DESIGN AND SYNTHESIS OF N, O-CONTAINING HETEROCYCLES

Ph.D. THESIS

by

DANISH KHAN

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGYROORKEE
ROORKEE – 247 667 (INDIA)
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DESIGN AND SYNTHESIS OF N, O-CONTAINING HETEROCYCLES

A THESIS

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in

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by

DANISH KHAN

DEPARTMENT OF CHEMISTRY
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STUDENT'S DECLARATION

I hereby certify that the work presented in the thesis entitled "***DESIGN AND SYNTHESIS OF N, O-CONTAINING HETEROCYCLES***" is my own work carried out during a period from January, 2016 to June, 2020 under the supervision of Dr. Naseem Ahmed, Professor Department of Chemistry.

The matter presented in the thesis has not been submitted for the award of any other degree of this or any other Institute.

Danish Khan

Dated: _October 19, 2020__ **(DANISH KHAN)**

SUPERVISOR'S DECLARATION

This is to certify that the above mentioned work is carried out under my supervision.

Dated: _October 19, 2020__ **(NASEEM AHMED)**

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ABSTRACT

The thesis entitled **"*Design and synthesis of N, O-containing heterocycles*"** is reported in five chapters.

The present work is aimed to design and synthesis of N and O containing heterocyclic compound via different novel methodology involving C—C, C—O, C—N bonds formation using different reactions like knoevenagel condensation, Aza Michael addition with sequential dehydrogenation, oxiadative C—C bond cleavage and Ullman type reaction. The synthesized compounds were characterization through different analytical techniques such as ^{1}H NMR, ^{13}C NMR, HRMS and x-ray diffraction and their biological evaluations were reported as calcium calmodulin dependent protein kinase applications.

Chapter 1. Introduction

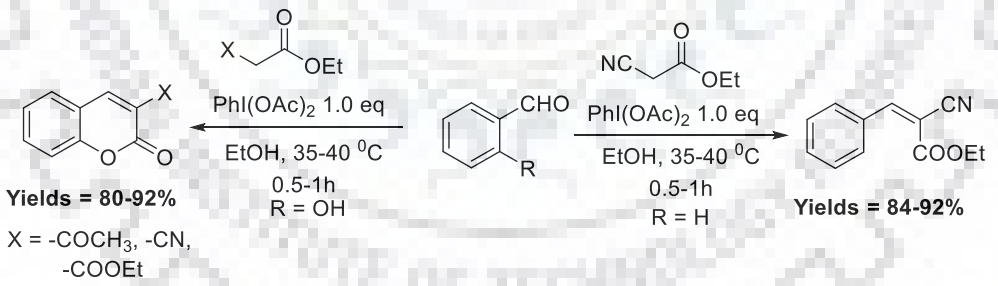
Heterocyclic compounds are widely distributed in nature. All living things are made up of genetic material and this genetic material are made up of DNA, Which contains heterocycles moities like purine and pyrimidine as base. Beside these naturally occurring alkaloids such as morphine, vinblastine, papaverine, phenazine; anibiotics such as penicillin, cephalosporin moieties contains heterocyclic rings. Vitamin B complex contains corrin and benzimidazole heterocyclic rings. There are many of natural product having heterocyclic rings such as ascorbic acid, chlorophyll, hemoglobin, ATP, soft drinks, dyes, amino acid. The colour of flowers due to anthocyanin which is the large class of flavonoid family. Consequently the design of structurally diverse heterocyclic compound is one of the driving forces for the development of organic chemistry. The ability to create new heterocyclic compounds in an involuntary and efficient manner is fundamental in many fields; for instance, in the industry heterocyclic compounds are used in making cosmetics, textiles, plastics, lubricants and paints. Moreover they are most extensively used in pharmaceuticals, because 90% of the medicines like analgesic, antitumor, anticancer, antihypertensive drugs are made up of heterocyclic compounds. Therefore, the precise synthesis of heterocyclic compounds is one of the main aims for an organic chemist.

Natural product is a substance or compounds, created *via* living organism such as - plants, fruits and microorganisms, etc. exclusively found in nature, formed with metabolism. For the development in the field of organic chemistry, Natural products have participated a vital role by providing confronting synthetic targets in drug development and drug synthesis. Directly and indirectly, a huge percentage of drugs in modern medicine are

originated from natural sources. Traditionally significant concept for the natural products is that it is applied as a therapeutic agent in different disease such as Cancer infectious disease and reduced pain Flavonoids, Carotenoids, Chromenes, coumarins, alkaloids and quinolines etc. are considered as a significant part of natural products and usually utilized around the world due to their assorted pharmacological properties. In Particular, flavonoids, chromene and quinoline have occupied a considerable interest, owing to its diverse pharmacological, therapeutic and chemo-sensor applications.

Chapter 2. $PhI(OAc)_2$ mediated an efficient Knoevenagel reaction and their synthetic application for coumarin derivatives

In this chapter, We describe the synthesis and stereospecific characterization of ethyl-2-cyano-3-phenylacrylate and different type of substituted coumarins by Knoevenagel reaction and cyclization process using different type of active methylene compounds and benzaldehyde or salicylaldehyde in the presence of phenyl iododiacetate (PIDA) as mediator. Optimization of the reaction conditions and screening of PIDA 1.0 equivalent was found to be best in ethanol solvent for the reaction. The method needs no base and features wide substrate scope and good functional group tolerance with environmentally benign and high yields (80-92%) under mild reaction conditions.



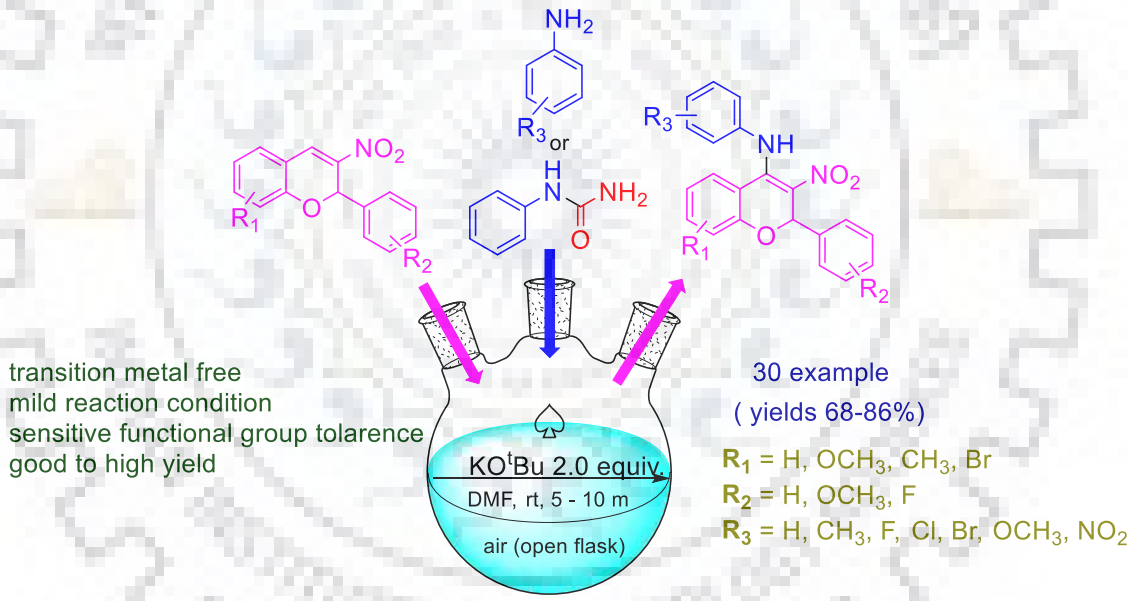
Scheme: 2 Synthesis of ethyl-2-cyano-3-phenylacrylate and coumarins using active methylene compounds and aldehyde.

All synthesized compounds were fully characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR and HRMS.

ABSTRACT

Chapter 3. Synthesis of 3-nitro-N, 2-diphenyl-2H-chromen-4-amines and their Pharmacological activities against Calcium/Calmodulin dependent Protein Kinase IV (CaMKIV) Inhibitors.

In this chapter, A potassium tertiary butoxide mediated Aza-Michael addition with sequential dehydrogenation reaction of substituted 3-nitrochromene with aniline or N-phenyl urea is reported using DMF as solvent. The most important feature of this method is here molecular oxygen (O_2) used as oxidant through the oxidative C(sp^2)-H amination. This strategy signifies an attractive, cost-effective and operationally convenient tool for synthesis of a wide range of 3-nitro-N, 2-diphenyl-2H-chromen-4-amine derivatives with good to high yields at room temperature. This methodology can be applied to a gram scale synthesis with good to excellent yield (75–90%), a natural product with a broad range of biological activities.



Scheme: 3 Synthesis of aminated nitrochromene derivative.

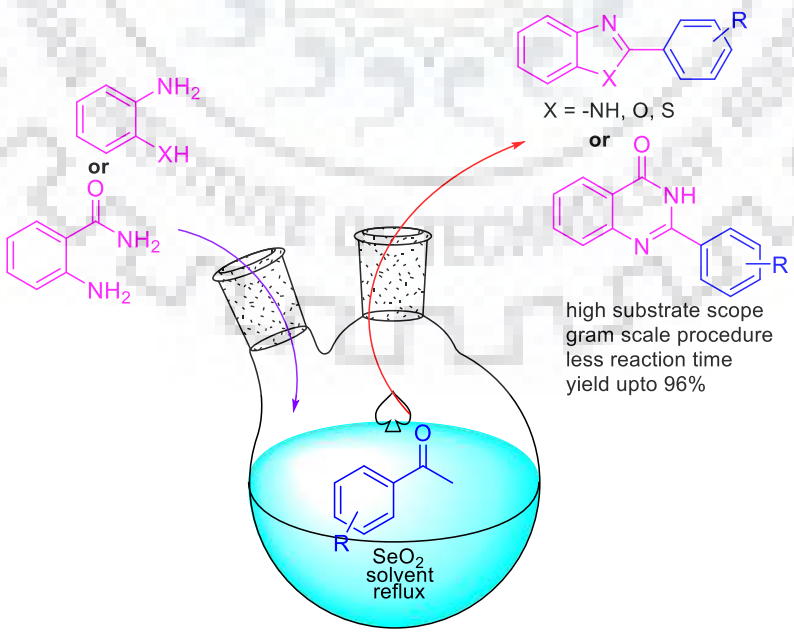
All Synthesized compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, HRMS and single crystal (XRD).

We report activity of aminated chromene compound againts Calcium/calmodulin dependent protein kinase IV (CaMKIV) phosphorylates various transcription activators and subsequently regulates cellular activities which triggered by CaMKK-CaMKIV signalling. However, abnormal expression of CaMKIV is often associated with cancer and neurodegenerative diseases. Here, we have synthesized and characterized a series of 3-nitro-2-phenyl-2H-chromenes and tested their inhibition potential and binding affinity

with the CaMKIV. Among the synthesised compounds, the IC_{50} value (50% of ATPase activity) for compounds **D19** and **D22** was observed as 12.22±1.12 µM and 16.10± 1.30 µM, respectively. The fluorescence binding and dot-blot assay further complements inhibitory potential, indicating a better binding affinity. These compounds were tested against human cancerous cells (HepG2) and we observed a significant inhibition of cell viability, induced apoptosis and lowered the tau-phosphorylation. In cell viability studies, the IC_{50} values for compounds **D19** and **D22** was 18.33±1.12 and 26.22±1.30 µM, respectively. These results suggested that compounds **D19** and **D22** are non-toxic to the normal cells and specifically inhibits the proliferation of cancerous cells.

Chapter 4. SeO_2 mediated synthesis of selected heterocycles by oxidative C—C bond cleavage of acetophenone derivatives

In this chapter a series of various heterocycles like benzoxazole, benzothiazole, benzimidazole and quinazolinone were designed and efficiently synthesized *via* SeO_2-mediated oxidative C—C cleavage using acetophenone with various *O*-substituted anilines. The reaction likely involves sequential C—N, C—O and C—S bond formation followed by C(CO)−C(alkyl) bond cleavage. This method provided good-to-excellent product yields in shorter reaction time. The reaction has a number of advantages over existing procedures, for example, it is inexpensive, tolerates various functional groups under mild reaction conditions.



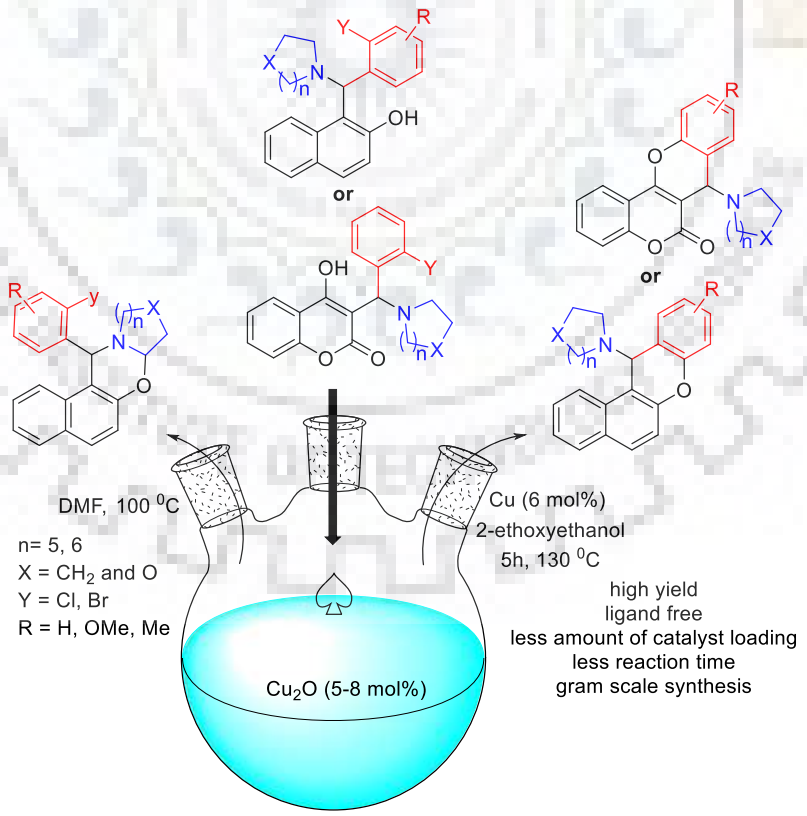
Scheme: 4 Synthesis of various heterocyclic compounds.

ABSTRACT

All synthesized compounds were fully characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR, HRMS.

Chapter 5. Cu (0) and Cu (I) oxide catalysed cyclisation of halo-betti base via ullmann couling: synthesis of fused banzo-xanthene and oxazine.

In this chapter, An operationally simple copper (I) and copper (0)-catalyzed cyclization of halo Betti base has been developed in 2-ethoxy ethanol in basic medium at 130 ^{0}C and 100 ^{0}C leads to the corresponding Benzo-xenthene and oxazine with high selectivity. By this reagent combination, Iodide, bromide and chloride can be replace by oxygen and C—O bond formed without any ligand involving with good to excellent yield. The reaction is companionable with numerous electron-withdrawing or electron-donating groups. All synthesized compounds were fully characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR, HRMS.



Scheme: 5 Synthesis of benzo-xenthene and 1,3 naphthoxazine by a Betti base

ABBREVIATIONS

$CDCl_3$	Deuterated chloroform
DMSO-d_6	Deuterated dimethyl sulphoxide
DMSO	Dimethyl sulphoxide
DMF	Dimethyl formamide
DCM	Dichloromethane
ACN	Acetonitrile
THF	Tetrahydrofuran
PIDA	Phenyl Iododiacetate
HEK-293	human embryonic kidney cells
HepG2	human hepatoma G2
HRMS	High Resolution Mass Spectrometry
NMR	Nuclear magnetic resonance
UV lamp	Ultra violet lamp
TLC	Thin layer chromatography
ORTEP	The Oak Ridge Thermal Ellipsoid Plot
HIV	Human Immunodeficiency Virus
IC_{50}	Half maximal inhibitory concentration
GC-MS	Gas chromatography Mass Spectrometry
CAMKIV	Calcium/Calmodulin-dependent protein kinase IV
MCF-7	Michigan Cancer Foundation-7
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
ROS	Reactive oxygen species
SAR	Structure activity relationship
µg	Microgram
ml	Millilitre
µM	Micro Molar

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Introduction

1.1 . Introduction

1.1.1. General information of flavonoid

Flavonoids (or bioflavonoids) are main sort of natural compounds, Flavonoids were discovered in 1938 by a Hungarian scientist, who used the term vitamin P to describe them. They are an assorted group of phytonutrients (plant chemicals) found in almost all fruits and vegetables [6]. Flavonoids are usually found in plants as glycosylated derivatives and have numerous functions for flower coloration, including attracting insects for pollination and dispersal of seeds, transport of auxin, acting in defence systems, root and shoot development, modulation of reactive oxygen species, (e.g., as UV-B protectants and phytoalexins), signalling between plants and microbes [7-9]. These compounds also have antioxidant and chelating properties and therefore show many health promoting effects [10]. In addition, they have antibacterial, antioxidant, anticancer effects, antiulcer, anti-viral, cardiovascular disorders, diabetes mellitus and celiac disease [11]. Moreover, epidemiologic studies propose studies a defensive quality of dietary flavonoids besides coronary heart disease [12].

Various additional properties ascribed to flavonoids include: Non-steroidal anti-inflammatory drugs (NSAIDS) intended for the rationales of dipping swelling, reducing fever, reducing pain affecting Alzheimer's $\alpha\beta$ production on the basis of NFκB dependent mechanism and aromatase inhibitors enzyme [13-14].

1.1.2. Classification of flavonoids

Chemically flavonoids are polyphenolic constituents that support the flavan nucleus, which are classified on the basis of fifteen-carbon skeleton (C6-C3-C6) containing two benzene rings *i.e.* A and B joined through a pyran heterocyclic ring (C) (Figure 1.1, 1.2) [15]. Flavonoids are classified into one of many subclasses which are different in the level of central ring oxidation, absence or presence of double bond, and form of substitution on the C ring. The flavonoid class on the basis of location of ring B at 2-position are called flavonoids *i.e.* 2-phenyl-benzopyrans, at 3-position is called isoflavonoids *i.e.* 3-phenyl-benzopyrans and at 4-position are called neoflavonoids *i.e.* 4-phenyl-benzopyrans (Figure 1.3). The major flavonoid groups when the B ring is attached with 2 carbon *i.e.* flavones, flavanones, flavonols, flavanols, chalcones, aurones (Figure 1.4). Isoflavonoids embrace isoflavones *i.e.* the analogue of flavones. Next is 4-arylcoumarin, its reduced form is 3,

4-dihydro-4-arylcoumarin main neoflavonoids which derived from neoflavan structure [16].

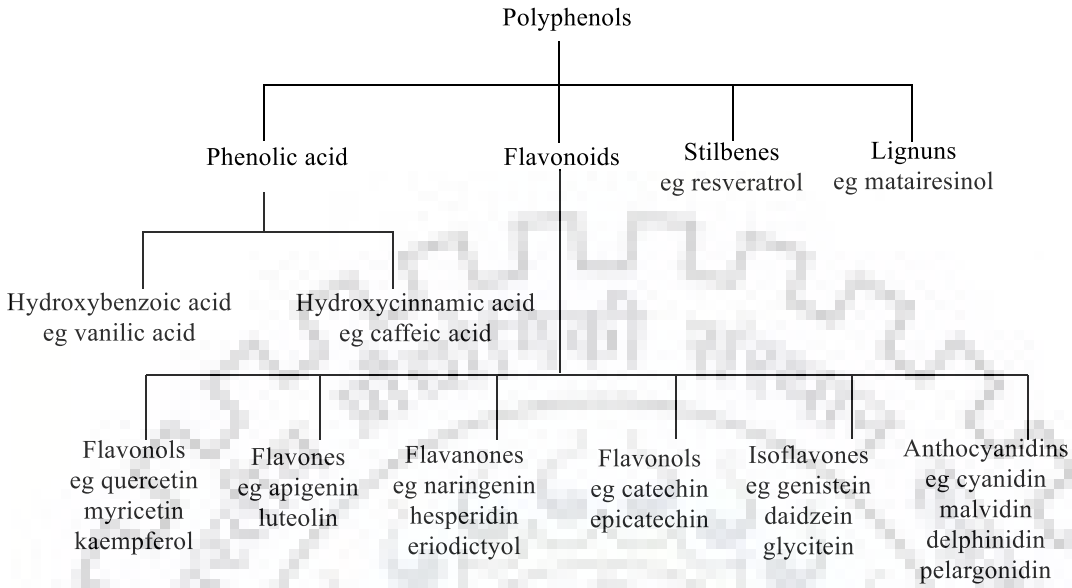


Figure.1.1. Classification of flavonoid

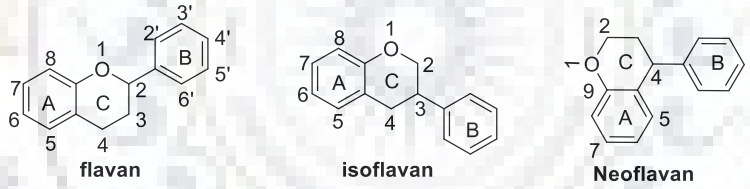


Figure.1.2. Basic skelton flavan, isoflavan and neoflavan structure.

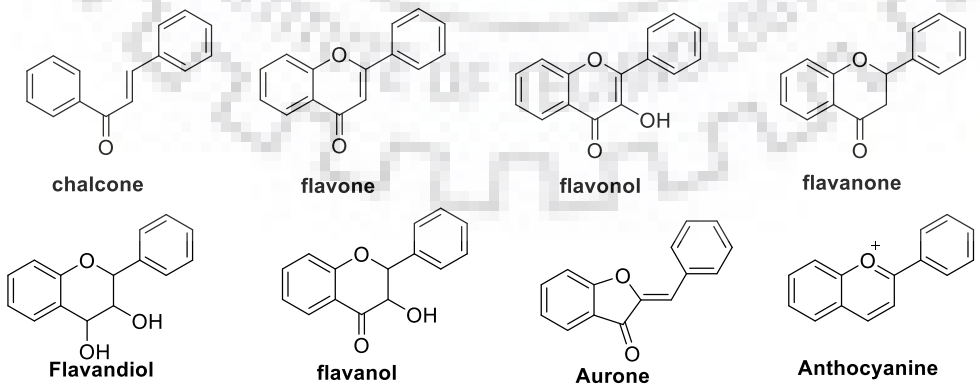


Figure.1.3. General structures of flavonoids.

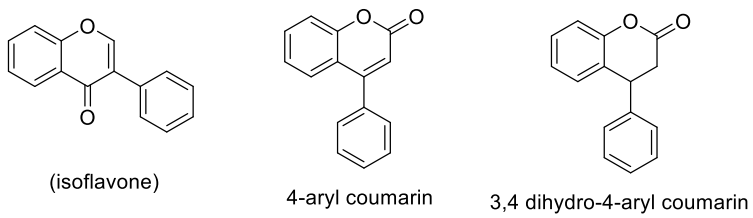


Figure.1.4. General structures of neo-flavonoid and isoflavonoid.

1.1.3. Natural Occurring Biologically Active Flavonoids

Some Natural, synthetic and semi-synthetic flavonoids (Figure 1.5) have been extensively accounted to exhibit diverse biological activities and are of significant interest in the development of innovative therapeutic agents to treat different diseases [17-23].

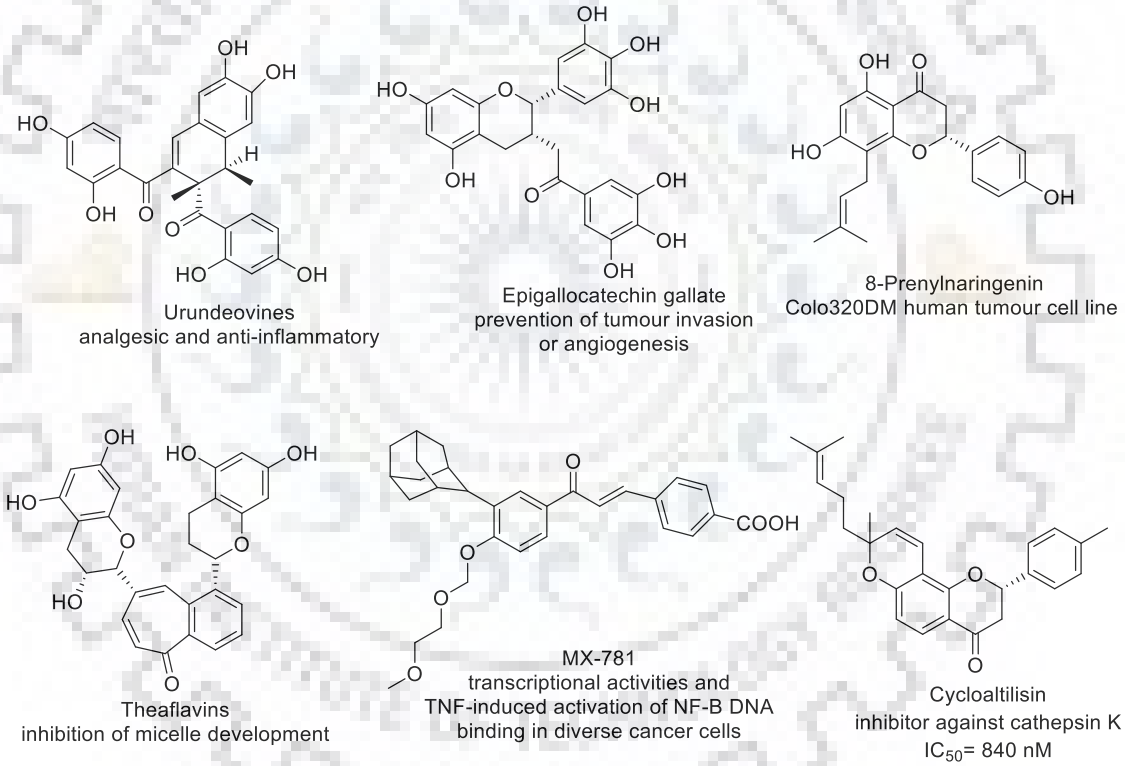


Figure.1.5. Some Natural and synthetic and semi-synthetic flavonoids structure.

Some alternations and inclusion of new functional groups like hydroxyl and aryl group in the flavonoids structure, lead to considerable alteration in biological activities, for *e.g;* quercetin has more antioxidant activity as compared to the chrysin, owing to the presence of three supplementary hydroxyl groups [24], yet chrysin and flavone are more efficient

in the inhibition of the human aromatase enzyme as compared to the biochanin A. (Figure 1.6) [25].

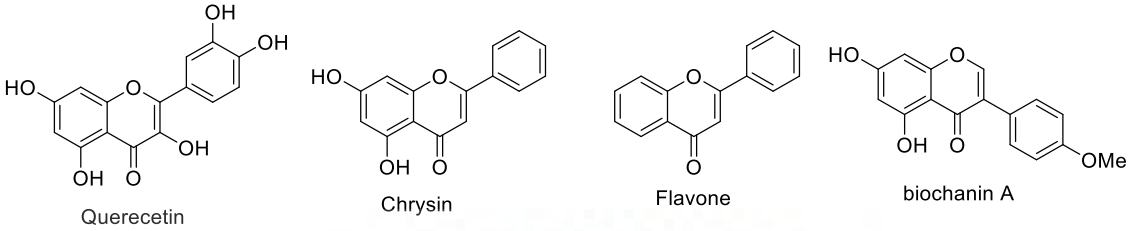


Figure.1.6. Structure of quercetin, chrysin, Flavone and biochanin A.

1.2. Coumarin

Coumarins are classified as member of oxygen containing heterocyclic compounds of the benzopyrone group. In benzopyrones, benzene ring is fused with a pyrone ring which is a six membered oxygen atom containing ring. Based on the position of carbonyl group with respect to the oxygen atom, benzopyrone can be classified in two categories α-benzopyrone and γ-benzopyrone. α-benzopyrone are known as Coumarin or 2H chromen-2-one and other member of family are belongs to γ-benzopyrone are known as chromones whose systematic nomenclature was established by IUPAC given in Figure 1.7 [26].

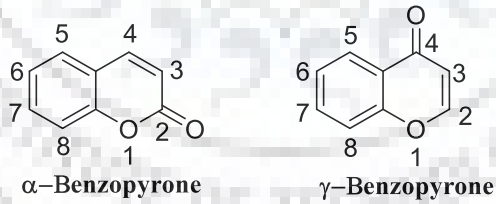


Figure 1.7. Chemical structure of the benzopyrone sub-classes (a) α-benzopyrone (coumarin) (b) γ-benzopyrone (chromones).

According to literature report coumarin was first isolated by A. Vogel of Munich in 1820 from tonka beans found in plants of the species Dipteryxodorata, commonly known as cumaru and the name Coumarins comes from owe their class name to 'Coumarou', the scientific name of the tonka bean (Dipteryxodorata Willd., Fabaceae) [27]. It is a white crystalline substance and the structure of the coumarin was first determined in 1868. Coumarins also occur naturally as secondary metabolites in the different part of plants

such as fruits, roots, seeds, leaves, flowers, and stems includes sweet grass (Hierochloe odorata), sweet-clover (Melilotus ssp.), sweet woodruff (Galium odoratum), vanilla grass (Anthoxanthum odoratum), cassia cinnamon (Cinnamomum cassia), mullein (Verbascum spp.), deertongue (Dichanthelium clandestinum) and many varieties of cherry blossom tree of Prunus genus [28]. On the basis of natural occurance of coumarin from plants can be roughly classified into four main classes viz. simple coumarins, furanocoumarins, pyranocoumarins and pyrone-substituted coumarins (Figure 1.8) [29].

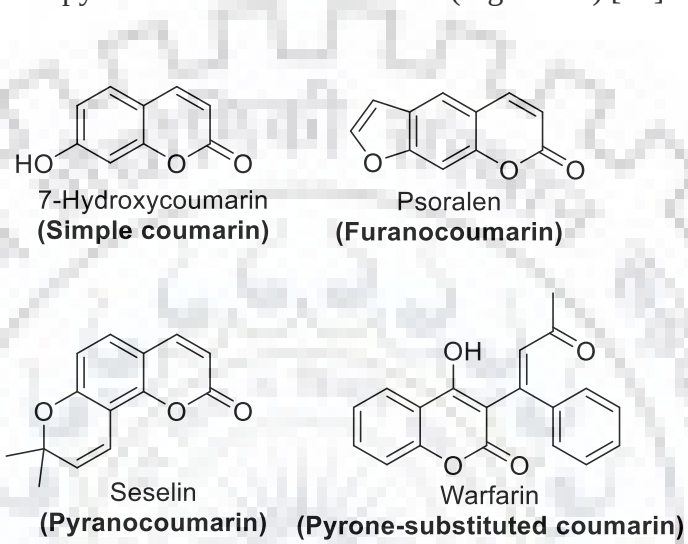


Figure 1.8. Types and example of coumarins.

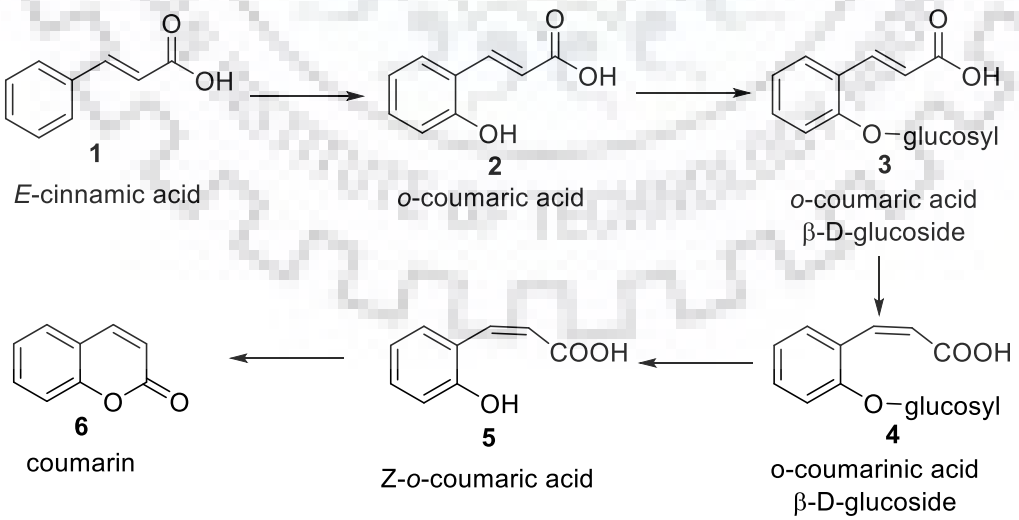
Due to its pleasant and persistence odour, coumarin immediately found the attention in perfumes industry since 1882 [30]. Coumarin present in edible plants are not harmful to humans [31] but use of coumarin as food flavouring agent has been banned by U.S. food and Drug Administration because of its hepatotoxic effects. In contrast, the Council of the European Communities in 1988, set a maximum limit of 2 mg/kg for coumarin in many foods and beverages due to its beneficial effects in humans [32]. Coumarin also employed as a starting molecule for the preparation of a variety of synthetic drugs like dicoumarol, warfarin and even some more potent rodenticides etc, [33]. Additionally, coumarin derivatives have been found to have various therapeutics applications including anti-HIV therapy, photochemotherapy, antitumor, antibacterial, antimicrobial, antiviral, molluscacidal, anti-inflammatory, vasodilator, estrogenic, dermal photosensitising, sedative, anthelmintic, and hypnotic, analgesic and as central nervous system (CNS) stimulators, as antioxidants and enzyme inhibitors etc [34-39]. Instead of this Literature survey reveals that substituent on coumarin on benzene ring as well as on pyrene ring significantly change the properties of molecule in desired manner [40]. Diverse

pharmacological and optical properties of coumarin derivatives have created a lot of interest in recent times [41].

1.2.1. Methods for the synthesis of coumarin and its derivative

1.2.1.1. Biosynthetic method of coumarin

According to literature reviews the presence of coumarins in higher plant and their wide applications in several areas, different types of biosynthesis pathways for the synthesis of coumarin in plants has been reported [42]. Generally, hypothetical P-450 reaction is critical for the course for the biosynthesis of simple coumarin, umbelliferone and other hydroxylated coumarins in plants. L-Phenylalanine is a starting compound for the synthesis of coumarin **6** in *melilotus alba*. L-Phenylalanine is first converted to E-cinnamic acid **1** by the action of phenylalanine ammonia lyase (PAL) and then converted into ortho-coumaric acid **2** by the action of cinnamic acid-o-hydroxylase. The ortho-coumaric acid **2** is then transformed into ortho-coumaric acid β-D-glucoside **3**, by UDP-glucose and o-glucosyltransferase, which on UV-light mediated E-Z (trans-cis) rearrangement produce the isomeric β-D-glucoside **4**. Under various condition the β-D-glucoside **4** is cleaved by co-occurring β-D-glucosidase into glucose and coumaric acid **5**, which spontaneously cyclized to coumarin **6** (Scheme 1.1) [43].



Scheme 1.1. Biosynthetic method of coumarin

1.2.1.2. Synthetic methods of coumarin

William Henry Perkin was the first scientist who synthesised coumarin in 1868 in laboratory via Perkin reaction and many simple coumarins are still prepared by this method [44]. By the classical Perkin reaction coumarin is synthesised via heating of salicylaldehyde with acetic anhydride in the presence of sodium acetate. Later, more simple synthetic methods have been developed for coumarin ring system including Knoevenagel, Pechmann condensation, Claisen rearrangement, Baker-Venkataraman rearrangement, Kostanecki acylation, Wittig reactions, Reformatsky, Baylis–Hillman reaction, catalytic cyclization reaction and by flash vacuum pyrolysis etc [45-49]. Some of these important synthetic methods are listed in Figure 1.9.

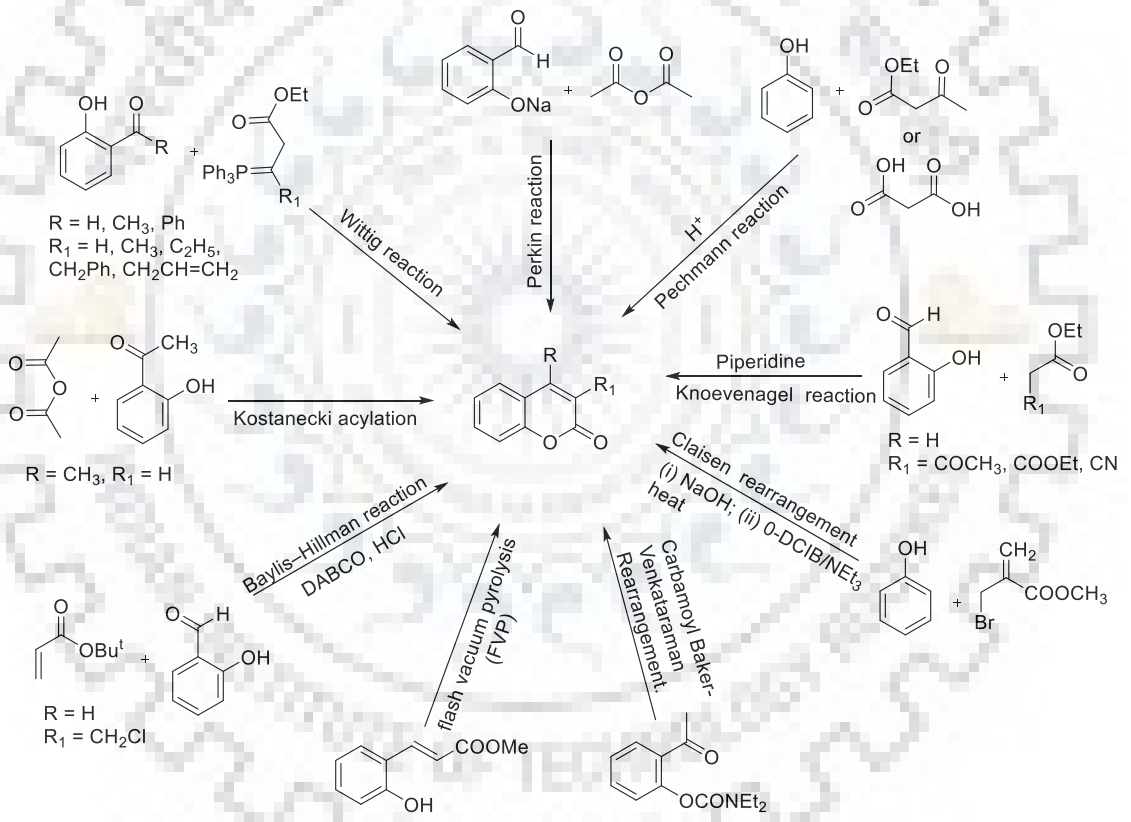
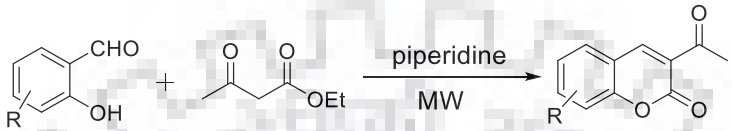


Figure 1.9. Schematic representation of various methods for the synthesis and substituted coumarins

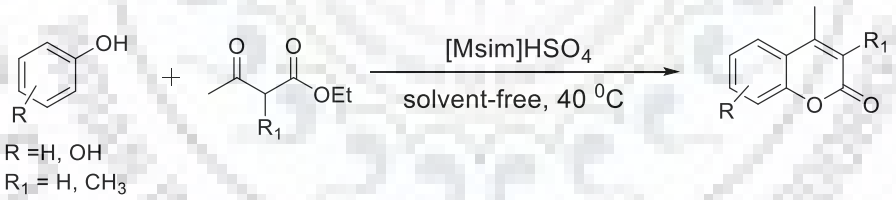
Among all the reported methods, Pechmann reaction is the most commonly used method for coumarin synthesis by the use of easily available starting materials such as phenols and ethylacetoacetate β-carbonyl group to obtain coumarin or its derivatives under acidic conditions [50] and the variety of acidic reagents such as hydrochloric acid, sulphuric acid, phosphorus pentoxide, aluminium chloride, zinc chloride, iron chloride and trifluoroacetic acid, montmorillonite and other clays and many ionic liquids are well

reported in the literature [51, 52]. Various green methods have been developed for the synthesis coumarin using nonconventional energy sources, such as microwave, ultrasound irradiation and metal free and solvent-free conditions [53] some of them are given below. In 2010, Ajani *et al.* [54] developed highly efficient piperidine catalyzed method for the synthesis of 3-acetylcoumarin by the reaction of salisaldehyde with ethyl acetoacetate under microwave condition (Scheme 1.2).



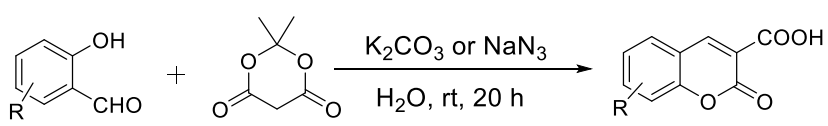
Scheme 1.2. Microwave assisted synthesis of 3-acetylcoumarin

Ionic liquid medium have been attracted considerable interest in last few years because of its recyclable nature. In 2012, Khaligh and co-workers synthesised coumarin using ionic liquid [Msim]HSO_4 as catalyst [55] under solvent-free conditions. The advantageous features of this method are ionic liquid could be recycled and reused several times without any noticeable decrease in the catalytic activity, use of non-toxic and halogen-free catalyst, excellent yields, high reaction rates and a simple experimental procedure (Scheme 1.3).



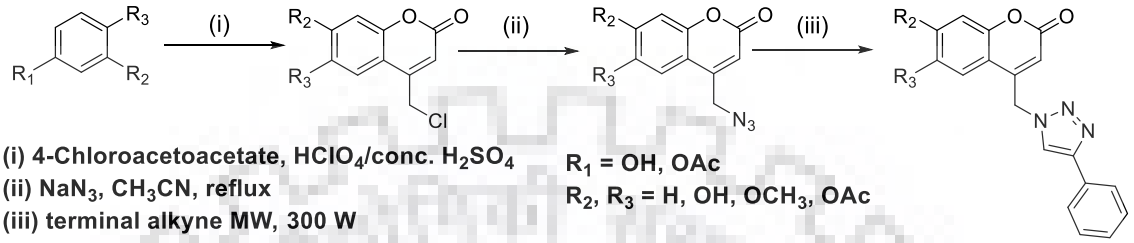
Scheme 1.3. [Msim]HSO_4 catalysed synthesis of coumarin derivatives under neat condition

In 2015, Brahmachari *et. al.* [56] introduced base induced Knoevenagel condensation followed by intramolecular cyclization using 2-hydroxybenzaldehydes with Meldrum's acid for the synthesis of a series of potentially bio-active coumarin-3-carboxylic acids. This one-pot reaction was performed in water as solvent at room temperature (Scheme 1.4).



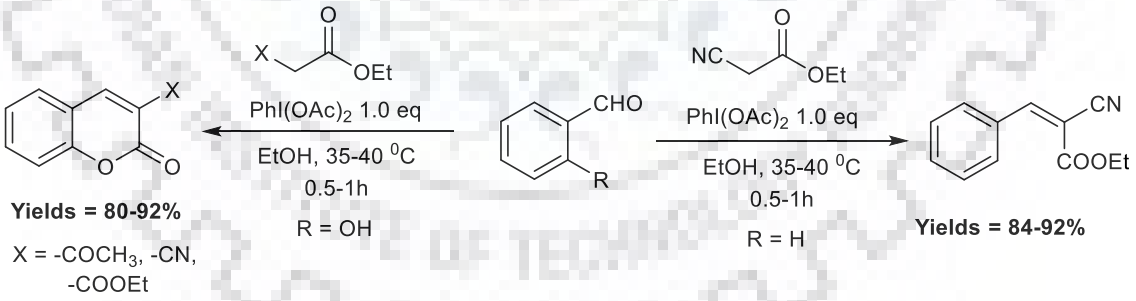
Scheme 1.4. One pot synthesis of coumarin 3-carboxylic acid

Most recently, Raić-Malić and co-workers [57] described an efficient and facile method to obtain 4-aryl-1,2,3-triazolyl appended coumarin-related compounds by the green click chemistry under microwave irradiation (Scheme 1.5).



Scheme 1.5. Synthesis of triazolyl appended coumarin-related compounds under microwave irradiation

In the area of coumarin, we have developed an efficient method for the synthesis of biologically active 3-substituted coumarins via knoevenagel condensation using easily available chemicals such as active methylene compounds and salicylaldehyde in ethanol solvent. The reaction is simple and promoted by Phenyl iododiacetate (DIB). The main advantage of the method is easy workup process and no need to purify the compounds by column chromatography, compounds can be purified by simple crystallisation method or by washing with cold ethanol [58].



Scheme 1.6. Synthesis of acrylates and 3-substituted coumarin

1.3. 3-nitro-2*H*-chromenes

3-Nitro-2H-chromenes is an oxygen-containing heterocyclic compound in which pyran ring fused with benzene ring having conjugated double bond with nitro group at 3-position (figure 1.10). This system are very similar to conjugated nitro alkenes and shows

similar properties in reactivity with nitro alkenes. In recent years 3-Nitro-2H-chromenes have been extensively studied. First synthetic report of one of the representatives of this family dates back to 1938 [59]. However, systematic study of 3-nitro-2H-chromenes began only in the 1970s. Nowadays, study of this family continue to dynamically develop because of the availability of simple methods for the synthesis of 3-nitro-2H-chromenes from easily available nitro alkenes and salicylaldehydes. Many chromene and chromane (3,4-dihydro-2H-1-benzopyran) derivatives are widely distributed in the plant kingdom and these naturally occurring compounds have proven to be promising medication and pesticides [60]. Due to the availability and reactivity of chromene compounds and their derivatives are used as starting substrates for formation of more complex biologically active molecules. From the past few years reactivity tho the 3-nitro-2H-chromenes is mainly determined by comparing with nitroalkene moiety; however, substituent on the 2-position bonded to the sp^3-hybridized carbon atom shows significant effect on the rate and direction of some reactions**.**

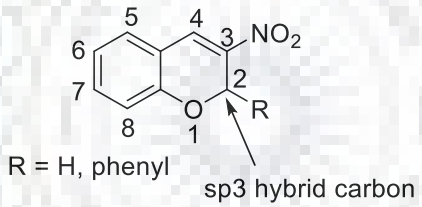
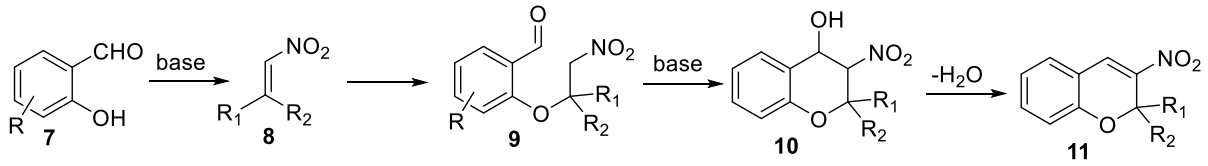


Figure: 1.10. Structure of 2H-3-nitrochromene

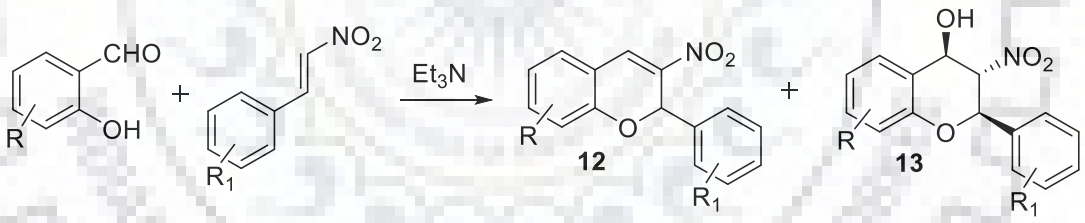
1.3.1. Synthesis from salicylaldehydes and nitroalkenes

Most common route for the Synthesis of 3-nitro-2H-chromenes **11** by condensation of salicylaldehydes **7** with conjugated nitro alkenes **8** in the presence of base. These reagents are (aliphatic and aromatic nitroalkenes) relatively easily available. In the presence of base a phenolate anion is formed which is nucleophilically added to the nitro alkene molecule to give intermediate **9**, this intermediate CH_2 having nitro group is enough acid to form anion which undergoes intramolecular condensation with formyl group to convert into 4-hydroxy-3-nitrochromane **10**. Further dehydration of **10** resulting in target product **11**. This method can be used for the synthesis of wide series of nitrochromenes containing different substituents both in the 2-position of the pyran ring and in the aromatic ring (Scheme 1.7) [61].



Scheme 1.7. Synthesis of 3-nitro-2H-chromene from salicylaldehydes and nitro alkenes

In 1938 Hahn and Stiehl, first describe the synthesis of 3-nitrochromene derivatives, starting from the reaction between 2-(1-hydroxy-2-nitroethyl) phenol and salicylaldehyde with methylamine [62]. Sakakibara *et al.* In 1978 outlined the synthesis of 2-aryl-3-nitrochromenes **12** starting from readily available β-nitrostyrene and salicylaldehyde in the presence of triethylamine at room temperature. Sakakibara observed that approximately equimolar amounts of 3-nitro-2-phenyl-2H-chromene **12** and trans-trans-4 hydroxy-3-nitro-2-phenylchromane **13** in 69% yield was obtained [63]. The presence of 4 hydroxychromane requires, additional purification stages, which complicate the isolation of the target product. After that many of the method has been given using different reagent.

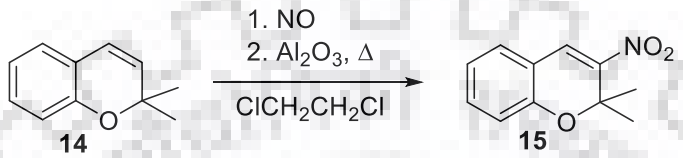


Scheme 1.8. Triethyl amine catalysed Synthesis of 3-nitro-2H-chromene

These modified methods provide complete dehydration of the formed 4-hydroxychromane intermediates **13** by performing the reaction under heating [64], with triethylamine in a melt at room temperature [65], under ultrasonicating conditions basic alumina or Al_2O_3 is used as dehydrating agents [66], catalytic amount of trimethylamine and L-proline in toluene under reflux condition [67]. Yao *et. al.* explored highly efficient DABCO catalysed synthesis of 3-nitrochromene under neat conditions at 40 ^{0}C [68].

1.3.2. Nitration of 2H-chromenes

Introduction of the nitro group selectively into the 3-position of chromenes **14** leads to 3-nitrochromene **15**, which is done by successive treatment of chromenes with nitrogen monoxide (NO) at room temperature and then dehydration of the intermediate nitrochromanol, using acidic alumina with boiling for 30 mins (Scheme 1.9) [69].

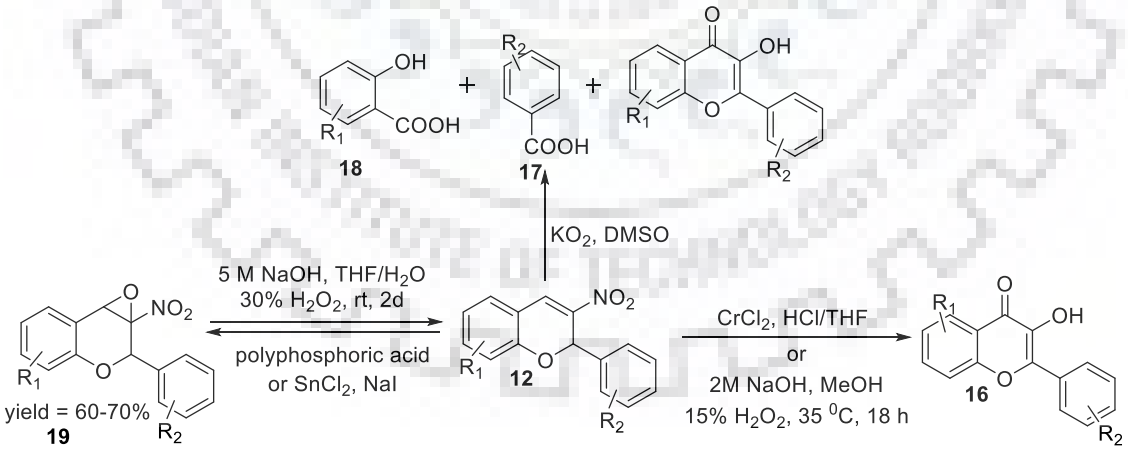


Scheme 1.9. Selective nitration of 3-nitrochromene using NO, Al_2O_3 in 1,2-dichloroethane

1.3.3. Chemical properties and application

1.3.3.1. Oxidations

The variety of reagent are used for the oxidation of 3-nitro-2H-chromenes **12**. Several methodologies has been developed using different oxidizing reagent (Scheme 1.10).



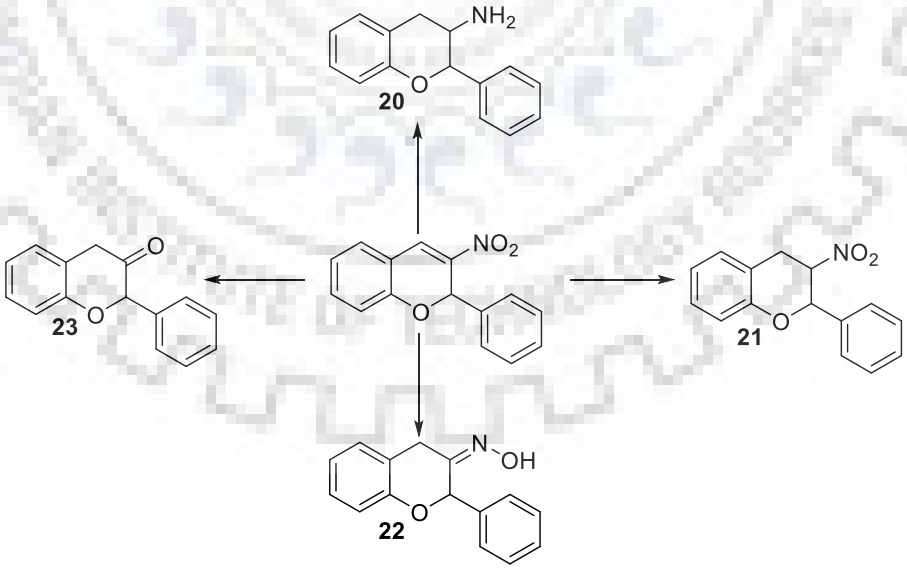
Scheme 1.10. Oxidation reactions of 3-nitro-2H-chromenes

For example $CrCl_2$ in HCl/THF [70] or 15% H_2O_2 with 2M aqueous NaOH in methanol at 35 ^{0}C for 18 h [71] led to the formation of flavonols **16** as the main product. Furthermore, potassium superoxide was also used, resulting mainly in cleavage towards benzoic acids **17** and **18**, and flavonols in diminished yields (10-15%) [72].

In 2015 Ahmed and Pathe report a method in which the synthesis of nitrochromene epoxides **19** were successfully conducted with 30% hydrogen peroxide, 5M aqueous NaOH, in THF/H_2O, and their subsequent deoxygenation by using polyphosphoric acid [73] or $SnCl_2$ and NaI in boiling ethanol [74].

1.3.3.2. Reduction

A larger variety of product outcomes after the reduction of 3-nitrochromene (Scheme 1.11). The reduction of the nitro group as well as double bond towards 3-aminochromanes **20** has been accomplished by using several methodologies, such as borane in THF and sodium borohydride [75] sodium borohydride followed by Raney nickel and hydrazine [76] lithium aluminium hydride [77], or hydrogen on Pd/C or copper (II) acetate with sodium borohydride [78]. Furthermore, sodium borohydride [79] or baker's yeast [80] was proved to be effected for the selective reduction of the nitroalkene double bond into 3-nitrochromane **21**. Nitro group reduce into oxime **22** when 3-nitrochromene is treated with stannous chloride [81], tin in combination with hydrochloric acid [78] or Raney nickel together with hydrazine [82]. An another possibility is the formation of 3-oxo-chromanes **23** via the employment of chromous chloride [83], or titanium(III)chloride and ammonium chloride in dioxane-acetic acid [84].

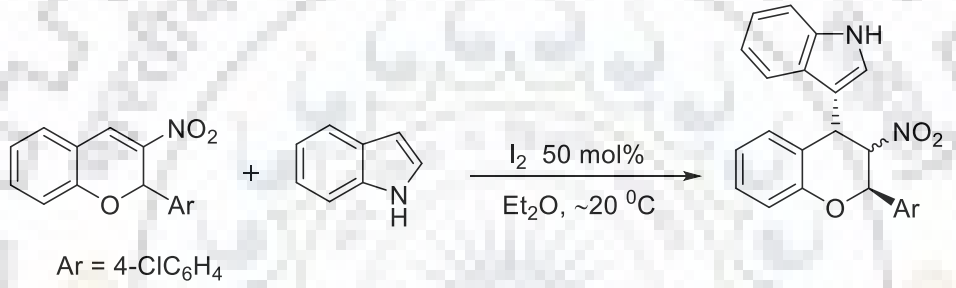


Scheme 1.11. Reduction reactions of 3-nitro-2H-chromenes

1.3.3.3. Conjugate additions

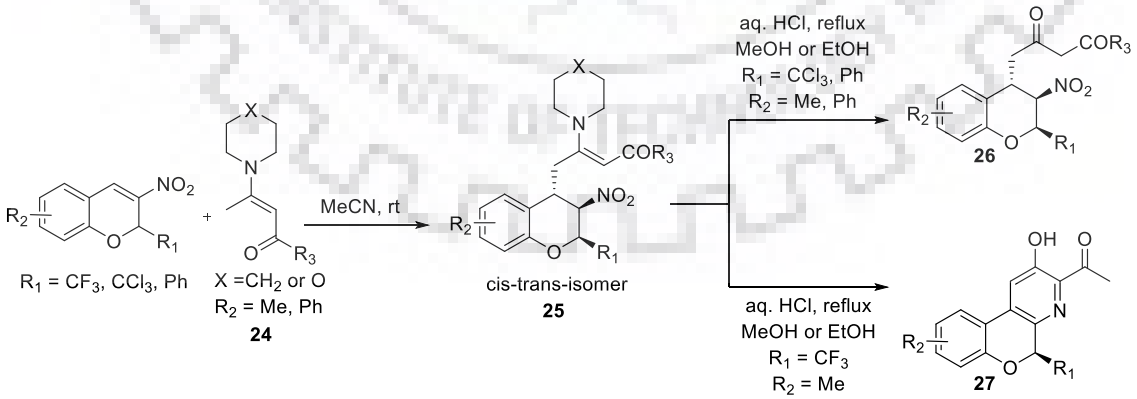
3-nitrochromenes behaves as an excellent Michael acceptors due to the presence of nitro group conjugated to the alkene, makes the nitroalkene type moiety and the resulting reactions are often called nitro Michael additions [85] In general, In Michael addition reactions a nucleophile attack on the double bond in conjugative manner. Generous amount of examples have been reported because of the wide applicability of this reaction using several nucleophiles such as carbon nucleophiles, i.e. enolates [86], organomagnesium [87], organolithium [88] and species enamines [89, 90], indoles [91, 92] and pyrroles [93, 94] and other carbon-centered [95, 96], nitrogen [97, 98] and phosphorus-centered [99] nucleophiles.

Michael addition of indole at the C(4) atom of 2-aryl-3-nitro-2H-chromenes is the best example of C-nucleophiles (scheme 1.12) [100].



Scheme 1.12. Iodine catalysed Michael addition of indole to 3-nitro 2H-chromene

Push-pull enamines derived from secondary cyclic amines (piperidine and morpholine) and acetyl acetone **24** were also tested and found to behave like a tertiary enamines derived from acetoacetic esters.

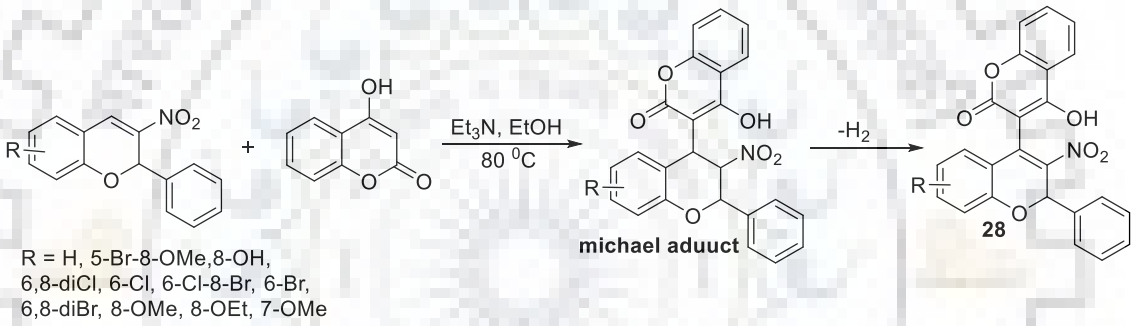


Scheme 1.13. Use of tertiary push-pull enamines of acetylacetones in 1,4-additions to 3-nitrochromenes.

Prepared enamines **24** reacting via the vinylogous β-methyl group and resulting mainly in the diastereoselective formation of cis-trans-isomers product **25** and E-configuration

of the double bond. Which was proven by NMR coupling constants ($^3J \approx 2$ Hz) and an X-ray diffraction study and the treatment of product **25** with Aq. HCl in methanol or ethanol gives different product **26** and **27** depend upon the substituent present on pyrane ring (Scheme 1.13) [101, 102].

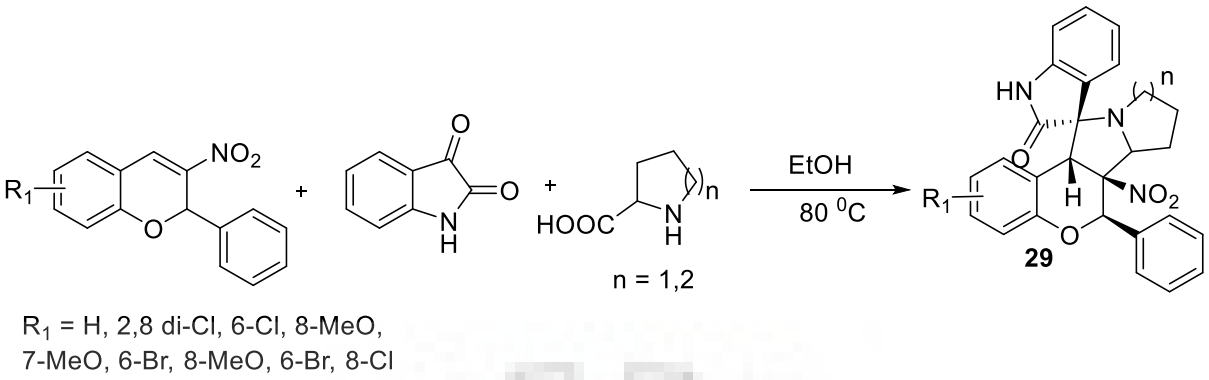
Michael addition of 4-hydroxy coumarin followed by an aerobic oxidation yields 4-substituted-3-nitrochromenes. In this reaction 4-hydroxy coumarin act as a nucleophile followed by air oxidation, rendering 4-hydroxycoumarin-3-nitrochromene conjugates **28** in the presence triethylamine in ethanol at 80 ^{0}C (Scheme 1.14). This method is very useful in terms of product isolation, in which product isolated by simple precipitation in ethanol. The extended conjugation of 4-hydroxycoumarin to the nitroalkene drives the Dehydrogenation of Michael adduct [103].



R = H, 5-Br-8-OMe,8-OH, 6,8-diCl, 6-Cl, 6-Cl-8-Br, 6-Br, 6,8-diBr, 8-OMe, 8-OEt, 7-OMe

Scheme 1.14. Michael addition-oxidation of 4-hydroxycoumarin to 3-nitro-2-phenyl 2H-chromenes

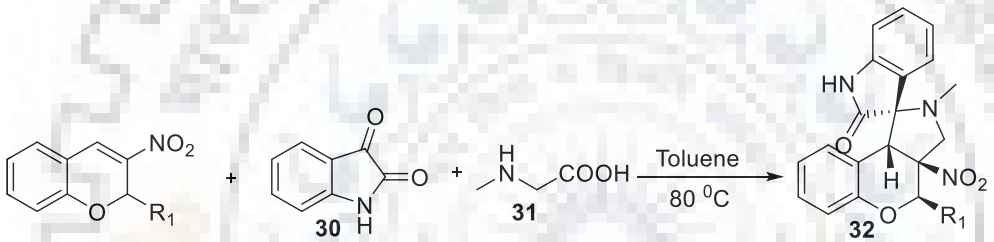
An eco-friendly protocol has been developed for the synthesis of spirooxindole-pyrrolidine/piperidine fused nitrochromanes **29** (Scheme 1.15) using ethanol at 80 ^{0}C in short reaction time. The advantage of this method is easy isolation of product by precipitation as single isomer from the reaction mixture [104].



R_1 = H, 2,8 di-Cl, 6-Cl, 8-MeO, 7-MeO, 6-Br, 8-MeO, 6-Br, 8-Cl

Scheme 1.15. Green synthesis of spirooxindole-pyrrolidine-piperidine derived nitrochromans

Use of isatin **30** and its derivatives in the preparation of azomethine ylides led to interesting and highly complex spirooxindole nitrochromanes **32.**

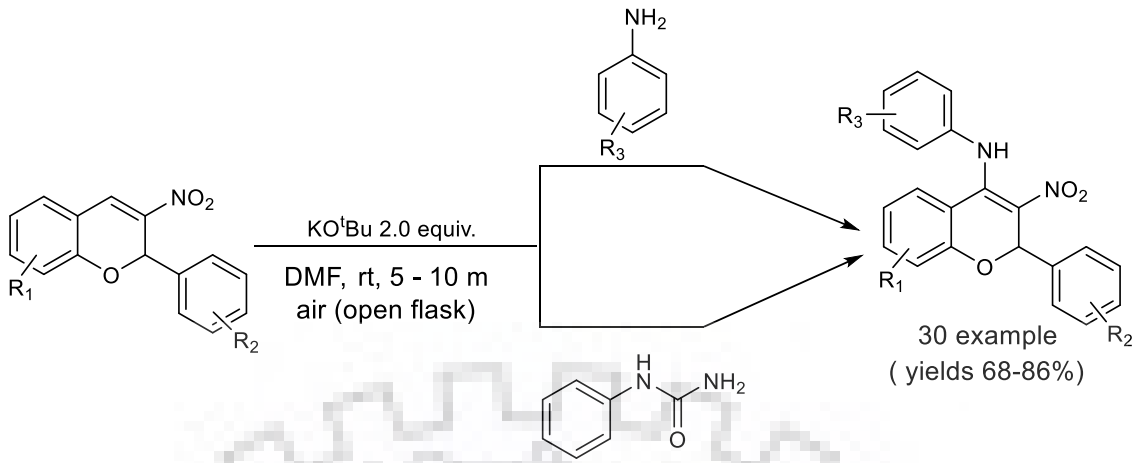


R_1 = phenyl, 4-methoxyphenyl, 1-naphthyl, n-methyl, 3-indole, ferrocenyl

Scheme 1.16. 1,3-Dipolar cycloaddtion of azomethine ylides towards spirooxindole based chromanes

Azomethine ylides were obtained from the thermal decarboxylative reaction between isatin **30** and sarcosine **31** in toluene with removal of water [105].

In the field, of 3-nitrochromene we have discovered potassium tertiary butoxide mediated oxidative Aza Michael addition to produce 4-amino substituted-3-nitrochromenes. This method is vary cost effective in term of reaction time and reagent because there is no need of additional oxidant, metal catalyst. In This transformation, wide range of functional groups have been tolerated and good to excellent yields of the final products obtained. The main features of this method is easily accessible starting materials and operational simplicity. These synthesised molecule have been tested for Calcium/Calmodulin Dependent Protein Kinase IV(CAMKIV) Inhibitors [106].



Scheme 1.17. Oxidative aza micheal addition of aniline and N-phenyl urea on 3-nitrochromene

1.4. Benzoxazole, benzothaiazole, benzimidazole and quinazolinone

Benzoxazole, Benzothiazole and Benzimidazole are heterocyclic compound in which benzene ring fused with oxazole, thiazol and imidazole ring structure [107, 108]. Substituted benzoxazole, benzothiazoles and benzimidazoles derivatives have been the aim of many researchers for many years, because they constitute an important class of heterocyclic compounds. Many structural variations of these compounds can be prepared by inserting the different functionalities on benzene ring and other active groups at the 2-position of oxazole, thiazole and imidazole to create good biological active compounds and shows broad spectrum of biological activity such as anticancer, antimicrobial, anti HIV and dopamine D_4 agonists [109-114]. In spite of this one of the derivative of benzothiazole is the light-emitting component of luciferin, found in fireflies [115]. Some dyes, such as thioflavin, and pharmaceutical drugs, like riluzole, contain benzothiazoles as a structural motif [116, 117]. In nature N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand in vitamin B_{12} [118]. Benzimidazole, system, has been used as carbon skeletons for N-heterocyclic carbenes. The NHCs ligands are generally used as ligands for transition metal complexes [119]. Quinazolinones is also a heterocyclic compound in which benzene ring fused with six membered heterocyclic ring, this six membered ring contains two nitrogen atoms. Quinazolinones, occur in many natural compounds like alkaloids [120], exhibit various kinds of biological activities, including anticancer [121], antifungal [122], antihypertensive [123], antimalarial [124], antibacterial [125], other activities [126]. Moreover, Quinazolinones are important building blocks in the synthesis of bioactive compounds and natural products [127]

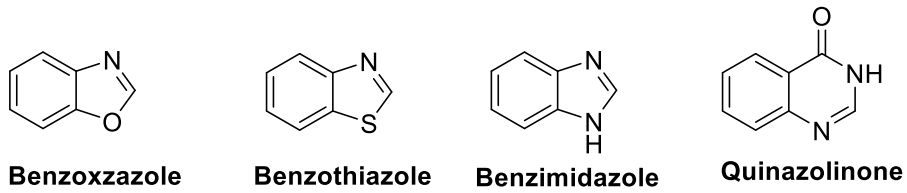
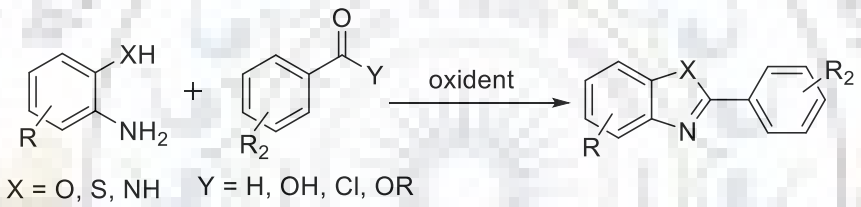


Figure 1.11. Structure of benzoxazole, benzothiazole, benzimidazole and quinazolinone

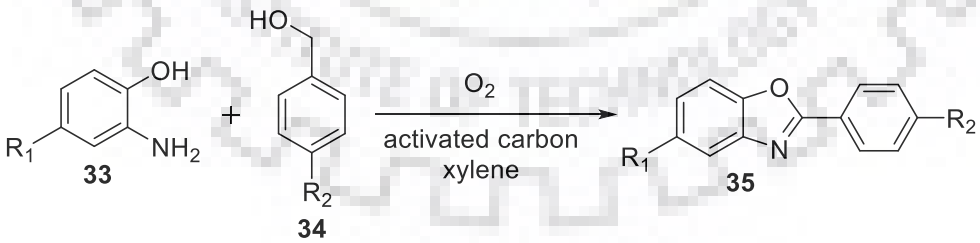
1.4.1. Synthesis benzoxazole, benzothiazole, benzimidazole and quinazolinone

The classical methods for the synthesis of and benzoxazoles, benzothiazole and benzimidazoles involve the condensation of and 2-aminophenol and 2-aminothiaphenol and 2-aminoaniline with either carboxylic acid derivatives, in the presence of acids or aldehydes under oxidative conditions (scheme 1.18) [128].



Scheme 1.18. Synthesis of benzoxazole, benzothiazole and benzimidazole by acid derivatives

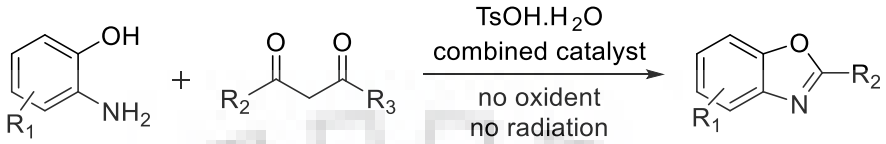
2-Arylbenzoxazoles **35** were synthesized from 2-aminophenols **33** and benzyl alcohol **34** in the presence of activated carbon under an oxygen atmosphere in xylene as solvent.



Scheme 1.19. Synthesis of benzoxazole by benzyl alcohol in the presence of oxygen gas

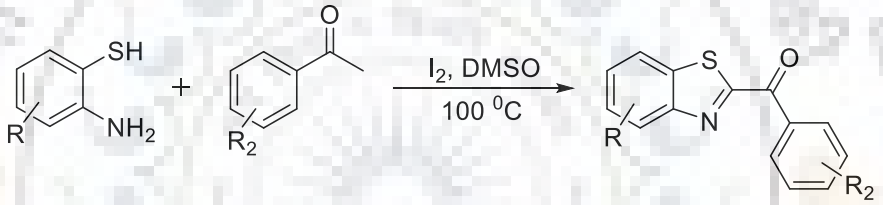
This reaction involves oxygen gas as oxidant and covert benzyl alcohol into aldehyde. The advantage of this method is use of cheap and easily available oxidant with moderate to good yield of products and good tolerance of functional groups (scheme 1.19) [129].

Brønsted acid (p-Toluenesulfonic acid) and CuI catalysed Cyclization reactions of 2-aminophenols with 1-3-diketones are presented. This protocol does not need any additional oxidant and Various 2-substituted benzoxazoles were obtained through these reactions. (Scheme 1.20) [130].



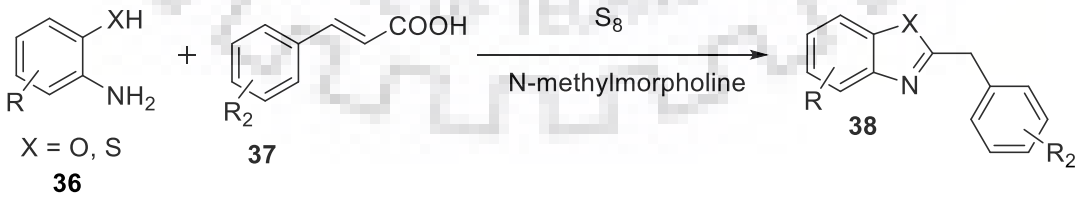
Scheme 1.20. Preparation of benzoxazole via 1,3 diketone in acidic medium

An-Xin Wu and co-worker in 2012 reported a metal-free and oxidant free I_2 promoted sp^3 C—H bond functionalization protocol to construct 2-acylbenzothiazoles and their derivatives (scheme 1.21) [131].



Scheme 1.21. Synthetic rout of benzothiazole by acetophenone derivatives using iodine as catalyst

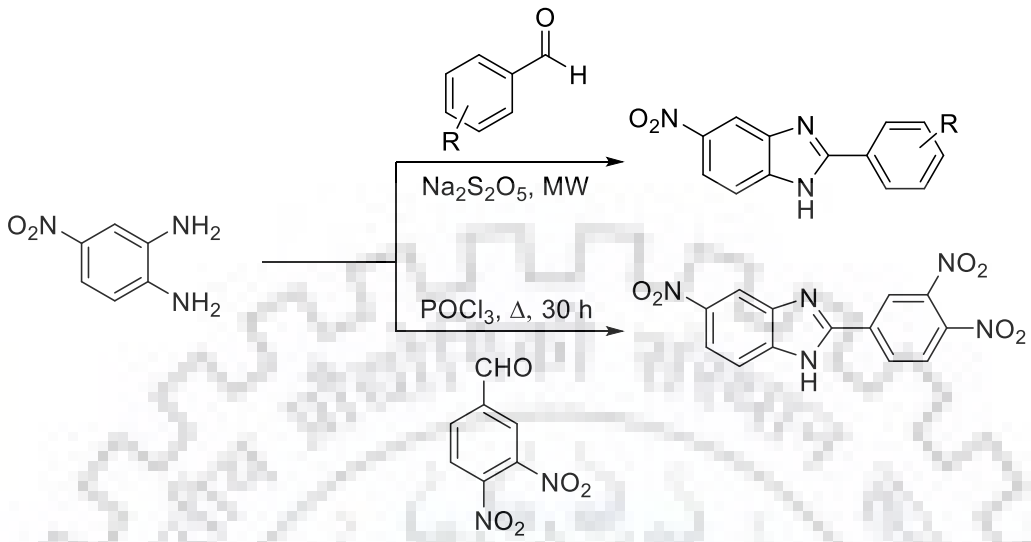
1n 2016 Krishna Nand Singh *et. al.* developed the a new strategy for the synthesis of benzoxazole and benzothiazole **38** involving elemental sulfur mediated decarboxylative coupling of 2-hydroxy/mercapto/amino-anilines **36** with cinnamic acid **37** under metal free and solvent-free conditions (Scheme 1.22) [132].



Scheme 1.22. Synthesis of benzoxazole and benzothiazole starting with cinnemic acid

Under microwave irradiation Castro *et. al.* demonstrated the synthesis of benzimidazole derivatives by heating the mixture of substituted aromatic aldehydes and 4-nitro-1,2-phenylenediamine using $Na_2S_2O_5$ as oxidant. However, in some cases the dinitro

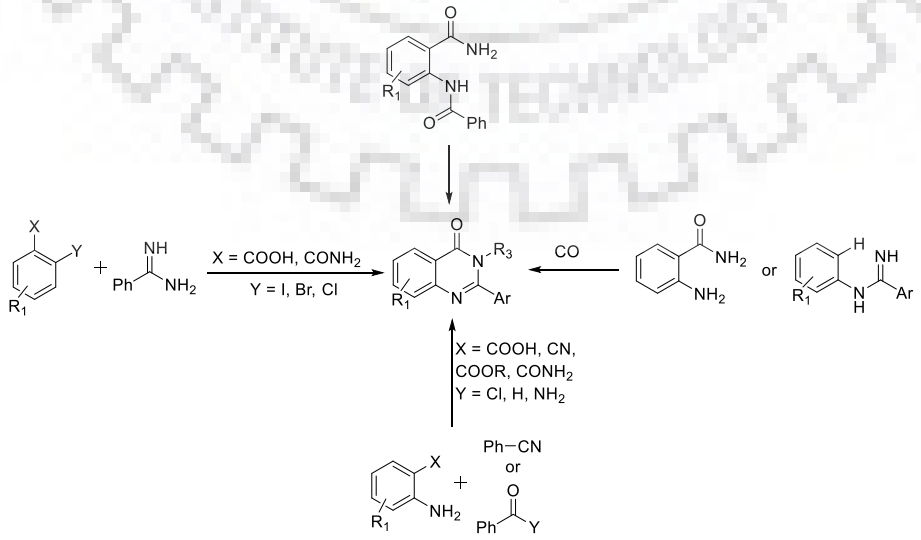
substituted aromatic aldehydes cyclize with 1,2-phenylenediamine in 30 h using $POCl_3$ as acid catalyst (scheme 1.23) [133].



Scheme 1.23. Synthesis of biologically active benzimidazole

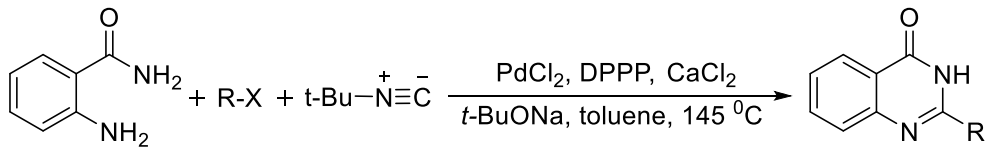
1.4.2. Synthesis of quinazolinones

Numerous methods for the synthesis of quinazolinones have been reported these mathods are based on the condensation of 2-aminobenzoic acids or their derivatives with aldehydes, acid chlorides, or carboxylic acid shown blow (Scheme 1.24) [134]. More recently Shun-Jun Ji in 2014, developed palladium catalysed isocyanide insertion reaction for the synthesis



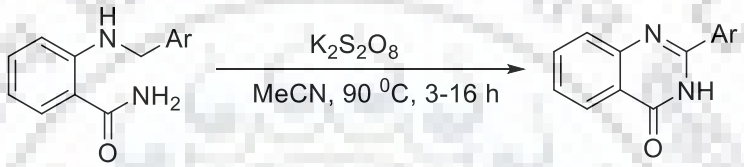
Scheme 1.24. Synthesis of qunazolinone by classical methods

of quinazolin-4(3H)-ones by easily accessible anthranilamide and aryl halides (Scheme 1.25) [135].



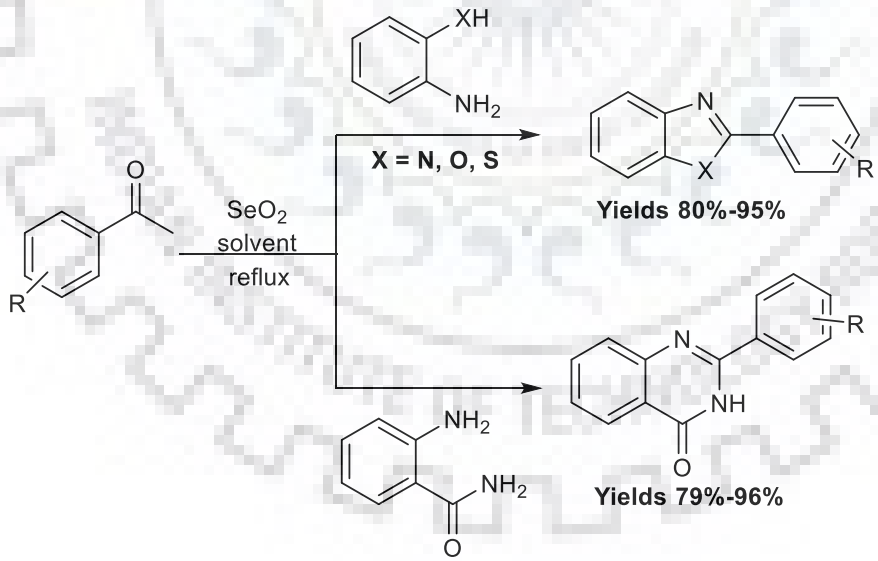
Scheme 1.25. Synthesis of quinazolinone by palladium catalysed isocyanide insertion

Nidhi Patel *et al.* prepared quinazolinone by Sulfate Radical Anion ($SO^{4\bullet-}$) Mediated C(sp^3)−H Nitrogenation/ Oxygenation in N-Aryl Benzylic (scheme 1.26) [136].



Scheme 1.26. Synthesis of quinazolinone by oxidative C—N coupling

A facile and interesting cyclization reactions of ketones with 2-amino aniline derivatives promoted by SeO_2 (oxidant) are reported for the synthesis



Scheme 1.27. Synthesis of benzoxazole, benzothiazole, benzimidazole and quinazolinone through the oxidative C—C cleavage of acetophenone.

of benzoxazole, benzothiazole, benzimidazole and quinazolinone through the oxidative C—C cleavage of acetophenone. The reaction likely involves sequential C—O, C—S and C—N bond formation followed by (CO)C—C bond cleavage. Various fused heterocycles

are formed in good to excellent yields in a one step from readily available acetophenones. This method is also applicable for gram scale synthesis [137].

1.5. Betti base

Mario Betti (1875-1942) had been worked in the field of asymmetric compounds and he worked towards the direct resolution of racemic compounds. He was also interested in relationship between molecular constitution and optical rotatory power, and asymmetric synthesis with the aid of chiral auxiliaries or in the presence of circularly polarised light. However, he is known for his work for the preparation of aminobenzylnaphthol that was called the Betti base and the reaction is known as Betti reaction [138-141].

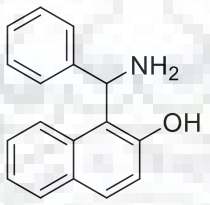
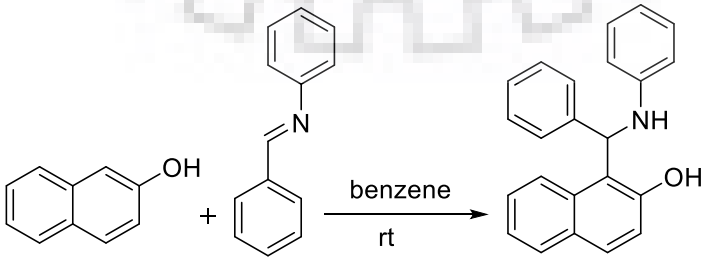


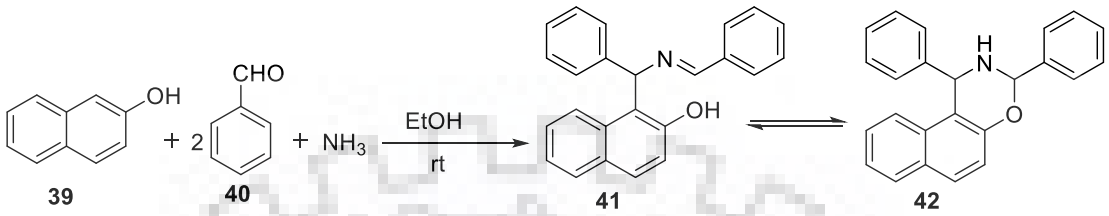
Figure 1.12. Structure of Betti base

In the end of 19th century this synthetic strategy originated and in the beginning of the 20th century when research in several laboratories was performed on reactions between ammonia, or amines (primary or secondary), formaldehyde and enolisable carbonyl compounds [142]. The first two components yield an imine or Schiff base that reacts with the carbonyl compound. These procedures are commonly used for Mannich amino alkylations, after the systematic work of the latter author, which began in 1912, thus subsequent to the Betti research [140, 141]. In 1900, Betti had hypothesised, and later proved that 2-naphthol should be a good carbon-carbon nucleophile towards the imine or Schiff base produced from benzaldehyde and aniline, as represented in Scheme 1.28.



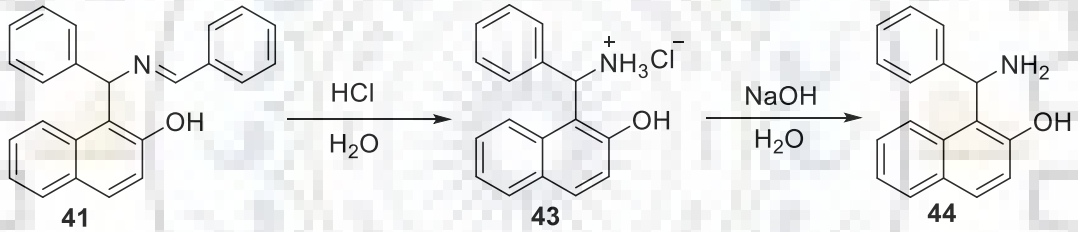
Scheme 1.28. Reaction between 2-naphthol and an imine

Later, Betti also describe that product **41** and **42** (Scheme 1.29) could be obtained from a three component condensation of 2-naphthol **39**, an ethanolic solution of ammonia and benzaldehyde **40**. Actually, the product of the reaction, as later proved, is represented by the forms **41** and **42** in equilibrium [141].



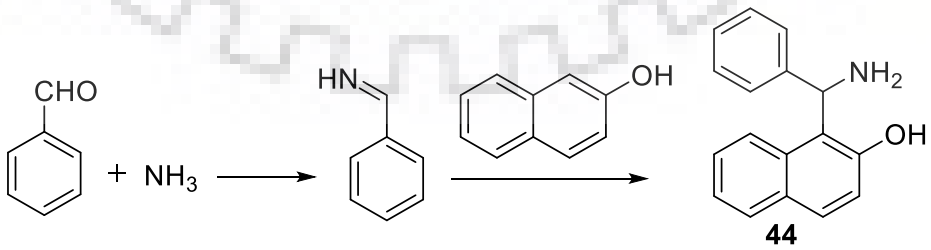
Scheme 1.29. The Betti formation

The intermediate **41** was treated with hydrochloric acid to obtain the salt of the Betti base **43** in 91% yield. After treatment of **43** with solution of sodium hydroxide, yielded Betti base **44** with 75% yield (Scheme 1.30) [140, 141].



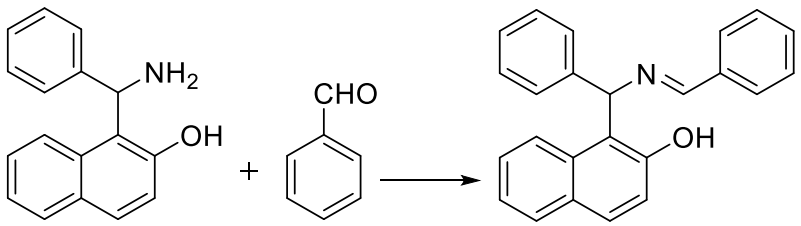
Scheme 1.30. Transformation of imine Betti base chloride salt into Betti base by formation of ammonium salt.

Scheme 1.31 reports the reaction of ammonia and benzaldehyde to yield the corresponding imine or Schiff base, that after reaction with 2-naphthol gives betti base **44** [141].



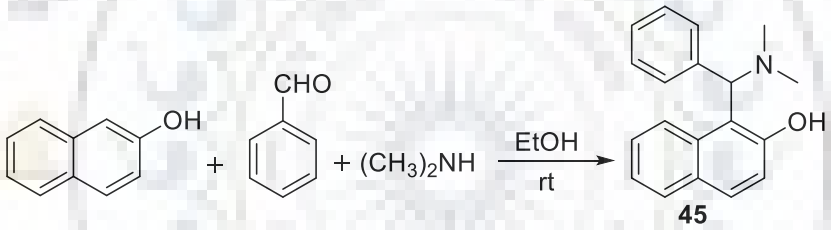
Scheme 1.31. Mechanism of Betti base formation

The Betti base subsequently react with aldehyde to formed imine of the corresponding betti base (Scheme 1.32).



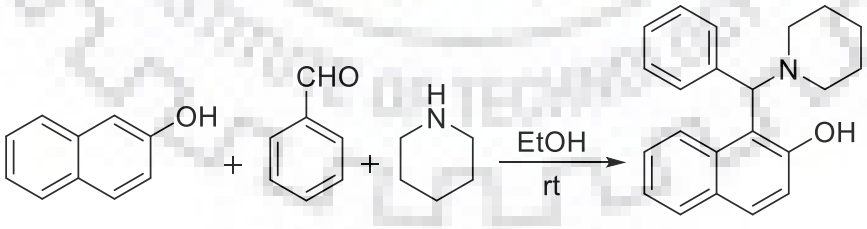
Scheme 1.32. The formation of the imine/oxazine.

The Betti formation, that is, a simple and straightforward condensation between 2-naphthol, aryl aldehydes and ammonia, or amines could be used to synthesize more complex molecular structures by assembling these three simple components. However, a long period of silence occurred after an initial interest that included the work performed by Littmann and Brode, who used different amines instead of ammonia. For example, the use of dimethylamine yielded the dimethylamino-derivative of the Betti base **45** in a one-pot multicomponent process with 71% yield (Scheme 1.33) [143].



Scheme 1.33. The Betti reaction with dimethylamine

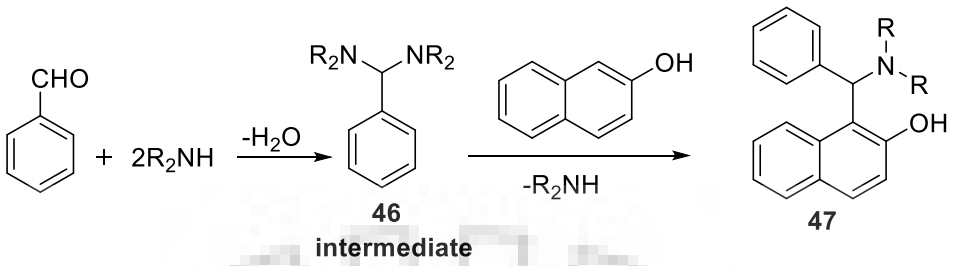
On the other hand, the use of piperidine gave 1-(1-piperidylbenzyl)- 2-naphthol (73% yield, Scheme 1.34) [144].



Scheme 1.34. The Betti preparation with piperidine

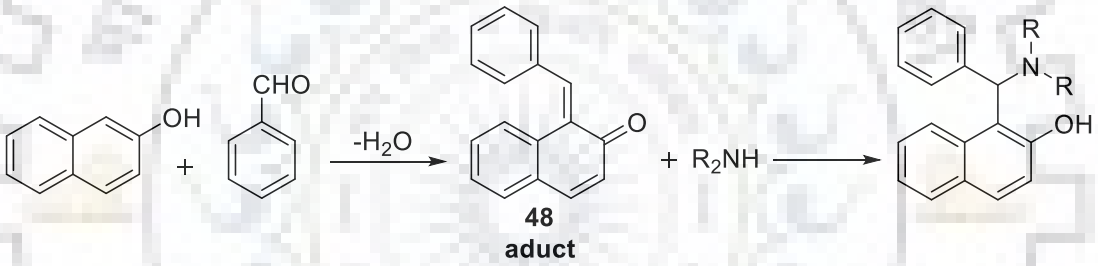
This compound was also resolved into its enantiomers with the aid of camphor sulfonic acid. A different mechanism should be operative in these reactions. According to Littmann and Brode, secondary amines should react with benzaldehyde via the formation of a benzylidinediamine **46**, as shown in Scheme 1.35. This intermediate attacks the 2-

naphthol and yields aminobenzylnaphthol **47**, after the elimination of an amine molecule [145].



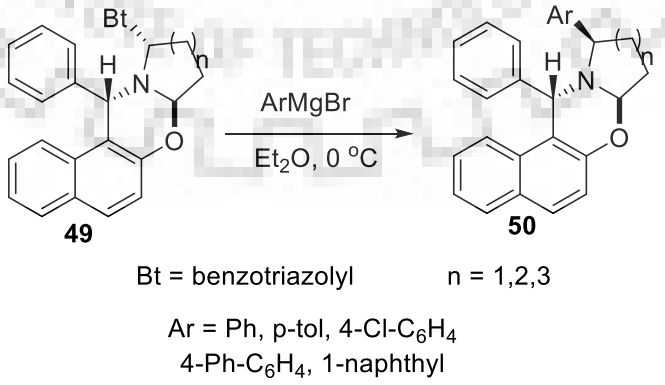
Scheme 1.35. Betti base preparation path with secondary amine

However, in principle the alternative mechanism represented in Scheme 1.36, based upon the reaction between the amine and adduct **48** formed between 2-naphthol and benzaldehyde cannot be ruled out.



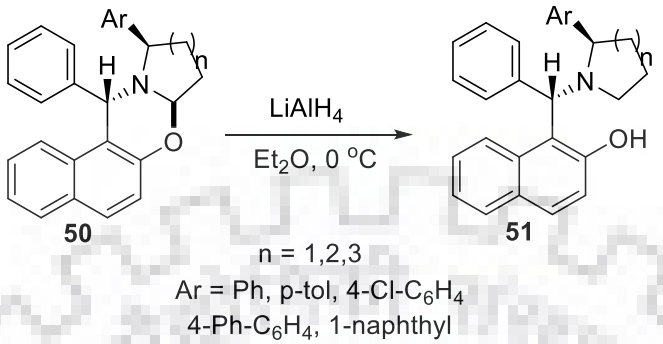
Scheme 1.36. An alternative path for Betti base preparation with secondary amine

The regio- and stereoselective arylation of oxazines **49** at its α-position (Scheme 1.37) by treatment with aryl magnesium bromides to give the new oxazines compound **50** in good yields (73–85%) [146, 147].



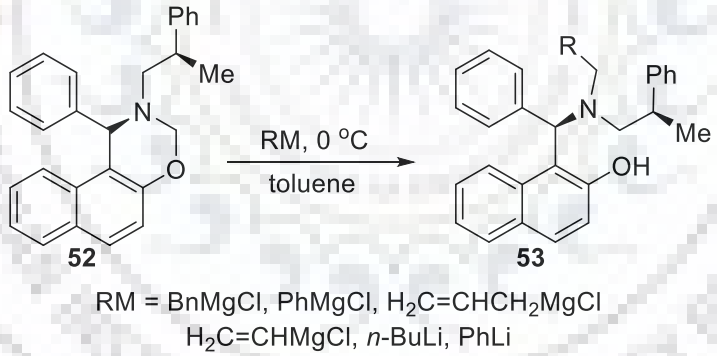
Scheme 1.37. Highly stereoselective reaction of arylmagnesium bromides to give oxazines derived from the Betti base

An another family of N-alkylated Betti bases, that is, 1-[a-(2-arylpiperidyl)benzyl]-2-naphthols) **51** was prepared by the reduction of arylated oxazine derivatives **50** by $LiAlH_4$ (Scheme 1.38).



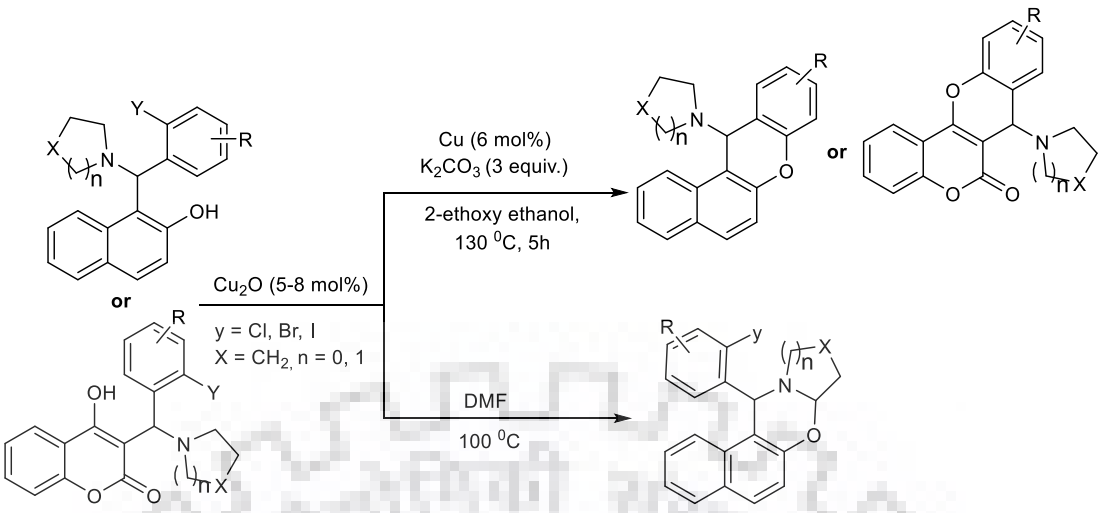
Scheme 1.38. Reduction of the arylated oxazine derivatives

Palmieri *et al.* observed that oxazine **52** reaction with organometallic reagents at 0 ^{0}C by the ring opening reaction to produce Betti base **53**, in this case higher yields were obtained with Grignard reagents or with n-butyllithium and with N-methyl- or N-allyl-substituted aminonaphthols (Scheme 1.39) [148].



Scheme 1.39. Reaction of organometallic reagents with oxazine **52**.

In this area of research, a novel and efficient Cu (0) and Cu (I) oxide catalysed cyclisation of halo-Betti Base was developed via an Ullmann type coupling. The reaction proceeded smoothly under mild reaction conditions and produced fused banzo-xanthene and 1,3 naphthoxazine in good to excellent yields with a good tolerance of functional groups. The main features of this methods is operational simplicity and uses readily available catalyst.



Scheme 1.40. Synthesis of benzofused xanthene and 1,3- naphthoxazine

1.7. References

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Chapter-2

$PhI(OAc)_2$ mediated an efficient Knoevenagel reaction and their synthetic application for coumarin derivatives

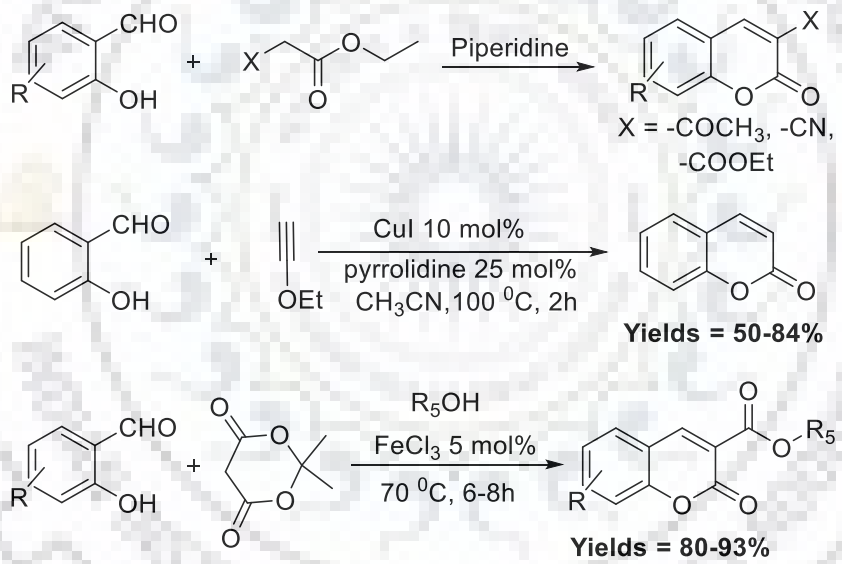
Tetrahedron Lett., **2017**, *58*, 3183-3187

2.1. Introduction

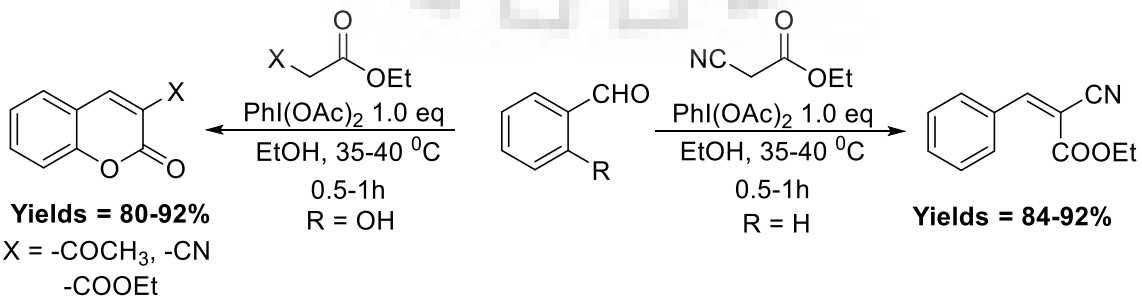
The Knoevenagel condensation reaction is widely employed methods for the formation of C–C bonds [1] with numerous applications in the synthesis of fine chemicals [2], hetero Diels-Alder reactions [3] and in the synthesis of heterocyclic [4] as well as carbocyclic compounds of various biological importance. Several active methylene compounds have been used as starting materials for the Knoevenagel condensation that include malononitrile, cyano-ethylacetate, ethyl-acetoacetate and arylidene-malononitriles, etc. In general, the Knoevenagel condensation is catalyzed by organic bases such as amines, pyridine, piperidine, a mixture of a secondary amine and amino acids such as L-proline [5]. The reaction also can be catalyzed by Lewis acids, including CdI_2 [6], $ZnCl_2$ [7], Al_2O_3 [8], MgO, ZnO [9], $TiCl_4$ [10], KF-Al_2O_3 [11], $AlPO_4$-Al_2O_3 [12], natural hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) [13] and ammonium acetate (NH_4OAc)-basic alumina [14]. Because of the formation of undesirable side products the use of such bases/acids have led to environmental problems as to dispose large amount of organic wastes. For the reactions, electrochemical, microwave and ultrasound activation methods have also been reported [15]. On the other hand, ionic liquids (ILs) are also well-known reaction media. In particular, ‘‘task-specific” ionic liquid catalysts with basic and acidic functional groups have been reported for the Knoevenagel reactions [16].

Coumarins are class of oxygen containing heterocycles, found in numerous natural products including edible vegetables and fruits, with α-benzopyrone skeletal framework [17]. They are also used as additives in food and cosmetics, optical brightening agents and dispersed fluorescent, laser dyes and used as ligand in Suzuki miyaura and Mizorokie-Heck cross coupling reaction [18]. They also displayed remarkable biological activity such as anti-HIV [19], antifungal [20], anti-inflammatory [21], anticancer [22], antimicrobial, antioxidant [23], and dyslipidemic [24] activity. Derivatives obtained from 4-hydroxycoumarin protects liver cells from damage by peroxides [25]. Among these properties, cytotoxic effects were extensively studied [26]. Synthesis of coumarin derivatives can be achieved by Perkin, Pechmann, Wittig, Reformatsky, Claisen and Knoevenagel condensations [27]. The classical methods for the synthesis of 3-acetylcoumarin, ethyl coumarin-3-carbaoxylate and 3-cyanocoumarin is the Knoevenagel condensation using salicylaldehyde with ethyl acetoacetate, diethyl malonate and α-cyano-ethylacetate compounds respectively, followed by intramolecular cyclization (Scheme 2.1) [28]. This traditional methods generally required harsh reaction conditions and often resulted in low product yields. Therefore, in organic synthesis an

effective method for the straightforward synthesis of coumarins from simple, easily available and cheap starting materials is still in high demand. Reddy *et al.* in 2013 described Cu-catalyzed A^3 coupling reaction to afford coumarins using ethoxyacetylene, pyrrolidine and salicylaldehydes (Scheme 2.1) [29]. In 2015, X. He *et al.* reported the reaction of salicylaldehydes with Meldrum's acid in the presence of catalytic amount of anhydrous $FeCl_3$ in ethanol solvent for the synthesis of ethyl-coumarin-3-carboxylate [30]. Recently, S. Fiorito *et al.* successfully developed ytterbium triflate catalyzed and crop derived products methods in the coumarins synthesis [31]. In the past few years, hypervalent iodine reagents, such as phenyliododiacetate (PIDA) have been used for the formation of C−C bonds, without involvement of a toxic, transition-metal-containing reagent [32].



Scheme 2.1. Previous work



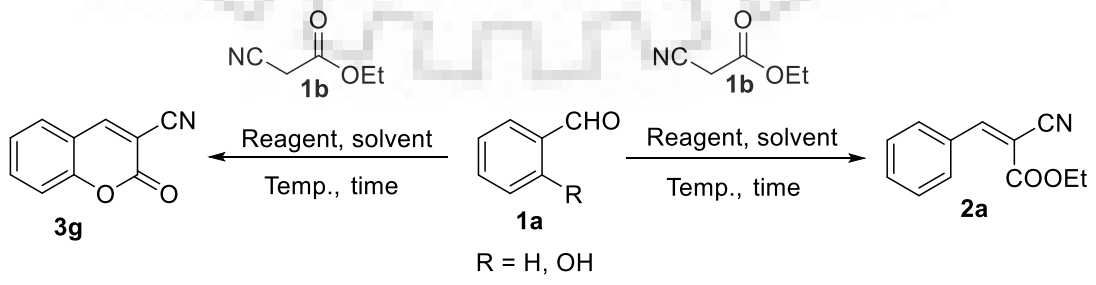
Scheme 2.2. Present work

There are few examples reported for the oxidative C−C bond formation by hypervalent iodine reagent [33]. Herein, we report a facile methodology for Knoevenagel reaction and their application for coumarins synthesis using salicylaldehyde with α-substituted ethylacetate and $PhI(OAc)_2$ in ethanol (scheme 2.2).

2.2. Results and discussion

In an initial study, aldehyde **1a** and α-cyano-ethylacetate **1b** were tested for the Knoevenagel reaction in the presence of PIDA, which afforded 90% and 92% yield of product respectively (Table 2.1, entry 3). To verify the role of PIDA, we performed a comparative experiment without PIDA. However, the reaction failed to afford the desired product **2a** and **3g** (Table 2.1, entry 1). It confirmed that PIDA is necessary to promote the process. To optimize the product yield, we also found that treating with 20 mol% (0.2 equiv.) of PIDA, generated trace amount of the desired product (Table 2.1, entry 2). When PIDA increased to 0.5 equiv., the product yield was enhanced (Table 2.1, entry 10). Use of 1.0 equiv. of PIDA afforded maximum yield (Table 2.1, entry 3). Furthermore, increase of PIDA 2.0 equiv., the product yield was decreased (Table 2.1, entry 9). The effects of molecular iodine and other hypervalent iodine reagents such as IBX, PhIO and Dess-Martin were investigated. In case of molecular iodine, no conversion was observed (Table 2.1, entry 5). Moreover, IBX, PhIO and Dess-Martin were catalysed the process with lower yields and longer reaction time (Table 2.1, entries 6, 7 and 8). PIFA also gave the similar result (Table 2.1, entry 4).

Table 2.1. Optimization of Reaction Conditions:



Entry	Reagent (1 equiv.)	Solvent	Time (h)	Yield[a](%) **2a/3g**
1	-	Ethanol	1.0	0/0
2[b]	PIDA	Ethanol	1.0	Trace

3	**PIDA**	**Ethanol**	**1.0/0.5**	**90/92**
4	PIFA	Ethanol	1.5	90/92
5	I_2	Ethanol	1.0	0/0
6	IBX	Ethanol	1.0	67/70
7	PhIO	Ethanol	12	40/44
8	Dess martin	Ethanol	8	58/63
9[c]	PIDA	Ethanol	1.0	68/72
10[d]	PIDA	Ethanol	1.0	46/52
11[e]	PIDA	Ethanol	2	0/0
12	PIDA	DCM	6	30/30
13	PIDA	DMSO	3	63/62
14	PIDA	THF	8	37/38
15	PIDA	ACN	6	49/49
16	PIDA	DMF	3	66/64

[a]**Reaction condition:** benzaldehyde/salicylaldehyde (1.0 mmol), α-cyano-ethylacetate (1.0 mmol) and PIDA (1.0 mmol) in ethanol (5 mL) at 35-40 ^{0}C. [b]PIDA (20 mol%). [c]PIDA (2.0 equiv). [d]PIDA (0.5 equiv). [e]at 80 ^{0}C. [f]Isolated yields.

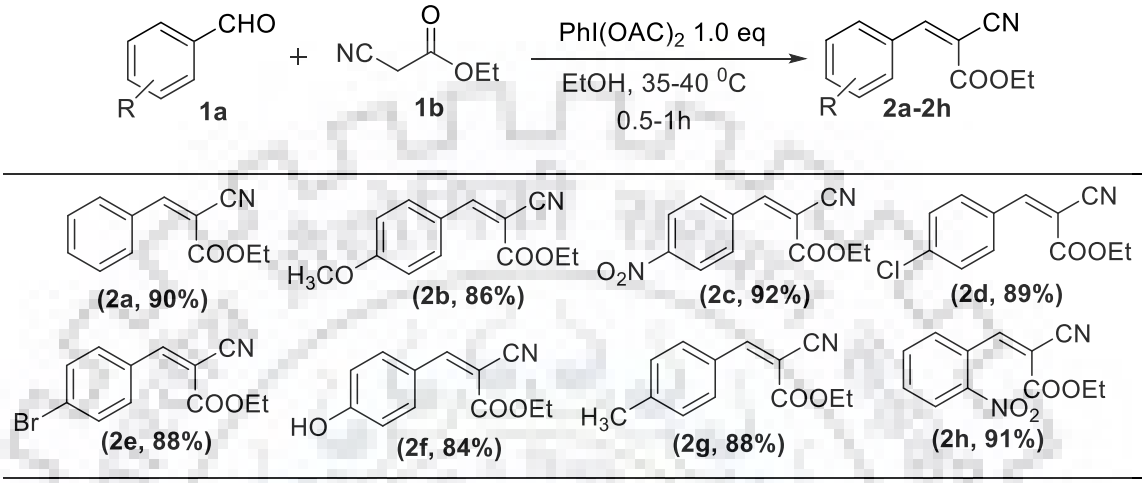
Similarly, other solvents including DMSO, THF, DCM, acetonitrile and DMF were screened but poor yields were obtained (Table 2.1, entries 12–16). In addition, it was found that at high/refluxed temperature, no product formation was observed (Table 2.1, entry 11). Therefore, this reaction could be best performed with 1.0 equiv. $PhI(OAc)_2$ in ethanol at 35-40 ^{0}C for 0.5-1 h [35].

2.3. Substrate scope

The substituent effects on the benzaldehyde ring were examined. Both electron-donating and electron withdrawing groups were well tolerated, and good to excellent yields of the corresponding substituted ethyl-2-cyano-3-phenylacrylate were obtained (Scheme 2.3). Replacing chloro in the **1a** to other halogen, such as bromo, did not affect the yield to any significant degree (**2d** and **2e**). We observed that, yield was slightly higher for electron withdrawing group (**2c** and **2h**). Similarly, the para-substituted hydroxyl substrates with respect to aldehyde group

slightly decreased the yield might be due to electron donating tendency via resonance (**2f**), which decreased the electrophilic nature of the aldehyde group.

Scheme 2.3. Synthesis of alkene



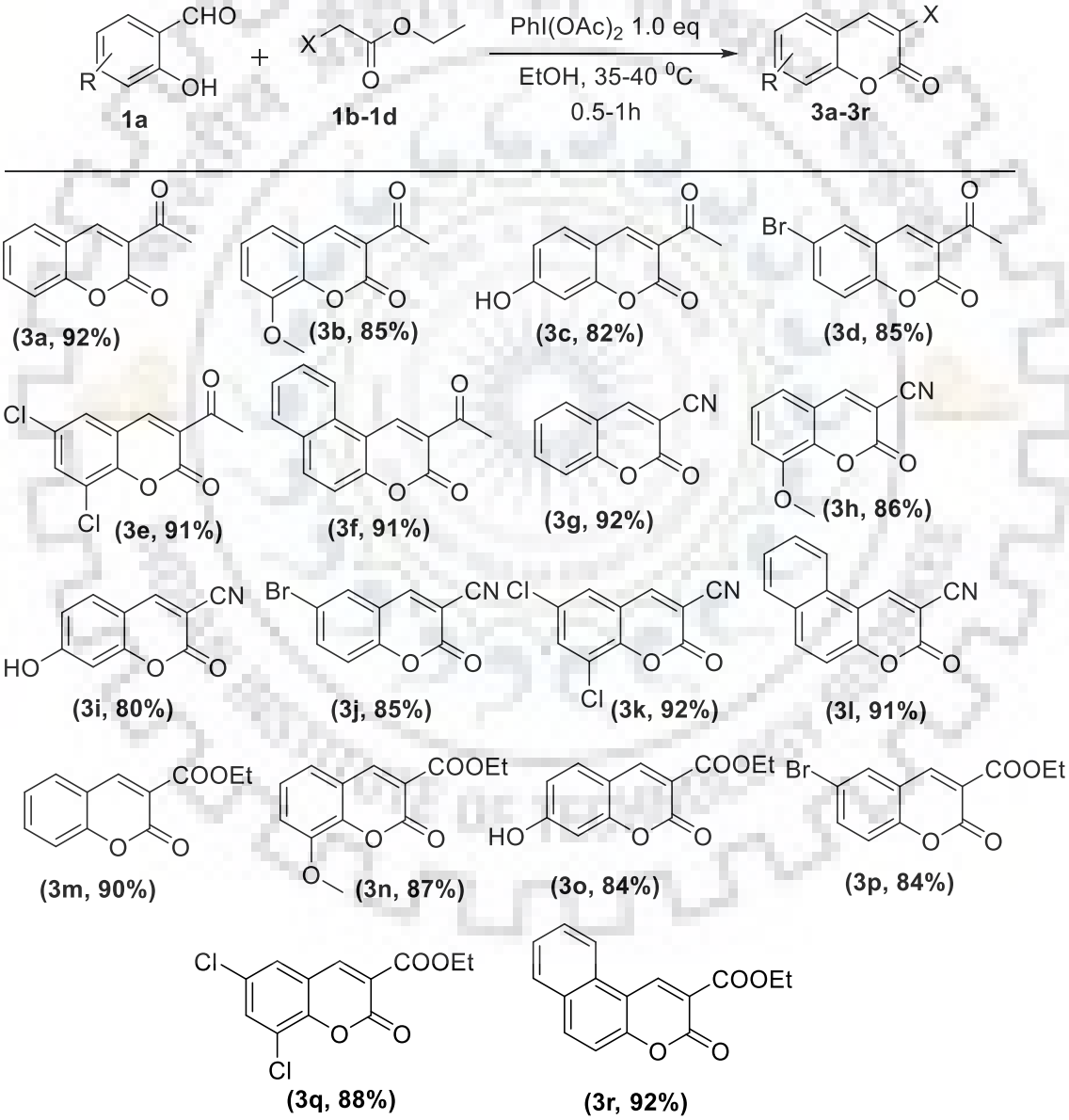
Scheme 2.3. Benzaldehyde (1.0 mmol, 0.1061gm), α-cyano-ethylacetate (1.0 mmol, 0.1131gm) and PIDA (1.0 mmol, 0.3221gm) in ethanol (5 ml) at 35-40 ^{0}C.

Salicylaldehyde **1a** bearing a variety of substituents on the benzene ring reacted very smoothly to afford the corresponding coumarins (**3a-3r**) in 80–92% yield, indicated that the substituents on the aromatic ring of **1a** did not have significant influence on the reaction. Salicylaldehydes possessing several functional groups such as methoxy, hydroxyl, chloro, bromo and 2-hydroxy-1-naphthaldehyde were also tolerated in this reaction, and good yields of corresponding products were obtained. When ethyl-acetoacetate was subjected to the reaction, the corresponding product (**3a**) was obtained in 92% yield. Under the optimum conditions, α-cyano-ethylacetate and diethyl malonate were smoothly converted to 3-cyano-coumarin (**3g**) and ethyl coumarin 3-carboxylate (**3m**) in 92% and 90% yield, respectively (Scheme 2.4). However, some reactants required more reaction time. In addition, it was found that electron donating group at para position to aldehyde group converted slowly, the corresponding product (**3c**, **3i** and **3o**) was obtained in 82%, 80% and 84% yield respectively. While more conjugated system converted more smoothly and required less reaction time. The respective product (**3f**, **3l** and **3r**) was obtained in 91%, 91% and 92% yield respectively.

The structure elucidation of **2b** and **3b** was done on the basis of the collective information obtained from various spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR and HRMS.

Disappearance of aldehyde proton in ^{1}H NMR spectrum of **2b** and **3b** and appearance of singlet at d 8.14 and d 8.47 ppm respectively confirmed the formation of product **2b** and **3b**. In ^{13}C NMR spectrum of **2b** and **3b** showed eleven and twelve signals respectively. Further the structure of the product **2b** and **3b** was confirmed by HRMS. The m/z molecular ion peak of compound **2b** and **3b** appears as $[M+Na]^{+}$ at 254.0746 and 242.0504.

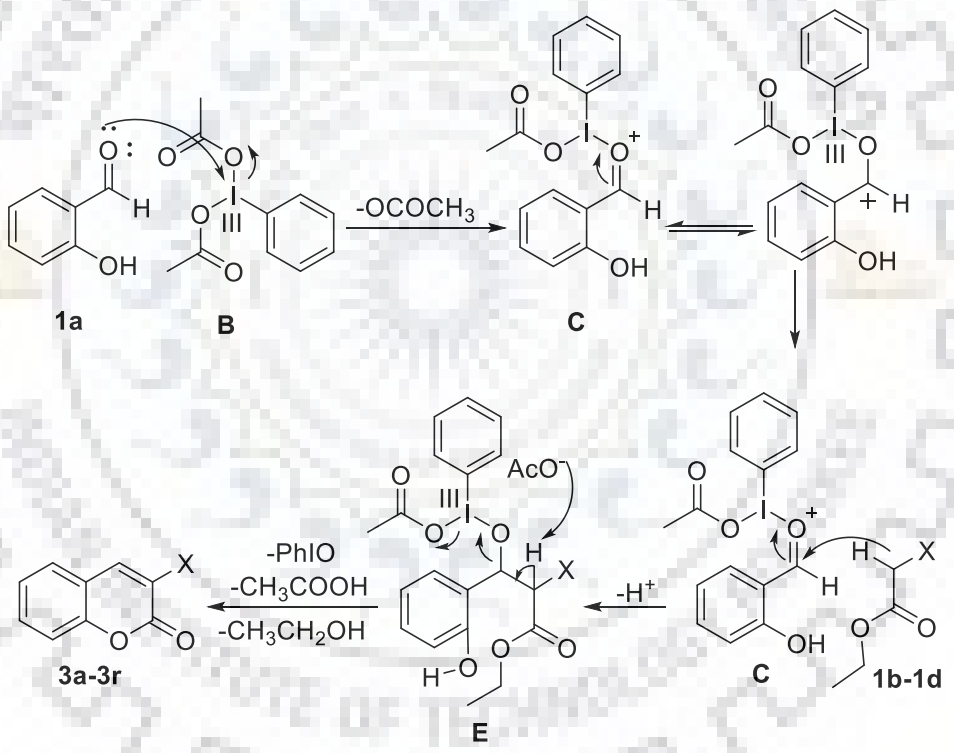
Scheme 2.4. Synthesis of coumarin derivatives



Scheme 2.4. salicylaldehyde (1.0 mmol, 0.1221gm), α-substuted ethylacetate (1.0 mmol) and PIDA (1.0 mmol, 0.3221gm) in ethanol (5 ml) at 35-40 ^{0}C.

2.4. Reaction Mechanism

In order to understand the reaction mechanism, we examined the reaction of salicylaldehyde **1a** with α-substituted ethylacetate **1b-1d** promoted by $PhI(OAc)_2$ **B** at room temperature. On the basis literature survey [34]. A possible reaction mechanism is proposed in (Scheme 2.5). The Iodine center in DIB act as good electrophilic in nature and the nucleophilic attack of aldehyde (**1a**) to DIB (**B**) gives intermediate **C**. Subsequently, Active methylene compounds (**1b-1d**) attack the electron-deficient carbonyl carbon leading to the formation of intermediate **E**, which after the loss of a proton from **E** by acetate ion and simultaneous cyclisation affords final product.



Scheme 2.5. Proposed Mechanism

2.5. Conclusion

In conclusion, we have developed a highly efficient and environmental friendly method for Knoevenagel reaction and their synthetic application for coumarin derivatives using $PhI(OAc)_2$ in good to excellent yield under mild reaction conditions. This method tolerated a wide range of functional groups.

2.6. Experimental Section

2.6.1. General Information

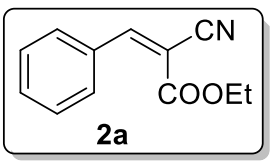
Organic solvents were dried by standard methods; the reagents (chemicals) were purchased from commercial sources, and used without further purification. All reactions were monitored by TLC using precoated silica gel aluminum plates. Visualization of TLC plates was accomplished with an UV lamp. Melting points were recorded on Perfit apparatus and are uncorrected. All products were characterized by NMR and HRMS spectra. ^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform and dimethyl sulphoxide ($CDCl_3$ and DMSO-d_6) on a 400 MHz and 100 MHz spectrometer (Jeol) respectively. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). GC-MS recorded on Perkin-Elmer using chloroform solvent between 80-180 ^{0}C oven temperatures.

2.6.2. General procedure for the synthesis of alkene/Coumarins:

α-substituted ethyl acetate (1.0 mmol) and Phenyliodiacetate (1.0 mmol) was dissolved in ethanol (5 ml) with constant stirring. After 10 minutes benzaldehyde/salicylaldehyde (1.0 mmol), was added and the mixture was allowed to stir for appropriate time. Then the progress of the reaction was monitored by thin layer chromatography. After completion of reaction as indicated by TLC, ethanol was evaporated under reduce pressure. The product was extracted with ethyl acetate, dried over Na_2SO_4 and solvent was evaporated under reduce pressure. The residue obtained was recrystallized by ethyl acetate and hexane to product **2a-2h** and **3a-3r**.

2.7. Characterization data

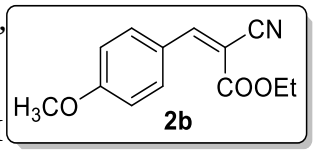
Ethyl-2-cyano-3-phenylacrylate (2a):



2a

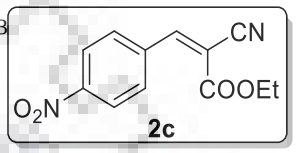
White solid; Yield: 90%; m. p. 48-49 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.23 (s, 1H), 7.98(t, *J* = 9.36 Hz, 2H), 7.49 (q, *J* = 8.58 Hz, 3H), 4.37 (q, *J* = 8.0, 2H), 1.38 (t, *J* = 8.64 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.32, 153.50, 139.68, 132.30, 129.94, 129.76, 115.37, 103.53, 62.97, 14.23; HRMS (ESI): calcd for $C_{12}H_{11}NO_2$ $[M+Na]^+$ 224.0687; found 224.0661.

Ethyl-2-cyano-3-(4-methoxyphenyl)acrylate (2b):



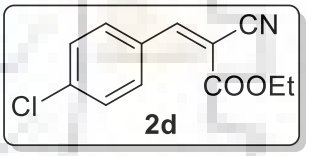
White solid; Yield: 86%; m. p. 51-53 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.14 (s, 1H), 7.97 (d, *J* = 8.88 Hz, 2H), 6 .97 (d, *J* = 8.88 Hz, 2H), 4.34 (q, *J* = 7.13, 2H), 3.87 (s, 1H), 1.36 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (CDCl3, 100 MHz) δ ppm 163.86, 163.19, 154.45, 133.71, 124.45, 116.29, 114.84, 99.44, 62.49, 55.69, 14.23; HRMS (ESI): calcd for $C_{13}H_{13}NO_3$ $[M+Na]^+$ 254.0793; found 254.0746.

Ethyl-2-cyano-3-(4-nitrophenyl)acrylate (2c):



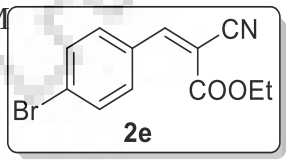
White solid; Yield: 92%; m. p. 168-169 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.33 (d, *J* = 8.76 Hz, 2H), 8.28 (s, 1H), 8. 11 (d, *J* = 8.72 Hz, 2H), 4.40 (q, *J* = 7.13, 2H), 1.40 (t, *J* = 7. 16 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 161.48, 151.79, 149.81, 136.98, 131.58, 124.40, 114.59, 107.48, 63.42, 55.69, 14.17; HRMS (ESI): calcd for $C_{12}H_{10}N_2O_4$ $[M+Na]^+$ 269.0538; found 269.0501.

Ethyl-3-(4-chlorophenyl)-2-cyanoacrylate (2d):



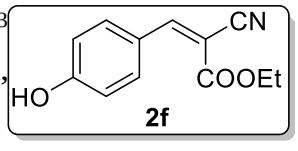
White solid; Yield: 89%; m. p. 91-93 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.17 (s, 1H), 7.91 (d, *J* = 8.56 Hz, 2H), 7 .46 (d, *J* = 8.56 Hz, 2H), 4.36 (q, *J* = 7.14, 2H), 1.38 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.32, 153.50, 139.68, 132.30, 129.94, 129.76, 115.37, 103.53, 62.97, 14.23; HRMS (ESI): calcd for $C_{12}H_{10}ClNO_2$ $[M+Na]^+$ 258.0298, 260.0268; found 258.0258, 260.0229.

Ethyl-3-(4-bromophenyl)-2-cyanoacrylate (2e):



White solid; Yield: 88%; m. p. 88-89 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 M Hz,) δ 8.16 (s, 1H), 7.83 (d, *J* = 8.92 Hz, 2H), 7.62 (d, *J* = 8.92 H z, 2H), 4.37 (q, *J* = 7.54 Hz, 2H), 1.38 (t, *J* = 7.20 Hz, 3H); ^{13}C N MR ($CDCl_3$, 100 MHz,) δ 162.34, 153.68, 132.77, 132.36, 130.32, 128.40, 115.40, 103.62, 63.02, 14.26; HRMS (ESI): calcd for $C_{12}H_{10}BrNO_2$ $[M+Na]^+$ 301.9793, 303.9772; found 301.9752, 303.9746.

Ethyl-2-cyano-3-(4-hydroxyphenyl)acrylate (2f):

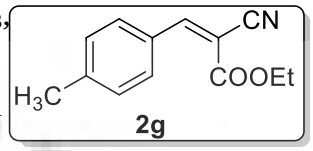


White solid; Yield: 84%; m. p. 167-168 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 8.18 (s, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz,

3H); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 163.18, 160.91, 154.99, 133.97, 124.37, 116.53, 116.27, 99.21, 62.63, 14.27; HRMS (ESI): calcd for $C_{12}H_{11}NO_3$ $[M+Na]^+$ 240.0637; found 240.0606.

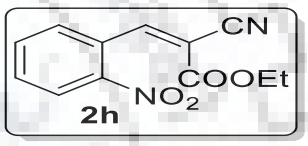
Ethyl-2-cyano-3-(p-tolyl)acrylate (2g):

White solid; Yield: 88%; m. p. 92-93 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 8.19 (s, 1H), 7.88 (d, *J* = 8.24 Hz, 2H), 7.28 (d, *J* = 8.08 Hz, 2H), 4.35 (q, *J* = 7.140 Hz, 2H), 1.37 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz,) δ 162.85, 155.08, 144.72, 131.33, 130.11, 128.97, 115.85, 101.67, 62.66, 21.93, 14.24; HRMS (ESI): calcd for $C_{13}H_{13}NO_2$ $[M+Na]^+$ 238.0844; found 238.0817.



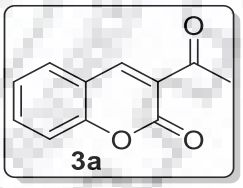
Ethyl-2-cyano-3-(2-nitrophenyl)acrylate (2h) :

light brown solid; Yield: 91%; m. p. 140-141^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 8.70 (s, 1H), 8.26 (d, *J* = 8.64 Hz, 1H), 7.85 (d, *J* = 8.12 Hz, 1H), 7.80 (t, *J* = 7.52 Hz, 1H), 7.70 (t, *J* = 8.44 Hz, 1H), 4.41 (q, *J* = 7.39 Hz, 3H), 1.40 (t, *J* = 7.28 Hz, 4H); ^{13}C NMR ($CDCl_3$,100 MHz,) δ 161.13, 153.34, 147.41, 134.66, 132.33, 130.72, 128.22, 125.56, 114.04, 108.67, 63.29, 14.21; HRMS (ESI): calcd for $C_{12}H_{10}N_2O_4$ $[M+Na]^+$ 269.0538; found 269.0504.



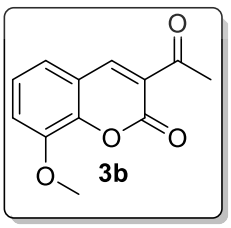
3-acetyl-2H-chromen-2-one (3a):

White solid; Yield: 92%; m. p. 121-122 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.49 (s, 1H), 7.65-7.61 (m, 2H), 7.35 (d, *J* = 9.28 Hz, 1H), 7.31 (d, *J* = 7.56 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 195.54, 159.24, 155.28, 147.45, 134.39, 130.20, 124.96, 124.45, 118.21, 116.63, 30.50; HRMS (ESI): calcd for $C_{11}H_8O_3$ $[M + Na]^+$ 211.0371; found 211.0336.

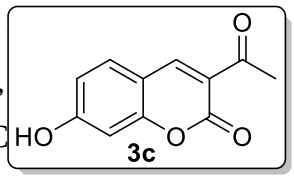


3-acetyl-8-methoxy-2H-chromen-2-one (3b):

Light yellow solid; Yield: 85%; m. p. 167-168 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.47 (s, 1H), 7.29-7.18 (m, 3H), 3.98 (s, 3H), 2.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 195.71,158.81, 147.85, 147.77, 147.09, 145.04, 124.68, 121.39, 118.90, 115.91, 56.40, 30.65; HRMS (ESI): calcd for $C_{12}H_{10}O_4$ $[M+Na]^+$ 242.0477; found 241.0422.

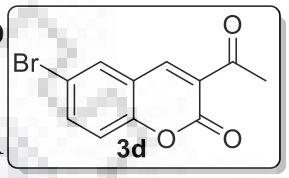


3-acetyl-7-hydroxy-2H-chromen-2-one (3c):



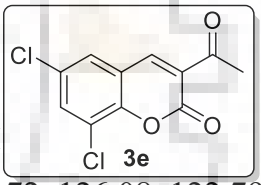
Light pink solid; Yield: 82%; m. p. 236-237 ^{0}C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm 8.58 (s, 1H), 7.77 (d, *J* = 8.60 Hz, 1H), 6.83 (d, *J* = 8.60 Hz, 1H), 6.73 (s, 1H), 2.54 (s, 3H); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm 195.22, 165.10, 159.63, 157.85, 148.40, 133.22, 119.50, 114.92, 111.19, 102.31, 30.59; HRMS (ESI): calcd for $C_{11}H_8O_4$ $[M+Na]^+$ 227.0320; found 227.0301.

3-acetyl-6-bromo-2H-chromen-2-one (3d):



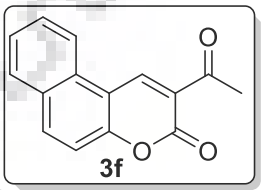
White solid; Yield: 85%; m. p. 232-233 ^{0}C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm 8.61 (s, 1H), 8.22 (s, 1H), 7.89 (d, *J* =8.68 Hz, 1H), 7.45 (d, *J* = 8.56 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm 195.20, 157.70, 149.47, 145.87, 133.60, 129.16, 128.98, 129.60, 121.30, 121.13, 30.48; HRMS (ESI): calcd for $C_{11}H_7BrO_3$ $[M+Na]^+$ 288.9476, 290.9456 ; found 288.9452, 290.9401.

3-acetyl-6,8-dichloro-2H-chromen-2-one (3e):



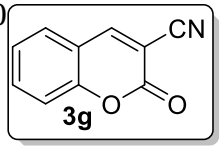
White solid; Yield: 91%; m. p. 169-171 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.38 (s, 1H), 7.69 (d, *J* = 2.32 Hz, 1H), 7.55 (d, *J* = 2.36 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 194.77, 157.61, 149.57, 145.79, 134.10, 130.20, 127.72, 126.08, 122.79, 120.04, 30.63; HRMS (ESI): calcd for $C_{11}H_6Cl_2O_3$ $[M + Na]^+$ 278.9592, 280.9562; found 278.9541, 280.9538.

2-acetyl-3H-benzo[f]chromen-3-one (3f):



Light yellow solid; Yield: 91%; m. p. 185-187 ^{0}C; ^{1}H NMR($CDCl_3$, 400 MHz) δ ppm 9.28 (s, 1H), 8.34 (d, *J* = 8.40 Hz, 1H), 8.09 (d, *J* = 9.04 Hz, 1H), 7.92 (d, *J* = 8.08 1H), 7.74 (t, *J* = 7.20 Hz, 1H), 7.61 (t, *J* = 7.80 Hz, 1H), 7.45 (d, *J* = 9.04 Hz, 1H), 2.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 195.55, 159.39, 156.10, 143.24, 136.27, 130.15, 129.78, 129.18, 126.61, 122.35, 121.64, 116.42, 112.71, 30.65; HRMS (ESI): calcd for $C_{15}H_{10}O_3$ $[M+Na]^+$ 261.0528; found 261.0504.

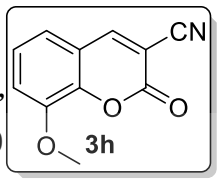
2-oxo-2H-chromene-3-carbonitrile (3g):



White solid; Yield: 92%; m. p. 181-183 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.26 (s, 1H), 7.721 (t, *J* = 7.64 Hz 1H), 7.60 (d, *J* = 8.04 Hz, 1H), 7.42-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ

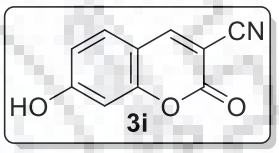
ppm 158.53, 154.67, 151.92, 135.66, 129.37, 125.80, 117.55, 117.21, 113.61, 103.61; HRMS (ESI): calcd for $C_{10}H_5NO_2$ $[M+Na]^+$ 194.0218; found 194.0212.

8-methoxy-2-oxo-2H-chromene-3-carbonitrile (3h):



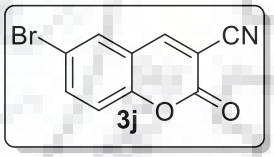
White solid; 86%; m. p. 224-226 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.20 (s, 1H), 7.49 (d, *J* = 7.72 Hz, 1H), 7.39 (t, *J* = 8.08 Hz, 1H), 7.09 (d, *J* = 8.24 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.52, 160.03, 155.08, 132.72, 130.30, 124.27, 120.14, 115.61, 114.61, 103.20, 55.52; HRMS (ESI): calcd for $C_{11}H_7NO_3$ $[M+Na]^+$ 224.0324; found 224.0308.

7-hydroxy-2-oxo-2H-chromene-3-carbonitrile(3i):



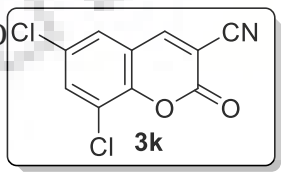
Light yellow solid; Yield: 80%; m. p. 247-248 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.59 (s, 1H), 8.19 (d, *J* = 8.56 Hz, 1H), 7.52 (s, 1H), 7.38 (d, *J* = 8.56 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 161.72, 149.86, 139.50, 137.34, 130.60, 130.43, 128.40, 128.09, 114.79, 106.45; HRMS (ESI): calcd for $C_{10}H_5NO_3$ $[M+Na]^+$ 210.0117; found 210.0104.

6-bromo-2-oxo-2H-chromene-3-carbonitrile (3j):



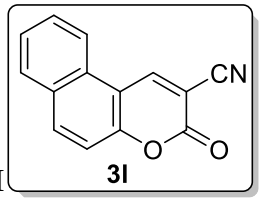
White solid; Yield: 85%; m. p. 196-198 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.43 (s, 1H), 7.76 (s, 1H), 7.28 (d, *J* = 9.32 Hz, 1H), 7.26 (d, *J* = 8.96 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.59, 155.93, 153.89, 147.01, 136.90, 131.48, 119.29, 118.49, 117.30, 99.86; HRMS (ESI): calcd for $C_{10}H_4BrNO_2$ $[M+Na]^+$ 271.9323, 273.9303; found 271.9315, 273.9301.

6,8-dichloro-2-oxo-2H-chromene-3-carbonitrile (3k):



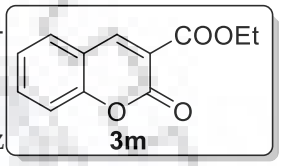
White solid; Yield: 92%; m. p. 166-168 ^{0}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 8.62 (s, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.76 (d, *J* = 2.36 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.20, 152.26, 149.06, 134.58, 129.53, 128.35, 121.94, 120.38, 114.54, 104.99; HRMS (ESI): calcd for $C_{10}H_3Cl_2NO_2$ $[M+Na]^+$ 261.9439, 263.9409; found 261.9416, 263.9402.

3-oxo-3H-benzo[f]chromene-2-carbonitrile (3l):



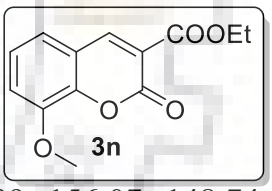
Light green solid; Yield: 91%; m. p. 295-297 ^{0}C; ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm 9.79 (s, 1H), 8.63 (d, *J* = 8.44, 1H), 8.38 (d, *J* = 9.08 Hz, 1H), 8.11 (d, *J* = 8.04 Hz, 1H), 7.81 (t, *J* = 7.28, 1H), 7.69 (t, *J* = 7.76 Hz, 1H), 7.64 (d, *J* = 9.08 Hz, 1H); ^{13}C NMR (DMSO d_6, 100 MHz) δ ppm 157.72, 155.54, 150.10, 137.69, 130.49, 129.90, 129.59, 129.30, 127.39, 123.06, 117.27, 115.55, 112.83, 101.30; HRMS (ESI): calcd for $C_{14}H_7NO_2$ $[M+Na]^+$ 244.0374; found 244.0347.

Ethyl 2-oxo-2H-chromene-3-carboxylate (3m):



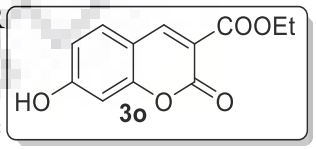
White solid; Yield: 90%; m. p. 90-92 ^{0}C; ^{1}H NMR (CDCl3, 400MHz) δ ppm 8.53 (s, 1H), 7.64 (q, *J* = 14.4 Hz, 2H), 7.34 (t, *J* = 7.92 Hz, 2H), 4.42 (q, *J* = 7.12 2H), 1.41 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.95, 156.62, 155.06, 148.47, 134.24, 129.42, 124.76, 118.24, 117.79, 116.67, 61.87, 14.13; HRMS (ESI): calcd for $C_{12}H_{10}O_4$ $[M+Na]^+$ 241.0477; found 241.0472.

Ethyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (3n):



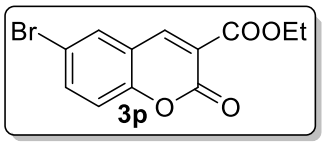
Light yellow solid; Yield: 87%; m. p. 90-91 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.46 (s, 1H), 7.19 (t, *J* = 7.84 Hz, 1H), 7.13 (d, *J* = 7.92 Hz, 2H), 4.37 (q, *J* = 7.14 Hz, 2H), 1.36 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.99, 156.07, 148.74, 146.95, 144.74, 124.62, 120.50, 118.37, 118.34, 115.71, 61.87, 56.21, 14.14; HRMS (ESI): calcd for $C_{13}H_{12}O_5$ $[M+Na]^+$ 271.0582; found 271.05474.

Ethyl 7-hydroxy-2-oxo-2H-chromene-3-carboxylate (3o):



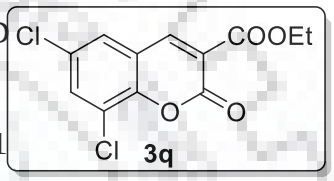
Light brown solid; Yield: 84%; m. p. 172-174 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.67 (s, 1H), 7.75 (d, *J* = 8.56 Hz, 1H), 6.84 (d, *J* = 8.52 Hz, 2H), 6.72 (s, 1H), 4.26 (q, *J* = 6.92 Hz, 2H), 1.29 (t, *J* = 6.88 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 164.69, 163.47, 157.65, 156.93, 149.96, 132.63, 114.56, 112.52, 110.91, 102.31, 61.32, 14.66; HRMS (ESI): calcd for $C_{12}H_{10}O_5$ $[M+Na]^+$ 257.0426; found 257.0409.

Ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (3p):



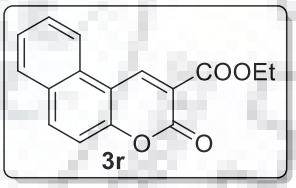
White solid; Yield: 84%; m. p. 164-165 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.44 (s, 1H), 7.76-7.71 (m, 2H), 7.26 (d, *J* = 8.76 Hz, 1H), 4.42 (q, *J* = 7.14 Hz, 2H), 1.41 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.57, 155.94, 153.88, 147.01, 136.89, 131.48, 119.38, 119.28, 118.48, 117.30, 62.17, 14.13; HRMS (ESI): calcd for $C_{12}H_9BrO_4$ $[M+Na]^+$ 318.9582, 320.9561; found 318.9546, 320.9528.

Ethyl 6,8-dichloro-2-oxo-2H-chromene-3-carboxylate (3q):



White solid; Yield: 88%; m. p. 204-206 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.41 (s, 1H), 7.68 (t, *J* = 2.32 Hz, 1H), 7.52 (d, *J* = 2.36 Hz, 2H), 4.42 (q, *J* = 7.14 Hz, 2H), 1.41 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.22, 156.77, 149.35, 146.67, 133.87, 129.87, 126.96, 122.71, 120.19, 119.54, 62.35, 14.11; HRMS (ESI): calcd for $C_{12}H_8Cl_2O_4$ $[M+Na]^+$ 308.9697, 310.9697; found 308.9676, 310.9668.

Ethyl 3-oxo-3H-benzo[f]chromene-2-carboxylate (3r):



Light brown solid; Yield: 92%; m. p. 115-117 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 9.27 (s, 1H), 8.28 (d, *J* = 8.40 Hz, 1H), 8.07 (d, *J* = 9.04 Hz, 1H), 7.91 (d, *J* = 8.04 Hz, 1H), 7.74 (t, *J* = 7.48 Hz, 1H), 7.60 (t, *J* = 7.56 Hz, 1H), 7.43 (d, *J* = 9.04 Hz, 1H), 4.48 (q, *J* = 7.03, 2H), 1.46 (t, *J* = 7.08, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 163.61, 156.96, 155.98, 144.54, 136.20, 130.22, 129.42, 129.32, 129.19, 126.64, 121.51, 116.68, 116.42, 112.30, 62.14, 14.40; HRMS (ESI): calcd for $C_{16}H_{12}O_4$ $[M+Na]^+$ 291.0633; found 291.0621.

2.8. References

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Chapter-3

Synthesis of 3-nitro-N, 2-diphenyl-2H-chromen-4-amines and their Pharmacological activities against Calcium/Calmodulin dependent Protein Kinase IV (CAMKIV) Inhibitors

Eur. J. Org. Chem. **2018**, 3454-3463
ChemistrySelect **2020**, *5*, 498-505

3.1. Introduction

In the nervous system, many intracellular responses to elevate calcium are mediated by calmodulin protein kinases (CaMKs). Their activities are initially modulated by binding Ca^{2+}/calmodulin (Ca^{2+}-CaM) and subsequently by protein phosphorylation. A multi-functional CaMKs such as CaMKII and CaM-K cascades (CaMKK, CaMKI, and CaMKIV) are present in most mammalian tissues, although they are highly abundant in brain, where phosphorylation take place and then regulate numerous protein substrates. Ca^{2+} sensitive calcium/calmodulin-dependent protein kinase IV (CaMKIV), plays a crucial role in the memory consolidation [1, 2] by neuronal communication [3, 4]. The CaMKIV is highly expressed in thymus [5], T-lymphocytes, chromatid body [6] and brain [7]. Intracellular Ca^{2+} signaling plays a critical role in a broad array of cell functions and is directly involved in the transcription, cell-cycle regulation, regulation of apoptosis and cell signaling processes via phosphorylation/dephosphorylation [8, 9]. Calcium ion with calmodulin (CaM) also forms a complex and regulates many functions by increasing its affinity for its targets [10]. The CaMKIV activation depends on calcium concentration. Therefore, it has been noticed that functions of the cell nucleus such as cell-proliferation, cell-cycle regulation, apoptosis and gene expression is perturb with changes in the intra cellular calcium signal. It has been also documented that cell survival and various cell death modalities like necrosis, apoptosis, anoikis, and necroptosis is regulated by intracellular Ca^{2+} process [11-13]. It has been reported that hydrogen peroxide (H_2O_2) induced oxidative stress, produces rapid increase of the CaMKIV cascade, thereby activates stimulated anti-apoptotic Akt and ERK signalling pathways in MCF-7 breast cancer cells in Jurkat T-lymphocyte [14,15]. Some reports are providing the over-expression of CaMKIV in lungs [16] and hepatocellular carcinoma [17]. Many evidences are suggesting that over-expressed CaMKIV also associated with other disorders such as ischemic stroke [18], Systemic lupus erythematosus [19] and infectious diseases [20]. Collectively, all these observations are suggesting that like other human kinases [21, 22], CaMKIV can also be a potential drug target [23].

2-Aryl-3-nitro-2H-chromenes and 2, 3, 4-trisubstituted chromenes are important building blocks for the synthesis of natural products, pharmaceutical molecules, and functional materials. They have also shown a number of biological properties, such as anti-viral, anti-oxidant [24], anti-tumor [25], anti-microbial [26] and anti-proliferative [27] activities (Figure 3.1).

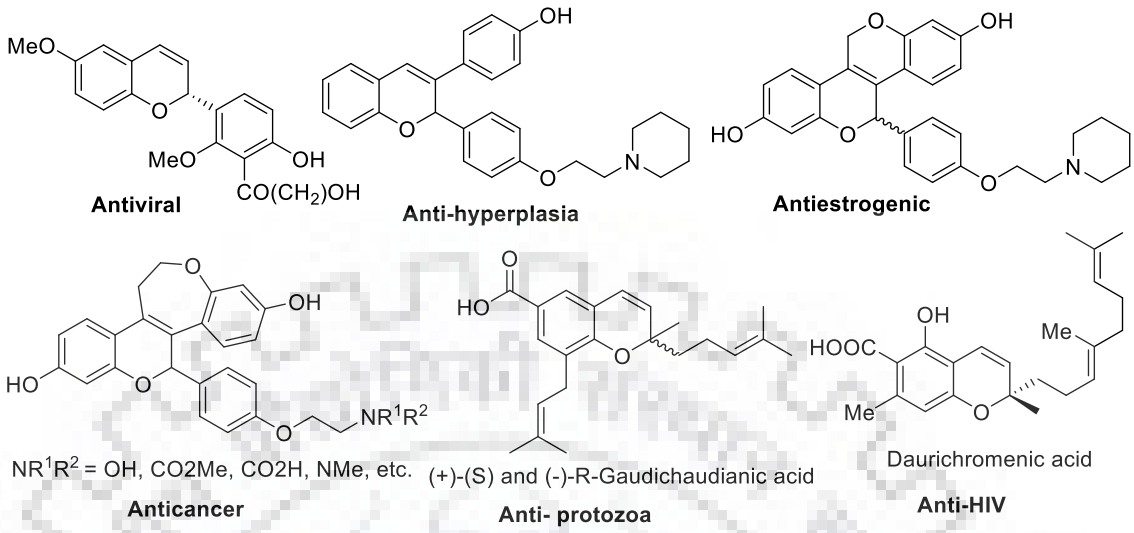
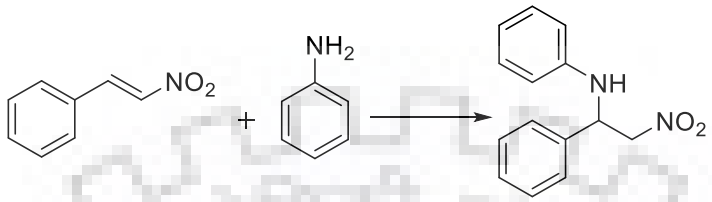


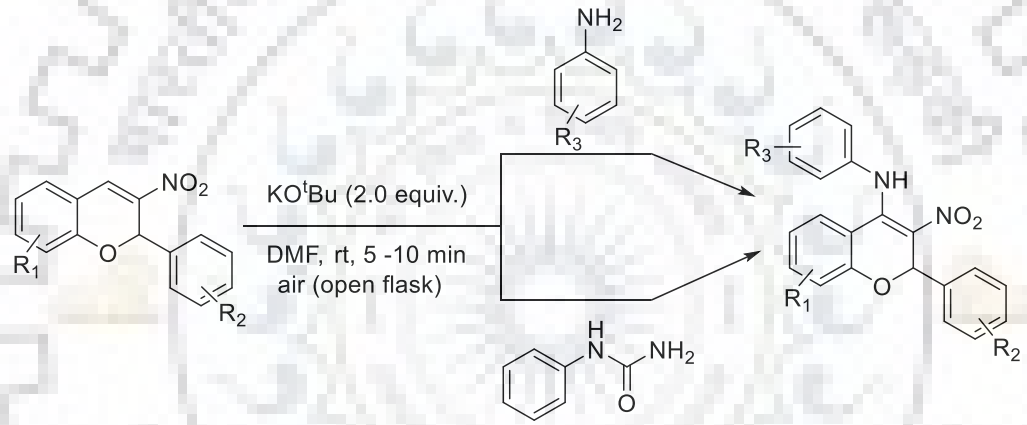
Figure 3.1. Some chromene-containing biologically active compounds

The development of efficient methods for the synthesis of this class of compounds has received great attention. For example, the nitro group of 3-nitro-2H-chromene derivatives can be transformed into various functional groups to produce new derivatives. This versatile nature of the nitro group has led it to be described as a "chemical chameleon" [28]. Similarly, inter- and intramolecular C–N bond formations are important in both academic and industrial chemistry due to the high prevalence of nitrogen-containing biologically active compounds [29]. Although Michael addition reactions of carbon based nucleophiles to α, β-unsaturated compounds for the formation of C–C bonds are well studied, the corresponding aza-Michael addition reactions of amines have received less attention [29c]. However, different catalyst systems (Pd and Cu combinations) have been reported for amination reactions of aryl halides for the construction of C–N bonds [30-44], and also oxidative C–H aminations with or without metal catalysts [45]. Stoichiometric amounts of palladium and copper salts are also known to activate aryl halides, but have limited scope to react with amine nucleophiles. Hence, the generation of significant amounts of palladium and copper salts as waste under harsh reaction conditions limits the synthetic utility of such procedures. Tu and co-workers reported a microwave-assisted direct amination of electron-rich aryl halides using KO^tBu in DMSO [46]. Recently, catalytic C–H bond activation by using Ru [47], Rh [48], and Pd [49, 50] was also accomplished for C–N bond formation. Additionally, $Fe(NO_3)_3 \cdot 9H_2O$-catalyzed aza-Michael addition reactions of *β*-nitrostyrene have been reported [51], and also the

Michael addition of aryl amines to *β*-nitrostyrenes has been developed under solvent-free or catalytic conditions in aqueous media (scheme 3.1) [52].



Scheme 3.1. Previous work



Scheme 3.2. This work

It has been found that the use of KO^{t}Bu in C–C and C–heteroatom bond formation is more efficient and environmentally friendly than transition-metal-catalyzed reactions [53]. Also, the KO^{t}Bu-mediated C–H hydroxylation of carbonyl compounds was recently reported to furnish α-hydroxy carbonyl compounds [54]. Furthermore, the intramolecular oxidative C(sp^3)–H amination of unprotected anilines using KO^{t}Bu, molecular oxygen, and DMF has been developed [45].

Herein, we report for the first time a versatile synthesis of 4-phenylamino-3-nitro-2-phenyl-2H-chromenes (68–86 %) by KO^{t}Bu-mediated aza-Michael addition of aromatic amines or N-phenylurea derivatives to 3-nitro-2-phenyl-2H-chromenes followed by aerobic dehydrogenation at 35-40 ^{0}C within 5-10 min (scheme 3.2). Which are efficiently bind to the human CaMKIV over-expressed in several cancers. We treated human hepatocyte carcinoma (HepG2) and human embryonic kidney (HEK293) cells with

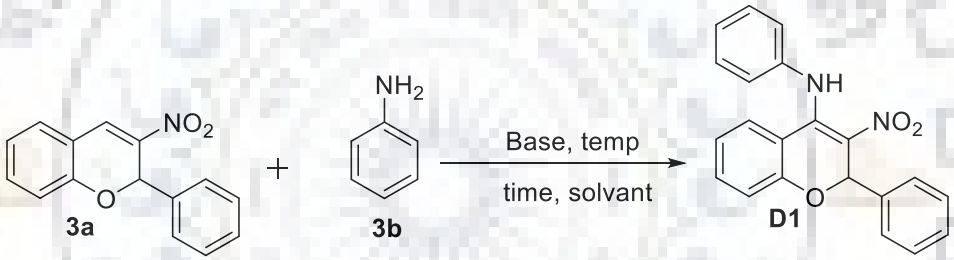
increasing concentration of the compounds. We found that these derivatives induce apoptosis in HepG2 cancer cell lines by inhibiting CaMKIV.

3.2. Chemistry

3.2.1. Results and discussion

Following the literature report [51], we commenced a model reaction of 3-nitro-2-phenyl-2H-chromene (**3a**) and aniline (**3b**) in the presence of $Fe(NO_3)_3.9H_2O$ for 5 h at 80 ^{0}C in 1,2-DCE solvent. The reaction failed to give the product **D1** and reactants **3a** and **3b** recovered quantitatively (Table 3.1, entry 1).

Table. 3.1. Optimization of conditions for the reaction of chromene **3a** and aniline **3b**.



Entry	Base (equiv)	Solvent	Time	Yield(%)[e]
1[a]	-	1,2 DCE	5h	NR
2[b]	-	ACN	10h	NR
3	K_2CO_3(2.0)	DMF	2h	NR
4	Cs_2CO_3(2.0)	DMF	2h	NR
5	LiO^tBu(2.0)	DMF	2h	57
6	KOH(2.0)	DMF	2h	36
7	NaOH(2.0)	DMF	2h	32
8	NaH(2.0)	DMF	2h	58
9	KH(2.0)	DMF	2h	65
10	KO^tBu(0.5)	DMF	20h	39
11	KO^tBu(1.0)	DMF	20h	64
12	KO^tBu(1.5)	DMF	20h	72
13	**KO^tBu(2.0)**	**DMF**	**10 min**	**82**
14	KO^tBu(3.0)	DMF	10 min	63
15[c]	KO^tBu(2.0)	DMF	2h	75
16	Et_3N(2.0)	DMF	5h	NR
17	Et_2NH(2.0)	DMF	5h	NR

18	Piperidine(2.0)	DMF	5h	NR
19	KO^{t}Bu(2.0)	DMSO	10 min	68
20	KO^{t}Bu(2.0)	DCM	14h	trace
21	KO^{t}Bu(2.0)	$CHCl_3$	14h	trace
22	KO^{t}Bu(2.0)	EtOH	12h	NR
23	KO^{t}Bu(2.0)	toluene	8h	46
24	KO^{t}Bu(2.0)	ACN	12h	64
25	KO^{t}Bu(2.0)	benzene	12h	25
26[d]	KO^{t}Bu(2.0)	DMF	10 min	82

Reaction condition: [a]$Fe(NO_3)_3.9H_2O$ at 80 ^{0}C, [b]$FeCl_3$ (20 mol%) + DDQ (2 equiv.) at 80 ^{0}C, [c]at 110 ^{0}C. [d]at 0 ^{0}C, [e]Isolated yields.

Then the reaction was performed by using catalytic amounts of anhydrous $FeCl_3$ and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as oxidizing reagent at 80 ^{0}C in ACN as solvent [45b], but again no product was obtained (Table 3.1, entry 2). We replaced both the $Fe(NO_3)_3 \cdot 9H_2O$ catalyst and 1,2-DCE with a base and DMF, respectively. Bases like K_2CO_3 and Cs_2CO_3 failed to give the product and the starting materials were recovered (Table 3.1, entries 3 and 4). Interestingly, the use of LiO^{t}Bu afforded the product **D1** in 57 % yield in DMF within 2 h (Table 3.1, entry 5). To optimize the reaction conditions for the synthesis of **D1**, the bases KO^{t}Bu, NaOH, KOH, NaH, KH, Et_2NH, Et_3N, and piperidine were screened (Table 3.1, entries 6-9). Hydride bases such as NaH and KH afforded good product yields (Table 3.1, entries 8 and 9), however, bases such as KOH and NaOH were less effective, giving lower yields (Table 3.1, entries 6 and 7). We also changed the molar ratio of the bases, for example, 0.5, 1.0, and 1.5 equivalents of KO^{t}Bu in DMF, which afforded the product in yields of 39, 64, and 72 %, respectively. However, the reactions were slow and gave incomplete conversions even after 20 h (Table 3.1, entries 10-12). When the base ratio was enhanced from 1.5 to 2.0 equivalents, the product yield improved to 82 % within 10 minutes (Table 3.1, entry 13). A further increase in base ratio (i.e., to 3.0 equiv.) gave an appreciably lower yield (Table 3.1, entry 14). Surprisingly, the reaction provided a lower yield at reflux temperature, and over a longer reaction time (Table 3.1, entry 15). We also tested different solvents, such as DMSO, DCM, $CHCl_3$, ethanol, toluene, CH_3CN, and benzene, in the reaction. Solvents like DCM, $CHCl_3$, and ethanol were found to be unsuitable for the reaction; in these solvents only trace amounts of the product **D1** were obtained (Table 3.1, entries 20-22). The reaction in

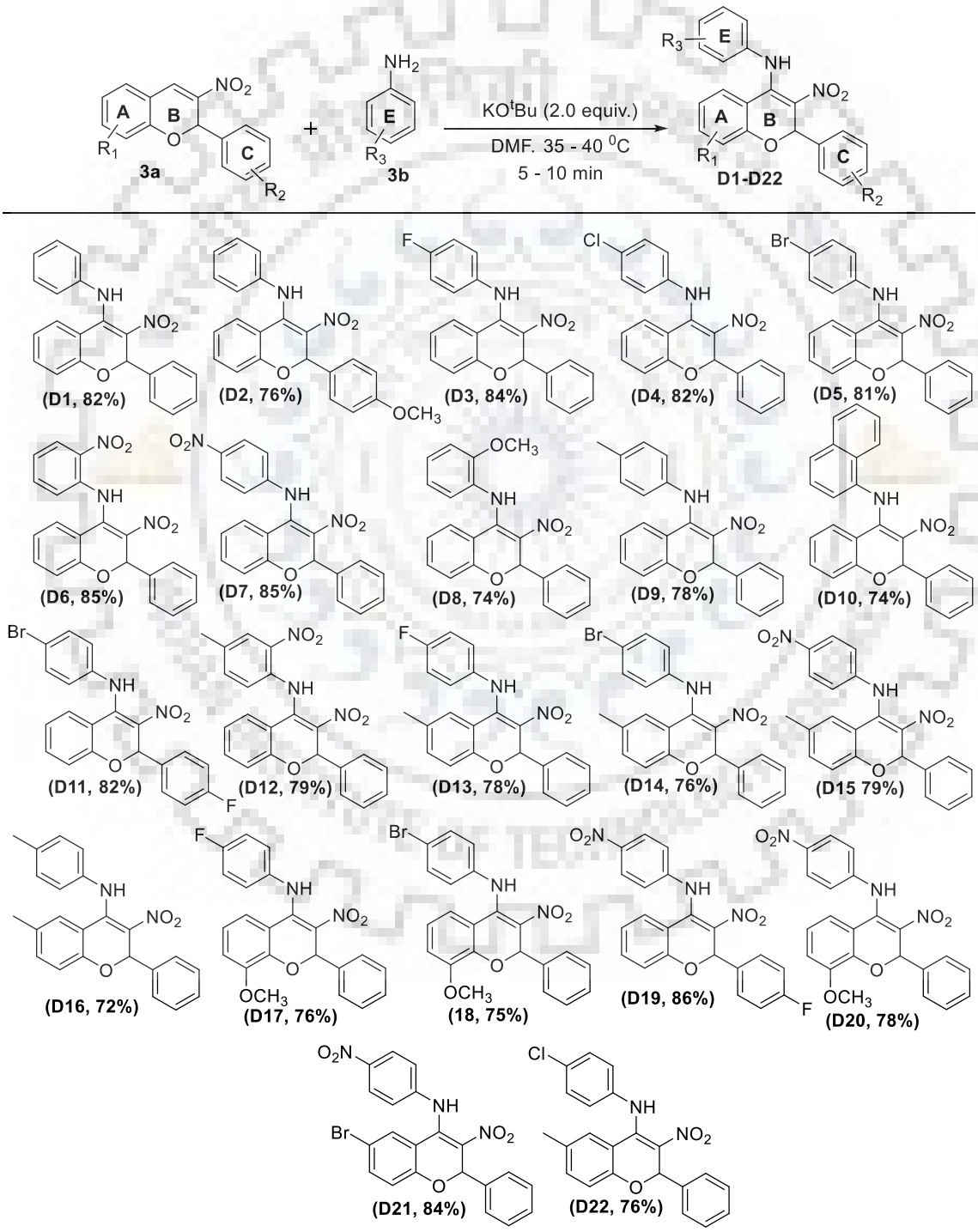
toluene afforded product **D1** in 46 % yield in 8 hours (Table 3.1, entry 23). With acetonitrile and benzene as solvents the product **D1** was furnished in yields of 64 and 25 %, respectively (Table 3.1, entries 24 and 25), whereas the use of DMSO gave a 68 % yield of **D1** within 10 min (Table 3.1, entry 19). Of the solvents tested, DMF was found to be the best in terms of yield and reaction time. Furthermore, lowering the temperature from 40 to 0 ^{0}C with KO^{t}Bu as base did not improve the yield of **D1** (Table 3.1, entry 26). Organic bases were ineffective, even at the elevated temperature of 110 °C (Table 3.1, entries 16-18). Thus, the best product yield of 82 % was obtained with 2.0 equivalents of the potassium salt KO^{t}Bu in DMF within 10 min at room temperature.

3.2.2. Substrate scope

With the optimized reaction conditions in hand, the substrate scope was explored by performing the reaction with a wide range of 3-nitro-2-phenyl-2H-chromenes and aniline derivatives to determine the effect of electronic and steric factors on the efficiency of the reaction protocol. It is noteworthy that the reaction tolerated diverse substituents on the 3-nitro-2-phenyl-2H-chromene and aniline. Much to our satisfaction, the electronic properties of aryl substituents bearing either electron withdrawing or -releasing groups were shown to have a notable effect on the efficiency of the reaction. The structures of the products were characterized by ^{1}H and ^{13}C NMR and IR spectroscopy and HRMS (see the Supporting Information). Furthermore, the structure of **D23** was established by X-ray crystallographic analysis. In more detail, we studied the scope and tolerance of the reaction with a series of substituents on rings A, C, and E. Under the optimal reaction conditions, the reaction of **3a** with **3b** without substituents on these rings smoothly proceeded to give **D1** within 10 minutes in 82 % yield (Scheme 3.3). We first studied the electronic effects of substituents on ring A, and found that electron-releasing groups like methyl and methoxy decreased the yields without gaining any advantage in terms of reaction time, but electron-withdrawing substituents like bromine on ring A favored the transformation with high yield. We also considered the electronic effect of substituents on ring C. An electron-releasing group such as the methoxy group decreased the yield of the product (**D2**), but in the case of para-fluoro substitution, there was a considerable increase in the yield without any improvement in the reaction time (**D11**). We further

extended our study to ring E; it was observed that there was a notable electronic effect on the yield of the product as well as the reaction time. Halogen-bearing anilines showed good reactivity and required less time (e.g., **D3**, **D4**, and **D5**).

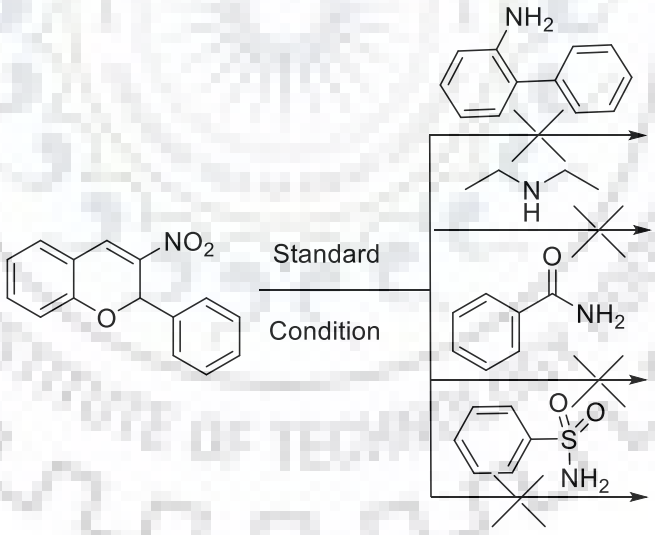
Scheme 3.3. Scope of 3-nitrochromine with aniline



[a]**Reaction conditions: 3a** (1.0 mmol), **3b** (1.0 mmol) and KO^{t}Bu (2.0 mmol) in DMF (5 mL) at 35-40 ^{0}C.

The enhanced yields of compounds **D6**, **D7**, and **D19** and lower reaction times are due to the presence of nitro groups on ring E. Furthermore, the yields of the products decreased with methyl and methoxy groups on ring E, for example, products **D8** and **D9**. The reaction of a disubstituted aniline containing both an electron-donating and -withdrawing group proceeded smoothly to give the corresponding product **D12** in 79 % yield in less than 10 minutes. 1-Naphthylamine is a more conjugated system and reacted smoothly to produce the corresponding product **D10** in less than 10 minutes (Scheme 3.3).

Similarly, steric factors play an important role in the reaction; ortho-and para substituted anilines reacted smoothly, but a sterically hindered aniline having a phenyl group at the ortho position did no undergo reaction either at 35-40 ^{0}C or at reflux temperature (Scheme 3.4). To extend our work, we also studied the possible reaction with aliphatic amines under the same reaction conditions, but no product was detected and the starting materials were isolated. Similarly, benzamide and benzene sulfonamide showed no reaction with 3-nitrochromene (Scheme 3.4).

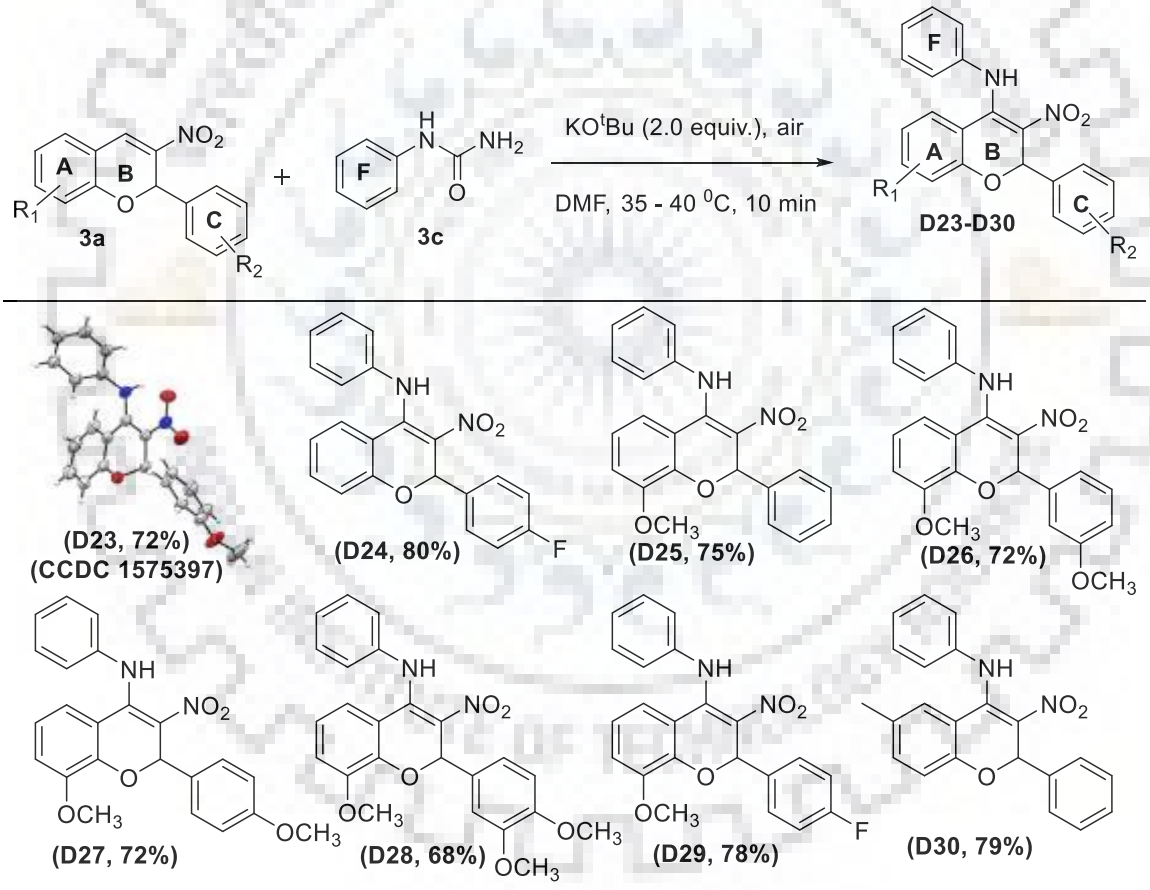


Scheme 3.4. Reaction with sterically hindered, aliphatic amine and amides.

According to a literature report [58], N-phenylurea undergoes hydrolysis to form aniline in a basic medium. Therefore, we turned our attention towards the scope and tolerance of the reactions of 3-nitro-2-phenylchromenes with urea **4a**. The reaction of **3a** with N-phenylurea (**4a**) under the optimal conditions furnished **D23** in 72 % yield in 10 minutes (Scheme 3.5). The reactions of N-phenylurea with other 3-nitrochromene derivatives

were also explored. It was found that the reactions proceeded quite smoothly under the optimized conditions with electron-donating groups on rings A and C decreasing the yields of the product (e.g., **D23**, **D25**, and **D30**). Similarly, the yields of the products decreased when the number of electron-donating groups was increased (**D26**, **D27**, and **D28**). In the case of fluoro substituents, the yields of the products increased (**D24** and **D29**) and the reactions were completed within 10 minutes. Comparing the amination reagents, aniline and N-phenylurea both gave similar yields, but in the cases of anilines bearing electron-withdrawing groups, the reaction times were reduced (Scheme 3.5).

Scheme 3.5. Scope of 3-nitrochromine with N-phenylurea

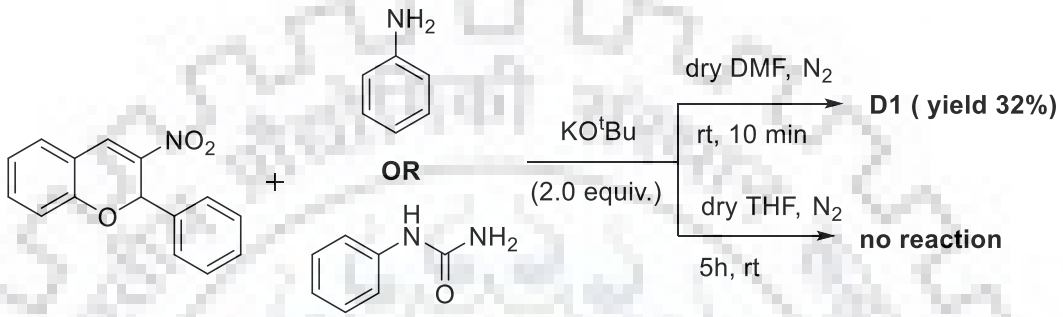


Reaction conditions: 3a (1.0 mmol), **3c** (1.0 mmol) and KO^{t}Bu (2.0 mmol) in DMF (5 mL) at 35-40 ^{0}C.

3.2.3. Solvent and inert atmosphere effects

Furthermore, to confirm the role of air and DMF as oxidant, the reactions of **3a** with aniline and N-phenylurea were performed under nitrogen, and the reactions provided a low yield (32 %) of the product **D1** in DMF. However, the same reaction in THF under

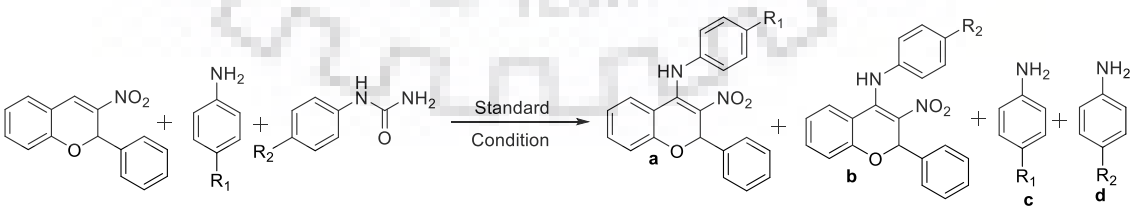
nitrogen gave no product (Scheme 3.6). It has been reported in the literature that DMSO can behave as an oxidant [58], Because the reaction in DMF also afforded a moderate yield of the product (32 %), we reasoned that it might also be acting as an oxidant in this reaction. The reaction was also performed in the presence of TEMPO, which led to the product **D1** in 80 % yield.



Scheme 3.6. Solvent and inert atmosphere effects.

3.2.4. Compare the reactivity of aniline and N-phenylurea

To compare the reactivity of aniline and N-phenylurea, we performed control experiments by treating 1 equivalent of the Michael acceptor with a mixture of aniline and urea, **1** equivalent each, under the standard reaction conditions. The product distribution showed that aniline reacted faster than N-phenylurea, affording the products **a** and **b** in yields of 52 and 12 % under conditions (**i**) and in yields of 53 and 10 %, respectively, under conditions (**ii**), along with unreacted anilines **c** and **d** in slightly different ratios (Scheme 3.7). This result also suggests that proton abstraction is not directly from urea.

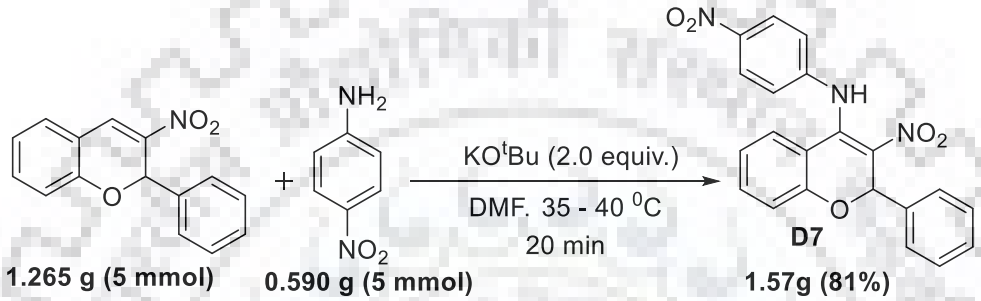


condition (i) $R_1 = CH_3$, $R_2 = H$,
yields = a = 52%, b = 12%, c = 32%, d = 68%
condition (ii) $R_1 = H$, $R_2 = CH_3$,
yields = a = 53%, b = 10%, c = 28%, d = 66%

Scheme 3.7. Competition between the Michael donors.

3.2.5. Gram scale synthesis

For more insight into the utility of this reaction, we carried out the gram-scale reaction of 3-nitro-2-phenyl-2*H*-chromene (**3a**) and *p*-nitroaniline under the same reaction conditions; the reaction proceeded smoothly to furnish **D7** in 81 % yield in 20 minutes (Scheme 3.8).



Scheme 3.8. Gram scale synthesis of **D7**

3.2.6. Single Crystal X-ray Analysis

Single crystal of products **D23** was obtained through slow evaporation (at room temperature) of a solution in dichloromethane-methanol. Single crystal data of products **D23** was collected on X-ray diffractometer using graphite monochromated MoKα radiation (λ = 0.7106 Å) at 293 K. Suitable size of crystals reported here were mounted on nylon CryoLoop. In the reduction of data Lorentz and polarization corrections, empirical absorption corrections were applied [59]. Crystal structures was solved by direct method. Structure solution, refinement and data output was carried out with the SHELXTL program [60, 61]. Non-hydrogen atoms were refined anisotropically. Refinements were carried out with a full matrix least squares method against F2 using the SHELXTL program. Hydrogen atoms were placed in calculated positions (C-H = 0.93 Å) and included as riding atoms with isotropic displacement parameters 1.2-1.5 times *Ueq* of the attached C atoms. Structure was examined using the ADDSYM sub-routine of PLATON 4 to 14 assures that no additional symmetry could be applied to the models.

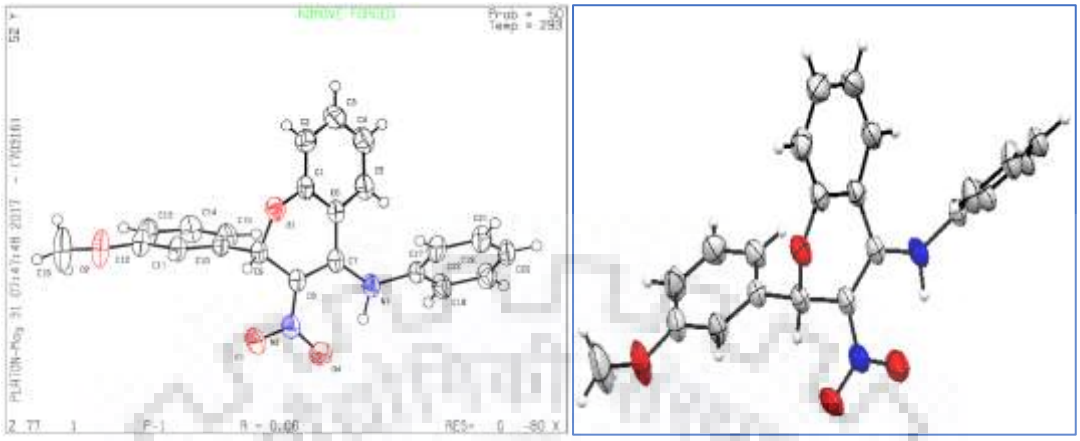


Figure 3.2. ORTEP: Plot of Compound **D23**

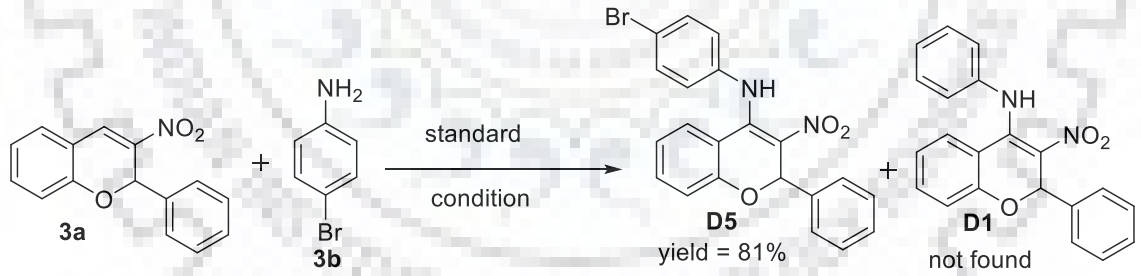
Table 3.2. Important crystal data of compound D23.

Empirical formula	$C_{22}\ H_{18}\ N_2\ O_4$
Formula weight	374.38
Temperature	293 K
Wavelength	0.71069
Space group	P -1 P-1
-*Unit cell dimensions	a=9.566(5)A^o α = 83.162
	b=9.674(5)A^o β = 72.653
	c=10.988(5)A^{o}γ = 74.893
Volume	936.1(8)
Z	2
Density (calculated)	1.328 g/cm^3
Absorption coefficient (Mu)	0.093 mm^{-1}
F(000)	392.0
h,k,l_{max}	12,12,14
N_{ref}	4688
Data completeness	0.992
Absorption correction	MULTI-SCAN
$Theta_{max}$	28.360
Refinement method	Full-matrix least-squares on F^2
R(reflections)	0.0574(3534)
wR2(reflections)	0.2090(4652)

3.2.7. Mechanistic study

Based on the above results and previous literature reports [58, 62], we explored the mechanism for the formation of **D1** from aniline and N-phenylurea under basic conditions. In a reaction without 3-nitro-2-phenyl-2H-chromene we found that N-phenylurea and KO^{t}Bu in DMF with stirring at room temperature gave aniline, which was confirmed by ^{1}H and ^{13}C NMR spectroscopy. However, N-phenylurea was not converted into aniline without the base. This proves that the abstraction of protons from aniline and N-phenylurea requires KO^{t}Bu, which gives less nucleophilic amine anions (soft nucleophile) due to resonance stabilization that can then undergo aza-Michael addition to reactant **3a**. Subsequent aerobic dehydrogenation in an open-flask reaction would give the product **D1** (see Scheme 3.10 below) [55, 56].

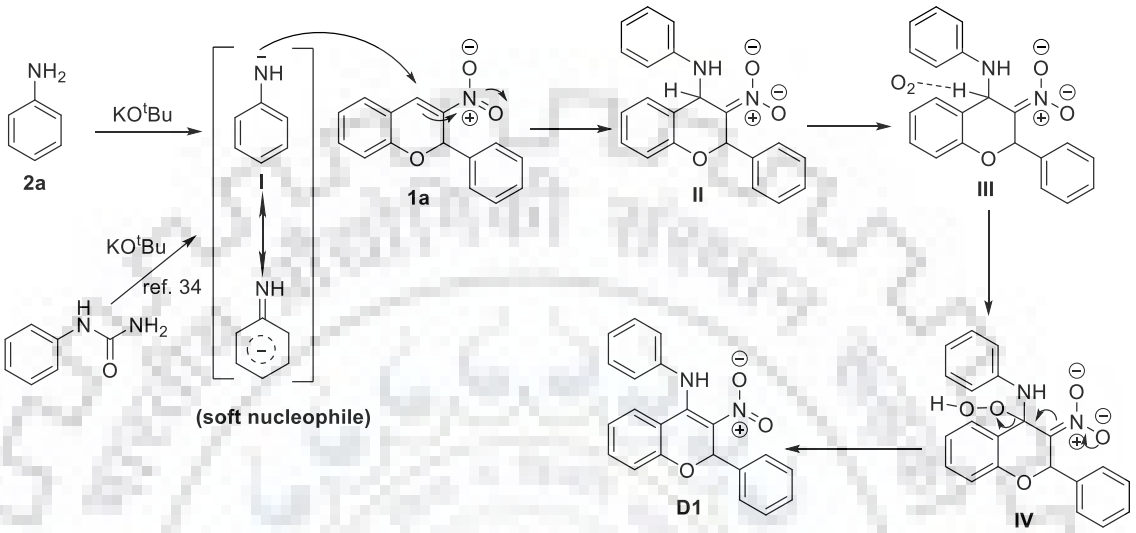
We also performed additional mechanistic studies, in which the reaction between 4-bromoaniline (**3b**) and 3-nitrochromene **3a** was performed under the standard reaction conditions to investigate the possibility of these reagents undergoing a single-electron transfer (SET) or other mechanisms (Scheme 3.9).



Scheme 3.9. Prediction of reaction path by halogen substrate

It was found that only product **D5** was formed, not the dehalogenated product **D1** [45, 57]. Therefore we can say that the reaction path follows a non-free-radical mechanism. Based on the results and literature studies mentioned above [58] a possible mechanism for the formation of **D1** was proposed (Scheme 3.10). The abstraction of a proton from aniline or N-phenylurea by KO^{t}Bu leads to aniline anion **I** (soft nucleophile), which reacts with **3a** to form intermediate **II**. Interaction of atmospheric oxygen with the hydrogen as shown in transition state **III** could result in transfer of the hydrogen to oxygen, leading to

a hydroperoxide radical and the carbon-centered radical of intermediate **IV**, which upon combination yield the desired product [62].



Scheme 3.10. Proposed mechanism

3.3. Biology

3.3.1. Molecular docking

The structure coordinates of CaMKIV was taken from protein data bank (PDB ID: 2 W4O). The molecular docking of CaMKIV with respective ligands was carried out using Autodock (version 4.2) [63a]. The standard docking protocol was used as described earlier [63b]. The final docked complex was used for structure analysis and binding energy prediction. Molecular docking was used to see the binding residues and type of interactions offered by binding site residues of CaMKIV to each of the selected compounds. The results of docking showed that both of the molecules occupy the same active site cavity of CaMKIV and interacts through different type of interactions (Figure 3.3). Compound **D19** forms two hydrogen bonds, one with Phe186 and one with Gly187. Besides hydrogen bonds, it also interacts with Val60, Val121, Ala73, Leu52, Leu118, Leu171, Glu125, Gly53, Lys75 and Asn169through several Van der Waals and electrostatic interactions with -8.40 kcal/mol of binding free energy. While the complex of CaMKIV with compound **D22** was stabilized by one hydrogen bond, exist with Gly55.

Other residues of CaMKIV that interacts with compound **D22** are Leu52, Gly53, Gly55, Ala56, Val60, Glu168 and Leu171. The binding free energy of CaMKIV compound **D22** complex is -8.00 kcal/mol. These results clearly suggested that the compounds **D19** and **D22** form stable complex with CaMKIV and this binding might be responsible for their inhibition potential.

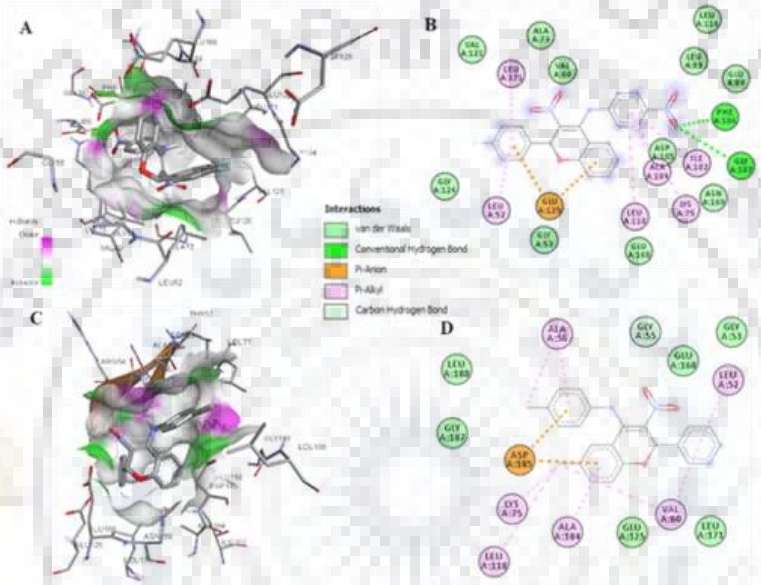


Figure 3.3. Molecular docking studies of selected compounds with CaMKIV: Three-dimensional focused view of CaMKIV binding pocket with (A) compound **D19**, (C) compound **D22** shows the hydrogen bond donoracceptor residues. Two-dimensional presentation of binding pose of CaMKIV with (B) compound **D19**, (D) compound **D22**. Residues involved in van der Waals interactions, hydrogen bonding, charge or polar interactions are represented by respective colour in inset.

3.3.2. Binding studies using fluorescence spectroscopy

Fluorescence quenching experiments were carried out on Cary Eclipse fluorescence spectrophotometer (Agilent technologies) using 10 mm quartz cuvette. The tryptophan fluorescence emission spectrum of CaMKIV (6 µM in 20 mM phosphate buffer, pH 7.4) was recorded in the range of 290-400 nm by keeping the excitation wavelength constant at 280 nm in the presence of various concentrations of ligand. The excitation and emission slit widths were kept at 5 nm. Binding studies of synthesized molecules (ligands) with the CaMKIV were performed using fluorescence spectroscopy. 5 µM of CaMKIV was titrated by the successive addition of 5.0 mM stock solution of ligands whose

concentrations were varied from 0 to 25 μM. Figures 3.4, 3.5 and 3.6 show the effect of three ligands (**D19**, **D12** and **D22**) on the fluorescence emission spectra of CaMKIV at 298 K respectively. The fluorescence intensity of CaMKIV at emission maxima was gradually quenched when titrated with increasing concentrations of ligands, while ligands display no intrinsic fluorescence in this range. This observation suggests that the compounds (**D19**, **D12** and **D22**) show binding interaction with the protein. The fluorescence intensity at λ_{max} was plotted against [ligand] and then modified Stern-Volmer equation (Eq. 1) was used to derive binding parameters viz., binding constant (Kb) and number of binding sites (n) per molecule of protein for ligand – CaMKIV system (Table 3.3).

log (F0-F/F) = log Kb + n log [Q]…….(Eq. 1)

Out of the three compounds tested, **D19** showed the maximum binding affinity for the CaMKIV (8.69 × 10-4 M-1), followed by **D12** (5.62 × 10-3 M-1) and **D22** (4.39× 10-2 M-1).

Table 3.3. Binding parameters of CaMKIV-ligand interaction.

Ligand	Binding Constant, Kb (M-1)	Number of binding sites, n
D19	8.69 × 10 -4 ± 0.22	1 ± 0.04
D12	5.62 × 10 -3 ± 0.20	0.8 ± 0.04
D22	4.39× 10 -2 ± 0.16	0.62 ± 0.03

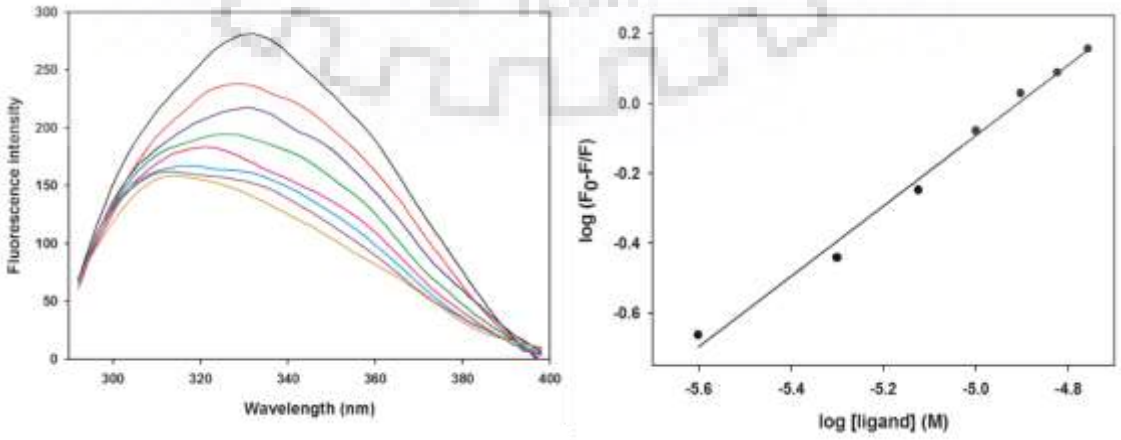


Figure 3.4. Fluorescence binding study of compound **D19** with the CaMKIV. **(A)**. Fluorescence spectra of CaMKIV (6 µM) with increasing concentrations of ligand 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 µM (from top to bottom) at pH 7.4. The protein was excited at 280 nm and emission spectra were recorded in the range of 290-400 nm **(B).** Modified Stern-Volmer plot for tryptophan quenching of CaMKIV by compound **D19** used for the calculation of binding affinity.

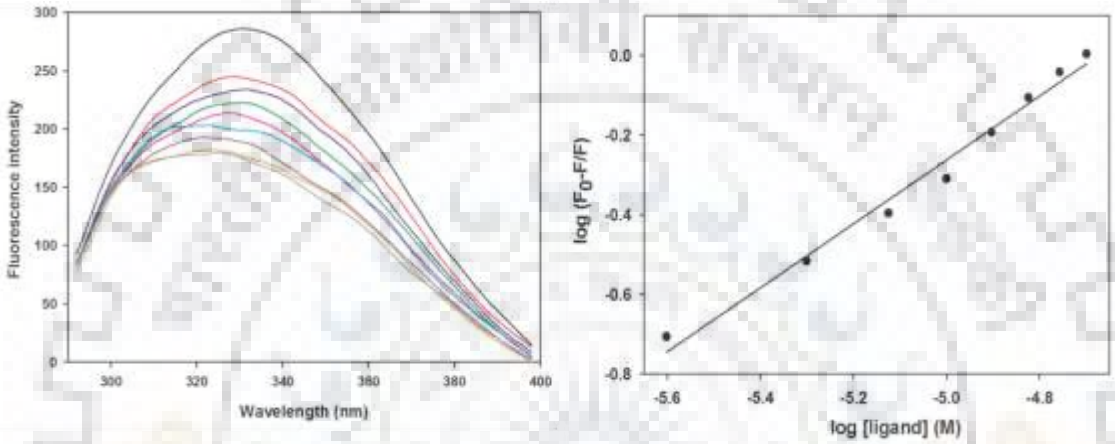


Figure 3.5. Fluorescence binding study of compound **D12** with the CaMKIV. **(A)**. Fluorescence spectra of CaMKIV (6 µM) with increasing concentrations of ligand 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5 µM (from top to bottom) at pH 7.4. The protein was excited at 280 nm and emission spectra were recorded in the range of 290-400 nm **(B).** Modified Stern-Volmer plot for tryptophan quenching of CaMKIV by compound **D12** used for the calculation of binding affinity.

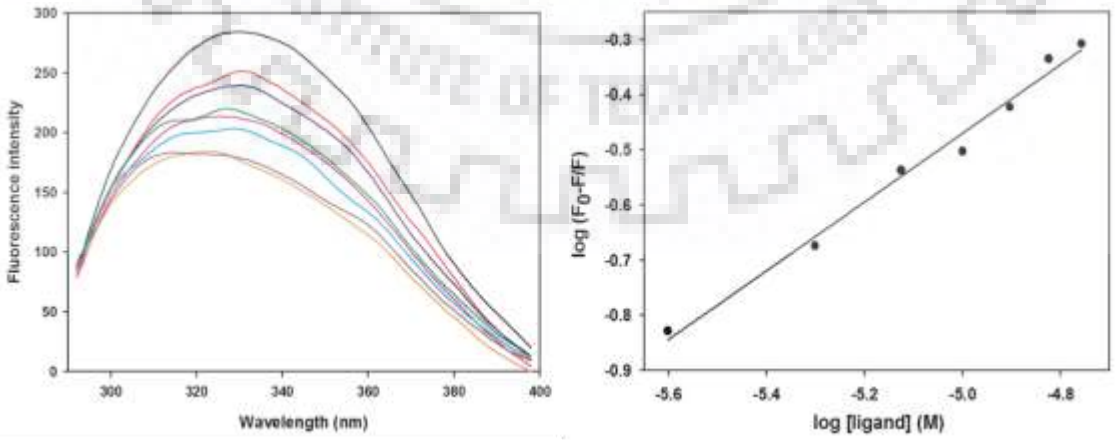


Figure 3.6. Fluorescence binding study of compound **D22** with the CaMKIV. **(A)**. Fluorescence spectra of CaMKIV (6 µM) with increasing concentrations of 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 µM (from top to bottom) at pH 7.4. The protein was excited at 280 nm and emission spectra were recorded in the range of 290-400 nm **(B).**

Modified Stern-Volmer plot for tryptophan quenching of CaMKIV by compound **D22** used for the calculation of binding affinity.

3.3.3. Kinase inhibition assay

Activity of purified CaMKIV was carried out using Malachite Green based (Biomol Green reagent, Enzo Life Sciences) microtitre-plate assay as described previously [64]. CaMKIV (250 ng) and ATP (20 μM) were incubated for 15 min at 25 ^{0}C in the presence of increasing concentrations (0 to 25 μM) of selected compounds. After 15 min incubation, the enzyme-inhibitor reaction was stopped by the adding 100 μl of Biomol Green reagent. The absorbance of ending reaction products was taken at 620 nm on a multi-plate ELISA reader (Bio-Rad). Inorganic phosphate standard curve was used to quantify the hydrolyzed phosphate, as supplied by the manufacturer (Biomol Green reagent, Enzo Life Sciences).

3.3.4. Cell culture and cell viability assay

HEK-293 and HepG2 cell lines were maintained in DMEM medium supplemented with 10% heat-inactivated fetal bovine serum (Gibco) and 1% penicillin, streptomycin solution (Gibco), in a 5% CO_2 humidified incubator at 37 ^{0}C. In order to see the effect of selected compounds on cell viability and proliferation, calorimetry based MTT assay was used. [65] Briefly, 8000–9000 cells/well (HEK293 and HepG2 cells) were seeded in a 96-well plate and allowed to grow for 24 h. On the next day, the cells were dosed with increasing concentrations (1–200 μM) of selected synthesized compounds for 48 h at 37 ^{0}C in a CO_2 incubator. Following the treatment time, ~20 μl of MTT solution (from 5 mg/ml stock solution in phosphate buffer saline, pH 7.4) was dispensed to each well and plates were incubated additionally for 4-5 h at 37 ^{0}C in the CO_2 incubator.

The supernatant was removed and the coloured formazan crystal was dissolved by adding 150 μl of DMSO. After proper shaking of plates on an orbital shaker, the absorbance (A) of end product was recorded at 570 nm on a multi-plate ELISA reader (Bio-Rad). The percentage cell viability was calculated and used to measure the IC_{50} (50% inhibitory concentration) for each of studied compound. For cell viability studies paclitaxel has been used as positive control.

3.3.5. Cell apoptosis assay

To study the apoptotic potential of compound **D19** and compound **D22**, annexin-V staining was used as per previous protocols [66, 67]. In brief, HepG2 cells were incubated with IC_{50} dose of compound **D19** and compound **D22** for 48 h at 37 ^{0}C, in a 5% CO_2 humidified incubator. The cells treated with media were used as control cells. After 24 h incubation, approximately 2.0-2.5 x 106 cells collected by trypsinization. Then collected cells were washed twice with 5-7 ml of PBS. Followed the washing, staining of cells were performed with FITC labelled Annexin-V antibodies with the help of FITC-Annexin-V kit by following the manufacturer's protocols (BD-Biosciences, USA). Nearly, 10,000 events were investigated for each sample on BD LSR II Flow Cytometry Analyzer and Flow Jo.

3.3.6. Kinase assay

Firstly, the synthesized compounds were screened with CaMKIV by using fluorescence based binding assay. It was found that out of all the synthesized compounds, three compounds (**D12**, **D19** and **D22**) show significant binding with CaMKIV. So, to further study the inhibitory potential of these selected compounds, enzyme assay of CaMKIV was carried out with increasing concentrations of compounds **D12**, **D19** and **D22** (0-25 μM). The enzyme inhibition studies shows that in the studied concentration range only compound **D19** and **D22** inhibits CaMKIV. The IC_{50} value (50% of ATPase activity for compounds **D19** and **D22** was estimated as 12.22±1.12 μM and 16.10±1.30 μM respectively (Figure 3.7). These results showed that compounds **D19** and **D22** inhibit CaMKIV and considered as possible inhibitor for CaMKIV.

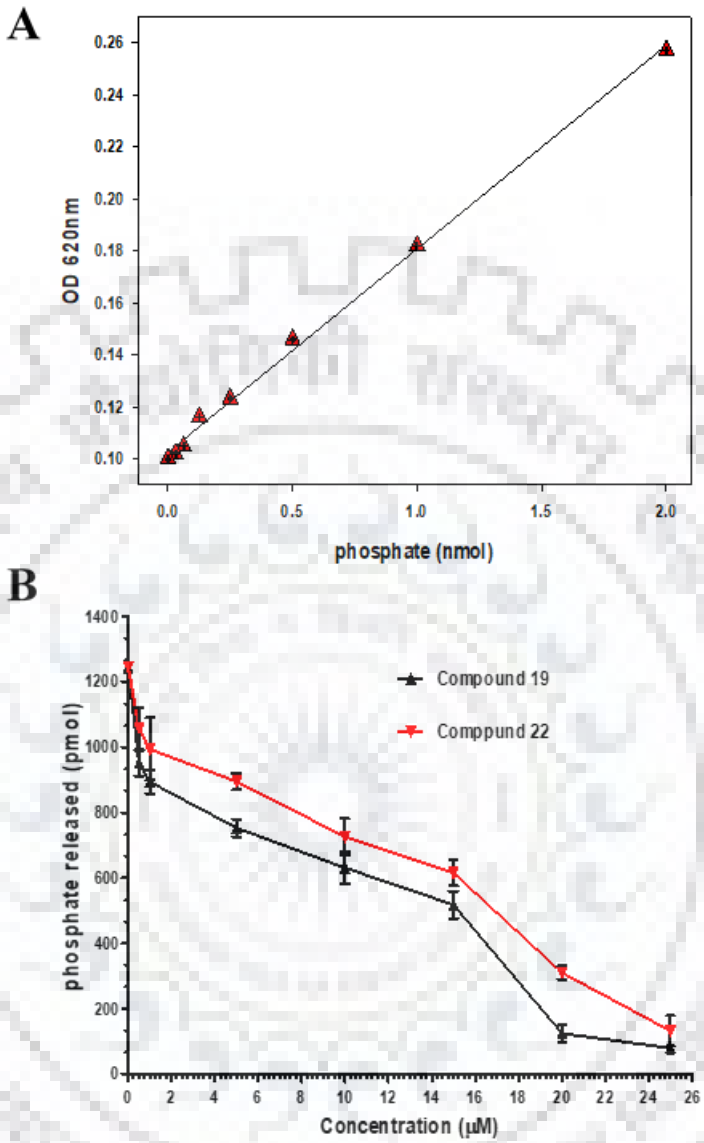


Figure 3.7. CaMKIV enzyme activity profile of selected compounds: (A) Standard phosphate hydrolysis curve; used to quantify the hydrolyzed phosphate released as a result of kinase activity of CaMKIV. (B) Enzyme inhibition (% hydrolysis of phosphate) with increasing concentrations of compound **D19** and **D22** as estimated by comparing with standard phosphate hydrolysis curve.

3.3.7. Cell proliferation assay

On the basis of binding and enzyme activity studies, it was found that compounds **D19** and **D22** inhibit CaMKIV, so these compounds were further evaluated for their cell growth inhibitory/cytotoxicity potential on Human heptoma cells (HepG2), and Human embryonic kidney cells (HEK293) by MTT assay. In case of HEK293 cells, compounds

D19 and **D22** were screened in 0-200 μM concentration range for 24 and 48 h. Where as in case of HepG2 cells, the compounds **D19** and **D22** were screened in 0-100 μM concentration range for 48 h (Figure. 3.8).

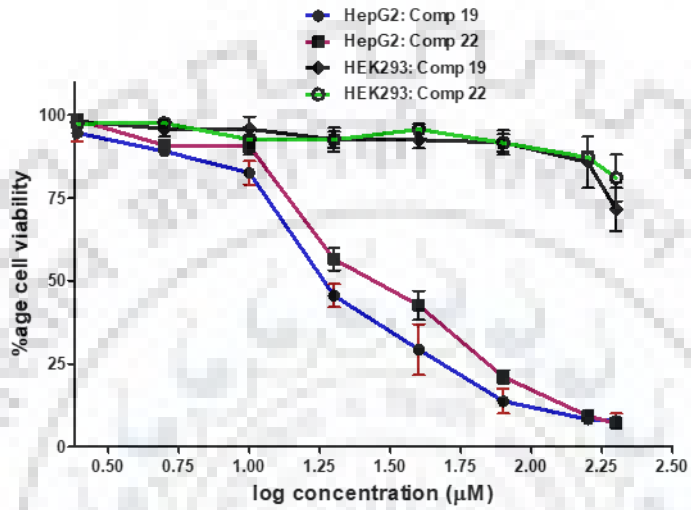


Figure 3.8. Cell viability studies. Outcome of compound **D19** and **D22** treatment on the viabilities of HEK293 and HepG2 cells. Cells were treated with increasing concentrations of compounds **D19** and **D22** for 48 h. Cell viabilities were estimated as the percentage of number of viable cells to that of the control. Each data point shown is the mean ± SD from n=3.

Cytotoxicity results performed on HEK293 cells had shown that in the studied concentration range compounds **D19** and **D22** do not inhibits the growth of HEK293 cells, only very less inhibition was observed after 100 μM (Figure 3.8). But in case of HepG2 cells, compounds **D19** and **D22** inhibits cell proliferation in a concentration dependent manner. The IC_{50} values of compounds **D19** and **D22** was 18.33±1.12 and 26.22 ±1.30 μM respectively. These results suggested that compounds **D19** and **D22** are non-toxic to normal cells and specifically inhibits the proliferation of cancerous cells.

3.3.8. Apoptosis assay

In order to examine whether the decrease observed in cell growth through MTT assay was apoptosis driven or not, HepG2 cells were treated with compounds **D19** and **D22** at their respective of IC_{50} concentrations for 48 h. After 24 h treatment the cells were processed, stained with Annexin V/7AAD and analyzed by flow cytometry. Apoptosis is

the process of programmed cell death and large number anti-cancer drugs/similar synthetic compounds have been reported to inhibit cell have been reported to inhibit cell proliferation by activating apoptosis.[65, 67-69] CaMKIV overexpression also supports the growth of cancerous cells, and inhibition of CaMKIV also leads to apoptosis induction [70]. Thus apoptosis induction was examined.

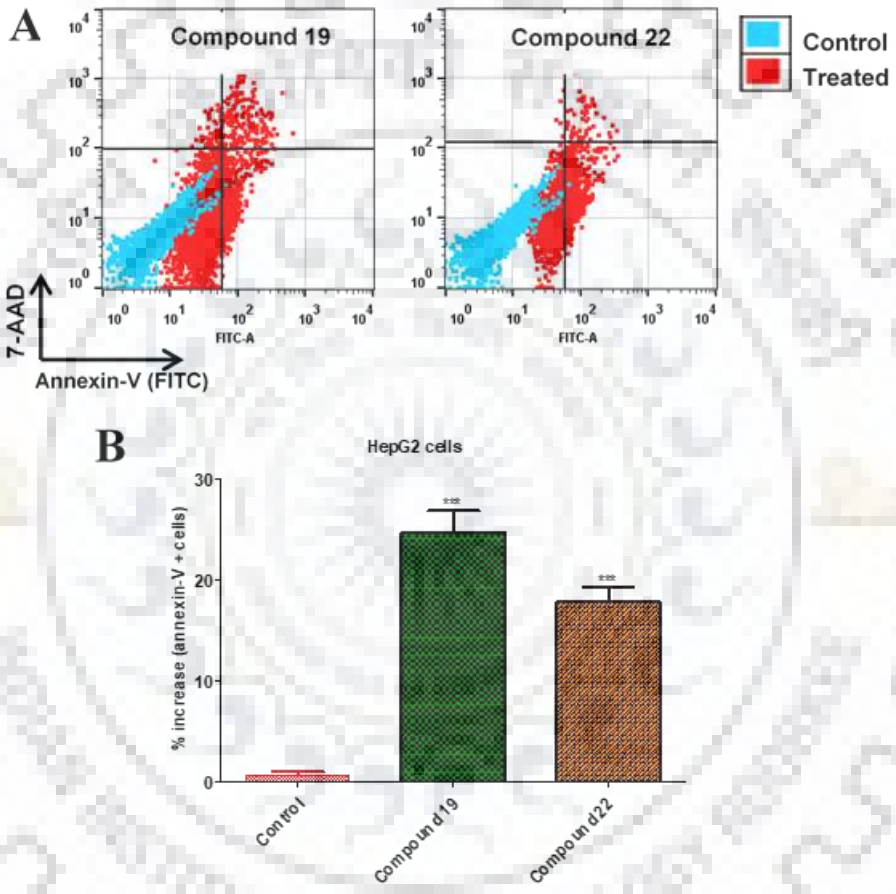


Figure 3.9. Apoptosis studies. (A) Annexin-V staining of HepG2 cells; cells were incubated with IC_{50} concentrations of compounds **D19** and **D22** for 48 h. Cells were stained with FITC labelled Annexin-V and quantified by flow cytometry. Representative images showing FITC-Annexin-V positive cells. (B) Bar graph representation of HepG2 cells that showed the percentage of apoptotic cells for duplicate measurements ± SD.**p < 0.001, compared with the control (untreated cells). Statistical analysis was done using t-test for unpaired samples. For anticancer activities doxorubicin has been taken as positive control.

3.4. Conclusion

We have developed an efficient KO^{t}Bu-mediated aza-Michael addition reaction between anilines or N-phenylurea derivatives (soft nucleophiles) and 3-nitro-2-phenyl-2H-chromenes under mild transition-metal-free reaction conditions. This method provided good-to-excellent product yields (68–86 %) after sequential aerobic dehydrogenation. The reaction has a number of advantages over existing procedures, for example, it is inexpensive, has a shorter reaction time, and tolerates various functional groups under mild reaction conditions and screened for their calcium/cadmodulin-dependent protein kinase type IV (CaMKIV) enzyme inhibitors, cytotoxicity and anti-proliferative effects in the human liver cancer cell (HepG2). Among the synthesized compound, the IC_{50} value (50% of ATPase activity) for compounds **D19** and **D22** was estimated as 12.22 ±1.12 μM and 16.10 ±1.30 μM respectively. Then fluorescence binding and dot blot assay of these compounds were found in μM range, indicating a better binding affinity. In vitro study of these compounds against cancerous cells (HepG2) inhibited the cell viability, induced apoptosis and lowered the tau-phosphorylation. Cell viability studies of compounds gave the IC_{50} values of compounds **D19** and **D22** was 18.33±1.12 and 26.22±1.30 μM respectively. These results suggested that compounds **D19** and **D22** are non-toxic to normal cells and specifically inhibits the proliferation of cancerous cells.

3.5. Experimental Section

3.5.1. General information

Unless otherwise noted, chemicals were purchased from commercial suppliers at the highest purity available and were used without further purification. 3-Nitro-2 phenyl-2H-chromene derivatives were prepared by the following literature methods [71-73]. TLC was performed on 0.25 mm silica gel plates (60F-254) using UV light as the visualizing agent. Silica gel (100-200 mesh) was used for column chromatography. Melting points were determined with a capillary point apparatus equipped with a digital thermometer. IR spectra were recorded with a Nicolet FT-IR spectrometer. NMR spectra were recorded with Jeol ECX400 MHz and Bruker spectrospin DPX 500 MHz spectrometers. Chemical shifts (δ) are reported in parts

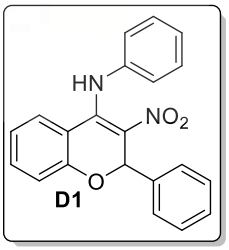
per million (ppm) and coupling constants are expressed in Hz. ^{1}H NMR chemical shifts are given relative to residual chloroform (δ = 7.26 ppm) or DMSO (δ = 2.5 ppm) in deuteriated solvent or with tetramethylsilane (TMS, δ = 0.00 ppm) as internal standard. ^{13}C NMR spectra are referenced to $CDCl_3$ (δ = 77.0274 ppm, middle peak) and DMSO d_6 (δ = 39.5 ppm, middle peak). The following abbreviations denote the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets. HRMS were recorded with a micro TOF-Q analyzer spectrometer in electrospray mode.

3.5.2. General procedure

Aniline or N-phenylurea (1.0 mmol) and potassium tert-butoxide (2.0 mmol) were added to a stirred solution of 3-nitro-2-diphenyl-2H-chromene derivative (1.0 mmol) in DMF (5 mL) and the mixture was stirred at 35-40 ^{0}C for an appropriate time. After completion of the reaction, as shown by TLC, the mixture was poured into cold ice/water and neutralized carefully using 1 N hydrochloric acid (30 mL), which precipitated product. The product was filtered and washed with water under vacuum. The crude reaction mixture was purified by column chromatography on silica gel (100–200 mesh) using ethyl acetate/hexanes (30:70) as the eluting system to afford the desired product as a yellow crystalline solid.

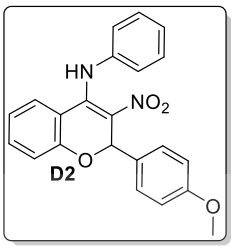
3.6. Characterization data

3-Nitro-N,2-diphenyl-2H-chromen-4-amine (D1):



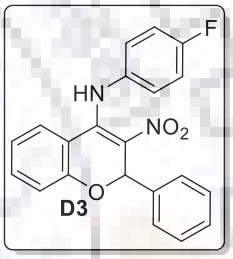
Yellow crystalline solid; Yield: 282 mg (82 %); m. p. 171.8-172.6 ^{0}C; FTIR (KBr): $\tilde{\nu}$ = 3443, 3126, 1818, 1601, 1555, 1359, 1226, 959 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.04 (s, 1H), 7.33 (d, *J* = 7.5 Hz , 2H), 7.29 (q, *J* = 7.5 Hz, 3H), 7.23 (d, *J* = 6.4 Hz, 3H), 7.18 (d, *J* = 7. 7 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.81 (s, 1H), 6.61 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.7, 147.4, 139.2, 136.9, 133.8, 129.60, 129.3, 128.6, 128.4, 127.2, 126.6, 124.6, 121.3, 121.3, 119.6, 115.5, 74.4; HRMS (EI): calcd. for $C_{21}H_{16}N_2O_3$ $[M+Na]^+$ 367.1059; found 367.1081.

2-(4-Methoxyphenyl)-3-nitro-N-phenyl-2H-chromen-4-amine (D2):



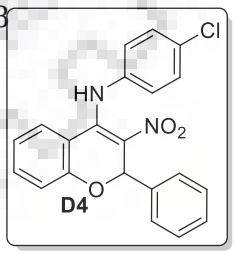
Yellow crystalline solid; Yield: 284 mg (76 %); m. p. 149.6-150.7 ^{0}C; FTIR (KBr): ν˜ = 3446, 3064, 2838, 1616, 1558, 1364, 1243, 1156, 98 8 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm12.02 (s, 1H), 7.31 (t, *J* = 7 .6 Hz, 2H), 7.19 (q, *J* = 6.9 Hz, 4H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.73 (t, *J* = 4.7 Hz, 3H), 6.60 (t, *J* = 7.6 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm159.8, 156.8, 147.5, 139.3, 134, 129.6, 129.3, 128.9, 128.7, 126.7, 124.6, 121.5, 121.3, 119.8, 115.7, 113.8, 74.3, 55.6; HRMS (EI): calcd. for $C_{22}H_{18}N_2O_4$ $[M+Na]^+$ 397.1164; found 397.1172.

N-(4-Fluorophenyl)-3-nitro-2-phenyl-2H-chromen-4-amine (D3):



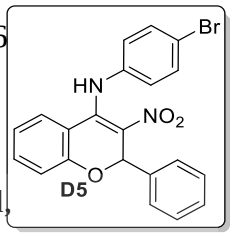
Yellow crystalline solid. Yield; 304 mg (84 %); m. p. 179.6-17 8.3 ^{0}C; FTIR (KBr): ν˜ = 3421, 2934, 2103, 1596, 1424, 1356, 1155, 890 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.96 (s, 1 H), 7.28-7.19 (m, 6H), 7.09-7.06 (m, 2H), 7.02 (t, *J* = 8.2 Hz, 2 H), 6.94 (t, *J* = 10.8 Hz, 2H), 6.80 (s, 1H), 6.63 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 161 (^1J = 246.27 Hz), 156.9, 147.6, 136.7, 135.4 (^4J = 3.49 Hz), 134.2, 129.2, 128.7, 128.5, 127.2, 126.4 (^3J = 8.70 Hz), 121.4, 121.3, 119.8, 116.6 (^2J = 22.97 Hz), 115.4, 74.5; HRMS (EI): calcd. For $C_{21}H_{15}FN_2O_3$ $[M+Na]^+$ 385.0964; found 385.1031.

N-(4-Chlorophenyl)-3-nitro-2-phenyl-2H-chromen-4-amine (D4):



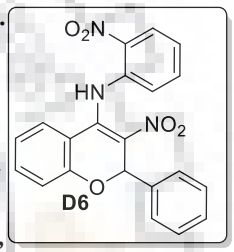
Yellow crystalline solid; Yield: 309 mg (82 %); m. p. 195.9-196.8 ^{0}C; FTIR (KBr): ν˜ = 3406, 2896, 2144, 1568, 1410, 1348, 920, 7 62 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.86 (s, 1H), 7.30 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 3H), 7.23-7.20 (m, 4H), 7.00 (t, *J* = 8. 5 Hz, 3H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.80 (s, 1 H), 6.67 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.7, 146.9, 137.9, 136.7, 134.1, 132, 129.7, 129, 128.7, 128.4, 127.1, 125.6, 121.8, 121.44, 119.8, 115.2, 74.4; HRMS (EI): calcd. for $C_{21}H_{15}ClN_2O_3$ $[M+Na]^+$ 401.0669, 403.0639; found 401.0719, 403.0716.

N-(4-Bromophenyl)-3-nitro-2-phenyl-2H-chromen-4-amine (D5):



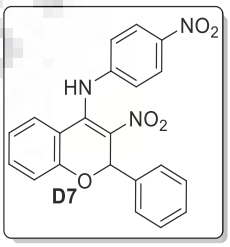
Yellow crystalline solid; Yield: 341 mg (81 %); m. p. 198.3-199.6 ^{0}C; FTIR (KBr): ν˜ = 3435, 2922, 2142, 1620, 1456, 1364, 890, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.81 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.28-7.22 (m, 6H), 7 (d, *J* = 8 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 3H), 6.80 (s, 1H), 6.67 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.7, 146.9, 138.5, 136.7, 134.2, 132.8, 129.1, 128.8, 128.5, 127.2, 125.1, 122, 121.6, 119.9, 119.8, 115.3, 74.4; HRMS (EI): calcd. for $C_{21}H_{15}BrN_2O_3$ $[M+Na]^+$ 445.0164, 447.0143; found 445.0226, 447.0208.

3-Nitro-N-(2-nitrophenyl)-2-phenyl-2H-chromen-4-amine (D6):



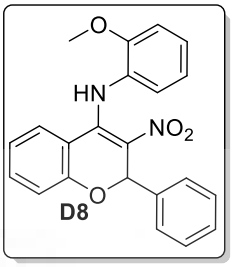
Yellow crystalline solid; Yield: 330 mg (85 %); m. p. 233.1-234.7 ^{0}C; FTIR (KBr): ν˜ = 3421, 2934, 2103, 1596, 1424, 1356, 1155, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.44 (d, *J* = 7.9 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.79 (t, *J* = 7.2 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 3.2 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 4.9 Hz, 3H), 7.26 (s, 1H), 7.2 (t, *J* = 6.8 Hz, 2 H), 4.61 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 153.6, 144.8, 141.2, 136.9, 135.7, 134.4, 130.5, 129.5, 129.4, 128.9, 127.1, 126.3, 122.6, 118.8, 118.0, 117.3, 117.0, 74.3; HRMS (EI): calcd. for $C_{21}H_{15}N_3O_5$ $[M+Na]^+$ 412.0909; found 412.0911.

3-Nitro-N-(4-nitrophenyl)-2-phenyl-2H-chromen-4-amine (D7):



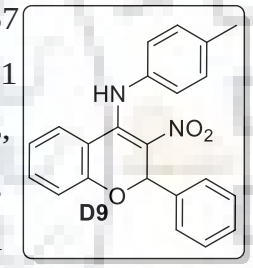
Yellow crystalline solid; Yield: 330 mg (85 %); m. p. 210.9-211.9 ^{0}C; FTIR (KBr): ν˜ = 3435, 2922, 2142, 1620, 1456, 1364, 890, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.43 (s, 1H), 8.16 (d, *J* = 9.0 Hz, 2H), 7.28-7.23 (m, 6H), 7.12 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.82 (s, 1H), 6.73 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.4, 145.6, 144.9, 144.7, 136.2, 134.7, 129.1, 128.8, 128.7, 127.2, 125.2, 124.5, 123.3, 121.9, 120.0, 115.0, 74.3; HRMS (EI): calcd. for $C_{21}H_{15}N_3O_5$ $[M+Na]^+$ 412.0909; found 412.0941.

N-(2-Methoxyphenyl)-3-nitro-2-phenyl-2H-chromen-4-amine (D8):



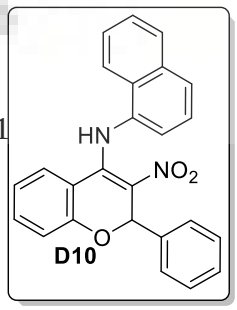
Yellow crystalline solid; Yield: 276 mg (74 %); m. p. 229.8-230.6 ^{0}C; FTIR (KBr): ν˜ = 3367, 2899, 2210, 1605, 1466, 1375, 1066, 886 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.45 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.79 (t, *J* = 7.2 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.63-7.61 (m, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 4.9 Hz, 3H), 7.26 (s, 1H), 7.22-7.19 (m, 2H), 4.66 (s, 1H), 3.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 159.6, 156.8, 147.5, 139.2, 138.5, 134.1, 129.6, 129.5, 129.4, 126.7, 124.7, 121.4, 121.2, 119.7, 119.6, 115.6, 113.7, 113.3, 74.4, 55.3; HRMS (EI): calcd. for $C_{22}H_{18}N_2O_4$ $[M+Na]^+$ 397.1164; found 397.1173.

3-Nitro-2-phenyl-N-(p-tolyl)-2H-chromen-4-amine (D9):



Yellow crystalline solid; Yield: 279 mg (78 %); m. p. 156.9-157.6 ^{0}C; FTIR (KBr): ν˜ = 3441, 2968, 2103, 1558, 1426, 1354, 1155, 922, 766 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.11 (s, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.22 (d, *J* = 6.3 Hz, 3H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.81 (s, 1H), 6.62 (t, *J* = 7.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.7, 147.7, 136.9, 136.7, 136.4, 133.9, 130.1, 129.3, 128.5, 128.3, 127.1, 124.4, 121.2, 120.8, 119.6, 115.6, 74.5, 20.9; HRMS (EI): calcd. for $C_{22}H_{18}N_2O_3$ $[M+Na]^+$ 381.1215; found 381.1257.

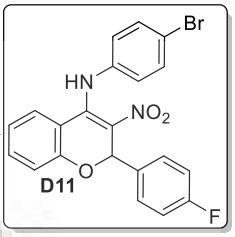
N-(1-Naphthyl)-3-nitro-2-phenyl-2H-chromen-4-amine (D10):



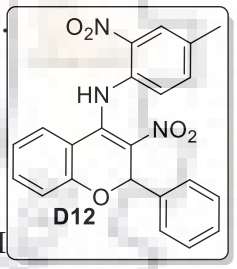
Orange crystalline solid; Yield: 291 mg (74 %); m. p. 162.2-163.8 ^{0}C; FTIR (KBr): ν˜ = 3453, 2824, 2120, 1566, 1399, 1358, 1216, 1028, 856 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.34 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.63-7.59 (m, 2H), 7.34 (d, *J* = 7.6 Hz, 3H), 7.26-7.24 (m, 3H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.87 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.43 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 156.7, 148.9, 137.1, 135.6, 134.4, 134,

128.8, 128.7, 128.5, 127.6, 127.3, 127.2, 125.5, 123.5, 122.2, 121.4, 119.6, 115.8, 74.6; HRMS (EI): calcd. for $C_{25}H_{18}N_2O_3$ $[M+Na]^+$ 417.1215; found 417.1266.

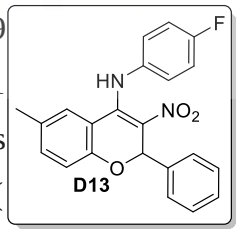
N-(4-Bromophenyl)-2-(4-fluorophenyl)-3-nitro-2H-chromen-4-amine (D11): Yellow crystalline solid; Yield: 360 mg (82 %); m. p. 226.9-227.8 ^{0}C; FTIR (KBr): ν̃ = 3412, 2954, 2143, 1576, 1413, 1357, 1125, 1057, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.82 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 1H), 7.23 (d, *J* = 6.5 Hz, 2H), 7 (d, *J* = 8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.91 (t, *J* = 7.8 Hz, 3H), 6.75 (s, 1H), 6.70 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.3 (^1J = 246.5 Hz), 156.5, 146.9, 138.4, 137.2, 134.5, 134.4, 132.8, 132.5 (^4J = 3.2 Hz), 129.1 (^3J = 8.3 Hz), 126, 121.7, 120.1, 119.9, 115.5 (^2J = 21.7 Hz), 115.3, 73.7; HRMS (EI): calcd. For $C_{21}H_{14}BrFN_2O_3$ $[M+Na]^+$ 463.0070, 465.0049; found 463.0110, 465.0099.



N-(4-Methyl-2-nitrophenyl)-3-nitro-2-phenyl-2H-chromen-4-amine (D12): Yellow crystalline solid; Yield: 318 mg (79 %); m. p. 218.3-219.5 ^{0}C; FTIR (KBr): ν̃ = 3442, 2898, 2102, 1584, 1426, 1342, 1022, 876 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.37 (d, *J* = 7.7Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.82 (s, 1H), 7.61-7.57 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 5.0 Hz, 3H), 7.25 (s, 1H), 7.17 (t, *J* = 9.4 Hz, 2 H), 4.91 (s, 1 H), 2.53 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 152.6, 142.8, 141.2, 137.3, 137.2, 136.8, 134.4, 130.5, 129.5. 1294, 128.9, 127.1, 126.7, 125.4, 122.6, 118.8, 118.0, 117.3, 74.3, 20.1; HRMS (EI): calcd. for $C_{22}H_{17}N_3O_5$ $[M+Na]^+$ 426.1066; found 406.1106.

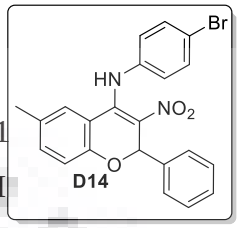


N-(4-Fluorophenyl)-6-methyl-3-nitro-2-phenyl-2H-chromen-4-amine (D13): Yellow crystalline solid; Yield: 293 mg (78 %); m. p. 168.5-169.9 ^{0}C; FTIR (KBr): ν̃ = 3478, 2858, 2045, 1586, 1464, 1346, 1102, 1021, 798 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.02 (s, 1H), 7.26 (s, 2H), 7.26-7.22 (m, 3H), 7.11-7.05 (m, 3H), 7.04 (s, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.79 (s, 1H), 6.71 (s, 1H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 161 (^1J = 246.3 Hz), 154.8, 147.8, 137, 135.4 (^4J = 3.5 Hz), 135.1, 130.8, 129.4, 128.6, 128.4, 127.2, 126.5 (^3J = 8.6

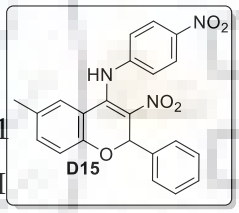


Hz), 121.2, 119.5, 116.5 (^2J = 22.9 Hz), 114.9, 74.4, 20.6; HRMS (EI): calcd. for $C_{22}H_{17}FN_2O_3$ $[M+Na]^+$ 399.1121; found 399.1137.

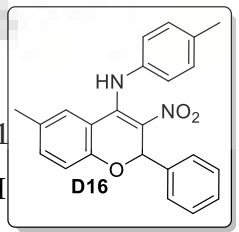
N-(4-Bromophenyl)-6-methyl-3-nitro-2-phenyl-2H-chromen-4-amine (D14): Yellow crystalline solid; Yield: 331 mg (76 %); m. p. 212.8-213.5 ^{0}C; FTIR (KBr): ν̃ = 3450, 2886, 2098, 1596, 1424, 1356, 1125, 1025, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.86 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 3H), 7.23 (d, *J* = 5.1 Hz, 3H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 10.2 Hz, 2H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 154.6, 147.1, 138.5, 136.9, 135.2, 132.6, 130.9, 129.2, 128.7, 128.4, 127.2, 125.9, 121.9, 119.8, 119.5, 114.9, 74.4, 20.7; HRMS (EI): calcd. for $C_{22}H_{17}BrN_2O_3$ $[M+Na]^+$ 459.0320, 461.0300; found 459.0342, 461.0300.



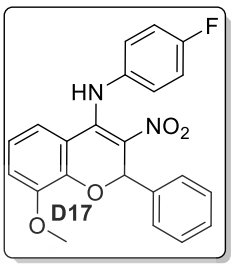
6-Methyl-3-nitro-N-(4-nitrophenyl)-2-phenyl-2H-chromen-4-amine (D15): Yellow crystalline solid; Yield: 318 mg (79 %); m. p. 188.3-189.6 ^{0}C; FTIR (KBr): ν̃ = 3513, 2987, 2123, 1546, 1398, 1354, 1255, 1037, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.44 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 2H), 7.25 (s, 6H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.78 (s, 1H), 6.79 (s, 1H), 6.78 (s, 1H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 154.2, 145.6, 144.9, 144.5, 136.3, 135.6, 131.4, 128.9, 128.6, 128.5, 127.1, 125, 124.5, 123.1, 119.7, 114.6, 74.1, 20.6; HRMS (EI): calcd. for $C_{22}H_{17}N_3O_5$ $[M+Na]^+$ 426.1066; found 426.1061.



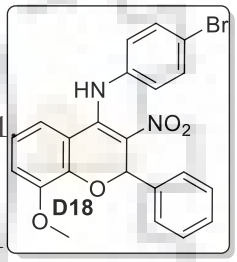
6-Methyl-3-nitro-2-phenyl-N-(p-tolyl)-2H-chromen-4-amine (D16): Yellow crystalline solid; Yield: 267 mg (72 %); m. p. 158.9-159.7 ^{0}C; FTIR (KBr): ν̃ = 3431, 2924, 2113, 1576, 1474, 1354, 1175, 1028, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.16 (s, 1H), 7.28 (d, *J* = 6.4 Hz, 2H), 7.26 (s, 1H), 7.23 (d, *J* = 6.6 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 3H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.78 (s, 1H), 6.76 (s, 1H), 2.36 (s, 3H), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 154.7, 148.1, 137.2, 136.8, 136.5, 134.9, 130.6, 130.1, 129.6, 128.5, 128.4, 127.3, 124.6, 120.8, 119.3, 115.3, 74.5, 21.1, 20.6; HRMS (EI): calcd. for $C_{23}H_{20}N_2O_3$ $[M+Na]^+$ 395.1372; found 395.1403.



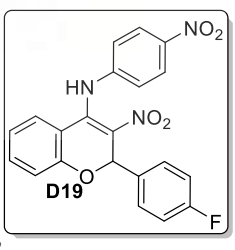
N-(4-Fluorophenyl)-8-methoxy-3-nitro-2-phenyl-2H-chromen-4-amine (D17): Yellow crystalline solid; Yield: 297 mg (76 %); m. p. 220 .2-221.7 ^{0}C; FTIR (KBr): ν̃ = 3456, 2925, 2118, 1565, 1471, 135 4, 1168, 1023, 821 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.9 6 (s, 1H), 7.32 (t, *J* = 3.5 Hz, 2H), 7.24-7.22 (m, 3H), 7.07-6.99 (m, 4H), 6.90 (s, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.58 (t, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 3.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 160.9 (^1J = 246 Hz), 150.3, 147.5, 146.6, 136.9, 135.3 (^4J = 3.4 Hz), 128.5, 128.3, 126.8, 126.3 (^3J = 8.5 Hz), 121.7, 121.1, 120.7, 116.4 (^2J = 22.8 Hz), 116.3, 115.7, 114.1, 74.7, 56.3; HRMS (EI): calcd. For $C_{22}H_{17}FN_2O_4$ $[M+Na]^+$ 415.1070; found 415.1100.



N-(4-Bromophenyl)-8-methoxy-3-nitro-2-phenyl-2H-chromen-4-amine (D18): Yellow crystalline solid; Yield: 339 mg (75 %); m. p. 20 7.1-208.6 ^{0}C; FTIR (KBr): ν̃ = 3422, 2896, 2112, 1581, 1421, 1 351, 1162, 995, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11 81 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 3.4 Hz, 2H), 7.2 2 (d, *J* = 4.2 Hz, 3H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.89 (s, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.62 (t, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 150.4, 146.9, 146.5, 138.5, 136.8, 132.6, 128.7, 128.4, 126.9, 125.1, 122.4, 121.4, 120.7, 119.8, 116.3, 115.8, 74.7, 56.4; HRMS (EI): calcd. for $C_{22}H_{17}BrN_2O_4$ $[M+Na]^+$ 475.0269, 477.0249; found 475.0309, 477.0299.

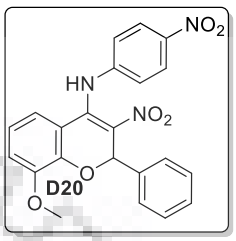


2-(4-Fluorophenyl)-3-nitro-N-(4-nitrophenyl)-2H-chromen-4-amine (D19): Yellow crystalline solid; Yield: 350 mg (86 %); m. p. 235.6-236. 9 ^{0}C. FTIR (KBr): ν̃ = 3403, 2868, 2145, 1561, 1411, 1350, 109 8, 1053, 786 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.45 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.26-7.23 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8 Hz, 1H), 6.94 (q, *J* = 8.5 Hz, 3H), 6.78 (s, 1H), 6.75 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 163 (^1J = 246.9 Hz), 156.2, 145.5, 145, 144.8, 134.8, 132 (^4J = 3.6 Hz), 129.1 (^3J = 8.7 Hz), 128.8, 125.2, 124.3, 123.4, 122.9, 120, 115.7 (^2J = 21.8

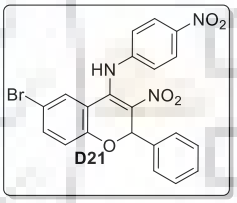


Hz), 115, 73.7; HRMS (EI): calcd. For $C_{21}H_{14}FN_3O_5$ $[M+Na]^+$ 430.0815; found 430.0865.

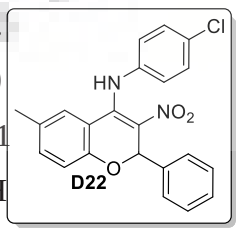
8-Methoxy-3-nitro-N-(4-nitrophenyl)-2-phenyl-2H-chromen-4-amine (D20): Yellow crystalline solid; Yield: 326 mg (78 %); m. p. 216.4-217.6 ^{0}C; FTIR (KBr): ν˜ = 3435, 2912, 2089, 1556, 1467, 1350, 1145, 1016, 798 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.43 (s, 1H), 8.15 (d, *J* = 8.7 Hz, 2H), 7.32-7.30 (m, 2H), 7.24 (t, *J* = 3.4 Hz, 3H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.91 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.67 (t, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (CDCl3, 100 MHz) δ ppm 150.6, 146, 145.7, 144.1, 144.7, 136.3, 128.9, 128.6, 126.8, 125.2, 124.9, 123.3, 121.8, 120.3, 116.2, 116, 74.4, 56.4; HRMS (EI): calcd. for $C_{22}H_{17}N_3O_6$ $[M+Na]^+$ 442.1015; found 422.1045.



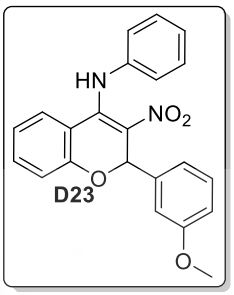
6-Bromo-3-nitro-N-(4-nitrophenyl)-2-phenyl-2H-chromen-4-amine (D19): Yellow crystalline solid; Yield: 392 mg (84 %); m. p. 197.9-198.8 ^{0}C; FTIR (KBr): ν˜ = 3502, 2923, 2109, 1586, 1486, 1346, 1181, 1036, 803 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.29 (s, 1H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.36 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.29-7.27 (m, 5H), 7.12 (d, *J* = 8.9 Hz, 2H), 7.10 (d, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.82 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ pmm 155.2, 145.1, 144.8, 143.2, 137.2, 135.7, 131.0, 129.3, 128.9, 128.8, 127.2, 125.4, 123.2, 121.7, 116.8, 114.1, 74.5; HRMS (EI): calcd. For $C_{21}H_{14}BrN_3O_5$ $[M+Na]^+$ 490.0015, 491.9994; found 490.0065, 492.0034.



N-(4-Chlorophenyl)-6-methyl-3-nitro-2-phenyl-2H-chromen-4-amine (D22): Yellow crystalline solid; Yield: 297 mg (76 %); m. p. 212.3-213.5 ^{0}C; FTIR (KBr): ν˜ = 3435, 2848, 2042, 1589, 1465, 1342, 1106, 1015, 789 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 11.90 (s, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.26 (s, 2H), 7.23 (d, *J* = 5.2 Hz, 3H), 7.02 (d, *J* = 8.4 Hz, 3H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.78 (s, 1H), 6.74 (s, 1H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 154.6, 147.2, 137.9, 136.8, 135.2, 131.9, 130.8, 129.5, 129.2, 128.6, 128.4, 127.1, 125.6, 121.7, 119.4, 114.8, 74.3, 20.5; HRMS (EI): calcd. For $C_{22}H_{17}ClN_2O_3$ $[M+Na]^+$ 415.0825, 417.0796; found 415.0865, 417.0826.

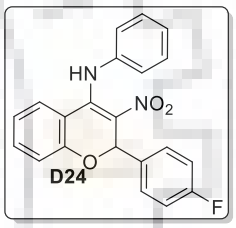


2-(3-Methoxyphenyl)-3-nitro-N-phenyl-2H-chromen-4-amine (D23):



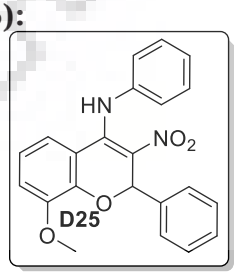
Yellow crystalline solid; Yield: 276 mg (72 %); m. p. 162.8-163.5 ^{0}C; FTIR (KBr): ν̃ = 3447, 3060, 1610, 1591, 1557, 1371, 1250, 1098, 995 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.03 (s, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23-7.18 (m, 2H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 3H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.79 (s, 1H), 6.75 (d, *J* = 9.4 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 159.6, 156.7, 147.4, 139.2, 138.5, 133.9, 129.5, 129.4, 129.3, 126.6, 124.6, 121.3, 121.2, 119.6, 119.5, 115.5, 113.8, 113.2, 74.4, 55.2; HRMS (EI): calcd. for $C_{22}H_{18}N_2O_4$ [M+Na]$^+$ 397.1164; found 397.1174.

2-(4-Fluorophenyl)-3-nitro-N-phenyl-2H-chromen-4-amine (D24):



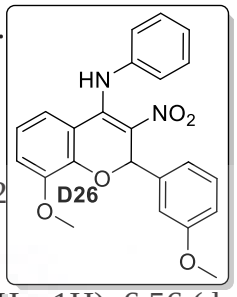
Yellow crystalline solid; Yield: 289 mg (80 %); m. p. 196.8-197.9 ^{0}C; FTIR (KBr): ν̃ = 3405, 2959, 2140, 1602, 1429, 1367, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.05 (s, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 6.5 Hz, 3H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 3H), 6.77 (s, 1H), 6.63 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.8 (^1J = 246.1 Hz), 156.5, 147.5, 139.1, 134.2, 132.8 (^4J = 3.4 Hz), 129.7, 129.3, 129.1 (^3J = 8.1 Hz), 126.8, 124.7, 121.5, 121.1, 119.7, 115.5 (^2J = 22.5 Hz), 73.9; HRMS (EI): calcd. for $C_{21}H_{15}FN_2O_3$ [M+Na]$^+$ 385.0964; found 385.1018.

8-Methoxy-3-nitro-N,2-diphenyl-2H-chromen-4-amine (D25):

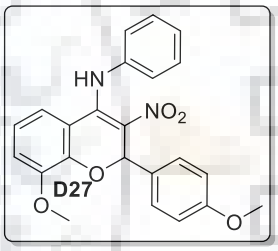


Yellow crystalline solid; Yield: 280 mg (75 %); m. p. 250.3-251.6 ^{0}C; FTIR (KBr): ν̃ = 3356, 2868, 2103, 1574, 1454, 1340, 1164, 1028, 796 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.04 (s, 1H), 7.34-7.31 (m, 3H), 7.29 (s, 1H), 7.24-7.20 (m, 4H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.91 (s, 1H), 6.80-6.78 (m, 1H), 6.57 (s, 1 H), 6.55 (d, *J* = 3.2 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 150.2, 147.5, 146.5, 139.2, 136.9, 129.5, 128.5, 128.3, 126.8, 126.6, 124.6, 121.7, 121.1, 120.9, 116.5, 115.6, 74.7, 56.3; HRMS (EI): calcd. For $C_{22}H_{18}N_2O_4$ [M+Na]$^+$ 397.1164; found 397.1165.

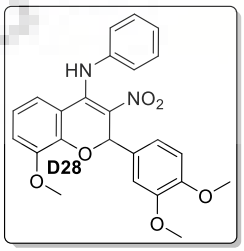
8-Methoxy-2-(3-methoxyphenyl)-3-nitro-N-phenyl-2H-chromen-4-amine (D26): Yellow crystalline solid; Yield: 290 mg (72 %); m. p. 206.5-207.9 ^{0}C; FTIR (KBr): ν˜ = 3465, 2901, 2123, 1595, 1420, 1349, 1122, 1039, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.02 (s, 1H), 7.30 (t, *J* = 7.64 Hz, 2H), 7.22 (t, *J* = 7.20 Hz, 1H), 7.12 (t, *J* = 7.92 Hz, 1H), 7.07 (d, *J* = 7.88 Hz, 2H), 6.95 (s, 1H), 6.87 (d, *J* = 10.24 Hz, 2H), 6.80 (t, *J* = 4.72 Hz, 1H), 6.74 (d, *J* = 8.12 Hz, 1H), 6.56 (d, *J* = 4.68 Hz, 2H), 3.84 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 159.7, 150.3, 147.5, 146.6, 139.3, 138.7, 129.4, 126.6, 124.7, 121.8, 121.1, 119.1, 116.6, 115.6, 114.4, 112.3, 74.7, 56.4, 55.2; HRMS (EI): calcd. for $C_{23}H_{20}N_2O_5$ $[M+Na]^+$ 427.1270; found 427.1271.



8-Methoxy-2-(4-methoxyphenyl)-3-nitro-N-phenyl-2H-chromen-4-amine (D27): Yellow crystalline solid; Yield: 290 mg (72 %); m. p. 235.6-236.9 ^{0}C; FTIR (KBr): ν˜ = 3489, 2986, 2136, 1578, 1404, 1352, 1155, 1058, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.00 (s, 1H), 7.30 (t, *J* = 7.52 Hz, 3H), 7.21 (d, *J* = 6.24 Hz, 2H), 7.06 (d, *J* = 7.72 Hz, 2H), 6.82 (s, 1H), 6.77 (d, *J* = 7.20 Hz, 1H), 6.73 (d, *J* = 8.64 Hz, 2H), 6.55 (d, *J* = 7.32 Hz, 2H), 3.80 (s, 3H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 160.5, 148.7, 146.4, 142.7, 141.6, 129.4, 129.2, 129.1, 129.0, 128.8, 128.6, 118.9, 118.6, 116.8, 115.2, 114.2, 74.0, 56.4, 55.3; HRMS (EI): calcd. for $C_{23}H_{20}N_2O_5$ $[M+Na]^+$ 427.1270; found 427.1331.

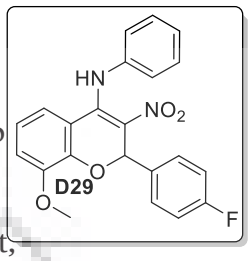


2-(3,4-Dimethoxyphenyl)-8-methoxy-3-nitro-N-phenyl-2Hchromen-4-amine (D28): Yellow crystalline solid; Yield: 295 mg (68 %); m. p. 191.4-192.6 ^{0}C; FTIR (KBr): ν˜ = 3422, 2944, 2203, 1696, 1524,1346, 1125, 1026, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.03 (s, 1H), 7.31 (t, *J* = 7.64 Hz, 2H), 7.22 (t, *J* = 7.20 Hz, 1H), 7.08 (d, *J* = 7.84 Hz, 2H), 7.03 (s, 1H), 6.85 (s, 1H), 6.79 (t, *J* = 4.72 Hz, 1H), 6.73 (d, *J* = 8.40 Hz, 1H), 6.66 (d, *J* = 8.28 Hz, 1H), 6.57 (d, *J* = 4.64 Hz, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 150.3, 149.2, 148.9, 147.6, 146.4, 139.3, 129.5, 129.4, 126.6, 124.6,

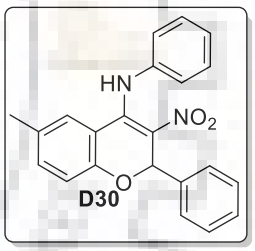


121.9, 121.2, 120.9, 119.1, 116.8, 115.4, 110.4, 110.2, 74.7, 56.2, 55.8, 55.8 ppm. HRMS (EI): calcd. For $C_{24}H_{22}N_2O_6$ $[M+Na]^+$ 457.1356; found 457.1409.

2-(4-Fluorophenyl)-8-methoxy-3-nitro-N-phenyl-2H-chromen-4-amine (D29): Yellow crystalline solid; Yield: 305 mg (78 %); m. p. 209.4-210.6 ^{0}C; FTIR (KBr): ν˜ = 3421, 2934, 2153, 1566, 1446, 1355, 1145, 1042, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.06 (s, 1H), 7.34 (s, 1H), 7.32 (s, 1H), 7.30 (t, *J* = 3.92 Hz, 2H), 7.23 (t, *J* = 7.24 Hz, 1H), 7.08 (d, *J* = 7.68 Hz, 2H), 6.91 (t, *J* = 8.68 Hz, 2H), 6.85 (s, 1H), 6.82-6.79 (m, 1H), 6.58 (d, *J* = 3.16 Hz, 1H), 6.57 (s, 1H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 162.8 (^1J =245.89 Hz), 150.3, 147.6, 146.2, 139.2, 132.8 (^4J = 3.2 Hz), 129.6, 128.8 (^3J = 8.28 Hz), 126.8, 124.7, 121.5, 121.3, 120.9, 116.6, 115.7, 115.4 (^2J = 21.52 Hz), 74.2, 56.4; HRMS (EI): calcd. For $C_{24}H_{21}FN_2O_6$ $[M+Na]^+$ 415.1070; found 415.1085.



6-Methyl-3-nitro-N,2-diphenyl-2H-chromen-4-amine (D30): Yellow crystalline solid; Yield: 282 mg: 79 %; m. p. 177.3-178.6 ^{0}C; FTIR (KBr): ν˜ = 3418, 2944, 2107, 1546, 1434, 1354, 1155, 1054, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 12.11 (s, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 6.28 Hz, 2H), 7.24-7.21 (m, 4H), 7.10 (d, *J* = 7.88 Hz, 2H), 7.00 (d, *J* = 8.40 Hz, 1H), 6.82 (d, *J* = 8.36 Hz, 1H), 6.79 (s, 1H), 6.72 (s, 1H), 1.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 154.6, 147.7, 139.1, 137, 134.9, 130.5, 129.5, 129.4, 128.5, 128.3, 127.1, 126.6, 124.6, 121, 119.2, 115.1, 74.3, 20.4; HRMS (EI): calcd. for $C_{22}H_{18}N_2O_3$ $[M+ Na]^+$ 381.1215; found 381.1257.



X-ray Crystallographic Analyses: CCDC 1575397 (for **D23**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

3.7. References

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Chapter-4

SeO_2 Mediated Synthesis of Selected Heterocycles by Oxidative C–C Bond Cleavage of Acetophenone Derivatives

ChemistrySelect **2019**, *4*, 7585-7590

4.1. Introduction

Over the past 20 years, the functionalization of C(sp^3)-H bond has come into sight as a new and challenging area in organic chemistry [1]. Methyl arenes and aryl methyl ketones are major class of compounds, which has been explored prominently among the examples of C(sp^3)-H containing moieties. A direct functionalization of methyl carbon and methyl group in ketone via chemoselective cleavage of C(CO)-C bond is challenging task for the organic chemist [2]. The chemoselective cleavage of C(CO)-C has been reported mainly using catalytic amount of copper under oxygen atmosphere to give aldehyde [3], ester [4], and amide [5]. Wu and co-workers recently documented the construction of 1, 3, 4-oxadiazoles via molecular I_2-catalyzed deacylative C(CO)—C bond cleavage of aryl methyl ketones [6]. Sandip B. Bharate *et al.* described the synthesis of quinazolinones using molecular iodine as catalyst from acetophenone by C—C bond cleavage [7]. Similarly, Bathula *et al.* used acetophenone and I_2 as catalyst for benzimidazole synthesis [8]. Bhalchandra M. Bhanage synthesized quinazolines from commercially available aryl methyl ketones through chemoselective cleavage of C(CO)—C bond in the presence of molecular iodine [9].

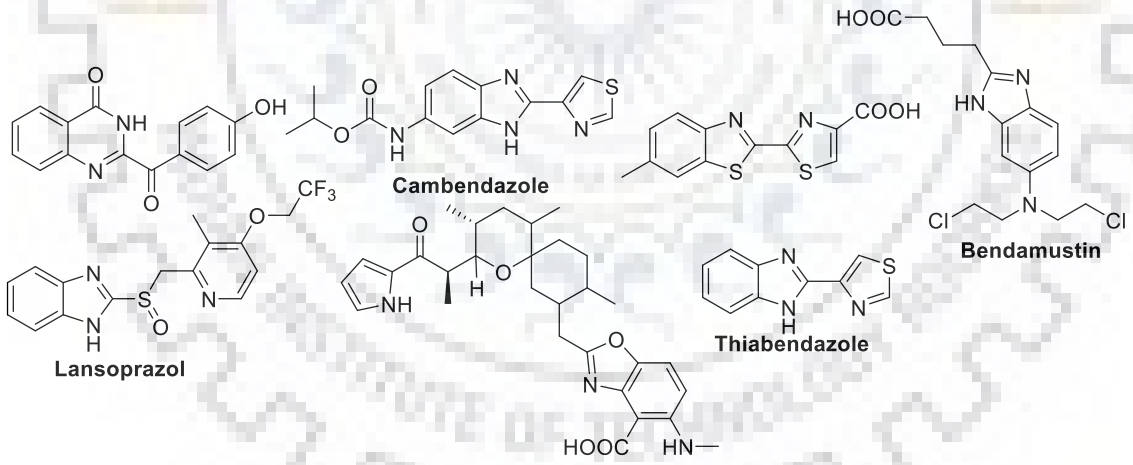
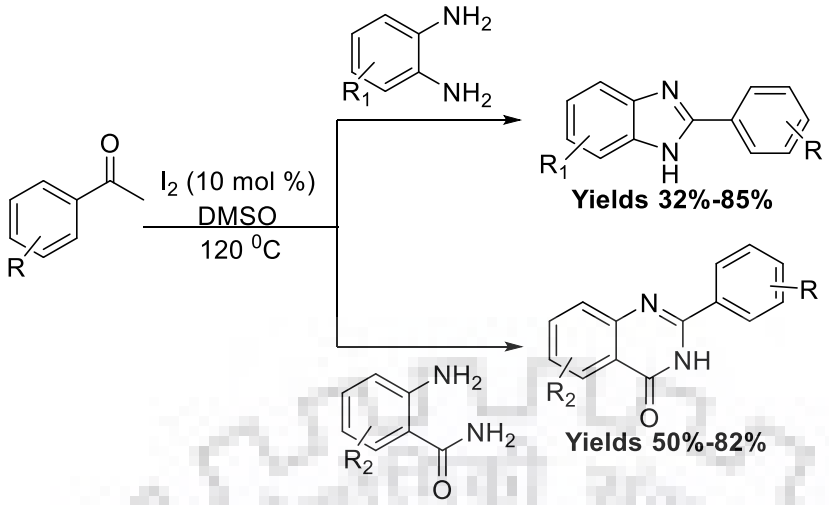


Figure 4.1. Some biologically active compounds

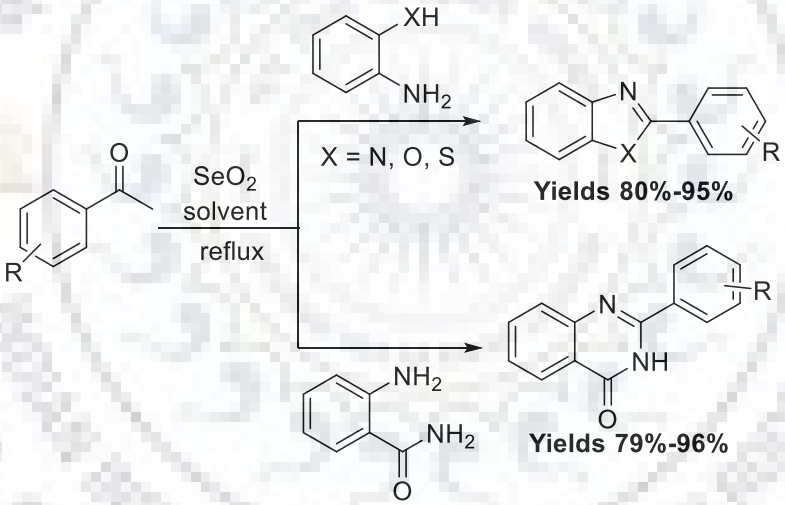
Despite the considerable development made in the area of C(CO)—C bond cleavage, it is still an attractive subject to work on the oxidative C(CO)—C bond cleavage of aryl methyl ketones for the development of heterocyclic compounds. Generally, these bicyclic compounds are prepared through condensation of anthranilamide, 1, 2-diaminoarenes, 2-aminophenol and 2-aminothiophenol with carboxylic acids [10], carboxylic acid derivatives [11], and aldehydes [12]. Ming lu et al. described iron-catalyzed synthesis of benzimidazole and benzothiazole from *o*-phenylenediamineand *o*-aminophenol under

solvent free condition under air as oxidant [13]. Recently, Blacker and coworkers used benzyl alcohol in place of carbonyl compound to synthesize these compounds via ruthenium catalyzed hydrogen transfer method [14]. On the other hand, Yongbozhou group developed the transition metal and oxidant free protocol for production of benzimidazole and benzothiazole by selective C—C cleavage [15]. Like the benzimidazole, there are various transformations reported for synthesis of quinazolinones by metal and metal free approach with condensation of anthranilamide with various simple aryl precursors. Various reports on this approach includes Zn [16], Pd [17], Ir [18] or I_2/DMSO-catalyzed [19] benzylic C—H amidation with benzyl alcohols, or condensation with benzyl halides or benzyl amine. Remarkably, an interesting $Pd(OAc)_2$/$BuPAd_2$/CO catalyzed carbonylative synthesis of quinazolinones was reported by Wu group [20]. In a multi-component reaction protocol was established for the synthesis of quinazolin- 4(3H)-ones from anthranilamide and aryl halides via a palladium-catalyzed isocyanide insertion [21]. Recently sharada *et al.* describe copper catalyzed synthesis of Quinazolin-4-ones by α-C—H Amination via Ring Opening Cyclization Strategy and their application to Application in Rutaecarpine Synthesis [22]. Quinazolin-4(3H)-ones, Benzimidazoles, Benzothiazoles and Benzoxazoles represent an important and abundant class of fused heterocycles that have many applications in both pharmaceutical and industrial research [23]. They are widely found in bioorganic like Panipanoid C [23a], Cyanocobalamin [24], Calcimycin [25], Rifamycin P, Rifamycin Q and vitamin B_1 [26] and also shows various biological activity such as anti-tumour, anticonvulsant, and anti-viral and several other properties [27]. The drug sildenafil (Viagra) [26] which is used for the treatment of erectile dysfunction contains a pyrazolo[4,3-d]pyrimidin7(6H)-one pharmacophore [28]. They have also found applications in industry as a dopant in a light-emitting organic electroluminescent device and vulcanization accelerators [29]. Therefore, herein we describe the use of aryl methyl ketones as a coupling partner, which are cheap, commercially available, and relatively stable. This might be due to the involvement of the oxidative C (CO)—C bond cleavage for the construction of selected N, O and S containing heterocycles with high efficiency.

a) **Previous work:** Iodine catalysed formation of benzimidazoles and quinazolinones [7,8].



b) This work: selenium dioxide mediated synthesis of benzoxzzole, benzothiazole, benzimidazole and quinazolinones.

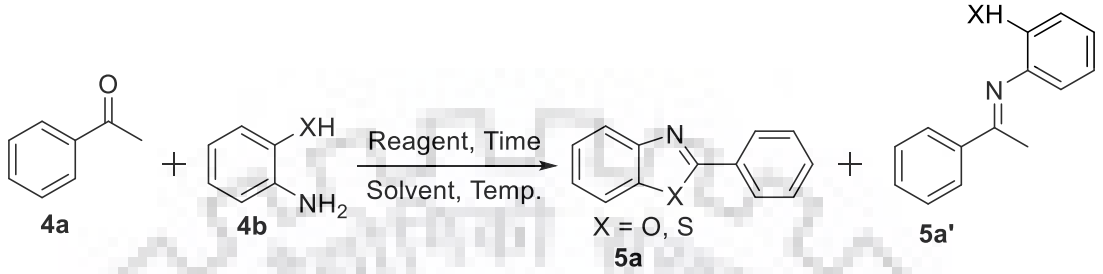


4.2. Results and discussion

Initially, the test reaction between acetophenone (**4a**, mmol) and 2-amino phenol (**4b**, 1 mmol) was carried out in the presence of selenium dioxide (0.50 mmol) in 1, 4-dioxane at room temperature. As expected, the above combination of reagents gave the desired product (**5a**) but in trace amount (Table 4.1, entry 1). Further, increase in temperature from rt to 80 ^{0}C with 0.50 mmol of selenium dioxide furnished **5a** in 25% yield in 17 h, even the Schiff's base was also not formed and starting material remains in the reaction mixture (Table 4.1, entry 2). This can be ascribed by possible chemical equilibrium during imine formation and can be solved by adding molecular sieves in the reaction

mixture. It was observed that addition of molecular sieves (4 Å) improved the yield of **5a** to 40% along with Schiff's base **5a'** (Table 4.1, entry 3).

Table 4.1. Optimization of reaction conditions for benzoxazole and benzothiazole



Entry	Reagent mmol	solvent	Drying agent	Temp.	Time (hr)	Yield (%)	
						5a	**5a'**
1	SeO_2(0.5)	1,4-dioxane	-	Rt	17	trace	0
2	SeO_2(0.5)	1,4-dioxane	-	80	17	25	0
3	SeO_2(0.5)	1,4 dioxane	- MS	80	17	40	45
4	SeO_2(0.75)	1,4-dioxane	MS	80	17	61	28
5	SeO_2(1.0)	1,4-dioxane	MS	80	17	81	Trace
6	SeO_2(1.5)	1,4-dioxane	MS	80	8	86	0
7	SeO_2(2.0)	1,4-dioxane	MS	80	6	86	0
8	SeO_2(1.5)	1,4 dioxane	- MS	100	6	86	0
9	SeO_2(1.5)	Benzene	MS	100	6	72	0
10	SeO_2(1.5)	DMSO	MS	120	6	80	0
11	SeO_2(1.5)	CH_3CN	MS	100	6	76	0
12	SeO_2(1.5)	DMF	MS	120	6	82	0

[a]**Reaction conditions: 4a** (1.0 mmol), **4b** (1.0 mmol) and SeO_2 (1.5 to 2 mmol) in 1,4- dioaxane at 80 ^{0}C with MS (Molecular sieves) (4Å).

When SeO_2 mmol was increased from 0.50 to 0.75, the yield of **5a** was increased up to 20% (Table 4.1, entry 4). Further increase in the quantity of SeO_2 to 1 mmol resulted in further improvement in **5a** yield along with trace amount of **5a'** (Table 4.1, entry 5). As

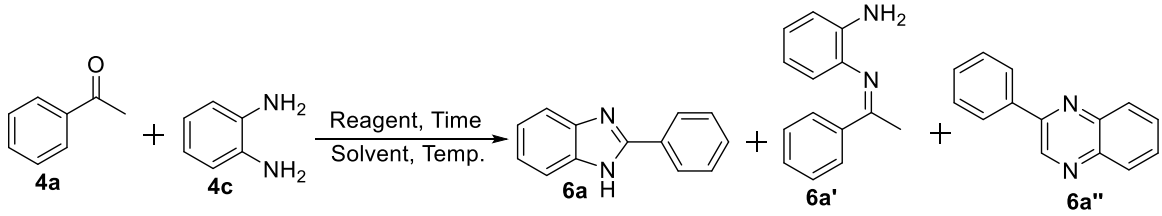
seen in the entry 6, 1.5 mmol selenium dioxide produces only desired product **5a** in less reaction time and therefore, we further intended to use higher equivalents of SeO_2 and less reaction time. These efforts indicated that 2 mmol of SeO_2 in 1, 4-dioxane in the presence of molecular sieves, resulted the desired product **5a** (86%) formation in 6 h (Table 4.1, entry 7). These results concluded that the promoter loading played a crucial role in selective formation of product **5a**.

Furthermore, additional increase in temperature did not improve the yield of the products (Table 4.1, entry 8). Change of solvents to benzene, DMSO, CH_3CN, and DMF was also not advantageous (Table 4.1, entries 9-11,) to improve the yield.

To extend our work, we also studied the possible reaction with o-phenylenediamine **4c** with acetophenone **4a** under the same reaction conditions, the product was detected with 36% yield (Table 4.2, entry 1). Inspired by the results obtained further we examined the reaction condition for scheme 4.3. We began our study by changing the amount of selenium dioxide as we investigated the reaction of **4a** with **4c** using 2 mmol of SeO_2 in 1, 4-dioxane as a solvent in an open air atmosphere at 80 ^{0}C; however, reaction does not provide the quantitative amount of product **6a** even Schiff's base **6a'** was formed along with trace amount of **6a''**. Then we decided to first screen the solvent and temperature conditions for the quantitative production of **6a**. Even, the reaction in $CHCl_3$ and DCM for 16 h (Table 4.2, entries 3 and 4) almost no desired product **6a** was observed. The conversion of starting material was completed in other solvents such as THF, MeCN, DMSO, and DMF, a better yield was observed of **6a** with minimal formation of side product (Table 4.2, entries 5-8). On the other hand, change of solvents to benzene was advantageous (Table 4.2, entries 9 and 10) to improve the yield of **6a** in less reaction time and no side product was detected. Just because of the toxic nature of benzene we decide to optimize some more solvent which is less toxic in nature as compare to benzene and does not effect the yield of product for this purpose first we optimize toluene and xylene. Same yield was observed in case of toluene but in case of xylene there is a slight decrease in yield (Table 4.2, entry 11 and 12).Product **6a''** was confirmed by ^{1}H NMR (see supporting).

The aforementioned results prompted us to test the fate of the more challenging anthranilamide for the formation of quinazolinones in same reaction condition used for scheme 4.4 then we found quinazolinones formed in good yield but reaction took more time due to less nucleophilic character of amide $–NH_2$.

Table 4.2. Optimization of reaction conditions for benzimidazole



Entry	Reagent (mmol)	Solvent	Temp.	time	Yield (%)		
					6a	**6a'**	**6a''**
1	SeO_2 (1.5)	1,4 dioxane	80	8h	36	45	0
2	SeO_2 (2.0)	1,4 dioxane	80	8h	36	40	Trace
3	SeO_2 (2.0)	$CHCl_3$	60	16		Nr	
4	SeO_2 (2.0)	DCM	60	16		Nr	
5	SeO_2 (2.0)	THF	80	10	45	35	Trace
6	SeO_2 (2.0)	MeCN	100	10	48	35	Trace
7	SeO_2 (2.0)	DMF	120	9	56	30	0
8	SeO_2 (2.0)	DMSO	120	9	60	20	0
9	SeO_2 (2.0)	Benzene	100	8	76	0	15
10	SeO_2 (1.5)	Benzene	100	8	85	0	0
11	SeO_2 (1.5)	Toluene	100	8	85	0	0
12	SeO_2 (1.5)	m-Xylene	100	8	80	0	0

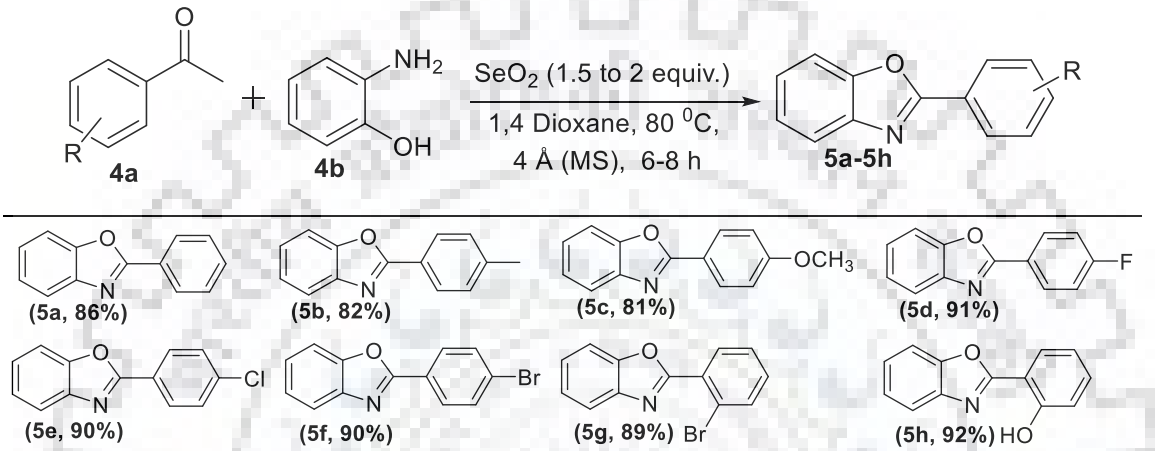
[a]**Reaction condition: 4a** (1.0 mmol), **4c** (1.0 mmol) and SeO_2 (1.5 mmol) in toluene at 100 ^{0}C with molecular sieves (4Å).

4.3. Substrate scope

Expanding the scope of the reaction, different acetophenones were employed in this reaction. Both electron donating and electron withdrawing group were well tolerated in reaction (scheme 4.1). Under the optimal reaction conditions, the reaction of **4a** with **4b** without substituents on aryl rings smoothly proceeded to give **5a** in 86% yield within 6 h (Scheme 4.1). We studied the electronic effects of substituents on acetophenone and found that electron-releasing groups like methyl and methoxy decreased the yields

without gaining any advantage in terms of reaction time. It was also observed that in case of halogen, there was a notable effect on the yield of the product as well as the reaction time. A para-fluoro substituted acetophenone reacts faster and produced 91% yield of the product **5d**. In case of *p*-chloro and *p*-bromo showed good reactivity and required less time with slightly decreased yield (e. g., **5e** and **5f**).

Scheme 4.1. Scope of benzoxazole



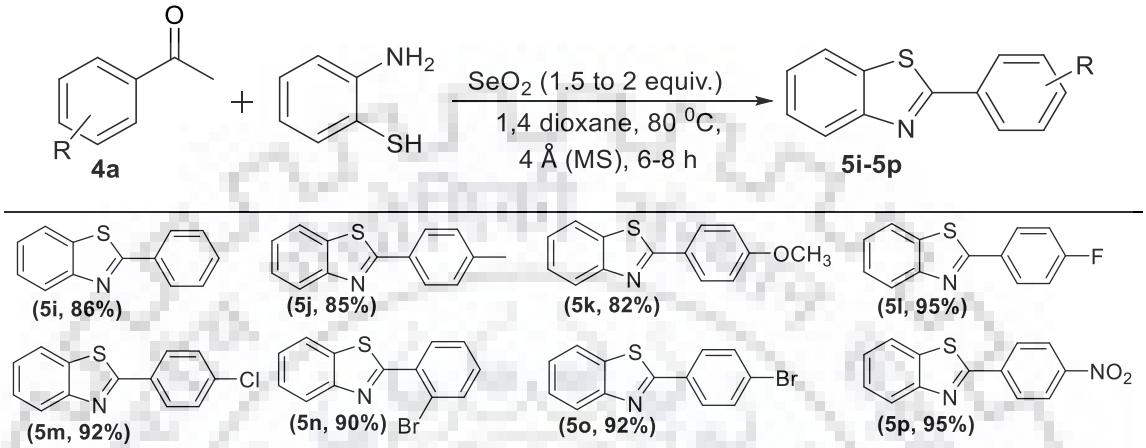
Reaction condition: **4a** (1.0 mmol), **4b** (1.0 mmol) and SeO_2 (1.5 mmol) in 1, 4-dioxane at 80 ^{0}C and molecular sievies (4 Å).

Electron-withdrawing substituents like bromine on ortho position favoured the transformation with high yield, the corresponding product (**5g**) in 89% yield. There was a considerable increase in the yield of *o*-hydroxyacetophenone without any improvement in the reaction time (3h). Again, we also study the substituent effect on acetophenone for the production of benzothiazole. Methyl and methoxy substituted acetophenone displayed lower reactivity and the product **5j** and **5k** showed minor difference in yield with more reaction time (scheme 4.2). Furthermore, *4*-fluoro, *4*-chloro, *4*-bromo and *2*-bromo acetophenone produced product **5l** (95%), **5m** (92%), **5n** (90%) and **5o** (92%) in excellent yields with consumption of starting material in 6 h. Additionally, *4*-nitro substituted acetophenone furnished the product **5p** in 95% yield.

In addition to benzothiazole, we also we also tested the scope of the standard reaction condition using different substituent on acetophenone for the formation of benzimidazole derivatives. Under similar condition, we got less yield as compared to benzothiazole in almost all the cases. Then, we changed the solvent and temperature as in scheme 4.3. We got good to excellent yield (79-90%) with different substituents and functional groups such as methyl, methoxy, hydroxyl on acetophenones. It might be due to the solvent

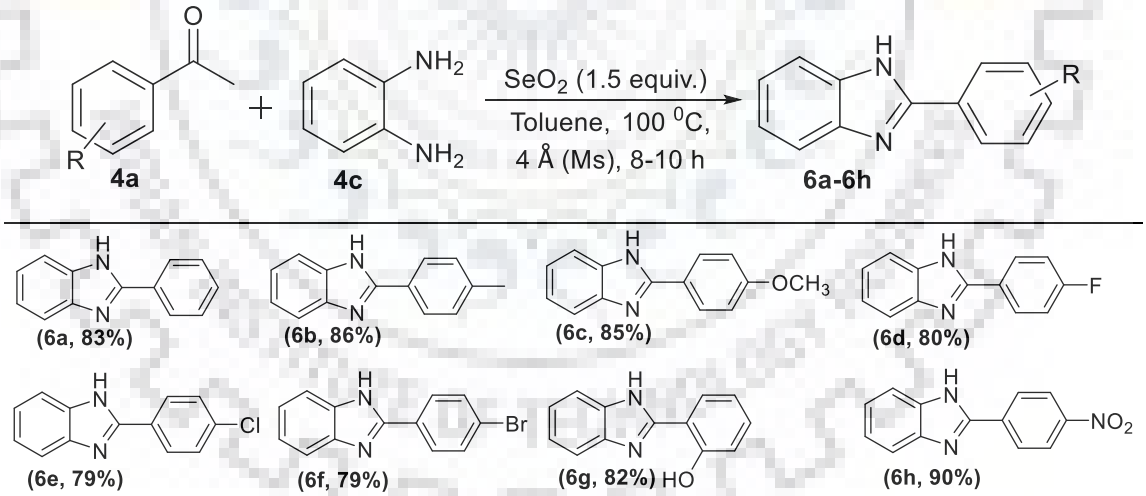
effect. We also observed that para-halogen containing ketone react smoothly but slightly lower yields of product **6d**, **6e** and **6f** formed.

Scheme 4.2. Scope of benzothiazole



Reaction condition: 4a (1.0 mmol), **4b** (1.0 mmol) and SeO_2 (1.5 mmol) in 1,4-dioxane at 80 ^{0}C and molecular sievies (4 Å).

Scheme 4.3. Scope of benzimidazole

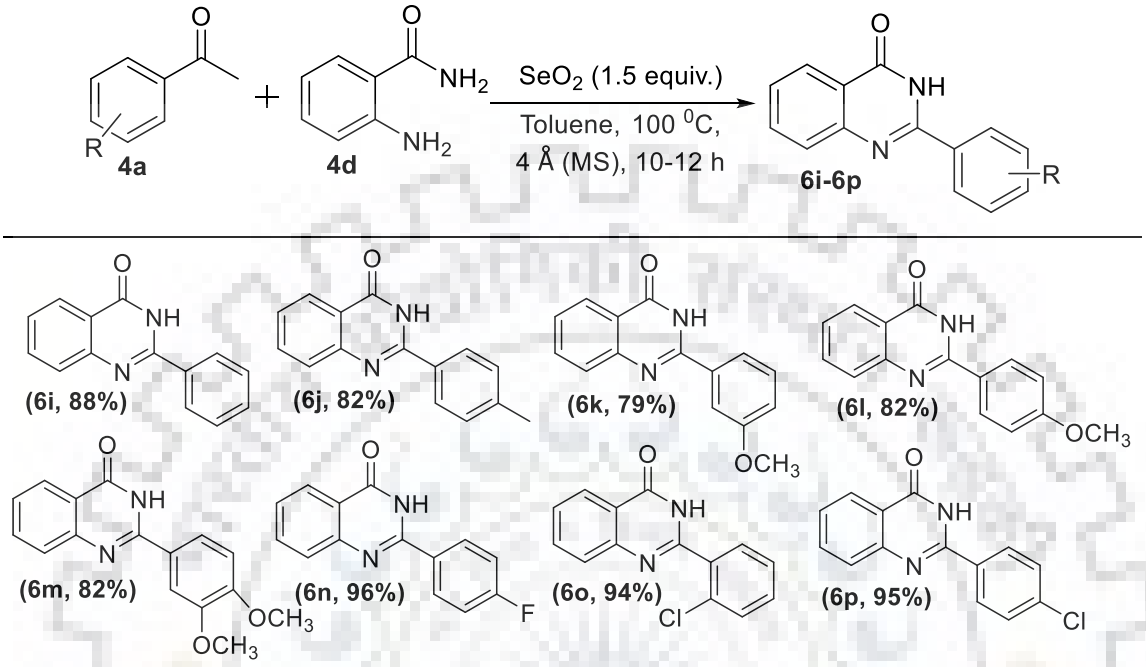


Reaction condition: 4a (1.0 mmol), **4c** (1.0 mmol) and SeO_2 (1.5 mmol) in toluene at 100 ^{0}C and molecular sievies (4 Å).

The reaction of *p*-nitro acetophenone proceeded to give the corresponding product **6h** in 90% yield in less than 8 hrs. We turned our attention to amide. Interestingly, anthranilamide and position of the substituents on the aromatic ketone does not appear to affect the reaction. It may be also noted that electron donating group including methyl, methoxy, all reacted cleanly to give the corresponding products (**6j**, **6k**, **6k** and **6m**) in

consistently high yields (79%-82%). It may be also noted that halogen substituted acetophenone required less reaction time with improved yields.

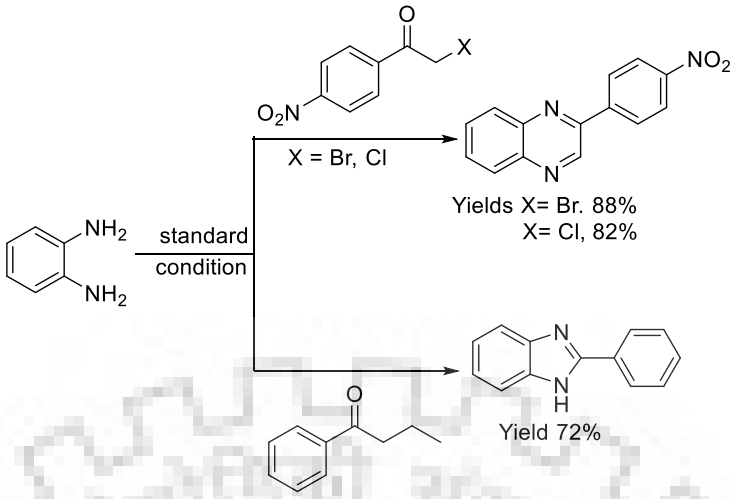
Scheme 4.4. Scope of quinazolinone



Reaction condition: **4a** (1.0 mmol), **4d** (1.0 mmol) and SeO_2 (1.5 mmol) in benzene at 100 ^{0}C and molecular sievies (4 Å).

4.4. Reaction with helophenacyl and butyrophenone

On treating the halophenacyl with phenylenediamine in the presence of selenium dioxide in benzene, the phenyl quinoxaline were formed as the major product the formation of imidazole were not be observed (scheme 4.5). When butyrophenone was reacting with *o*-phenylenediamine in the standard condition, interestingly the cleavage of C(O)—C was observed and benzinmidazole was formed as major product with 72% yield in case of butyrophenone, propionaldehyde eliminate which was confirmed by GC-MS (figure 4.2).



Scheme 4.5. Reaction with Halophenacyl and butyrophenone

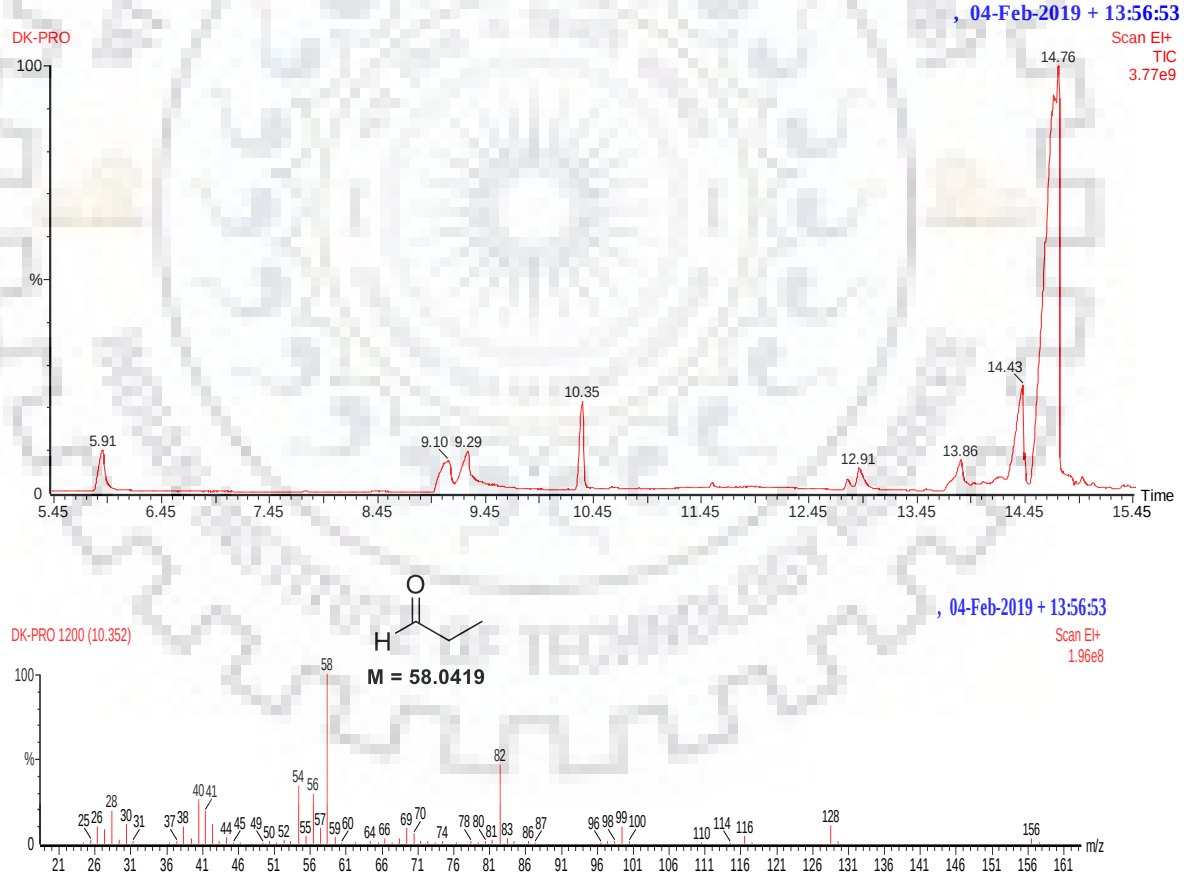
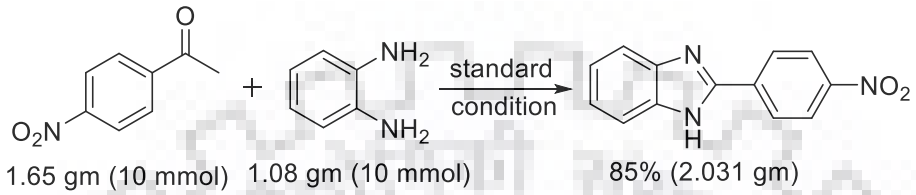


Figure 4.2. GC MS spectra of reaction mixture

4.5. Gram scale synthesis

Into the utility of this reaction, we carried out the gram-scale reaction of *o*-phenylenediamine and *p*-nitro acetophenone under the same reaction conditions and the reaction proceeded smoothly to furnish **5h** in 85% yield (Scheme 4.6).

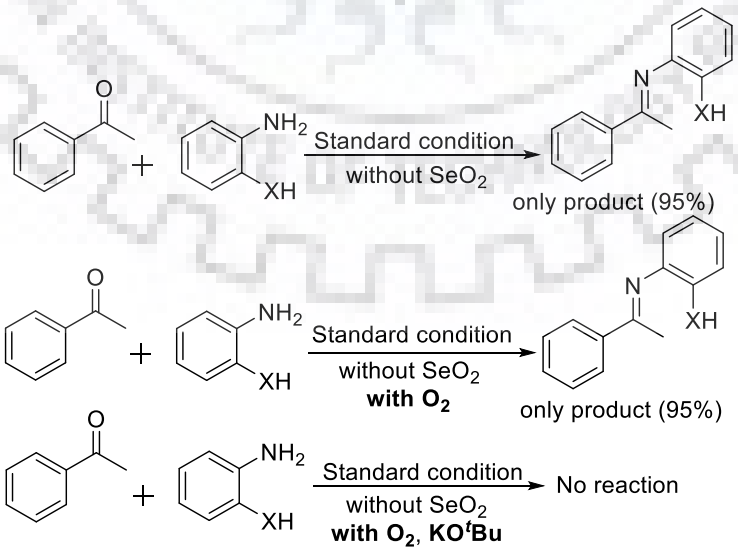


Scheme 4.6. Gram scale synthesis of 5h.

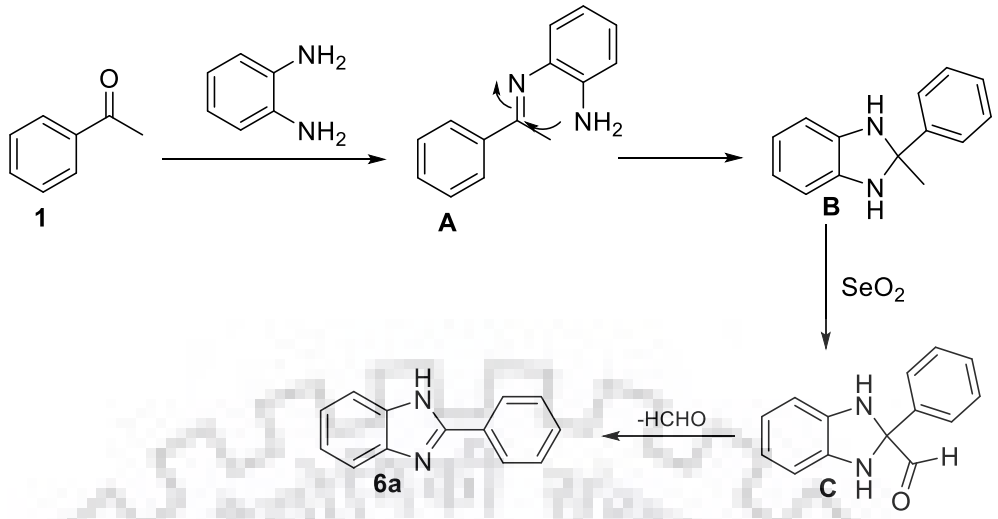
4.6. Some controlled experiment for mechanistic study

Additionally, control experiments in the absence of selenium dioxide were performed and interrupted after 20 h. analysis of the formed compound revealed the formation of Schiff's base as a single product.

In the second experiment oxygen used as an oxidant and it was found that no desired product was formed. We did one more experiment to identify the role of selenium dioxide in the presence of base (KO^{t}Bu) and oxygen and in this case there was no reaction and the starting material are isolated from the reaction mixture (scheme 4.7).



Scheme 4.7. Controlled experiment



Scheme 4.8. Proposed mechanism

On the basis of the experimental results and literaturereferences [7–9], a plausible mechanism was proposed for the selenium dioxide formation of fused heterocycles (Scheme 4.8). The acetophenone **1** formed Schiff's base with *o*-phenylenediamine, which undergoes an intramolecular cyclization to give intermediate **B**. Methyl group of Intermediate **B** oxidized by selenium dioxide to produce intermediate **C** (characterized by mass, see supporting information), which upon deformylation to converted into final product **6a**.

4.7. Conclusions

We have developed an efficient selenium dioxide mediated selected heterocycles by C—C bond cleavage of acetophenones. This method provided good-to-excellent product yields in shorter reaction time. The reaction has a number of advantages over existing procedures, for example, it is inexpensive, tolerates various functional groups under mild reaction conditions.

4.8. Experimental section

4.8.1. General Information

Unless otherwise noted, chemicals were purchased from commercial suppliers at the highest purity grade available and were used without further purification. Thin layer

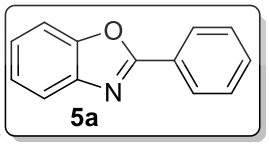
chromatography was performed on 0.25 mm silica gel plates (60F- 254) using UV light as the visualizing agent. Silica gel (100-200 mesh) was used for column chromatography. Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. IR spectra of the compounds were recorded on Thermo Nicolet FT-IR spectrometer with and are expressed as wave number (cm^{-1}). Nuclear magnetic resonance spectra were recorded on Jeol resonance ECX400MHz and Bruckers pectrospin DPX 500 MHz spectrometer, and chemical shifts are reported in δ units, parts per million (ppm), relative to residual chloroform (7.26 ppm) or DMSO (2.5 ppm) in the deuterated solvent or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.0274 ppm, the middle peak) and DMSO-d_6 (δ 39.5 ppm, the middle peak). Coupling constants were expressed in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet.

4.8.2. General procedure

To a stirred solution of acetopheone (1.0 mmol) in 5 mL of 1, 4-dioxane/toluene was added amine (1.0 mmol) and selenium dioxide (1.5 to 2.0 mmol) and the mixture was allowed to reflux for an appropriate time. After completion of the reaction as shown by TLC, the mixture was filtered on a slite pad and the solvent evaporated using vacuum. The solid crude product was obtained which was directly purified by column chromatography on silica gel (100-200 mesh) using ethyl acetate/hexanes (30:70) as the eluting system, which afforded the desired products.

4.9. Characterization data

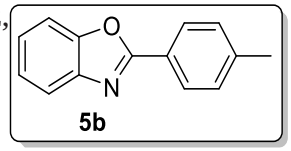
2-phenylbenzo[d]oxazole (5a):



5a

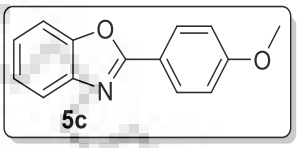
White solid; m. p. 102-104 ^0C; Yield: 86%; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.58 (d, *J* = 8.08 Hz, 2H), 7.08 (d, *J* = 7.76 Hz, 2H), 7.01 (d, *J* = 8.08 Hz, 2H), 6.93-6.83 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm157.15, 152.36, 135.88, 135.52, 131.70, 128.96, 128.89, 128.83, 120.13, 115.88, 115.03; HRMS (EI) m/z calcd for $C_{13}H_9NO$ $[M+H]^+$ 196.0762; found 196.0784.

2-(p-tolyl)benzo[d]oxazole (5b):



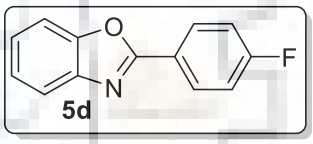
White solid; m. p. 123-1204 ^{0}C; Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm7.50 (d, *J* = 7.76 Hz, 2H), 7.36 (d, *J* = 7.88 Hz, 2 H), 7.31-7.27 (m, 1H), 7.23-7.21 (m, 1H), 7.04 (d, *J* = 7.92Hz, 2 H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 151.32, 146.48, 136.48, 129.94, 127.55, 123.81, 123.03, 122.84, 114.27, 110.06, 109.13, 15.85; HRMS (EI) m/z calcd for $C_{14}H_{11}NO$ $[M+H]^+$ 210.0919; found 210.1013.

2-(4-methoxyphenyl)benzo[d]oxazole (5c):



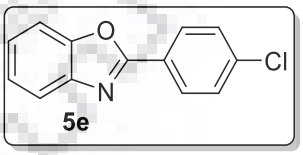
White solid; m. p. 104-106 ^{0}C; Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 (d, *J* = 7.84 Hz, 2H), 7.31-7.21 (m, 3H), 7.1 4 (t, *J* = 7.88 Hz, 1H), 7.09-7.06 (m, 1H), 6.83 (d, *J* = 9.4 Hz, 1 H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.55, 156.63, 152.12, 135.95, 130.59, 128.93, 128.32, 120.07 115.79, 114.81, 114.33, 55.47; HRMS (EI) m/z calcd for $C_{14}H_{11}NO_2$ $[M+H]^+$ 226.0868; found 226.0921.

2-(4-fluorophenyl)benzo[d]oxazole (5d):



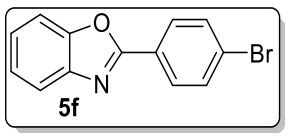
White solid; m. p. 93-94 ^{0}C; Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49-7.44 (m, 3H), 7.34 (d, *J* = 8.16 Hz, 1H), 7 .27 (d, *J* = 7.4 Hz, 2H), 7.24-7.20 (m, 2H); ^{13}C NMR (125 MH z, $CDCl_3$) δ ppm 164.60 (^1J =251.6 Hz), 155.38, 152.02, 135.09, 131.96, 130.51 (^3J = 8.71 Hz), 128.72, 119.86, 115.82 (^2J = 21.46), 115.54, 114.81; HRMS (EI) m/z calcd for $C_{13}H_8FNO$ $[M+H]^+$ 214.0668; found 214.0682.

2-(4-chlorophenyl)benzo[d]oxazole (5e):



White solid; m. p. 152-154 ^{0}C; Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.65 (d, *J* = 7.7 Hz, 1H), 7.54-7.45 (m, 4H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.30-7.25 (m, 1H), 7.21 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 154.99, 151.87, 137.16, 134.66, 133.81, 129.36, 128.71, 119.63, 115.30, 114.64; HRMS (EI) m/z calcd for $C_{13}H_8ClNO$ $[M+H]^+$ 230.0373, 232.0343; found 230.0391, 232.0361.

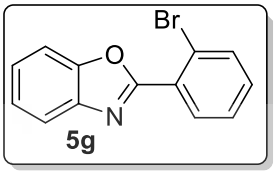
2-(4-bromophenyl)benzo[d]oxazole (5f):



White solid; m. p. 157-158 ^{0}C; Yield: 90%; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.39-8.38 (m, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.1 Hz, 3H), 7.32-7.29 (m, 1H), 7.26 (d, *J* = 7.4 Hz, 2H);

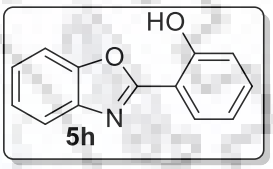
^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 149.80, 146.61, 129.35, 128.91, 126.32, 124.26, 123.49, 120.38, 114.40, 110.09, 109.43; HRMS (EI) m/z calcd for $C_{13}H_8BrNO$ $[M+H]^+$ 273.9868, 275.9847; found 273.9876, 275.9969.

2-(2-bromophenyl)benzo[d]oxazole (5g):



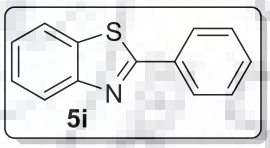
White solid; m. p. 102-104 ^0C; Yield: 89%; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.86 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 1H), 7.48-7.43 (m, 2H), 7.33-7.30 (m, 1H), 7.27 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.98, 152.62, 135.35, 134.30, 133.55, 132.72, 129.64, 128.91, 127.85, 126.37, 120.33, 116.35, 115.28; HRMS (EI) m/z calcd for $C_{13}H_8BrNO$ $[M+H]^+$ 273.9868, 275.9847; found 274.0102, 276.0101.

2-(benzo[d]oxazol-2-yl)phenol (5h):



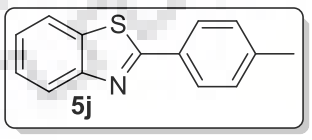
White solid; m. p. 122-124 ^0C; Yield: 92%; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.30-7.24 (m, 2H), 7.22-7.16 (m, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.88 (t, *J* = 7.7 Hz, 1H), 5.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.03, 161.16, 150.85, 135.46, 132.75, 132.12, 127.95, 119.96, 119.52, 118.79, 117.07, 116.82; HRMS (EI) m/z calcd for $C_{13}H_9NO_2$ $[M+H]^+$ 212.0712; found 212.0597.

2-phenylbenzo[d]thiazole (5i):



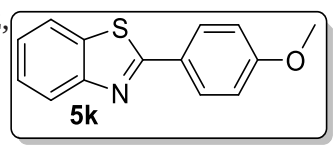
White solid; m. p. 112-113 ^0C; Yield: 86%; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.10-8.07 (m, 3H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.50 -7.46 (m, 4H), 7.38 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, C DCl$_3$) δ ppm 168.06, 154.04, 134.98, 133.51, 130.95, 128.99, 127.50, 126.20, 125.16, 123.16, 121.60; HRMS (EI) m/z calcd for $C_{13}H_9NS$ $[M+H]^+$ 212.0534; found 212.0672.

2-(p-tolyl)benzo[d]thiazole (5j):



White solid; m. p. 87-89 ^0C; Yield; 85%; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.09 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 2 H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.52-7.49 (m, 1H), 7.39 (t, *J* = 8 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.25, 154.18, 141.43, 134.96, 130.98, 129.72, 127.50, 126.24, 125.00, 123.05, 121.56, 21.51; HRMS (EI) m/z calcd for $C_{14}H_{11}NS$ $[M+H]^+$ 226.0690; found 226.0712.

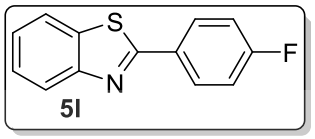
2-(4-methoxyphenyl)benzo[d]thiazole (5k):



White solid; m. p. 87-89 ^0C; Yield: 82%; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.03-8.00 (m, 3H), 7.85 (d, *J* = 7.96 Hz, 1H), 7.45 (t, *J* = 7.52 Hz, 1H), 7.33 (t, *J* = 7.64 Hz, 1H), 6.98 (d, *J*

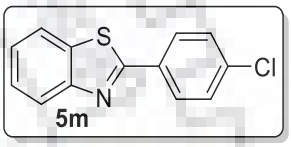
= 8.8 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.97, 161.99, 154.30, 134.94, 129.19, 126.49, 126.30, 124.89, 122.90, 121.62, 114.44, 55.55; HRMS (EI) m/z calcd for $C_{14}H_{11}NOS$ $[M+H]^+$ 242.0640; found 242.0682.

2-(4-fluorophenyl)benzo[d]thiazole (5l):



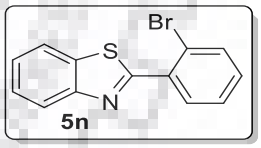
White solid; m. p. 96-97 ^{0}C; Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.09-8.04 (m, 3H), 7.88 (d, *J* = 7.96 Hz, 1H), 7.48 (t, *J* = 7.52 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.87, 164.54 (^1J = 250.52 Hz), 154.15, 135.11, 130.02 (^4J = 3.3 Hz), 129.61 (^3J = 8.7 Hz), 126.53, 125.36, 123.26, 121.73, 116.27 (^2J = 21.97Hz); HRMS (EI) m/z calcd for $C_{13}H_8FNS$ $[M+H]^+$ 230.0440; found 230.0482.

2-(4-chlorophenyl)benzo[d]thiazole (5m):



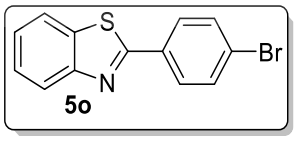
White solid; m. p. 114-116 ^{0}C; Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.81, 154.11, 135.10, 132.58, 132.32, 128.98, 126.62, 125.56, 125.52, 123.39, 121.78; HRMS (EI) m/z calcd for $C_{13}H_8ClNS$ $[M+H]^+$ 246.0144, 248.0115; found 246.0162, 248.0311.

2-(2-bromophenyl)benzo[d]thiazole (5n):



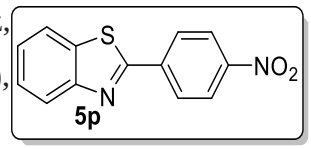
Pale yellow solid; m. p. 68-69 ^{0}C; Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.79-6.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.42, 146.31, 141.62, 133.00, 129.74, 128.08, 127.70, 126.22, 125.62, 122.11, 121.68, 121.17, 110.48; HRMS (EI) m/z calcd for $C_{13}H_8BrNS$ $[M+H]^+$ 289.9639, 291.9619; found 290.0101, 292.0113.

2-(4-bromophenyl)benzo[d]thiazole (5o):



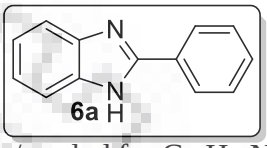
White solid; m. p. 131-132 ^{0}C; Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (d, *J* = 8.1 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.72, 154.13, 137.11, 135.12, 132.16, 129.36, 128.79, 126.59, 125.51, 123.38, 121.79; HRMS (EI) m/z calcd for $C_{13}H_8BrNS$ $[M+H]^+$ 289.9639, 291.9619; found 290.0110, 292.0103.

2-(4-nitrophenyl)benzo[d]thiazole (5p):



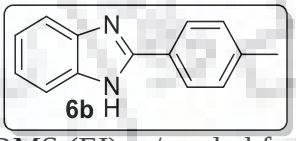
White solid; m. p. 296-297 ^{0}C; Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.34 (d, *J* = 8.6 Hz, 2H), 8.14 (d, *J* = 8.6 Hz, 2H), 7.67 (m, 1H), 7.24-7.20 (m, 2H), 7.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.08, 149.57, 147.79, 141.34, 132.97, 129.83, 128.21, 127.25, 126.22, 124.19, 117.11; HRMS (EI) m/z calcd for $C_{13}H_8N_2O_2S$ $[M+H]^+$ 257.0385; found 257.0409;

2-phenyl-1H-benzo[d]imidazole (6a):



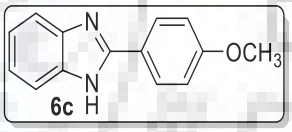
White solid; m. p. 290-292 ^{0}C; Yield: 83%; ^{1}H NMR (400 MHz, DMSO) δ ppm 12.52 (s, 1H), 8.15-8.13 (m, 3H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.55-7.46 (m, 4H); HRMS (EI) m/z calcd for $C_{13}H_{10}N_2$ $[M+H]^+$ 195.0922; found 195.1012.

2-(p-tolyl)-1H-benzo[d]imidazole (6b):



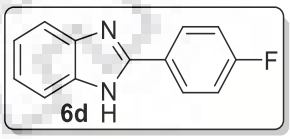
White solid; m. p. 274-276 ^{0}C; Yield: 86%; ^{1}H NMR (400 MHz, DMSO) δ ppm 12.78 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.53 (s, 2 H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.15-7.13 (m, 2H), 2.34 (s, 3H); HRMS (EI) m/z calcd for $C_{14}H_{12}N_2$ $[M+H]^+$ 209.1079; found 209.1087.

2-(4-methoxyphenyl)-1H-benzo[d]imidazole (6c):



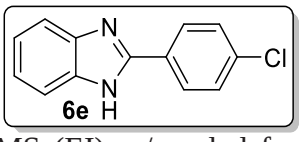
White solid; m. p. 225-226 ^{0}C; Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.30 (d, *J* = 8.0 Hz, 5H), 7.80 (d, *J* =8.1 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.02 (s, 1H), 4.03 (s, 3H); HRMS (EI) m/z calcd for $C_{14}H_{12}N_2O$ $[M+H]^+$ 225.1028; found 225.1042.

2-(4-fluorophenyl)-1H-benzo[d]imidazole (6d):



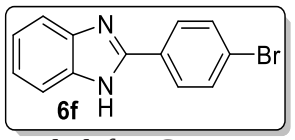
White solid; m. p. 245-247 ^{0}C; Yield: 80%; ^{1}H NMR (400 MHz, DMSO+$CDCl_3$) δ ppm 12.19 (s, 1H), 7.84-7.82 (m, 2H), 7.24-7 .22 (m, 2H), 6.83-6.78(m, 4H); HRMS (EI) m/z calcd for $C_{13}H_9FN_2$ $[M+H]^+$ 213.0828; found 213.0832.

2-(4-chlorophenyl)-1H-benzo[d]imidazole (6e):



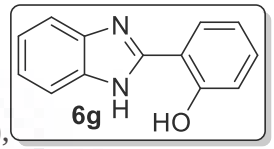
White solid; m. p. 268-270 ^{0}C; Yield: 79%; ^{1}H NMR (400 MHz, DMSO+$CDCl_3$) δ ppm 12.25 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 2H), 7. 17 (s, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.80-6.76 (m, 2H); HRMS (EI) m/z calcd for $C_{13}H_9ClN_2$ $[M+H]^+$ 229.0533, 231.0503; found 229.0583, 231.0556**.**

2-(4-bromophenyl)-1H-benzo[d]imidazole (6f):



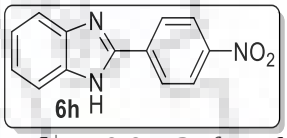
hite solid; m. p. 255-257 ^{0}C; Yield: 79%; ^{1}H NMR (400 MHz, DMSO+$CDCl_3$) δ ppm 12.14 (s, 1H), 7.65-7.63 (m, 2H), 7.17-7.14 (m, 3H), 7.04 (s, 1H), 6.77-6.74 (m, 2H); HRMS (EI) m/z calcd for $C_{13}H_9BrN_2$ $[M+H]^+$ 273.0027, 275.0007 found 273.0063, 275.0047.

2-(1H-benzo[d]imidazol-2-yl)phenol (6g):



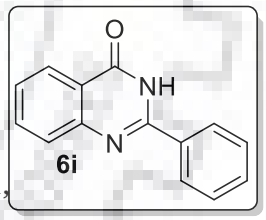
White solid; m. p. 240-242 ^{0}C; Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.75 (s, 1H), 12.23 (s, 1H), 8.11-8.06 (m, 2H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.81-7.72 (m, 2H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.94, 142.69, 140.93, 138.44, 133.07, 131.15, 129.76, 129.39, 127.68, 126.80, 119.50, 118.93, 117.31; HRMS (EI) m/z calcd for $C_{13}H_{10}N_2O$ $[M+H]^+$ 211.0871; found 211.0881.

2-(4-nitrophenyl)-1H-benzo[d]imidazole (6h):



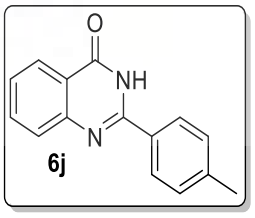
Yellow solid; m. p. 263-264 ^{0}C; Yield: 90%; ^{1}H NMR (400 MHz, DMSO) δ ppm 13.26 (s, 1H), 8.36-8.35 (m, 4H), 7.69-7.53 (m, 2H), 7.24-7.22 (m, 2H); HRMS (EI) m/z calcd for $C_{13}H_9N_3O_2$ $[M+H]^+$ 240.0773; found 240.0606.

2-phenylquinazolin-4(3H)-one (6i):



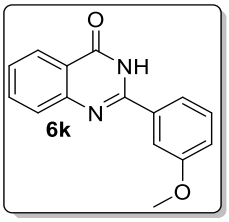
White solid; m. p. 232-235 ^{0}C; Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.07 (s, 1H), 8.32-8.27 (m, 3H), 7.83-7.76 (m, 2H), 7.57-7.56 (m, 3H), 7.48 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm164.20, 151.93, 149.62, 134.99, 132.90, 131.71, 129.09, 128.07, 127.58, 126.85, 126.43, 120.89; HRMS (EI) m/z calcd for $C_{14}H_{10}N_2O$ $[M+H]^+$ 223.0871; found 223.0943.

2-(p-tolyl)quinazolin-4(3H)-one (6j):



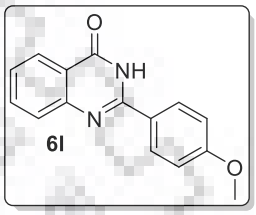
White solid; m. p. 239-242 ^{0}C; Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.13 (s, 1H), 8.31 (d, *J* = 7.92 Hz, 1H), 8.09 (d, *J* = 7.96 Hz, 2H), 7.82-7.76 (m, 1H), 7.48 (t, *J* = 7.68 Hz, 1H), 7.38-7.33 (m. 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.08, 151.95, 149.69, 142.26, 134.92, 130.04, 129.83, 127.95, 127.45, 126.64, 126.43, 120.83, 21.64; HRMS (EI) m/z calcd for $C_{15}H_{12}N_2O$ $[M+H]^+$ 237.1028; found 237.1042.

2-(3-methoxyphenyl)quinazolin-4(3H)-one (6k):



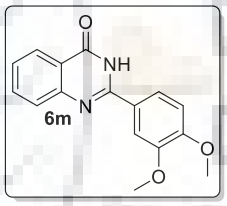
White solid; m. p. 208-210 ^{0}C; Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.73 (s, 1H), 8.29 (d, *J* = 7.9 Hz, 1H), 7.84-7.77 (m, 4H), 7.47 (q, *J* = 8.36 Hz, 2H), 7.12 -7.10 (m, 1H), 3.95 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.07, 160.20, 151.80, 149.52, 135.00, 134.20, 130.17, 128.10, 126.92, 126.40, 120.95, 119.83, 118.37, 112.22, 55.68; HRMS (EI) m/z calcd for $C_{15}H_{12}N_2O_2$ $[M+H]^+$ 253.0977; found 253.1033.

2-(4-methoxyphenyl)quinazolin-4(3H)-one (6l):



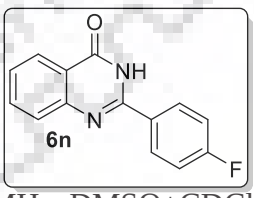
White solid; m. p. 247-249 ^{0}C; Yield: 82%; ^{1}H NMR (400 MHz, DMSO+$CDCl_3$) δ ppm 12.20 (s, 1H), 8.13 (d, *J* = 8.6 Hz, 2H), 8.0 7 (d, *J* = 7.8 Hz, 1H), 7.70 -7.66 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.37-7.34 (m, 1H), 7.97-6.94 (m, 2H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, DMSO+$CDCl_3$) δ ppm162.95, 162.25, 152.33, 149.25, 134.65, 129.80, 127.45, 126.26, 126.18, 125.21, 121.08, 114.22, 55.70; HRMS (EI) m/z calcd for $C_{15}H_{12}N_2O_2$ $[M+H]^+$ 253.0977; found 253.1041.

2-(3,4-dimethoxyphenyl)quinazolin-4(3H)-one (6m):



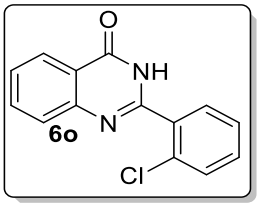
Yellow solid; m. p. 245-247 ^{0}C; Yield: 82%; ^{1}H NMR (400 MHz, DMSO) δ ppm 11.76 (s, 1H), 7.79-7.77 (m, 1H), 7.44-7.40 (m, 2H), 7.32 (s, 2H), 7.00 (s, 1H), 658-6.56 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 162.89, 152.37, 152.10, 149.42, 149.06, 135.09, 127.83, 126.66, 126.35, 125.25, 121.67, 121.19, 111.82, 111.18, 56.19, 56.14; HRMS (EI) m/z calcd for $C_{16}H_{14}N_2O_3$ $[M+H]^+$ 283.1083; found 283.1101.

2-(4-fluorophenyl)quinazolin-4(3H)-one (6n):



White solid; m. p. 240-242 ^{0}C; Yield: 96%; ^{1}H NMR (400 MHz, DMSO+$CDCl_3$) δ ppm 12.52 (s, 1H), 8.22-8.19 (m, 2H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO+$CDCl_3$) δ ppm 164.56 (^1J = 248.24 Hz), 162.79, 151.90, 149.13, 135.11, 130.87 (^3J = 9.1 Hz), 129.71 (^4J = 3.2 Hz), 127.91, 127.09, 126.36, 121.37, 116.12 (^2J = 21.86 Hz); HRMS (EI) m/z calcd for $C_{14}H_9FN_2O$ $[M+H]^+$ 241.0777; found 241.0791.

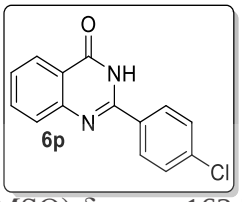
2-(2-chlorophenyl)quinazolin-4(3H)-one (6o):



White solid; m. p. 198-199 ^{0}C; Yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.22 (s, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 7.80-7.77 (m, 2H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.50-7.46 (m, 2H), 7.44-7.36

(m, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 162.74, 151.33, 149.05, 135.02, 132.88, 132.19, 123.03, 131.40, 130.60, 128.02, 127.50, 127.46, 126.55, 121.08; HRMS (EI) m/z calcd for $C_{14}H_9ClN_2O$ $[M+H]^+$ 257.0482, 259.0452 found 257.0417, 259.0478.

2-(4-chlorophenyl)quinazolin-4(3H)-one (6p):



White solid; m. p. 300-301 ^{0}C; Yield: 95%; ^{1}H NMR (400 MHz, DMSO) δ ppm 12.58 (s, 1H), 8.16 (d, *J* = 9.0 Hz, 2H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.87-7.77 (m, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 2H), 7.52-7.43 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ pmm 162.71, 151.89, 149.10, 136.84, 135.23, 132.07, 130.16, 129.23, 128.06, 127.33, 126.41, 121.51; HRMS (EI) m/z calcd for $C_{14}H_9ClN_2O$ $[M+H]^+$ 257.0482, 259.0452 found 257.0515, 259.0482.

4.10. References

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Chapter-5

Cu (0) and Cu (I) oxide catalysed cyclisation of halo-betti base via ullmann couling: synthesis of fused banzo-xanthene and oxazine

5.1. Introduction

Coupling reaction is one of the most important methods for the construction of carbon-carbon and carbon-hetero atom bond such as oxygen and nitrogen of various heterocyclic compounds and natural products [1]. Most classical method used for the formation of various types of bond is the Ullmann. This classical coupling method, however, have several drawback and several limitations such as high reaction temperature, use of stoichiometric or greater quantities of the copper salt and copper complexes, long reaction time and only moderate yields of product [2]. Recently, several methodology have been developed for the production of corbon-heteroatom bond by adding chelating ligand such as aminoacids [3], 8-Hydroxyquinoline [4], diamine [5], diketone [6], phenanthroline [7], phosphazene P4-*t*-Bu base [8], neocuproine [9], monodendate and bidendate ligands [10], picolinic acid [11], 2,2,6,6-tetramethylhep-tane-3,5-dione [12] aminophenols [13] pivalic acid [14] diimine ligands [15] and ethylene glycol [10] as solvent to enhance the solubility of copper salts for giving better yields of product. Cu_2O/MNBO-Catalyzed Aryl Amination with High Turnovers was reported after the Discovery of N-(Naphthalen-1-yl)-N′-alkyl Oxalamide types Ligands [16]. Recently Dawei Ma *et al*. described Diaryl Ether Formation from (Hetero)aryl Halides by using very low amount of Copper (I) Catalyst [17]. "On Water'' Promoted Ullmann-Type C—N Bond-Formation was reported in 2018 by Jyotirmayee Dash and co-workers using Carbazole Alkaloids by Selective N-Arylation of Aminophenols [18].

Recently, attraction of scientist towards in the chemistry of the Betti base [19] has increased due to their biological [20] and catalytic [21] properties and it was also found that betti base is an interesting precursor for various transformation [22]. Betti base (1-α-aminobenzyl-2-naphthol) are prepared by condensation of β-naphthol, benzaldehyde and ammonia and contains two potentially reactive functional groups like amino and hydroxyl and two rigid rings such as phenyl and naphthyl, but it is thermally unstable and therefore, it is not easy to synthesize their corresponding N-alkyl and N, N-dialkyl derivatives [23]. However, the alkyl and dialkyl derivative of Betti base has been prepared by the original Betti procedure [24] The most valuable method was reported by Katritzky and co-worker by substitution of the benzotriazole moiety from N-[a-(dialkylami-no)alkyl] benzotriazoles with phenolate anions under refluxing condition [25]. In the beginning of the twentieth century, Betti base and its derivatives have been known [26], however their application in research area has remained silent some time. Due to the chiral center in Betti base, in recent decades there has been an increasing focus on the application in

asymmetric reactions. Betti base and their derivatives have been used as a chiral catalyst for the asymmetric addition of Et_2Zn to aldehydes [27] and the asymmetric allylic alkylation reaction [28]

Xanthenes and benzoxanthenes is class of heterocyclic compounds having pyran ring, these compounds are synthetically important due to broad biological spectrum such as anti-inflammatory, antiviral, and antibacterial activities and dyes (figure 5.1) [29]. Xenthene and benzoxenthene are also used as sensitizer for destroying the tumor cells in photodynamic therapy [30], pH sensitive fluorescent materials for visualization of biomolecules [31], antagonists of the paralyzing action of zoxazolamine [32] and in the laser technology [33]

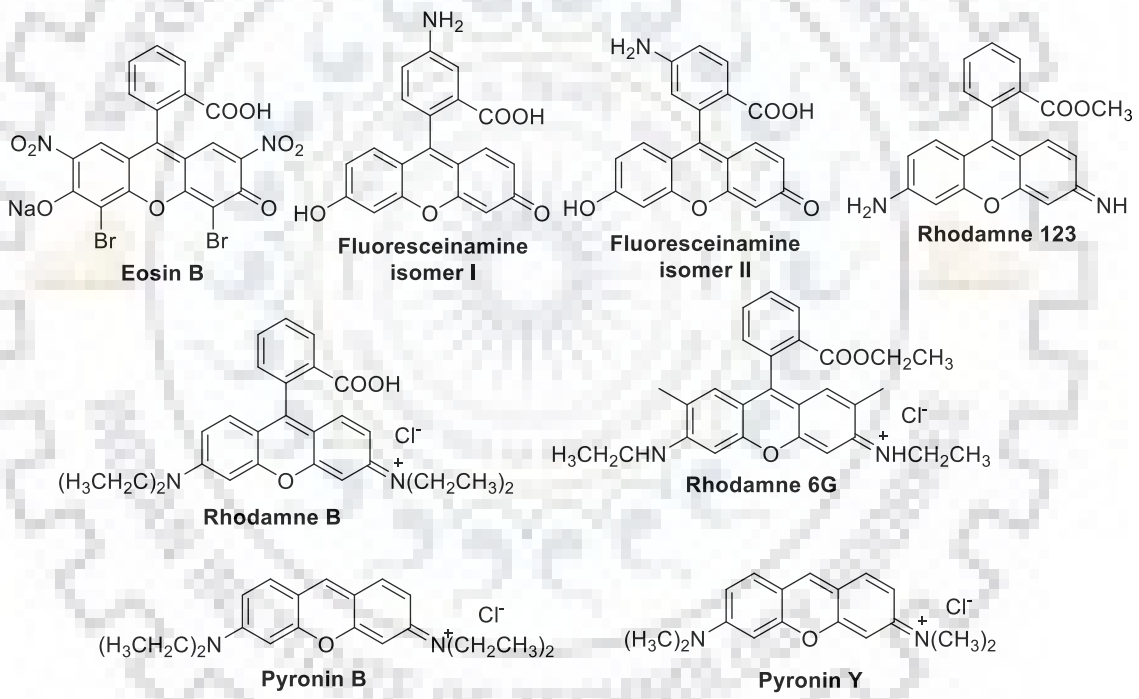
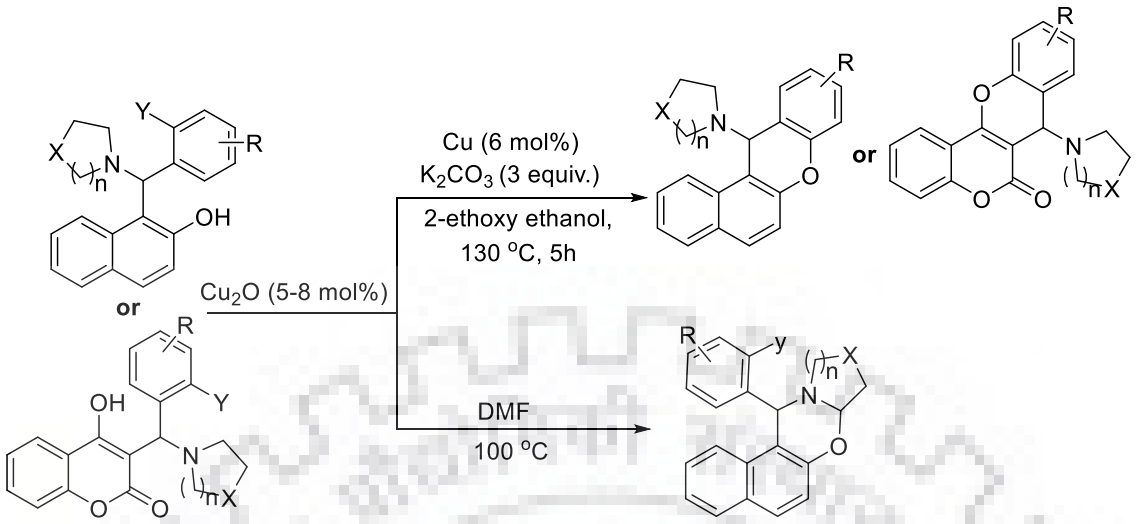


Figure 5.1. Structure of xanthene dyes

Dihydro-1,3-oxazine and their derivatives are also important class of heterocyclic molecules with their pharmacological activity including antituberculosis [34], fungicidal [35], antitumor [36] antibacterial [37] and anti-HIV [38]. Naphthoxazine derivatives are shows excellent biological activity towards Parkinson's disease and are also used as potent nonsteroidal progesterone receptor agonists [39]. Therefore, design and syntheses of these types of compounds are highly desirable for drug discovery and medicinal chemistry.



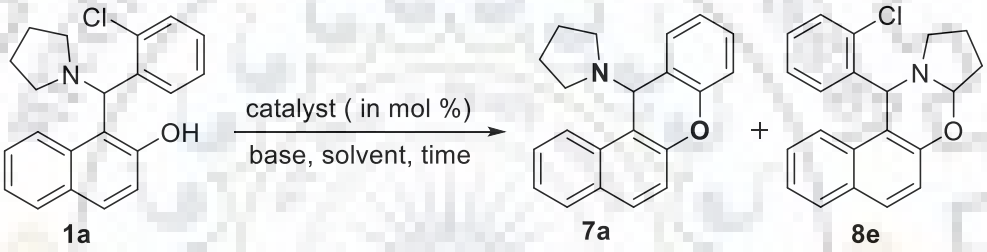
Scheme 5.1. Synthesis of benzofused xanthene and oxazine

5.2. Results and discussion

We started our initial study, using substrate **1a** (Betti base) were tested for the Ullmann type coupling reaction in the presence of copper salt. Following a literature report [40] we first studied the model reaction of 1a in the presence CuI using 2.5 mol% for 28 hours at 80 ^{0}C in DMF (dimethylformamide) as solvent with K_2CO_3 (3 equiv.) base. The reaction was failed to give the product **7a** along with **8e** in 40% yield (Table 5.1, entry 1). Than we decided to change the CuI by other Copper salt like Cu_2O. Than we started our optimisation with 2.5 mol% of Cu_2O in DMF with base K_2CO_3, 3 equiv. and realise that reaction condition worked and afforded the product **7a** and **8e** in 25% and 56% yield respectively (Table 5.1, entry 2) in 24 minutes. To verify the role of Cu_2O, we performed a comparative experiment without Cu_2O and base (Table 5.1, entry 3). However, the reaction failed to afford the desired product **7a** and also **8e**, the starting substrate recovered as it is from the reaction flask. This experiment confirmed that Cu_2O and base is necessary to promote the process. To optimize the product **7a** yield, we performed many experiment changing the amount of Cu_2O and found that if we raised the amount of Cu_2O from 2.5 to 4 mol%, yield of product **7a** was not increased but yield of **8e** was reached upto 65% and no improvement in time observed (Table 5.1, Entry 4). Instead of Cu_2O the use of copper (Cu) powder along with base did not much effective for the production of **7a** (Table 5.1, entry 5). On the other hand use of CuI with Copper powder also not

effective and we got lower yield of desired product **7a** in comparison to **8e** (Table 5.1, entry 6). When the addition of copper powder (Cu) with Cu_2O enhanced the product yield. Within the reaction condition we decided to add copper powder with Cu_2O and optimise how much amount is necessary for maximum yield of **7a**. We observed the addition of 8 mole% copper powder with 4 mole% Cu_2O increased the product **7a** yield upto 69% (Table 5.1, entry 7). The use of Copper powder 9 mol% afforded the product **7a** in yield (75%) in DMF within 12 h, although **8e** was also formed in minor amount (Table 5.1, entry 8). It was found that 12 mol% Copper powder did not improve the product yield and not benefit for the reaction time (Table5.1, entry 9).

Table 5.1. Optimization of the reaction conditions.



1a **7a** **8e**

Entry	Catalyst in mol%	solvent	Base 3 eqv.	Time	[b]Yield % **7a**	**8e**
1	CuI (2.5)	DMF	K_2CO_3	28 h	0	40
2	Cu_2O(2.5)	DMF	K_2CO_3	24 min	25	56
3	-	DMF	-	28	0	0
4	Cu_2O (4)	DMF	K_2CO_3	24 min	25	65
5	Cu (8)	DMF	K_2CO_3	24 h	32	0
6	Cu (8), CuI (6)	DMF	K_2CO_3	16 h	40	45
7	Cu (8), Cu_2O (4)	DMF	K_2CO_3	12 h	69	20
8	Cu (9), Cu_2O (4)	DMF	K_2CO_3	12 h	75	10
9	Cu (12), Cu_2O (4)	DMF	K_2CO_3	12 h	75	trace
10	Cu (9), Cu_2O (8)	DMF	K_2CO_3	12 h	75	trace
11	Cu (6), Cu_2O (8)	DMF	K_2CO_3	12 h	86	0
12	Cu (4), Cu_2O (8)	DMF	Na_2CO_3	18 h	62	0

13	Cu (6), Cu_2O (8)	DMF	Cs_2CO_3	12 h	86	0
14	Cu (6), Cu_2O (8)	DMF	K_3PO_4	12 h	86	0
15	Cu (6), Cu_2O (8)	DMF	Pipredine	36 h	12	Trace
16	Cu (6), Cu_2O (8)	DMF	pyridine	36 h	10	Trace
17	Cu (6), Cu_2O (8)	DMF	triethylamine	36 h	13	Trace
18	Cu (6), Cu_2O (8)	DCM	K_2CO_3	23 h	52	0
19	Cu (6), Cu_2O (8)	MeOH	K_2CO_3	24 h	40	0
20	Cu (6), Cu_2O (8)	EtOH	K_2CO_3	24 h	41	0
21	Cu (6), Cu_2O (8)	Toluene	K_2CO_3	24 h	60	25
22	Cu (6), Cu_2O (8)	ACN	K_2CO_3	16 h	66	20
23	Cu (6), Cu_2O (8)	DMSO	K_2CO_3	12 h	76	0
[c]24	Cu (6), Cu_2O (8)	2-ethoxy ethanol	K_2CO_3	5 h	82	0
25	**Cu (6), Cu_2O (8)**	**2-ethoxy ethanol**	**K_2CO_3**	**5 h**	**92**	**0**
26	Cu (6), Cu_2O (8)	Ethylene glycol	K_2CO_3	8 h	85	0
27	Cu (6), Cu_2O (8)	Glycerol	K_2CO_3	8 h	81	0

Reaction condition: 1a (1.0 mmol), Cu (6 mol%), Cu_2O (8 mol%) in 2-ethoxyethanol (5ml) at 130 ^{0}C; [c]100 ^{0}C; [b]Isolated yields.

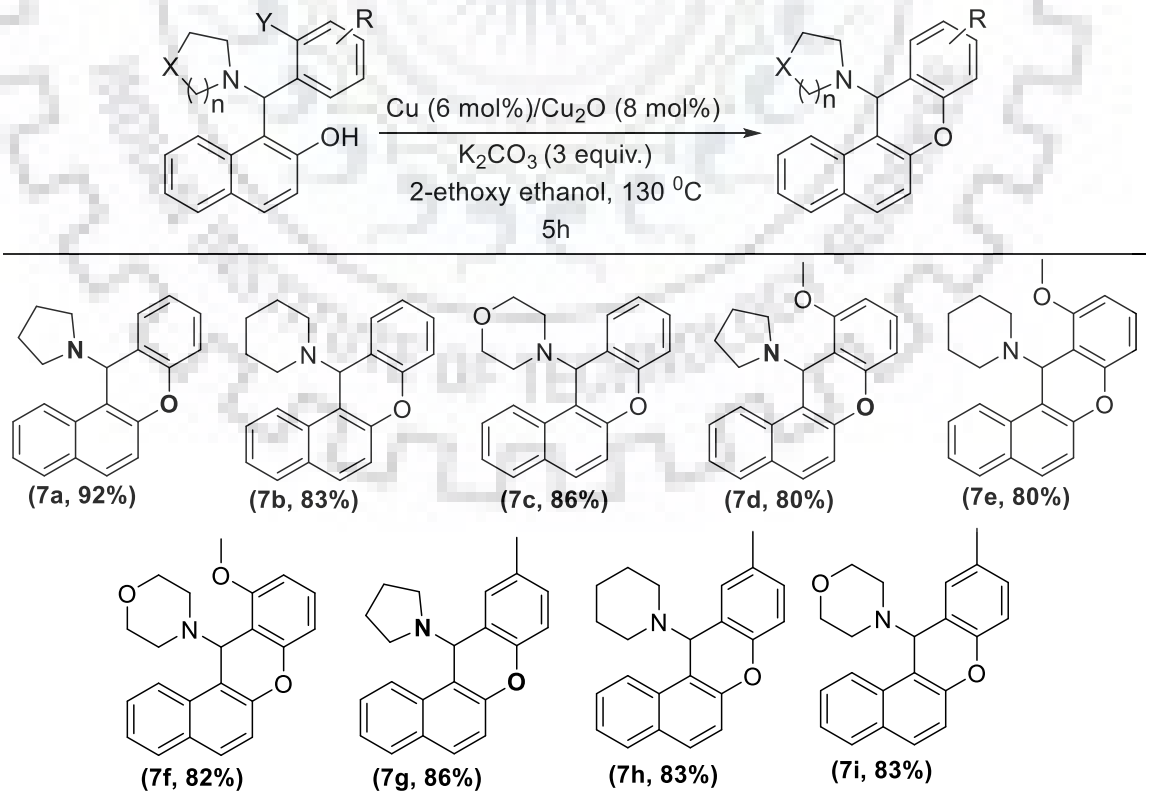
After the above observation we also studied the reaction by changing Cu_2O amount and observed that 6 mole% copper powder and 8 mole % Cu_2O gave the highest yield (86 %) in DMF in 12 hours (Table 5.1, entry 11). Further the inorganic bases like Na_2CO_3, Cs_2CO_3 and K_3PO_4 were also screened (Table 5.1, entries 12-14) but no improvement of yield of **7a** and time was observed. Organic base such as pipredine, pyridine and triethylamine were not effective and gave the less amount of the product **7a** along with trace amount of **8e** (Table 5.1, entry 15-17). We also tested different solvents, such as DMSO, CH_3CN, DCM, methanol, ethanol, toluene and 2-ethoxy ethanol in the reaction. Solvents like DCM, Methanol and ethanol were found to be unsuitable for the reaction;

in these solvents low yield of the product **7a** were obtained (Table 5.1, entries 18, 19 and 20). The reaction in toluene afforded product **7a** in 60% yield in 24 hours (Table 5.1, entry 21). With acetonitrile the product **7a** was furnished in yields of 66% (Table 5.1, entry 22), whereas the use of DMSO gave 72% yield of **7a** within 12 hours (Table 5.1, entry 23). Solvent like 2-ethoxy ethanol found to be more effective in this reaction and produced **7a** with 82 % yield in 5 hours at 100 ^{0}C (Table 5.1 entry 24). Increment of temperature from 100 ^{0}C to 130 ^{0}C increase the yield of product **7a** without the formation of **8e** (Table 5.1, entry 25). We also screened diol and triol like ethylene glycol and glycerol but less amount of product was formed (Table 5.1, entry 26 and 27). Of the solvents tested, 2-ethoxy ethanol was found to be the best in terms of yield and reaction time.

5.3. Substrate scope of reaction

5.3.1. Cyclization of β-naphthol based Betti base

Scheme 5.3.1 Cyclization of β-naphthol based Betti base

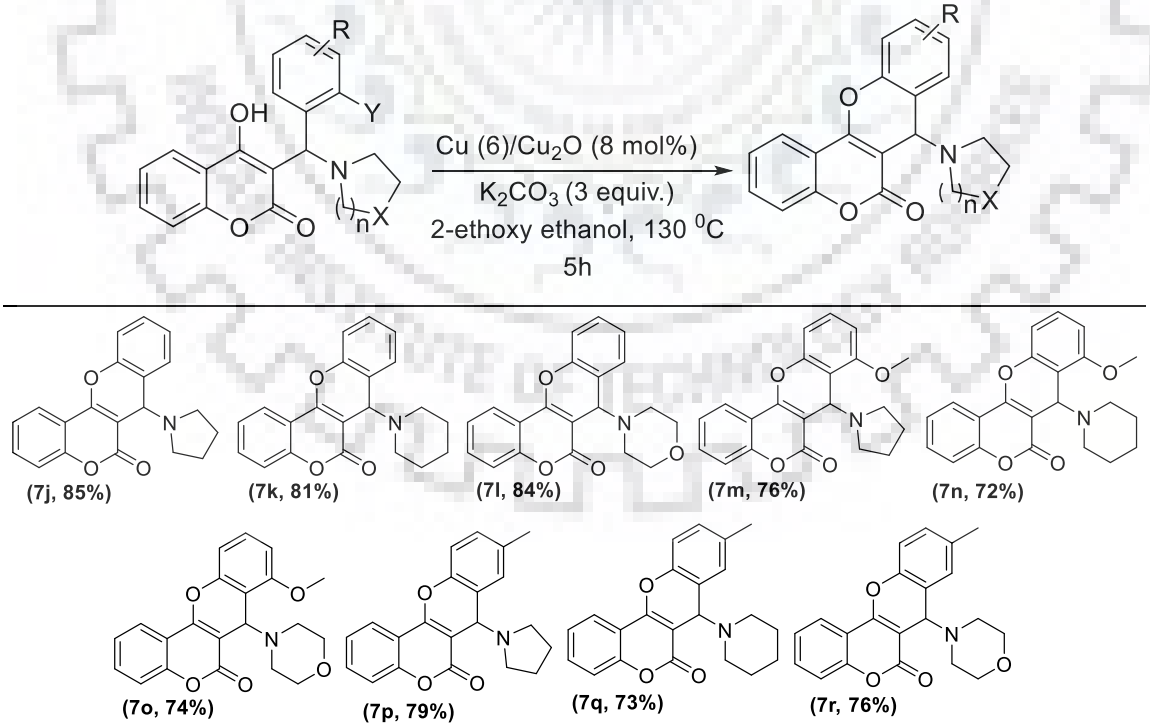


Reaction condition; 1a (1.0 mmol), Cu (6 mol%), Cu_2O (8 mol%) in 2-ethoxyethanol (5ml) at 130 ^{0}C

Under optimized reaction conditions, we further explored the scope of substrates in Copper catalyzed reaction of 1-((2-halophenyl)(pyrrolidin-1-yl)methyl)naphthalen-2-ol derivatives for the synthesis of xanthene fused derivatives (Scheme 5.3.1). Under the optimal reaction conditions, the reaction of **1a** without substituents on these rings smoothly proceeded to give **7a** within 5 hours in 92 % yield (Scheme 5.3.1). We first studied the different type of cyclic secondary amine like Pyrrolidine, piperidine and morpholine. In case of pyrrolidine the cyclisation reaction was fast and the desired product produced in high yield such **7a**, as the ring size increases from five membered to six membered the corresponding product (**7b**, **7c**) was obtained with lower yield. This effect followed all the compound. We also optimized the electronic effect on the ring phenyl ring, and found that electron-releasing groups like methoxy and methyl decreased the yields of the product without gaining any advantage in terms of reaction time (e.g., **7d** to **7i**).

5.3.2. Cyclisation of 4-hydroxy coumarin based Betti base

Scheme 5.3.2. Cyclization of 4-hydroxy coumarin based Betti base



Reaction condition; 1a (1.0 mmol), Cu (6 mol%), Cu_2O (8 mol%) in 2-ethoxyethanol (5ml) at 130 ^{0}C

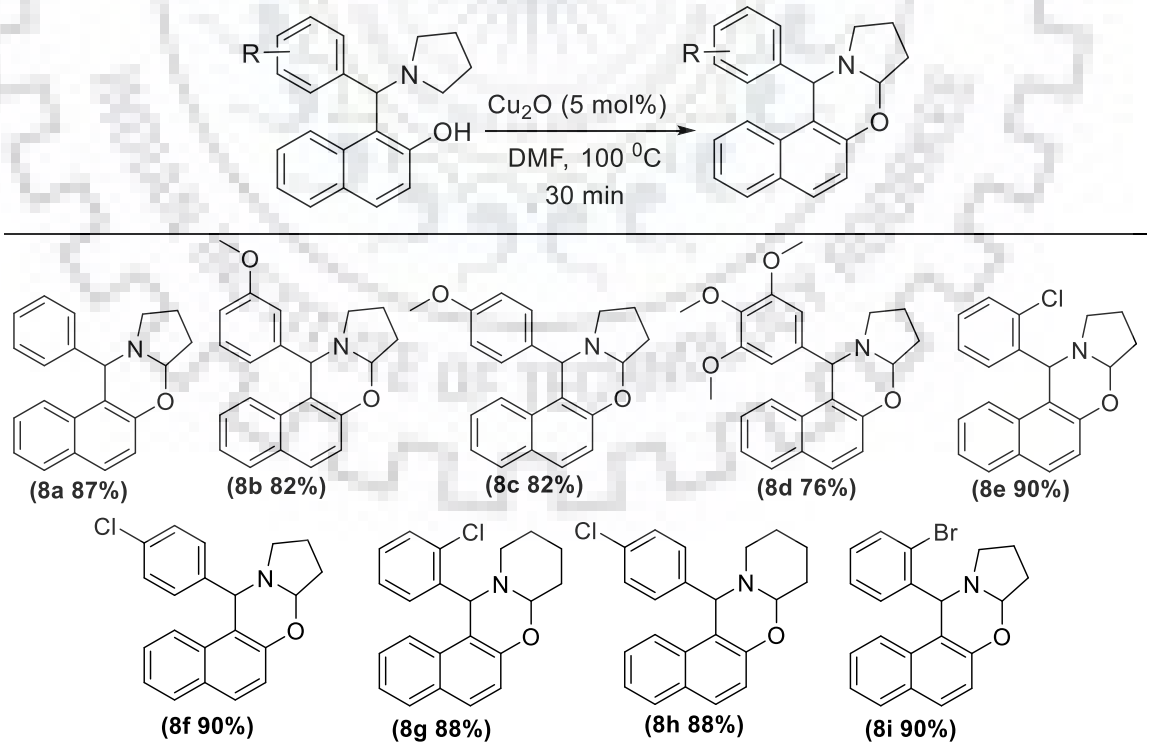
We further extended our study and changed the β-naphthol to 4-hydroxy coumarin. It was observed that in case of 4-hydroxy coumarin the reaction condition worked well and the cyclic product formed with 85% yield.

Furthermore, the yields of the products did not much effected by the amine ring size and the corresponding product (**7k** and **7l**) was formed in 81% and 84% yields respectively. Under the optimized reaction condition the effect of electron releasing was also optimize and observed that electron donating groups such as methoxy and methyl on phenyl ring decrease the product yield also with coumarin partner (**7m** to **7r**).

5.3.3. Cyclisation of Betti base into oxazine

More extension of this work with oxazine formation has also been explored and found that different substituent on phenyl ring effect the yield of product in different way (scheme 5.3.3).

Scheme 5.3.3. Cyclisation of Betti base into oxazine



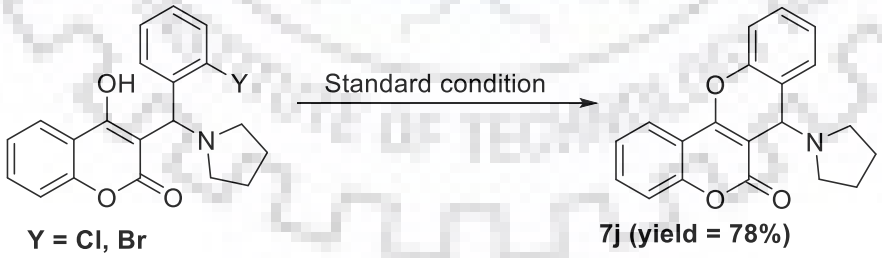
Reaction condition; 1a (1.0 mmol), Cu_2O (5 mol%) in DMF (5ml) at 100 ^{0}C.

During the observation it was found that electron withdrawing groups like Chlorine and bromine shows good reactivity for reaction and convert into oxazine (**8e**, **8f**, **8g**, **8h** and **8i**) faster with higher yield as compare to product **8a**. Moreover, electron donating group such as methoxy on phenyl ring decreased the yield of corresponding product **8b** and **8c**, increase the number of methoxy group on phenyl ring shows lower will be the yield of the product (ex. **8d**).

The structure elucidation of $C_{21}H_{19}NO$ (**7a**) was done on the basis of the collective information obtained from various spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS. Compound **7a** was obtained as a white solid. The IR spectrum of **7a** showed absorptions at 1271, 1027 cm^{-1} for C—O—C (ether). **1a** shows –OH at 3430 $cm^{-1}$and the disappearance of 3430 (–OH) cm^{-1} peak in **8a** confirmed the cyclization product. In ^{13}C NMR spectrum of **8a** shows nineteen signals due to asymmetry of ring benzene. Further the cyclized structure of the product $C_{21}H_{19}NO$ was confirmed by HRMS. The m/z molecular ion peak [M+H] at 302.1545 due to removal of one Halo-group from **7a**.

5.4. Gram scale synthesis

For more insight into the utility of this reaction, we carried out the gram-scale reaction of (**1a**) under the same reaction conditions; the reaction proceeded smoothly to furnish (**7j)** in 78% yield in 8h hours (Scheme 5.4).



Scheme 5.4. Gram scale synthesis of **7j**

5.5. Conclusion

In conclusion, we have developed a highly efficient and environmental friendly method for cyclisation halo-Betti base to convert into xanthene and oxazine. The synthetic procedure is very simple, no need for additional ligand (ligand free) and vary cheap in

coast. The given method is effective for gram scale synthesis and tolerate wide range of functional groups with less catalytic loading, reaction time and produce high yield of products.

5.6. Experimental Section

5.6.1. General information

Organic solvents were dried by standard methods; the reagents (chemicals) were purchased from commercial sources, and used without further purification. All reactions were monitored by TLC using precoated silica gel aluminum plates. Visualization of TLC plates was accomplished with an UV lamp. Melting points were recorded on Perfit apparatus and are uncorrected. All products were characterized by NMR and HRMS. ^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform and dimethyl sulphoxide ($CDCl_3$ and DMSO-d_6) on a 500MHz, 400 MHz, 125 MHz and 100 MHz spectrometer (Bruker and Jeol) respectively. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (brs). HRMS were recorded with a micro TOF-Q analyzer spectrometer in electrospray mode.

5.6.2. General procedure for Betti base: In a 50 ml round bottom flask take 1.0 mmol β-naphthol/4-hydroxy coumarin, 2-halo benzaldehyde (1.0 mmol) and secondary amine (1.5 mmol) was dissolved in ethanol (5 ml) and the resulting solution was stirred at room temperature for appropriate time. After some time precipitate was formed. The progress of the reaction was checked by TLC. After completion of reaction as indicated by TLC formed precipitate was filtered and washed with cold ethanol, dry it and used for next reaction.

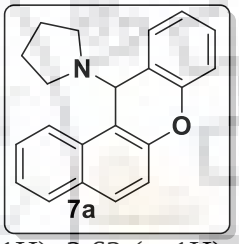
5.6.3. General procedure for the coupling reaction: In a stirred solution of Betti baes (1.0 mmol) in 2-ethoxy ethanol was add Cu powder (6 mol%), Cu_2O (8 mol%) and K_2CO_3 (3 mmol) and the mixture was allowed to heat for appropriate time at 130 ^{0}C. After completion of reaction as indicated by TLC. The reaction mixture was cool to room temperature and poured into ice chilled water and add 20 ml 10 N HCl to neutralize the

reaction component. After addition of dilute HCl precipitate was formed filter it, dry it and purify by column chromatography using hexane and ethyl acetate as elutent (9:1).

5.6.4. General procedure for oxazine: In 25 ml round bottom flask charged with Cu_2O (5 mol%) in DMF was add Betti baes (1.0 mmol) and the reaction mixture was stir at 100 ^{0}C. After completion of reaction as indicated by TLC. The reaction mixture was cool to room temperature and poured into ice chilled water to formed precipitate, filter it, dry it and purify by column chromatography using hexane and ethyl acetate as elutent (9.5:0.5).

5.7. Characterization data

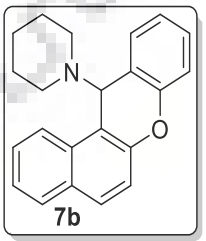
1-(12H-benzo[a]xanthen-12-yl)pyrrolidine (7a):



7a

White solid; Yield: 92%; m. p. 146.8-147.6 ^{0}C; FTIR (KBr): ν/cm^{-1} 1818, 1601, 1555, 1359, 1226, 959; ^{1}H NMR ($CDCl_3$ + DMSO, 400 MHz) δ ppm 7.89 (d, *J* = 8.5 Hz, 1H), 7.61-7.50 (m, 2H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.20-7.13 (m, 1H), 7.06-7.00 (m, 2H), 6.88-6.87 (m, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.57 (t, *J* = 6.3 Hz, 1H), 5.78 (s, 1H), 3.12 (s, 1H), 2.62 (s, 1H), 2.27 (s, 1H), 2.03 (s, 1H), 1.71 (d, *J* = 35.0 Hz, 4H); ^{13}C NMR ($CDCl_3$ + DMSO, 100 MHz) δ ppm 156.51, 140.06, 132.90, 132.31, 130.76, 129.67, 129.52, 128.70, 128.62, 128.40, 126.64, 124.62, 122.55, 121.67, 120.13, 116.47, 67.30, 54.67, 49.78, 23.45, 23.36; HRMS (EI): calcd. for $C_{21}H_{19}NO$ $[M+H]^+$ 302.1545; found 302.1235.

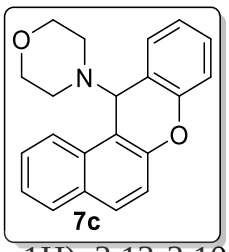
1-(12H-benzo[a]xanthen-12-yl)piperidine (7b):



7b

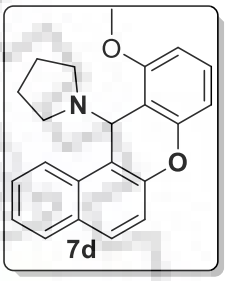
White solid; Yield: 83%; m. p. 132.8-133.8 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1816, 1596, 1586, 1298, 1256, 894; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.88 (d, *J* = 8.5 Hz, 1H), 7.67 (t, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 3.08 (s, 1H), 2.70 (s, 1H), 2.49 (s, 1H), 1.76-1.55 (m, 6H), 1.38 (s, 1H); ^{13}C ($CDCl_3$, 100 MHz) δ ppm 156.69, 137.64, 134.40, 132.91, 131.11, 129.68, 129.52, 129.28, 128.83, 128.63, 128.12, 126.73, 122.59, 121.40, 120.20, 120.16, 115.94, 66.42, 54.95, 49.47, 26.51, 26.04, 24.14; HRMS (EI): calcd. for $C_{22}H_{21}NO$ $[M+H]^+$ 316.1701; found 316.1802.

4-(12H-benzo[a]xanthen-12-yl)morpholine (7c):



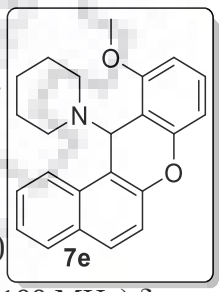
White solid; Yield: 86%; m. p. 158.5-159.7 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1905, 1658, 1495, 1347, 1265, 968; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.94 (d, *J* = 8.6 Hz, 1H), 7.70 -7.67 (m, 2H), 7.46 (d, *J* = 7.68 Hz, 1H), 7.33 (t, *J* = 7.04 Hz, 1H), 7.24 -7.16 (m, 3H), 7.04 (t, *J* = 7.64 Hz, 1H), 6.79 -6.73 (m, 2H), 5.83 (s, 1H), 3.90-3.82 (m, 3H), 3.66-3.59 (m, 1H), 3.13-3.10 (m, 1H), 2.93 (s, 1H), 2.61-2.56 (m, 2H); HRMS (EI): calcd. for$C_{21}H_{19}NO_2$ $[M+H]^+$ 318.1494; found 318.1623.

1-(11-methoxy-12H-benzo[a]xanthen-12-yl)pyrrolidine (7d):



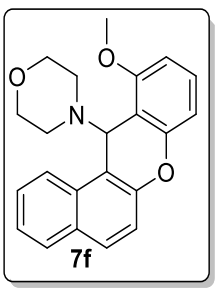
White solid; Yield: 80%; m. p. 159.4-160.7 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1902, 1596, 1463, 1343, 1278, 856; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.98 (d, *J* = 8.6 Hz, 1H), 7.68-7.63 (m, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.71-6.65 (m, 2H), 5.82 (s, 1H), 3.86 (s, 3H), 3.27 (s, 1H), 2.74 (s, 1H), 2.46-2.35 (m, 2H), 1.91 -1.71 (m, 4H); ^{13}C ($CDCl_3$, 100 MHz) δ ppm 156.26, 146.16, 142.75, 132.44, 129.17, 128.54, 128.43, 126.94, 126.36, 122.29, 121.78, 121.48, 120.33, 119.94, 116.93, 109.45, 61.35, 55.93, 54.51, 50.52, 23.39; HRMS (EI): calcd. for $C_{22}H_{21}NO_2$ $[M+H]^+$ 332.1651; found 332.1491.

1-(11-methoxy-12H-benzo[a]xanthen-12-yl)piperidine (7e):



White solid; Yield: 80%; m. p. 162.1-163.6 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1986, 1586, 1589, 1294, 1221, 986; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.91 (d, *J* = 8.6 Hz, 1H), 7.67-7.62 (m, 2H), 7.32 (t, *J* = 7.16 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11-7.09 (m, 2H), 6.68-6.66 (m, 2H), 5.76 (s, 1H), 3.86 (s, 3H), 3.31-3.28 (m, 1H), 2.77-2.75 (m, 1H), 2.23-2.15 (m, 2H), 1.72-1.63 (m, 4H), 1.56-1.48 (m, 1H), 1.27-1.24 (m, 1H); ^{13}C ($CDCl_3$, 100 MHz) δ ppm 156.42, 146.18, 143.45, 133.06, 129.12, 128.65, 128.57, 126.43, 125.33, 122.33, 121.77, 120.44, 116.52, 109.58, 62.67, 55.98, 54.79, 49.76, 26.40, 26.06, 24.29; HRMS (EI): calcd. for $C_{23}H_{23}NO_2$ $[M+H]^+$ 346.1807; found 346.1923.

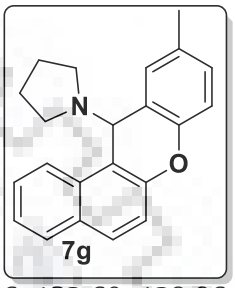
4-(11-methoxy-12H-benzo[a]xanthen-12-yl)morpholine (7f):



White solid; Yield: 82%; m. p. 201.1-202.6 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1896, 1609, 1554, 1389, 1227, 996; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.93 (d, *J* = 8.64 Hz, 1H), 7.67 (t, *J* = 7.84 Hz, 2H), 7.35 (t, *J* = 7.16 Hz, 1H), 7.21 (t, *J* = 7.48 Hz, 1H), 7.14-7.10 (m, 2H), 6.69-6.68 (m, 2H), 5.8

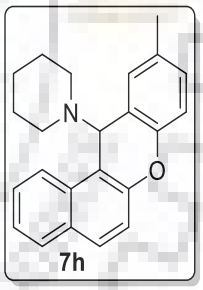
3 (s, 1H), 3.85 (s, 1H), 3.78 (s, 3H), 3.75-3.63 (m, 1H), 3.62-3.57 (m, 1 H), 3.12-3.09 (m, 1H), 2.56-2.51 (m, 3H); ^{13}C ($CDCl_3$, 100 MHz) δ ppm 155.54, 146.24, 143.61, 133.02, 129.53, 128.79, 128.70, 126.66, 124.33, 121.78, 121.61, 120.57, 119.80, 115.58, 109.89, 67.42, 66.87, 62.56, 56.02, 54.01, 49.49; HRMS (EI): calcd. for $C_{22}H_{21}NO_3$ $[M+H]^+$ 348.1600; found 348.1659.

1-(10-methyl-12H-benzo[a]xanthen-12-yl)pyrrolidine (7g):



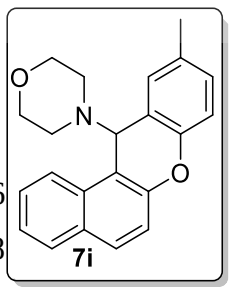
White solid; Yield: 86%; m. p. 179.4-180.5 ^{0}C; FT-IR (KBr) ν/cm^{-1}19 18, 1681, 1575, 1369, 1296, 949; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.95 (d, *J* = 8.6 Hz, 1H), 7.68 (t, *J* = 8.8 Hz, 2H), 7.33-7.30 (m, 2H), 7.20-7.17 (m, 2H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.78 (s, 1H), 3.15 (s, 1H), 2.72 (s, 2H), 2.55 (s, 1H), 2.14 (s, 3H), 1.8 5-1.80 (m, 4H); ^{13}C ($CDCl_3$ + DMSO, 100 MHz) δ ppm 156.72, 151.96, 132.60, 129.96, 129.39, 129.29, 129.01, 128.54, 128.36, 127.08, 126.28, 122.24, 122.04, 120.26, 117.33, 115.52, 58.06, 54.52, 50.33, 23.74, 23.27, 20.74; HRMS (EI): calcd. for $C_{22}H_{21}NO$ $[M+H]^+$ 316.1701; found 316.1802.

1-(10-methyl-12H-benzo[a]xanthen-12-yl)piperidine (7h):



White solid; Yield: 83%; m. p. 145.4-146.7 ^{0}C; FT-IR (KBr) ν/cm^{-1} 18 28, 1671, 1525, 1339, 1216, 969; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7. 91 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.24-7.17 (m, 3H), 6.86-6.79 (m, 2H), 5.78 (s, 1H), 3.18 (s, 1H), 2.78 (s, 1H), 2.47 (s, 1H), 2.13 (s, 3H), 1.77-1.56 (m, 6H), 1.35 (s, 1H); ^{13}C ($CDCl_3$, 100 MHz) δ ppm 156.36, 146.26, 142.80, 132.43, 129.14, 128.56, 128.41, 127.02, 126.39, 122.33, 121.74, 121.35, 120.33, 119.96, 117.02, 109.48, 62.97, 47.28, 45.71, 42.29, 16.41, 16.36, 14.59; HRMS (EI): calcd. for $C_{23}H_{23}NO$ $[M+H]^+$ 330.1858; found 330.1891.

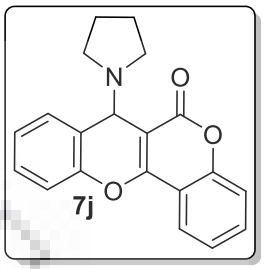
4-(10-methyl-12H-benzo[a]xanthen-12-yl)morpholine (7i):



White solid; Yield: 83%; m. p. 203.6-204.4 ^{0}C; FT-IR (KBr) ν/cm^{-1} 18 48, 1661, 1455, 1389, 1126, 894; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.92 (d, *J* = 8.60 Hz, 1H), 7.69 (t, *J* = 6.76 Hz, 2H), 7.33 (t, *J* = 7.48 H z, 1H), 7.23 – 7.20 (m, 2H), 7.17 (d, *J* = 8.92 Hz, 1H), 6.85 (d, *J* = 8.16 Hz, 1H), 6.67 (d, *J* = 8.16 Hz, 1H), 5.84 (s, 1H), 3.92-3.78 (m, 2H), 3.8 3-3.78 (m, 1H), 3.68-3.63 (m, 1H), 3.12-3.09 (m, 1H), 2.65-2.59 (m, 3H), 2.10 (s, 3H); ^{13}C ($CDCl_3$, 100 MHz) δ ppm 155.52, 151.60, 133.00, 132.54, 132.34, 130.71, 129.97,

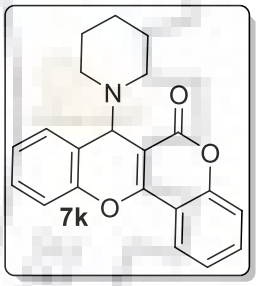
129.56, 128.86, 128.73, 128.51, 126.67, 123.65, 122.76, 121.82, 119.84, 67.50, 67.30, 66.94, 31.07, 29.30, 20.74; HRMS (EI): calcd. For $C_{22}H_{21}NO_2$ $[M+H]^+$ 332.1651; found 332.1489.

7-(pyrrolidin-1-yl)-6a,12a-dihydro-6H,7H-chromeno[4,3-b]chromen-6-one (7j):



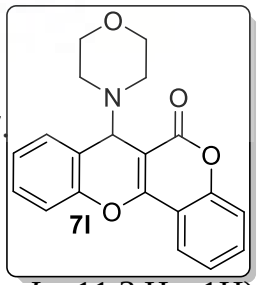
White solid; Yield: 85%; m. p. 157.1-158.6 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1741, 1598, 1565, 1459, 1326, 1059; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.97 (d, *J* = 7.9 Hz, 1H), 7.93 (d, *J* = 7.0 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.24-7.22 (m, 4H), 5.90 (s, 1H), 3.67-3.61 (m, 1H), 3.21-3.15 (m, 1H), 2.99-2.94 (m, 1H), 2.87-2.80 (m, 1H), 2.15-2.06 (m, 3H), 1.96 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.49, 163.96, 154.26, 135.23, 134.57, 131.53, 130.63, 130.31, 129.96, 128.24, 124.12, 123.14, 120.95, 116.71, 95.18, 65.35, 54.83, 50.29, 23.86, 23.38; HRMS (EI): calcd. for $C_{20}H_{17}NO_3$ $[M+H]^+$ 320.1287; found 320.1309.

7-(piperidin-1-yl)-6a,12a-dihydro-6H,7H-chromeno[4,3-b]chromen-6-one (7k):



White solid; Yield: 81%; m. p. 206.3-207.4 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1735, 1701, 1655, 1399, 1296, 1059; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.97 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.24-7.19 (m, 4H), 5.81 (s, 1H), 3.81-3.78 (m, 1H), 2.87-2.79 (m, 2H), 2.65-2.59 (m, 1H), 1.86-1.79 (m, 4H), 1.69–1.66 (m, 1H), 1.43-1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 174.59, 164.08, 154.23, 135.28, 133.44, 131.54, 130.89, 130.69, 129.95, 128.17, 124.18, 123.12, 120.77, 116.72, 94.20, 66.72, 54.50, 48.80, 31.04, 24.71, 22.61; HRMS (EI): calcd. For $C_{21}H_{19}NO_3$ $[M+H]^+$ 334.1443; found 334.1507.

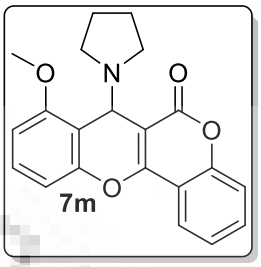
7-morpholino-6a,12a-dihydro-6H,7H-chromeno[4,3-b]chromen-6-one (7l):



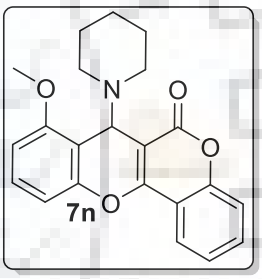
White solid; Yield: 84%; m. p. 196.7-198.5 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1739, 1701, 1648, 1459, 1316, 1156; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.92 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.30-7.26 (m, 2H), 7.23-7.17 (m, 2H), 5.66 (s, 1H), 3.98 (d, *J* = 12.3 Hz, 1H), 3.90 (d, *J* = 12.1 Hz, 1H), 3.74 (t, *J* = 12.0 Hz, 1H), 3.60 (t, *J* = 11.9 Hz, 1H), 3.33 (d, *J* = 12.1 Hz, 1H), 2.90 (t, *J* = 11.3 Hz, 1H), 2.71 (t, *J* = 11.2 Hz, 1H), 2.47 (d, *J* = 11.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 168.94, 162.73, 153.86, 135.66, 133.84, 132.12, 130.39, 130.23, 129.97,

127.96, 123.65, 117.77, 116.77, 98.57, 66.54, 66.11, 65.87, 53.67, 48.45; HRMS (EI): calcd. for $C_{20}H_{17}NO_4$ $[M+H]^+$ 336.1236; found 336.1341.

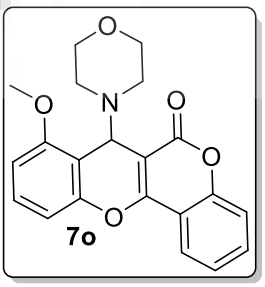
8-methoxy-7-(pyrrolidin-1-yl)-6a,12a-dihydro-6H,7H-chromeno[4,3-b]chromen-6-one (7m): White solid; Yield: 76%; m. p. 167.6-168.6 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1728, 1656, 1585, 1399, 1336, 1123, 986; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.00 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.21 (q, *J* = 7.1 Hz, 3H), 6.67 (t, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 5.90 (s, 1H), 3.67 (s, 1H), 3.52 (s, 3H), 3.30 (s, 2H), 3.08 (s, 1H), 2.10-2.01 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 175.42, 165.34, 153.94, 144.52, 131.42, 124.56, 123.96, 123.20, 121.47, 119.89, 116.45, 111.04, 95.39, 58.37, 55.57, 54.35, 23.82, 23.51, 18.43; HRMS (EI): calcd. for $C_{21}H_{19}NO_4$ $[M+ Na]^+$ 350.1392; found 350.1327.



8-methoxy-7-(piperidin-1-yl)-6a,12a-dihydro-6H,7H-chromeno[4,3-b]chromen-6-one (7n): White solid; Yield: 72%; m. p. 168.1-167.9 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1736, 1712, 1542, 1359, 1216, 1059; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.01 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.65 (t, *J* = 7.9 Hz, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 5.85 (s, 1H), 3.80 (d, *J* = 12.0 Hz, 1H), 3.47 (s, 3H), 3.11 (d, *J* = 10.7 Hz, 1H), 2.87 (t, *J* = 12.2 Hz, 1H), 2.74 (t, *J* = 12.4 Hz, 1H), 1.93-1.63 (m, 5H), 1.41 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 175.68, 165.48, 154.08, 145.15, 131.40, 124.53, 123.18, 121.50, 121.26, 120.91, 119.61, 119.56, 116.60, 110.90, 94.06, 55.43, 53.53, 45.88, 24.63, 23.40, 22.54; HRMS (EI): calcd. for $C_{22}H_{21}NO_4$ $[M+H]^+$ 364.1549; found 364.1531.

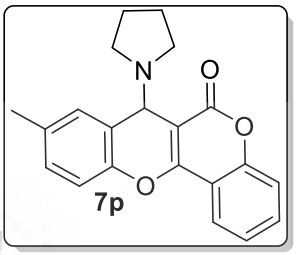


8-methoxy-7-morpholino-6a,12a-dihydro-6H,7H-chromeno[4,3-b]chromen-6-one (7o): White solid; Yield: 74%; m. p. 199.8-202.0 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1745, 1691, 1545, 1319, 1296, 1159; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.93 (d, *J* = 7.76 Hz, 2H), 7.57 (s, 1H), 7.42 (t, *J* = 7.76 Hz, 2H), 7.29 (d, *J* = 8.48 Hz, 1H), 7.19-7.12 (m, 4H), 6.77 (d, *J* = 8.84 Hz, 1H), 6.15 (s, 1H), 3.89 (t, *J* = 4.64 Hz, 4H), 3.79 (s, 3H), 3.33 (t, *J* = 4.88 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 171.09, 167.84, 152.75, 151.02, 139.31, 133.18, 132.92, 131.81, 125.15, 124.04, 123.91, 119.91,

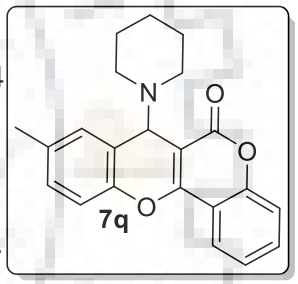


115.80, 113.25, 102.96, 64.06, 58.50, 56.48, 44.32, 18.48; HRMS (EI): calcd. for $C_{21}H_{19}NO_5$ $[M+H]^+$ 366.1341; found 366.1312.

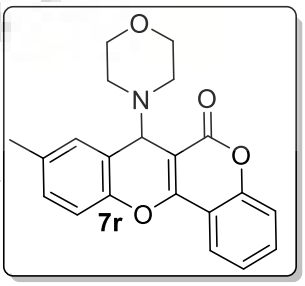
9-methyl-7-(pyrrolidin-1-yl)-6a,12a-dihydro-6H,7H-chromeno[4,3-b]chromen-6-one (7p): White solid; Yield: 79%; m. p. 206.1-207.6 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1750, 1698, 1485, 1342, 1193, 1009; ^{1}H NMR (CD Cl$_3$, 400 MHz) δ ppm 7.92 (d, *J* = 7.8 Hz, 1H), 7.76 (s, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 5.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 5.89 (s, 1H), 2.99 (t, *J* = 5.9 Hz, 4 H), 2.40 (s, 3H), 1.74 (t, *J* = 6.3 Hz, 4H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 174.50, 169.16, 152.31, 135.29, 134.53, 132.70, 132.48, 130.56, 130.33, 129.92, 128.18, 123.82, 120.51, 116.47, 115.39, 95.21, 46.67, 25.23, 23.58, 20.93, 20.91; HRMS (EI): calcd. for $C_{21}H_{19}NO_3$ $[M+H]^+$ 334.1443; found 334.1409.



9-methyl-7-(piperidin-1-yl)-6a,12a-dihydro-6H,7H-chromeno[4,3-b]chromen-6-one (7q): White solid; Yield: 73%; m. p. 159.8-160.7 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1739, 1621, 1596, 1345, 1289, 1036; ^{1}H NMR (CDCl$_3$, 4 00 MHz) δ ppm 7.78 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.25 (t, *J* = 6.9 Hz, 2H), 7.21–7.17 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 5.80 (s, 1H), 3.79 (d, *J* = 11.9 Hz, 1H), 2.87-2. 79 (m, 2H), 2.61 (t, *J* = 11.7 Hz, 1H), 2.39 (s, 3H), 1.92-1.83 (m, 4H), 1.71–1.62 (m, 1H), 1.45-139 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 174.52, 164.21, 152.31, 135.29, 133.52, 132.72, 132.48, 130.88, 130.68, 129.98, 128.18, 123.86, 120.27, 116.51, 94.32, 66.74, 54.49, 48.77, 24.28, 24.73, 22.66, 20.91; HRMS (EI): calcd. for $C_{22}H_{21}NO_3$ $[M+H]^+$ 348.1600; found 348.1659.

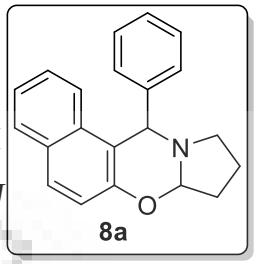


9-methyl-7-morpholino-6a,12a-dihydro-6H,7H-chromeno[4,3-b]chromen-6-one (7r): White solid; Yield: 76%; m. p. 185.8-186.6 ^{0}C; FT-IR (K Br) ν/cm^{-1} 1738, 1565, 1385, 1245, 1045; ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 7.71 (s, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 1H), 7 .19 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 5.65 (s, 1H), 3. 98-3.87 (m, 2H), 3.76-3.68 (m, 1H), 3.59 (t, *J* = 11.8 Hz, 1H), 3.31 (d, *J* = 11.6 Hz, 1H), 2.89 (t, *J* = 10.7 Hz, 1H), 2.71 (t, *J* = 11.6 Hz, 1H), 2.46 (d, *J* = 11.9 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm 168.89, 162.93, 151.97, 135.66, 133.92, 133.37, 133.13, 130.35, 130.21, 129.94, 127.93, 123.27, 117.32, 116.55, 98.63, 66.58, 66.12,



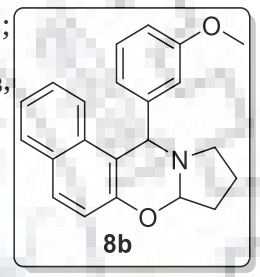
65.85, 53.65, 48.45, 20.98; HRMS (EI): calcd. for $C_{21}H_{19}NO_4$ [M+H]+ 350.1392; found 350.1280.

12-phenyl-7a,8,9,10-tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazine (8a): White solid; Yield: 87%; m. p. 121-123 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1848, 1665, 1485, 1345, 1145; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.76 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.29-7.24 (m, 7H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.46 (s, 1H), 5.11 (d, *J* = 3.0 Hz, 1H), 3.37-3.32 (m, 1H), 2.93 (q, *J* = 8.3 Hz, 1H), 2.12-2.01 (m, 4H); HRMS (EI): calcd. for $C_{21}H_{19}NO$ [M]$^+$ 301.1467; found 301.0603.



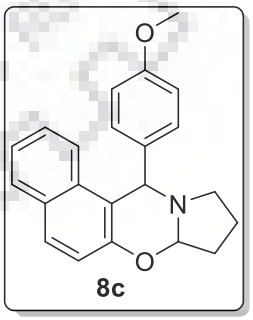
8a

12-(3-methoxyphenyl)-7a,8,9,10-tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazine (8b): White solid; Yield: 82%; m. p. 138.6-138.1 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1838, 1652, 1490, 1295, 1063; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.75 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.31-7.24 (m, 2H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 8.9 Hz, 1H), 6.85-6.83 (m, 2H), 6.78 (d, *J* = 8.1 Hz, 1H), 5.42 (s, 1H), 5.14 (d, *J* = 3.3 Hz, 1H), 3.73 (s, 3H), 3.35-3.30 (m, 1H), 2.91 (q, *J* = 8.3 Hz, 1H), 2.10-2.00 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 159.73, 151.82, 145.19, 132.60, 129.44, 129.08, 128.98, 128.59, 126.56, 123.04, 122.72, 121.25, 118.89, 114.94, 112.25, 110.34, 86.48, 56.42, 55.24, 50.56, 32.11, 21.06; HRMS (EI): calcd. for $C_{22}H_{21}NO_2$ [M+H]$^+$ 332.1651; found 332.1603.



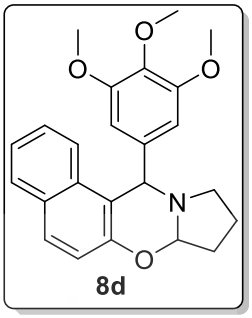
8b

12-(4-methoxyphenyl)-7a,8,9,10-tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazine (8c): White solid; Yield: 82%; m. p. 116-118 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1811, 1547, 1236, 1189, 936; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.75 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.31-7.24 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.41 (s, 1H), 5.10 (s, 1H), 3.75 (s, 3H), 3.33-3.28 (m, 1H), 2.89 (q, *J* = 8.2 Hz, 1H), 2.09-1.99 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 158.84, 151.89, 135.86, 132.70, 129.97, 129.07, 128.70, 126.63, 123.14, 122.88, 119.04, 113.87, 110.79, 86.52, 55.84, 55.32, 50.40, 32.18, 21.19; HRMS (EI): calcd. For $C_{22}H_{21}NO_2$ [M+H]$^+$ 332.1651; found 332.1603.



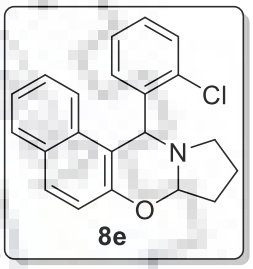
8c

12-(3,4,5-trimethoxyphenyl)-7a,8,9,10-tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazine (8d): White solid; Yield: 76%; m. p. 145.8-146.6 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1825, 1658, 1456, 1281, 968; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.73 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.28-7.24 (m, 1H), 7.06 (d, *J* = 8.9 Hz, 1H), 5.35 (s, 1H), 5.18 (d, *J* = 2.6 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 6H), 3.32-3.27 (m, 1H), 2.87 (q, *J* = 8.4 Hz, 1H), 2.12-2.07 (m, 2H), 2.03-1.97 (m, 2H); HRMS (EI): calcd. For $C_{24}H_{25}NO_4$ $[M+H]^+$ 392.1862; found 392.1901.



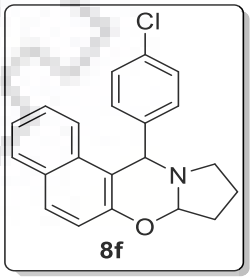
8d

12-(2-chlorophenyl)-7a,8,9,10-tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazine (8e): White solid; Yield: 90%; m. p. 158.9-160.2 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1738, 1565, 1385, 1245, 1045; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.73 (t, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.27- 7.24 (m, 2H), 7.19-7.15 (m, 2H), 7.09 (d, *J* = 8.9 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 5.83 (s, 1H), 5.10 (d, *J* = 3.5 Hz, 1H), 3.47-3.43 (m, 1H), 2.95 (q, *J* = 8.2 Hz, 1H), 2.11-1.97 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 152.36, 142.33, 133.45, 132.15, 130.25, 129.29, 129.10, 128.90, 128.63, 127.26, 126.76, 125.13, 123.19, 122.65, 118.90, 109.87, 86.25, 55.78, 50.54, 32.02, 21.04; HRMS (EI): calcd. for $C_{21}H_{18}ClNO$ $[M+H]^+$ 336.1155, 338.1126; found 336.1171, 338.1152.



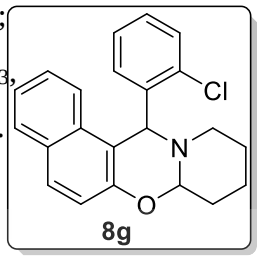
8e

12-(4-chlorophenyl)-7a,8,9,10-tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazine (8f): White solid; Yield: 90%; m. p. 124.6-125.9 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1765, 1546, 1396, 1123, 958; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.78 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.36-7.29 (m, 3H), 7.22 (q, *J* = 8.12 Hz, 4H), 7.10 (d, *J* = 8.9 Hz, 1H), 5.43 (s, 1H), 5.04 (d, *J* = 2.6 Hz, 1H), 3.36-3.32 (m, 1H), 2.92 (q, *J* = 8.3 Hz, 1H), 2.13-2.10 (m, 1H), 2.07-2.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 151.96, 142.03, 133.12, 132.51, 130.27, 129.35, 129.02, 128.76, 128.65, 126.76, 123.25, 122.58, 119.07, 109.88, 86.42, 55.69, 50.51, 32.15, 21.13; HRMS (EI): HRMS (EI): calcd. for $C_{21}H_{18}ClNO$ $[M+H]^+$ 336.1155, 338.1126; found 336.1171, 338.1152.



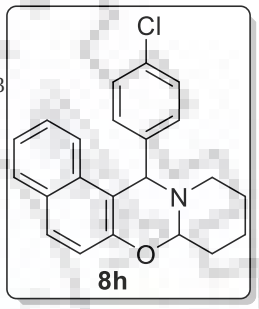
8f

13-(2-chlorophenyl)-7a,8,10,11-tetrahydro-9H,13H-naphtho[1,2-e]pyrido[2,1-b][1,3]oxazine (8g): White solid; Yield: 88%; m. p. 158.6-159.4 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1833, 1689, 1456, 1369, 1097; ^{1}H NMR ($CDCl_3$, 400 MHz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 152.96, 140.28, 134.84, 132.29, 131.18, 130.16, 129.20, 129.13, 128.66, 128.62, 126.65, 126.22, 123.16, 122.68, 118.78, 110.39, 81.38, 60.07, 48.10, 29.47, 25.46, 18.48; HRMS (EI): calcd. for $C_{22}H_{20}ClNO$ $[M+H]^+$ 350.1312, 352.1282; found 350.1325, 352.1298.



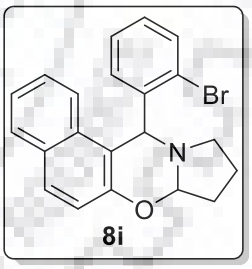
8g

13-(4-chlorophenyl)-7a,8,10,11-tetrahydro-9H,13H-naphtho[1,2-e]pyrido[2,1-b][1,3]oxazine (8h): White solid; Yield: 88%; m. p. 162.1-163.4 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1845, 1661, 1458, 1293, 1125; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.77 (d, *J* = 5.8 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.28-7.26 (m, 3H), 7.23 (d, *J* = 9.4 Hz, 1H), 7.20-7.15 (m, 3H), 7.11 (d, *J* = 8.9 Hz, 1H), 5.10 (s, 1H), 4.81 (s, 1H), 2.83 (d, *J* = 4.5 Hz, 2 H), 1.96 (d, *J* = 12.1 Hz, 1H), 1.77-1.70 (m, 3H), 1.56-1.56 (m, 2H); HRMS (EI): calcd. for $C_{22}H_{20}ClNO$ [M+H]+ 350.1312, 352.1282; found 350.1325, 352.1298.



8h

12-(2-bromophenyl)-7a,8,9,10-tetrahydro-12H-naphtho[1,2-e]pyrrolo[2,1-b][1,3]oxazine (8i): White solid; Yield: 90%; m. p. 156.8-157.6 ^{0}C; FT-IR (KBr) ν/cm^{-1} 1798, 1548, 1486, 1285, 993; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.74-7.67 (m, 3H), 7.28-7.23 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.10-7.08 (m, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 7.3 Hz, 1H), 5.77 (s, 1H), 5.10 (d, *J* = 3.3 Hz, 1H), 3.52-3.47 (m, 1H), 2.94 (q, *J* = 8.2 Hz, 1H), 2.09-1.99 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.46, 139.51, 135.16, 133.69, 131.96, 130.77, 129.97, 129.47, 129.12, 128.72, 126.85, 126.81, 123.30, 122.36, 118.96, 109.16, 86.18, 52.85, 50.45, 32.02, 21.01; HRMS (EI): calcd. for $C_{21}H_{18}BrNO$ $[M+H]^+$ 380.0650, 382.0630; found 380.0622, 382.0642.



8i

5.8. References

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SPECTRA OF SELECTED COMPOUNDS

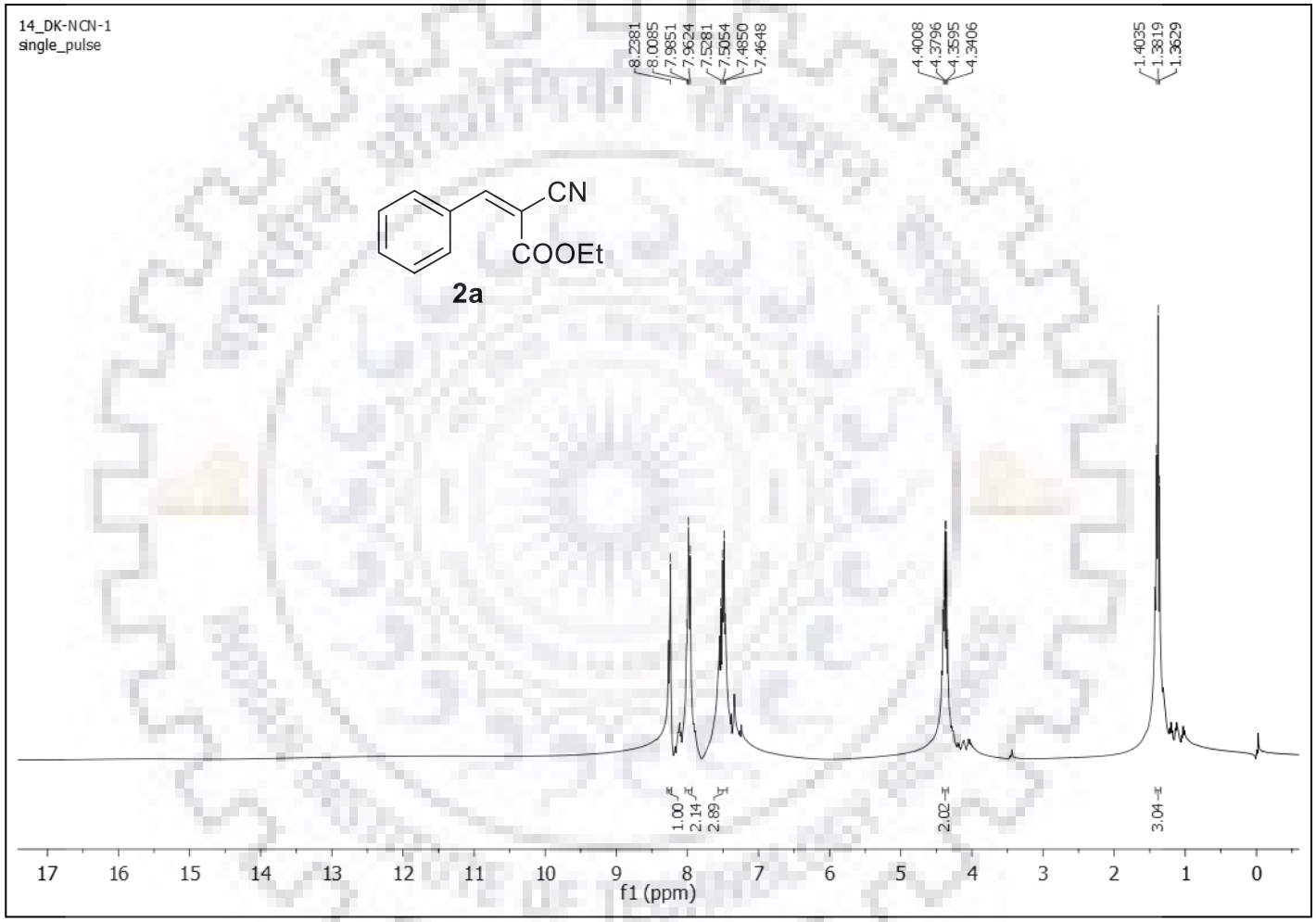

Figure S-1: ^{1}H NMR Spectrum of **2a** in $CDCl_3$.

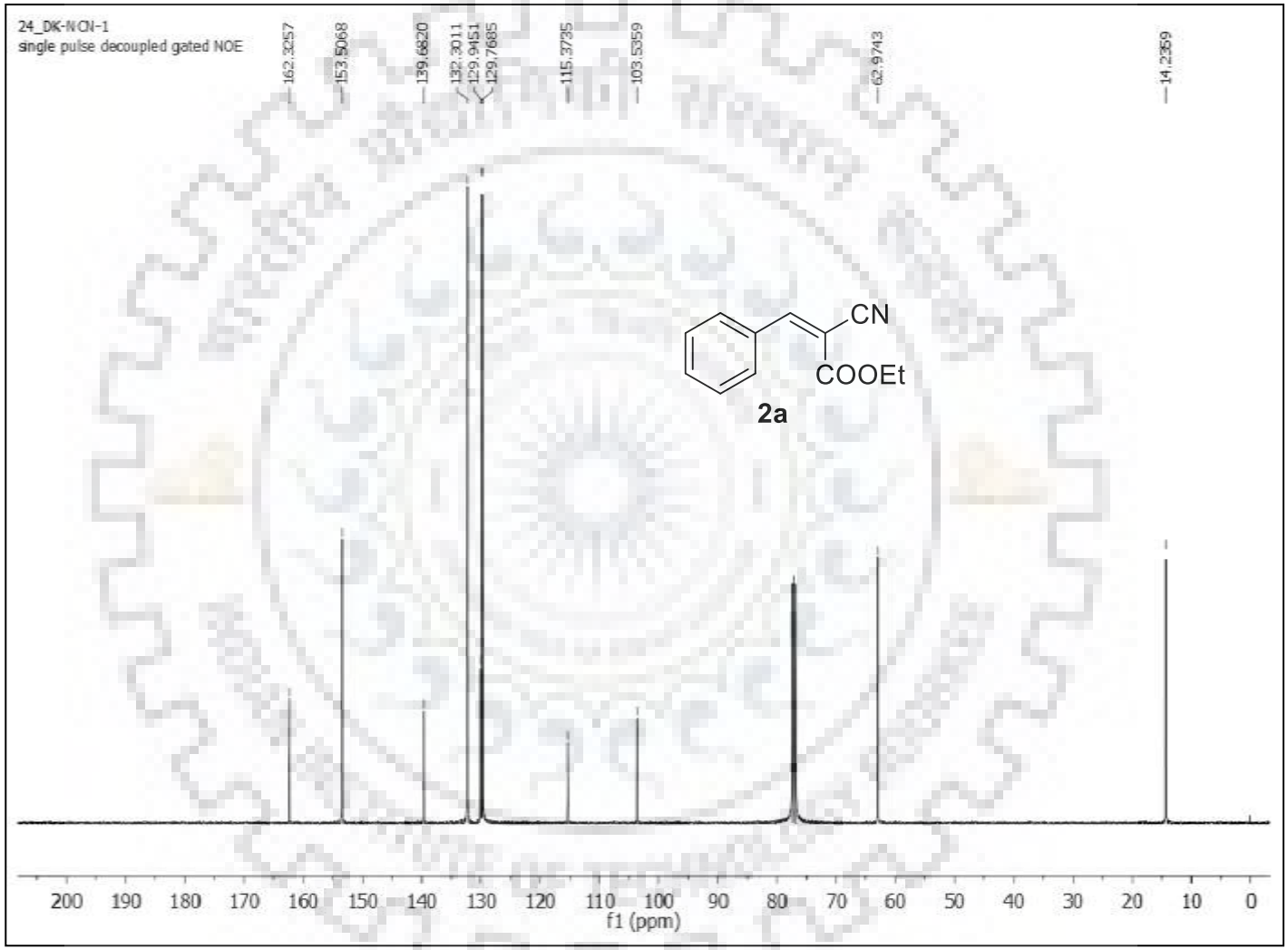

Figure S-2: ^{13}C NMR Spectrum of **2a** in $CDCl_3$.

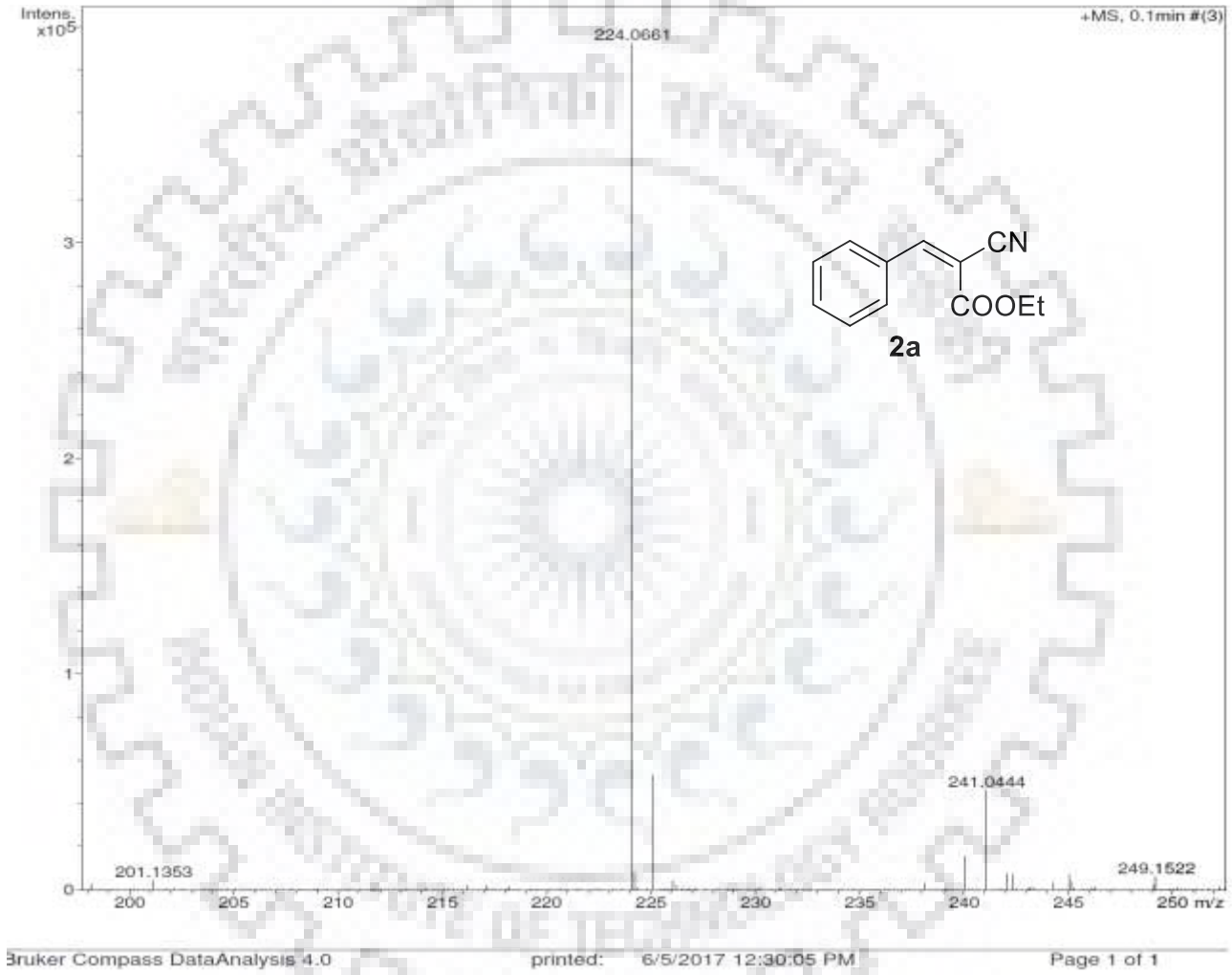

Figure S-3: HRMS Spectrum of **2a**.

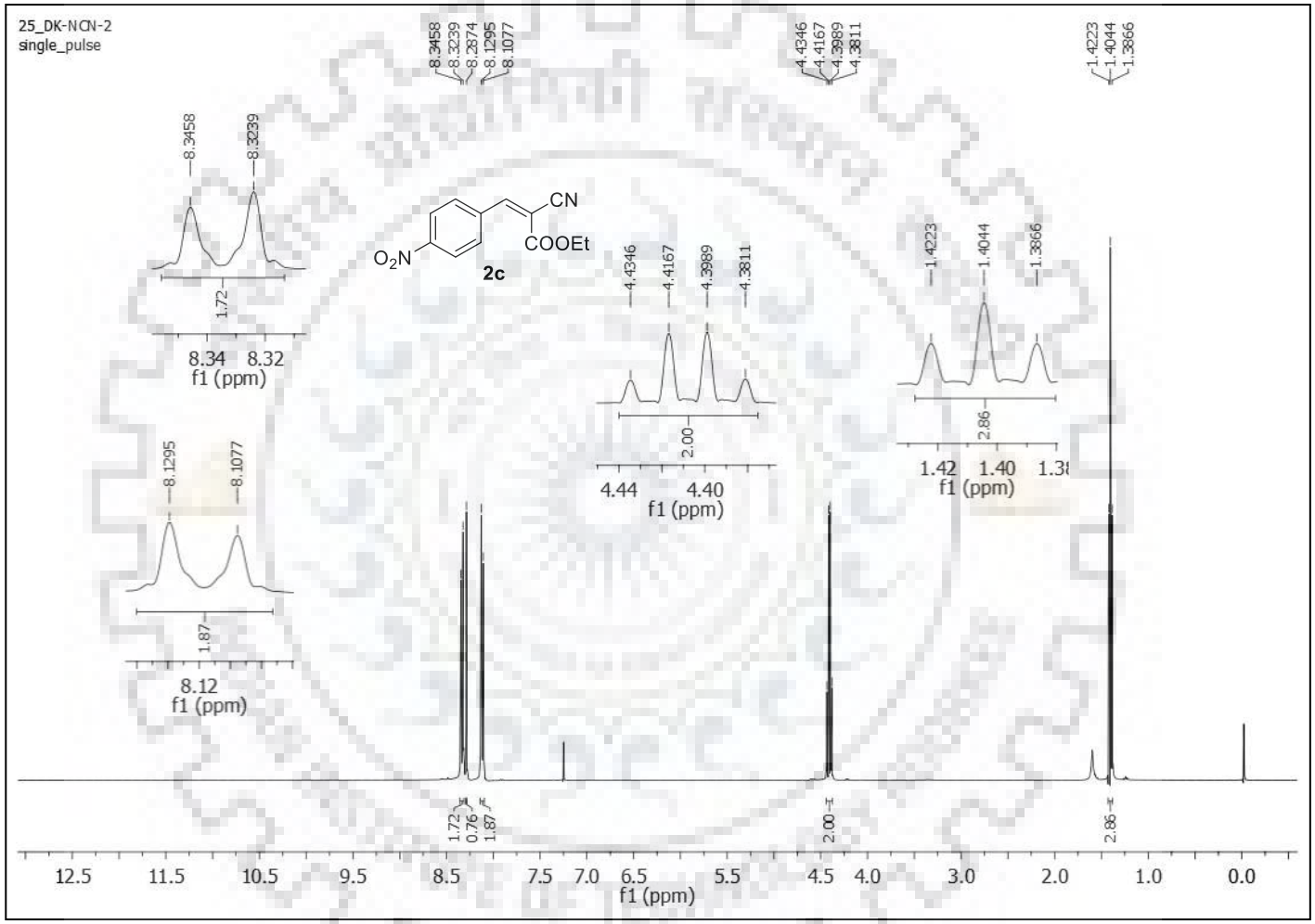

Figure S-4: ^{1}H NMR Spectrum of **2c** in $CDCl_3$.

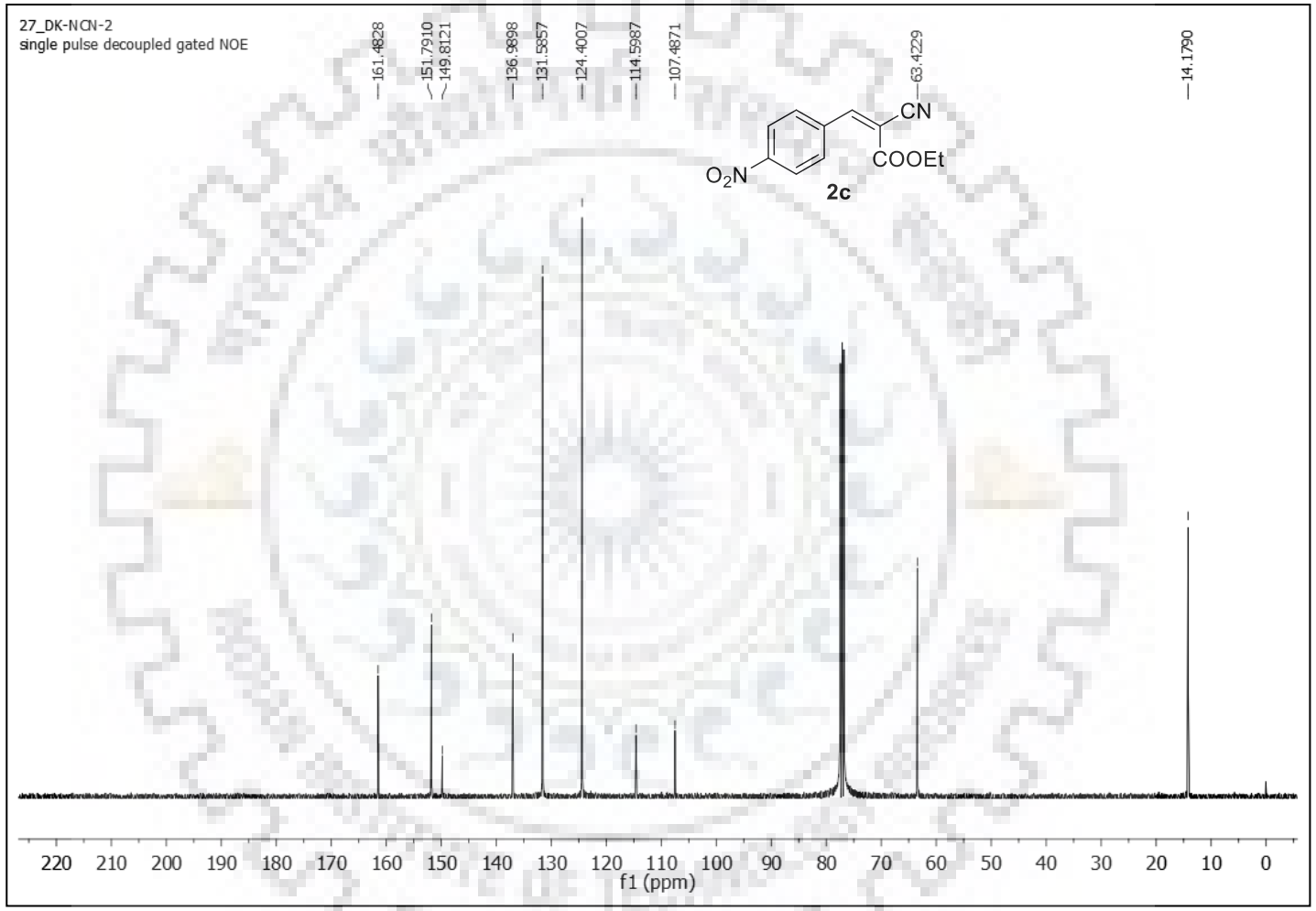

Figure S-5: ^{13}C NMR Spectrum of **2c** in $CDCl_3$.

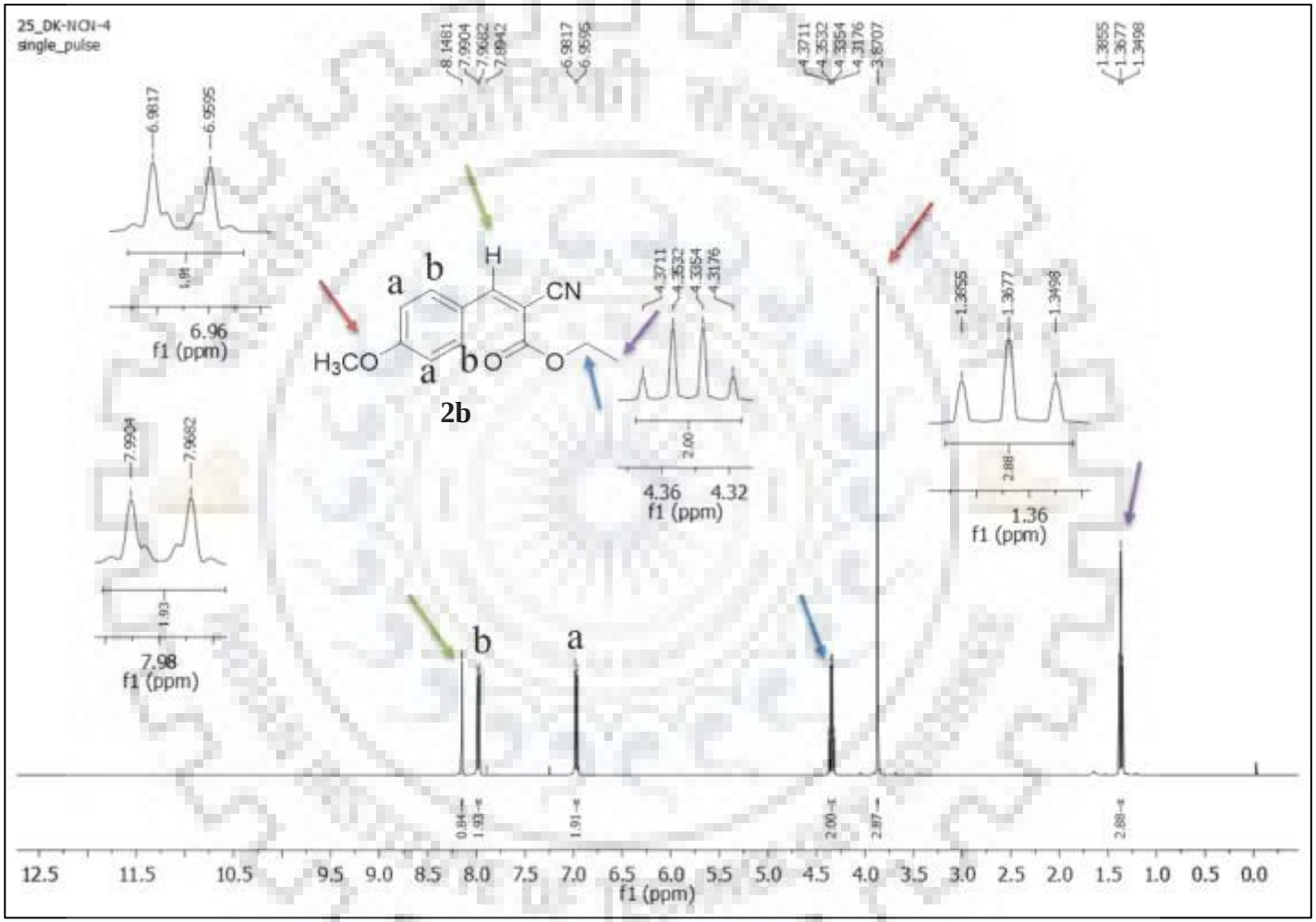

Figure S-6: ^{1}H NMR Spectrum of **2b** in $CDCl_3$.

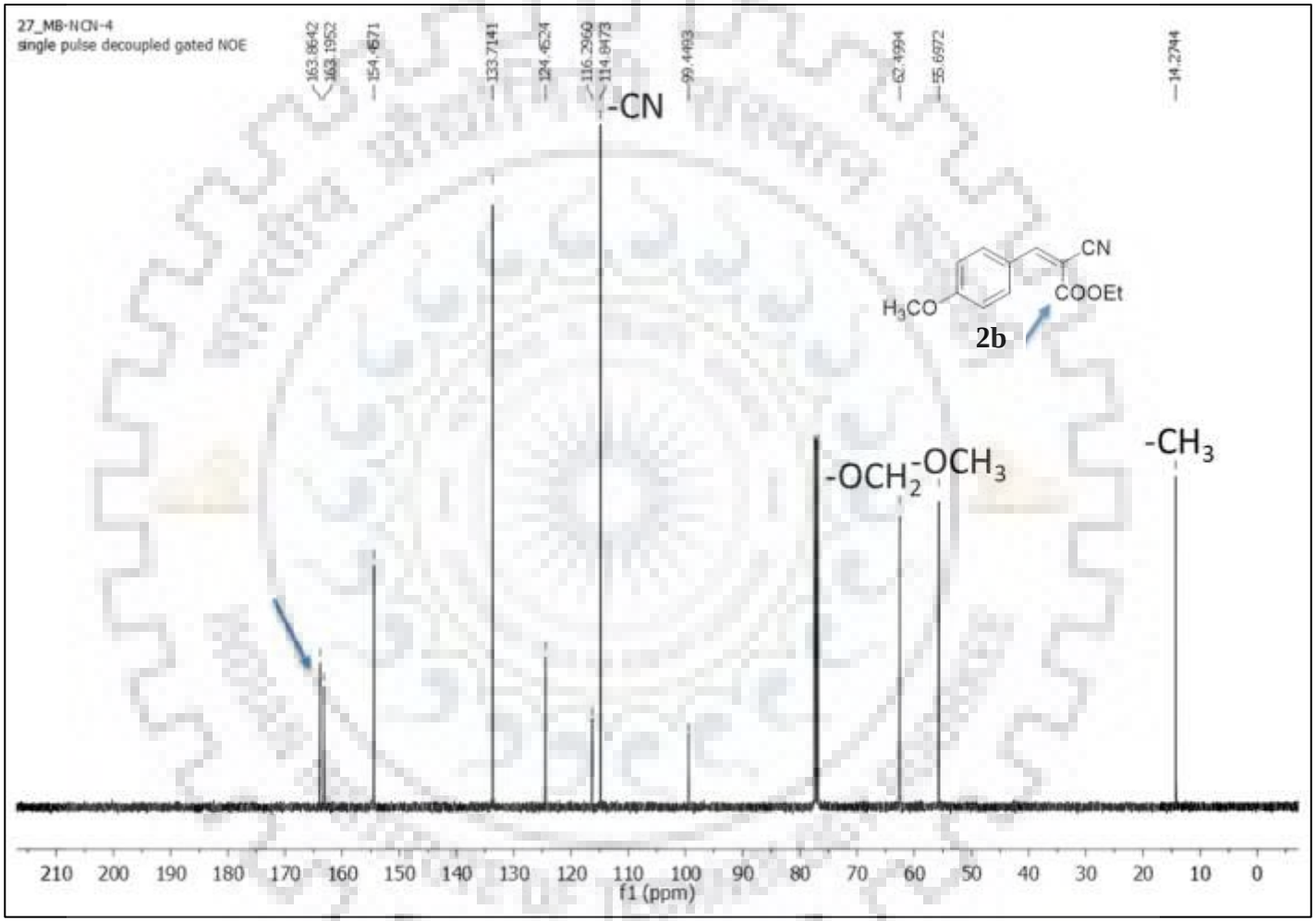

Figure S-7: ^{13}C NMR Spectrum of **2b** in $CDCl_3$.

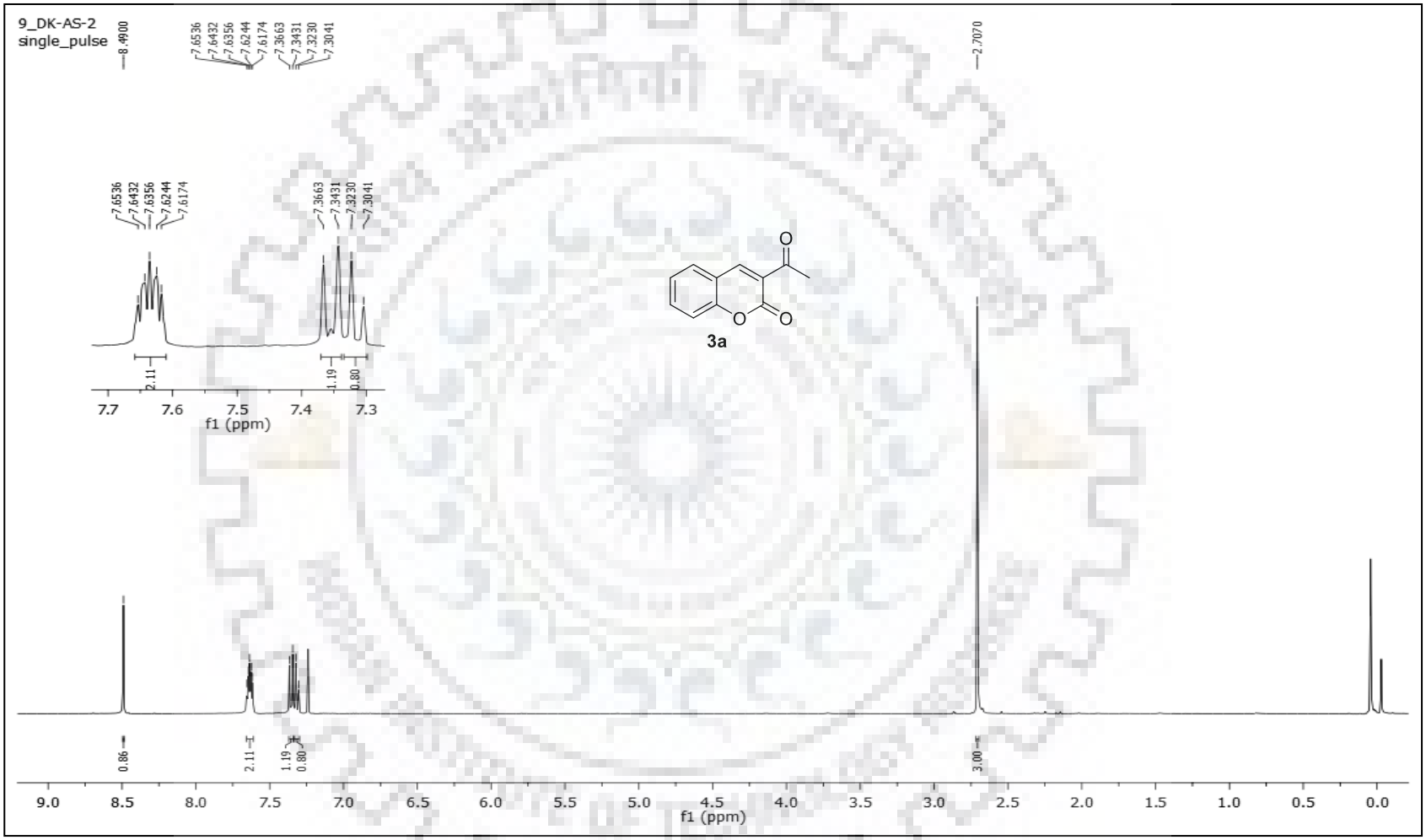

Figure S-8: ^{1}H NMR Spectrum of **3a** in $CDCl_3$.

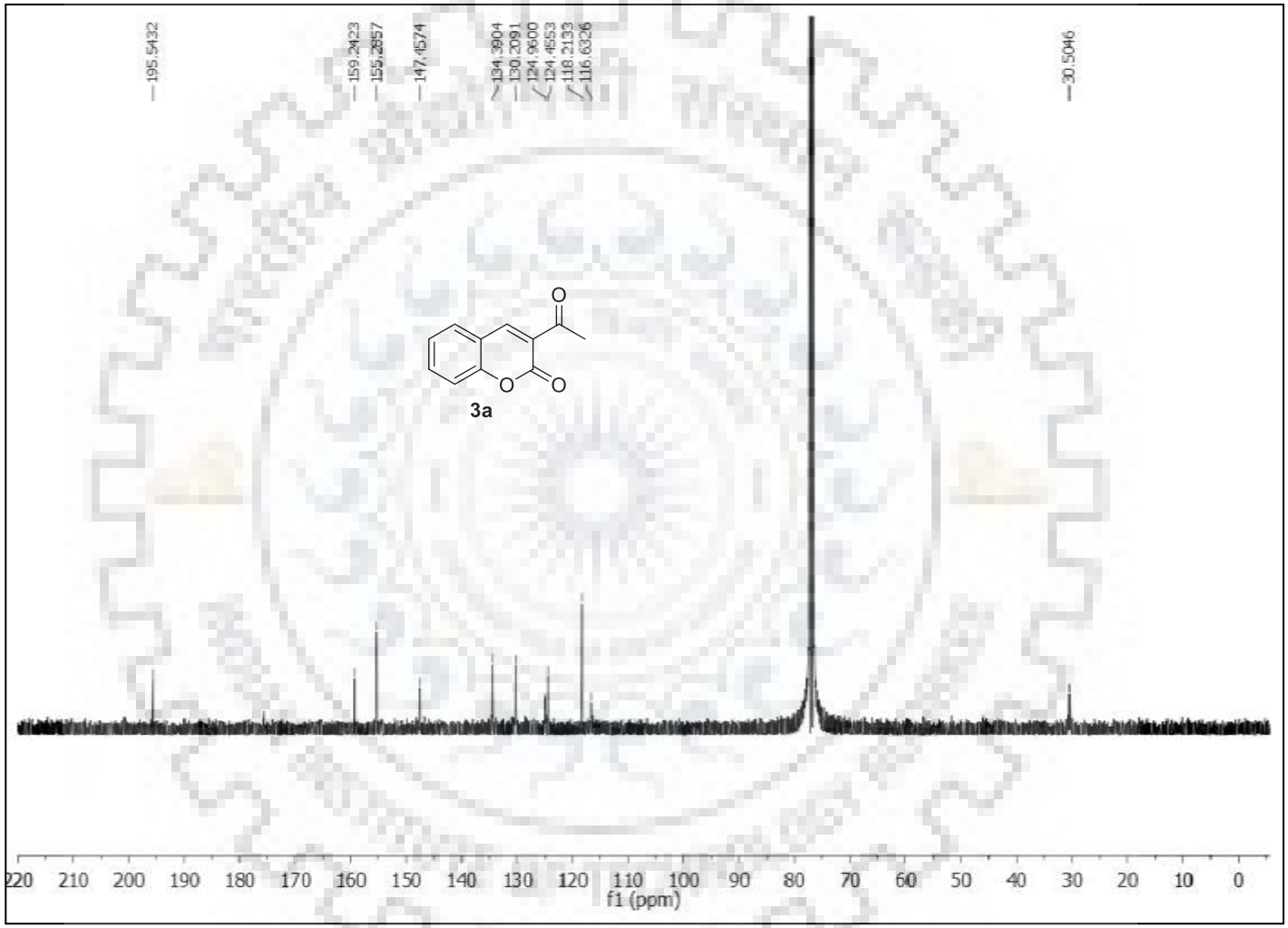

Figure S-9: ^{13}C NMR Spectrum of **3a** in $CDCl_3$.

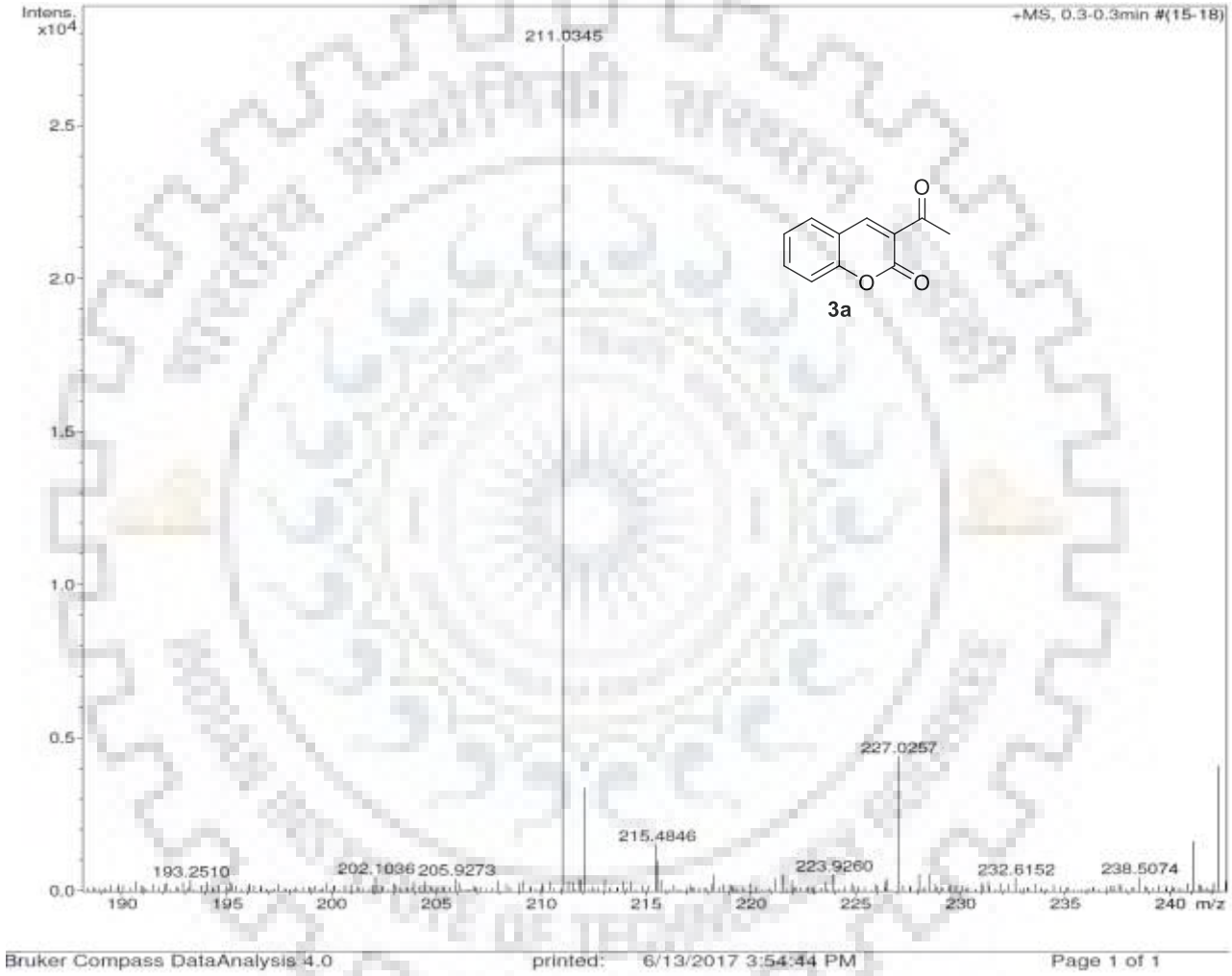

Figure S-10: HRMS Spectrum of **3a**.

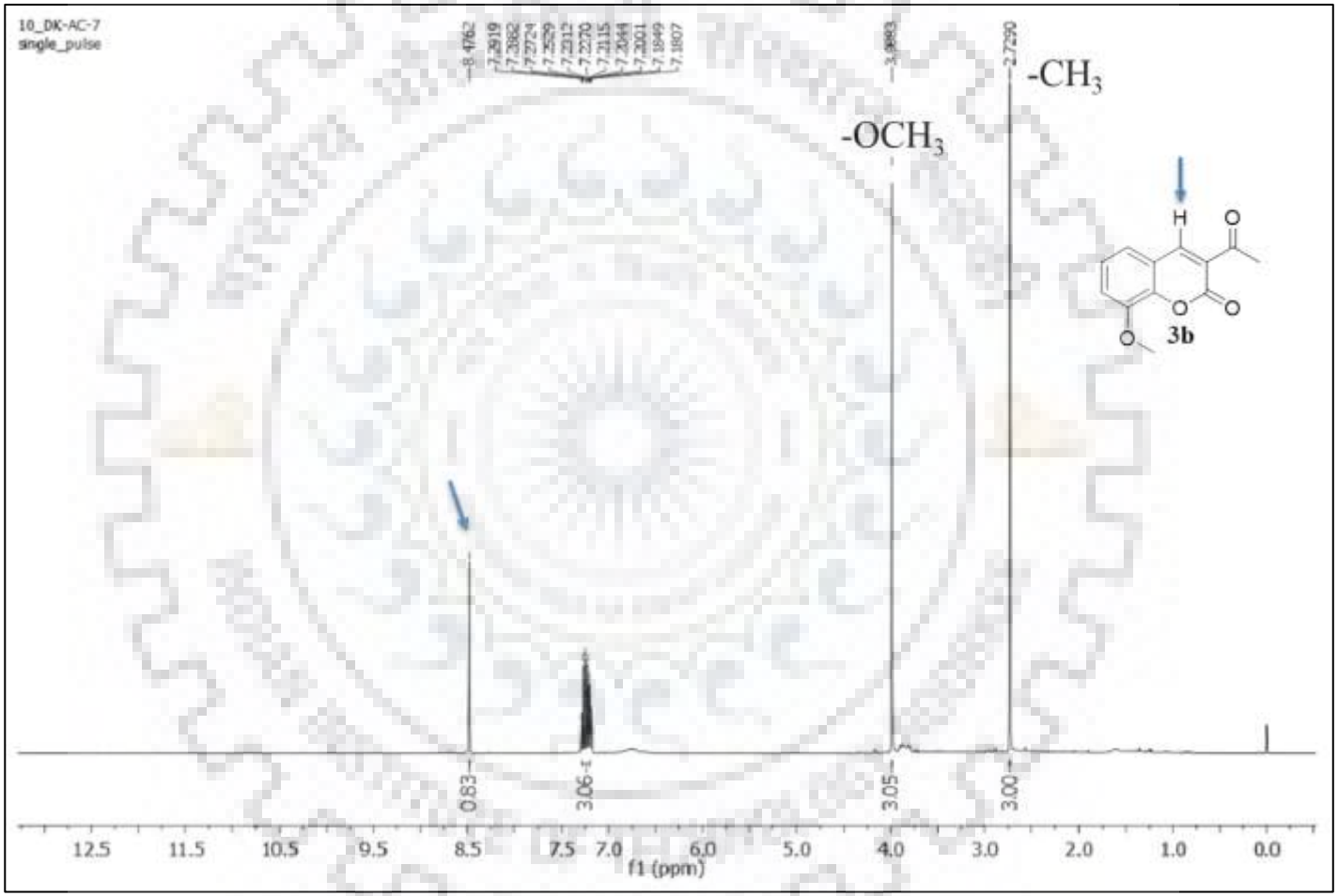

Figure S-11: ^{1}H NMR Spectrum of **3b** in $CDCl_3$.

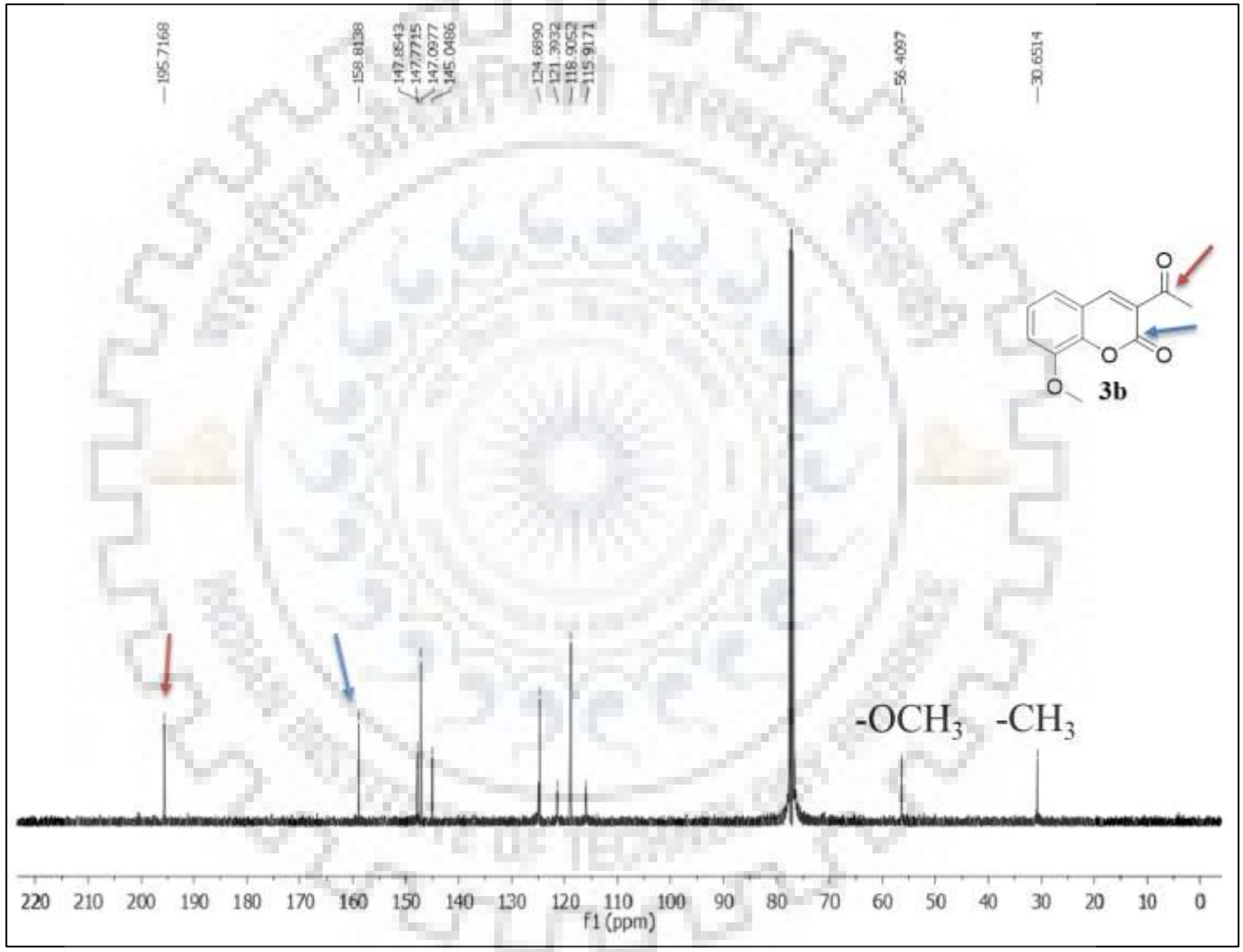

Figure S-12: ^{13}C NMR Spectrum of **3b** in $CDCl_3$.

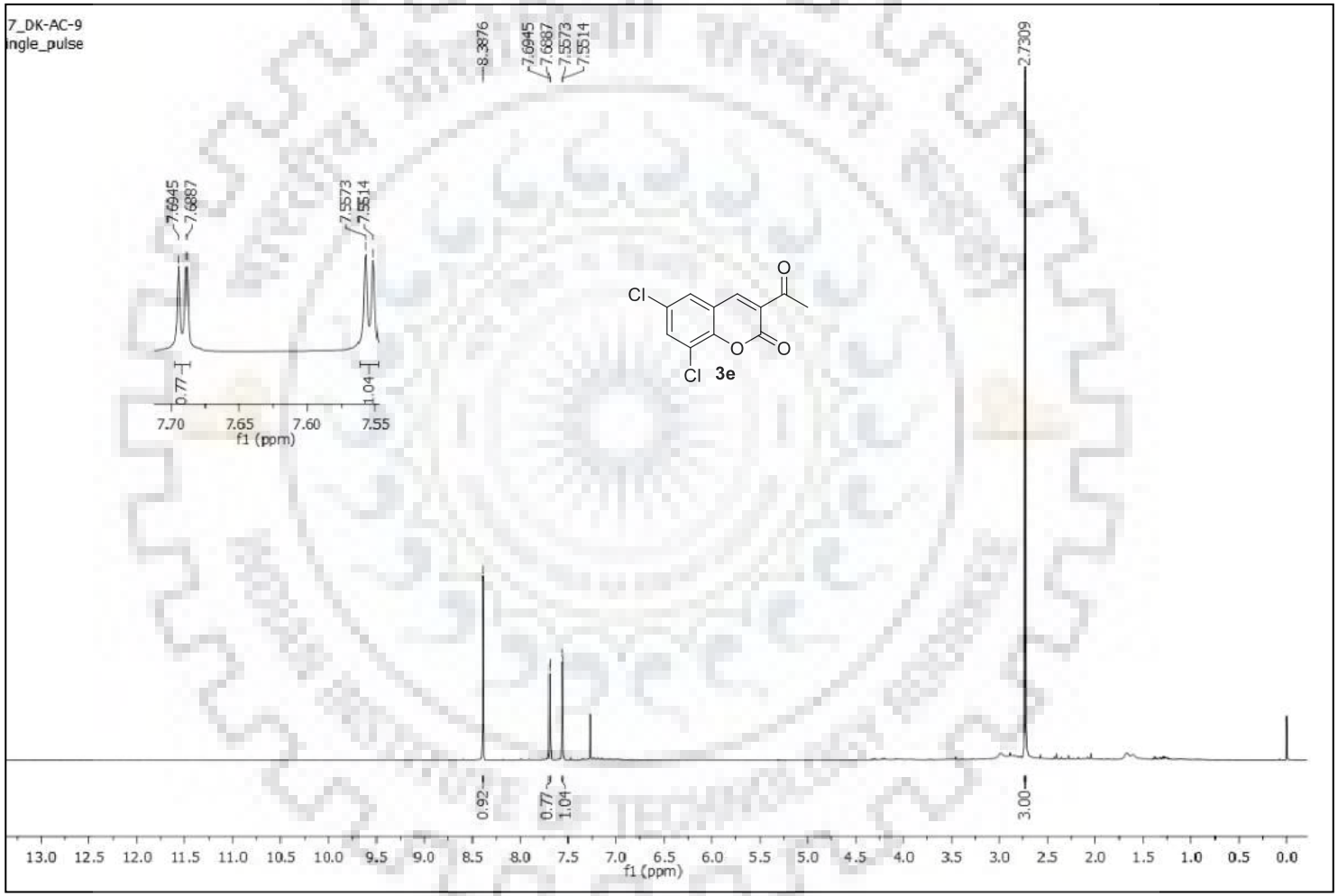

Figure S-13: ^{1}H NMR Spectrum of **3e** in $CDCl_3$.

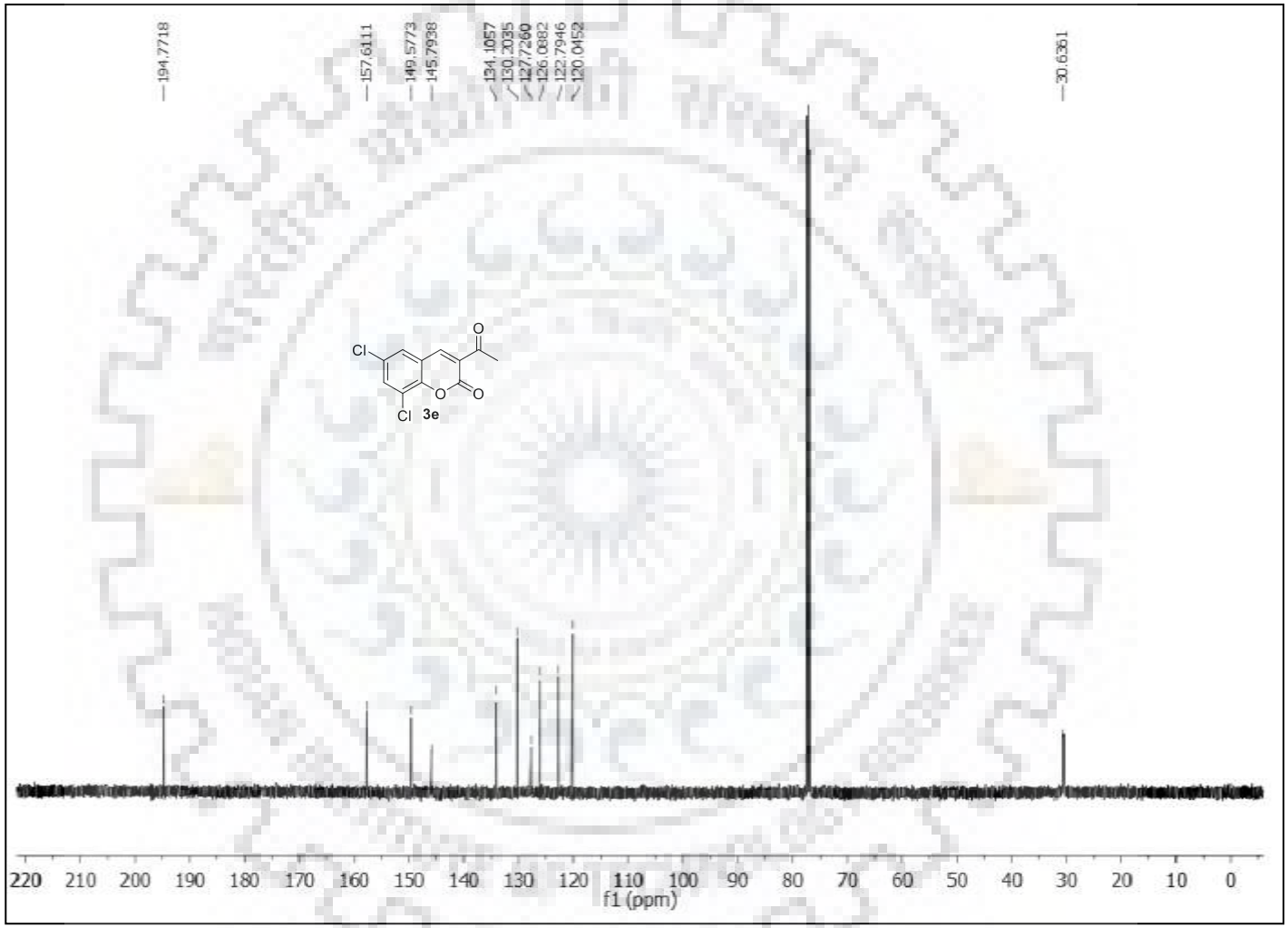

Figure S-14: ^{13}C NMR Spectrum of **3e** in $CDCl_3$.

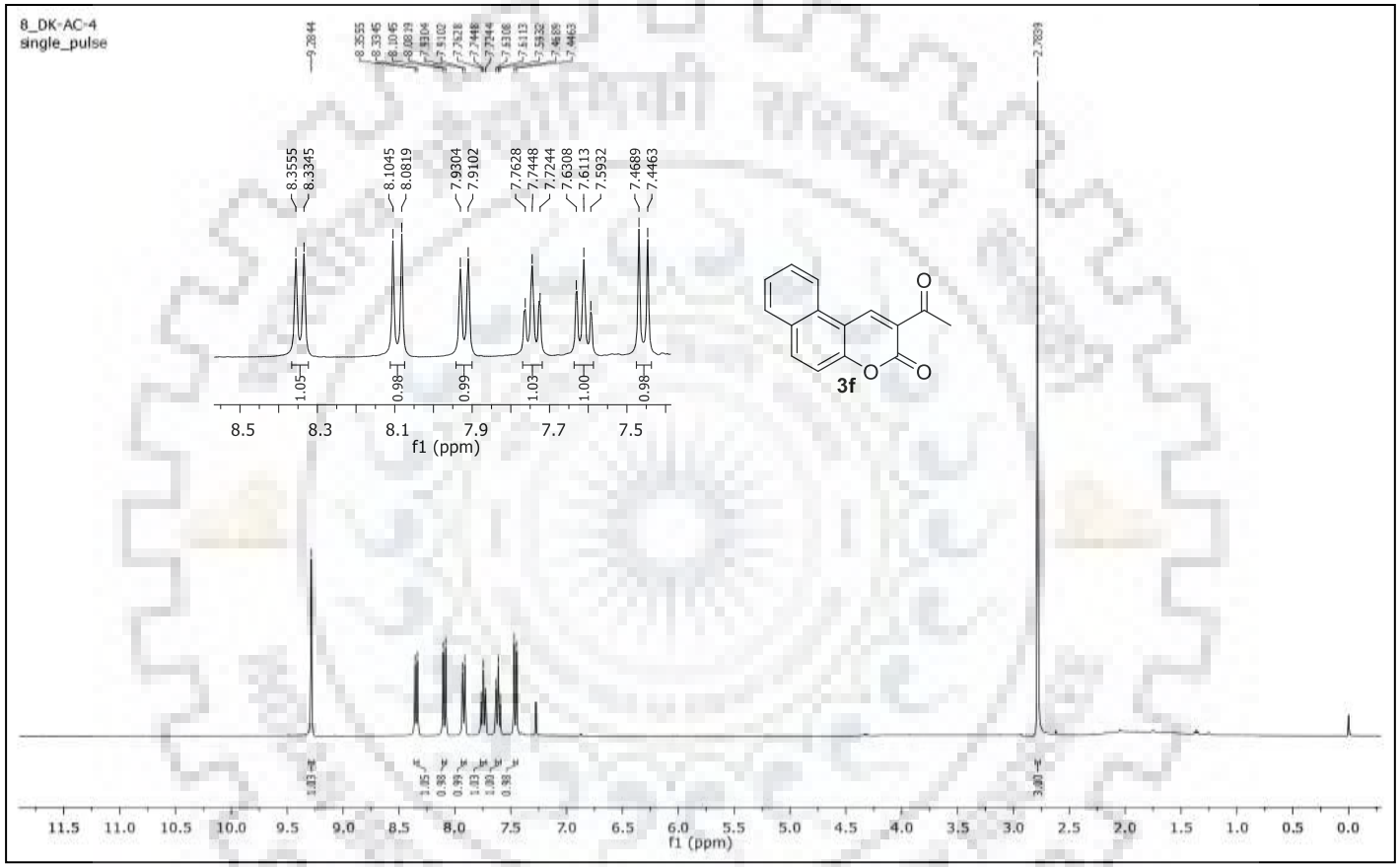

Figure S-15: ^{1}H NMR Spectrum of **3f** in $CDCl_3$.

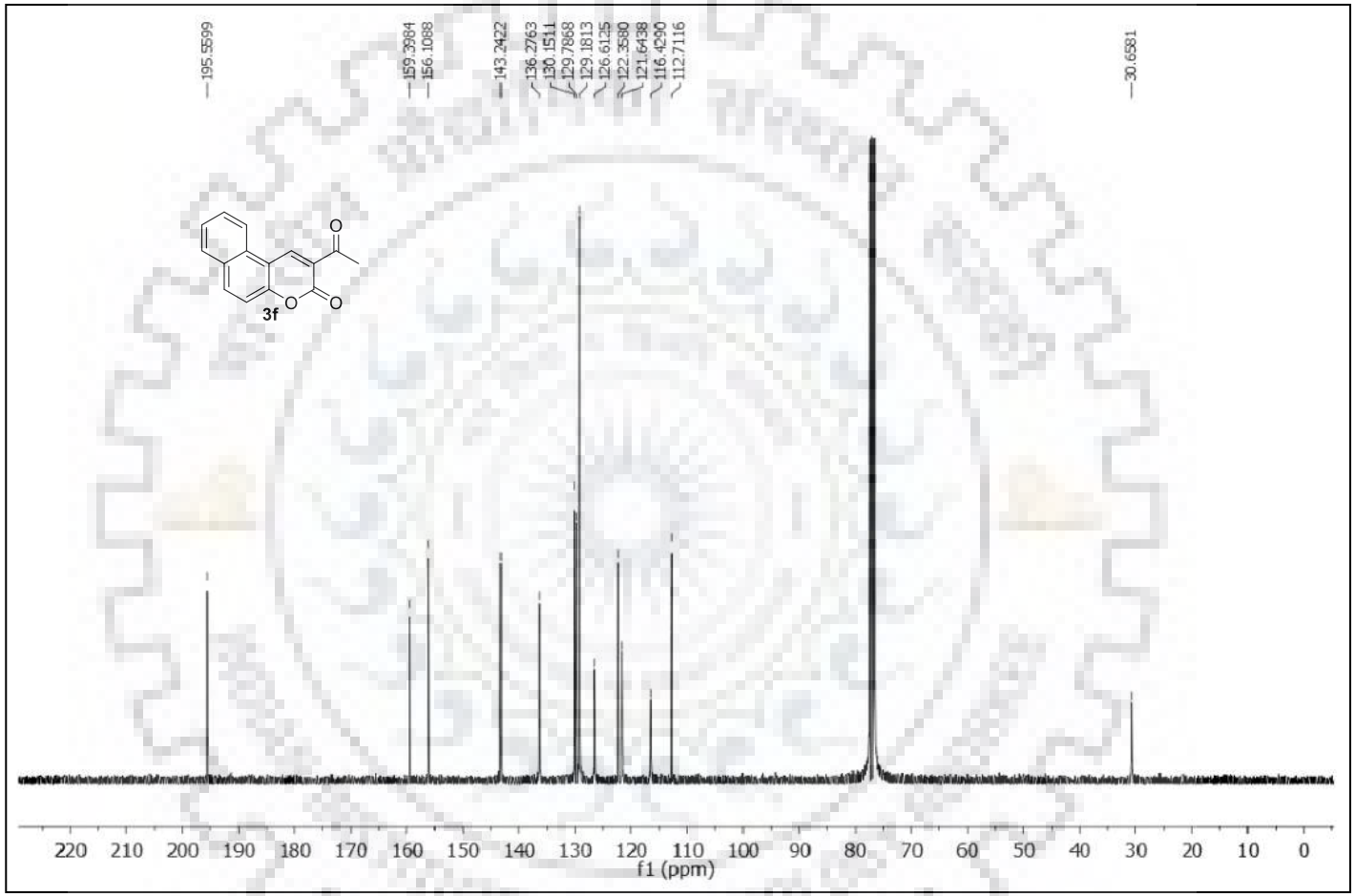

Figure S-16: ^{13}C NMR Spectrum of **3f** in $CDCl_3$.

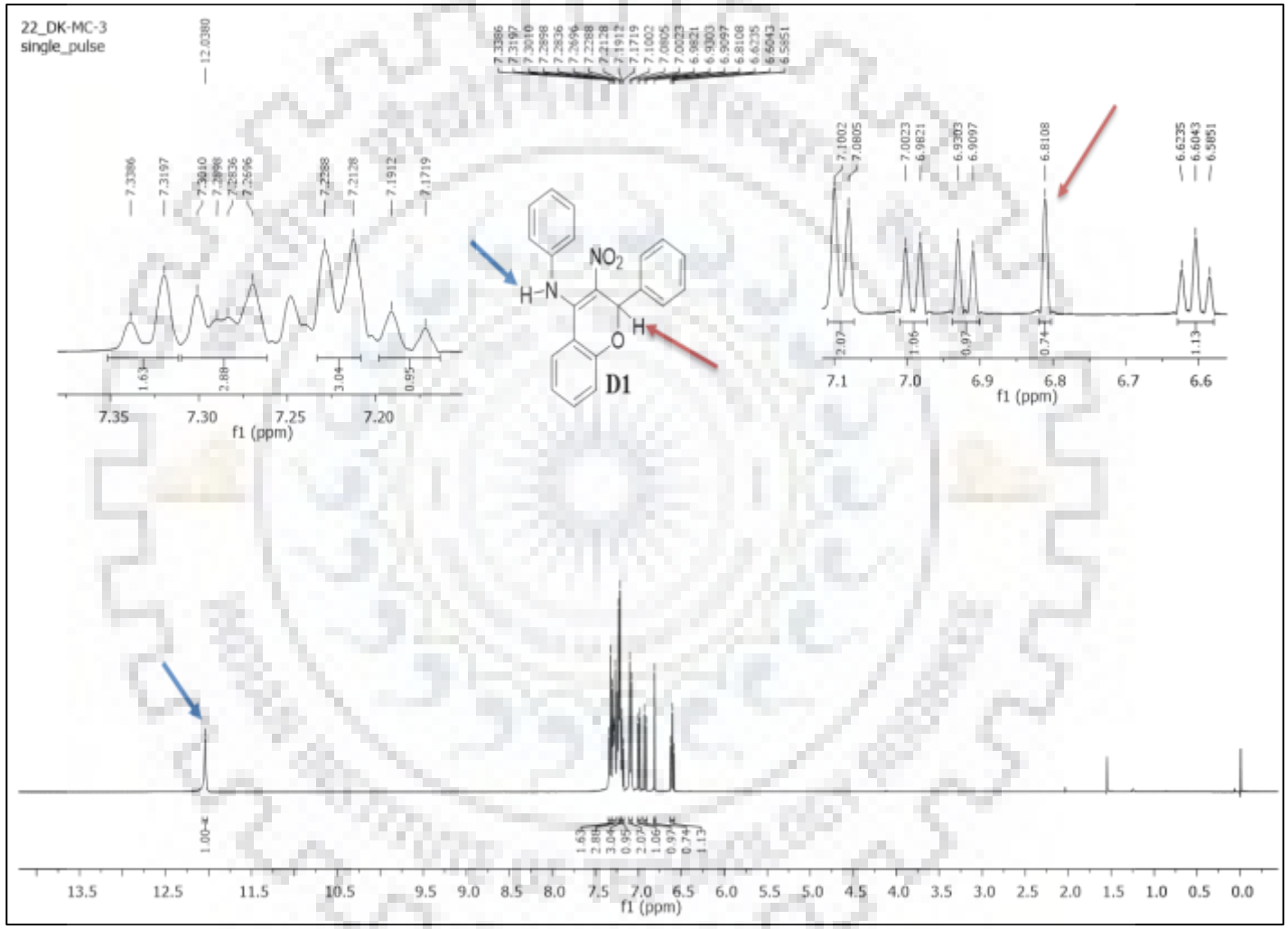

Figure S-17: ^{1}H NMR Spectrum of **D1** in $CDCl_3$.

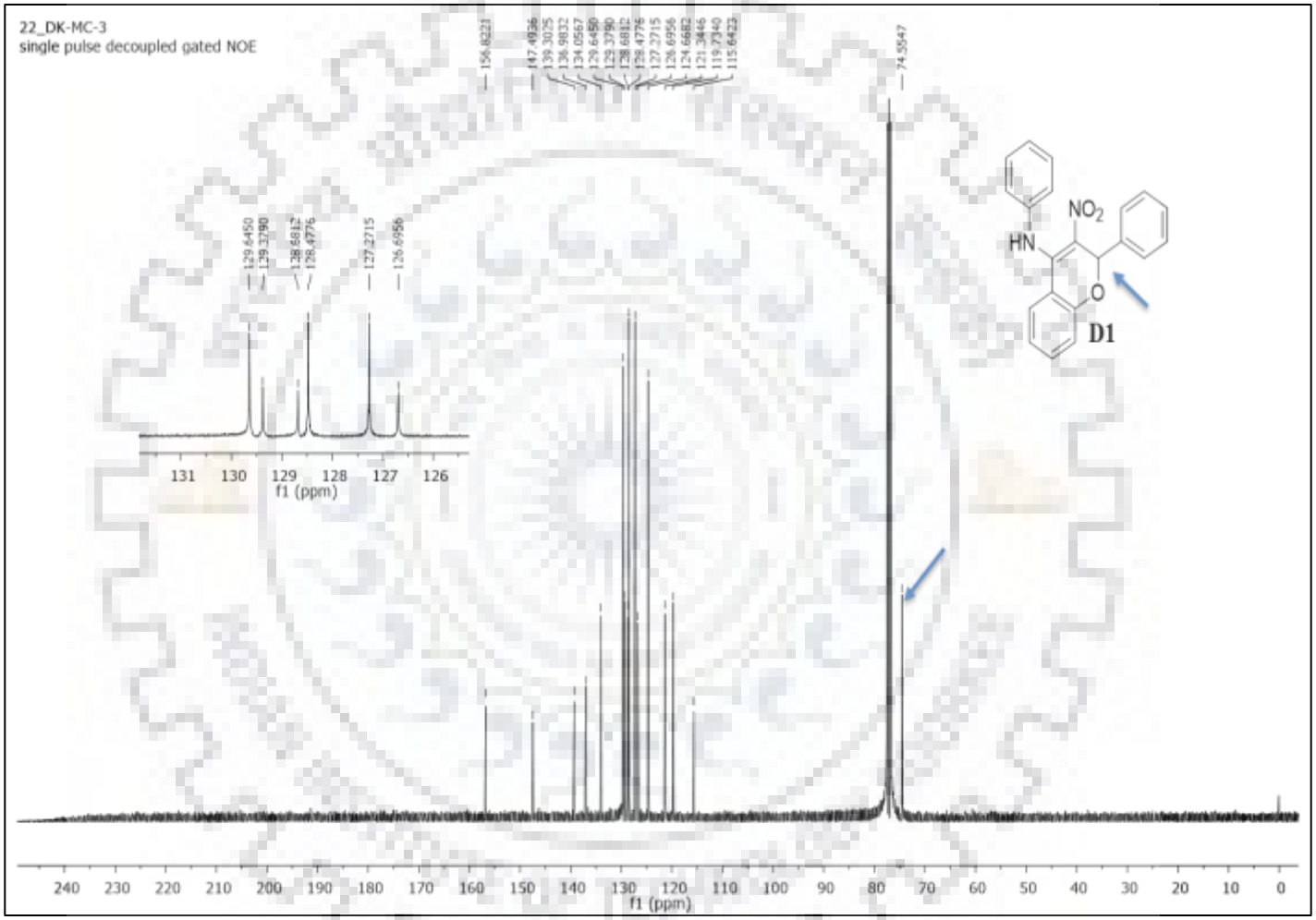

Figure S-18: ^{13}C NMR Spectrum of **D1** in $CDCl_3$.

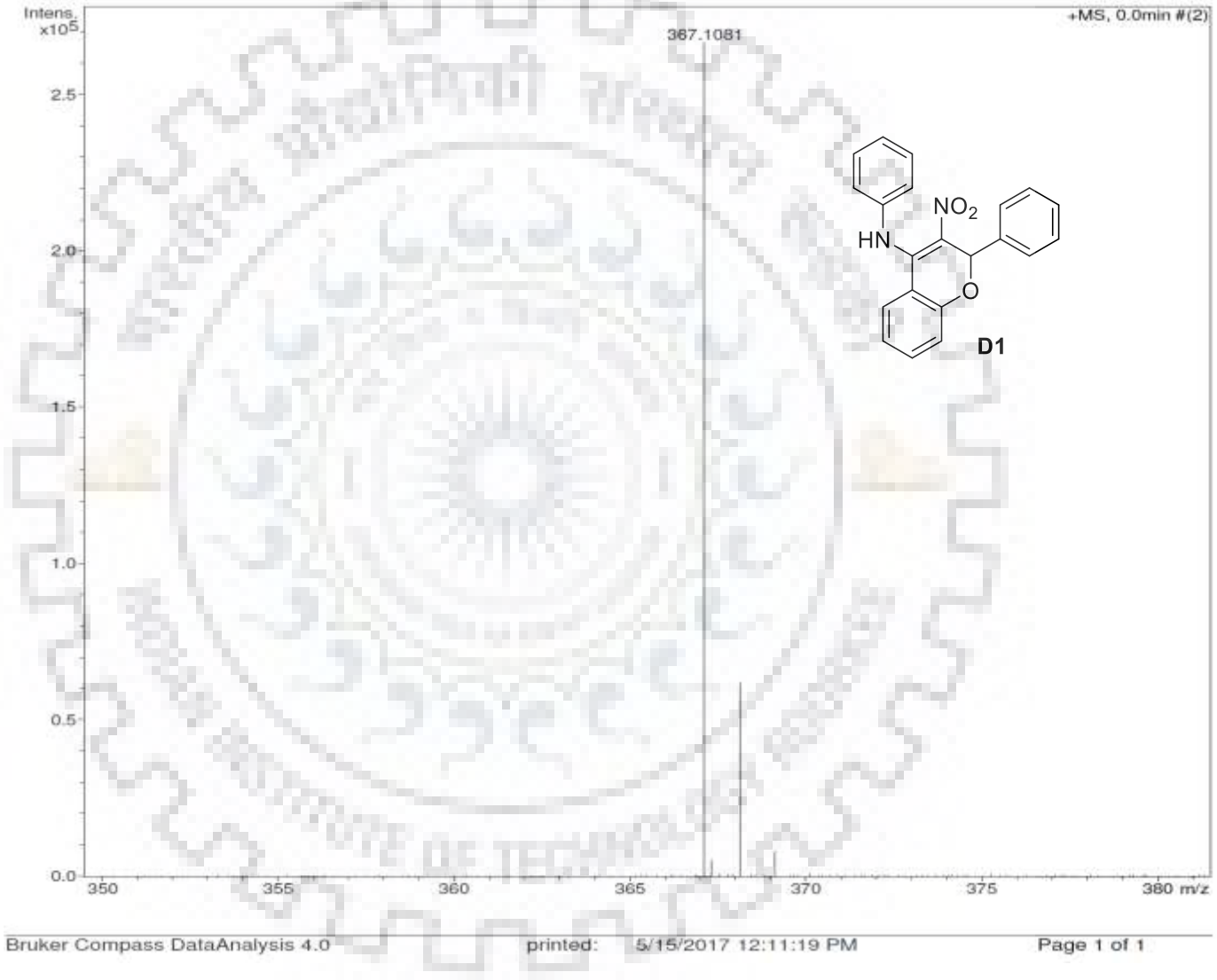

Figure S-19: HRMS Spectrum of **D1**.

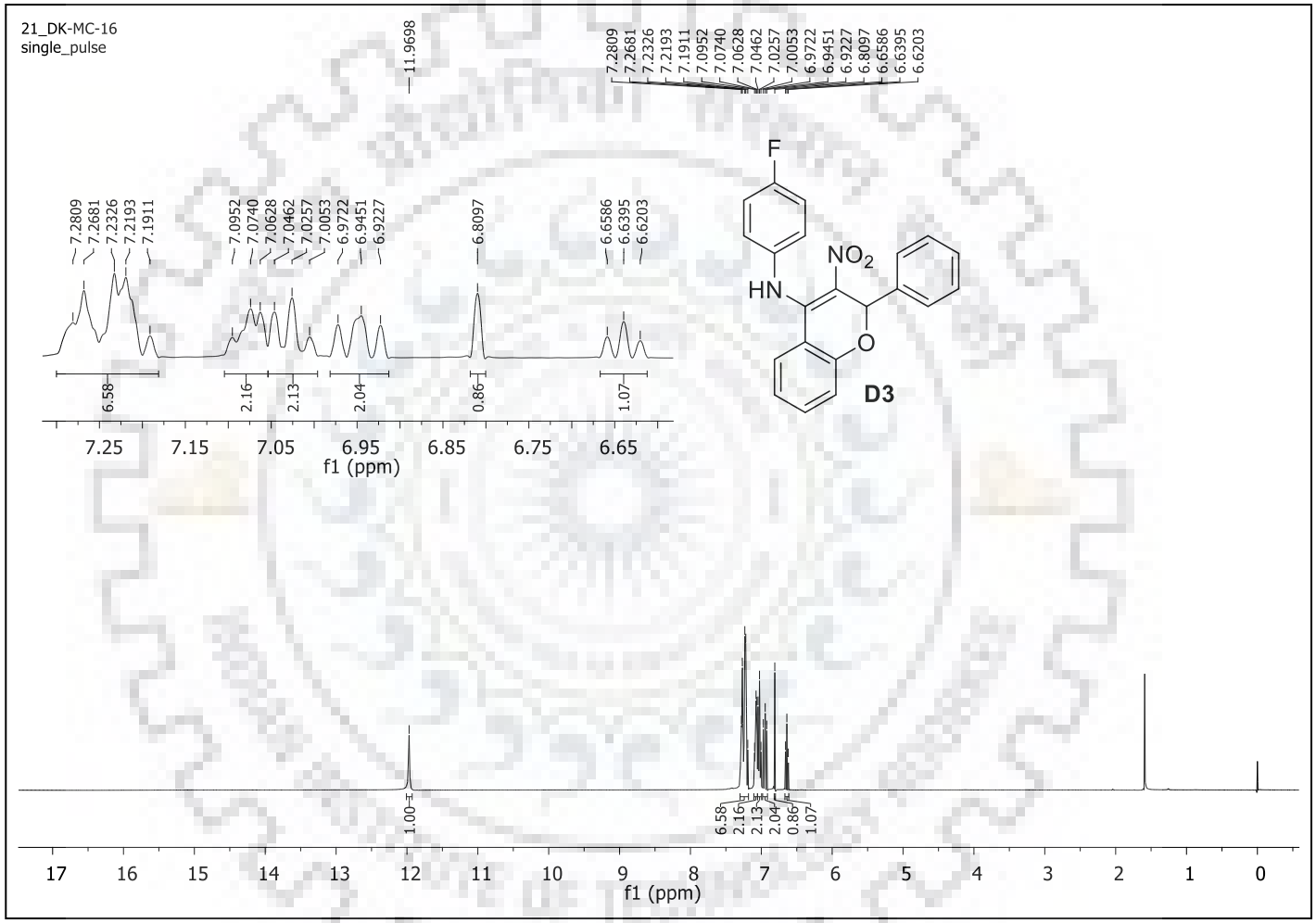

Figure S-20: ^{1}H NMR Spectrum of **D3** in $CDCl_3$.

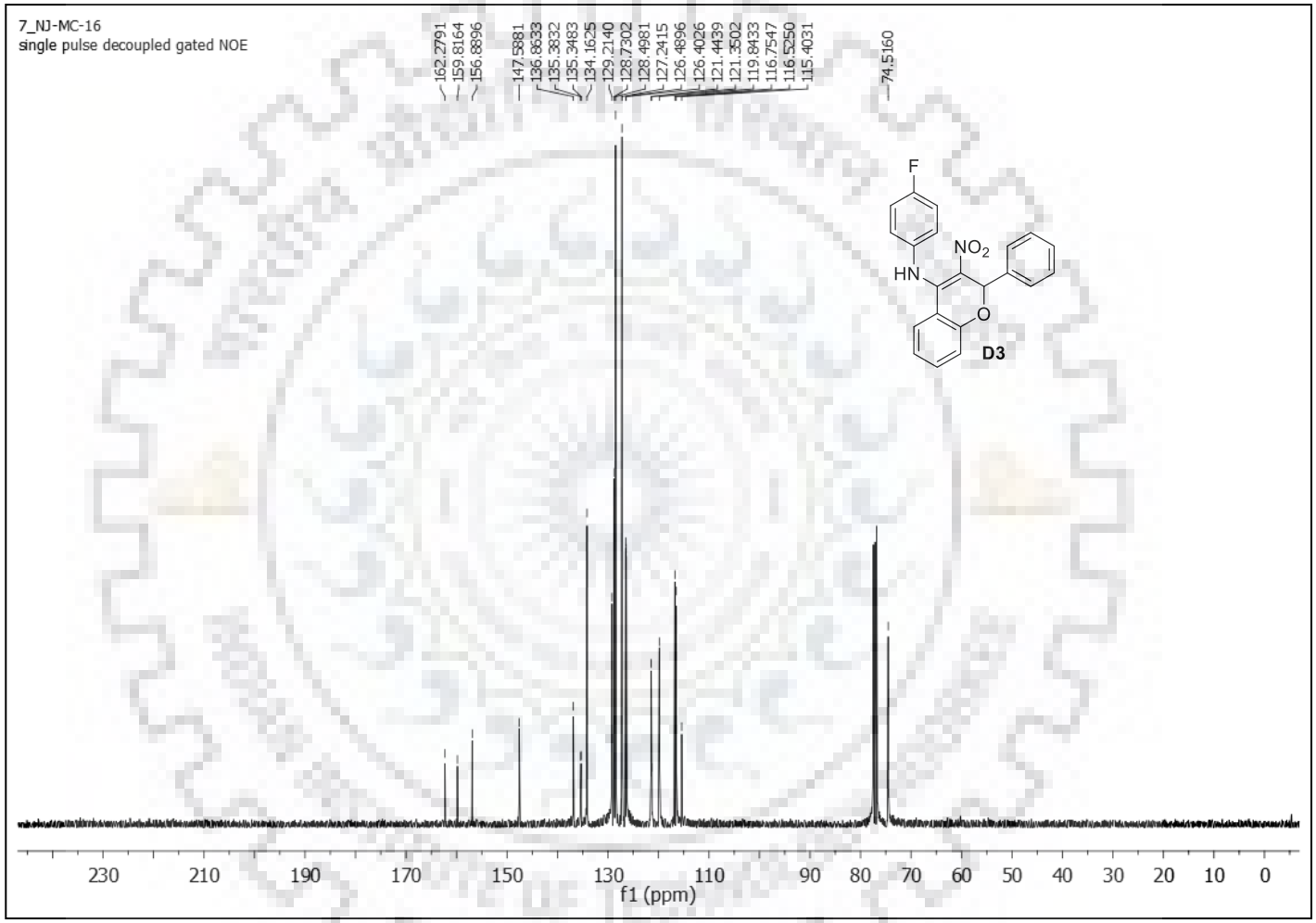

Figure S-21: ^{13}C NMR Spectrum of **D3** in $CDCl_3$.

Figure S-22: HRMS Spectrum of **D3**.

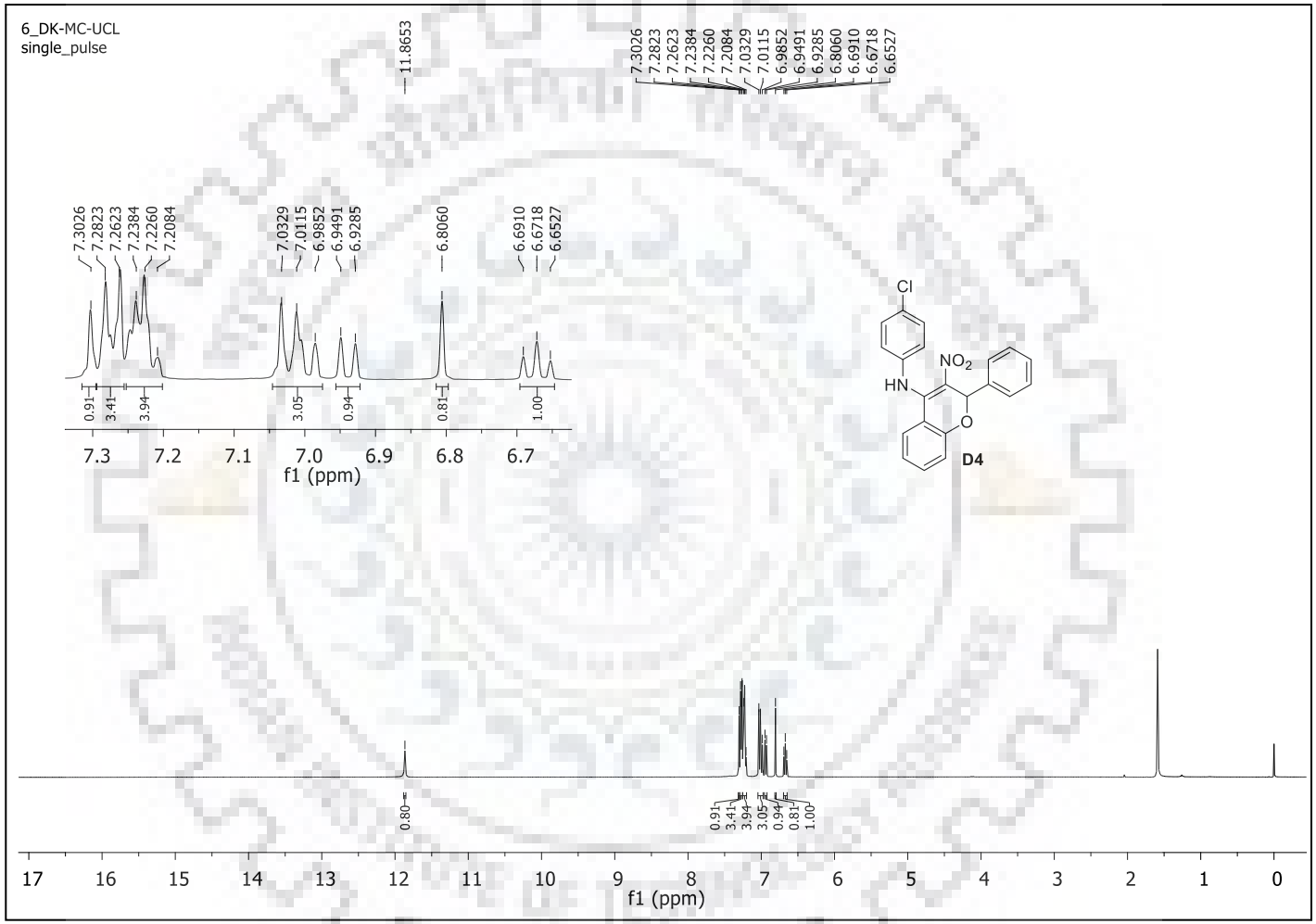

Figure S-23: ^{1}H NMR Spectrum of **D4** in $CDCl_3$.

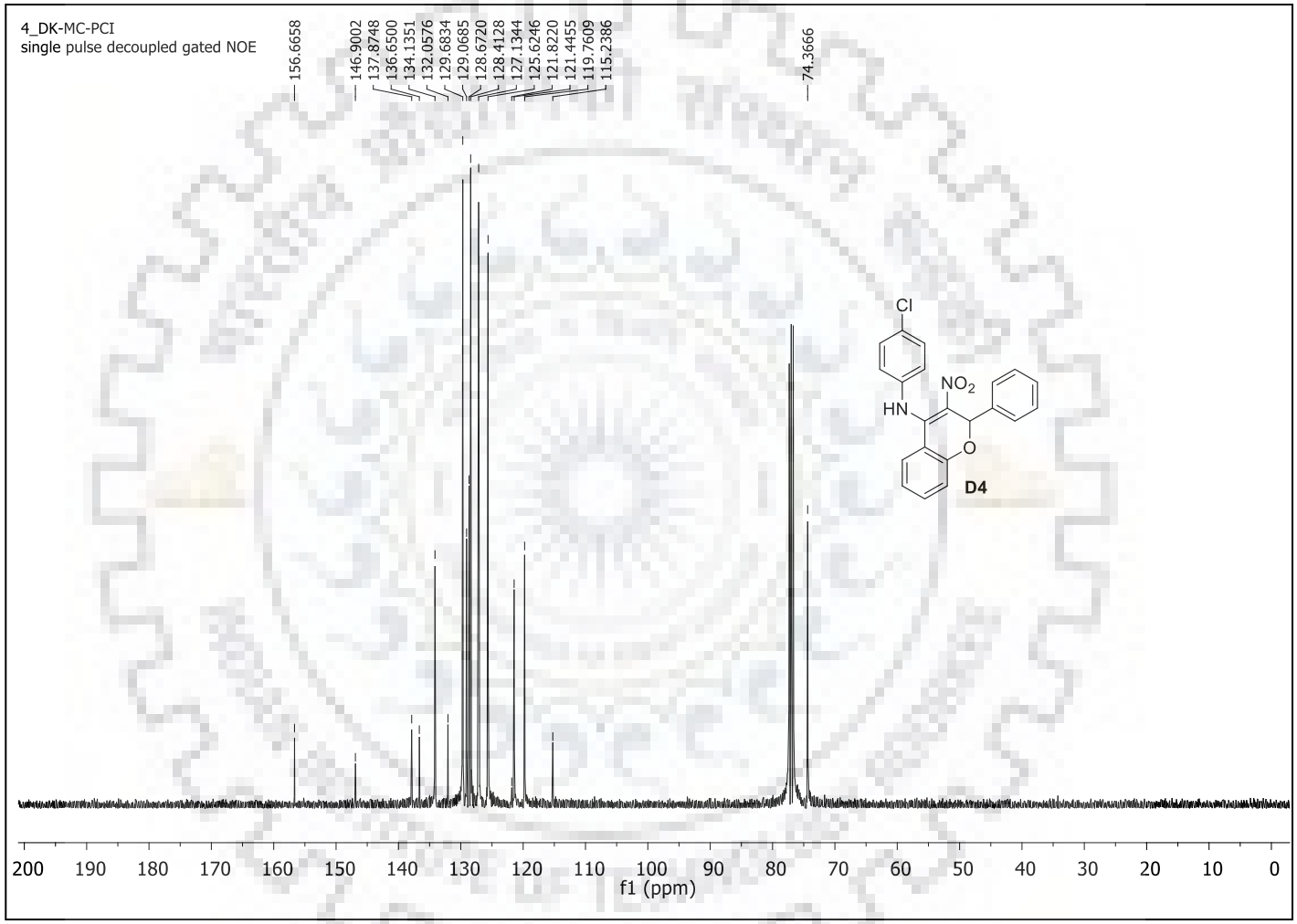

Figure S-24: ^{13}C NMR Spectrum of **D4** in $CDCl_3$.

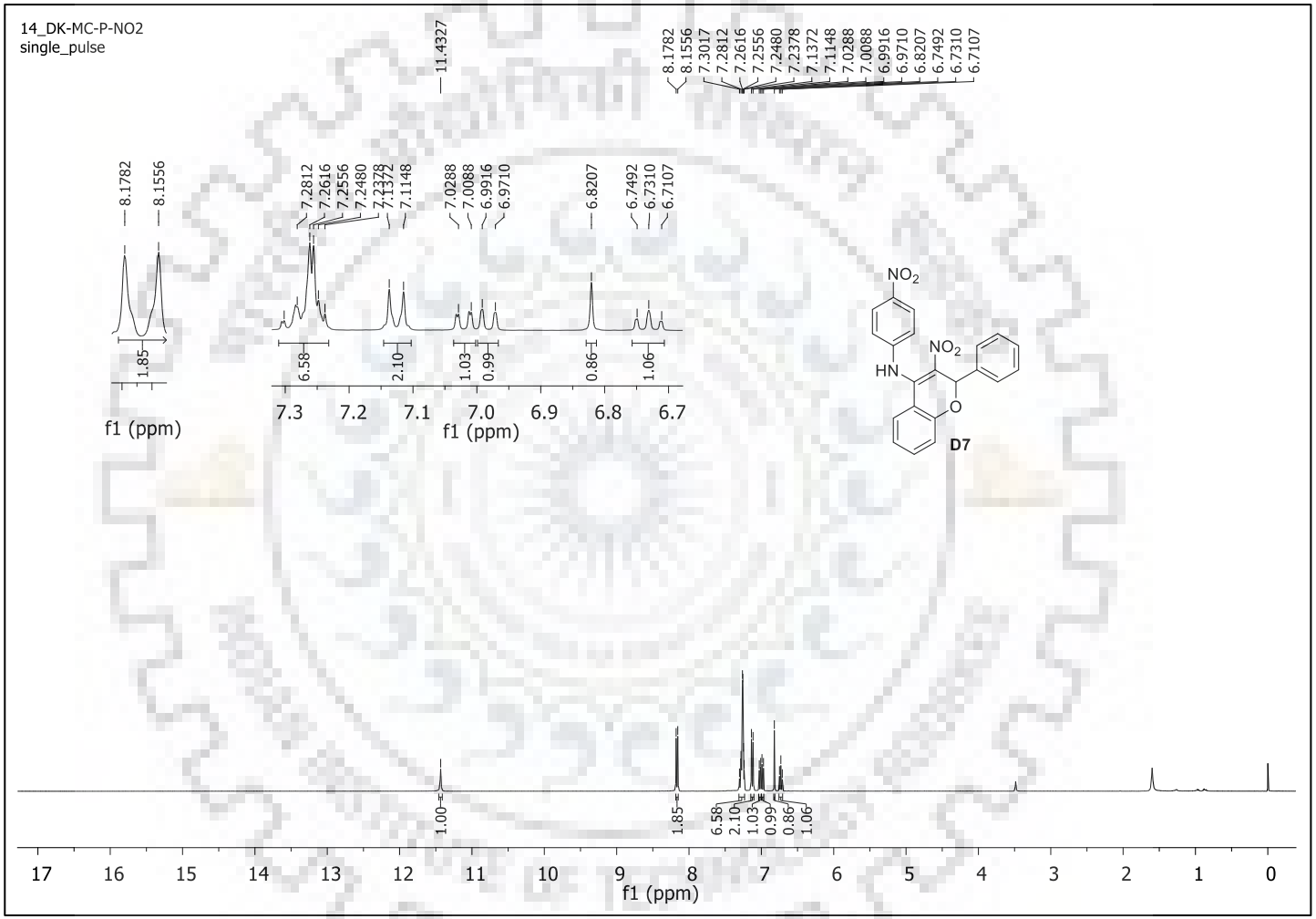

Figure S-25: ^{1}H NMR Spectrum of **D7** in $CDCl_3$.

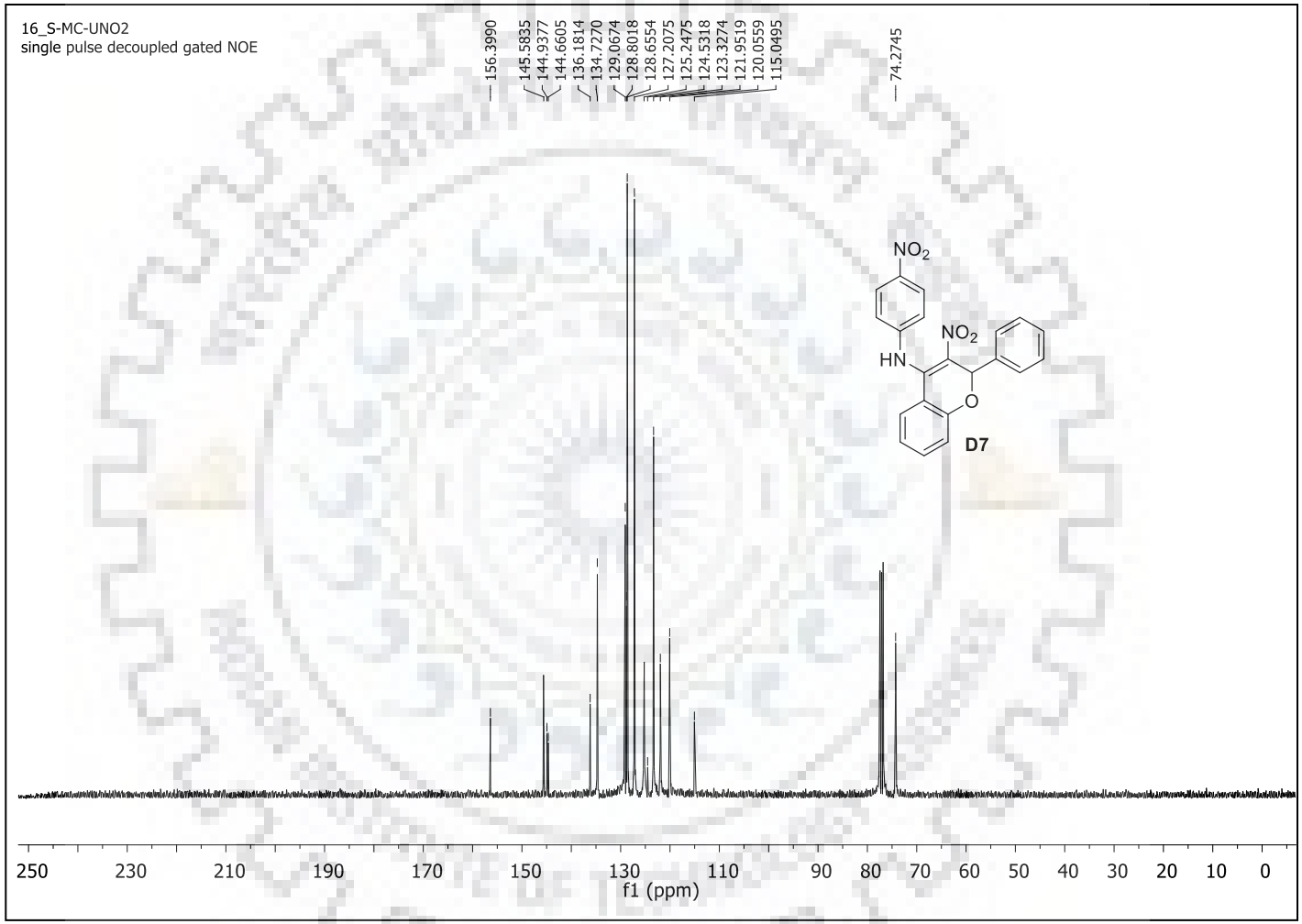

Figure S-26: ^{13}C NMR Spectrum of **D7** in $CDCl_3$.

Figure S-27: ^{1}H NMR Spectrum of **D8** in $CDCl_3$.

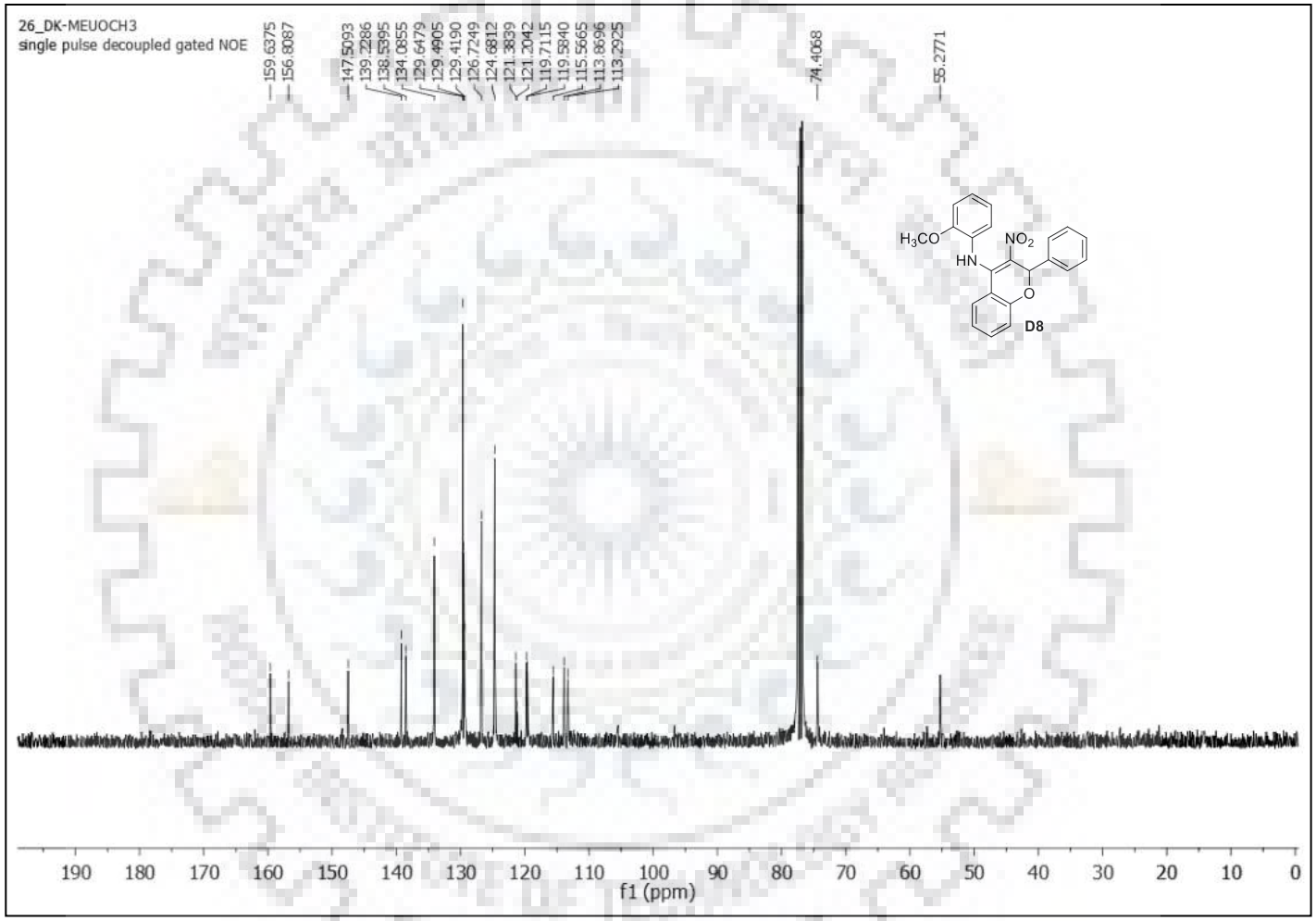

Figure S-28: ^{13}C NMR Spectrum **D8** in $CDCl_3$.

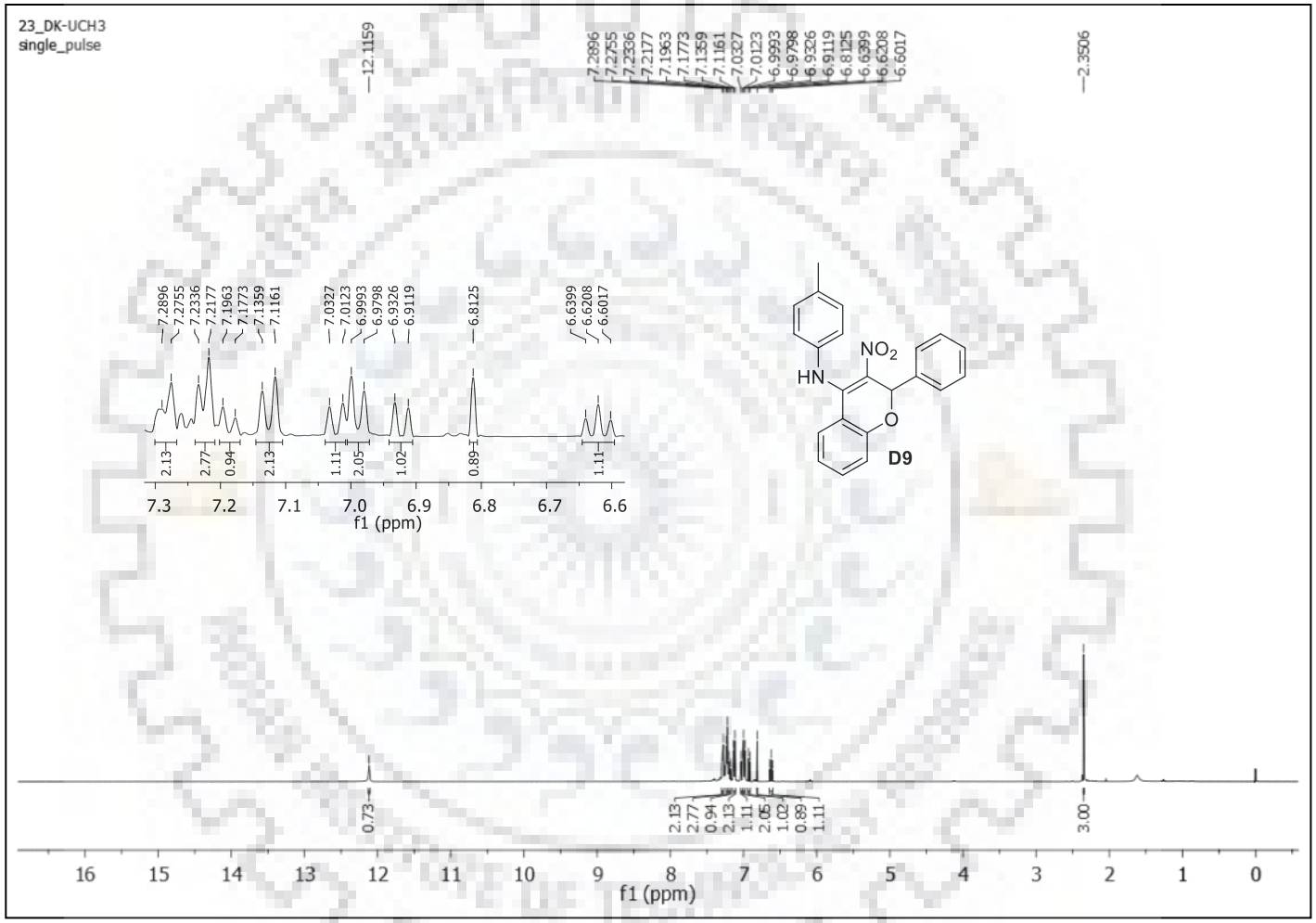

Figure S-29: ^{1}H NMR Spectrum of **D9** in $CDCl_3$.

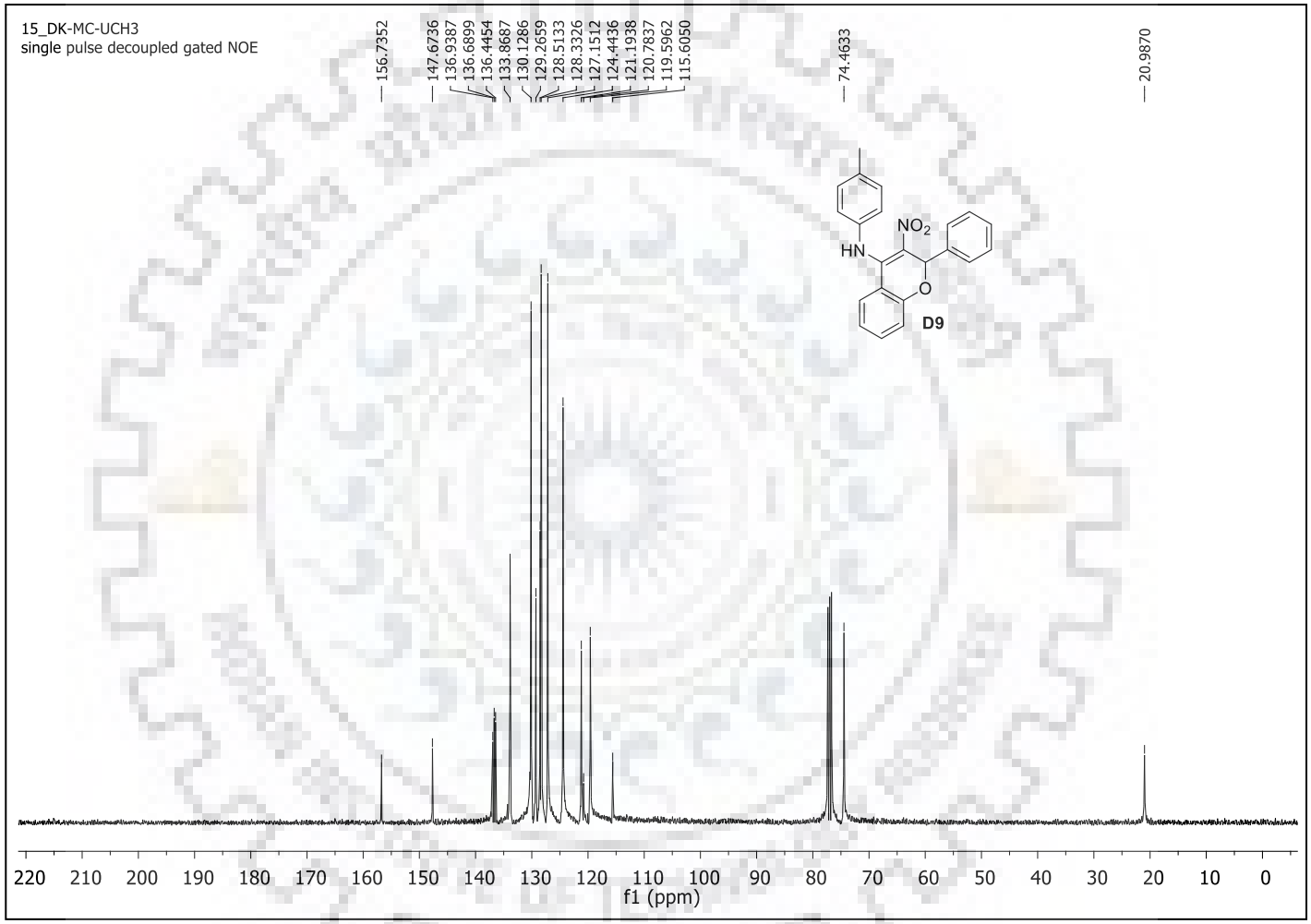

Figure S-30: ^{13}C NMR Spectrum of **D9** in $CDCl_3$.

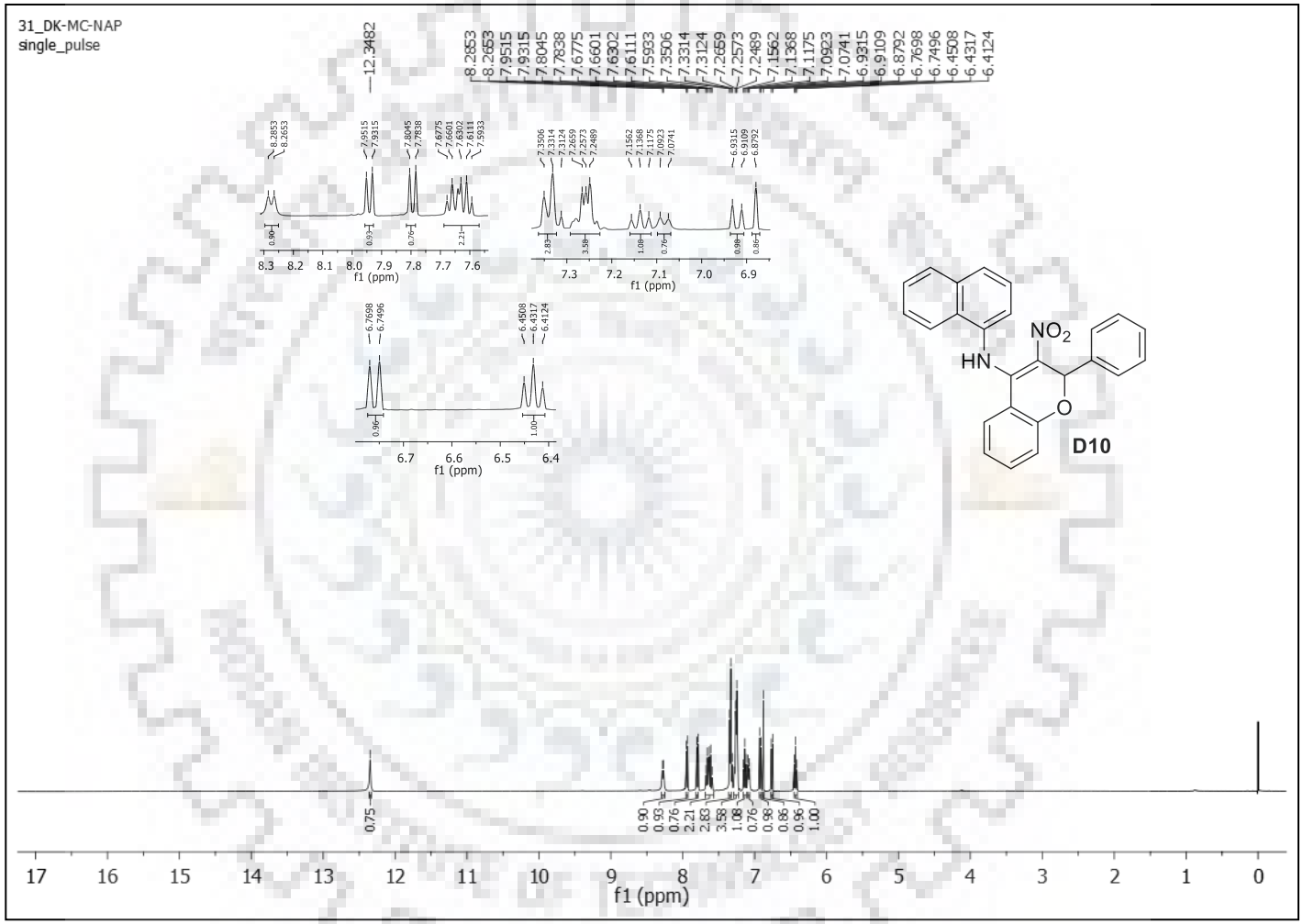

Figure S-31: ^{1}H NMR Spectrum of **D10** in $CDCl_3$.

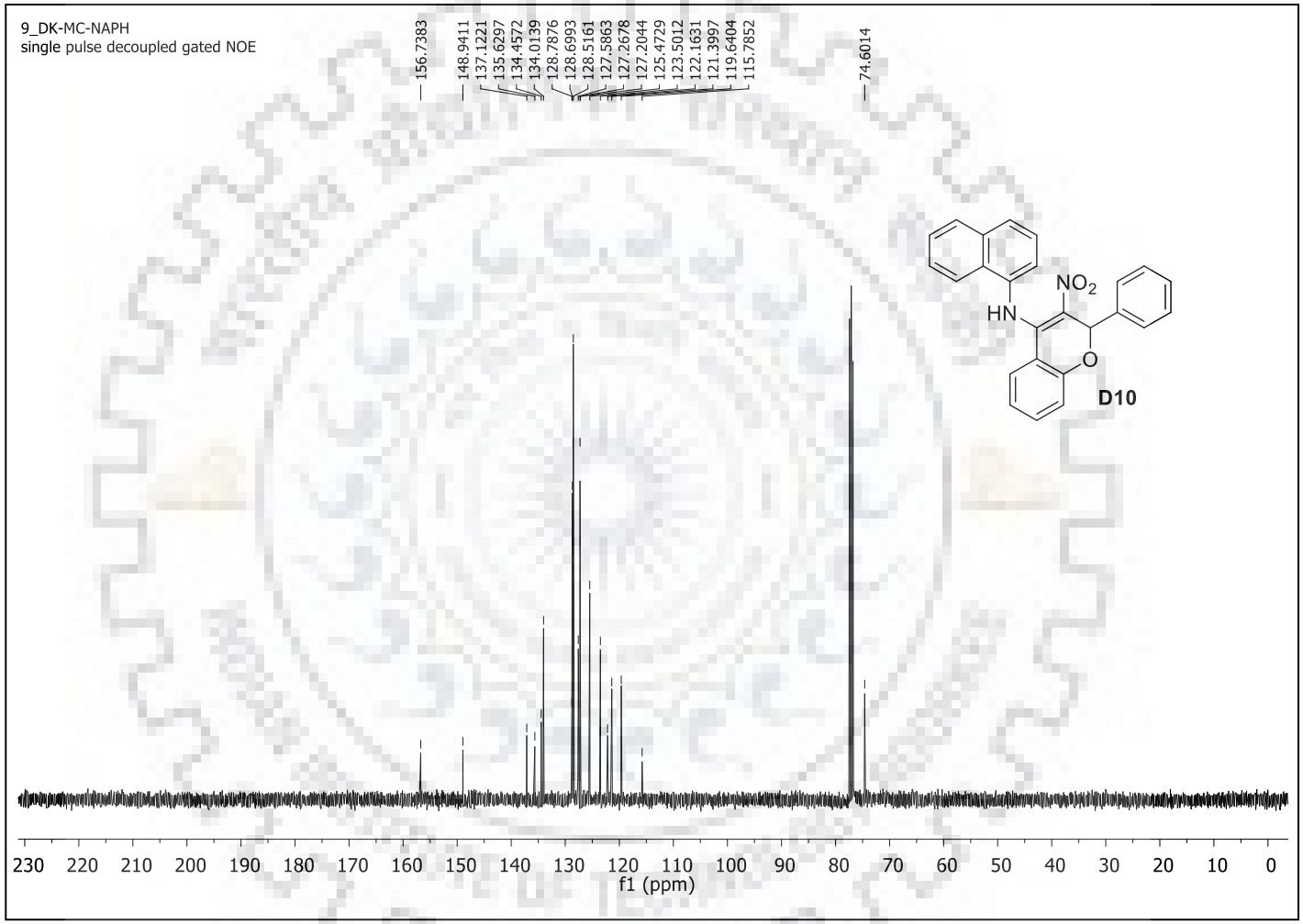

Figure S-32: ^{13}C NMR Spectrum of **D10** in $CDCl_3$.

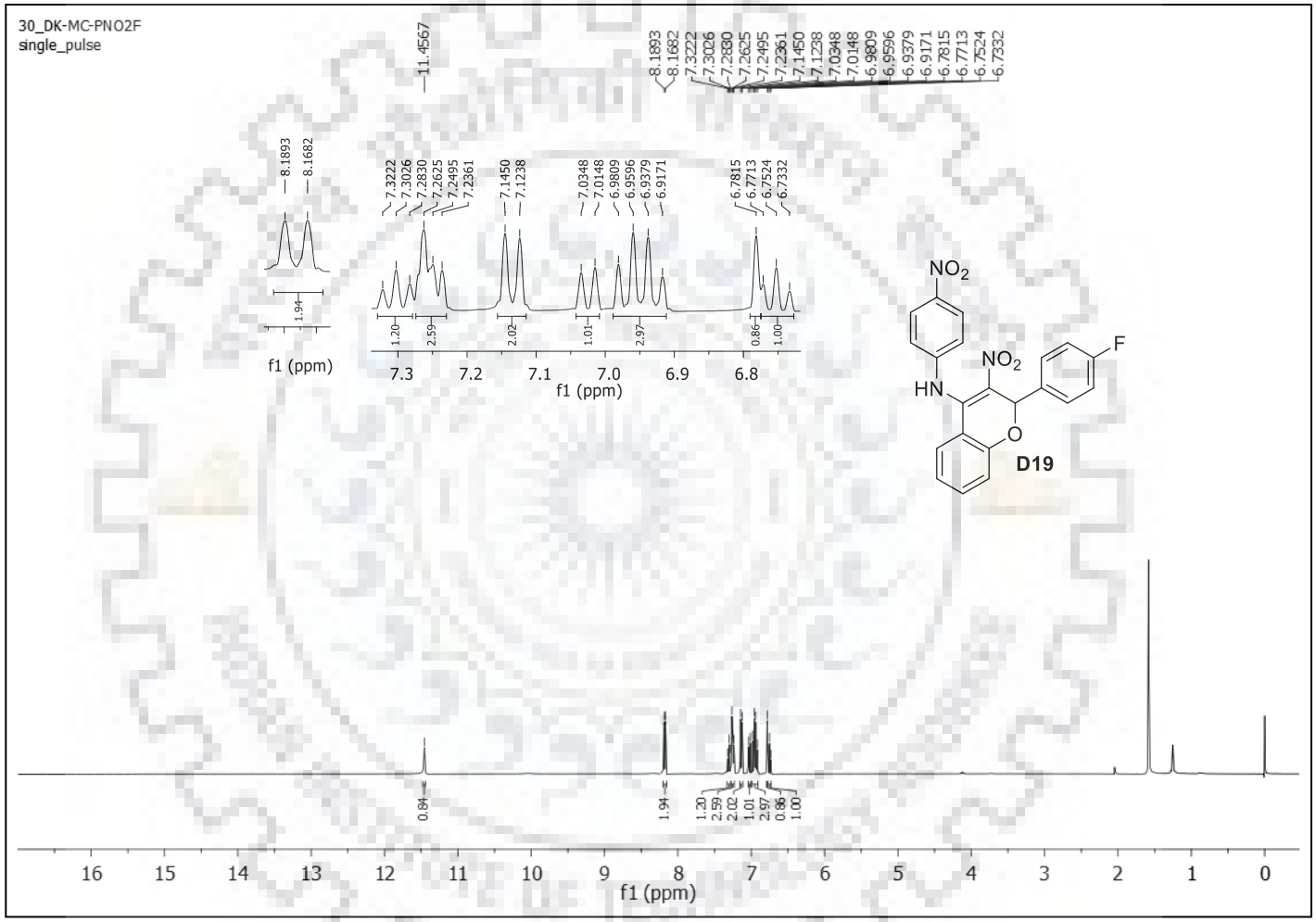

Figure S-33: ^{1}H NMR Spectrum of **D19** in $CDCl_3$.

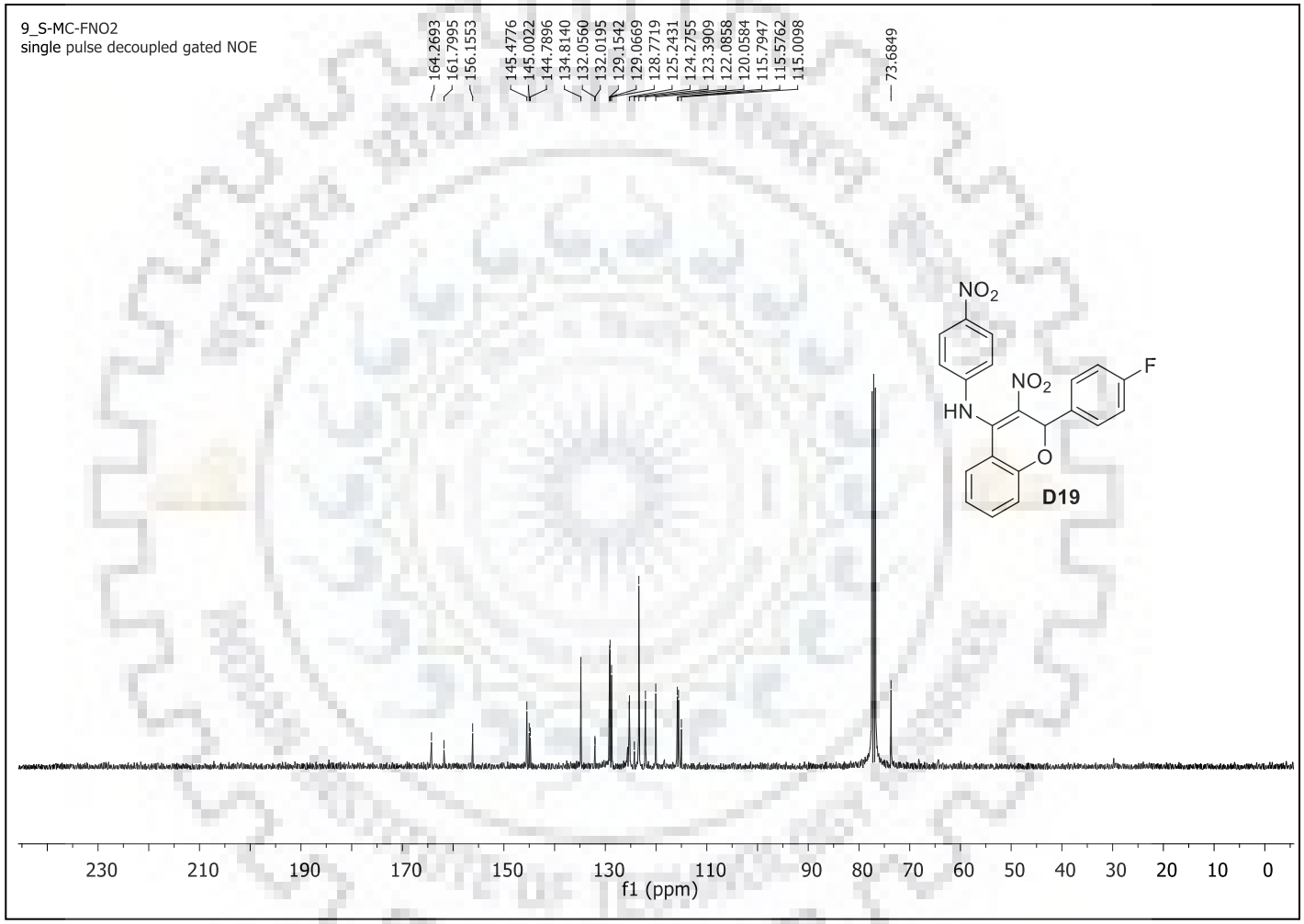

Figure S-34: ^{13}C NMR Spectrum of **D19** in $CDCl_3$.

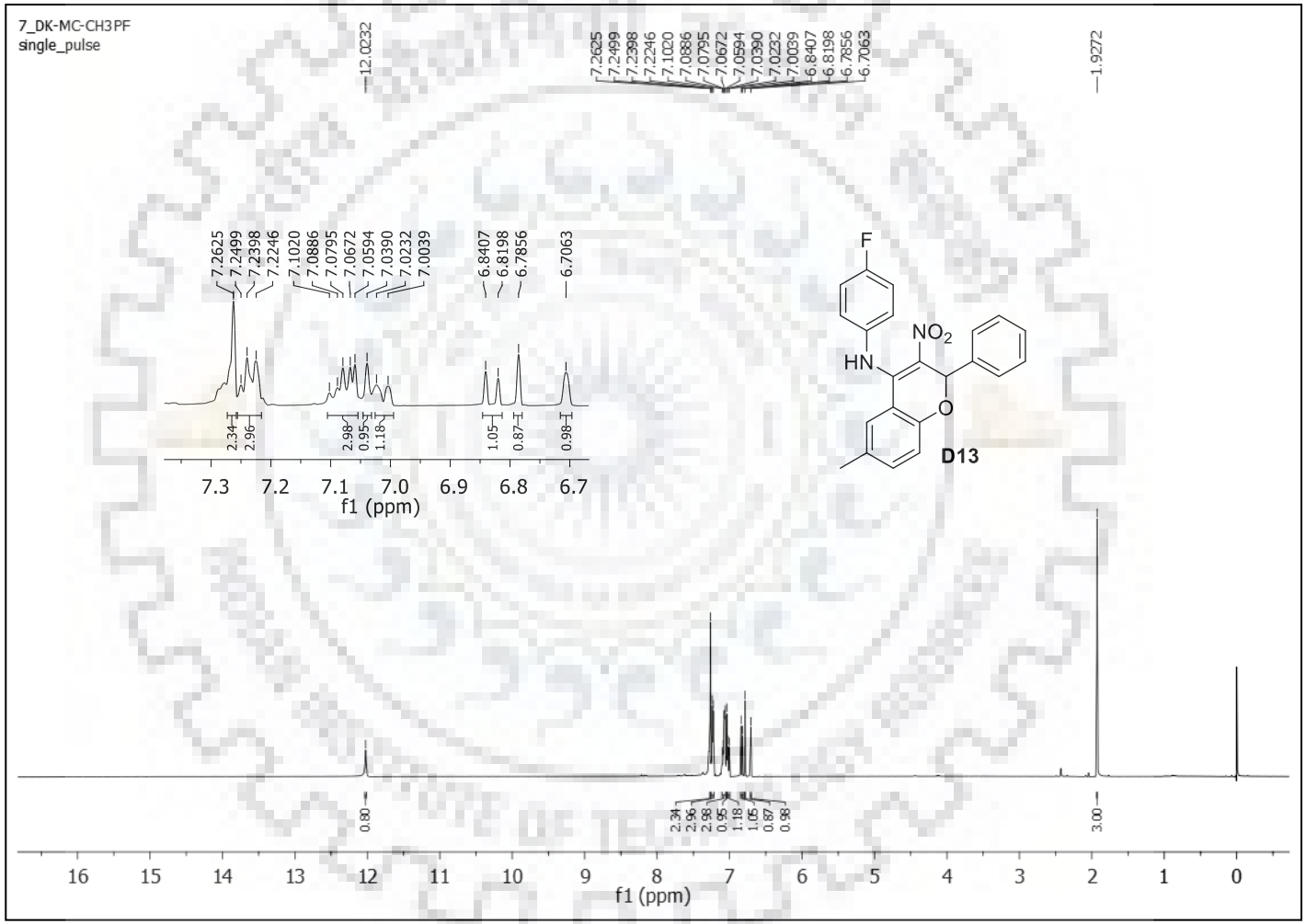

Figure S-35: ^{1}H NMR Spectrum of **D13** in $CDCl_3$.

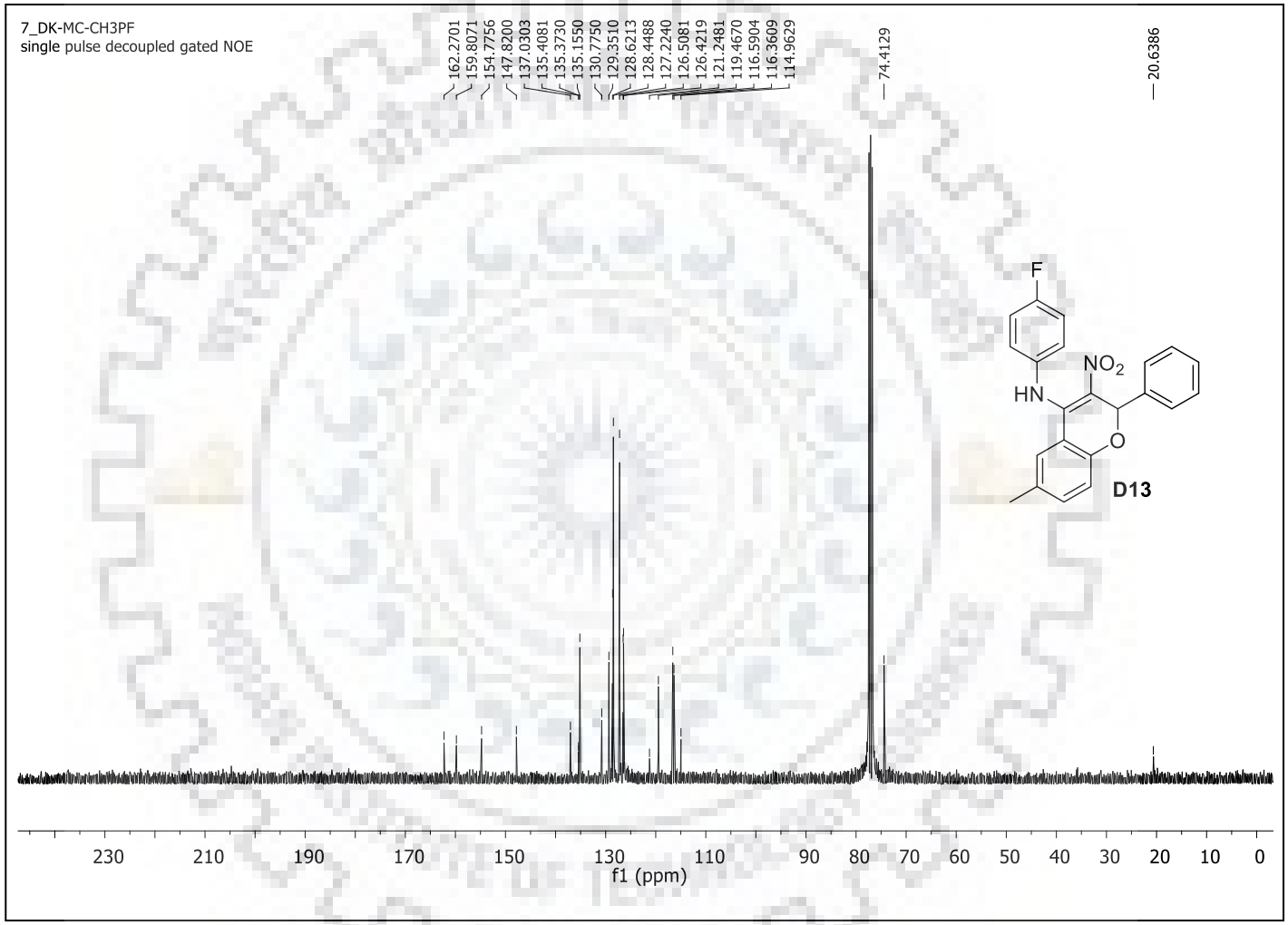

Figure S-36: ^{13}C NMR Spectrum of **D13** in $CDCl_3$.

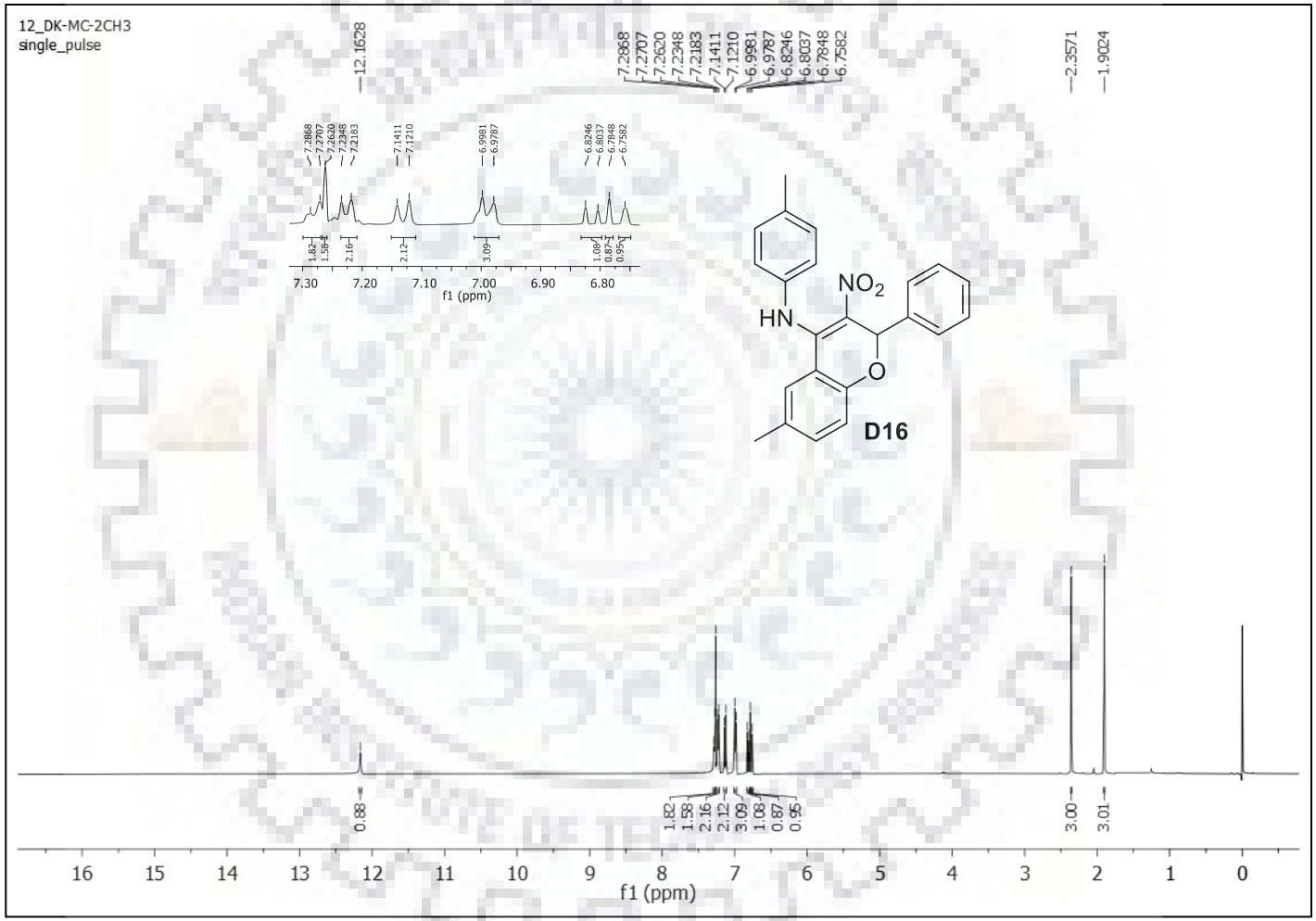

Figure S-37: ^{1}H NMR Spectrum of **D16** in $CDCl_3$.

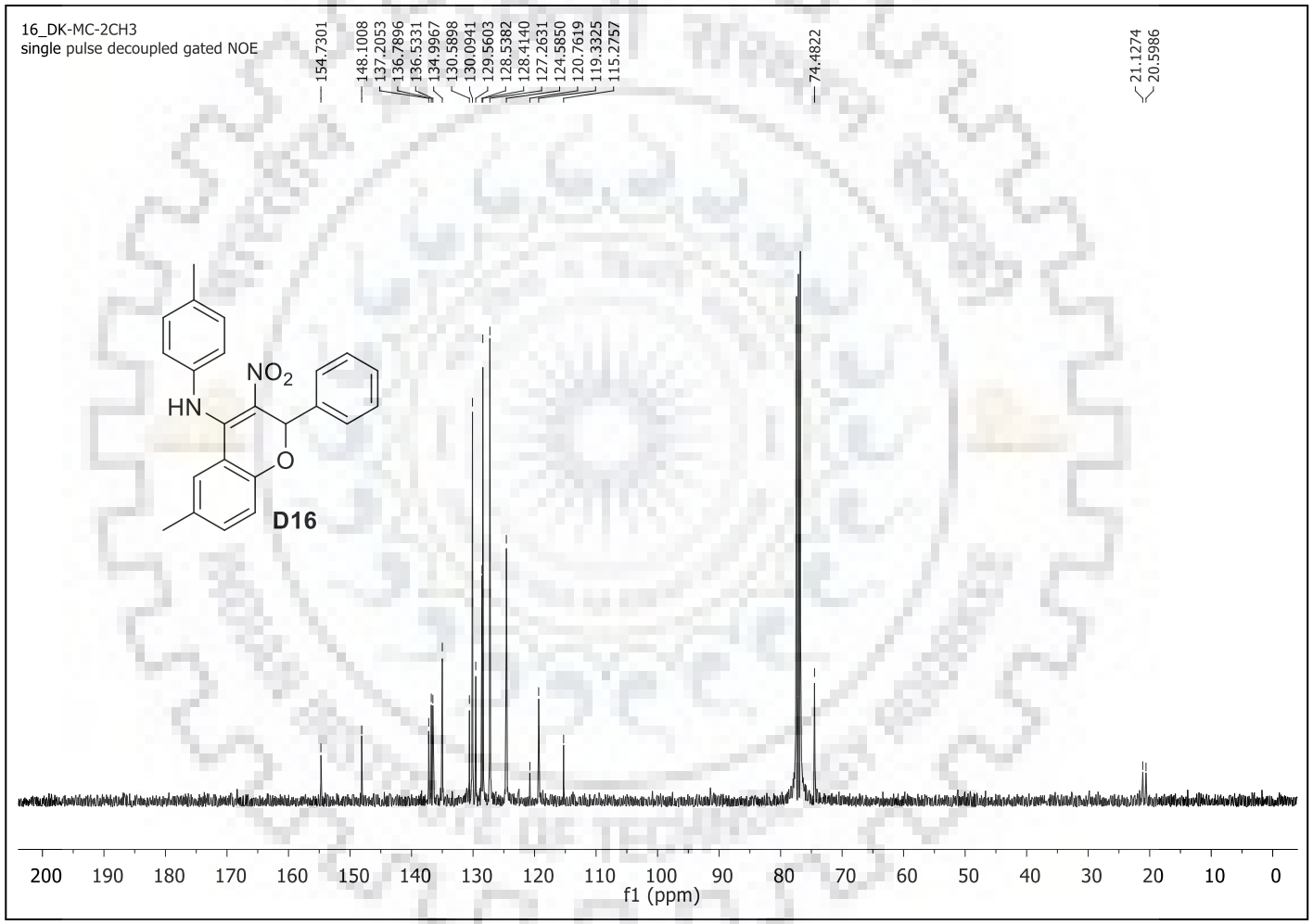

Figure S-38: ^{13}C NMR Spectrum of **D16** in $CDCl_3$.

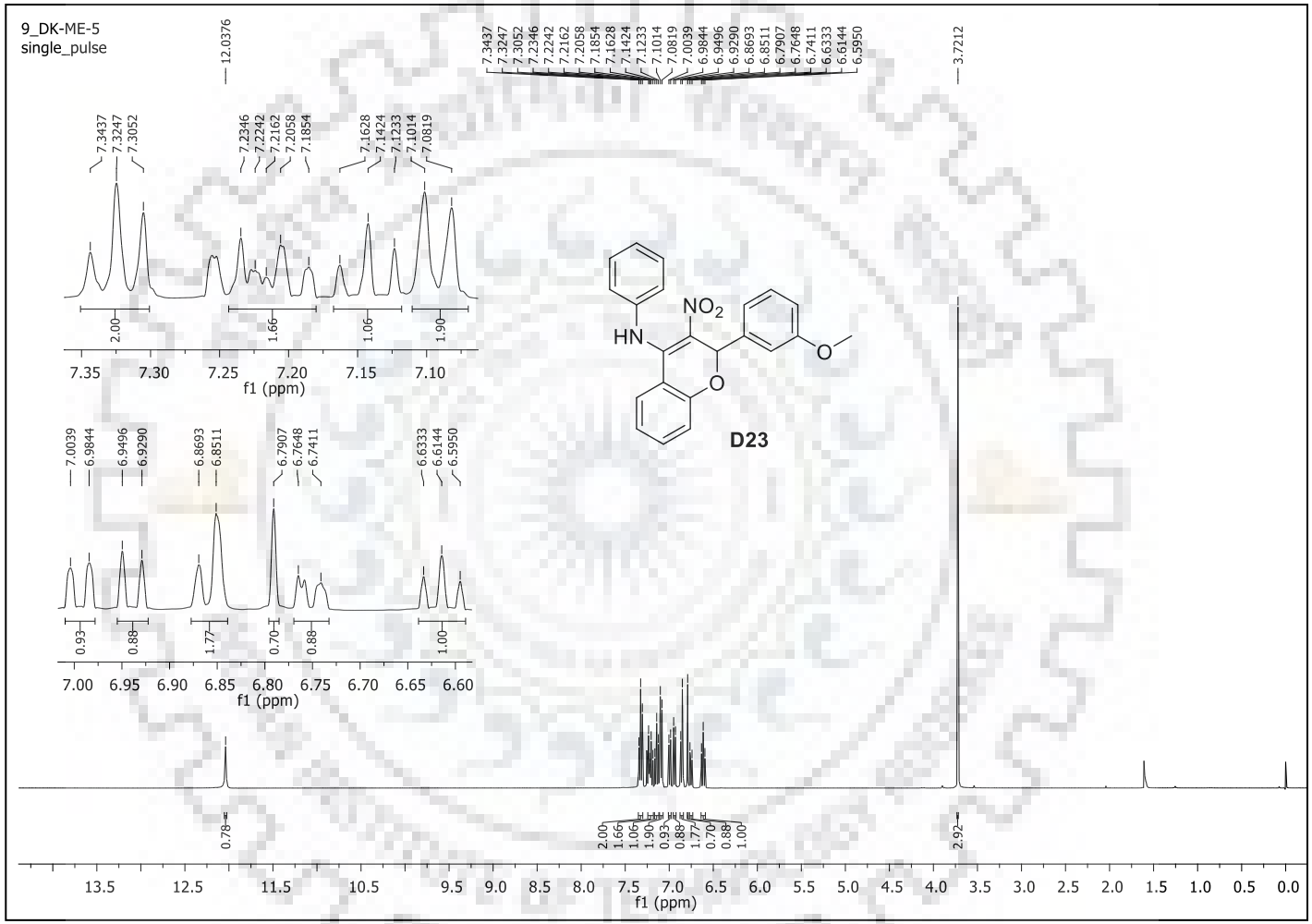

Figure S-39: ^{1}H NMR Spectrum of **D23** in $CDCl_3$.

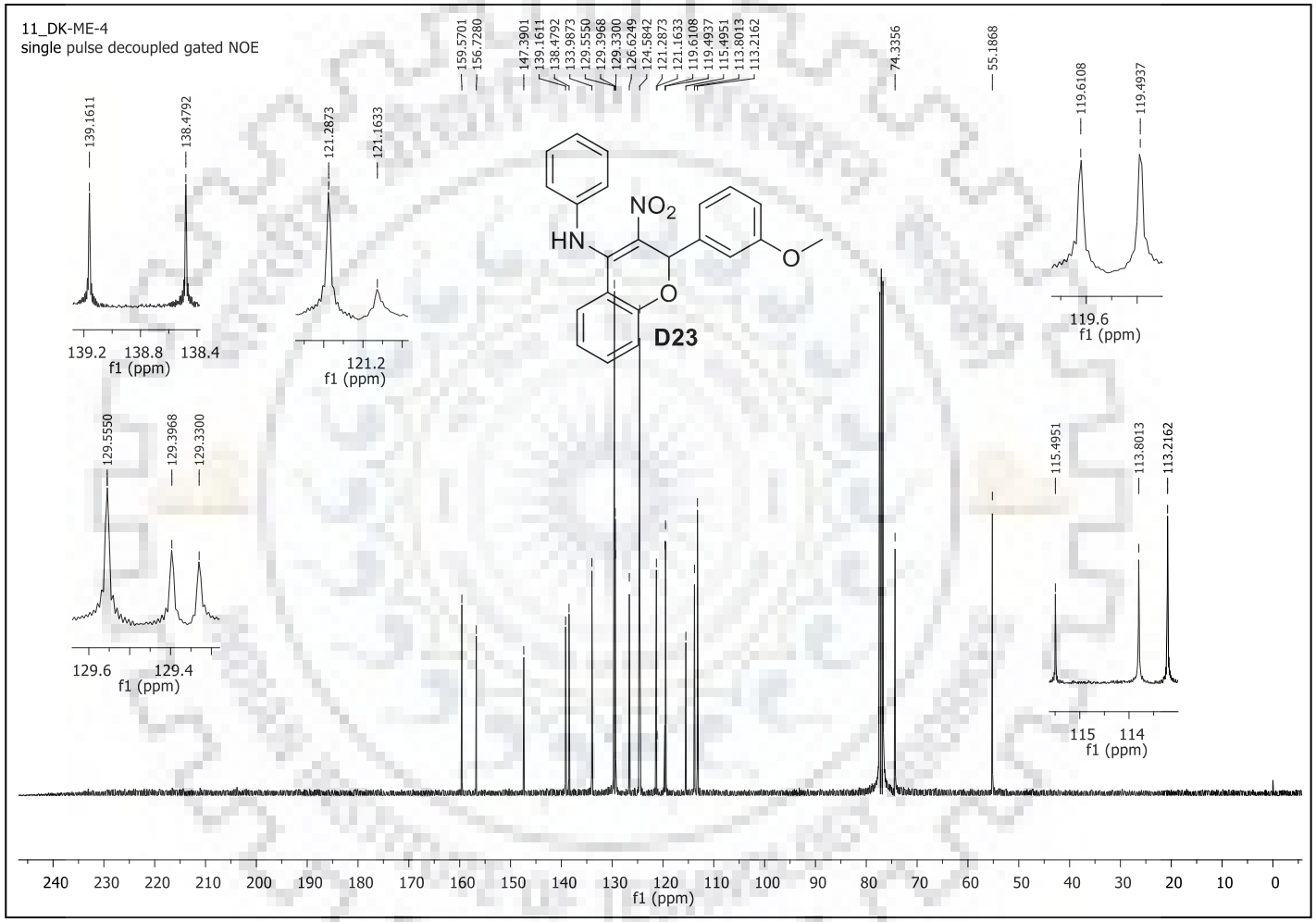

Figure S-40: ^{13}C NMR Spectrum of **D23** in $CDCl_3$.

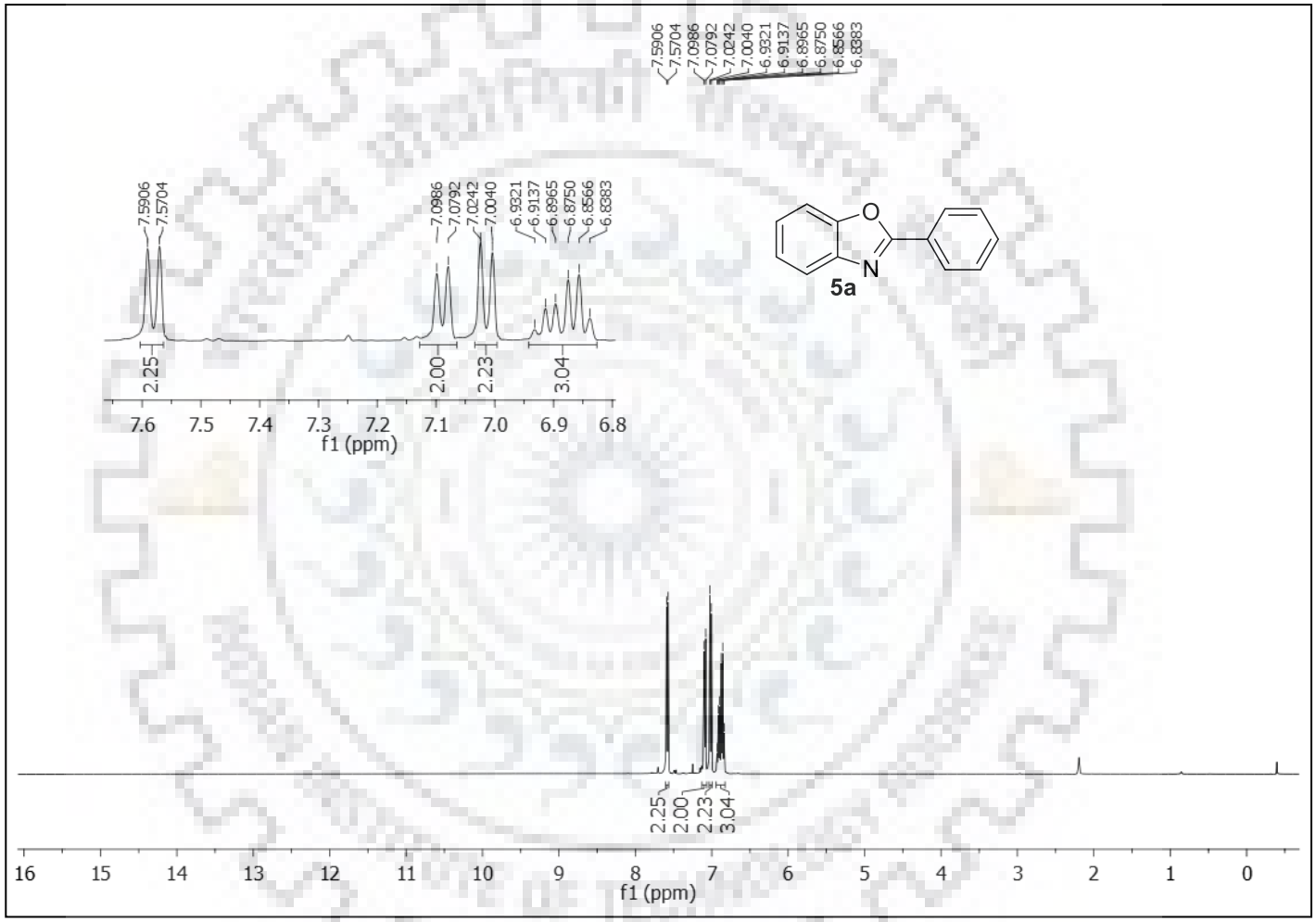

Figure S-41: ^{1}H NMR Spectrum of **5a** in $CDCl_3$.

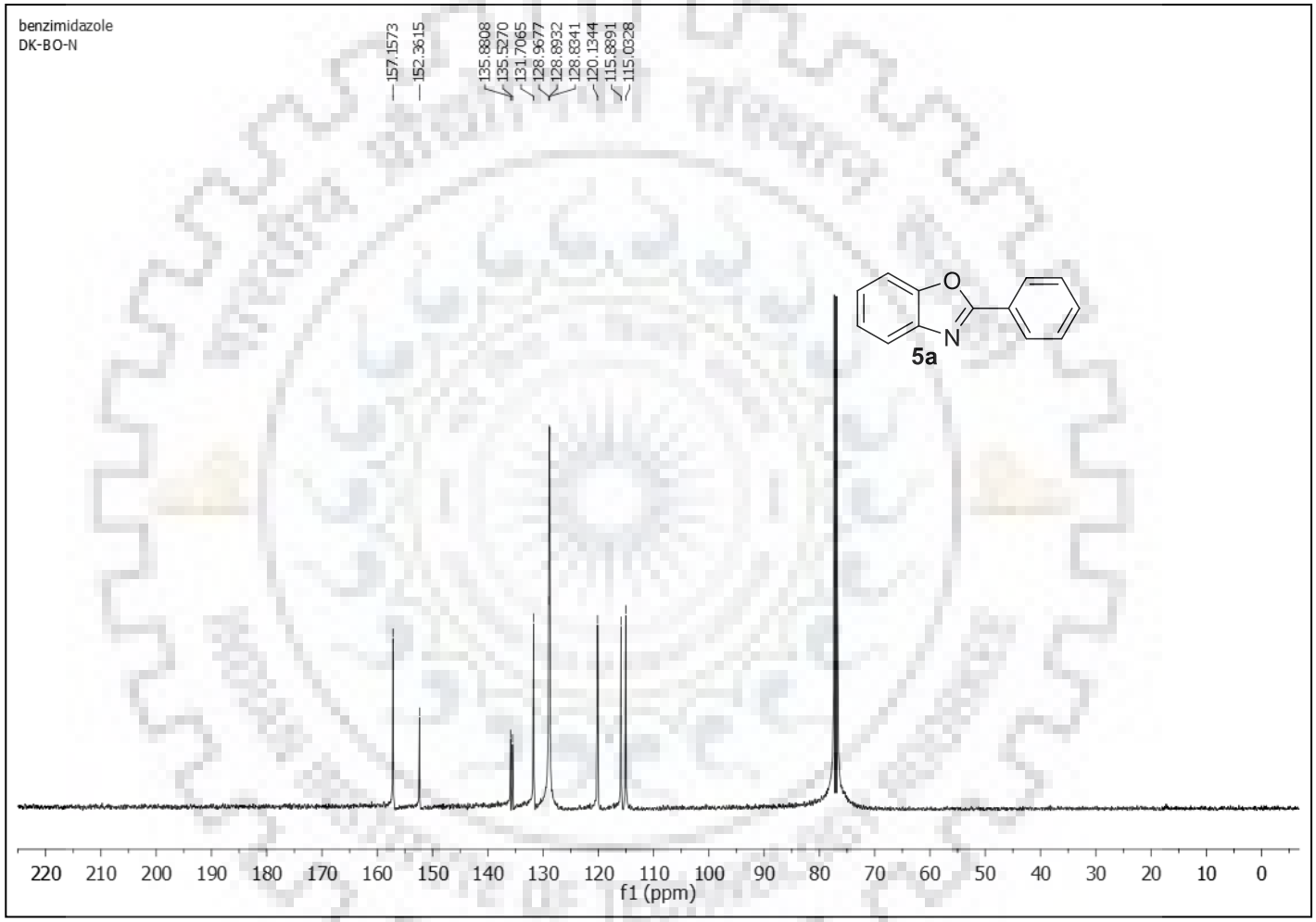

Figure S-42: ^{13}C NMR Spectrum of **5a** in $CDCl_3$.

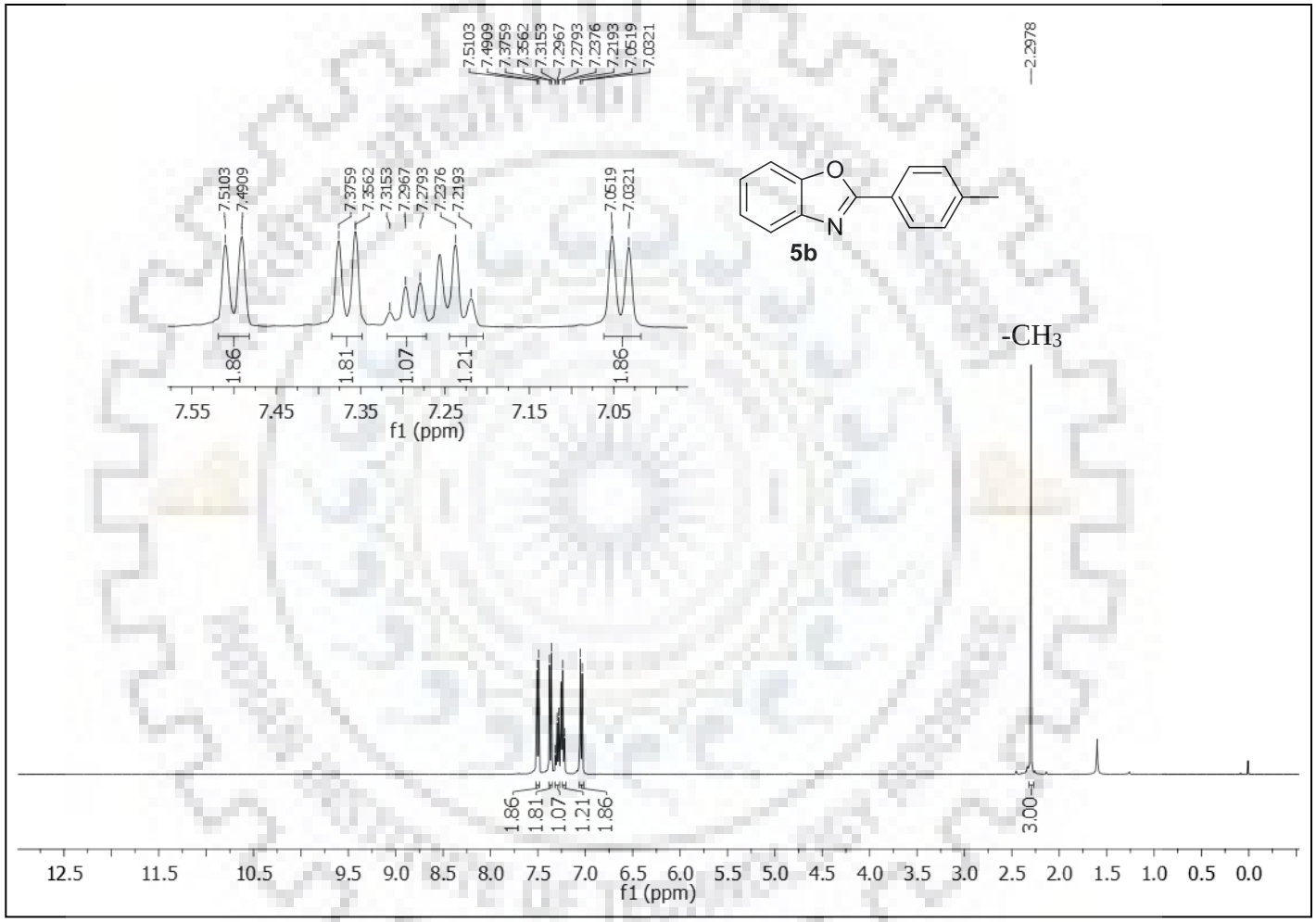

Figure S-43: ^{1}H NMR Spectrum of **5b** in $CDCl_3$.

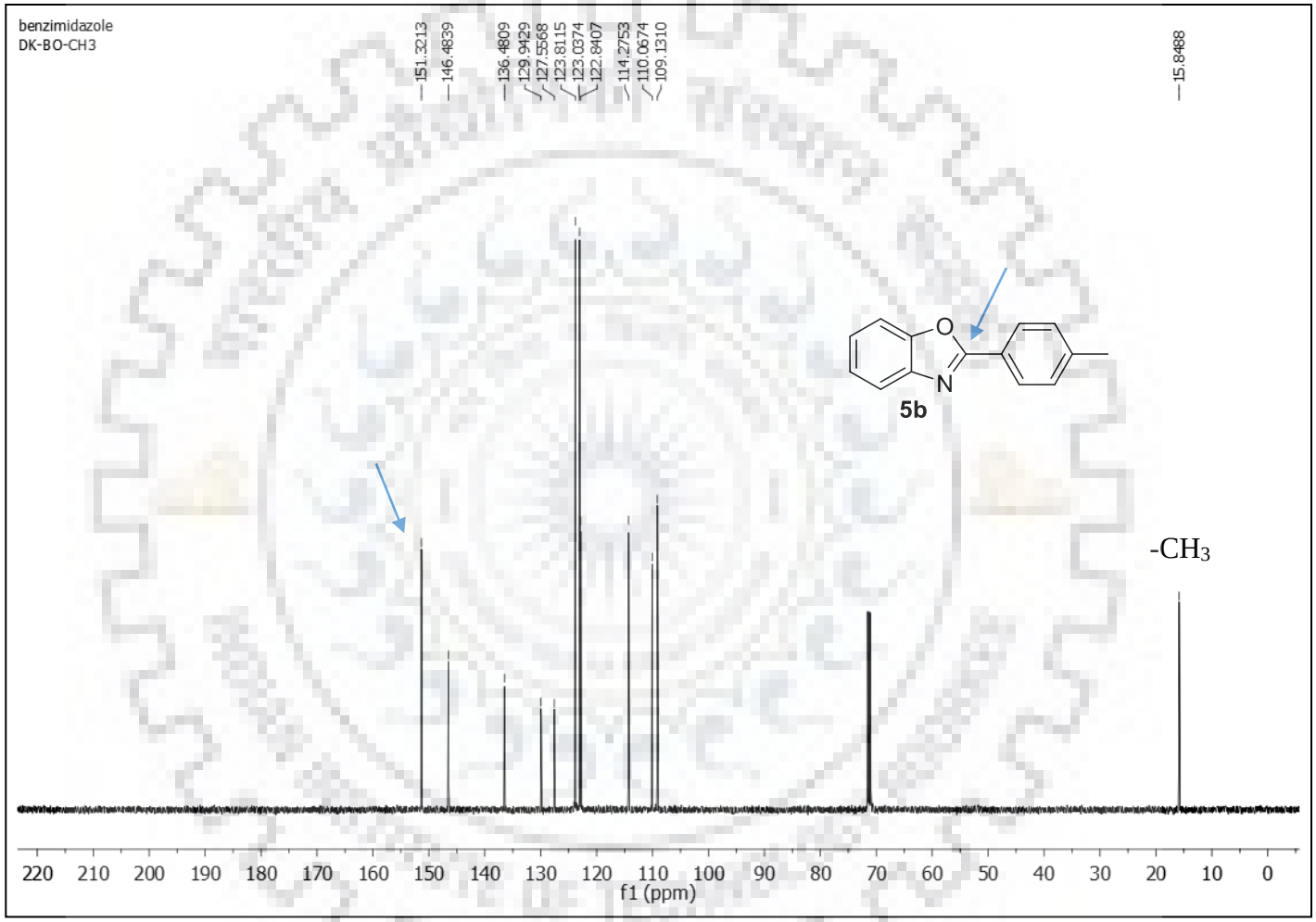

Figure S-44: ^{13}C NMR Spectrum of **5b** in $CDCl_3$.

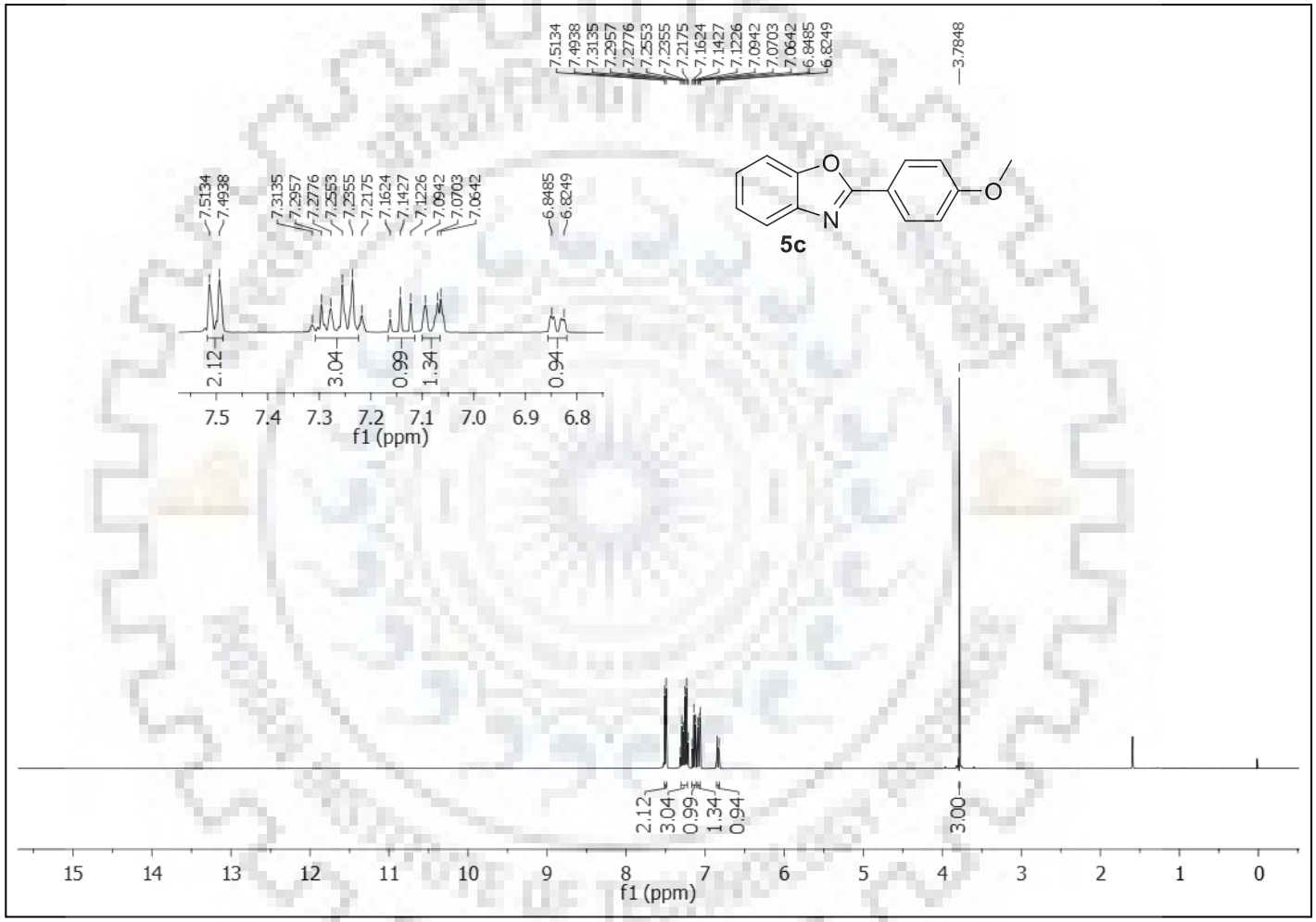

Figure S-45: ^{1}H NMR Spectrum of **5c** in $CDCl_3$.

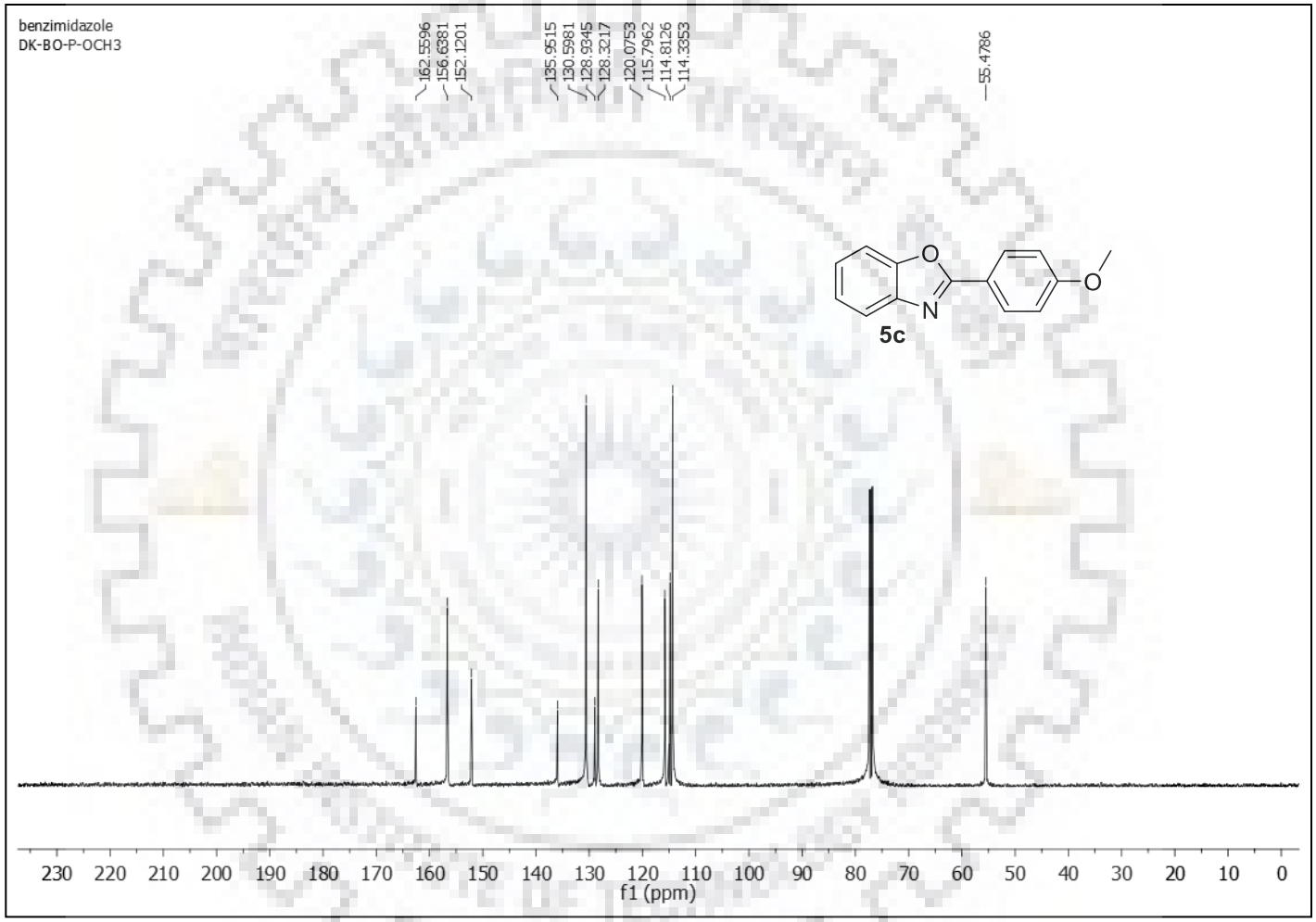

Figure S-46: ^{13}C NMR Spectrum of **5c** in $CDCl_3$.

Figure S-47: ^{1}H NMR Spectrum of **5h** in $CDCl_3$.

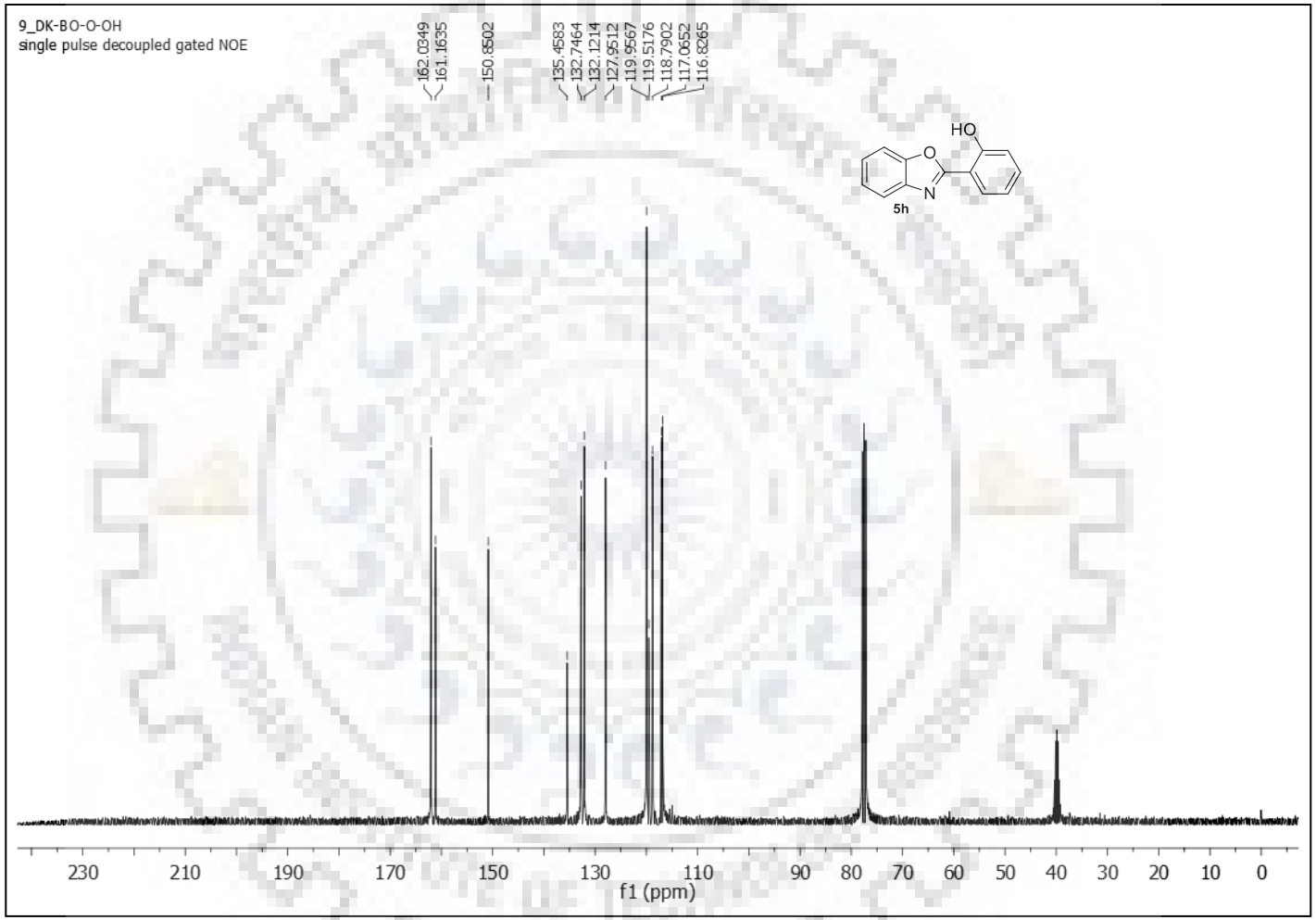

Figure S-48: ^{13}C NMR Spectrum of **5h** in $CDCl_3$.

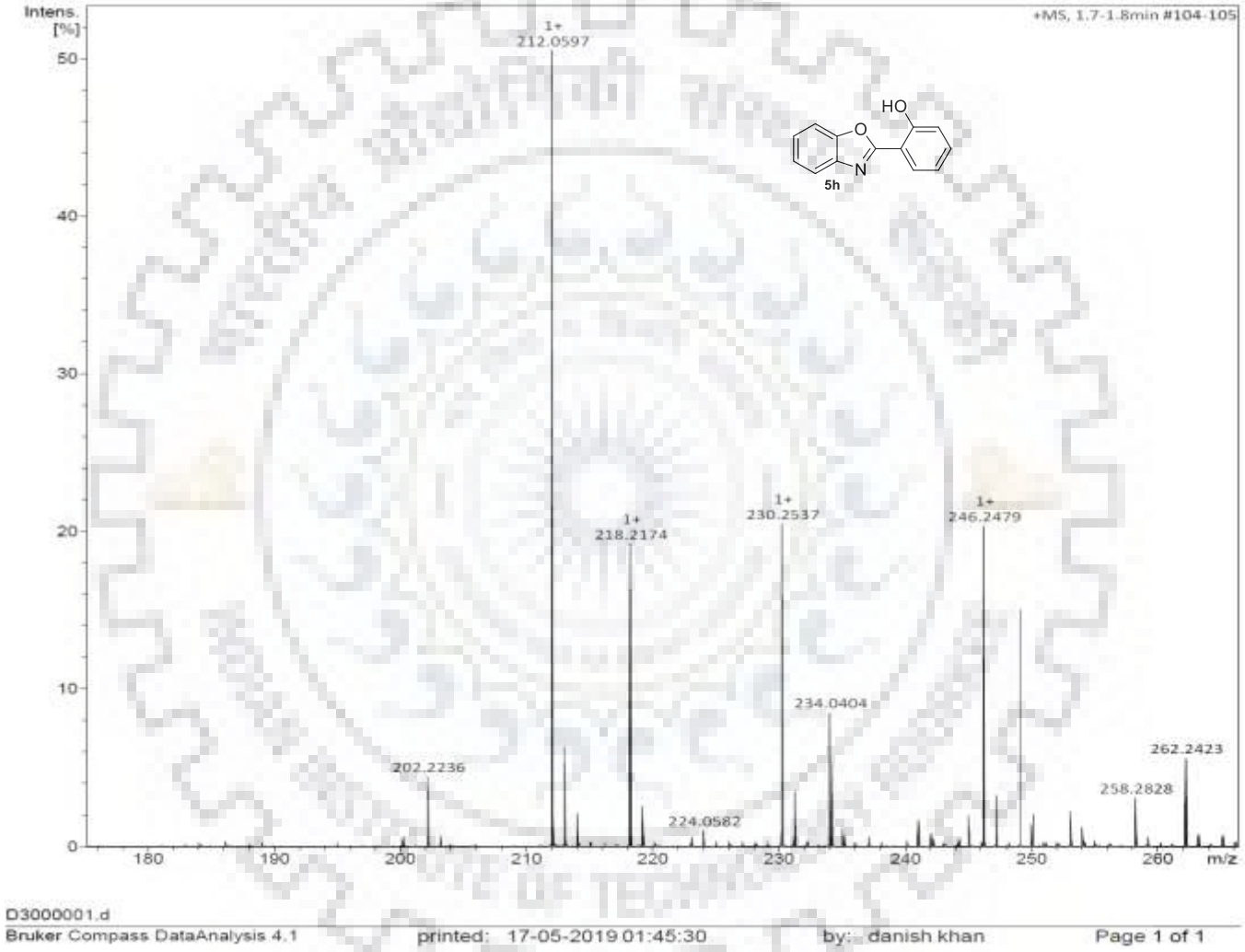

Figure S-49: HRMS Spectrum of **5h**.

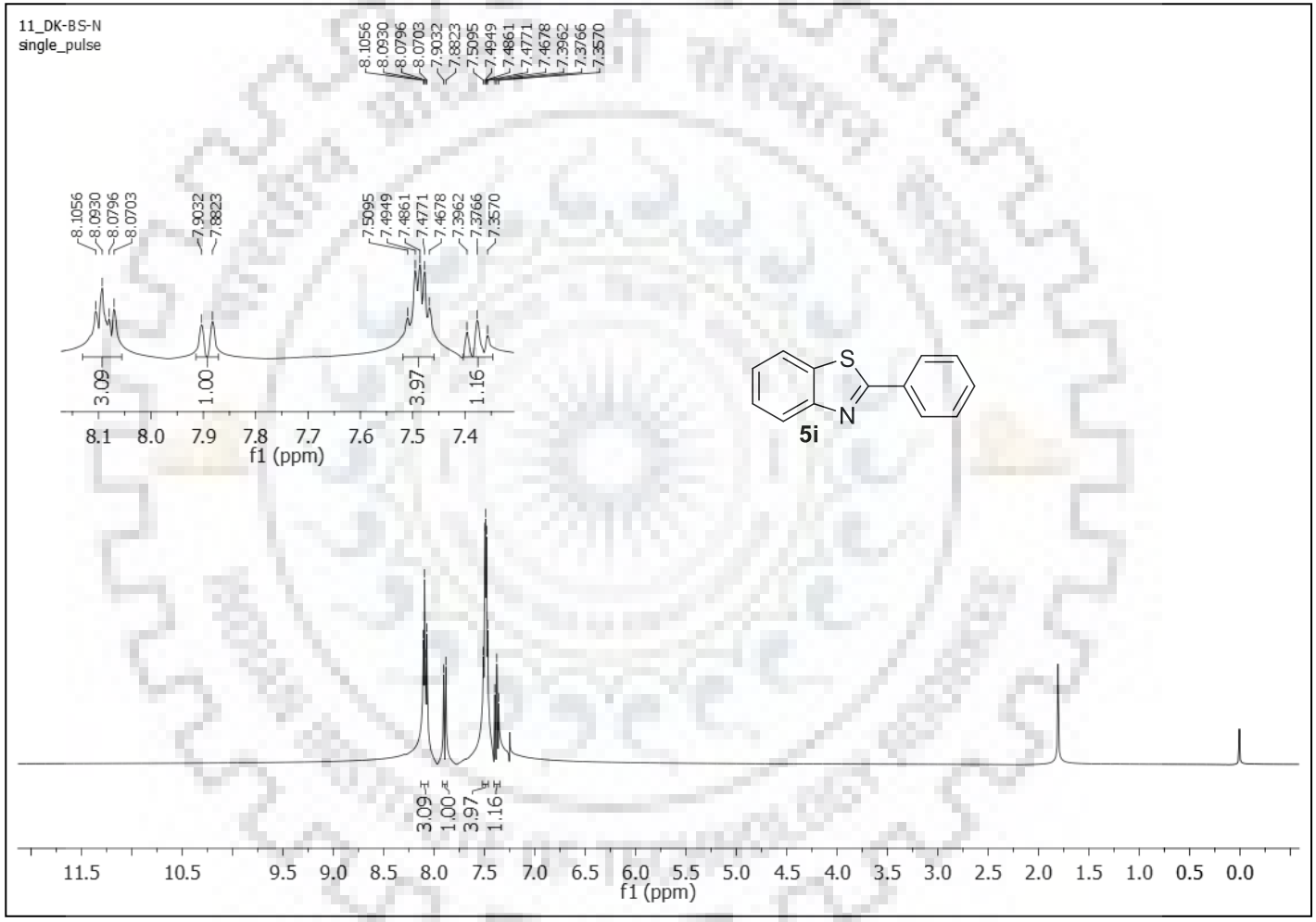

Figure S-50: ^{1}H NMR Spectrum of **5i** in $CDCl_3$.

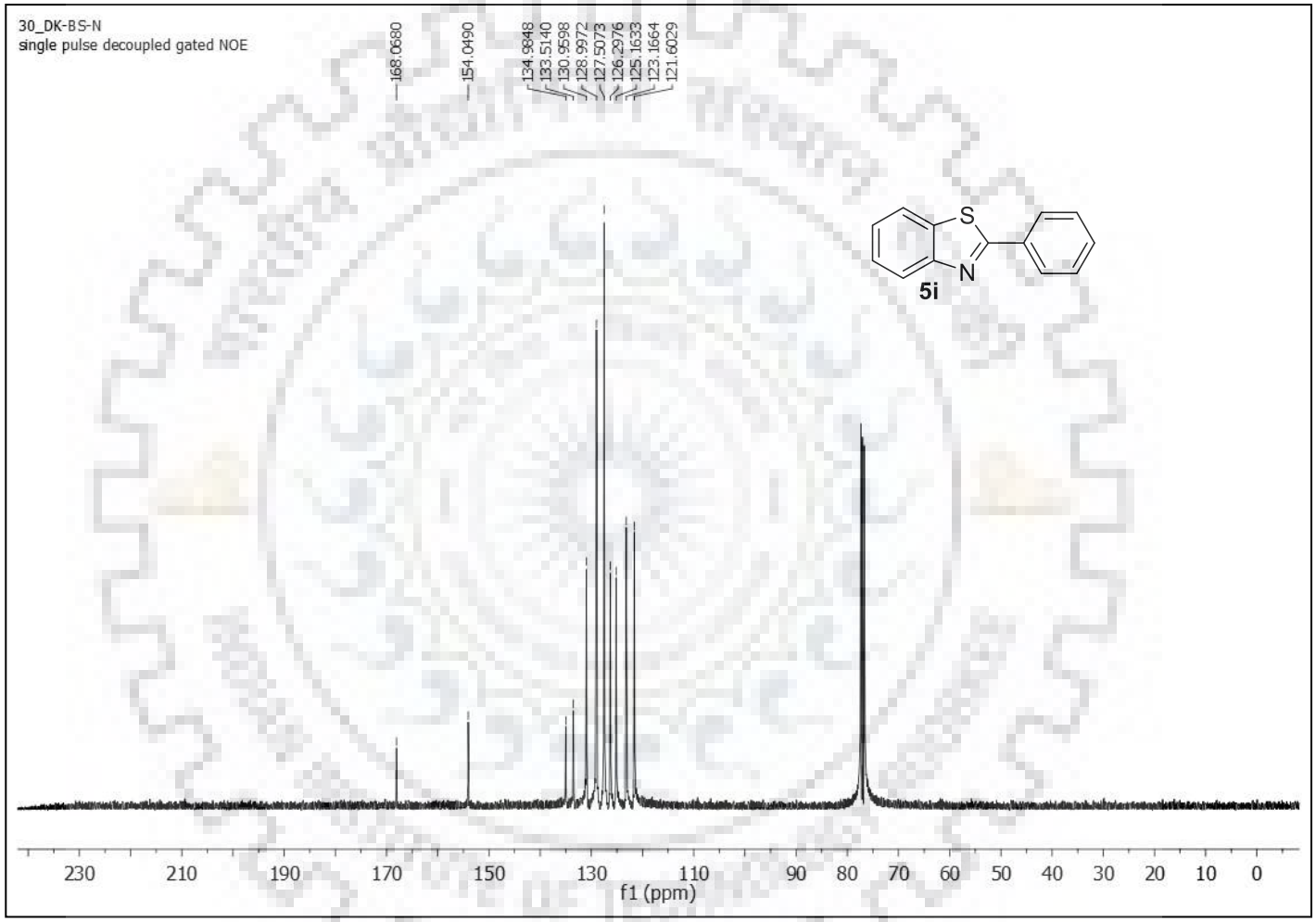

Figure S-51: ^{13}C NMR Spectrum of **5i** in $CDCl_3$.

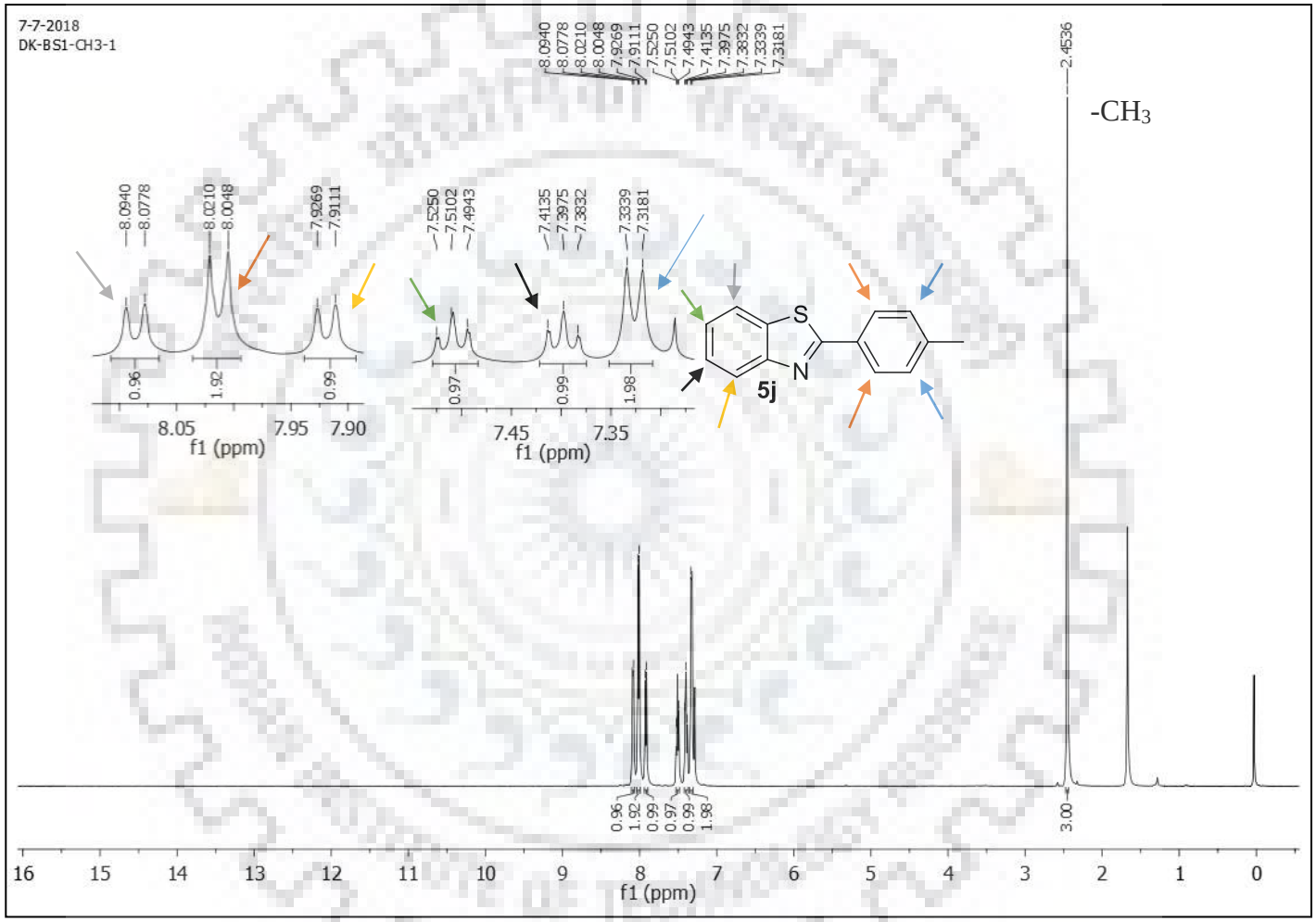

Figure S-52: ^{1}H NMR Spectrum of **5j** in $CDCl_3$.

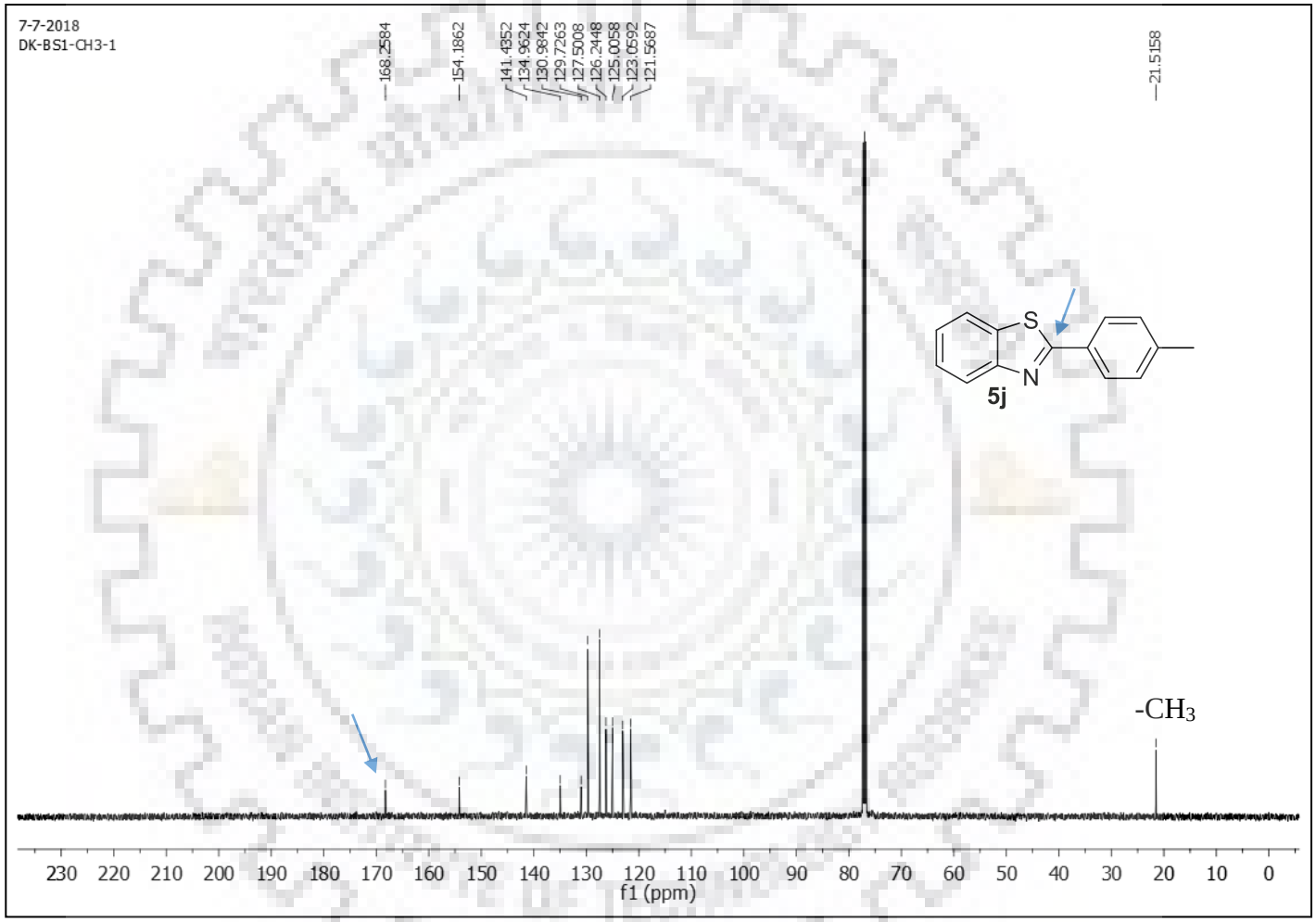

Figure S-53: ^{13}C NMR Spectrum of **5j** in $CDCl_3$.

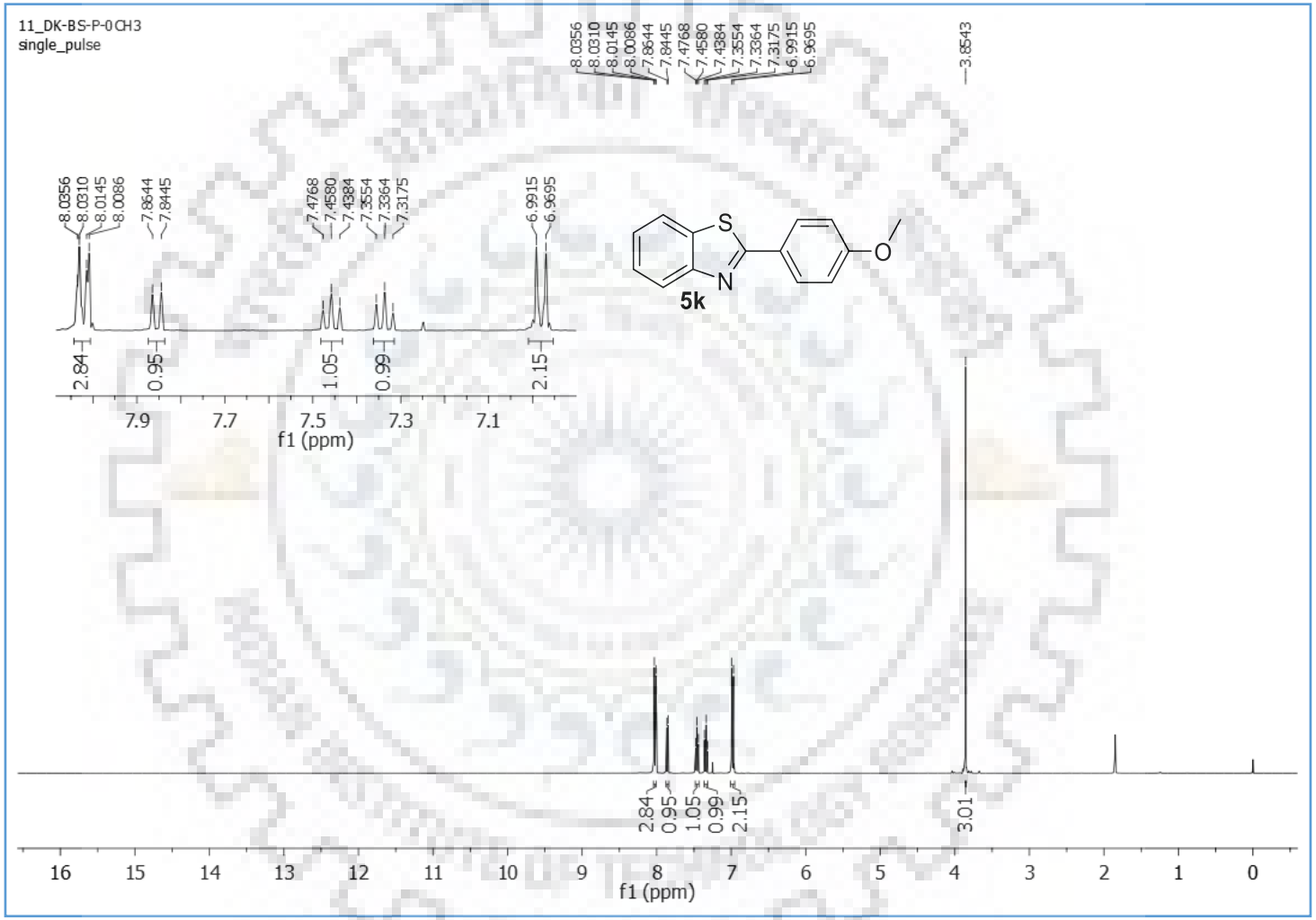

Figure S-54: ^{1}H NMR Spectrum of **5K** in $CDCl_3$.

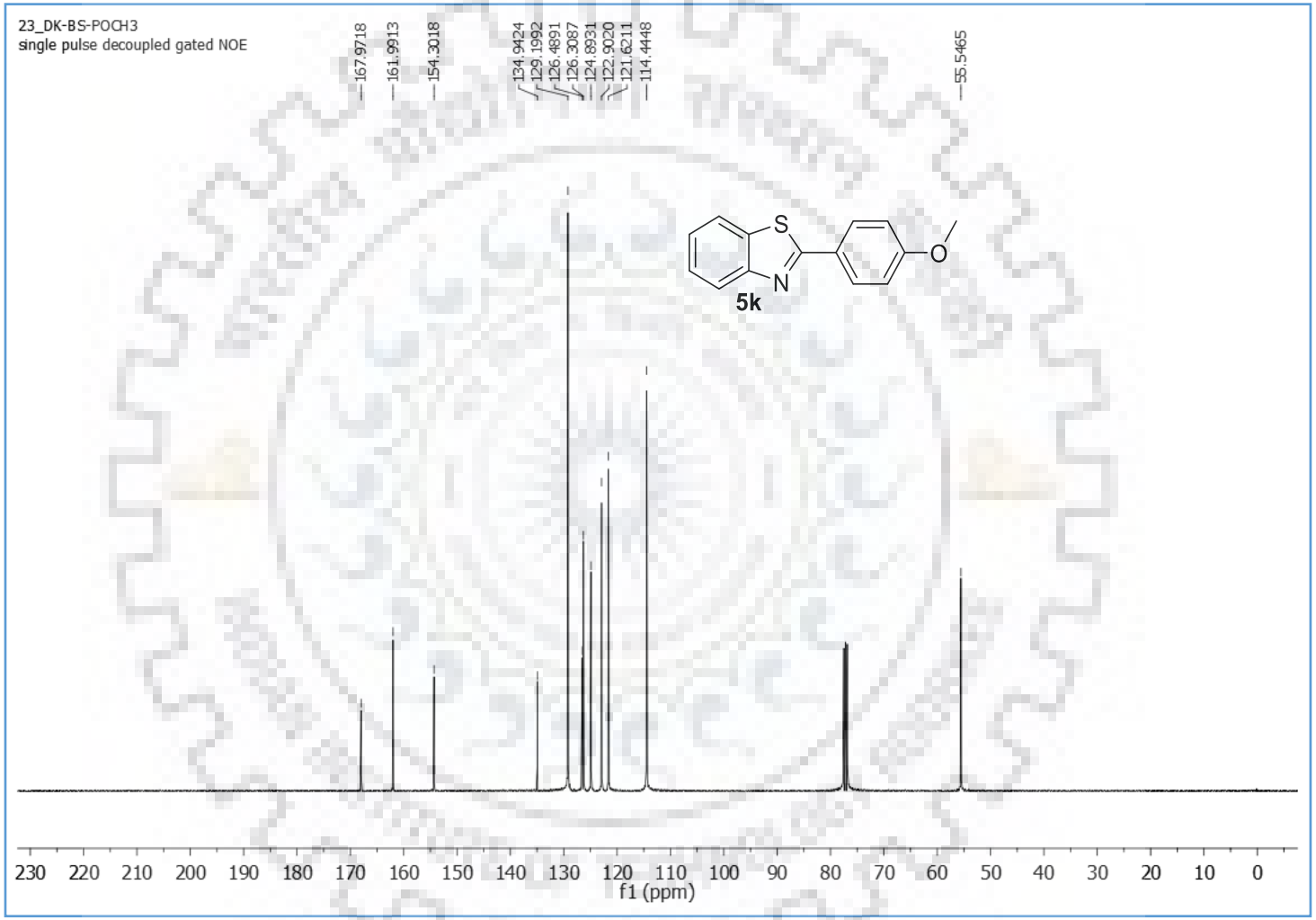

Figure S-55: ^{13}C NMR Spectrum of **5k** in $CDCl_3$.

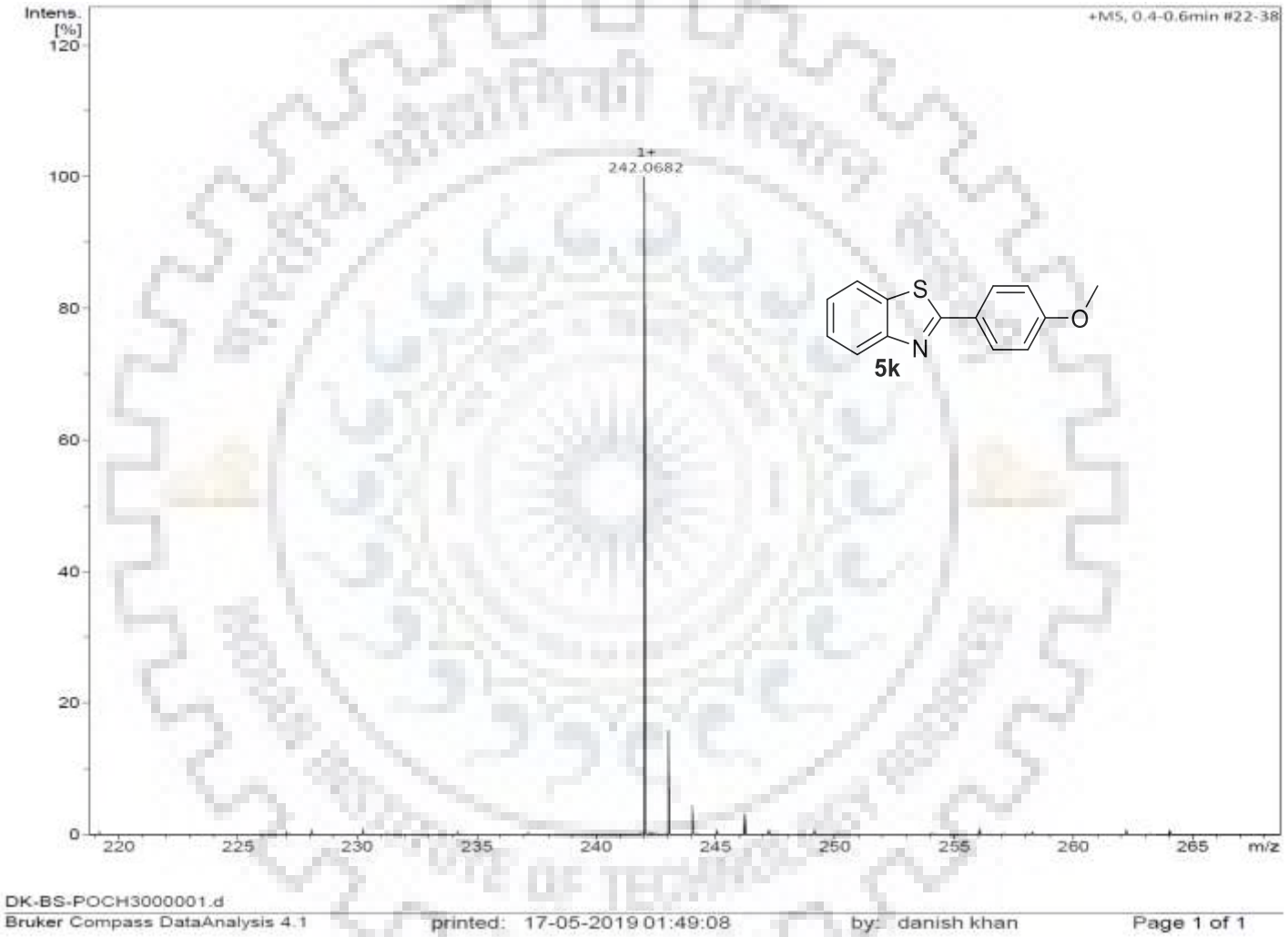

Figure S-56: HRMS Spectrum of **5k**.

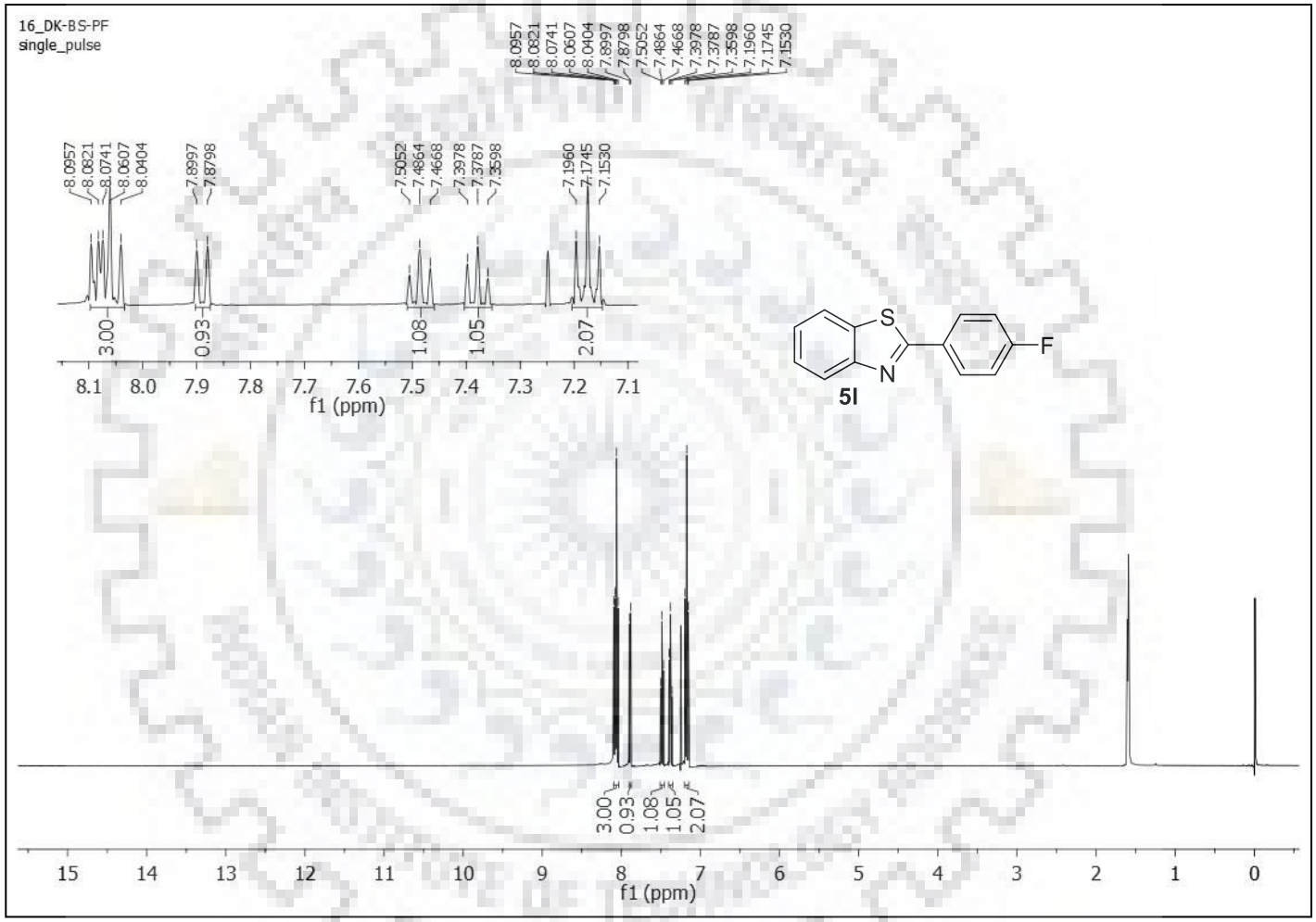

Figure S-57: ^{1}H NMR Spectrum of **5l** in $CDCl_3$.

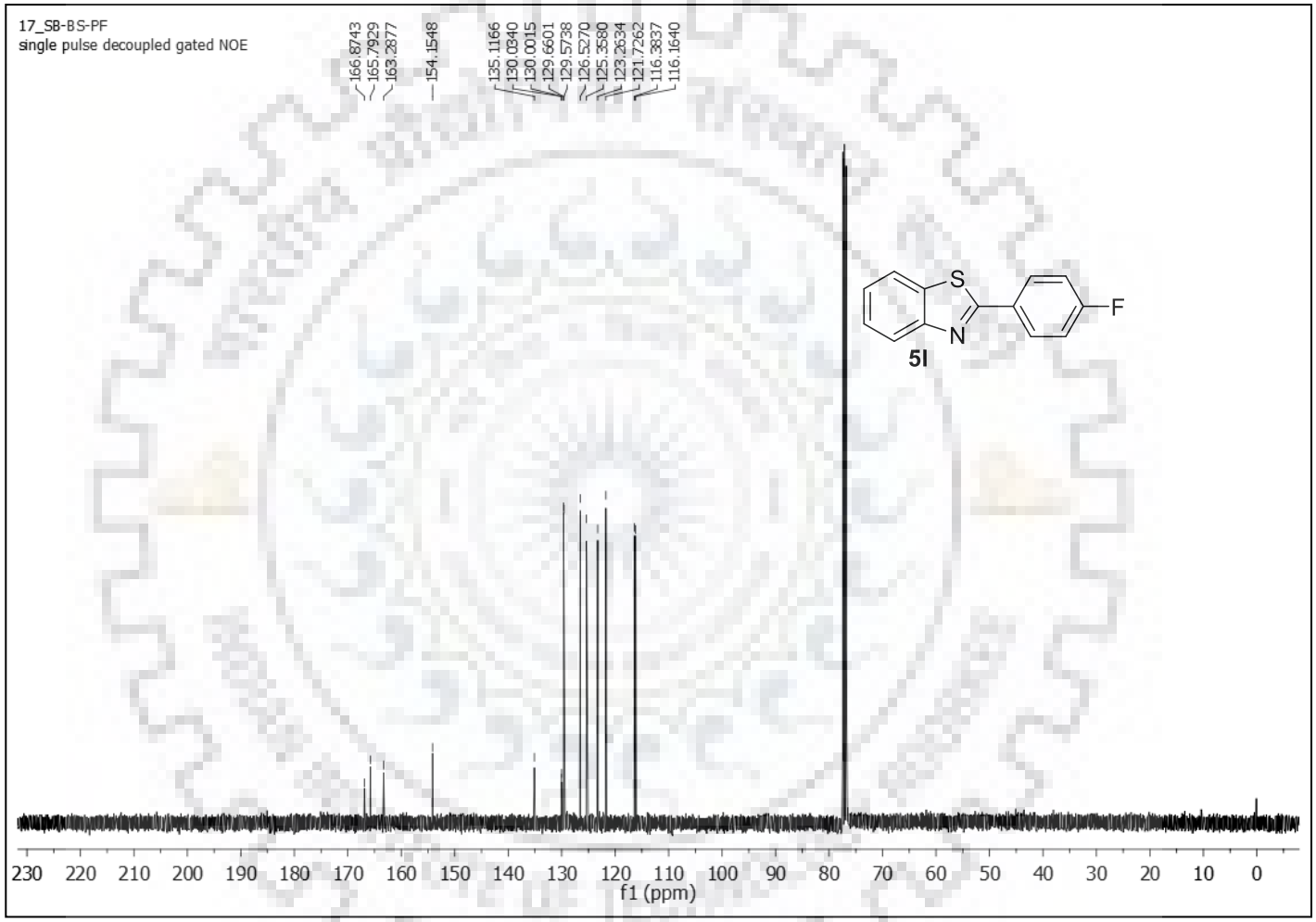

Figure S-58: ^{13}C NMR Spectrum of **5l** in $CDCl_3$.

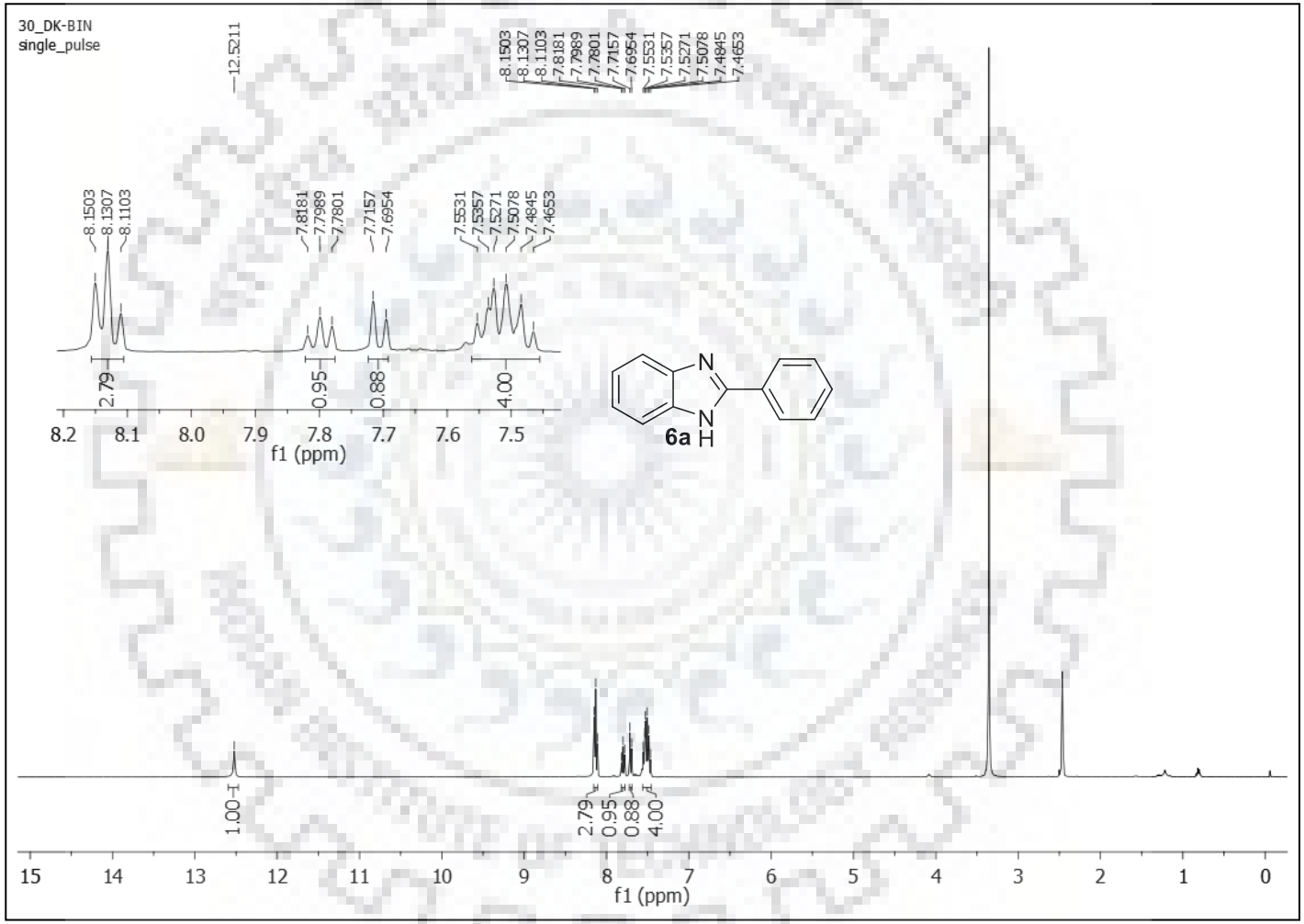

Figure S-59: ^{1}H NMR Spectrum of **6a** in DMSO d_6.

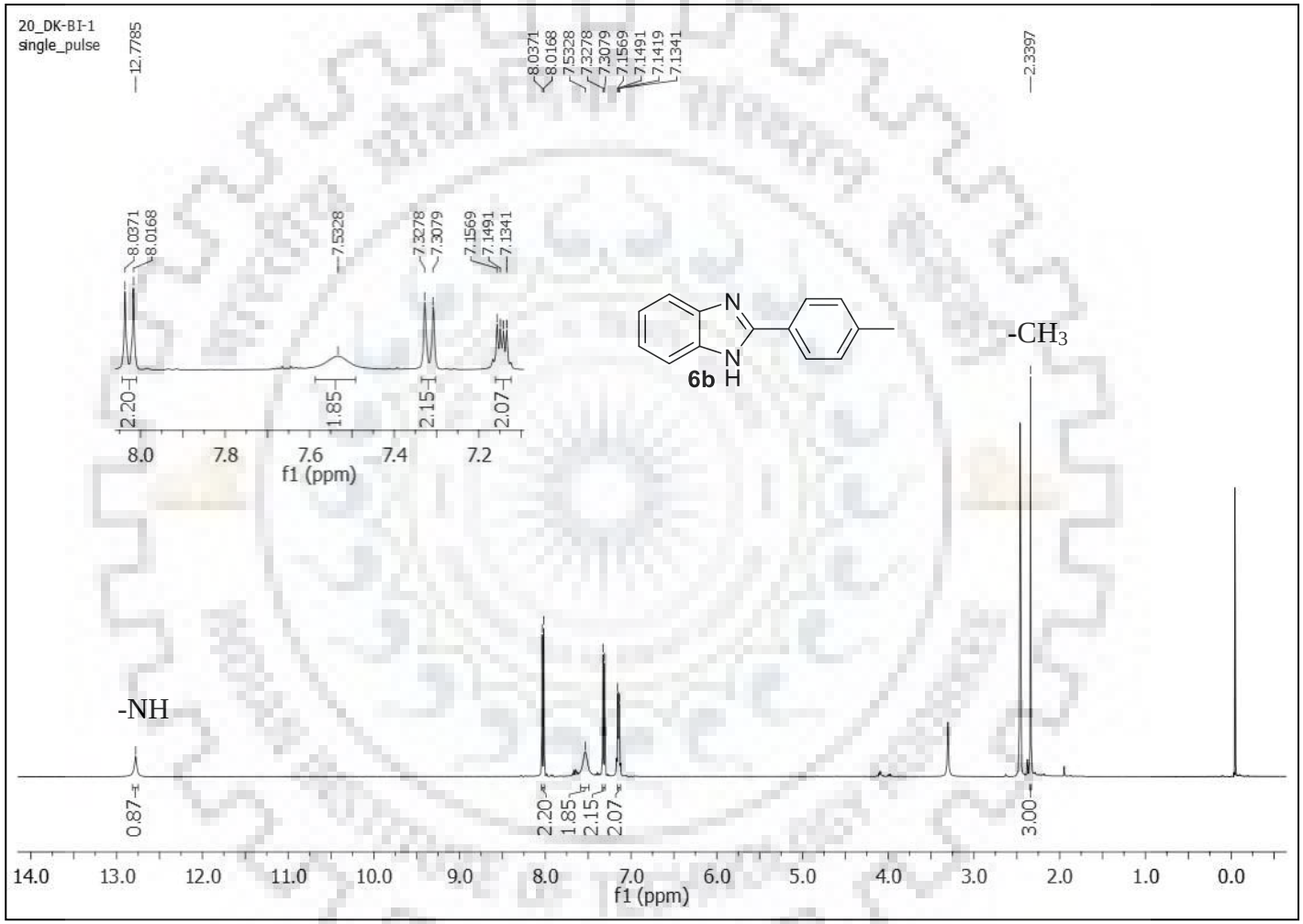

Figure S-60: ^{13}C NMR Spectrum of **6b** in DMSO d_6.

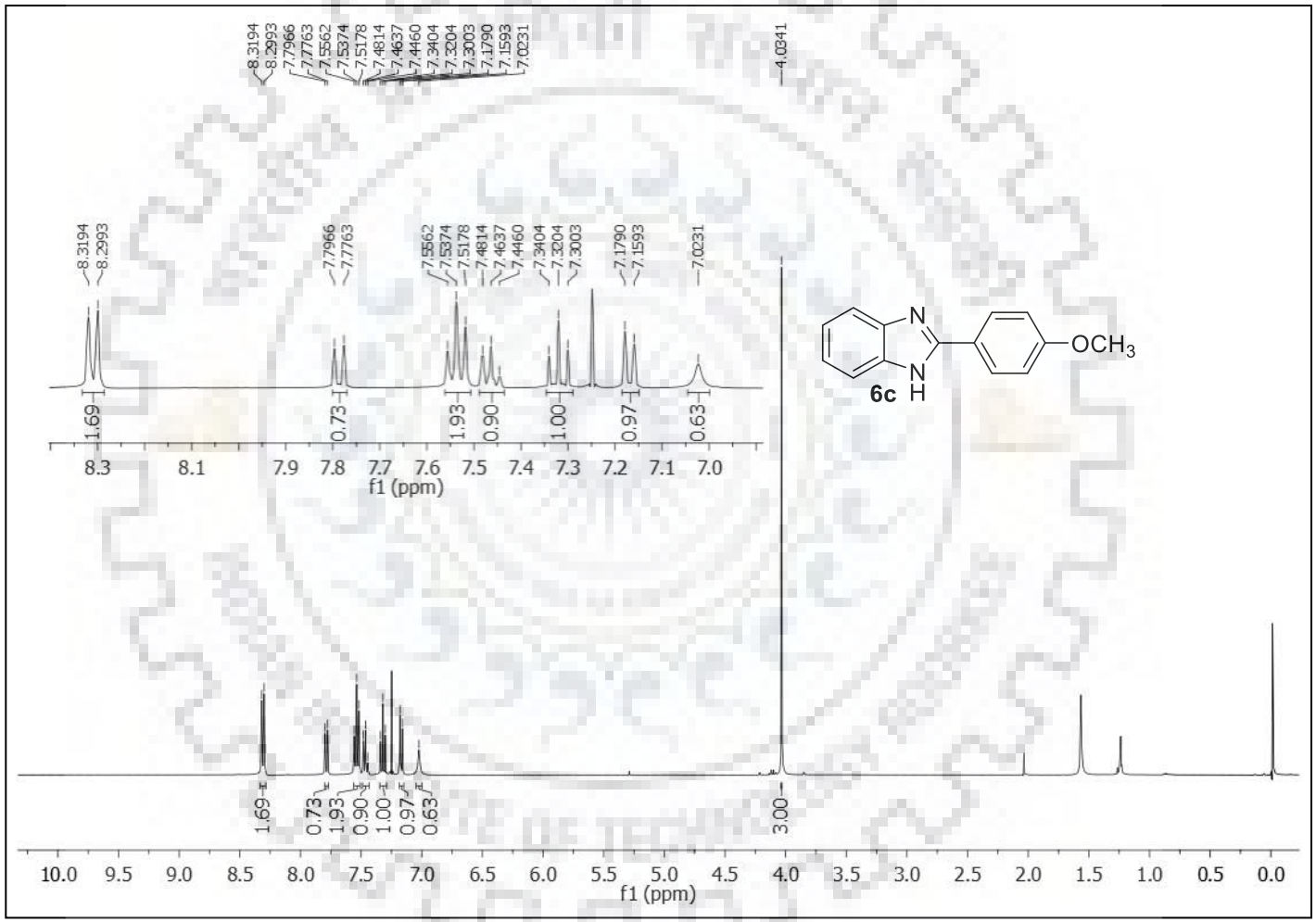

Figure S-61: ^{1}H NMR Spectrum of **6c** in $CDCl_3$.

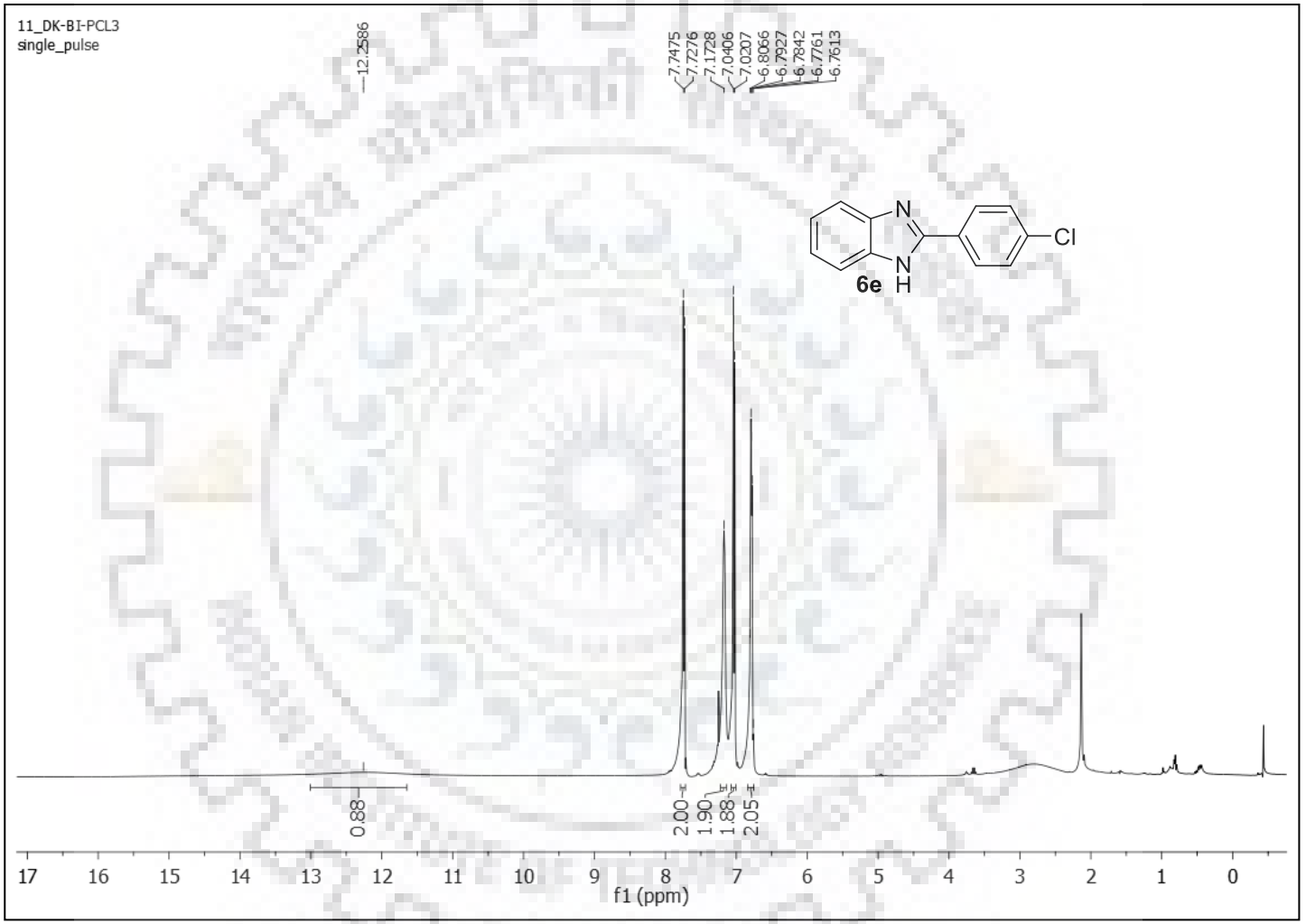

Figure S-62: ^{13}C NMR Spectrum of **6e** in DMSO d_6.

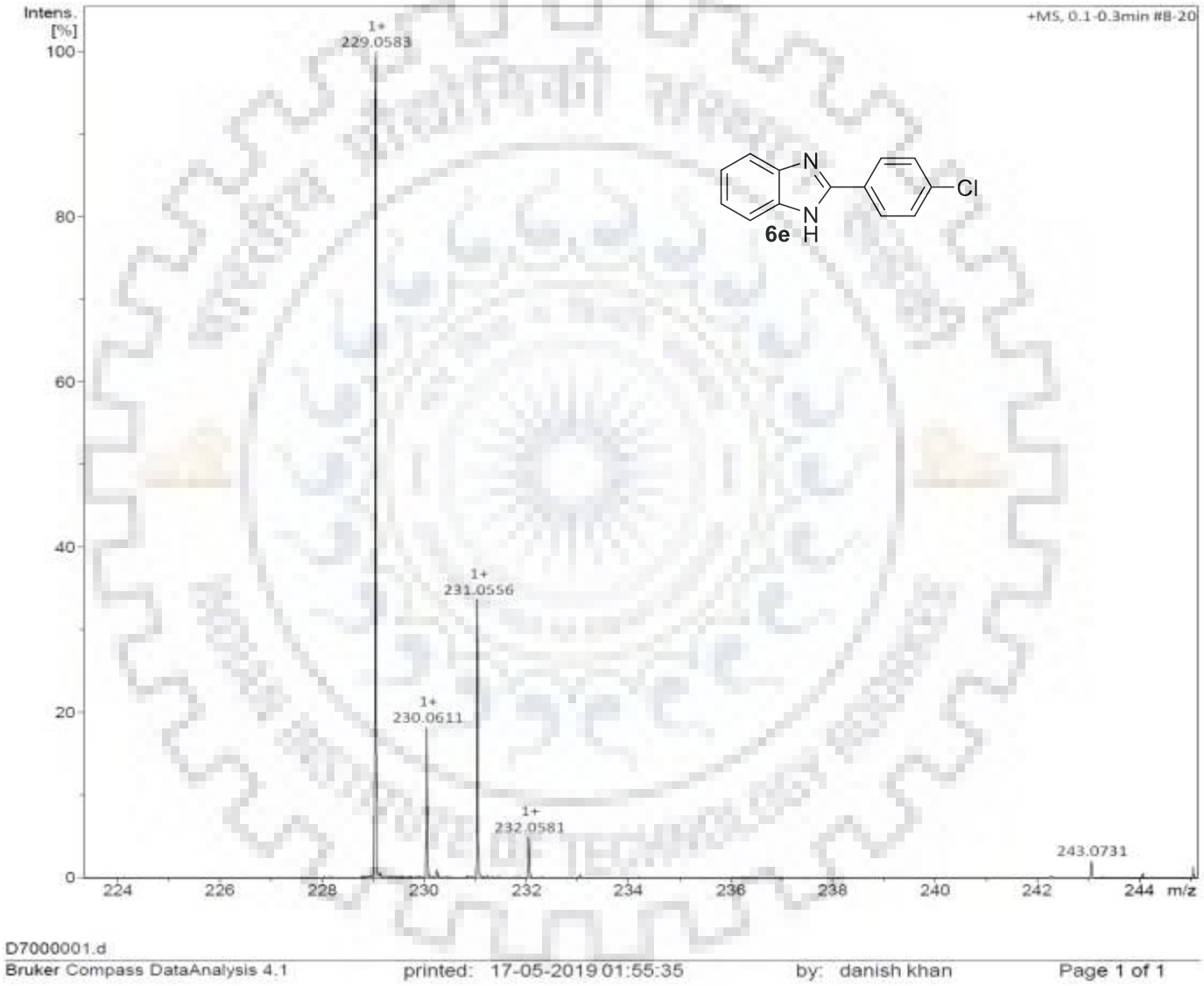

Figure S-63: HRMS Spectrum of **5h**.

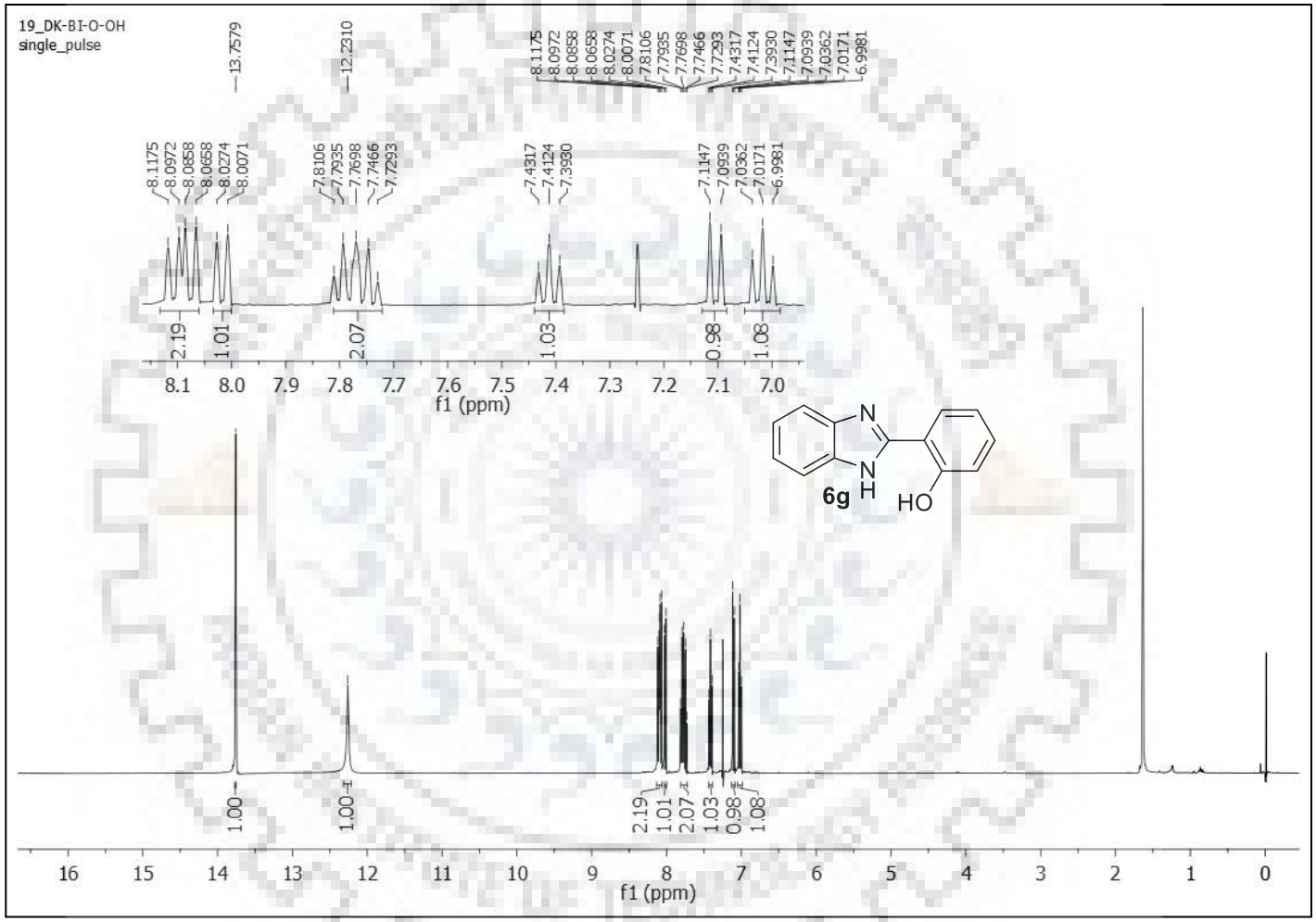

Figure S-64: ^{1}H NMR Spectrum of **6g** in $CDCl_3$.

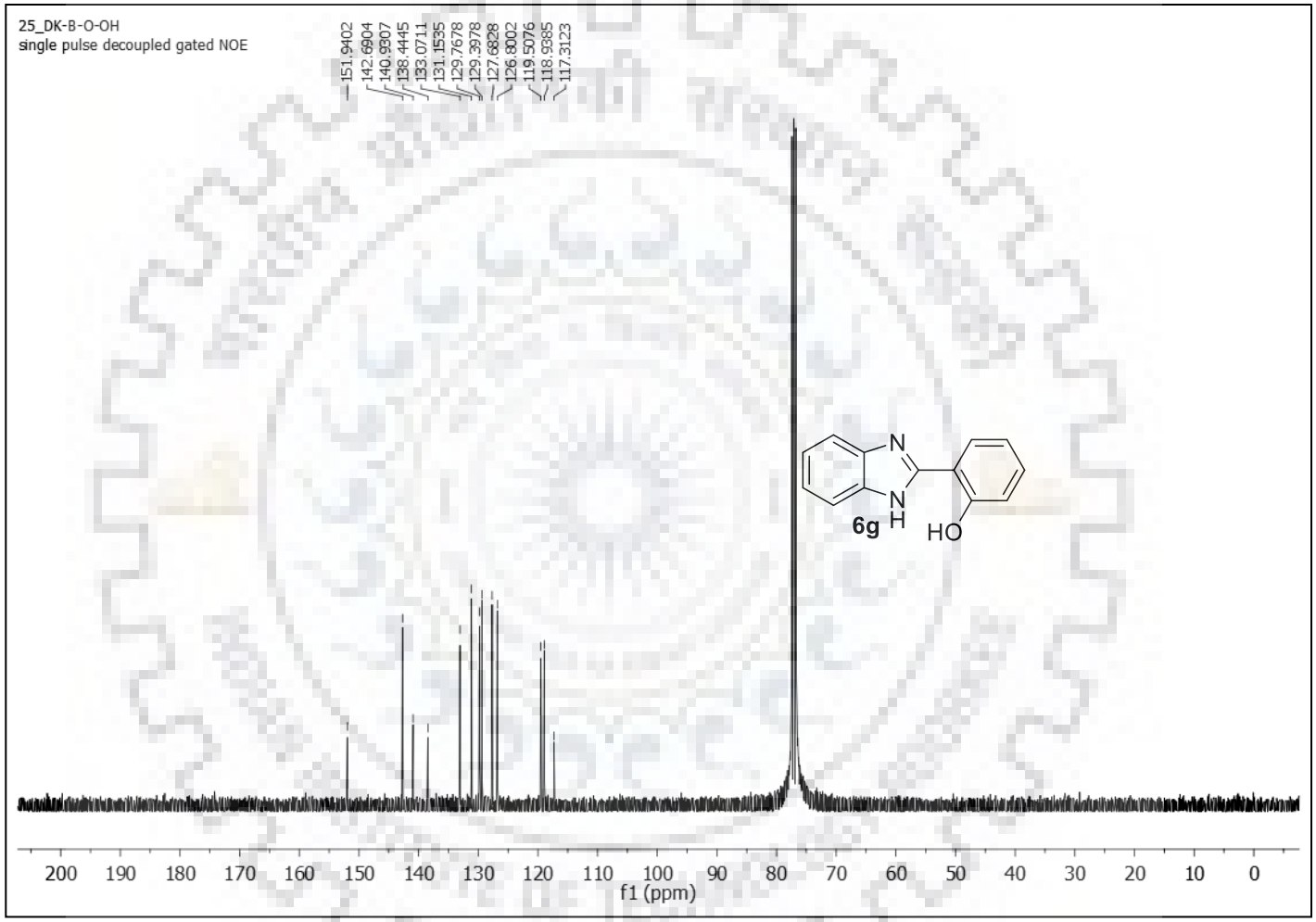

Figure S-65: ^{13}C NMR Spectrum of **6g** in $CDCl_3$.

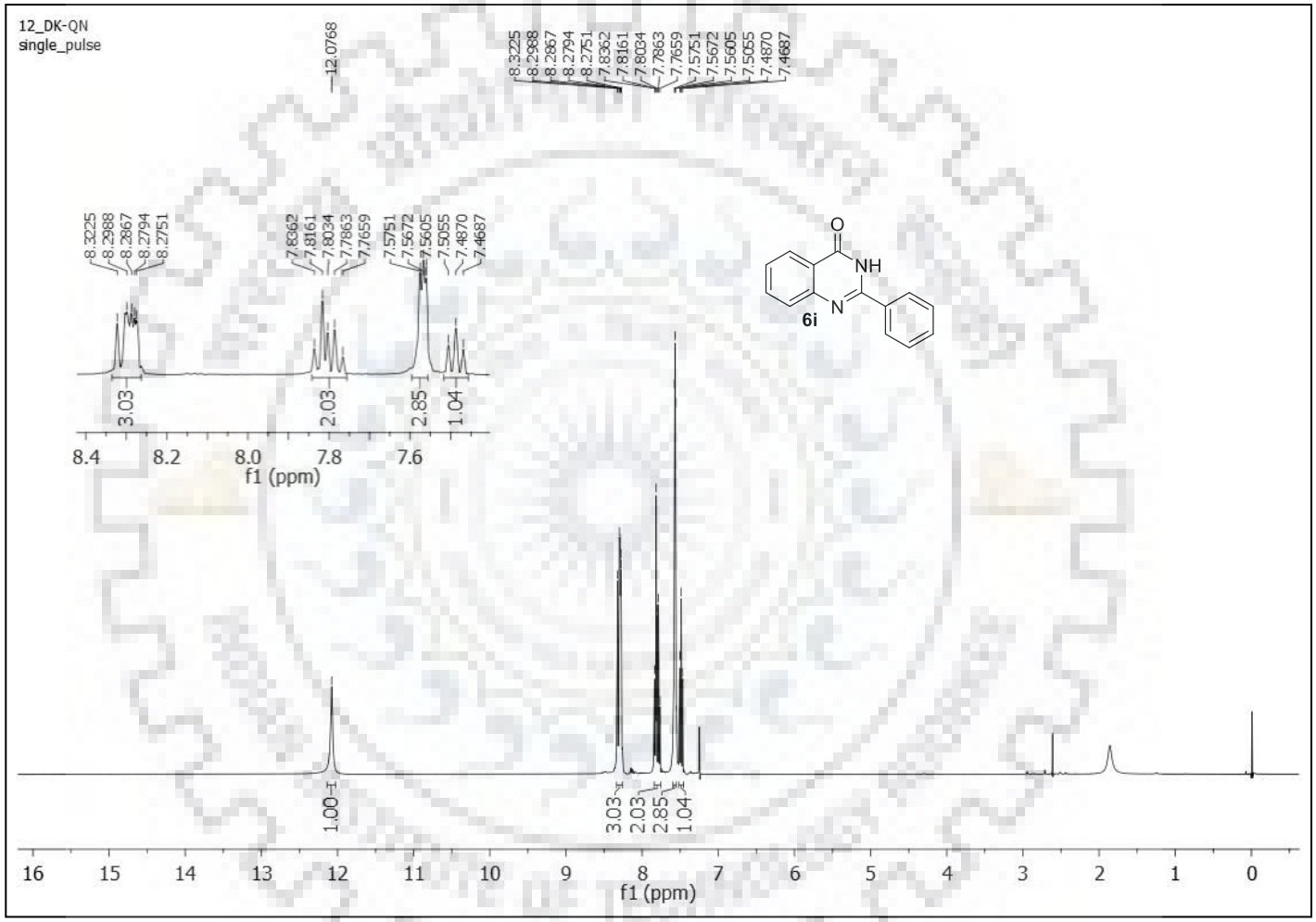

Figure S-66: ^{1}H NMR Spectrum of **6i** in $CDCl_3$.

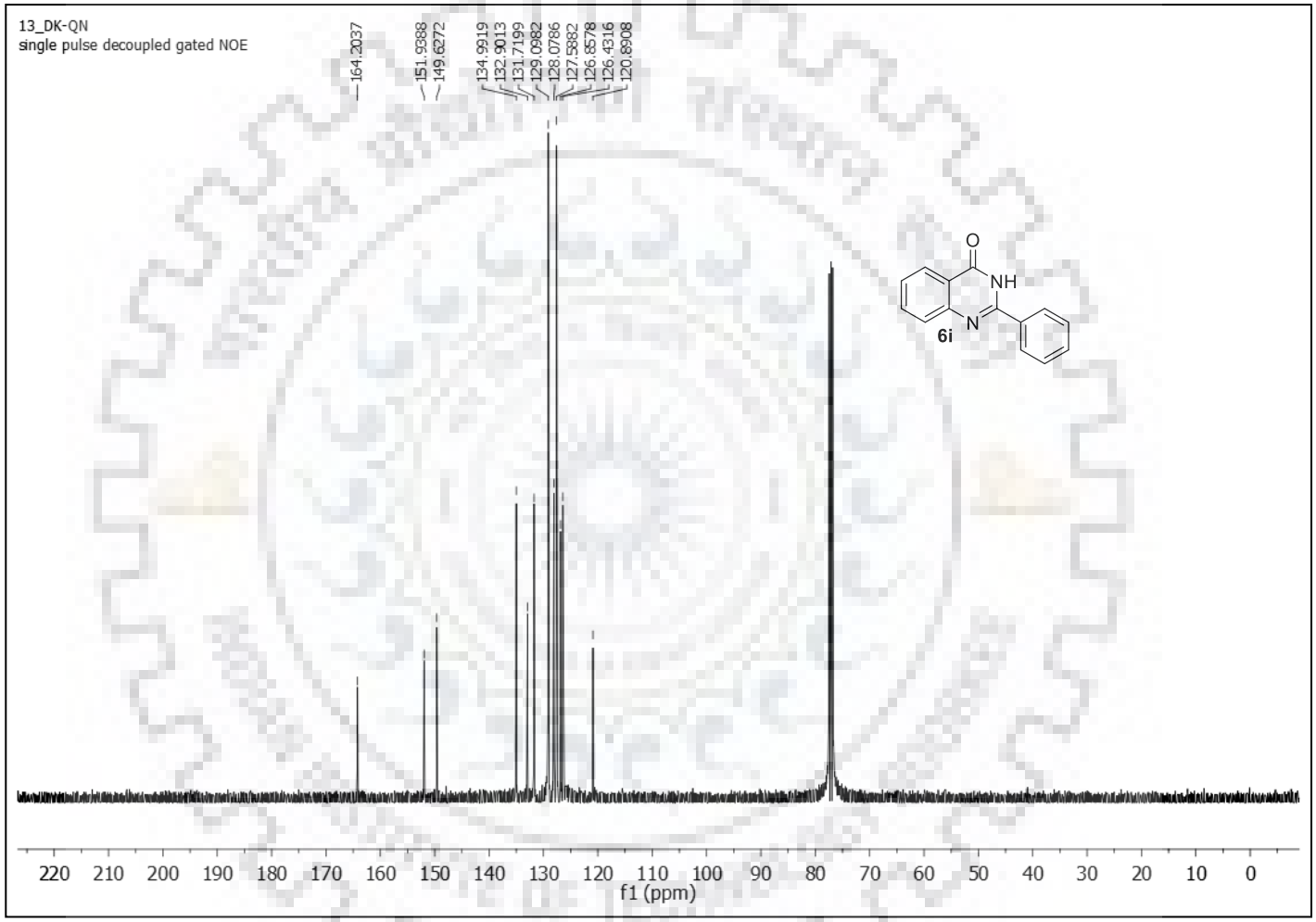

Figure S-67: ^{13}C NMR Spectrum of **6i** in $CDCl_3$**.**

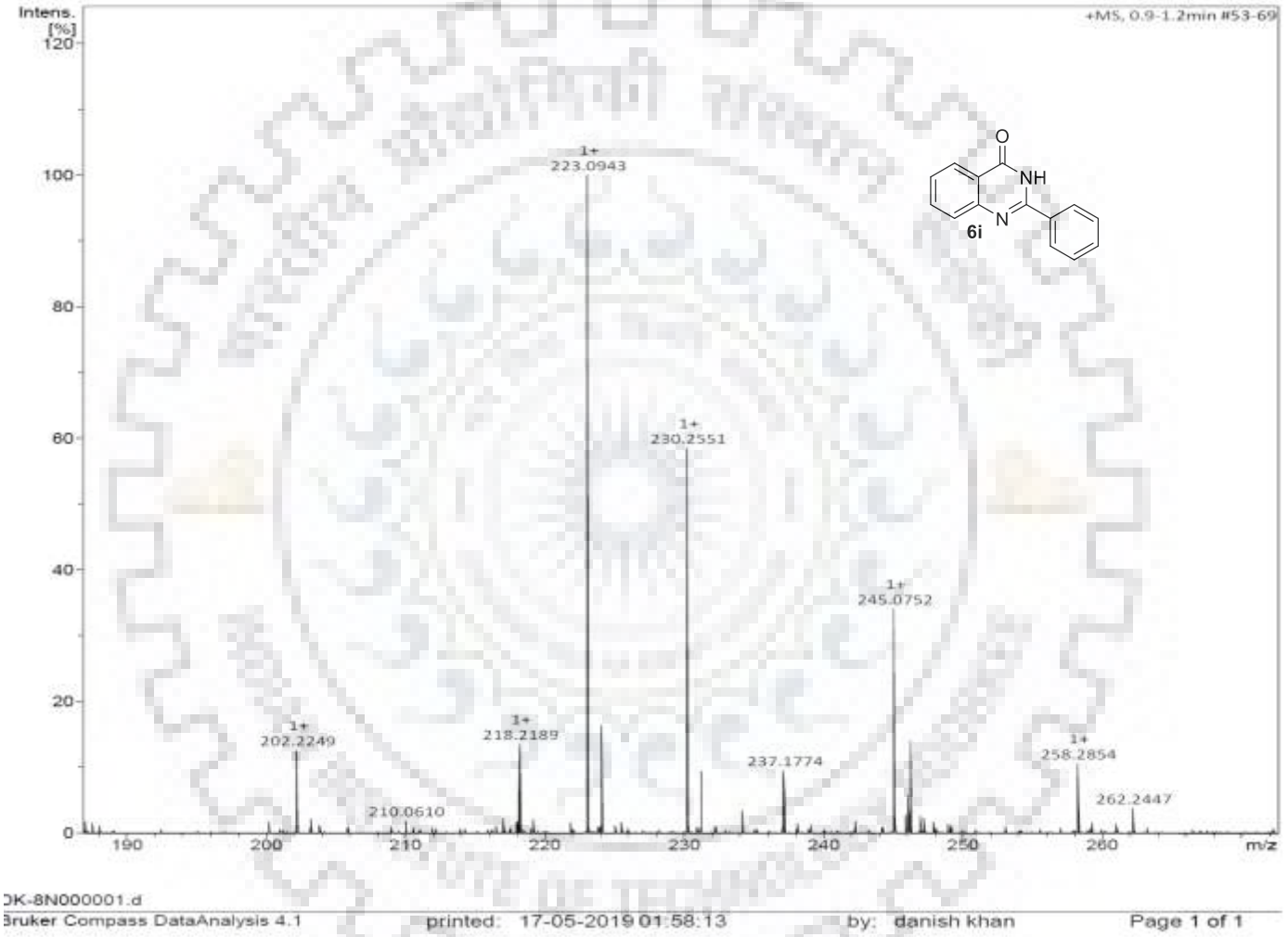

Figure S-68: HRMS Spectrum of **6i.**

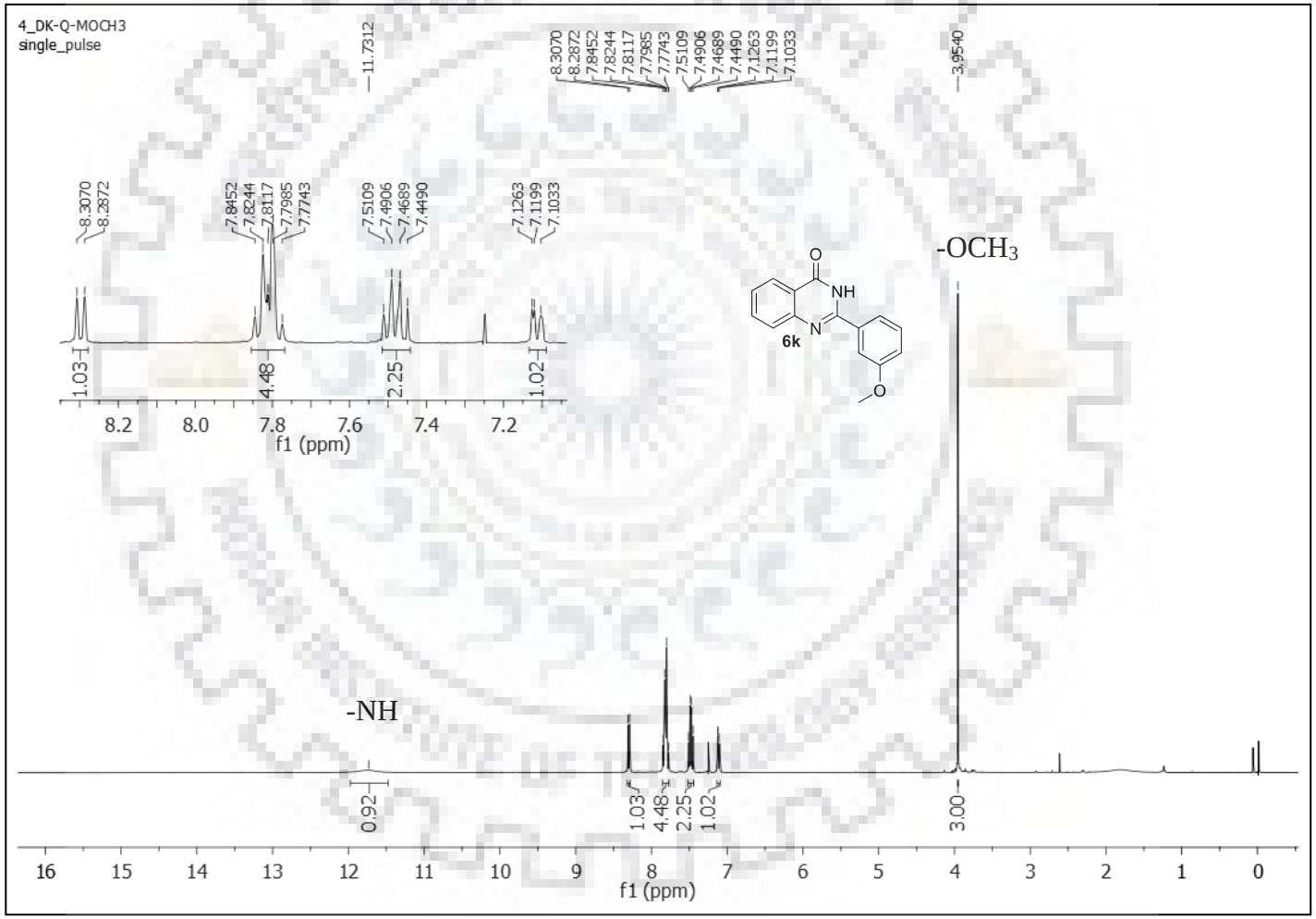

Figure S-69: ^{1}H NMR Spectrum of **6k** in $CDCl_3$.

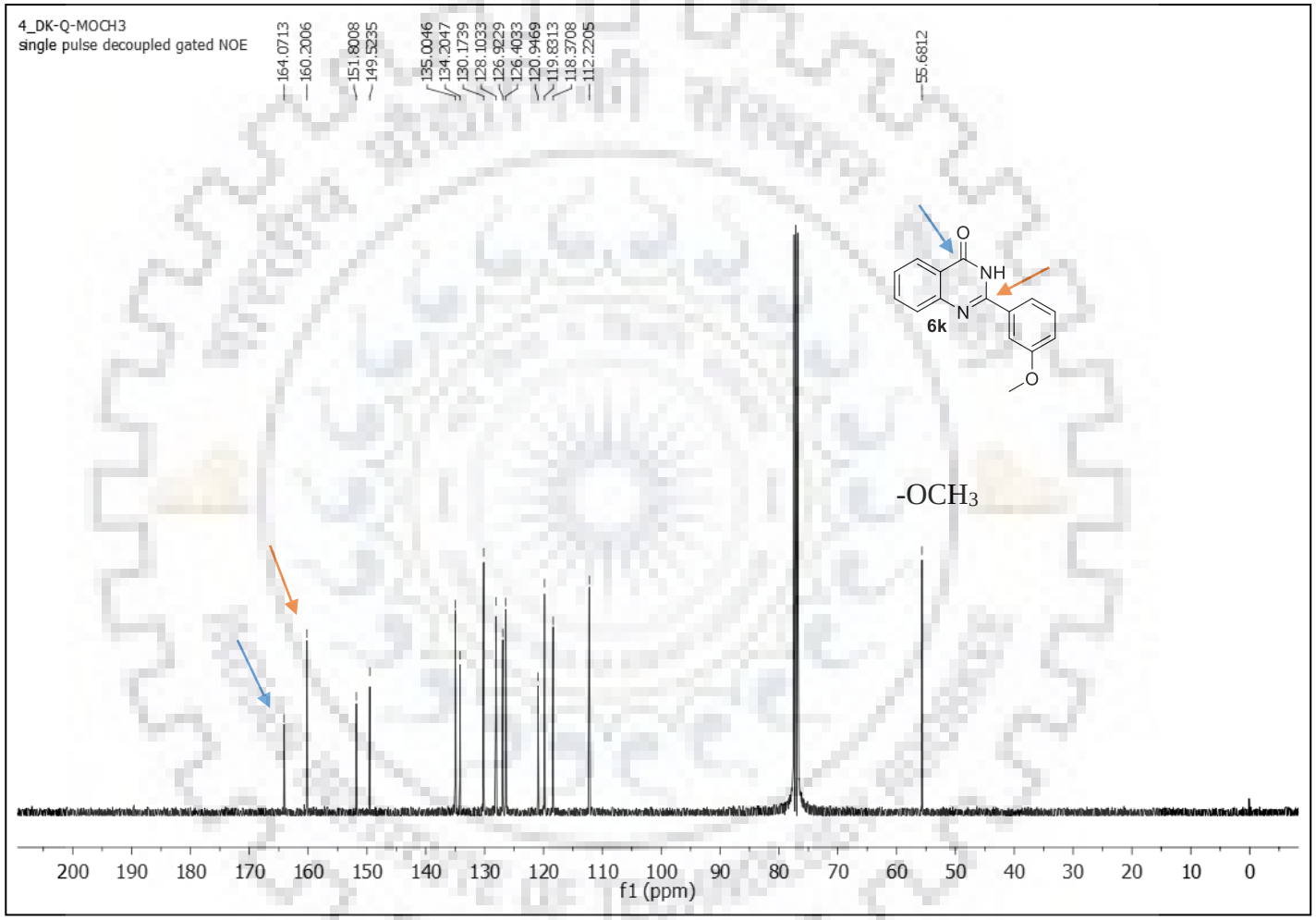

Figure S-70: ^{13}C NMR Spectrum of **6k** in $CDCl_3$.

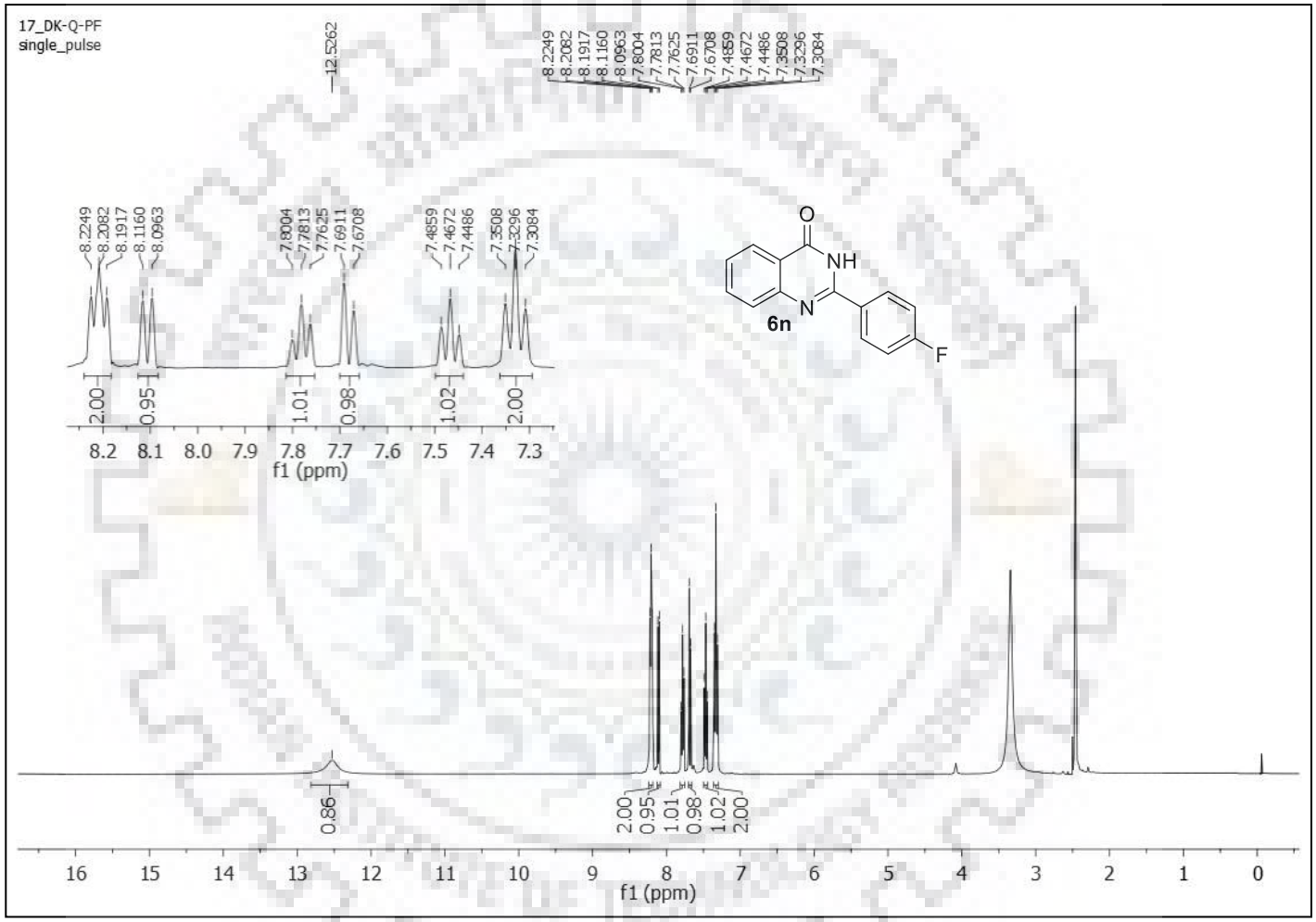

Figure S-71: ^{1}H NMR Spectrum of **6n** in $CDCl_3$+DMSO d_6.

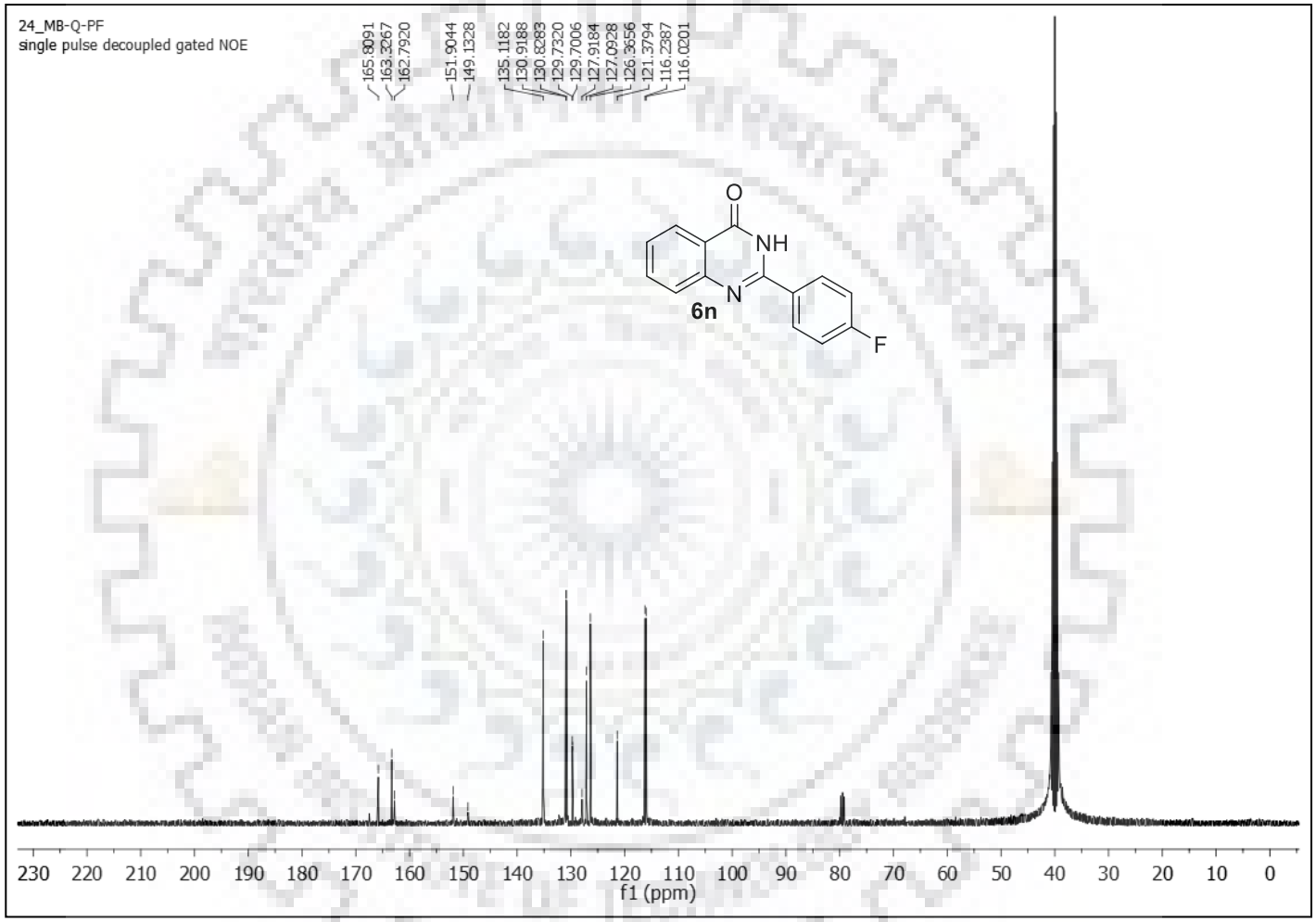

Figure S-72: ^{13}C NMR Spectrum of **6n** in $CDCl_3$+DMSO d_6.

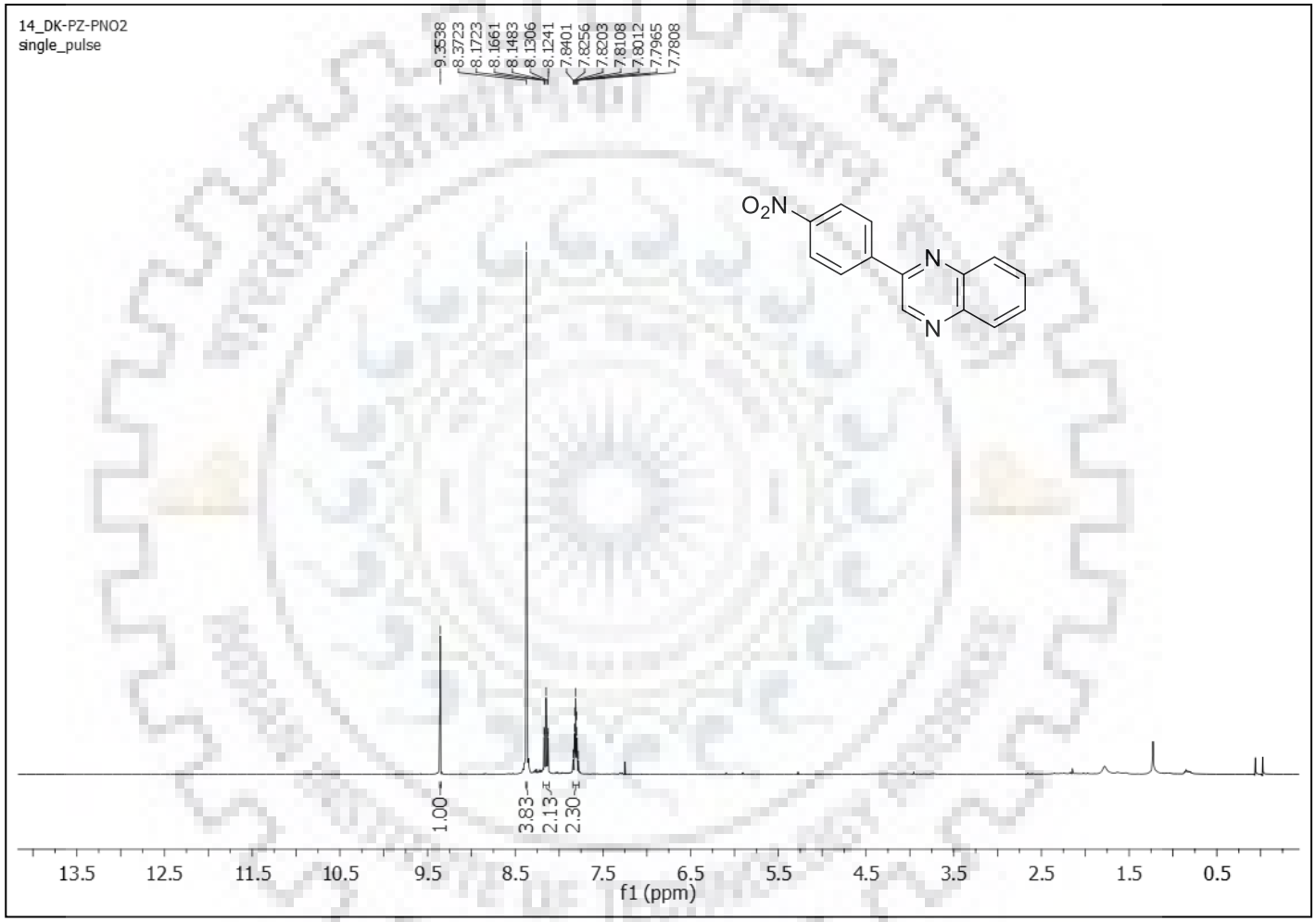

Figure S-73: ^{1}H NMR Spectrum of **6j** in $CDCl_3$.

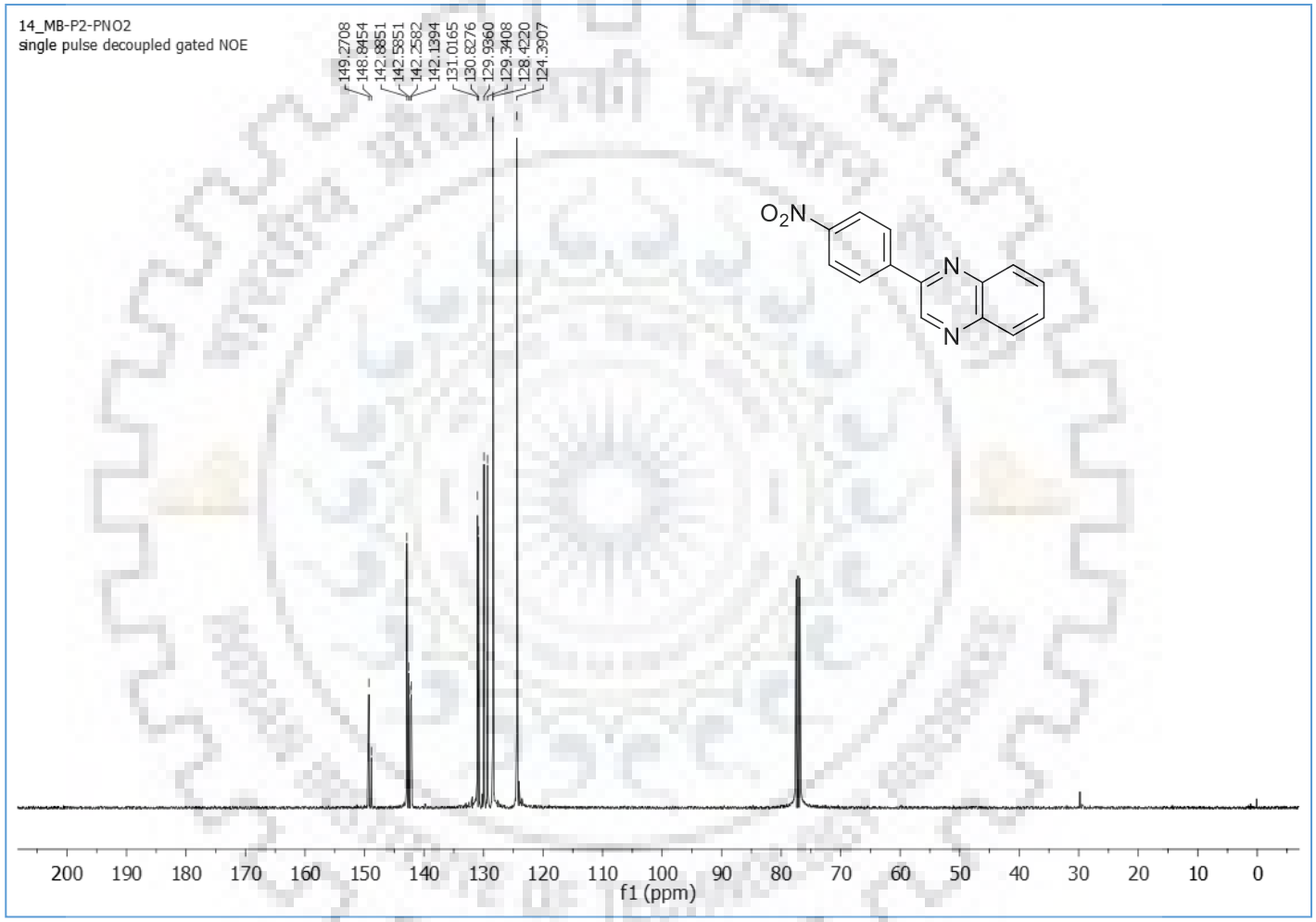

Figure S-74: ^{13}C NMR Spectrum of **6j** in $CDCl_3$.

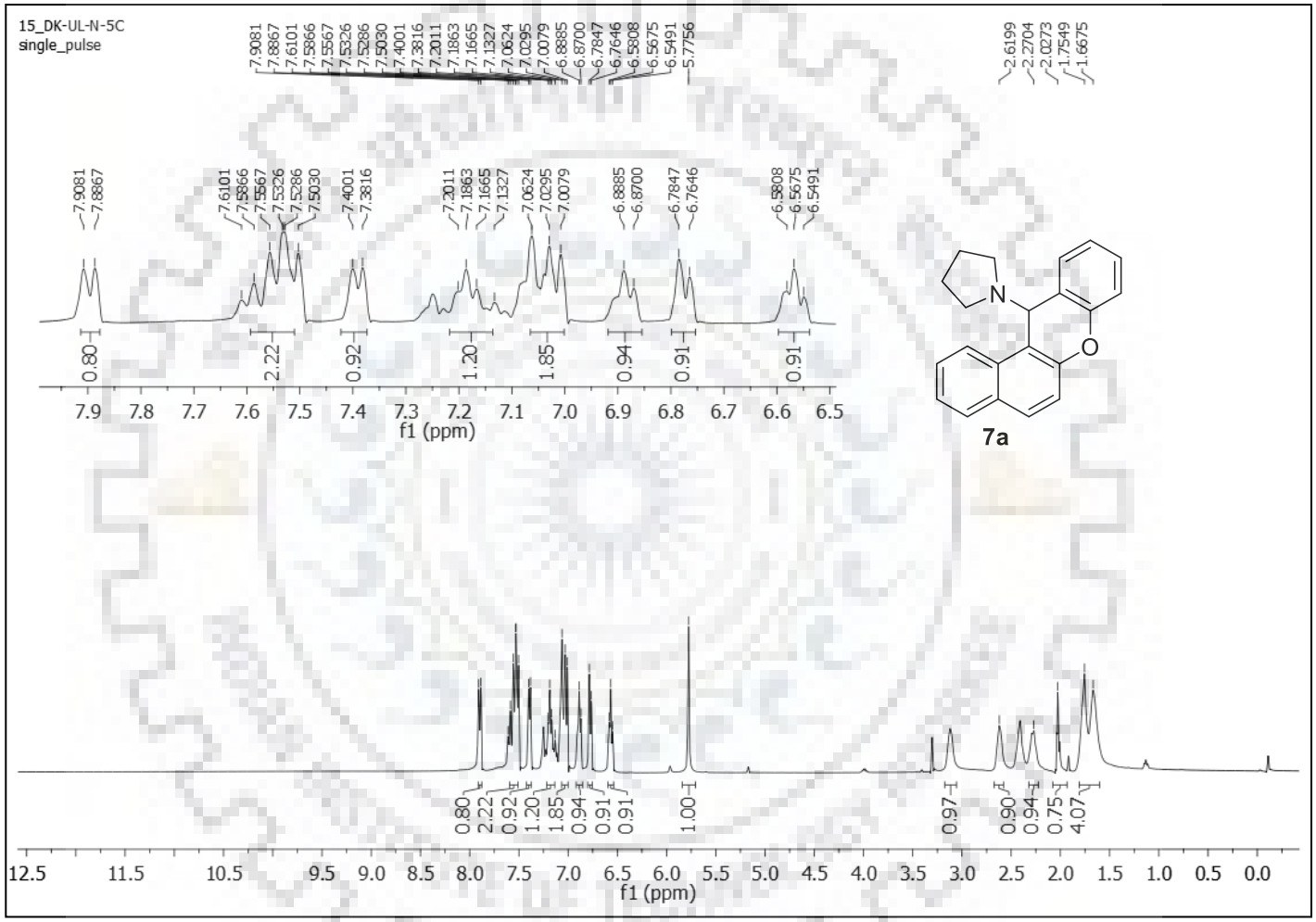

Figure S-75: ^{1}H NMR Spectrum of **7a** in $CDCl_3$+DMSO d_6.

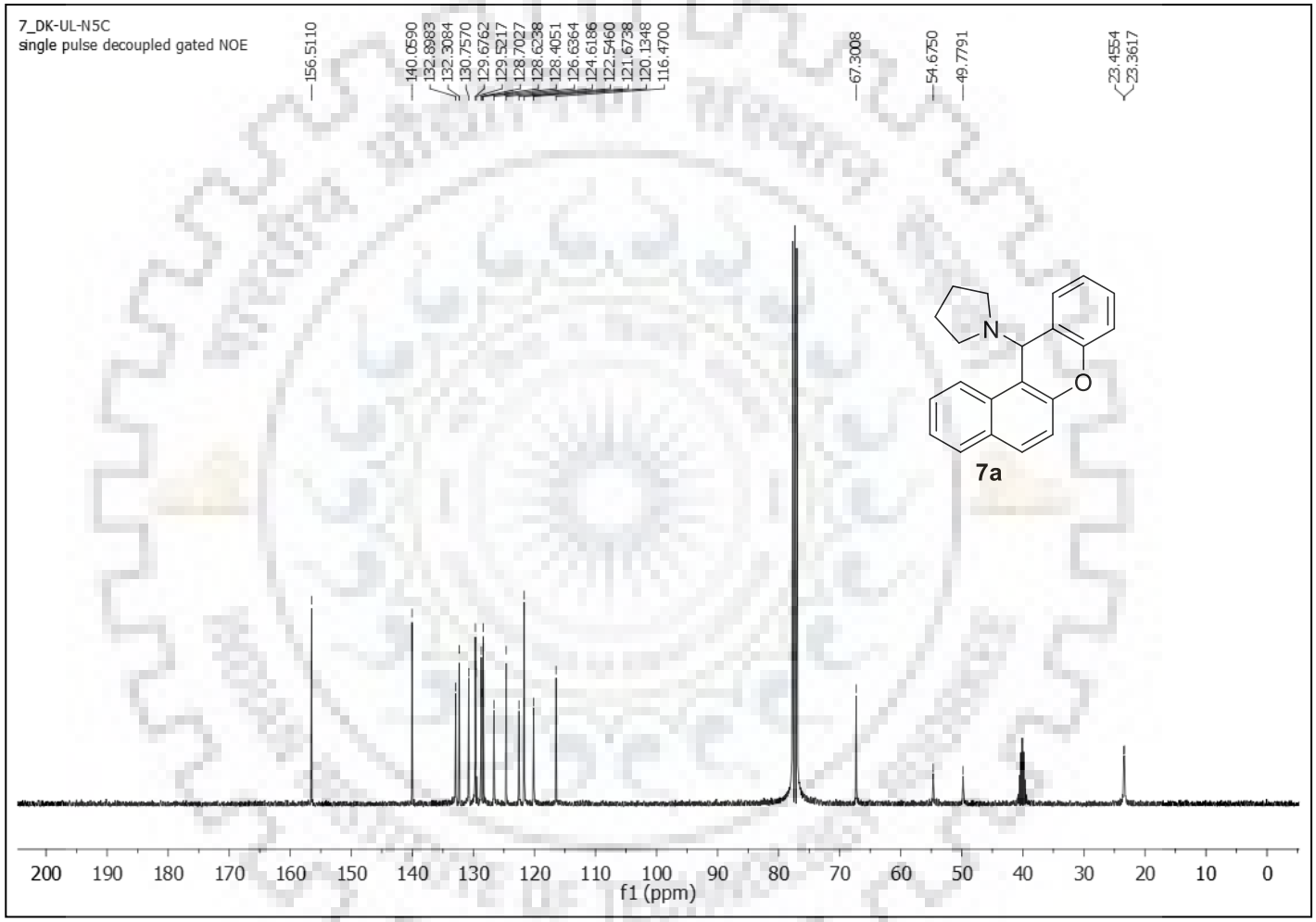

Figure S-76: ^{13}C NMR Spectrum of **7a** $CDCl_3$+DMSO d_6.

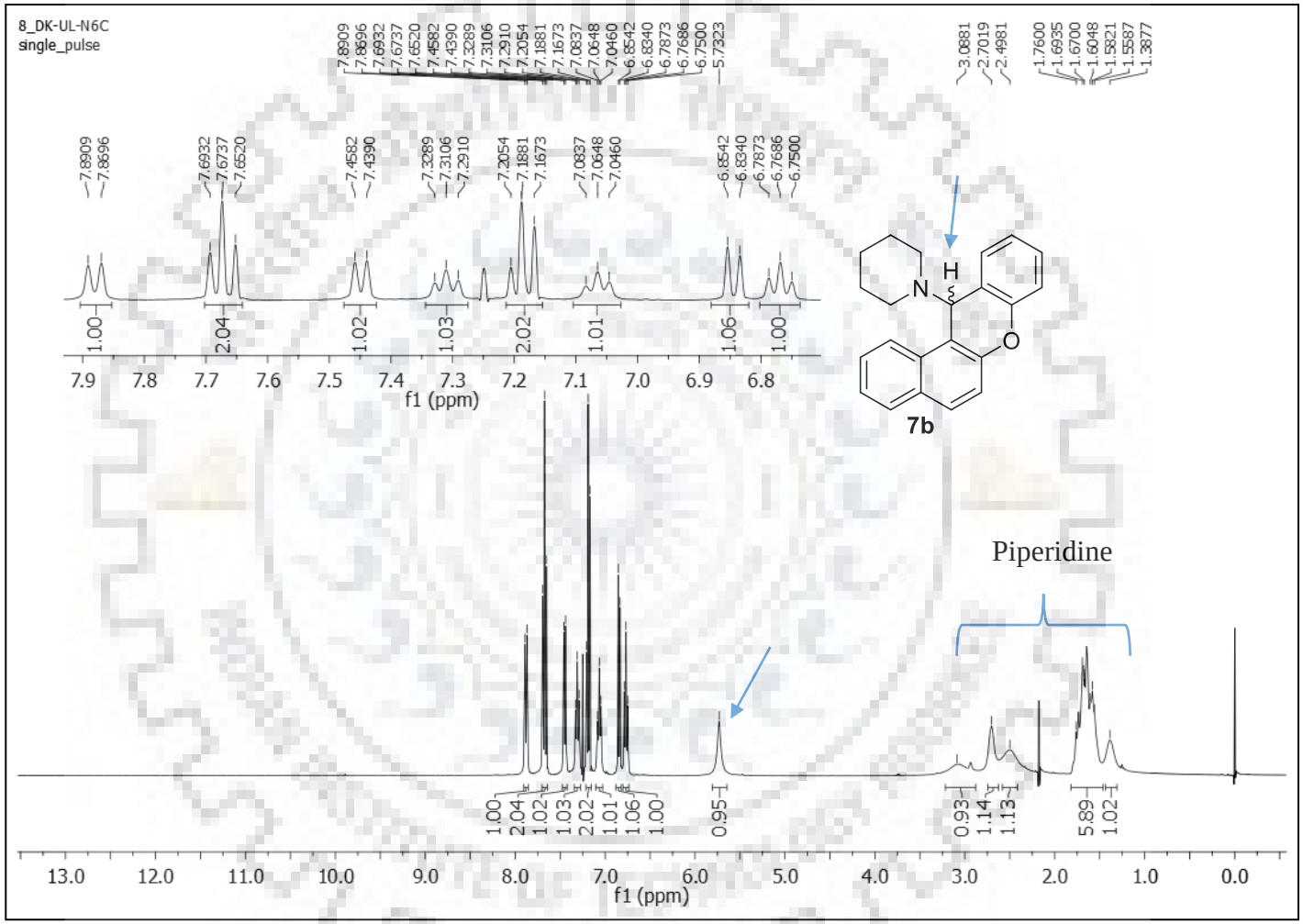

Figure S-77: ^{1}H NMR Spectrum of **7b** in $CDCl_3$.

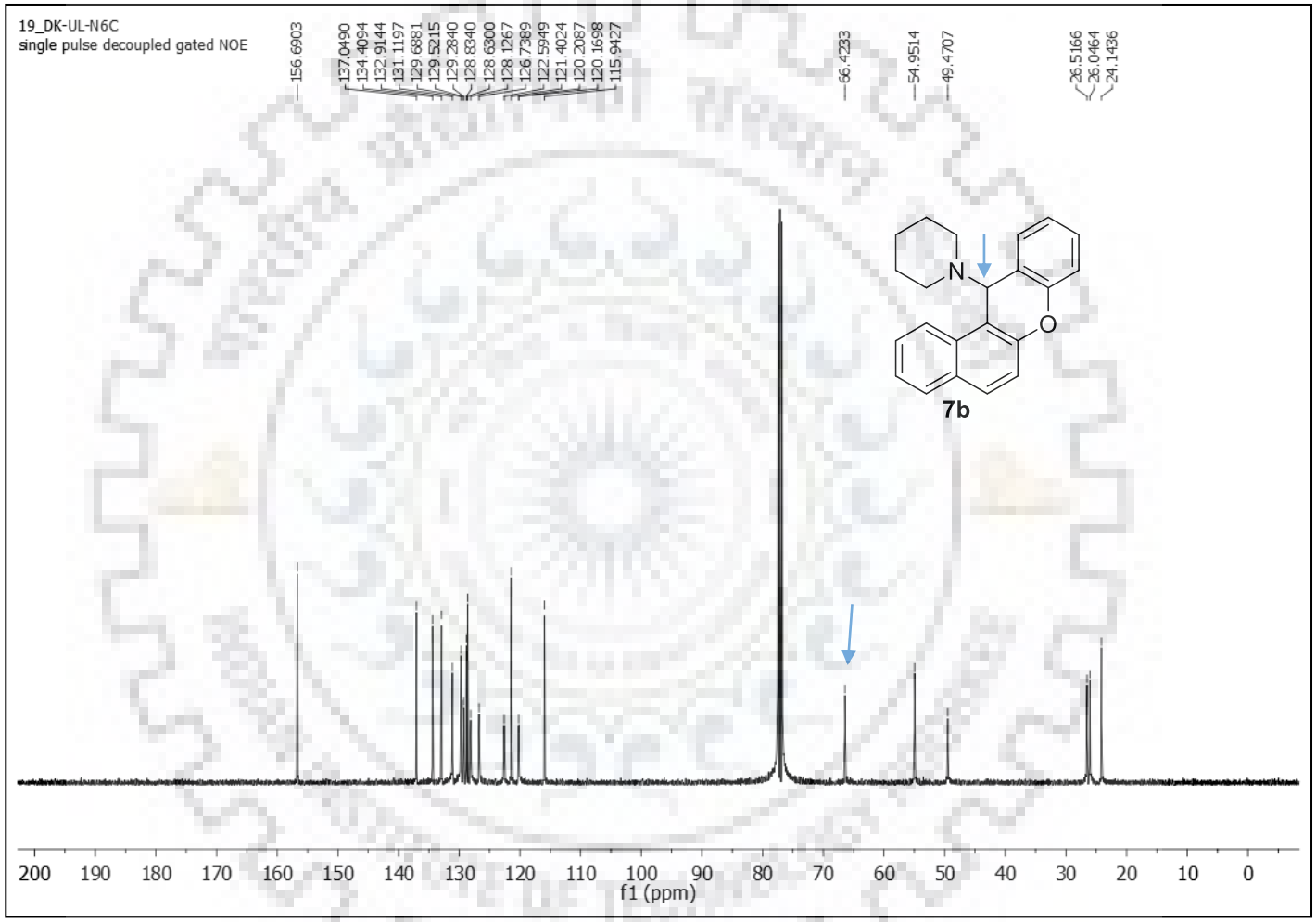

Figure S-78: ^{13}C NMR Spectrum of **7b** in $CDCl_3$.

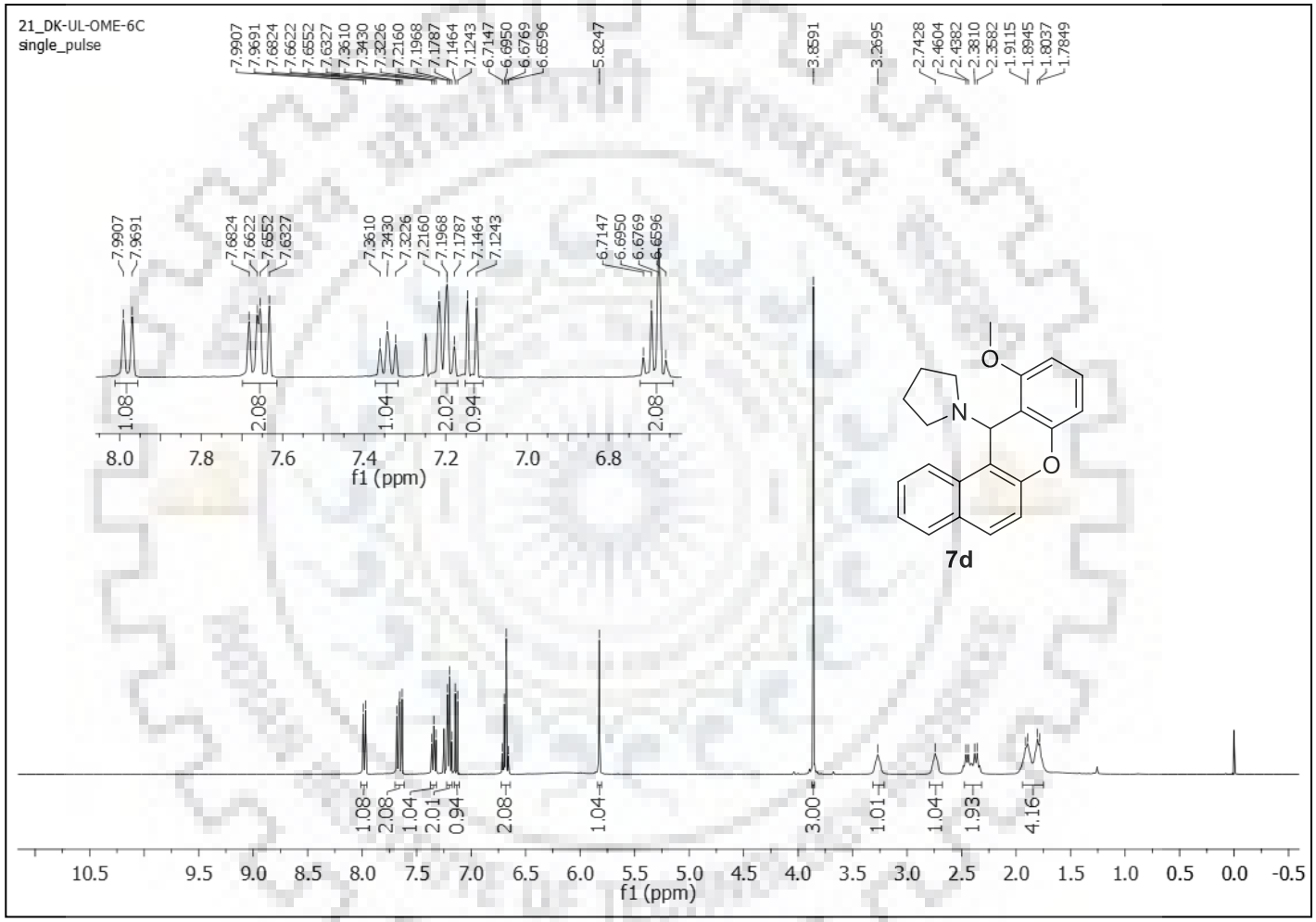

Figure S-79: ^{1}H NMR Spectrum of **7d** in $CDCl_3$.

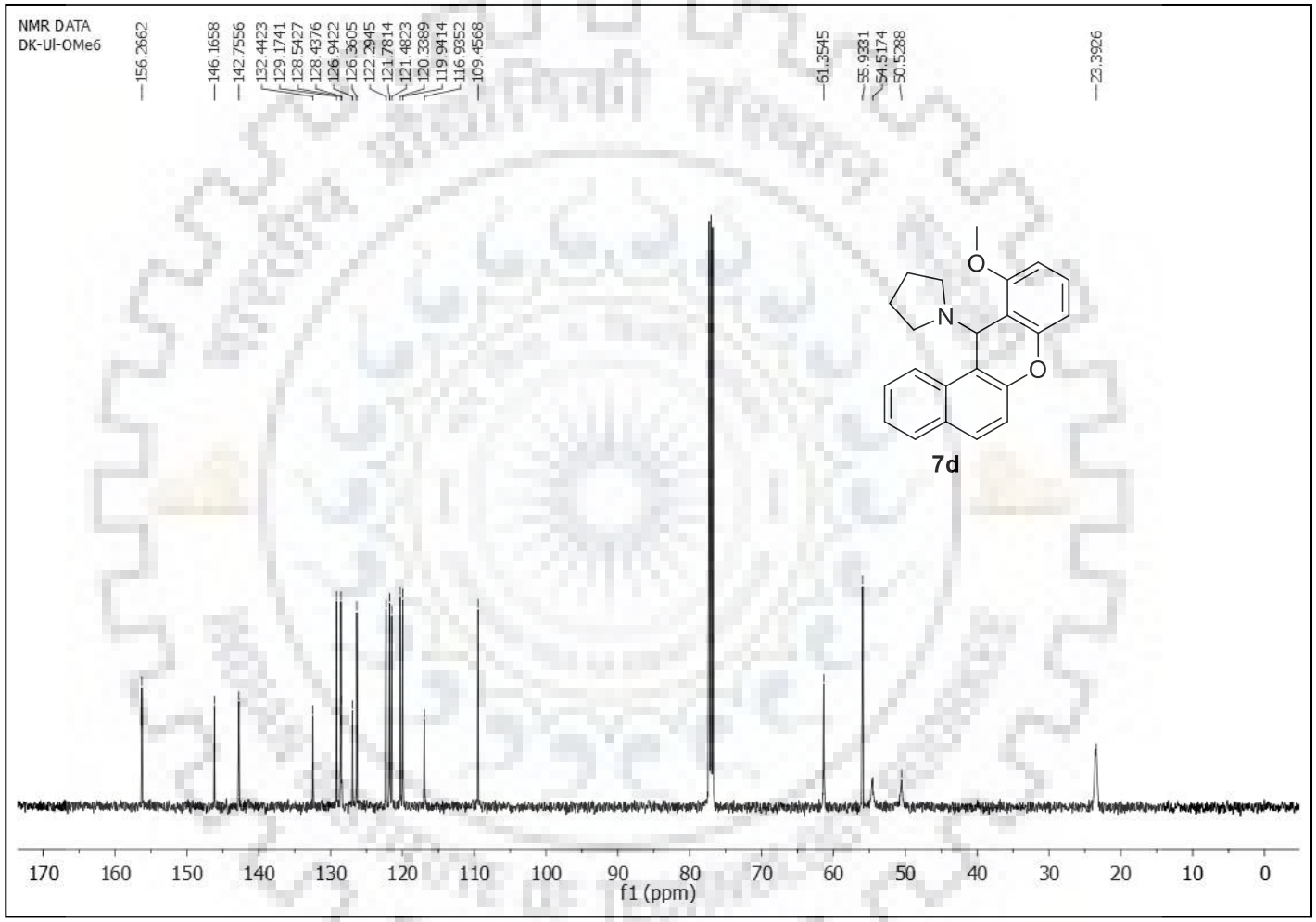

Figure S-80: ^{13}C NMR Spectrum of **7d** in $CDCl_3$.

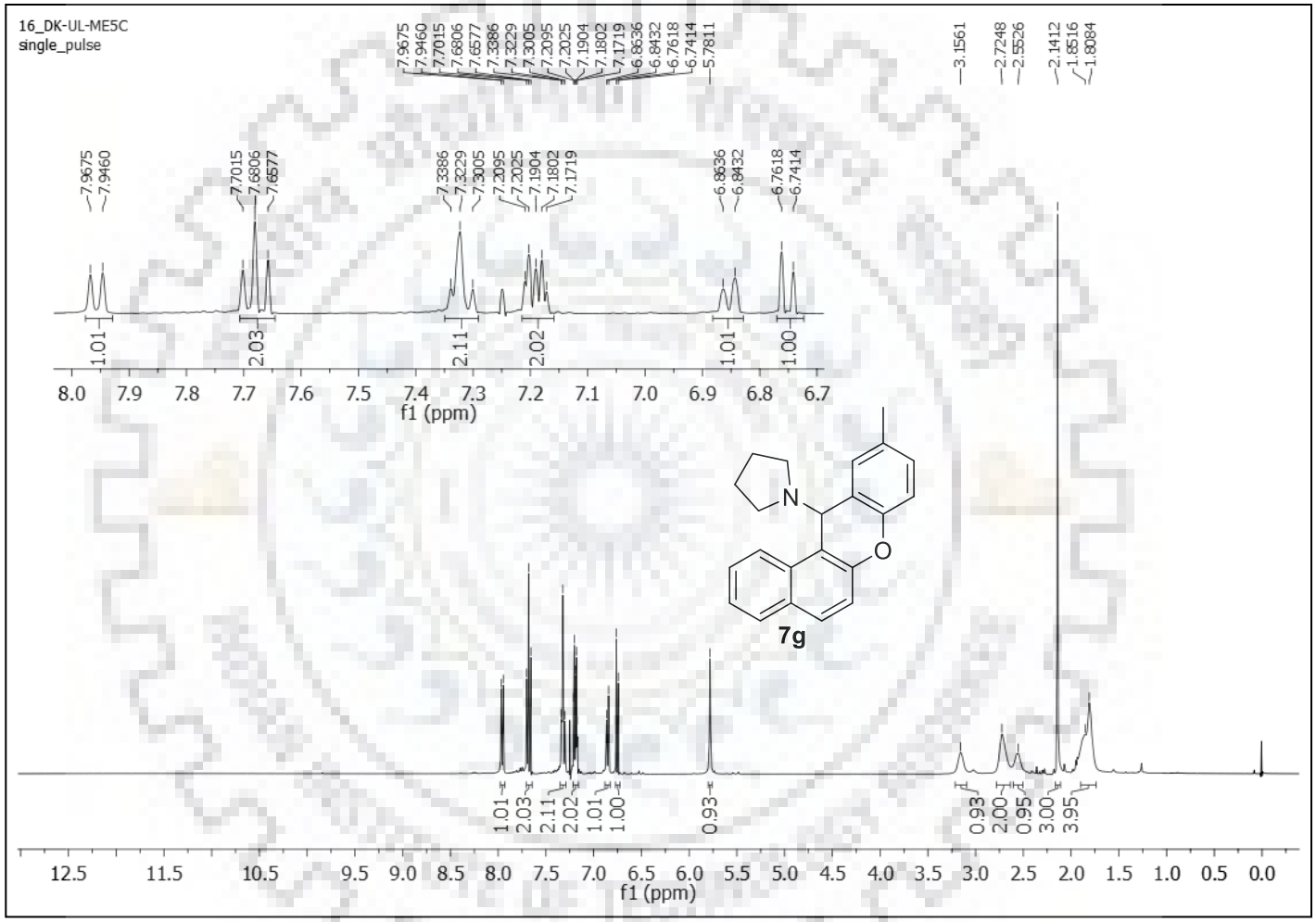

Figure S-81: ^{1}H NMR Spectrum of **7g** in $CDCl_3$.

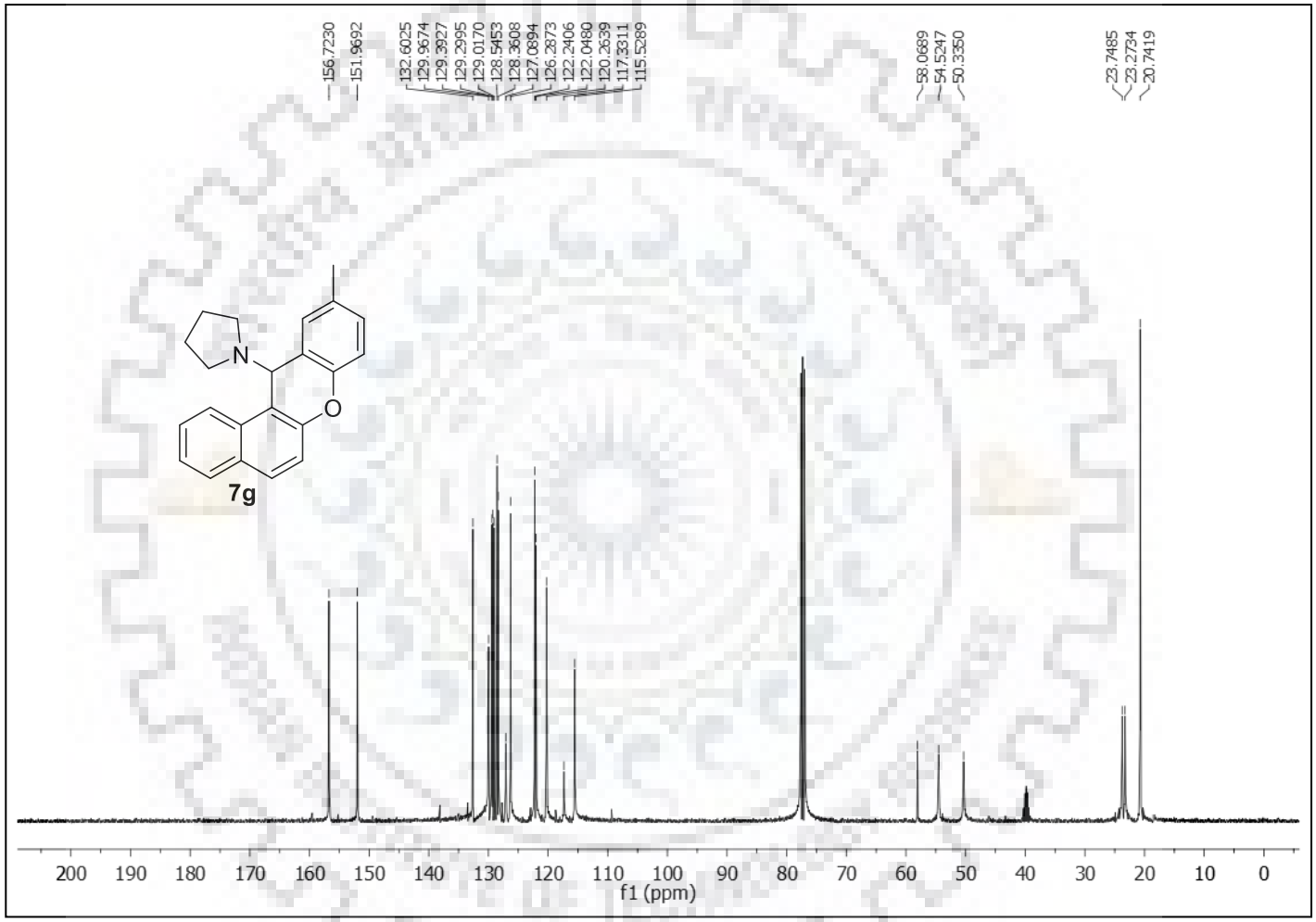

Figure S-82: ^{13}C NMR Spectrum of **7g** in $CDCl_3$+DMSO d_6.

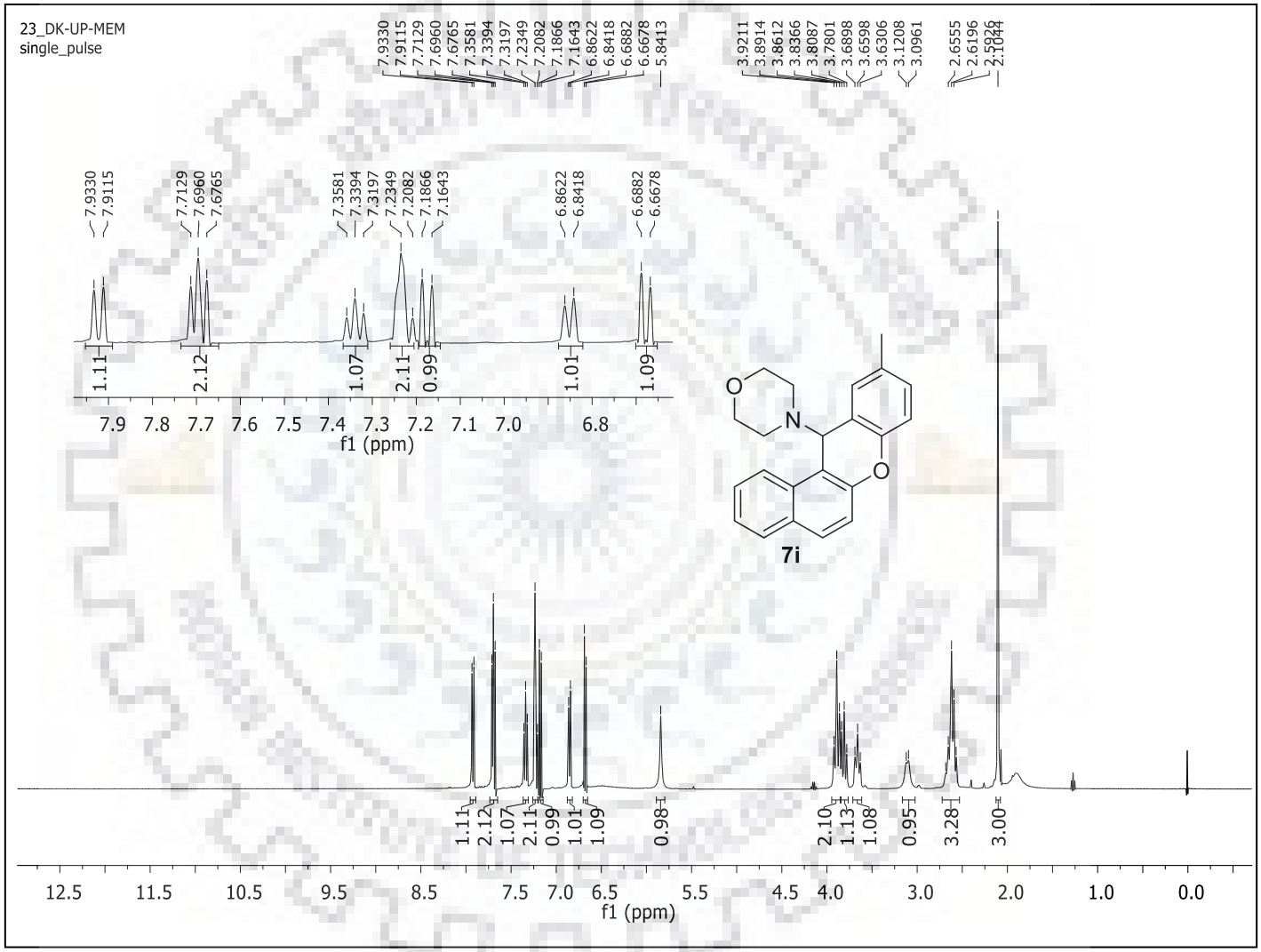

Figure S-83: ^{1}H NMR Spectrum of **7i** in $CDCl_3$.

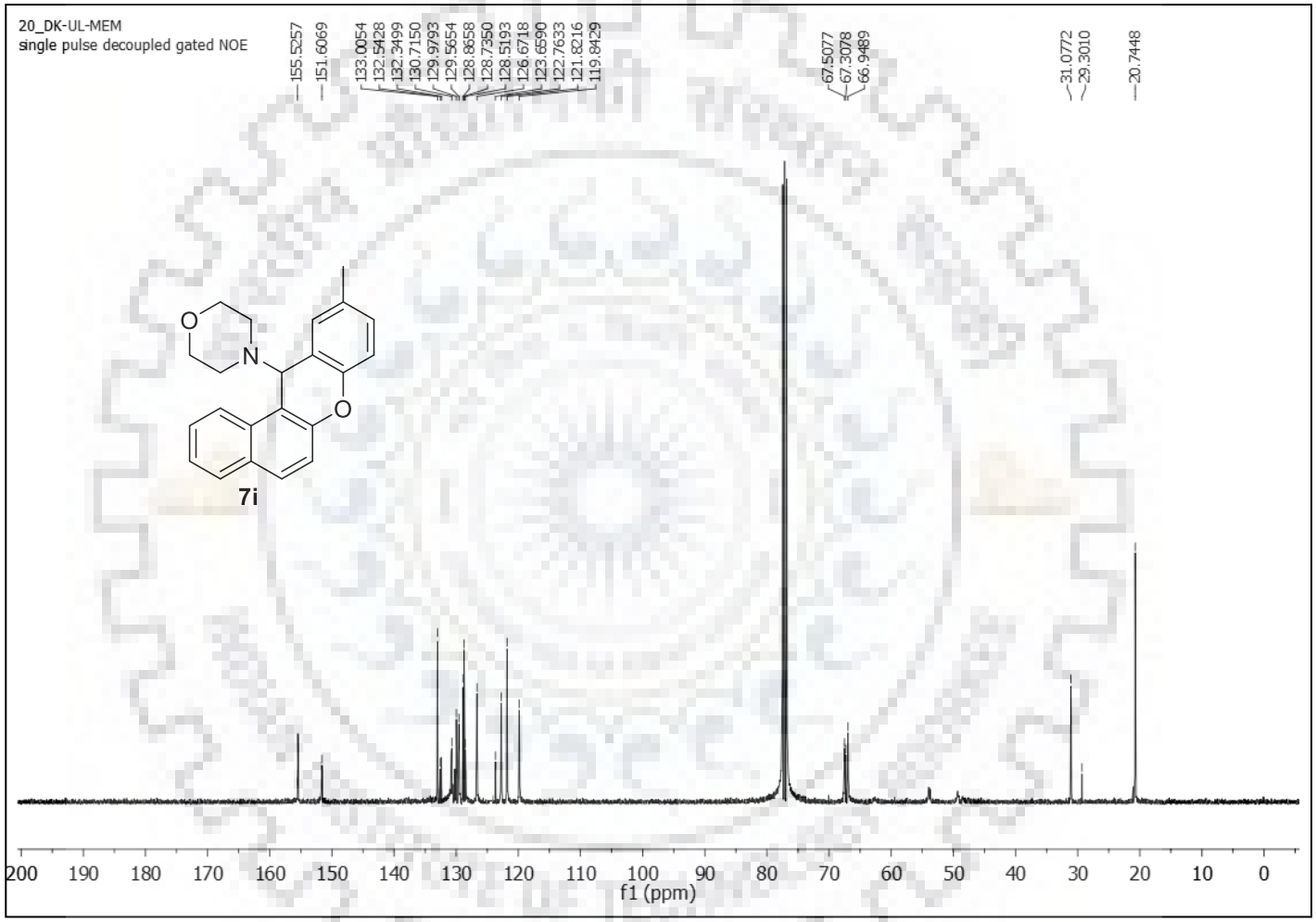

Figure S-84: ^{13}C NMR Spectrum of **7i** in $CDCl_3$.

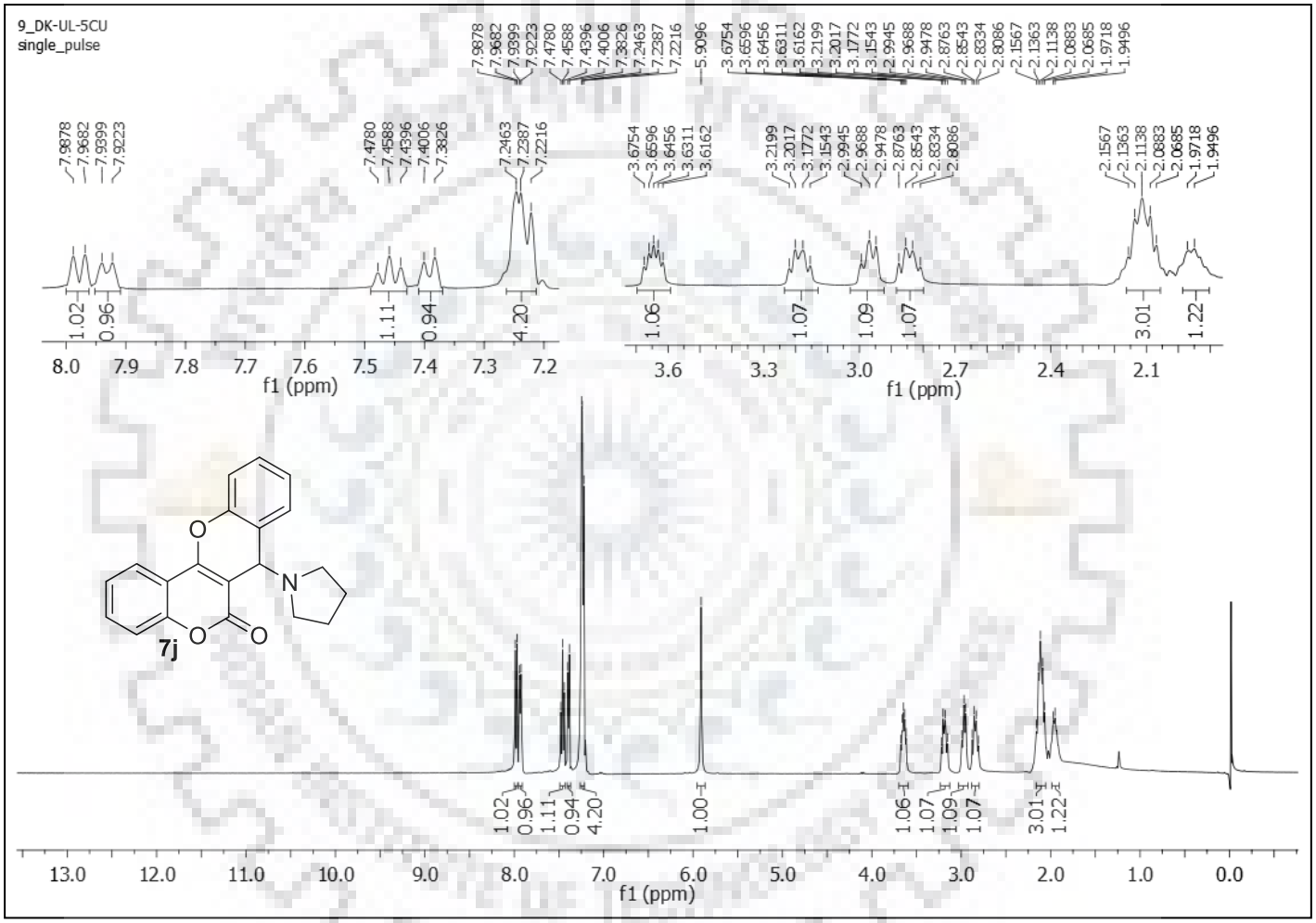

Figure S-85: ^{1}H NMR Spectrum of **7j** in $CDCl_3$.

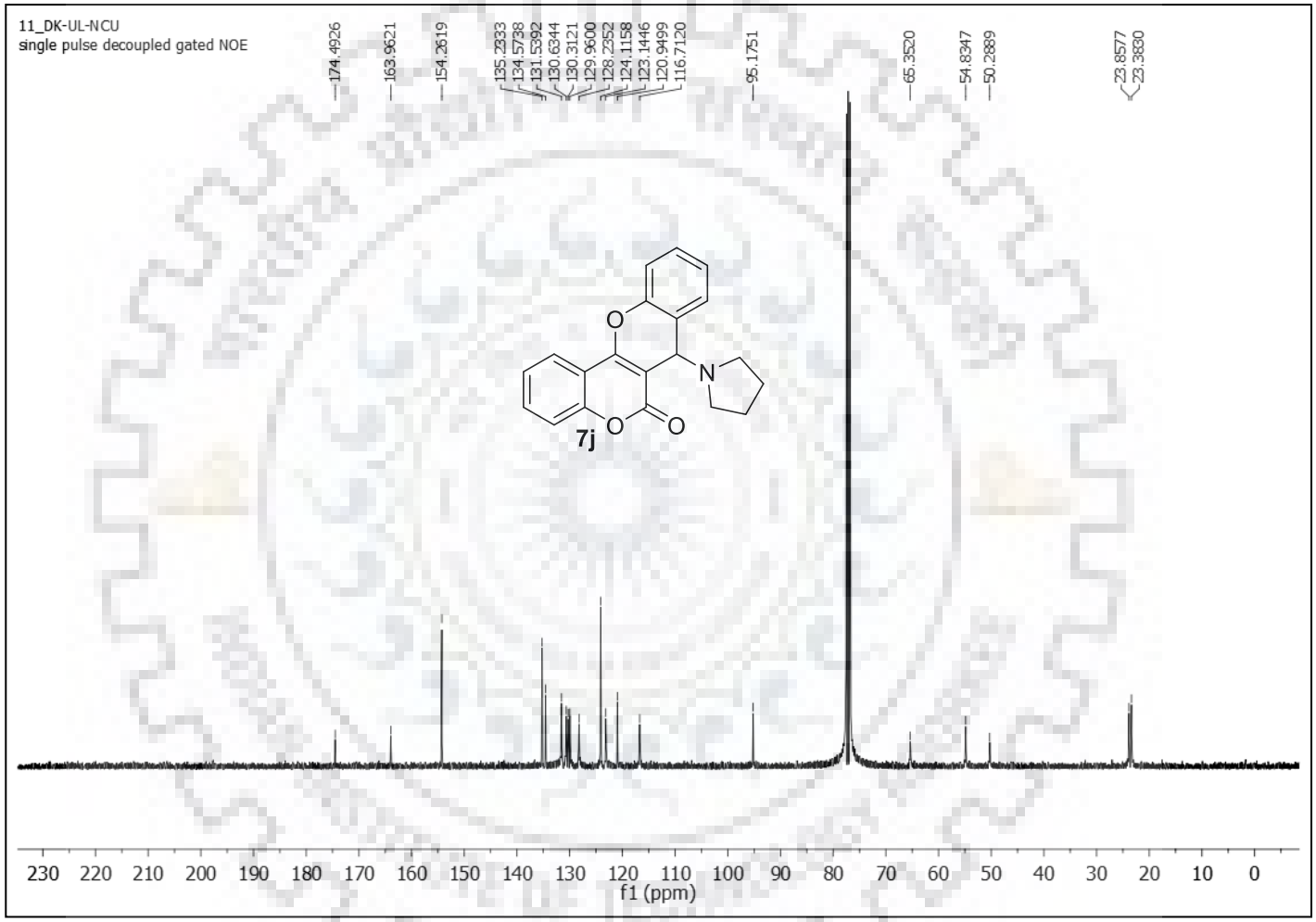

Figure S-86: ^{13}C NMR Spectrum of **7j** in $CDCl_3$.

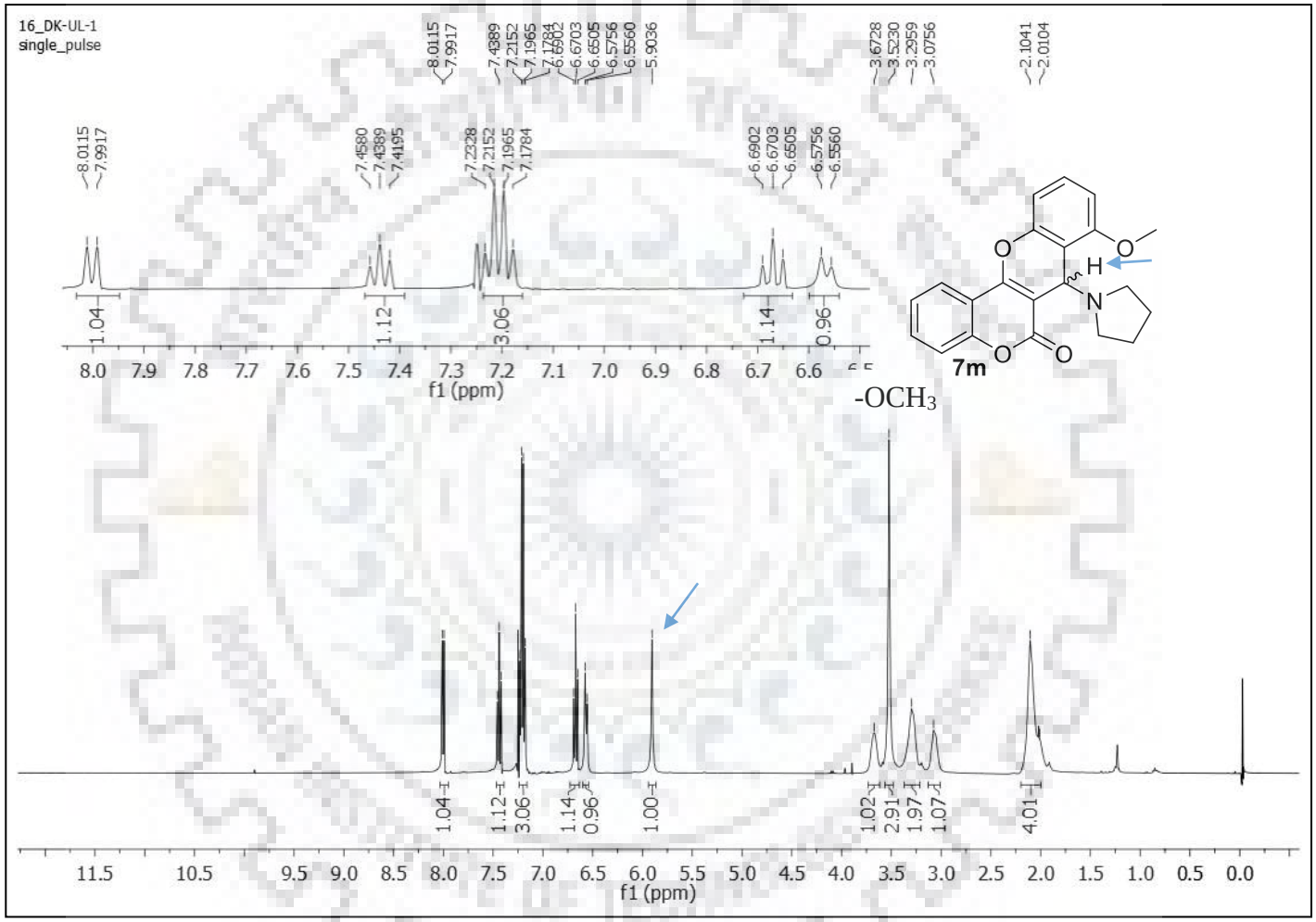

Figure S-87: ^{1}H NMR Spectrum of **7m** in $CDCl_3$.

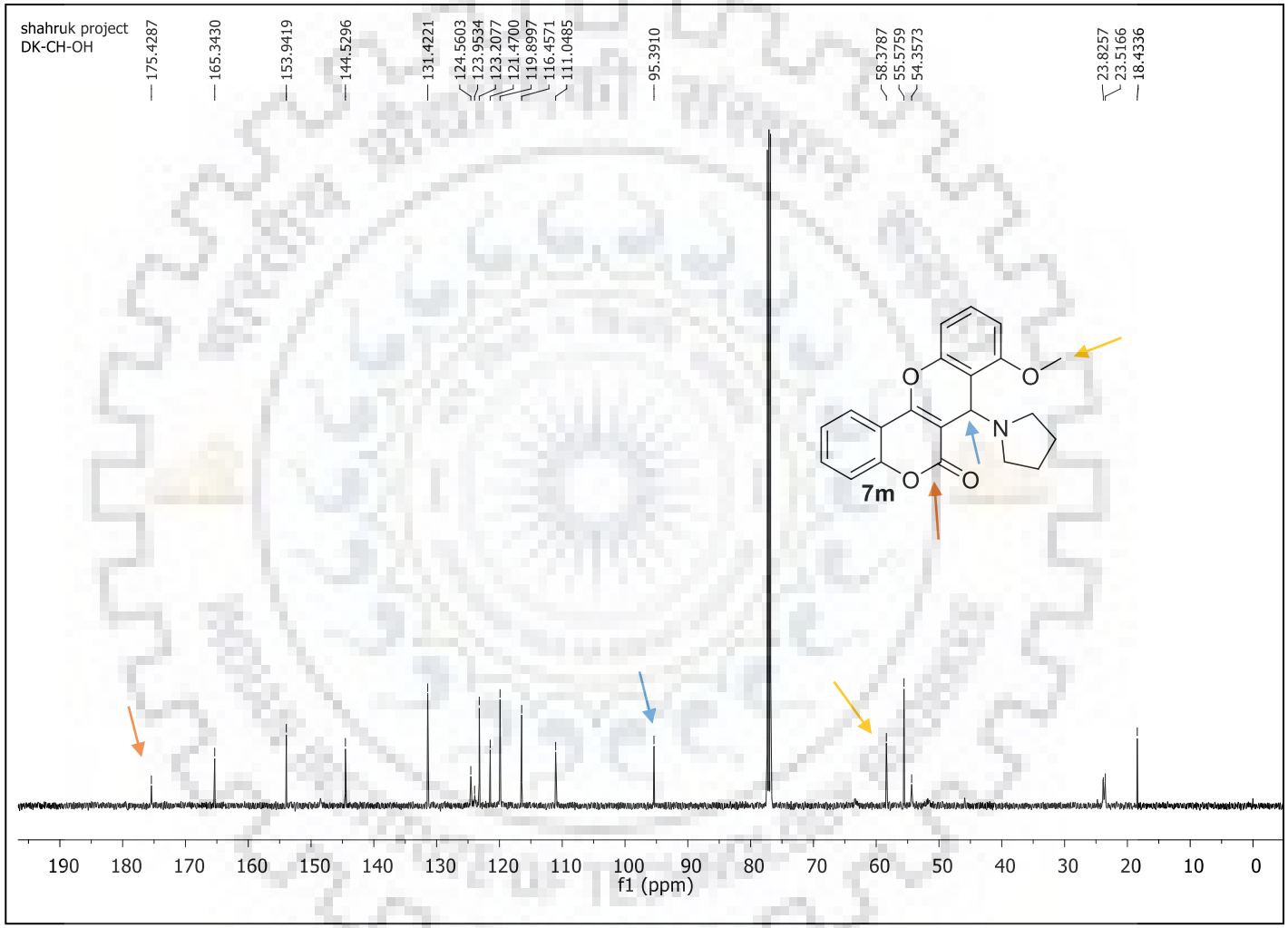

Figure S-88: ^{13}C NMR Spectrum of **7m** in $CDCl_3$.

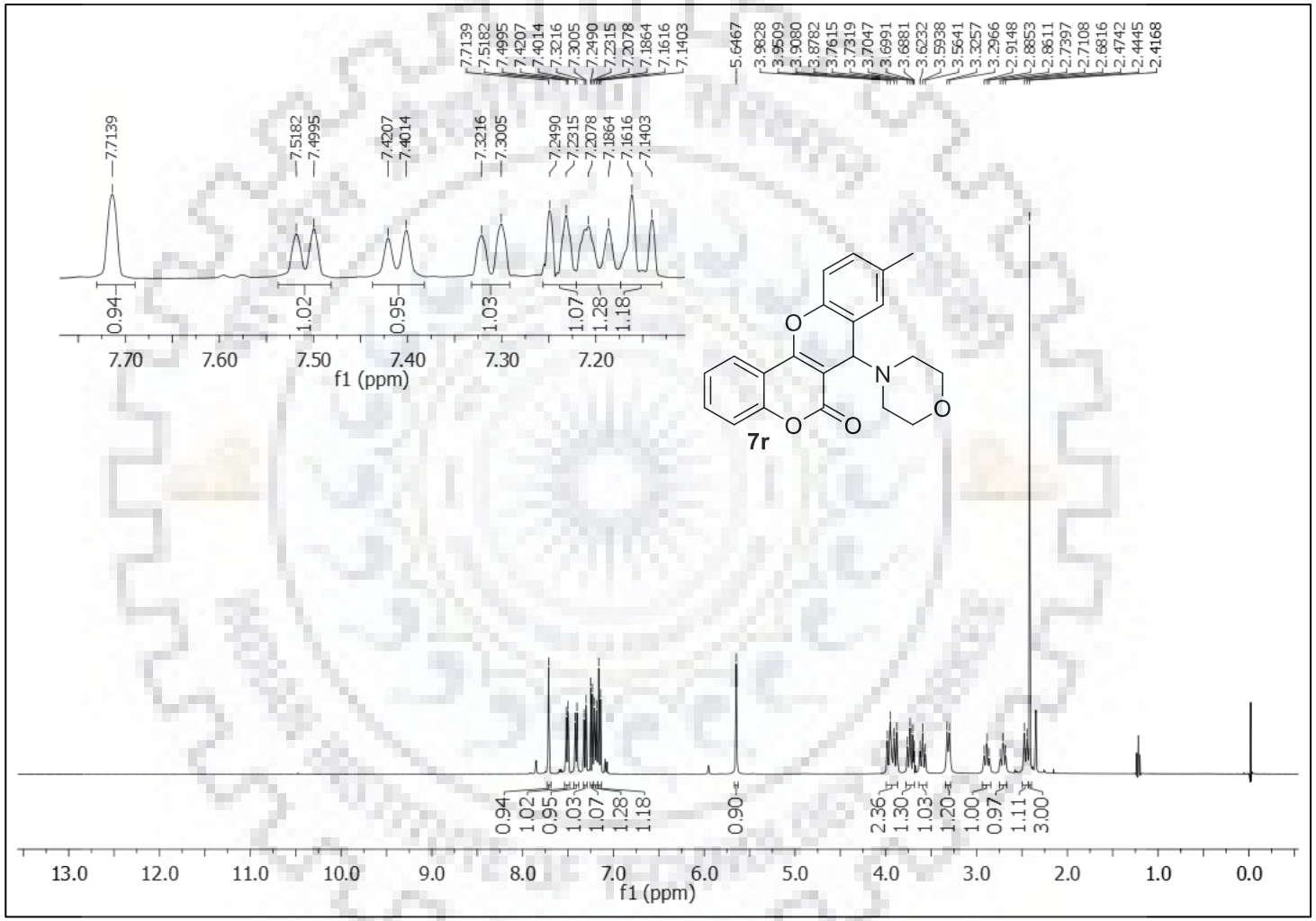

Figure S-89: ^{1}H NMR Spectrum of **7q** in $CDCl_3$.

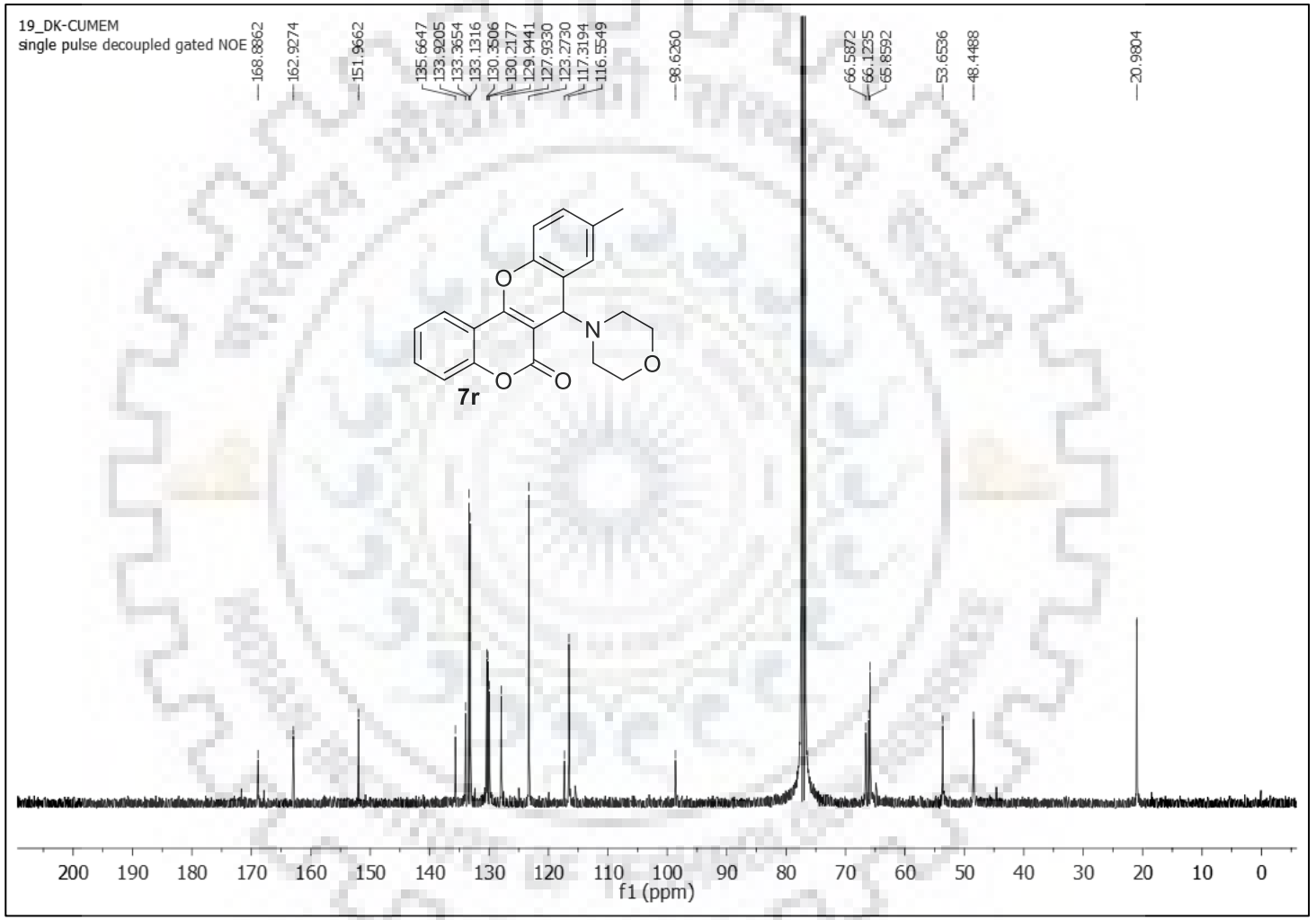

Figure S-90: ^{13}C NMR Spectrum of **7q** in $CDCl_3$.

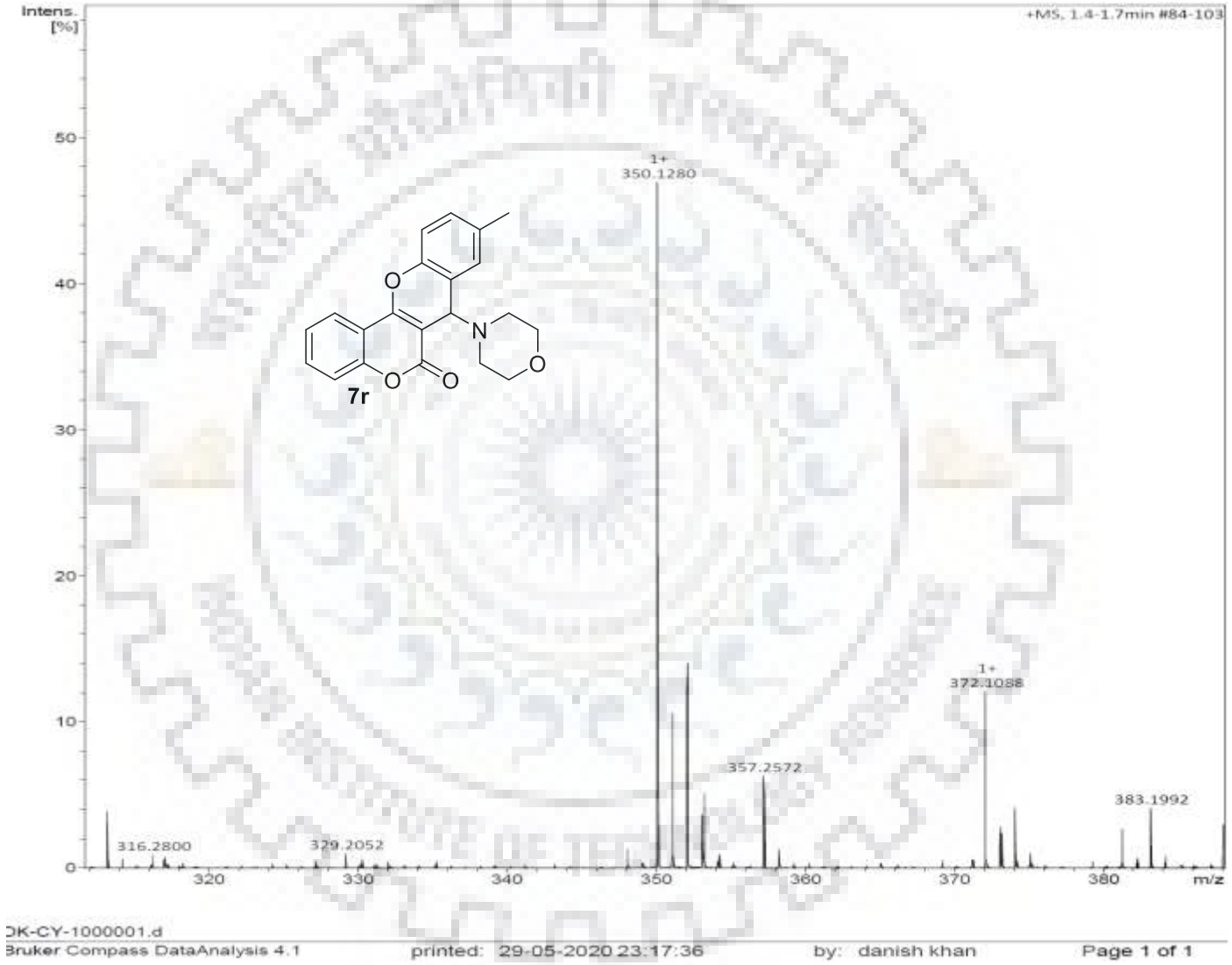

Figure S-91: HRMS Spectrum of **7r**.

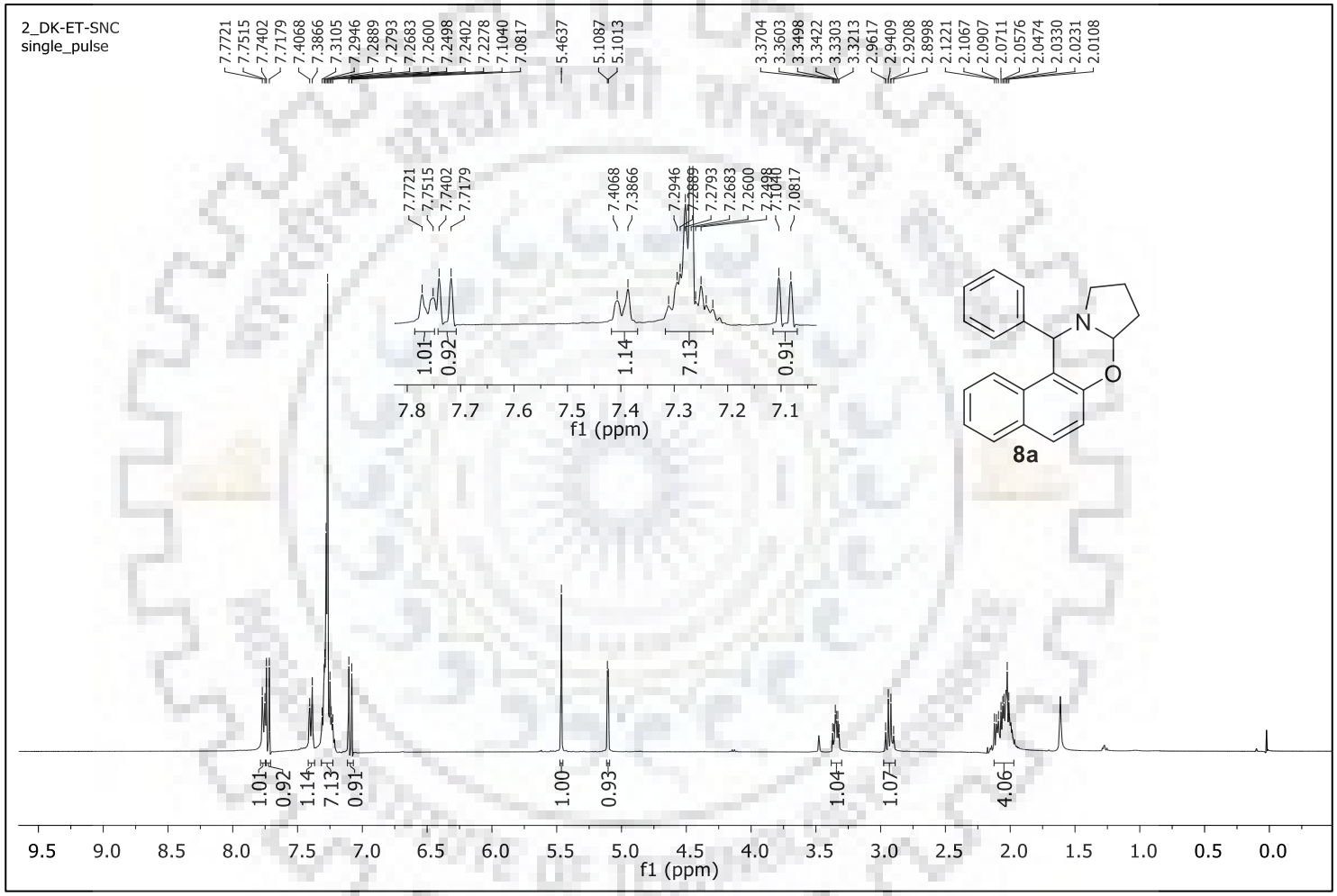

Figure S-92: ^{1}H NMR Spectrum of **8a** in $CDCl_3$.

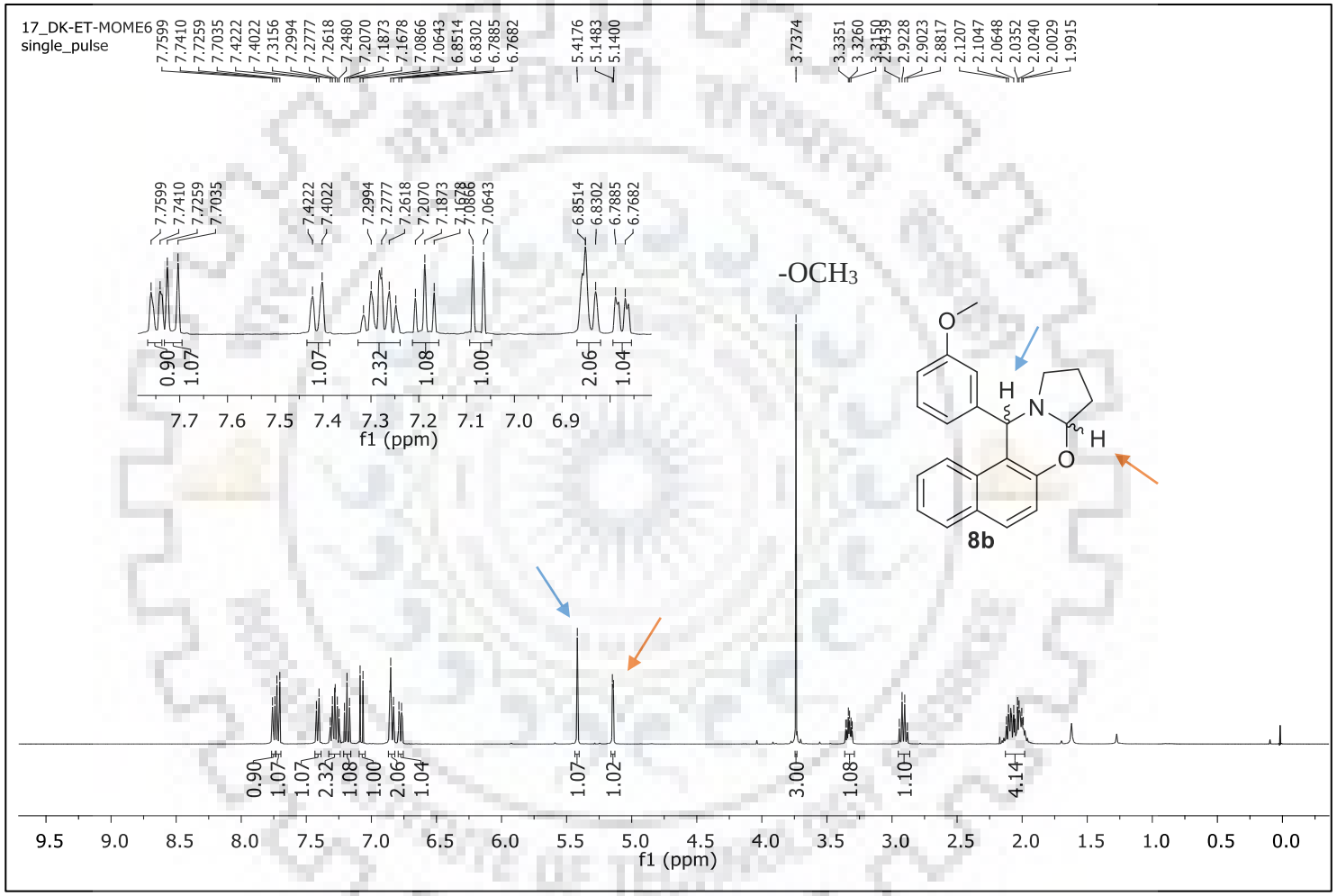

Figure S-93: ^{1}H NMR Spectrum of **8b** in $CDCl_3$.

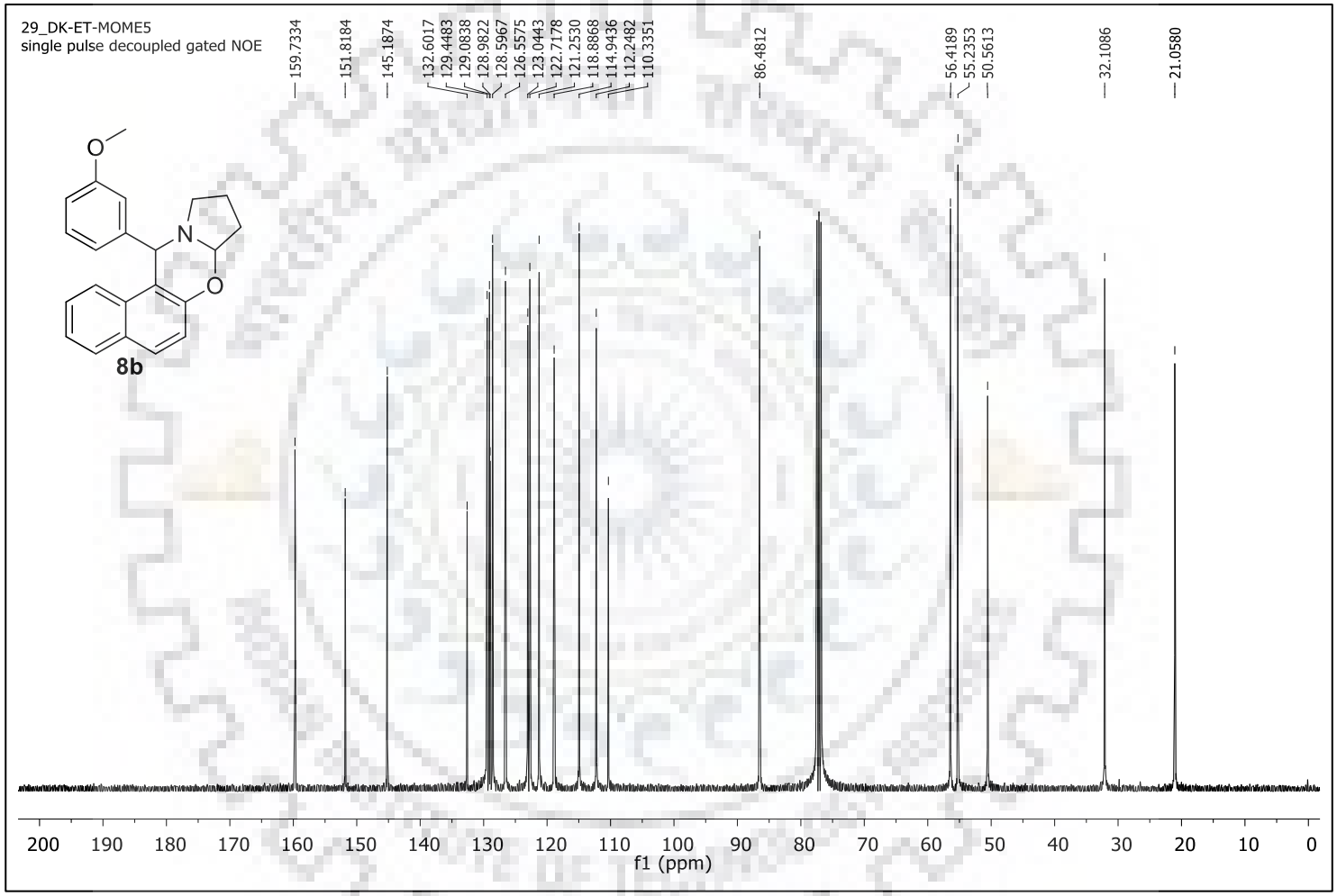

Figure S-94: ^{13}C NMR Spectrum of **8b** in $CDCl_3$.

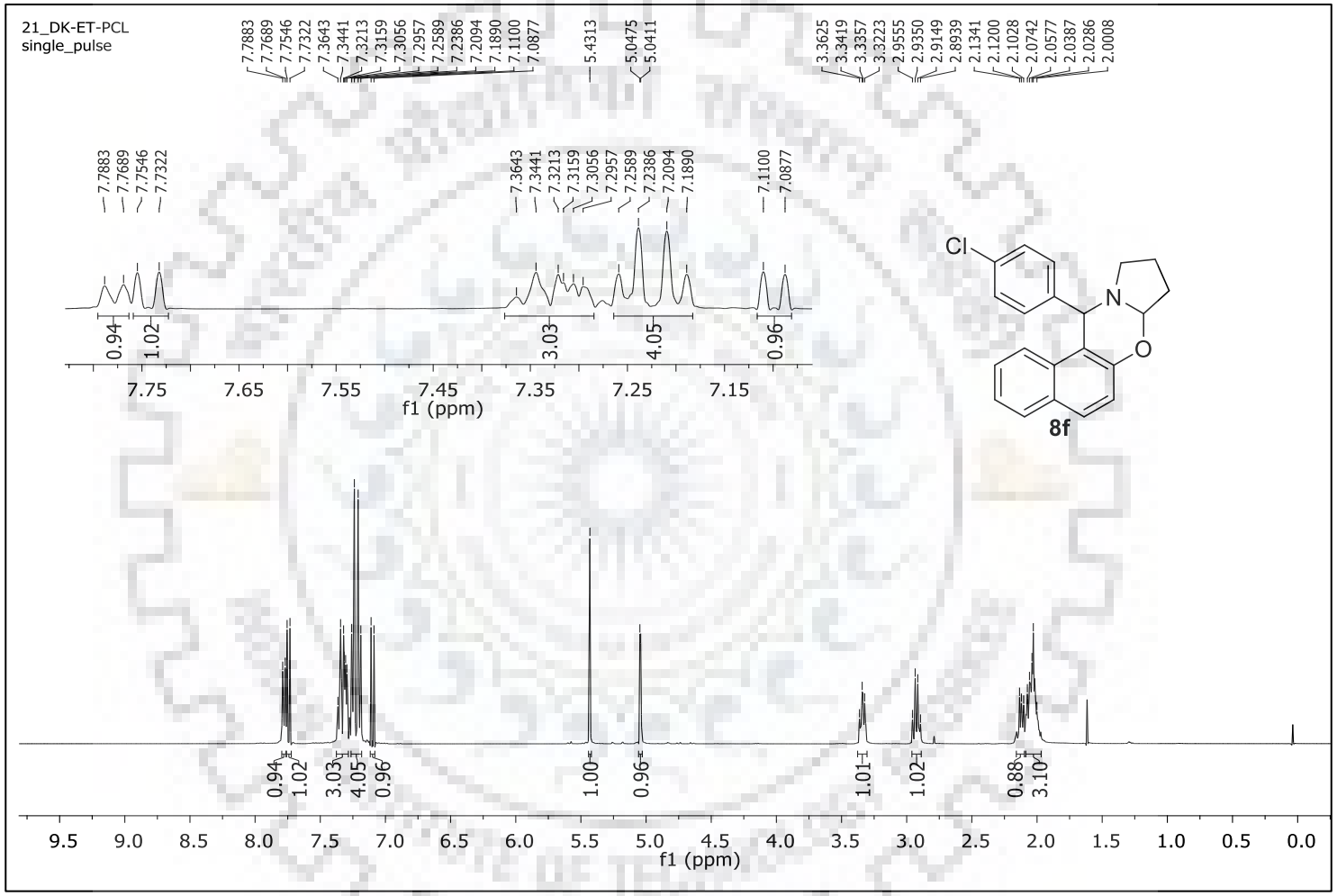

Figure S-95: ^{1}H NMR Spectrum of **8f** in $CDCl_3$.

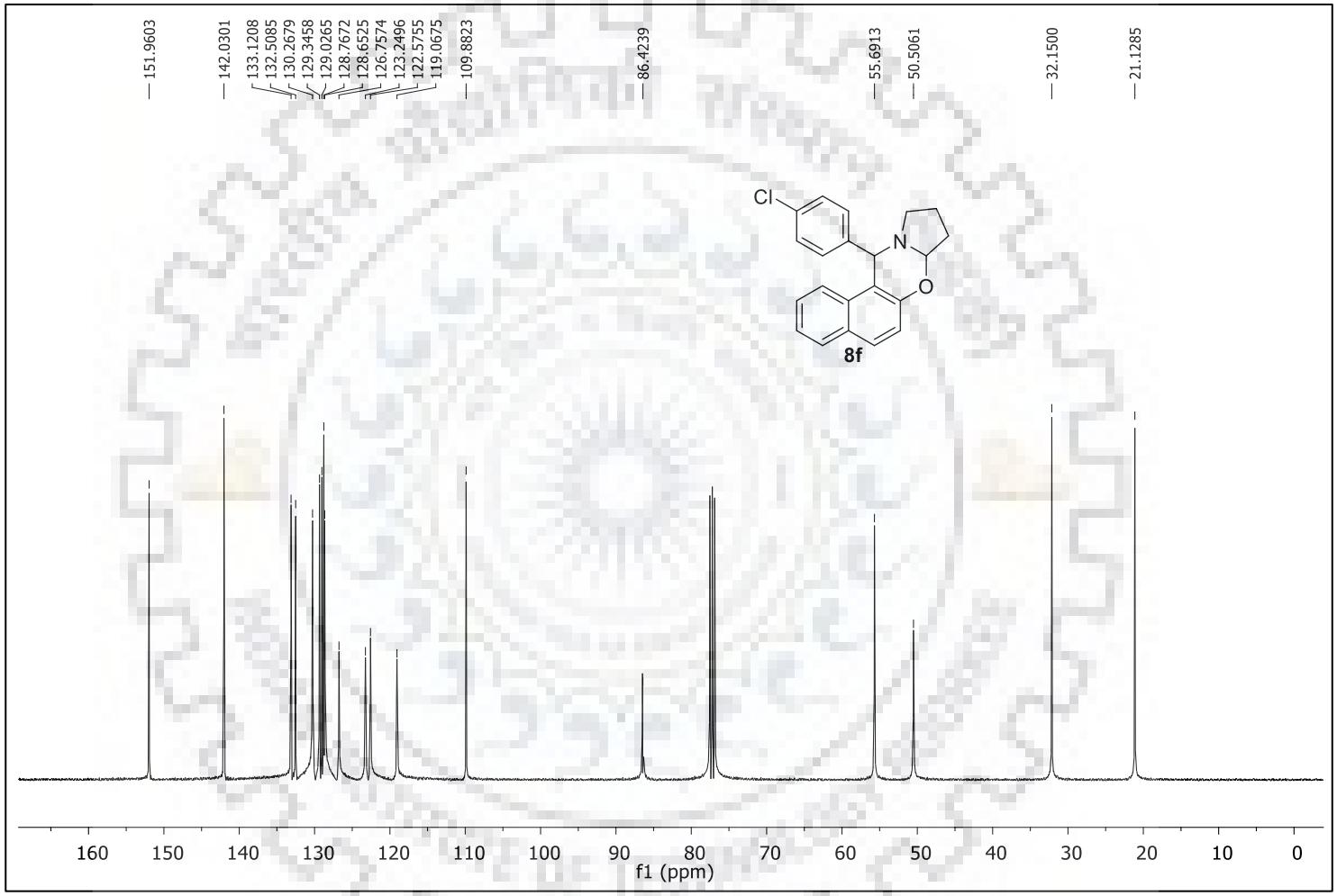

Figure S-96: ^{13}C NMR Spectrum of **8f** in $CDCl_3$.

Figure S-97: HRMS Spectrum of **8f**.

LIST OF PUBLICATIONS

1. **Khan, D**.; Mukhtar S.; Alsharif, M. A .; Alhamdi. M. I.; Ahmed, N. "PhI(OAc)2 mediated an efficient Knoevenagel reaction and their synthetic application for coumarin derivatives" *Tetrahedron Lett.* **2017**, *58*, 3183–3187.
2. Alsharif, M. A.;[‡] **Khan, D**.;[‡] Mukhtar, S.; Alahmdi, M. I.; Ahmed, N. "KOtBu-Mediated Aza-Michael Addition of Aromatic Amines or N-Phenylurea to 3-Nitro-2-phenyl-2H-chromenes and Sequential Aerobic Dehydrogenation" *Eur. J. Org. Chem*. **2018**, 3454-3463.
3. Parveen, I.; **Khan, D**.; Ahmed, N. "Regioselective Hydrodehalogenation of Aromatic α- and α-Halo carbonyl Compounds by CuI in Isopropanol" *Eur. J. Org. Chem.* **2019**, 759-764.
4. **Khan, D**.; Ahmed, N.; Mukhtar S.; Alsharif, M. A .; Alhamdi. M. I. "SeO_2 Mediated Synthesis of Selected Heterocycles by Oxidative C-C Bond Cleavage of AcetophenoneDerivatives" *ChemistrySelect* **2019**, *4*, 7585-7590
5. Alsharif, M. A.;* **Khan, D**.;* Mukhtar, S.; Alahmdi, M. I.; Ahmed, N. "Pharmacological Activities of Novel Chromene Derivatives as Calcium/Calmodulin Dependent Protein Kinase IV (CAMKIV) Inhibitors" *ChemistrySelect* **2020**, *5*, 498-505.

LIST OF CONFERENCE/SYMPOSIUM

1. Hands on advanced instruments of water quality monitoring and testing.
2. Contemporary facet in organic synthesis 2017.
3. ACS on campus.
4. National conference on emerging trends in chemical science.