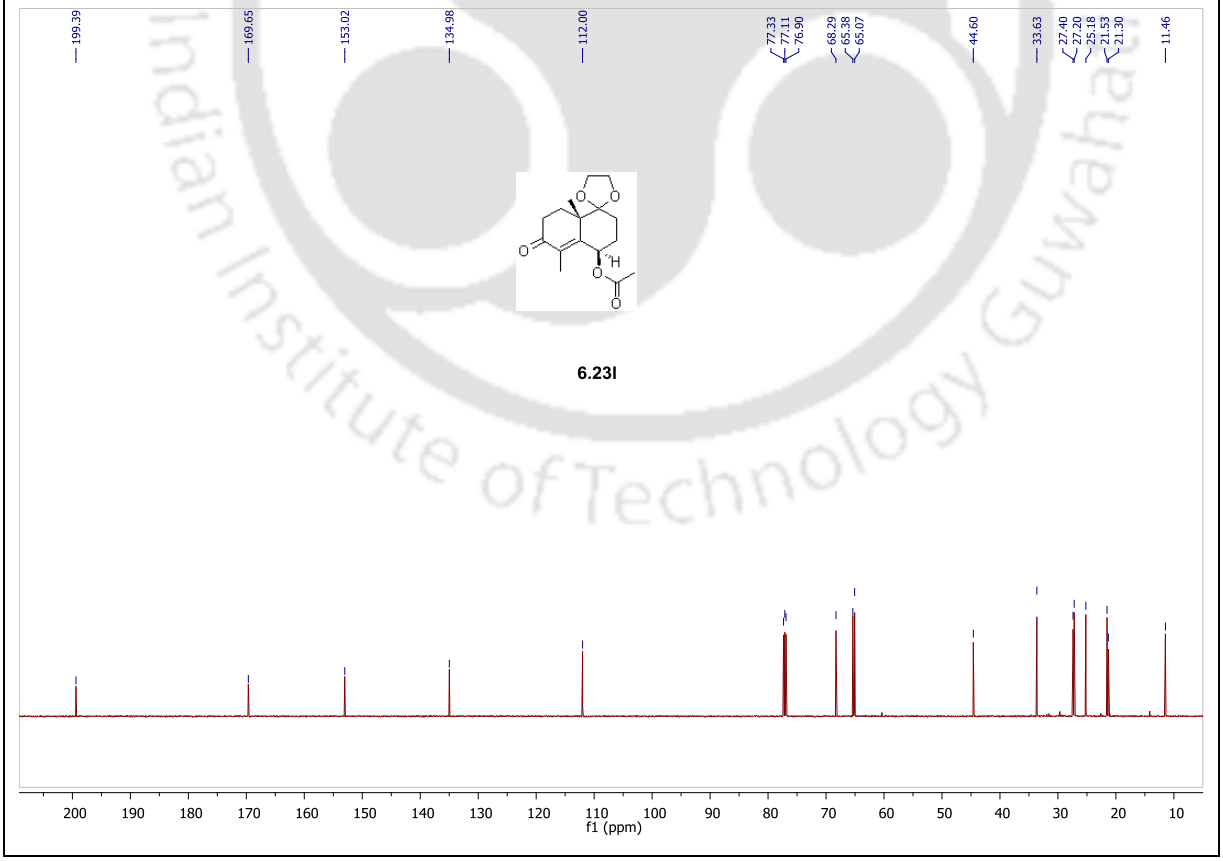

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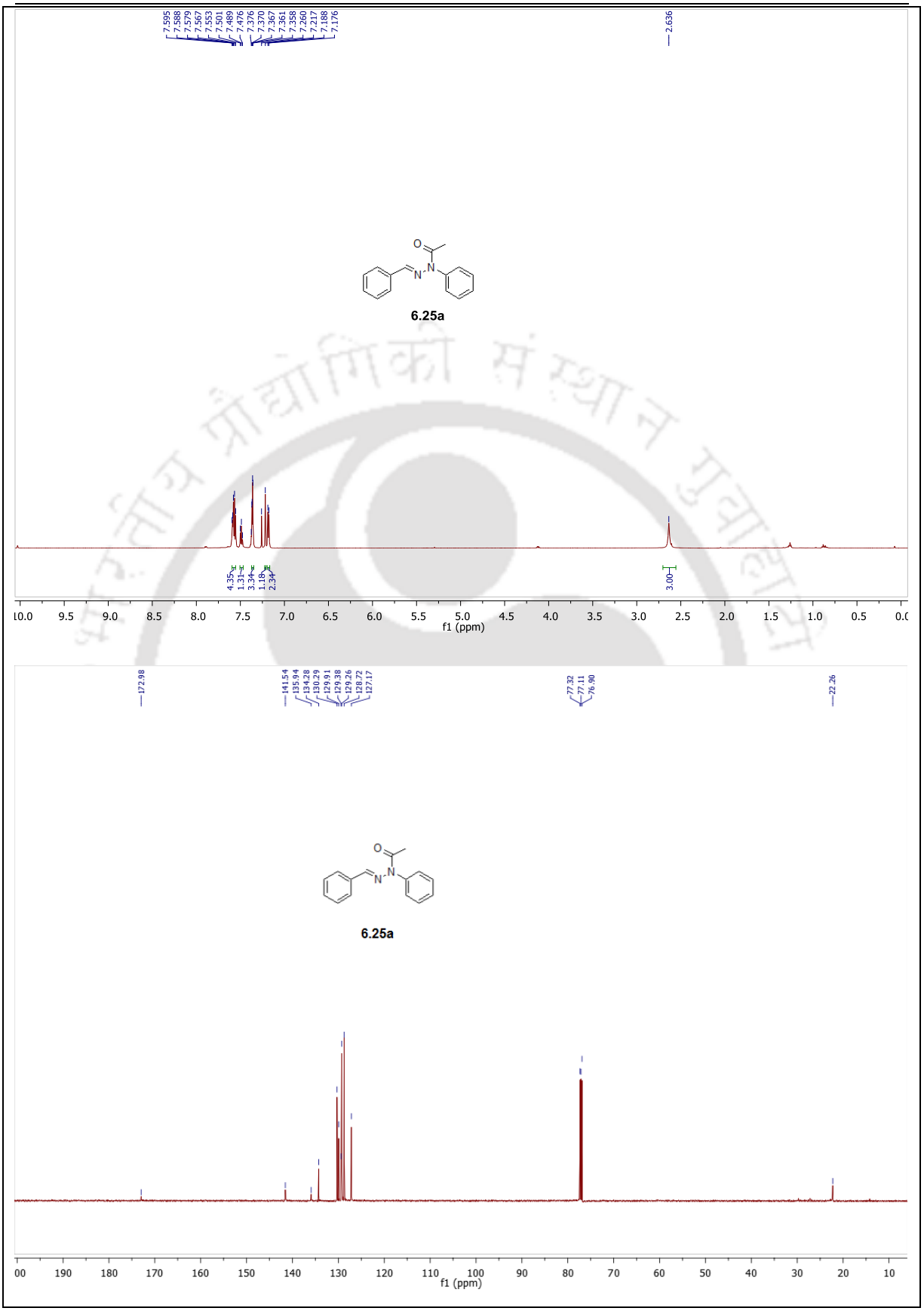

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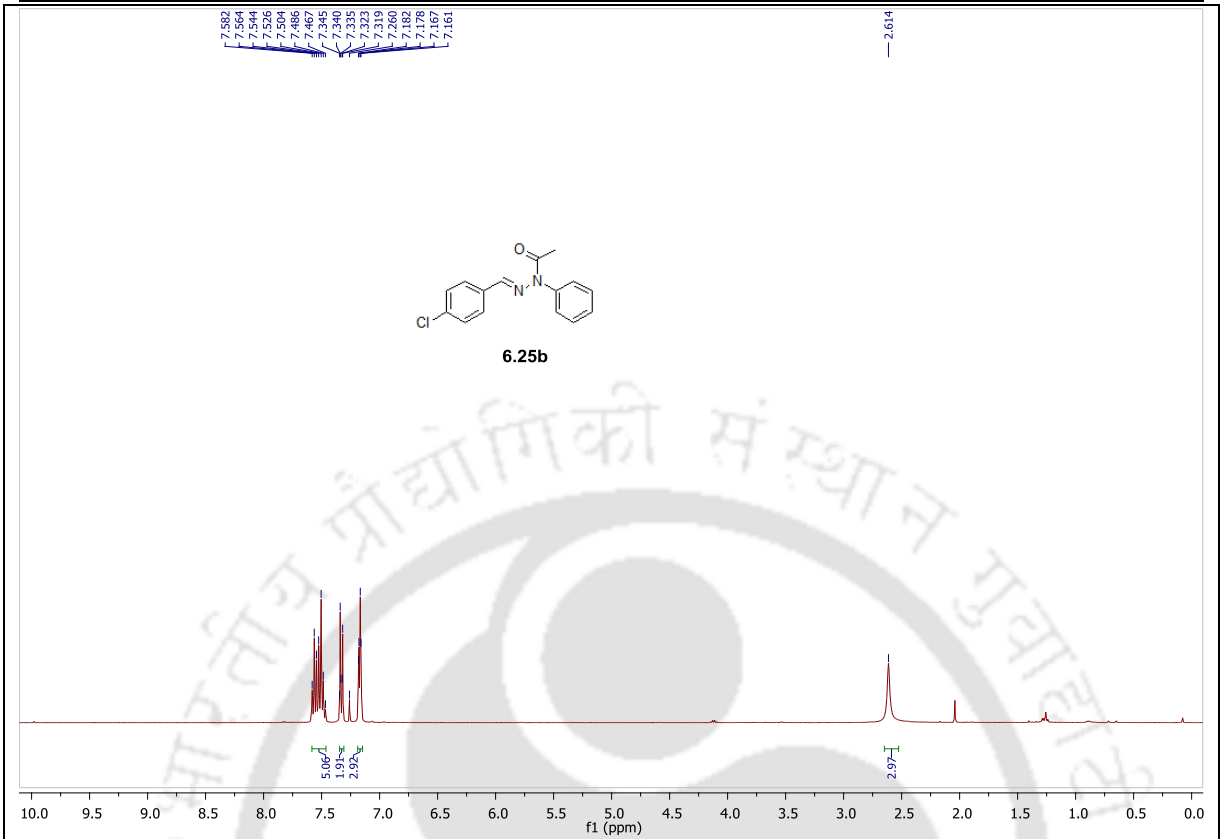

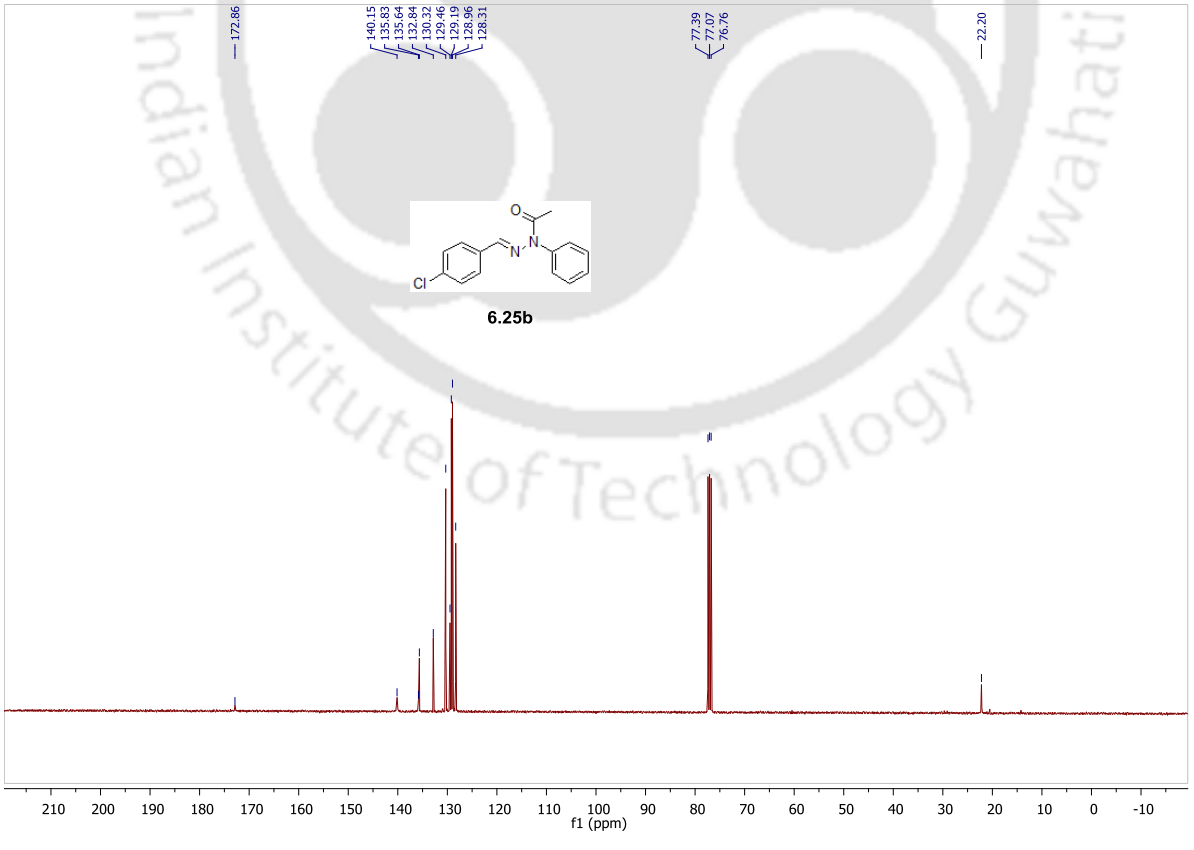

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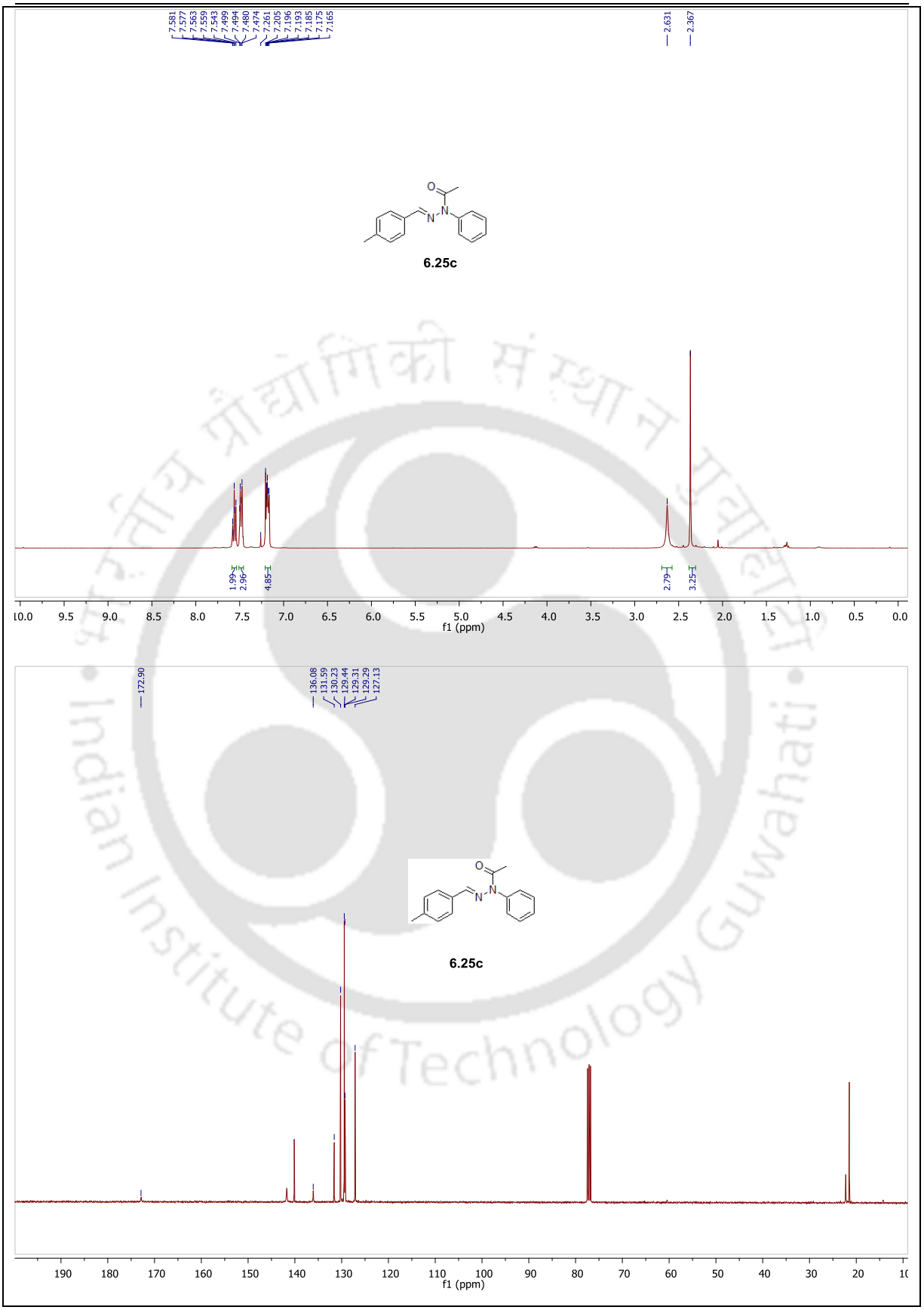

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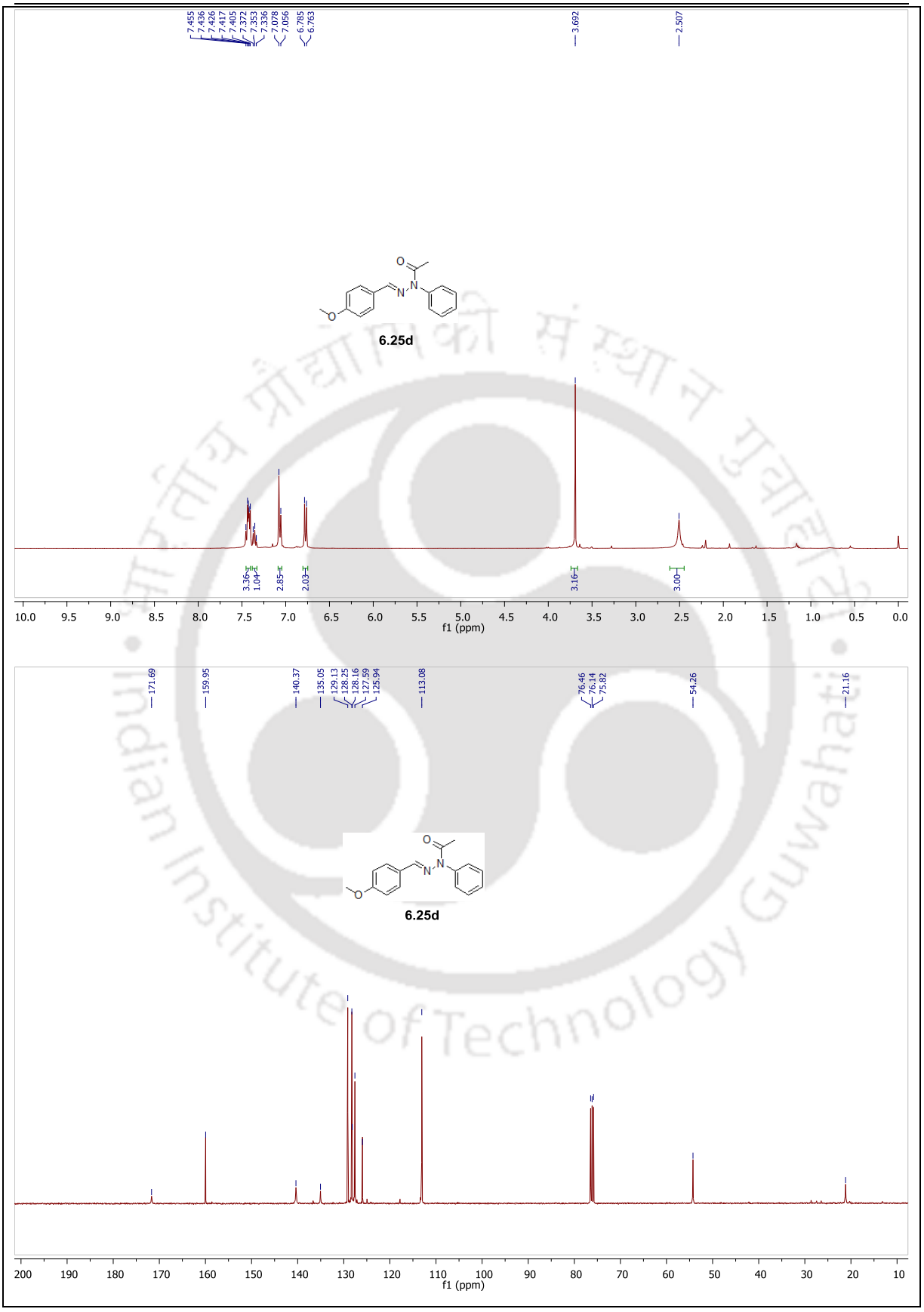

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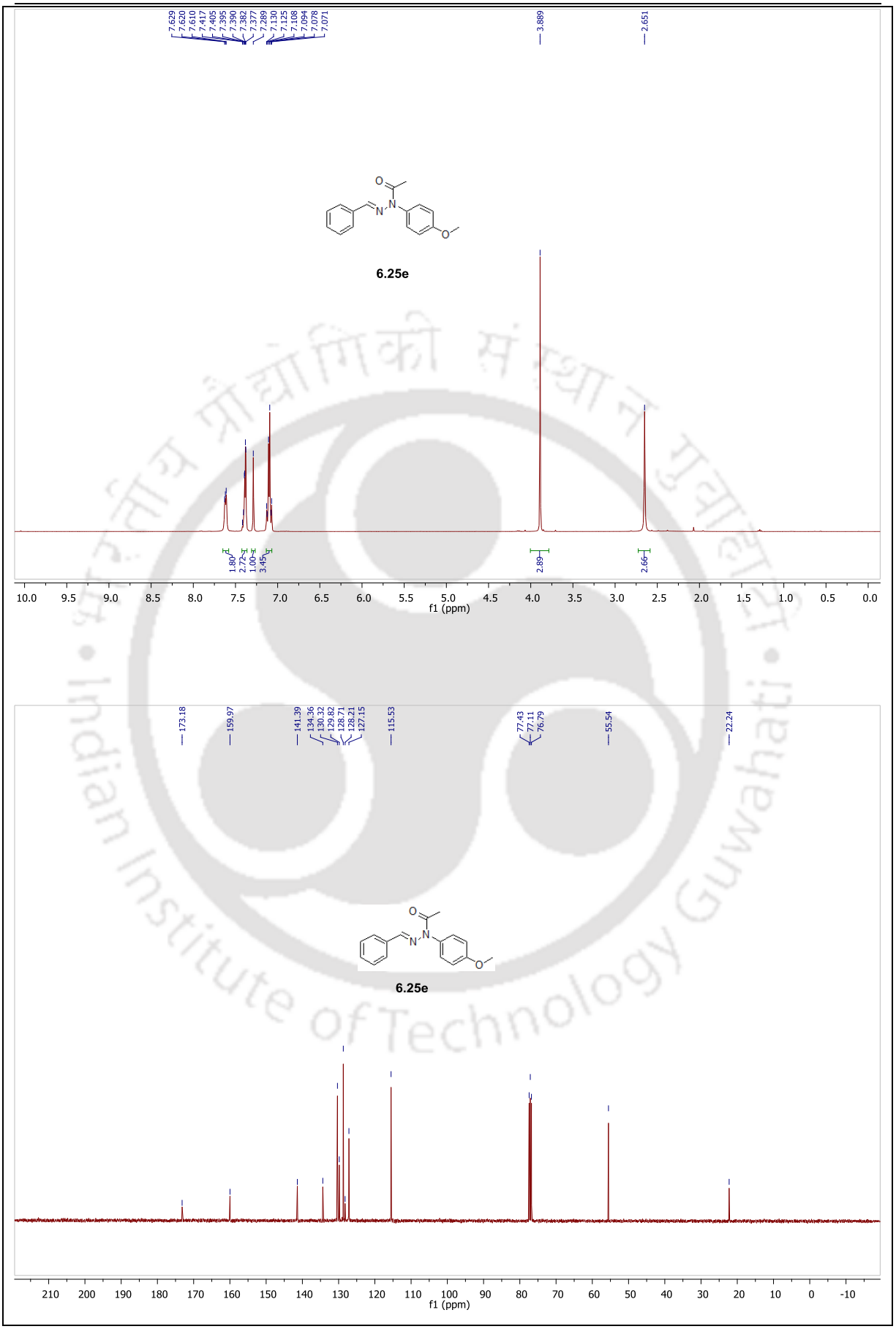

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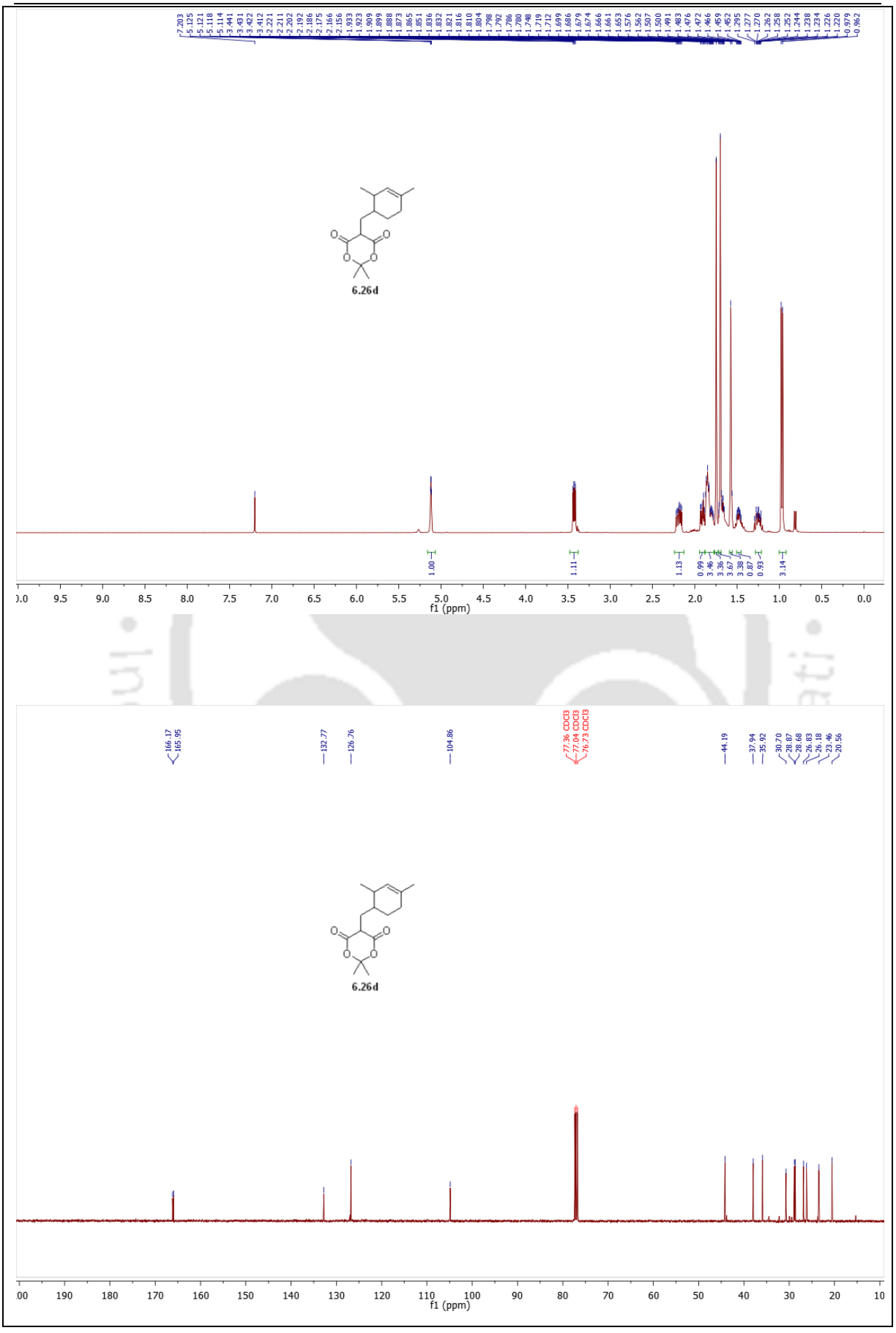

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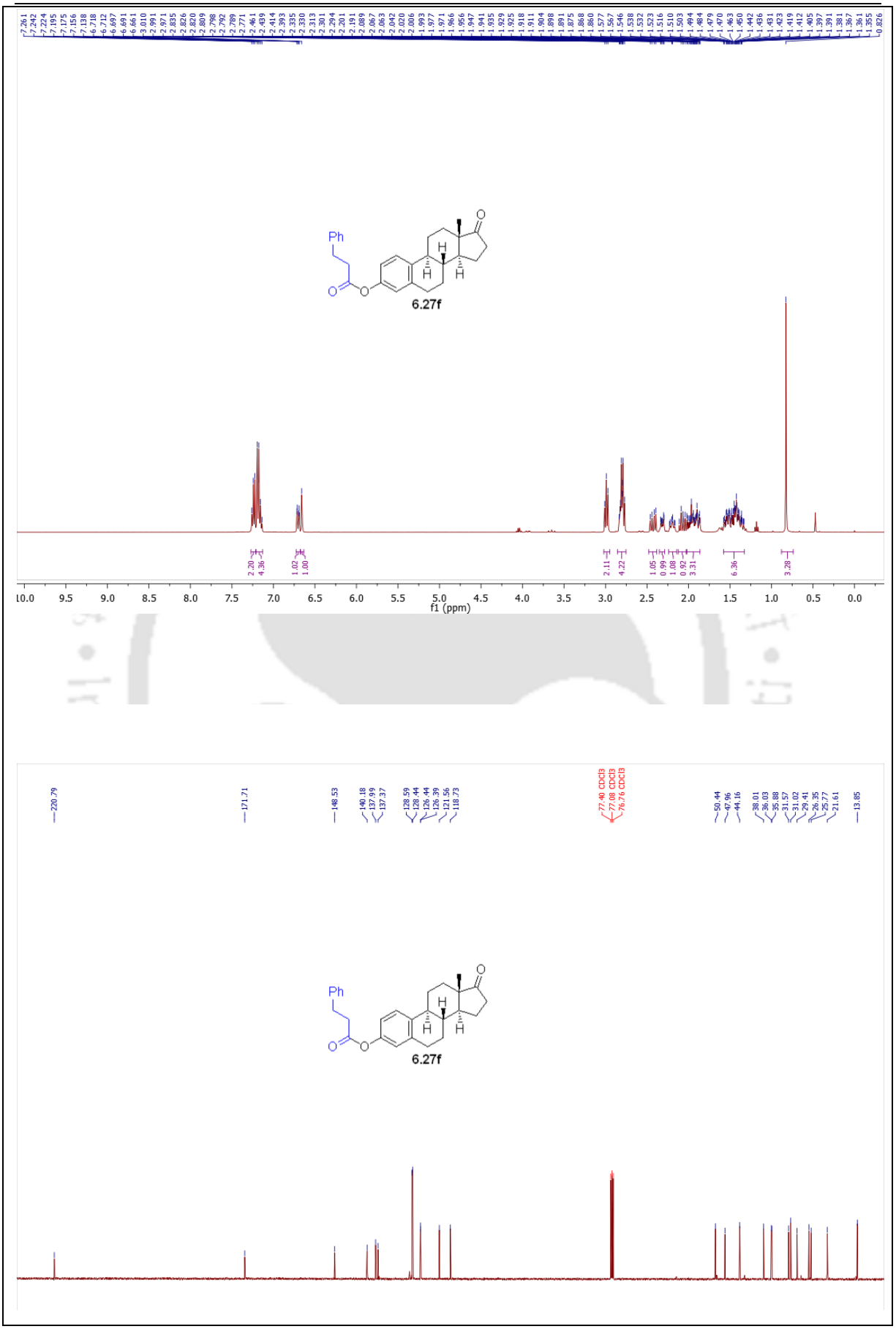

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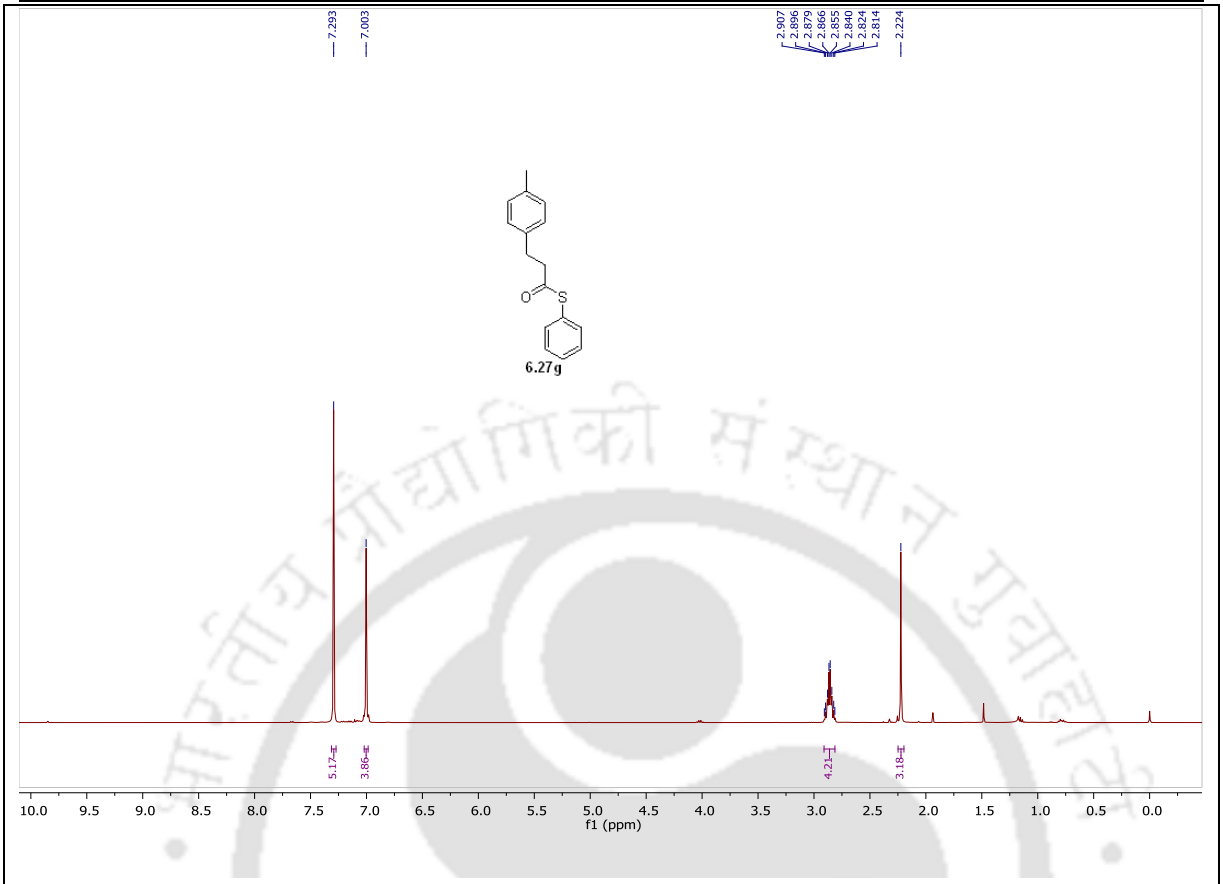

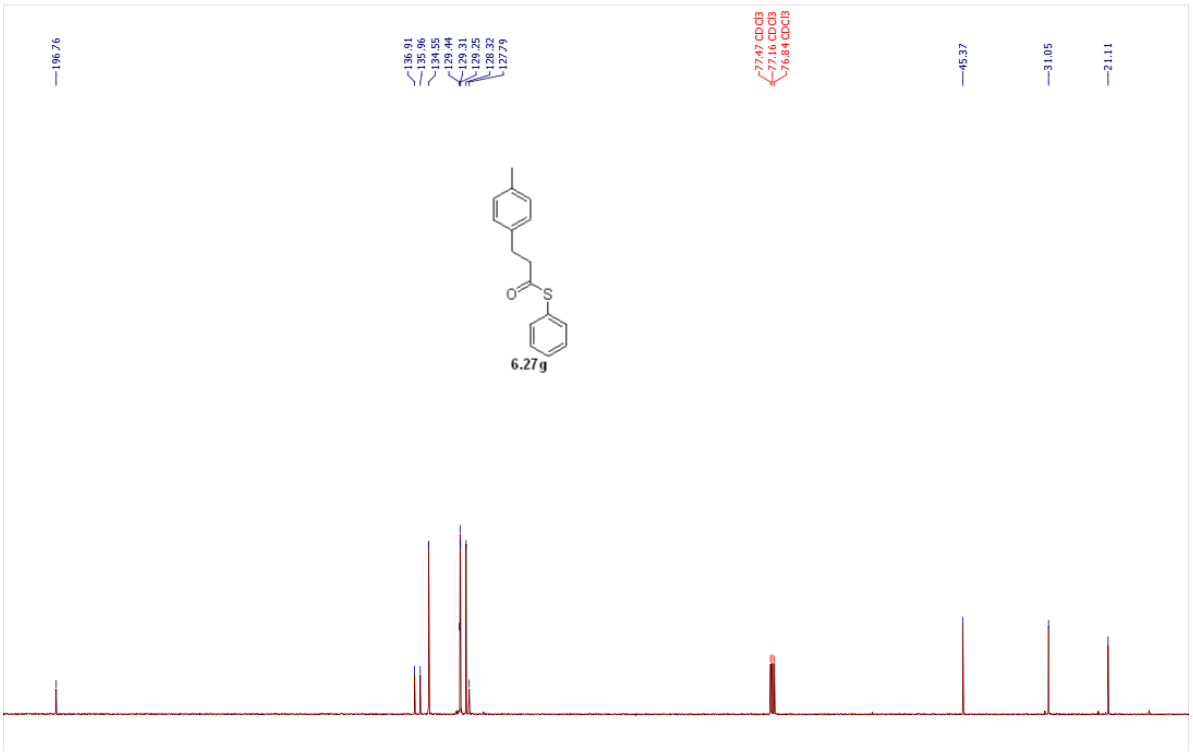

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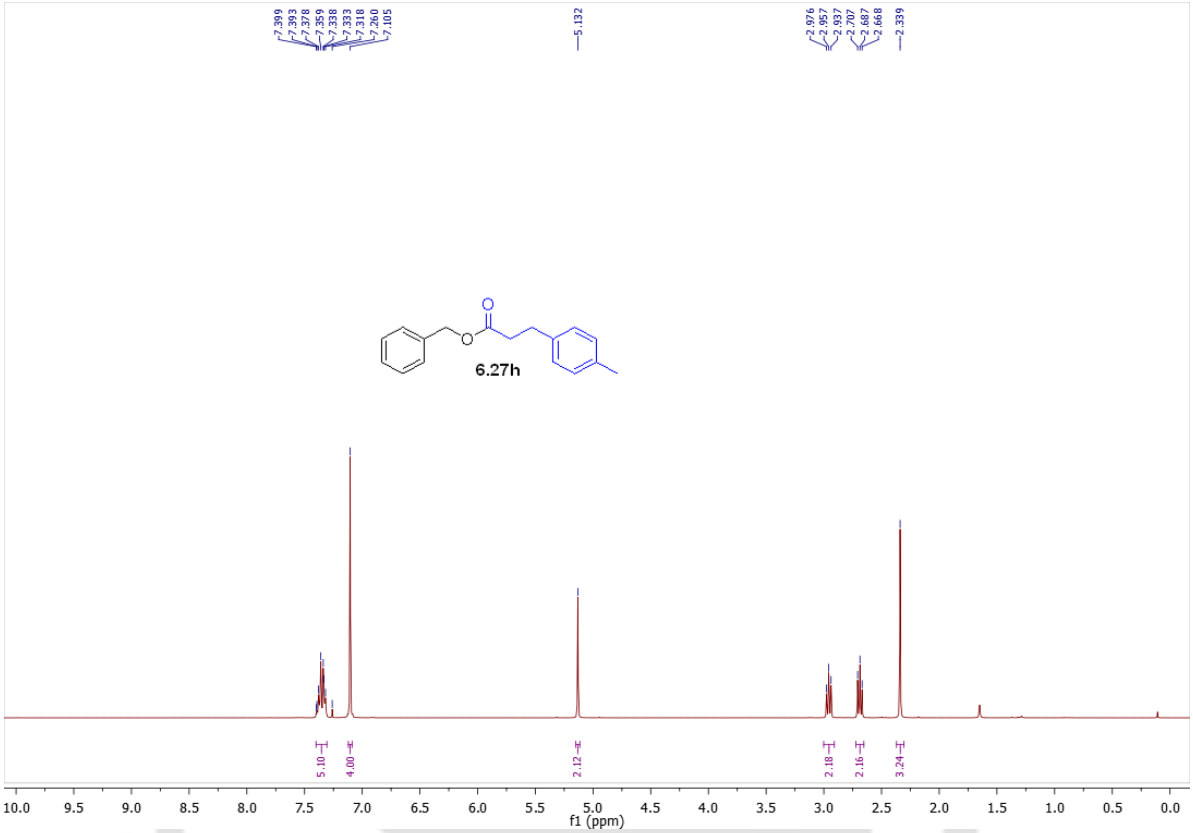

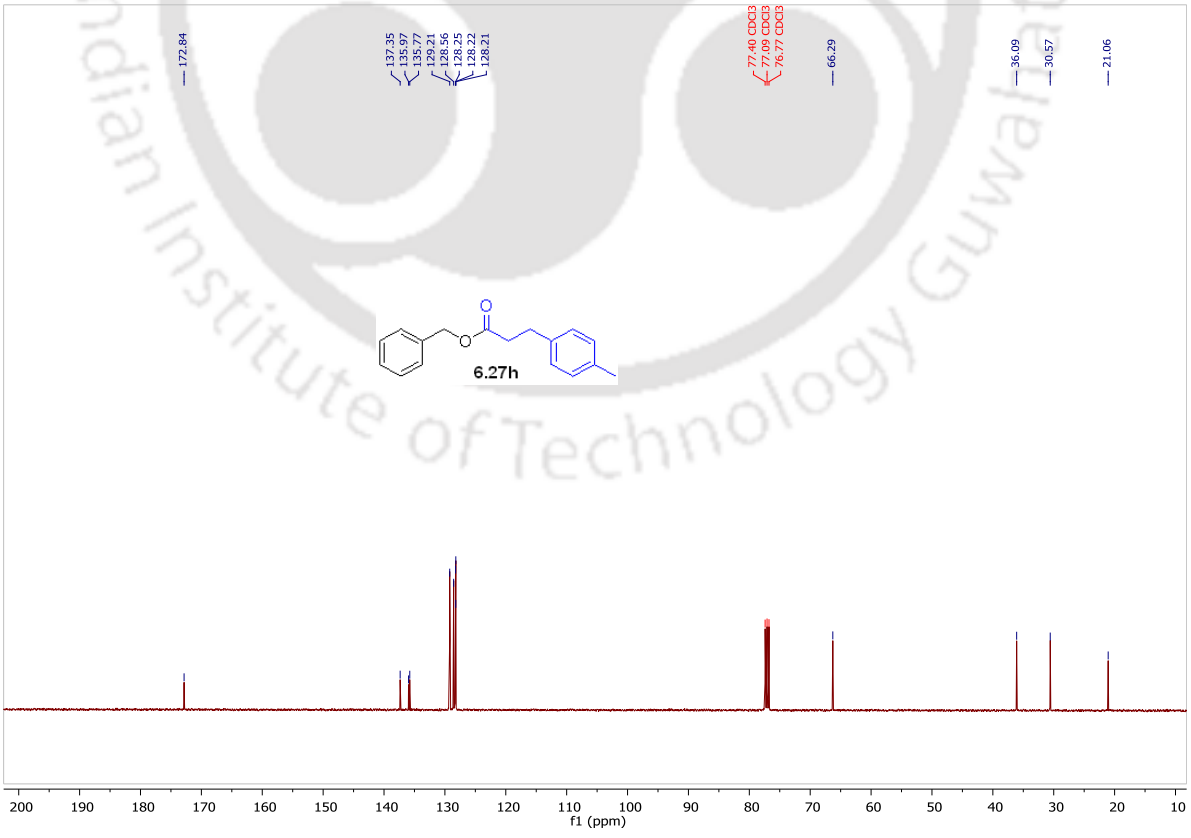

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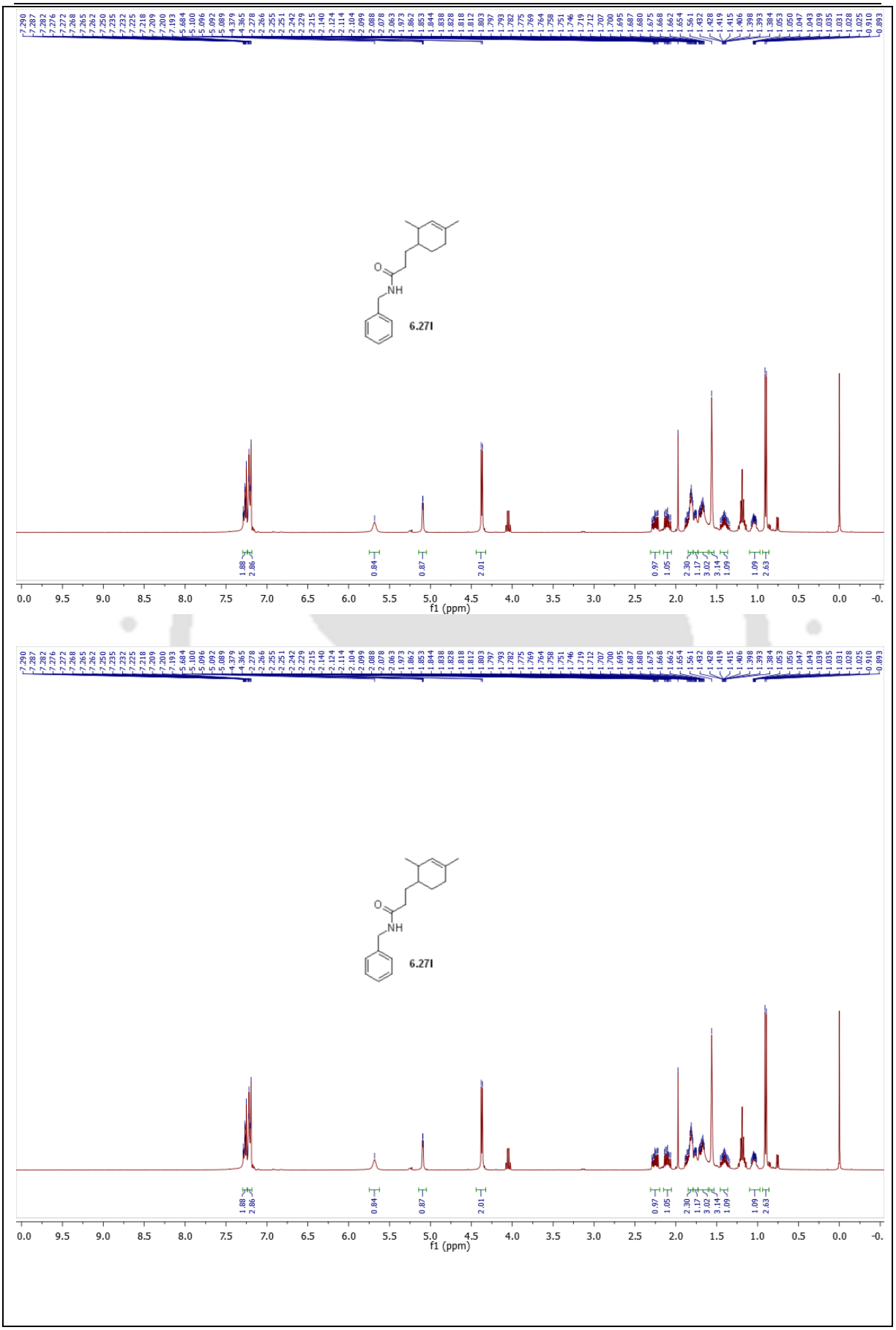

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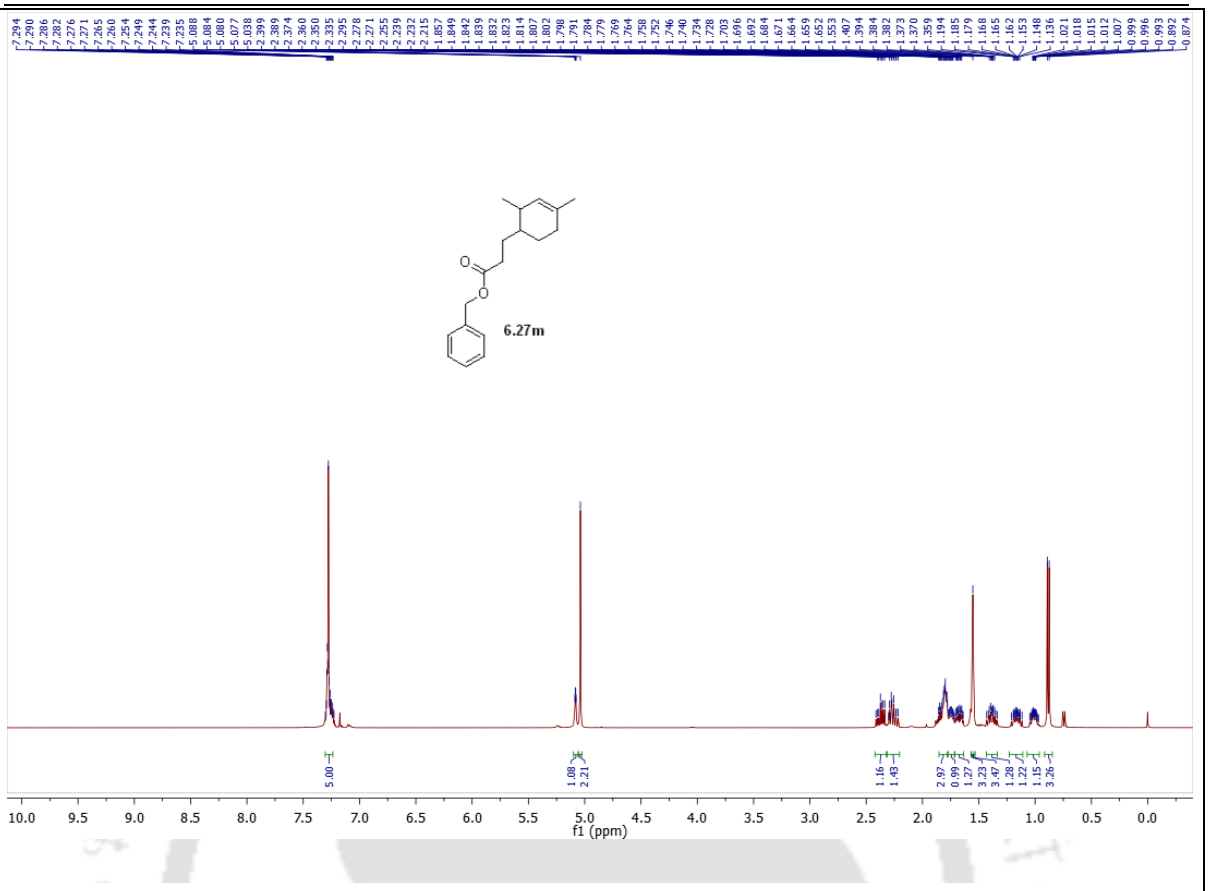

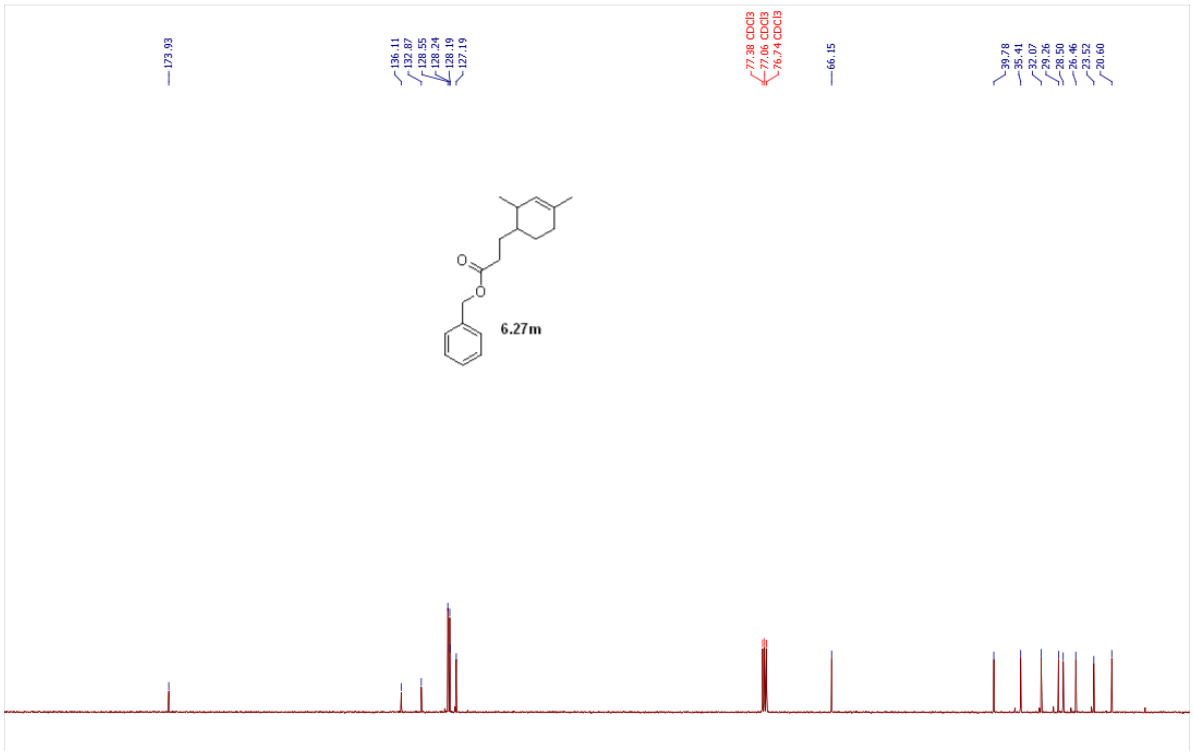

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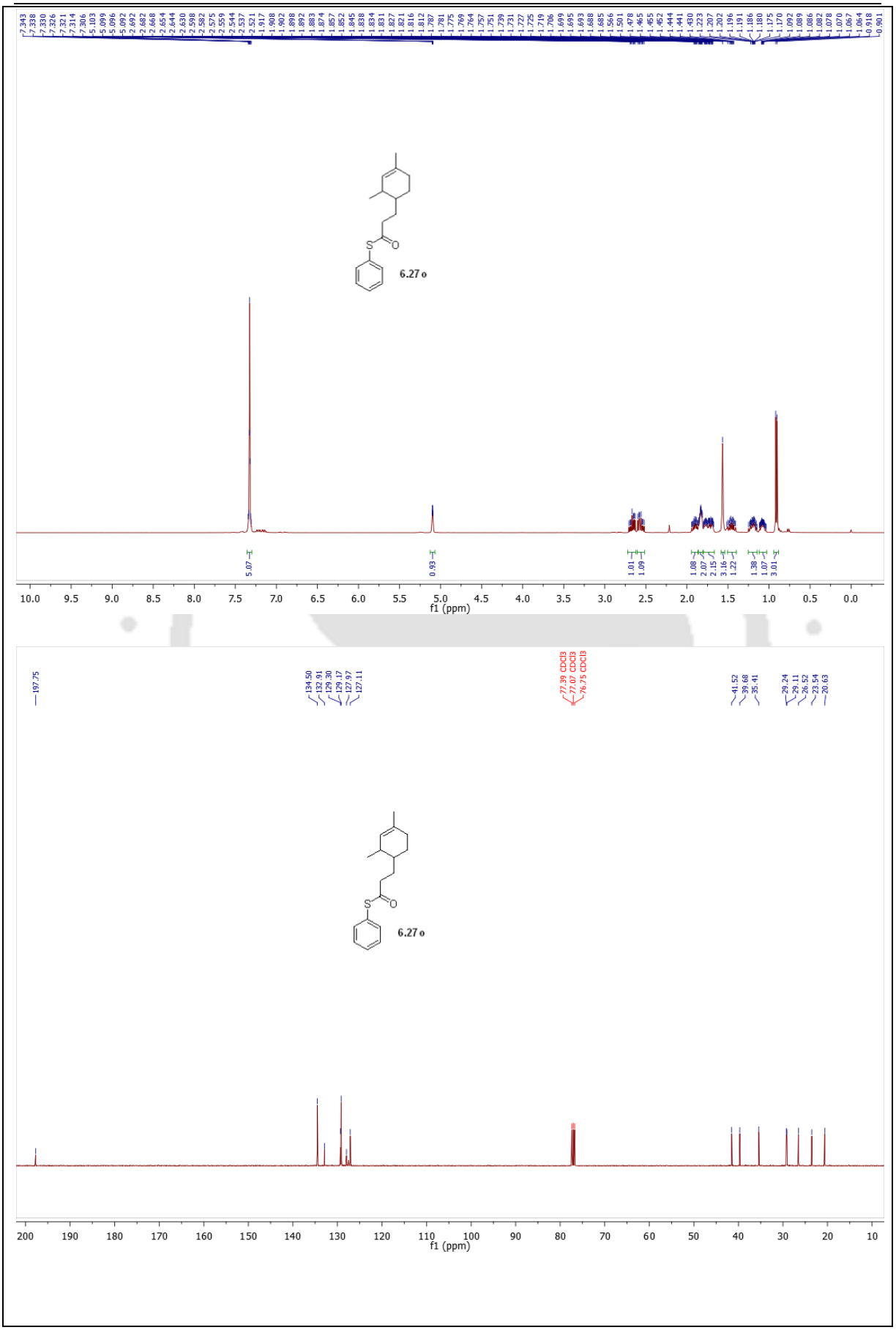

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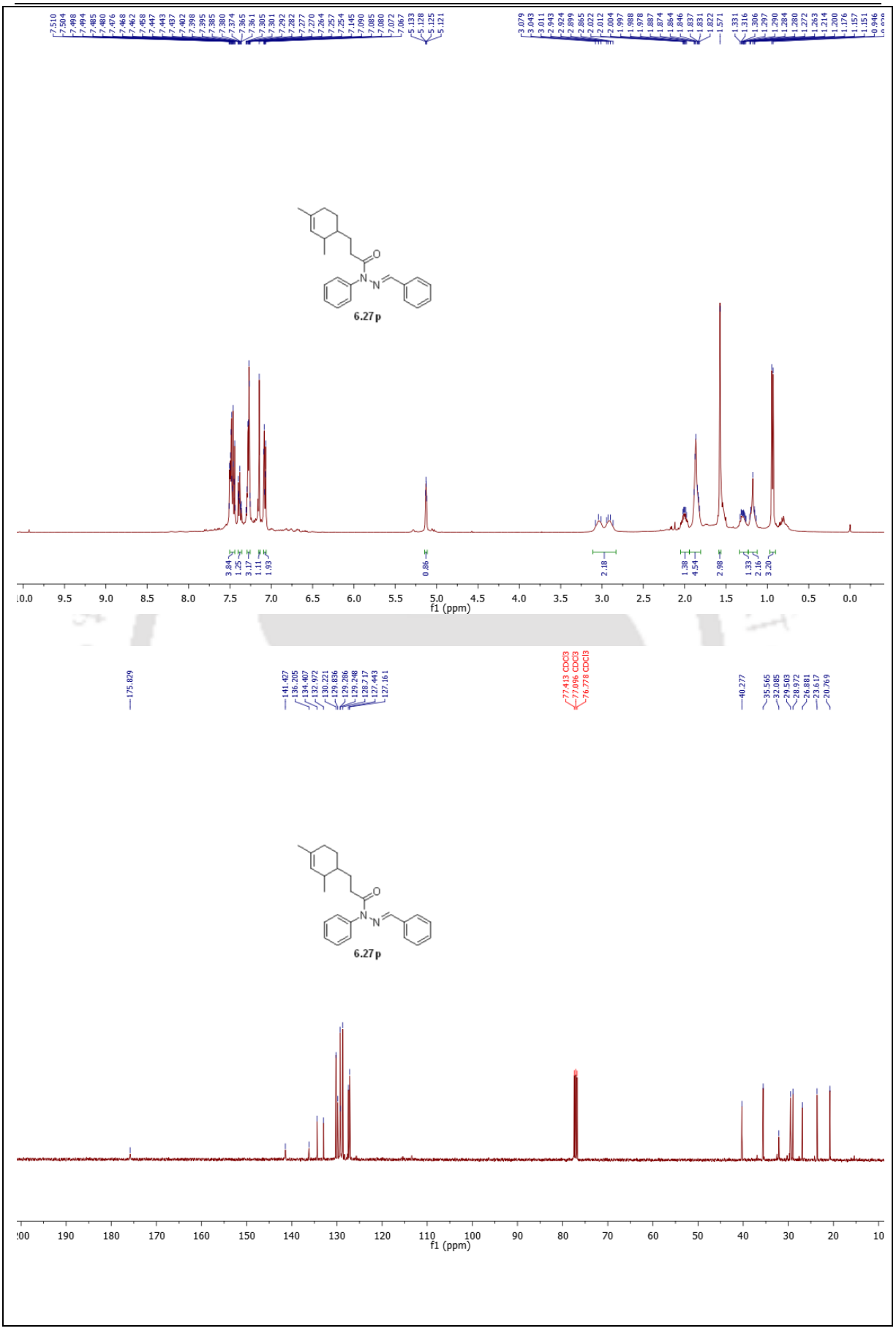

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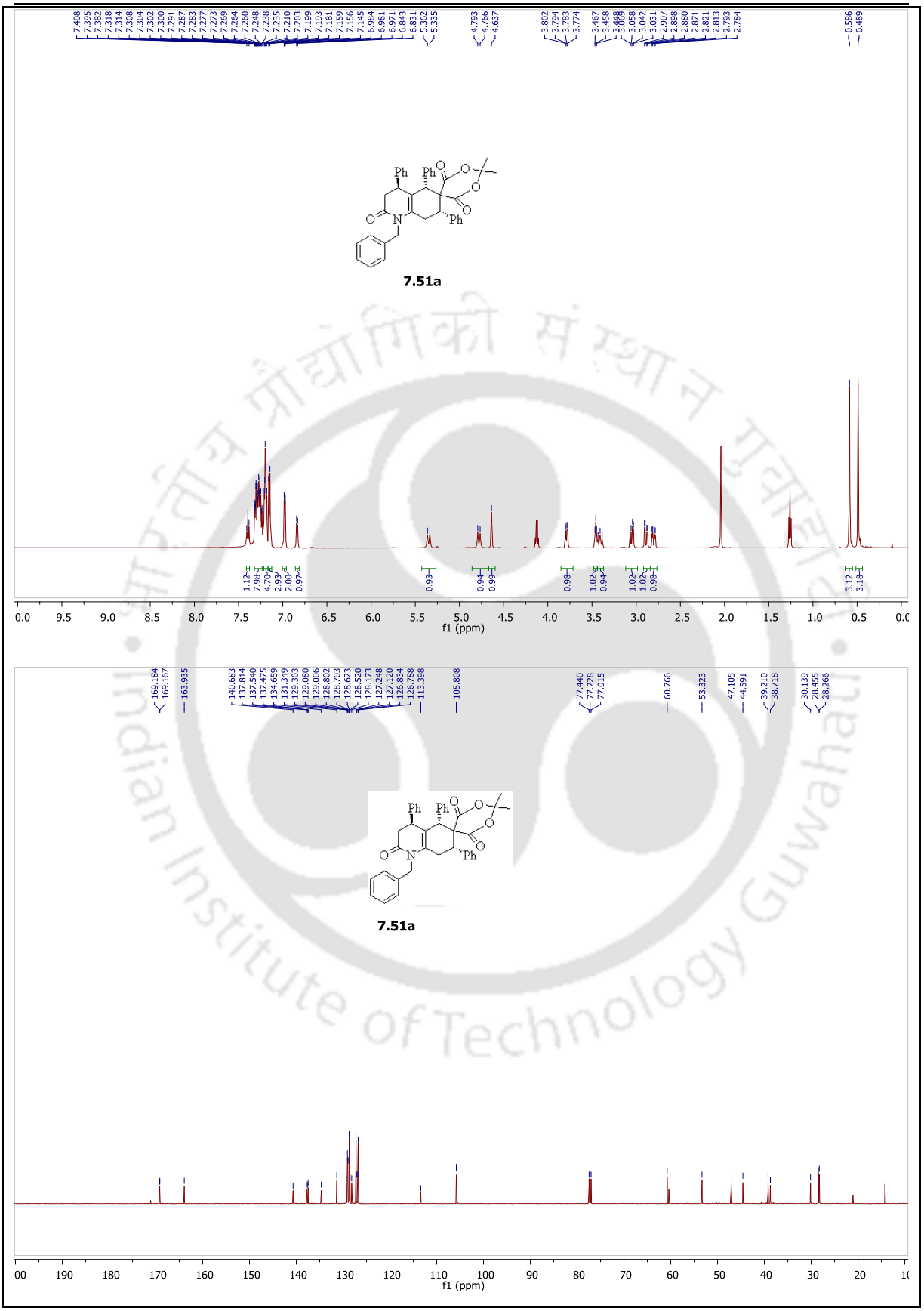

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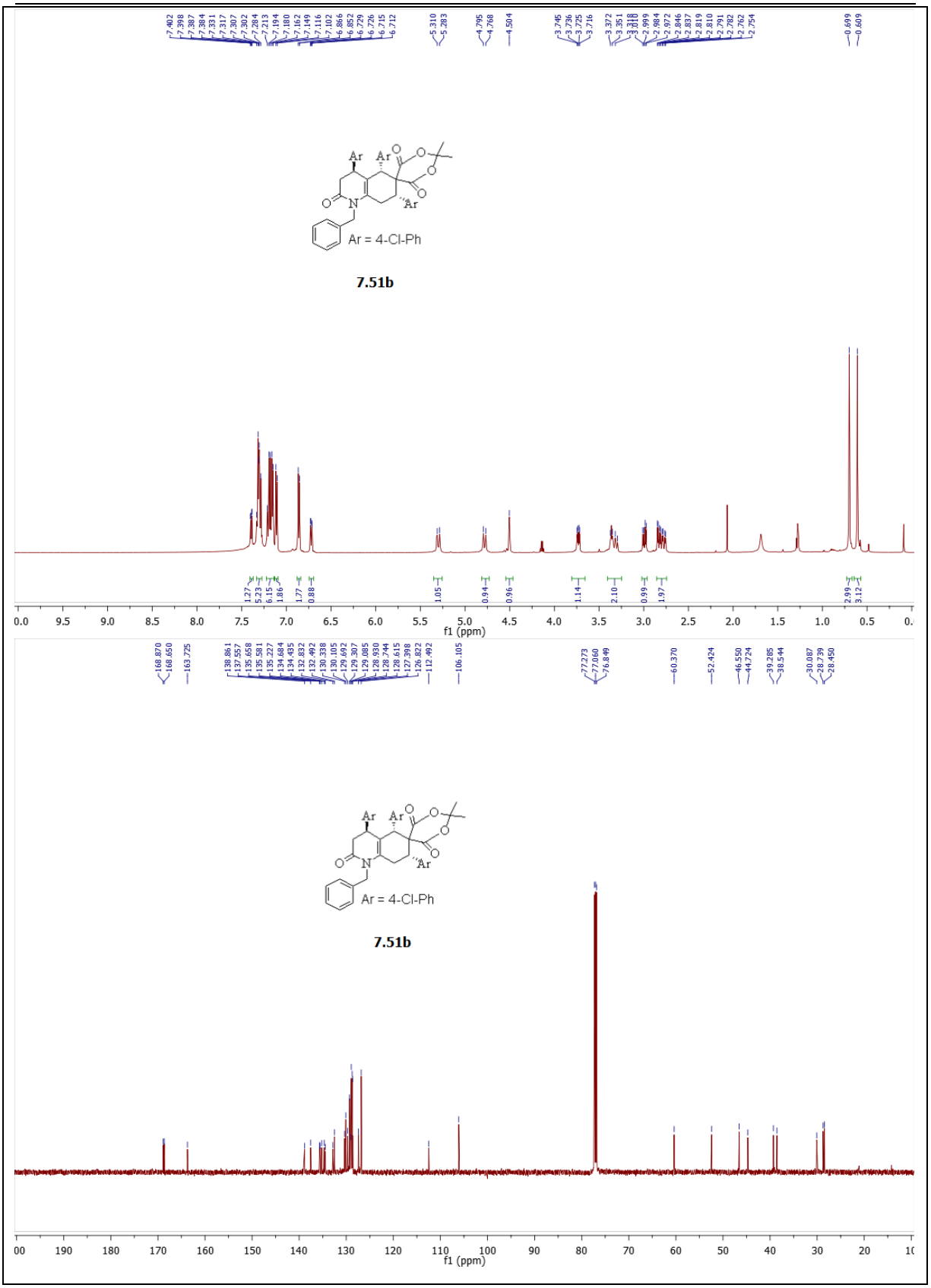

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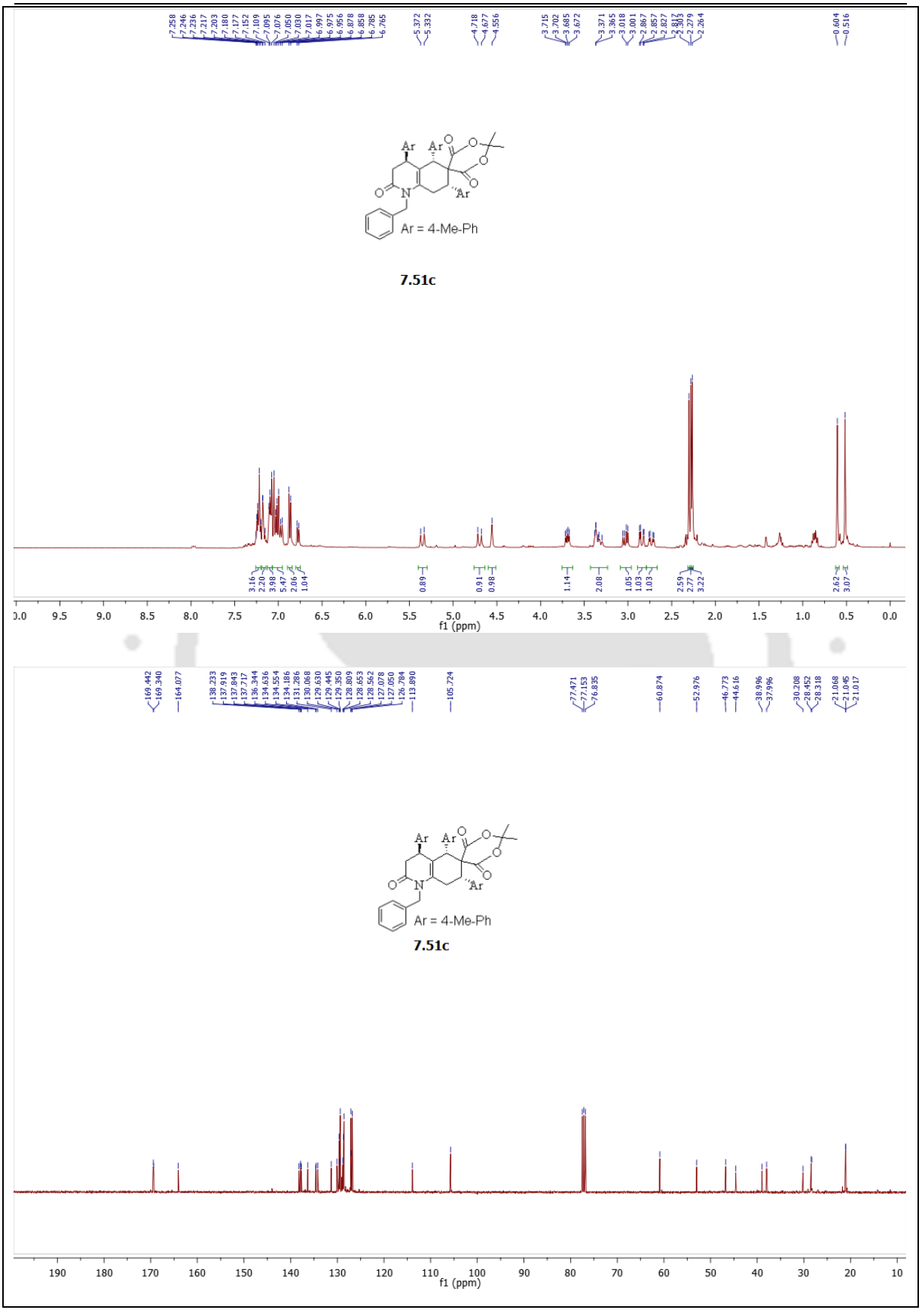

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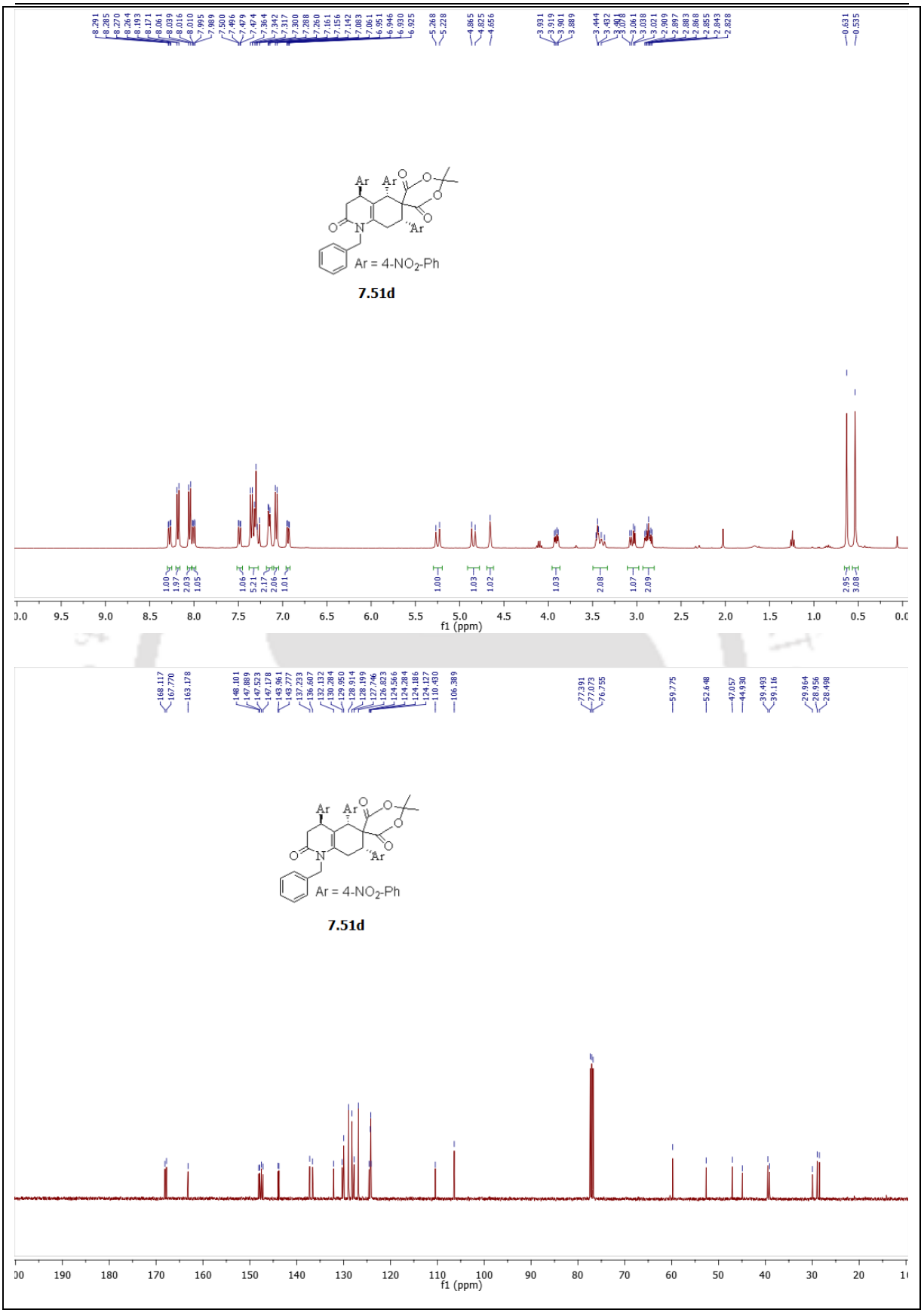

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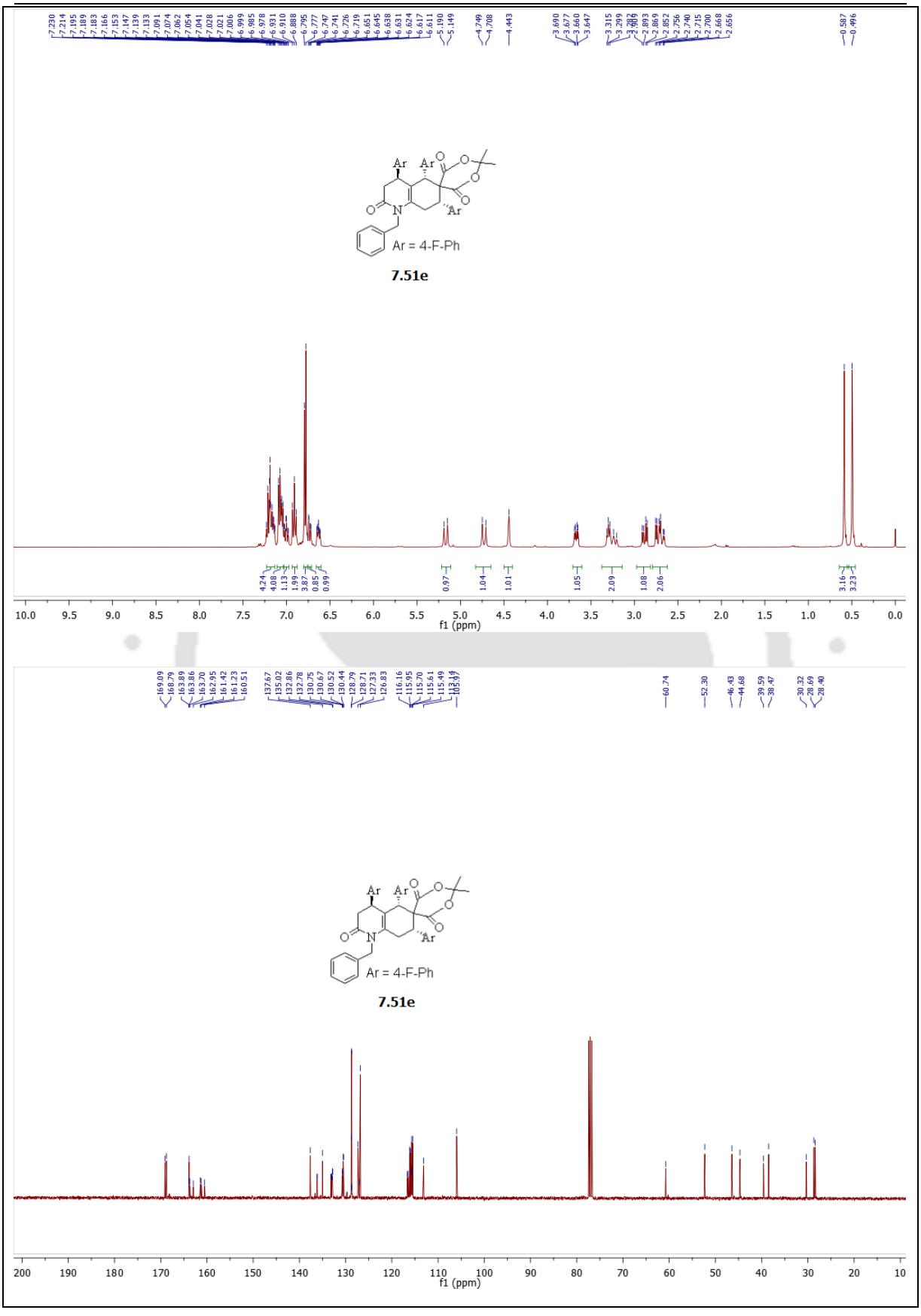

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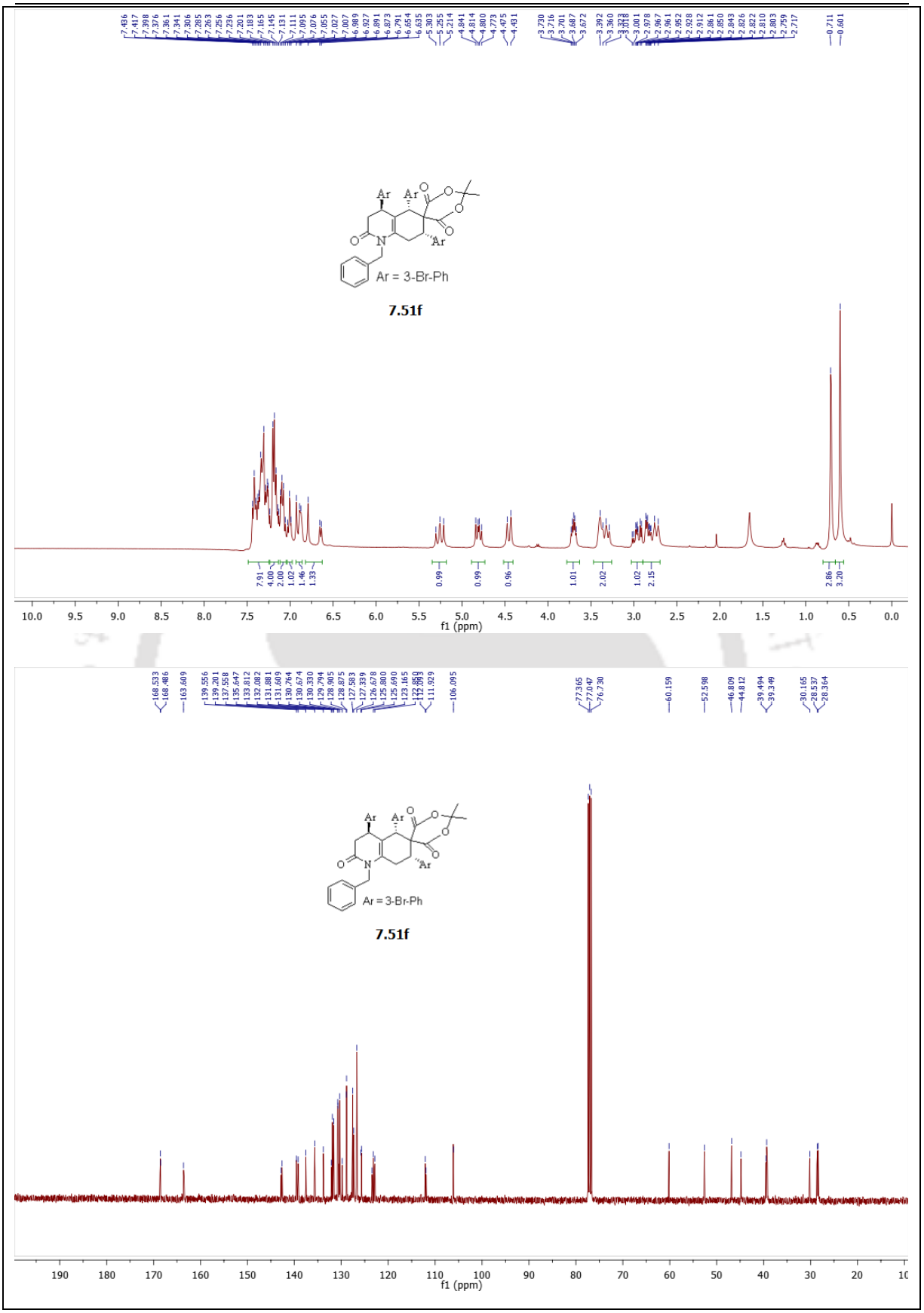

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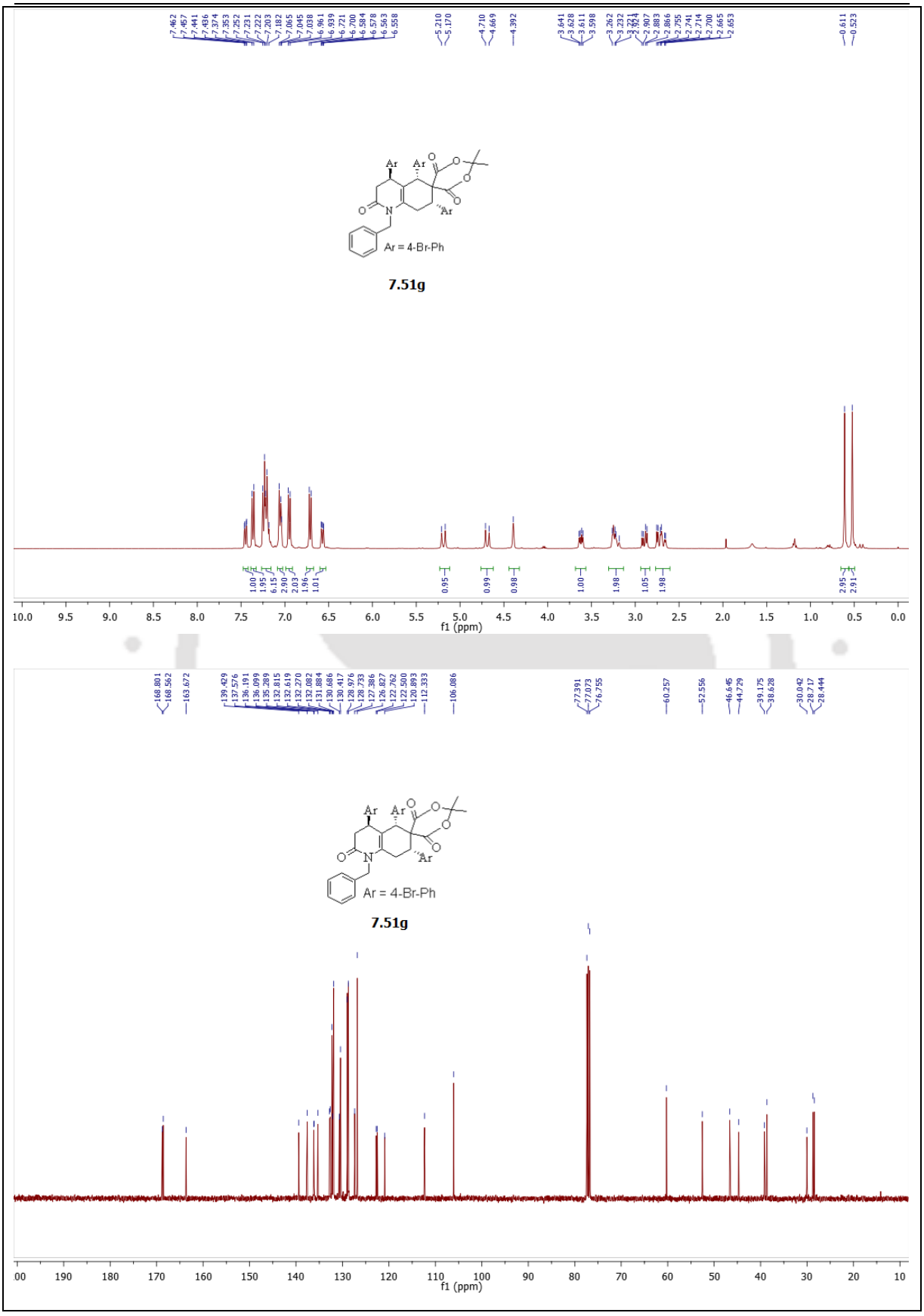

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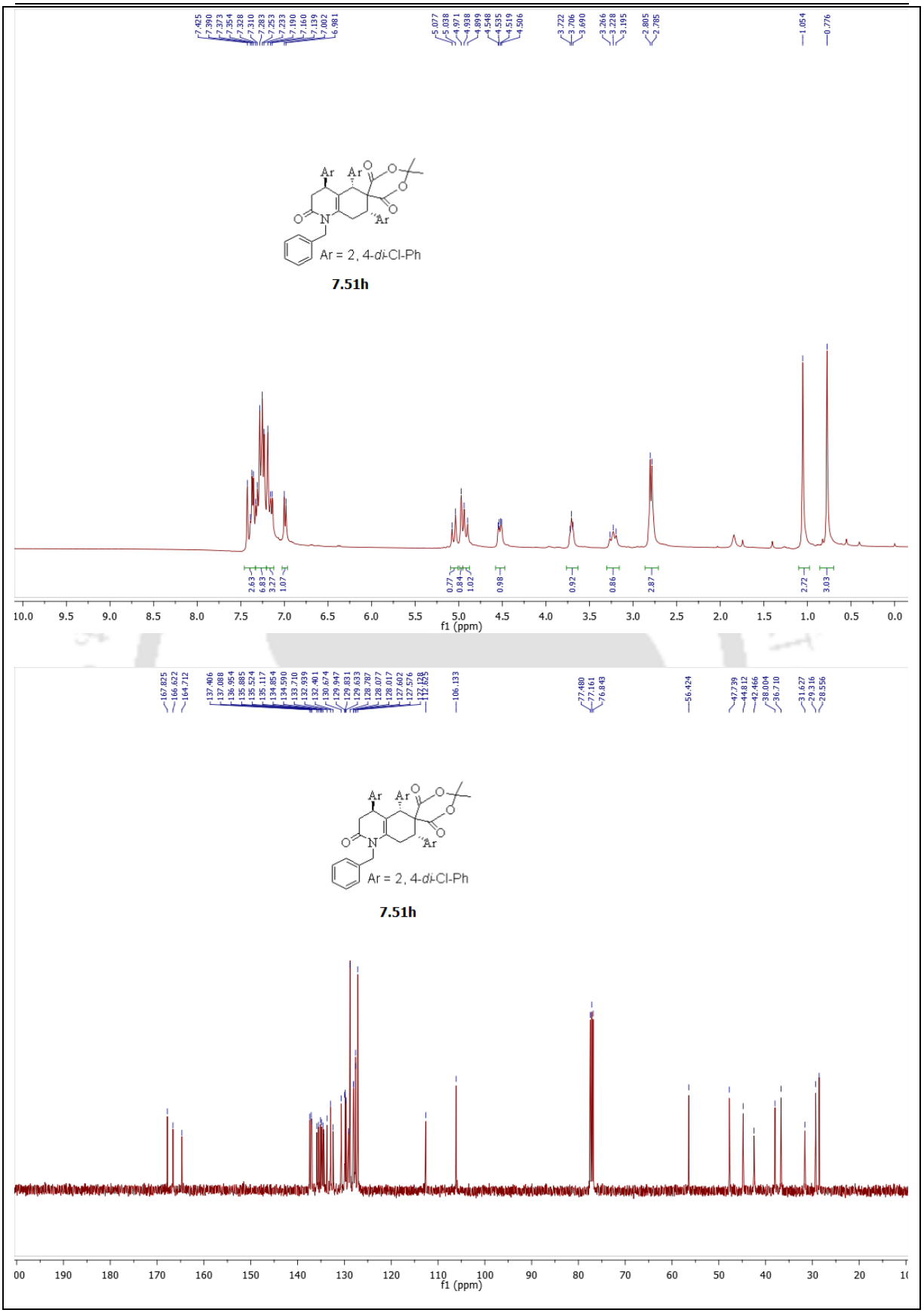

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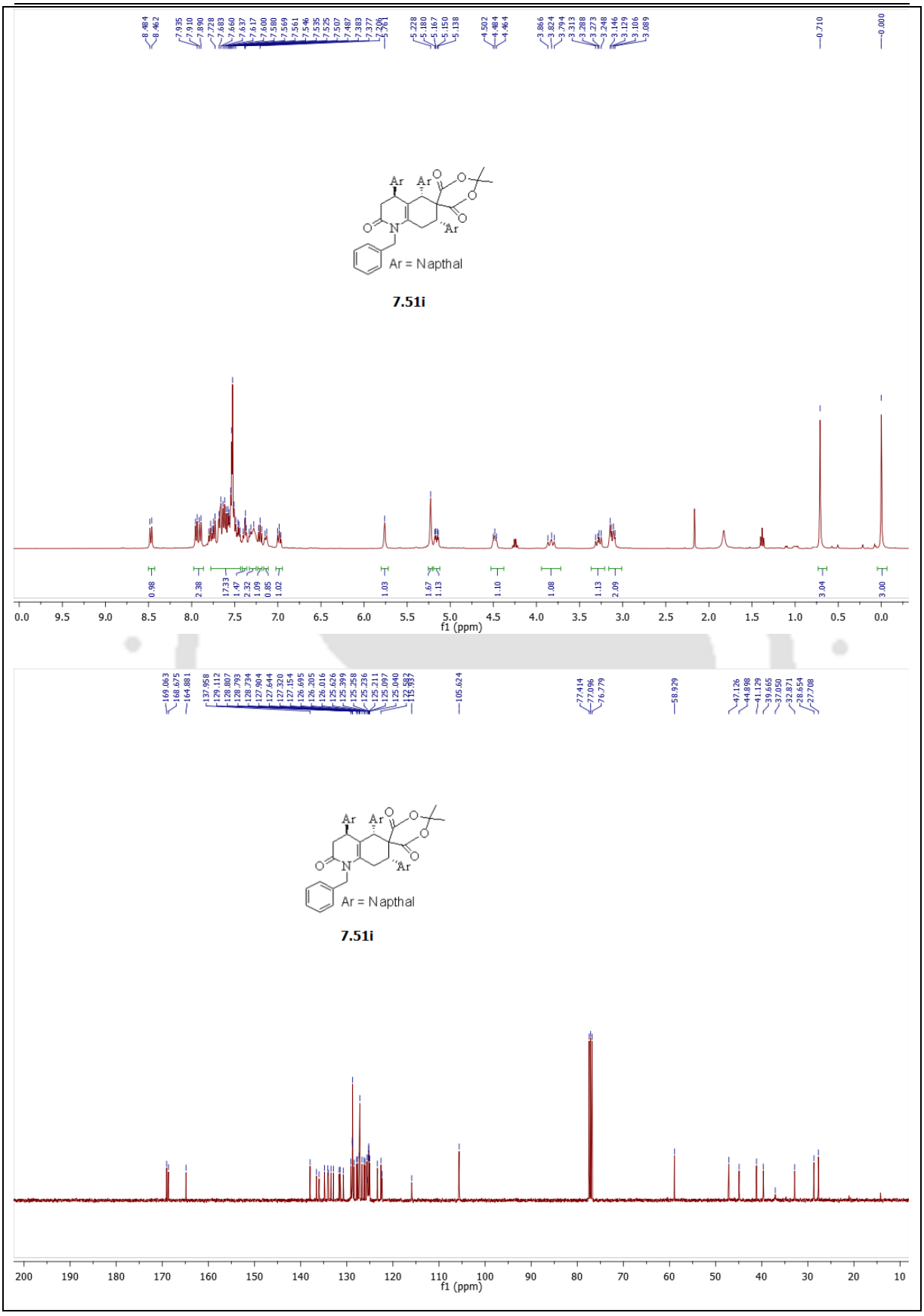

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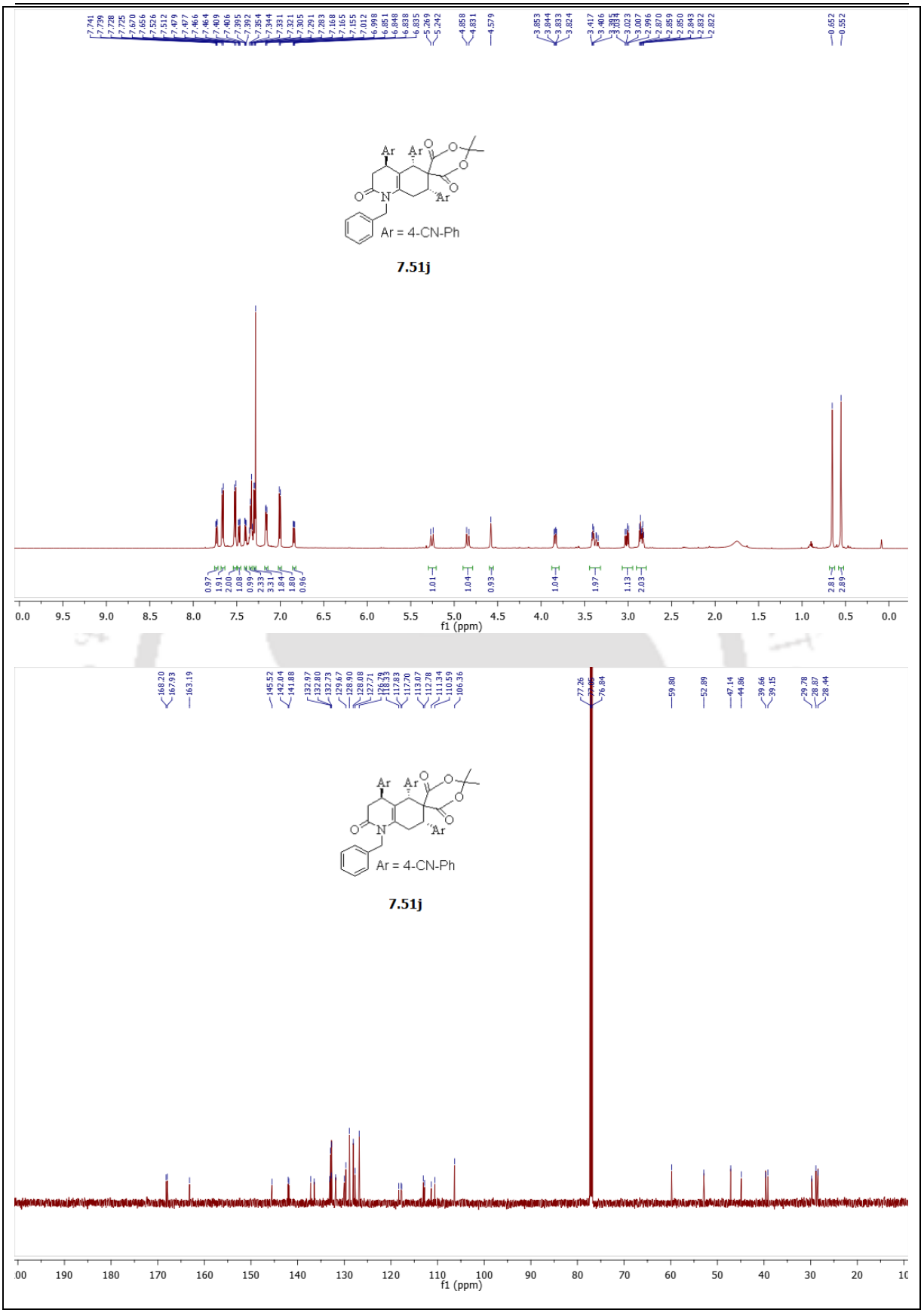

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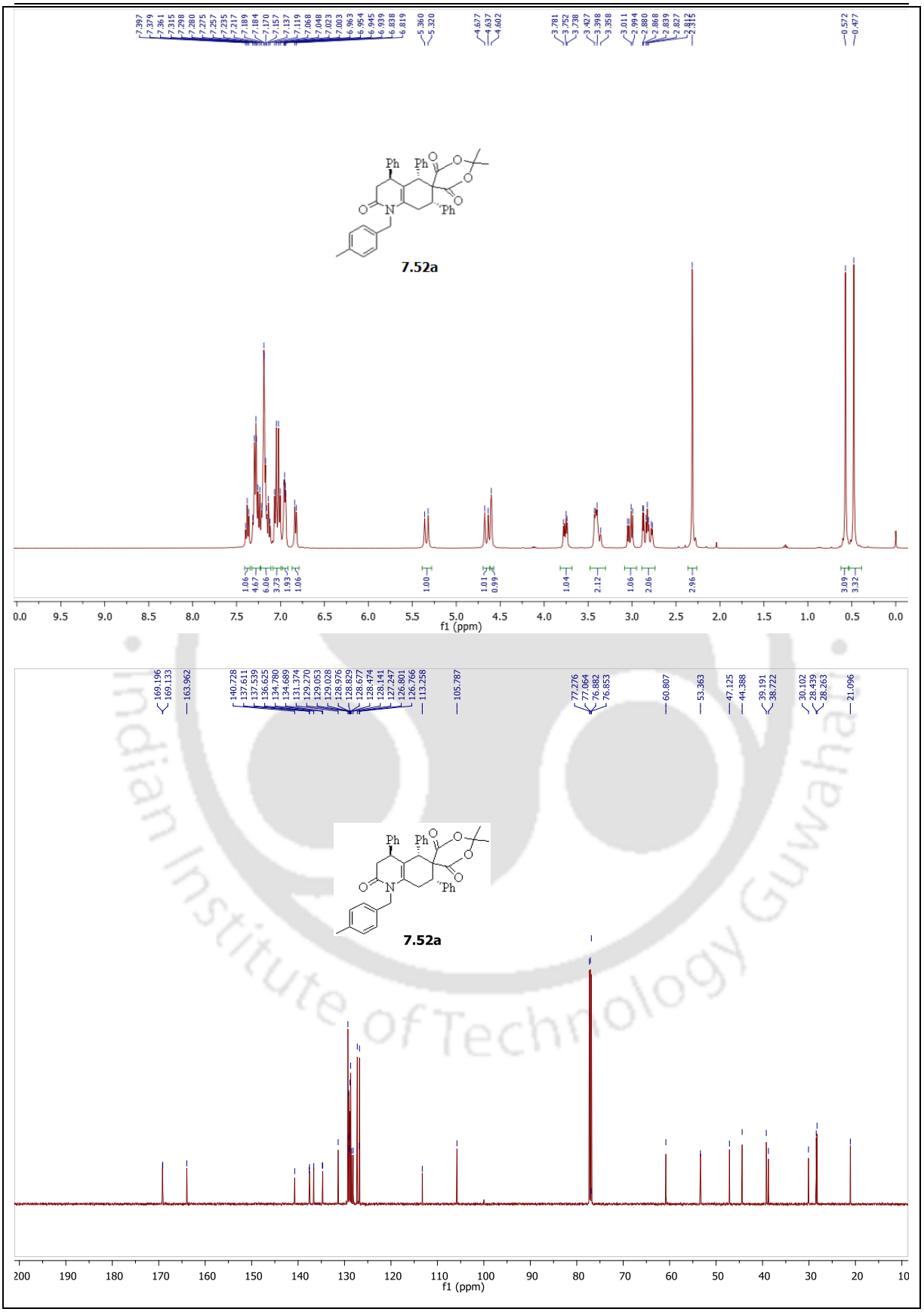

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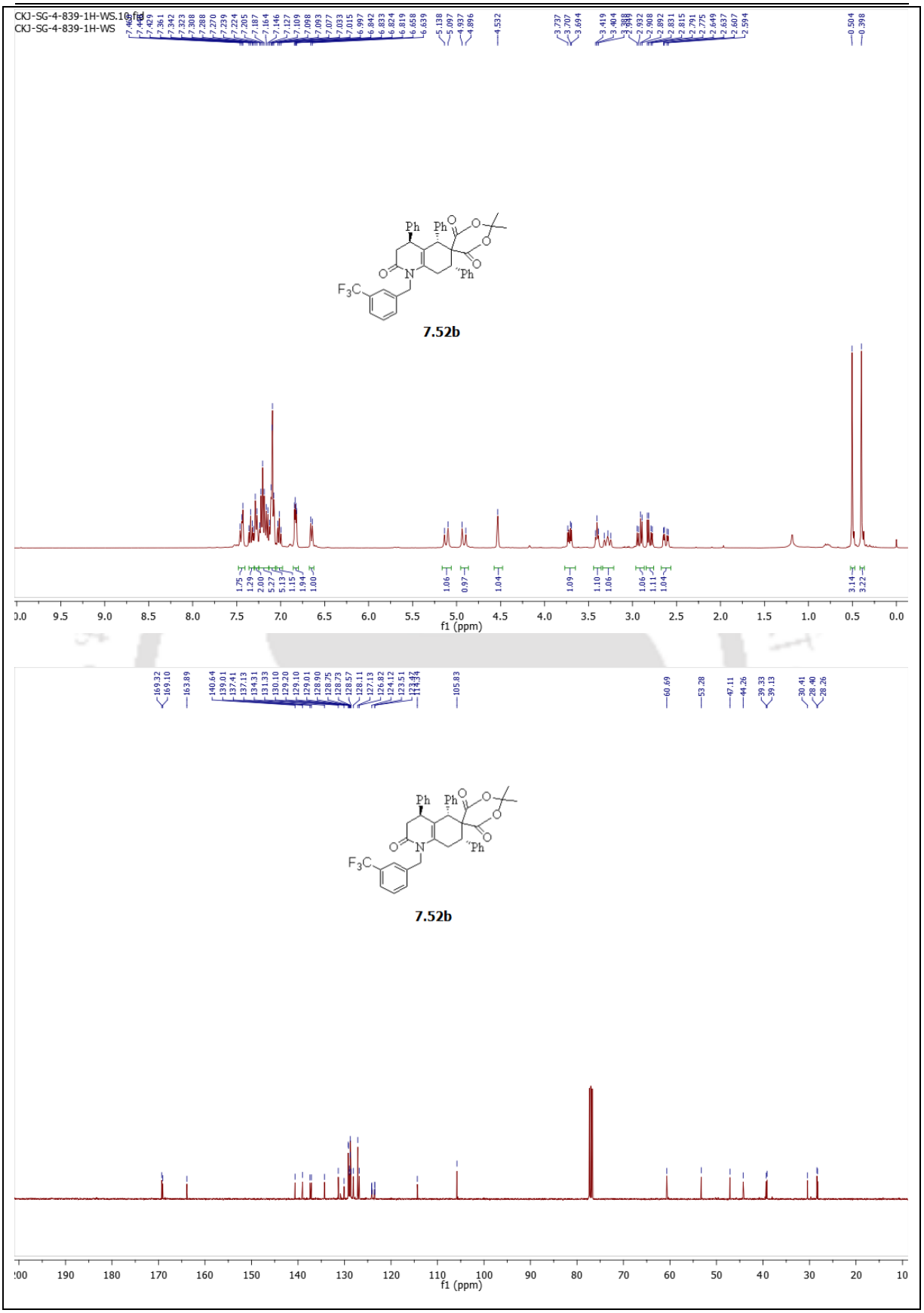

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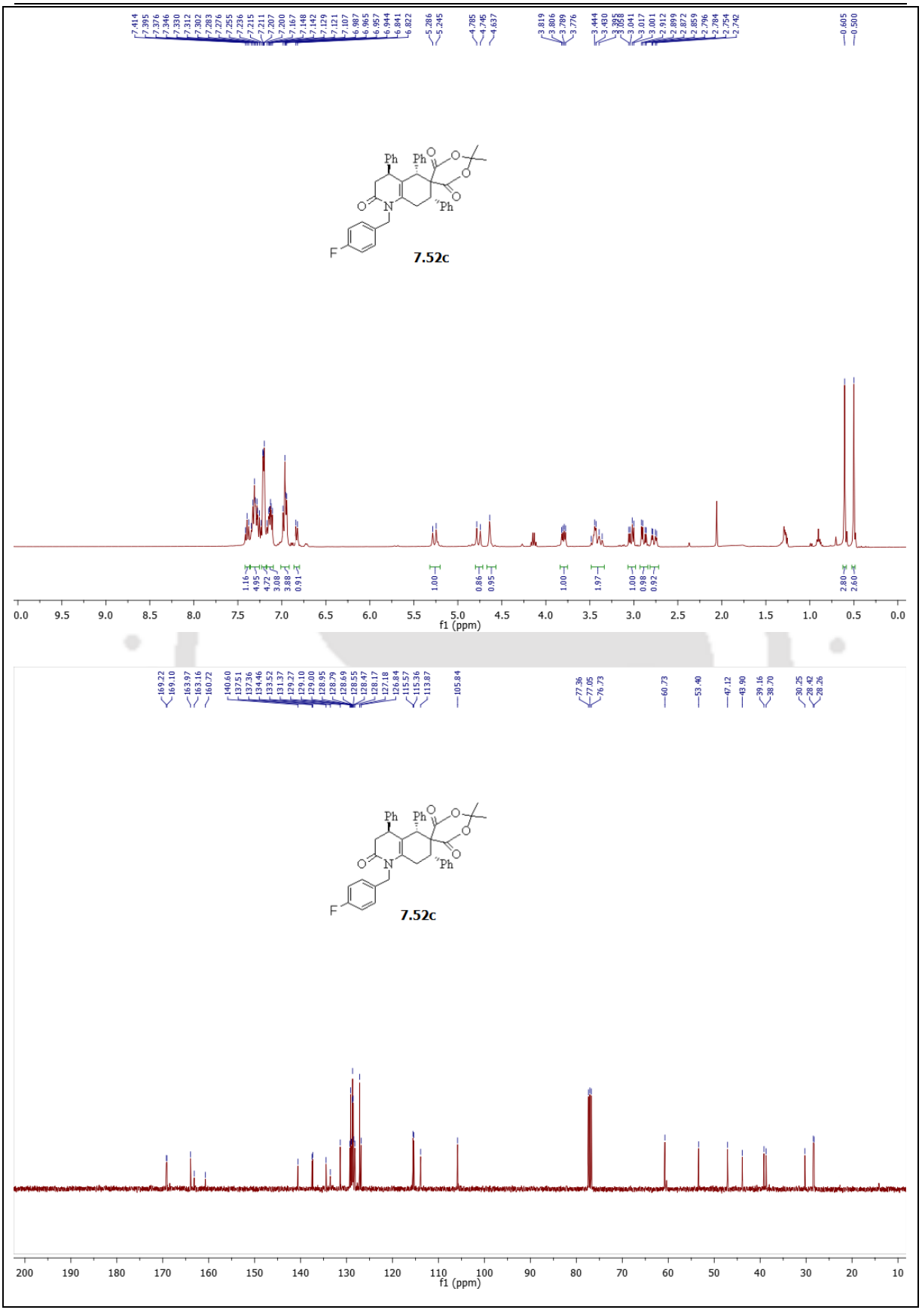

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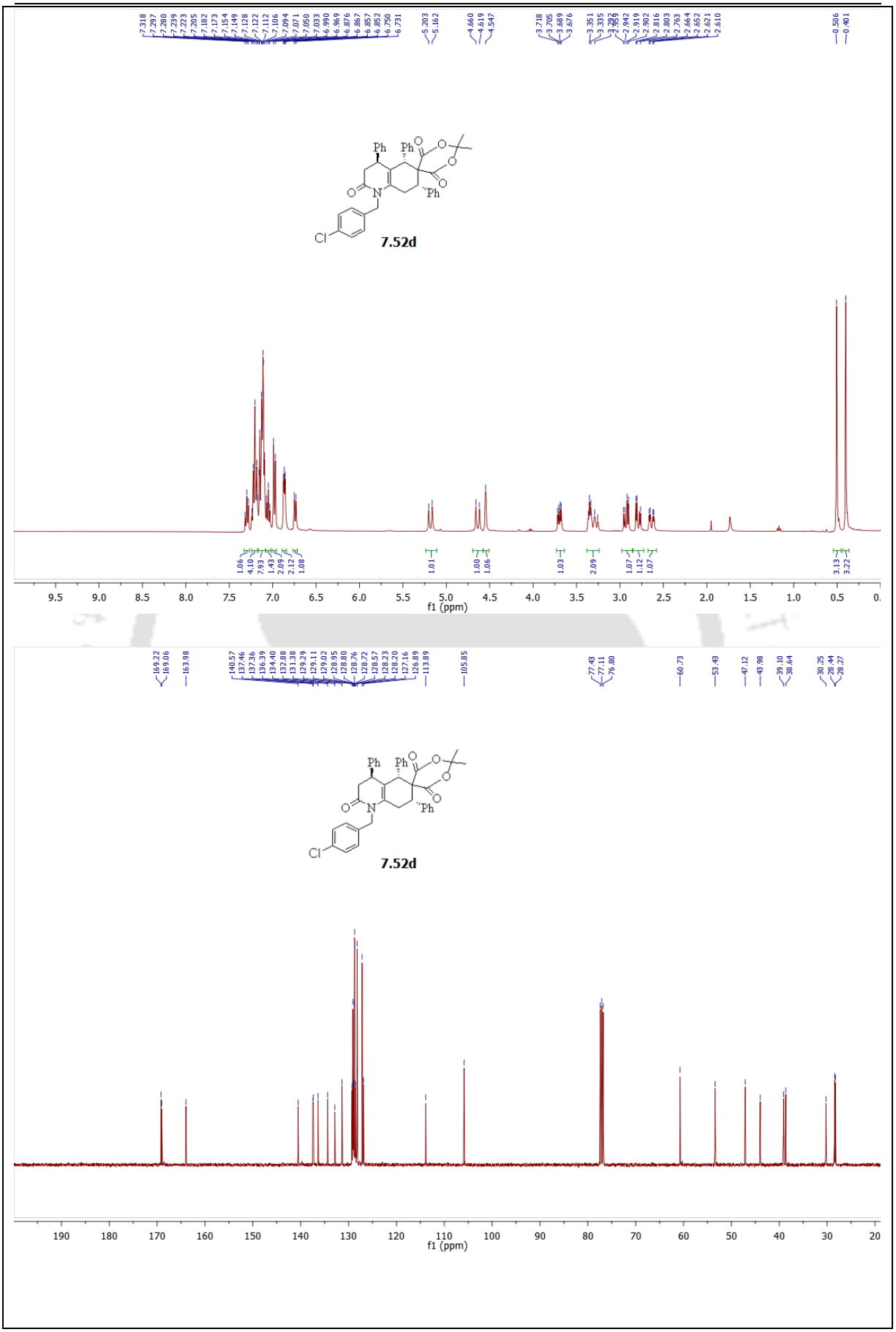

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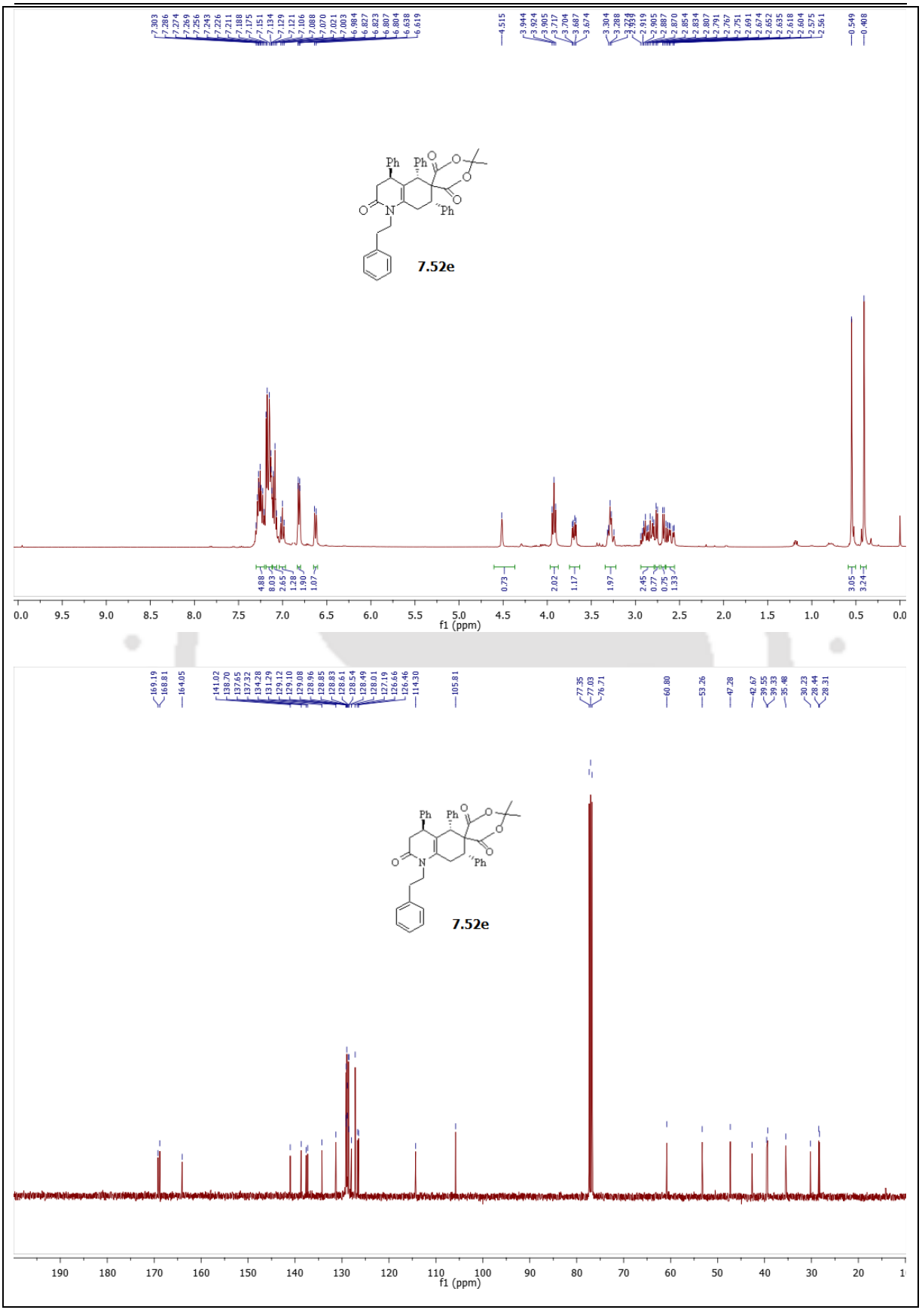

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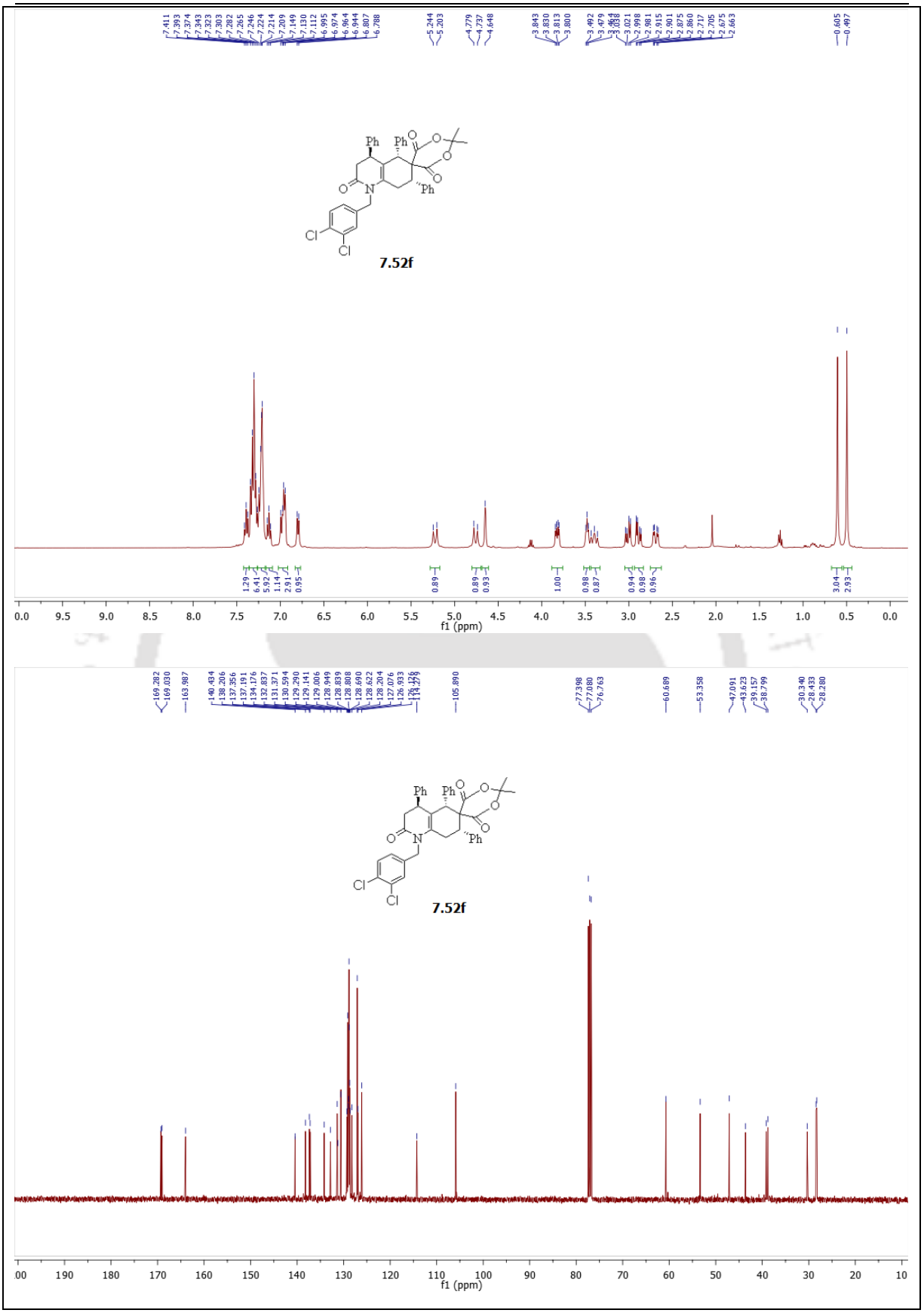

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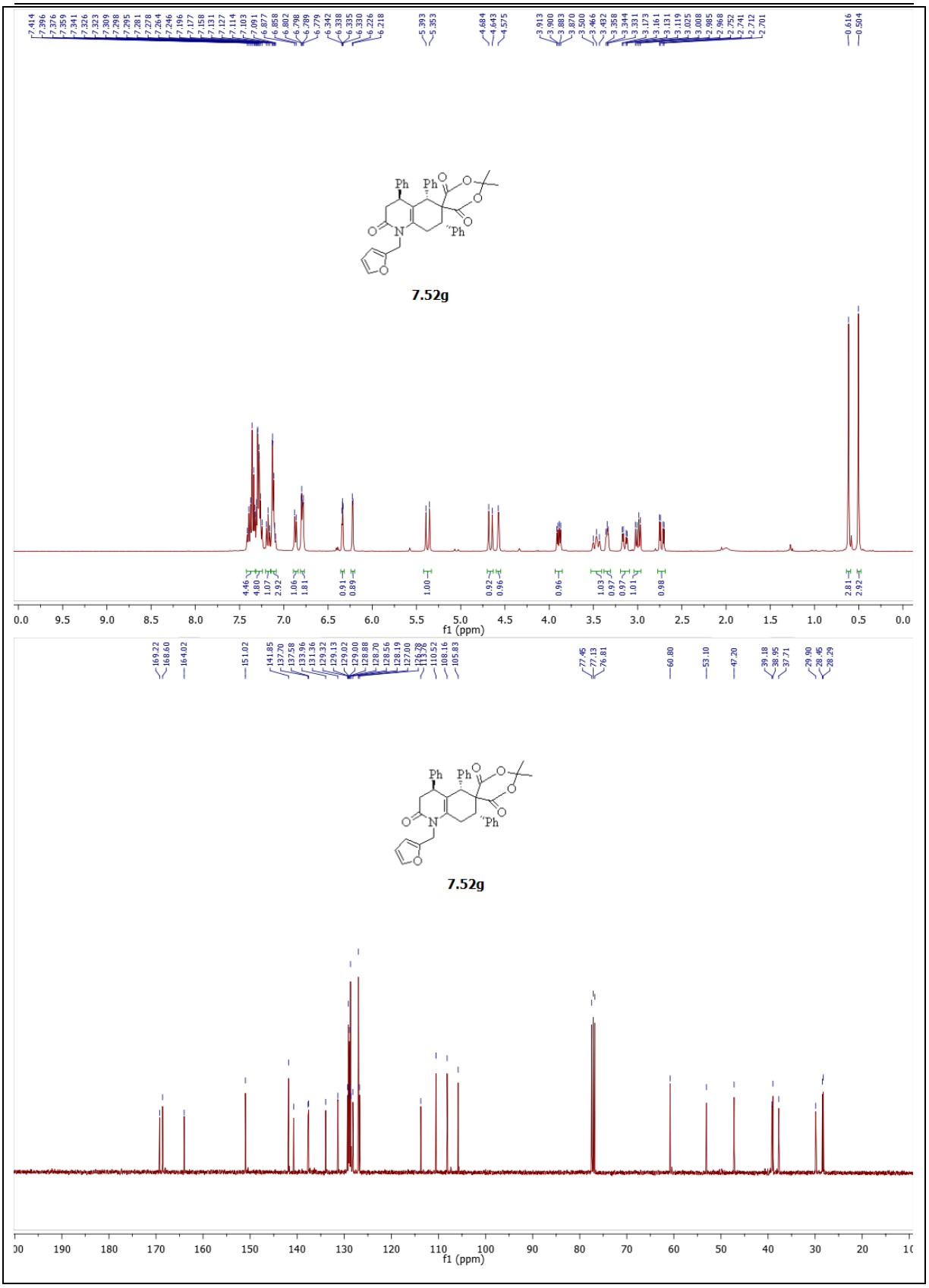
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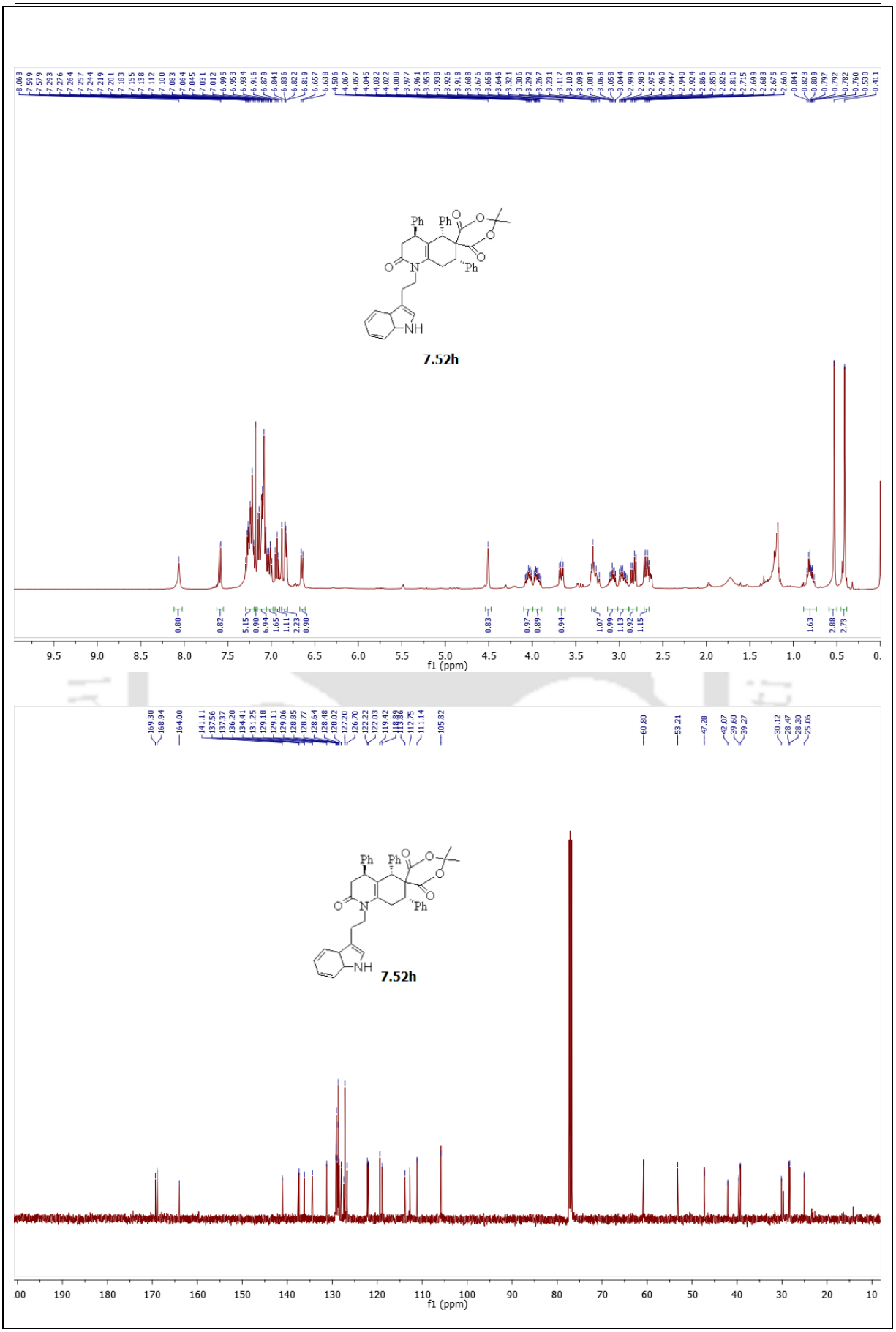

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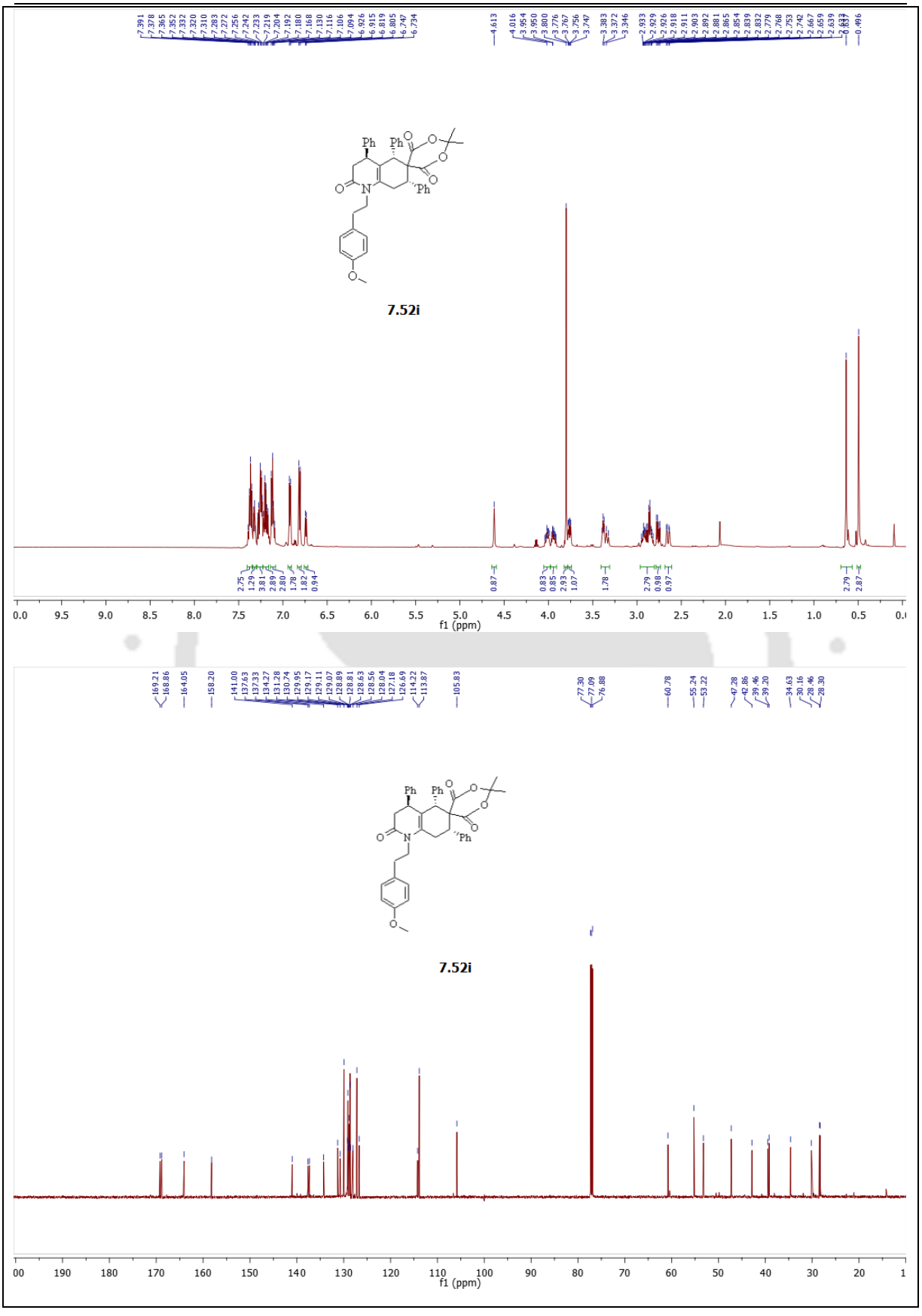

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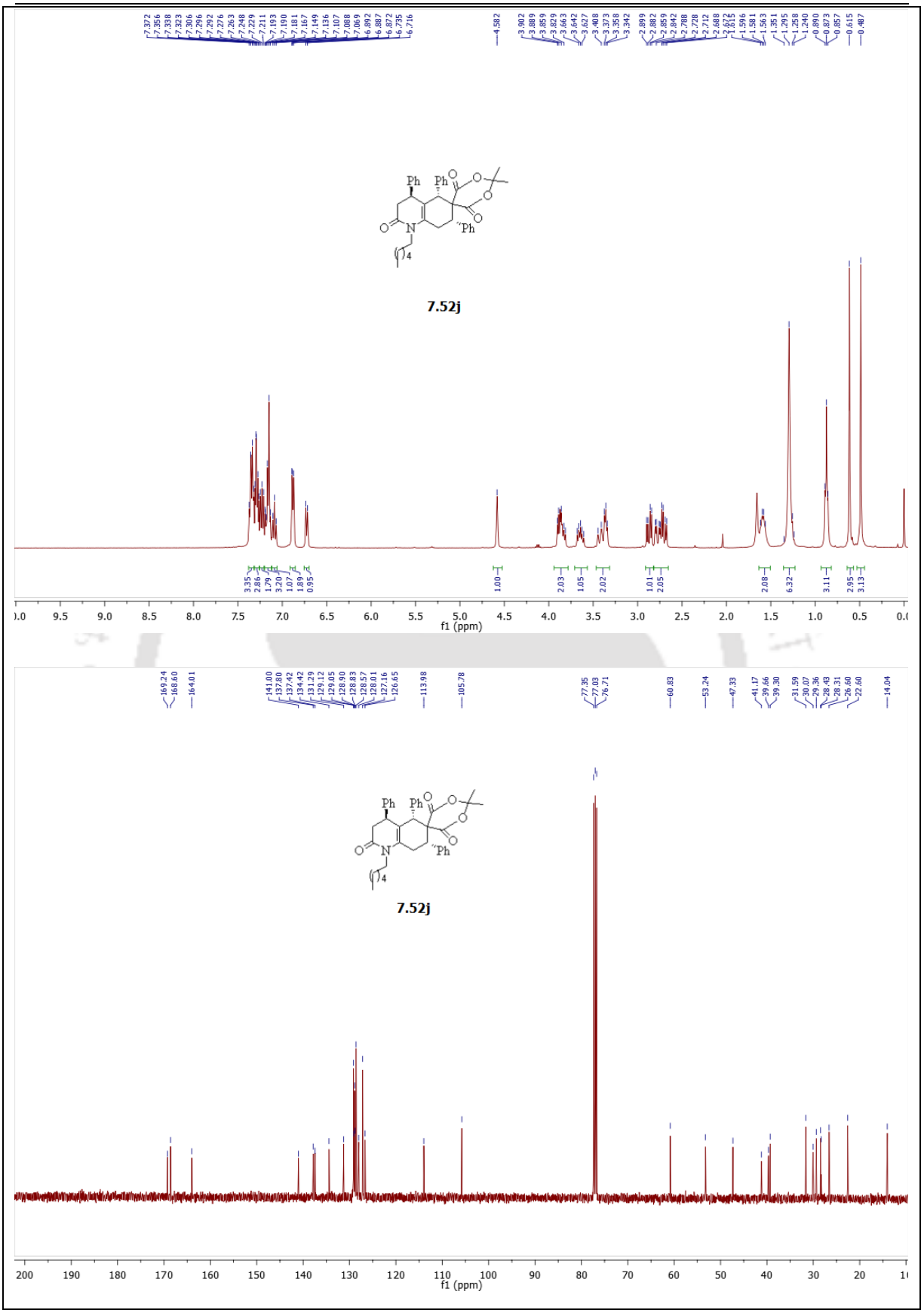

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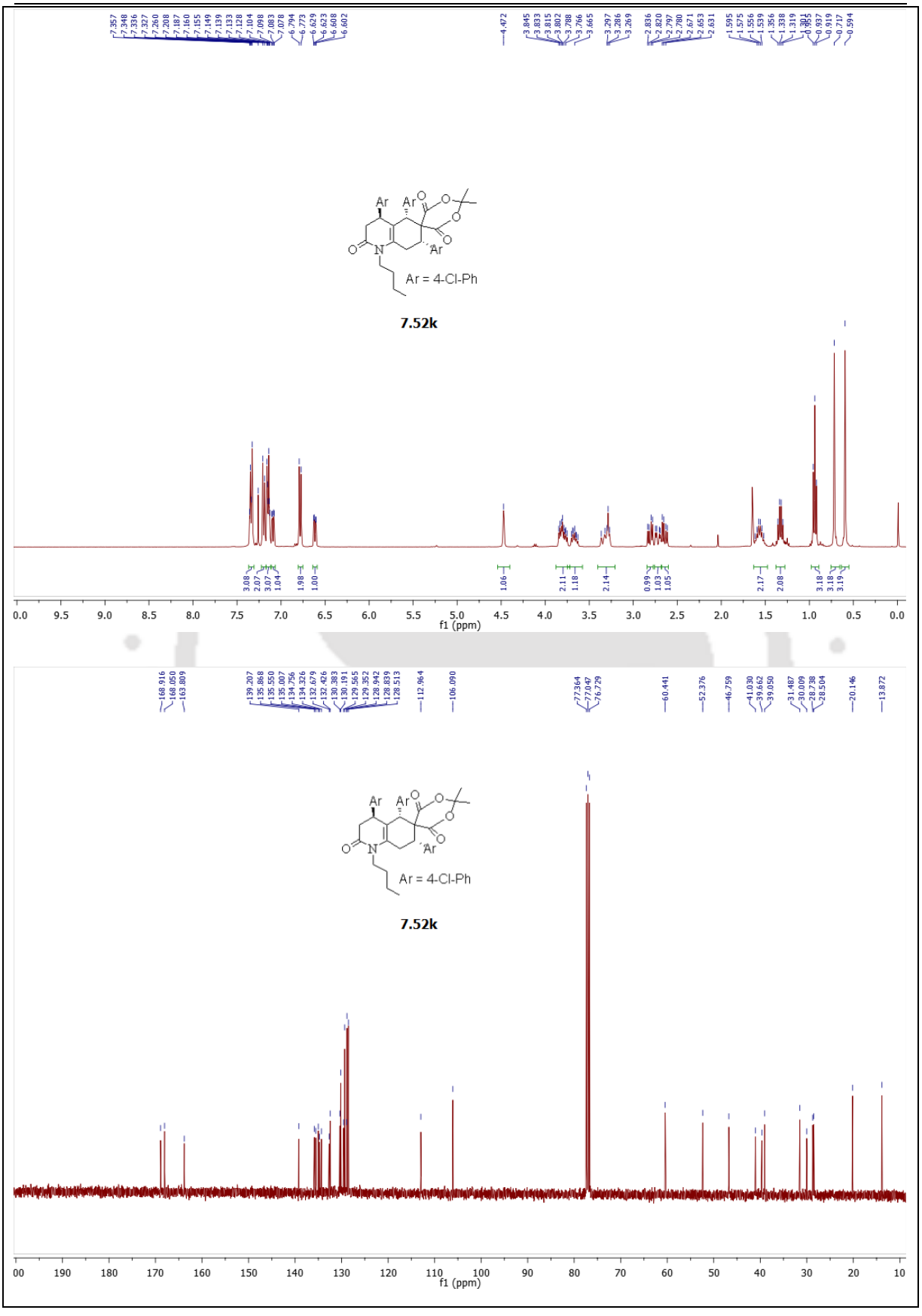

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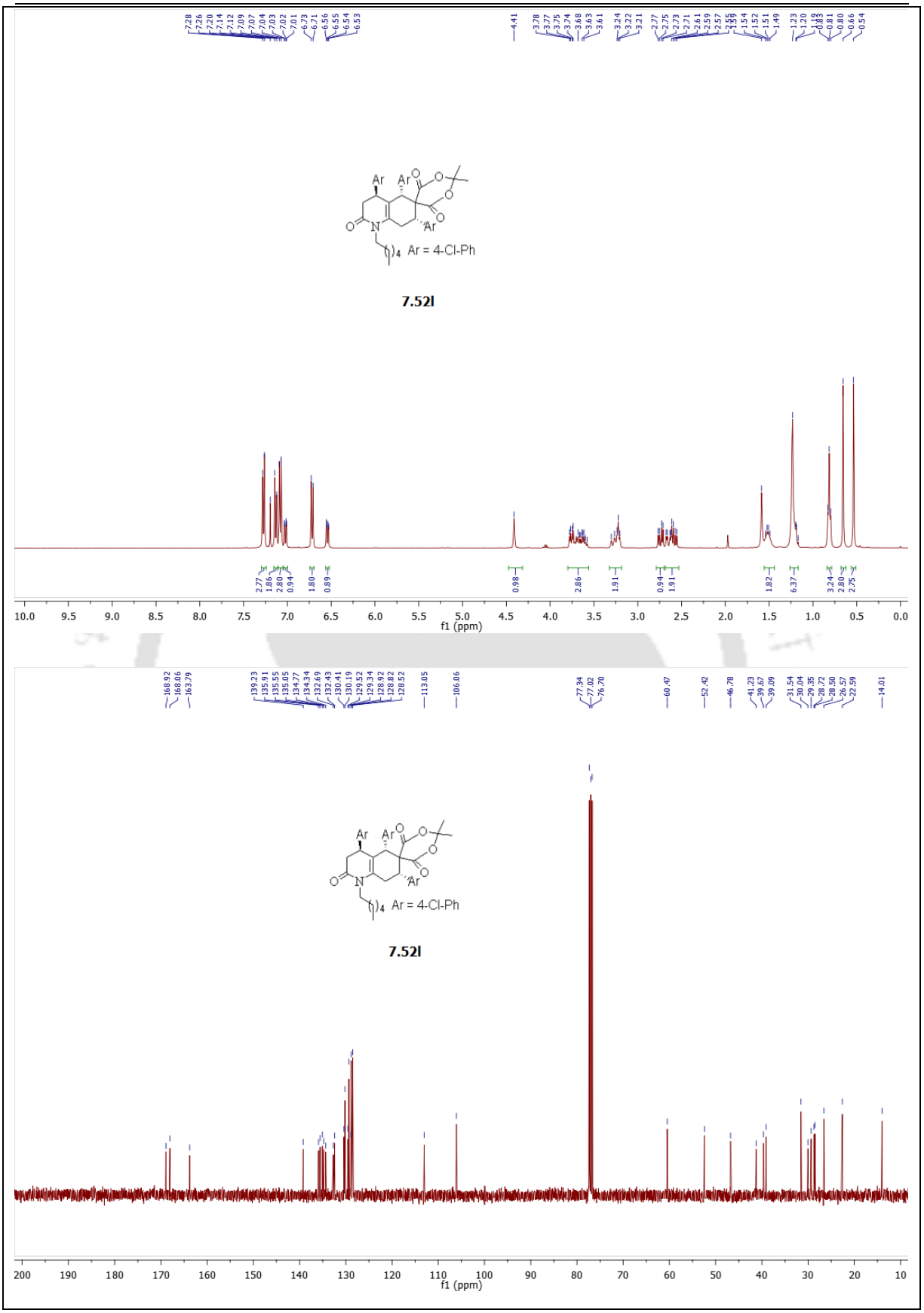

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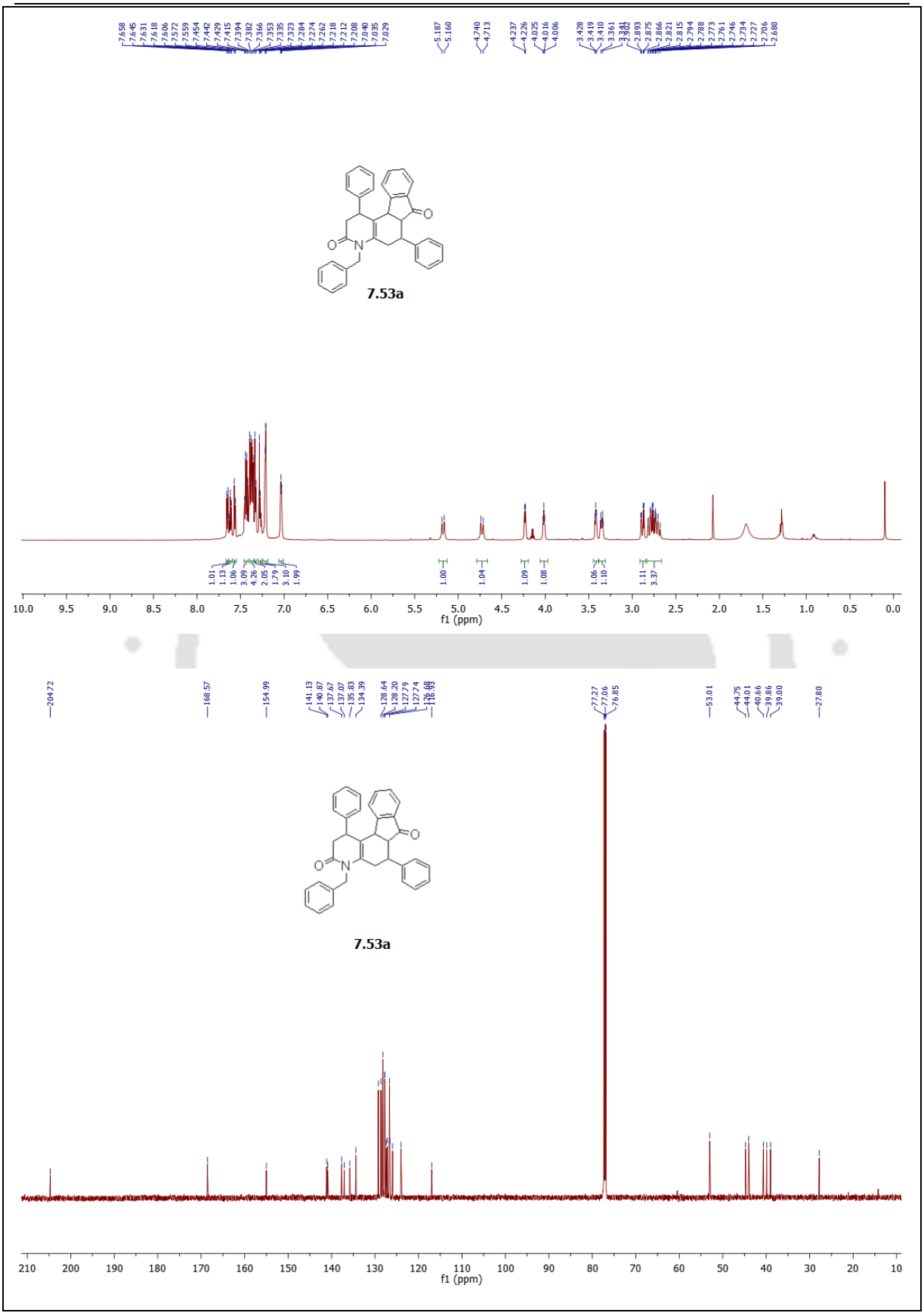

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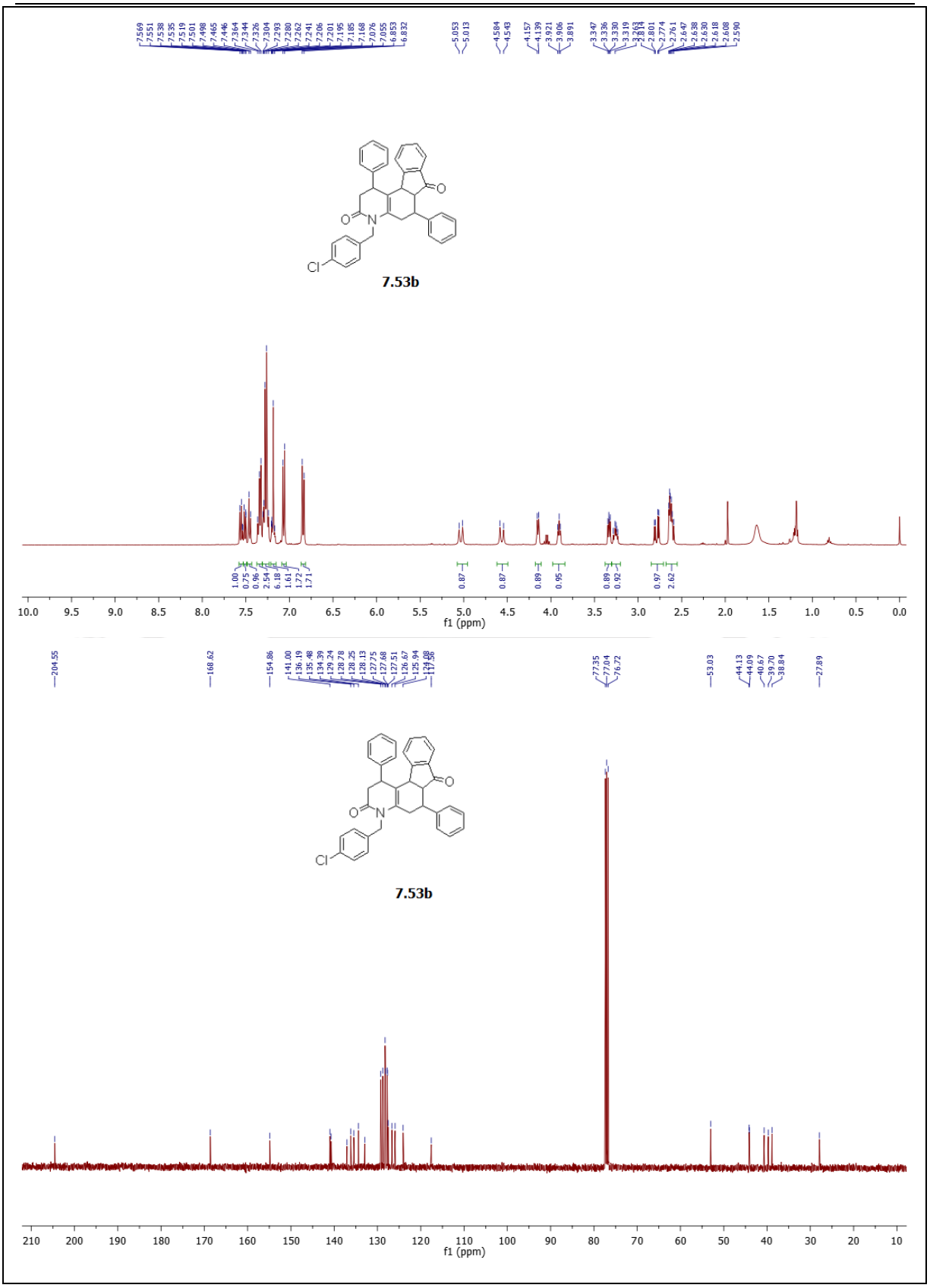

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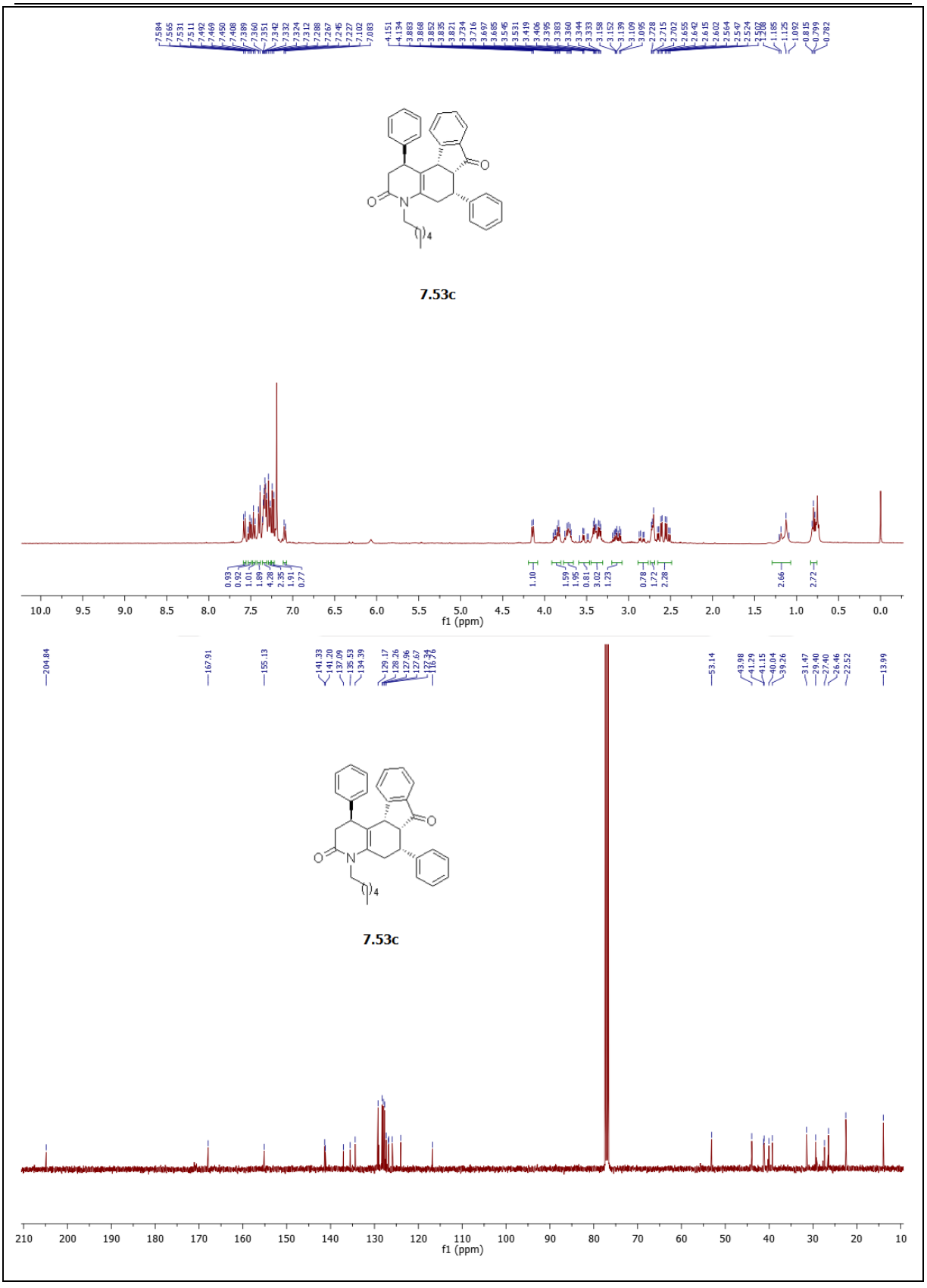

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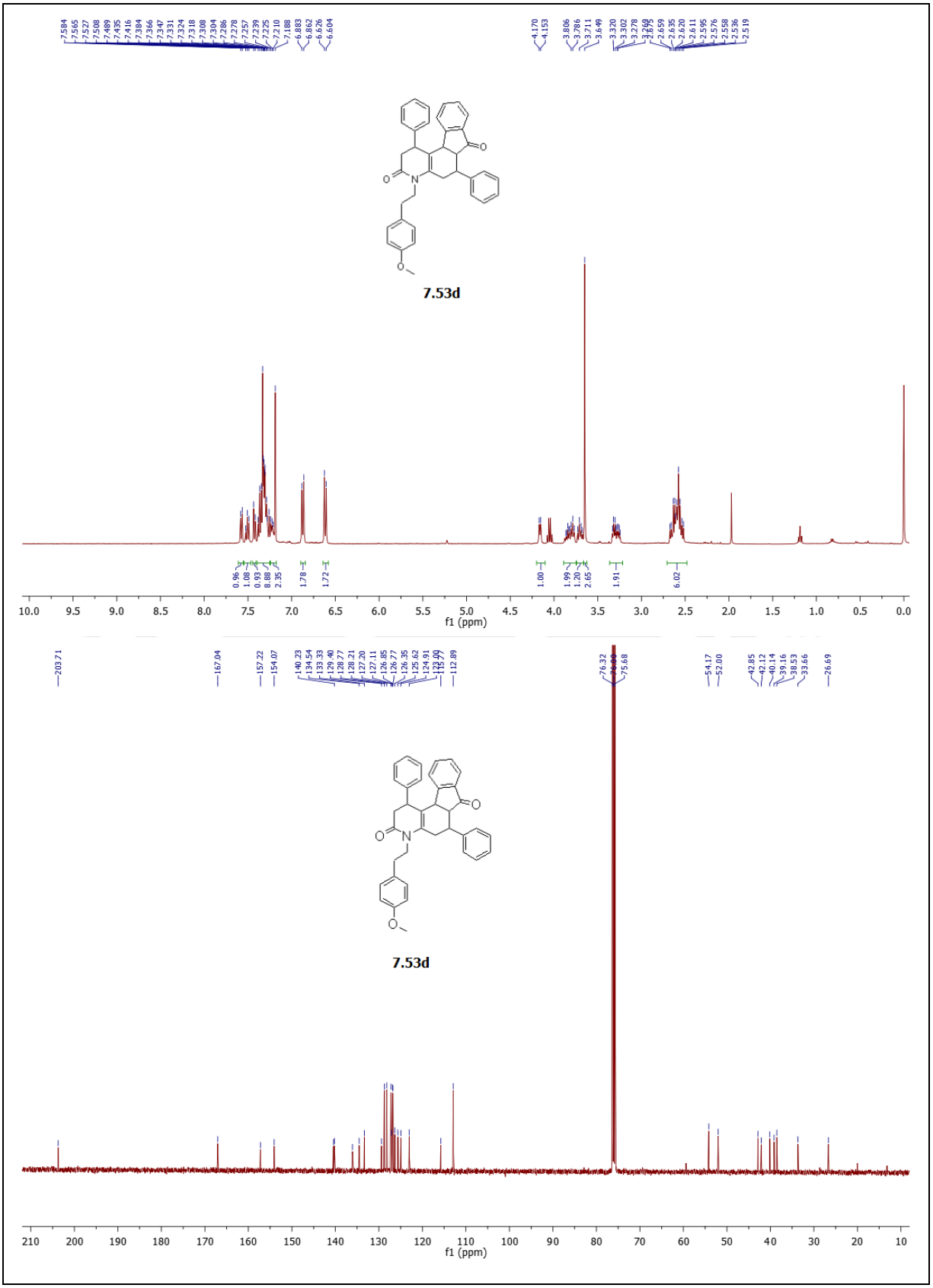
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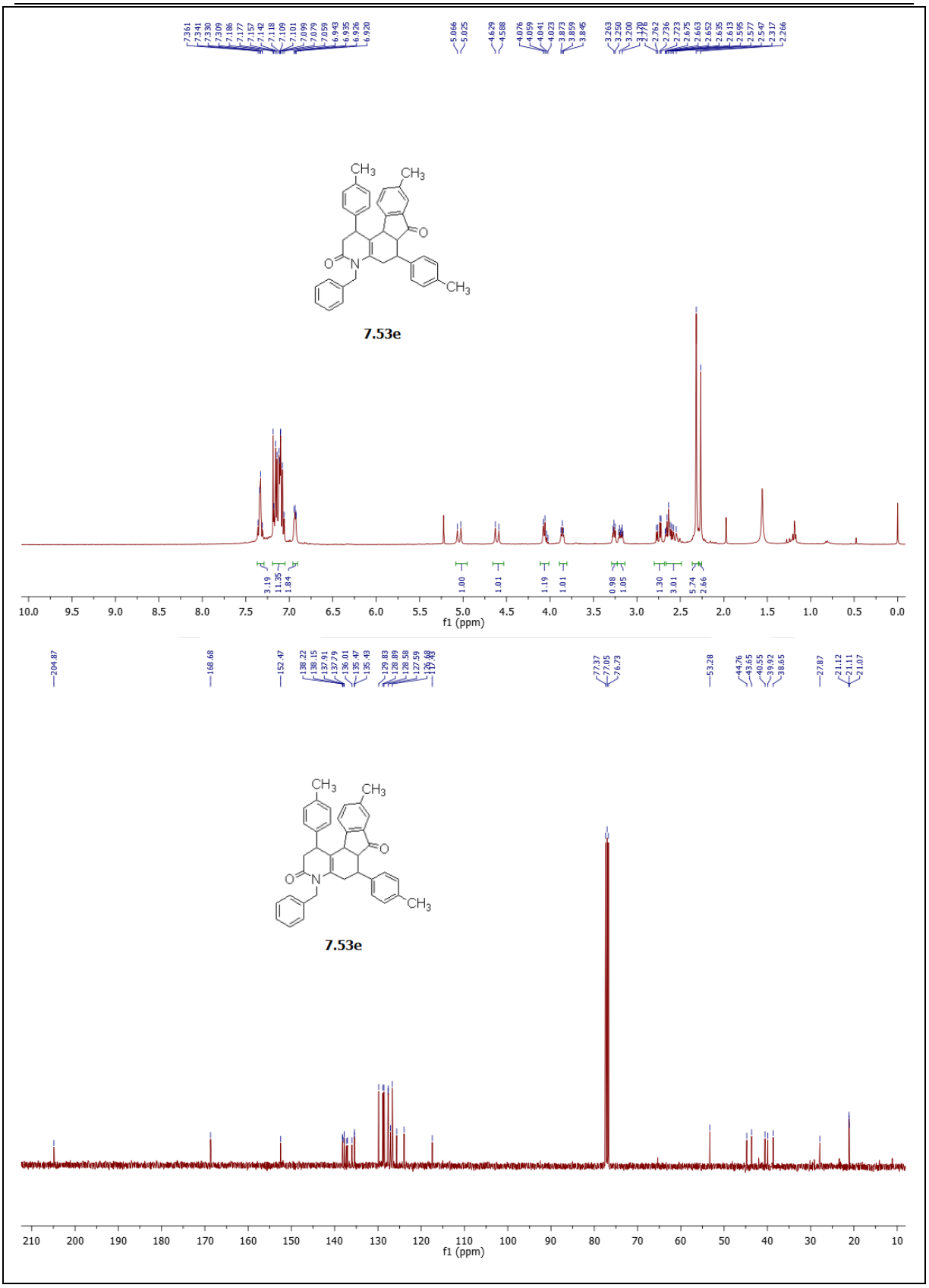

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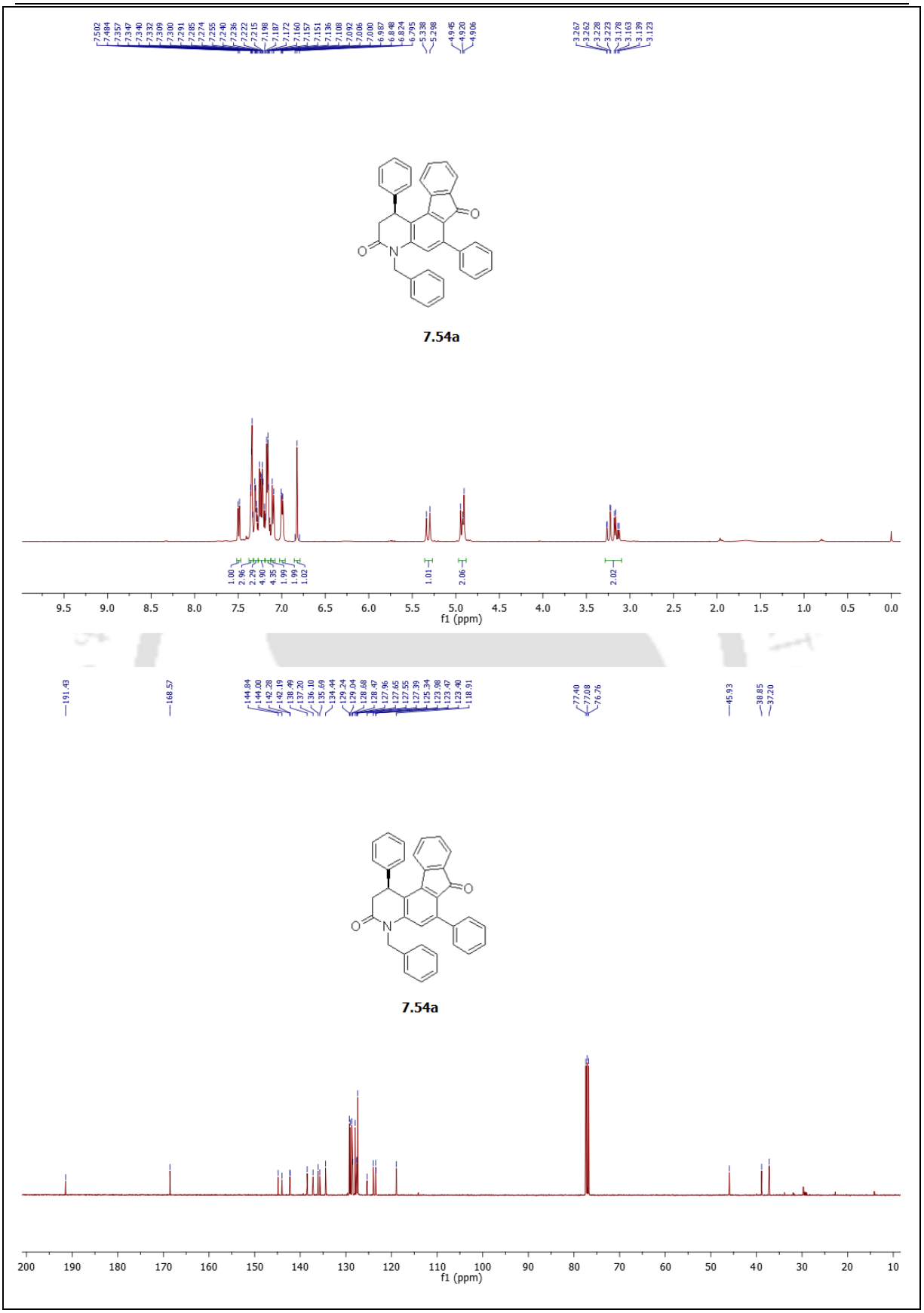

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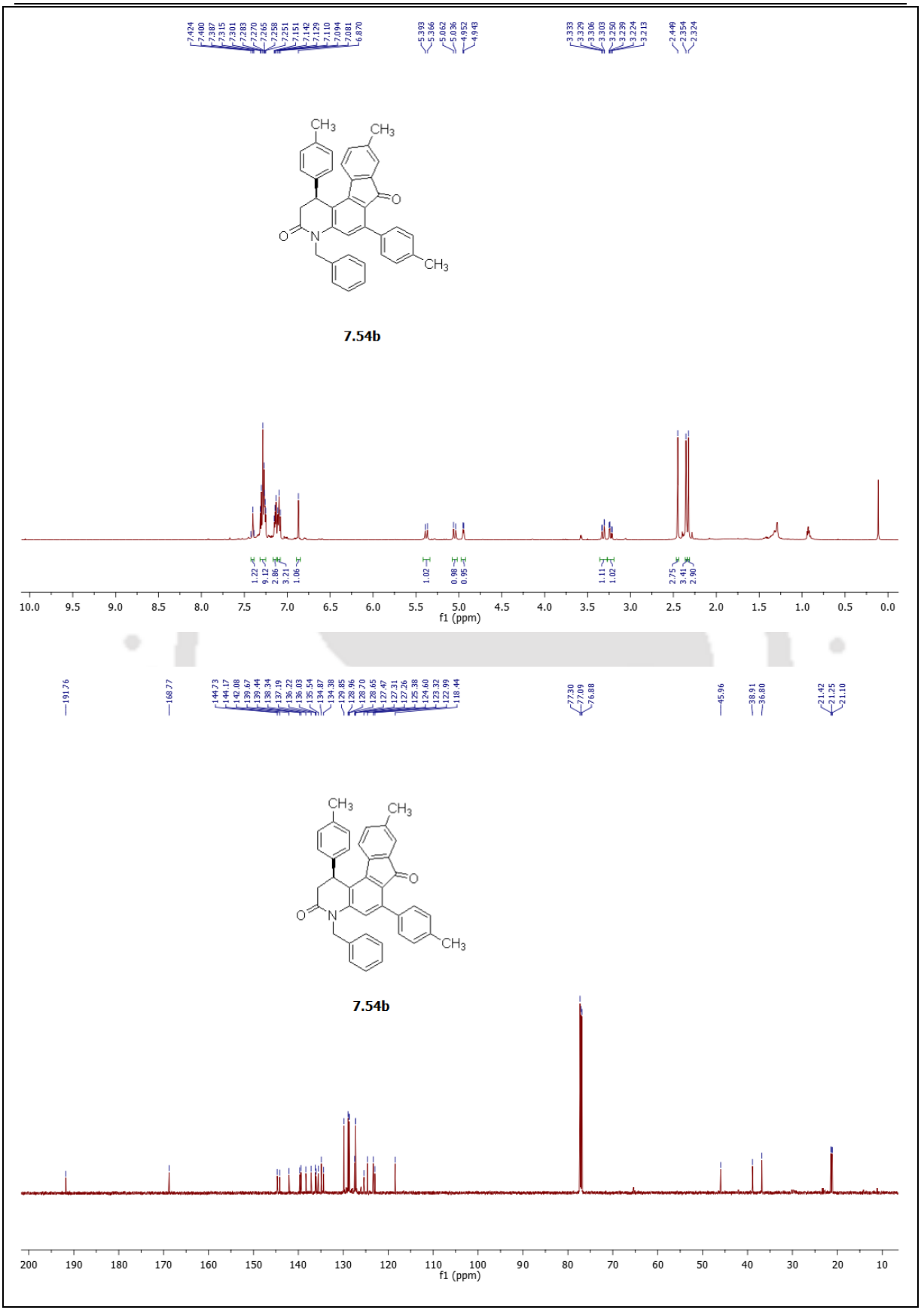

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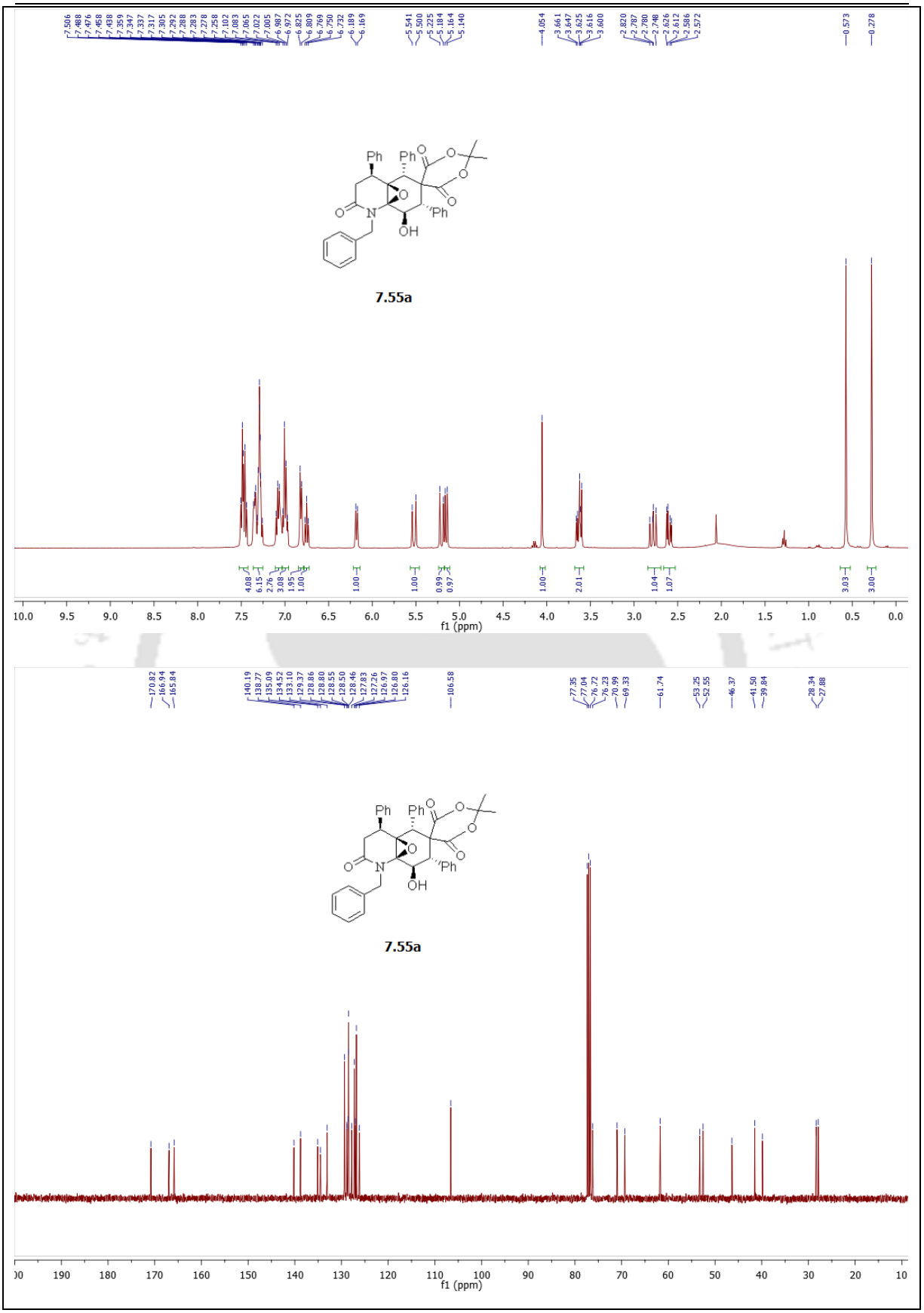

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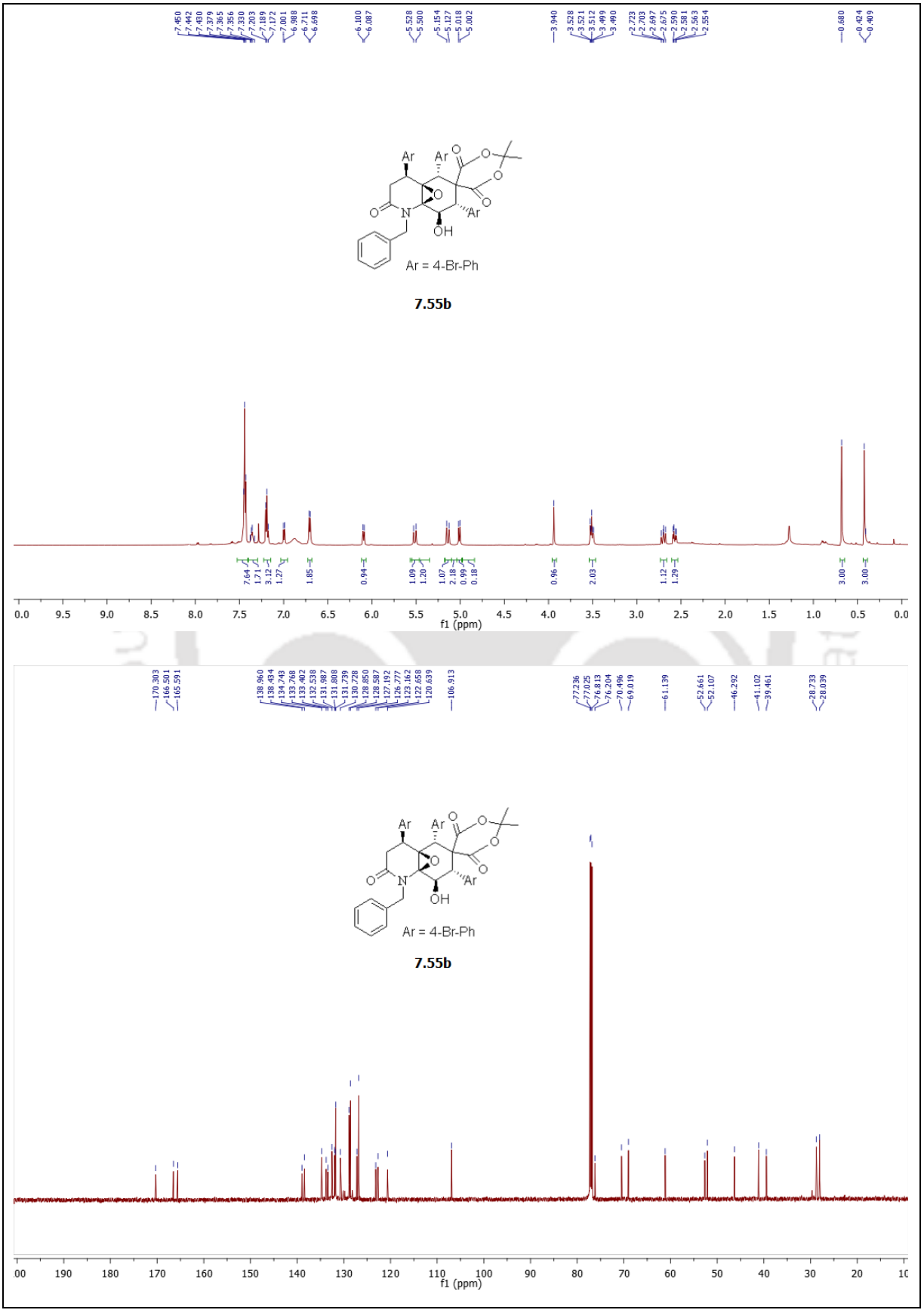

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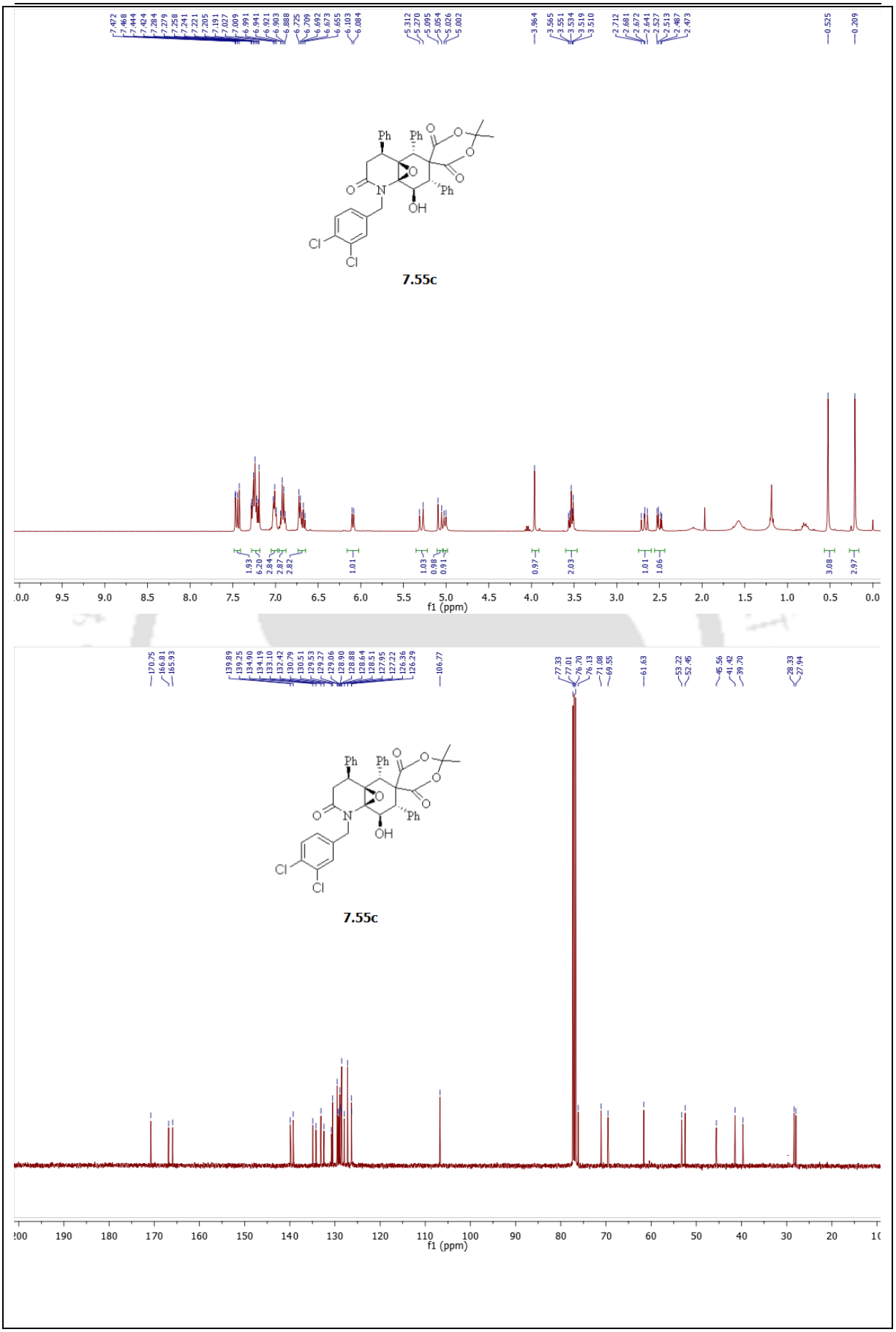

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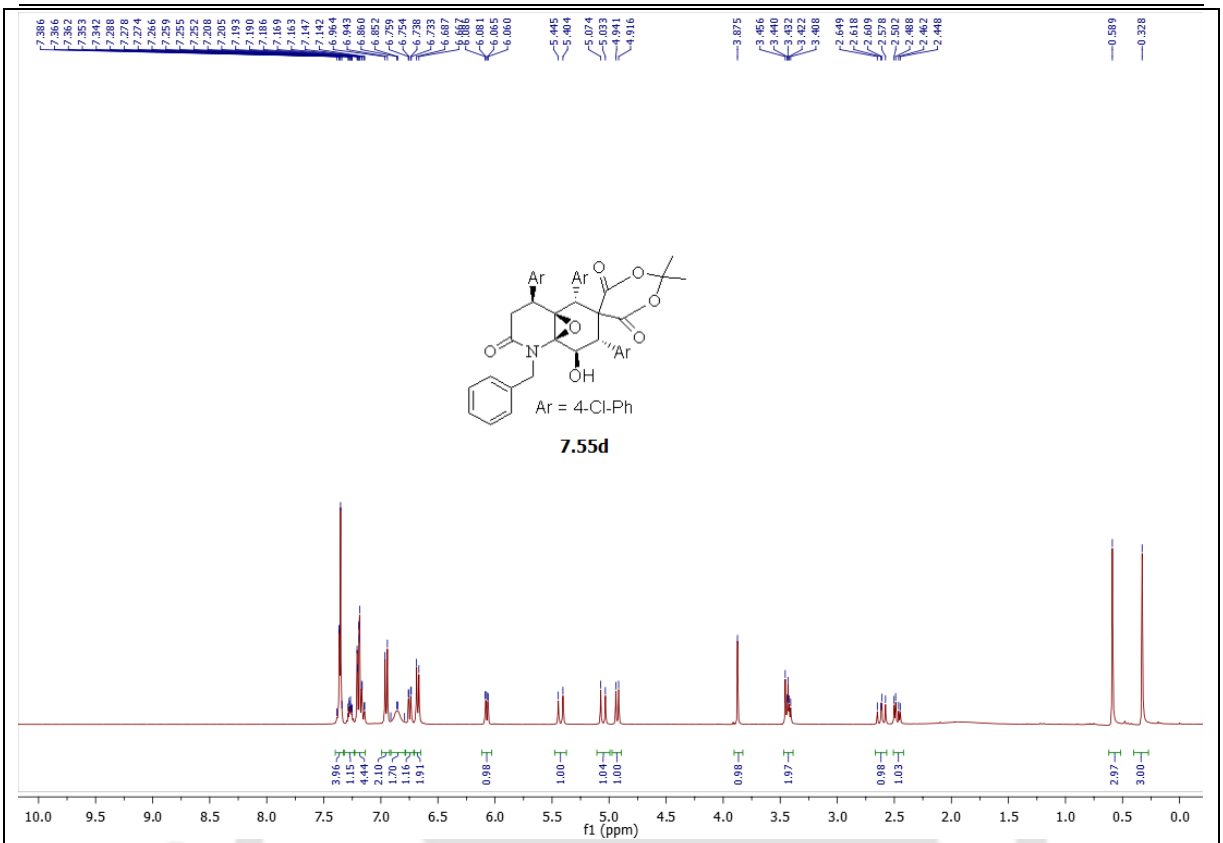

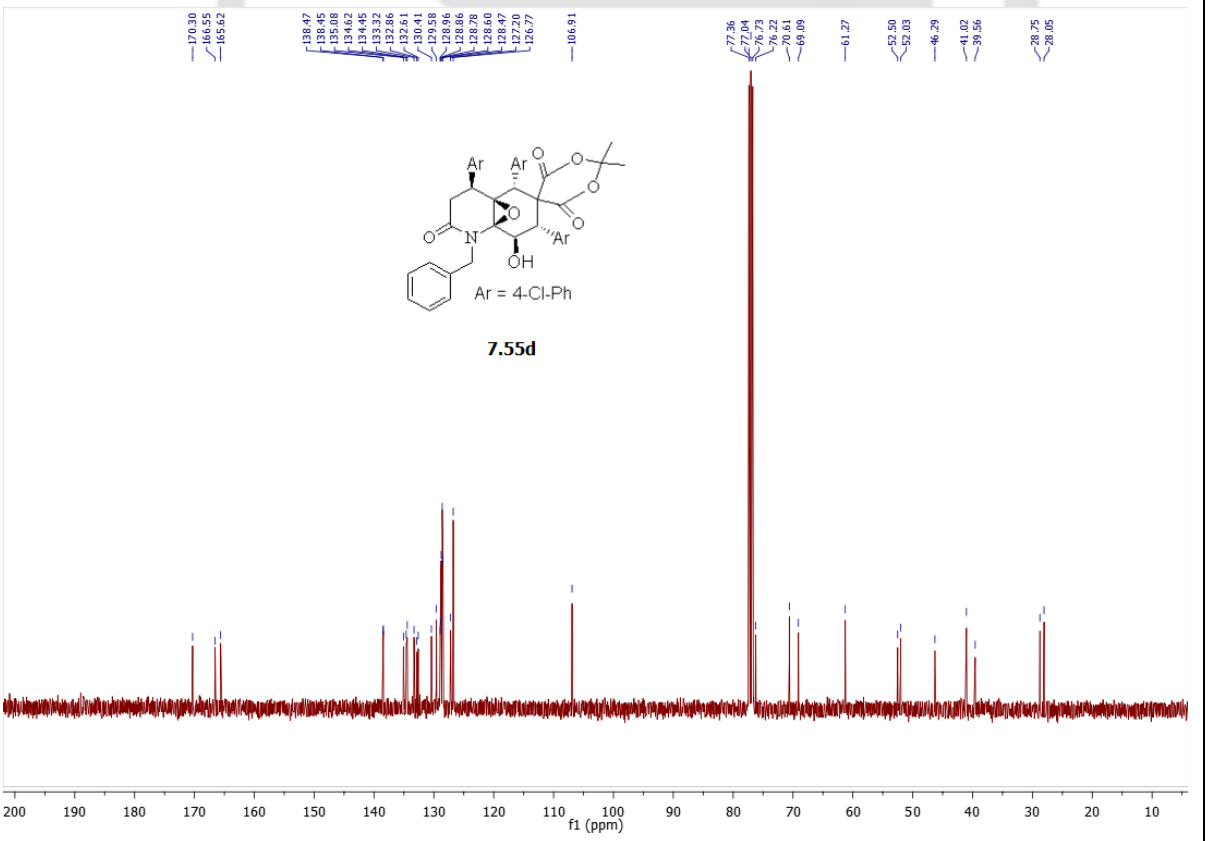

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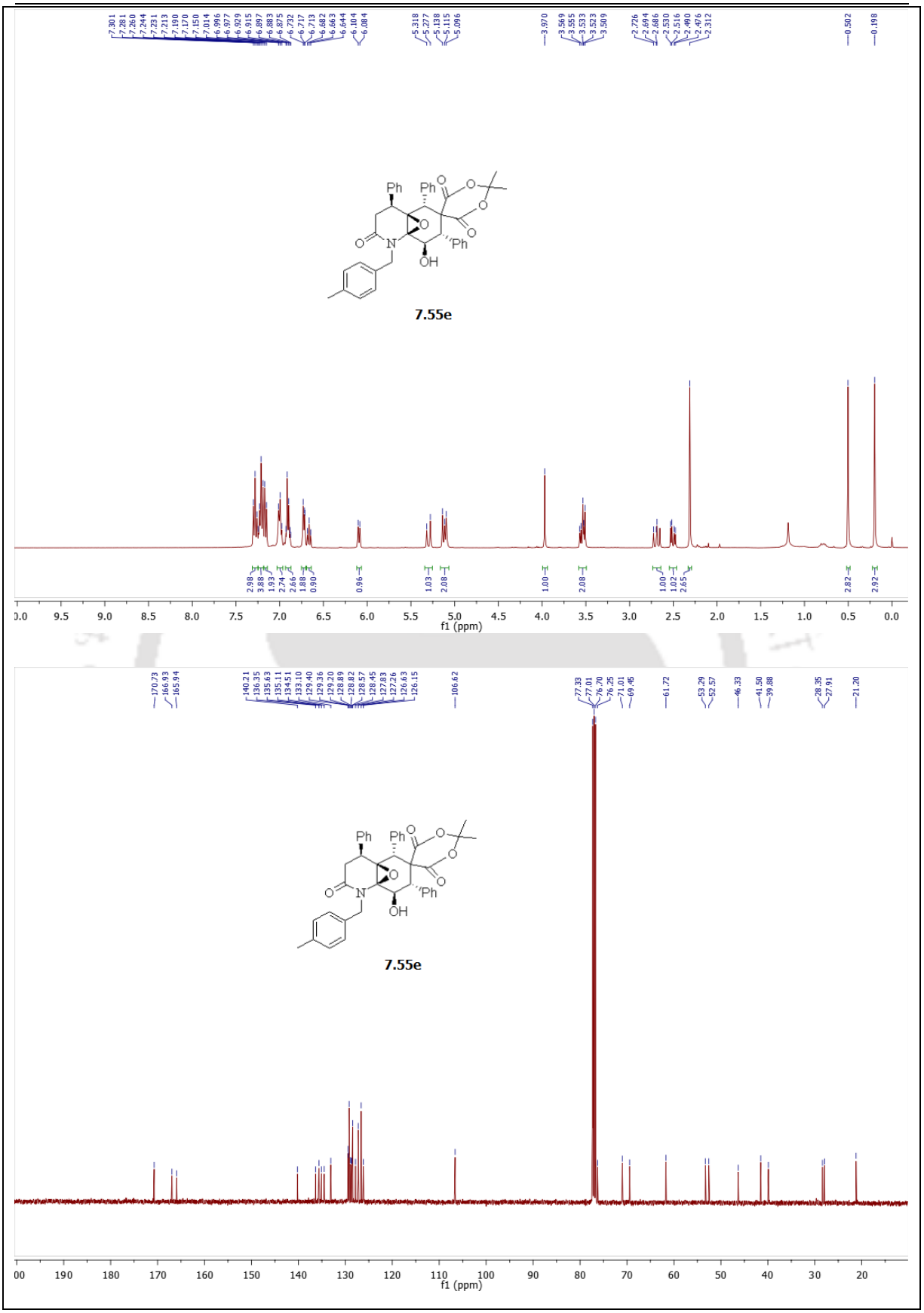

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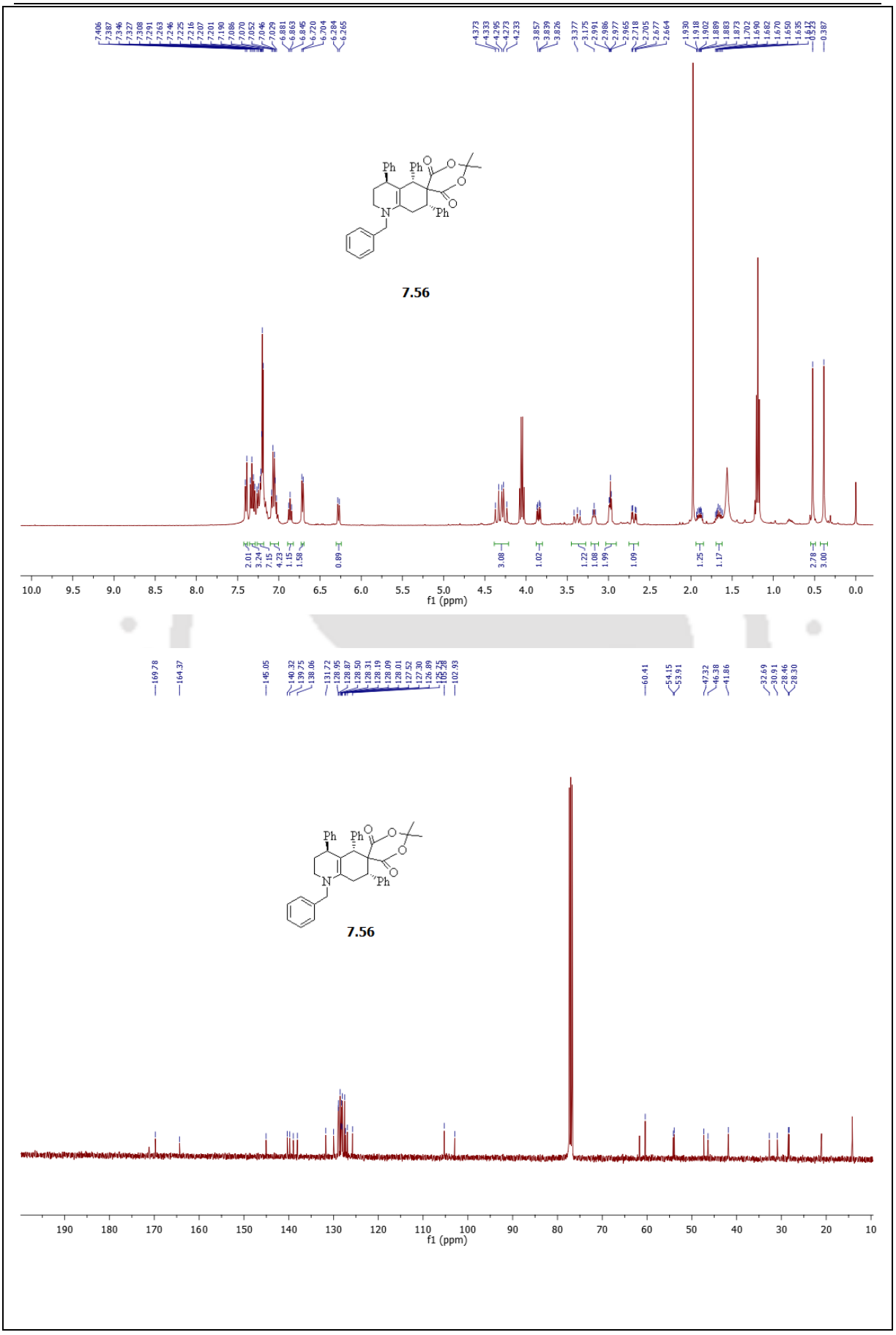

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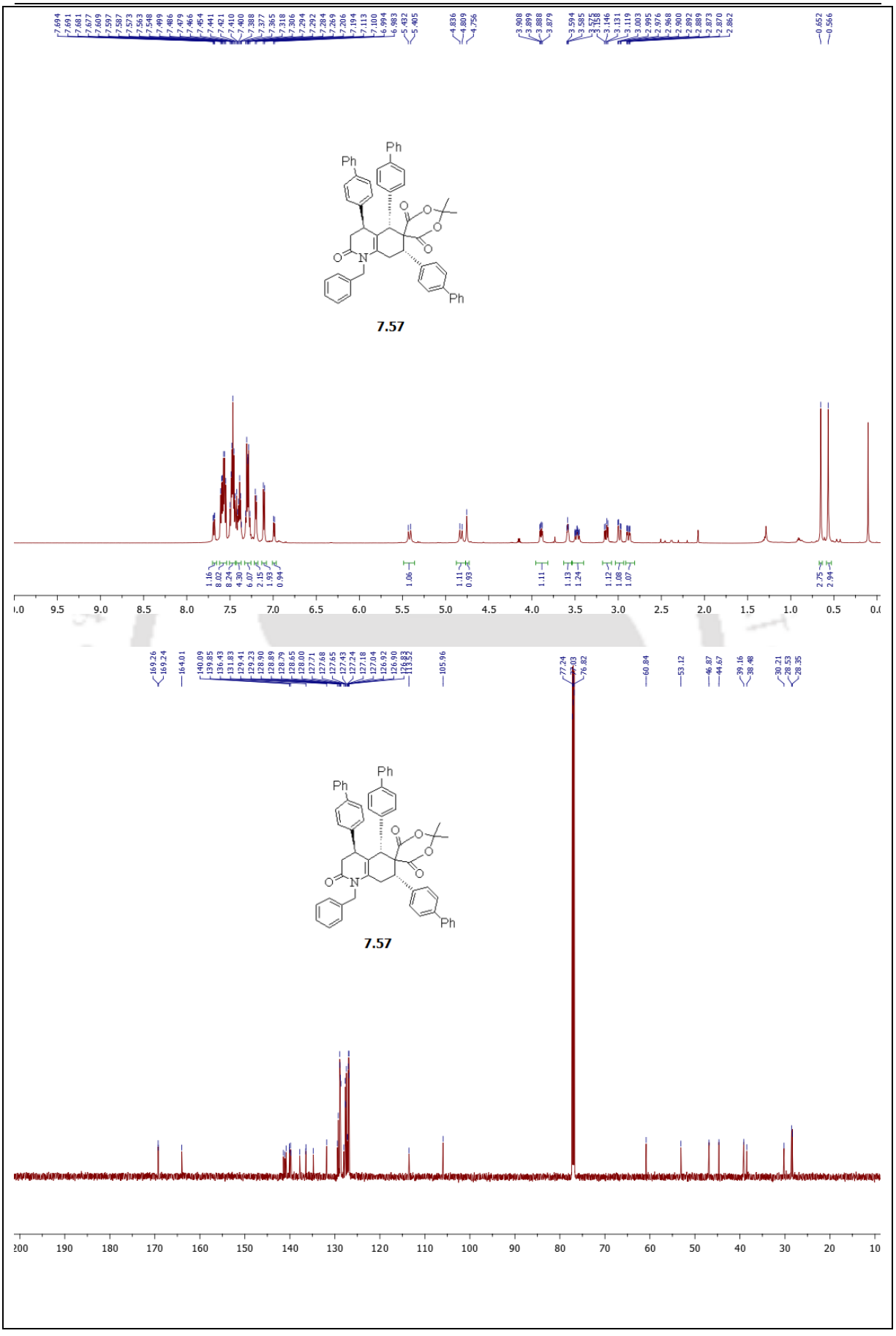

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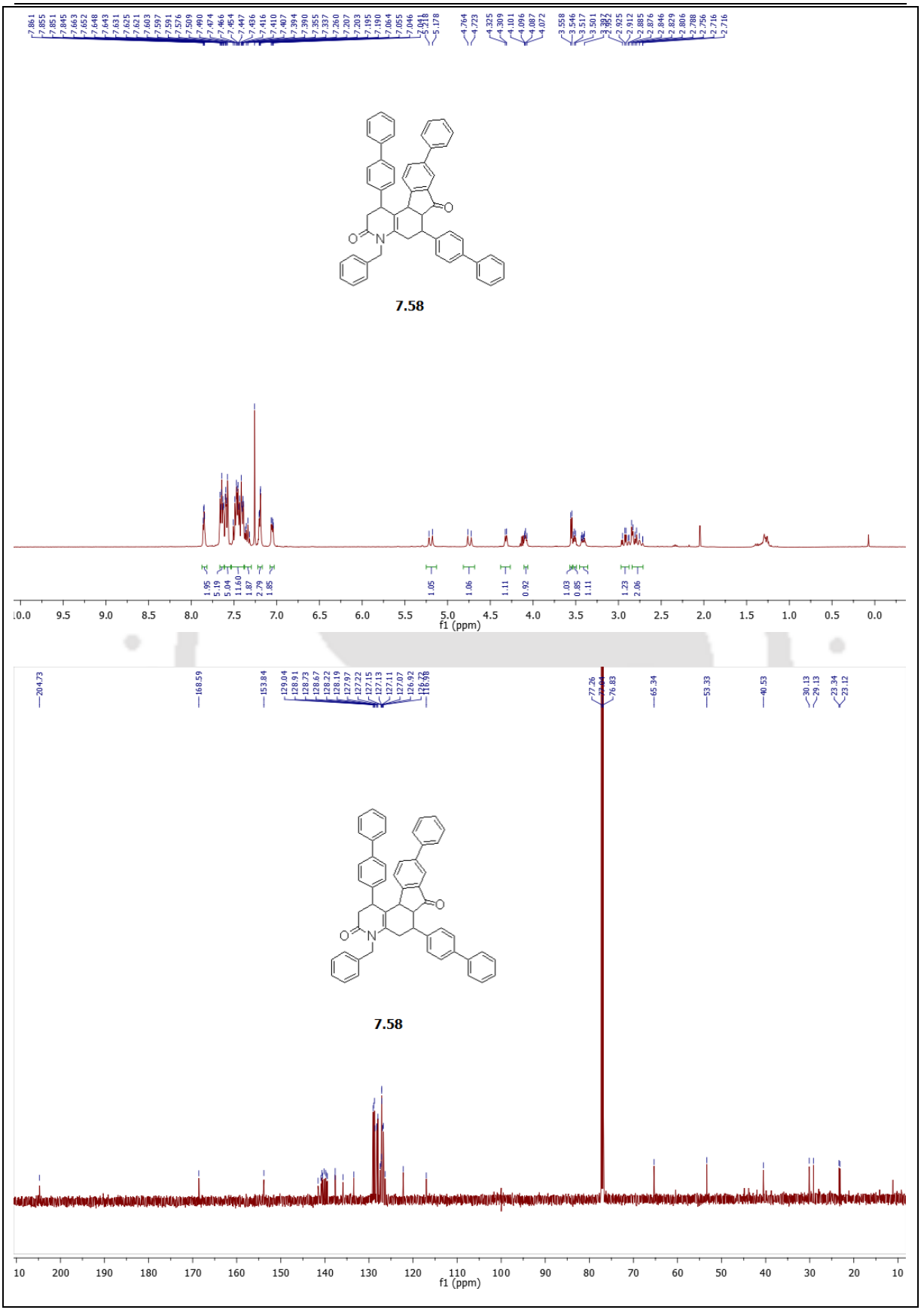

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