# ULTRASONIC-ACCELERATED RAPID PROTOCOL FOR THE GREEN SYNTHESIS OF HETEROCYCLICS AND AROMATIC COMPOUNDS

**by**

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## ABSTRACT

The need to improve chemical practices, so as to minimize their negative impact on health and environment has encouraged the academics and industry to move toward employing and designing more environmentally friendly techniques and methodologies. As a result, 'Green chemistry' has emerged as an approach that aims to reduce environmental damage that comes from the use of toxic substances and the waste that is produced thereafter and also to reduce the amount of energy consumed by chemical processes.

Natural products are a rich source of drug candidates, expansion of MCRs have generated increased chemical diversity in fewer steps, hence it has allowed for production of more complex natural product analogues. Several MCRs in aqueous media, without using large amount of solvent have been reported. Water as a solvent offers many practical and economic advantages including low cost, safe handling and environmental compatibility. In recent years researchers have discovered the use of ultrasound irradiation as a clean and beneficial approach in organic synthesis. Compared to conventional heating, which provides thermal energy in the macro system, ultrasonification improves mass transfer, reduces reaction times, improves yields and minimizes side product formation by providing the activation energy in micro environment. As this technology involves energy conservation and minimal waste generation, it is widely accepted as a green approach. Ultrasound irradiation together with the method of multicomponent reactions (MCRs) have become the biggest requirements in modern organic synthesis as green synthetic tool and method used to account for green chemistry.

Green synthetic protocols are described for the one-pot synthesis of two classes of heterocyclic and one class of aromatic compounds with wanted properties.

1. Synthesis of pyrazoles, via multicomponent reaction of aromatic aldehydes, hydrazine monohydrate, ethyl acetoacetate and malononitrile in water under ultrasound irradiation. Seventeen pyrazole derivatives were successfully synthesized and characterized.
2. Synthesis of functionalized 1,4-dihydropyridine derivatives via a multi-component reaction of dimethylacetylenedicarboxylate, arylamine, malononitrile and various substituted aldehydes. Eleven derivatives were synthesized and characterized.

3. Synthesis of Dicarbonitriles, via multicomponent reaction of aromatic/aliphatic aldehydes, malononitrile and 3-methyl-cyclohexanone in water under ultrasound irradiation. Eleven derivatives were synthesized and characterized.

All the compounds synthesized under ultrasound irradiation were achieved in good to excellent yields (60-97%) in short reactions times (0.25-2.5 hours). No chromatographic methods were required for workup, thus there was no need for volatile organic solvents which are generally required for workup and purification in many existing procedures. All the compounds synthesized were washed with water, acetone or ethanol and filtered under vacuum and they were fully characterized by, FTIR, $^{1}$H NMR, $^{13}$C NMR and MS.

## DECLARATIONS

## DECLARATION 1 - PLAGIARISM

I, **Nhlanhla Gracious Shabalala,** declare that

1. The research reported in this thesis, except where otherwise indicated is my original research.
2. This thesis has not been submitted for any degree or examination at any other university.
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## DECLARATION 2 - PUBLICATIONS

DETAILS OF CONTRIBUTION TO PUBLICATIONS that form part and/or include research presented in this thesis (include publications, submitted, *in press* and published and give details of the contributions of each author to the experimental work and writing of each publication)

1. **Nhlanhla Gracious Shabalala**, Ramakanth Pagadala and Sreekantha B. Jonnalagadda. "Ultrasonic-accelerated rapid protocol for the improved synthesis of pyrazoles." *Ultrasonics Sonochemistry*, 2015, 27:423-429,

   **My contribution:** I synthesized and characterized all the derivatives under the supervision of Prof. Jonnalagadda (Supervisor) and Dr. R. Pagadala (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article. I was first-author and both the co-authors.

2. **Nhlanhla Gracious Shabalala**, Suresh Maddila and Sreekantha B Jonnalagadda "Functionalized 1,4-dihydropyridine derivatives via a multi-component one pot reaction between dimethylacetylenedicarboxylate, arylamine, malononitrile and various substituted aldehydes". *New Journal of Chemistry*, (Accepted for publication)

   **My contribution:** I synthesized and characterized all the derivatives under the supervision of Prof. Jonnalagadda (Supervisor) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article. I am the first-author and both the co-authors.

3. **Nhlanhla Gracious Shabalala**, Suresh Maddila and Sreekantha B Jonnalagadda. "Facile one-pot synthesis of tetrahydrobiphenylene-1,3-dicarbonitriles in aqueous media under ultrasound irradiation". (Submitted).

   **My contribution:** I synthesized and characterized all the derivatives under the supervision of Prof. Jonnalagadda (Supervisor) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article. I am the first-author and both the co-authors.

Signed:……

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## LIST OF ABBREVIATIONS

| Abbreviations | Full name |
|---|---|
| 3-CR | Three component reaction |
| 4-CR | Four component reaction |
| $^{1}$HNMR | Proton Nuclear Magnetic Resonance |
| $^{13}$CNMR | Carbon-13 Nuclear Magnetic Resonance |
| °C | Degrees Celcius |
| ArH | Aromatic ring proton |
| [bmim] Br | 1-butyl-methylimidazolium bromide |
| ArH | Aromatic ring proton |
| [bmim]$BF_4$ | 1-butyl-3-methylimidazolium tetrafluoroborate |
| [bmim]$FeCl_4$ | butylmethylimidazolium tetrachloroferrate |
| Calcd | Calculated |
| C-C | Carbon-Carbon bond |
| $CDCl_3$ | Deuterated Chloroform |
| COSY | Correlation spectroscopy |
| DMAD | Dimethyl acetylenedicarboxylate |
| DMF | Dimethyl formamide |
| DMSO | Dimethyl sulfoxide |
| DMSO-$d_6$- | Deuterated-dimethyl sulfoxide |
| Dd | Doublet of doublet |
| D | Doublet |
| Dt | Doublet of triplet |
| EtOAc | Ethyl acetate |
| EtOH | Ethanol |
| FT-IR | Fourier Transform Infrared Spectroscopy |
| GBB | Groebke-Blackburn-Bienaymre |
| $GlyNO_3$ | Glycine nitrate |
| $H_2O$ | Water |
| HMBC | Heteronuclear Multiple Bond Coherence |
| HSQC | Heteronuclear Single Quantum Coherence |

| | |
|---|---|
| Hz | Hertz |
| HRMS | High Resolution Mass Spectrometry |
| $I_2$ | Iodine |
| IL | Ionic Liquids |
| IMCRs | Isocyanide-based Multicomponent Reactions |
| KHz | Kilo Hertz |
| MCRs | Multicomponent reactions |
| MHz | Mega Hertz |
| M | Multiplet |
| MW | Microwave |
| PEG 600 | Poly (ethylene glycol) 600 |
| Ppm | Parts Per Million |
| r.t | Room temperature |
| SFexZr | Sulfated zirconia |
| S | Singlet |
| $S_8$ | Elemental Sulfur |
| SONAR | Sound Navigation and Ranging |
| TEBA | Triethylbenzylammonium chloride |
| TBAB | Tetrabutylammomium bromide |
| THF | Tetrahydrofuran |
| TLC | Thin Layer Chromatography |
| TMSCN | Trimethylsilylcyanide |
| T | Triplet |
| $TsOH.H_2O$ | 4-methylbenzenesulfonic acid monohydrate |
| U-4CR | Ugi-four Component Reaction |
| u.s | Ultrasound |
| UV | Ultraviolet |

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# CHAPTER - 1

## INTRODUCTION

### 1. GREEN CHEMISTRY

Sustainable development is known as the development that facilitates the needs of the present generation without compromising the ability to meet the needs of the future generation.[1],[2] In other words the natural resources we have now, it is our responsibility to see to it that they are not depleted as a result of our practices as a society.[3] The natural resources are being depleted as a result of our practices as the society and we are also responsible for the release of hazardous materials into the environment in large quantities.[4] Chemical industries are known to be the major contributors to the release of hazardous materials into the environment, as they use and create new materials or chemicals daily.[5] The chemical materials that the chemical industry produce are also needed to serve basic human needs. However, these products come at a price as they are created using processes that are energy consuming, that use hazardous starting materials and processes that also generate waste.[6] As much as the chemical industry provide for human needs, it is at the same time responsible for producing harmful waste to humans as well as the environment.[7] This has brought a big challenge which faces the government, industry as well as academia, which is managing the risk that is produced as new materials are created daily. In addressing this challenge, a group of stake holders came together, in 1990 the Pollution Prevention Act introduced a new approach which aims to eliminate the hazard at the source.[6] The new approach that has emerged is known as Green chemistry, this approach avoids the trouble that comes with trying to reduce the risk of the hazard by minimizing the exposure rather it eliminate the hazard itself from the source.[8],[9] Green chemistry is the chemistry that aims to prevent pollution by utilizing renewable raw materials, minimize production of waste and avoiding the use of toxic substances when manufacturing and applying chemical products.[1],[10] Green Chemistry has been officially defined by environmental protection agency (EPA) in USA as the use of chemistry for pollution prevention and design of chemical products and processes that are more environmentally benign.[11] This approach comes with guidelines that helps the chemists to adopt it and therefore achieve their goal of sustainability[12], the guidelines are known as the twelve principles of green chemistry,[13],[14] were introduced and published by Anastas and Werner, 1998.[15]

### 1.1.Main principles of Green Chemistry:[15]

- **Prevention of waste**: It is better when waste is prevented at source than to treat or clean it after it has formed.
- **Atom economy**: All materials used in the chemical process should be incorporated in the final product.
- **Renewable feed stock**: When technically practicable a raw material should be renewable and not depleting.
- **Design for safer chemicals**: The design of chemical products should be to preserve efficacy of their desired function while minimizing their toxicity.
- **Use of Safer solvents**: If possible the use of substances such as solvents as well as separating agents should be avoided or innocuous when used.
- **Energy efficiency**: It is important that chemical reactions be conducted at ambient temperature and pressure. This reduces the environmental and economic impacts that come with use of energy.
- **Design for less hazardous chemical synthesis**: The design of synthetic methodologies should be that they use and produce substances that possess little or no toxicity to human health and the environment.
- **Reduce derivatives**: The use of blocking group, protection/deprotection as derivatization, should be avoided whenever possible.
- **Use of catalyst**: Catalysts should be as selective as possible and superior to stoichiometric reagents.
- **Degradation**: Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
- **Real-time analysis for pollution prevention**: Methodologies should allow for real-time in process control and monitoring before the formation of hazardous substances.
- **Safe chemistry for accident prevention**: Chemical processes should use a substance that minimizes accidents.

### 1.2. Adoption of Green Chemistry:

The collaborative efforts in academia, industries, and government are needed so as to accelerate the adoption of green chemistry.[4] The academic research in green chemistry is a major sector that helps in the adoption of this approach, academia helps provide data for the development of new chemical processes that are green and also provides fundamental knowledge related to new chemical products and processes. Academia also makes sure that the need of sustainability through the adoption of green chemistry is emphasized so that the students can see the application of their work within a global context.[16],[7],[17]

The green chemistry approach aims to minimize different types of hazards (such as toxic physical and global) which are as a result of chemical substances used and chemical processes followed in order to produce new materials. Green Chemistry research put more emphasis on pollution prevention, as the first principle of green chemistry addresses that it is better to prevent waste than to treat or clean it up, in short prevention is better than cure. Researchers have therefore considered the processes in which they produce new chemical products, making sure that their processes use safer starting (preferable renewable) materials, avoids the use of toxic solvents, use lower energy inputs and release safe substances into the environment. The new processes are known as green chemistry processes and are not only ensuring environmental, health and safety but they are also economically profitable.[18],[19]

The major concern that academic research has raised is the release of hazardous substances in the environment, this is because solvents are mostly used in academia as well as in industries. Solvents are used in areas such as synthesis and analytical chemistry, manufacturing of pharmaceutical drugs, food and flavor industries as well as in materials sciences. Many of the commonly used solvents are volatile organic compounds (VOCs), air pollutants, flammable as well as toxic. Following the guide of the main principles of green chemistry the researchers have identified and replaced these solvents with solvents that they believe are less toxic.[14] Solvents such as supercritical carbon dioxide, [20] ionic liquids,[21] water[22] (especially in organic synthesis) and preferable no solvent at all. As far as green chemistry is concerned it is important for researchers to minimize the number of solvents changes in their chemical processes,[23] therefore it is important for them to design chemical processes in such a way that they use green solvents and that the products formed are further purified using a green solvent.[24]

The implementation of green chemistry has now moved to industries, pharmaceutical companies are now introducing green chemistry techniques in drug discovery and manufacture.[25] In 2005 companies like Lilly Merck and Pfizer started to incorporate green chemistry principles in the stages of drug design and were successful and in 2014 sixteen more companies joined in among which are, Amgen, AstraZeneca, Boehringer and Ingelhem.[26] Green chemistry in drug discovery has led chemist to go back into the study of heterocyclic and aromatic chemistry all over again in order to design greener methods and to find suitable chemical substances and solvents to synthesize these compounds.[27],[28] In light of this, Sonochemistry has therefore been the field of considerable interest in recent research as it helps in promoting chemical reactions and mass transfer. It also offers the potential for shorter reaction times, less extreme physical conditions and easy work-up.[29]

## 2. SONOCHEMISTRY

### 2.1. Background:

Sonochemistry is known as the application of ultrasound energy to chemical reactions and processes, this energy induces chemical effects in the reaction and thus forming free radicals that accelerates chemical reactions.[30] Application of ultrasound also results in mechanical effects such as the increase of the surface area between reactants, accelerating dissolution as well as renewing the surface of a solid reactant or catalyst.[31] The effect of ultrasound energy in chemical reactions was discovered as far back as 1880 when the piezoelectric effect and it its inverse was discovered by Jacques Curie and Pierre Curie. The Curie brothers showed that some crystals such as quartz generate electrical polarization as a result of the application of mechanical energy. The first application of ultrasound was first reported in 1917 by Langevin when he was checking the depth of water using his echo-sounding technique. Chemical reactions induced by mechanical and chemical effects of ultrasound were reported as far back as 1945 due to the increased understanding of the phenomenon of cavitation.[32],[33] This field of study involving cavitation has gained much interest in recent years and has found application in the field of science including medicine, chemistry and biochemistry.

### 2.2. Ultrasound frequencies ranging:

Ultrasounds forms part of the sonic spectrum ranging from 20 kHz to 10 MHz, which is greater than the limit of human hearing that ranges from 16 Hz - 16 kHz. Ultrasound frequency

ranges can be subdivided to two regions including conventional power ultrasound and diagnostic ultrasound. The former has frequencies ranging from 20 kHz - 100 kHz it affects chemical reactions in liquids and the latter has frequencies ranging from 1 MHz to 10 MHz and is used for physical measurements in medicine (including imaging of the fetus as well as subcutaneous surgical implements) and material processing.[32] In this study the focus is on how power ultrasound influences chemical reaction.

### 2.3. Power ultrasound:

Ultrasound application within this frequency range (20 kHz-100 kHz) is a result of acoustic cavitation.[34],[35] According to the literature review, Thorneycroft and Barnaby were the first, who accidentally discovered the cavitation theory in 1895. These two scientists noticed the poor speed performance of the screw driven destroyer, H.M.S. Daring, after they were called in to investigate its performance. They noticed the formation of microbubbles in water, then depicted this to be due to the rapid motion of the propeller blades, this motion produced enough negative pressure to break apart the water molecule, this phenomena is known as cavitation.[36]

### 2.4. Cavitation phenomena*:*

A cavitation bubble originates in an irradiated liquid and is associated with turbulent flow of liquid. The bubbles are formed as a result of the transfer of ultrasound energy (in an ultrasound probe or cleaning bath) to the reaction mixture; this energy is transformed from electrical to mechanical through a piezoelectric transducer. As the energy of sufficient intensity passes through a liquid, it exerts high negative pressure to the liquid. The exerted pressure is strong enough to break down the intermolecular van der Waals forces that hold the liquid together, leading to the formation of small cavities or gas-filled microbubbles.[37] The bubbles formed absorbs energy (energy which is delivered from the transducer to the liquid medium) and they grow yet at the later stages the microbubbles reach a point where they can no longer absorb the sufficient amount of energy. The bubbles therefore collapse in the absence of energy absorption, this process is known as cavitation. The collapsing bubbles creates high temperature and pressure conditions and results in the emission of light known as sonoluminescence.[32],[38] The high temperature and pressure conditions resulting from bubble breakdown are is known as 'local hot spots' with temperatures estimated to be between 4500 and 5000 K,[39] and pressure to

be around 1700 atm.[40],[41] These conditions, thus create turbulence and facilitates the mass transfer in the neighborhood.[37, 42]

### 2.5. Sources of ultrasound energy

For chemists to understand how chemical reactions proceed under ultrasound irradiation (how power ultrasound facilitates chemical reactions), they need to familiarize themselves with the type of ultrasound devices they use for their work. Research shows that it was only in 1945 that the electric circuitry or transducer devices were developed in order to convert electrical energy to mechanical energy. The source of ultrasound energy is a piezoelectric material such as quartz; this material is under high voltage alternating current with a frequency ranging from 15 kHz to 10 MHz. The two mostly used ultrasound laboratory devices are the (Figure 1 **A** and **C**), ultrasound cleaning bath and a probe system or a horn, both these devices are powered by a power amplifier. The former is the low intensity system, a liquid filled tank with multiple transducers bonded around walls and the latter does not depend on transfer of energy through the liquid vessel walls rather energy is transferred directly to the chemical reaction though a horn or velocity transformer. For the ultrasonic bath, the reaction vessel used is normally the conical flask or the round bottomed flask, this vessel is submerged such that the level of the liquid in the flask is just above that of water surface in the cleaning bath. Both the equipment's provide easy accessibility to the reaction media.

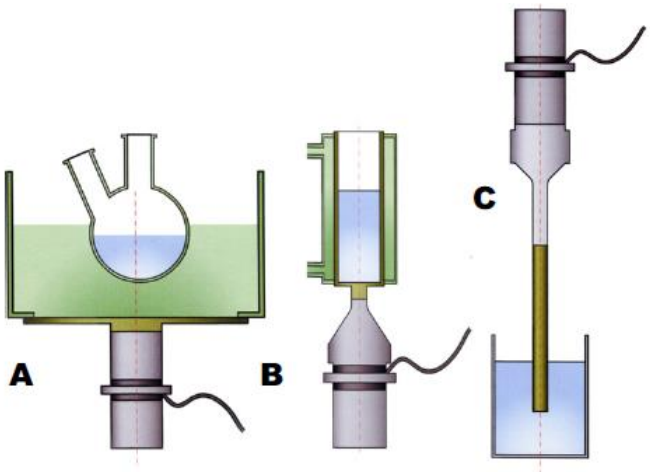
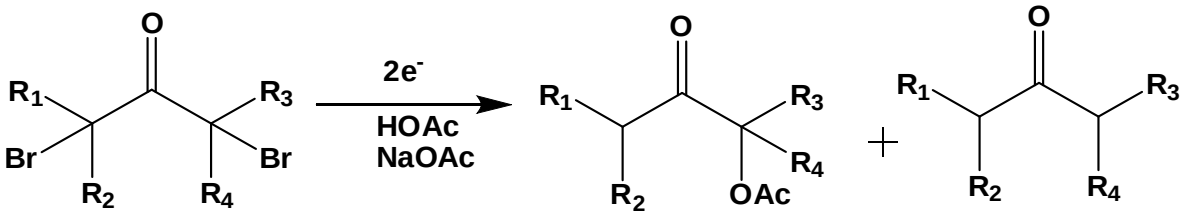



**Figure 1**: Schematized are the most commonly used ultrasonic devices (transducers) with high intensity ultrasound. (A) ultrasound cleaning bath, (B) Cup horn cavitating tube, (C) Immersion horn.[37]

## 2.6. Uses of ultrasound:

Sound navigation and ranging (SONAR) system is the best known use of ultrasound, it is used to determine the depth or distance of the target in surrounding medium such as water using reflected sound waves. This technique is mostly used to detect the depth of water in the sea. Recently ultrasound has also been used in many different fields of science including biology or biochemistry, engineering, dentistry, geography or geology, industrial, medicine and mostly in chemistry as it aids chemical reactions.

The first Sonochemistry application was with A.J Fry in 1978, [43] when he reduced α-α'-dibromoketones to α-acetoxyketones using the sonochemically dispersed mercury in acetic acid using ultrasonic cleaning bath (Scheme 1).[44]




**Scheme 1:** The reduction of α-α'-dibromoketones to α-acetoxyketones via ultrasound irradiation.[44]

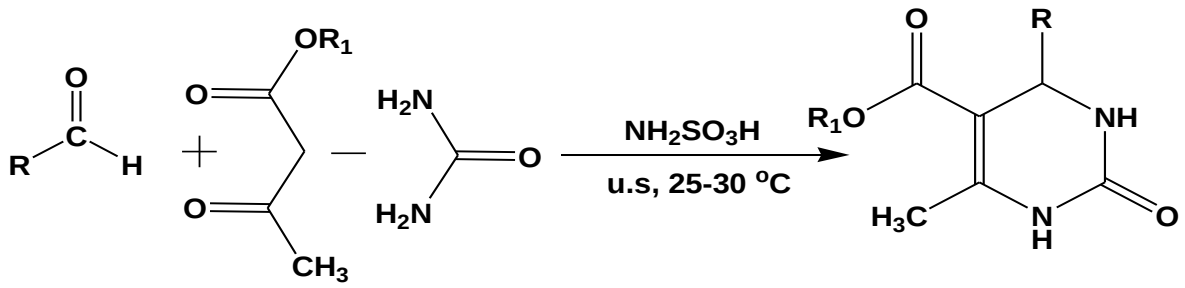
## 2.7. Organic synthesis with ultrasonication:

Ultrasound irradiation has gained recognition and found application in organic synthesis as it allows mass transfer and activates hard metal surfaces and imparts high energy in the reaction medium based on the phenomenon of acoustic cavitation.[45] Ultrasound irradiation has been widely accepted as a green chemistry tool that helps facilitate the carbon–carbon and Carbon–nitrogen bond formation in organic synthesis thus leading to the successful synthesis of a large number of highly complex organic compounds. These compounds are of great importance and are in great demand due to their medicinal and pharmacological properties. The advantages of ultrasound in chemical reactions, is that it reduces reaction times[46], produce higher yields,[47] reduces generation of waste[48] and uses green sound energy.[49] Sonochemistry has become an alternative method, almost replacing the reflux method, as it facilitate the rapid and facile synthesis of heterocyclic compounds.[46] Heterocyclic compounds have found application in wide variety of spectrums including pharmaceutical and biomedicinals fields. This is due to their possession of biological activities such as anti-inflammatory,[50] molluscicidal, insecticidal,

antitumor, and anticancer properties.[51] These compounds have contributed to the growth of the field of medicinal chemistry as they play a huge part in the design and discovery of new pharmacologically active compounds.[52],[53] According to researchers, organic reactions for the synthesis of heterocyclic compounds can be carried out under ultrasound irradiation achieving products in higher yields and in short reaction time. The following (Scheme 2-18) are catalysed and uncatalyzed reactions successfully carried out in ultrasound.

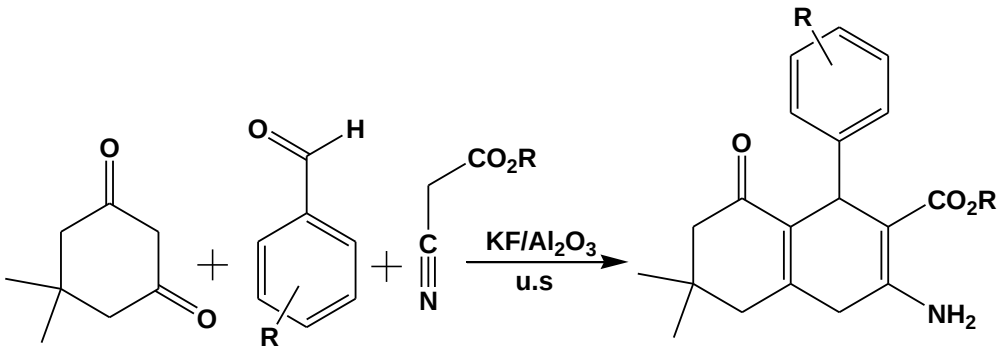
### *2.7.1. Catalysed organic synthesis under ultrasound irradiation*

Li et al. (2004) synthesised 3, 4-dihydropyrimidin-2-ones following Biginelli reaction (1983), the reaction was catalysed by sulfamic acid ($NH_2SO_3H$) in ethanol (Scheme 2), high yields were obtained (62-98%) in short reaction times (25-60 min). [54]



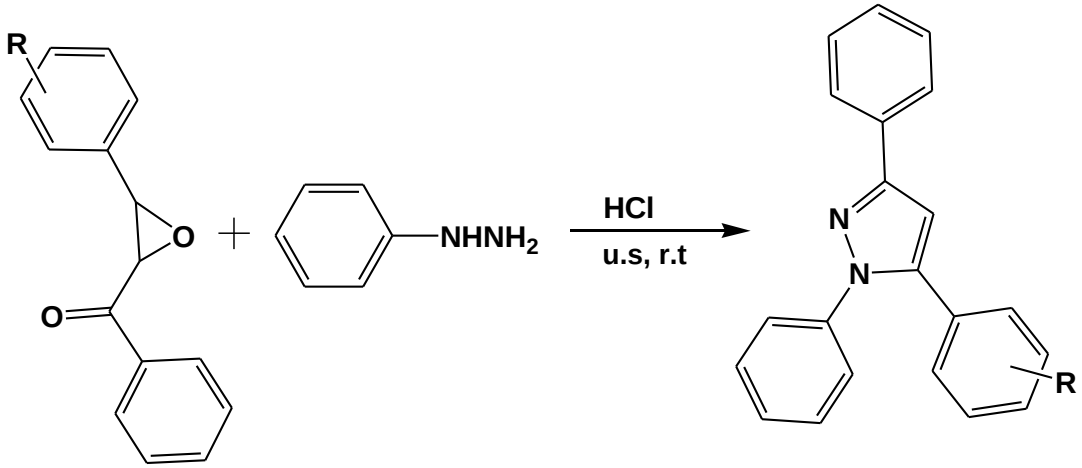

**Scheme 2**: Synthesis of 3,4-dihydropyrimidin-2-one derivatives.[54]

Li et al. (2004) described a three component reaction (3-CR) of aromatic aldehydes, cyanoacetic esters and 5,5-dimethyl-1,3-cyclohexanedione in the presence of KF/basic $Al_2O_3$ in ethanol to afford 4H-benzo[b]pyran derivatives (Scheme 3) in excellent yields (81-98%).[55]



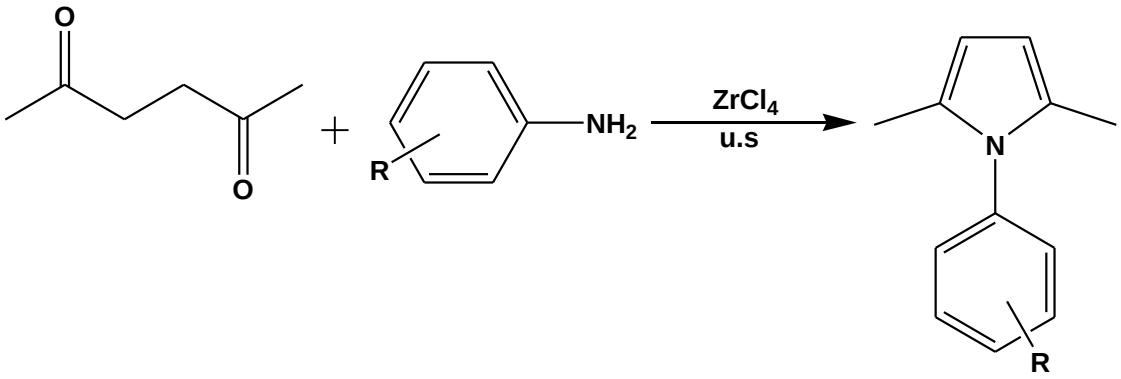

**Scheme 3**: Synthesis of 4H-benzo[b]pyran derivatives.[55]

Li et al (2010) also reported the synthesis of 5-aryl-1, 3-diphenylpyrazole via the reactions of 3-aryl-2,3-epoxy-1-phenyl-1-propanone with phenylhydrazine (Scheme 4). The reaction was carried out in high yields between (69–99%) at room temperature under ultrasound irradiation. This method provides several advantages such as operational simplicity, higher yields and environmental compatibility.[56]



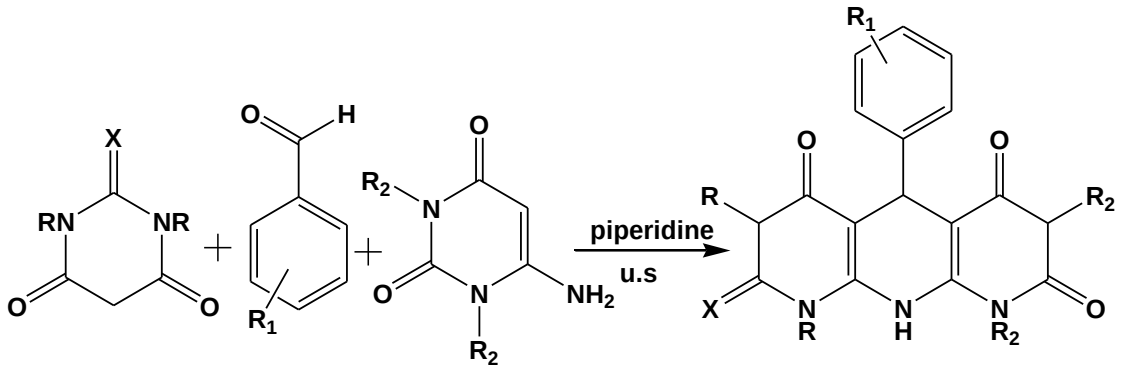

**Scheme 4**: Synthesis of 5-aryl-1,3-diphenylpyrazole.[56]

Zhang at al. (2008) reported the straight forward synthesis of substituted pyrroles using zirconium chloride-catalysed modified Paal-Knorr method under ultrasound irradiation (Scheme 5). The pyrroles were obtained in good to excellent yields (45- 95%) and in short reaction times.[57]



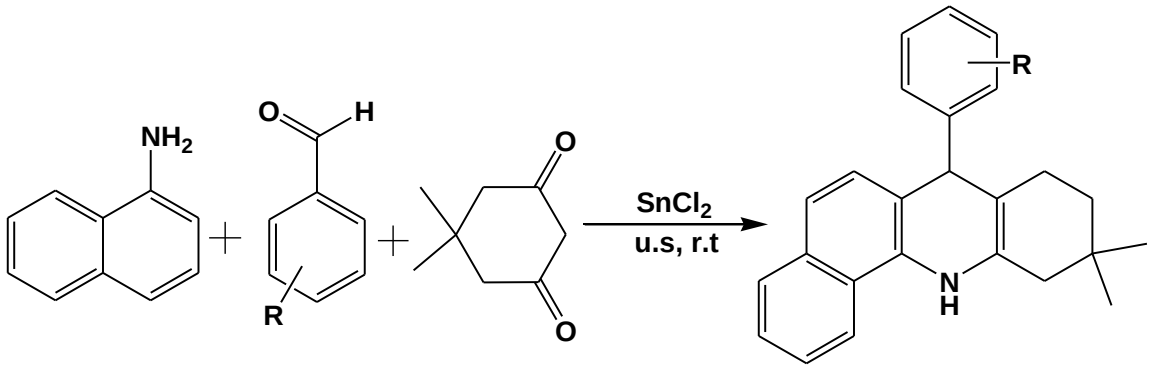

**Scheme 5**: Synthesis of substituted pyrroles.[57]

Mosslemin et al. (2010) reported a one-pot 3CR between enamine, barbituric acid and aromatic aldehydes in the presence of piperidine in water (Scheme 6). The reaction gave desired product (heterocyclic pyrimidines) in good yields (78-91%).[58]



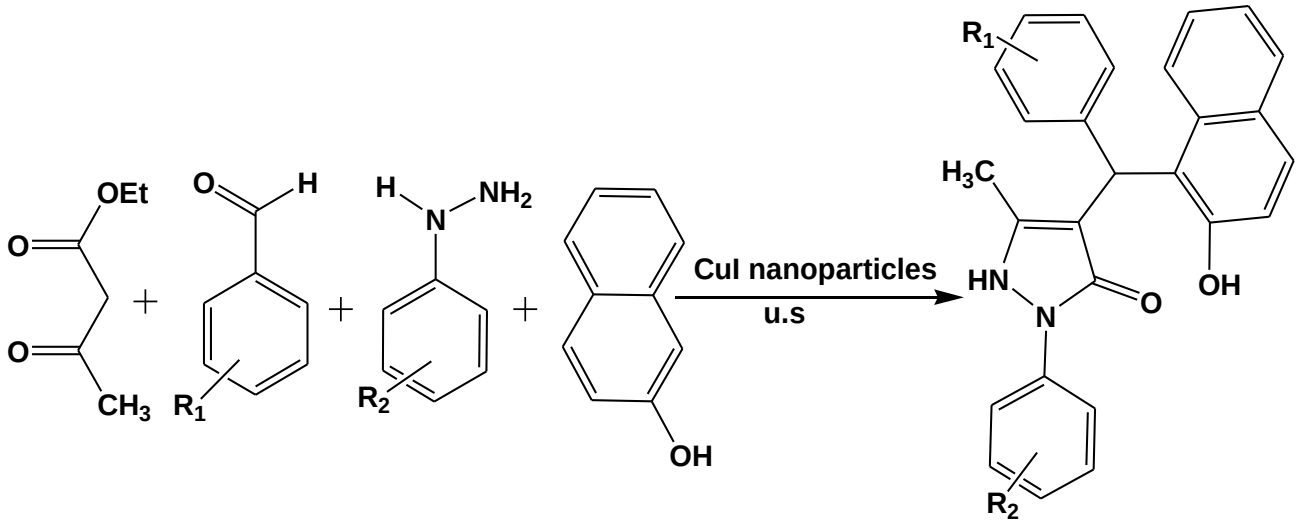

**Scheme 6**: Synthesis of heterocyclic pyrimidines.[58]

Zang et al. (2011) reported the reaction of dimedone with, 1-naphthylamine, aromatic aldehydes and 5,5 dimethycyclohexane-1,3-dione catalysed by stannous chloride ($SnCl_2$) to afford 7,10,11,12-tetrahydrobenzo[c]acridin-9*H*-one derivatives (Scheme 7). The reaction was carried out under ultrasound irradiation at 25-30 °C, to give products in good to excellent yields (83-97%) in short reaction time (1 hour).[59]



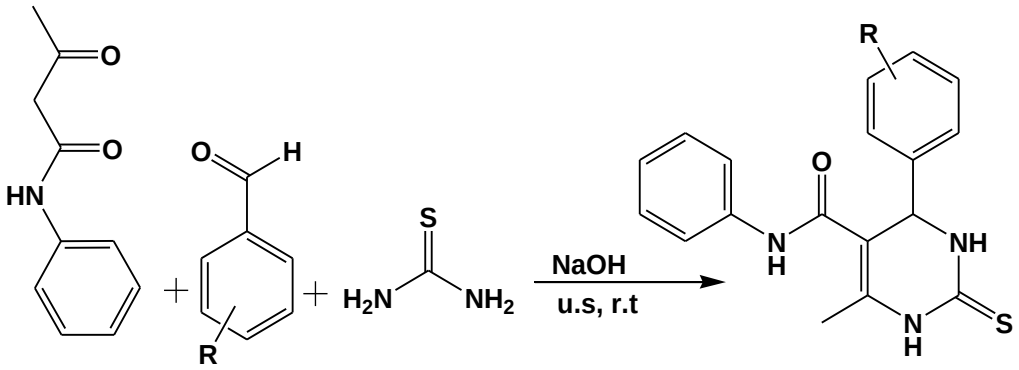

**Scheme 7**: Synthesis of 7,10,11,12-tetrahydrobenzo[c]acridin-9*H*-one derivatives under ultrasound irradiation.[59]

Ziarati et al. (2013) developed a green process to synthesize 2-aryl-5-methyl -2,3-dihydro-1*H*-3-pyrazolone derivatives catalysed by copper iodide (Scheme 8). The product was achieved in high yields (88-93%) in short reaction time (30-45 min) from the 4-CR of phenyl hydrazines, ethyl acetoacetate, aldehydes and β-naphthol in water under ultrasound irradiation.[60]




**Scheme 8**: Synthesis of pyrazolones in the presence of CuI nanoparticles under reflux and sonication conditions.[60]

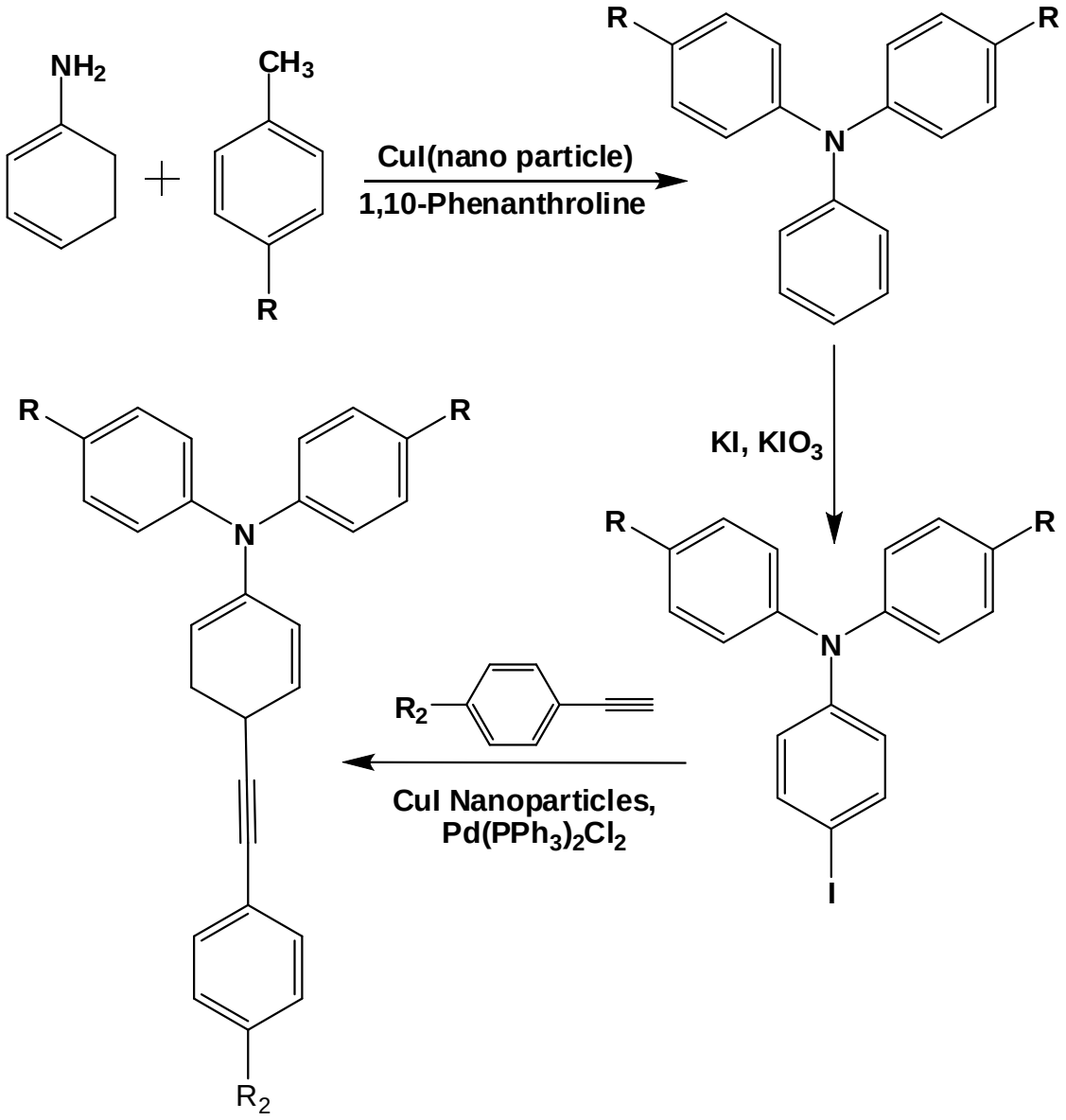
Pagadala et al. (2014) reported the synthesis of highly functionalized pyrimidine derivatives in excellent yields (85-98%) in the presence of sodium hydroxide at room temperature (Scheme 9). Pyrimidine derivatives were synthesized from reaction of aromatic aldehydes, thiourea and acetoacetanilide in water as solvent in shorter reaction times (1.5 - 2.0 hours).[61]




**Scheme 9**: Synthesis of highly functionalized pyrimidine derivatives under ultrasound irradiation.[61]

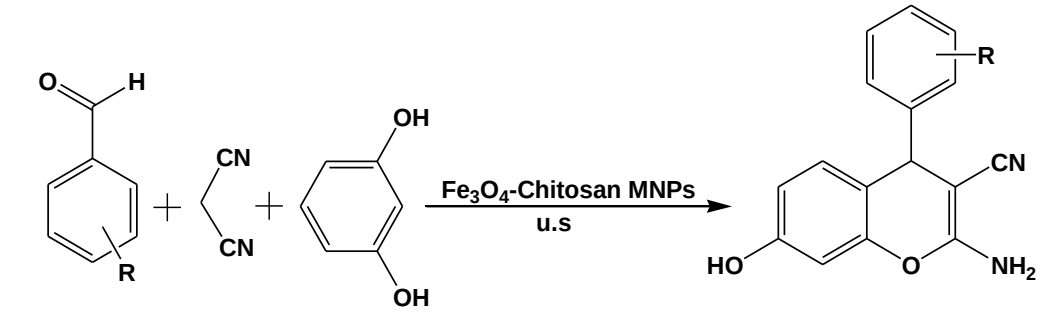
Due to the advantages that ultrasound irradiation holds, it has been applied together with nanotechnology. Both these techniques were used for the synthesis of aryl ethyl linked triarylamine, reported in 2014 by Safaei-Ghomi et al. The reaction was carried out following the

Sonogashira coupling using CuI nanoparticles and Pd $(PPh_3)_2Cl_2$ as a highly efficient catalytic system under ultrasound irradiation (Scheme 10).[62]




**Scheme 10**: Synthesis of arylethylnyl linked triaryl amine.[62]

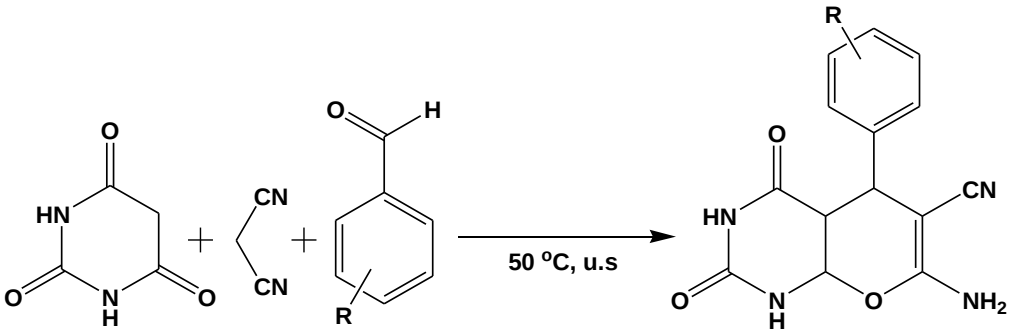
Safari et al. (2015) reported the synthesis of 2-amino-4*H*-chromenes derivatives following the condensation of aromatic aldehyde with malononitrile and resorcinol using chitosan as a magnetic catalyst under ultrasound irradiation (Scheme 11). This reaction produced products is in excellent yields (92-98%) in short reaction times (1-2.5hrs).[63]




**Scheme 11**: One-pot synthesis of 2-amino-4H-chromenes catalysed by $Fe_3O_4$-chitosan nanoparticles under ultrasound irradiation at 50 °C.[63]

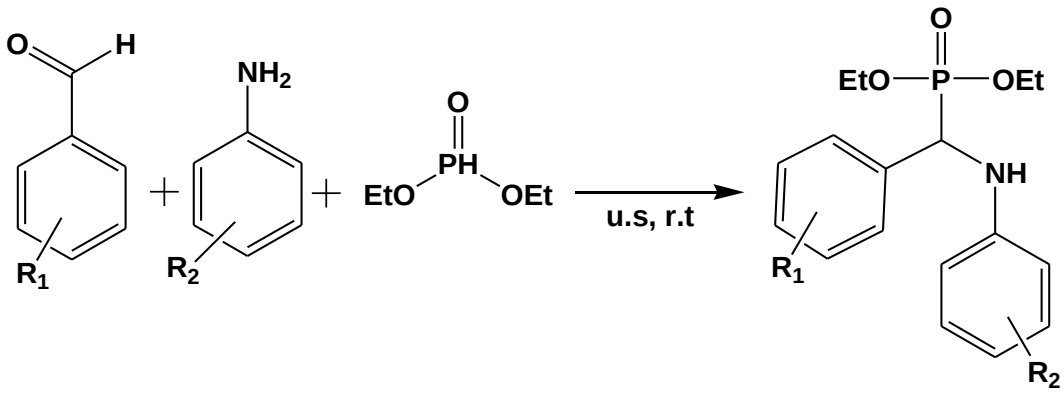
### *2.7.2. Catalyst-free organic synthesis reactions under ultrasound irradiation*

Jin et al. (2005) reported the catalyst-free synthesis of 7-amino-5-aryl-6-cyano-1,5-dihydro-2*H*-pyrano[2,3-d]pyrimidine-2,4(3*H*)-diones (Scheme 12), via a three-component reaction of aromatic aldehydes, malononitrile and barbituric acid using water as a green solvent under ultrasound irradiation to achieve good yields (62-87%).[64]



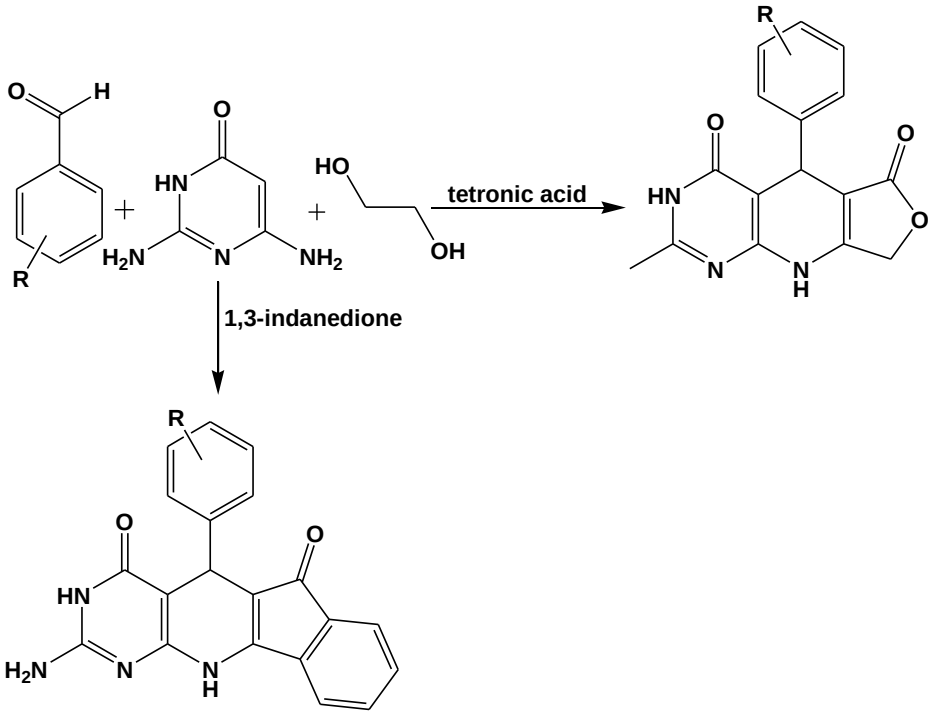

**Scheme 12**: Synthesis of 7-amino-5-aryl-6-cyano-1,5-dihydro-2*H*-pyrano[2,3-d]pyrimidine-2,4(3*H*)-diones under ultrasound irradiation.[64]

Xia et al. (2007) synthesized amino phosphonates from a 3-CR of aromatic aldehydes, amines, diethylphosphite in good yields (61-92%). Reactions proceeded without catalyst application and without the use of a solvent (Scheme 13).[65]



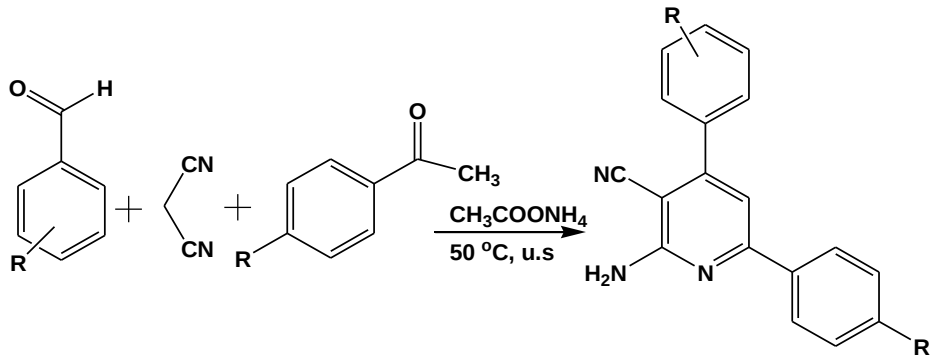

**Scheme 13**: A three-component reaction for the synthesis of amino phosphonates under ultrasound irradiation.[65]

Tu et al. (2008) successfully synthesized a series of pyrido-[2,3-d]-pyrimidine derivatives and related compounds (Scheme 14), the reaction follows the condensation of an aldehyde, 2,6-diaminopyrimidine-4(3*H*)-one and 1,3-indanedione, reaction occurred without the use of a catalyst and gave high yields (90-95%) under ultrasound irradiation.[66]



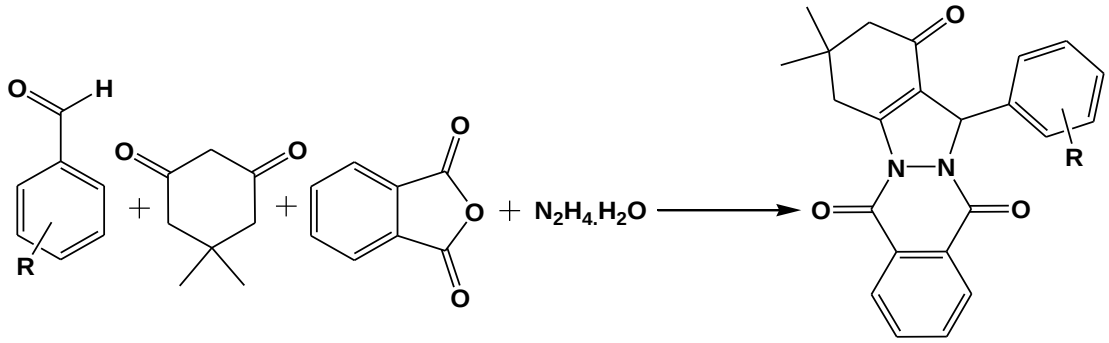

**Scheme 14**: Synthesis of pyrido [2,3-d]pyrimidine derivatives and related compounds.[66]

Safari et al. (2012) synthesised 2-amino-4,6-diphenylnicotinonitriles in water under ultrasound via a four-component reaction of malononitrile, aromatic aldehydes, acetophenone derivatives and ammonium acetate (Scheme 15). The product was achieved in good to excellent yields (75-99%) in short reaction times (5-30 min).[67]




**Scheme 15**: Synthesis of 2-amino-4,6-diphenylnicotinonitriles in water under ultrasound irradiation.[67]

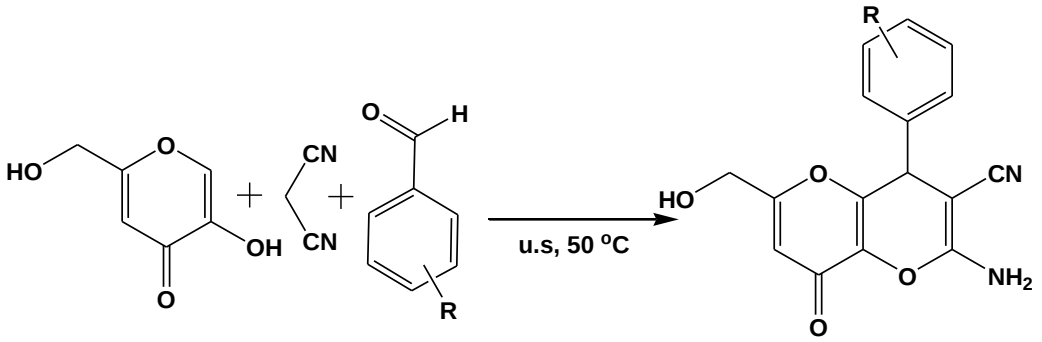
Shekouhy et al. (2012) reported a catalyst-free one-pot four component synthesis of 2*H*-indazolo [2,1-b]phthalazinetriones with the use of ultrasound irradiation (Scheme 16). The one-pot reaction was between dimedone, benzaldehyde, hydrazinium hydroxide and phthalic anhydride. The product was achieved in high yields (89-95%).[68]




**Scheme 16**: One-pot four component synthesis of 2*H*-indazolo [2,1-b]phthalazinetriones.[68]

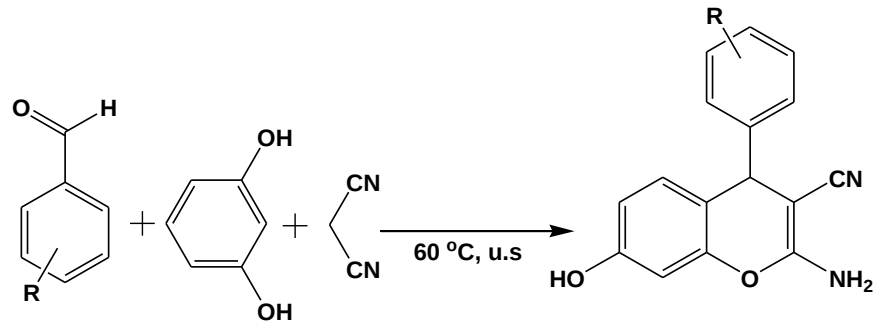
Sonochemical reaction that led to the formation of 2-amino-4,8-dihydropyrano-[3,2-b]- pyran-3-carbonitrile (Scheme 17), following a three-component reaction kojic acid, malononitrile and substituted aromatic aldehydes was reported by Banitaba et al.(2013). This reaction also accounts

for the green chemistry principle which is the use of safer solvents, the use of water as the reaction media. [37]



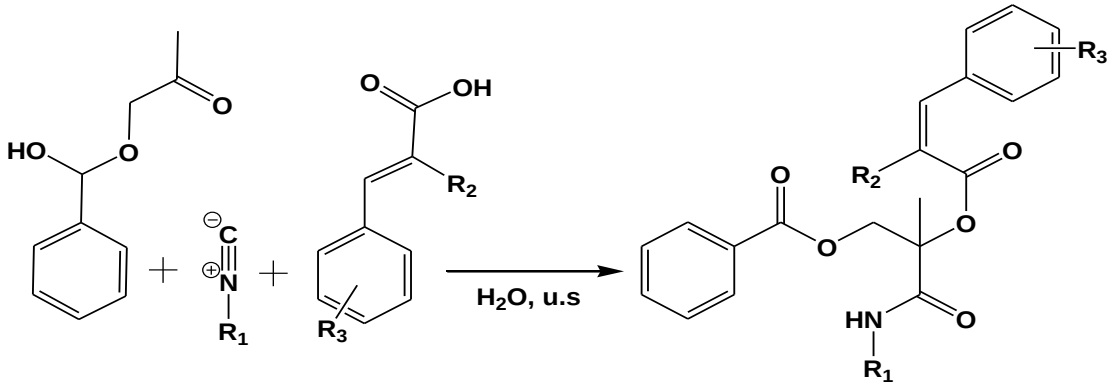

**Scheme 17**:Synthesis of 2-amino-4,8-dihydropyrano-[3,2-b]- pyran-3-carbonitriles.[37]

Safari et al. (2014) successfully synthesised 2-amino-7-hydroxy-4*H*-chromene derivatives under ultrasound irradiation (Scheme 18), various aldehydes (which include acyclic, aromatic and hetero-aromatic) were used as one of the reagents to achieve excellent yields (91-98%) in short reaction tine (1-2.5 hours).[69]




**Scheme 18**: Synthesis of 2-amino-7-hydroxy-4*H*-chromenes under ultrasound irradiation.[69]

Ramazani et al. (2016) developed a clean and efficient approach for the synthesis of propanamide derivatives (Scheme 19). The product was obtained from a 3-CR of an isocyanide (tert-butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide), carboxylic acids (cinnamic acid and aromatic carboxylic acid) and 2-oxopropyl benzoate in water without catalyst application. High yields (87-93%) were obtained in short reaction times (1hr).[70]




**Scheme 19**: Synthesis of highly substituted propanamide derivatives.[70]

## 3. MULTICOMPONENT REACTIONS (MCRs)

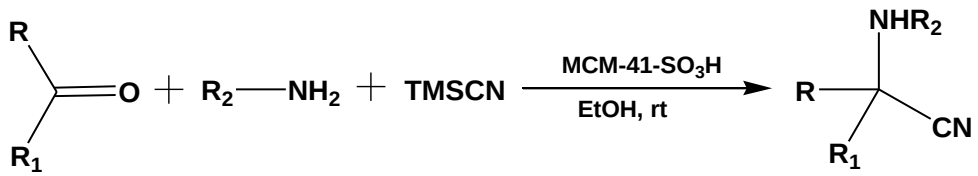
### 3.1. Background

Synthetic chemistry researchers are concerned about the inefficiency of the conventional multistep synthesis that is usually followed in the synthesis of complex molecules possessing wanted properties. The draw backs of these multistep synthetic methods involve larger number of synthetic operations such as extraction and purification steps involved in each individual reaction step. These steps are time consuming, high amount of energy is consumed, waste is produced from each reaction step and product is lost in the process thus leading to overall chemical yield being low.[71],[72] As chemistry research focuses on becoming more and more green and sustainable so as to avoid the harm from coming to humans and the environment, researchers all over the world have been working hard so as to contribute to the overall improvement of the chemistry research through green chemistry.[49] The continued research has therefore lead to the recognition and use of ancient method of synthesis which has been around for 150 years.[73] The recently discovered method of synthesis is known as the multicomponent reactions (MCRs) method, and has found application in organic synthesis. It is the process where three or more starting materials react together in one reaction vessel to produce one single pure product in high yields.[74],[75] This process is sometimes referred to as the one-pot (one reaction vessel) multicomponent reaction, as it allows all the reactants, catalyst and reagents to be added at the same time thus allowing them to react in a unique manner but under the same conditions.[76] In MCRs a single product is obtained that have all the atoms of the of the reactants

trapped in the final product, thus allowing the formation of more than two new bonds in one operation[77], this thus makes MCRs to be high atomic economic[78], convergent and suitable to generate highly complex molecules.[79],[80] MCRs have gained much interest since the emerging of green chemistry as it produces products with diverse functional groups thus allowing access to numerous libraries of complex organic compounds (with MCRs for instance using a four component reaction (4-CR) and only hundred starting materials for each component a library of $10^8$ products can be produced thus exceeding the size of all existing compound libraries).[81],[82],[83],[84],[85] MCRs are not only efficient in step reduction but they also reduce waste produced in a chemical process as the only known by- product of these reactions is water[86] and the starting material used are commercially available or they are easy to prepare.

### *3.1.1. Strecker reaction:*

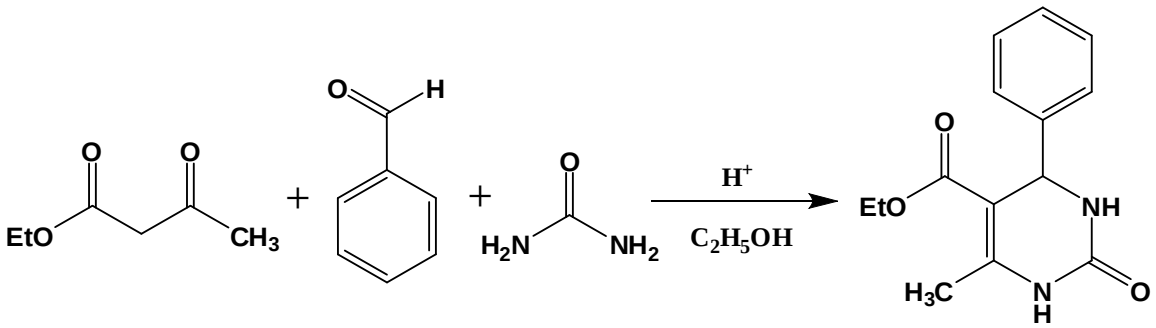
The oldest known multicomponent reaction was reported in 1850, it is known as the Strecker reaction for the synthesis of α-amino acids. The Strecker reaction comprises of the condensation of an aldehyde, ammonia and a cyanide source followed by the hydrolysis of the resulting α-amino nitrile (Scheme 20).[87] The resulting α-amino acids have found application in pharmaceutical industries, they have significant wide spread use in the field of chemistry and biology as they are precursors for the synthesis of proteins and also chiral building blocks.




**Scheme 20**: Strecker reaction of carbonyl compounds and amines with TMSCN (trimethylsilyl cyanide) catalyzed by MCM (mesoporous materials)-41-$SO_3H$.[87]

### *3.1.2. The Biginelli reaction:*

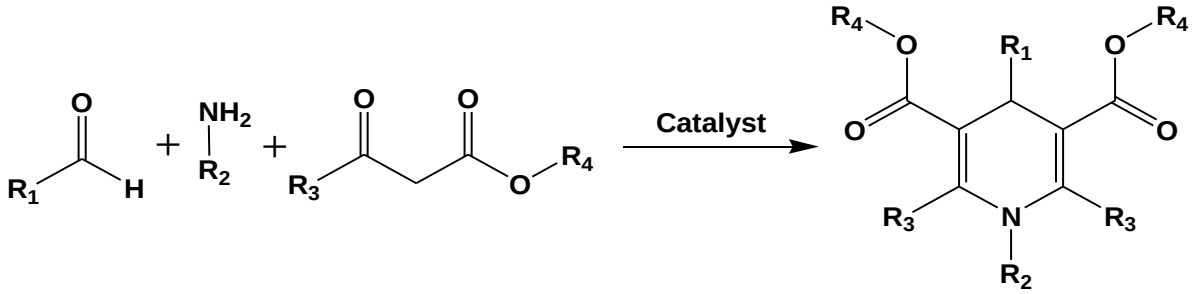
The Biginelli reaction was named by italian chemist Pietro in 1891, the reaction of an aldehyde, ethylacetoacetate and urea gave 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme 21).[77]




**Scheme 21**: General scheme for Biginelli reaction.[77]

### *3.1.3. Hantzsch reaction:*

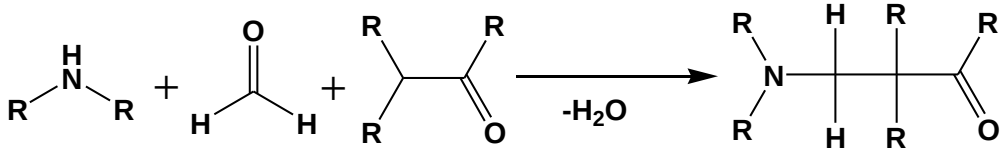
A non-isocyanide based multicomponent reaction of an aldehyde (formaldehyde), ethylacetoacetate (a β-keto ester) and ammonium acetate (a nitrogen donor) to form dihydropyridine which oxidises to form pyridine (Scheme 22), this reaction which was reported in 1881 by Arthur Rudolf Hantzsch is called the Hantzsch pyridine reaction.[88],[89] This reaction is also used for the synthesis of anti-inflammatory drugs.




**Scheme 22**: General scheme for Hantzsch reaction.[88],[89]

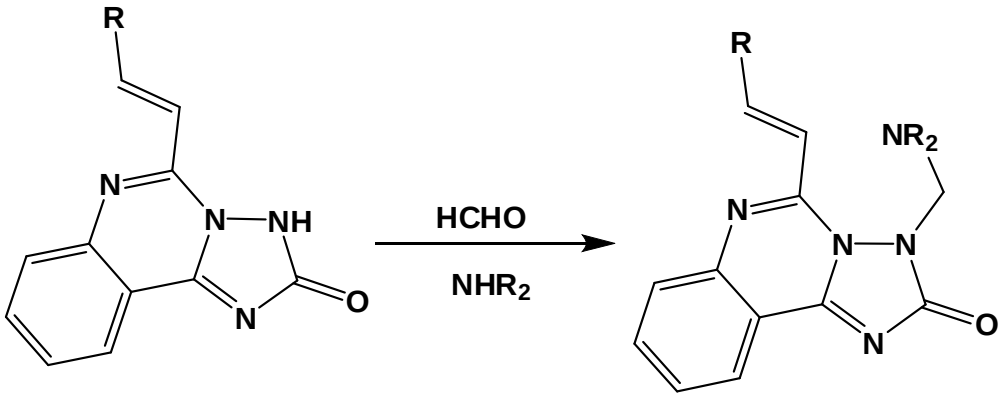
### *3.1.4. Mannich reaction:*

Mannich involves a carbonyl functional group, a formaldehyde and ammonia with a primary or secondary amine to form a β-amino carbonyl compound known as the Mannich base (Scheme 23). The Mannich reaction was discovered by Carl Mannich in 1912.[90]




**Scheme 23**: General scheme for the Mannich reaction.[90]

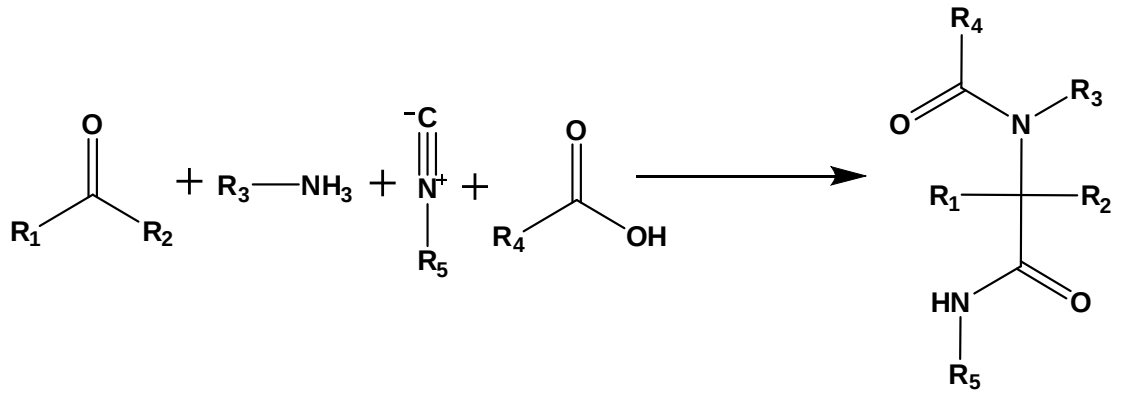
Using the Mannich reaction method the synthesis of a series of novel substituted [1,2,4] triazolo[1,5-c]-quinazolinone derivatives has been reported by Meenu Chaudhary et al (Scheme 24). Quinazolinone is a compound made up of two fused six membered simple aromatic rings-benzene and pyrimidine ring and it possess versatile type of biological activities such as anticancer, anticonvulsant, anti-inflammatory, antihelminthic, antimicrobial activities.[91] The compound was synthesized by mannich reaction using formaldehyde and different secondary amines.




**Scheme 24**: Synthesis of substituted quinazolinone derivatives.[92]

### *3.1.5. Ugi reaction:*

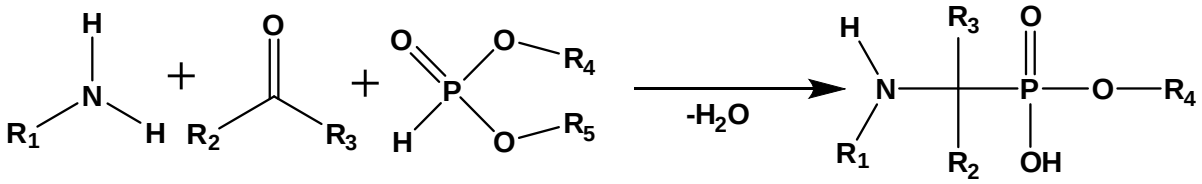
The Ugi reaction is an isocynide based multi-component reaction (IMCRs), which allows access to peptide-like structures. The Ugi reaction is carried out in polar protic solvents, where a ketone or aldehyde, an amine, an isocyanide and a carboxylic acid reacts together to form a bis-amide (Scheme 25). The Ugi reaction takes a few minutes to complete, this is because of the exothermic nature that it possesses. The reaction was named after Ivar Karl Ugi in 1959.[93] Three-component and four-component reactions (3-CR and 4-CR) are possible with Ugi arrangement.



**Scheme 25**: General scheme for 4-component Ugi reaction.[93]

### *3.1.6. Kabachanik reaction:*

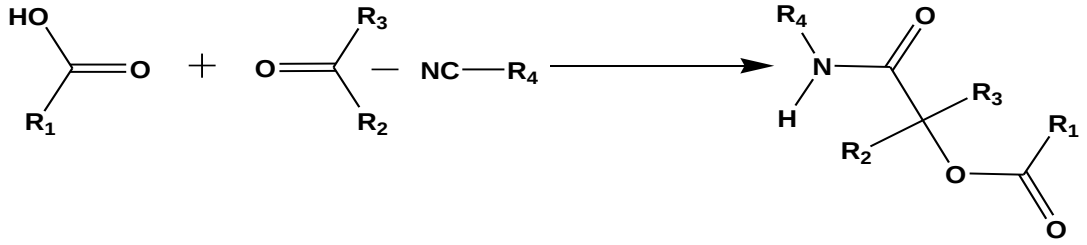
Kabachanik reaction is a multicomponent reaction between an amine, a carbonyl compound and dialkyl phosphonate to form α-amino phosphonate (Scheme 26).[94] This reaction was discovered by Martin Izrailevich Kabachnik and Ellis K. Fields in 1952 and is used in the synthesis of anti-inflammatory drugs.



**Scheme 26**: General scheme for the Kabachnik-Fields reaction.[94]

### *3.1.7. Passerini reaction:*

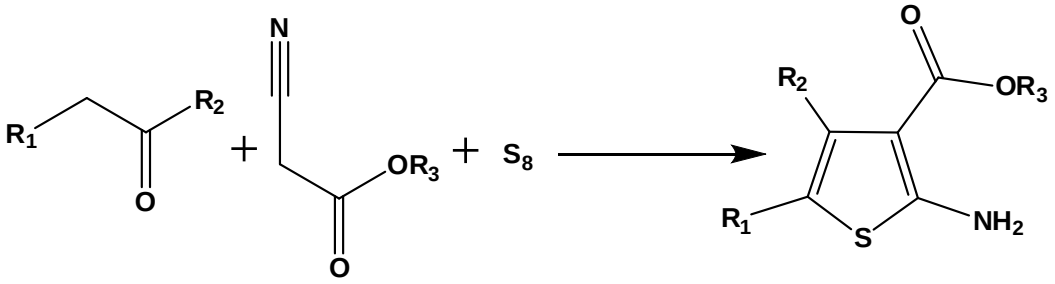
Passerini reaction is the first (IMCRs) to be reported, it was discovered in 1921 by an organic chemist named Mario Passerini. This is the three-component reaction carried out with high concentration of starting materials and with using aprotic solvents, it is the first MCR that lead to the formation of α-acyloxy amide.[95] The reaction involves an aldehyde or acetone, an isocyanide and a carboxylic acid (Scheme 27).




**Scheme 27**: General scheme for Passerini reaction.[96],[86]

### *3.1.8. Gewald reaction:*

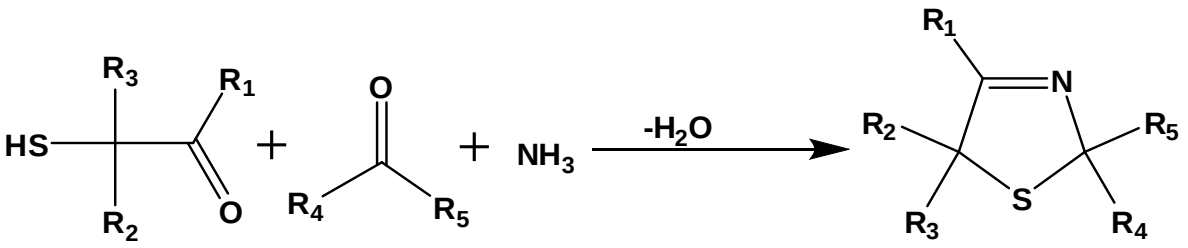
In 1966 a German chemist, Karl Gewald discovered the reaction that lead to the formation of 2-aminothiophenes called the Gewald reaction.[97] Gewald reaction involves the condensation of an aldehyde or ketone, α-cyanoester in the presence of elemental sulfur and a base to afford a poly-substitituted 2-amino-thiophene. Following this reaction multi-substituted 2-aminothiophenes were successfully synthesized, these compounds are used to produce bioactive drugs that are useful in pharmaceutical industry. (Scheme 28). [98] Gewald reaction was used to synthesize anti-inflammatory drugs, such as acetone-1-(2-amino-5-isopropyl-thiophene-3-carbinitrile derivatives, thieno-[2,3-d]-pyrimidine derivatives, 5-ethyl-2-amino-3-pyrazolyl-4-methylthiophenecarboxylate and 2-thioxo-$N_3$-aminothieno-[2,3-d]-pyrimidines.




**Scheme 28**: synthesis of multisubstituted 2-aminothiophenes.[99],[100]

### *3.1.9. Asinger reaction:*

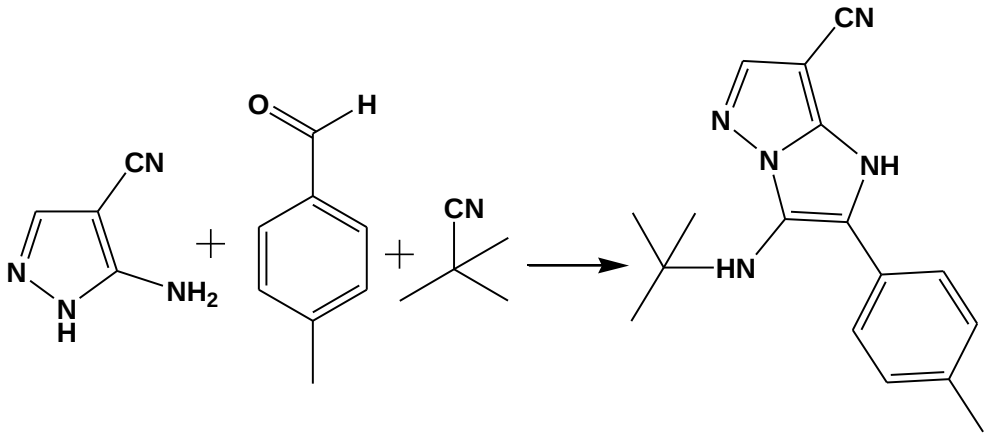
The reaction to the formation of 3-thiazolines was therefore named Asinger reaction after Friedrich Asinger. Asinger, an industrial organic chemist discovered the reaction for the synthesis of 3-thiazolines in 1957, his work was only published in 1958. The 3-thiazolines were formed from a monothiolation in the position to the keto group and subsequent α-amino alkylation followed by ring closure with elimination of water (Scheme 29).[101] Asinger and his team also confirmed that the derivatives of 3-thiazolines are possible.




**Scheme 29**: Asinger reaction.[101]

### *3.1.10. Groebke-Blackburn-Bienaymre (GBB) reaction:*

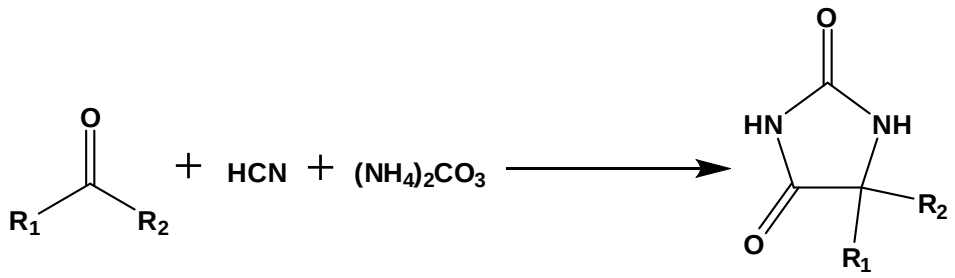
Groebke (from Switzerland), Christopher Blackburn (Cambridge in USA), and Hugues Bienayme (from France) they all independently disclosed the (GBB) reaction for the first time in 1998. GBB reaction involves an aldehyde reacting with aminoazine and an isonitrile in the presence of a suitable catalyst (generally a Lewis acid or Bronsted acid), this produces a highly substituted and fused imidazole derivative (Scheme 30). The GBB reaction is classified as a four-center, three component reaction and has found application in the drug discovery research industries.[102],[103]




**Scheme 30**: Synthesis of Imidazo[1,2-b]pyrazoles via GBB reaction.[104]

### *3.1.11. Bucherer-Bergs reaction:*

In 1934 Bucherer and Bergs discovered a method for the synthesis of hydantoins, their method involved a one-pot procedure, where the reacting compounds were hydrogen cyanide, aldehydes or ketones, ammonia and carbon dioxide, the product formed could be easily transformed following hydrolysis to form α-amino acids (Scheme 31).[105]




**Scheme 31**: Bucherer-Bergs multicomponent synthesis of hydantoins.[105]

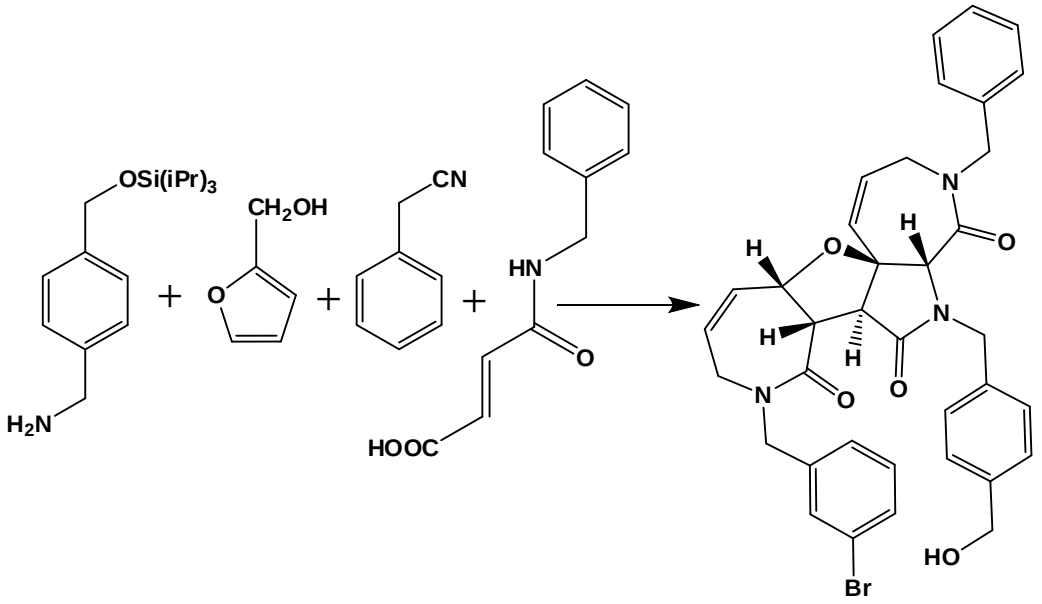
### 3.2. Classes of MCRs

MCRs can be classified into two classes namely isocyanide based (IMCRs) and non-isocyanide reactions, the former are more diverse compared to the latter. Non-isocyanide MCRs involves the reaction of an activated carbonyl species, examples of such reactions are Hantzsch and Biginelli reactions. IMCRs are now popular in combinatorial chemistry as a results of their versatility, allowing access to a number of complex organic compounds[76] and also because of the interesting chemistry of the isocyanide, that it is both nucleophilic($C^-$) and electrophilic ($N^+$).[106] Over two decades ago the field of IMCRs has been growing in line with the discovery and development of classical Passerini and Ugi reactions, the two well know and mostly used isocyanide based reactions. The first reaction was described by Mario Passerini in 1921, which was in turn named after him, this reaction was carried out using high concentration of starting materials and also using aprotic solvents.[95] The second known IMCR is that reported by Ivar Ugi in 1959, see scheme 26, this type of reaction allows access to peptide-like structures and is carried out in polar protic solvents.[86] MCRs have been mostly utilized as method of synthesis in the field of medicinal chemistry,[107] drug discovery programmes, combinatorial chemistry, natural product synthesis, agrochemistry as well as polymer chemistry. Advantages of using this method of MCRs are that it is selective (chemo- and region- selective),[71] and minimizes waste production as the isolation steps does not make use of extensive amounts of chromatographic solvents.[108]

### 3.3. Application of MCRs:

MCRs gained recognition in the early 1990s the same time academia was working on establishing high through-put screening facilities through related library synthesis as the field of combinatorial chemistry became advent during that time.[109] Thus natural products were

considered to be rich source of drug candidates,[110] but the traditional classical synthetic methods for these molecules were too long and too expensive. But the emergence of green chemistry opened the eyes of researchers to an already existing alternative solution to this problem which the use MCRs,[111] they discovered that it they can use MCRs to synthesize these natural products or use them to generate artificial natural-product-like molecules.[112] Example of this taken from Daesung et al.,[113] they reported on the use of complexity-generating reactions in diversity-oriented organic synthesis of natural product like molecules (Scheme 32).

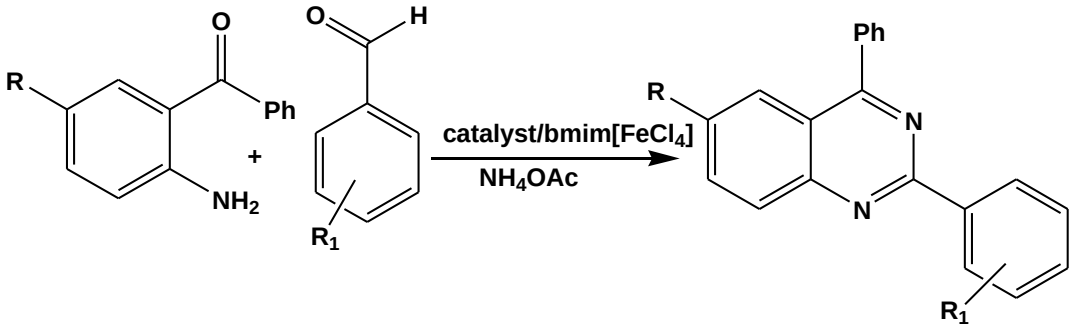



**Scheme 32**: Diversity generating synthesis scheme using MCR and building a natural product-like molecules.[113]

The continuous search for MCRs products as biological drug candidates has resulted to a need for catalyst application. A variety of catalyzed MCRs have been reported in literature, showing the successful application of acid, base, heterogeneous and homogenous catalyst.

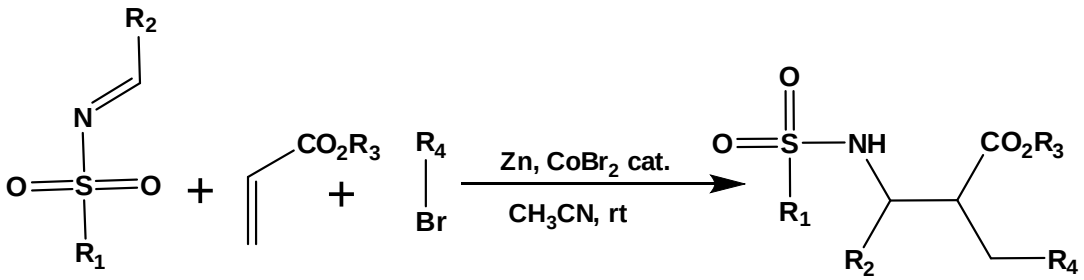
### *3.3.1. Catalyzed multicomponent reactions:*

Panja and Saha., (2013) reported a solvent-free synthesis of highly functionalized quinazoline derivatives from the one-pot reaction of 2-aminobenzophenone, aromatic aldehydes and ammonium acetate. This reaction was the first successful application of magnetic ionic liquid, butylmethylimidazolium tetrachloroferrate (bmim [$FeCl_4$] as the catalyst, achieving high yields (65-95%) (Scheme 33).[114]



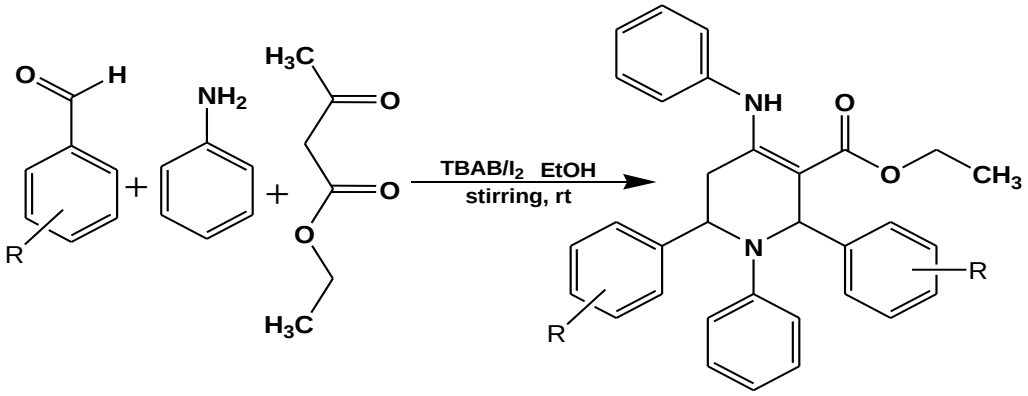

**Scheme 33**: Synthesis of highly functionalized quinazoline derivatives.[114]

Erwan et al. (2014) reported a MCR involving zinc mediated, cobalt catalyzed 3-CR between sulfonylimines, acrylates and organic bromides (Scheme 34). This is also an example of a Mannich reaction and it offers efficient synthetic route to a variety of β-aminocarbonyl compounds.[115]



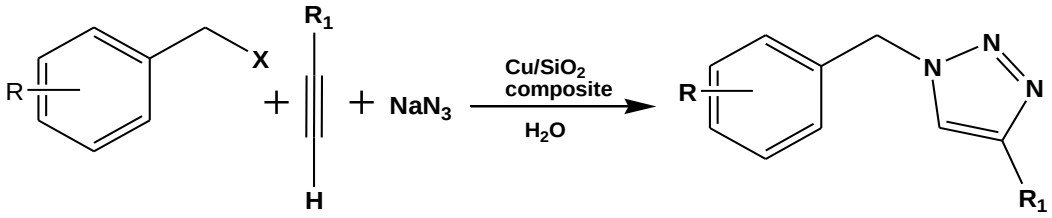

**Scheme 34**: Multicomponent approach to the synthesis of N-Sulfonyl $\beta^{2,3}$-amino esters.[115]

Chinnaraja and Rajalakshmi, (2014) reported the synthesis of tetrahydropyridines by a multicomponent reaction of ethyl acetoacetate, aromatic aldehydes and aliphatic/aromatic amine in the presence catalytic amount of tetrabutyl/ammonium bromide and iodine (Scheme 35). The reaction proceeded via Mannich type reaction.[116]



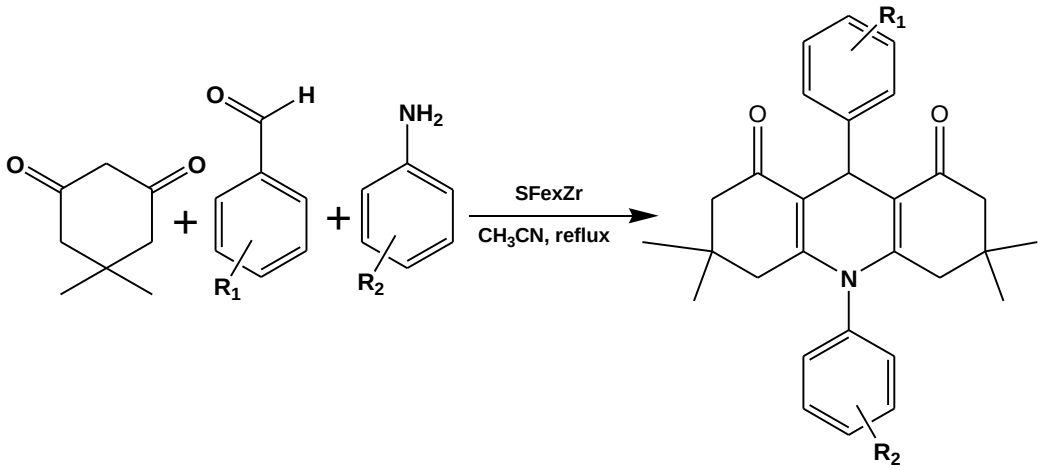

**Scheme 35**: Multicomponent synthesis of tetrahydropyridines.[116]

Radatz et al. (2014) reported an eco-friendly multicomponent reaction for the synthesis of 1, 2,3-triazoles using a recyclable $Cu/SiO_2$ catalyst (Scheme 36). The reaction proceeded by mixing benzyl halide, sodium azide, alkyne and the catalyst in an aqueous medium, and it produced high yields of product. The catalyst used in reaction showed efficiency in that it is easily recoverable, recyclable and therefore waste is avoided. This reaction also display how the use of microwave irradiation is good when substituting for conventional heating, in terms of affording high yields (69-79%) and reducing reaction time.[117]



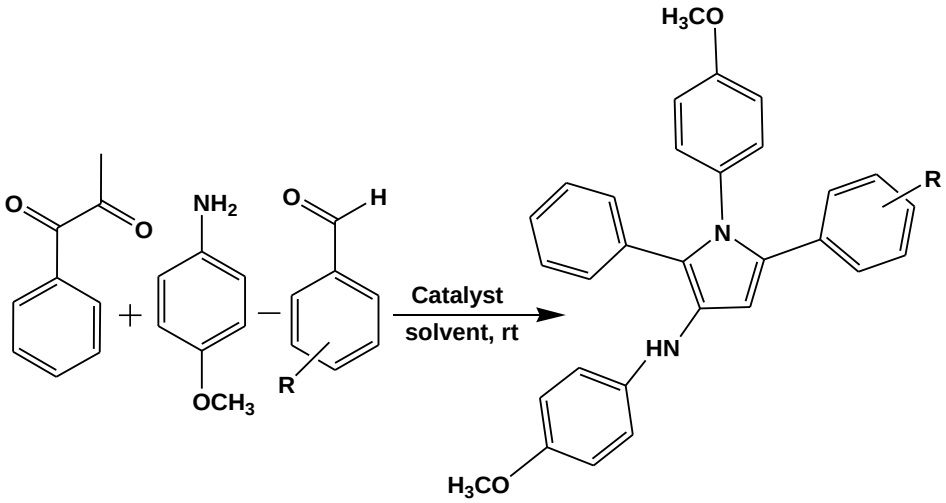

**Scheme 36**: Eco-friendly multicomponent reaction for the synthesis of 1,2,3-triazoles using a recyclable $Cu/SiO_2$.[118]

Pradhan and Mishra (2015) reported the synthesis of a series of 1,8-dioxo-decahydroacridines (Scheme 37) following multicomponent condensation of dimedome, substituted aryl aldehydes and substituted anilines using sulfated zirconia, with products obtained in high yields (80-90%) and purity.[119]




**Scheme 37**: Multicomponent synthesis of a series of 1,8-dioxo-decahydroacridines.[119]

Zheng et al. (2015) developed an organocatalyzed 3-CR of 1,2-diones, aldehydes and arylamines to afford polysubstituted pyrroles (Scheme 38).[120] The reaction was catalyzed by 4-methylbenzenesulfonic acid monohydrate ($TsOH.H_2O$) and acceptable to good yield (up to 80%) were obtained under mild reaction conditions.



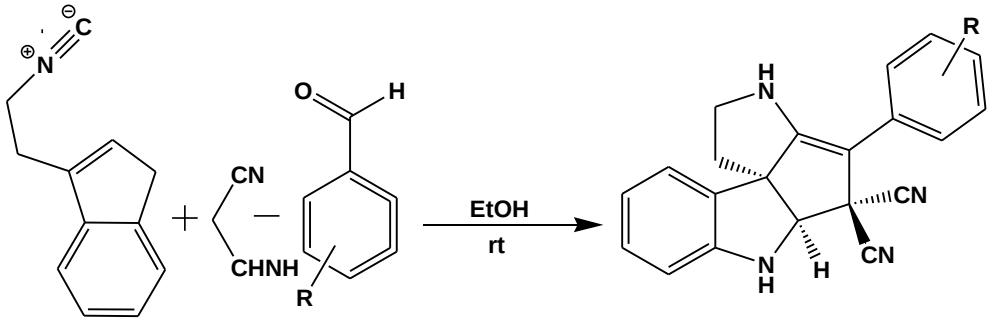

**Scheme 38**: Synthesis of polysubstituted pyrroles.[120]

### *3.3.2. Catalyst-free Multicomponent Reactions:*

As research on MCRs grew further, researchers learnt that it also possible to carry out one-pot synthesis without catalyst application. What encouraged this research on catalyst-free synthesis was that the catalyst used are either expensive, difficult to separate and add the amount of waste

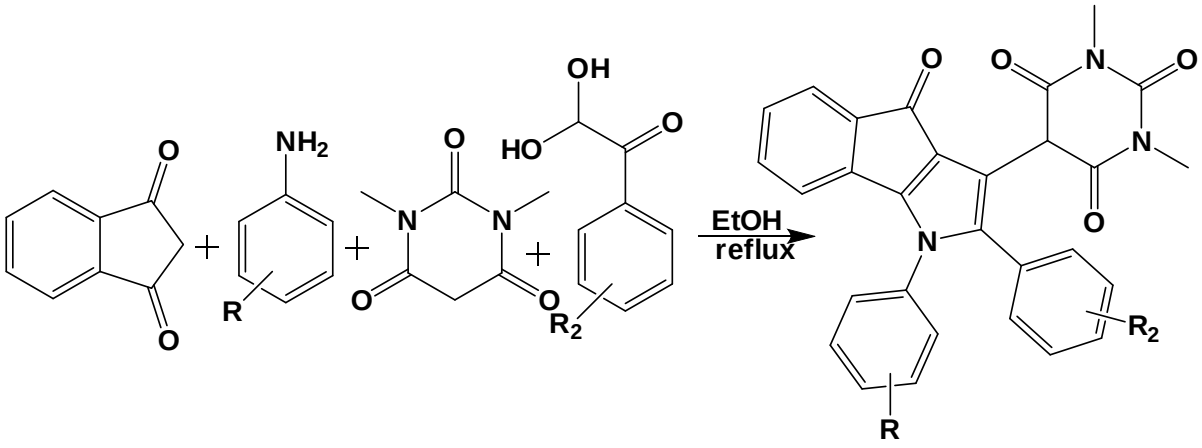
generated. Hence there is still definite longing less expensive and catalyst-free protocols. The following (Scheme 39 - 41) are a list of catalyst-free MCRs methods which are reported to be successful in literature.

Wang et al. (2013) presented the one-pot synthesis of polycyclic spiro-indoles from the reaction of readily available 2-isocyanoethylindole with nineteen aromatic aldehydes and malononitrile under mild reaction conditions to afford the desired product in good to excellent yields (up to 90%) with high diastereoselectivity (Scheme 39).[121]



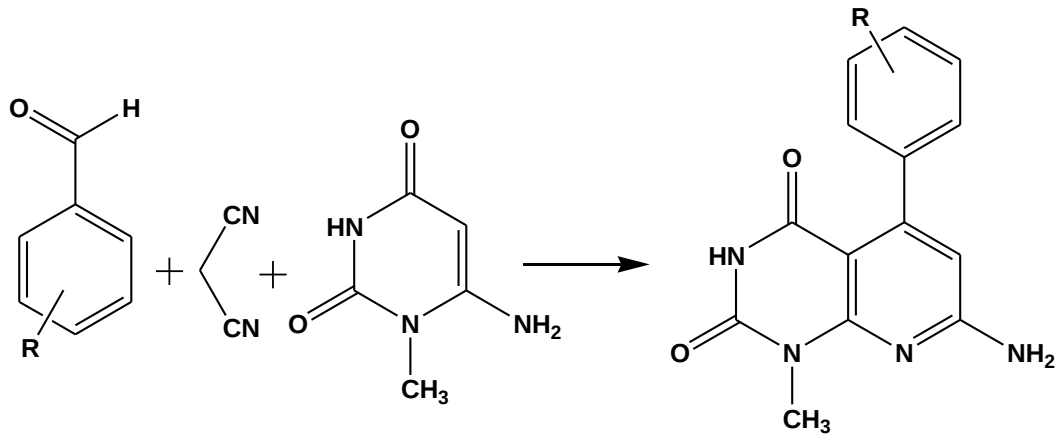

**Scheme 39**: A novel catalyst-free one-pot tandem reaction for the stereoselective construction of polycyclic spiro-indolines.[121]

Dommaraju et al. (2015) developed an efficient method for the synthesis of pyrimidine functionalized pyrrolo-annelated derivatives via a catalyst-free, one-pot reaction of 1,3-indanedione-1,4-methoxy aniline, 1,3-dimethyl barbituric acid and 4-methylphenylglyoxal hydrate (Scheme 40).[122] With this method, ease of execution, separation and high yields (69-87%) were obtained.




**Scheme 40**: Synthesis of pyrimidine functionalized pyrrolo-annelated derivatives.[122]

Singh et al. (2015) developed a clean and efficient strategy for the synthesis of pyrido[2,3-d]pyrimidines a catalyst-free using glycerol as promoting media (Scheme 41).[123]




**Scheme 41**: Catalyst-free synthesis of pyrido[2,3-d]pyrimidines.[123]

### 3.4. Effect of Solvent's in MCRs:

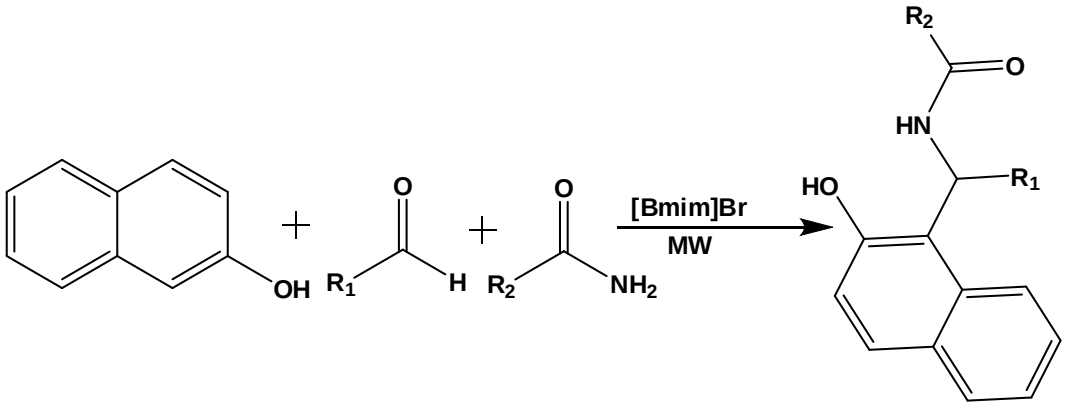
The efficiency of MCRs is crucially dependent on the nature of solvents, catalysts, concentration and excess reagents used.[124] Researchers are concerned about maintaining the greenness of MCRs synthetic procedures, thus they have focused their attention towards the use of greener reaction conditions,[125] such as using alternative solvents instead of volatile organic solvents.[126],[127],[128],[129] Alternative solvents such as ionic liquids[130], supercritical carbon dioxide, ethanol, water,[131],[132] and no solvent at all,[133],[134] have gained much use since the green chemistry become a driving force in organic synthesis. The focus of this review is on two main contenders in green chemistry solvents such as ionic liquids and water, thus summary of recent achievements in carrying out MCR in benign solvents is outlined.

### 3.5. Ionic Liquids:

Ionic liquids (IL) are green organic media suitable for multiple bond forming transformation in MCRs synthesis in cases where the entropy of reaction is decreased in the transition state. They have a unique ionic character, structural organization, and possess physicochemical properties such as relatively low vapor pressure, low volatility as well as tunable polarity and miscibility.[71] IL can be used in MCRs with catalyst or without catalyst and they can also be used as a catalysts themselves. They generate internal pressure, encourage association of reactants in solvent during the activation process and also ensure easy

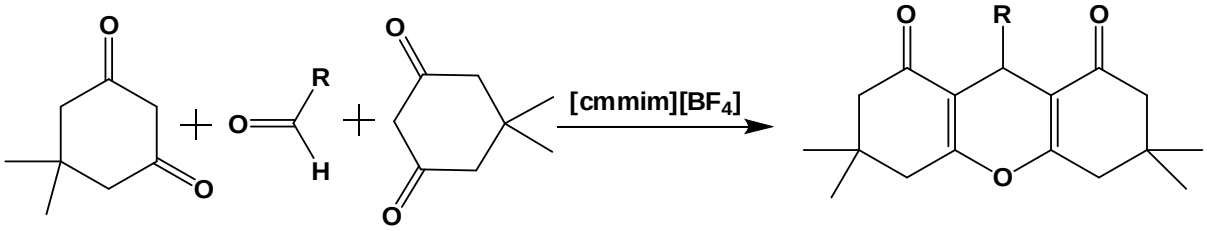
immobilization, separation and recyclability of ionic or polar catalysts.[135] Thus have found application in organic synthesis, material science, and electrochemistry. IL are not only environmentally benign,[136] they are also able to dissolve a range of organic and inorganic compounds as a result they have been widely applied in reactions such as Biginelli, Friedel craft and Diels-Alder reactions among others.[137] Among other reactions is the reaction which was described by (Scheme 42-46)

Zare et al. (2011) described a simple method for the preparation of 1-amidoalkyl-2-naphthols as biologically interesting compounds from one-pot condensation of β-naphthol, aromatic aldehyde and acetamide in ionic liquid 1-butyl-3-methylimidazolium bromide ([Bmim]Br) under microwave condition and catalyst-free conditions (Scheme 42).[138] The product was obtained in high yields (85-94%) in short reaction time (25-40 min).



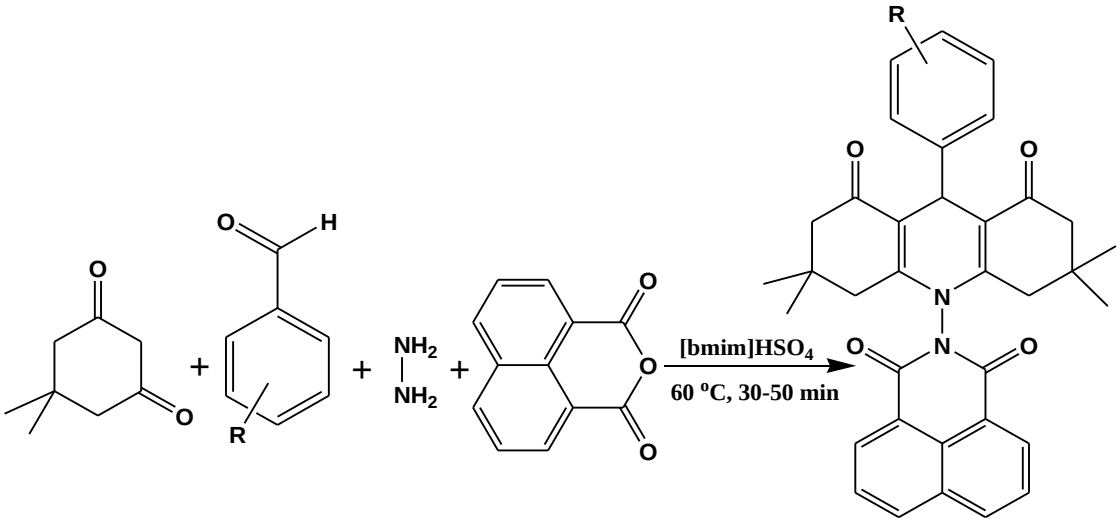

**Scheme 42:** One-pot 3-CR for the preparation of 1-amidoalkyl-2-naphthols.[138]

Dadhania et al. (2012) described an efficient synthesis of 1,8-dioxo-octahydroxanthene derivatives from the condensation of 5, 5-dimethyl-1,3-cyclohexanedione and structurally diverse aldehydes (Scheme 43). Carboxy functionalized ionic liquid 1-carboxymethyl-3-methylimidazolium tetrafluoroborate was used as reaction media. The product was achieved in high yields (78-92%) and purity.



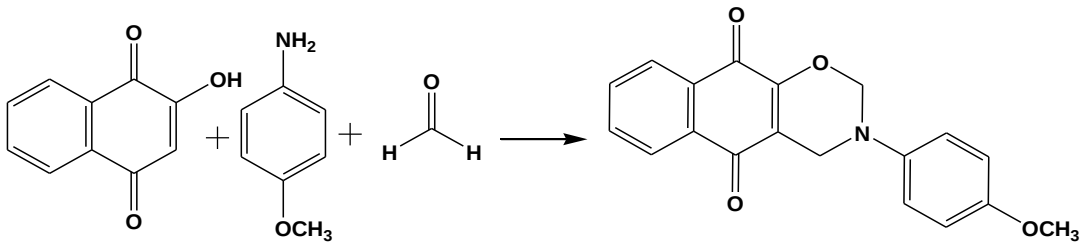
**Scheme 43**: Efficient synthesis of 1,8-dioxo-octahydroxanthene derivatives.[139]

Kumar et al. (2015) reported the successful synthesis of novel naphthalimide-based acridine-1.8-dione derivatives, the product was achieved by reaction of dimedone, aromatic aldehydes, hydrazine hydrate and 1.8-naphthanoic anhydride in the presence of a [bmim] $HSO_4$ ionic liquid (Scheme 44).[130] The use of ionic liquid for this protocol makes it environmentally desirable as this solvent is easily recovered and recyclable.




**Scheme 44**: One-pot multicomponent synthesis of novel naphthalimide-based acridine-1.8-dione derivatives.[130]

Khanna et al. (2015) reported a catalyst-free MCR for the synthesis of novel 3,4-dihydro-2H-naphtho[2,3-e]-[1,3]oxazine-5,10-dione derivatives (Scheme 45).[140] The one-pot three component reaction between 2-hydroxy-1,4-naphthoquinone, aromatic amine and formaldehyde in ionic liquid [bmim]$BF_4$ afforded products in high yields (87-91%) and short reaction time (15-20 min). Products were easily separated.

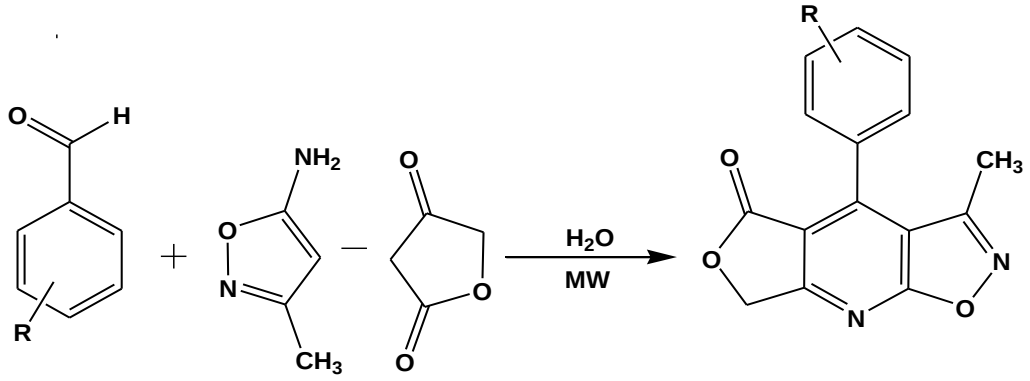


**Scheme 45:** Synthesis of novel 3,4-dihydro-2*H*-naphtho[2,3-e]-[1,3]oxazine-5,10-diones.[140]

### 3.6. Effect of Water:

Water as solvent behaves differently than other organic solvents due to the unique physical properties it exhibit, such as high surface tension, high dielectric constant, high specific heat, large cohesive density, also amphoteric nature and ability to from hydrogen bonds.[141] Water is widely accepted as a green chemistry solvent and has been applied in many organic reactions, this is as due to that it is low in cost, easy to handle[142], readily available and environmental acceptable.[143],[61],[129, 144] Water improves the greenness of MCRs in that it is non-toxic and non-flammable,[145] and most of all it accelerates MCRs by increasing reaction rates,[146] providing selective products, and allows easy separation of the products. Following the path of green chemistry MCRs in water reduces the generation of unwanted by-products and thus the preferred product is obtained in high yields.[147] The unique selectivity that reactions in water exhibit, given it is not attained in reaction of conventional organic solvents has attracted considerable attention in synthetic organic chemistry and medicinal chemistry.[129] The following schemes (46 and 47) display the successful organic reactions carried out in aqueous media, thus there are others not outlined here but are found in literature.

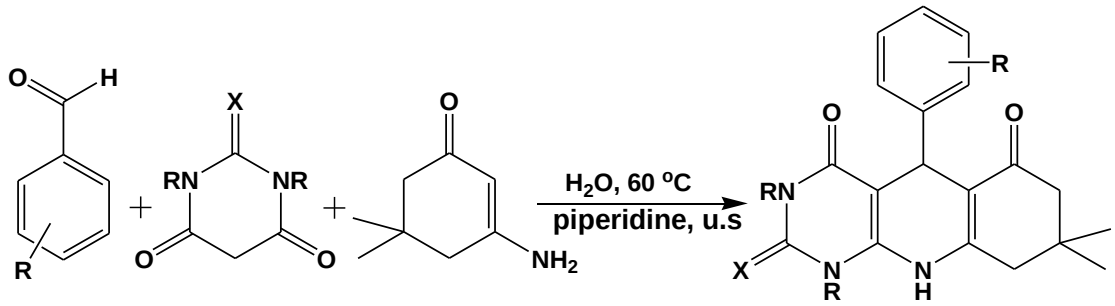
Shu-Jiang Tu et al. (2009) reported the synthesis of a series of new polycyclic-fused isoxalo[5,4-b]pyridines from one pot reaction under microwave irradiation in water without the use of catalyst (Scheme 46).[132]




**Scheme 46**: Synthesis of polycyclic-fused isoxalo[5,4-b]pyridines.[132]

Mosslemin et al. (2010) reported the synthesis of pyridopyrimidines from the reaction of an aldehyde, enamine, and aminocyclohex-2-enone under ultrasonic irradiation using water as

reaction media (Scheme 47).[58] The desired product was achieved in high yields (78-91%) in short reaction time (1 hour).




**Scheme 47**: Synthesis of pyridopyrimidines.[58]

## 4. SYNTHESIS OF NATURAL PRODUCT ANALOGUES

There has always been a great need for combinatorial synthesis to create libraries with compounds that have comparable structural diversity as natural products. [124] As reported in literature and as outlined above, MCRs and ultrasound irradiation can be successfully applied together as convenient combinatorial methods to achieve natural-product-like synthesis, thus it is possible to build large libraries of compounds that exhibit wanted properties.[148],[51],[149] Much desired compounds are aromatic, heterocyclic, and fused heterocyclic compounds. These compounds have been conventionally synthesized through stepwise linear-type protocols. This approach itself had drawbacks such as prolonged reaction times, a number of steps which are time consuming and low yields. The development for drug discovery was hindered by such drawbacks and the discovery of MCRs has allowed the combinatorial chemistry and drug discovery fields to grow further. In continued pursuit to develop new libraries for natural-product-like compounds, this study focuses on the development of one-pot MCR protocols for the synthesis of selected pyrazole, pyridine and simple aromatic derivatives using ultrasonic irradiation.

### 4.1. Pyrazoles:

Pyrazoles are five-membered ring containing two adjacent nitrogen atoms (see figure 2), their motif makes up a number of molecules that exhibit a wide range agricultural and pharmaceutical activities such as anticoagulant, anticancer[150],[151], antimicrobial, antibacterial,

antitumor, antipyretic, anti-diabetic, analgesic, anti-inflammatory,[152] anti-hyperglycemic[153] antineoplastic and antidepressive activities[154],[155],[156].

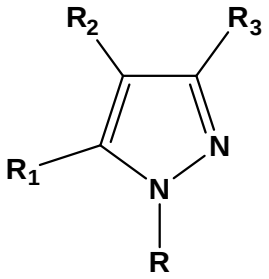
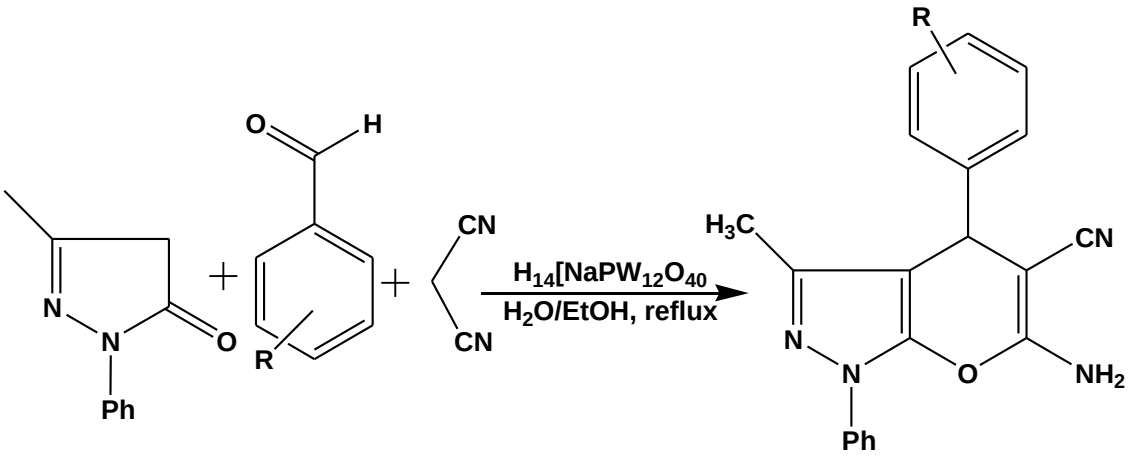



Figure 2: Pyrazole.

Pyrazoles form part of countless pharmaceutical agents, drug candidates, photoactive materials as well as natural products. Hence their motif is contained in numeral drugs such as Celecoxib (non-stereoidal drugs used for treatment of arthritis and acute pain), Fipronil (insecticide) and Viagra (relaxes muscles and increase blood flow to particular areas of the body) among others.[157] Thus pyrazoles have become compounds of interest in organic and medicinal chemistry,[158] and have found application in agrochemical industries as UV stabilizers, pharmaceutical industries for drug development and in materials. The interesting pyrazole motif has motivated organic chemistry researchers to further develop the chemistry of such class of compounds. This was achieved through a synthesis of a range of derivatives of pyrazoles in different reaction conditions via optimization. Reactions have been carried out with or without catalyst application, in different solvents or without solvents and also different reaction temperatures. Several pyrazole derivatives have been successfully synthesized, the following are numerous reaction methods that have been reported in literature on the one-pot synthesis of pyrazoles.

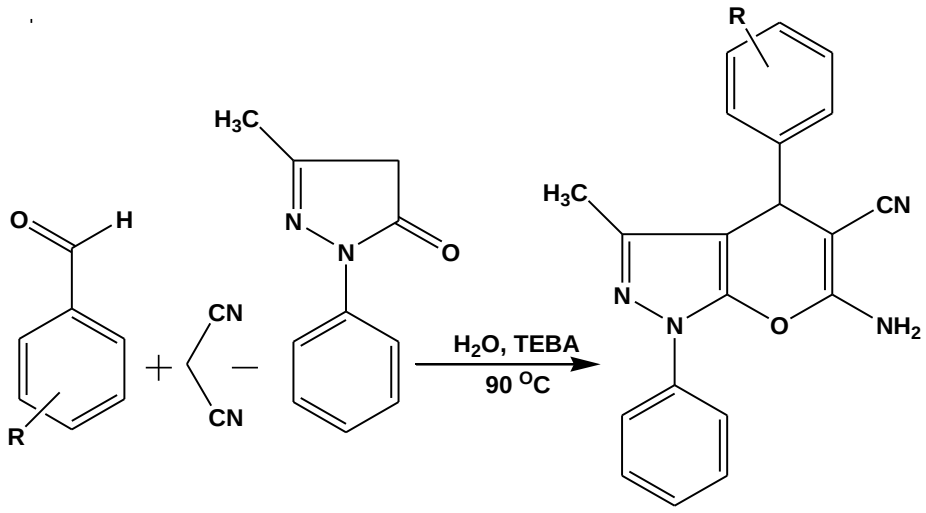
### *4.1.1. Synthesis of pyrazoles under conventional methods*

Heravi et al. (2010) reported an efficient and clean facile method for the synthesis of 1,4-dihydropyrano[2,3-c] pyrazoles via a three component one-pot condensation of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one, aldehydes and malononitrile in the presence of catalytic amounts preyssler type heteropoly acid in water under reflux conditions (Scheme 48).[157]




**Scheme 48**: one-pot MCR for the synthesis of 1,4-dihydropyrano[2,3-c] pyrazoles.[157]

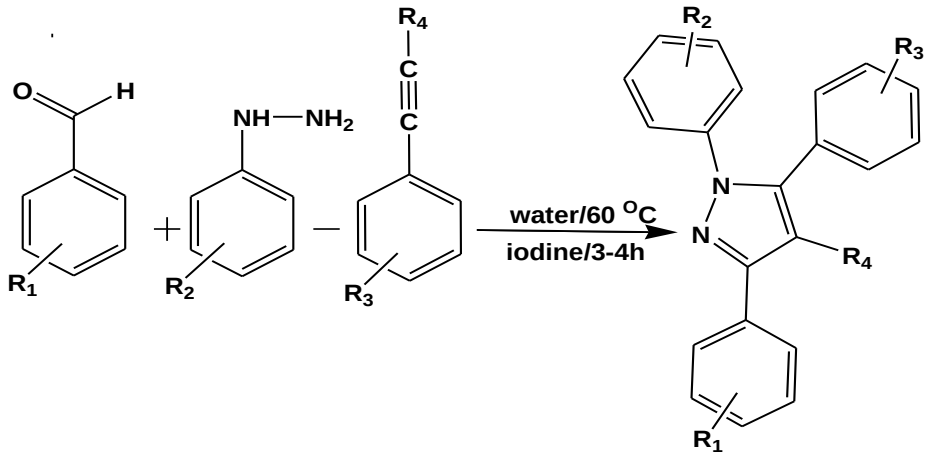
Shi at al. (2004) synthesized 6-Amino-5-cyano-4-aryl-1,4-dihydropyrano [2,3-c] pyrazoles from a 3-CR of aromatic aldehydes, malononitrile, and 3-methyl-1-phenyl-2-pyrazolin-5-one using triethyl-benzyl ammonium chloride (TEBA) as catalyst in aqueous media (Scheme 49).[159] The reaction has the advantages such as good yield (82-94%), less pollution; ease of separation, and it is environment friendly.




**Scheme 49**: Synthesis of 6-amino-5-cyano-4-aryl-1,4-dihydropyrano[2,3]pyrazoles.[159]

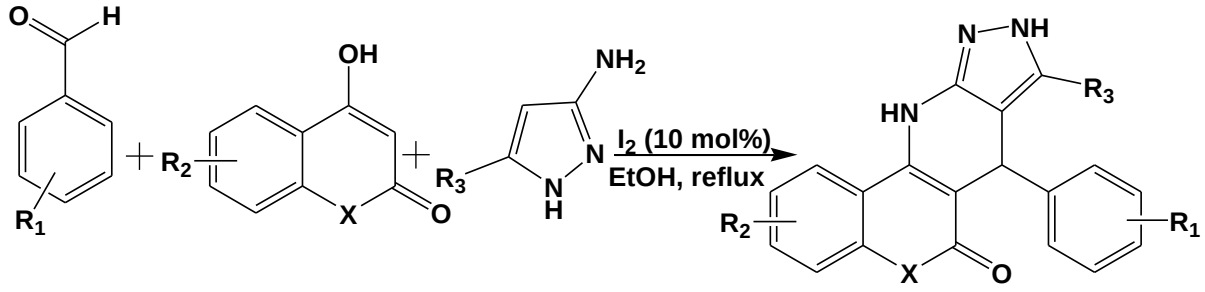
Rai et al. (2013) synthesized a library of 1,3,5-trisubstituted pyrazoles from the multicomponent reaction of an aldehyde, phenylhydrazine and alkynes in the presence of iodine in aqueous media

(Scheme 50). This reaction resulted in the generation of new carbon carbon and carbon nitrogen bonds, and desired product in higher yields (71-91%).[160] Iodine has received attention as a result of its easily available, green and eco-efficient properties thus eco-efficient organic synthesis is achievable.

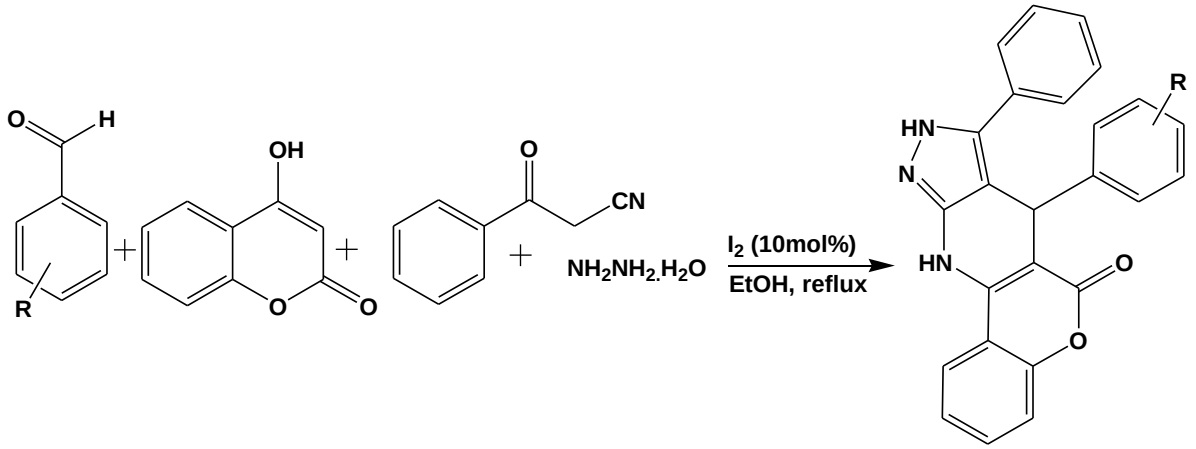



**Scheme 50**: Synthesis of a library of 1,3,5-trisubstituted pyrazoles.[160]

Pal et al. (2013) reported a simple reaction for the synthesis of dihydrochromeno[4,3-b]pyrazolo[4,3-e-pyridin-6(7H)-ones via a multicomponent reaction of aromatic aldehydes, 4-hydroxycoumarin and 3-aminopyrazoles catalyzed by molecular iodine. They also applied the same catalyst for the 4-CR of aromatic aldehydes, 4-hydroxycoumarin, benzoylacetonitrile and hydrazine hydrate (Scheme 51 and 52). The catalyst used in this reactions was environmentally friendly.[161]

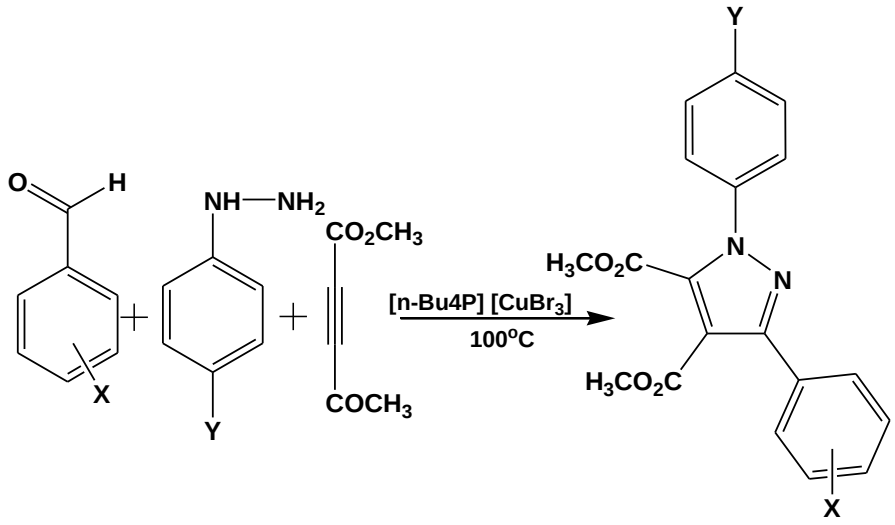



**Scheme 51**: Synthesis of dihydrochromeno[4,3-b]pyrazolo[4,3-e-pyridin-6(7H)-ones via 3-CR multicomponent reaction.[161]



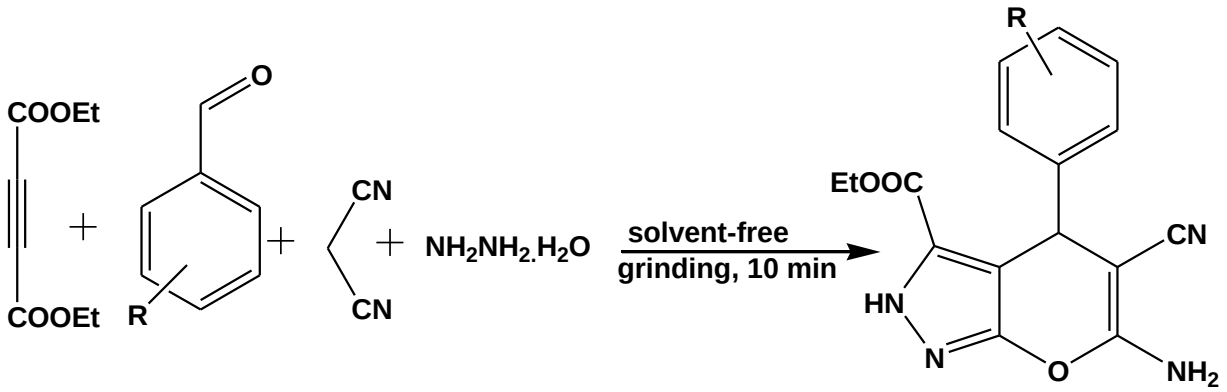

**Scheme 52**: Synthesis of dihydrochromeno-[4,3-b]-pyrazolo-[4,3-e-pyridin-6(7H)-ones via 4-CR multicomponent reaction.[161]

Safaei et al. (2013) used the room temperature ionic liquid, [n-Bu4P] [$CuBr_3$] as an efficient and reusable catalyst for the three-component synthesis of fully substituted pyrazoles (Scheme 53). The pyrazoles were obtained in high yields, from the reaction of aldehydes, arylhydrazines and dimethyl acetylenedicarboxylate (DMAD).[162]



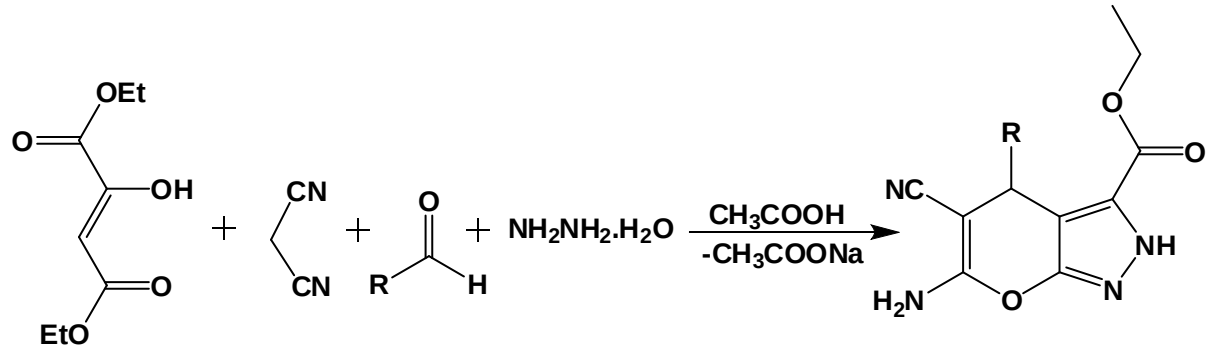

**Scheme 53**: Synthesis of pyrazoles via cyclization-aromatization of hydrazones with DMAD in the presence of [n-Bu4P] [$CuBr_3$] as catalyst.[162]

Ambethkar et al. (2015) described an efficient grinding protocol for the synthesis of dihydropyrano[2,3-c]pyrazoles from the reaction of acetylene ester, hydrazine hydrate, aryl halide, malononitrile under solvent-free conditions (Scheme 54).[163] The pyrazoles were obtained in high yield (65-93%).



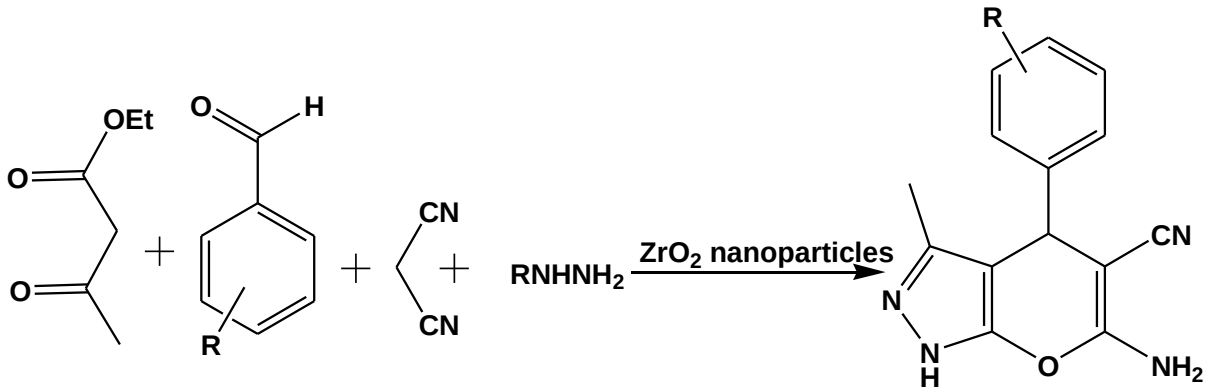

**Scheme 54:** Efficient grinding protocol for the synthesis of dihydropyrano[2,3-c]pyrazoles.[163]

Gein et al. (2014) developed a method for synthesis for 6-amino-4-aryl-5-cyano-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylates via a 4-CR of sodium salt of diethyloxaloacetate, an aromatic aldehyde, hydrazine hydrate and malononitrile (Scheme 55).[164] The products were achieved in moderate to high yields (71-92%).



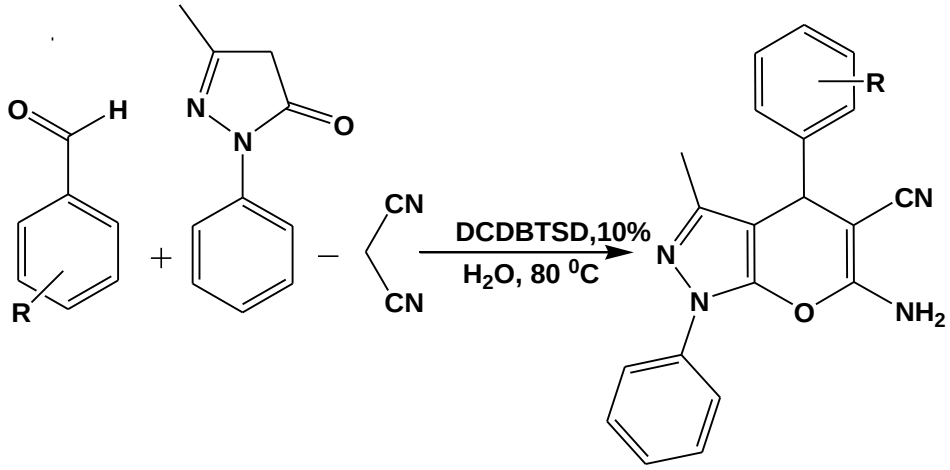

**Scheme 55**: Synthesis for 6-amino-4-aryl-5-cyano-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylates.[164]

Saha et al. (2015) developed a facile one-pot synthesis of bio-active pyrano[2,3-c]pyrazoles using $ZrO_2$ nanoparticles as a catalyst at room temperature (Scheme 56).[165] High yields of product were obtained in short reaction times (2-10 min).



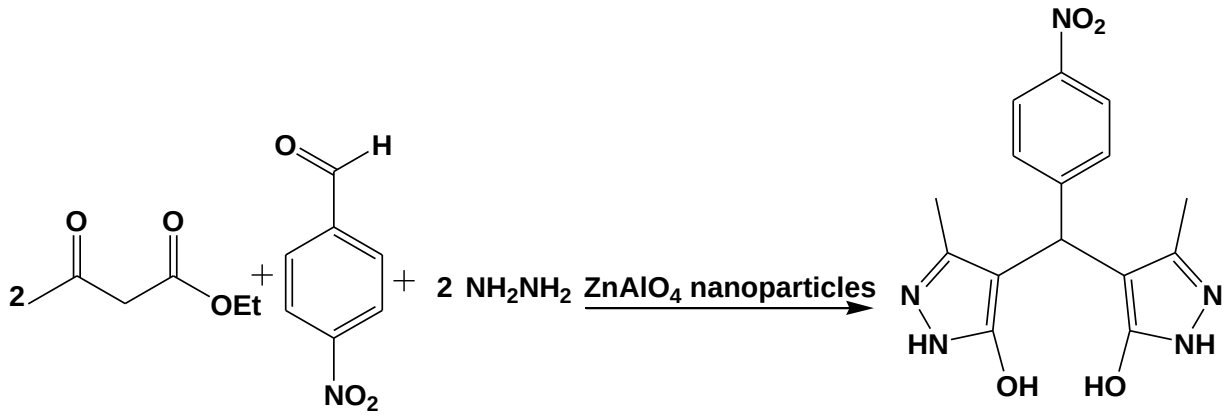

**Scheme 56**: Synthesis of bio-active pyrano[2,3-c]pyrazoles using $ZrO_2$ nanoparticles.[165]

Khazaei et al. (2015) described the synthesis of 4H-pyran, pyranopyrazole (Scheme 57) and pyrazolo[1,2-b]phthalazine through the application of N,2-Dibromo-6-chloro-3.4-dihydro-2H-benzo-[e][1,2,4]-thiadiazine-7-sulfonamide-1,1-dioxide (DCDBTSD) as a homogeneous catalyst in water. This reaction provided high yields of 4H-pyran derivatives (82-95%) dihydropyranopyrazoles (up to 95%) and pyrazolo[1,2-b]phthalazine (up to 95%).[150]




**Scheme 57**: Multicomponent synthesis of 1,4-dihydropyrano[2,3-c]pyrazoles in aqueous media.[150]

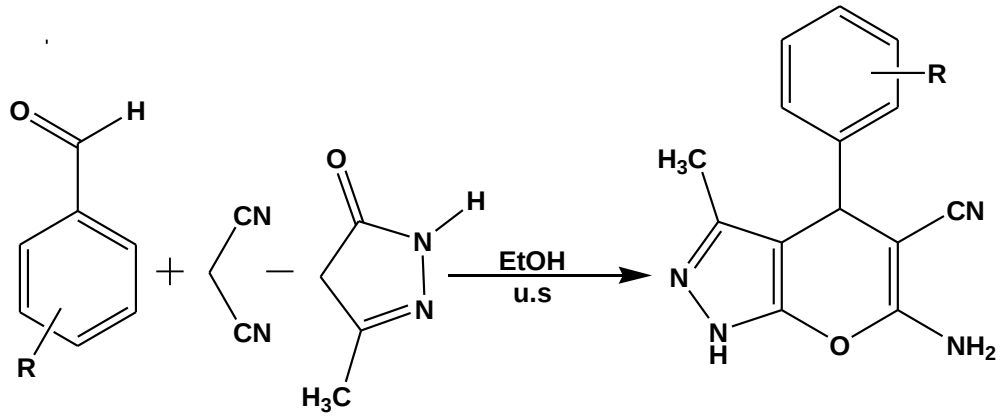
Safaei-Ghomi et al. (2014) reported the synthesis of 4,4-(arylmethylene)bis(3-methyl-1H-prazol-5-ol) derivatives in the presence of $ZnAlO_4$ nanoparticles (Scheme 58).[166] The product was achieved from a pseudo five-component reaction of hydrazine hydrate, ethyl acetoacetate and aldehydes in water at 60°C. The reaction provided excellent yields in short reaction times and the method proved to be environmentally friendly.




**Scheme 58**: Synthesis of 4,4-(arylmethylene)bis(3-methyl-1H-prazol-5-ol) derivatives in the presence of $ZnAlO_4$ nanoparticles.[166]

### *4.1.2. Synthesis of pyrazoles under ultrasound irradiation.*

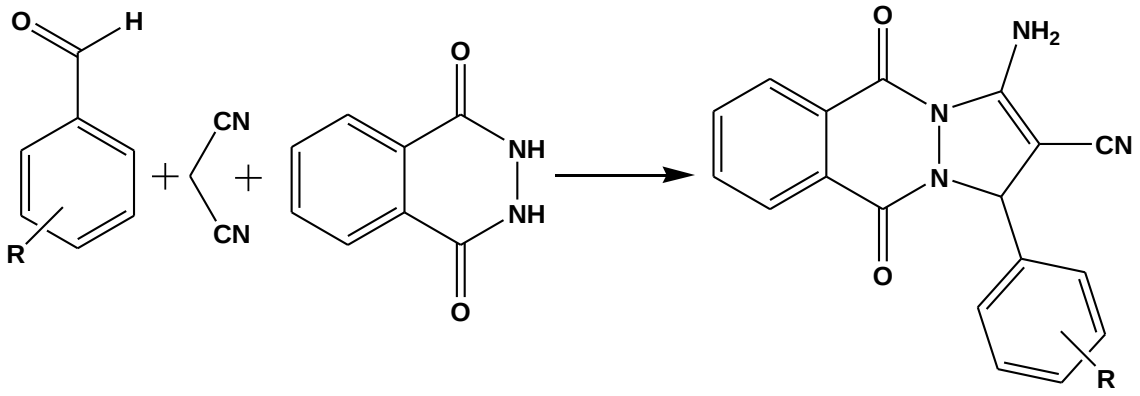
Xiang et al. (2005) reported on the successful synthesis of a series of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydro-pyrano[2,3-c]pyrazoles, obtaining the product with 84-95% yields (Scheme 59). The reaction followed the condensation of aromatic aldehydes, malononitrile with 3-methyl-1-phenyl-2-pyrazolin-5-one without the addition of a catalyst. Dihydropyrazole derivatives have become an attractive class of biologically active compounds that possess a wide range of antitumor,[167] antibacterial,[168] antifungal,[169] antiobesity,[170] and insecticidal activities.[171]




**Scheme 59:** Multicomponent synthesis of a series of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydro-pyrano[2,3-c]pyrazoles.[172]

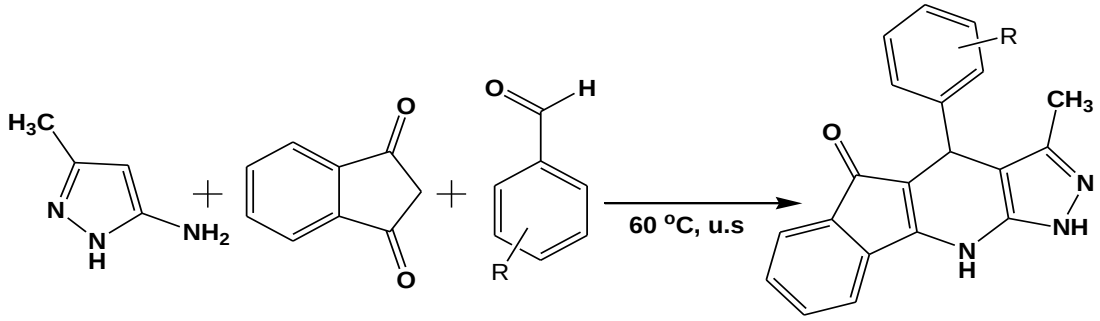
Nabid et al. (2009) described an efficient method for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones using trimethylamine as catalyst (Scheme 60).[173] The product was

obtained from a one-pot reaction of phthalhydrazide, aromatic aldehydes, and malononitrile in ethanol under ultrasound irradiation. The method used was proven to be environmentally benign and they used a readily available and inexpensive catalyst.



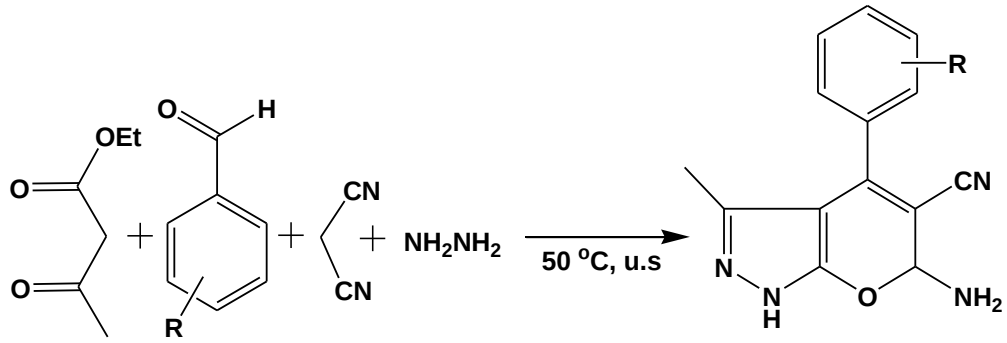

**Scheme 60**: Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones.[173]

Nikpassand et al. (2010) synthesized fused polycyclic 4-aryl-3-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-b]pyridines (Scheme 61) via three component reaction of 5-amino-3-methyl-1H-pyrazole, 2H-indene-1,3-dione and aryl aldehydes using ethanol as solvent under ultrasound irradiation, product produced in excellent yields (88-97%).



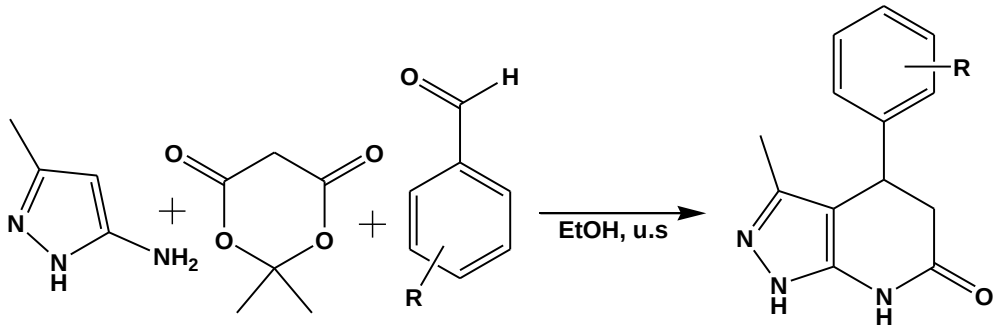

**Scheme 61**: Synthesis of fused polycyclic 4-aryl-3-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-b]pyridines.[174]

Zou et al. (2011) following the use of ultrasound, synthesised dihydropyrano-[2,3-c]-pyrazoles in water via a four-component reaction of aromatic aldehydes, hydrazine, ethyl acetoacetate, and malononitrile (Scheme 62).[154] Excellent yields (79-95%) were obtained in short reaction time (15-40 min).




**Scheme 62**: Synthesis of dihydropyrano-[2,3-c]-pyrazoles in water under ultrasound. [154]

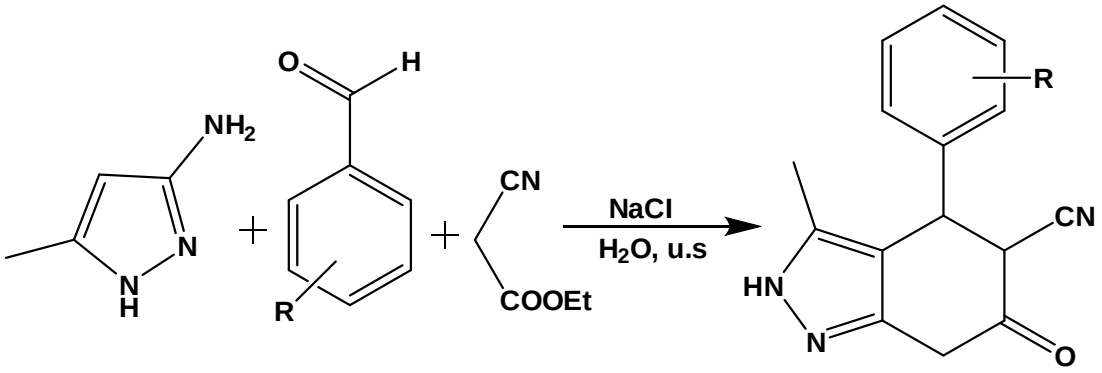
Roshan et al. (2012) developed an efficient method for the synthesis of novel 4-aryl-3-methyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-ones from a reaction of 5-amino-3-methyl-1H-pyrazole, meldrums acid and various aryl aldehydes (Scheme 63). Excellent yields were obtained (87-95%) in short reaction times (3-4 min).[175]




**Scheme 63**: Synthesis of novel 4-aryl-3-methyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridin-6(7H)-ones.[175]

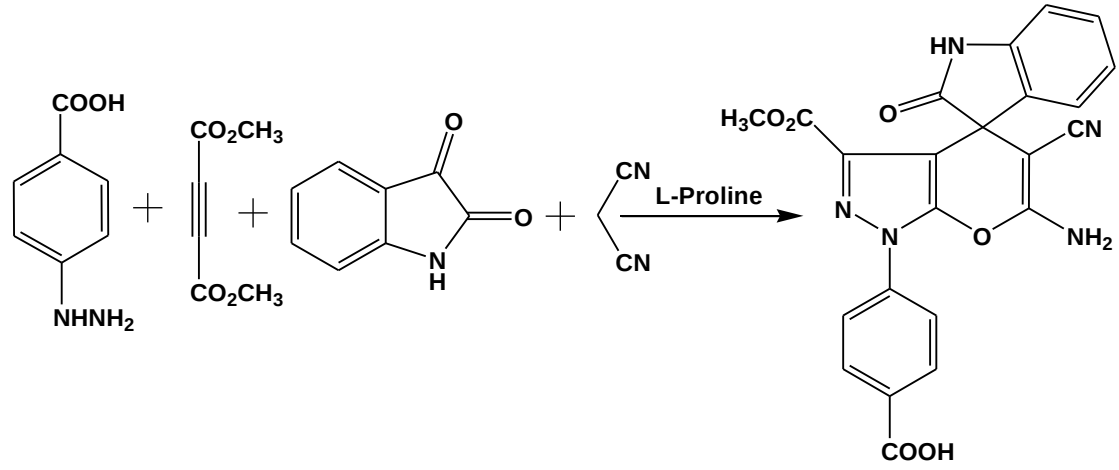
Dandia et al. (2014) synthesized pyrazolo[3,4-b]pyridines via a 3-CR of 3-amino-5-methylpyrazole, ethyl cyanoacetate and aldehydes (Scheme 64), this reaction was catalyzed by sodium chloride and was carried out under ultrasound irradiation. This method offered advantages such as cleaner reaction profile, use of easily available, cheap and environmentally friendly catalyst, high yields and simple experimental workup. Pyranopyridines are used to treat

stress related illness such as depression, alzheimers as well as gastrointestinal diseases.[176]




**Scheme 64**: Synthesized pyrazolo[3,4-b]pyridines via a 3-CR of 3-amino-5-methylpyrazoles.[48]

Wang Liju et al. (2015) reported the one-pot synthesis of spiro[indoline-3.4'-pyrano[2,3-c]pyrazole derivatives (Scheme 65) following the reaction of substituted phenyl hydrazines, di-alkylacetylenedicarboxylate with substituted isatin and malononitrile, the reaction was catalysed by L-proline with excellent yields were obtained (85-93%) in short reaction time (30-60 min).[177]

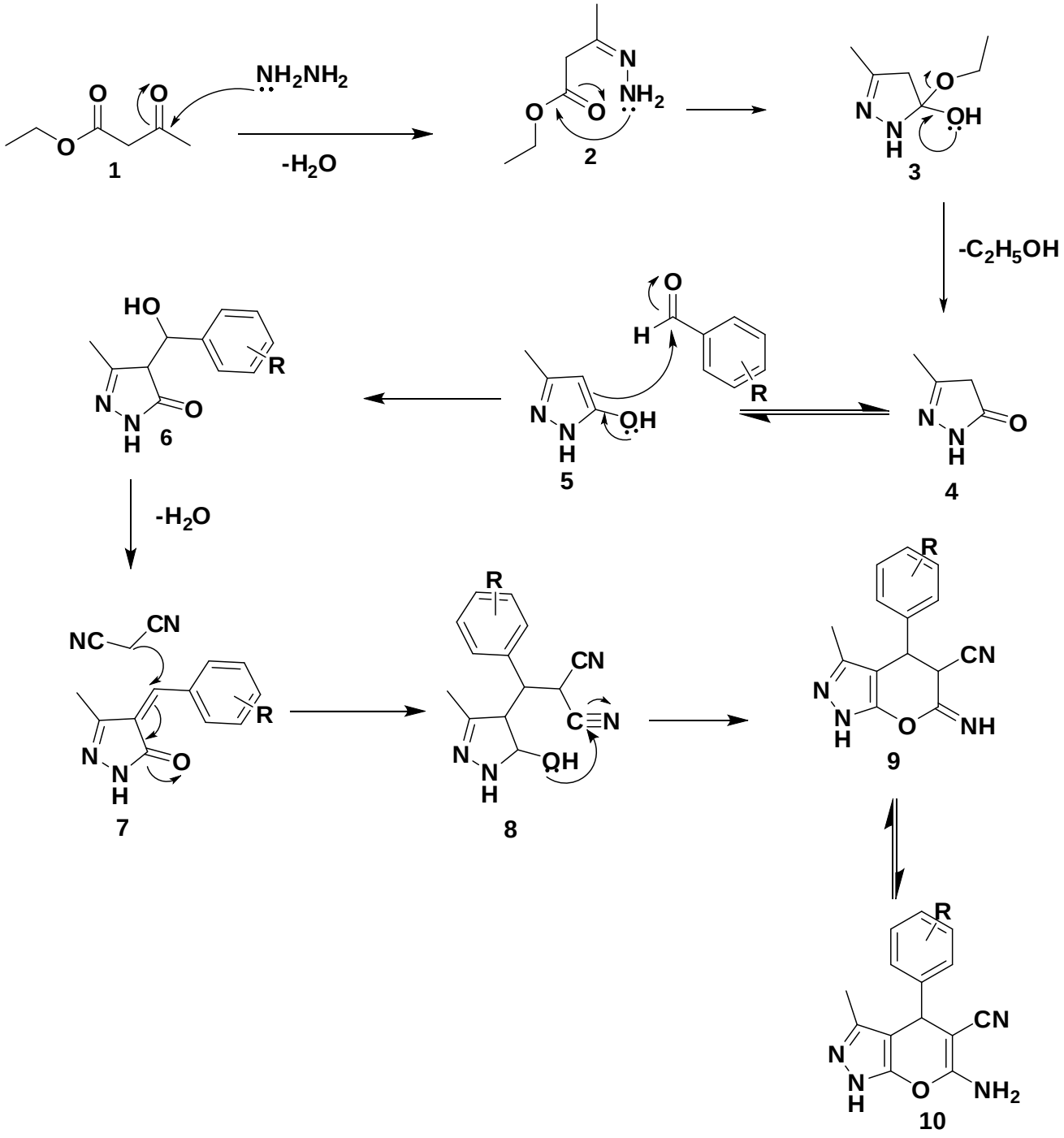



**Scheme 65**: One-pot synthesis of spiro[indoline-3,4'-pyrano[2,3-c]-pyrazole derivatives catalysed by L-proline under ultrasound irradiation.[177]

It is clear that there are still few reactions that has been carried out under ultrasound irradiation and using environmentally benign solvents. Hence there is still a need to improve the already existing methodologies via optimization of reaction conditions for multicomponent and ultrasound reactions. With MCR and ultrasound irradiation working perfectly when applied together in organic synthesis, a number of compounds libraries can be created not just pyrazoles, but also pyridines and carbonitriles among others.

### *4.1.3. Plausible mechanism for the formation of pyrazoles:*

Scheme 66, shows the proposed mechanism for the formation of compound **10**, a full and detailed mechanism for this reaction is to be clarified. The formation of compound **10** follows a series of steps including the knoevenagel condensation, Michael addition as well as tautomerisation. The reaction of hydrazine hydrate with ethyl acetoacetate (**1)** leads to the formation of intermediate **(2)**. The condensation of aromatic aldehyde with intermediate (**4)**, gives intermediate (**6).** Then, the next step is a Michael addition of the carbanion of malononitrile to intermediate (**6**) to yield adduct **8**, followed by an intramolecular condensation reaction of intermediate (**8)** to afford (**9)**. Finally, after the tautomeric proton shift, the desired product (**10)** is formed.[54]




**Scheme 66** : Mechanism for the synthesis of pyrazoles.[54]

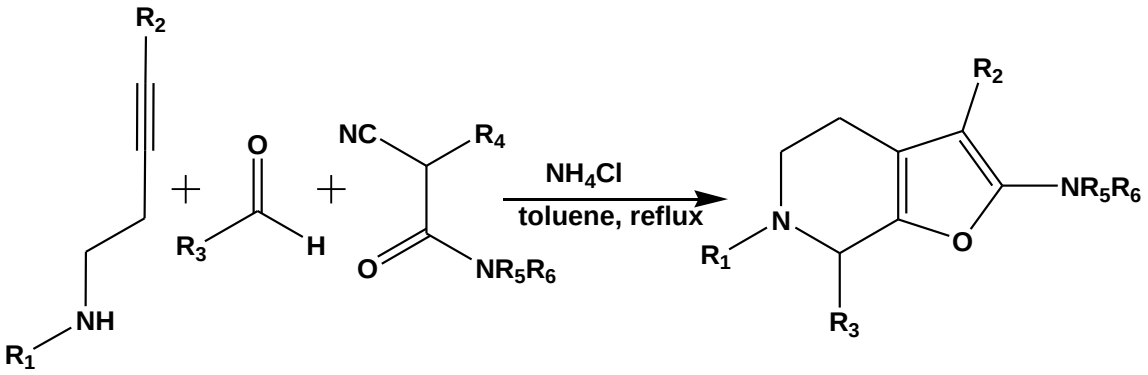
### 4.2. Pyridines:

Pyridines are six membered nitrogen containing heterocycles and are one of the most wanted heterocycles. Their structural motif makes up numerical compounds of natural products, pharmaceuticals, advanced materials, catalysis and ligands. They display a broad spectrum of

activities such as bio-, physio- and pharmacological properties.[178],[179] They are advantageous structures that are of most importance in bio-organic and medicinal chemistry.[180] They can be used as precursors to synthesize chiral dihydro- and tetrahydropyridines as well as piperidines. Pyridines generally are synthesized from Hantzsch reaction via a cyclo-condensation of aldehydes, β-ketoester and ammonia in acetic acid or in alcohol.[181] The known natural products that contain pyridine core include diploclidine, streptonigrin and lavendamycin, these compounds display a significant and diverse medicinal properties such as antibacterial, anticancer and potassium channel opener for treatment of urinary incontinence and antihepatitis B virus infection among others.[182] Owing to the wide applications of pyridine and pyridine derivatives, designing and developing new methodologies for their synthesis have attracted a huge attention from both synthetic and medicinal chemists. A plethora of methods for the synthesis of pyridines have been reported in literature most which are multicomponent reaction methods. Among them are the following reactions (scheme 67- 79) which successfully yielded different derivatives of pyridines.

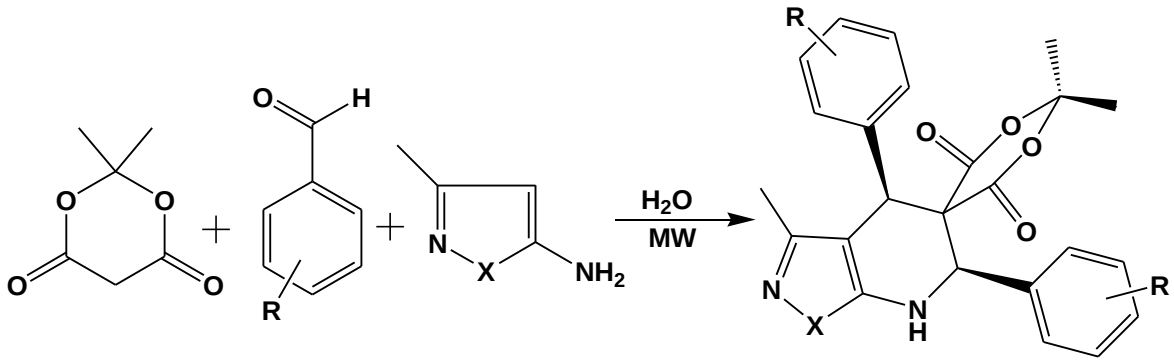
### *4.2.1. Synthesis of pyridines:*

Furopyridines in this case tetrahydrofuro[2,3-c]pyridines are found in numerous medicinally relevant synthetic compounds such as HIV inhibitors. These compounds have been synthesized via a 3-CR of r-isocyanoacetamide, aminopentynoate and an aldehyde in the presence of ammonium chloride (Scheme 67).[183] This work was reported by Fayol and Jieping in 2004.



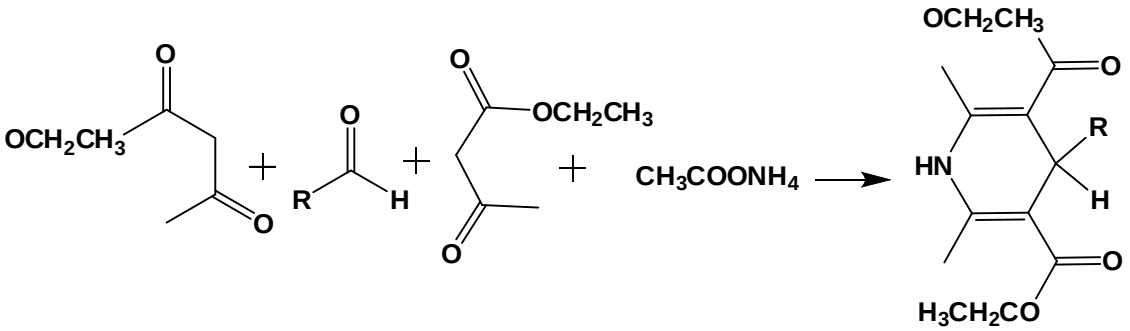

**Scheme 67**: Synthesis of polysubstituted 4, 5,6,7-tetrahydrofuro[2,3-c]pyridines.[183]

Ma et al. (2010) synthesized spiro[1,3]dioxanopyridine via a reaction of aldehydes, pyrazolo-amines and meldrums acid in water under microwave irradiation (Scheme 68).[184] These compounds are of chemical and biological importance.



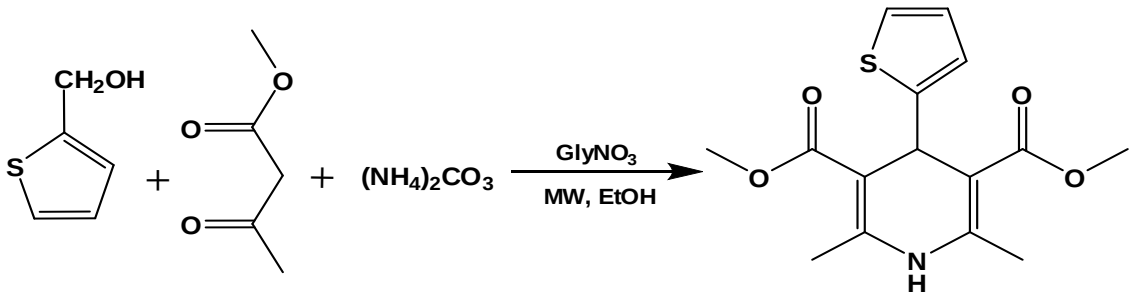

**Scheme 68**: Synthesis of spiro[1,3]dioxanopyridine-4,6-diones.[184]

Murthy et al. (2012) reported the Hantzsch reaction for the synthesis of 1,4-dihydropyridines under solvent-free conditions in the presence of cellulose sulfuric acid as a heterogeneous catalyst (Scheme 69).[185] The products were obtained from the reaction of aldehydes, ethyl acetoacetate and ammonium acetate.



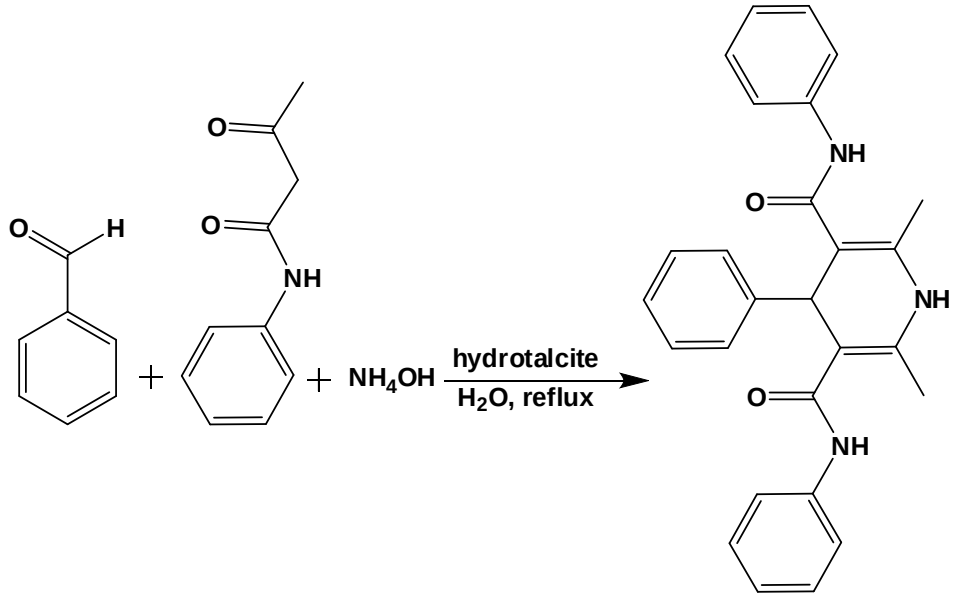

**Scheme 69**: Hantzsch reaction for the synthesis of 1,4-dihydropyridines.[185]

Kumar et al. (2014) reported the use of inexpensive and recyclable glycine nitrate ($GlyNO_3$) ionic liquid as catalyst to afford up 93% yield of 1,4-dihydropyridines (Scheme 70).[186] The product was obtained from the 3-CR and 4-CR, this methodology is practical, recyclable and economical.



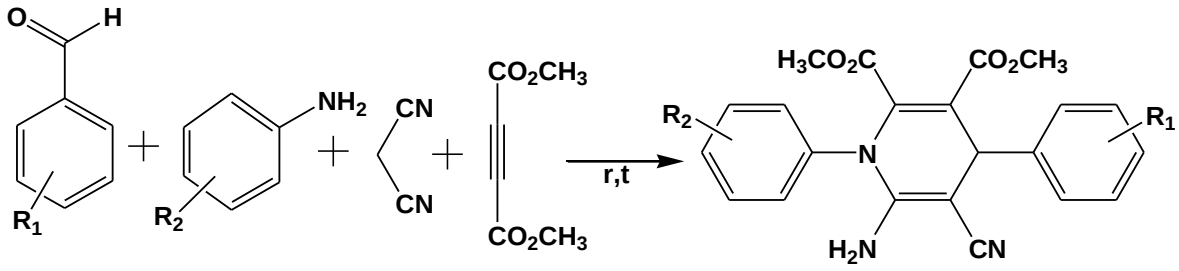

**Scheme 70**: Synthesis of 1,4-dihydropyridines.[186]

Pagadala et al. (2014) reported the one pot synthesis of triphenylpyridine-3,5-dicarboxamide via a Hantzsch reaction of acetoacetanilide, ammonium hydroxide and various aromatic aldehydes in the presence of hydrotalcite as catalyst (Scheme 71).[187] Triphenylpyridine-3,5-dicarboxamide derivatives exhibit biological activities, therefore are useful in the treatment of congestive heart failure and angina pectoris. The products were achieved in good yields (85-93%).




**Scheme 71**: Hantzsch reaction for one pot synthesis of triphenylpyridine-3,5-dicarboxamide.[187]

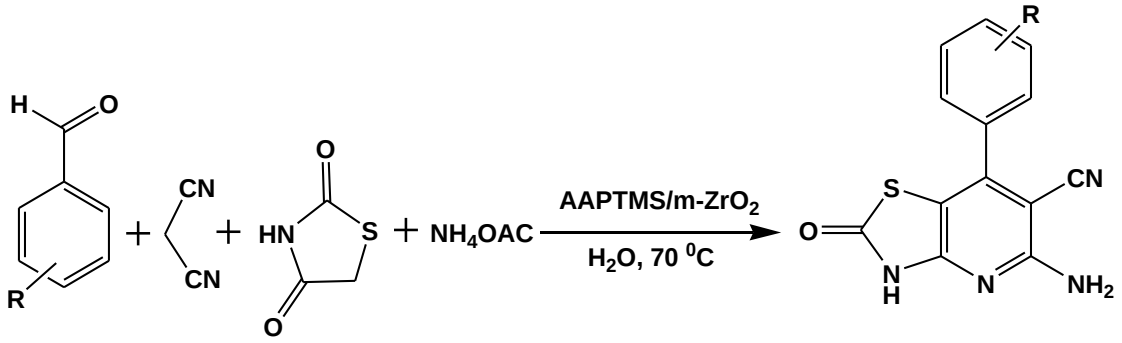
Pal et al. (2013) reported the synthesis of substituted dihydropyridines via the reaction of different aromatic aldehydes, anilines, malononitrile derivatives and dimethyl acetylenedicarboxylate in the presence of polyethylene glycol (Scheme 72).[188]




**Scheme 72**: Four-component reaction for the synthesis of dihydropyridine derivatives.[188]

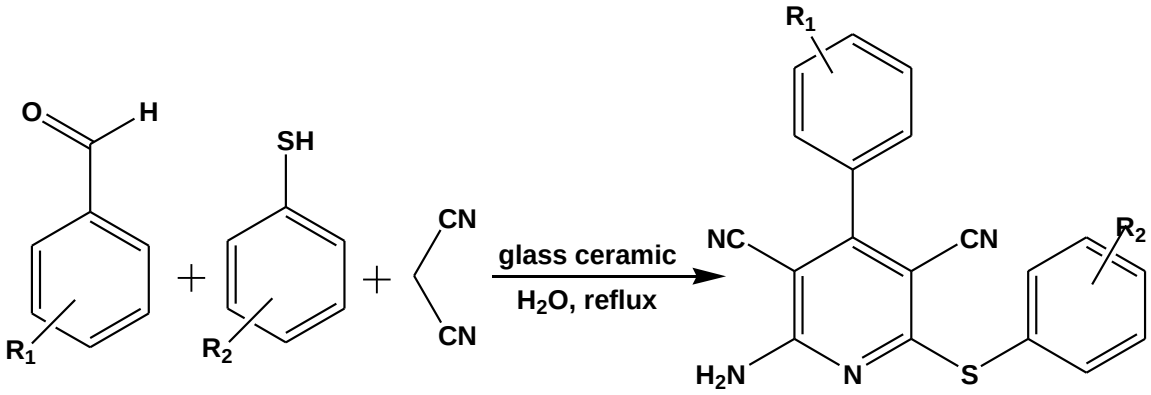
Pagadala et al. (2015) developed a new and straight forward method for the synthesis of heterocyclic fused pyridine derivatives in aqueous media from knoevenagel condensation of

aromatic aldehyde, and an active methylene compound followed by Michael addition of a ketone in the presence of diamine functionalized-[N-(2aminoethyl)-3-amino propyl trimethoxy silane (AAPTMS)] mesoporous $ZrO_2$ (Scheme 73).[189] Fused pyridines were synthesized in high yields (84-94%).



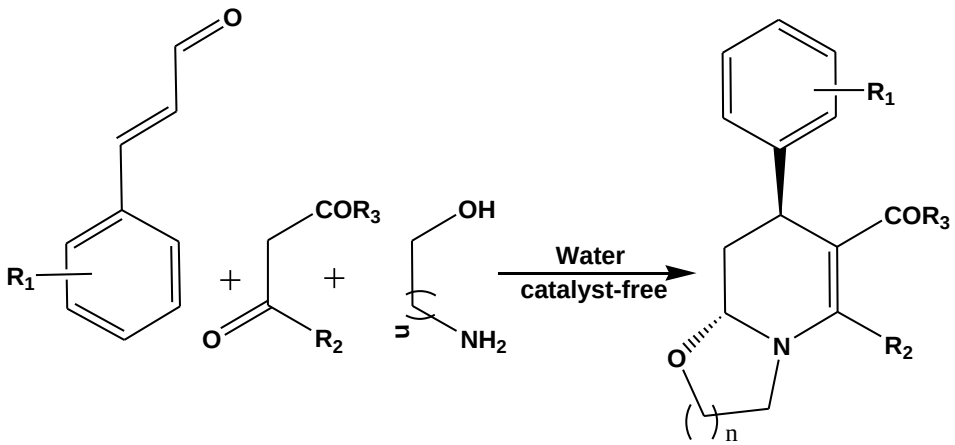

**Scheme 73**: Catalyzed multicomponent synthesis of heterocyclic fused pyridines.[189]

Manna et al. (2015) synthesized 2-amino-3,5-dicarbonitriles-6-arylthio-pyridines in the presence of a glass-ceramic material which was used as catalyst (Scheme 74).[190] The product was obtained from a reaction of aromatic aldehyde, thiophenol and malononitrile in water. Amino-3,5-dicarbonitrile-6-arylthio-pyridine structural motif exhibit significant and biological, activities thus can be used as antibacterial and anticancer agents.



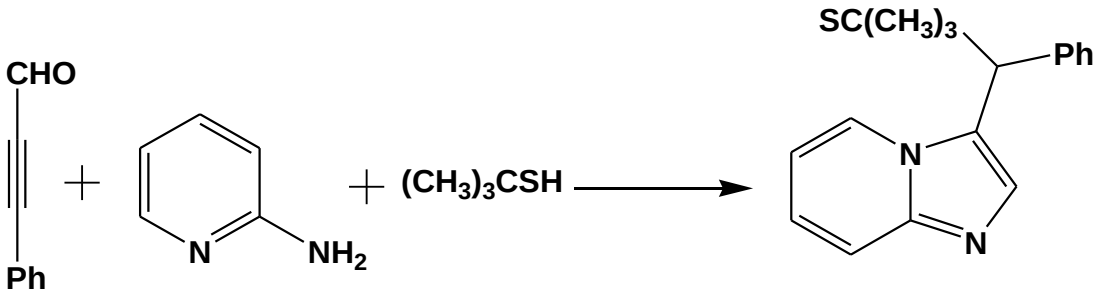

**Scheme 74**: Synthesis of 2-amino-3,5-dicarbonitriles-6-arylthio-pyridines.[190]

Vinoth et al. (2015) reported the successful synthesis of fused tetrahydropyridines in water without the application of a catalyst (Scheme 75). The product was obtained in high yields (66-80%) from a 3-CR of amino alcohols, 1,3-dicarbonyl compounds and unsaturated aldehydes, the steps that were involved include Michael addition, intramolecular cyclization and iminium ion cyclization.[191]




**Scheme 75**: Catalyst-free multicomponent synthesis of synthesis of fused tetrahydropyridines in water.[191]

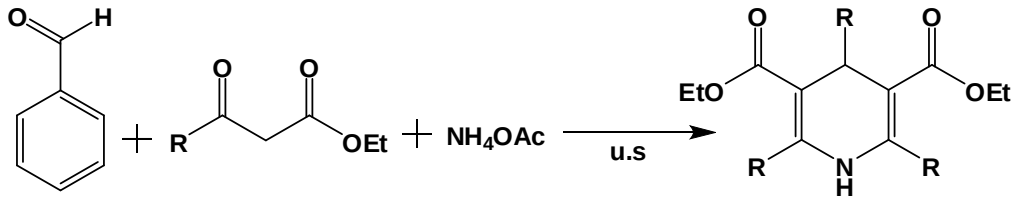
Zhan et al. (2015) reported the synthesis of imidazo[1,2-a]pyridine derivatives via a 3-CR of 3-phenylpropionaldehyde, pyridine-2-amines and thiols in the presence of $F_3CCO_2H$ under microwave conditions (Scheme 76).[192]Imidazole[1,2-a]pyridines are important class of heterocycles and display remarkable biological activities.




**Scheme 76**: Synthesis of imidazo[1,2-a]pyridines.[192]

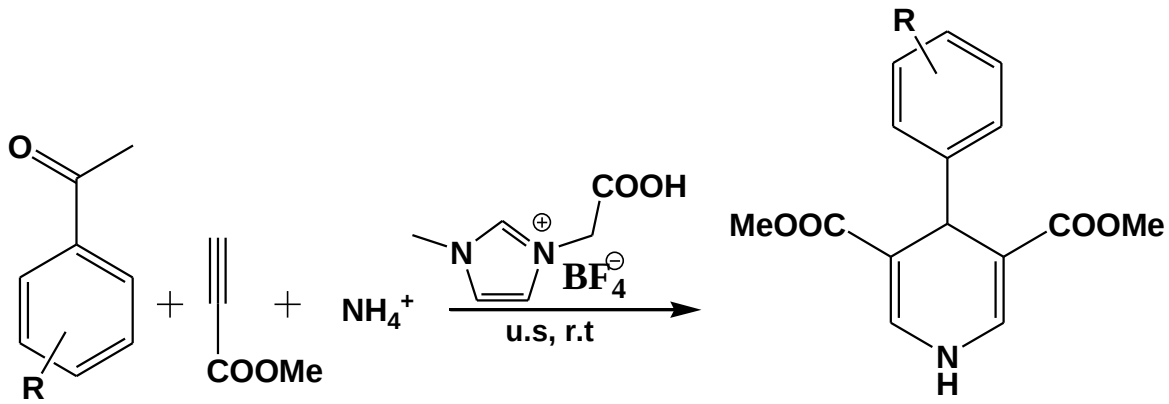
### *4.2.2. Synthesis of pyridines under ultrasound:*

Wang et al. (2008) synthesized 1, 4-dihydropyridines from the condensation of aldehydes, ethyl acetoacetate and ammonium acetate without solvent and catalyst application (Scheme 77).[193] The product was achieved in good to excellent yields (82-99%) in shorter reaction times (30-70 min).



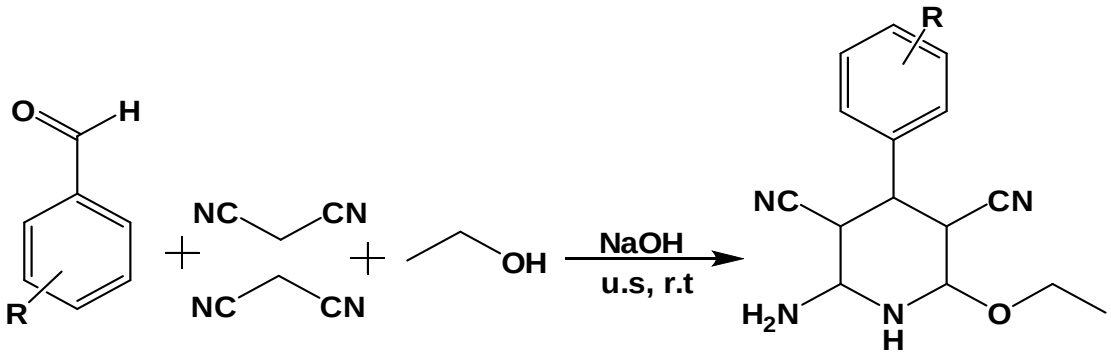

**Scheme 77**: Synthesis of 1, 4-dihydropyridine derivatives under ultrasound irradiation.[193]

He at al. (2015) reported the successful synthesis of 4-substituted-1, 4-dihydropyridine-3, 5-dicarboxylates under ultrasound irradiation (Scheme 78), the reaction was catalysed by 1-carboxymethyl-3-methylimidazolium tetraflouroborate the reaction moved without the use of any organic solvent.[194]




**Scheme 78**: Synthesis of 4-substituted-1,4-dihydropyridine-3,5-dicarboxylates under ultrasound irradiation.[194]

Pagadala et al. (2014) reported the synthesis of pyridine derivatives form the reaction of aromatic aldehydes, malononitrile, ethanol and sodium hydroxide as base catalyst (Scheme 82).[61] High yield of product obtained (88-98%) in short reaction times (1.5-2.0 hours).




**Scheme 79**: Synthesis of tetra substituted pyridine derivatives.[61]

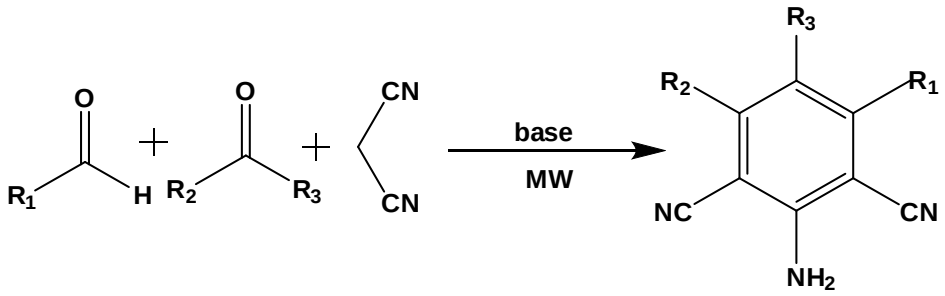
Most of the reactions reported above are for the synthesis of dihydropyridines. Dihydropyridine were first reported by Hantzsch in 1882, these have become predominant and are available in various natural products and synthetic pharmaceuticals. They are known to be key intermediates for the synthesis of several biologically active compounds,[195] such as those for the treatment of cardiovascular disease, hypertension, and potent calcium channel antagonist/agonist.[196] They also have therapeutic application, they are used as cerebal anti-ischemic agents,[197] chemosensitizers, platelet anti-aggregators and neuroprotectants (as treatment of stress related illness such as depression and alzheimers disease).[198],[199]They also display biological activities that are of use in the treatment of congestive heart failure and angina pectoris. [200]

### 4.3. Carbonitriles:

Unlike heterocycles, aromatic compounds do not have any heteroatom making part of the ring system, but they also have wanted properties, and have also been prepared via one-pot MCRs. The properties of aromatic compounds that have substituents such as a hydroxyl, nitrile, and alkene as well amino groups are of most importance. These substituents or functional groups are polar and have π-electrons in the form of double and triple bonds, thus have high adsorption tendency and hence they are easily and economically synthesized. [201],[202]Carbonitriles are among such classes of compounds, and they constitute both a nitrile and amino groups.[85] Most predominant of such compounds are those containing 2-amino-1,3-dicarbonitrile group, these are known to be typical acceptor-donor-acceptor (A-D-A) systems.[203] They are key constituents of numerous bioactive compounds.[204] They are used as precursors for asymmetric synthesis,[205]and as basis for artificial photosynthetic systems. The general reaction for their

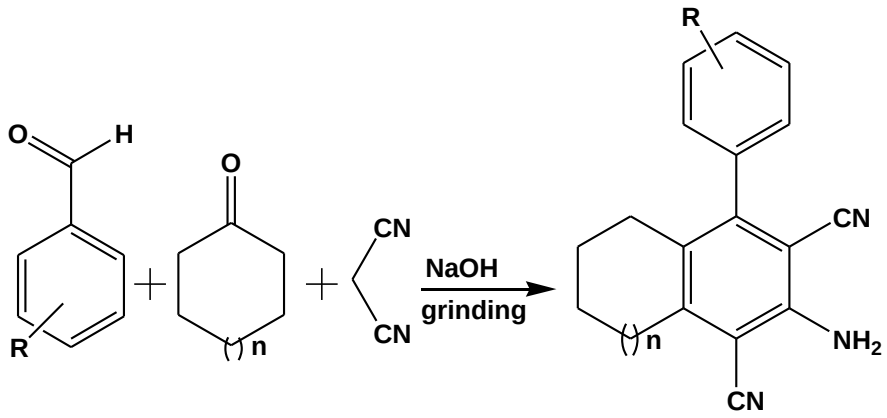
synthesis involves a one-pot 3-CR of acetone, aromatic aldehyde and malononitrile (Scheme 83-87).[206] the following reactions (Scheme 80-84) have been reported on the synthesis of different carbonitriles via one-pot MCRs.

Cui et al. (2005) developed a facile synthesis of polysubstituted-2,6-dicyanoanilines via a 3-CR of aldehydes, ketones and propanedinitrile under microwave conditions(Scheme 80).[207]




**Scheme 80**: One-pot 3-CR for the synthesis of polysubstituted-2,6-dicyanoanilines.[207]

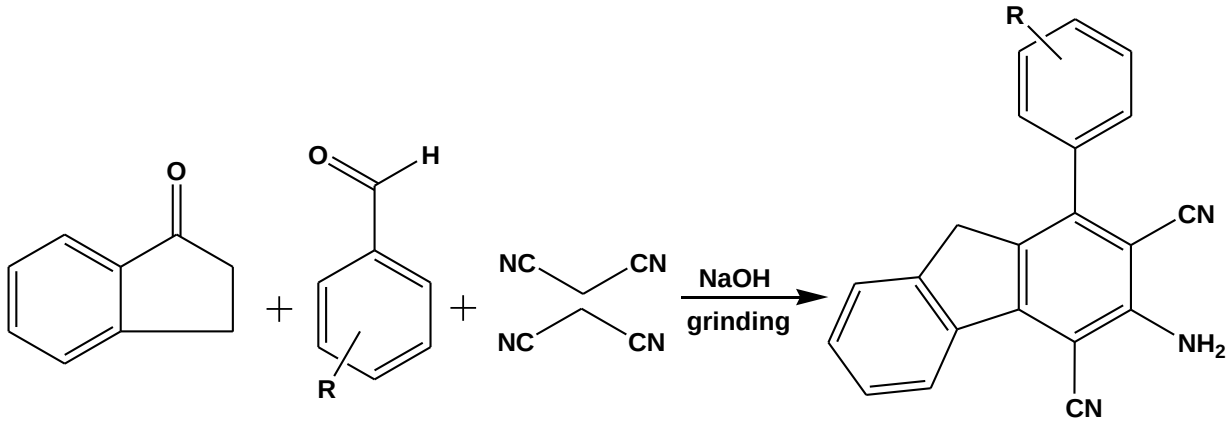
Rong et al. (2008) developed an efficient method for the synthesis of 2,6-dicyanoaniline via a one-pot reaction of aldehydes, malononitrile and cyclic ketones in the presence of NaOH under solvent-free conditions using a grinding method (Scheme 81).[208]




**Scheme 81**: Synthesis of 2,6-dicyanoaniline derivatives.[208]

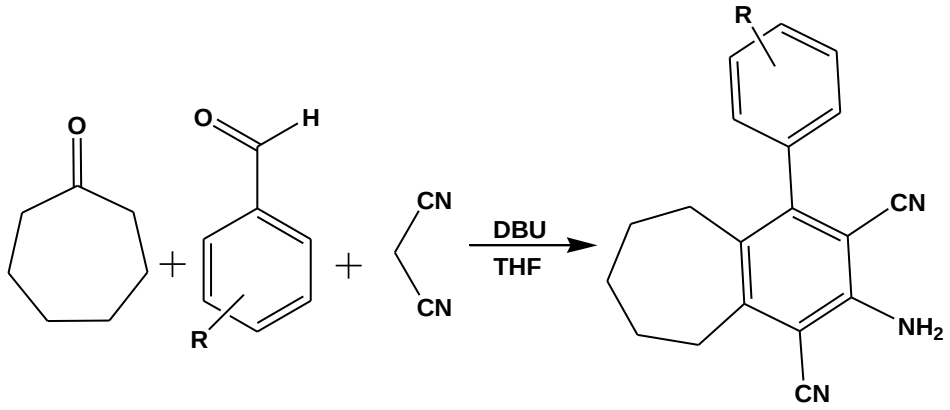
Rong et al. (2009) reported the efficient route for the synthesis of 3-amino-1-aryl-9H-flourene-2,4-dicarbonitriles via a multicomponent reaction of 1-indanone, aromatic aldehydes and malononitrile under solvent-free conditions (Scheme 82).[209] Good yields of product were

obtained (75-87%). These compounds are used as inhibitors of bone loss or bone resorption.



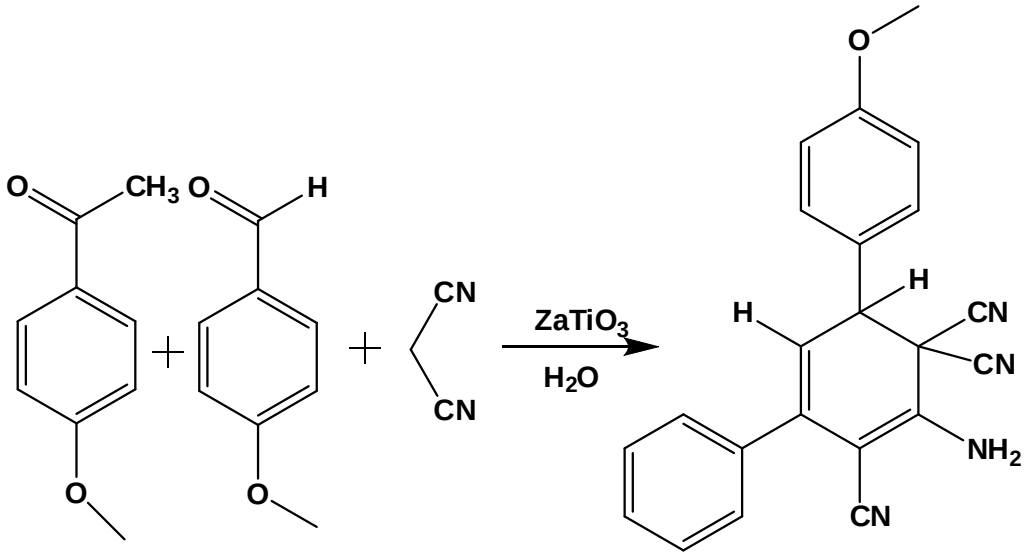

**Scheme 82**: Synthesis 3-amino-1-aryl-9H-flourene-2,4-dicarbonitriles.[209]

Rong et al. (2012) reported a facile and convenient method for the preparation of 2-amino-4-aryl-6,7,8,9-tetrahydro-5H-benzo[7] annulene-1,3-dicarbonitrile derivatives in THF using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst (Scheme 83).[206] These compounds comprises of one electron donor two electron acceptors.




**Scheme 83**: The preparation of 2-amino-4-aryl-6,7,8,9-tetrahydro-5H-benzo[7] annulene-1,3-dicarbonitrile derivatives.[206]

Das el al. (2012) reported the reaction of zinc acetate [$(CH_3COO_2)_2Zn$], ethylene glycoltitanium butoxide ($C_{16}H_{36}O_4Ti$) and citric acid anhydrous [$(C_3H_9(OH)(COOH)_3$] to afford 2,6-dicyanoanilines (Scheme 84) in good yields (58-72%). The biaryl unit of these compounds are found in several compounds of current interest including natural products, polymers, advanced materials, liquid crystals, ligands and medicinal compounds.[210]




**Scheme 84:** Synthesis of 2,6-dicyanoanilines.[210]

All reaction reported above are carried out under conventional reaction conditions, thus there is the need to improve such conditions in order to increase reaction yields and efficiency of the protocol, this can be achieved using the ultrasound approach.

## 4.4. Objectives of the study:

Aim of the study is to develop and optimize simple, green protocols using ultrasonification for the one-pot multicomponent synthesis, using environmentally benign solvents and to compare the efficiencies of ultrasound methods with the conventional reflux approach. The studies are focused on the synthesis of series of

i) Pyrazole derivatives
ii) 1,4-dihydropyridine derivatives and
iii) Tetrahydrobiphenylene-1,3-dicarbonitriles

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## CHAPTER-2

# ULTRASONIC-ACCELERATED RAPID PROTOCOL FOR THE IMPROVED SYNTHESIS OF PYRAZOLES

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Ultrasonic-accelerated rapid protocol for the improved synthesis of pyrazoles

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**Abstract**

A simple, catalyst-free, green synthetic protocol is described for the one-pot synthesis of pyrazoles *via* multicomponent reaction of aromatic aldehydes, hydrazine monohydrate, ethyl acetoacetate and malononitrile/ammonium acetate in water under ultrasound irradiation. This protocol avoids traditional chromatography and purification steps and it affords highly selective conversion with no byproducts.

**Keywords:** Ultrasound, multicomponent reaction (MCR), one-pot synthesis, pyrazole derivatives, water as solvent.

## 1. INTRODUCTION

Development of simple and eco-friendly procedures for synthesis of compounds with biological interest is the driving force for the discovery and design of new bioactive compounds. Multicomponent reactions (MCRs) are gaining importance and are in high demand in modern organic synthesis. It is particularly true in case of heterocycles [1] as those reactions facilitate formation of several bonds in one unit operation.[2,3] In the recent years, ultrasound irradiation has gained recognition as a clean and advantageous approach in organic synthesis.[4] The sonochemical phenomenon is the result of the interaction of suitable field of acoustic waves with

potentially reacting chemical system. This phenomenon occurs through acoustic cavitation. The phenomenon of cavitation in an irradiated solution may be expressed as a sequential process of involving the bubble formation, its growth and breakdown. Cavitation phenomenon develops high temperature and pressure in the micro environment which creates turbulence and facilitates the mass transfer in the neighborhood. Compared to conventional heating which provides thermal energy in the macro system, ultra sonification reduces reaction times, improves yields and minimizes side product formation by providing the activation energy in micro environment.[5] As this technology involves energy conservation and minimal waste generation, it is widely accepted as a green chemistry approach.[6] Furthermore, this technique can be applied to a variety of organic syntheses accomplishing better yields, under mild reaction conditions and shorter reaction times.[7]

Countless biologically and pharmacologically important compounds constitute pyrazoles and their derivatives.[8] A number of pyrazole containing compounds such as Celebrex, Viagra and Acomplia have been successfully commercialized.[9] Pyrazoles have also found applications in the agrochemical industry as ultraviolet stabilizers and energetic materials and in the field of photoprotectors.[10] Owing to the attractive pharmacological properties of pyrazoles, new methodologies for the design of different pyrazoles have attracted the attention of the researchers. Several methods are available in literature for one-pot synthesis of pyrazoles derivatives in presence or absence of catalysts.[11] Certain protocols reported to use catalysts such as triethyamine,[12] hydrotalcite,[13] L-proline in [bmim]$BF_4$[14] and using water as a solvent in catalyst-free condition,[15] to mention a few. While Dabiri *et al.*[16] have reported the synthesis of tetrahydropyrazolopyridine derivatives using ethanol as solvent; Zhao *et al.*[17] have synthesized tetrahydropyrazolopyridine derivatives using a pre-formed pyrazolone and ethanol as solvent under refluxing conditions. Many of the reported methods suffer some drawbacks, like high temperature requirements, prolonged reaction times, toxic solvents and/or expensive reagents. Some of the protocols have limitations of low yields or undesired product formation due to poor selectivity of the process. Hence, there is definite longing for less expensive and catalyst free protocols. Thus, the greater demand for better and efficient protocols materials has accentuated the need to develop novel, value-added, eco-compatible and green routes motivated the present work.

## 2. MATERIALS AND METHODS

### 2.1. Apparatus and analysis

All chemicals used were reagent grade and were used as received without further purification. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 25 $^{o}C$ at 400 MHz and 100 MHz (Bruker Avance) instrument respectively, using TMS as internal standard. Chemical shifts are given in parts per million (ppm). The FT-IR spectroscopy of samples was carried out on a Perkin Elmer Perkin Elmer Precisely 100 FT-IR spectrometer in the 400-4000 $cm^{-1}$ region. The HRMS were recorded on a waters micromass LCT premier mass spectrometer using electrospray ionization in the positive or negative mode. The ultrasonic assisted reactions are carried out in a ‘‘Spectralab model UMC 20 Ultrsonic cleaner” with a frequency of 40 kHz and a nominal power 250 W. Melting points were recorded on a hot stage melting point apparatus Ernst Leitz Wetzlar, Germany and were uncorrected. All the reactions and the purity of products were monitored using thin layer chromatography (TLC) on aluminum-backed plates coated with Merck Kieselgel 60 F254 silica gel, visualizing the spots under ultraviolet light and iodine chamber.

***2.2. General procedure for the synthesis tetrahydropyrazolopyridine under silent conditions***

A mixture of hydrazine hydrate (2.0 mmol) and ethyl acetoacetate (2.0 mmol) in $H_2O$ (15 mL) was magnetically stirred for 30 min at room temperature (25°C) followed by addition of aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol). The reaction mixture was heated at 70$^{o}$C for appropriate time as shown in Table 2. After the starting material was completely consumed, the reaction mixture was cooled to room temperature and water (10 mL) was added and the resulting mixture was stirred for 30 min. The precipitated product was filtered, washed with water and acetone then dried under vacuum. In most cases no further purification was necessary.

***2.3. General procedure for the synthesis of tetrahydropyrazolopyridine under ultrasound irradiation***

A 50 mL conical flask was charged with a mixture of hydrazine hydrate (2.0 mmol) and ethyl acetoacetate (2.0 mmol) in $H_2O$ (15 mL). The mixture was irradiated for 10 min at room temperature followed by addition of aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol). The reaction mixture was irradiated under sonication at 50$^{o}$C for appropriate time as shown in Table 2. To maintain the ultrasonic bath temperature, cold/hot water was either added or removed manually. After the starting material was completely consumed, the reaction mixture

was cooled to room temperature and water (10 mL) was added and the resulting mixture was irradiated for 15 min. The precipitated product was filtered, washed with water and acetone then dried under vacuum. In most cases no further purification was necessary.

### *2.3.1. Physical data*

***3,5-Dimethyl-4-phenyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5a)***

Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 2.07 (6H, s), 4.80 (1H, s), 7.08-7.21 (5H, m), 11.19 (3H, br, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 10.8, 33.5, 104.7, 125.8, 127.9, 128.1, 140.5, 143.9, 161.5; IR (KBr, cm$^{-1}$): 3274 (NH); HRMS of [$C_{15}H_{15}N_5$ + Na] (m/z): 288.0845 (100%); Calc. Mass: 288.0822.

***4-(4-Methoxy-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5b)***

Pale yellow solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 2.03 (6H, s), 3.82 (3H, s), 4.53 (1H, s), 7.03 (2H, d, *J* = 8.7 Hz), 7.79 (2H, d, *J* = 8.6 Hz), 8.99 (3H, br, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 10.3, 31.9, 54.9, 104.4, 113.0, 128.3, 135.1, 139.6, 157.1, 161.0; IR (KBr, cm$^{-1}$): 3266 (NH); HRMS of [$C_{16}H_{17}N_5O$ + 1] (m/z): 296.1975 (100%); Calc. Mass: 296.1909.

***4-(4-Bromo-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5c)***

Pale yellow solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 2.07 (6H, s), 4.78 (1H, s), 7.04 (2H, d, *J* = 8.3 Hz), 7.37 (2H, d, *J* = 8.4 Hz), 11.32 (3H, br, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 10.2, 32.2, 104.4, 118.4, 129.7, 130.4, 131.9, 142.7, 157.5; IR (KBr, cm$^{-1}$): 3225 (NH); HRMS of [$C_{15}H_{14}BrN_5$ + 1] (m/z): 344.0255 (100%); Calc. Mass: 344.0260.

***[4-(3,5-Dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridin-4-yl)-phenyl]-dimethyl-amine (5d)***

Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 2.05 (6H, s), 2.8 (6H, s), 4.69 (1H, s), 6.56 (2H, d, *J* = 8.8 Hz), 6.92 (2H, d, *J* = 8.5 Hz), 10.91 (3H, br, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 10.3, 31.7, 40.4, 104.7, 112.2, 127.8, 131.1, 148.5, 159.7, 161.0; IR (KBr, cm$^{-1}$): 3170 (NH); MS (ESI), *m*/*z* = 309 (M+1, 100%); Anal. Calcd ($C_{17}H_{20}N_6$): C 66.21, H 6.54, N 27.25%. Found: C 66.19, H 6.51, N 27.20%.

***4-(3,5-Dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridin-4-yl)-phenol (5e)***

Pale yellow solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 2.06 (6H, s), 4.71 (1H, s), 6.59 (2H, d, *J* = 8.5 Hz), 6.90 (2H, d, *J* = 8.4 Hz), 9.28 (1H, br, s), 11.04 (1H, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 10.3, 31.8, 104.6, 114.4, 128.2, 133.3, 139.7, 155.0, 161.0; IR (KBr, cm$^{-1}$): 3267 (NH); HRMS of [$C_{15}H_{14}BrN_5$ + Na] (m/z): 304.1229 (100%); Calc. Mass: 304.1239.

***4-(2-Bromo-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5f)***

Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.92 (6H, s), 5.04 (1H, s), 7.05-7.53 (4H, m), 10.79 (3H, br, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 10.5, 30.6, 102.3, 126.8, 127.7, 128.2, 130.8, 132.3, 138.4, 142.3, 160.6; IR (KBr, $cm^{-1}$): 3174 (NH); MS (ESI), *m*/*z* = 366 (M+Na, 100%); Anal. Calcd ($C_{15}H_{14}BrN_5$): C 52.34, H 4.10, N 20.35%. Found: C 52.26, H 4.03, N 20.28%.

***4-(2-Methoxy-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5g)***

White solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 2.04 (6H, s), 3.72 (3H, s), 5.05 (1H, s), 6.77-7.52 (4H, m), 10.75 (3H, br, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 10.3, 30.6, 55.3, 103.8, 110.3, 119.6, 126.6, 128.9, 131.8, 138.3, 155.8, 160.3; IR (KBr, $cm^{-1}$): 3077 (NH); HRMS of [$C_{16}H_{17}N_5O$ + 1] (m/z): 296.1996 (100%); Calc. Mass: 296.1909.

***4-(2-Chloro-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5h)***

Pale yellow solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.94 (6H, s), 5.08 (1H, s), 7.13-7.55 (4H, m), 10.85 (3H, br, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 10.3, 30.6, 102.3, 126.3, 127.4, 128.9, 130.5, 132.2, 138.7, 140.6, 160.6; IR (KBr, $cm^{-1}$): 3199 (NH); HRMS of [$C_{15}H_{14}ClN_5$ + Na] (m/z): 322.1119 (100%); Calc. Mass: 322.1110.

***3,5-Dimethyl-4-(2-nitro-phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5i)***

Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.92 (6H, s), 5.44 (1H, s), 7.37-7.68 (4H, m), 10.98 (3H, br, s); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 10.0, 28.9, 101.9, 123.8, 127.1, 130.2, 131.6, 136.2, 138.6, 149.5, 160.5; IR (KBr, $cm^{-1}$): 3381 (NH); HRMS of [$C_{15}H_{14}N_6O_2$ + 1] (m/z): 311.1052 (100%); Calc. Mass: 311.1062.

### *2.4. General procedure for the synthesis pyrazoles under silent conditions*

To a solution of arylaldehyde (2.0 mmol), malononitrile (2.0 mmol), hydrazine hydrate (2.0 mmol) and ethyl acetoacetate (2 mmol) in water (15 mL). The reaction mixture was stirred at 70ºC for the period of time as indicated in Table 2. After the completion of the reaction (The reaction was monitored by TLC), the reaction mixture cooled to room temperature, the residue was filtered and was washed with ethanol to produce the desired solid.

### *2.5. General procedure for the synthesis of pyrazoles under ultrasound irradiation*

A 50 mL conical flask was charged with freshly distilled benzaldehyde (2.0 mmol), malanonitrile (2.0 mmol), hydrazine hydrate (2.0 mmol) and ethyl acetoacetate (2 mmol) in water (15 mL). The reaction mixture was irradiated at 50ºC for the period of time (The reaction was monitored by TLC) as indicated in Table 2. After the completion of the reaction, the reaction

mixture cooled to room temperature, the residue was filtered and was washed with ethanol to produce the desired solid.

### *2.5.1. Physical data*

***6-Amino-3-methyl-4-phenyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7a)***

White solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.77 (3H, s), 4.58 (1H, s), 6.85 (2H, s, -$NH_2$), 7.15-7.32 (5H, m), 12.09 (1H, s, -NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 9.6, 36.1, 57.1, 97.6, 120.7, 126.7, 127.4, 128.4, 135.6, 144.3, 154.7, 160.8; IR (KBr, $cm^{-1}$): 2191 (CN), 3369 ($NH_2$); HRMS of [$C_{14}H_{12}N_4O$ - 1] (m/z): 251.0929 (100%); Calc. Mass: 251.0933.

***6-Amino-4-(4-methoxy-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7b)***

White solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.77 (3H, s), 3.71 (3H, s), 4.53 (1H, s), 6.85 (2H, s, -$NH_2$), 6.85 (2H, d, *J* = 8.6 Hz), 7.06 (2H, d, *J* = 8.6 Hz ), 12.07 (1H, s, -NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 9.6, 35.3, 54.9, 57.6, 97.8, 113.7, 120.8, 128.4, 135.5, 136.4, 157.9, 160.6; IR (KBr, $cm^{-1}$): 2191 (CN), 3256 ($NH_2$); HRMS of [$C_{15}H_{14}N_4O_2$ - 1] (m/z): 281.1039 (100%); Calc. Mass: 281.1039.

***6-Amino-4-(4-bromo-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7c)***

White solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.78 (3H, s), 4.61 (1H, s), 6.91(2H, s, -$NH_2$), 7.12 (2H, d, *J* = 8.4 Hz), 7.48 (2H, d, *J* = 8.3 Hz ), 12.14 (1H, s, -NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 9.6, 35.6, 56.7, 97.0, 119.7, 120.6, 129.6, 131.3, 135.7, 143.8, 154.6, 160.8; IR (KBr, $cm^{-1}$): 2189 (CN), 3395 ($NH_2$); HRMS of [$C_{14}H_{11}BrN_4O$ - 1] (m/z): 329.0049 (100%); Calc. Mass: 329.0038.

***6-Amino-4-(4-dimethylamino-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7d)***

Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.78 (3H, s), 2.84 (6H, s), 4.44 (1H, s), 6.63 (2H, d, *J* = 8.6 Hz), 6.73 (2H, s, -$NH_2$), 6.94 (2H, d, *J* = 8.6 Hz), 12.03 (1H, s, -NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 9.7, 35.3, 40.1, 57.9, 98.1, 112.2, 120.9, 127.9, 131.9, 135.4, 149.1, 154.7, 160.5; IR (KBr, $cm^{-1}$): 2187 (CN), 3344 ($NH_2$); HRMS of [$C_{16}H_{17}N_5O$ - 1] (m/z): 294.1366 (100%); Calc. Mass: 294.1355.

***6-Amino-4-(4-hydroxy-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7e)***

White solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.77 (3H, s), 4.46 (1H, s), 6.67 (2H, d, *J* = 8.4 Hz), 6.76 (2H, s, -$NH_2$), 6.93 (2H, d, *J* = 8.4 Hz), 9.29 (1H, s, -OH), 12.04 (1H, s, -NH); $^{13}$C

NMR (100 MHz, DMSO-$d_6$): δ 9.6, 35.4, 57.7, 98.0, 115.0, 120.8, 128.3, 134.7, 135.5, 154.7, 155.9, 160.5; IR (KBr, $cm^{-1}$): 2174 (CN), 3371 ($NH_2$); HRMS of [$C_{14}H_{12}N_4O_2$ - 1] (m/z): 267.0878 (100%); Calc. Mass: 267.0882.

***6-Amino-4-(2-methoxy-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7f)***

White solid; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ = 1.78 (3H, s), 3.77 (3H, s), 4.97 (1H, s), 6.78 (2H, s, -$NH_2$), 6.87-7.20 (4H, m), 12.01 (1H, s, -NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 9.4, 29.1, 55.5, 56.3, 97.7, 111.2, 120.7, 120.8, 127.8, 128.5, 132.0, 135.0, 155.0, 156.3, 161.4; IR (KBr, $cm^{-1}$): 2194 (CN), 3374 ($NH_2$); HRMS of [$C_{15}H_{14}N_4O_2$ - 1] (m/z): 281.1028 (100%); Calc. Mass: 281.1039.

***6-Amino-4-(2-bromo-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7g)***

White solid; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ = 1.75 (3H, s), 5.06 (1H, s), 6.94 (2H, s, -$NH_2$), 7.13-7.58 (4H, m), 12.14 (1H, s, -NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 9.6, 35.8, 55.9, 97.0, 120.2, 122.3, 128.3, 128.8, 130.9, 132.6, 135.4, 142.5, 154.8, 161.1; IR (KBr, $cm^{-1}$): 2189 (CN), 3389 ($NH_2$); HRMS of [$C_{14}H_{11}BrN_4O$ - 1] (m/z): 329.0033 (100%); Calc. Mass: 329.0038.

***6-Amino-4-(2-chloro-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7h)***

White solid; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ = 1.75 (3H, s), 5.06 (1H, s), 6.93 (2H, s, -$NH_2$), 7.16-7.41 (4H, m), 12.13 (1H, s, -NH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 9.4, 33.4, 55.7, 96.8, 120.3, 127.7, 128.5, 129.4, 130.6, 131.9, 135.3, 140.8, 154.9, 161.2; IR (KBr, $cm^{-1}$): 2189 (CN), 3389 ($NH_2$); HRMS of [$C_{14}H_{11}ClN_4O$ - 1] (m/z): 285.0539 (100%); Calc. Mass: 285.0543.

## 3. RESULTS AND DISCUSSION

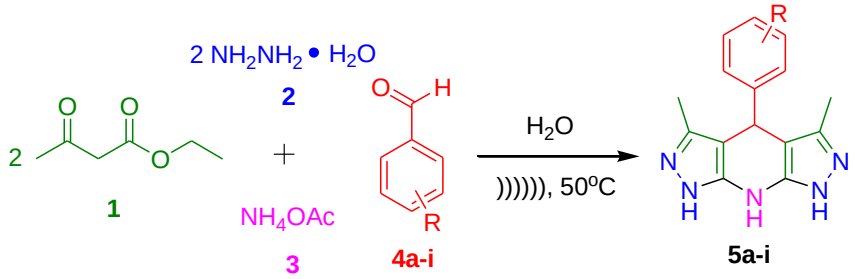
Recently, we have reported some multicomponent reactions that provide easy access to develop eco-sustainable and clean synthetic routes for the synthesis of various heterocyclic derivatives[18] and an ultrasonic-assisted method for synthesis of polysubstituted pyridines.[2a] With sustained interest in development of useful multicomponent reactions, in this communication we report an expedient approach to prepare pyrazole derivatives under ultrasound irradiation for the first time and using water as a solvent.

Literature survey shows that there are no reports either on the synthesis of tetrahydropyrazolopyridines under ultrasound irradiation, with or without catalyst, under solvent-free conditions or by using water as a solvent. Our intention was to develop an eco-friendly,

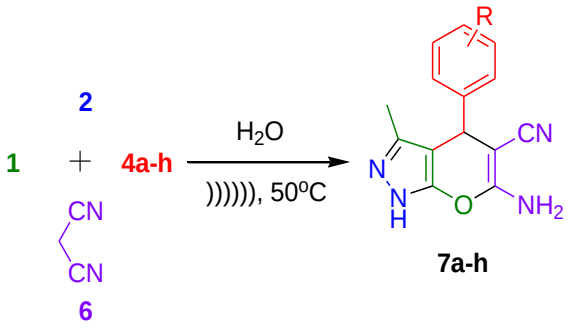
methodology for the synthesis of heterocyclics of biological significance under sonochemical conditions. In that pursuit, we report our success in the one-pot synthesis of tetrahydropyrazolopyridine derivatives (**5a-i**) and pyranopyrazoles (**7a-h**) via four-component coupling reaction under ultrasound irradiation at 50 $^{o}$C in water media (**Scheme 1&2**).

**Schemes**

**Scheme 1.** multicomponent synthesis of tetrahydropyrazolopyridine **5a-i**




**Scheme 2.** multicomponent synthesis of pyrazoles derivatives **7a-h**




Preliminary studies were carried out using hydrazine hydrate (2.0 mmol), ethyl acetoacetate (2.0 mmol) and benzaldehyde 4a (1.0 mmol) under silent and ultrasound irradiation at room temperature (rt) separately, with using EtOH and water as a solvent. We did not observe any trace of the desired product under the silent conditions (Table 1, entries 1-3). The reaction was also carried out under silent conditions at increased temperatures above 50$^{o}$C, reaction occurred, but with low yields. Preliminary experiments with appropriate reagents were conducted using water under ultrasound irradiation at 25 (rt), 40 and 50$^{o}$C and with conventional heating at 70$^{o}$C. The increase in the reaction temperature under ultrasonification improved the yields and reduced the reaction times. Impressively, at 50$^{o}$C, the ultrasonic method gave the preferred product (5a) selectively with 95% yield, which could be possibly due the phenomenon

of cavitations produced by ultrasound. Cavitation induces very high local temperatures and pressure inside the bubbles, leading to a turbulent flow in the liquid and enhanced mass transfer in the area. Based on the results, taking 50$^{o}$C as optimum condition, all the reactions were conducted at that temperature, and obtained results are summarized in Table 1. This study validates that sonochemical approach with water as media is ideal for one-pot, four-component reactions to achieve excellent yields.

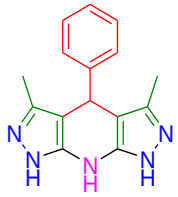
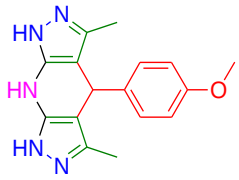
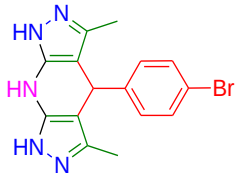
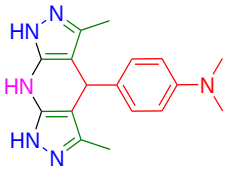
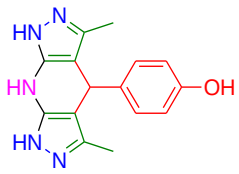
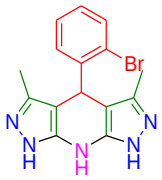
**Table 1.** Optimization of reaction conditions of the four-component reactions

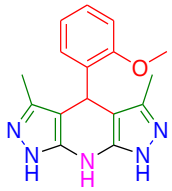
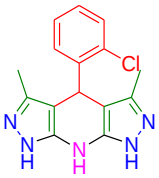
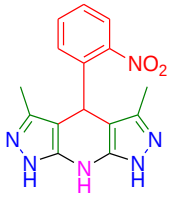
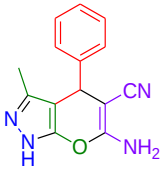
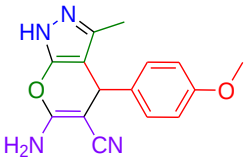
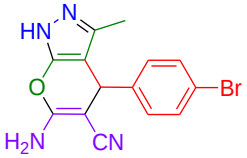
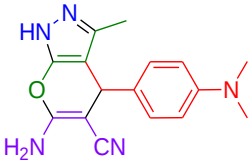
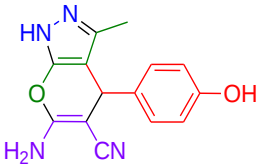
| **Entry** | **Product No.** | **Temperature ($^{o}$C)** | **Solvent** | **Conventional** | | **Sonication** | |
|---|---|---|---|---|---|---|---|
| | | | | **Time (h)** | **Yield [a](%)** | **Time (h)** | **Yield [a](%)** |
| 1 | **5a** | 25 | EtOH | 7.0 | b | 4.0 | b |
| 2 | **5a** | 25 | $H_2O$/EtOH | 8.0 | b | 4.0 | b |
| 3 | **5a** | 25 | $H_2O$ | 8.0 | b | 4.0 | 38 |
| 4 | **5a** | 70 | $H_2O$ | 7.0 | 64 | c | c |
| 5 | **5a** | 50 | $H_2O$ | 8.0 | 52 | 2.0 | 95 |
| 7 | **7a** | 70 | EtOH | 6.0 | 62 | c | c |
| 8 | **7a** | 50 | EtOH | 8.0 | 50 | 1.5 | 85 |
| 9 | **7a** | 50 | $H_2O$ | 8.0 | 59 | 1.0 | 92 |

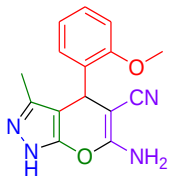
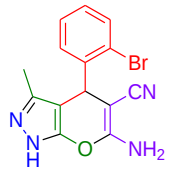
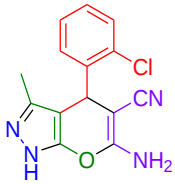
[a] Isolated yields, [b] Products were not found, [c] Reaction was not performed.

The versatility of the protocol is further demonstrated by repeating the procedure for synthesizing an array of tetrahydropyrazolopyridine (**5a-i**) and pyranopyrazoles (**7a-h**) derivatives (Table 2). In this protocol, in addition to aromatic aldehydes, spatially-hindered aldehydes such as 2-methoxy, 2-bromo and 2-chloro were also found acceptable giving good yields.

**Table 2.** Four-component reaction for the synthesis of tetrahydropyrazolopyridine (5**a-i**) and pyranopyrazoles (**7a-h**) under both ultrasonic irradiation and silent condition

| Entry | Product No. | Product | Conventional | | Sonication | | MP/(ºC) | |
|---|---|---|---|---|---|---|---|---|
| | | | Time (h) | Yield [a](%) | Time (h) | Yield [a](%) | Found | Reported |
| 1 | **5a** |  | 7.0 | 64.0 | 2.0 | 95.0 | 239-240 | 240-241 [17] |
| 2 | **5b** |  | 6.0 | 60.0 | 2.5 | 96.0 | 183-184 | 185-187 [17] |
| 3 | **5c** |  | 6.0 | 58.0 | 2.0 | 94.0 | 165-166 | - |
| 4 | **5d** |  | 6.5 | 61.0 | 2.5 | 92.0 | 235-236 | - |
| 5 | **5e** |  | 6.0 | 63.0 | 2.5 | 90.0 | 267-268 | 268-270 [17] |
| 6 | **5f** |  | 6.0 | 55.0 | 2.0 | 92.0 | 160-161 | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 7 | **5g** |  | 5.5 | 60.0 | 1.5 | 91.0 | 171-172 | - |
| 8 | **5h** |  | 6.0 | 64.0 | 2.0 | 94.0 | 164-165 | - |
| 9 | **5i** |  | 6.5 | 60.0 | 2.5 | 92.0 | 187-188 | - |
| 10 | **7a** |  | 3.5 | 70.0 | 1.0 | 92.0 | 204-205 | 205-207 [4f] |
| 11 | **7b** |  | 2.0 | 69.0 | 1.0 | 94.0 | 210-211 | - |
| 12 | **7c** |  | 3.0 | 80.0 | 0.5 | 97.0 | 214-215 | 213-215 [4f] |
| 13 | **7d** |  | 3.5 | 64.0 | 1.0 | 96.0 | 217-218 | - |
| 14 | **7e** |  | 3.5 | 73.0 | 1.5 | 90.0 | 217- | 219-221 [4f] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 218 | |
| 15 | **7f** |  | 3.0 | 67.0 | 1.0 | 91.0 | 249-250 | - |
| 16 | **7g** |  | 3.0 | 72.0 | 1.0 | 94.0 | 201-202 | - |
| 17 | **7h** |  | 2.5 | 78.0 | 1.0 | 96.0 | 220-221 | 224-226 [4f] |

[a] Isolated yields.

All the synthesized compounds could be purified without applying any chromatographic method. Thus escaping the need of volatile organic solvents generally required for work-up and purification in many existing procedures. To our belief, this new technique is an excellent method for the synthesis of tetrahydropyrazolopyridine derivatives and pyranopyrazoles. Moreover, it is worth noting that new C-C and C-heteroatom bonds were formed with concomitant creation of a pyrazoles involving four-component in one-pot process. All the reaction products were totally characterized by various spectroscopic technics including, FTIR, $^{1}$H NMR, $^{13}$C NMR and MS (Supplementary Materials Data - **I**).

The results of Table 2 confirm the advantage of ultrasound method over conventional thermal method, in terms of (i) time required for the formation of new C-C and C-heteroatom bonds under ultrasonic irradiation is shorter, (ii) cyclization takes place at low temperature compare to conventional heating, (iii) the isolated products are higher yields, and additionally (iv) the reaction and work-up is simple to execute.

## 4. CONCLUSIONS

In summary, we report a remarkable, eco-friendly and expedient one-pot technique for rapid synthesis of pyrazole derivatives from easily accessible starting materials, within 0.5 - 2.5 h. Ultrasound has accelerated the multicomponent reaction in good to excellent chemical yields are achieved. Furthermore, sterically hindered substrates were also well accepted resulting in good yields. This method will be of choice for the preparation of a variety of pyrazole derivatives some of which are difficult to make *via* silent approaches.

## 5. ACKNOWLEDGMENTS

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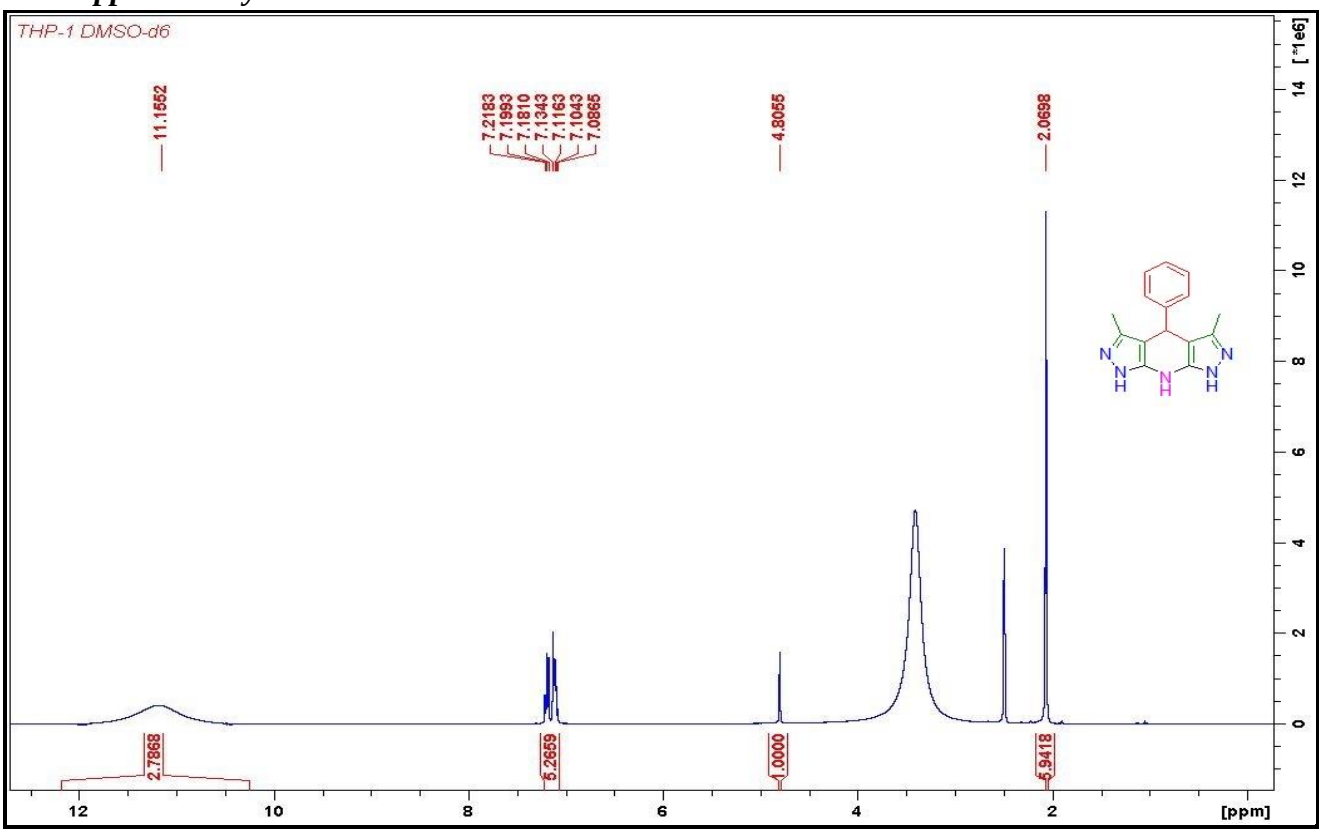
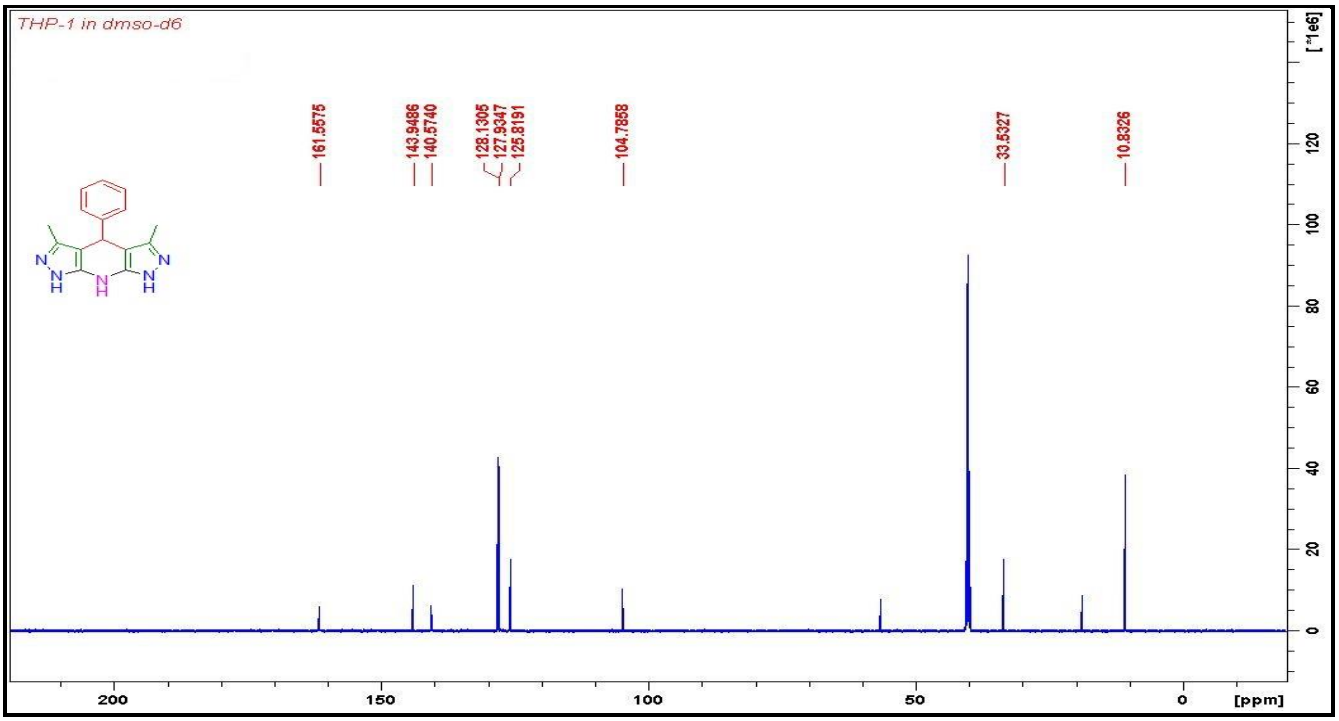
## *6.1. Supplementary Materials Data - I*




$^{1}$H NMR spectra of compound **5a**

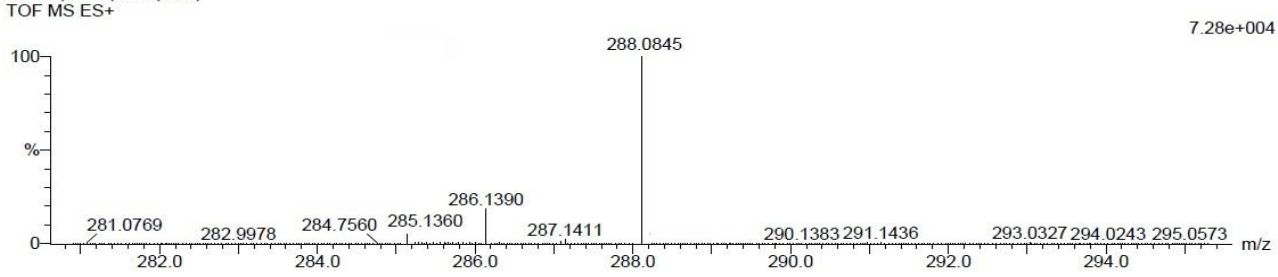



$^{13}$C NMR spectra of compound **5a**

**Elemental Composition Report** **Page 1**

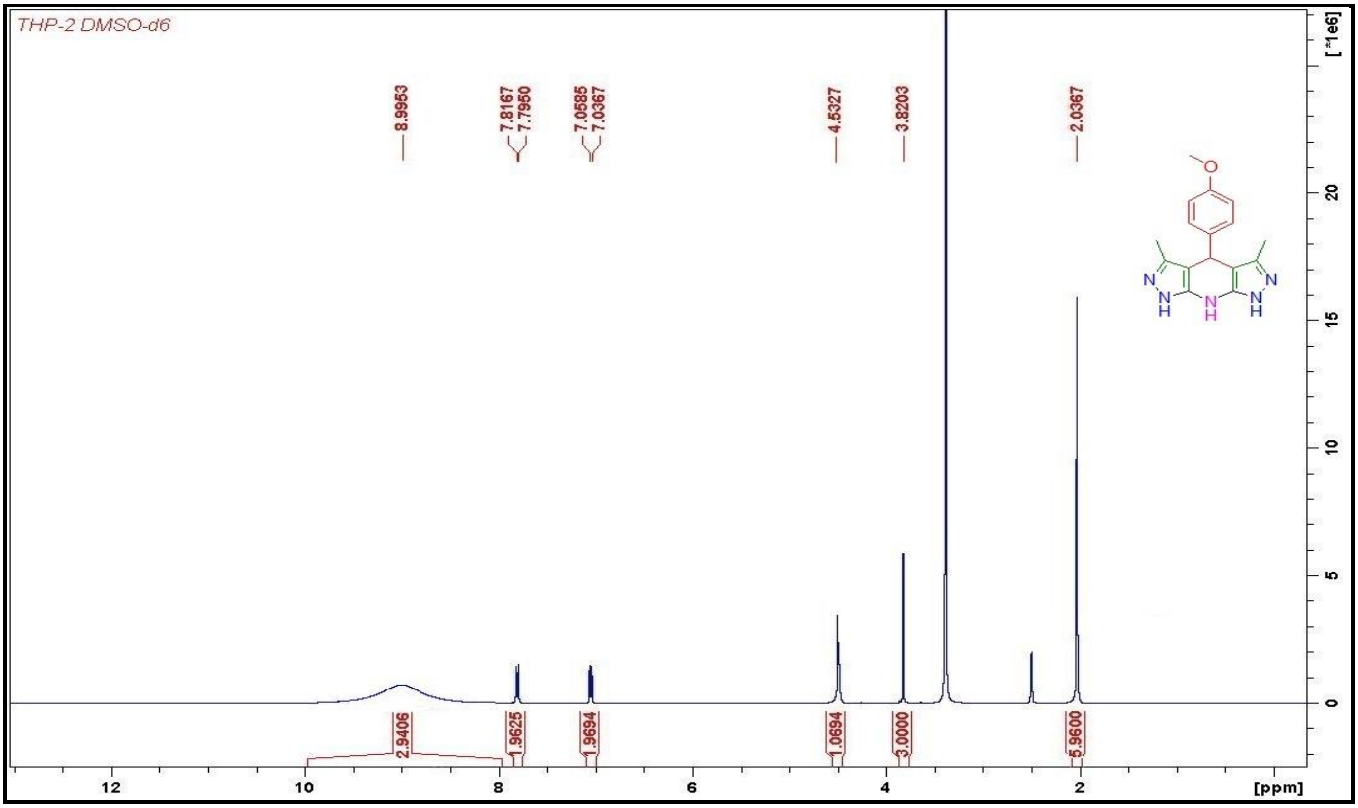
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
279 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 5-50 H: 5-50 N: 0-10 Na: 0-1
5A 43 (0.717) Cm (1:60)
TOF MS ES+

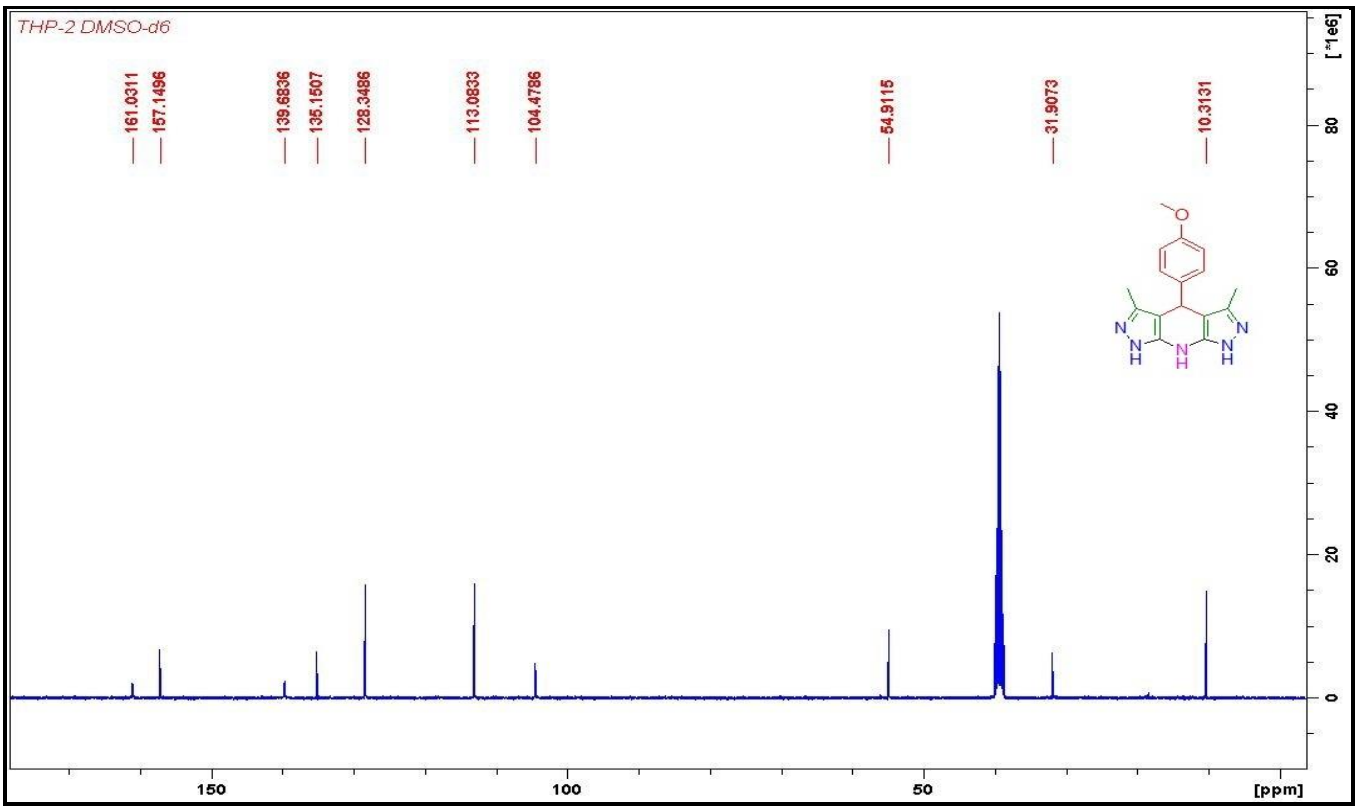



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 288.0845 | 288.0822 | 0.8 | 2.8 | 9.5 | 579.6 | 0.0 | C15 H15 N5 Na |

HRMS spectra of compound **5a**




$^{1}$H NMR spectra of compound **5b**

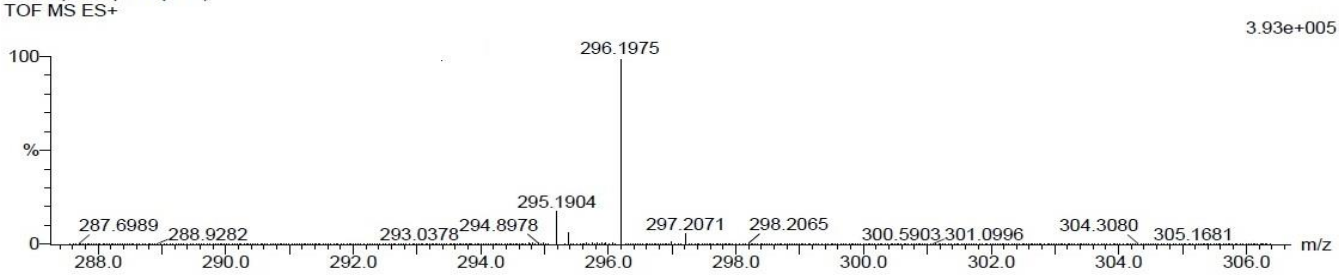



$^{13}$C NMR spectra of compound **5b**

**Elemental Composition Report** **Page 1**

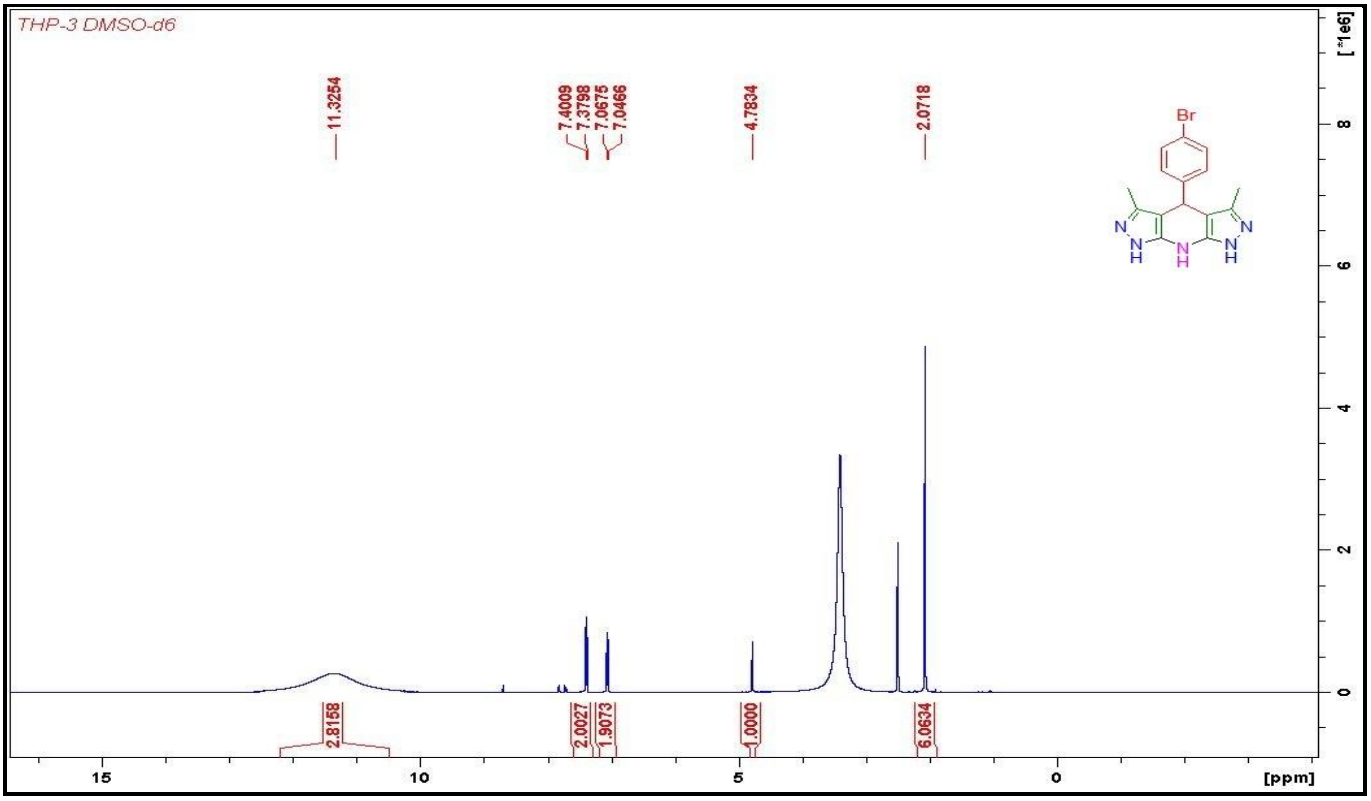
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
606 formula(e) evaluated with 2 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 0-50 H: 0-50 N: 0-10 O: 0-10
5B 21 (0.341) Cm (1:60)
TOF MS ES+

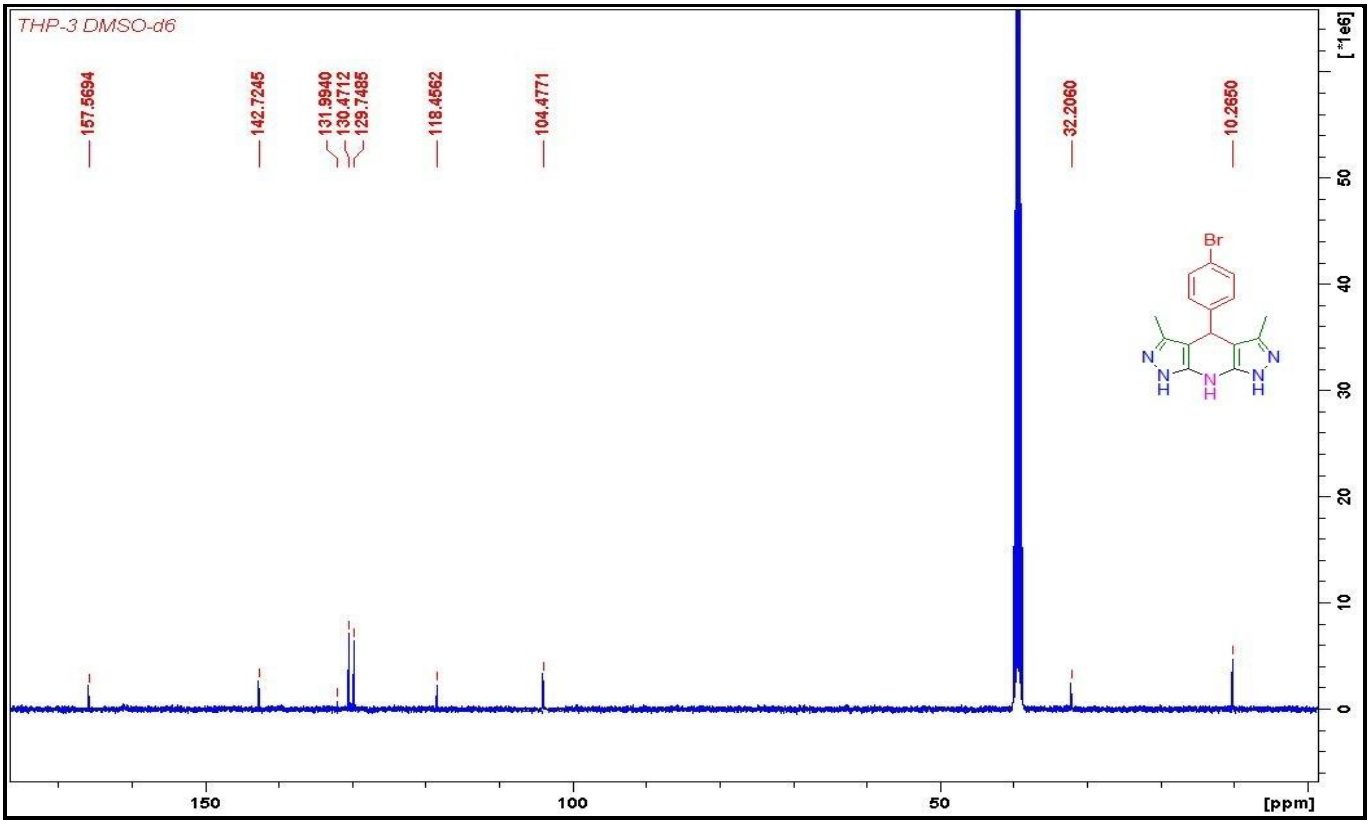



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 296.1975 | 296.1909 | 0.5 | 1.7 | 6.5 | 708.0 | 0.9 | C16 H18 N5 O |

HRMS spectra of compound **5b**




$^{1}$H NMR spectra of compound **5c**



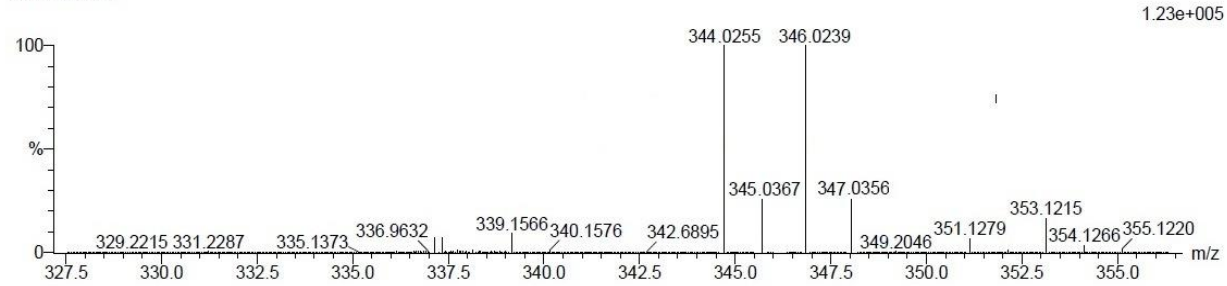

$^{13}$C NMR spectra of compound **5c**

**Elemental Composition Report** **Page 1**

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
715 formula(e) evaluated with 6 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 0-50 H: 0-50 N: 0-10 Br: 1-1

5C 42 (0.699) Cm (1:60)
TOF MS ES+




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
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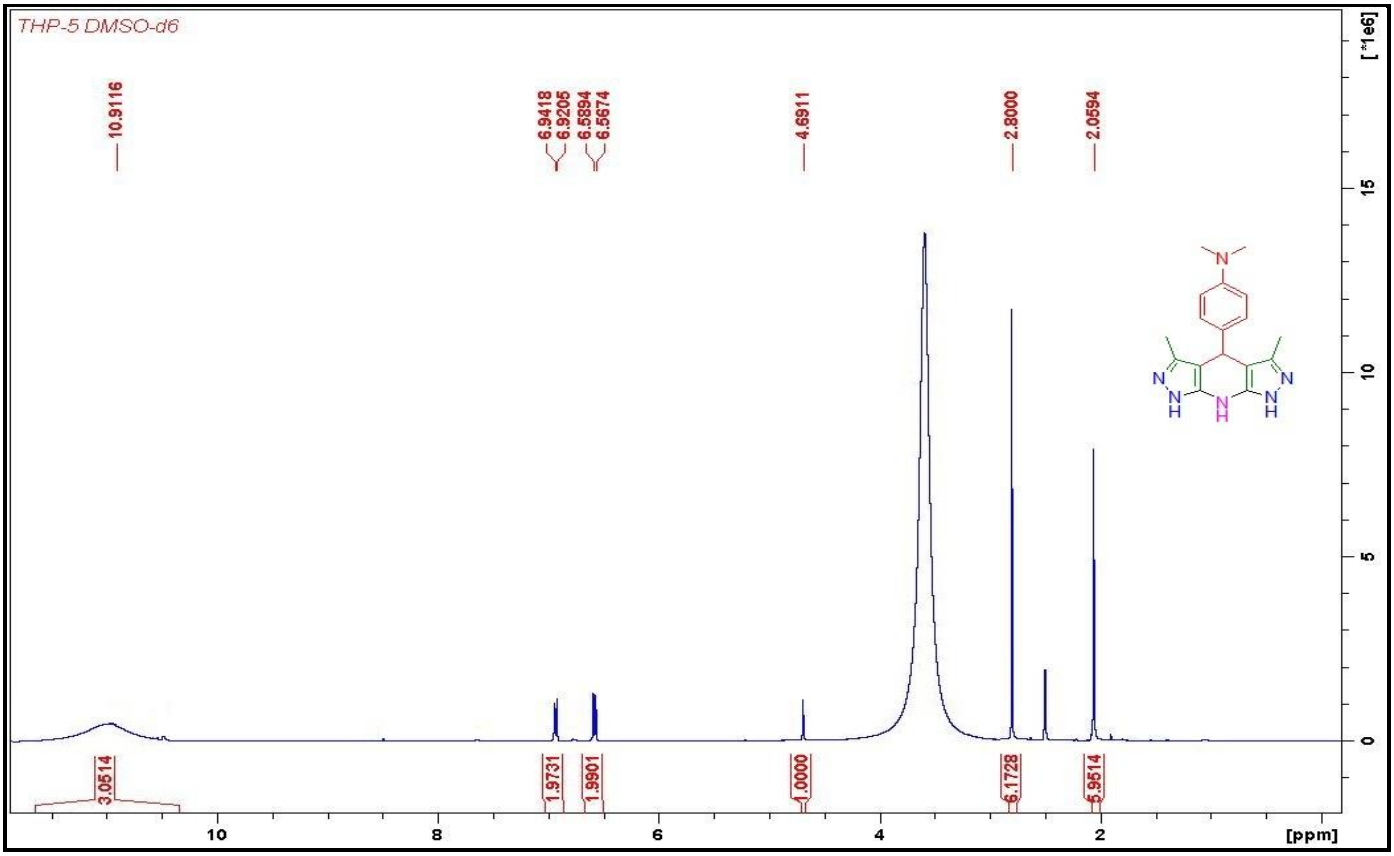
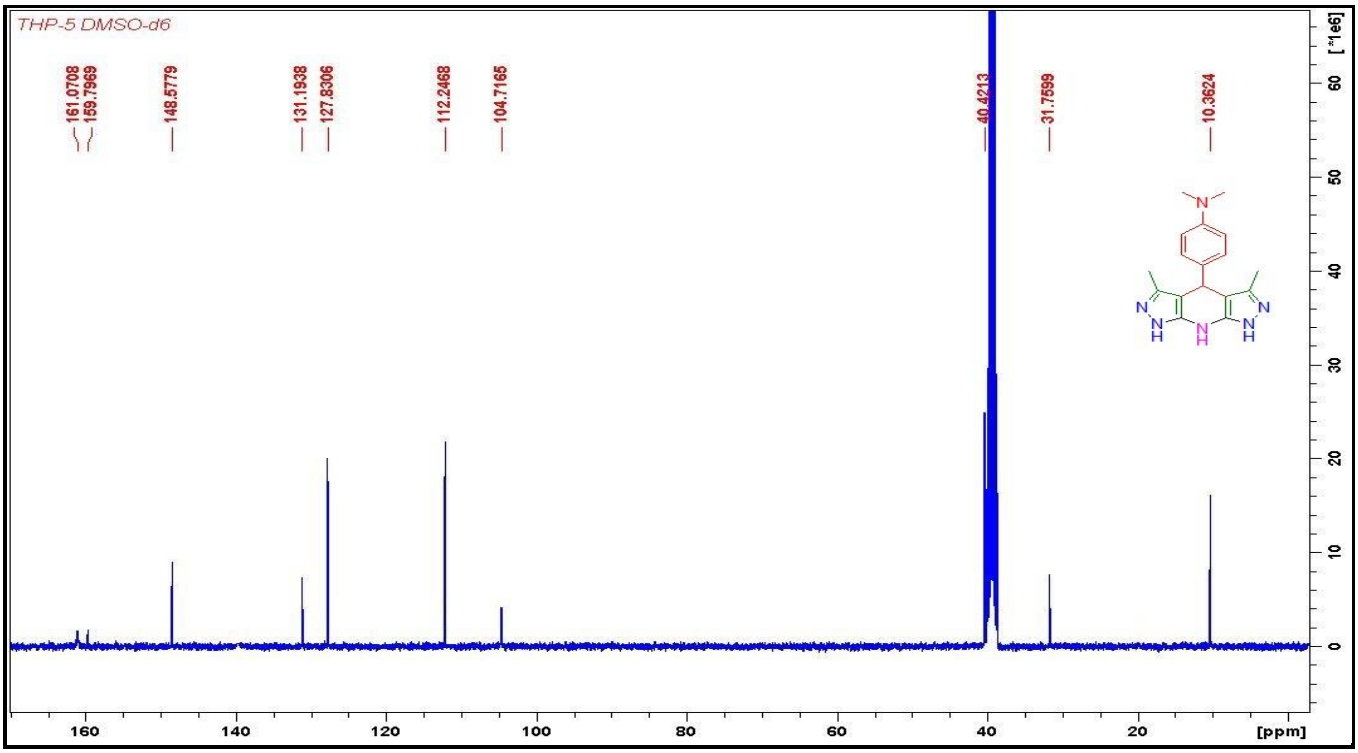
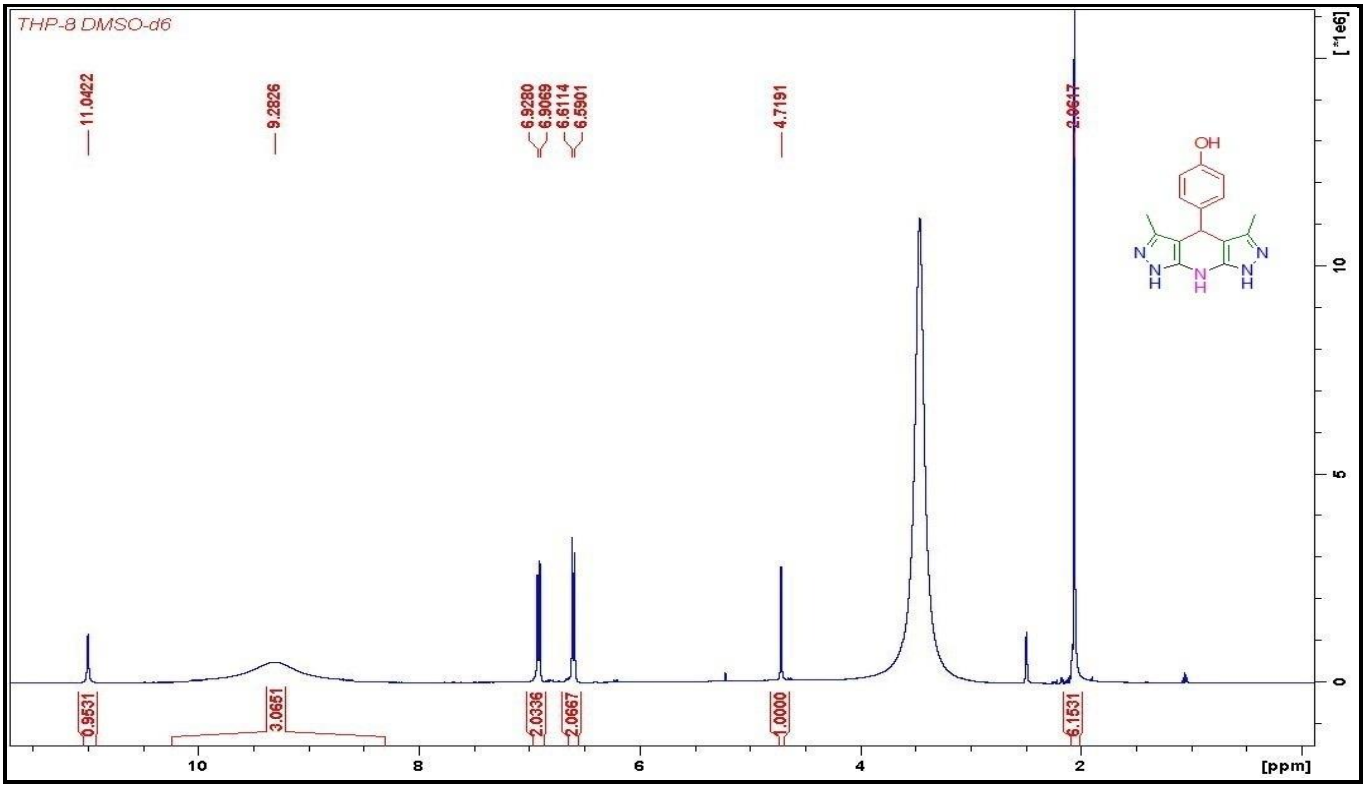
HRMS spectra of compound **5c**



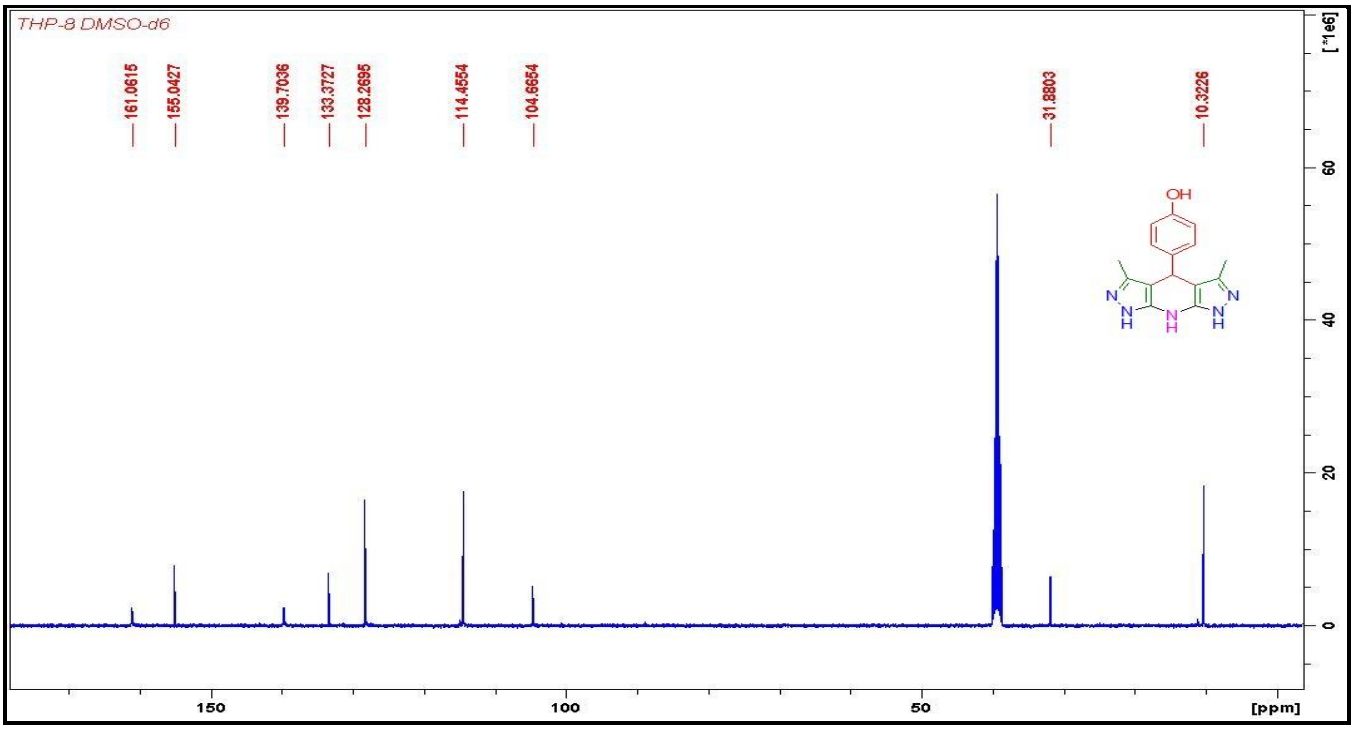

$^{1}$H NMR spectra of compound **5d**




$^{13}$C NMR spectra of compound **5d**




$^{1}$H NMR spectra of compound **5e**

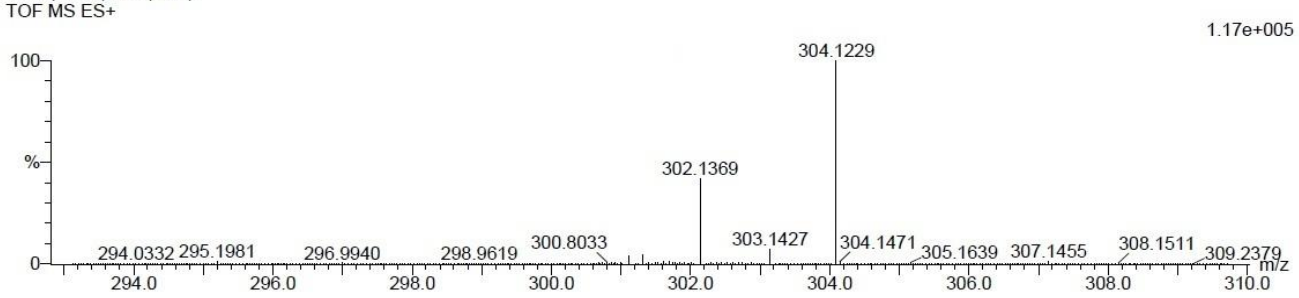



$^{13}$C NMR spectra of compound **5e**

**Elemental Composition Report** **Page 1**

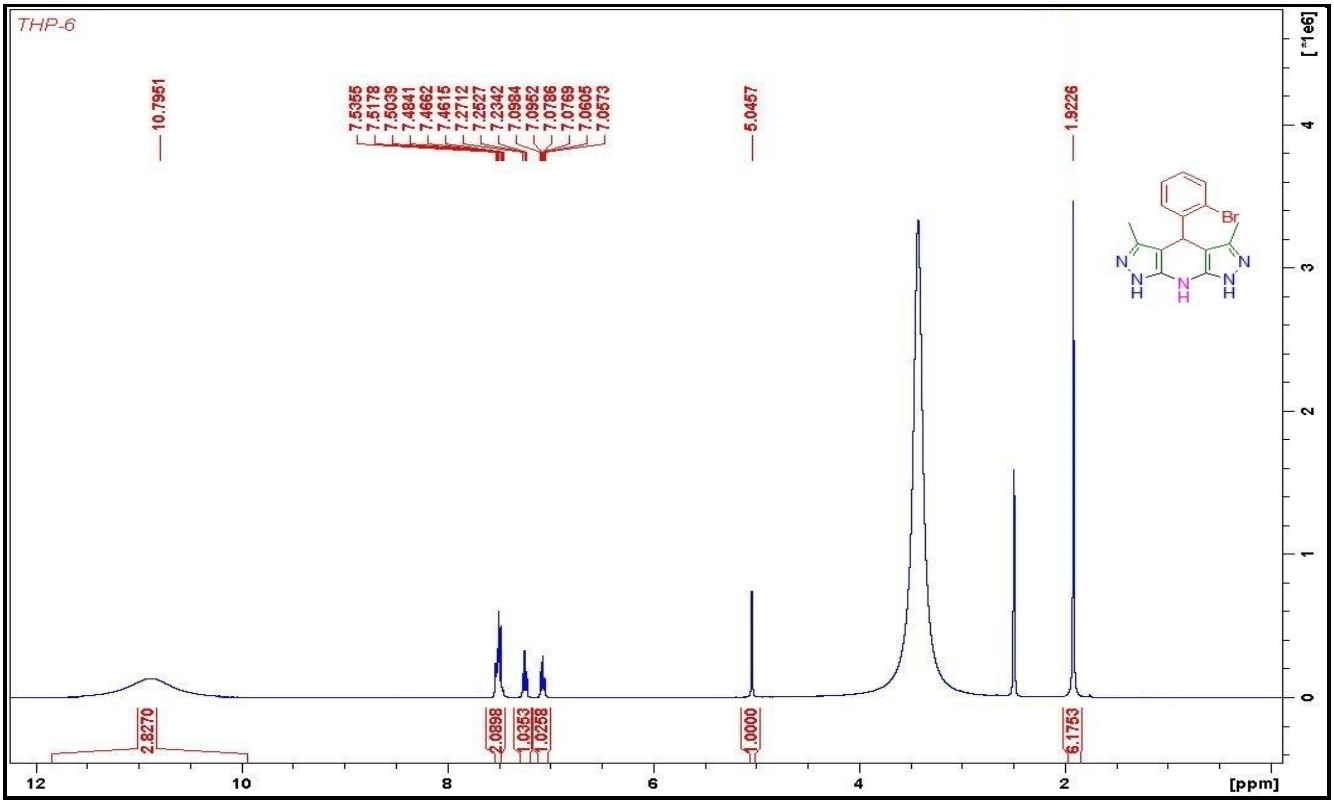
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
385 formula(e) evaluated with 2 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 0-50 H: 0-50 N: 0-10 O: 0-10 Na: 0-1
5E 9 (0.270) Cm (1:61)
TOF MS ES+

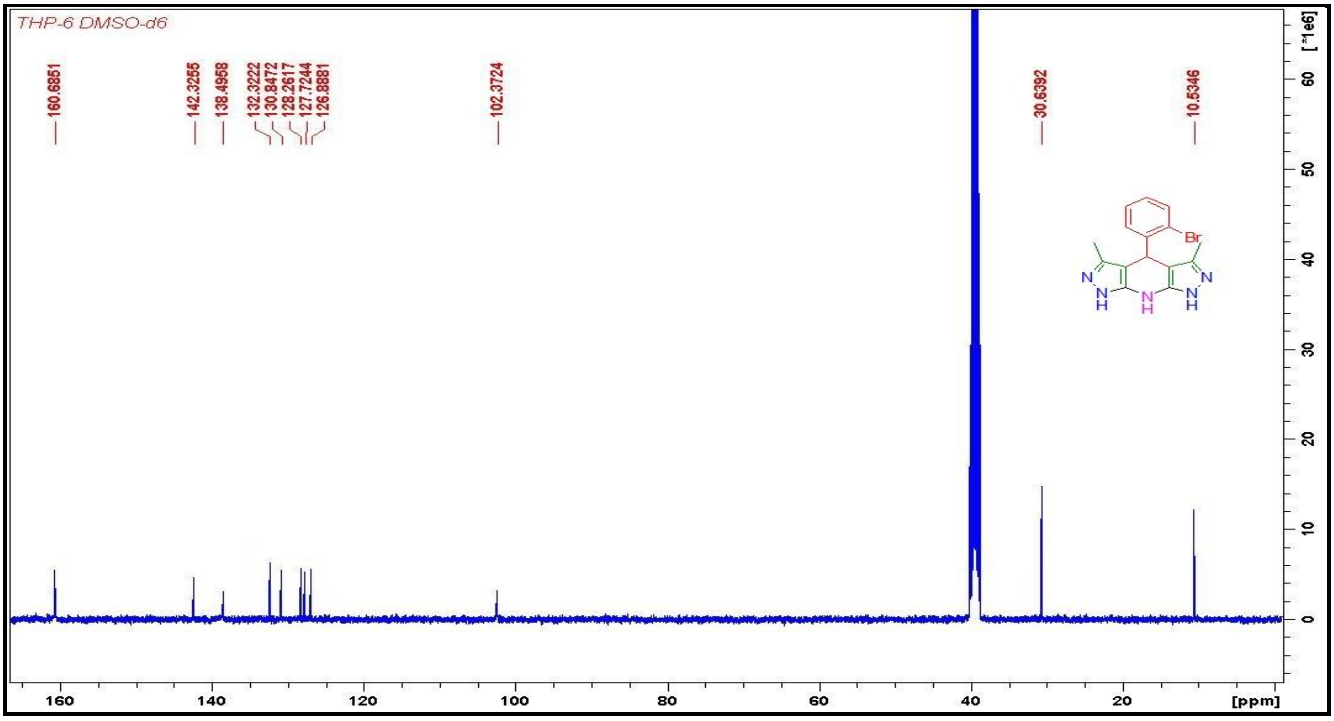



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 304.1229 | 304.1239 | 0.0 | 0.0 | 13.5 | 645.2 | 0.0 | C15 H15 N5 O Na |

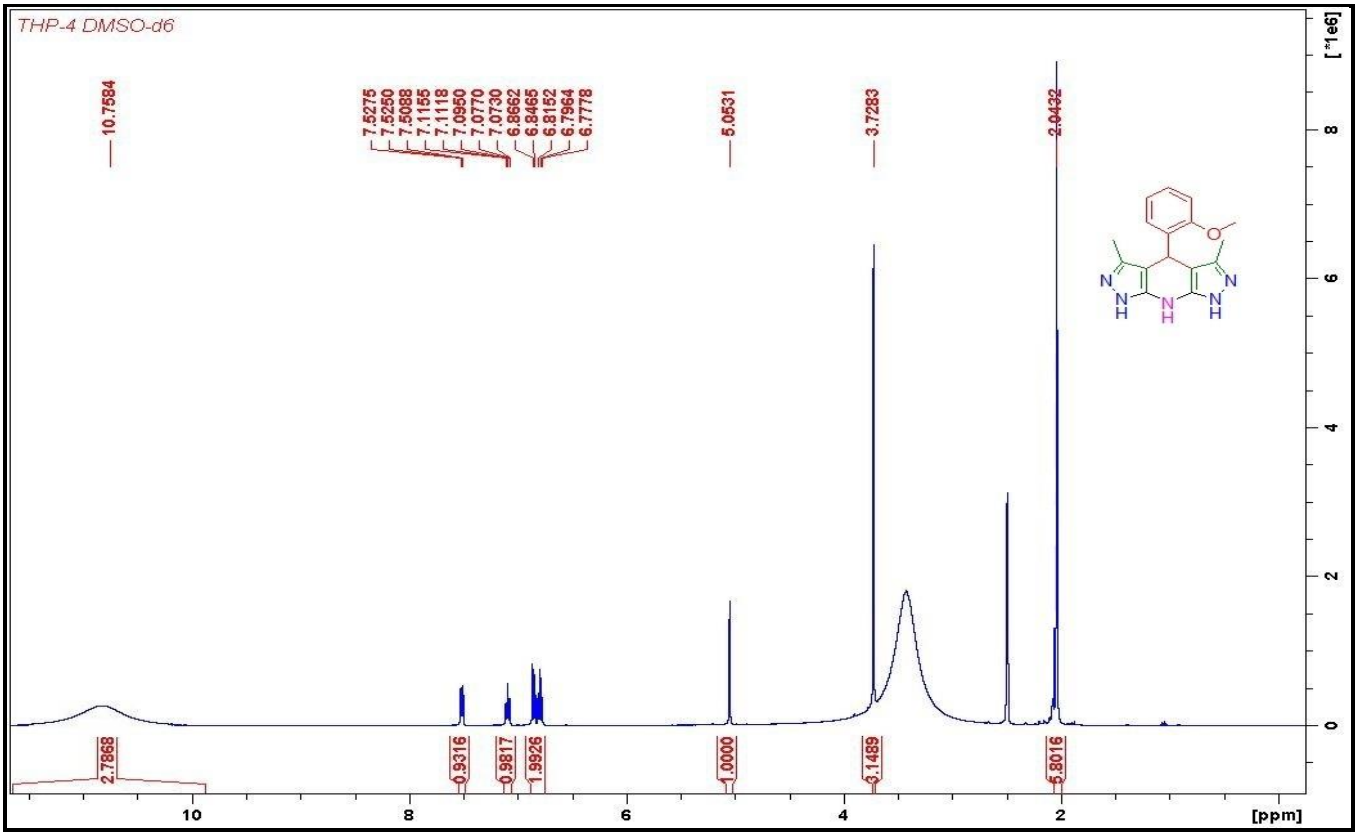
HRMS spectra of compound **5e**



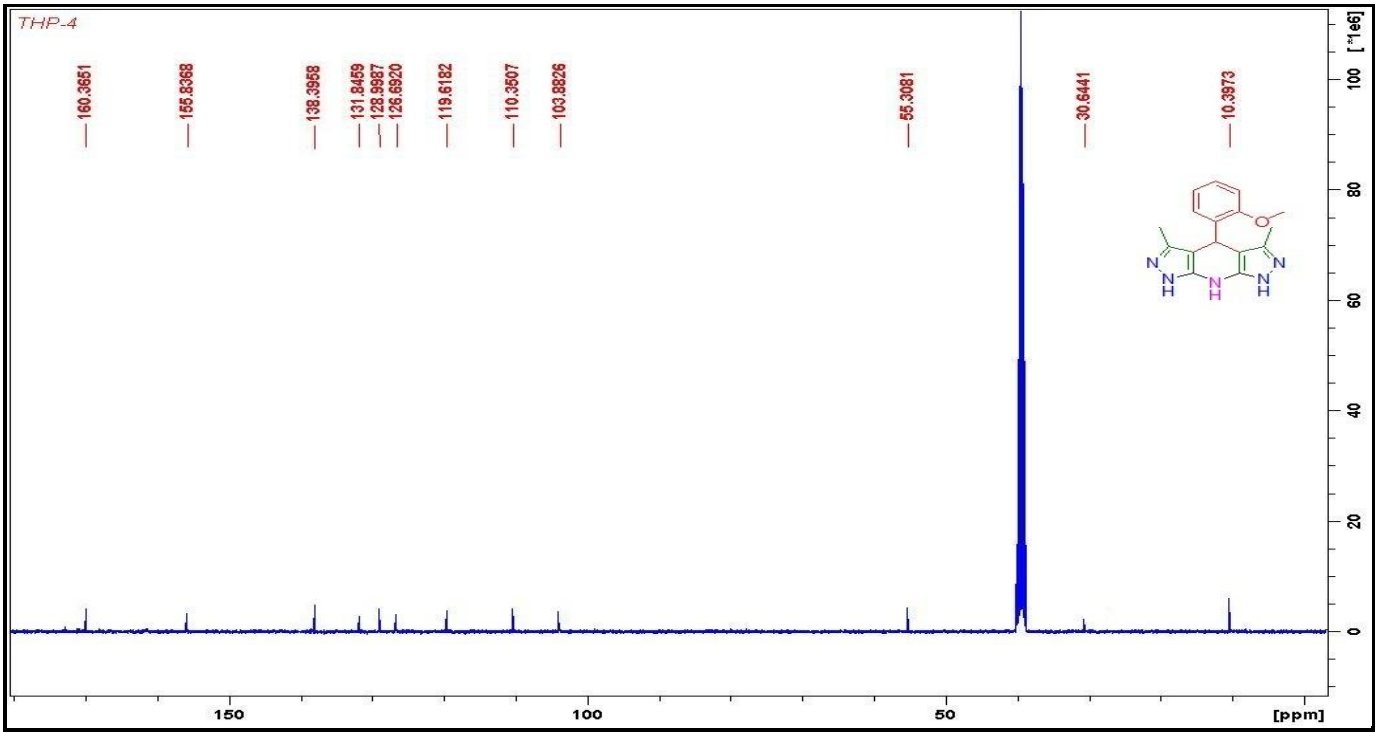

$^{1}$H NMR spectra of compound **5f**




$^{13}$C NMR spectra of compound **5f**




$^{1}$H NMR spectra of compound **5g**

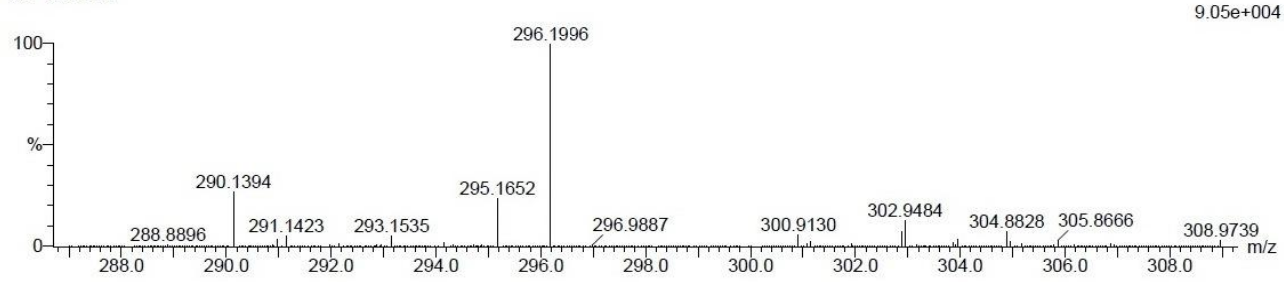



$^{13}$C NMR spectra of compound **5g**

**Elemental Composition Report** **Page 1**

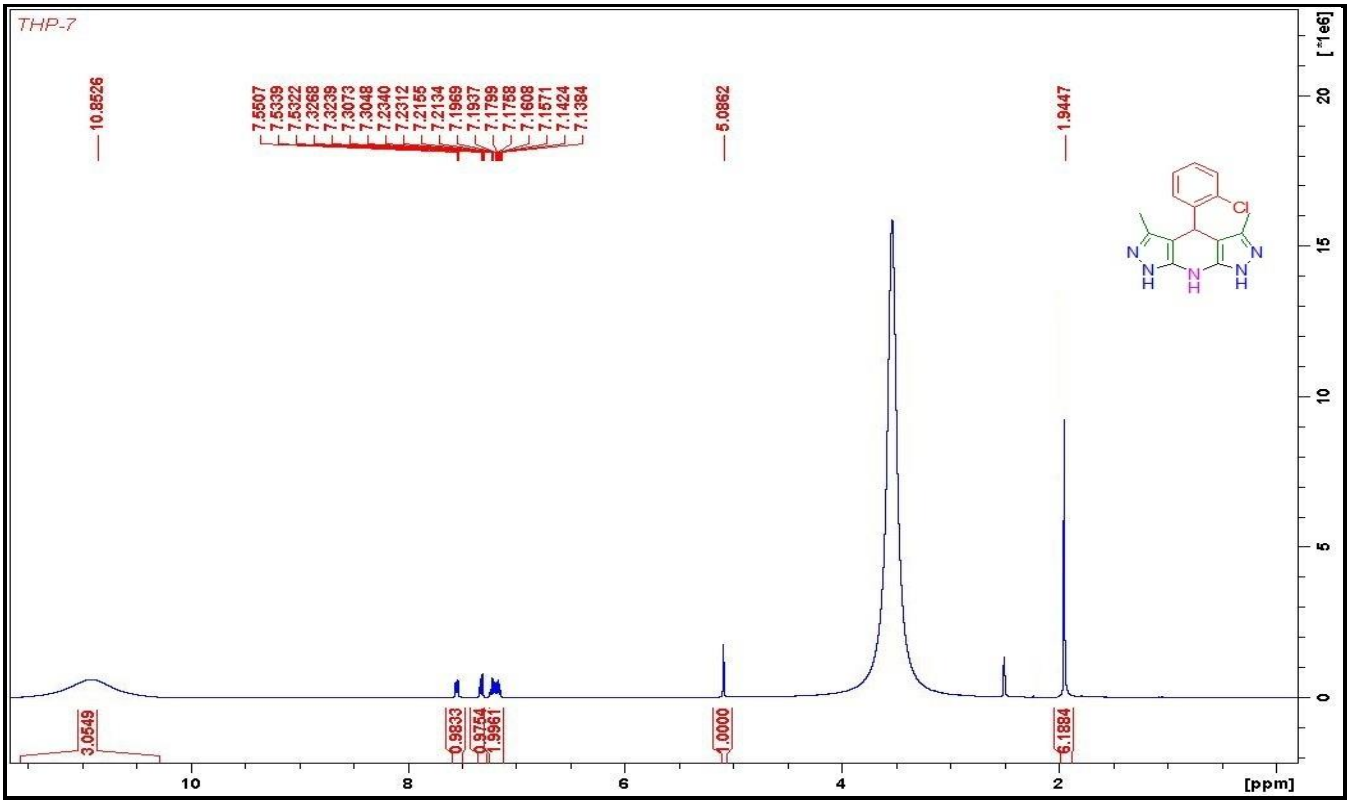
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
818 formula(e) evaluated with 4 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 0-50 H: 0-50 N: 0-10 O: 0-10
5G 40 (1.316) Cm (1:61)
TOF MS ES+

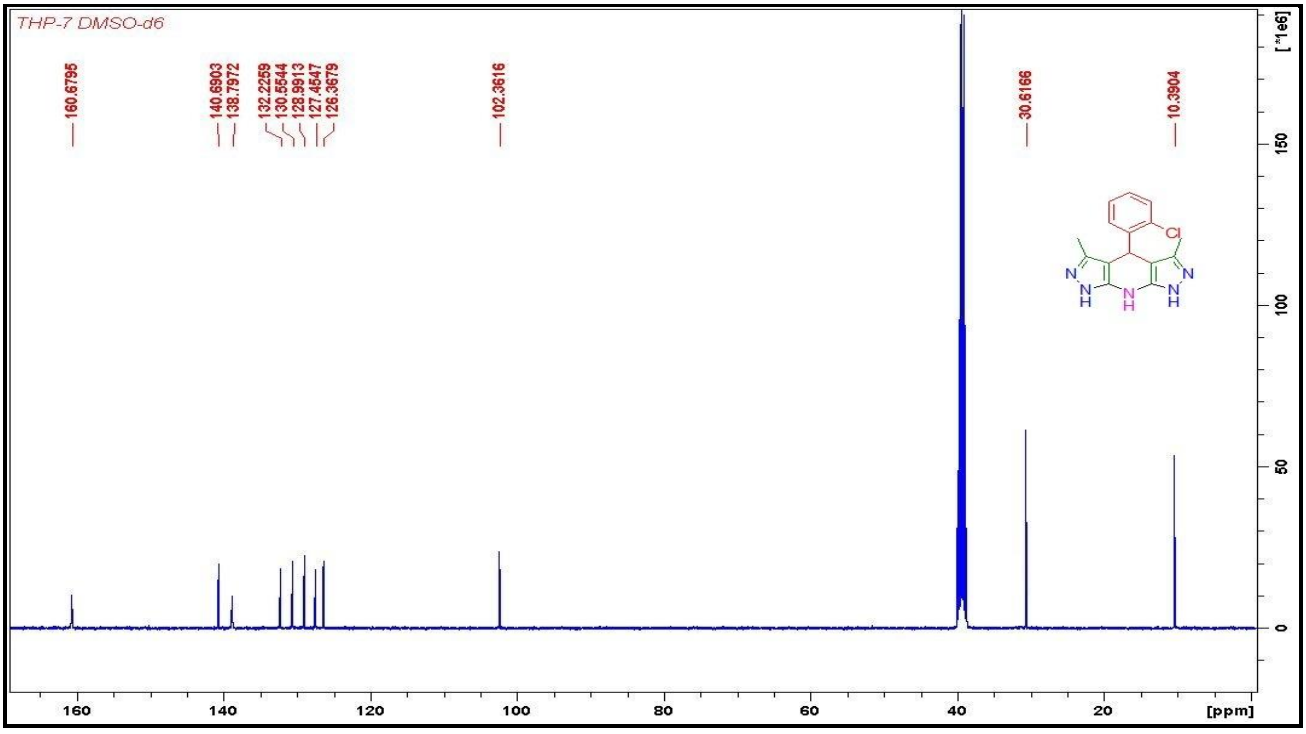



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 296.1996 | 296.1909 | 0.5 | 1.5 | 7.5 | 609.3 | 1.2 | C16 H18 N5 O |

HRMS spectra of compound **5g**




$^{1}$H NMR spectra of compound **5h**

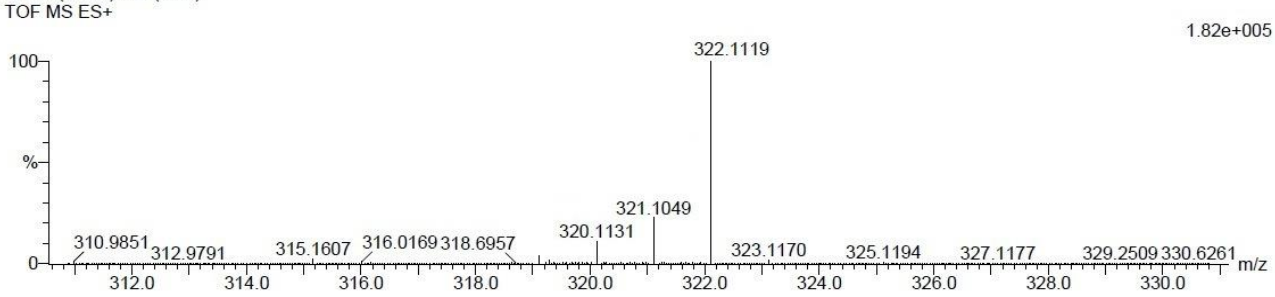



$^{13}$C NMR spectra of compound **5h**

**Elemental Composition Report** **Page 1**

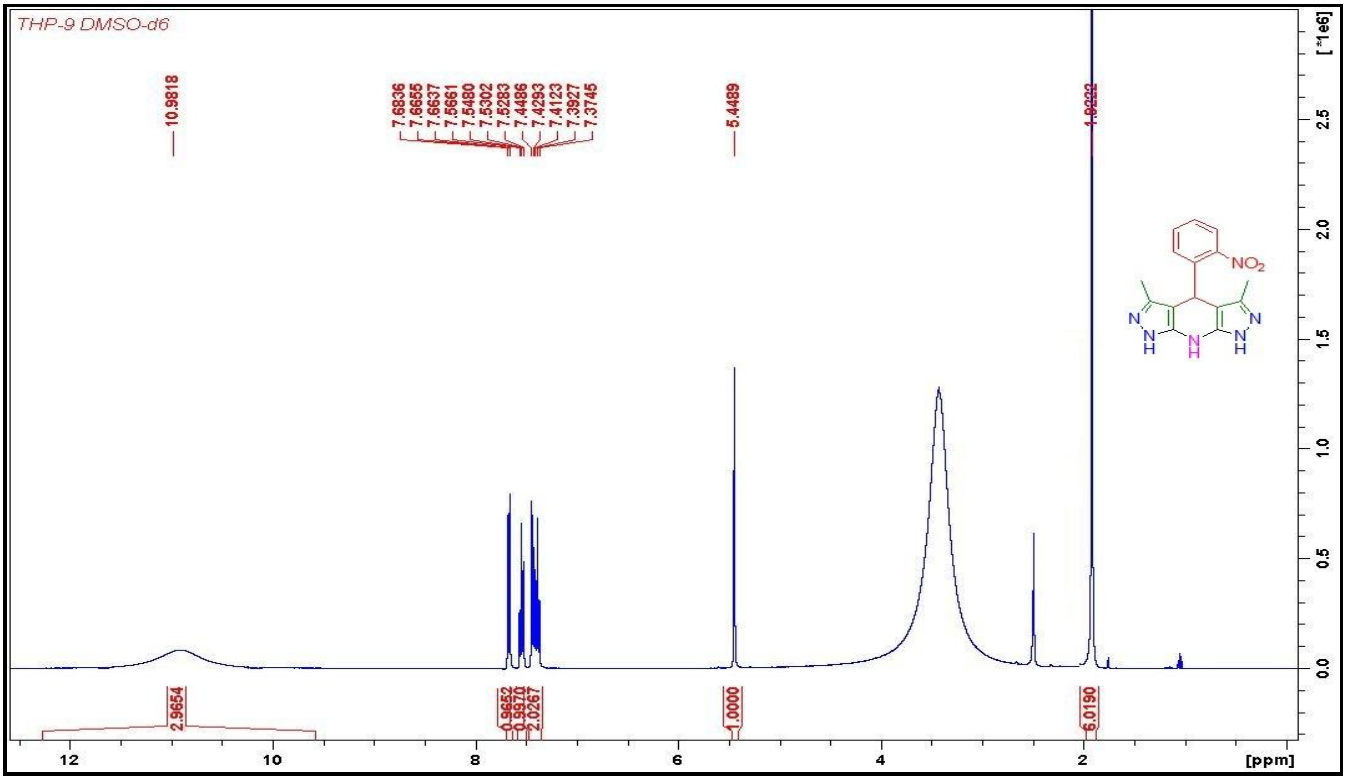
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
642 formula(e) evaluated with 4 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 0-50 H: 0-50 N: 0-10 Na: 0-1 Cl: 1-1
5H 34 (1.113) Cm (1:61)
TOF MS ES+

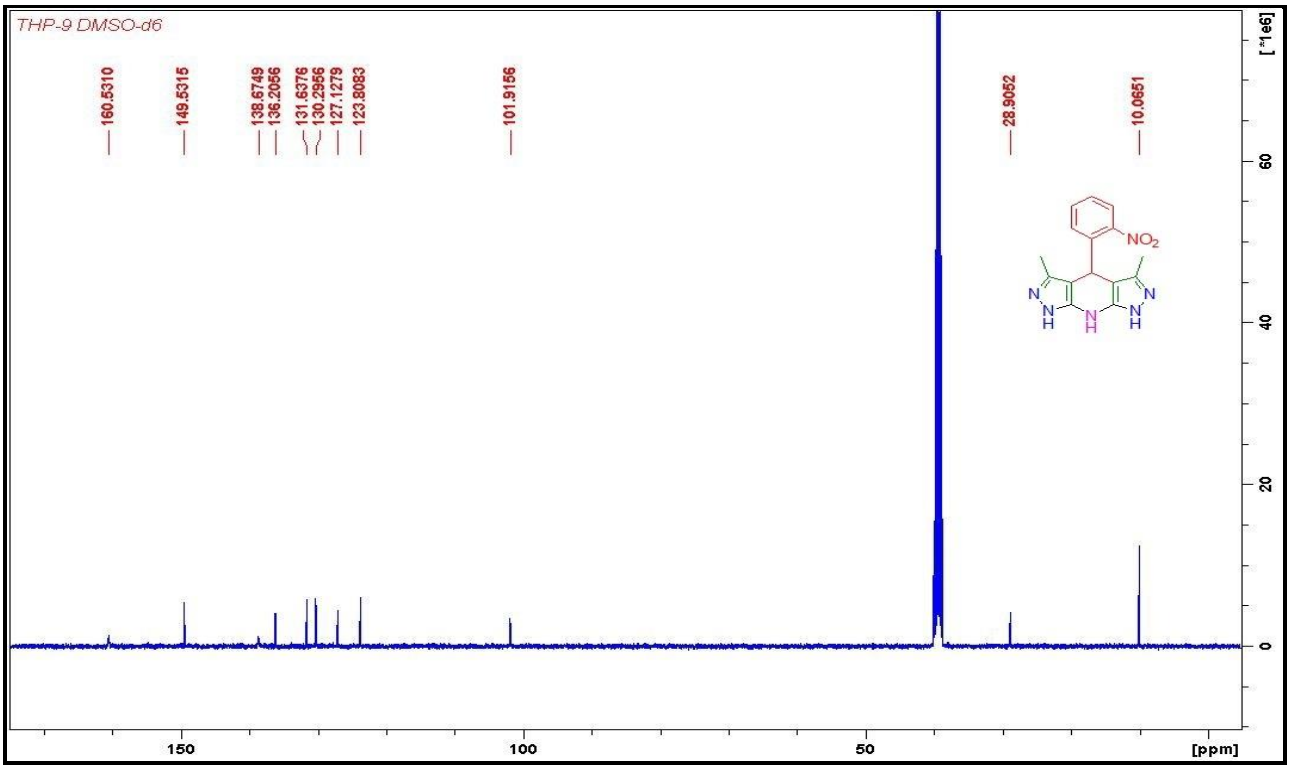



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 322.1119 | 322.1110 | -0.4 | -1.3 | 2.5 | 665.7 | 2.6 | C15 H14 N5 Na Cl |

HRMS spectra of compound **5h**




$^{1}$H NMR spectra of compound **5i**

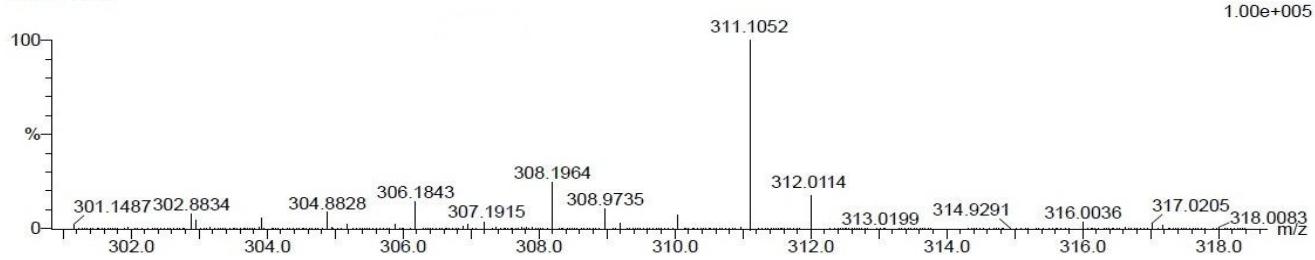



$^{13}$C NMR spectra of compound **5i**

**Elemental Composition Report** **Page 1**

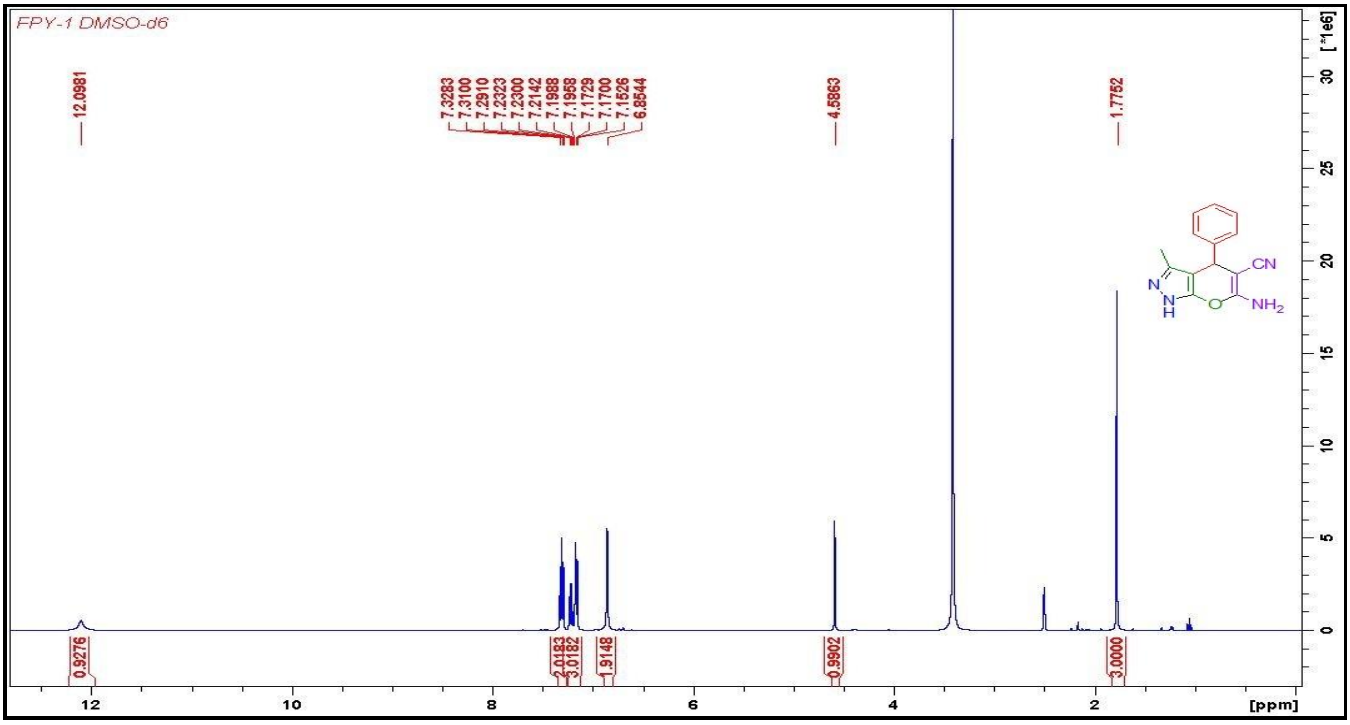
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
861 formula(e) evaluated with 4 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 0-50 H: 0-50 N: 0-10 O: 0-10
5I 17 (0.540) Cm (1:60)
TOF MS ES+

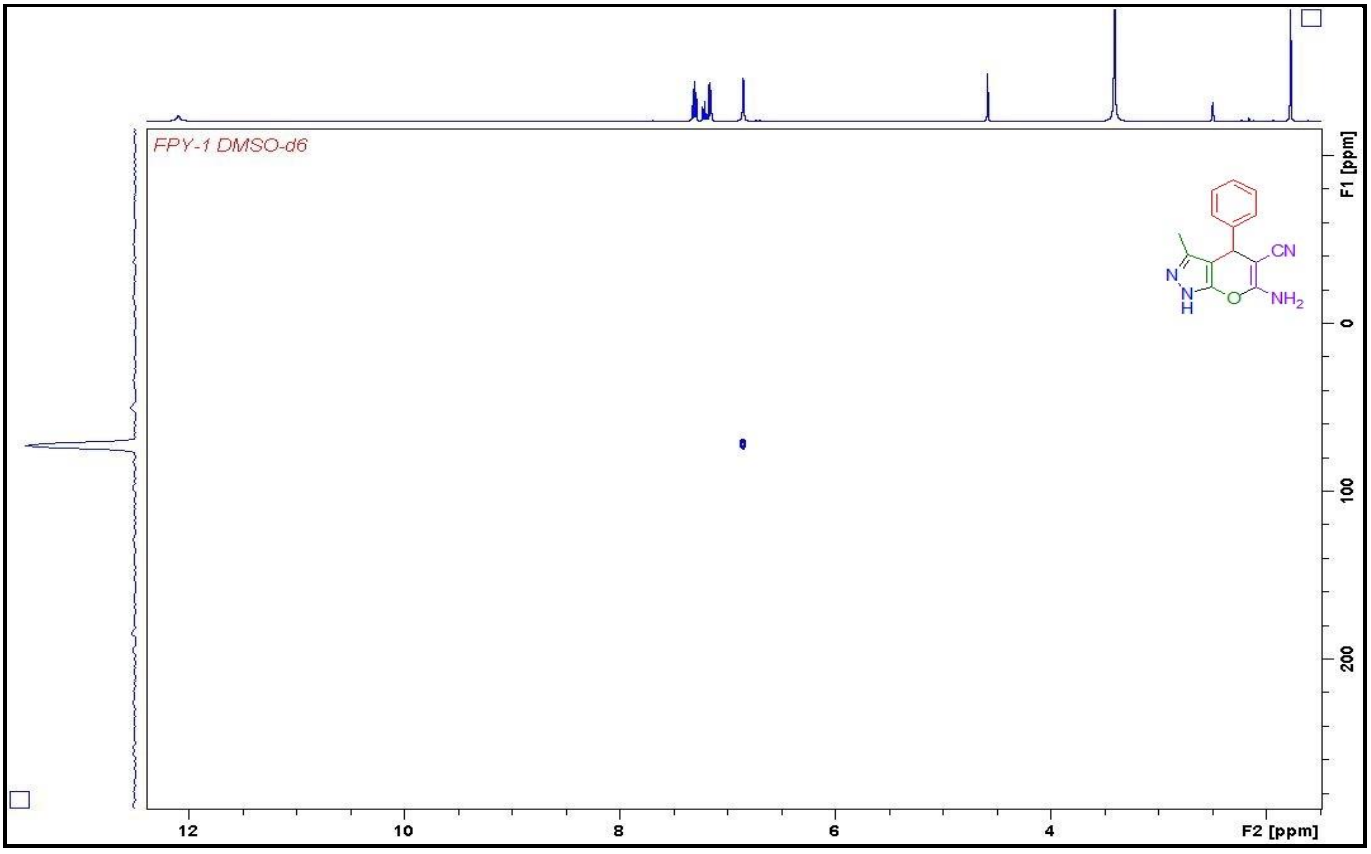



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 311.1052 | 311.1062 | -1.0 | -2.8 | 14.5 | 648.4 | 0.8 | C15 H15 N6 O2 |

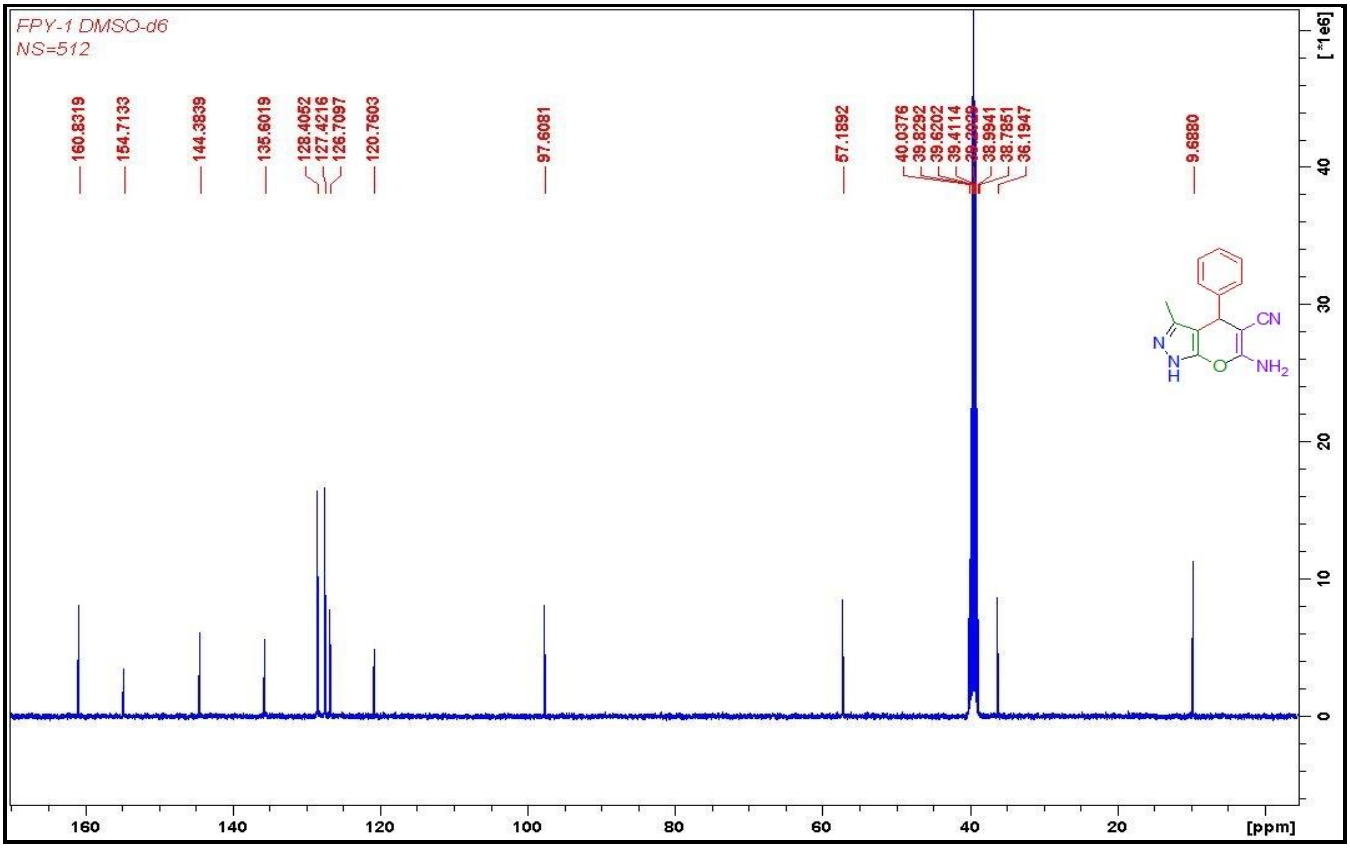
HRMS spectra of compound **5i**



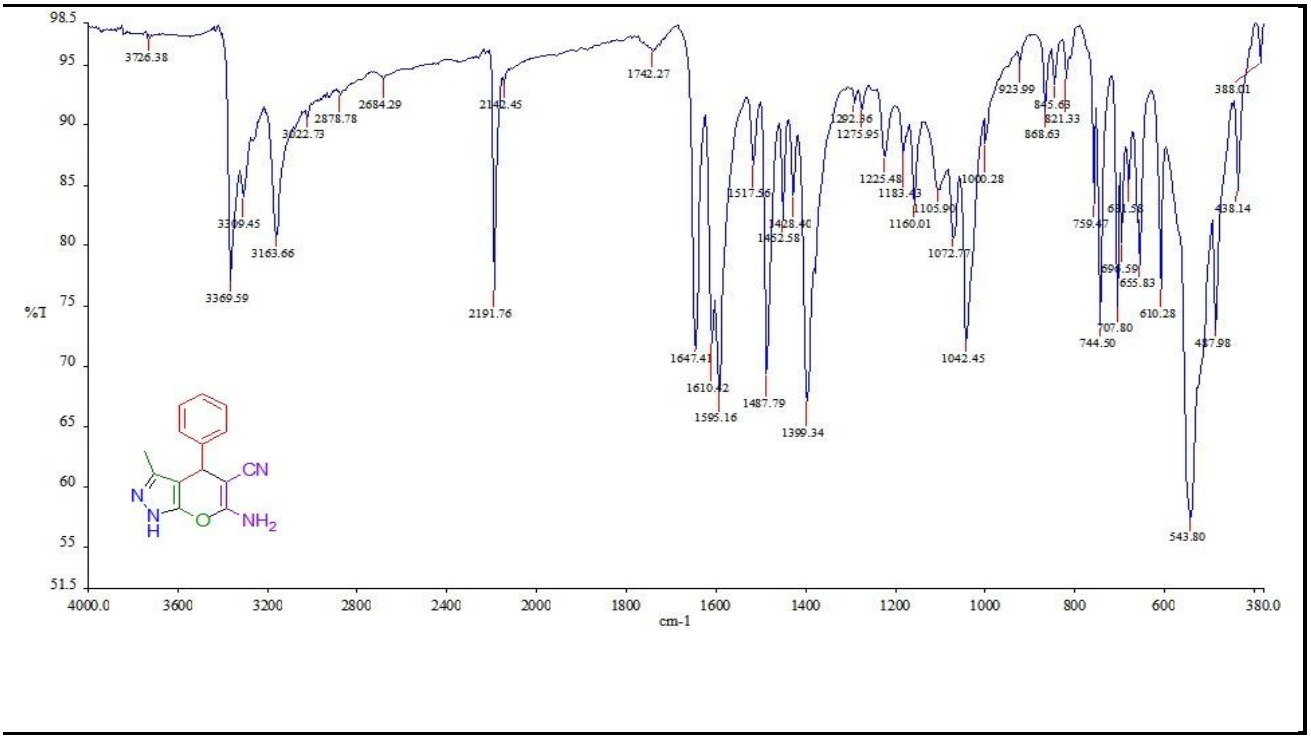

$^{1}$H NMR spectra of compound **7a**




$^{15}$N NMR (ghsqc) spectra of compound **7a**




$^{13}$C NMR spectra of compound **7a**

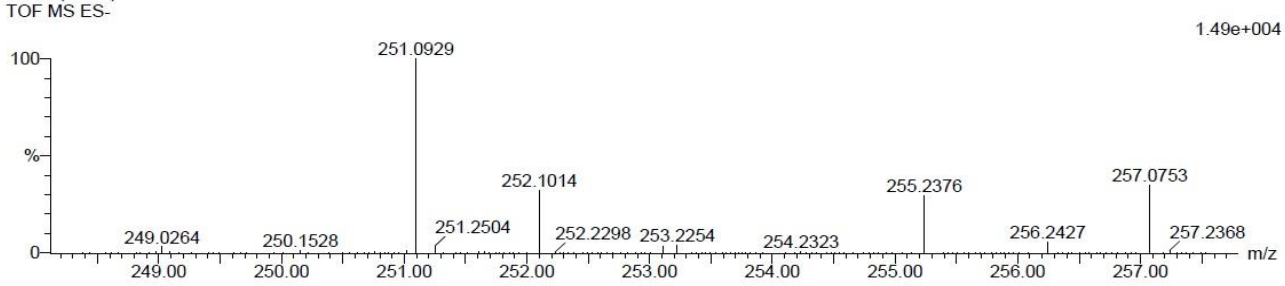



FTIR spectra of compound **7a**

**Elemental Composition Report** **Page 1**

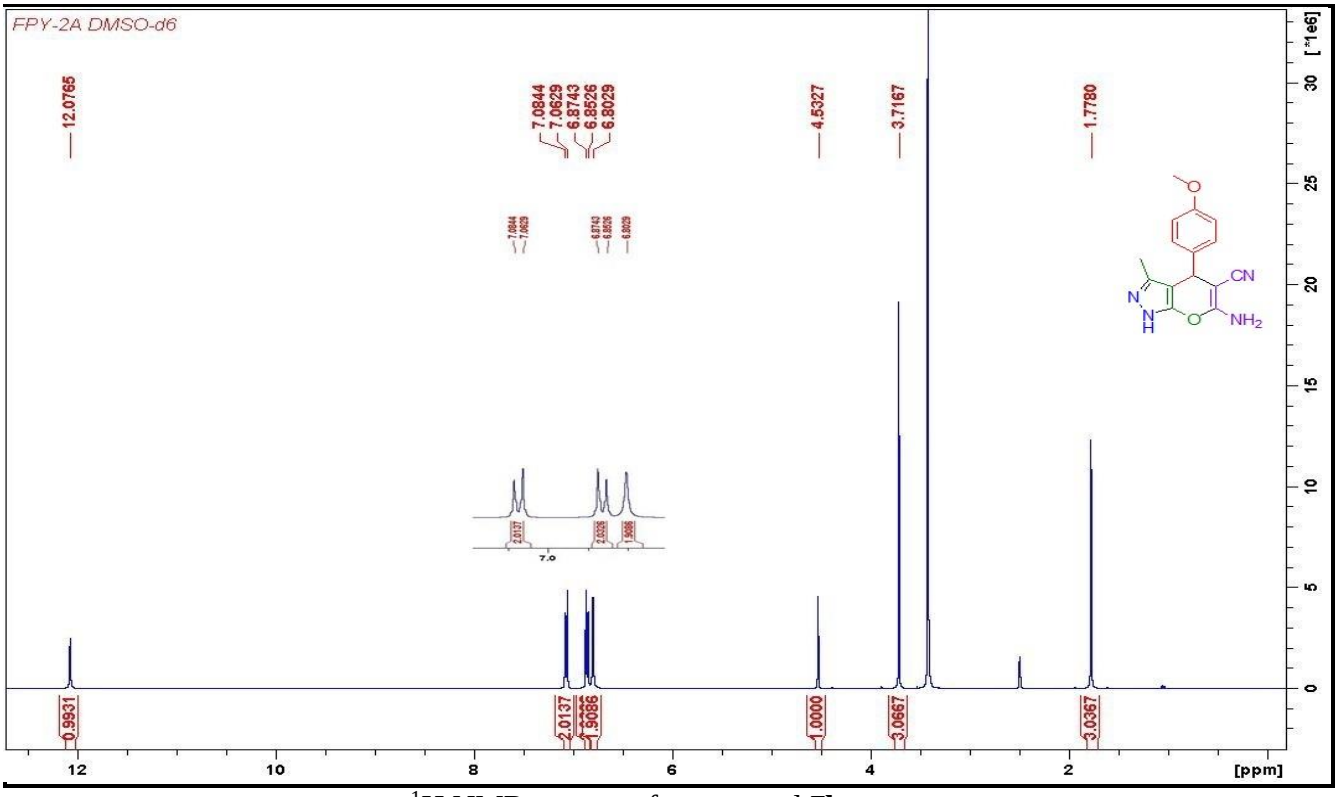
**Single Mass Analysis**
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
17 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 10-15 H: 10-15 N: 0-5 O: 0-5
7A 57 (1.888)
TOF MS ES-

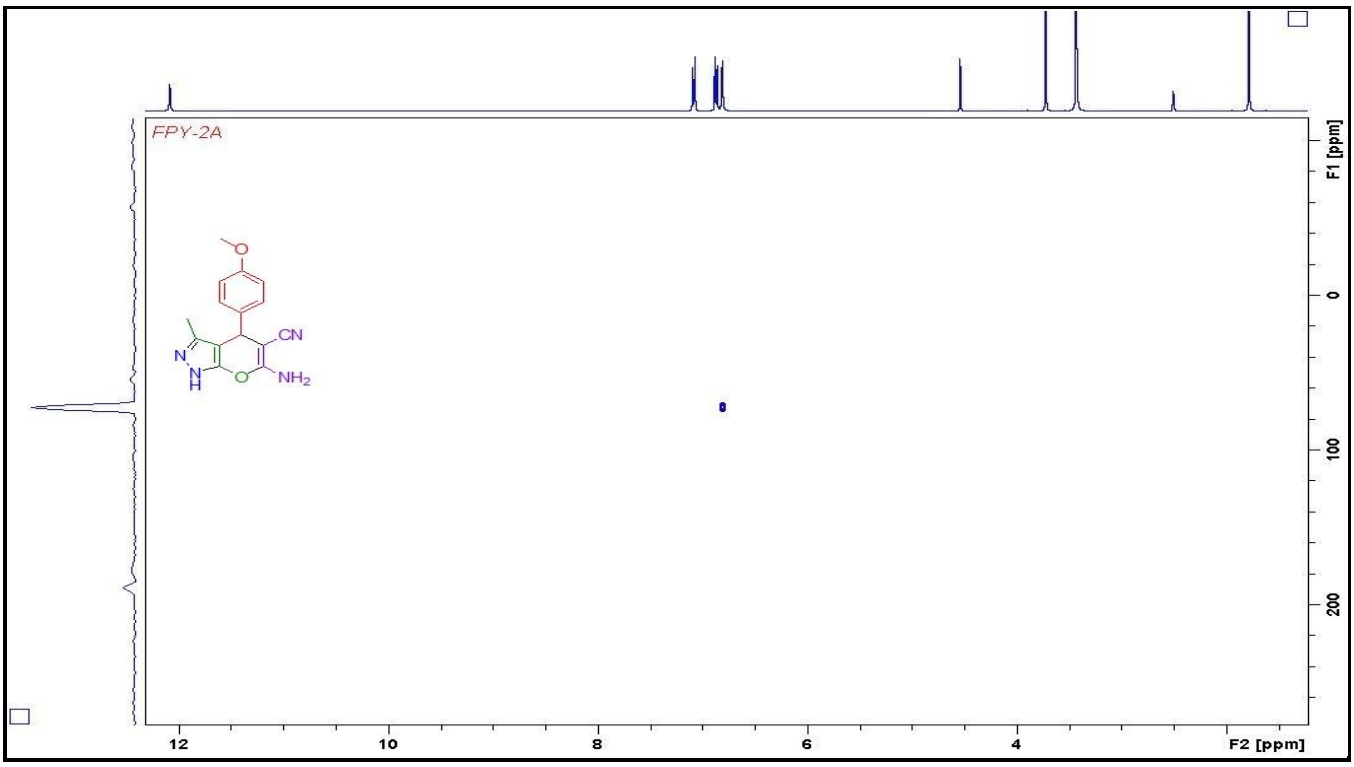



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | | |
| Maximum: | | 5.0 | 3.0 | 100.0 | | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula | |
| 251.0929 | 251.0933 | -0.4 | -1.6 | 11.5 | 280.8 | 0.0 | C14 H11 N4 O | |

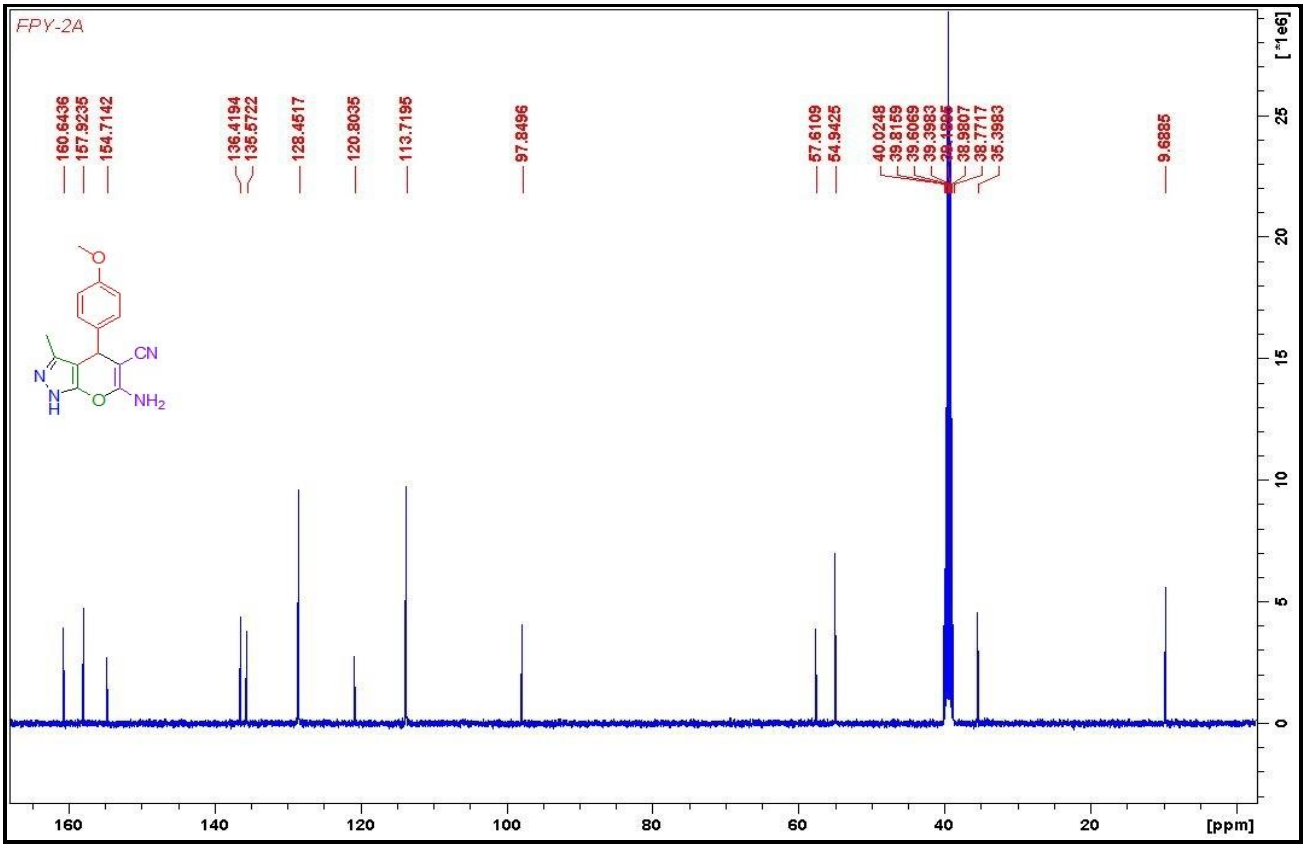
HRMS spectra of compound **7a**



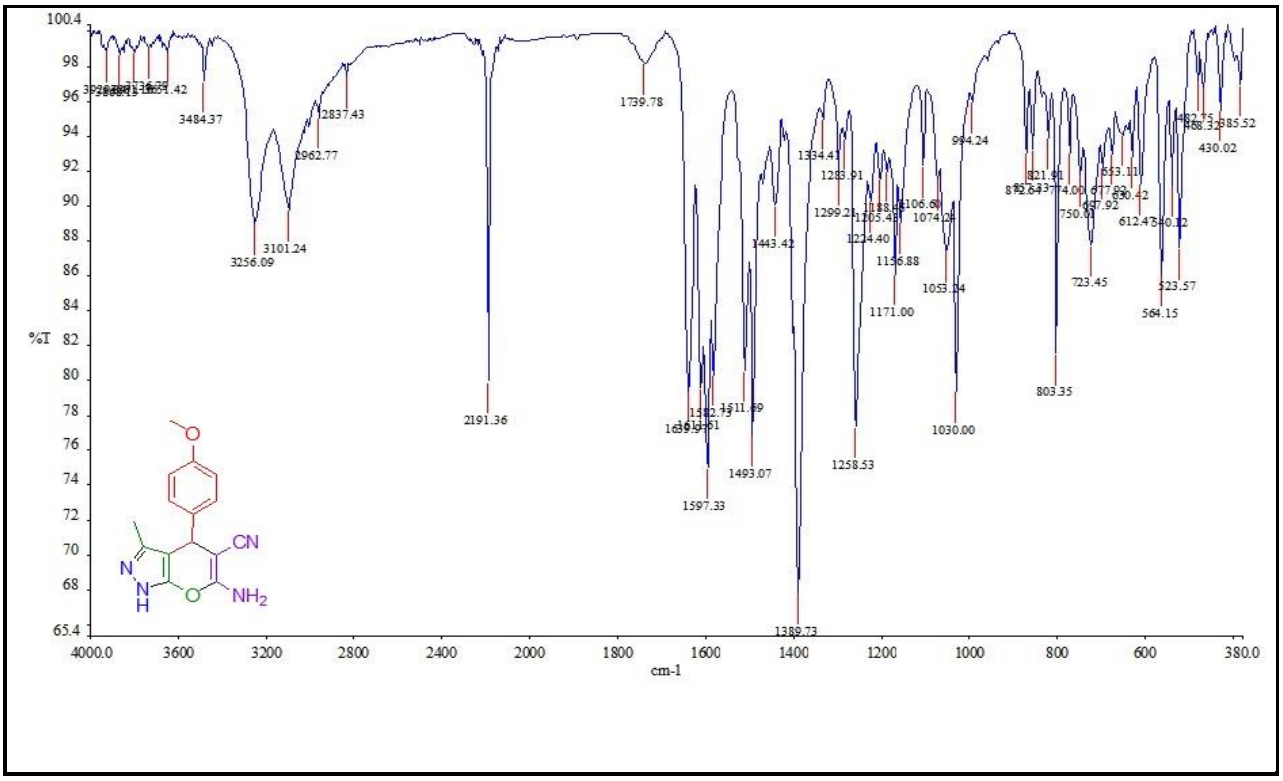

$^{1}$H NMR spectra of compound **7b**




$^{15}$N NMR (ghsqc) spectra of compound **7b**




$^{13}$C NMR spectra of compound **7b**

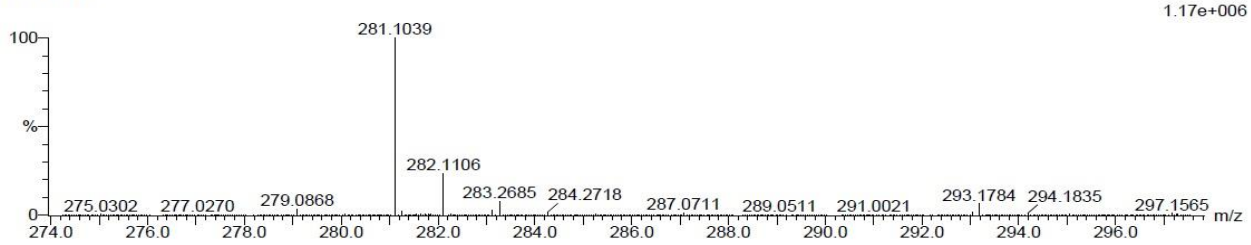


FTIR spectra of compound **7b**

**Elemental Composition Report** **Page 1**

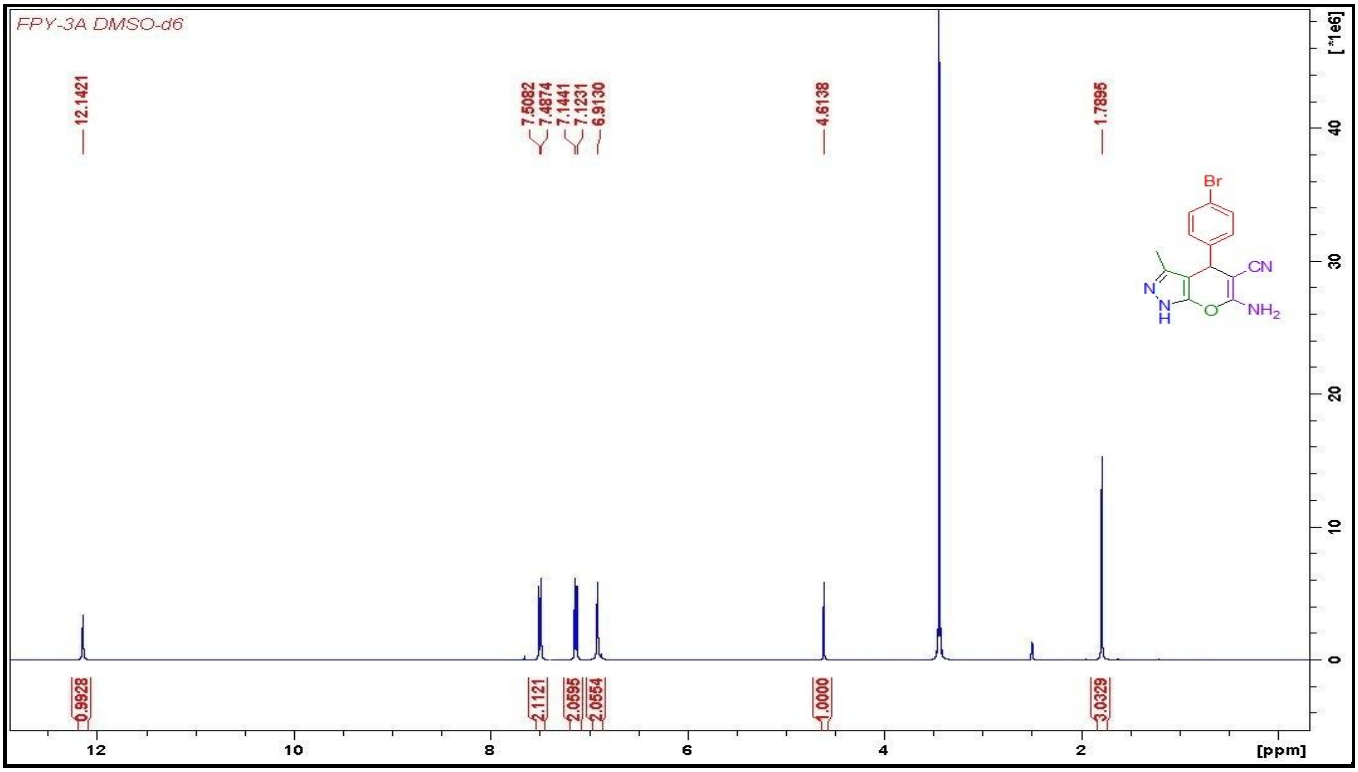
**Single Mass Analysis**
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
18 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 10-15 H: 10-15 N: 0-5 O: 0-5
7B 58 (1.923) Cm (1:61)
TOF MS ES-

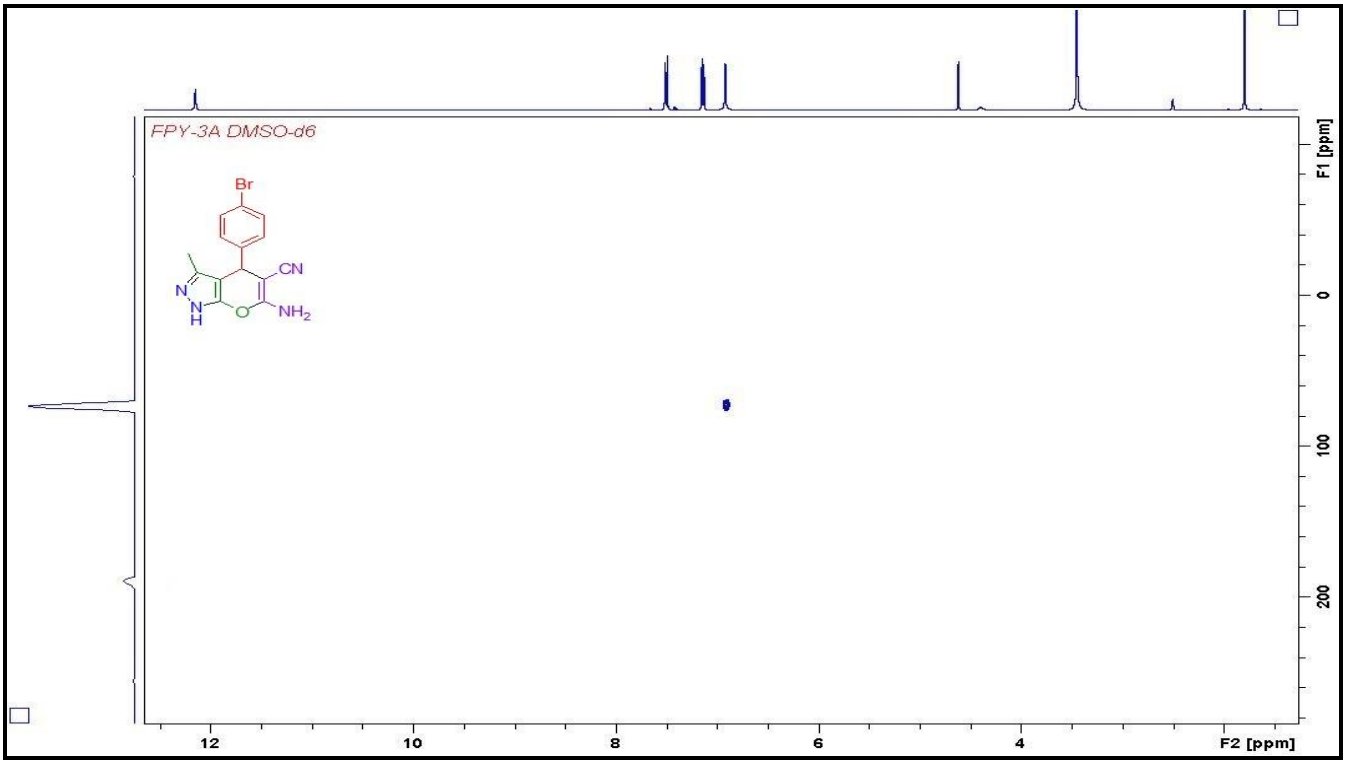



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 3.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 281.1039 | 281.1039 | 0.0 | 0.0 | 11.5 | 795.9 | 0.0 | C15 H13 N4 O2 |

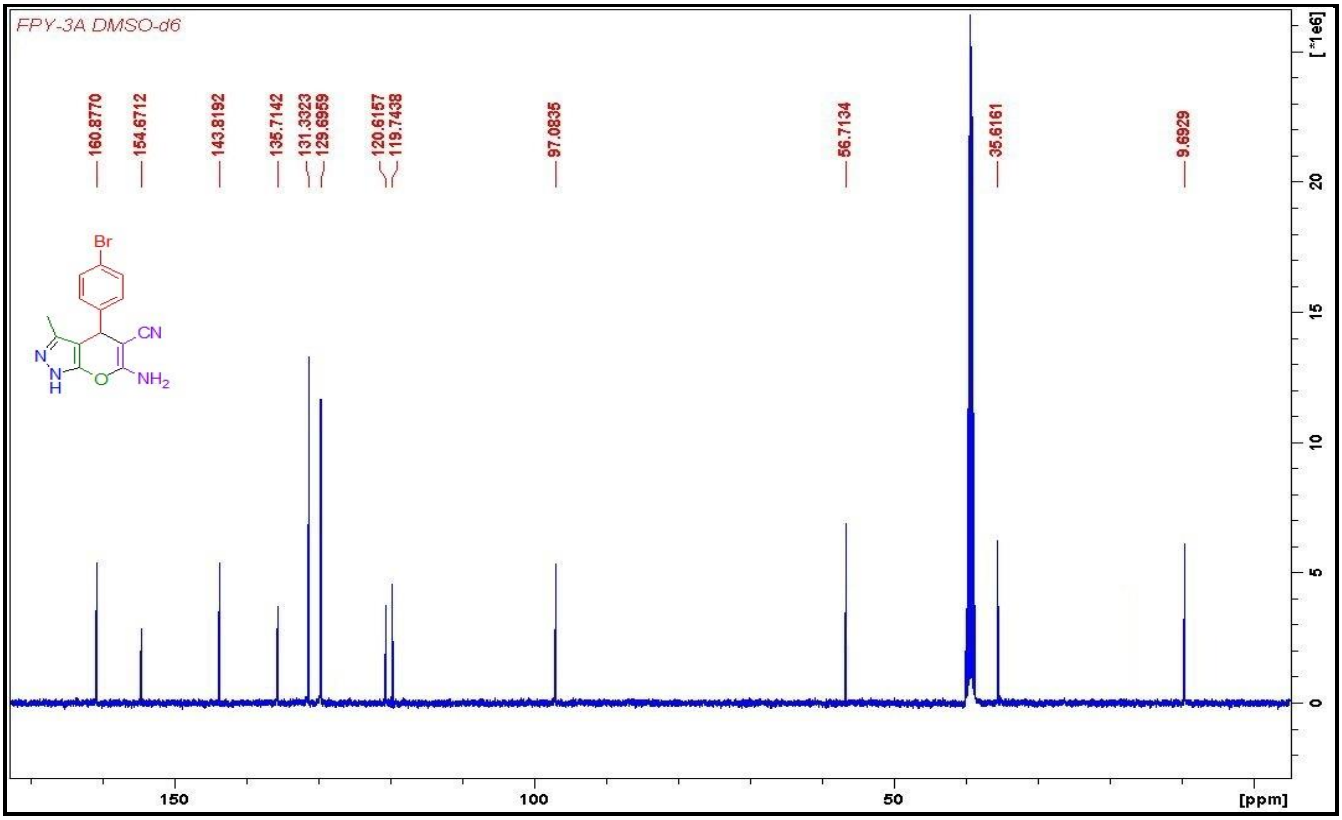
HRMS spectra of compound **7b**



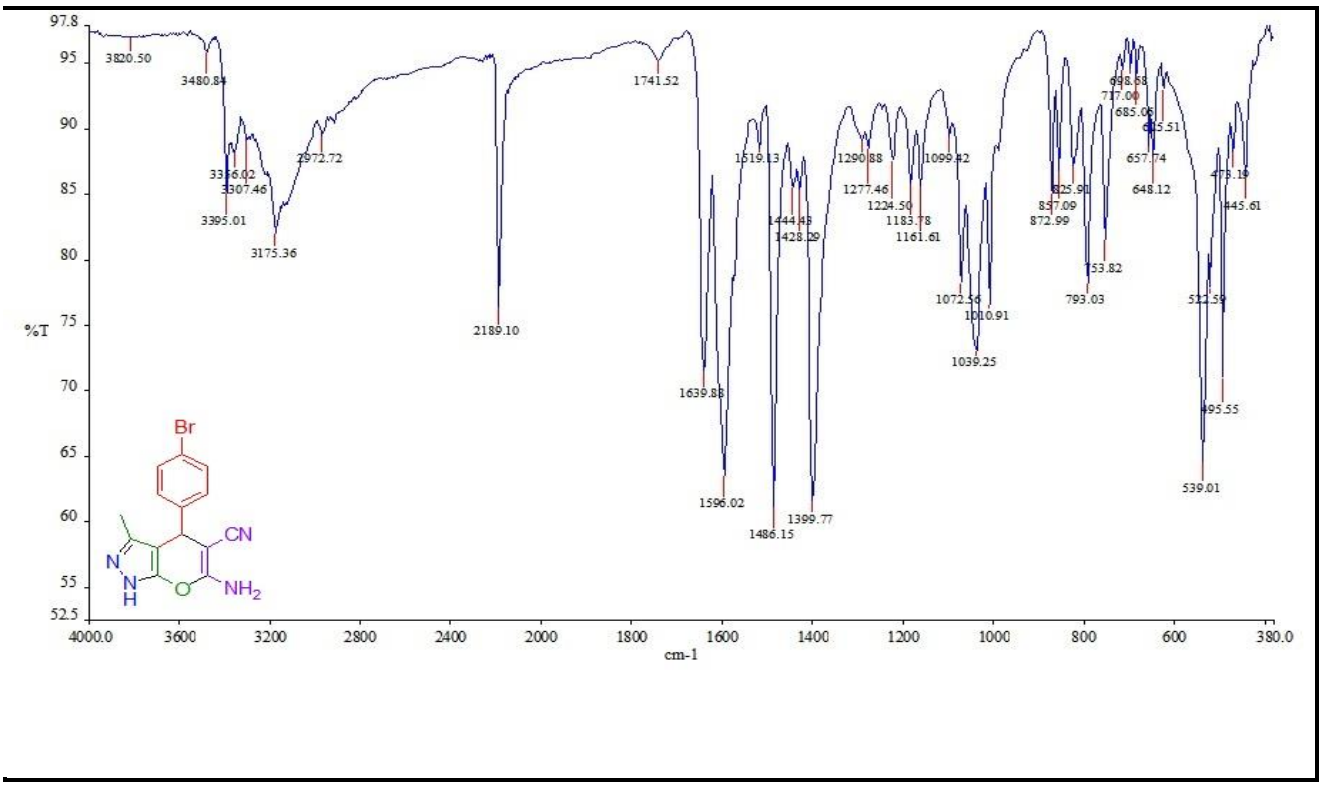

$^{1}$H NMR spectra of compound **7c**




$^{15}$N NMR (ghsqc) spectra of compound **7c**




$^{13}$C NMR spectra of compound **7c**



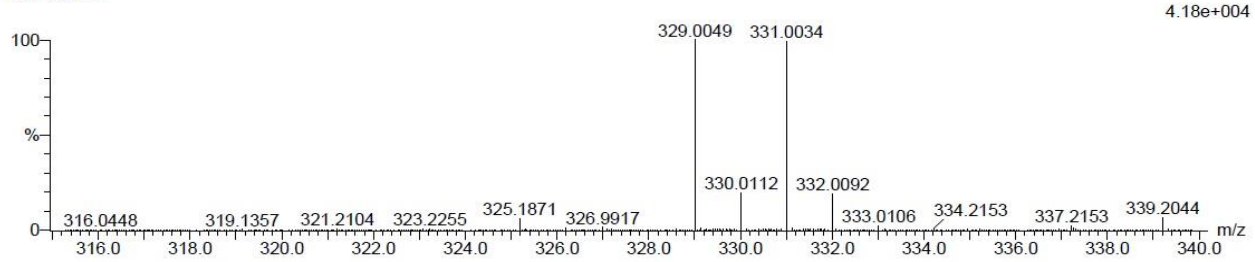

FTIR spectra of compound **7c**

**Elemental Composition Report** **Page 1**

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

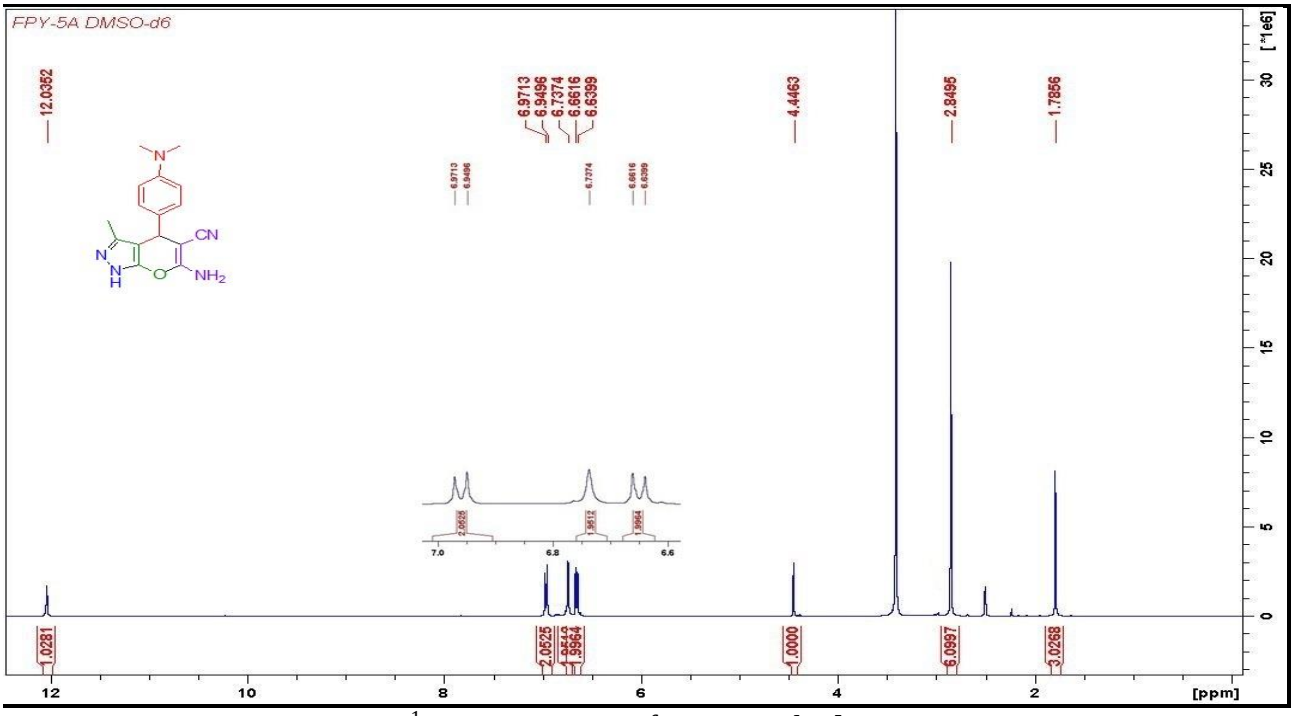
Monoisotopic Mass, Even Electron Ions
17 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 10-15 H: 10-15 N: 0-5 O: 0-5 Br: 1-1

7C 2 (0.034) Cm (1:18)
TOF MS ES-

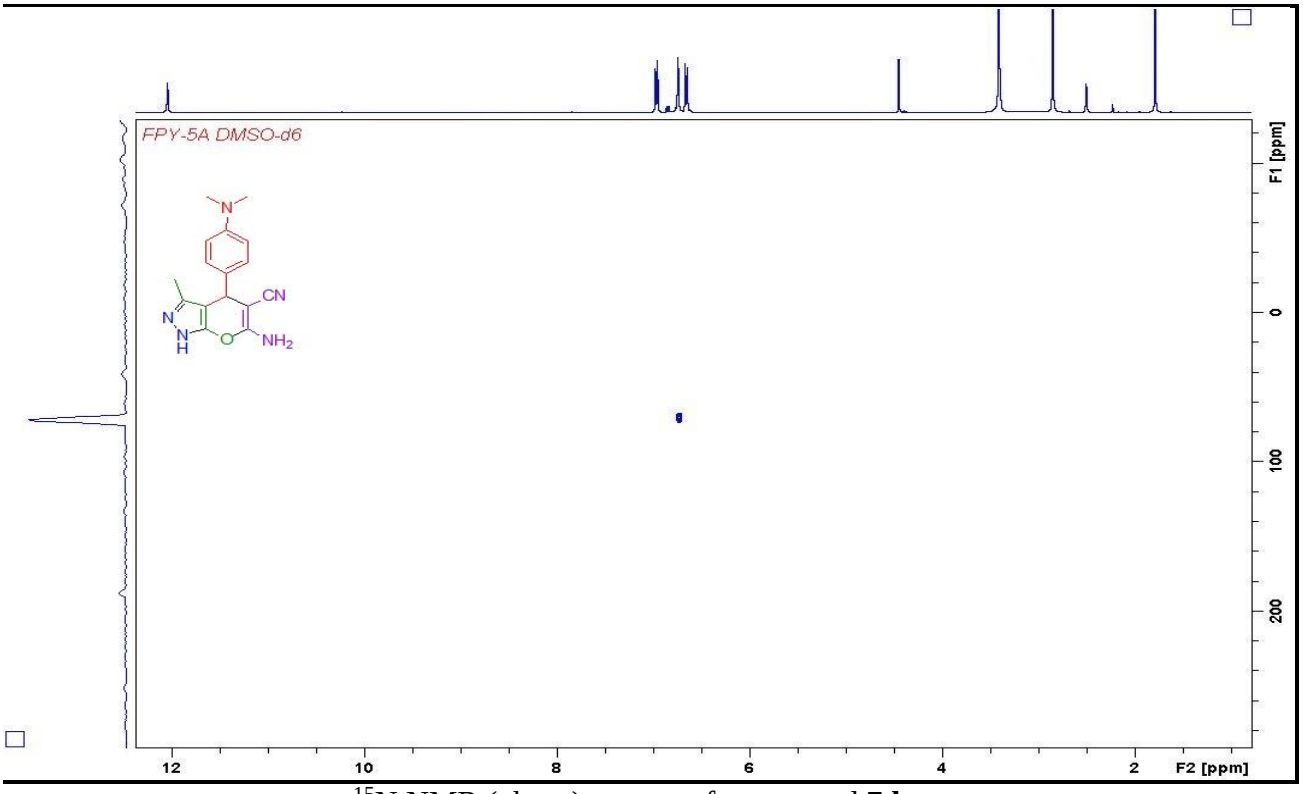



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 329.0049 | 329.0038 | 1.1 | 3.3 | 11.5 | 405.4 | 0.0 | C14 H10 N4 O Br |

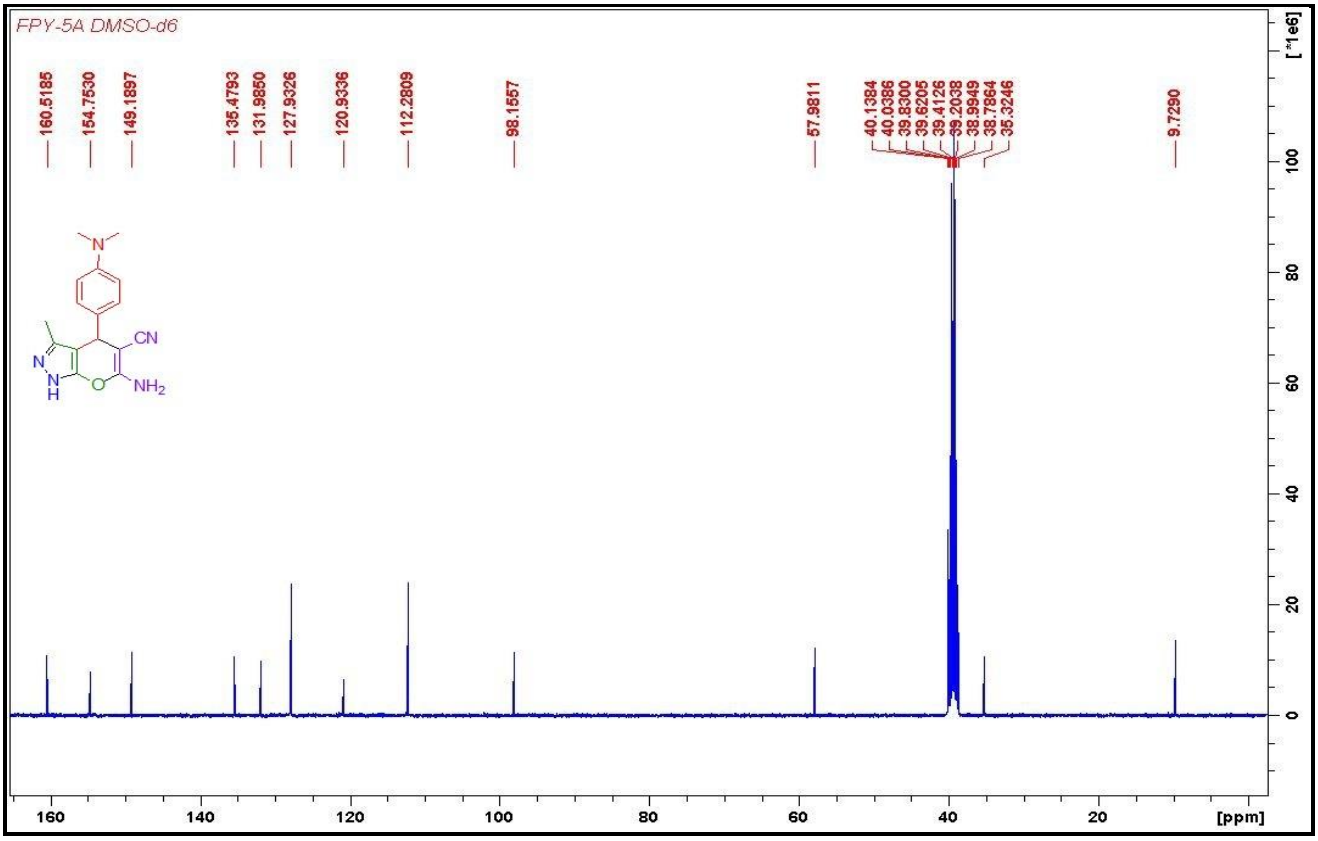
HRMS spectra of compound **7c**



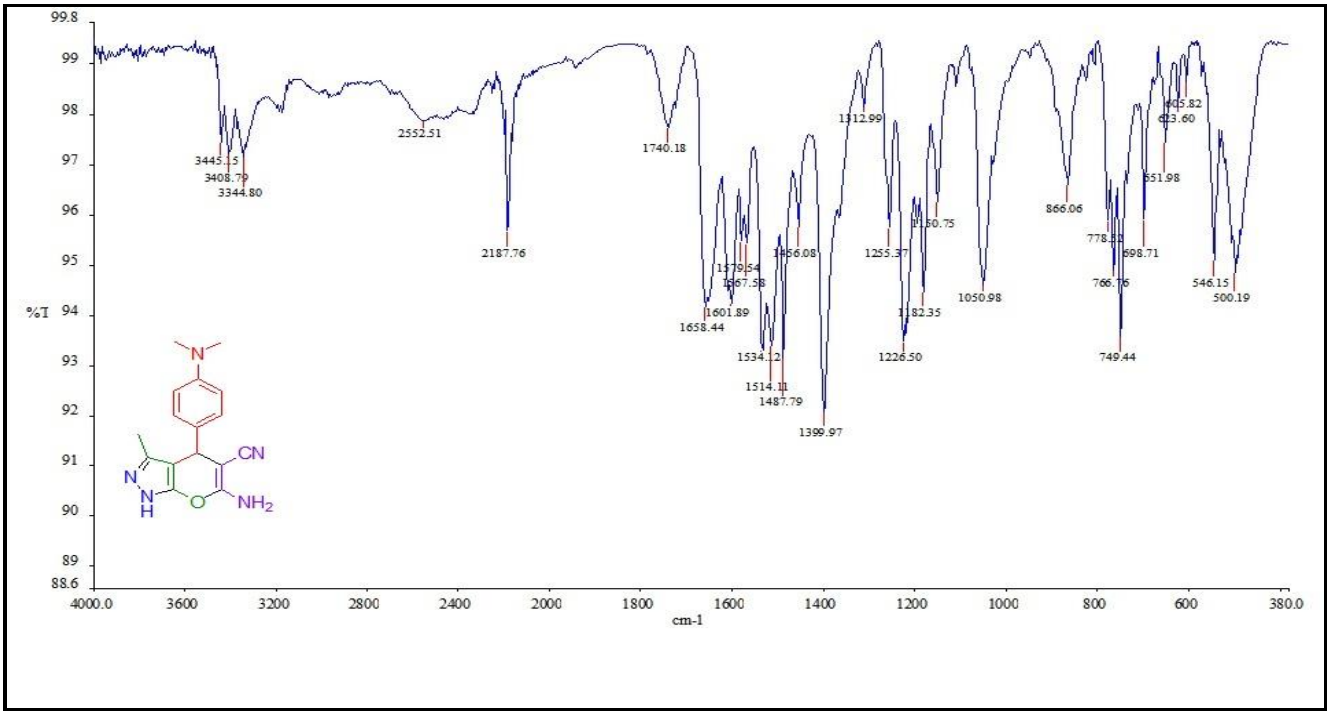

$^{1}$H NMR spectra of compound **7d**




$^{15}$N NMR (ghsqc) spectra of compound **7d**




$^{13}$C NMR spectra of compound **7d**

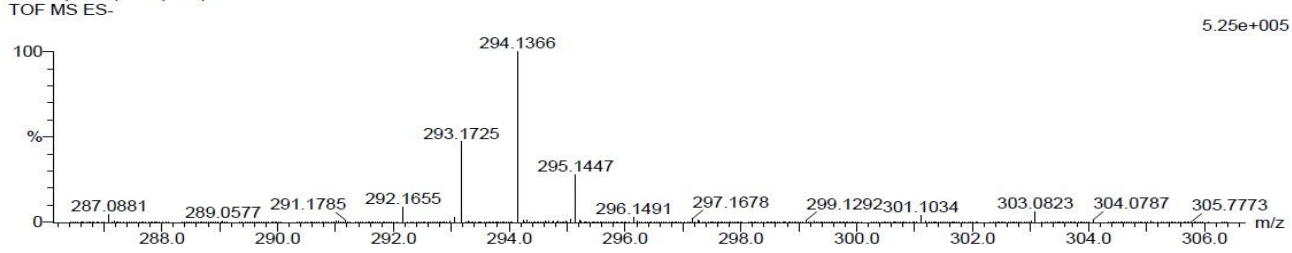



FTIR spectra of compound **7d**

**Elemental Composition Report** **Page 1**

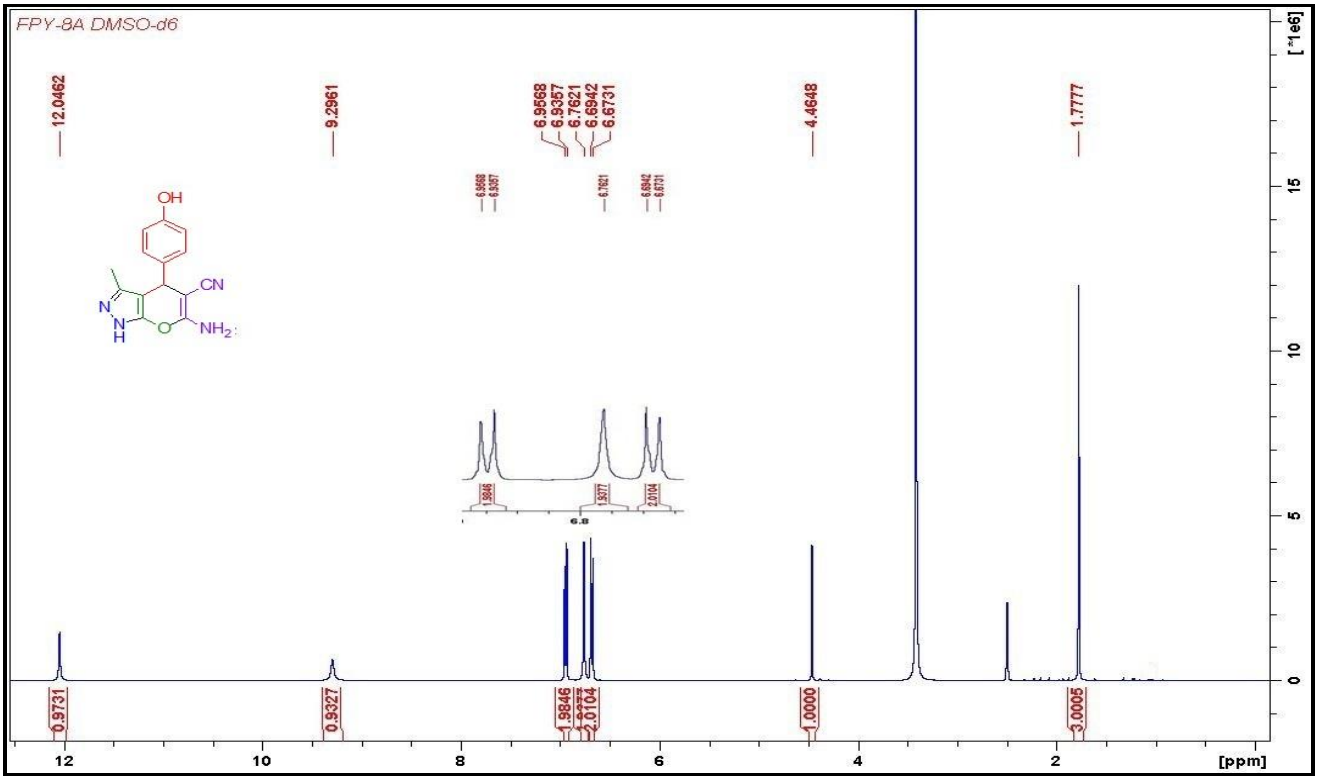
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 N: 0-5 O: 0-5
7D 36 (1.180) Cm (1:61)
TOF MS ES-

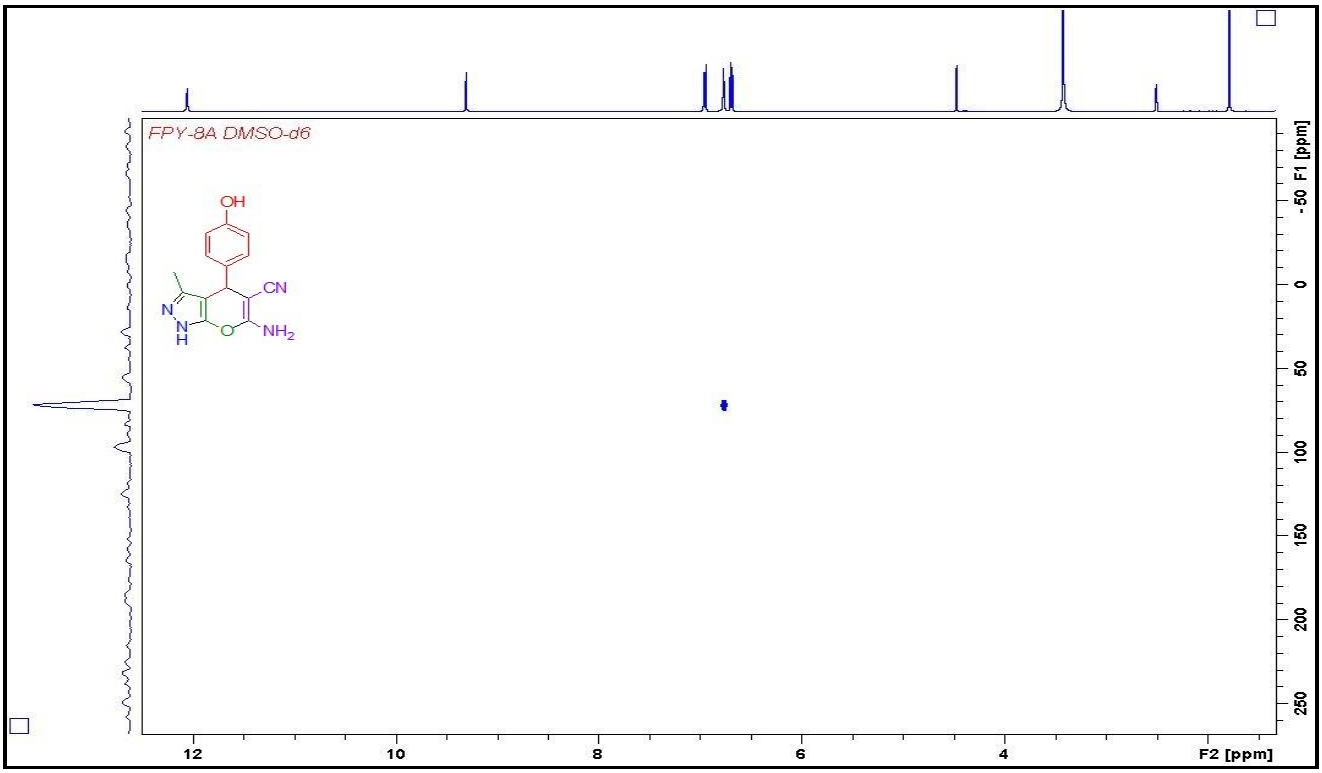



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 294.1366 | 294.1355 | 1.1 | 3.7 | 11.5 | 791.3 | 0.0 | C16 H16 N5 O |

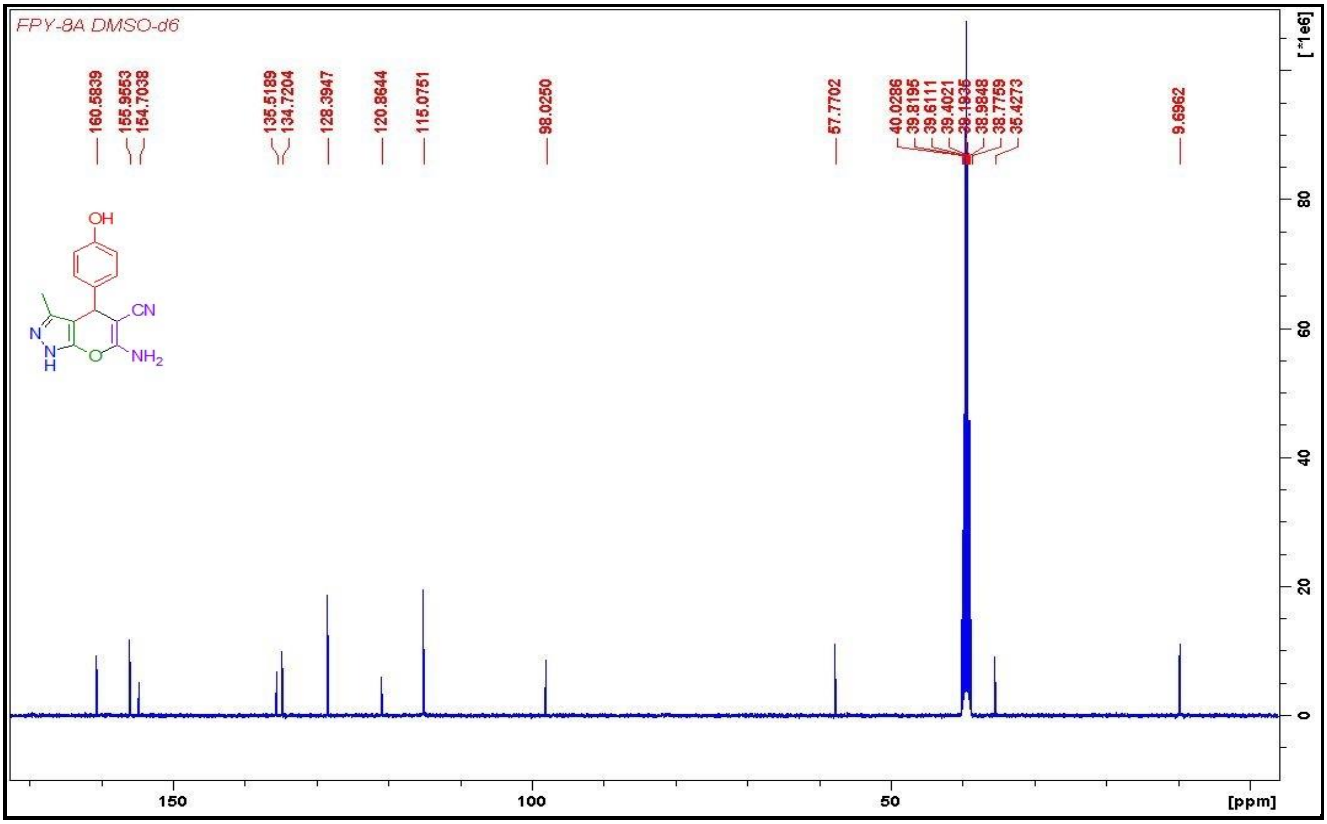
HRMS spectra of compound **7d**



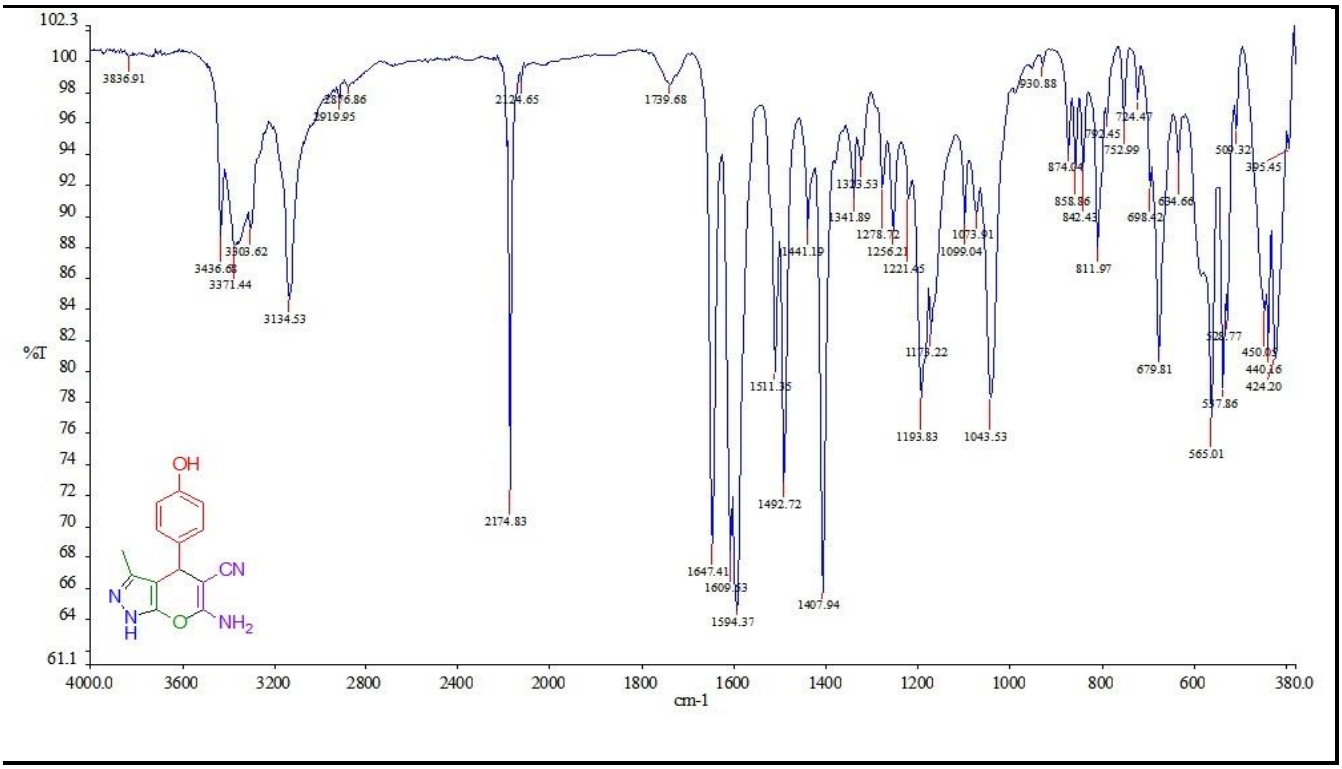

$^{1}$H NMR spectra of compound **7e**




$^{15}$N NMR (ghsqc) spectra of compound **7e**




$^{13}$C NMR spectra of compound **7e**

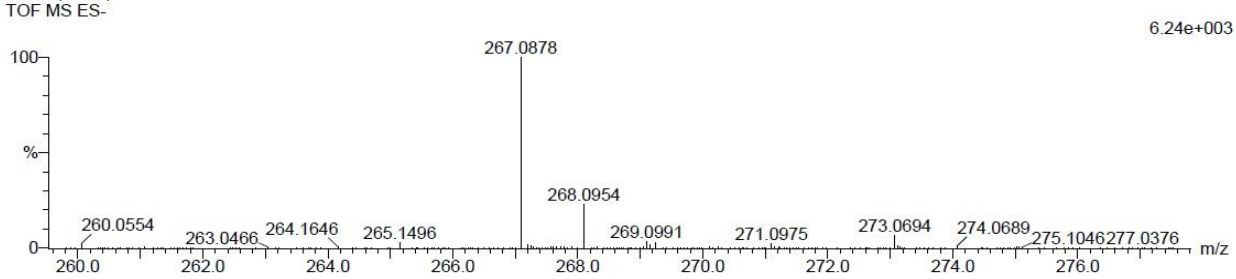



FTIR spectra of compound **7e**

**Elemental Composition Report** **Page 1**

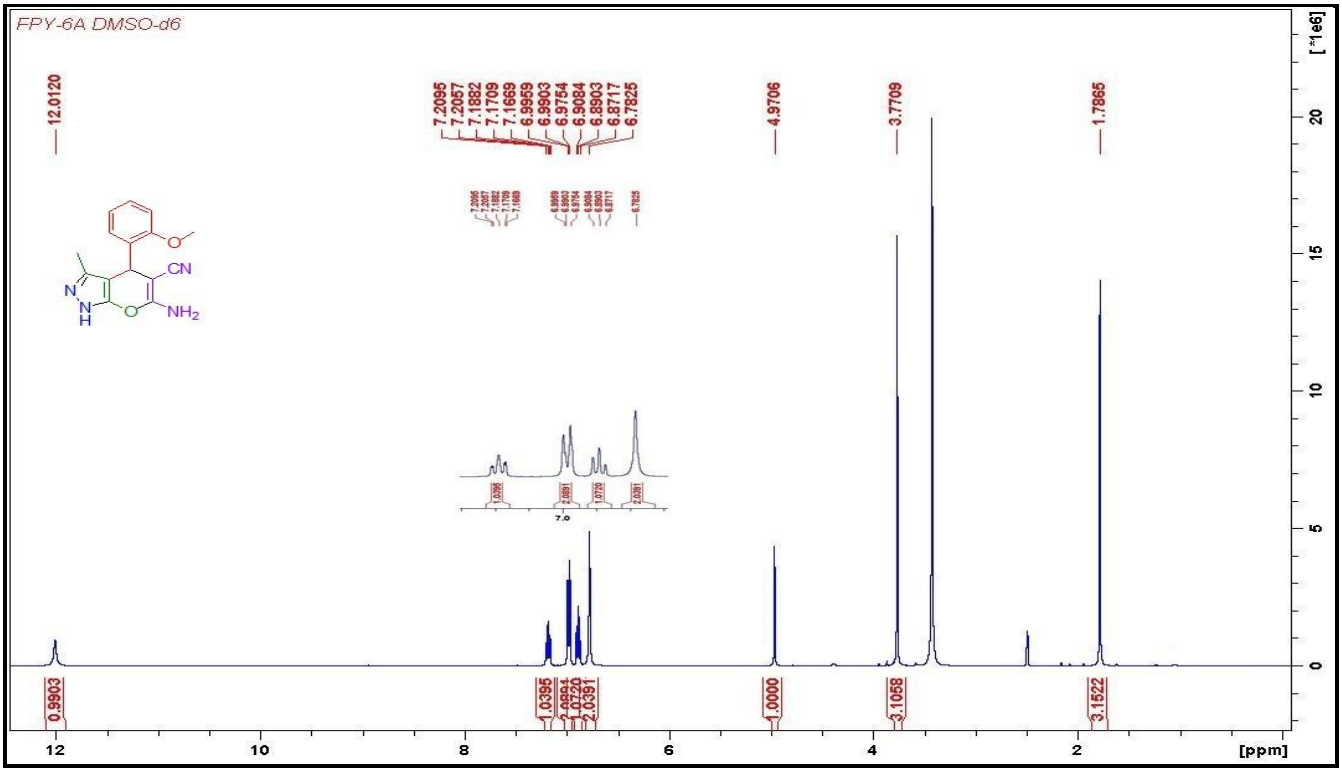
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
16 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 10-15 H: 10-15 N: 0-5 O: 0-5
7E 61 (2.025)
TOF MS ES-

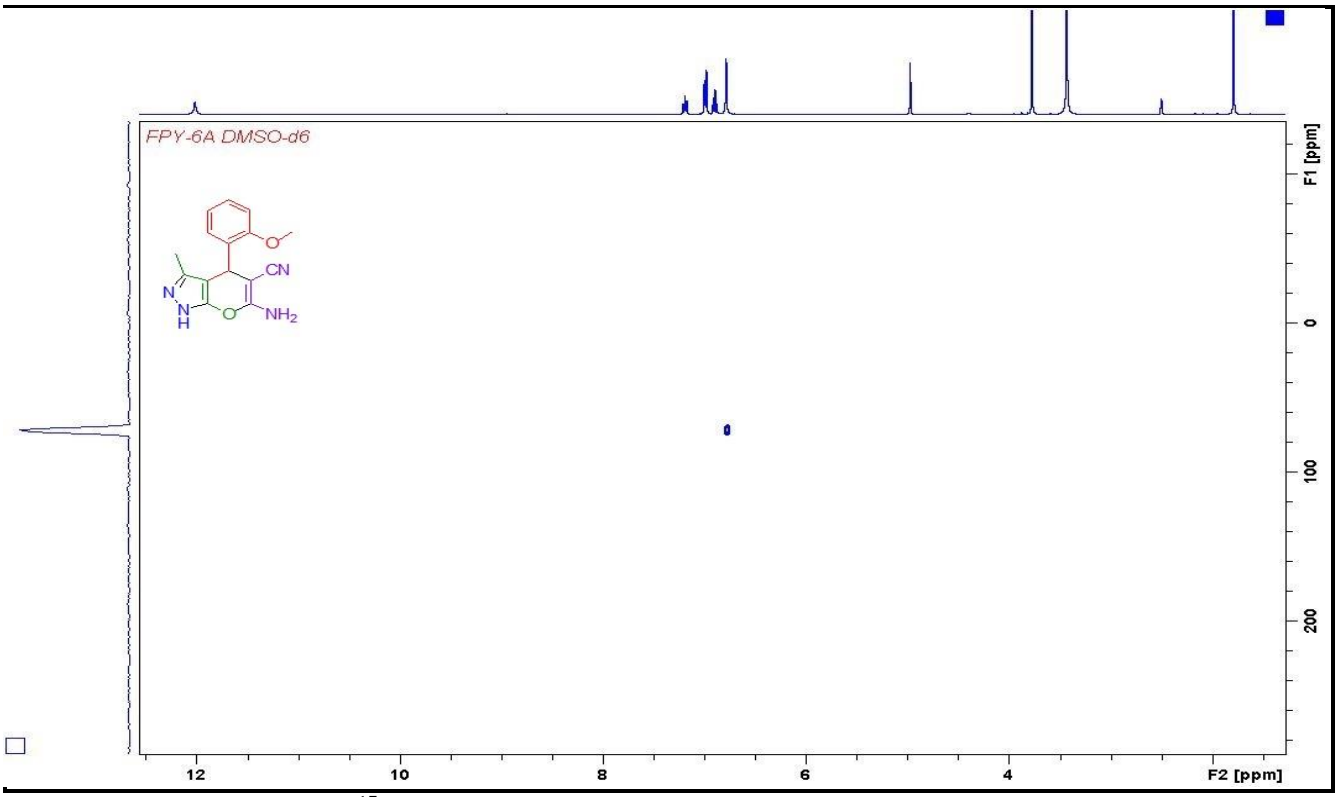



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 267.0878 | 267.0882 | -0.4 | -1.5 | 11.5 | 249.1 | 0.0 | C14 H11 N4 O2 |

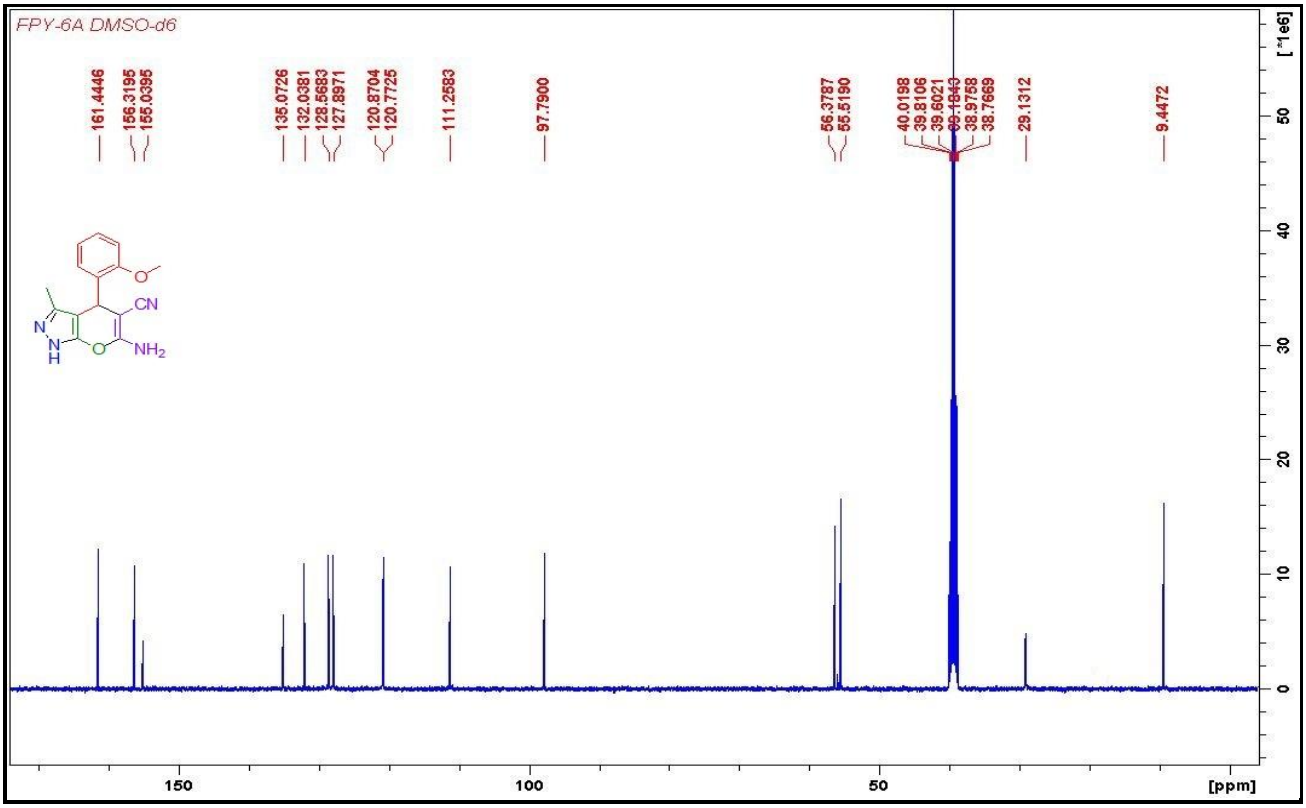
HRMS spectra of compound **7e**



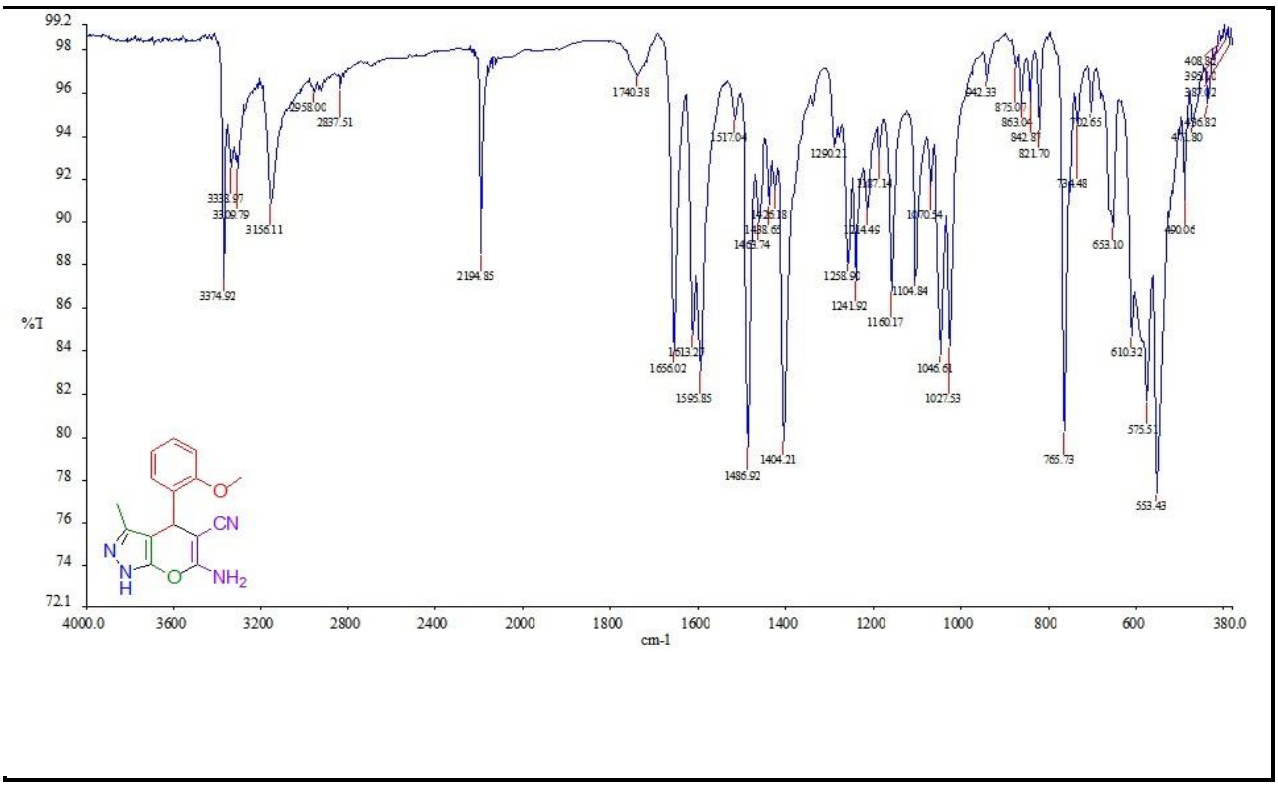

$^{1}$H NMR spectra of compound **7f**




$^{15}$N NMR (ghsqc) spectra of compound **7f**




$^{13}$C NMR spectra of compound **7f**

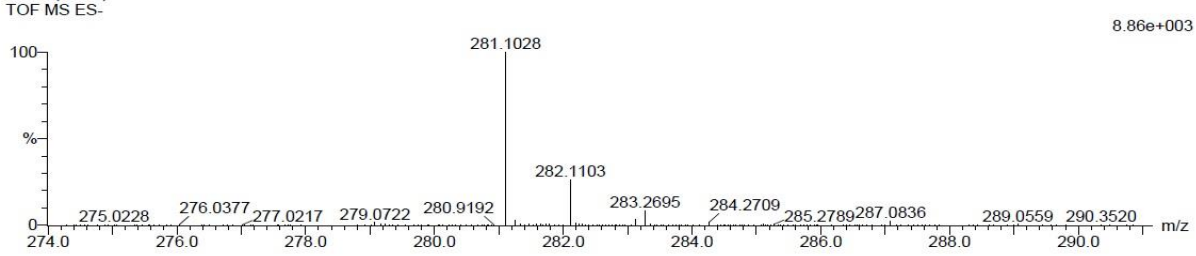



FTIR spectra of compound **7f**

**Elemental Composition Report** **Page 1**

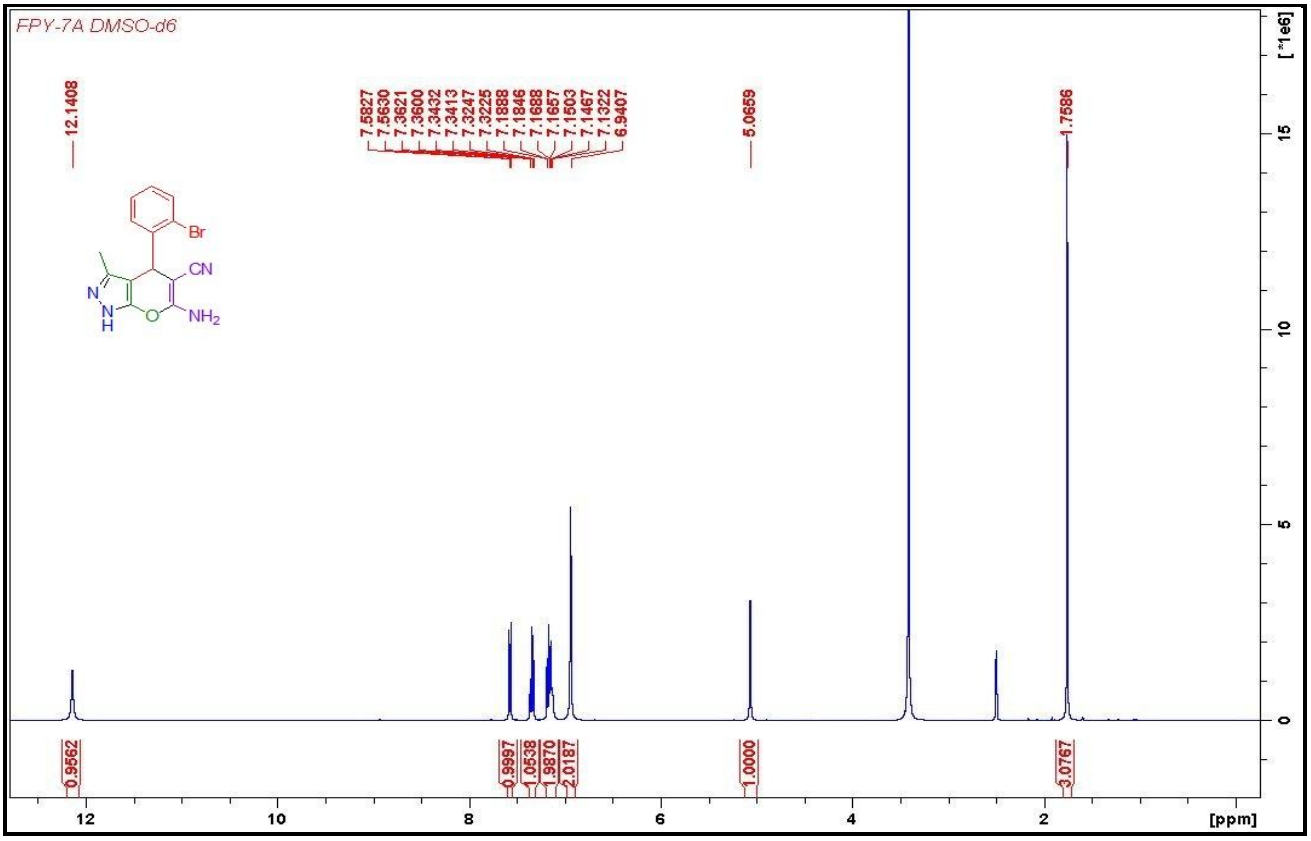
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
18 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 10-15 H: 10-15 N: 0-5 O: 0-5
7F 53 (1.754)
TOF MS ES-

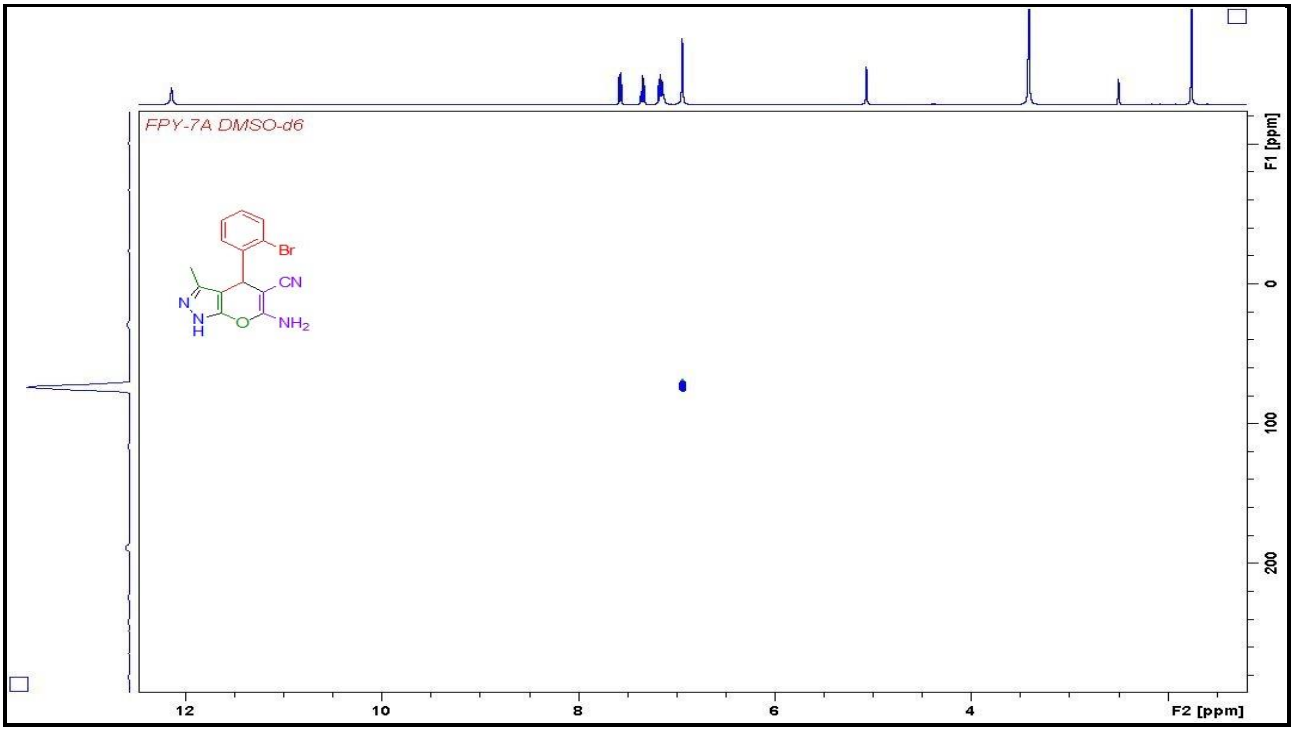



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 281.1028 | 281.1039 | -1.1 | -3.9 | 11.5 | 255.3 | 0.0 | C15 H13 N4 O2 |

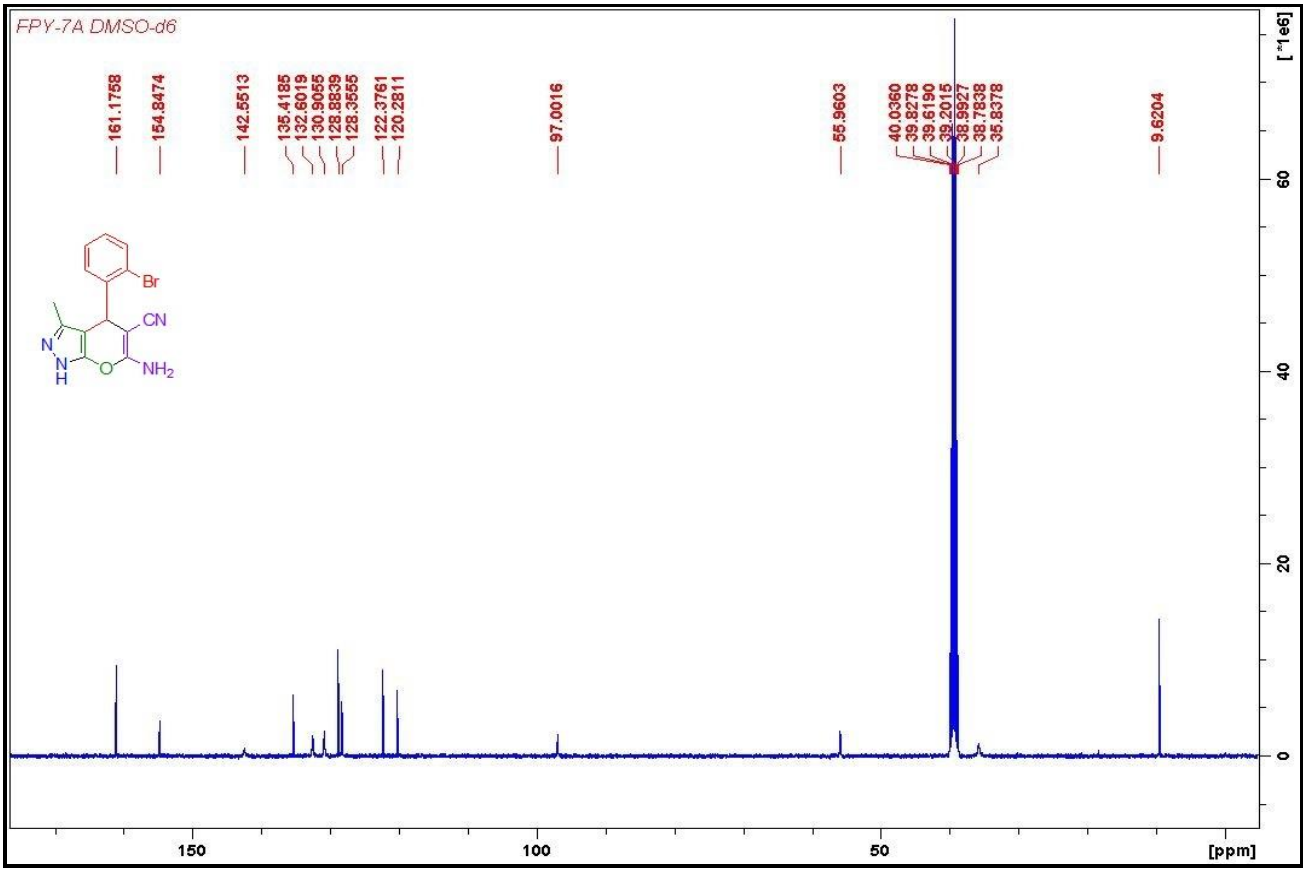
HRMS spectra of compound **7f**



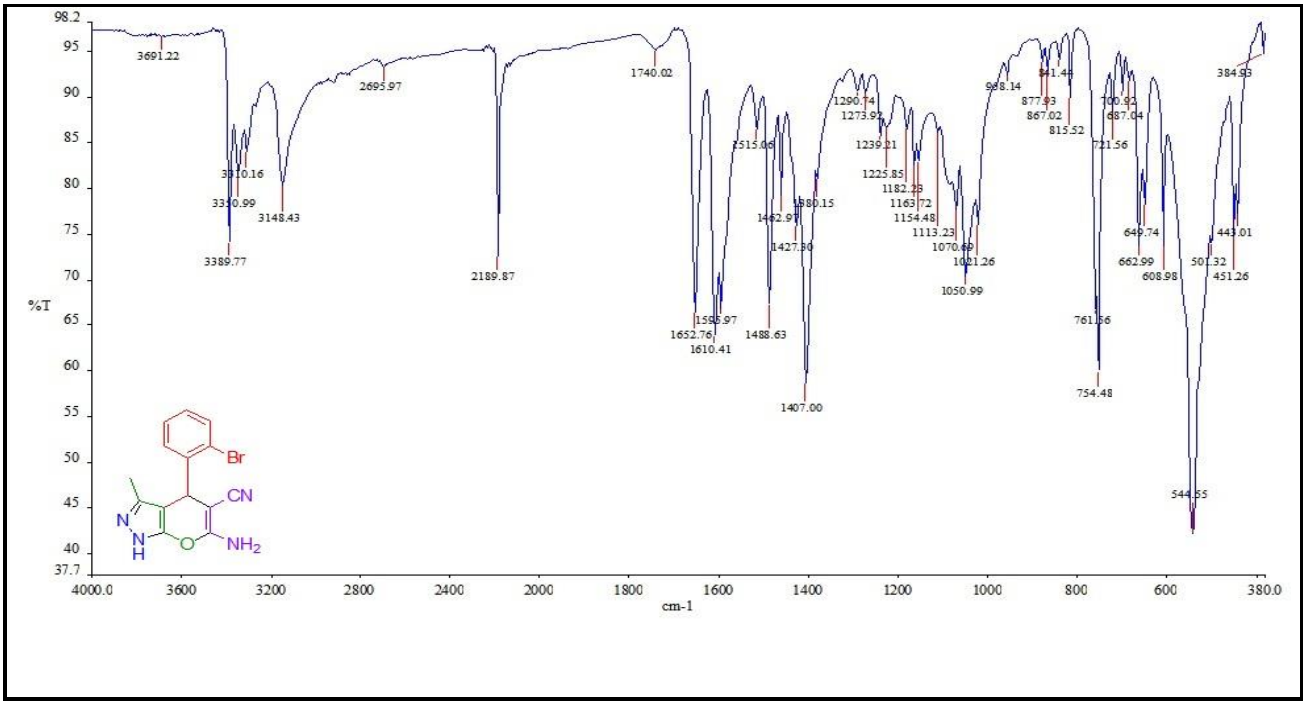

$^{1}$H NMR spectra of compound **7g**




$^{15}$N NMR (ghsqc) spectra of compound **7g**




$^{13}$C NMR spectra of compound **7g**



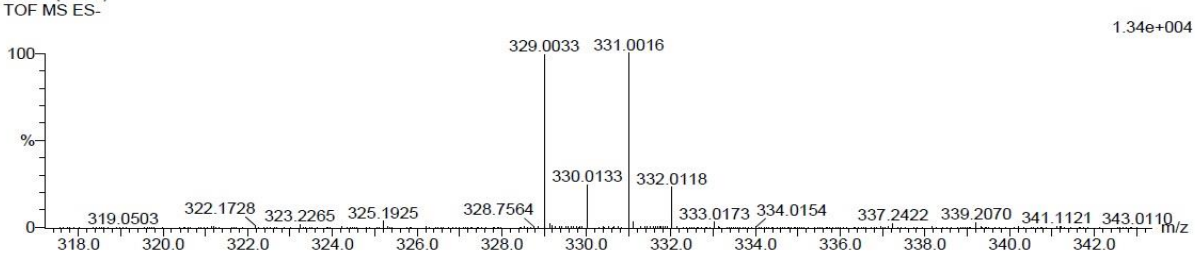

FTIR spectra of compound **7g**

**Elemental Composition Report** **Page 1**

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

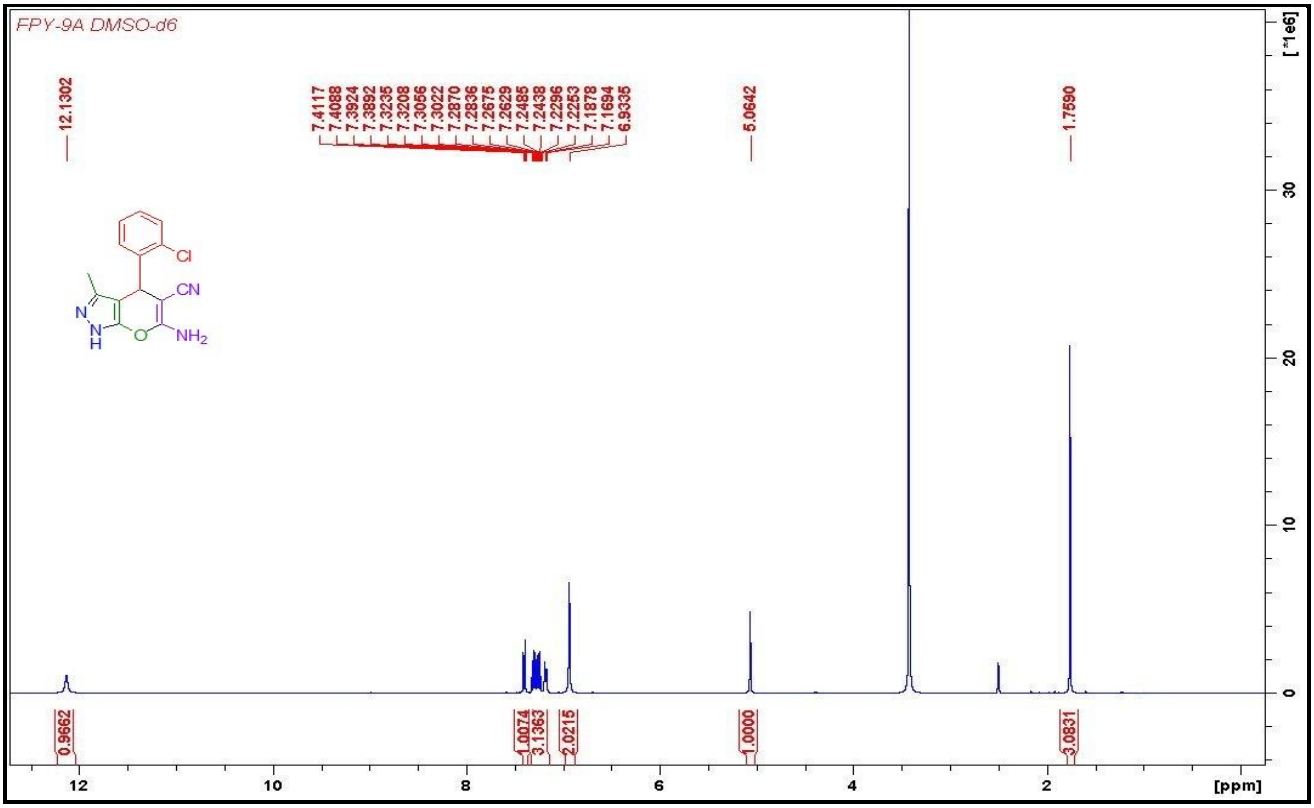
Monoisotopic Mass, Even Electron Ions
13 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 10-15 H: 10-13 N: 0-5 O: 0-5 Br: 1-1

7G 61 (2.024)
TOF MS ES-

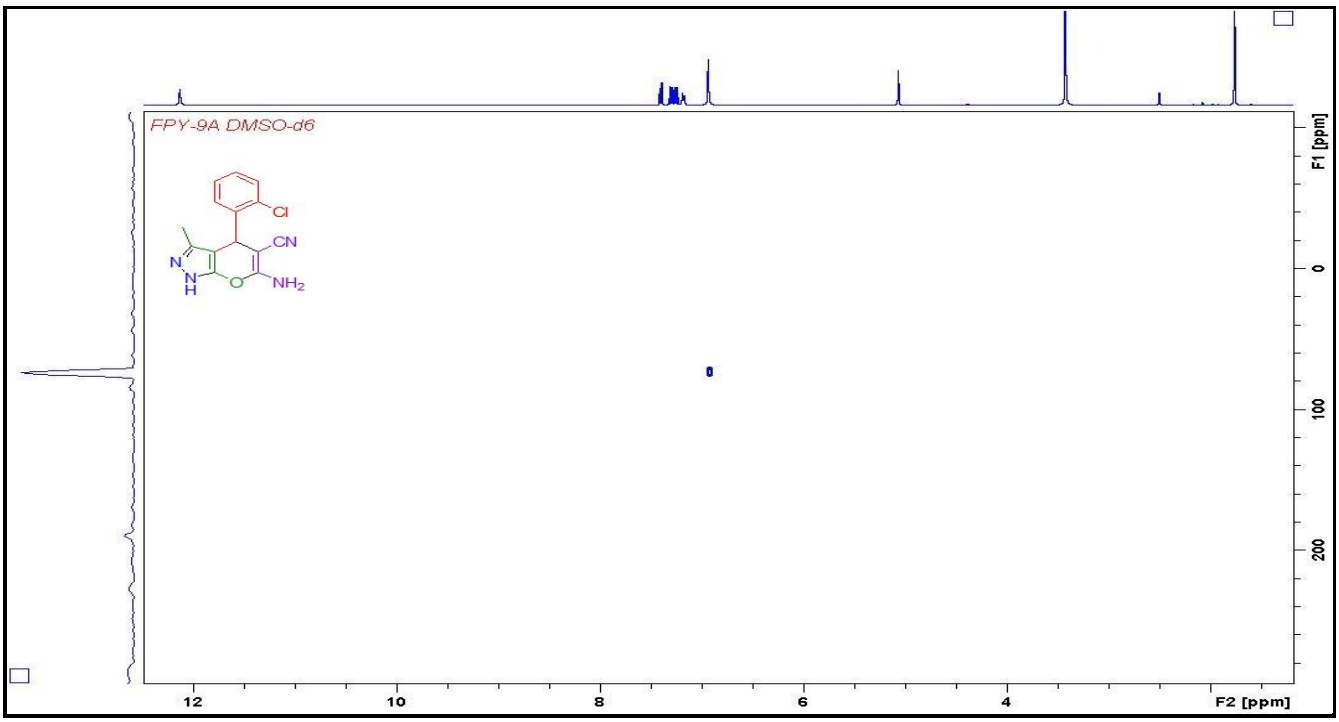



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 329.0033 | 329.0038 | -0.5 | -1.5 | 11.5 | 211.5 | 0.0 | C14 H10 N4 O Br |

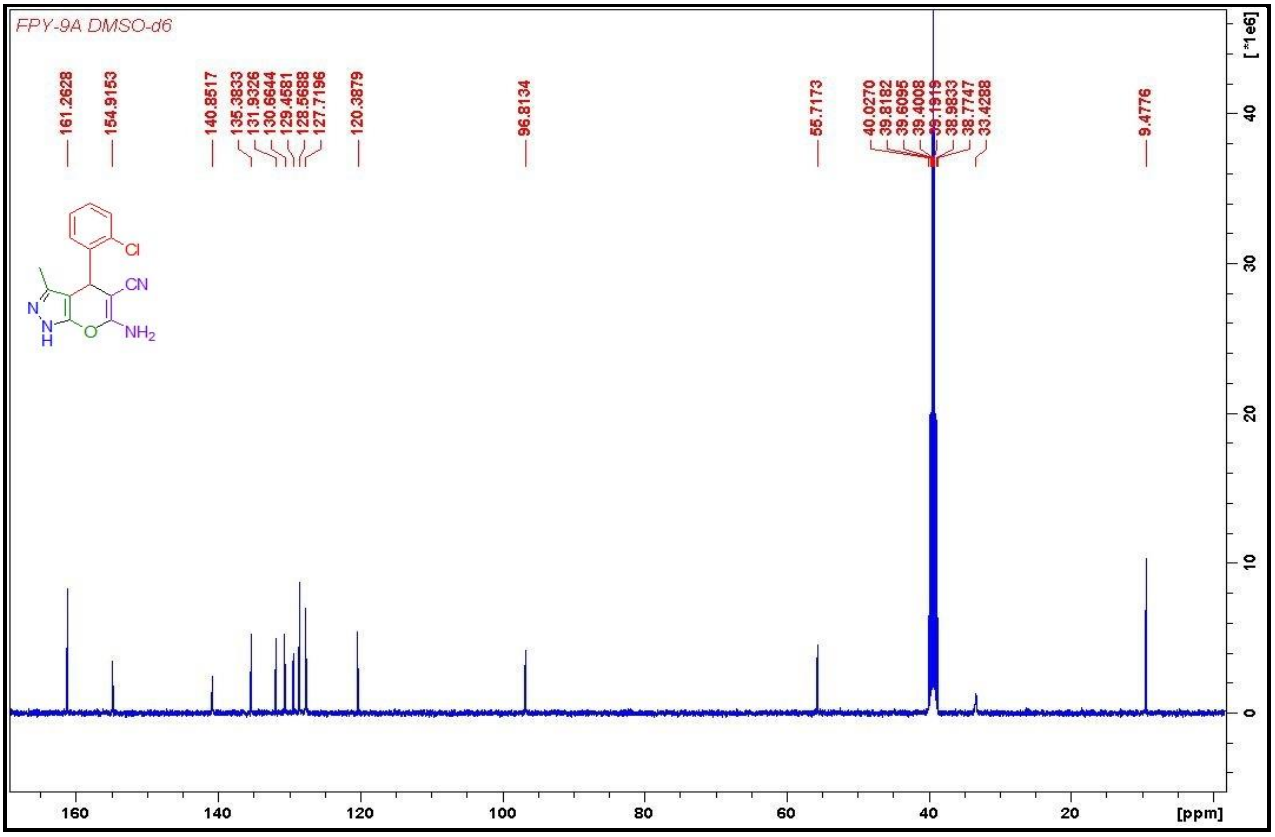
HRMS spectra of compound **7g**



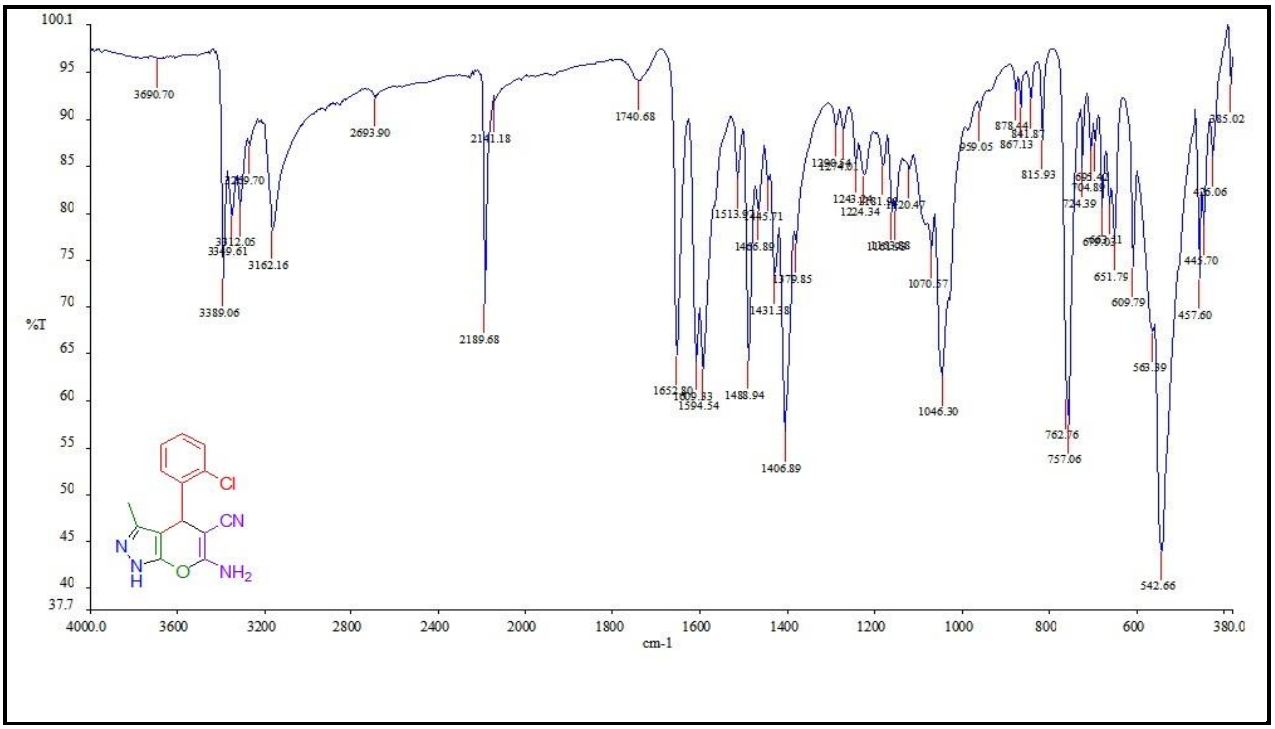

$^{1}$H NMR spectra of compound **7h**




$^{15}$N NMR (ghsqc) spectra of compound **7h**




$^{13}$C NMR spectra of compound **7h**

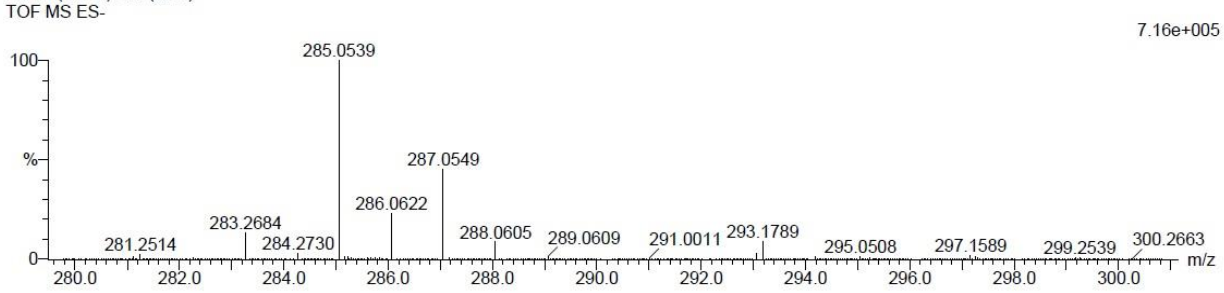



FTIR spectra of compound **7h**

**Elemental Composition Report** **Page 1**

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
13 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 10-15 H: 10-13 N: 0-5 O: 0-5 Cl: 1-1
7H 53 (1.754) Cm (1:61)
TOF MS ES-




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 285.0539 | 285.0543 | -0.4 | -1.4 | 11.5 | 740.1 | 0.0 | C14 H10 N4 O Cl |

HRMS spectra of compound **7h**

# CHAPTER - 3

# CATALYST-FREE, ONE-POT, FOUR-COMPONENT GREEN SYNTHESIS OF FUNCTIONALIZED 1,4-DIHYDROPYRIDINE DERIVATIVES UNDER ULTRASOUND IRRADIATION

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**Abstract:**

An environmental friendly catalyst-free synthesis protocol for functionalized 1,4-dihydropyridine derivatives involving four components under ultrasonic irradiation in aqueous ethanol is reported. Eleven new compounds were synthesized using multi-component one pot reaction of dimethylacetylenedicarboxylate, arylamine, malononitrile and various substituted aldehydes. The establishment of multiple carbon–carbon bonds occur in absence of any hazardous organic solvents or catalyst. The target compounds were obtained in excellent yields (89-96%). All the new compounds were identified and validated by IR, $^{1}$H NMR, $^{13}$C NMR, $^{15}$N NMR and HRMS spectral data. The new procedure has noteworthy advantages including safety, short reaction times, environmentally benign mild conditions and high yields.

**Keywords:** Green synthesis; Functionalized pyridines; Multicomponent reactions; One-pot synthesis; Ultra sonication.

## 1. INTRODUCTION:

Multicomponent reaction (MCRs) refers to the condition in which at least three functional groups are joined through covalent bonds to form a product that is derived from all components in the system.[1-3] MCRs allow the formation of structurally diverse compounds from simple starting materials in one pot, and these have proven to be green and efficient for the synthesis of heterocyclic compounds.[4] MCRs consist atom economy and high functional group tolerance.[4-6] These reactions gained much attention in organic synthesis because there is no need for isolation of intermediates, which saves both energy and raw material consumption plus reduces time.[6] In most of the cases no further purification is needed as due to high selectivity.[5]

Ultrasound irradiation is an vital tool in heterocyclic chemistry, which allows reactions under mild conditions and known to enhance the yields reducing the reaction times.[7,8] Researchers attempted to use the green approach of ultrasound irradiation to further improve the known MCRs.[7-9] Ultrasound accelerates reaction rates by facilitating mass transfer in the microenvironment, through the process of acoustic cavitation. Cavitation occurs in an irradiated liquid, involving bubble formation, growth and impulsive collapse.[10-12] The collapsing bubbles induce high temperature and pressure, in the form of hot spots with sufficient energy to facilitate chemical reactions.[12] Ultrasound offer advantages such as improved yields, short reaction times, minimal waste production, and energy savings among others, therefore it is convenient as green chemistry approach.

Heterocyclics are ubiquitously imperative structural units and major building blocks of a diverse variety of natural products. The development of new templates of heterocyclic systems with enhanced biological activity has been the continued pursuit of the synthetic chemists, as most of the medicinal, pharmaceuticals and agronomy chemicals have been derived from the heterocyclic structures.[13-15] The pyridine nucleus is one of the most important heterocycles found in many natural products and functional materials.[16] The pyridines and their derivatives shows a wide range of biological properties, such as antibacterial,[17] antifungal,[18] antioxidant, [19] anticancer,[20] anticonvulsant,[21] and antiviral activity.[22] The pyridines are also known for their anti-inflammatory activity and can act as antagonists inhibitors.[23] Furthermore, many pyridine derivatives are used as herbicides and insecticidal agents.[24,25] Essential vitamins, niacin and pyridoxine and highly toxic alkaloids, such as nicotine possess pyridine units in their structures.[26] Literature survey reveals that only three preparation methods have been reported

for various 1,4-dihydropyridine derivatives. The reported protocols employed TEA, NaOH and PEG-600 as catalysts to facilitate the reactions,[27-29] which also involve costly reagents, acidic or basic conditions, high temperature, long reaction times, tedious handling processes and harsh reaction conditions, but low yields. Consequently, development of improved green protocols for their synthesis and design of the new *N*-containing heterocyclic units is paramount and justified.

In previous studies, we reported methods for various heterocycles in heterocyclic synthesis using reusable heterogeneous catalysts.[30-33] More recently, we have reported a green approach for the synthesis of pyrazole molecules without the use of catalysts, under ultrasonication.[34] We have also published protocols for different heterocycles such as 1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazoles for anti-inflammatory, tetrazole linked triazole for insecticidal, pyrazoles for antioxidant, 1,3,4-thiadiazoles and 1,4-dihydropyrimidine-5-carboxylate derivatives for potent antimicrobial activity. [35-39] In continuation of our interest to improve a facile process under green conditions, this communication describes a green protocol for the synthesis of functionalized 1,4-dihydropyridines using aqueous ethanol solvent under ultrasound irradiation under catalyst-free conditions. No literature report on the preparation of 1,4-dihydropyridines by one-pot condensation of substituted aldehyde, malononitrile, dimethylacetylenedicarboxylate and arylamine in aqueous ethanol solvent using ultrasonic irradiation at RT has been reported earlier.

## 2. EXPERIMENTAL SECTION

### *2.1.General procedure for the synthesis under silent conditions*

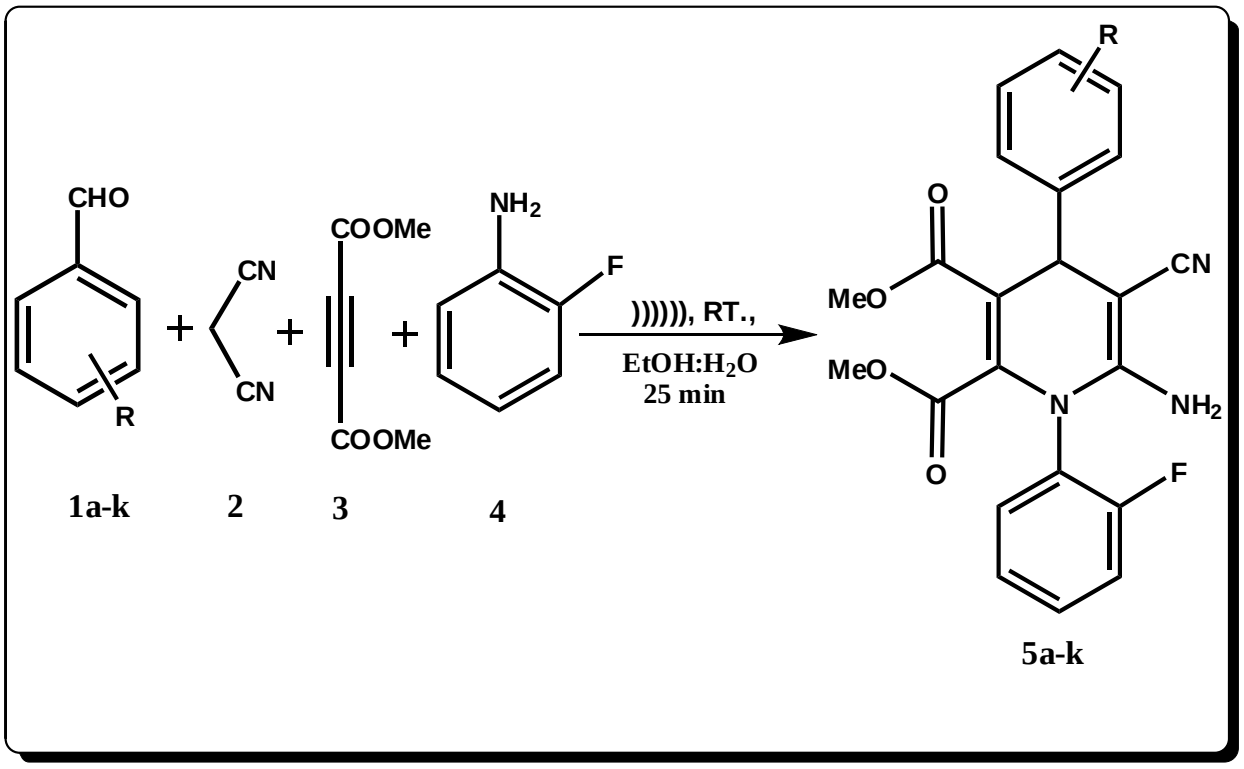
A flask containing a mixture of substituted aldehyde (1.0 mmol), malononitrile (1.1 mmol), dimethylacetylenedicarboxylate (1.0 mmol) and arylamine (1.0 mmol) in aqueous ethanol (10 ml) was employed and stirred at RT for 12 h. The reaction was observed by TLC analysis to detect the reaction completion. After the reaction, product was recovered by evaporation of solvent under vacuum, which was recrystallized from EtOH due to mixed products.

### *2.2.General procedure for the synthesis under ultrasound irradiation (5a-k)*

Initially an aqueous ethanol (5 mL) solution of substituted aldehyde (1.0 mmol) and malononitrile (1.1 mmol) was stirred at room temperature for 5 minutes. Subsequently, a solution of dimethylacetylenedicarboxylate (1.0 mmol) and arylamine (1.0 mmol) in aqueous ethanol (5

mL) was added to this mixture and was stirred at RT under ultrasonication for appropriate time. The reaction progress was monitored by TLC (Scheme 1). On completion of the reaction, the flask was alienated from the probe and the content was transferred into a beaker. Then, the solvent was evaporated to obtain product the product in high purity. No further recrystallization was needed. All the products were characterized by various spectral data. Experimental section and other compounds characterization data (5a-k) are described in the supporting information (S1).

**Scheme 1:** Synthesis of functionalized 1,4-dihydropyridine derivatives



### *2.2.1. Physical data*

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (5a)*:** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 3H, $OCH_3$), 3.59 (s, 3H, $OCH_3$), 4.04 (s, 2H, $NH_2$), 4.65 (s, 1H, CH), 7.25 (d, *J* = 7.68 Hz, 1H, ArH), 7.28 (d, *J* = 7.08 Hz, 2H, ArH), 7.34–7.39 (m, 5H, ArH), 7.50–7.53 (m, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 38.78, 52.08, 52.69, 61.34, 106.37, 116.06, 116.28, 116.91, 117.14, 120.08, 127.26, 132.83, 132.91, 144.39, 150.13, 162.77, 163.46, 164.52, 165.59; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 4.04 (s, 2H, $NH_2$); FT-IR**:** 757, 1025, 1254, 1410, 1580, 1651, 1737, 2184, 2953, 3367, 3387, 3463; HRMS of $[C_{22}H_{18}FN_3O_4 + Na]^+$ (m/z): 430.1179; Calcd: 430.1179.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(4-bromophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5b)*:** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 3H, $OCH_3$), 3.59 (s, 3H, $OCH_3$), 4.11 (s, 2H, $NH_2$), 4.62 (s, 1H, CH), 7.25 (d, *J* = 6.12 Hz, 1H, ArH), 7.28 (d, *J* = 3.28 Hz, 1H, ArH), 7.33–7.39 (m, 5H, ArH) 7.49–7.54 (m, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 38.33, 52.14, 52.75, 63.53, 105.91, 117.22, 117.42, 119.94, 122.80, 122.94, 125.10, 128.93, 133.04, 141.39, 143.02, 149.23, 163.26, 165.36; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 4.11 (s, 2H, $NH_2$); FT-IR**:** 774, 1023, 1233, 1416, 1584, 1657, 1750, 2189, 2951, 3317, 3378, 3450; HRMS of $[C_{22}H_{16}BrFN_3O_4 – H]^+$ (m/z): 484.0314; Calcd: 484.0308.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(2-methoxyphenyl)-1,4-dihydro--pyridine-2,3-dicarboxylate (5c):*** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 3H, $OCH_3$), 3.56 (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 3.96 (s, 2H, $NH_2$), 5.16 (s, 1H, CH), 6.91–6.99 (m, 2H, ArH), 7.23–7.27 (m, 3H, ArH), 7.36–7.39 (m, 2H, ArH); 7.47–7.52 (m, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 32.16, 52.04, 52.69, 55.75, 63.01, 104.73, 111.15, 117.09, 120.88, 127.74, 128.31, 131.34, 131.75, 132.32, 132.40, 132.55, 142.54, 149.98, 156.77, 161.90, 163.79, 164.40, 165.86; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 3.96 (s, 2H, $NH_2$); FT-IR: 773, 1023, 1256, 1416, 1584, 1657, 1751, 2190, 2951, 3225, 3317, 3449; HRMS of $[C_{23}H_{20}FN_3O_5 + Na]^+$ (m/z): 460.1287; Calcd: 460.1285.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(2,3-dimethoxyphenyl)-1,4-dihydro--pyridine-2,3-dicarboxylate (5d):*** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 3H, $OCH_3$), 3.56 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 3.97 (s, 3H, $OCH_3$), 4.01 (s, 2H, $NH_2$), 5.14 (s, 1H, CH), 6.81 (t, *J* = 6.64 Hz, 1H, ArH), 7.05 (d, *J* = 7.44 Hz, 2H, ArH), 7.25 (d, *J* = 8.44 Hz, 1H, ArH), 7.27 (d, *J* = 8.00 Hz, 1H, ArH), 7.41–7.52 (m, 2H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 33.32, 51.99, 52.63, 55.73, 61.32, 64.01, 106.35, 111.39, 117.33, 120.35, 121.02, 124.16, 125.02, 132.74,

132.82, 141.62, 163.55, 165.73; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 4.01 (s, 2H, $NH_2$); FT-IR**:** 775, 1023, 1256, 1416, 1584, 1657, 1751, 2190, 2951, 3226, 3317, 3448; HRMS of [$C_{24}H_{22}FN_3O_6$ + Na]$^+$ (m/z): 490.1399; Calcd: 490.1390.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(2-fluorophenyl)-1,4-dihydro--pyridine-2,3-dicarboxylate (5e)*****:** $^1$H NMR (400 MHz, $CDCl_3$) δ 3.34 (s, 3H, $OCH_3$), 3.48 (s, 3H, $OCH_3$), 4.85 (s, 1H, CH), 5.83 (s, 2H, $NH_2$), 7.19–7.25 (m, 2H, ArH), 7.30–7.40 (m, 5H, ArH), 7.56–7.61 (m, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 37.92, 52.02, 52.74, 62.33, 105.01, 117.18, 119.86, 122.78, 128.25, 128.66, 129.90, 130.82, 132.43, 132.52, 133.20, 142.26, 143.99, 149.65, 162.01, 163.38, 164.52; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 5.83 (s, 2H, $NH_2$); FT-IR**:** 773, 1024, 1254, 1416, 1578, 1650, 1742, 2178, 2951, 3205, 3316, 3407; HRMS of [$C_{22}H_{17}F_2N_3O_4$ + Na]$^+$ (m/z): 448.1087; Calcd: 448.1085.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(2-chlorophenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5f)*****:** $^1$H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 3H, $OCH_3$), 3.56 (s, 3H, $OCH_3$), 4.10 (s, 2H, $NH_2$), 5.32 (s, 1H, CH), 7.17 (t, *J* = 7.28 Hz, 1H, ArH), 7.27–7.35 (m, 5H, ArH), 7.37–7.55 (m, 2H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 34.61, 52.27, 52.73, 62.04, 105.92, 116.89, 117.20, 119.97, 127.43, 128.47, 129.89, 130.08, 132.45, 132.54, 141.89, 142.37, 149.69, 162.20, 163.50, 165.40; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 4.10 (s, 2H, $NH_2$); FT-IR**:** 771, 1024, 1254, 1416, 1578, 1650, 1743, 2179, 2950, 3226, 3317, 3412; HRMS of [$C_{22}H_{17}ClFN_3O_4$ + Na]$^+$ (m/z): 464.0785; Calcd: 464.0789.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5g)*****:** $^1$H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 3H, $OCH_3$), 3.60 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 4.05 (s, 2H, $NH_2$), 4.59 (s, 1H, CH), 6.85 (d, *J* = 8.28 Hz, 1H, ArH), 6.94 (t, *J* = 7.52 Hz, 2H, ArH), 7.25 (d, *J* = 7.12 Hz, 1H, ArH), 7.27 (d, *J* = 7.12 Hz, 1H, ArH), 7.36 (d, *J* = 6.16 Hz, 1H, ArH), 7.49–7.54 (m, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 38.41, 58.09, 52.69, 55.74, 55.88, 64.43, 106.35, 110.45, 111.19, 117.15, 117.34, 125.11, 131.99, 132.85, 132.93, 137.30, 148.21, 149.23, 163.47, 165.66; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 4.05 (s, 2H, $NH_2$); FT-IR**:** 772, 1023, 1247, 1418, 1581, 1654, 1744, 2180, 2949, 3225, 3318, 3407; HRMS of [$C_{24}H_{22}FN_3O_6$ + Na]$^+$ (m/z): 490.1405; Calcd: 490.1390.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(2,5-dimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5h)*****:** $^1$H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 3H, $OCH_3$), 3.57 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 3.97 (s, 2H, $NH_2$), 5.14 (s, 1H, CH), 6.76 (dd, *J* = 8.84 Hz, 3.04 Hz, 1H, ArH), 6.86 (d, *J* = 8.88 Hz, 1H, ArH), 6.93 (s, 1H, ArH), 7.25 (d, *J* = 5.36 Hz,

1H, ArH), 7.26 (d, *J* = 5.36 Hz, 1H, ArH), 7.36–7.40 (m, 1H, ArH), 7.48–7.52 (m, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 32.55, 52.09, 52.67, 55.58, 56.65, 63.98, 105.65, 112.55, 117.13, 117.34, 120.18, 123.17, 125.05, 132.70, 132.78, 133.88, 142.10, 154.01, 163.58, 165.68; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 3.97 (s, 2H, $NH_2$); FT-IR**:** 771, 1023, 1248, 1418, 1581, 1655, 1744, 2180, 2950, 3227, 3318, 3409; HRMS of $[C_{24}H_{22}FN_3O_6 + H]^+$ (m/z): 468.1578; Calcd: 468.1571.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(4-fluorophenyl)-1,4-dihydro--pyridine-2,3-dicarboxylate (5i)*****:** $^1$H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 3H, $OCH_3$), 3.58 (s, 3H, $OCH_3$), 4.09 (s, 2H, $NH_2$), 4.64 (s, 1H, CH), 7.04 (t, *J* = 8.68 Hz, 2H, ArH), 7.25 (d, *J* = 5.26 Hz, 1H, ArH), 7.28 (d, *J* = 7.00 Hz, 1H, ArH), 7.38 (t, *J* = 7.36 Hz, 3H, ArH), 7.51–7.54 (m, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 38.17, 52.12, 52.74, 63.96, 106.22, 115.48, 115.69, 120.01, 125.15, 128.93, 132.94, 133.02, 140.38, 149.08, 160.82, 163.26, 165.46; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 4.09 (s, 2H, $NH_2$); FT-IR**:** 770, 1023, 1254, 1418, 1583, 1650, 1742, 2187, 2950, 3227, 3318, 3460; HRMS of $[C_{22}H_{17}F_2N_3O_4 - H]^+$ (m/z): 424.1101; Calcd: 424.1109.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(4-ethylphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5j)*****:** $^1$H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.04 Hz, 3H, $CH_3$), 2.61–2.67 (m, 2H, $CH_2$), 3.45 (s, 3H, $OCH_3$), 3.60 (s, 3H, $OCH_3$), 4.02 (s, 2H, $NH_2$), 4.62 (s, 1H, CH), 7.18 (d, *J* = 7.96, 2H, ArH), 7.25 (d *J* = 8.20 Hz, 1H, ArH), 7.29 (t, *J* = 5.04 Hz, 3H, ArH), 7.39 (t, *J* = 7.44 Hz, 1H, ArH), 7.49–7.51 (m, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 15.48, 28.41, 37.99, 52.08, 52.51, 63.68, 105.79, 116.95, 117.15, 120.40, 126.87, 128.31, 131.11, 131.15, 132.31, 132.40, 141.88, 143.11, 149.45, 161.96, 163.59, 164.47, 165.75; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 4.02 (s, 2H, $NH_2$); FT-IR**:** 770, 1025, 1256, 1418, 1561, 1649, 1739, 2190, 2950, 3226, 3316, 3448; HRMS of $[C_{24}H_{22}FN_3O_4 + Na]^+$ (m/z): 458.1490; Calcd: 458.1492.

***Dimethyl 6-amino-5-cyano-1-(2-fluorophenyl)-4-(4-methoxyphenyl)-1,4-dihydro--pyridine-2,3-dicarboxylate (5k)*****:** $^1$H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 3H, $OCH_3$), 3.58 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 4.05 (s, 2H, $NH_2$), 4.60 (s, 1H, CH), 6.89 (d, *J* = 8.56 Hz, 2H, ArH), 7.24 (s, 1H, ArH), 7.28 (d, *J* = 3.00 Hz, 1H, ArH), 7.31 (d, *J* = 7.68 Hz, 2H, ArH), 7.48 (t, *J* = 7.48 Hz, 1H, ArH), 7.48-7.52 (m, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): 38.00, 46.18, 52.06, 52.66, 55.25, 106.58, 114.12, 117.15, 117.34, 120.21, 123.18, 125.04, 128.46, 132.81, 132.89, 136.92, 158.77, 165.66; $^{15}$N NMR (40.55 MHz, $CDCl_3$) δ 4.60 (s, 2H, $NH_2$); FT-IR: 770, 1024, 1254, 1420, 1568, 1650, 1744, 2181, 2950, 3225, 3337, 3464; HRMS of $[C_{23}H_{20}FN_3O_5 + H]^+$ (m/z): 438.1461; Calcd: 438.1465.

## 3. RESULTS AND DISCUSSION

### 3.1. Optimization of reaction conditions and scope of the reaction

To initiate our study, we checked the multicomponent reaction of aldehyde, malononitrile, dimethylacetylenedicarboxylate and arylamine as model reaction. The effect of various reaction parameters, such as the effect of solvents, catalysts and temperature and reaction conditions were evaluated to optimize the reaction under silent and thermal conditions. Firstly, the effect of various solvents (non-polar, protic and aprotic) on formation of the pyridines was investigated under silent and ultrasonification (Table 1). It was noteworthy that, in the absence of catalyst and solvent at room temperature (RT) and heating, no desired compound was identified under both reaction conditions (Table 1, entries 1 & 2). Next, in non-polar solvents like benzene and toluene, the reaction did not take place even after prolonged reaction time (Table 1, entries 3 & 4) under catalyst-free condition. Conducting the reactions in polar aprotic solvents, such as acetonitrile, acetone and dichloromethane, the reaction was very slow and resulted in lower product yield (Table 1, entries 5-7) in under silent and thermal conditions. Next, we tested with polar protic solvents such as methanol, ethanol and water (Table 1, entries 8-10), the yield of the desired products were good, however excellent yield was afforded using $H_2O$ and EtOH (1:1, v/v) as the solvent (Table 1, entry 11) in the absence of catalyst under ultrasound irradiation. Further, the scope of the various types of catalysts was then explored to improve the yield and reaction conditions. However, the starting materials were restricted by inorganic and organic catalysts such as NaOH, $Na_2CO_3$, TEA, piperidine and L-proline at RT in aqueous alcoholic media and gave moderate to good yields (Table 1, entries 12-16) under ultrasound irradiation. Furthermore, the above reaction was carried out in aqueous ethanol in the absence of catalyst for 2 h at reflux temperature under silent and thermal conditions (Table 1, entry 17). Therefore, the reaction was optimized using a cheap, safe, and environmentally benign reaction medium as opposed to the other synthetic solvents and catalysts. An aqueous ethanol could also be used as the best solvent for the synthesis.

**Table 1:** Optimization of various conditions for the synthesis of 1,4-dihydropyridine derivatives under sonication and conventional conditions[a]

| Entry | Solvent | Catalyst | Temperature | Conventional | | Sonication | |
|---|---|---|---|---|---|---|---|
| | | | | Time (h) | Yield (%) | Time (h) | Yield (%) |
| 1 | -- | -- | RT | 24 | b | 6 | b |
| 2 | -- | -- | 60 °C | 12 | b | 6 | b |
| 3 | benzene | -- | RT | 24 | b | 6 | b |
| 4 | toluene | -- | RT | 24 | b | 6 | b |
| 5 | $CH_3CN$ | -- | RT | 24 | 09 | 4.5 | 18 |
| 6 | acetone | -- | RT | 24 | 12 | 4.0 | 19 |
| 7 | DCM | -- | RT | 24 | 18 | 4.5 | 24 |
| 8 | MeOH | -- | RT | 12 | 48 | 3.0 | 65 |
| 9 | EtOH | -- | RT | 12 | 59 | 1.0 | 83 |
| 10 | $H_2O$ | -- | RT | 12 | 56 | 1.5 | 76 |
| 11 | EtOH:$H_2O$ (1:1) | -- | RT | 12 | 88 | 0.40 | 96 |
| 12 | EtOH:$H_2O$ (1:1) | NaOH | RT | 12 | 75 | 2.5 | 81 |
| 13 | EtOH:$H_2O$ (1:1) | $Na_2CO_3$ | RT | 12 | 56 | 3.0 | 62 |
| 14 | EtOH:$H_2O$ (1:1) | TEA | RT | 12 | 68 | 2.5 | 70 |
| 15 | EtOH:$H_2O$ (1:1) | piperidine | RT | 12 | 43 | 3.0 | 55 |
| 16 | EtOH:$H_2O$ (1:1) | L-proline | RT | 12 | 49 | 6.0 | 51 |
| 17 | EtOH:$H_2O$ (1:1) | -- | heat | 6 | 52 | 2.0 | 63 |

[a]All products were characterized by IR, $^1$HNMR, $^{13}$C NMR, $^{15}$N NMR & HRMS spectral data.

[b]No reaction

-- No solvent/catalyst

Using the optimized reaction conditions, we used the various aromatic aldehydes to react with malononitrile, dimethylacetylenedicarboxylate and arylamine and a series of functionalized 1,4-dihydropyridines derivatives were synthesized with excellent yield. The results of the reactions are summarized in Table 2. As shown in Table 2, we found that all the reactions were carried out smoothly, and the aromatic aldehydes, with either electron-withdrawing groups or electron-donating groups could all be used for the synthesis of functionalized 1,4-dihydropyridine derivatives with excellent yields. Structures of all the new synthesized products 5a–k were identified by physical and spectroscopic data including IR, $^{1}H$ NMR, $^{15}N$ NMR, $^{13}C$ NMR and HRMS spectral analysis. All the compounds details are showed in supplementary information (S2).

**Table 2:** Synthesis of functionalized 1,4-dihydropyridine derivatives in aqueous ethanol under ultrasonic irradiation at room temperature

| Entry | R | Product | Yield (%) | Mp °C | Lit Mp °C |
|---|---|---|---|---|---|
| 1 | H | **5a** | 96 | 195-196 | -- |
| 2 | 4-Br | **5b** | 92 | 205-206 | -- |
| 3 | 2-OMe | **5c** | 94 | 191-192 | -- |
| 4 | 2,3-$(OMe)_2$ | **5d** | 90 | 222-223 | -- |
| 5 | 2-F | **5e** | 93 | 231-232 | -- |
| 6 | 2-Cl | **5f** | 89 | 211-213 | -- |
| 7 | 3,4-$(OMe)_2$ | **5g** | 91 | 238-239 | -- |
| 8 | 2,5-$(OMe)_2$ | **5h** | 94 | 218-220 | -- |
| 9 | 4-F | **5i** | 89 | 209-210 | -- |
| 10 | 4-$C_2H_5$ | **5j** | 92 | 215-216 | -- |
| 11 | 4-OMe | **5k** | 95 | 226-228 | -- |

-- New compounds/no literature available.

## 4. CONCLUSION:

In summary, we have developed a rapid, clean and highly efficient methodology for the one-pot, four-component reactions by catalyst-free under ultrasound irradiation to afford functionalized 1,4-dihydropyridine derivatives as the desired products in short time span and in excellent yields by a simple and economical protocol. The reaction time, yield and handling highlight the efficiency of this protocol. Overall the present approach is facile, leading to higher yield of functionalized 1,4-dihydropyridines by a one-pot and four component reaction under ultrasound irradiation in aqueous ethanol. We assume this method to discover wide-range application in the field of pharmaceutical chemistry, diversity-oriented synthesis, large scale preparation and drug discovery.

## 5. ACKNOWLEDGEMENTS

The authors are thankful to the National Research Foundation (NRF) of South Africa, and University of KwaZulu-Natal, Durban, for financial support and research facilities.

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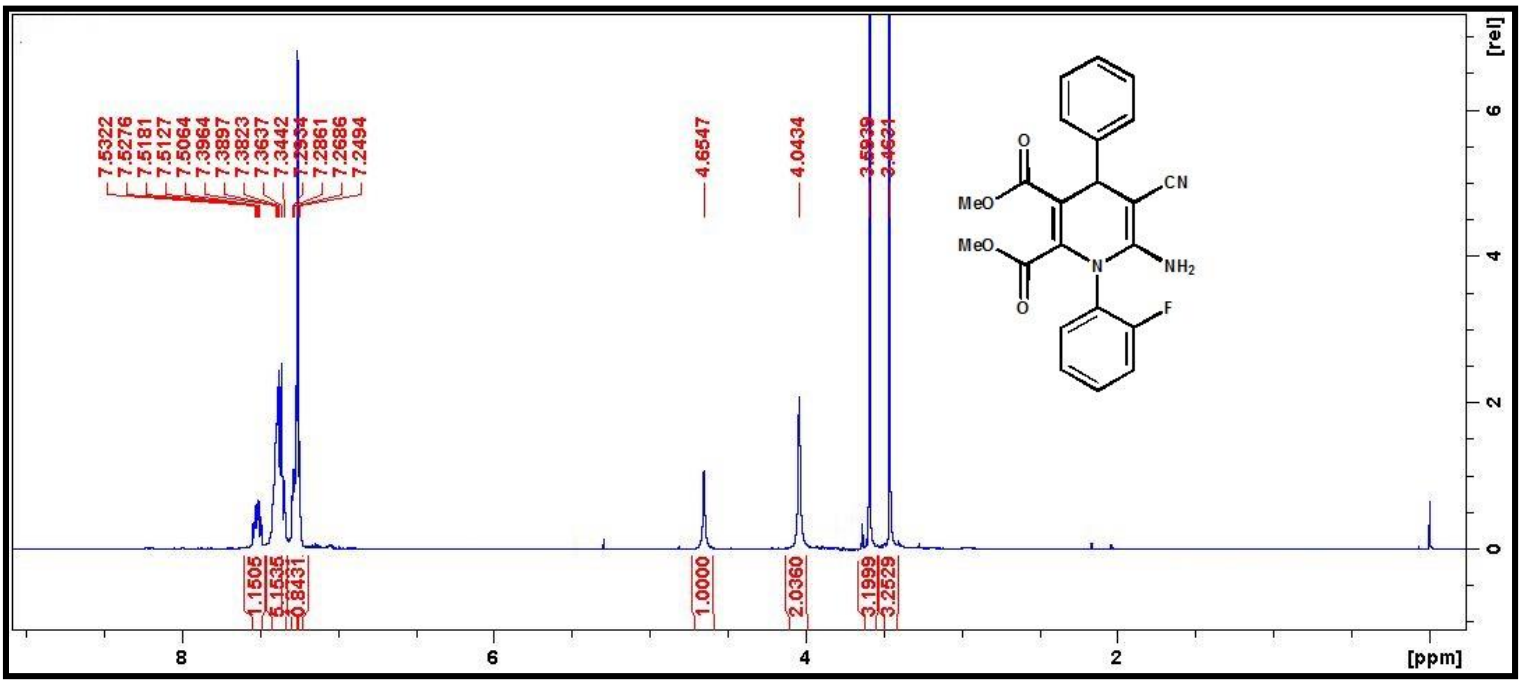
## 7. Supporting information:

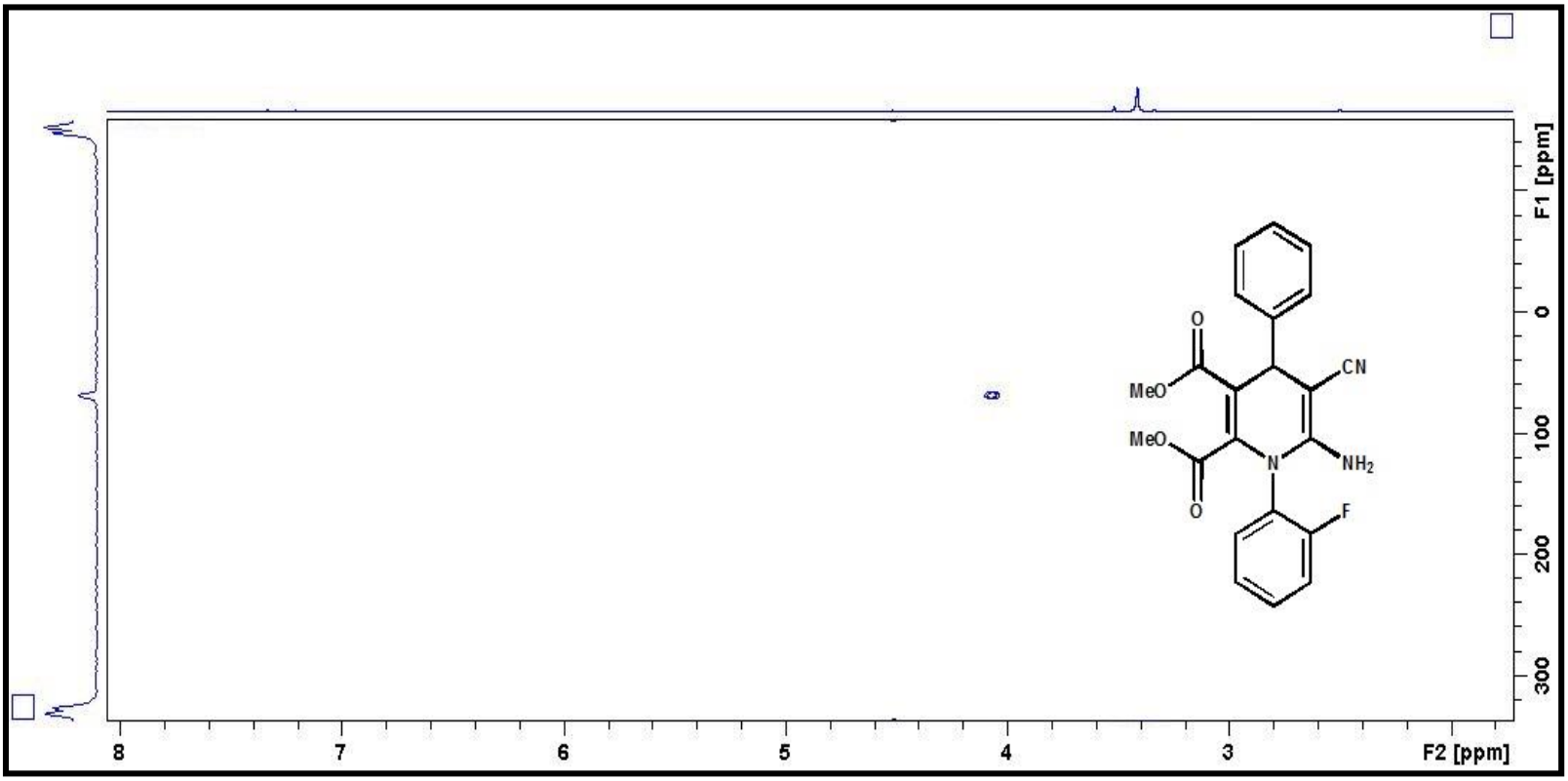
### *7.1. Materials, methods and instruments*

All chemicals used were reagent grade and were used as received without further purification. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 25 $^{o}C$ at 400 MHz and 100 MHz (Bruker Avance) instrument respectively, using TMS as internal standard. Chemical shifts are given in parts per million (ppm). The FT-IR spectroscopy of samples was carried out on a Perkin Elmer Perkin Elmer Precisely 100 FT-IR spectrometer in the 400-4000 $cm^{-1}$ region. The HRMS were recorded on a waters micromass LCT premier mass spectrometer using electrospray ionization in the positive or negative mode. The ultrasonic assisted reactions are carried out in a ‘‘Spectralab model UMC 20 Ultrsonic cleaner” with a frequency of 40 kHz and a nominal power 250 W. Melting points were recorded on a hot stage melting point apparatus Ernst Leitz Wetzlar, Germany and were uncorrected. All the reactions and the purity of products were monitored using thin layer chromatography (TLC) on aluminum-backed plates coated with Merck Kieselgel 60 F254 silica gel, visualizing the spots under ultraviolet light and iodine chamber.

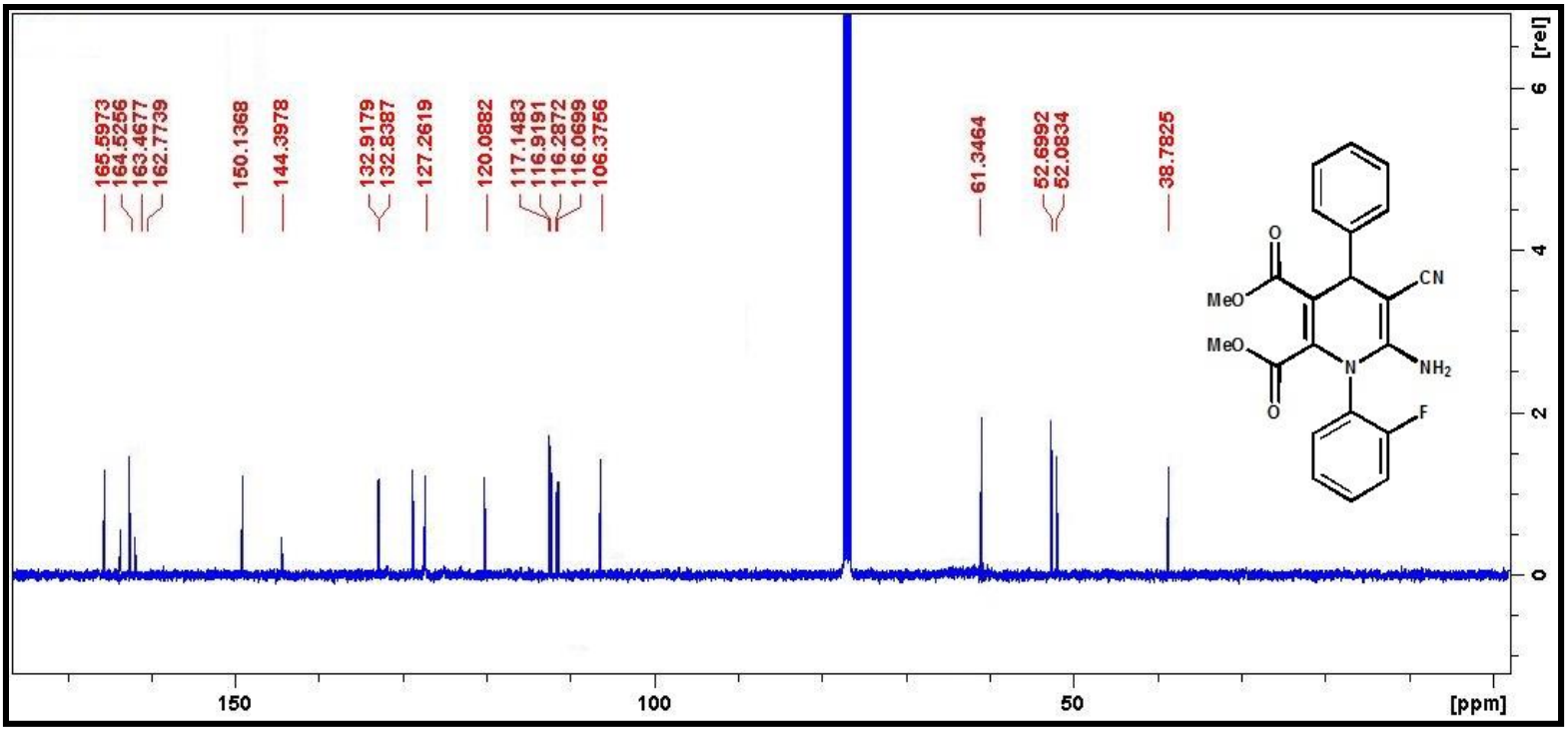
### *7.2. Supplementary information (S2).*




1H NMR spectra of 5a




$^{15}$N NMR spectra of **5a**




**$^{13}$C NMR spectra of 5a**

**Elemental Composition Report** Page 1

**Single Mass Analysis**
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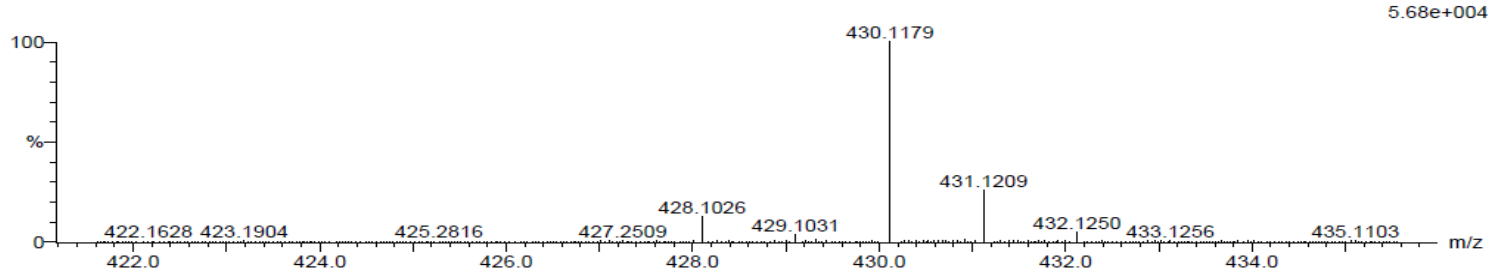
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
12 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 15-20 N: 0-5 O: 0-5 F: 1-1 Na: 1-1
2FA19 44 (1.451) Cm (1:61)
TOF MS ES+




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
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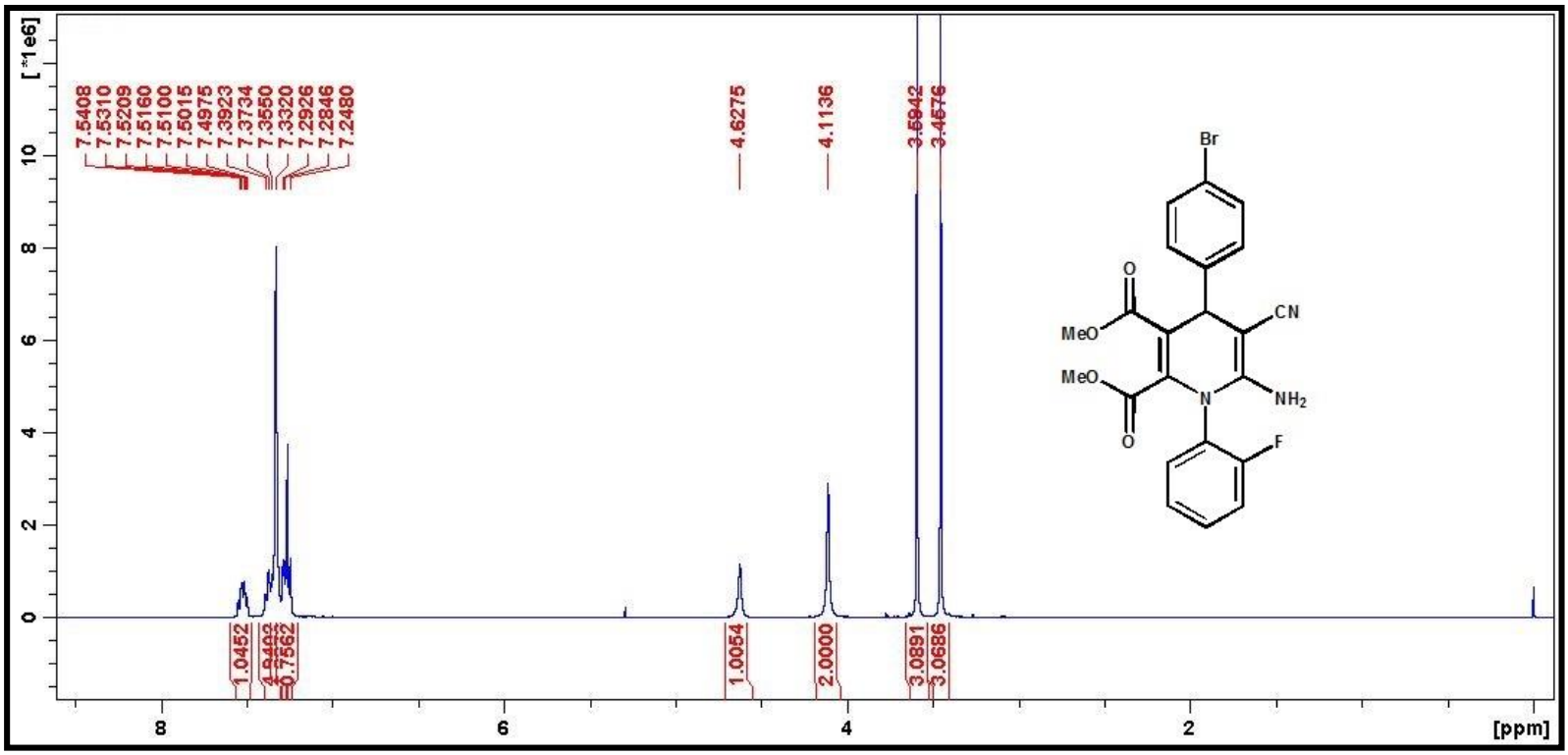
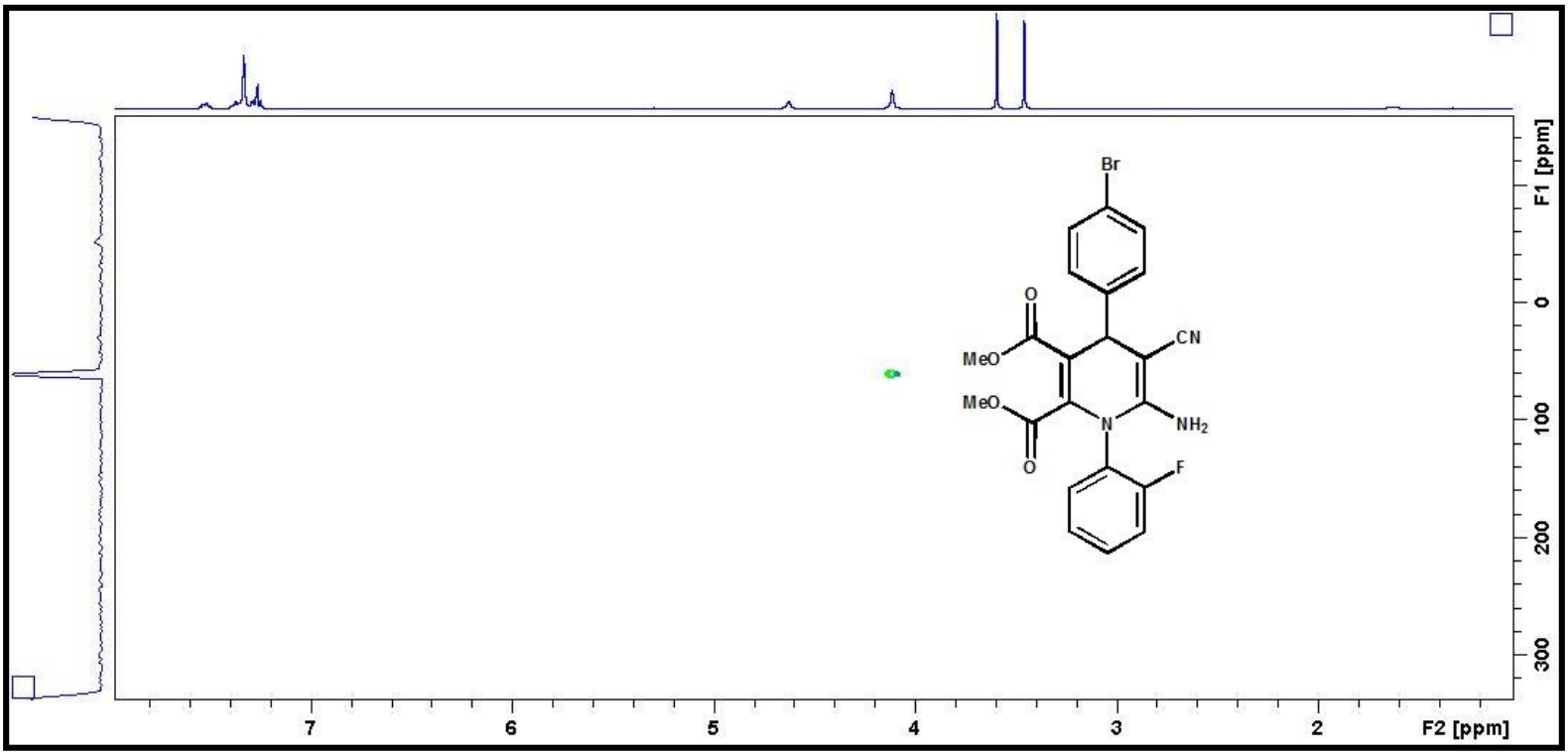
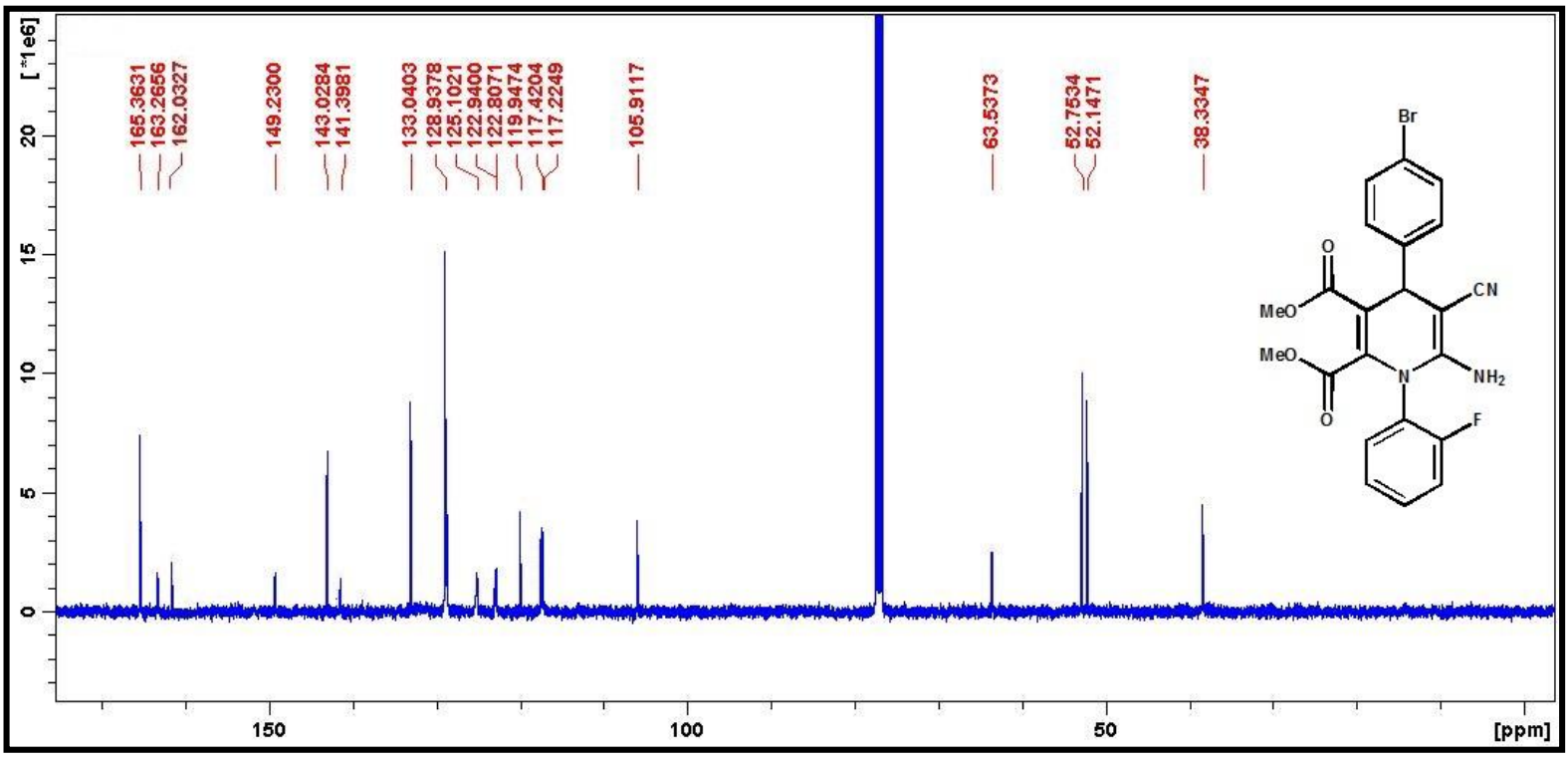
**HRMS spectra of 5a**



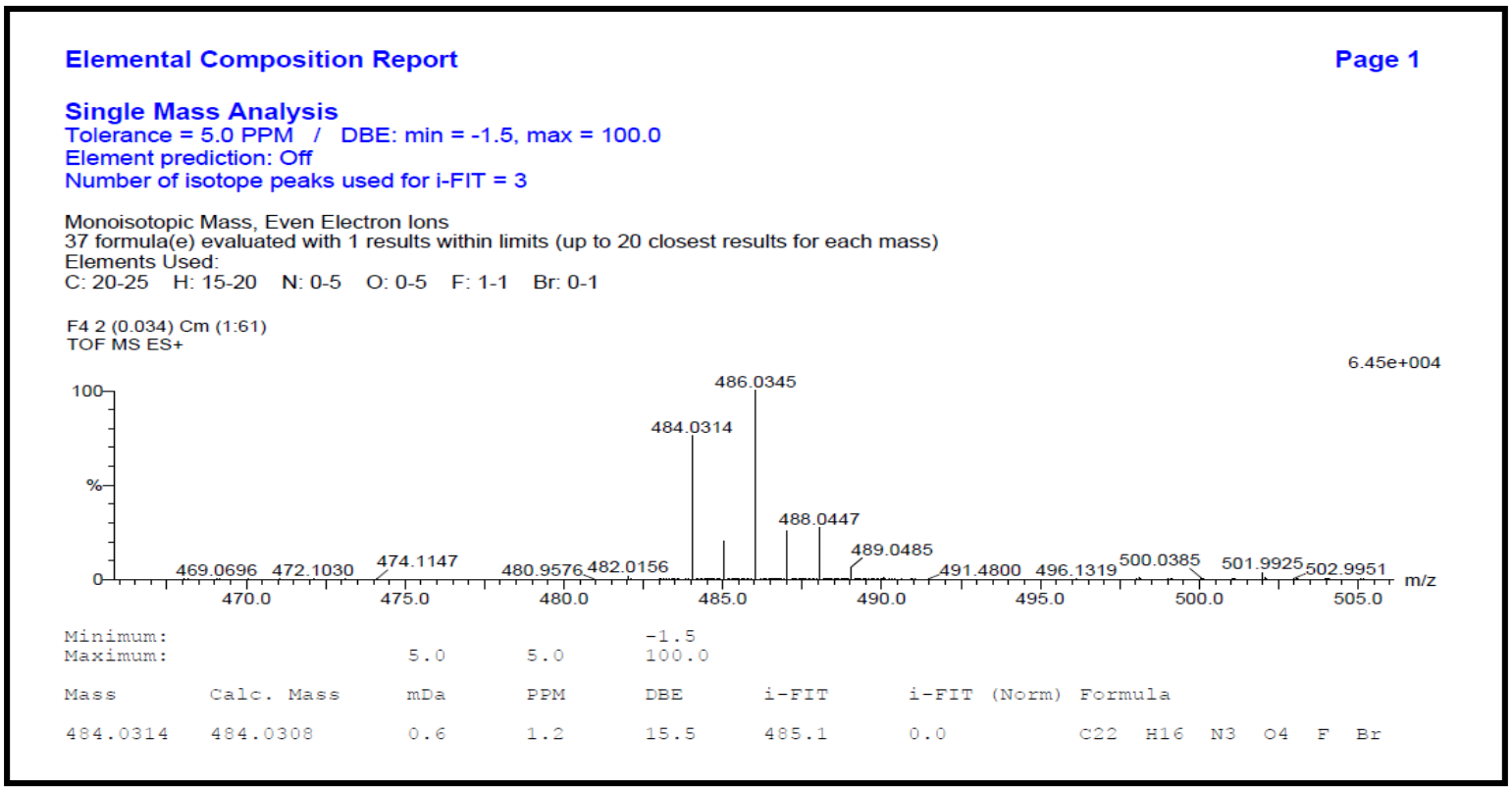

$^{1}$H NMR spectra of **5b**



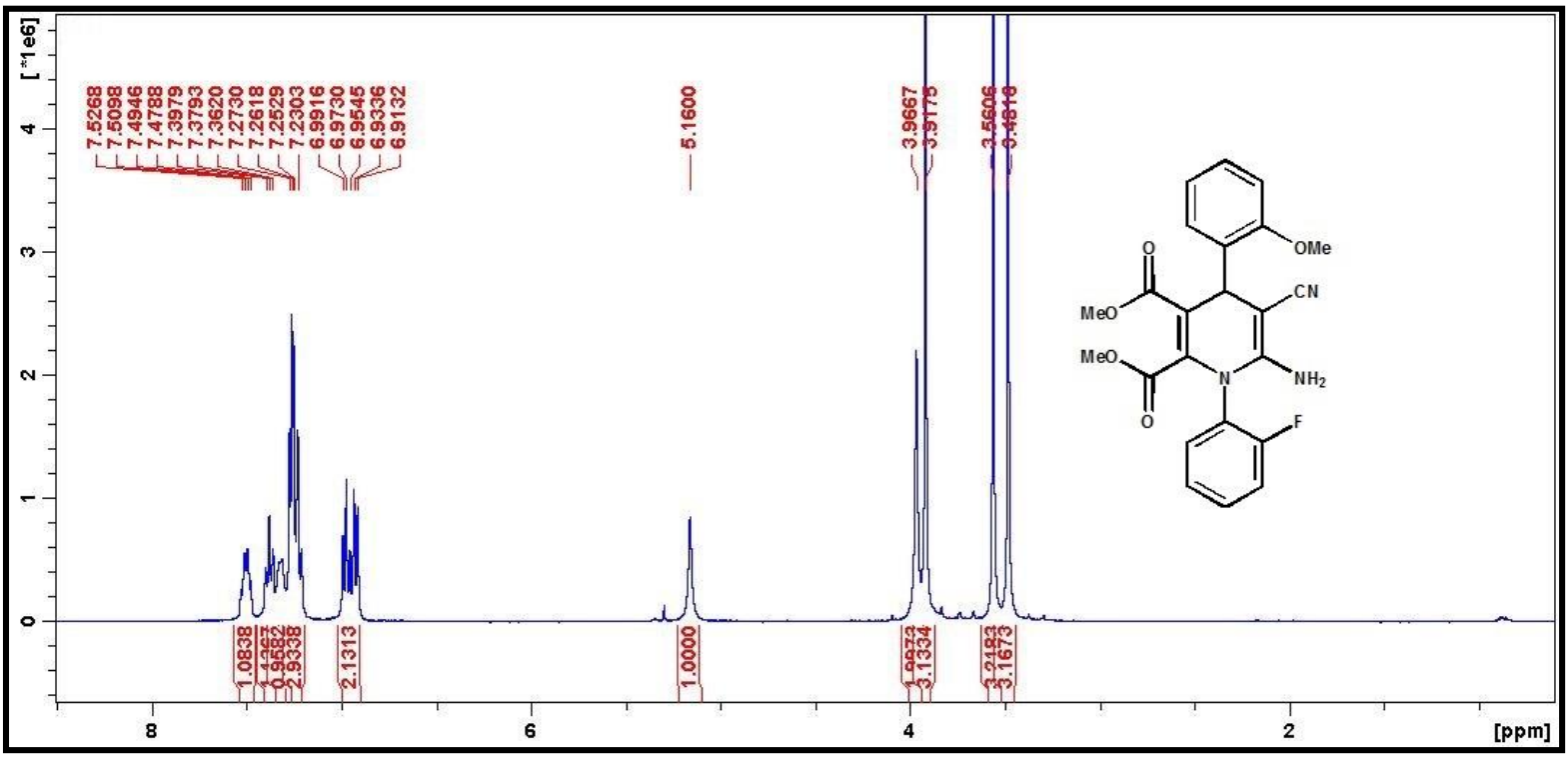

$^{15}$N NMR spectra of **5b**



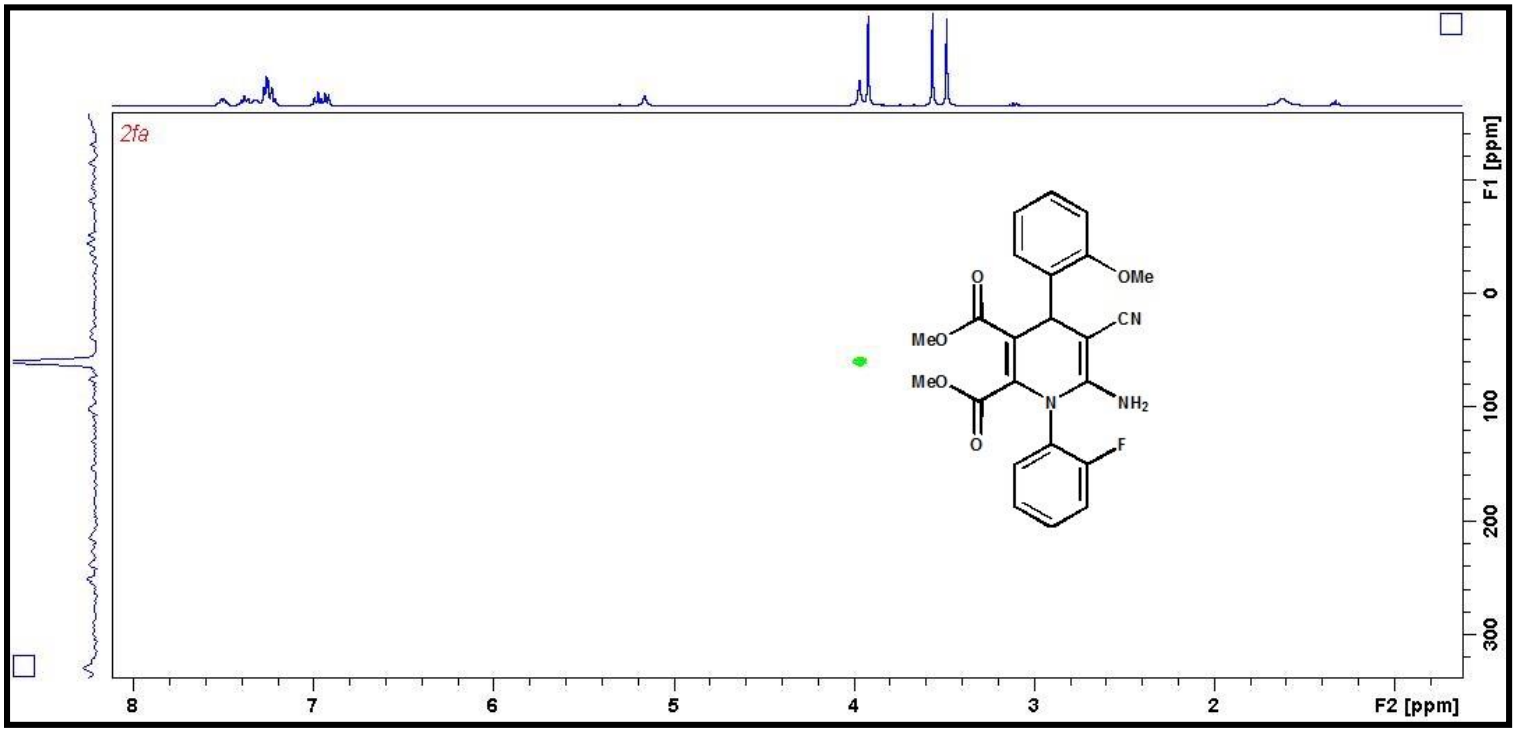

$^{13}$C NMR spectra of **5b**



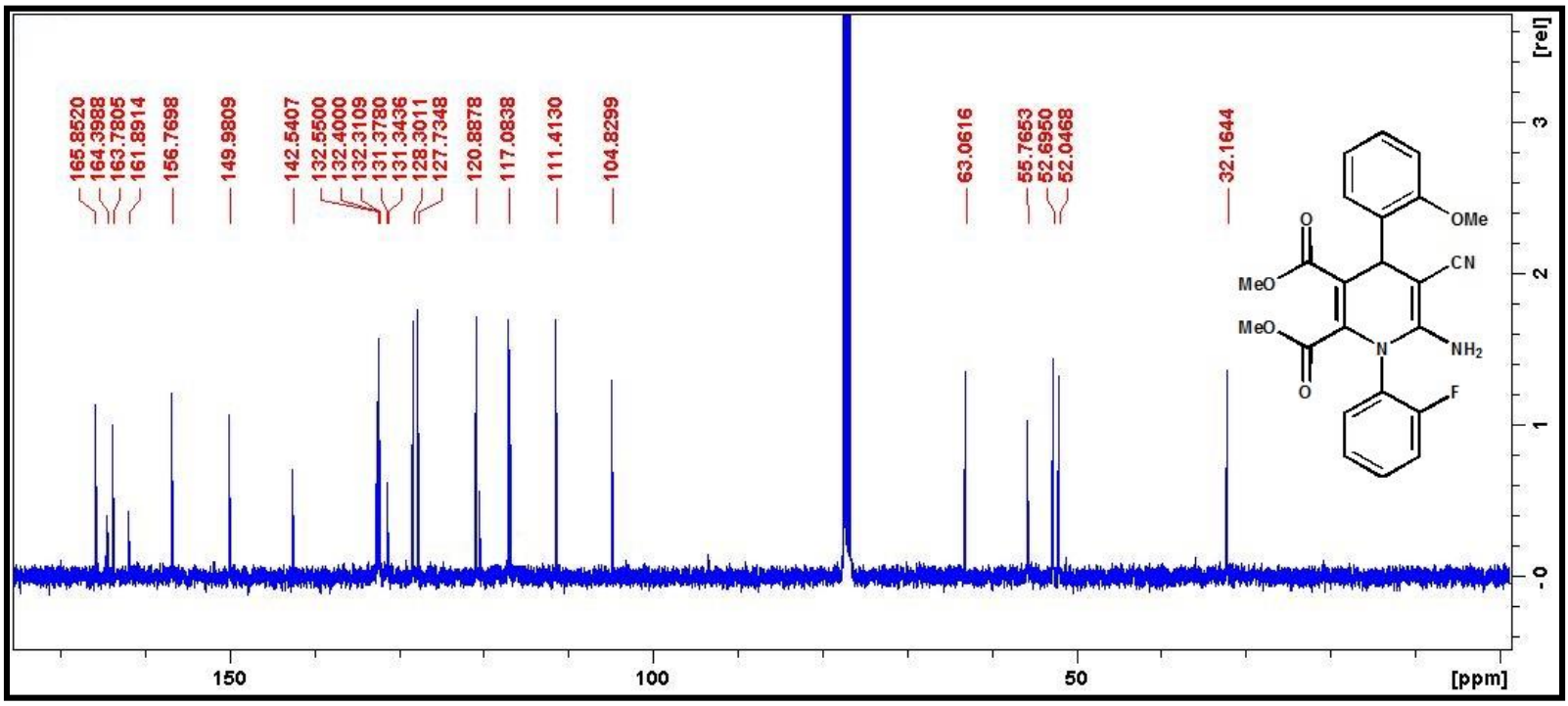

HRMS spectra of **5b**




$^{1}$H NMR spectra of **5c**




$^{15}$N NMR spectra of **5c**

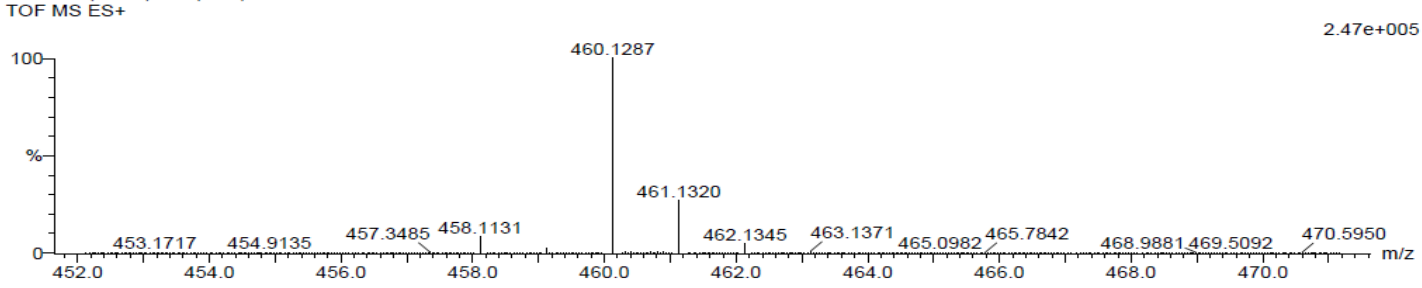



$^{13}$C NMR spectra of **5c**

**Elemental Composition Report** Page 1

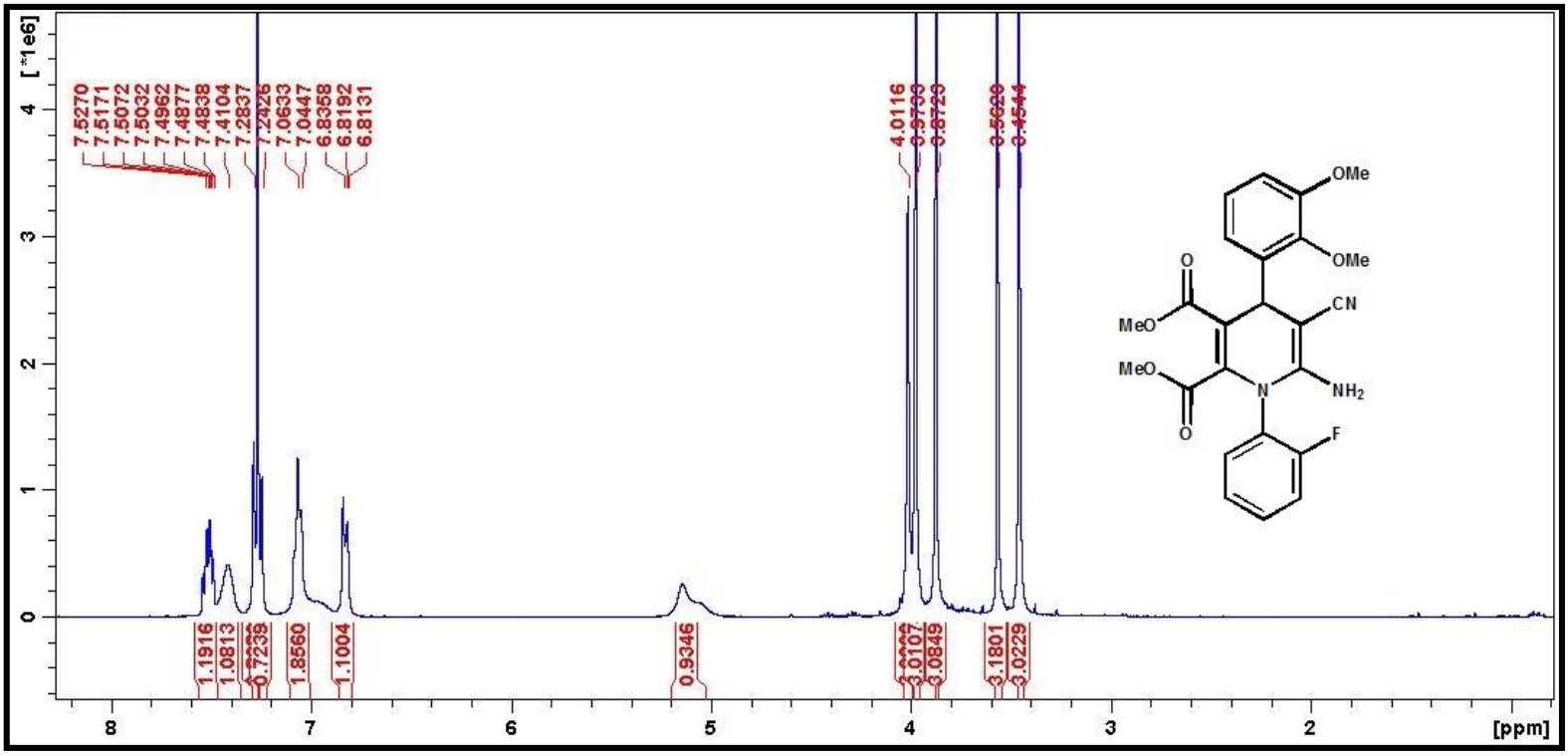
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
38 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 15-25 N: 0-5 O: 0-10 F: 1-1 Na: 1-1
2FA2 14 (0.439) Cm (1:61)
TOF MS ES+

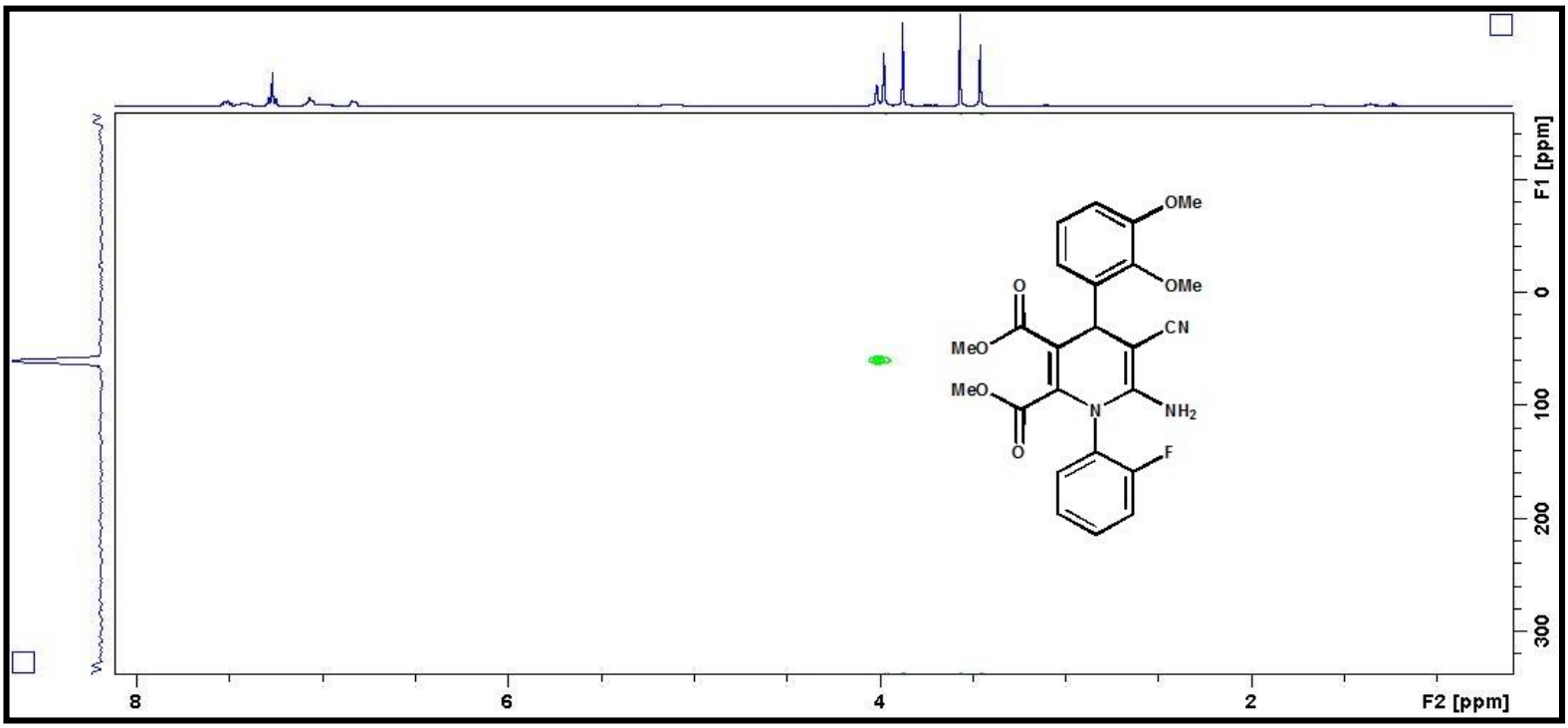



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 460.1287 | 460.1285 | 0.2 | 0.4 | 14.5 | 554.4 | 0.0 | C23 H20 N3 O5 F Na |

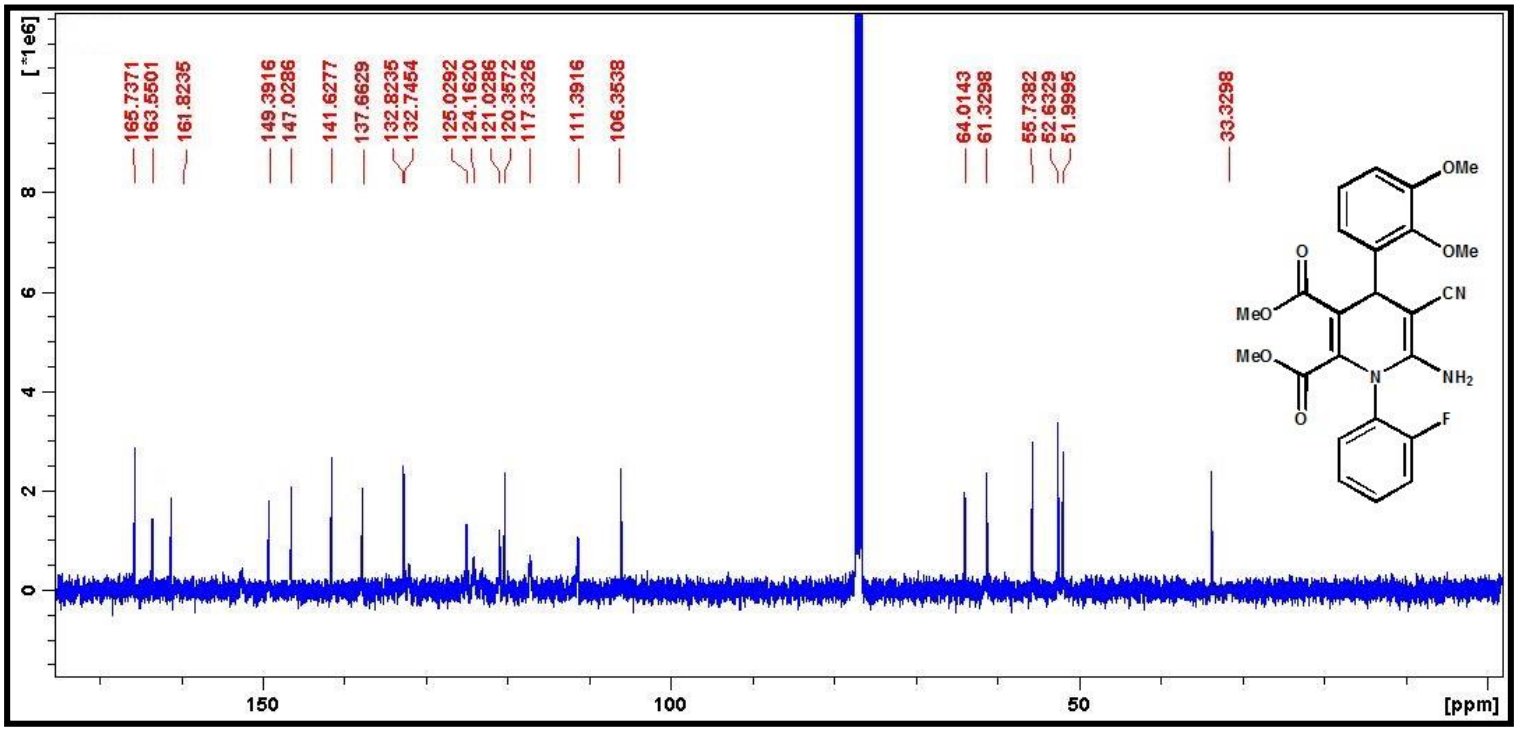
HRMS spectra of **5c**




$^{1}$H NMR spectra of **5d**




$^{15}$N NMR spectra of **5d**

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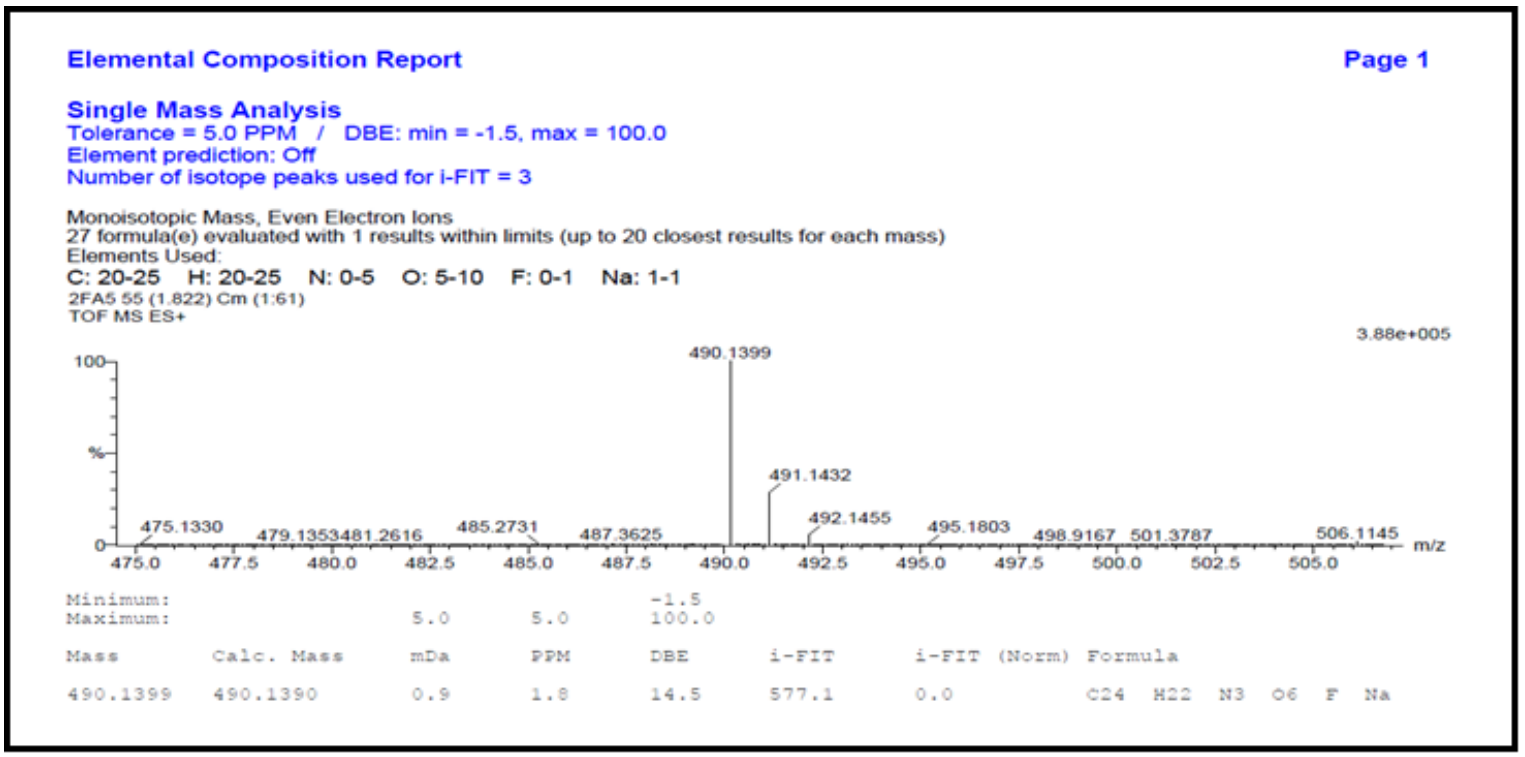
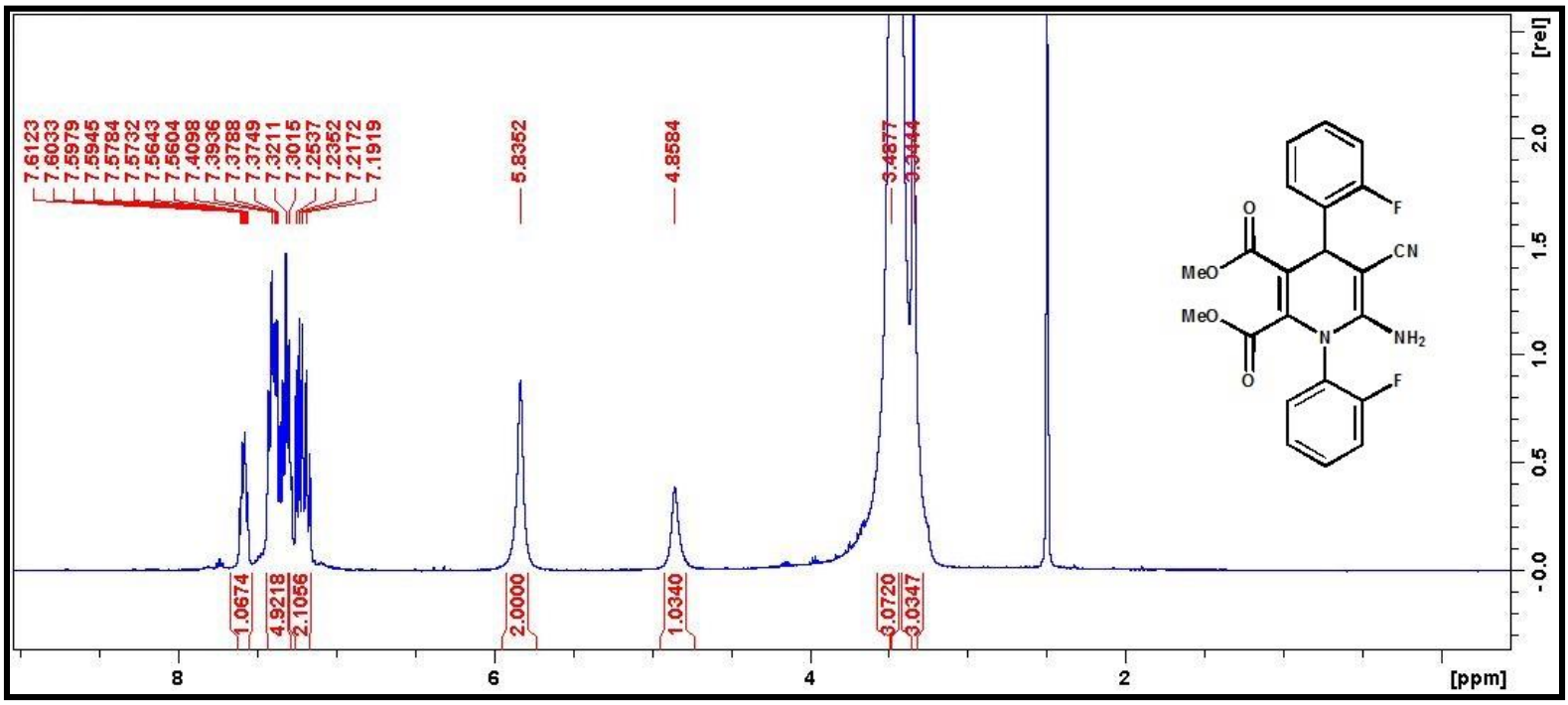
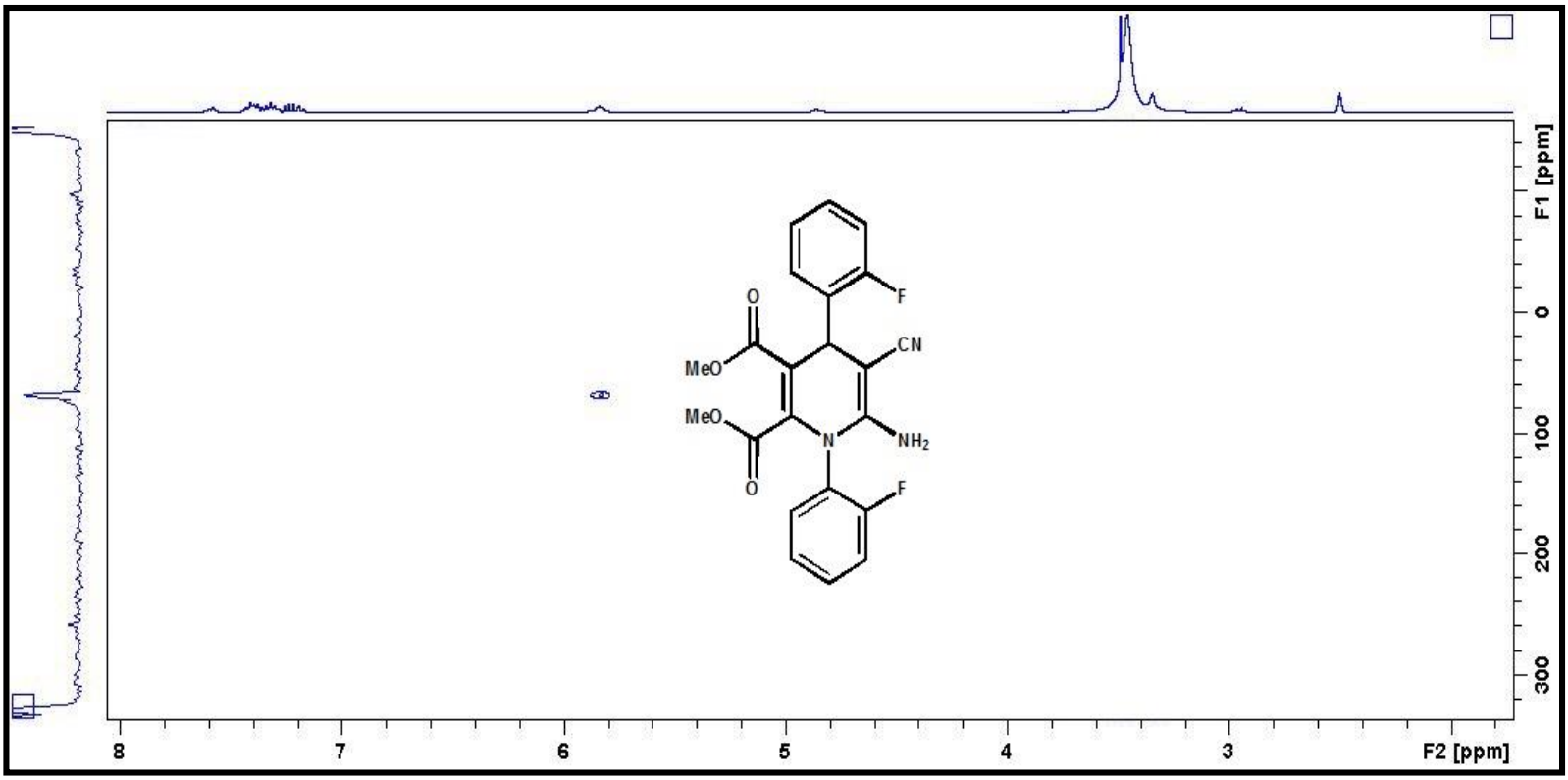


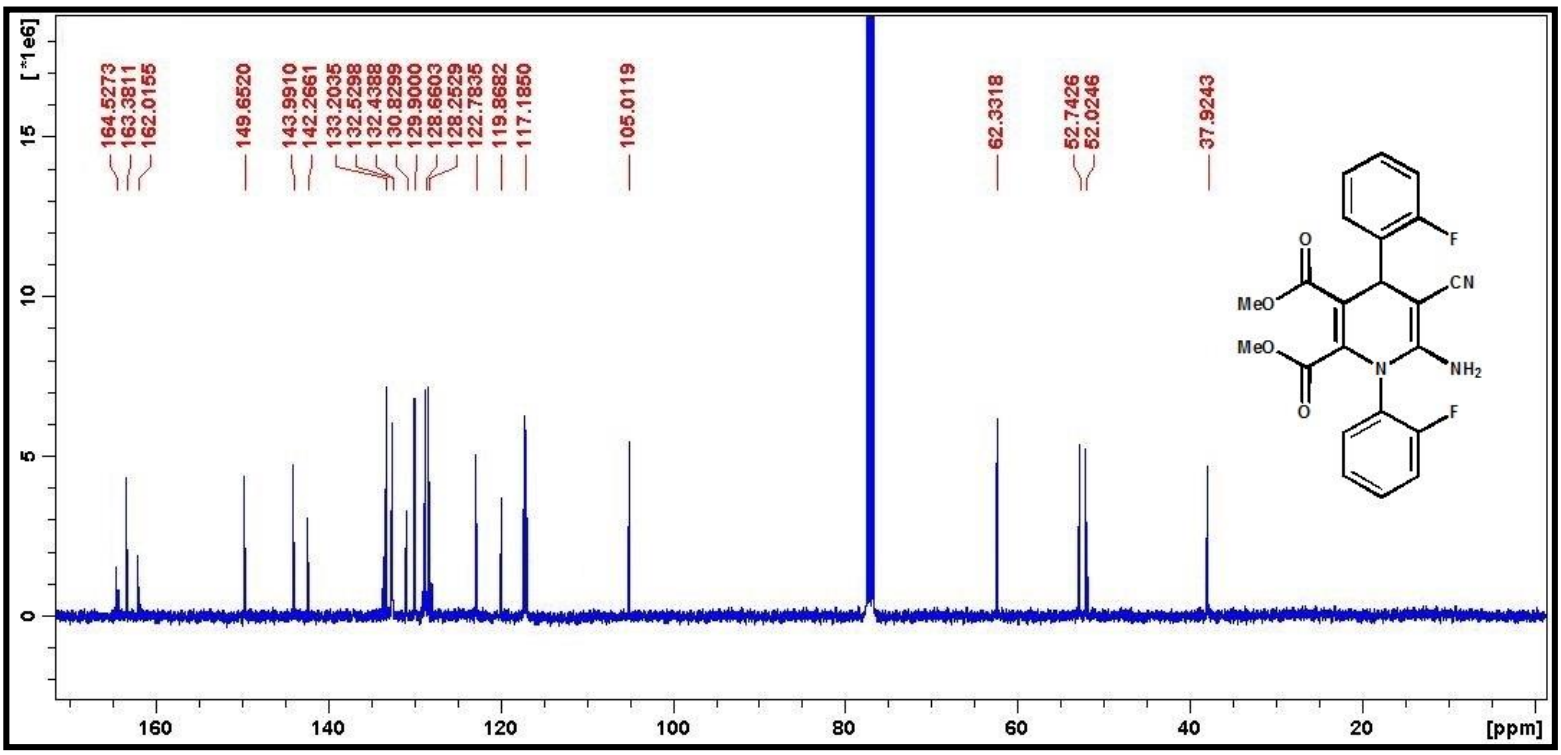

HRMS spectra of **5d**



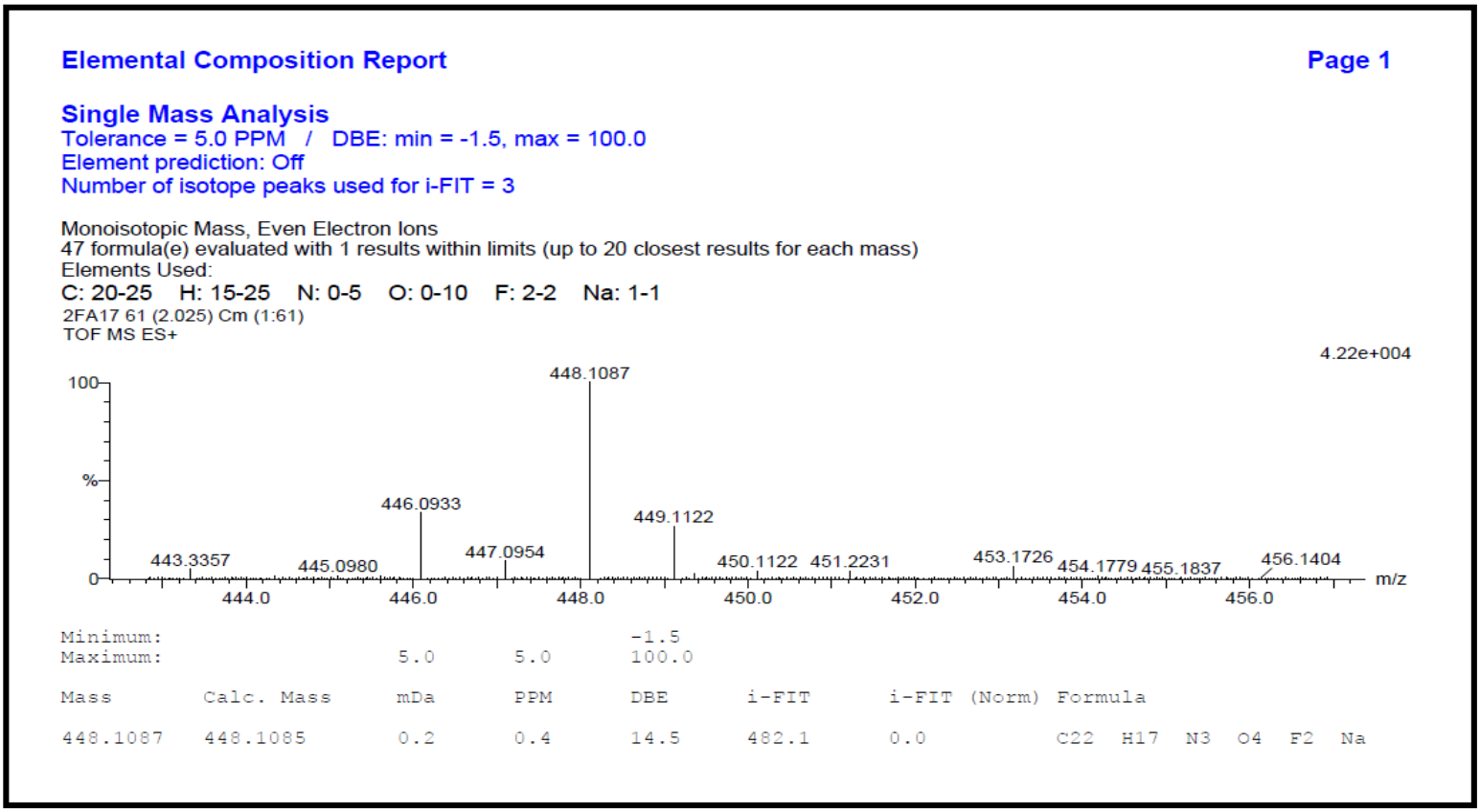

$^{1}$H NMR spectra of **5e**



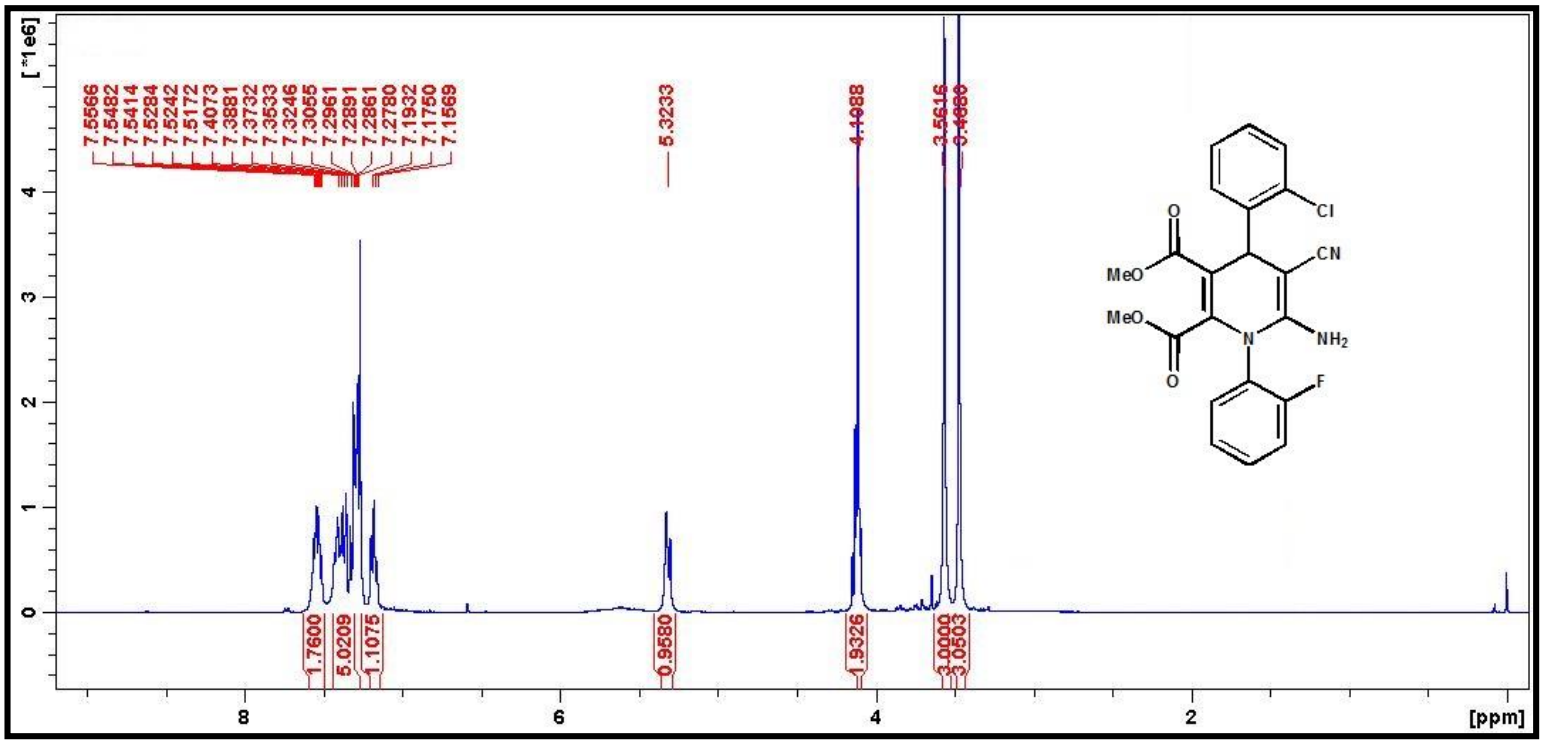

$^{15}$N NMR spectra of **5e**



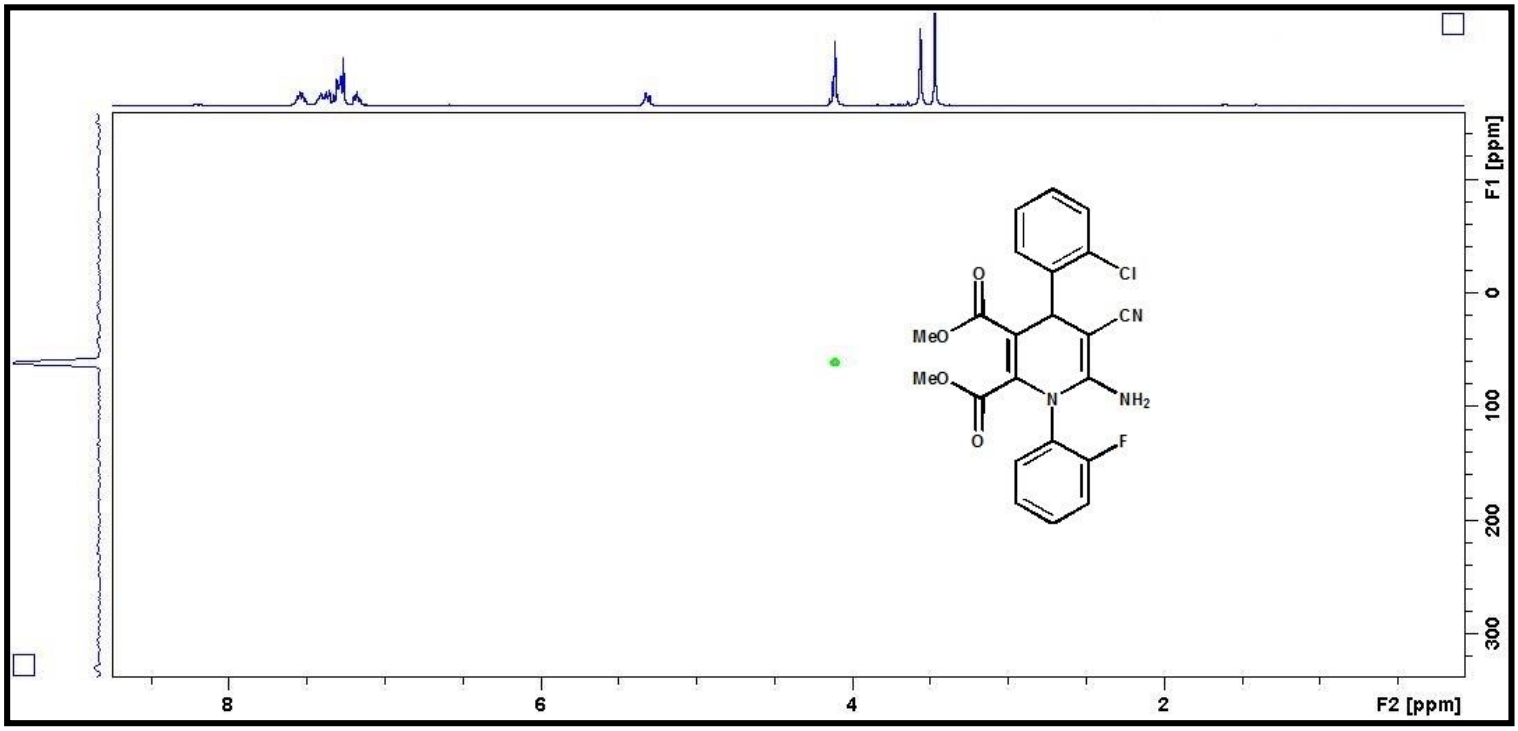

$^{13}$C NMR spectra of **5e**



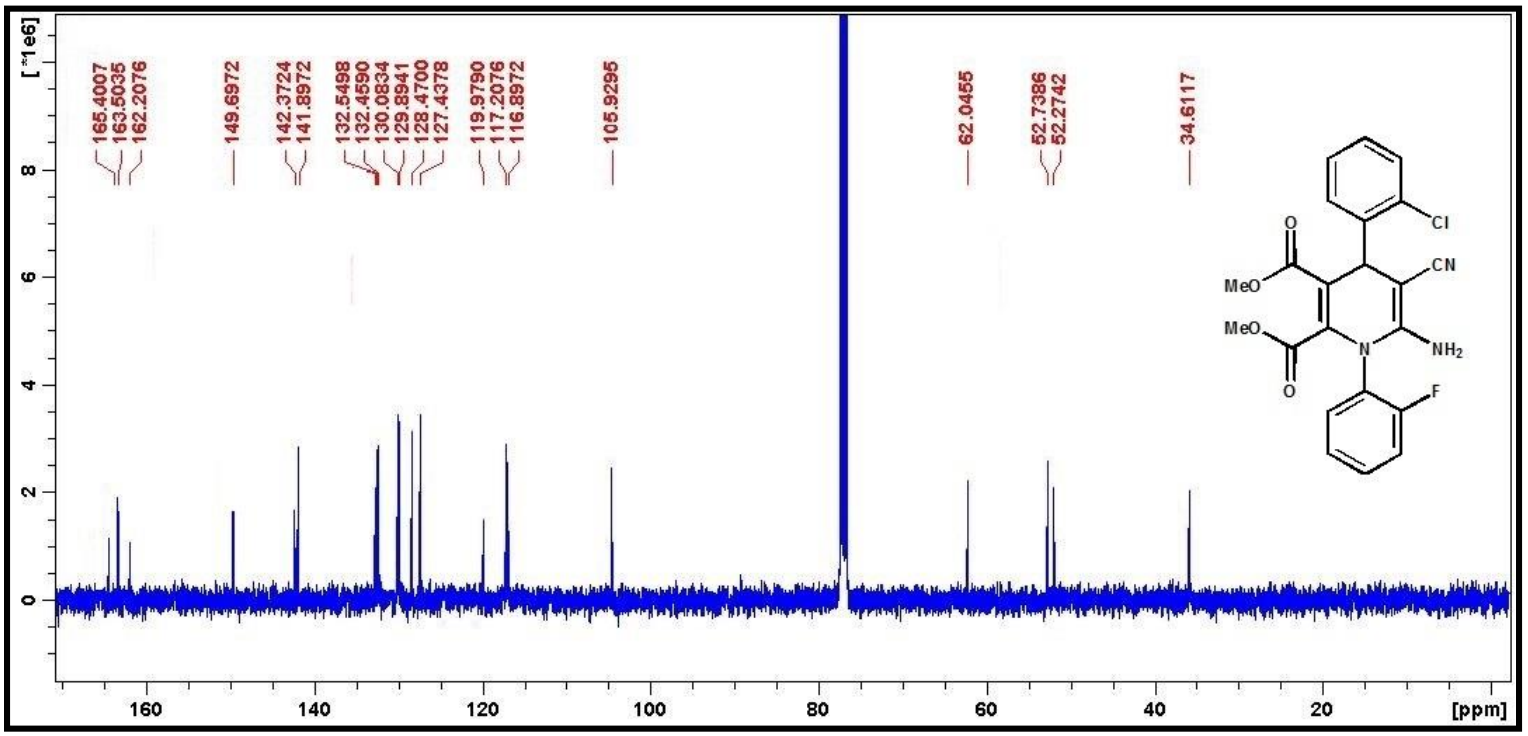

HRMS spectra of **5e**



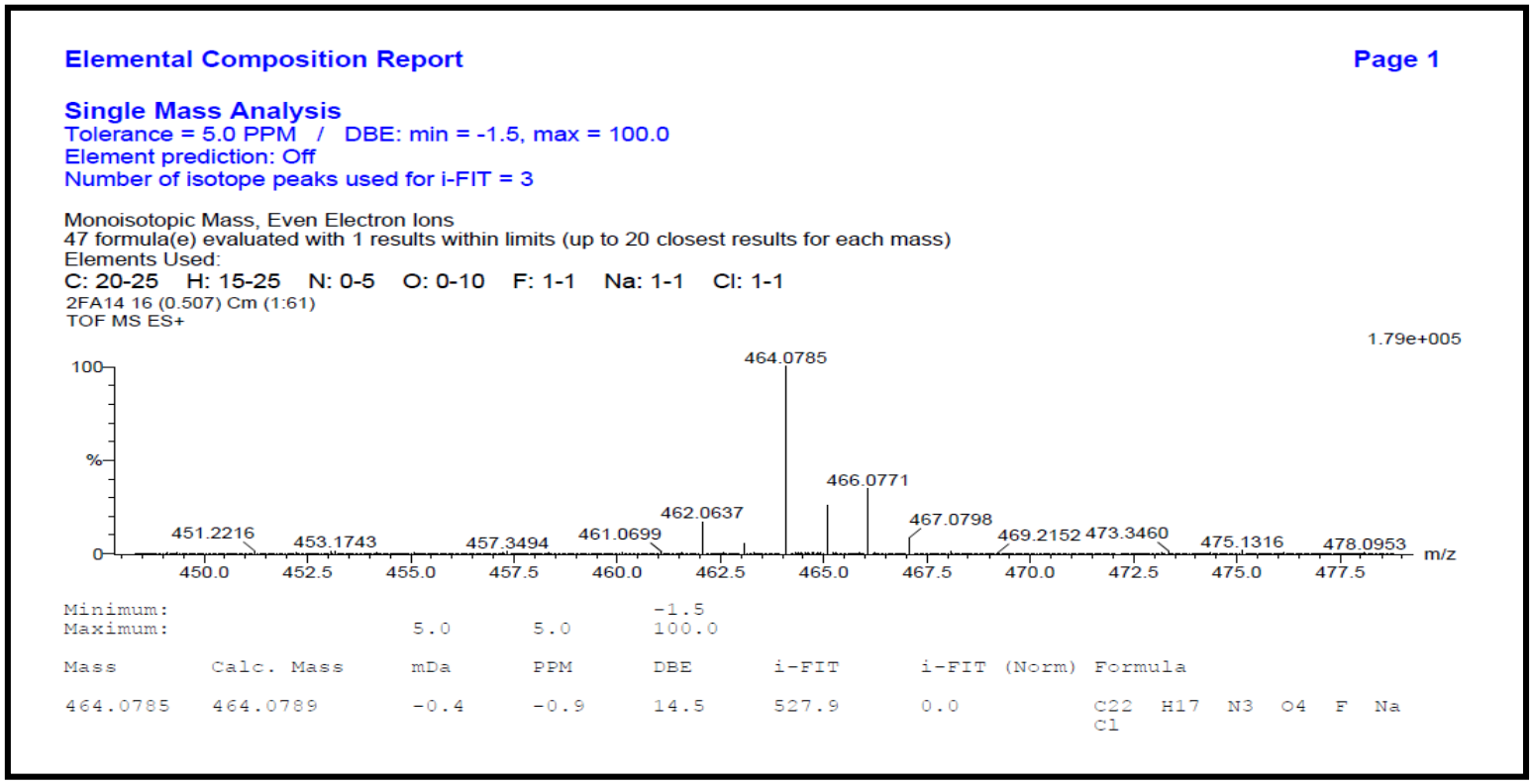

$^{1}$H NMR spectra of **5f**



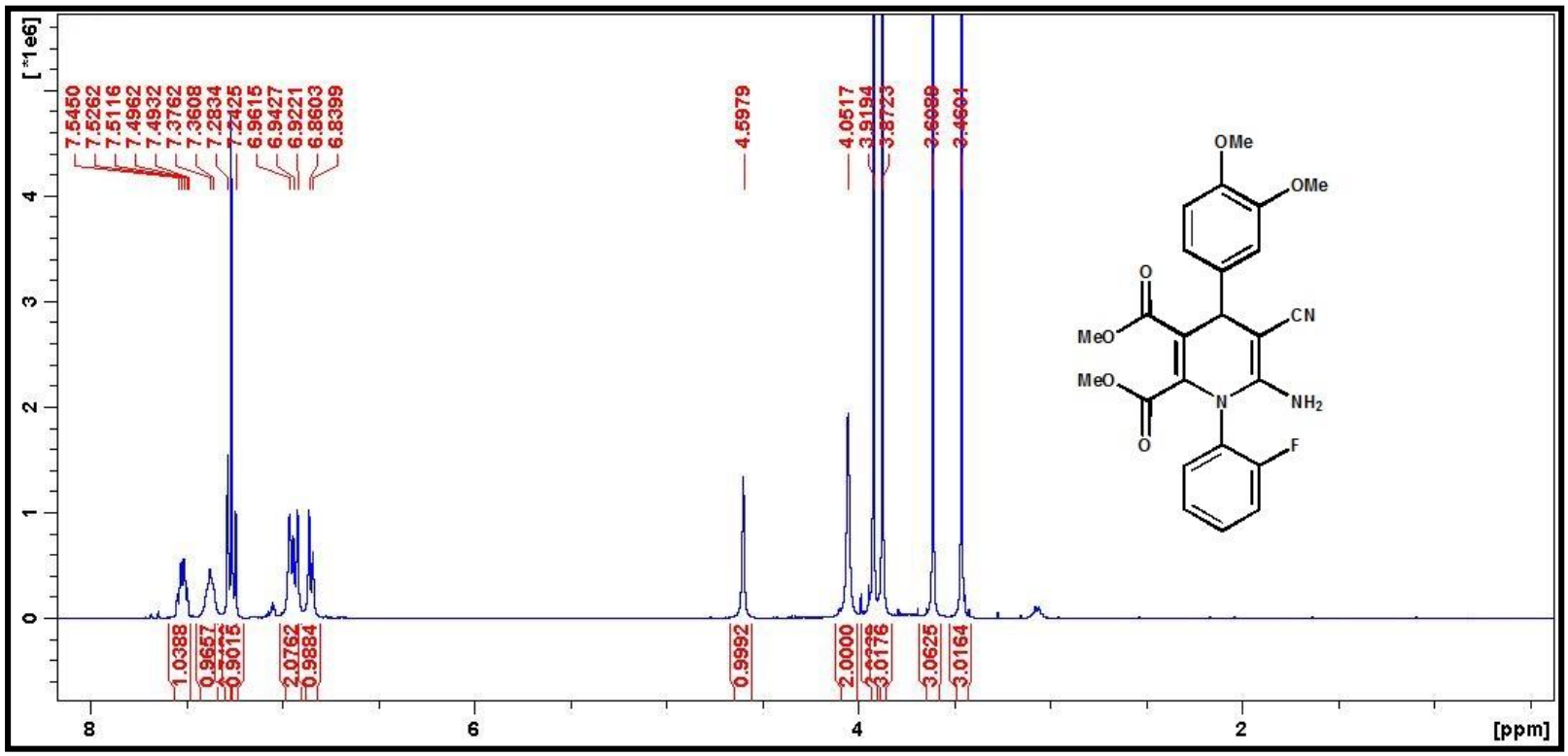

$^{15}$N NMR spectra of **5f**



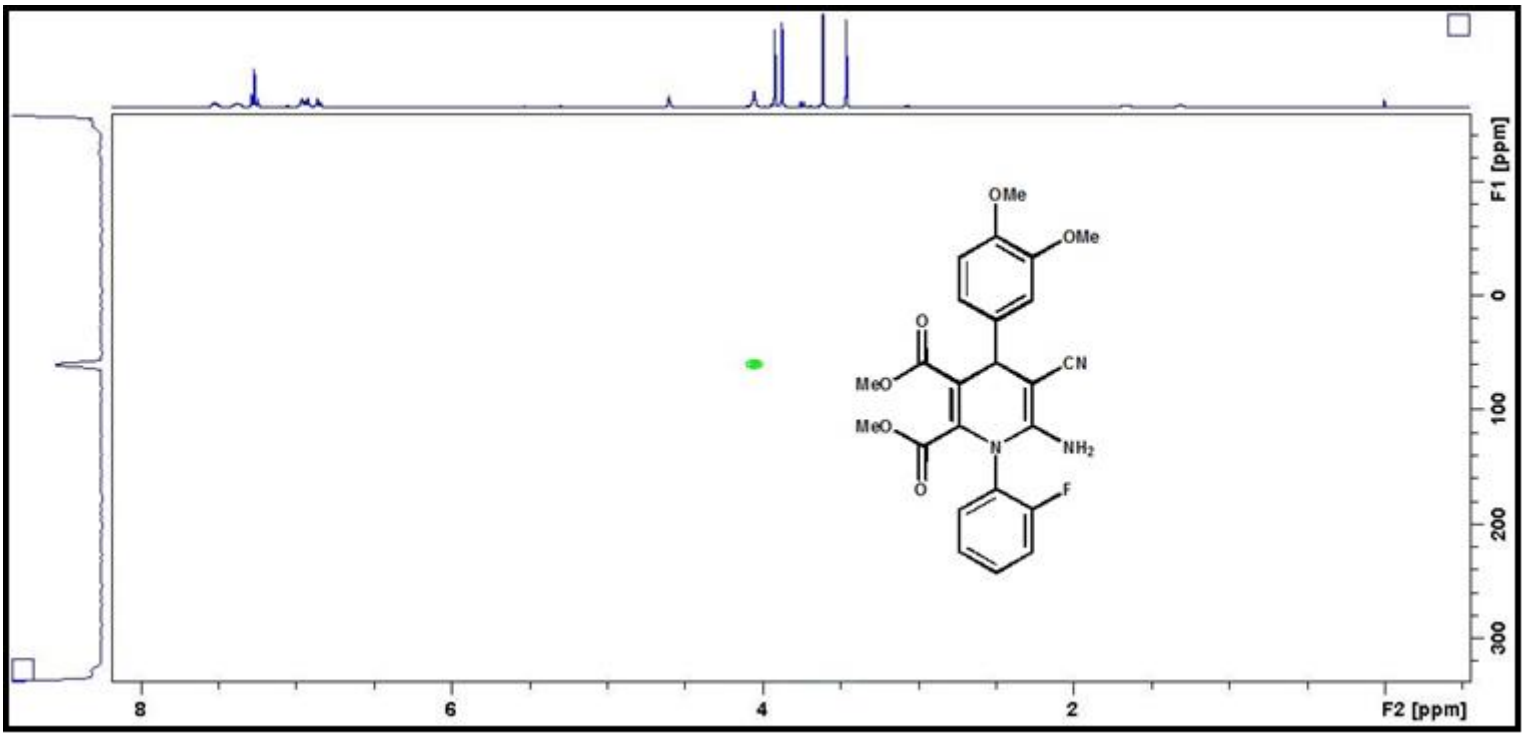

$^{13}$C NMR spectra of **5f**



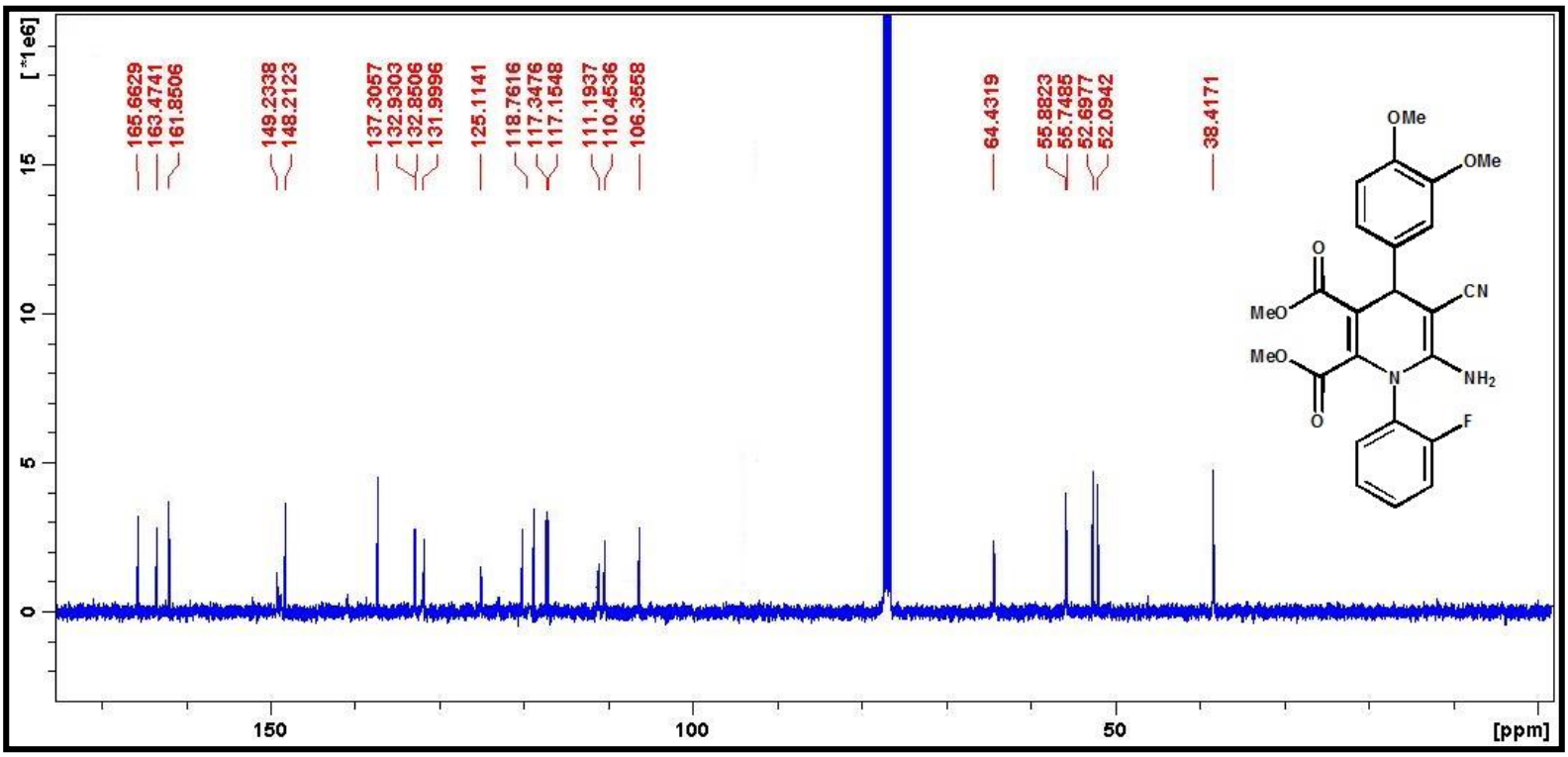

HRMS spectra of **5f**




$^{1}$H NMR spectra of **5g**




$^{15}$N NMR spectra of **5g**

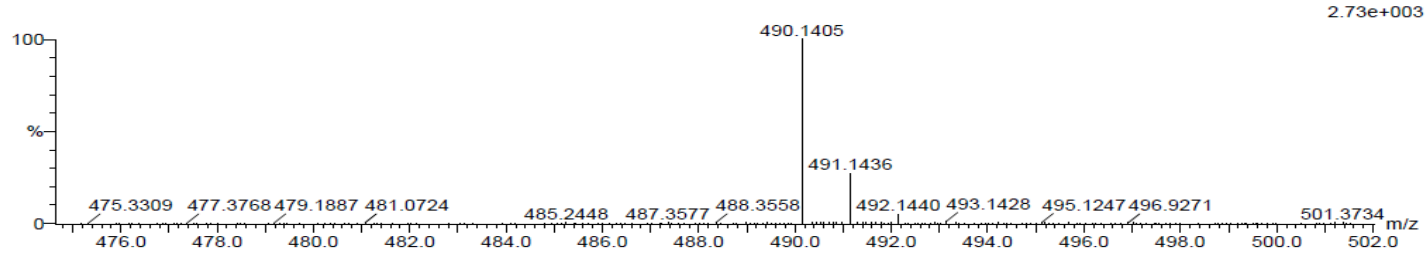



$^{13}$C NMR spectra of **5g**

**Elemental Composition Report** **Page 1**

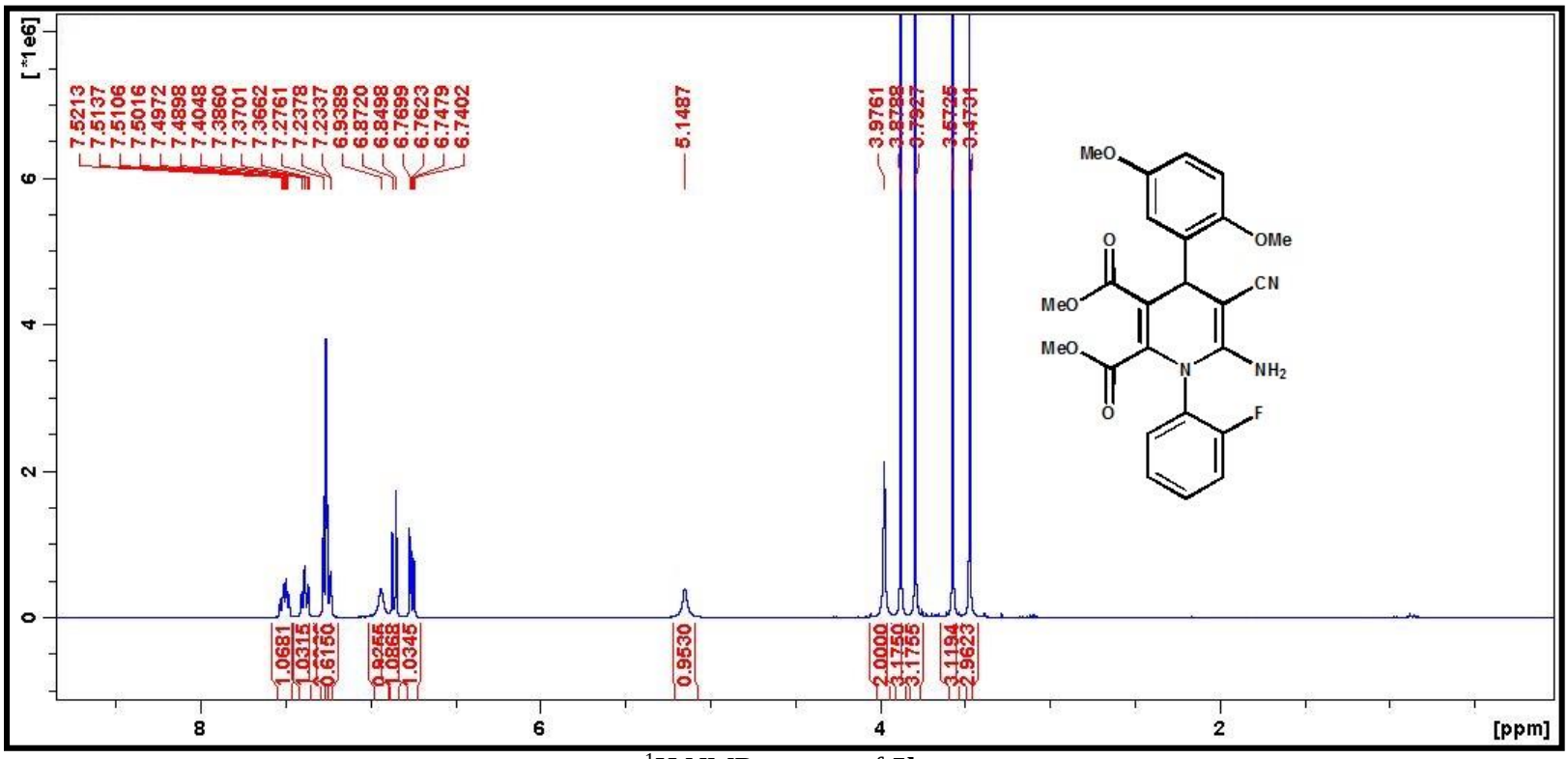
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
27 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 20-25 N: 0-5 O: 5-10 F: 0-1 Na: 1-1
2FA3 6 (0.169)
TOF MS ES+

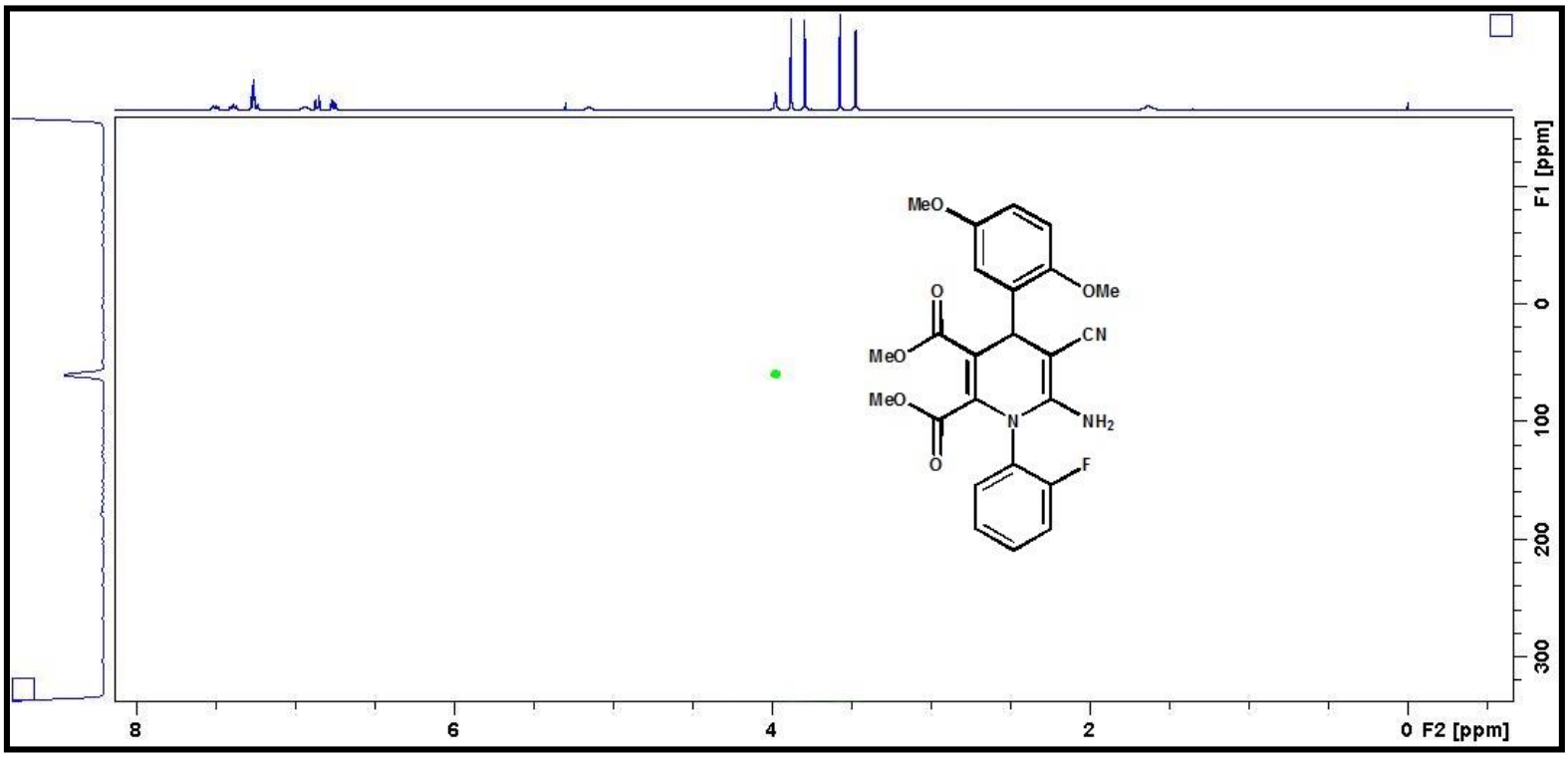



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 490.1405 | 490.1390 | 1.5 | 3.1 | 14.5 | 97.7 | 0.0 | C24 H22 N3 O6 F Na |

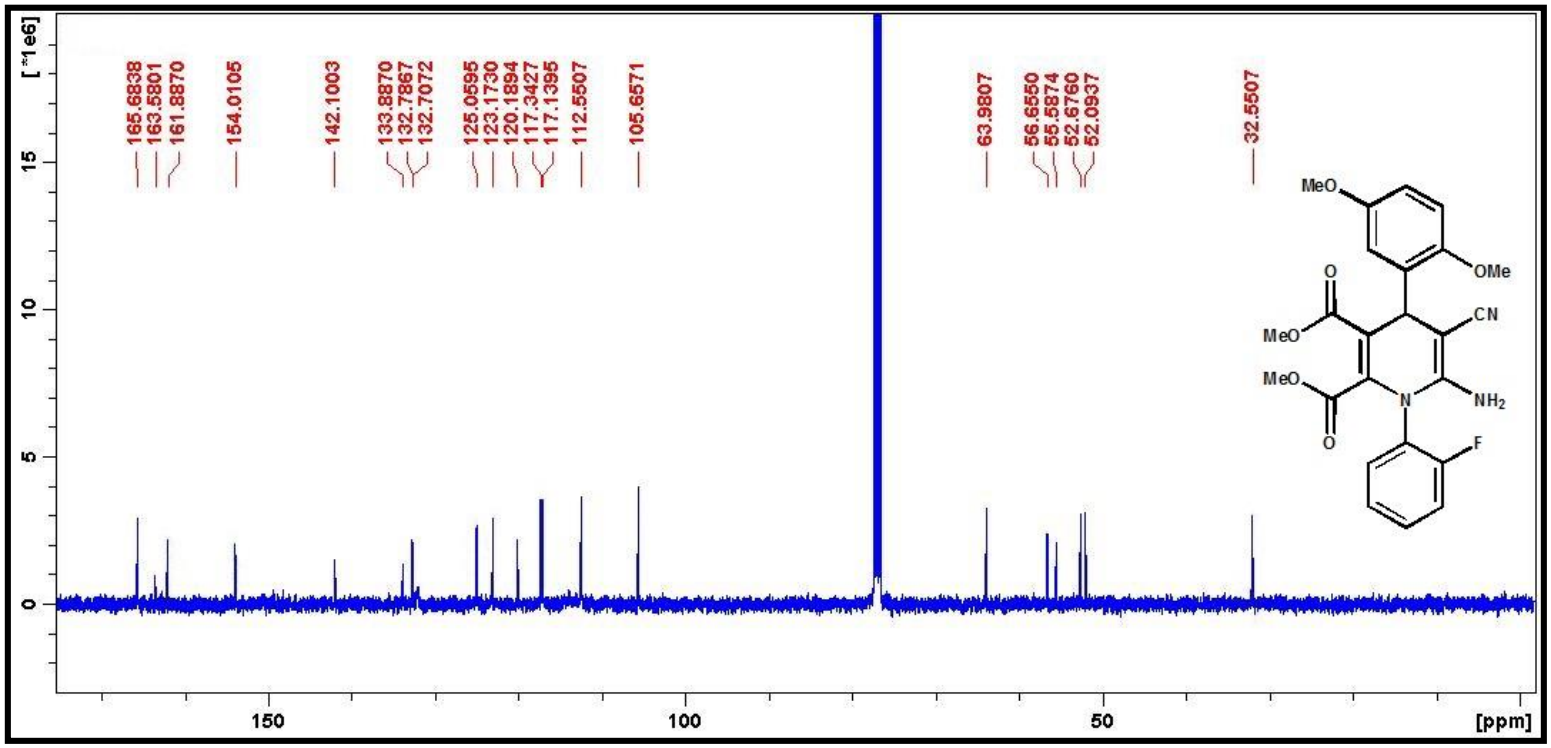
HRMS spectra of **5g**




$^{1}$H NMR spectra of **5h**




$^{15}$N NMR spectra of **5h**

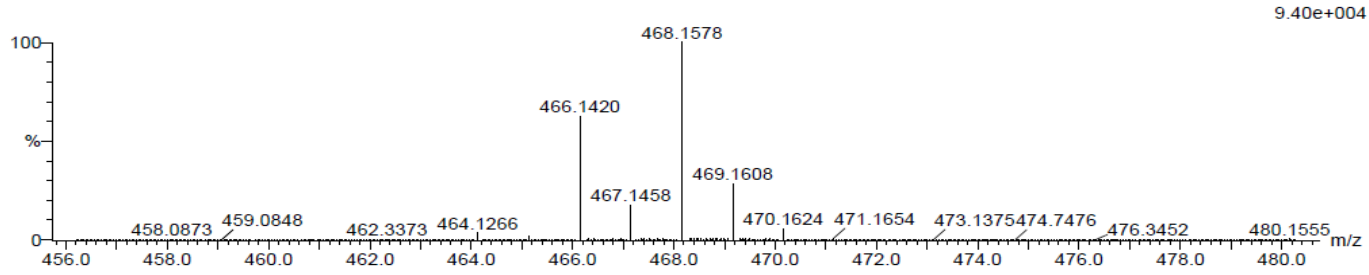



$^{13}$C NMR spectra of **5h**

**Elemental Composition Report** **Page 1**

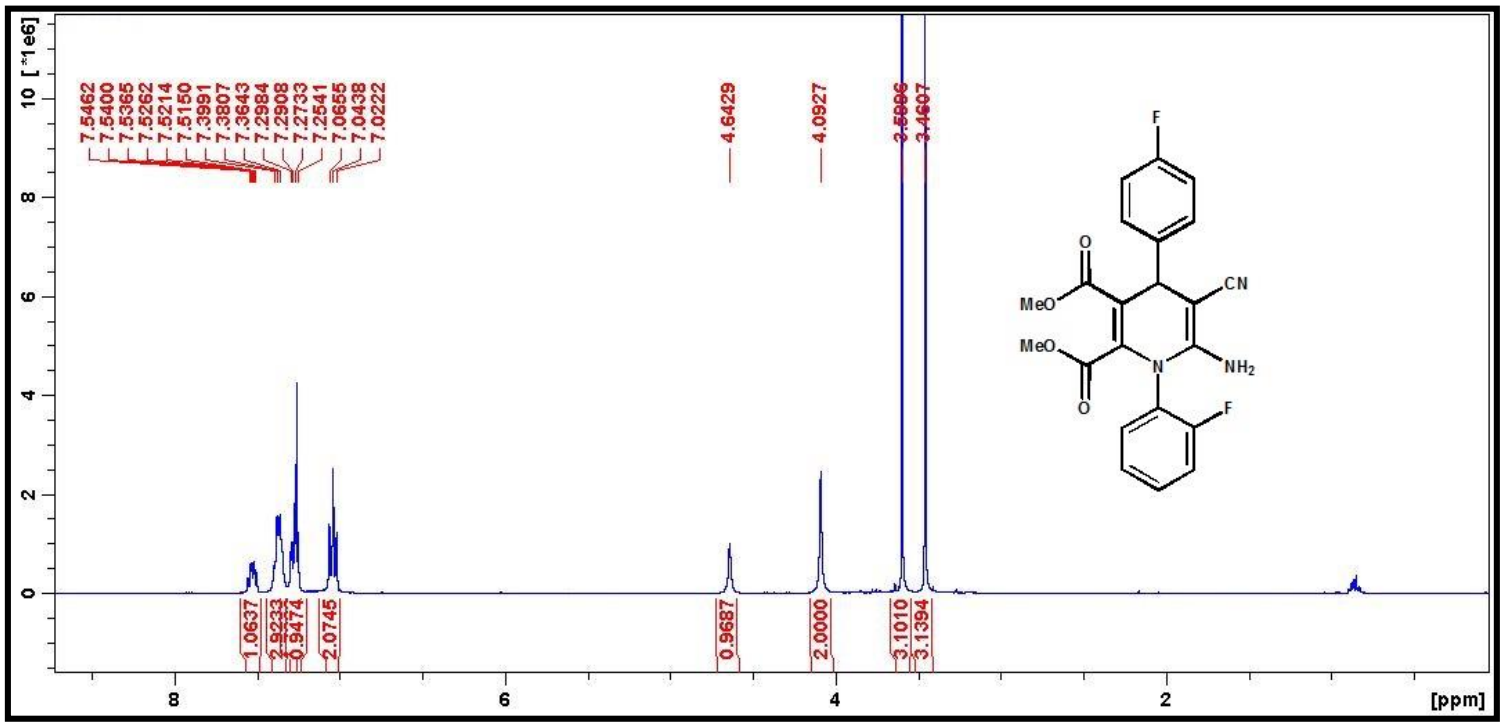
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
45 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 15-25 N: 0-5 O: 0-10 F: 1-1
F5 23 (0.742) Cm (1:61)
TOF MS ES+

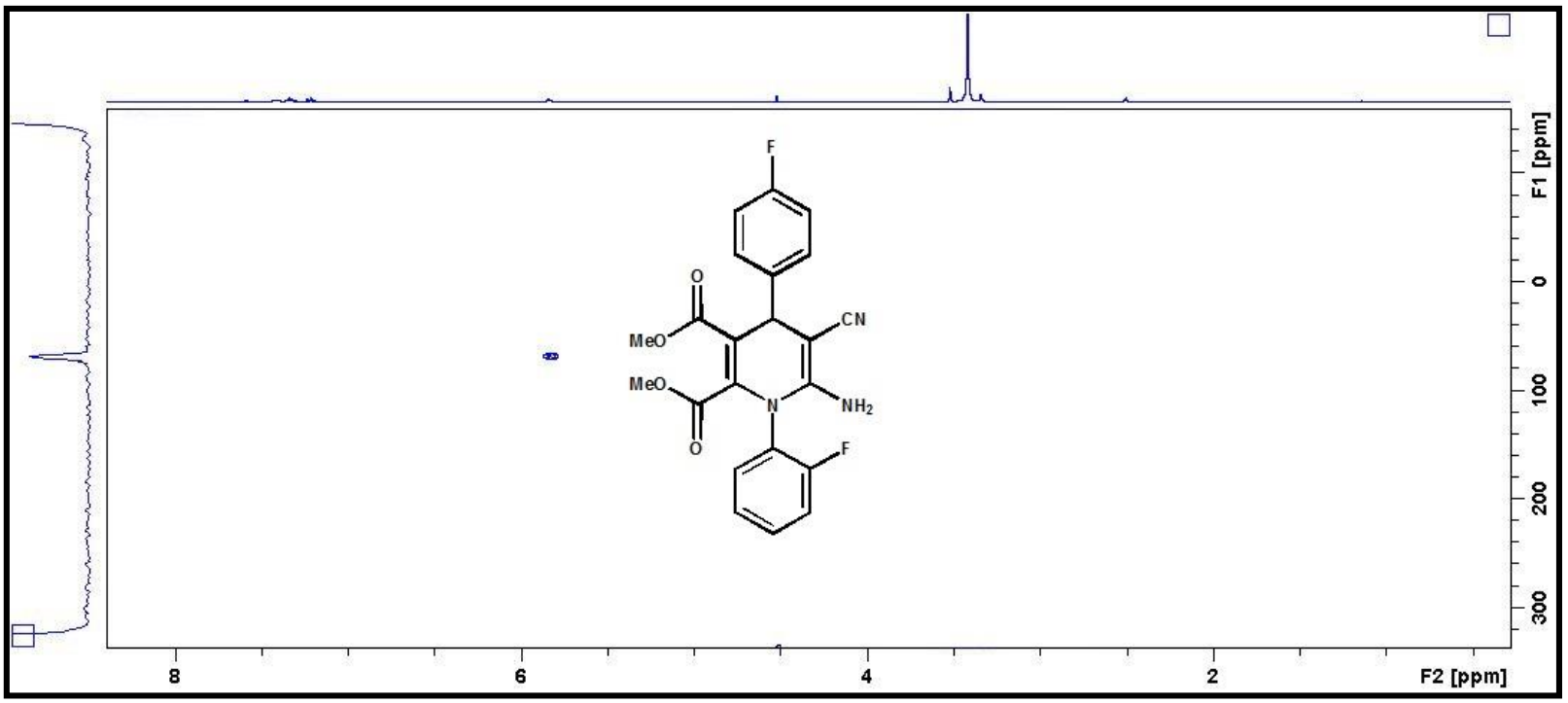



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 468.1578 | 468.1571 | 0.7 | 1.5 | 14.5 | 499.7 | 0.0 | C24 H23 N3 O6 F |

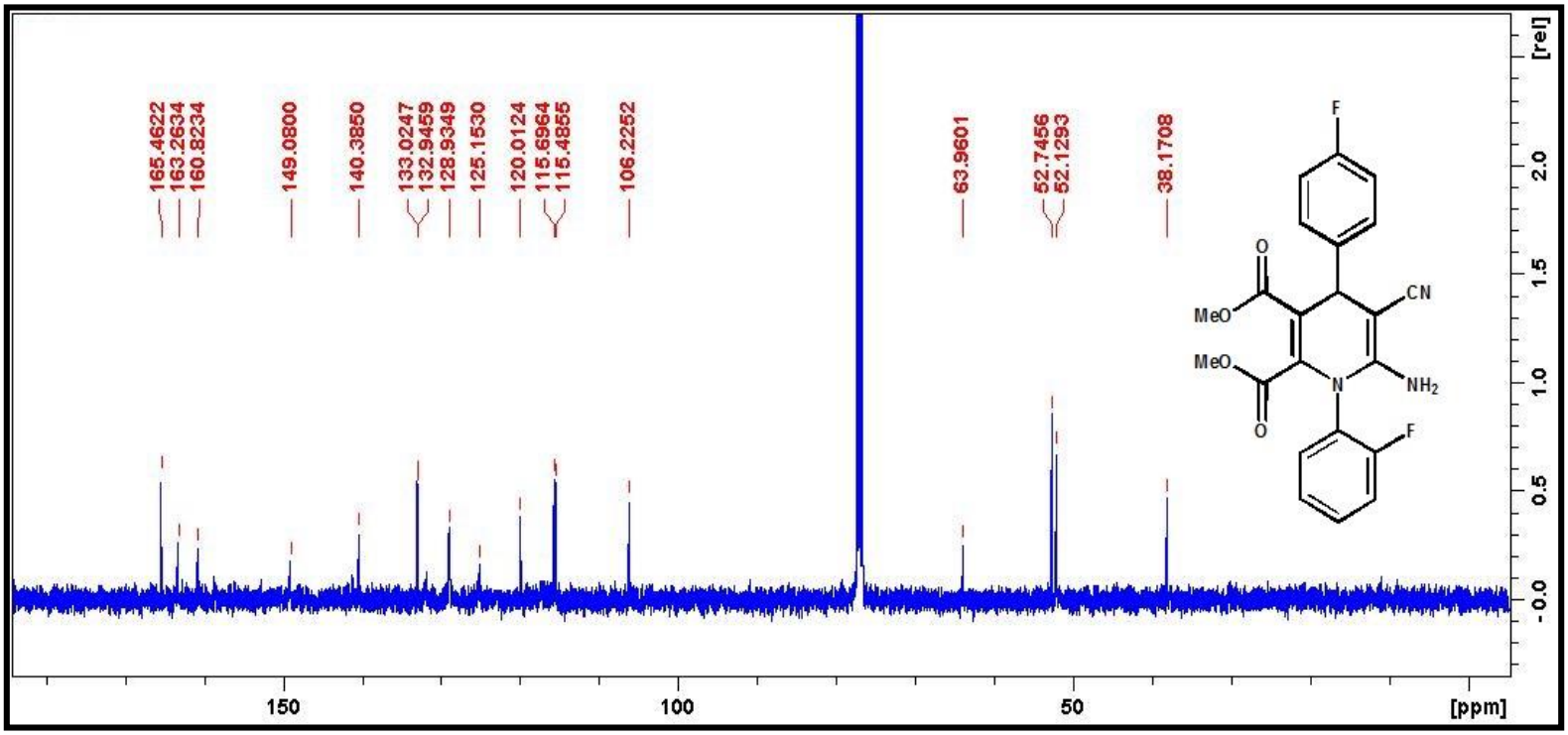
HRMS spectra of **5h**



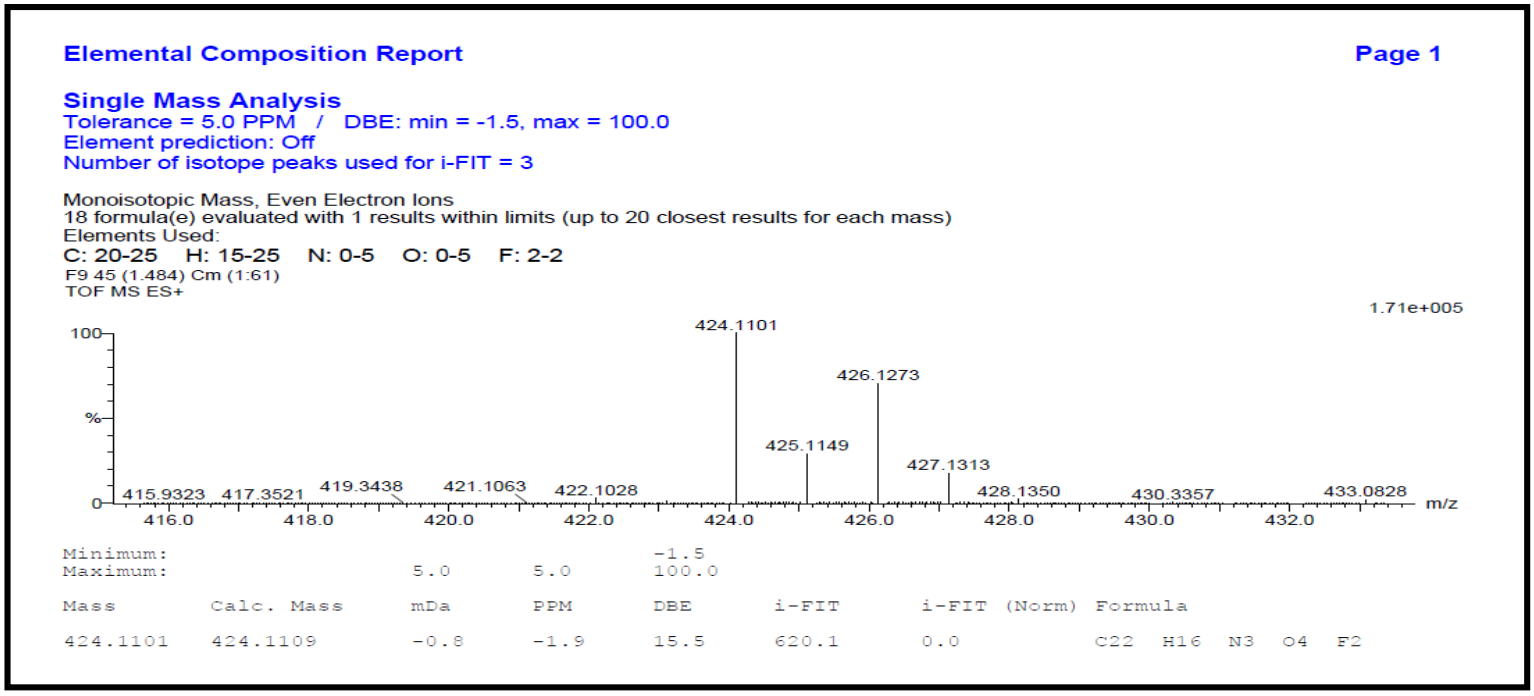

$^{1}$H NMR spectra of **5i**



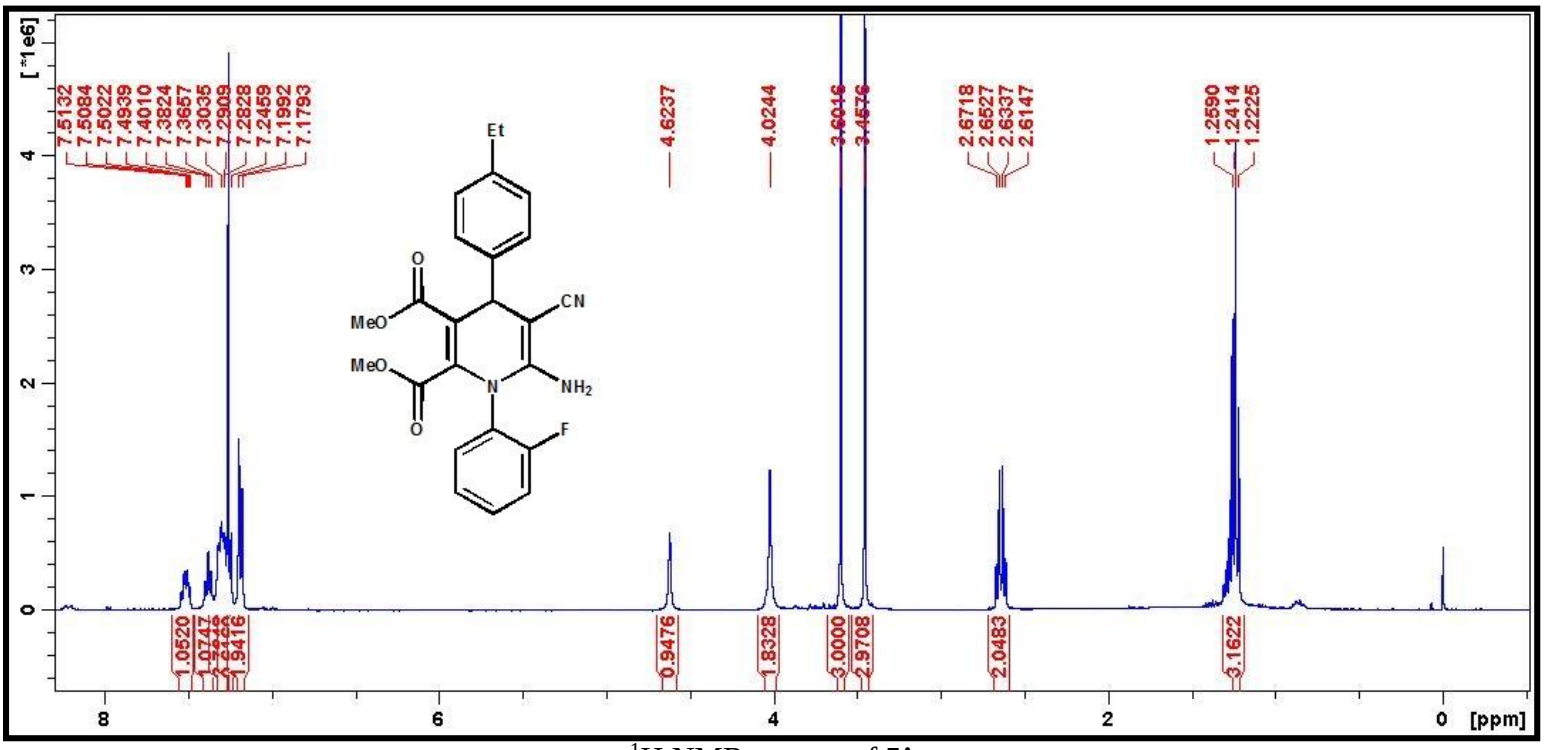

$^{15}$N NMR spectra of **5i**



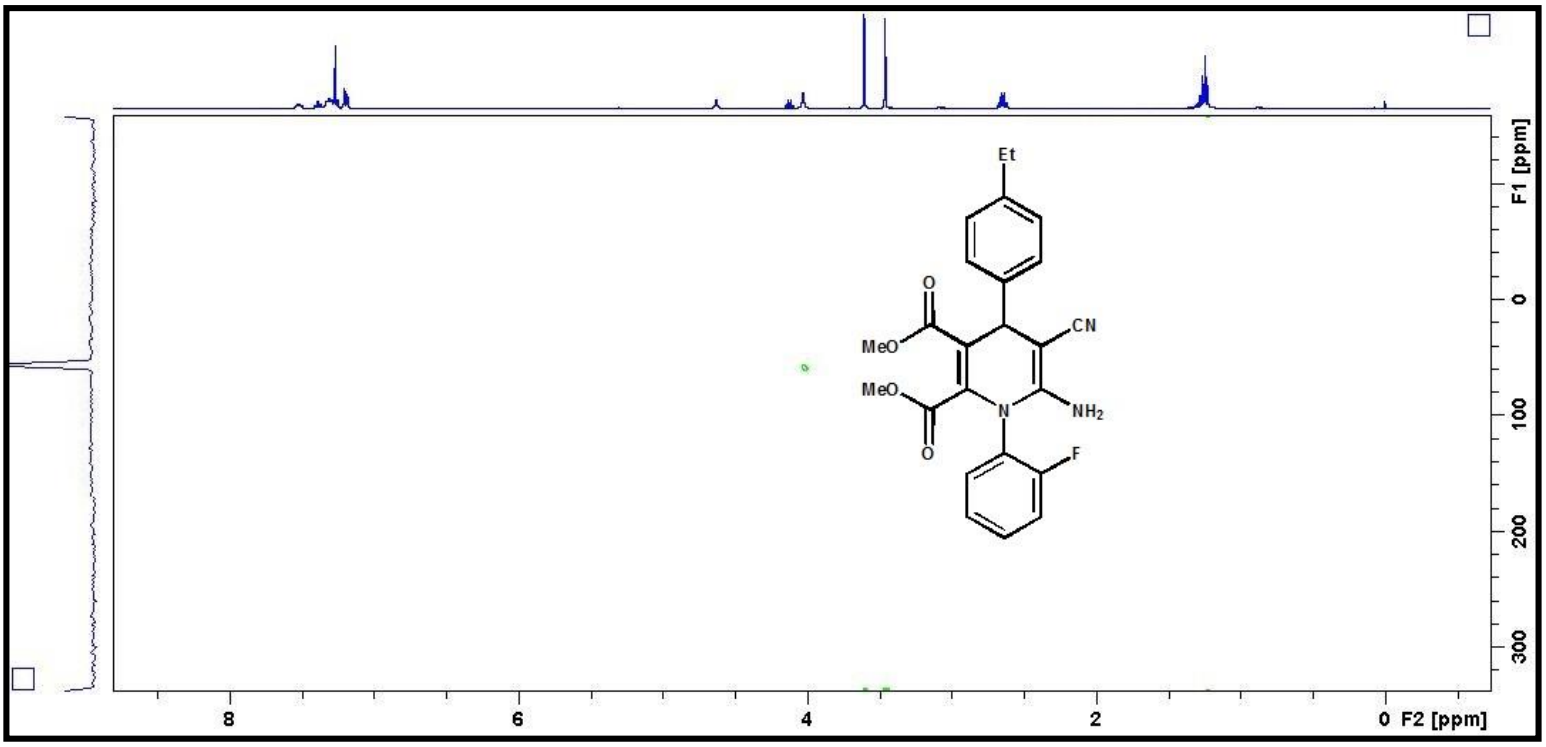

$^{13}$C NMR spectra of **5i**



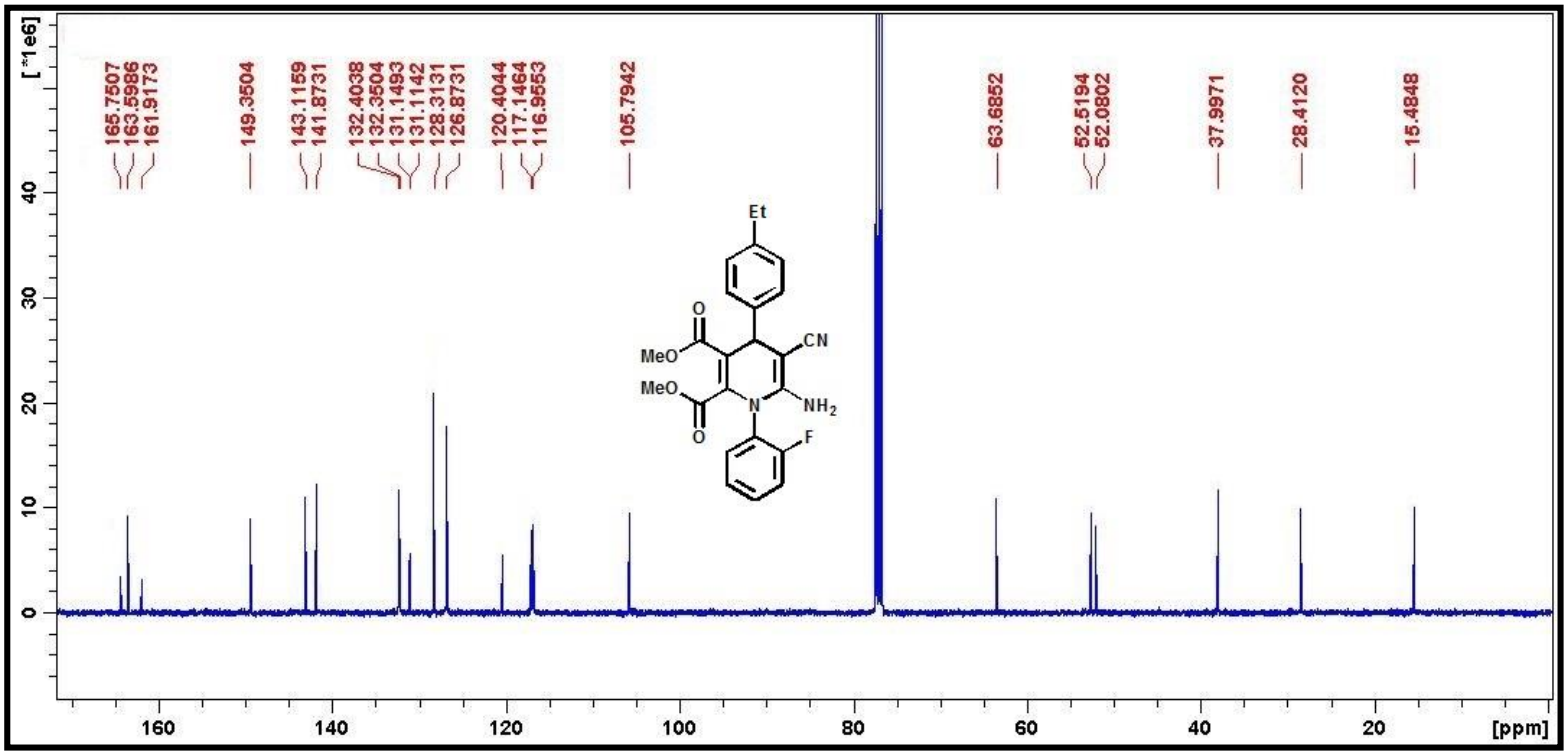

HRMS spectra of **5i**



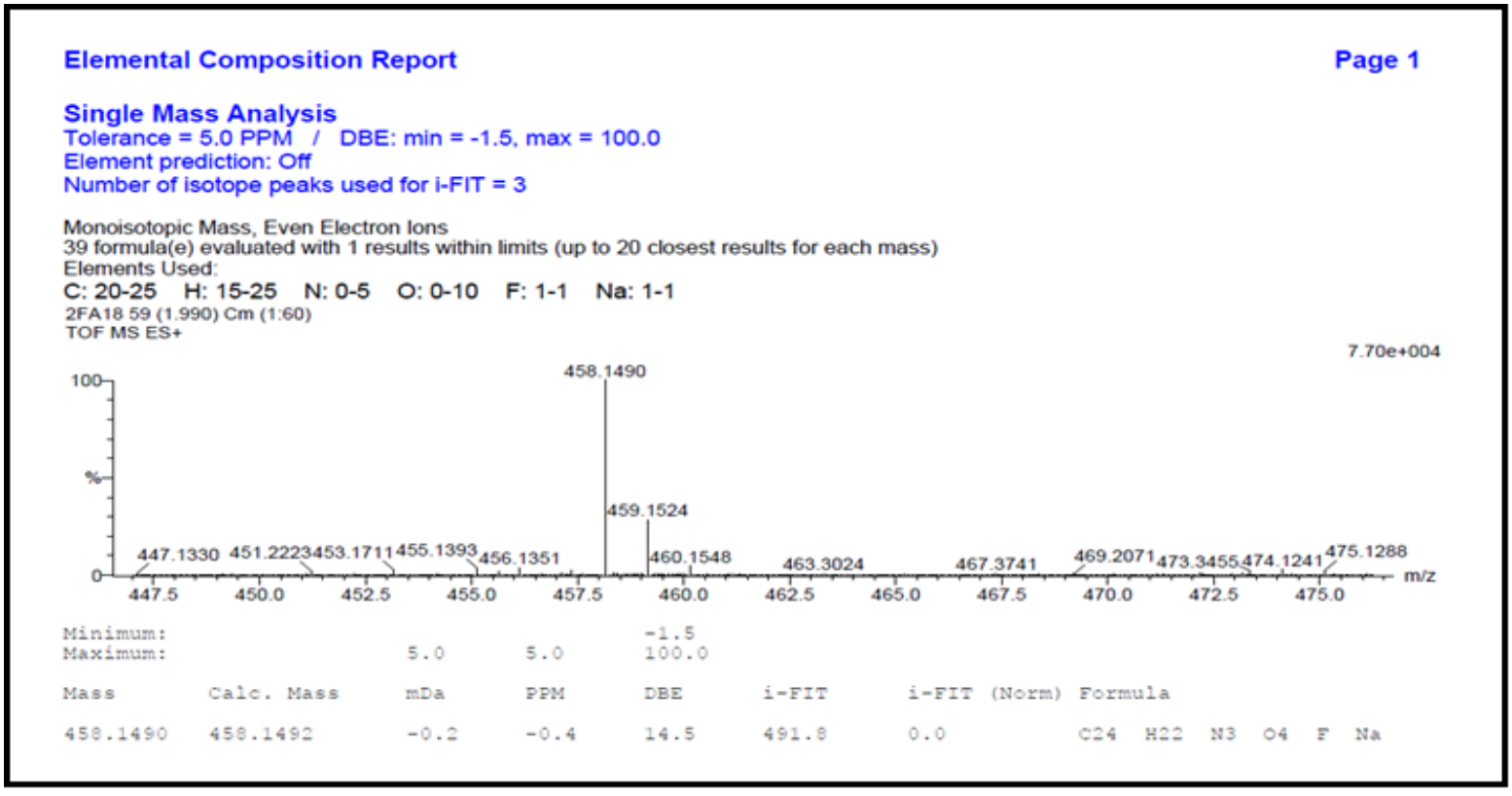

$^{1}$H NMR spectra of **5j**



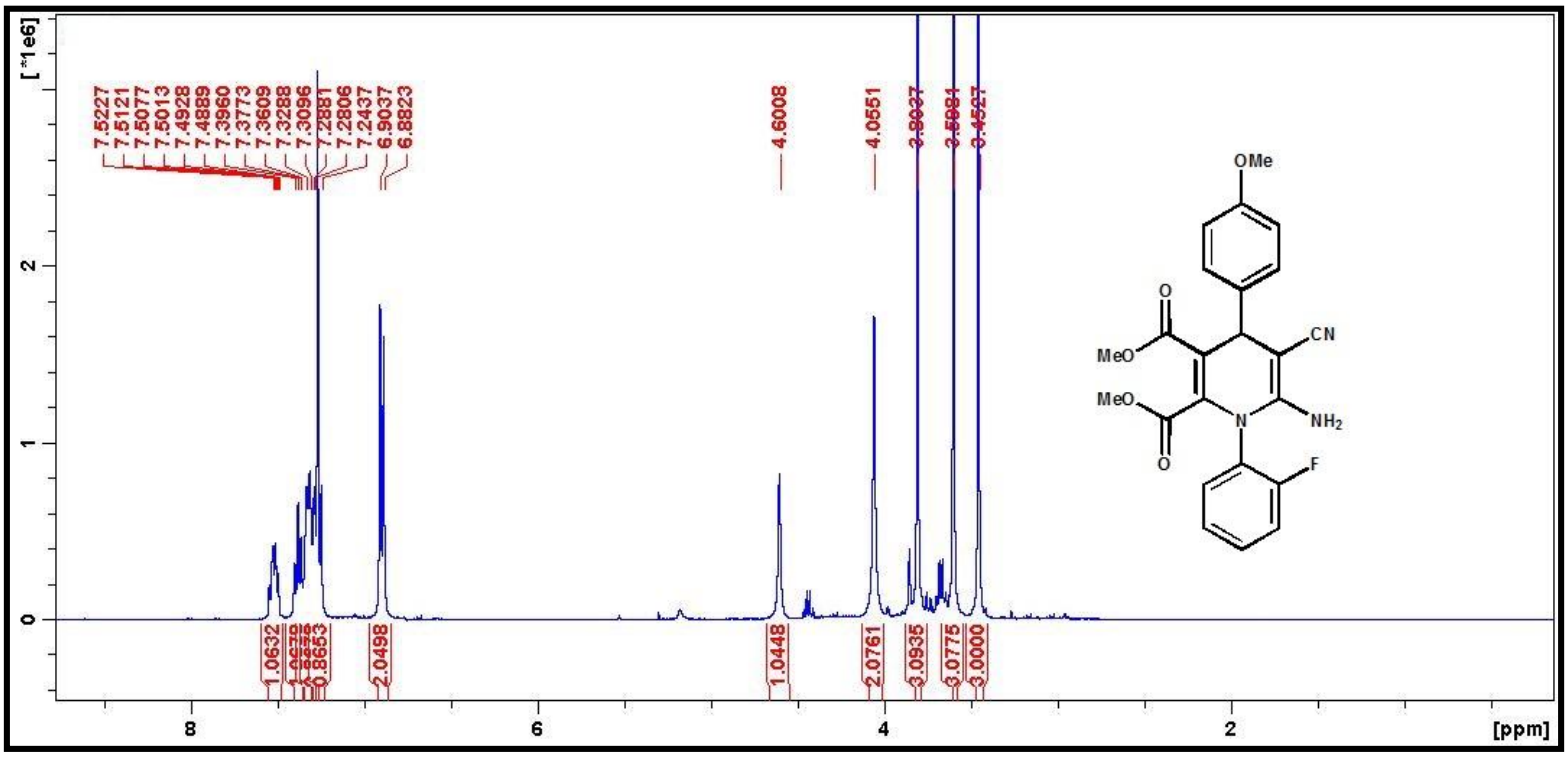

$^{15}$N NMR spectra of **5j**



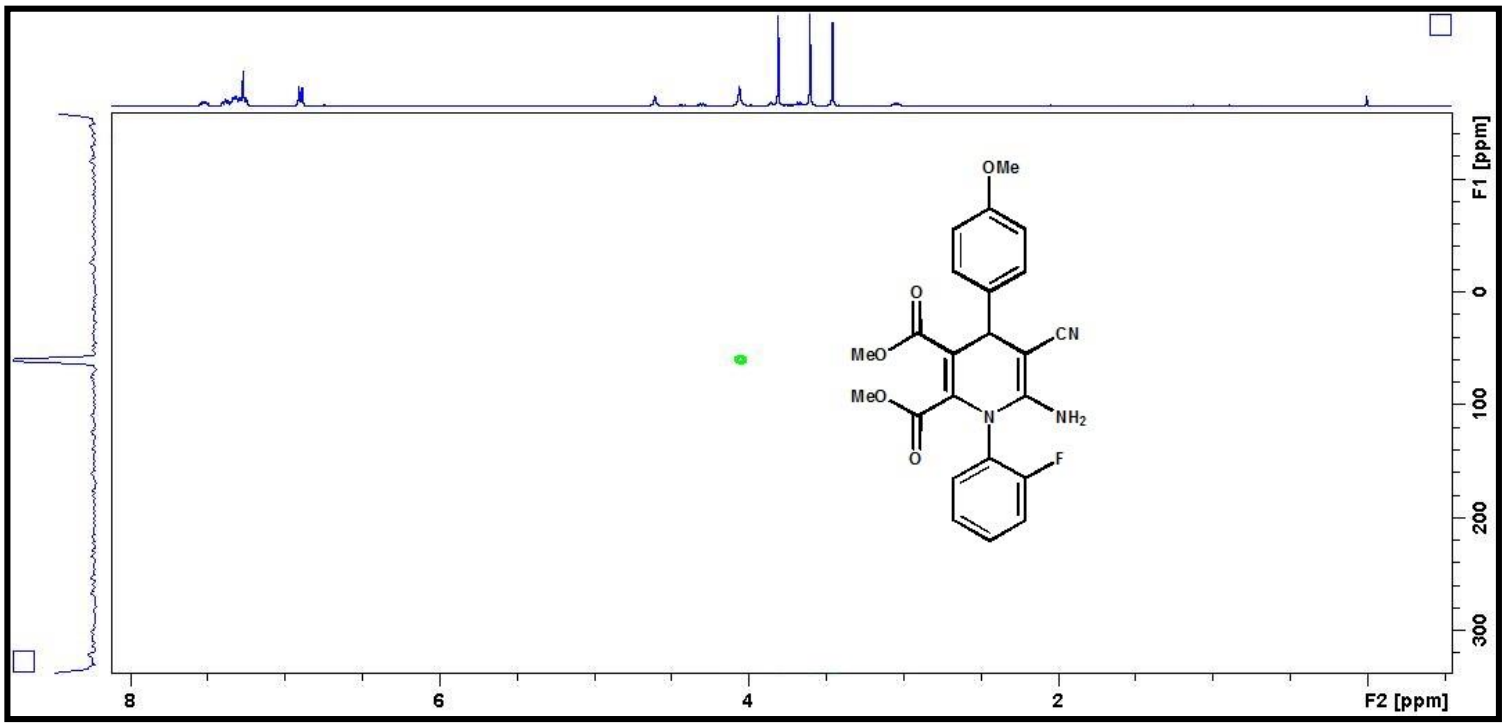

$^{13}$C NMR spectra of **5j**



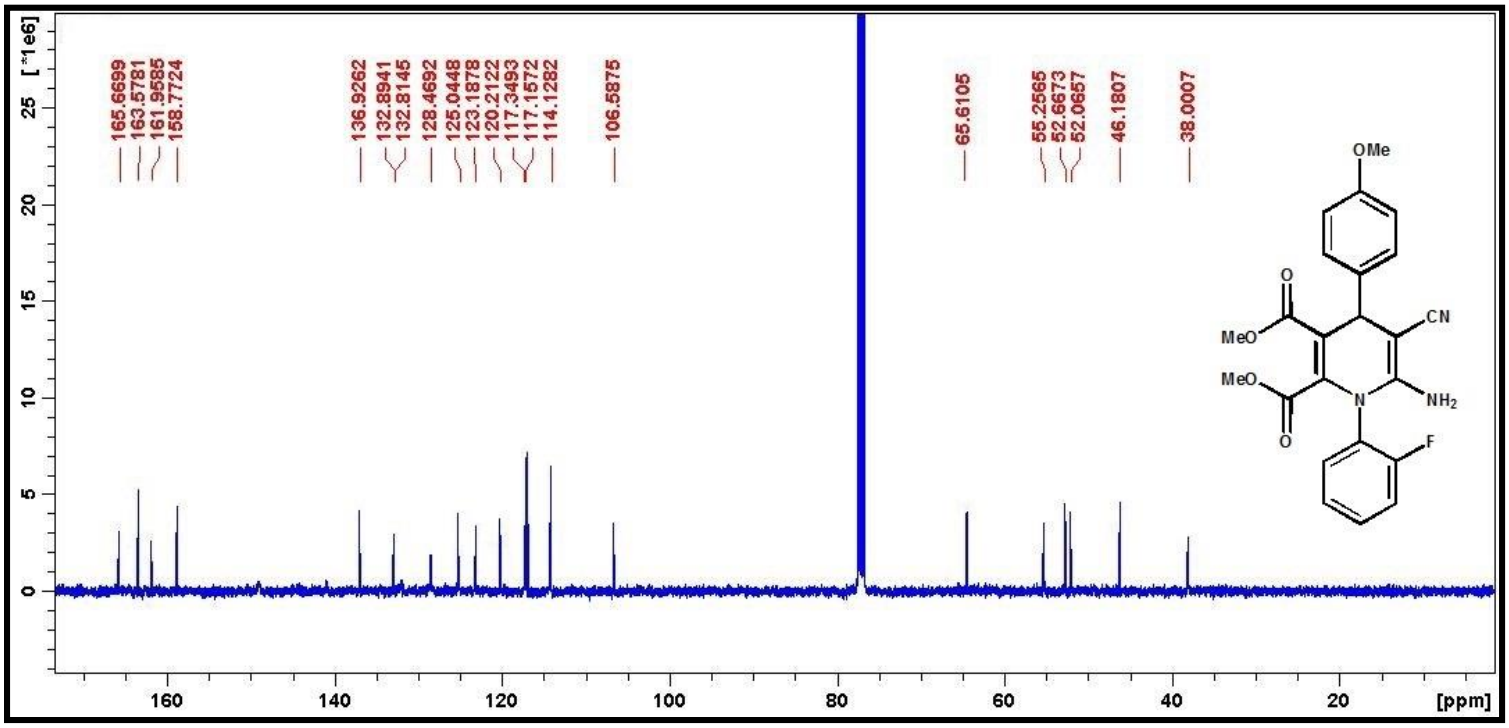

HRMS spectra of **5j**




$^{1}$H NMR spectra of **5k**




$^{15}$N NMR spectra of **5k**

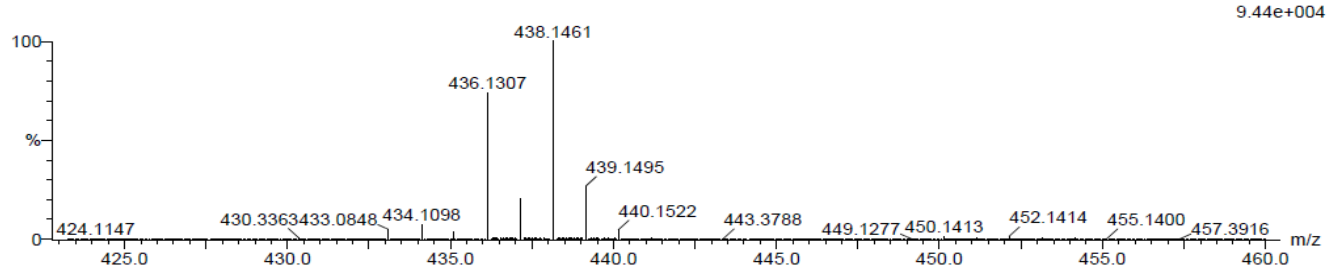



$^{13}$C NMR spectra of **5k**

**Elemental Composition Report** **Page 1**

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
28 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 20-25 N: 0-5 O: 0-5 F: 0-1
F1 2 (0.034) Cm (1:61)
TOF MS ES+




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 438.1461 | 438.1465 | -0.4 | -0.9 | 14.5 | 532.1 | 0.0 | C23 H21 N3 O5 F |

HRMS spectra of **5k**

## CHAPTER - 4

## FACILE ONE-POT SYNTHESIS OF TETRAHYDROBIPHENYLENE-1,3-DICARBONITRILES IN AQUEOUS MEDIA UNDER ULTRASOUND IRRADIATION

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**Abstract:**

An efficient and rapid procedure for the synthesis of eleven novel tetrahydrobiphenylene-1,3-dicarbonitrile derivatives (**4a-k**) is described by the reaction of aromatic aldehydes, malononitrile and 3-methyl-cyclohexanone at room temperature in water, under ultrasonic irradiation using NaOH as a catalyst. The attractive features of this methodology over conventional methods are the green principles, operational simplicity, easy handling, excellent yield, time-reducing, mild reaction conditions and no by-product production.

**Keywords:** Green synthesis; One-pot synthesis; Functionalized aromatics; Multicomponent reactions; Ultrasound irradiation.

## 1. INTRODUCTION

Chemical reactions induced by mechanical and chemical effects of ultrasound were reported as far back as 1945 due to the increased understanding of the phenomenon of cavitation.[1] This field of study involving cavitation which has gained much interest in recent years is now known as sonochemistry and has found applications in the many fields of science including medicine, chemistry and biochemistry.[2] This phenomenon was first discovered by accident by Jacques Curie and Pierre Curie in the early 1880s.[3] It is a sequence involving the formation, growth, and impulsive breakdown of bubbles in an irradiated liquid.[4-7] Research shows that the cavitational bubbles produces very high local temperature and pressure at their final stages of breakdown, thus facilitating mass transfer in the neighborhood.[8] When applied to organic synthesis this phenomenon accelerates multicomponent reactions for carbon-carbon, carbon-nitrogen and carbon-heteroatom bond formation,[9] thus leading to the formation of complex organic compounds in short reaction time[9-11] This technique offers advantages including high yields, improved selectivity and mass transfer, safety and energy savings. [7,12,13]

To avoid the chemical and toxic waste and anthropogenic pollution, the chemical approaches are becoming greener and sustainable; researchers all over the world have been striving for overall improvement in reaction protocols. Researchers are therefore concerned with the limitations with conventional multistep methods for synthesis of complex organic molecules, which involve a number of synthetic operations such as extraction and purification steps.[14,15] These steps are time consuming and they produce large amount of waste. This has thus attracted the attention of chemistry and medicinal chemistry research towards the one-pot multicomponent reactions (MCRs).[16] MCRs involve three or more starting materials reacting together in one reaction vessel to produce single pure product in high yields.[17] This approach has gained popularity as green chemistry, as it produces products with diverse functional groups, thus allowing access to a number of libraries of complex organic compounds.[18-20] Compared to conventional multistep synthesis, MCR has proven to be more beneficial as it allows the formation of several carbon-carbon and carbon-heteroatom bonds in one unit operation.[21] Thus medicinal chemistry and drug discovery researchers have got attracted towards this method of synthesis and most of them were well rewarded.[22] Organic compounds that have been successfully synthesized via MCRs and using ultrasound irradiation include aromatic, heterocyclic and fused heterocyclic compounds.[23] Tetrahydrobiphenylene-1,3-dicarbonitriles

are among these compounds, which are of enormous importance, as they are used pharmaceutically as cancer treatment and possess a wide range of antitumor, [24] antibacterial, [25] antifungal, [26] anti-inflammatory and insecticidal activities[27,28] etc.

In order to maintain benign synthetic procedures, researchers has been focusing on the use reaction conditions based on green principles,[29] such as using alternative solvents instead of volatile organic solvents.[30,31] Alternative solvents such as ionic liquids,[32] supercritical carbon dioxide, ethanol, water [33,34] and no solvent at all, [34-36] have gained importance, since the green chemistry is becoming a driving force in organic synthesis. In continuation of our research towards the improvement of new green routes for the synthesis of heterocyclic compounds, using green reaction methods with reusable catalysts [37,38]. Recently, we have reported on the successful catalyst-free synthesis of pyranopyrazoles derivatives in water under ultrasound irradiation.[39]

Thus in this communication, we report on the use of water as a green solvent that meets the expectation of green chemistry practices. Water as solvent offers many advantages including its low cost, availability, easy to handle, environmentally friendly, and it also accelerates multicomponent reactions.[40-42] Here we report an efficient, convenient and facile green synthesis of novel tetrahydrobiphenylene-1,3-dicarbonitrile derivatives through the one-pot reaction of aromatic aldehyde, malononitrile, 3-methyl-cyclohexanone in the presence of NaOH under aqueous condition, through ultrasound irradiation at room temperature. No similar reaction has been reported earlier in the literature.

## 2. MATERIALS AND METHODS

### 2.1. General procedure for the synthesis under silent conditions

In the preliminary studies without ultrasonic irradiation, the mixture of aromatic aldehyde (1.0 mmol) and malononitrile (2.0 mmol) in water (10 mL) was magnetically stirred for 10 min at room temperature followed by addition of 3-methyl-cyclohexanone (1.0 mmol) and sodium hydroxide solution (1.0 mmol in 10 ml water). The reaction mixture was stirred for 3 h. After the starting material was completely consumed, the reaction mixture was washed with water and ethanol. The precipitated product was filtered then dried under vacuum.

## 2.2. General procedure for the synthesis under ultrasound irradiation

A 100 mL reaction flask was charged with aromatic aldehyde (1.0 mmol) and malononitrile (2.0 mmol) in water (10 mL) and the mixture was exposed to sonification for 15 min at room temperature followed by addition of 3-methyl-cyclohexanone (1.0 mmol) and sodium hydroxide solution (1 mmol in 10 ml water) (**Scheme 1**). The reaction flask was placed in an ultrasonic bath, where the surface of reactants is slightly lower than the level of water and the reaction mixture was irradiated under sonication at room temperature and the reaction progress was monitored by TLC. The crude product was filtered and washed with water followed by drying under vacuum. In most cases no further purification was necessary. The structures of the resulting products were established on the basis of their physical properties and spectral data. The instrumentation details are given in supporting information (S1).

### *2.2.1. Physical data:*

***2-Amino-7-methyl-4-phenyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4a):*** Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.01 (d, *J* = 6.44 Hz, 3H, $CH_3$), 1.09-1.20 (m, 1H, CH), 1.67-1.76 (m, 2H, $CH_2$), 2.11-2.26 (m, 2H, $CH_2$), 2.35-2.42 (m, 1H, CH), 2.97 (dd, *J* = 17.76 Hz, *J* = 4.56 Hz, 1H, CH), 6.39 (s, 2H, $NH_2$), 7.24 (t, *J* = 6.72 Hz, 2H, ArH), 7.69 (t, *J* = 7.04 Hz, 2H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 21.28, 26.73, 27.51, 30.05, 37.25, 95.51, 115.36, 115.66, 123.72, 128.06, 128.14, 128.46, 128.55, 128.65, 137.28, 146.55, 149.91; IR (ATR, $cm^{-1}$): 3352 ($NH_2$), 2221(CN); HRMS of [$C_{19}H_{17}N_3$-1] (m/z): 286.1340 (100%); Calc. Mass: 287.1422

***2-Amino-4-(4-bromophenyl)-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4b):*** Yellow solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.01 (d, *J* = 6.44 Hz, 3H, $CH_3$), 1.12-1.17 (m, 1H, CH), 1.68-1.76 (m, 2H, $CH_2$), 2.11-2.23 (m, 2H, $CH_2$), 2.35-2.42 (dd, *J* = 17.68, *J* = 4.56 Hz, 1H), 6.45 (s, 2H, $NH_2$), 7.24 (t, *J* = 6.48 Hz, 2H, ArH), 7.67-7.71 (m, 2H, ArH ); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 21.2, 27.4, 30.0, 38.8, 95.8, 115.2, 115.6, 122,0, 123.6,130.4, 131.5, 131.6, 136.4, 146.7, 148.6, 150.6; IR (ATR, $cm^{-1}$): 3338 ($NH_2$), 2208 (CN); HRMS of [$C_{19}H_{16}BrN_3$-1] (m/z): 364.045 (100%); Calc. Mass: 365.0528

***2-Amino-4-(4-methoxyphenyl)-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4c):***

Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.02 (d, *J* = 6.48 Hz, 3H, $CH_3$), 1.11-1.17 (m, 1H, CH), 1.68-1.76 (m, 2H, $CH_2$), 2.18-2.26 (m, 1H, CH), 2.35-2.42 (m, 1H, CH), 2.97 (dd,

*J* = 17.8, *J* = 4.84 Hz, CH), 3.80 (s, 3H, $OCH_3$), 6.35 (s, 2H, $NH_2$), 7.02-7.06 (m, 2H, ArH), 7.17-7.21 (m, 2H, ArH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): 21.2, 26.6, 27.4, 29.9, 37.2, 38.7, 95.2, 95.8, 115.2, 115.6, 122.0, 123.0, 130.4, 130.5, 131.6, 136.4, 146.7, 148.6, 150.6; IR ATR, $cm^{-1}$): 3253 ($NH_2$), 2225 (CN); HRMS of [$C_{20}H_{19}N_3O$-1] (m/z): 316.1440 (100%); Calc. Mass: 317.1528.

***2-Amino-4-(4-(dimethylamino)-phenyl-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4d):***

Yellow solid; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ = 1.02 (d, *J* = 6.48 Hz, 3H, $CH_3$), 1.10-1.15 (m, 1H, CH), 1.68-1.76 (m, 2H, $CH_2$), 2.24-2.31 (m, 2H, $CH_2$), 2.33-2.41 (dd, *J* = 8.0 Hz, 1H, CH), 2.92 (d, *J* = 4.96 Hz, 1H, CH), 2.95 (s, 6H, $N(CH_3)_2$), 6.26 (s, 2H, $NH_2$), 6.78 (d, 2H, J = 6.56 Hz, ArH), 7.08 (d, *J* = 5.92 Hz, 2H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): 21.3, 26.9, 27.6, 30.2, 37.3, 94.7, 95.9, 111, 6, 115.5, 116.1, 124.1, 124.3, 129.1, 146.0, 150.0, 150.5, 150.8; IR (ATR, $cm^{-1}$): 3349 ($NH_2$), 2208 (CN); HRMS of [$C_{21}H_{22}N_4$-1] (m/z: 329.1763 (100%); Calc. Mass: 330.3860

***2-Amino-4-(2-methoxyphenyl)-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4e):***

Off-white solid; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ = 1.01 (d, *J* = 6.48 Hz, 3H, $CH_3$), 1.12-1.18 (m, 1H, CH), 1.66-1.75 (m, 2H, $CH_2$), 2.11-2.18 (m, 2H, $CH_2$), 2.36-2.45 (m, 1H, CH), 2.90-2.99 (m, 1H, CH), 3.72 (s, 3H, OMe), 6.31 (s, 2H, $NH_2$), 7.04-7.08 (m, 2H, ArH), 7.13-7.17 (m, 1H, ArH), 7.43-7.45 (m, 1H, ArH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 21.2, 25.4, 27.6, 30.0, 37.1, 55.4, 95.4, 96.2, 111.6, 115, 6, 120.7, 124.7, 125.7, 129.4, 130.3, 146.2, 147.3, 150.6, 155.4, 155.7 ; IR (ATR, $cm^{-1}$): 3151 ($NH_2$), 2215 (CN); HRMS of [$C_{20}H_{19}N_3O$-1] (m/z): 316.1449 (100%); Calc. Mass: 317.1528

***2-Amino-4-(2-bromophenyl)-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4f):***

Off-white solid; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ = 1.00-1.01 (d, *J* = 6.52 Hz, 3H, $CH_3$), 1.17-1.23 (m, 1H, CH), 1.69-1.78 (m, 2H, $CH_2$), 2.08-2.11 (m, 2H, $CH_2$), 2.37-2.45 (m, 1H, CH), 2.93-2.99 (m, 1H, CH), 6.50 (s, 2H, $NH_2$), 7.28-7.31 (m, 1H, CH), 7.39-7.43 (m, 1H, ArH), 7.50-7.55 (m, 1H, ArH), 7.77-7.78 (dd, *J* = 7.44 Hz, *J* = 2.80 Hz, 1H, ArH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 21.0, 25.7, 27.5, 29.7, 37.1, 38.8, 96.1, 115.2, 121.5, 123.6, 128.3, 129.8, 130.6, 132.7, 138.0, 146.9, 148.6,150.7; IR (ATR, $cm^{-1}$): 3345 ($NH_2$), 2215 (CN); HRMS of [$C_{19}H_{16}BrN_3$-1]: (m/z): 364.0440 (100%); Calc. Mass: 365.0528

***2-Amino-4-(2-chlorophenyl)-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4g):***

Pale yellow solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.01 (d, 3H, *J* = 6.44 Hz, $CH_3$), 1.16-1.21 (m, 1H, CH), 1.68-1.76 (m, 2H, $CH_2$), 2.02-2.13 (m, 2H, $CH_2$), 2.39-2.45 (m, 1H, CH), 2.92-3.00 (m, 1H, CH), 6.50 (s, 2H, $NH_2$), 7.29-7.33 (m, 1H, ArH), 7.48-7.50 (m, 2H, ArH), 7.61-7.64 (m, 1H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 21.0, 26.2, 29.6, 37.1, 38.8, 95.3, 96.2, 115.1, 123.8, 129.6, 130.6, 131.3, 135.9, 147.0, 150.7; IR (ATR, $cm^{-1}$): 3348 ($NH_2$), 2217 (CN). HRMS of [$C_{19}H_{16}ClN_3$ -1] (m/z):320.0953(100%); Calc. Mass: 321.1033

***2-Amino-4-butyl-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4h):***

Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 0.95 (t, *J* = 7.32 Hz, 3H, $CH_3$), 1.01 (d, *J* = 6.52 Hz, 3H, $CH_3$) 1.20-1.28 (m, 1H, CH), 1.44-1.48 (m, 2H, $CH_2$), 1.71-1.83 (m, 2H, $CH_2$), 2.27-2.34 (m, 1H, CH), 2.45-2.49 (m, 2H, $CH_2$), 2.62-2.66 (m, 3H, $CH_2$), 2.83 (dd, *J* = 17.72 Hz, *J* = 4.08 Hz, 1H), 6.23 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 14.0, 21.2, 22.2, 24.5, 27.4, 30.0, 33.5, 37.3, 38.7, 94.2, 95.1, 115.4, 115.8, 123.7, 146.0, 150.1, 150.7; IR (ATR , $cm^{-1}$): 3344, ($NH_2$), 2210 (CN); HRMS of [$C_{17}H_{21}N_3$-1] Calc. Mass: 267.1735

***2-Amino-4-(4-chlorophenyl)-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4i):***

Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.01 (d, *J* = 6.48 Hz, 3H, $CH_3$), 1.11-1.14 (m, 1H, CH), 1.67-1.75 (m, 2H, $CH_2$), 2.20-2.15 (m, 2H, $CH_2$), 2.34-2.41 (m, 1H, CH), 2.92-2.98 (dd, *J* = 17.72 Hz, *J* = 4.48 Hz, 1H), 6.45 (s, 2H, $NH_2$), 7.28-7.32 (t, *J* =6.52 Hz, 2H, ArH), 7.53-7.57 (dd, 2H, *J* =7.60 Hz, *J* =6.28 Hz, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 21.2, 27.4,30.0, 37.2, 95.8, 115.5, 123.6, 128.6, 128.7, 130.2, 133.3, 136.0, 146.7, 148.5, 150.7; IR (ATR, $cm^{-1}$): 3342 ($NH_2$), 2222 (CN); HRMS of [$C_{19}H_{16}ClN_3$0-] (m/z): 320.0951(100%); Calc. Mass: 321.1033

***2-Amino-4-(4-ethylphenyl)-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4j):***

Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.01 (d, *J* = 6.28 Hz, 3H, $CH_3$), 1.09-1.16 (m, 1H, CH), 1.22 (t, *J* = 7.52 Hz, 3H, $CH_3$), 1.66-1.74 (m, 2H, $CH_2$), 2.13-2.24 (m, 2H, $CH_2$), 2.34-2.41 (m, 1H, CH), 2.65-2.67 (m, 2H, $CH_2$), 2.93 (dd, *J* = 17.64 Hz, *J* = 3.88 Hz, 1H, CH), 6.36 (s, 2H, $NH_2$), 7.15 (d, *J* = 7.52 Hz, 2H, ArH), 7.31 (d, *J* = 7.52 Hz, 2H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 21.0, 25.7, 27.5, 29.6, 37.1, 95.3, 96.1, 115.2, 121.4, 121.5, 123.6, 128.3, 129.8, 130.6, 132.6, 132.7, 137.9, 138.0, 146.5, 146.9, 148.6,150.7; IR (ATR, $cm^{-1}$): 3338 ($NH_2$), 2208(CN); HRMS of [$C_{21}H_{21}N_3$-1] (m/z): 314.1651 (100%); Calc. Mass: 315.1735.

***2-Amino-4-(2,4-dimethylphenyl)-7-methyl-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4k):*** Off-white solid; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ = 1.01 (d, *J* = 6.32 Hz, 3H, $CH_3$), 1.14-1.18 (m, 1H, CH), 1.67-1.76 (m, 2H, CH), 1.94 (s, 4H, $CH_2$), 2.06-2.14 (m, 1H, CH), 2.38-2.45

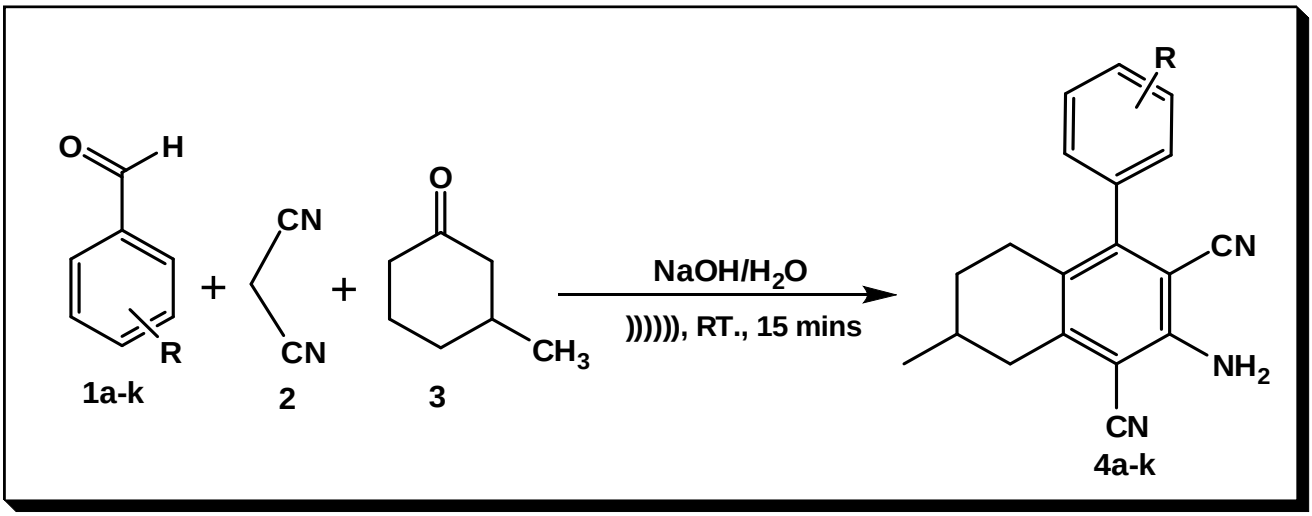
(m, 1H, CH), 2.93-2.97 (d, *J* = 16.76 Hz, 1H, CH), 6.39 (s, 2H, $NH_2$), 6.93 (dd, *J* = 7.44 Hz, *J* = 2.28 Hz, 1H, ArH), 7.09-7.16 (m, 2H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 18.6, 20.7, 21.2, 25.8, 26.5, 27.5, 37.1, 95.5, 115.3, 124.0, 126.9, 127.6, 130.9, 134.1, 137.7, 146.5, 146.6, 149.9, 150.7; IR (ATR, $cm^{-1}$): 3349 ($NH_2$), 2216 (CN); HRMS of [$C_{21}H_{21}N_3$-1] (m/z): 314.1649 (100%); Calc. Mass: 315.1735.

## 3. RESULTS AND DISCUSSION

### 3.1. Reaction Optimization

Choosing the reaction between equimolar quantities of aromatic aldehyde **1b** (1.0 mmol), malononitrile **2** (2.0 mmol), 3-methyl-cyclohexanone **3** (1.0 mmol) and NaOH catalyst (1 mmol) in water (10 ml) and using ultrasound irradiation at room temperature as the model reaction, impact of various parameters on the yield and reaction duration were investigated to optimize the reaction conditions (Scheme 1).

**Scheme 1:** Synthesis of functionalized tetrahydrobiphenylene-1,3-dicarbonitrile derivatives




The model reaction for the synthesis of tetrahydrobiphenylene-1,3-dicarbonitrile was carried out in the absence and presence of different catalysts conditions under magnetic stirring and ultrasonication in the presence of aqueous solvent (Table 1). Without the catalyst, the reaction neither occurred at room temperature nor under heating, even for prolonged reaction times, neither under conventional nor ultrasonication conditions (Table 1, entry 1 & 2). Only a trace amount of products was obtained by the using of organic basic catalysts like pyridine and

TEA in both conditions (Table 1, entries 3 & 4). Thereafter, the reaction was conducted in the presence of ionic liquid like (Bmim)$BF_4$ and Proline. Yields were low at RT condition, and product was obtained only after 3.5 h ultrasound irradiation (Table 1, entry 5 & 6). The model reaction was also investigated employing other inorganic bases, such as $NaHCO_3$, $Na_2CO_3$, and $K_2CO_3$. In the presence of these bases after 3.5 h, only moderate yield was observed under silent conditions, but the yield could be improved under ultrasound irradiation, complimented by shorter reaction times (Table 1, entries 7-9).

**Table 1:** Effect of various catalysts on the model reaction[a], compound **4b**

| Entry | Catalyst | Condition | Conventional | | Sonication | |
|---|---|---|---|---|---|---|
| | | | Time (h) | Yield[b] (%) | Time (h) | Yield[b] (%) |
| **1** | No catalyst | RT | 12 | -- | 6.0 | -- |
| **2** | No catalyst | Heat | 12 | -- | 6.0 | -- |
| **3** | Pyridine | RT | 8 | Trace | 4.0 | Trace |
| **4** | $Et_3N$ | RT | 7 | Trace | 4.0 | Trace |
| **5** | (Bmim)$NO_3$ | RT | 6.0 | 18 | 3.5 | 29 |
| **6** | (Bmim)$BF_4$ | RT | 6.0 | 15 | 3.5 | 24 |
| **7** | $NaHCO_3$ | RT | 4.0 | 26 | 2.6 | 41 |
| **8** | $Na_2CO_3$ | RT | 3.5 | 33 | 2.5 | 45 |
| **9** | $K_2CO_3$ | RT | 3.5 | 38 | 2.5 | 52 |
| **10** | NaOH | RT | 2.0 | 68 | 0.25 | 97 |
| **11** | KOH | RT | 2.0 | 65 | 0.50 | 91 |

[a]All products were characterized by IR, $^1$HNMR, $^{13}$C NMR, $^{15}$N NMR & HRMS spectral data

[b]Isolated yields; -- No reaction

Impressively, when the inorganic bases, NaOH and KOH were used as catalyst, an ample improvement in yield was observed under silent and ultrasonication conditions (Table 1, entries 10 & 11). The reactions catalyzed by NaOH and KOH respectively gave better yields (68 & 65%) with 2.0 h reaction time under normal conditions and yields (97 & 91%) within 30 min under sound irradiation.

The effect of various solvents (non-polar, protic and aprotic) on formation of the tetrahydrobiphenylene-1,3-dicarbonitriles was also investigated in the presence of NaOH catalyst

under silent and ultrasonification modes (Table 2). Under solvent free conditions, even in presence of catalyst and prolonged reaction times, the reaction did not take place (Table 2, entry 1). In non-polar solvents, such as 1, 4-dioxane and n-hexane also no reaction was observed (Table 2, entries 2 & 3). With polar aprotic solvents, like DMF and THF, merely low yields were obtained (Table 2, entries 4 & 5). Although with polar solvents such as methanol and ethanol (Table 1, entries 6 & 7), the yield of the desired product was better, excellent yield was accomplished with $H_2O$ as the solvent (Table 2, entry 8). Thus, this investigation endorses that ultrasonication method with water as solvent is the ideal for the three-component/one-pot title reaction to attain excellent yields.

**Table 2:** Optimization of various solvent condition for the synthesis of chromenes by NaOH catalyst for compound **4b**

| **Entry** | **Solvent** | **Conventional** | | **Sonication[b]** | |
|---|---|---|---|---|---|
| | | Time (h) | Yield[a] (%) | Time (h) | Yield[a] (%) |
| 1 | No catalyst | 12 | -- | 3 | -- |
| 2 | 1,4-dioxane | 12 | -- | 3 | -- |
| 3 | n-hexane | 12 | -- | 3 | -- |
| 4 | THF | 8.0 | 15 | 1.5 | 21 |
| 5 | DMF | 7.5 | 12 | 2.0 | 33 |
| 6 | MeOH | 5.5 | 59 | 1.0 | 69 |
| 7 | EtOH | 4.0 | 67 | 1.0 | 74 |
| 8 | $H_2O$ | 3.0 | 60 | 0.25 | 97 |

[a]Isolated yields; [b]room temperature; -- Products were not found;

To demonstrate the robustness of the new protocol, reactions with several aromatic aldehydes substituted with varied electron-withdrawing or electron-releasing groups were assessed and obtained results are summarized in Table 3. In all cases, all the substitued aromatic aldehydes irrespective of electron-donating or electron-withdrawing substituents reacted excellently giving respective derivatives in high yields. Structures of all the isolated products 4a–k were deducted and validated by physical and spectroscopic data including IR, $^{1}H$ NMR, $^{15}N$

NMR and $^{13}C$ NMR spectral analysis. All the compounds details are showed in supplementary information (S2).

**Table 3:** Synthesis of functionalized tetrahydrobiphenylene-1,3-dicarbonitrile derivatives catalyzed by NaOH catalyst

| Entry | R | Product | Yield (%) | Mp °C | Lit Mp °C |
|---|---|---|---|---|---|
| 1 | H | **4a** | 95 | 215-218 | -- |
| 2 | 4-Br | **4b** | 97 | 210-214 | -- |
| 3 | 4-OMe | **4c** | 92 | 195-200 | -- |
| 4 | 4-$N(Me)_2$ | **4d** | 94 | 220-223 | -- |
| 5 | 2-OMe | **4e** | 91 | 196-200 | -- |
| 6 | 2-Br | **4f** | 90 | 211-214 | -- |
| 7 | 2-Cl | **4g** | 80 | 241-242 | -- |
| 8 | $C_3H_7$ | **4h** | 60 | 218-220 | -- |
| 9 | 4-Cl | **4i** | 94 | 238-241 | -- |
| 10 | 4-$C_2H_5$ | **4j** | 92 | 215-218 | -- |
| 11 | 2,4-$(Me)_2$ | **4k** | 90 | 239-240 | -- |

-- New compounds/no literature available.

## 4. CONCLUSION:

In conclusion, we have successfully developed new green protocol for synthesis of eleven novel tetrahydrobiphenylene-1,3-dicarbonitriles (**4a-k**) in aqueous medium under ultrasonic irradiation and at room temperature. This methodology has several advantages over conventional methods that include benign conditions, easy workup, analytically pure product and excellent yields. This method can be effectively used for large-scale production of tetrahydrobiphenylene-1,3-dicarbonitriles in shorter reaction times.

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38. Pagadala, R., S. Maddila, and S.B. Jonnalagadda, Eco-efficient ultrasonic responsive synthesis of pyrimidines/pyridines. Ultrasonics Sonochemistry, 2014. **21**(2): p. 472-477.
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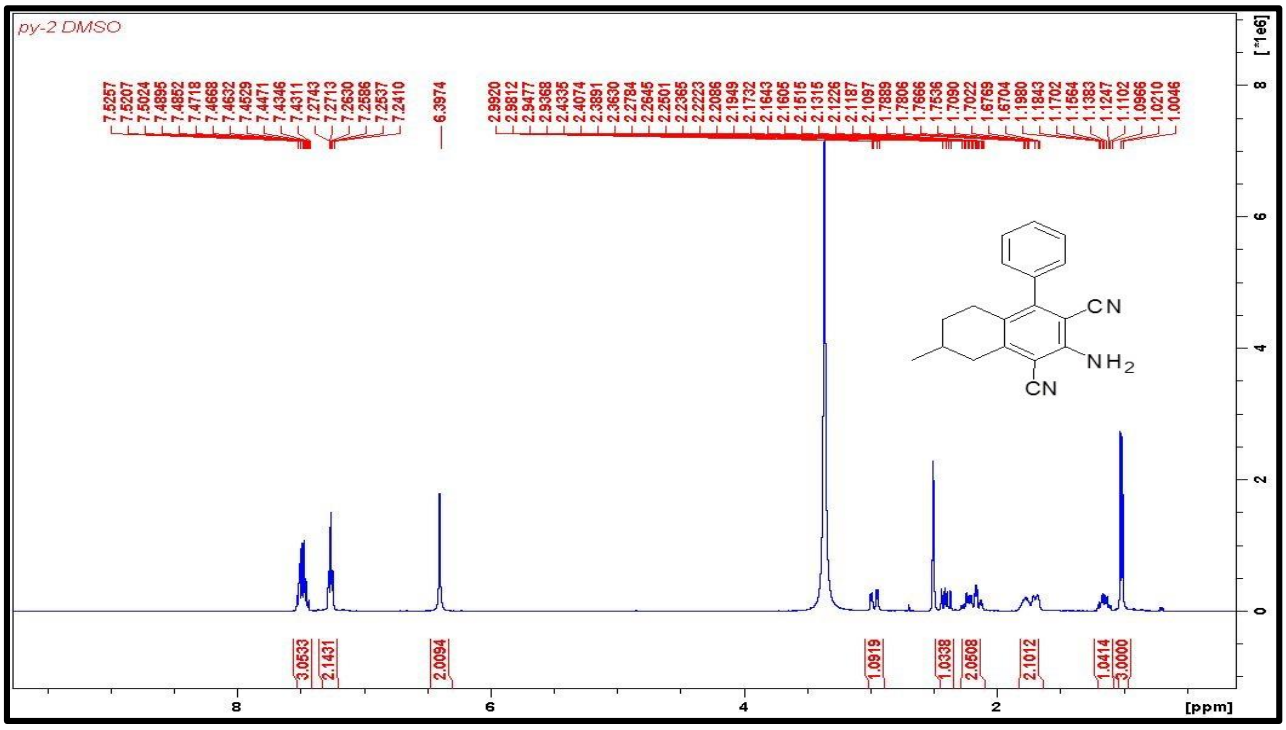
40. Maddila, S.N., et al., Mn doped $ZrO_2$ as a green, efficient and reusable heterogeneous catalyst for the multicomponent synthesis of pyrano[2,3-d]-pyrimidine derivatives. RSC Advances, 2015. **5**(47): p. 37360-37366.
41. Maddila, S. N.; Maddila, S.; van Zyl, W. E.; Jonnalagadda, S. B.., Multicomponent synthesis of pyridines via diamine functionalized mesoporous ZrO 2 domino intramolecular tandem Michael type addition. RSC Advances, 2015. **5**(8): p. 5627-5632.
42. Shabalala, N.G., R. Pagadala, and S.B. Jonnalagadda, Ultrasonic-accelerated rapid protocol for the improved synthesis of pyrazoles. Ultrasonics Sonochemistry, 2015. **27**(0): p. 423-429.

## 7. SUPPORTING INFORMATION:

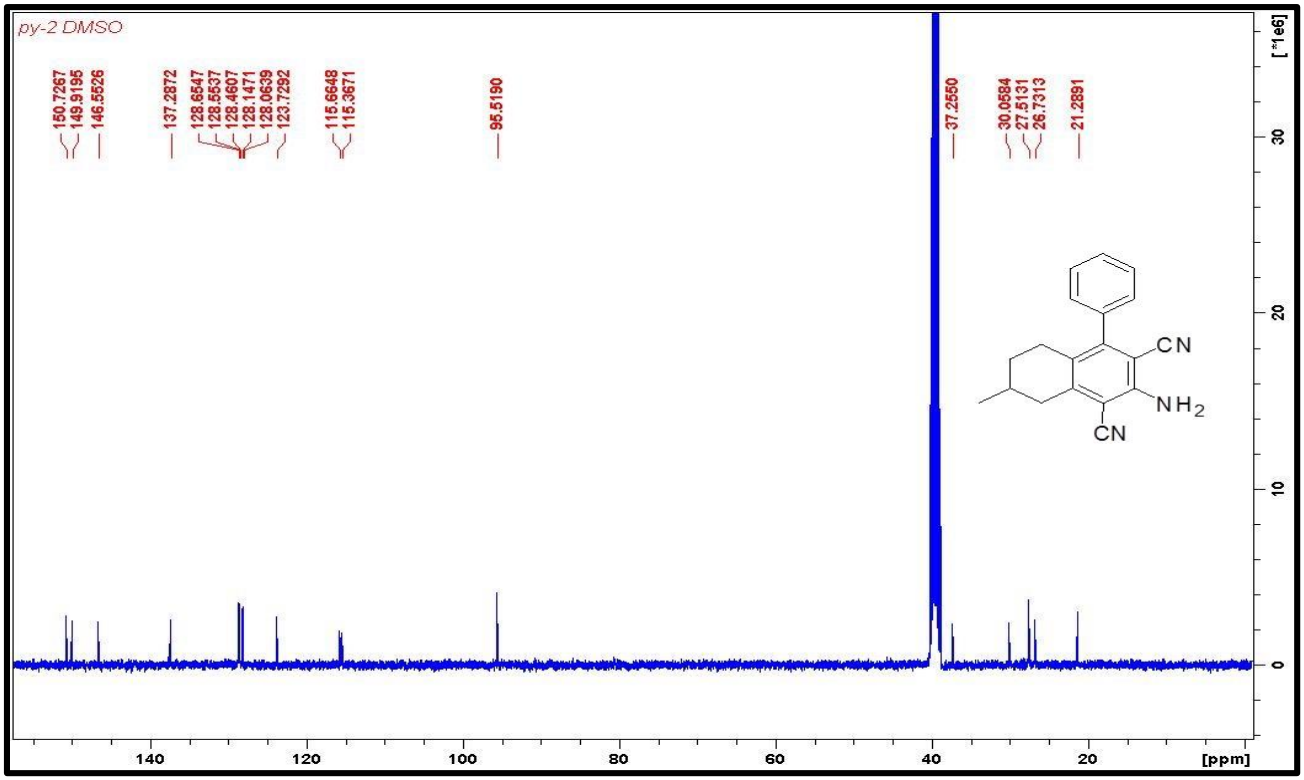
### *7.1. Materials, methods and instruments*

All chemicals used were reagent grade and were used as received without further purification. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 25 $^{o}C$ at 400 MHz and 100 MHz (Bruker Avance) instrument respectively, using TMS as internal standard. Chemical shifts are given in parts per million (ppm). The FT-IR spectroscopy of samples was carried out on a Perkin Elmer Perkin Elmer Precisely 100 FT-IR spectrometer in the 400-4000 $cm^{-1}$ region. The HRMS were recorded on a waters micromass LCT premier mass spectrometer using electrospray ionization in the positive or negative mode. The ultrasonic assisted reactions are carried out in a ‘‘Spectralab model UMC 20 Ultrsonic cleaner” with a frequency of 40 kHz and a nominal power 250 W. Melting points were recorded on a hot stage melting point apparatus Ernst Leitz Wetzlar, Germany and were uncorrected. All the reactions and the purity of products were monitored using thin layer chromatography (TLC) on aluminum-backed plates coated with Merck Kieselgel 60 F254 silica gel, visualizing the spots under ultraviolet light and iodine chamber.

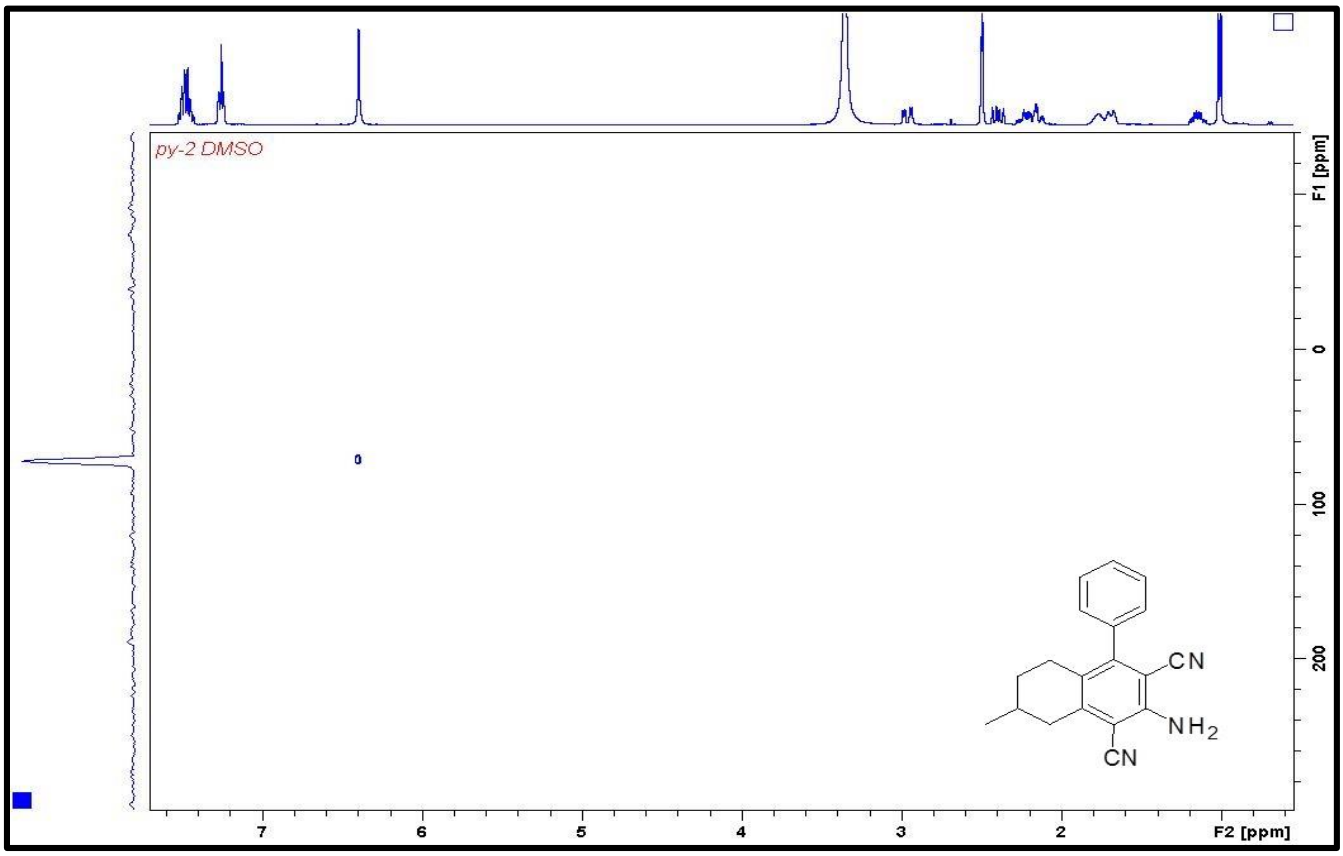
## *7.2 Supplementary information (S2)*



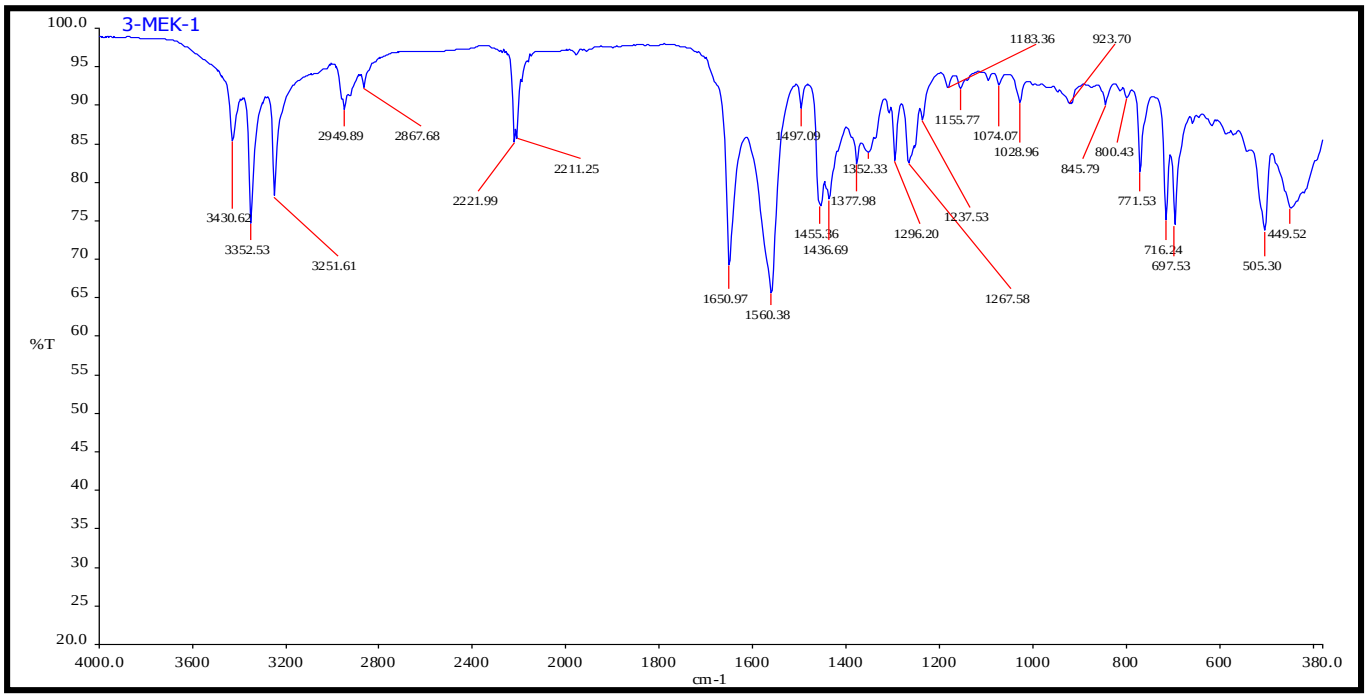

$^{1}$H NMR spectra of compound **4a**




$^{13}$C NMR spectra of compound **4a**




$^{15}$N NMR spectra of compound **4a**

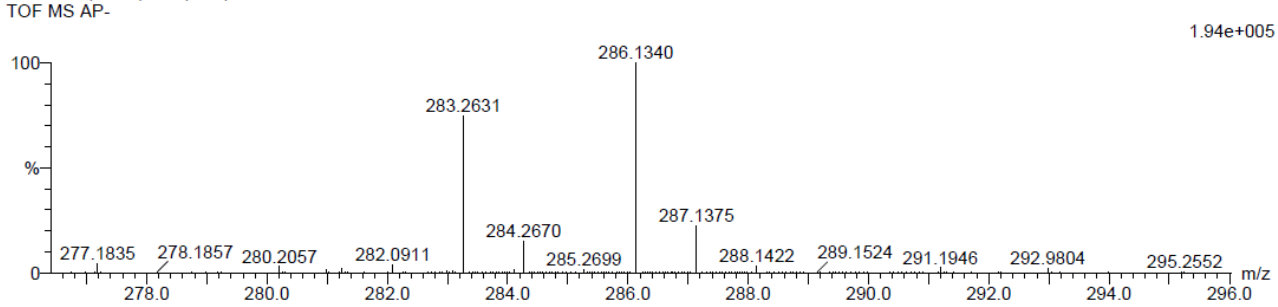



FTIR spectra of compound **4a**

**Elemental Composition Report** **Page 1**

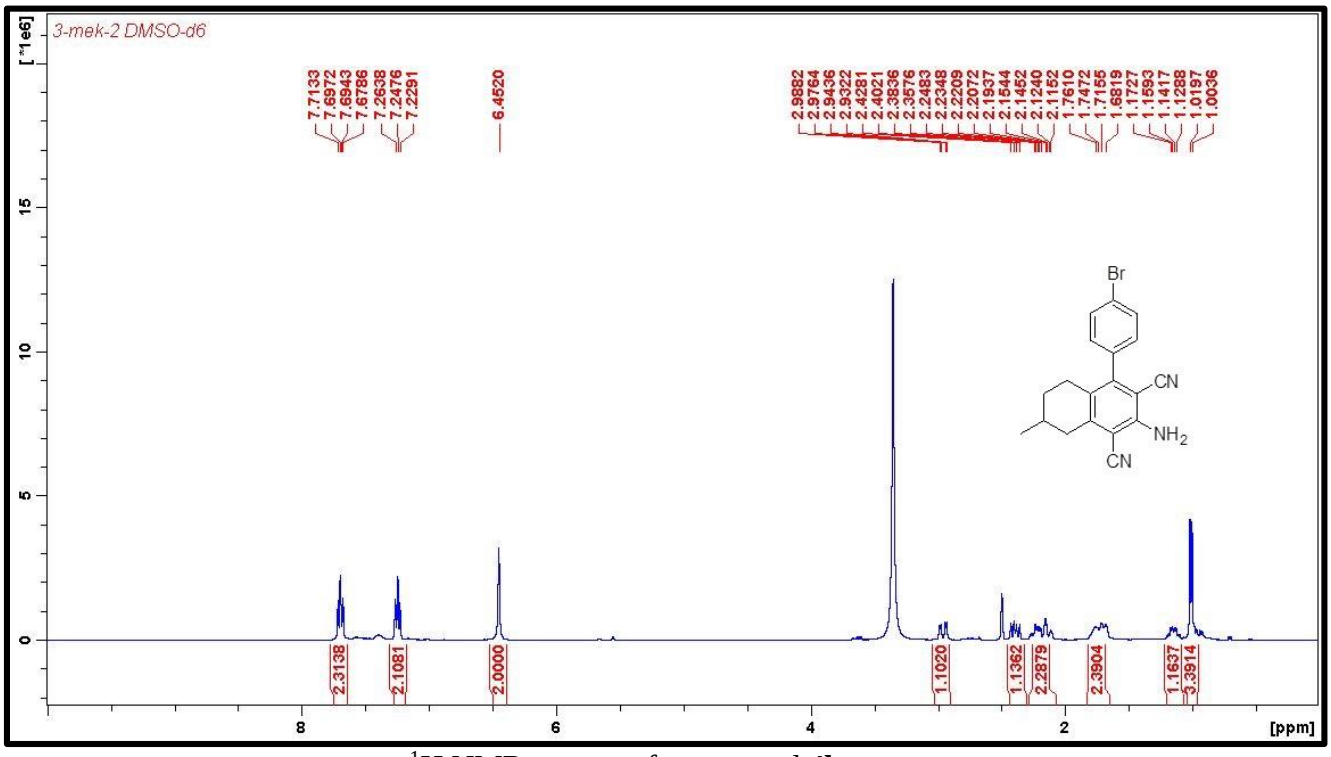
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20 H: 15-20 N: 0-5
mek-1 14 (0.439) Cm (1:61)
TOF MS AP-

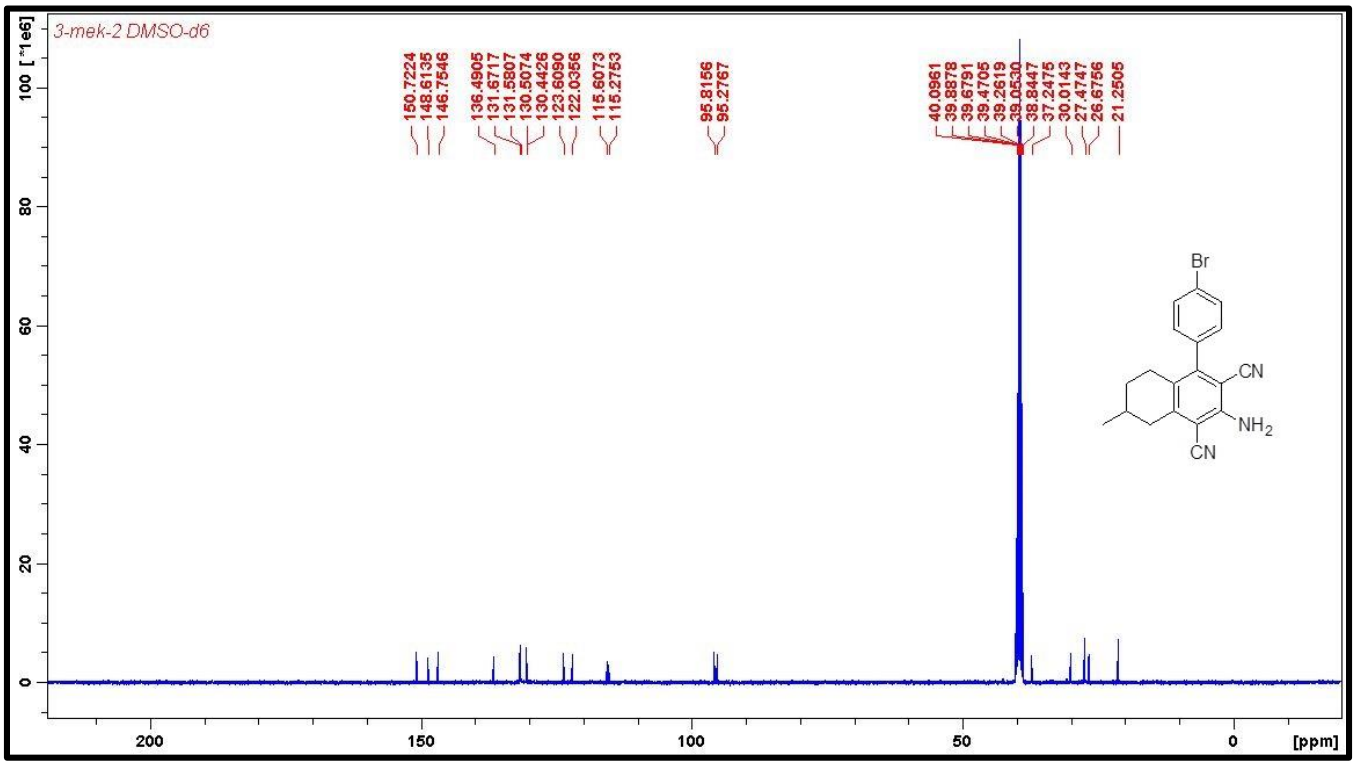



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 286.1340 | 286.1344 | -0.4 | -1.4 | 13.5 | 640.0 | 0.0 | C19 H16 N3 |

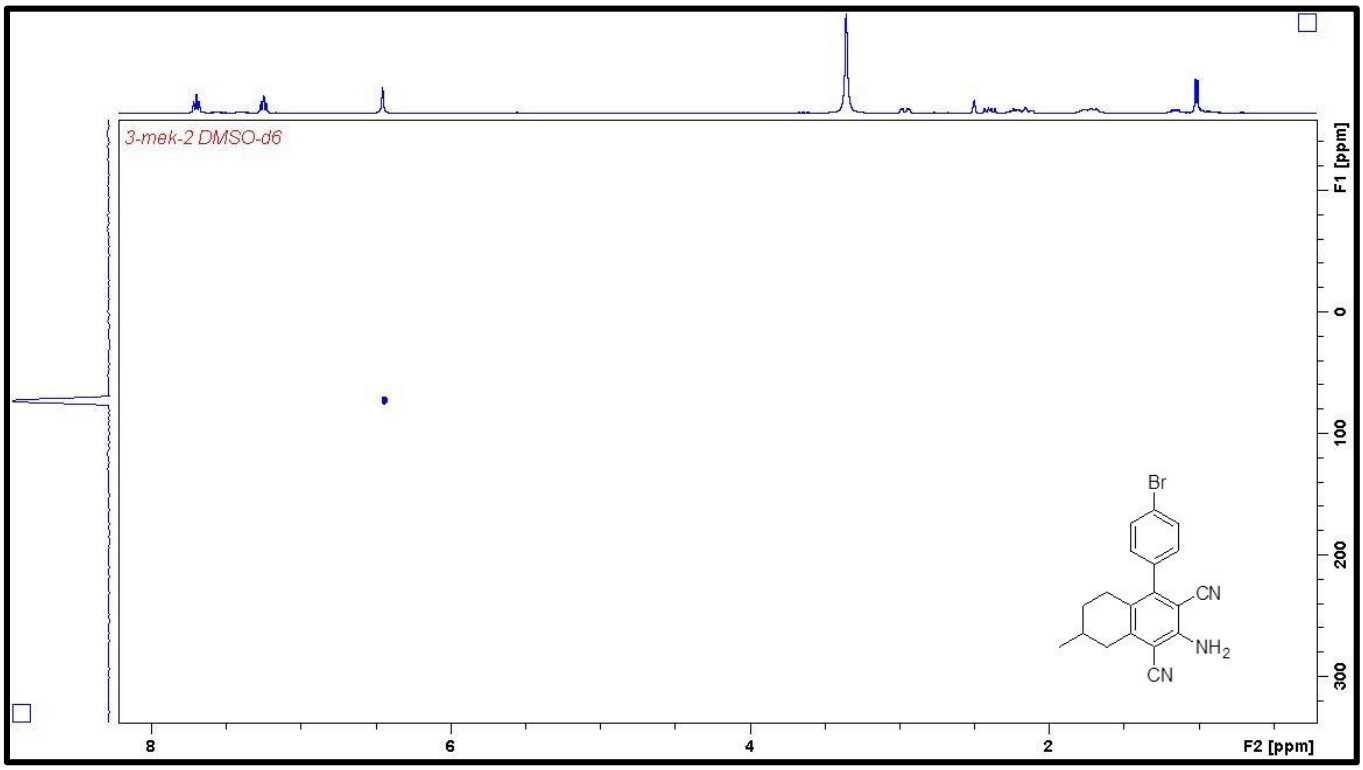
HRMS spectra of **4a**



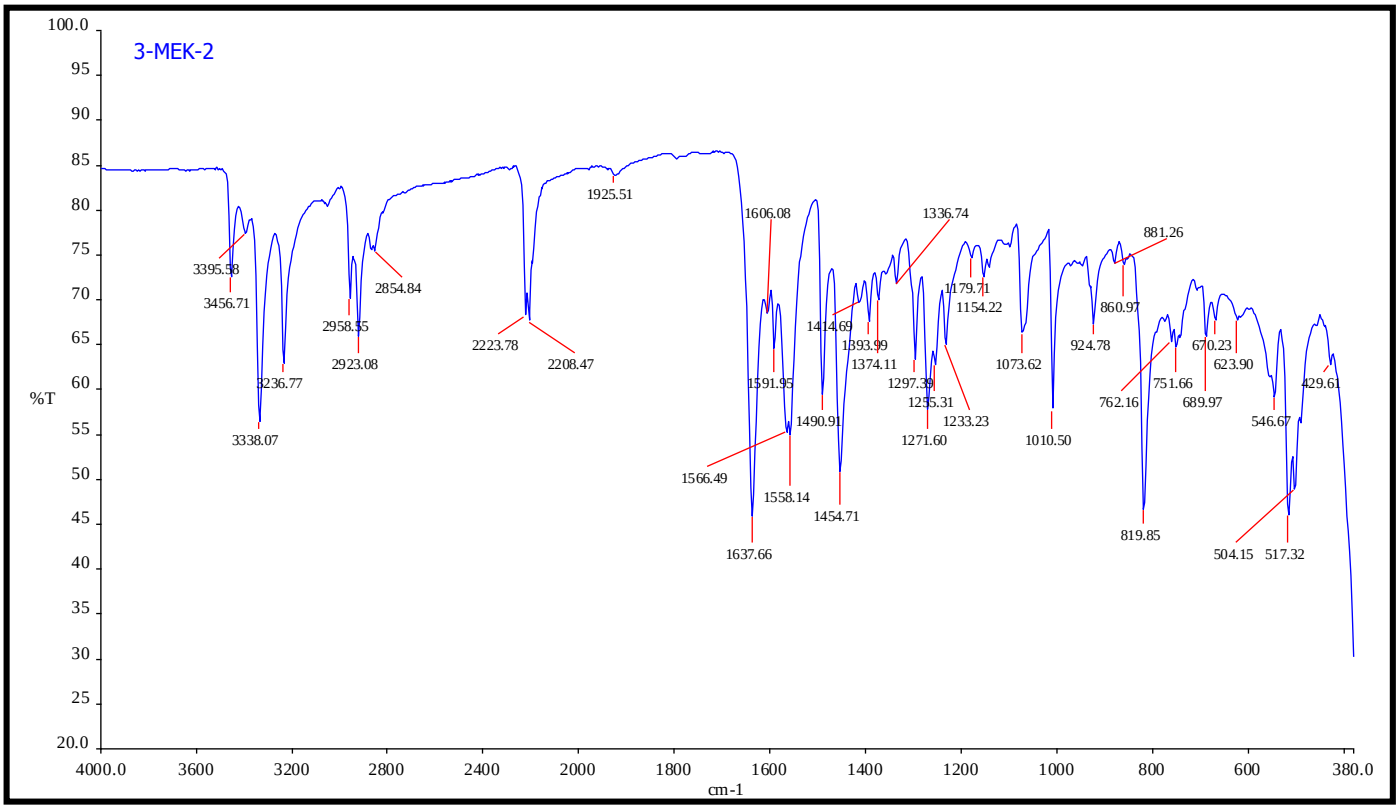

$^{1}$H NMR spectra of compound **4b**




$^{13}$C NMR spectra of compound **4b**




$^{15}$N NMR spectra of compound **4b**




FTIR spectra of compound **4b**

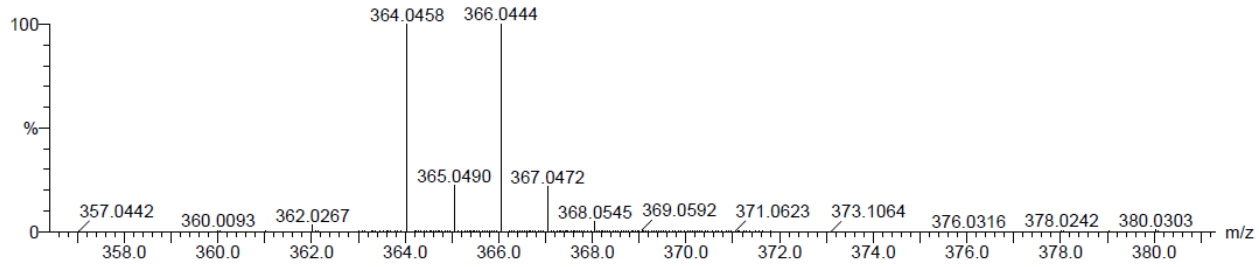
**Elemental Composition Report** **Page 1**

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
7 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20 H: 15-20 N: 0-5 Br: 0-1

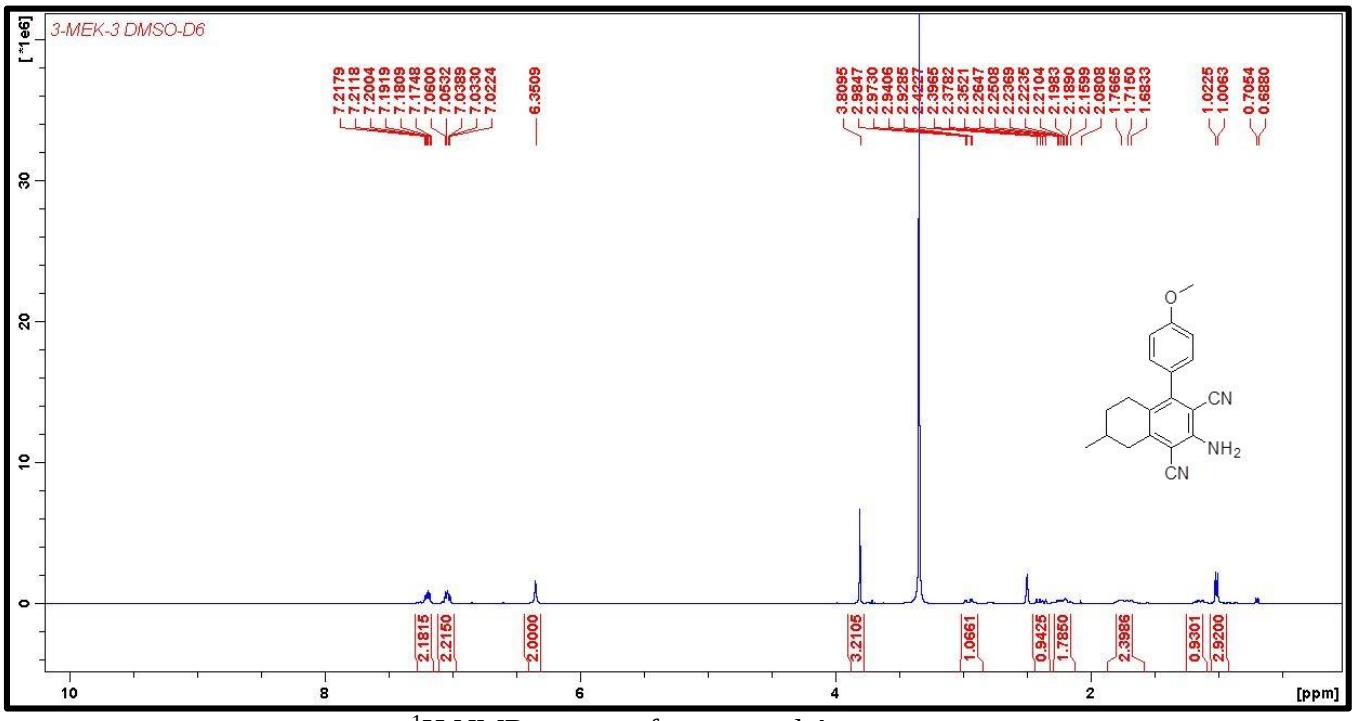
mek-2 30 (0.978) Cm (1:61)
TOF MS AP-

9.21e+004

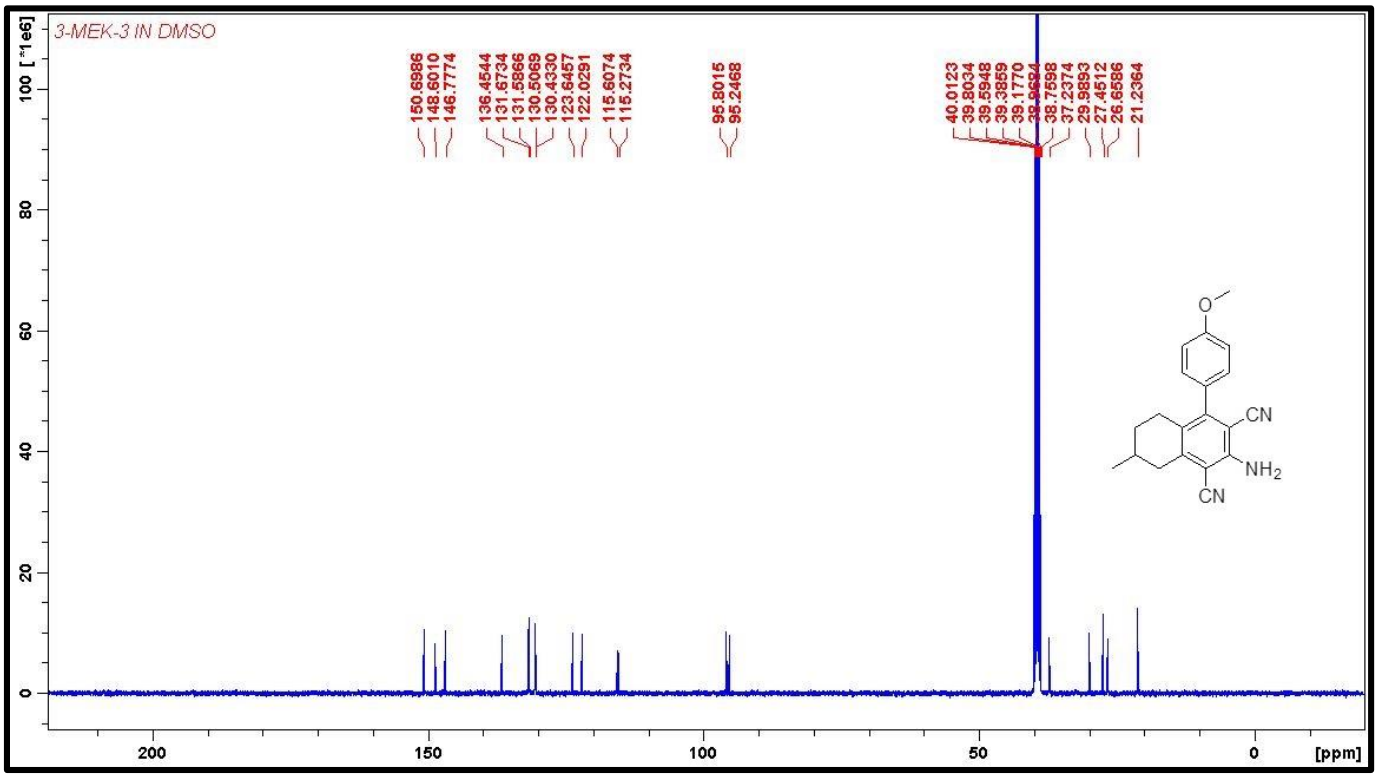



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 364.0458 | 364.0449 | 0.9 | 2.5 | 13.5 | 545.0 | 0.0 | C19 H15 N3 Br |

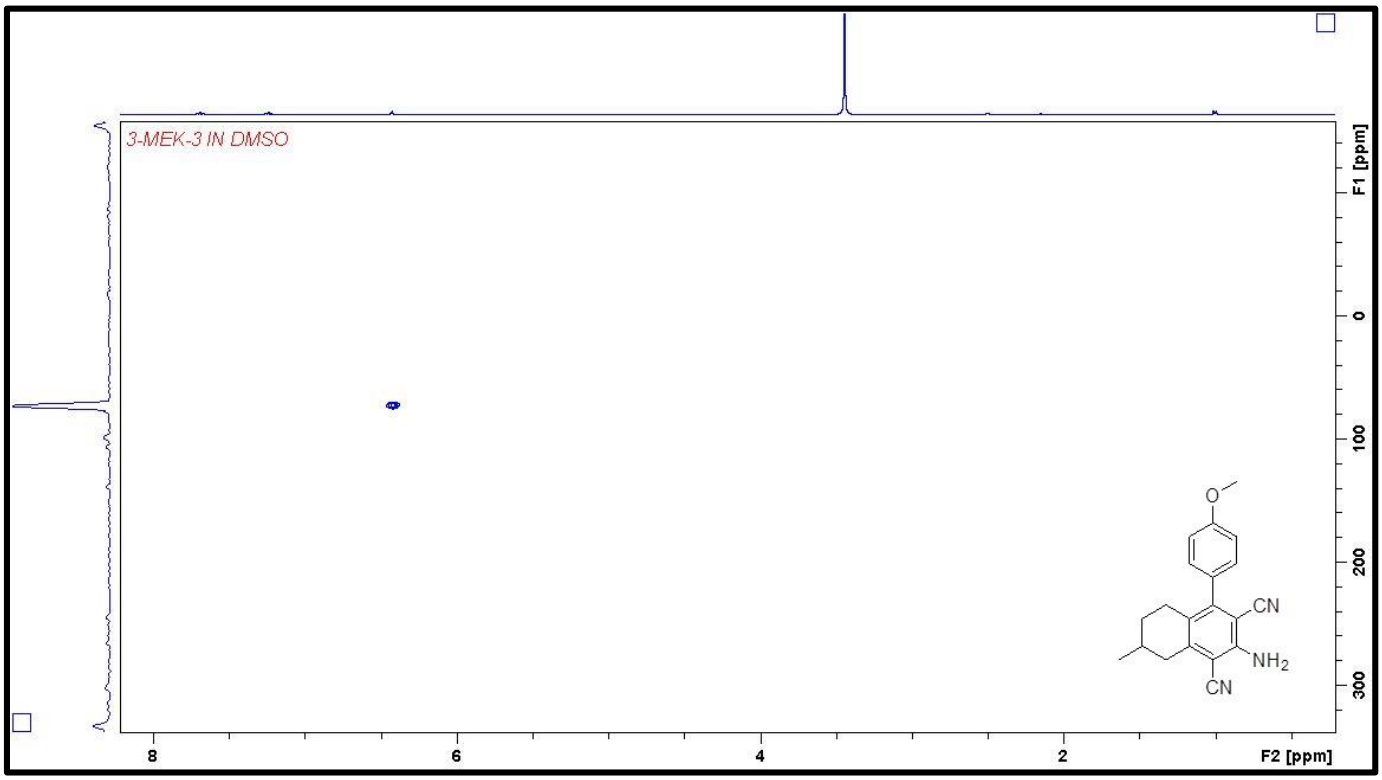
HRMS spectra of **4b**



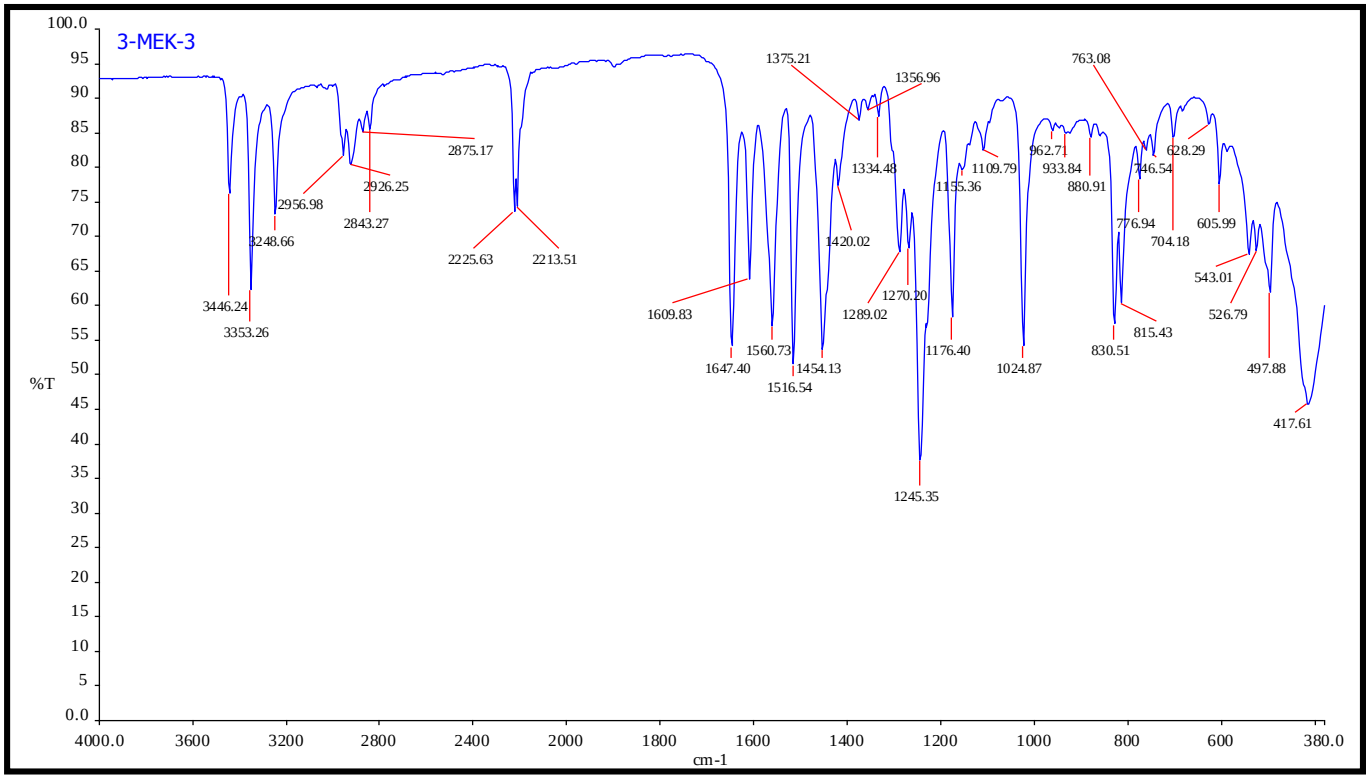

$^{1}$H NMR spectra of compound **4c**




$^{13}$C NMR spectra of compound **4c**




$^{15}$N NMR spectra of compound **4c**



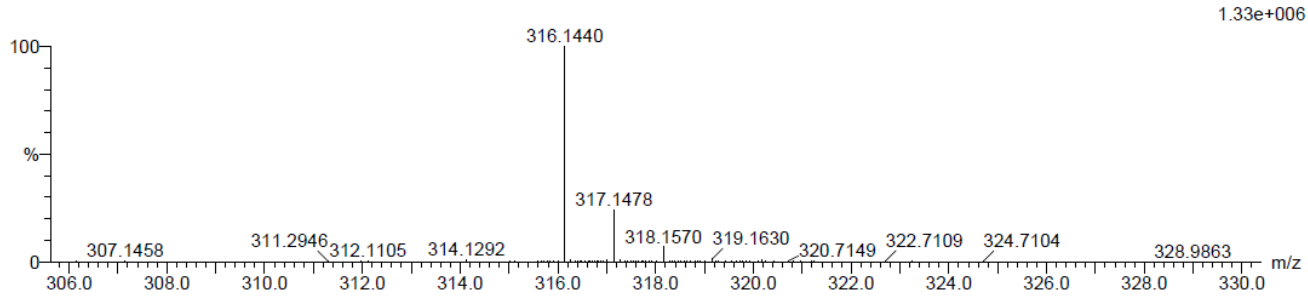

FTIR spectra of compound **4c**

**Elemental Composition Report** **Page 1**

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

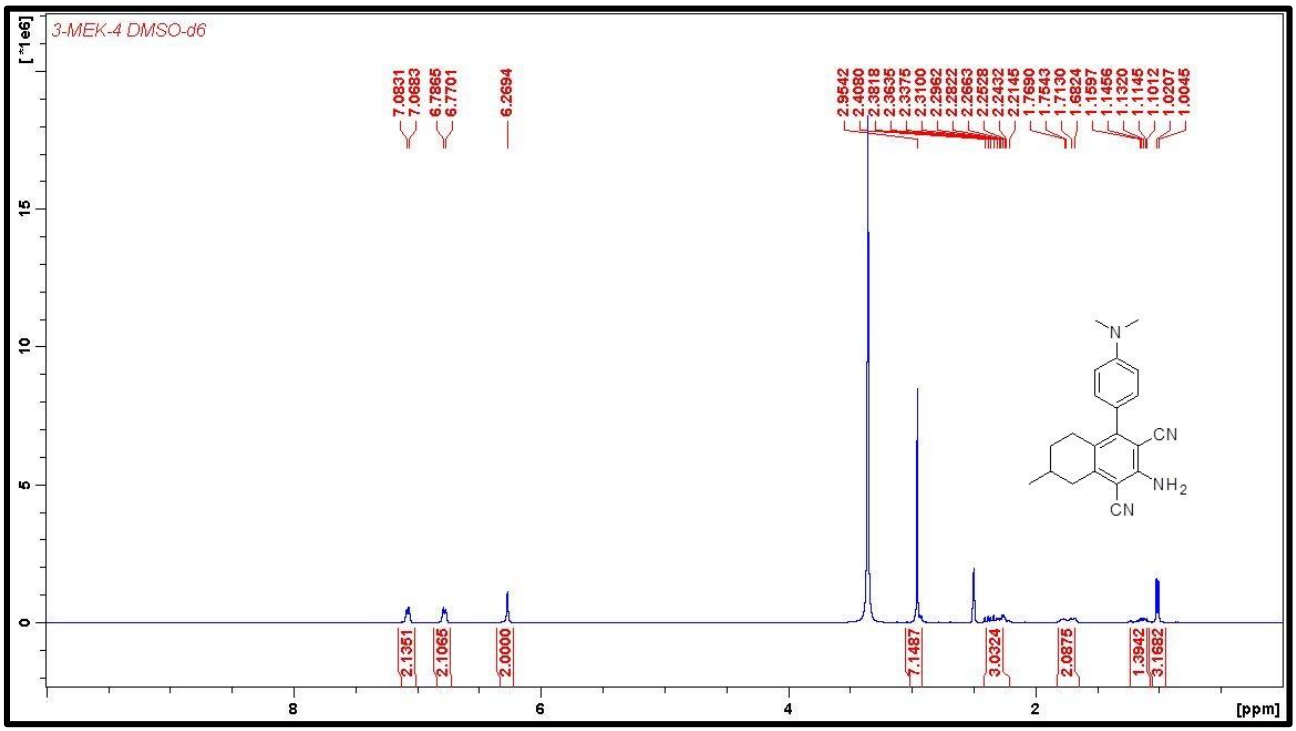
Monoisotopic Mass, Odd and Even Electron Ions
15 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20 H: 15-20 N: 0-5 O: 0-5

mek-3 3 (0.068) Cm (1:61)
TOF MS AP-

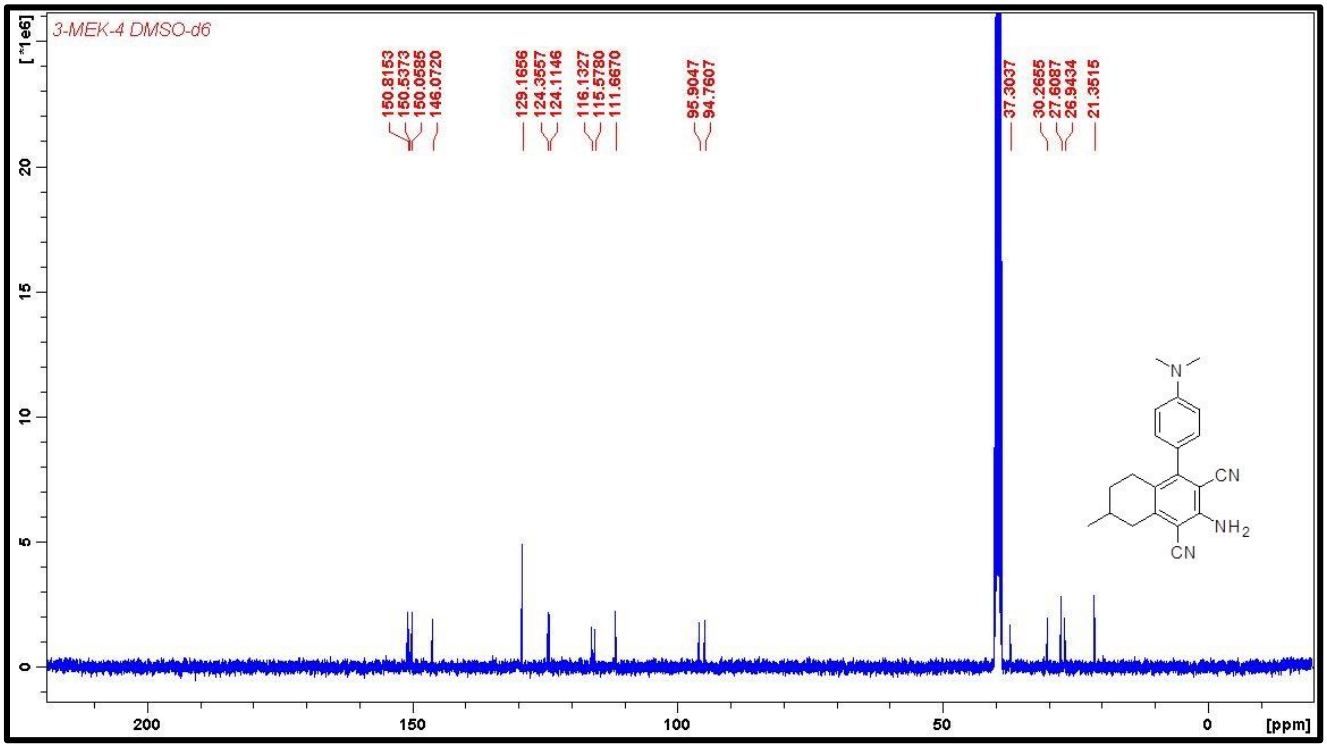



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 316.1440 | 316.1450 | -1.0 | -3.2 | 13.5 | 788.6 | 0.0 | C20 H18 N3 O |

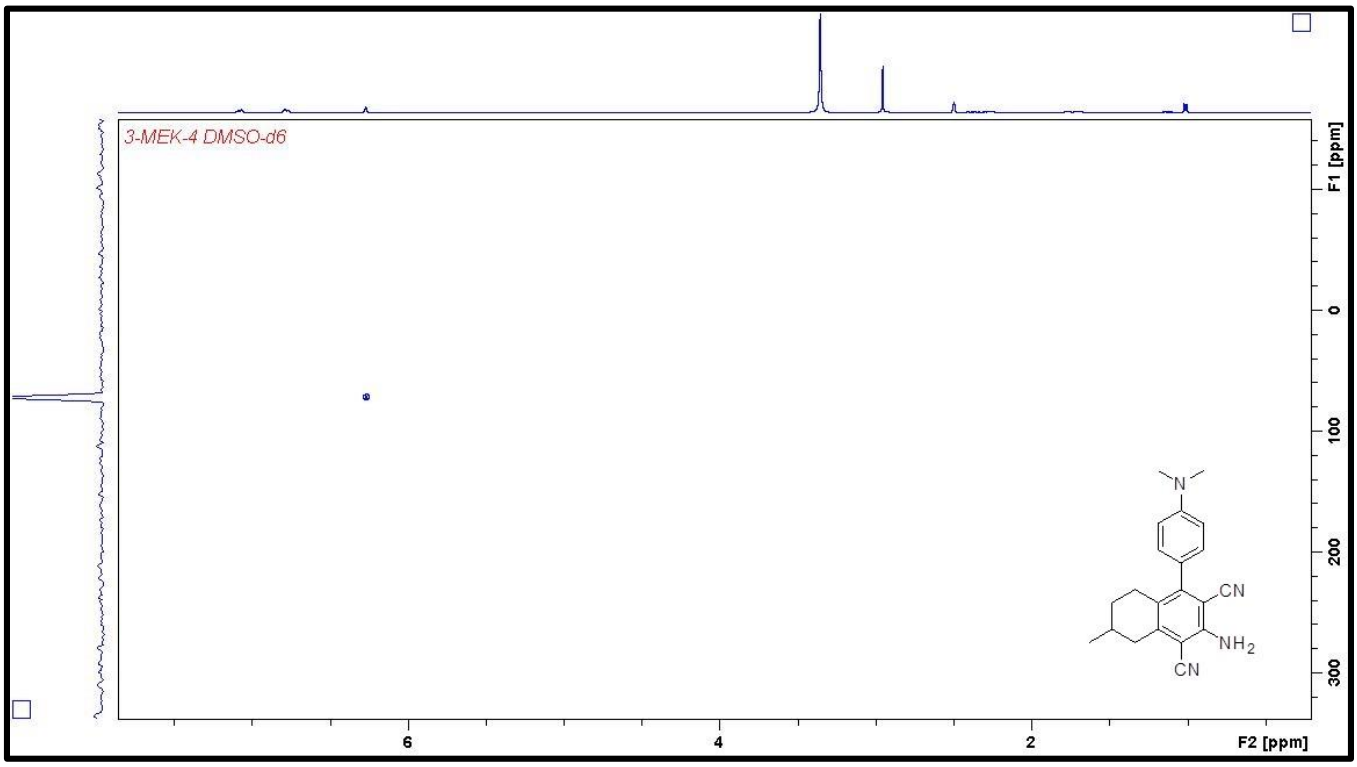
HRMS spectra of **4c**



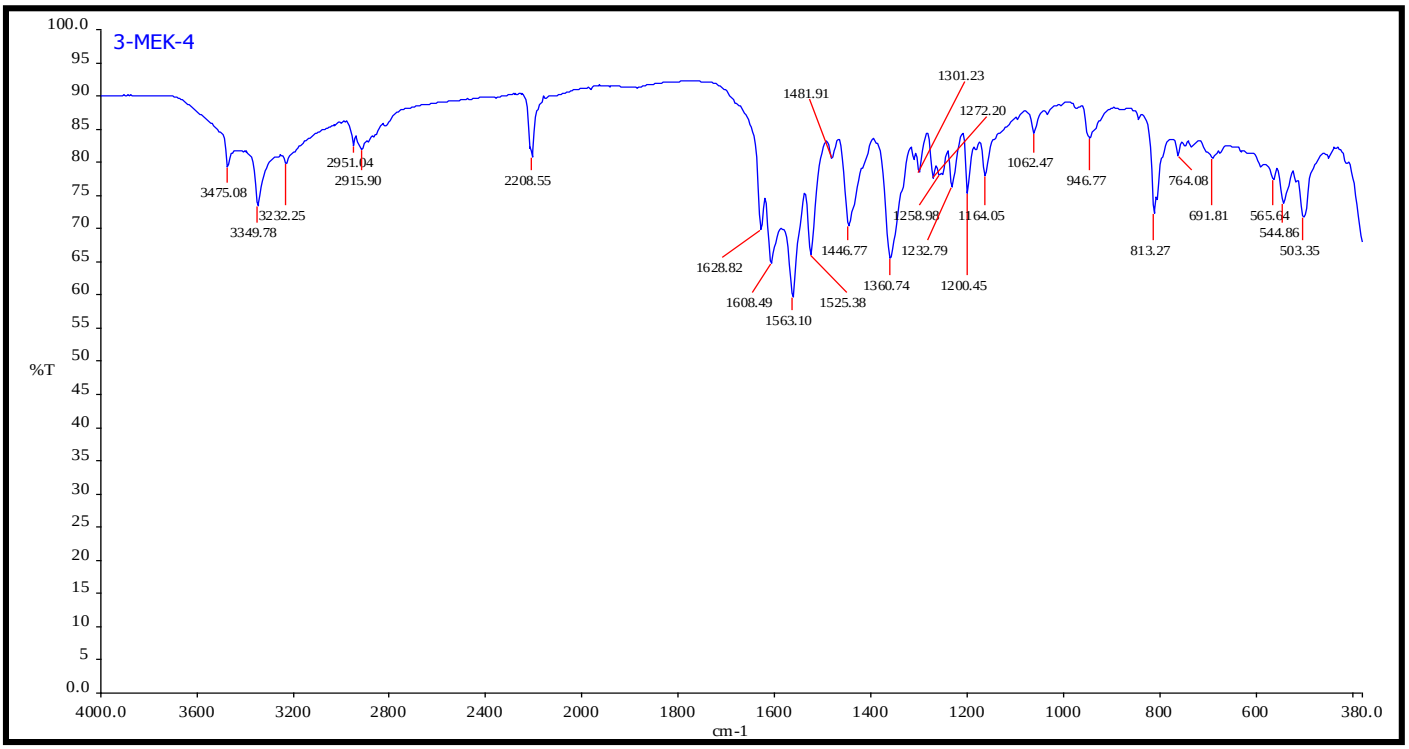

$^{1}$H NMR spectra of compound **4d**




$^{13}$C NMR spectra of compound **4d**




$^{1}$H NMR spectra of compound **4d**

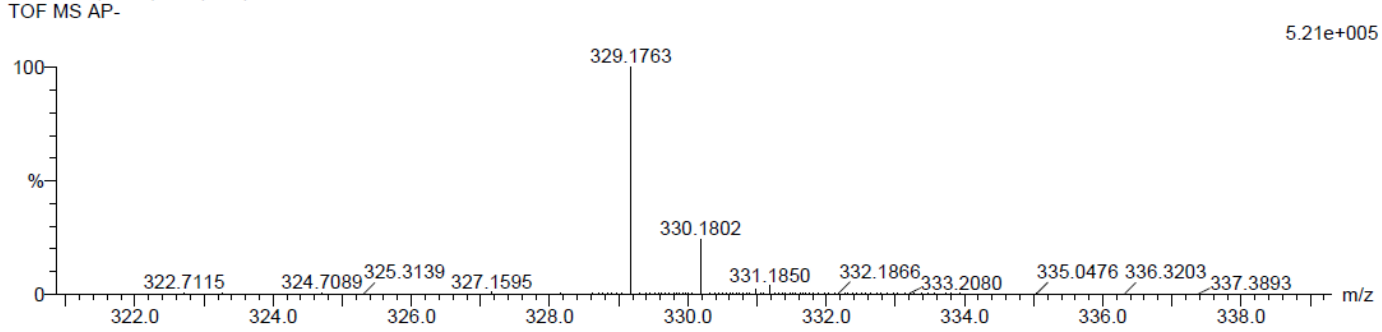



FTIR spectra of compound **4d**

**Elemental Composition Report** **Page 1**

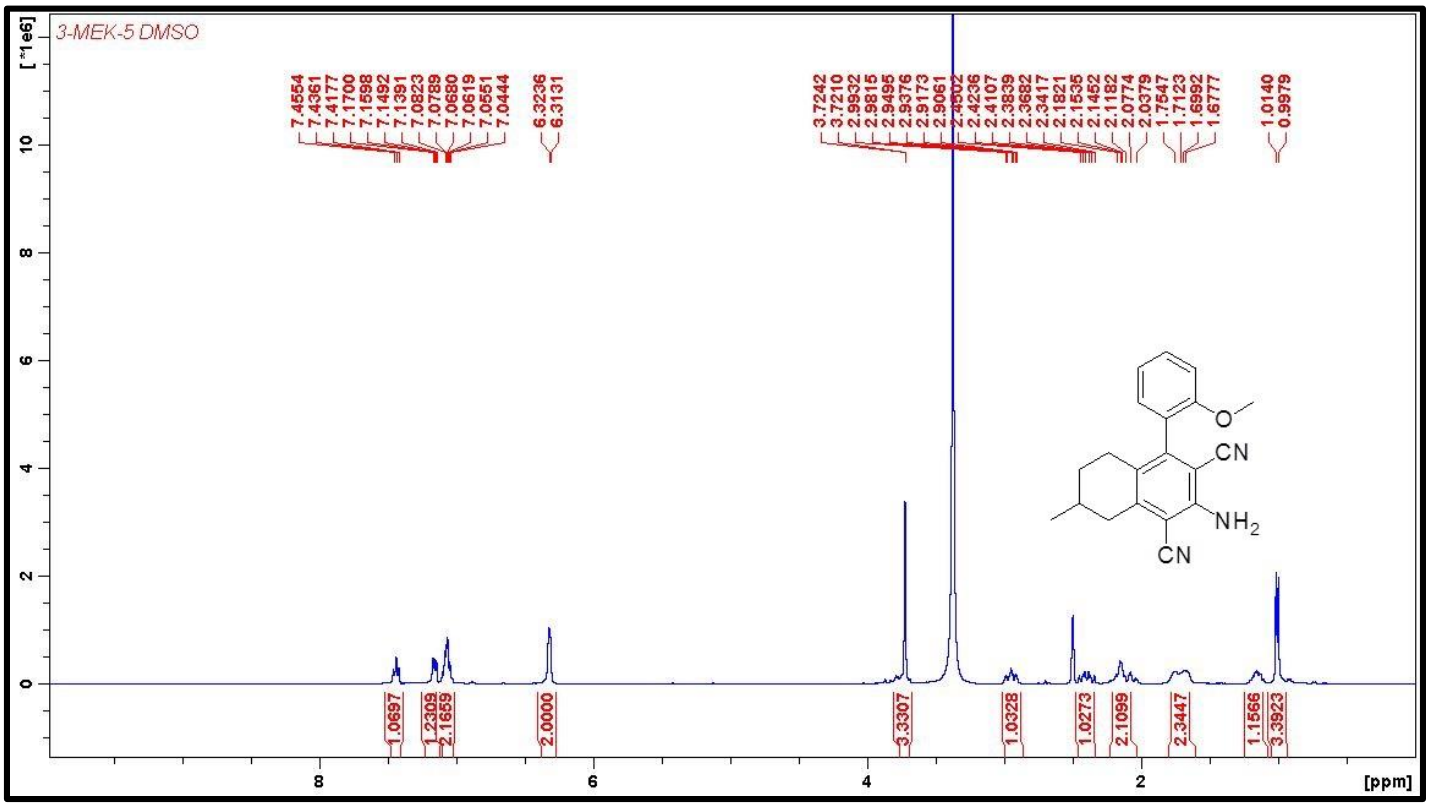
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
5 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-25 H: 15-25 N: 0-5
mek-4 34 (1.114) Cm (1:61)
TOF MS AP-

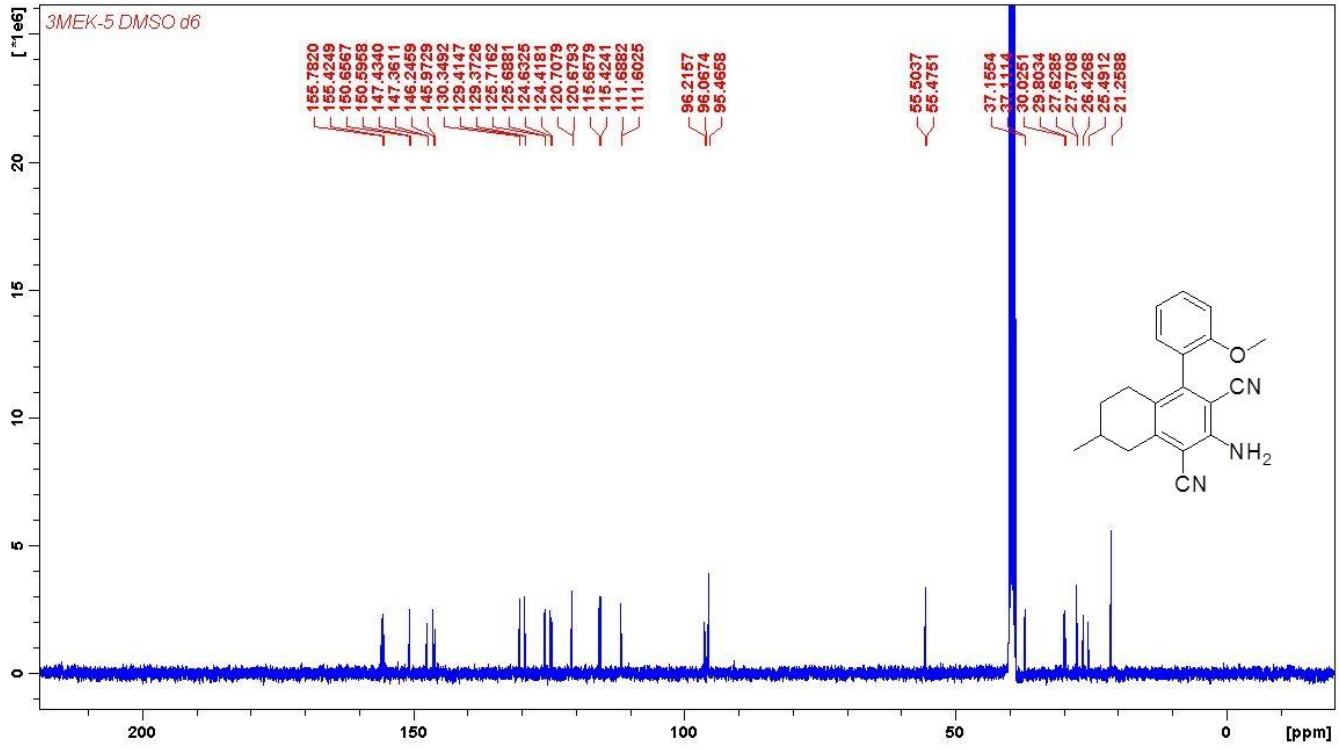



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 329.1763 | 329.1766 | -0.3 | -0.9 | 13.5 | 674.9 | 0.0 | C21 H21 N4 |

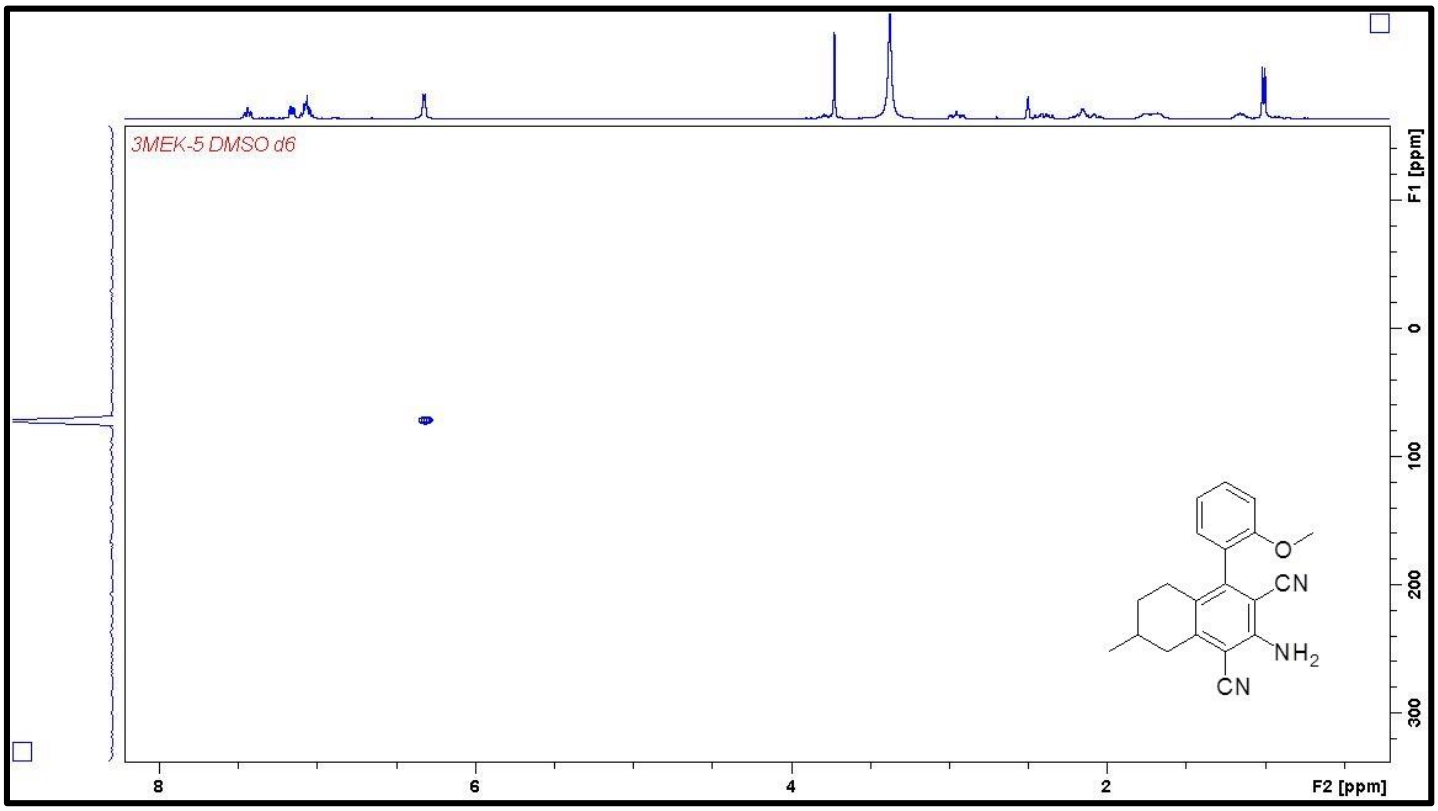
HRMS spectra of **4d**



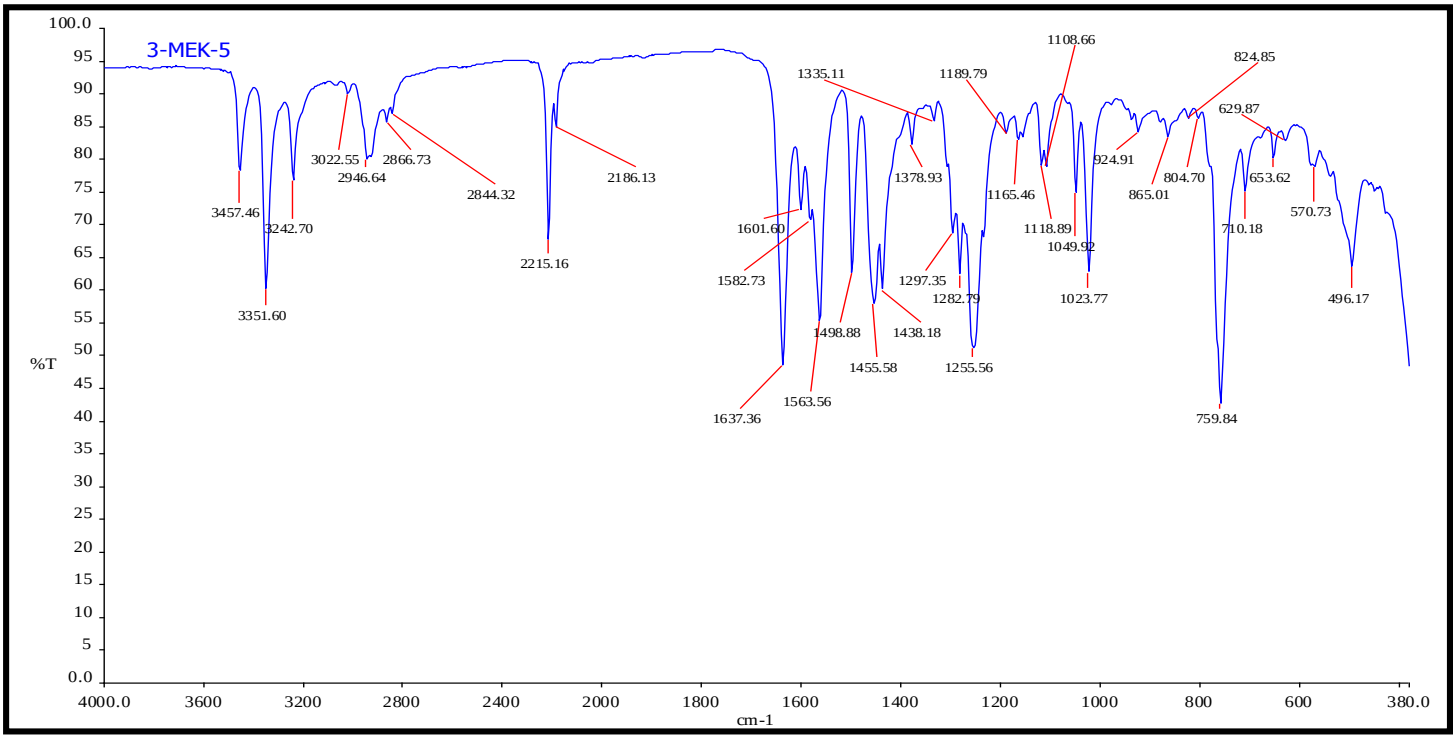

$^{1}$H NMR spectra of compound **4e**




$^{13}$C NMR spectra of compound **4e**




$^{15}$N NMR (ghsqc) spectra of compound **4e**

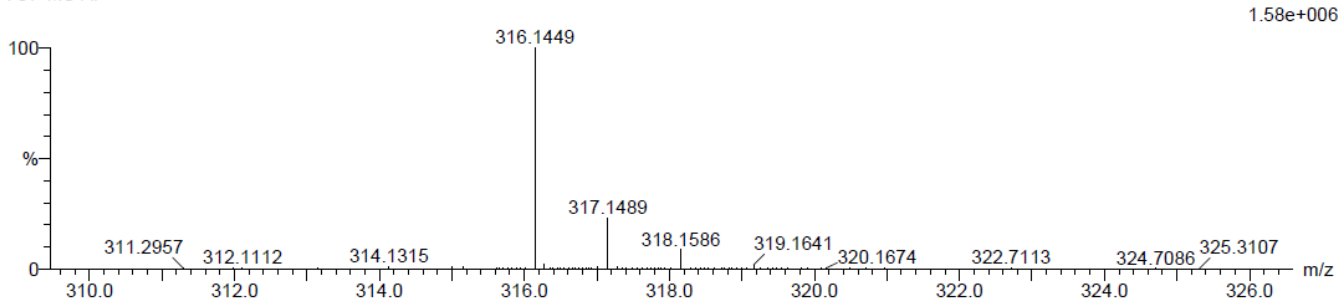



FTIR spectra of compound **4e**

**Elemental Composition Report** **Page 1**

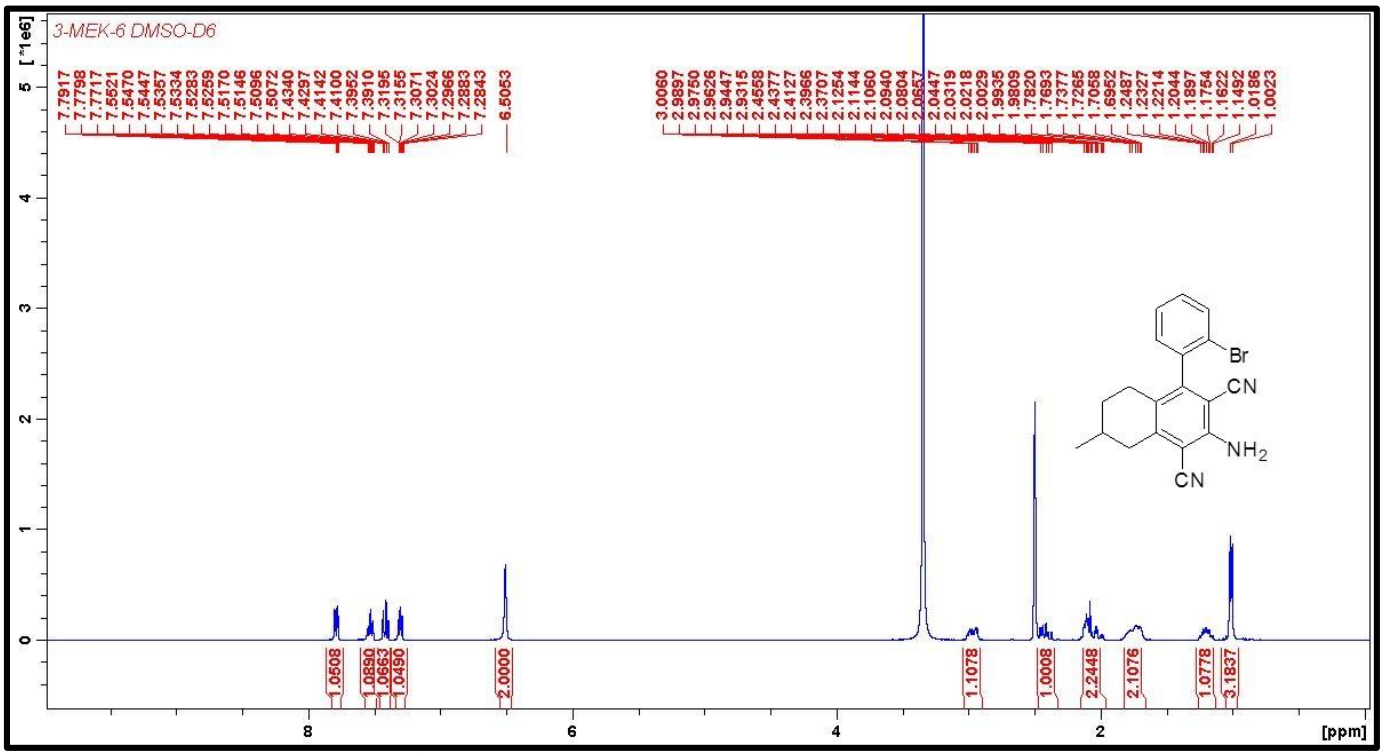
**Single Mass Analysis**
Tolerance = 4.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
23 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 15-20 N: 0-5 O: 0-5
mek-5 58 (1.924) Cm (1:61)
TOF MS AP-

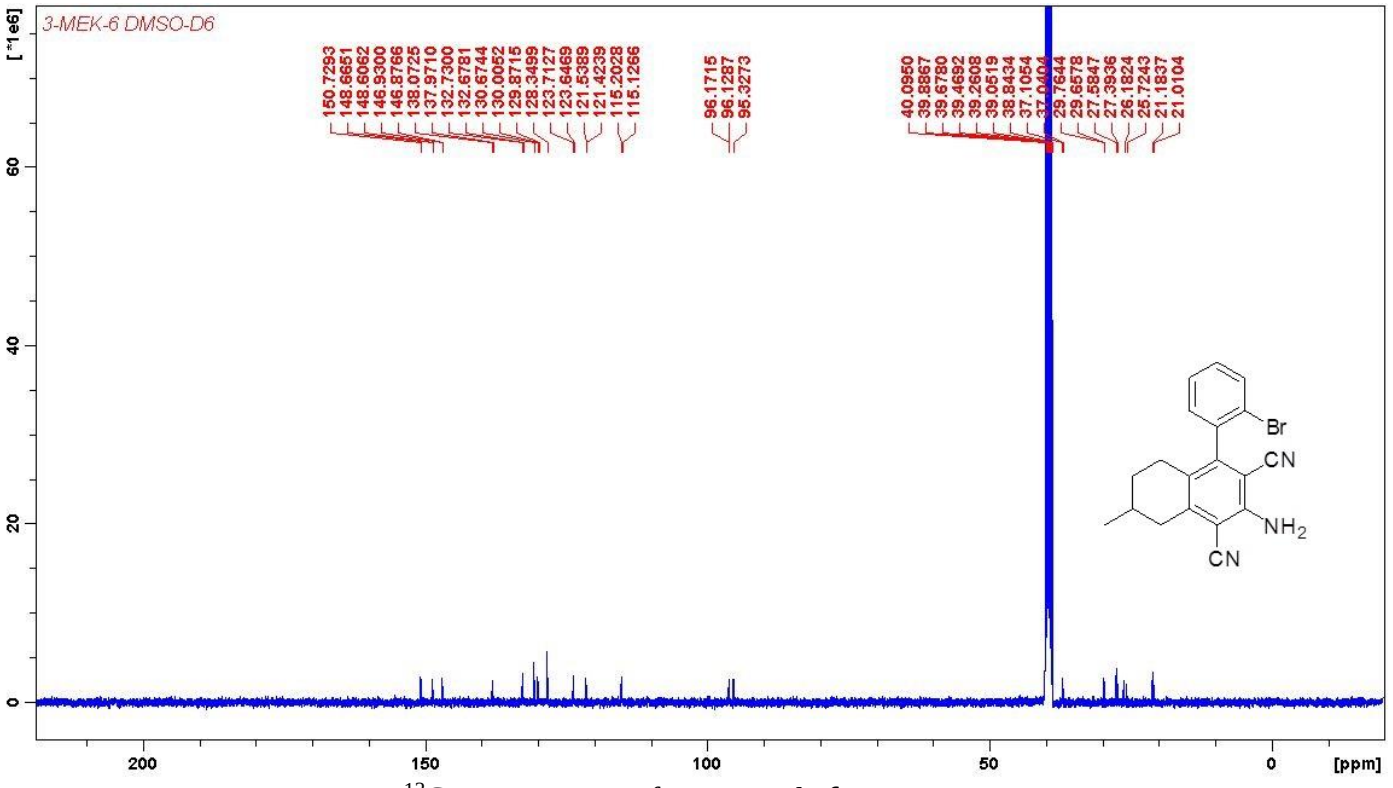



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 4.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 316.1449 | 316.1450 | -0.1 | -0.3 | 13.5 | 773.1 | 0.0 | C20 H18 N3 O |

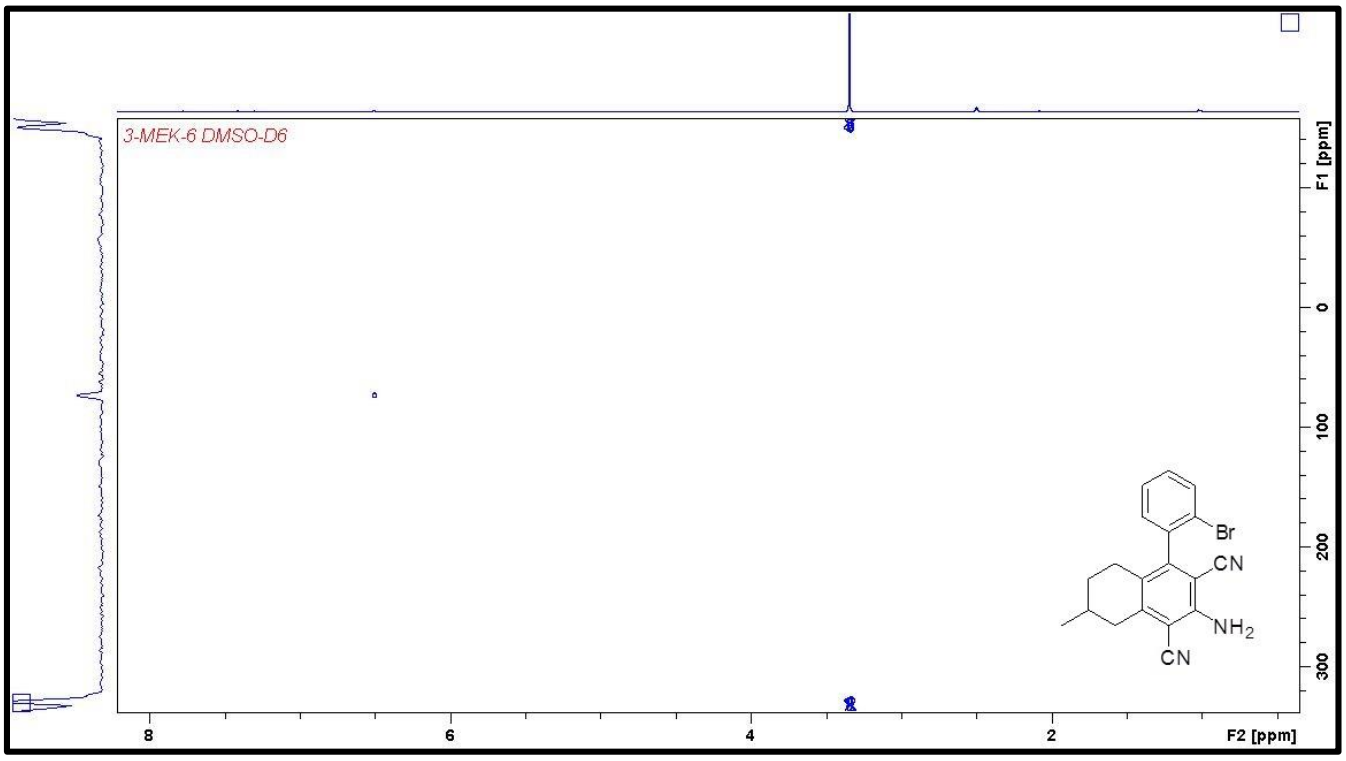
HRMS spectra of **4e**



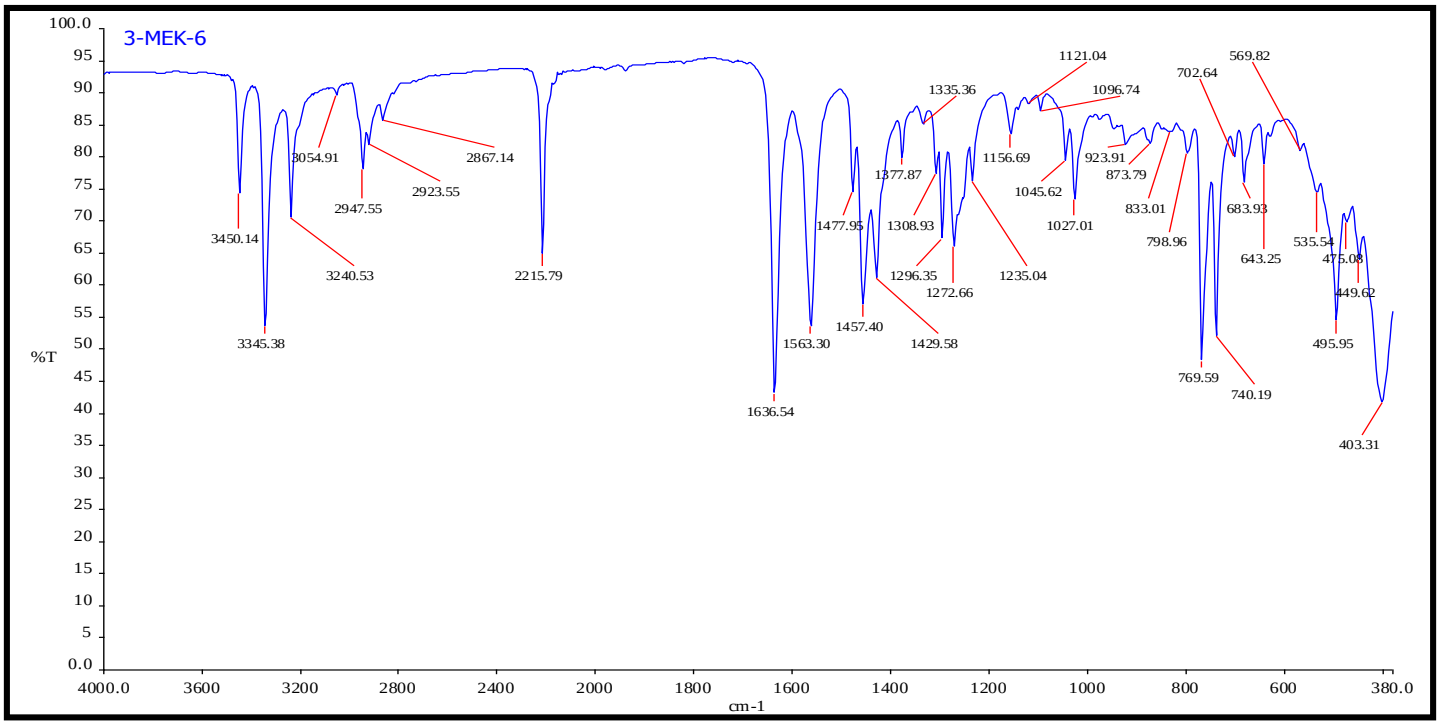

$^{1}$H NMR spectra of compound **4f**




$^{13}$C NMR spectra of compound **4f**




$^{15}$N NMR spectra of compound **4f**



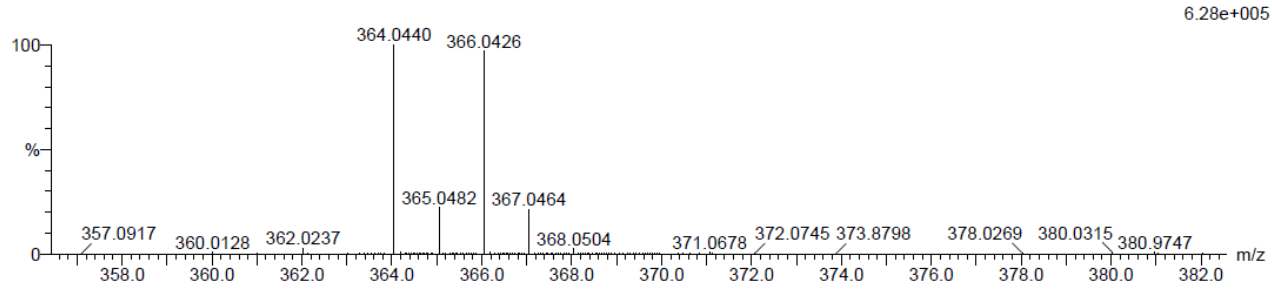

FTIR spectra of compound **4f**

**Elemental Composition Report** **Page 1**

**Single Mass Analysis**
Tolerance = 4.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

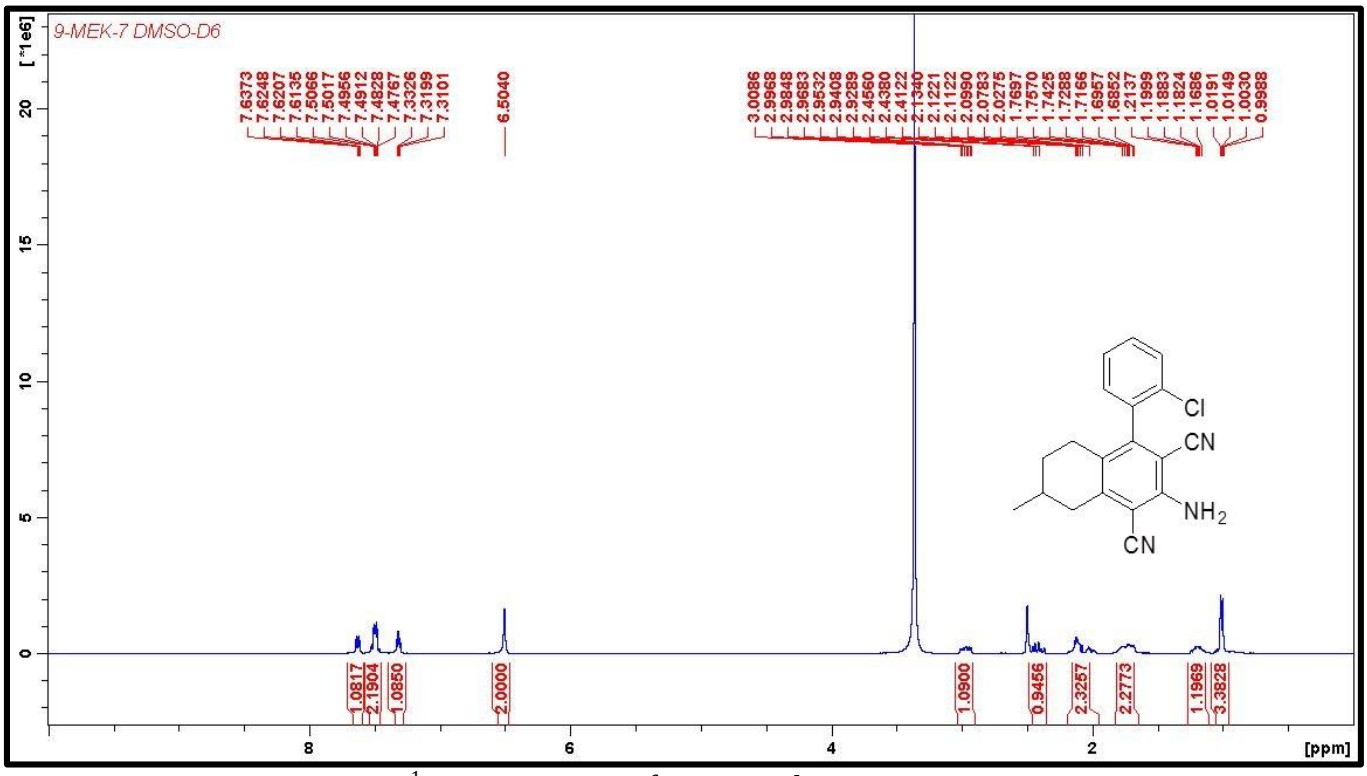
Monoisotopic Mass, Odd and Even Electron Ions
7 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20 H: 15-20 N: 0-5 Br: 0-1

mek-6 2 (0.034) Cm (1:61)
TOF MS AP-

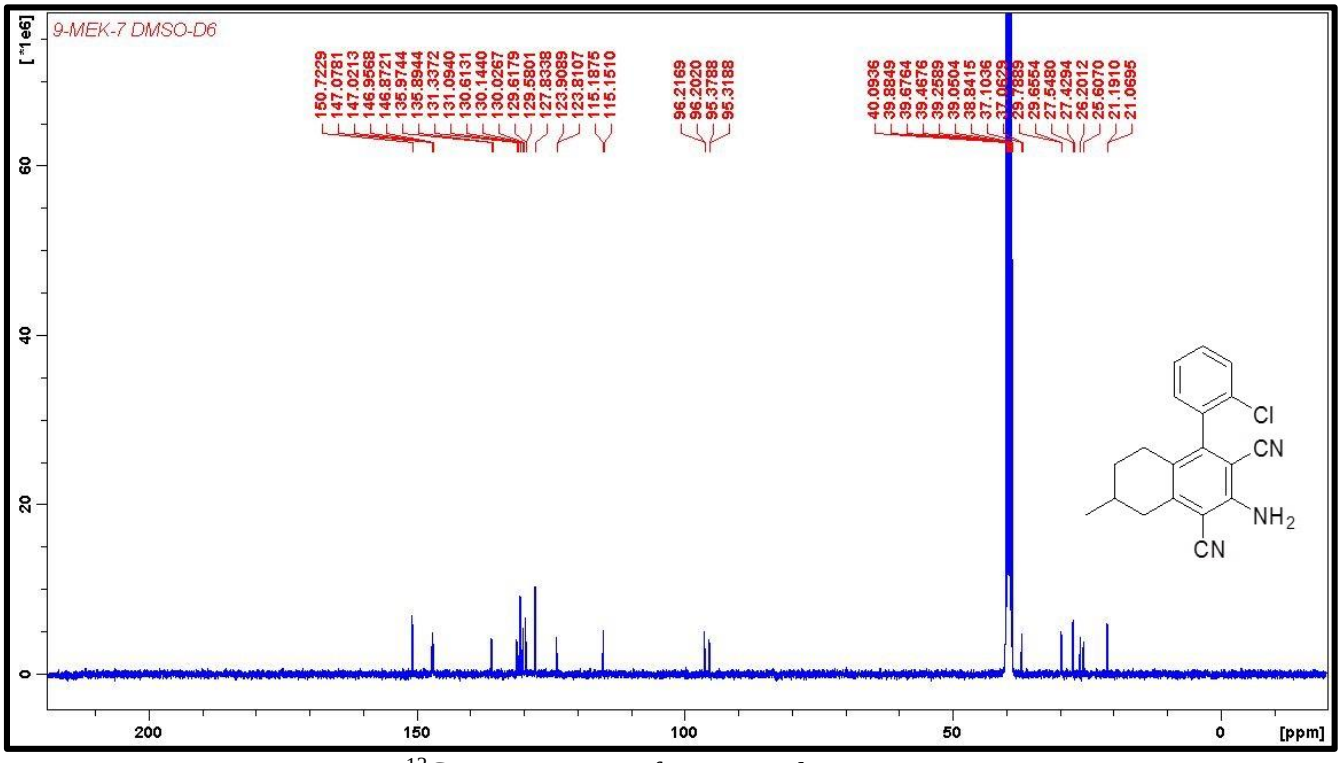



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 4.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 364.0440 | 364.0449 | -0.9 | -2.5 | 13.5 | 694.2 | 0.0 | C19 H15 N3 Br |

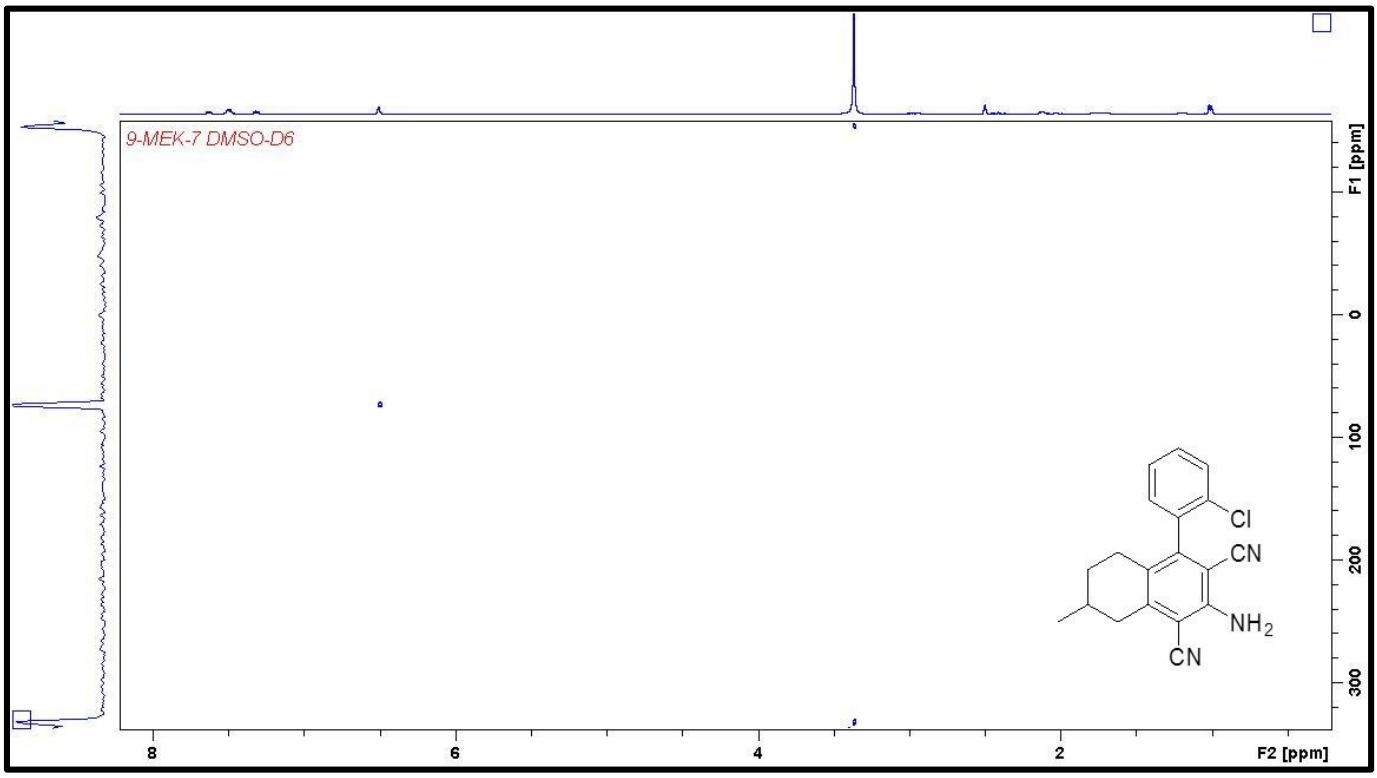
HRMS spectra of **4f**



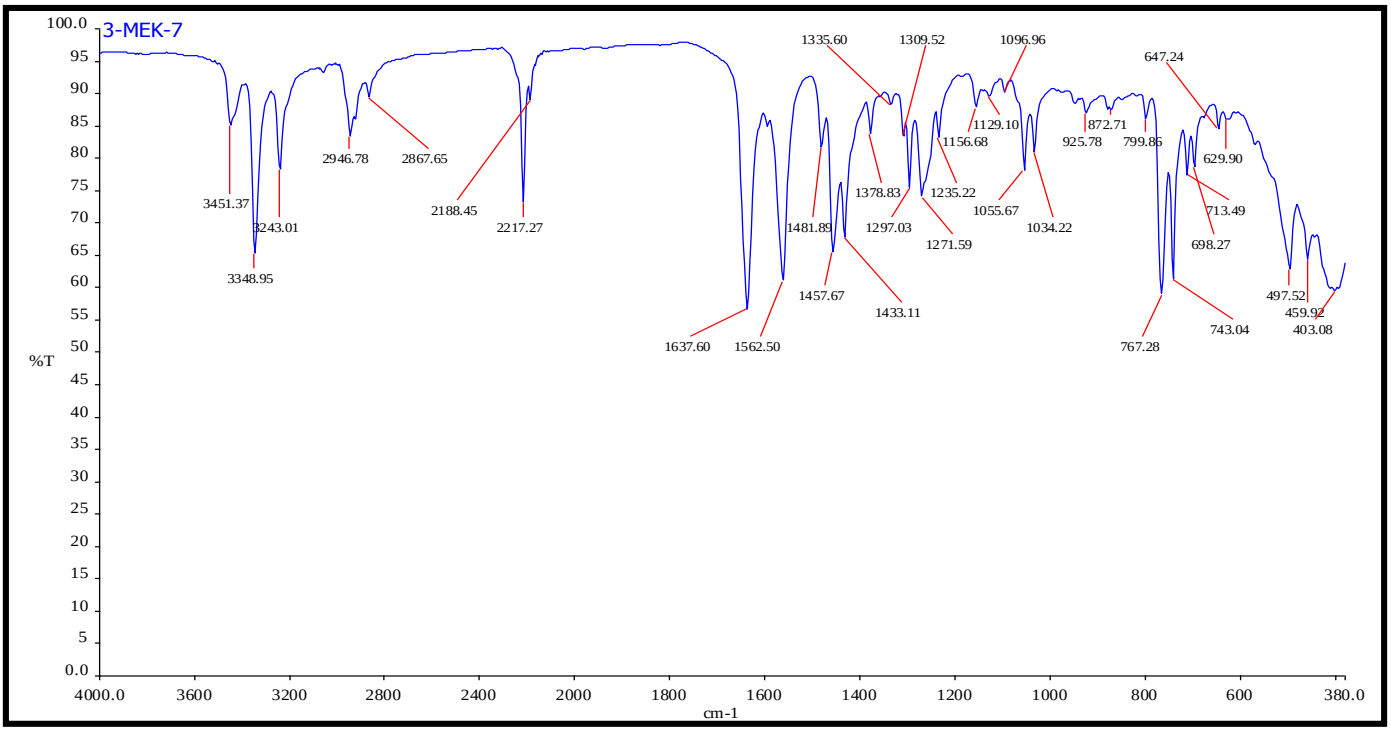

$^{1}$H NMR spectra of compound **4g**




$^{13}$C NMR spectra of compound **4g**




$^{15}$N NMR (ghsqc) spectra of compound **4g**

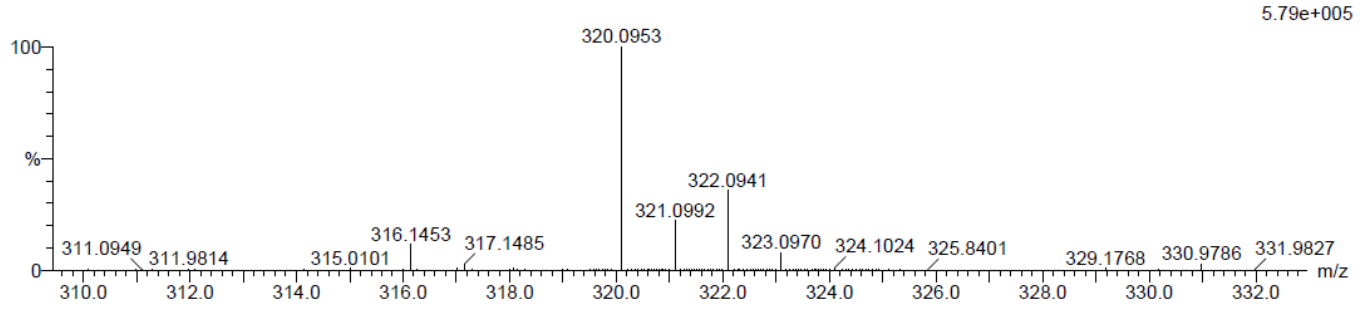



FTIR spectra of compound **4g**

**Elemental Composition Report** **Page 1**

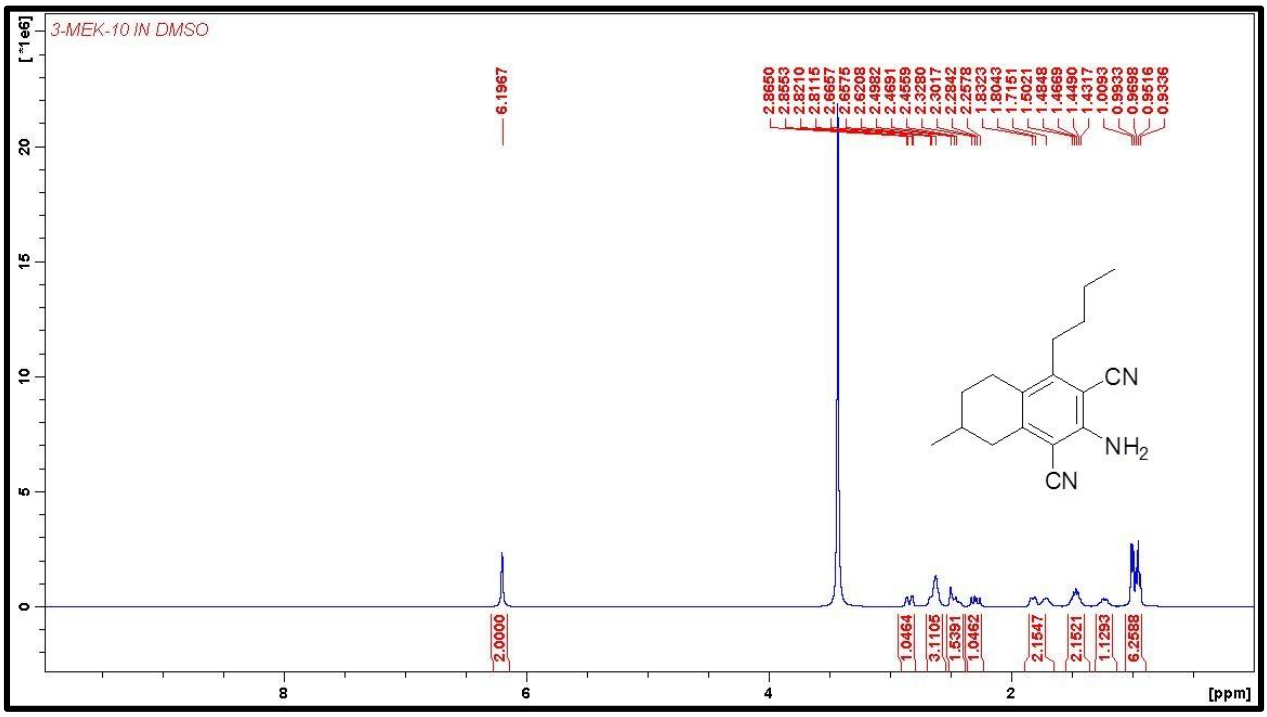
**Single Mass Analysis**
Tolerance = 4.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
4 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20 H: 15-20 N: 0-5 Cl: 0-1
mek-7 4 (0.102) Cm (1:61)
TOF MS AP-

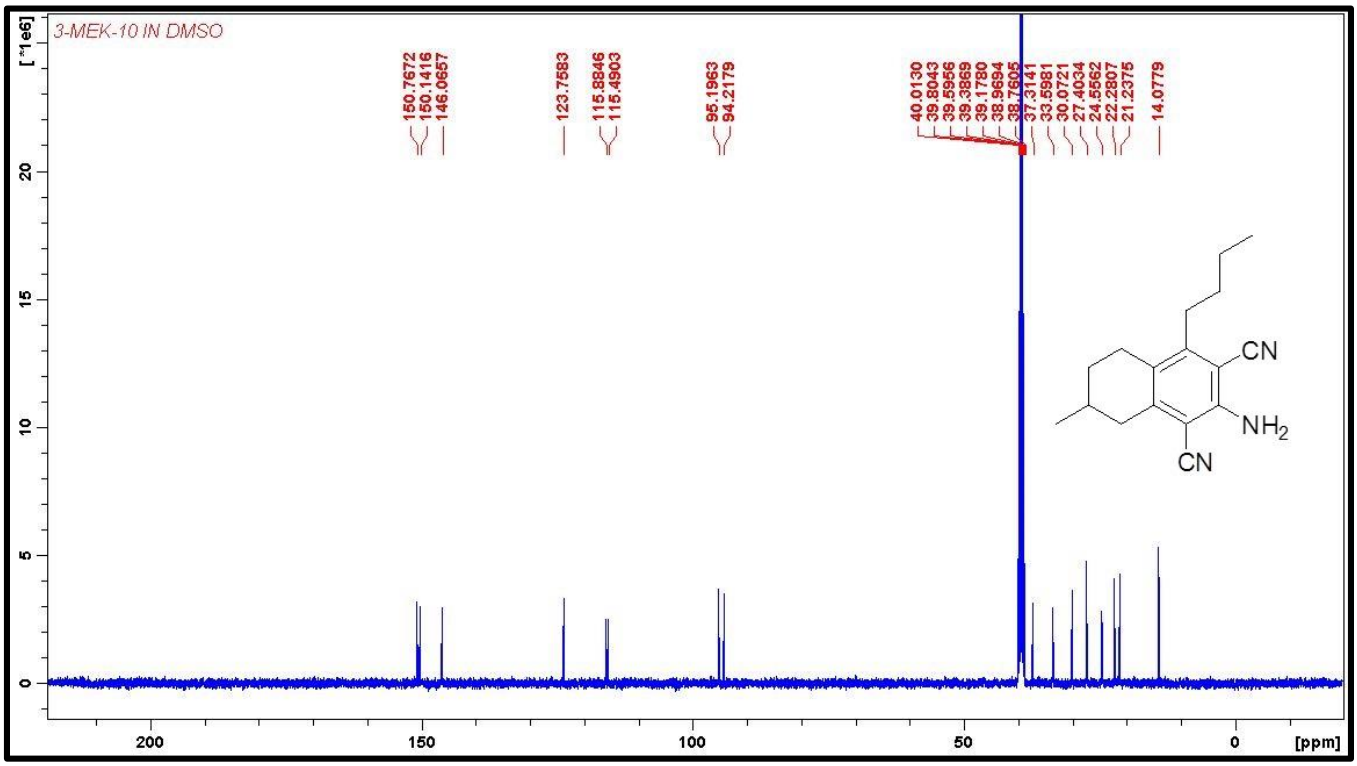



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 4.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 320.0953 | 320.0955 | -0.2 | -0.6 | 13.5 | 697.5 | 0.0 | C19 H15 N3 Cl |

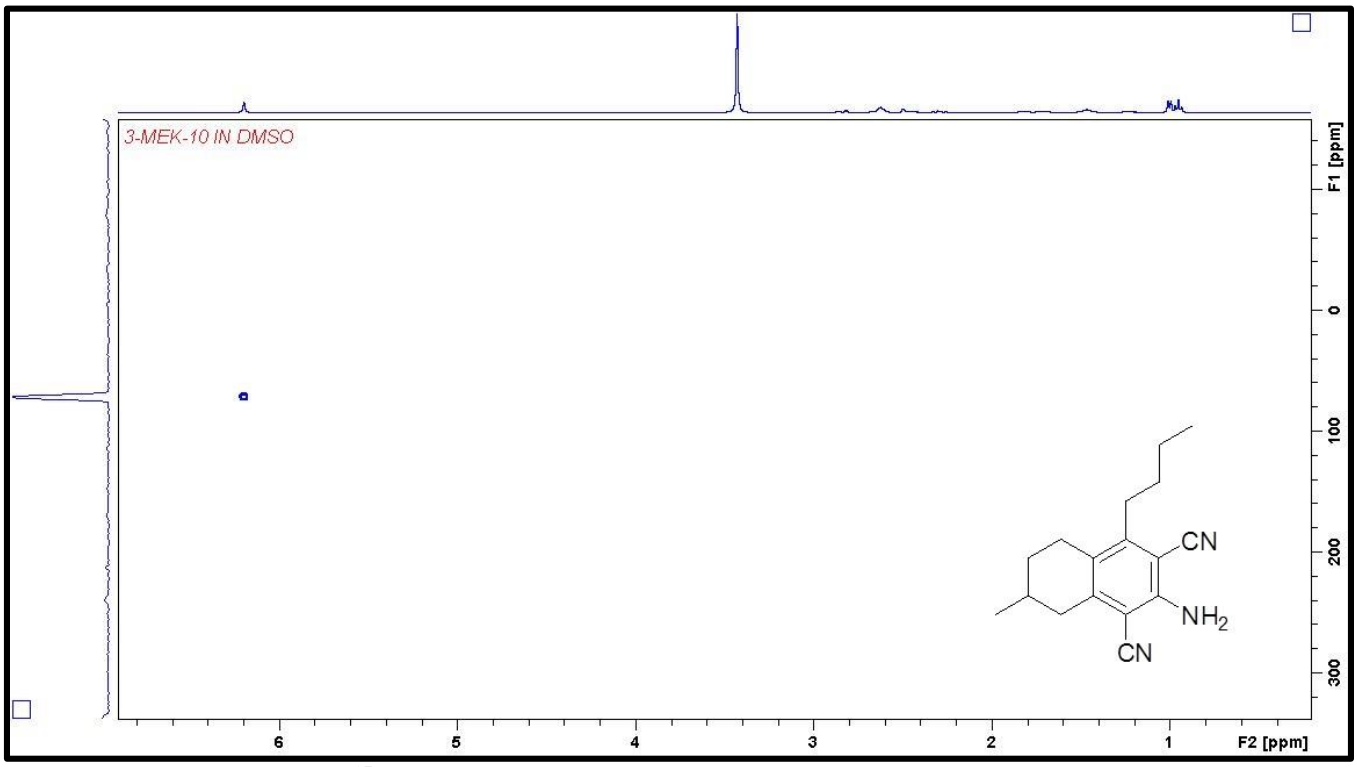
HRMS spectra of **4g**



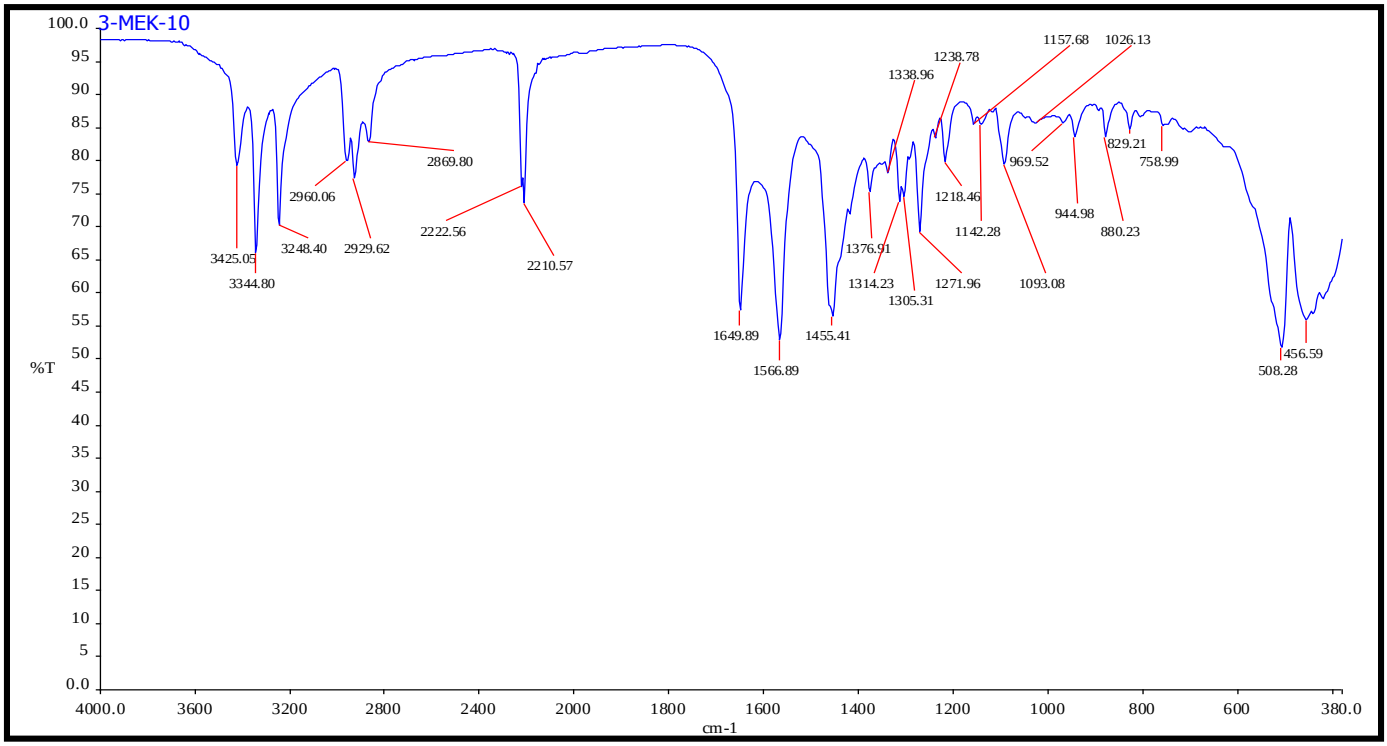

$^{1}$H NMR spectra of compound **4h**



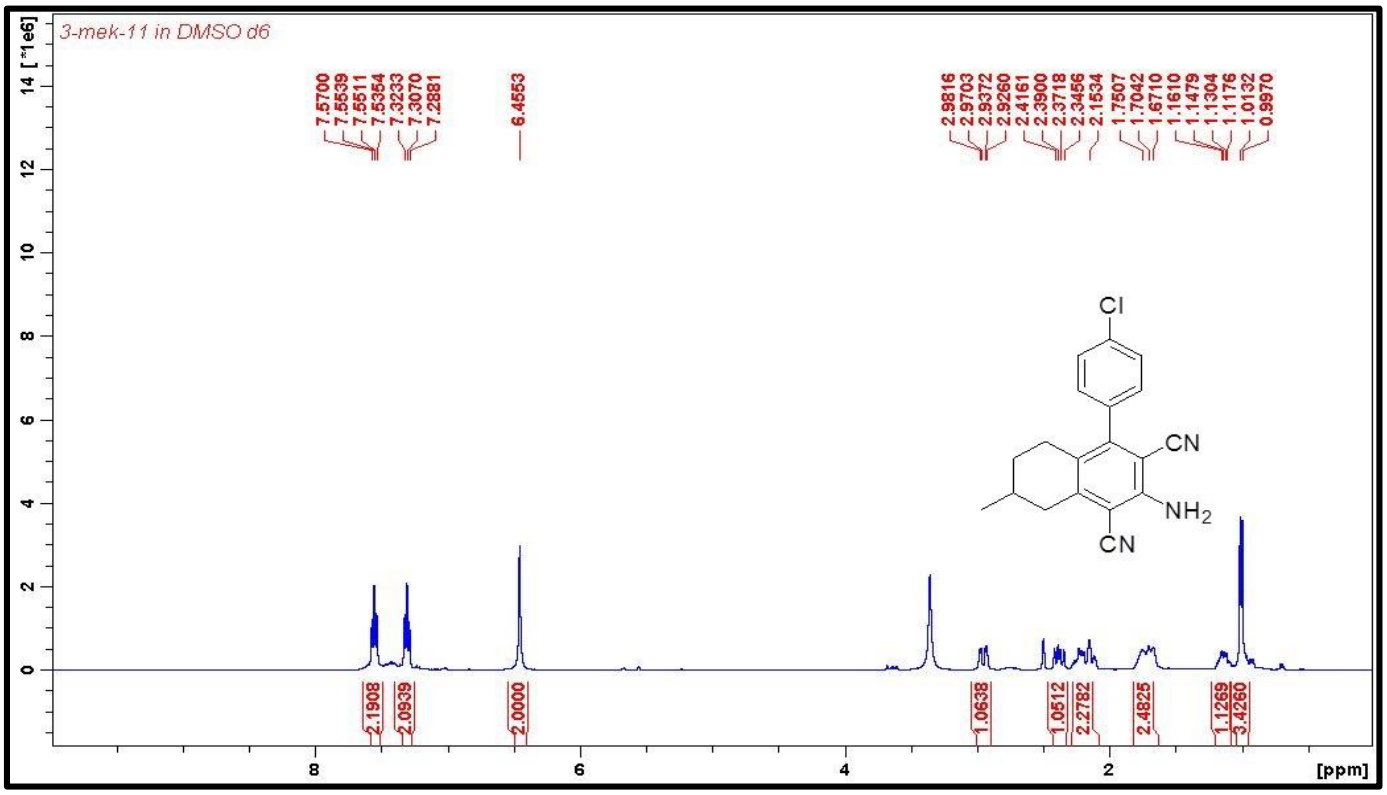

$^{13}$C NMR spectra of compound **4h**



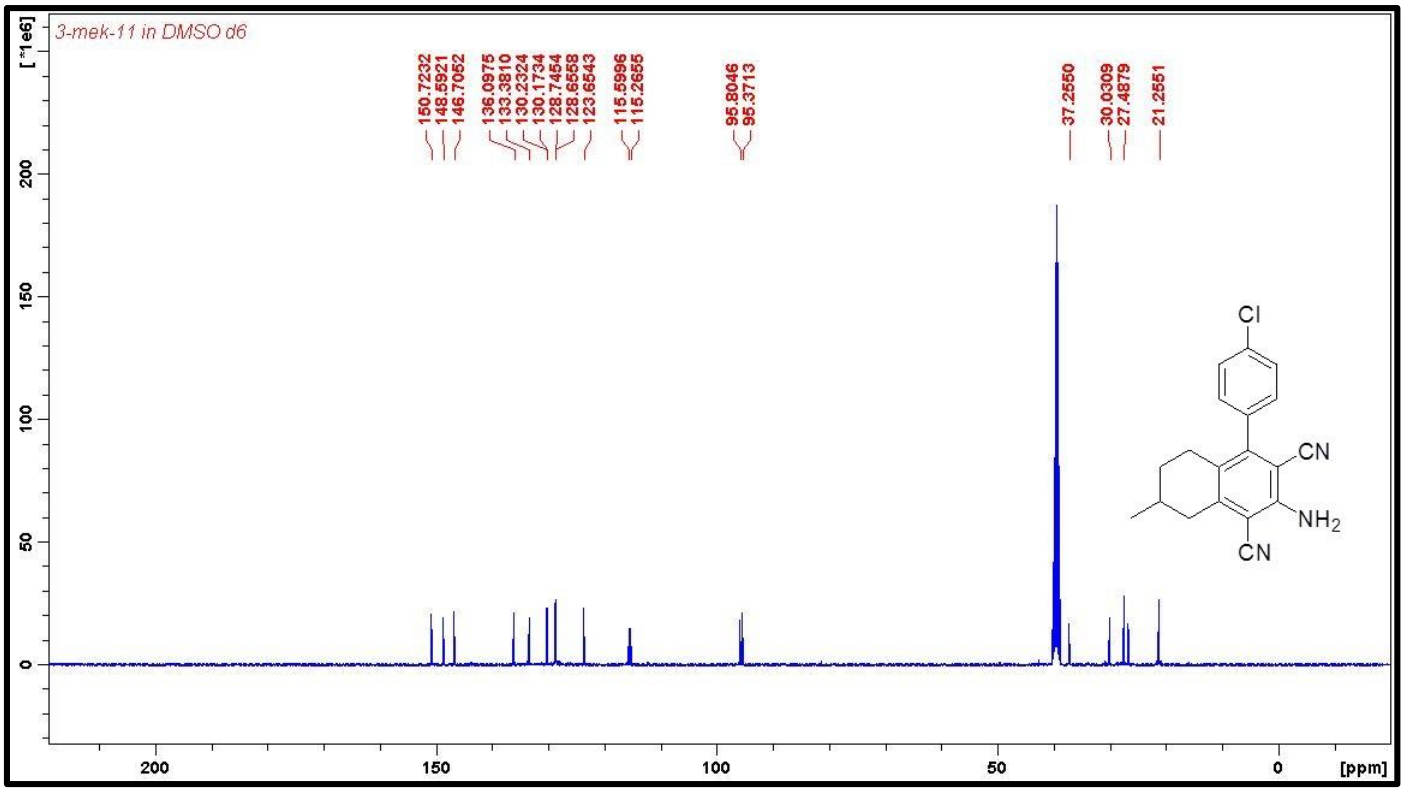

$^{15}$N NMR (ghsqc) spectra of compound **4h**



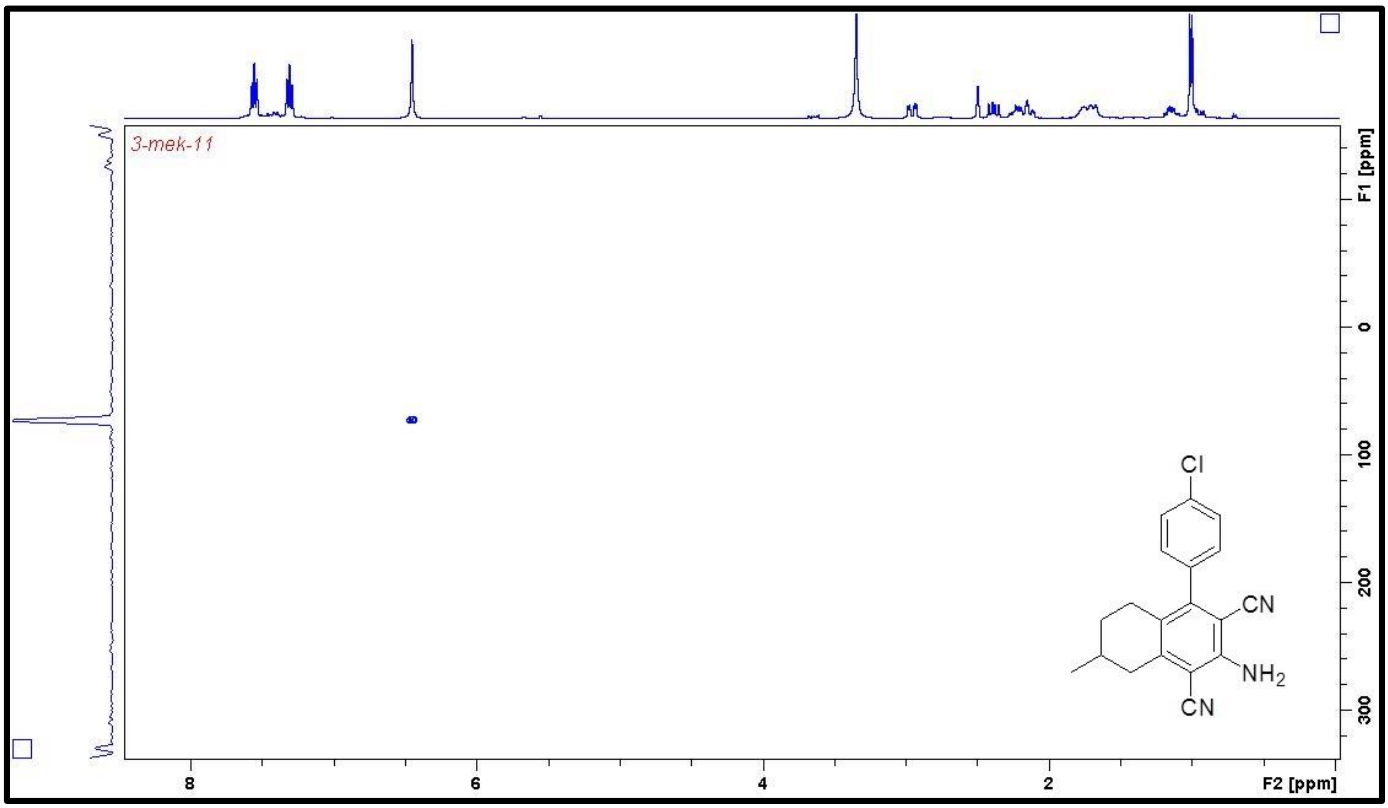

FTIR spectra of compound **4h**



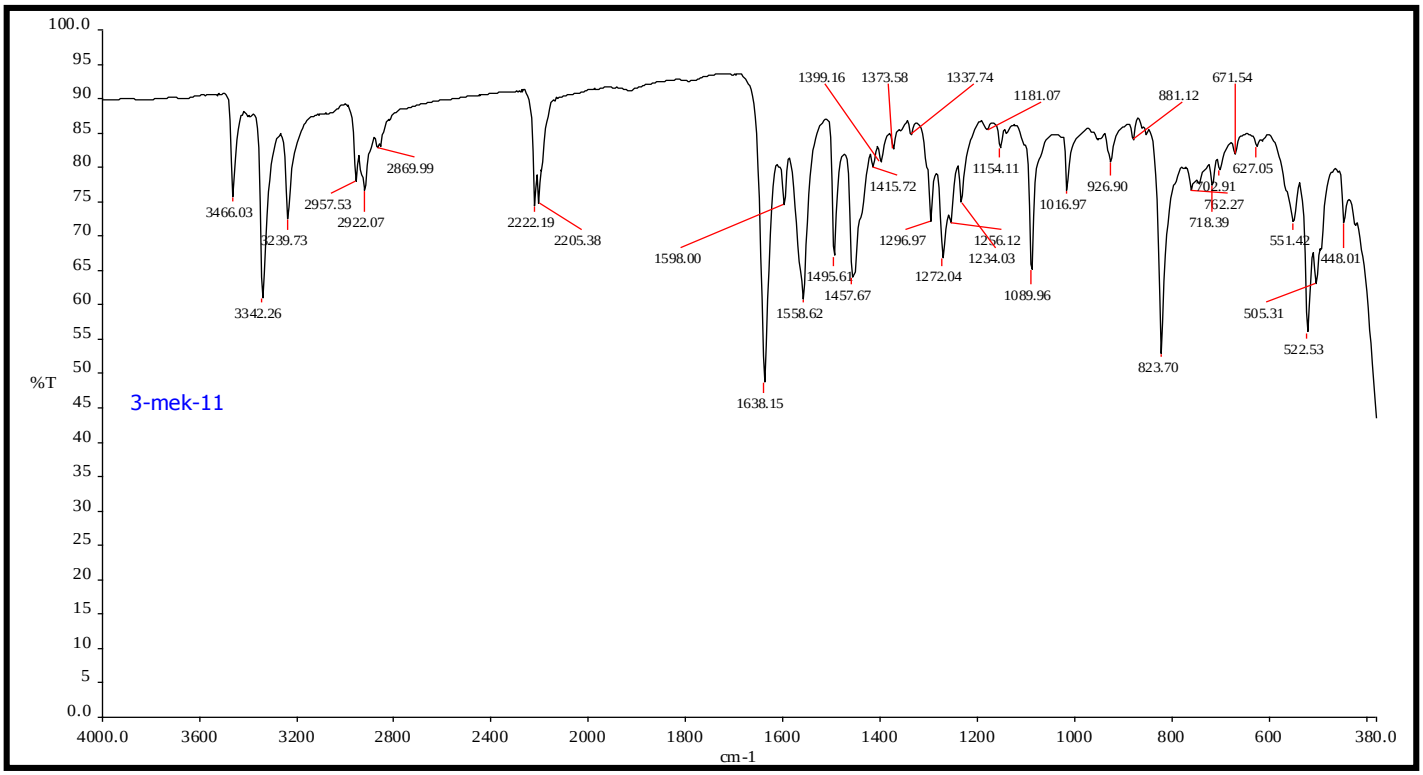

$^{1}$H NMR spectra of compound **4i**




$^{13}$C NMR spectra of compound **4i**




$^{15}$N NMR (ghsqc) spectra of compound **4i**

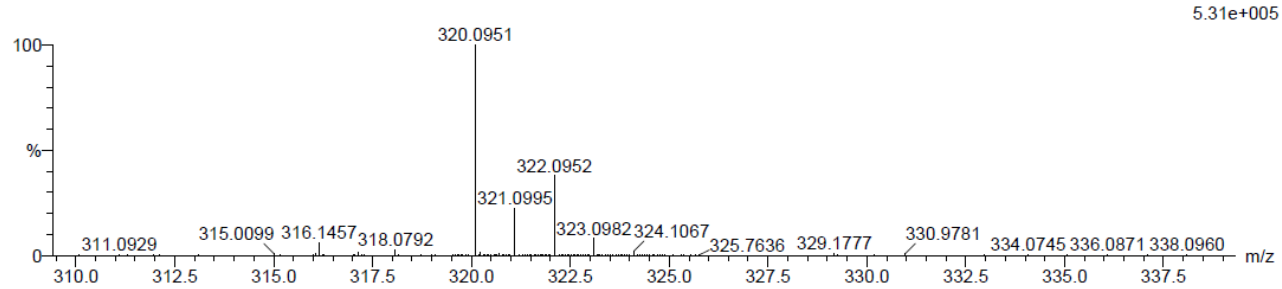



FTIR spectra of compound **4i**

**Elemental Composition Report** **Page 1**

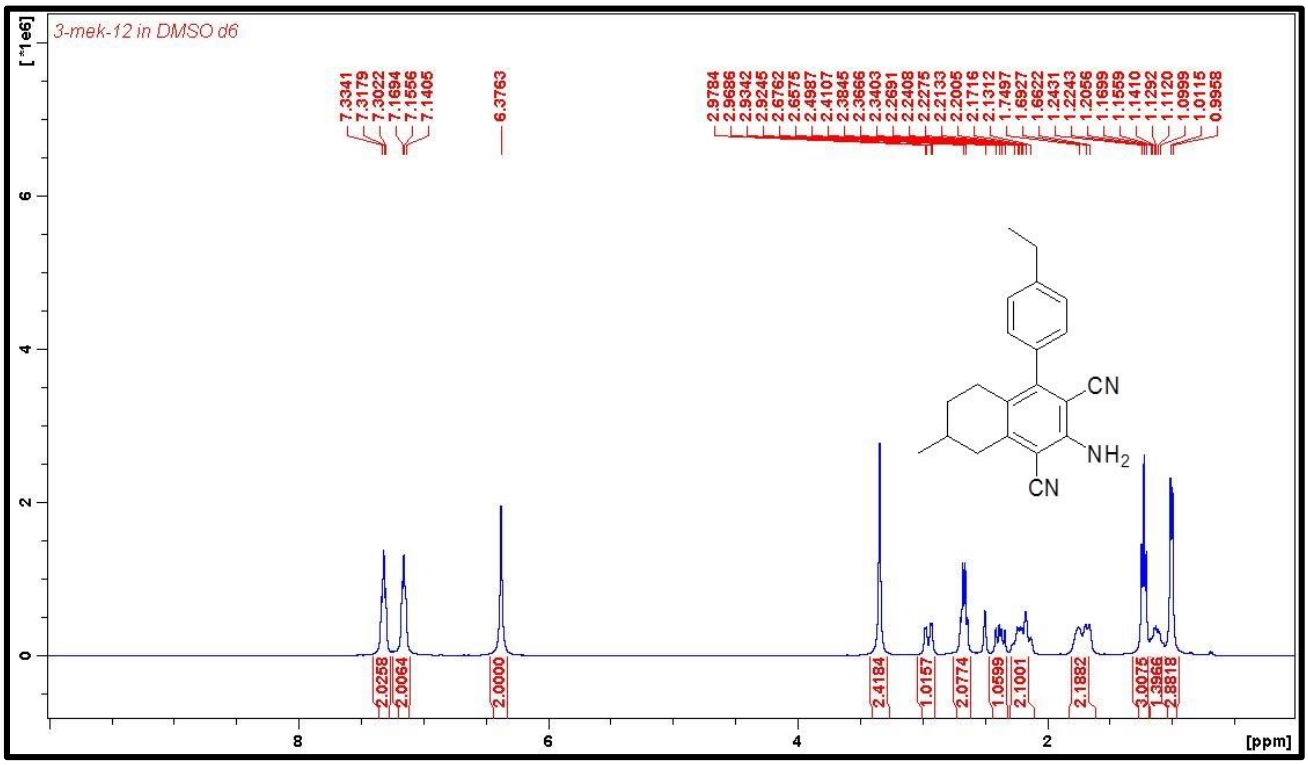
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
4 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20 H: 15-20 N: 0-5 Cl: 0-1
mek-11 31 (0.511) Cm (1:59)
TOF MS AP-

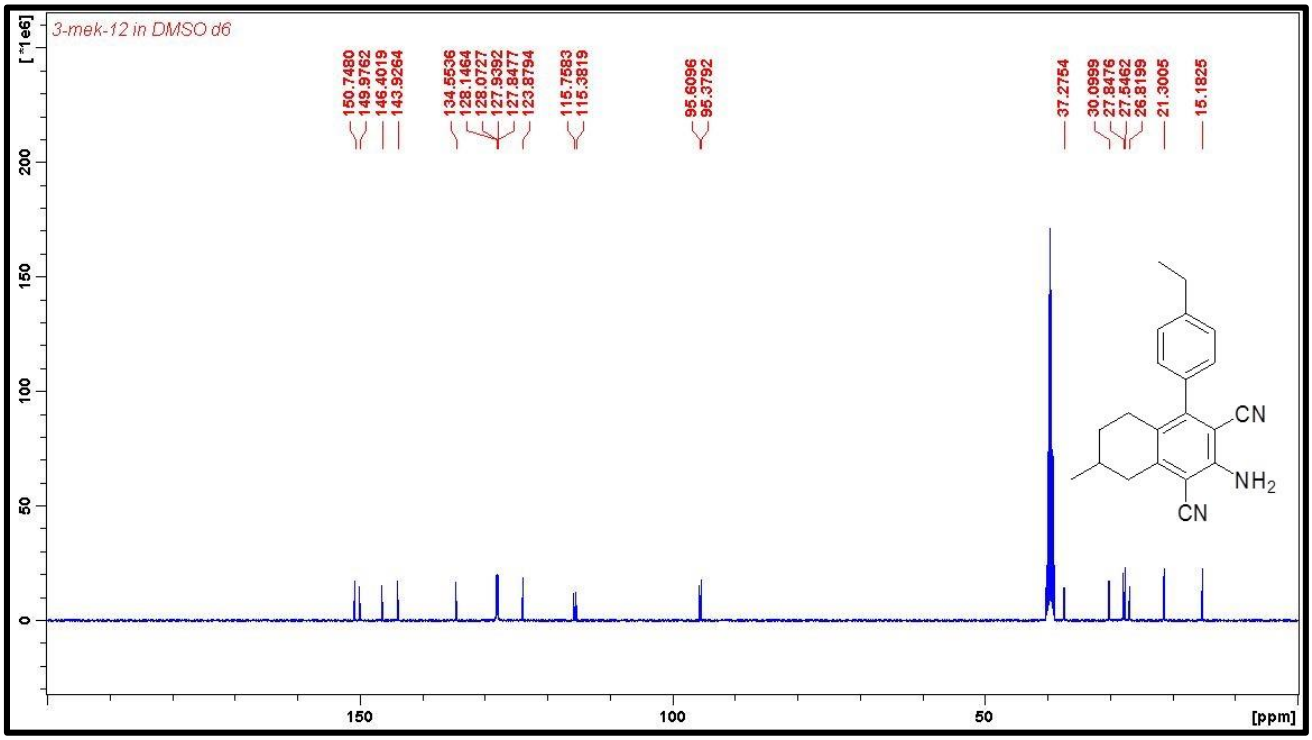



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 320.0951 | 320.0955 | -0.4 | -1.2 | 13.5 | 693.2 | 0.0 | C19 H15 N3 Cl |

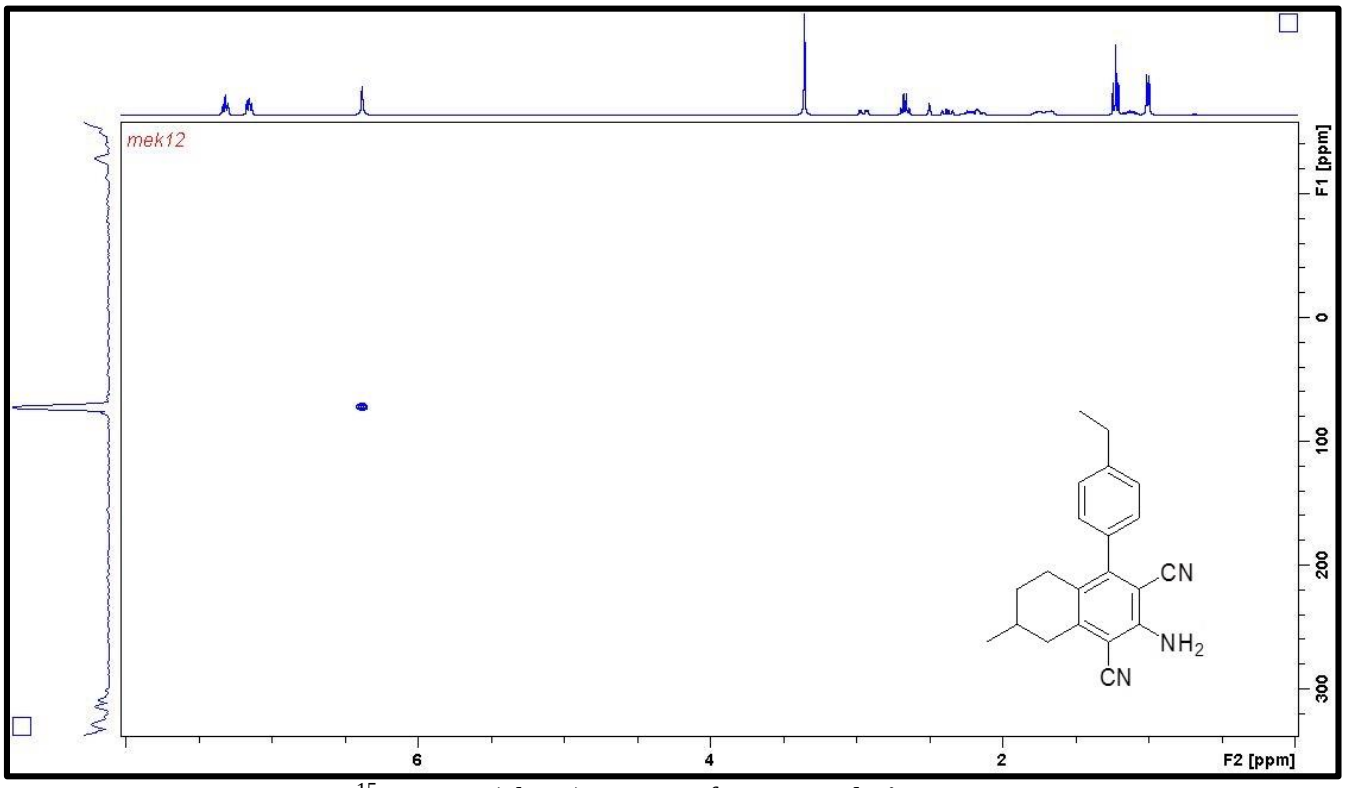
HRMS spectra of **4i**



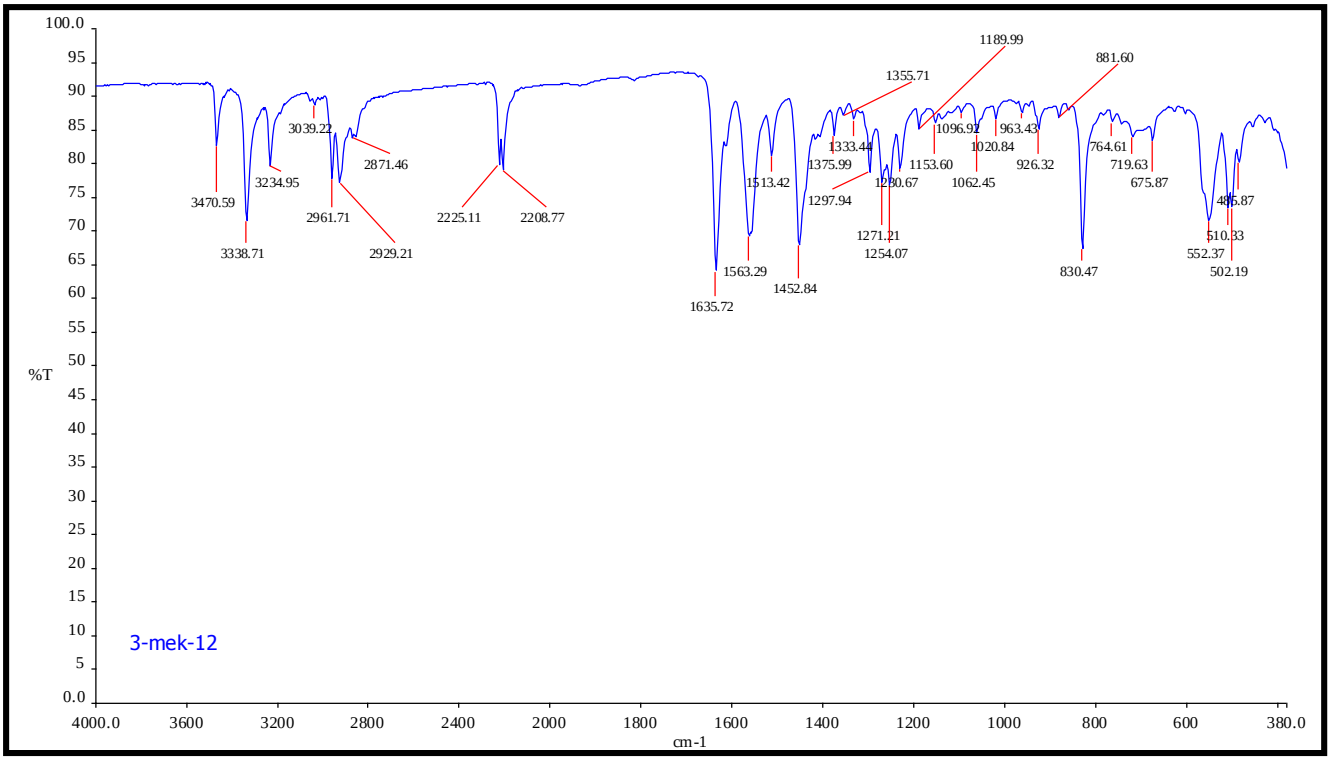

$^{1}$H NMR spectra of compound **4j**




$^{13}$C NMR spectra of compound **4j**




$^{15}$N NMR (ghsqc) spectra of compound **4j**

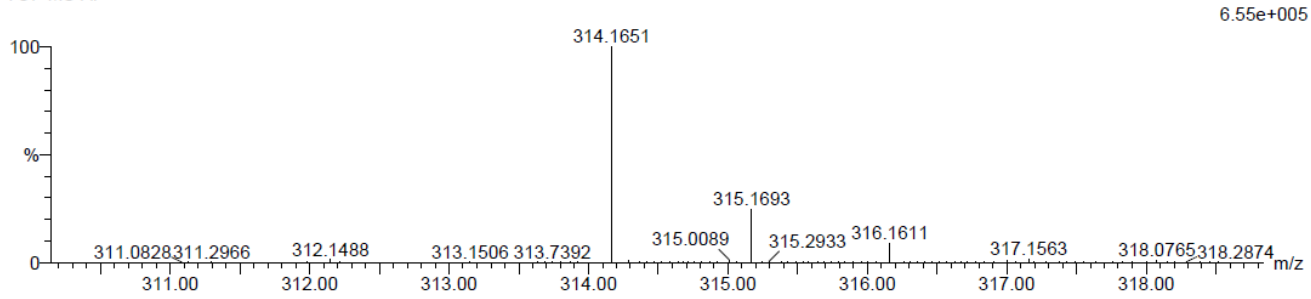



FTIR spectra of compound **4j**

**Elemental Composition Report** **Page 1**

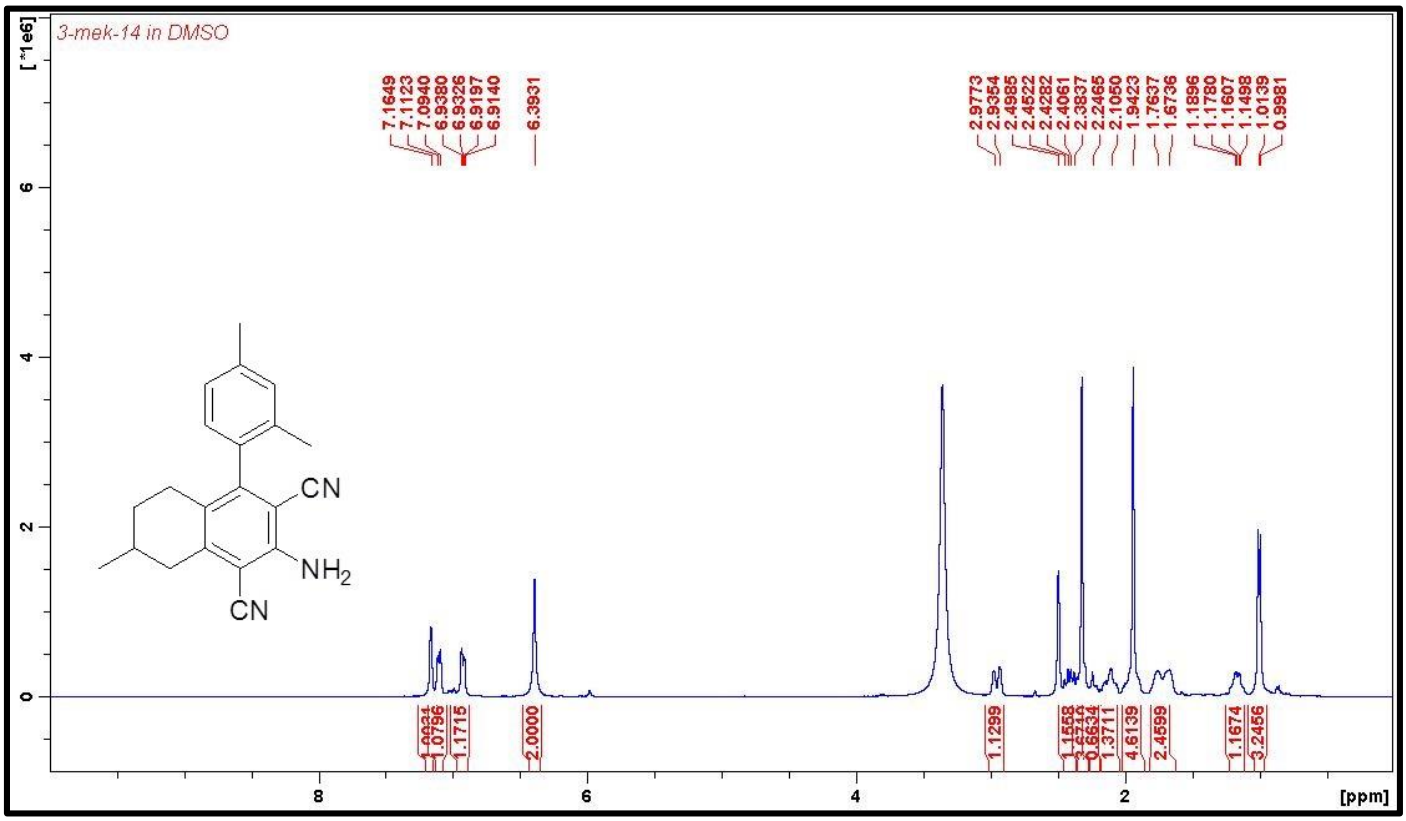
**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
3 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 20-25 N: 0-5
mek-12 5 (0.135) Cm (1:61)
TOF MS AP-

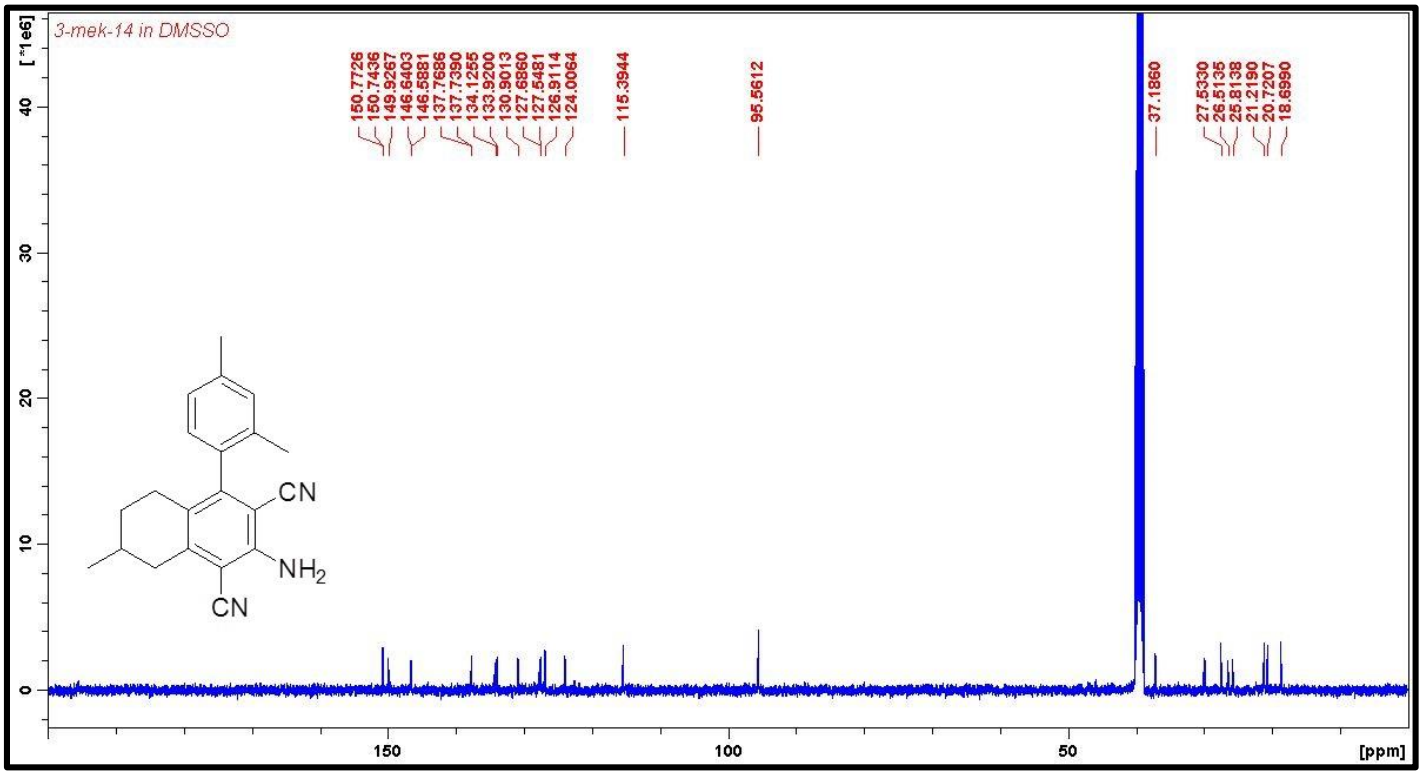



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 314.1651 | 314.1657 | -0.6 | -1.9 | 13.5 | 748.3 | 0.0 | C21 H20 N3 |

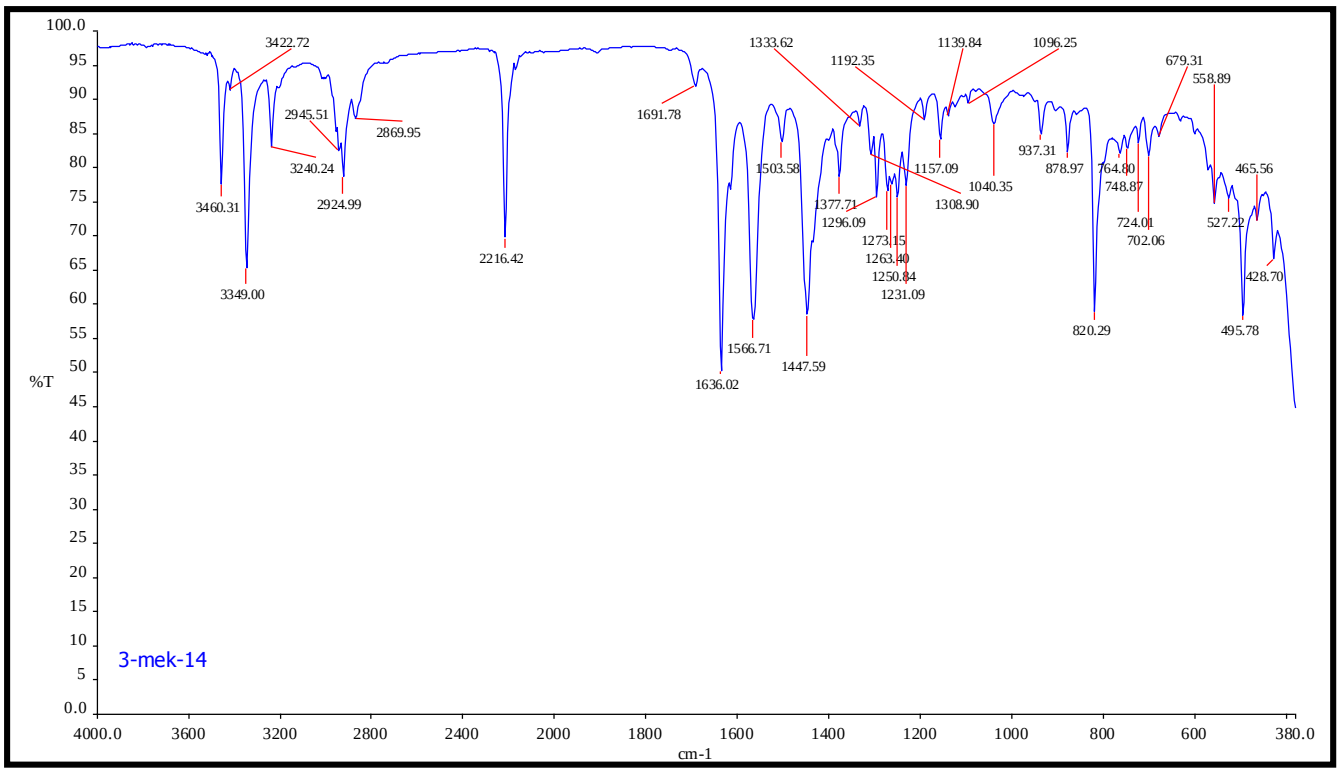
HRMS spectra of **4j**



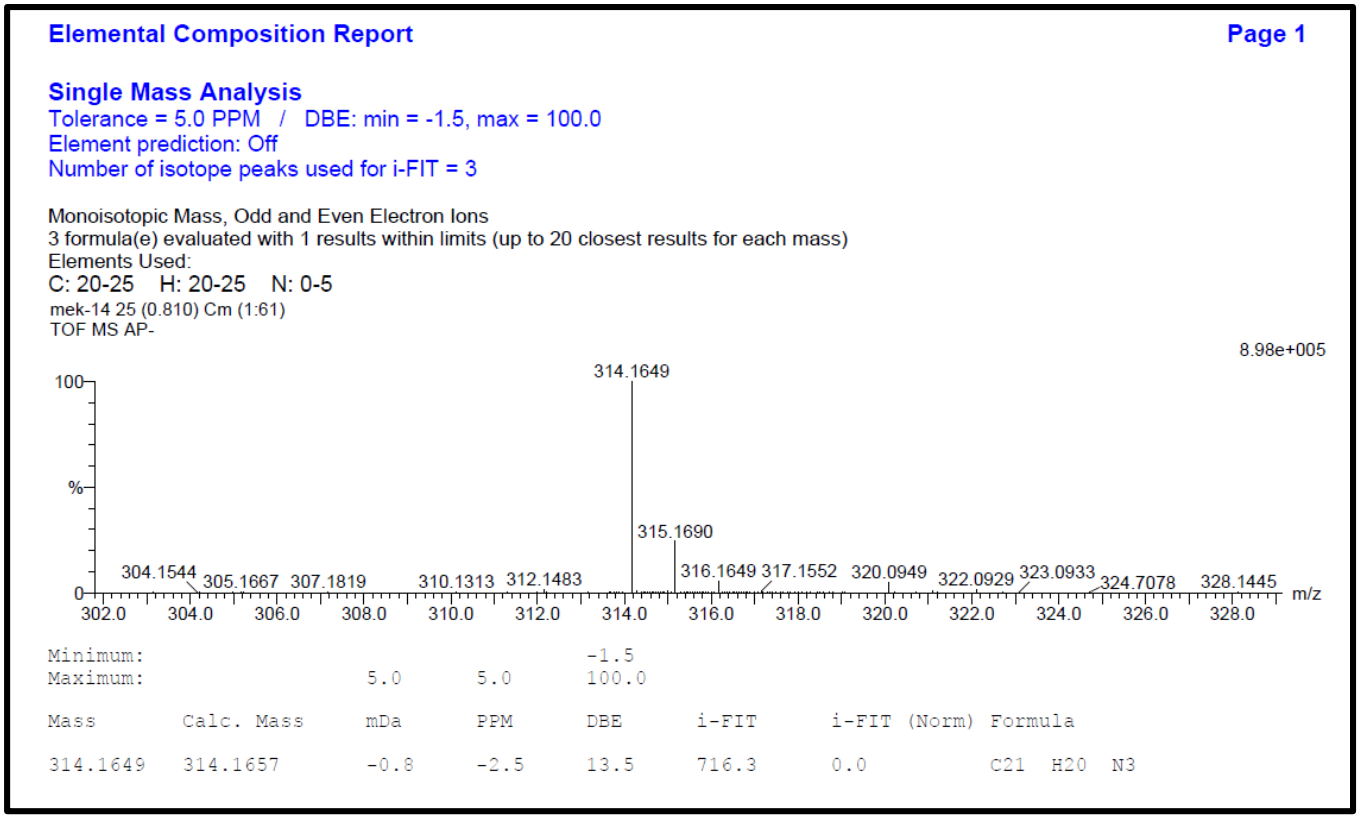

$^{1}$H NMR spectra of compound **4k**




$^{13}$C NMR spectra of compound **4k**




FTIR spectra of compound **4k**




HRMS spectra of **4k**

# CHAPTER-5

# CONCLUSION

The aim of this study was to demonstrate the versatility of the ultrasound approach as a green synthetic tool in organic synthesis. The study has shown that ultrasound is able to accelerate multicomponent reactions, improve the yields of product, and minimise side product formation and waste production. The study was conducted for the synthesis of both heterocyclic and aromatic compounds, where pyrazole, dihydropyridine and dicarbonitrile derivatives were synthesized under conventional or reflux and ultrasound conditions separately. The reactions for the synthesis of these compounds were optimised in order to determine optimum reaction conditions in terms of the most efficient solvent, catalyst and reaction temperatures in order to achieve the preferred product in good to excellent yields in short reaction time. This thesis contains the synthesis of tetrahydropyrazolopyridine and dihydropyranopyrazole derivatives, Functionalized 1,4-dihydropyridine derivatives and functionalized tetrahydrobiphenylene-1,3-dicarbonitrile derivatives under reflux and ultrasound conditions.

## 5.1. Synthesis of pyrazoles

Dihydropyrano pyrazoles were successfully synthesized in excellent yields (90-97%) under ultrasound in short reaction times (0.5-1.5 hours). The formation of the product was confirmed by NMR and IR analysis, in the proton NMR two singlets were observed at chemical shift 6.85 and 12.09 ppm denoting the presence of $NH_2$ and NH protons respectively. Thus from the IR symmetrical and unsymmetrical stretching frequencies are observe at 3163-3369 $cm^{-1}$ denoting the presence of an amine group ($NH_2$), stretching vibrations of nitrile group (CN) were also observed in the region between 2191 $cm^{-1}$.

Tetrahydropyrazolopyridines were successfully synthesized in excellent yields (90-96%) under ultrasound in short reaction times (1.0-2.5 hours). The formation of the product was confirmed by proton NMR which showed the presence of two singlets at chemical shift 4.53 and 8.99 ppm denoting the presence of the six membered ring and NH and the pyrazole ring NH protons respectively.

## 5.2. Synthesis of Functionalized 1,4-dihydropyridine derivatives

Functionalized 1,4-dihydropyridine derivatives were successfully synthesized in excellent yields (89-96%) under ultrasound in 40 minutes. The formation of the product was confirmed by the proton NMR, showing a singlet at chemical shift around 4.04 ppm denoting the presence of ($NH_2$) amino protons.

## 5.3. Synthesis of tetrahydrobiphenylene-1,3-dicarbonitrile derivatives

Tetrahydrobiphenylene-1,3-dicarbonitrile derivatives were successfully synthesized in good to excellent yields (60-97%) under ultrasound in (15-30 minutes). The formation of the product was confirmed by NMR and IR analysis, in the proton NMR one singlet was observed at chemical shift 6.45 ppm denoting the presence of $NH_2$ group thus the formation of CN-C=C-$NH_2$ ( 2-amino-1,3-dicarbonitrile group). Thus from the IR symmetrical and unsymmetrical stretching frequencies are observe at 3336-3350 $cm^{-1}$ denoting the presence of an amine group ($NH_2$), stretching vibrations of nitrile group (CN) were also observed in the region between 2190-2210 $cm^{-1}$.

## 5.4. Optimisation

Optimising the reaction conditions showed that water as solvent is ideal for the synthesis of pyrazoles and also tetrahydrobiphenylene-1,3-dicarbonitrile derivatives. This is due to that the hydrophobic effects of water has strongly enhanced reaction rates in that the transfer of ultrasound energy is high in water than in any other solvents. Ethanol has also been an ideal solvent for the synthesis 1,4-dihydropyridine derivatives. Polar solvents such as water and ethanol gave excellent yields, this is possible because both these solvents allows for fast occurrence of cavitation nuclei therefore fast heat dissipation which accelerates the cavitation process and at the same time providing ideal reaction conditions for maximum conversion of reactants to final product in short reaction times. This showed that it is possible to apply principles of green chemistry for generation interesting products using aqueous media methods, because they less toxic and less expensive compared to those with organic solvents.

## 5.5. Future work

- Study the kinetics and mechanism of the reaction for the formation of using UV/VIS spectrophotometry.

- Carry out multicomponent reaction for the synthesis of heterocyclic compounds under solvent-free and microwave conditions.