SYNTHESIS OF PYRAZOLES BY DIAZA-NAZAROV CYCLIZATION AND FUNCTIONALIZED SULFONES

Ph.D. THESIS

by

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DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY
ROORKEE 247 667, (INDIA)
JUNE, 2018

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A THESIS

Submitted in partial fulfilment of the requirements for the award of the degree

of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

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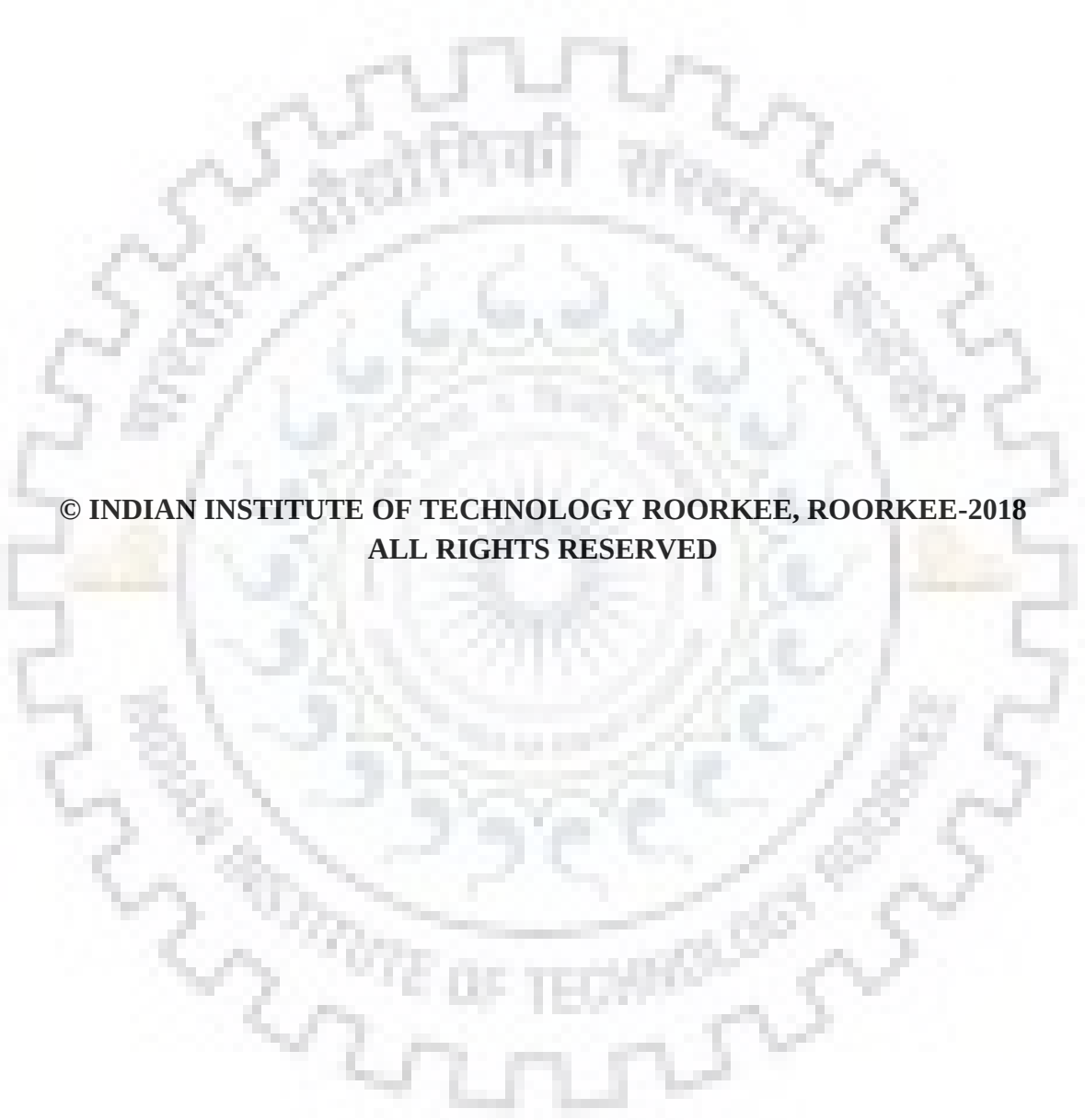

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled "**SYNTHESIS OF PYRAZOLES BY DIAZA-NAZAROV CYCLIZATION AND FUNCTIONALIZED SULFONES**" in partial fulfilment for the award of the degree of Doctor of Philosophy and submitted in the Department of Chemistry of the Indian Institute of Technology Roorkee, Roorkee is an authentic record of my own work carried out during a period of January, 2013 to April, 2018 under the supervision of Dr. Rama Krishna Peddinti, Associate Professor, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee.

The Matter Presented in the thesis has not been submitted by me for the award of any other degree of this or any other institution.

(**BALAKRISHNA AEGURLA**)

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

Date:___June, 2018

(R .K. Peddinti)
Supervisor

ACKNOWLEDGEMENTS

First of all, I must express my utmost gratitude to the almighty of Nature for bestowing upon me the courage to face the complexities of life and complete this thesis successfully.

My last task in regards to the writing of this thesis is to thank those people who have helped me get to this point.

The last five years have been a roller coaster of emotions and I don't know if I will truly be able to find the words to express the depth of my gratitude to my research supervisor ***Dr. Rama Krishna Peddinti****. You have had such an incredibly important influence in my life on both an academic and personal level. Your passion for chemistry was truly contagious and your ability to guide us, especially when "it is what it is", was truly remarkable. Thank you for teaching me and to have faith in my ability to solve this problem. Most importantly, thank you for showing me a successful career in chemistry. I feel equally glad to thank mam Mrs. Shavitri for occasional parties (especially Diwali and Holi) and making us feel like home away from home.*

I take this opportunity to sincerely acknowledge The University Grants Commission (UGC), Government of India, New Delhi, for providing financial assistance which buttressed me to perform my work comfortably.

I am highly grateful to the department of chemistry, IITR for accepting me as research scholar and also I wish to extend my gratitude to Prof. M. R. Maurya, present Head of the Department (HOD) and Prof. Anil Kumar, Former Head of the Department (HOD) Chemistry for arranging the necessary infrastructures to carry out my doctoral studies. I would also take to the opportunity to thank all the faculty members of the department especially Dr. Anuj Sharma (SRC internal expert) and Prof. Anil Kumar (SRC Chairman) for their insightful comments and timely assistance.

I am obliged to Prof Ghosh and Prof M. Shanker, coordinator, NMR facility at IIC of the institute and department of chemistry IITR, respectively, for their kind help in NMR data collection. My sincere thanks to Prof. U. P. Singh, Dr. Neetu Singh and Mr. Aurobindo for recording single crystal XRD. I sincerely appreciate technical staff for their efficiency in recording spectra, which forms an integral part of my thesis - Mr Charan Singh (NMR

IIC), Mr. Anuj- The writer (NMR, department of chemistry), Mr. Madan Pal (IR), Mr. Pankaj (Melting Point). I also express my thanks to the office staff - Mr. S. P. Singh, Mr. Ankur, Aashu bhaiya and all others in the chemistry department office.

With great pleasure I would like to thank my fellow researchers Dr. Ram Tilak, Dr. Santhosh Kumar Reddy, Dr. Arun Sharma, Dr Shivangi Sharma, Dr. Srinivas Palla Dr. Ujjwal kumar bhagat, Dr. Jyothi tomar, Dr. Nisha Jarwal, Dr Pallavi Singh, Peeyush, Neha Dua, Deepti, Rajat, Hemkant, and Pradeep. It is a good experience to work with you all and thanks for all the good moments. Special words of appreciation go to Tilak Anna, Chicha, Srinu Anna, Mukku, putti and Nikku for their support and help during the research and thesis writing. I also thank my friends Dr. Harish Anna, Dr. Naveen, Dr. Rajendra, Dr. Venkateswarlu, Dr. Venkat, Dr. Govardhan, Dr. Kamal, Harisht Mahandra, Dr. Asifh, and many more for the love, care and support when required and for making my stay more memorable at IIT Roorkee. A special thanks to my friend and lab mate Arun Bro for his wonderful sense of humor helped me to see positive aspect.

It has been a matter of contentment to associate with all these wonderful people, who collectively made my stay a memorable one at IITR . I thank especially to my friends Dr. Pnakaj, Anand, Dr. Gulab. You people made my journey unforgettable with long ride adventurous trips. I am very much obliged to my friend Anand Ratnam, for providing single crystal X-ray structures.

I am indebted to my Friends ***Naresh thota*** *and* ***Dr. Mukundam*** *for their constant encouragement and motivation which makes me confidant in my career to clear UGC-NET.*

I will forever be thankful to all my teachers and Friends right from nursery to doctoral degree for their fruitful thoughts and encouragement to build the carrier in right direction, especially I am grateful to late ***Prof. Anjaiaha sir****, for his never ending support and valuable suggestions.*

I wish to express my sincere thanks to my Boss ***Dr. Shambabu Joseph*** *(Principal Scientist-GVK Biosciences Pvt Ltd) for your support and encouragement to do Ph. D.*

I would like to convey my heart full thanks to Mrs. Shavitri Peddinti for her wonderful hospitality and treating me like her brother. I appreciate her valuable suggestions in my personal life. Also, I appreciate their children namely Bharati, Goutami for their friendly interactions.

And most of all for my loving, encouraging, patient and supportive wife, ***Shravani Aegurla*** *for her unconditional love and support in every way possible throughout the process of this course. Her love and persistent trust on me along with her bold initiative and compromising gesture made a highly challenging path feasible.*

I would like to say a few words for my sisters kids ***Sowmya, Sanjai, Akira Nandan*** *and my little nephew* ***Minnu****, for "them" to grow up and see how lovely them has been to me and I really enjoyed the each moment with them.*

I am especially grateful to my parents for the tremendous sacrifices they made to ensure that I had an excellent education. I always knew that they believed in me and wanted the best for me. All the support they have provided me over the years was the greatest gift anyone has ever given me. I would not have made it this far without them. I dedicate this book to my mother ***Smt. Laxmidevi*** *and my father late* ***Shri. komuraiah****. My Sisters* ***Mrs. Rajeshwari*** *and* ***Nagalaxmi*** *has been my best friend all my life. I consider myself the luckiest in the world to have such a loving sisters, standing behind me with his love and support.*

The Grates gifts from Nature my father and my son, the bond between son and father is a special one. My son ***Avankrish Aegurla****, I adore his smile, I cherish his hugs and I admire his heart.*

Balakrishna Aegurla

CONTENTS

LIST OF ABBREVIATIONS

B3LYP	Becke, 3-parameter, Lee–Yang–Parr
m-CPBA	*m*-chloroperbenzoic acid
CDC	cross-dehydrogenative coupling
DA	Diels–Alder
DAN	diaza-Nazarov cyclization
DIDAN	denitrative-imino-diaza-Nazarov cyclization
DNSF	denitrative sulfono functionalization
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DIB	Diacetoxyiodobenzene
DIBAL-H	diisobutylaluminium hydride
DMF	Dimethylformamide
DMC	dimehtyl carbonate
DMSO	Dimethylsulfoxide
DTBP	di-*tert*-butyl peroxide
EDG	electron-donating group
ET	Ethylene
EWG	electron-withdrawing group
HIV	human immunodeficiency virus
HMPA	Hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectroscopy
IR	infra red
KIE	kinetic isotope effect
LUMO	lowest unoccupied molecular orbital
MOB	masked *o*-benzoquinone
MPB	masked *p*-benzoquinone
MT	Montmorillonite

MVK	methyl vinyl ketone
MW	microwave
NBS	*N*-bromo succinimide
NCS	*N*-chlorosuccinimide
NED	normal electron-demand
NMR	nuclear magnetic resonance
PIFA	phenyliodonium bis(trifluoroacetate)
PTSA	*para*-toluenesulfonic acid
SET	single-electron-transfer
SPE	single-point energy
TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TEAB	tetraethylammonium bromide
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid
TFE	tetrafluoroethylene
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane




50
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ABSTRACT

The thesis entitled "**Synthesis of pyrazoles by diaza-Nazarov cyclization and functionalized sulfones**" is divided into three chapters, *viz*. (i) Introduction, (ii) Objectives, Results and Discussion, and (iii) Experimental.

We have developed novel and rapid protocols for the synthesis of pyrazoles, vinyl sulfones, γ-keto sulfones and nuclephilic substitution of γ-keto sulfones-derived γ-hydroxy sulfones. The pyrazoles were synthesized from *in situ* generated benzaldehyde hydrozone with acetphenone derivatives by using environmentally benign and inexpensive molecular iodine. We have also carried out theoretical studies on diaza-Nazarov-type 4π-elctrocyclization (DAN) leading to pyrazoles by using B3LYP/6-311G** theory to better understand the experimentally observed regioselectivity of DAN cyclization.

Chapter 1: Introduction

Nazarov cyclization reaction is emerged as one of the most privileged techniques for the construction of 5-membered carbo- and hetero-cycles since its revelation. This 5-membered carbo- and hetero-cycles are prevalent structural motif in several natural products and pharmaceutically active compounds. Owing to its importance, various elegant approaches have been developed for target 5-membered carbo- and hetero-cyclic compounds; among them, Nazarov-type cyclization reaction is one of the most versatile and efficient methods for C–C and C–N bonds formation.

Carbon-carbon and carbon-heteroatom bond construction (C–N, C–S) is an essential quest for the development of novel and efficient chemical building blocks in present research scenario. Due to the significance of carbon-heteroatom bond generation, specifically C–S bond forming reactions have gained huge attention in synthetic community. Gneerally sulfones, thioethers are the most common skeletons in sulfur containing drugs which are useful for the treatment of leprosy, dermatitis herpetiformis, and tuberculosis. Scientists have also determined various therapeutic activities of sulfone containing compounds including antibacterial, antifungal, antimalarial, cysteine protease inhibitor, anti-

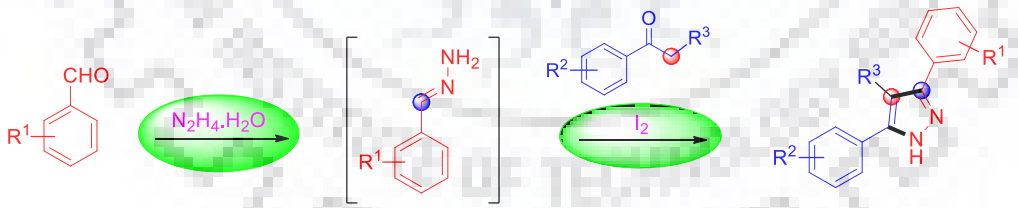
HIV, anti-proliferative, anti-cancer, protein phosphatase methylesterase-1 inhibitors, thyroid receptor antagonist. Because of the potential applications of organosulfur compounds numerous protocols has been established for C–S bond construction during the last few decades.

Chapter 2: Objectives, Results and Discussion

This chapter deals with the objectives, results and discussion which are divided into four sections.

2.1. Synthesis of pyrazoles *via* diaza-Nazarov (DAN) cyclization and theoretical investigation

In this section, unprecedented iodine-mediated diaza-Nazarov (DAN) type cyclization for the construction of substituted pyrazoles from easily available starting materials *via* an enamine–iminium ion intermediate is described. The oxidative cyclization worked under green conditions with remarkable regioselectivity. This one-pot, efficient and operationally simple three-component intramolecular regioselective DAN cycliza-tion displayed a wide range of substrates scope. The dichotomy of reaction pathways has been explored with density functional theory in the gas phase and solution phase. Of the possible 1,5-, 1,6-, and 1,7- electrocyclizations, the DAN cyclization, *i.e.*, the 1,5-pathway offers lowest activation energy barrier supporting our experimental observations. (Scheme 1).

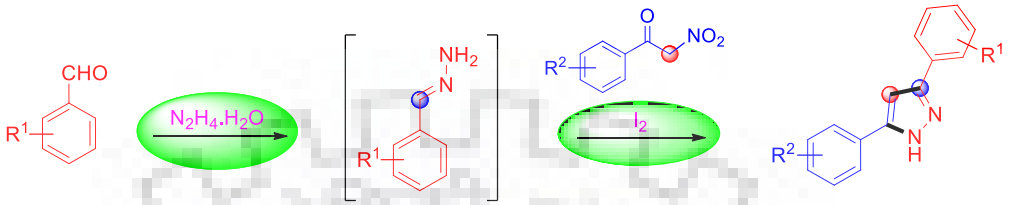


Scheme 1: The diaza-Nazarov cyclization for the synthesis of polysubstituted pyrazoles.

2.2. Synthesis of pyrazoles *via* denitrative-imino-diaza-Nazarov (DIDAN) cyclization

A novel, efficient and unprecedented green methodology for the construction of pyrazoles has been established from easily accessible, *in situ* generated benzaldehyde hydrozone with α-nitro carbonyl derivatives through denitrative imino-diaza-Nazarov

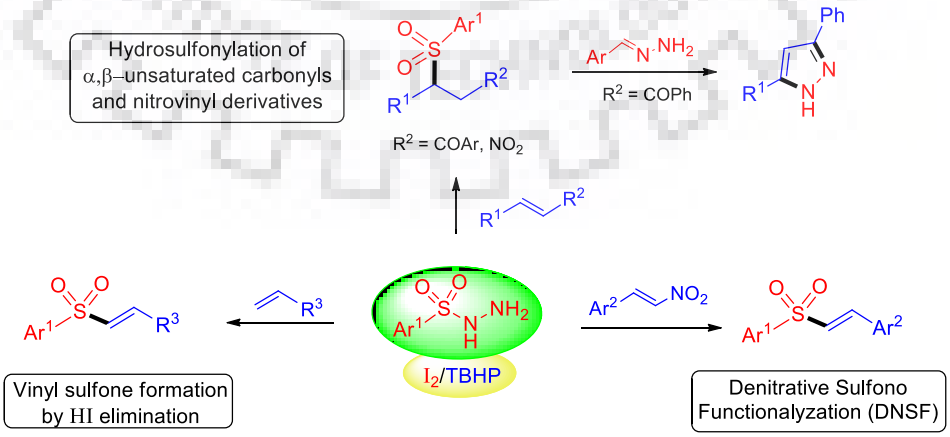
(DIDAN) cyclization in the presence of iodine as powerful catalyst in EtOH. The corresponding aryl pyrazoles are obtained in high to excellent yields. A catalytic amount of inexpensive and non-toxic iodine drives the reaction and no exclusion of air and use expensive ligands is required (Scheme 2).



Scheme 2: The denitrative imino-diaza-Nazarov cyclization for the synthesis of disubstituted pyrazoles.

2.3. Synthesis of vinyl sulfones and hydrosulfonylation of chalcones

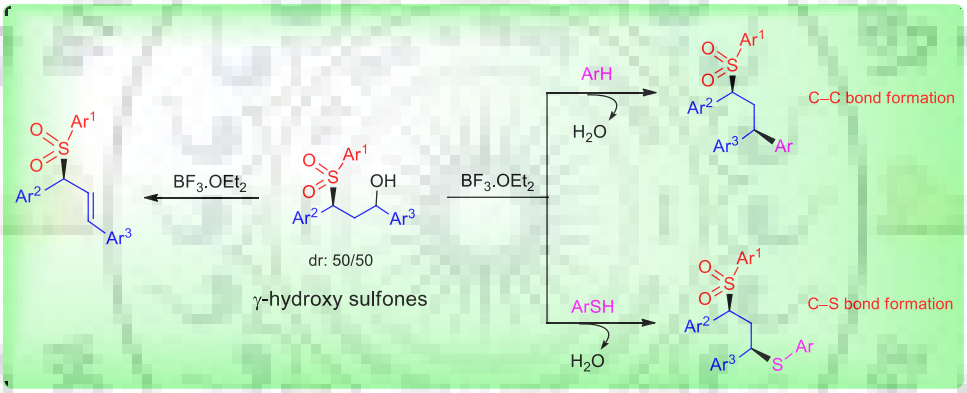
A facile iodine/*tert*-butyl hydroperoxide (TBHP)-mediated protocol has been developed for the formation of C(sp^2)–SO_2 and C(sp^3)–SO_2 bonds through radical pathway and ionic pathway, respectively. The denitrative sulfono functionalization (DNSF) of β-nitrostyrenes with arylsulfonyl hydrazides under solvent-free and base-free conditions is described. The DNSF process appears to proceed through an addition–elimination pathway. The sulfonylation of olefins that contain electron-withdrawing groups was also examined under solvent-free conditions which afforded the corre- sponding alkenyl sulfones through the elimination of HI from the β-sulfonyl-iodo intermediate. The hydrosulfonylation of chalcones and β-nitrostyrenes proceeded in the presence of an organic base in acetonitrile through a sulfa-Michael addition (Scheme 3).



Scheme 3: Metal-free sulfonylation of α,β-unsaturated systems by using sulfonyl hydrazides.

2.4. Synthesis of sulfonylpropane derivatives by dehydrative substitution of γ-hydroxysufones

The first dehydrative C- and S-alkylation by nucleophilic substitution of γ-hydroxysufones with arenes and thiophenols is reported. This study represents elegant and ecological concept to construct C−C and C−S bonds for novel and unsymmetrical 1,1- and 3,3-branched propanes. The γ-hydroxysufones underwent $BF_3{\cdot}OEt_2$ mediated dehydrative arylation and thiolation at room temperature and elimination at 40 ^oC. The nucleophile attack occurs on the less hindered phase of planar benzylic carbocation to furnish the title compounds in good diastereoselectivity (Scheme 4).



Scheme 4: Dehydrative C- and S-alkylation: Access to highly substituted 1-sulfonylpropanes.

Chapter 3: Experimental

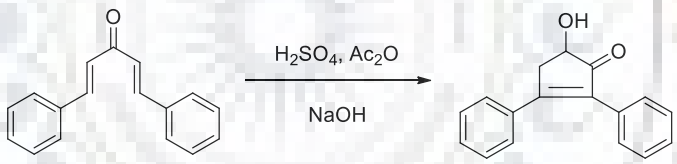
The third chapter provides experimental procedures in detail along with physical constants and spectral data including IR, ^1H NMR, ^{13}C NMR, 2D-NMR and mass spectral data.

1. INTRODUCTION

Nazarov cyclization reaction is emerged as one of the most privileged techniques for the construction of 5-membered carbo- and heterocycles since its revelation. The 5-membered carbo- and hetero-cycles are prevalent structural motifs in several natural products and pharmaceutically active compounds [1–4]. Owing to their importance, various elegant approaches have been developed for target 5-membered carbo- and heterocyclic compounds. Among them, Nazarov-type cyclization reaction is one of the most versatile and efficient methods for C–C and C–N bond formation [5–7].

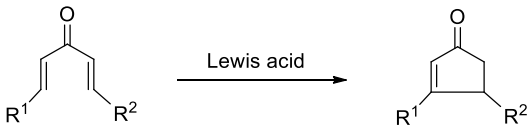
1.1. Nzarov reaction

In 1903, Vorländer, for the first time, revealed the study of Nazarov reaction the conversion of dibenzylidene acetone to 5-membered cyclic ketol. Nevertheless, the reported ketol-structure was basically misassigned. Later, Allen and co-workers corrected it by interpreting using UV light absorption spectroscopy in 1955 (Scheme 1) [8].



Scheme 1: First reported cyclization of divinyl ketone to ketol.

In 1941, Ivan Nikolaevich Nazarov developed an efficient method for the transformation of divinyl ketones into cyclopetenones (Scheme 2). Nazarov reaction mechanism involves in, conrotatory 4π-electrocyclization of divinyl ketone systems into cyclopentenones through pentadienyl or oxyallyl cation intermediate in the presence of Lewis-acid. The resulting oxyallyl cation either facilitates the elimination of *β*-hydrogen and subsequent tautomerization of the enolate to provide a cyclopentenone or on the other hand oxyallyl cation can be trapped with different functionalities to produce a new structural frameworks (Figure 1) [9–11].



Scheme 2: First reported Nazarov reaction.

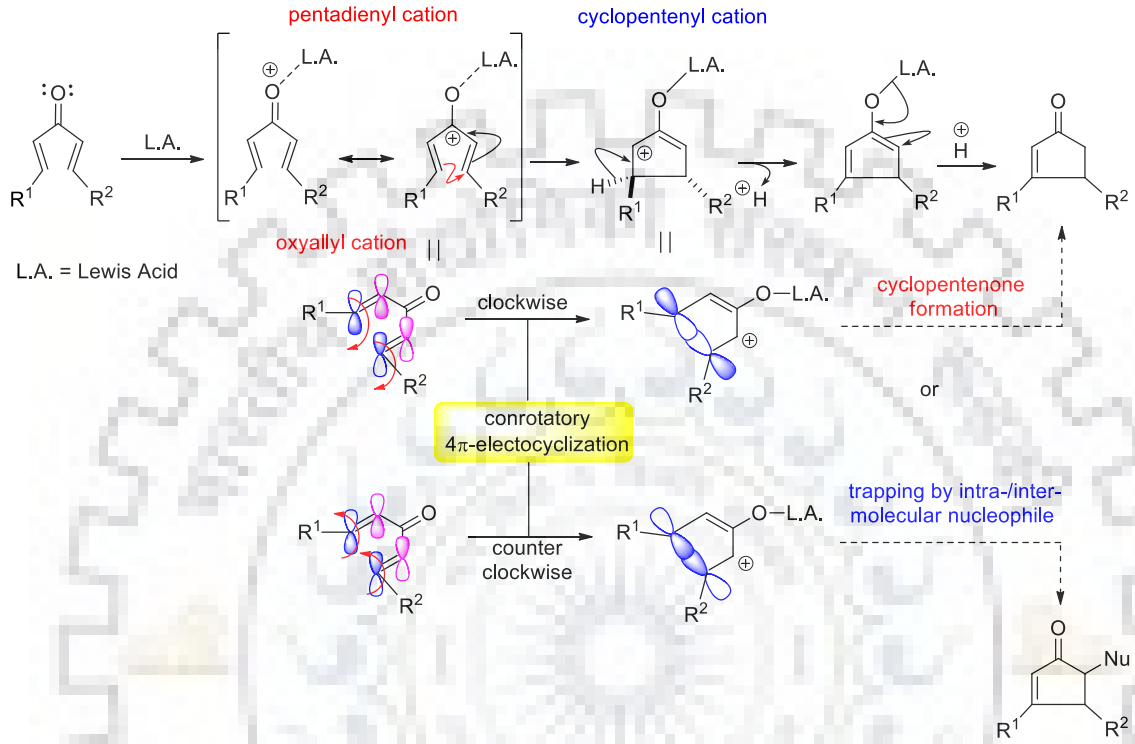


Figure 1: Mechanism of the Nazarov reaction.

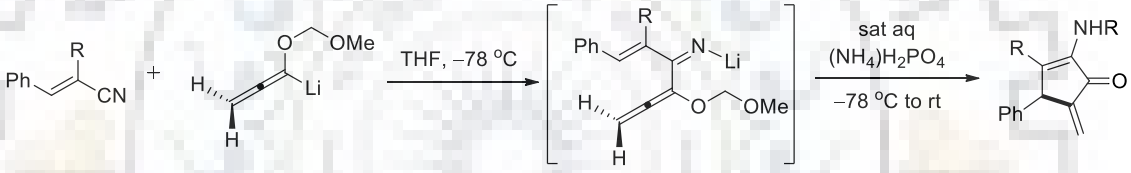
On the basis of Woodward and Hoffman electrocyclization rules and by elucidation of mechanism, it was confirmed that Nazarov reaction follows pericyclic ring closure reaction pathway. After Woodward's revelation, there was a significant progress in the Nazarov cyclization reaction for the development of different heterocycles rather than 5-membered carbocycles such as (i) employing nitrogen, which involves an imino/enamine-imino intermediate generation during the course of Nazarov reaction instead of the classical ketone functionality called the imino-Nazarov reaction, (ii) introduction of a nitrogen into the ring system for the production of 5-membered heterocycles, termed as aza-Nazarov reaction, and (iii) during the course of the reaction, cyclopentenylcation system can be trapped with different essential functionalities to generate new important bonds forming events describe the interrupted Nazarov reaction [12–17].

In this introduction chapter, we focused on the nitrogen obliged Nazarov type reaction and some related examples are demonstrated. In this context, the heteroatom accountable Nazarov-type cyclization approach has led to the development of 5-memberd heterocyclic compounds. So far, only a few reports are available for the nitrogen embedded Nazarov-type cyclization reactions.

1.1.1. Iminino-Nazarov cyclization
1.1.2. Aza-Nazarov cyclization
1.1.3. Enamine-iminium ion Nazarov cyclization

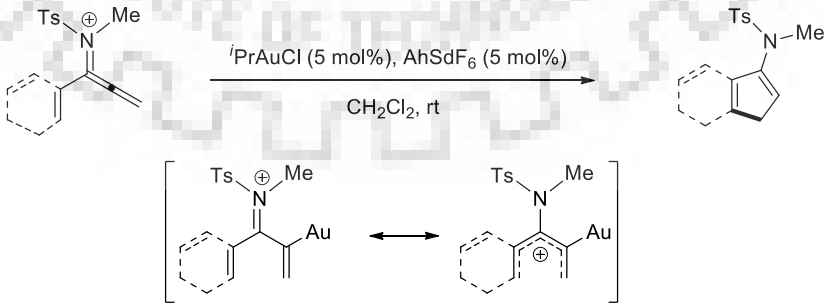
1.1.1. Iminino-Nazarov cyclization

Tius *et al*. introduced a novel and efficient protocol for the synthesis of cross-conjugated α-aminocyclopentenones in a single operation from α,β-unsaturated nitriles and (methoxy)-methoxyallenes *via* imino-Nazarov 4π-electrocyclization pathway in the presence of monoammonium phosphate (Scheme 3) [18].



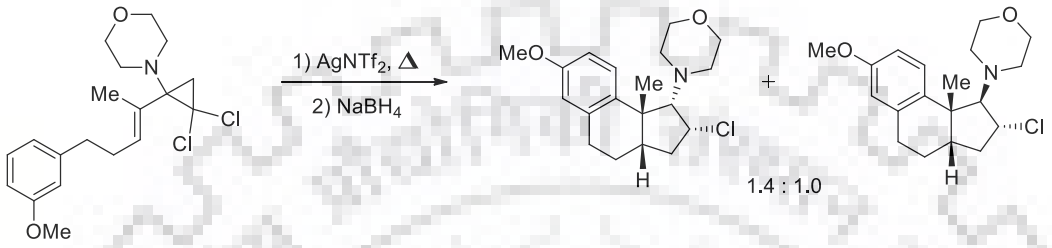
Scheme 3: Synthesis of 2-aminocyclopent-2-enones.

Hsung and co-workers demonstrated the regioselective synthesis of synthetically valuable aromatic-ring incorporated cyclopentenamides from α-aryl-substituted allenamides under gold(I) catalysis. This reaction proceeded through an imino-Nazarov 4π-electrocyclic ring closure process (Scheme 4) [19].



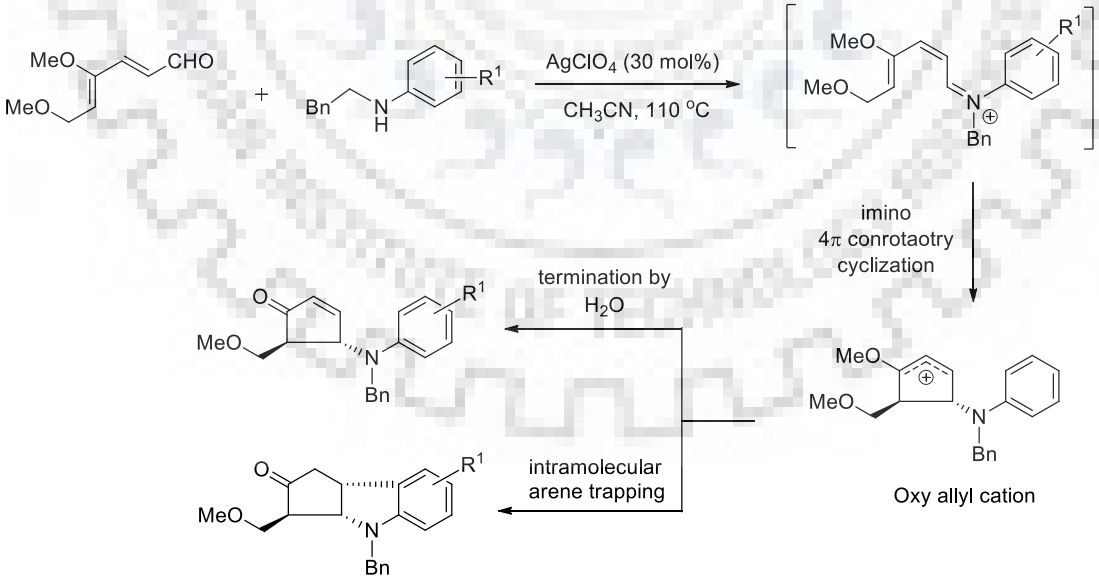
Scheme 4: Imino-Nazarov reaction for the synthesis of amine-substituted cyclopente-namides.

West *et al*. described a new alternative method for the construction of amine-substituted cyclopentanoid products from silver-assisted electrocyclic opening of 1-amino-1-alkenyl-2,2-dichlorocyclopropanes. The silver-assisted *gem*-dichlorocyclopropane species furnishes 3-aminopentadienyl cation. Subsequently these intermediates can undergo imino-Nazarov 4π-electrocyclization process leading to cyclopentenone iminium salts, which afford allylic amines upon reduction (Scheme 5) [20].



Scheme 5: Synthesis of polycyclic amines *via* imino-Nazarov cyclization.

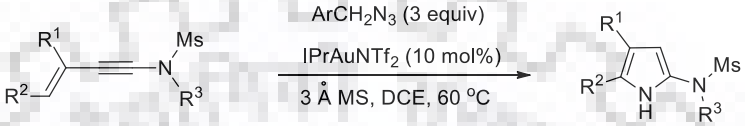
Liu *et al*. have described an efficient imino-Nazarov cyclization of an iminium ion generated from simple condensation of an aldehyde and secondary aniline and subsequent 4π-electrocyclic ring closure. They developed an interrupted imino-Nazarov process by intramolecular arene trapping of the cyclic oxyallyl cation in the presence of a silver(I) catalyst to provide a convenient access to indoline-fused cyclopentanones (Scheme 6) [21].



Scheme 6: Synthesis of indoline-fused cyclopentanones *via* interrupted imino-Nazarov cyclization.

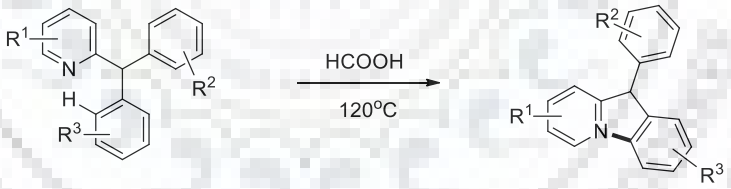
1.1.2. Aza-Nazarov cyclization

Lu and Ye *et al*. reported an intermolecular ynamide amination-initiated method for the construction of 2-aminopyrroles *via* 4π-electrocyclization of aza-Nazarov reaction in the presence of gold catalyst. They synthesized several useful 2-aminopyrroles under mild conditions, and examined the mechanistic rationale for this tandem protocol. The observed high regioselectivity was also well supported by DFT calculations (Scheme 7) [22].



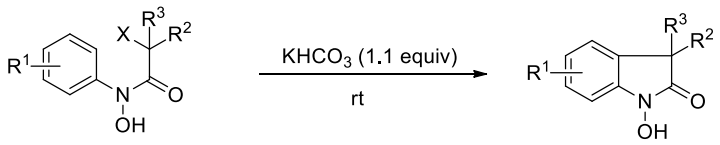
Scheme 7: Synthesis of 2-aminopyrroles *via* aza-Nazarov cyclization.

Sekar and his co-workers demonstrated the Brønsted acid mediated intramolecular aza-Nazarov cyclization reaction for the synthesis of biologically important pyrido[1,2-*a*] indole under transition metal-free conditions. This aza-Nazarov type strategy provided a wide substrate scope and good functional group tolerance for the synthesis of pyrido[1,2-*a*] indole derivatives. Further they found axial chirality in the cyclized products bearing bulky groups in *ortho* position (Scheme 8) [23].



Scheme 8: Synthesis of pyrido-fused indoles *via* aza-Nazarov cyclization.

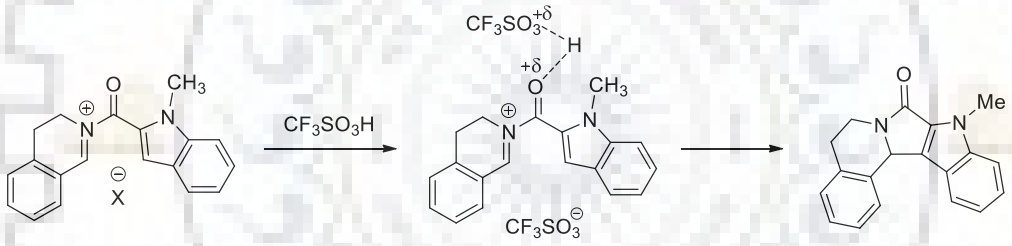
Liao and his co-workers developed a transition metal-free approach for the synthesis of oxindoles by an aza-Nazarov-type reaction involving azaoxyallyl cation intermediates. The reaction was carried out under mild reaction conditions with broad functional group tolerance. In addition, a one-pot procedure was developed to make the system more applicable. This reaction afforded an alternative approach to oxindoles and their bioactive compounds (Scheme 9) [24].



Scheme 9: Synthesis of oxindoles *via* aza-Nazarov cyclization.

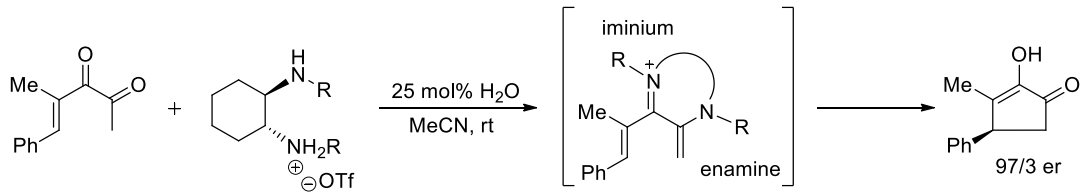
1.1.3. Enamine-iminium ion aza-Nazarov cyclization

Klumpp *et al*. introduced an unprecedented, efficient and mild protocol for the synthesis of varied heterocyclic products *via* enamine-iminium ion aza-Nazarov cyclization under superacid-catalyzed conditions. This Nazarov-type transformation provided amide and pyrrole-fused ring systems from *N*-acyliminium ion salts with acid catalyst. DFT caluculations suggested that the protonation of the *N*-acyliminium ion in the presence of superelectrophilic species made the reaction more favourable by decreasing the activation energy (Scheme 10) [25].



Scheme 10: Synthesis of varied heterocyclic products *via* enamine-iminium ion aza-Nazarov cyclization.

Tius *et al.* reported the reaction between mono-triflate salts of chiral nonracemic 1,2-diamines and α-ketoenones involving an enamine-iminium ion rearrangement which resulted in the products of Nazarov cyclization in high enantiomeric ratio. It was an iminium ion mediated asymmetric Nazarov cyclization of α-diketones in which enamine-iminium ion was generated under Brønsted acid catalysis for subsequent cyclization (Scheme 11) [26].



Scheme 11: Synthesis of oxindoles *via* enamine-iminium Nazarov-type cyclization.

1.2. Pyrazoles

Pyrazole moiety belongs to an important class of five-membered heterocycles incorporated two nearby nitrogen atoms (Figure 2) [27,28]. The pyrazole scaffolds frequently occurr in many natural products and biologically active compounds [29] such as celecoxib [30], DNA gyrase inhibitor [31], protein kinase inhibitors [32], pyrazofurin (cytotoxicity), fezolamine (antidepressant), rimonabant (treat obesity), (anti-MAO activity), zometapine and viagra [33], possess pyrazole ring in their core structure (Figure 2). Pyrazole ring containing compounds exhibit antidiabetic, anticancer, antiinflammatory, antiviral, antileukemic, antibacterial and analegesic activities. These are also important building blocks in agrochemical industries. Apart from these applications, polysubstituted pyrazoles can be used as ligands in various coupling reactions (Figure 3) [34–40].

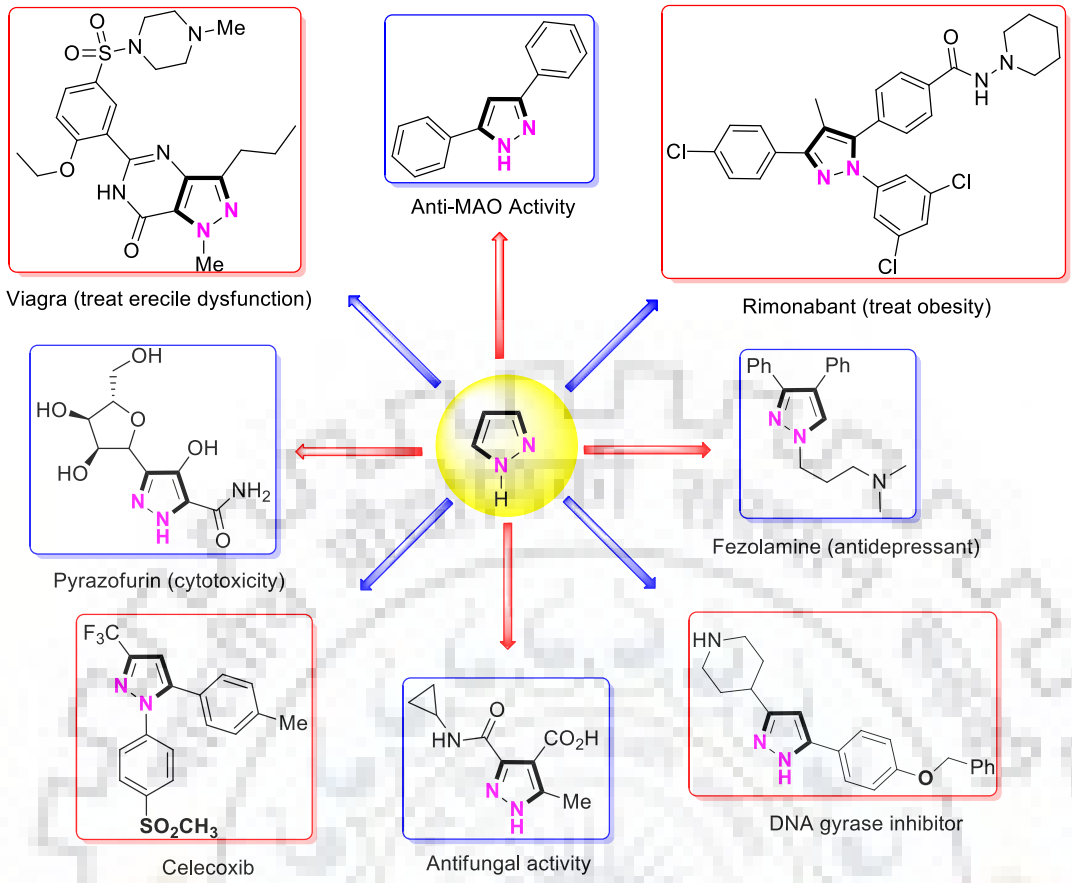


Figure 2: Pyrazole containing drugs.

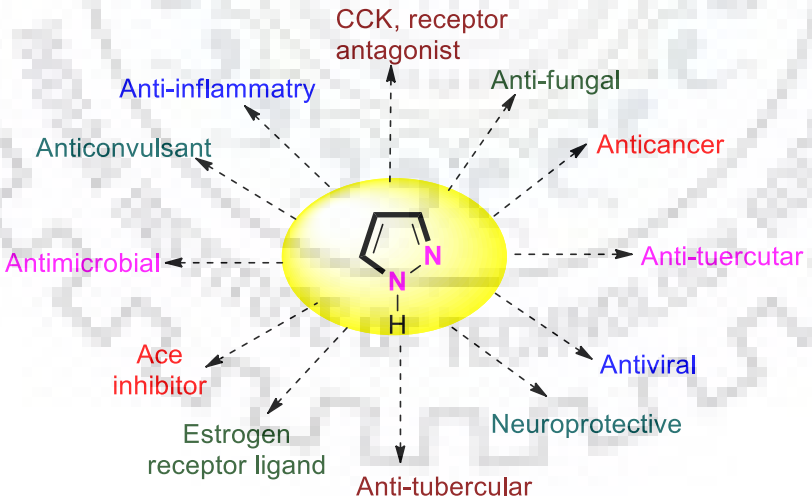
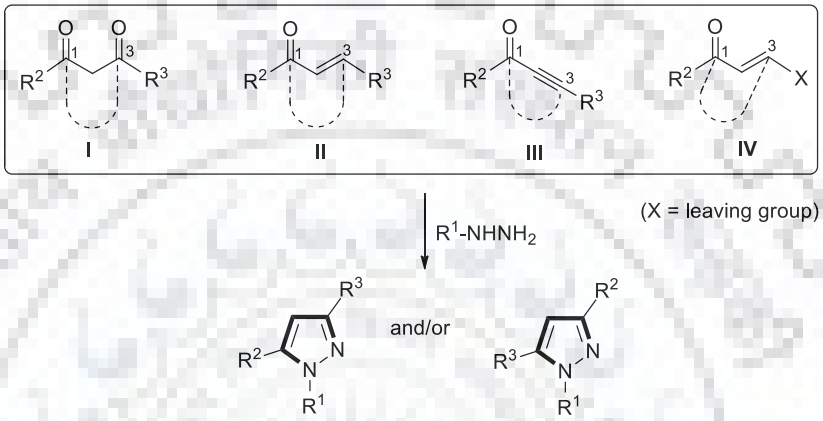


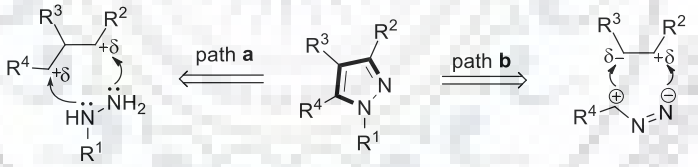
Figure 3: Different biological activities displayed by compound containing pyrazole moiety.

Synthesis of pyrazoles

Notably, due to the importance of the biologically active pyrazoles several methods have been developed for synthesis of diversely substituted pyrazoles in the present research scenario [41,42]. The general methods for the synthesis of pyrazoles are (*i*) the condensation of hydrazines with 1,3-diketones (Schemes 12), (*ii*) 1,3-dipolar cycloaddition of diazo compounds with alkynes, and (*iii*) the reaction of α,β-unsaturated aldehydes/ketones with hydrazines (Schemes 13).



Scheme 12: General approach (two C–N bonds generation) by condensation of hydrazines with 1,3-dicarbonyls and α,β-unsaturated compounds.

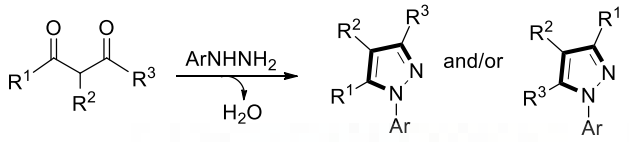


Scheme 13: Genearl approach two C–N bonds generation *via* path **a** or C–N and C–C bonds generation *via* path **b** by condensation of hydrazines with 1,3-dielectrophilic equivalents.

Apart from this an alternative and elegant strategies are progressed in recent years in the field of research [43–44].

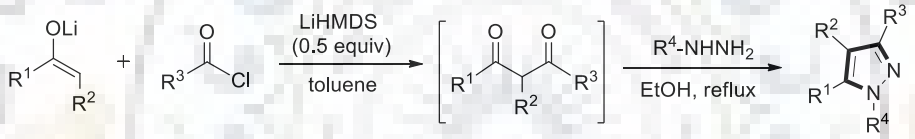
1. One-pot, three-component approach for the synthesis of pyrazoles
2. Metal-mediated synthesis of pyrazoles
3. Metal-free synthesis of pyrazoles
4. Iodine-mediated synthesis of pyrazoles
5. Cross dehdrogenative coupling (CDC) approach for pyrazoles synthesis.

In 1883, German Chemist Ludwig Knorr discovered arylhydrazines to afford pyrazole derivatives. The first synthetic method for the synthesis of pyrazole, which employed the use of 1,3-diketones (Scheme 14) [45].



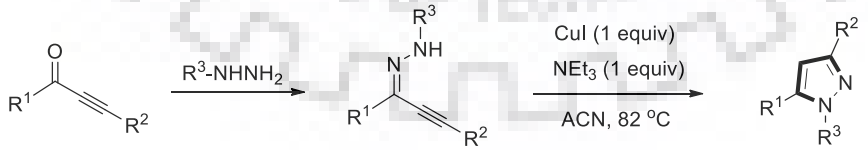
Scheme 14: First synthesis of pyrazoles.

Heller *et al*. developed an efficient one-pot synthesis of highly substituted pyrazoles, by employing 1,3-diketones generated *in situ* from enolate and acid chlorides with hydrazines. This rapid protocol, provided previously unapproachable pyrazoles and synthetically challenging in pyrazole fused containing building blocks and exhibited good functional group tolerance and chemoselectivity (Scheme 15) [46].



Scheme 15: One-pot synthesis of pyrazoles.

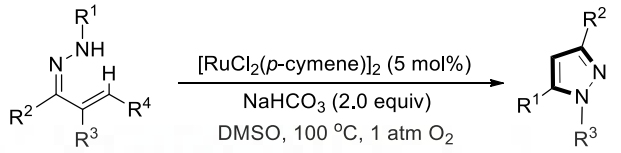
Zora *et al*. reported an electrophilic cyclization process for the synthesis of pyrazoles from *α,β*-alkynic hydrazones by using copper(I) iodide in the presence of triethylamine. They employed *α,β*-alkynic hydrazones, generated from easily available hydrazines and propargyl aldehydes or ketones. This electrophilic cyclization reaction provided pyrazoles in good to excellent yields (Scheme 16) [47].



Scheme 16: CuI-mediated synthesis of pyrazoles.

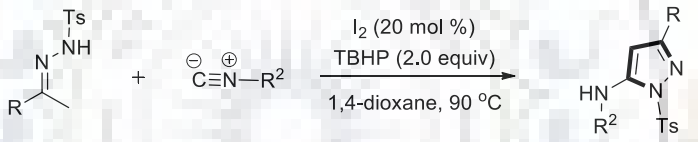
Rao *et al*. developed a novel protocol for the production of a diversified synthetically demanding polysubstituted pyrazoles using ruthenium(II)-catalyst *via* oxidative C–N

coupling reaction. The target products can be obtained smoothly from easily available starting materials using dioxygen as an oxidant. The scope of the reaction was explored by using various tri- and tetra-substituted starting materials (Scheme 17) [48].



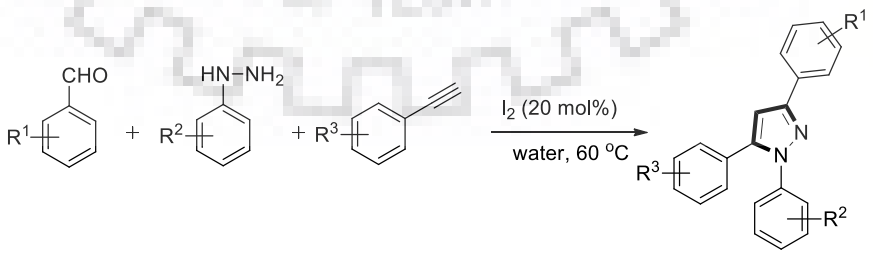
Scheme 17: Ruthenium catalyzed synthesis of pyrazoles.

Wang *et al*. reported straightforward approach for the synthesis of 5-aminopyrazoles through formal [4 + 1] annulation through *in situ* generated azoalkene formed from *N*-sulfonyl hydrazones with isocyanides in the presence of catalytic amount of molecular iodine using TBHP as an oxidant. This metal/alkyne-free strategy proceeded through C–C and C–N bond construction *via* oxidative cross coupling reaction (Scheme 18) [49].



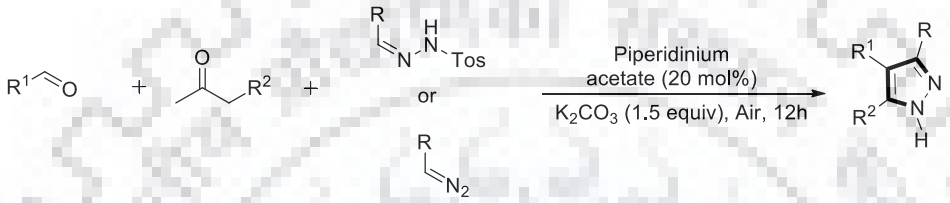
Scheme 18: Iodine/TBHP mediated pyrazoles synthesis.

Singh and his co-workers introduced a method for the synthesis of library of trisubstituted pyrazoles in the presence of iodine. In this protocol, the reaction proceeded through an eco-friendly green solvent *i.e.*, water. Then the present one-pot domino process generated new C–C, and C–N bonds *via* Schiff base, Mannich addition followed by intramolecular cyclization under mild conditions (Scheme 19) [50].



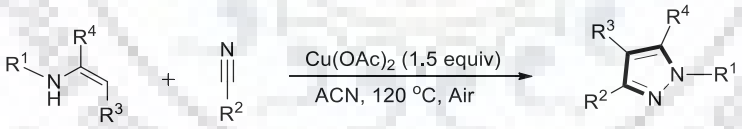
Scheme 19: Iodine catalysed synthesis of pyrazoles.

Kamal and his co-workers developed highly efficient and mild protocol for the direct synthesis of polyfunctional pyrazoles. This method involved the one-pot, three-component coupling of aldehydes, 1,3-dicarbonyls, and diazo compounds as well as tosyl hydrazones. This multicomponent reaction does not required isolatation of intermediates, use of toxic metal-catalyst or oxidants. The reaction involves the generation of two C−C and one C−N bonds *via* Knoevenagel condensation, 1,3-dipolar cycloaddition followed by oxidative aromatization. The scope of the reaction was established by employing a series of carbonyl, and diazo substrates (Scheme 20) [51].



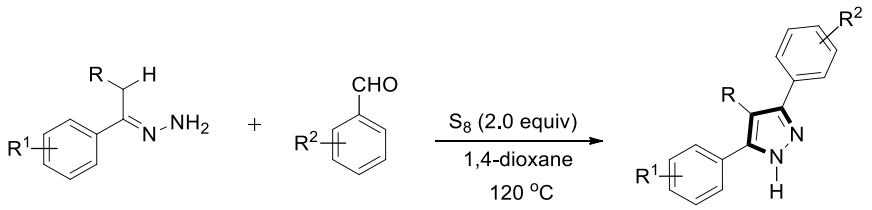
Scheme 20: Base catalysed pyrazoles synthesis *via* intramolecular oxidative cyclization.

Glorius *et al*. described an unprecedented copper mediated intramolecular oxidative cyclization of enaminones for the formation of pyrazoles from easily available starting compounds, such as amines, ketones, and nitriles. This protocol did not require any hydrazine precursors for C−C and C−N bond formation. Further, this methodology afforded pyrazoles regiospecifically under aerobic conditions (Scheme 21) [52].



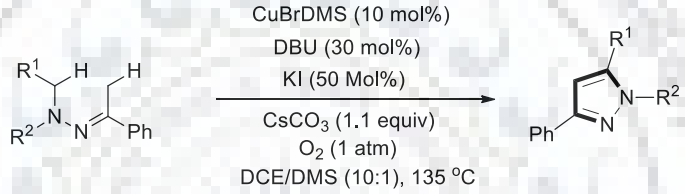
Scheme 21: Cooper mediated [3 + 2] cycloaddition for pyrazoles synthesis.

Singh and his group introduced a novel method for the synthesis of poly substituted pyrazoles through cross dehydrogenative cyclization (CDC) by the involvement of acetophenone hydrazones and aldehydes. They developed elemental sulphur-mediated Csp^3–Csp^2 bond formation *via* C–H bond functionalization for the generation of functionally-rich pyrazoles (Scheme 22) [53].



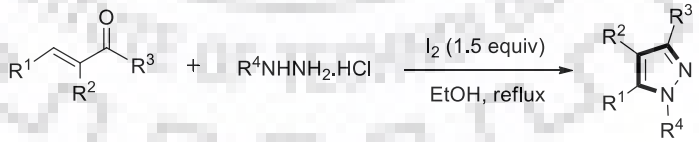
Scheme 22: Sulphur mediated pyrazoles synthesis *via* cross dehydrogenative cyclization.

Ge and his co-worker revealed a novel copper catalyzed approach for the construction pyrazoles *via* intramolecular cross-dehydrogenative coupling through Csp^3–Csp^3 bond formation under aerobic conditions. They reported the first oxidative cross dehydrogenative cyclization (CDC) of hydrazones by involving iminium ion intermediate for the synthesis of pyrazoles *via* Csp^3–H bond activation (Scheme 23) [54].



Scheme 23: Iodine/Copper catalyzed synthesis of pyrazoles *via* CDC approach.

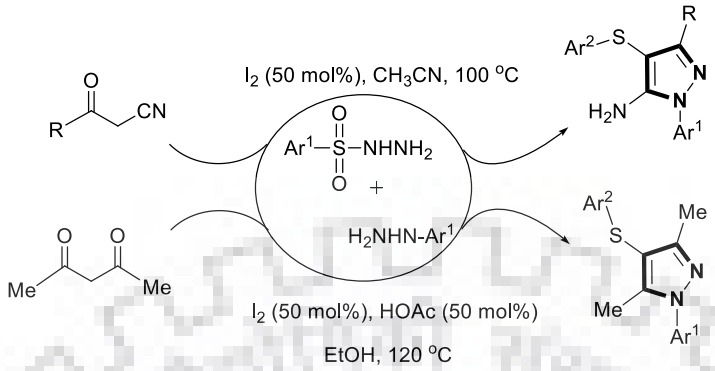
Yu *et al.* established a facile one-pot and metal-free strategy for the synthesis of regioselective tri-substituted pyrazole using an I_2-mediated oxidative C–N bond construction. This green methodology did not require purification of hydrazone intermediates. This metal-free approach afforded a wide variety of pyrazole derivatives from economically available α,β-unsaturated carbonyls and hydrazine salts (Scheme 24) [55].



Scheme 24: Iodine mediated C–N bond generation *via* oxidative cyclization.

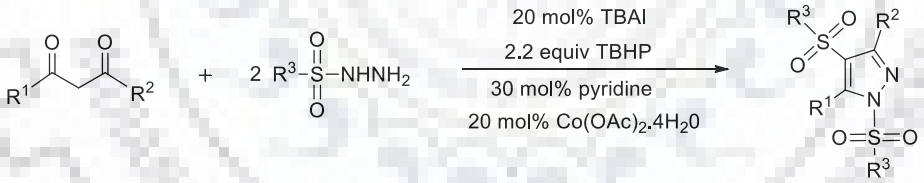
Tu and co-workers established an efficient, metal-free method for the synthesis of diversely decorated pyrazoles by iodine-catalyzed multi-component [3 + 2] annulation of ketonitriles and acetyl acetone, arylhydrazines, and aryl sulfonyl hydrazides. This annulation strategy proceeded mainly through sequential cleavage of S−O, S−N, C−O bonds and a

subsequent one C−S and two C−N bonds generation was realised. This simple one-pot protocol has broad substrate scope by using inexpensive precursors (Scheme 25) [56].



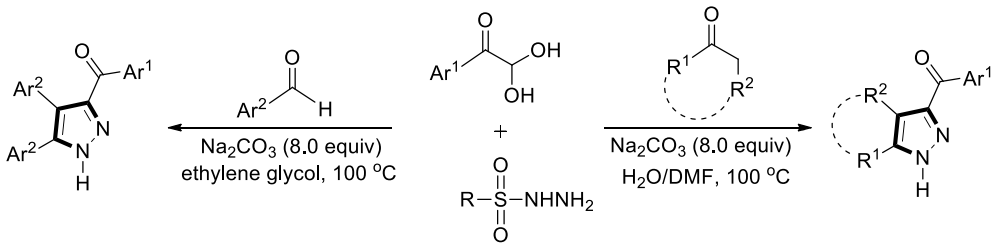
Scheme 25: Iodine-catalyzed multi-component [3 + 2] annulation of pyrazoles synthesis.

Wan and co-workers disclosed an efficient protocol for the development of sulfone substituted pyrazoles from easily available sulfonyl hydrazides and 1,3-diketones by using combination of TBAI/$Co(OAc)_2$ as a catalyst, pyridine as base and TBHP as an oxidant. This practical and operationally simple methodology led to an N- and C-sulfonyl installation successfully under eco-friendly conditions with a wide range of substrate and functional group tolerance (Scheme 26) [57].



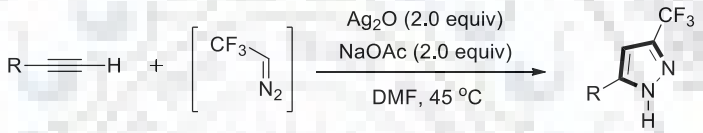
Scheme 26: Iodine/TBHP catalyzed synthesis of sulfone substituted pyrazoles.

Wu and his co-workers reported a versatile base mediated one-pot, three-component approach for the construction of polyfunctional pyrazoles from easily available arylglyoxal monohydrates, *p*-tosylhydrazine, and arylaldehydes. The present synthetic methodology has significant applications for the development of pyrazoles with excellent regioselectivity (Scheme 27) [58].



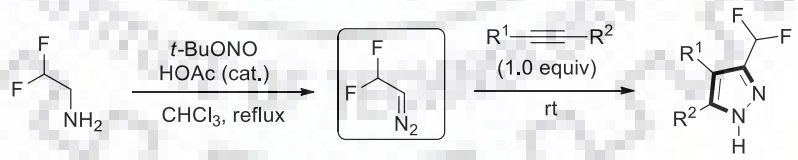
Scheme 27: Base mediated synthesis of pyrazoles.

Ma and co-workers developed a novel and unprecedented, silver-promoted synthesis of trifluoromethyl-substituted pyrazoles through cycloaddition reaction with *in situ* generated reagent CF_3CHN_2 from cheaply available $CF_3CH_2NH_2.HCl$. Importance of this strategy was to provide pyrazoles with high regioselectivity. The protocol has highly useful synthetic applications in organic field (Scheme 28) [59].



Scheme 28: Silver oxide-mediated synthesis of pyrazoles.

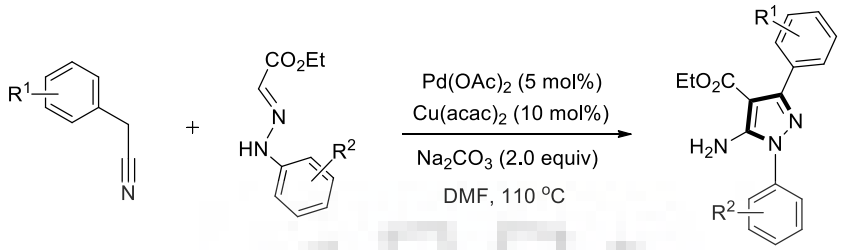
Mykhailiuk and co-workers developed a novel methodology to access agrochemically useful difluoromethyl-substituted pyrazoles and for the first time they used *in situ* generated reagent CF_2CHN_2 in [3 + 2] cycloadition reaction with alkynes. This one-pot transformation significantly avoided any metal catalysts and elude the use of toxic and explosive gaseous by-products (Scheme 29) [60].



Scheme 29: Synthesis of difluoromethyl-substituted pyrazoles.

Huang and co-workers have developed a novel method for the synthesis of aminopyrazoles under the influence of combined $Pd(OAc)_2/Cu(acac)_2$ catalyst reaction. This one-pot protocol involves intermolecular cyclization *via* C–C and C–N bond construction of acetonitriles and hydrazones. This protocol revealed higher reactivity of aromatic substrates

than their aliphatic counterparts, and gave the scope to medicinal chemists to explore their pharmacological profile (Scheme 30) [61].



Scheme 30: Pd/Cu-catalyzed synthesis of pyrazoles.

1.3. Sulfones

Carbon–carbon [62–68] and carbon–heteroatom bond construction (C–N, C–S) [69–74] is an essential quest for the development of novel and efficient chemical building blocks in present research scenario. Due to the importance of C-heteroatom bond generation, specifically C–S bond forming reactions have gained huge attention in synthetic community. Generally sulfones and thioethers are the most common skeletons in sulfur containing drugs which are useful for the treatment of leprosy, dermatitis herpetiformis, and tuberculosis. Scientists have also determined that sulfone bearing structural architectures displayed a diverse range of therapeutic and biological properties such as antibacterial, antifungal, antimalarial, cysteine protease inhibitor, anti-HIV, anti-proliferative, anticancer, protein phosphatase methylesterase-1 inhibitors, thyroid receptor antagonist *etc.* (Figures 4 and 5). Because of the potential applications of organosulfur compounds, numerous protocols have been established for C–S bond construction during the last few decades [75–78].

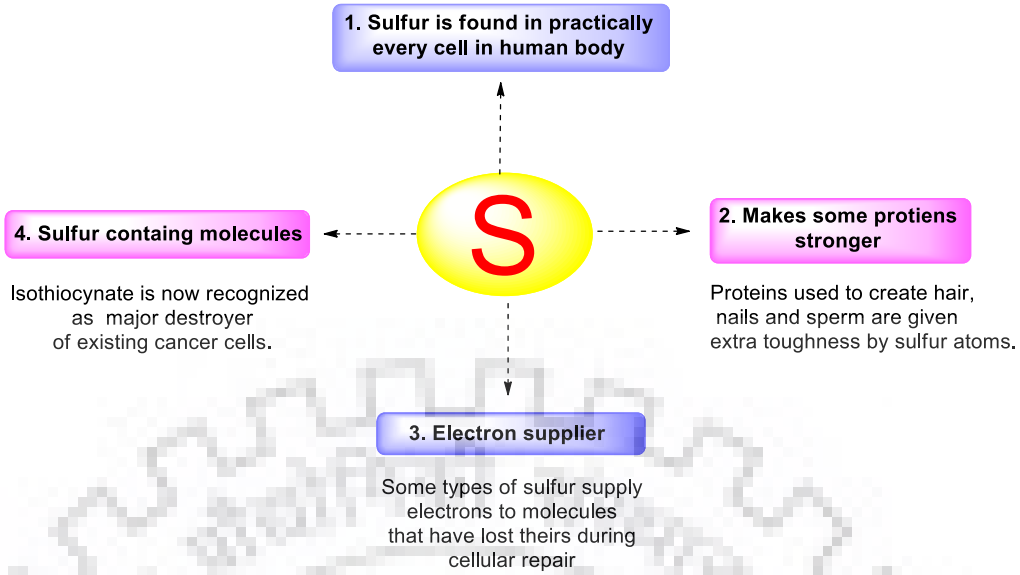


Figure 4: Sulphur activity in biological system.

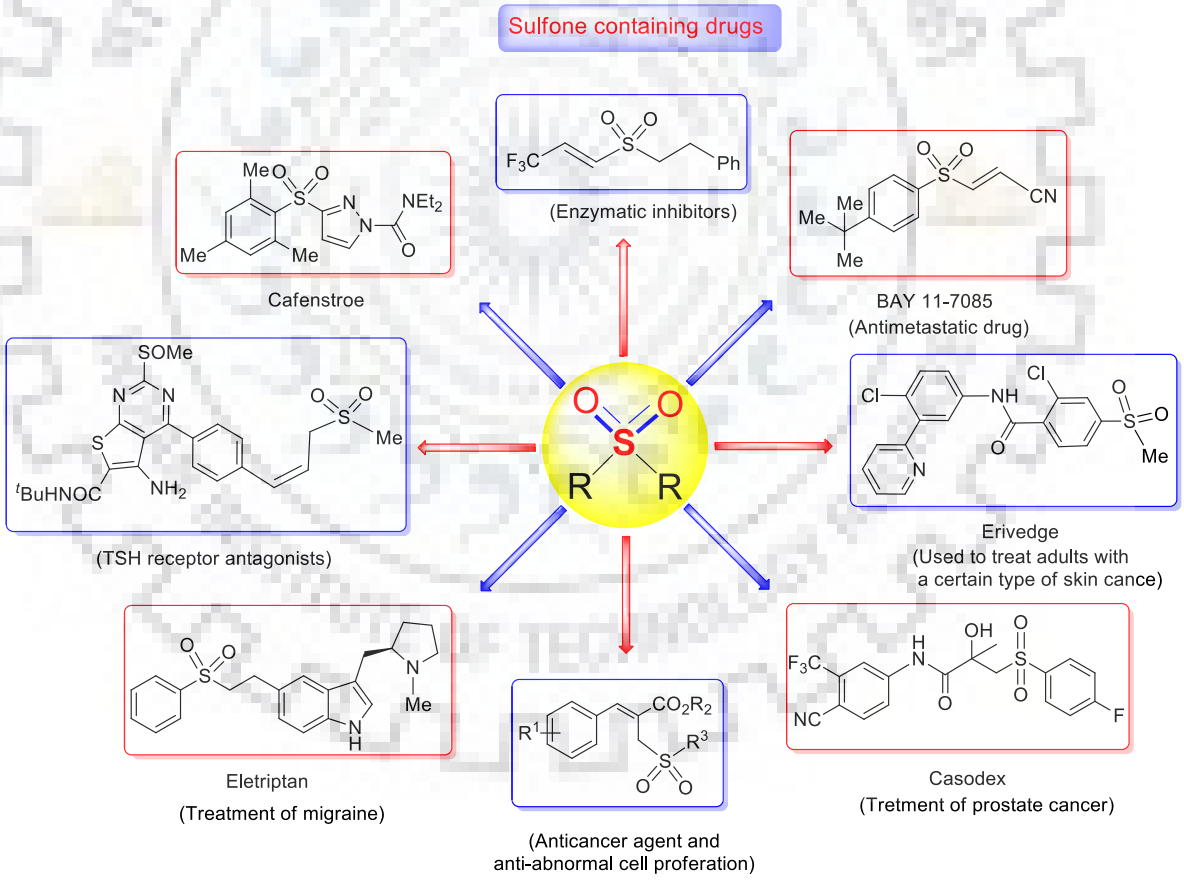


Figure 5: Sulfone containing valuable biologically active organosulfur compounds.

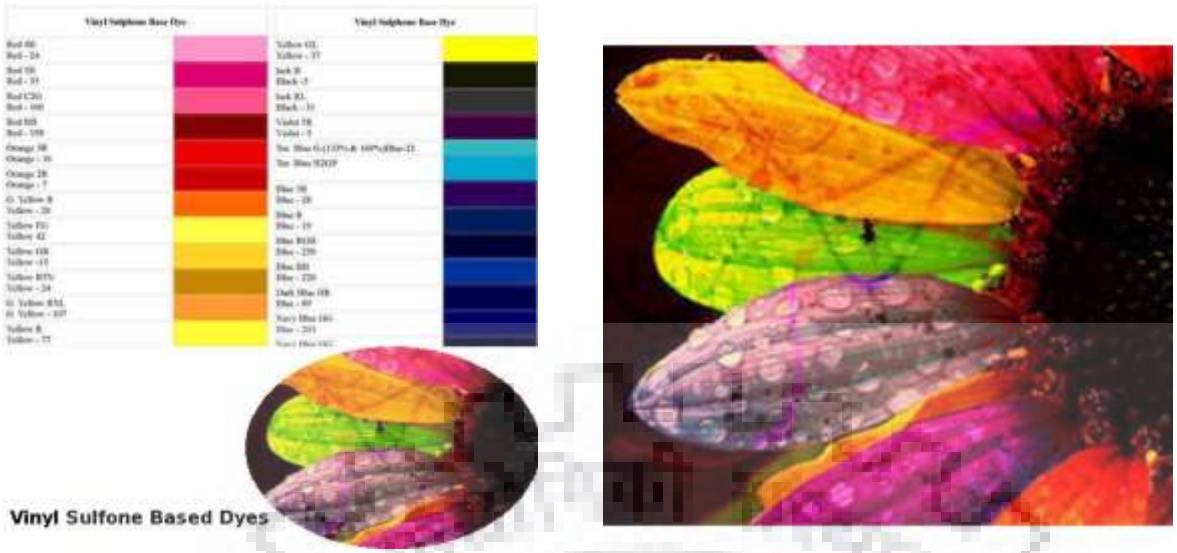


Figure 6: Vinyl sulfone based dyes.

Sulfone skeleton has been recognised as an essential functional group, Fuchs *et al.* termed them as "pluripotent" and Trost termed them as "chemical chameleons". The introduction of sulfone moiety into the organic context is of great interest and fascinates organic chemists towards synthesis of new sulfone based drugs and materials in synthetic community (Figure 8) [79]. Due to the importance of sulfones, over the years, several strategies have been developed for the production of sulfone containing organic molecules through C–S bond formation under transition metal and metal-free conditions [80–82].

The discussion here is focused on sulfone derivatives such as vinyl sufones, reactions such as hydrosulfonylation and C- and S-alkylation.

Sufonylation reactions have become a potent and reliable synthetic approach for the production of vinyl sulfones. These vinyl sulfones are significant scaffolds in pharmaceuticals as well as in dye industries (Figure 6). Generally sulfonylation sources are *p*-toluenesulfonylmethyl isocyanide (TsMIC), sodium sulfinate salts, sulfinyl chlorides, sulfonic acids and sulfonylhydrazides *etc*. Among all sources, arylsulfonyl hydrazides is the most versatile synthon for sufonylation and thiolation depending upon the nature of the organic transformation (Figure 4) [83].

On the other hand, hydrazine hydrates and their derivatives serve as powerful reagents for Wolf−Kishner reduction and Fisher-indole synthesis [84]. Mostly hydrazine

hydrates are used for the preparation of useful precursors such as hydrazones for the generation of carbenes, di-aza intermediates for coupling reactions and mainly involve in the construction of heterocyclic systems containing two nitrogen atoms. Moreover, sulfonyl hydrazides are widely useful in the identification of functional groups of carbonyl compounds and carbohydrates. In addition, they have been employed in various organic conversions such as Shapiro reaction, sulfonylation, thiolation, and sulfono based pyrazoles construction [85].

This section deals with the results and discussion as shown below

1.3.1. Synthesis of vinyl sulfones
1.3.2. Hydrosulfonylation
1.3.3. Dehydrative alkylation reactions

1.3.1. Synthesis of vinyl sulfones

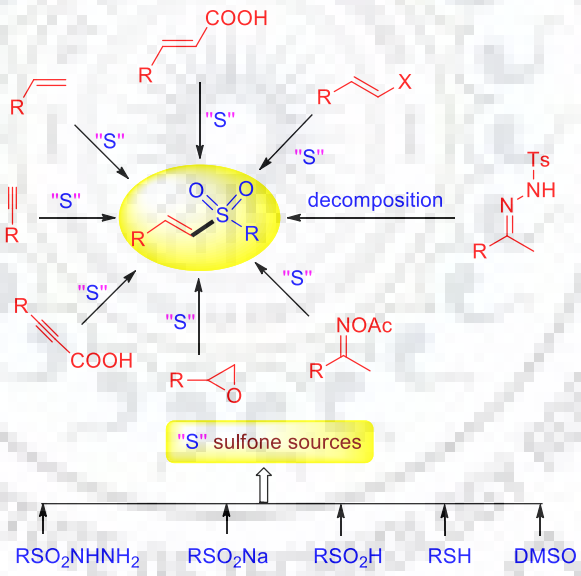
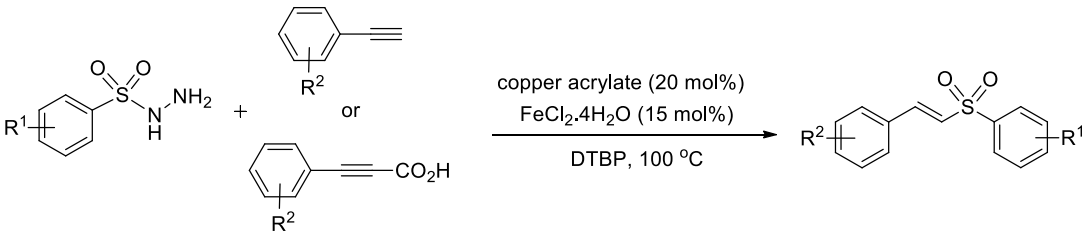


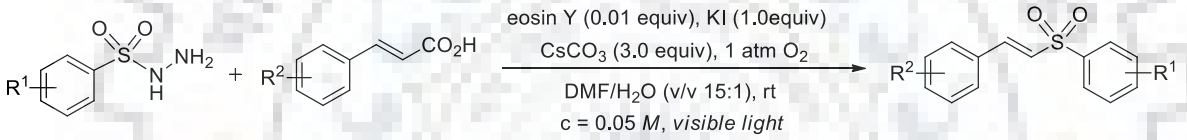
Figure 7: Different approaches for the synthesis of vinyl sulfones.

Mao *et al*. introduced a novel Cu/Fe co-catalyzed approach for the fabrication of Vinyl sulfones using arylpropiolic acid and aryl sulfonyl hydrazides *via* decarboxylative process. They developed different sulfone derivatives by replacing arylpropiolic acid with phenylacetylene *via* C–H functionalization. The inexpensive Fe/Cu co-catalyzed protocol provided with a good substrate scope (Scheme 31) [86].



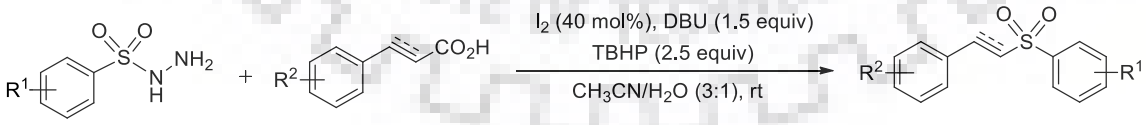
Scheme 31: Cu/Fe co-catalyzed vinyl sulfones synthesis.

Cai and his co-workers established a practical synthesis of vinyl sulfones through decarboxylative C–S coupling reaction of cinnamic acids with sulfonyl hydrazides, catalyzed by organic dye-type photocatalyst eosin Y under visible light treatment with KI and Cs_2CO_3. This straightforward approach furnished a variety of vinyl sulfones with realistic yields under mild conditions with oxygen as the only terminal oxidant (Scheme 32). [87]



Scheme 32: Visible light-induced decarboxylative sulfonylation for the synthesis of vinyl sulfones.

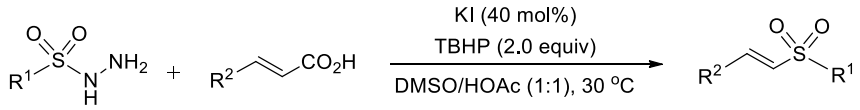
Singh *et al*. disclosed a novel reagent system I_2/TBHP and DBU promoted methodology for the synthesis of vinyl sulfones, from easily available cinnamic acids and arylsulfonyl hydrazides *via* decarboxylative C–S bond formation. This metal-free approach afforded a variety of unsaturated sulfone derivatives with regio- and stereoselectivity under aerobic conditions (Scheme 33) [88].



Scheme 33: A metal-free vinyl sulfones synthesis *via* decarboxylative sulfono functionalization.

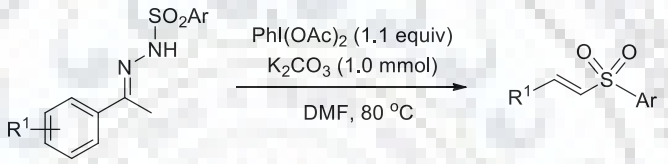
Lei and co-workers demonstrated an alkenylation reaction for the production of vinyl sulfones from sulfonyl hydrazides and alkenes using KI catalyzed system. This alkenylation of sulfonyl hydrazide approach proceeded *via* a radical mechanism followed by HI

elimination under metal free conditions. They proved iodine work as transition metals for the β-hydride elimination during the transformation for the synthesis of vinyl sulfones (Scheme 34) [89].



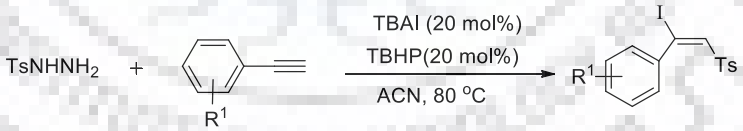
Scheme 34: Iodine-catalyzed alkenylation *via* radical oxidative β-hydride elimination.

Luo and his co-workers introduced an efficient methodology for the construction of vinyl sulfones using hypervalent iodine through decomposition of arylsulfonyl hydrazones (Scheme 35) [90].



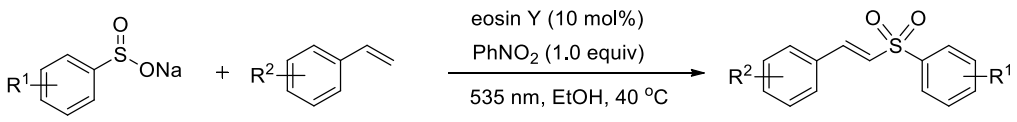
Scheme 35: DAIB mediated synthesis of vinyl sulfones.

Li and Xu *et al*. reported a straightforward approach for the synthesis of β-iodovinyl surgeons using TBAI/TBHP mediated reaction between *p*-tosylhydrazide and arylacetylene. The method is adorned with various attributes of green chemistry and high atom economy with simple experimental conditions and less by-product formation (Scheme 36) [91].



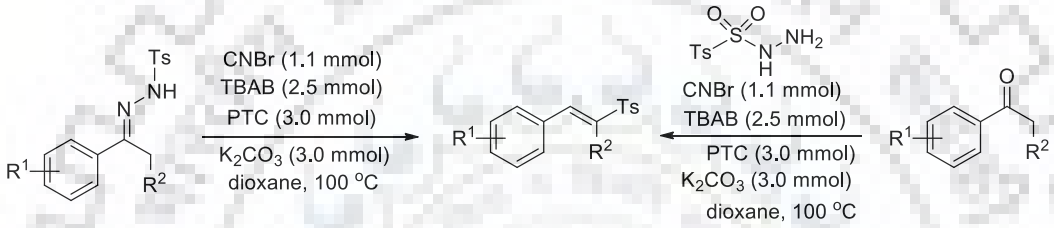
Scheme 36: TBAI/TBHP mediated construction of β-iodo vinyl sulfones.

König and co-workers established visible light and eosin Y catalyzed new approach to the selective synthesis of vinyl sulfones by using sodium aryl sulfinates and styrenes. This simple metal-free and environmentally benign conversion afford an alternative methodology for the rapid production of synthetically valuable vinyl sulfones (Scheme 37) [92].



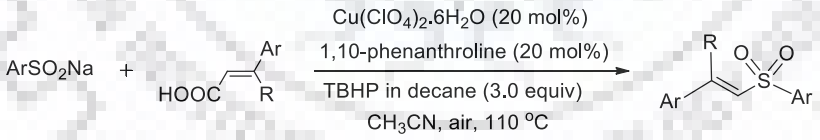
Scheme 37: Visible light-mediated production of vinyl sulfones.

Prabhu *et al*. developed an unprecedented protocol for the synthesis of vinyl sulfones using CNBr/TBAB *via* intramolecular tosyl group migration from *in situ* generated tosyhydrazone. The decomposition of tosyhydrazone facilitates the liberation diazo ion species to furnish target compounds. The reported tosyl group migration proceeded through a radical mechanism under mild conditions (Scheme 38) [84].



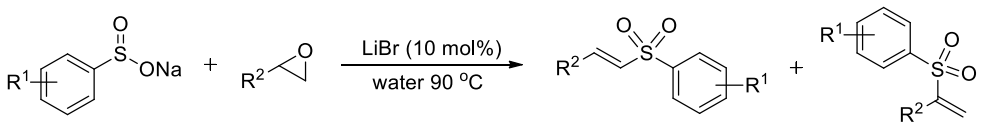
Scheme 38: Metal-free regioselective construction of vinyl sulfones.

Prabhu and his co-workers developed a copper-catalyzed, ligand-mediated decarboxylative sulfonylation with α,β-unsaturated acids and sodium sulfinates. This novel approach furnished vinyl sulfones *via* C−S bond formation by radical process (Scheme 39) [93].



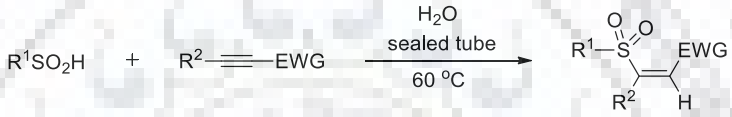
Scheme 39: Copper-mediated production of vinyl sulfones.

Yadav *et al*. disclosed a one-pot LiBr-catalyzed regioselective ring opening of terminal epoxides with sodium sulfinates followed by dehydrative elimination to access vinyl sulfones. This eco-friendly vinyl sulfones synthesis offered highly valuable features such as reaction proceeded through in aqueous medium, high atom economy and operational simple operation for isolation of the regioisomers (Scheme 40) [94].



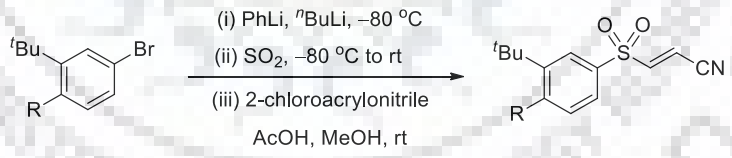
Scheme 40: Formation of vinyl sulfones in aqueous media.

He *et al*. introduced a direct route to synthesize β-sulfonyl-α,β-unsaturated carbonyl scaffolds *via* hydrosulfonation of alkynylcarbonyl compounds with sulfinic acid in aqueous medium. The sulfinic acid displayed different roles such as the source of sulfonylated reagent, hydrogenation and activating reagent for hydrosufonylation. The authors carried out the mechanistic studies by conducting various control and deuterated labelling experiments (Scheme 41) [95].



Scheme 41: Water-mediated regio and stereoselective route for vinyl sulfones synthesis.

Zificsa *et al.* synthesized biologically valuable sulfonylacrylonitriles. The reaction performed under sequential experimental conditions for the production of vinyl sulfone analogues. They synthesized a series of sulfone analogues which are essential for the proapoptotic activity in cancer cells (Scheme 42) [96].

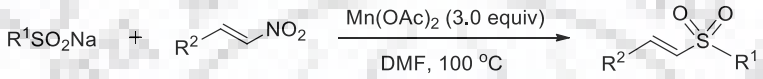


Scheme 42: Synthesis of sulfonyl acrylonitriles.

Yadav and his co-workers for the first time reported an efficient strategy for the construction of vinyl sulfones through denitrative sulfono fuctionalization using readily available precursors such as sodium sulfinates and β-nitrostyrenes under mild reaction conditions. The reaction proceeded through radical addition followed by elimination process to furnish the target vinyl sulfone products (Scheme 43) [97].

Scheme 43: Denitrative sulfonylation of β-nitrostyrenes.

Very recently, Chen and co-workers reported Mn(III)-mediated (*E*)-vinyl sulfones *via* denitrative coupling reaction of sodium sulfinates with β-nitrostyrenes. The merits of this synthetic protocol include easily available substrate, simple experimental and aerobic conditions with decent yields. The mechanistic studies revealed that the reaction proceeded through a radical pathway (Scheme 44) [98].

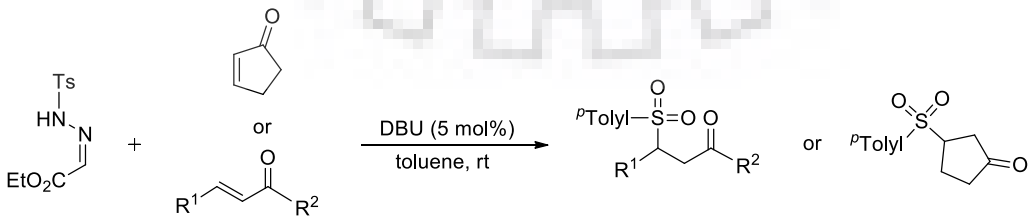


Scheme 44: Denitrative sulfonylation of β-nitrostyrenes.

1.3.2. Hydrosulfonylation reactions

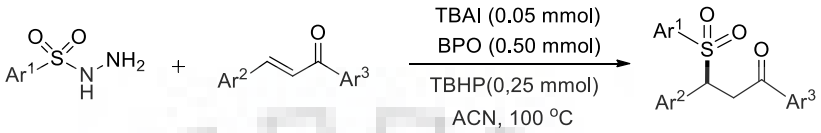
Hydrosulfonylation reaction is key step for the construction of plethora of compounds in the research field. The aliphatic α-substituted sulfone derivatives serve as the powerful synthons for C–C bond construction *via* Ramberg–Bäcklund reaction and Julia olefination, through activation of the α-carbon by sulfonyl group [99–101].

Vicario *et al*. found that *N*-tosylhydrazones can act as a sulfone source for sulfonylation to synthesis γ-ketosulfones from α,β-conjugated carbonyls and ethyl glyoxylate *N*-tosylhydrazone. This hydrosulfonylation reaction proceeded through sulfa-Michael addition using DBU as catalyst. Additionally, they developed γ-hydroxy sulfones by the reduction of γ-ketosulfones under mild conditions (Scheme 45) [102].



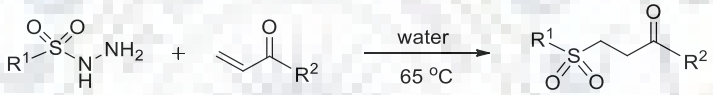
Scheme 45: DBU mediated hydrosulfonylation of α,β-conjugated carbonyls.

Tu and his workers revealed TBAI/Cu co-catalyzed hydrosulfonylation of α,β-unsaturated carbonyls with sulfonyl hydrazides. The reaction of γ-ketosulfones proceeded through radical pathway with benzoyl peroxide (BPO) as an oxidant and TBHP as an additive (Scheme 46) [103].



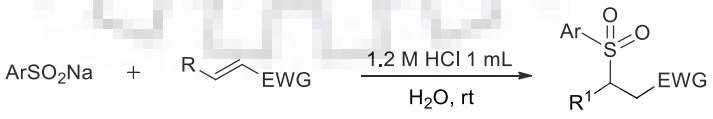
Scheme 46: Hydrosulfonylation of α,β-unsaturated carbonyls.

Wang *et al*. developed an efficient protocol for the synthesis of β-sulfone esters/amides using acrylates and sulfonyl hydrazides in aqueous medium. The catalyst-free sulfonylation approach offered an eco-friendly, ligand and additive-free approach for the synthesis of mono- substituted ethyl sulfones (Scheme 47) [79].



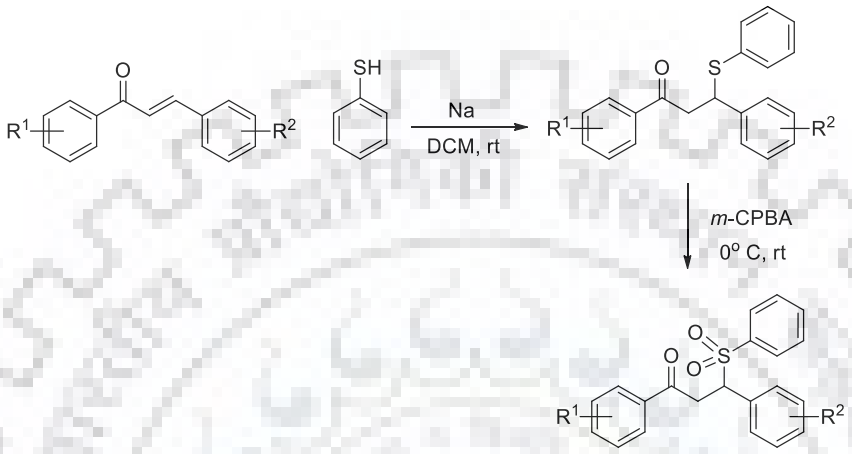
Scheme 47: Water mediated sulfa-Michael reaction of acrylates.

Zhou and co-workers introduced an efficient strategy for the hydrosulfonylation of activated alkenes using sodium arylsulfinates in aqueous medium. Based on the experimental conditions and quantum chemical calculations, water when compared with other solvents was proved to be necessary to improve the transformation big activating the olefinic bond by protonation. The protocol featured inexpensive HCl promoted and environmentally benign method for the synthesis of diverse substituted β-sulfonyl ketones (Scheme 48) [104].



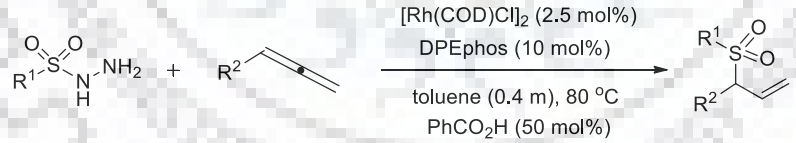
Scheme 48: Sulfa-Michael reaction of activated alkenes.

Ahmed and his co-workers reported hydrosulfonylation of chalcone derivatives by using easily available chalcones and thiophenols *via* thia-Michael reaction followed by oxidation in the presence of *m*-CPBA. Additionally, they developed bisulfones analogues and studied antibacterial and antifungal evaluation of some of γ-keto sulfone (Scheme 49) [105].



Scheme 49: Thia-Michael reaction of chalcones and oxidation.

Breit and co-workers developed rhodium-catalyzed regioselective synthesis of allylic sulfones using sulfonyl hydrazides and allenes. This protocol allowed the production of several admirable branched allylic sulfones with good substrate scope in excellent yields (Scheme 50) [106].



Scheme 50: Rhodium-catalyzed synthesis of allylic sulfones.

1.3.3. Dehydrative substitution of alcohols

Alcohols are natural abundant potent scaffolds in the reserch domain. The skeletal motif of an alcohol such as benzylic alcohol promptly integrated with a target molecule to construct the natural products and bioactive compounds by emancipating of water as sole side product. From this key point of view, alcohols are emerged as conservative and "greener" substitute for toxic alkyl halide reagents for alkylation reactions. During the past

decade elegant approaches have been established for the construction of valuable complex building blocks *via* cross-coupling of alcohols such as (i) dehydrative coupling reactions. (ii) nuclephilic substitution reaction. (iii) Friedel–Crafts alkylation reactions (F–C). (iv) hydrogen-borrowing strategy (HB) or hydrogen auto-transfer (HA) reactions (Figure 8) [107–117].

Most of the F–C and nucleophilic substitution reactions of alcohols required robust method for the construction of C–C and C–hetroatom bond by removal of water as a side product. Naturally alcohols act as perfect electrophiles for nucleophiles substitution reaction with carbon and heteroatom nucleophiles. Due to the importance of dehydrative substitution reaction of alcohols, various synthetic protocols have been developed *via* metal-mediated and metal-free conditions [118–122].

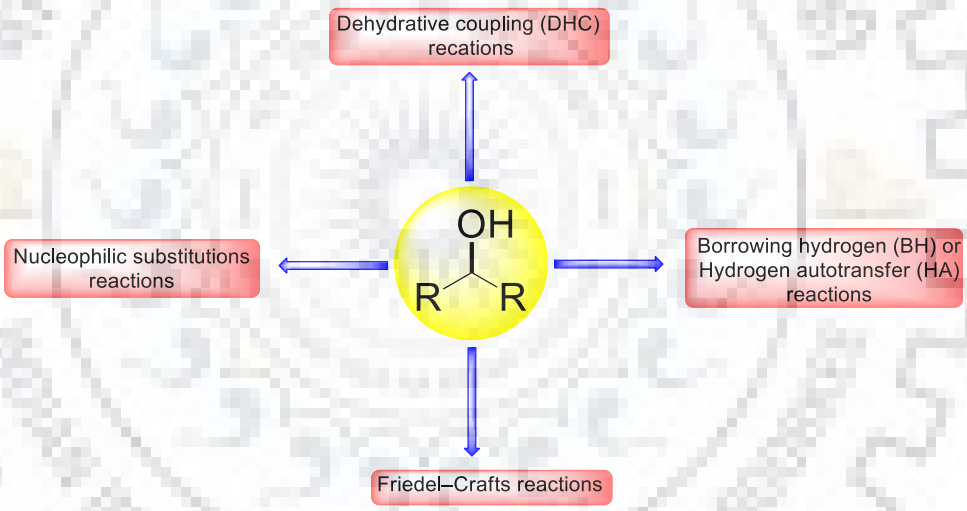
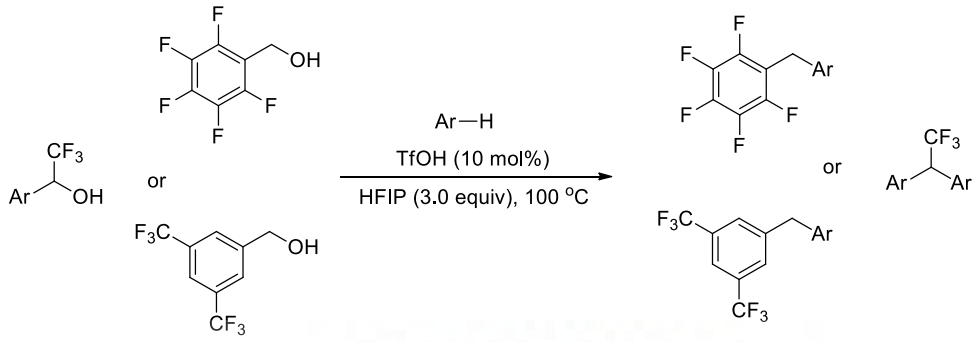


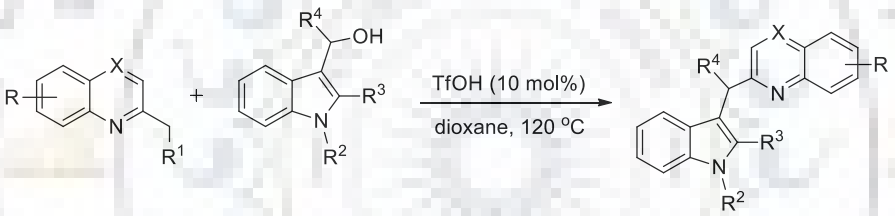
Figure 8: Dehydrative alkylation approaches.

Moran and co-workers explored a significant approach for the synthesis of fluorinated di-aryl alkanes *via* Friedel–Crafts reaction of electronically deactive fluorinated benzylic alcohols with aryls using TfOH as catalyst in HFIP as solvent through S_N1 mechanism. Work-up and kinetic experiments suggested that affiliation between TfOH and HFIP required for advancement in reaction through H-bond acceptability (Scheme 51) [123].



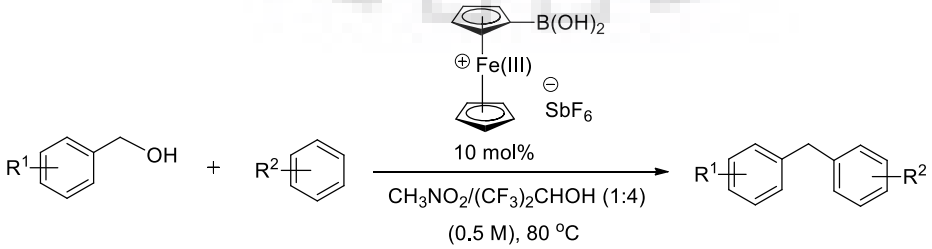
Scheme 51: Metal-free dehydrative Friedel–Crafts reactions.

Xiao *et al*. reported S_N1-type C(sp^3)–H functionalization of alcohols incorporated with 2-methyl-*N*-heteroaromatics for the synthesis of indole-based compounds using TfOH as catalyst. This organocatalytic alkylation transformation afforded a green and efficient synthesis of indole and ferrocene-functionalized *N*-heteroaromatic system in high yields *via* S_N1-type pathway (Scheme 52) [124].



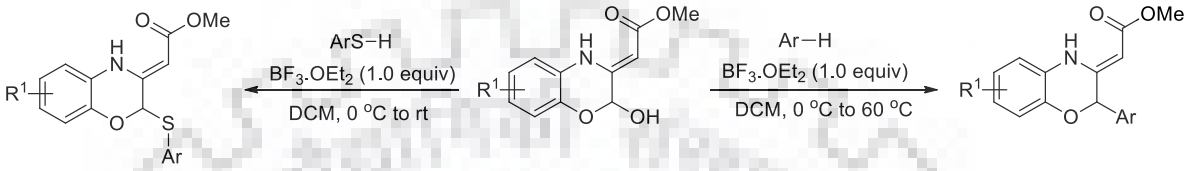
Scheme 52: Metal-free S_N1-type alkylation 2-methyl-*N*-heteroaromatics with alcohols.

Hall and co-workers disclosed an essential approach for the synthesis of highly regioselctive 1,1-diarylalkanes from inactivated arenes and benzylic alcohols using ferrocenium boronic acid hexafluoroantimonate salt as catalyst. This atom economic transformation suggested that the reaction proceeded through the Friedel–Crafts alkylation by S_N1 pathway. This strategy provided various pharmaceutically valuable compounds (Scheme 53) [125].



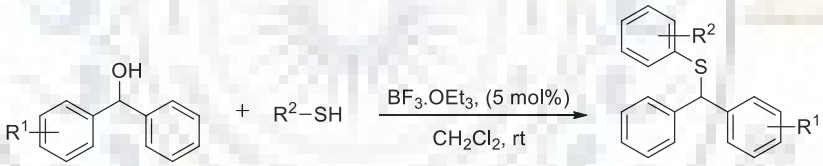
Scheme 53: S_N1-type alkylation of 2-Methyl-N-heteroaromatics with alcohols.

Our group successfully established a new approach to metal-free C-, and S-alkylation of 1,4-benzoxazinols in the presence of $BF_3.OEt_2$ to deliver various biologically important 2-aryl- and 2-arylthio-benzoxazin derivatives. This methodology involved Friedel–Crafts alkylation of 2-hydroxy-1,4-benzoxazine derivatives with electron-rich arenes. On the other hand S-alkylation protocol involves simple nuclephilic substitution reaction between thio-phenols and 2-hydroxy-1,4-benzoxazine derivatives (Scheme 54) [126,230].



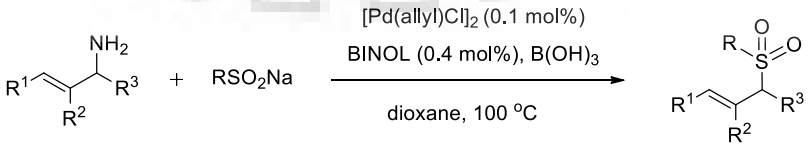
Scheme 54: Metal-free C-, and S-alkylation of benzoxazine based alcohols.

Our group also documented a rapid and efficient protocol for the synthesis of diverse diarylmethyl thioethers from diaryl carbinols and thiols using $BF_3.OEt_2$ as catalyst by elimination of water as by-product. The significant features of this methodology high atom economy, inexpensive activator and gram-scale synthesis (Scheme 55) [127].



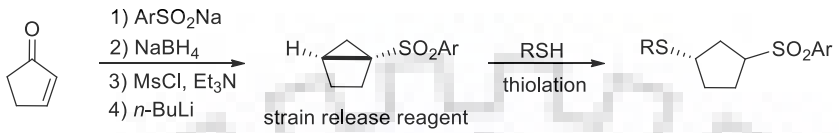
Scheme 55: Metal-free dehydrative S-alkylation.

Tian and co-workers established Pd catalyzed, synthesis of diverse allylic sulfones using primary allylic amines with sodium sulfinates through efficiently substituted in α-selective fashion. The methodology afforded biologically important allylic sulfones in excellent regio- and stereoselectivities and in good to excellent yields (Scheme 56) [101].



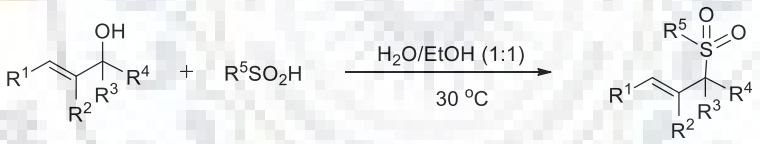
Scheme 56: Substitution reaction of primary allylic amines with sulfinate salts.

Baran and his co-workers reported remarkable and unprecedented simple straightforward approach for the strain-release cyclopentylation of thiols through strain-release heteroatom functionalization. This protocol provided the functional group tolerance with various nucleophiles such as amines, alcohols, thiols, carboxylic acids, and other heteroatoms is introduced for strain releas alkylation (Scheme 57) [128,129].



Scheme 57: Strain-release cyclopentylation thiols.

Recently, Xie and co-workers introduced an unprecedented metal-free dehydrative sulfonylation strategy for the synthesis of a wide range of allylic sulfones. This regioselective transformation deliverd the desired allylic sulfones from both aliphatic and aromatic sulfinic acids with several allylic alcohols in aqueous medium. Further, the DFT calculations suggested that water is essential for the C–S bond fromation to provide the products in high yields (Scheme 58) [130].



Scheme 58: Water-mediated dehydrative sulfonylation.

2.1. OBJECTIVES

- Iodine has been attracted great consideration since its innovation 1811. Today iodine has been recognized as a resourceful, economical, environmentally benign reagent. Iodine serves as an electrophilic and oxidizing reagent for the construction of C–C, C–heteroatom and heteroatom–heteroatom bonds *via* oxidative coupling and cyclization reactions under metal-free reaction conditions. Moderate redox potential of iodine renders it to act as one of the best alternatives to the metal catalysts in oxidative coupling and cyclization reactions. These properties of iodine have received significant attention for the invention of green protocols during the past decade (Figure 1).

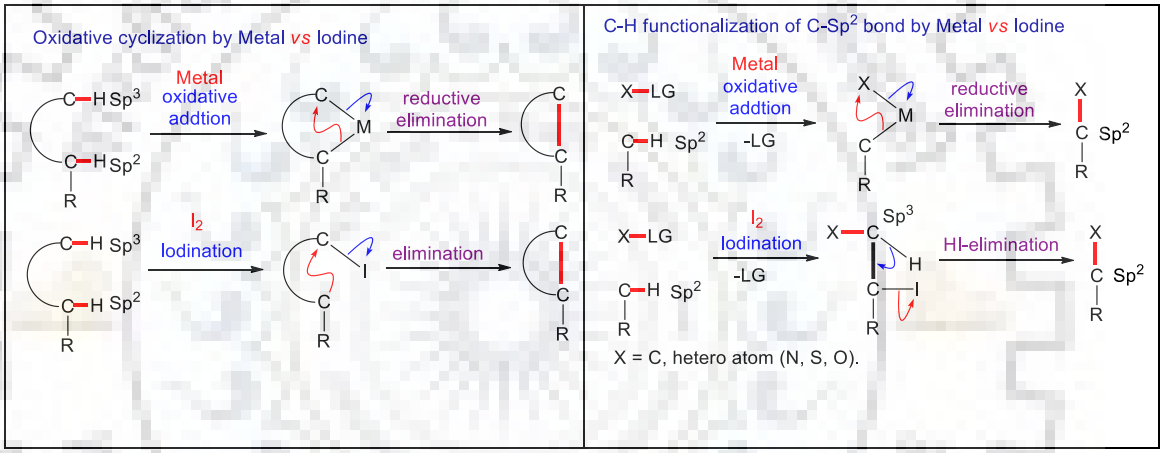
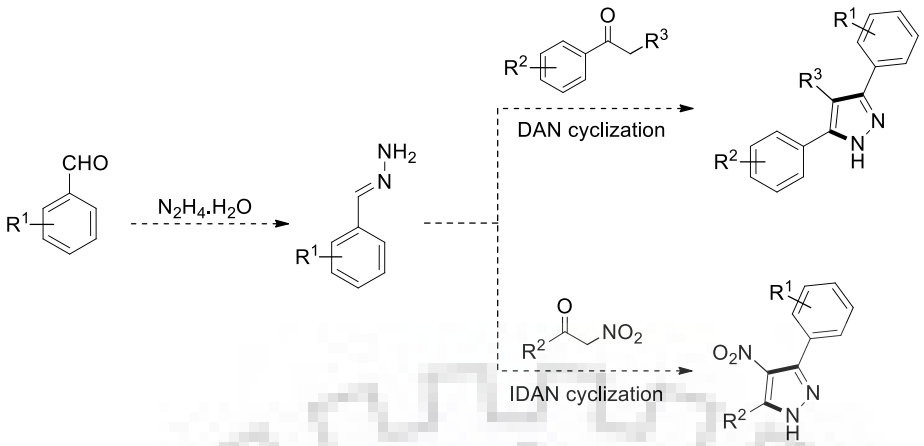


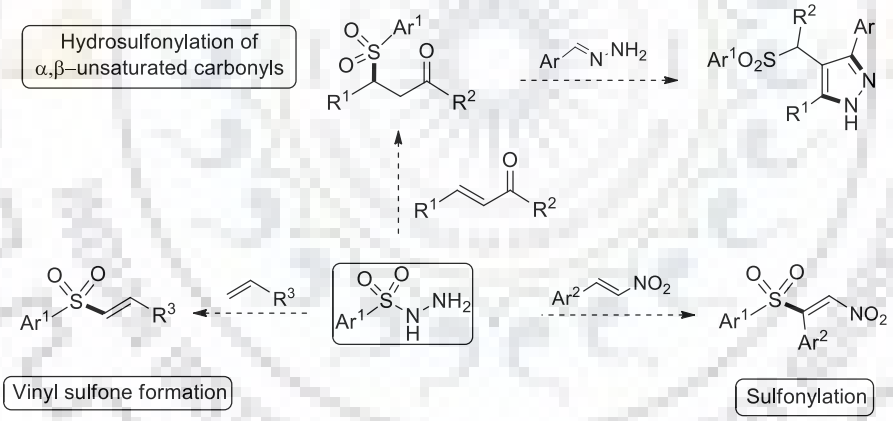
Figure 1: Iodine behaviour as metal-catalysts.

- Inspired by the Nazarov cyclization reactions and iodine promoted green protocols, we became interested to persist this approach for the synthesis of substituted pyrazoles, vinylsulfones, γ-ketosulfones and sulfonylpropaness.

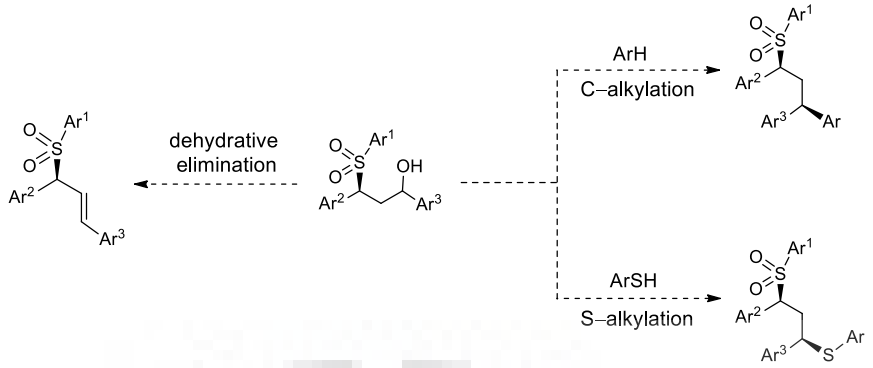
- Enthralled by the application of pyrazoles in modern organic synthesis and their application in the development of complex natural compounds, we envisaged the synthesis of pyrazole derivatives *via* diaza-Nazarove (DAN) cyclization with iodine reagents. Further we became interested to develop green protocols for the synthesis of pyrazoles from easily accessible α-nitro carbonyl derivatives through imino-diaza-Nazarov (IDAN) cyclization in the presence of iodine as catalyst.



- Riveted by the various biological and the pharmacological values of organosulfur compounds and intrigued by the principles of green chemistry, we envisaged to develop simple and proficient approaches for the synthesis of vinyl sulfones from *β*-nitrostyrenes with arylsulfonyl hydrazides using iodine as catalyst and in the presence of an oxidant. We further interested to perform the sulfonylation of olefins containing and sulfa-Michael addition of chalcones and *β*-nitrostyrenes.



- In the eco-friendly quest, we were interested to extend the hydrosulfonylation of chalcones. The γ-ketosufones expected from the above study would undergo reduction with $NaBH_4$ to furnish γ-hydroxysufones. Further it was planned to alkylate the *γ*-hydroxysufones with electron-rich compounds and thiolation with aryl thiols *via* dehydrative coupling.



2.2. RESULTS AND DISCUSSION

This chapter deals with the results and discussion as shown below

2.2.1 Synthesis of pyrazoles *via* diaza-Nazarov (DAN) cyclization and theoretical investigation

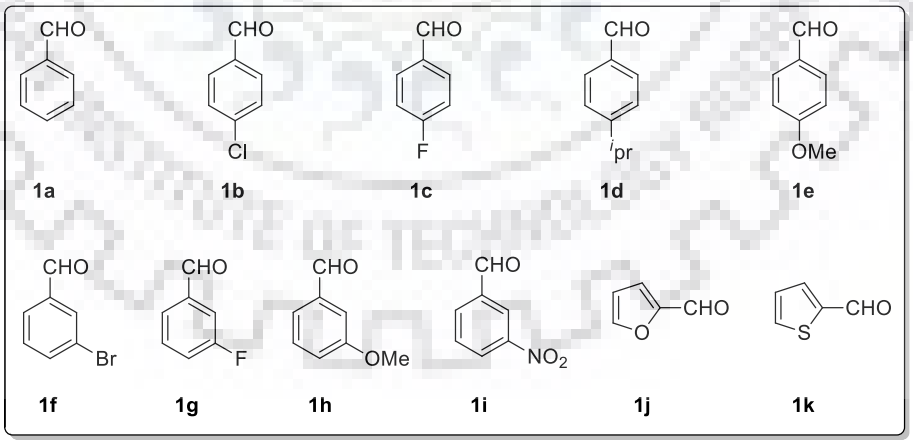
2.2.2 Synthesis of pyrazoles *via* denitrative-imino-diaza-Nazarov (DIDAN) cyclization

2.2.3 Synthesis of vinyl sulfones and hydrosulfonylation of chalcones

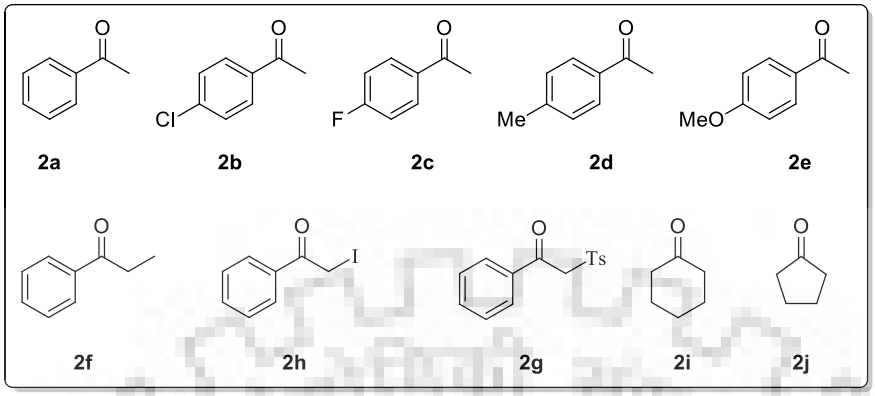
2.2.4. Synthesis of sulfonylpropanes derivatives *via* dehydrative substitution of γ-hydroxysulfones

The starting materials are numbered as shown below for clarify to facilitate the discussion throughout the thesis:

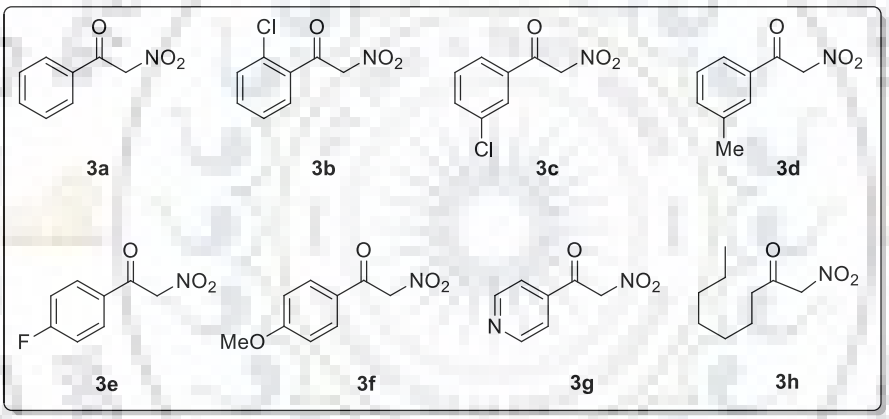
Aldehydes



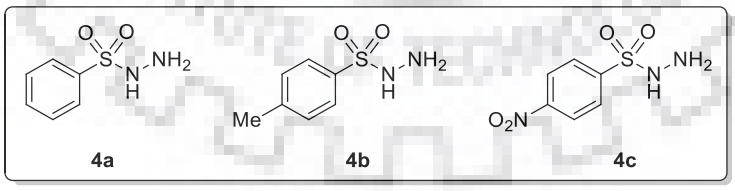
Acetophenones



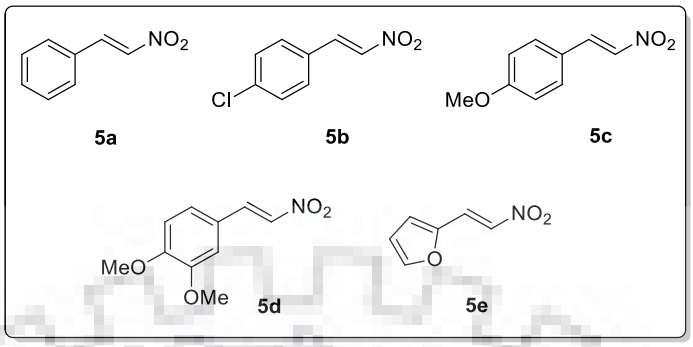
α-Nitro-acetophenones



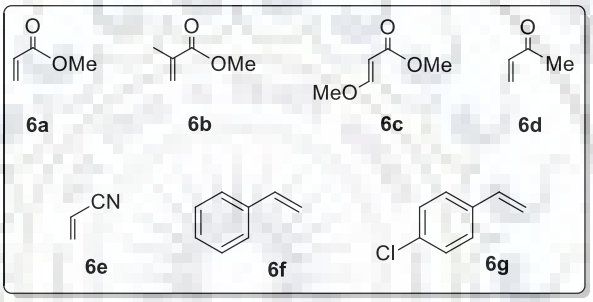
Sulfonyl hydrazides



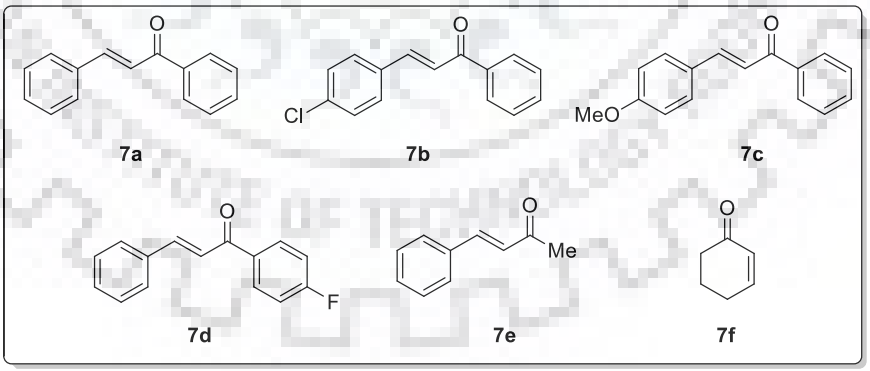
β-Nitrostyrenes



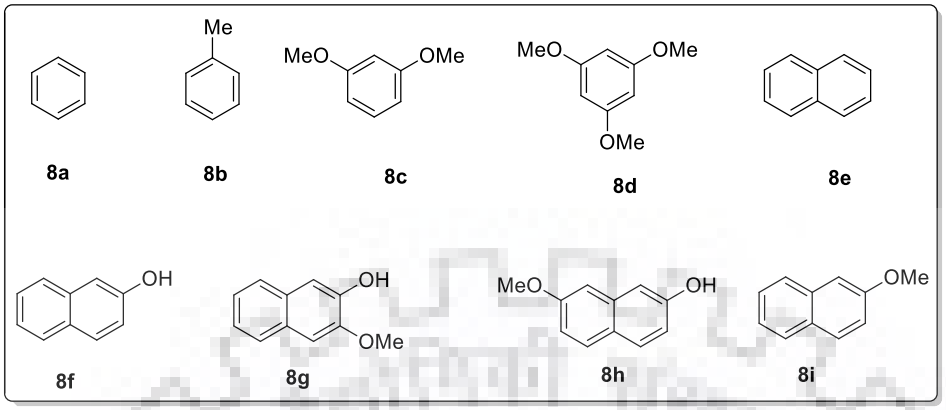
α,β-Unsaturated olefins



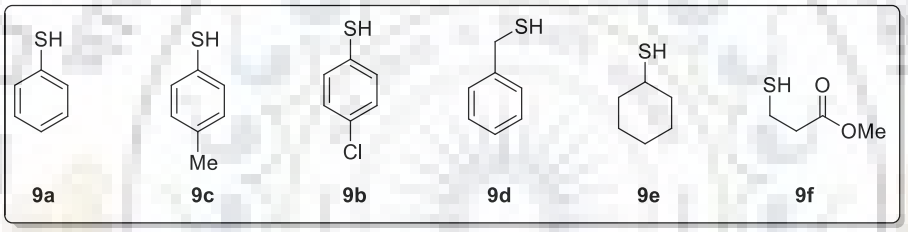
Chalcones



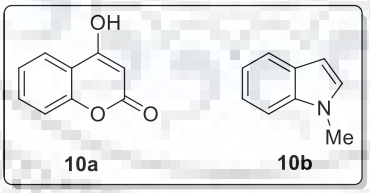
Electronrich-arenes



Thiophenols



Heteroatom-fused arenes



2.2.1. Synthesis of pyrazoles *via* diaza-Nazarov (DAN) cyclization and theoretical investigations

The pyrazole moiety belongs to an important class of heteroaromatic compounds owing to its frequent occurrence in many natural products and biologically active compounds [43,131,132]. Pyrazole ring containing compounds exhibit antidiabetic [133], anticancer [4], antiinflammatory, and analegesic [34] activities. These are also important building blocks in agrochemical industry [28,135]. On account of their great biological importance, diverse approaches have been established for the synthesis of pyrazoles. Traditionally, pyrazoles can be synthesized by the reaction of 1,3-diketones/*α,β*-unsaturated carbonyls with hydrazine derivatives [46,136], 1,3-dipolar cycloaddition of hydrazines with alkenes/ alkynes [49,51,137–139]. With the growing interest in the synthesis of pyrazoles, many transition metal [47,48,52,140–143] and metal-free [53,56,58,144,145] approaches have been reported in the past few years. In 2014, Chang and co-workers established iodine mediated synthesis of pyrazoles from *α,β*-unsaturated aldehydes/ketones and hydrazones [55]. In 2015, Singh *et al*. reported sulphur-promoted synthesis of pyrazoles through cross dehydrogenative cyclization of acetophenone hydrazones with aldehydes [146]. Attracted by the importance of pyrazoles, we developed molecular iodine-mediated diaza-Nazarov reaction for the synthesis of substituted pyrazoles from benzaldehyde hydrazone and acetophenone (v*ide infra*).

In recent years, Lewis acid mediated Nazarov-type cyclization has been emerged as an important tool for the synthesis of five-membered carbocyclic compounds from dienones [12,147]. In general, the key step for Nazarov reaction is 4π-electrocyclization of pentadienyl cation. Heteroatom involved Nazarov-type approach has attracted incredibly wide attention in the present research scenario owing to its remarkable facility to cationic 4π-electrocyclization of a pentadienyl system bearing an imino group instead of the classical ketone functionality. So far, only a few reports are known describing the imino-Nazarov reaction. In 2007, Klumpp research group developed aza-Nazarov cyclization reaction of *N*-acyliminium salts with CF_3SO_3H [25]. Later in 2010, Tius and co-workers revealed enamine-iminium ion Nazarov cyclization of α-ketoenones *via* diamine salt catalyzed enamine-iminium ion formation [26, 148]. It is a big challenge to develop Nazarov-type reaction since the cyclization event of stable acyclic imino diene is not favourable in comparison to conventional Nazarov-type reactions. Subsequently Hsung [19], West [20], and Liu [21], explored interrupted imino-Nazarov electrocyclization. Recently, Liao group reported aza-Nazarov reaction for the

synthesis of *N*-hydroxy oxyindoles where they described the involvement of azaoxyallyl cation as an intermediate [24]. In 2009, Würthwein group disclosed the synthesis of dihydrospiroindenepyrazoles and dihydroindenodiazepine derivatives by 1,5- and 1,7-cascade electrocyclizations under the superelectrophilic solvation conditions, with the involvement of iminium cation intermediate. To support the mechanism, they calculated relative energies for the intermediates of both cyclizations by Hückel- and Möbius-type computationally [149, 150] to the best of our knowledge, diaza-Nazarov-type 4π-elctrocyclization is not known for the synthesis of pyrazoles. We, for the first time, developed iodine-mediated metal-free one-pot approach for the synthesis of substituted pyrazoles *via* diaza-Nazarov-type cyclization of enamine-imino ion under mild conditions by employing *in situ* generated aldehyde hydrazones and acetophenone derivatives as starting materials (Figure 2).

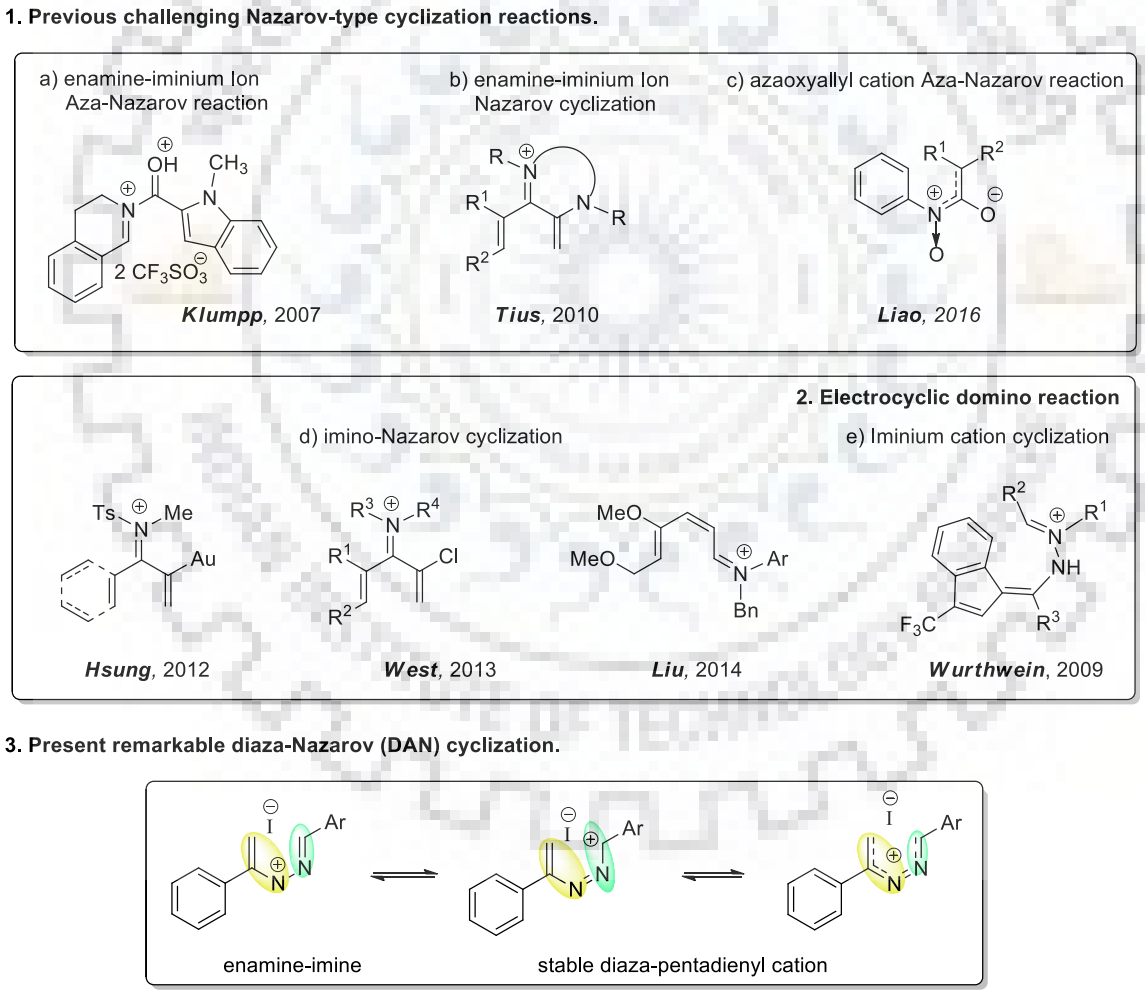
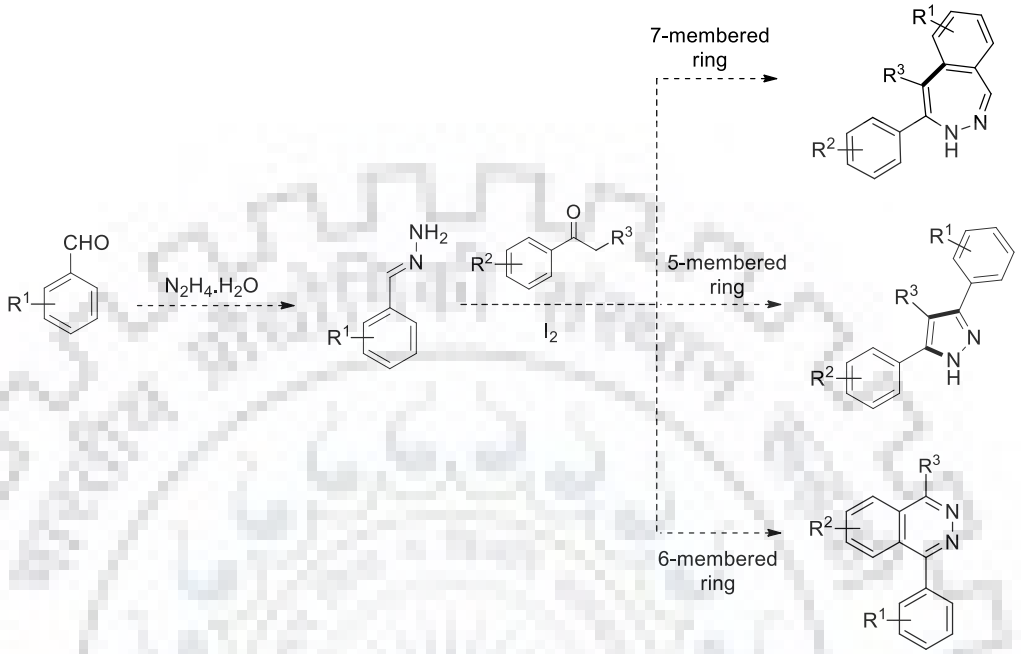


Figure 2: Nazarov-type cyclizations

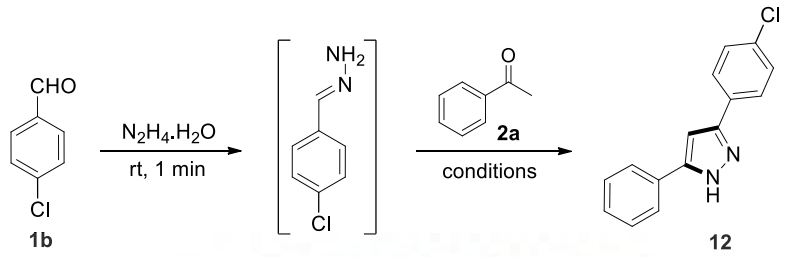
We reasoned that the *in situ* generated aldehyde hydrazones under the influence of molecular iodine, react with acetophenones in three possible electrocyclization (i) 1,5-electrocyclizations, (ii) 1,6-electrocyclization and (iii) 1,7-electrocyclization (Scheme 1).



Scheme 1: Working hypothesis for the oxidative cyclization reaction for the nitrogen containing heterocyclic systems.

We envisaged that cyclization with a 1,3-diene embedded with two nitrogen atoms would lead to the generation of heterocycles (Scheme 1). As a prelude to our objective, we started our investigation by choosing 4-chlorobenzaldehyde (**1b**) and acetophenone (**2a**) as model substrates. At the beginning, we performed a straightforward condensation of benzaldehyde and hydrazine hydrate under solvent-free conditions for *in situ* generation of the corresponding hydrazone within a minute. The *in situ* generated hydrazone was then treated with acetophenone in the presence of various promoters. To our delight, when the reaction was carried out in MeOH using molecular iodine (1.2 equiv), the pyrazole derivative **12** was obtained in 24 h in 65% yield (Table 1, entry 1). To evaluate the effect of solvent in the reaction, we screened various solvents such as THF, CH_3CN, 1,4-dioxane, H_2O and EtOH. The former solvents provided pyrazole **12** in 44, 56, 44, and 33% yields, respectively (entries 2–5). The reaction in EtOH afforded the pyrazole **12** in maximum yield of 70% (entry 6). The reaction, when performed under solvent-free conditions, afforded the desired product **12** in

Table 1 Optimization of reaction conditions.[a]

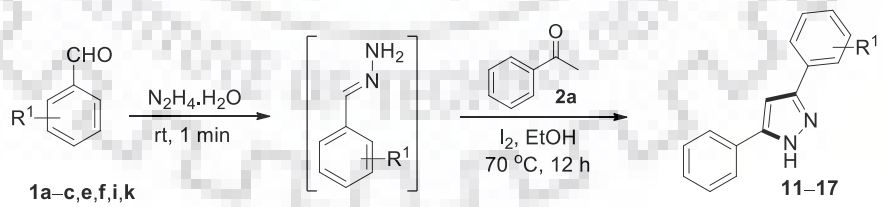


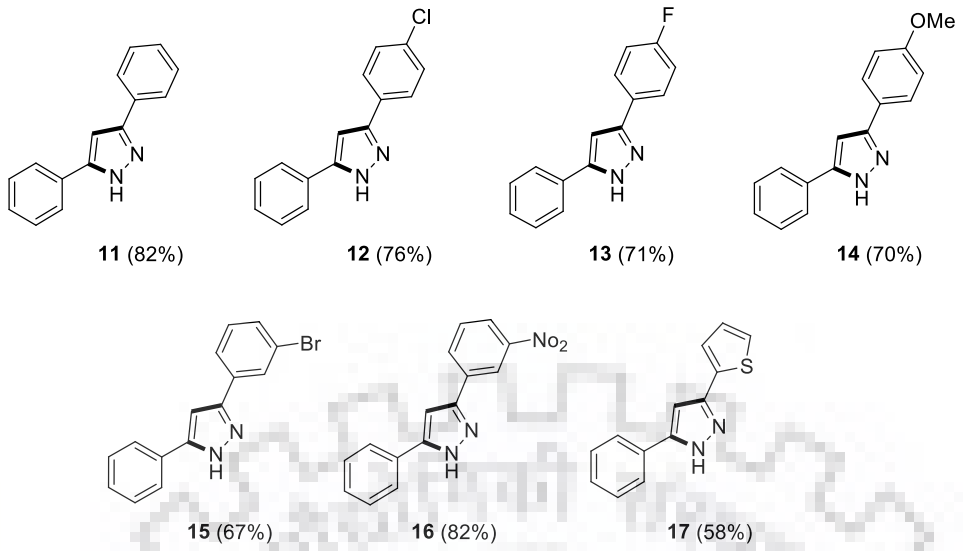
Entry	Reagent	Solvent	Temp °C	Time h	Yield (%)[b]
1	I_2	MeOH	rt	24	65
2	I_2	THF	rt	24	44
3	I_2	ACN	rt	24	56
4	I_2	1,4-dioxane	rt	24	44
5	I_2	H_2O	rt	24	33
6	I_2	EtOH	rt	24	70
7	I_2	Neat	rt	24	42
8	NCS	EtOH	rt	24	54
9	NBS	EtOH	rt	24	57
10	NIS	EtOH	rt	24	traces
11	KI	EtOH	rt	24	nr
12	DAIB	EtOH	rt	24	nr
13[c]	I_2	EtOH	rt	24	52
14[d]	I_2	EtOH	rt	24	60
15	I_2	EtOH	50	12	69
16	I_2	EtOH	70	12	76
17	I_2	EtOH	90	12	72
18	$BF_3.OEt_2$	EtOH	70	12	nr
19	$ZrCl_4$	EtOH	70	12	nr
20	$ZnCl_2$	EtOH	70	12	nr

[a]Reaction conditions: **1a** (0.6 mmol), hydrazine hydrate 80% (1 mmol), **2a** (0.50 mmol), reagent (0.6 mmol).
[b]Isolated yield. nr = no reaction.
[c]I_2: 0.5 equiv.
[d]I_2: 1.5 equiv.

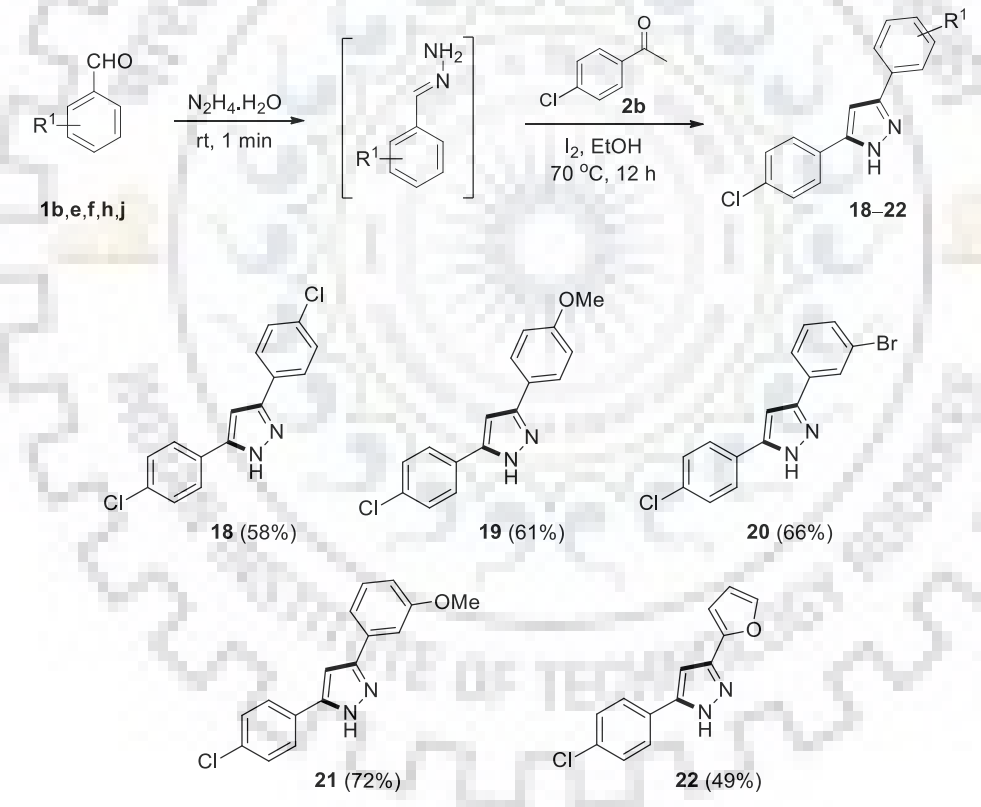
42% yield in 24 h (entry 7). By choosing EtOH as optimum solvent, reagents such as NCS, NBS, NIS, KI and $PhI(OAc)_2$ were screened. No improvement was observed in the yield of the product with NCS and NBS-mediated reactions (entries 8 and 9). When the reaction was performed with NIS, the starting material was recovered along with traces of the product (entry 10). The reaction was inefficient in the presence of KI and $PhI(OAc)_2$ (entries 11 and 12). The yield was diminished by reducing the amount of iodine to 0.5 equiv (entry 13). We observed lower yield of the product when the amount of iodine was increased to 1.5 equiv (entry 14). To further improve the efficiency of the reaction, we evaluated temperature effect. For that we performed the reaction at 50 ^oC, which afforded the product **12** in 69% yield (entry 15). An increase in the yield of product was observed when we performed the model reaction at 70 ^oC (entry 16). The reaction at 90 ^oC led to the formation of the product in marginally lower yield (entry 17). We further studied the effect of different reagents such as $BF_3.OEt_2$, $ZrCl_4$ and $ZnCl_2$ on the reaction, but no product was formed these reagents (entries 18–20). Thus these studies identified EtOH as optimum solvent at 70 ^oC and iodine as promoter for the reaction (entry 16).

With the optimized reaction conditions in hand, we explored the scope of this one-pot, three-component diaza-Nazarov cyclization. Thus various substituted aldehydes **1** having electron-withdrawing **1b**,**c**,**f**,**i** as well as electron-donating groups **1e** were selected and performed their reactions with acetophenone (**2a**) under optimized reaction conditions. In all cases, the reaction went cleanly to furnish the corresponding pyrazole derivatives **11**–**16** in good to high yields of 67–82%. The reaction of thiophene aldehyde **1k** with acetophenone (**2a**) under similar set of conditions, furnished the product **17** in moderate yield (Scheme 2).





Scheme 2: I_2–mediated reactions of aldehydes **1** with acetophenone **2a**.



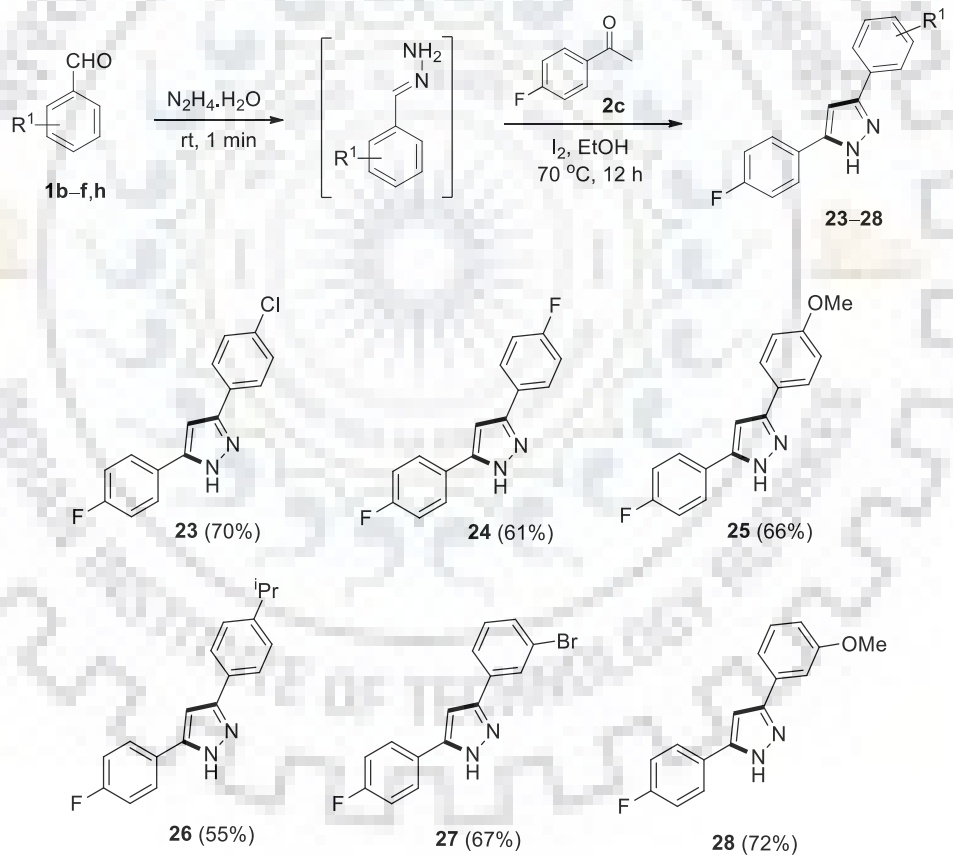
Scheme 3: I_2–mediated reaction of 4-chloroacetophenone (**2b)** with benzaldehydes **1b**,**e**,**f**,**h**,**j**.

Encouraged by the successful results obtained from the aldehydes **1** and acetophenone **2a**, we further tested the scope of the reaction with a series of acetophenones **2b**–**e**. The reactions were well tolerated with both electron-withdrawing and electron-releasing groups

on acetophenone. In the case of 4-chloroacetephenone (**2b)** the reaction was successful with the *in situ* generated hydrazones to afford the corresponding pyrazole derivatives **18**–**22** in 12 h in good to high yields 49–72% (Scheme 3).

The products were characterized on the basis of detailed spectral analysis of the data obtained from IR, ^{1}H and ^{13}C NMR, DEPT, and HRMS experiments of pure and isolated products and the structure of the pyrazole **18** was further confirmed from its single crystal X-ray analysis **(**Figure 3, Table 2).

To explore this DAN cyclization protocol further, we investigated the reaction of acetophenone **2c** having electron-withdrawing floro substitution at the 4-position and it reacted successfully with *in situ* generated benzaldehyde hydrazones **1b**–**f**,**h** to furnish **23**–**28** in 12 h in good yields of 55–72% (Scheme 4).



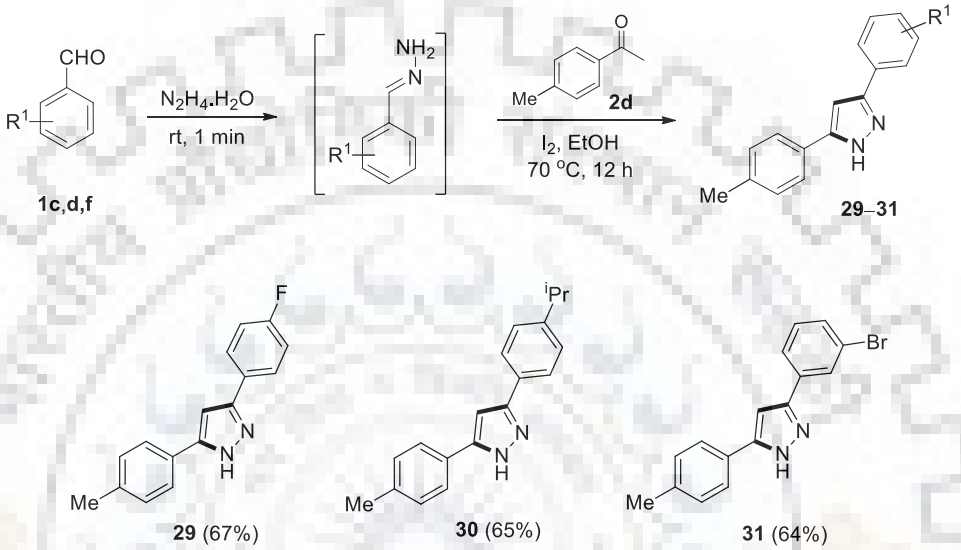
Scheme 4: DAN reactions of 4-floroacetophenone with aldehydes **1b**–**f**,**h**.

Figure 3: ORTEP Representation of crystal structure of **18**.

Table 2: Crystallographic data for **18**.

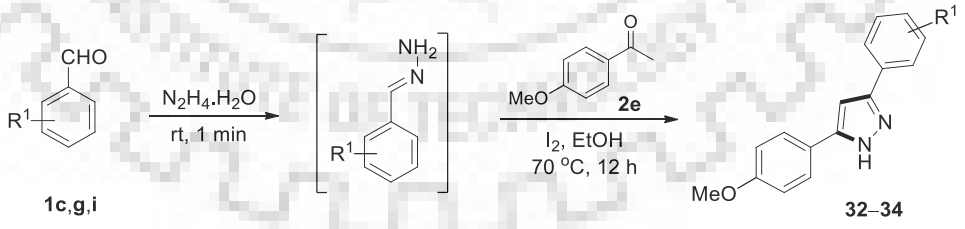
Formula	$C_{15}H_{10}Cl_2N_2$
Formula Wt.	289.15
Crystal habit	Blocks
Crystal color	White
Crystal system	Triclinic
Space group	P 21/n
a (Å)	15.2929(5)
b (Å)	4.8030(1)
c (Å)	17.5928(6)
α (deg)	90
β (deg)	92.928(2)
γ (deg)	90
V (Å^3)	1290.54(7)
Z	4
D_{calc} (g cm^{-3})	1.488
T (K)	293 K
λ (Mo-Kα)	0.71073
μ (mm^{-1})	0.488
Limiting indices	$-17 \leq h \geq 17$
	$-5 \leq k \geq 5$
	$-19 \leq l \geq 19$
F(000)	572.0
No. of Reflns. Measured	5536
No. of Parameters	228
GOF on F^2	2.680
R1 [I>2σ(I)]	0.0282(1519)
wR2	0.0884(1945)

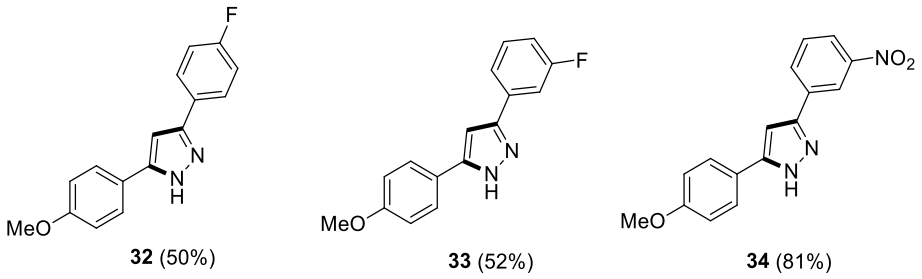
Inspired by the applicability of the present DAN approach, we further examined the scope of the reaction of acetophenones **2d** and **2e** bearing electron-releasing groups. Thus, first we carried out the reaction of *in situ* generated benzaldehyde hydrazones **1c**,**d**,**f** with 4-methyl acetophenone **2d**. The reaction was approachable under standard reaction conditions and progressed efficiently to provide the cyclized products **29**–**31** in 10 h in 64–67% yields (Scheme 5).



Scheme 5: DAN reactions of 4-methylacetophenone with aldehydes **1c**,**d**,**f**.

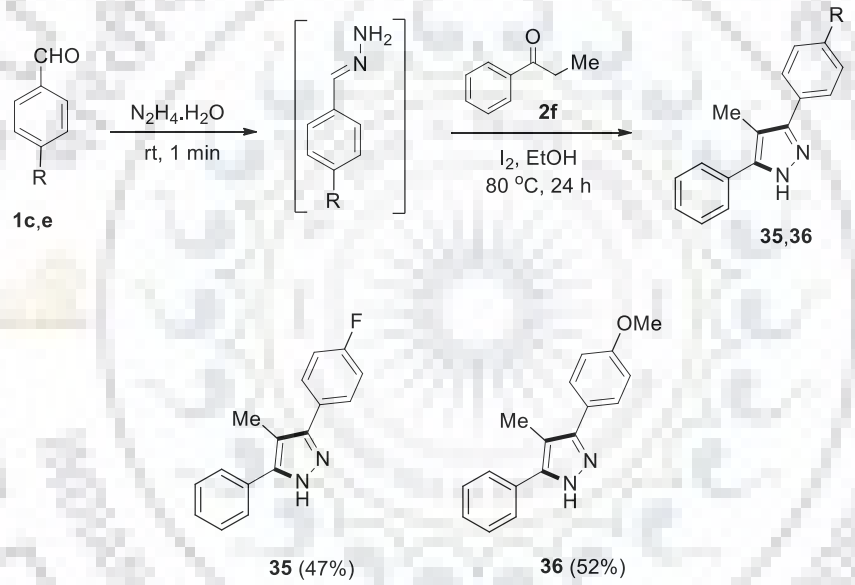
Then we have tested the possibility of the DAN cyclization with 4-methoxyacetophenone (**2e)** under established conditions. In all the cases, the reaction worked well to furnish the corresponding pyrazoles **32**–**34** in good yields (Scheme 6).





Scheme 6:. DAN reactions of 4-methoxyacetophenone with aldehydes **1c**,**g**,**i**.

We further extended the scope of the reaction by using α-substituted acetophenone **2f** with aldehydes **1b**,**c** at 80 °C. To our delight, the cyclized products **35** and **36** were obtained in 24 h with 47 and 52% yields, respectively (Scheme 7).

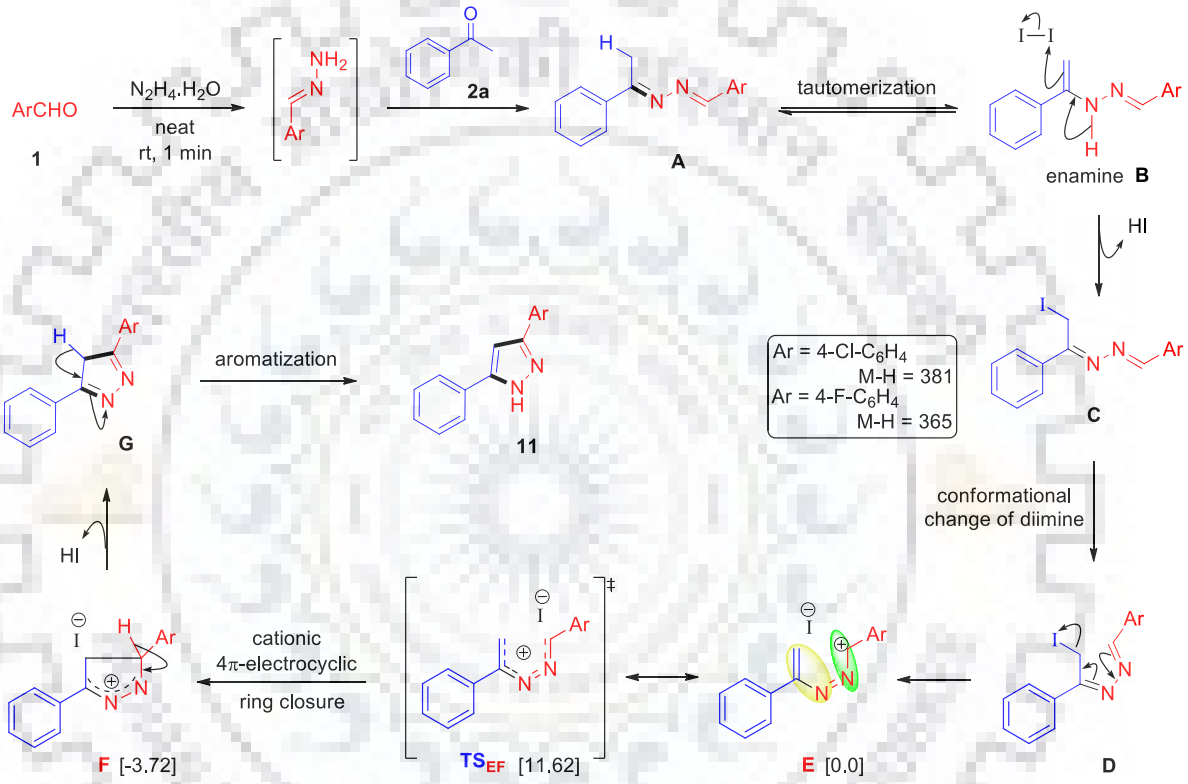


Scheme 7: DAN approach with propiophenone (**2f**).

It is noteworthy to mention here that about 10–15% of aryl aldehydes **1a**–**k** were recovered from these reactions. Aldehydes were formed from the decomposition of the corresponding hydrazones presumably due to the presence of by-product HI (Schemes 3–7).

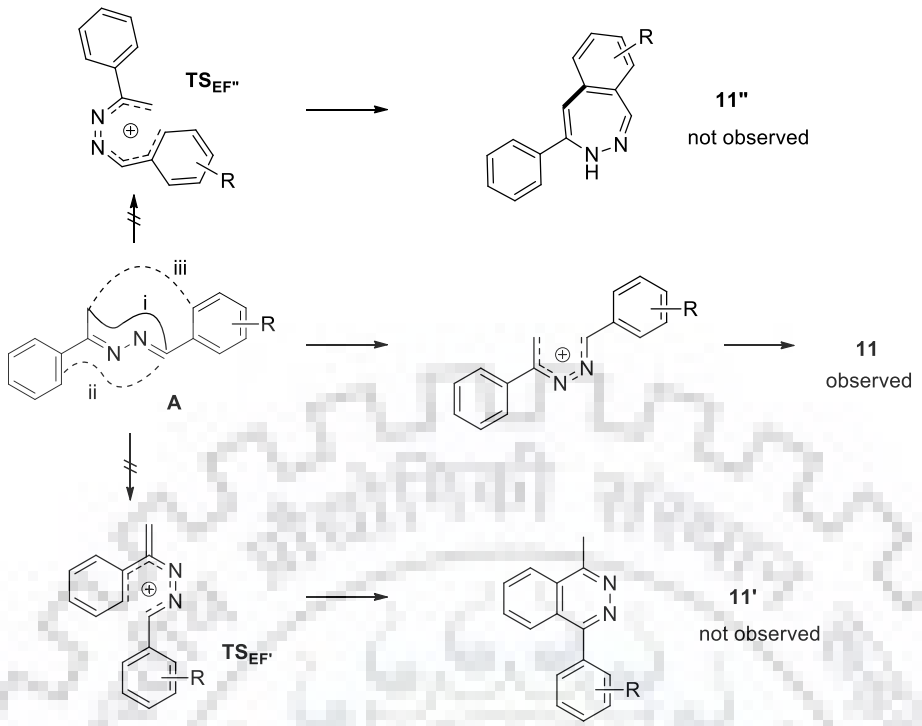
To verify the radical pathway of the reaction, radical trapping agent TEMPO was used in varied amounts. However, the reaction was not inhibited, albeit the product **11** was obtained in relatively lower yield. Based on the above results and the previous reports [19–26,149,150], a plausible mechanism for the formation of **11** is depicted in Scheme 8. The hydrazone,

generated from aldehyde **1a** and hydrazine hydrate, undergoes condensation with acetophenone **2a** to generate intermediate **A**. α-Iodination of tautomer **B** with molecular iodine provides alkyl iodide **C** with concomitant removal of HI. Conformational change of s-*trans* diimine **C** to s-*cis* diimine **D** followed by deiodination leads to 2,3-diaza-pentadienyl cation **E**, which is stabilized by the delocalization of positive charge. This enamine-iminium ion undergoes 4π-electrocyclization ring closure to generate diaza-allyl cation **F**, which upon dehydrohalogenation and aromatization furnished exclusively five-membered heterocycle **11**.



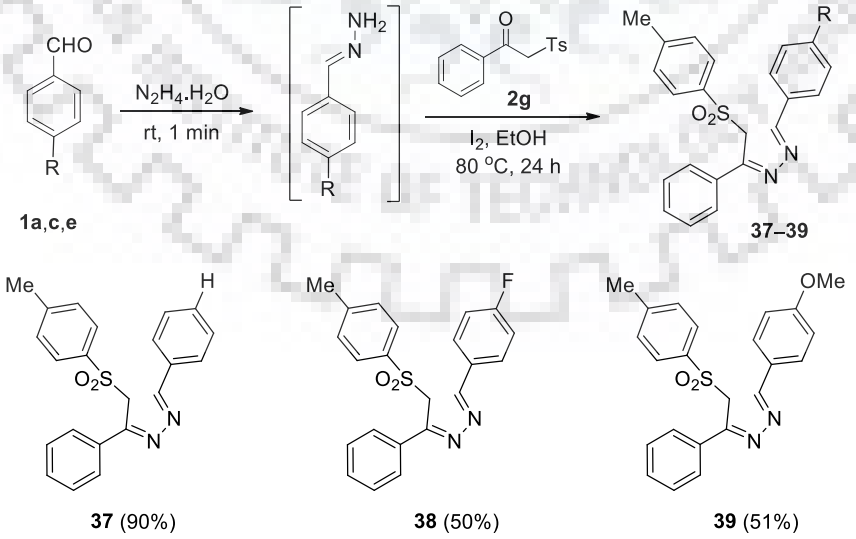
Scheme 8: Plausible reaction mechanism.

The other possible nirogenembedded regioisomers from 6π-electron-6-atom and 6π-electron-7-atom oxidative electrocyclizations [150] were not formed in this reaction (Scheme 9).



Scheme 9: Possible regioisomers during cyclization.

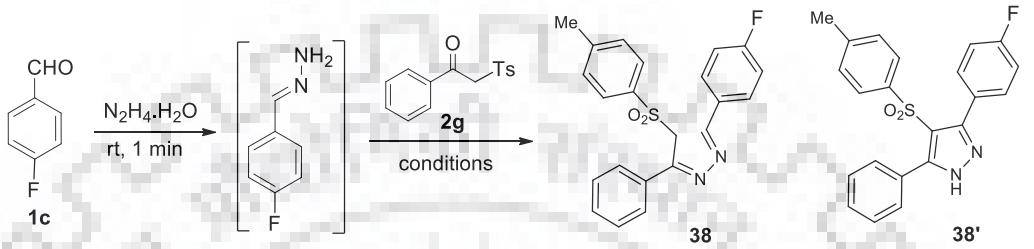
For more insights into the mechanism, we performed the reaction of tosyl substituted acetophenone **2g** with **1a**,**c**,**e** under optimized conditions. In all the cases, noncyclized 2,3-diaza-1,3-dienes **37**–**39** were isolated in 24 h in 50–90% yields. This clearly indicates that the formation of 2,3-diaza-pentadienyl cation does not occur and hence no diaza-Nazarov cyclized product (Scheme 10).



Scheme 10: Reaction of α-tosyl acetophenone (**2g**)

Our efforts to cyclise **38** in the presence of reagents such as I_2/TFA, $SnCl_4$ and $FeCl_3$ were not successful (Table 3). Since the α-position of aza-diene was blocked with tosyl group, α-iodination did not take place. Thus it was proved indirectly that α-iodination (as in intermediates **C** and **D**) is essential for the success of the DAN cyclization (Scheme 8).

Table 3: Attempted cyclization of heterodienes.[a]

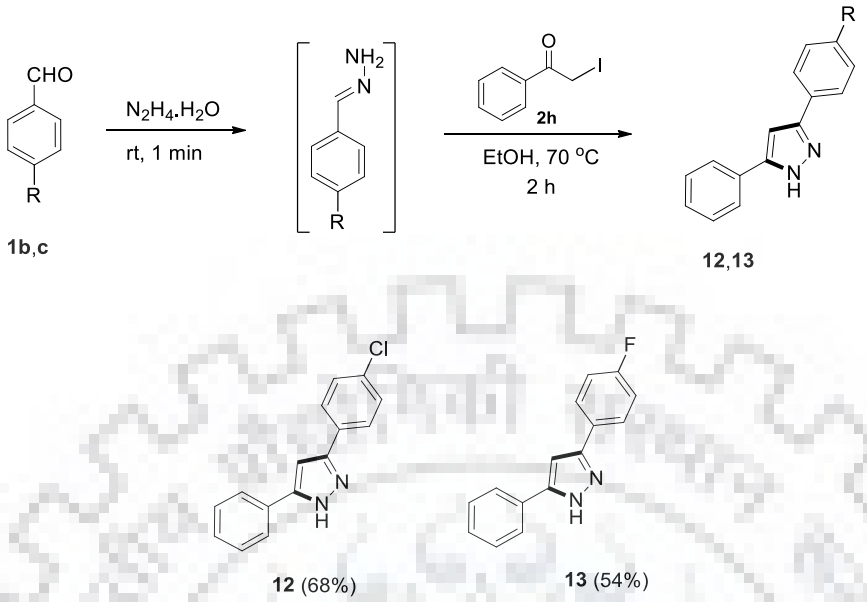


Entry	Conditions	Product **38** Yield[b] (%)	Product **38′** Yield (%)
1	I_2/TFA, EtOH, 80 °C, 12 h	52	Not observed
2	I_2/TFA, EtOH, 120 °C, 12 h	54	Not observed
3	$SnCl_4$, EtOH, 80 °C, 12 h	46	Not observed
4	$SnCl_4$, EtOH, 120 °C, 12 h	45	Not observed
5[c]	$FeCl_3$, EtOH, 80 °C, 12 h	0	Not observed
6[c]	$FeCl_3$, EtOH, 120 °C, 12 h	0	Not observed

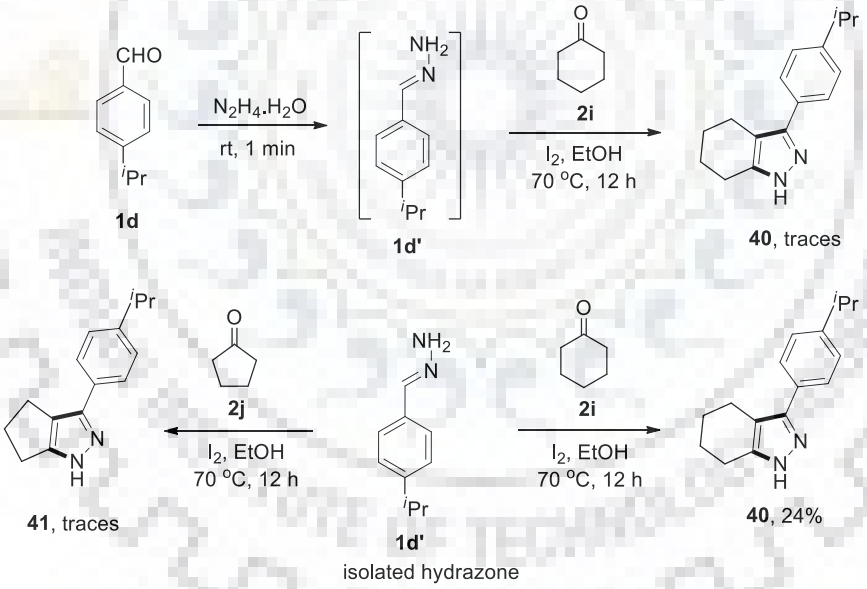
[a] Conditions: **1c** (0.5 mmol), hydrazine hydrate (1 mmol), **2g** (0.6 mmol).
[b] Yield of pure and isolated product.
[c] Starting materials **1c** and **2g** were recovered as such.

The obtained mass spectral evidence for the intermediate **C** (Ar = Ph, 4-Cl-C_6H_4) also supported the proposed mechanism (Tables 4 and 5). The reaction of α-iodoacetophenone (**2h**) with aldehydes **1b** and **1c** provided pyrazoles **12** and **13**, which also confirms the generation of intermediate **C** (Ar = Ph, 4-Cl-C_6H_4) (Scheme 11 and Table 5).

The reaction between 4-*i*propylbenzaldehyde (**1d**) and ketones such as cyclohexanone and cyclopentanone did not proceed under standard conditions. However, the isolated hydrazone derived from **1d** reacted with cyclohexanone to furnish the corresponding DAN product **40** in 24% yield. Cyclopentanone and valeraldehyde failed to produce the products with **2i** under the optimized conditions (Scheme 12).

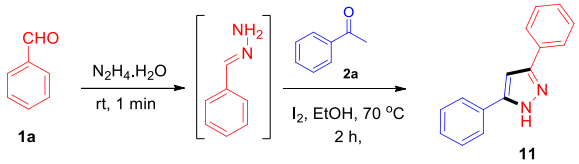


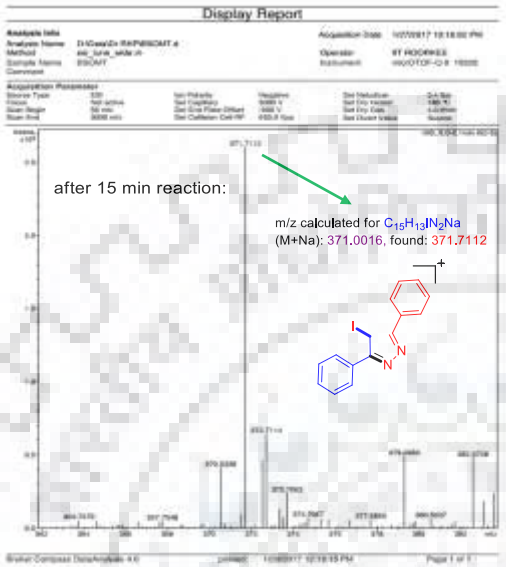
Scheme 11: DAN approach with α-iodoacetophenone (**10**)



Scheme 12: Substrate scope of DAN reaction.

Table 4: Monitoring reactions with mass spectral analysis.





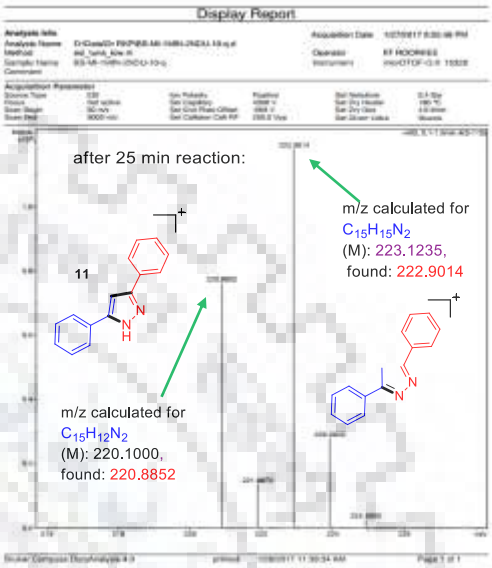
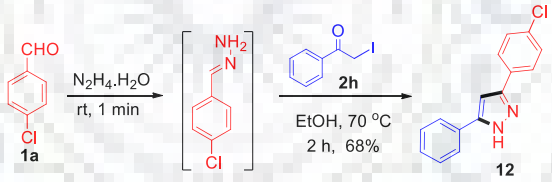
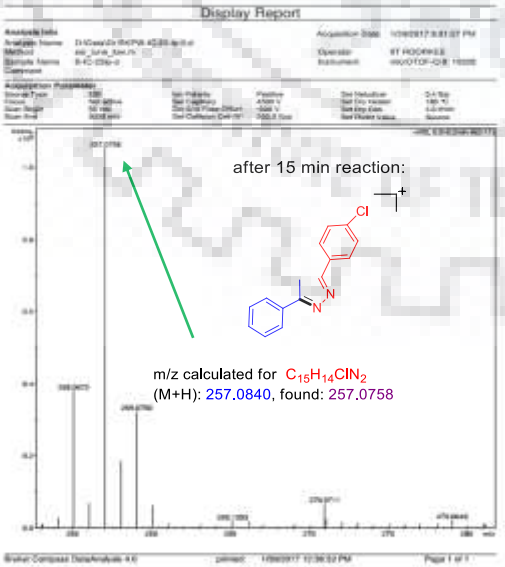
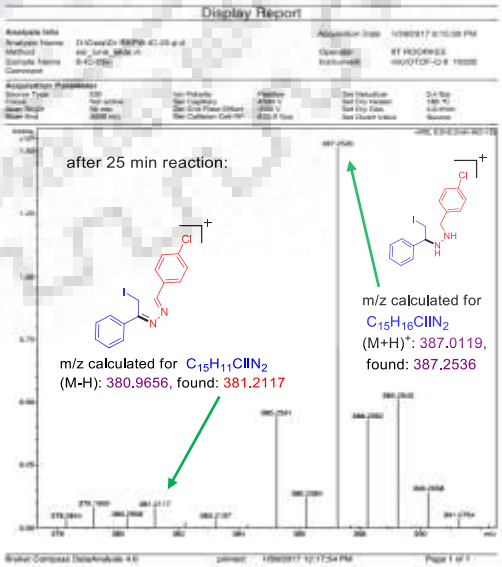


Table 5: Monitoring reactions with mass spectral analysis.





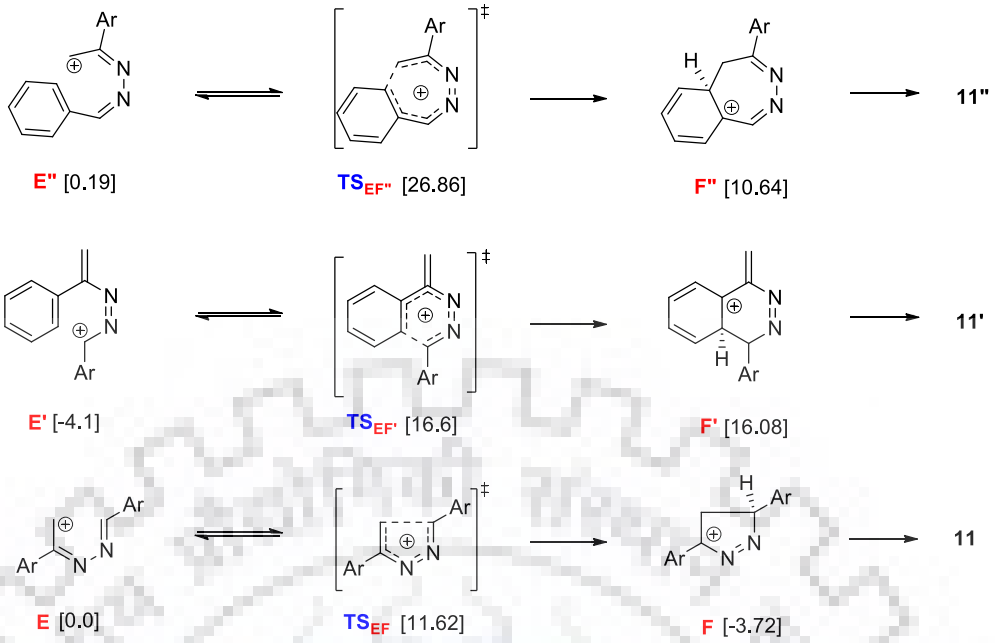


Theoretical investigations for DAN cyclization:

Theoretical studies based on density functional theory (DFT) calculations provided a useful data about the structure of the molecules, *viz* intermediates, transition state structures, *etc*., which was valuable in investigating the reaction pathway and such information was infrequently achieved from experimental results. The outcome of the reaction can be anticipated approximately around by these strategies with no plan of action to experiment.

In order to pay attention to a better understanding of the plausible mechanism of electrocyclization step **E** to **F** of diaza-Nazarov reaction and to validate the results found experimentally, we performed quantum chemical calculations using hybrid B3LYP functional [152, 153] with 6-311G** basis set [154] in gas phase. All DFT calculations were performed using G09, revision A.02, programme package [155]. All structures of 1,5- 1,6- and 1,7-electrocyclization pathways were optimized. Frequency calculations were also performed to confirm that the structures are minima with all positive frequencies and transition states (TSs) with one imaginary frequency. Intrinsic reaction coordinate (IRC) calculations were also run to confirm the nature of transition states (TSs).

The electrocyclic step begins with three different conformations of diaza-pentadienyl (DAP) cation for DFT calculations of 1,5-, 1,6- and 1,7-electrocyclization pathways. The conformations were obtained from IRC calculations starting from the transition state structures and lowest energy conformer (1,5-) differ in energy by about –4.10 (1,6-) and 0.19 (1,7-) kcal/mol (Scheme 13). From our results, two important things were observed for DAN cyclization reaction using DFT calculations (i) A comparative DFT study of 1,5-, 1,6- and 1,7- electrocyclization pathways, and (ii) DFT calculations preferred 4π-1,5-electrocyclization pathway with lowest activation energy barrier (11.62 kcal/mol) supporting our experimentally observed 1,5-DAP. As shown in Figure 3, the 1,6- (20.70 kcal/mol) and 1,7- (26.67 kcal/mol) electocyclization pathways lead to higher activation energy barriers by 9.08 and 15.05 kcal/mol, respectively, than that of 4π-1,5-electrocyclization pathway. DFT calculations showed that the cyclization of 1,5-DAP cation can be considered as a process with a low activation barrier and exothermicity (ΔH, –3.11 kcal/mol), while the unfavorable



Scheme 13: Calculated electronic energies (E_{rel}) in kcal mol^{-1} relative to 2,3-diaza-pentadienyl cation (**E**) for the 1,5-, 1,6- and 1,7-cyclization pathways of electrocyclization step of the diaza-Nazarov reaction at the B3LYP/6-311G** level of theory in the gas phase.

1,6- and 1,7-cyclization products formed *via* a higher activation barriers and predicted to be highly endothermic with 19.89 and 11.05 kcal/mol, respectively. Negative Gibbs free energy (ΔG) results show that 1,5-cyclization pathway (–1.49 kcal/mol) was most favorable than six- (22.15 kcal/mol) and seven- (14.36 kcal/mol) cyclization pathways (Tables 6–11). To evaluate the effect of solvent on activation barriers of electronic energy, we performed B3LYP/6-311G** calculations using CPCM model with ethanol solvent. The activation energy barriers in gas phase and solution phase are very close (less than 1 kcal/mol) and there is no significant change (Figure 4).

Table 6. Calculated electronic energies (in Hartree) for the B3LYP/6-311G** optimized structures of 1,5-, 1,6- and 1,7-cyclization pathways for electrocyclization step of diaza-Nazarov reaction in gas phase.

Pathway	Energy	**R**	**TS**	**P**
1,5-	E	–688.76357468	–688.7450556	–688.7694985
	H	–688.508430	–688.491138	–688.513388
	G	–688.567734	–688.546576	–688.570101
1,6-	E	–688.7701048	–688.7371205	–688.737944
	H	–688.514615	–688.483234	–688.482915
	G	–688.573574	–688.537699	–688.538274
1,7-	E	–688.7632717	–688.7207741	–688.7466207
	H	–688.508123	–688.466286	–688.490507
	G	–688.567709	–688.520559	–688.544822

Table 7. Calculated relative electronic energies (in kcal/mol) for the B3LYP/6-311G** optimized structures of 1,5-, 1,6- and 1,7-cyclization pathways for electrocyclization step of diaza-Nazarov reaction in gas phase.

Pathway	**Energy**	**R**	**TS**	**P**
1,5-	ΔE	0	11.62	–3.72
	ΔH	0	10.85	–3.11
	ΔG	0	13.28	–1.49
1,6-	ΔE	0	20.70	20.18
	ΔH	0	19.69	19.89
	ΔG	0	22.51	22.15
1,7-	ΔE	0	26.67	10.45
	ΔH	0	26.25	11.05
	ΔG	0	29.59	14.36

Table 8. Calculated electronic energies (in Hartree) for the structures of 1,5-, 1,6- and 1,7-cyclization pathways for electrocyclization step of diaza-Nazarov reaction optimized at B3LYP/6-311G** level of theory using CPCM solvation model, with ethanol solvent.

Pathway	Energy	**R**	**TS**	**P**
1,5-	E	–688.7635747	–688.7450556	–688.7694985
	H	–688.508430	–688.491138	–688.513388
	G	–688.567734	–688.546576	–688.570101
1,6-	E	–688.7701048	–688.7371204	–688.737944
	H	–688.514615	–688.483234	–688.482915
	G	–688.573574	–688.537700	–688.538274
1,7-	E	–688.7632717	–688.7207743	–688.7466207
	H	–688.508123	–688.466288	–688.490507
	G	–688.567709	–688.520560	–688.544822

Table 9. Calculated electronic energies (in kcal/mol) for the structures of 1,5-, 1,6- and 1,7-cyclization pathways for electrocyclization step of diaza-Nazarov reaction optimized at B3LYP/6-311G** level of theory using CPCM solvation model, with ethanol solvent.

Pathway	Energy	R	TS	P
1,5-	ΔE	0	11.62	–3.72
	ΔH	0	10.85	–3.11
	ΔG	0	13.28	–1.49
1,6-	ΔE	0	20.69	20.18
	ΔH	0	19.69	19.89
	ΔG	0	22.51	22.15
1,7-	ΔE	0	26.67	10.45
	ΔH	0	26.44	11.25
	ΔG	0	29.60	14.37

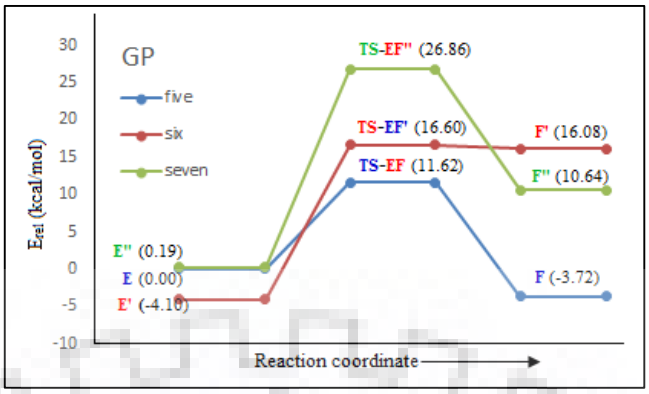
Table 10. Single point electronic energy, E (in Hartree) for the structures of 1,5-, 1,6- and 1,7-cyclization pathways for electrocyclization step of diaza-Nazarov reaction calculated at M06/6-311+G(d,p)//B3LYP/6-311G** level of theory using CPCM solvation model, with ethanol solvent

Pathway	Energy	R	TS	P
1,5-	E	–688.2902521	–688.2709314	–688.3065877
1,6-	E	–688.2960064	–688.2722362	–688.2768907
1,7-	E	–688.290431	–688.2525481	–688.2866835

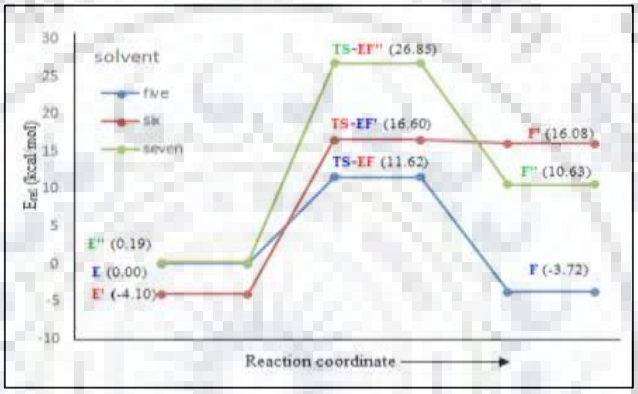
Table 11. Single point electronic energy, E (in kcal/mol) for the structures of 1,5-, 1,6- and 1,7-cyclization pathways for electrocyclization step of diaza-Nazarov reaction calculated at M06/6-311+G(d,p)//B3LYP/6-311G** level of theory using CPCM solvation model, with ethanol solvent.

Pathway	Energy	R	TS	P
1,5-	ΔE	0	12.12	–10.25
1,6-	ΔE	0	14.91	11.99
1,7-	ΔE	0	23.77	2.35

(a) Gas phase energies:



(b) Solvent phase energies:



(c) Single point energies:

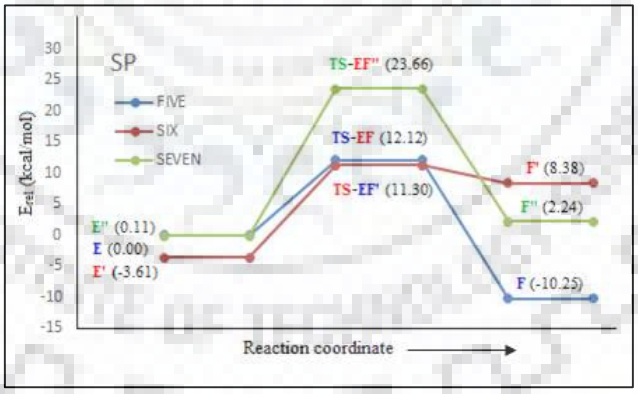


Figure 4. Comparative energy profile diagrams for the 1,5-, 1,6- and 1,7-cyclization pathways of electrocyclization step of diaza-Nazarov reaction for (a) gas phase (optimized at B3LYP/6-311G** level), (b) Solution phase (optimized at B3LYP/6-311G** level using Ethanol solvent with CPCM model) and (c) Single point energies (at M06/6-311+G(d,p)//B3LYP/6-311G** level using Ethanol solvent with CPCM model).

We generated HOMO and LUMO plots using B3LYP/6-311G** optimized geometries of TSs by using Gauss view visualization software [156]. The binding interaction in TSEF is dominated by HOMO−1 as shown in Figure. 4, while HOMO is localized at the heterocyclic part (Figure 5).

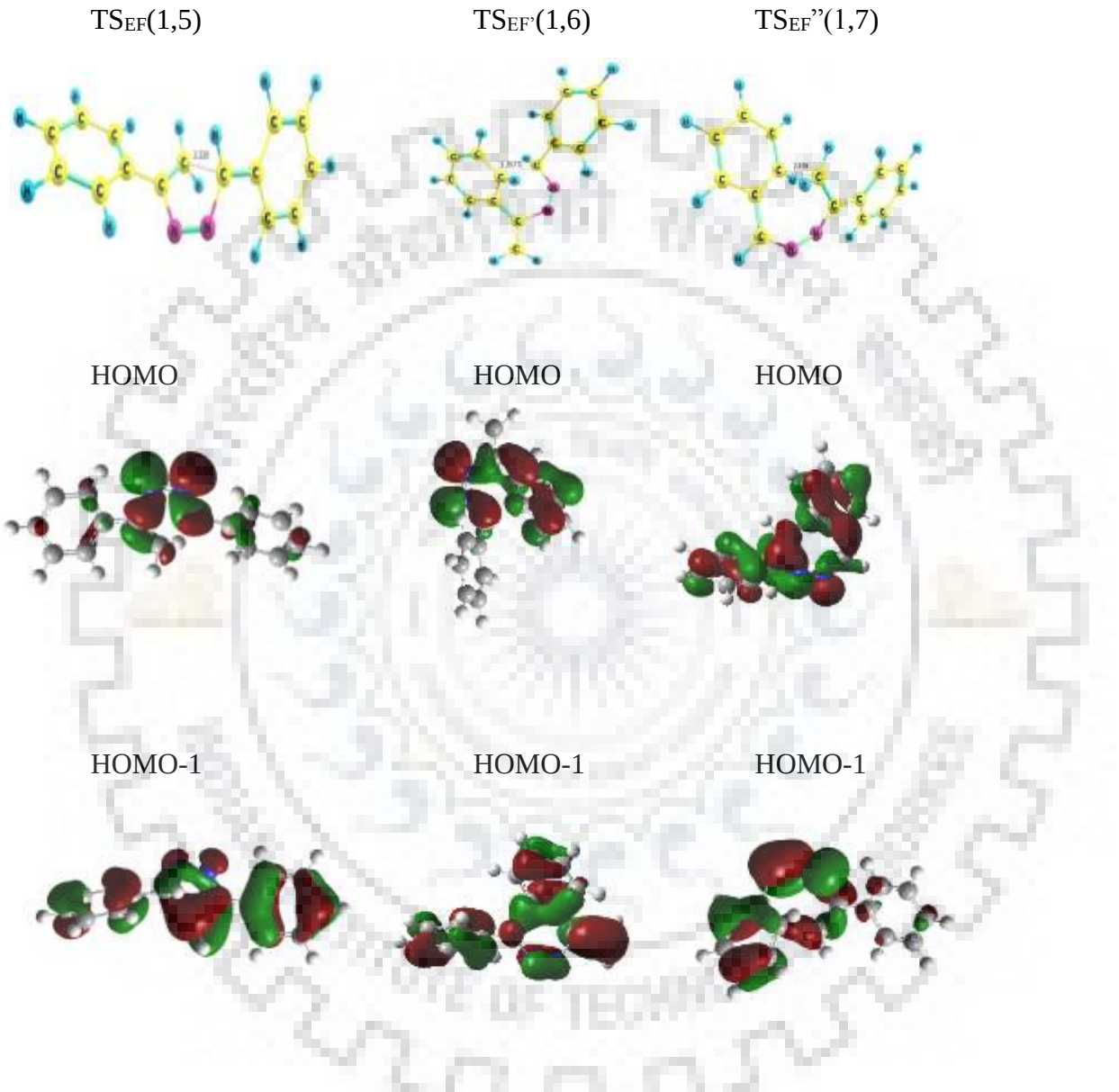


Figure 5: Optimized structures of TSs with HOMO and HOMO-1 molecular diagrams of each TS of the 1,5-, 1,6- and 1,7-cyclization pathways of electrocyclization step of diaza-Nazarov reaction at B3LYP/6-311G** level of theory in gas phase (the bond forming distances between terminal atoms of TS are in Å).

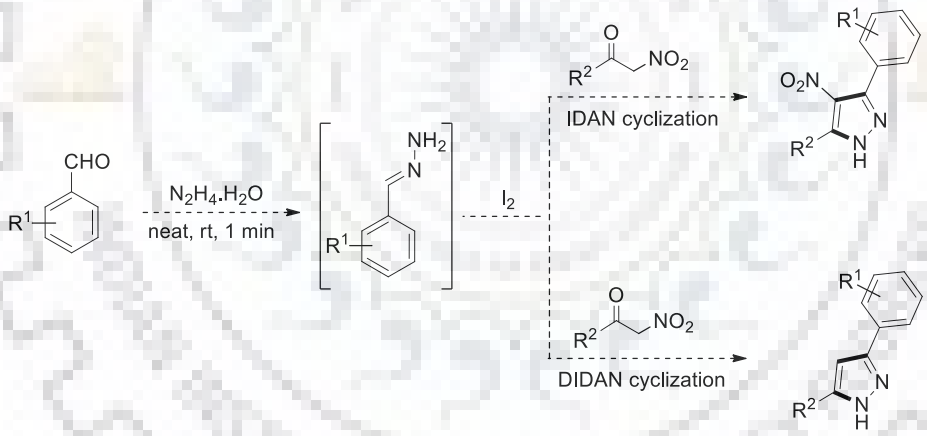
2.2.2. Synthesis of pyrazoles *via* denitrative-imino-diaza-Nazarov (DIDAN) cyclization

Five-membered nitrogen containing heterocyclic rings are excellent auxiliary structures that broadly exist in natural products, biologically active compounds, and functional materials [43,131,132,157]. Of particular note is the pyrazole that form the core scaffold of bioactive molecules that display antibacterial [133], anti-inflammatory [158], antimicrobial [159] and analgesic [34] actions. They also form core valuable structural architecture of therapeutic agents [4,160] that have been successfully commercialized, such as the bestseller drugs viagra, celebrex, and acomplia [33, 161, and 162]. Apart from these applications, pyrazoles can also be used as ligands in various transition metal-catalyzed cross-coupling reactions [163–166]. As a result, numerous synthetic routes have been investigated for the preparation of pyrazoles *via* cyclization process [167–175]. Routinely, these pyrazoles can be synthesized by the reaction of 1,3-dipolar cycloaddition of hydrazines with alkenes/alkynes [46,136], the 1,3-diketones/α,β-unsaturated carbonyls [49,51,137–139] and β-nitrostyrenes [176–179] with hydrazine derivatives. With the developing enthusiasm for the construction of pyrazoles, several transition metal [48,52,140,142] and metal-free [56,144,145] approaches have been explored in the past few decades.

As a result, new and sustainable synthetic techniques for the synthesis of pyrazoles with high selectivity utilizing mild and economy conditions are still of high demand in the synthetic field. Among them Nazarov-type cyclization reaction is one of the most versatile and efficient methods for C–C and C–N bond formation for the construction of 5-memberd heterocyclic compounds [5–7,12]. On the basis of Woodward and Hoffman electrocyclization rules and by elucidation of mechanism, it was confirmed that Nazarov reaction follows pericyclic ring closure reaction pathway. After Woodward's revelation, there was a significant progress in the Nazarov cyclization reaction for the development of different 5-membered heterocycles [13–17]. In the begning of 20^{th} century the concept of imino/aza-Nazarov cyclization has been introduced which involves an imino/enamine-imino intermediate generation during the course of Nazarov reaction instead of the classical ketone functionality called the imino-Nazarov reaction. Frontier [13], Tius [18,26], Klummp [25], Husung [18] and west [6,20] research groups well explored the advancement of Nazrov cyclization reactions.

We successfully established a new approach for the synthesis of polysubstituted pyrazoles *via* diaza-Nazarov (DAN) cyclization involving a 2,3-diaza-pentadienyl cation using iodine as reagent (Section 2.2.1) [181]. Thus, in continuation of our work and endeavours on the development of green conventions [182,183], we carried out the reaction of aldehydes with α-nitro acetophenones in the presence of iodine under the DAN cyclization conditions. The reaction proceeded through regioselective denitrative imino-diaza-Nazarov (DIDAN) cyclization and gave pyrazoles. The reaction occurs between easily accessible *in situ* generated aldehyde hydrazones and α-nitro acetophenone derivatives through the enamine–iminium ion intermediate to furnish various substituted pyrazoles in excellent yields (v*ide infra*). To the best of our knowledge, α-nitro acetophenone is not accounted for the construction of pyrazoles.

It occurred to us that the *in situ* generated aldehydes hydrazones would undergo molecular iodine promoted IDAN cyclization and/or DIDAN cyclization to provide the corresponding pyrazoles (Scheme 14).

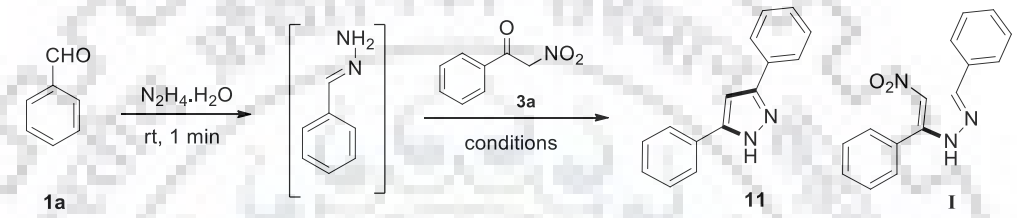


Scheme 14: Working hypothesis for the synthesis of substituted pyrazoles from α-nitro acetophenones.

To probe the conceived objective, in a pilot experiment we inspected the reaction between benzaldehyde (**1a**), α-nitroacetophenone (**3a**) and hydrazine hydrate, under the solvent-free conditions. The *in situ* generated hydrazone underwent reaction with α-nitroacetophenone (**3a**) in the presence of equimolar molecular iodine in EtOH at 80 ^{o}C. The reaction was accomplished in 6 h to offer a complex mixture of product from which the major denitrative pyrazole derivative **11** isolated in 66% yield along with uncyclized compound **I** in 20% yield

(Table 12, entry 1). When 50 mol% I_2 was used in the reaction, the product **11** was obtained in an improved yield of 78% (entry 2). A perfect isolation of **11** in 94% yield was found when the reaction was carried out in the presence of 20 mol% iodine in 2 h (entry 3). No improvement in the yield of **11** was observed on further decrease of iodine (entry 4). Screening of the reaction temperature revealed that 80 ^oC was optimal to obtain the maximum yield of the product (entries 5 and 6). To check the effect of the solvent in the reaction, we performed the reaction in solvents such as MeOH, CH_3CN, THF, and DCE. These reactions afforded

Table 12: Optimization of reaction conditions.[a]

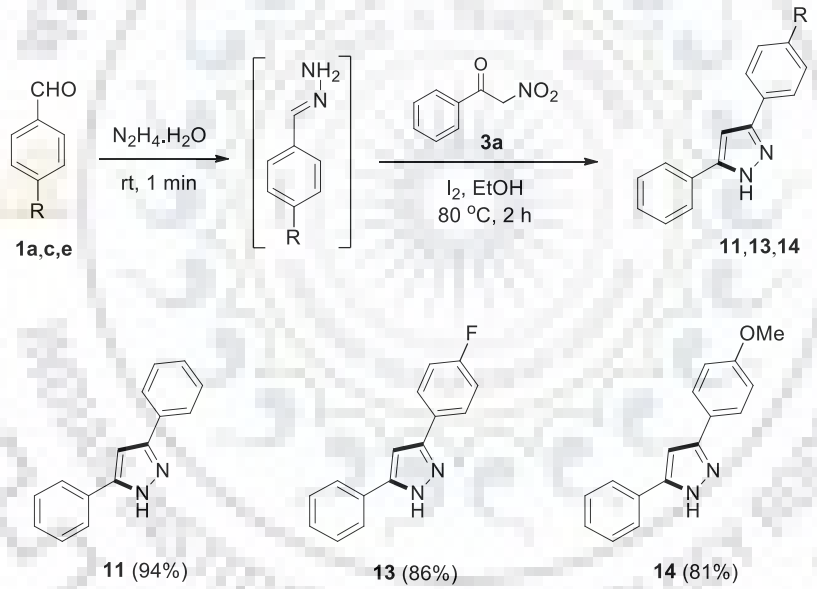


Entry	Reagent (mol%)	Solvent	Temp (^oC)	Time (h)	Yield[b] (%) **11**/**I**
1	I_2 (100)	EtOH	80	6	67/20
2	I_2 (50)	EtOH	80	6	78/12
3	I_2 (20)	EtOH	80	2	94/traces
4	I_2 (10)	EtOH	80	4	91/traces
5	I_2 (20)	EtOH	90	2	90/taces
6	I_2 (20)	EtOH	70	2	86/traces
7	I_2 (20)	MeOH	80	24	76/19
8	I_2 (20)	ACN	80	24	77/20
9	I_2 (20)	THF	80	24	57/16
10	I_2 (20)	DCE	80	24	64/23
11	PTSA (20)	EtOH	80	24	86/traces
12	$BF_3.OEt_2$ (20)	EtOH	80	24	71/15
13	TFA (20)	EtOH	80	24	78/traces

[a] Reaction conditions: **1a** (0.6 mmol), hydrazine hydrate 80% (1 mmol), **3a** (0.4 mmol), reagent (0.08 mmol).
[b] Isolated yield.

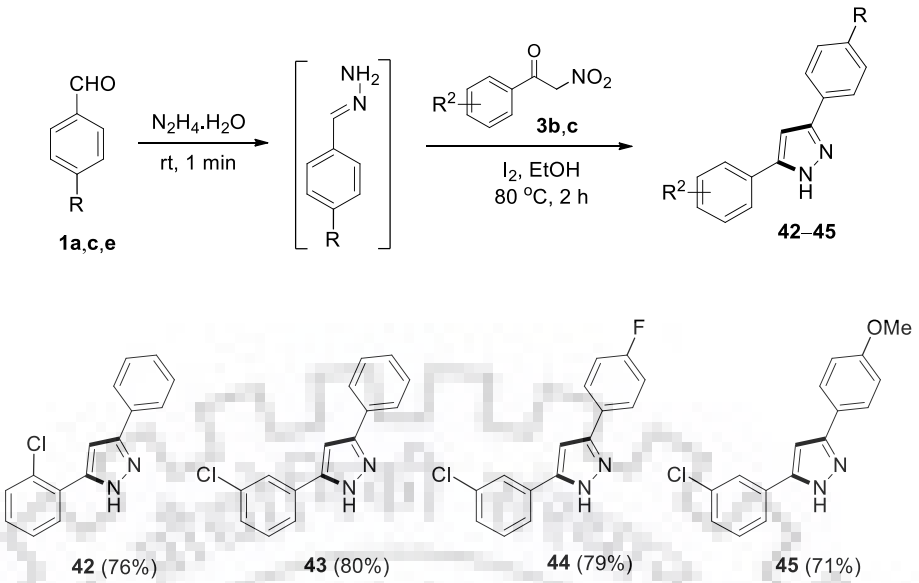
pyrazole **11** in 76, 77, 57, and 64% yield, respectively, and along with uncyclized product **I** (entries 7–10). EtOH was considered best solvent for this transformation (entry 3). Further catalysts such as PTSA, $BF_3.OEt_2$ and TFA were screened. No progress was perceived in the yield of the product **11** with these promoters (entries 11–13). On the basis of above verdicts, we recognised that iodine as the catalyst and EtOH as the optimum solvent at 80 °C for the most affirmative reaction condition (entry 3).

With the optimized reaction conditions in hand, we scrutinized the generality of this one-pot, iodine catalyzed denitrative-imino-diaza-Nazarov-type (DIDAN) cyclization. In this direction, we have chosen different benzaldehydes **1a**,**c**,**e** and performed the reaction with α-nitroacetophenone **3a**, under the optimized conditions. In these cases, benzaldehyde bearing electron-withdrawing **1c** as well as electron-releasing substituent **1e** provided the corresponding pyrazole derivatives **11**,**13** and **14** in high to excellent yield (Scheme 15).



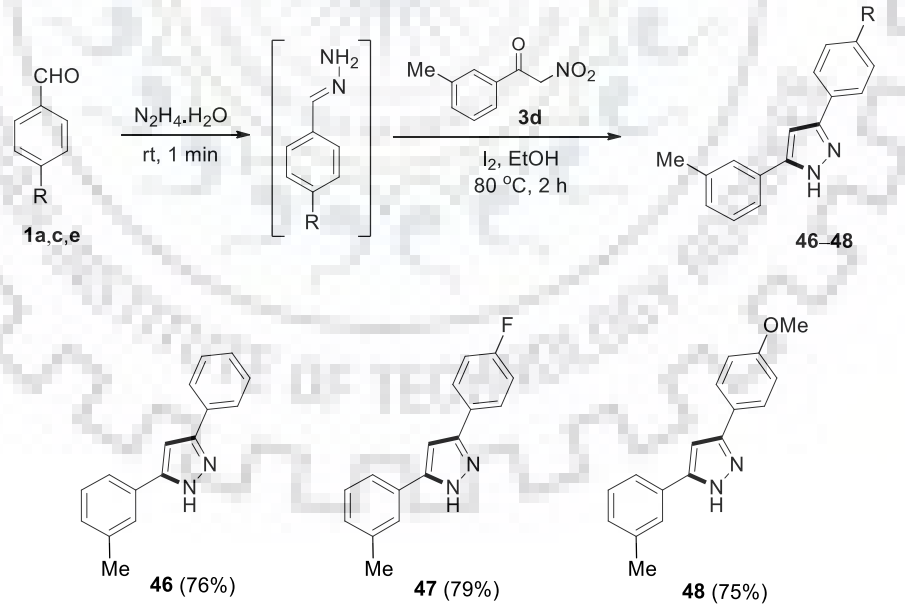
Scheme 15: Reaction of benzaldehydes **1a**,**c**,**e** with α-nitroacetophenone (**3a**).

After effectively completing the reactions of benzaldehydes **1a**,**c**,**e** with α-nitroacetophenones (**3a**), we further showed the viability of the present transformation by carrying out the reactions of several benzaldehydes **1a**,**c**,**e** with chloro substituted α-nitro acetophenones **3b** and **3c** under standard conditions to deliver the relating pyrazoles **42**–**45** in very good yields (Scheme 16).



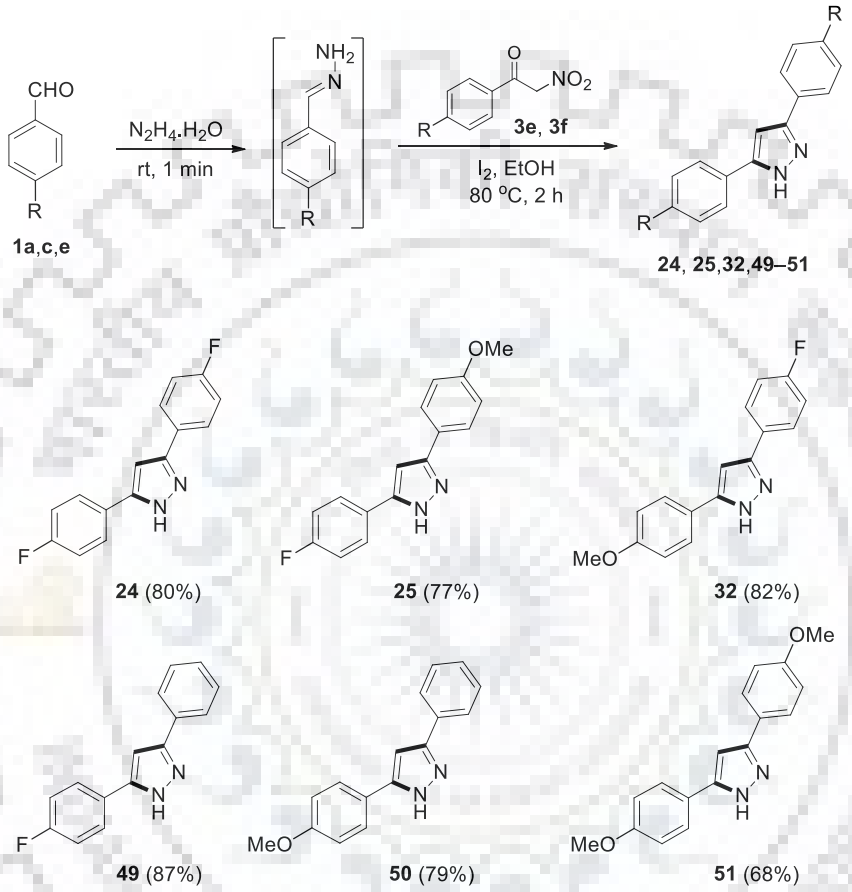
Scheme 16: Reaction of aldehydes **1a**,**c**,**e** with α-nitro-acetophenones **3b** and **3c**.

We further successfully expanded this system for the reaction of α-nitroacetophenone **3d** bearing *m*-methyl group with the same set of benzaldehyde derivatives **1a**,**c**,**e** under the iodine catalyzed conditions that produced the corresponding pyrazoles **46**–**48** in 75–79% yields (Scheme 17).



Scheme 17: Reactions of aldehydes **1a**,**c**,**e** with α-nitro-3-methyl acetophenone (**3d)**.

At this juncture, we scrutinized the reactivity of *para*-substituted α-nitroacetophenones **3e** and **3f** with benzaldehydes **1a**, **1c** and **1e** by subjecting to the optimized conditions. In all the cases, benzaldehydes bearing electron-withdrawing (**1c**) as well as electron-donating (**1e**) substituent provided the resultant pyrazole derivatives **24**,**25**,**32**,**49**–**51** in high yields of 77–87% (Scheme 18).



Scheme 18: Reaction of 4-substituted α-nitroacetophenones **3e**,**f** with aldehydes **1a**,**c**,**e**.

The structures of the DIDAN cyclized products were assigned on the basis of their ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR, DEPT spectroscopic, and ESI-MS spectrometric analysis. The structure of the pyrazole **48** was further confirme by single-crystal X-ray diffraction analysis (Figure 6).

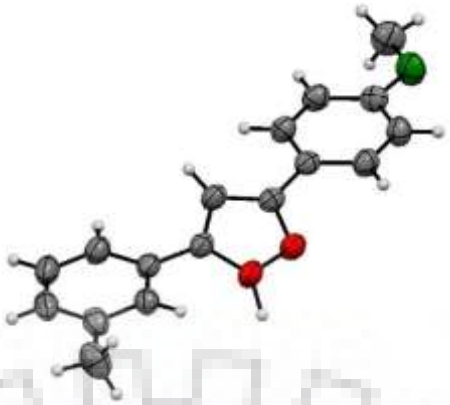
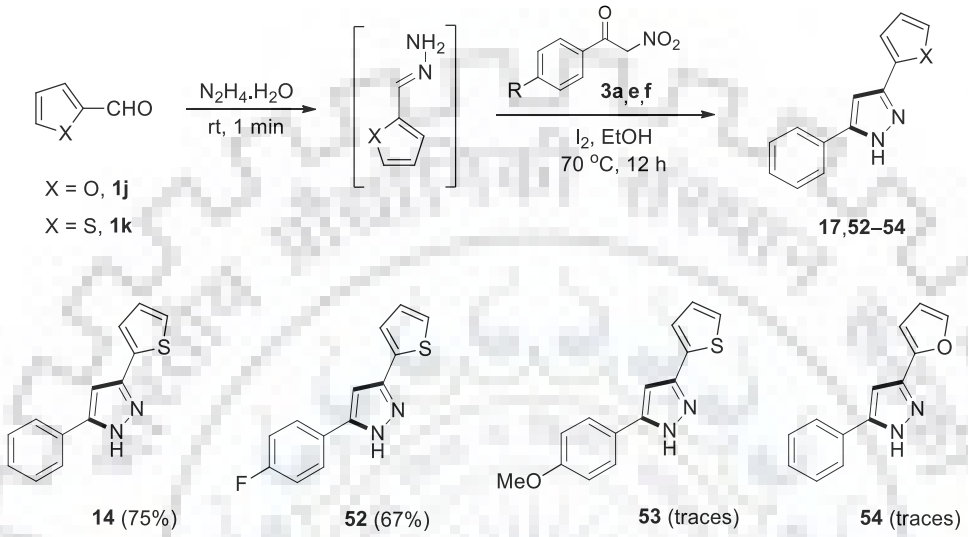


Figure 6: ORTEP Representation of crystal structure of **48**.

Table 13: Crystallographic data for **48**.

Formula	$C_{17}H_{16}N_2O$
Formula Wt.	264.32
Crystal habit	Blocks
Crystal color	White
Crystal system	Monoclinic
Space group	P 21/c
a (Å)	12.4739(14)
b (Å)	7.4371(8)
c (Å)	16.2909(19)
α (deg)	90
β (deg)	110.590(5)
γ (deg)	90
V (Å^3)	1414.8(3)
Z	2
D_{calc} (g cm^{-3})	1.241
T (K)	293 K
λ (Mo-Kα)	0.71073
μ (mm^{-1})	0.078
Limiting indices	$-19 \le h \ge 19$ $-11 \le k \ge 11$ $-24 \le l \ge 24$
F(000)	560.0
No. of Reflns. Measured	5252
No. of Parameters	280
GOF on F^2	0.597
R1 [I>2σ(I)]	0.0472(3082)
wR2	0.1794(4308)

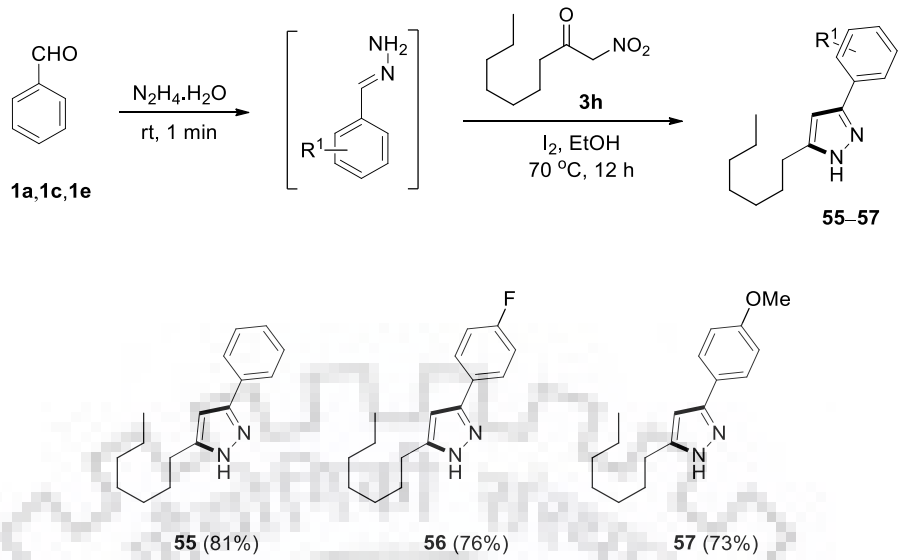
Further to investigate the extent of this metal-free DIDAN potocol we tested heteroaromatic aldehydes such as furfural **1j** and formylthiophene **1k**. Notable, the reaction of **3a**,**e** with **1k** afforded products **14** and **52** in 2 h in 75 and 67% yield respectively. In case of **3f**, the reaction afforded pyrazole product **53** only in trace amount. Next, we performed the reaction between **1j** and **3a** and the pyrazole derivative **54** was obtained in traces (Scheme 19).



Scheme 19: Reaction of α-nitroacetophenones **3a**,**e**,**f** with heteroaromatic aldehydes **1j**,**k**.

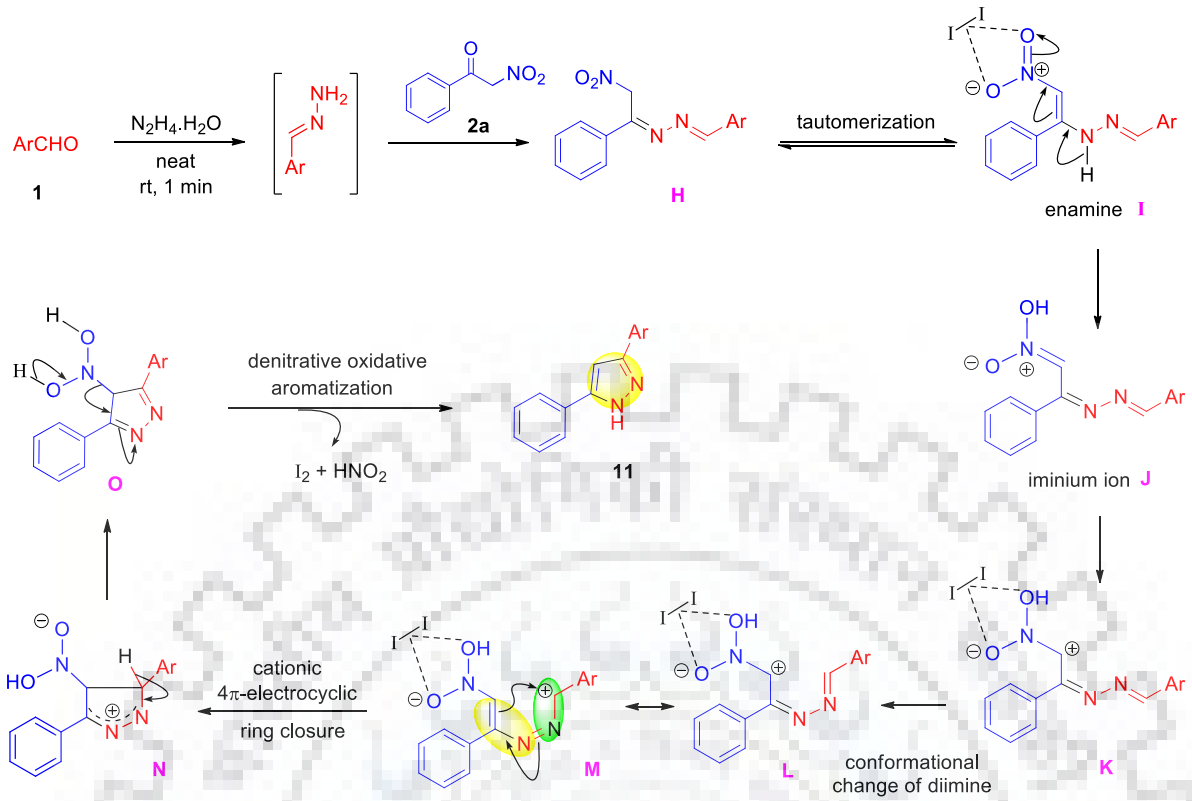
Generally, the iodine catalytic process was effective and amenable for DIDAN cyclization process. In our denitrative methodology, a wide range of α-nitroacetophenones **3a**–**f** could be rapidly combined with aromatic aldehydes **1a**,**c**,**e** in the presence of iodine to deliver corresponding pyrazoles **42**–**51** in high to excellent yields. However, distantly lower yields were observed in the case of aldehyde bearing heretrocycles substituents **1j** and **1k**.

The functionalization of the aliphatic compounds is a more challenging task than functionalizing aromatic compounds due to the less reactivity of the former nitro compounds. Our previous DAN approach failed to provide the cyclized product in the case of aliphatic ketones. Notably, this current one-pot, three-component DIDAN strategy was successful with easily accessible aliphatic α-nitrononan-2-one **2h** with aldehydes **1a**,**c**,**e**. To our delight, the cyclized products **55**–**57** were obtained in 2 h in high yields 71–83% (Scheme 20).



Scheme 20: Scope of the DIDAN cyclization reaction of aliphatic α-nitroacetophenone **3h** with benzaldehyde **1a**,**1c**,**1e**.

Based on the above findings and previous literature studies [19–26,149,150,181], a plausible mechanism for the DIDAN cyclization has been proposed in Scheme 21. Initially the hydrazone, generated from aldehyde **1a** and hydrazine hydrate, undergoes condensation with α-nitroacetophenone **2a** to produce intermediate **H** which tautomerizes to tautomer **I**. Next the molecular iodine activates the nitro group to deliver iminium ion intermediate **J**. The conformational variation of s-*trans* diimine **K** to s-*cis* diimine **L** subsequently leads to 2,3-diaza-pentadienyl cations **L** and **M**, which are stabilized by the delocalization of positive charge. This enamine–iminium ion experiences 4π-electrocyclization ring closure to produce diaza-allyl cation **N**, which upon denitrative aromatization provides exclusively five-membered heterocycle **11**.



Scheme 21: Plausible mechanism of cyclization for the synthesis of pyrazoles.

2.2.3. Synthesis of vinyl sulfones and hydrosulfonylation of chalcones

The sulfonylation reactions have long served as versatile tools for C–S bond formation in synthetic organic chemistry [75,77,184]. The construction of the C–S bond is still challenging and become more significant today because of the ubiquitous nature of sulfur-containing compounds as natural products and bioactive compounds and their importance in materials science [96,105,185–187]. Over the last decades, an enormous number of protocols have been developed for the generation of C–S bonds through metal-mediated [92,188–190] and metal-free [79,90,91,94,95,104] processes. Particularly, the formation of Csp^2–SO_2 and Csp^3–SO_2 bonds has garnered considerable attention for the synthesis of sulfone-containing organic compounds.

To avoid the inherent drawbacks of transition metals [63–66,73,190], simple, metal-free, and direct synthetic routes are still in demand for carbon–heteroatom bond formation [80-82,191]. Electron transfer is the main role of catalysts in cross-coupling reactions for the construction of carbon–heteroatom bonds [192–194]. Although transition metals have often been used for such types of reactions. The moderate redox potential of iodine renders it as one of the best alternatives to metal catalysts in the construction of carbon–heteroatom bonds [89, 195]. Iodine is capable of generating radicals, which are key in the formation of C–SO_2 bonds. As a result, iodine-catalyzed sulfonylation by using sulfonyl hydrazide was explored to a large extent [57,83,196,197].

The study of C–SO_2 bonds from a synthetic standpoint has become more established over the last few years. Various research groups have conducted pioneering studies on Csp^2–SO_2 bond formation under metal-mediated [85,86,93,98,198] and metal-free [88,199–201] conditions through decarboxylative and denitrative sulfono functionalization (DNSF) reactions to access vinylsulfones. Recently, Vicario and co-workers accomplished the construction of the Csp^3–SO_2 bond by using a sulfa-Michael addition reaction [102]. Chen *et al*. [103] established the hydrosulfonylation of α,β-conjugated systems, and Jiang and co-workers [202] achieved the halosulfonylation of 1,7-enynes by radical processes [197,203,204].

In continuation of our interest in the development of iodine-catalyzed protocols for the synthesis of valuable compounds [205,206], we carried out an efficient, straightforward, and

operationally simple protocol. This approach employs arylsulfonyl hydrazides and either nitrostyrenes or acrylates/styrenes for the formation of C(sp^2)–SO_2 bonds through denitrative sulfono functionalization and C–H functionalization through HI elimination. A hydrosulfonylation reaction between α,β-conjugated systems and β-nitrostyrenes to form a C(sp^3)–SO_2 bond is also described (Scheme 22).

This section deals with the results and discussion as shown below

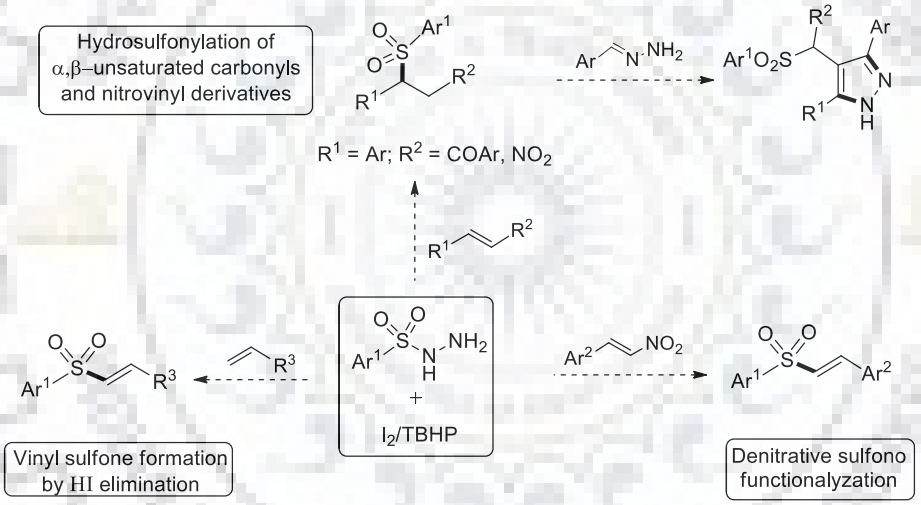
2.2.3.1. Synthesis of vinyl sulfones from β-nitrostyrenes **58**–**66**

2.2.3.2. Hydrosulfonylation of β-nitrostyrenes **67**–**69**

2.2.3.3. Synthesis of vinyl sulfones from acrylates **70**–**75**

2.2.3.4. Hydrosulfonylation of chalcones **78**–**89**

2.2.3.5. Synthesis of pyrazole **90**

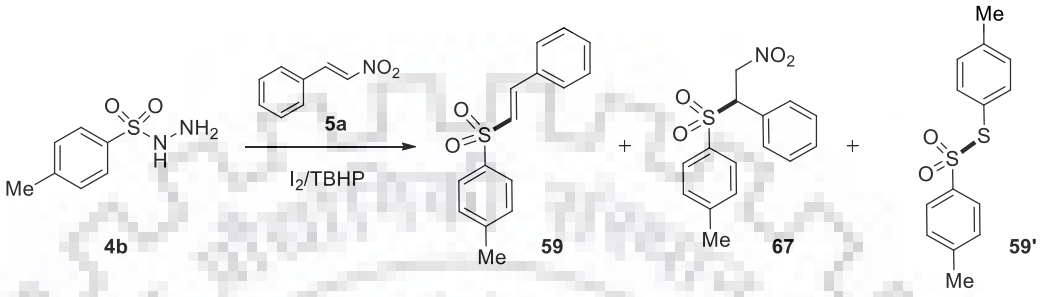


Scheme 22: Working hypothesis for the sulfonylation of olefins.

Our investigation began by choosing sulfonyl hydrazide **4b** and β-nitrostyrene (**5a**) as model substrates. The reaction was performed in the presence of a catalytic amount of iodine (20 mol%) and TBHP (3 equiv) as the oxidant under solvent-free conditions. To our delight, denitrative sulfonylated product **59** was obtained within 2 min in 52% yield along with the release of nitrogen gas bubbles from the evolution of heat and with 60% conversion of **5a** (Table 14, entry 1). Despite performing the reaction for a prolonged time of the reaction 24 h (entry 2), there was no significant improvement in the yield of **59**. Next, we examined various reaction parameters to improve the conversion of **5a** and the yield of the product. The reactions

were carried out with variable mounts of reactants. The reaction of β-nitrostyrene (**5a**) with 1.5 equiv of **4b** afforded **59** in 55% yield (entry 3). The reaction of 2 equiv of **4b** furnished **59** in a similar yield along with 18% of sulfonyl sulfide **59′** (entry 4). To further

Table 14: Optimization for vinylsulfonation and hydrosulfonylation of nitrostyrenes[a]



Entry	**4b**:**5a** (equiv)	I_2 (mol%)/ TBHP (equiv)	Solvent	Time	% Conversion **5a**	Yield (%)[b] **59**/**67**/**59′**
1	1.2:1	10/3	-	2 min	60	52/traces/traces
2	1.2:1	10/3	-	24 h	62	53/traces/traces
3	1.5:1	10/3	-	1 h	65	55/traces/traces
4	2.0:1	10/3	-	1 h	62	54/traces/18
5	2.0:1	20/3	-	2 min	61	64/ traces/21
6	1.2:1	20/5	-	2 min	78	83/traces/traces
7	1.2:1	50/5	-	2 min	78	73/traces/traces
8[c]	1.2:1	20/5	-	24 h	74	71/traces/traces
9	1.2:1	20/5	ACN	24 h	55	41/traces/traces
10	1.2:1	20/5	DCM	24 h	60	54/traces/traces
11	1.2:1	20/5	EtOH	24 h	-	nr
12[d]	1.2:1	20/3	-	1 h	54	traces/45/traces
13[d]	1.2:1	20/3	ACN	1 h	66	traces/56/traces

[a] Reaction conditions: **4b** (0.6 mmol), **5a** (0.5 mmol), TBHP (2.5 mmol), I_2 (20 mol%).
[b] Isolated yield based on consumed nitrostyrene **5a**. nr : no reaction.
[c] Reaction at 60 ºC.
[d] In presence of 50 mol% base morpholine.

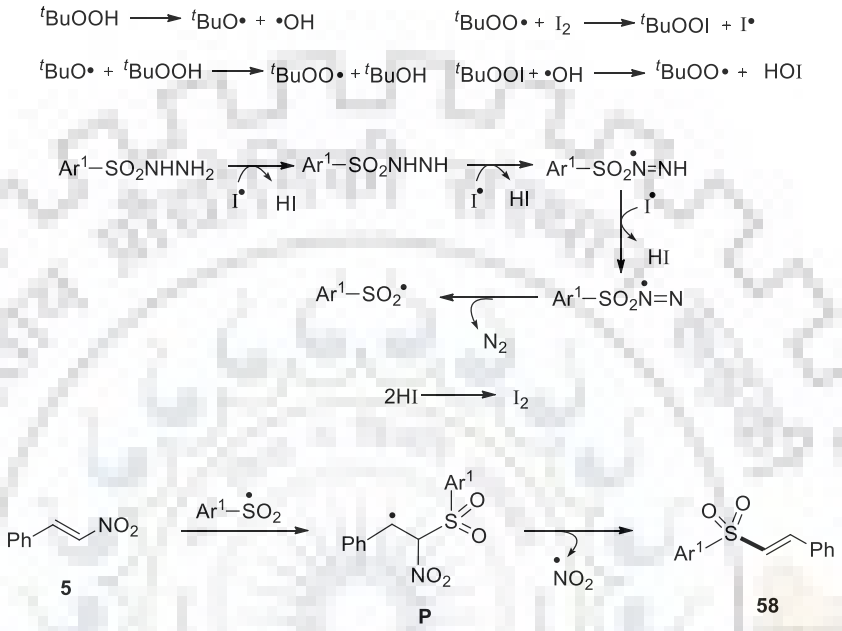
evaluate the reaction, we screened the reaction by changing various amounts of both iodine and TBHP (entries 5 and 6). When we increased the amount of I_2 and TBHP, the reaction proceeded rapidly with 78% conversion of nitrostyrene to furnish **59** in 83% yield (entry 6). The product **59** was obtained in a reduced yield of 73% when the amount of iodine was raised to 50 mol% (entry 7), and no improvement in the yield was observed when the reaction was carried out at 60 ºC (entry 8). To evaluate the effect of different solvents on the reaction, we performed the reaction in CH_3CN and dichloromethane, which provided product **59** in still lower yields (entries 9 and 10). Notably, the sulfonylation of **5a** with **4b** in EtOH did not proceed (entry 11). To evaluate the effect of added base, the reaction was then performed in the presence of iodine (20 mol %), TBHP (3 equiv), and morpholine (50 mol %) under solvent-free conditions. To our delight, hydrosulfonated product **67** was obtained within 2 h in 45 % yield (entry 12). When we performed the reaction in the presence of morpholine (50 mol %) and acetonitrile as the solvent, **67** was isolated in 56 % yield (entry 13). On the basis of these results, it was clear that the I_2 (20 mol%)/TBHP (5 equiv) reagent system under neat conditions is crucial for the DNSF of nitrostyrene (entry 6). Furthermore, the hydrosulfonation of **5a** proceeded with the morpholine (50 mol %)/TBHP (3 equiv)/I_2 (20 mol%) system in acetonitrile to give **5a** in high yield (Table 14, entry 13).

2.2.3.1. Synthesis of vinyl sulfones from β-nitrostyrenes

We further investigated the transformation of nitrostyrene **5a**. The reaction of tosyl hydrazide (**4b**) with nitrostyrene (**5a**) in the presence of I_2/TBHP furnished vinyl sulfone **59** by a denitrative sulfono-functionalization (DNSF) process. To the best of our knowledge, there have been no reports for the generation of a $C(sp^2)$-SO_2 bond through a DNSF from sulfonyl hydrazides. To know whether or not a radical pathway is occurring, TEMPO (2 equiv) was added to the reaction mixture of **4b** and **5a**. Upon the addition, the reaction ceased, which suggests a radical process is taking place (Scheme 23). Nevertheless, the reaction that proceeds with the addition of morpholine to lead to formation of a $C(sp^3)$–SO_2 bond presumably occurs through a sulfa-Michael addition reaction to afford hydrosulfonylation product **67** in a moderate yield (Scheme 25).

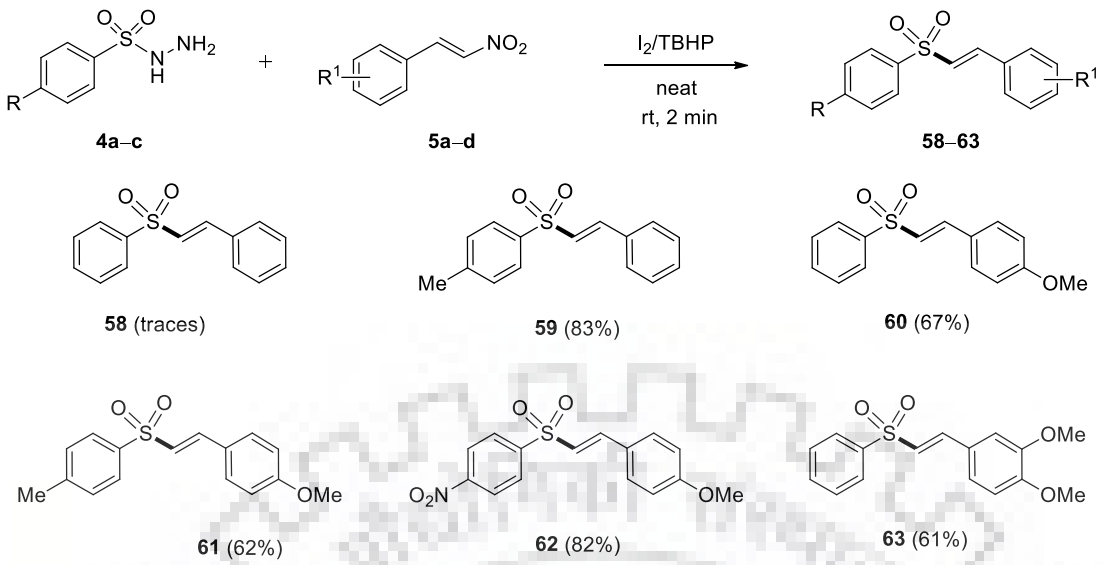
On the basis of the above findings and reports in the literature [85,86,93,98,198–201], a plausible mechanism for the DNSF of nitrostyrene has been proposed. Under the reaction

conditions, the sulfonyl hydrazide decomposes into a sulfonyl radical, which subsequently undergoes addition to nitrostyrene **5** to generate carbon-centered benzylic radical **P**. Finally, **P** undergoes β-elimination to give α,β-unsaturated arylsulfone **58** (Scheme 23). The hydosulfonylation of nitrostyrene with sulfonyl hydrazide, however, appears to proceed through the mechanism that has been described for chalcones (Scheme 35).



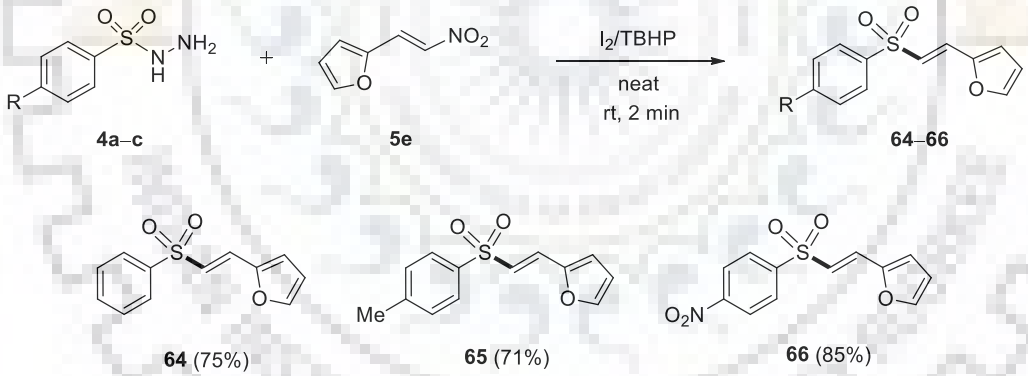
Scheme 23: Plausible mechanism for the formation of denitrative vinylsulfones.

Having established the optimized reaction conditions for the denitrative sulfonylation and hydrosulfonylation of β-nitrostyrenes, we then proceeded to probe the substrate scope (Scheme 24). The iodine/TBHP-catalyzed oxidative reaction of β-nitrostyrenes **5** with sulfonyl hydrazides **4** in the absence of base provided addition–elimination products **58**–**63**. Thus, a range of β-nitrostyrenes **5c**,**d** containing electron-rich groups on the phenyl ring were well tolerated under the reaction conditions, and the corresponding products **58**–**63** were obtained in good yields. Interestingly, the reaction of 4-chloro-β-nitrostyrene (**5b**) did not offer the addition–elimination product under the DNSF conditions, and hydrosulfonylation product **69** was isolated instead. This outcome suggested that electron-rich substituents on the aryl moiety of the β-nitrosyrene favored the DNSF reaction, whereas electron-deficient substituents did not honour for denitrative sulfonylation (Scheme 26).



Scheme 24: Reaction of denitrative vinylsulfones synthesis.

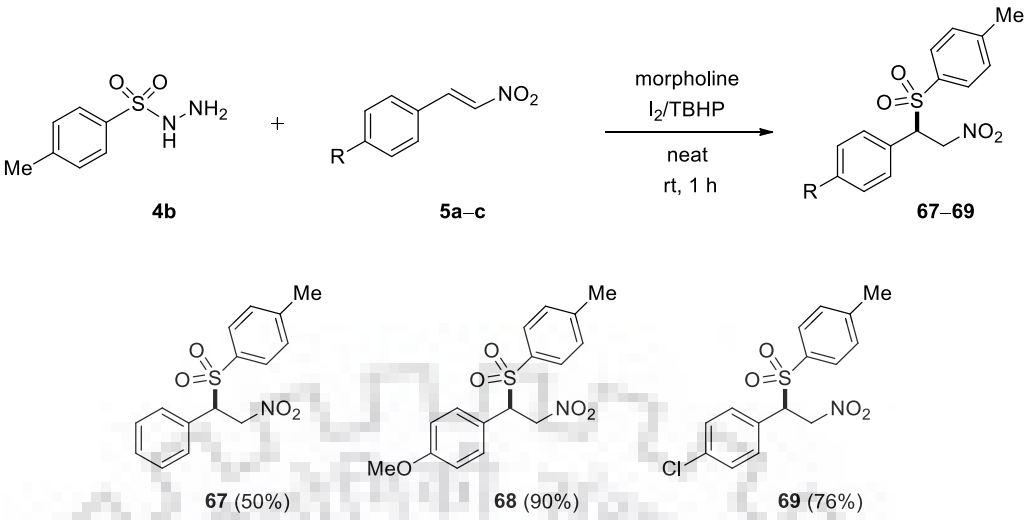
Gratifyingly, we were pleased to observe the reaction of 2-(2-nitrovinyl)-furan (**5e**) with sulfonyl hydrazides **4a**–**c** proceeded well under the standard conditions to give the corresponding DNSF products **64**–**66** in yields of 71–85% (Scheme 25).



Scheme 25: Reaction of 2-(2-nitrovinyl)-furan (**5e**) with sulfonyl hydrazides **4**.

2.2.3.2. Hydrosulfonylation of β-nitrostyrenes

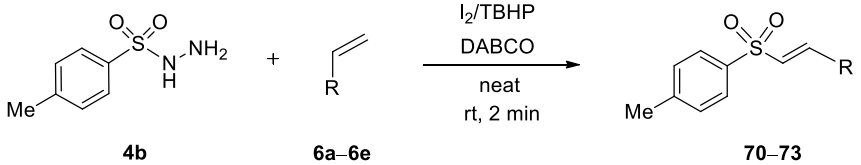
Our investigations revealed that the sulfonyl hydrazides that contain electron-deficient groups on the aryl moiety are more reactive than those with electron-rich groups. Next the iodine/TBHP-catalyzed reaction in the presence of morpholine resulted in the formation of the corresponding β-nitrosulfones **67**–**69** in yields of 50–90% (Scheme 26).

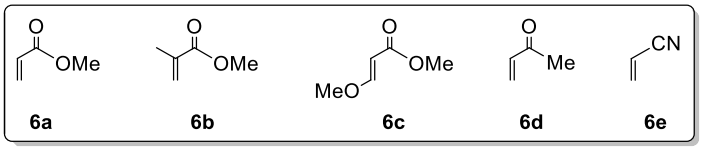


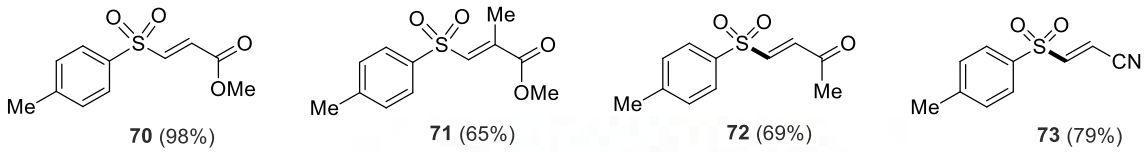
Scheme26: Hydrosulfonylation of nitrostyrenes **5** with sulfonyl hydrazides **4b**.

2.2.3.3. Synthesis of vinyl sulfones from acrylates

At this juncture, we turned our attention to the sulfonylation of olefins that contain other electron-withdrawing groups. Thus, we selected acrylates **6a**–**e** and styrene derivatives **6f**,**6g** for this transformation. The reaction of methyl acrylate and **4b** in the presence of an iodine/TBHP, DABCO system in solvents such as dichloromethane, acetonitrile, or ethanol gave the sulfone **70** (Ar^1 = Ph, R = CO_2Me) in 81–90% yield in 1 h, and the reaction in 1,2-dichlorethane (DCE) led to the formation of **70** in an increased yield of 95%. Under solvent-free conditions, however, the reaction afforded the product after 2 min in quantitative yield. In 2014, Tang *et al*. reported the sulfonation of *tert*-butyl acrylate with **4b** under harsh conditions in the presence of KI/TBHP in DMSO/acetic acid at 80 ^oC to produce the tert-butyl β-tosylacrylate in comparatively low yield of 69% in 10 h [89]. With the encouraging initial results in hand, we examined the scope of the reaction under neat conditions (Scheme 28). Thus the reactions of methyl acrylate (**6a**), methyl methacrylate (**6b**), trans-methoxy vinyl methyl ketone (**6c**), methyl vinyl ketone (**6d**) and acrylonitrile (**6e**) with arylsulfonyl hydrazide **4b** proceeded rapidly under the optimized conditions to give vinyl sulfones **70**–**73** in good to excellent yields (Scheme 27).

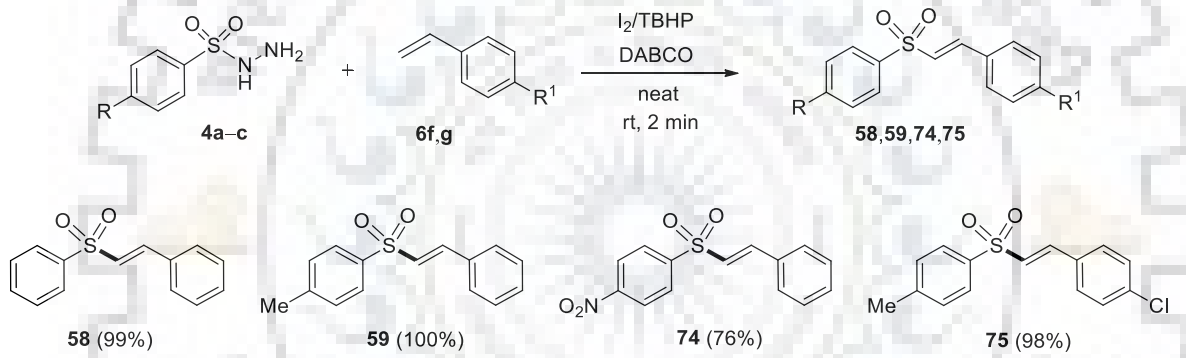






Scheme 27: Sulfonylation of olefins with electron-withdrawing groups.

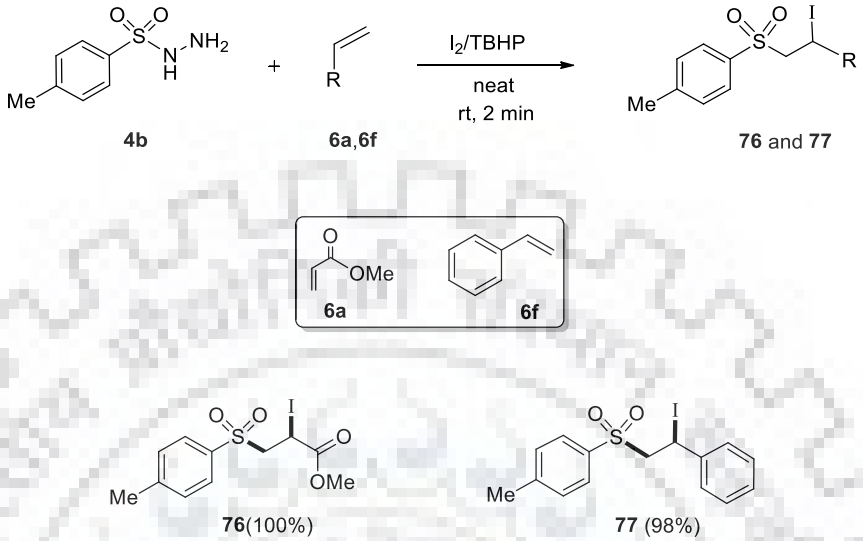
Then we performed the reaction of sulfonyl hydrazides **4a–c** with **6f** and **6g** under I_2/TBHP, DABCO conditions and reaction provided the products **58**,**59**,**74**,**75** with excellent yields (Scheme 28).



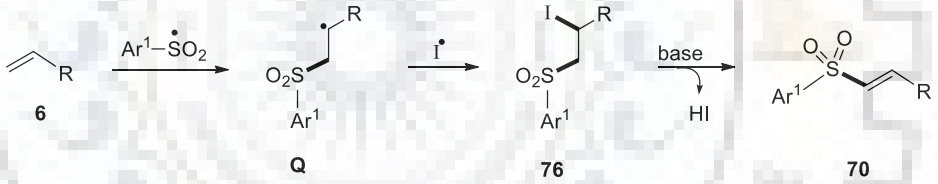
Scheme 28: Sulfonylation of styrenes with sulfonyl hydrazides **4a**–**c**.

In the process of understanding the reaction pathway, we conducted the reactions of **4b** with **6a** and **6f** in the presence of the iodine/TBHP system under solvent-free and base-free conditions. Surprisingly, α-iodo-β-sulfones **76** and **77** were obtained in 100 and 98% yields, respectively, which indicate that the aryl sulfonyl radical trigger the reaction by attacking the less hindered carbon of **6** to give radical **Q** (Schemes 29 and 30). The radical then couples with the iodine radical to liberate β-sulfonyliodo compound **76**, and the subsequent elimination of HI from **76** under basic conditions, generates vinyl sulfone **70**.

This suggests that the action of iodine are similar to that of a metal, which can be used to promote coupling reactions in which an oxidative addition followes by reductive β-hydride elimination (Figure 1).



Scheme 29: Control experiments for the synthesis of α-iodo-β-sulfones **76** and **77**.

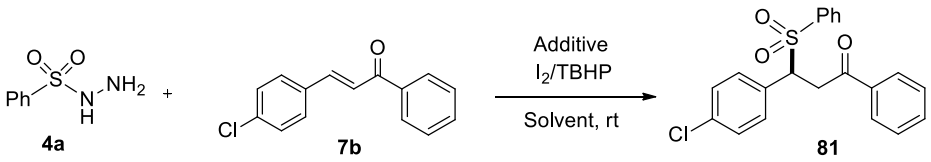


Scheme 30: Plausible mechanism for vinylsulfones synthesis *via* β-hydride elimination.

2.2.3.4. Hydrosulfonylation of chalcones

Encouraged by the above results for the hydrosulfonyation of nitrostyrene **5**, we then explored the scope of this transformation for sulfonyl hydrazides **4** and α,β-conjugated systems **7** under the optimized reaction conditions (Table 15). Among the all reaction conditions morpholine (1 equiv)/TBHP (3 equiv) iodine (20 mol%) in acetonitrile found to be the optimum condition for the reaction to proceed in excellent yield (Table 15, entry 9).

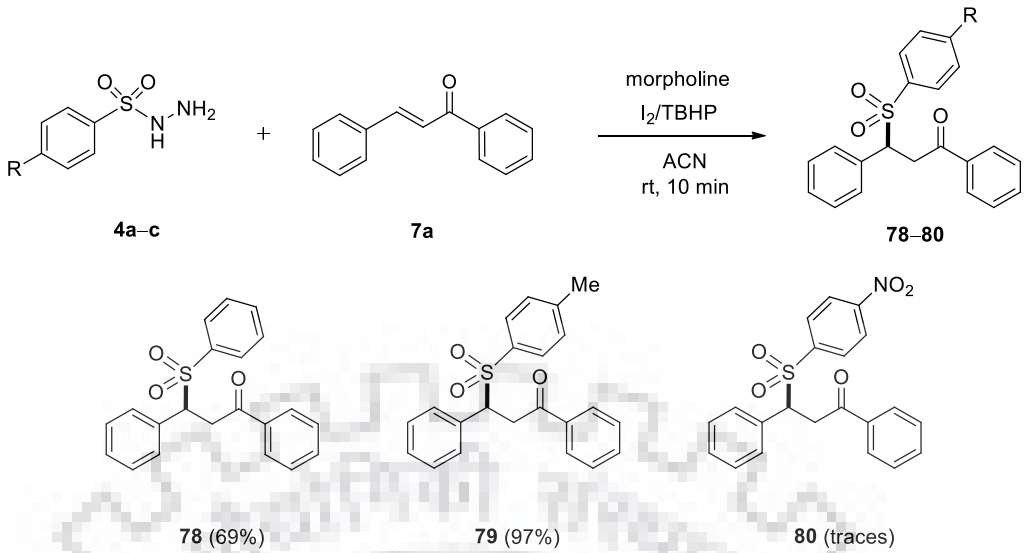
Table 15: Optimization of hydrosulfonylation α,β-conjugated systems.[a]



Entry	Additive (equiv)	Solvent	Time (h)	Yield[b] (%)
1[c]	Morpholine (0.5)	neat	2	52
2	Morpholine (0.5)	neat	2	81
3[d]	Morpholine (0.5)	neat	2	82
4	DABCO (0.5)	neat	2	79
5	DBU (0.5)	neat	2	67
6	TEA (1)	neat	2	45
7	K_2CO_3 (1)	ACN	2	65
8	Morpholine (0.5)	ACN	2	85
9	Morpholine (1)	ACN	10 min	95
10	Morpholine (1)	THF	1	85
11	Morpholine (1)	DCM	1	61
12	Morpholine (1)	H_2O	1	nr
13[e]	Morpholine (1)	ACN	1	80
14	Morpholine (0.25)	ACN	12	69

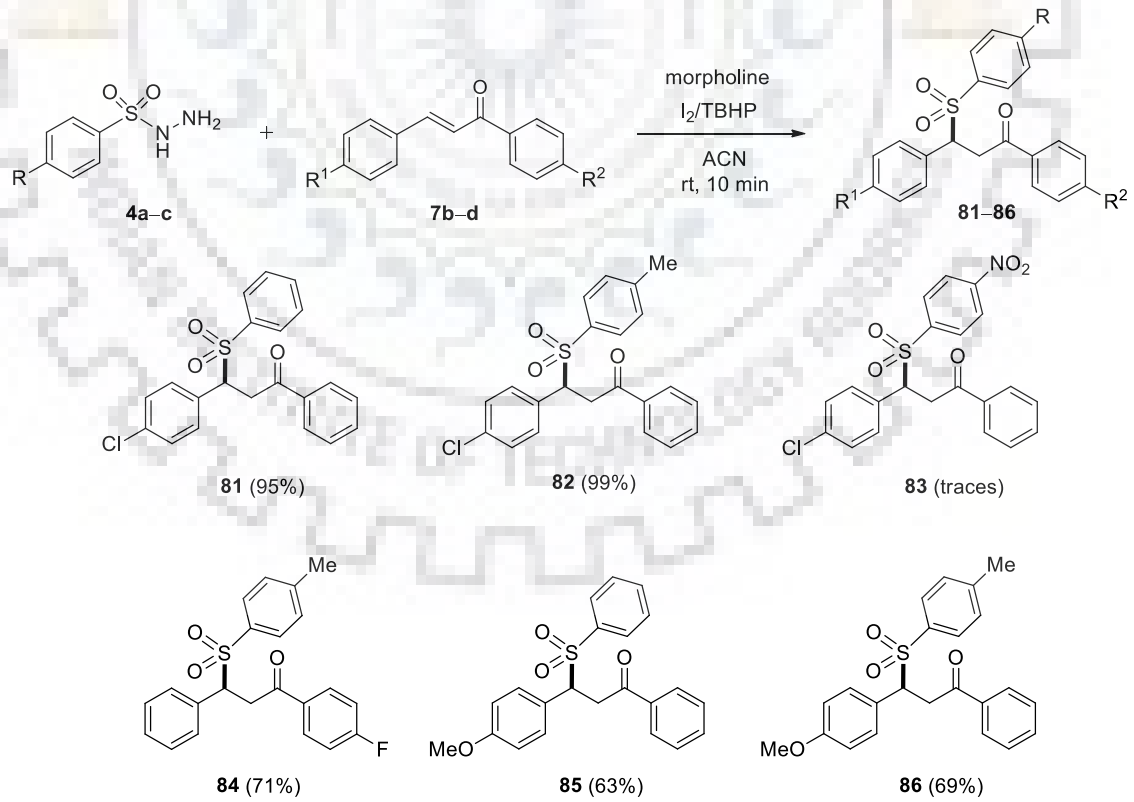
[a] Reaction conditions: **4a** (1.0 mmol), **7b** (0.5 mmol), additive (0.5 mmol), TBHP (1.5 mmol), I_2 (20 mol%), unless otherwise stated.
[b] Yield of pure and isolated compounds. nr: no reaction.
[c] 0.5 mmol of **4a** was used.
[d] 1.5 mmol of **4a** was used.
[e] Addition sequence: TBHP/I_2/additive.

It was pleasing to find that sulfonyl hydrazides **4a** and **4b** were able to undergo reaction with **7a** in 10 min to furnish the corresponding products **78** and **79** in 69 and 97% yields, respectively. When we performed the reaction of **7a** with 4-nitrophenylsulfonyl hydrazide (**4c**), only trace amount of the product **80** was formed (Scheme 31).



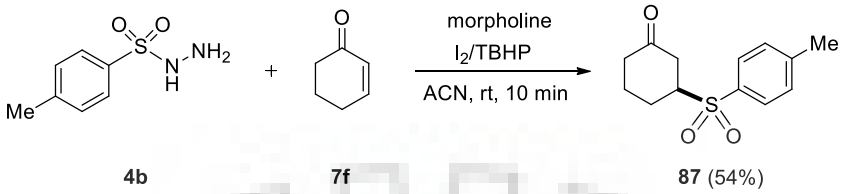
Scheme 31: Reaction of chalcone **7a** with sulfonyl hydrazides **4a**–**c**.

We further studied the scope of the reaction by evaluating the effect of chalcones consisting electronically diverse groups at the *para*-position of the phenyl group. These groups were well tolerated under the reaction conditions and the corresponding products **81**–**86** were obtained excellent yields of 63–99% (Scheme 32).



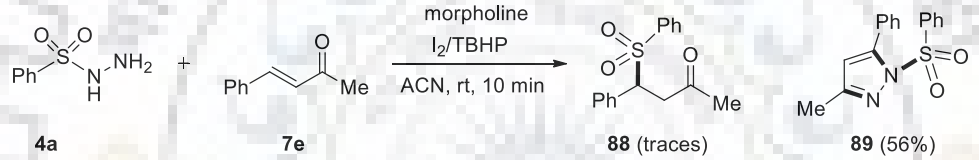
Scheme 32: Reaction of α,β-conjugated systems **7b**–**d** with sulfonylhydrazides **4a**–**c**.

Next we studied the scope of the current transformation between cyclohexenone (**7f**) and **4b** by following the optimized conditions. To our delight, **87** was obtained in 54% yield (Scheme 33).



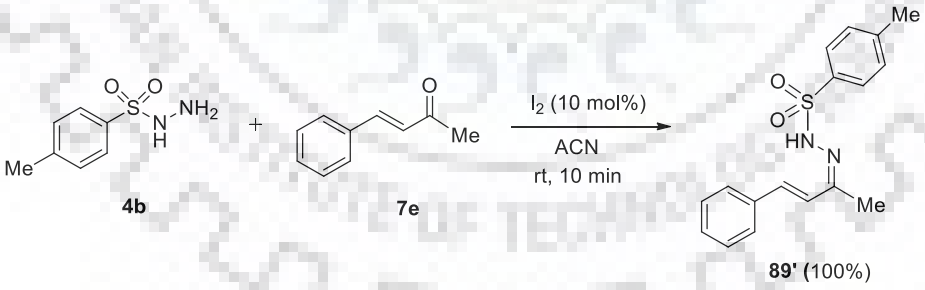
Scheme 33: Reaction of cyclohexenone (**7f)** with **4b**.

However, the reaction of benzylidineacetone (**7e**) and **4a**, afforded the pyrazole derivative **89** in 56% yield. The expected hydrosulfonylation product **88** was obtained in traces only (Scheme 34).



Scheme 34: Reaction of benzylidineacetone (**7e**) with **4a**.

Interestingly, the reaction of **7e** with **4b** in the presence of 10 mol% of molecular iodine at room temperature, furnished the hydrazone **89′** in quantitative yield in 10 min (Scheme 35).

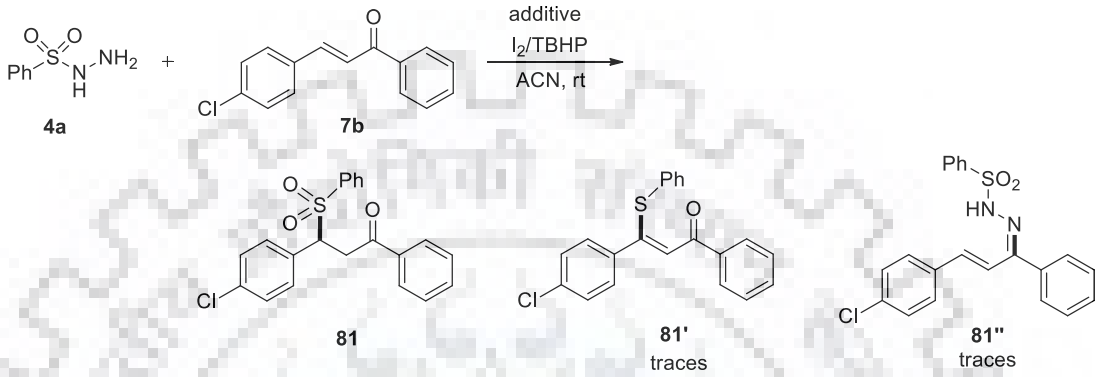


Scheme 35: Formation of hydrazone **89′** from **7e**.

To understand the course of the reaction, we carried out some control experiments (Table 16 and Scheme 37). We observed that the reaction between **7b** and **4a** reached completion in the presence of morpholine after 24 h (Table 16, entry 2). This reaction appears to be Michael addition of phenyl sulfinate anion to **7b**. To further gain insight into the

mechanism, we examined the reaction in the presence of only I_2/TBHP. Delightfully, the reaction proceeded well in the absence of the base to afford **81** in a moderate yield (entry 3). Further experimental conditions revealed that the combination of I_2/TBHP and morpholine was essential to get best results.

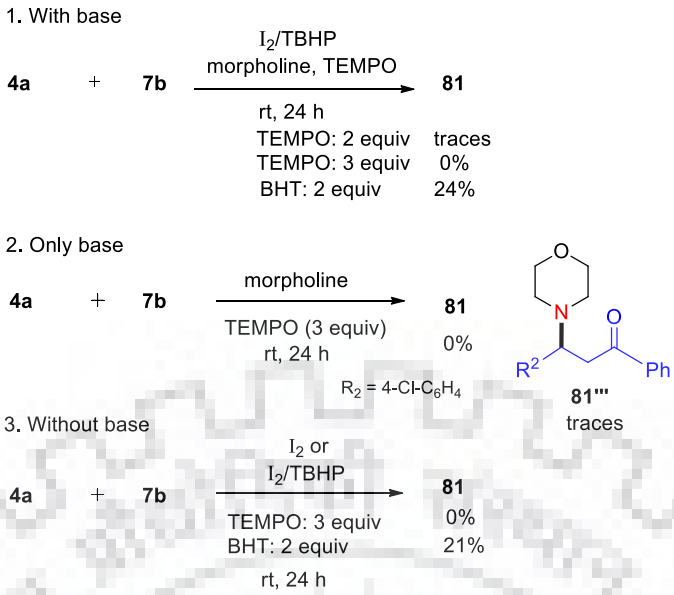
Table 16: Control experiments for hydrosulfonylation of chalcones[a]



Entry	I_2 (mol%)	TBHP (equiv)	Additive	Solvet	Time (h)	Yield[b] (%) **81**
1	20	-	morpholine (mol%)	ACN	20	94
2	-	-	morpholine (mol%)	ACN	24	94
3	20	3	-	neat	24	51
4	20	-	-	neat	24	traces
5	10	-	-	ACN	24	traces
6	-	3	-	ACN	24	traces

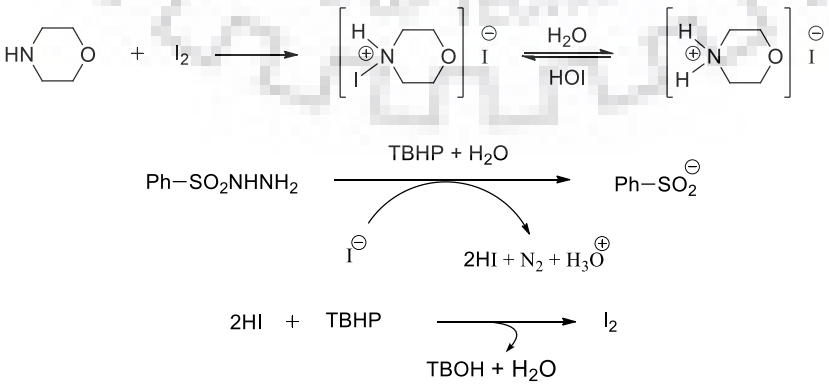
[a] Reaction conditions: **4a** (1.0 mmol), **7b** (0.5 mmol) and morpholine (0.5 mmol).
[b] Yield of pure and isolated compounds

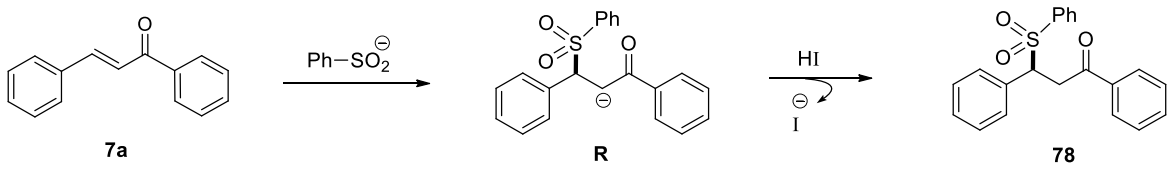
As mentioned above, the reaction was significantly inhibited in the presence of a radical scavenger, either TEMPO or butylhydroxyltoluene (BHT), (Scheme 37, reaction 1). No product was observed when the reaction was carried out with only base in the presence of TEMPO (Scheme 37, reaction 2). In this case, TEMPO only consumed the morpholine before the reaction was induced. When an oxidant or reductant was involved, the TEMPO itself could directly undergo action with such agent. The reaction was completely inhibited by the addition of TEMPO without the presence of the base (Scheme 36, reaction 3). These results suggest that a radical pathway may be involved in the absence of base.



Scheme 36: Control experiments.

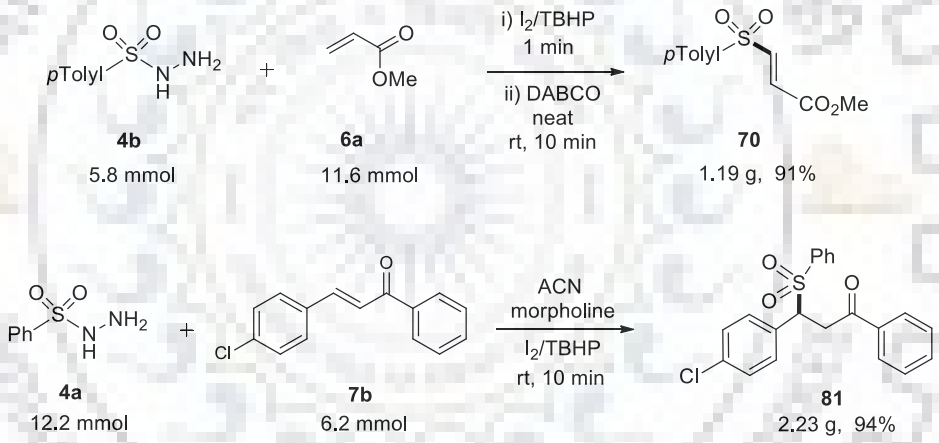
Morpholine has been shown to act as a quaternary salt and assist in the rapid generation of iodide. The combination of iodide and TBHP may facilitate the generation of the sulfonyl anion from sulfonyl hydrazide **4a** and concurrent heat evolution. Thus, these control experiments indicate the necessity of morpholine/TBHP/I_2 system for a rapid hydrosulfonylation reaction. On the basis of the above experimental findings and previous reports [57,83,103,196,197,202], we propose a plausible mechanism for the hydrosulfonylation of the chalcone derivatives (Scheme 38). Initially, morpholine combines with iodine to form morpholinium iodide along with the generation of heat. This iodide ion then facilitates the generation of the sulfonyl anion from the arylsulfonyl hydrazide. The sulfonyl anion attacks the β-carbon of enone **7a** to produce β-sulfonyl anion species **R**, which upon protonation liberates γ-ketosulfone **78**.





Scheme 37: A plausible mechanism for the hydrosulfonylation of chalcones.

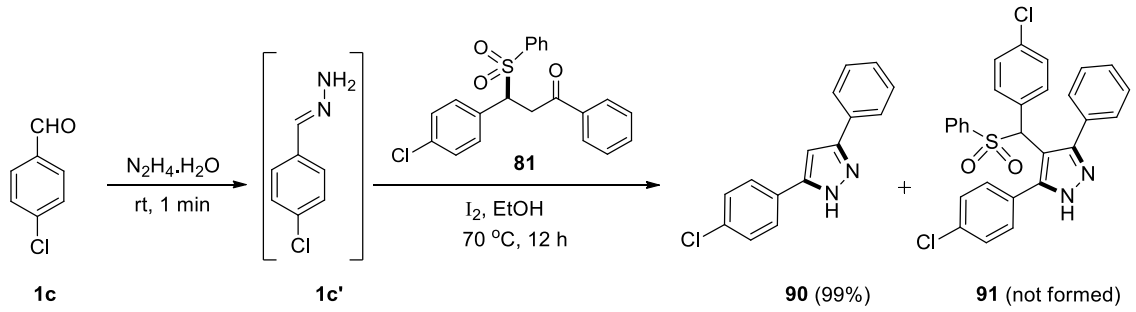
Encouraged by the current environmental benign protocol for the synthesis of γ-ketosulfones as well as vinyl sulfones, and to demonstrate the synthetic utility of this transformation, we then scaled up the reaction. For this, we performed the alkenylation reaction of **4b** (5.8 mmol) with methyl acrylate (**6a**, 11.6 mmol) under solvent-free conditions, which gave the vinylsulfone in high yield (Scheme 39). Next, we carried out the gram-scale reaction of phenylsulfonyl hydrazide **4a** (12.2 mmol) and chalcone **7b** (6.2 mmol) under the optimized conditions to provide the corresponding γ-ketosulfone **81** in excellent yield.



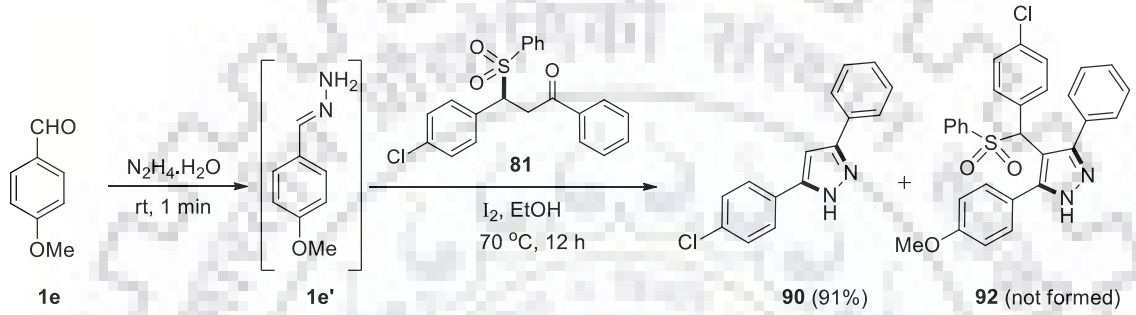
Scheme 39: Gram-scale reactions.

2.2.3.5. Synthesis of pyrazoles

Finally, to explore the synthetic versatility of the prepared γ-ketosulfones, compound **81** was treated with the *in situ* generated hydrazones **1c′** and **1e′** [181] in the presence of iodine in ethanol solvent under aerobic conditions. In both cases it furnished the functionally-rich pyrazole **90** in excellent yield instead of expected products **91** and **92** (Schemes 40 and 41).

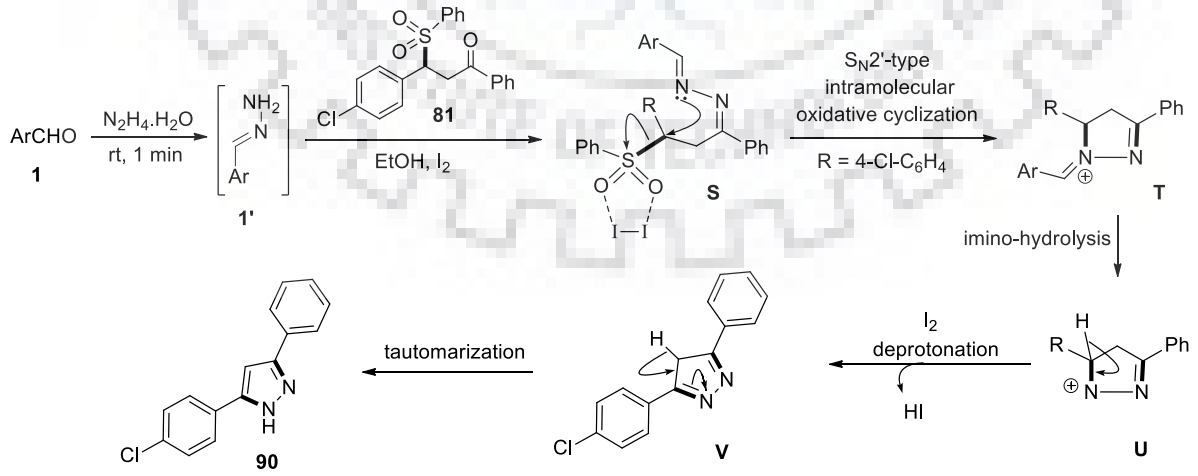


Scheme 40: Reaction of γ-ketosulfone **81** with hydrazone **1c′**.



Scheme 41: Reaction of γ-ketosulfone **81** with hydrazone **1e′**.

The reaction is presumed to proceed by condensation of γ-keto sulfone **81** with *in situ* generated hydrazone **1′** to provide intermediate **S**. Subsequently, **S** gets converted into intermediate **T** *via* an iodine-mediated oxidative S_N2'-type cyclization. Finally, the subsequent imino-hydrolysis, deprotonation and ene-enamine tautomarization gives the pyrazole **90** (Scheme 42).



Scheme 42: Plausible mechanism for the formation of pyrazole.

2.2.4. Synthesis of sulfonylpropanes derivatives *via* dehydrative substitution of γ-hydroxysufones

The sulfones containing structural motifs are versatile building blocks and bioactive natural agents for pharmaceuticals [207,208], along with some of the best-selling drugs such as eletriptan ([2H]-SB-3CT) for the treatment of migraine headache and MMP-2, MMP-9 inhibitor for the treatment of prostate cancer (Figure 7) [210]. The aliphatic α-substituted sulfones serve as important scaffolds in a number of C–C bond-forming reactions, such as Ramberg–Bäcklund reaction and Julia olefination, through activation of the α-carbon by the sulfonyl group [211–214]. In the context of eco-friendly quest, it is challenging to develop novel sulfone motifs from easily accessible precursors in an environmentally benign approach with water as by-product under mild reaction conditions [110–113,115]. The dehydrative nucleophilic substitution of alcohols [125, 215] with various carbon and sulfur nucleophiles deliver a powerful approach for the generation of C−C and C–S bonds [216-219,126,127].

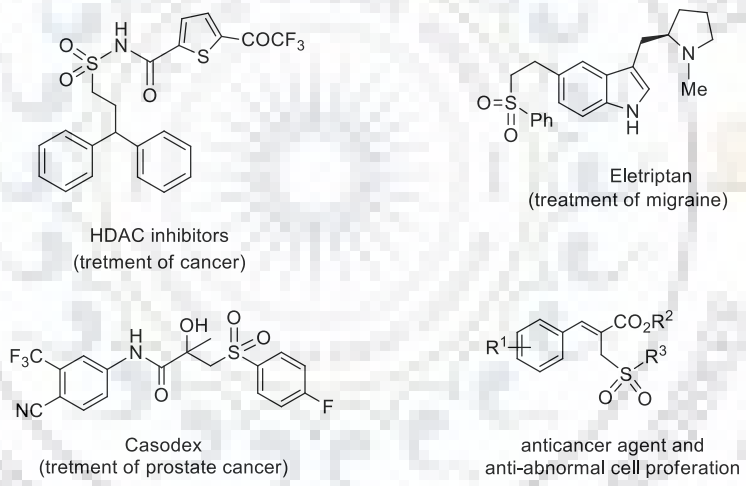


Figure 7: Sulfones moiety in biologically active molecules.

The Friedel–Crafts (F–C) alkylation reaction serves as key step for the production of a plethora of compounds in organic synthesis including 1,1-diarylalkanes. These substituted diarylalkanes are important building blocks in many pharmaceuticals HDAC inhibitors (Figure 7) [108], and are considered as relevant arenes in industry [220,221]. In general, F−C alkylation reaction employs toxic alkyl halides as alkylating reagents with stoichiometric amount of base that result the formation of waste salts as byproduct [114,222]. To overcome these drawbacks, enormous alternative protocols have been designed for alkylation reaction

replacing the toxic alkyl halides [223−227]. Recently many groups developed C−C bond formation reactions *via* metal-catalyzed dehydrative coupling reactions with benzylic alcohols [116-119,120-122]. The F−C substitution reaction is among the most robust strategies for C−C bond formation. Consecutively, Moran and co-workers described the catalytic F–C reactions of highly electronically deactivated benzylic alcohols [18,19,109,123,183]. Later, Xiao research group disclosed S_N1-type alkylation of *N*-heteroaromatics with benzylic alcohols [124].

Additionally, carbon–sulfur bond construction is an essential strategy for the development of novel and chemical building blocks in the current research scenario since the sulfur-containing compounds constitute important structural units in natural products, medicinal chemistry, and functional materials [74,75,77]. Recently Baran *et al*. introduced an remarkable and new simple straightforward protocol for strain-release thiolation by strain-release agent in under mild conditions [129]. Consequently, Zhang and co-workers developed another kind of strain-release thiolation using stable thiol selective radio-iodination agent [109].[18]

This section deals with the results and discussion as shown below

2.2.4.1. Synthesis of γ-hydroxysufones

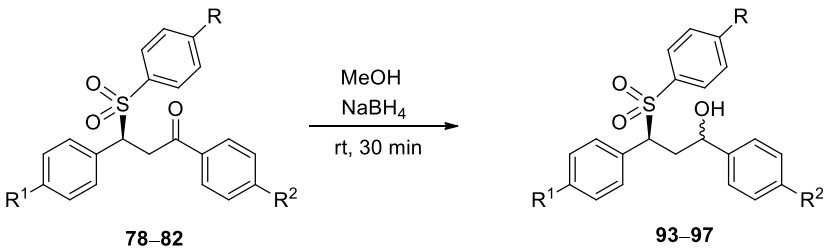
2.2.4.2. Friedel–Crafts (F–C) alkylation reaction

2.2.4.3. Dehydrative thiolation of γ-hydroxysufones

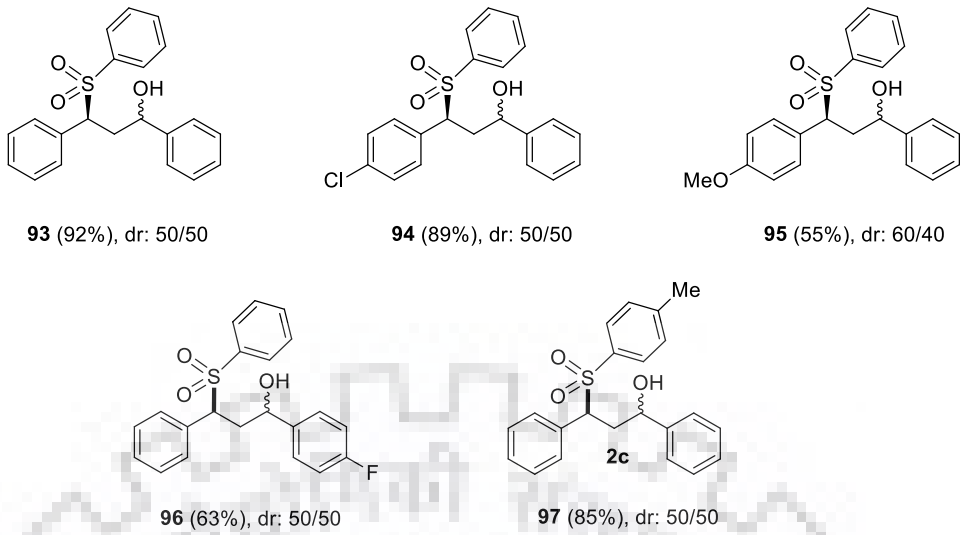
2.2.4.4. Synthesis of allylic sulfones

2.2.4.1. Synthesis of γ-hydroxysufones

Motivated by the synthesis of γ-ketosulfones by Baran [129] and Yan [228] and by our group [183], we reduced γ-ketosulfones **78**–**82** using $NaBH_4$ to access γ-hydroxysulfones **93**–**97** in good to excellent yield with a mixture of two diastereomers. Diastereomeric ratio of the products was determined by ^1H NMR analysis (Scheme 43).



78–82 **93–97**



93 (92%), dr: 50/50 **94** (89%), dr: 50/50 **95** (55%), dr: 60/40

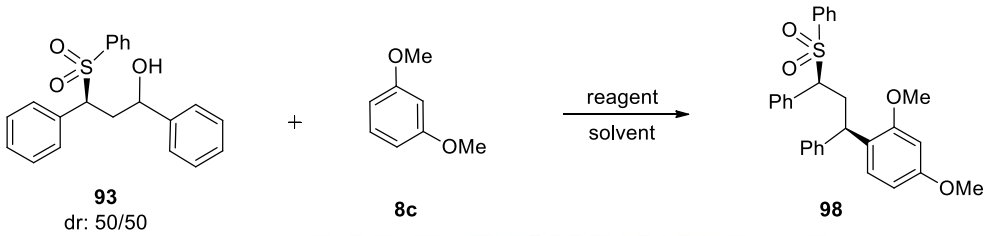
96 (63%), dr: 50/50 **97** (85%), dr: 50/50

Scheme 43: Synthesis of γ-hydroxysulfones.

Herein, we present the results from diastereoselective synthesis of 1-sulfono-3-aryl propanes and 1-sulfono-3-sulfanepropane derivatives from γ-hydroxysulfones by using $BF_3{\cdot}OEt_2$ as Lewis acid. To the best of our knowledge, till date, there are no reports for C-alkylation or S-alkylation of γ-hydroxysufones in the literature.

In the initial study, γ-hydroxysufone **93** was chosen as a benzylating agent to react with 1,3-dimethoxybenzene (**8c**) in the model reaction. Notably, no product formation was observed, when the reaction was conducted in the presence of I_2 at rt and at 80 ^oC in EtOH (Table 1, entries 1 and 2). Even under Brønsted acid conditions, no reaction was perceived and the starting materials were recovered (entries 3 and 4). Interestingly, switching the solvent system from EtOH to DCM with I_2 as reagent at rt, the desired sulfono-substituted diarylalkane **98** was obtained in 1 h in very good yield with good diastereoselectivity of 84:16 (entry 5). Encouraged by this result, we screened various Brønsted/Lewis acid promoters (TFA, $FeCl_3$, and $BF_3{\cdot}OEt_2$) to improve the yield and selectivity of the reaction (entries 6−9). These studies indicated that $BF_3{\cdot}OEt_2$ is an optimum reagent for this transformation. Thus the reaction of **93** with **8c** in the presence of $BF_3{\cdot}OEt_2$ at room temperature afforded the corresponding arene **98** in 1 h with a maximum yield of 91% without any change in diastereoselectivity (entry 9). Optimization studies of solvents indicated DCM as best solvent for the reaction (entries 9−14). In an attempt to improve the yield and selectivity of the reaction, we varied the loading of $BF_3{\cdot}OEt_2$ (entries 15–18). Delightfully, when the reaction

Table 17: Optimization for Friedel–Crafts alkylation reaction[a]



entry	reagent (equiv)	solvent	time	dr[b]	yield[c] **98** (%)
1	I_2 (1)	EtOH	24 h	–	nr
2[d]	I_2 (1)	EtOH	24 h	–	nr
3	*p*-TSA·H_2O (1)	EtOH	24 h	–	nr
4[d]	*p*-TSA·H_2O (1)	EtOH	24 h	–	nr
5	I_2 (1)	DCM	1 h	84:16	81
6	*p*-TSA·H_2O (1)	DCM	1 h	–	traces
7	TFA (1)	DCM	2 h	–	nr
8	$FeCl_3$ (1)	DCM	24 h	85:15	56
9	BF_3·OEt_2 (1)	DCM	1 h	84:16	91
10	BF_3·OEt_2 (1)	ACN	1 h	89:11	86
11	BF_3·OEt_2 (1)	DCE	1 h	86:14	85
12	BF_3·OEt_2 (1)	THF	1 h	84:16	52
13	BF_3·OEt_2 (1)	Toluene	1 h	–	73
14	BF_3·OEt_2 (1)	EtOH	24 h	–	nr
15	BF_3·OEt_2 (1.2)	DCM	2 min	85:15	94
16	BF_3·OEt_2 (1.5)	DCM	2 min	81:19	92
17	BF_3·OEt_2 (0.5)	DCM	1 h	83:17	76
18[e]	BF_3·OEt_2 (1.2)	DCM	24 h	86:14	82

[a] Reaction conditions: **93** (0.2 mmol), **8c** (0.22 mmol), solvent (1 mL).

[b] Diastereomeric ratio was determined by ^{1}H NMR of the crude product.

[c] Yield of isolated product. nr: no reaction.

[d] Temperature: 80 °C

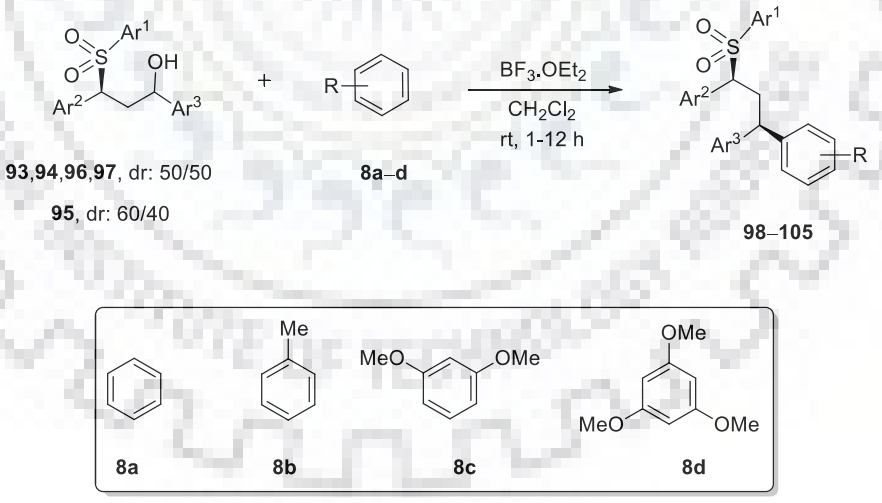
[e] Temperature: 0 °C.

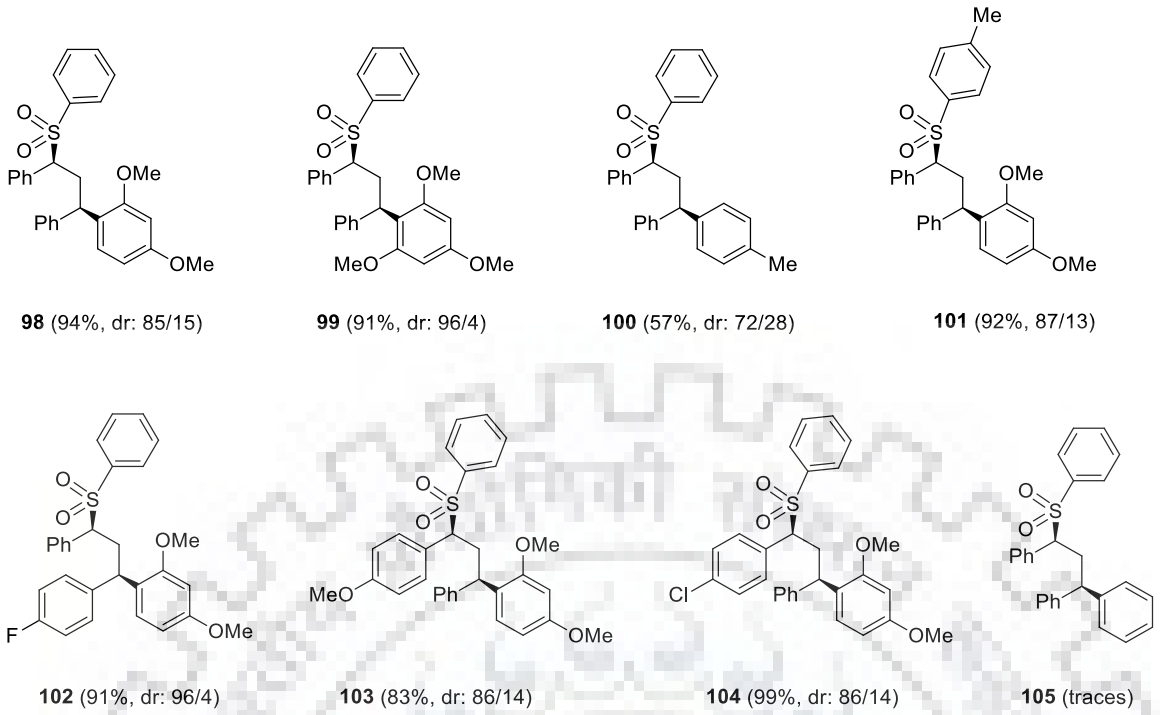
is carried out with 1.2 equiv of BF_3·OEt_2, we observed an increase in the yield with 85:15 diastereomeric ratio (entry 15). Further, increase in the amount of BF_3·OEt_2 from 1.2 to 1.5 equiv had no significant improvement in the yield of the reaction (entry 16). By decreasing

the amount of $BF_3 \cdot OEt_2$ from 1.2 to 0.5 equiv, resulted in the reduced efficiency (entry 17). No appreciable advancement in selectivity was observed despite lowering the temperature to 0 ^oC (entry 18).

2.2.4.2. Friedel–Crafts (F–C) alkylation reaction

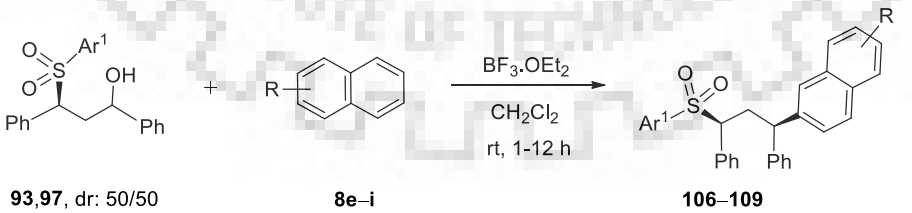
Having established optimum reaction conditions in hand, various electron-rich arenes **8** and γ-hydroxysufones **93**–**97** were then tested to understand the versatility of this synthetic protocol. At the outset, the successful alkylation reaction of secondary alcohols **93**–**97** with a series of aromatic systems **8a**–**d** bearing electron-donating substituents afforded the corresponding products **98**–**109** in good to excellent yields and good diastereoselectivity (Schemes 43 and 44). As shown, the reactions of 1,3-dimethoxybenzene (**8c**) and 1,3,5-trimethoxybenzene (**8d**), with differently substituted benzylic alcohols **93**–**97** proceeded smoothly, and the corresponding alkylated products **98**–**104** were obtained in good diastereoselectivity and excellent yields. The moderate yield and diastereoselectivity of product **100** may be attributed to low nucleophilicity and inadequate steric encumbrance of toluene (**8b**) for stereodifferentiation in dehydrative coupling reaction compared to that of **8c** and **8d**. The dehydrative coupling of **93** with benzene **8a** was not successful to furnish product **105** (Scheme 43).

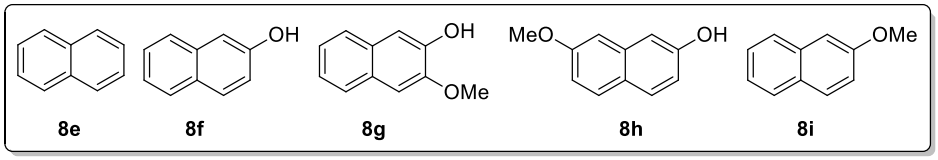


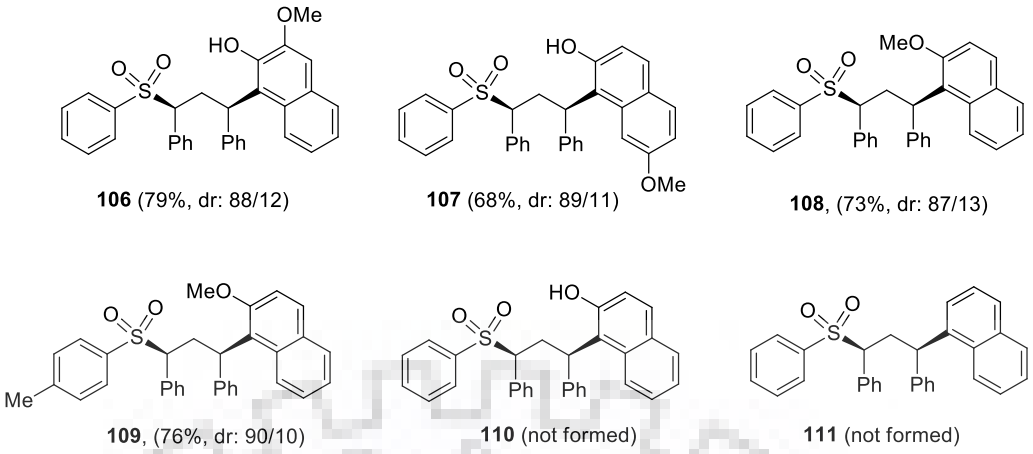


Scheme 43: Substrate scope for DH-alkylation for C−C bond formation.

The dehydrative alkylation of **93** with naphthalene **8e** was not fruitful. It is noteworthy that the reaction of **93** did not proceed with β-naphthol **8f** due to its decreased nucleophilicity in the presence of $BF_3{\cdot}OEt_2$. Nevertheless, when substituted naphthols such as 3-methoxy-β-naphthol (**8g**) and 7-methoxy-β-naphthol (**8h**) were subjected to the transformation under standard conditions, the expected products **106** and **107** were isolated in 79 and 68% yields, respectively, with improved diastereoselectivity (Scheme 44). However, the reaction of **93** and **97** with 2-OMe-naphthalene (**8i**) successfully furnished the corresponding products **108** and **109** in 73% and 76% yield, respectively.

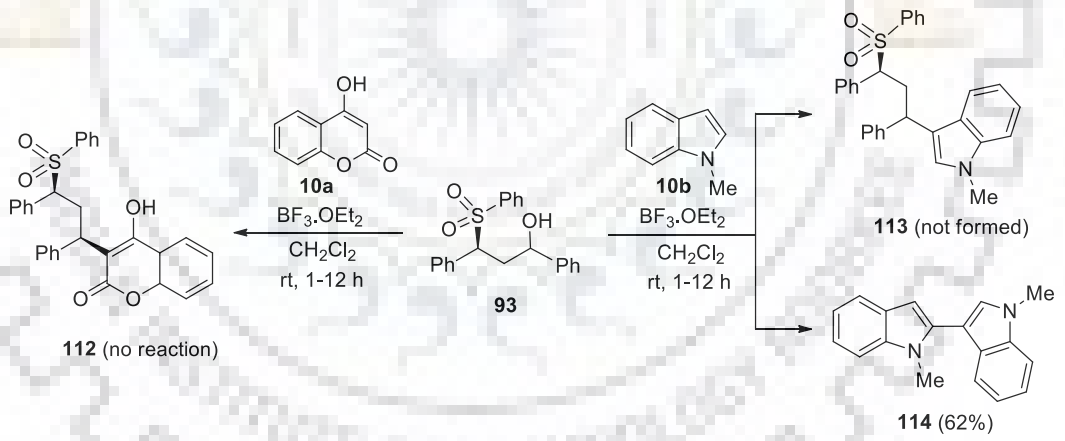






Scheme 44: Substrate scope for DH-alkylation for C−C bond formation.

At this level we attempted to explore the heterocycle 4-hydroxycoumarin **10a**, and *N*-methylindole **10b** for C-alkylation with **93** under established reaction conditions. The reaction did not yield desired products **112** and **113**. Nevertheless in case of *N*-methylindole **10b**, the dimer 1,1'-dimethyl-1*H*,1'*H*-2,3'-bisindole (**114**) was obtained in 62% yield (Scheme 45) [231].



Scheme 45: Substrate scope for DH-alkylation for C−C bond formation.

The products were characterized on the basis of spectroscopic evidence. The connectivities between protons H-1, H-2 and H-3 in **106** were identified by $^{1}H-^{1}H$ COSY and $^{1}H-^{13}C$ COSY experiments, respectively, and 2D NOESY experiments (Figures 8–11) [229,230]. The structure of the major diastereomer of propane derivative **106** was further confirmed from its single crystal X-ray analysis (Figure 12).

In case of C-alkylation, the benzylic protons H-3 and H-1 resonate at δ 4.86−4.83 ppm, and 4.21−4.18 ppm, respectively. C-*H*3 resonates at more deshielded region, while C-*H*1 appeared in shielded region. Further, these chemical shifts were confirmed by 2D experiments. In HMBC experiment of **106**, the proton C-*H*3 displayed correlation with *C*-OH, which conforms its position in ^{1}H NMR (Figure 10). A significant correlation between *H*-1 and *H*-3 was observed in the NOESY experiments of **106** and indicating the *syn*-orientation of these two protons.

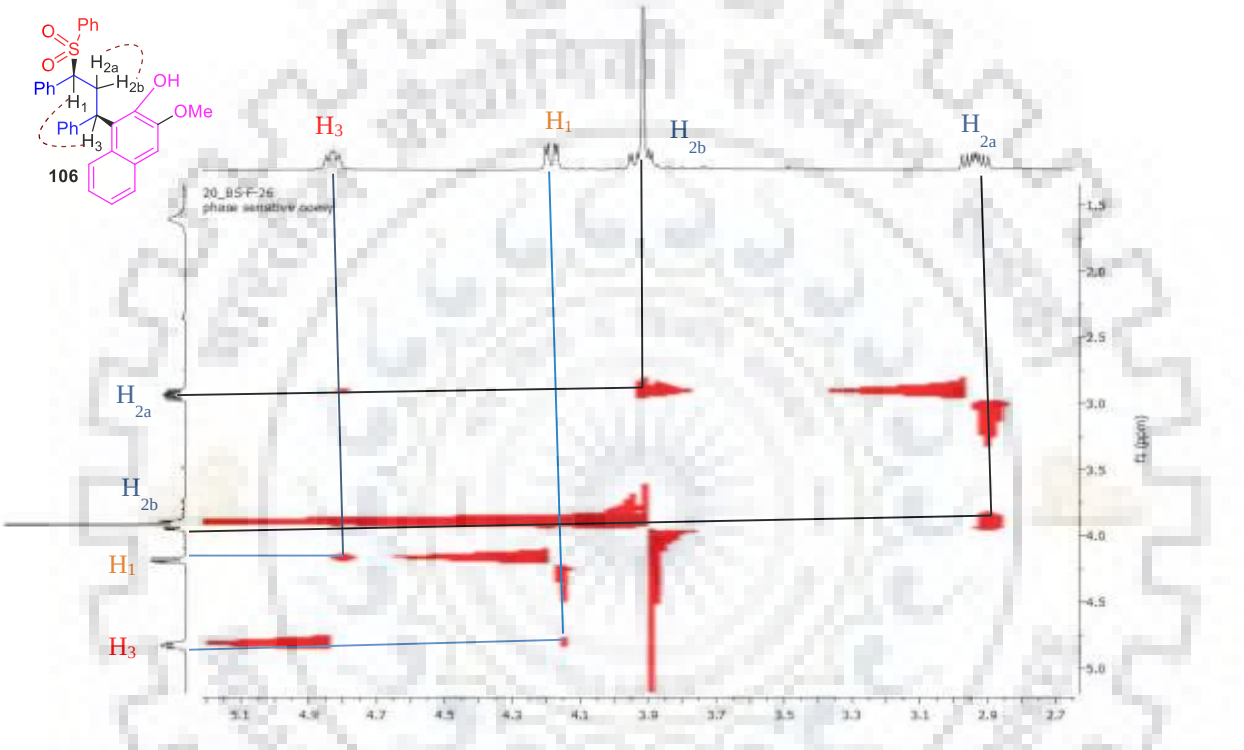


Figure 8: ^{1}H–^{1}H NOESY spectrum of **106**.

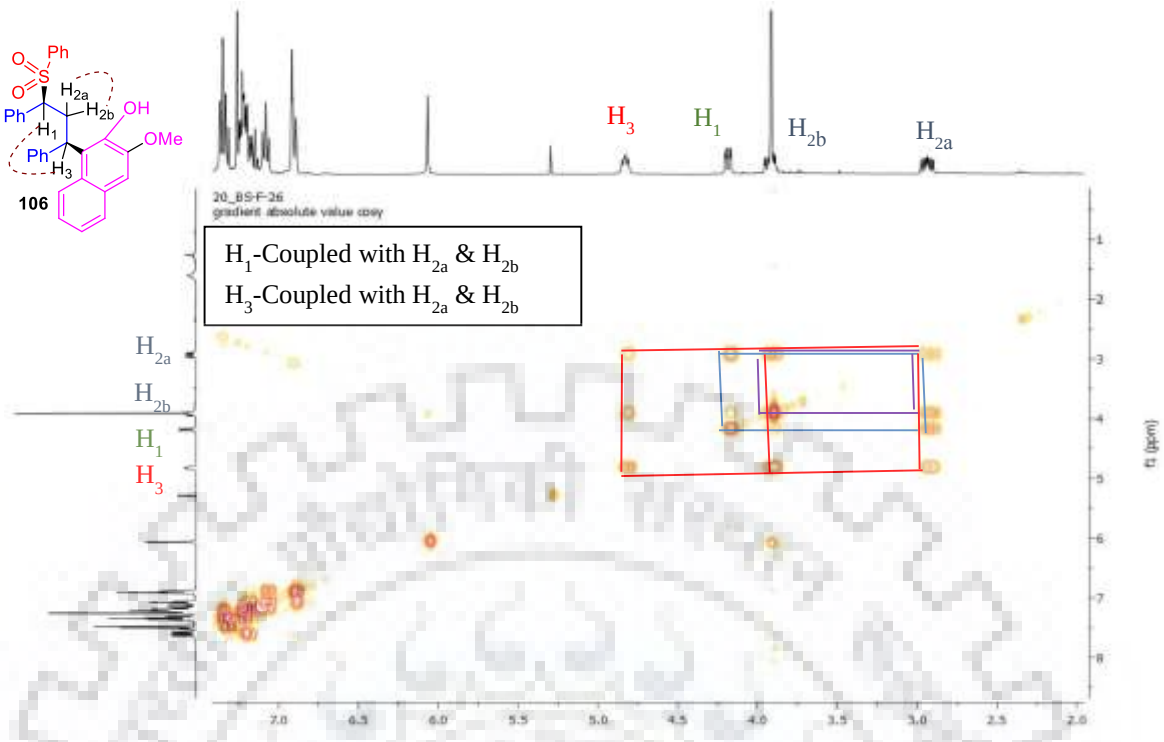


Figure 9: $^{1}H–^{1}H$ COSY spectrum of **106**.

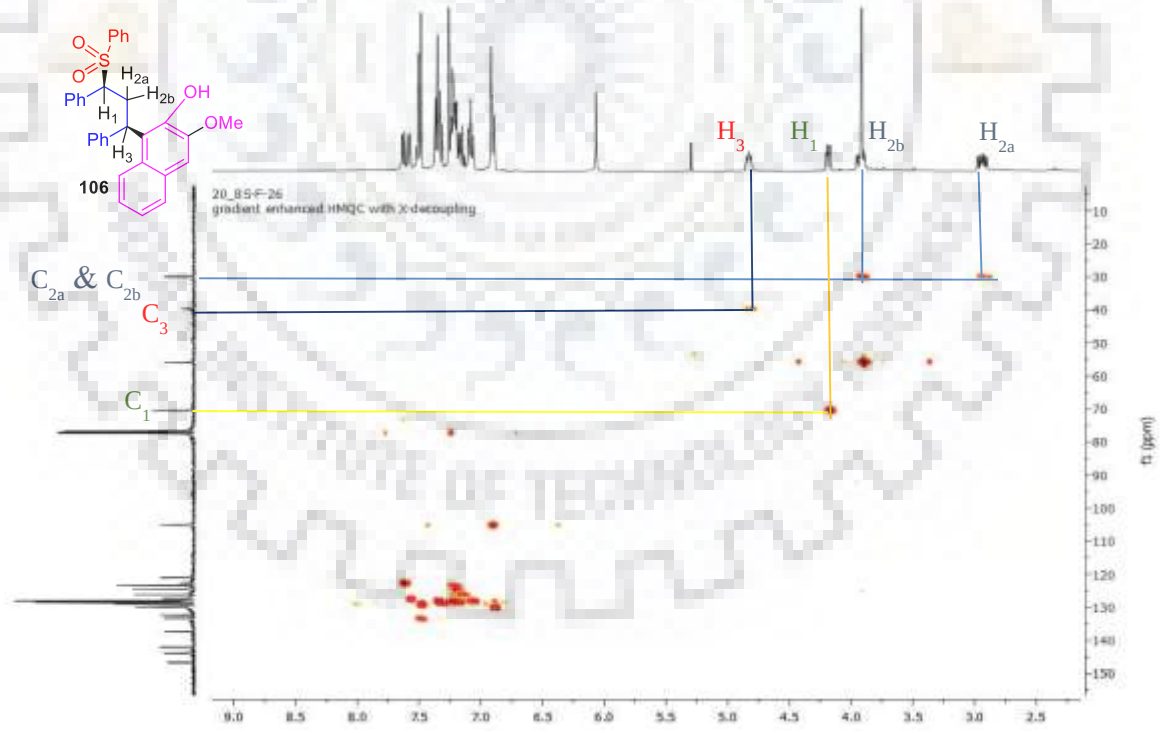


Figure 10: $^{1}H–^{13}C$ HMQC spectrum of **3h**.

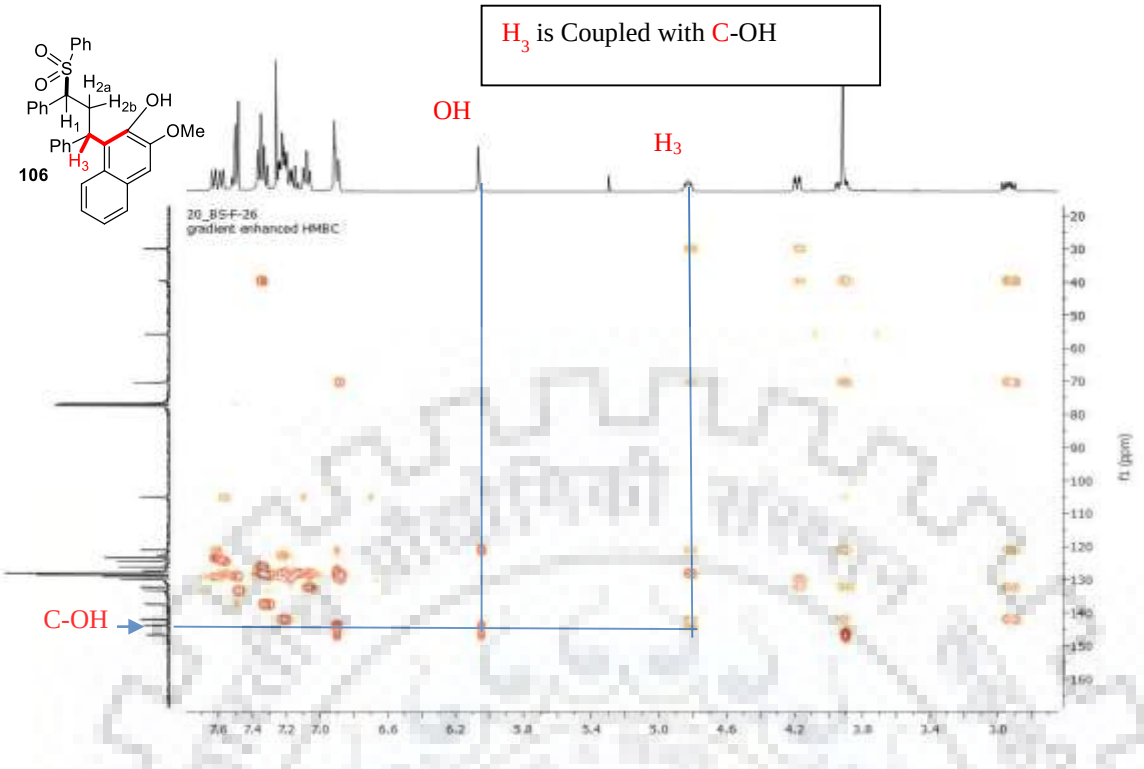


Figure 11: $^{1}H–^{13}C$ HMBC spectrum of **106**.

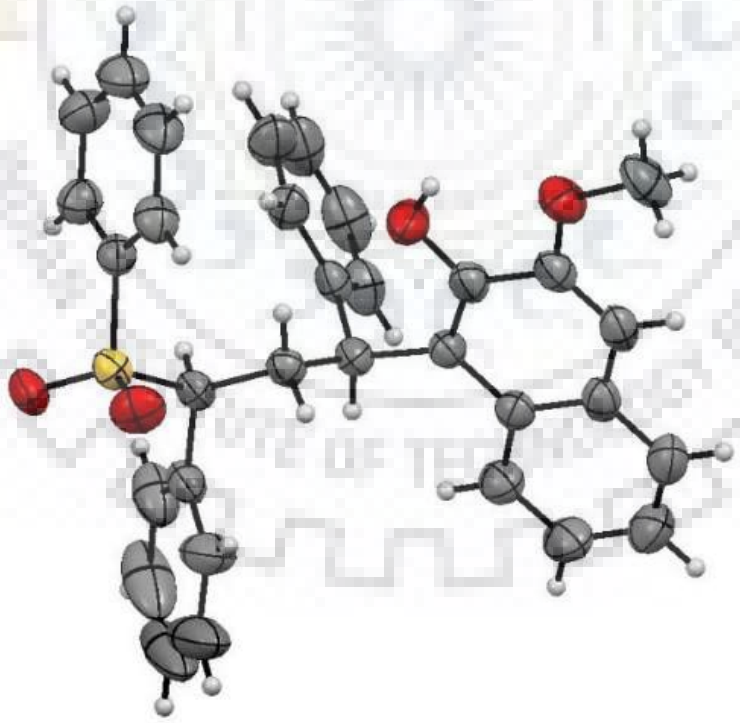


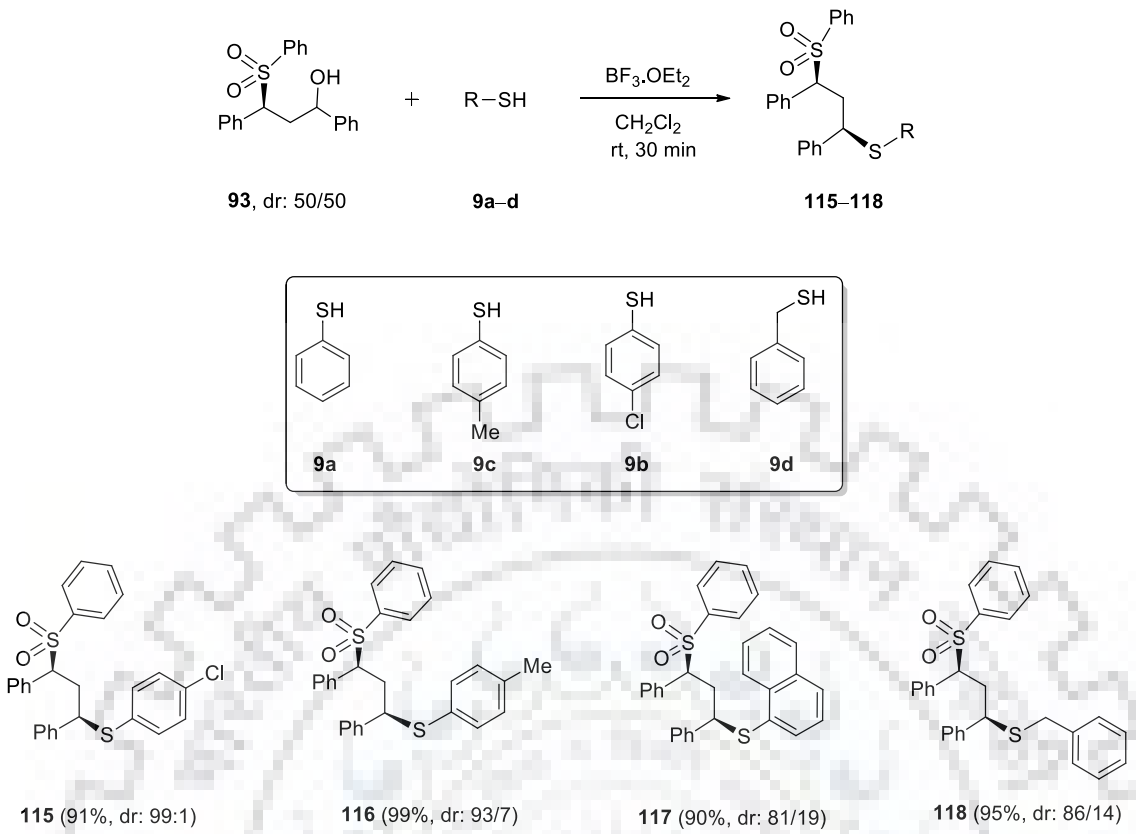
Figure 12: ORTEP Representation of crystal structure of **106**.

Table 18: Crystallographic data for **106**.

Formula	$C_{32}H_{28}O_4S$
Formula Wt.	508.60
Crystal habit	Blocks
Crystal color	Colorless
Crystal system	Triclinic
Space group	P 21/n
a (Å)	11.9576(9)
b (Å)	13.0070(9)
c (Å)	16.7973(12)
α (deg)	90.00
β (deg)	93.290(4)
γ (deg)	90
V (Å^3)	2608.2 (3)
Z	4
D_{calc} (g cm^{-3})	1.295
T (K)	293 K
λ (Mo-Kα)	0.71073
μ (mm^{-1})	0.161
2θ range (deg)	28.3
Limiting indices	$-15 \leq h \geq 15$
	$-17 \leq k \geq 17$
	$-22 \leq l \geq 22$
F(000)	1072.0
No. of Reflns. Measured	6510
No. of Parameters	334
GOF on F^2	0.887
R1 [I>2σ(I)]	0.1185
wR2	0.2303(6487)

2.2.4.3. Dehydrative thiolation of γ-hydroxysulfones

Next, we turned our attention towards exploring the applicability of the reaction for thiols as nucleophiles for the synthesis of novel 1,3-diaryl-1-sulfono-3-sulfane propanes *via* dehydrative nucleophilic substitution reaction. In order to enlarge the scope of thiolation of benzylic alcohol **93** and to demonstrate the versatility of substituted thiophenols **9a**−**d**, we performed reactions under similar conditions. Gratifyingly, the reactions of secondary alcohols **93** with a series of thiophenols **9a**−**d** provided the expected 1,3-diaryl-1-sulfono-3-sulfane propanes **115**−**118** in high to excellent yields (86−99%) with good diastereoselectivity as shown in Scheme 46.



Scheme 46: Substrate scope for DH-thiolation for C−S bond formation.

The connectivities between protons H-1, H-2 and H-3 in **116** were identified by 2D NOESY experiment (Figures 13). In case of S-alkylation, the benzylic protons H-3 and H-1 resonate at δ 3.76−3.23 ppm, respectively. A significant correlation between *H*-1 and *H*-3 was observed in the NOESY experiments of **116** indicating the *syn*-orientation of these two protons.

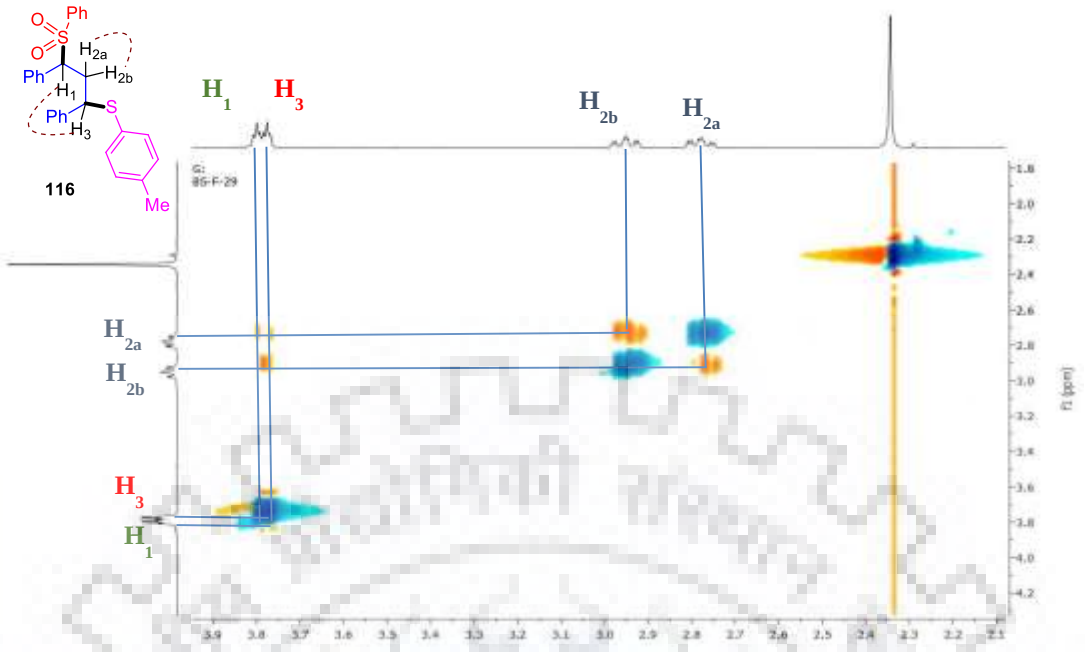
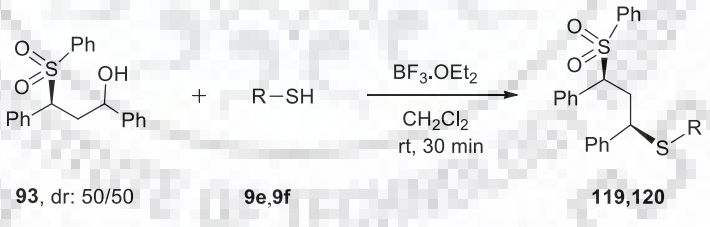
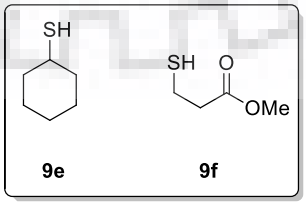
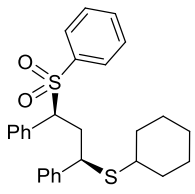


Figure 13: ^{1}H–^{1}H NOESY spectrum of **116**.

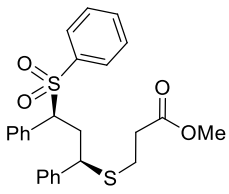
The reactions of **93** were conducted with cyclohexanethiol (**9e**) and methyl-3-mercaptopropionate (**9f**) to furnish the cyclohexyl thioether **119** and methyl propionate thioether **120** in 94% and 92% yields, respectively. Significantly, the obtained results showed similar diastereoselectivity. It is noteworthy to mention here that in 2006, Carter employed phenyl-(3-(phenylsulfonyl)propyl)-sulfane for the synthesis of toxin azaspiracid-1 (Scheme 47) [228].







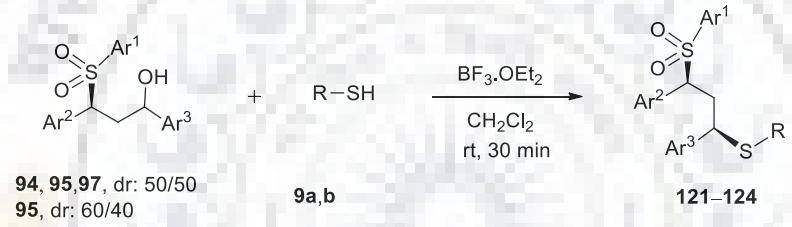
119 (94%, dr: 89/11)



120 (92%, dr: 79/21)

Scheme 47: Reaction of **93** with thiols **9e**,**f**.

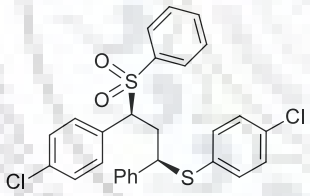
In order to study the substitution effect on γ-hydroxysulfones **94**–**97**, we performed reaction with chosen thiophenols **9a**,**b** under established conditions. Considerably, in all the cases reactions were reached completion in 30 min to provide the corresponding sulfonylpropanes derivatives **121–124** in high to excellent yields and the attained results displayed decent diastereoselectivity (Scheme 48).



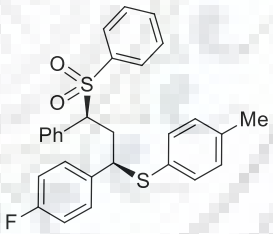
94, **95**,**97**, dr: 50/50
95, dr: 60/40

9a,**b**

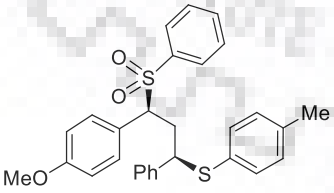
121–**124**



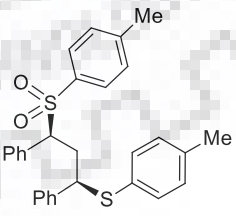
121 (86%, dr: 86/14)



122 (99%, dr: 86/14)



123 (96%, dr: 88/12)

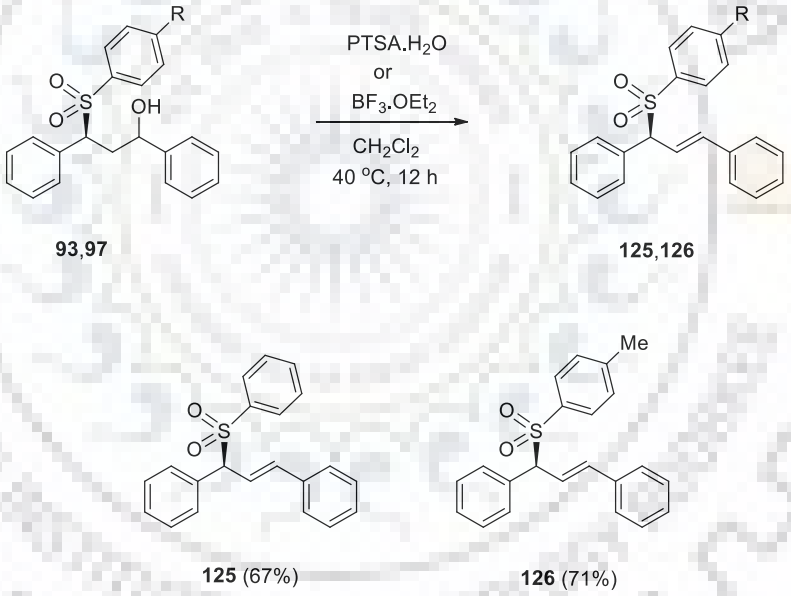


124 (98%, dr: 89/11)

Scheme 48: Substrate scope for DH-thiolation.

2.2.4.4. Synthesis of allylic sulfones

During our optimization studies, when we conducted the reaction of **93** with **8c** in the presence of $BF_3 \cdot OEt_2$ at 40 ^oC, α,β-unsaturated sulfono derivative **125** was obtained *via* dehydrative elimination process instead of arylated product **98** (Scheme 44). We anticipated that it would be possible to build allylic sulfones **125** and **126**, through dehydrative elimination process wherein the hydroxyl function of γ-hydroxysulfone **93**,**97** serves as an effective leaving group. Thus the dehydration of **93**,**97** in the presence of $BF_3.OEt_2$ or *p*-$TSA.H_2O$ furnished allylic sulfones **125** and **126**, respectively, in good yields (Scheme 50). Allylic sulfones are versatile building blocks and display interesting biological activities such as anticancer agents (Figure 7) [101,232–234]. It is worth mentioning here that very recently Loh co-workers described water-promoted C–S bond formation reactions from direct substitution of Morita–Baylis–Hillman alcohol with sulfinate salts to produce allylic sulfones [130].



Scheme 49: Substrate scope for DH-elimination for allylic sulfone formation.

Depending upon the diastereoselectivity obtained in the current protocol, these reactions outwardly promote *via* dehydrative mechanism as depicted in Scheme 50. Initially, $BF_3 \cdot OEt_2$ activates γ-hydroxysulfone **93** to generate benzylic carbocation **W** and **X**. Next, the planar carbocation triggers the nucleophilic attack by **8** or **9**, majorly on sterically less hindered side, for C−C or C−S bond formation leading to a mixture of diastereomers. Then we turned our attention to understand the reaction mechanism. After fixing the stereochemistry at the sulfone substituted carbon (C-1), we performed DFT single point energy calculations in solvent phase for the intermediate structures **W** and **X**. The DFT calculation suggested that the nucleophilic attack on species **W** (ΔE = 0.0) in *anti*-fashion is less favorable which leads to minor diastereomers **98′** and **115′** and attack on species **X** (ΔE = −10.94) in *syn*-fashion is more favorable which leads to major diastereomers **98** and **115**. These results supported the expemental findings (Figure 14, Tables 19 and 20).

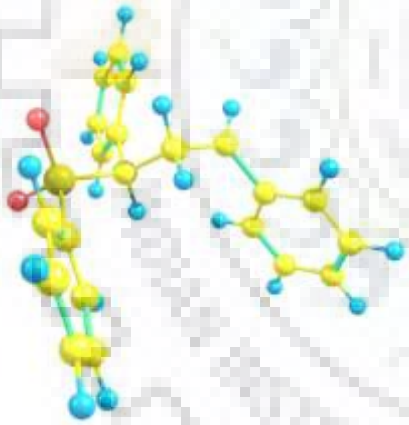
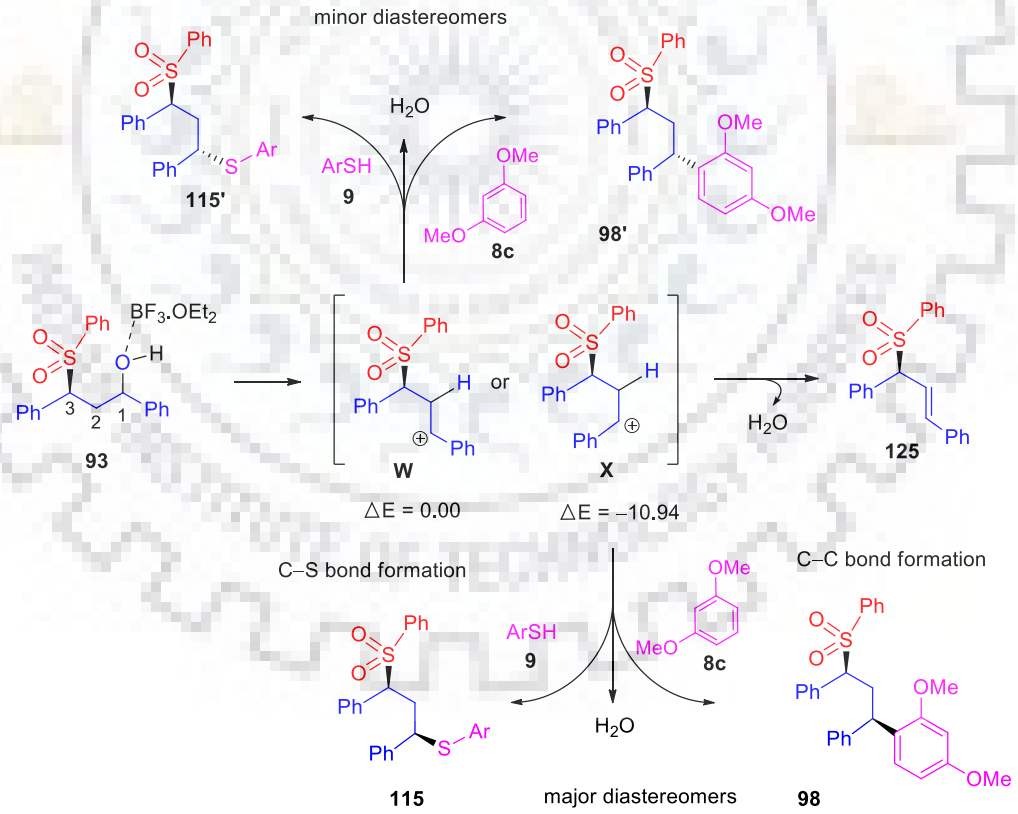
Intermediate **W** *anti*-face attack to sulfone group	Proposed intermediate **X** *syn*-face attack to sulfone group
	
ΔE = 0.0 kcal/mol	ΔE = −10.9412 kcal/mol

Figure 14: Single point electronic energy, for the intermediate structures **W** and **X**.

Table 19. Single point electronic energy, E (in Hartree) for the structures of intermediate **W** and **X** for alkylation step of substitution reaction calculated at M06/6-311+G(d,p)//B3LYP/6-311G** level of theory using CPCM solvation model, with DCM solvent.		
Pathway	Energy	Intermediate **A**
anti-face attack	E	−1359.4590632
syn-face attack	E	−1359.4764991

Table 20. Single point electronic energy, E (in kcal/mol) for the structures of intermediate **W** and **X** for alkylation step of substitution reaction calculated at M06/6-311+G(d,p)//B3LYP/6-311G** level of theory using CPCM solvation model, with DCM solvent.		
Pathway	Energy	Intermediate **A**
anti-face attack	ΔE	0.00
syn-face attack	ΔE	−10.9412



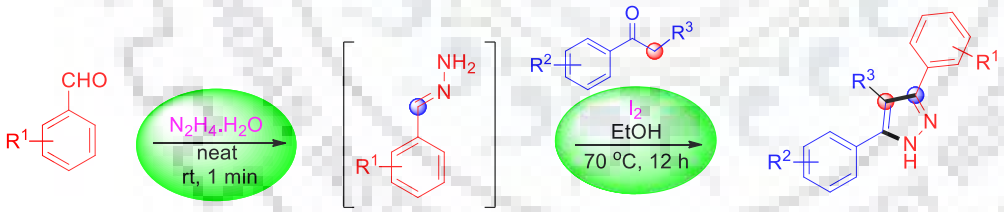
Scheme 50: Plausible mechanism for dehydrative coupling reactions.

2.3. CONCLUSIONS

In summary, we have developed several protocols for the production of C–C, C–N bonds *via* diaza-Nazarov cyclization reactions and C–S bond through oxidative coupling using iodine as promoter in environmental benign conditions. We have explored the theortical investigation for regioselectivities of diaza-Nazarov cyclization. We have also studied the dehydrative C-alkylation and S-alkylation reactions.

Synthesis of pyrazoles via diaza-Nazarov (DAN) cyclization and theoretical investigations

We have described the first examples of diaza-Nazarov cyclization employing *in situ* generated hydrazones and acetophenones. This iodine-mediated expedient process furnished functionally-rich pyrazoles in ethanol under aerobic conditions. The cascade reaction for the pyrazole formation proceeds through enamine-imino diaza-Nazarov 4π-electrocyclization. The title five-membered heterocycles are accessed in good to high yields from a one-pot three-component protocol under mild conditions. The simplicity of the experimental procedure and the ready accessibility of starting materials thus render this an experimentally attractive method for the preparation of the nitrogenous heterocycles. Computational studies predicted that the cyclization of 1,5-DAP cation is most favourable pathway than 1,6- and 1,7-cyclizations and hence supporting the experimental results obtained through DAN pathway.

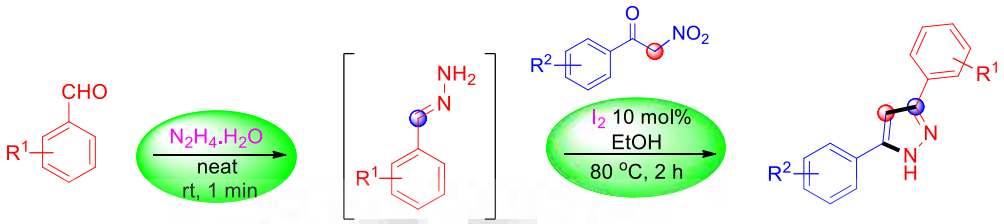


Scheme 51: Synthesis of polysubstituted pyrazoles from DAN cyclization.

Synthesis of pyrazoles via denitrative-imino-diaza-Nazarov (DIDAN) cyclization

We have delineated the unprecedented iodine-catalyzed denitrative-imino-diaza-Nazarov cyclization for the synthesis of pyrazoles using *in situ* generated hydrazones and α-nitroacetophenones. This one-pot, three-component protocol provided the pyrazoles in good to excellent yields under eco-friendly conditions. The course transformation carried out through enamine–imino diaza-Nazarov 4π-electrocyclization. This straightforward protocol

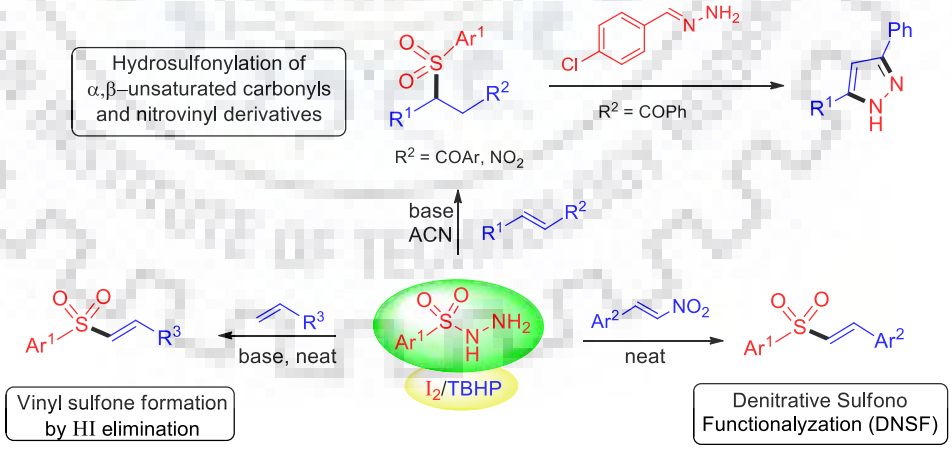
and the easily accessibility of precursors facilitates a practically attractive technique for the construction of the nitrogenous heterocycles.



Scheme 52: Synthesis of disubstituted pyrazoles from DIDAN cyclization.

Synthesis of vinyl sulfones and hydrosulfonylation of chalcones

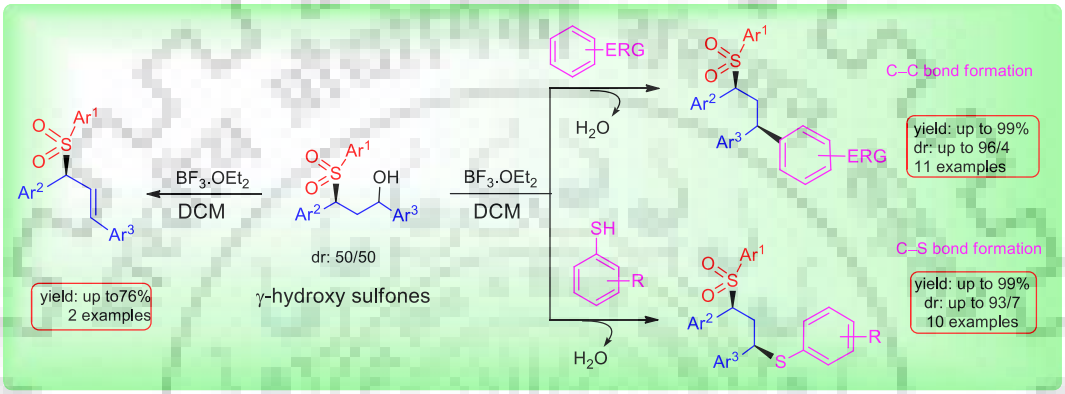
The synthesis of vinylsulfones through the denitrative sulfone functionalization (DNSF) of β-nitrostyrenes and arylsulfonyl hydrazides has been developed under metal-free conditions. A rapid protocol for the sulfonylation of styrenes and olefins that contain electron-withdrawing groups has also been realized. Moreover, we have developed an efficient and expedient hydrosulfonylation method that can be applied for chalcones and β-nitrostyrenes. There are two possible pathways leading to different products that are provided from the same precursors. The base serves an important role. The ecofriendly and rapid C(sp^2)–SO_2 and C(sp^3)–SO_2 bond forming methods developed herein may be helpful in the expansion of the scope of sulfonylation chemistry.



Scheme 53: Metal-free sulfonylation of α,β-unsaturated systems by using sulfonyl hydrazides.

Synthesis of sulfonylpropane derivatives by dehydrative substitution of γ-hydroxysufones

We described Lewis-acid mediated dehydrative arylation and thiolation of easily accessible γ-hydroxysufones *via* nucleophilic substitution reaction to provide a number of novel 1-sulfonylpropanes. The presented environmentally benign and metal-free protocol works under mild conditions and obviates the use of toxic alkyl halides to furnish a wide variety of unsymmetrical 1,1- and 3,3-branched propanes in high to excellent yields with good diastereoselectivity through C−C and C−S bonds construction.



Scheme 54: Dehydrative C- and S-alkylations access to highly substituted 1-sulfonylpropanes.

3.1. GENERAL REMARKS

The reactions associated with the formation of gasses and applications of heat were performed in a well-ventilated hood for safety reasons. Moisture sensitive reactions were carried out by using guard tube filled with either blue silica gel or calcium chloride. Reagents and solvents were transferred under nitrogen using syringes or cannulae, whenever required.

3.1.1. Solvents

The solvents for anhydrous reactions were dried and purified according to standard techniques

Acetonitrile	Distilled over P_2O_5
CH_2Cl_2	Distilled over P_2O_5
DCE	Distilled over P_2O_5
DMSO	Purchased from S. D. Fine chemicals and used as such
EtOH	Distilled from magnesium cake
MeOH	Distilled from magnesium cake
THF	Distilled from Na/benzophenone ketyl radical

3.1.2. Chemicals

The chemicals were purchased from the companies Sigma-Aldrich, Alfa-Aesar, Avra, Hi-media and S. D. Fine chemicals at the highest purity grade available and were used without further purification, unless otherwise stated.

3.1.3. Determination of the physical properties of the synthesized compounds

^{1}H NMR Spectroscopy

^{1}H NMR Spectra were recorded on Brüker AMX-500 instrument (500 MHz) and JEOL Delta-400 instrument (400 MHz). Chemical shifts are given in ppm relative to tetramethylsilane (δ 0.00). Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), DMSO (δ 2.50 ppm) or with tetramethylsilane (TMS, δ 0.00 ppm) as

the internal standard. Coupling patterns are described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), dt (doublet of triplet), td (triplet of doublet), dd (doublet of doublet), m (multiplet), br (broad). Coupling constants are given in Hertz.

^{13}C NMR Spectroscopy

^{13}C NMR Spectra were recorded on Brüker AMX-500 spectrometer (125 MHz) and JEOL Delta-400 instrument (100 MHz). Chemical shifts are given in ppm and referenced to $CDCl_3$ (δ 77.0 ppm, the middle peak) and DMSO (δ 39.5 ppm, the middle peak).

IR Spectroscopy

IR Spectra were measured on a Perkin-Elmer spectrometer as KBr pellets or neat (in case of liquid compounds). Only characteristic absorption bands were reported. Absorptions are given in wave numbers (cm^{-1}).

Mass Spectrometry

High resolution mass spectra (HRMS) were recorded on Brüker micrOTOF™-Q II mass spectrometer (ESI–MS) using electron spray ionization.

Melting Points

Melting points were measured in open glass capillaries with Perfit and Opti Melt automated melting point apparatus and is uncorrected.

3.1.4. X-Ray crystallographic

Single crystal data of products were collected on X-ray diffractometer using graphite monochromated MoKα radiation (λ = 0.71070 Å) at 296 K.

3.1.5. Chromatographic Methods

Preparative Column Chromatography

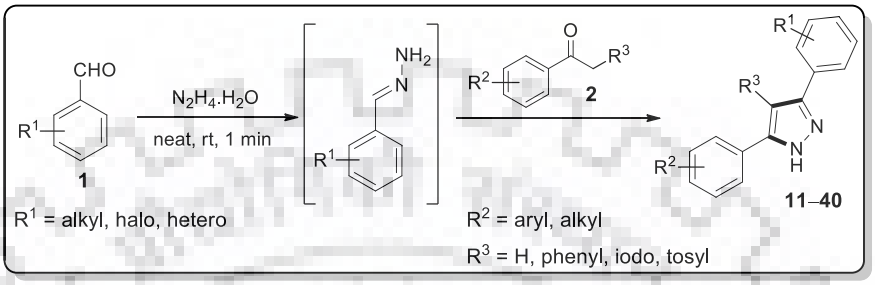
Purification by gravity column chromatography was carried out on glass column (10–50 mm diameter) using silica gel with 100–200 mesh.

Thin Layer Chromatography

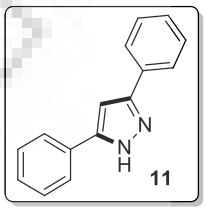
Thin layer chromatography was performed on Merck pre-coated 0.25 mm silica gel plates (60F-254) using UV light as visualizing agent and/or iodine as developing agent.

3.2. SYNTHETIC PROCEDURES

3.2.1. General procedure for the synthesis of substituted pyrazoles 11–40:



To a benzaldehyde derivative **1** (0.6 mmol) was added hydrazine hydrate (80% in water, 0.020 g, 1.0 mmol) under solvent-free conditions. After the addition of hydrazine hydrate, a yellow solid was formed within a minute which indicated the formation of the hydrazone derivative. To the thus formed hydrazone derivative was added acetophenone derivative **2** (0.5 mmol) in EtOH (3 mL) followed by iodine (0.154 g, 1.2 mmol). Then the reaction mixture was refluxed at 70 °C on a pre-heated oil bath for 12 h. After completion of the reaction, as checked by TLC, the reaction was quenched with a saturated sodium thiosulfate solution and extracted twice with ethyl acetate (2 × 15 mL). The organic layer was washed with water and dried over anhyd. sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography using ethyl acetate in hexanes as the eluent to afford a pure pyrazole derivative **11**–**40**.



3,5-Diphenyl-1*H*-pyrazole (11):

Reaction time: 12 h.

Yield: 0.091 g (82%) as a brown solid.

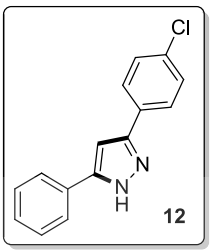
MP: 218–219 °C.

IR (KBr): ν_{max} 3443, 1636, 1489, 1386, 1309, 1259, 1180, 1088, 1021, 968, 826 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.50 (m, 4H), 7.46–7.07 (m, 4H), 7.04–7.01 (m, 2H), 6.58 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 130.9, 127.9, 127.0, 124.6, 98.5ppm.

3-(4-Chlorophenyl)-5-phenyl-1*H*-pyrazole (12):



Reaction time: 12 h.

Yield: 0.096 g (76%) as a brown solid.

MP: 218–219 °C.

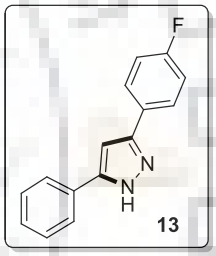
IR (KBr): ν_{max} 3443, 1636, 1489, 1386, 1309, 1259, 1180, 1088, 1021, 968, 826 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.85 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7 (d, $1J_{C,F}$ = 113 Hz), 135.3, 130.0, 128.5, 128.1, 127.4, 124.9, 124.8, 122.2, 99.3 ppm.

HRMS (ESI+): *m/z* calcd for $C_{15}H_{12}ClN_2$ $[M + Na]^+$: 255.0689, found: 255.0686.

3-(4-Fluorophenyl)-5-phenyl-1*H*-pyrazole (13):



Reaction time: 12 h.

Yield: 0.084 g (71%) as a brown solid.

MP: 189–190 °C.

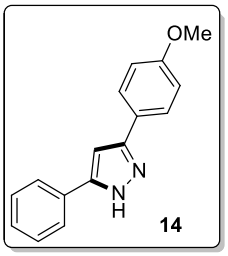
IR (KBr): ν_{max} 3443, 1620, 1510, 1467, 1444, 1304, 1253, 1181, 1029, 987, 865 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.23 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d6): δ 128.8, 126.8, 125.1, 99.9 ppm.

HRMS (ESI+): *m/z* calcd for $C_{15}H_{12}FN_2$ $[M + Na]^+$: 239.0979, found: 239.0950.

3-(4-Methoxyphenyl)-5-phenyl-1*H*-pyrazole (14):



Reaction time: 15 min.

Yield: 0.087 g (70%) as a brown solid.

MP: 155–156 °C.

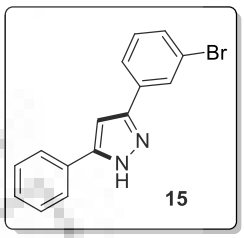
IR (KBr): ν_{max} 3443, 1620, 1510, 1467, 1444, 1304, 1253, 1181, 1029, 987, 865 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 6.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.32–7.30 (m, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.73 (s, 1H) 3.81 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 131.4, 128.7, 128.0, 126.8, 125.5, 123.8, 114.1, 99.4, 55.2 ppm.

HRMS (ESI+): *m/z* calcd for $C_{16}H_{15}N_2O$ $[M + Na]^+$: 251.1179, found: 251.1178.

3-(3-Bromophenyl)-5-phenyl-1*H*-pyrazole (15):



Reaction time: 15 min.

Yield: 0.099 g (67%) as a brown solid.

MP: 155–156 °C.

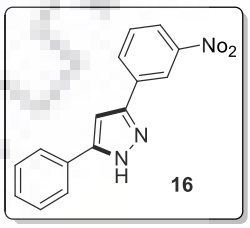
IR (KBr): ν_{max} 3456, 2360, 1637, 1503, 1442, 1371, 1312, 1079, 976 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 (d, *J* = 6.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.32–7.30 (m, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.73 (s, 1H) 3.81 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO- d_6): δ 159.5, 131.4, 128.7, 128.0, 126.8, 125.5, 123.8, 114.1, 99.4, 55.2 ppm.

HRMS (ESI+): *m/z* calcd for $C_{16}H_{15}N_2O$ $[M + Na]^+$: 251.1179, found: 251.1178.

3-(3-Nitrophenyl)-5-phenyl-1*H*-pyrazole (16):



Reaction time: 15 min.

Yield: 0.108 g (82%) as a brown solid.

MP: 207–209°C.

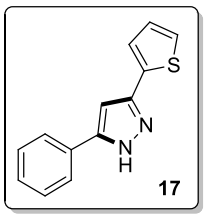
IR (KBr): ν_{max} 3440, 1572, 1533, 1506, 1446 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 3H), 7.26 (dd, *J* = 5.6 Hz, 7.6 Hz, 2H), 7.01 (t, *J* = 4.4 Hz, 1H), 6.74 (t, *J* = 4.4 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 129.1, 127.4, 126.6, 126.2, 124.0, 123.1, 122.3, 122.1, 98.0 ppm.

HRMS (ESI+): *m/z* calcd for $C_{13}H_{11}N_2S$ $[M + Na]^+$: 227.0637, found: 227.0619.

5-Phenyl-3-(thiophen-2-yl)-1*H*-pyrazole (17):



Reaction time: 12 h.

Yield: 0.065 g (58%) as a brown solid.

MP: 207–209°C.

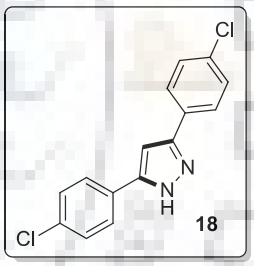
IR (KBr): ν_{max} 3415, 1577, 1487, 1404, 1174, 844, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 13.63 (brs, 1H, NH), 8.67 (s, 1H), 8.30 (d, *J* = 7.5 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.48 (t, J = 7.0 Hz, 2H), 7.43 (s, 1H) 7.37 (t, *J* = 7.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 147.0, 133.1, 129.9, 128.9, 128.4, 127.4, 126.7, 124.0, 123.7, 120.5, 118.4, 98.6 ppm.

HRMS (ESI+): *m/z* calcd for $C_{15}H_{12}N_3O_2$ $(M + H)^+$: 266.0924, found: 266.0921.

3,5-Bis(4-chlorophenyl)-1*H*-pyrazole (18):



Reaction time: 12 h.

Yield: 0.084 g (58%) as a brown solid.

MP: 240–241 °C.

IR (KBr): ν_{max} 3448, 1638, 1506, 1025, 994, 829 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (d, *J* = 8.4 Hz, 4H), 7.35 (d, *J* = 8.4 Hz, 4H), 6.93 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 144.8, 131.1, 128.5, 127.0, 125.0, 98.0 ppm.

HRMS (ESI+): *m/z* calcd for $C_{15}H_{11}Cl_2N_2$ $[M + Na]^+$: 289.0294, found: 289.0298.

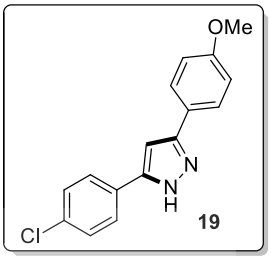
5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole (19):

Reaction time: 12 h.

Yield: 0.086 g (61%) as a brown solid.

MP: 157–159 °C.

IR (KBr): ν_{max} 3425, 2911, 1615, 1508, 1450, 1254, 1074, 821 cm^{-1}.

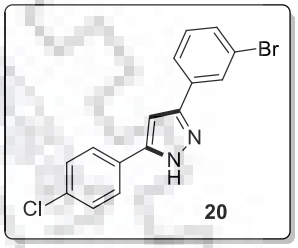


^{1}H NMR (400 MHz, DMSO-d_6): δ 13.27 (brs, 1H, NH), 7.85 (d, *J* = 5.5 Hz, 2H), 7.74 (d, *J* = 6.5 Hz, 2H), 7.49 (s, 2H), 7.09 (s, 1H), 7.02 (d, *J* = 6.5 Hz, 2H), 3.79 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.1, 128.9, 128.7, 126.7, 126.5, 114.3, 99.0, 55.1 ppm.

HRMS (ESI+): *m/z* calcd for $C_{15}H_{11}C_{l2}N_2$ $[M + Na]^+$: 289.0294, found: 289.0298.

3-(3-Bromophenyl)-5-(4-chlorophenyl)-1*H*-pyrazole (20):



Reaction time: 12 h.

Yield: 0.109 g (66%) as a brown solid.

IR (KBr): ν_{max} 3478, 3413, 1625, 1490, 1365, 629 cm^{-1}.

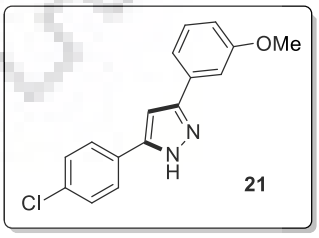
MP: 202–203 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 13.52 (brs, 1H, NH), 8.05 (s, 1H), 7.85 (s, 3H), 7.52–7.41 (m, 4H), 7.32 (d, *J* = 3.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 131.0, 128.9, 127.5, 126.7, 124.0, 100.6 ppm.

HRMS (ESI+): *m/z* calcd $C_{15}H_{11}BrClN_2$ $[M + Na]^+$: 334.9769, found: 334.9770.

5-(4-Chlorophenyl)-3-(3-methoxyphenyl)-1*H*-pyrazole (21):



Reaction time: 12 h.

Yield: 0.102 g (72%) as a brown solid.

MP: 165–166 °C.

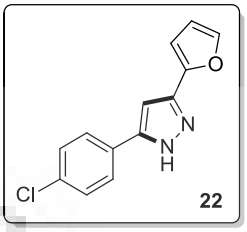
IR (KBr): ν_{max} 3418, 2925, 1621, 1491, 1453, 1300, 1232, 1159, 1062, 994 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ 13.42 (brs, 1H, NH), 7.87 (s, 2H), 7.50–7.36 (m, 5H), 7.23 (s, 1H), 6.92 (s, 1H), 3.82 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.6, 129.9, 128.8, 127.7, 125.1, 117.5, 113.4, 110.4, 99.9, 54.9 ppm.

HRMS (ESI+): *m/z* calcd $C_{16}H_{14}ClN_2$ $[M + Na]^+$: 285.0789, found: 285.0772.

5-(4-Chlorophenyl)-3-(furan-2-yl)-1*H*-pyrazole (22):



Reaction time: 12 h.

Yield: 0.052 g (49%) as a brown solid.

MP: 180–181 °C.

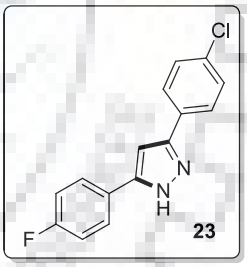
IR (KBr): ν_{max} 3415, 1624, 1471, 1230, 1156, 1094, 611 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.42 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.69 (s, 1H), 6.60 (d, *J* = 3.5 Hz, 1H), 6.45 (d, *J* = 1.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 142.5, 139.4, 134.2, 129.5, 129.0, 128.9, 126.9, 115.5, 107.0, 99.3 ppm.

HRMS (ESI+): *m/z* calcd $C_{13}H_9ClN_2NaO$ $(M+Na)^+$: 267.0296, found: 267.0271.

3-(4-Chlorophenyl)-5-(4-fluorophenyl)-1*H*-pyrazole (23):



Reaction time: 12 h.

Yield: 0.096 g (70%) as a brown solid.

MP: 209–210 °C.

IR (KBr): ν_{max} 3468, 1618, 1508, 1306, 1247, 1174, 1035, 912 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ 713.44 (brs, 1H, N*H*), 7.84 (s. 4H), 7.50 (s, 2H), 7.28 (s, 2H), 7.17 (s, 1H) ppm.

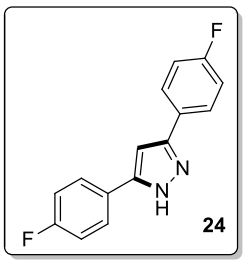
^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 161.8 (d, $1J_{C,F}$ = 245 Hz), 132.7, 128.2, 126.7, 126.6, 126.2, 115.2, 114.9, 98.8 ppm.

HRMS (ESI+): *m/z* calcd $C_{15}H_{11}ClFN_2$ $[M + Na]^+$: 273.0589, found: 273.0589.

3,5-Bis(4-fluorophenyl)-1*H*-pyrazole (24):

Reaction time: 12 h.

Yield: 0.078 g (61%) as a brown solid.



MP: 168–169 °C.

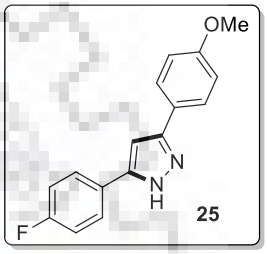
^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 13.41 (brs, 1H, NH), 7.87 (s, 4H), 7.27 (s, 4H), 7.11 (s, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 161.8 (d, $1J_{C,F}$ = 243 Hz), 127.1, 127.1, 115.8, 115.5, 99.5 ppm.

HRMS (ESI+): *m/z* calcd $C_{15}H_{11}F_2N_2$ $[M + Na]^+$: 257.0885, found: 257.0862.

5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole (25):

Reaction time: 12 h.



Yield: 0.088 g (66%) as a brown solid.

IR (KBr): ν_{max} 3470, 1627, 1503, 1450, 1256, 1177, 965 cm^{-1}.

MP: 205–206 °C.

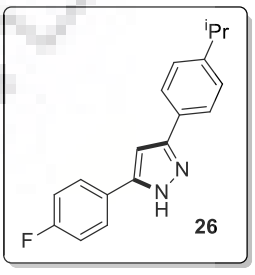
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.57 (q, *J* = 5.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 6.92 (t, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 6.57 (s, 1H), 3.77 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 161.7 (d, 1JC,F = 245 Hz), 159.3, 148.0 (d, 2JC,F = 104), 127.9, 127.1, 123.1, 115.5, 115.4, 114.0, 98.7, 55.0 ppm.

HRMS (ESI+): *m/z* calcd $C_{16}H_{14}FN_2O$ $[M + Na]^+$: 269.1085, found: 269.1087.

5-(4-Fluorophenyl)-3-(4-isopropylphenyl)-1*H*-pyrazole (26):

Reaction time: 12 h.



Yield: 0.077 g (55%) as a brown solid.

MP: 179–181 °C.

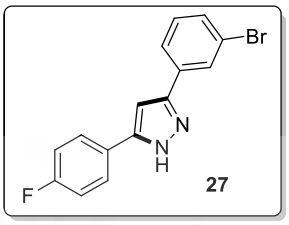
IR (KBr): ν_{max} 3414, 1624, 1450, 1321, 1177, 1024, 832 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 12.13 (brs, 1H, NH), 7.57 (q, *J* = 6.5 Hz, 2H), 7.53 (d, *J* = 10.5 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 11.0 Hz, 2H), 6.61 (s, 1H), 2.88 (sp, *J* = 8.5 Hz, 1H), 1.26 (d, *J* = 9.0 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (d, $1J_{C,F}$ = 246 Hz), 148.7, 148.1 (d, $^2J_{C,F}$ = 35 Hz), 128.1, 127.7, 127.1, 126.7, 125.4, 115.5, 115.3, 99.2, 33.7, 23.7 ppm.

HRMS (ESI+): *m/z* calcd $C_{18}H_{18}FN_2$ $[M + Na]^+$: 281.1449, found: 281.1448.

3-(3-Bromophenyl)-5-(4-fluorophenyl)-1*H*-pyrazole (27):



Reaction time: 12 h.

Yield: 0.106 g (67%) as a brown solid.

MP: 150–151°C.

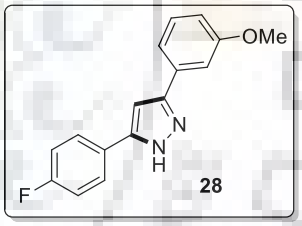
IR (KBr): ν_{max} 3415, 1621, 1495, 1233, 1165, 1091, 968, 826, 773 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ 13.50 (brs, 1H, NH), 7.86 (s, 4H), 7.48–7.13 (m, 5H)ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.8 (d, $1J_{C,F}$ = 244 Hz), 15.6, 143.0, 132.3, 128.8, 127.2, 127.1, 126.4, 115.8, 115.6, 99.8 ppm.

HRMS (ESI+): *m/z* calcd $C_{15}H_{10}BrFN_2$ $(M + Na)^+$: 338.9904, found: 338.9912.

5-(4-Fluorophenyl)-3-(3-methoxyphenyl)-1*H*-pyrazole (28):



Reaction time: 12 h.

Yield: 0.096 g (72%) as a brown solid.

MP: 162–163°C.

IR (KBr): ν_{max} 3415, 1628, 1468, 1165, 1035, 985, 762cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (t, *J* = 5.6 Hz, 2H), 7.46–7.43 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.18 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H) ppm.

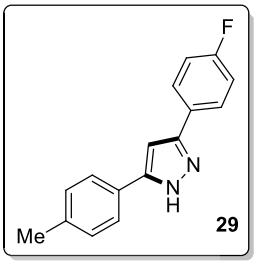
^{13}C NMR (100 MHz, DMSO-d_6): δ 161.8 (d, 1JC,F = 243 Hz), 159.7, 129.9, 127.2, 127.1, 117.6, 115.7, 115.5, 113.4, 110.6, 99.8, 55.1 ppm.

HRMS (ESI+): *m/z* calcd $C_{16}H_{14}FN_2O$ $[M + Na]^+$: 269.1085, found: 269.1088.

3-(4-Fluorophenyl)-5-p-tolyl-1*H*-pyrazole (29):

Reaction time: 12 h.

Yield: 0.084 g (67%)as a brown solid.



MP: 162–163°C.

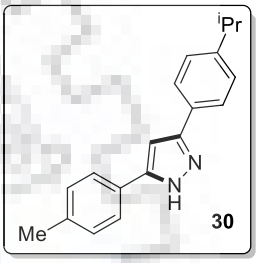
IR (KBr): ν_{max} 3417, 2984, 1629, 1506, 1447, 1177, 959, 785 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 13.31 (brs, 1H, NH), 7.88–7.70 (m, 4H), 7.26 (s, 4H), 7.11 (s, 1H), 2.32 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 161.7 (d, $^1J_{C,F}$ = 243 Hz), 129.3, 127.0, 127.0, 125.0, 115.5, 99.1, 20.7 ppm.

HRMS (ESI+): *m/z* calcd $C_{16}H_{14}FN_2$ $[M + Na]^+$: 253.1136, found: 253.1110.

3-(4-Isopropylphenyl)-5-*p*-tolyl-1*H*-pyrazole (30):



Reaction time: 12 h.

Yield: 0.086 g (65%) as a brown solid.

MP: 182–183 °C.

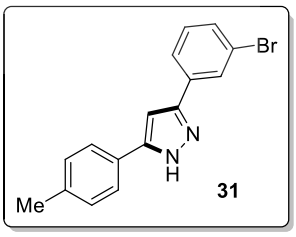
IR (KBr): ν_{max} 3417, 2985, 1629, 1506, 1447, 1177, 959, 785 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.73 (s, 1H), 2.91 (septet, *J* = 6.5 Hz, 1H), 2.35 (s, 3H), 1.27 (d, J = 7.0 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 148.7, 148.5, 137.8, 129.4, 128.8, 128.5, 126.8, 125.6, 125.5, 99.4, 33.8, 23.8, 21.3 ppm.

HRMS (ESI+): *m/z* calcd $C_{19}H_{21}N_2$ $[M + Na]^+$: 277.1699, found: 277.1670.

3-(3-Bromophenyl)-5-*p*-tolyl-1*H*-pyrazole (31):



Reaction time: 12 h.

Yield: 0.100 g (64%) as a brown solid.

MP: 149–151 °C.

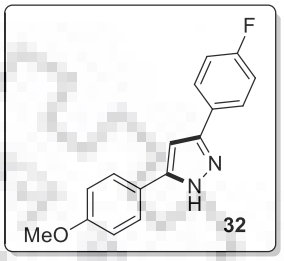
IR (KBr): ν_{max} 3479, 2947, 1629, 1315, 1180, 1024, 991 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 13.42 (brs, 1H, NH), 8.06 (s, 1H), 7.85 (d, *J* = 6.5 Hz, 1H), 7.72 (d, *J* =6.0 Hz,2H), 7.51 (d, *J* =6.0 Hz,1H), 7.40 (t, *J* = 6.5 Hz, 1H), 7.26 (d, *J* = 6.0 Hz, 2H), 7.23 (s, 1H), 2.32 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 137.3, 130.9, 130.2, 129.4, 127.5, 125.0, 124.0, 122.2, 99.8, 20.8 ppm.

HRMS (ESI+): *m/z* calcd $C_{16}H_{14}BrN_2$ $[M + Na]^+$: 313.0335, found: 313.0335.

3-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (32):



Reaction time: 12 h.

Yield: 0.067 g (50%) as a brown solid.

MP: 128–129°C.

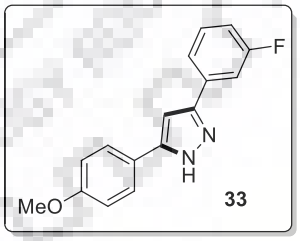
IR (KBr): ν_{max} 3416, 2935, 1625, 1515, 1450, 1241, 1306, 1174, 1032 cm^{-1}

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 13.28 (brs, 1H, NH), 7.89 (t, *J* = 6.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 4.0 Hz, 2H), 7.01 (s, 1H), 3.78 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 161.7 (d, 1JC,F = 243 Hz), 159.1 127.1, 127.0, 126.5, 115.7, 115.6, 114.9, 114.3, 114.2, 98.5, 55.1 ppm.

HRMS (ESI+): *m/z* calcd $C_{16}H_{14}FN_2O$ $[M + Na]^+$: 269.1085, found: 269.1087.

3-(3-Fluorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (33):



Reaction time: 12 h.

Yield: 0.069 g (52%) as a brown solid.

Mp: 131–132 °C.

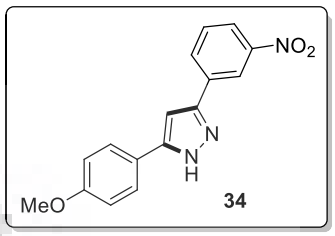
IR (KBr): ν_{max} 463, 2920, 1620, 1510, 1467, 1444, 1304, 1253, 1181, 1029, 987, 865 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 13.39 (brs, 1H, N*H*), 7.77 (d, *J* = 8.5 Hz, 2H), 7.70 (t, *J* = 6.5 Hz, 2H), 7.46 (q, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.0 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 162.6 (d, $1J_{C,F}$ = 241 Hz), 159.1, 134.9, 130.7, 126.5, 123.5, 121.1, 114.2, 114.1, 111.7, 111.5, 99.3, 55.1 ppm.

HRMS: m/z calcd for $C_{16}H_{14}FN_2O$ $[M + Na]^+$: 269.1085, found: 269.1082.

5-(4-Methoxyphenyl)-3-(3-nitrophenyl)-1*H*-pyrazole (34):



Reaction time: 12 h.

Yield: 0.119 g (81%) as a brown solid.

Mp: 209–210 °C;

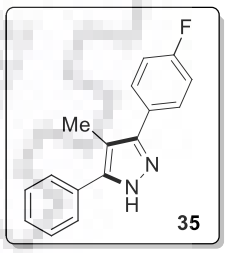
IR (KBr): ν_{max} 415, 2945, 1165, 1098, 1052, 964, 835 cm^{-1}

1H NMR (500 MHz, DMSO-*d*$_6$): δ 13.46 (brs, 1H, N*H*), 8.65 (s, 1H), 8.27 (d, *J* = 7.5 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 3.79 (s, 3H) ppm.

13C NMR (100 MHz, DMSO-*d*$_6$): δ 159.1, 132.1, 128.7, 126.7, 126.5, 114.3, 99.0, 55.1 ppm.

HRMS: m/z calcd for $C_{16}H_{14}N_3O_3$ $[M + Na]^+$: 296.1031, found: 296.1030.

3-(4-Fluorophenyl)-4-methyl-5-phenyl-1*H*-pyrazole (35):



Reaction time: 12 h.

Yield: 0.059 g (47%) as a brown solid.

Mp: 199–200 °C.

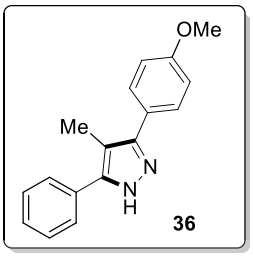
IR (KBr): ν_{max} 3432, 2926, 1608, 1505, 1441, 1403, 1250, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-*d*$_6$): δ 7.56–7.52 (m, 4H), 7.38 (t, *J* = 8.8 Hz, 2H), 7.29 (t, *J* = 5.6 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 2H), 2.23 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d6): δ 162.1 (d, 1JC,F = 245 Hz), 129.2, 128.8, 128.4, 127.6, 127.5, 115.4, 115.2, 110.0, 10.0 ppm.

HRMS: m/z calculated for $C_{16}H_{14}FN_2$ $[M + Na]^+$: 253.1136, found: 253.1140.

3-(4-Methoxyphenyl)-4-methyl-5-phenyl-1*H*-pyrazole (36):



Reaction time: 12 h.

Yield: 0.069 g (52%) as a brown solid.

Mp: 196–197 °C.

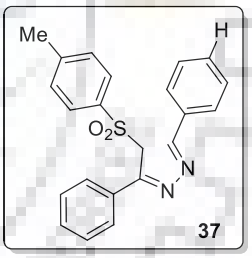
IR(KBr): ν_{max} 3429, 2852, 2357, 1638, 1403, 1023, 994 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.56 (d, J = 8.0 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H), 2.23 (s, 3H) ppm.

^{13}C NMR (100 MHz, CDCl3 + DMSO-d_6): δ 159.0, 128.7, 128.3, 127.5, 127.3, 124.6, 113.8, 109.6, 55.1, 10.0 ppm.

HRMS: m/z calcd for $C_{17}H_{17}N_2O$ $[M + Na]^+$: 265.1335, found: 265.1342.

1-Benzylidene-2-(1-phenyl-2-tosylethylidene)hydrazine (37):



Reaction time: 24 h.

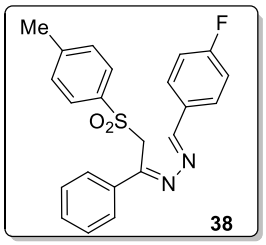
Yield: 0.168 g (90%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07–8.06 (m, 3H), 7.59 (t, *J* = 6.8 Hz, 2H), 7.48 (d, *J* = 6.8 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 4H), 7.48–7.45 (m, 3H), 7.43–7.39 (m, *J* = 7.2 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 5.14 (s, 2H), 2.09 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 156.5, 144.6, 135.7, 135.4, 133.7, 131.3, 130.9, 129.4, 128.6, 128.4, 128.4, 128.3, 128.2, 127.7, 55.0, 21.2 ppm.

HRMS: m/z calcd for $C_{22}H_{20}N_2NaO_2S$ $[M + Na]^+$: 399.1138, found: 399.1125.

1-(4-Fluorobenzylidene)-2-(1-phenyl-2-*p*-tosylethylidene)hydrazine (38):



Reaction time: 24 h.

Yield: 0.098 g (50%) as a brown solid.

Mp: 151–152 °C.

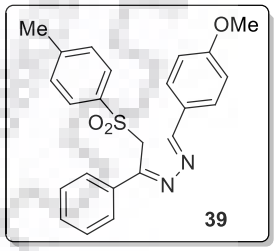
IR (KBr): ν_{max} 432, 2922, 1585, 1508, 1459, 1405, 1301, 1253, 1075, 1033, 969, 830, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.2 Hz, 2H), 7.70 (t, *J* = 9.2 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 3H), 7.10 (d, *J* = 8.8 Hz, 1H), 7.06 (t, *J* = 4.8 Hz, 2H), 6.79 (s, 1H), 4.87 (s, 2H), 2.28 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8–161.4 (d, 1JC,F = 247 Hz), 155.6, 144.7, 136.7, 135.2, 131.1, 129.5, 128.9, 128.3, 128.0, 127.3, 125.5, 115.8–115.6 (d, $1J_{C,F}$ = 21 Hz), 99.9, 55.0, 21.5 ppm.

HRMS: m/z calcd for $C_{22}H_{20}FN_2O_2S$ $[M + Na]^+$: 395.1224, found: 395.1232.

1-(4-Methoxybenzylidene)-2-(1-phenyl-2-*p*-tosylethylidene)hydrazine (39):



Reaction time: 24 h.

Yield: 0.099 g (51%) as a yellow solid.

Mp: 155–156 °C.

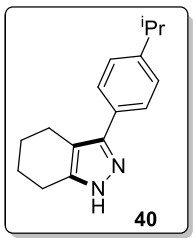
IR (KBr): νmax 3463, 2910, 1545, 1485, 1042, 839 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (m, 3H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.48 (m, 3H), 6.97 (d, *J* = 7.2 Hz, 2H), 6.93 (d, *J* = 7.2 Hz, 2H), 5.13 (s, 2H), 3.86 (s, 3H), 2.10 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 159.1, 155.8, 144.5, 135.8, 135.5, 130.6, 130.4, 129.3, 128.4, 128.3, 127.6, 126.6, 113.9, 55.3, 54.8, 21.3 ppm.

HRMS: m/z cal- culated for $C_{23}H_{22}N_2NaO_3S$ $(M + Na)^+$: 429.1243, found: 429.1259.

3-(4-Isopropylphenyl)-4,5,6,7-tetrahydro-1*H*-indazole (40):



Reaction time: 12 h.

Yield: 0.029 g (24%) as a brown solid.

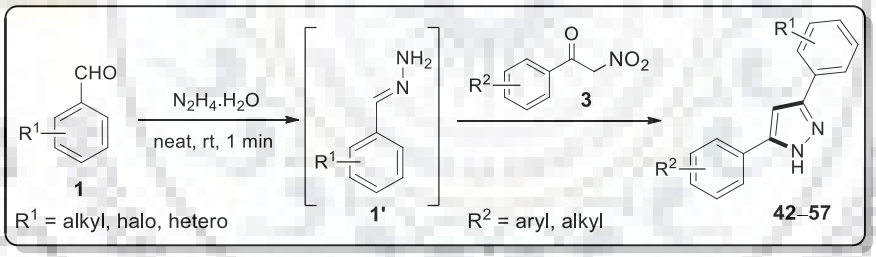
Mp: 197–198 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 2.92 (sp, J = 7.4 Hz, 1H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.59 (t, *J* = 6.0 Hz, 2H), 1.87–1.85 (m, 2H), 1.76–1.73 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 147.4, 139.5, 131.9, 126.5, 126.4, 113.4, 35.4, 33.8, 23.9, 23.2, 22.3, 21.6 ppm.

HRMS: m/z calcd for $C_{16}H_{21}N_2$ $(M + H)^+$: 241.1699, found: 241.1682.

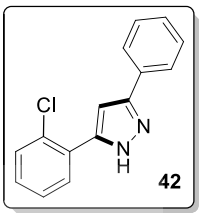
3.2.2. General procedure for the synthesis of di-substituted pyrazoles (42-57):



To a benzaldehyde derivative **1** (0.4 mmol) was added hydrazine hydrate (80% in water, 0.033 g, 1.0 mmol) under solvent-free conditions. After the addition of hydrazine hydrate, a yellow solid was formed within a minute which indicated the formation of the hydrazone derivative. To the thus formed hydrazone derivative was added α-nitro acetophenone derivative **3** (0.3 mmol) in EtOH (4 mL) followed by iodine (0.016 g, 20 mol%). Then the reaction mixture was refluxed at 80 °C on a pre-heated oil bath for 2 h. After completion of the reaction, as checked by TLC, the reaction was quenched with a saturated sodium thiosulfate solution and extracted twice with ethyl acetate (2 × 15 mL). The organic layer was washed with water and dried over anhyd. sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to silica gel column

chromatography using ethyl acetate in hexanes as the eluent to afford a pure pyrazole derivative **42**–**57**.

5-(2-Chlorophenyl)-3-phenyl-1*H*-pyrazole (42):



Reaction time: 2 h.

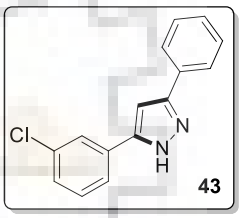
Yield: 0.058 g (76%) as brown solid.

Mp: 218–219 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.39–7.30 (m, 3H), 7.27–7.11 (m, 2H), 6.99 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.8; 131.3, 130.4, 130.2, 129.8, 129.2, 128.7, 128.0, 127.0, 125.7, 103.6 ppm.

5-(3-Chlorophenyl)-3-phenyl-1*H*-pyrazole (43):



Reaction time: 2 h.

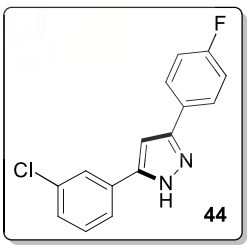
Yield: 0.060 g (80%) as brown solid.

mp: 208–207 ºC;

^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.73–7.58 (m, 4H), 7.32–7.14 (m, 5H), 6.73 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 134.2, 129.7, 128.5, 127.7, 127.3, 125.2, 99.4 ppm.

5-(3-Chlorophenyl)-3-(4-fluorophenyl)-1*H*-pyrazole (44):



Reaction time: 2 h.

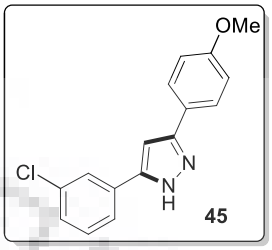
Yield: 0.065 g (79%) as brown solid.

Mp: 202–201 ºC.

^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.66 (d, *J* = 6.8 Hz, 2H), 7.31–7.22 (m, 4H), 7.16 (d, *J* = 4.0 Hz, 1H), 6.97 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 146.3, 144.4, 135.3, 130.4, 128.5, 127.8, 127.3, 125.3, 124.2, 123.5, 99.4 ppm.

5-(3-Chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole (45):



Reaction time: 2 h.

Yield: 0.061 g (71%) as brown solid.

Mp: 128–129 ºC.

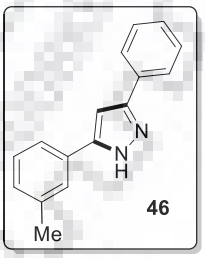
^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.74 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 3H), 7.26–7.16 (m, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.56 (s, 1H), 3.73 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.2, 148.1, 146.5, 132.2, 129.7, 127.3, 126.6, 125.3, 123.4, 123.3, 113.9, 99.8 ppm.

3-Phenyl-5-(*m*-tolyl)-1*H*-pyrazole (46):

Reaction time: 2 h.

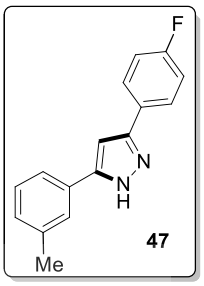
Yield: 0.053 g (76%) as brown solid.



Mp: 180–182 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71–7.69 (m, 2H), 7.49–7.47 (m, 2H), 7.29–7.26 (m, 3H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 2.25 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 138.2, 131.3, 130.1, 128.6, 128.5, 127.8, 126.2, 125.5, 122.7, 99.7, 21.3 ppm.



3-(4-Fluorophenyl)-5-(*m*-tolyl)-1*H*-pyrazole (47):

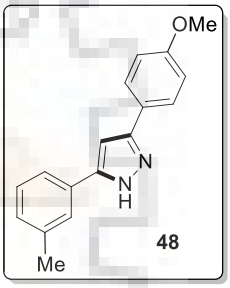
Reaction time: 2 h.

Yield: 0.060 g (79%) as brown solid.

Mp: 158–159 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.66 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 8.8 Hz, 2H), 6.74 (s, 1H), 2.32 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5 (d, $^{1}J_{C,F}$ = 246 Hz), 148.6, 148.0, 138.4, 130.5, 128.9, 128.7, 127.8, 127.2, 126.2, 122.6, 115.7, 99.7, 21.3 ppm.



3-(4-Methoxyphenyl)-5-(*m*-tolyl)-1*H*-pyrazole (48):

Reaction time: 2 h.

Yield: 0.060 g (75%) as brown solid.

Mp: 127–128 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 6.8 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 2H), 6.67 (s, 1H), 3.77 (s, 3H), 2.26 (s, 3H) ppm.

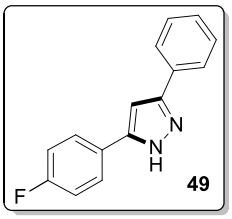
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 148.9, 148.0, 138.1, 131.4, 128.5, 126.8, 126.2, 123.9, 122.7, 113.9, 99.0, 55.0, 21.2 ppm.

5-(4-Fluorophenyl)-3-phenyl-1*H*-pyrazole (49):

Reaction time: 2 h.

Yield: 0.062 g (87%) as brown solid.

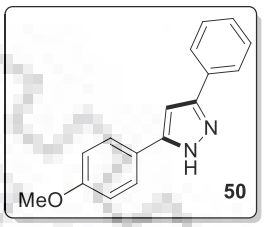
Mp: 188–190 °C.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (m, 4H), 7.33 (s, 3H), 7.01 (s, 2H), 6.73 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (d, $^{1}J_{C,F}$ = 246 Hz) 148.7, 148.0, 130.6, 128.9, 128.3, 127.8, 127.4, 125.5, 115.8, 99.0 ppm.

5-(4-Methoxyphenyl)-3-phenyl-1*H*-pyrazole (50):



Reaction time: 2 h.

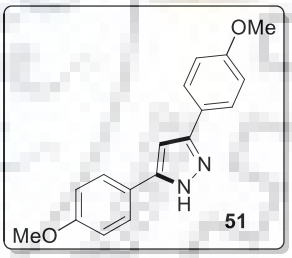
Yield: 0.060 g (79%) as brown solid.

Mp: 153–154 °C.

^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 9.2 Hz, 2H), 7.32–7.23 (m, 3H), 6.81 (t, *J* = 9.2 Hz, 2H), 6.69 (s, *J* = 8.5 Hz, 1H), 3.77 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.4, 148.9, 147.9, 131.6, 128.6, 127.8, 126.8, 125.5, 123.8, 114.0, 99.1, 55.1 ppm.

3,5-bis(4-methoxyphenyl)-1*H*-pyrazole (51):



Reaction time: 2 h.

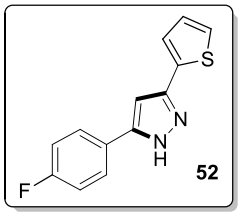
Yield: 0.057 g (68%) as brown solid.

Mp: 171-173 °C.

^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ 7.61 (d, *J* = 9.2 Hz, 4H), 6.83 (d, *J* = 9.2 Hz, 4H), 6.60 (s, 1H), 3.75 (s, 6H (2-OCH_3)) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 159.2, 148.0, 126.7, 124.3, 113.9, 98.2, 55.0 ppm.

5-(4-Fluorophenyl)-3-(furan-2-yl)-1*H*-pyrazole (52):



Reaction time: 2 h.

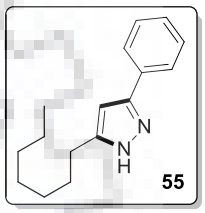
Yield: 0.050 g (67%) as brown solid

Mp: 183–186 ºC.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.55–7.52 (m, 2H), 7.1 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 4.8 Hz, 1H), 6.90–6.84 (m, 3H), 6.47 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ **^{13}C NMR (100 MHz, DMSO-d_6):** δ 161.8 (d, $^{1}J_{C,F}$ = 244 Hz) 127.0, 126.8, 126.7, 124.0, 123.2, 115.2, 115.0, 98.9 ppm.

5-Heptyl-3-phenyl-1*H*-pyrazole (55):



Reaction time: 2 h.

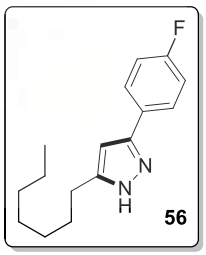
Yield: 0.059 g (81%) as brown solid

Mp: 222–223 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.32–7.28 (m, 1H), 6.36 (s, 1H), 2.62 (t, *J* = 8.4 Hz, 2H), 1.69–1.61 (m, 2H), 1.32–1.27 (m, 8H), 0.88 (t, *J* = 8.4 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 147.9, 132,7, 128.6, 127.7, 125.7, 101.0, 31.8, 29.2, 29.0, 26.4, 22.6, 14.1 ppm.

3-(4-fluorophenyl)-5-heptyl-1*H*-pyrazole (56):



Reaction time: 2 h.

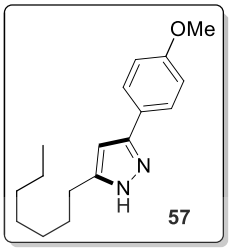
Yield: 0.059 g (76%) as brown solid

Mp: 214–215 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (t, *J* = 6.8 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 2H), 6.31 (s, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.69-1.61 (m, 2H), 1.32–1.27 (m, 8H), 0.88 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5 (d, $^1J_{C,F}$ = 246 Hz) 149.9, 147.3, 129.1, 127.3, 127.3 115.7, 115.4, 100.8, 31.7, 29.2, 29.0, 26.2, 22.6, 14.1 ppm.

5-Heptyl-3-(4-methoxyphenyl)-1*H*-pyrazole (57):



Reaction time: 2 h.

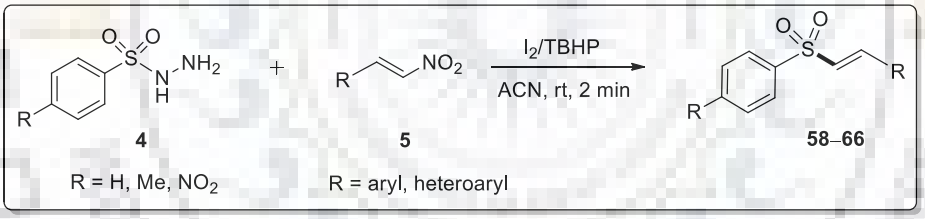
Yield: 0.073 g (69%) as brown solid

Mp: 207–208 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.27 (s, 1H), 3.81 (s, 3H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.66–1.60 (m, 2H), 1.28–1.26 (m, 8H), 0.88 (t, *J* = 6.0 Hz, 3H) ppm.

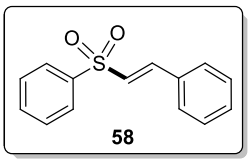
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 149.5, 148.1, 126.9, 125.4, 114.0, 100.3, 55.2, 31.7, 29.3, 29.0, 26.5, 22.6, 14.0 ppm.

3.2.3. General procedure for synthesis of vinyl sulfones from nitrostyrenes 58–66:



To nitrostyrene **5** (0.5 mmol) were sequentially added sulfonyl hydrazide **4** (0.6 mmol), tert-butyl hydroperoxide (80% solution in water, 0.135 g, 1.5 mmol, 3.0 equiv), and iodine (0.026 g, 20 mol%) under solvent-free conditions at room temperature. The contents were stirred at room temperature for 2 min. Upon completion (progress monitored by TLC analysis), the reaction was quenched by the addition of a saturated sodium thiosulfate solution, and the resulting mixture was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with water, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography ethyl acetate (10–20%) in hexanes to afford the pure vinyl sulfone derivative **58**–**66**.

2-(Phenylsulfonyl)vinylbenzene (58):



Reaction time: 2 min.

Yield A from β-nitro styrene: traces.

Yield B from styrene: 0.121 g (99%) brown solid.

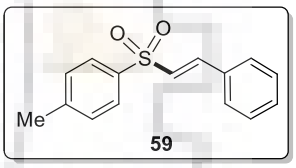
M.p.: 64–68 ºC;

IR (KBr): ν_{max} 3420, 3411, 2814, 1621, 1416, 1325, 1154, 1123 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J=8.4 Hz, 2H), 7.57 (d, J=15.6 Hz, 1H), 7.47 (t, J=6.0 Hz, 1H), 7.44–7.39 (m, 2H), 7.34 (d, J=5.2 Hz, 2H), 7.27–7.24 (m, 3H), 6.77 ppm (d, J= 15.6 Hz, 1H);

^{13}CNMR (100 MHz, $CDCl_3$): δ 142.3, 140.4, 133.2, 132.1, 131.1, 129.2, 128.9, 128.4, 127.4, 127.0 ppm.

1-Methyl-4-(styrylsulfonyl)benzene (59):



Reaction time: 2 min.

Yield A from b**-nitro styrene:** 0.107 g (83%) as a brown solid.

Yield B from styrene: 0.129 g (100%) as a brown solid.

Mp: 145–147 ºC.

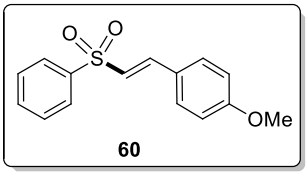
IR (KBr): ν_{max} 3438, 3419, 2941, 1628, 1424, 1309, 1114, 1101 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.2 Hz, 2H), 7.65 (d, *J* = 15.2 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.38–7.37 (m, 3H), 7.33 (d, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 15.2 Hz, 1H), 2.42 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 144.3, 141.8, 137.6, 132.3, 131.0, 129.9, 128.9, 128.4, 127.6, 127.5, 21.5 ppm.

HRMS: m/z calcd for $C_{15}H_{14}NaO_2S$ $(M + Na)^+$: 281.0612, found: 281.0621.

1-Methoxy-4-(2-(phenylsulfonyl)vinyl)benzene (60):



60

Reaction time: 2 min.

Yield: (convertion of **2c** was 75%) 0.069 g (67%) as a brown solid;

Mp: 151–152 ºC.

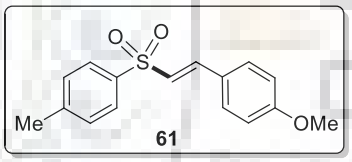
IR (KBr): ν_{max} 3429, 2895, 1920, 1599, 1566, 1234, 1062, cm^{-1}.

^{1}HNMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.2 Hz, 3H), 7.66–7.54 (m, 3H), 7.45–7.27 (m, 2H), 6.91 (d, *J* = 9.2 Hz, 2H), 6.72 (d, *J* = 17.6 Hz, 1H), 3.84 (s, 3H) ppm.

^{13}CNMR (100 MHz, DMSO-d_6): 162.0, 142.2, 136.3, 133.1, 131.4, 130.3, 129.6, 129.2, 127.4, 124.3, 114.4, 55.4 ppm.

HRMS: m/z calcd for $C_{15}H_{14}NaO_3S$ $(M + Na)^+$: 297.0561, found: 297.0574.

1-Methoxy-4-(2-tosylvinyl)benzene (61):



61

Reaction time: 2 min.

Yield: (convertion of **2c** was 80%) 0.072 g (62%) as a brown solid.

Mp: 146–149 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 5.2 Hz, 2H), 7.59 (d, *J* = 15.2 Hz, 1H), 7.41 (d, *J* = 6.4 Hz, 2H), 7.32 (d, *J* = 4.8 Hz, 2H), 6.89 (d, *J* = 5.6, 2H), 6.70 (d, *J* = 15.2 Hz, 1H), 3.81 (s, 3H), 2.41 (s, 3H) ppm.

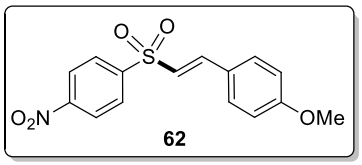
^{13}C NMR (100 MHz, $CDCl_3$): 161.9, 144.1, 141.7, 138.0, 130.2, 129.8, 127.5, 124.9, 124.7, 114.4, 55.4, 21.5 ppm.

HRMS: m/z calcd for $C_{16}H_{16}NaO_3S$ $(M + Na)^+$: 311.0718, found: 311.0713.

1-Methoxy-4-(2-((4-nitrophenyl)sulfonyl)vinyl)benzene (62):

Reaction time: 2 min.

Yield: (convertion of **2c** was 90%) 0.118 g (82%) as a brown solid.



62

Mp: 160–161 ºC.

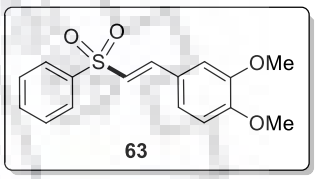
IR (KBr): ν_{max} 3445, 2915, 1624, 1602, 1334, 1055 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 15.2 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8, 2H), 6.69 (d, *J* = 15.2 Hz, 1H), 3.84 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 162.6, 150.3, 147.0, 144.8, 130.7, 128.8, 128.4, 124.9, 122.6, 114.7, 55.5 ppm.

HRMS: m/z calculated for $C_{15}H_{13}NNaO_5S$ $(M + Na)^+$: 342.0412, found: 342.0417.

1,2-Dimethoxy-4-(2-tosylvinyl)benzene (63):



63

Reaction time: 2 min.

Yield: (convertion of **2e** was 70%) 0.068 g (61%) as a brown liquid.

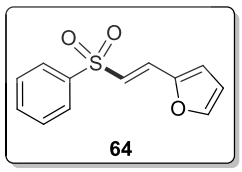
IR (KBr): ν_{max} 3461, 2951, 2942, 1616, 1303, 1018 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 15.6 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.08 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.95 (d, *J* = 1.6, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 16.0 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.43 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 151.6, 149.1, 144.0, 142.0, 138.0, 129.8, 127.5, 125.1, 124.9, 123.4, 110.9, 109.8, 55.9, 21.5 ppm.

HRMS: m/z calcd for $C_{17}H_{18}NaO_4S$ $(M + Na)^+$: 341.0818, found: 341.0833.

2-(2-(Phenylsulfonyl)vinyl)furan (64):



64

Reaction time: 2 min.

Yield: (convertion of **2f** was 85%) 0.074 g (75%) as a brown liquid oil.

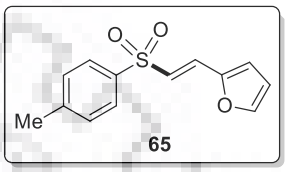
IR (KBr): ν_{max}3441, 3133, 2931, 2861, 1624, 1610, 1524, 1373, 1102 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.55–7.52 (m, 2H), 7.47 (s, 1H), 7.44 (d, *J* = 15.2 Hz, 1H), 6.74 (d, *J* = 14.8 Hz, 1H), 6.70 (d, *J* = 3.2 Hz, 1H), 6.48 (dd, *J* = 1.2, 4.4 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 148.6, 145.7, 140.8, 133.3, 129.3, 128.9, 127.5, 124.6, 117.0, 112.6 ppm.

HRMS: m/z calcd for $C_{12}H_{11}O_3S$ $(M + H)^+$: 235.0423, found: 235.0439.

2-(2-Tosylvinyl)furan (65):



65

Reaction time: 2 min.

Yield: (convertion of **2f** was 90%) 0.079 g (71%) as a brown liquid oil.

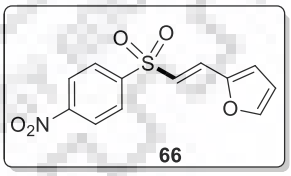
IR (KBr): ν_{max} 3420, 3210, 2815, 1924, 1620, 1516, 1303, 1065 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 1.2 Hz, 1H), 7.40 (d, *J* = 14.8 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 15.2 Hz, 1H), 6.68 (d, *J* = 3.6 Hz, 1H), 6.46 (dd, *J* = 1.6, 3.2 Hz, 1H), 2.42 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 148.7, 145.5, 144.3, 137.8, 129.8, 128.4, 127.5, 125.0, 116.7, 112.5, 21.6 ppm.

HRMS: m/z calcd for $C_{13}H_{12}NaO_3S$ $(M + Na)^+$: 271.0405 found: 271.0399.

2-(2-((4-Nitrophenyl)sulfonyl)vinyl)furan (66):



66

Reaction time: 2 min.

Yield: (convertion of **2f** 85%) 0.101 g (85%) as a brown solid.

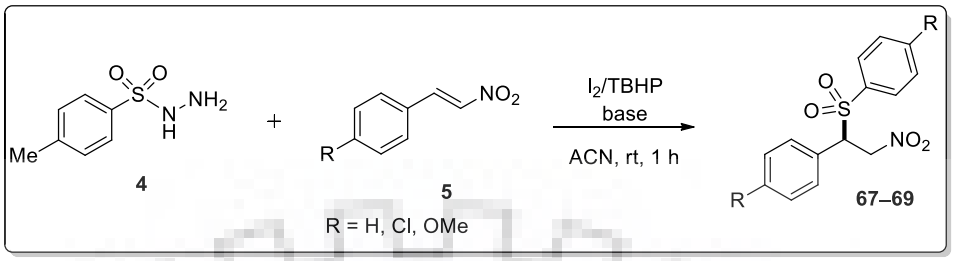
Mp: 135–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 2H), 7.53–7.49 (m, 2H), 6.79 (d, *J* = 3.6 Hz, 1H), 6.72 (d, *J* = 15.2 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): 150.4, 148.3, 146.6, 146.4, 130.8, 128.9, 124.5, 122.7, 118.4, 112.9 ppm.

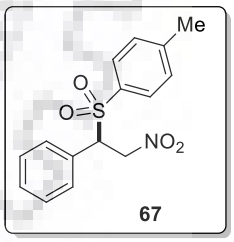
HRMS: m/z calcd for $C_{12}H_9NNaO_5S$ $(M + Na)^+$: 302.0094, found: 302.0098.

3.2.4. General procedure for hydrosulfonylation of nitrostyrenes:



To astirred solution of nitrostyrene **5** (0.5 mmol) in ACN (1 mL) were sequentially added arylsulfonyl hydrazide **4** (1.0 mmol), morpholine (0.022 g, 0.25 mmol), and tert-butyl hydroperoxide (80% solution in water, 0.135 g, 1.5 mmol, 3.0 equiv) at room temperature. Then, iodine (20 mol%, 0.026 g) was added, and the resulting mixture was stirred at room temperature for 1h. Upon completion (progress monitored by TLC analysis), the reaction was quenched by the addition of asaturated sodium thiosulfate solution, and the resulting mixture was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with water,dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography ethyl acetate (10–20%) in hexanes to afford the pure sulfone derivatives **67**–**69**.

1-Methyl-4-((2-nitro-1-phenylethyl)sulfonyl)benzene (67):



Reaction time: 1 h.

Yield: (convertion of **2b** was 66%) 0.050g (50%) as a brown solid.

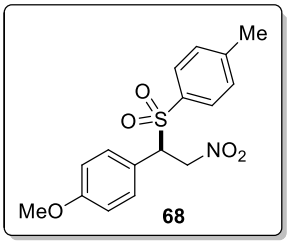
Mp: 218–219 ^oC; IR (KBr): νmax3447, 2925, 1641, 1321, 1303, 1121 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = .7.6 Hz, 2H), 7.36-7.33 (m, 1H), 7.29-7.25 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 5.33 (dd, *J* = 4.4, 13.6, 1H), 5.06 (dd, *J* = 10.0, 14.0 Hz, 1H), 4.95 (dd, *J* = 4.8, 9.2 Hz, 1H), 2.41 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 145.8, 132.8, 129.7, 129.4, 129.0, 128.9, 128.8, 72.8, 67.9, 21.7 ppm.

HRMS: m/z calcd for $C_{15}H_{15}NNaO_4S$ $(M+H)^+$: 306.0795, found: 306.0793.

1-Methoxy-4-(2-nitro-1-tosylethyl)benzene (68):



Reaction time: 1 h.

Yield: (convertion of **2c** was 85%) 0.128 g (90%) as a brown solid;

Mp: 218–219 ºC.

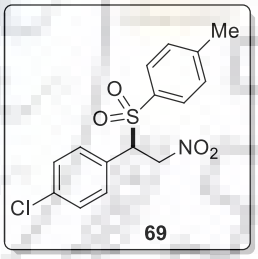
IR (KBr): ν_{max} 3431, 2914, 2891, 1652, 1334, 1323, 1012 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.29 (dd, *J* = 4.4, 13.6, 1H) 5.01 (dd, *J* = 10.0, 13.6 Hz, 1H), 4.90 (dd, *J* = 4.4, 10.0 Hz, 1H), 3.77 (s, 3H), 2.41 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 160.6, 145.7, 132.9, 130.7, 129.6, 129.0, 120.3, 114.3, 72.9, 67.3, 55.2, 21.7 ppm.

HRMS: m/z calcd for $C_{16}H_{17}NNaO_5S$ $(M + Na)^+$: 358.0720, found: 358.0728.

1-(4-Chlorophenyl)-3-phenyl-3-tosylpropan-1-one (69):



Reaction time: 1 h.

Yield: (convertion of **2d** was 70%) 0.086 g (76%) as a white solid;

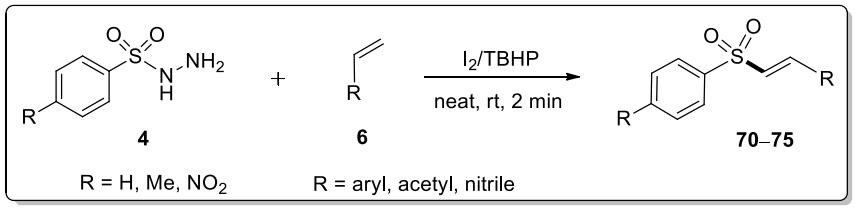
Mp: 218–219 ºC; IR (KBr): ν_{max} 3424, 2933, 1390, 1299, 1249, 1120 813, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 3.2 Hz, 2H), 7.26 (m, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 5.31 (dd, *J* = 4.4, 13.6 Hz, 1H), 5.02 (dd, *J* = 10.4, 13.6 Hz, 1H), 4.92 (dd, *J* = 4.4, 14.4 Hz, 1H), 2.43 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 146.1, 136.2, 132.7, 129.9, 129.2, 129.1, 127.3, 72.7, 67.2 ppm.

HRMS: m/z calcd for $C_{15}H_{15}NO_4SNa$ $(M + Na)^+$: 340.0405, found: 340.0430.

3.2.5. General procedure for synthesis of vinyl sulfones 70–75:

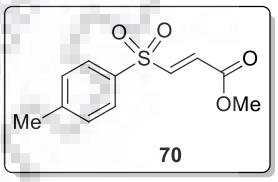


To a stirred solution of acrylate/styrene **6** (1.0 mmol) in an open flask were sequentially added sulfonyl hydrazide **4** (0.5 mmol), tert-butyl hydro- peroxide (80% solution in water, 0.135 g, 1.5 mmol, 3.0 equiv), and iodine (0.026 g, 20 mol%) under solvent-free conditions at room temperature. After 1 min, DABCO (0.028 g, 0.25 mmol) was added to this mixture, which led to the heating of the reaction vessel. The flask was shaken occasionally to bring the contents to asyrupy liquid. When considered complete [progress monitored by TLC analysis (after an additional 1 min)], the reaction was quenched by the addition of a saturated sodium thiosulfate solution, and the resulting mixture was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with water, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography ethyl acetate (10–20%) in hexanes to give the pure vinylsulfone **70**–**75**.

Method for **76** and **77:**

Methyl 3-(*p*-tosyl)acrylate (70):

Reaction time: 2 min.



Yield: 0.117 g (98%) as a brown solid.

Mp: 118–119 ^{o}C.

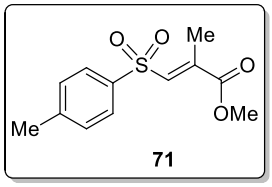
IR (KBr): ν_{max} 3434, 3024, 2911, 1532, 1436, 1312, 1131, 1058, 971 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 15.2 Hz, 1H), 6.78 (d, *J* = 15.2 Hz, 1H), 3.77 (s, 3H), 2.43 (s, 3H) ppm.

^{13}C NMR (100 MHz, DMSO-*d*$_6$): 163.9, 145.6, 143.6, 135.2, 130.2, 129.9, 128.3, 52.7, 21.6 ppm.

HRMS: m/z calcd for $C_{11}H_{12}NaO_4S$ $(M + Na)^+$: 263.0349, found: 263.0350.

Methyl 2-methyl-3-(*p*-tosyl)acrylate (71):



Reaction time: 2 min.

Yield: 0.083 g (65%) as a brown oil.

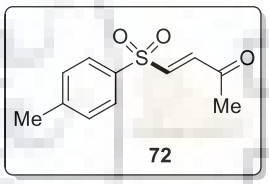
IR (KBr): ν_{max} 3446, 3047, 2925, 1715, 1632, 1436, 1313, 1147, 1085, 970 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.21 (s, 2H), 3.75 (s, 3H), 2.44 (s, 3H), 2.31 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 166.1, 145.1, 140.6, 137.5, 130.3, 130.0, 127.6, 53.0, 21.6, 13.3 ppm.

HRMS: m/z calcd for $C_{12}H_{14}NaO_4S$ $(M + Na)^+$: 277.0505, found: 277.0524.

Methyl 2-methyl-3-tosylacrylate (72):



Reaction time: 2 min.

Yield: 0.077 g (69%) as a brown solid.

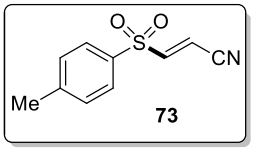
Mp: 110–112 °C.

IR (KBr): ν_{max} 3430, 3171, 1665, 1621, 1333, 1141 1085 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.07 (d, *J* = 0.8 Hz, 1H), 2.55 (s, 3H), 2.41 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 145.5, 143.5, 143.2, 135.0, 129.9, 127.8, 109.7, 21.7, 13.1 ppm.

3-Tosylacrylonitrile (73):



Reaction time: 2 min.

Yield: 0.088 g (79%) as a brown solid.

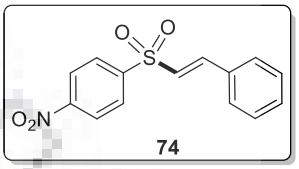
IR (KBr): ν_{max} 3430, 3041, 2265, 1621, 1416, 1325, 1220, 1164, 1015 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 15.6 Hz, 1H), 6.50 (d, *J* = 15.6 Hz, 1H), 2.47 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 149.3, 146.5, 134.1, 130.5, 128.5, 113.4, 110.1, 21.7 ppm.

HRMS: m/z calcd for $C_{10}H_9NNaO_2S$ $(M + Na)^+$: 230.0246, found: 230.0250.

Nitro-4-(styrylsulfonyl)benzene (74):



74

Reaction time: 2 min.

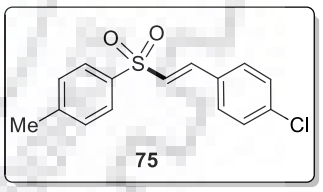
Yield: 0.110 g (76%) as a brown solid.

MP: 155–156 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 15.6 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.46–7.42 (m, 3H) 6.86 (d, *J* = 15.2 Hz, 1H), ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 150.4, 146.5, 144.9, 131.8, 131.8, 129.2, 129.0, 128.8, 125.6, 124.5 ppm.

1-Chloro-4-(styrylsulfonyl)benzene (75):



75

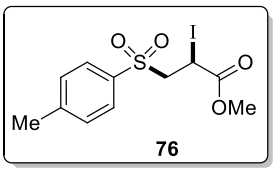
Reaction time: 2 min.

Yield: 0.136 g (98%) as a brown solid.

MP: 114–117 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 15.2 Hz, 2H), 7.58–7.51 (m, 2H), 7.39 (d, *J* = 9.2 Hz, 2H), 7.32 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 15.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 140.8, 140.2, 136.9, 133.3, 130.6, 129.6, 129.2, 129.1, 127.7, 127.4 ppm.

Methyl 2-iodo-3-tosylpropanoate (76):



76

Reaction time: 2 min.

Yield: 0.184 g (100%) as a white solid.

Mp: 115–116 °C.

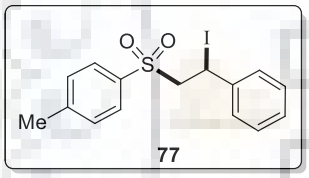
IR (KBr): ν_{max} 3312, 3121, 1735, 1614, 1426, 1325, 1332, 1214, 1015, 814 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.62 (dd, *J* = 2.8, 12.0 Hz, 1H), 4.14 (dd, *J* = 12.0, 14.4, 1H), 3.56 (dd, *J* = 2.8, 14.4 Hz, 1H), 3.64 (s, 3H), 2.43 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 169.8, 145.5, 135.2, 123.0, 128.2, 61.7, 53.3, 21.6, 5.6 ppm.

HRMS: m/z calcd for $C_{11}H_{13}INaO_4S$ $(M + Na)^+$: 390.9471, found: 390.9479.

1-((2-Iodo-2-phenylethyl)sulfonyl)-4-methylbenzene (77):



77

Reaction time: 2 min.

Yield: 0.188 g (98%) as a white solid.

Mp: 134–135 °C.

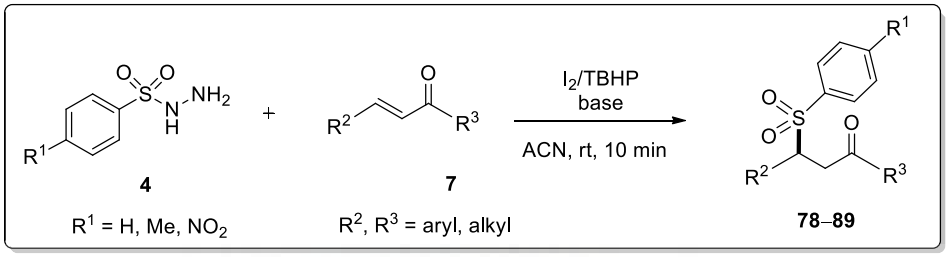
IR (KBr): ν_{max} 3312, 3121, 1654, 1446, 1342, 1124, 836 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 2H), 7.20 (d, *J* = 6.0 Hz, 2H), 7.12–7.11 (m, 5H), 5.55 (dd, *J* = 10.8, 15.2 Hz, 1H), 4.29 (dd, *J* = 6.0, 9.2, 1H), 4.06 (dd, *J* = 5.6, 10.4 Hz, 1H), 2.34 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 144.5, 140.4, 135.9, 129.5, 128.5, 128.3, 127.9, 127.0, 65.7, 21.4, 18.1 ppm.

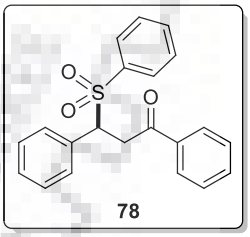
HRMS: m/z calcd for $C_{15}H_{15}INaO_2S$ $(M + H)^+$: 408.9730, found: 408.9763.

3.2.6. General procedure for hydrosulfonylation of chalcone derivatives:



To a stirred solution of chalcone dervative **7** (0.5 mmol) in ACN (1 mL) were sequentially added arylsulfonyl hydrazide **4** (1.0 mmol), morpholine (0.5, 0.022 g, mmol), and tert-butyl hydroperoxide (80% solution in water, 1.5 mmol, 3.0 equiv) at room temperature. Then iodine (0.026 g, 20 mol%) was added, and the resulting mixture was stirred at room temperature for 10 min. Upon completion (progress monitored by TLC analysis), the reaction was quenched by the addition of asaturated sodium thiosulfate solution, and the resulting mixture was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with water,dried with anhy- drous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography ethyl acetate (10–20%) in hexanes to afford in pure yields **78**–**89**.

1,3-Diphenyl-3-(phenylsulfonyl)propan-1-one (78):



Reaction time: 10 min.

Yield: 0.121 g (69%) as a white solid.

Mp: 156–157 ^{o}C.

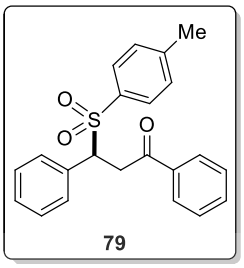
IR (KBr): ν_{max} 3447, 2925, 1640, 1415, 1305, 1251, 1140 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.59–7.53 (m, 4H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.24–7.21 (m, 1H), 7.19 (d, *J* = 4.4 Hz, 4H), 4.94 (dd, *J* = 3.6, 9.6 Hz, 1H), 4.13 (dd, *J* = 3.2, 17.6 Hz, 1H), 3.94 (dd, *J* = 9.6, 18.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, DMSO-*d_6*): 194.8, 136.8, 136.1, 133.7, 132.5, 129.8, 129.6, 129.0, 128.9, 128.7, 128.6, 128.3, 128.1, 66.5, 36.8 ppm.

HRMS: m/z calcd for $C_{21}H_{18}NaO_3S$ $(M + Na)^+$: 373.0869, found: 373.0891.

1,3-Diphenyl-3-tosylpropan-1-one (79):



Reaction time: 10 min.

Yield: 0.176 g (97%) as a white solid.

Mp: 180–181 ºC.

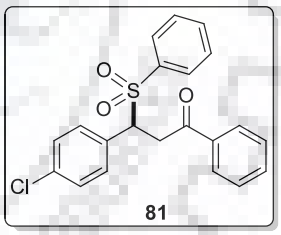
IR (KBr): ν_{max} 3425, 2912, 1632, 1425, 1315, 1221, 1340 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.49–7.44 (m, 4H), 7.21 (d, *J* = 8.4 Hz, 3H), 7.19–7.13 (m, 4H), 4.87 (dd, *J* = 3.6, 10.0 Hz, 1H), 4.09 (dd, *J* = 3.2, 13.6 Hz, 1H) 3.88 (dd, *J* = 10.0, 18.0 Hz, 1H), 2.41 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 192.9, 144.0, 137.7, 136.1, 133.6, 132.5, 129.7, 129.3, 129.0, 128.7, 128.4, 128.1, 127.0, 66.4, 36.9, 21.6 ppm.

HRMS: m/z calcd for $C_{22}H_{20}NaO_3S$ $(M + Na)^+$: 387.1025, found: 387.1043.

3-(4-Chlorophenyl)-1-phenyl-3-(phenylsulfonyl)propan-1-one (81)



Reaction time: 10 min.

Yield: 0.182 g (95%) as a white solid.

Mp: 190–192 ºC.

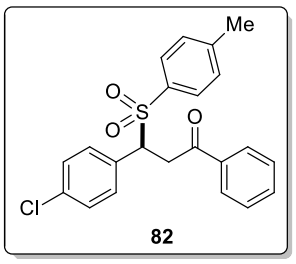
IR (KBr): ν_{max} 3434, 2937, 1615, 1431, 1319, 1310, 821 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 4H), 7.49–7.41 (m, 5H), 7.20–7.12 (m, 3H), 4.90 (dd, *J* = 3.6, 10.0 Hz, 1H), 4.12 (dd, *J* = 3.2, 17.6 Hz, 1H) 3.89 (dd, *J* = 10.0, 18.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-*d_6*): 194.1, 136.1, 136.0, 135.4, 134.3, 133.6, 133.4, 130.6, 128.5, 128.4, 128.3, 128.1, 127.6, 65.2, 36.4 ppm.

HRMS: m/z calcd for $C_{21}H_{17}ClNaO_3S$ $(M + Na)^+$: 407.0479, found: 407.0491.

3-(4-Chlorophenyl)-1-phenyl-3-tosylpropan-1-one (82):



82

Reaction time: 10 min.

Yield: 0.197 g (99%) as a white solid.

Mp: 164–165 ºC.

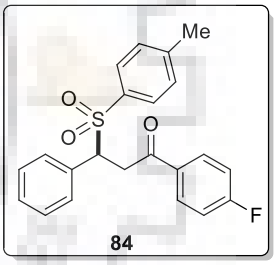
IR (KBr): ν_{max} 3456, 2934, 1619, 1219, 119 1129, 1070, 911 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.60–7.57 (m, 1H), 7.48–7.44 (m, 4H), 7.22–7.18 (m, 5H), 7.16 (s, 1H), 4.87 (dd, *J* = 3.2, 10.0 Hz, 1H), 4.09 (dd, *J* = 3.2, 18.0 Hz, 1H), 3.87 (dd, *J* = 10.0, 18.0 Hz, 1H), 2.40 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-*d_6*): 194.7, 145.0, 135.9, 134.8, 133.7, 131.2, 131.1, 129.6, 129.5, 129.0, 128.8, 128.8, 128.1, 65.8, 37.0, 21.6 ppm.

HRMS: m/z calcd for $C_{22}H_{19}ClNaO_3S$ $(M + Na)^+$: 421.0636, found: 421.0652.

1-(4-Fluorophenyl)-3-phenyl-3-tosylpropan-1-one (84):



84

Reaction time: 10 min.

Yield: 0.136 g (71%) as a white solid.

Mp: 163–164 ºC.

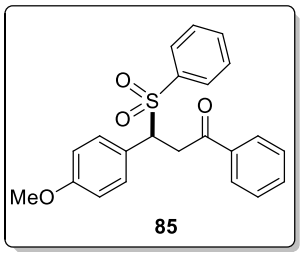
IR (KBr): ν_{max} 3417, 2955, 1621, 1435, 1241, 1021, 912 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (t, *J* = 6.8 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.25–7.23 (m, 2H), 7.19–7.16 (m, 6H), 7.12 (d, *J* = 8.0 Hz, 1H), 4.89 (dd, *J* = 3.6, 9.6 Hz, 1H), 4.10 (dd, *J* = 3.6, 18.0 Hz, 1H), 3.87 (dd, *J* = 10.0, 18.4 Hz, 1H), 2.38 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 193.4, 166.1 (d, $J_{C–F}$ = 253.6 Hz), 144.8, 133.9, 132.6, 130.9, 130.8, 129.5, 129.3, 128.9, 128.4, 116.1, 66.5, 36.9, 21.6 ppm.

HRMS: m/z calcd for $C_{22}H_{19}FO_3NaS$ $(M + Na)^+$: 405.0931, found: 405.0941.

3-(4-Methoxyphenyl)-1-phenyl-3-(phenylsulfonyl)propan-1-one (85):



85

Reaction time: 10 min.

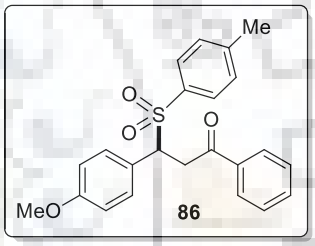
Yield: 0.120 g (63%) as a white solid.

Mp: 178–179 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.6 Hz, 2H), 7.60–7.54 (m, 4H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H) 4.88 (dd, *J* = 3.6, 10.0 Hz, 1H), 4.09 (dd, *J* = 3.2, 17.6 Hz, 1H), 3.90 (dd, *J* = 10.0, 17.6 Hz, 1H), 3.74 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 195.0, 159.9, 137.0, 136.1, 133.7, 129.0, 128.7, 128.1, 124.2, 113.9, 65.8, 55.2, 36.9 ppm.

3-(4-Methoxyphenyl)-1-phenyl-3-tosylpropan-1-one (86):



86

Reaction time: 10 min.

Yield: 0.136 g (69%) as a white solid.

Mp: 151–152 ºC.

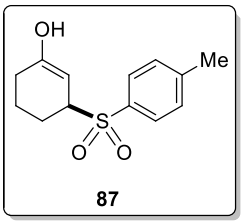
IR (KBr): ν_{max} 3481, 3211, 2995, 1620, 1435, 1308, 1281 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.47–7.43 (m, 4H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 4.86 (dd, *J* = 3.6, 10.0 Hz, 1H), 4.06 (dd, *J* = 3.6, 18.0 Hz, 1H), 3.88 (dd, *J* = 10, 18.0 Hz, 1H), 3.75 (s, 3H), 2.39 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 195.0, 159.8, 144.6, 136.2, 134.0, 133.6, 130.9, 129.4, 129.0, 128.7, 128.1, 124.4, 113.9, 65.8, 55.2, 37.0, 21.6 ppm.

HRMS: m/z calcd for $C_{23}H_{22}NaO_4S$ $(M + Na)^+$: 417.1131, found: 417.1130.

3-Tosylcyclohex-1-enol (87):



87

Reaction time: 10 min.

Yield: 0.069 g (54%) as a brown solid.

Mp:163–164 ^oC.

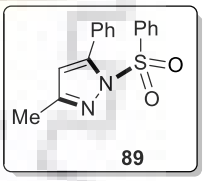
IR (KBr): ν_{max} 3547, 3341, 2925, 1630, 1435, 1299, 1281, 1140 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (br, 1H, O*H*), 7.84 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 2H), 6.25–6.20 (m, 1H), 6.90 (d, *J* = 10.4 Hz, 1H), 2.40 (S, 3H), 2.29 (t, *J* = 6.4 Hz, 2H), 2.11–2.10 (m, 2H), 1.72 (q, *J* = 5.4 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 154.5, 143.9, 137.3, 135.4, 129.5, 127.9, 127.1, 24.4, 23.9, 21.5, 20.7 ppm.

HRMS: m/z calcd for $C_{13}H_{16}NaO_3S$ $(M + Na)^+$: 275.0712, found: 275.0720.

3-Methyl-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrazole (89):



89

Reaction time: 10 min.

Yield: 0.083 g (56%) as a brown solid.

Mp: 120–121 ^oC.

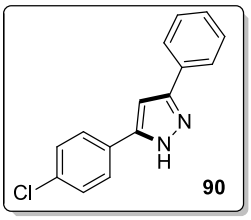
IR (KBr): ν_{max} 3423, 2955, 2210, 1570, 1423, 1303, 1259, 1022, 1014, 966 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 7.68–7.64 (m, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 3H), 7.38 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 7.2 Hz, 1H), 1.27 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 149.5, 145.2, 137.9, 137.8, 136.6, 133.6, 130.8, 130.3, 129.2, 128.7, 128.0, 14.0 ppm.

HRMS: m/z calcd for $C_{16}H_{14}O_3NaS$ $(M + Na)^+$: 321.0668, found: 321.0674.

3,5-Diphenyl-1*H*-pyrazole (90):



Reaction time: 10 min.

Yield: 0.125 g (99%) (from **9a**) and 0.115 g (91%) (from **9b**) as brown solid.

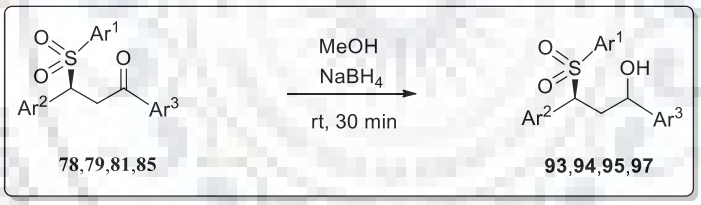
Mp: 184–186 °C; IR (KBr): ν_{max} 3443,1636, 1489, 1386, 1309, 1259, 1180, 1088, 1021, 968, 826 cm^{-1}.

^{1}H NMR (400 MHz,$CDCl_3$ + DMSO-d_6): δ 13.08 (br, 1H, N*H*), 7.62 (s, 4H), 7.24–7.20 (m, 3H), 7.16–7.12 (m, 2H), 6.73 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 131.5, 127.4, 126.5, 125.4, 124.0, 98.1 ppm.

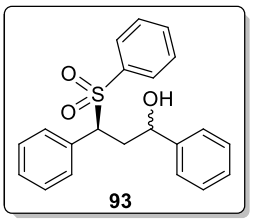
HRMS: m/z calcd for $C_{15}H_{11}ClN_2Na$ $(M + Na)^+$: 277.0503, found: 277.0525.

3.2.7. General procedure for the preparation of γ-hydroxysulfones 93,94,95,97:



To a stirred solution of γ-keto sulfone derivative **78**,**79**,**81**,**85** (1.4 g, 4.0 mmol) in MeOH (3 mL) at room temperature $NaBH_4$ (0.296 g, 8.0 mmol) was added portion-wise and the reaction mixture was stirred for 30 min at rt. After completion of the reaction, as checked by TLC, The solvent was evaporated under reduced pressure and extracted with ethyl acetate (2 × 15 mL). The organic layer was washed with water and dried over anhyd sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was washed with a 2:10 mixture of DCM/hexane (3 × 11 mL) and dried *in vacuo* to furnish a mixture of two diastereomers of γ-hydroxy sulfone derivative **93**,**94**,**95**,**97** in good yield. Diastereomeric ratio was determined by ^{1}H NMR of products.

1,3-Diphenyl-3-(phenylsulfonyl)propanol (93):



Reaction time: 30 min.

Yield: mixture of two diastereomers; 1.3 g (92%) as a white colour solid.

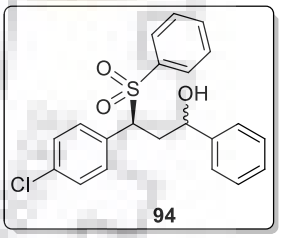
Mp: 158–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.51 (m, 4H), 7.44 (d, *J* = 6.0 Hz, 2H), 7.36–7.27 (m, 16H), 7.26–7.18 (m, 6H), 7.01 (d, *J* = 5.6 Hz, 2H), 4.78 (t, *J* = 5.6, 1H), 4.56 (dd, *J* = 2.4, 9.2 Hz, 1H), 4.38 (dd, *J* = 1.6, 8.4 Hz, 1H), 4.03 (dd, *J* = 4.4, 6.8 Hz, 1H), 2.88–2.26 (m, 2H), 2.61–2.55 (m, 1H), 2.49–2.43 (m, 1H), 2.01 (br, 2H, 2-O*H*) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 142.6, 137.0, 133.5, 132.7, 132.0, 130.1, 129.8, 129.0, 129.0, 128.9, 128.8, 128.7, 128.6, 128.6, 128.6, 128.5, 128.2, 128.0, 126.0, 125.6, 72.0, 70.8, 68.6, 68.0, 37.5, 36.8 ppm.

HRMS: m/z calculated for $C_{21}H_{20}O_3SNa$ $(M + Na)^+$: 352.1025, found: 352.1036.

1-Phenyl-1-(4-chlorophenyl)-3-(phenylsulfonyl)propanol (94):



Reaction time: 30 min.

Yield: mixture of two diastereomers; 1.374 g (89%) as a white colour solid.

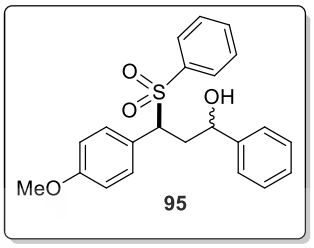
Mp: 140–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.55 (m, 3H), 7.49–7.47 (m, 2H), 7.44–7.39 (m, 3H), 7.34–7.31 (m, 4H), 7.29–7.260 (m, 9H), 7.19 (d, *J* = 8.4 Hz, 3H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.79 (dt, *J* = 3.6, 7.6 Hz, 1H), 4.54 (dd, *J* = 4.0, 12.0 Hz, 1H), 4.34–4.32 (m, 1H), 4.03 (dd, *J* = 5.6, 8.8 Hz, 1H), 2.87–2.74 (m, 2H), 2.56–2.50 (m, 1H), 2.48–2.40 (m, 1H), 2.13 (d, *J* = 4.0 Hz, 1H, O*H*), 1.85 (d, *J* = 4.8 Hz, 1H, O*H*) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-*d_6*): δ 144.4, 143.1, 137.3, 136.8, 134.9, 134.8, 133.8, 131.6, 131.4, 131.3, 130.7, 128.9, 128.7, 128.6, 128.1, 126.3, 126.1, 125.8, 125.6, 71.5, 70.0, 67.9, 67.4, 37.4, 37.3, 37.1 ppm.

HRMS: m/z calculated for $C_{21}H_{19}ClO_3SNa$ $(M + Na)^+$: 409.0636, found: 409.0647.

1-(4-Methoxyphenyl)-3-phenyl-1-(phenylsulfonyl)propanol (95):



95

Reaction time: 30 min.

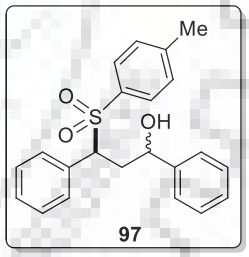
Yield: mixture of two diastereomers; (0.5 mmol scale reaction) 0.105 g (55%) as a white colour solid.

Mp: 155–157 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.52 (m, 4H), 7.45 (d, *J* = 7.6 Hz, 3H),7.39–7.27 (m, 10H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.74 (t, *J* = 7.2 Hz, 1H), 4.50 (dd, *J* = 3.2, 11.6 Hz, 1H), 4.38 (d, *J* = 8.4 Hz, 1H), 3.95 (dd, *J* = 5.6, 8.8 Hz, 1H), 3.79 (s, 2H), 3.77 (s, 3H), 2.83–2.74 (m, 2H), 2.58–2.50 (m, 1H), 2.43–2.36 (m, 1H), ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.33, 137.3, 135.8, 133.5, 132.0, 130.3, 130.1, 130.0, 128.6, 127.5, 127.0, 126.8, 1, 122.2, 120.7, 117.4, 114.0, 113.8, 70.3, 69.8, 68.8, 68.6, 68.1, 55.2 ppm.

1,3-Diphenyl-1-tosylpropanol (97):



97

Reaction time: 30 min.

Yield: mixture of two diastereomers; (1.0 mmol scale reaction) 0.311 g (85%) as a white colour solid.

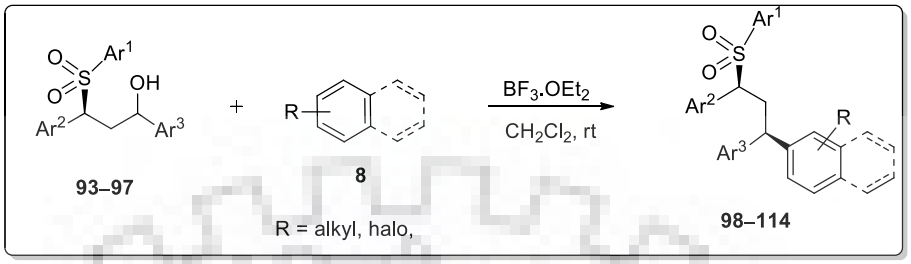
Mp: 160–161 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.0 Hz, 1H), 7.32–7.25 (m, 14H), 7.21–7.19 (m, 7H), 7.21 (d, *J* = 8.4 Hz, 3H), 7.02 (d, *J* = 7.6 Hz, 2H), 4.78 (dt, *J* = 3.2, 6.8 Hz, 1H), 4.52 (dd, *J* = 3.6, 7.6 Hz, 1H), 4.37 (d, *J* = 10.8 Hz, 1H),), 4.03–3.99 (m, 1H), 2.87–2.79 (m, 1H), 2.77–2.73 (m, 1H), 2.47–2.41 (m, 1H), 2.36 (s, 6H), 2.16 (s, 1H, O*H*), 1.19 (s, 1H, O*H*) ppm.

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 145.0, 144.3, 143.4, 133.8, 132.4, 128.9, 129.1, 128.7, 128.6, 128.2, 127.5, 127.2, 126.01, 125.4, 70.9, 70.8, 69.2, 68.2, 67.8, 39.3, 37.3, 37.1, 21.4 ppm.

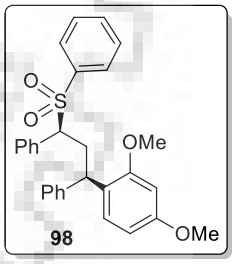
HRMS: m/z calculated for $C_{22}H_{22}O_3SNa$ $(M + Na)^+$: 389.1182, found: 389.1194.

3.2.8. General procedure for the synthesis of sulfono propanes alkylation 98-114 *via* C-:



To a stirred solution of γ-hydroxysulfone **93**–**97** (0.2 mmol) in 1 mL of CH_2Cl_2 was added an electron-rich arene **8** (0.22 mmol). Then $BF_3{\cdot}OEt_2$ (0.030 g, 0.24 mmol) was added slowly drop-wise, and the mixture was allowed to stir at rt for an appropriate time. After completion of the reaction, as shown by TLC, the reaction mixture was concentrated under reduced pressure and subjected to silica gel column chromatography using ethyl acetate/hexanes (20:80) as the eluting system to afford the diastereomeric mixture of propane derivative **98**–**114**.

3-(3,5-Dimethoxyphenyl)-1,3-diphenyl-1-(phenylsulfonyl)propane (98):



Reaction time: 1 h.

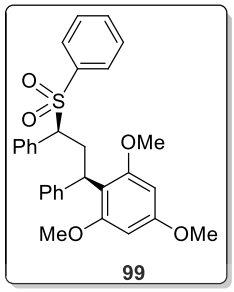
Yield: mixture of two diastereomers; 0.089 g (94%) as a colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.27–7.25 (m, 4H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.05 (t, *J* = 5.2 Hz, 4H), 6.89 (d, *J* = 9.2 Hz, 1H), 6.36–6.34 (m, 2H), 3.96 (dd, *J* = 3.6, 12.0 Hz, 1H), 3.87 (dd, *J* = 2.8, 12.0 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.00 (dt, *J* = 2.8, 14.0 Hz, 1H), 2.75 (dt, *J* = 4.0, 8.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 157.3, 144.2, 141.2, 137.2, 133.2, 131.4, 130.2, 129.9, 128.7, 128.4, 128.1, 127.8, 126.4, 124.9, 121.2, 103.7, 98.4, 69.6, 55.1, 54.9, 40.3, 31.8 ppm.

HRMS: m/z calculated for $C_{29}H_{28}O_4SNa$ $(M + Na)^+$: 495.1601 found 495.1611.

1,3-Diphenyl-1-(phenylsulfonyl)-3-(2,4,6-trimethoxyphenyl)propane (99):



99

Reaction time: 1 h.

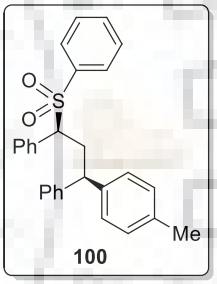
Yield: mixture of two diastereomers; 91 mg (91%) as a colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.50 (m, 3H), 7.36 (t, *J* = 8.4 Hz, 2H), 7.25–7.11 (m, 7H), 6.97 (d, *J* = 8.4 Hz, 2H), 5.94 (s, 3H), 4.43 (dd, *J* = 6.4, 10.8 Hz, 1H), 4.04 (d, *J* = 13.2 Hz, 1H), 3.76 (d, *J* = 18.0 Hz, 1H), 3.71 (s, 3H), 3.56 (s, 6H), 2.76–2.67 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 158.7, 142.9, 137.7, 133.2, 132.4, 130.1, 129.0, 128.4, 128.2, 128.1, 127.9, 127.8, 125.6, 112.9, 90.9, 70.5, 55.4, 55.2, 37.1, 30.1 ppm.

HRMS: m/z calculated for $C_{30}H_{30}O_5SNa$ $(M + Na)^+$: 525.1706 found 525.1702.

1,3-Diphenyl-1-(phenylsulfonyl)-3-(*p*-tolyl)propane (100):



100

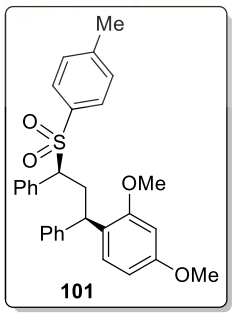
Reaction time: 12 h.

Yield: mixture of two diastereomers; 49 mg (57%) as a colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.36–7.31 (m, 4H), 7.27 (s, 1H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.16–7.12 (m, 2H), 7.09–7.02 (m, 5H), 6.94 (d, *J* = 7.6 Hz, 1H), 3.88 (t, *J* = 10.4 Hz, 1H), 3.68–3.64 (m, 1H), 3.17 (t, *J* = 12.0 Hz, 1H), 2.78 (dt, *J* = 4.0, 13.2 Hz, 1H), 2.32 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 138.6, 137.3, 136.4, 133.4, 131.8, 130.1, 129.5, 129.2, 129.0, 128.6, 127.9, 127.3, 126.4, 69.6, 47.2, 33.2, 21.0, 20.9 ppm.

3-(3,5-Dimethoxyphenyl)-1,3-diphenyl-1-(tosyl)propane (101):



101

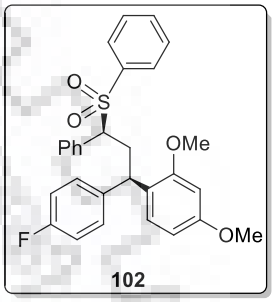
Reaction time: 1 h.

Yield: mixture of two diastereomers; 89 mg (92%) as a colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.27–7.23 (m, 4H), 7.21 (d, *J* = 6.8 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 7.2 Hz, 4H), 6.90 (d, *J* = 9.2 Hz, 1H), 6.36–6.34 (m, 2H), 3.96 (dd, *J* = 4.0, 12.0 Hz, 1H), 3.86 (dd, *J* = 2.8, 12.0 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.03–2.97 (m, 1H), 2.73 (dt, *J* = 4.0, 13.6 Hz, 1H), 2.38 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 157.3, 144.2, 141.3, 134.4, 131.6, 130.3, 129.1, 129.1, 128.9, 128.4, 128.1, 127.9, 126.4, 125.1, 103.7, 98.5, 69.7, 55.2, 55.0, 40.4, 32.0, 21.5 ppm.

3-(3,5-Dimethoxybenzene)-3-(4-fluorophenyl)-1-phenyl-1-(phenylsulfonyl)propane (102):



102

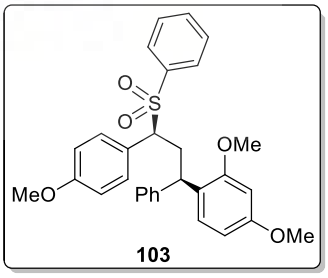
Reaction time: 5 h.

Yield: mixture of two diastereomers; 0.089 g (91%) as a colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.33–7.30 (m, 1H), 7.26–7.23 (m, 2H), 7.04–6.99 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.92–6.89 (m, 1H), 6.38–6.34 (m, 2H), 3.94 (dd, J =8.0, 12.0 Hz, 1H), 3.82 (dd, *J* = 2.8, 12.0 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 2.99 (dt, *J* = 2.8, 12.4 Hz, 1H), 2.76 (dt, *J* = 3.6, 13.2 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (d, $^1J_{C,F}$ = 242 Hz), 159.5, 157.4, 137.1, 133.4, 131.4, 130.2, 129.9, 129.8, 128.9, 128.6, 128.3, 127.7, 124.9, 115.4, 115.2, 103.7, 98.6, 69.7, 55.3, 55.0, 39.8, 31.9 ppm.

3-(1,3-Dimethoxybenzene)-1-(4-methoxyphenyl)-3-phenyl-1-(phenylsulfonyl)propane (103):



103

Reaction time: 5 h.

Yield: mixture of two diastereomers; 0.083 g (83%) as a colourless viscous liquid.

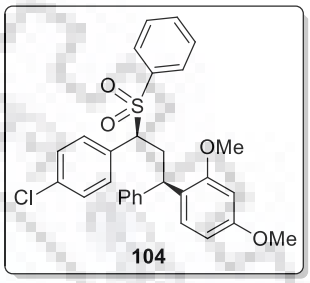
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56–7.49 (m, 3H), 7.40–7.36 (m, 2H), 7.27–7.21 (m, 3H), 7.05–7.03 (d, *J* = 7.2 Hz, 2H), 6.98 (d, *J* = 7.6 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* =

8.0 Hz, 2H), 6.36 (s, 2H), 3.98 (d, *J* = 12.0 Hz, 1H), 3.85 (d, *J* = 10.8, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 2.98 (t, *J* = 12.8, 1H), 2.69 (t, *J* = 15.2 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 159.3, 157.4, 141.3, 137.4, 133.2, 131.4, 129.9, 128.5, 128.4, 127.9, 126.4, 125.2, 123.1, 113.6, 103.7, 98.5, 69.0, 55.2, 40.3, 31.8 ppm.

HRMS: m/z calculated for $C_{30}H_{30}NaO_5S$ $(M + Na)^+$: 525.1706 found 525.1700.

1-(4-Chlorophenyl)-3-(3,5-dimethoxybenzene)-3-phenyl-1-(phenylsulfonyl)propane (104):



104

Reaction time: 5 h.

Yield: Mixture of two diastereomers; 0.100 g (99%) as a colourless viscous liquid;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.26–7.24 (m, 5H), 7.03–6.99 (m, 4H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.35 (s, 2H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.97 (t, *J* = 13.2 Hz, 1H), 2.69 (t, *J* = 13.2 Hz, 1H) ppm.

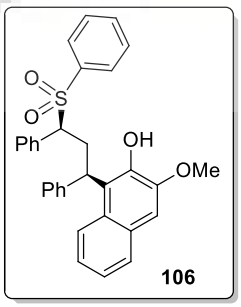
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 157.2, 140.9, 137.1, 134.8, 133.5, 131.5, 131.4, 130.1, 128.8, 128.6, 128.5, 126.5, 124.8, 103.8, 98.5, 69.0, 55.0, 40.4, 31.8 ppm.

HRMS: m/z calculated for $C_{29}H_{27}ClNaO_4S$ $(M + Na)^+$: 529.1211 found 529.1221.

1,3-Diphenyl-3-(3-methoxy-*β*-naphthol)-1-(phenylsulfonyl)propane (106):

Reaction time: 5 h.

yield: mixture of two diastereomers; 0.080 g (79%).as a white solid.



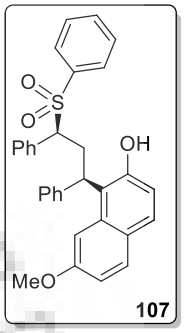
106

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 3H), 7.38–7.31 (m, 4H), 7.26–7.14 (m, 6H), 7.09 (t, *J* = 7.6 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 3H), 6.08 (br, 1H, O*H*), 4.86–4.82 (m, 1H), 4.20 (dd, *J* = 2.8, 10.8 Hz, 1H), 3.97–3.93 (m, 1H), 3.91 (s, 3H), 2.99–2.91 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 143.8, 142.0, 137.4, 133.3, 132.3, 129.8, 129.1, 129.0, 128.5, 128.2, 128.0, 127.4, 126.1, 124.3, 123.4, 122.6, 121.0, 105.1, 70.4, 55.8, 39.7, 30.0 ppm.

HRMS: m/z calculated for $C_{32}H_{28}O_4SNa$ $(M + Na)^+$: 531.1601 found 531.1609.

1,3-Diphenyl-3-(7-methoxy-β-naphthol)-1-(phenylsulfonyl)propane (107):



Reaction time: 5 h.

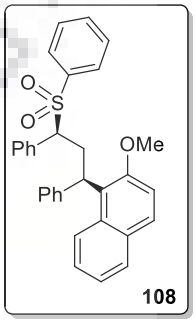
Yield: mixture of two diastereomers; 0.069 g (68%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 9.2 Hz, 1H), 7.52–7.45 (m, 4H), .7.80 (d, *J* = 8.0 Hz, 2H), .7.33 (d, *J* = 8.0 Hz, 2H), 7.28–7.23 (m, 2H), 7.21–7.17 (m, 2H), 7.09 (t, *J* = 8.0 Hz, 2H), 6.99–6.87 (m, 4H), 6.77 (d, *J* = 9.2 Hz, 1H), 5.65 (br, 1H, O*H*), 4.92 (t, *J* = 8.0 Hz, 1H), 4.24 (dd, *J* = 4.4, 12.0 Hz, 1H), 4.00–3.93 (m, 1H), 3.56 (s, 3H), 2.91–2.83 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 152.6, 142.0 137.1, 134.1, 132.7, 130.2, 129.8, 129.0, 128.8, 128.6, 128.3, 128.1, 127.7, 126.4, 124.9, 120.7, 116.3, 115.4, 101.9, 70.0, 55.0, 39.1, 29.9 ppm.

HRMS: m/z calculated for $C_{32}H_{28}NaO_4S$ $(M + Na)^+$: 531.1601 found 531.1609.

1,3-Diphenyl-3-(2-methoxy-naphthlene)-1-(phenylsulfonyl)propane (108):



Reaction time: 12 h.

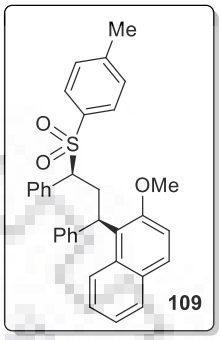
Yield: mixture of two diastereomers; 0.072 g (73%) as a colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.65 (m, 4H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.40–7.28 (m, 6H), 7.26–7.21 (m, 3H), 7.17–7.07 (m, 4H), 6.92 (d, *J* = 8.4 Hz, 2H), 4.92–4.88 (m, 1H), 4.24 (dd, *J* = 3.2, 11.2 Hz, 1H), 3.91 (d, *J* = 13.6 Hz, 1H), 3.59 (s, 3H), 2.90–2.82 (m, 1H), ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 155.1, 143.5, 142.3, 137.3, 133.3, 132.5, 132.3, 130.3, 130.0, 129.9, 129.4, 129.0, 128.6, 128.5, 128.1, 127.8, 127.4, 126.5, 125.8, 124.9, 123.1, 114.0, 70.3, 55.9, 39.1, 30.3 ppm.

HRMS: m/z calculated for $C_{32}H_{28}NaO3S$ $(M + Na)^+$: 515.1651 found 531.1609.

1,3-Diphenyl-3-(2-methoxynaphthlene)-1-(tosyl)propane (109):



Reaction time: 12 h.

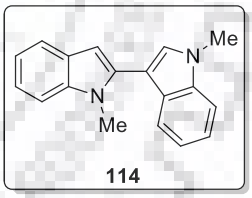
Yield: mixture of two diastereomers; 77 mg (76%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72–7.64 (m, 3H), 7.39 (d, *J* = 8.8 Hz, 3H), 7.31–7.26(m, 3H), 7.22 (t, *J* = 8.0 Hz, 2H), 7.15–7.06 (m, 6H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.78 (s, 1H), 4.21 (d, *J* = 14.4 Hz, 1H), 3.93–3.76 (m, 2H), 3.59 (s, 3H), 2.85–2.77 (m, 1H), 2.36 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 144.3, 142.4, 134.4, 132.6, 130.1, 129.9, 129.4, 129.2, 129.2, 129.1, 128.9, 128.8, 128.6, 128.5, 128.4, 128.0, 127.9, 127.4, 126.7, 126.4, 125.0, 123.1, 115.9, 114.0, 70.4, 55.9, 30.4, 21.5 ppm.

HRMS: m/z calculated for $C_{33}H_{30}O_3SNa$ $(M + Na)^+$: 529.1808 found 529.1802.

1,1'-Dimethyl-1*H*,1'*H*-2,3'-biindole (3′) (114):



Reaction time: 12 h.

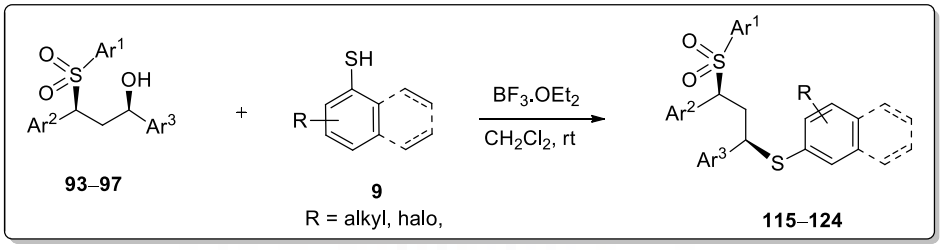
Yield: 0.040 g (62%) as a brown solid.

Mp: 216–217 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 7.73 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.43-7.39 (m, 3H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 6.8 Hz, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 3.90 (s, 3H), 3.78 (s, 3H).

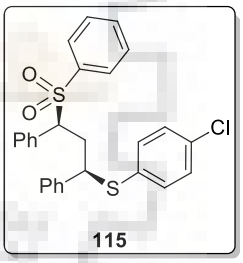
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 136.9, 128.3, 127.6, 122.4, 121.1, 120.3, 120.0, 119.5, 109.5, 109.3, 107.2, 33.0, 32.9 ppm.

3.2.9. General procedure for the synthesis of sulfono propanes by S-alkylation:



To a stirred solution of γ-hydroxysulfone **93–97 (**0.2 mmol) in 1 mL of CH_2Cl_2 was added an electron-rich arene **8** (0.22 mmol). Then $BF_3{\cdot}OEt_2$ (0.030 g, 0.24 mmol) was added slowly drop-wise, and the mixture was allowed to stir at rt for an appropriate time. After completion of the reaction, as shown by TLC, the reaction mixture was concentrated under reduced pressure and subjected to silica gel column chromatography using ethyl acetate/hexanes (20:80) as the eluting system to afford the diastereomeric mixture of propane derivative **115–124**.

3-(4-Chlorophenylthio)-1,3-diphenyl-1-(phenylsulfonyl)propane (115):



Reaction time: 30 min.

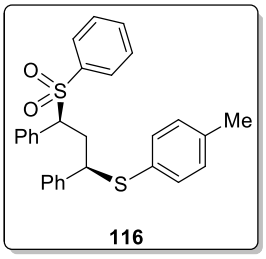
Yield: mixture of two diastereomers; 0.087 mg (91%) as a colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 3H), 7.17–7.12 (m, 5H), 7.08 (d, *J* = 7.2 Hz, 2H), 7.00 (d, *J* = 7.2 Hz, 2H), 6.90–6.89 (m, 2H), 6.79 (d, *J* = 7.6 Hz, 2H), 3.69 (d, *J* = 13.6 Hz, 2H), 2.90–2.83 (m, 1H), 2.68–2.61 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 136.9, 134.3, 133.9, 133.5, 132.1, 131.0, 129.8, 128.8, 128.6, 128.1, 127.8, 68.7, 50.1, 33.4 ppm.

HRMS: m/z calculated for $C_{27}H_{23}ClO_2S_2Na$ $(M + Na)^+$: 501.0720, found 501.0720.

1,3-Diphenyl-1-(phenylsulfonyl)-3-(*p*-tolylthio)propane (116):



116

Reaction time: 30 min.

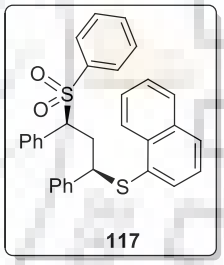
Yield: mixture of two diastereomers; 0.091 g (99%) as colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.46 (m, 1H), 7.39 (d, *J* = 9.2 Hz, 2H), 7.31–7.27 (m, 3H), 7.22–7.16 (m, 5H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.01–6.90 (m, 4H), 6.82 (d, *J* = 8.8 Hz, 2H), 3.74 (d, *J* = 14.0 Hz, 2H), 2.91 (t, *J* = 14.0 Hz, 1H), 2.73 (t, *J* = 13.6 Hz, 1H), 2.29 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.4, 137.8, 136.9, 133.4, 130.9, 129.8, 129.5, 129.5, 128.8, 128.5, 127.7, 68.7, 50.0, 33.3, 21.1 ppm.

HRMS: m/z calculated for $C_{28}H_{26}O_2S_2Na$ $(M + Na)^+$: 481.1266, found 481.1264.

1,3-Diphenyl-1-phenylsulfonyl-3-(naphthalenthio)propane (117):



117

Reaction time: 30 min.

Yield: mixture of two diastereomers; 0.089 g (90%).as a colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.71–7.68 (m, 3H), 7.50–7.46 (m, 3H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.35–7.26 (m, 8H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.10–7.09 (m, 2H), 6.89 (d, *J* = 7.6 Hz, 2H), 4.02 (d, *J* = 11.2 Hz, 1H), 3.83 (d, *J* = 11.6 Hz, 1H), 3.03 (t, *J* = 12.0 Hz, 1H), 2.85 (t, *J* = 12.4 Hz, 1H), ppm.

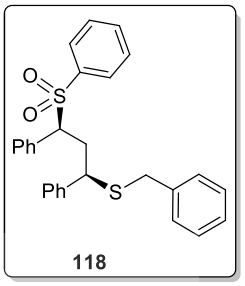
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 136.8, 133.4, 132.3, 131.3, 131.2, 130.9, 130.3, 129.9, 129.7, 129.5, 129.1, 128.9, 128.6, 128.4, 128.0, 127.9, 127.7, 127.6, 127.3, 126.3, 68.7, 49.5, 33.5 ppm.

HRMS: m/z calculated for $C_{31}H_{26}O_2S_2Na$ $(M + Na)^+$: 517.1266, found 517.1262.

3-Benzylthio-1,3-diphenyl-3-(phenylsulfonyl)propane (5d) (118):

Reaction time: 30 min.

Yield: mixture of two diastereomers; 0.087 g (95%) as a colourless viscous liquid.

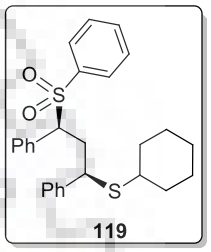


118

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.29–7.26 (m, 4H), 7.22–7.18 (m, 5H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.99–6.97 (m, 2H), 6.90 (d, *J* = 7.6 Hz, 2H), 3.73 (dd, *J* = 3.2, 11.6 Hz, 1H), 3.47 (d, *J* = 7.6 Hz, 2H), 3.42–3.38 (m, 1H), 2.91–2.84 (m, 1H), 2.74–2.66 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 137.5, 136.9, 133.4, 131.0, 129.9, 128.9, 128.7, 128.5, 128.3, 127.8, 126.9, 68.9, 45.6, 35.7, 33.7 ppm.

3-Cyclohexylthio-1,3-diphenyl-1-(phenylsulfonyl)propane (119):



119

Reaction time: 30 min.

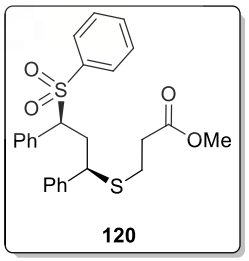
Yield: mixture of two diastereomers; 0.085 g (94%) as a colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 3H), 7.28–7.25 (m, 5H), 7.02–7.00 (m, 4H), 3.76 (dd, *J* = 3.6, 11.2 Hz, 1H), 3.58 (dd, *J* = 3.2, 11.2 Hz, 1H), 2.82 (dt, *J* = 3.2, 12.0 Hz, 1H), 2.69 (dt, *J* = 4.4, 12.0 Hz, 1H), 2.37–2.32 (m, 1H), 1.80 (d, *J* = 13.2, Hz, 1H), 1.65–1.49 (m, 5H), 1.17–1.10 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 137.0, 133.4, 131.2, 129.9, 128.9, 128.6, 127.6, 68.9, 44.3, 42.9, 34.4, 33.5, 33.2, 25.7 ppm.

HRMS: m/z calculated for $C_{27}H_{30}O_2S_2Na$ $(M + Na)^+$: 473.1579 found 473.1577.

1,3-Diphenyl-1-(phenylsulfonyl)-3-thio(methylpropanoate)propane (120):



120

Reaction time: 30 min.

Yield: mixture of two diastereomers; 0.084 g (92%) as a colourless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (t, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.35–7.30 (m, 3H), 7.27–7.26 (m, 2H), 7.25–7.23 (m, 2H), 7.03–6.97 (m, 4H), 3.76 (dd, *J* = 4.0, 11.6

Hz, 1H), 3.59 (s, 3H), 3.52 (dd, *J* = 4.4, 11.6 Hz, 1H), 2.88–2.81 (m, 1H), 2.69 (dt, *J* = 4.4, 12.0 Hz, 1H), 2.51–2.45 (m, 2H),), 2.32 (t, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 139.6, 136.8, 133.5, 131.1, 129.9, 129.0, 128.9, 128.8, 128.6, 127.8, 127.7, 127.5, 68.8, 51.6, 46.3, 34.1, 33.8, 26.1 ppm.

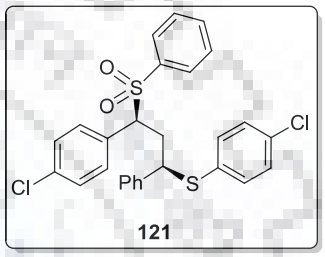
HRMS: m/z calculated for $C_{25}H_{26}O_4S_2Na$ $(M + Na)^+$: 477.1165 found 477.1165.

HRMS: m/z calculated for $C_{28}H_{26}O_2S_2Na$ $(M + Na)^+$: 481.1266, found 481.1273.

1-(4-Chlorophenyl)-3-(4-chlorophenylthio)-3-phenyl-1-(phenylsulfonyl)propane (121):

Reaction time: 30 min.

Yield: mixture of two diastereomers; 0.088 g (86%) as a white solid.



121

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (t, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.38–7.34 (m, 2H), 7.25–7.21 (m, 5H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 6.95 (d, *J* = 5.2 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 3.76–3.72 (m, 2H), 2.96–2.89 (m, 1H), 2.70–2.64 (m, 1H) ppm.

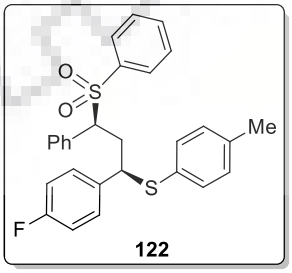
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 136.6, 135.2, 134.6, 134.5, 134.1, 133.7, 131.8, 131.0, 129.5, 128.9, 128.9, 128.8, 128.0, 127.6, 68.0, 50.1, 33.3 ppm.

HRMS: m/z calculated for $C_{27}H_{22}Cl_2NaO_2S_2$ $(M + Na)^+$: 535.0330, found 535.0347.

3-(4-Fluorophenyl)-1-phenyl-1-(phenylsulfonyl)-3-(*p*-tolylthio)propane (122):

Reaction time: 30 min.

Yield: mixture of two diastereomers; 0.094 g (99%) as colourless viscous liquid.



122

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56–7.49 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.37–7.18 (m, 2H), 7.23–7.07 (m, 2H), 7.01 (t, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.97–6.88 (m, 4H), 6.83 (d, *J* = 8.4 Hz, 3H), 3.84–3.78 (m, 1H), 3.76–3.71 (m, 1H), 3.01–2.86 (m, 1H), 2.79–2.59 (m, 1H), 2.31 (s, 3H) ppm.

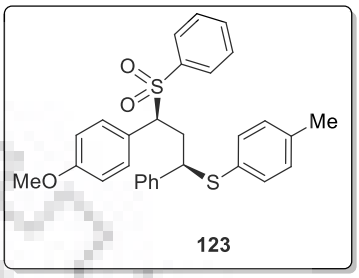
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, (d, $^1J_{C,F}$ = 245 Hz), 138.1, 136.8, 134.8, 134.3, 133.6, 133.5, 130.8, 129.7, 129.6, 129.5, 128.8, 128.5, 115.6, 115.4, 68.8, 49.4, 33.2, 21.0 ppm.

HRMS: m/z calculated for $C_{28}H_{25}O_2S_2Na$ $(M + Na)^+$: 499.1172, found 499.1171.

1-(4-Methoxyphenyl)-3-phenyl-1-(phenylsulfonyl)-3-(*p*-tolylthio)propane (123):

Reaction time: 30 min.

Yield: mixture of two diastereomers; 0.094 g (96%) as a colourless viscous liquid.



123

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.23 (br, 3H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.97–6.96 (m, 2H), 6.77 (d, *J* = 4.4 Hz, 1H), 6.74 (br, 3H), 3.80 (s, 3H), 3.74 (dd, *J* = 4.0, 11.6 Hz, 1H), 3.68 (dd, *J* = 3.2, 12.0 Hz, 1H), 2.90–2.82 (m, 1H), 2.71–2.65 (m, 1H), 2.31 (s, 3H) ppm.

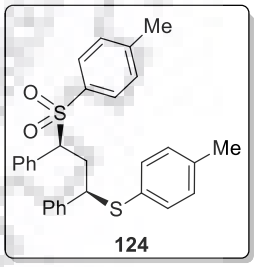
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 139.0, 137.9, 137.1, 133.4, 131.1, 130.0, 129.6, 128.9, 128.6, 127.8, 122.5, 113.9, 68.1, 55.2, 50.1, 33.3, 21.1 ppm.

HRMS: m/z calculated for $C_{29}H_{28}O_3S_2Na$ $(M + Na)^+$: 511.1372, found 511.1377.

1,3-Diphenyl-3-(*p*-tolylthio)-1-(tosyl)propane (124)

Reaction time: 30 min.

Yield: mixture of two diastereomers; 0.093 g (98%) as a colourless viscous liquid;



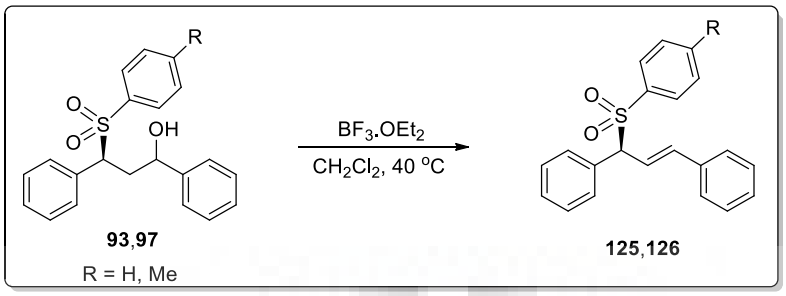
124

^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.38–7.28 (m, 7H), 7.24–7.23 (m, 1H), 7.17–7.13 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.04–7.02 (m, 2H), 6.97 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.83–3.76 (m, 2H), 3.00–2.92 (m, 1H), 2.81–2.74 (m, 1H), 2.41 (s, 3H), 2.36 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 139.0, 137.9, 134.0, 133.4, 131.1, 129.9, 129.5, 129.2, 128.98, 128.7, 128.5, 127.8, 68.7, 50.1, 33.4, 21.5, 21.0 ppm.

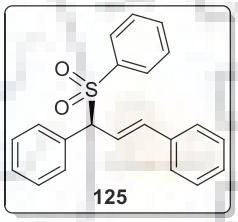
HRMS: m/z calculated for $C_{29}H_{28}O_2S_2Na$ $(M + Na)^+$: 495.1423, found 495.1423.

3.2.10. General procedure for the synthesis of allylic sulfones (125,126):



To a stirred solution of γ-hydroxysulfones **93**,**97** (0.2 mmol) in 1 mL of CH_2Cl_2, $BF_3{\cdot}OEt_2$ (0.030 g, 0.24 mmol) or PTSA.H_2O (0.042 g, 0.24 mmol) was added and the mixture was allowed to stir at 40 °C for 12 h. After completion of the reaction, as shown by TLC, the resulting mixture was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel using ethyl acetate/hexanes (30:70) as the eluting system to afford pure allylic sulfones **125**,**126**.

1,3-Diphenyl-1-(phenylsulfonyl)propene (125):



Reaction time: 12 h.

Yield: 0.061 g (67 %) as a brown solid.

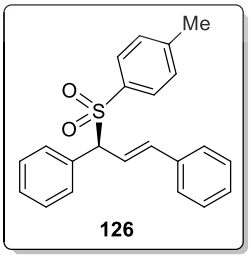
Mp: 218–219 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.32–7.26 (m, 10H), 6.61–6.49 (m, 2H), 4.83 (d, *J* = 8.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 137.4, 135.9, 133.7, 132.3, 129.8, 129.4, 129.0, 128.7, 126.8, 120.0, 90.5 ppm.

HRMS: m/z calculated for $C_{21}H_{18}O_2SNa$ $(M + Na)^+$: 357.0920 found 357.0918.

1,3-Diphenyl-1-(tosyl)propene (126):



Reaction time: 12 h.

Yield: 0.049 g (71%) as a brown solid

Mp: 218–219 ^{o}C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.37-7.36 (m, 1H), 7.35-7.318 (m, 8H), 7.29-7.27 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.58-6.51 (m, 2H), 4.82 (dd, *J* = 8.0 Hz, 1H), 2.40 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 137.9, 135.9, 134.4, 132.4, 129.6, 129.2, 128.8, 128.4, 126.7, 120.2, 75.3, 21.6 ppm.

HRMS: m/z calculated for $C_{22}H_{20}O_2SNa$ $(M + Na)^+$: 371.1076 found 371.1057.

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NMR Spectra for Selected Compounds

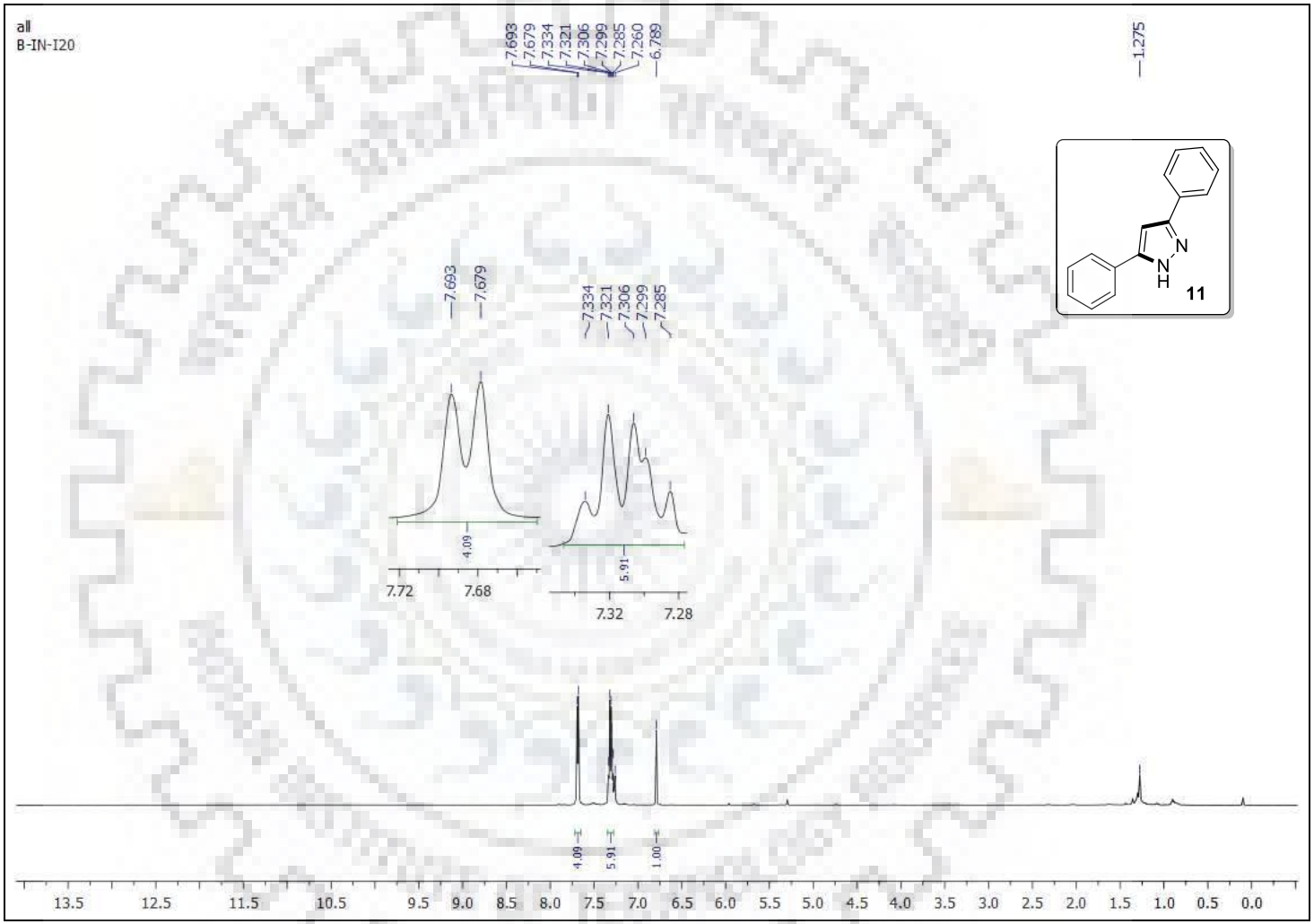


Figure S-1: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **11**.

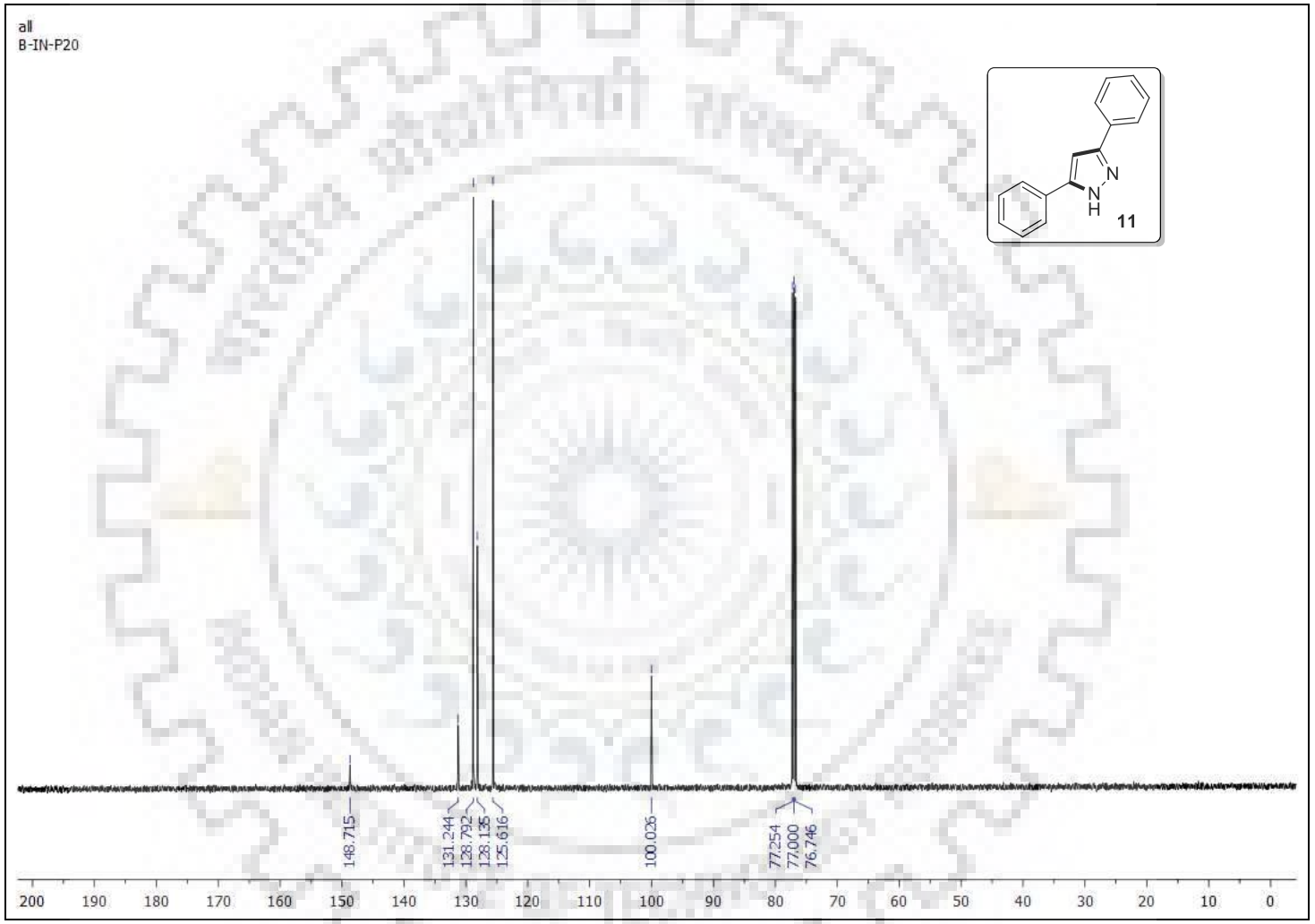


Figure S-2: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **11**.

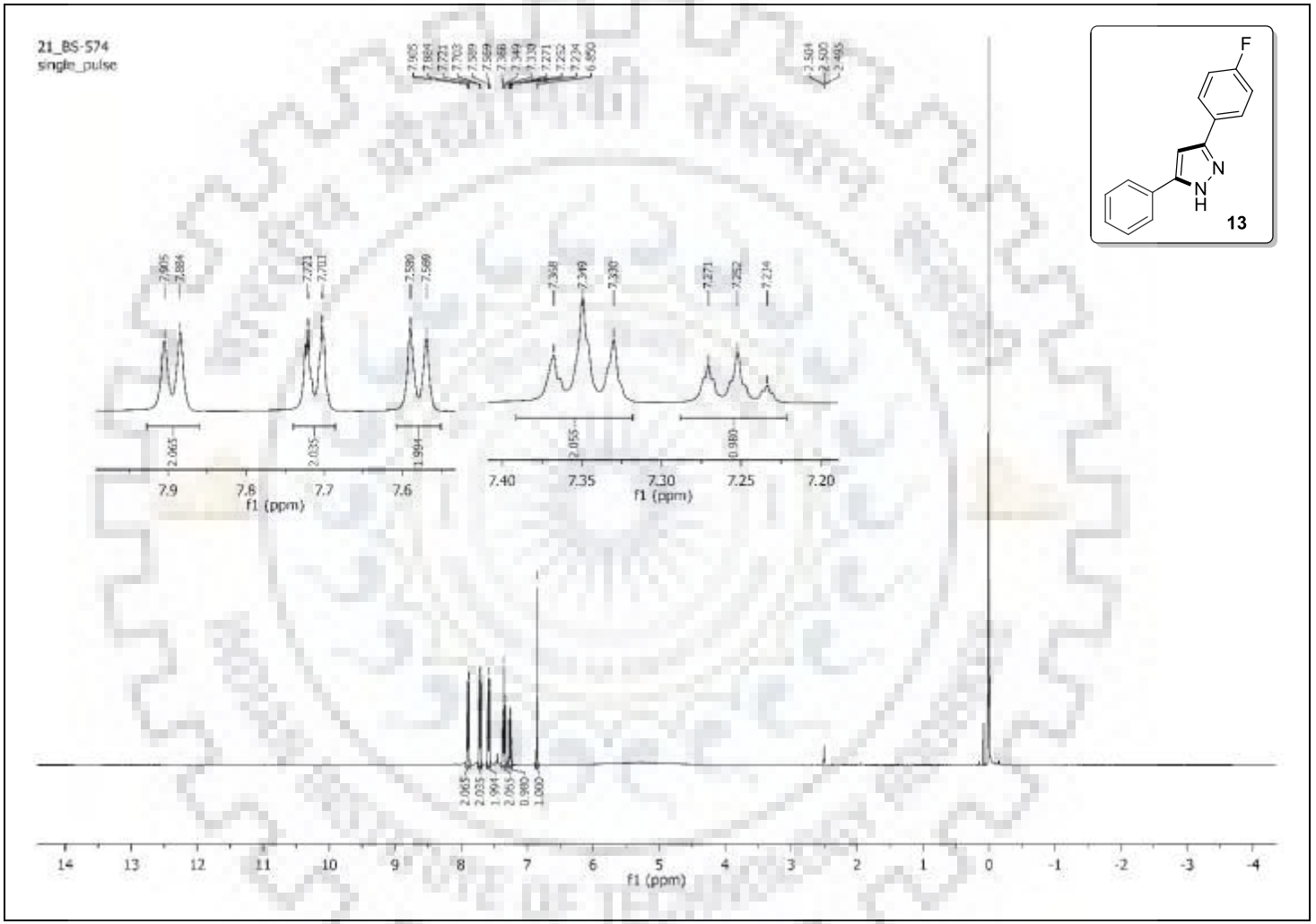


Figure S-3: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **13**.

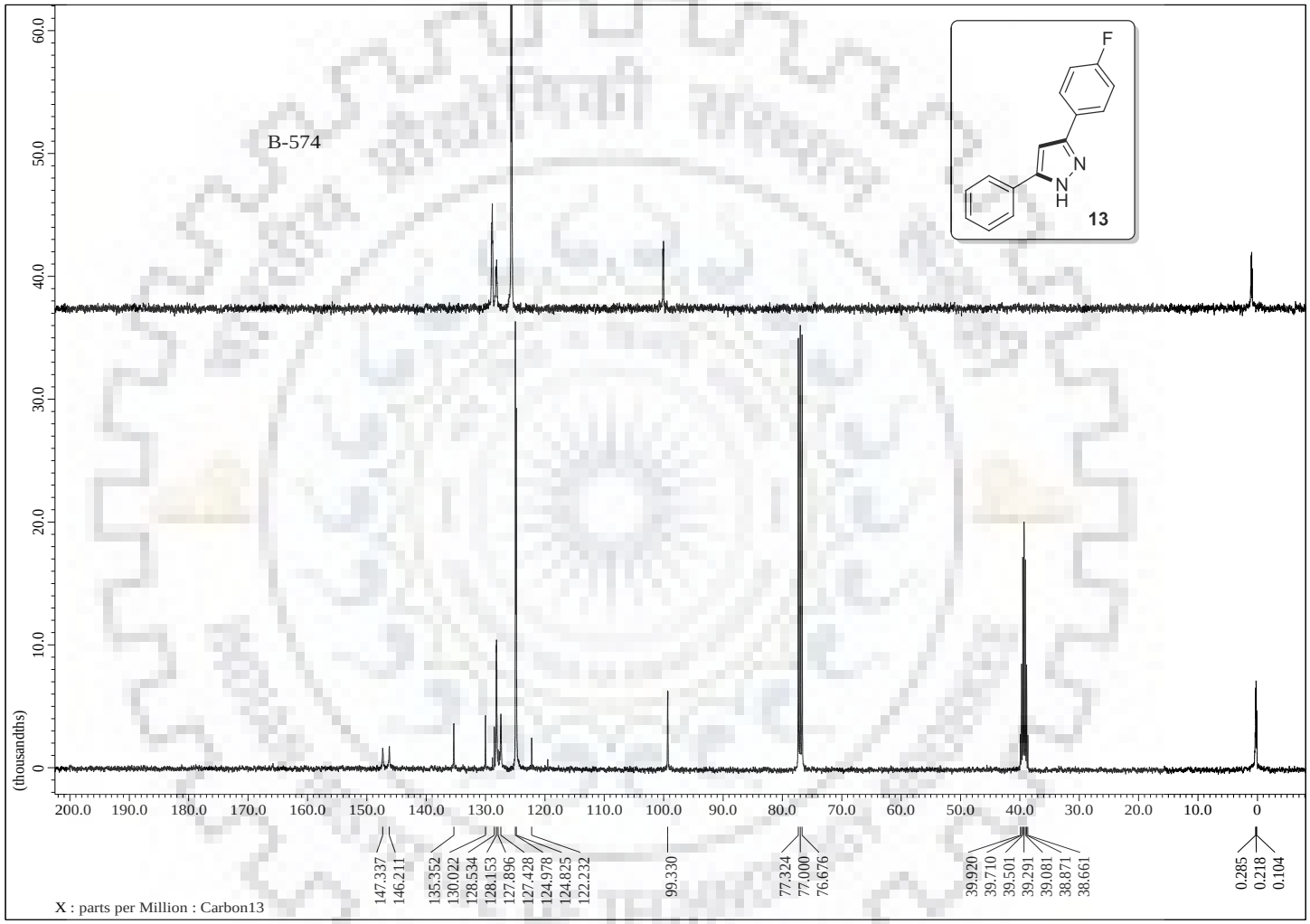


Figure S-4: ^{13}C and DEPT (100 MHz, $CDCl_3$ + DMSO-d_6) Spectra of **13**.

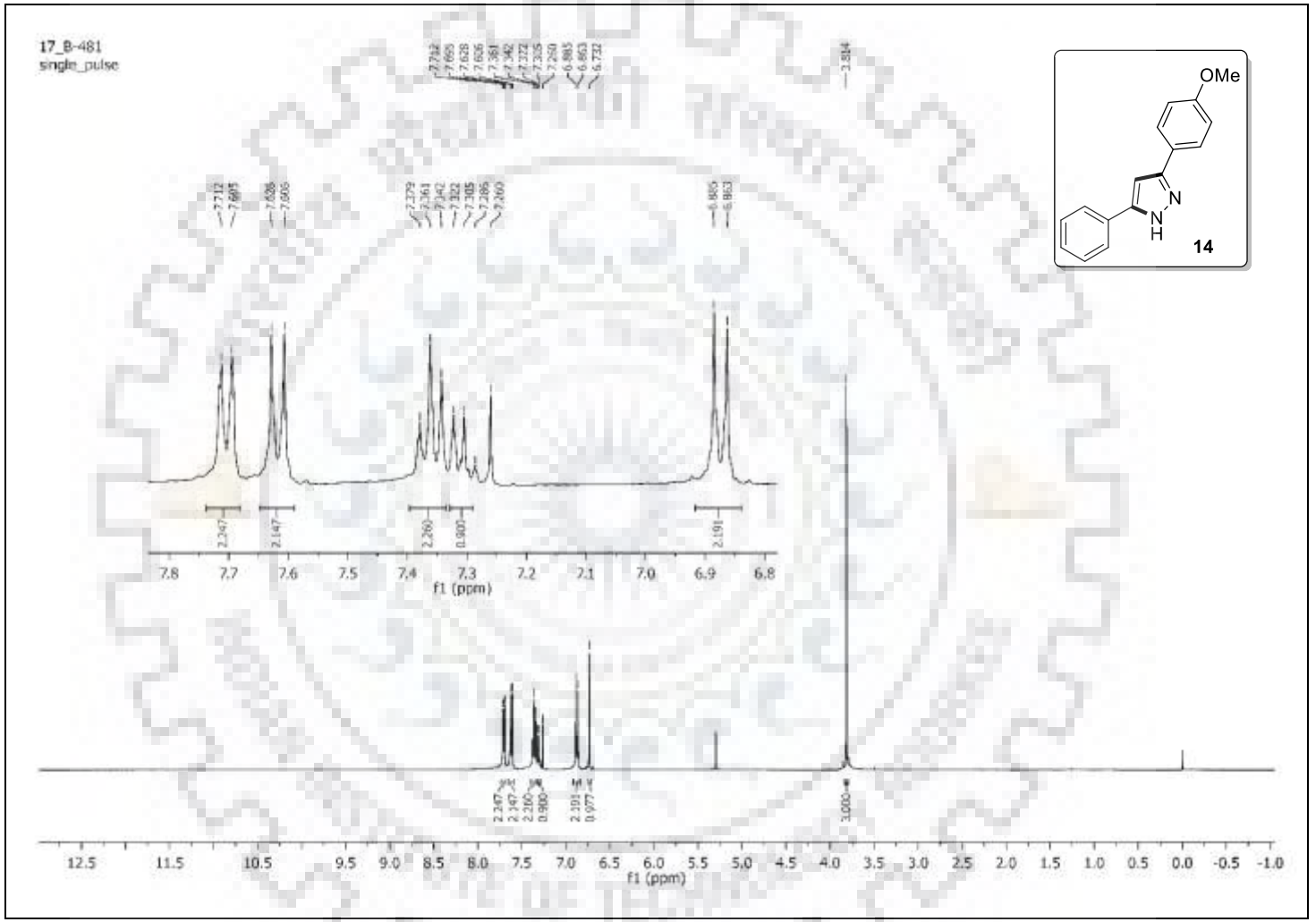


Figure S-5: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **14**.

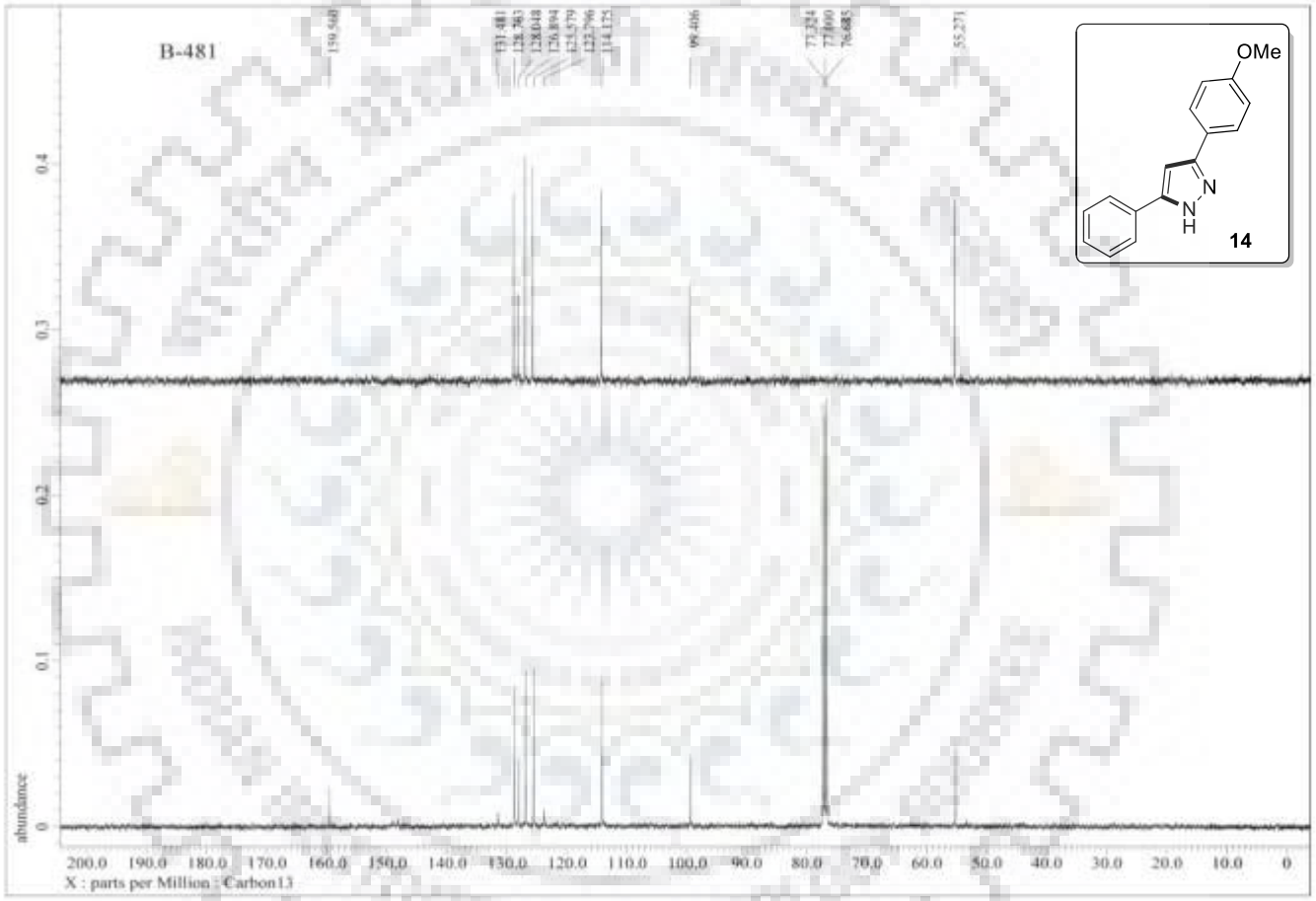


Figure S-6: ^{13}C and DEPT (100 MHz, $CDCl_3$) Spectra of **14**.

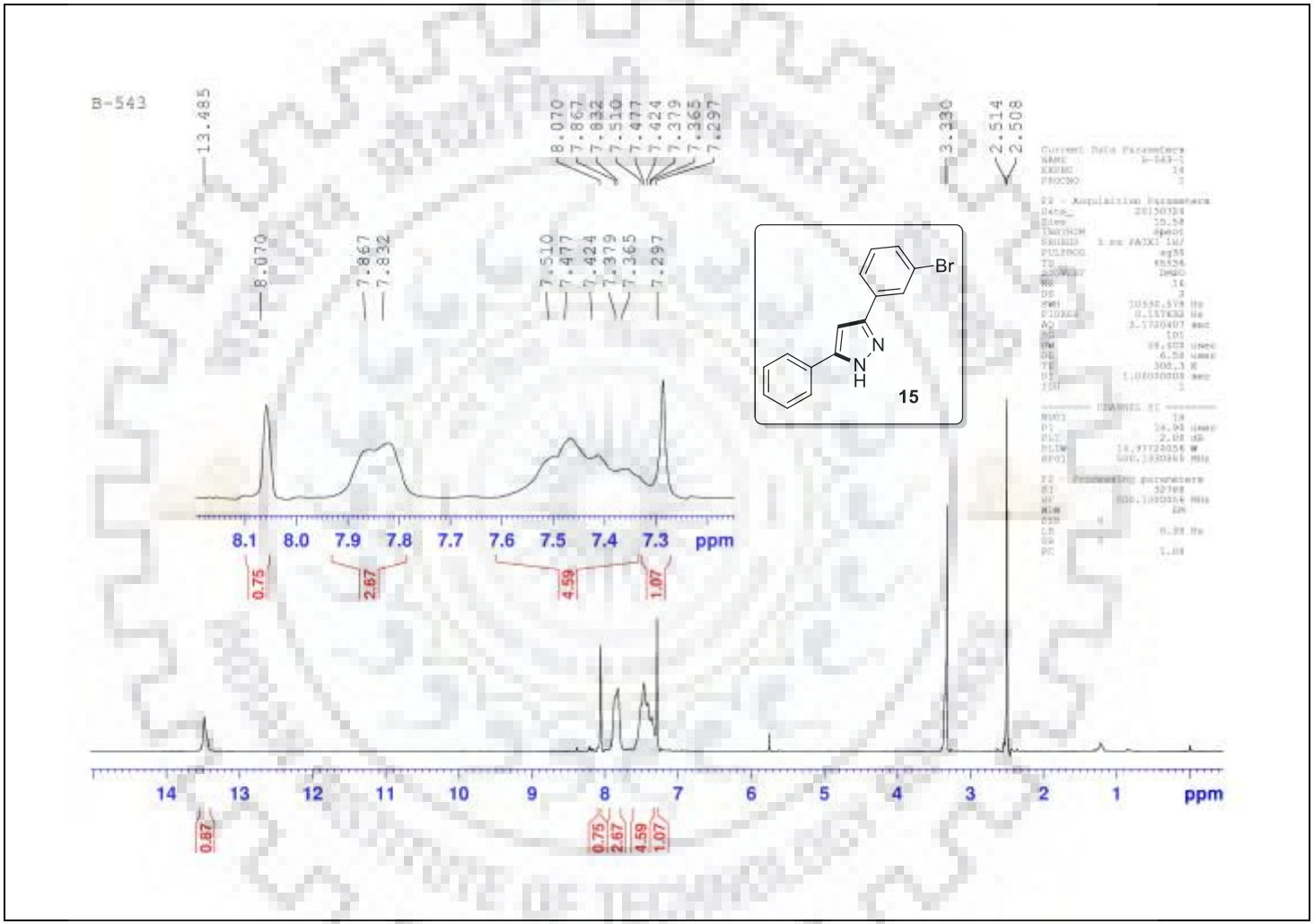


Figure S-7: ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6) Spectrum of **15**.

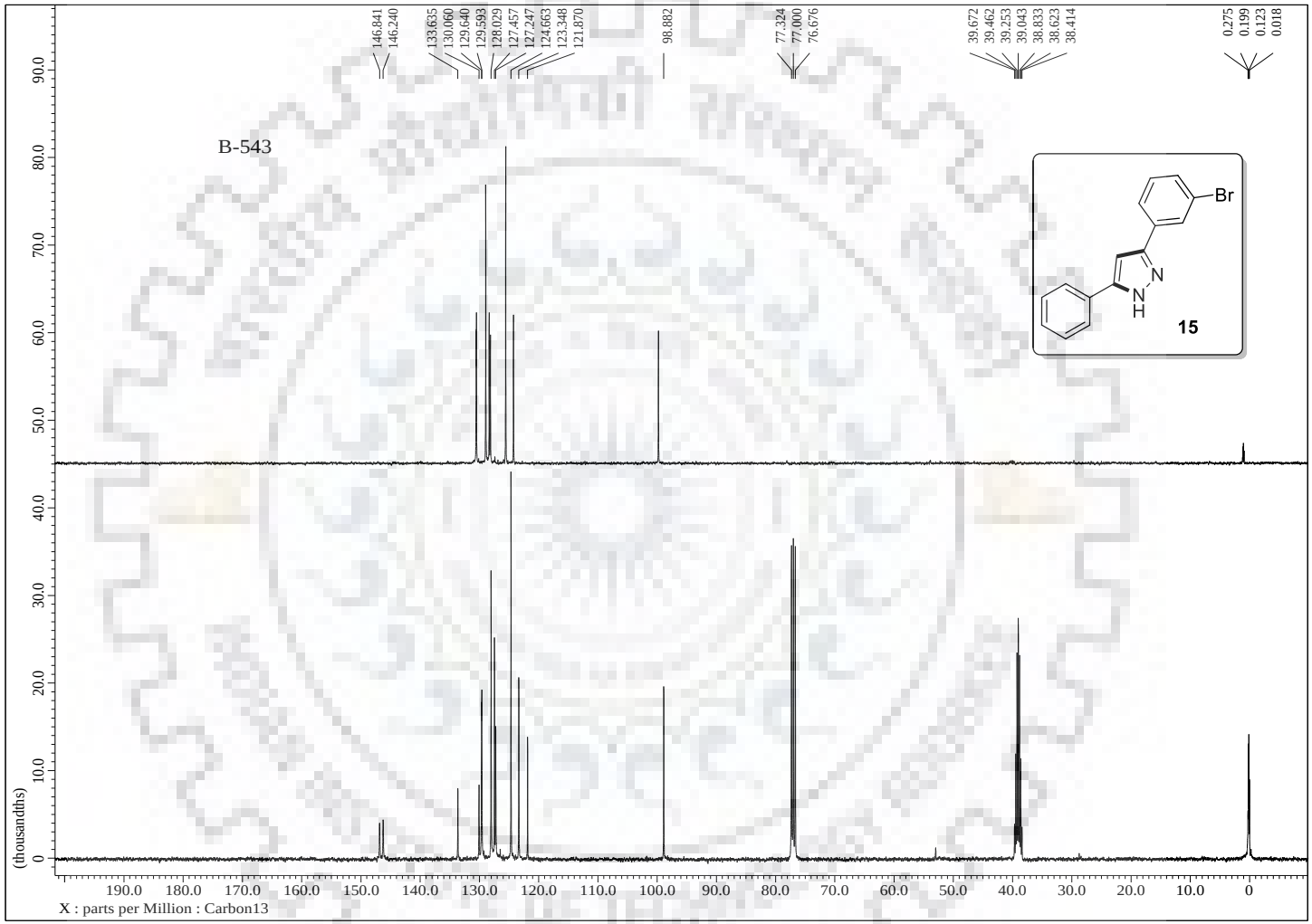


Figure S-8: ^{13}C and DEPT (100 MHz, $CDCl_3$ + DMSO-d_6) Spectra of **15**.

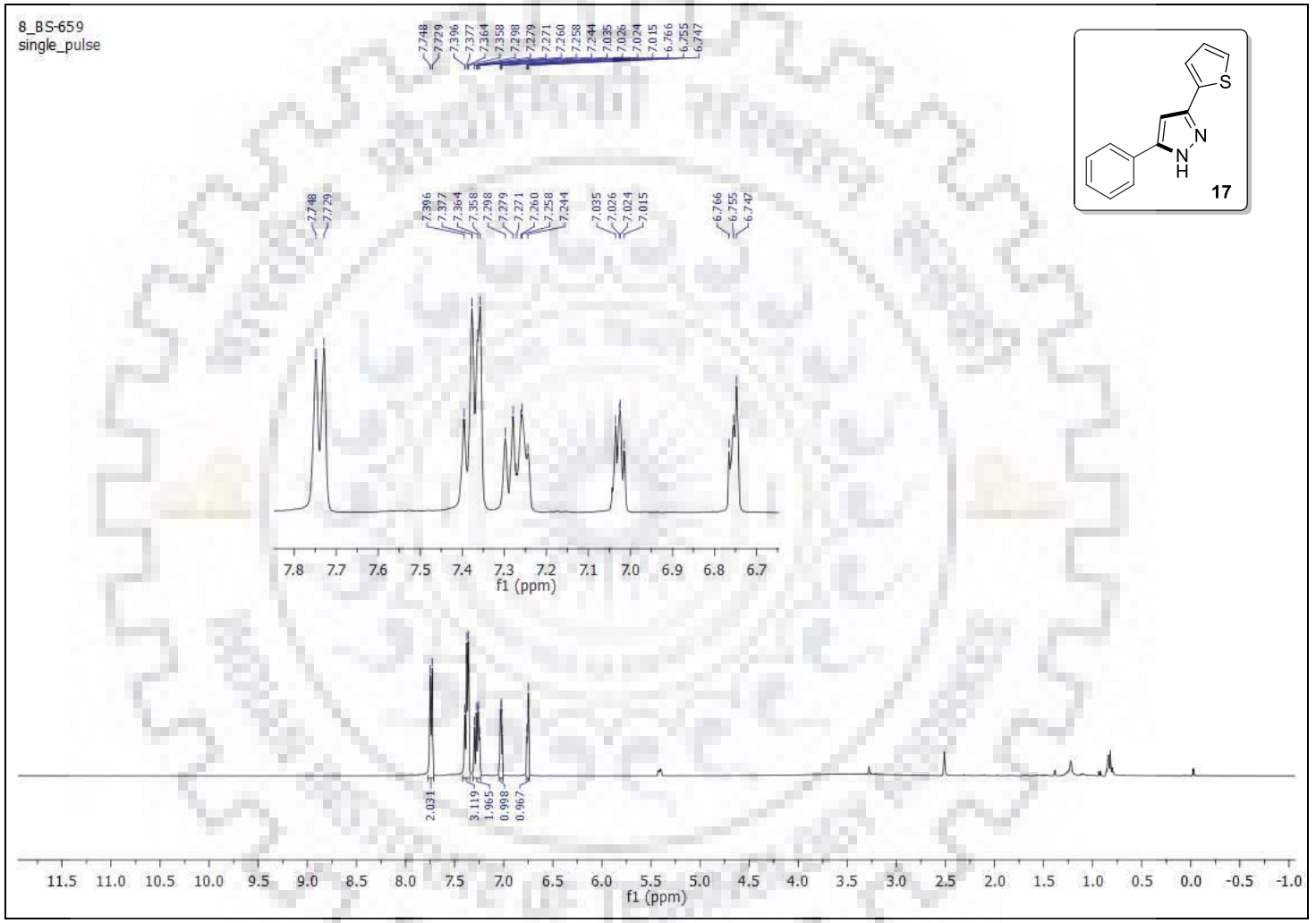


Figure S-9: ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6) Spectrum of **17**.

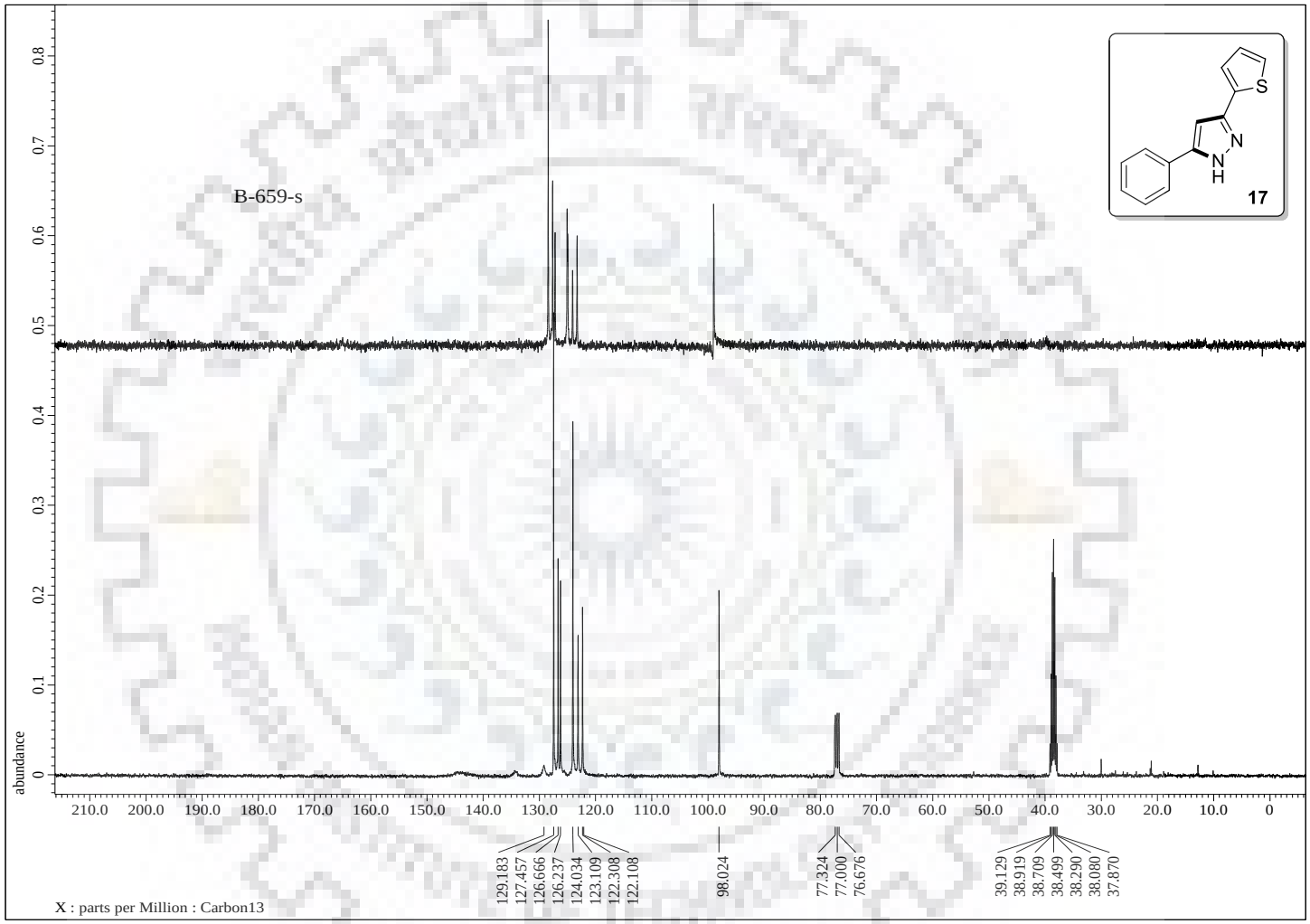


Figure S-10: ^{13}C and DEPT (100 MHz, $CDCl_3$ + DMSO-d_6) Spectra of **17**.

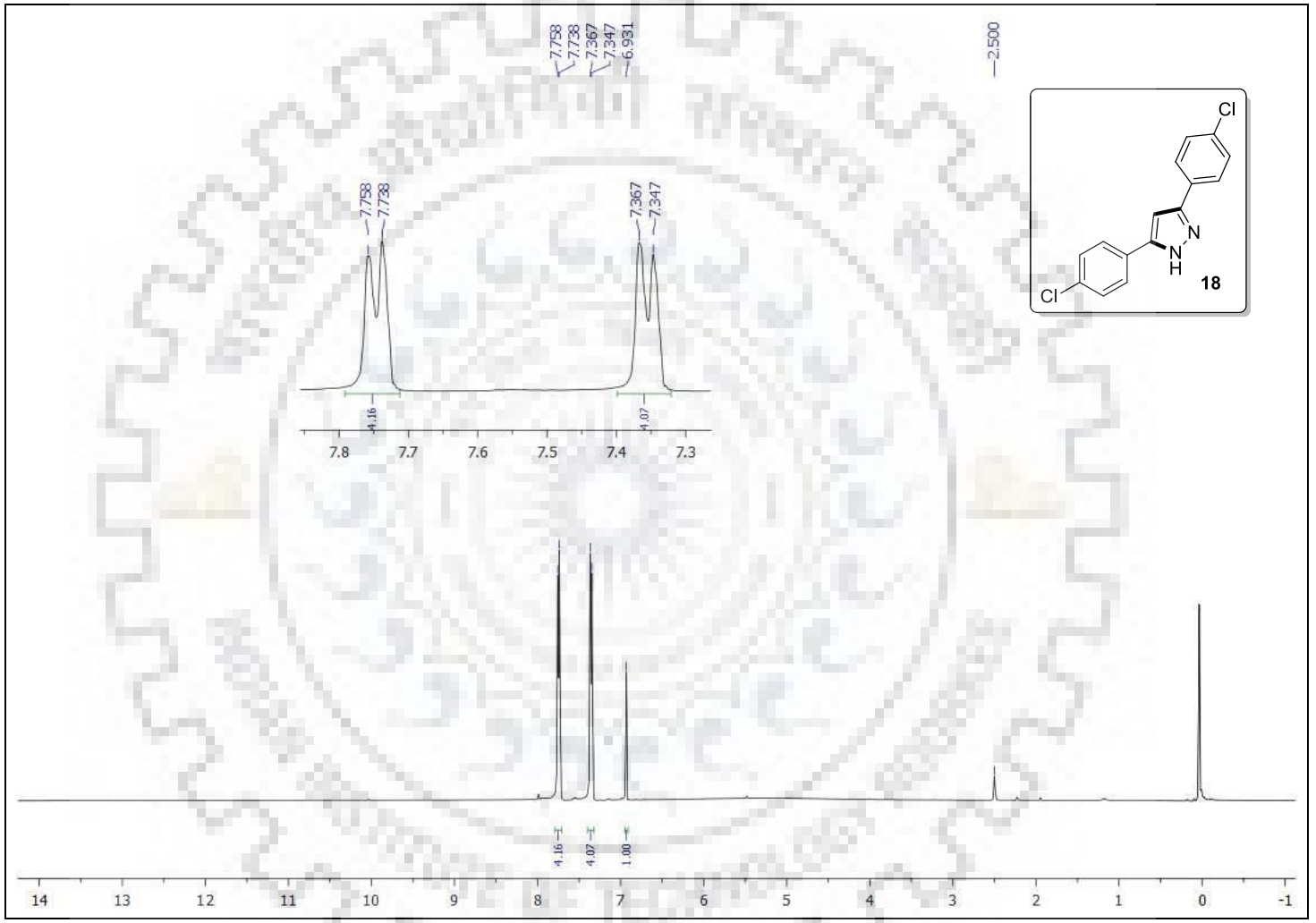


Figure S-11: ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6) Spectrum of **18**.

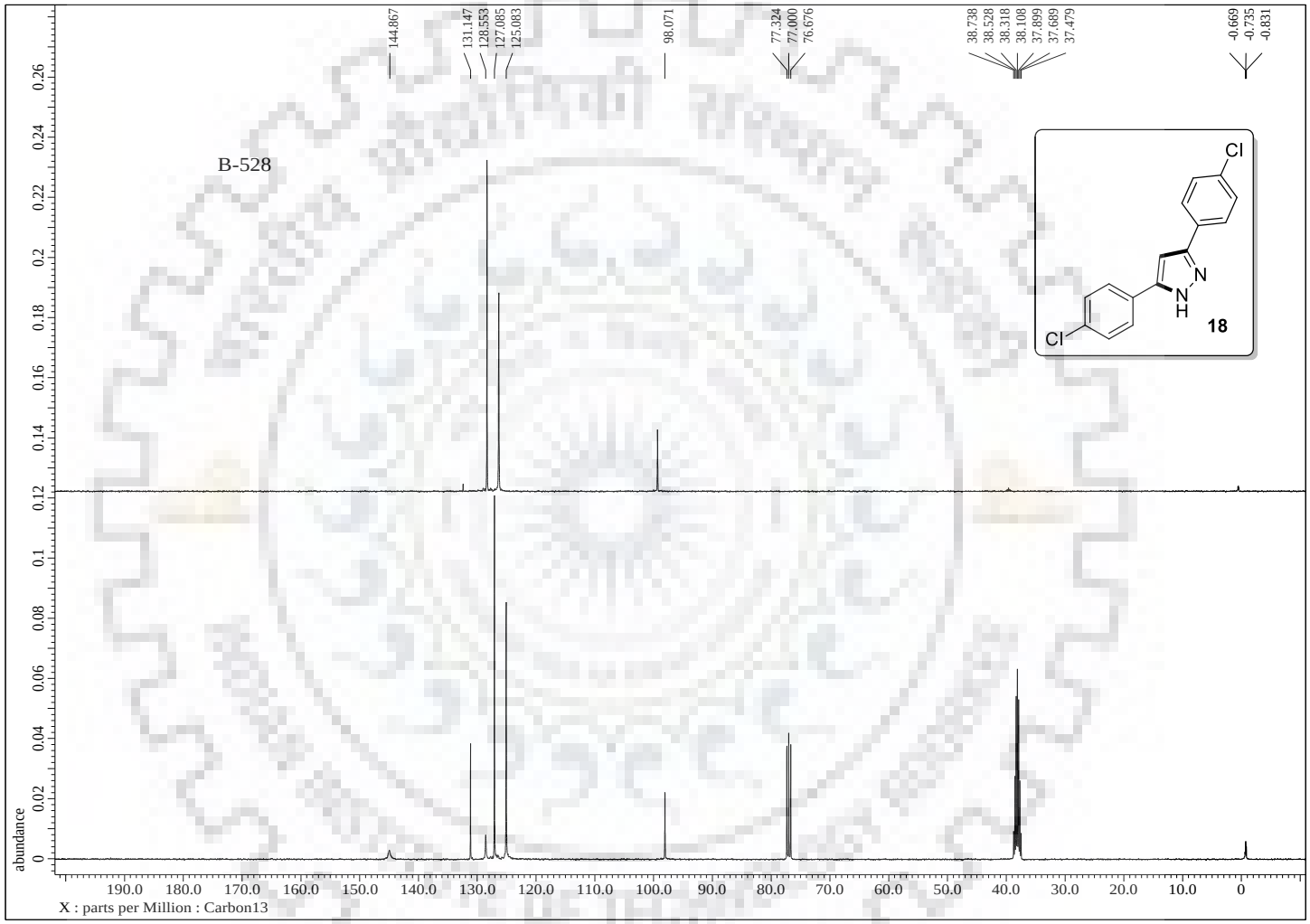


Figure S-12: ^{13}C (100 MHz, $CDCl_3$ + DMSO-d_6) Spectra of **18**.

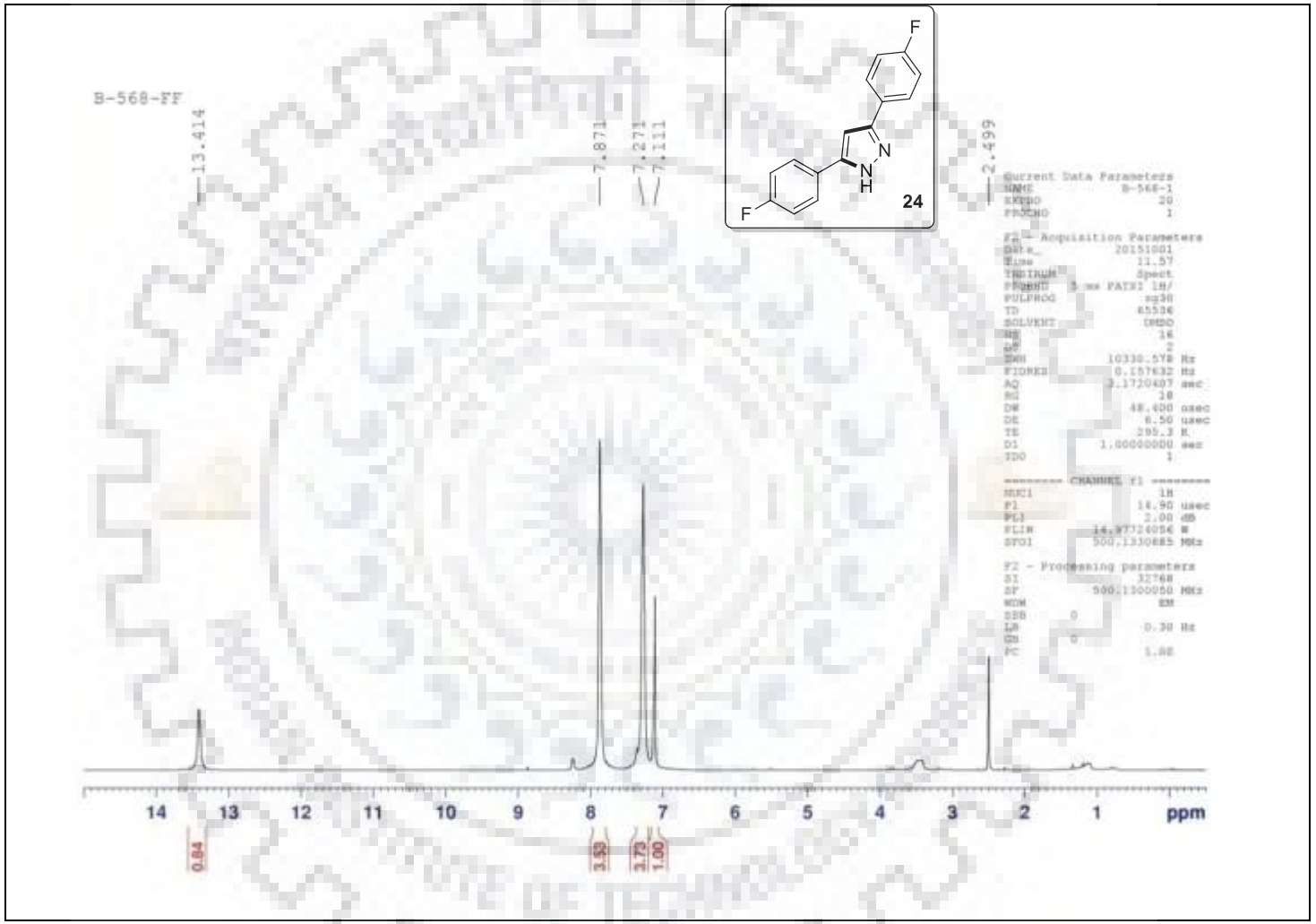


Figure S-13: ^{1}H NMR (100 MHz, DMSO-d_6) Spectrum of **24**.

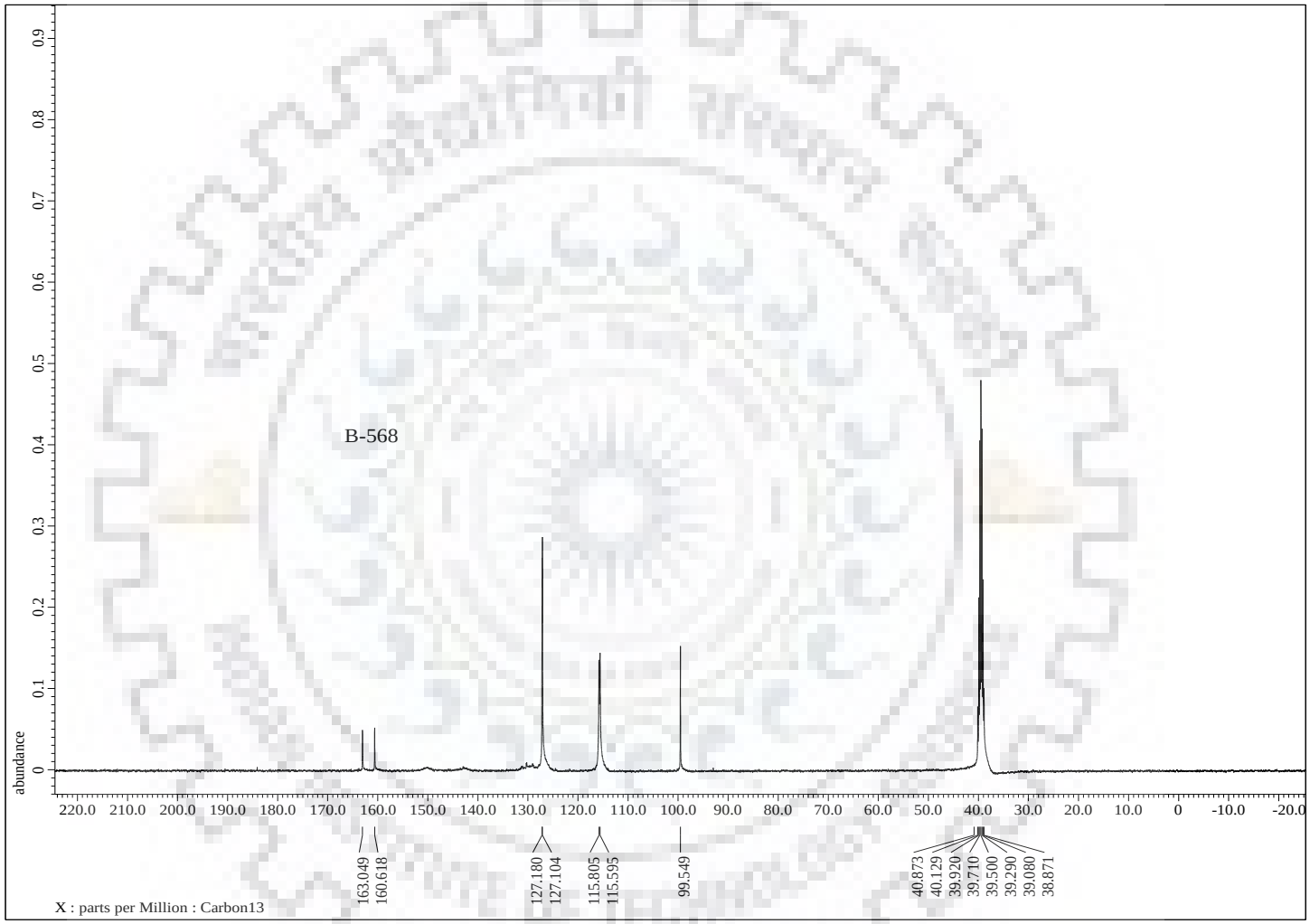


Figure S-14: ^{13}C (100 MHz, DMSO-d_6) Spectra of **24**.

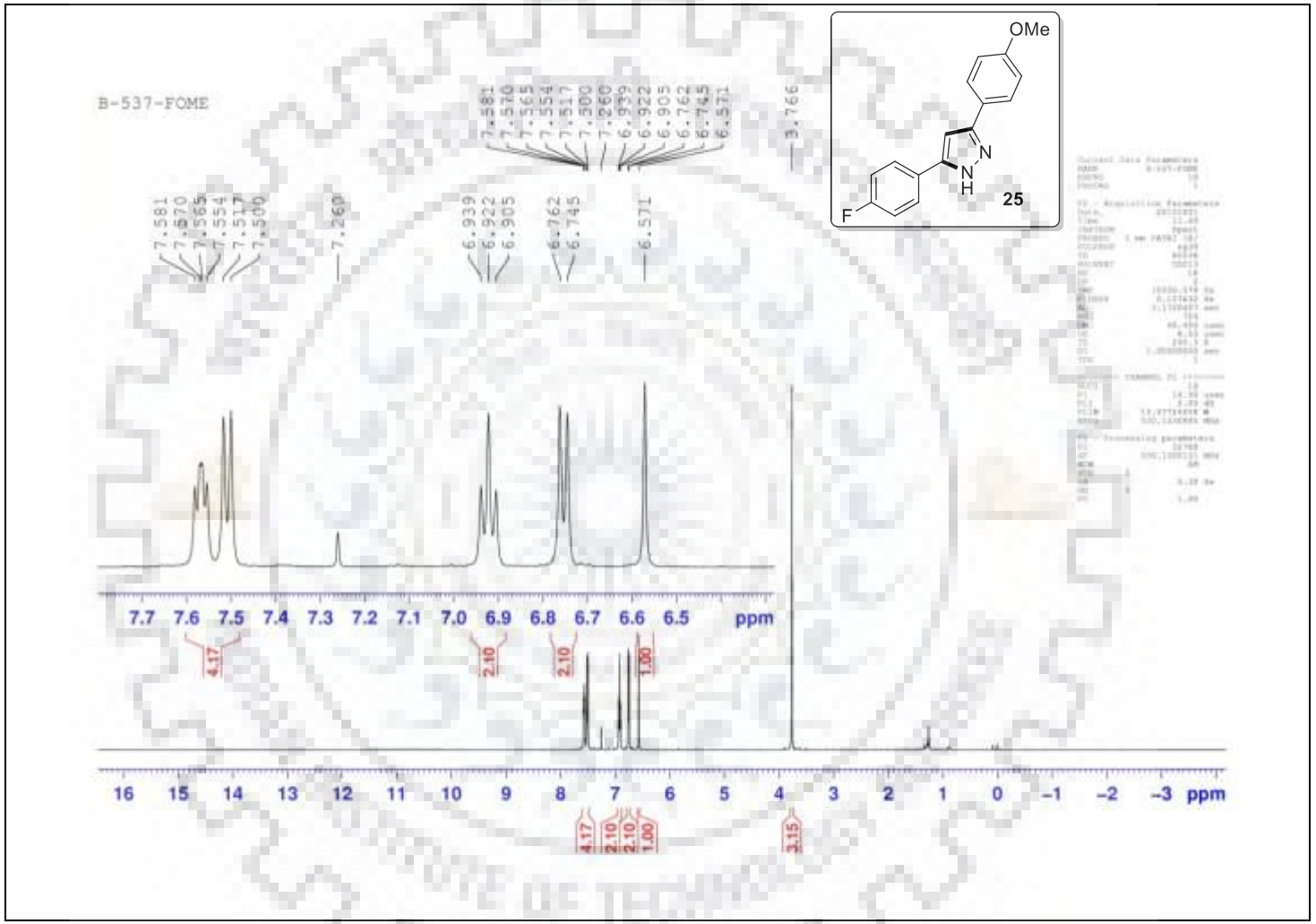


Figure S-15: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **25**.

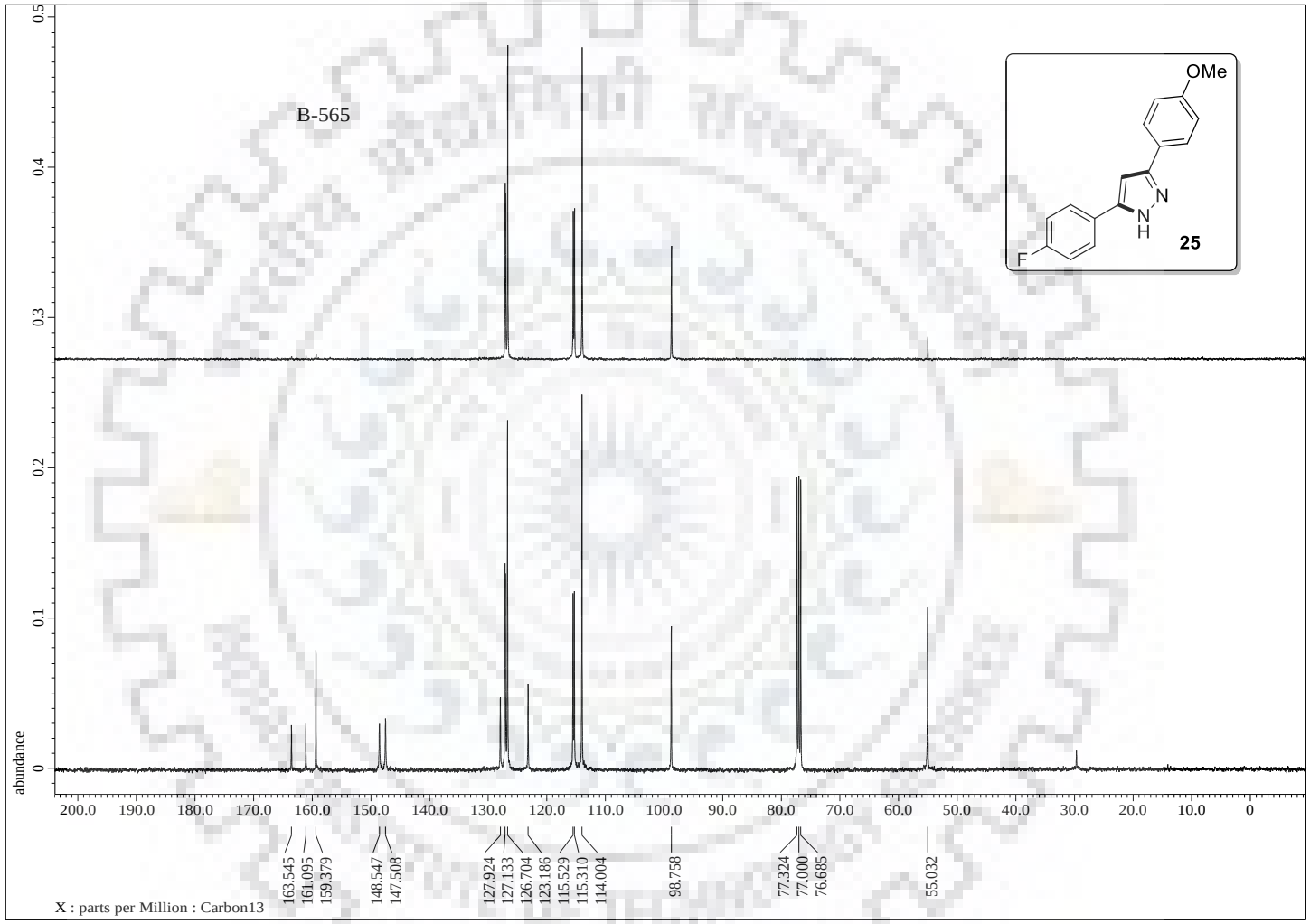


Figure S-16: ^{13}C and DEPT (100 MHz, $CDCl_3$) Spectra of **25**.

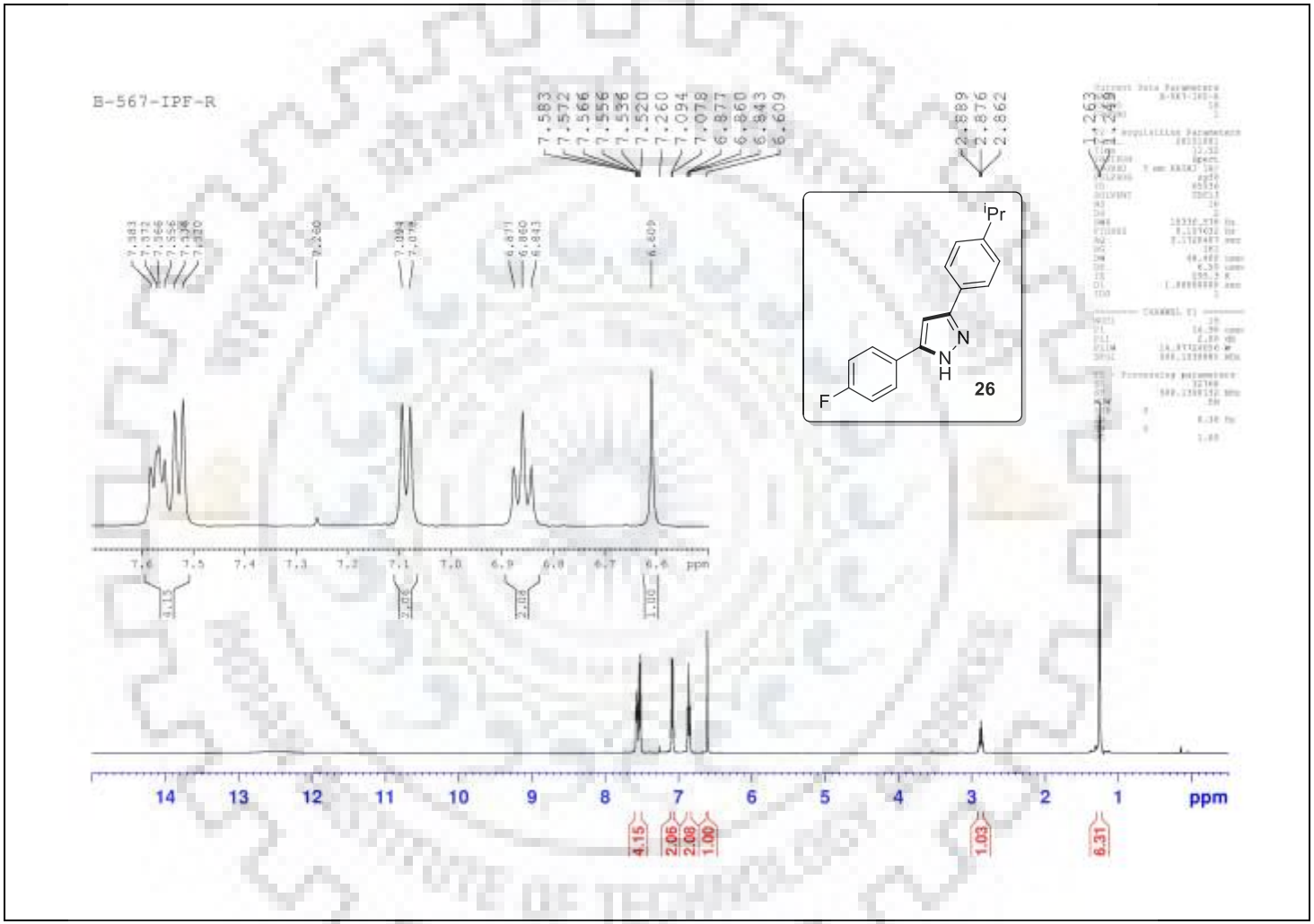


Figure S-17: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **26**.

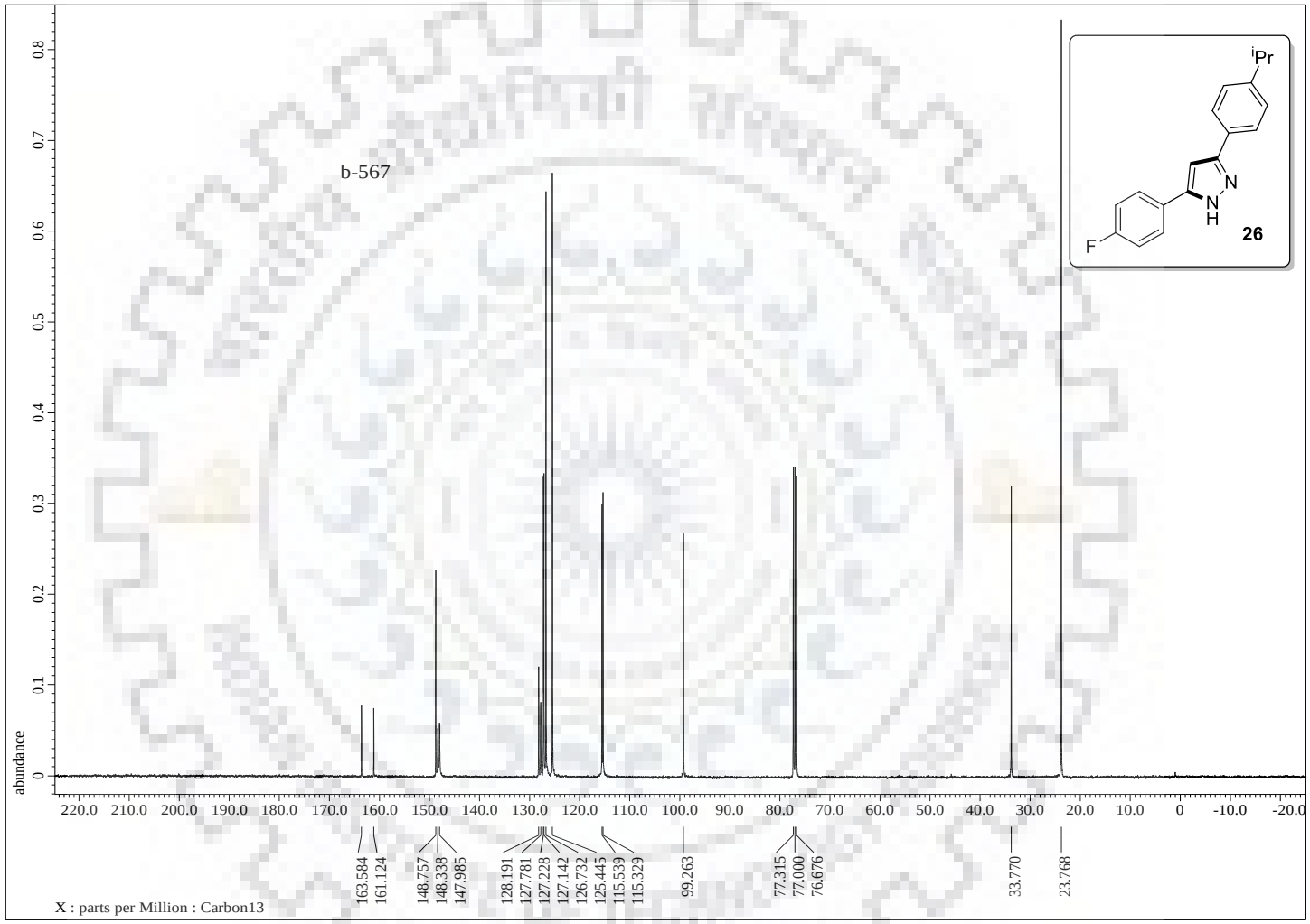


Figure S-18: ^{13}C NMR (125 MHz, $CDCl_3$) Spectra of **26**.

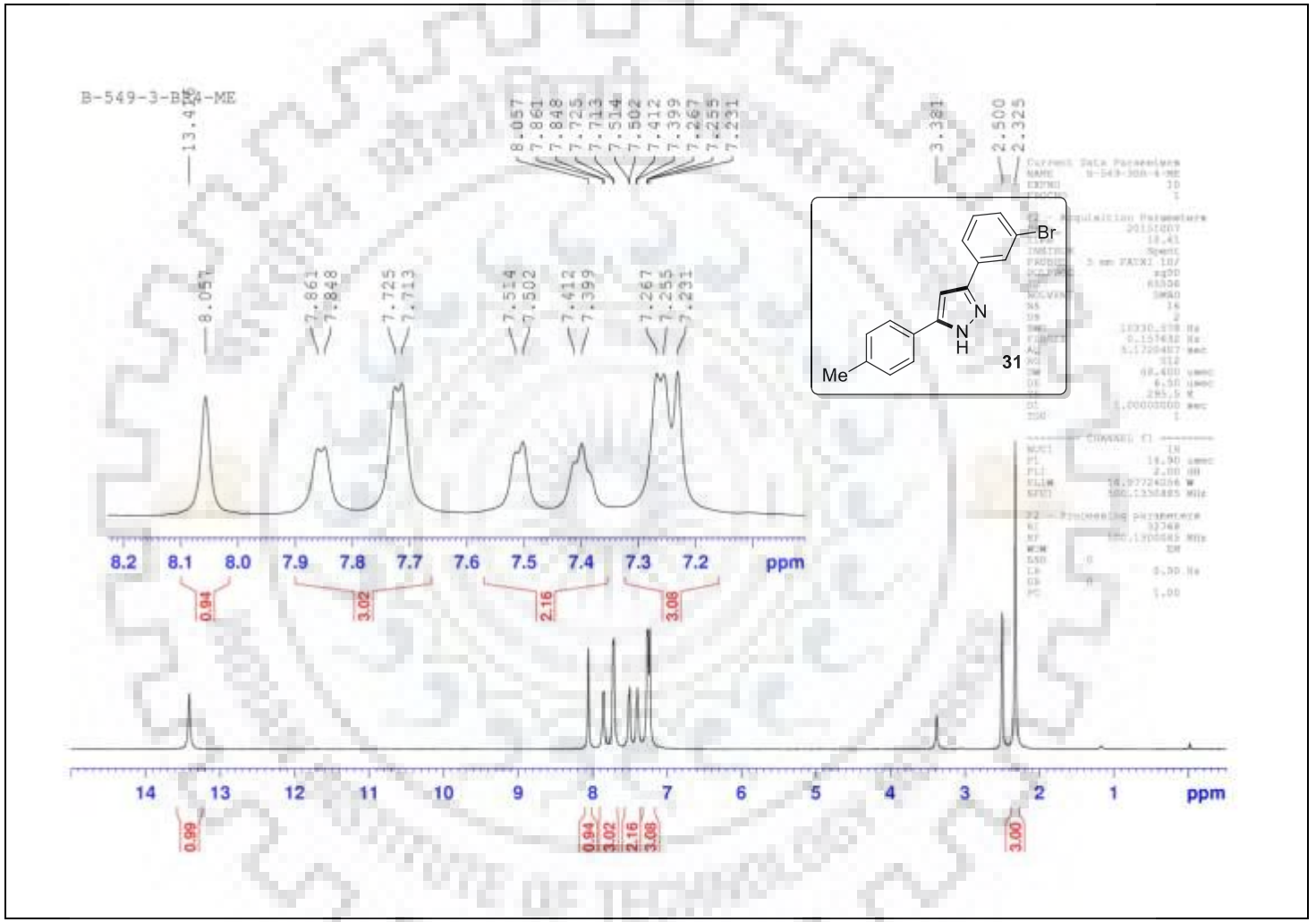


Figure S-19: ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6) Spectrum of **31**.

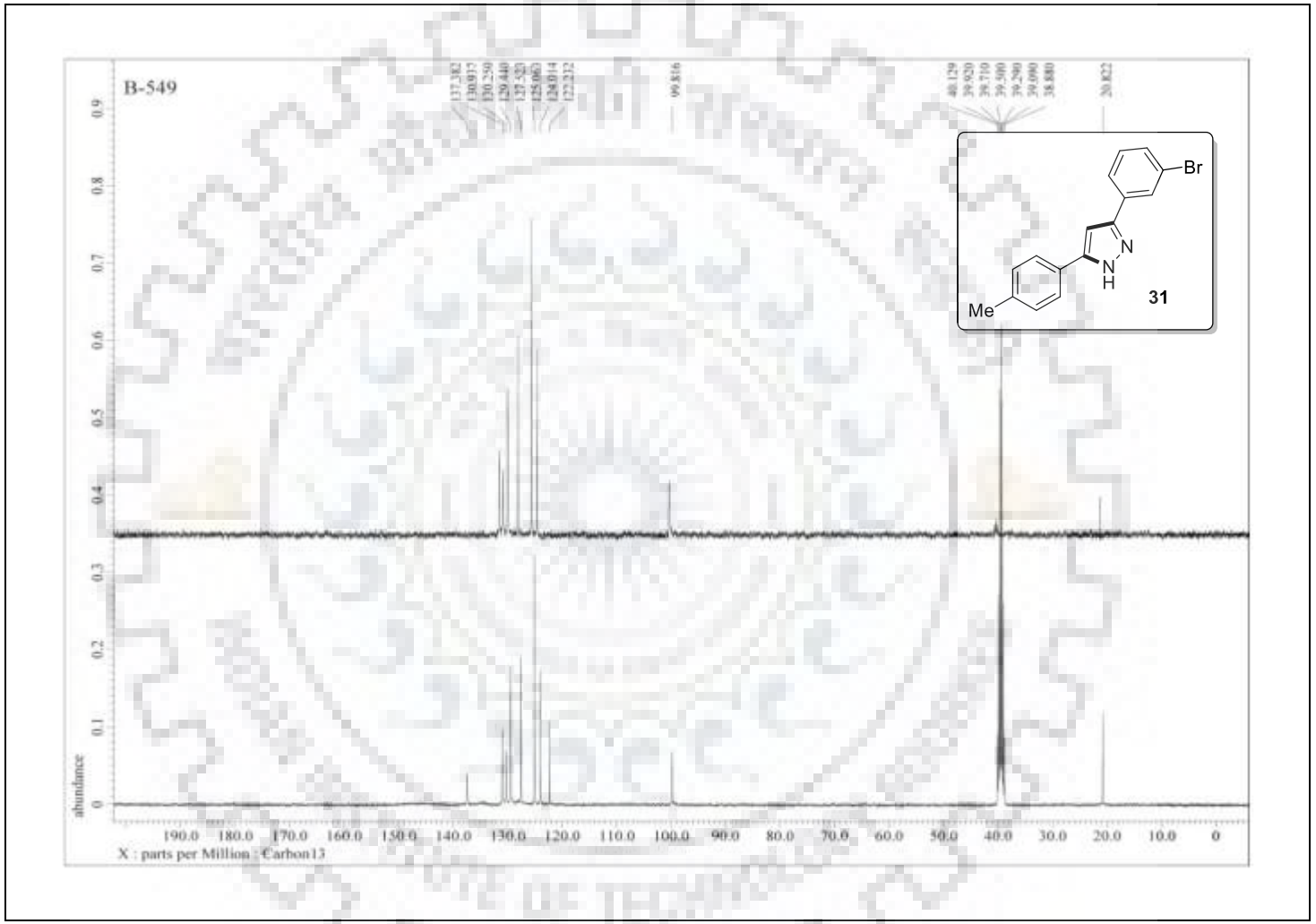


Figure S-20: ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) Spectra of **31**.

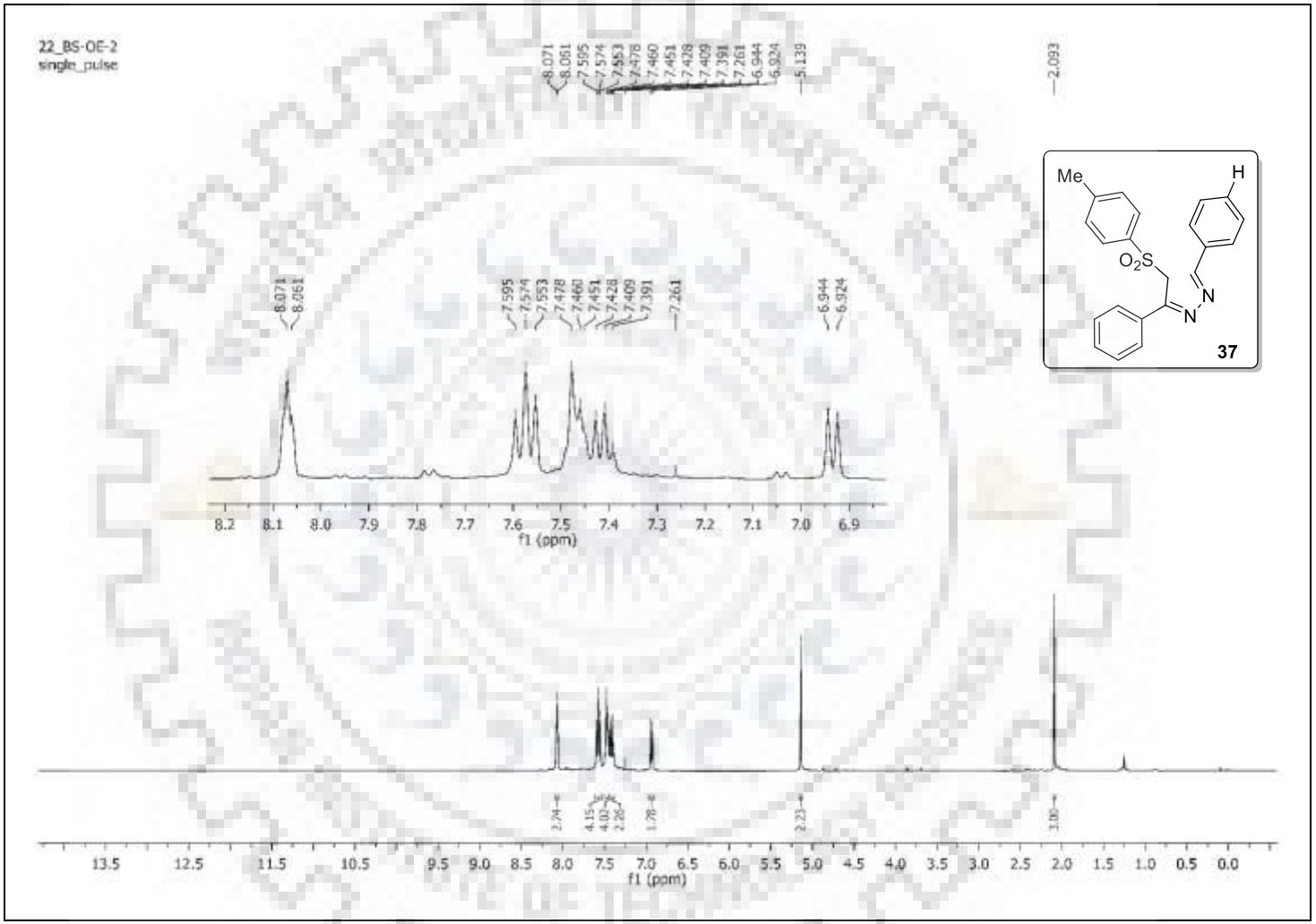


Figure S-21: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **37**.

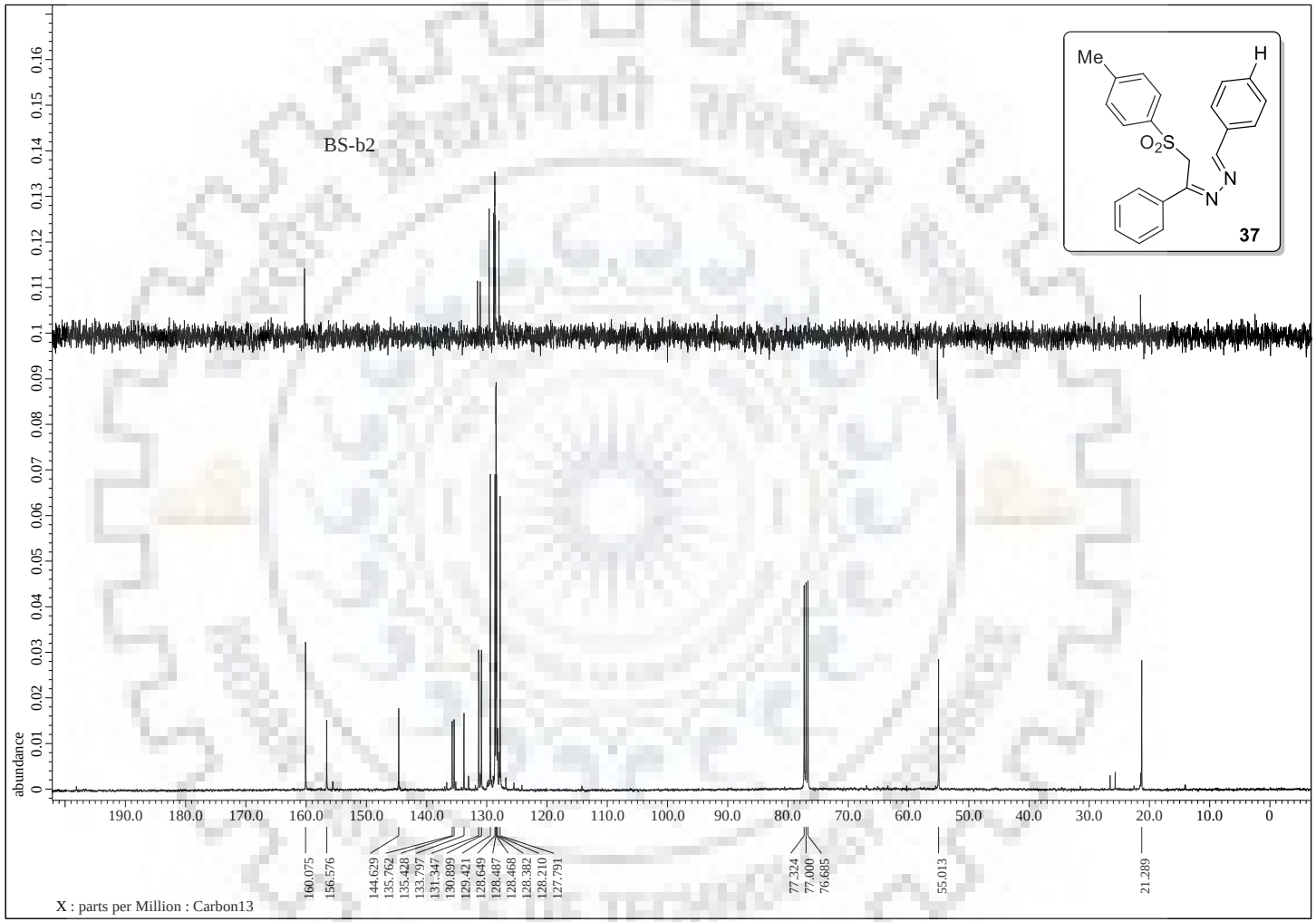


Figure S-22: ^{13}C and DEPT (100 MHz, $CDCl_3$) Spectra of **37**.

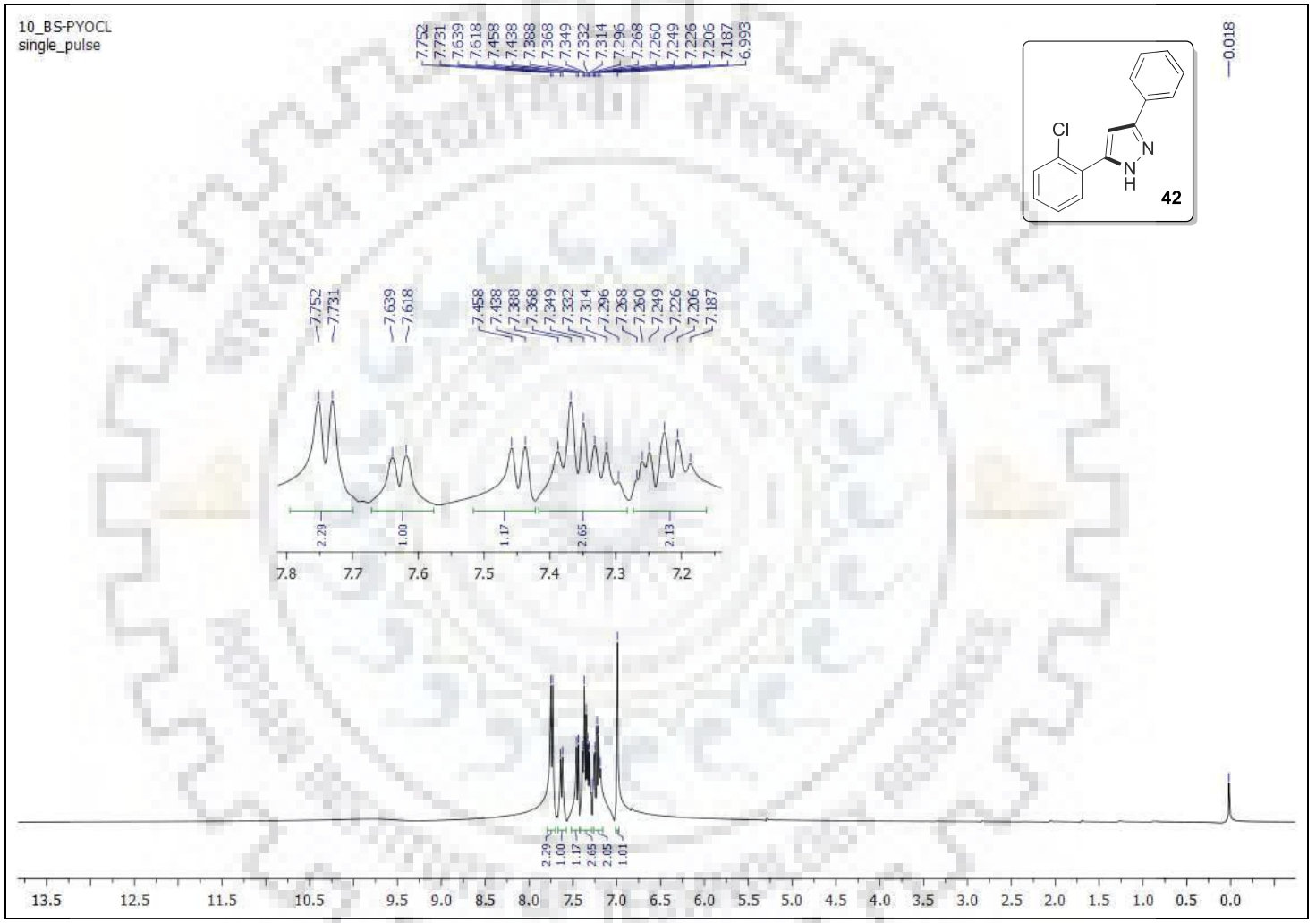


Figure S-23: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **42**.

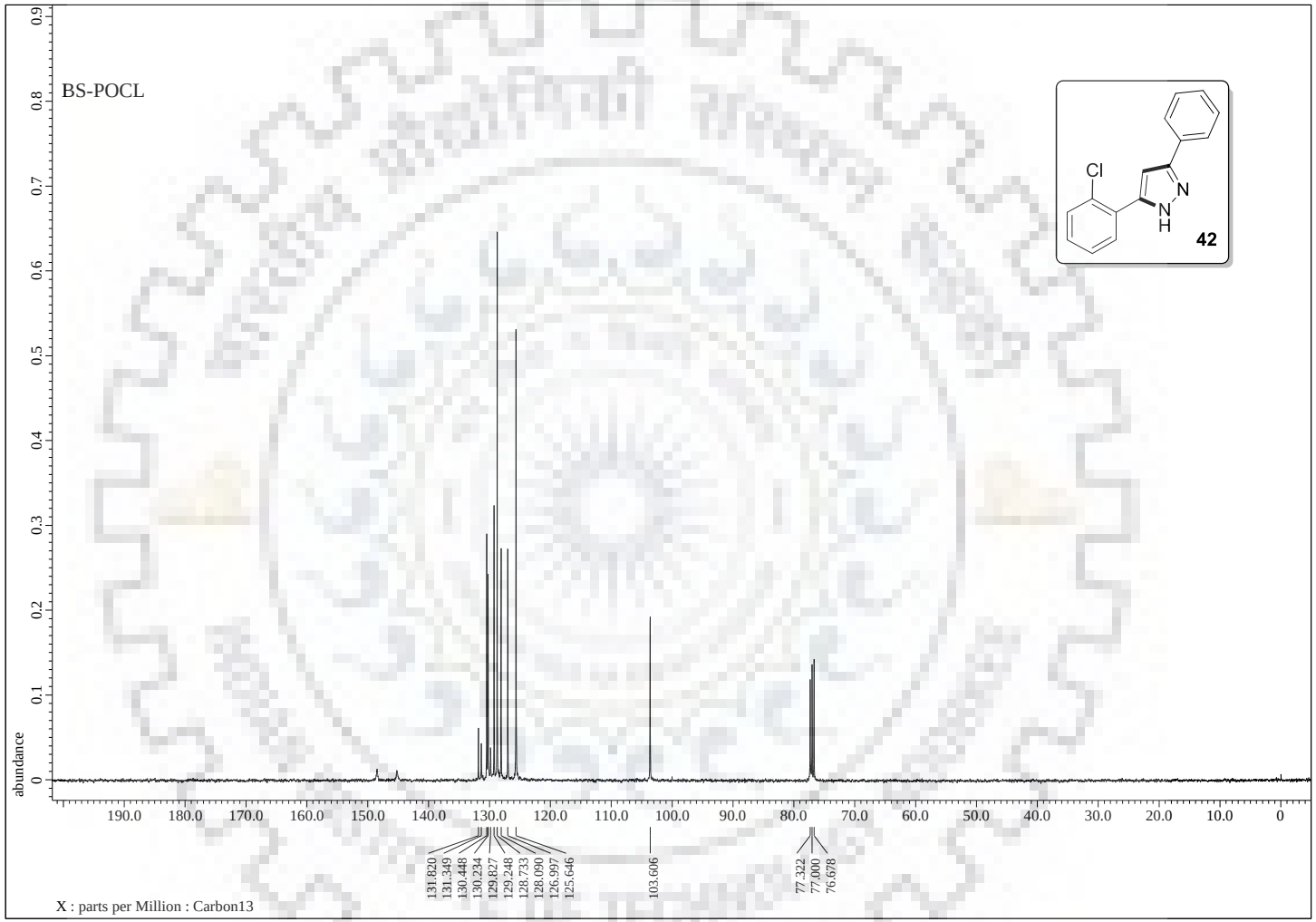


Figure S-24: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **42**.

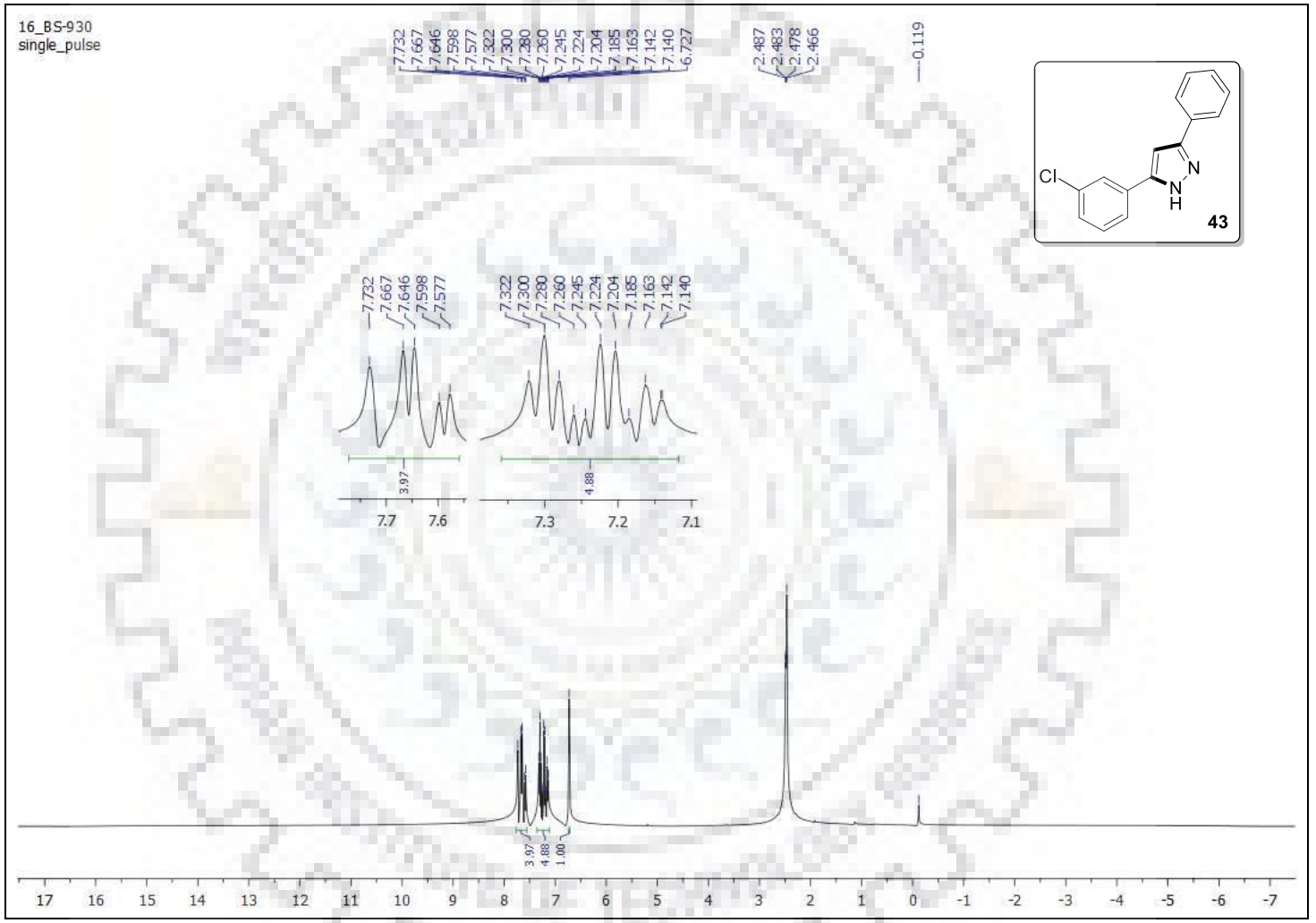


Figure S-25: ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) Spectrum of **43**.

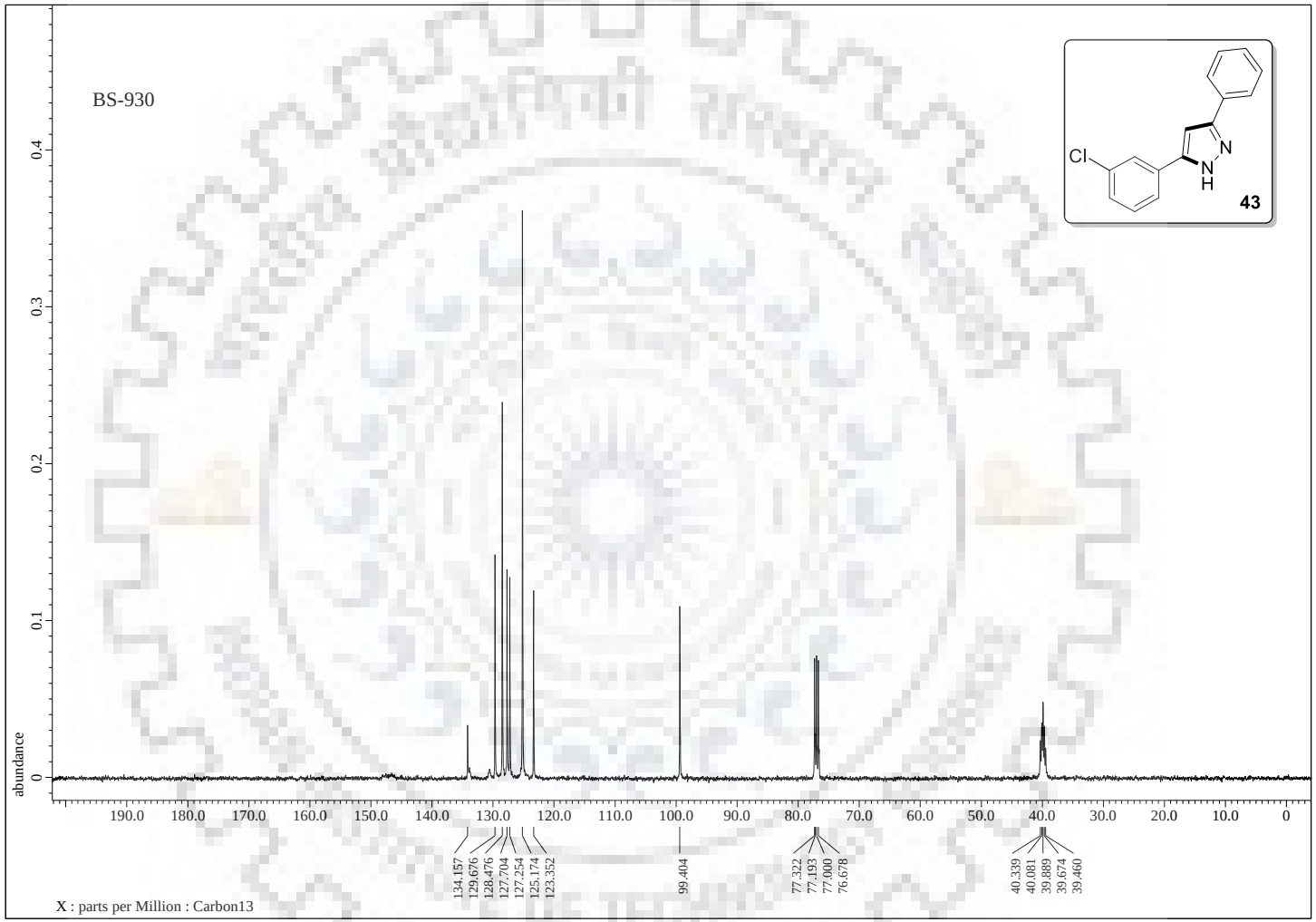


Figure S-26: ^{13}C (100 MHz, $CDCl_3$ + DMSO-d_6) Spectrum of **43**.

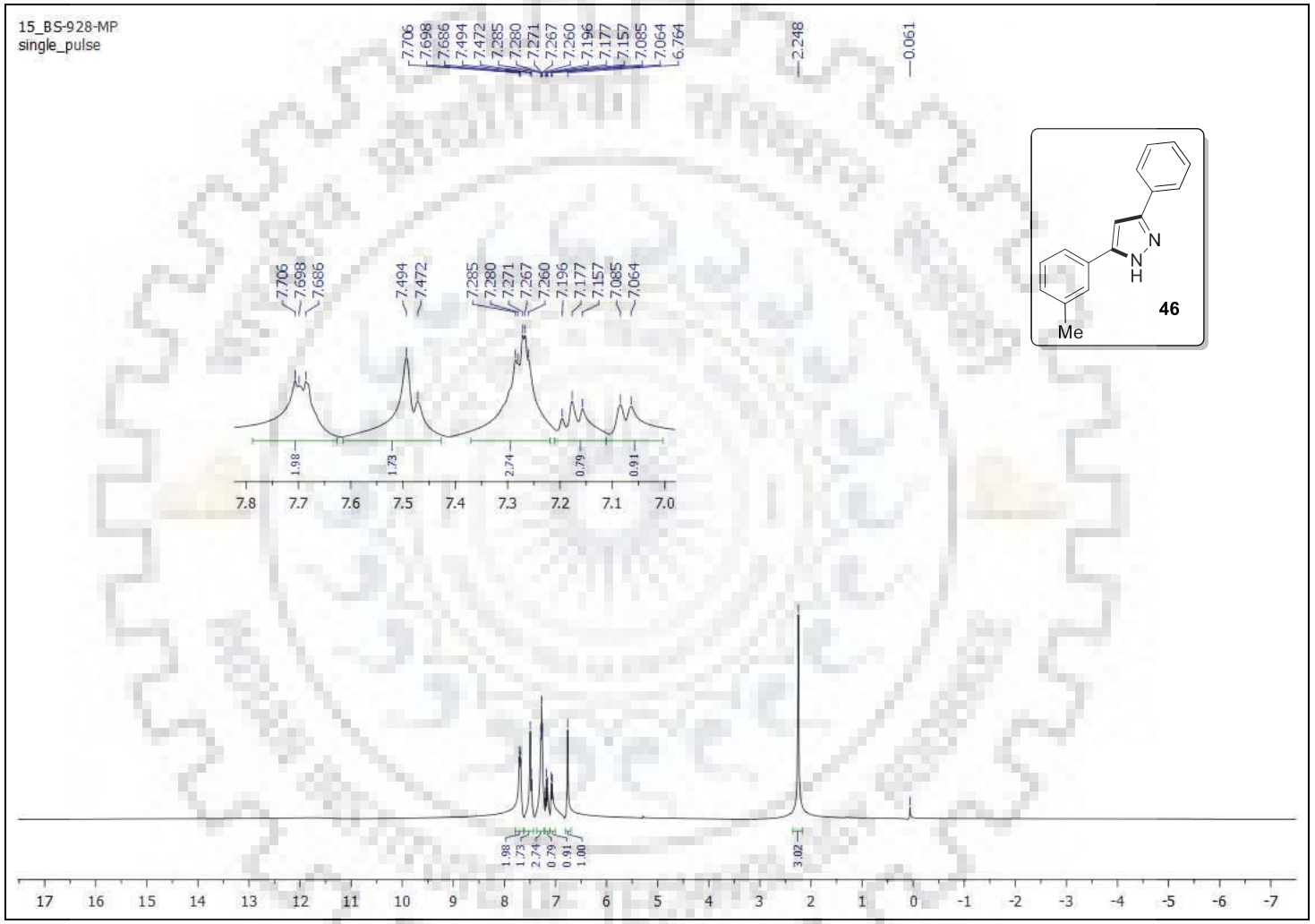


Figure S-27: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **46**.

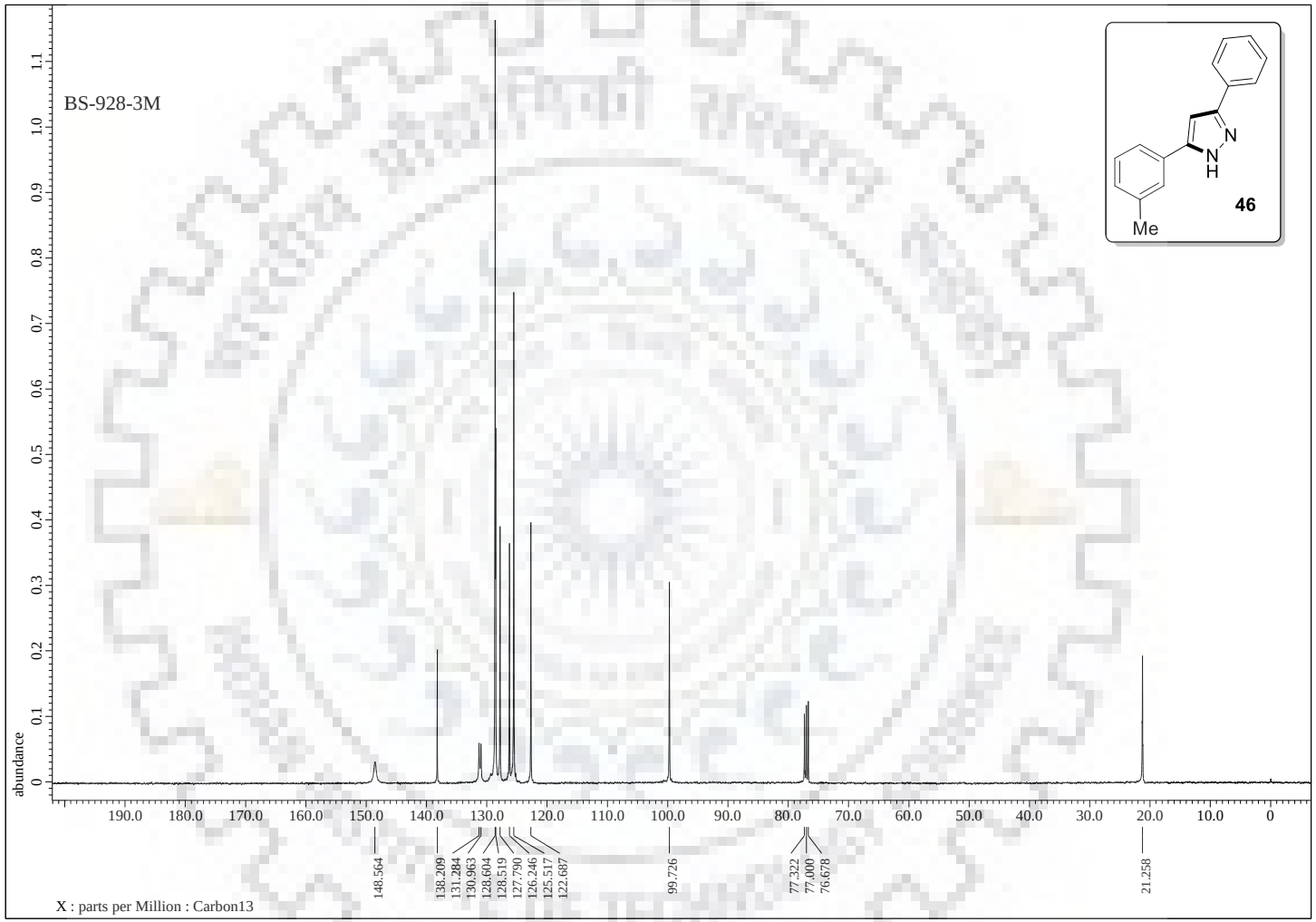


Figure S-28: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **46**.

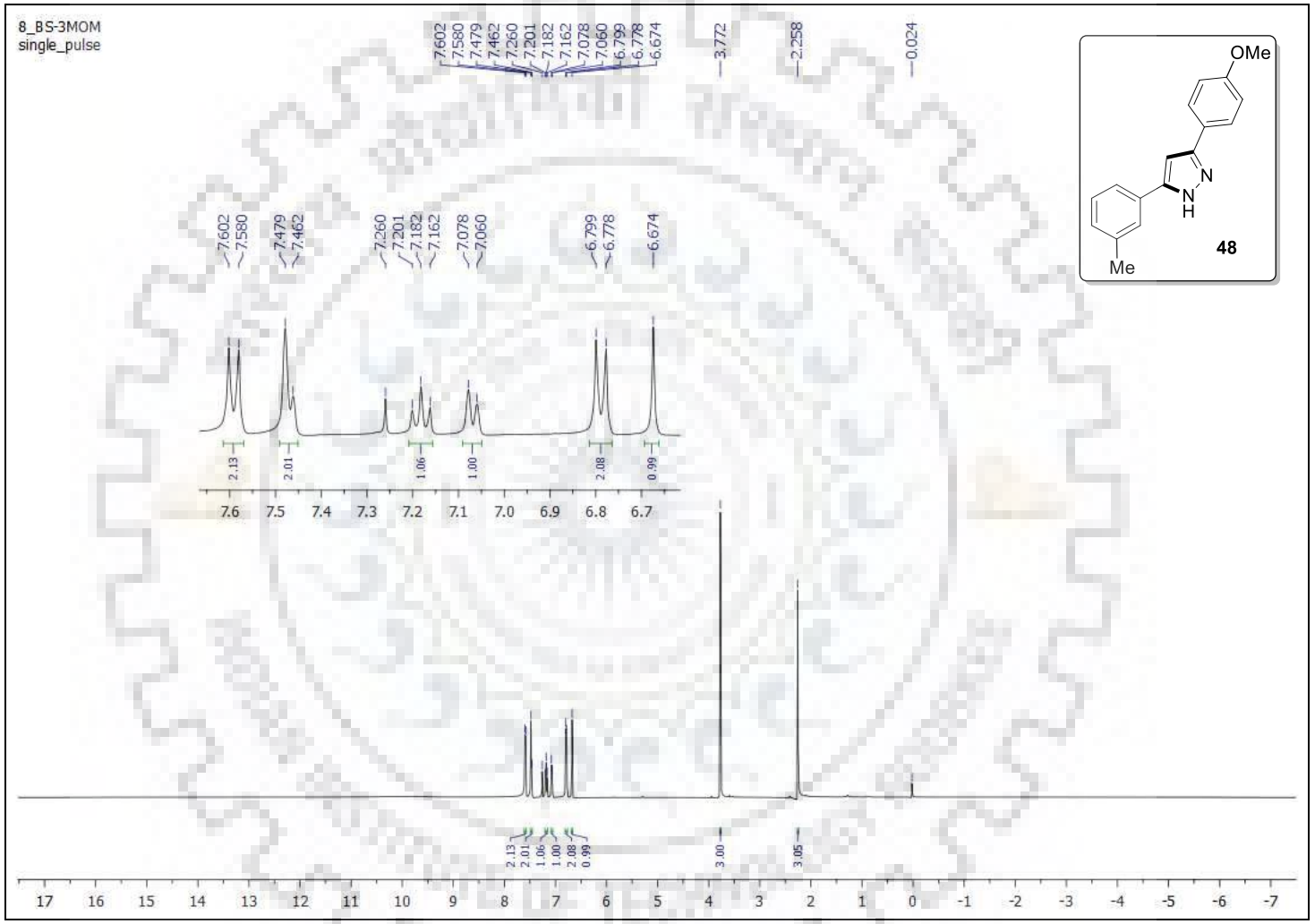


Figure S-29: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **48**.

Figure S-30: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **48**.

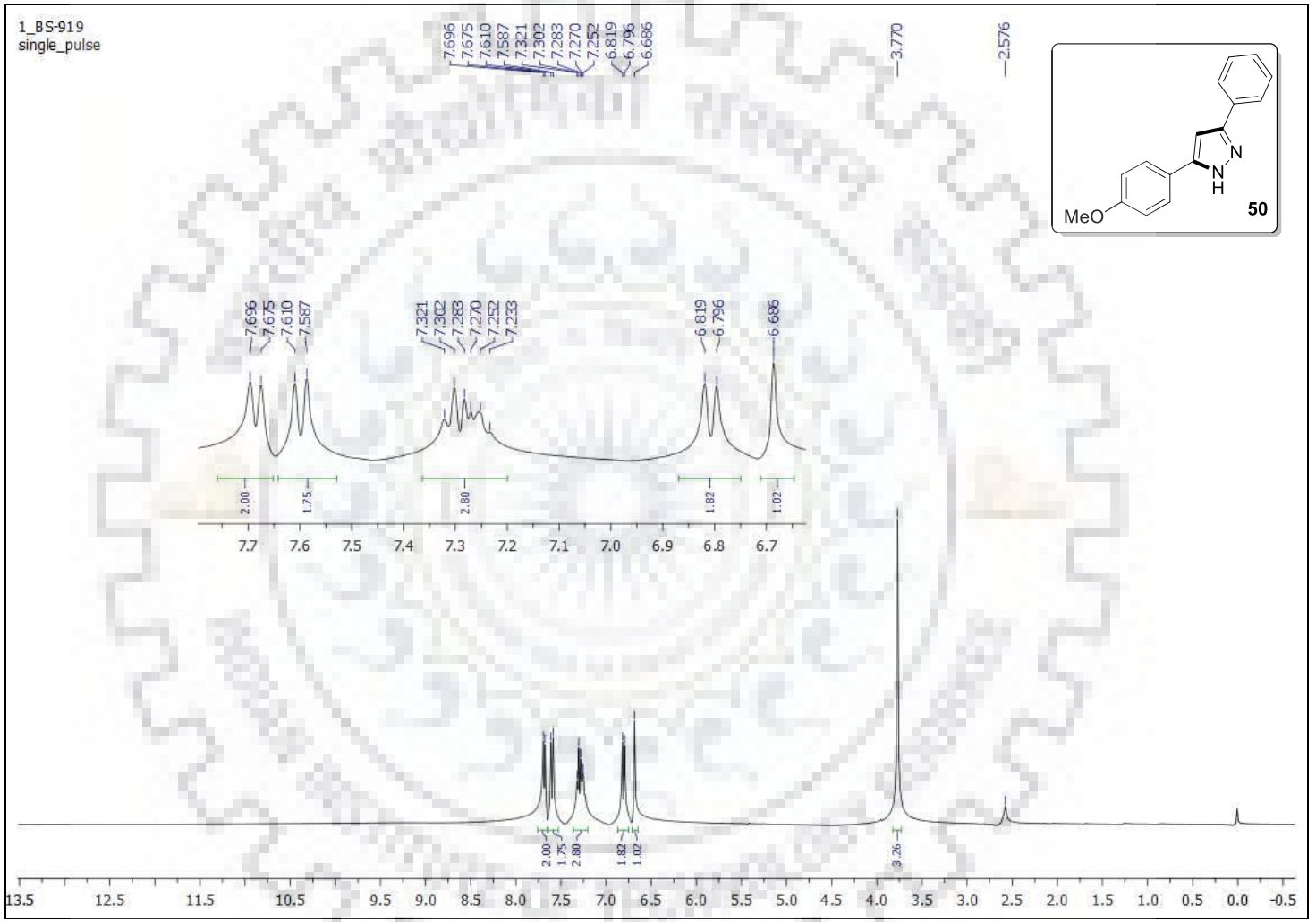


Figure S-31: ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) Spectrum of **50**.

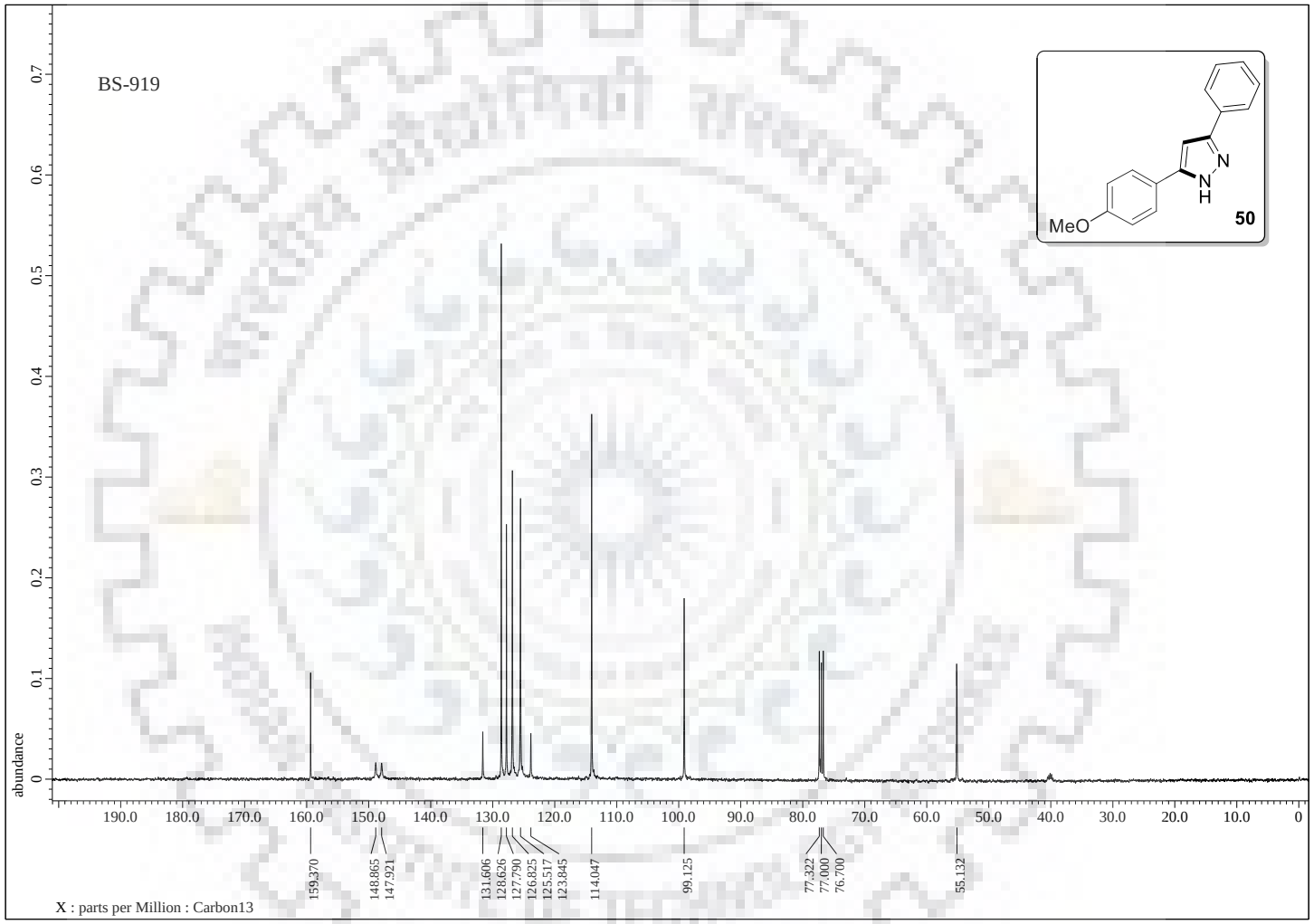


Figure S-32: ^{13}C (100 MHz, $CDCl_3$ + DMSO-d_6) Spectrum of **50**.

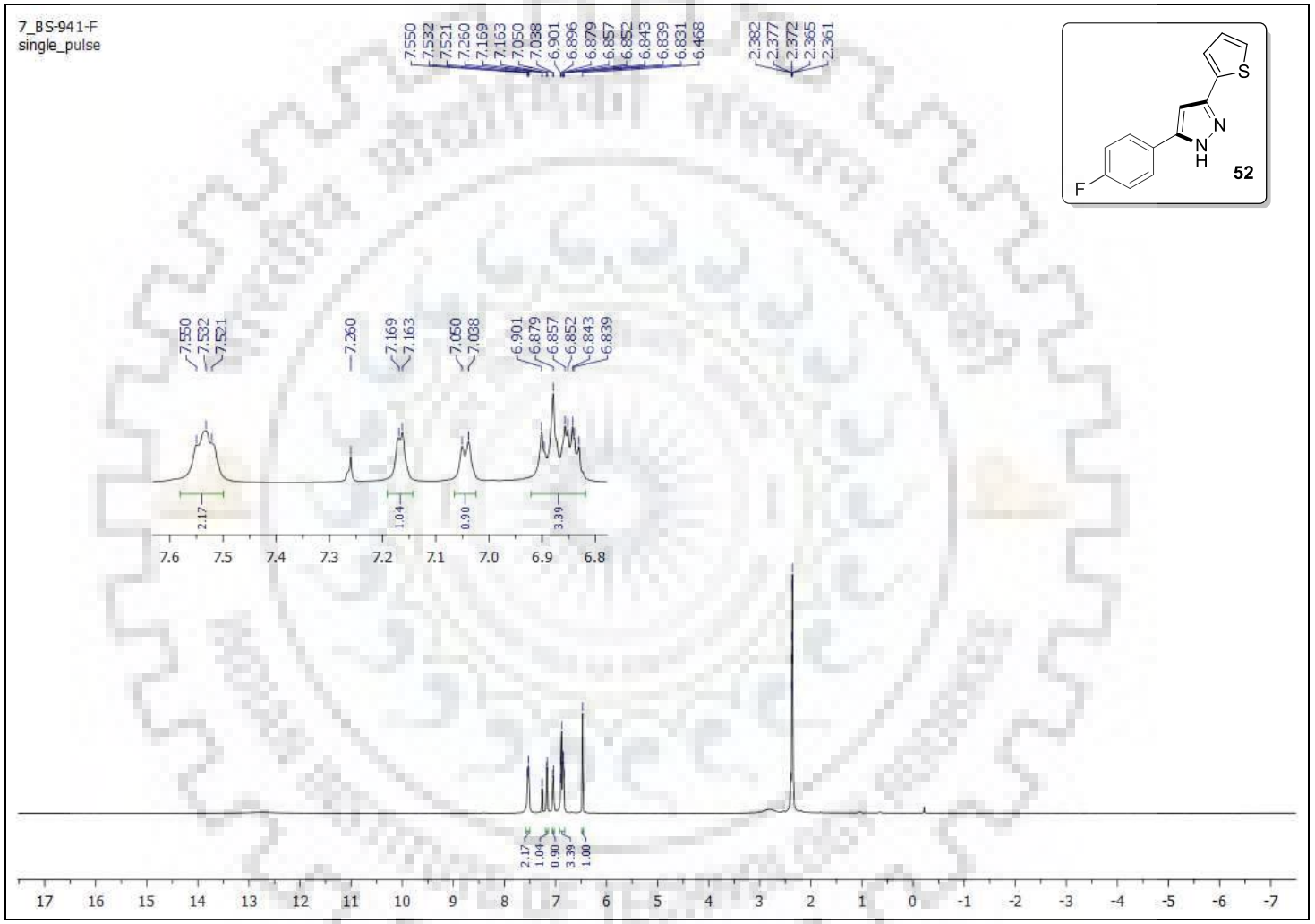


Figure S-33: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **52**.

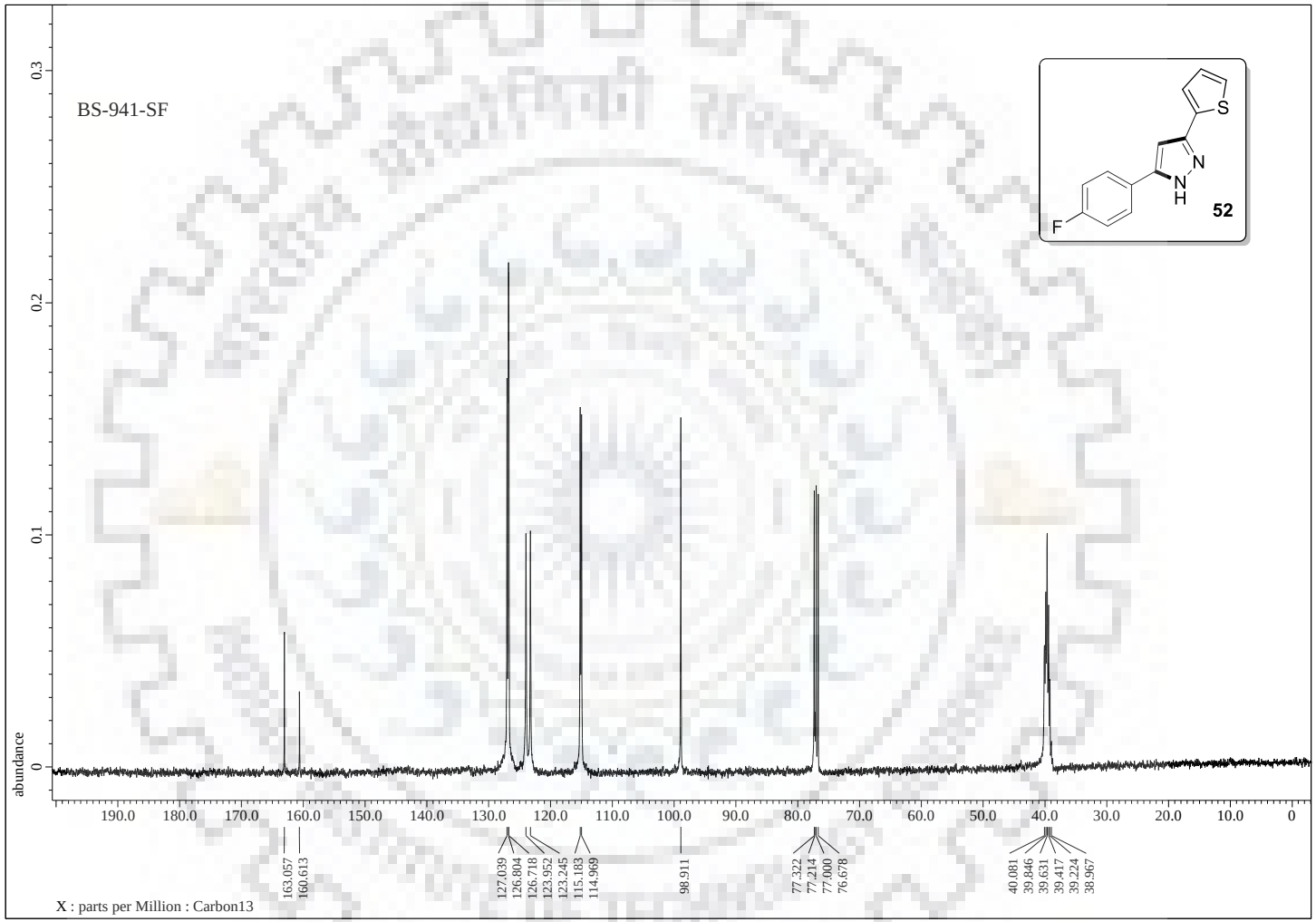


Figure S-34: ^{13}C (100 MHz, $CDCl_3$ + DMSO-d_6) Spectrum of **52**.

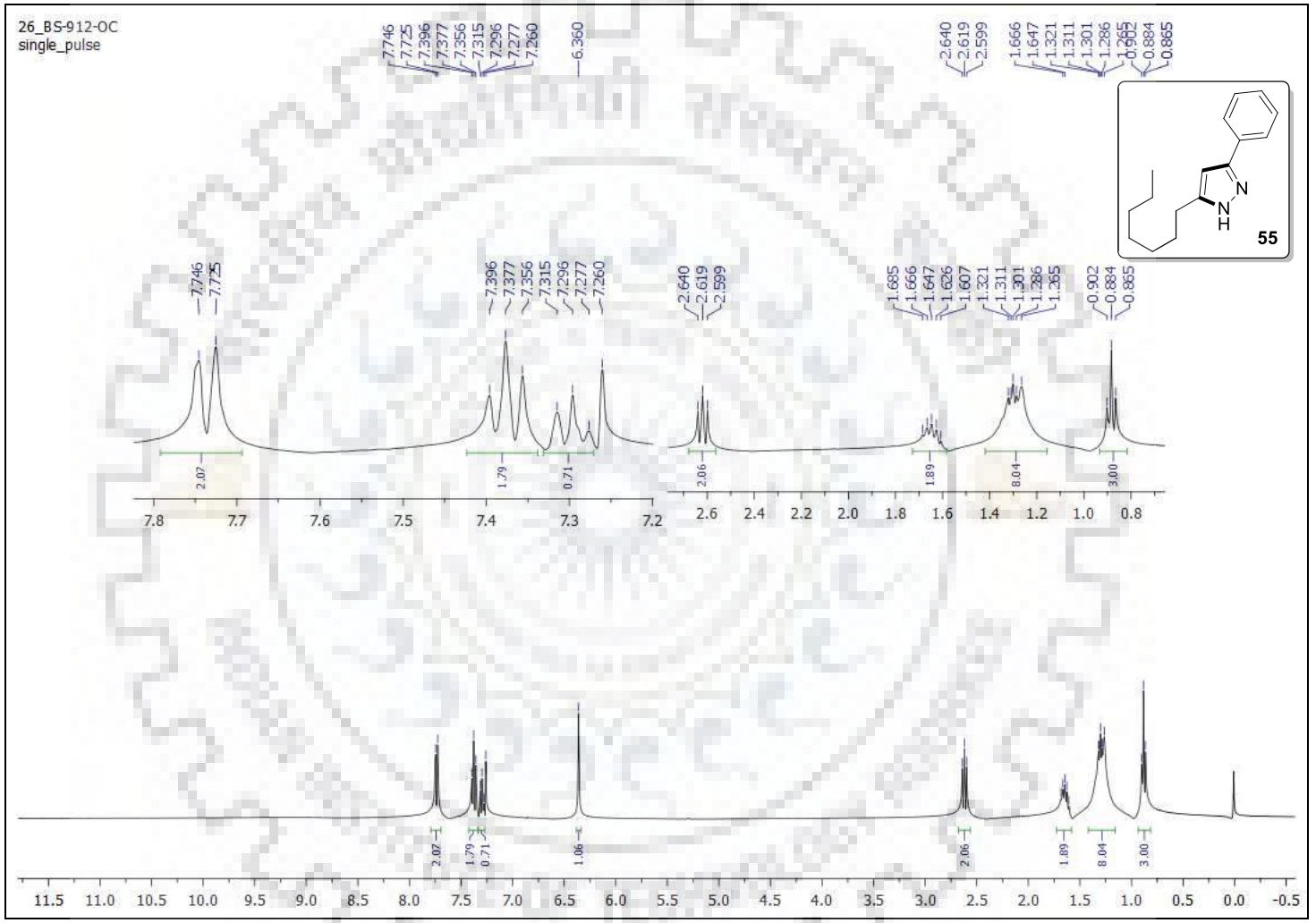


Figure S-35: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **55**.

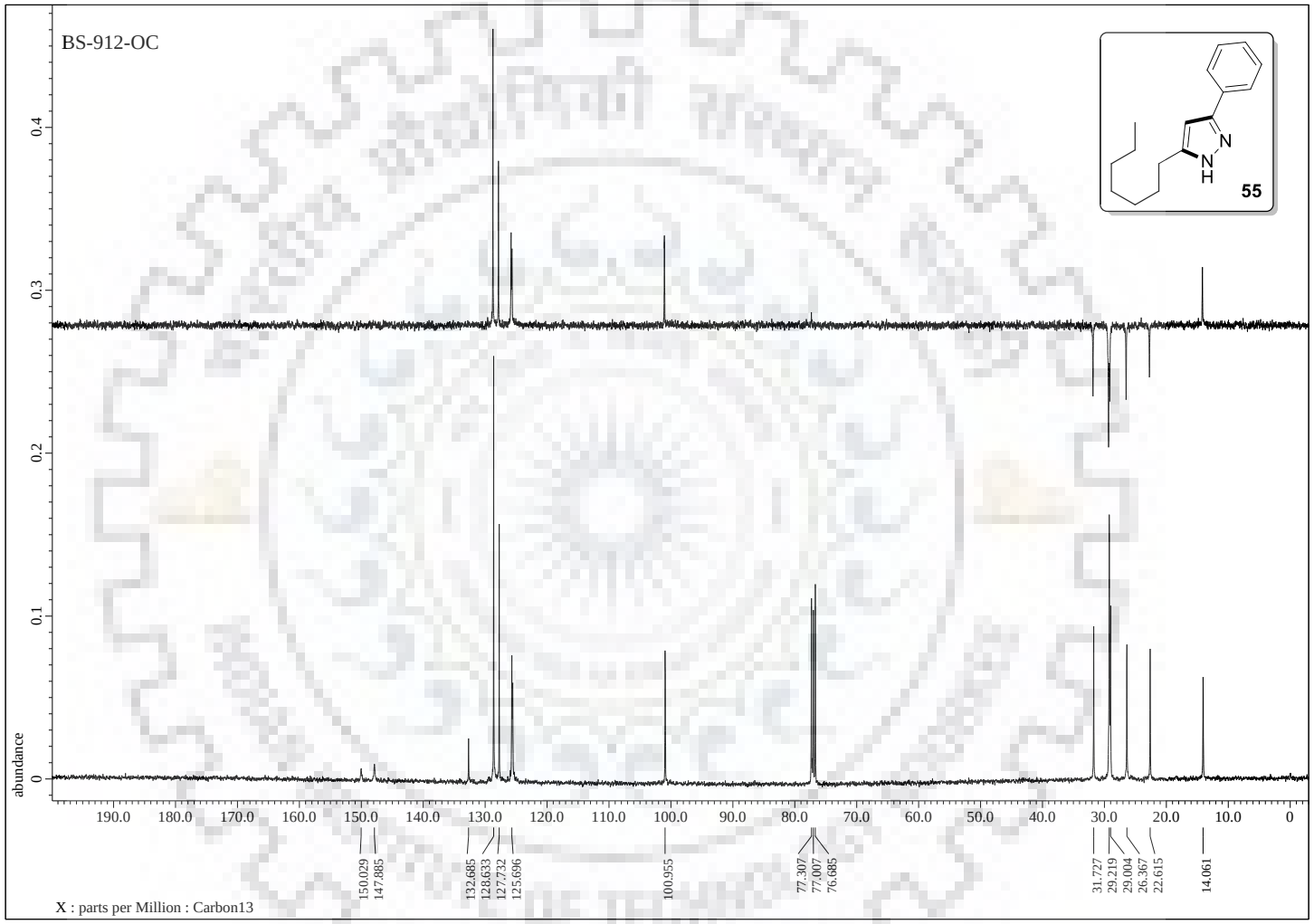


Figure S-36: ^{13}C and DEPT (100 MHz, $CDCl_3$) Spectra of **55**.

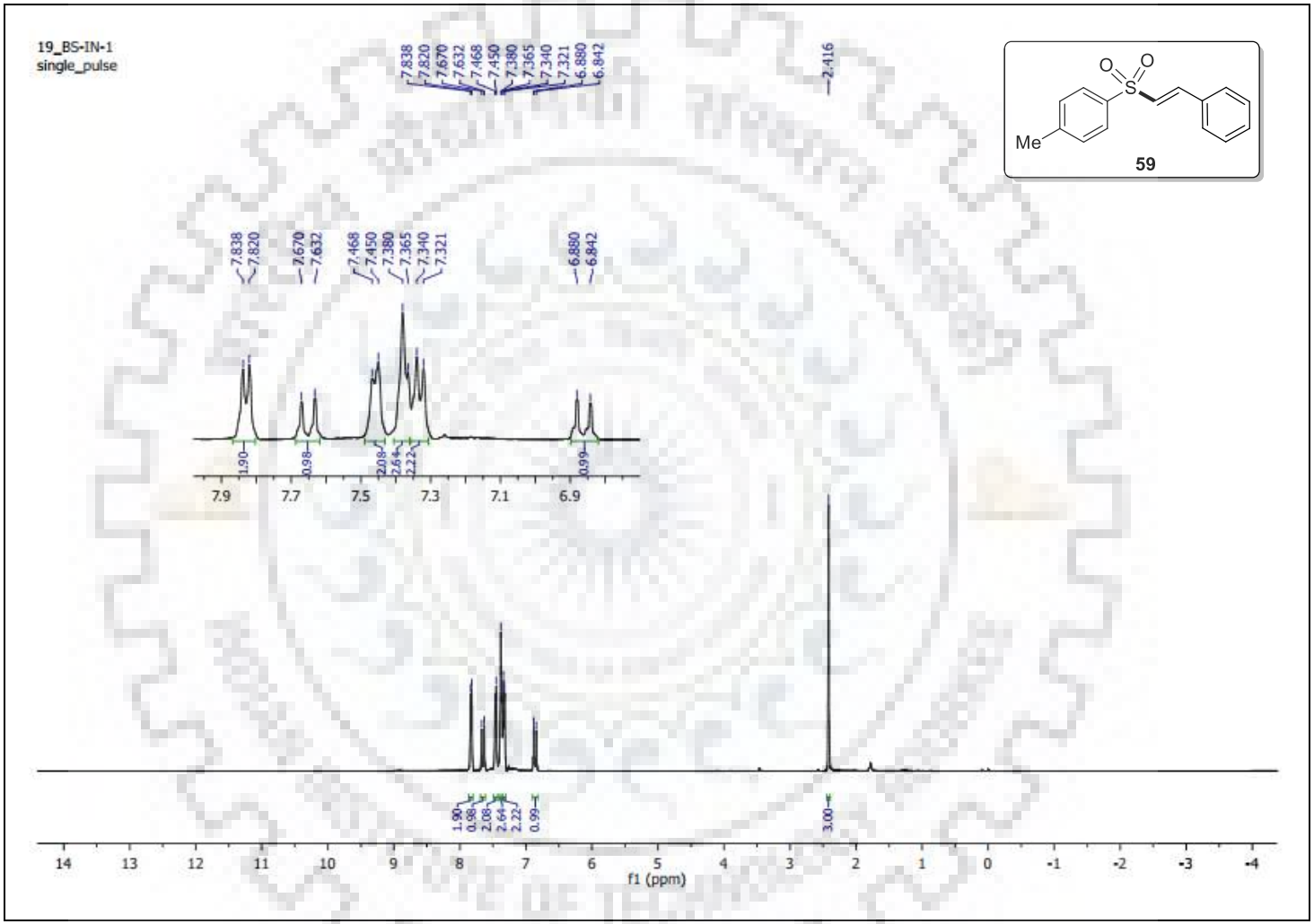


Figure S-37: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **59**.

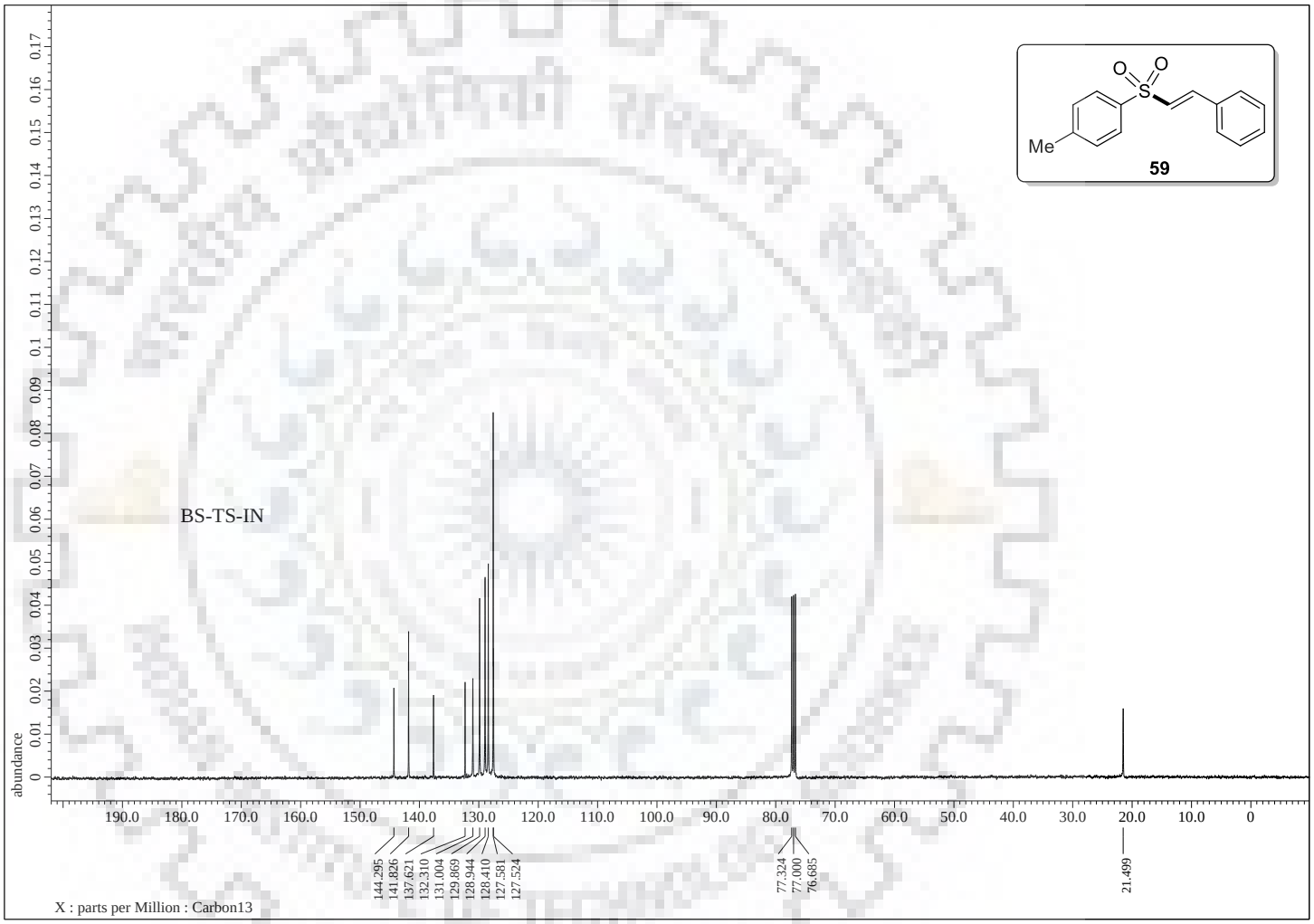


Figure S-38: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **59**.

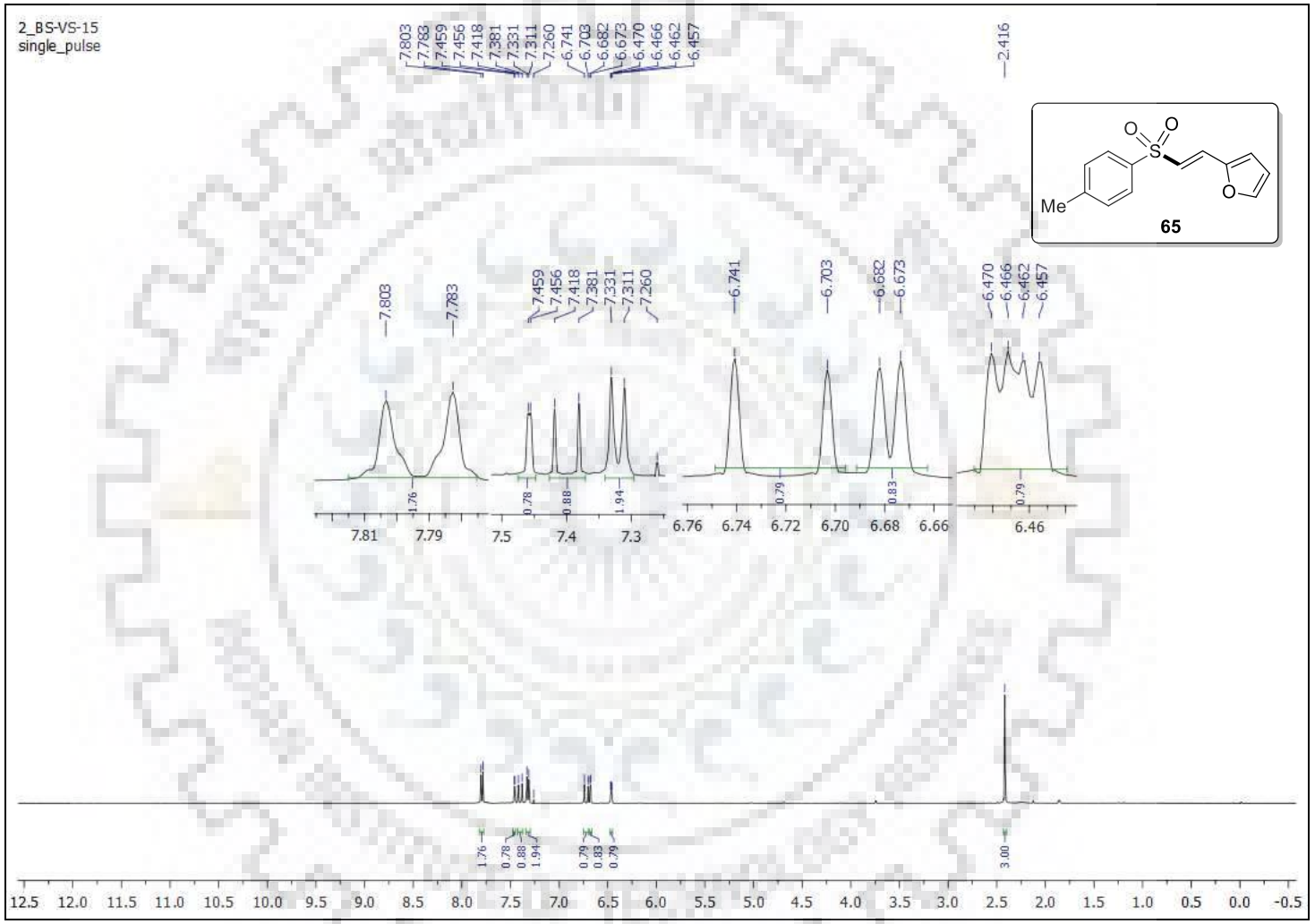


Figure S-39: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **65**.

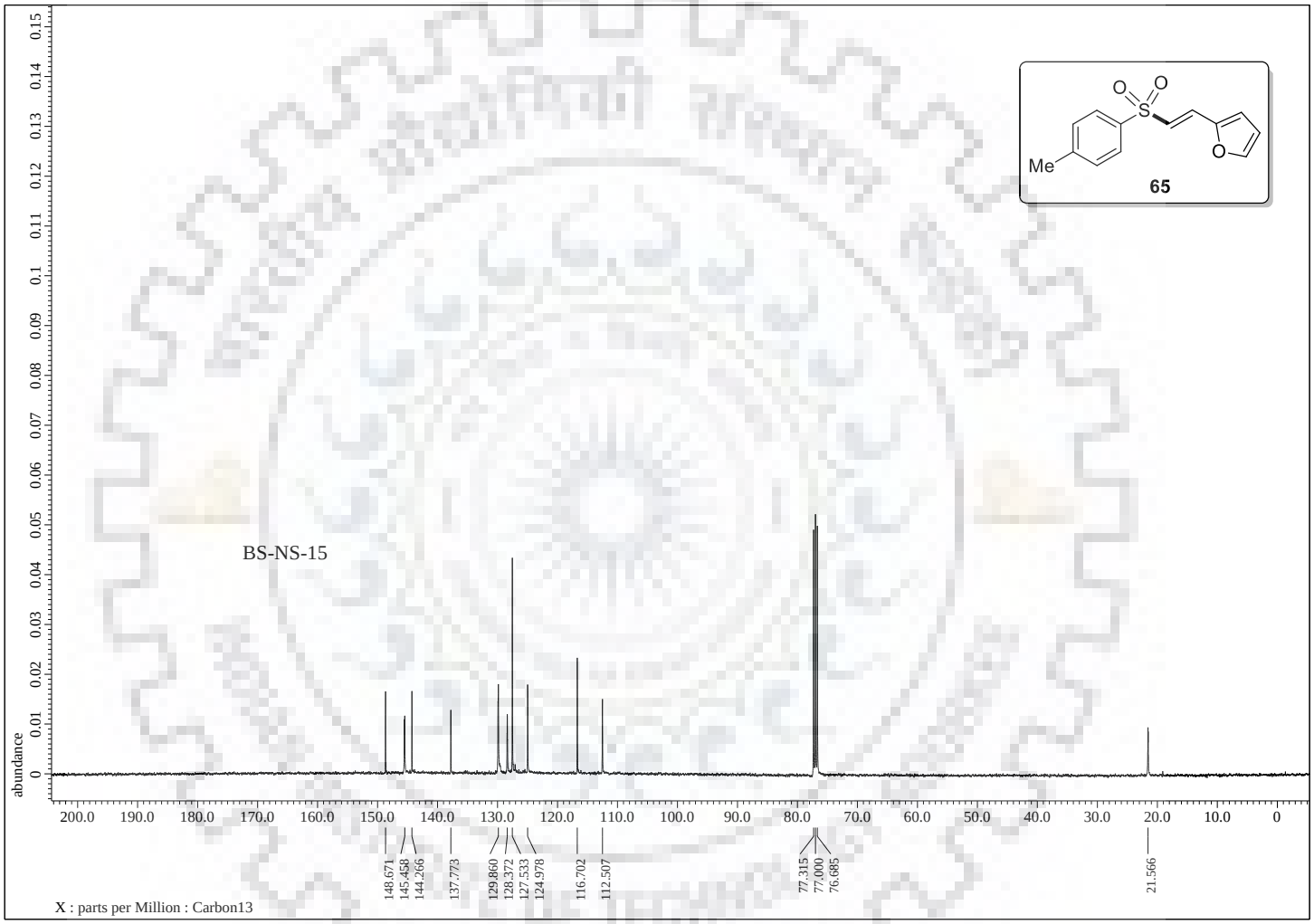


Figure S-40: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **65**.

Figure S-41: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **67.**

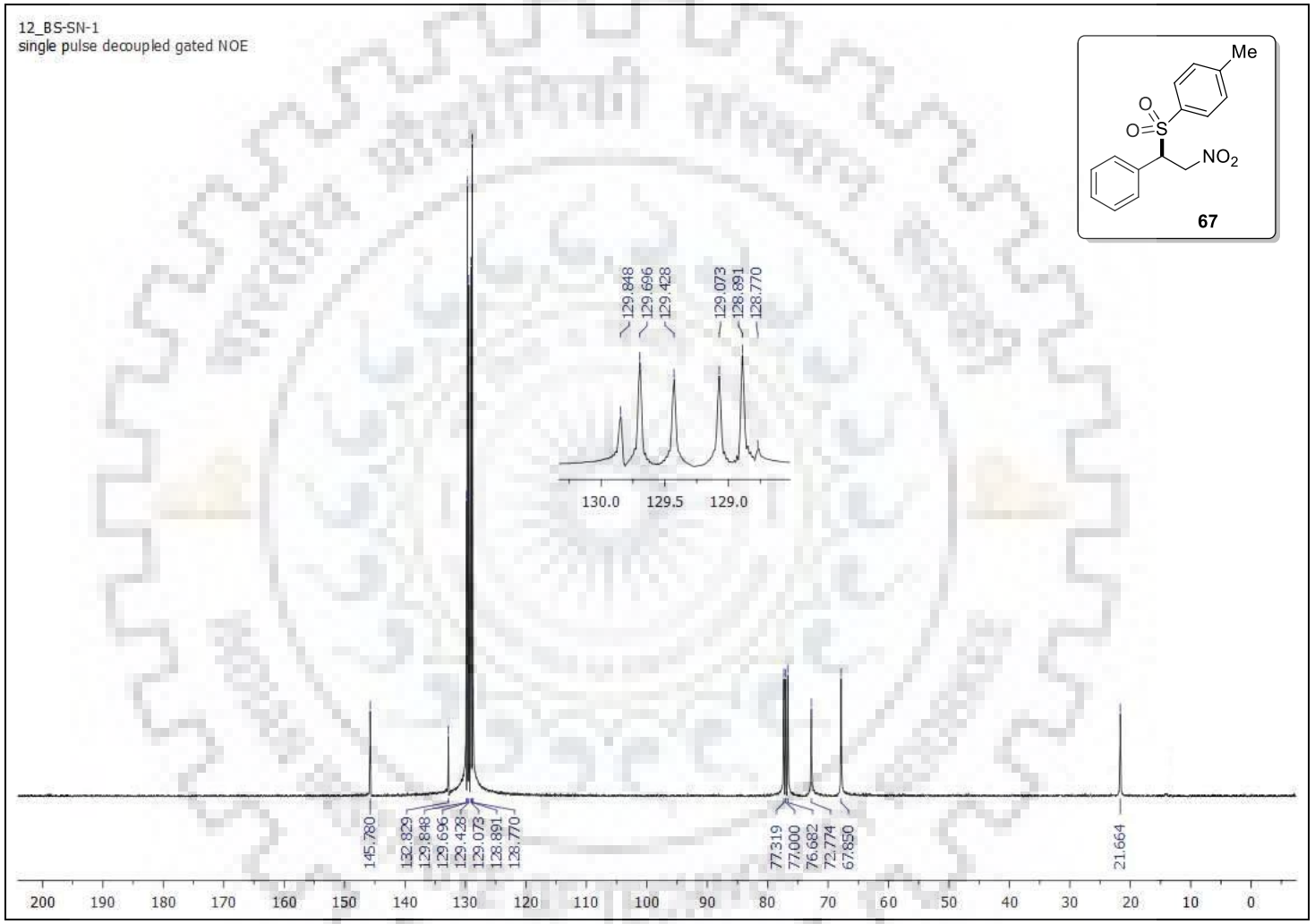


Figure S-42: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **67**.

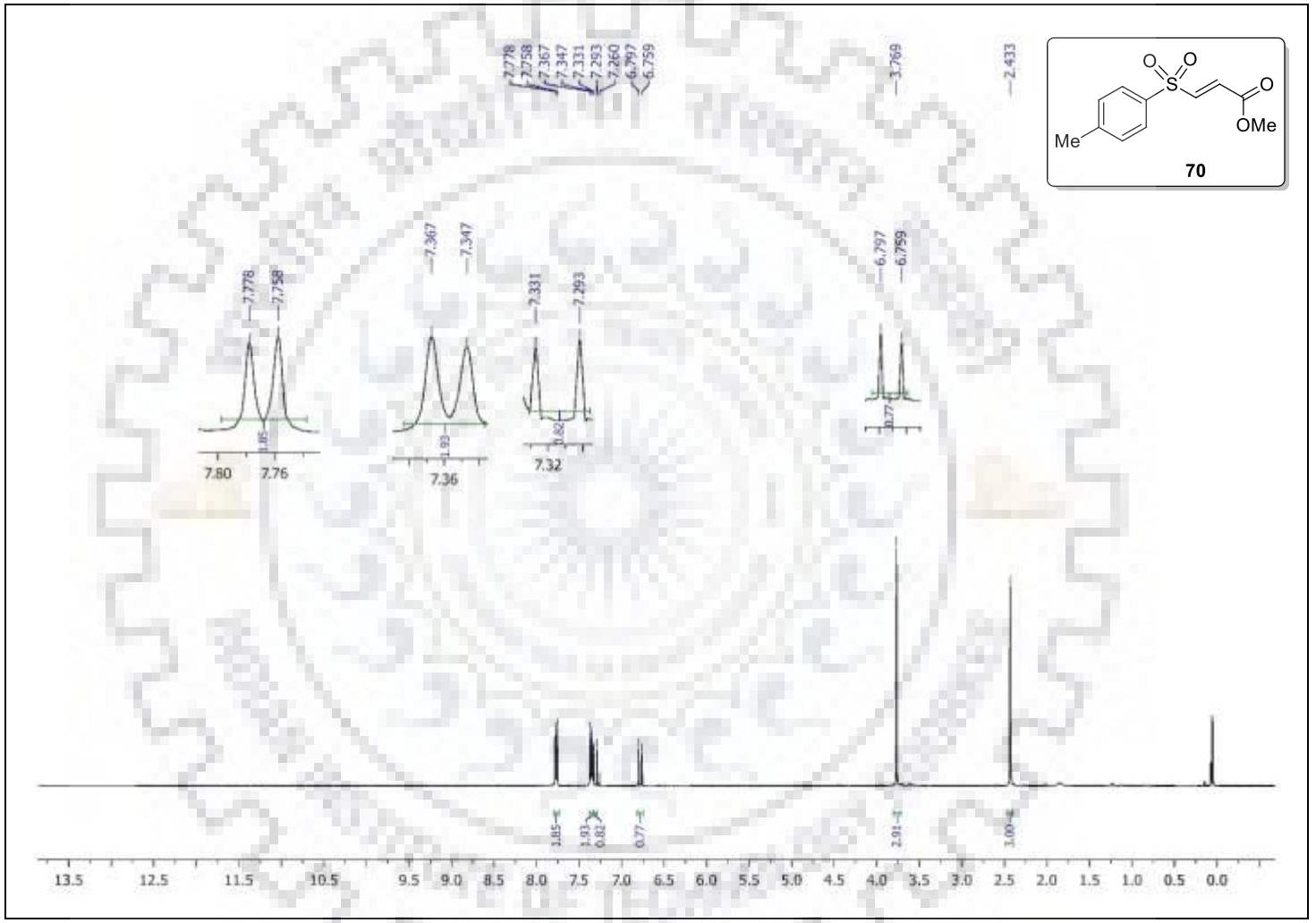


Figure S-43: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **70**.

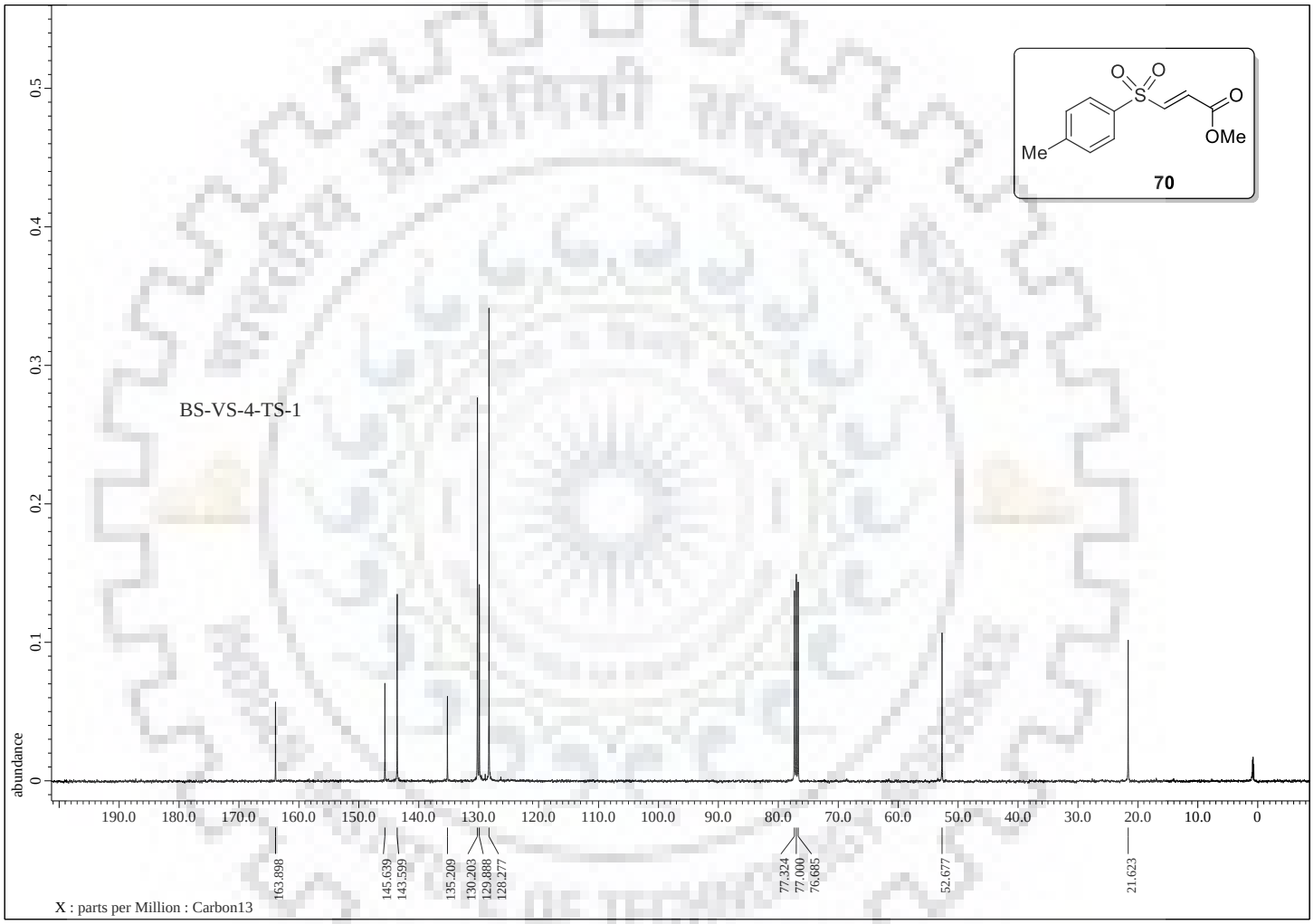


Figure S-44: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **70**.

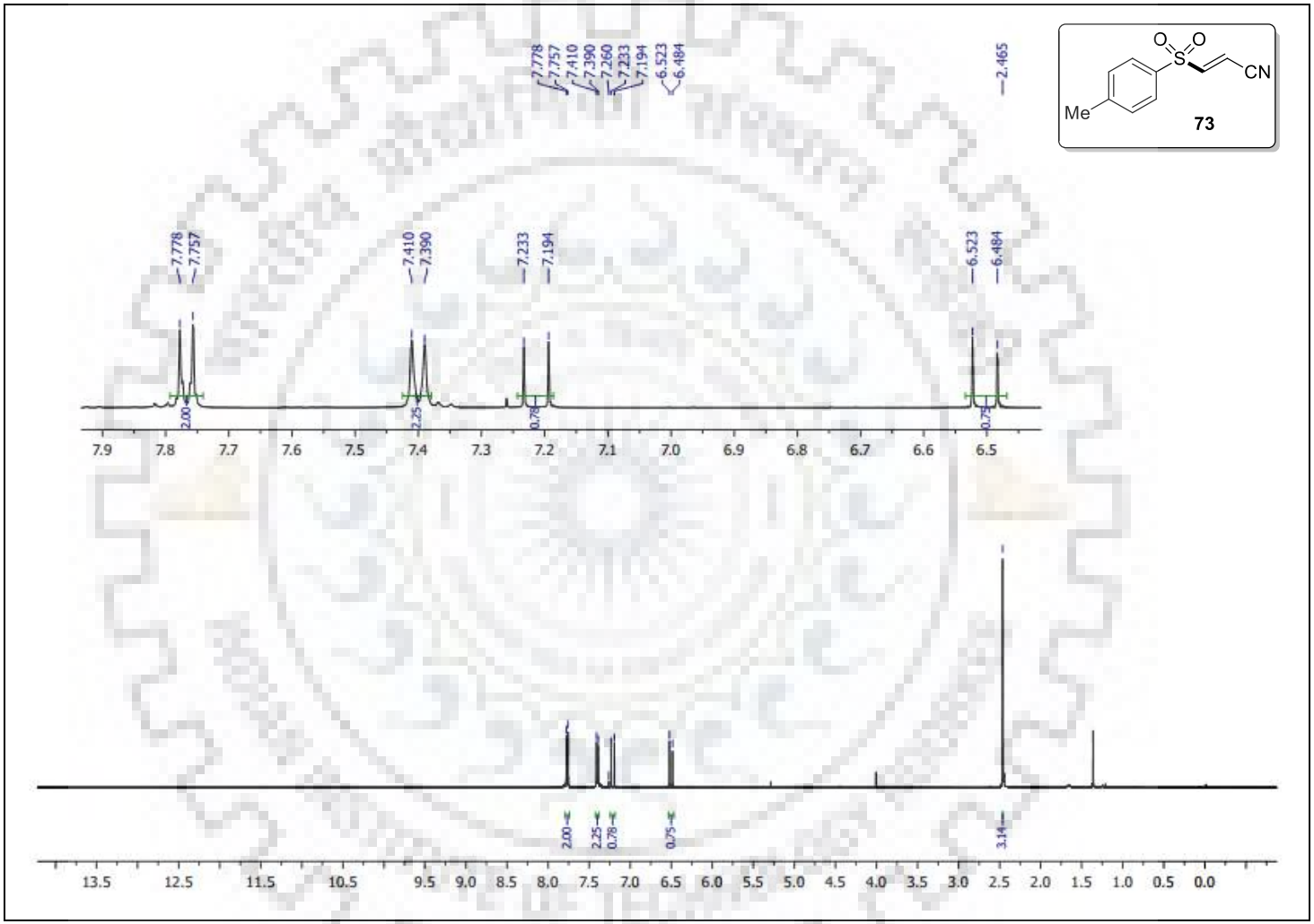


Figure S-45: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **73**.

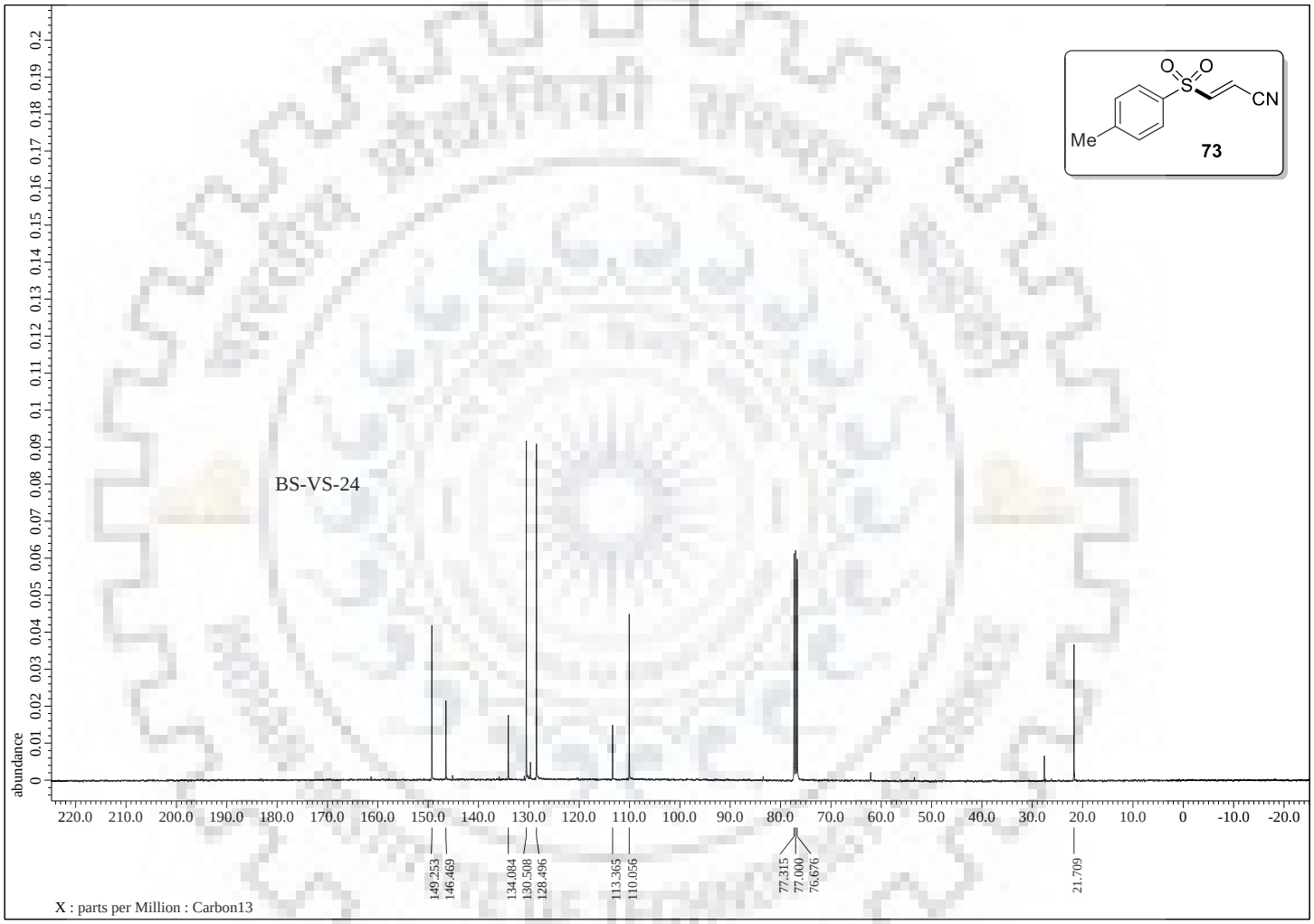


Figure S-46: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **73**.

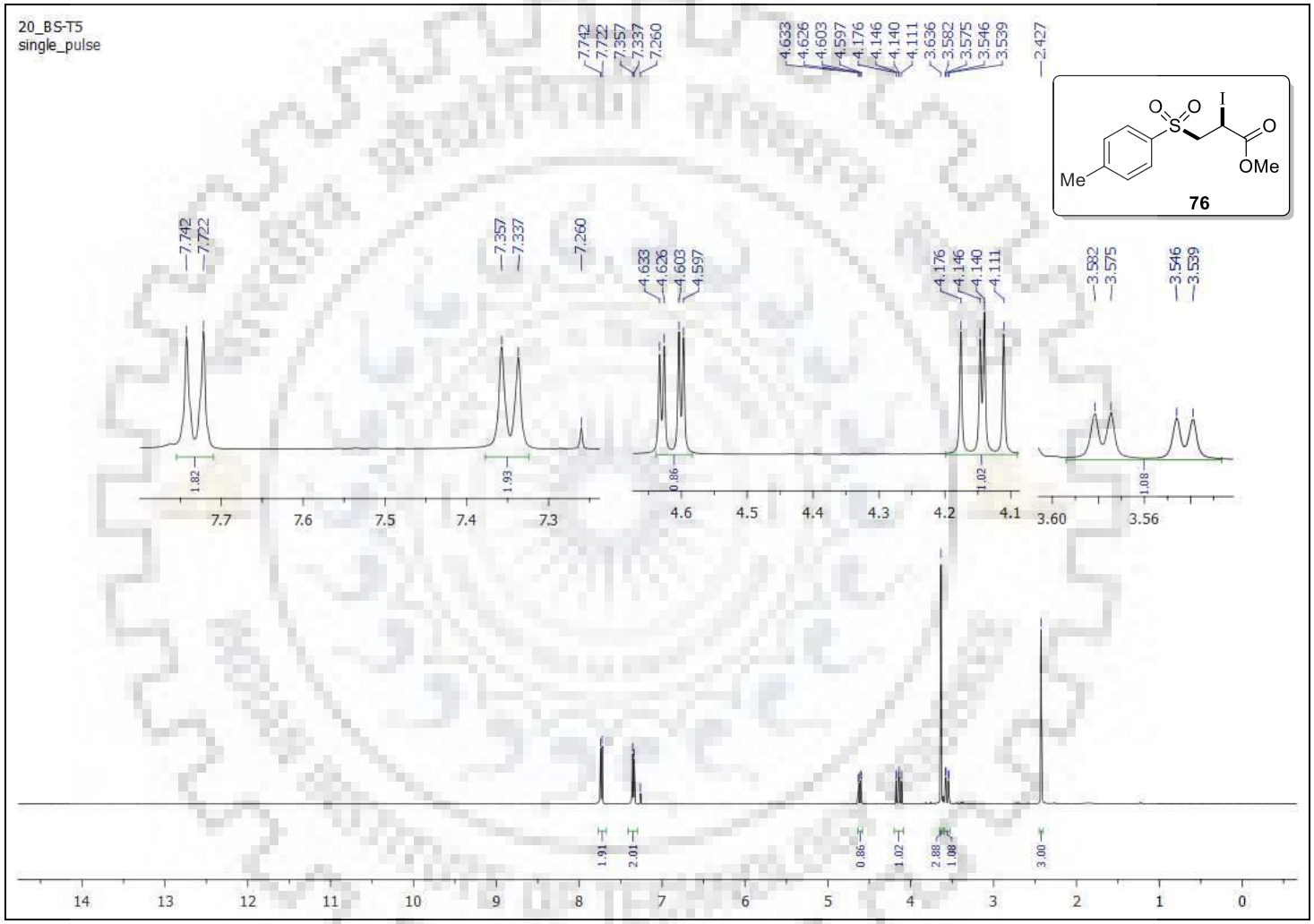


Figure S-47: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **76**.

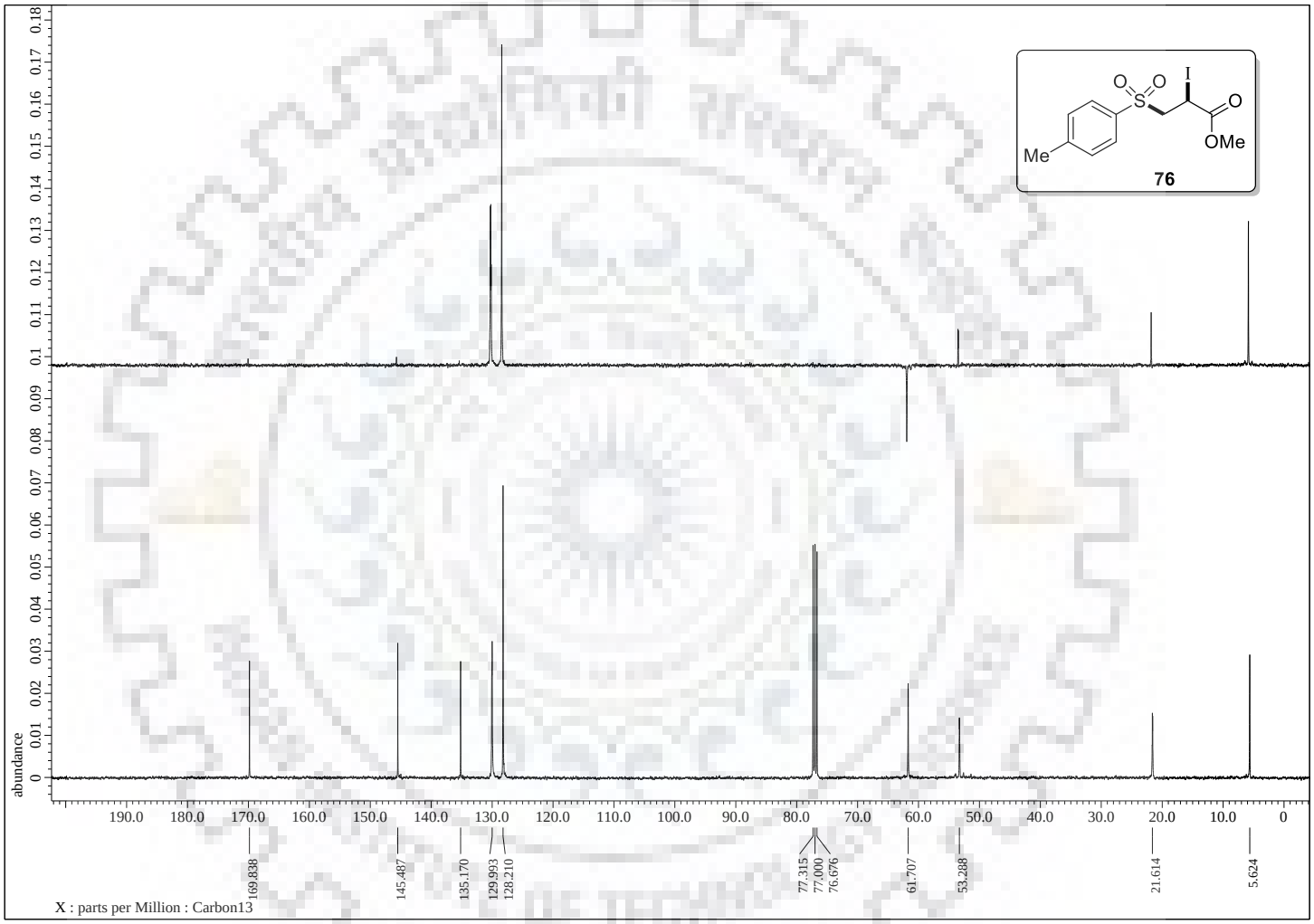


Figure S-48: ^{13}C and DEPT (100 MHz, $CDCl_3$) Spectra of **76**.

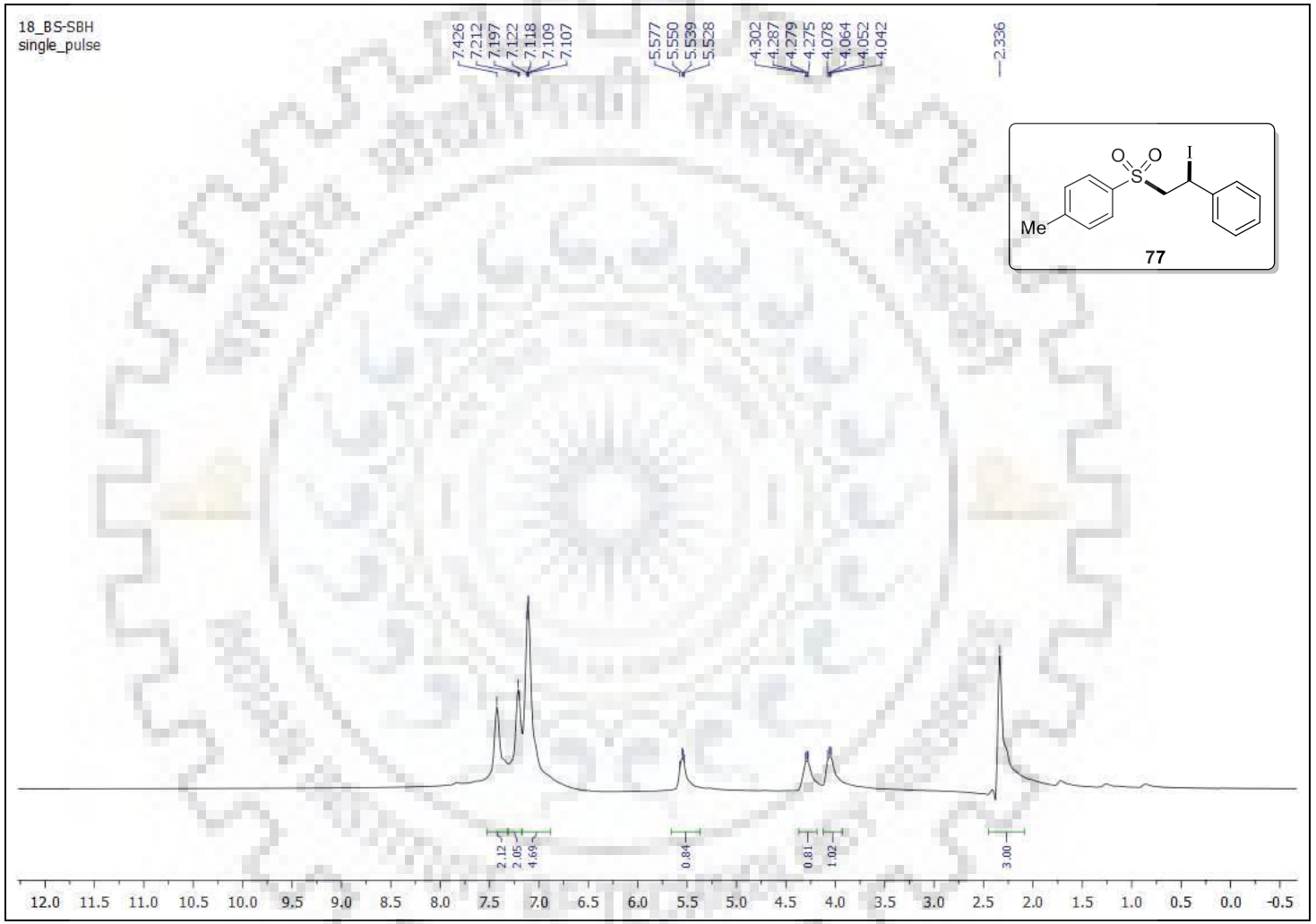


Figure S-49: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **77**.

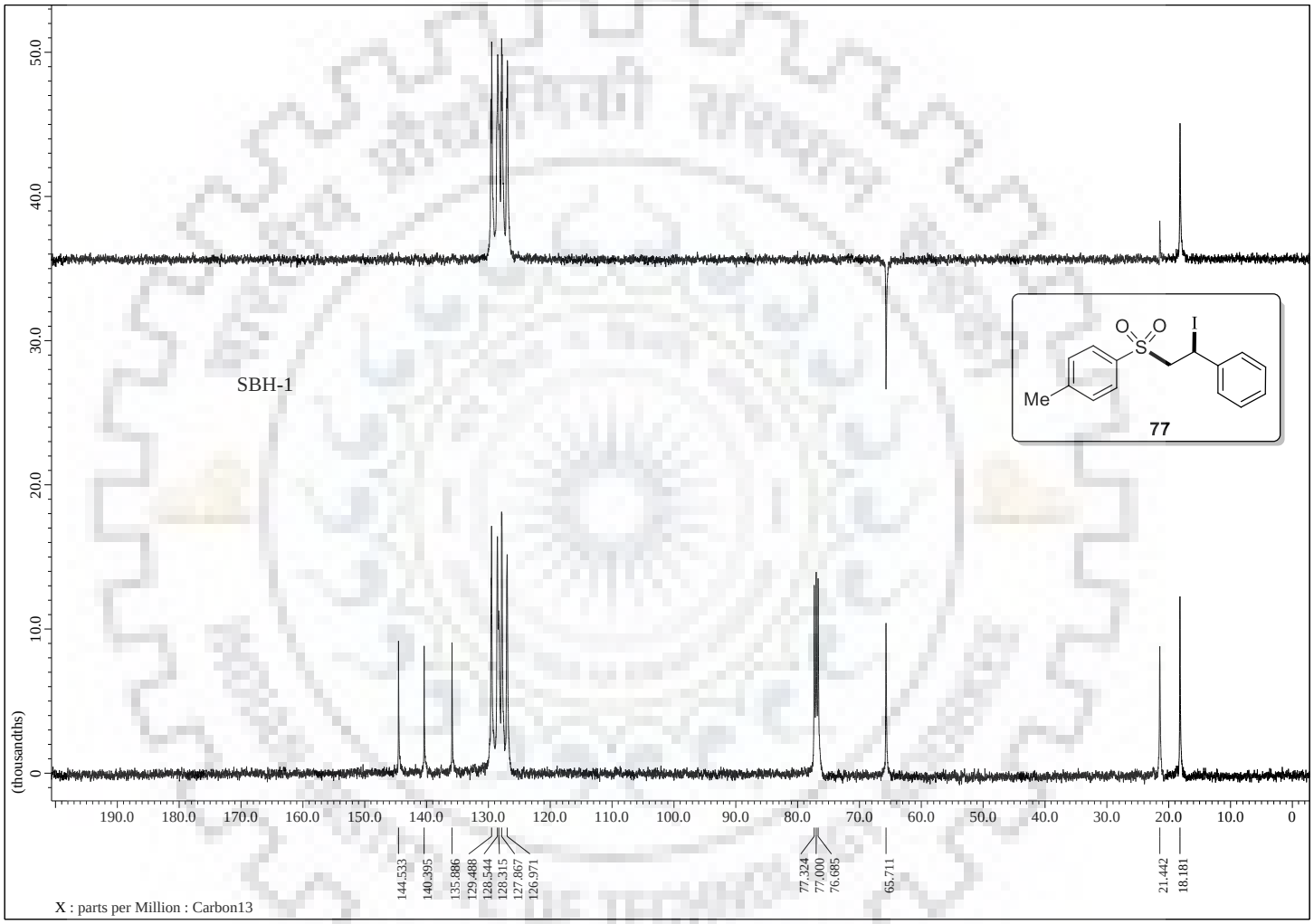


Figure S-50: ^{13}C and DEPT (100 MHz, $CDCl_3$) Spectra **77**.

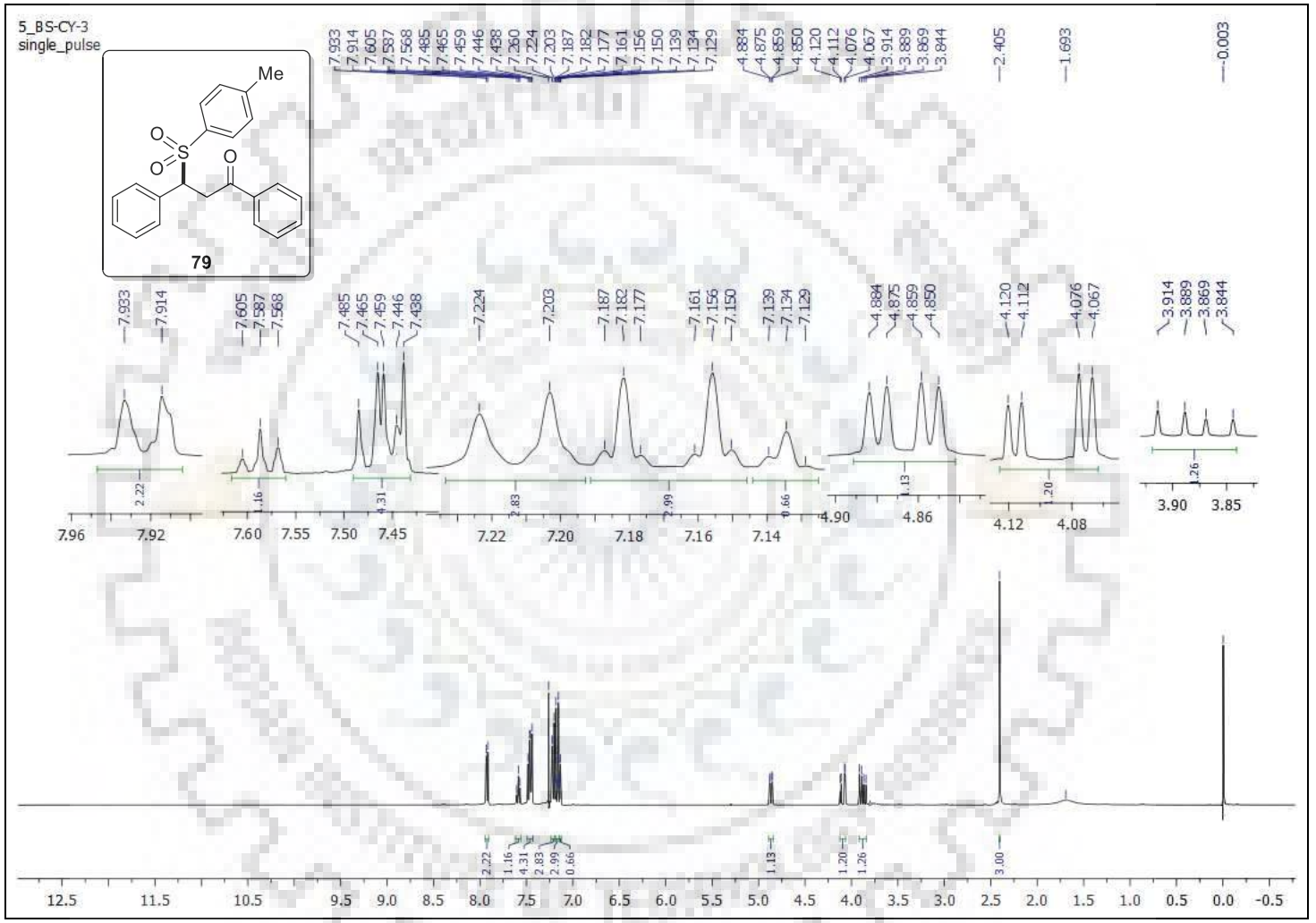


Figure S-51: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **79**.

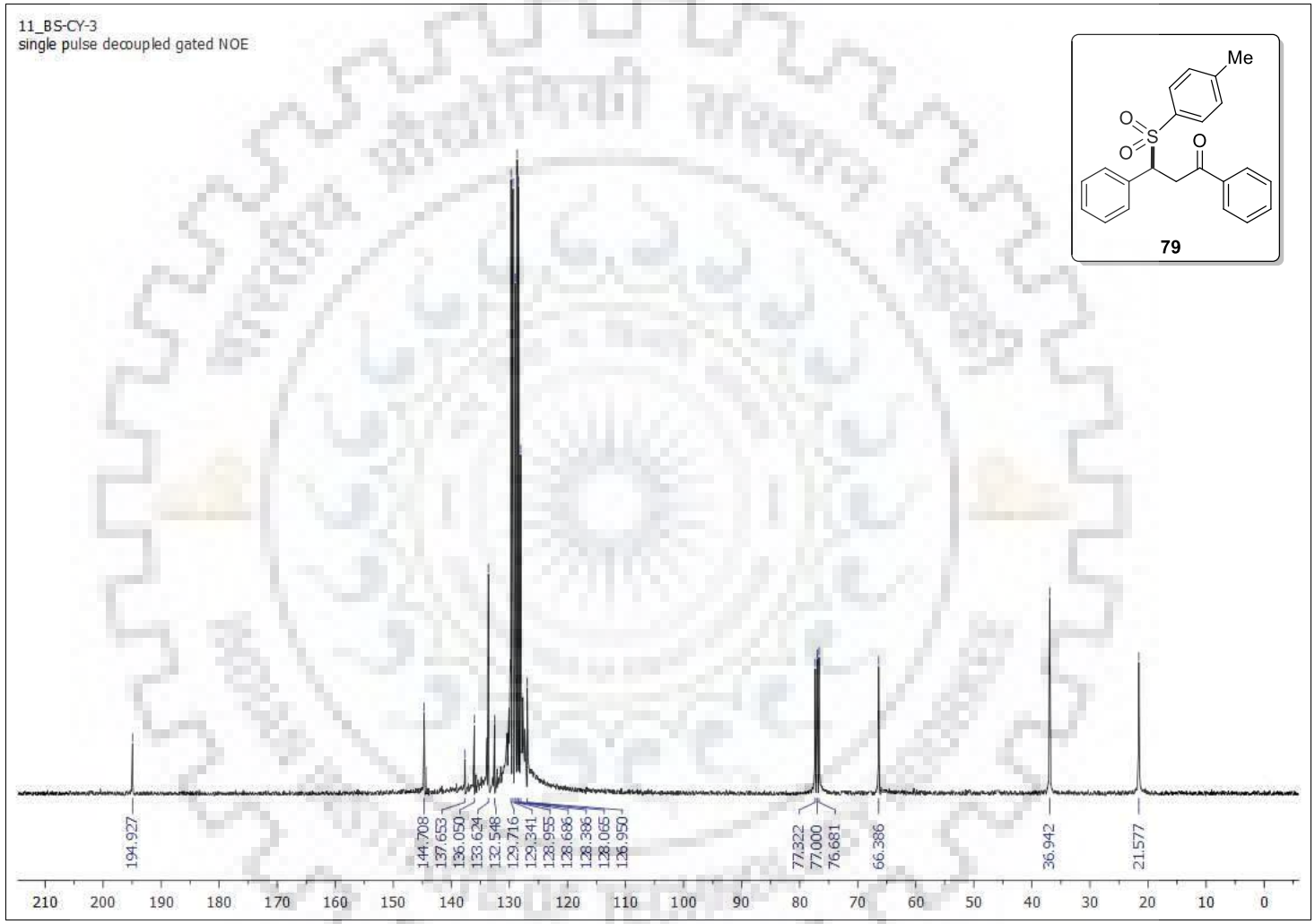


Figure S-52: ^{13}C (14 MHz, $CDCl_3$) Spectrum of **79**.

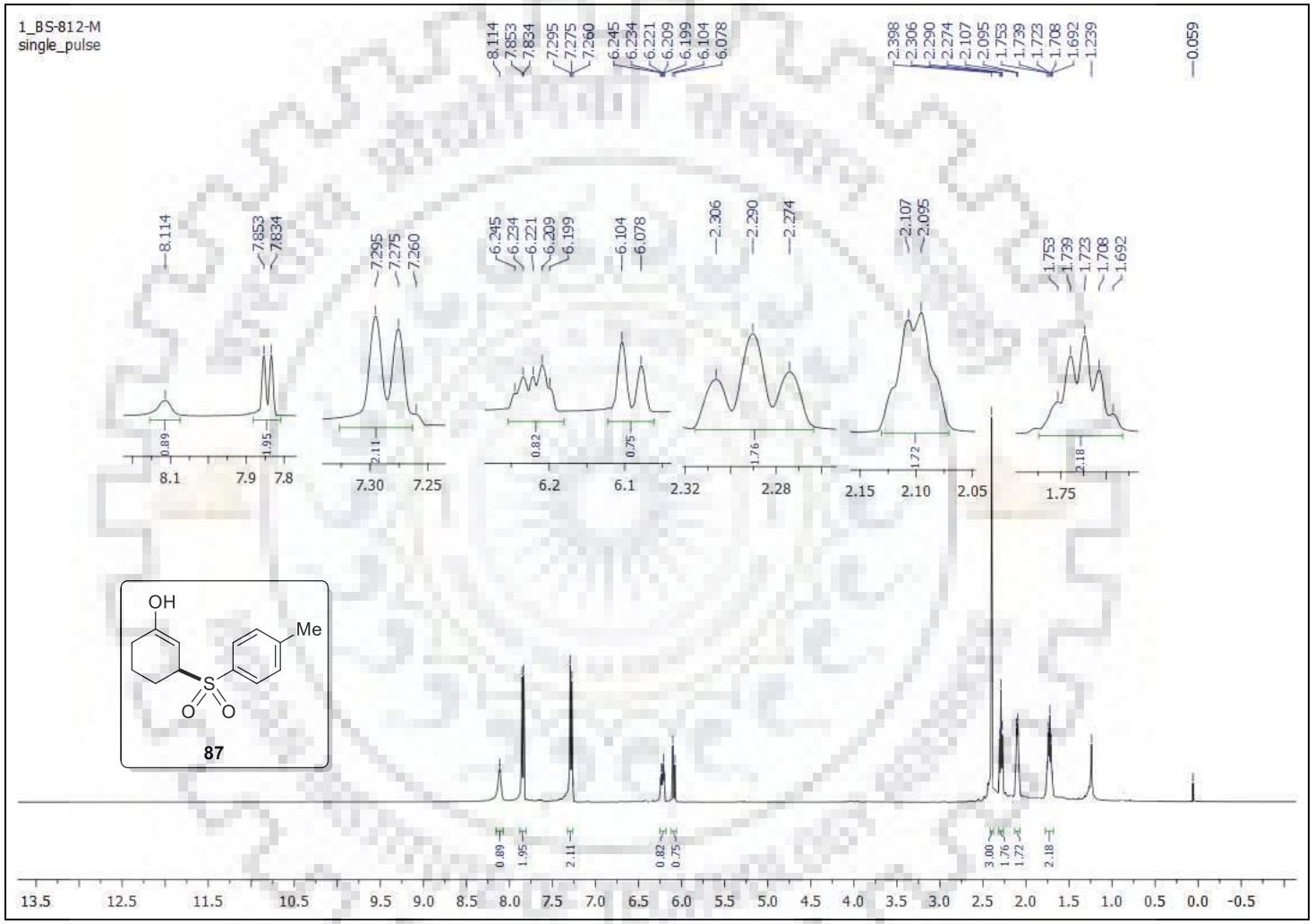


Figure S-53: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **87**.

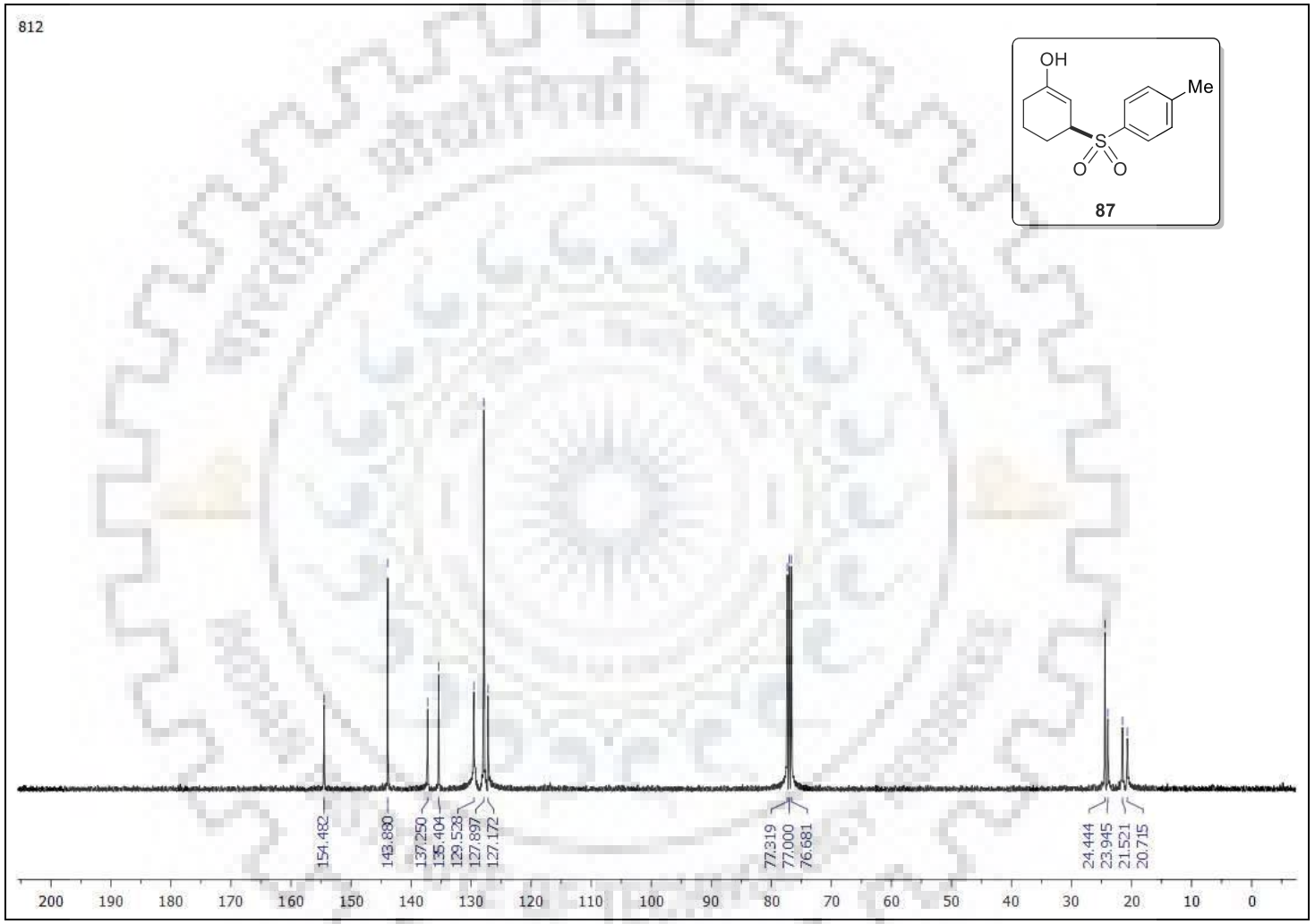


Figure S-54: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **87**.

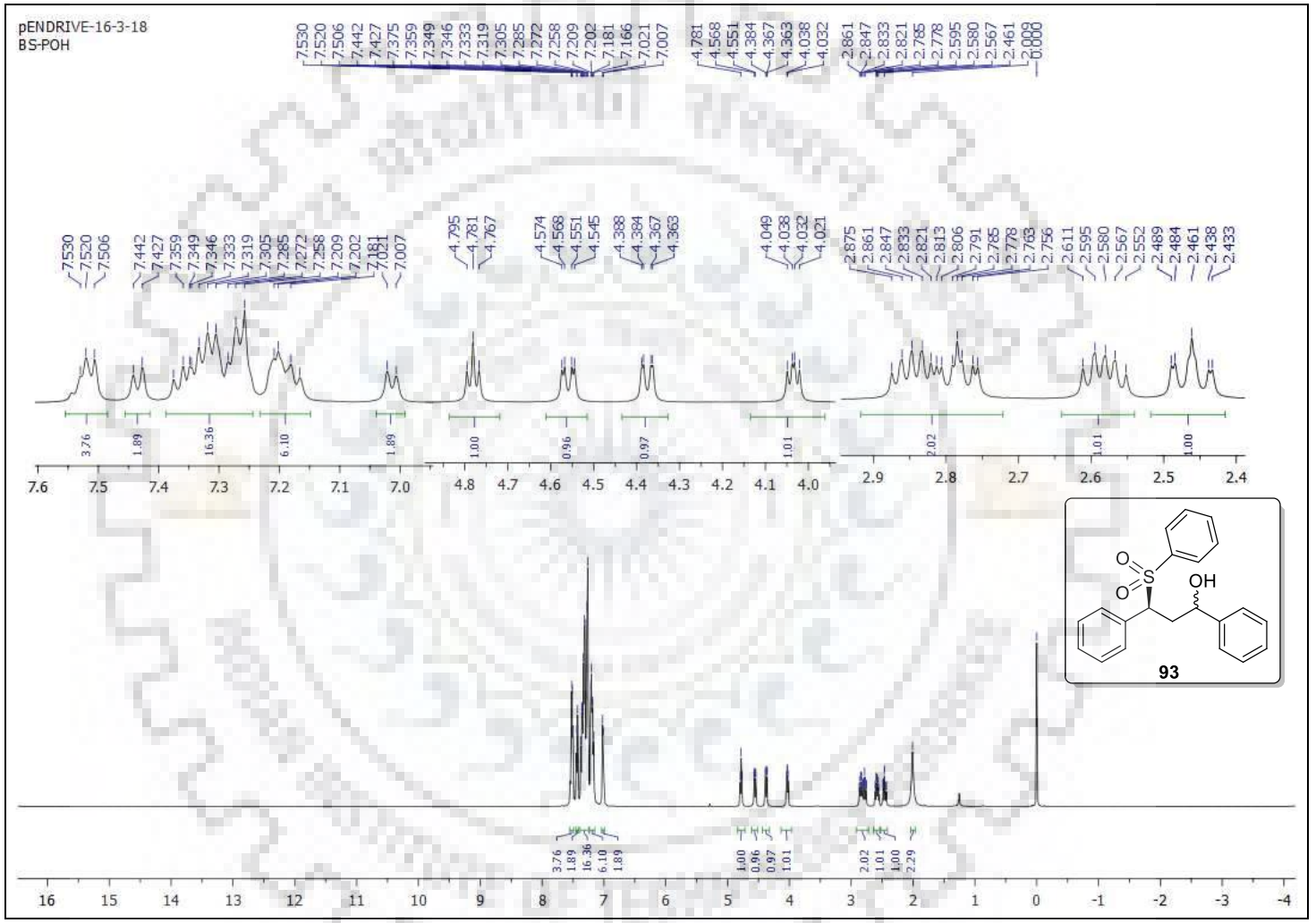


Figure S-55: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **93**.

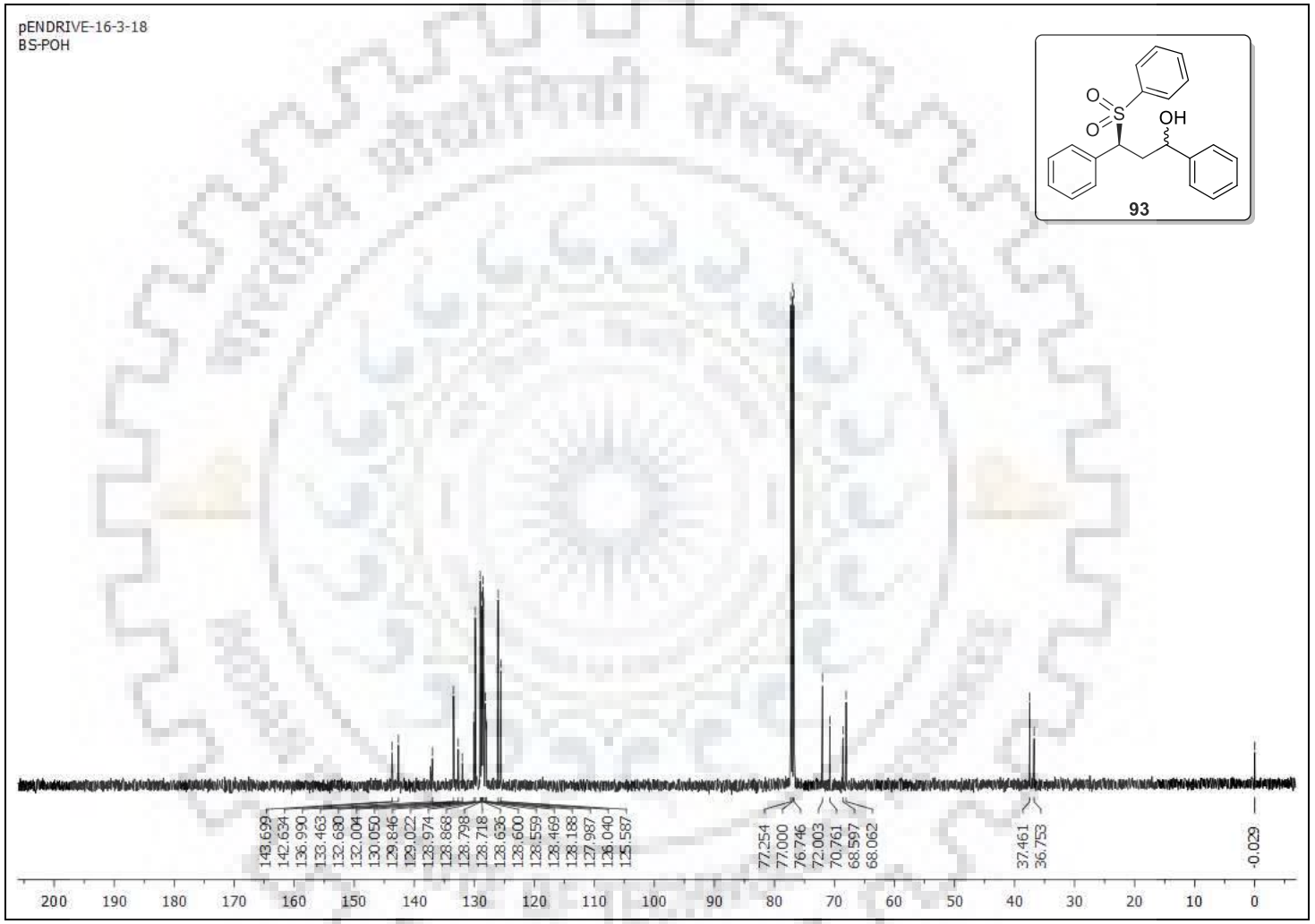


Figure S-56: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **93**.

Figure S-57: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **98**.

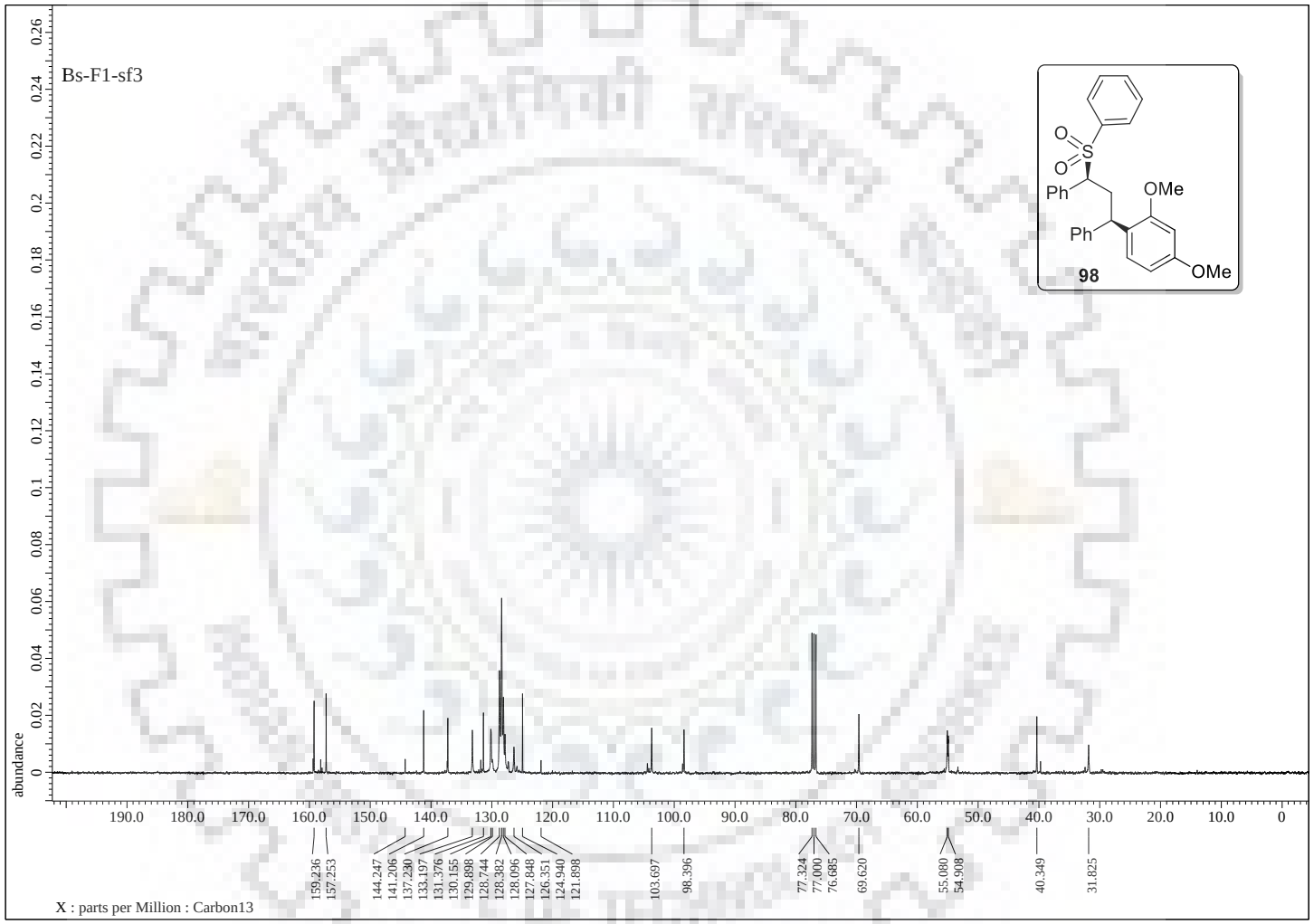


Figure S-58: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **98**.

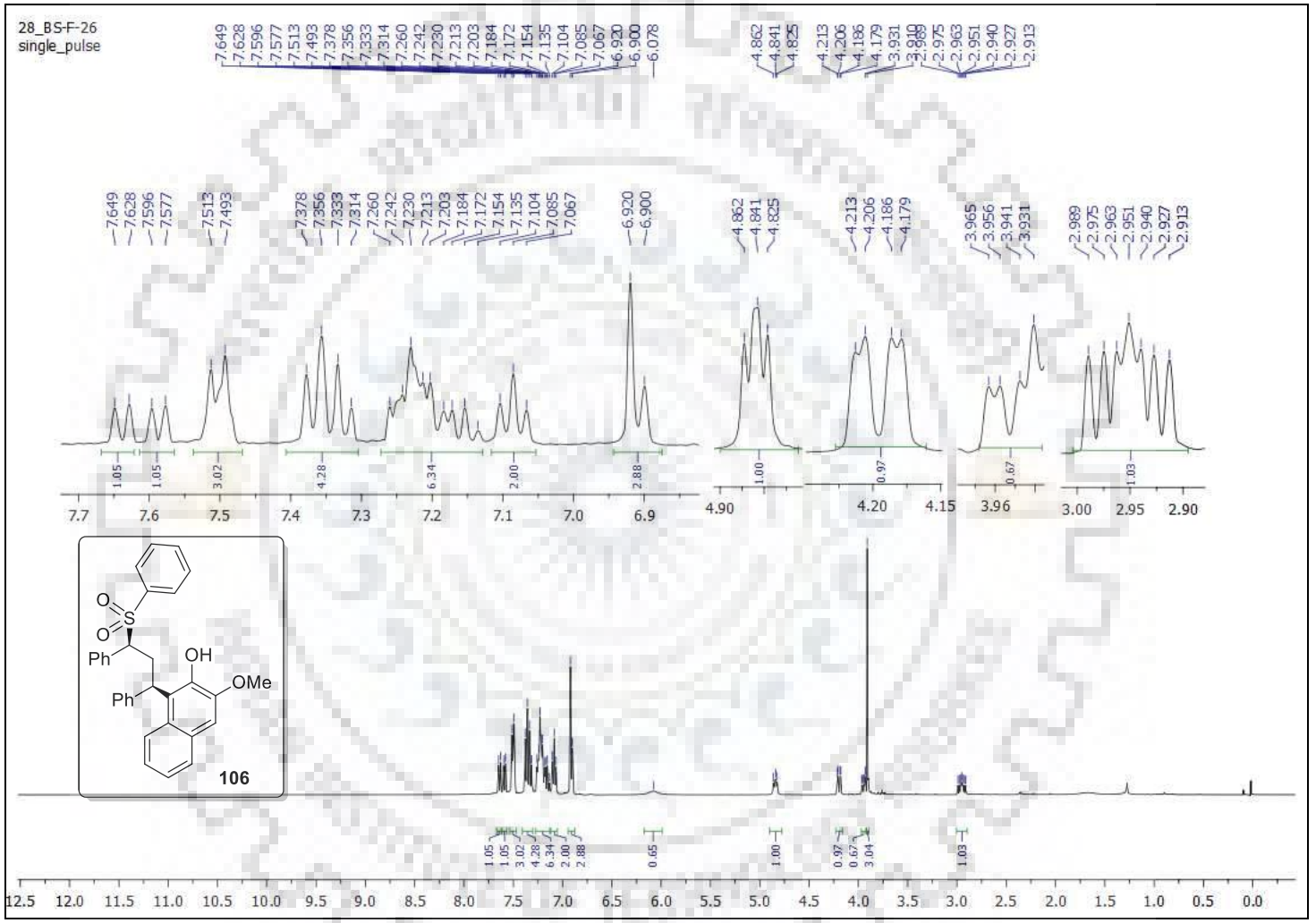


Figure S-59: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **106**.

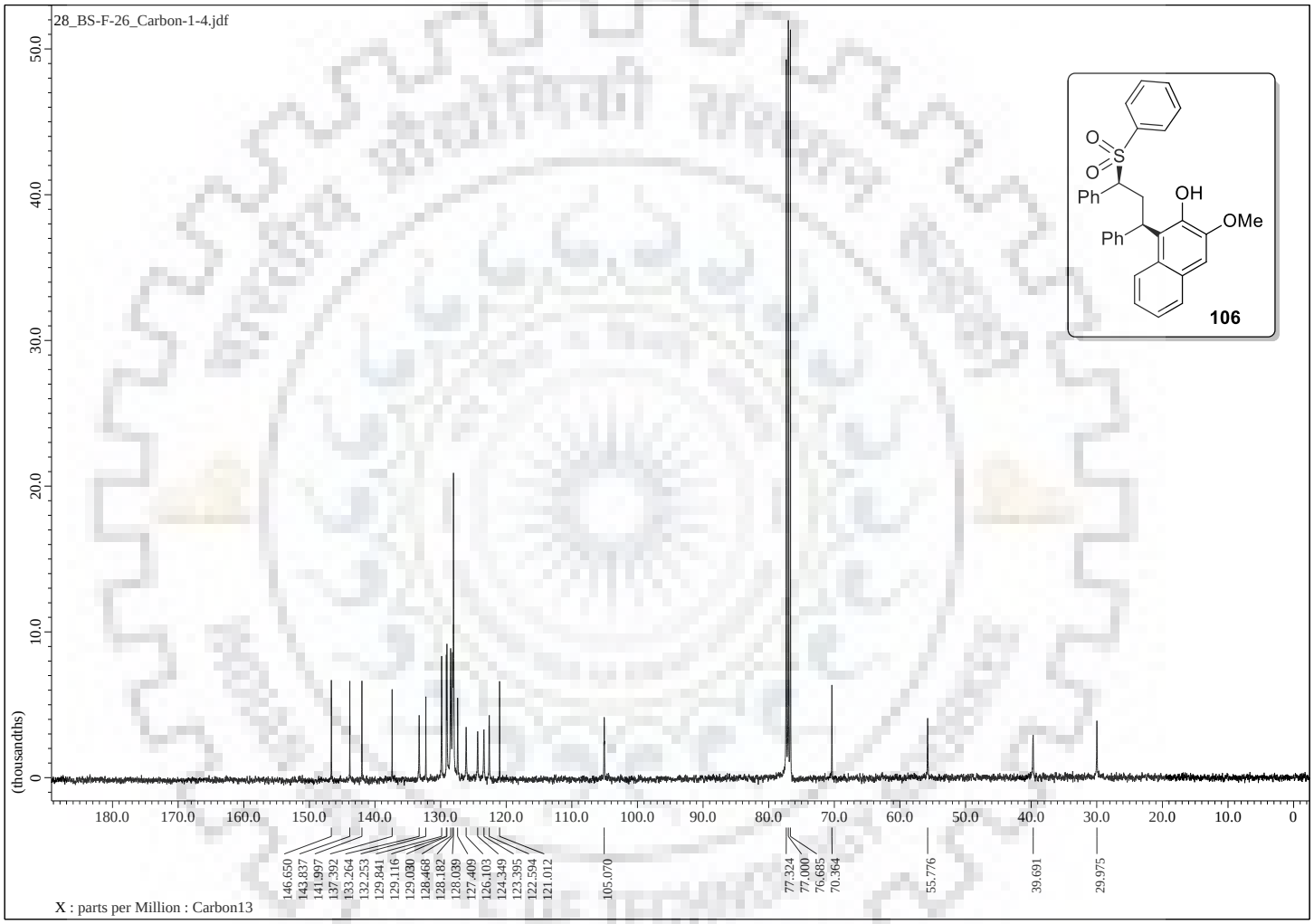


Figure S-60: ^{13}C (100 MHz, $CDCl_3$) Spectra of **106**.

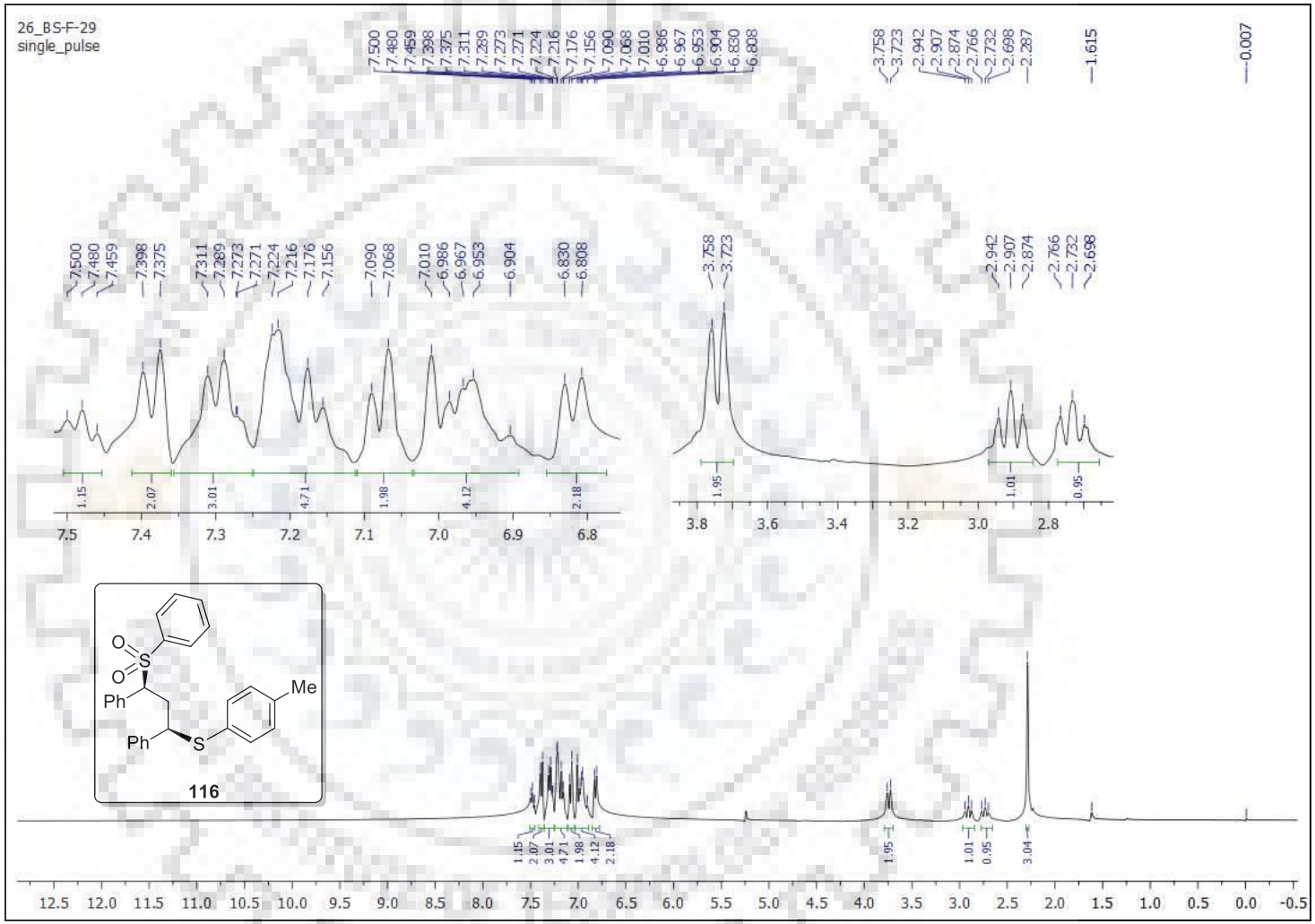


Figure S-61: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **116**.

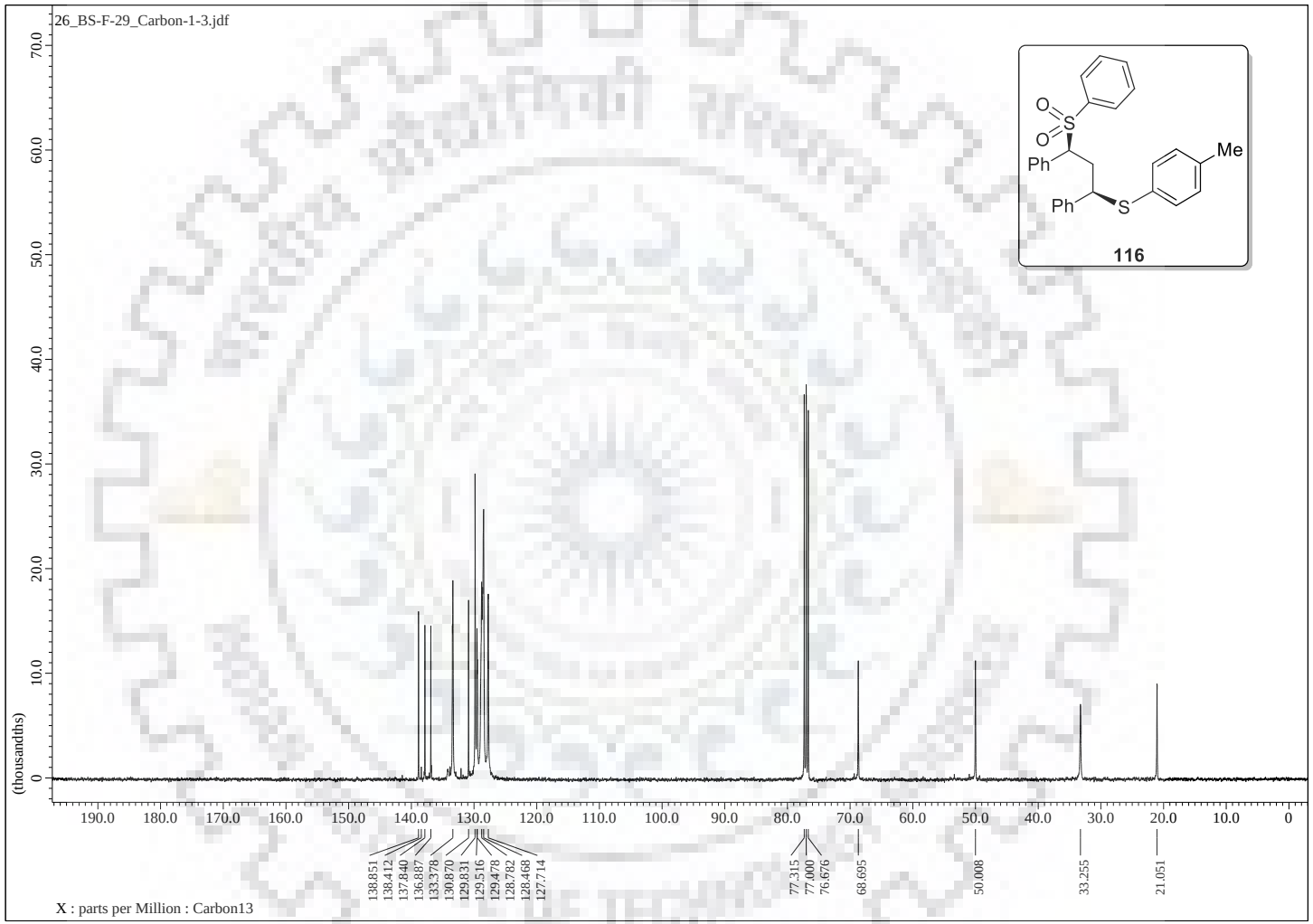


Figure S-62: ^{13}C (100 MHz, $CDCl_3$) Spectra of **116**.

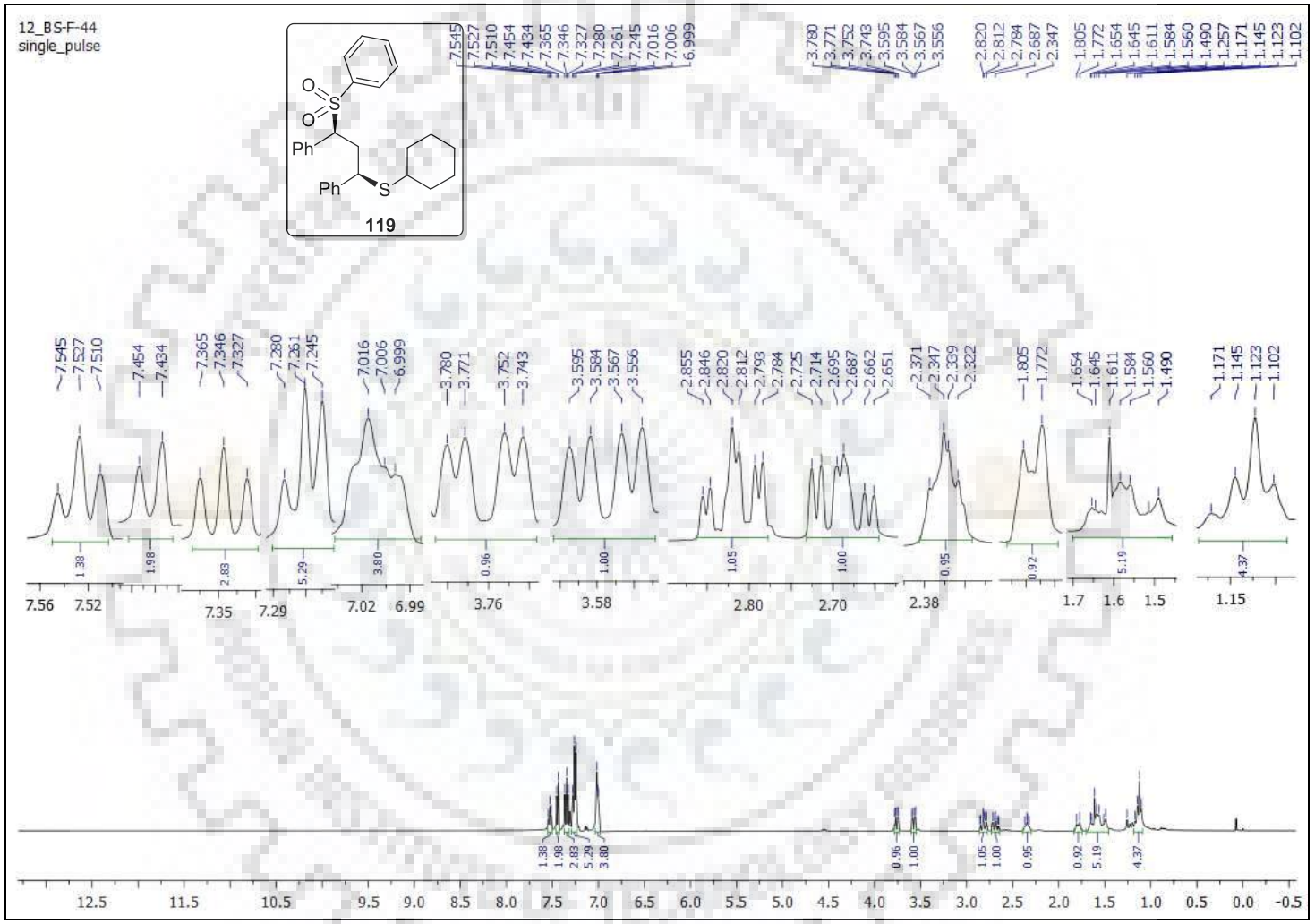


Figure S-63: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **119**.

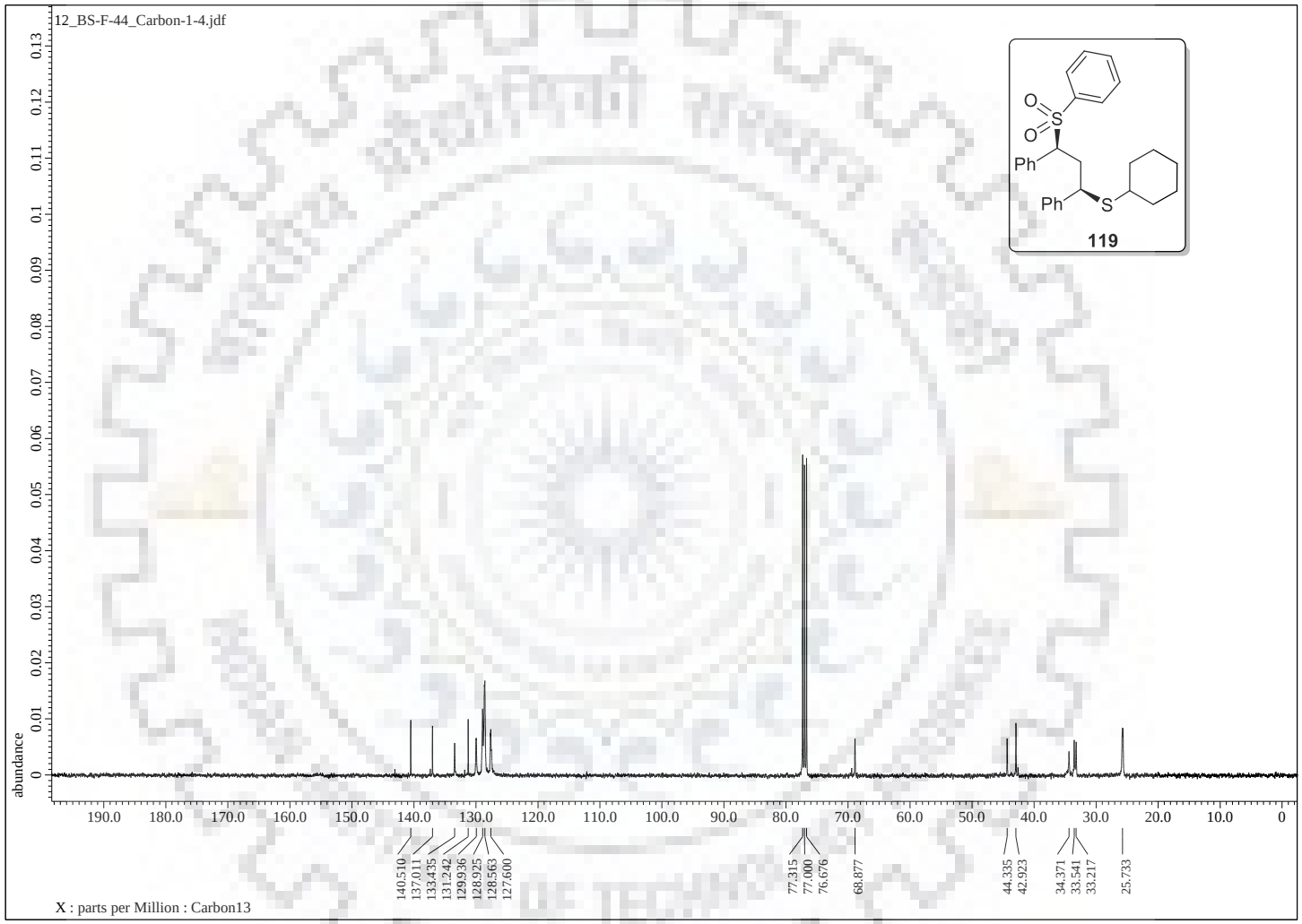


Figure S-64: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **119**.

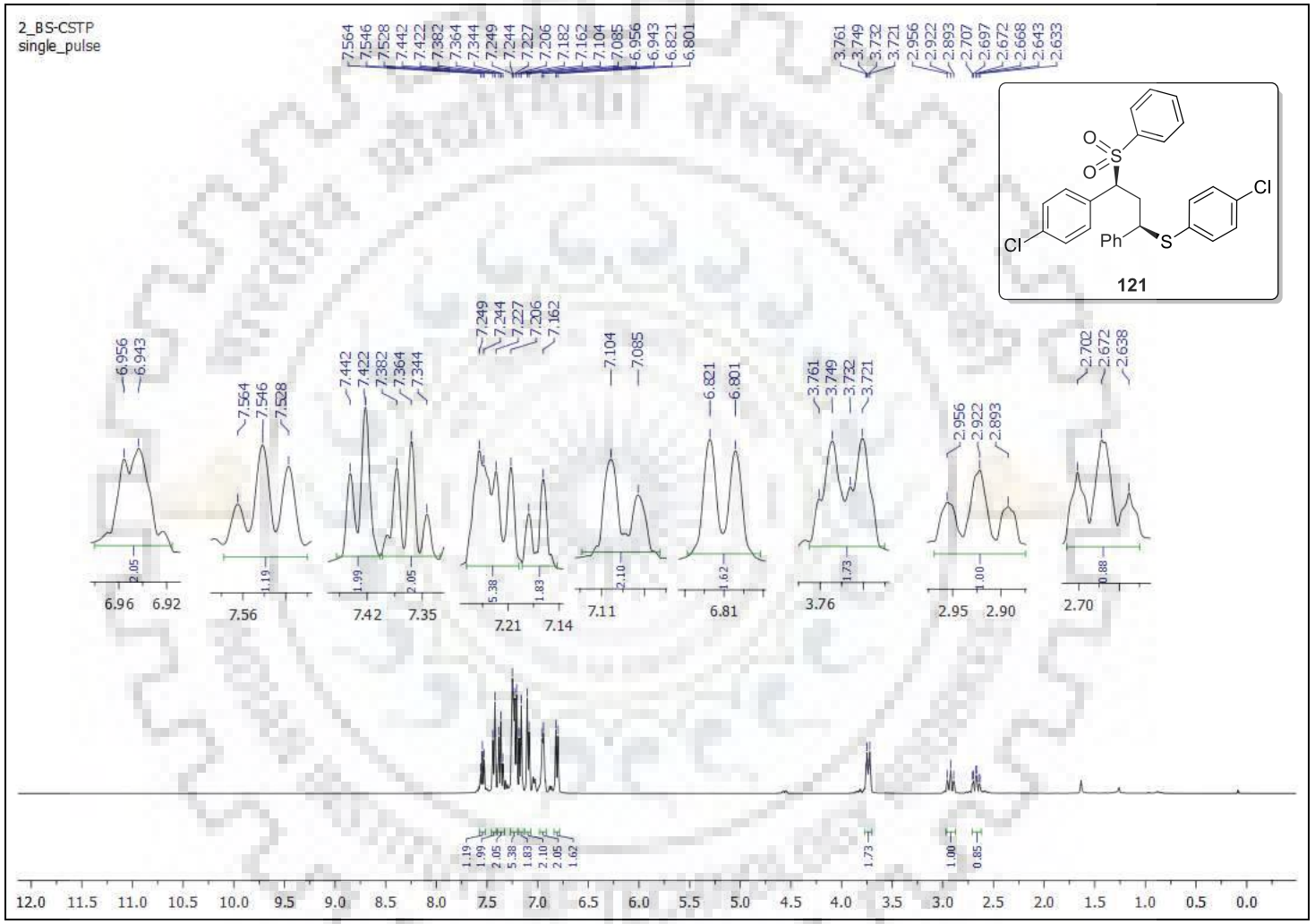


Figure S-65: ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **121**.

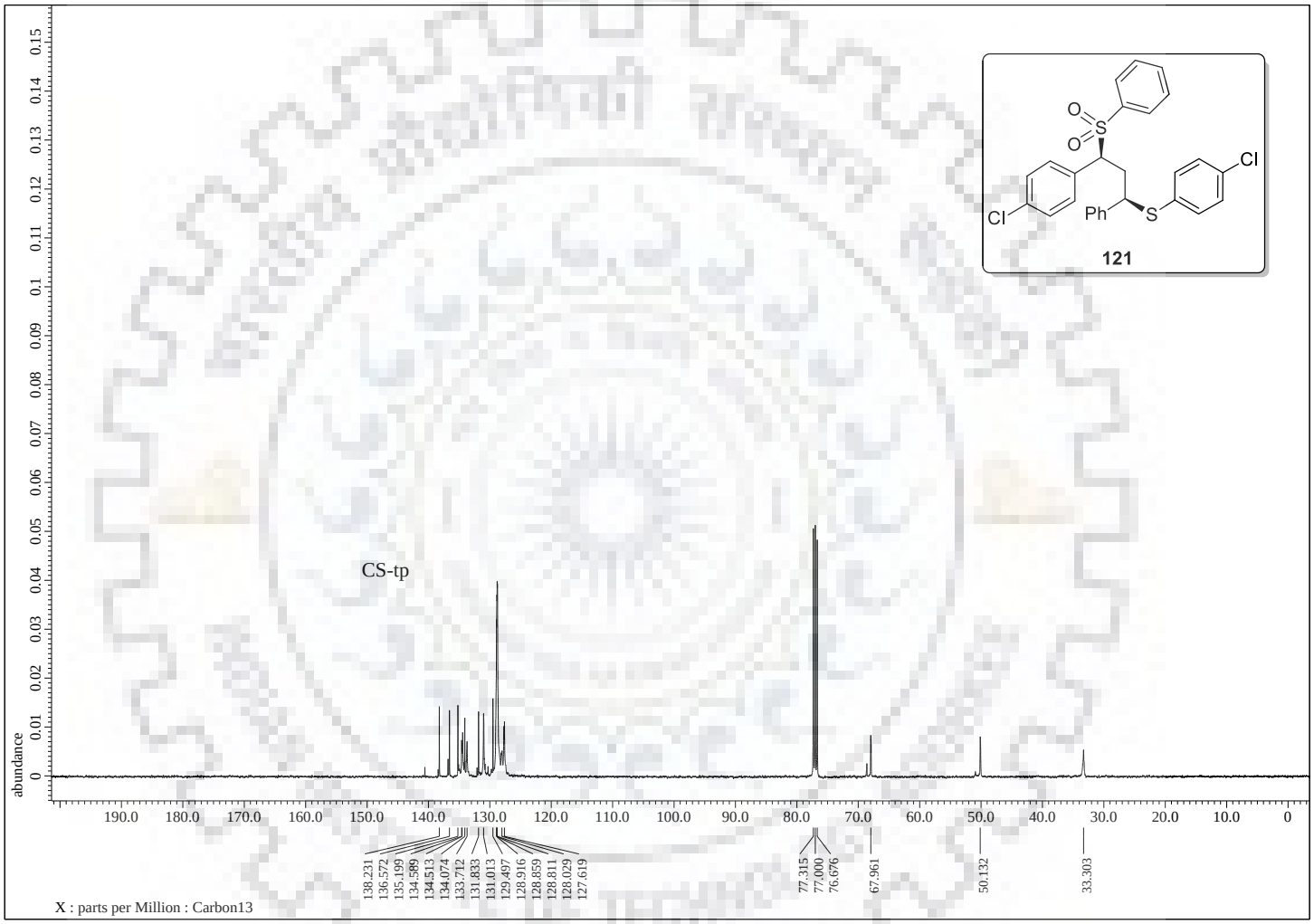


Figure S-66: ^{13}C (100 MHz, $CDCl_3$) Spectrum of **121**.

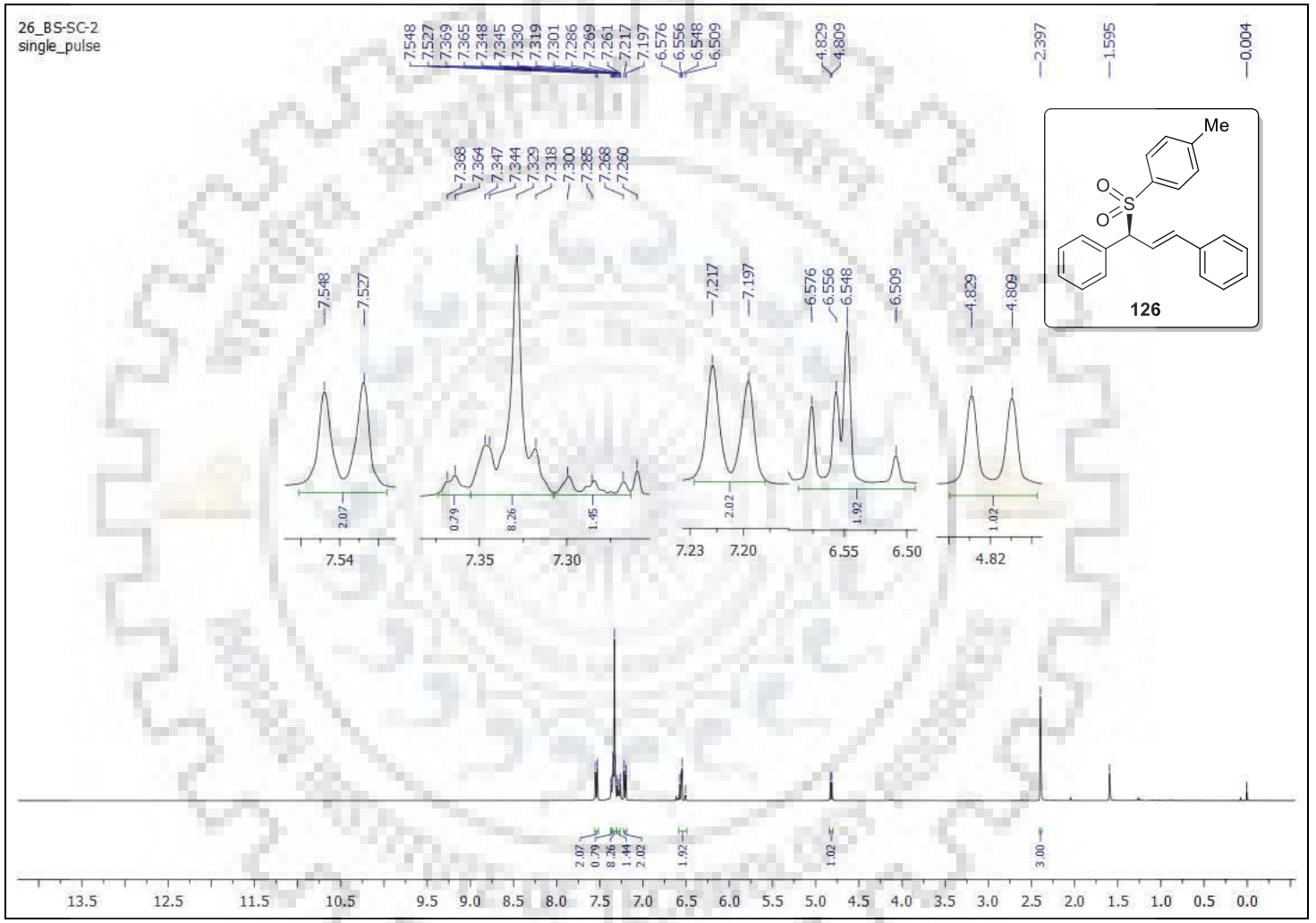


Figure S-67: ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **126**.

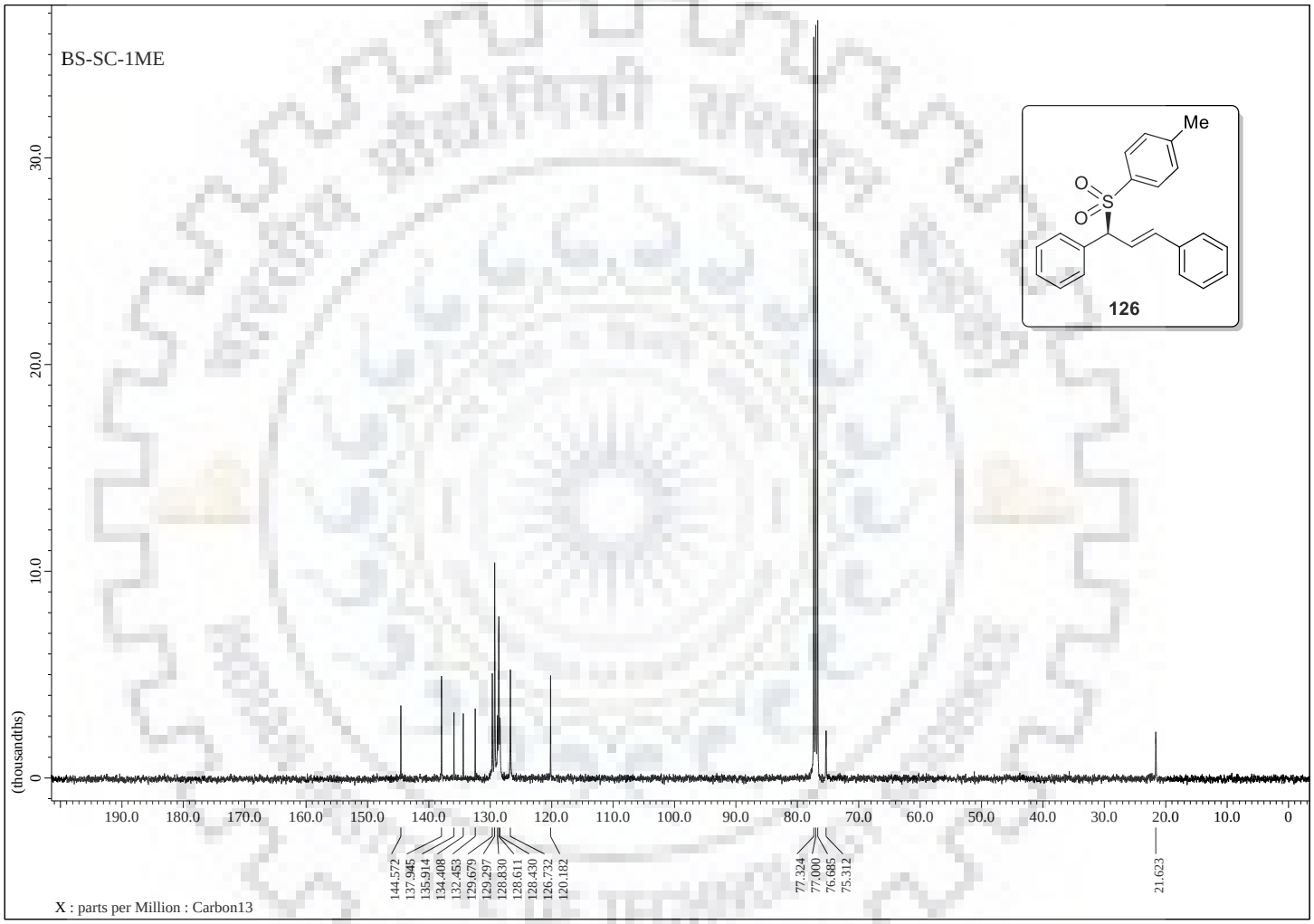
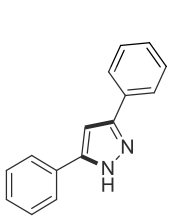


Figure S-68: ^{13}C and DEPT (125 MHz, $CDCl_3$) Spectra of **126**.

STRUCTURES OF COMPOUNDS SYNTHESIZED



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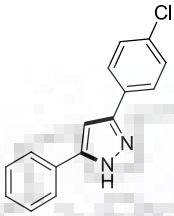

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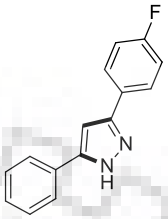

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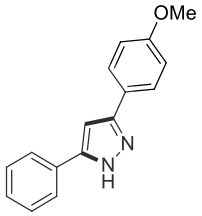

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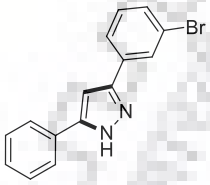

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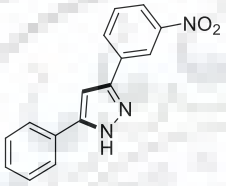

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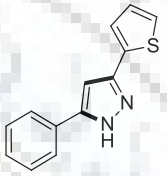

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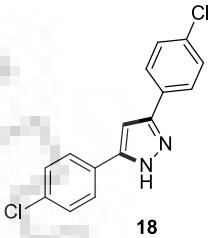

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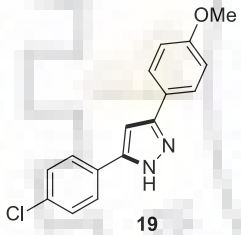

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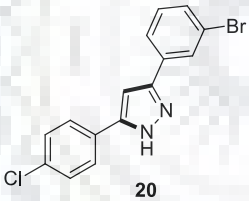

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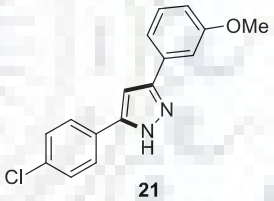

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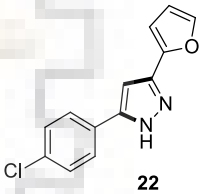

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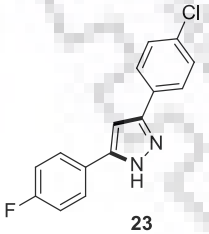

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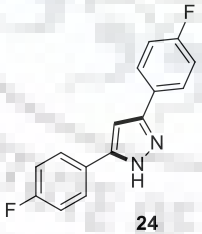

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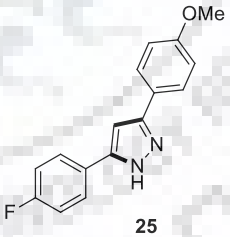

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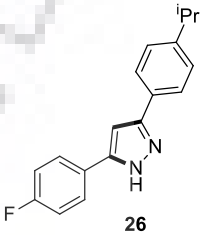

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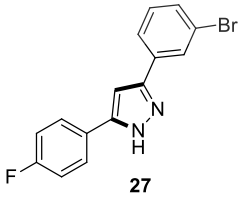

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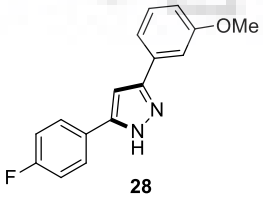

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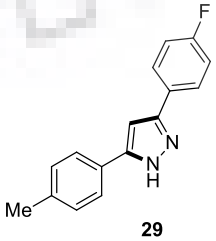

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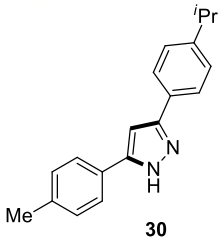

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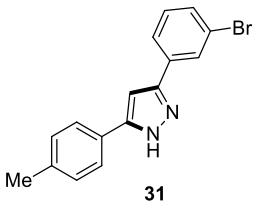

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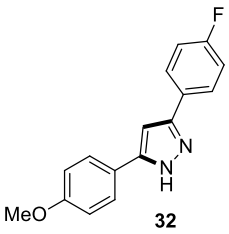

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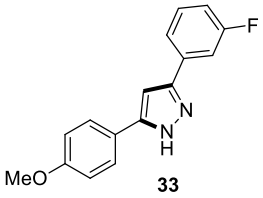

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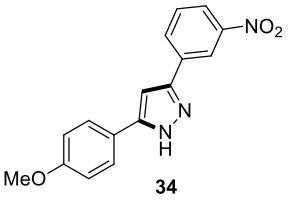

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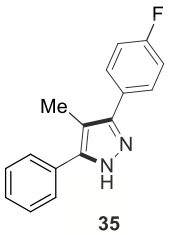

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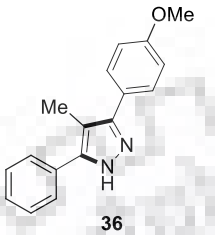

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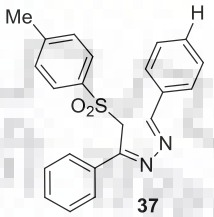

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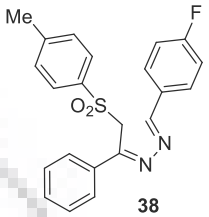

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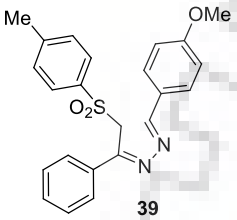

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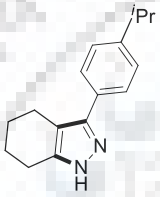

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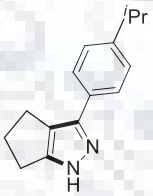

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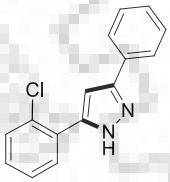

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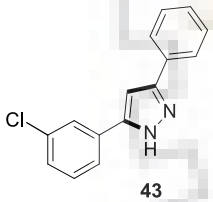

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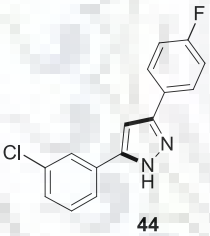

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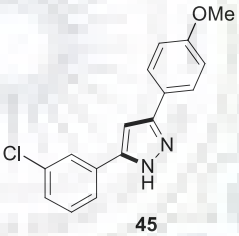

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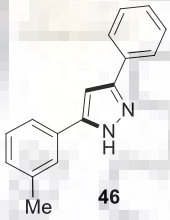

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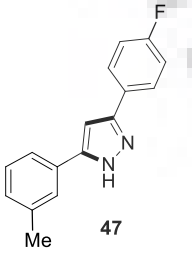

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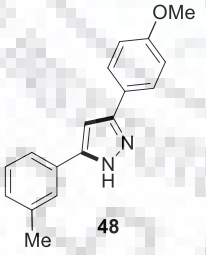

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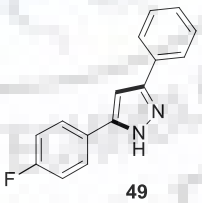

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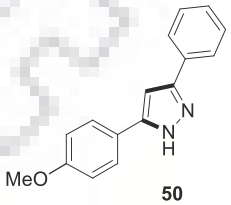

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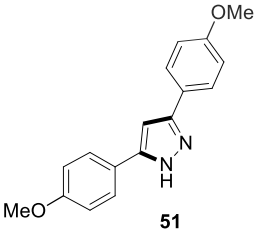

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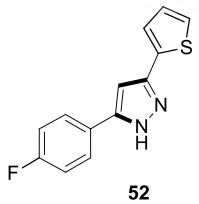

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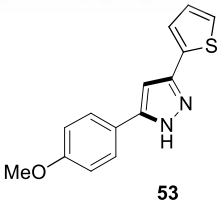

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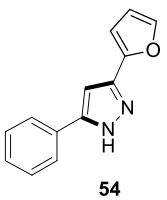

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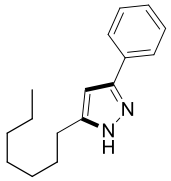

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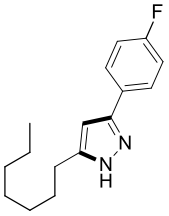

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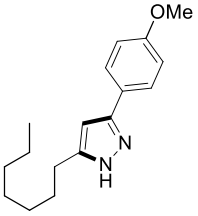

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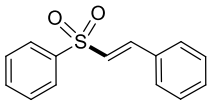

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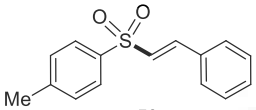

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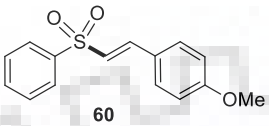

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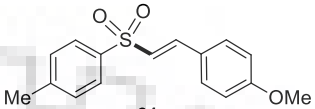

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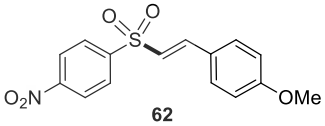

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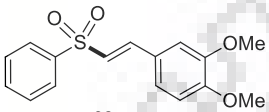

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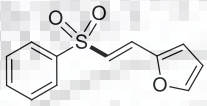

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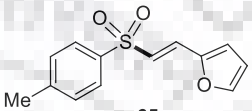

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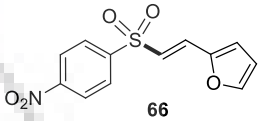

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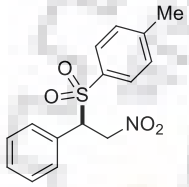

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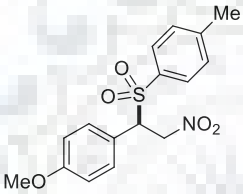

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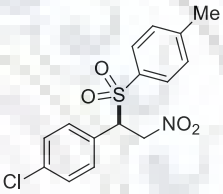

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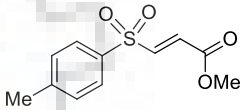

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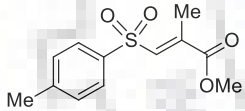

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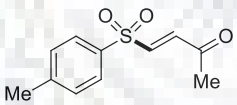

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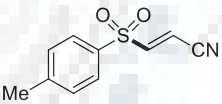

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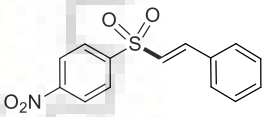

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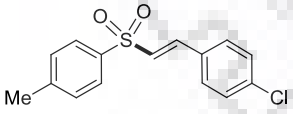

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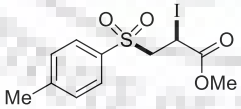

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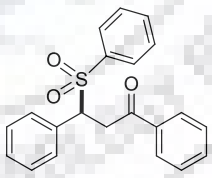

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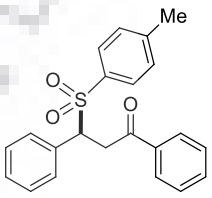

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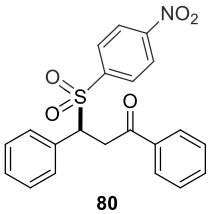

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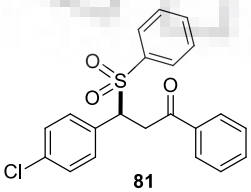

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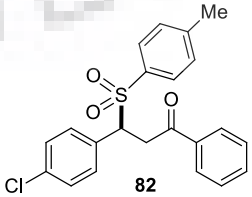

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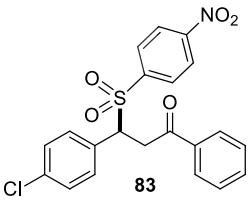

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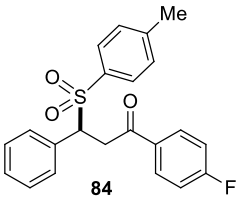
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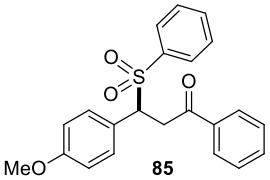
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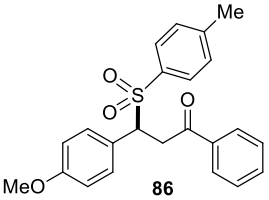
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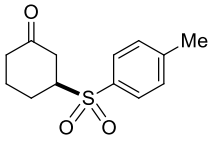
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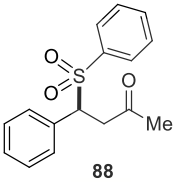
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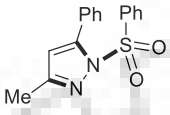
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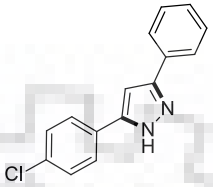
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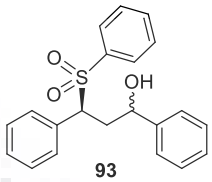
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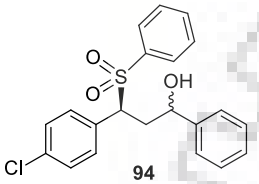
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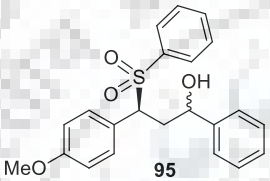
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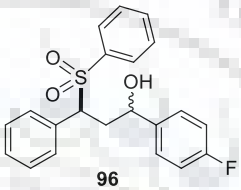
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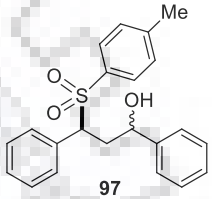
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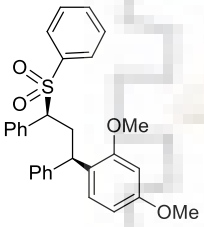
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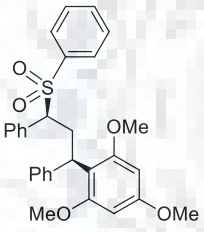
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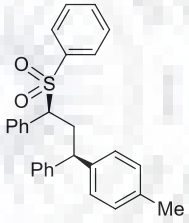
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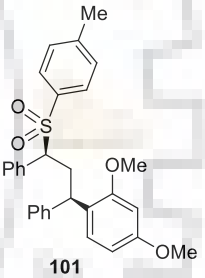
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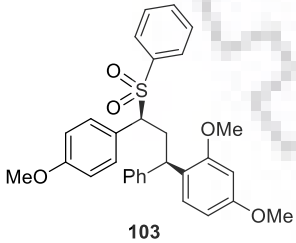
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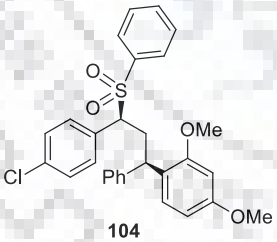
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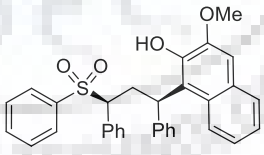
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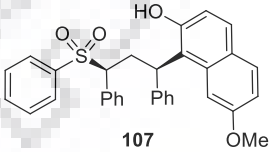
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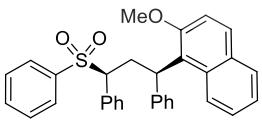
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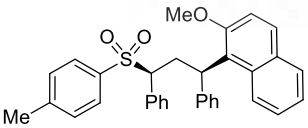
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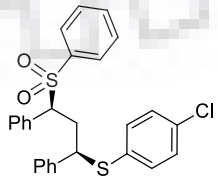
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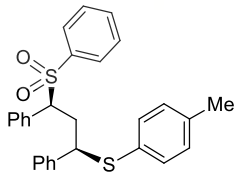
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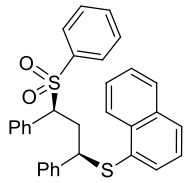

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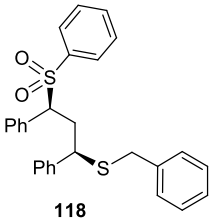

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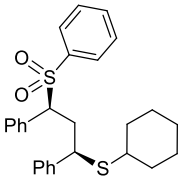

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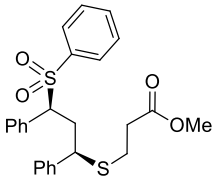

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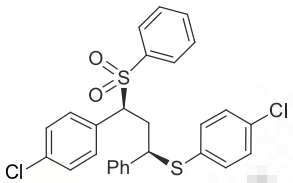

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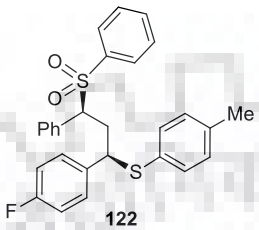
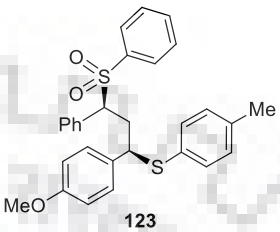


122



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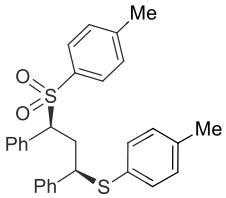

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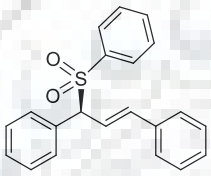
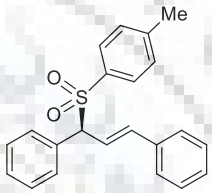


125



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VITAE

The author was born on 01 January 1985, at Edurugatla, Vemulawada, Telangana. Following his early education, he joined in S. R. R. Degree and P. G. College, Karimnagar and received his B.Sc. degree from Kakatiya University in 2007. He got admitted into Vaagdevi Degree and P. G. College, Warangal for M.Sc. and obtained the degree in 2010. He registered for Ph.D. in January 2013 at Indian Institute of Technology Roorkee. He was awarded JRF and SRF by UGC, New Delhi.

LIST OF PUBLICATIONS

1. The diaza-Nazarov cyclization involving a 2,3-diaza-pentadienyl cation for the synthesis of polysubstituted pyrazoles
   B. Aegurla and R. K. Peddinti
   Org. Biomol. Chem., **2017**, *15*, 9643−9652.

2. Iodine-catalysed regioselective synthesis of β-hydroxysulfides
   P. Tehri, **B. Aegurula**, and R. K. Peddinti
   Tetrahedron Lett. **2017**, *58*, 2062−2065.

3. Metal-free sulfonylation of *α,β*-conjugated systems by using sulfonyl hydrazides
   B. Aegurla and R. K. Peddinti
   Asian J. Org. Chem., **2018**, *7*, 946−954.

4. Dehydrative C- and S-alkylation: Access to highly substituted 1-Sulfonylpropanes
   B. Aegurla, R. K. Peddinti
   Manuscript under preparation.

5. Denitrative-imino-diaza-Nazarov cyclization for the synthesis of disubstitutrd pyrazoles
   B. Aegurla, R. K. Peddinti
   Manuscript under preparation.

Conferences attended

Aegurla Balakrishna, R. K. Peddinti.
Metal-Free Sulfonylation of α,β-Conjugated Systems by Using Sulfonyl Hydrazides.
Poster presented in **ACS on campus** held at IIT-Roorkee, on 7th February 2018.

Aegurla Balakrishna, R. K. Peddinti.
The diaza-Nazarov cyclization for the synthesis of substituted pyrazoles.
Poster presented in **CFOS-Contemporary Facets in Organic Synthesis** held at IIT-Roorkee during December 22-24, 2017.

Aegurla Balakrishna, R. K. Peddinti.
The diaza-Nazarov cyclization involving a 2,3-diaza-pentadienyl cation for the synthesis of polysubstituted pyrazoles.
Poster presented in The **21st CRSI-ACS National Symposium-**2017–IICT Hyderabad during December 13-16 july, 2017.

Aegurla Balakrishna, R. K. Peddinti.
One pot, three-component approach for the synthesis of substituted pyrazoles through a metal-free Csp^3–Csp^2 crossdehydogentaive coupling (CDC).
Poster presented in **Pre-ICOS Conference** held at IISER Bhopal during December 9-10, 2016