

**SUPPORTED HETEROGENEOUS CATALYSTS IN
SYNTHETIC AND MECHANISTIC STUDIES OF CERTAIN
HETEROCYCLIC REACTIONS**

by

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Submitted in fulfillment of the academic requirements for the degree of
Doctor of Philosophy in the Department of Chemistry, School of Chemistry & Physics
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April 2017

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ABSTRACT

Heterogeneous mixed metal oxides as catalysts have received greater attention in many valued organic transformations. Such systems were successfully employed for the improvement of heterocyclic synthetic procedures and to design the green chemistry protocols. Heterogeneous catalytic processes based on metal oxide catalysts are simpler, highly efficient and eco-friendly with greater selectivity. Heterogeneous catalysts possess a number of good characteristics, such as thermal stability, shape selectivity, acidic or basic nature, non-toxic crystalline solid. In addition, easy handling and reusability of materials facilitate the introduction of such systems in the organic conversions.

The synthesis of heterocyclic products through multicomponent reactions (MCRs) has gained significance the past decade. MCR is a viable synthetic methodology and relies on a process, where many bonds are formed and broken in a single one-pot reaction. MCRs are eloquent and eco-compatible and considered as a key aspects of green chemistry. Hence, considering current legislations and industry needs, heterogeneous catalysis is an ideal option for one-pot multicomponent synthetic reactions. Heterocyclic systems are ubiquitous in nature and form an integral part of the chemical research. It has the propensity for applications in the design of physiological and pharmacologically active substrates. The study of heterocyclic chemistry is a large field of research within the organic chemistry, due to their proven significance in biological, pharmaceutical, biochemical and material science. Many natural antibiotics, nucleic acids, dyes, pesticides, pigments, vitamins, plastics, etc. have heterocyclic rings in their structures.

New materials using different metals and oxide supports were developed to be used as recyclable heterogenous catalysts. The scope of the new materials as catalysts was investigated to design multicomponent synthetic protocols for organic synthesis, based on green principles. New protocols using the mixed oxide catalysts were explored to synthesise novel heterocyclic moieties and reaction conditions were optimised. The details of the catalysts developed and series of heterocyclic compounds synthesized are as described below:

1. An efficient and facile green method for synthesis of 3-methyl-4-(phenyl)methyleneisoxazole-5(4*H*)-one (**4a-m**) *via* room temperature reaction of hydroxylamine, ethylacetoacetate and substituted aromatic aldehydes is designed, using Ag/SiO₂ as catalyst with water as solvent.
2. A simple and an efficient method has been established for the one-pot multicomponent synthesis of pyrano[2,3-*d*]-pyrimidine derivatives from the condensation of dimethylbarbituric acid, aromatic aldehyde and malononitrile in the presence of Mn/ZrO₂ heterogeneous catalyst with ethanol/water mixture as solvent with short reaction time (1 h).
3. An efficient green protocol for the synthesis of the 2-amino-3-cyano-4*H*-pyran derivatives employing a multicomponent one-pot condensation reaction of 5,5-dimethylcyclohexane-1,3-dione, aromatic aldehyde and malononitrile was designed using a Ce-V/SiO₂ heterogeneous catalyst in the of the eco-compatible solvent (ethanol).
4. An efficient, green and facile protocol for synthesis of pyranopyrazole derivatives through the reaction of aromatic aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate is developed using Ru loaded hydroxyapatite (Ru-CaHAp) as catalyst.
5. An efficient, atom-economical, four-component one-pot reaction method was developed for pyrano[2,3-*c*]pyrazole-3-carboxylates using dimethylacetylenedicarboxylate, hydrazine hydrate, malononitrile and aromatic aldehydes, using a RuCaHAp catalyst.
6. The ceria doped zirconia (CeO₂/ZrO₂) catalysed synthesis of pyrano[2,3-*c*]-pyrazoles via the four-component reaction of malononitrile, hydrazine hydrate, ethyl acetoacetate and substituted aldehydes is described.

While all the synthesized catalysts were fully characterized by PXRD, TEM, SEM and BET surface area analysis, the chemical structures of the synthesized organic compounds were identified and confirmed by ¹H NMR, ¹⁵N NMR, ¹³C NMR, FT-IR and HR-MS spectral data. The significant advantages offered by the newly developed methods are ecofriendly simple procedures, mild conditions, short reaction times, recyclable catalyst and good to excellent yields of products.

DECLARATION 1 - PLAGIARISM

I, **Surya N Maddila**, 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. **Surya Narayana Maddila**, Suresh Maddila, Werner E. van Zyl and Sreekantha B. Jonnalagadda. “Mn doped ZrO₂ as a green, efficient and reusable heterogeneous catalyst for the multicomponent synthesis of pyrano[2,3-d]-pyrimidine derivatives.” **RSC Advances**. 5 (2015) 37360-37366.

My contribution: I synthesized and characterized all the derivatives under the supervision of Prof. Jonnalagadda (Supervisor), Prof. Werner E. van Zyl (Co-supervisor) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article. I was first-author, while Prof. Jonnalagadda was corresponding author.

2. **Surya Narayana Maddila**, Suresh Maddila, Werner E. van Zyl and Sreekantha B. Jonnalagadda. “Swift and green protocol for one-pot synthesis of pyrano[2,3-c]pyrazole-3-carboxylates with RuCaHAp as catalyst”. **Current Organic Chemistry**. 20(20) (2016), 2125-2133.

My contribution: I synthesized and characterized all the derivatives under the supervision of Prof. Jonnalagadda (Supervisor), Prof. Werner E. van Zyl (Co-supervisor) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article. I was first-author, while Prof. Jonnalagadda was corresponding author.

3. **Surya Narayana Maddila**, Suresh Maddila, Werner E. van Zyl and Sreekantha B. Jonnalagadda.

“One-pot synthesis of pyranopyrazoles using Ru-hydroxyapatite as reusable catalyst- a green approach”. **Current Organic Synthesis**. 13(6) (2016) 893-900.

My contribution: I synthesized and characterized all the derivatives under the supervision of Prof. Jonnalagadda (Supervisor), Prof. Werner E. van Zyl (Co-supervisor) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article. I was first-author and Prof. Jonnalagadda was corresponding author.

4. **Surya Narayana Maddila**, Suresh Maddila, Werner E. van Zyl and Sreekantha B. Jonnalagadda.

“Ce-V/SiO₂ catalyzed cascade for C-C and C-O bond activation: Green one-pot synthesis of 2-amino-3-cyano-4H-pyrans”. **ChemistryOpen. 5 (2016) 38–42.**

My contribution: I synthesized and characterized all the derivatives under the supervision of Prof. Jonnalagadda (Supervisor), Prof. Werner E. van Zyl (Co-supervisor) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article. I was first-author, while Prof. Jonnalagadda was corresponding author.

5. **Surya Narayana Maddila**, Suresh Maddila, Werner E. van Zyl and Sreekantha B. Jonnalagadda.

“Ag/SiO₂ as a recyclable catalyst for the facile green synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4H)-ones”. **Research on Chemical Intermediates. 42 (2016) 2553-2566.**

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6. **Surya Narayana Maddila**, Suresh Maddila, Werner E. van Zyl and Sreekantha B. Jonnalagadda.

CeO₂/ZrO₂ as Green catalyst for the one-pot synthesis of novel pyrano[2,3-c]-pyrazoles. **Research on Chemical Intermediates** (DOI 10.1007/s11164-017-2878-7).

My contribution: I synthesized and characterized all the derivatives under the supervision of Prof. Jonnalagadda (Supervisor), Prof. Werner E. van Zyl (Co-supervisor) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article. I was first-author, while Prof. Jonnalagadda was corresponding author.

Signed:.....

ACKNOWLEDGEMENTS

I wish to express my sincere thanks and appreciation to the following people

- ◆ Professor Sreekantha B. Jonnalagadda, for his invaluable supervision and guidance during the course of this study.
- ◆ Professor Werner E. van Zyl, for his expert guidance, supervision throughout the entirety of this project.
- ◆ My sincere thanks goes to the School of Chemistry and Physics, College of Agriculture Engineering and Science, University of KwaZulu-Natal for an enabling environment to carry out my research. Special thanks to Mr. Dilip Jagjivan, Mr. Kishore Singh and Mr. Gregory Moodley for their support, and always willing to help me during the course of this work.
- ◆ Department of Electron Microscopy, University of KwaZulu- Natal, for the use of the TEM, SEM.
- ◆ It is such a pleasure for me to thank all my Co-Ph.D members for their valuable suggestions and precise time.
- ◆ All the staff of the Department of Chemistry, University of KwaZulu-Natal.
- ◆ I would like to express my special appreciation to Mrs. Rukmini Jonnalagadda, for her support during my stay in Durban.
- ◆ I owe my thanks to Mr. H.N. Bandaru, Mr. VHSS Bhasakaruni, Dr. S. Rana, Dr. KK. Gangu and Dr. N. Kerru for their support.
- ◆ I would like to express my deep gratefulness and appreciation to my friends for their encouragement, helpful, support and attention during the course of this study.
- ◆ My unreserved gratitude in no particular order goes to Dr. Suresh Maddila and Dr. Sridevi Gorle, who have supported me throughout my thesis. Without his generous support, this work would be completely impossible.
- ◆ Last, but not the least I would like to thank my family. Without their constant love, encouragement and support I would never have been able to pursue my doctoral degree. You people have always been my strength and words cannot even begin to say how appreciative I am of everything you people have done for me.

CONFERENCE PARTICIPATION

1. Surya Narayana Maddila, Suresh Maddila, Werner E. van Zyl and Sreekantha B. Jonnalagadda. “Mn doped ZrO₂ as a green, efficient and reusable heterogeneous catalyst for the multicomponent synthesis of pyrano[2,3-d]-pyrimidine derivatives”. For a Poster presentation at the **College of Agriculture, Engineering and Science Research Day**, 22nd September 2015, *Pietermaritzburg campus, UKZN*.
2. Suryanarayana Maddila, Suresh Maddila, Kranthi Kumar Gangu, Werner E. van Zyl and Sreekantha B Jonnalagadda “Sm/Fluoroapatite as a reusable catalyst for the facile, green, one-pot synthesis of triazolidine-3-thione derivatives under aqueous conditions”. For a Poster presentation at the **College of Agriculture, Engineering and Science Research Day**, 29th November 2016, *Howard College Campus, UKZN*.
3. Suryanarayana Maddila, Suresh Maddila, Werner E. van Zyl and Sreekantha B Jonnalagadda. “*Synthesis, molecular docking study and in vitro anticancer activity of tetrazole linked benzochromene derivatives*”. **Drug Discovery and Development in Chemistry – 2015 (DDDC - 2015)**. *Dept. of Chemistry, S.V.University, Tirupati, India*. September, 14–15, 2015.

LIST OF ABBREVIATIONS

Abbreviations	Full name
3-CR	Three component reaction
4-CR	Four component reaction
1,4-DHPs	1,4-Dihydropyridines
¹ HNMR	Proton Nuclear Magnetic Resonance
¹³ CNMR	Carbon-13 Nuclear Magnetic Resonance
°C	Degrees Celcius
[ADDPY][OH]	4-Amino-1-(2,3-dihydroxypropyl) Pyridinium hydroxide
ArH	Aromatic ring proton
AgNO ₃ .9H ₂ O	Silver nitrate hydrate
[Bmim] Br	1-butyl-methylimidazolium bromide
[Bmim]BF ₄	1-butyl-3-methylimidazolium tetrafluoroborate
[Bmim]FeCl ₄	butylmethylimidazolium tetrachloroferrate
BET	Brunauer-Emmett-Teller
Calcd	Calculated
C-C	Carbon-Carbon bond
CeO ₂ /ZrO ₂	Ceria doped zirconia
COSY	Correlation spectrascopy
DAMP	4-Dimethylaminopyridine
DCM	Dichloromethane
DMAD	Dimethyl acetylenedicarboxylate
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMSO-d ₆ -	Deutarated dimethyl sulfoxide
dd	Doublet of doublet
d	Doublet
dt	Doublet of triplet
EDX	Enrgy-dispersive X-ray
EtOAc	Ethyl acetate

EtOH	Ethanol
FT-IR	Fourier Transform Infrared Spectroscopy
GBB	Groebke-Blackburn-Bienaymre
GlyNO ₃	Glycine nitrate
HAp _s	Hydroxyapatites
HMBC	Heteronuclear Multiple Bond Coherence
HSQC	Heteronuclear Multiple Quantum Coherence
Hz	Hertz
HRMS	High Resolution Mass Spectrometry
I ₂	Iodine
ICPOES	Inductively Coupled Plasma/Optical Emission Spectroscopy
IL	Ionic Liquids
IMCRs	Isocyanide-based Multicomponent Reactions
KHz	Kilo Hertz
MCRs	Multicomponent reactions
MHz	Mega Hertz
m	Multiplet
MW	Microwave
NH ₄ OAc	Ammonium acetate
NHR ₂	Secondary amine
PEG 600	Poly (ethylene glycol) 600
Pd(PPh ₃) ₂ Cl ₂	Bis (triphenylphosphine)palladium(II)dichloride
ppm	Parts Per Million
PTSA	p-toluene sulfonic acid
PXRD	Powder X-Ray Diffraction
RT	Room temperature
RuCl ₃ .XH ₂ O	Ruthenium (III) chloride hydrate
Ru-CaHAp	Ruthenium Hydroxyapatite
SEM	Scanning Electron Microscopy
SFexZr	Sulfated zirconia
s	Singlet

S ₈	Elemental Sulfur
TBAB	Tetrabutylammomium bromide
TEA	Triethylamine
TEBA	Triethylbenzylammonium chloride
TEM	Transmission Electron Microscopy
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMSCN	Trimethylsilylcyamide
t	Triplet
TsOH.H ₂ O	4-methylbenzenesulfonic acid monohydrate
U-4CR	Ugi-four Component Reaction
UV	Ultraviolet
VO ₂ SO ₄ .xH ₂ O	vanadyl sulfate hydrate,

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CHAPTER – 1

1. Introduction

Catalysis is a process by which rates of chemical reactions are enriched by small amounts of an extraneous substance, called catalysts [1]. It is estimated that around 90% of all commercially produced chemicals consume catalysts at some stage in the production development [2]. Catalysts play a vital role, in a number of areas, including bulk chemicals, fine chemicals, food processing and energy processing [3], making catalysis a very significant technology in today's world. Industrial catalysis is commonly divided into two types, heterogeneous and homogeneous [4]. Heterogeneous catalysis is wherever the catalyst and the reactant are in different physical phases, whereas homogeneous is where both are in the same phase [3]. A large number of industrial processes are heterogeneously catalysed. In general, it is useful to know the nature of the surface/interface in heterogeneous catalysis [5]. This is important for assessing the efficiency of the process and even the smallest amount of additives can poison or promote the reaction in which the catalyst is used. A suitable catalyst can enhance the rate of a thermodynamically feasible reaction, but cannot change the position of the thermodynamic equilibrium [6]. The catalytic reaction is a cyclic process. According to a simplified model, the reactant or reactants form a complex with the catalyst, thereby opening a pathway for their transformation into the product or products [7]. Afterwards the catalyst is released and the next cycle can proceed. It is suggested that the phenomenon of catalysis was first recognized by Berzelius in 1836 [8]. However, some catalytic reactions such as the production of alcoholic beverages by fermentation or the manufacture of vinegar by ethanol oxidation were practiced even before that [9]. Production of soap by fat hydrolysis and diethyl ether by dehydration of ethanol belong to the catalytic reactions that were performed in the 16th and 17th centuries [10]. Besides Berzelius, Mitscherlich was also involved at the same time in the study of catalytic reactions accelerated by solids [11]. He introduced the term contact catalysis which was a term used for heterogeneous catalysis that lasted for more than 100 years. Industrial production of chemicals relies on catalysts, and catalysis is becoming more and more important in energy production and pollution control [12].

It is well established that the catalysis field is a critical science for modern industry and improvements in catalytic processes will increase efficiencies of chemical transformations while reducing waste and environmental footprints [13]. However, although our understanding of catalytic processes has expanded in the last few decades, the structure of industrial heterogeneous catalysts is still relatively simple, mainly constructed of metallic nanoparticles dispersed on oxide support [14-17]. The simple structure of heterogeneous catalysts thus limits their scope and excludes the activation of complex reactions [16]. The construction of well-designed catalysts with an active site in a specific environment will expand the focus of catalysis research from the nanoscale into the mesoscale, opening up new reaction routes to novel catalytic transformations.

1.1.1. Importance of heterogeneous catalysis

Heterogeneous catalysts are accountable for a large number of chemical transformations of fossil fuels such as methane, coal and liquid petroleum into useful products [18,19] and the impact of catalysis on the United States economy, was stated as “one-third of material gross national product in the US involves a catalytic process somewhere in the production chain” [20]. The manufacturing of catalysts alone accounts for over \$10 billion of sales revenue in four major sectors, refining, chemicals, polymerization and emission. Globally, approximately 90% of the chemical practices and 60% of the chemicals produced utilise either heterogeneous or homogeneous catalysts [21]. The income generated due to catalyst sales is outweighed enormously by the overall value of the generated products. Examples of such products include pesticides, antibiotics, cosmetics, polymers, paints, plastics, cleaning products and chemical intermediates. In 1998, the annual global impact in the area of catalysis on the whole was estimated to be in excess of \$10 trillion [22]. It is likely that currently this figure is even higher.

As heterogeneous catalysis evolved, it has become more apparent that it has a large part to play in “green chemistry” and thus removing or substantially reducing the pollution and undesirable by-products from both chemical and refining processes [23]. This means that these by-products do not end up as either harmful emissions or waste materials that are dangerous and detrimental to the ecosystems and the environment globally [24].

In heterogeneous catalysis, the phase of the reactants or products and that of the catalyst is different, making the surface of the catalyst, which is the interface between catalyst and reactants or products, of great importance [25,26]. The big advantage of heterogeneous catalysts

in contrast to homogeneous catalysts lies in the practical use, namely the simple separation of the reaction products from the catalyst [27]. However, heterogeneous catalysts are systems that are often not well-defined which makes it complicated to get a good understanding of the catalytic mechanism [28]. Heterogeneous catalysts with higher stability and lower loss can improve the efficiency of reactions, and be recycled and reused without further treatment. Due to these advantages, the heterogeneous catalysts are used widely in various reactions. The efficiency of the catalytic process depends to a great extent on the catalyst and its surface properties as well as the acid/base condition of the surface active sites [29]. The most important factor for an efficient heterogeneous system is the choice of catalysts; currently the catalysts that are most studied include metal oxides, and metals or metal oxides on supports.

1.1.2. Structure and properties of supported metal catalysts

An important group of heterogeneous catalysts is the group of supported metal catalysts, generally containing small metal particles dispersed over a porous support [30]. The metallic component is the catalytically active component of the catalyst. The transition metals like Co, Fe, Ni, Mn, Rh, Ru, Ag, Au, Cu, Zr and V are of great importance [30] as they catalyze oxidation, dehydrogenation, hydrogenolysis, cyclization, aromatization and isomerization reactions [31,32]. Metal dispersion can be expressed as the ratio of metal atoms on the surface to the total number of metal atoms, which enhances surface area and hence the catalytic activity [33]. The supports, such as silica, magnesia, zirconia, alumina, and phosphates have large surface areas and provide anchoring sites for the metal particles [34]. In general, the noble metals show better catalytic activity than transition metals. However, the transition metals are relatively inexpensive, has higher thermal stability, and moderate mechanical strength, which is why it is widely used in catalysts [35-37]. The support further provides the mechanical strength of the catalyst. The supports can also contribute to the catalytic activity and selectivity of the catalyst [38]. Indirectly, it works as a structural promoter of the active sites of the metallic component via the so-called metal-support interaction [39]. Directly, it can supply active sites itself in a bi-functional catalyst used in various reactions.

1.1.3. Bimetallic catalyst

The performance of a catalyst can often be improved if one is able to optimize the electronic and geometric properties thereof [40]. The development of bimetallic catalysts is one way to improve the catalyst activity, selective and/or stability [41]. Until the end of the 1960's

the development of bimetallic catalysts was strongly stimulated by the rigid band theory that describes the electronic properties of alloys [42]. In the rigid band theory a uniform valence band structure was assumed for transition metals and it was believed that by mixing two metals a different degree of occupation of the valence and charge bands was occupied to an intermediate level [43]. This was found to be incorrect through measurements of metals and alloys. Moreover, in the metal band approach the global structure of metals (the electronic band structures) is mainly taken into account while it is expected that the local structure is of greatest importance in heterogeneous catalysis.

Nowadays the importance of geometric properties of bimetallic catalysts is emphasized in the understanding of the catalyst [44]. The surface composition of a bimetallic catalyst strongly influences the size composition and number of specific particles [45]. In this way it influences the type and number of active sites (ensemble effect). In alloys (e.g. Cu-Ni, Au-Pd, Au-Pt) with an active and “inactive” constituent, the active component is diluted by the inactive component reducing that ensemble size of the active component [46]. This suppresses for example hydrogenolysis reactions that require a relatively large ensemble size, but does not influence (de)hydrogenation reactions since only one metal surface atom is involved in the catalyst process of these reactions [47]. The introduction of another metal in a supported metal catalyst may lead to a change in the poisoning of the catalyst by carbon or sulfur deposits during hydrocarbon reactions [48]. An increase in poisoning of the catalyst can be responsible for an increase in selectivity for reactions proceeding over small ensembles (self poisoning effect) [46-48]. A decrease in poisoning can be responsible for a longer lifetime of the catalyst. For example, a Pd-Pt catalyst used in hydrogenation reactions has a higher tolerance of poisoning compounds containing sulfur and nitrogen than the monometallic catalysts. The second metal can also work as a kind of “glue” or barrier, anchoring particles to the support and preventing them from sintering.

1.1.4. Metal supported interaction

Metal-support interaction is a collective noun for interface phenomena which result in the catalytic properties of the metal particles being modified by the support material [49,50]. Analogous to the early studies on bimetallic catalyst, (delocalized) electronic effects were supposed to be dominant in metal-support interaction that influence catalytic properties, as put forward by Schwab and Solymosi and their co-workers in the late 1950's and 1960's [51,52].

Nowadays, metal-support interaction is more believed to relate to processes such as wetting, sintering encapsulation or other morphological changes of metal particles induced by the support, diffusion of the metal into the support, spillover of adsorbates from metal particles, etc [53].

Tauster et al. introduced the term strong metal support interaction after observing a large suppression of hydrogen and carbon monoxide chemisorption on transition metals dispersed over titania and a number of other reducible oxides after reduction at 500 °C [54]. During this treatment, the support is reduced by spillover of hydrogen from the metal [55]. The chemisorption capacity can be restored by oxidation treatments [54,55]. Several explanations have been given such as morphological effects, alloy formation, or electron transfer between the support and metal [56]. The bulk of the evidence that has been gathered indicates that the metal particles are decorated by reduced titania species masking the metal particles for chemisorption [57].

The behaviour of metal-supported interface is in a certain way comparable with that of the metal-gas interface [58]. It can be said that the metal component not only acts as a catalyst in the interaction with adsorbates, but also as a catalyst or reactant in the interaction with the support [59]. In this way, the metal can be modified for interaction with adsorbates due to the interaction with the support, which results in modified catalytic properties.

1.1.5. Synergetic effects in heterogeneous catalysis

The basic properties of the supported metal catalyst such as particle size and composition strongly influence the catalytic performance. It is not trivial to establish the relation between properties and performance of the catalyst because of the heterogeneity of the catalyst and because the various properties often depend on each other. For example, there is a long term debate whether Cu^0 or Cu^+ sites on the surface of the Cu/ZnO catalyst are the active sites for the methanol synthesis from synthesis gas. A linear correlation between the Cu^0 metal area and the catalytic activity was found [60], however it was mentioned by the author that the presence of CO_2 also results in the presence of a constant fraction of oxidized Cu. Thus, the linear correlation between Cu^0 and activity also represents a linear relationship between Cu^+ and activity.

Model systems have been used to make a systematic study possible. For example, the influence of atom size on hydrogen and deuterium chemisorption has been studied on naked gas-phase transition-metal clusters of 1-25 atoms in a fast-flow reactor using photoionization mass

spectrometry. Whetten et al. found that the reactivity of the gas-phase metal clusters exists between reactivity and cluster ionization [61]. Xu et al. prepared supported Ir₄ and Ir₆ clusters from organometallic precursors and found that the size dependency of the catalytic performances of the supported clusters is consistent with the observations of unique reactivities of size-selected gas-phase metal collections [62].

When a change in catalytic performance of technical metal catalysts is observed for catalyst with different metal particle sizes, it may point to a particle size effect [63]. However, it cannot always be excluded that other effects are responsible for the change in catalytic behaviour, because properties such as metal-supported interface may change simultaneously when changing the particle size.

The discussion above might give the impression that all catalytic reactions are very sensitive to the structure of the catalyst. However, as pointed out by Boudart, also structure insensitive reactions exist (e.g. hydrogenation of hydrocarbons, oxidation of carbon monoxide, hydrogen-deuterium exchange) which are independent of particle size, structure etc [64].

1.1.6. Preparation of supported metal catalyst

In the past, useful catalysts were often prepared by “trial and error” and nowadays much more attention is paid to the chemistry of preparing catalyst to the structure and properties of supported metal catalysts that result in an optimum catalytic performance. One of the successful preparation methods is to distribute the active (and often expensive) metallic phase over the surface of the support in a highly dispersed form to maximize the activity per weight of active compound (and minimize the costs). Although it is possible to deposit a metal directly from the vapour phase onto the support (as has been used to prepare model catalysts), the common industrially important preparation methods are multistep processes consisting of distribution, calcination, and activation steps. The choice of the precursor and the conditions of distribution, calcination, and activation steps determine the basic properties of the catalyst such as metal-support interaction, particle size etc.

1.2. Heterogeneous catalysis in green chemistry

It is generally recognized that the ultimate goal in catalytic studies is to be able to develop a detailed understanding of the catalyst systems to allow tuning of the design of nanoscale materials to create new heterogeneous catalysts and thus green catalytic processes [65]. One of the major issues in this area is catalyst performance, which is affected by shape,

size, composition and structure of the active ingredient as well as the support material used. There are four major classes of organic reactions in which heterogeneous catalysts are used; dehydrogenation, alkylation, hydrogenation and selective oxidations [66].

The first of this reaction type, dehydrogenation is a well-known approach for generation of simple and stable aldehydes and ketones as these reactions are reversible [67]. Alkylation reactions [68] are important for the production of gasoline that meets current stringent environmental standards and so researchers are seeking to develop solid-catalyst processes for alkylation technology [69,70]. Hydrogenation reactions [71-73] are commonly used in the food industry to make spreads and margarines from liquid oils and so are vital to this industry. Finally, selective oxidations [74,75] are extensively used in organic synthesis for the formation of many important compounds and intermediates to branch in other areas. However, a great deal of these selective catalytic oxidations relies on the use of high valence bimetallic catalytic systems [76,77]. In recent times, the use of supported metal systems has been highlighted in the literature, which includes some initial studies using carbon nanotubes as both catalysts in their own right and as supports for heterogeneous catalysts [78,79].

1.2.0 The principles of green chemistry

It is vital to understand why the work that follows is designed to adhere to the principles and so at this point, they are listed in a reworded shortened version for information purposes [80].

- 1.2.1. Prevent waste:** Design of processes to prevent waste, thus leaving no waste behind that requires treatment.
- 1.2.2. Maximize atom economy:** Design processes that leaves the final product incorporating the maximum amount of raw material used to make it.
- 1.2.3. Design less hazardous chemical syntheses:** Design processes that require the use of little or wherever possible no toxic substances that could be detrimental to human health or the environment.
- 1.2.4. Create safer chemicals:** Design products that are fully effective and minimize or eliminate toxicity.
- 1.2.5. Use safer solvents:** Create processes that use environmentally friendly substances such as water as solvents or separation agents.

- 1.2.6. Design for energy efficiency:** Work at ambient temperature and pressure whenever possible.
- 1.2.7. Use renewable feedstocks:** Use renewable raw materials and feedstocks wherever possible instead of depleting non-renewable materials.
- 1.2.8. Reduce derivatives:** Avoid or minimize the use of protecting and blocking groups in reactions as they often require additional reagents and generate waste.
- 1.2.9. Use catalysts instead of reagents:** Use catalytic reactions that use small amounts of material and thus minimize waste.
- 1.2.10. Design for degradation:** Design chemical products that break down into harmless materials that do not remain in the environment.
- 1.2.11. Prevent pollution in real time:** Monitor and control the process to minimize or eliminate the formation of hazardous by products.
- 1.2.12. Minimize the potential for accidents:** Design chemicals and processes that minimize the potential for accidents such as explosions, fires and toxic releases into the environment.

The primary aim of this work is to follow as closely as possible to the twelve principles of green chemistry across the entire process from manufacture of the catalysts right through to the testing of them in reactions that are challenging to carry out in an environmentally benign manner.

1.3. Multicomponent reactions

Recently, multi-component reactions (MCRs) earned prominence as a great synthetic tool for the formation of structurally combined molecular frameworks with attractive biological structures [81,82]. The entire procedure usually relies upon the formation and breaking of numerous C–C and C–heteroatom bonds in one-pot [83]. MCRs proposes significant benefits comprising easy handling, convergence, shorter reaction times, higher chemical yields, reduction in the quantity of extraction, minimization of the requisite reagents and purification stages, thus minimizing the quantity of waste generation, rendering the chemical transformations green and environment friendly [84-86]. These reactions are also valuable for the convenient generation of chemical libraries of biologically active compounds with impressive diversity and high levels of molecular complexity, thus contributing towards the optimization and identification of prospective compounds in drug discovery and pharmaceutical programmes

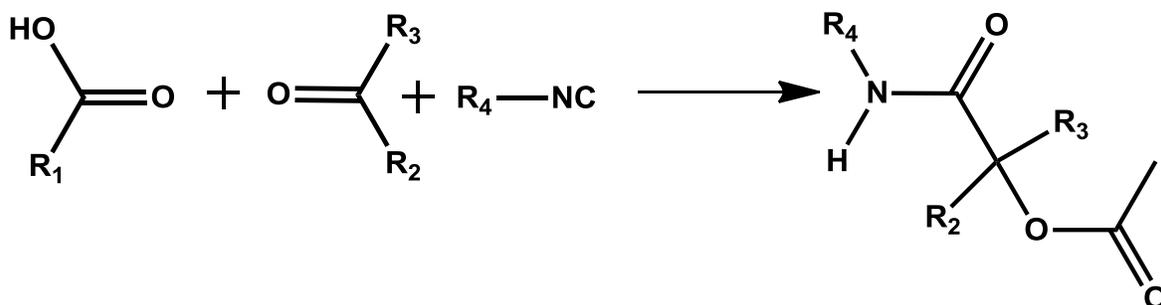
[87,88]. Consequently, designing new MCRs toward the synthesis of novel heterocyclic compounds from simple and readily accessible feedstock with green processes has huge significance, particularly in the areas of organic synthesis and drug discovery [89]. Though there are reviews describing the main MCR approaches applied to the synthesis of a great diversity of heterocycles like isoxazole, pyrroles etc., the use of MCRs in the synthesis of five, six and fused cyclic nitrogen-containing heterocycles has hardly been reported [90]. The current work is aimed at presenting recent, MCR methodologies to access these heterocycles in one-pot.

The history of MCRs date back to at least 1850, when the Strecker three-component reaction of amino cyanides from carbonyl compounds, ammonia and hydrogen cyanide has been reported [91]. In 1882, the reaction proceeded to the Hantzsch synthesis of symmetrical 1,4-dihydropyridines by the reaction of aldehydes, amines and β -ketoesters [92]. In 1917, Robinson accomplished the total synthesis of the alkaloid tropinone by using a three-component strategy based on Mannich-type reactions [93]. This reaction is the oldest application of MCRs in natural product synthesis [94]. The Passerini reaction described in 1921 is considered as the first isocyanide based MCR and over the years this reaction has become increasingly important and has been highlighted [95]. Another classical MCR which leads to amino acids is the Bucherer-Bergs reaction, which was first reported in 1929 [96]. This reaction is closely related to the Strecker reaction, with CO_2 as the fourth component. The Biginelli dihydropyrimidine synthesis (1891), Mannich reaction (1912) and Ugi four component reactions (U-4CR) (1959) are the other three very important MCRs useful for multipurpose synthetic processes. In recent years, many novel MCRs- including Michael addition-initiated three component domino sequences, Knoevenagel/hetero-Diels-Alder-based MCRs [97], radical chain MCRs [98], transition metal-catalysed Pauson-Khand MCRs [99], as well as Petasis MCRs [100], have been added to the chemist's synthesis toolbox and successfully applied to all fields of organic synthesis. Some recent examples depicting elegant developments in the catalytic construction of various heterocycles are discussed in the following sections.

1.3.1 Passerini reaction:

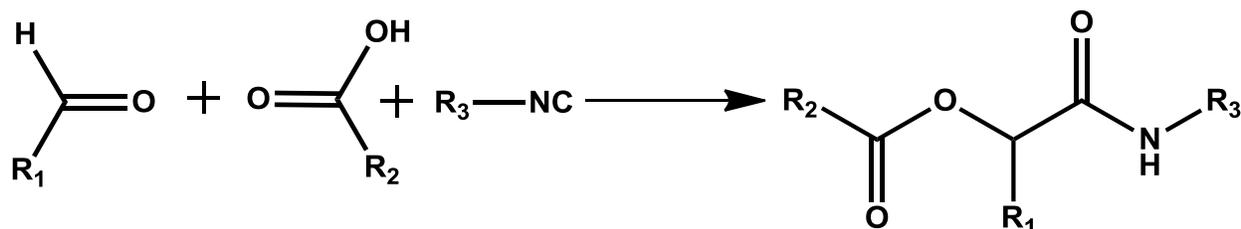
MCRs that involve isocyanides as starting materials, named after Mario Passerini are by far the most versatile reactions in terms of available scaffolds and numbers of accessible compounds [101]. The oldest among this category is the three-component Passerini MCR, which

involves the reaction between an aldehyde, an acid and an isocyanides to obtain α -acyloxyamides in one step (Scheme 1).



Scheme 1: General scheme for the Passerini reaction

Adib et al., have described interesting new variants of the Passerini-3CR [102]. The reaction of aldehydes, carboxylic acids and isocyanides led to the final products, which cyclized on treatment with NaHCO_3 in a one-pot procedure at reflux condition. These authors obtained the substituted α -acyloxyamides in medium to good yields (Scheme 2).

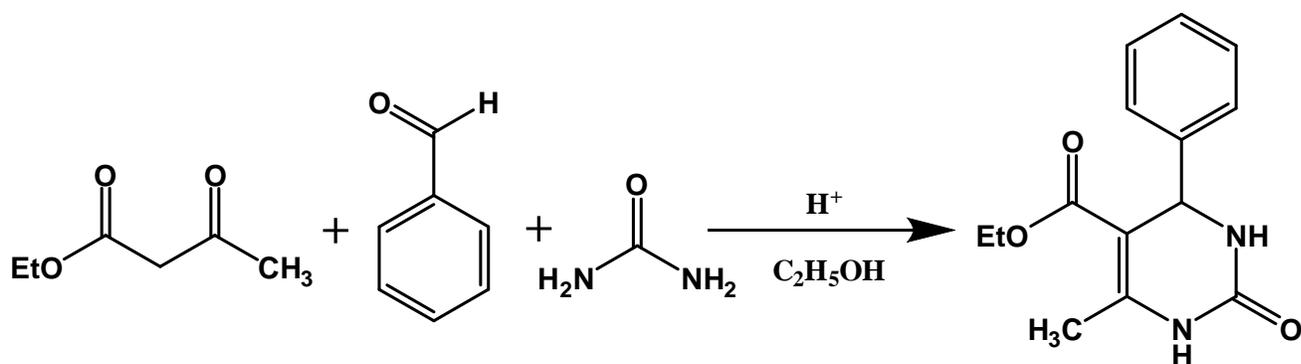


Scheme 2: Synthesis of substituted α -acyloxyamides

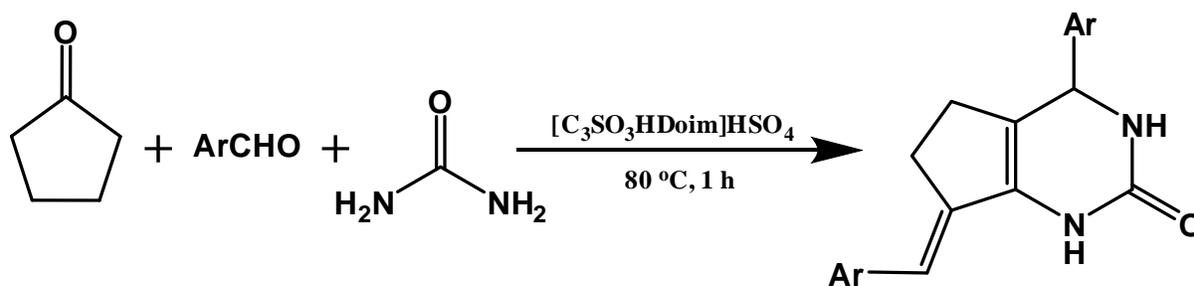
1.3.2. The Biginelli reaction:

The Biginelli reaction was named by the Italian chemist Pietro in 1893, the reaction of an aldehyde, ethylacetoacetate and urea gave 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme 3) [103]. The synthetic potential of this particular condensation remained unexplored until the beginning of the 1980s.

Zhou and co-authors recently reported multicomponent Biginelli reaction catalysed by Bronsted acidic ionic liquid $[\text{C}_3\text{SO}_3\text{HDoim}]\text{HSO}_4$. The condensation of cyclopentanone with aromatic aldehydes and urea provided the corresponding pyrimidinones in good to excellent yields (up to 96%) under solvent-free condition (Scheme 4)[104].



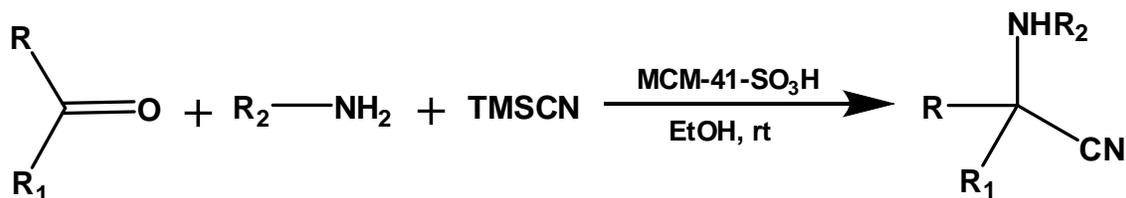
Scheme 3: General scheme for the Biginelli reaction



Scheme 4: Preparation of pyrimidinones

1.3.3. Strecker reaction

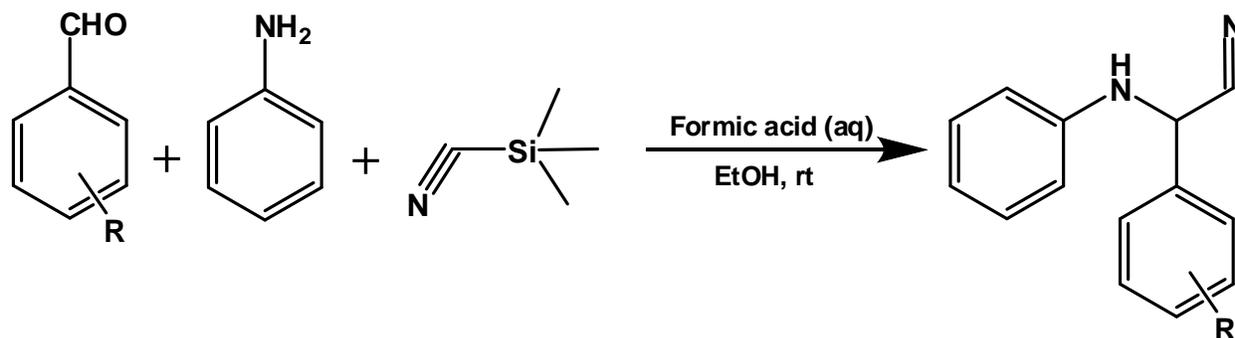
The oldest known multicomponent reaction was reported in 1850, for the preparation of α -amino acids, which known as the Strecker reaction. The Strecker reaction involves the condensation of an ammonia, aldehyde and cyanide group followed by the hydrolysis of the resulting α -amino nitrile (Scheme 5) [105]. The resulting α -amino acids have found application in pharmaceutical industries; they have significant widespread use in the field of chemistry and biology, as they are predecessors for the preparation of proteins and chiral building blocks.



Scheme 5: Strecker reaction of carbonyl molecules and amines with TMSCN (trimethylsilyl cyanide) catalysed by MCM-41-SO₃H

Ghafuri and Roshani (Scheme 6) developed a very efficient synthesis protocol for derivatives of α -aminonitrile scaffold. A reaction of aldehyde, aniline and TMSCN in ethanol solvent at RT with aqueous formic acid as a catalyst lead to formation of α -aminonitrile as solids

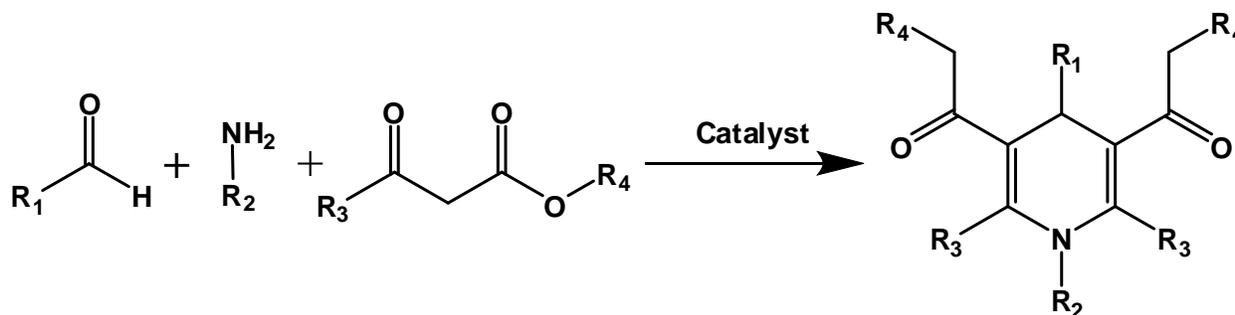
in 1 h. Products precipitated from the reaction mixture, thus avoiding the need for chromatography [106].



Scheme 6: Synthesis of α -aminonitrile derivatives

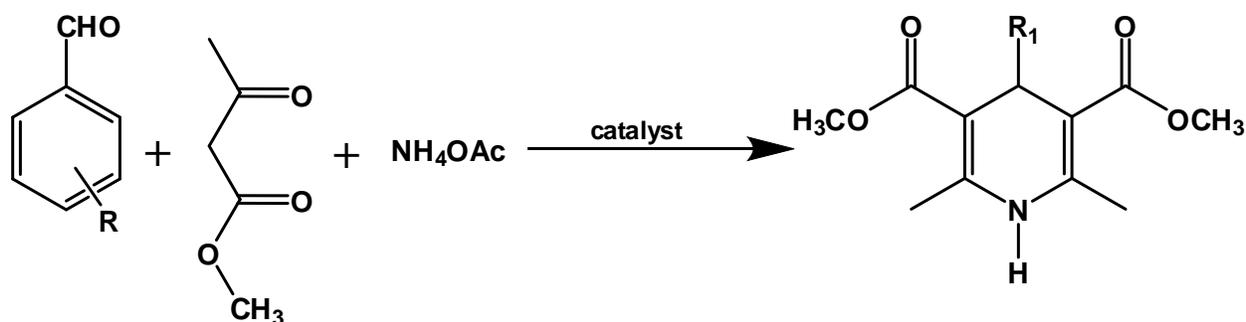
1.3.4. Hantzsch reaction

1,4-Dihydropyridine derivatives (1,4-DHPs) are a significant class of biological active molecules and are also working as biomimetic reducing agents. These classes of compounds are generally accessible by use of Hantzsch reaction, which was reported in 1882 [107]. The multicomponent reaction consists of aldehyde, ethylacetoacetate and ammonium acetate to form dihydropyridine, which gets oxidised to form a pyridine derivative (Scheme 7).



Scheme 7: General scheme for the Hantzsch reaction

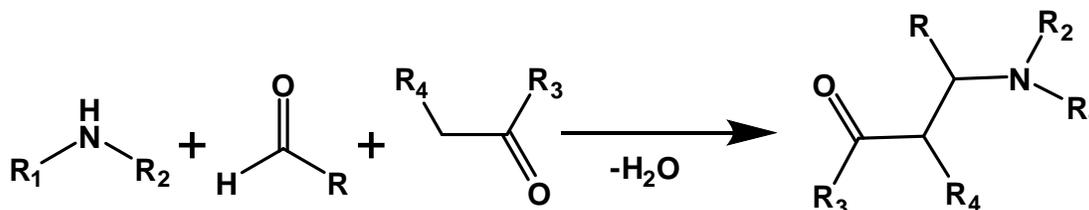
A reaction of methyl acetoacetate, ammonium acetate and aromatic aldehydes was used for the one-pot multicomponent synthesis of functionalized 1,4-dihydropyridines (Scheme 8). Mn and Ce oxides under solvent-free conditions catalysed the reaction. The yields were good (69-87%) in the case of the benzaldehydes, both with electron withdrawing and electron donating groups [108].



Scheme 8: Synthesis of functionalized 1,4-dihydropyridines

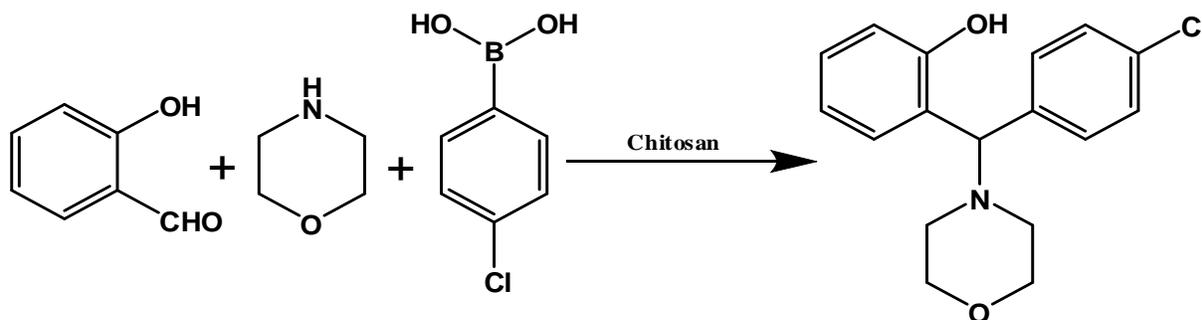
1.3.5. Mannich reaction

The Mannich reaction [109-111] is a conventional process for the synthesis of β -amino ketones and aldehydes and it involves the multi-component reaction between an amine, enolizable CH-acidic carbonyl compound and aromatic aldehyde (Scheme 9). It is anticipated that methylene iminium salts are formed in tiny amounts, by a series of equilibria. Carl Mannich discovered the Mannich reaction in 1917.



Scheme 9: General scheme for the Mannich reaction

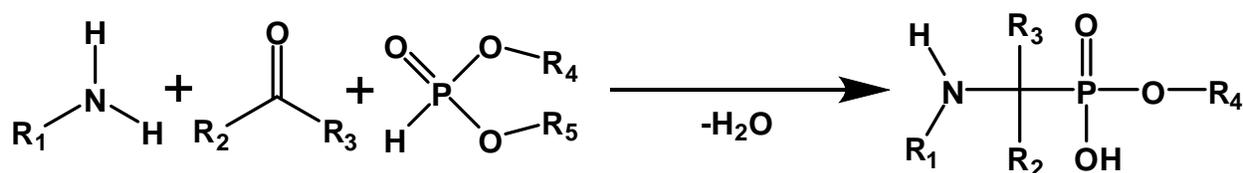
Reddy et al., via Mannich reaction (Scheme 10), have reported synthesis of a series of novel alkylaminophenol derivatives. The target compound was synthesized through Patis borono-Mannich reaction using secondary amines, *o*-hydroxy aldehydes and various boronic acids in the presence of a biopolymer catalyst such as chitosan under 1,4-dioxane solvent under reflux [110].



Scheme 10: Synthesis of substituted quinazolinone derivatives

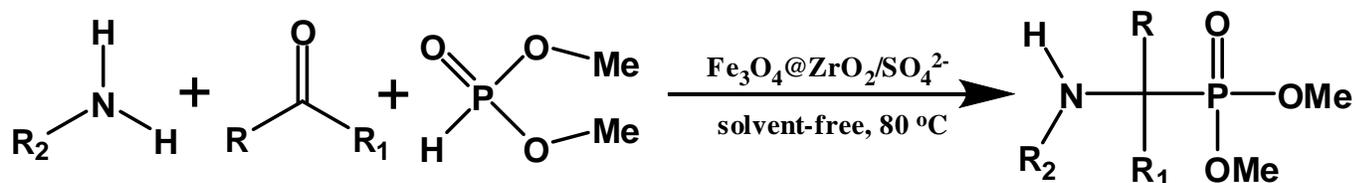
1.3.6. Kabachnik reaction

The Kabachnik reaction is a multicomponent reaction between an amine, a carbonyl compound and dialkyl phosphonate to form α -amino phosphonate (Scheme 11). Kabachnik and Fields discovered the reaction in 1952 and used in the synthesis of anti-inflammatory drugs [111].



Scheme 11: General scheme for the Kabachnik-Fields reaction

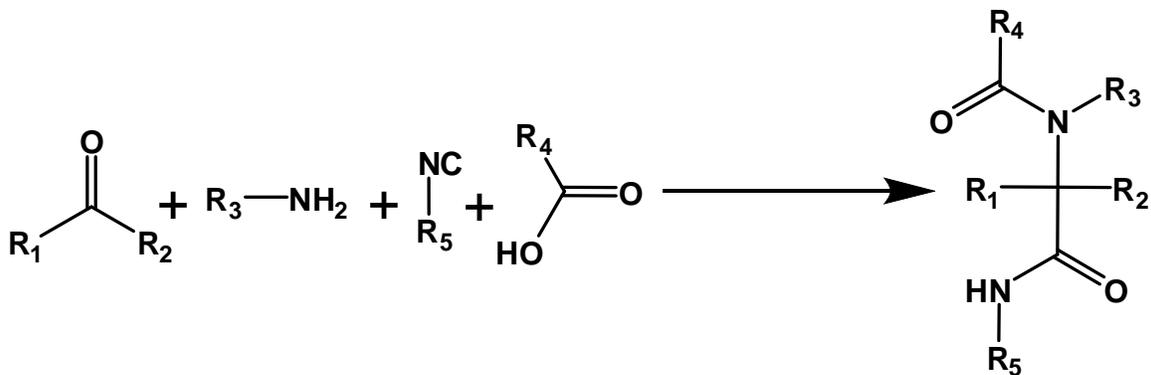
Recently, Ghafuri et al. reported a nanomagnetic sulfated zirconia catalysed Kabachnik reaction of α -aminophosphonates using aromatic aldehydes, anilines and dimethyl phosphite carried out in absence of solvent at 80 °C (Scheme 12). Like many other heterogeneous catalysts, Nano-Fe₃O₄@ZrO₂/SO₄²⁻, an acidic catalyst offers many benefits including easy workup, short reaction times, high activity and yields, plus easy separation and reusability environmentally benign reaction conditions [112].



Scheme 12: Synthesis of the substituted α -aminophosphonates

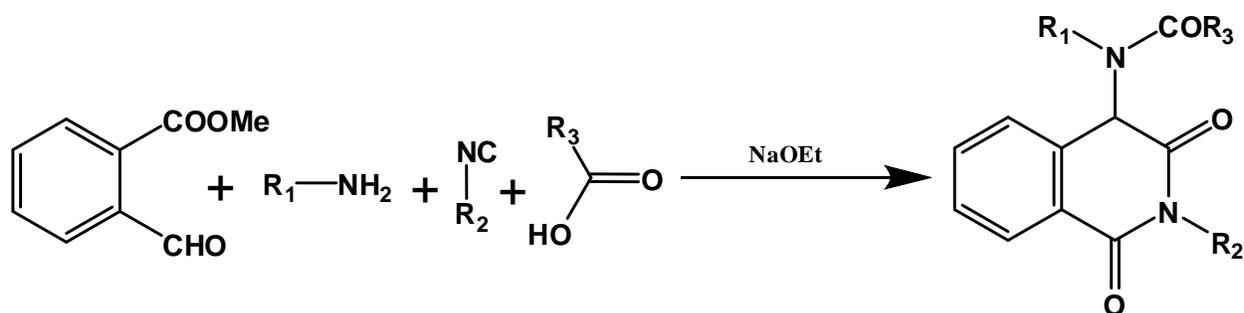
1.3.7. Ugi reaction

The Ugi reaction denotes one of the highly powerful reactions in MCRs with broad spectrum of applications [113]. First described in 1959, the Ugi-4CR describes the one-step creation of peptide-like structures by combining a carbonyl compound, a carboxylic acid, an amine and an isocyanide (Scheme 13). The Ugi reaction takes only a few minutes to complete due to the exothermic nature of the reaction. Three-component and four-component reactions (3-CR and 4-CR) are possible with Ugi arrangement.



Scheme 13: General scheme for 4-component Ugi reaction

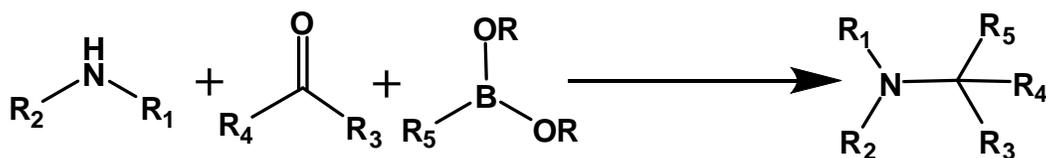
Yuan et al. [114] described a facile, multi-component reaction involving condensation of methyl 2-formylbenzoate, amine, isocyanate and carboxylic acid at room temperature in the presence of NaOEt to obtain a series isoquinoline-1,3-(2*H*,4*H*)-diones with good to excellent yields (Scheme 14).



Scheme 14: Synthesis of the isoquinoline-1,3-(2*H*,4*H*)-diones

1.3.8. Petasis reaction

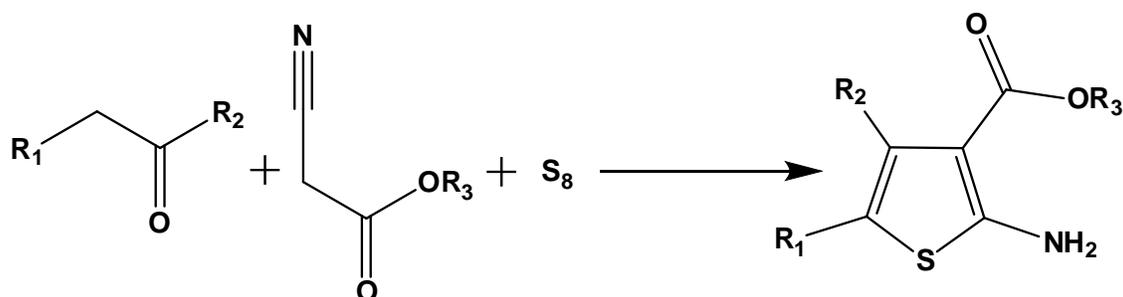
Allylic amines are widely used as building blocks in synthesis of variety of organic compounds with wide range of biological activities. Petasis et al., in 1993 have reported the efficient method for synthesis of allylic compounds using a modified Mannich reaction, where vinylboronic acids served as the nucleophilic component [115]. This new and mechanistically distinct three component reaction that combines amines, aldehydes and vinylboronic or arylboronic acids is referred to as the Petasis boronic acid-Mannich reaction or Petasis three-component reaction (Petasis 3CR, Scheme 15) [116].



Scheme 15: General scheme for the Petasis reaction

1.3.9. Gewald reaction

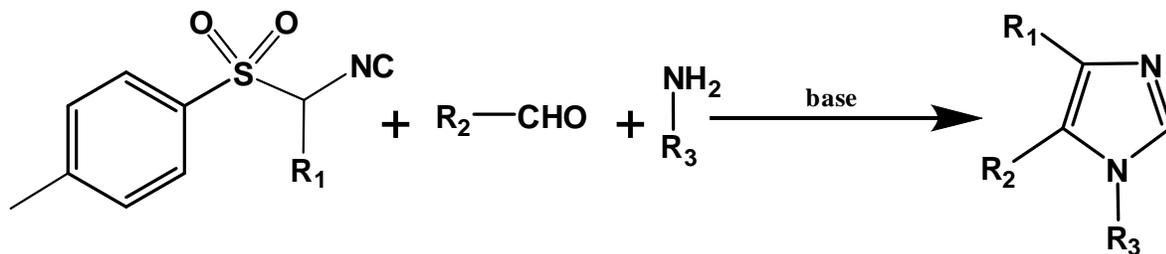
In 1966, the German chemist Karl Gewald discovered the reaction that lead to the formation of 2-aminothiophenes called the Gewald reaction [117]. The Gewald reaction involves the condensation of an aldehyde or ketone, α -cyanoester in the presence of elemental sulfur and a base to afford a poly-substituted 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 (Schem 16) [118]. The 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-N₃-aminothiemo-[2,3-d]-pyrimidines [119,120].



Scheme 16: Synthesis of multisubstituted 2-aminothiophenes

1.3.10. van Leusen reaction

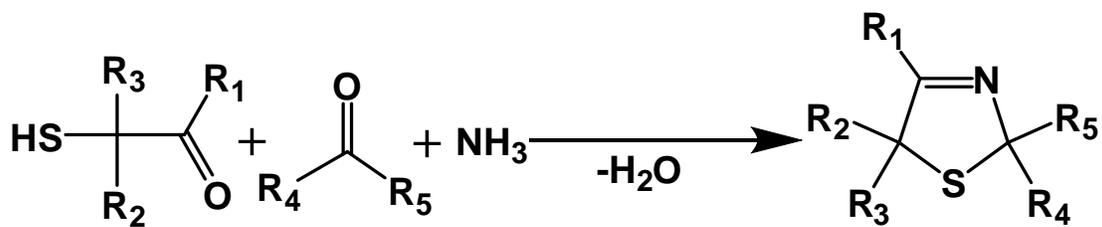
The Dutch chemist, van Leusen discovered tosylmethylisocyanide and subsequently investigated the reactivity and synthetic perspectives offered by this multifunctional reagent [121]. The chemistry of tosylmethylisocyanide is diverse, because of its acidic character, the reactivity of the isocyano function towards nucleophiles and electrophiles and the leaving group ability of the sulfone is of interest (Scheme 17).



Scheme 17: General scheme for the van Leusen reaction

1.3.11. The Asinger reaction

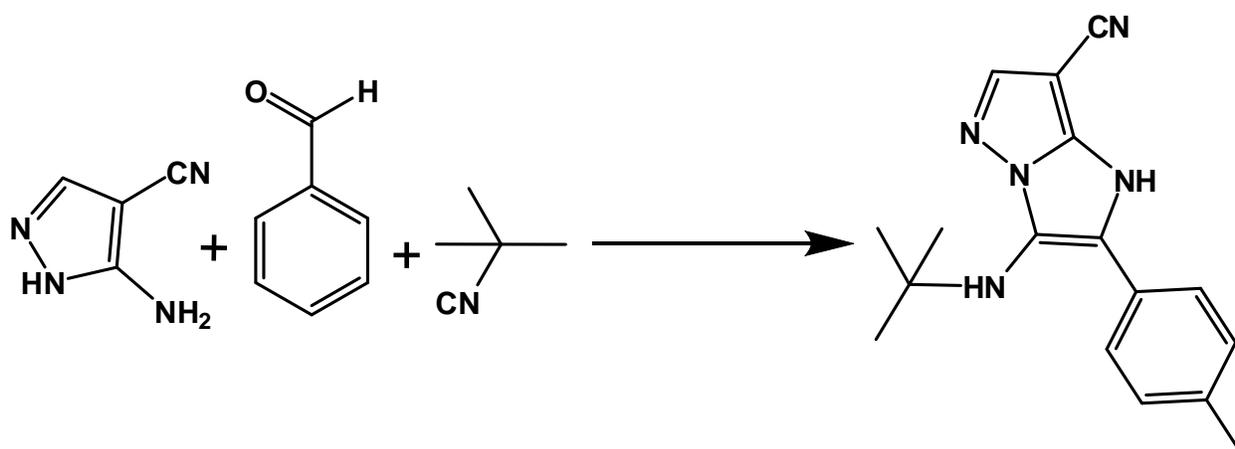
The reaction to form 3-thiazolines was named after Friedrich Asinger. Asinger, an industrial organic chemist discovered the reaction for the synthesis of 3-thiazolines in 1956 [122]. The 3-thiazoline derivatives were formed from a monothiolation and subsequent α -amino alkylation followed by ring closure with elimination of water (Scheme 18). Asinger and his team also confirmed that the derivatives of 3-thiazolines are possible.



Scheme 18: General reaction of the Asinger reaction

1.3.12. Groebke-Blackburn-Bienayme (GBB) reaction

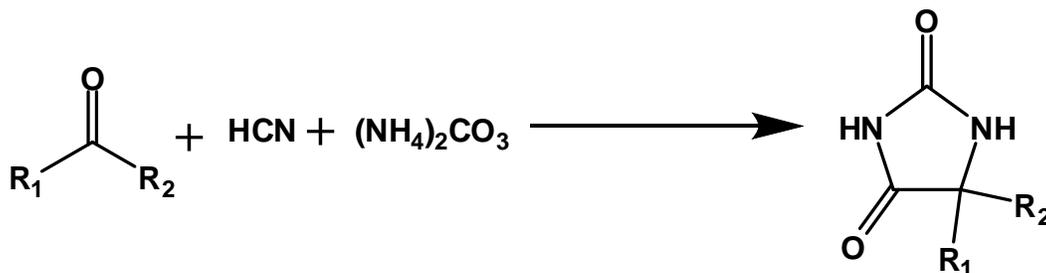
Groebke (from Switzerland), Christopher Blackburn (Cambridge in USA), and Hugues Bienayme (from France) all independently reported the (GBB) reaction for the first time in 1998. GBB reaction involves an aldehyde reacting with aminoazine and an isonitrile in the presence of a suitable catalyst (generally a Lewis acid or Bronsted acid), this produces a highly substituted and fused imidazole derivative (Scheme 19). The GBB reaction is classified as a four-center, three component reaction and has found application in the drug discovery research industries [123,124].



Scheme 19: Synthesis of imidazo[1,2-b]pyrazoles via GBB reaction.

1.3.13. The 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 20) [125].



Scheme 20: The Bucherer-Bergs multicomponent synthesis of hydantoins

1.4. Synthesis of catalyst assisted hetero nucleic compounds

Nitrogen and oxygen containing heterocyclic compounds has attracted considerable attention due to their wide range of physicochemical and pharmacological properties [126,127]. Heterocyclic molecules offer a high degree of structural variety and are proven to be useful as therapeutic agents [128]. New and more efficient and sustainable synthetic routes continuously replace the conventional preparation methods for heterocycles [129]. The development of environmental, practical, and economical procedures for the preparation of heterocyclic compounds continues to be a challenging area for organic chemists [130,131]. One-pot synthetic pathways are remarkably advantageous to access diversely functionalized molecules which are useful as fine chemicals, chiral catalysts, ligands, drug candidates and drug intermediates [130-132]. One-pot reactions for the synthesis of heterocyclic compounds have been extensively studied [132-134]. In comparison to multi-step synthetic procedures, these reactions are highly economical to construct varying substituted molecules in just one reactor by avoiding the separation and purification of intermediates. Transition metal catalysed one-pot reactions are well-established approaches for the synthesis of heterocyclic compounds [135,136]. This will certainly increase the interest of heterogeneous catalysed one-pot reactions in the near future.

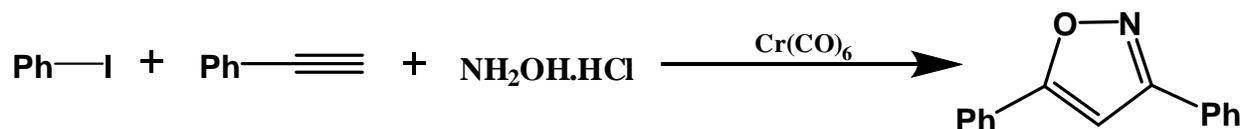
Heterocyclic chemistry, which forms the major division of conventional organic chemistry, is a challenging and interesting arena. [137]. Majority of pharmaceuticals [138], biologically active agrochemicals [139], additives and modifiers used in industrial applications

are heterocyclic in nature [140,141]. A large number of alkaloids derived from heterocyclic molecules are used as drugs [141]. Thus, pharmaceutical and agrochemical industries have made rapid and significant progress develop suitable heterocyclic compounds for the benefit of humankind [142]. The attractive feature of heterocyclic chemistry is the scope and provision to vary the core scaffold with innovative substitutions and variations. Among different heterocycles, the chemistry of nitrogen and sulfur containing heterocycles has undergone remarkable advances in the last couple of decades, ever since their initial use in agriculture commenced [143-145]. The pesticidal, potential chemotherapeutic, fungicidal and antiviral properties have been the reasons for the upswing in the interest and development of these heterocyclic compounds in general and pyrazoles, pyrans and isoxazoles in particular.

1.4.1. Isoxazoles

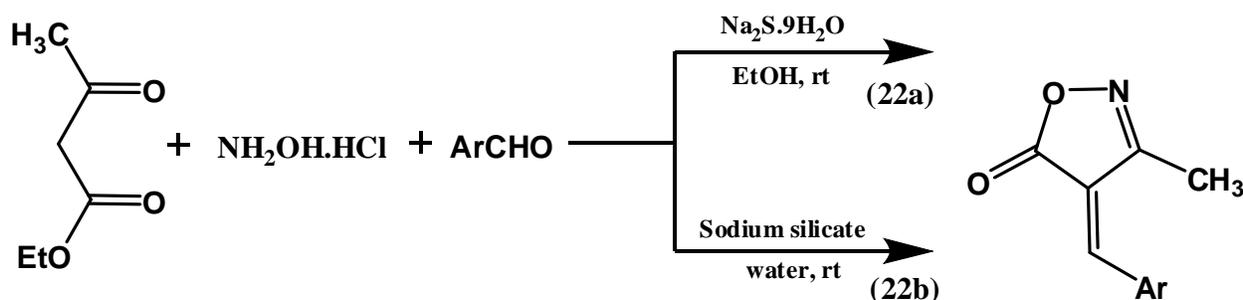
Nitrogen containing five membered heterocyclic compounds with an oxygen atom in the ring are considered vital class of compounds in pharmaceutical and medicinal chemistry because of their varied biological uses [146]. The exploitation of a simple molecule with diverse functionalities for the synthesis of heterocyclic is a worthwhile contribution in the organic chemistry [147]. Isoxazole is a five membered heterocyclic compound containing oxygen and nitrogen atoms in side-by-side positions. The core ring system, isoxazole is historically old and an isolated compound, but not identified until 1888 [148]. Isoxazoles have an illustrious history and named as “monazole”, their chemistry is associated with Ludwig Claisen, who first recognized the cyclic structure of 3-methyl-5-phenylisoxazole in 1888. Isoxazoles are known to possess aromatic resembling properties under basic conditions [149]. This is a vital class of heterocycles, which are largely employed in the area of pharmaceuticals and therapeutics such as insecticidal [150], antibacterial [151], anti-tumor [152], antifungal [153], anti-tuberculosis [154] and ulcerogenic compounds [155]. Isoxazole derivatives are used in the market as COX-2 inhibitor and anti-inflammatory drugs [156,157]. Isoxazole derivatives such as sulfamethoxazole, sulfisoxazole, oxacillin, cycloserine and acivicin have been in commercial use for many years [157]. Cycloserine is the best known antibiotic drug that possess anti-tubercular, antibacterial activities and in treatment of leprosy. Due to their potential applications in several fields including agriculture, and scope for synthesis of varied compounds with distinct properties, isoxazoles have been comprehensively investigated.

Iranpoor and co-authors described the use of a phosphine and copper-free palladium as a heterogeneous catalyst for the synthesis of isoxazole derivatives (Scheme 21) [158] via Sonogashira carbonylative coupling reaction. Under heating conditions, the reaction required one equivalent of base to confirm high reaction rates. However, the reaction could be carried out quantitatively at 70 °C in 5 h with excellent yields.



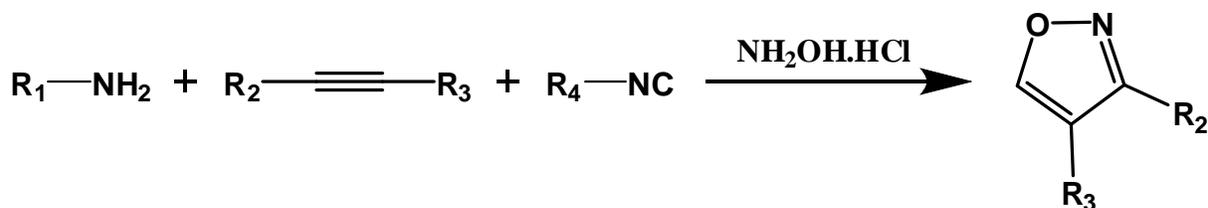
Scheme 21: Synthesis of the isoxazole derivatives

Liu et al., have reported that sodium sulfide (Na₂S) is an excellent catalyst for the preparation of 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones in ethanol solvent. When the reactions were performed with hydroxylamine hydrochloride, various aldehydes and ethyl acetoacetate at RT of ethanol, the corresponding target products were obtained in excellent yields between 63–81% for 1-2.5 h (Scheme 22a) [159]. The same authors have improved a convenient and efficacy synthesis of isoxazole derivatives by the condensation of hydroxylamine hydrochloride, ethyl acetoacetate and aromatic aldehydes in aqueous solvent under sodium silicate pentahydrate as an efficient catalyst conditions (Scheme 22b) [160].



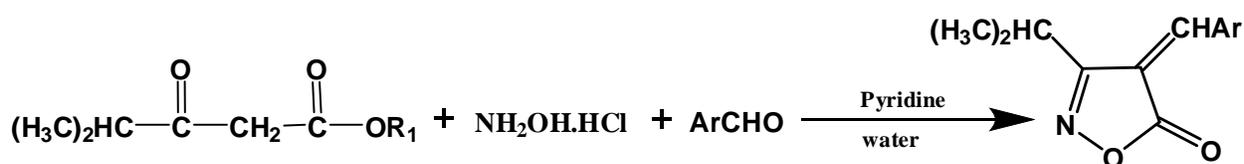
Scheme 22: Synthesis of the 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones

The titanium-catalysed regioselective synthesis of 3,4-disubstituted isoxazole derivatives have been reported by Dissanayake and Odom. (Scheme 23) [161]. A direct coupling reaction of cyclohexylamine, aniline, tert-butylisonitrile and hydroxylamine was used for the synthesis of isoxazoles, avoiding the use of organic catalysts. Microwave heating has shown enhancement in reaction yields over conventional heating.



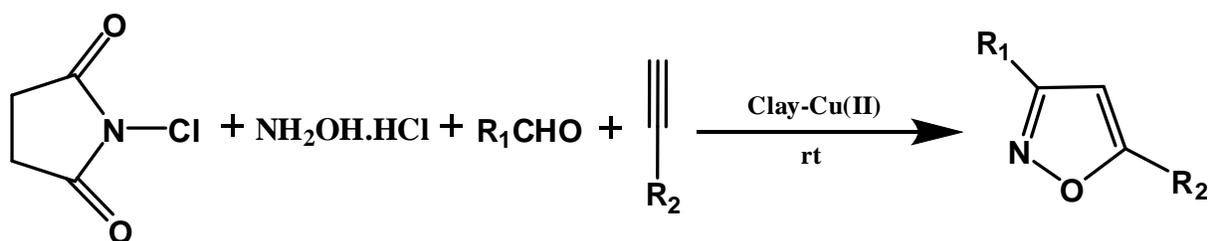
Scheme 23: Synthesis of the 3,4-disubstituted isoxazole derivatives

Ablajan and Xiamuxi reported the one-pot, multicomponent reaction of hydroxylamine, aromatic aldehydes and methyl 4-methyl-3-oxovalerate to produce 4-arylmethylidene-3-isopropylisoxazol-5-ones under ultrasonication in the presence of pyridine catalyst, in good to excellent yields [162] at RT condition. These approaches have some benefits towards green methods and good target product yields (Scheme 24).



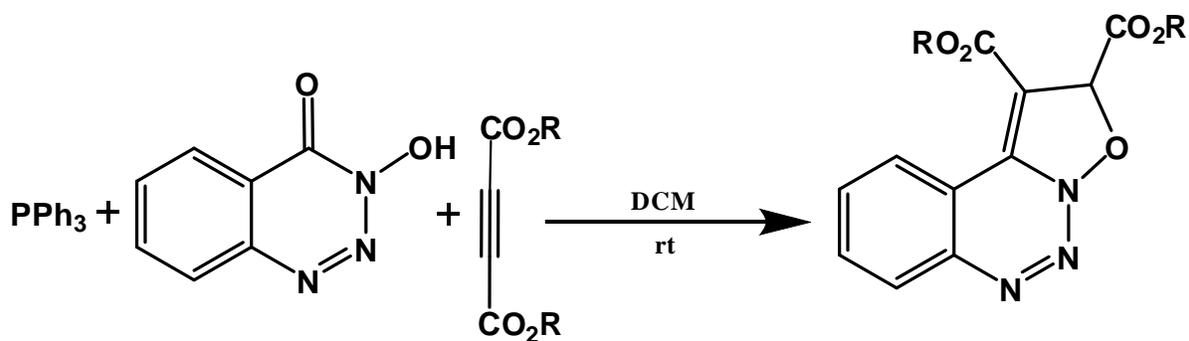
Scheme 24: Synthesis of the 4-Arylmethylidene-3-isopropylisoxazol-5-ones derivatives

Bharate et al., have developed a simple eco-friendly multicomponent one-pot synthetic procedure for novel 3,5-disubstituted isoxazoles (Scheme 25) [163]. The products were prepared in good yields from aromatic aldehyde, hydroxylamine hydrochloride and *N*-chlorosuccinamide in the presence of montmorillonite clay supported Cu(II)/NaN₃ catalytic system under green solvent conditions with good yields.



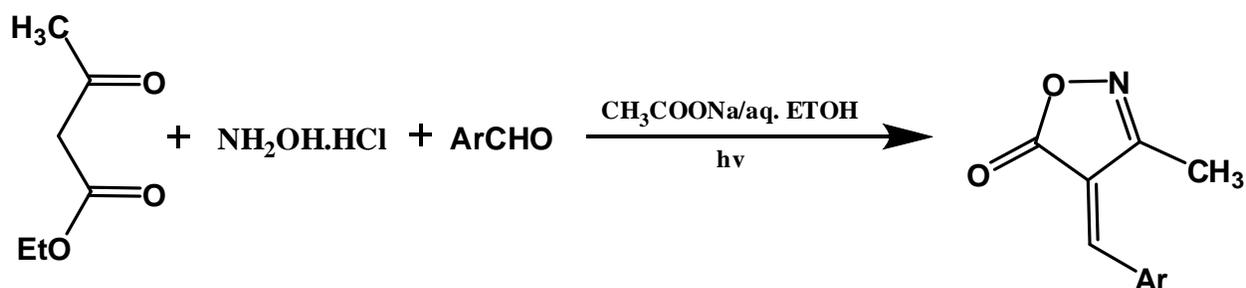
Scheme 25: Synthesis of the novel 3,5-disubstituted isoxazole derivatives

Farjam and Arab-Salmanabadi have discovered the novel highly substituted isoxazole derivatives by using this multicomponent reaction via an intramolecular Wittig reaction (Scheme 26). This was performed using dialkyl acethylenedicarboxylates, triphenylphosphine and 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine in the presence of DCM solvent at RT conditions [164].



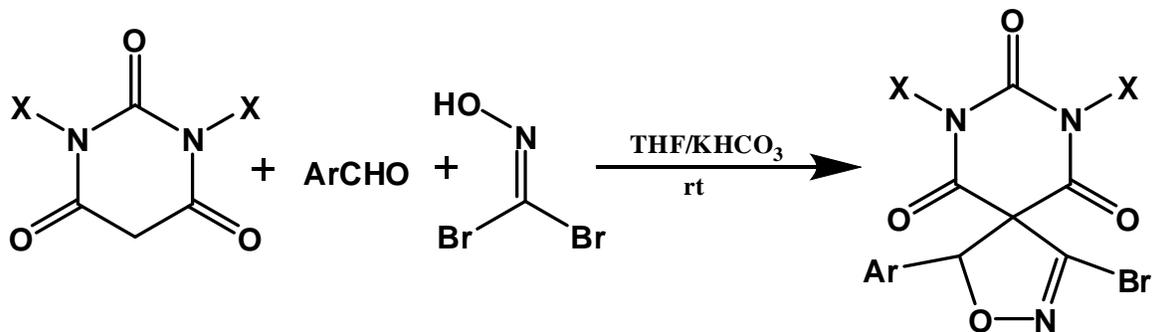
Scheme 26: Synthesis of novel highly substituted isoxazole derivatives

Saikh and co-workers have established a highly efficient synthetic protocol for synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4*H*)-ones using sodium acetate as a promoter and a visible light induced one-pot reaction involving ethyl acetoacetate, hydroxylamine hydrochloride and aromatic aldehydes in the presence of aqueous ethanol as solvent (Scheme 27) [165].



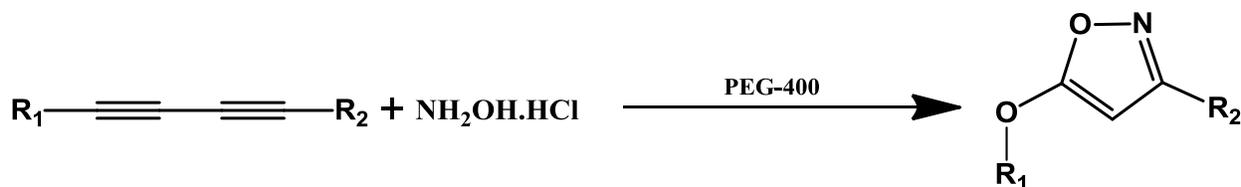
Scheme 27: Synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4*H*)-one derivatives

Soleimani and co-workers described a novel atom-economy protocol to give access to spiro-3-bromo-4,5-dihydroisoxazoles in 59-84% yield. They studied the scope of the process by employing various aldehydes, barbituric acid and dibromoformaldoxime. The reaction succeed via [1,3] dipolar cycloaddition at RT under THF solvent conditions (Scheme 28)[166].



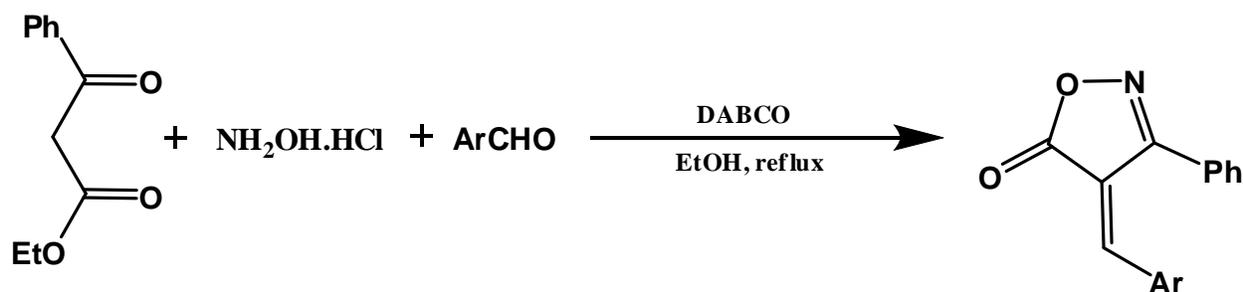
Scheme 28: Synthesis of spiro-3-bromo-4,5-dihydroisoxazoles

An efficient, atom-economic approach for the preparation of a new series of 3,5-disubstituted-1,2-isoxazoles was designated by Bassaco and co-authors through a consecutive one-pot, three-component condensation reaction of easily available symmetric or unsymmetric 1,3-diyne-indoles with hydroxylamine (Scheme 29). The reaction was accomplished in the presence of PEG-400 with TEA at RT in DMF solvent to yield the products in moderate to good yields [167].



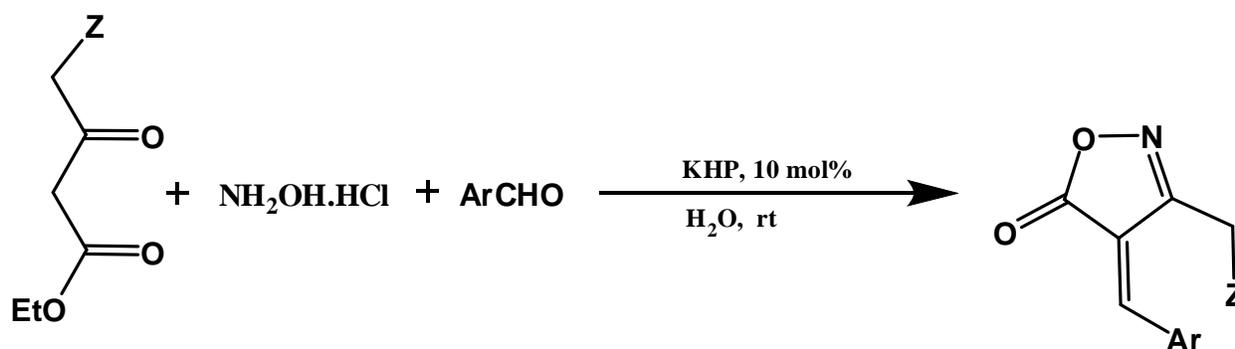
Scheme 29: Synthesis of a new series of 3,5-disubstituted-1,2-isoxazoles

Mirzazadeh and Mahdavinia revealed that DABCO could be an efficient catalytic system for this MCR and achieved the synthesis of novel 4-arylidene-3-phenylisoxazol-5-ones via a one-pot reaction of aromatic aldehydes, ethyl benzoylacetate and hydroxylamine in ethanol solvent under reflux condition (Scheme 30). This method presented the advantages of a simple, clean atom-economic, under mild conditions, with short reaction times, and low environmental impact and high yields [168].



Scheme 30: Synthesis of a new series of 4-arylidene-3-phenylisoxazol-5-one derivatives

Kiyani and Ghorbani proved that potassium hydrogen phthalate (10% KHP) as a catalyst and water as a solvent system may act as a very suitable medium for the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones by using ethyl cyanoacetate, aromatic aldehyde and hydroxylamine as a starting material (Scheme 31). The process is a facile, straightforward method for synthesis of a variety of pyranannulated compounds, isoxazol-5(4*H*)-one-containing heterocycles and Knoevenagel adducts. The reaction is safe, uses mild conditions, and is environmentally benign. Other notable advantages are reuse of the catalyst, no use of hazardous organic solvents, and ease of work-up [169].

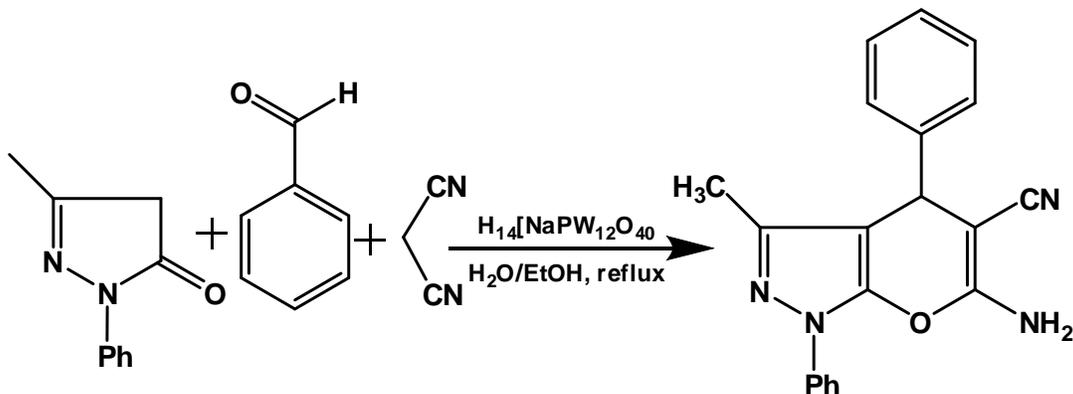


Scheme 31: Preparation of 3,4-disubstituted isoxazol-5(4*H*)-ones

1.4.2. Pyrazoles

A five membered cyclic diene consisting of three carbons and two nitrogens where the two heteroatoms are in adjacent position are known as a pyrazole. Knorr synthesized the first pyrazole derived compound, which steered path to the discovery of antipyrine and other derivatives [170]. Antipyrine was the first pyrazolone derivative in 1884, employed to treat pain, inflammation and fever [171]. The common structure of pyrazole is described in Figure 1. Pyrazoline was first reported in 1894 by Curtius and Wirsing through the spontaneous reaction of acrolein with hydrazine (Eqn.1) [172]. Pyrazoles are one of the most significant heterocyclic molecules. They are prepared as the main structure in a large diversity of molecules that display an important role in medicinal and pharmaceutical research, with activities such as antibacterial, antifungal, antitumor, antipyretic, anti-diabetic, anti-inflammatory, analgesic, anti-hyperglycemic, antineoplastic, anti-oxidant, anti-tubercular and anti-depressive activities [173-175]. Further, substituted pyrazole derivatives are used as interesting templates for combinatorial chemistry [174]. Moreover, these derivatives are found in a broad range of agricultural and industrial applications [176]. Several pyrazole derivatives have been successfully synthesized and the following are a few among the numerous methods that reported on the one-pot synthesis of pyrazoles.

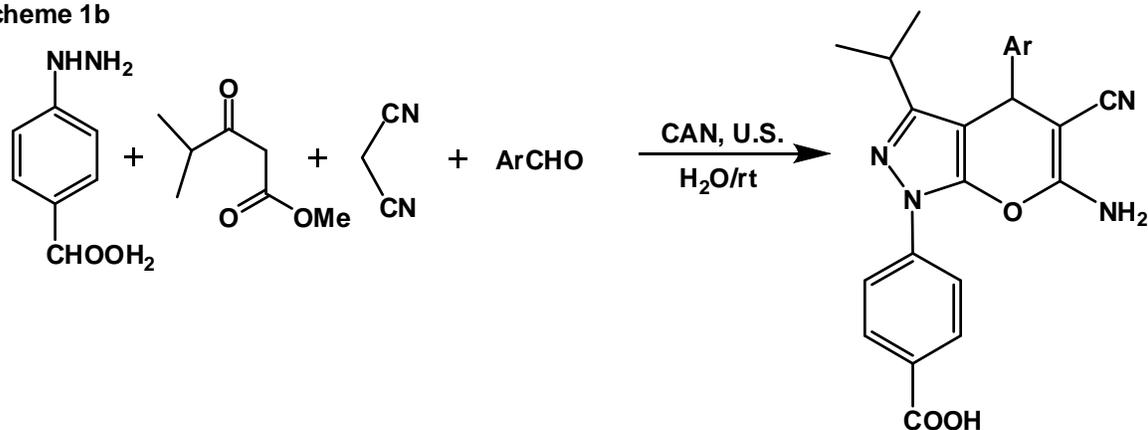
Heravi and co-workers described, a facile and an efficient method for the synthesis of 1,4-dihydropyrano[2,3-*c*]-pyrazole derivatives via a multi-component, one-pot condensation of aldehydes, malononitrile and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one in the presence of catalytic amounts Preyssler type heteropoly acid with aqueous solvent at reflux conditions (Scheme 32) [177].



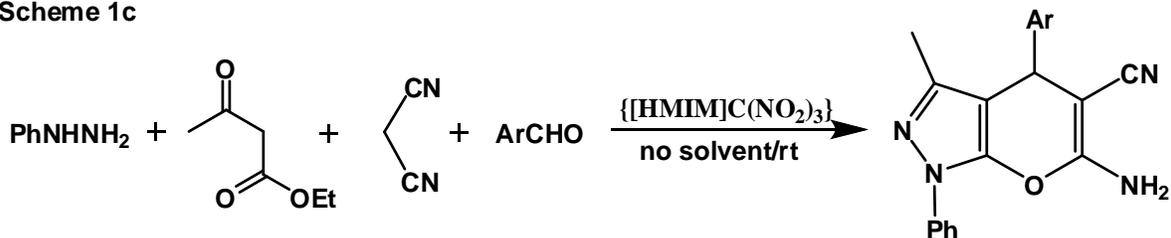
Scheme 32: One-pot MCR for the synthesis of 1,4-dihydropyrano[2,3-c] pyrazoles.^[157]

Syntheses of multi-substituted pyrano[2,3-c]pyrazole derivatives were reported by Ablajan and co-workers in 2013 [178]. The compounds were produced by the one-pot reaction between aromatic aldehydes, malononitrile, hydrazinobenzoic acid and β -keto ester, using cerium ammonium nitrate at RT under ultrasound irradiation with water as a solvent (Scheme 33a). Recently, Zolfigol and co-workers [179] have reported the synthesis of pyrazoles using a one-pot, multicomponent reaction of aromatic aldehydes, malononitrile, phenylhydrazine, β -keto ester and 1-methylimidazolium trinitromethanide and $\{[\text{HMIM}]\text{C}(\text{NO}_2)_3\}$ as a catalyst in the absence of solvent at room temperature. Good to high yields were reported after several minutes of reaction (Scheme 33b).

Scheme 1b

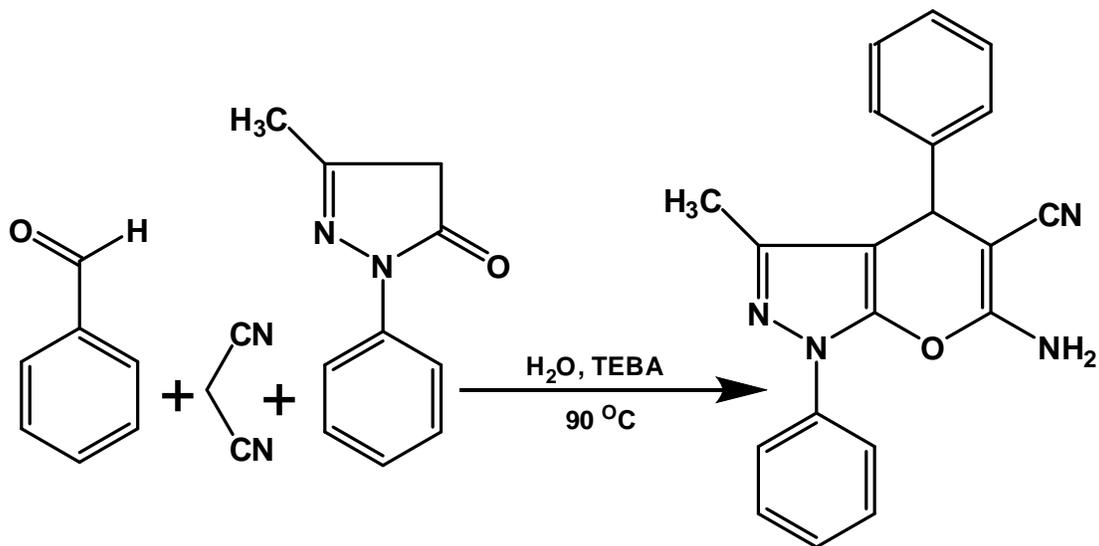


Scheme 1c



Scheme 33: Synthesis of multi-substituted pyrano[2,3-c]pyrazole derivatives

Zou and co-authors (2011) prepared 6-amino-5-cyano-4-aryl-1,4-dihydropyrano-[2,3-c]-pyrazoles from a 3-CR of malononitrile, aromatic aldehydes and 3-methyl-1-phenyl-2-pyrazolin-5-one using triethyl-benzyl ammonium chloride (TEBA) as catalyst in aqueous media (Scheme 34). The reaction offers many benefits such as good yield (82-94%), less pollution, ease of separation and eco-friendly [180].



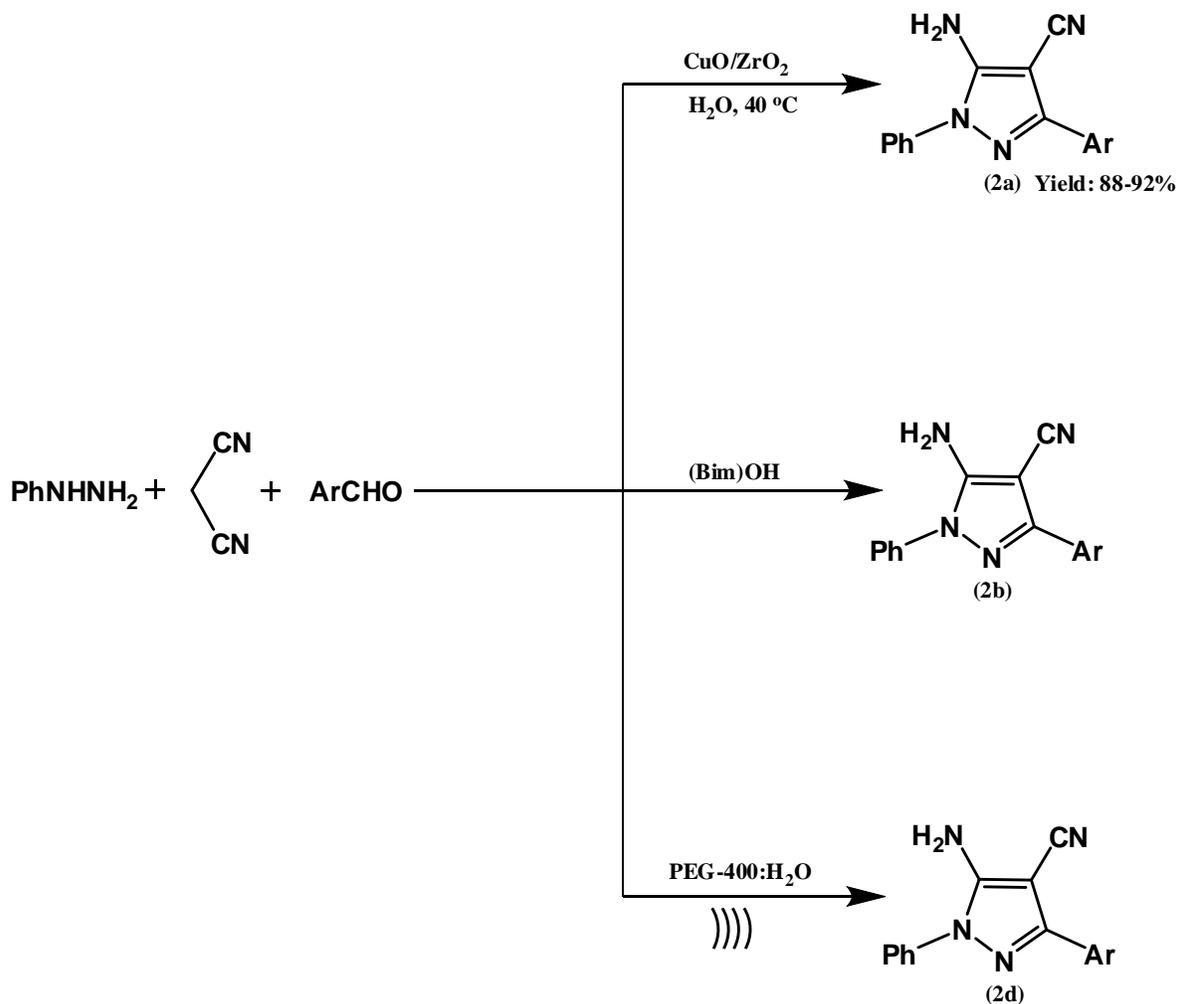
Scheme 34: Synthesis of 6-amino-5-cyano-4-aryl-1,4-dihydropyrano[2,3]pyrazoles^[159]

Copper oxide loaded zirconia (CuO/ZrO₂) was used as a catalyst for the three-component cyclo-condensation reaction of phenyl hydrazine, malononitrile and substituted aromatic aldehydes to synthesize 12 novel pyrazole-4-carbonitriles (Scheme 35a). The target molecules were afforded in good to excellent yields within 2 h. The heterogeneous catalyst used was cost-effective, well recyclable and reusable for over 5 cycles, conserving its high activity [181].

Recently, Srivastava and co-workers have improved the preparation of highly functionalized pyrazoles under grinding conditions with (Bim)OH, ionic liquid as a catalyst (Scheme 35b) [182]. The three-component cyclocondensation reaction between phenyl hydrazine, malononitrile and aromatic aldehydes in the presence of the ionic liquid was carried out in water as a solvent. A wide variety of functionalized pyrazoles was reported with high yields (88–97%) within 15-30 min.

Recently, Nemati et al., have developed the one-pot, multicomponent synthesis of highly substituted pyrazoles reacting assorted aldehydes with phenylhydrazine and malononitrile in the presence of PEG-400 in water medium at room temperature under ultrasound irradiation

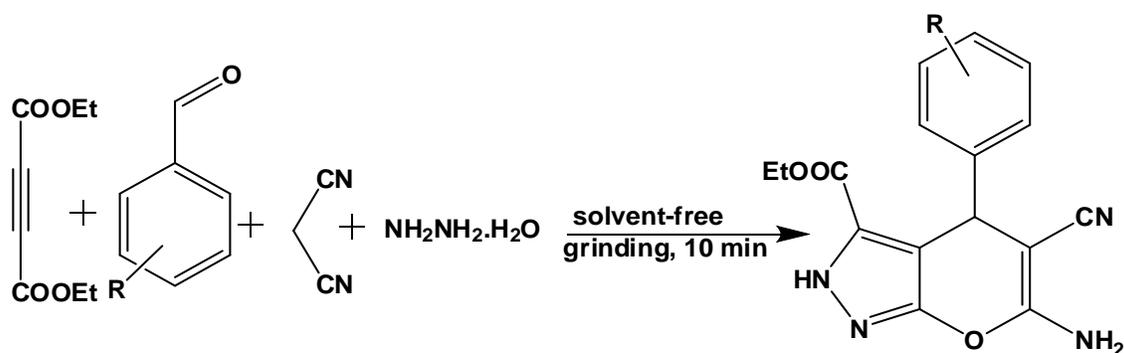
(Scheme 35c). Excellent yields (92–99%) of the pyrazole derivative have been reported [183]. The benefits of this catalyst-free protocol were use of cheaper starting materials, reduced environmental impact and short reaction times plus operational simplicity (< 1.5 h).



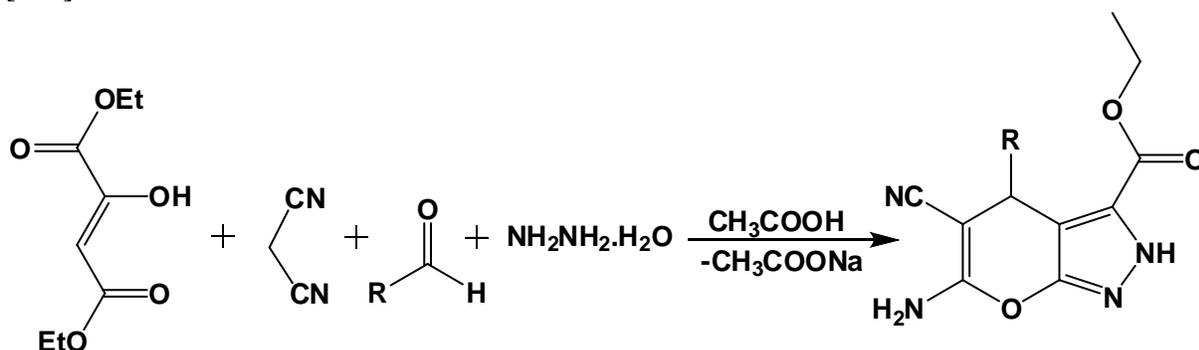
Scheme 35: Synthesis of multi-substituted pyrazole derivatives

Ambethkar et al. (2014) described an efficient grinding protocol for the synthesis of dihydropyrano[2,3-c]pyrazoles from the reaction of aryl halide, acetylene ester, hydrazine hydrate and malononitrile under solvent-free conditions (Scheme 36). The pyrazole derivatives were afforded in high yield (65-93%) [184].

Gein and co-workers (2014) developed a novel procedure for the synthesis for 6-amino-4-aryl-5-cyano-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate derivatives via a 4-CR of sodium salt of diethyloxaloacetate, an aromatic aldehyde, hydrazine hydrate and malononitrile (Scheme 37). The products were achieved in moderate to high yields (71-92%).

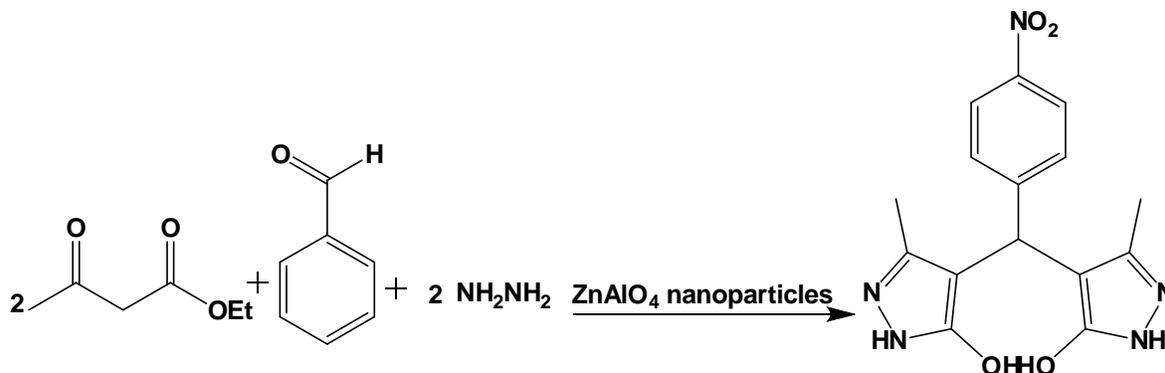


Scheme 36: Efficient grinding protocol for the synthesis of dihydropyrano[2,3-c]pyrazoles [185].



Scheme 37: Synthesis for 6-amino-4-aryl-5-cyano-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylates.

Safaei-Ghomi et al. (2014) described the synthesis of 4,4-(arylmethylene)bis(3-methyl-1H-prazol-5-ol) derivatives in the presence of ZnAlO₄ nanoparticles (Scheme 38). The product was formed from a The reaction used hydrazine hydrate, ethyl acetoacetate and aldehydes in water at 60 °C and provided excellent yields in short reaction times. The method is environment friendly.



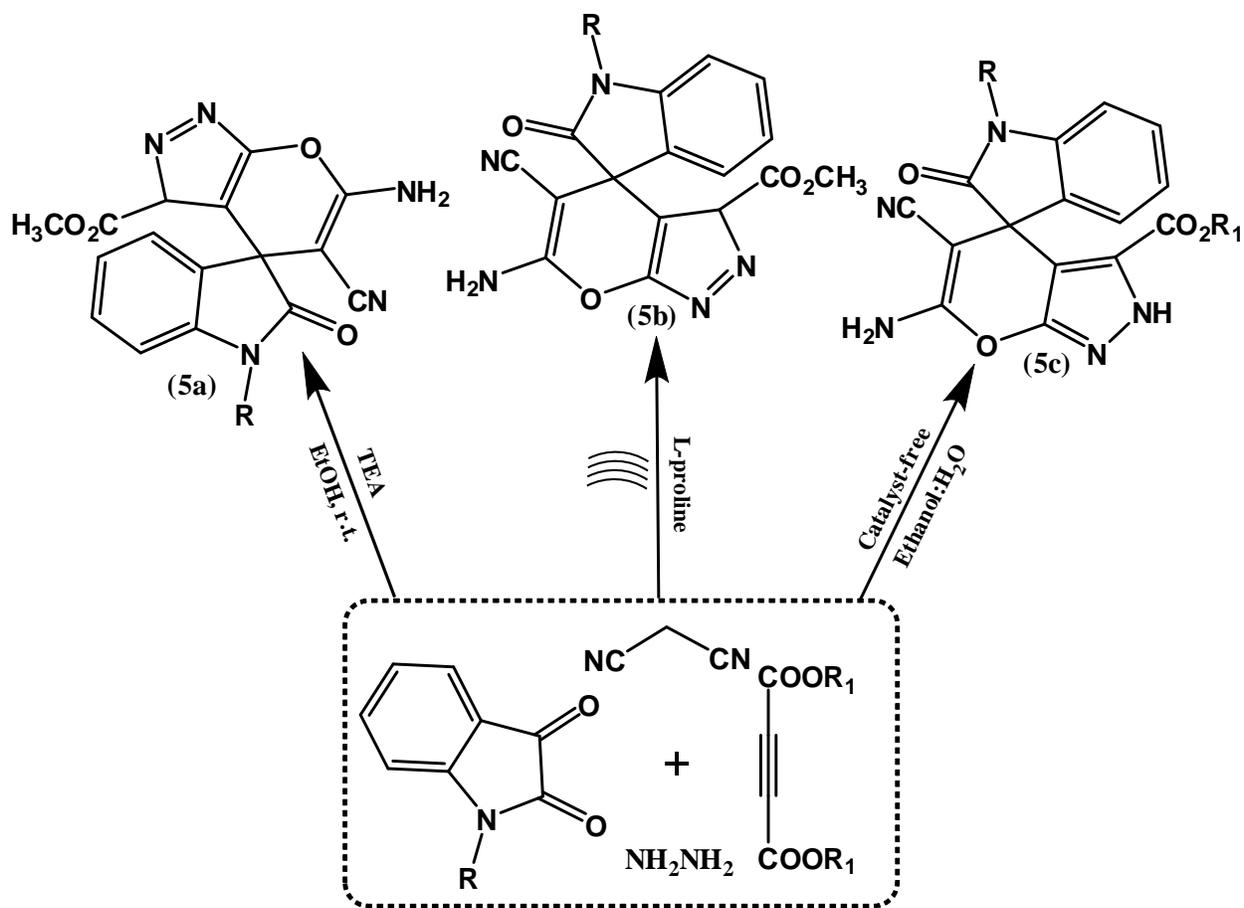
Scheme 38: Synthesis of 4,4-(arylmethylene)bis(3-methyl-1H-prazol-5-ol) derivatives in the presence of ZnAlO₄ nanoparticles [186].

A facile, efficient spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] and spiro[acenaphthyl-3,4-pyrano[2,3-c]pyrazoles] derivatives have synthesized by Wang et al.,. This was done through a one-pot, four component reaction of hydrate hydrazine, dimethyl acetylenedicarboxylate, malononitrile as well as ethylcyanoacetate. Triethylamine was used to catalyze the reaction which proceeded in ethanol solvent (Scheme 39a). The corresponding yields for the model reaction were satisfactory (75-85%). The reaction proceeded for 5 h, at RT. For comparison, acenaphthenequinone substrate was used to replace ethylcyanoacetate. The reaction proceeded at room temperature for 24 h to obtain spiro[acenaphthyl-3,4'-pyrano[2,3-c]pyrazoles] with 85-92% yields.

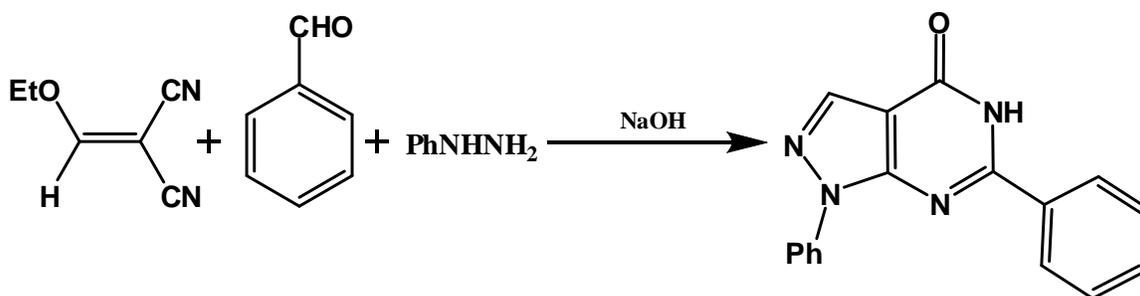
Liju and co-authors have improved an ideal reaction using an efficient, one-pot ultrasound irradiation procedure for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]. L-proline was used as catalyst for the reaction at room temperature (Scheme 39b) [187]. The reaction involved four component system of malononitrile, diethyl acetylenedicarboxylate, isatin and 4-hydrazinobenzoic acid in the presence of a mixture of aqueous ethanol (H₂O/EtOH, 1:1 v/v). The L-proline catalyst gave 90% yield for this reaction and L-proline (10 mol%) was found optimal. To avoid the reaction rate acceleration by the temperature variation due to ultrasonication, the reaction was carried in a water bath to maintain the temperature at 25 °C.

Pore et al. explored a green approach to synthesize novel spiro pyranopyrazole derivatives in the absence of catalyst [188]. The four-component/one-pot reaction between hydrazine hydrate, malononitrile, dimethyl acetylenedicarboxylate and isatin (Scheme 39c) proceeded well in polar solvent under reflux for 2 h, with moderate yield, but water:ethanol (80:20, v/v) as solvent gave 86% of desired product. This green reaction is environmentally friendly with no waste.

Ming-Xing and co-authors have established an innovative base catalysed synthetic route for the preparation of pyrazolo[3,4-d]pyrimidinone derivatives via tandem heterocyclization by the one-pot, multicomponent condensation of hydrazine, methylenemalononitrile and aldehyde under reflux conditions [189,190]. The reaction progressed efficiently at a faster rate in toluene using NaOH (0.2 mmol). The yields of the products were good to excellent (77–91%) depending upon substituents (Scheme 40).

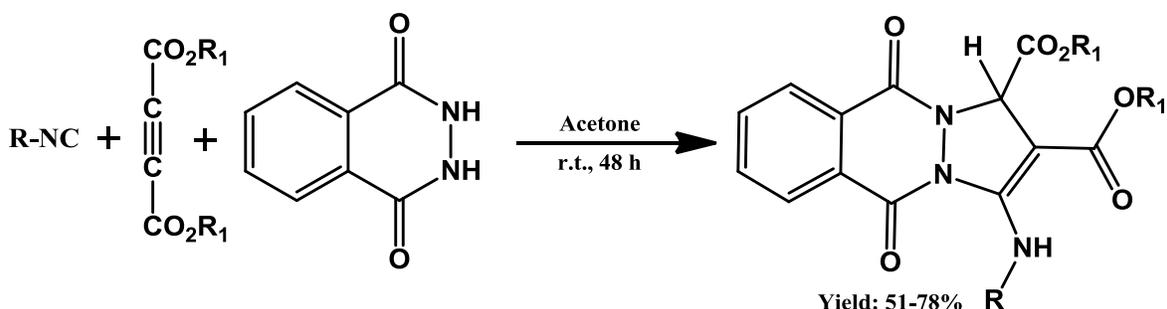


Scheme 39: Synthesis of novel spiro pyranopyrazole derivatives



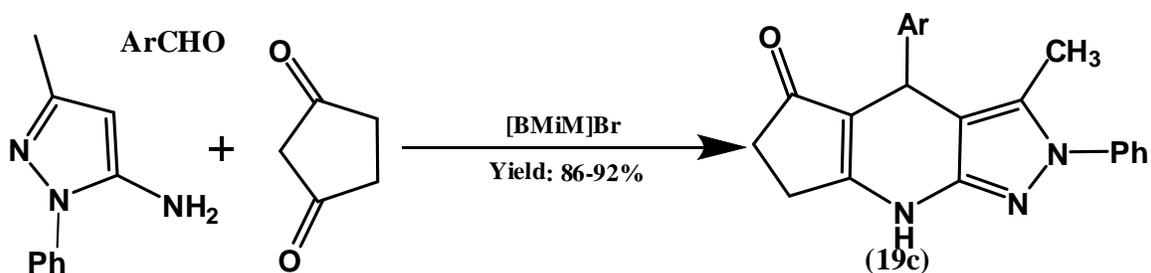
Scheme 40: Synthesis of novel pyrazolo[3,4-d]pyrimidinone derivatives

An expedient, effective, eco-friendly and catalyst-free method had been established by Teimouri leading to a series of 1*H*-pyrazolo-[1,2-*b*]-phthalazine-5,10-diones (Scheme 41) [191]. The procedure is an excellent means for synthesis of one-pot multicomponent reactions. Due to their convergence and efficiency, this innovative synthetic approach could be fascinating from a green chemistry point of view.



Scheme 41: Synthesis of 1*H*-pyrazolo-[1,2-*b*]-phthalazine-5,10-dione derivatives

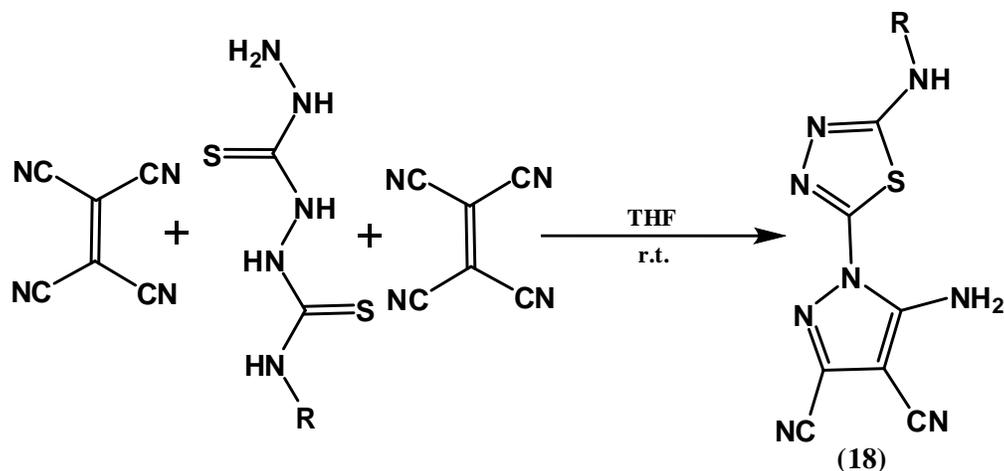
Bin-Bin and his group have produced fused polycyclic 4-aryl-3-methyl-1-phenyl-7,8-dihydro-1*H*-pyrazolo[3,4-*b*][1,6]naphthyridin-5(4*H*) by using as precursors aromatic aldehyde, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and piperidine-2,4-dione in the presence of ionic liquids. Initially the reaction was tested with different varieties of ionic liquids and finally [BMIm]Br was optimized for this organic transformation (Scheme 42) [192].



Scheme 42: Synthesis of fused polycyclic 4-aryl-3-methyl-1-phenyl-7,8-dihydro-1*H*-pyrazolo[3,4-*b*][1,6]naphthyridin-5(4*H*) derivatives

Hassan and co-workers [193] have established tetracyanoethylene as a mediator for condensation–cyclization succession containing the reaction of thiocarbonohydrazides and tetracyanoethylene at RT in the presence of THF solvent. The process carried out the preparation of 5-substituted amino-1,3,4-thiadiazolyl-1*H*-pyrazoles with good yields (Scheme 43).

Synthesis of spiro-indoline-3,4'-pyrano[2,3-*c*]pyrazoles have been reported by an efficient ultrasound-assisted four component Knoevenagel condensation a through Michael addition reaction in liquid phase in the presence of ethanol at room temperature after 1 h. It was carried out using piperidine as a catalyst. Various 1,3-diketones, phenyl hydrazine, isatin, and malononitrile gave the corresponding spiropyrano[2,3-*c*]pyrazole derivatives in excellent yields (77–93%) (Scheme 44a) [194].



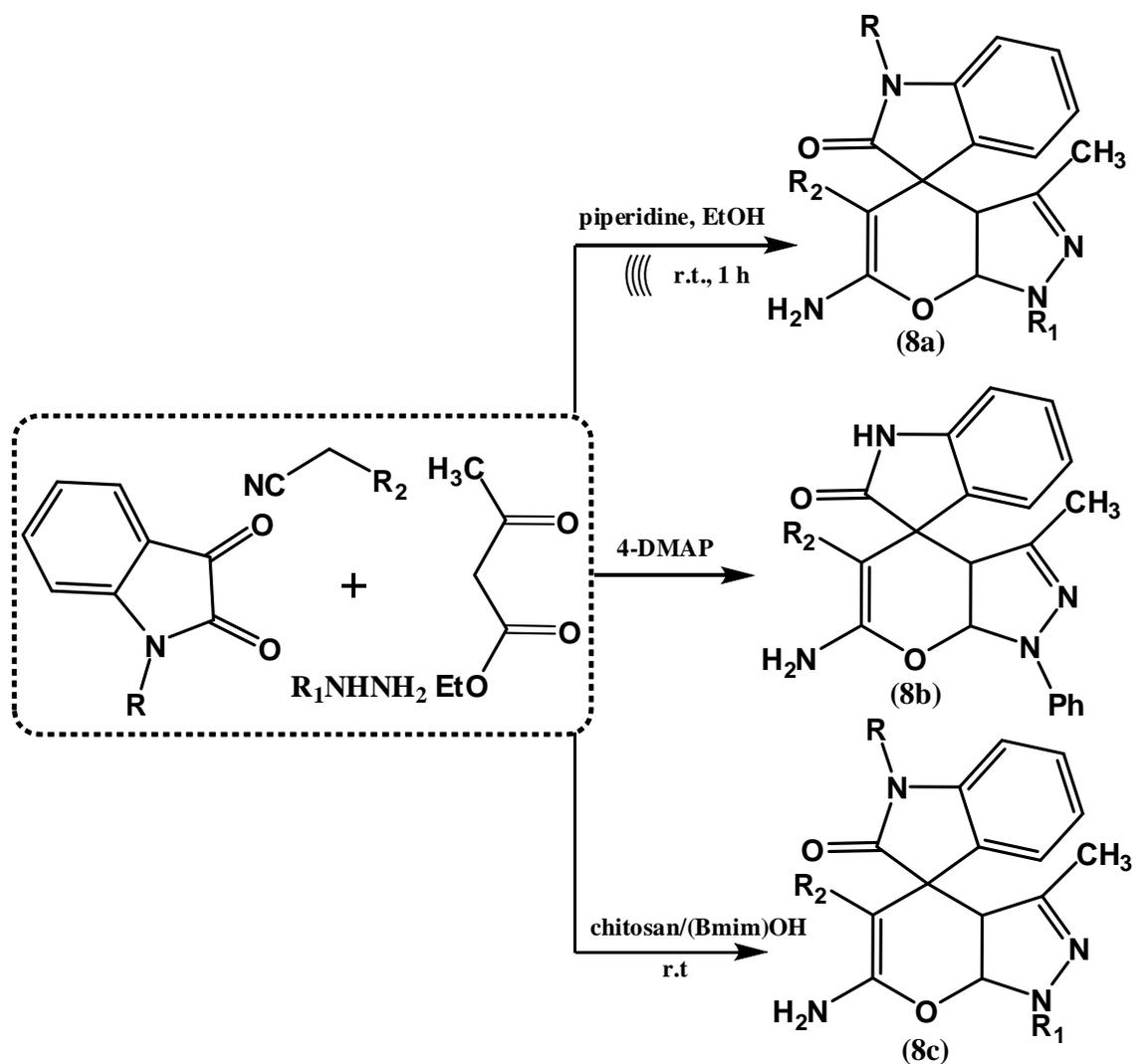
Scheme 43: Synthesis of 5-substituted amino-1,3,4-thiadiazolyl-1*H*-pyrazoles

Recently, Feng et al., have synthesized diverse indoline-3,4'-pyrano[2,3-*c*]pyrazoles using a 4-dimethylaminopyridine (4-DMAP) as a catalyst (Scheme 44b). As a result, various spiropyrazole derivatives were achieved with improved yields from the reaction of isatins, malononitrile, phenylhydrazine and 1,3-dicarbonyl compounds at 60 °C in ethanol as the solvent and 1 h reaction time [195].

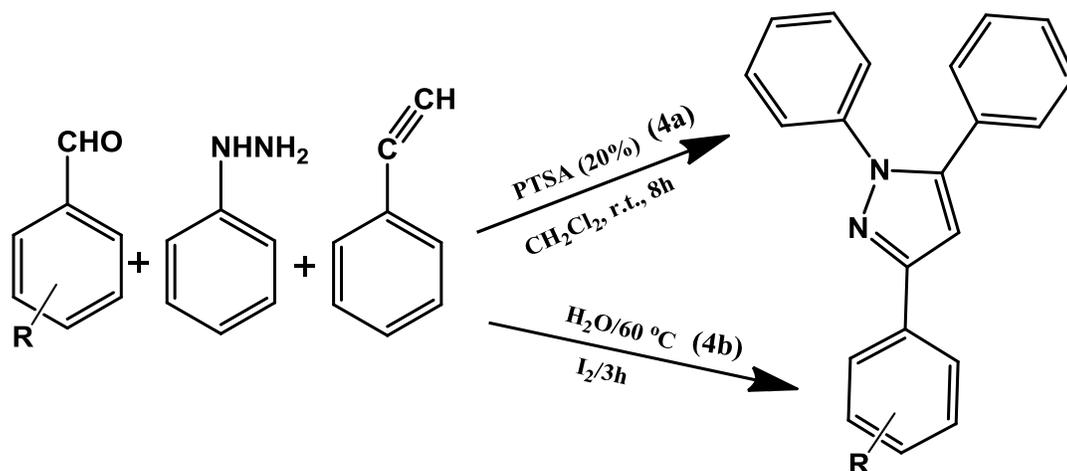
More recently, Rai et al. have reported the cyclocondensation of ethylacetoacetate, phenylhydrazine, malononitrile, isatin and chitosan/(Bmim)OH as a heterogeneous catalyst. Reactions were completed smoothly in the absence of any solvent at room temperature to obtain the corresponding spiropyrazole derivatives in excellent yields (Scheme 44c). In this reaction, the catalyst was fully recyclable and recorded no appreciable change in activity for 4-6 cycles [196].

Liu et al.,¹¹⁹ revealed that phenylhydrazine efficiently react with alkyne and aromatic aldehydes to deliver 1,3,5-substituted pyrazole derivatives in the presence of *p*-toluenesulfonic acid (PTSA) as an active multifunctional catalyst at RT, but with long reaction time (8 h) leading to low yields (Scheme 45a) [197]. This synthesis method proceeded through the Mannich type-cyclization tandem process.

Recently, highly functionalized 1,3,5-trisubstituted pyrazoles were reported by intramolecular cyclization of aromatic aldehydes, phenylacetylene and phenylhydrazine in the presence of iodine as a catalyst in a aqueous medium reaction (Scheme 45b) [198]. All the target protocols were completed within 3 h at 60 °C with good to high yields (79–93%).



Scheme 44: Synthesis of spiroprano[2,3-c]pyrazoles

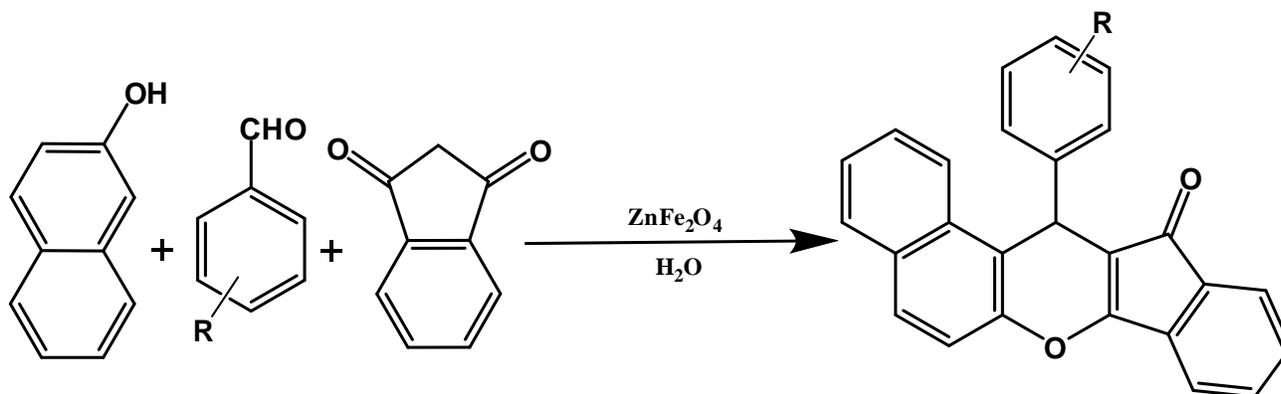


Scheme 45: Synthesis of highly functionalized 1,3,5-trisubstituted pyrazole derivatives

1.4.3. Pyrans

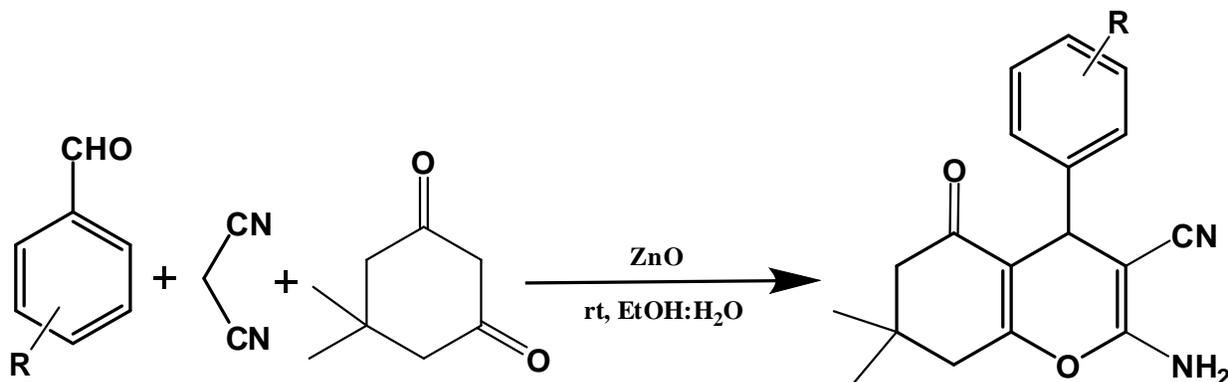
Pyrans are six membered oxygen containing heterocycles and are one of the most desired heterocycles. Their structural motif makes up numerous natural products, pharmaceuticals, advanced materials, catalysis and ligands. They exhibit a wide-range spectrum of activities with bio-, physio- and pharmacological properties [199]. They are beneficial compounds of importance in bio-organic and medicinal chemistry. Those can be used as precursors to synthesize chiral dihydro- and tetrahydropyrans. Pyrans generally are synthesized from cyclocondensation of aldehydes, β -ketoester and malononitrile in alcohol [200]. The known natural products that contain a pyran core include Uvafzlelin, Conrauinone A, Erysenegalensein C, Cromakalim and Acronycine [201], these compounds display significant and diverse medicinal properties such as antibacterial [202], as potential 5-HT_{1A} receptor antagonists [203] and anticancer agent [204]. Owing to the wide applications of pyran and their derivatives, designing and developing new methodologies for their synthesis have attracted attention from both synthetic and medicinal chemists [201]. The synthesis of pyrans that have been reported in the literature are mostly through multicomponent reaction methods. Among them are the following reactions (scheme 67-79) which successfully yielded different derivatives of pyrans.

Das and co-workers have described in good yield the synthesis of pyrano-pyrazole compounds namely, ethyl 6-amino-4-aryl-5-cyano-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylates by one-pot multi-component reaction employing aldehyde, β -naphthol and indane-1,3-dione in the presence of ZnFe_2O_4 nanopowder as catalyst, for the transformation into the desired product at RT under aqueous conditions (Scheme 46)[205].



Scheme 46: Synthesis ethyl 6-amino-4-aryl-5-cyano-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylates

Banerjee and Saha prepared tetrahydrobenzo[b]pyran compounds, by using nano free-ZnO, as a heterogeneous reusable catalyst used with a combination of aldehyde, malonitrile and dimedone in aqueous ethanol at RT. In this study, nano ZnO particles with its unique viscoelastic properties facilitated the reaction (Scheme 47) [206].

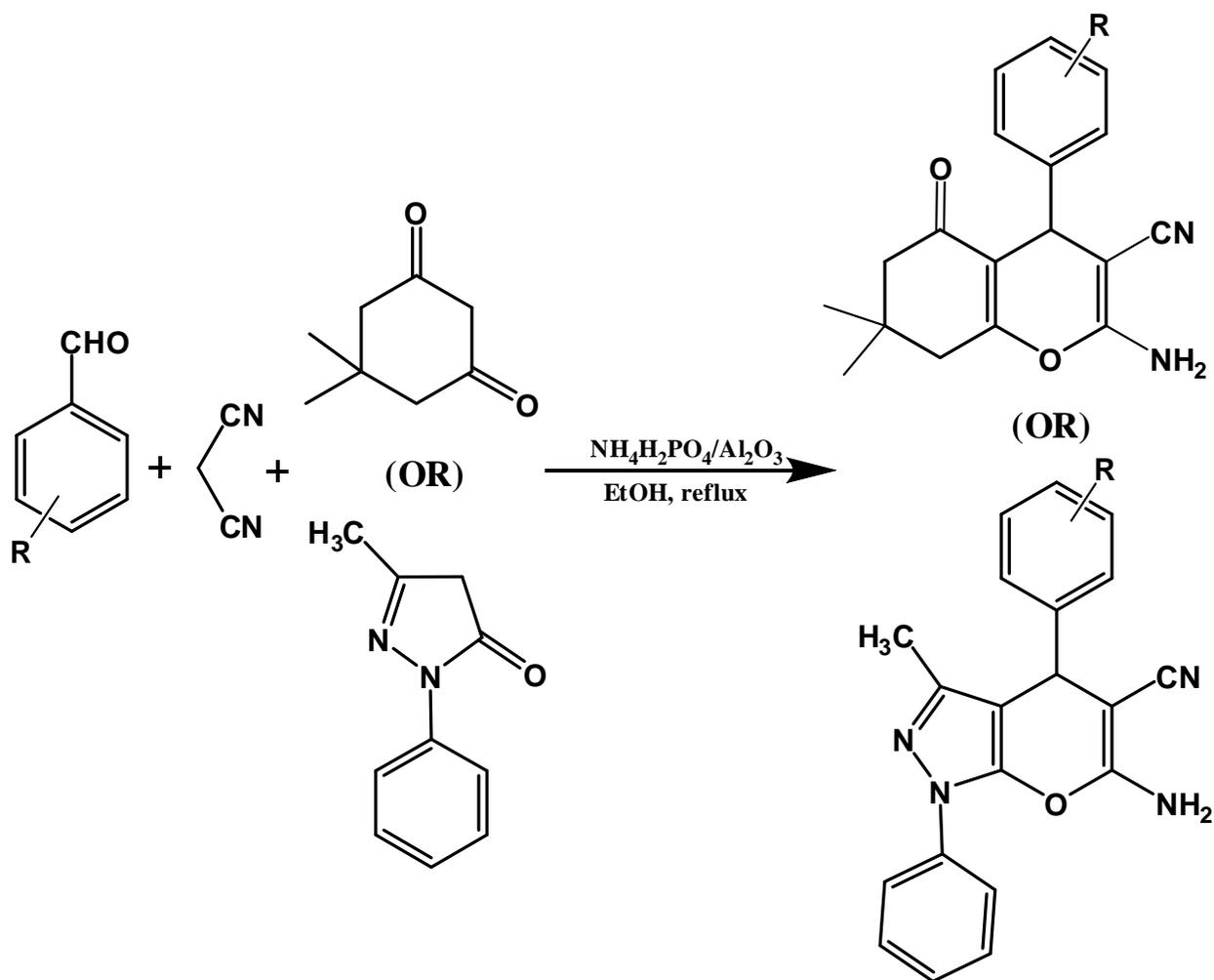


Scheme 47: Synthesis tetrahydrobenzo[b]pyran derivatives

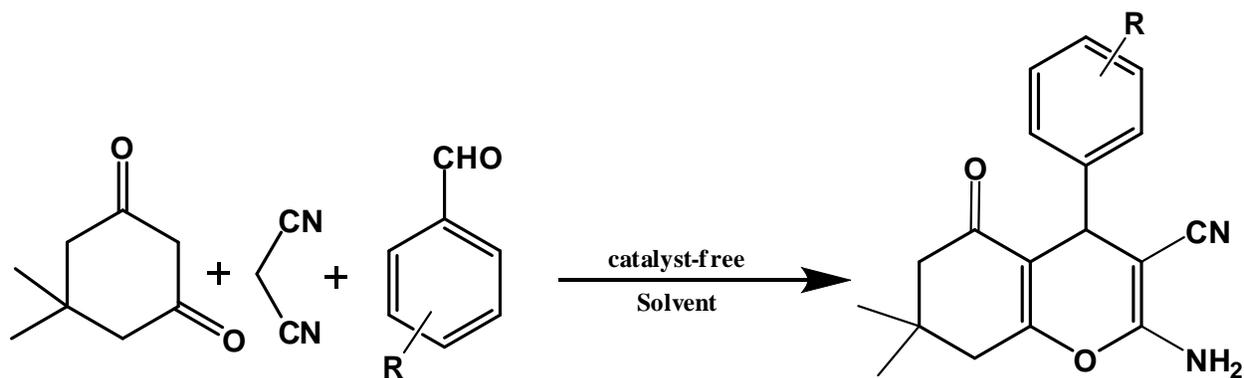
Maleki and Ashrafi have synthesized heterocycles with a pyrazole moiety using Nano Al_2O_3 supported ammonium dihydrogen phosphate ($\text{NH}_4\text{H}_2\text{PO}_4/\text{Al}_2\text{O}_3$) as excellent catalysts and described the ease of recovery, reusability with the avoidance of environmentally inappropriate solvents. They synthesized the pharmaceutically relevant and easily work-up synthesis of tetrahydrobenzo[b]pyran and pyrano[2,3-*c*]pyrazole derivatives with aromatic aldehyde, malononitrile and 1,3-dicarbonyl compounds in the presence of $\text{NH}_4\text{H}_2\text{PO}_4/\text{Al}_2\text{O}_3$ in ethanolic medium under reflux conditions (Scheme 48)[207].

Safaei et al.,[208] have focused on the preparation of 4*H*-pyrans derivatives using glycerol as a biodegradable and reusable promoting solvent at 80 °C under catalyst-free conditions. The proposed mechanism suggested that the intermediates pyrazolone and 2-benzylidenemalononitrile formed underwent Michael addition to form the desired product through an environmentally benign procedure (Scheme 49).

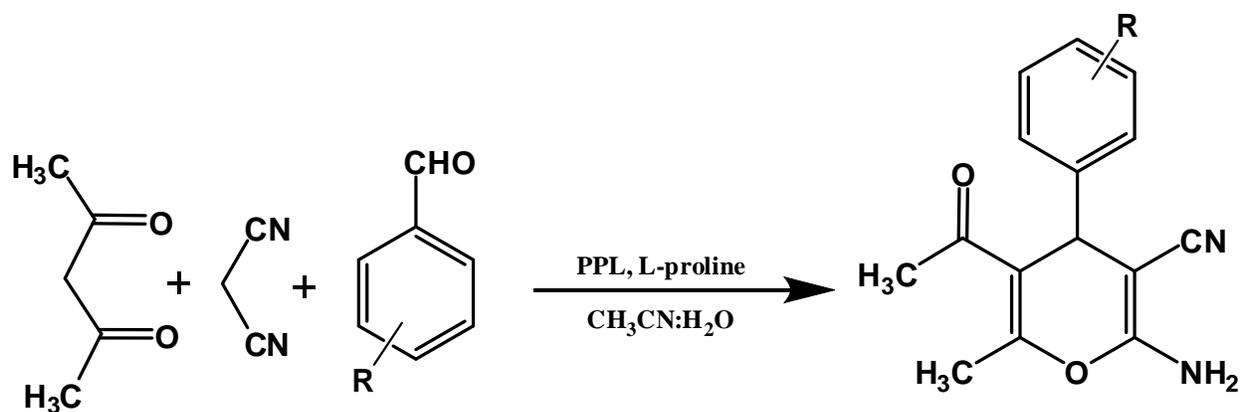
Bora and coworkers showed a unique procedure for the preparation of medicinally viable polyfunctionalized 4*H*-pyrans, with lipase as catalysts. Ionic liquids are not congenial to many organic syntheses, but here the desired product was obtained by using cheap and stable catalyst, PPL as catalyst for the precursor's aryl aldehydes, malononitrile, acetyl acetone (Scheme 50) [209].



Scheme 48: Synthesis tetrahydrobenzo[b]pyran and pyrano[2,3-c]pyrazole derivatives

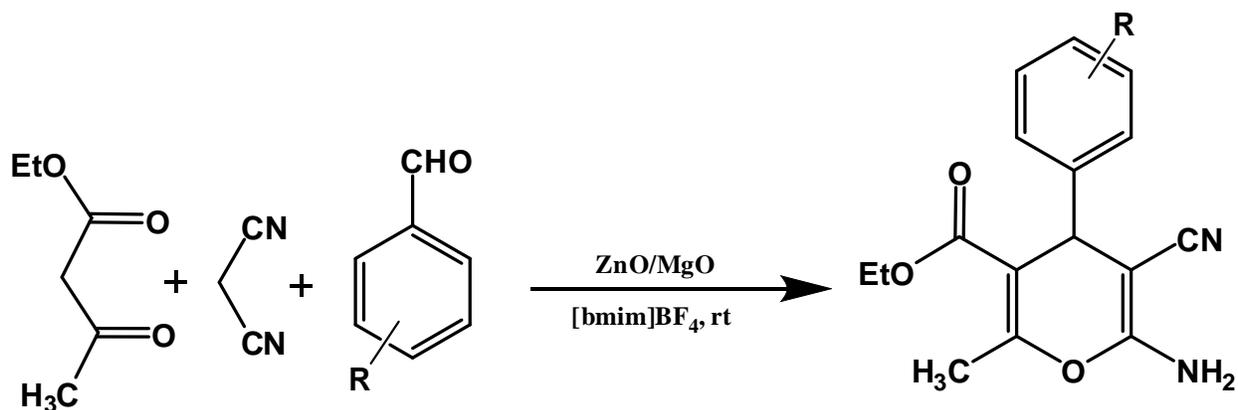


Scheme 49: Synthesis of the 4H-pyran derivatives



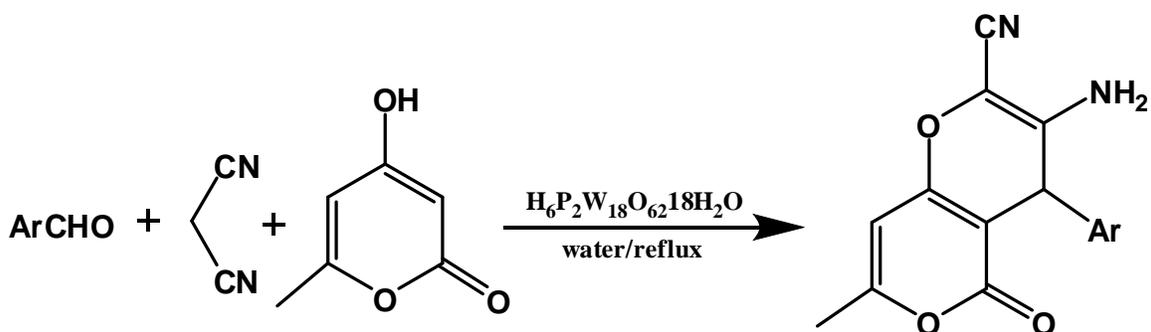
Scheme 50: Synthesis of the polyfunctionalized 4*H*-pyran derivatives

Valizadeha and Azimi groups described the synthesis of 4*H*-pyrans using a nano ZnO/MgO heterogeneous catalyst. In this study the mixture ethylacetoacetate, benzaldehyde, malononitrile, ZnO/MgO catalyst were reacted at RT under [bmim]BF₄ as a solvent. The protocol proposed here is an environmentally friendly procedure, including stable, easily storable, easy recovery and reusability of nanocatalyst (Scheme 51) [210].



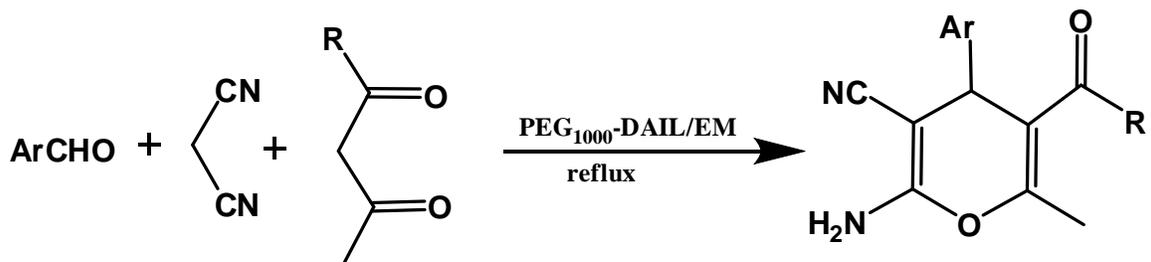
Scheme 51: Synthesis of the 4*H*-pyran derivatives

Rajguru and coauthors have developed a convenient, efficient and environmentally benign method for pyrano[4,3-*b*]pyran derivatives starting with aromatic aldehyde, malononitrile and 4-hydroxy-6-methylpyran-2-one and using H₆P₂W₁₈O₆₂18H₂O as heterogeneous catalyst. The catalyst offers non-toxicity, ready availability and strong oxidizing benefits. The study revealed that 1 mol% of H₆P₂W₁₈O₆₂18H₂O is efficient to reach the desired outcome (Scheme 52) [211].



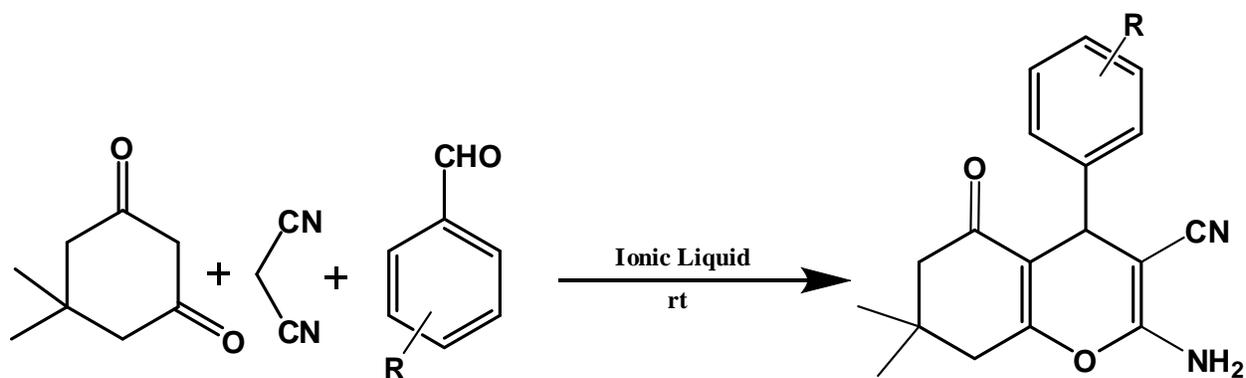
Scheme 52: Synthesis of the pyrano[4,3-b]pyran derivatives

Fang et al., have fabricated hermol-regulated PEG1000-based ionic liquid/EM and its catalytic behavior was identified with the preparation of 4*H*-pyrans containing organic compounds. The authors synthesized pyran derivatives through a one-pot, multi-component condensation of malonitrile, ethyl acetoacetate and aromatic aldehyde compounds in the presence of the catalyst. The used acidic ionic liquid catalyst was separated with help of temperature-dependent phase-separation catalytic field and re-used with no loss of catalytic activity (Scheme 53) [212].



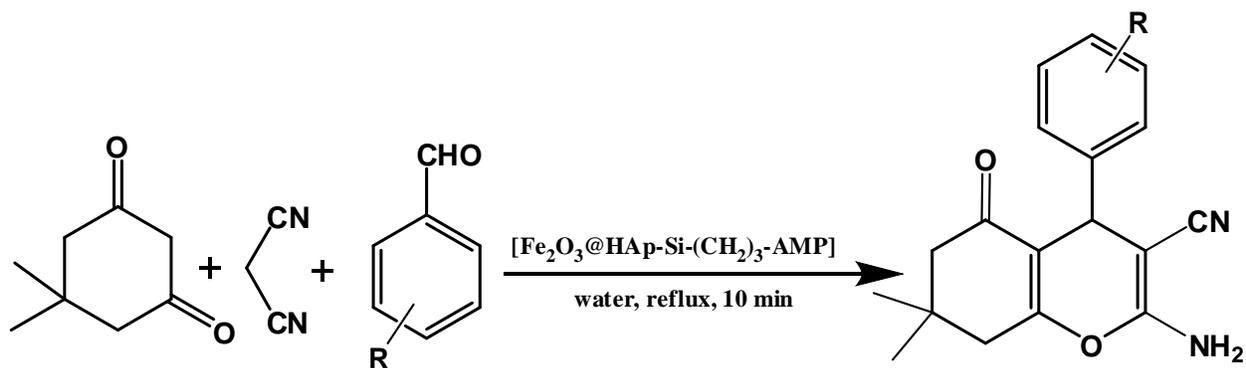
Scheme 53: Synthesis of novel pyrazolo[3,4-d]pyrimidinone derivatives

Salvi et al., have investigated the preparation of tetrahydrobenzo[*b*]pyran derivatives employing a novel functionalized basic ionic liquid, 4-amino-1-(2,3-dihydroxy propyl) pyridinium hydroxide [ADPPY][OH]. The best condition for the preparation of tetrahydrobenzo[*b*]pyrans with good yields was reported to be with equal ratio of aryl aldehyde, malononitrile and dimedone in the presence of 10% catalyst at RT in the presence of water as a solvent (Scheme 54) [213].



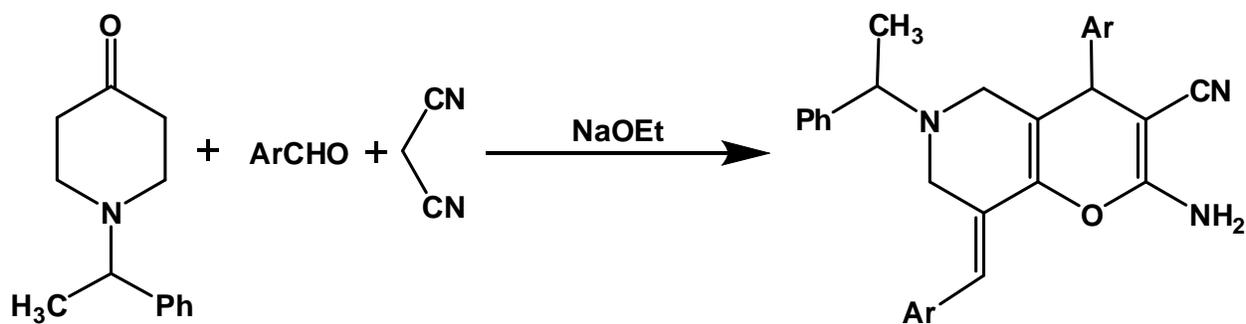
Scheme 54: Synthesis of novel pyrazolo[3,4-d]pyrimidinone derivatives

Khoobi et al., prepared 4H-benzo[b]pyran and dihydropyrano[c]chromene derivatives by using basic non-volatile inorganic–organic hybrid magnetic nanocatalyst $[\gamma\text{-Fe}_2\text{O}_3\text{@HAp-Si-(CH}_2\text{)}_3\text{-AMP}]$, as heterogeneous catalyst under ambient conditions using an equal proportion of aromatic aldehyde, hydrazine hydrate, malononitrile and 4-hydroxycoumarin/ dimedone. The study showed that 1.5 mol% catalyst was optimum for the reaction in order to achieve 88% yield of the final product in 10 min reaction time (Scheme 55) [214].



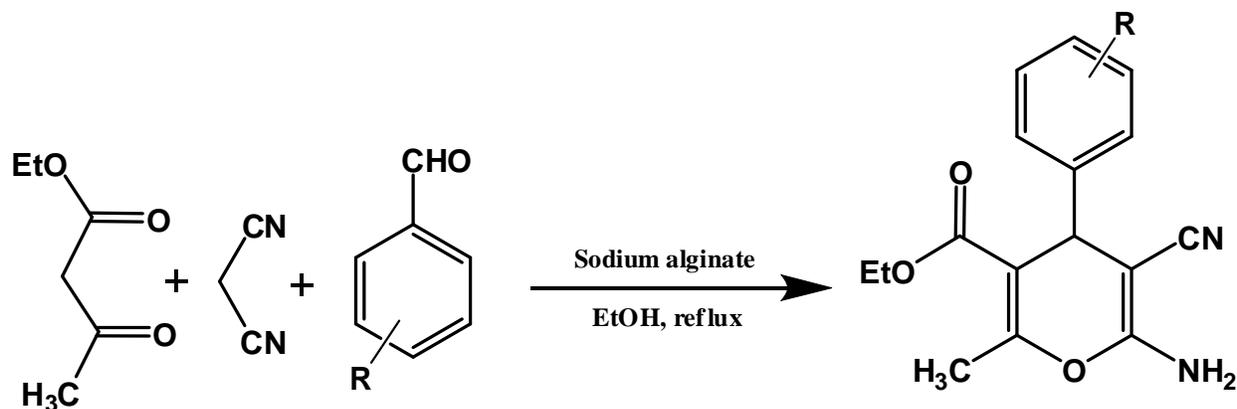
Scheme 55: Synthesis of novel pyrazolo[3,4-d]pyrimidinone derivatives

Almansour and co-workers designed a facile method for the preparation of biologically active 4(H)-pyran derivatives by using sodium ethoxide as a basic catalyst. The results suggested that the catalyst works best for the reaction having the mixture of arylaldehyde, malononitrile and (R)-1-(1-phenylethyl)tetrahydro-4(1H)-pyridinone within short period of time to get the 4(H)-pyrans in good yield under solvent-free conditions (Scheme 56)[215].



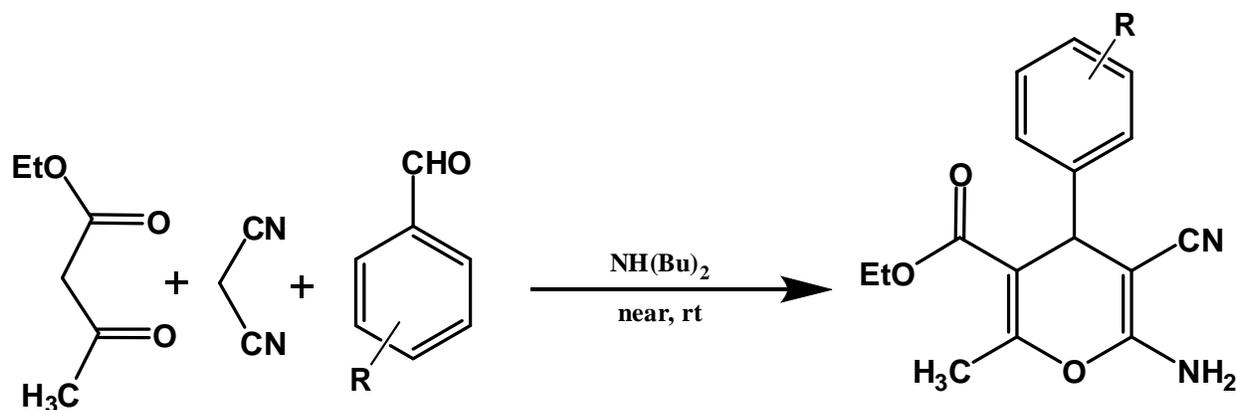
Scheme 56: Synthesis of biologically active 4(H)-pyran derivatives

Dekamin et al., have prepared 2-amino-4H-pyran derivatives through one-pot, three-component condensation of aromatic aldehydes, malononitrile and 1,3-dicarbonyl compounds in ethanol solvent at 80 °C by using sodium alginate as biopolymeric green catalyst. In compliance with the green chemistry principles, optimum reaction conditions were reported as 80 °C, catalyst (10 mol%), green solvent, where the anticipated product was obtained in good to high yield within a short reaction time (Scheme 57) [216].



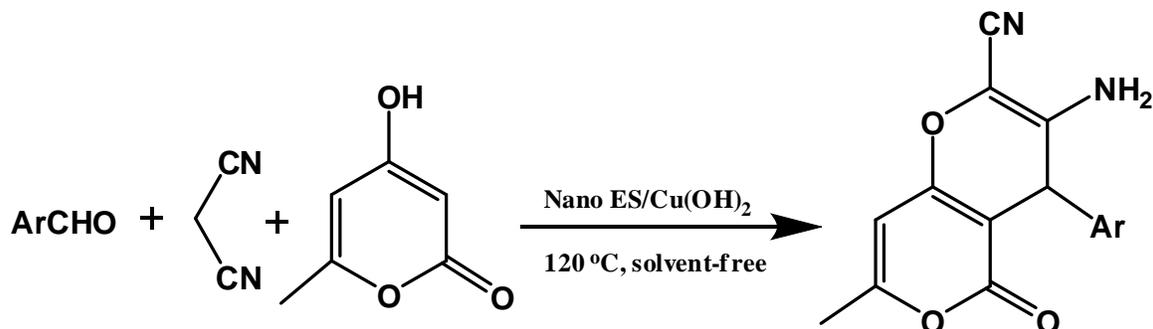
Scheme 57: Synthesis of 2-amino-4H-pyran derivatives

Kalla and co-workers have demonstrated the catalytic activity of dibutylamine towards the preparation of pyran derivatives from a one-pot, multi-component reaction of aromatic aldehydes, malononitrile and ethyl benzoylacetate. The authors proposed metal free organocatalysts for the organic transformations. This process offers more benefits, because it is mild, environmentally friendly, gives good to high yields in short reaction times. Moreover, the product did not necessitate separation via extraction and column chromatography (Scheme 58) [217].



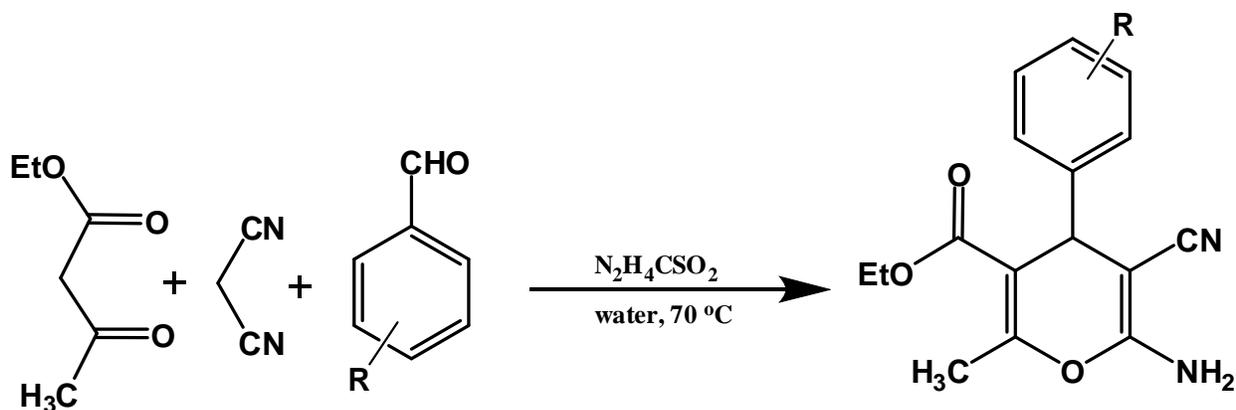
Scheme 58: Synthesis of substituted pyran derivatives

Mosaddegh and his group have prepared pyrano[4,3-b]pyran derivatives by using novel and highly effective heterogeneous catalyst as an eggshell (ES) supported $\text{Cu}(\text{OH})_2$ nanoribbons containing 8 wt.% Cu^{2+} , and meet the principles of green chemistry. A mixture of malononitrile with aldehyde and 4-hydroxy-6-methyl-2H-pyran-2-one were subjected to reaction in 0.1 g of catalyst in EtOH with final product having good yields. The study also stressed the good compatibility of ES/ $\text{Cu}(\text{OH})_2$ nanocomposite catalyst for the aldehydes precursor organic transformations (Scheme 59) [218].



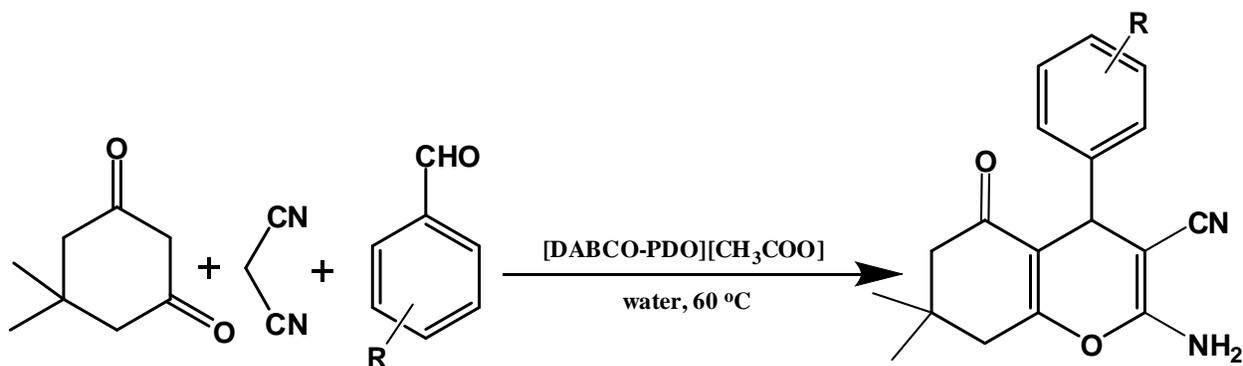
Scheme 59: Synthesis of novel pyrano[4,3-b]pyrans derivatives

Mansoor et al., have proposed thioureadioxide as an efficient, reusable organic catalyst for the synthesis of a series of 6-amino-5-cyano-4-aryl-2-methyl-4H-pyrans from the mixture of malononitrile, 4-hydroxycoumarin and aldehydes. Primarily thioureadioxide (10 mol%) catalyst was prepared from chemical precipitation method and at ambient conditions. The study revealed that the four component reaction in aqueous medium with this catalyst offers flexibility, fast and eco-friendly protocols (Scheme 60) [219].



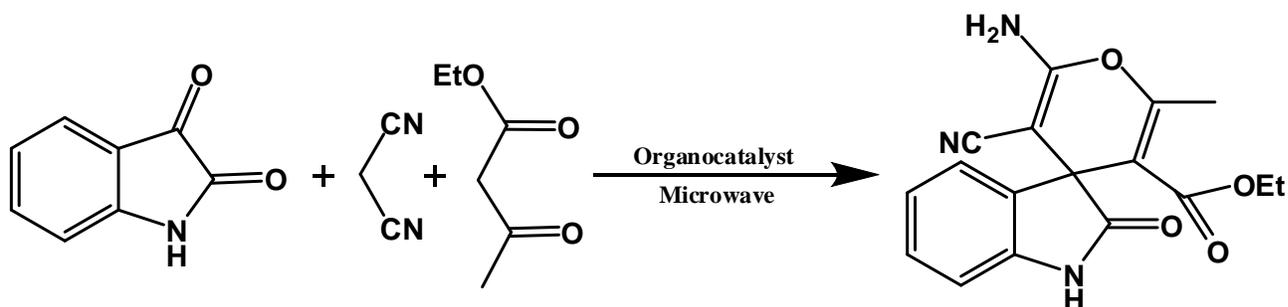
Scheme 60: Synthesis of series of 6-amino-5-cyano-4-aryl-2-methyl-4H-pyran derivatives

A facile, efficient tetrahydrobenzo[b]-pyran derivative have been synthesized by Yang et al., [220]. This was done through a one-pot, three component reaction of active methylene compound and dimedone. [DABCO-PDO][CH₃COO] was used to catalyze the reaction and reaction proceeded in the water solvent at 60 °C for 1 h (Scheme 61). The corresponding yields for the model reaction were satisfactory (83-95%).



Scheme 61: Synthesis of tetrahydrobenzo[b]-pyran derivatives

Zakeri and coworkers improved a reaction using an efficient, one-pot microwave irradiation procedure for the synthesis of spiro-4H-pyran derivatives. 4-Dimethylaminopyridine (DMAP) was used as organocatalyst for the reaction at reflux condition (Scheme 62) [221]. The reaction involved three component systems of malononitrile, isatin and 4-hydroxycoumarine (scheme 2) in the presence of aqueous solvent. The DMAP as catalyst gave 95% yield for this reaction and DMAP (5 mol%) was found optimal.



Scheme 62: Synthesis of novel spiro-4H-pyran derivatives

Ziarani et al. explored a green approach to synthesize novel spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives in the absence of solvent-free condition. The reaction of one-pot four-component between isatin, hydrazine hydrate, activated methylene compound and β -keto ester (Scheme 63) proceeded well in the presence of an amino-functionalized nano-porous silica SBA-15 catalyst at RT for 30 min with moderate to good yield. This green protocol of the reaction is environmentally friendly and no waste was produced [222].

All the above reported reactions are carried out using with harsh reaction conditions, thus there is the need to develop such conditions in order to increase the reaction yields and efficiency of the protocol, these can be accomplished using with the various reusable heterogeneous catalysts at room temperature conditions.

1.5. Objectives of the study

Aim of the study is to develop new heterogeneous materials with good activity as catalysts, to improve the efficiency of one-pot multicomponent protocols for synthesis of selected multi-substituted heterocyclic moieties, and to design facile protocols with improved efficacy using environmentally benign solvents under moderate conditions. The studies are focused on the development of appropriate catalyst materials and their characterization, and synthesis of six series of different heterocyclic compounds, namely

- i) Synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4H)-one derivatives
- ii) Synthesis of pyrano[2,3-d]-pyrimidine derivatives
- iii) Synthesis of 2-amino-3-cyano-4H-pyran derivatives
- iv) Synthesis of pyrano[2,3-c]pyrazoles derivatives
- v) Synthesis of pyrano[2,3-c]pyrazole-3-carboxylate derivatives
- vi) Synthesis of pyrano[2,3-c]pyrazoles

1.6. References

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CHAPTER-2

Ag/SiO₂ AS A RECYCLABLE CATALYST FOR THE FACILE GREEN SYNTHESIS OF 3-METHYL-4-(PHENYL)-METHYLENE-ISOXAZOLE--5(4H)-ONES

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Res Chem Intermed (2016) 42:2553–2566
DOI 10.1007/s11164-015-2167-2



Ag/SiO₂ as a recyclable catalyst for the facile green synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4H)-ones

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Received: 10 April 2015 / Accepted: 4 July 2015 / Published online: 15 July 2015
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This chapter is published in the journal of **Research on Chemical Intermediates** and has been structured according to the journal's format.

Ag/SiO₂ AS A RECYCLABLE CATALYST FOR THE FACILE GREEN SYNTHESIS OF 3-METHYL-4-(PHENYL)-METHYLENE-ISOXAZOLE-5(4*H*)-ONES

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Abstract:

An efficient and facile green method for synthesis of 3-methyl-4-(phenyl)methyleneisoxazole-5(4*H*)-one (**4a-m**) *via* room temperature reaction of hydroxylamine, ethylacetoacetate and substituted aromatic aldehydes is designed, using Ag/SiO₂ as catalyst with water as solvent. This protocol offers several advantages such as it being a benign, energy conserving and eco-friendly reaction with products obtained in excellent yields (88 to 93 %). The reaction requires relatively short reaction times (< 1 h), a simple workup procedure with good atom efficiency and easily recoverable catalyst. The heterogeneous catalyst, Ag/SiO₂ was fully characterized and is reusable without loss of activity for up to seven cycles with marginal activity loss.

Keywords: Green synthesis; Heterogeneous catalyst; Isoxazoles; Ag/SiO₂; One-Pot reaction.

2.1. Introduction

In recent years, multicomponent reactions (MCR) have captivated researchers due to a number of green principles including facile operation, environmental friendly and economic. MCRs allow three or more compounds to react together, providing products in high yields without having to isolate intermediates. This is an attractive option [1-3], thus making MCRs an important tool in the synthesis of heterocyclic molecules with applications in combinatorial, medicinal and agricultural chemistry [3-5]. The other advantages of these reactions include high bond-forming efficiency, cost effectiveness, energy saving and simple workup procedures [6,7].

Interest has increased in use of heterogeneous catalysts in organic syntheses due to improved selectivity, facile separation, reusability and low cost [8,9]. Metal oxides have emerged as candidates for such a role due to their proven record as catalysts, supports, and as ion-exchangers. Mixed metallic oxides with both acidic and basic sites can be generated by calcination at about 700 K. The calcined composites have moderate surface areas and can accelerate various condensation reactions. Relative to conventional linear syntheses, these eco-friendly protocols also have benefits, such as long catalytic life, thermal stability, cost effectiveness, atom economy and scope to modify the surface properties [10].

Silica (SiO_2), which is an acidic functional material in pure form is one of the widely used inorganic supports in the catalytic systems [11,12] used in the activation and stabilization of several metals [13,14]. The crystalline structure of SiO_2 has been documented as one of the key factors for justification of the structure-activity relationships of metal-based catalysts [15]. In organic synthesis, silica as support for various metal oxide catalysts allows the design of varied distribution of its Lewis and Brønsted acidic and basic sites [16-19] on the surface facilitating its use as catalyst for specific applications.

Isoxazoles are an important class of heterocyclic compounds, which are predominant in nature and display fascinating biological and pharmaceutical properties [20,21]. Isoxazole is considered a major scaffold compound in the discovery of combinatorial synthesis and protein kinase inhibitors, playing crucial role in development of chemotherapeutic agents [22,23]. Many isoxazole derivatives exhibit antibacterial [24], antifungal [25], antitumor [26], antioxidant [27], antiprotozoal [28], antiviral [29], anti-tubercular [30], anti-inflammatory [31] and anti-HIV [32] activities. Several procedures have been reported in the literature for the synthesis of isoxazole derivatives and their analogues. Literature survey shows quite many catalysed methods were

reported for synthesis of various isoxazole derivatives. To mention a few, such protocols employed sodium saccharin [33], ultrasonic irradiation [34], sodium silicate [35], sodium benzoate [36], pyridine [37,38], DABCO [39], $\text{CH}_3\text{COONa/UV}$ [40], sodium ascorbate [41], sodium tetraborate [42], sodium sulfide [43], pyridine/UV [44], and boric acid [45] as catalysts. Many of these methods have some limitations and drawbacks, such as use of toxic reagents, strong acidic or basic conditions, costly reagents and catalysts, strict reaction conditions, tedious steps, low product yields and/or long reaction times, which restrict their scope in practical applications. Therefore, a novel protocol with good and inexpensive catalyst demanding short reaction times is sought after.

In continuation of our interest in the environmental friendly protocols for the various synthesis of heterocyclic derivatives with better yields [46-49], we herein report the one-pot reaction of ethylacetoacetate, hydroxyl amine and substituted aldehydes in the presence of a catalyst Ag/SiO_2 for the synthesis of isoxazole derivatives in excellent yields.

2.2. Experimental section

2.2.1. Catalyst characterization

Micromeritics Tristar-II porosity and surface area analyzer was used to determine the values of surface area, pore size and pore volume of the catalyst material. The catalyst sample was degassed overnight using N_2 flow at 200 °C. The BJH adsorption-desorption curves were generated at -196 °C and were used to assess the catalyst's particulate properties. Employing a Bruker D8 Advance instrument (Cu K radiation source with a wave length of 1.5406 Å), the X-ray diffraction data related the structural phases of the catalyst were acquired. Using a Jeol JEM-1010 electron microscope and JEOL JSM-6100 microscope, the TEM and SEM analysis data was recorded. iTEM software was used analyze the TEM data and images. Employing the X-ray analyzer (energy-dispersive), EDX-analysis on the SEM images was conducted. To confirm the elemental composition catalyst materials Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES) (Optima 5300 DV) was used.

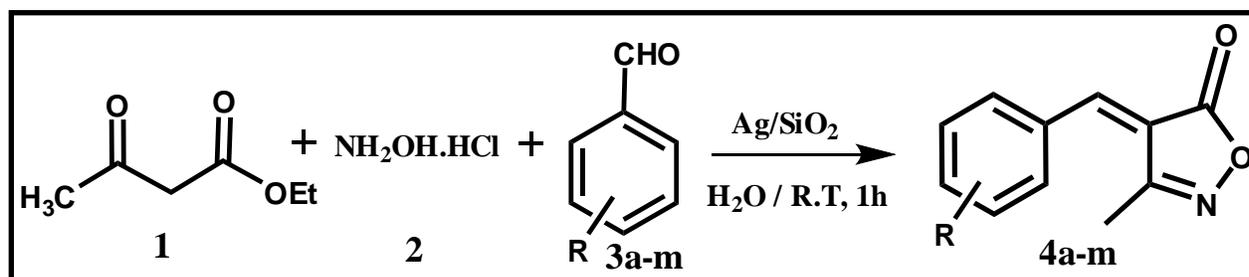
2.2.2. Preparation of catalyst

The wet impregnation method was used for the synthesis of catalyst material, Ag/SiO_2 . An appropriate amount of silver nitrate hydrate $\text{AgNO}_3 \cdot 9\text{H}_2\text{O}$, Aldrich (99.9%) was dissolved in double distilled water (50.0 ml) which was added to silica (3.0 g) with continuous stirring with a magnetic stirrer at room temperature for 12 h. Then the resulted slurry was dried in an oven at

110–130 °C for 12 h and calcined in presence of air, at 450 °C for 3 h to acquire the 5% ^{w/w} catalyst [50,51].

2.2.3. General procedure for the synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives

To equimolar ratios of hydroxylamine (1.1 mmol), ethylacetoacetate (1 mmol) and aldehyde (1 mmol) dissolved in water (10 ml) at room temperature (RT) using Ag/SiO₂ (30 mg) as catalyst. The reaction mixture was stirred continuously for 1 h at RT, (Scheme 1) using a magnetic stirrer. The progress of the reaction was monitored by TLC. The reaction mixture was then filtered, and the filtrate was subsequently extracted with ethyl acetate and evaporated under reduced pressure to obtain the crude product. Further, the crude product was purified with a 4:6 ratio of EtOAc:Hexane mobile solvent to afford pure products (4a-m). The recovered catalyst was subjected to washing with ethanol, dried, and could be reused for up to seven cycles.



Scheme 1. Synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives

3-Methyl-4-(4-hydroxyphenyl)methylene-isoxazole-5(4*H*)-one (4a): Yellow solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ = 2.24 (s, 3H, CH₃), 6.94 (d, *J* = 8.80 Hz, 2H, ArH), 7.78 (s, 1H, =CH), 8.44 (d, *J* = 8.84 Hz, 2H, ArH), 10.85 (s, 1H, OH); ¹³C NMR (100 MHz, CDCl₃): δ 11.24, 113.83, 116.12, 124.53, 137.44, 151.51, 162.24, 163.82, 168.78; IR (KBr, cm⁻¹): 3232, 2363, 1734, 1559, 1358, 1297, 1179, 669; HRMS of [C₁₁H₉NO₃ – H]⁺ (*m/z*): 202.0503; Calcd.: 202.0504.

3-Methyl-4-(4-methoxyphenyl)methylene-isoxazole-5(4*H*)-one (4b): Yellow solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ = 2.25 (s, 3H, CH₃), 3.89 (s, 3H, OCH₃), 7.14 (d, *J* = 8.96 Hz, 2H, ArH), 7.85 (s, 1H, =CH), 8.51 (d, *J* = 8.96 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 11.24, 55.80, 114.63, 115.19, 125.76, 136.86, 151.19, 132.23, 164.21, 168.57; IR (KBr, cm⁻¹): 3446, 2362, 1734, 1594, 1269, 1176, 668; HRMS of [C₁₂H₁₁NO₃ + Na]⁺ (*m/z*): 240.0641; Calcd.: 240.0637.

3-Methyl-4-phenyl-methylene-isoxazole-5(4H)-one (4c): Light yellow solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 2.29 (s, 3H, CH₃), 7.56-7.67 (m, 3H, ArH), 7.96 (s, 1H, =CH), 8.40 (d, J = 7.40 Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl₃): δ 11.25, 118.32, 128.84, 132.40, 133.51, 133.86, 151.62, 162.18, 167.78; IR (KBr, cm^{-1}): 3446, 2362, 1739, 1561, 1341, 1284, 1140, 685; HRMS of [C₁₁H₁₀NO₂ + Na]⁺ (m/z): 211.0618; Calcd.: 211.0609.

3-Methyl-4-(4-dimethylaminophenyl)methylene-isoxazole-5(4H)-one (4d): Red solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 2.20 (s, 3H, CH₃), 3.33 (s, 6H, N(CH₃)₂), 6.85 (d, J = 9.16 Hz, 2H, ArH), 7.60 (s, 1H, =CH), 8.45 (d, J = 8.80 Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl₃): δ 11.27, 108.98, 111.59, 120.95, 137.52, 150.44, 154.32, 162.08, 169.79; IR (KBr, cm^{-1}): 3432, 2362, 1709, 1582, 1380, 1202, 1161, 668; HRMS of [C₁₃H₁₄N₂O₂ + Na]⁺ (m/z): 253.0953; Calcd.: 253.0953.

Anal. calcd for C₁₃H₁₄N₂O₂: C 67.81, H 6.13, N 12.17; Found: C 67.83, H 6.10, N 12.14.

3-Methyl-4-(anthracen-9-yl)methylene-isoxazole-5(4H)-one (4e): Brown solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 2.57 (s, 3H, CH₃), 7.72-7.76 (m, 3H, ArH), 8.07-8.09 (m, 3H, ArH), 8.79 (d, J = 8.74 Hz, 3H, ArH), 8.86 (s, 1H, CH); ^{13}C NMR (100 MHz, CDCl₃): δ 11.46, 123.44, 125.05, 125.39, 125.73, 125.81, 127.05, 127.43, 128.72, 148.35, 158.68, 161.09, 166.22, 168.25, 168.78; IR (KBr, cm^{-1}): 3431, 2360, 1752, 1352, 1292, 1182, 668; HRMS of [C₁₉H₁₃NO₂ + Na]⁺ (m/z): 310.0848; Calcd.: 310.0844.

3-Methyl-4-(2,5-dihydroxyphenyl)methylene-isoxazole-5(4H)-one (4f): Yellow solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 2.23 (s, 3H, CH₃), 6.85 (d, J = 8.88 Hz, 1H, ArH), 6.97-7.00 (m, 1H, ArH), 8.02 (s, 1H, =CH), 8.23 (d, J = 8.78 Hz, 1H, ArH), 9.18 (s, 1H, OH), 10.38 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl₃): δ 11.16, 115.67, 116.45, 116.78, 119.69, 125.56, 144.98, 149.32, 153.36, 162.17, 168.23; IR (KBr, cm^{-1}): 3308, 2361, 1751, 1602, 1368, 1273, 1170, 668; HRMS of [C₁₁H₉NO₄ - H]⁺ (m/z): 218.0453; Calcd.: 218.0453.

3-Methyl-4-(3,4-dihydroxyphenyl)methylene-isoxazole-5(4H)-one (4g): Yellow solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 2.19 (s, 3H, CH₃), 6.42 (s, 2H, ArH), 7.96 (s, 1H, =CH), 8.97 (d, J = 8.81 Hz, 1H, ArH), 9.90 (s, 1H, OH), 11.06 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl₃): δ 11.17, 101.69, 109.02, 110.57, 113.01, 135.14, 143.94, 162.22, 163.10, 166.63, 169.40; IR (KBr, cm^{-1}): 3487, 2363, 1734, 1589, 1391, 1258, 1212, 761.

3-Methyl-4-(3-hydroxyphenyl)methylene-isoxazole-5(4H)-one (4h): Light yellow solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 2.27 (s, 3H, CH₃), 7.06 (d, J = 7.46 Hz, 1H, ArH), 7.37 (t, J =

7.90 Hz, 1H, ArH), 7.78 (d, $J = 7.88$ Hz, 1H, ArH), 7.85 (s, 1H, =CH), 7.92 (s, 1H, ArH), 9.90 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl_3): δ 11.25, 118.48, 119.38, 121.34, 125.25, 129.80, 133.57, 151.98, 157.35, 162.21, 167.71; IR (KBr, cm^{-1}): 3432, 2356, 1739, 1575, 1347, 1288, 1113, 668; HRMS of $[\text{C}_{11}\text{H}_9\text{NO}_3 - \text{H}]^+$ (m/z): 202.0512; Calcd.: 202.0504.

3-Methyl-4-(2,3-dimethoxyphenyl)methylene-isoxazole-5(4H)-one (4i): Light yellow solid: ^1H NMR (400 MHz, DMSO-d_6) $\delta = 2.29$ (s, 3H, CH_3), 3.86 (s, 6H, 2OMe), 7.06 (d, $J = 7.82$ Hz, 1H, ArH), 7.36 (d, $J = 7.64$ Hz, 1H, ArH), 7.99 (s, 1H, =CH), 8.22 (d, $J = 9.08$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 11.13, 56.00, 61.67, 118.83, 119.26, 123.34, 123.70, 125.63, 145.12, 149.85, 152.15, 162.02, 167.47; IR (KBr, cm^{-1}): 3432, 2362, 1698, 1524, 1268, 1125, 668.

3-Methyl-4-(2,5-dimethoxyphenyl)methylene-isoxazole-5(4H)-one (4j): Orange solid: ^1H NMR (400 MHz, DMSO-d_6) $\delta = 2.25$ (s, 3H, CH_3), 3.75 (s, 3H, OMe), 3.87 (s, 3H, OMe), 7.12-7.27 (m, 2H, ArH), 8.01 (s, 1H, =CH), 8.41 (d, $J = 8.04$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 11.12, 55.50, 56.50, 112.84, 115.78, 117.79, 120.79, 123.23, 144.21, 152.26, 154.43, 162.02, 168.01; IR (KBr, cm^{-1}): 3430, 2362, 1730, 1596, 1237, 1045, 668; HRMS of $[\text{C}_{13}\text{H}_{13}\text{NO}_4 + \text{Na}]^+$ (m/z): 270.0742; Calcd.: 270.0742.

3-Methyl-4-(2,4,6-trimethoxyphenyl)methylene-isoxazole-5(4H)-one (4k): Yellow solid: ^1H NMR (400 MHz, DMSO-d_6) $\delta = 2.22$ (s, 3H, CH_3), 3.76 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.25 (s, 1H, ArH), 6.35 (s, 1H, ArH), 7.72 (s, 1H, =CH), 8.11 (s, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 11.16, 55.76, 55.99, 56.07, 90.68, 90.96, 104.25, 117.47, 141.08, 142.33, 159.16, 160.02, 160.98, 165.58; IR (KBr, cm^{-1}): 3431, 2364, 1751, 1602, 1330, 1207, 1157, 668.

3-Methyl-4-(2,4-dimethylphenyl)methylene-isoxazole-5(4H)-one (4l): Cream solid: ^1H NMR (400 MHz, DMSO-d_6) $\delta = 2.29$ (s, 3H, CH_3), 2.34 (s, 3H, ArCH_3), 2.45 (s, 3H, ArCH_3), 7.14 (d, $J = 8.04$ Hz, 1H, ArH), 7.19 (s, 1H, ArH), 8.00 (s, 1H, =CH), 8.34 (d, $J = 8.84$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 11.16, 19.45, 21.28, 117.86, 126.46, 127.91, 131.32, 131.52, 141.04, 144.23, 149.26, 162.03, 167.76; IR (KBr, cm^{-1}): 3449, 2372, 1770, 1599, 1383, 1097, 658; HRMS of $[\text{C}_{13}\text{H}_{14}\text{NO}_2 + \text{H}]^+$ (m/z): 216.1032; Calcd.: 216.1025.

3-Methyl-4-(4-ethylphenyl)methylene-isoxazole-5(4H)-one (4m): White solid: ^1H NMR (400 MHz, DMSO-d_6) $\delta = 1.20$ (t, $J = 8.12$ Hz, 3H, CH_2CH_3), 2.27 (s, 3H, CH_3), 2.70 (q, $J = 7.57$ Hz, 2H, CH_2CH_3), 7.43 (d, $J = 8.28$, 2H, ArH), 7.91 (s, 1H, =CH), 8.36 (d, $J = 8.20$, 2H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 11.23, 14.84, 28.44, 117.62, 126.38, 128.38, 130.25, 131.79, 133.99,

151.09, 151.60, 162.20, 168.03; IR (KBr, cm^{-1}): 3446, 2368, 1740, 1594, 1344, 1257, 1103, 668; HRMS of $[\text{C}_{13}\text{H}_{14}\text{NO}_2 + \text{H}]^+$ (m/z): 216.1035; Calcd.: 216.1025.

2.3. Results and discussion

2.3.1. BET surface area (BET) and elemental (ICP) analysis

The texture of the prepared catalysts was determined by physisorption analysis. The N_2 adsorption-desorption isotherms showed a type-IV adsorption isotherm demonstrating the mesoporous nature of the catalysts (Figure 1). The prepared catalyst showed a surface area of $189 \text{ m}^2 \text{ g}^{-1}$ with a pore volume of 0.994 cc g^{-1} . The large surface area was obtained for the catalyst sample with high pore volumes due to the narrow pore size distribution of catalyst. The ICP analysis results showed the presence of a nominal amount of Ag in the catalyst (4.94 wt %).

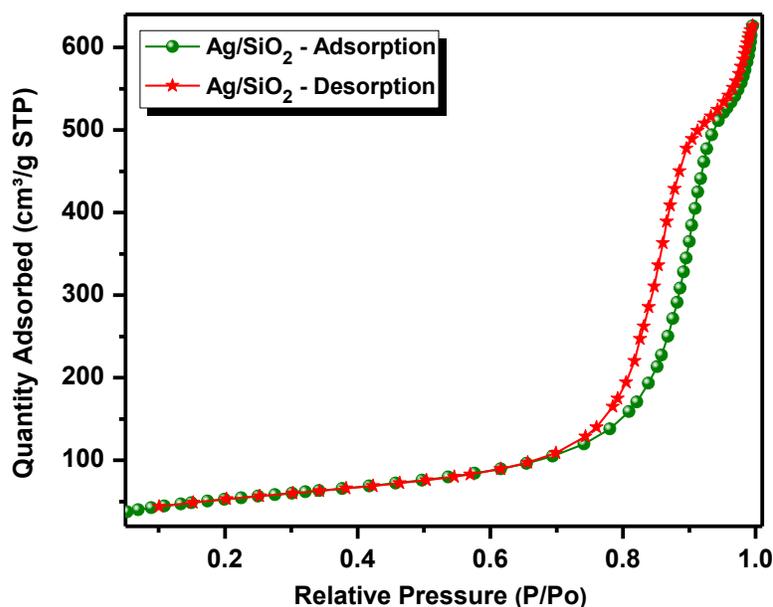


Figure 1. N_2 adsorption & desorption spectra of Ag/SiO_2 catalyst

2.3.2. TEM analysis

The TEM micrograph reveals more structural information of the catalyst. Figure 2 shows a distinctive TEM image of Ag loaded on silica catalyst, from which it can be seen that the Ag nanoparticles showed a sphere-shape with an average size of 13 nm and are highly dispersed and homogeneously distributed on the silica support with strong interaction between the AgNPs and silica supports.

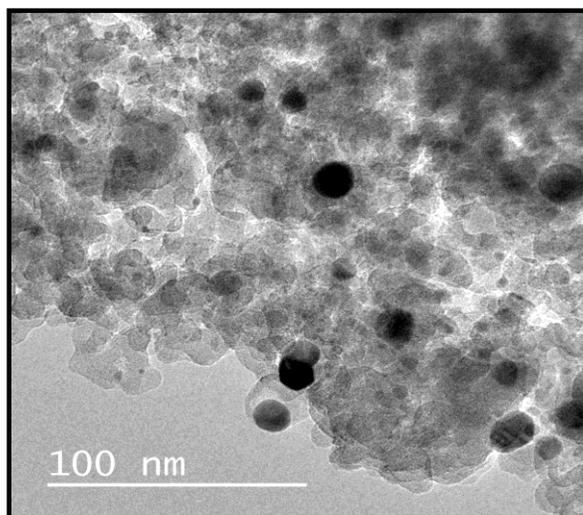


Figure 2. TEM micrograph of Ag/SiO₂ catalyst.

2.3.3. SEM analysis

Figure 3 shows an illustrative SEM morphologies micrograph of the sample Ag on silica. A lot of large white with elliptical irregular shapes are perceived from the low magnification SEM image of Ag/SiO₂. This micrograph reveals that the aggregative state of the silica important particles is with silver. While, a homogeneous distribution of Ag and silica on the catalyst is specified by the EDS analysis, elemental analysis by ICP-OES confirmed the elemental composition in the catalyst material (Figure 4). Furthermore, the morphology of the catalyst as per the SEM images noticeably point to the crystallinity and homogeneity of the sample.

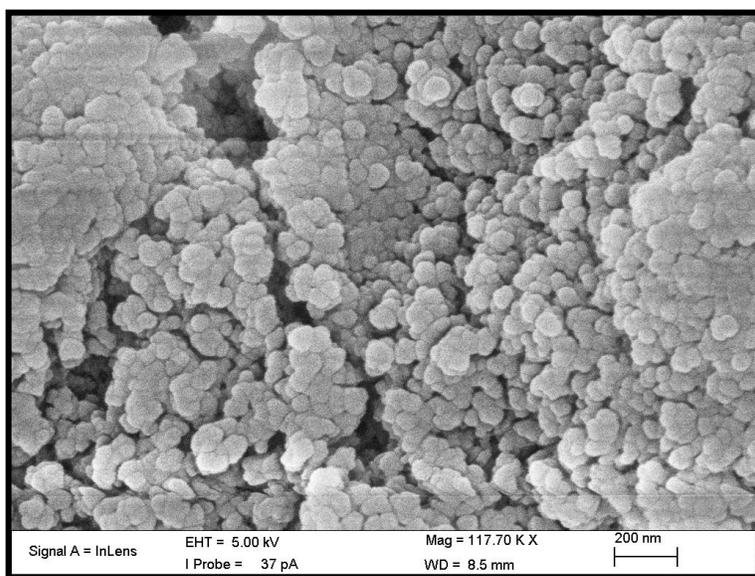


Figure 3. SEM micrograph of Ag/SiO₂ catalyst.

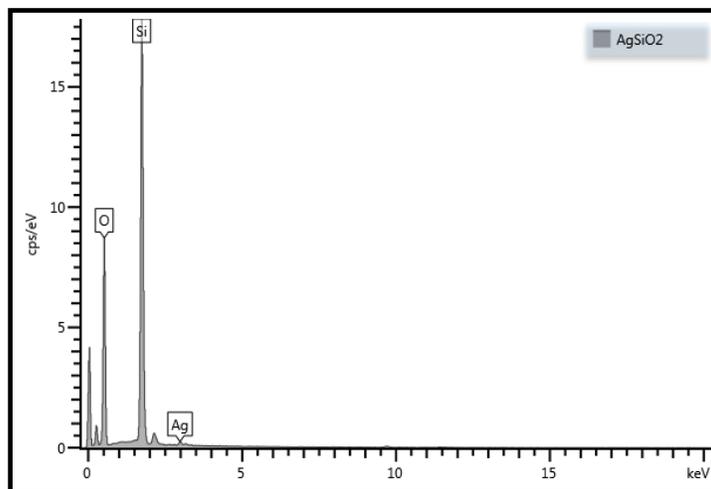


Figure 4. SEM-EDX spectra of Ag/SiO₂ catalyst

2.3.4. Powder X-ray diffractogram (XRD) analysis

XRD patterns of the calcined Ag/SiO₂ catalyst are shown in Figure 5. All of the PXRD diffraction patterns can be indexed to fcc silver. The calcined 2% Ag on SiO₂ sample showed diffraction peaks at 38.1°, 44.3°, 64.4° and 77.4° corresponding to the (1 1 1), (2 0 0), (2 2 0) and (3 1 1) lattice planes of hexagonal Ag₂O (JCPDS # 72-2108) and cubic Ag₂O₃ (JCPDS # 72-0607) respectively. Important peaks in the silver XRD spectra agree with the JCPDS-PDF # 00-004-0783 files, and the two broad peaks centered at 12.1° and 22.1° were due to the amorphous silica support.

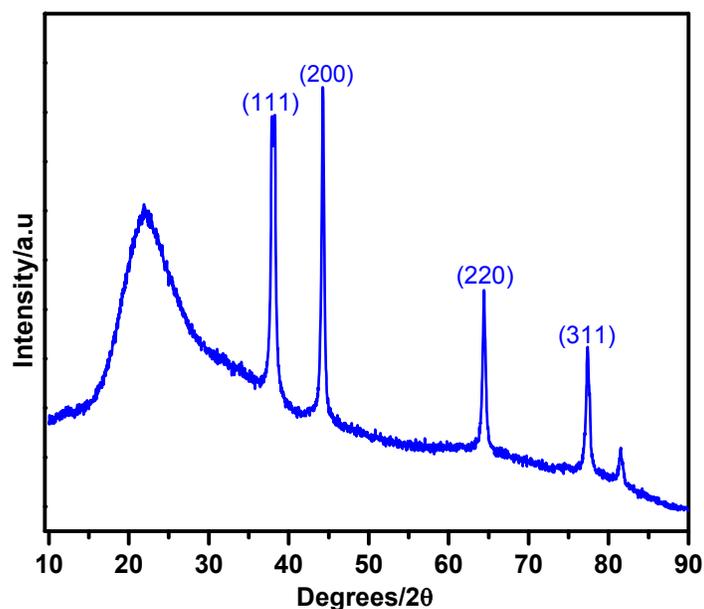


Figure 5. XRD spectrum of Ag/SiO₂ catalyst

2.3.5. Optimization procedure

At the start of the investigations, the impact of availability of catalyst material and solvents were examined. With ethyl acetoacetate, aromatic aldehyde, hydroxyl amine hydrochloride and water as solvent and with no catalyst, there was no reaction at RT even after 24 h under reflux conditions, (Table 1, entries 1 & 2). The same reaction was tried in ethanol in absence of any catalyst at RT for 12 h and failed to achieve any desired product (Table 1, entries 3 & 4). The scope of the various types of catalysts and use of NaOH and K_2CO_3 as a basic catalyst in aqueous media provided no yield at RT (Table 1, entry 5 & 6). The reaction was performed under reflux conditions in ethanol, using pyridine and Na_2S as basic catalysts, which gave improved yields (Table 1, entry 7 & 8). The use of ionic liquid (Bmim)BF₄ on the product yield was investigated, but yields were very low under reflux conditions (Table 1, entry 9). Use of pure heterogeneous acidic catalysts such as SiO_2 , Al_2O_3 , Fe_2O_3 , and CeO_2 at RT in aqueous media showed no reaction progress or yield (Table 1, entries 10-13). The reaction performed with $AgNO_3$ as catalyst gave 18% yield (Table 1, entry 14). When Ag loaded on SiO_2 was used as catalyst, a reaction occurred with an impressive 93 % yield of isoxazole derivative at RT after 1 h reaction time (Table 1, entry 15). The efficacy of this catalytic system was further tested by comparing it with two other silica supported catalysts under otherwise similar conditions. Use of $HClO_4-SiO_2$ and $FeCl_3/SiO_2$ gave lower product yields and took 4–6 h for completion of the reaction (Table 1, entry 16 & 17). Furthermore, the reaction using Ag/SiO_2 as catalyst under solvent free conditions gave a small yield even after prolonged reaction time (Table 1, entry 18).

Accepting Ag/SiO_2 as catalyst and water as solvent are ideal means for the reaction, the effect of amount of catalyst on the yield and reaction time was further investigated. Performing the reaction with >30 mg of catalyst had no significant improvement on the yield or reaction time. However, the decrease in amount of the catalyst used to 20 and 10 mg, affected the product yield by reducing to 70% and 63%, respectively (Table 1, entries 19-23). Therefore, 30 mg of Ag/SiO_2 at RT with water as solvent is assumed optimal condition for the model reaction giving conversion of 93% in 1 h.

A perusal of the experimental results and the effect of various polar and non-polar solvents on the three component reaction clearly indicate water as solvent plays a vital role in facilitating the reaction (Table 1). Noticeably, under otherwise similar conditions, the Ag/SiO_2 catalyzed reaction in presence of comparatively less polar solvents like CH_3CN , DMF, n-hexane

and 1,4-dioxane gave insignificant yields (Table 1 entries 24-27). The efficiency of methanol and ethanol relative to water was also investigated. Although comparable yields were observed (Table 1, entries 28 & 29), water had a marginal advantage, thus proving to be best medium for the reaction. A highly polar solvent which dissipates heat faster may provide optimum conditions for formation of intermediates, and their conversion to final products on the catalyst surface.

Table 1:

Optimization condition for the synthesis of isoxazole by Ag/SiO₂ catalyst^a

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%) ^b
1	No catalyst	H ₂ O	RT	24	--
2	No catalyst	H ₂ O	Reflux	24	--
3	No catalyst	EtOH	RT	12	--
4	No catalyst	EtOH	Reflux	12	--
5	NaOH	H ₂ O	RT	12	--
6	K ₂ CO ₃	H ₂ O	RT	12	--
7	Na ₂ S	EtOH	Reflux	2.5	61
8	Pyridine	EtOH	Reflux	5	42
9	(Bmim)BF ₄	EtOH	Reflux	3	23
10	SiO ₂	H ₂ O	RT	12	--
11	Al ₂ O ₃	H ₂ O	RT	12	--
12	Fe ₂ O ₃	H ₂ O	RT	12	--
13	CeO ₂	H ₂ O	RT	12	--
14	AgNO ₃	H ₂ O	RT	12	18
15	Ag/SiO ₂	H ₂ O	RT	1	93
16	HClO ₄ /SiO ₂	H ₂ O	RT	3	58
17	FeCl ₃ /SiO ₂	H ₂ O	RT	3.5	37
18	Ag/SiO ₂	--	RT	12	43
19	Ag/SiO ₂ (10 mg)	H ₂ O	RT	3	85
20	Ag/SiO ₂ (20 mg)	H ₂ O	RT	2	89
21	Ag/SiO ₂ (30 mg)	H ₂ O	RT	1	93
22	Ag/SiO ₂ (40 mg)	H ₂ O	RT	1	93
23	Ag/SiO ₂ (50 mg)	H ₂ O	RT	1.5	91
24	Ag/SiO ₂	CH ₃ CN	RT	3	29
25	Ag/SiO ₂	DMF	RT	2.5	32
26	Ag/SiO ₂	n-hexane	RT	8	13
27	Ag/SiO ₂	1,4-dioxane	RT	6	24
28	Ag/SiO ₂	EtOH	RT	1.5	78
29	Ag/SiO ₂	MeOH	RT	2	72

^a All products were characterised by IR, ¹H NMR, ¹³C NMR and HRMS spectral analysis.

^b Isolated yields.

-- No reaction

Table 2Synthesis of isoxazole derivatives catalyzed by Ag/SiO₂ catalyst

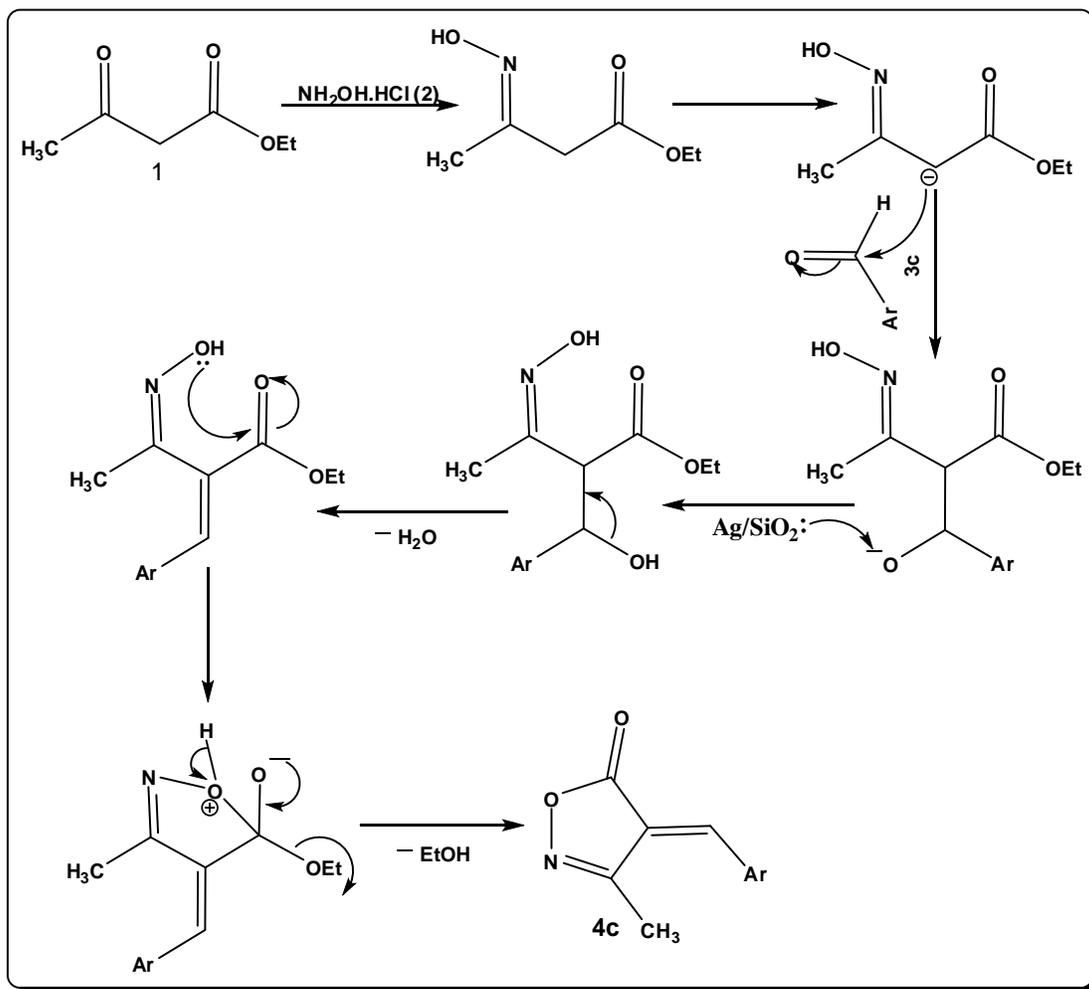
Entry	R	Product	Yield (%)	Mp °C	Lit Mp °C
1	4-OH	4a	92	214-215	214-216 [32]
2	4-OMe	4b	90	173-174	174-175[32]
3	H	4c	93	141-142	141-143[35]
4	4-N(Me) ₂	4d	92	227-228	226-228 [35]
5	anthracenyl	4e	90	219-221	--
6	2,5-(OH) ₂	4f	89	187-188	--
7	3,4-(OH) ₂	4g	90	212-213	--
8	3-OH	4h	92	164–166	--
9	2,3-(OMe) ₂	4i	90	210-211	--
10	2,5-(OMe) ₂	4j	89	178-179	--
11	2,4,6-(OMe) ₃	4k	88	232-233	--
12	2,4-(Me) ₂	4l	92	193-195	--
13	4-Et	4m	91	201-203	--

^a Reaction conditions: hydroxylamine (1.1 mmol), ethylacetoacetate (1.0 mmol), aromatic aldehyde (1.0 mmol) and water (10 mL), RT

^b All synthesized compounds are identified and their structures were conformed with IR, ¹H NMR, ¹³C NMR and HRMS spectral data and melting points as compared with literature values.
-- New compounds/no literature available.

Employing the optimised reaction conditions, the strength of the protocol was evaluated for the synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives from various aromatic aldehydes. The Ag/SiO₂ heterogeneous catalyst proved to catalyze the facile one-pot synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives with good to excellent yields. All the reaction products with other details are depicted in Table 2. Interestingly, the substrates used and reaction yields obtained shows that the reaction using several electron-withdrawing and electron donating substrates in ortho, meta and para positions of the aromatic ring have also contributed positively to obtain the desired isoxazole derivatives in good to excellent yields (Table 2). A reaction scheme is proposed based on the chemistry of the reacting substrates and observed selectivity towards the product (Reaction Mechanism). At first, the nucleophilic attack of hydroxylamine hydrochloride at the carbonyl carbon of the compound **1** to afford in intermediate compound oxime. When the intermediate lost one hydrogen atom, the

methylene group would convert to be the active carbon anion. Then, the aldehyde carbonyl group was attacked by carbon anion and subsequent Knoevenagel reaction occurred. After losing one ethanol molecule, ring-closing brought to the corresponding products. All the resultant products were characterized and structures were confirmed by FTIR, ^1H NMR, ^{13}C NMR and HRMS spectral analysis (Electronic Supplementary Information).



Proposed Reaction Mechanism:

2.3.6. Reusability of catalyst

Experiments were performed to investigate the recyclable phenomenon of the heterogeneous catalyst. The catalyst was recovered after filtration, washed with EtOH and dried under reduced pressure after the completion of reaction. The recovered catalyst was reused for seven consecutive runs following similar recovery procedure and observed loss of activity was minimal (Figure 6). No significant loss was observed in the first four cycles. The marginal loss

in the catalytic activity noticed after 4th run which can be attributed to the probable organic contaminations, trivial alterations and loss of catalyst material in the recovery process under the examined conditions.

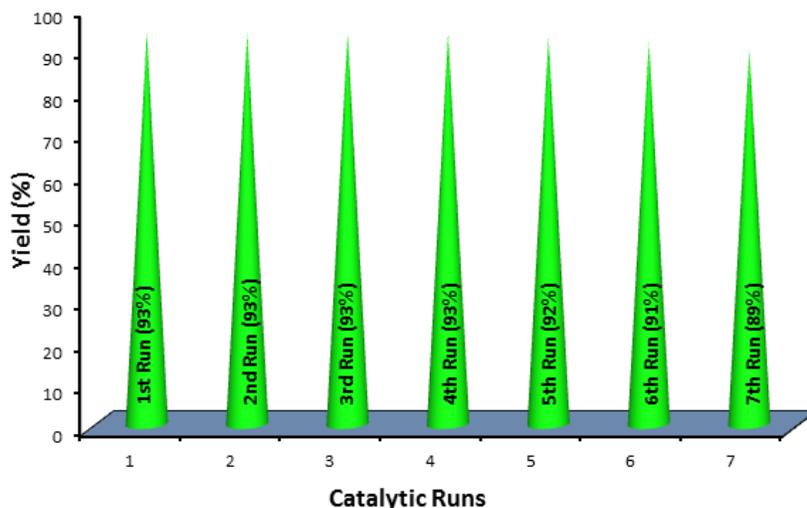


Figure 6. Recyclability of Ag/SiO₂ catalyst.

2.4. Conclusion

We have described a green, simple, efficient and environmentally benign one-pot multicomponent protocol for the synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives with good to excellent yields. The new heterogeneous catalyst, Ag/SiO₂ is simple, highly efficient and recyclable for MCR protocol at RT. Main advantages of this approach are green solvent, cheap materials, easy work up, non-hazardous and environment friendly reaction conditions, recyclable catalyst, excellent yields, and short reaction times.

2.5. Acknowledgement

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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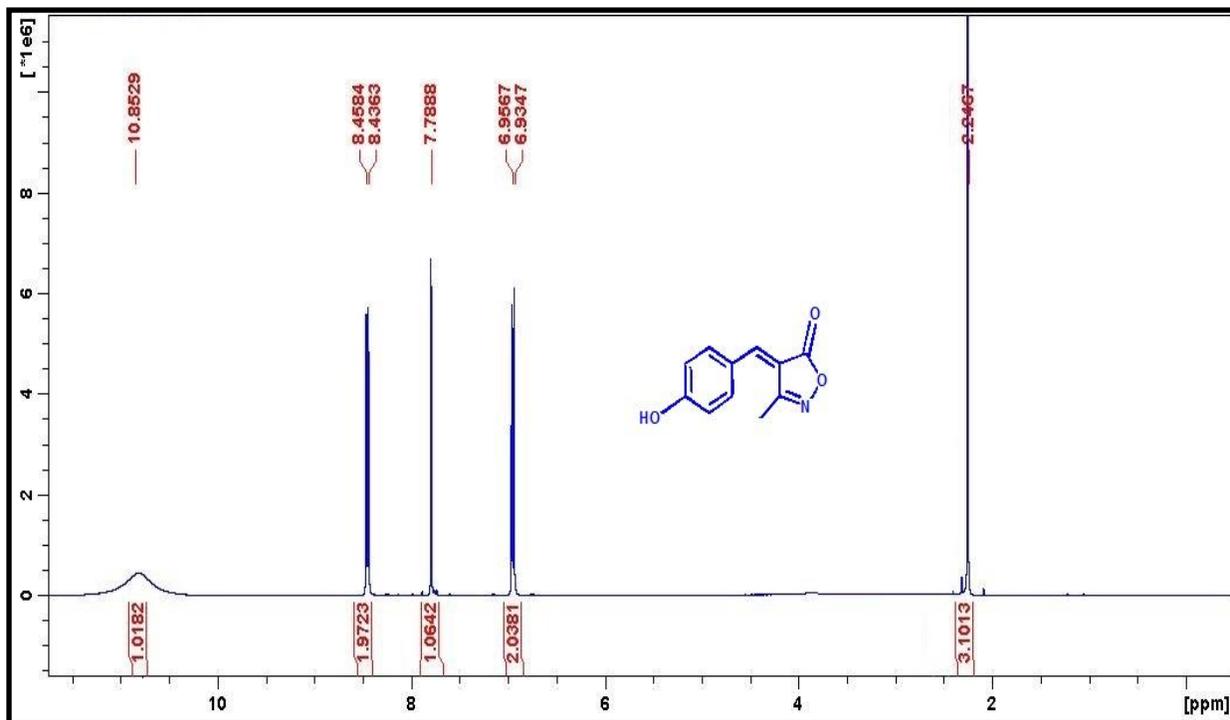
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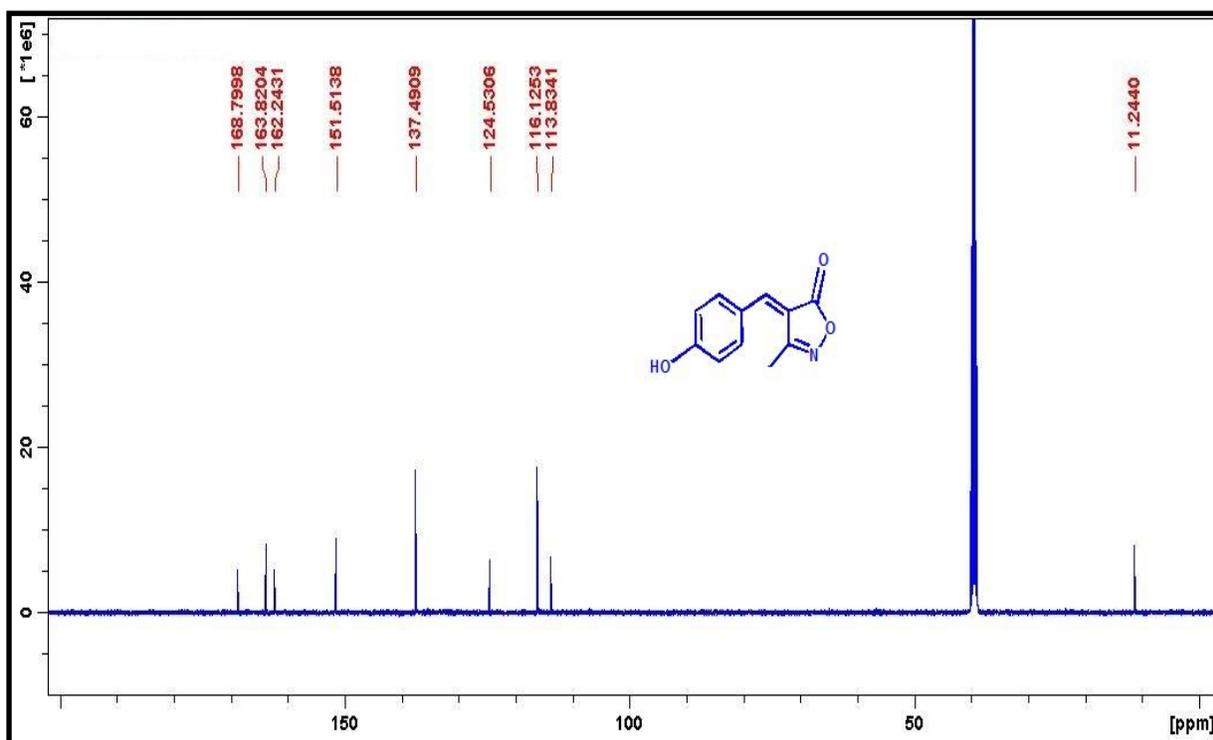
2.7. Supplementary materials data

2.7.1. General details

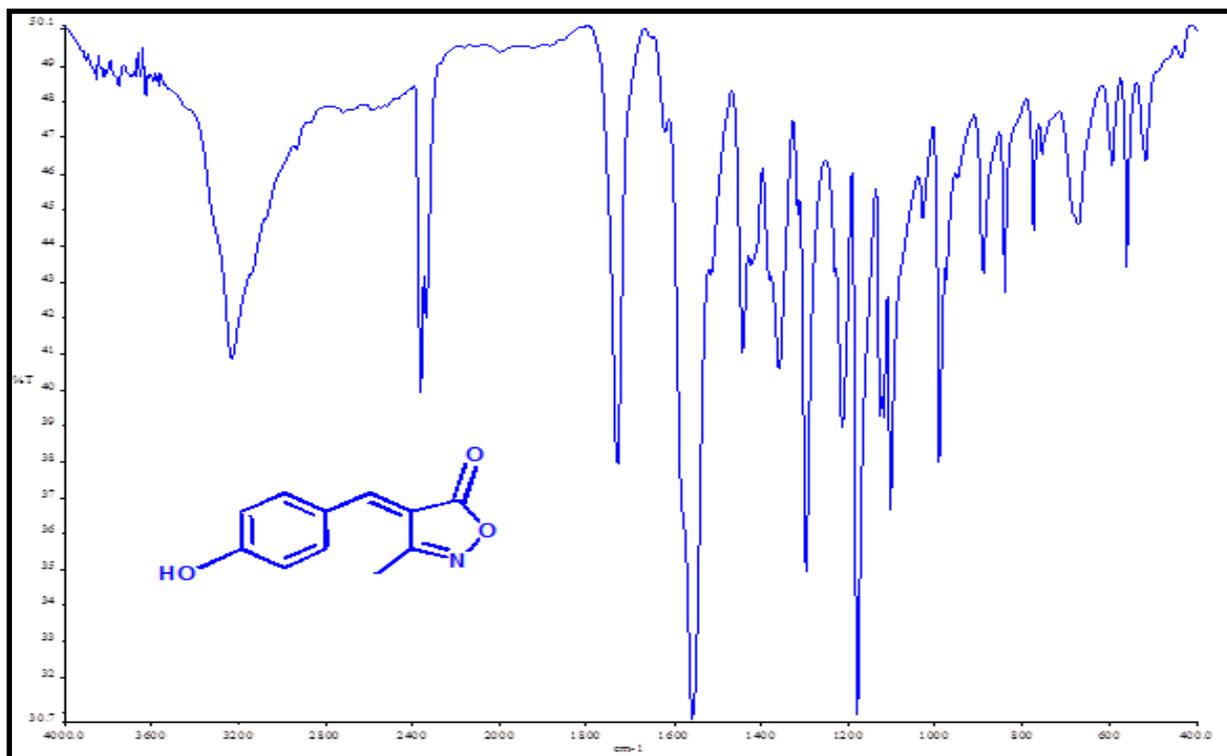
All chemicals and reagents required for the reaction were of analytical grade and were used without any further purification. Bruker AMX 400 MHz NMR spectrometer was used to record the ^1H NMR and ^{13}C NMR (400 MHz) spectral values. The $\text{CDCl}_3/\text{DMSO}-d_6$ solution was utilized for this while TMS served as the internal standard. TMS was further used as an internal standard for reporting the all chemical shifts in δ (ppm). The FT-IR spectrum for the samples was established using a Perkin Elmer Precisely 100 FT-IR spectrometer at the $400\text{-}4000\text{ cm}^{-1}$ area. High-resolution mass data were obtained using a Bruker micro TOF-Q II ESI instrument operating at ambient temperature.



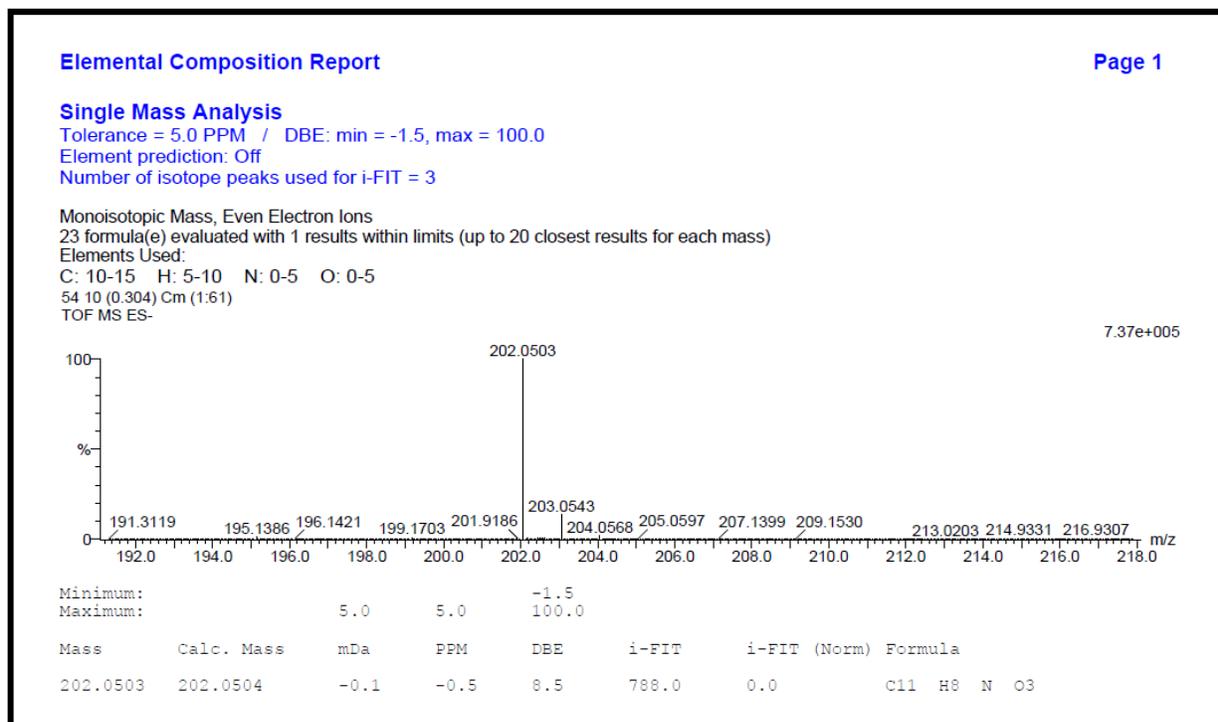
¹H NMR spectra of compound **4a**



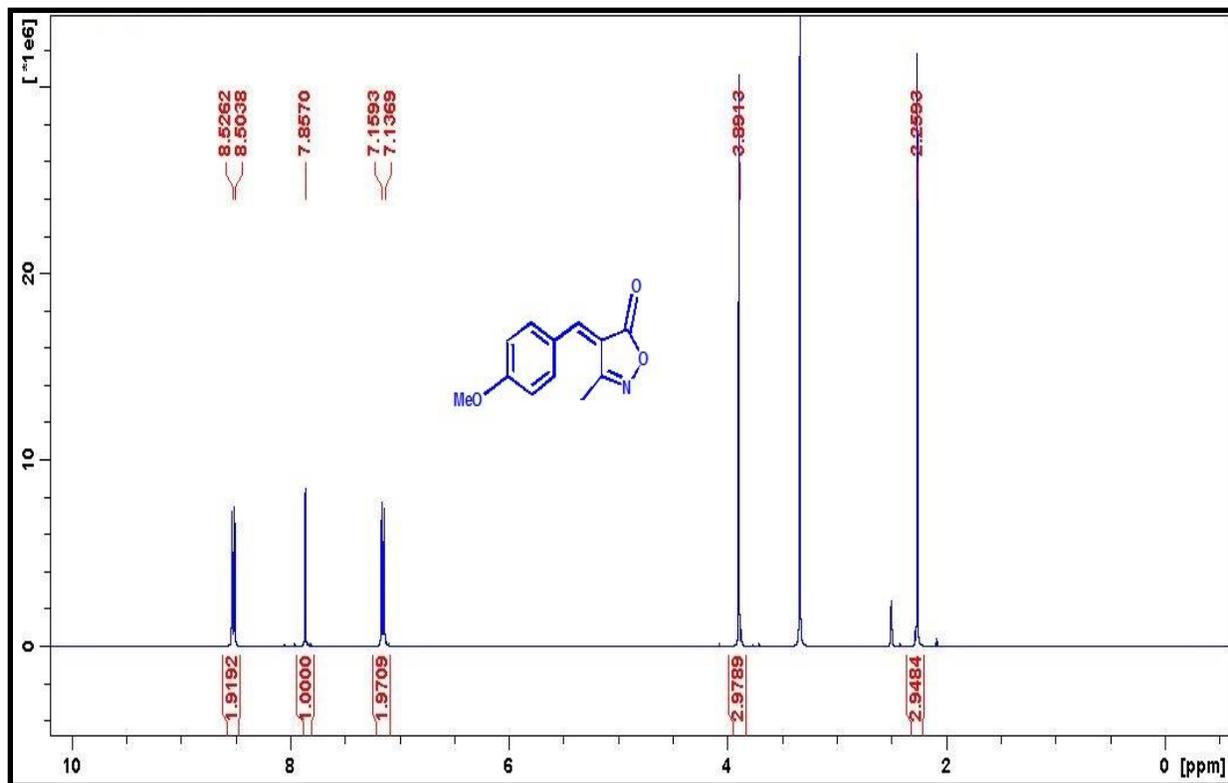
¹³C NMR spectra of compound **4a**



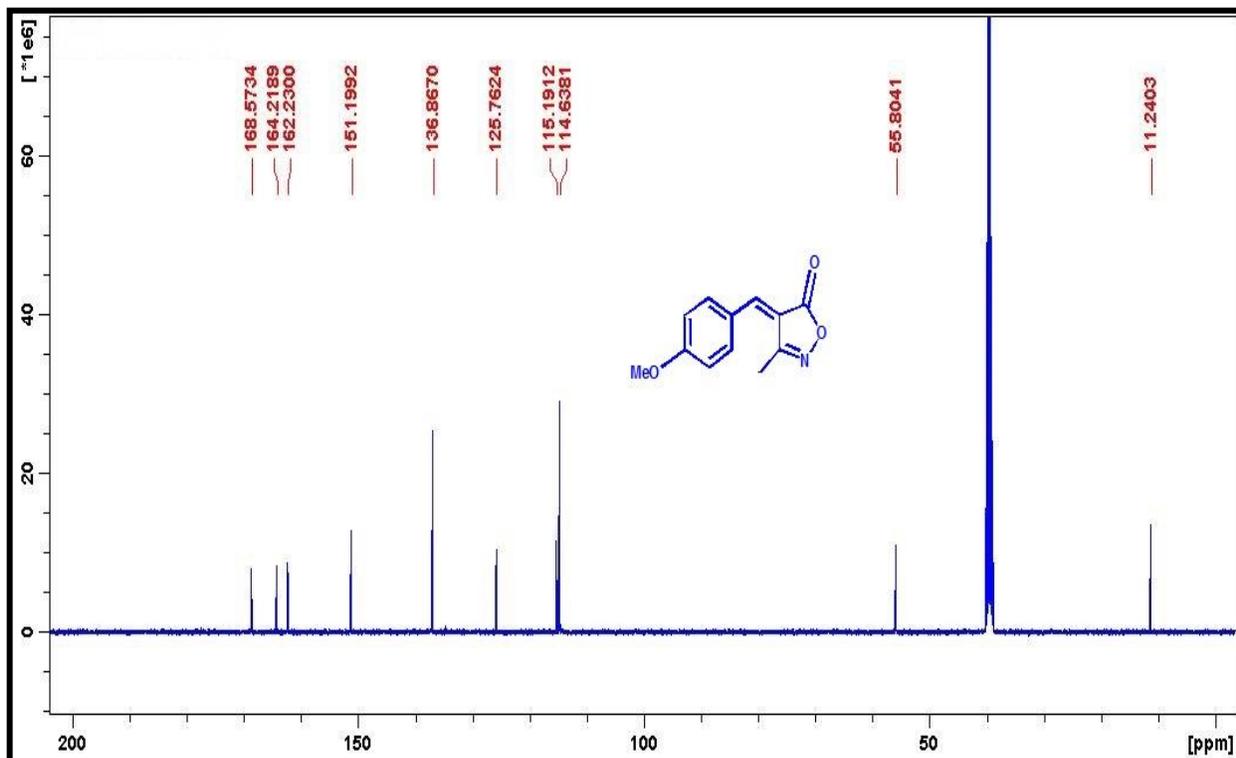
FT-IR spectra of compound **4a**



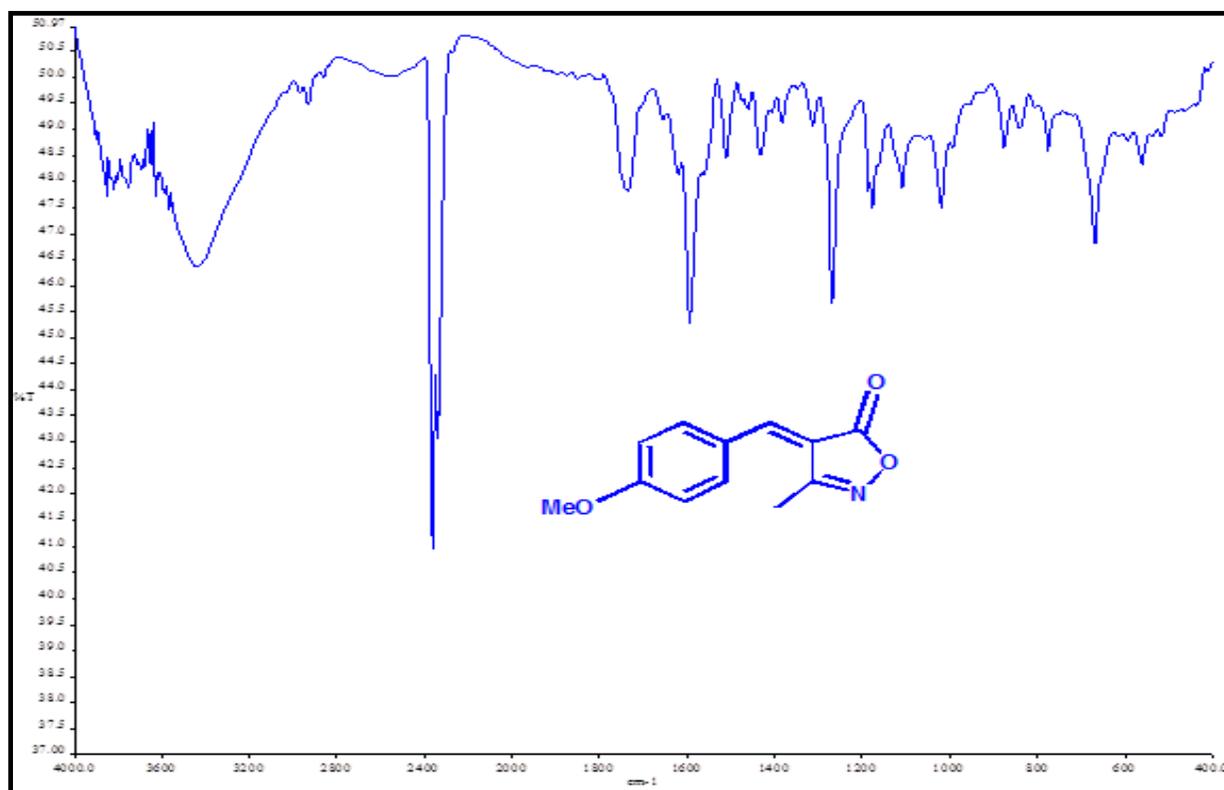
HRMS spectra of compound **4a**



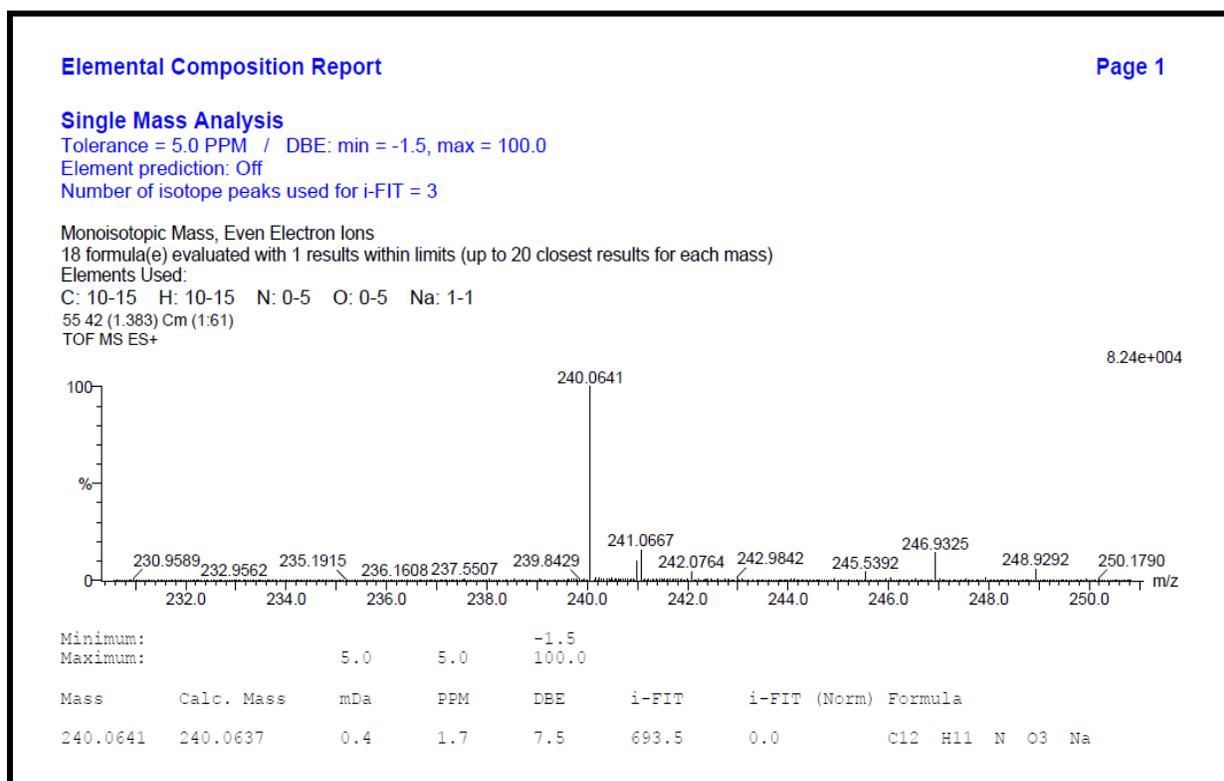
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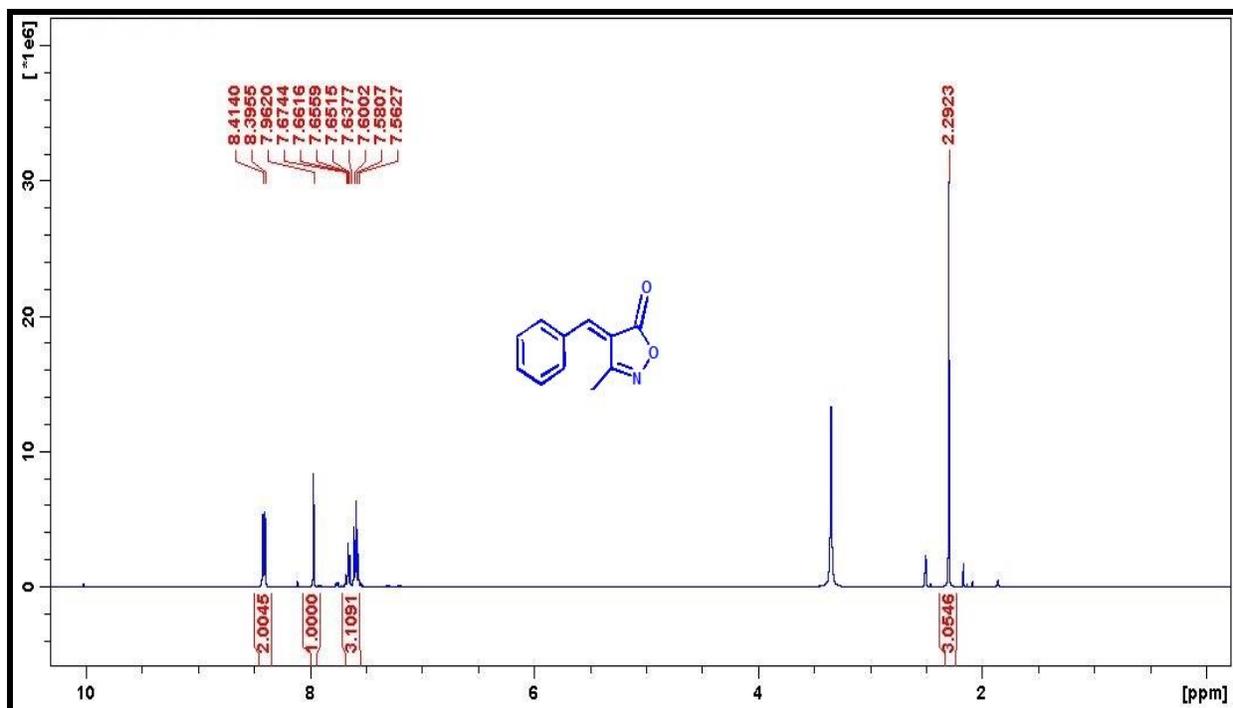
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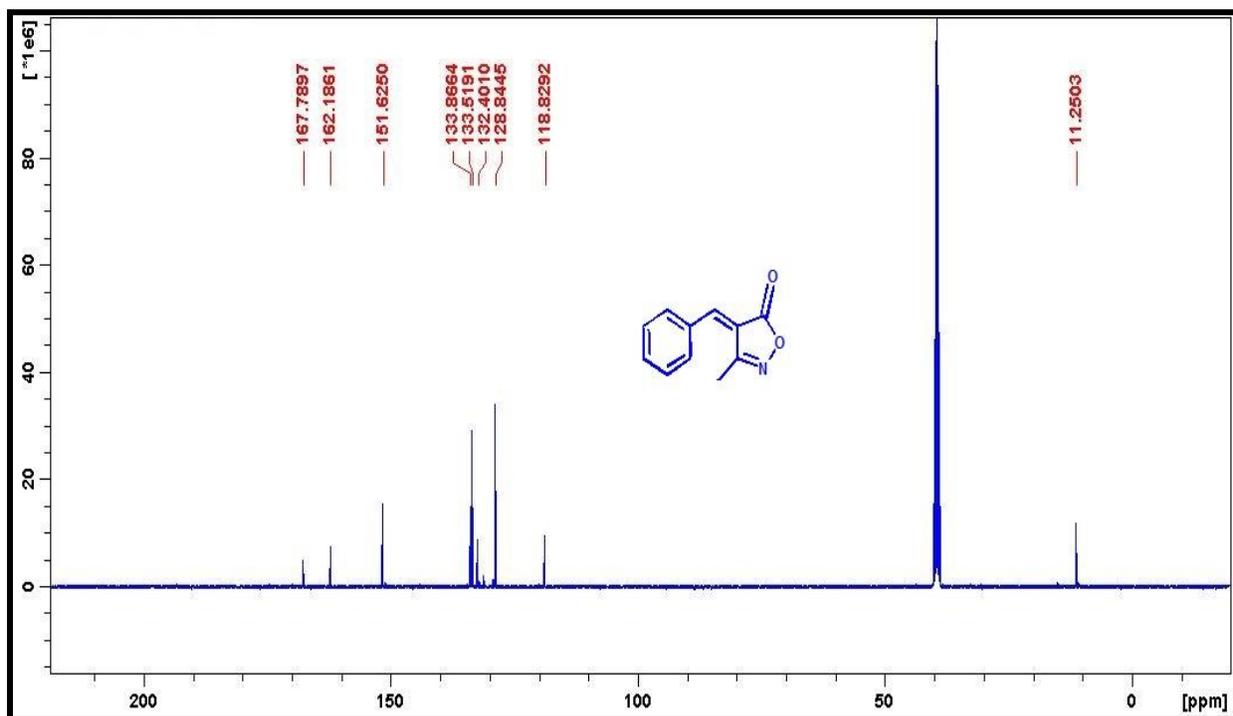
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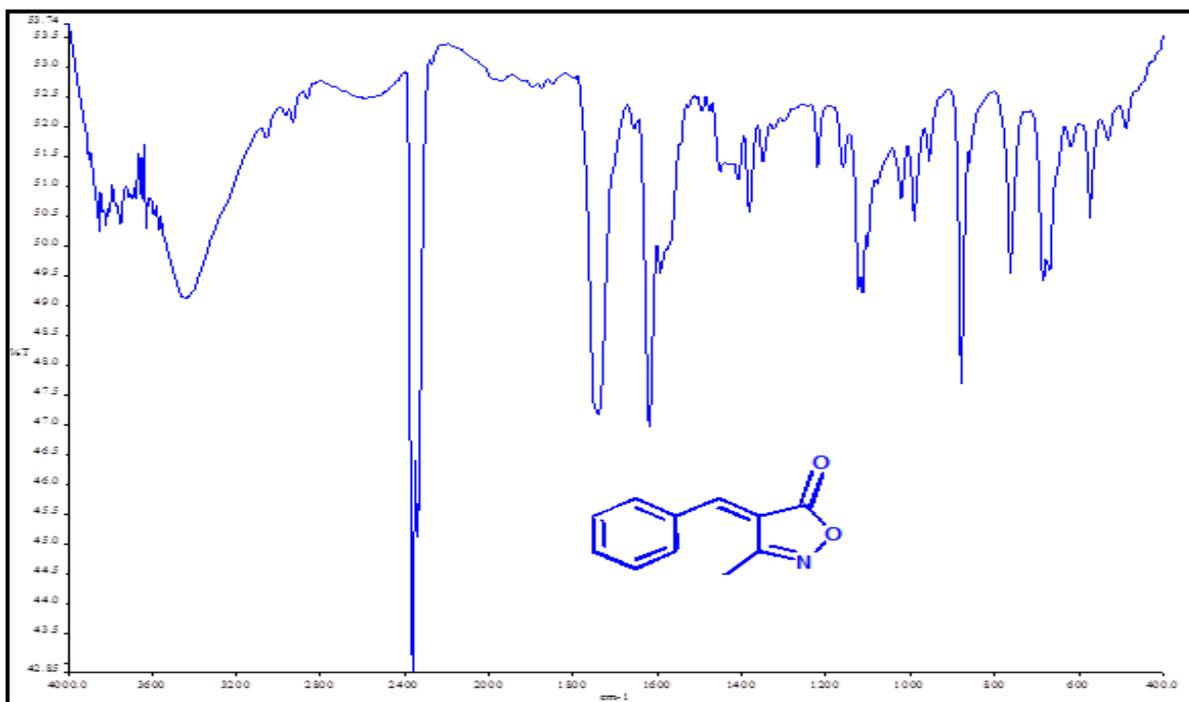
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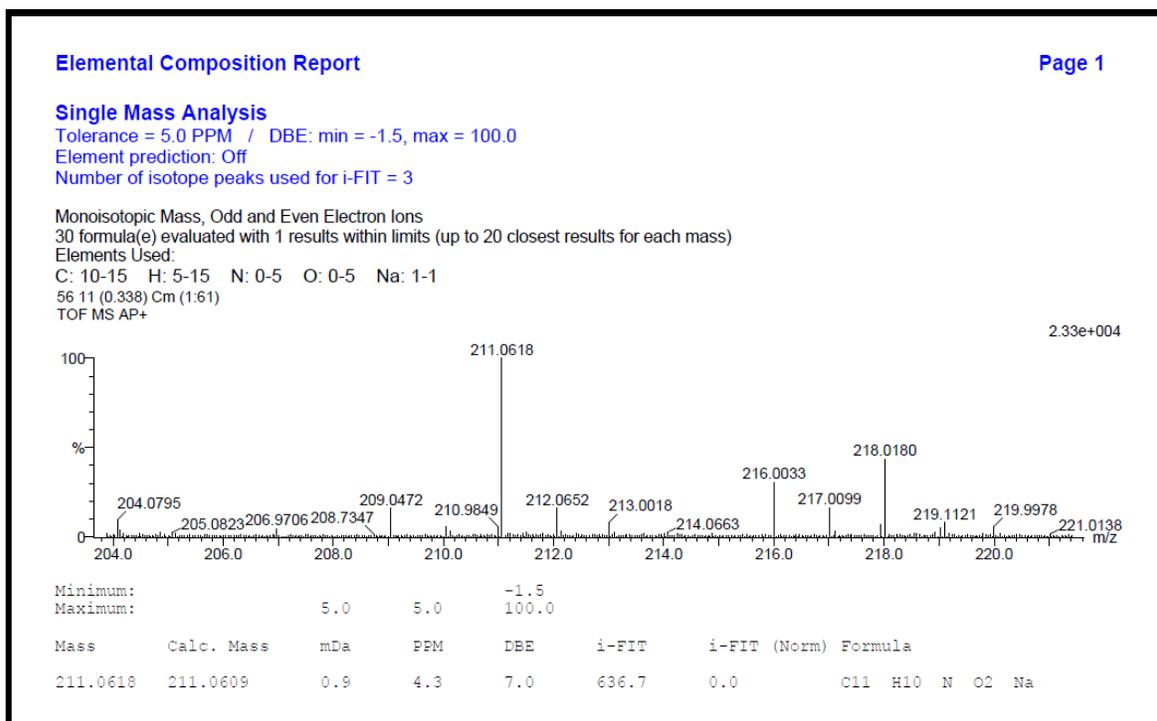
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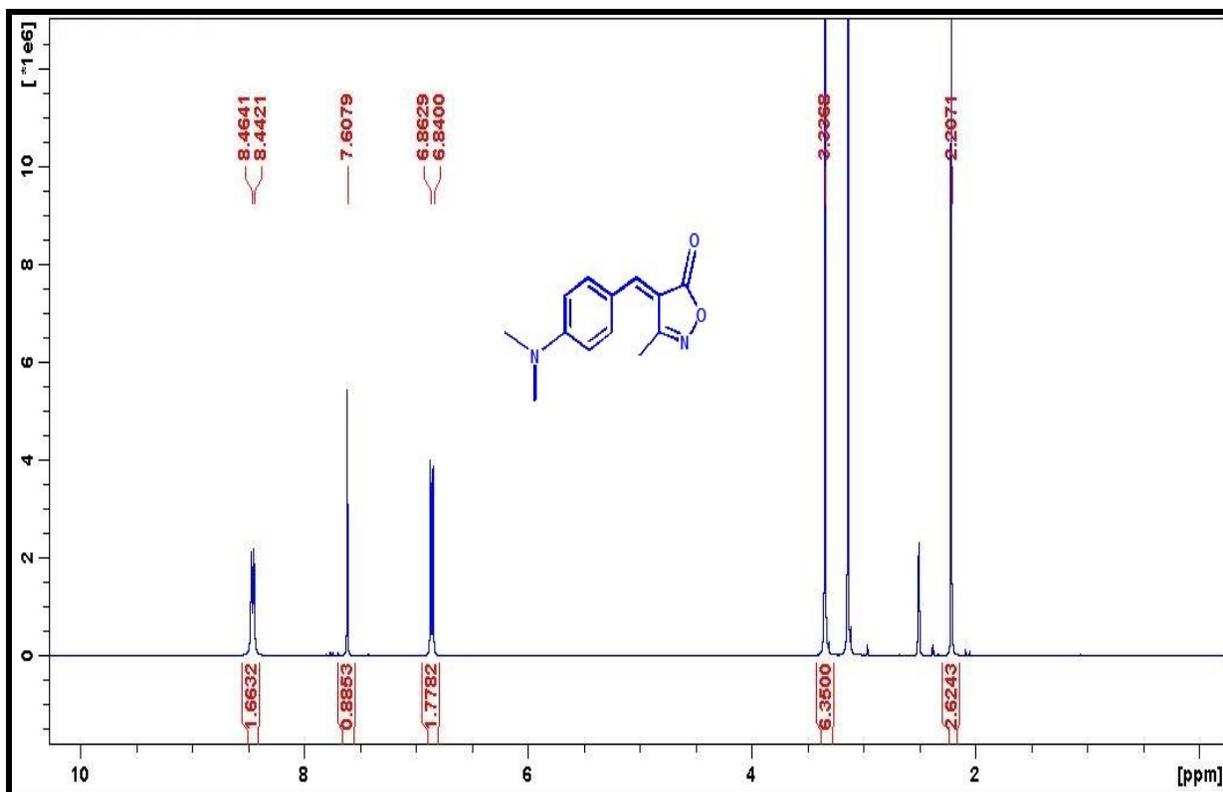
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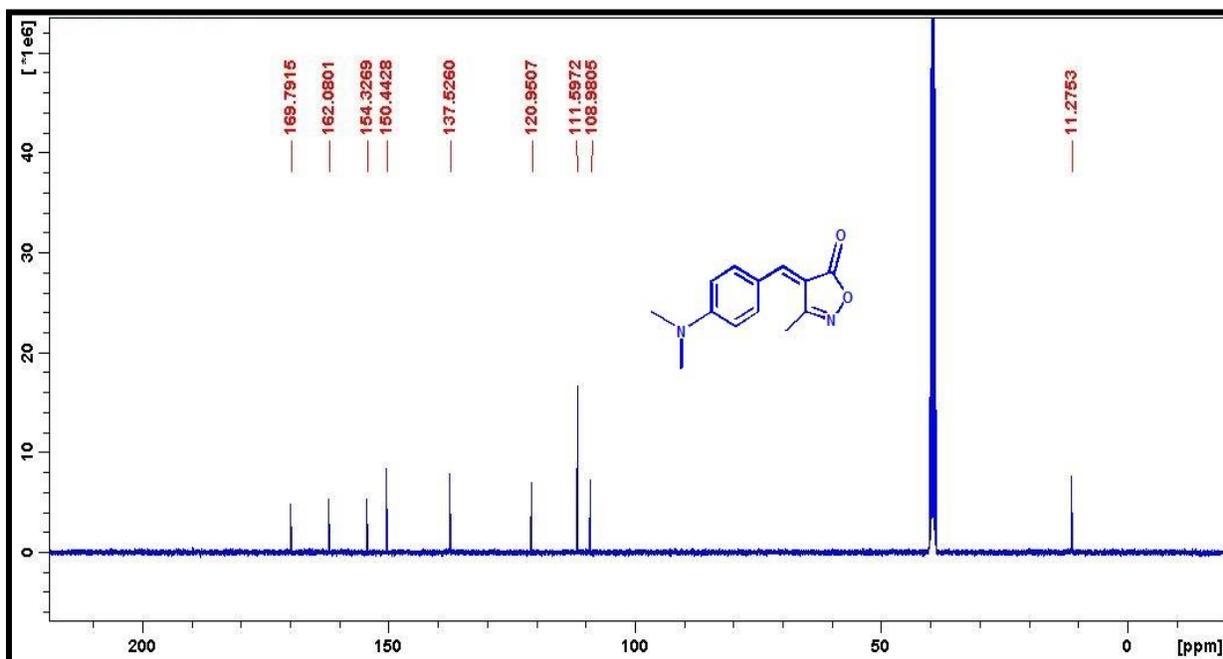
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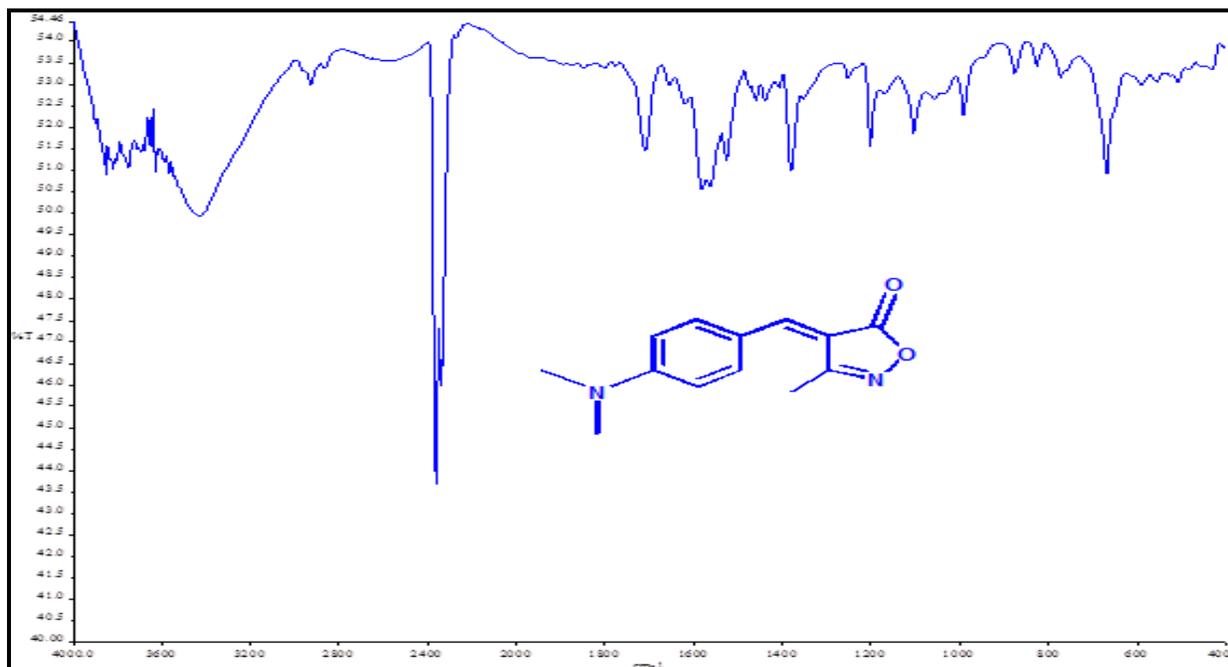
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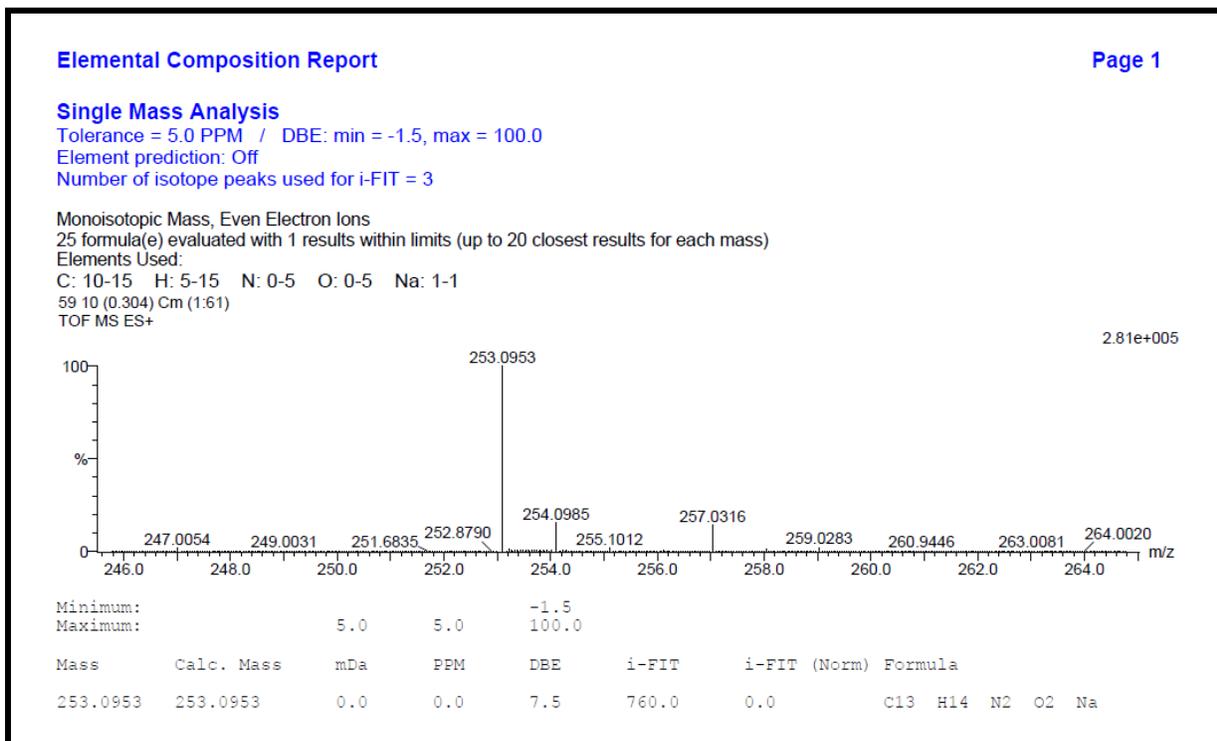
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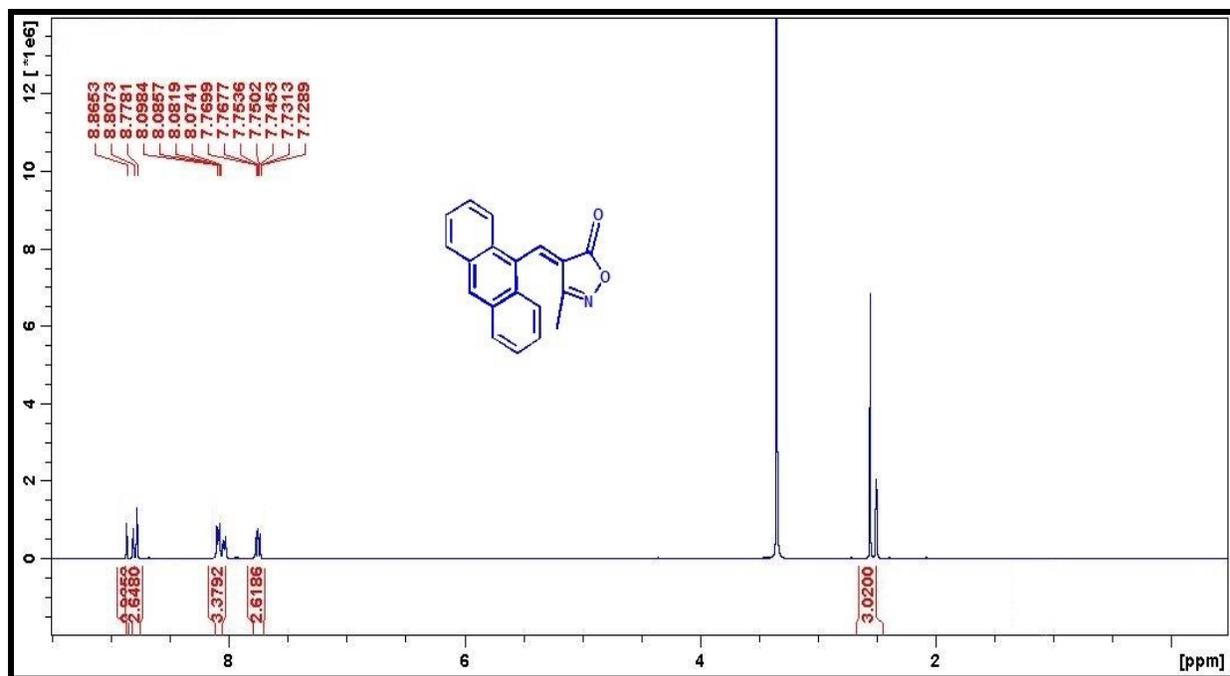
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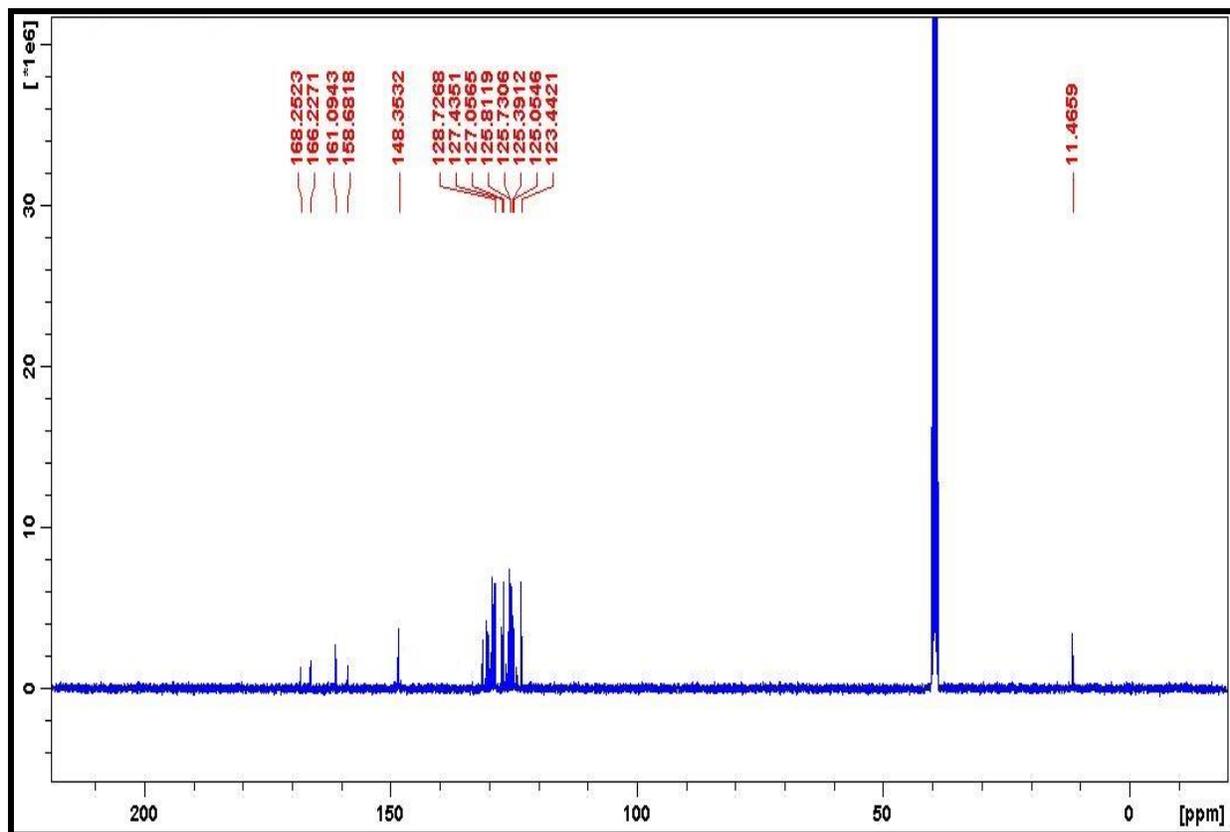
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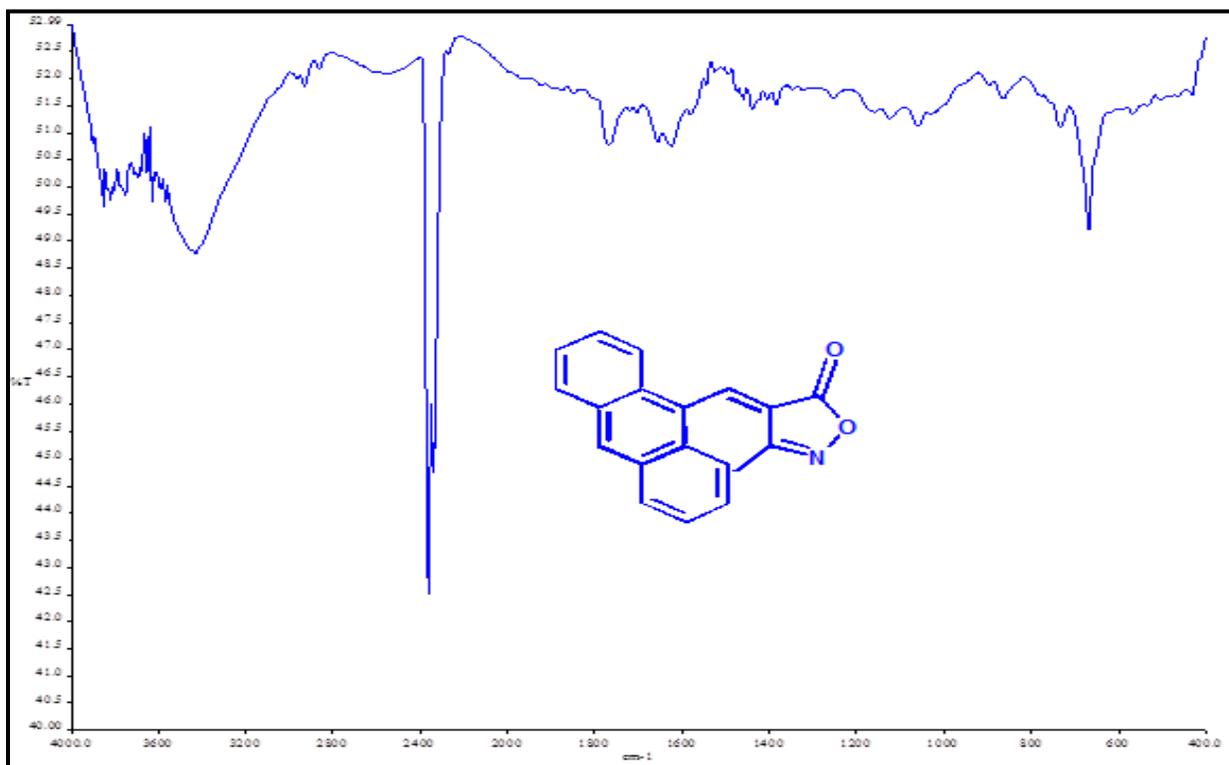
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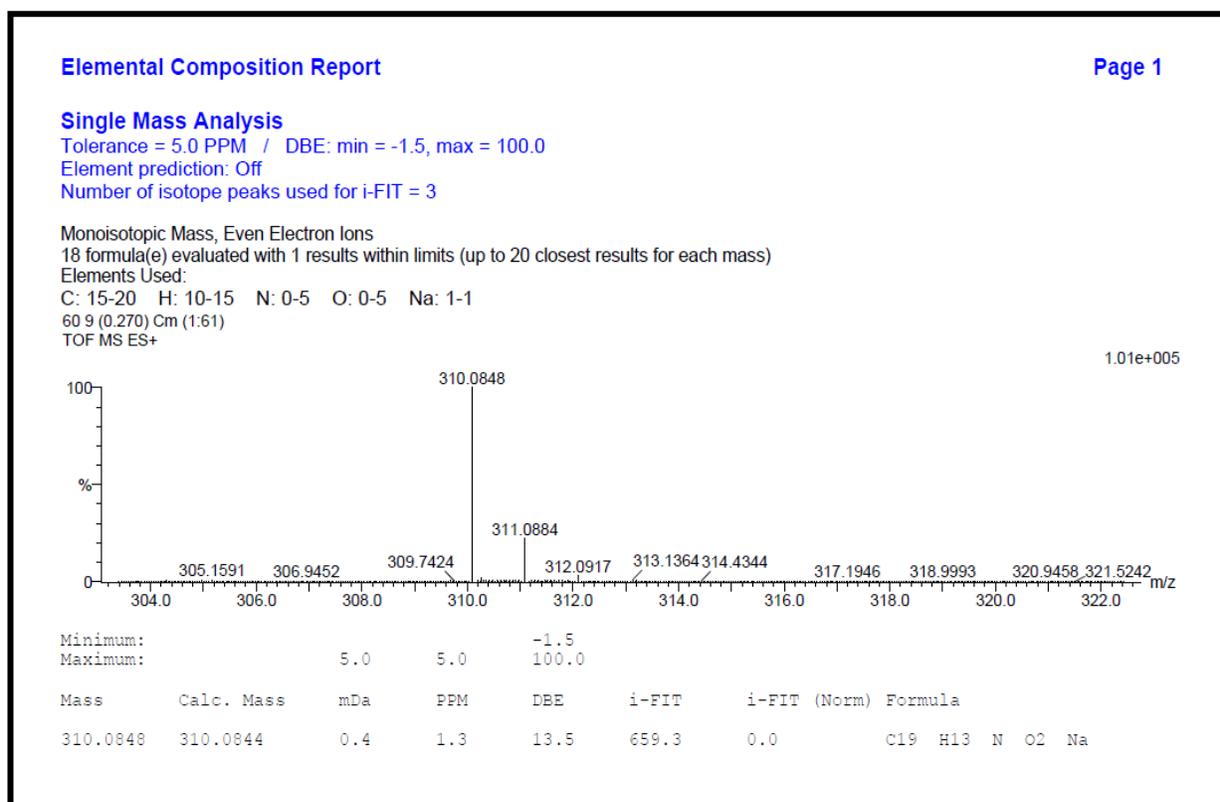
¹H NMR spectra of compound 4e



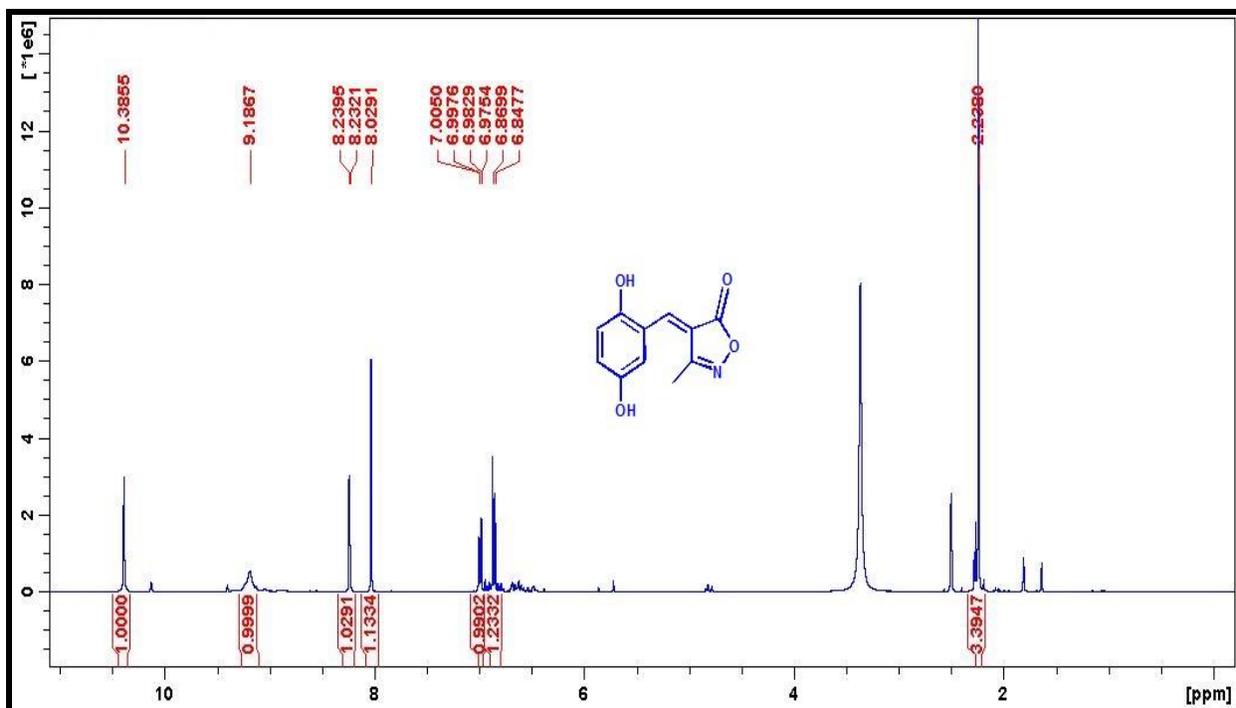
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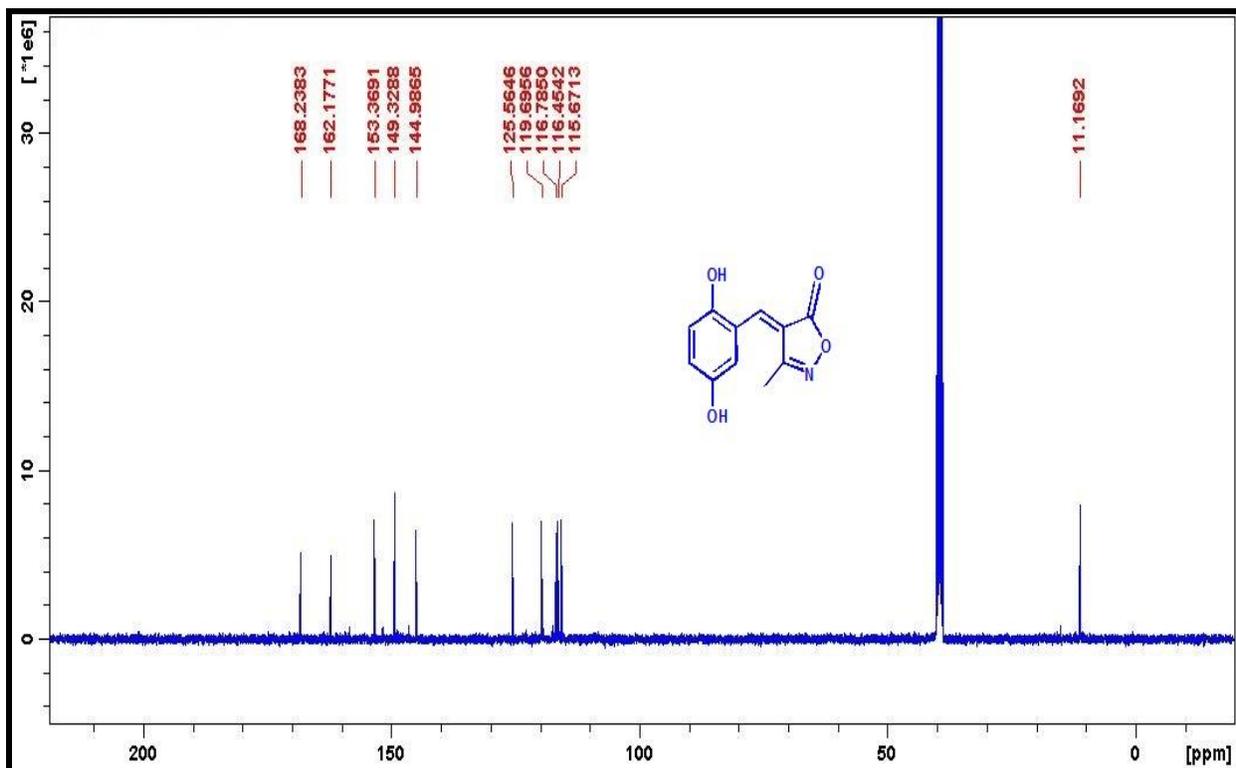
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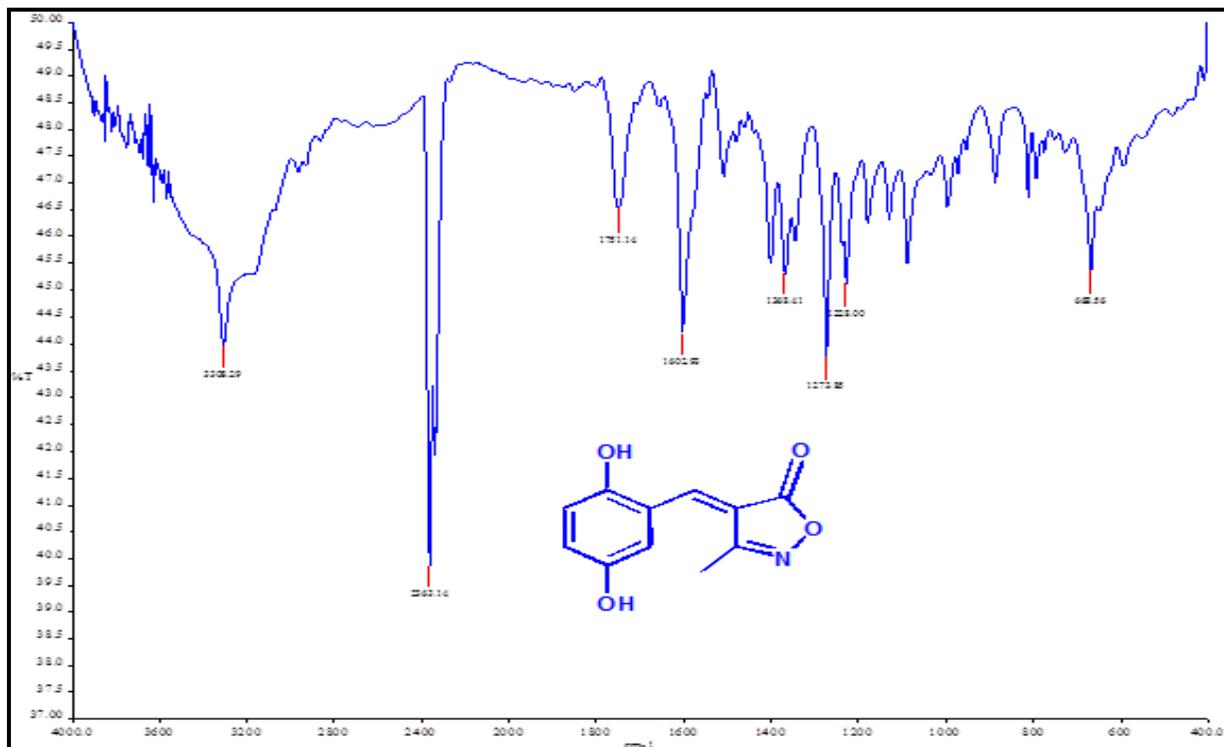
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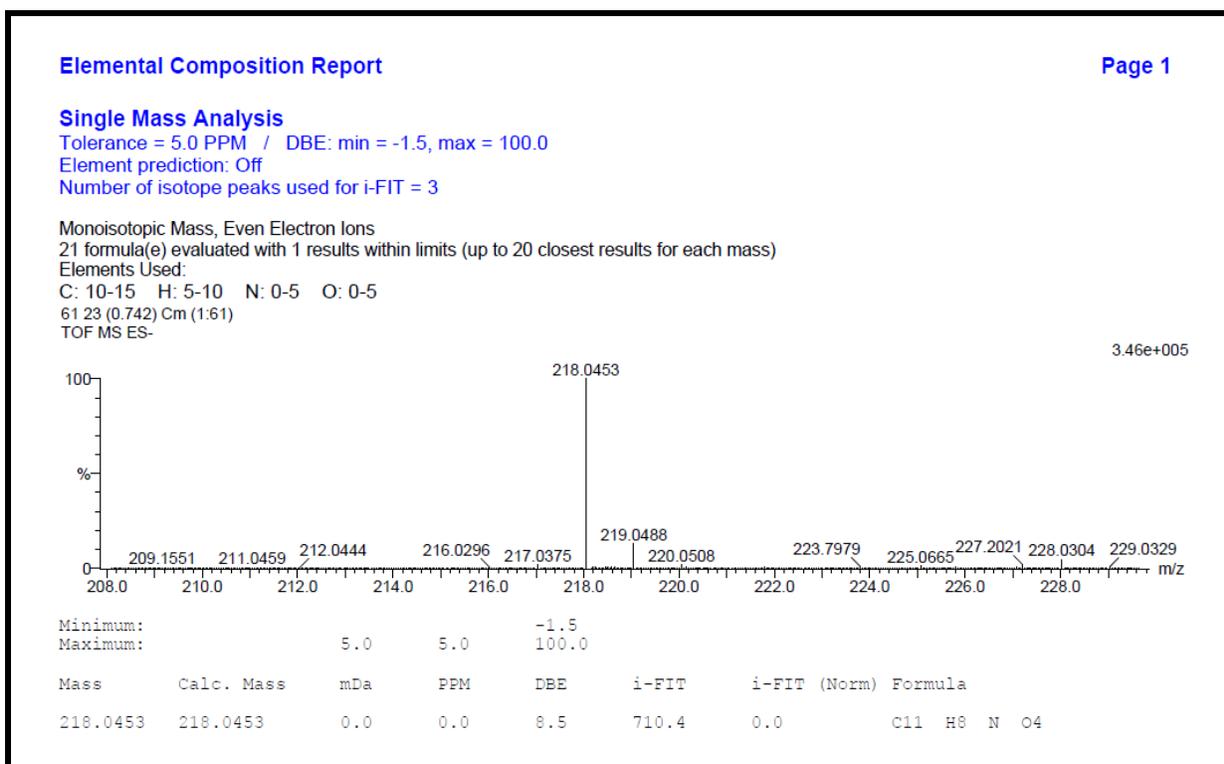
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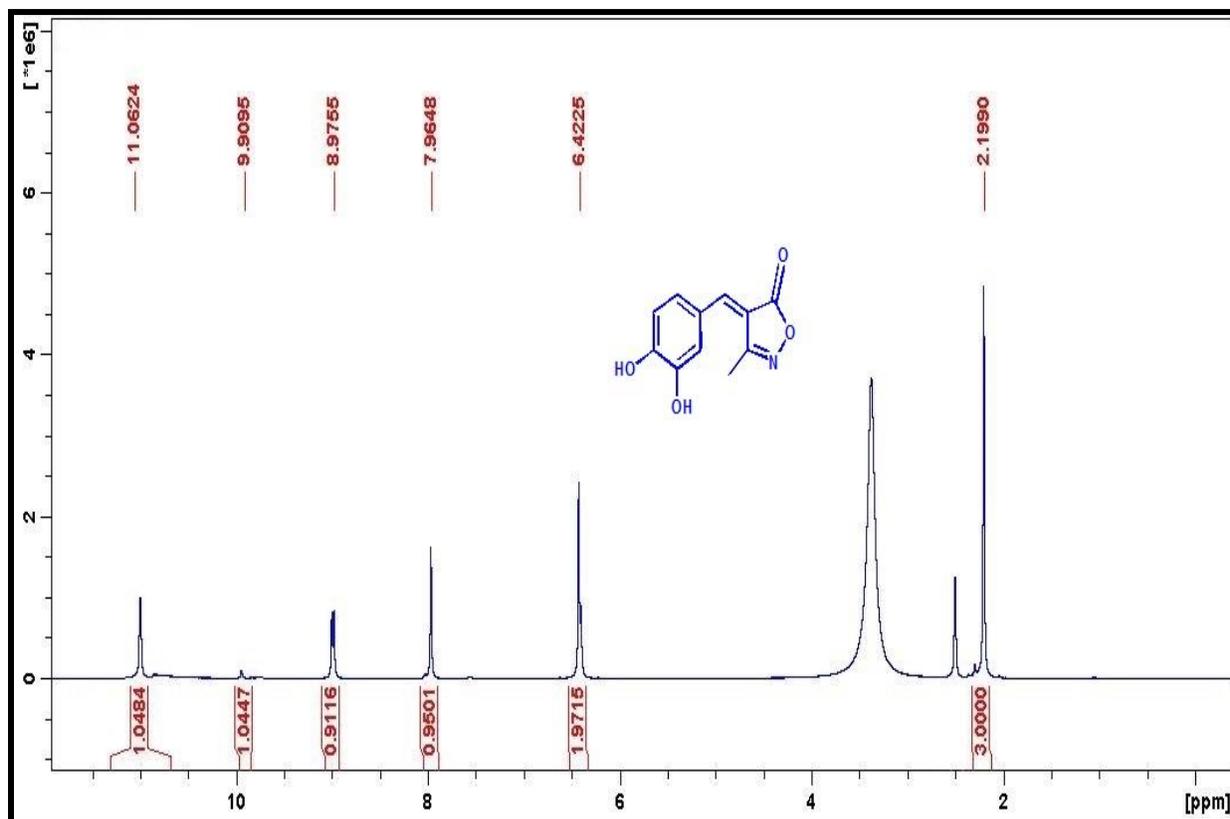
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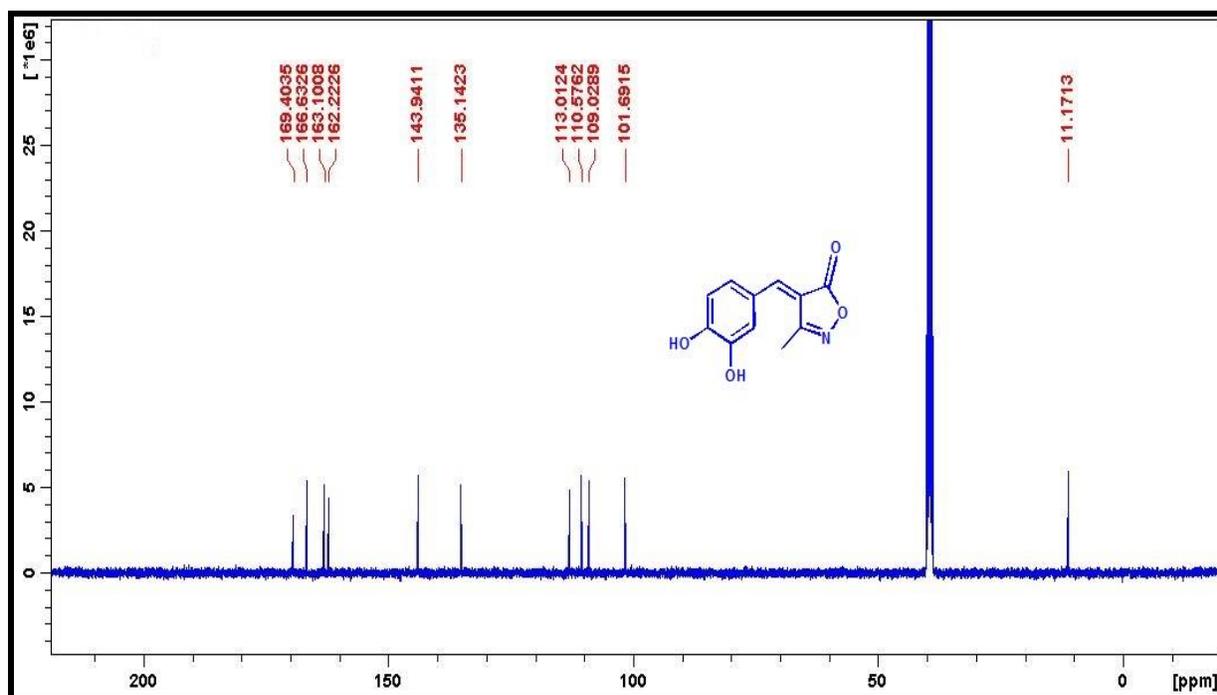
FT-IR spectra of compound **4f**



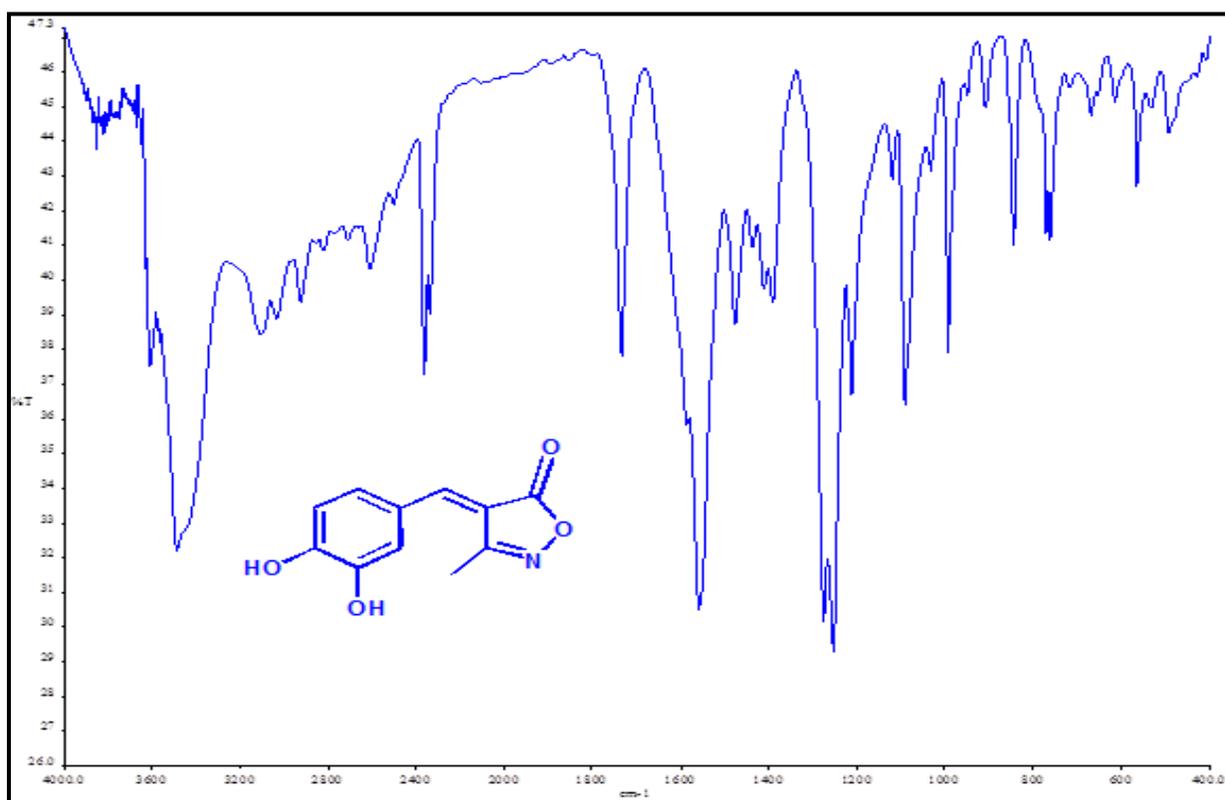
HRMS spectra of compound **4f**



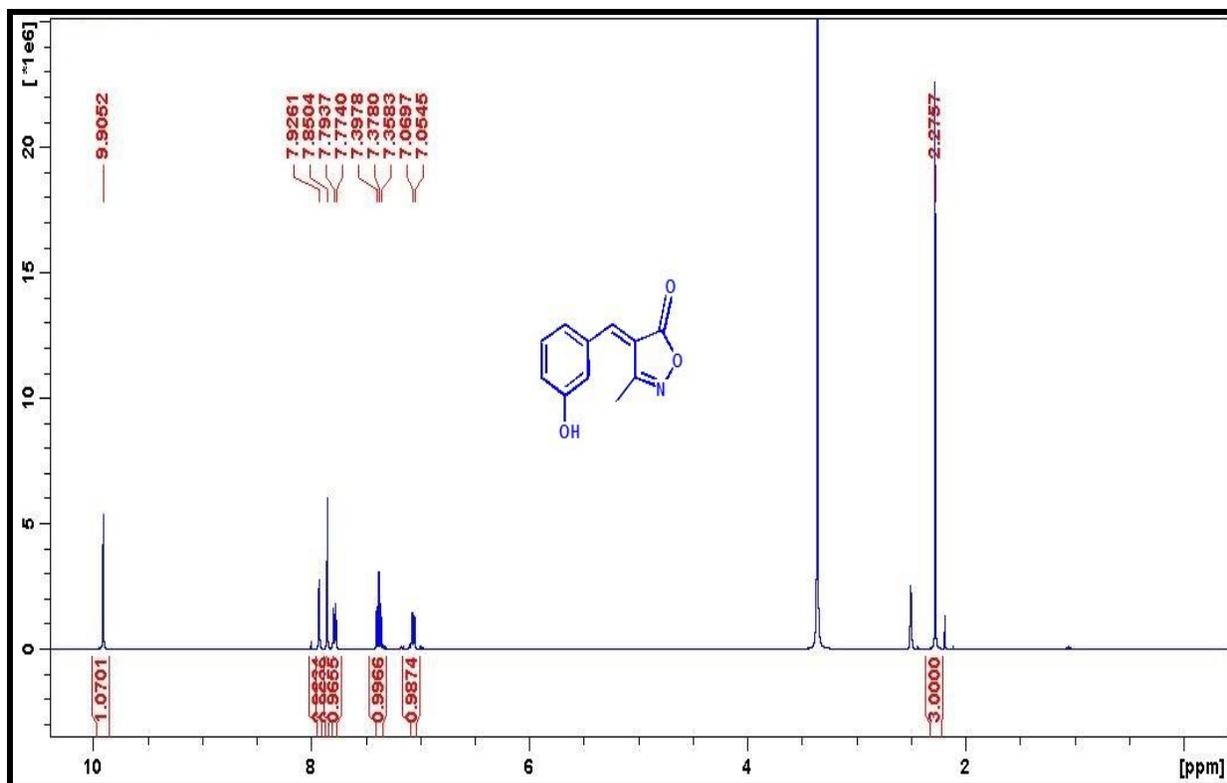
¹H NMR spectra of compound 4g



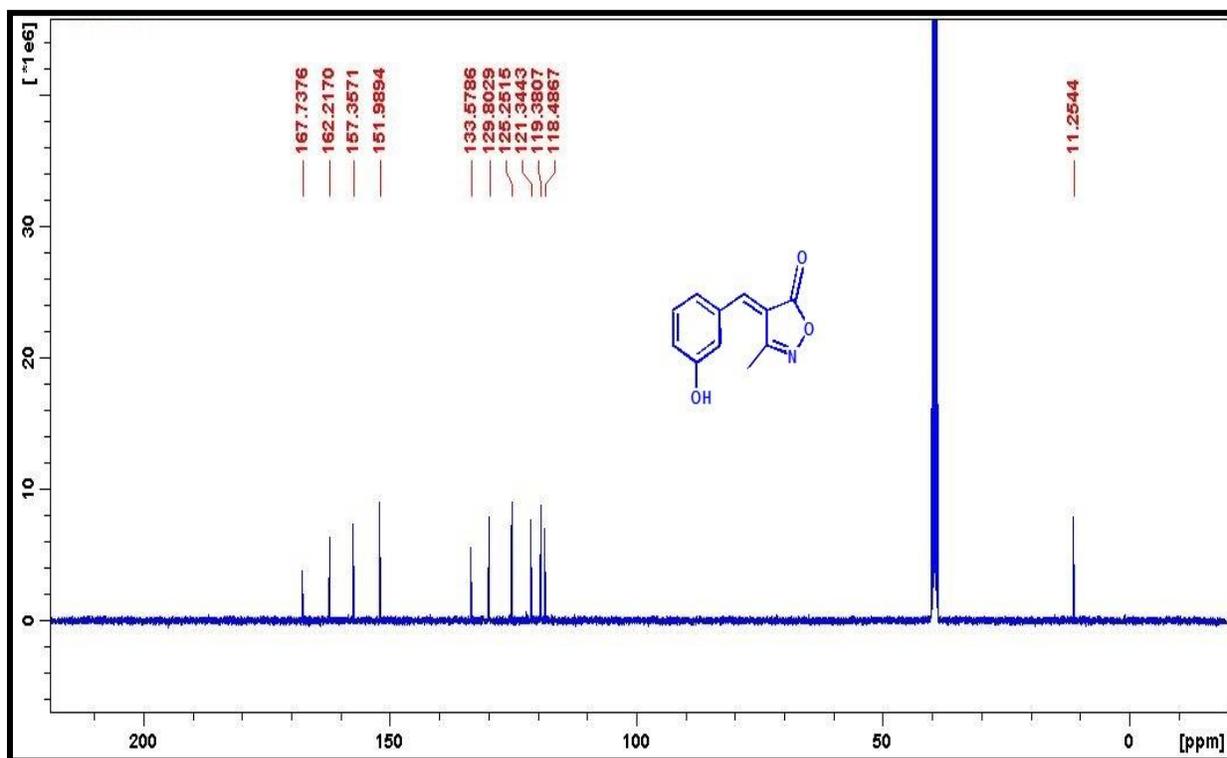
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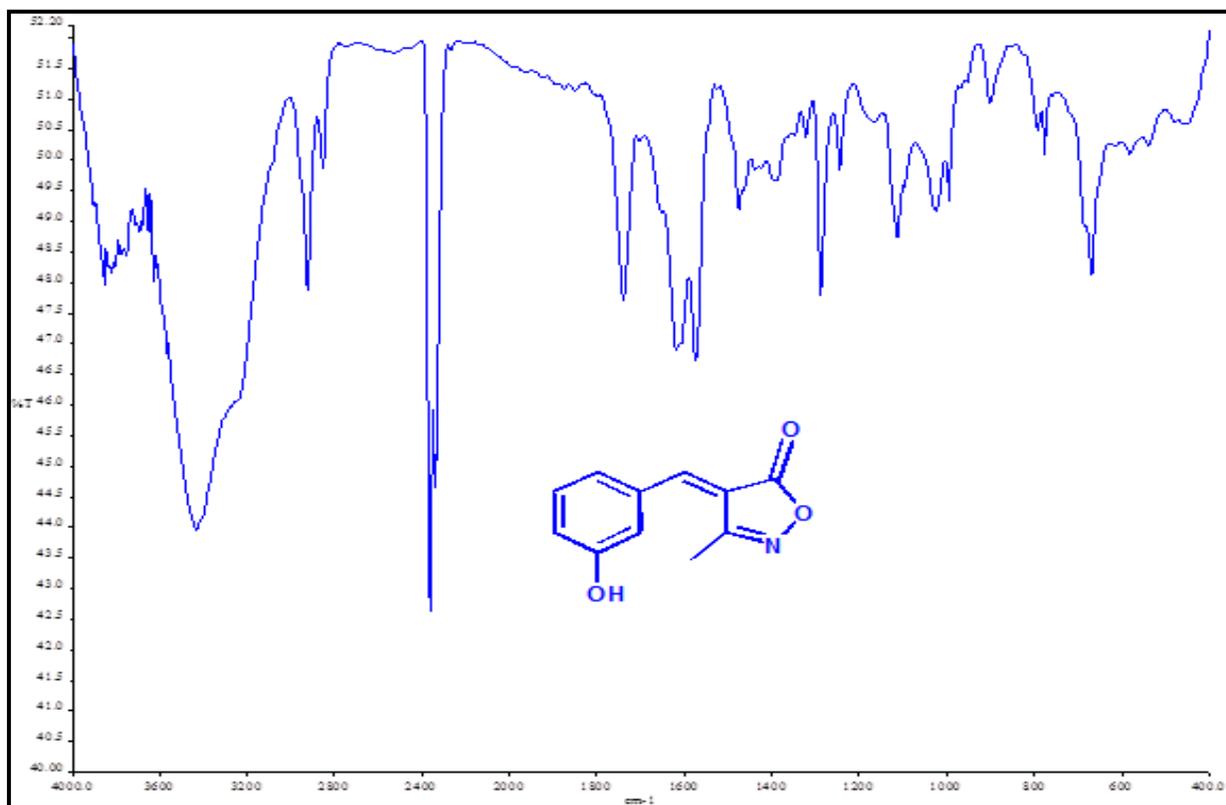
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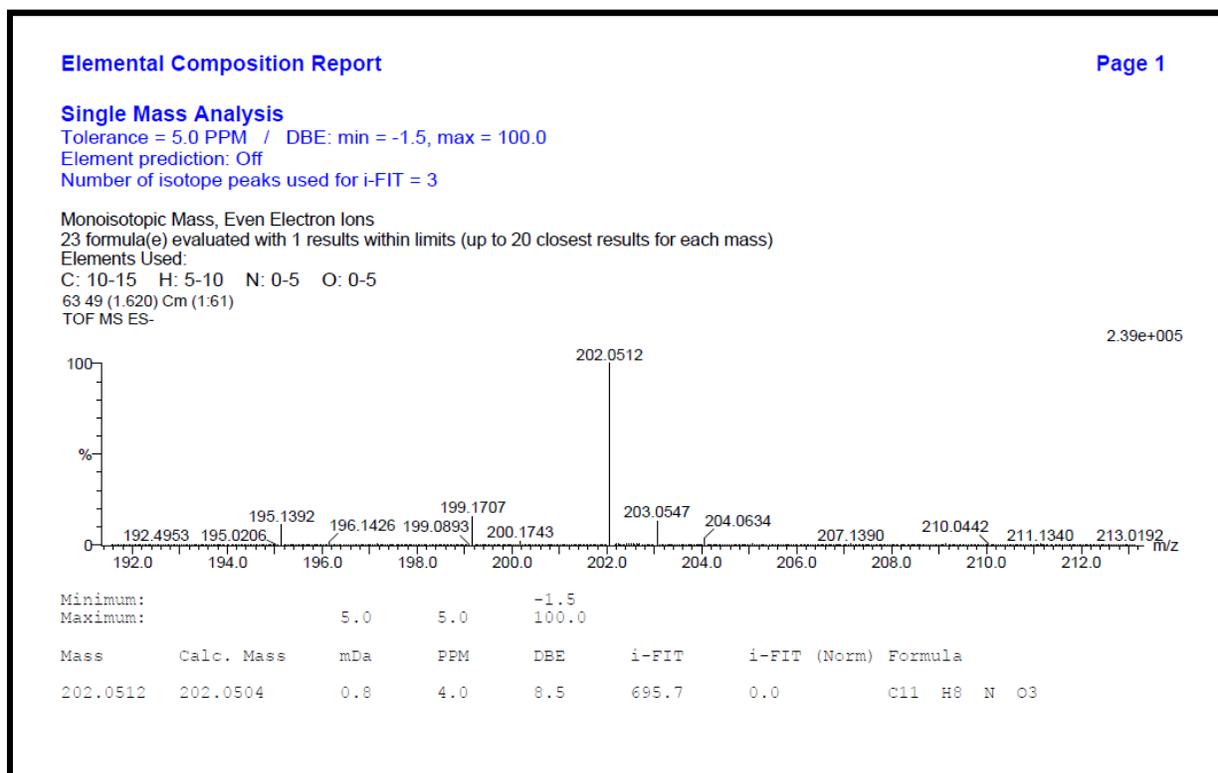
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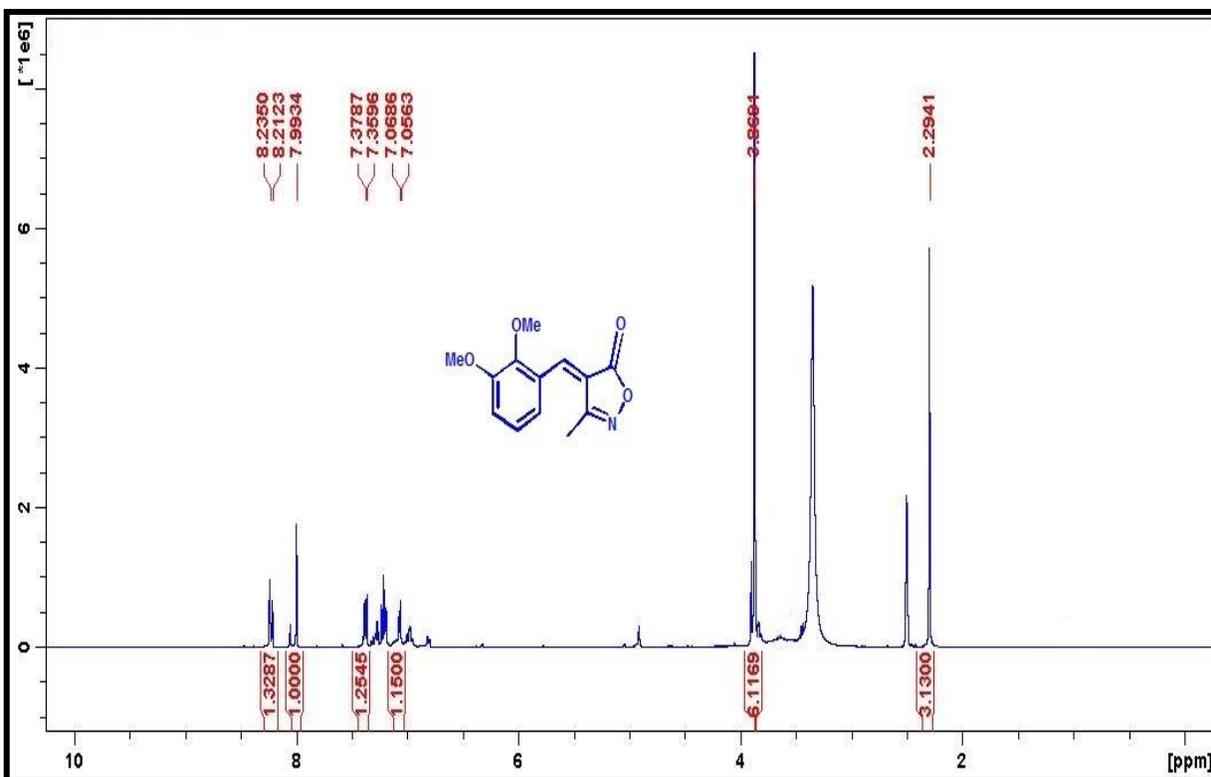
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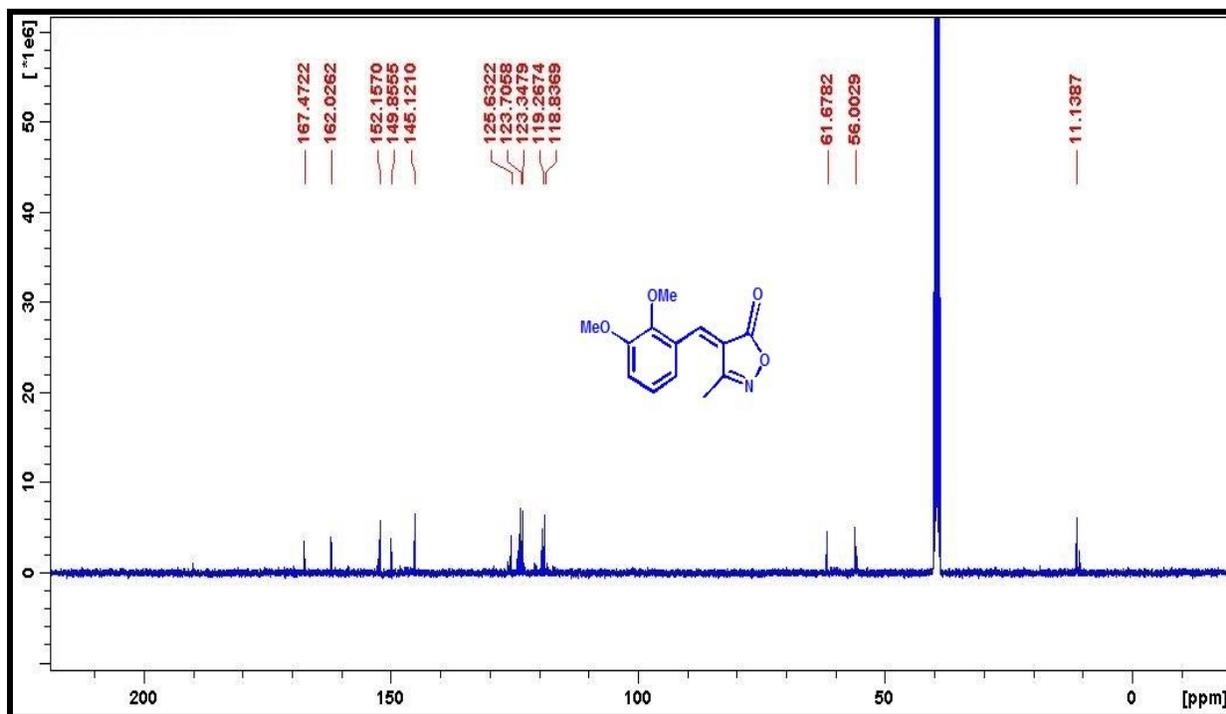
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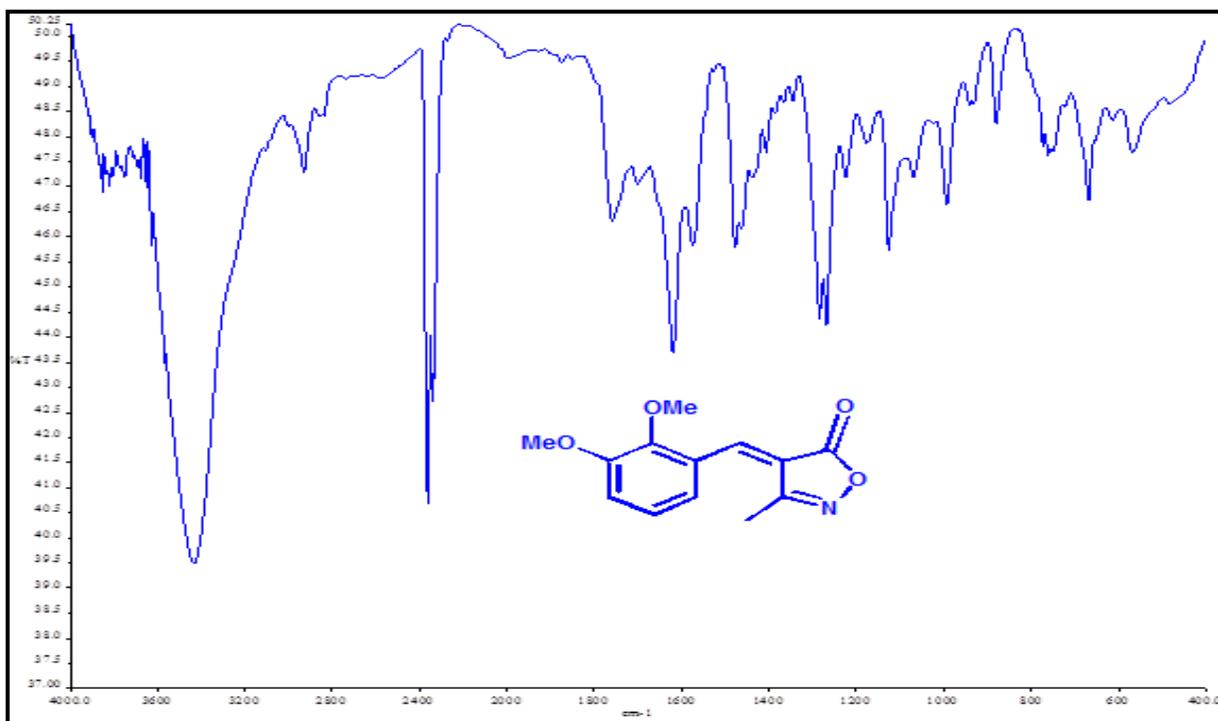
HRMS spectra of compound **4h**



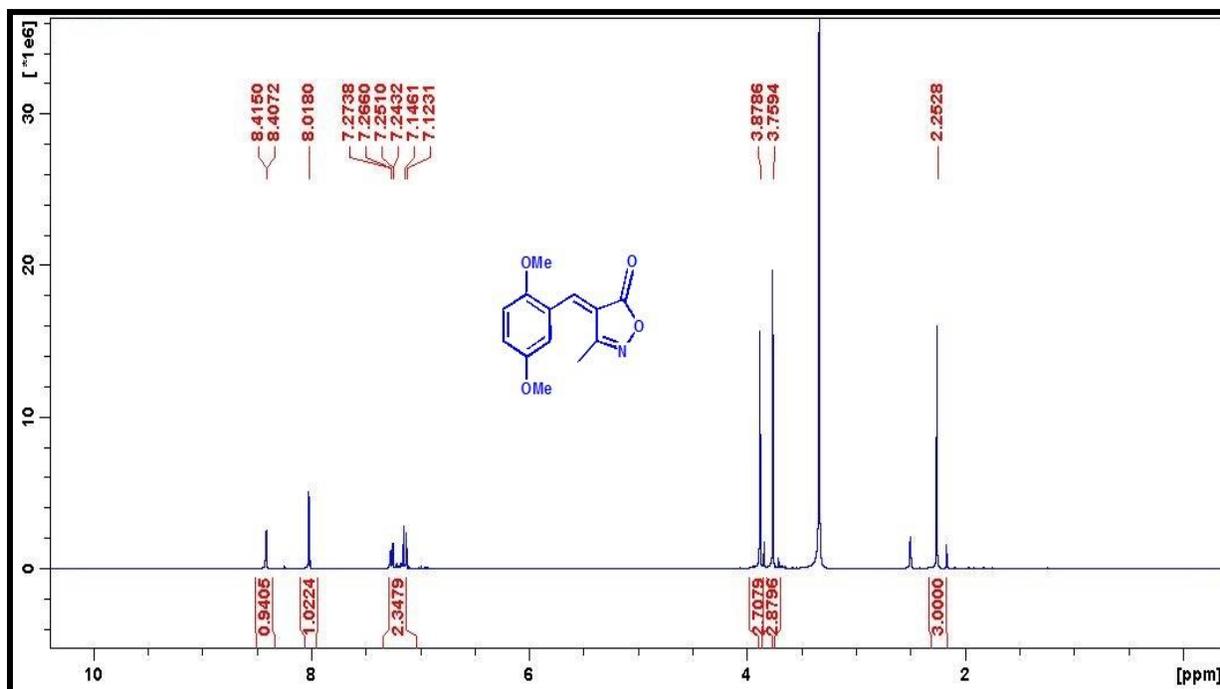
¹H NMR spectra of compound 4i



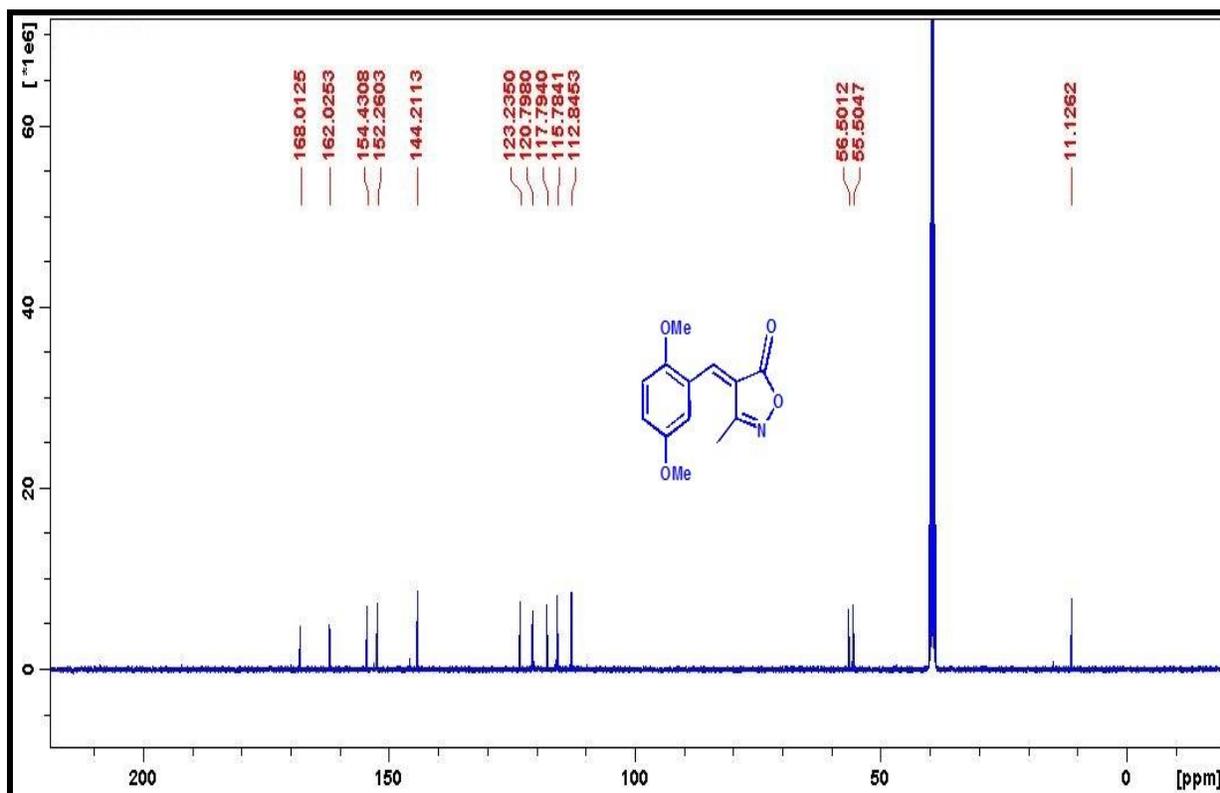
¹³C NMR spectra of compound 4i



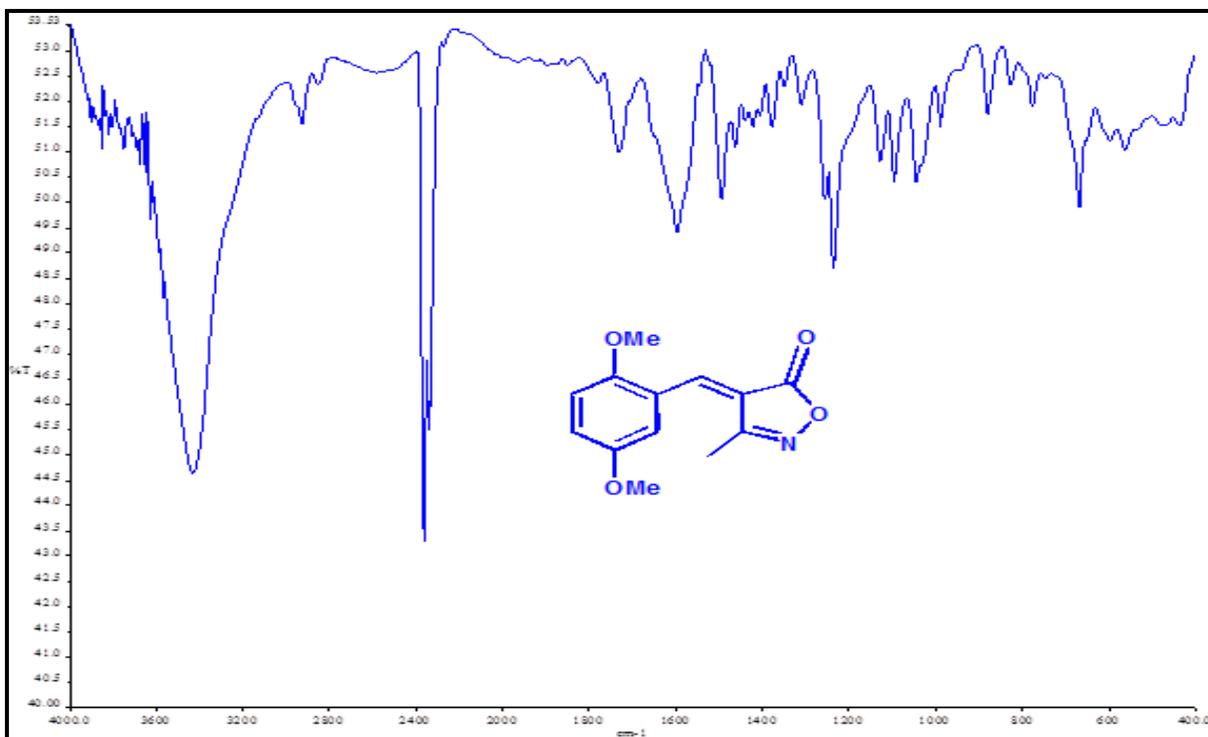
FT-IR spectra of compound **4i**



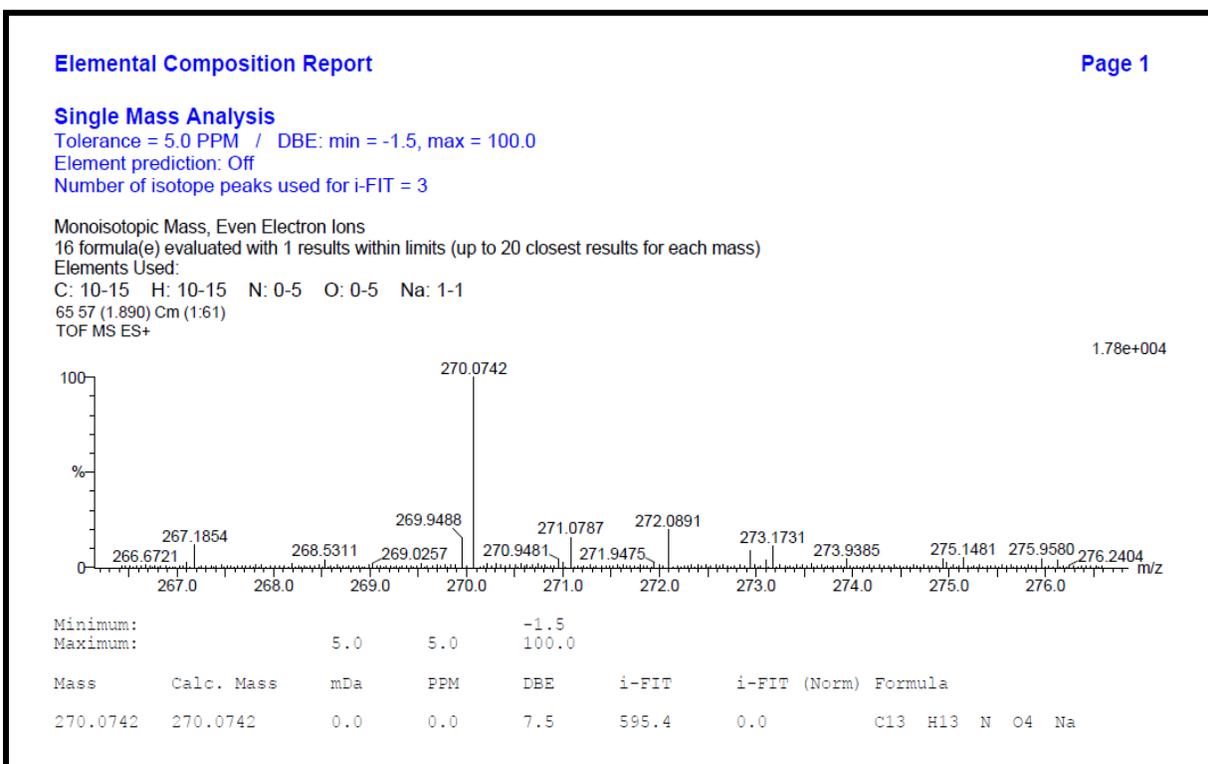
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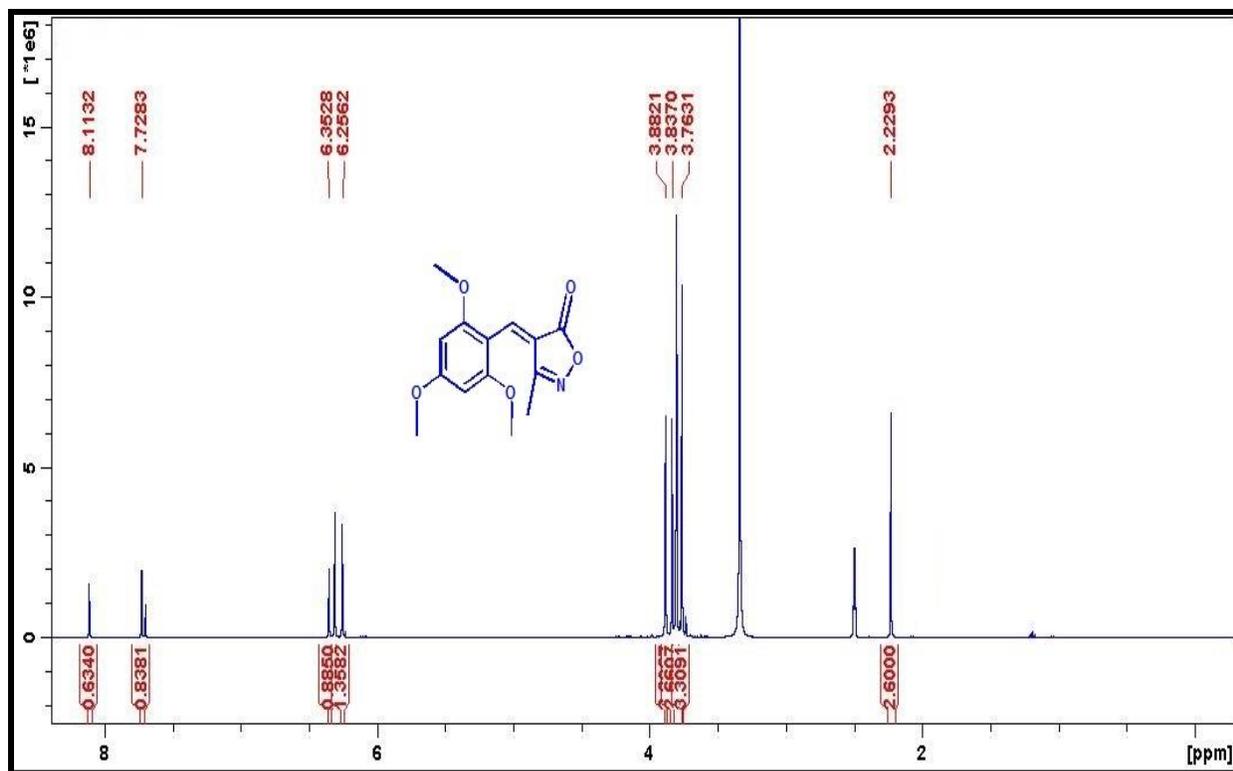
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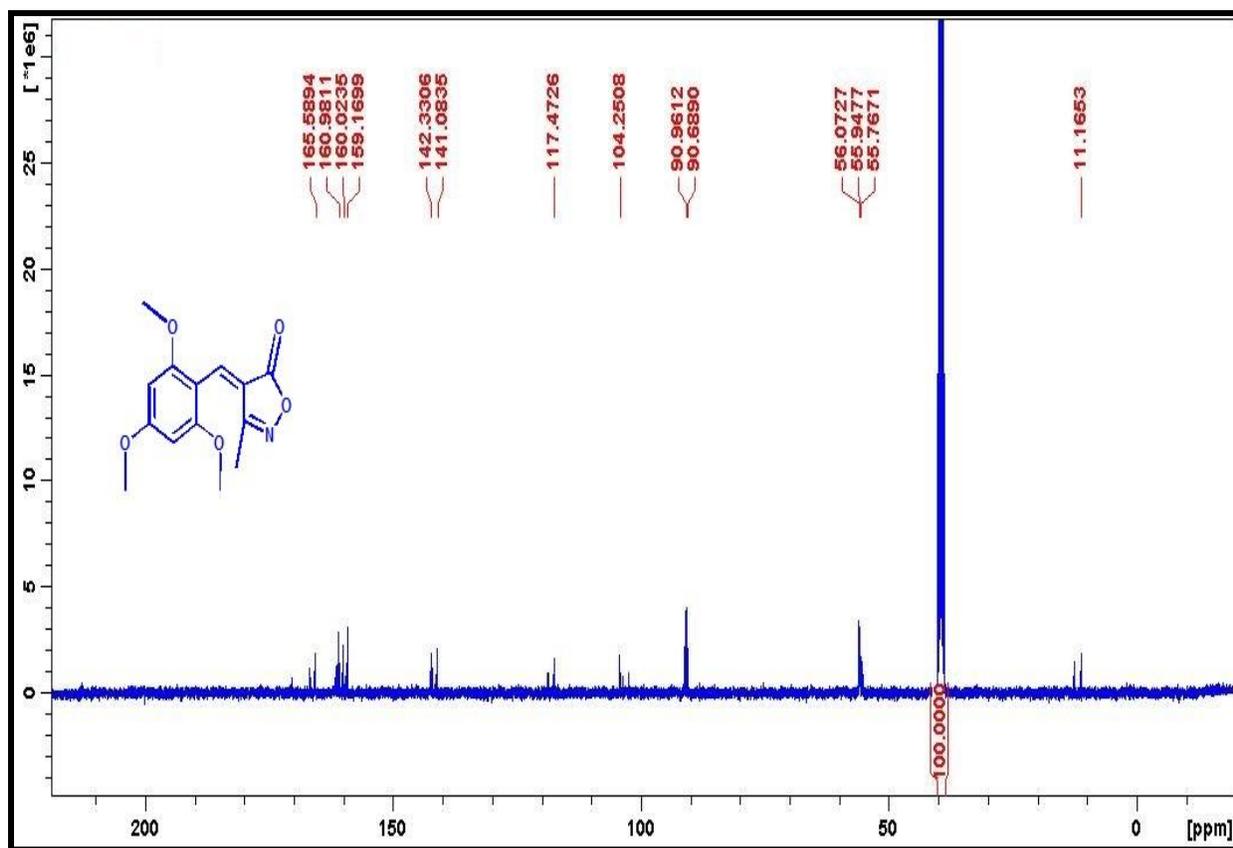
FT-IR spectra of compound **4j**



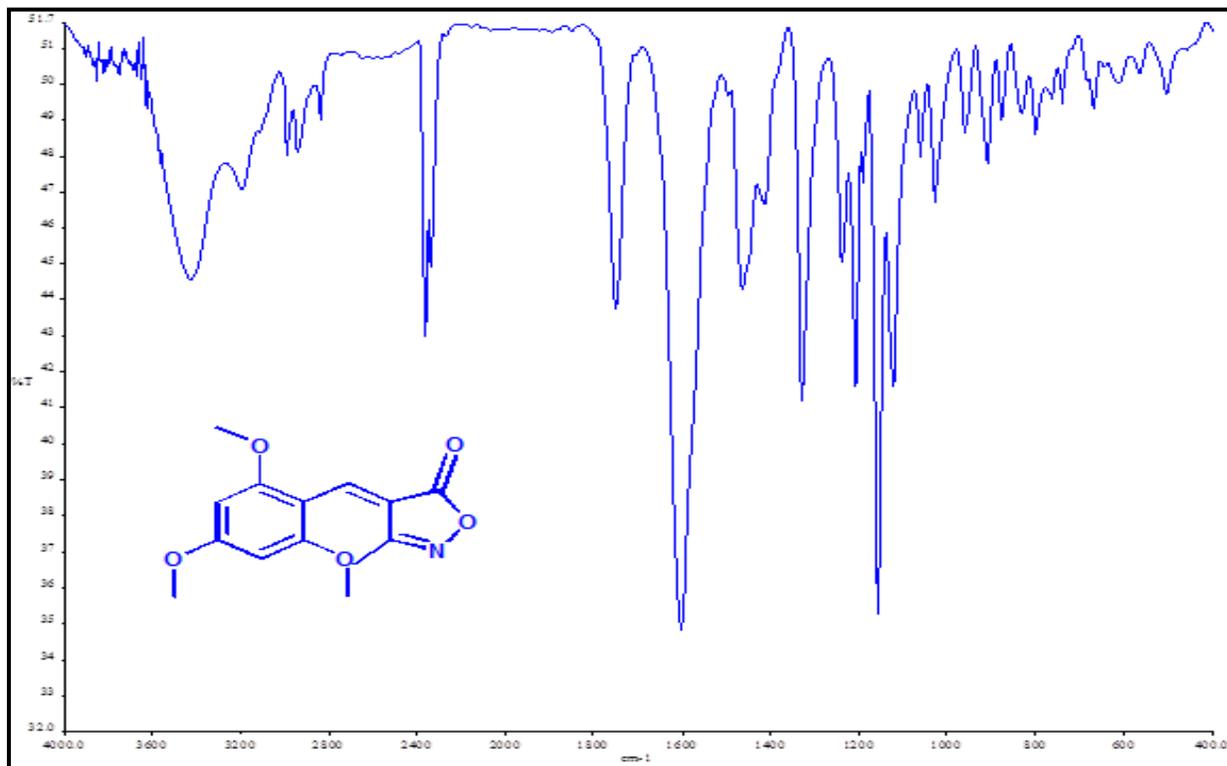
HRMS spectra of compound **4j**



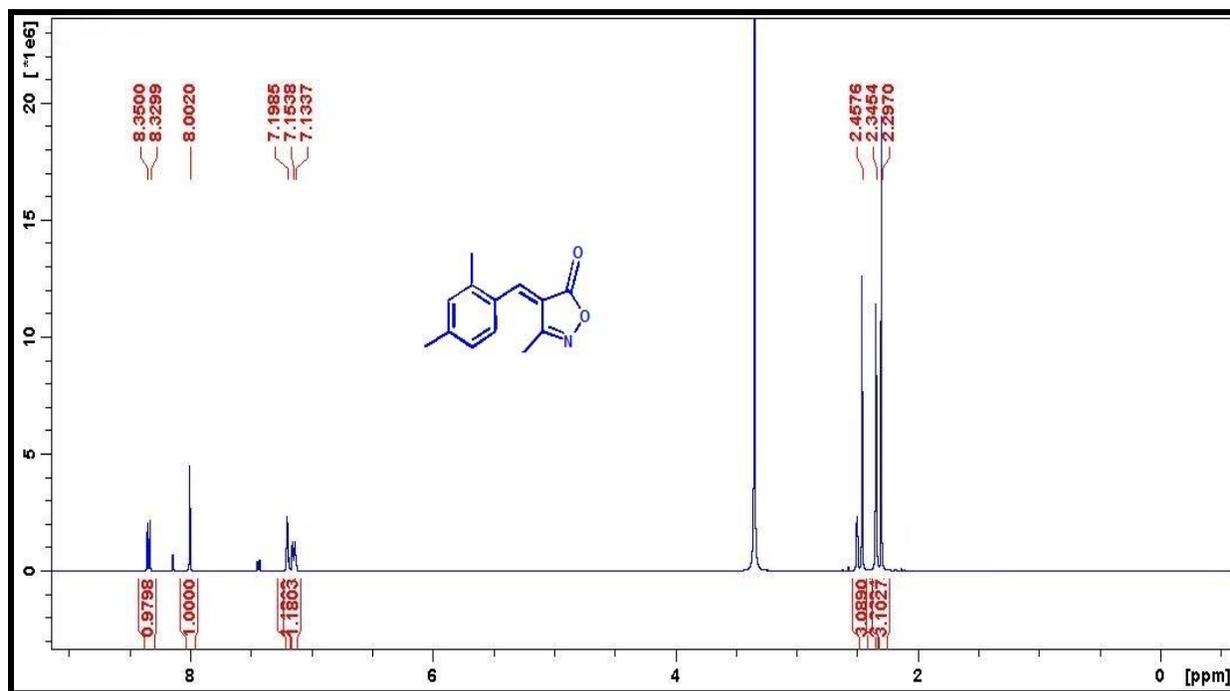
¹H NMR spectra of compound 4k



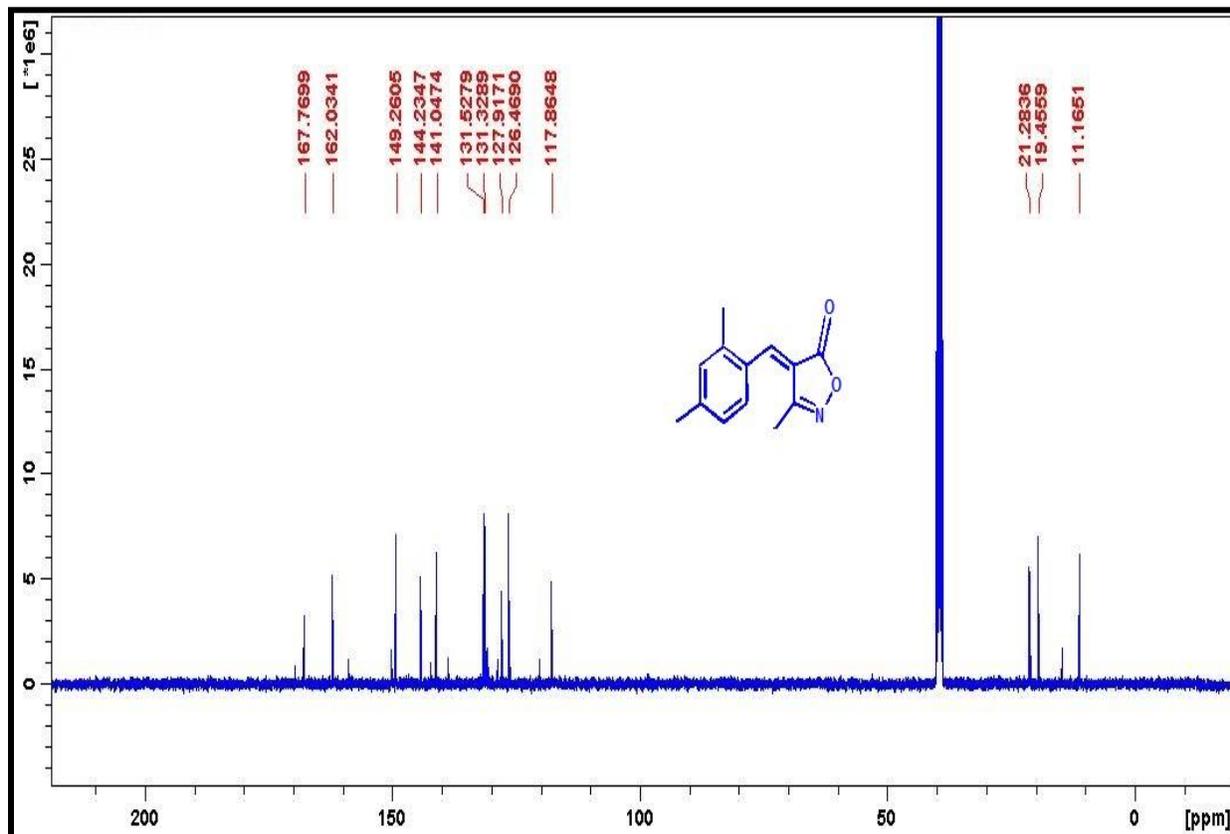
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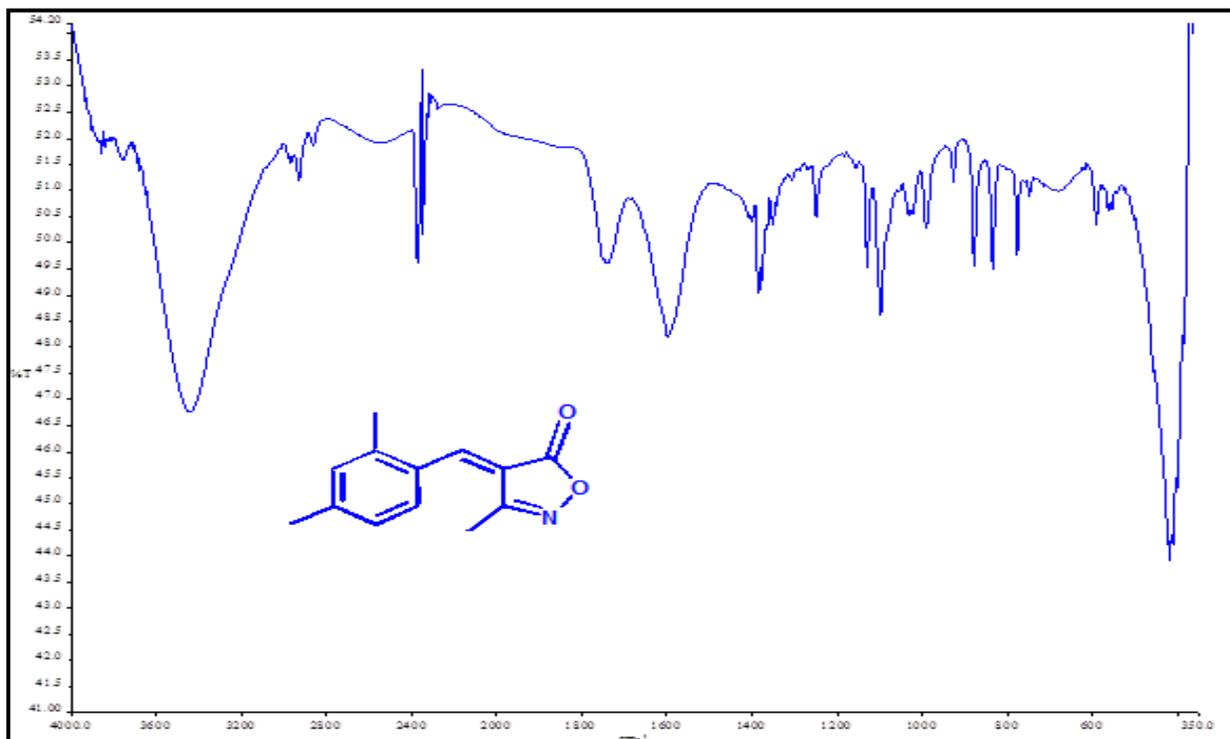
FT-IR spectra of compound **4k**



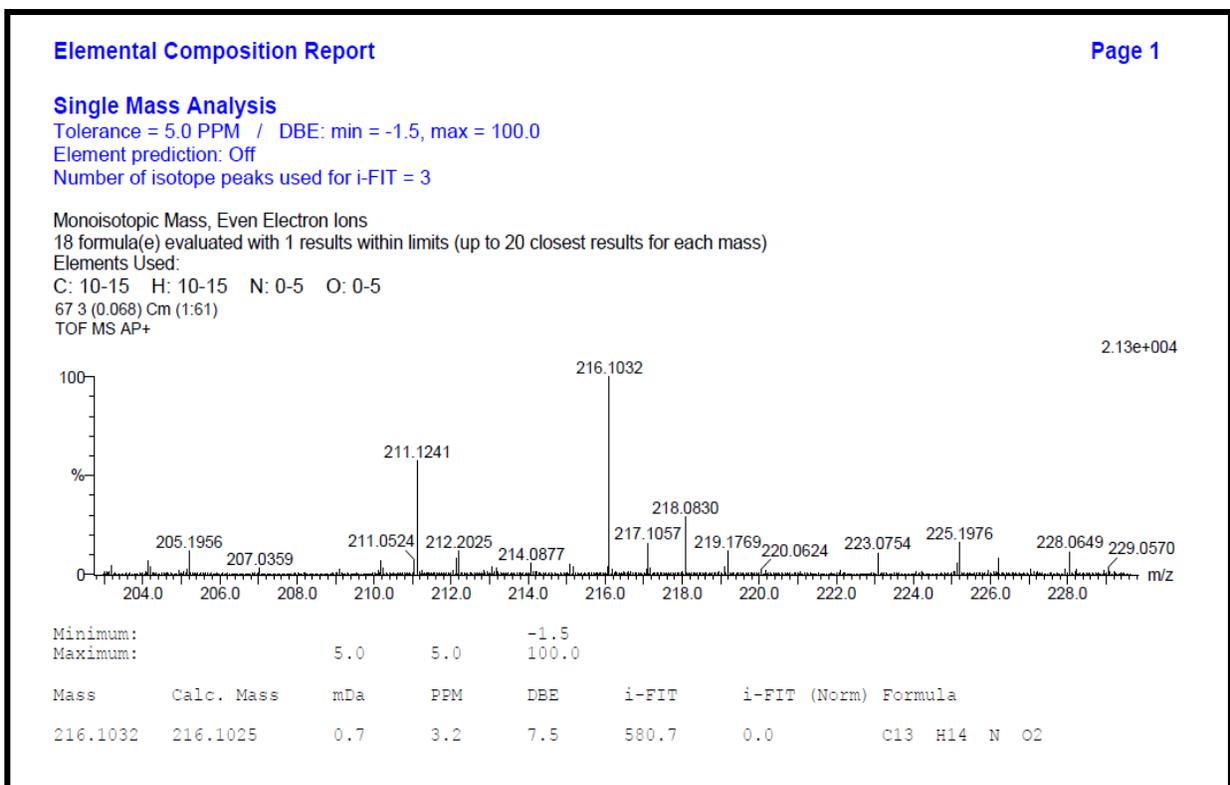
¹H NMR spectra of compound **4I**



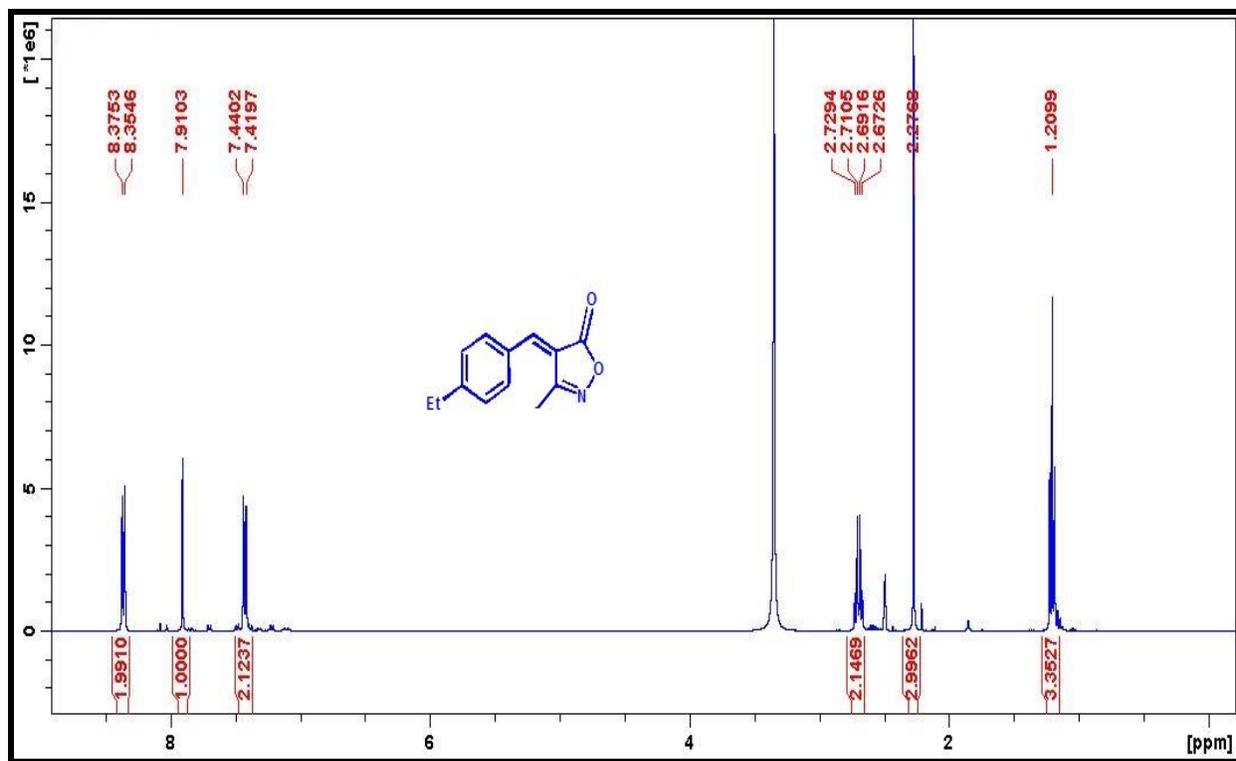
¹³C NMR spectra of compound **4I**



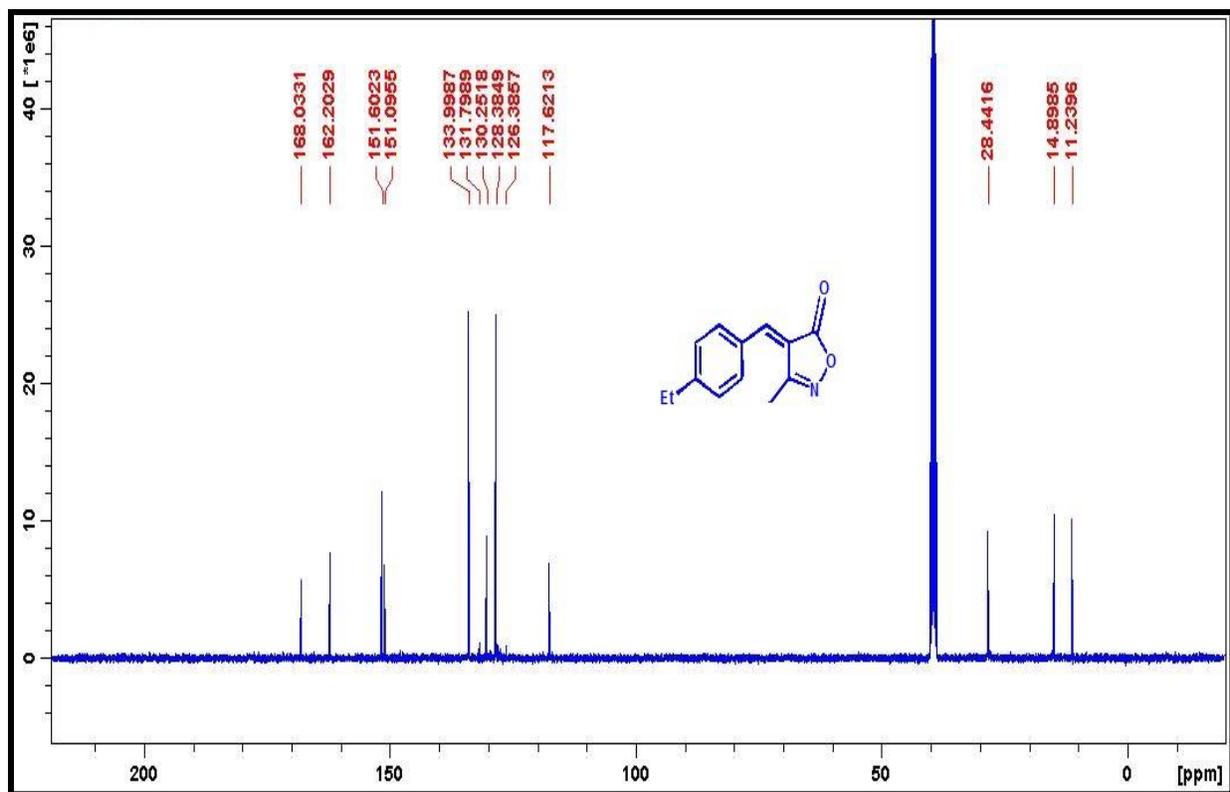
FT-IR spectra of compound **41**



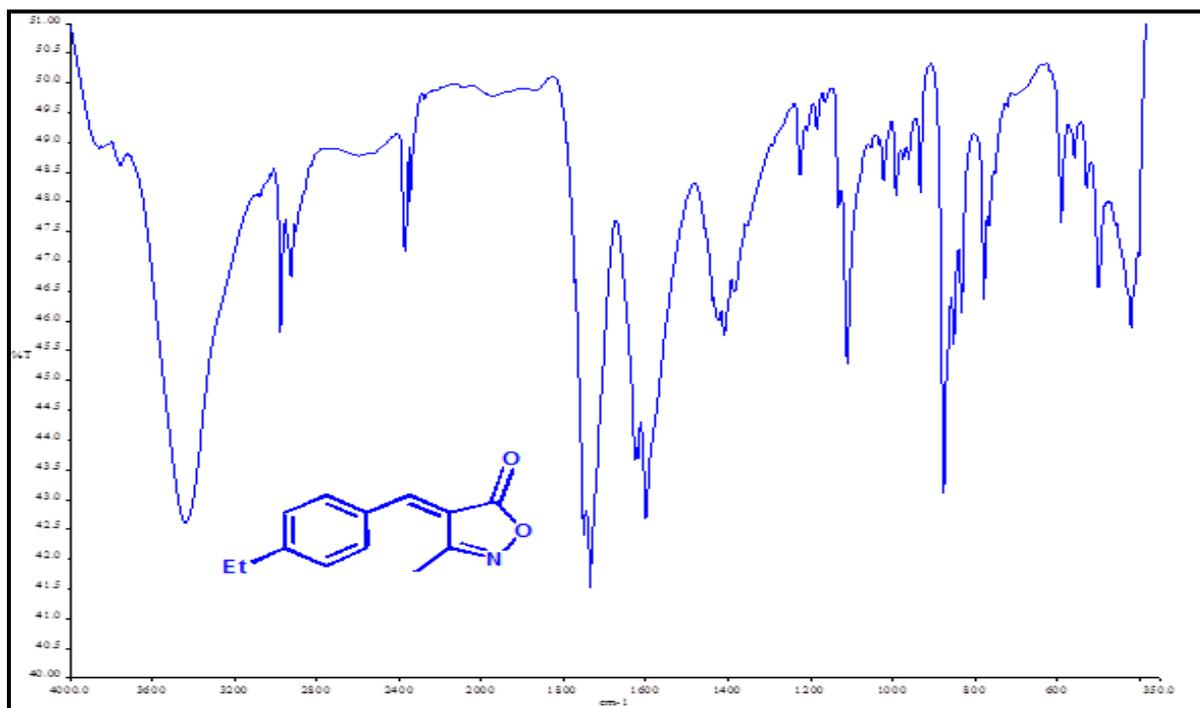
HRMS spectra of compound **41**



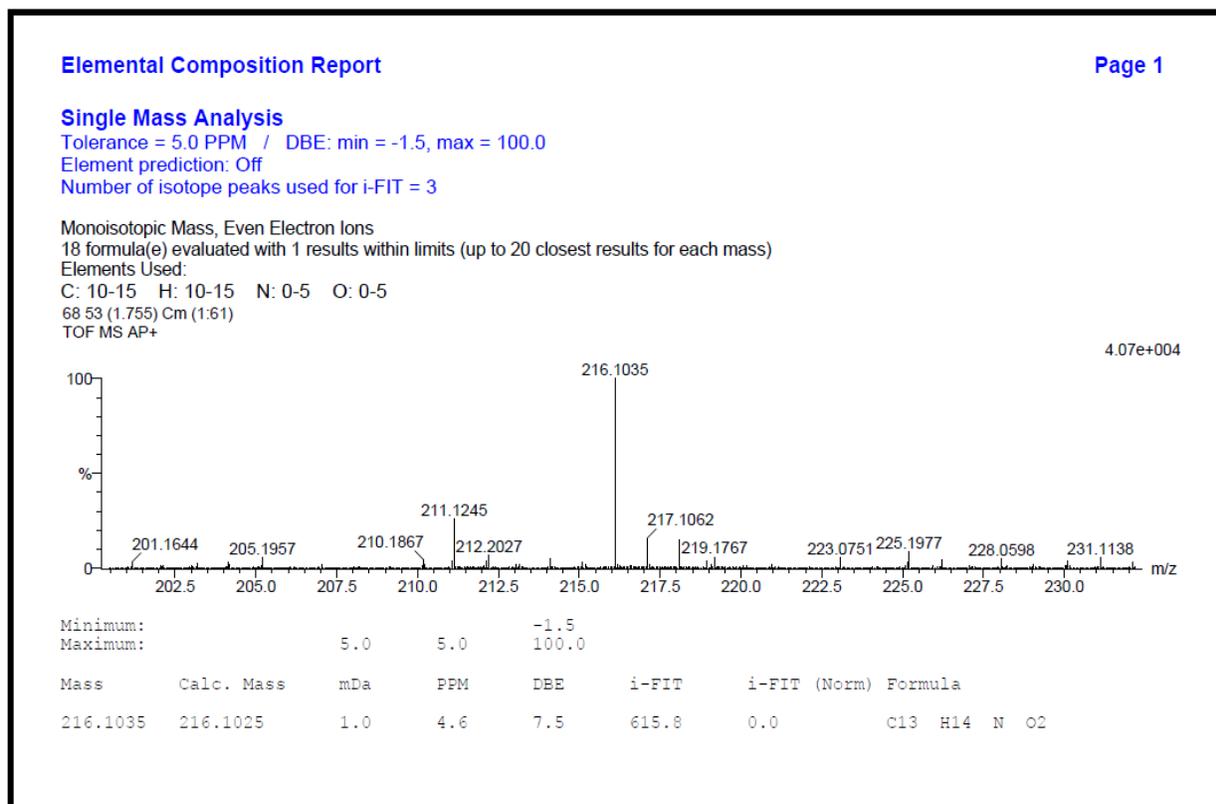
¹H NMR spectra of compound **4m**



¹³C NMR spectra of compound **4m**



FT-IR spectra of compound **4m**



HRMS spectra of compound **4m**

CHAPTER-3

Mn DOPED ZrO₂ AS A GREEN, EFFICIENT AND REUSABLE HETEROGENEOUS CATALYST FOR THE MULTICOMPONENT SYNTHESIS OF PYRANO[2,3-D]-PYRIMIDINE DERIVATIVES

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Cite this: *RSC Adv.*, 2015, 5, 37360

Received 9th April 2015
Accepted 17th April 2015
DOI: 10.1039/c5ra06373f
www.rsc.org/advances

Mn doped ZrO₂ as a green, efficient and reusable heterogeneous catalyst for the multicomponent synthesis of pyrano[2,3-d]-pyrimidine derivatives†

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This chapter is published in the journal of **RSC Advances** and has been structured according to the journal's format.

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Abstract

A simple and an efficient method has been developed for the one-pot multicomponent synthesis of pyrano[2,3-d]-pyrimidine derivatives. This was achieved through the condensation reaction between dimethylbarbituric acid, aromatic aldehyde and malononitrile in the presence of a Mn/ZrO₂ heterogeneous catalyst with ethanol/water mixture as solvent over only 1 hour. Further advantages to this synthesis methodology include excellent yields, mild reaction conditions, atom economy, environment friendly, reusable catalyst and no need for chromatographic separations.

Keywords: Green chemistry; Heterogeneous catalyst; pyranes; pyrimidines; Mn/ZrO₂; One-Pot synthesis.

3.1. Introduction

Multicomponent reactions (MCRs) have emerged as an exciting field of research where three or more reactants are all added together in a single-step to afford pure products in high yield. MCRs are mostly used in organic synthesis, biological discovery, combinatorial library and agrochemical synthesis.¹⁻⁴ The simple protocols, inexpensive reactants and green principles involved make MCRs an attractive field of study.⁴ Well planned MCRs afford higher chemical yields than multiple-step syntheses, resulting in conservation of energy and manpower and are often complete in relatively short reaction times⁵ making it an environmentally benign and elegant process.^{1,6,7}

The use of heterogeneous catalysts with recyclability and reusability potential add value to the one-pot reactions involving MCRs.⁸ The use of heterogeneous catalysts has gained prominence in the field of heterocyclic synthesis because of simple work-up, cost effectiveness, mild reaction conditions, atom economy, good activity, easy recyclability and scope to modify the surface properties.^{9,10} Heterogeneous materials are used as green reaction media due to their distinct chemical and physical properties such as non-volatility, thermal stability, non-inflammability, controlled miscibility¹⁰ and playing a vital role as catalysts in the MCRs. Metal oxides are good contenders in this regard as they have a proven track record as catalysts and supports. Thermal calcination of such materials at 773 K, lead to the formation of acidic/basic mixed metallic oxides with moderate surface-area and can act as catalysts for various condensation reactions.

Zirconia (ZrO_2) is an interesting support material where a particular zirconia phase (cubic, tetragonal etc.) can be stabilized down to room temperature by the amount of dopant added and this can promote the activity of the supported metal catalysts. ZrO_2 has good redox and chemical stability and is an acid-based bi-functional catalyst, which is stable in alkaline or acidic solutions.¹¹ ZrO_2 in combination with metals (cermets) have been used in organic synthesis¹² and manganese has previously been used as dopant in zirconia. The crystalline structure of ZrO_2 is one of the key factors affecting the structure-activity relationships of Mn-based catalysts.¹³ The Mn/ ZrO_2 solid material possesses both Bronsted and Lewis acids centers.

Pyranes and pyrimidine derivatives are an important class of heterocyclic compounds that feature in a number of pharmaceutical drugs and natural products of medicinal interest. This class of compounds exhibit a range of sought after features including antimicrobial,¹⁴

antioxidant,¹⁵ anti-tumor,¹⁶ antimalarial,¹⁷ antimetabolite,¹⁷ antileishmanial,¹⁸ antiviral,¹⁹ antihypertensive,²⁰ anti-convulsant,²¹ and anti-inflammatory activities.²² The computational chemistry of many of pyrimidine derivatives has also been documented.²³

Literature search shows several described methods for synthesis of various pyrano[2,3-*d*]pyrimidine derivatives. Such protocols employed [Ch-OSO₃H]₃W₁₂PO₄₀,²⁴ diammoniumhydrogenphosphate²⁵ microwave irradiation,^{26,27} DABCO,²⁸ electrolysis,^{29,30} γ -Fe₂O₃@HAp-Si(CH₂)₃SO₃H,³¹ L-proline,³² NaHCO₃³³ and urea³⁴ etc. as catalysts. In general terms, many of these approaches face few or more of the limitations such as using toxic reagents, strong acidic or basic conditions, costly reagents and catalysts, strict reaction conditions, tedious steps, and low product yields or long reaction times, which limit their use in practical applications. Thus, researchers are compelled to find new and improved approaches for environmental friendly synthesis of these heterocyclic molecules with impressive yields. The best of our knowledge there are no reports on the multicomponent facile one-pot synthesis of pyrano[2,3-*d*]pyrimidine derivatives and with EtOH/water mixture as solvent system. In this manuscript we report the synthesis of pyrano[2,3-*d*]pyrimidine derivatives by using Mn/ZrO₂ as a catalyst in the presence of equal ratio of EtOH:water for the first time. We report a novel protocol for the synthesis of those derivatives using an inexpensive and robust catalyst which accomplishes the reactions in short reaction times.

3.2. Results and discussions

Reactions were carried out during preliminary investigations to screen for various catalysts and under catalyst-free conditions and varying solvents. Reactions with 1,3-dimethylbarbituric acid (1 mmol), substituted aldehyde (1 mmol) and malononitrile (1.1 mmol) and water or ethanol as solvent and no catalyst showed no reaction at RT even after 12 h under reflux conditions, (Table 1, entries 1-4). To obtain the most efficient catalytic conditions, the title reaction was investigated in the presence of different catalyst materials such as alumina, silica, MnCl₂, and ZnCl₂ and in the presence of EtOH and water (50:50 v/v). The obtained results are summarized in (Table 1, entries 5-8) and indicate that the reaction did not occur in the presence of alumina or silica, and the yield obtained was very low with MnCl₂ or ZnCl₂. Further, we tested the scope of reaction in the presence of ionic liquids such as L-proline, (Bmim)BF₄ and (Bmim)OH, but yields were low (Table 1, entry 9-11).

The reactions were also investigated using 30 mg of CuO, MnO₂, ZrO₂, as catalysts under room temperature conditions in 1:1 ethanol/water mixture. The CuO, MnO₂ and ZrO₂ gave yields of 42%, 53% and 48%, respectively (Table 1 entry 12-14). The reaction was repeated under similar conditions using Mn/ZrO₂ which gave an excellent yield of 90% in 1 h once optimum dopant percentage had been established. The impact of Mn loading on zirconia in tuning its catalytic efficiency was further investigated. To find the ideal loading of Mn on ZrO₂ on catalyst activity, reactions with 1%, 2% and 5% Mn doped ZrO₂ were carried out under otherwise comparable conditions. The percentage of Mn loading was found to have an influence on the reaction yield as well as reaction time (Table 1, entries 15-17). Using 1% Mn/ZrO₂ catalyst yielded 76% product in 3 h under EtOH/water mixture solvent conditions (Table 1, entry 15). A 2.5% Mn loading was found optimal with 90 % yield in 1 h (Table 1, entry 16). A further increase of metal (5%) loading led to a slight decreased yield (88%) (Table 1, entry 17).

In an effort to find the optimal reaction conditions, the reaction was carried out using various amounts of catalyst at RT. It was found that 30 mg catalyst gave a maximum yield of 90% in 1 h. Using more than 30 mg of catalyst for the reaction had no significant improvement on the yield or the reaction time. However, the decrease in amount of the catalyst to 20 and 10 mg, decreased the product yield to 89%, 87%, 73% and 67%, respectively (Table 1, entries 18-21).

An interrogation of the experimental results and the effect of various polar and non-polar solvents on the three component reaction clearly indicate that the EtOH/water solvent system plays a vital role in facilitating the reaction (Table 1), comparatively less polar solvents like CH₃CN, DMF afforded poor yields (Table 1, entries 22,23). The protic polar (ethanol, water) solvents on their own failed to produce the anticipated high yield (Table 1, entry 24, 25) but interestingly, the miscible mixture of EtOH:H₂O (50:50 v/v) gave a high 90% yield. This effect can be explained by a simple acid-base bi-functional catalysis mechanism facilitated by the strong hydrogen bond interaction at the organic–aqueous ethanol interface which stabilizes the reaction intermediate. A highly-polar solvent which dissipates heat faster possibly provide optimum conditions for the formation of intermediates, and their conversion to final products on the catalyst surface.

Using the optimised reaction conditions, the applicability of the protocol was evaluated for the synthesis of other pyrano[2,3-d]pyrimidine derivatives with various aromatic aldehydes.

The Mn/ZrO₂ heterogeneous catalyst proved to be an ideal material to catalyse the facile one-pot synthesis of pyrano[2,3-*d*]-pyrimidine derivatives with good to excellent yields. All the reaction products with other details are depicted in Table 2. Interestingly, the substrates used and reaction yields obtained suggest that irrespective of electron-withdrawing and electron donating groups in ortho, meta and para positions of the aromatic ring, using Mn/ZrO₂ as catalyst, all the substrates gave good to excellent yields of desired pyrano[2,3-*d*]-pyrimidine derivatives (Table 2). The plausible reaction pathway is shown in Mechanism 1. All the resultant products were characterized and molecular structures were confirmed by FTIR, ¹H NMR, ¹³C NMR and ¹⁵N NMR (GHSQC) spectral analysis (Electronic Supplementary Information).

Table 1: Optimization condition for the synthesis of pyrano[2,3-*d*]-pyrimidines by Mn/ZrO₂ catalyst^a

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%) ^b
1	No catalyst	H ₂ O	R.T	24	--
2	No catalyst	EtOH	R.T	24	--
3	No catalyst	H ₂ O	Reflux	12	Trace
4	No catalyst	EtOH	Reflux	12	Trace
5	Al ₂ O ₃	EtOH:H ₂ O	R.T	10	--
6	SiO ₂	EtOH:H ₂ O	R.T	10	--
7	MnCl ₂	EtOH:H ₂ O	R.T	5	28
8	ZnCl ₂	EtOH:H ₂ O	R.T	8	18
9	L-proline	EtOH:H ₂ O	Reflux	3	48
10	(Bmim)BF ₄	EtOH:H ₂ O	Reflux	4	44
11	Bmim)OH	EtOH:H ₂ O	Reflux	3.5	51
12	CuO (30 mg)	EtOH:H ₂ O	R.T	6	42
13	MnO (30 mg)	EtOH:H ₂ O	R.T	3.5	53
14	ZrO ₂ (30 mg)	EtOH:H ₂ O	R.T	4	48
15	1% Mn/ZrO ₂ (30 mg)	EtOH:H ₂ O	R.T	3	76
16	2.5% Mn/ZrO ₂ (30 mg)	EtOH:H ₂ O	R.T	1	95
17	5% Mn/ZrO ₂ (30 mg)	EtOH:H ₂ O	R.T	1	93
18	Mn/ZrO ₂ (40 mg)	EtOH:H ₂ O	R.T	1	94
19	Mn/ZrO ₂ (50 mg)	EtOH:H ₂ O	R.T	1.5	92
20	Mn/ZrO ₂ (20 mg)	EtOH:H ₂ O	R.T	2	73
21	Mn/ZrO ₂ (10 mg)	EtOH:H ₂ O	R.T	2	67
22	Mn/ZrO ₂ (40 mg)	CH ₃ CN	R.T	3.5	46
23	Mn/ZrO ₂ (40 mg)	DMF	R.T	4	35
24	Mn/ZrO ₂ (30 mg)	EtOH	R.T	3	74
25	Mn/ZrO ₂ (30 mg)	H ₂ O	R.T	3.5	69

^aAll products were characterised by IR, ¹H NMR, ¹³C NMR and ¹⁵N NMR (GHSQC) spectral analysis.

^bIsolated yields; -- No reaction

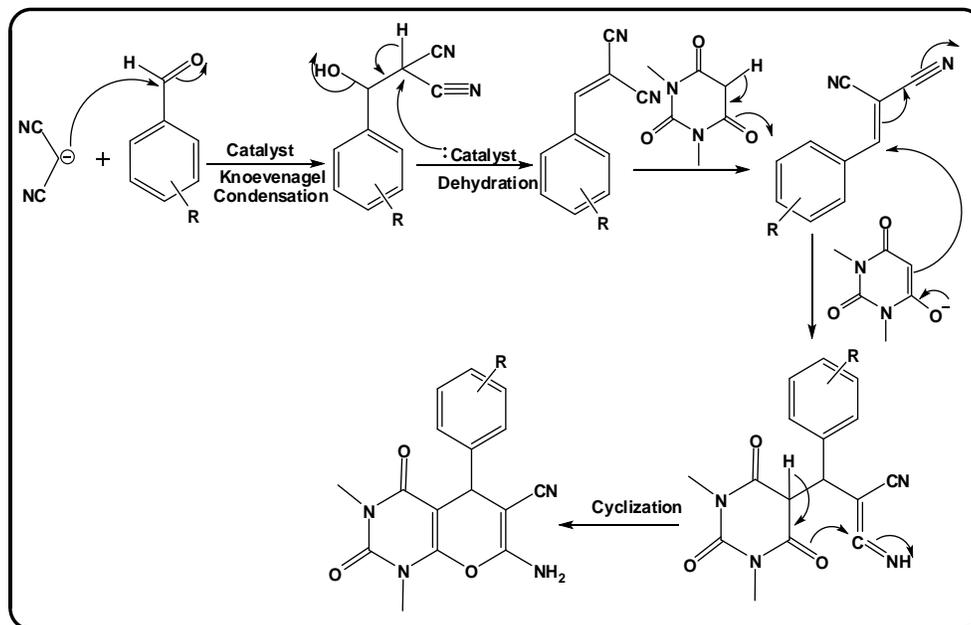
Table 2: Synthesis of pyrano[2,3-*d*]-pyrimidines derivatives catalyzed by Mn/ZrO₂ catalyst

Entry	R	Product	Yield (%)	Mp °C	Lit Mp °C
1	4-MeO-Ph	4a	91	225-226	225-227 [29]
2	2,3-(MeO) ₂ -Ph	4b	92	216-218	--
3	2,5-(MeO) ₂ -Ph	4c	90	231-233	--
4	2-Br-Ph	4d	92	202-203	--
5	4-Br-Ph	4e	90	210-211	--
6	2-Cl-Ph	4f	89	235-237	237-238 [29]
7	3-NO ₂ -Ph	4g	91	221-223	--
8	3-OH-Ph	4h	89	196-198	--
9	Ph	4i	90	219-220	219-222 [29]
10	2-F-Ph	4j	91	237-238	--
11	3-F-Ph	4k	89	214-215	--

^aReaction conditions: dimethylbarbituric acid (1.0 mmol), aromatic aldehyde (1.0 mmol) and malononitrile (1.0 mmol) and EtOH:water (1:1 v/v, 10 mL), RT.

^bAll synthesized compounds are identified and their structures were conformed with IR, ¹HNMR, ¹³C NMR spectral data and melting points as compared with literature values.

-- New compounds/no literature available.



Mechanism: Plausible reaction mechanism for the formation of pyrano[2,3-*d*]-pyrimidine derivatives

3.2.1. BET surface and ICP analysis

Figure 1 illustrates the N₂ adsorption–desorption isotherms and pore size distribution curves for the Mn doped ZrO₂. The catalyst displays the characteristic hysteresis loop of a Type IV isotherm (IUPAC) lying in the p/p₀ range of 0.6-0.95 typical for mesoporous materials. The pore size distribution and specific area was calculated from the Barrett-Joyner-Halenda (BJH adsorption) and Brunauer-Emmett-Teller methods respectively. The BET surface area of Mn/ZrO₂ was confirmed to be 188.47 m²/g with an average pore size and volume of 11.9 nm and 0.567 cm³/g respectively. The metal wt % obtained from ICP is in correlation with the nominal weight loading.

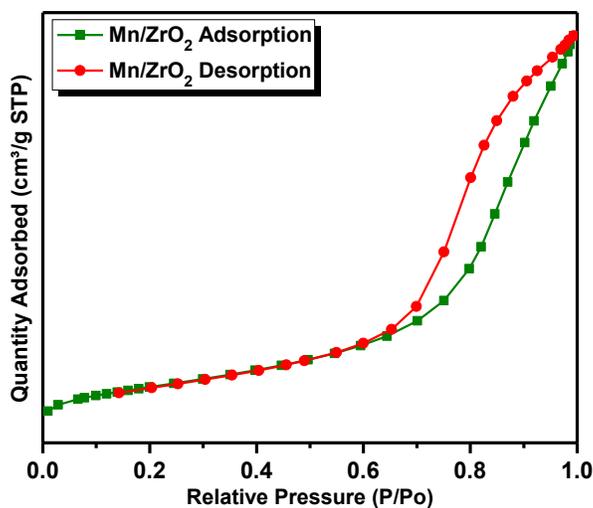


Figure 1: BET surface of Mn/ZrO₂ catalyst

3.2.2. Powder X-ray diffractogram (XRD) analysis

The XRD patterns of the calcined 2% Mn on ZrO₂ catalyst are demonstrated in Figure 2. The high intensity of the peaks suggested that all the prepared catalysts are polycrystalline in nature. The *d*-spacing's at 2 theta angles of 25.3, 34.9, 38.9, and 55.3 for Mn₂O₃ respectively. This is in good agreement with the ICDD PDF No. 65-7467. From the XRD diffractograms it is evidenced that Mn₂O₃ is the major phase in all the catalysts. There is a formation of additional phase i.e Mn₃O₄ is observed. The *d*-spacing's at a 2 theta angles of 32.5, 54.6 and 63.1 for Mn₃O₄ which is correspond to the ICDD PDF No. 39-1218 for Mn₃O₄ phase. The ZrO₂ showed the sharp peaks corresponding to tetragonal ZrO₂ (ICDD PDF No. 88-1007, 2θ = 25.7, 38.2, 49.8, and 55.7).

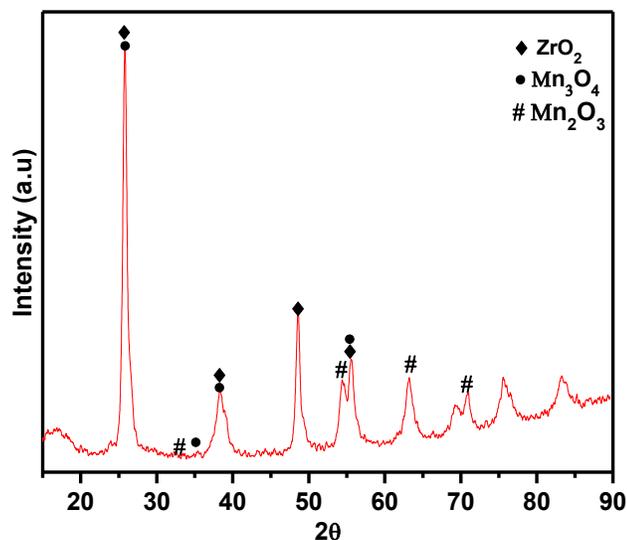


Figure. 2. Powder X-ray diffractogram spectra of Mn/ZrO₂ catalyst

3.2.3. Infrared-spectra (FT-IR) Figure 3 displays FT-IR spectra of mesoporous Mn on ZrO₂ catalyst exhibited characteristic absorption band at 3368.6 cm⁻¹, 1655.4 cm⁻¹ and 1368.3 cm⁻¹ corresponding to the vibration of hydroxyl group, which involve the O-H vibrating mode of traces of adsorbed water. Absorption band at 749.8 cm⁻¹ and 492.3 cm⁻¹ was due to stretching peaks of Mn-O-Mn and Mn-O vibrations, respectively in accord with literature values.³⁵ A strong absorption band was observed at 1136.3 cm⁻¹ for the asymmetric stretching of Zr-O group, supporting the formation of ZrO₂ groups on their surfaces. No organic groups were found to be surface adsorbed based on IR results.

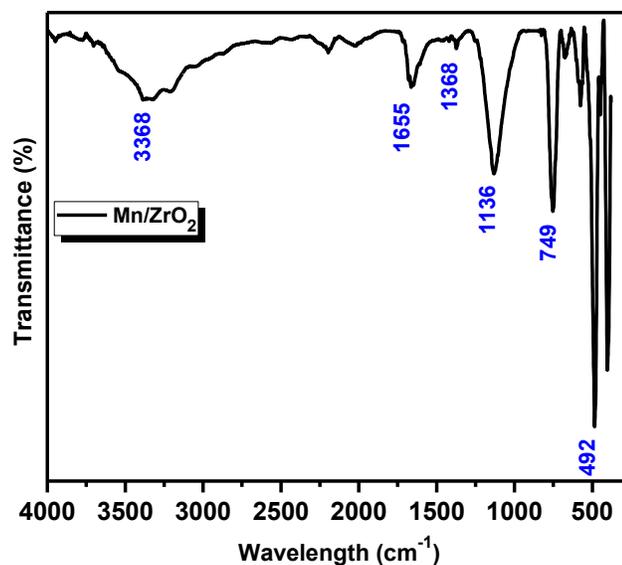


Figure 3. FT-IR image of Mn/ZrO₂ catalyst

3.2.4. SEM & TEM analysis

The SEM image of the prepared catalyst is shown in Figure 4. The catalyst was crystalline in nature but with a coarse surface morphology. The manganese oxide particles were observed as hexagonal-shaped particles which were dispersed on the surface of the zirconia. The manganese oxide particles are shown in a red colour circles in Figure 4. These observations are also in agreement with literature.³⁶ The TEM images showed that the zirconia particles are irregular and oval-shaped. The red circles in Figure 5 shows the manganese oxide particles which might be agglomerated on the surface of zirconia.

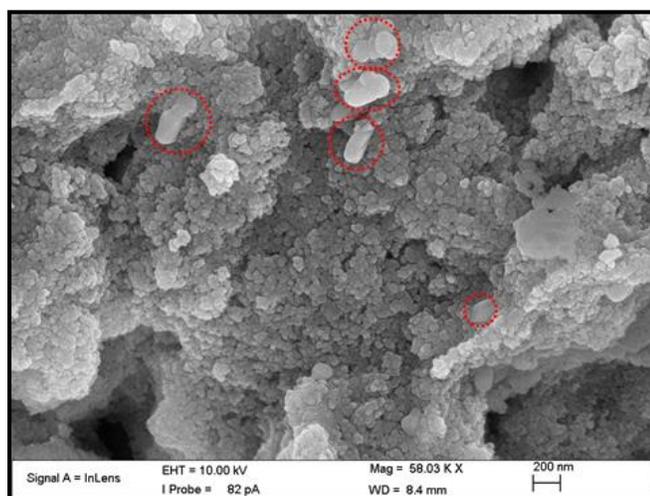


Figure 4. SEM image of Mn/ZrO₂ catalyst

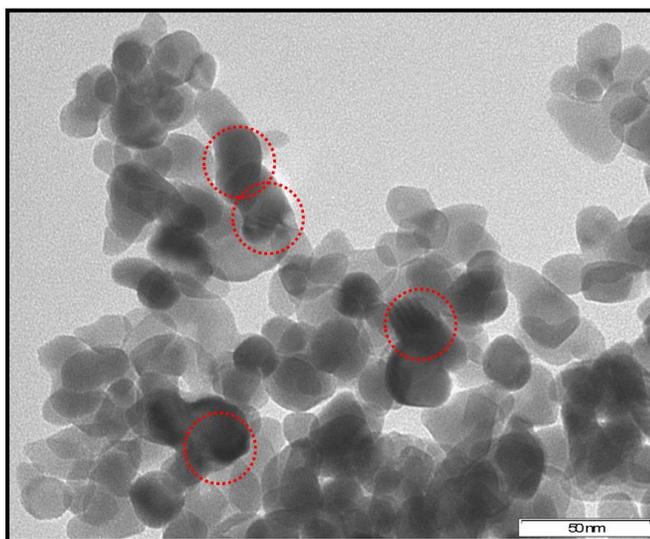


Figure 5. TEM image of Mn/ZrO₂ catalyst

3.2.5. Reusability of Mn/ZrO₂

To test reusability, a recycling experiment was employed using a model reaction. Thus, after completion of reaction, the catalyst was recovered by filtration, washed with ethanol and dried under vacuum. The recovered catalyst was re-used for six times with a slight loss in catalytic activity (Figure 6). The minor loss perceived in the catalytic activity after 6th run could be due to poisoning by organic impurities.

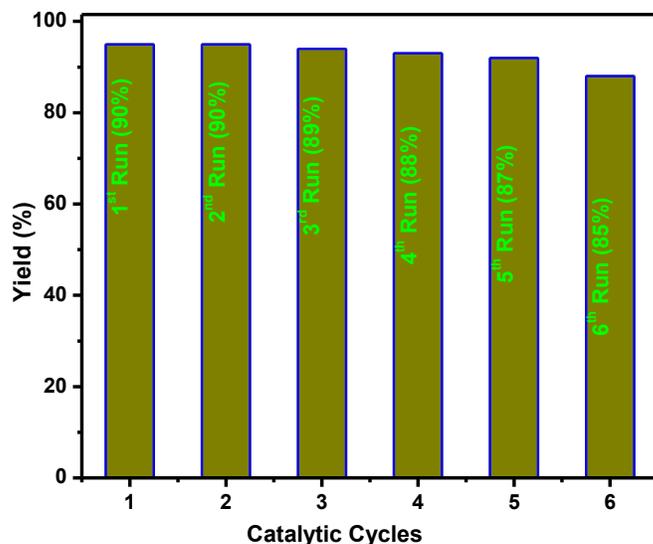


Figure 6. Recyclability of Mn/ZrO₂ catalyst

3.3. Experimental section

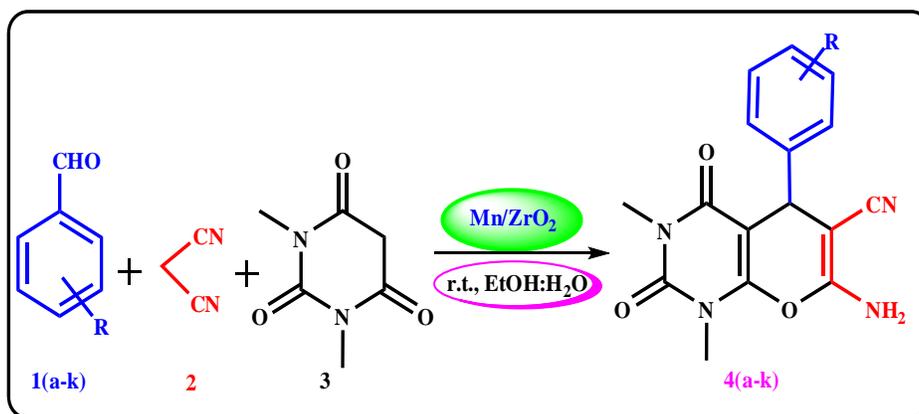
3.3.1. Catalyst preparation

Mn doped ZrO₂ of various wt.% was prepared by a wet impregnation technique as described in our earlier reports.^{37,38} 5.0 g of zirconium oxide powder (Alfa Aesar Chemical) was suspended in 250 mL of double distilled water and mixed with the desired masses of MnCl₂ (Manganese (II) chloride tetrahydrate, Aldrich) based on the weight percentages of interest. The mixture was stirred for 4 h using a magnetic stirrer at room temperature (RT) and then heated to 90 °C for 4 h. The precipitate was dried in an air oven at 110-120 °C for 12 h, followed by calcination at 450 °C for 5 h to afford the 1%, 2.5% & 5% w/w of the Mn/ZrO₂ catalysts.

3.3.2. General procedure for the synthesis of pyrano[2,3-d]-pyrimidines

A solution containing dimethylbarbituric acid (1 mmol), substituted aldehyde (1 mmol), malononitrile (1.1 mmol) and Mn/ZrO₂ (30 mg) in mixture of EtOH:H₂O (1:1 v/v, 10 mL) was continuously stirred for 1.0 h at RT using a magnetic stirrer (Scheme 1). The progress and

completion of the reaction was monitored by TLC. The reaction mixture was then filtered, and the filtrate was subsequently evaporated under reduced pressure to obtain the crude product which was recrystallized with ethanol to afford pure product (4a-k). The recovered catalyst was subjected to washing with ethanol, dried and re-used for up to six cycles.



Scheme 1: Synthesis of pyrano[2,3-d]-pyrimidine derivatives

7-Amino-5-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4a): ^1H NMR (400 MHz, DMSO- d_6) δ = 3.07 (s, 3H, NCH $_3$), 3.36 (s, 3H, NCH $_3$), 3.72 (s, 3H, OCH $_3$), 4.31 (s, 1H, CH), 6.83 (d, J = 8.2 Hz, 2H, ArH), 7.14 (d, J = 8.04 Hz, 2H, ArH), 7.29 (s, 2H, NH $_2$); ^{13}C NMR (100 MHz, DMSO- d_6): δ 27.64, 29.74, 35.81, 55.02, 58.55, 89.09, 113.64, 119.17, 128.18, 136.81, 149.95, 150.87, 157.88, 158.38, 160.45; ^{15}N NMR (40.55 MHz, DMSO- d_6) δ 7.29 (s, 2H, NH $_2$); IR (KBr, cm^{-1}): 3368, 3307, 3181, 2965, 2188, 1682, 1680, 1605, 1508; HRMS of [$\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_4 - \text{H}$] (m/z): 339.2011; Calcd.: 339.2021.

7-Amino-5-(2,3-dimethoxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4b): ^1H NMR (400 MHz, DMSO- d_6) δ = 3.06 (s, 3H, NCH $_3$), 3.36 (s, 3H, NCH $_3$), 3.75 (s, 3H, OCH $_3$), 3.78 (s, 3H, OCH $_3$), 4.61 (s, 1H, CH), 6.71 (d, J = 7.04 Hz, 1H, ArH), 6.87 (d, J = 8.00, 1H, ArH), 6.94 (t, J = 7.96, 1H, ArH), 7.22 (s, 2H, NH $_2$); ^{13}C NMR (100 MHz, DMSO- d_6): δ 27.59, 29.07, 31.06, 55.49, 58.15, 59.90, 83.77, 111.29, 119.07, 120.70, 123.60, 136.99, 146.32, 149.94, 151.28, 152.24, 157.85, 160.37; ^{15}N NMR (40.55 MHz, DMSO- d_6) δ 7.22 (s, 2H, NH $_2$); IR (KBr, cm^{-1}): 3317, 2937, 2188, 1681, 1645, 1474; HRMS of [$\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_5 + \text{Na}$] (m/z): 393.1166; Calcd.: 393.1175..

7-Amino-5-(2,5-dimethoxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4c): ^1H NMR (400 MHz, DMSO- d_6) δ = 3.07 (s, 3H,

NCH₃), 3.38 (s, 3H, NCH₃), 3.65 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃), 4.58 (s, 1H, CH), 6.64 (d, *J* = 3.02 Hz, 1H, ArH), 6.74 (dd, *J* = 8.9, 3 Hz, 1H, ArH), 6.89 (d, *J* = 8.9 Hz, 1H, ArH), 7.15 (s, 2H, NH₂); ¹³C NMR (100 MHz, DMSO-d₆): δ 27.59, 29.00, 31.32, 55.22, 56.34, 57.63, 88.05, 111.51, 112.76, 115.37, 119.02, 130.99, 150.00, 150.23, 151.52, 153.15, 158.15, 160.34; ¹⁵N NMR (40.55 MHz, DMSO-d₆) δ 7.15 (s, 2H, NH₂); IR (KBr, cm⁻¹): 3302, 3175, 2934, 2194, 1715, 1683, 1634, 1599, 1487; HRMS of [C₁₈H₁₈N₄O₅ - H] (m/z): 369.0389; Calcd.: 371.0395.

7-Amino-5-(2-bromophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4d): ¹H NMR (400 MHz, DMSO-d₆) δ = 3.05 (s, 3H, NCH₃), 3.36 (s, 3H, NCH₃), 4.86 (s, 1H, CH), 7.11-7.15 (m, 1H, ArH), 7.28 (d, *J* = 4.2 Hz, 2H, ArH), 7.33 (s, 2H, NH₂), 7.53 (d, *J* = 8.00 Hz, 1H, ArH); ¹³C NMR (100 MHz, DMSO-d₆): δ 27.58, 29.12, 35.80, 57.36, 88.23, 118.42, 122.77, 128.07, 128.64, 130.25, 132.45, 149.97, 151.47, 157.64, 160.28; ¹⁵N NMR (40.55 MHz, DMSO-d₆) δ 7.33 (s, 2H, NH₂); IR (KBr, cm⁻¹): 3310, 2930, 2913, 1684, 1637, 1470; HRMS of [C₁₆H₁₃BrN₄O₃ - H] (m/z): 387.0103; Calcd.: 387.0093..

7-Amino-5-(4-bromophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4e): ¹H NMR (400 MHz, DMSO-d₆) δ = 3.07 (s, 3H, NCH₃), 3.34 (s, 3H, NCH₃), 4.32 (s, 1H, CH), 7.21 (d, *J* = 8.00 Hz, 2H, ArH), 7.35 (s, 2H, NH₂), 7.47 (d, *J* = 8.00 Hz, 2H, ArH); ¹³C NMR (100 MHz, DMSO-d₆): δ 27.62, 29.09, 36.04, 58.03, 88.22, 118.85, 119.80, 129.67, 131.07, 143.54, 149.95, 151.15, 157.57, 160.43; ¹⁵N NMR (40.55 MHz, DMSO-d₆) δ 7.35 (s, 2H, NH₂); IR (KBr, cm⁻¹): 3426, 3299, 2930, 2189, 1683, 1633, 1487.

7-Amino-5-(2-chlorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4f): ¹H NMR (400 MHz, DMSO-d₆) δ = 3.06 (s, 3H, NCH₃), 3.36 (s, 3H, NCH₃), 4.86 (s, 1H, CH), 7.23-7.36 (m, 6H, ArH, NH₂); ¹³C NMR (100 MHz, DMSO-d₆): δ 27.59, 29.11, 33.52, 57.18, 87.97, 118.52, 127.46, 128.37, 129.24, 132.17, 141.08, 149.97, 151.50, 157.76, 160.28; ¹⁵N NMR (40.55 MHz, DMSO-d₆) δ 7.30 (s, 2H, NH₂); IR (KBr, cm⁻¹): 3382, 3310, 3193, 2959, 2193, 1703, 1684, 1638, 1474; HRMS of [C₁₆H₁₃ClN₄O₃ - H] (m/z): 343.0992; Calcd.: 343.1008.

7-Amino-5-(3-nitrophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4g): ¹H NMR (400 MHz, DMSO-d₆) δ = 3.01 (s, 3H, NCH₃), 3.34 (s, 3H, NCH₃), 5.12 (s, 1H, CH), 7.43 (d, *J* = 8.00 Hz, 1H, ArH), 7.48 (s, 2H, NH₂), 7.51 (s, 1H, ArH), 7.64 (t, *J* = 8.00, 1H, ArH), 7.83 (d, *J* = 8.00 Hz, 1H, ArH); ¹³C NMR (100 MHz, DMSO-d₆): δ 27.57, 29.11, 30.77, 56.62, 88.33, 118.40, 123.63, 128.02, 130.73, 133.42, 138.38, 149.05,

149.87, 151.82, 158.31, 160.50; ^{15}N NMR (40.55 MHz, DMSO- d_6) δ 7.48 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3373, 3306, 3184, 2957, 2196, 1706, 1683, 1632, 1522, 1490; HRMS of $[\text{C}_{16}\text{H}_{13}\text{N}_5\text{O}_5 - \text{H}]$ (m/z): 354.0844; Calcd.: 354.0838.

7-Amino-5-(3-hydroxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4h): ^1H NMR (400 MHz, DMSO- d_6) δ = 3.09 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 4.21 (s, 1H, CH), 6.58-6.66 (m, 3H, ArH), 7.06 (t, J = 8.00 Hz, 1H, ArH), 7.29 (s, 2H, NH_2), 8.42 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO- d_6): δ 27.65, 29.05, 36.35, 58.62, 88.98, 113.76, 114.15, 117.92, 119.05, 129.19, 145.48, 149.94, 150.96, 157.22, 160.43, 165.86; ^{15}N NMR (40.55 MHz, DMSO- d_6) δ 7.29 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3370, 3303, 3199, 2965, 2197, 1783, 1636, 1598, 1484; HRMS of $[\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_4 - \text{H}]$ (m/z): 325.0894; Calcd.: 325.0900.

7-Amino-1,3-dimethyl-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4i): ^1H NMR (400 MHz, DMSO- d_6) δ = 3.07 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 4.31 (s, 1H, CH), 7.18-7.28 (m, 5H, ArH), 7.30 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO- d_6): δ 27.63, 29.07, 36.47, 58.63, 88.78, 119.01, 126.73, 127.28, 129.49, 130.44, 144.08, 149.97, 151.09, 157.63, 160.45; ^{15}N NMR (40.55 MHz, DMSO- d_6) δ 7.30 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3380, 3307, 3193, 2866, 2196, 1703, 1682, 1639, 1607, 1493; HRMS of $[\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_3 - \text{H}]$ (m/z): 309.0984; Calcd.: 309.0988.

7-Amino-5-(2-fluorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4j): ^1H NMR (400 MHz, DMSO- d_6) δ = 3.06 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 4.61 (s, 1H, CH), 7.11 (t, J = 7.68 Hz, 2H, ArH), 7.24-7.27 (m, 2H, ArH), 7.35 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO- d_6): δ 27.60, 29.07, 30.42, 57.16, 87.59, 115.36, 118.74, 124.43, 128.70, 128.78, 129.69, 149.95, 151.43, 157.93, 158.78, 160.75; ^{15}N NMR (40.55 MHz, DMSO- d_6) δ 7.35 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3384, 3311, 3194, 2962, 2195, 1683, 1637, 1509, 1488; HRMS of $[\text{C}_{16}\text{H}_{13}\text{FN}_4\text{O}_3 - \text{H}]$ (m/z): 327.0889; Calcd.: 327.0893.

7-Amino-5-(3-fluorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4k): ^1H NMR (400 MHz, DMSO- d_6) δ = 3.07 (s, 3H, NCH_3), 3.34 (s, 3H, NCH_3), 4.36 (s, 1H, CH), 7.02-7.10 (m, 3H, ArH), 7.32-7.34 (m, 3H, ArH, NH_2); ^{13}C NMR (100 MHz, DMSO- d_6): δ 27.62, 29.08, 36.20, 58.10, 88.11, 113.89, 114.50, 118.85, 123.45, 130.05, 147.01, 147.07, 149.99, 151.29, 157.62, 160.51; ^{15}N NMR (40.55 MHz, DMSO- d_6) δ 7.32 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3382, 3305, 3192, 2194, 1711, 1683, 1635, 1613, 1490.

3.4. Conclusions

In conclusion, we report an environmentally benign and an efficient one-pot multicomponent green synthesis of pyrano-[2,3-d]-pyrimidine derivatives using Mn/ZrO₂ as catalyst in green solvent media and with good atom efficiency. This simple and recyclable heterogeneous catalyst, Mn/ZrO₂ shows high catalytic activity for multicomponent reactions. The current method deals several advantages such as short reaction time, cost-effectiveness, purity of products, excellent yields, use of small amount of inexpensive catalyst and environmentally benign green solvent.

3.5. Acknowledgements

Authors are grateful to the National Research Foundation of South Africa for financial support and University of KwaZulu-Natal for the research facilities.

3.6. References

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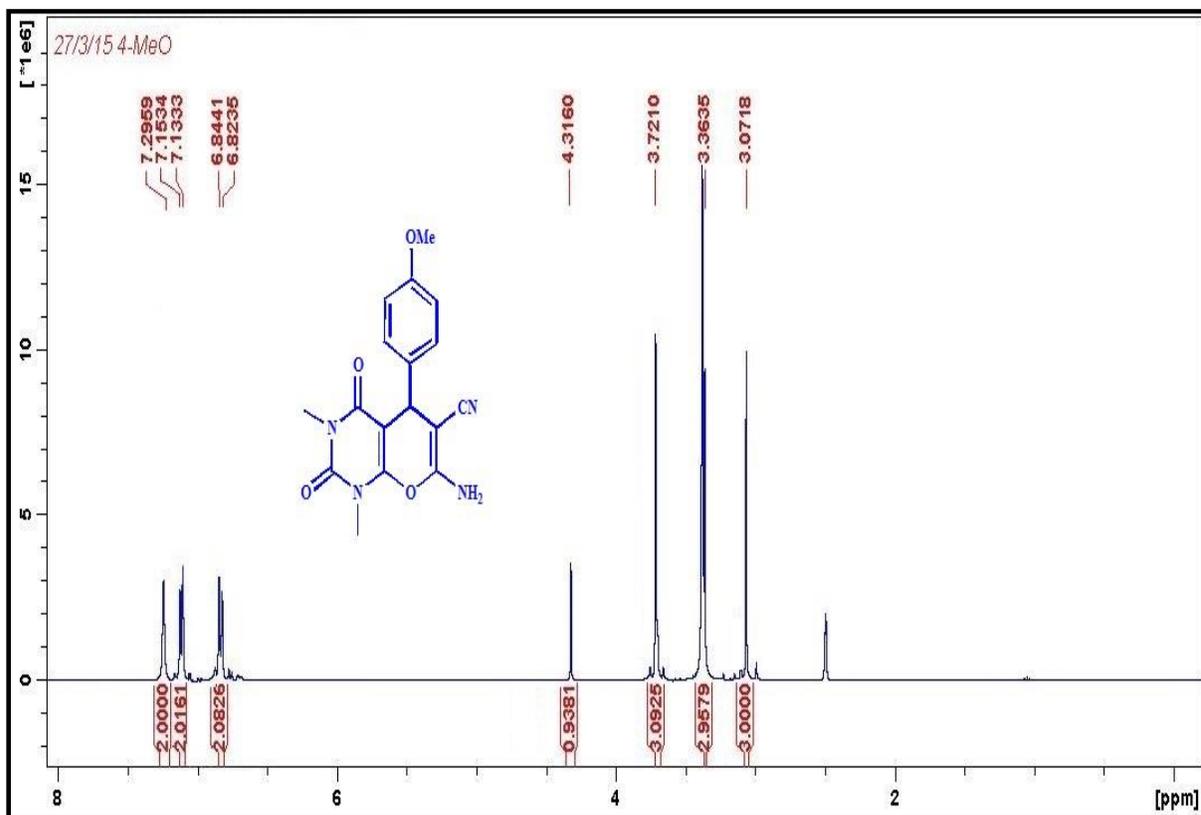
3.7. Supplementary materials data

3.7.1. Materials, methods and instruments

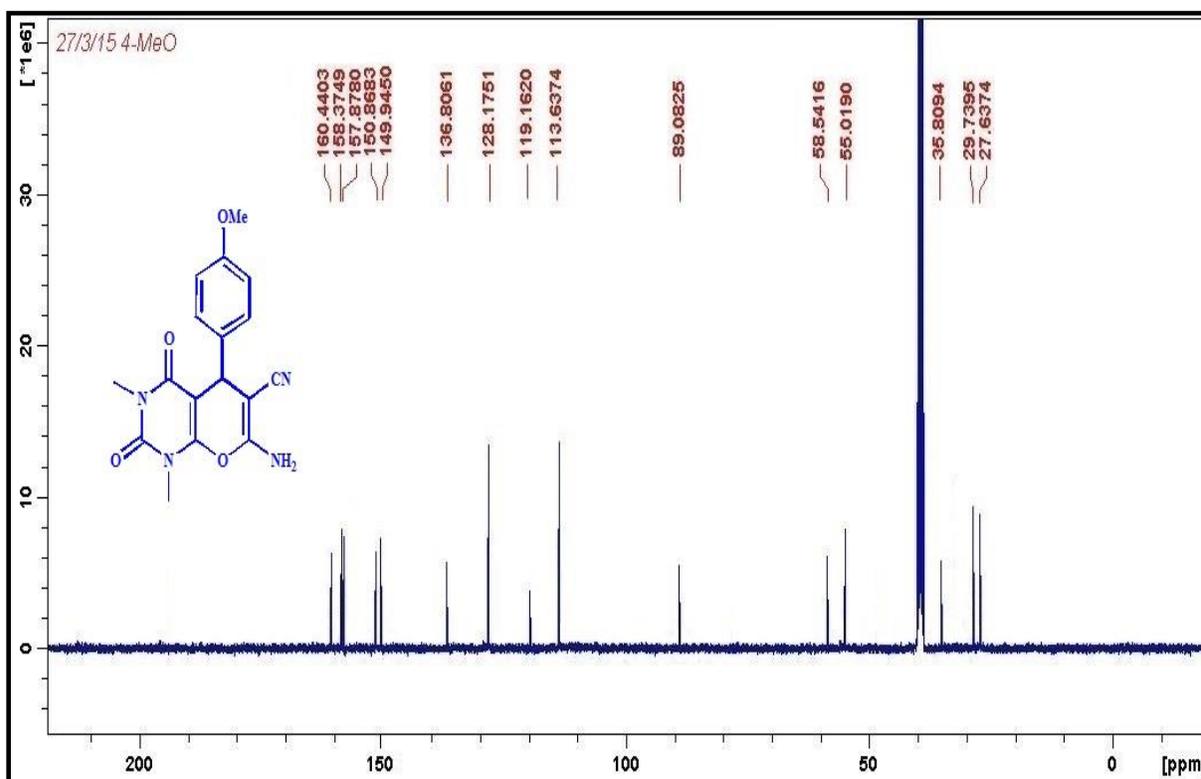
All chemicals and reagents required for the reaction were of analytical grade and were used without any further purification. Bruker AMX NMR spectrometer was used to record the ^1H NMR, ^{13}C NMR and ^{15}N NMR spectral values. The DMSO-d_6 solution was utilized for this while TMS served as the internal standard. TMS was further used as an internal standard for reporting the all chemical shifts in δ (ppm). The FT-IR spectrum for the samples was established using a Perkin Elmer Precisely 100 FT-IR spectrometer at the $400\text{-}4000\text{ cm}^{-1}$ area. Purity of all the reaction products was confirmed by TLC using aluminum plates coated with silica gel (Merck Kieselgel 60 F254).

3.7.2. Characterization of catalysts

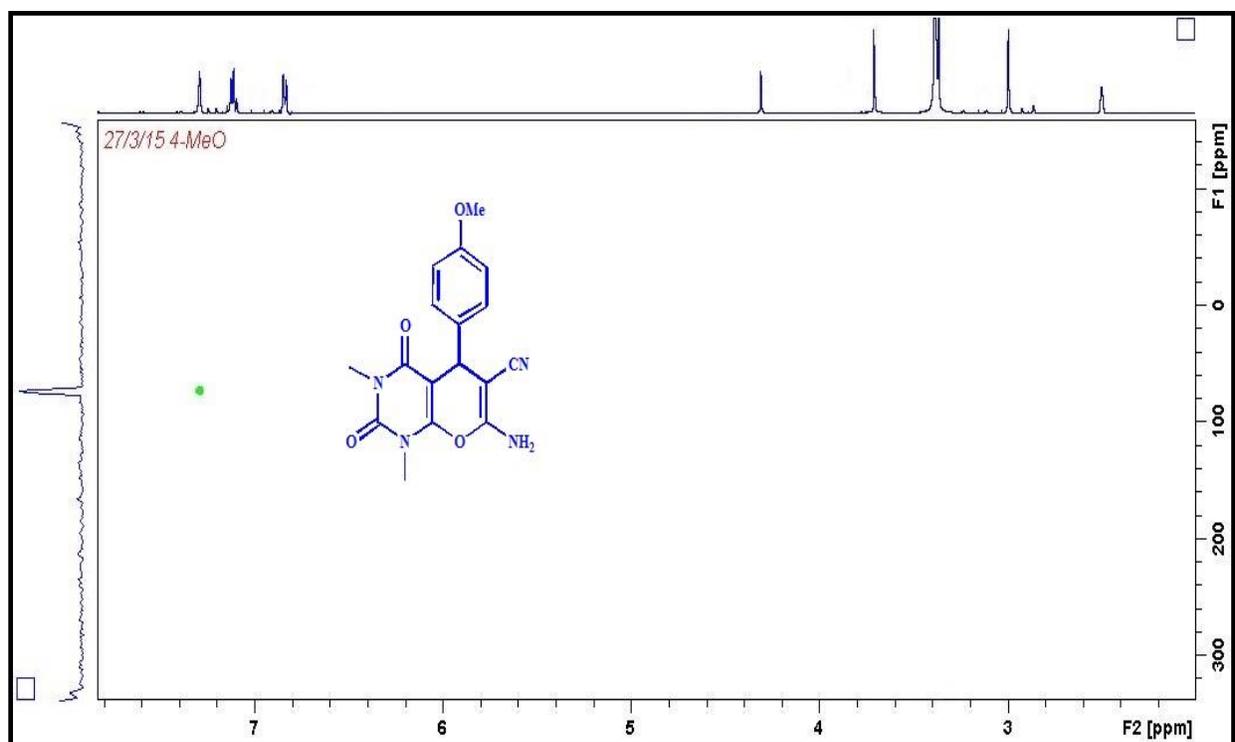
Micromeritics Tristar-II porosity and surface area analyzer was used estimation of pore size, pore volume and surface area of the catalysts. BJH adsorption-desorption curves were obtained at $-196\text{ }^\circ\text{C}$, to assess the particulate properties of the catalyst. All the catalyst materials were degassed by passing nitrogen overnight at $200\text{ }^\circ\text{C}$. Bruker D8 advance instrument with a Cu K radiation source by $\lambda = 1.5406$ was used for the X-ray diffraction data for the catalyst. Jeol JEM-1010 electron microscope and JEOL JSM-6100 microscope were used for TEM and SEM analysis respectively. In TEM analysis for particles distribution, size of 40-60 particles were averaged and with standard deviation. An emission current ($100\text{ }\mu\text{A}$) by a Tungsten (W) filament with 12 kV accelerator voltage was employed for EDX-analysis of the SEM images. Elemental composition of the catalyst materials was established by using Inductively Coupled Plasma Optical Emission Spectrometer (Optima 5300 DV).



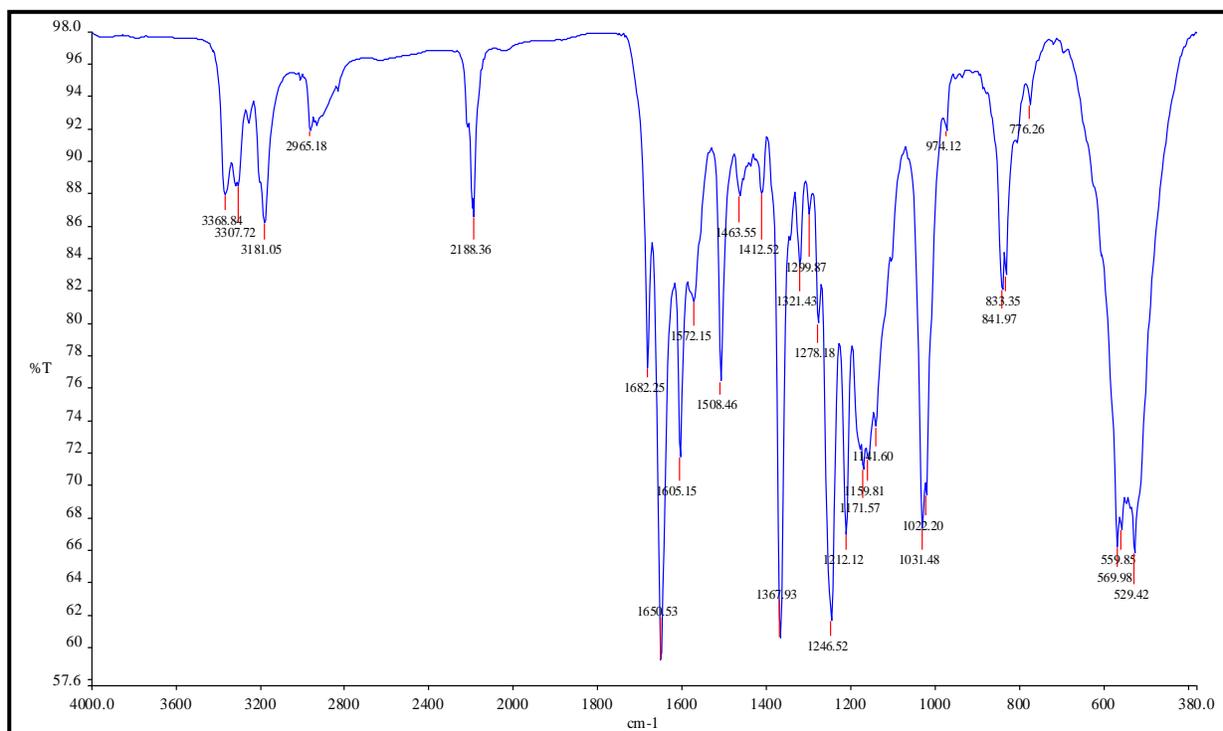
¹H NMR spectra of compound 4a



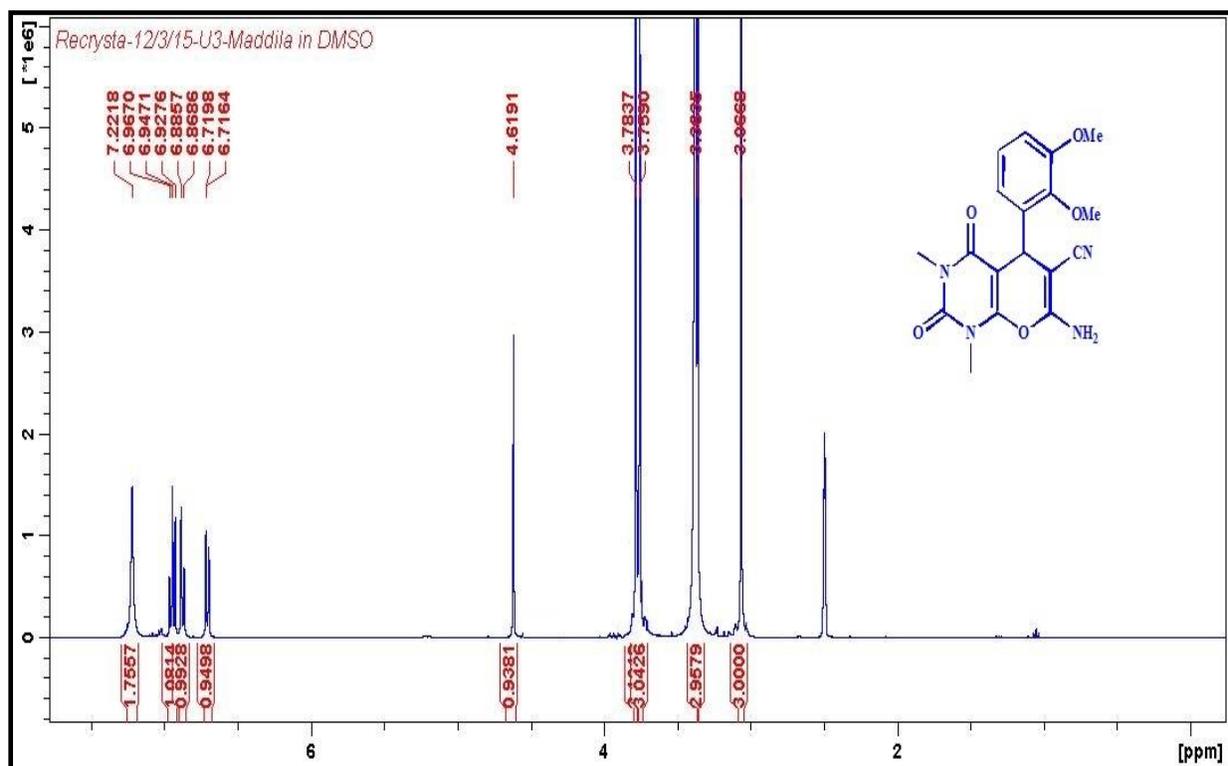
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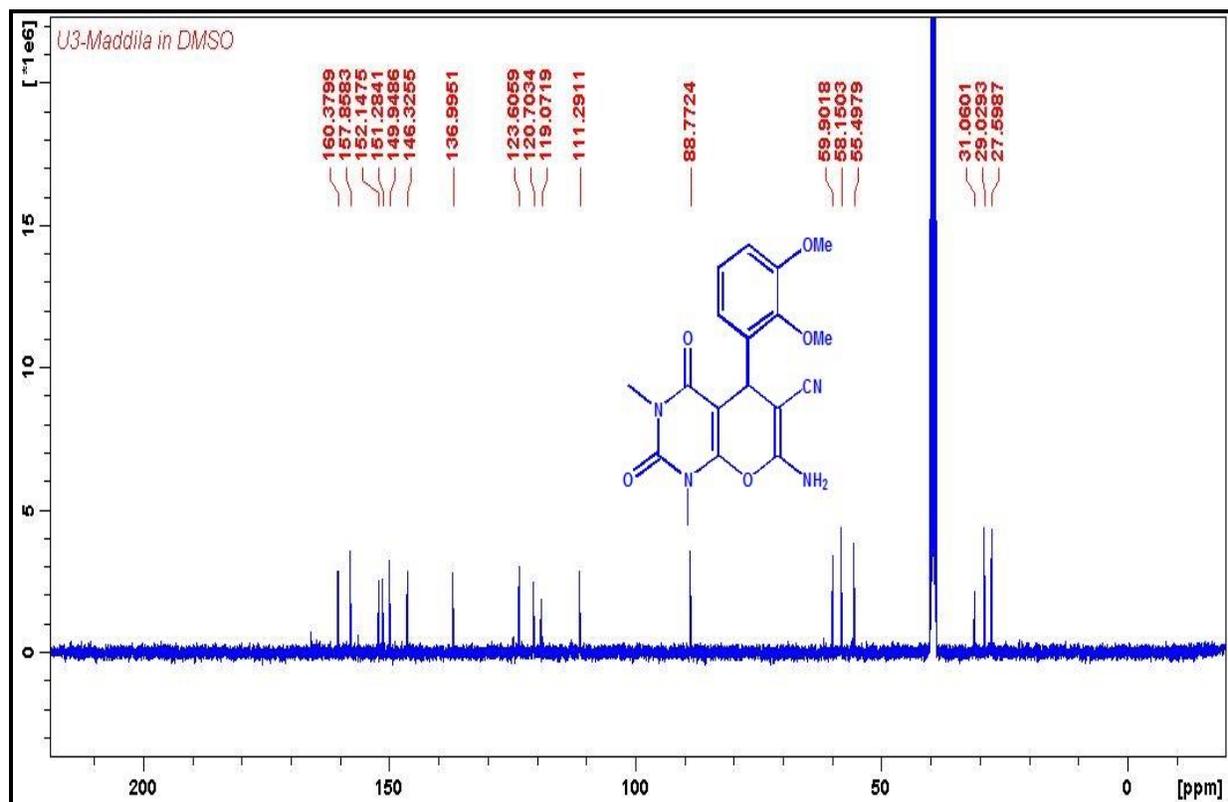
¹⁵N NMR (GHSQC) spectra of compound 4a



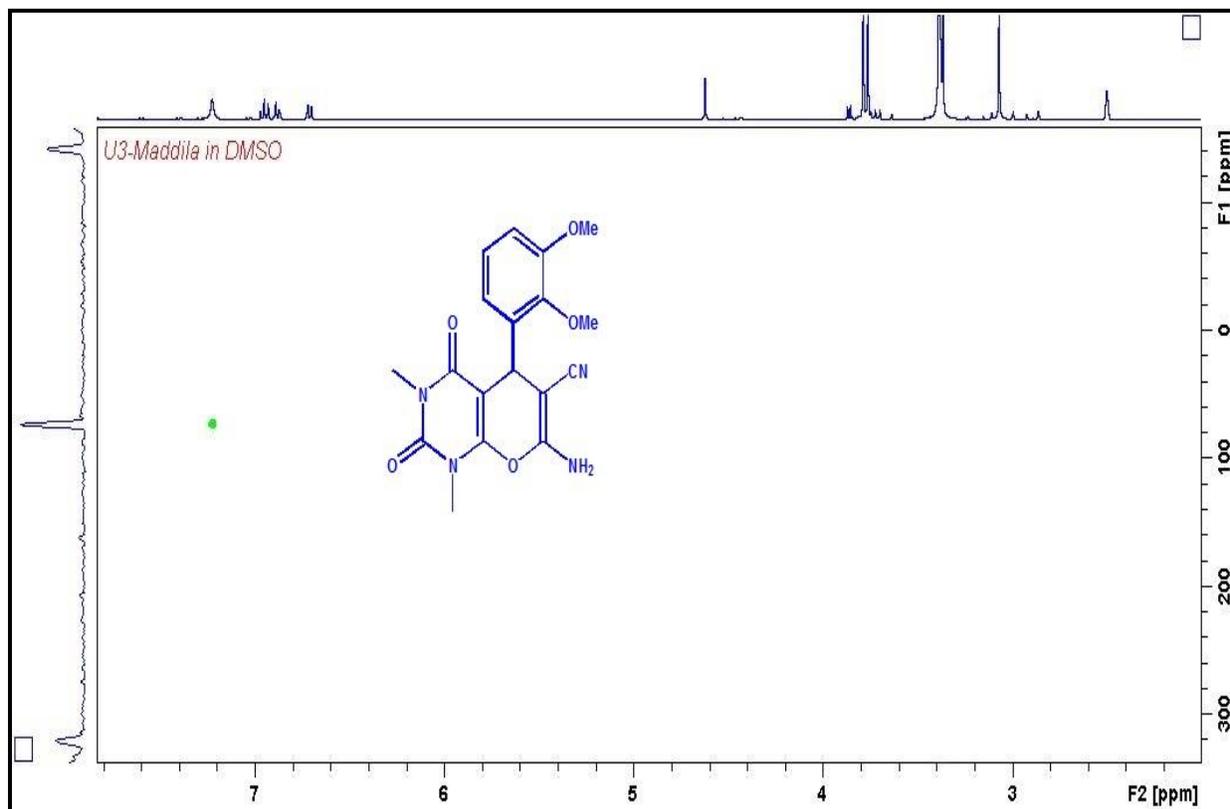
FT-IR spectra of compound 4a



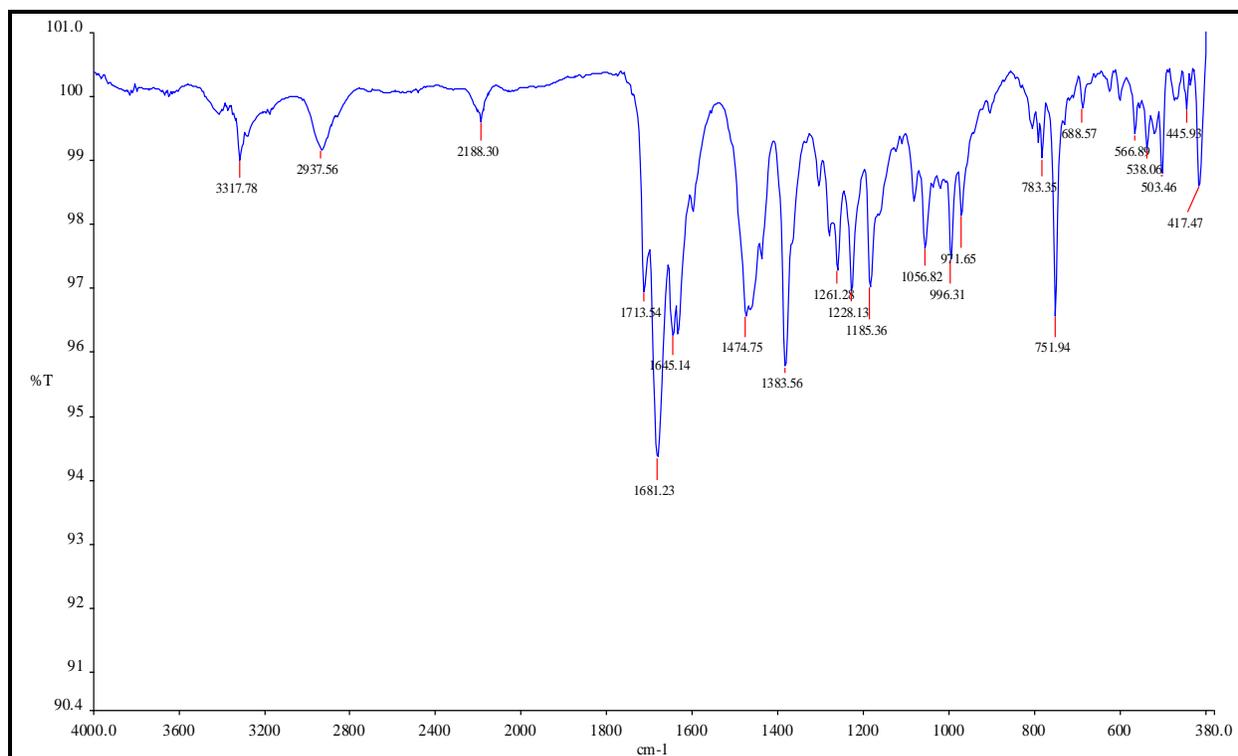
¹H NMR spectra of compound 4b



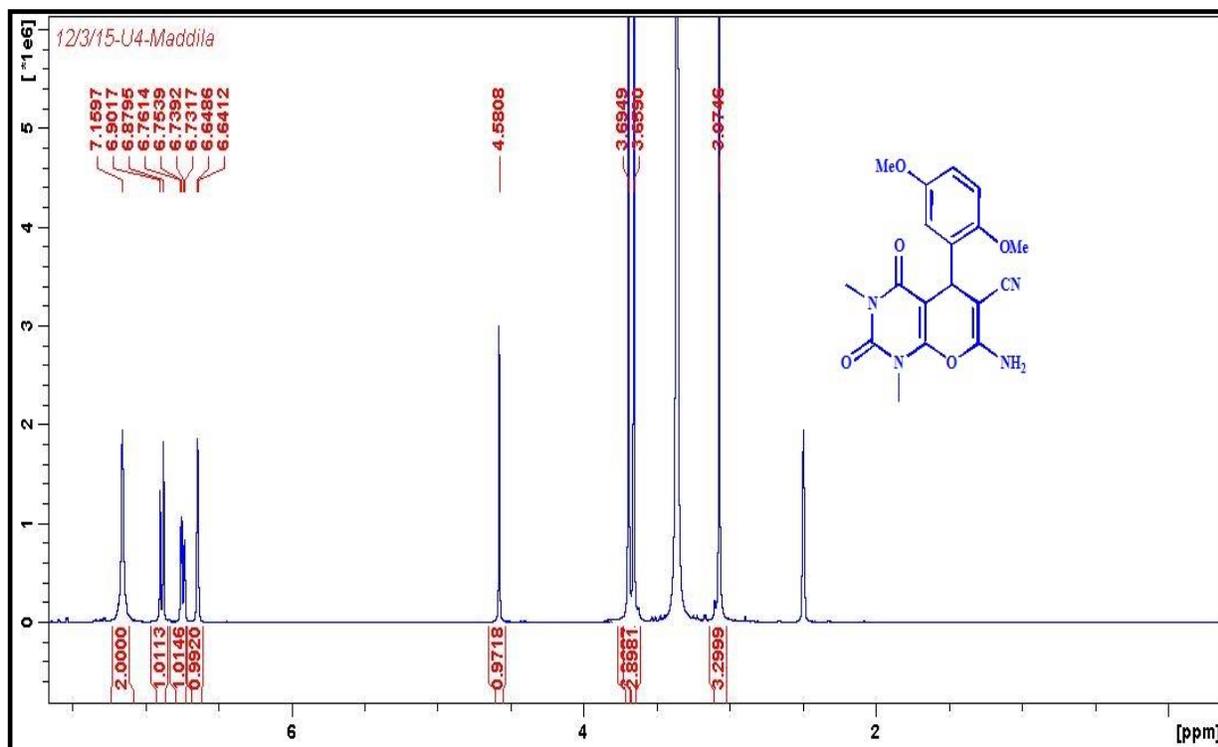
¹³C NMR spectra of compound 4b



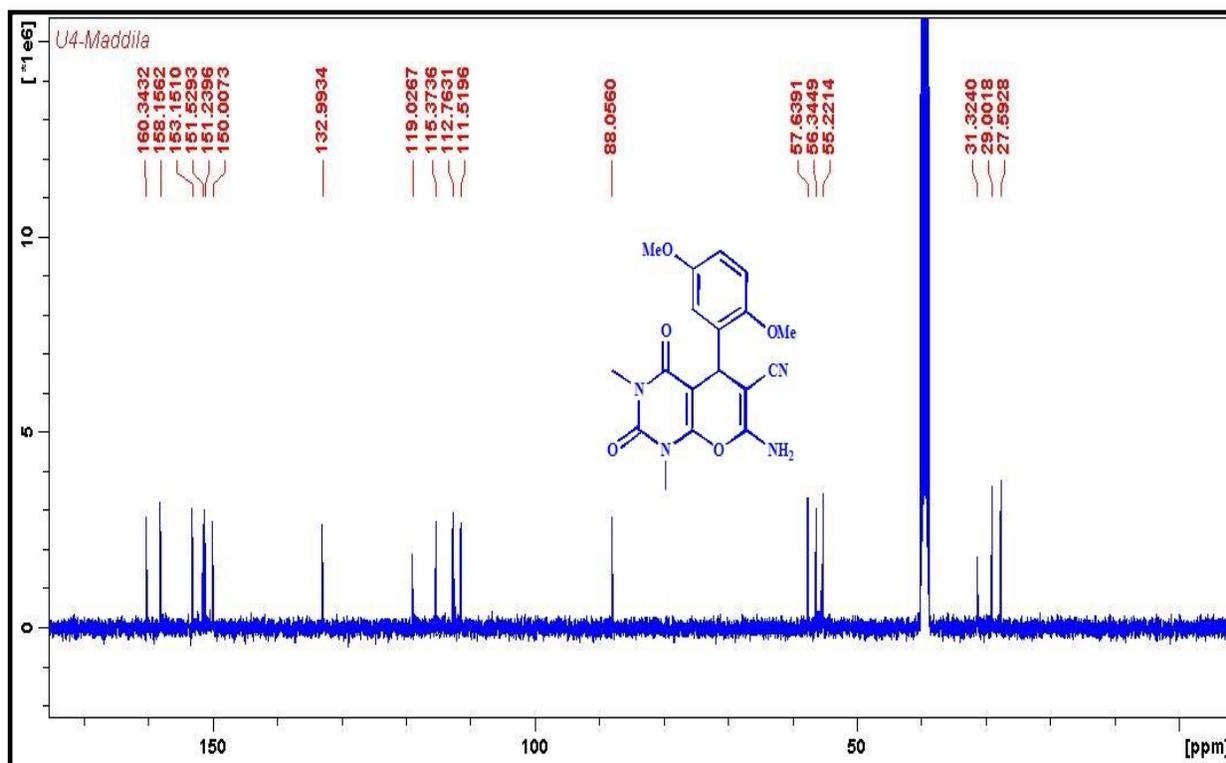
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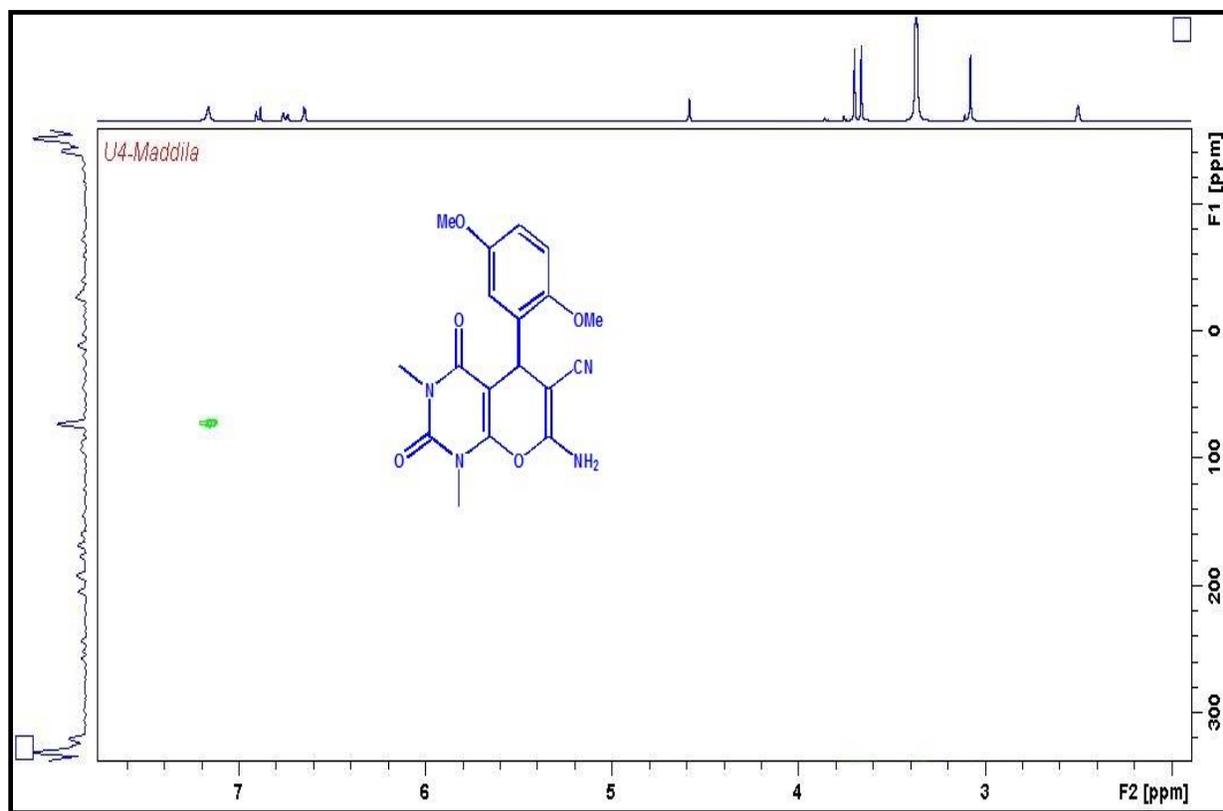
FT-IR spectra of compound 4b



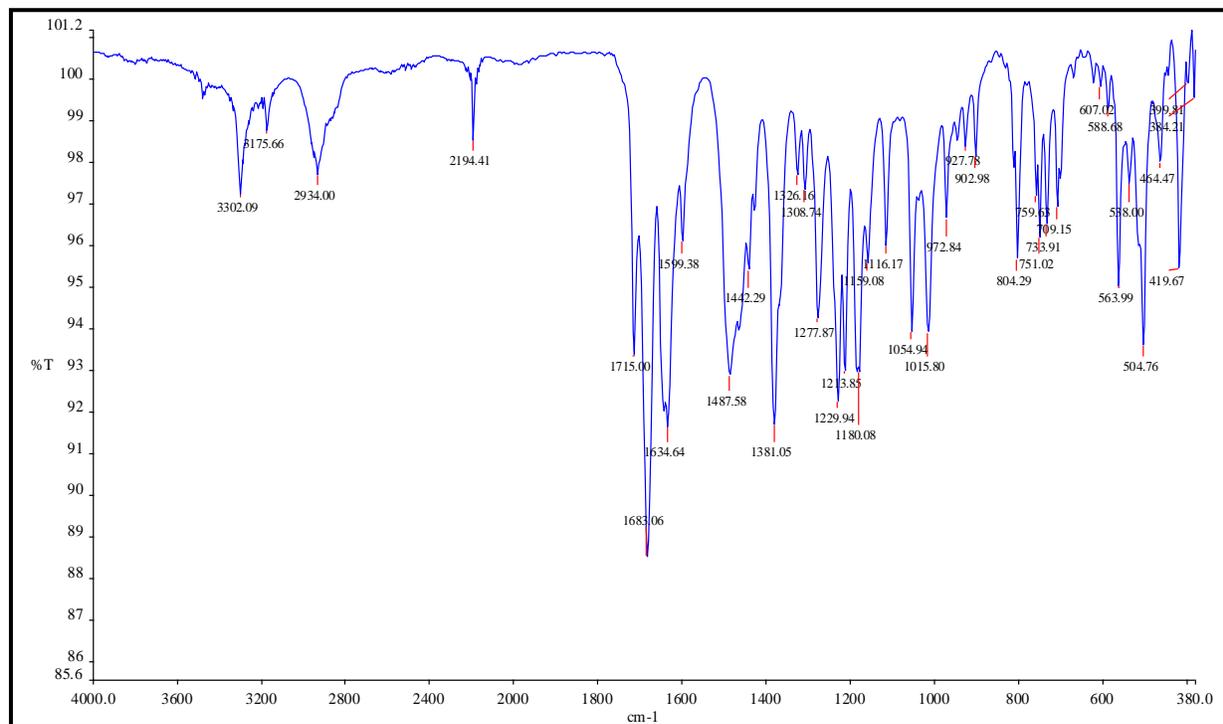
¹H NMR spectra of compound 4c



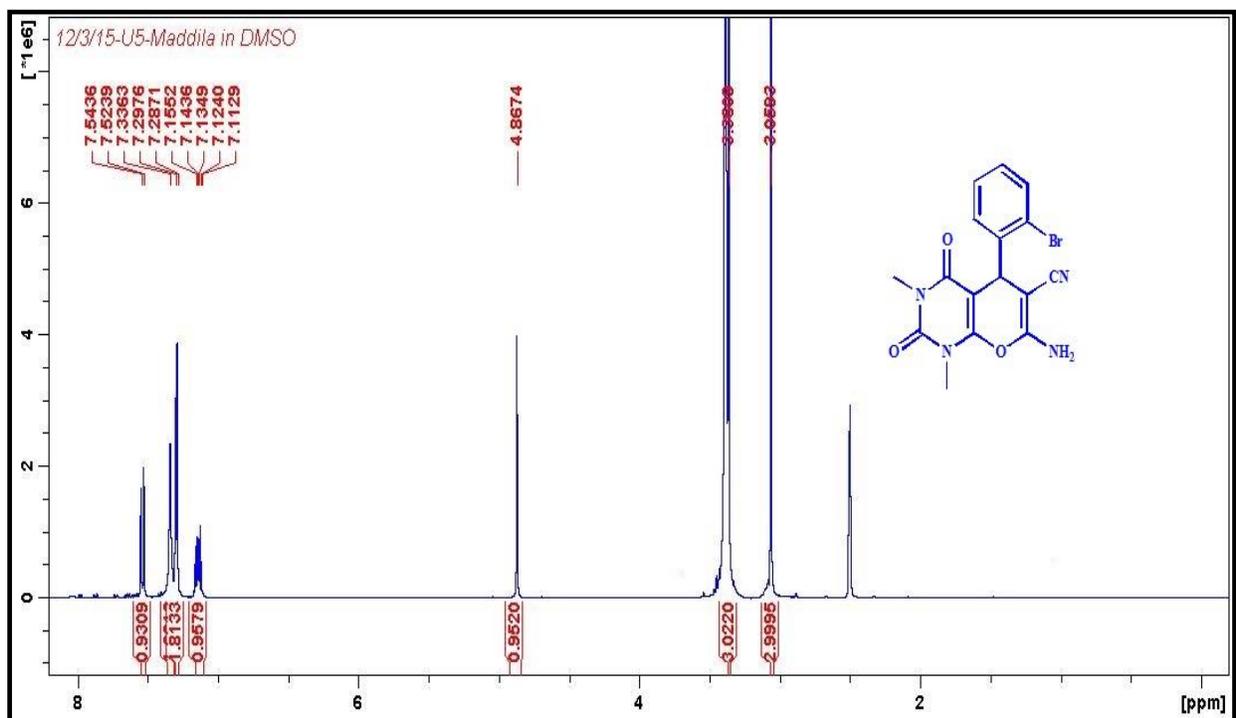
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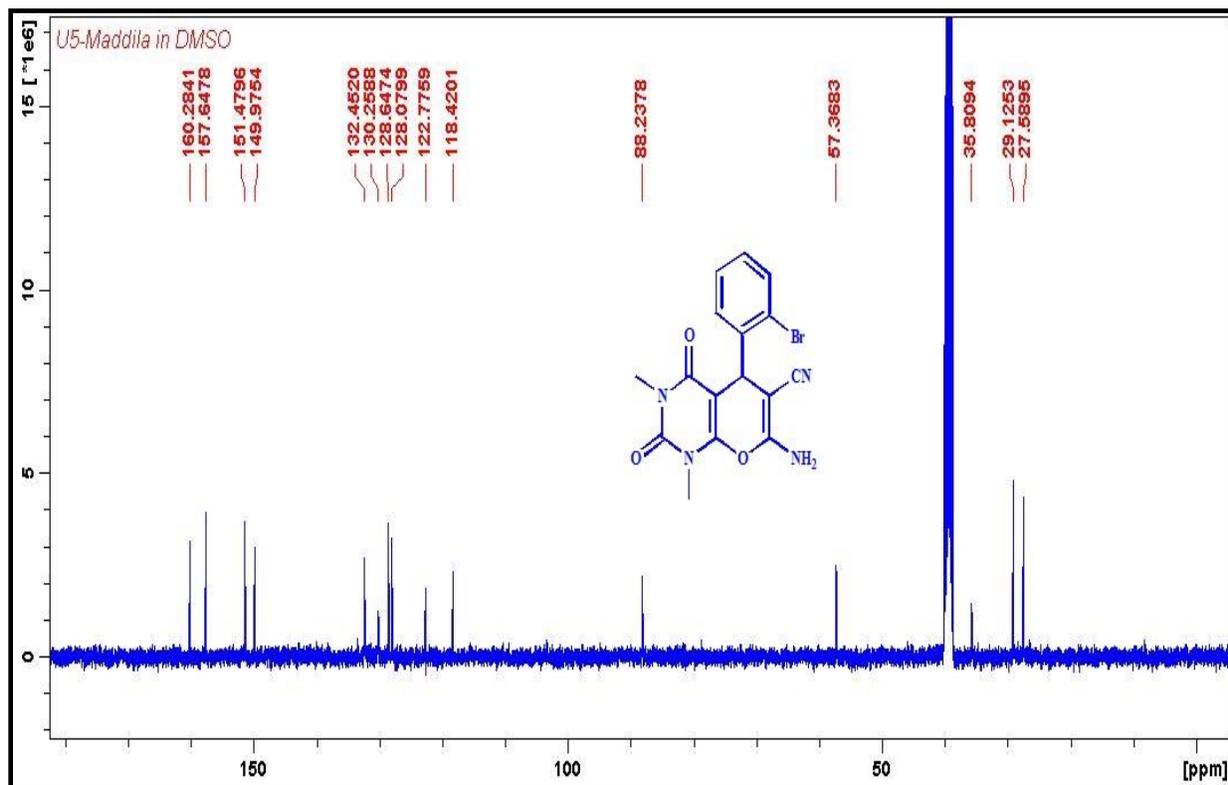
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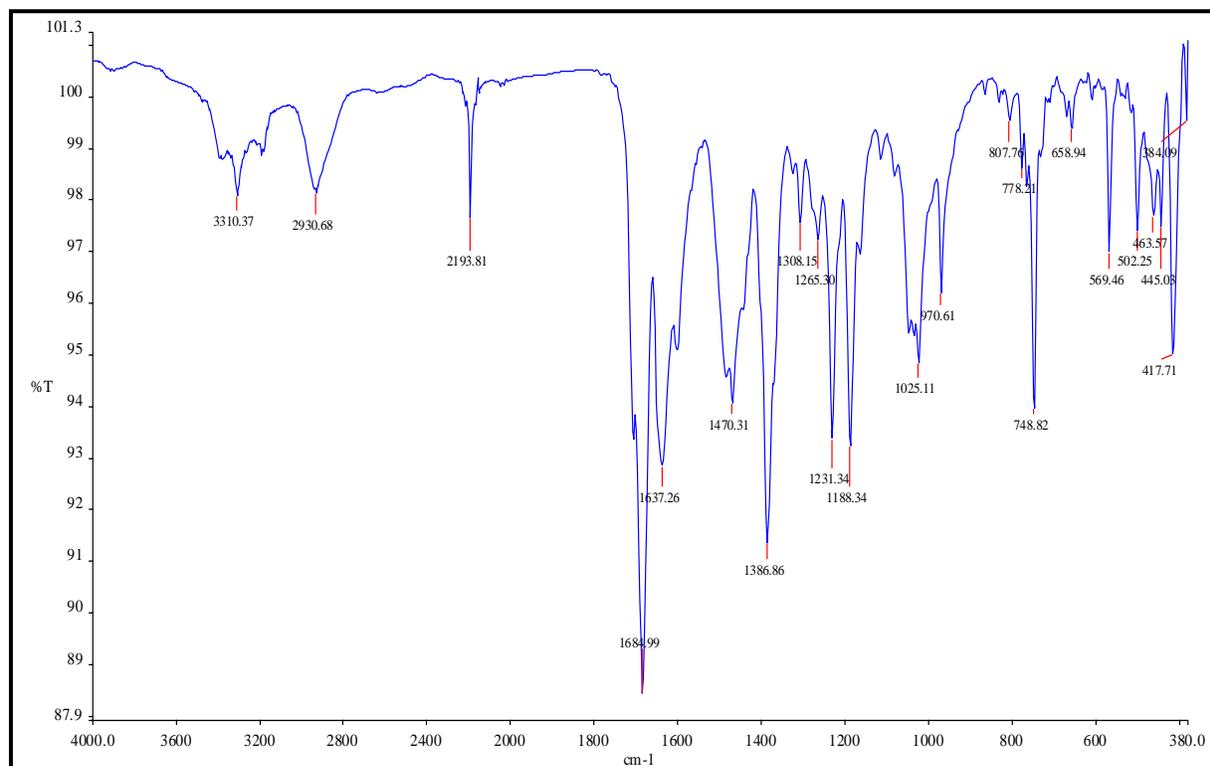
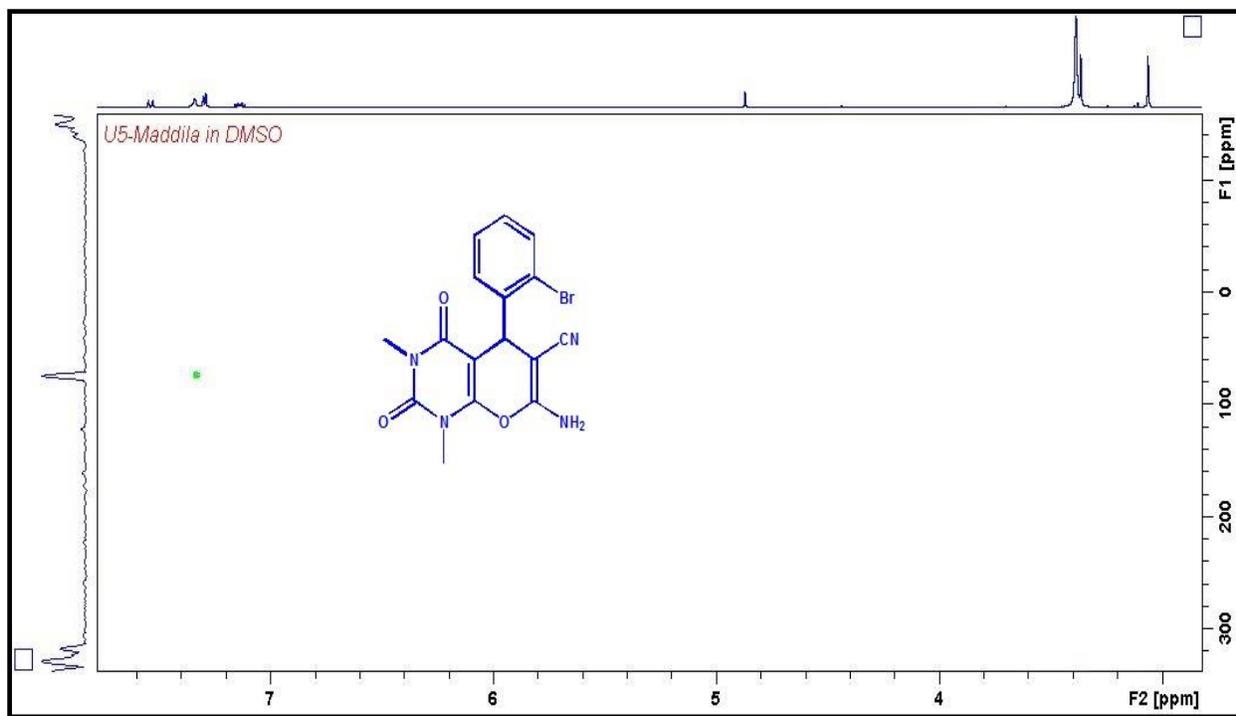
FT-IR spectra of compound 4c

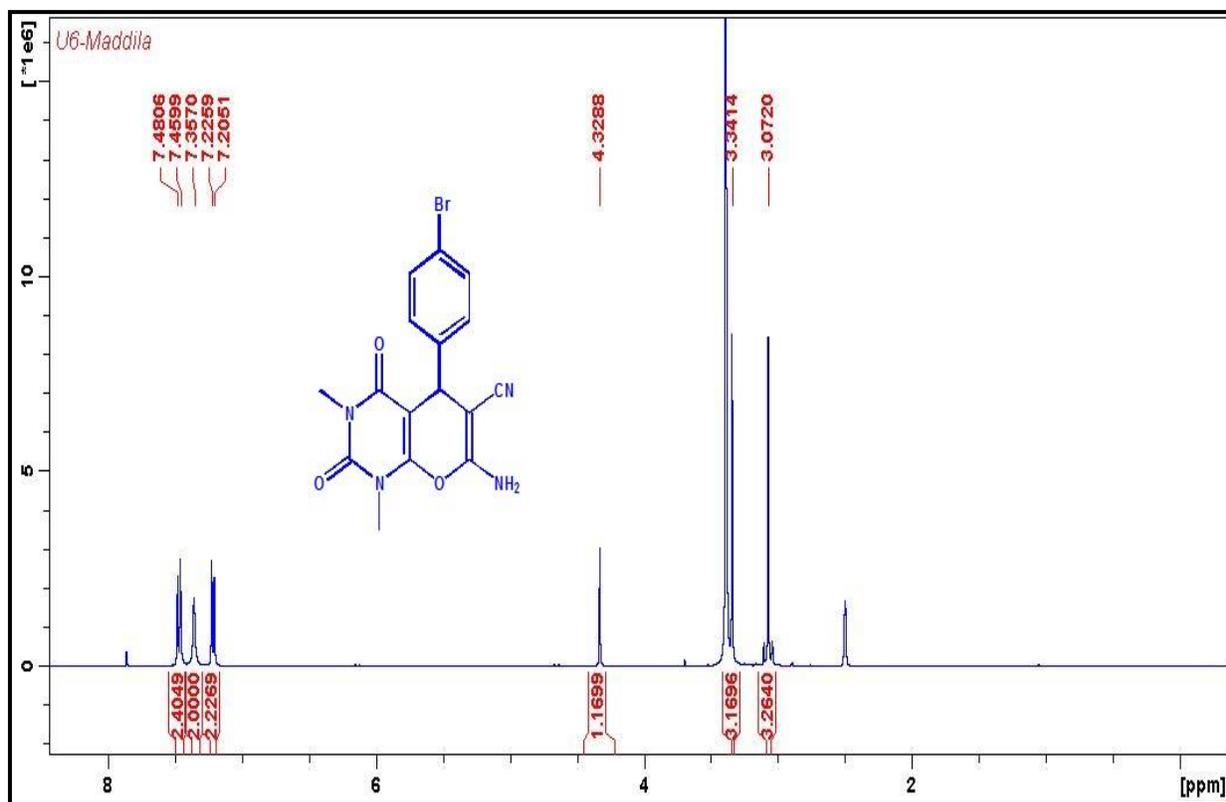


¹H NMR spectra of compound 4d

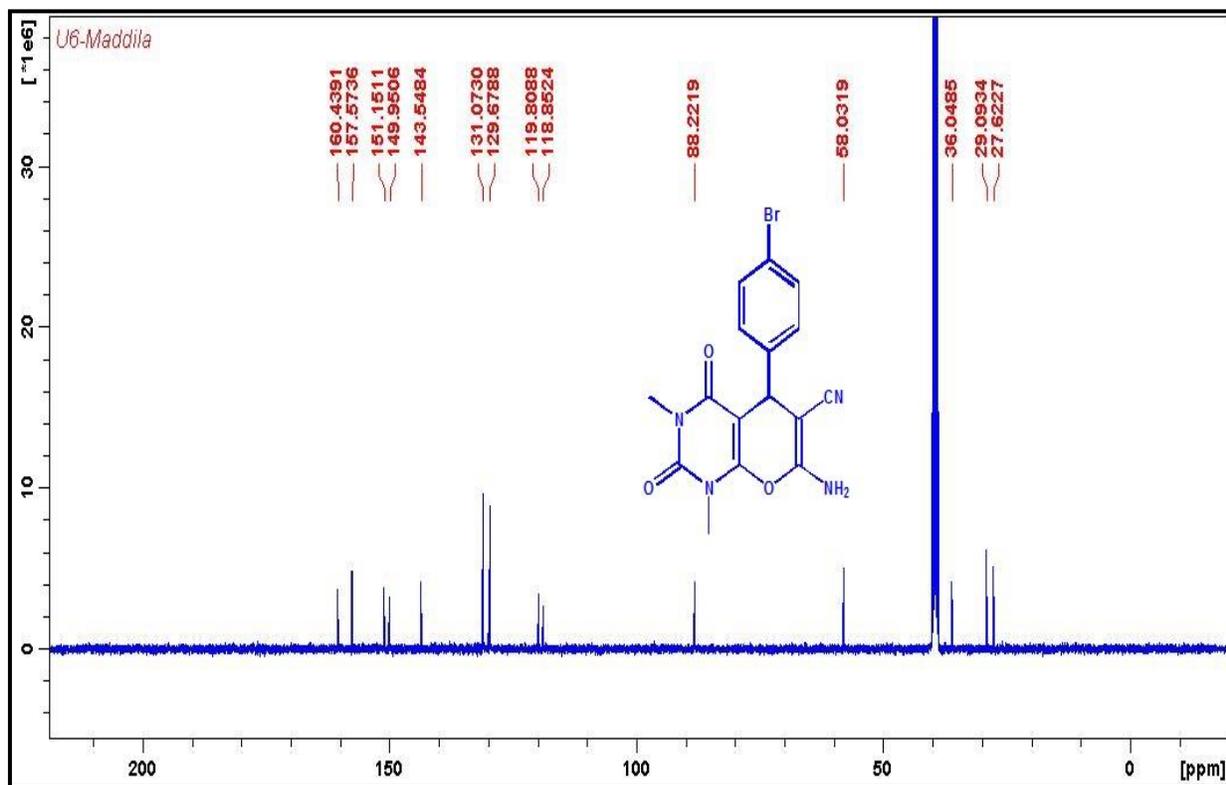


¹³C NMR spectra of compound 4d

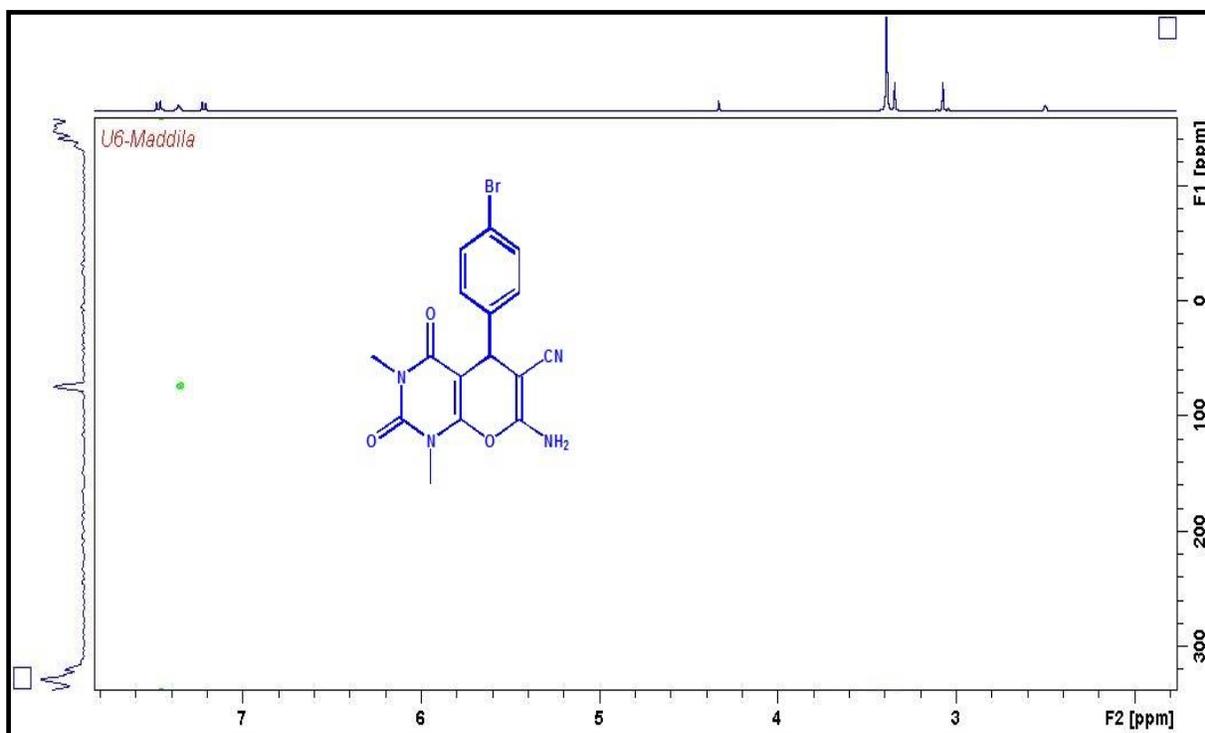




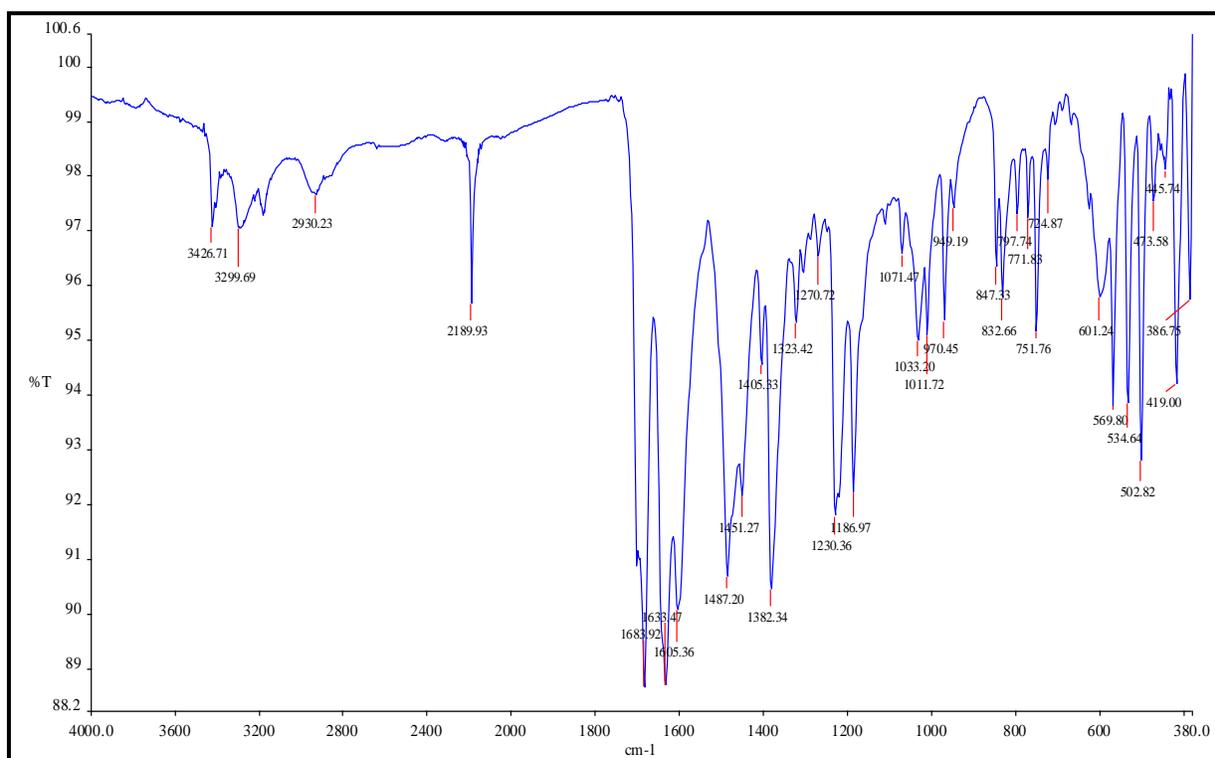
^1H NMR spectra of compound 4e



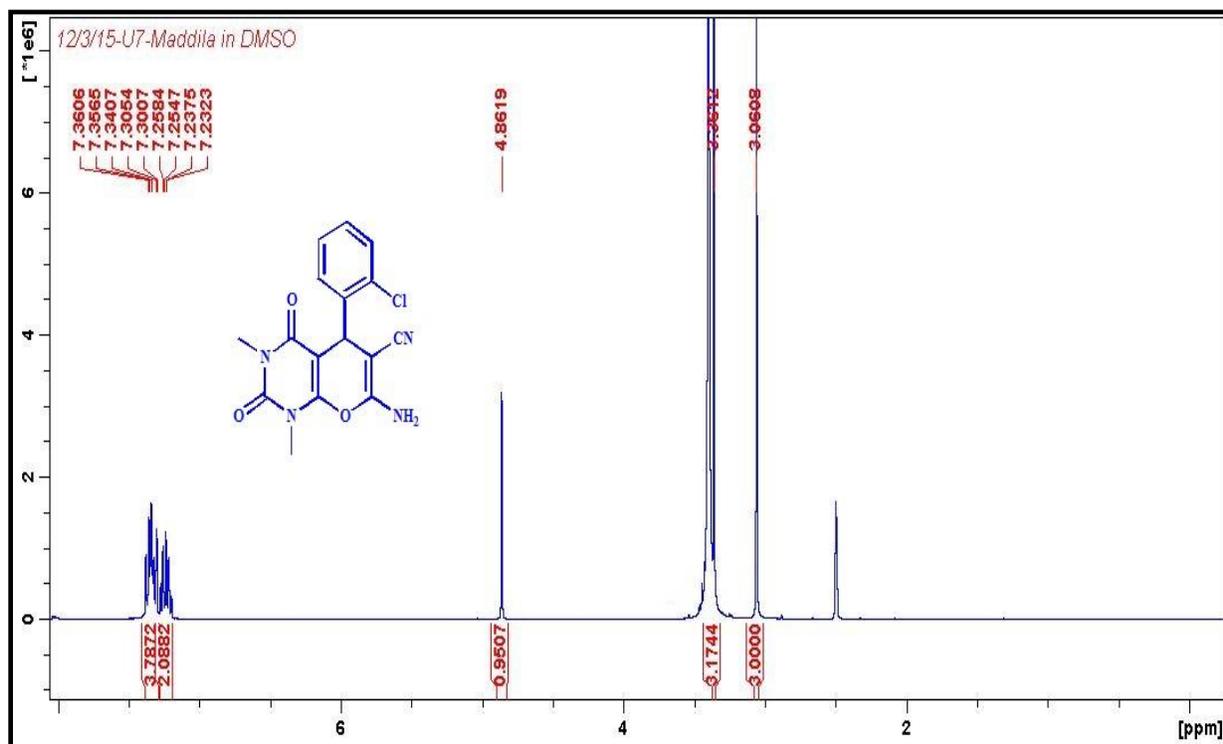
^{13}C NMR spectra of compound 4e



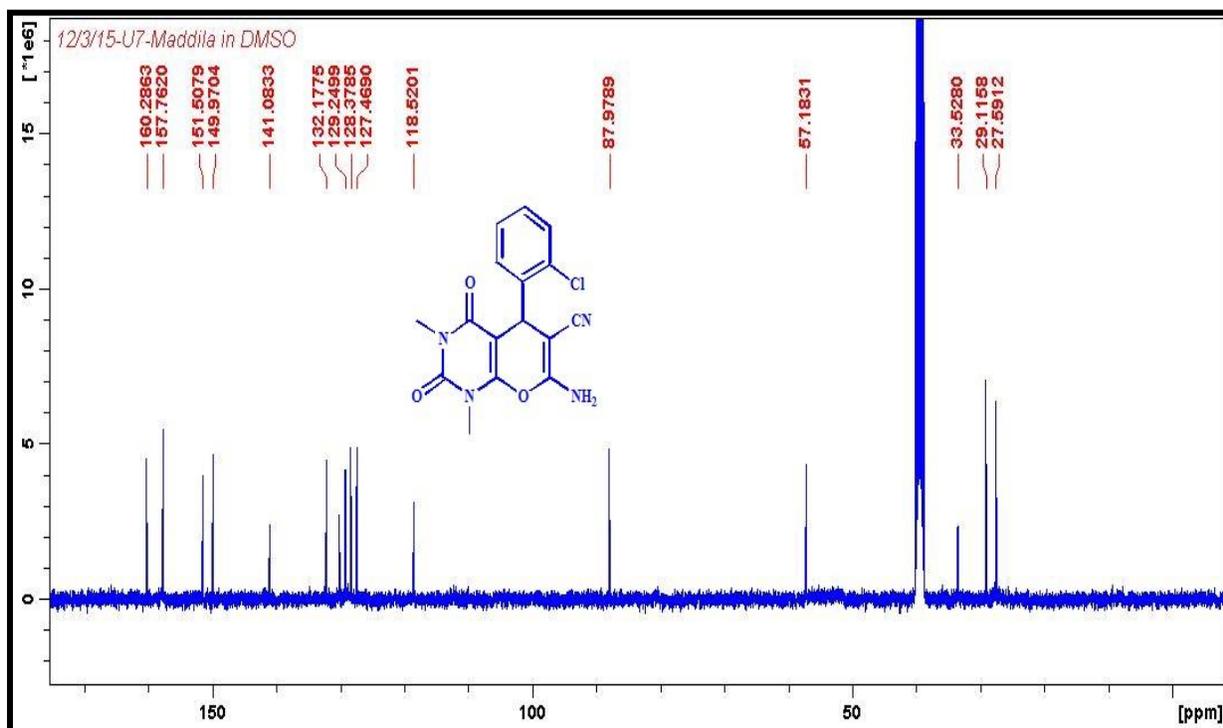
¹⁵N NMR (GHSQC) spectra of compound 4e



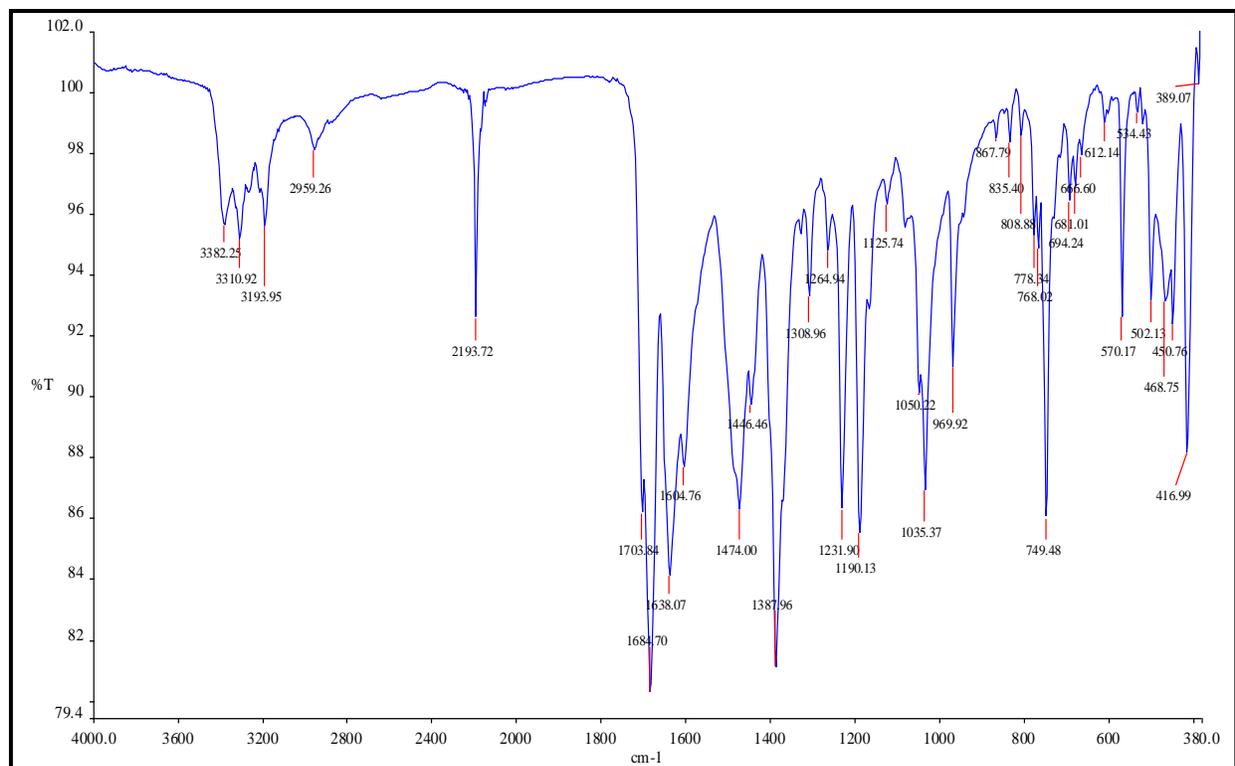
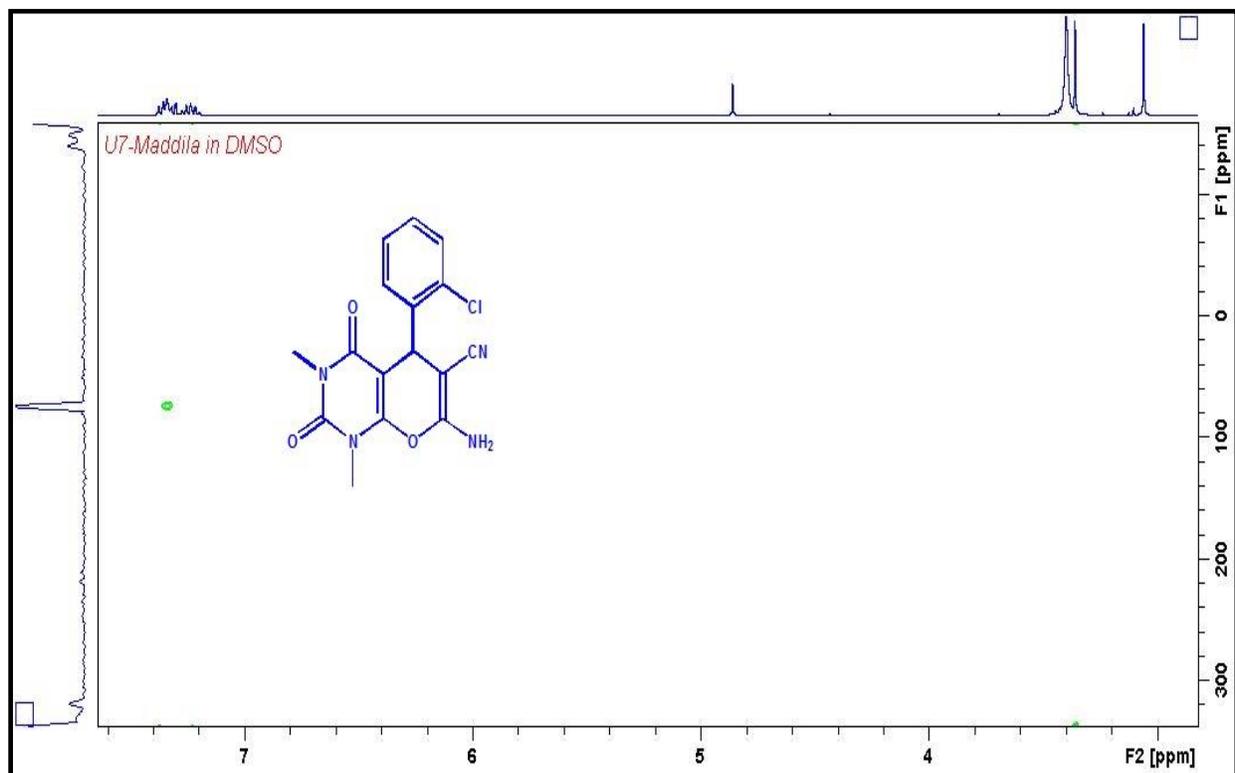
FT-IR spectra of compound 4e

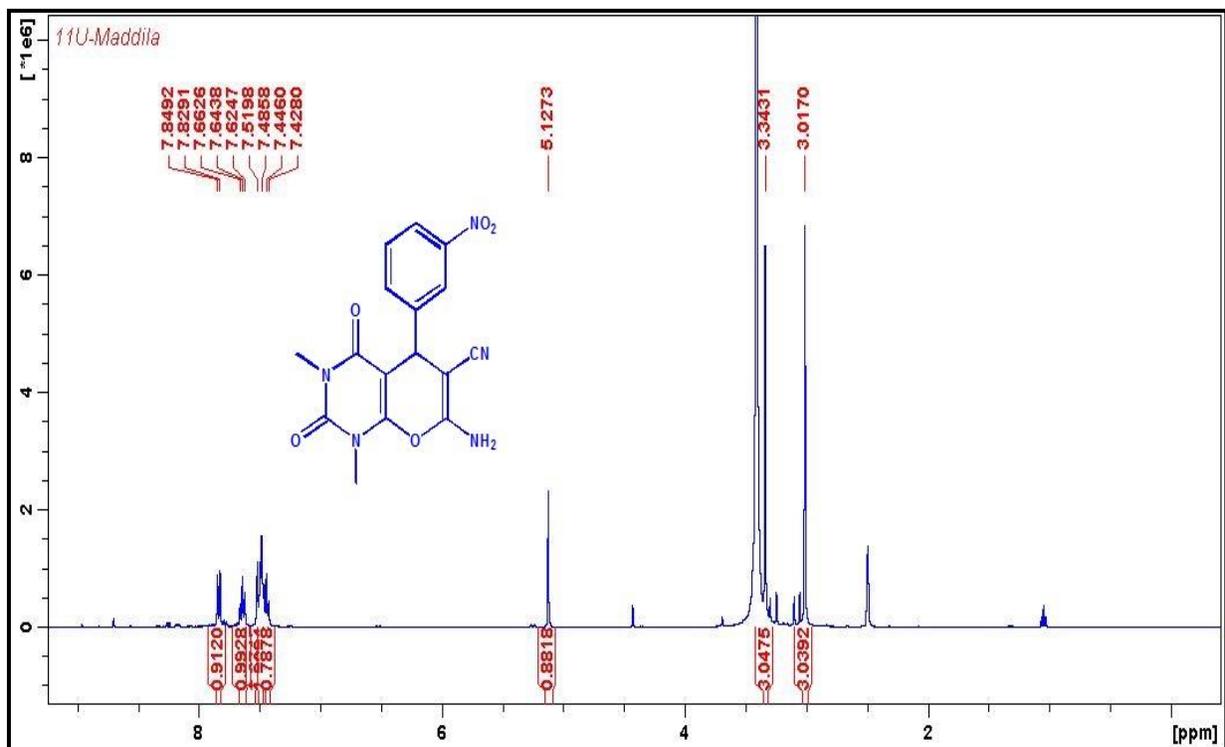


^1H NMR spectra of compound 4f

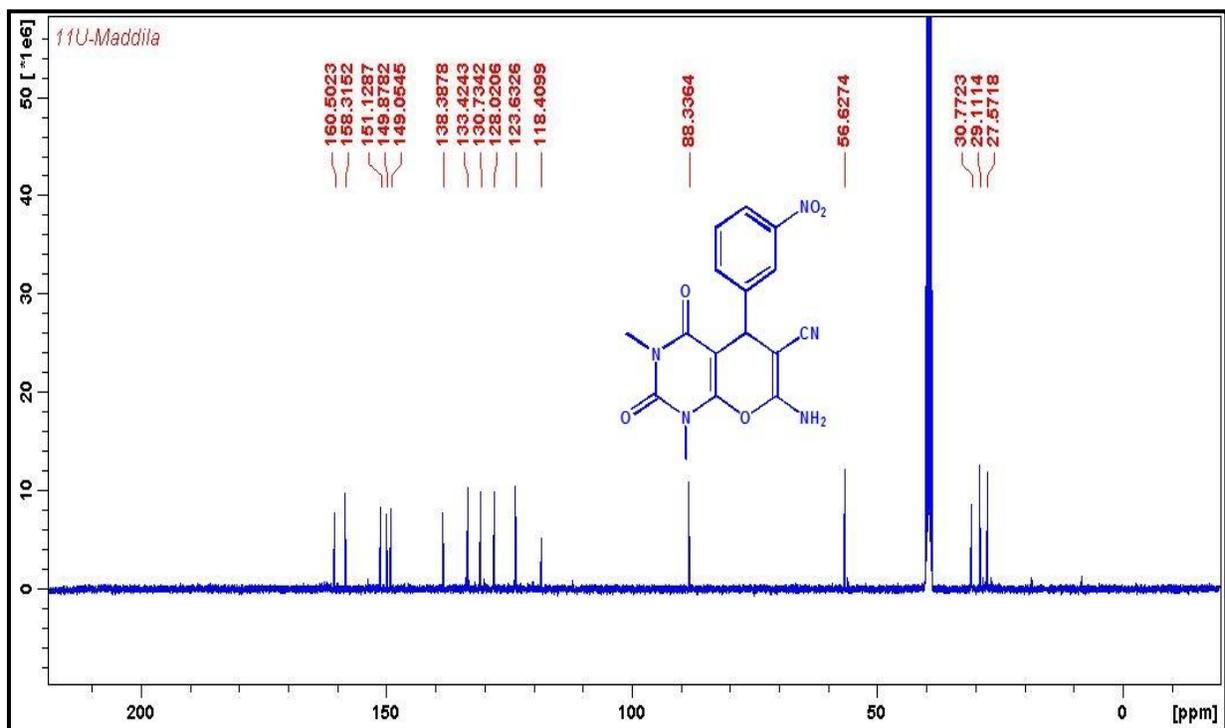


^{13}C NMR spectra of compound 4f

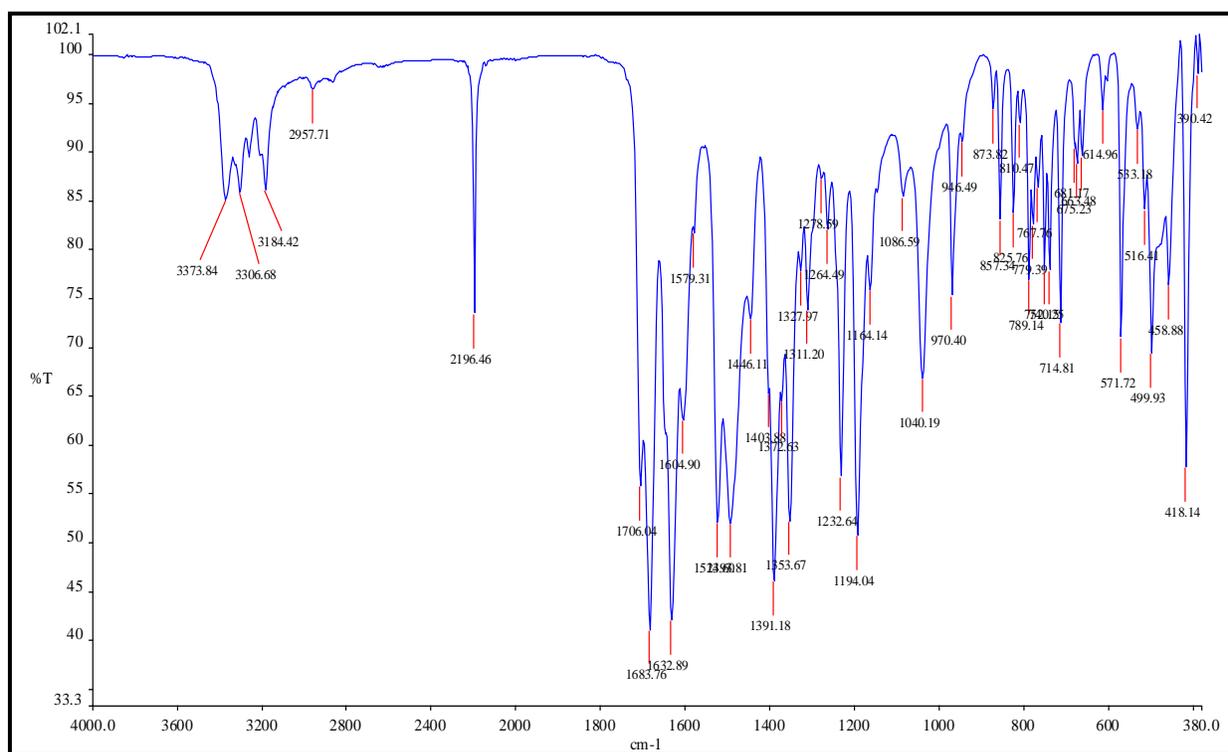
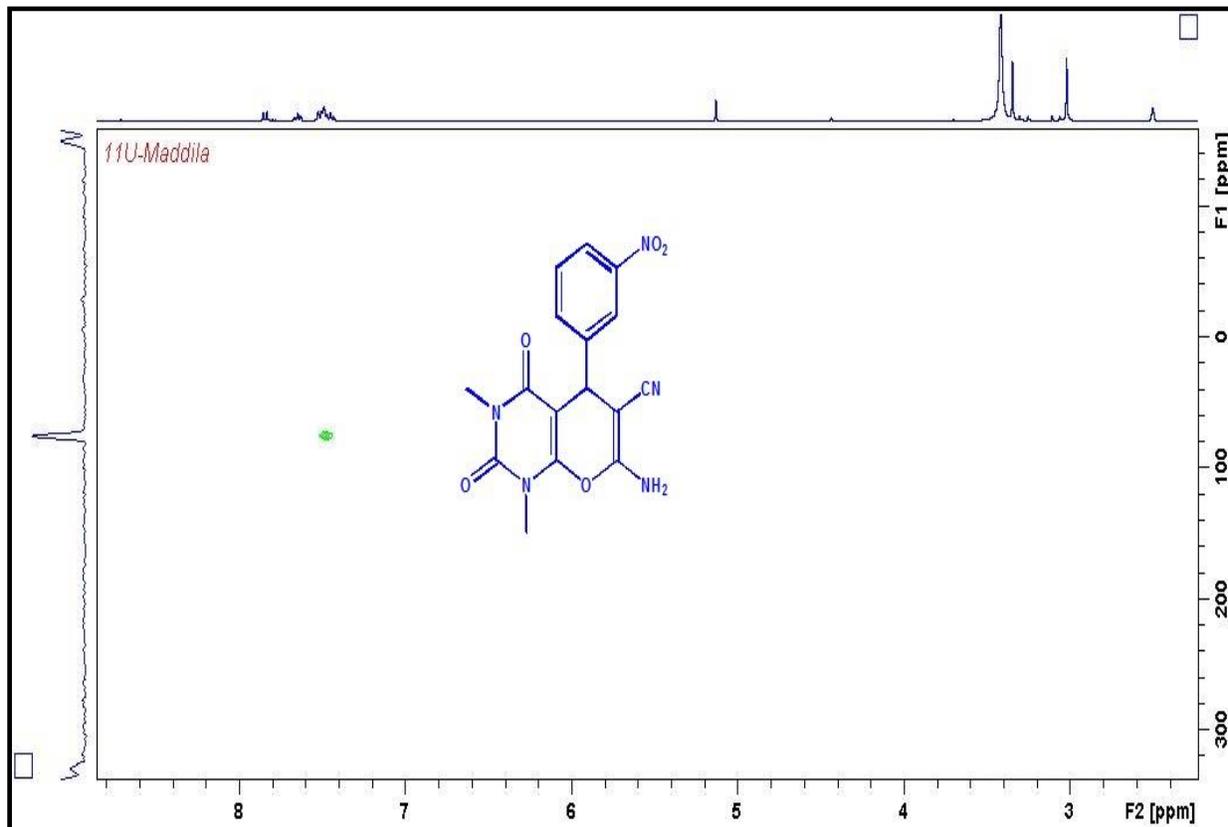


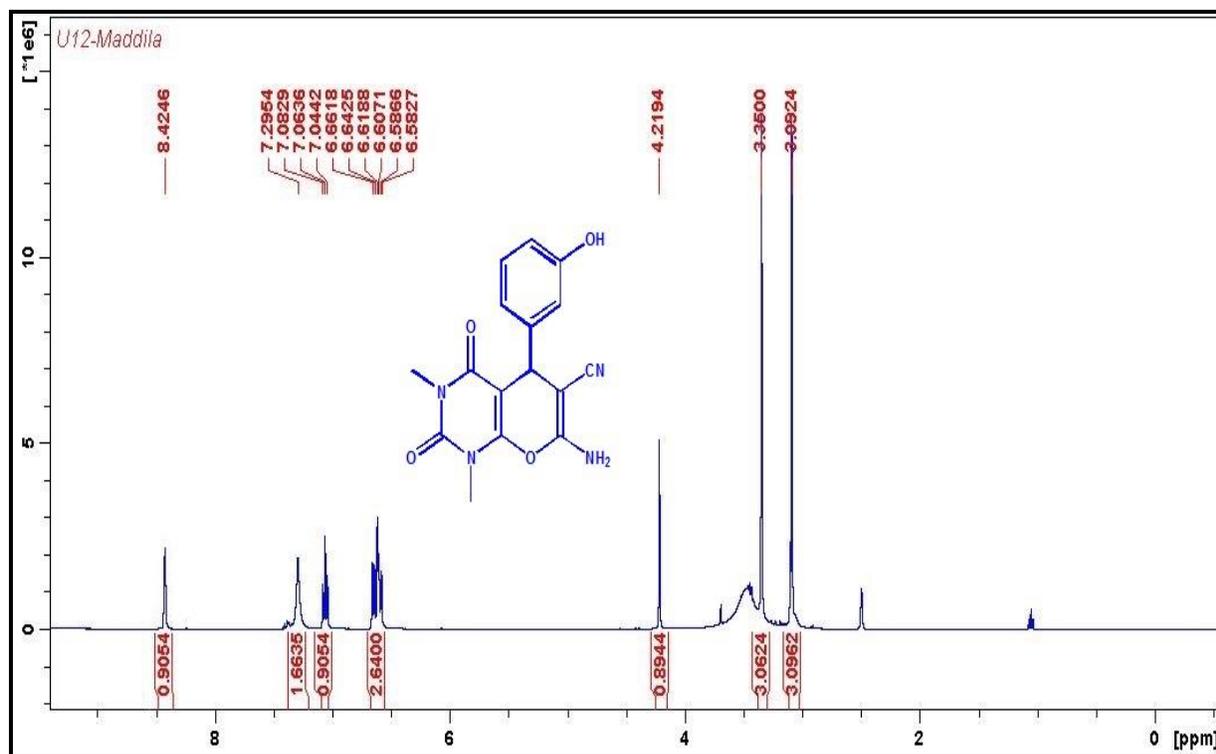


^1H NMR spectra of compound 4g

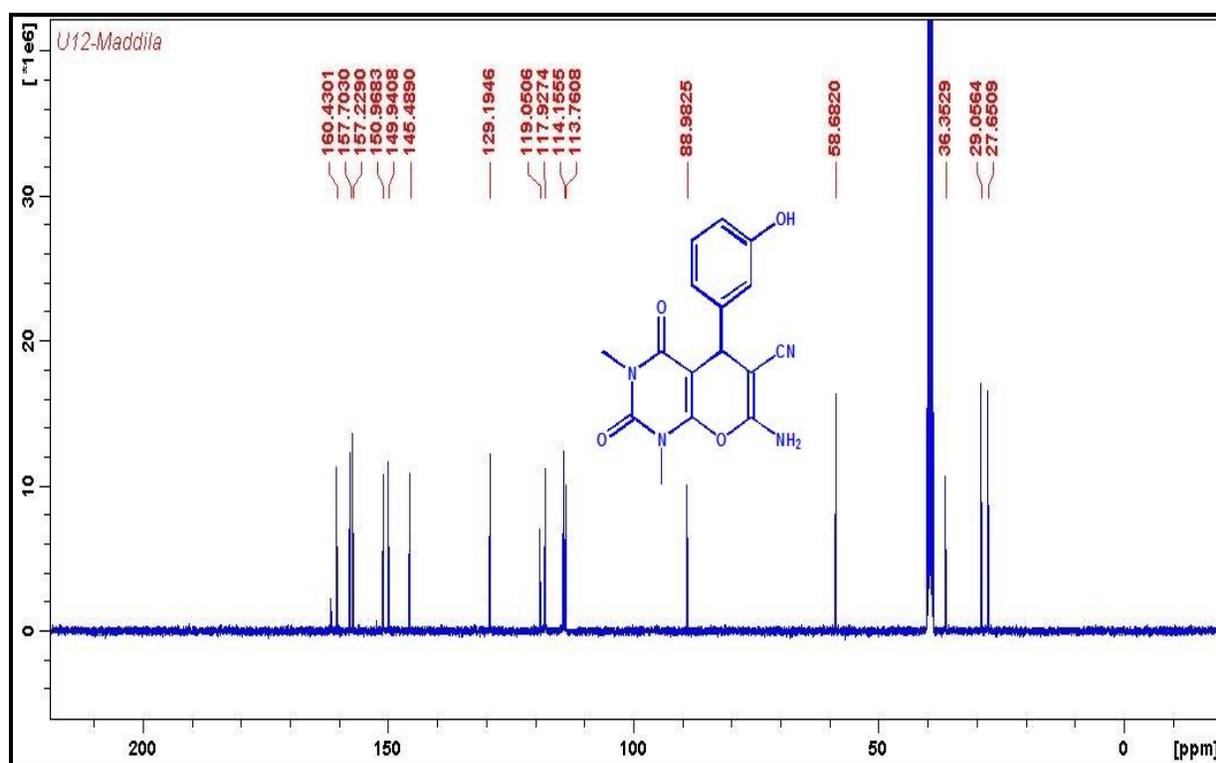


^{13}C NMR spectra of compound 4g

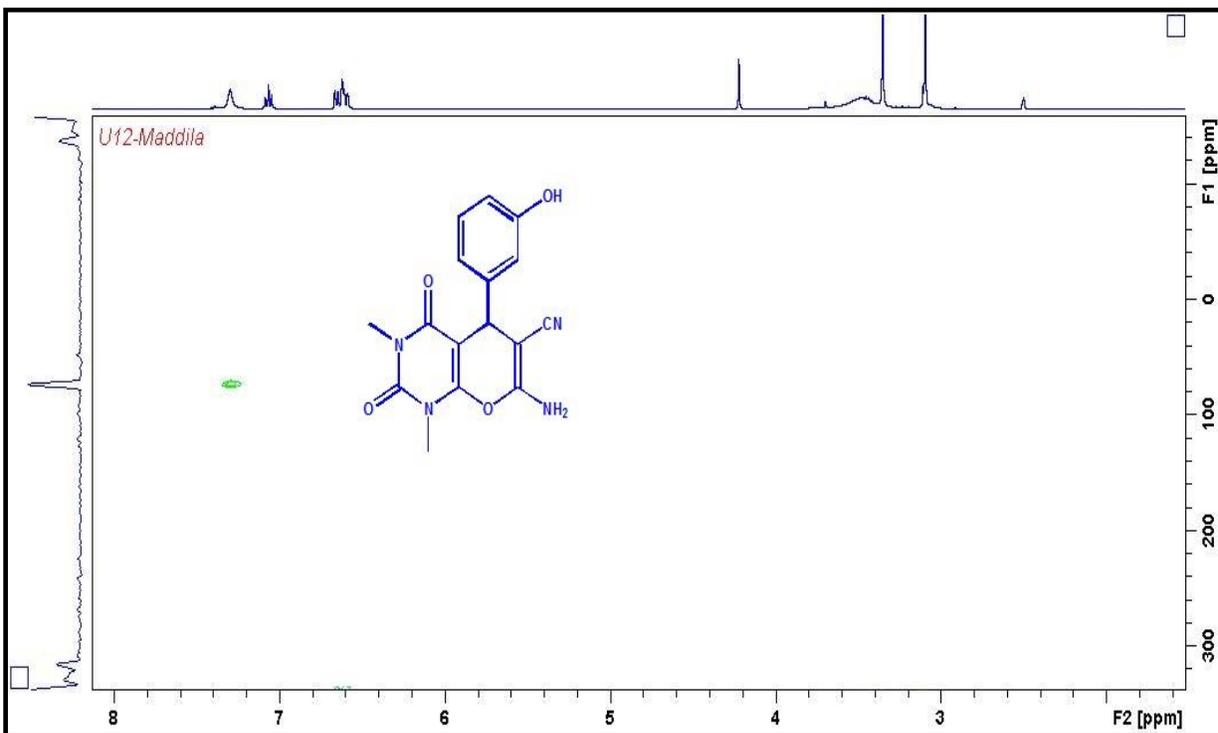




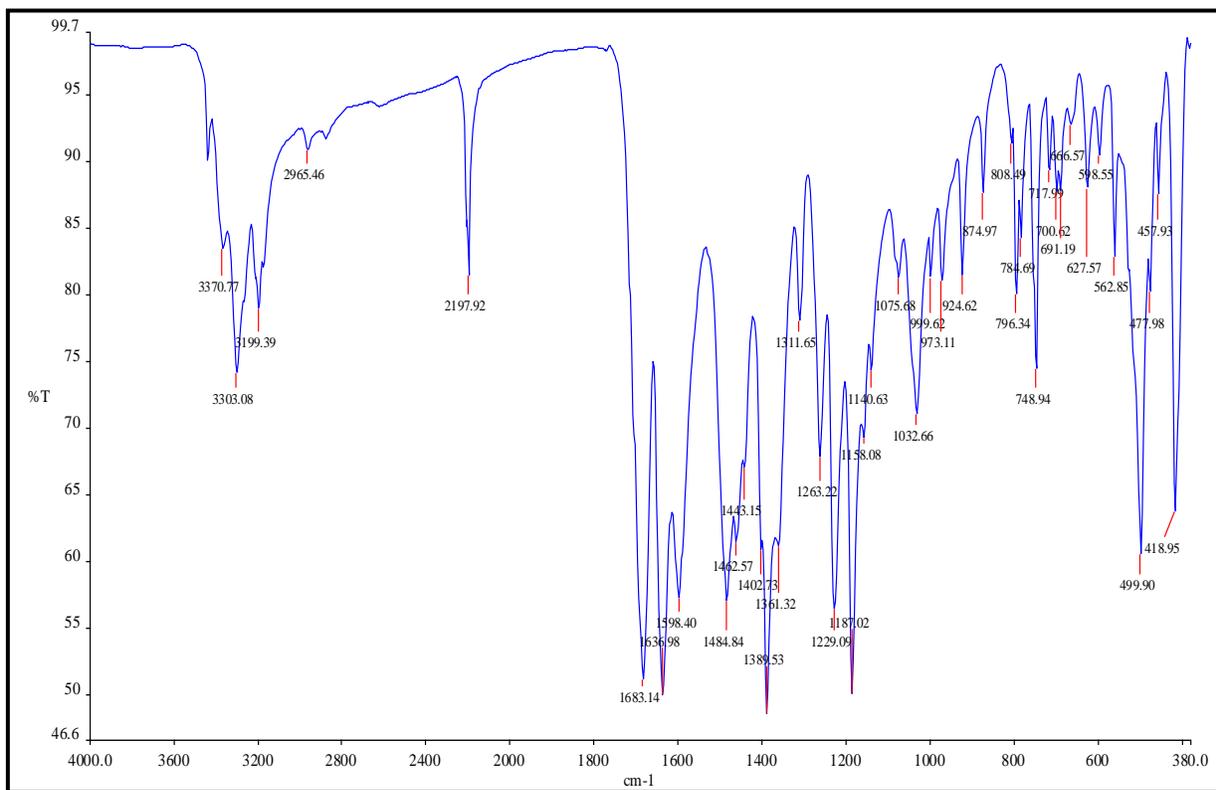
¹H NMR spectra of compound 4h



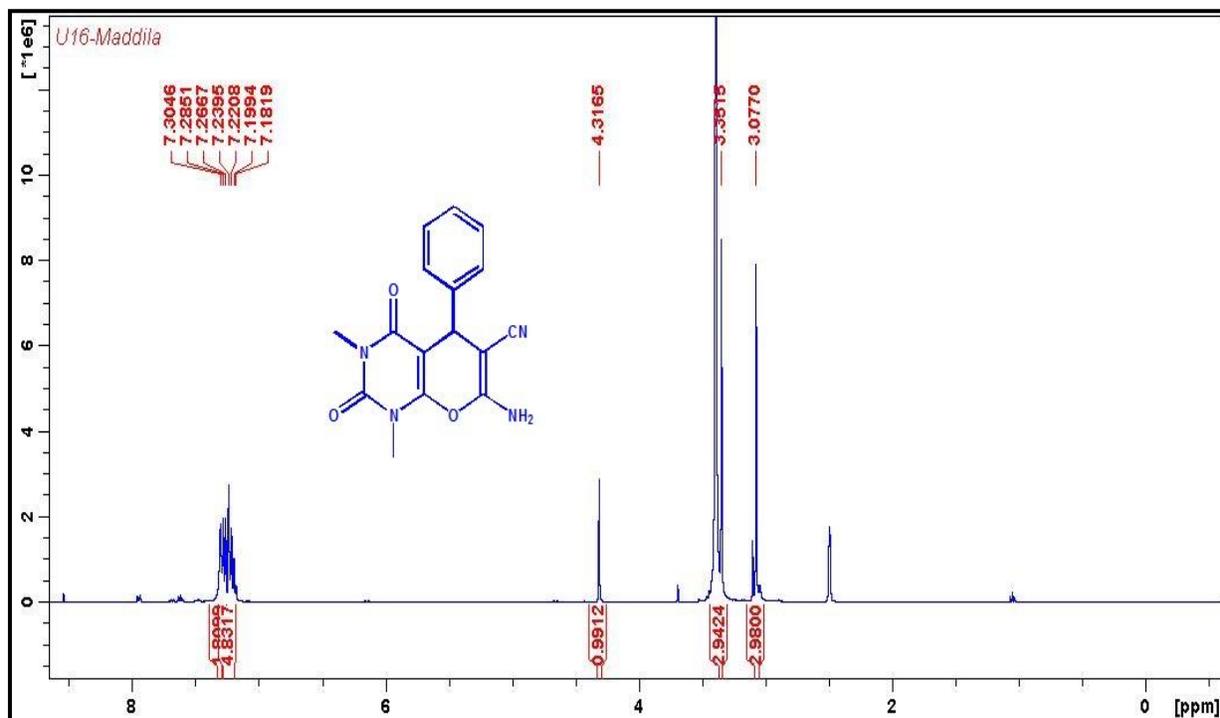
¹³C NMR spectra of compound 4h



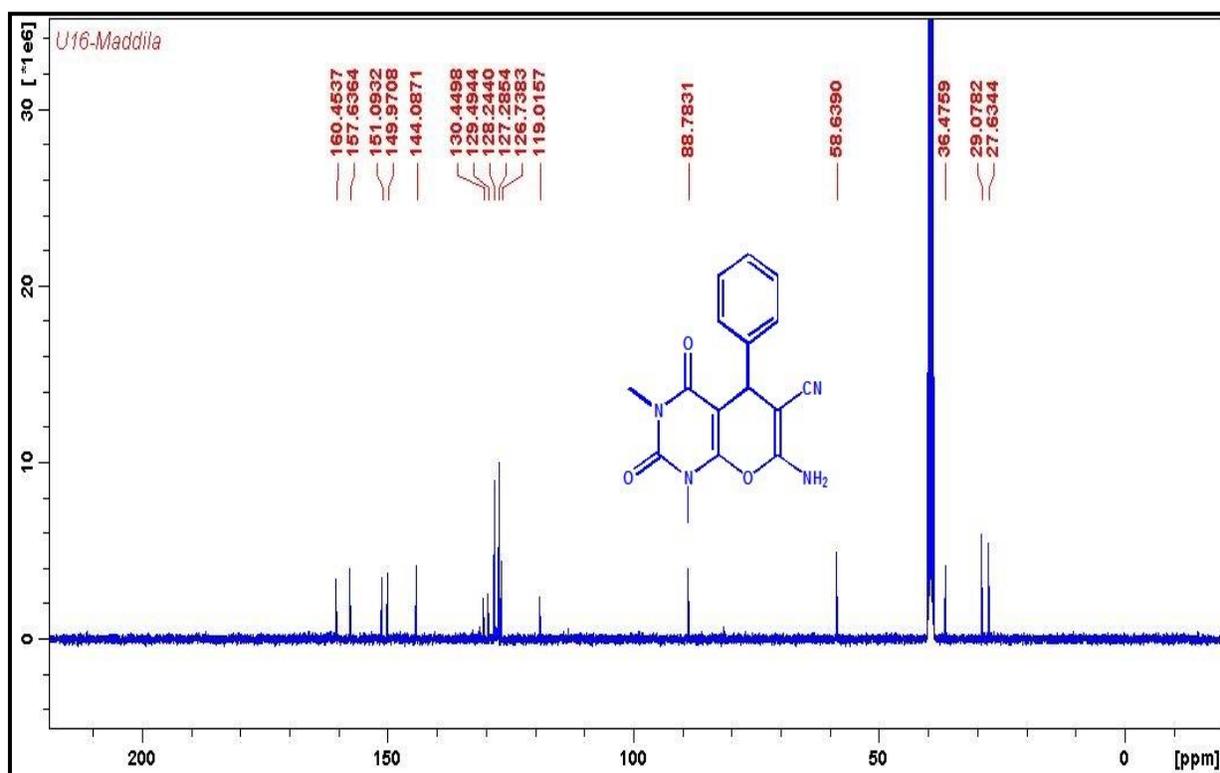
¹⁵N NMR (GHSQC) spectra of compound 4h



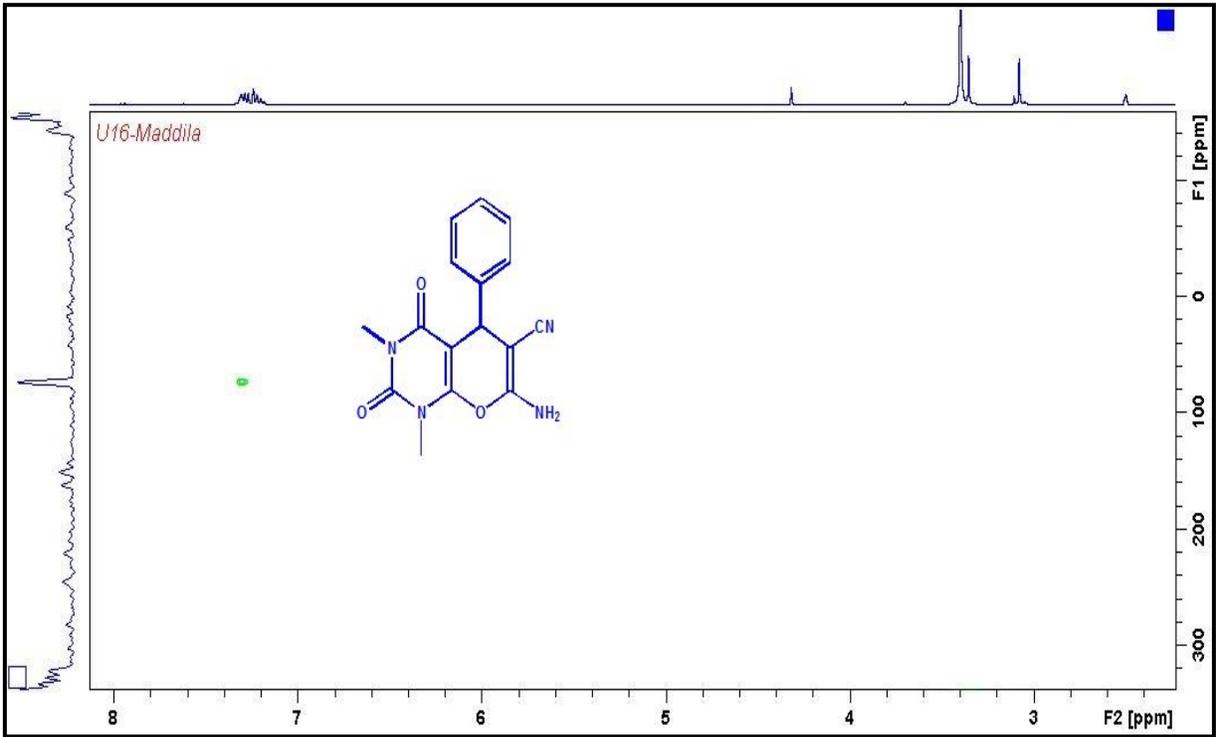
FT-IR spectra of compound 4h



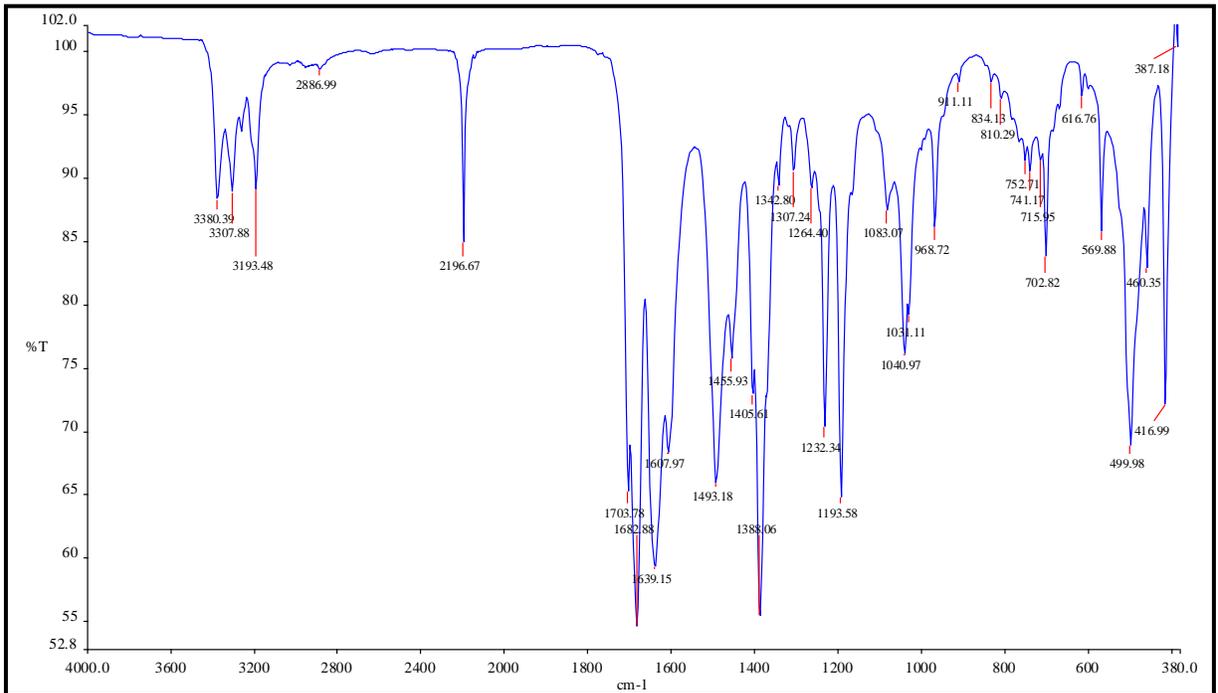
^1H NMR spectra of compound 4i



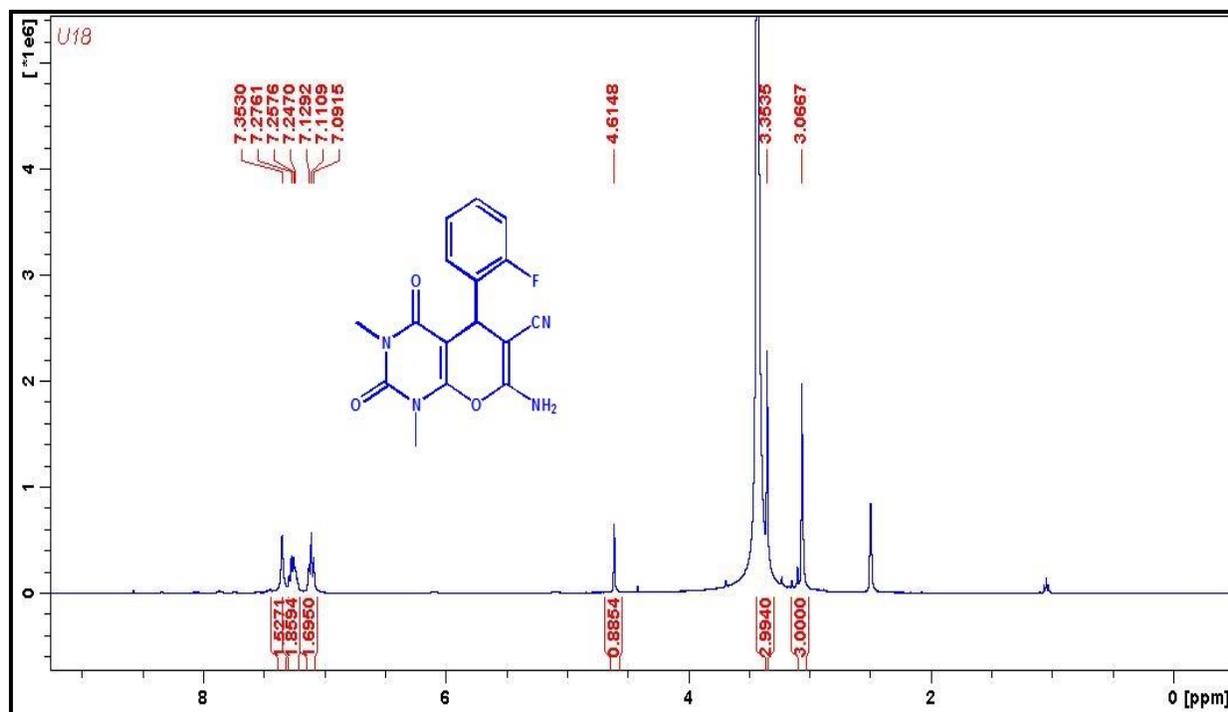
^{13}C NMR spectra of compound 4i



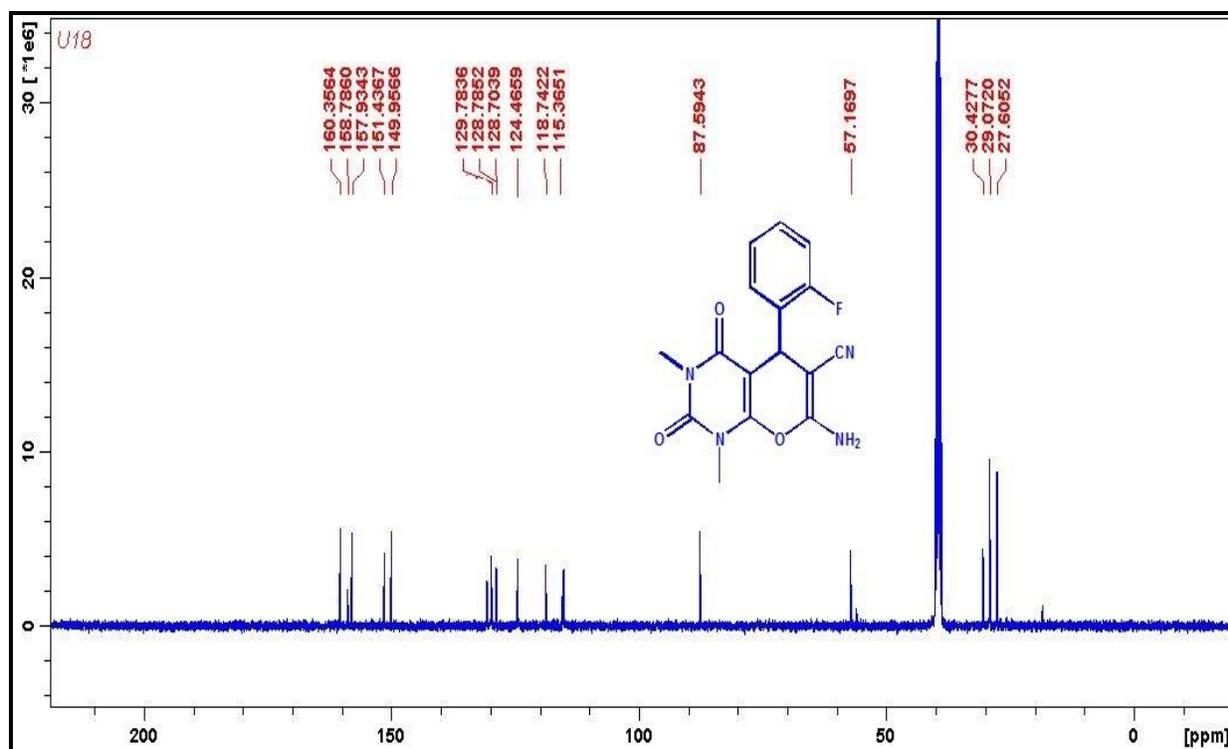
^{15}N NMR (GHSQC) spectra of compound 4i



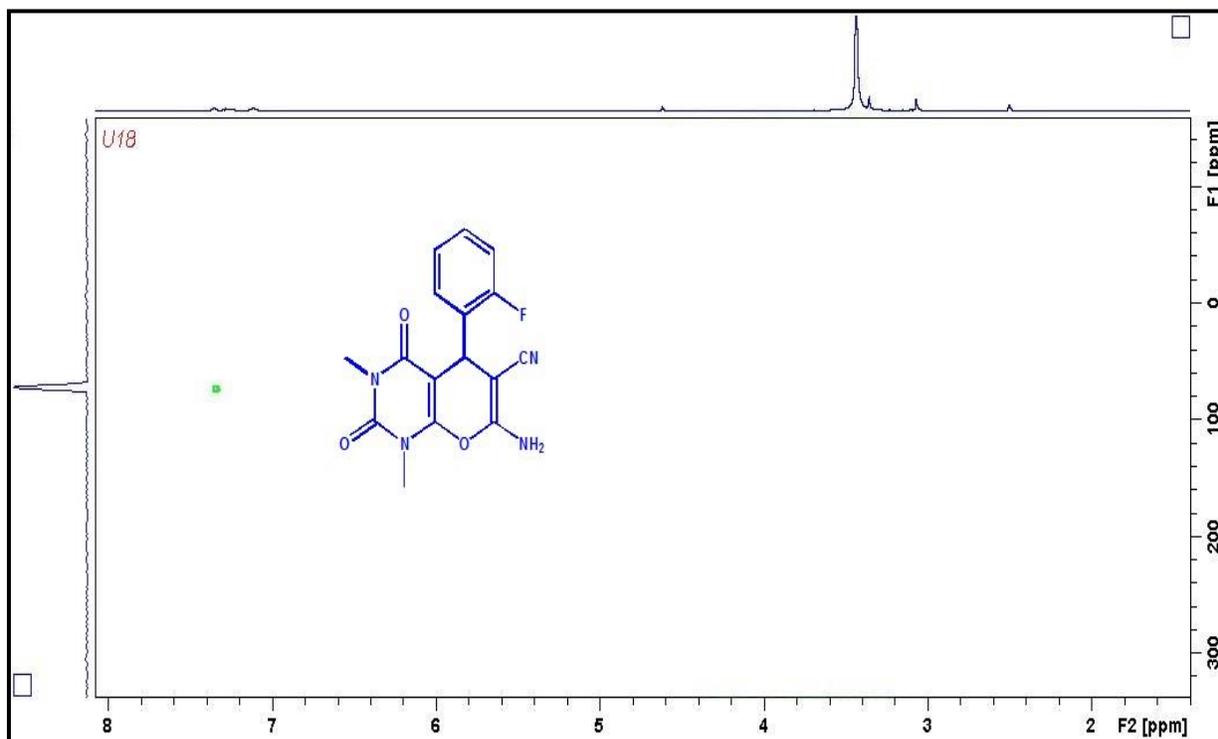
FT-IR spectra of compound 4i



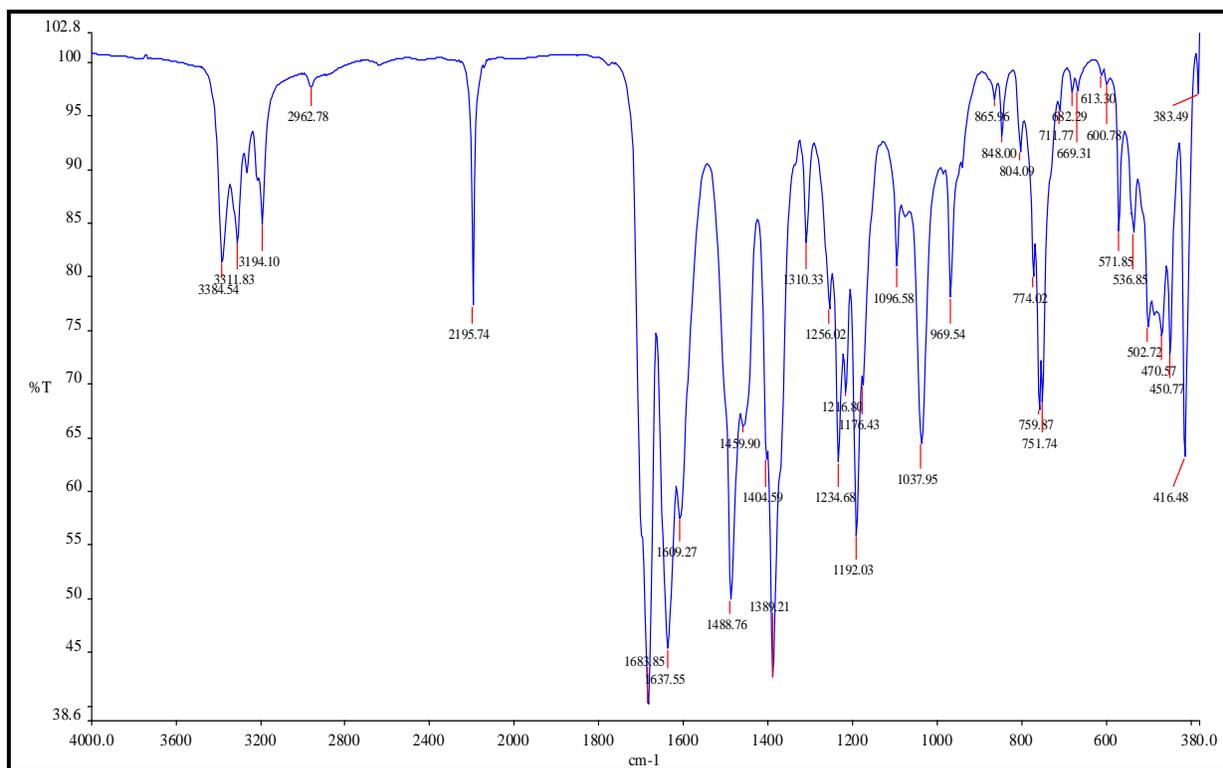
¹H NMR spectra of compound 4j



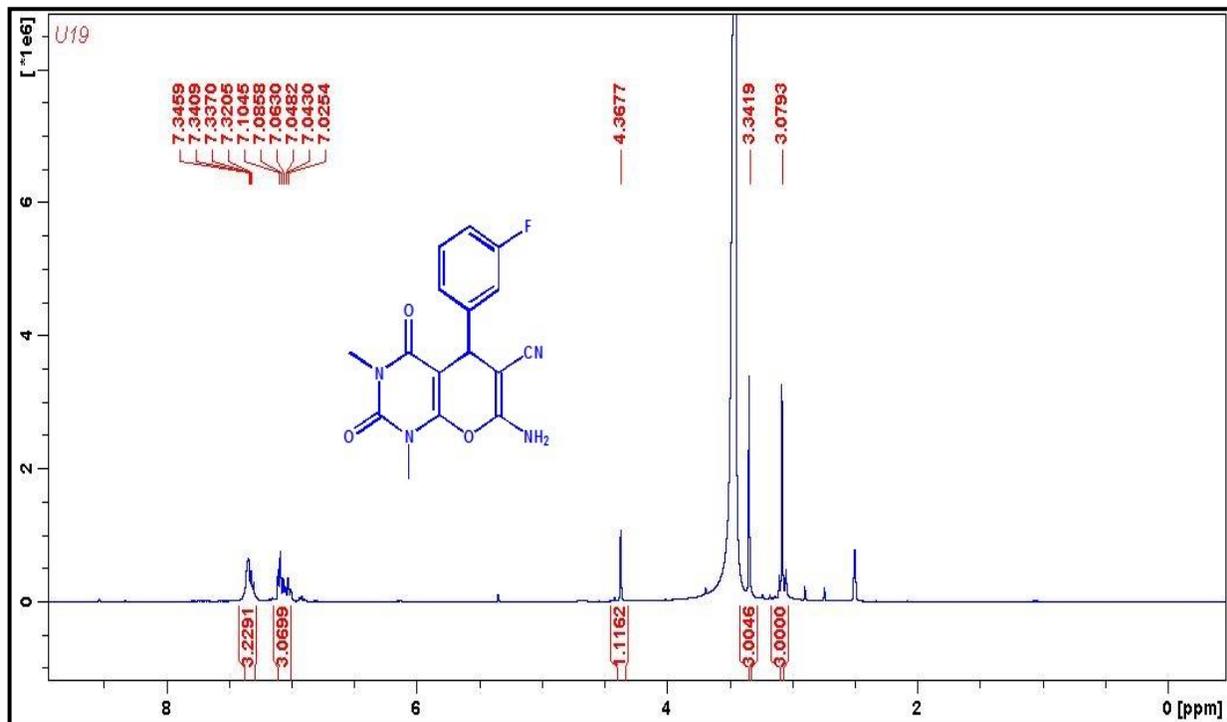
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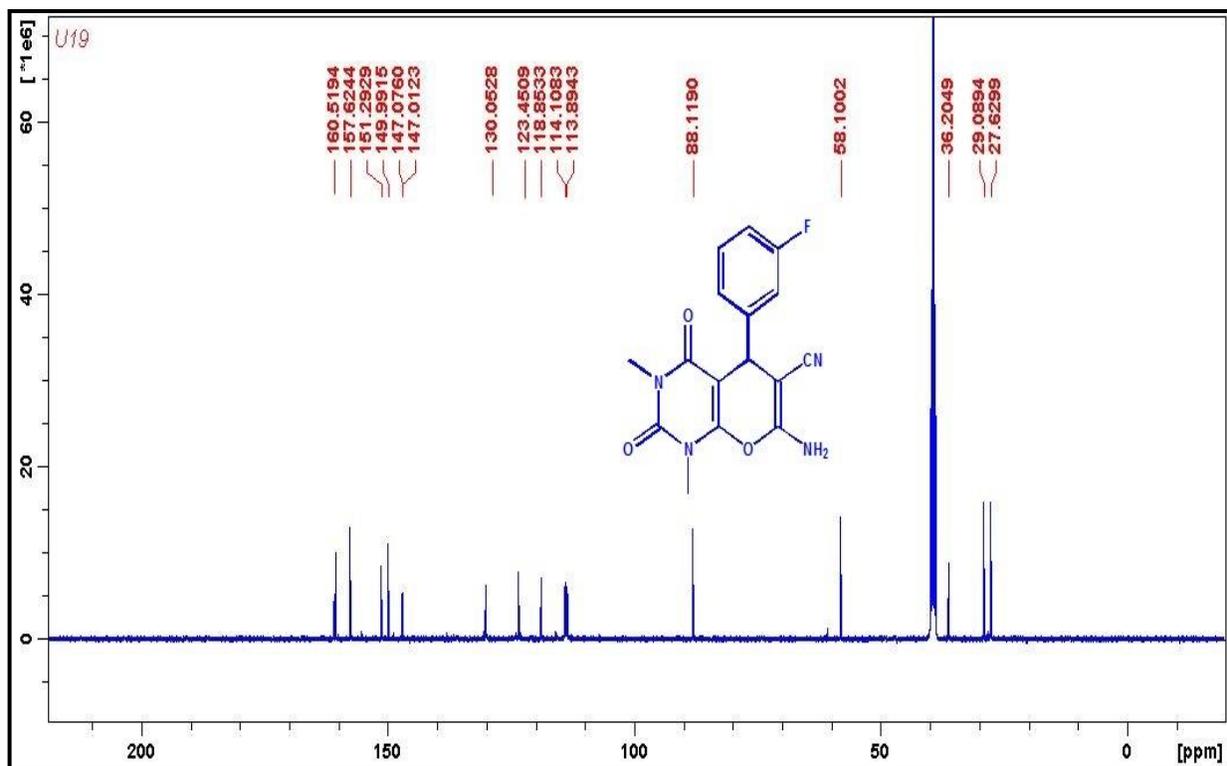
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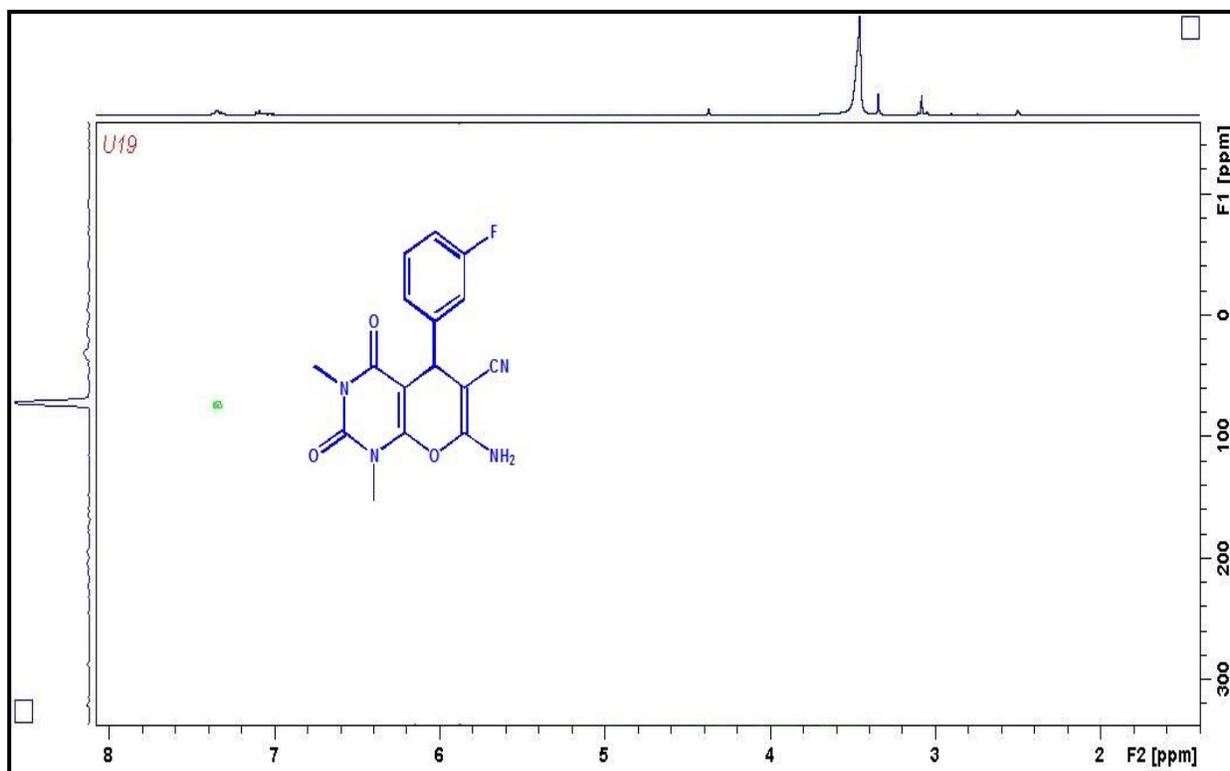
FT-IR spectra of compound 4j



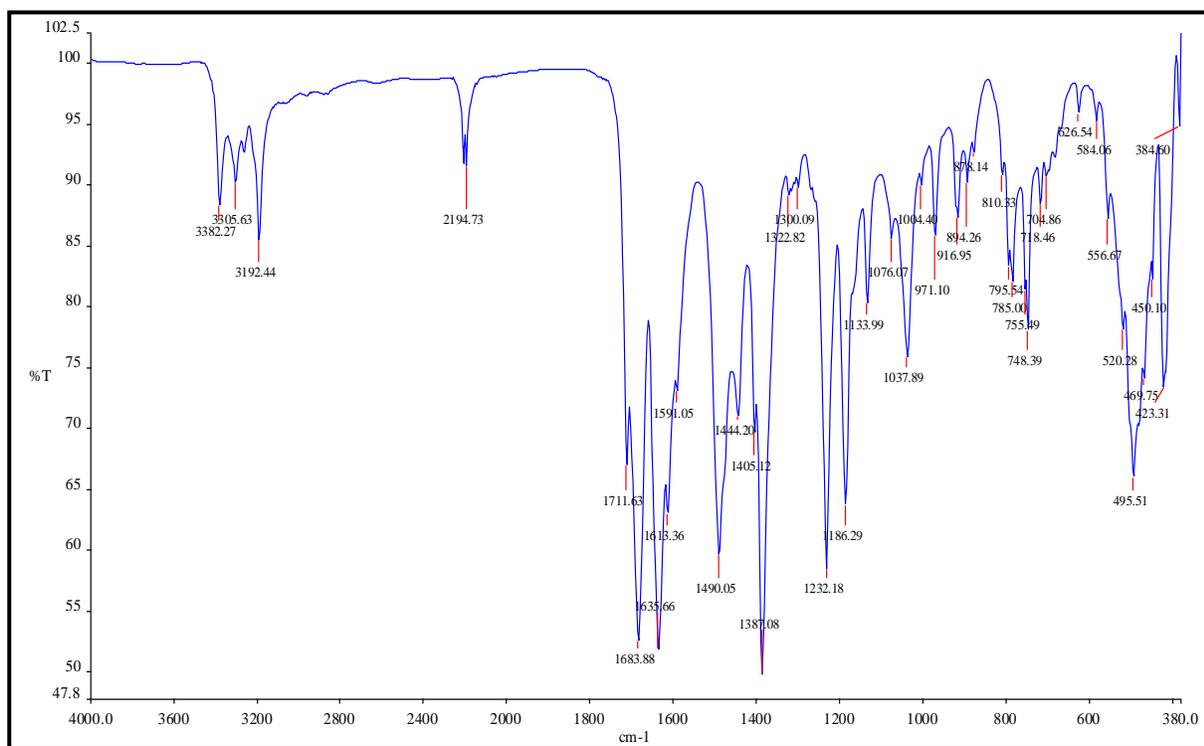
¹H NMR spectra of compound 4k



¹³C NMR spectra of compound 4k



¹⁵N NMR (GHSQC) spectra of compound 4k



FT-IR spectra of compound 4k

CHAPTER-4

Ce-V/SiO₂ catalyzed cascade for C–C and C–O bond activation: Green one-pot synthesis of 2-amino-3-cyano-4*H*-pyrans

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	DOI: 10.1002/open.201500159	
Ceria–Vanadia/Silica-Catalyzed Cascade for C–C and C–O Bond Activation: Green One-Pot Synthesis of 2-Amino-3-cyano-4<i>H</i>-pyrans		
Surya Narayana Maddila, Suresh Maddila, Werner E. van Zyl, and Sreekantha B. Jonnalagadda* ^[a]		

This chapter is published in the journal of **ChemistryOpen** and has been structured according to the journal's format.

Ce-V/SiO₂ catalyzed cascade for C–C and C–O bond activation:

Green one-pot synthesis of 2-amino-3-cyano-4*H*-pyrans

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Abstract

An efficient green protocol for the synthesis of the 2-amino-3-cyano-4*H*-pyran derivatives employing a multicomponent one-pot condensation reaction of 5,5-dimethylcyclohexane-1,3-dione, aromatic aldehyde and malononitrile was designed using a Ce-V/SiO₂ heterogeneous catalyst in the of the eco-compatible solvent (ethanol). The catalyst was synthesised and fully characterized by PXRD, TEM, SEM and BET surface area analysis. The reported procedure offers a number of advantages including reduced reaction times, mild conditions, high yields, operational simplicity, and environmentally benign and simple work-up procedures. Furthermore, the catalyst is economical, fully recyclable and reusable for over 5 runs while preserving its high activity.

Keywords: Green protocol, 4*H*-pyrans, Multicomponent synthesis, Ce-V/SiO₂, Recyclable

4.1. Introduction

Multicomponent reactions (MCRs) are exciting new synthetic protocols geared toward heterocyclic scaffolds as building blocks of biological and medicinal importance [1,2]. MCR have many advantages over conventional linear-type syntheses by virtue of their convergence, productivity, facile execution, and high yields [3]. Moreover, MCRs conform green principles such as one-pot conversions and atom efficiency, in addition to other conditions opted for synthesis of heterocyclics [4]. These single-step processes have distinctive suppleness in generating molecular diversity combined with minimization of time, cost efficiency plus moderate reaction conditions.

In the recent past, heterogeneous mixed metal oxide catalysts started to receive greater attention. Such systems are successfully utilised in the augmentation of heterocyclic synthesis and green reaction protocols [5]. Heterogeneous catalytic processes based on metal oxide catalysts are simpler, highly efficient and eco-friendly with greater selectivity [6]. Heterogeneous catalysts possess added advantages such as thermal stability, shape selectivity, acidic or basic nature, non-toxic crystalline solid and easy handling [6]. Easy salvage and reusability are additional benefits. Hence, considering current legislation and industry needs, heterogeneous catalysts is a notable option for one-pot synthesis involving multicomponent reactions.

Silica (SiO_2) is an efficient and cheap support material, which can readily promote the activity of the supported metal catalysts. SiO_2 has good acid-base properties, has a non-toxic nature and high chemical thermal stability [7]. It has high surface area and carries a vast concentration of active sites. SiO_2 by itself or in combination with metals (composites) have been used in organic synthesis [8]. This acid-based bi-functional catalyst has emerged as an attractive option as support material for the activation and stabilization of ceria and vanadia. The crystalline structure of SiO_2 has been reported as a key factor in explaining the structure-activity relationships of mixed oxides of Ce and V catalysts as the Ce-V/ SiO_2 solid material possesses both Bronsted and Lewis acid centers [9].

Due to variety of therapeutic, pharmacological, biological and agricultural applications for heterocyclics in the fields of organic, pharmaceutical, medicinal and combinatorial chemistry, heterocyclic compounds as catalysts have gained importance [10,11]. The pyrans and benzopyrans received significant attention in heterocyclic synthesis [12], as they possess an oxygen heteroatom and exhibit diverse biological properties such as anti-bacterial and antifungal

[13], anticancer [14], anti-inflammatory [15], antirheumatic [16], anti-HIV [17], and anti-Alzheimer activities [18] and is also used for treatment of disorder in the central nervous system [19]. Applications of pyran containing compounds as ligands in coordination chemistry, herbicidal, and insecticidal in pesticide chemistry are also well-documented. Thus, the synthesis of substituted pyran derivatives has been the topic of many research investigations and several approaches have been pursued using various catalysts, including HMTAB [20], $H_6P_2W_{12}O_{62}.H_2O$ [21], $RE(PFO)_3$ [22], phenylboronic acid [23], PPA-SiO₂ [24], per-6-amino- β -cyclodextrin [25], L-proline [26], DMAP [27], Bmim[BF₄] [28], MNP@P[imEt][Br] [29], TBAF [30] amongst others. However, many of these procedures have one or more drawbacks such as moderate yields, requirement of expensive reagents, toxic organic solvents, stoichiometric catalysts, extreme reaction conditions, lengthy procedures or long reaction times,. Moreover, in many cases, the catalysts used are not recyclable. Therefore, the development of an effective and facile procedure with high generality for the synthesis of 4*H*-pyrans would be timely and of considerable interest.

In continuing our research in developing new methodologies for synthesis of heterocycles [31,32] we here communicate an efficient method for the synthesis of 2-amino-3-cyano-4*H*-pyran derivatives (4a-k) in high yields in the presence of a Ce-V/SiO₂ heterogeneous and reusable catalyst under green conditions.

4.2. Experimental procedure

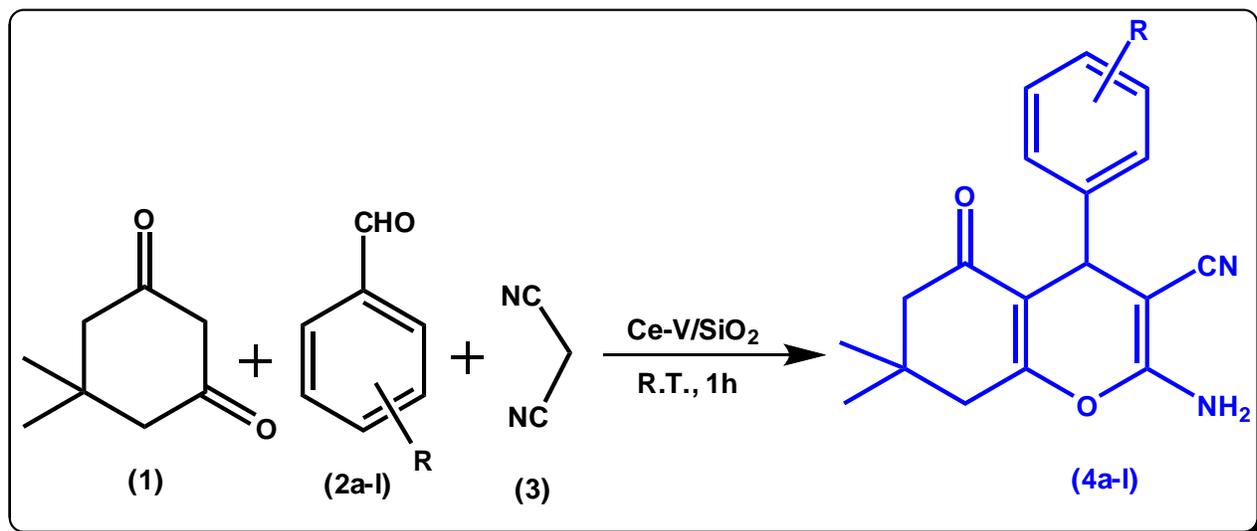
4.2.1 Catalyst preparation

Ce-V loaded silica mixed oxide (Ce-V) with a Ce:V molar ratio of 1:1 was synthesised by the wet impregnation method [33,34]. Cerium nitrate, Ce(NO₃)₃.6H₂O, (Aldrich-99%) and vanadyl sulfate, VOSO₄.xH₂O, (Aldrich-97%) were dissolved in 50 mL distilled water and this was followed by 2.0 g of silica (SiO₂, Aldrich) added to the mixture. The reaction mixture was continuously stirred for 4 h at room temperature (RT) and the mixture was further dried in an oven at 110 °C overnight and then calcined in air flow at 500 °C for 4 h to obtain the various 1, 2 and 4 wt % of mixed oxides of Ce and V loaded silica catalysts.

4.2.2 General procedure for the synthesis of 2-amino-3-cyano-4*H*-pyran derivatives

A mixture of 5,5-dimethylcyclohexane-1,3-dione **1** (1 mmol), aromatic aldehyde **2** (1 mmol), malononitrile **3** (1.1 mmol) were dissolved in EtOH (10 mL) at RT. The 2% Ce-V/SiO₂ catalyst (30 mg) was added to the reaction mixture and continuously stirred for 1 h. The

completion of the reaction mixture was monitored by thin-layer chromatography (TLC) analysis (**Scheme 1**). After completion of the reaction, the solid heterogeneous catalyst was filtered. The attained catalyst was washed with acetone and dried under reduced pressure in 70-80 °C for 2 h and kept aside for use in the next reaction. The filtrate was concentrated to obtain the crude product and purified by recrystallization in ethanol to afford compounds.



Scheme 1: Synthesis of 2-amino-3-cyano-4*H*-pyran derivatives

4.3. Results and discussion

To establish the optimum reaction conditions, to maximize the yield and reduce reaction times, the reaction was investigated under varied conditions of catalysts and solvents. The initial experiment was conducted with 5,5-dimethylcyclohexane-1,3-dione **1** (1 mmol), benzaldehyde **2a** (1 mmol) and malononitrile **3** (1.2 mmol) in aqueous media, without any catalyst at RT, and no reaction was observed. Even after 24 h under reflux conditions, the reaction showed no product (Table 1, entries 1 and 2). The same reaction was repeated with ethanol as solvent, but no product was obtained even after 12 h (Table 1, entry 3). Interestingly, a trace amount of the predicted product was observed, when MgO, Mn/Al₂O₃ or V/Al₂O₃ were used as catalysts in the ethanol media (Table 1, entry 4-6), but no reaction was apparent in presence of strongly basic catalysts, such as piperidine or K₂CO₃ and ethanol as solvent (Table 1, entries 7 & 8). The acidic catalysts PTSA, SiO₂ and ZnCl₂ were attempted, but found to be less effective as reactions gave only 21–34% yield of the expected product (Table 1, entries 9-11). The scope of reaction in the presence of the L-proline and also ionic liquids such as (Bmim)BF₄ and (Bmim)OH was also explored, but yields were low (Table 1, entries 12-14). With CeO₂/SiO₂ and V₂O₅/SiO₂ as a

catalyst in ethanol, yields of 55% and 58% were obtained (Table 1, entries 15, 16). This could be due to the high surface area of V_2O_5 on silica than Ce on silica which increases the availability of vanadium active sites for the reaction. Further, we examined $HClO_4/SiO_2$ catalyst to afford less yield 45%. Then, we investigated the range of Ce-V/ SiO_2 which is a bi-functional acid/base catalyst with ethanol as solvent. The reaction was repeated under similar conditions using Ce-V/ SiO_2 which gave an excellent yield of 95% in 1 h once optimum dopant percentage had been established. The impact of cerium, vanadia loading on silica in tuning its catalytic efficiency was further investigated. To find the ideal loading of Ce-V on SiO_2 on catalyst activity, reactions with 1%, 2% and 4% Ce-V doped SiO_2 were carried out under otherwise comparable conditions. The percentage of Ce-V loading was found to have an influence on the reaction yield as well as reaction time (Table 1, entries 18-20). Using 1% Ce-V/ SiO_2 catalyst yielded 79% product in 2.5 h under EtOH solvent conditions (Table 1, entry 18). A 2% Ce-V loading was found optimal with 95 % yield in 1 h (Table 1, entry 19). A further increase of metals (4%) loading led to a slight decreased yield (89%) (Table 1, entry 20). We were pleasantly surprised to discover the MCR was successful in only 1 h and at RT. The expected substituted pyrans (**4a**) were produced selectively and in good yield (95%) (Table 1, entry 19). Although it took about 1 h for the reaction for completion, the Ce-V/ SiO_2 catalysed reaction was found to start almost immediately. Reaction products were identified and confirmed by spectral and other analytical data. Excellent selectivity and yield could be achieved due the nature of the chosen catalyst with high surface area, which has presumably enhanced the accessibility of the substrate to the anchored acidic and basic groups.

The surface properties of the SiO_2 can be modified by loading cations of various properties. An optimal distribution of the acidic and basic sites due to loading of Ce-V on SiO_2 possibly contributed to its enhanced catalytic efficiency, which is evident from the high yield, selectivity and speed of the reaction achieved in the title reaction. In the proposed MCR, we speculate that the Ce-V/ SiO_2 catalyst display greater efficiency compared to the other catalysts investigated due to a synergetic effect between ceria and vanadia.

Taking advantage of proven performance of 2% Ce-V/ SiO_2 as catalyst for the MCR, we then focused on further improving the reaction efficiency. We screened for changes in the variation of catalyst Ce-V loading on silica support. The results are summarised (Table 2, entries 1-3) which indicate that an increase in loading of Ce-V on SiO_2 from 10 mg to 30 mg, resulted in

an increased yield from 71% to 95%. A further increase in loading of catalyst had only a marginal effect on product yield (Table 2, entries 4 & 5).

Table 1: Optimization condition for the synthesis of 2-amino-3-cyano-4*H*-pyran derivatives by Ce-V/SiO₂ catalyst^a

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%) ^b
1	No catalyst	H ₂ O	RT	24	--
2	No catalyst	H ₂ O	Reflux	24	--
3	No catalyst	EtOH	Reflux	12	--
4	MgO (50 mg)	EtOH	Reflux	10	Trace
5	Mn/Al ₂ O ₃ (50 mg)	EtOH	Reflux	12	Trace
6	V/Al ₂ O ₃ (50 mg)	EtOH	Reflux	12	Trace
7	Piperidine	EtOH	Reflux	12	--
8	K ₂ CO ₃	EtOH	Reflux	12	--
9	PTSA	EtOH	Reflux	7	21
10	SiO ₂	EtOH	Reflux	8	27
11	ZnCl ₂	EtOH	Reflux	5	34
12	L-proline	EtOH:H ₂ O	Reflux	4.5	38
13	(Bmim)BF ₄	EtOH:H ₂ O	Reflux	4	32
14	(Bmim)OH	EtOH:H ₂ O	Reflux	4	29
15	CeO ₂ /SiO ₂	EtOH	RT	2	55
16	V ₂ O ₅ /SiO ₂	EtOH	RT	2	58
17	HClO ₄ /SiO ₂	EtOH	RT	2.5	45
18	1% Ce-V/SiO ₂ (30 mg)	EtOH	RT	2.5	79
19	2% Ce-V/SiO ₂ (30 mg)	EtOH	RT	1	95
20	4% Ce-V/SiO ₂ (30 mg)	EtOH	RT	1	89
21	2% Ce-V/SiO ₂ (30 mg)	MeOH	RT	2	89
22	2% Ce-V/SiO ₂ (30 mg)	CH ₃ COCN	RT	2.5	78
23	2% Ce-V/SiO ₂ (30 mg)	DMF	RT	2.5	86
24	2% Ce-V/SiO ₂ (30 mg)	THF	RT	3	69
25	2% Ce-V/SiO ₂ (30 mg)	Toluene	RT	4	65

^aAll products were characterised by IR, ¹H NMR, ¹³C NMR, ¹⁵N NMR and HR-MS spectral analysis.

^bIsolated yields.

-- No reaction

Secondly, because solvents play an important role in design of MCRs, we also studied the influence of solvent in the title reaction. Efficiency of diverse solvents including methanol, acetonitrile, DMF, tetrahydrofuran, and toluene were compared under otherwise identical reaction conditions. We found that reaction proceeded smoothly in protonic solvents. Among all

the screened solvents, EtOH was found to be superior solvent for this multicomponent reaction. It is noteworthy to mention that from the results of optimization (Table 1, entries 21-25), the reaction temperature and polarity of the solvent appear to be important for this multicomponent reaction to achieve clean products in good to excellent yields. Polar protic solvents enhance the rate of reaction, whereas for the non-polar solvents the rate of the reaction was sluggish.

Table 2:

Optimization of the amount of 2% Ce-V loading on SiO₂ as catalyst in the reaction

Entry	Catalyst (mg)	Time (h)	Yield (%)
1	Ce-V/SiO ₂ (10 mg)	2.5	86
2	Ce-V/SiO ₂ (20 mg)	2.0	89
3	Ce-V/SiO ₂ (30 mg)	1	95
4	Ce-V/SiO ₂ (40 mg)	1	95
5	Ce-V/SiO ₂ (50 mg)	1.5	94

Table 3:

Synthesis of 2-amino-3-cyano-4*H*-pyran derivatives catalyzed by Ce-V/SiO₂ catalyst

Entry	R	Product	Yield (%)	Mp °C	Lit Mp °C
1	3-OMe	4a	92	210-212	--
2	4-OMe	4b	93	201-202	201-202 [30]
3	2-Br	4c	89	197-198	--
4	4-Br	4d	92	204-206	--
5	3-Cl	4e	94	210-211	--
6	2,3-(OMe) ₂	4f	90	215-217	--
7	2,4-(OMe) ₂	4g	92	220-221	--
8	3,4-(OMe) ₂	4h	90	208-209	--
9	2,4,6-(OMe) ₃	4i	91	232-234	--
10	H	4j	95	232-234	234-235 [30]
11	2-Furyl	4k	93	224-226	--
12	2-NO ₂	4l	87	231-232	--

^aReaction conditions: 5,5-dimethylcyclohexane-1,3-dione (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1.1 mmol) and EtOH (10 mL), RT.

^bAll synthesized compounds are identified and their structures were conformed with IR, ¹H NMR, ¹³C NMR, ¹⁵N NMR and HR-MS spectral data and melting points as compared with literature values.

-- New compounds/no literature available.

The wider scope of this MCR was further explored with other reagents. Choosing the optimised conditions for the synthesis of **4a**, i.e. 30 mg of Ce-V/SiO₂ at RT and ethanol as solvent (**Scheme 1**), we investigated the reactions with varied structurally different aldehydes (**2a-l**) for the MCR. To our delight, most of the reactions afforded the desired 2-amino-3-cyano-4*H*-pyran derivatives with excellent selectivity (**4a-l**) and yields (87–95%), and with no byproducts. The results are summarised in Table 3. Interestingly, the MCRs with substrates bearing both electron donating or electron-withdrawing groups on the aromatic ring performed well and gave corresponding target molecules in excellent yields. Structures of all the products (**4a-l**) were established and confirmed on the basis of their spectral data, ¹H NMR, ¹³C NMR, ¹⁵N NMR (GHSQC), FTIR and HRMS. The details of the product characterization are presented in the ESI.

4.3.1. X-Ray diffraction (XRD)

Figure 1 shows the XRD patterns of the Ce-V/SiO₂ powder catalyst calcined at 450 °C. The CeO₂ diffraction peaks at 2θ = 29.6°, 31.7°, 36.5°, 49.1° and 67.2° compare well with the standard database file (JCPDS34-0394). The mixed oxide shows the Ce-VO₄ phase in accord with the standard database file JCPDS12-757, with sharp diffraction peaks at 2θ = 22.2°, 26.2°, 32.2°, 42°, 54.6° and 71.8°. As can be seen from the figure, the vanadium oxide sample showed sharp diffraction peaks at 2θ = 17.3°, 29.1°, 38.1° and 49° (JCPDS41-1426). There are no other peaks, except V₂O₅, CeO₂, and CeVO₄ in XRD patterns for the Ce-V/SiO₂ sample, implying bulk purity.

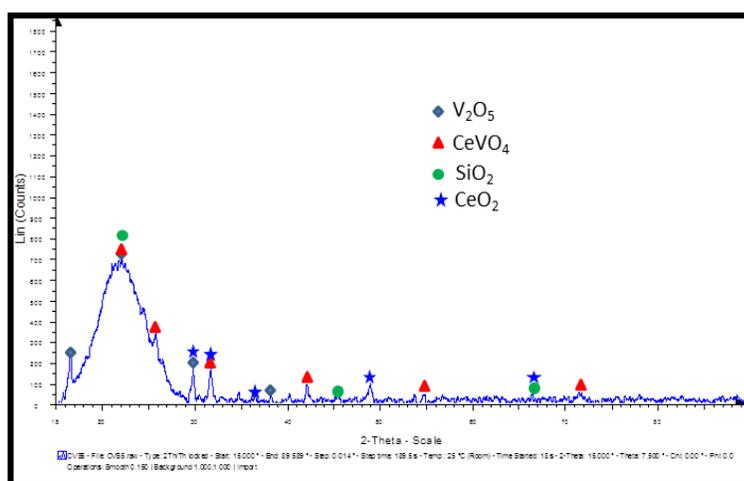


Figure 1. XRD spectra of Ce-V/SiO₂ catalyst

4.3.2. SEM, TEM and ICP-OES analysis

The SEM micrograph (Figure 2a) displays agglomeration of metal oxide particles which is caused by the calcination of the Ce-V/SiO₂ catalyst and these aggregates are in the size range from 0.81–2.00 μm. EDS semi-quantitative analysis of this catalyst showed that Ce and V are homogeneously distributed in the catalyst (Figure 2b), and the metal ratio (Ce:V:Si) is also in agreement with the ICP elemental analysis. The catalyst morphologies as indicated by the SEM image clearly point out the homogeneity in shapes for the sample and high crystallinity. ICP-OES analysis showed that the cerium to vanadium metal ratio is equal. TEM micrograph (Figure 3) showed that calcined catalyst has a cubic-like structure, which is characteristic of typical vanadate. These cubic planar structures are in the size of 21 ± 3 nm. The selected area diffractions showed that catalyst is polycrystalline in nature, which is further supported by the XRD diffractogram.

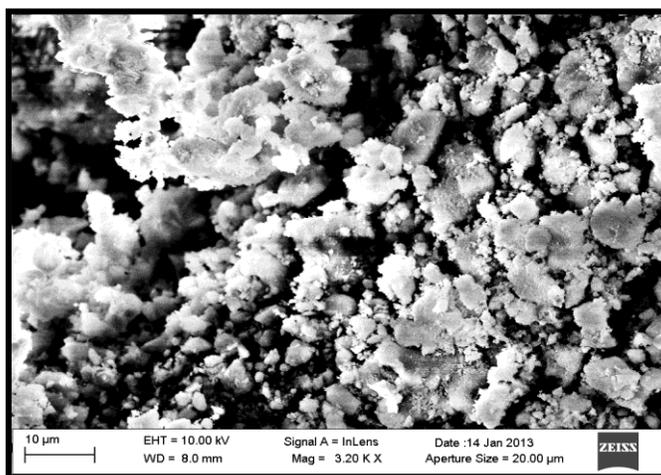


Figure 2a. SEM image of Ce-V/SiO₂ catalyst

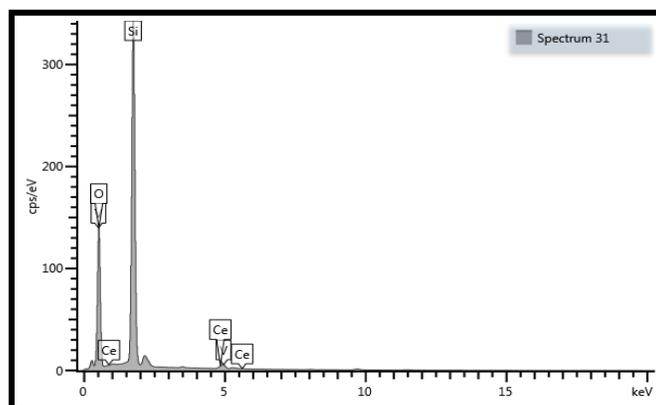


Figure 2b. SEM-EDX image of Ce-V/SiO₂ catalyst

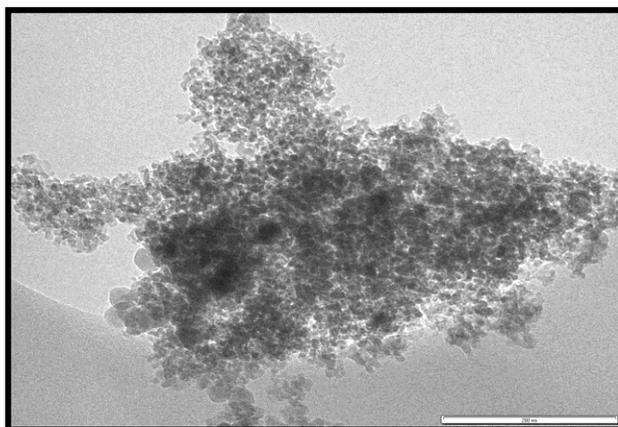


Figure 3. TEM spectra of Ce-V/SiO₂ catalyst

4.3.3. BET surface area

The nitrogen adsorption–desorption isotherms for the Ce-V/silica supported catalyst are shown in Figure 4. All the prepared catalysts have a similar pattern in adsorption–desorption isotherms and display the characteristic hysteresis loop of a type-IV isotherm (IUPAC) lying in the p/p° range of 0.7–0.85, demonstrating mesoporous character and indicates a small pore size and good homogeneity of the catalyst. A quite narrow and monomodal pore size distribution was obtained for the Ce-V doped on silica. This further indicated that the average pore size has increased with increasing the loading amount of silica. For the 2 wt% Ce-V loaded catalyst the parameters are specific surface area (17.1 m²/g), pore size (0.0139 cm³/g) and total pore volume (74 Å³). The low surface area of the prepared catalysts with compared to the bare silica support was probably due to the good dispersion of Ce-V on the surface of silica.

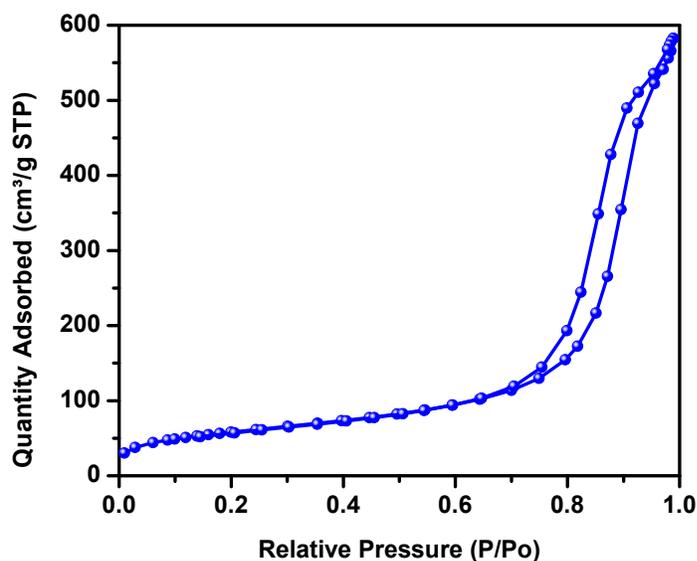


Figure 4. N₂ adsorption & desorption spectra and pore size distribution of Ce-V/SiO₂ catalyst

4.3.4. Reusability of the catalyst

The reusability of any heterogeneous catalyst is one of the important parameters for potential commercial adaptation. The reusability of the catalyst was assessed in the synthesis of 2-amino-3-cyano-4*H*-pyran derivatives (**Figure 5**). Gratifyingly, the heterogeneous Ce-V/SiO₂ could be recovered effectively from the reaction mixture by simple filtration and by washing the catalyst twice with acetone and dried at 70-80 °C under reduced pressure for 2 h to make it ready for a later run. There is no loss of Ce-V loading on silica was observed which is confirmed by ICP-OES analysis. The catalyst was tested for six runs. It was observed that recovered catalyst can be recycled in subsequent runs with minimal loss of its activity only after five runs which might be due to the agglomeration of Ce-V.

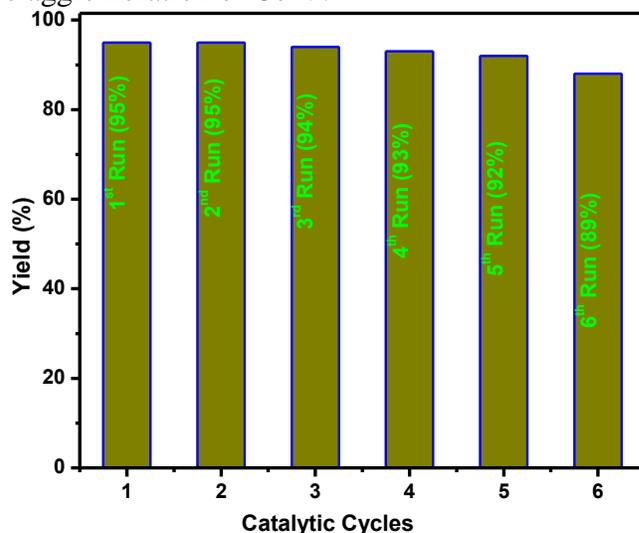


Figure 5. Recyclability of Ce-V/SiO₂ catalyst

4.4. Conclusion

In conclusion, we report an environmentally benign and an efficient one-pot multicomponent green synthesis of 2-amino-3-cyano-4*H*-pyran derivatives using Ce-V/SiO₂ as catalyst in green solvent media and with good atom efficiency. This simple and recyclable heterogeneous catalyst, Ce-V/SiO₂ shows high catalytic activity for multicomponent reactions. The current method deals several advantages such as short reaction time, excellent yields, purity of products, cost-effectiveness, use of small amount of inexpensive catalyst and environmentally benign green solvent.

4.5. Acknowledgements

Authors are grateful to the National Research Foundation (South Africa) for financial support and University of KwaZulu-Natal for the research facilities.

4.6. References

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4.7. Supplementary materials data

4.7.1. Materials, methods and instruments

All chemicals and reagents required for the reaction were of analytical grade and were used without any further purification. Bruker AMX 400 MHz NMR spectrometer was used to record the ^1H NMR, ^{13}C NMR and ^{15}N NMR spectral values. High-resolution mass data were obtained using a Bruker micro TOF-Q II ESI instrument operating at ambient temperature. The DMSO- d_6 solution was utilized for this while TMS served as the internal standard. TMS was further used as an internal standard for reporting the all chemical shifts in δ (ppm). The FT-IR spectrum for the samples was established using a Perkin Elmer Precisely 100 FT-IR spectrometer at the 400-4000 cm^{-1} area. Purity of all the reaction products was confirmed by TLC using aluminum plates coated with silica gel (Merck Kieselgel 60 F254).

4.7.2. Characterization of catalysts

Bruker D8 advance instrument with a Cu K radiation source by $\lambda = 1.5406$ was used for the X-ray diffraction data for the catalyst. Jeol JEM-1010 electron microscope and JEOL JSM-6100 microscope were used for TEM and SEM analysis respectively. In TEM analysis for particles distribution, size of 40-60 particles were averaged and with standard deviation. An emission current (100 μA) by a Tungsten (W) filament with 12 kV accelerator voltage was employed for EDX-analysis of the SEM images. Elemental composition of the catalyst materials was established by using Inductively Coupled Plasma Optical Emission Spectrometer (Optima 5300 DV). Micromeritics Tristar-II porosity and surface area analyzer was used estimation of pore size, pore volume and surface area of the catalysts. BJH adsorption-desorption curves were obtained at $-196\text{ }^\circ\text{C}$, to assess the particulate properties of the catalyst. All the catalyst materials were degassed by passing nitrogen overnight at $200\text{ }^\circ\text{C}$.

4.7.3. Physical data of compounds

2-Amino-4-(3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-

carbonitrile (4a): White solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 0.96 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.05 (d, J = 16.02 Hz, 1H, CH₂), 2.24 (d, J = 16.02 Hz, 1H, CH₂), 2.44 (d, J = 17.16 Hz, 1H, CH₂), 2.54 (d, J = 17.16 Hz, 1H, CH₂), 3.74 (s, 3H, OCH₃), 4.47 (s, 1H, CH), 6.80 (s, 2H, NH₂), 6.85 (d, J = 7.04 Hz, 1H, ArH), 6.93-6.99 (m, 2H, ArH), 7.15 (t, J = 7.64, 1H, ArH); ^{13}C NMR (100 MHz, CDCl₃): δ 26.51, 28.57, 30.29, 31.73, 50.00, 55.76, 57.34, 111.44, 111.85, 119.80, 120.29, 127.77, 128.51, 132.11, 156.79, 158.95, 163.06, 195.55; IR (KBr, cm^{-1}): 3469, 3323, 3183, 2933, 2198, 1682, 1367, 1244; HRMS of $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3 - \text{H}]^+$ (m/z): 323.1397; Calcd.: 323.1396.

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-

carbonitrile (4b): White solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 0.94 (s, 3H, CH₃), 1.02 (s, 3H, CH₃), 2.08 (d, J = 16.04 Hz, 1H, CH₂), 2.28 (d, J = 17.52 Hz, 1H, CH₂), 2.43 (d, J = 16.24 Hz, 1H, CH₂), 2.54 (d, J = 17.52 Hz, 1H, CH₂), 3.70 (s, 3H, OCH₃), 4.11 (s, 1H, CH), 6.83 (d, J = 8.24 Hz, 2H, ArH), 6.93 (s, 2H, NH₂), 7.04 (d, J = 8.04, 1H, ArH); ^{13}C NMR (100 MHz, CDCl₃): δ 26.72, 28.36, 31.73, 34.71, 49.97, 54.95, 58.54, 112.95, 113.63, 119.76, 128.17, 133.34, 136.80, 157.87, 158.37, 160.44, 162.11, 195.65; IR (KBr, cm^{-1}): 3368, 3307, 3181, 2965, 2188, 1650, 1367, 1241; HRMS of $[\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_3 - \text{H}]^+$ (m/z): 323.1057; Calcd.: 323.1059.

2-Amino-4-(2-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-

carbonitrile (4c): White solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 0.98 (s, 3H, CH₃), 1.04 (s, 3H, CH₃), 2.07 (d, J = 16.00 Hz, 1H, CH₂), 2.24 (d, J = 16.04 Hz, 1H, CH₂), 2.46 (d, J = 16.24 Hz, 1H, CH₂), 2.57 (d, J = 17.52 Hz, 1H, CH₂), 4.70 (s, 1H, CH), 7.01 (s, 2H, NH₂), 7.11-7.13 (m, 2H, ArH), 7.32 (t, J = 7.89 Hz, 1H, ArH), 7.52 (d, J = 7.16, 1H, ArH); ^{13}C NMR (100 MHz, CDCl₃): δ 26.93, 28.31, 31.73, 34.94, 49.91, 57.04, 112.05, 119.09, 122.65, 128.04, 128.43, 132.59, 143.32, 158.55, 163.03, 195.52; IR (KBr, cm^{-1}): 3375, 3322, 3192, 2967, 2189, 1651, 1366, 1212; HRMS of $[\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2\text{Br} - 2\text{H}]^+$ (m/z): 371.0389; Calcd.: 371.0395.

2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-

carbonitrile (4d): White solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 0.94 (s, 3H, CH₃), 1.02 (s,

3H, CH₃), 2.09 (d, *J* = 16.00 Hz, 1H, CH₂), 2.24 (d, *J* = 16.00 Hz, 1H, CH₂), 2.42 (d, *J* = 16.24 Hz, 1H, CH₂), 2.53 (d, *J* = 17.02 Hz, 1H, CH₂), 4.17 (s, 1H, CH), 7.04 (s, 2H, NH₂), 7.10 (d, *J* = 7.64 Hz, 2H, ArH), 7.46 (d, *J* = 7.45, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 26.82, 28.26, 31.75, 35.15, 49.90, 57.67, 112.21, 119.51, 119.57, 129.47, 131.17, 144.13, 158.44, 162.62, 195.68; IR (KBr, cm⁻¹): 3376, 3320, 3187, 2963, 2133, 1652, 1367, 1251.

2-Amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-

carbonitrile (4e): White solid: ¹H NMR (400 MHz, DMSO-d₆) δ = 0.97 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.07 (d, *J* = 16.04 Hz, 1H, CH₂), 2.24 (d, *J* = 16.04 Hz, 1H, CH₂), 2.46 (d, *J* = 16.99 Hz, 1H, CH₂), 2.52 (d, *J* = 17.36 Hz, 1H, CH₂), 4.68 (s, 1H, CH), 7.01 (s, 2H, NH₂), 7.15-7.19 (m, 2H, ArH), 7.21 (t, *J* = 7.78, 1H, ArH), 7.27 (d, *J* = 7.47, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 26.83, 28.36, 31.72, 32.81, 49.89, 56.78, 111.73, 119.21, 127.40, 128.18, 129.41, 129.91, 132.04, 141.51, 158.63, 163.13, 195.55; IR (KBr, cm⁻¹): 3375, 3322, 3189, 2961, 2190, 1652, 1366, 1250; HRMS of [C₁₈H₁₆N₂O₂Cl - H]⁺ (m/z): 327.0894; Calcd.: 327.0900.

2-Amino-4-(2,3-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-

carbonitrile (4f): White solid: ¹H NMR (400 MHz, DMSO-d₆) δ = 0.97 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.06 (d, *J* = 16.00 Hz, 1H, CH₂), 2.22 (d, *J* = 16.04 Hz, 1H, CH₂), 2.44 (d, *J* = 16.24 Hz, 1H, CH₂), 2.54 (d, *J* = 17.52 Hz, 1H, CH₂), 3.78 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 4.53 (s, 1H, CH), 6.57 (d, *J* = 7.64 Hz, 1H, ArH), 6.83 (s, 2H, NH₂), 6.85 (d, *J* = 6.81 Hz, 1H, ArH), 6.94 (t, *J* = 7.92, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 26.81, 28.35, 29.35, 31.77, 50.01, 55.48, 57.93, 59.97, 110.97, 112.58, 119.79, 120.10, 123.63, 146.01, 152.16, 158.66, 162.77, 195.65; IR (KBr, cm⁻¹): 3382, 3305, 3192, 2958, 2194, 1683, 1387, 1232.

2-Amino-4-(2,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-

carbonitrile (4g): White solid: ¹H NMR (400 MHz, DMSO-d₆) δ = 0.97 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.06 (d, *J* = 16.08 Hz, 1H, CH₂), 2.24 (d, *J* = 16.08 Hz, 1H, CH₂), 2.46 (d, *J* = 17.70 Hz, 1H, CH₂), 2.52 (d, *J* = 17.70 Hz, 1H, CH₂), 3.64 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃), 4.43 (s, 1H, CH), 6.50 (d, *J* = 7.01 Hz, 1H, ArH), 6.71 (d, *J* = 7.05 Hz, 1H, ArH), 6.81 (s, 2H, NH₂), 6.87 (d, *J* = 8.92 Hz, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 26.42, 28.60, 30.26, 31.71, 49.97, 55.15, 56.23, 57.28, 111.53, 111.73, 112.62, 114.77, 119.73, 133.41, 151.01, 153.04, 158.92,

163.16, 195.60; IR (KBr, cm^{-1}): 3384, 3311, 3194, 2962, 2195, 1683, 1389, 1234; HRMS of $[\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_4 - \text{H}]^+$ (m/z): 353.0844; Calcd.: 353.0838.

2-Amino-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4h): White solid: ^1H NMR (400 MHz, DMSO-d_6) δ = 0.96 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.05 (d, J = 16.32 Hz, 1H, CH_2), 2.25 (d, J = 18.25 Hz, 1H, CH_2), 2.44 (d, J = 17.21 Hz, 1H, CH_2), 2.54 (d, J = 17.21 Hz, 1H, CH_2), 3.69 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.47 (s, 1H, CH), 6.62-6.67 (m, 2H, ArH), 6.85 (d, J = 8.20 Hz, 1H, ArH), 6.92 (s, 2H, NH_2); ^{13}C NMR (100 MHz, CDCl_3): δ 26.58, 28.46, 31.70, 34.99, 49.96, 55.40, 55.45, 58.52, 110.97, 111.75, 112.77, 119.07, 119.76, 137.27, 147.50, 148.42, 158.34, 159.57, 162.31, 195.72; IR (KBr, cm^{-1}): 3384, 3327, 3193, 2934, 2193, 1652, 1363, 1238; HRMS of $[\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_4 - \text{H}]^+$ (m/z): 353.1511; Calcd.: 353.1501.

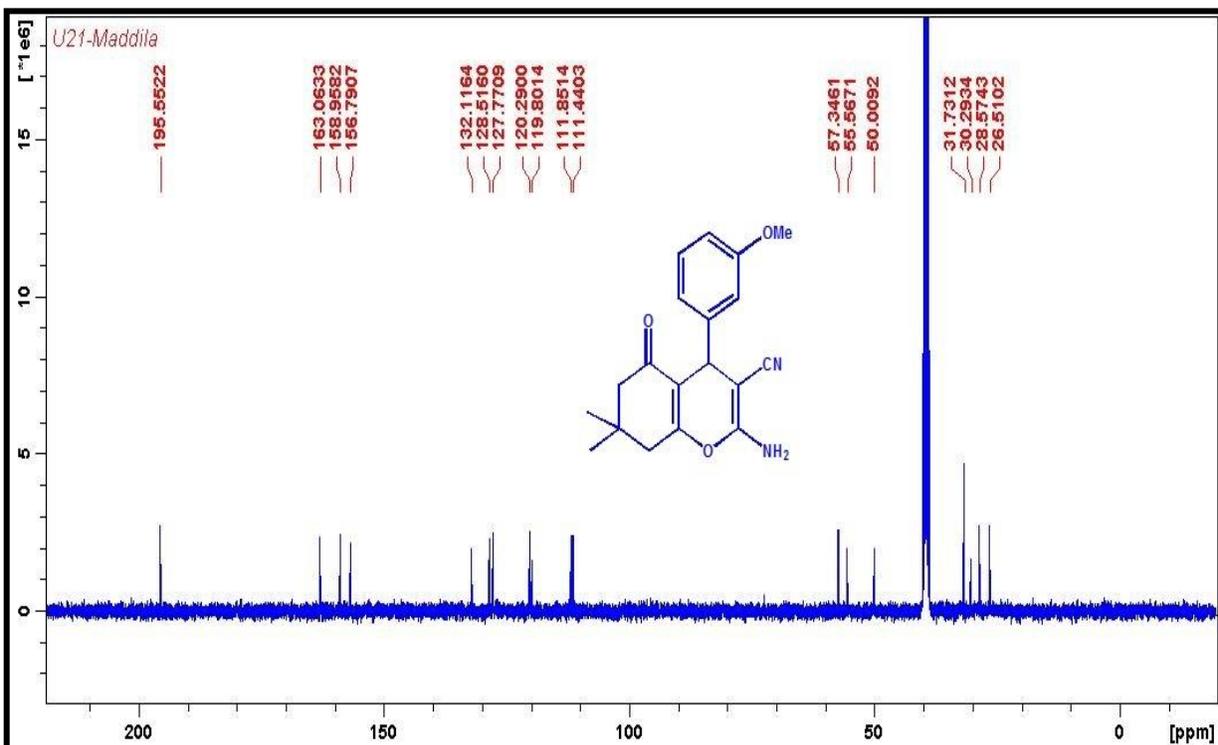
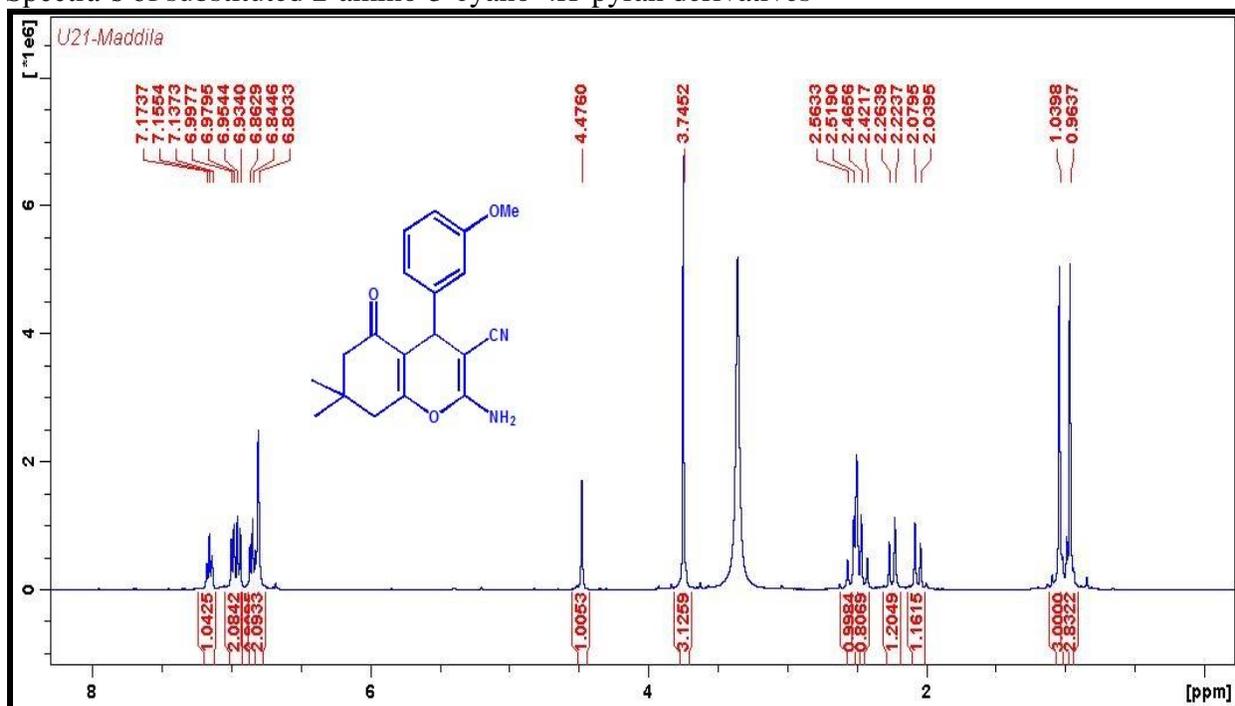
2-Amino-4-(2,4,6-trimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4i): White solid: ^1H NMR (400 MHz, DMSO-d_6) δ = 0.89 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.95 (d, J = 16.04 Hz, 1H, CH_2), 2.21 (d, J = 16.02 Hz, 1H, CH_2), 2.23 (d, J = 16.08 Hz, 1H, CH_2), 2.29 (d, J = 16.32 Hz, 1H, CH_2), 3.72 (s, 3H, OCH_3), 3.88 (s, 6H, 2OCH_3) 4.75 (s, 1H, CH), 6.60 (s, 2H, NH_2), 7.97 (s, 2H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 24.00, 25.86, 28.88, 31.58, 50.21, 55.00, 55.71, 56.12, 91.12, 91.25, 111.66, 111.99, 113.83, 116.36, 150.79, 159.48, 161.37, 162.82, 167.37, 195.42; IR (KBr, cm^{-1}): 3477, 3323, 3173, 2939, 2212, 1651, 1584, 1366, 1226; HRMS of $[\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_5 - 2\text{H}]^+$ (m/z): 383.0103; Calcd.: 383.0093.

2-Amino-4-phenyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4j): White solid: ^1H NMR (400 MHz, DMSO-d_6) δ = 0.95 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.10 (d, J = 16.02 Hz, 1H, CH_2), 2.25 (d, J = 16.02 Hz, 1H, CH_2), 2.49 (d, J = 17.18 Hz, 1H, CH_2), 2.53 (d, J = 17.18 Hz, 1H, CH_2), 4.18 (s, 1H, CH), 6.99 (s, 2H, NH_2), 7.13-7.19 (m, 3H, ArH), 7.28 (t, J = 7.64, 2H, ArH); ^{13}C NMR (100 MHz, CDCl_3): δ 26.77, 28.37, 31.76, 35.55, 49.95, 58.30, 112.72, 119.68, 126.53, 127.11, 128.29, 144.70, 158.46, 162.45, 195.60; IR (KBr, cm^{-1}): 3393, 3322, 3291, 2961, 2199, 1657, 1369, 1248; HRMS of $[\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2 - \text{H}]^+$ (m/z): 293.1302; Calcd.: 293.1290.

2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4k): White solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 0.98 (s, 3H, CH₃), 1.04 (s, 3H, CH₃), 2.16 (d, J = 16.04 Hz, 1H, CH₂), 2.28 (d, J = 16.04 Hz, 1H, CH₂), 2.44 (d, J = 16.00 Hz, 1H, CH₂), 2.53 (d, J = 16.00 Hz, 1H, CH₂), 4.32 (s, 1H, CH), 6.04 (d, J = 6.82 Hz, 1H, ArH), 6.31 (t, J = 7.10 Hz, 1H, ArH), 7.06 (s, 2H, NH₂), 7.47 (d, J = 7.32 Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl₃): δ 26.52, 28.38, 28.95, 31.77, 49.86, 55.76, 105.02, 110.32, 110.40, 119.51, 141.71, 155.69, 159.27, 163.22, 195.38; IR (KBr, cm^{-1}): 3390, 3324, 3213, 2874, 2195, 1655, 1361, 1247; HRMS of $[\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_3 - \text{H}]^+$ (m/z): 283.1079; Calcd.: 283.1083.

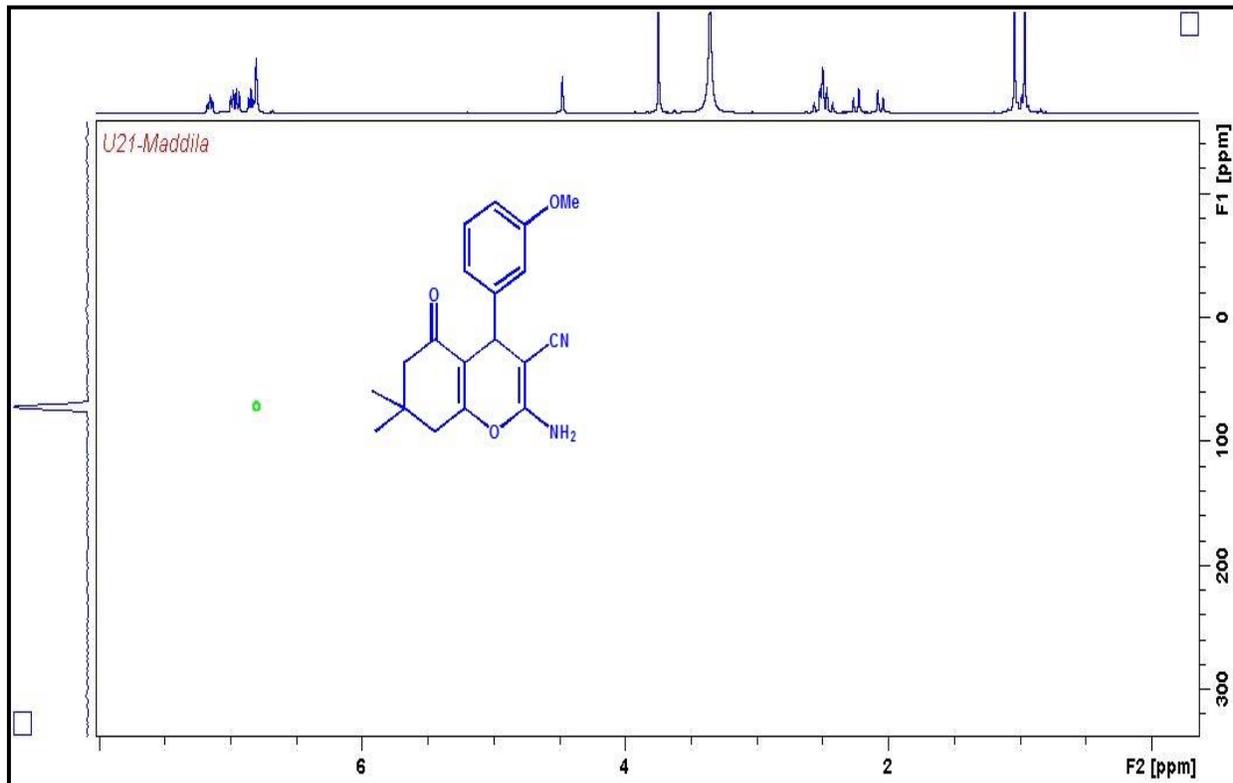
2-Amino-4-(2-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4l): White solid: ^1H NMR (400 MHz, DMSO- d_6) δ = 0.87 (s, 3H, CH₃), 1.00 (s, 3H, CH₃), 2.01 (d, J = 16.02 Hz, 1H, CH₂), 2.19 (d, J = 16.02 Hz, 1H, CH₂), 2.45 (d, J = 16.32 Hz, 1H, CH₂), 2.53 (d, J = 16.32 Hz, 1H, CH₂), 4.91 (s, 1H, CH), 7.18 (s, 2H, NH₂), 7.35 (d, J = 7.27 Hz, 1H, ArH), 7.42 (t, J = 7.25 Hz, 1H, ArH), 7.65 (t, J = 7.78, 1H, ArH), 7.80 (d, J = 7.05 Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl₃): δ 26.65, 28.25, 29.90, 31.80, 49.55, 56.32, 112.28, 119.03, 123.68, 127.82, 130.24, 133.32, 138.93, 148.93, 159.15, 162.68, 195.77; IR (KBr, cm^{-1}): 3393, 3327, 3214, 2964, 2195, 1659, 1364, 1251; HRMS of $[\text{C}_{18}\text{H}_{16}\text{N}_3\text{O}_4 - \text{H}]^+$ (m/z): 338.1141; Calcd.: 338.1141.

Spectra's of substituted 2-amino-3-cyano-4H-pyran derivatives



^1H NMR spectra of compound **4a**

^{13}C NMR 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, Even Electron Ions

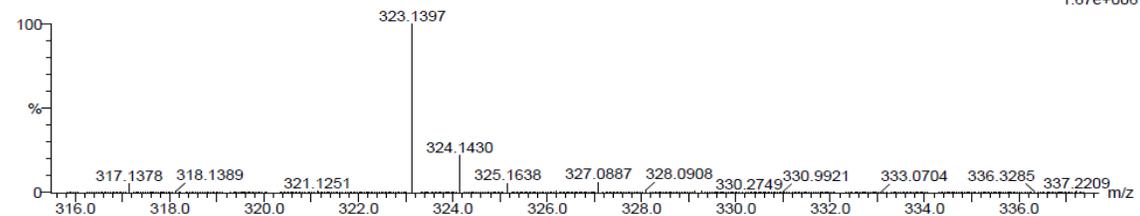
13 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

Elements Used:

C: 15-20 H: 15-20 N: 0-5 O: 0-5

U-21 32 (1.045) Cm (1.61)

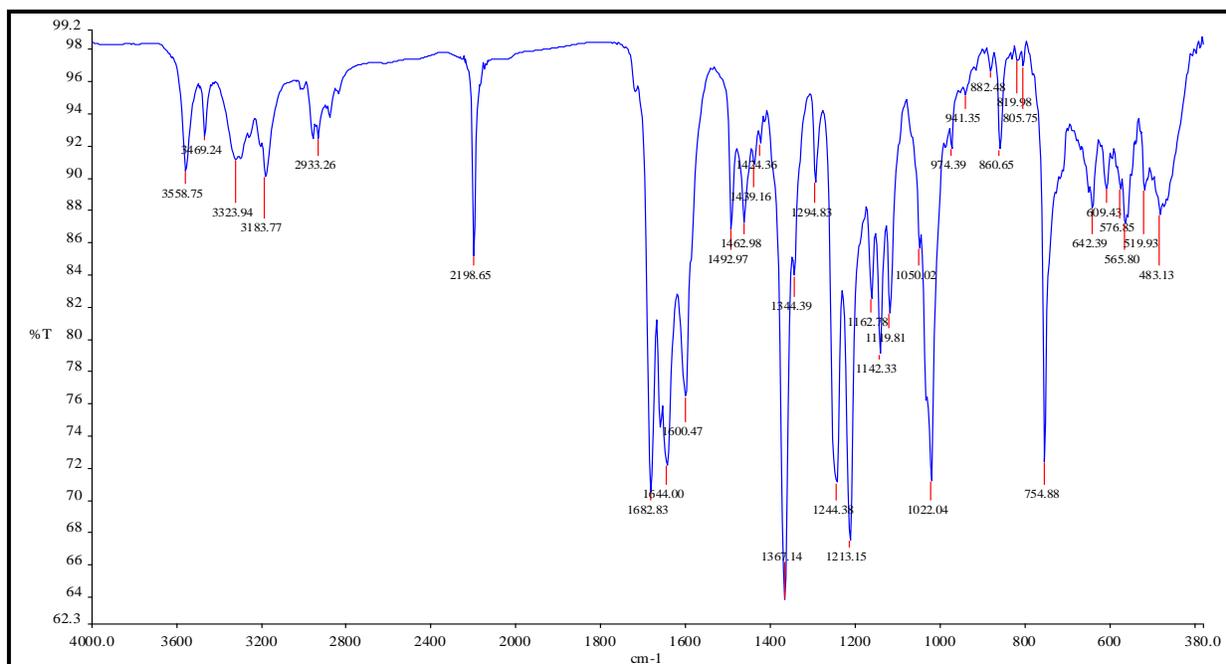
TOF MS ES-



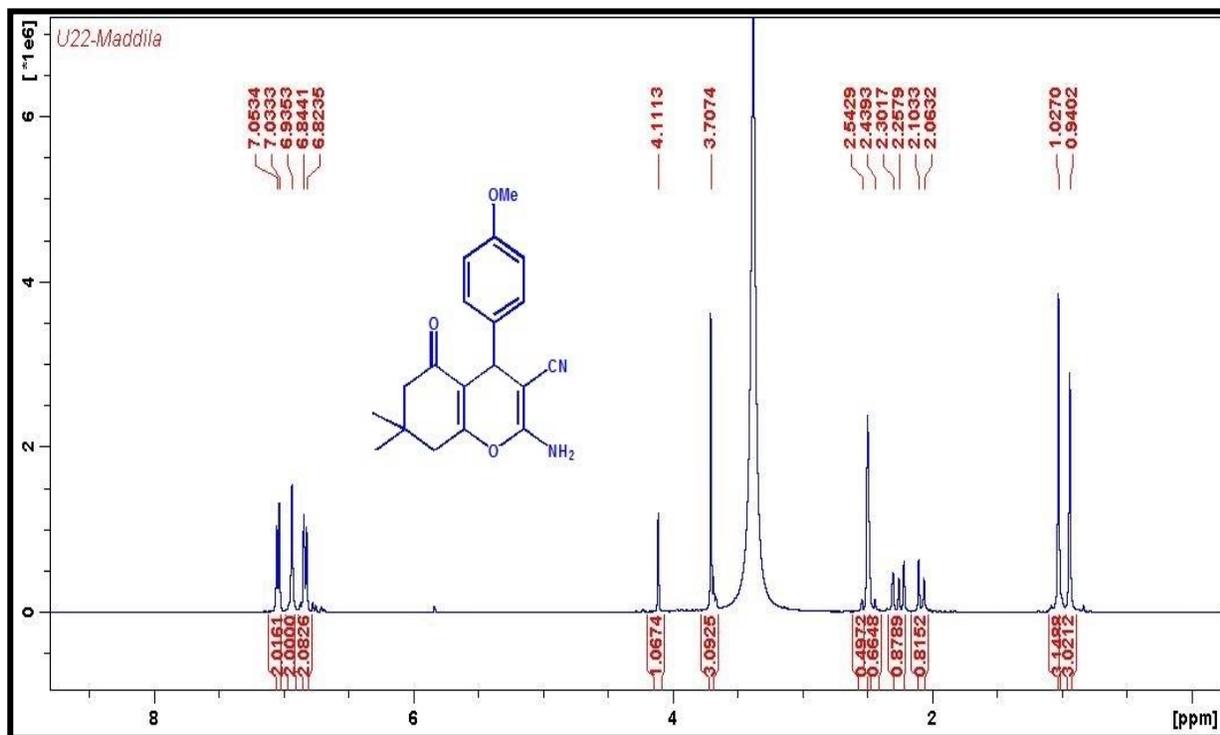
Minimum: -1.5
Maximum: 5.0 5.0 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
323.1397	323.1396	0.1	0.3	11.5	789.2	0.0	C19 H19 N2 O3

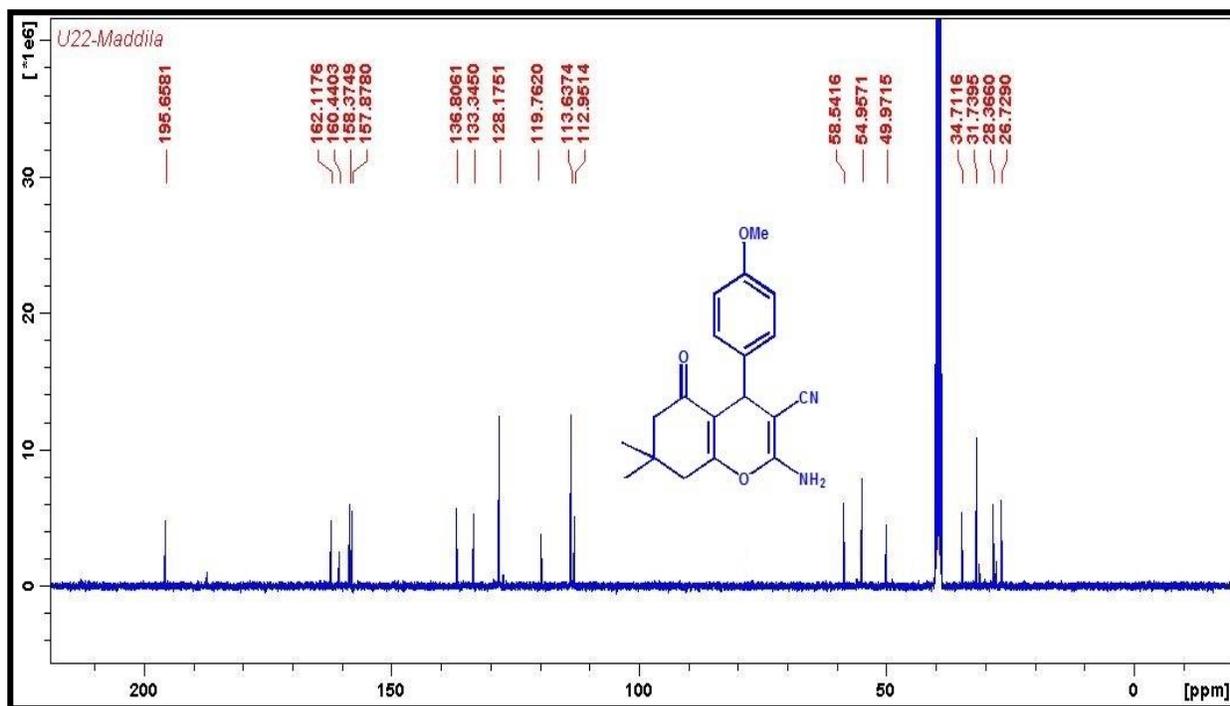
HRMS spectra of compound 4a



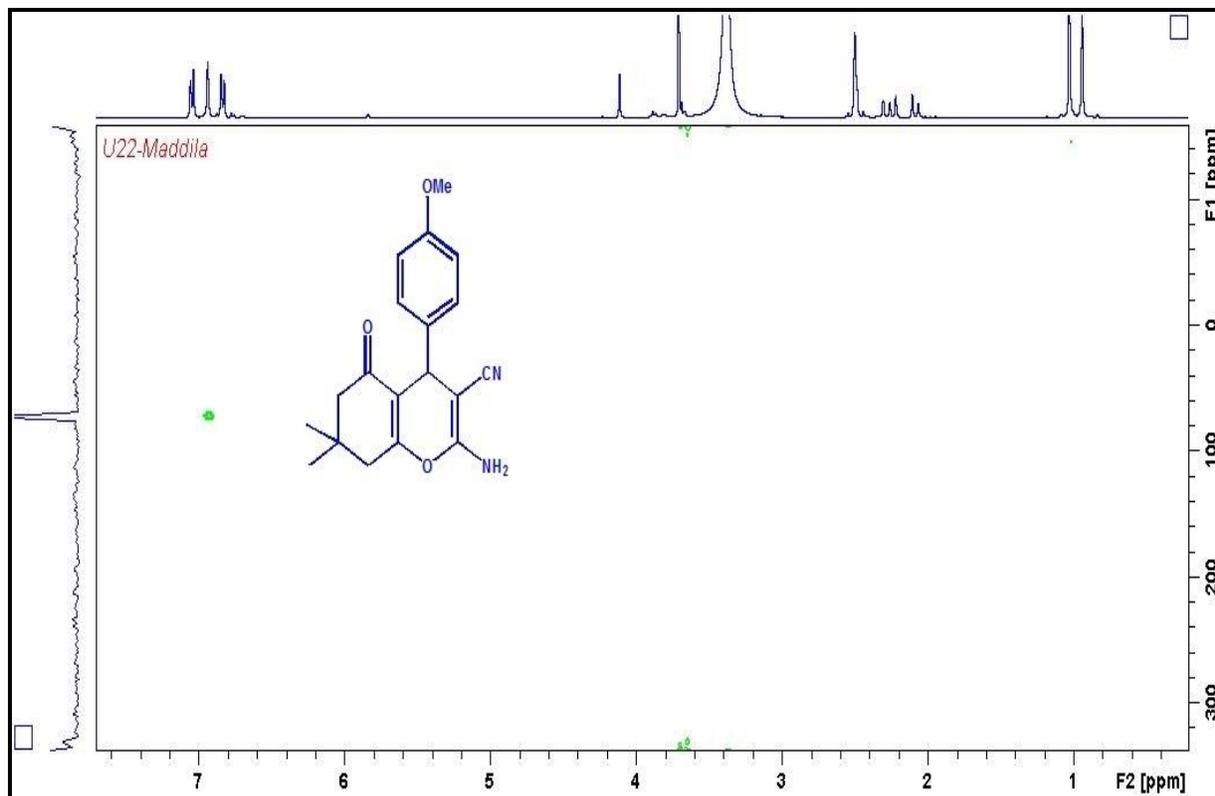
FTIR spectra of compound **4a**



^1H NMR spectra of compound **4b**



^{13}C NMR 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, Even Electron Ions

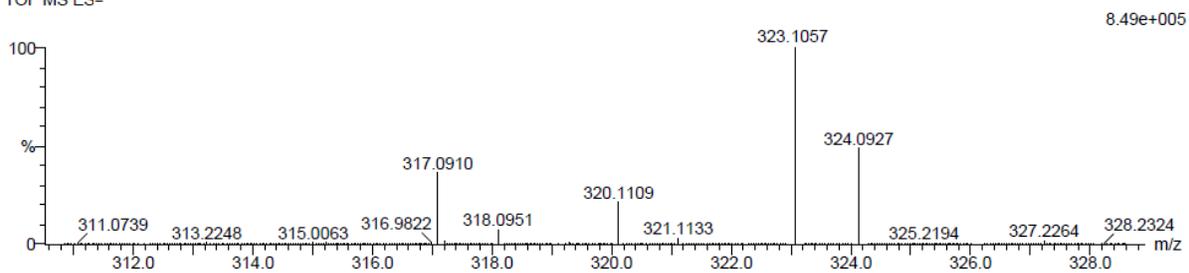
27 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)

Elements Used:

C: 15-20 H: 15-20 N: 0-5 O: 0-5

Compound 7 11 (0.337) Cm (1:61)

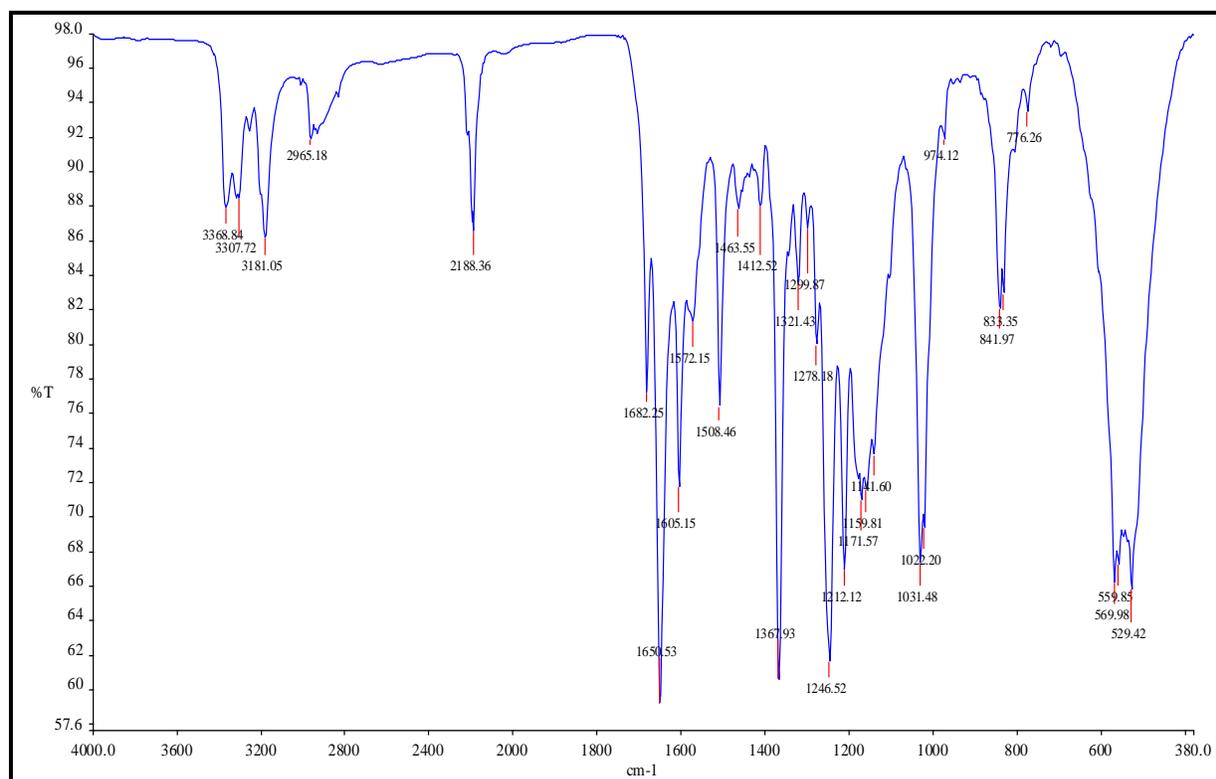
TOF MS ES-



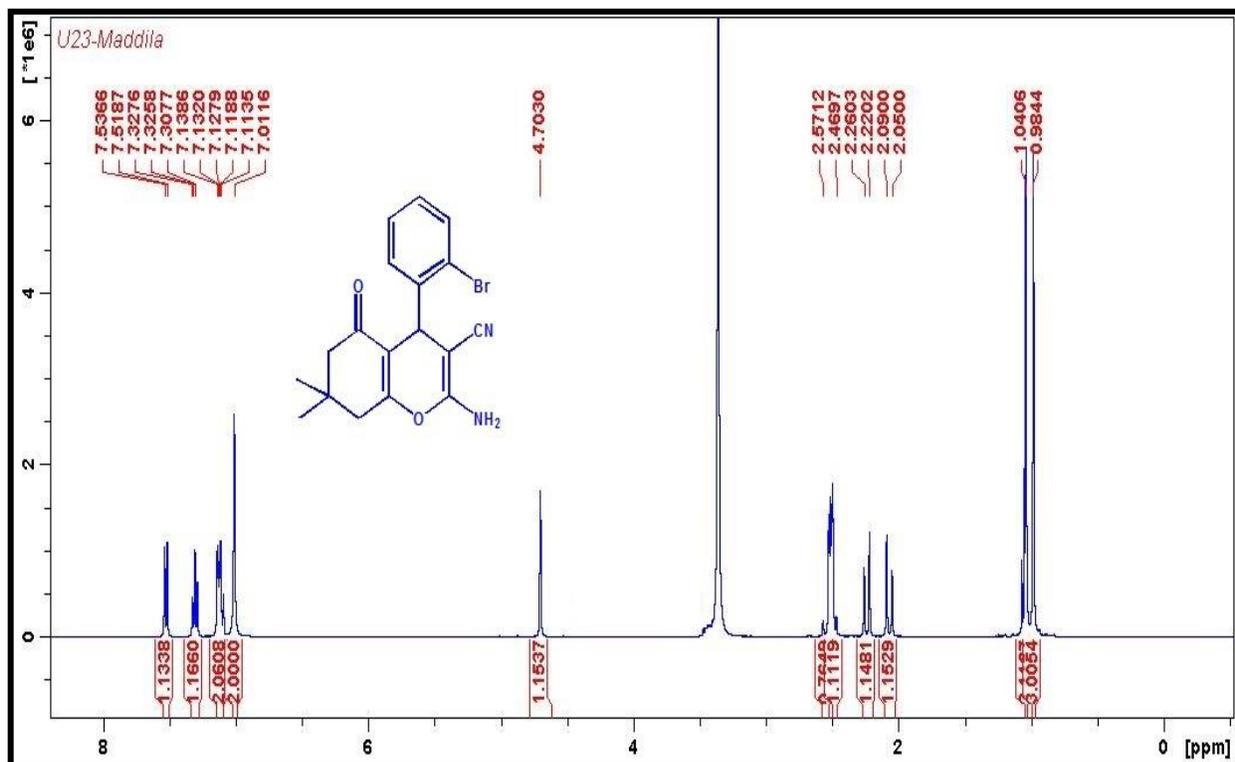
Minimum: -1.5
Maximum: 5.0 5.0 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
323.1057	323.1059	-0.2	-0.6	10.5	717.3	0.0	C19 H19 N2 O3

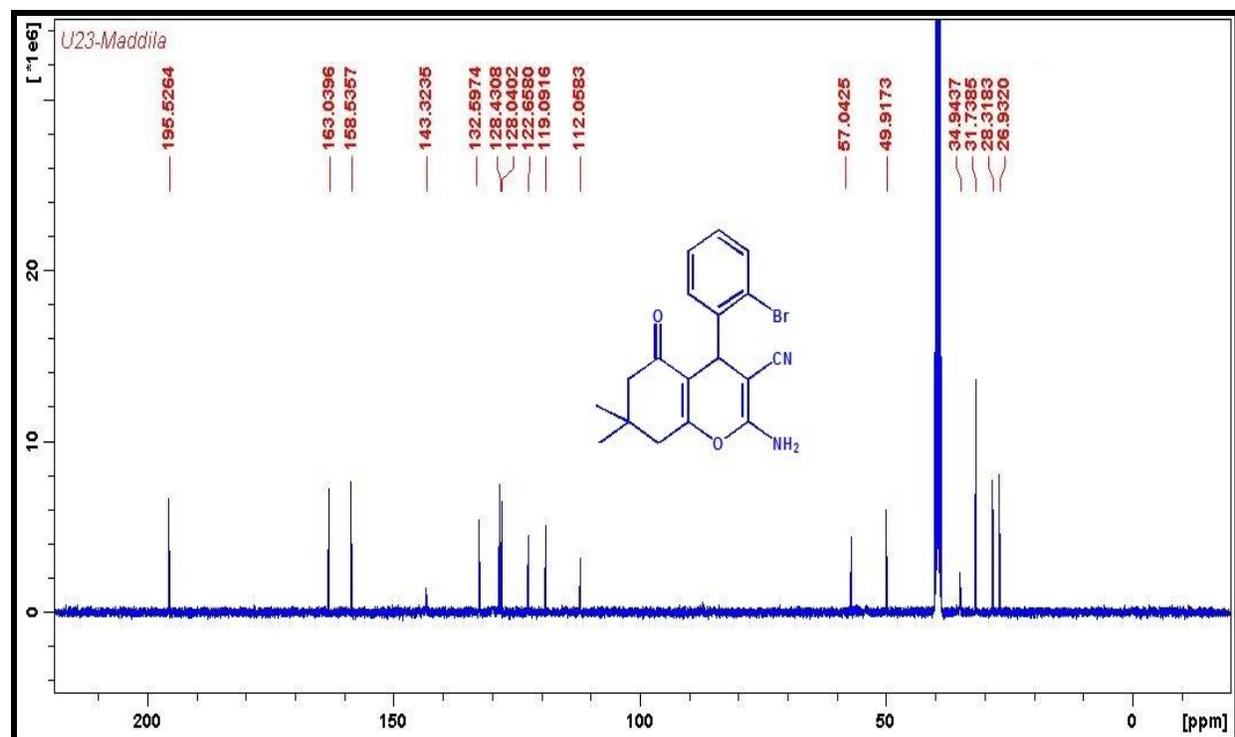
HRMS spectra of compound **4b**



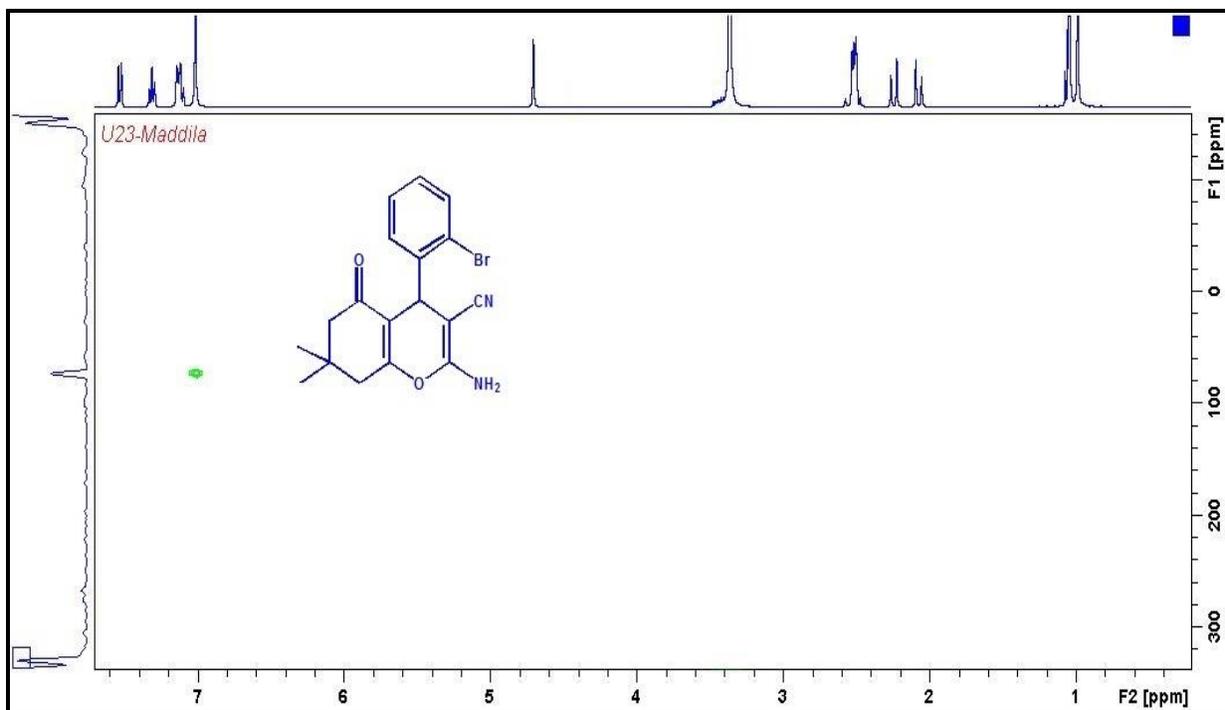
FTIR spectra of compound **4b**



^1H NMR spectra of compound 4c



^{13}C NMR 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, Even Electron Ions

34 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

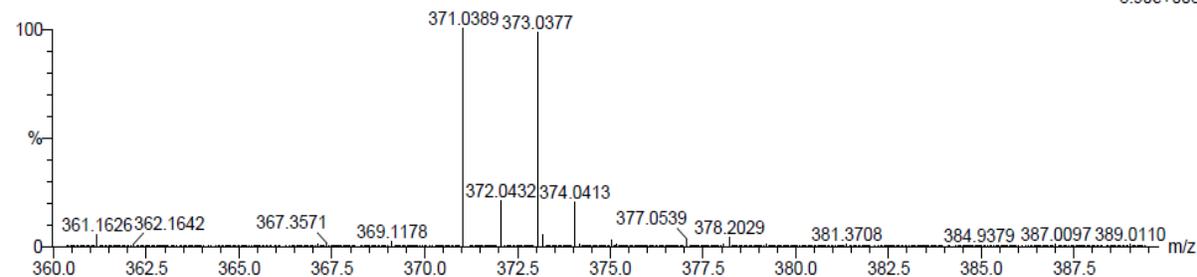
Elements Used:

C: 15-20 H: 15-20 N: 0-5 O: 0-5 Br: 0-1

U-24 42 (1.383) Cm (1:61)

TOF MS ES-

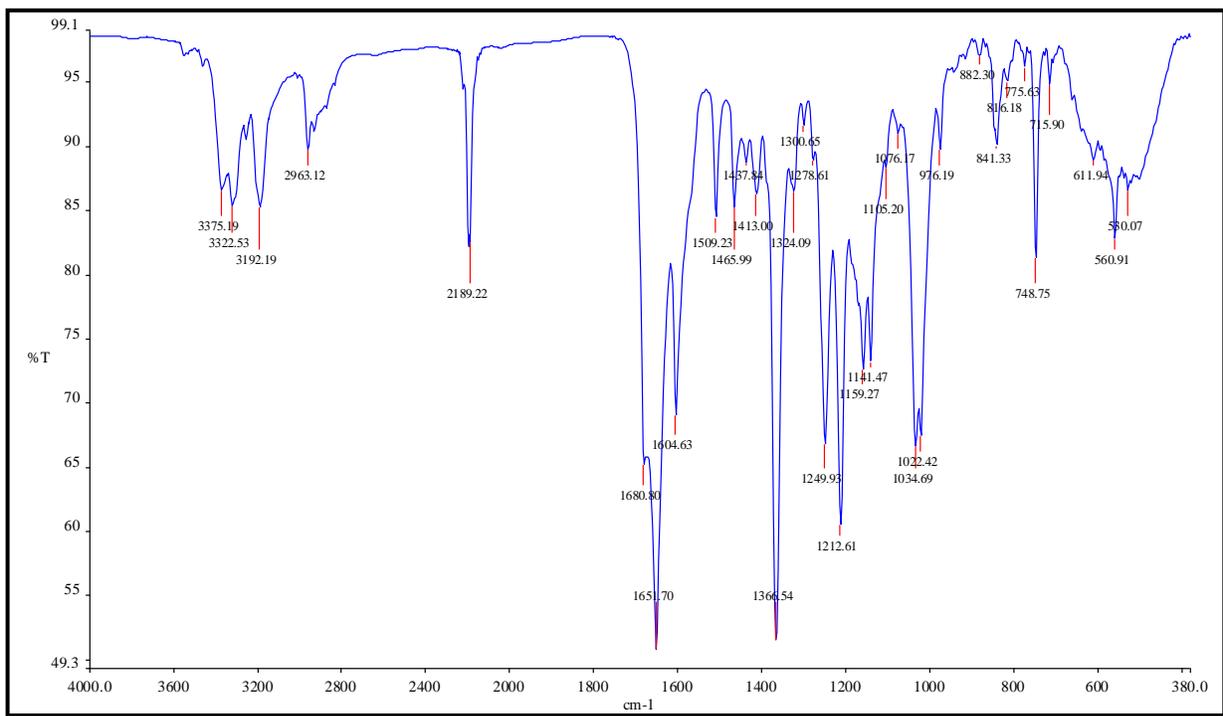
8.90e+005



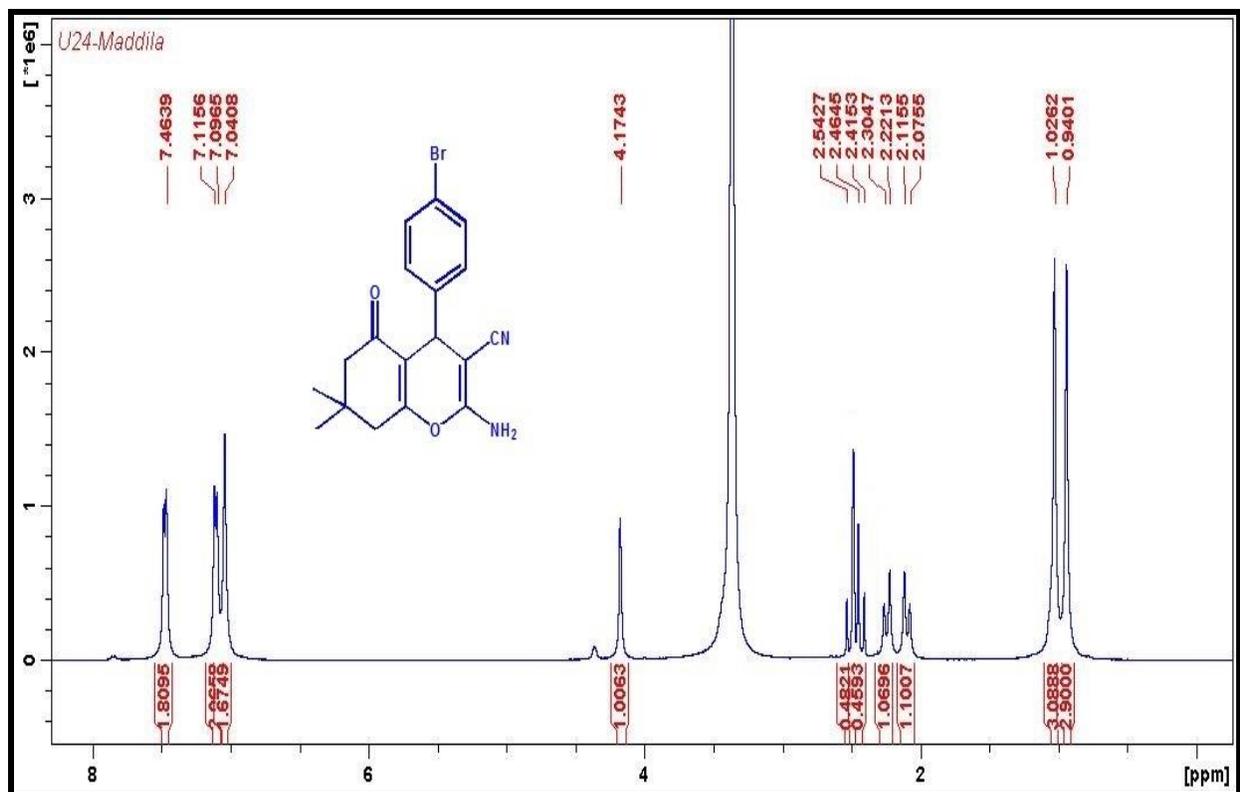
Minimum: -1.5
Maximum: 5.0 5.0 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
371.0389	371.0395	-0.6	-1.6	11.5	658.8	0.0	C18 H16 N2 O2 Br

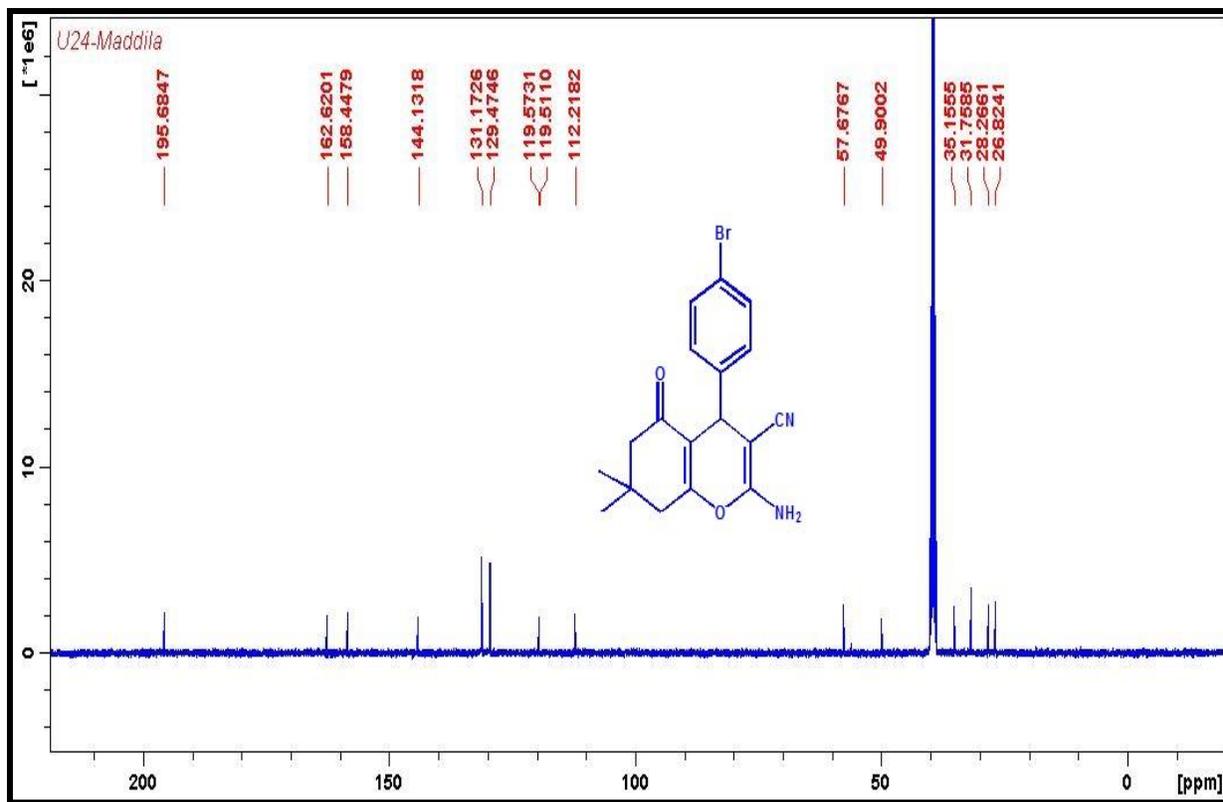
HRMS spectra of compound 4c



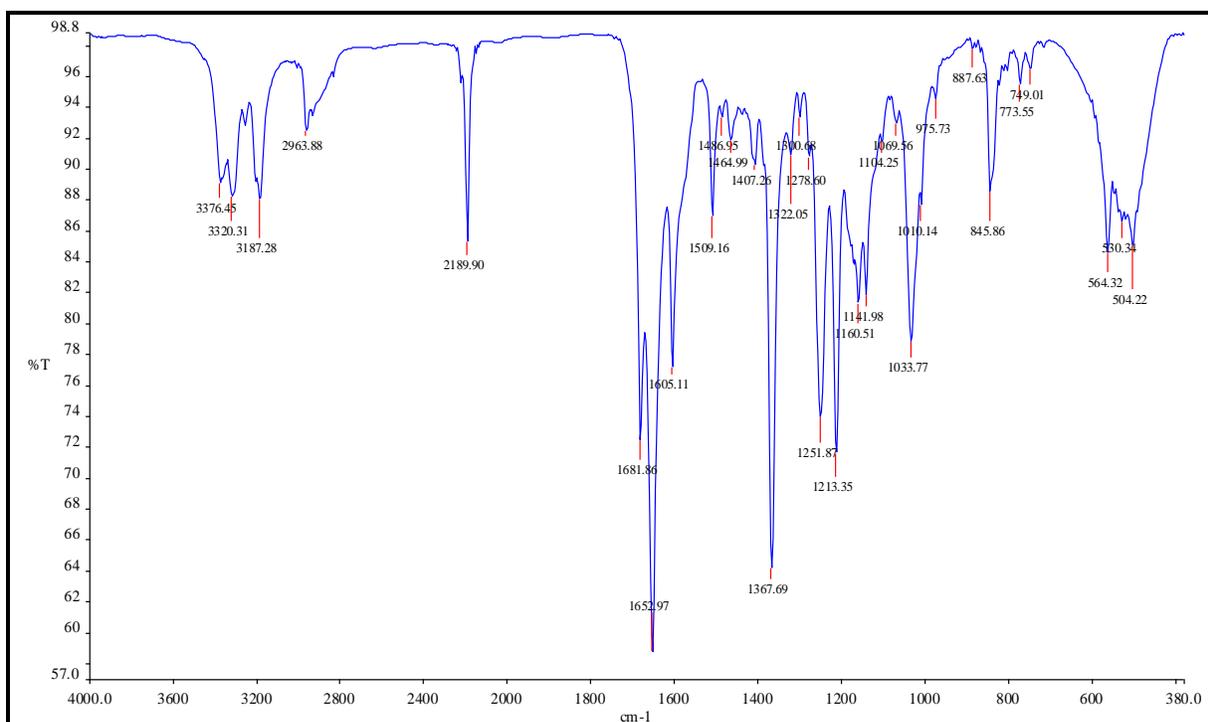
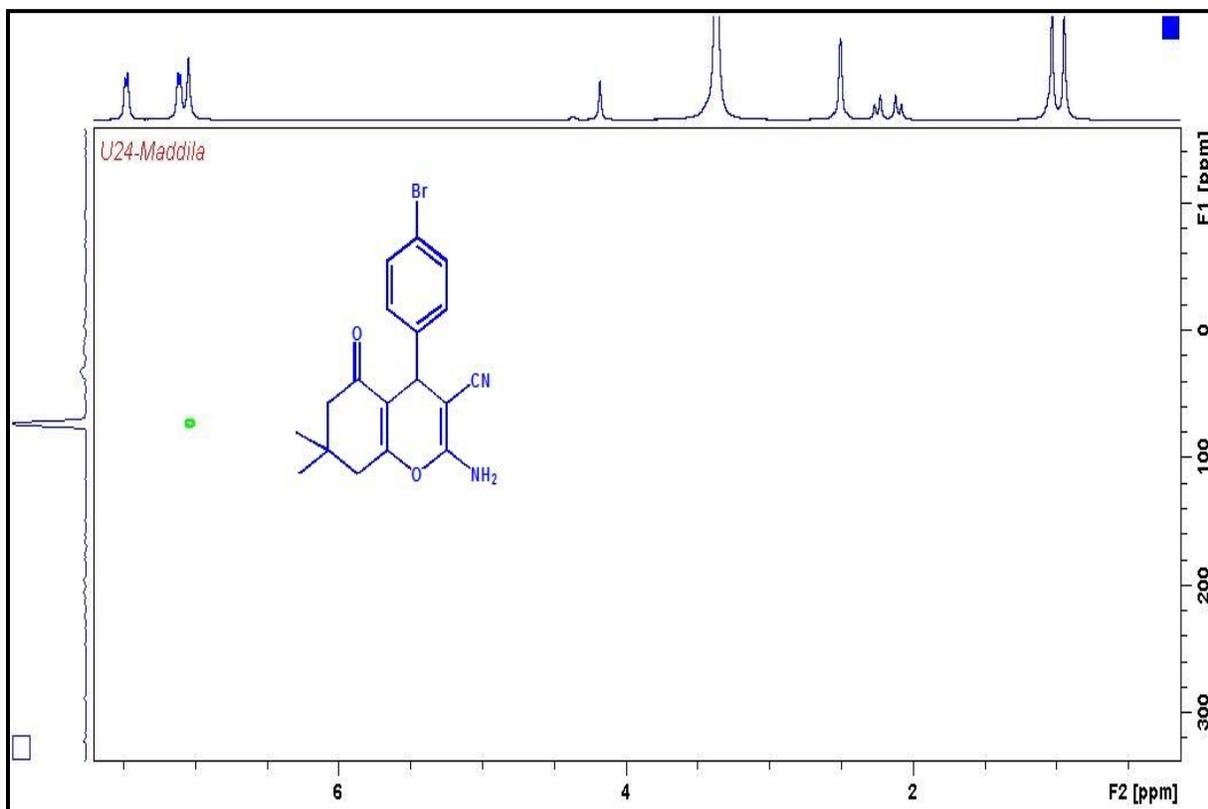
FTIR spectra of compound **4c**



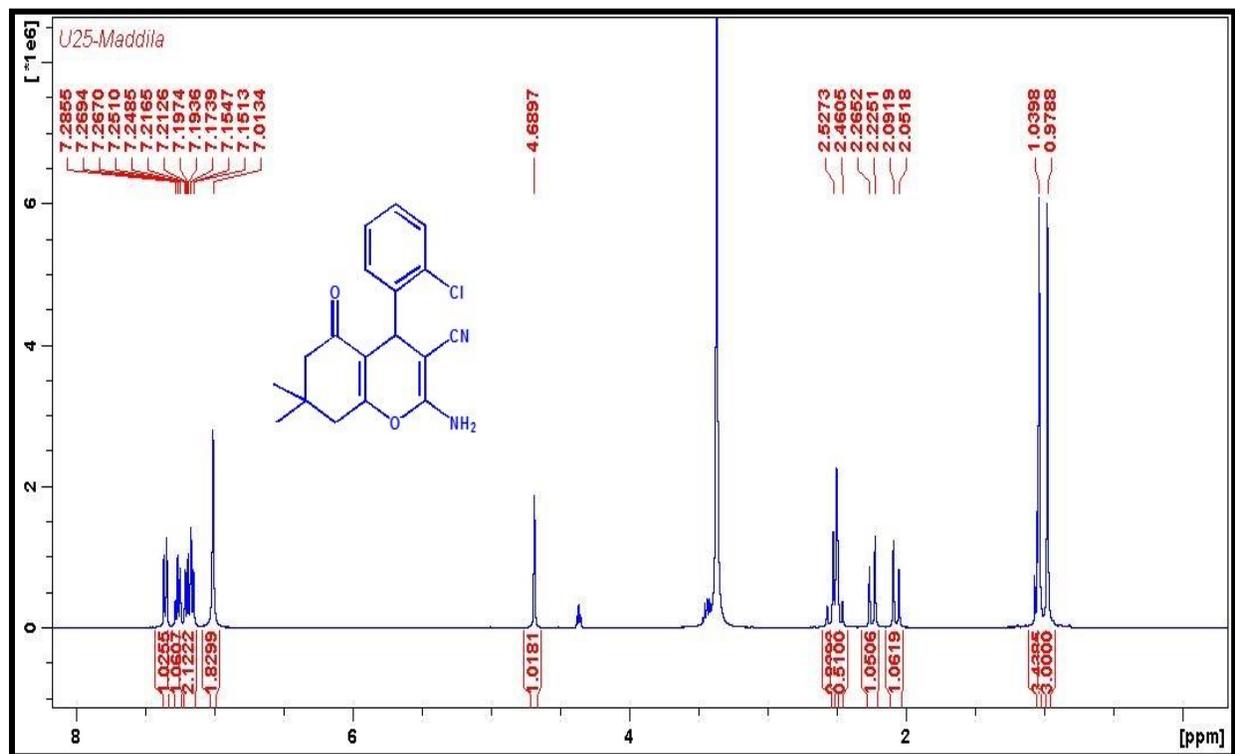
^1H NMR spectra of compound **4d**



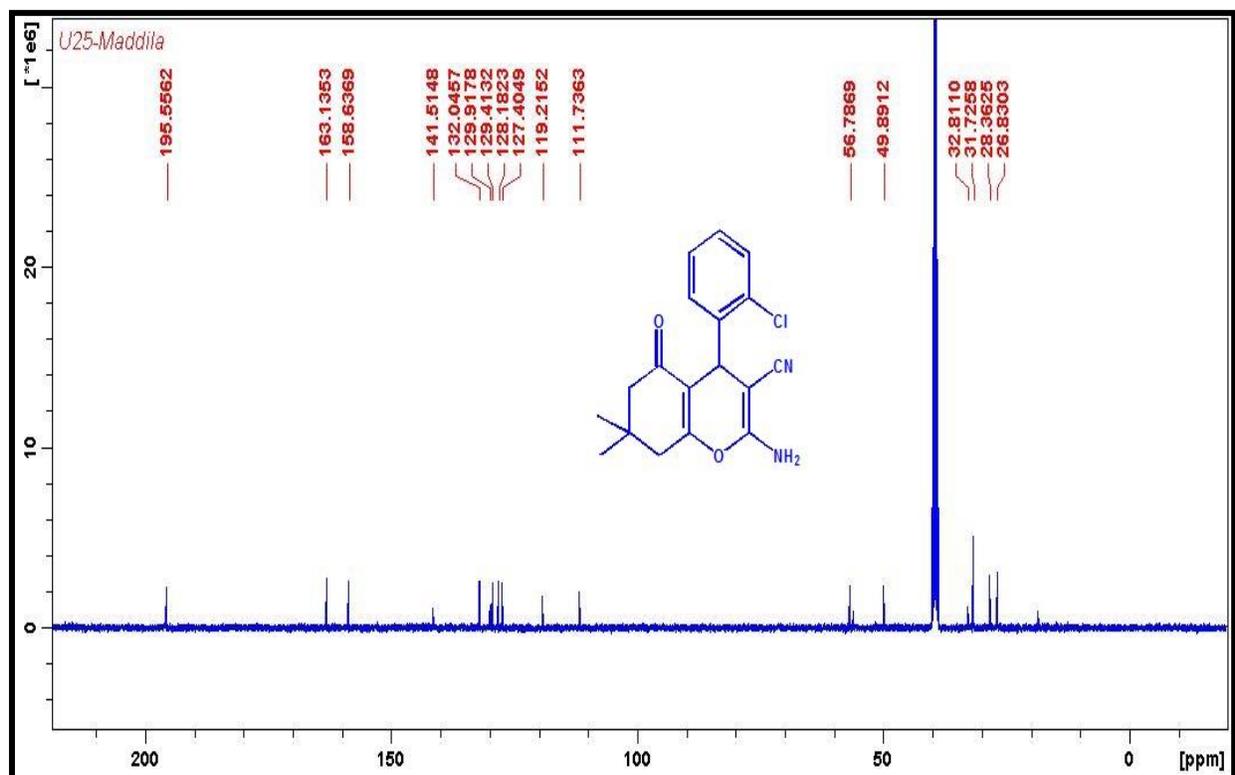
^{13}C NMR spectra of compound **4d**



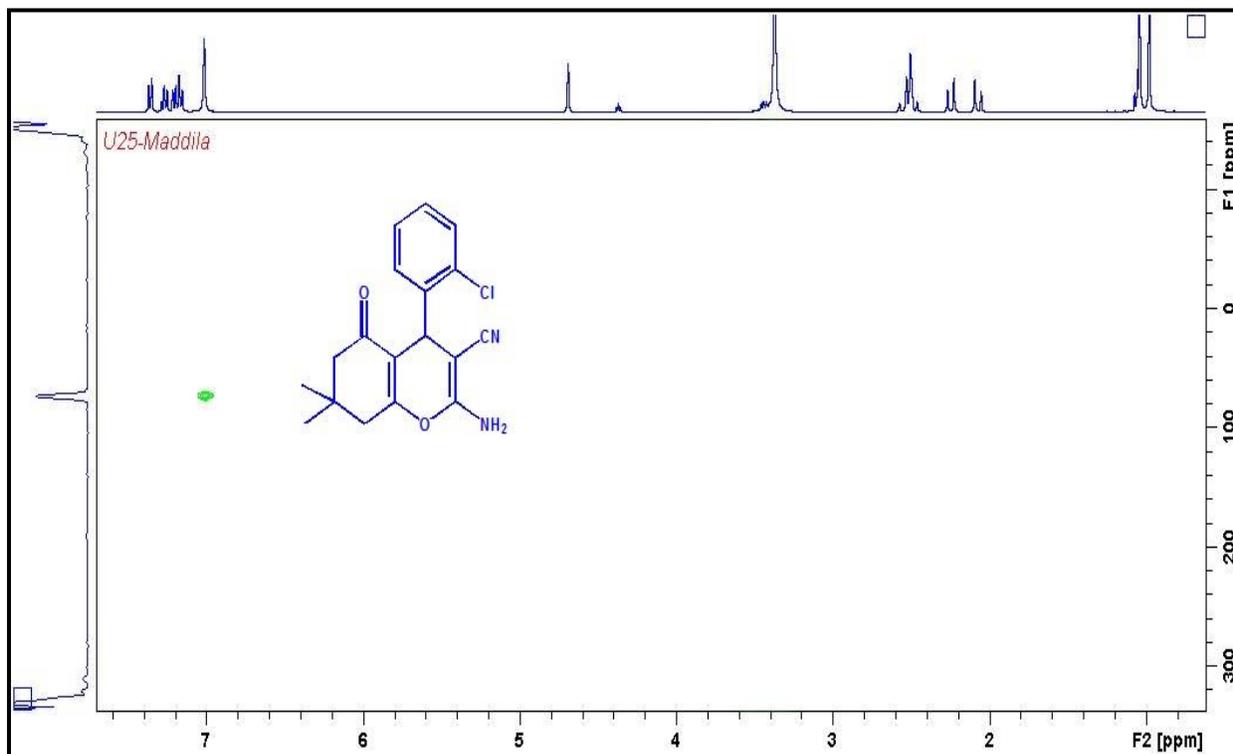
FTIR spectra of compound **4d**



¹H NMR spectra of compound 4e



¹³C NMR spectra of compound 4e



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

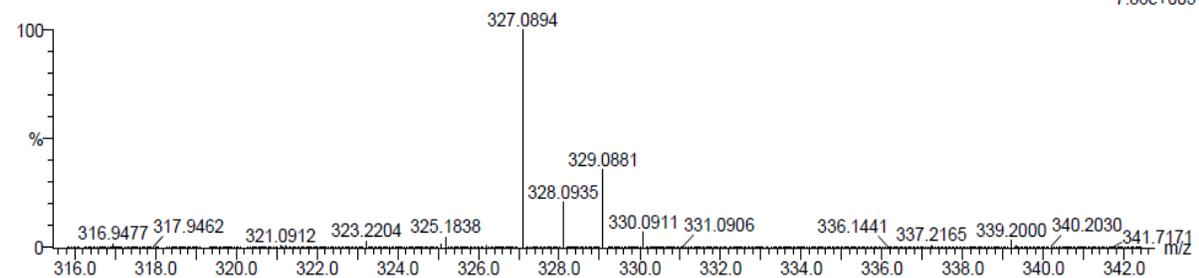
151 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

Elements Used:

C: 15-20 H: 15-20 N: 0-5 O: 0-5 Cl: 0-5

U-25 61 (2.024) Cm (1:61)

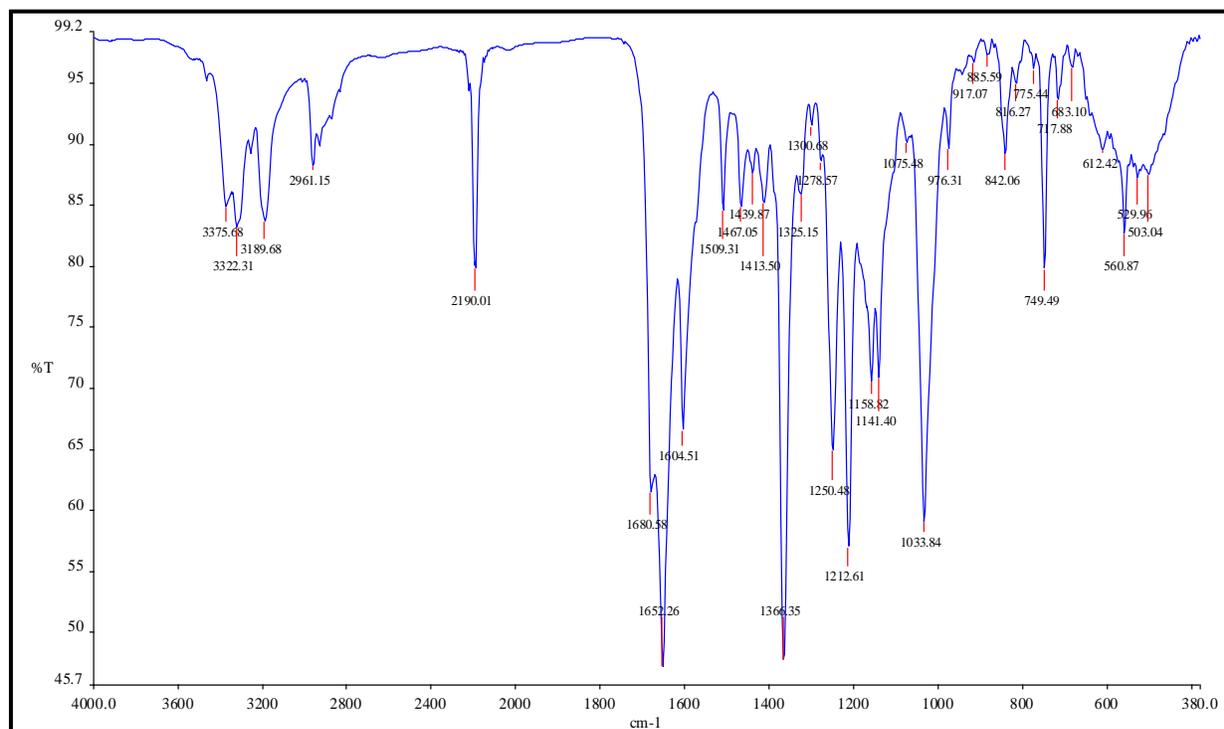
TOF MS ES-



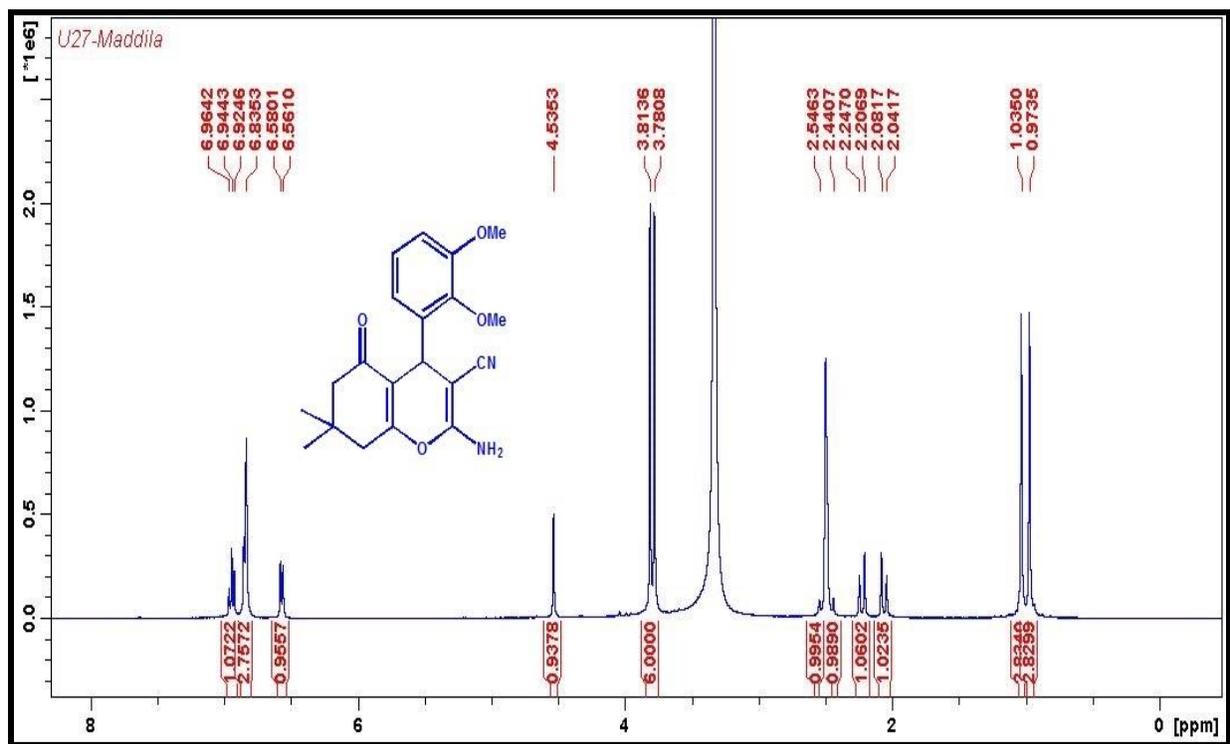
Minimum: -1.5
Maximum: 5.0 5.0 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
327.0894	327.0900	-0.6	-1.8	11.5	738.9	0.0	C18 H16 N2 O2 Cl

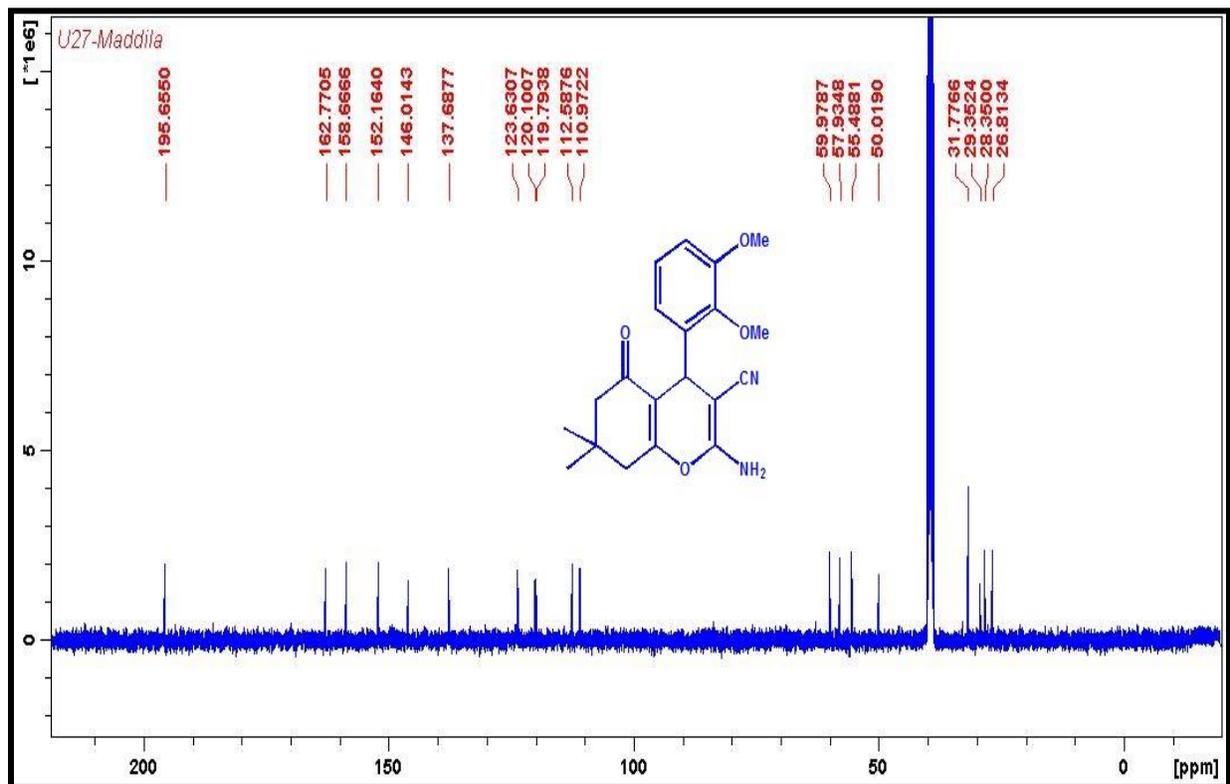
HRMS spectra of compound 4e



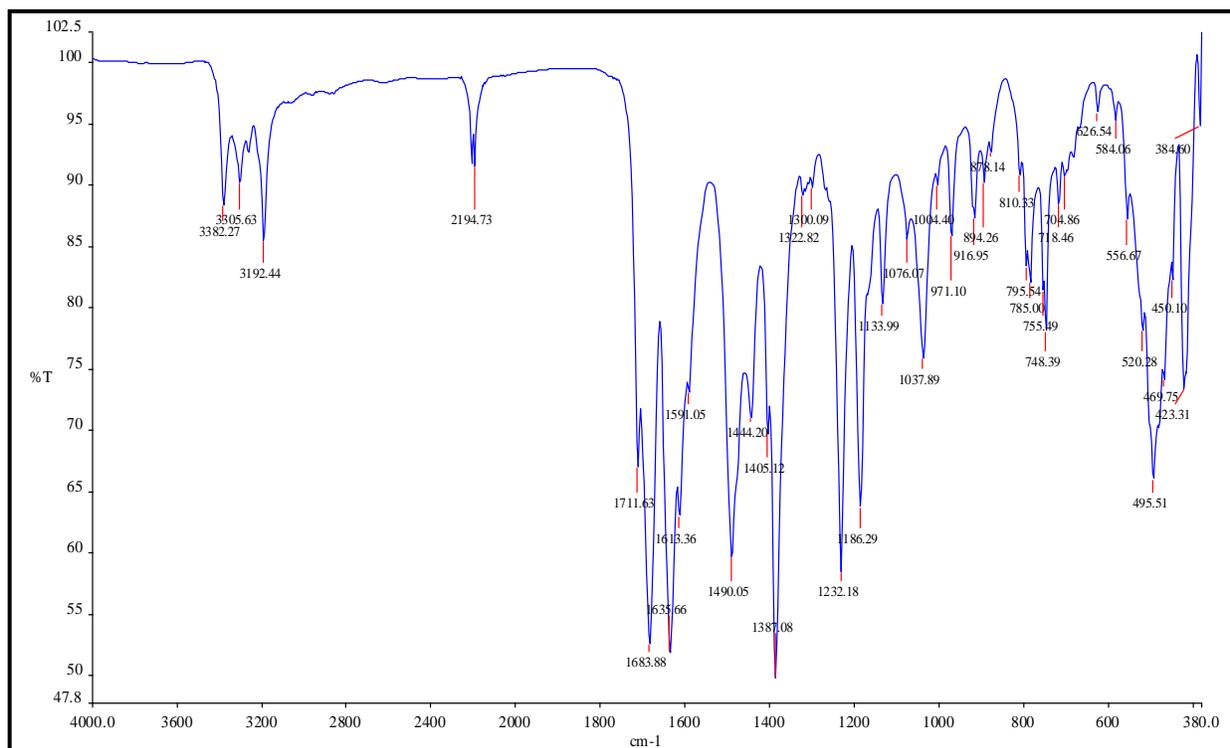
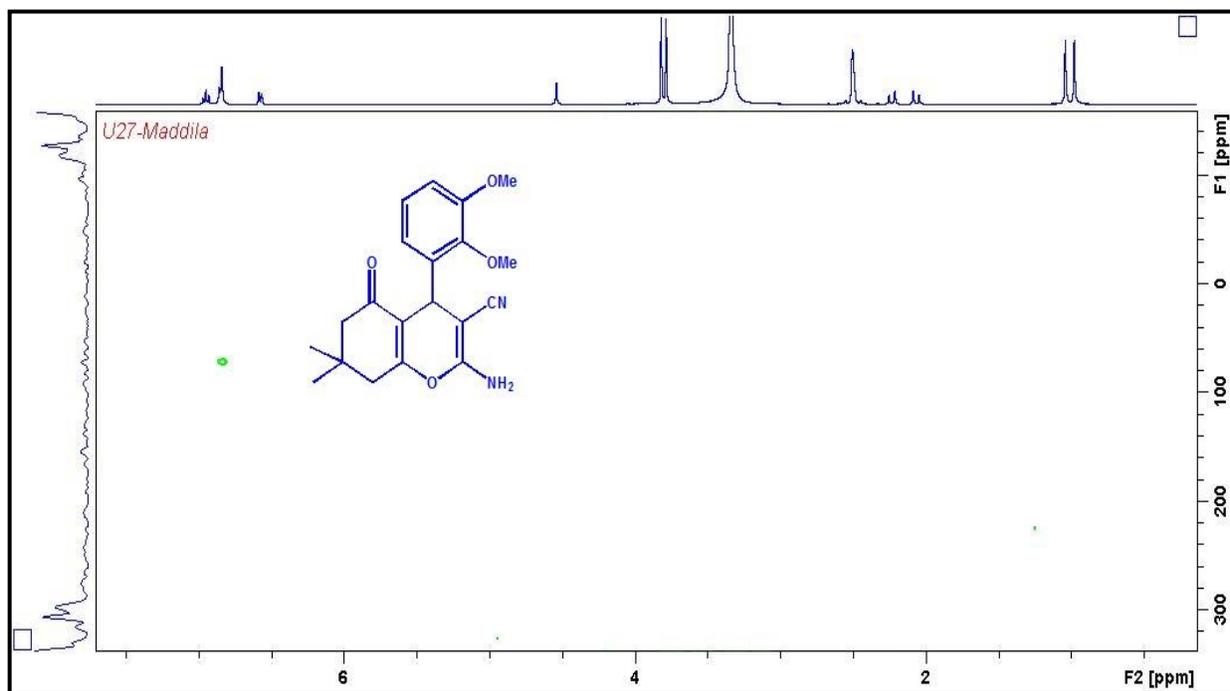
FTIR spectra of compound **4e**



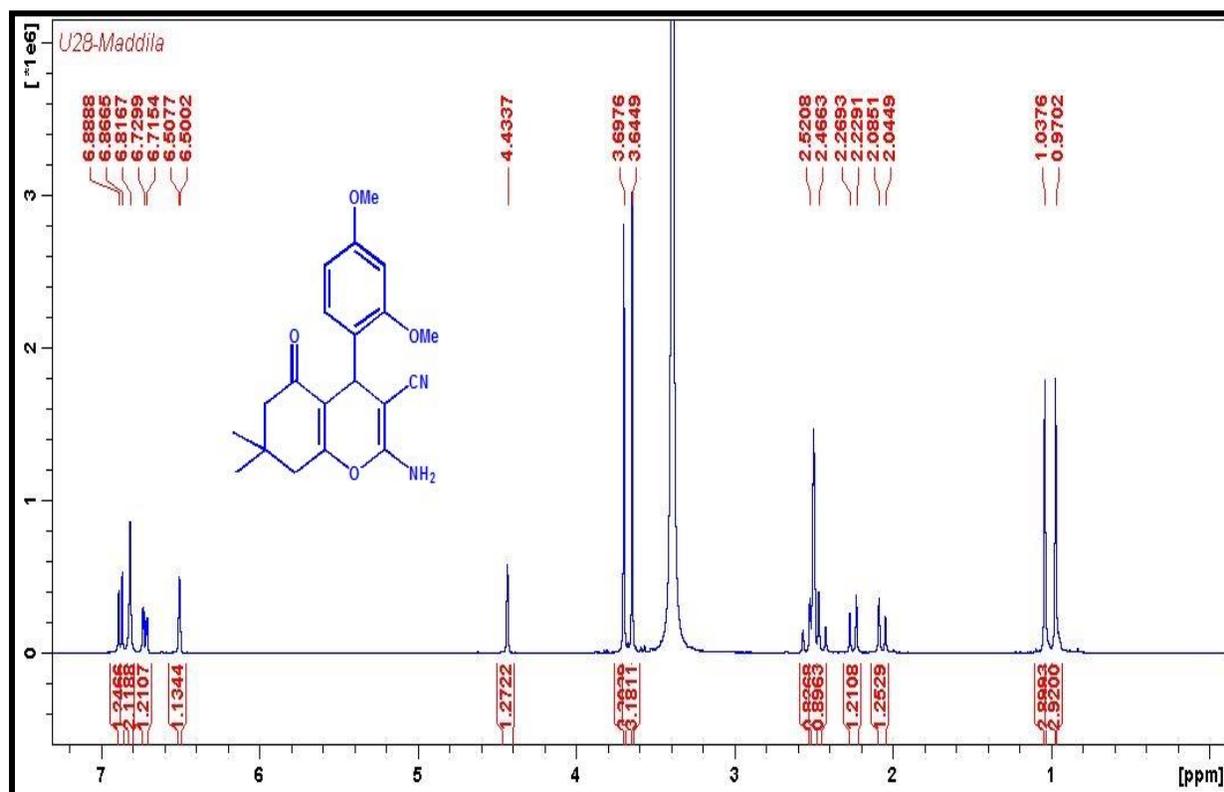
$^1\text{H NMR}$ spectra of compound 4f



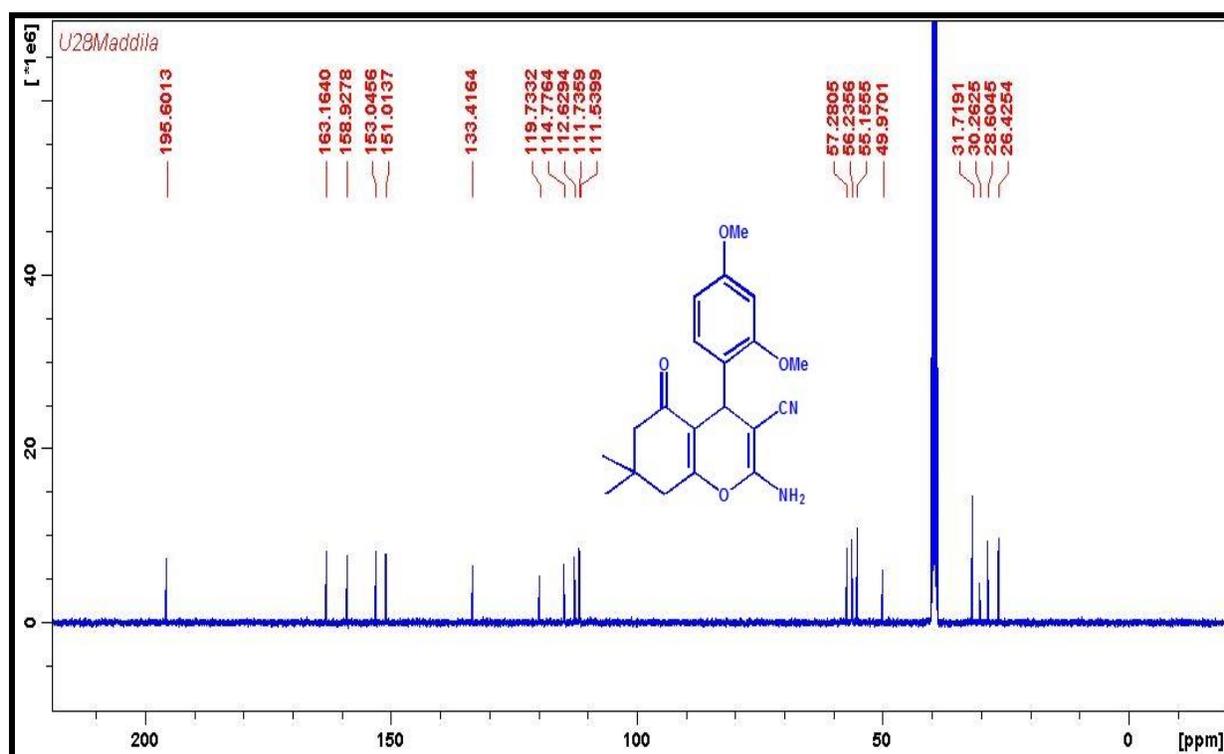
$^{13}\text{C NMR}$ spectra of compound 4f



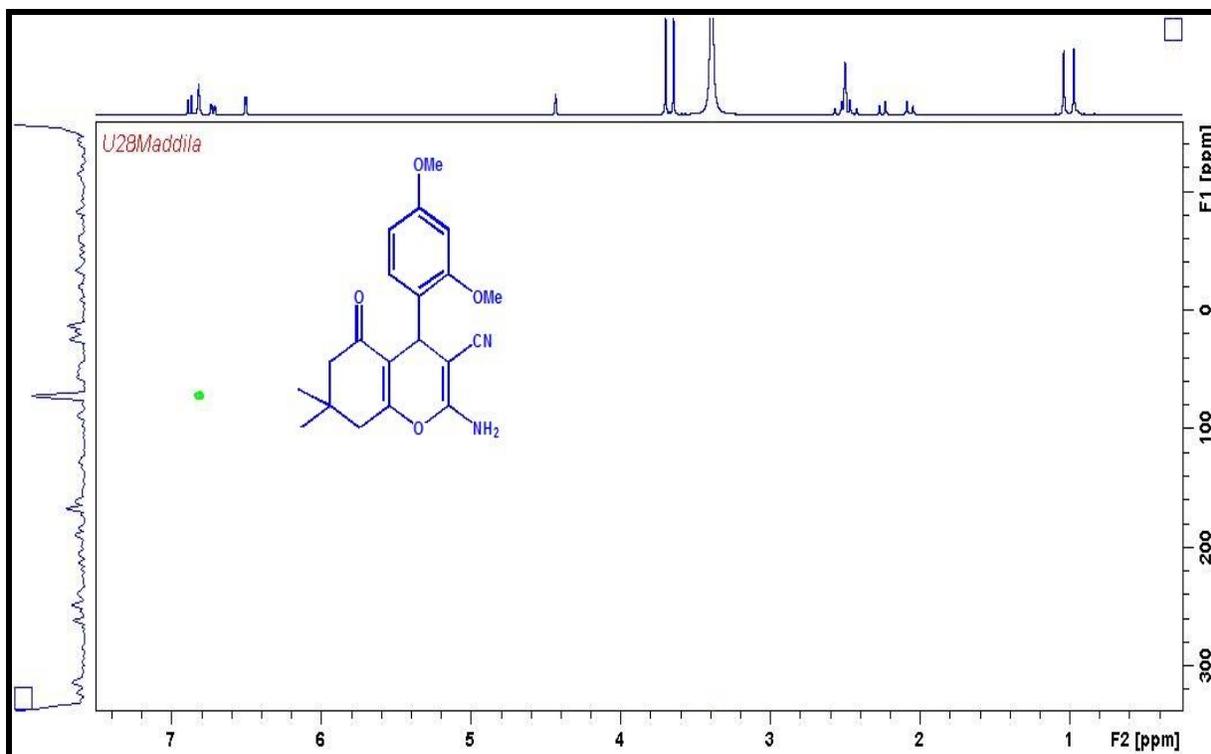
FTIR spectra of compound **4f**



¹H NMR spectra of compound 4g



¹³C NMR spectra of compound 4g



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

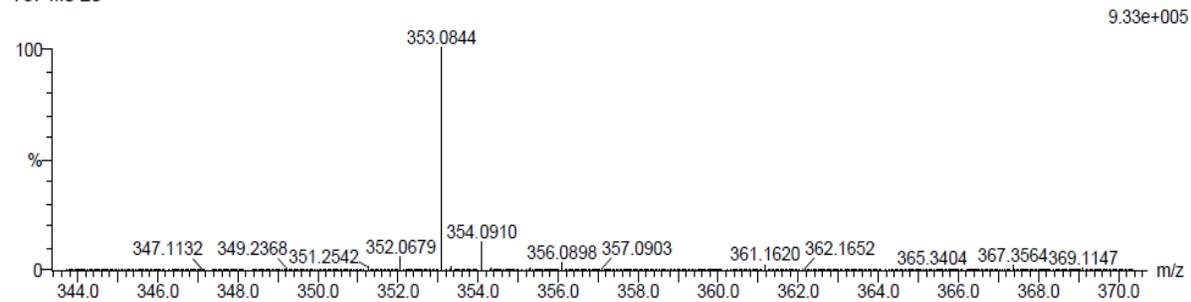
15 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

Elements Used:

C: 15-20 H: 20-25 N: 0-5 O: 0-5

U-11 55 (1.822) Cm (1.61)

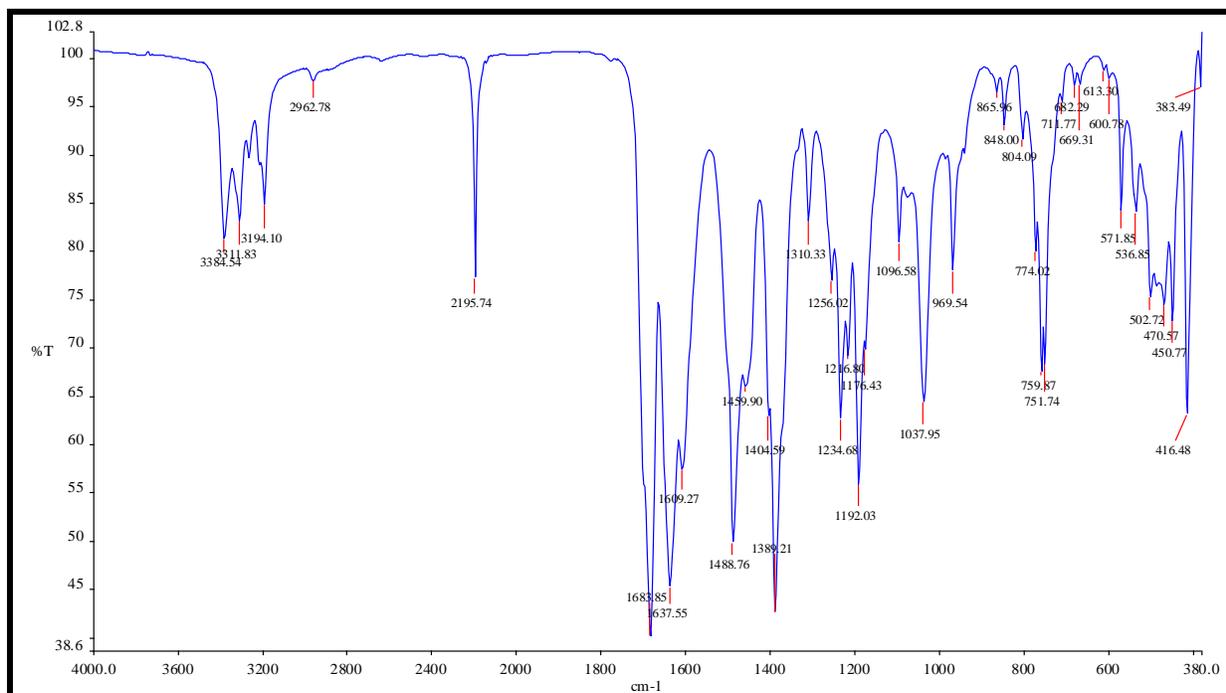
TOF MS ES-



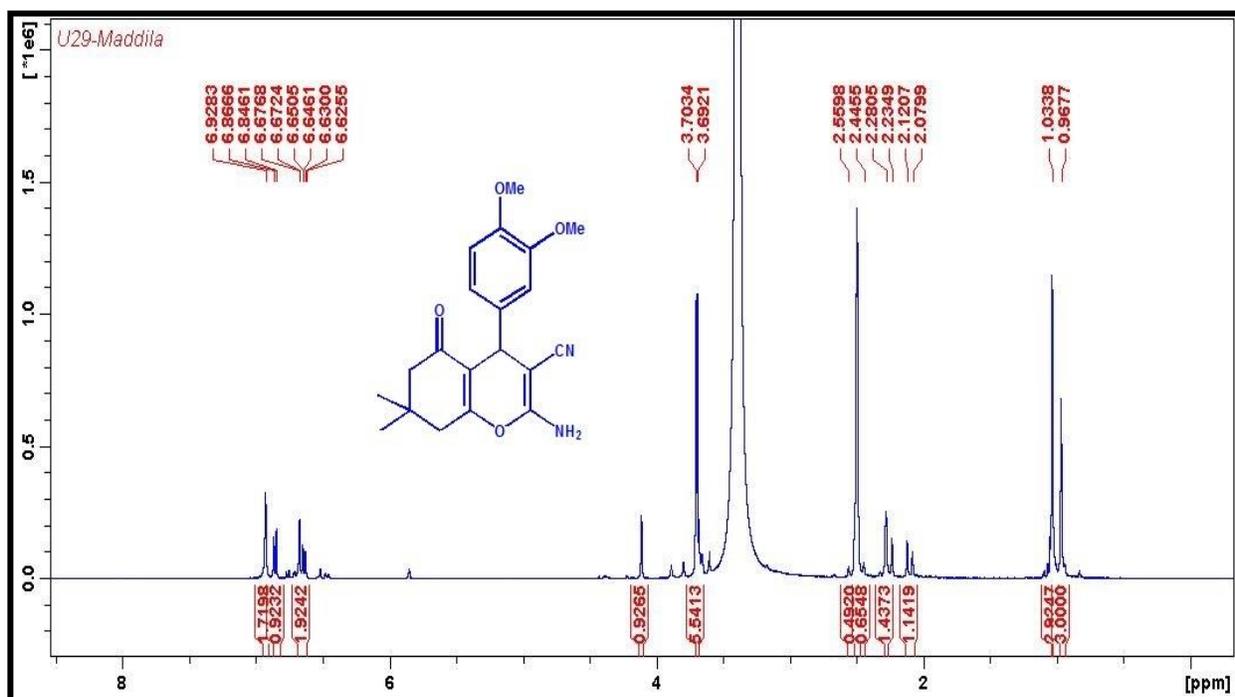
Minimum: -1.5
Maximum: 5.0 5.0 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
353.0844	353.0838	0.6	1.7	13.5	717.5	0.0	C20 H21 N2 O4

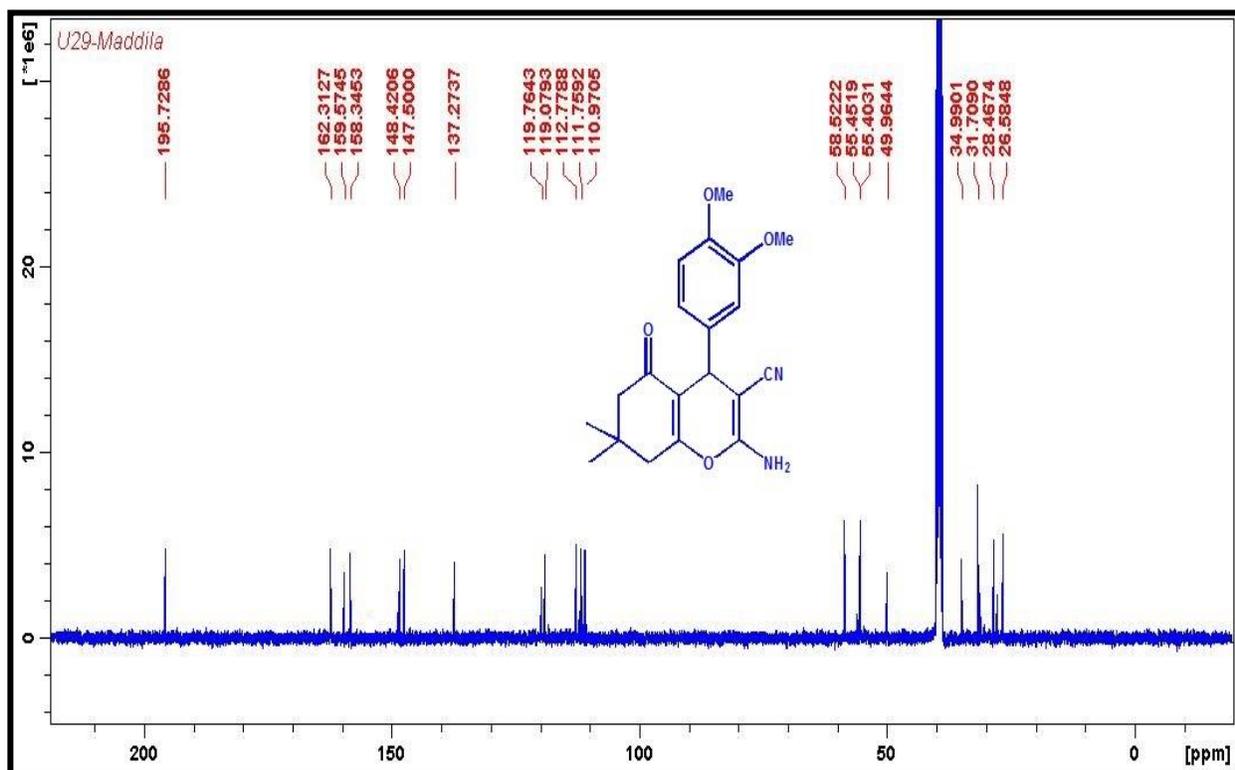
HRMS spectra of compound **4g**



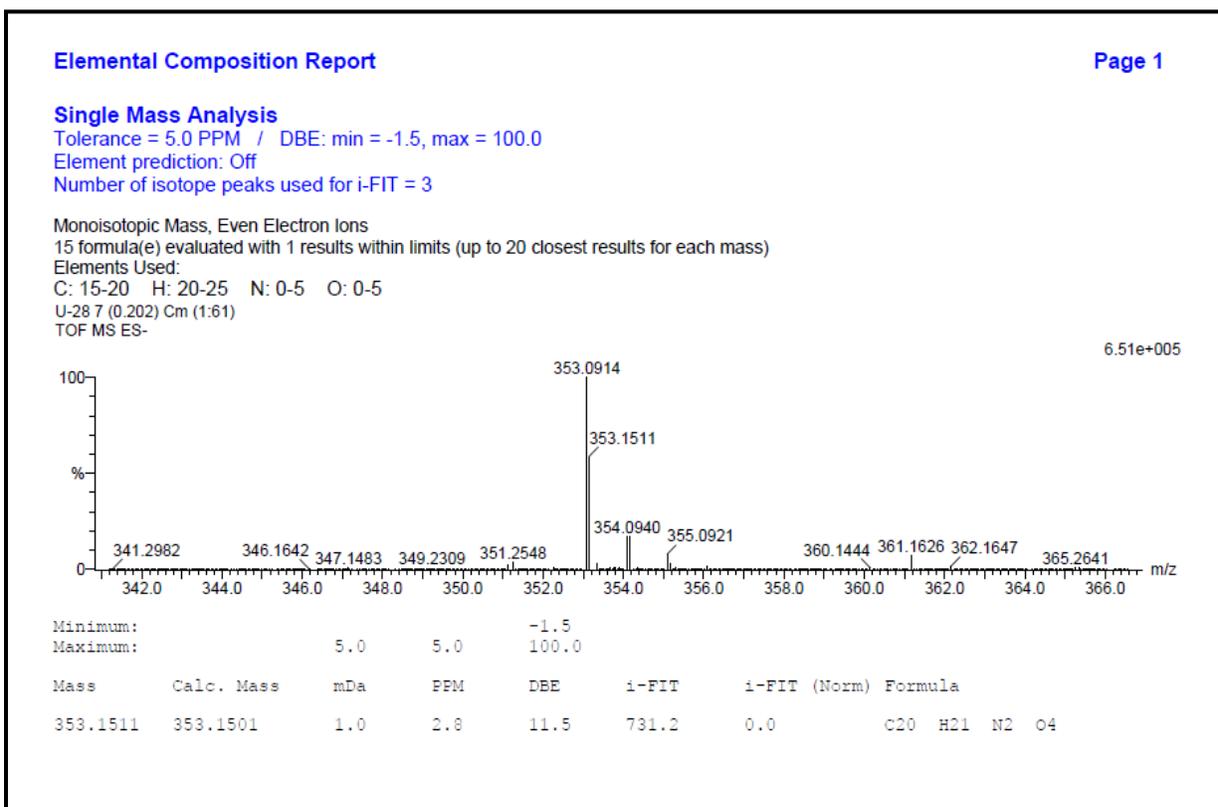
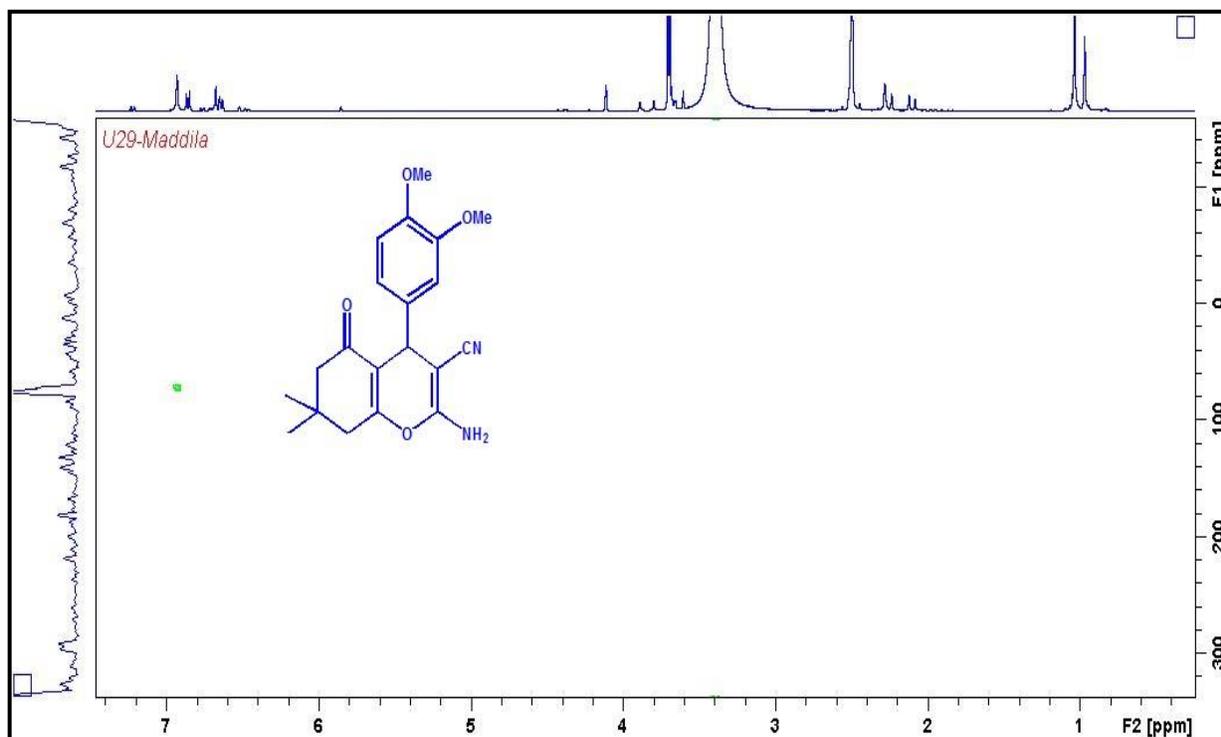
FTIR spectra of compound **4g**



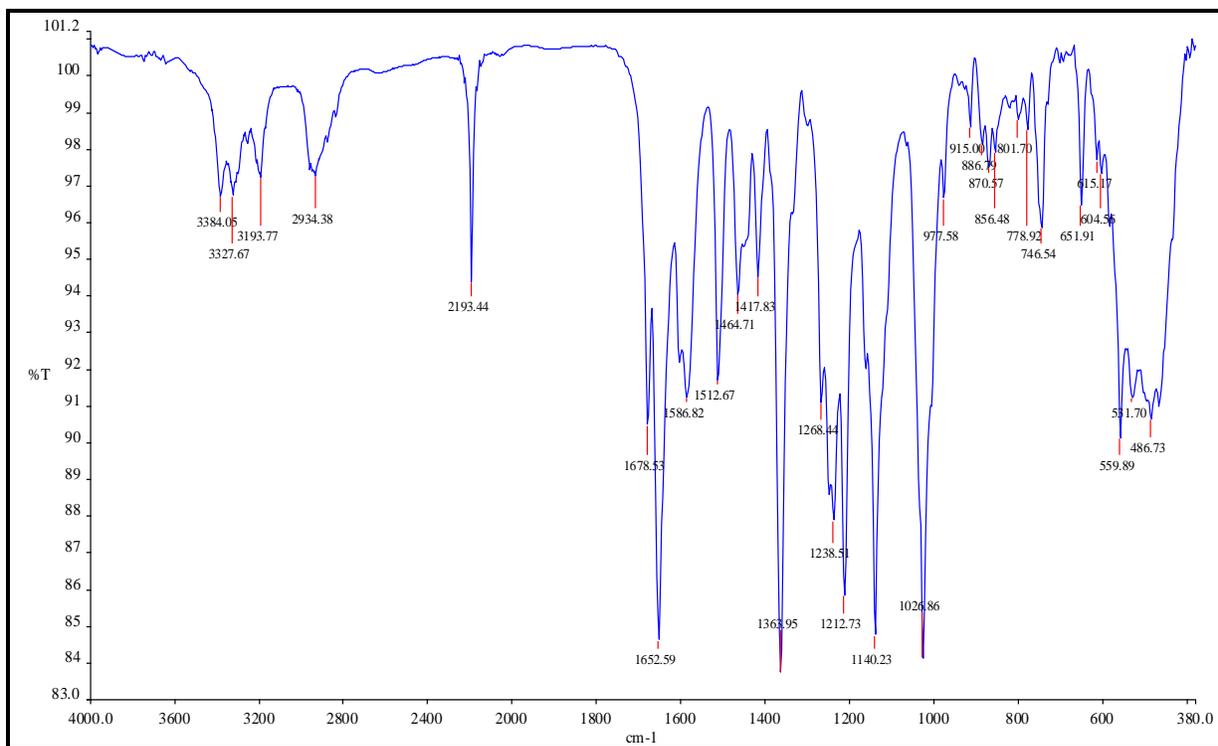
¹H NMR spectra of compound 4h



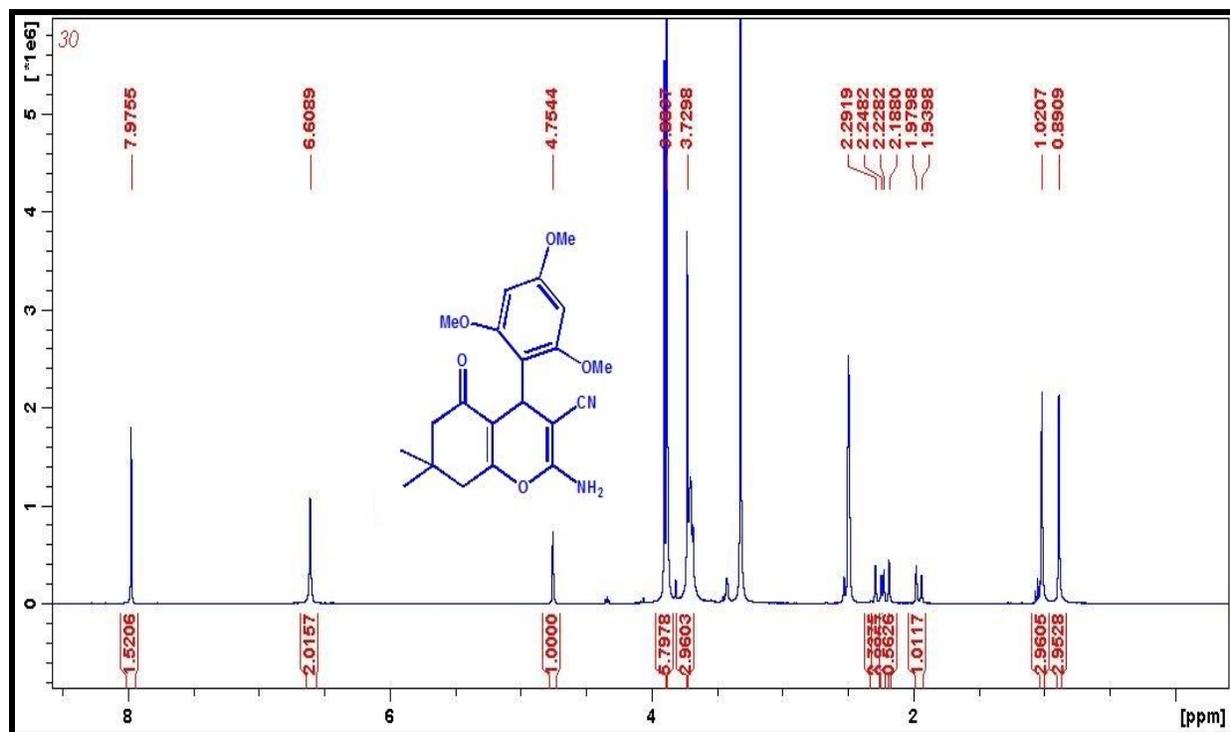
¹³C NMR spectra of compound 4h



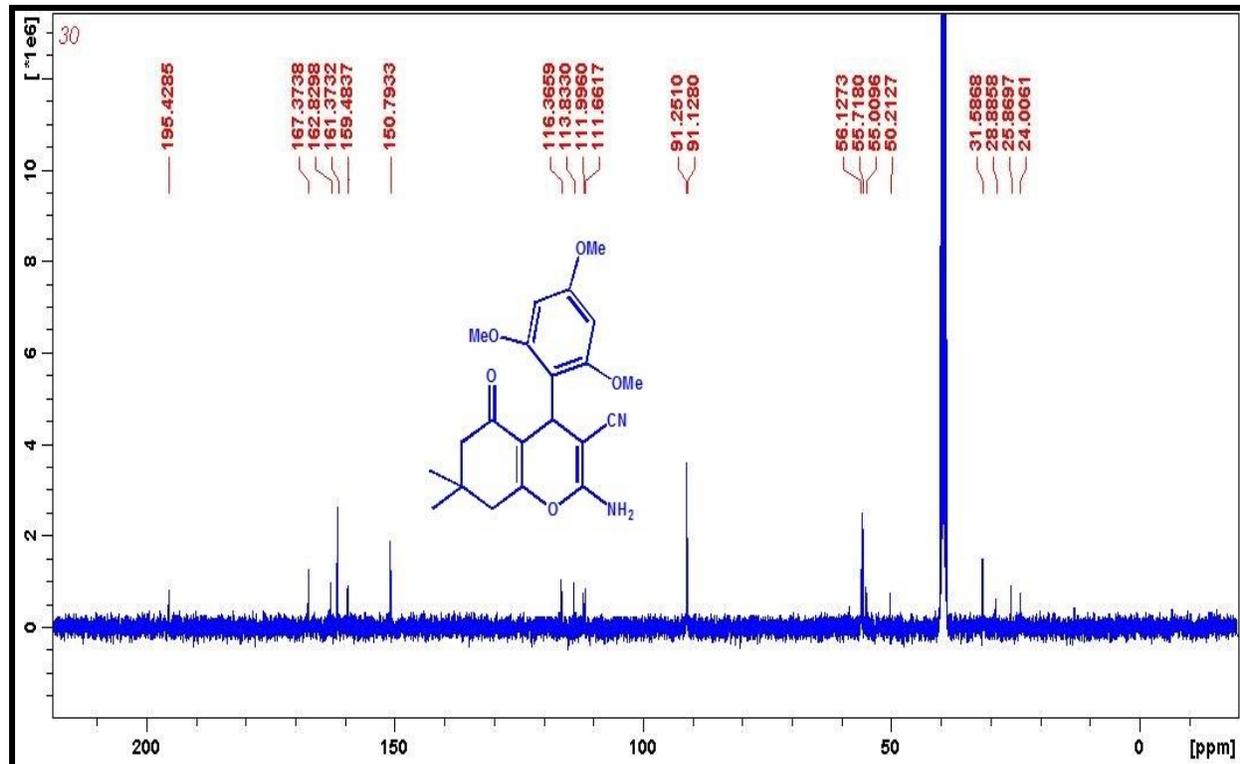
HRMS spectra of compound 4h



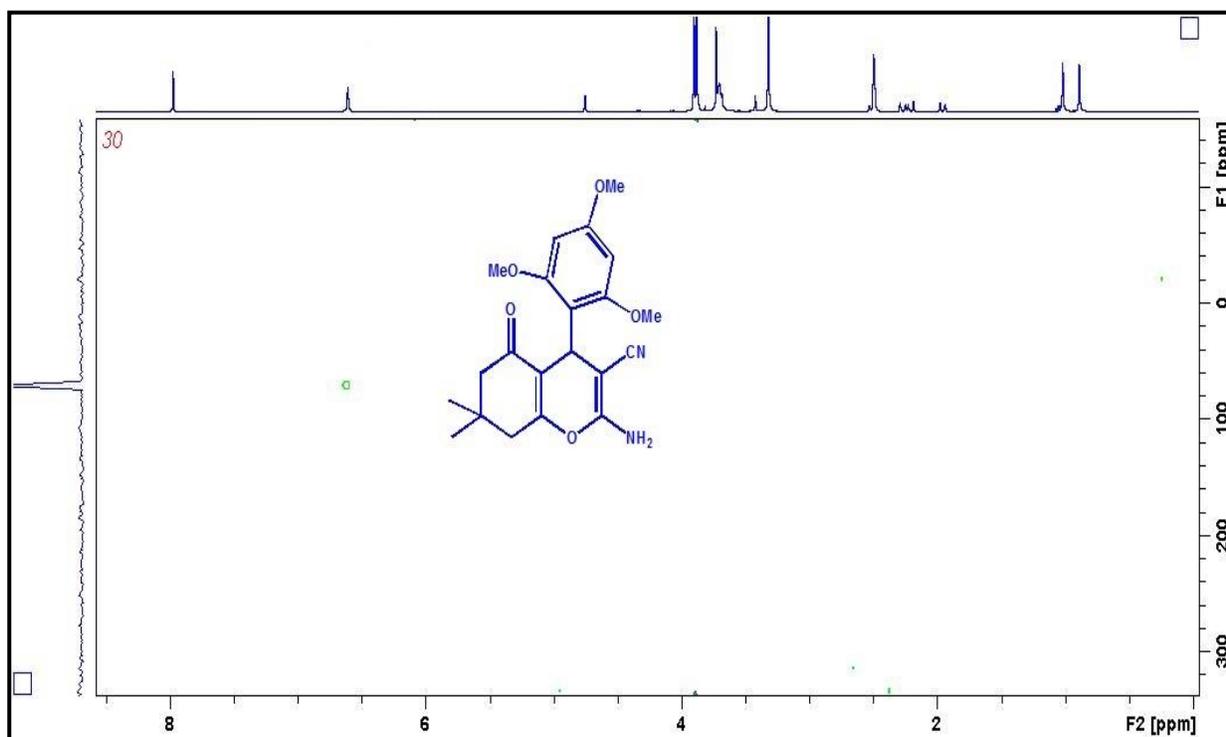
FTIR spectra of compound **4h**



¹H NMR spectra of compound 4i



¹³C NMR 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, Even Electron Ions

40 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

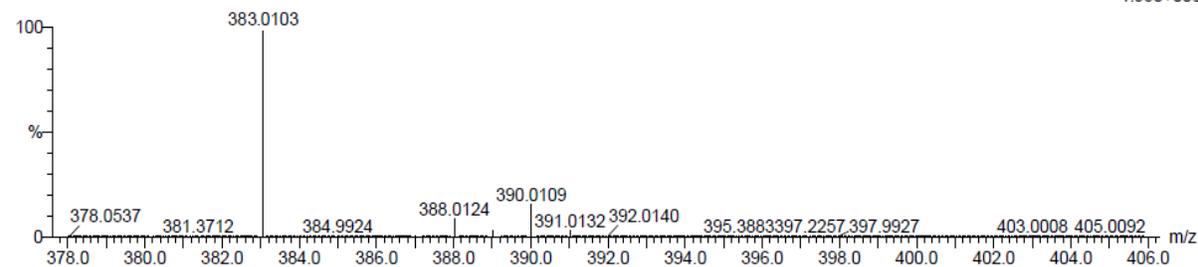
Elements Used:

C: 20-25 H: 20-25 N: 0-5 O: 0-5

U-6 53 (1.754) Cm (1:61)

TOF MS ES-

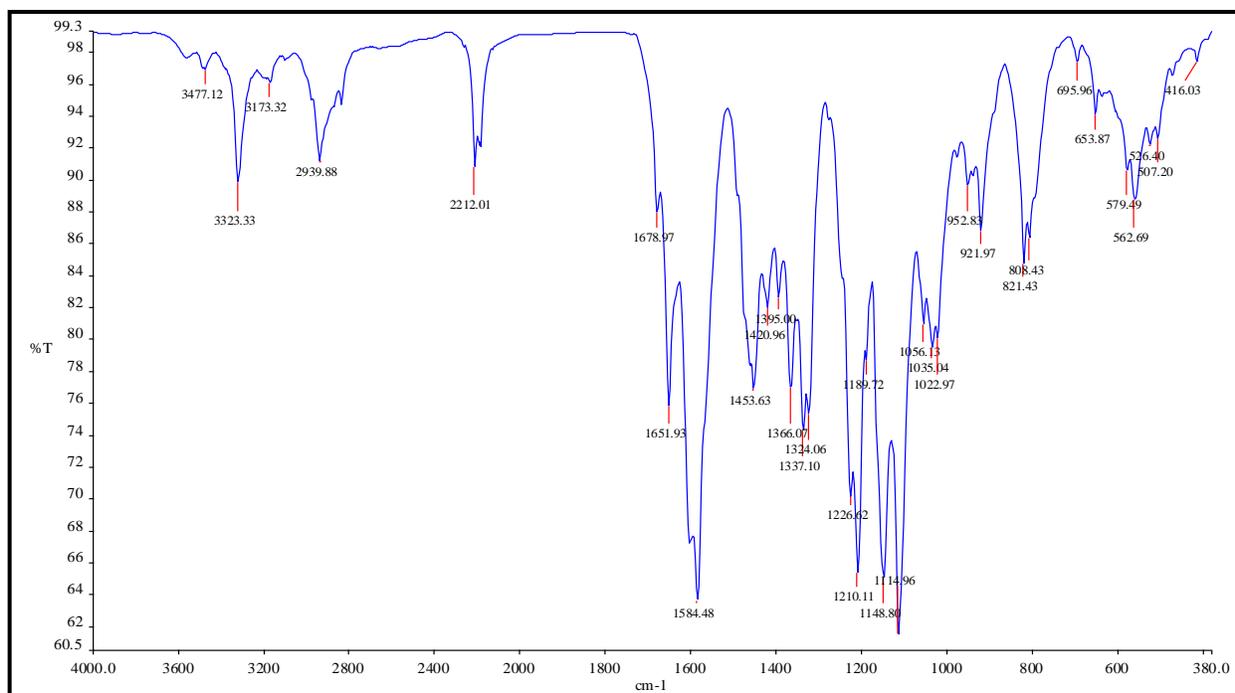
1.95e+006



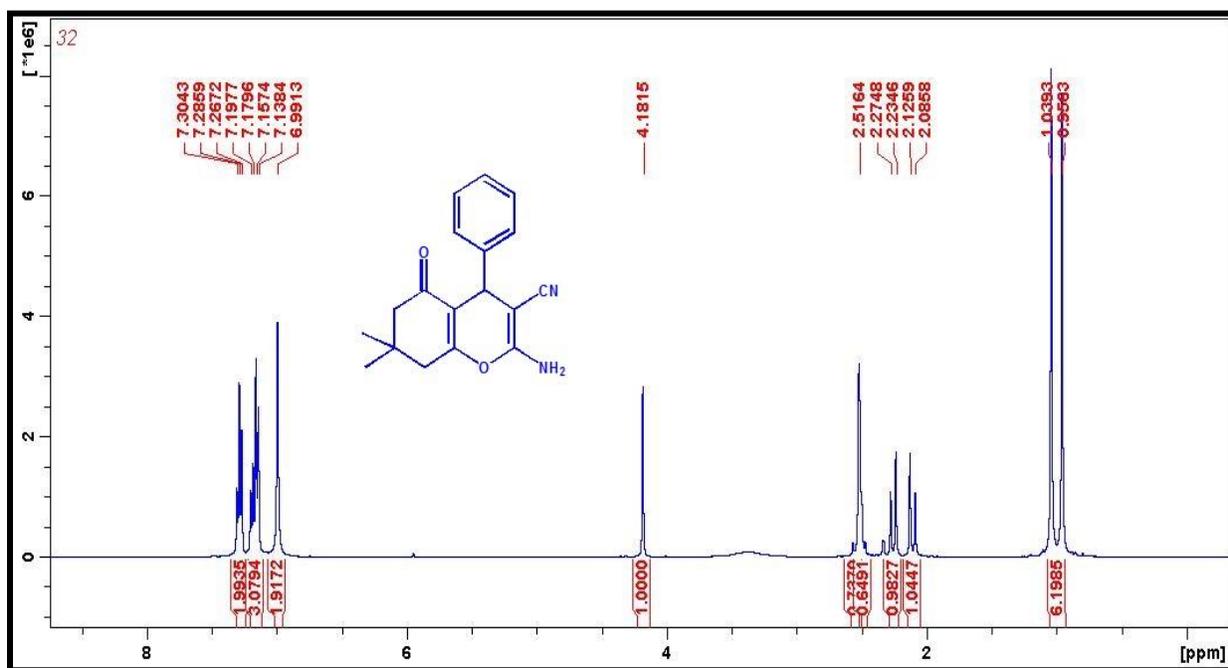
Minimum: -1.5
Maximum: 5.0 5.0 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
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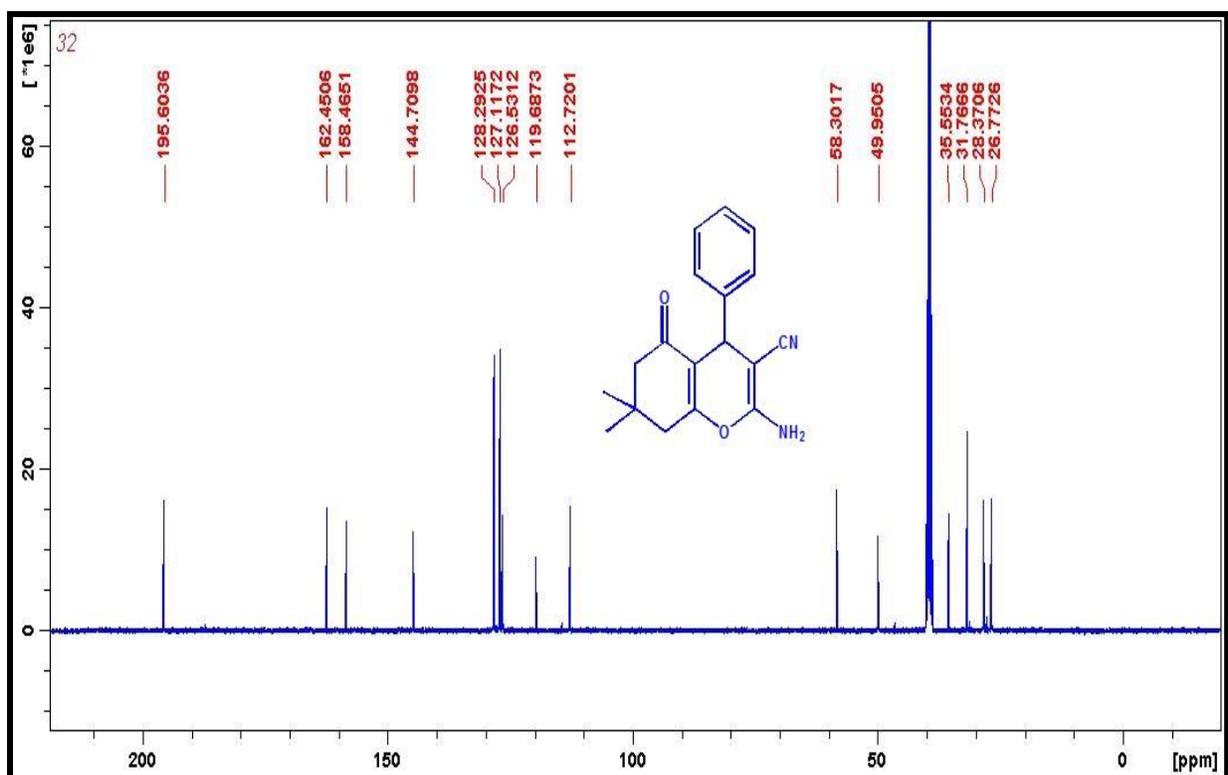
HRMS spectra of compound **4i**



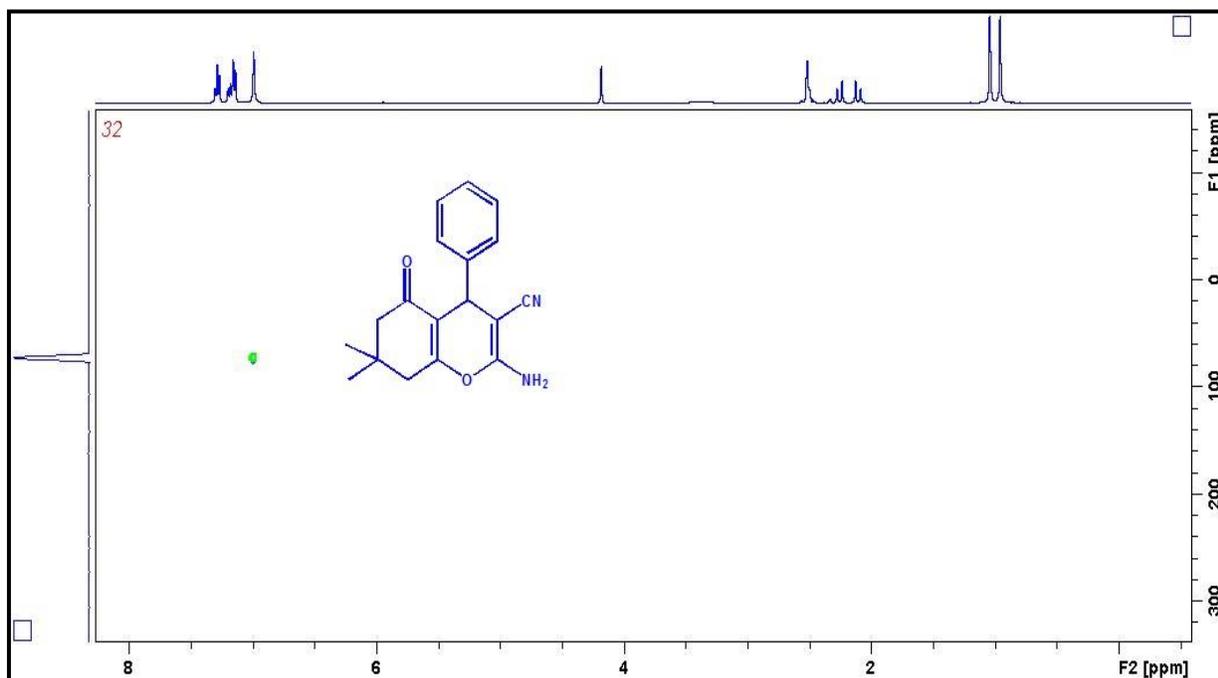
FTIR spectra of compound **4i**



^1H NMR spectra of compound 4j



^{13}C NMR 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, Even Electron Ions

15 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

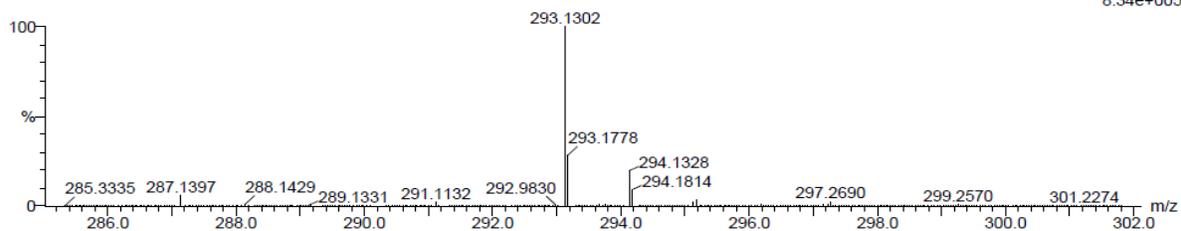
Elements Used:

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U-32 61 (2.024) Cm (1:61)

TOF MS ES-

8.34e+005

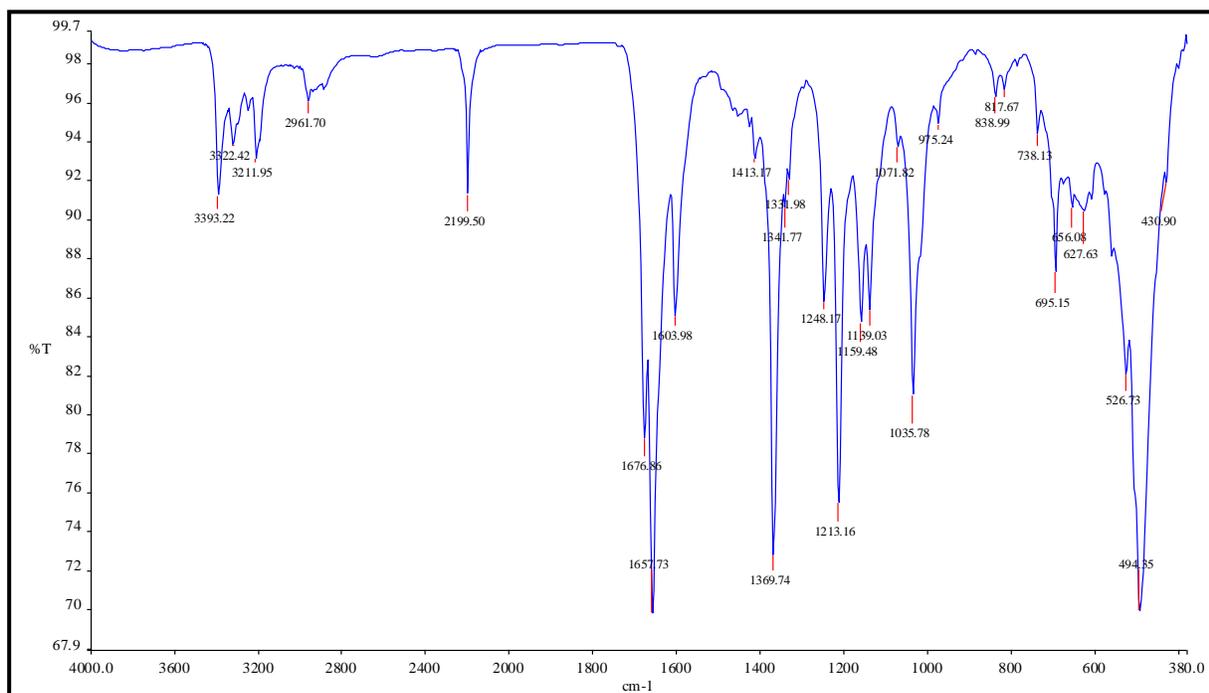


Minimum:

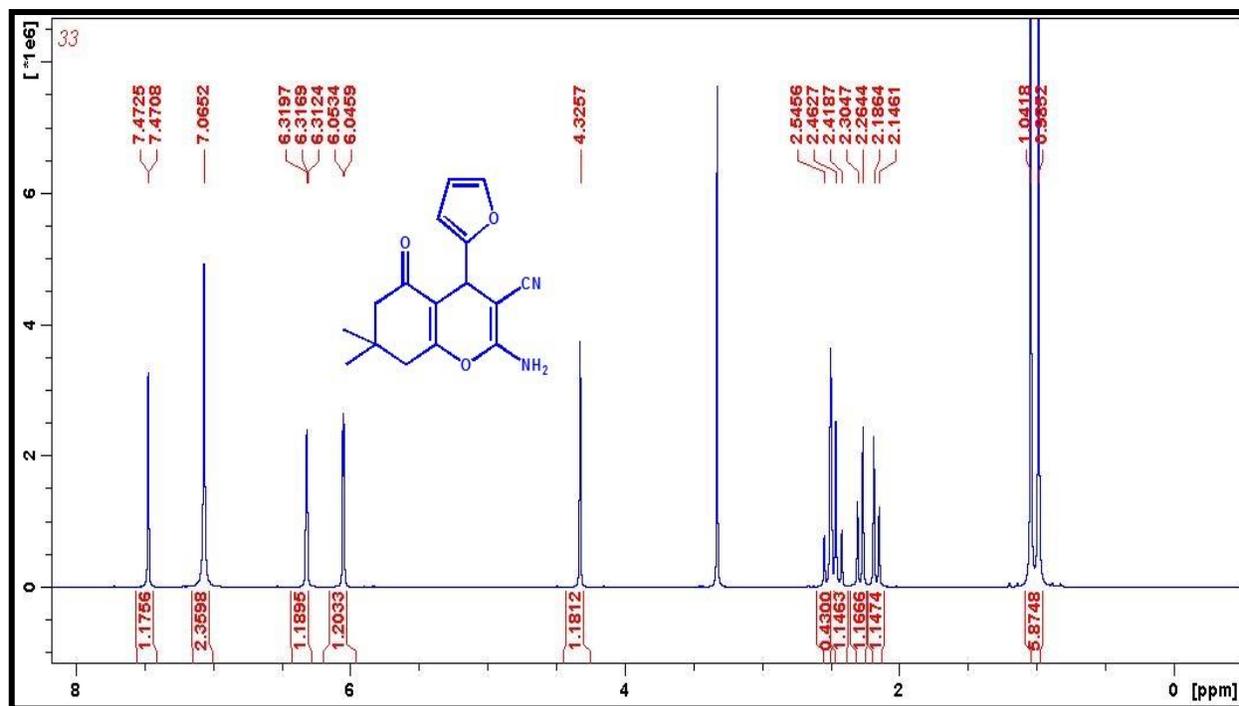
Maximum: 5.0 5.0 -1.5 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
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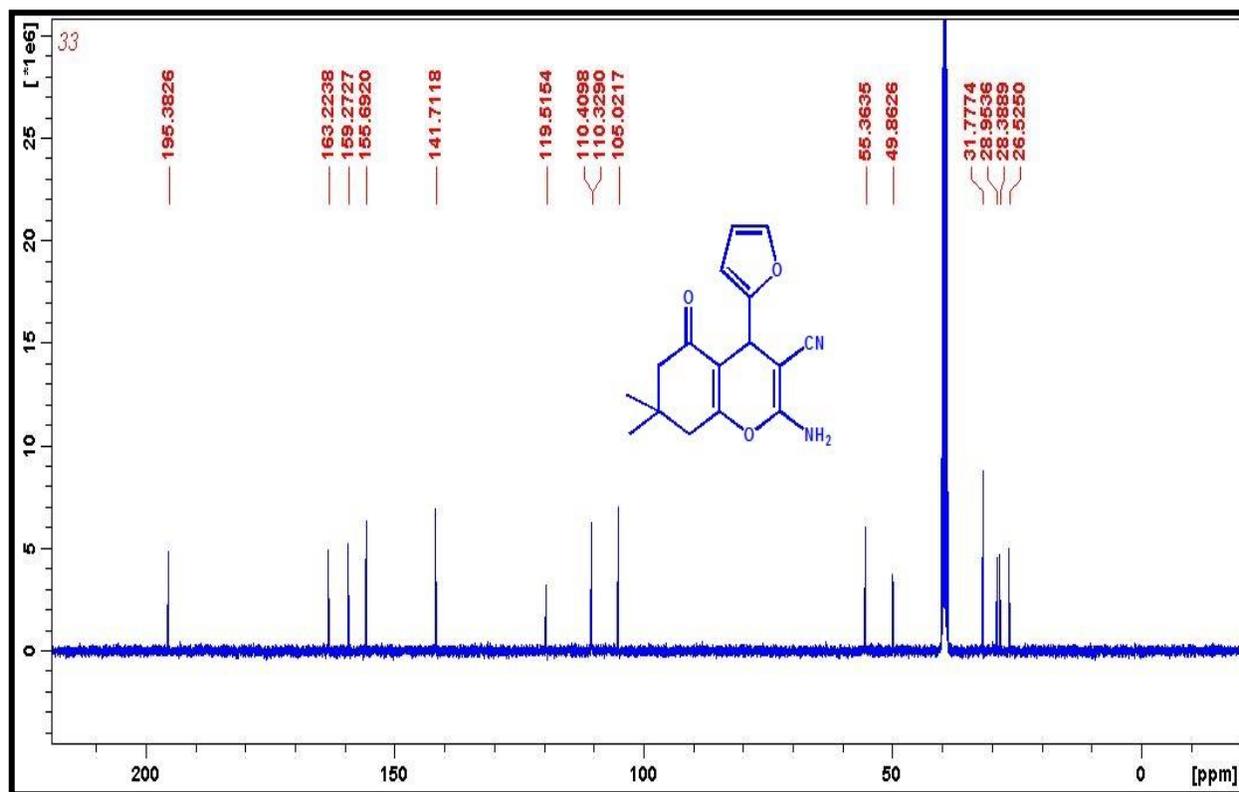
HRMS spectra of compound **4j**



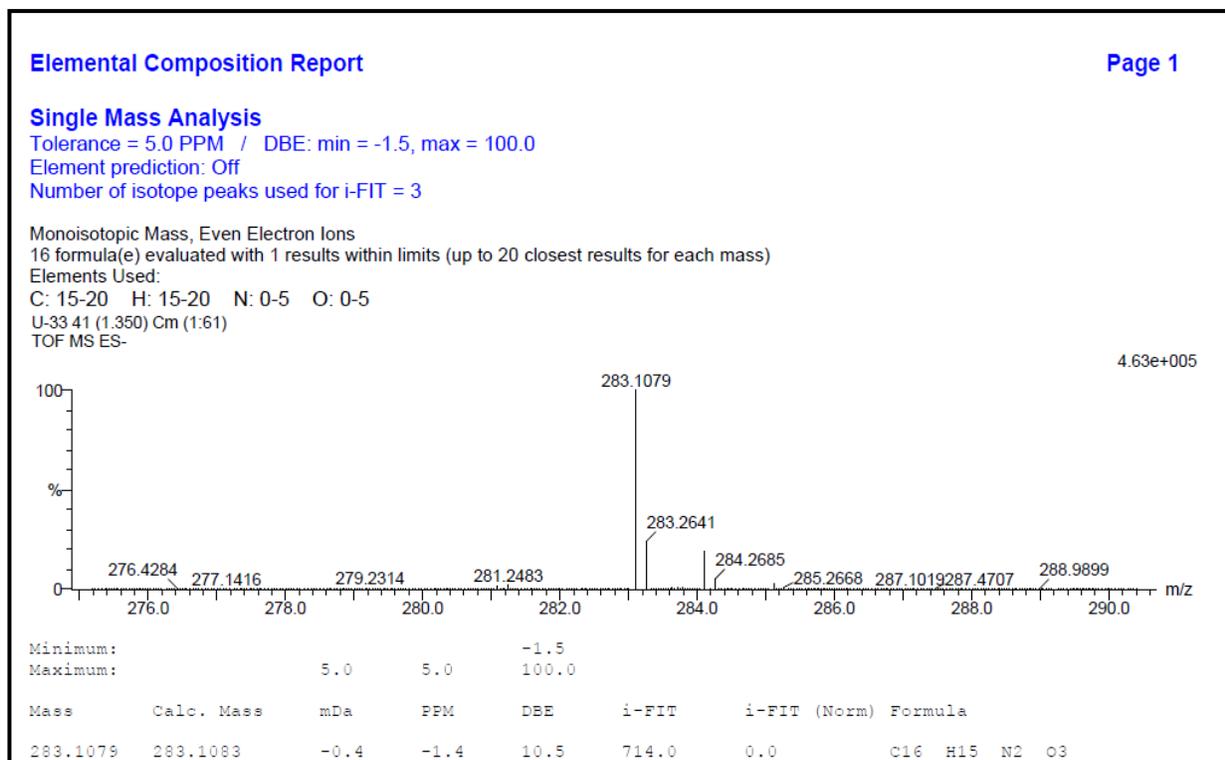
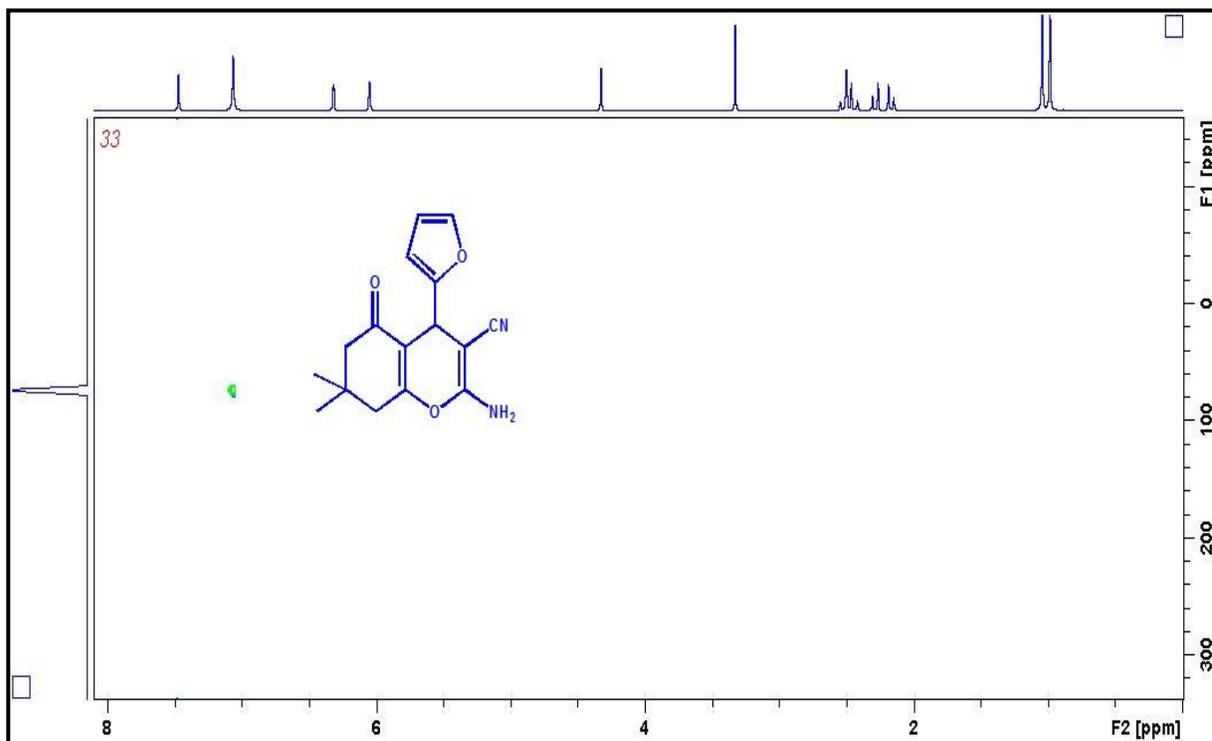
FTIR spectra of compound **4j**



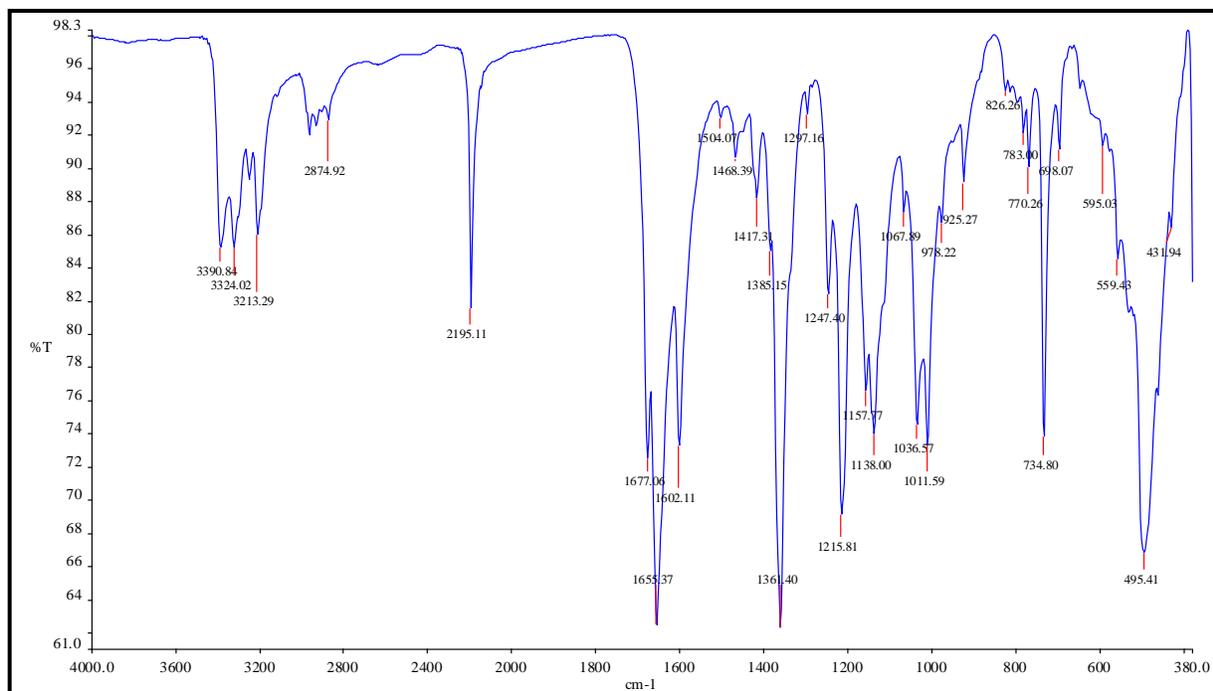
¹H NMR spectra of compound **4k**



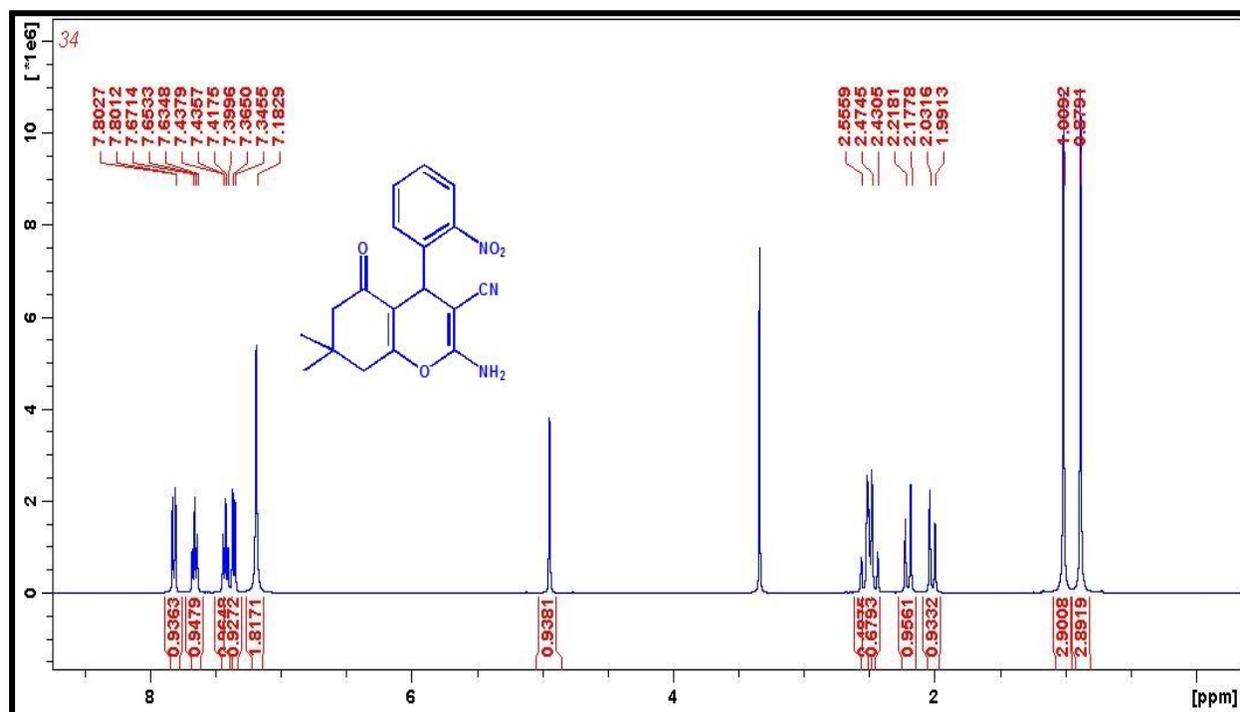
¹³C NMR spectra of compound **4k**



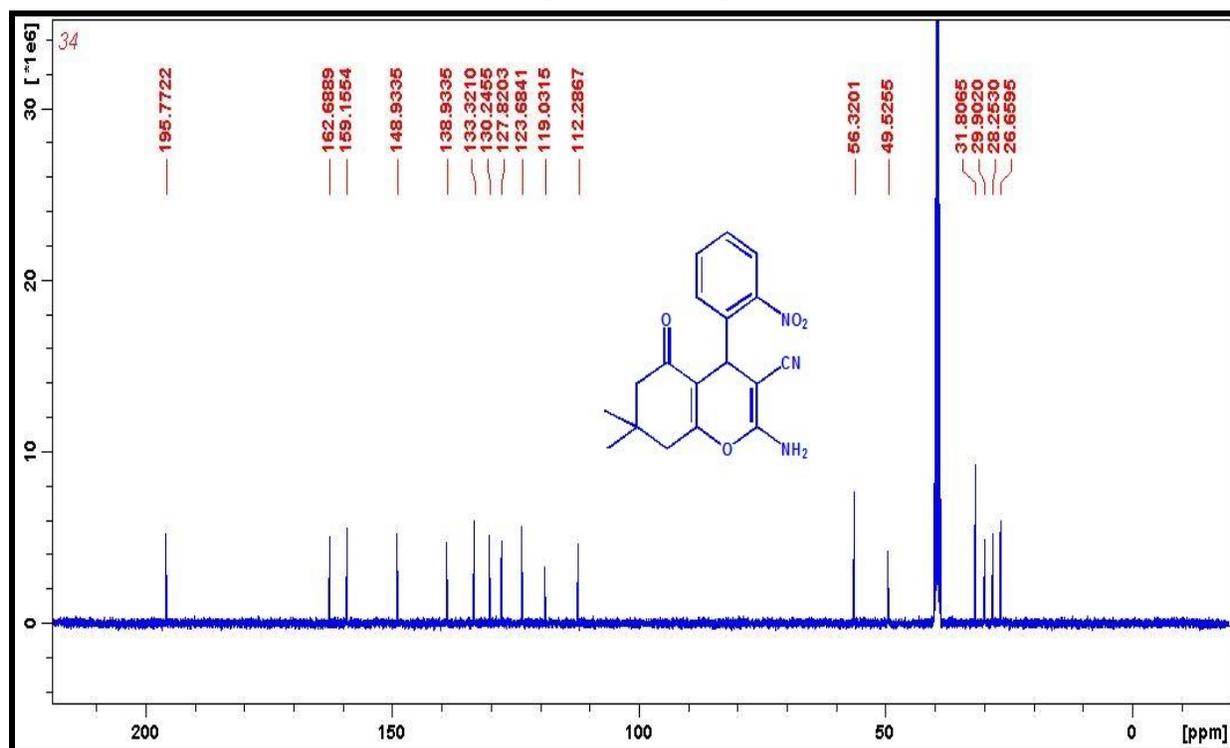
HRMS spectra of compound **4k**



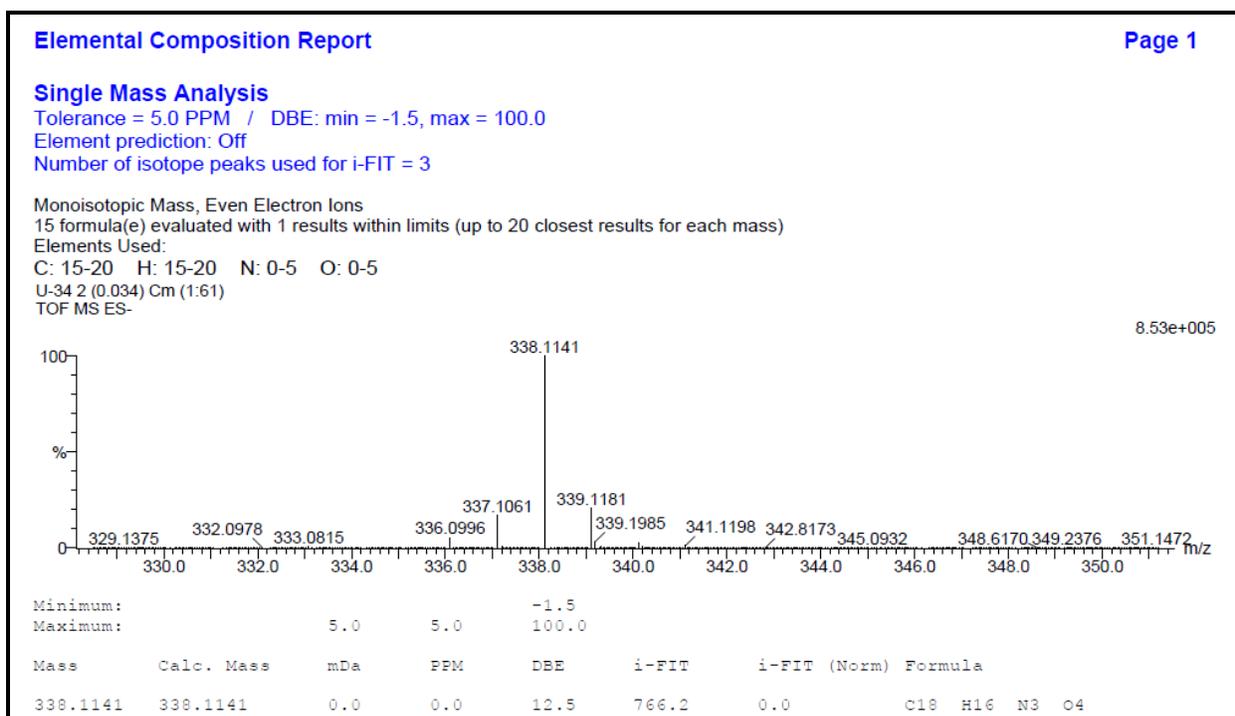
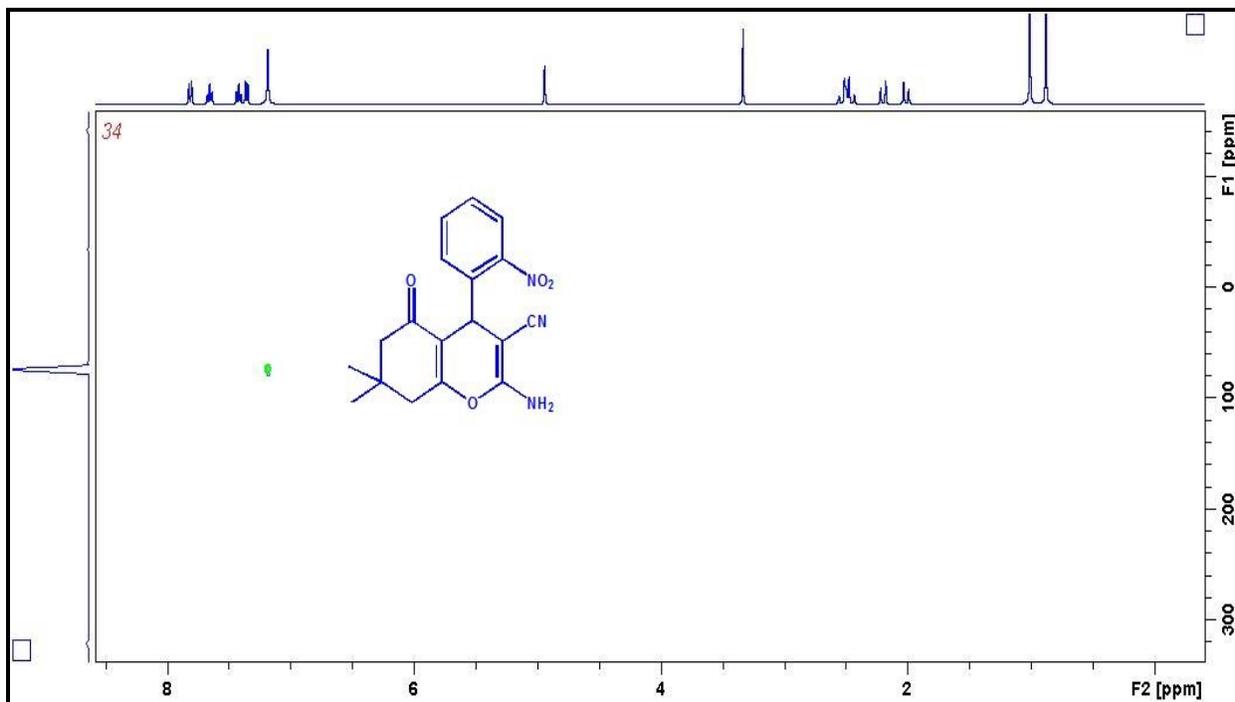
FTIR spectra of compound **4k**



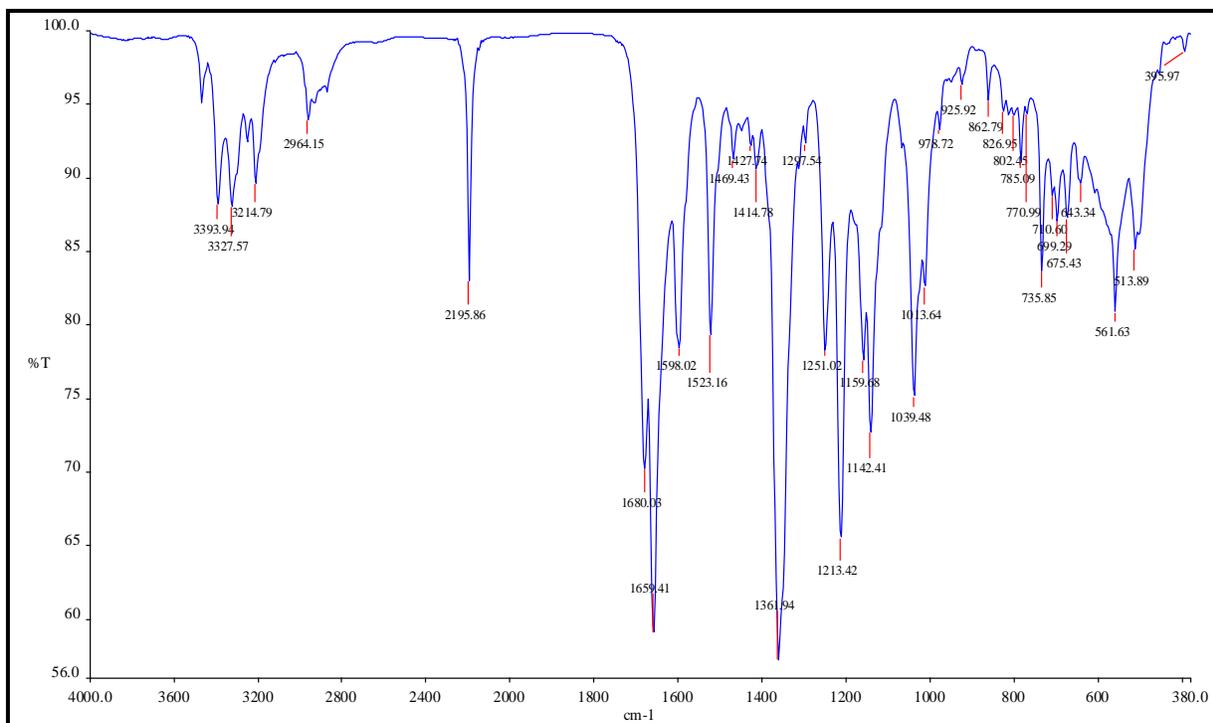
^1H NMR spectra of compound **41**



^{13}C NMR spectra of compound **41**



HRMS spectra of compound **41**



FTIR spectra of compound **4I**

CHAPTER-5

Ru-Hydroxyapatite: An Efficient And Reusable Catalyst For The Multicomponent Synthesis of Pyranopyrazoles Under Facile Green Conditions

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Current Organic Synthesis, 2016, 13, 893-900

RESEARCH ARTICLE



Ru-Hydroxyapatite: An Efficient and Reusable Catalyst for the Multicomponent Synthesis of Pyranopyrazoles under Facile Green Conditions



Surya Narayana Maddila, Suresh Maddila, Werner E. van Zyl and Sreekantha B. Jonnalagadda*

This chapter is published in the **Current Organic Synthesis** and has been structured according to the journal's format

Ru-Hydroxyapatite: An Efficient And Reusable Catalyst For The Multicomponent Synthesis of Pyranopyrazoles Under Facile Green Conditions

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Abstract: An efficient, green and facile protocol for synthesis of pyranopyrazole derivatives through the reaction of aromatic aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate is developed using Ru loaded hydroxyapatite (Ru-CaHAp) as catalyst. The eco-friendly one-pot reactions in ethanol-water mixture are fast (≈ 15 min) and occur at room temperature. Catalyst was fully characterized by various techniques. The chemical structures of the synthesized compounds were identified and confirmed by ^1H NMR, ^{15}N NMR, ^{13}C NMR, FT-IR and HR-MS spectral data. The noteworthy advantages offered by this method are environmentally-friendly simple procedure, mild conditions, short reaction times, recyclable catalyst and good to excellent (89 to 98%) yields of products.

Keywords: Green Synthesis, Multicomponent Reaction, One-pot reaction, Ru-CaHAp catalyst, Recyclable, Pyranopyrazole.

5.1. Introduction

Multicomponent reactions (MCRs), with three or more reactants combined in a single-step process to afford a single product in high yields have become increasingly popular in the recent years [1,2]. MCRs have fascinated researchers due to the governing green principles [3], and are ideally suited for combinatorial synthesis and for discovery of new drugs and agrochemicals [4-6]. The MCRs have become extremely significant synthetic methods, as they are efficient means for designing of organic compounds without isolation of intermediates or modification the reaction conditions. The other advantages of these reactions include high bond-forming efficiency, cost effectiveness, energy saving and simple workup procedures [6,7]. However, further improvement and discovery of new MCRs is still the need of the time.

In the recent past, the interest in exploring the scope of heterogeneous catalysts in organic synthesis has enhanced remarkably [8-10]. Compared to conventional synthetic methods, the use of heterogeneous catalysts has numerous advantages including reusability, benign and cost effectiveness [11]. Relative to conventional linear syntheses, these eco-friendly protocols have other benefits, such as varied surface characteristics, long catalytic life, thermal stability and atom economy [9-11].

Furthermore, these catalysts can be conveniently be handled and making the experimental procedure simple and more green.

Hydroxyapatites (HAPs) are known for high chemical stability and good affinity for organic compounds [12]. HAPs materials have both acidic and basic sites in crystal lattice and are anticipated to perform the both acidic and basic nature catalyst [13]. Normal HAPs possess calcium ions surrounded by phosphate anions parallel to the hexagonal axis. They have been used as biomaterials, adsorbents, and ion exchangers [14]. Recently, scope of hydroxyapatites as macro ligands for catalytically active centers has also been disclosed [15]. The catalytic properties of HAPs have been explored for the dehydration and dehydrogenation of alcohols [16], fertilizer production [17], water purification [18], and medical treatment like in targeted and controlled drug delivery systems [19]. In this communication, we report the preparation and characterization of new hydroxyapatites like compounds and modified hydroxyapatites loaded with transition metals and their performance as catalysts for the synthesis of heterocyclic molecules and carbon-carbon bond-forming reactions.

Pyranopyrazoles are an important class of heterocyclic compounds, which are essential components of many biologically active compounds and are interesting templates for use in medicinal chemistry. Many of these compounds exhibit antimicrobial, antitumour and anti-inflammatory activity [20-22]. Pyranopyrazoles have also been used as ingredients in pharmaceutical preparations and as biodegradable agrochemicals [23]. Literature survey shows that many catalyzed methods have been reported for synthesis of various pyranopyrazole derivatives. To mention a few, such protocols employed TEA [24], [ChCl][ZnCl₂]₂ [25], I₂ [26], [DBU][Ac] [27], [(CH₂)₄SO₃HMIM][HSO₄] [28], Nano TiO₂ [29], NaOH/microwave [30], Amberlyst A21 [31], Cinchona alkaloid [32], silicotungstic acid [33], imidazole [34], [Dsim]AlCl₄ [35], L-Proline [36], Per-6-ABCD [37], piperidine [38], TEABr [39] and FeNi₃/SiO₂/HPGMNP [40]. With exception of few, many of the catalysts are relatively toxic and non-recyclable. Bulk of the reactions give low product yields and need costly reagents, strong acidic/basic and strict reaction conditions, plus tedious handling processes and long reaction times. Thus, improved reaction protocols with short reaction times overcoming those limitations are much sought after.

Earlier, we have reported few efficient protocols with excellent yields, for synthesis of derivatives of pyridines using Mg-V/CO₃, pyrazoles using CuO/ZrO₂ and pyrimidines using Mn/ZrO₂ as recyclable catalysts [8,9,41]. In continuation of our quest for development of efficacious and environmentally friendly procedures for important organic transformations, we explored the catalytic efficiency of Ru-HAps towards the synthesis of pyranopyrazole derivatives in one-pot reaction under green conditions.

5.2. Experimental section

5.2.1. Catalyst characterization

Micromeritics Tristar-II porosity and surface area analyzer was used to determine the surface area, pore size and pore volume of the catalyst material. The catalyst sample was degassed overnight using N₂ flow at 200 °C. The BJH adsorption-desorption curves were generated at -196 °C and were used to assess the catalyst's particulate properties. Employing a Bruker D8 Advance instrument (Cu K radiation source with a wave length of 1.5406 Å), the X-ray diffraction data related the structural phases of the catalyst were acquired. Using a Jeol JEM-1010 electron microscope and JEOL JSM-6100 microscope, the TEM and SEM analysis data was recorded. iTEM software was used analyze the TEM data and images. Employing the X-ray

analyzer (energy-dispersive), EDX-analysis on the SEM images was conducted. To confirm the elemental composition catalyst materials Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES) (Optima 5300 DV) was used.

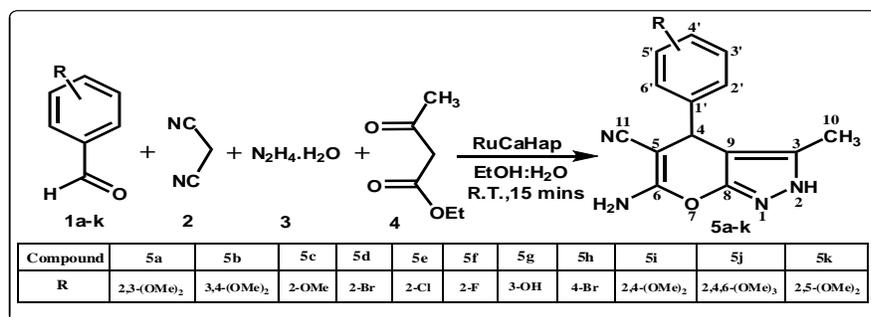
5.2.2. Preparation of catalyst

For the synthesis of Ca-hydroxyapatite (HAp) the co-precipitation approach was used [2-4] and a solution of diammonium hydrogen orthophosphate, $(\text{NH}_4)_2\text{HPO}_4$ (5.6 g), (1.00 mol) (Merck, 98.5 %) was adjusted to pH 11.0 using a dilute ammonia solution and then diluted to 250 mL with double distilled water. Similarly, a calcium nitrate tetrahydrate, $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ (23.7 g), (0.167 mol) (Merck, 99 %) solution was prepared and the pH adjusted to 11.0 and this solution was then diluted to 250 mL using double distilled water. The $(\text{NH}_4)_2\text{HPO}_4$ solution was added drop-wise to the $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ solution with constant and vigorous stirring at room temperature over a period of 1 h. The pH of the mixture was maintained at 11 throughout, using diluted ammonia. The resultant precipitate was heated to and maintained at 85 °C for 1.5 h and then allowed to cool to room temperature. Thereafter, the precipitate was filtered under vacuum and washed repeatedly until the filtrate was neutral, thus having ensured the removal of excess diluted ammonia. The HAp was then dried in an oven overnight at 120 °C and it was calcined at 500 °C for 6 hours. Supported catalysts were synthesized by adding the HAp to a solution of ruthenium (III) chloride hydrate ($\text{RuCl}_3 \cdot \text{XH}_2\text{O}$ (Aldrich 99.98 %)) to afford the weight percentage of 1.0 wt%, 2.5 wt% and 5.0 wt% of RuO_2 . The catalyst materials were dried overnight at 120 °C. The powdered form of the catalyst material was calcined at 500 °C for 6 h. The 2.5 wt% and 5.0 wt% Ru on CaHAp were prepared following similar procedure.

5.2.3. General procedure for the synthesis of pyranopyrazole derivatives:

The equimolar amounts of chosen aldehyde, taking the example of 2-methoxy benzaldehyde (0.516 g, 3.789 mmol), malononitrile (0.250 g, 3.789 mmol) and ethyl acetoacetate (0.493 g, 3.789 mmol) were mixed with hydrazine hydrate (0.284 g, 5.683 mmol) and dissolved in ethanol and water solvent (1:1, 10 ml) at room temperature (RT). Ru-HAp (50 mg) was added to the mixture as catalyst. The reaction mixture was stirred continuously for 15 minutes at RT, (Scheme 1) using a magnetic stirrer. The progress of the reaction was monitored by TLC. The reaction mixture was then filtered, and the filtrate was subsequently extracted with ethyl acetate and evaporated under reduced pressure to obtain the crude product. The crude product was further purified using EtOAc followed by hexane (4:6) to afford pure products. The recovered

catalyst was washed with dichloromethane, dried, and reused where necessary. The quantities of specific aldehydes and other reagents used and corresponding yields for each derivative are described in the physical data below:



Scheme 1. Synthesis of pyrano[2,3-c]pyrazoles derivatives

6-Amino-4-(2,3-dimethoxyphenyl)-3-methyl-2,4-dihydro--pyrano[2,3-c]pyrazole-5-carbonitrile (5a): 2,3-dimethoxybenzaldehyde (0.629 g, 3.785 mmol), malononitrile (0.250 g, 3.785 mmol); ethyl acetoacetate (0.492 g, 3.785 mmol), hydrazine hydrate (0.284 g, 5.677 mmol), and RuHAp (50 mg). Yield: 1.086 g (92%); ¹H NMR (400 MHz, DMSO-d₆) δ = 1.76 (s, 3H, CH₃), 3.64 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 4.82 (s, 1H, CH), 6.59 (dd, *J* = 7.5 Hz, 1.28 Hz, 1H, ArH), 6.80 (s, 2H, NH₂), 6.89 (d, *J* = 6.8 Hz, 1H, ArH), 6.99 (t, *J* = 8.0 Hz, 1H, ArH), 11.99 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): 9.42 (C10), 30.32 (C4), 55.48 (C8'), 56.66 (C5), 60.22 (C7'), 97.75 (C11), 111.06 (C1'), 120.72 (C5'), 120.97 (C4'), 123.98 (C6'), 135.09 (C9), 137.29 (C8), 146.19 (C3), 152.15 (C3'), 154.95 (C2'), 161.12 (C6); FT-IR (KBr, cm⁻¹): 1395, 1475, 1519, 1638, 2186, 3113, 3375; HRMS 2972, of [C₁₆H₁₆N₄O₃ - H]⁺ (*m/z*): 311.1139; Calcd.: 311.1144.

6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-2,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (5b): 3,4-dimethoxybenzaldehyde (0.629 g, 3.785 mmol), malononitrile (0.250 g, 3.785 mmol), ethyl acetoacetate (0.492 g, 3.785 mmol), hydrazine hydrate (0.284 g, 5.677 mmol), and Ru-HAp (50 mg); Yield: 1.062 g (90%); ¹H NMR (400 MHz, DMSO-d₆) δ = 1.82 (s, 3H, CH₃), 3.69 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 4.54 (s, 1H, CH), 6.69 (dd, *J* = 7.5 Hz, 2.0 Hz, 1H, ArH), 6.75 (d, *J* = 2.0 Hz, 1H, ArH), 6.80 (s, 1H, NH₂), 6.88 (d, *J* = 8.3 Hz, 1H, ArH), 12.1 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): 9.79 (C10), 35.79 (C4), 55.41 (C5), 57.42, 97.67 (C11), 111.19 (C5'), 111.72 (C2'), 119.46 (C1'), 120.81 (C6'), 135.63 (C9), 136.86 (C8), 147.53 (C3), 148.51 (C4'), 154.68 (C3'), 160.72 (C6); FT-IR (KBr, cm⁻¹): 1217, 1325, 1451, 1490, 1589, 1660, 2184, 3132; HRMS of [C₁₆H₁₆N₄O₃ - H]⁺ (*m/z*): 311.0734; Calcd.: 311.0737.

6-Amino-4-(2-methoxyphenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile (5c): 2-methoxybenzaldehyde (0.516 g, 3.789 mmol), malononitrile (0.250 g, 3.789 mmol), ethyl acetoacetate (0.493 g, 3.789 mmol), hydrazine hydrate (0.284 g, 5.683 mmol) and Ru-HAp (50 mg); Yield: 1.047 g (98%); ^1H NMR (400 MHz, DMSO- d_6) δ = 1.78 (s, 3H, CH₃), 3.77 (s, 3H, OCH₃), 4.96 (s, 1H, CH), 6.78 (s, 2H, NH₂), 6.89 (t, J = 14.7 Hz, 1H, ArH), 6.98 (t, J = 7.6 Hz, 2H, ArH), 7.17–7.21 (m, 1H, ArH), 12.00 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl₃): 9.45 (C10), 29.11 (C4), 55.53 (C5), 56.34 (C7'), 97.87 (C11), 111.26 (C1'), 120.77 (C3'), 120.85 (C5'), 127.88 (C4'), 128.57 (C6'), 132.06 (C9), 135.03 (C3), 155.02 (C8), 156.31 (C2'), 161.43 (C6); FT-IR (KBr, cm^{-1}): 1241, 1463, 1486, 1595, 1655, 2194, 2837, 3154, 3338, 3374; HRMS of $[\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_2 - \text{H}]^+$ (m/z): 281.1040; Calcd.: 281.1039.

6-Amino-4-(2-bromophenyl)-3-methyl-2,4-dihydropyrano--[2,3-c]pyrazole-5-carbonitrile (5d): 2-bromobenzaldehyde (0.700 g, 3.783 mmol), malononitrile (0.249 g, 3.783 mmol), ethyl acetoacetate (0.492 g, 3.783 mmol), hydrazine hydrate (0.284 g, 5.674 mmol), and Ru-HAp (50 mg); Yield: 0.716 g (92%); ^1H NMR (400 MHz, DMSO- d_6) δ = 1.76 (s, 3H, CH₃), 5.06 (s, 1H, CH), 6.94 (s, 2H, NH₂), 7.15–7.19 (m, 2H, ArH), 7.32–7.36 (m, 2H, ArH), 7.58 (dd, J = 8.06 Hz, 0.84 Hz, 1H, ArH), 12.12 (s, 1H, NH); ^{13}C NMR (100 MHz, CDCl₃): 9.62 (C10), 35.84 (C4), 55.96 (C5), 96.99 (C11), 120.25 (C8), 122.38 (C2'), 127.72 (C5'), 128.36 (C4'), 128.87 (C6'), 130.67 (C3'), 131.93 (C9), 135.38 (C3), 154.86 (C1'), 161.26 (C6); FT-IR (KBr, cm^{-1}): 1162, 1407, 1488, 1609, 1653, 2190, 2640, 3153, 3390; HRMS of $[\text{C}_{14}\text{H}_{11}\text{BrN}_4\text{O} - 2\text{H}]^+$ (m/z): 328.0434; Calcd.: 328.0441.

6-Amino-4-(2-chlorophenyl)-3-methyl-2,4-dihydropyrano--[2,3-c]pyrazole-5-carbonitrile (5e): 2-chlorobenzaldehyde (0.532 g, 3.784 mmol), malononitrile (0.250 g, 3.784 mmol), and ethyl acetoacetate (0.492 g, 3.784 mmol), hydrazine hydrate (0.284 g, 5.676 mmol) and RuHAp (50 mg); Yield: 0.809 g (94%); ^1H NMR (400 MHz, DMSO- d_6) δ = 1.76 (s, 3H, CH₃), 5.06 (s, 1H, CH), 6.93 (s, 2H, NH₂), 7.18 (d, J = 8.0 Hz, 1H, ArH), 7.24–7.31 (m, 2H, ArH), 7.41 (dd, J = 7.8 Hz, 1.5 Hz, 1H, ArH), 12.12 (s, 1H, NH); ^{13}C NMR (100 MHz, CDCl₃): 9.49 (C10), 28.56 (C4), 55.72 (C5), 96.82 (C11), 120.36 (C8), 127.72 (C2'), 128.56 (C4'/C5'), 129.45 (C6'), 130.67 (C3'), 131.93 (C9), 135.35 (C3), 154.90 (C1'), 161.26 (C6); FT-IR (KBr, cm^{-1}): 1047, 1408, 1609, 1653, 2189, 3390; HRMS of $[\text{C}_{14}\text{H}_{11}\text{N}_4\text{OCl} - \text{H}]^+$ (m/z): 285.0540; Calcd.: 285.0543.

6-Amino-4-(2-fluorophenyl)-3-methyl-2,4-dihydropyrano--[2,3-c]pyrazole-5-carbonitrile (5f): 2-fluorobenzaldehyde (0.470 g, 3.786 mmol), malononitrile (0.250 g, 3.786 mmol), ethyl

acetoacetate (0.492 g, 3.786 mmol), hydrazine hydrate (0.284 g, 5.679 mmol) and RuHAp (50 mg); Yield: 0.766 g(89%); ^1H NMR (400 MHz, DMSO- d_6) δ = 1.80 (s, 3H, CH₃), 4.86 (s, 1H, CH), 6.91 (s, 2H, NH₂), 7.14–7.18 (m, 3H, ArH), 7.25–7.29 (m, 1H, ArH), 12.10 (s, 1H, NH); ^{13}C NMR (100 MHz, CDCl₃): 9.36 (C10), 30.02 (C4), 55.52 (C5), 96.59 (C11), 115.49 (d, J = 23.11 Hz, C3'), 120.55 (C8), 124.68 (C1'), 128.82 (d, J = 9.3 Hz, C4'), 129.78 (d, J = 4.65 Hz, C5'), 130.72 (d, J = 12.22 Hz, C6'), 135.32 (C9), 154.87 (C6), 159.98 (d, J = 258.4 Hz, C2'); FT-IR (KBr, cm^{-1}): 1209, 1256, 1406, 1484, 1595, 1651, 2189, 3164, 3385; HRMS of [C₁₄H₁₁N₄O – H]⁺ (m/z): 269.0835; Calcd.: 269.0839.

6-Amino-4-(3-hydroxyphenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile (5g): 3-hydroxy benzaldehyde (0.462 g, 3.783 mmol), malononitrile (0.249 g, 3.783 mmol), ethyl acetoacetate (0.492 g, 3.783 mmol), hydrazine hydrate (0.284 g, 5.674 mmol) and RuHAp (50 mg); Yield: 0.905 g (90%); ^1H NMR (400 MHz, DMSO- d_6) δ = 1.81 (s, 3H, CH₃), 4.48 (s, 1H, CH), 6.53 (s, 1H, ArH), 6.59–6.62 (m 2H, ArH), 6.83 (s, 2H, NH₂), 7.09 (t, J = 7.8 Hz, 1H, ArH), 9.29 (s, 1H, OH), 12.07 (s, 1H, NH); ^{13}C NMR (100 MHz, CDCl₃): 9.73 (C10), 36.14 (C4), 57.26 (C5), 97.66 (C11), 113.80 (C4'), 114.10 (C2'), 118.15 (C6'), 120.77 (C5'), 129.23 (C1'), 135.53 (C9), 145.93 (C3), 154.73 (C8), 157.39 (C3'), 160.80 (C6); FT-IR (KBr, cm^{-1}): 1283, 1348, 1485, 1591, 1647, 2177, 3163, 3360; HRMS of [C₁₄H₁₂N₄O₂ – H]⁺ (m/z): 267.0878; Calcd.: 267.0882.

6-Amino-4-(4-bromophenyl)-3-methyl-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile (5h): 4-Bromobenzaldehyde (0.700 g, 3.783 mmol), malononitrile (0.249 g, 3.783 mmol), ethyl acetoacetate (0.492 g, 3.783 mmol), hydrazine hydrate (0.284 g, 5.674 mmol), and Ru-HAp (50 mg); Yield: 1.147 g (93%); ^1H NMR (400 MHz, DMSO- d_6) δ = 1.79 (s, 3H, CH₃), 4.61 (s, 1H, CH), 6.91 (s, 2H, NH₂), 7.13 (d, J = 8.4 Hz, 2H, ArH), 7.50 (d, J = 8.4 Hz, 2H, ArH), 12.12 (s, 1H, NH); ^{13}C NMR (100 MHz, CDCl₃): 9.70 (C10), 35.60 (C4), 56.68 (C5), 97.09 (C11), 119.72 (C9), 120.59 (C4'), 126.90 (C8), 129.70 (C2'/C6'), 131.34 (C3'/C5'), 135.65 (C1'), 143.86 (C3), 160.88 (C6); FT-IR (KBr, cm^{-1}): 1162, 1221, 1484, 1596, 1646, 2180, 3141; HRMS of [C₁₄H₁₁BrN₄O – 2H]⁺ (m/z): 328.0929; Calcd.: 328.0937.

6-Amino-4-(2,4-dimethoxyphenyl)-3-methyl-2,4-dihydro--pyrano[2,3-c]pyrazole-5-carbonitrile (5i): 2,4-dimethoxybenzaldehyde (0.629 g, 3.785 mmol), malononitrile (0.250 g, 3.785 mmol), ethyl acetoacetate (0.492 g, 3.785 mmol), hydrazine hydrate (0.284 g, 5.677 mmol), and Ru-HAp (50 mg); Yield: 1.062 g (90%); ^1H NMR (400 MHz, DMSO- d_6) δ = 1.78 (s,

3H, CH₃), 3.53 (s, 3H, OCH₃), 3.66 (s, 3H, OCH₃), 5.01 (s, 1H, CH), 6.13–6.21 (m, 2H, ArH), 6.29 (s, 1H, ArH), 6.53 (s, 2H, NH₂). 11.73 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): 9.13 (C10), 24.56 (C4), 55.03 (C7'/C8'), 55.43 (C5), 91.09 (C3'), 97.88 (C11), 111.73 (C5'), 121.43 (C6'), 133.86 (C9), 155.76 (C4'), 159.54 (C2'), 161.94 (C6); FT-IR (KBr, cm⁻¹): 1407, 1489, 1589, 1653, 2184, 3172; HRMS of [C₁₆H₁₆N₄O₃ – H]⁺ (m/z): 311.0984; Calcd.: 311.0988.

6-Amino-4-(2,4,6-trimethoxyphenyl)-3-methyl-2,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (5j): 2,4,6-trimethoxybenzaldehyde (0.743 g, 3.786 mmol), malononitrile (0.250 g, 3.786 mmol), ethyl acetoacetate (0.492 g, 3.786 mmol), hydrazine hydrate (0.284 g, 5.679 mmol), and Ru-HAp (50 mg); Yield: 1.147 g (89%); ¹H NMR (400 MHz, DMSO-d₆) δ = 1.79 (s, 3H, CH₃), 3.73 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 5.12 (s, 1H, CH), 6.29 (s, 2H, ArH), 6.69 (s, 2H, NH₂), 12.29 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): 9.66 (C10), 25.39 (C4), 51.50 (C4'), 55.01 (C2'), 55.42 (C6'), 55.63 (C5), 91.07 (C11), 112.27 (C3'/C5'), 130.57 (C9), 154.34 (C6'), (159.53 (C2'), 160.50 (C4'), 161.22 (C6);, FT-IR (KBr, cm⁻¹): 1227, 1397, 1454, 1645, 2189, 2943, 3202, 3322; HRMS of [C₁₇H₁₈N₄O₄ – H]⁺ (m/z): 341.0992; Calcd.: 341.1008.

6-Amino-4-(2,5-dimethoxyphenyl)-3-methyl-2,4-dihydro--pyrano[2,3-c]pyrazole-5-carbonitrile (5k): 2,5-dimethoxy-benzaldehyde (0.629 g, 3.785 mmol), malononitrile (0.250 g, 3.785 mmol), ethyl acetoacetate (0.492 g, 3.785 mmol), hydrazine hydrate (0.284 g, 5.677 mmol) and RuHAp (50 mg); Yield: 1.039 g (88%); ¹H NMR (400 MHz, DMSO-d₆) δ = 1.81 (s, 3H, CH₃), 3.76 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 4.95 (s, 1H, CH), 6.89 (s, 2H, NH₂), 7.09 (d, *J* = 1.2 Hz, 2H, ArH), 7.49 (s, 1H, ArH), 12.09 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): 9.61 (C10), 51.62 (C4), 55.44 (C8'), 119.45 (C1'), 56.28 (C7'), 103.92 (C11), 109.77 (C5), 112.84 (C3'), 113.61 (C4'), 122.00 (C6'), 133.56 (C9), 151.04 (C3), 152.64 (C8), 153.11 (C2'), 156.47 (C5'), 160.74 (C6); FT-IR (KBr, cm⁻¹): 1221,1331, 1492, 1653, 2202, 2939, 3194, 3375; HRMS of [C₁₆H₁₆N₄O₃ – H]⁺ (m/z): 311.0848; Calcd.: 311.0844.

5.3. Results and discussion

5.3.1. BET surface area (BET) and elemental (ICP) analysis

The texture of the prepared catalyst was determined by physisorption analysis. The N₂ physisorption isotherms for the Ru supported on CaHAp catalyst showed a characteristic hysteresis loop of type-IV adsorption isotherm demonstrating the mesoporous nature of the catalyst (**Figure 1**). The pore size data for the samples, exhibited values in the mesoporous

region ($3 \text{ nm} < \text{pore size} < 50 \text{ nm}$) and the p/p_0 ratio of the isotherms was in the range 0.81-0.96. The 1% catalyst showed a surface area of $46 \text{ m}^2 \text{ g}^{-1}$ with a pore volume of 0.217 cc g^{-1} . The ICP analysis results showed the presence of anticipated amount of 1% Ru in the catalyst (0.98 mol %).

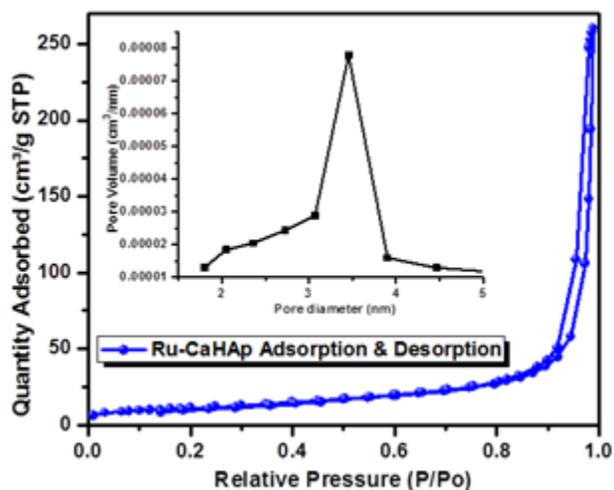


Figure 1. N₂ adsorption & desorption spectra of 1% Ru-CaHAp catalyst

5.3.2. TEM analysis

The TEM micrograph reveals more structural information of the catalyst. Figure 2 illustrates a distinctive TEM image of Ru supported on HAp, from which it can be seen that the Ru nanoparticles revealed rod-like shapes and particle dimension ranged between 220 and 250 nm. No drastic change was noticed in the morphology of the used catalyst.

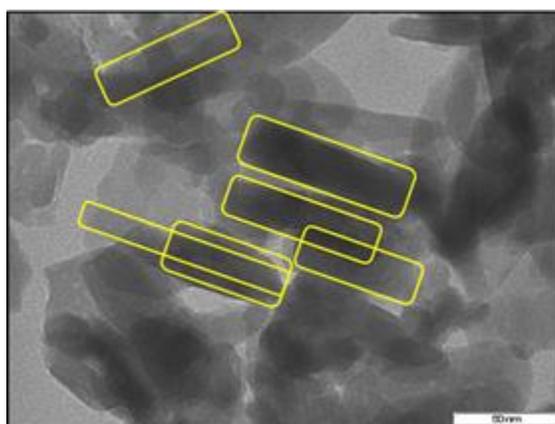


Figure 2. TEM micrograph of Ru-CaHAp catalyst

5.3.3. SEM analysis

Figure 3 shows an illustrative SEM surface morphology micrograph of the sample Ru on HAp. Significant large cubic sheet irregular shapes were perceived from the low magnification SEM image of Ru-HAp. This micrograph reveals that the aggregative state of the HAp important particles are with Ru. The SEM–EDX micrographs confirm the uniform distribution of ruthenium on the hydroxyapatite surface. The SEM-EDX agreed with the data from ICP elemental analysis. Furthermore, the morphology of the catalyst as per the SEM images noticeably point to the crystallinity and homogeneity of the sample.

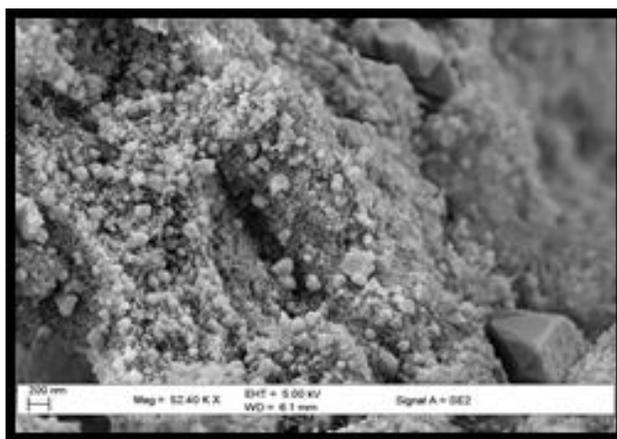


Figure 3. SEM micrograph of Ru-CaHAp catalyst

5.3.4. Powder X-ray diffractogram (XRD) analysis

The powdered XRD patterns of calcined Ru supported on CaHAp are shown in Figure. 4. The diffraction peak values 2θ of 25.86° , 31.91° , 32.83° , 32.94° , 46.62° , 49.34° , 52.98° , 62.82° and 64.05° were assigned to HAp. All these diffraction peaks agrees with the International Centre for Diffraction Data (JCPDS file no. 09-0390). 1% Ru supported on HAp sample showed diffraction peaks at a 2θ angles of 28.74° , 35.11° , 54.35° and 69.71° corresponding to the RuO₂ (JCPDS # 40-1290). The peaks identified in the diffractogram shows the polycrystalline nature of the materials. The average crystallite size of this sample was obtained to be 5.9 nm using the Scherrer equation based on the highest intensity diffraction peaks of Ru-HAp.

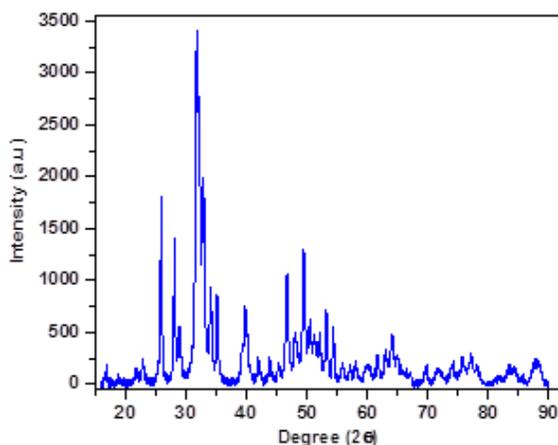


Figure 4. XRD spectrum of Ru-CaHAp catalyst

5.3.5. Optimization procedure

The model reaction involving 2-methoxybenzaldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1.5 mmol) and ethyl acetoacetate (1 mmol) as reactants in equimolar ratio was investigated in detail under varied conditions, i.e. in the absence and presence of various catalysts and using different solvents and temperature conditions to optimize reaction conditions.

When the reaction was carried out without a catalyst or solvent, at RT and reflux conditions, there was no reaction, even after 12 h (Table 1, entry 1 & 2). When the reaction was attempted with the various types of basic catalysts such as NaOH, K₂CO₃, triethylamine (TEA), piperidine and Na₂S in the presence of 1:1 ethanol and water as solvent, yield of product was small, even after 3 h (Table 1, entry 3-7). Reaction was performed in the presence of ionic liquids, L-proline with Al₂O₃ or (Bmim)BF₄ and the product yield was moderate at RT conditions (Table 1, entry 8 & 9). The use of pure heterogeneous acidic catalysts such as Fe₂O₃, Al₂O₃, SiO₂, and CeO₂ at RT in 1:1 EtOH/water mixture showed better yields (Table 1, entries 10-13). To screen the reactivity's of different hydroxyapatites, CaHAp, BaHAp SrHAp, reaction was repeated and after 45 min reaction time yields were moderate (65-78%) (Table 1, entry 14-16). When Ru supported on CaHAp was used as catalyst, a reaction occurred with an impressive 98% yield of pyranopyrazole derivative at RT within 15 min reaction time (Table 1, entry 17). The efficiency of this catalytic system was compared with two other Ru supported HAp's under

otherwise similar conditions. The use of Ru-BaHAp and Ru-SrHAp gave relatively lower product yields (Table 1, entry 18 & 19).

In heterogeneous catalysis, the surface area of the catalyst which determines the availability of catalytic sites and direction of the reaction plays a pivotal role. To assess the impact of amount of catalyst on the synthesis of pyrano[2,3-c]pyrazoles, the reaction of benzaldehyde, malononitrile hydrazine hydrate and ethyl acetoacetate was carried out with varying amounts of Ru-CaHAp, namely 10, 20, 30, 40, 50, 60, 75 and 100 mg. The 50 mg of catalyst was observed to be ample to promote the reaction with optimum efficiency and further amount of the catalyst did not improve either the yield or reaction time (Table 2). However, the decrease in amount of the catalyst used to < 50 mg, affected the product yield by reducing it to 85% (Table 2). Thus, 50 mg of Ru-CaHAp at RT with ethanol and water as solvent proved optimal for the model reaction giving 98% yield.

Table 1: Optimization for the synthesis of pyrano[2,3-c]--pyrazoles using various catalyst materials^a

Entry	Catalyst ^b	Solvent	Condition	Time (h)	Yield (%) ^c
1	--	--	RT	12	--
2	--	--	Reflux	12	--
3	NaOH	EtOH:H ₂ O	RT	3.0	25
4	K ₂ CO ₃	EtOH:H ₂ O	RT	3.0	29
5	TEA	EtOH:H ₂ O	RT	3.0	23
6	Piperidine	EtOH:H ₂ O	RT	3.0	30
7	Na ₂ S	EtOH:H ₂ O	RT	3.0	27
8	L-proline	EtOH:H ₂ O	RT	3.5	42
9	(Bmim)BF ₄	EtOH:H ₂ O	RT	3.5	39
10	Fe ₂ O ₃	EtOH:H ₂ O	RT	12	51
11	Al ₂ O ₃	EtOH:H ₂ O	RT	12	55
12	SiO ₂	EtOH:H ₂ O	RT	12	53
13	CeO ₂	EtOH:H ₂ O	RT	12	59
14	CaHAp	EtOH:H ₂ O	RT	0.75	78
15	BaHAp	EtOH:H ₂ O	RT	0.75	71
16	SrHAp	EtOH:H ₂ O	RT	0.83	65
17	Ru-CaHAp	EtOH:H ₂ O	RT	0.25	98
18	Ru-BaHAp	EtOH:H ₂ O	RT	0.25	93
19	Ru-SrHAp	EtOH:H ₂ O	RT	0.33	91

^aAll products were characterised by IR, ¹H NMR, ¹³C NMR, ¹⁵N NMR & HRMS spectral analysis.

Catalyst used 50 mg, ^c Isolated yields.

-- No reaction

Table 2: Optimization of the amount of 1% Ru-CaHAp as catalyst in the reaction

Entry	Catalyst (mg)	Time (min)	Yield (%)
1	10 mg	25	85
2	20 mg	20	88
3	30 mg	20	91
4	40 mg	20	93
5	50 mg	15	98
6	60 mg	15	97
7	75 mg	15	98
8	100 mg	15	96

A perusal of the experimental results and the effect of various polar and non-polar solvents on the four component reaction clearly indicate that ethanol and water mixture as solvent is vital for the reaction (Table 1). It was noteworthy that, under otherwise similar conditions, the Ru-CaHAp catalyzed reaction in presence of relatively non-polar solvents like 1,4-dioxane, toluene and n-hexane gave insignificant yields even after prolonged reaction times (Table 3 entries 1-3), and even with polar aprotic solvents such as DMF and CH₃CN, the reaction yield was low (Table3, Entry 4 & 5). The polar protic solvents such as ethanol, methanol and water on their own failed to facilitate high yields (Table 1, entry 6-8). Interestingly, the mixture of EtOH:H₂O (50:50 v/v) gave an impressive yield of 98%. A highly polar solvent which dissipates heat faster seems to provide optimum conditions for formation of intermediates, and their conversion to final products on the catalyst surface.

Table 3: Optimization of various solvent condition for the synthesis of pyrano[2,3-c]pyrazoles derivatives by Ru-CaHAp catalyst

Entry	Solvent	Yield (%)
1	1,4-Dioxane	09
2	Toluene	13
3	n-Hexane	10
4	DMF	34
5	CH ₃ CN	37
6	Ethanol	78
7	Methanol	69
8	H ₂ O	71
6	EtOH:H ₂ O	98

The Ru-CaHAp as catalyst proved to catalyze the facile one-pot synthesis reactions of pyranopyrazole derivatives with excellent yields. Under the chosen optimal reaction conditions, the versatility of the protocol was tested by replacing methoxybenzaldehyde with a range of aromatic aldehydes in the reaction. All the reactions using different electron-withdrawing or electron releasing substituents in ortho, meta and para positions on aryl ring of aldehydes, gave exciting results, producing derivatives of respective pyrano[2,3-c]pyrazoles with impressive yields (Table 4). All of the reaction products were characterized and structures were confirmed by FTIR, ¹H NMR, ¹⁵N NMR, ¹³C NMR and HRMS spectral data (Electronic Supplementary Information).

Table 4: Synthesis of pyrano[2,3-c]pyrazoles derivatives catalyzed by Ru-CaHAp catalyst

Entry	Product	Yield (%)	Mp °C	Lit Mp °C
1	5a	92	214-215	--
2	5b	90	191-193	192-194 [36]
3	5c	98	253-254	252-253 [40]
4	5d	92	258-260	259-261 [35]
5	5e	94	145-147	145-146 [37]
6	5f	89	259-260	--
7	5g	90	260-261	--
8	5h	93	178-180	178-179 [39]
9	5i	90	210-211	--
10	5j	89	227-229	--
11	5k	88	212-214	--

-- New compounds/no literature available.

5.3.6. Reusability of catalyst

The reusability of the synthesized heterogeneous catalysts is a significant parameter from environmental and fiscal point of view. In heterogeneous catalysis, poisoning of the catalyst and leaching of metal are the main limitations, which impact on activity for further reuse. In order to examine the stability of the catalyst, recycling experiments were performed. After each run, catalyst was separated by filtration. The recovered material was washed with deionized water followed by ethanol, then dried and reused for the next run under the similar conditions. No significant loss was observed in the first five cycles. The catalytic activity of the Ru/Ca-HAp decreased when the recovered catalytic system was reused in the 6th and 7th cycles (Figure 5).

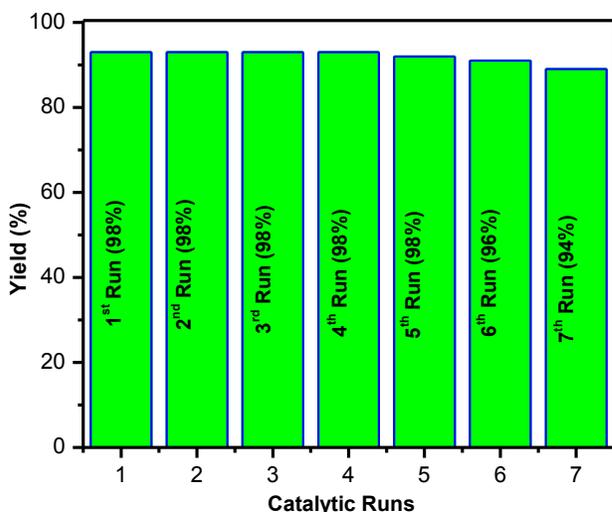


Figure 5. Recyclability of Ru-CaHAp catalyst

5.4. Conclusion

In summary, we have described a simple, efficient and green multicomponent one-pot procedure for the syntheses of pyrano[2,3-c]pyrazole derivatives in good to excellent yields using Ru-CaHAp as catalyst at RT. Ru-CaHAp is effective and recyclable catalyst for the MCR protocol. The advantages of the approach are excellent yields, cost-effectiveness, easy work up, environment friendly reaction conditions, short reaction times and use of green solvents and recyclable catalyst. Moreover, this procedure is appropriate for diversity oriented synthesis of potentially bioactive heterocycles.

5.5. Acknowledgement

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.

5.6. Supplementary material

Supportive/Supplementary material intended for publication must be numbered and referred to in the manuscript but should not be a part of the submitted paper. List all Supportive/Supplementary Material and include a brief caption line for each file describing its contents.

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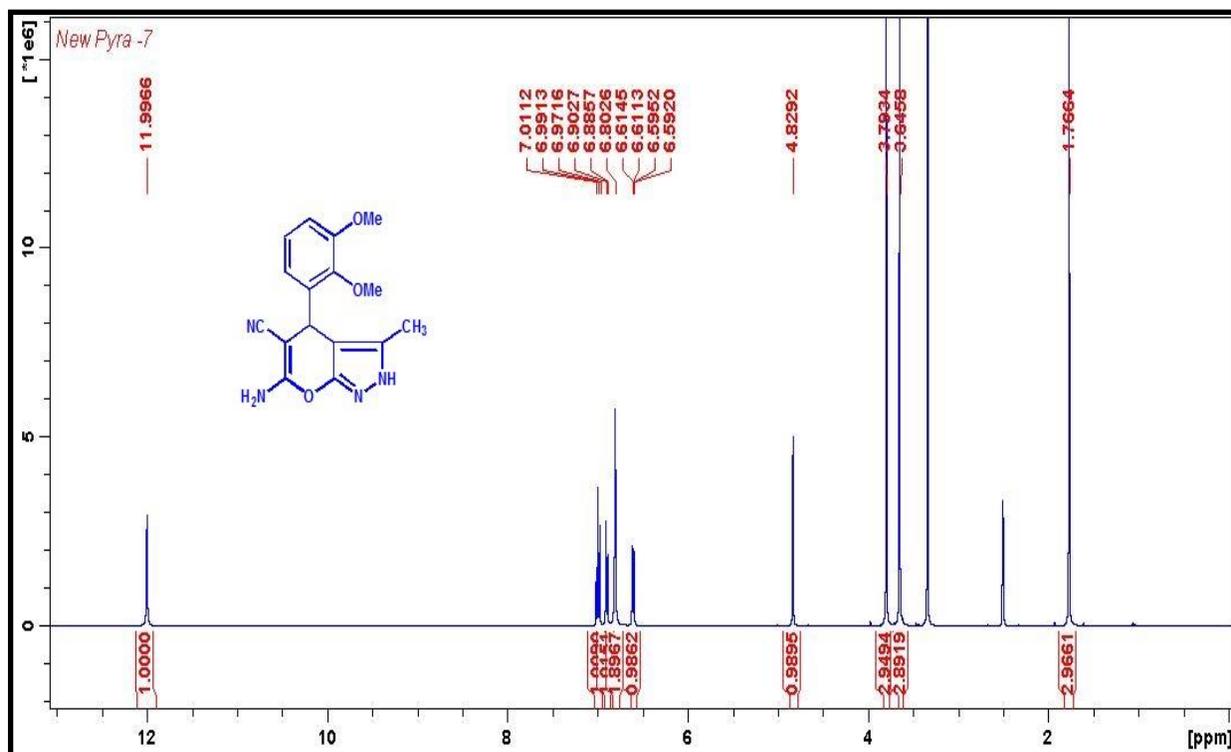
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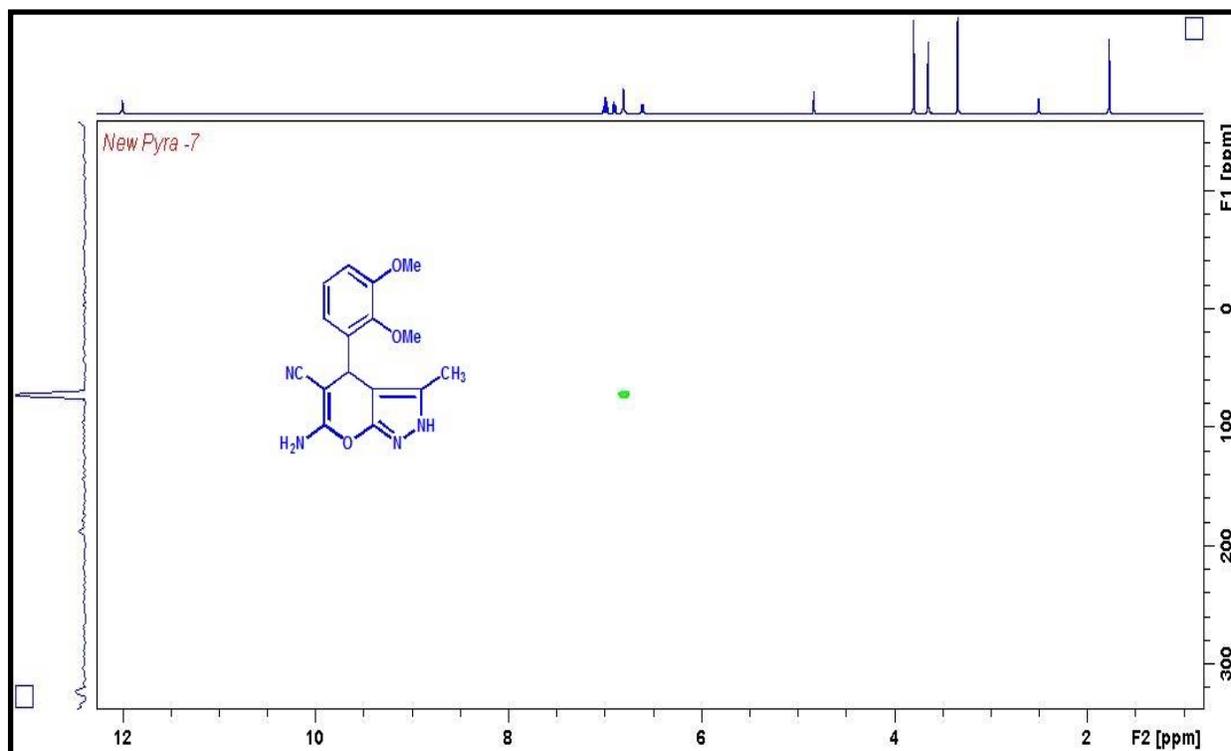
5.8. Supplementary material data

5.8.1. Materials, methods and instruments

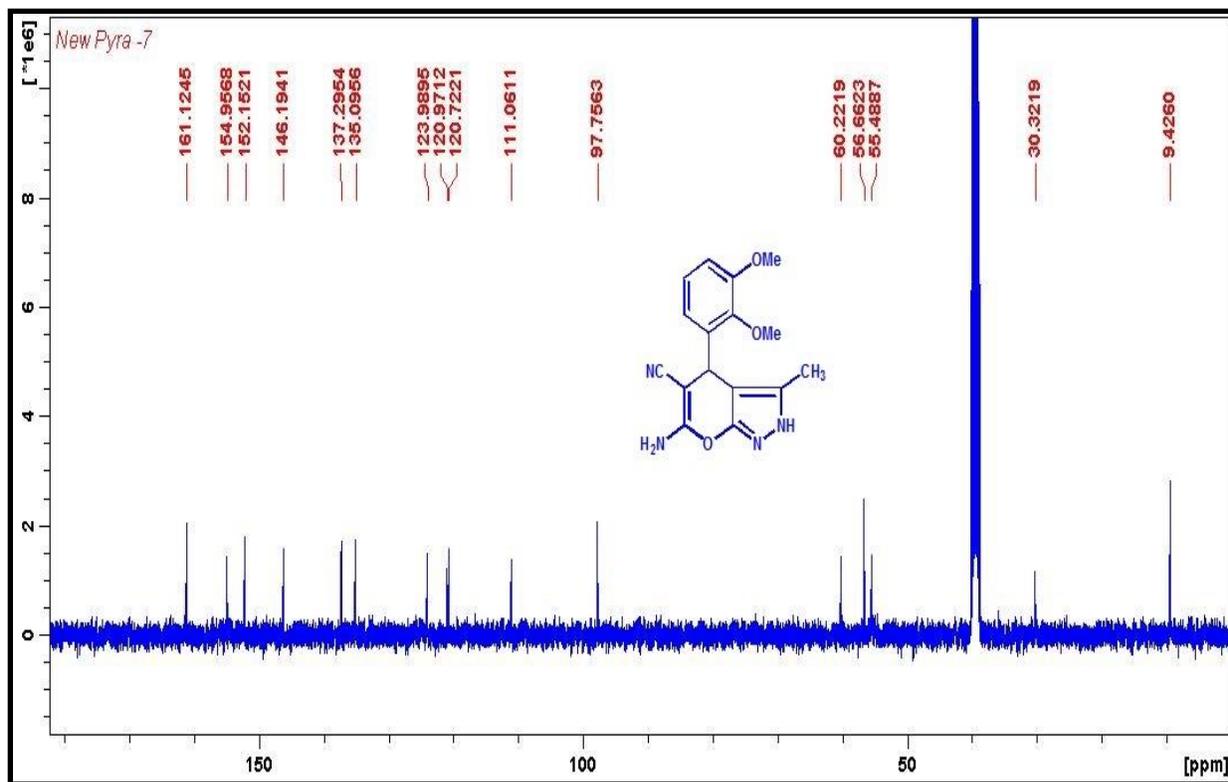
All chemicals and reagents required for the reaction were of analytical grade and were used without any further purification. Bruker AMX 400 MHz NMR spectrometer was used to record the ^1H NMR, ^{13}C NMR and ^{15}N NMR spectral values. High-resolution mass data were obtained using a Bruker micro TOF-Q II ESI instrument operating at ambient temperature. The DMSO-d_6 solution was utilized for this while TMS served as the internal standard. TMS was further used as an internal standard for reporting the all chemical shifts in δ (ppm). The FT-IR spectrum for the samples was established using a Perkin Elmer Precisely 100 FT-IR spectrometer at the $400\text{-}4000\text{ cm}^{-1}$ area. Purity of all the reaction products was confirmed by TLC using aluminum plates coated with silica gel (Merck Kieselgel 60 F254).



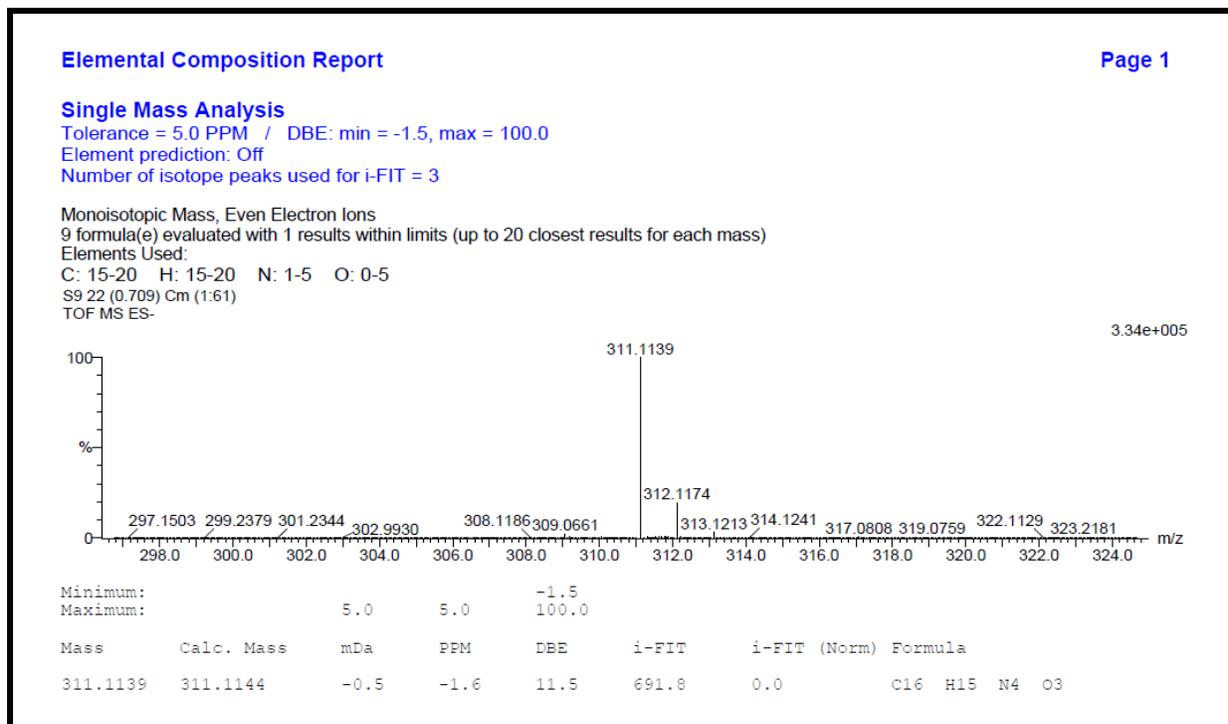
^1H NMR spectra of compound **5a**



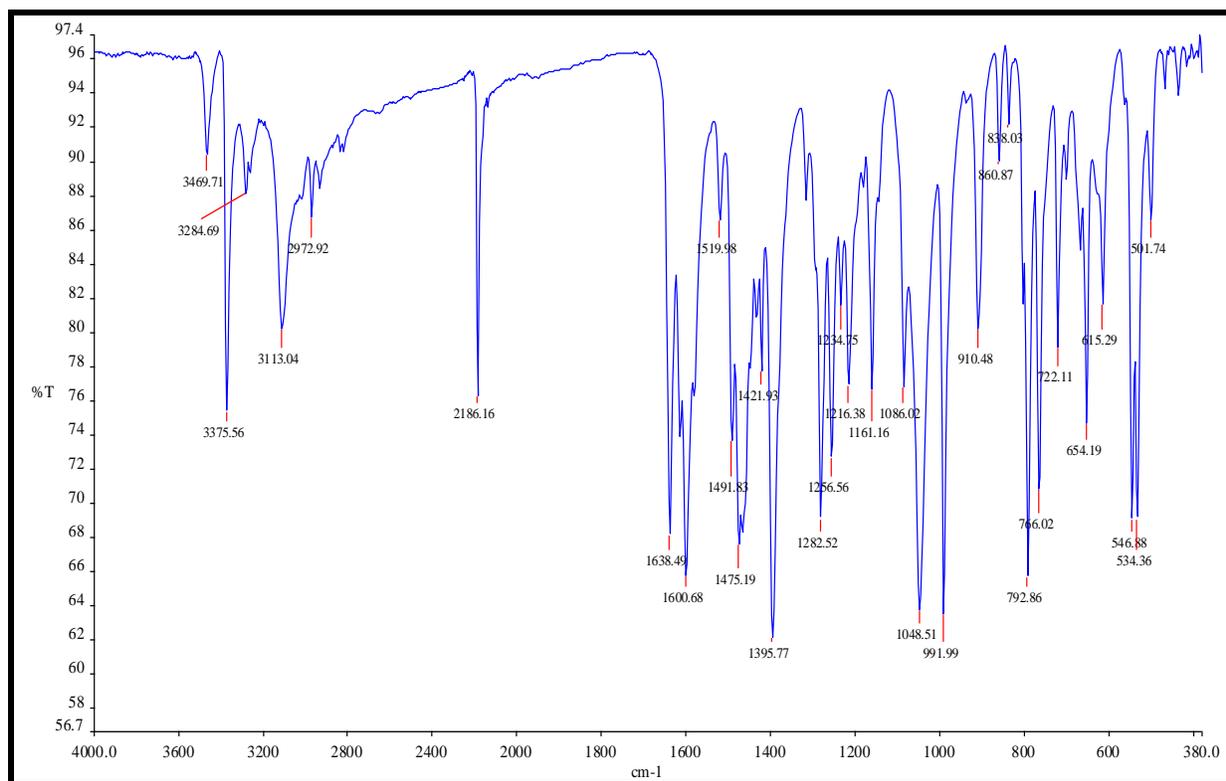
^{15}N NMR spectra of compound **5a**



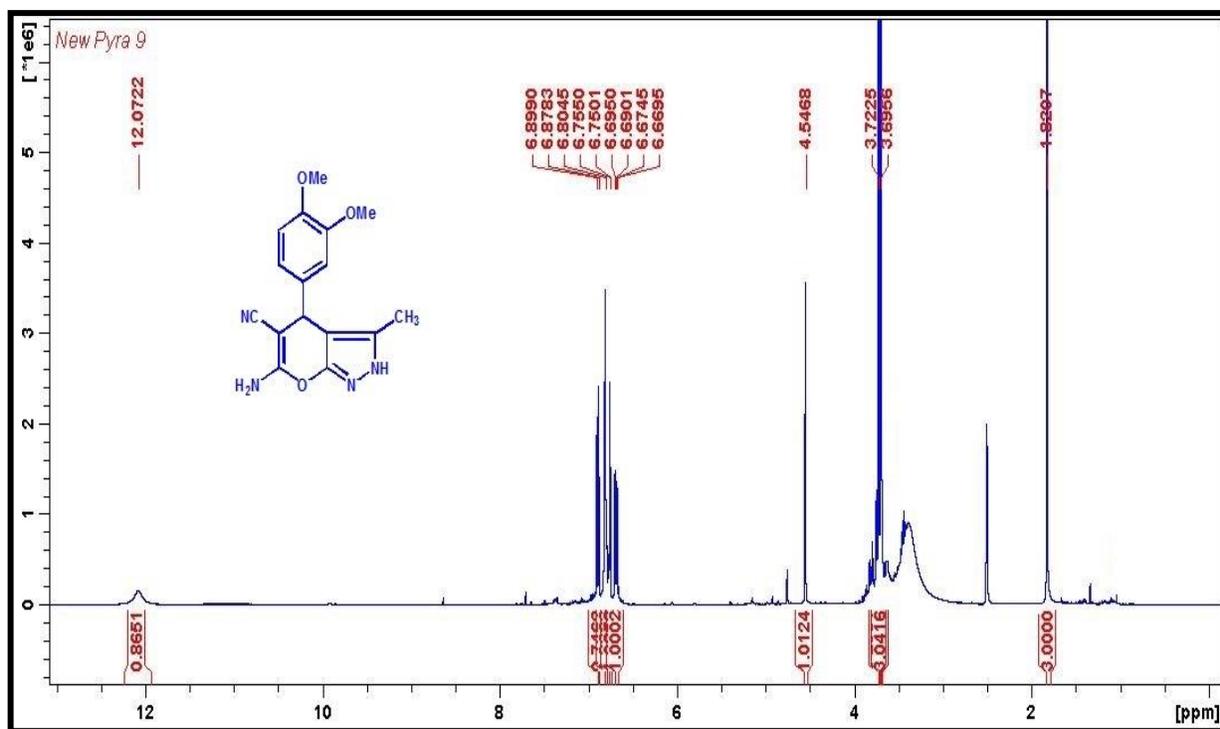
¹³C NMR spectra of compound 5a



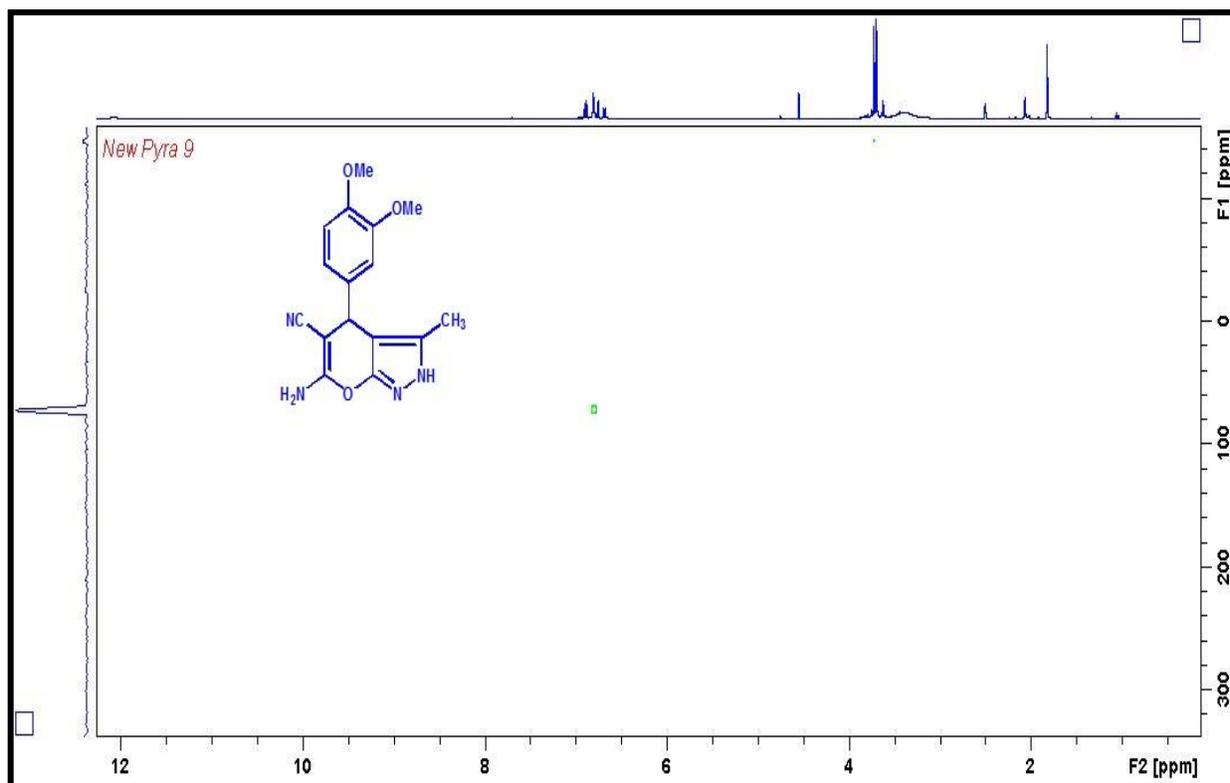
HR-MS spectra of compound 5a



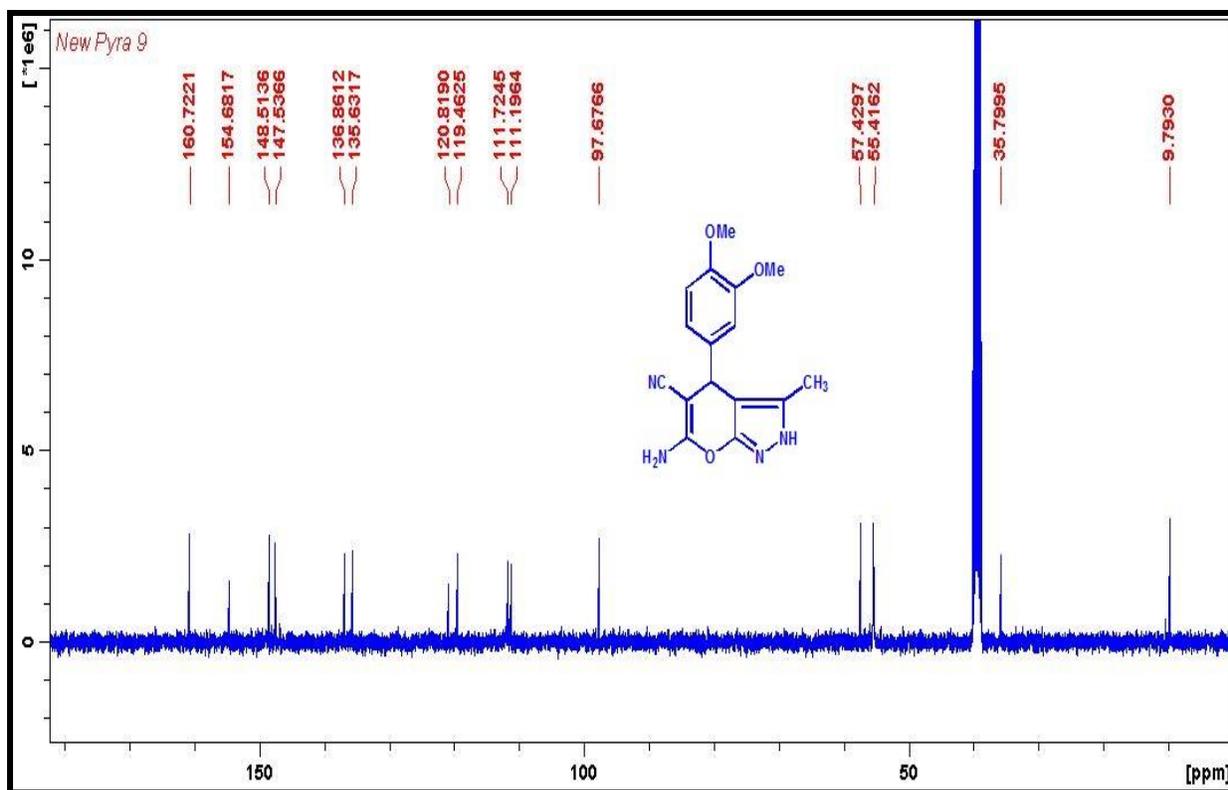
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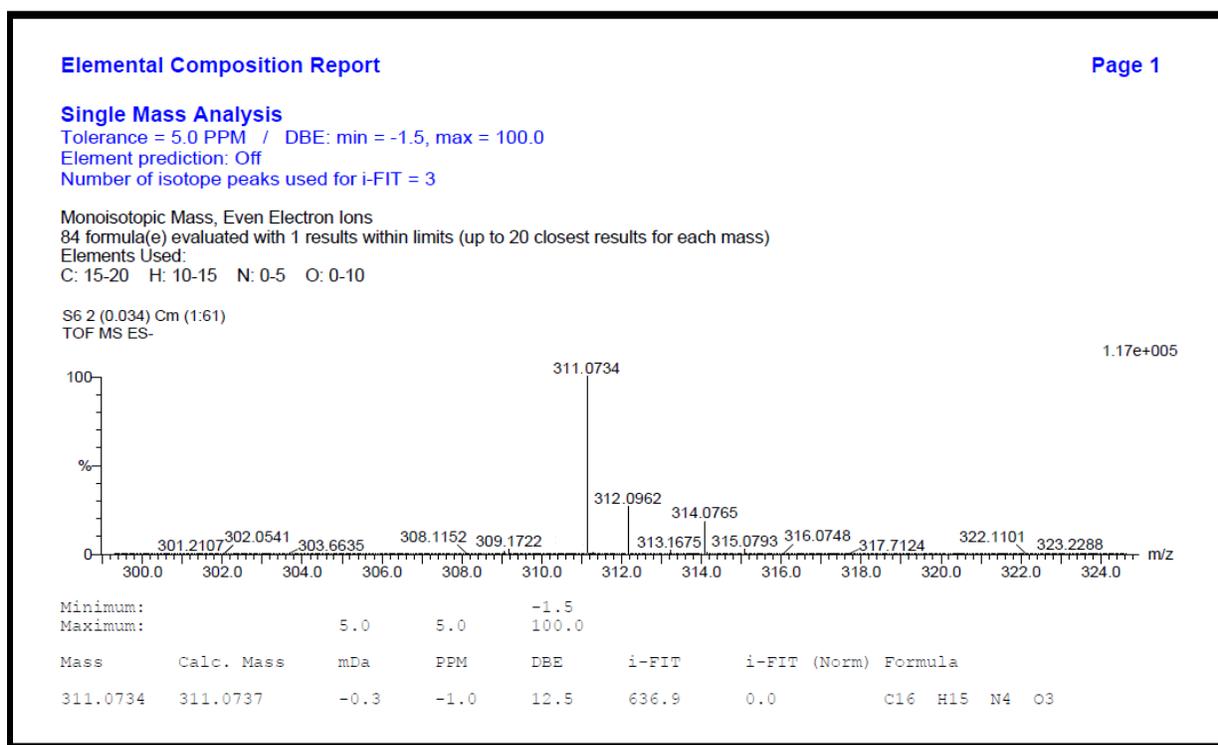
¹H NMR spectra of compound **5b**



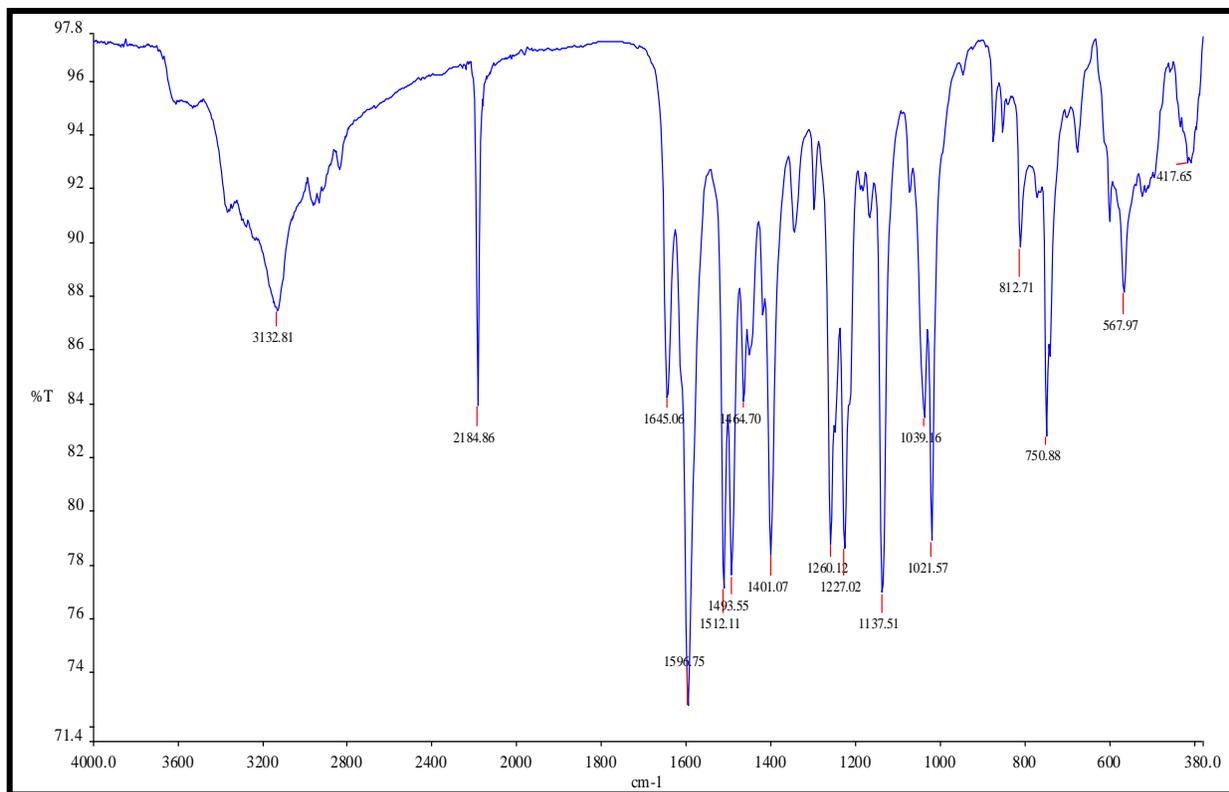
¹⁵N NMR spectra of compound **5b**



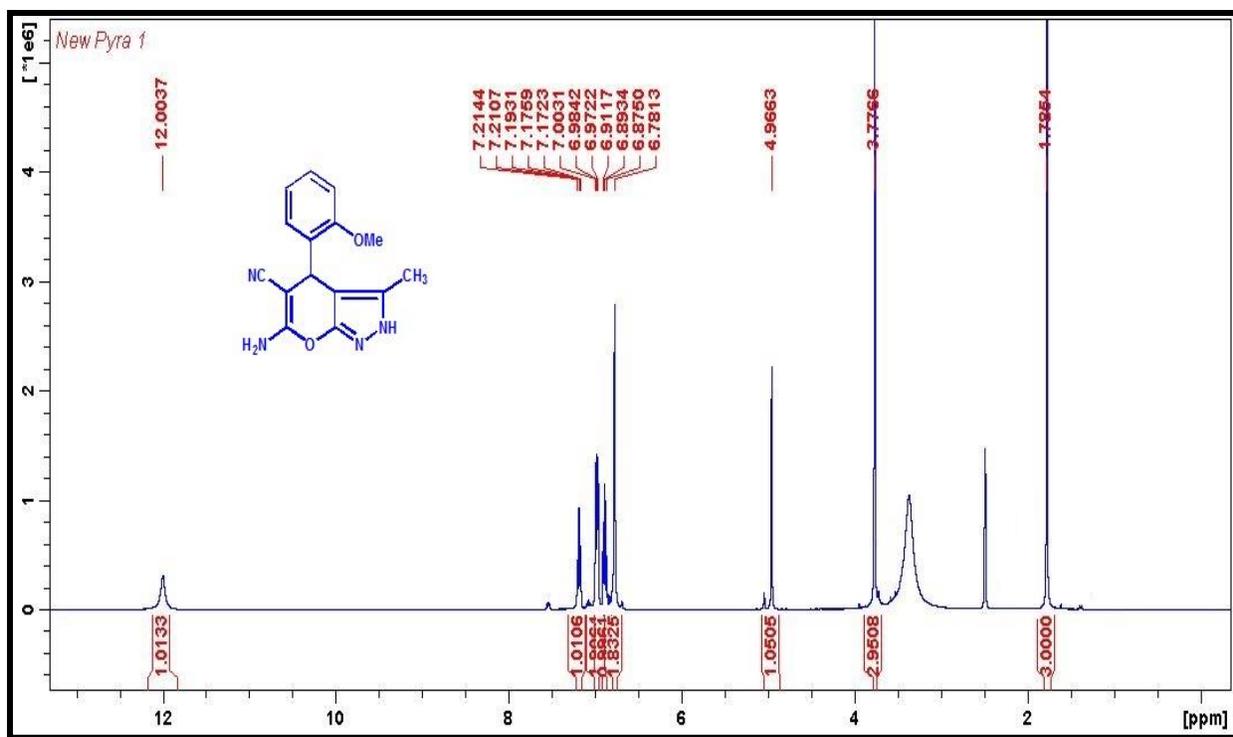
¹³C NMR spectra of compound **5b**



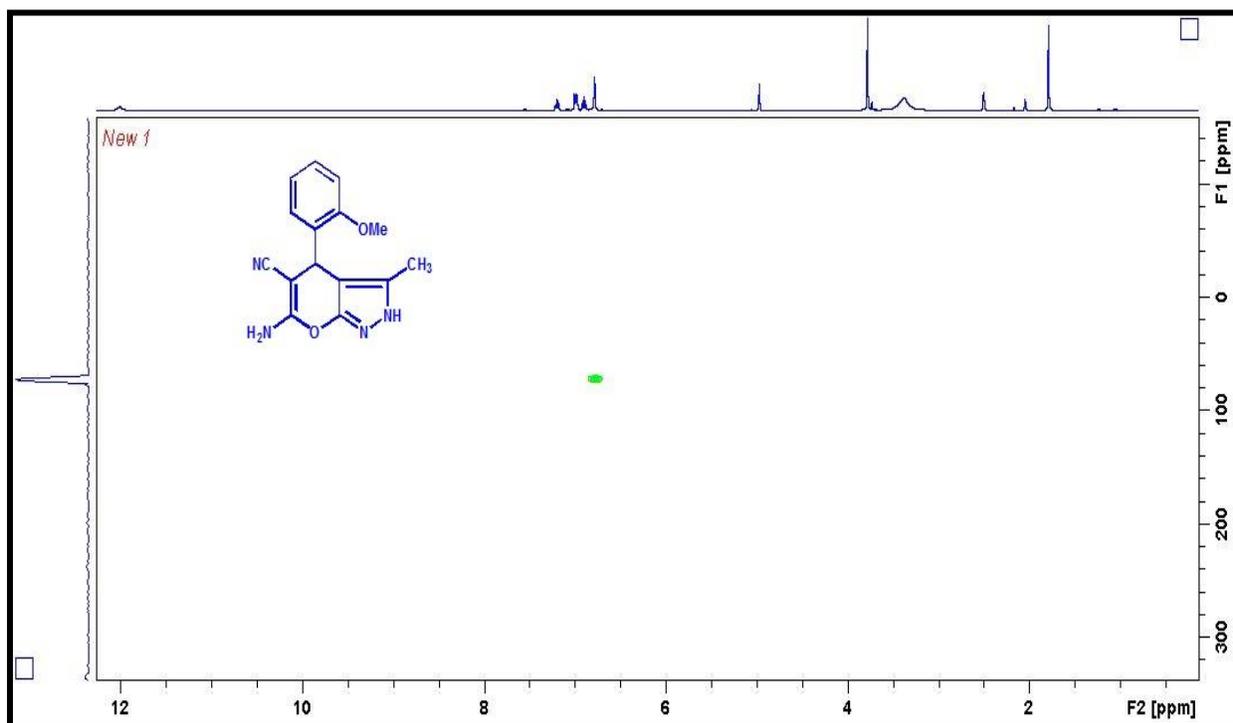
HR-MS spectra of compound **5b**



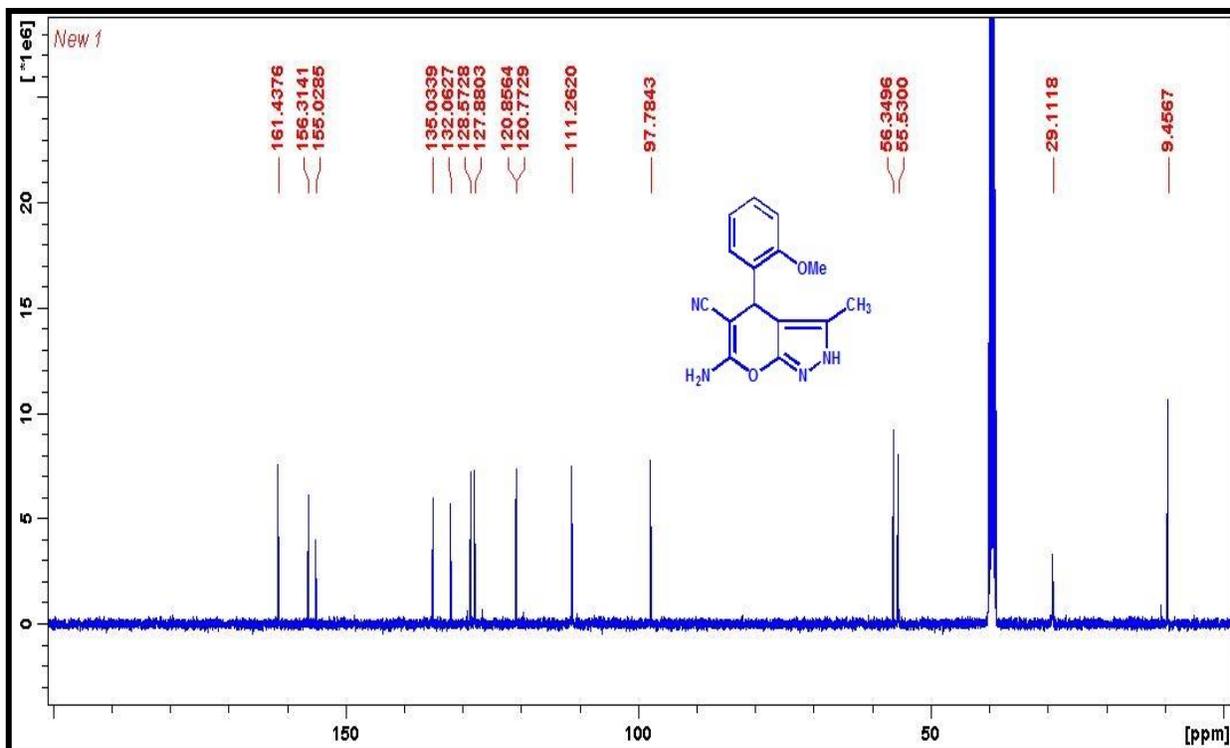
FT-IR spectra of compound **5b**



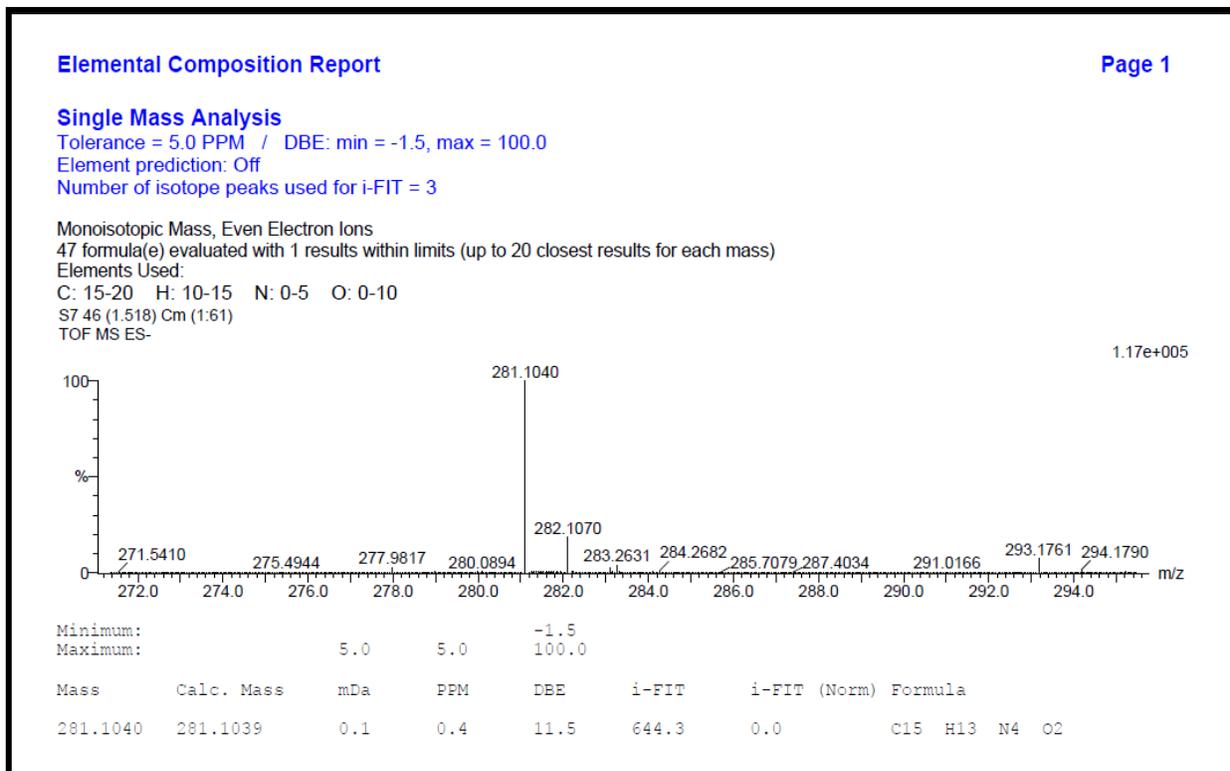
^1H NMR spectra of compound **5c**



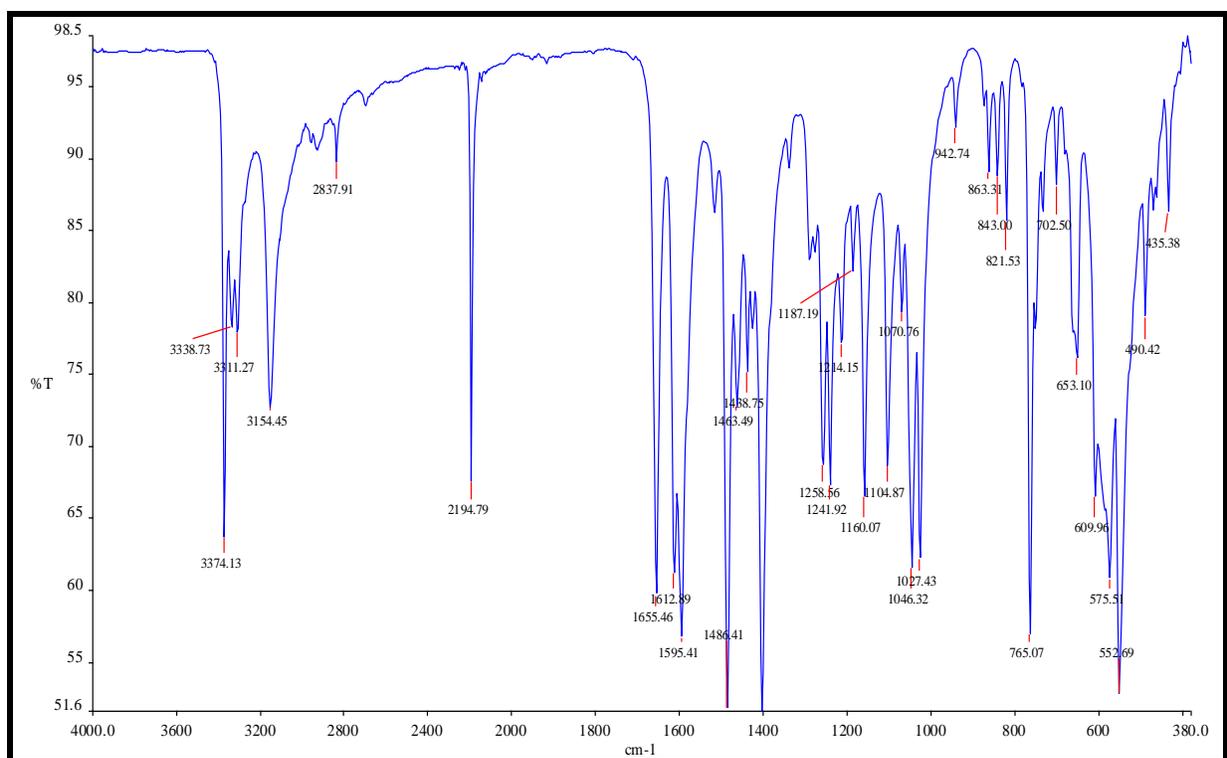
^{15}N NMR spectra of compound **5c**



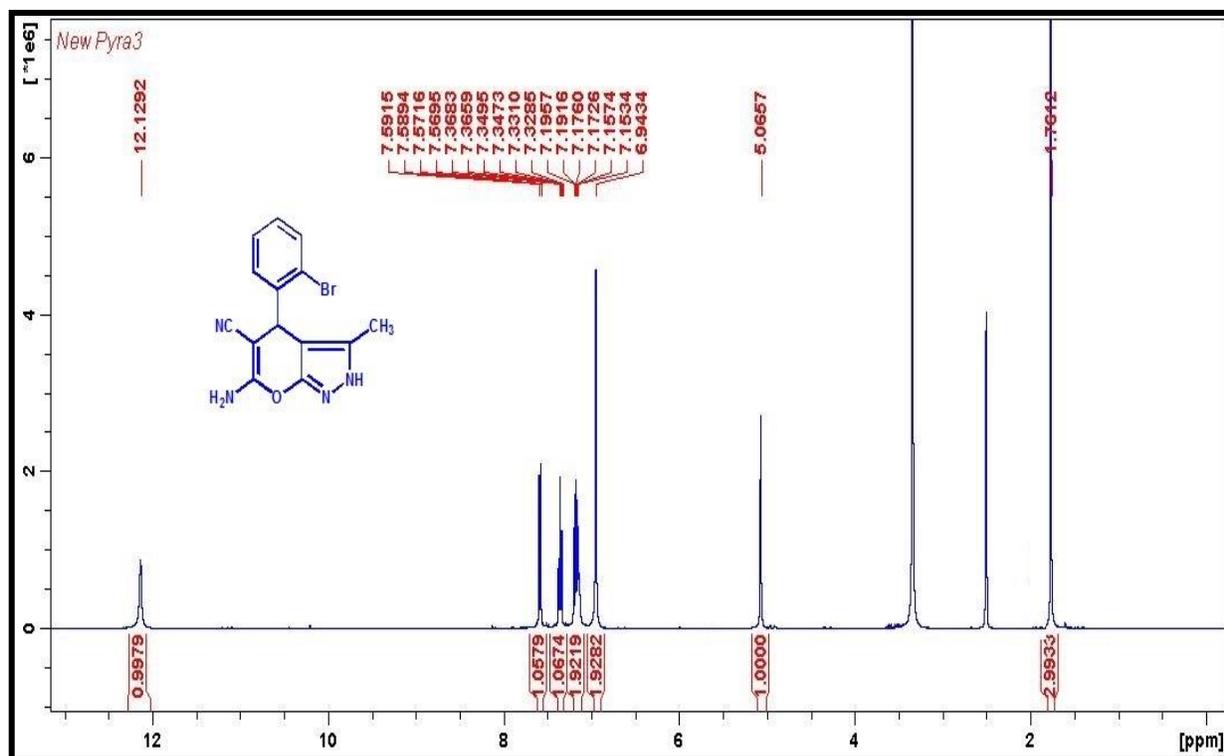
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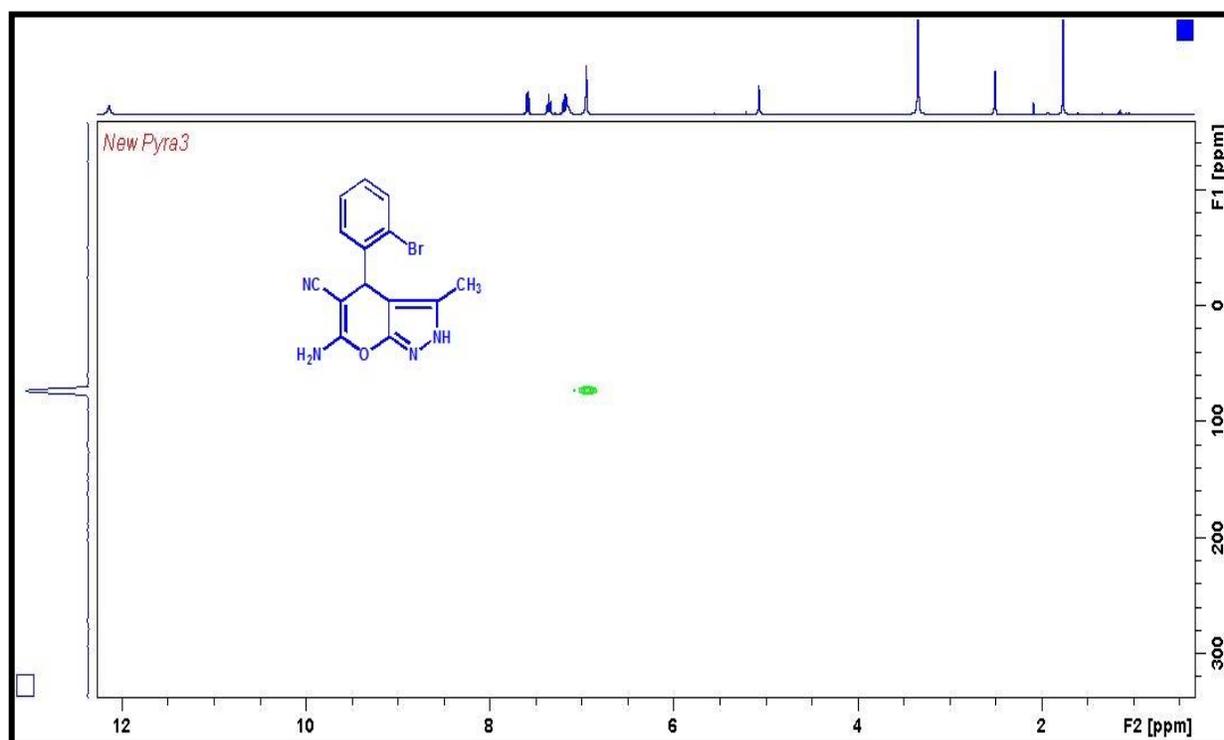
HR-MS spectra of compound 5c



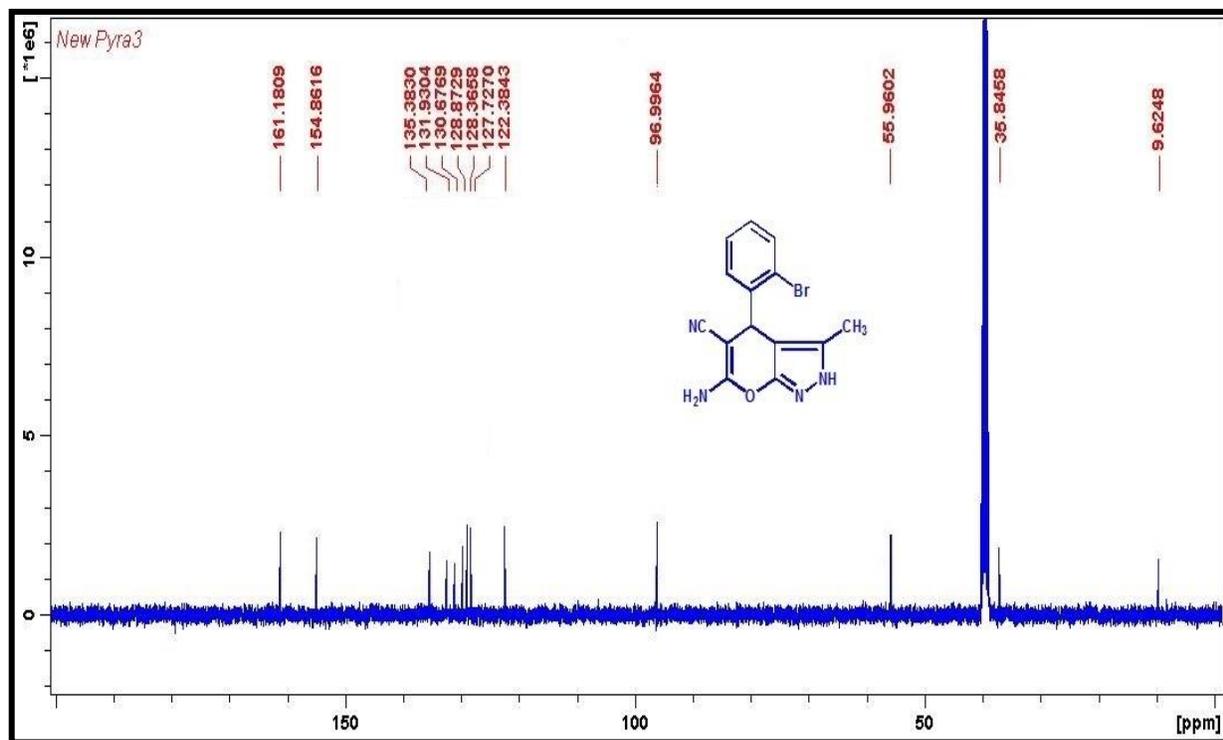
FT-IR spectra of compound 5c



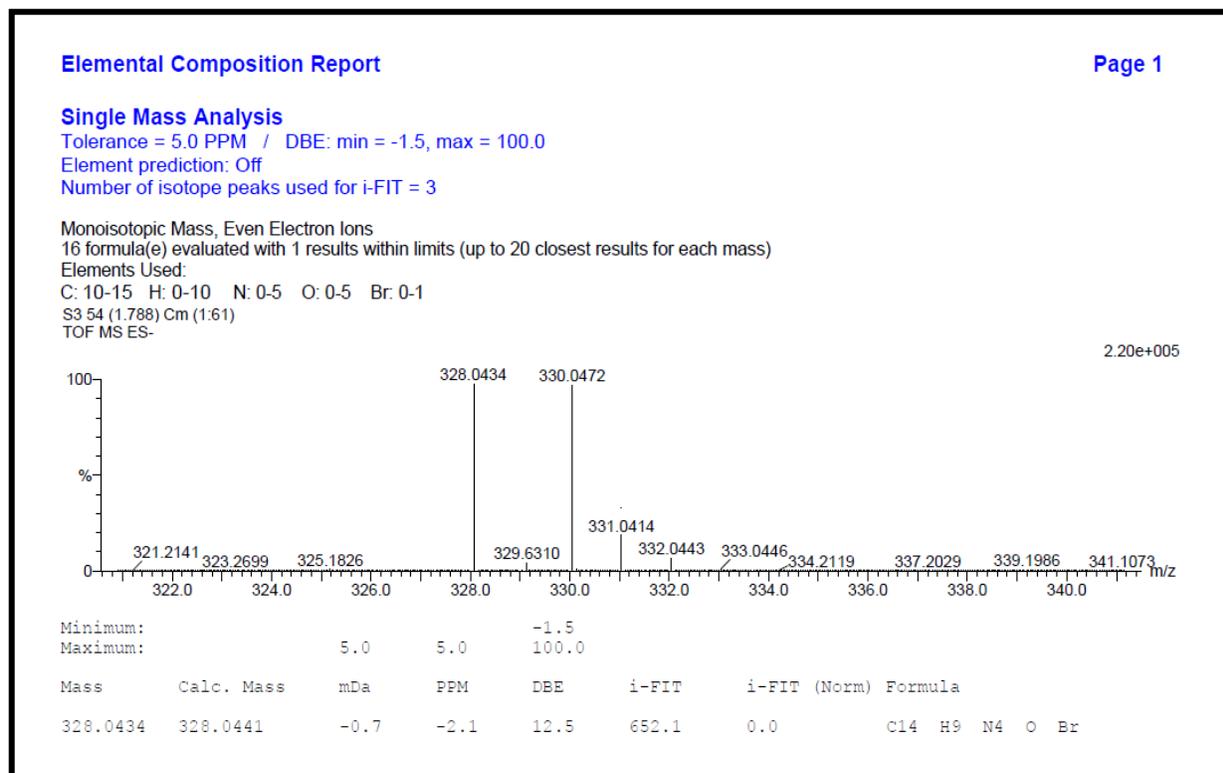
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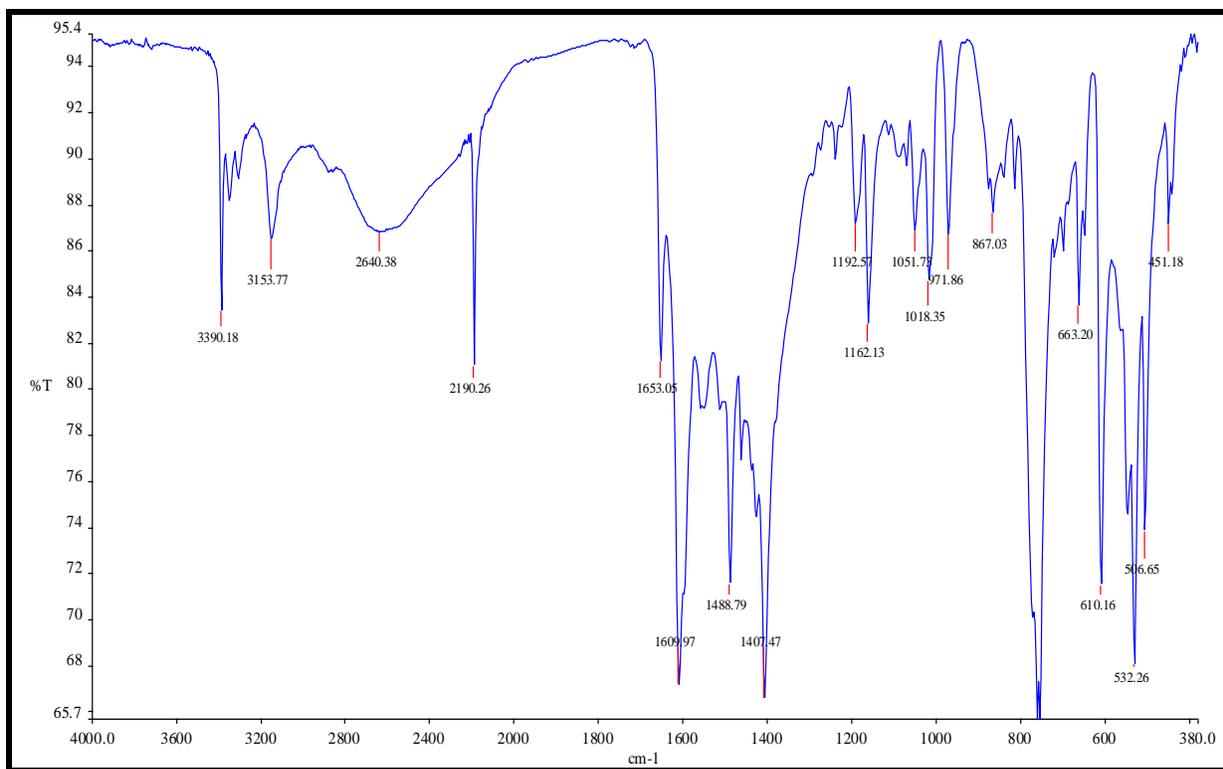
^{15}N NMR spectra of compound **5d**



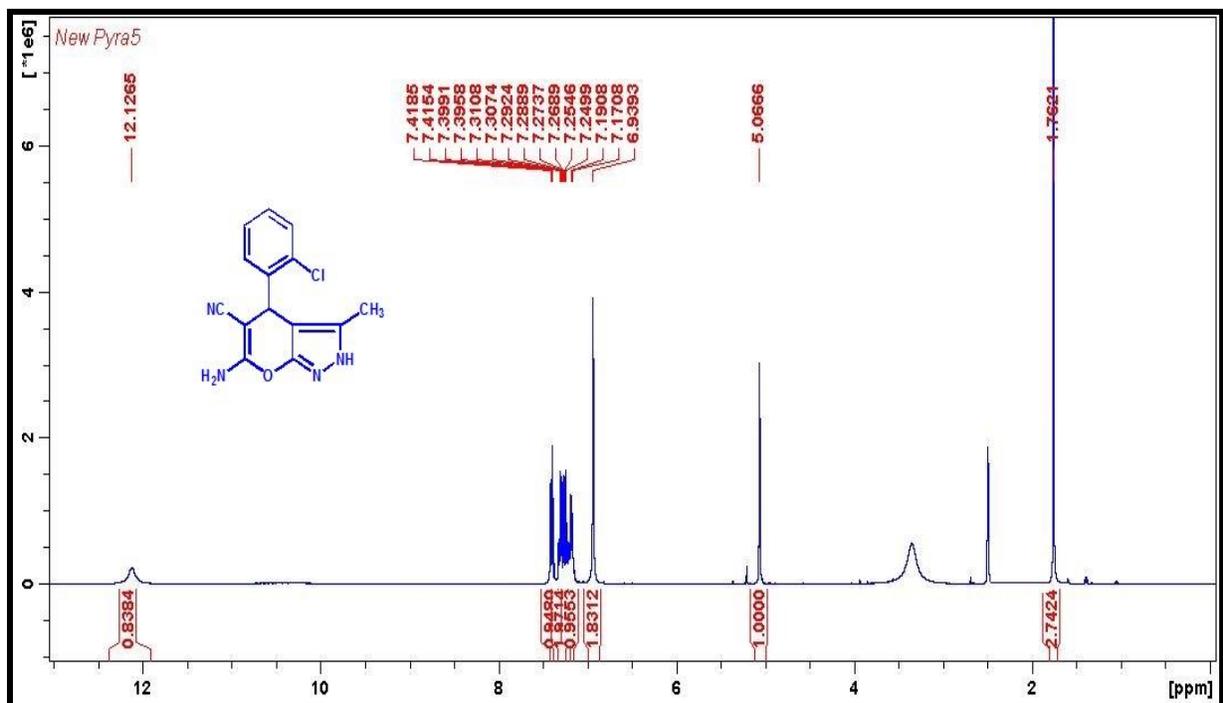
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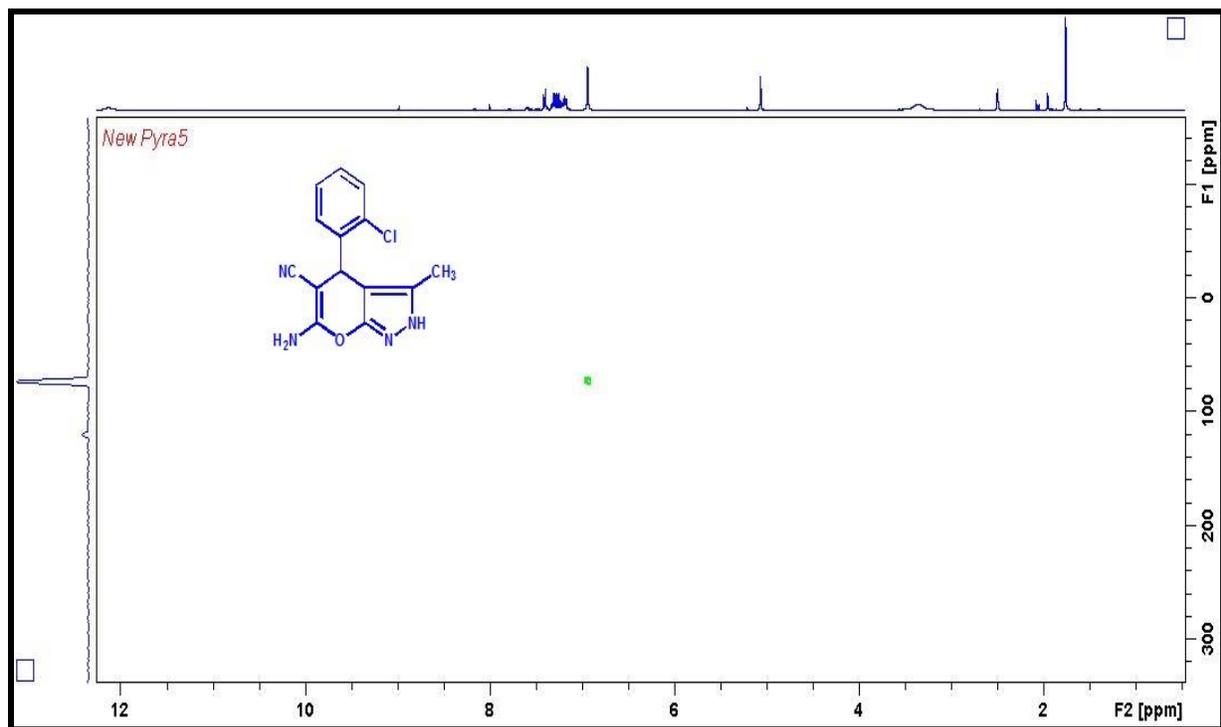
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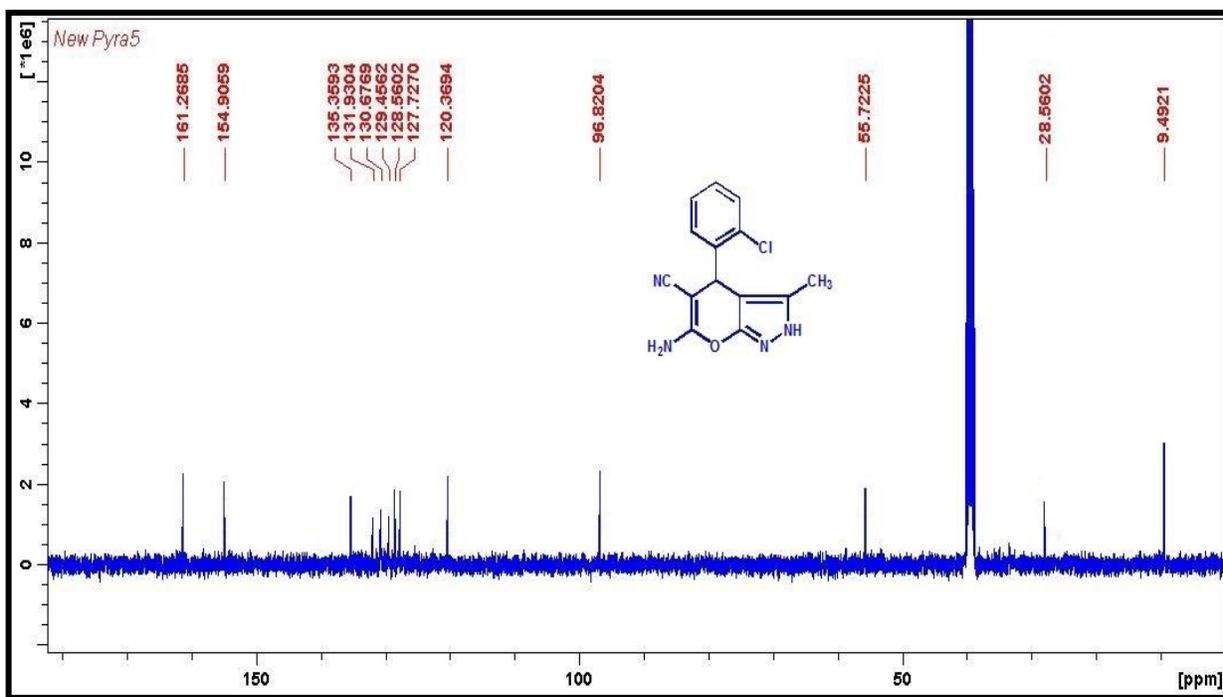
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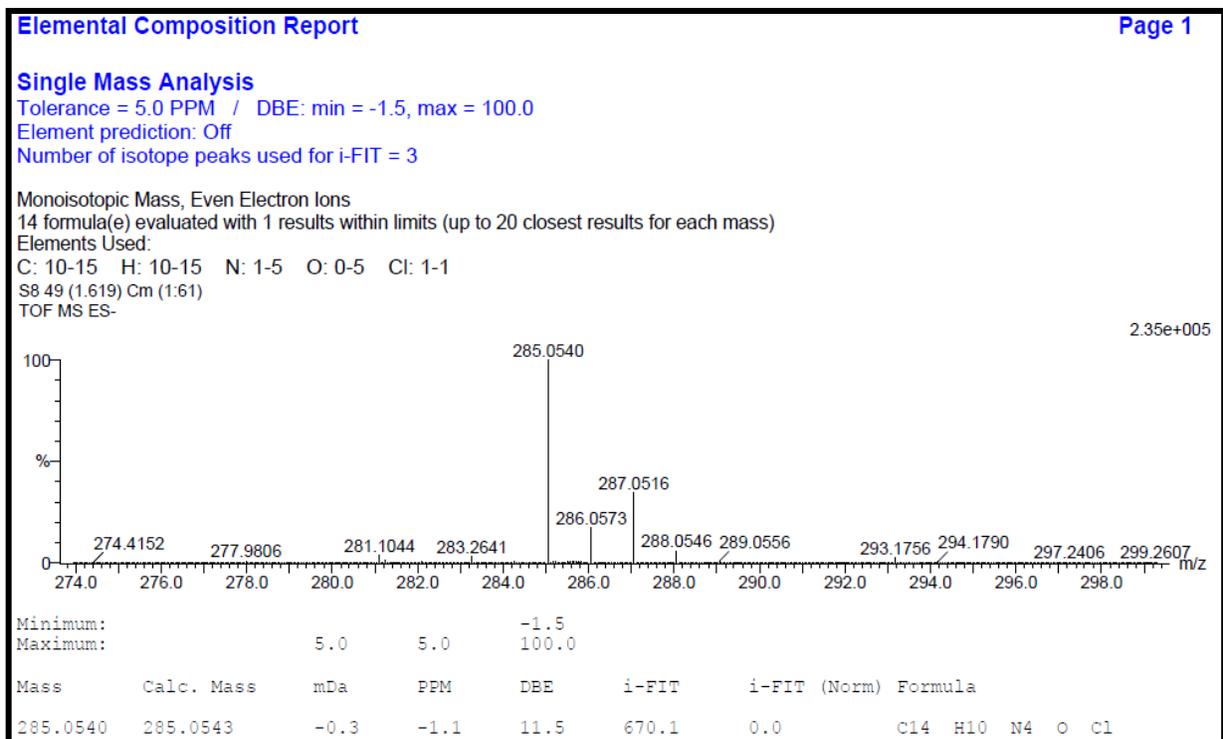
^1H NMR spectra of compound 5e



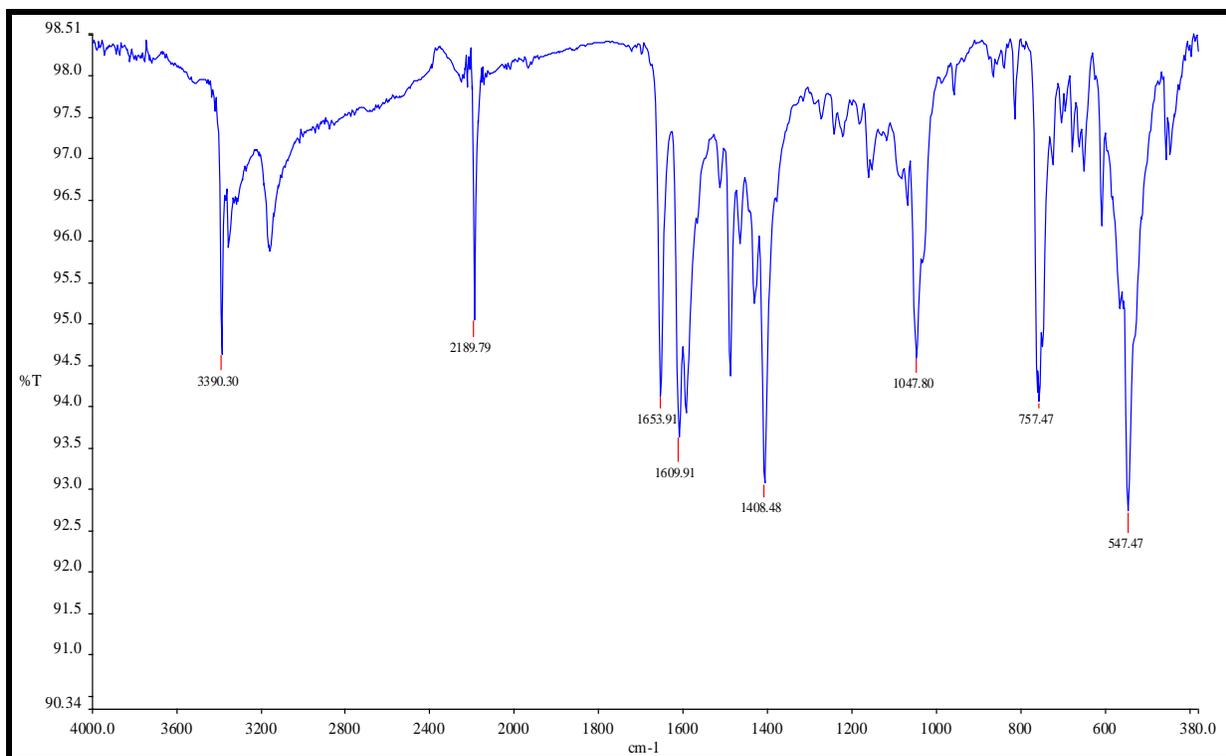
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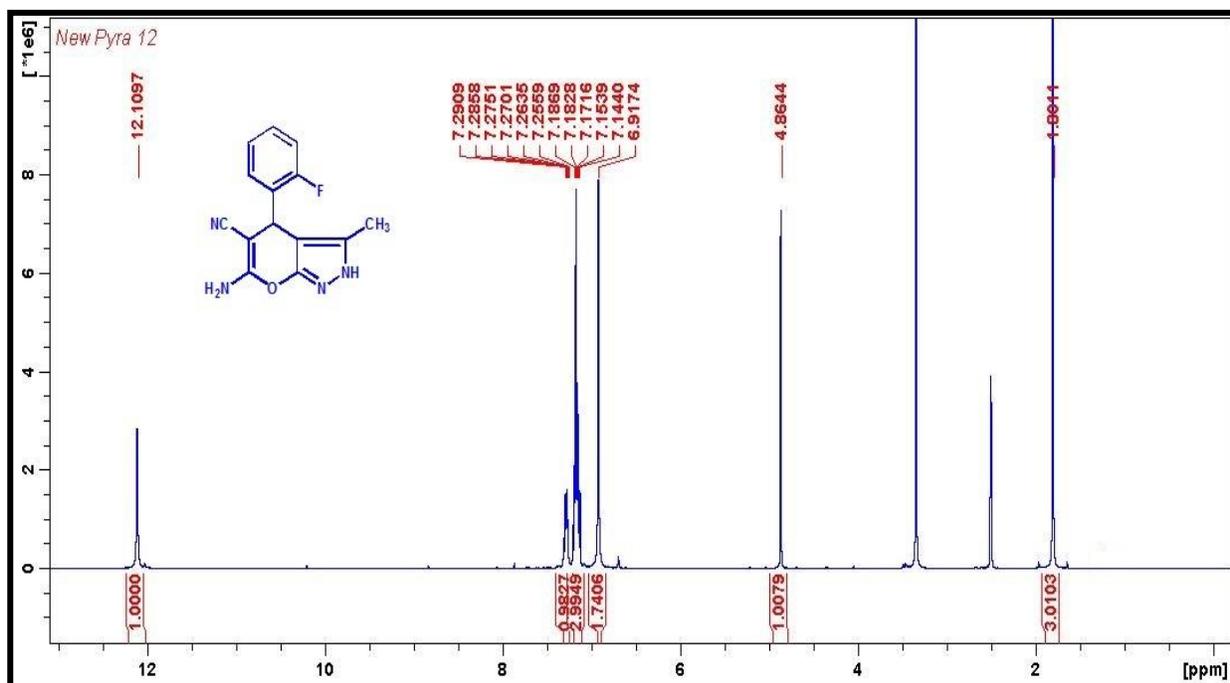
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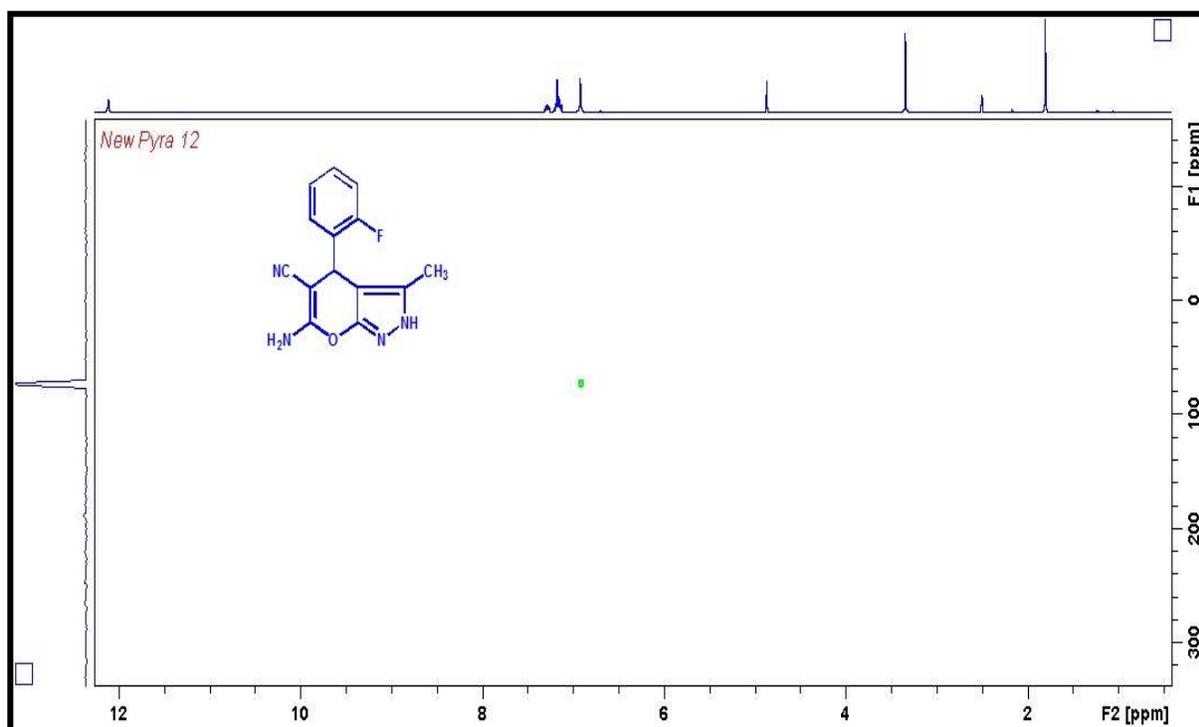
HR-MS spectra of compound **5e**



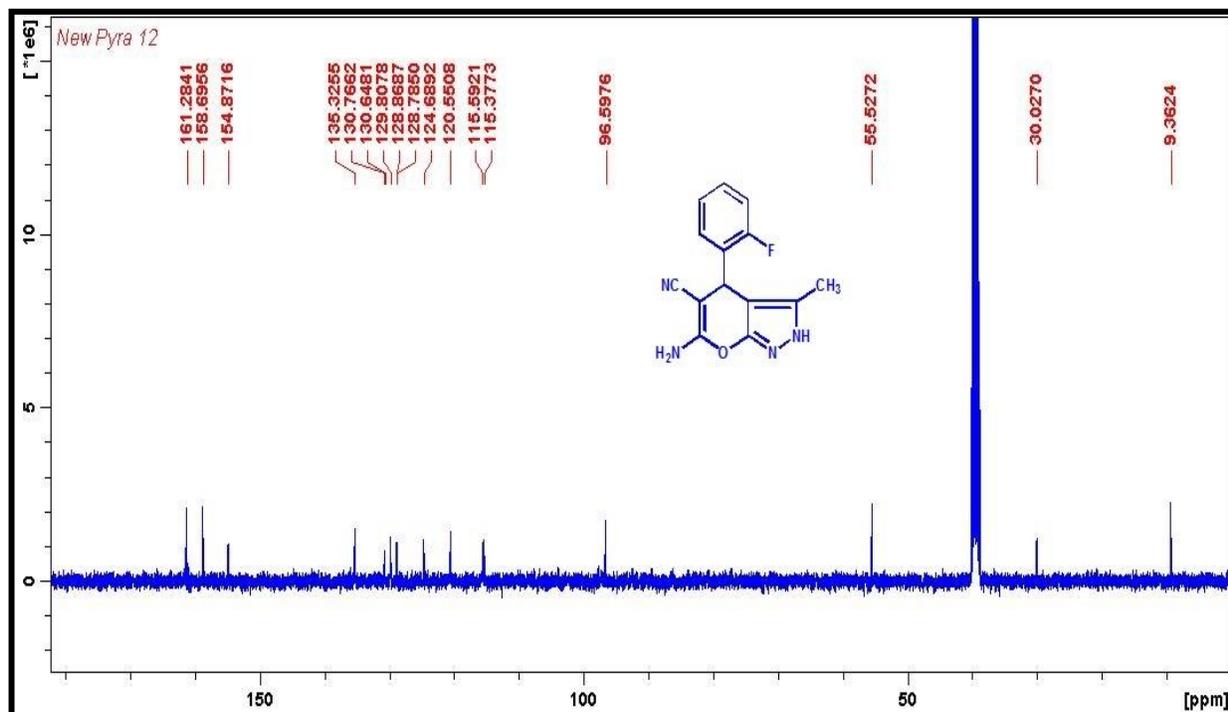
FT-IR spectra of compound **5e**



¹H NMR spectra of compound **5f**



¹⁵N NMR spectra of compound **5f**



¹³C NMR spectra of compound **5f**

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)

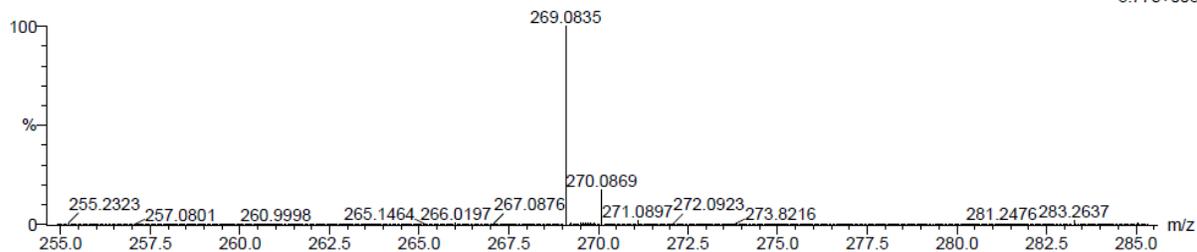
Elements Used:

C: 10-15 H: 10-15 N: 1-5 O: 0-5 F: 0-1

S11 19 (0.607) Cm (1:61)

TOF MS ES-

3.77e+005



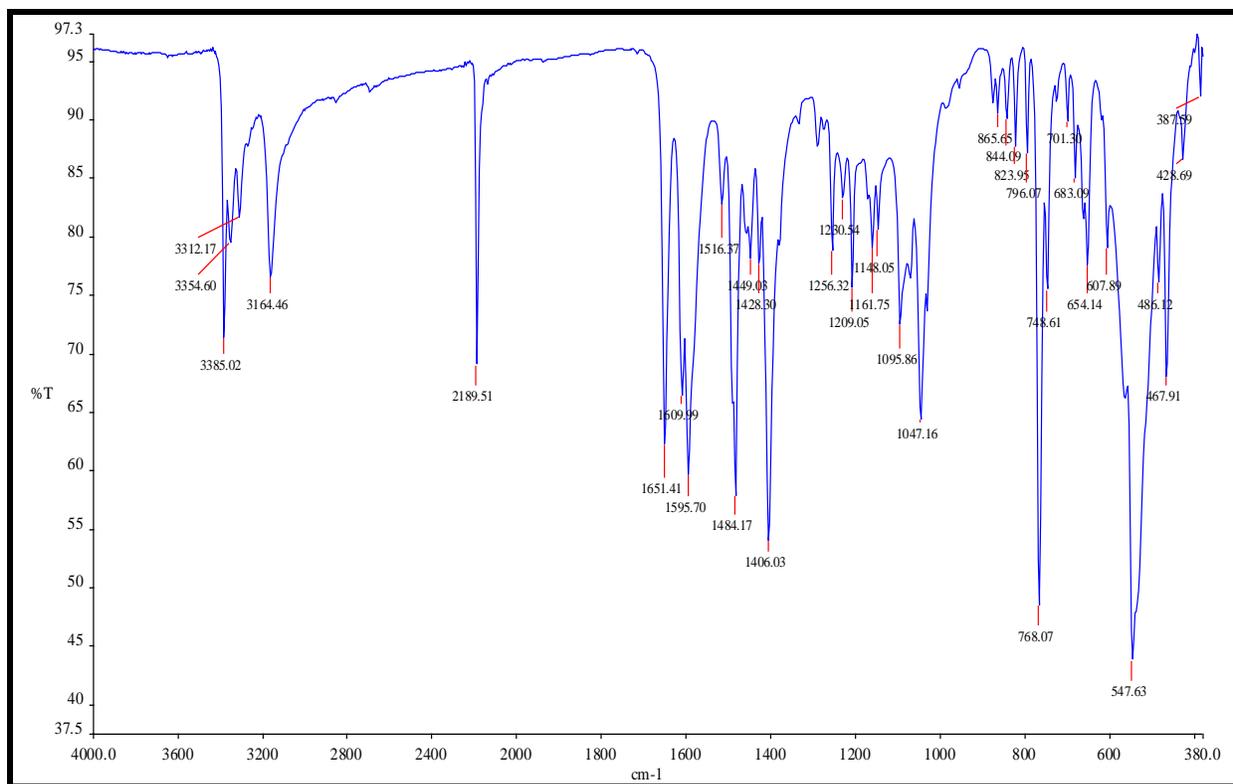
Minimum:

Maximum: 5.0 5.0 -1.5 100.0

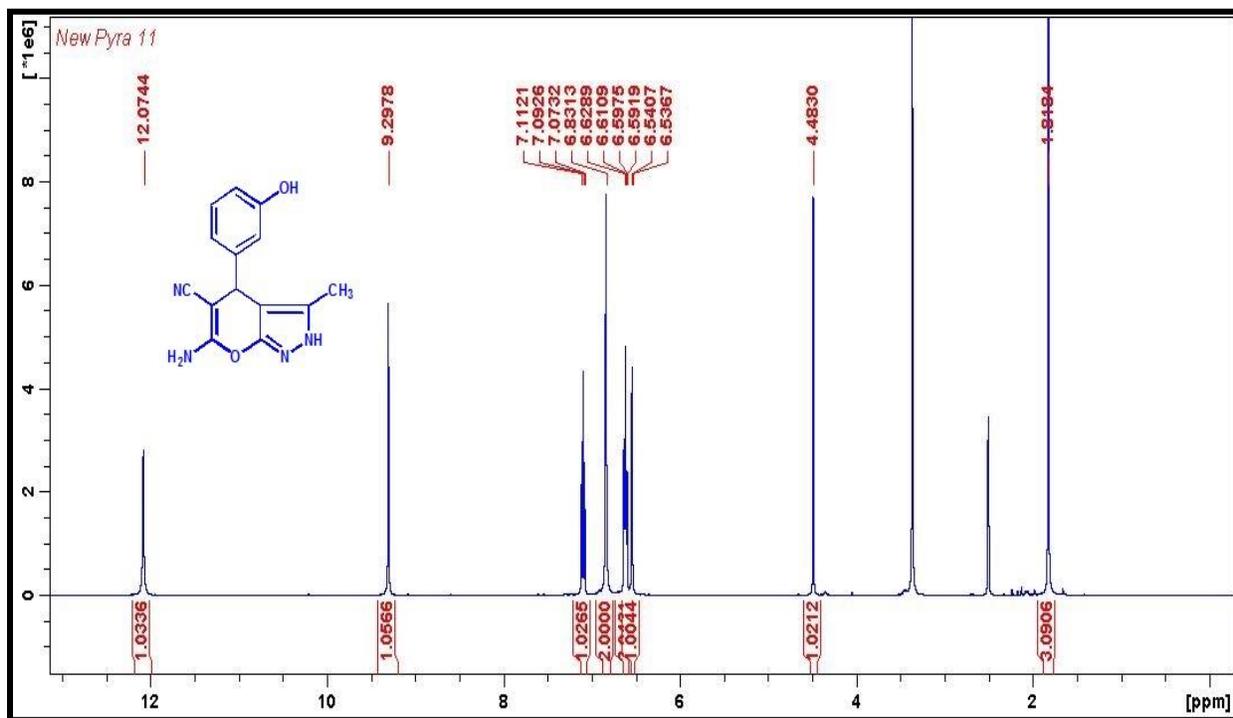
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
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269.0835	269.0839	-0.4	-1.5	11.5	735.8	0.0	C14 H10 N4 O F
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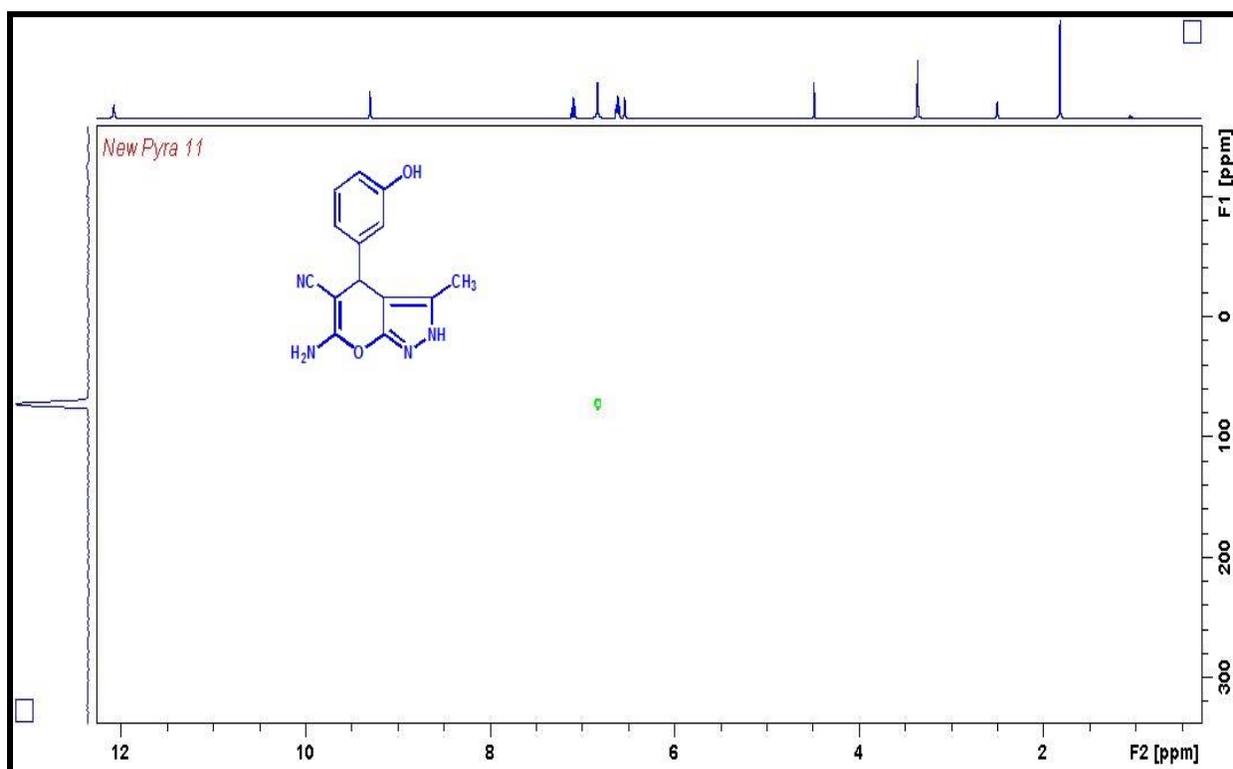
HR-MS spectra of compound **5f**



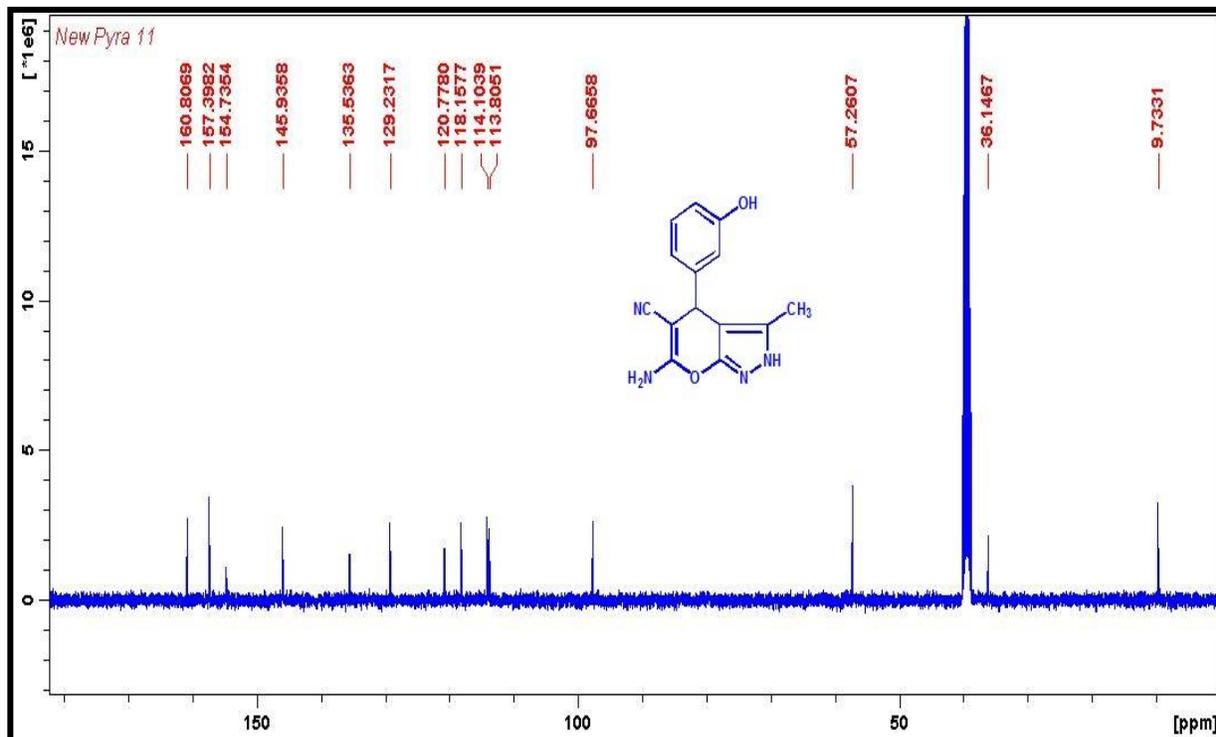
FT-IR spectra of compound **5f**



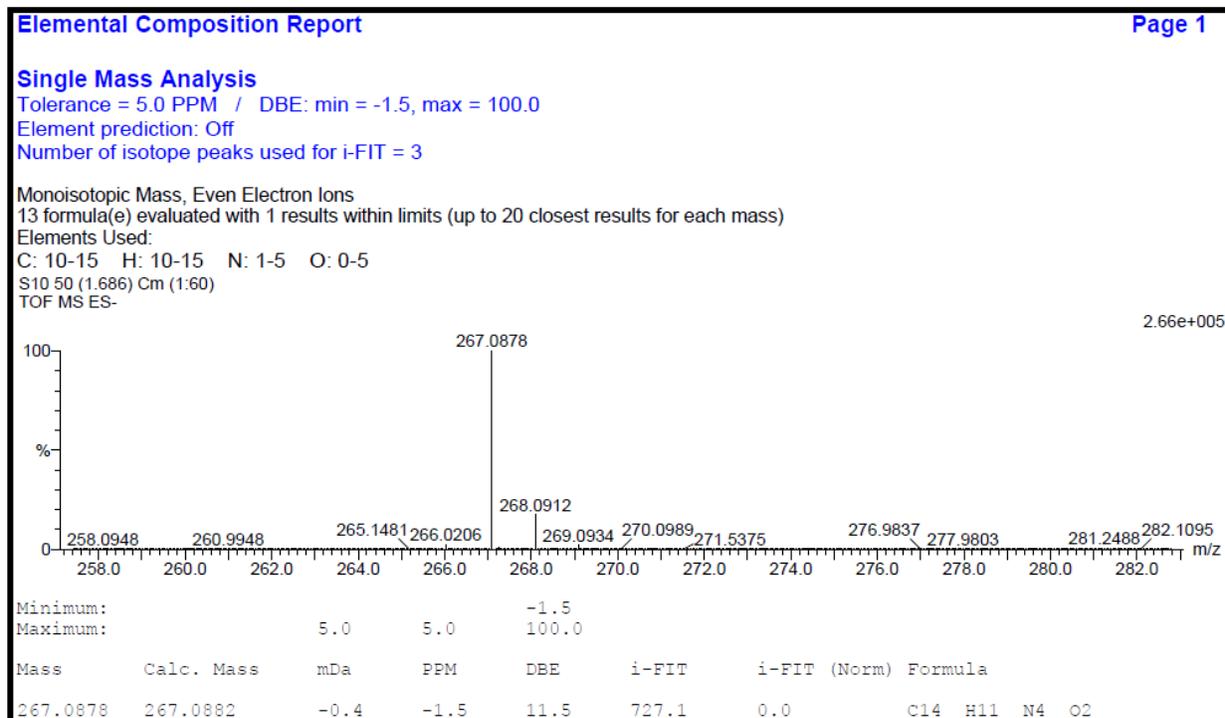
^1H NMR spectra of compound **5g**



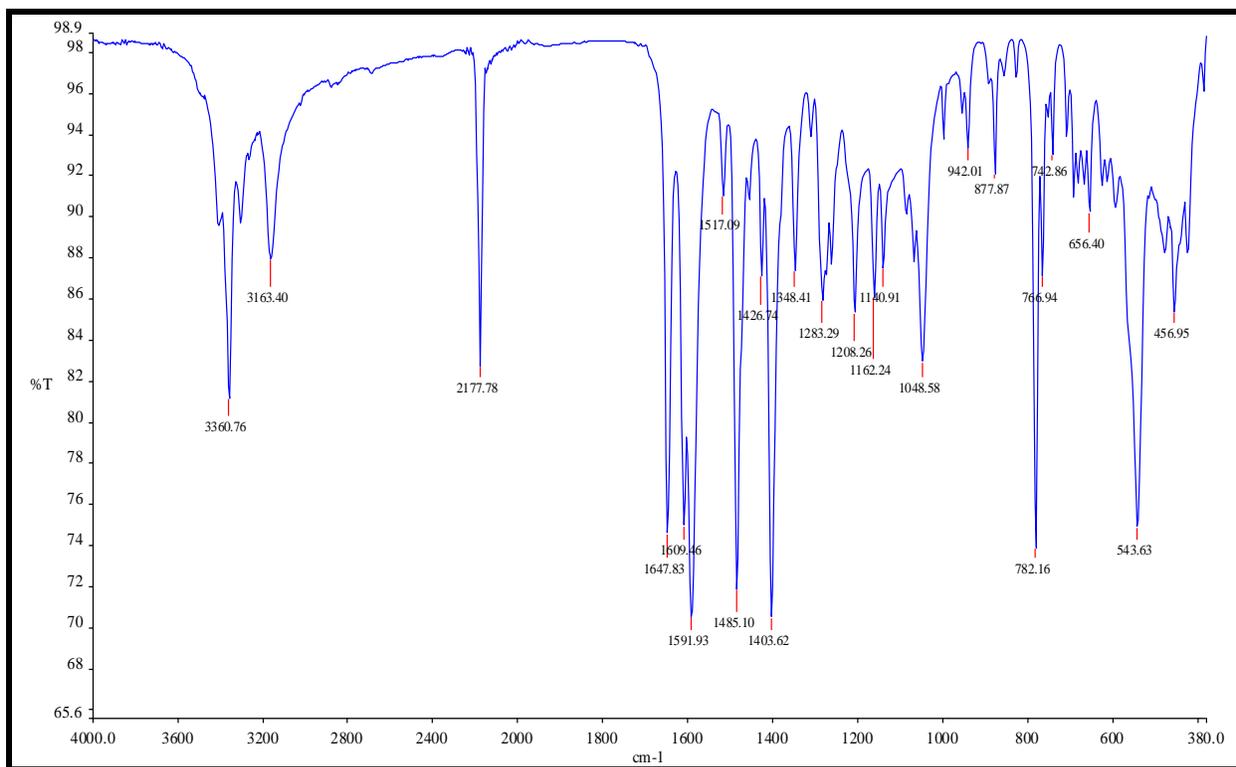
^{15}N NMR spectra of compound **5g**



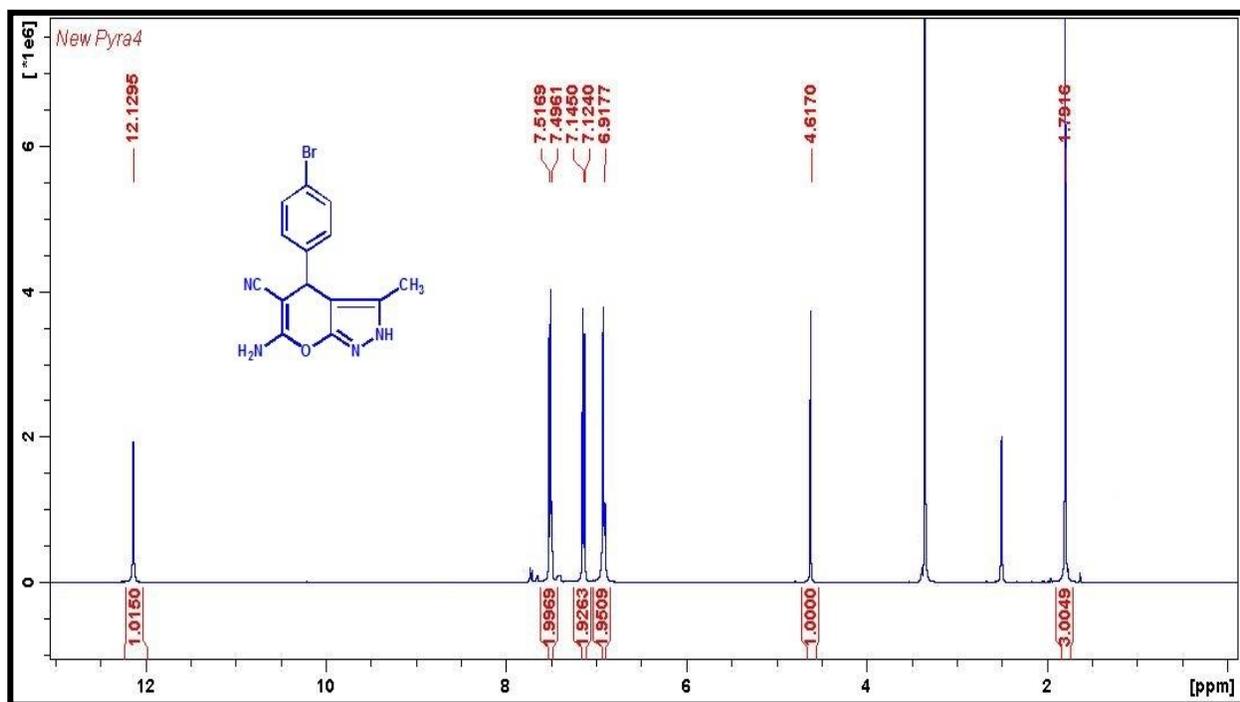
¹³C NMR spectra of compound **5g**



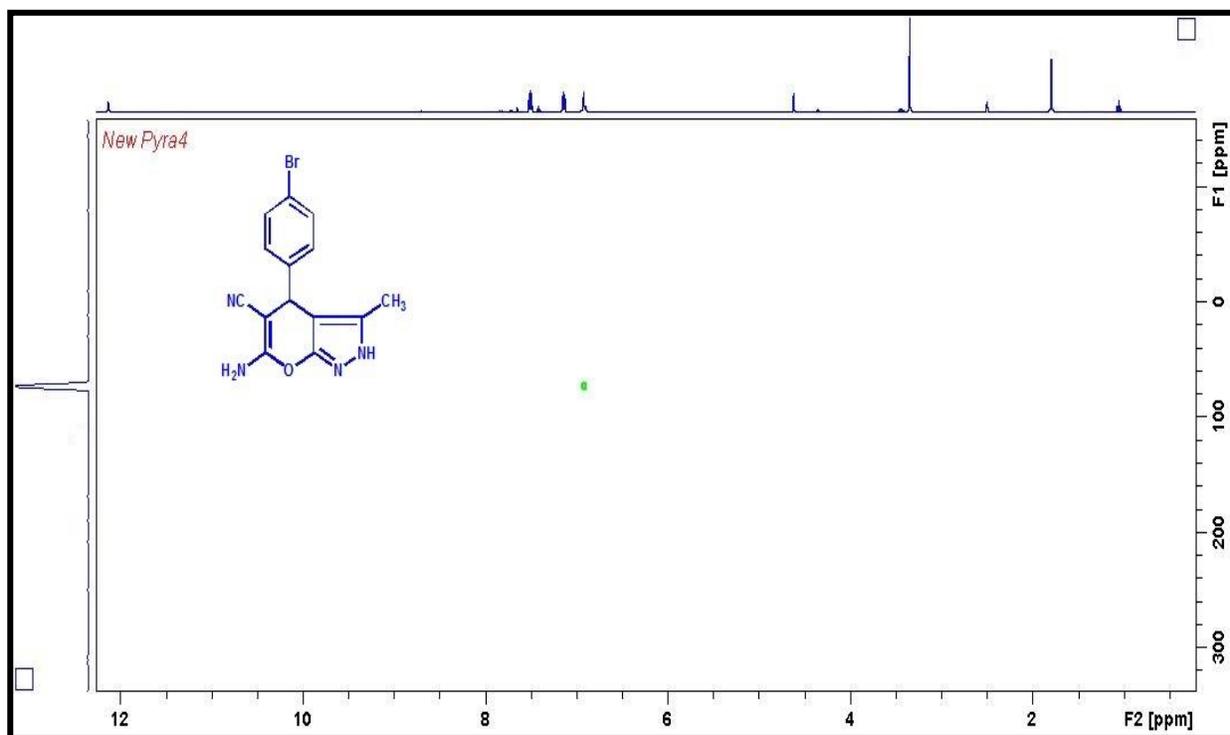
HR-MS spectra of compound **5g**



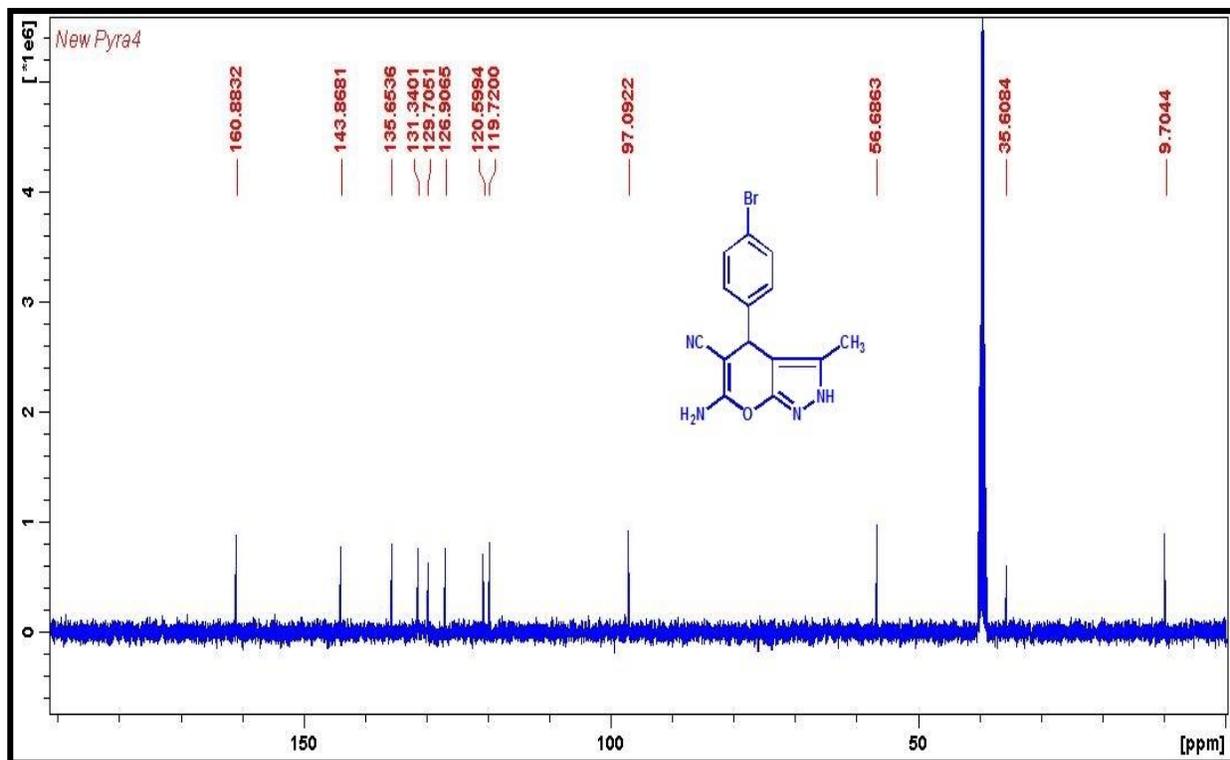
FT-IR spectra of compound **5g**



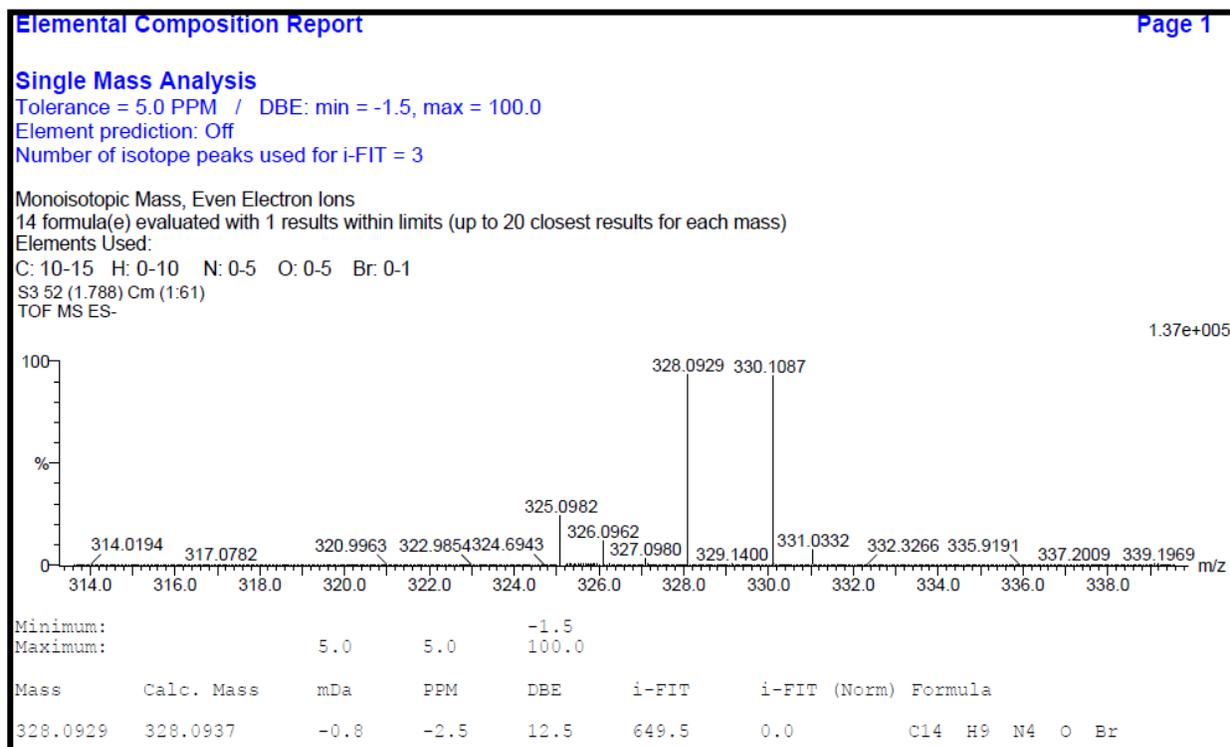
^1H NMR spectra of compound **5h**



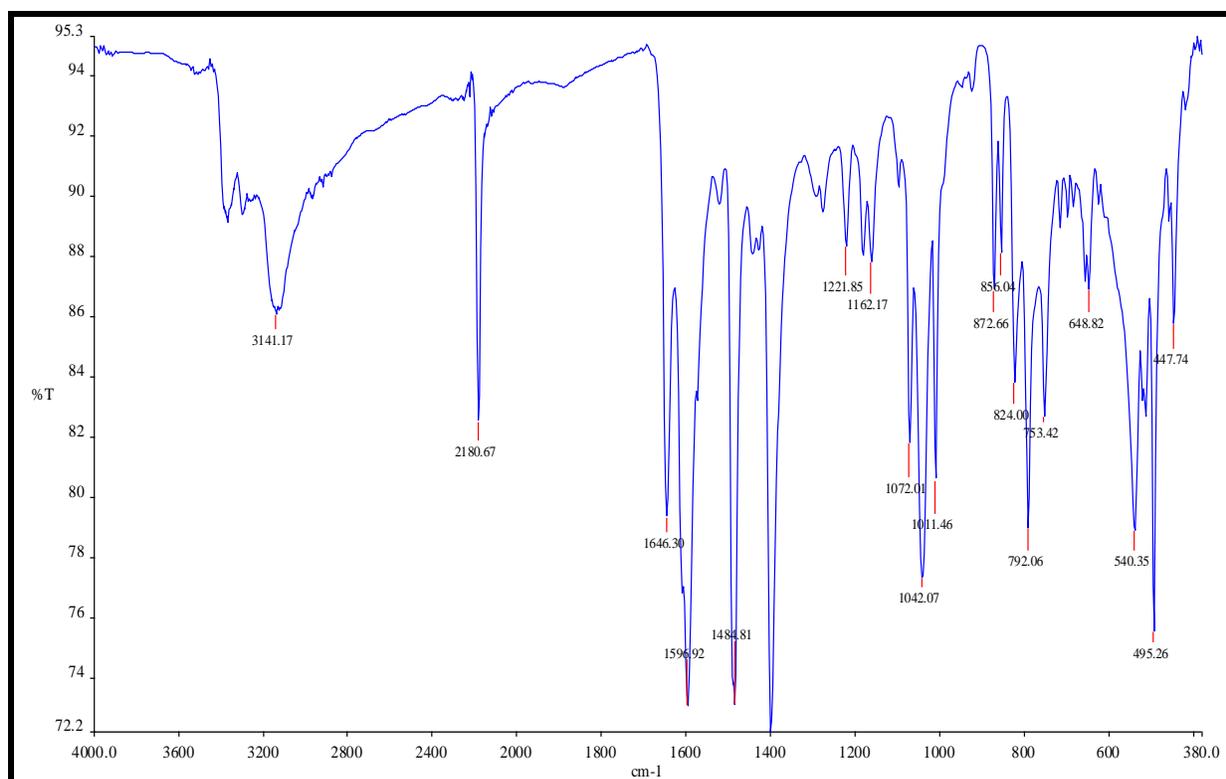
^{15}N NMR spectra of compound **5h**



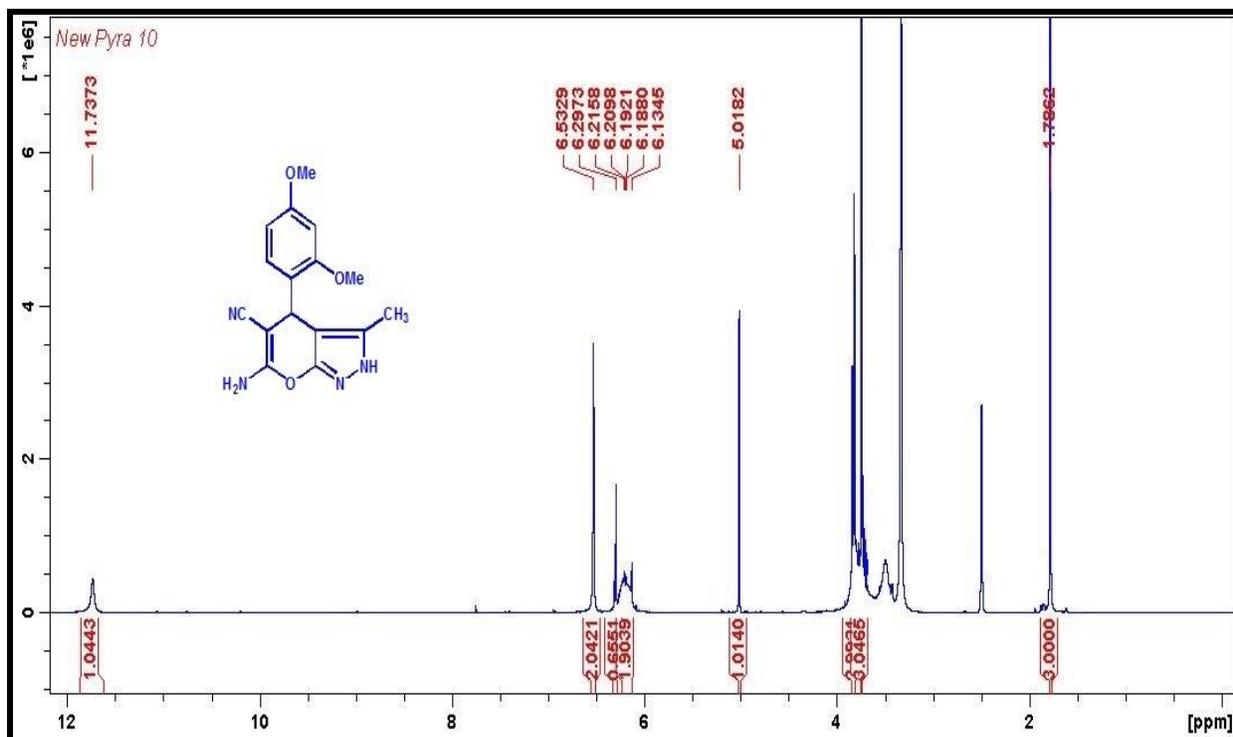
^{13}C NMR spectra of compound **5h**



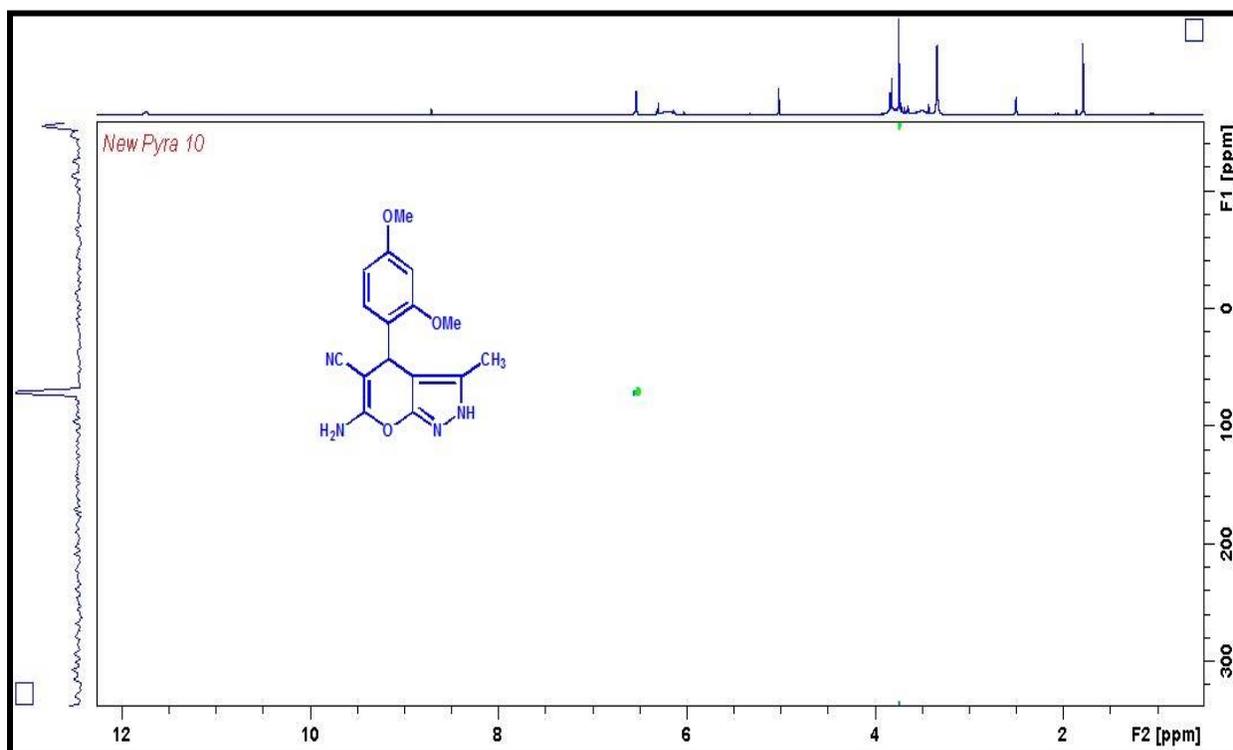
HR-MS spectra of compound **5h**



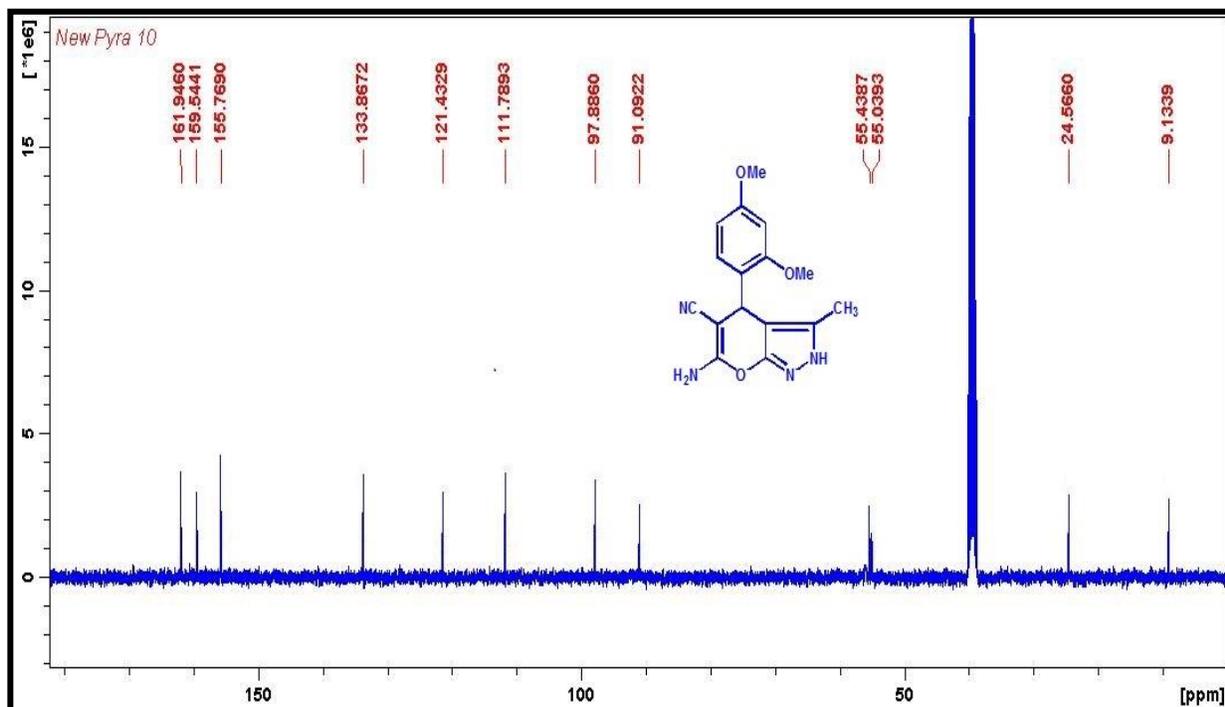
FT-IR spectra of compound **5h**



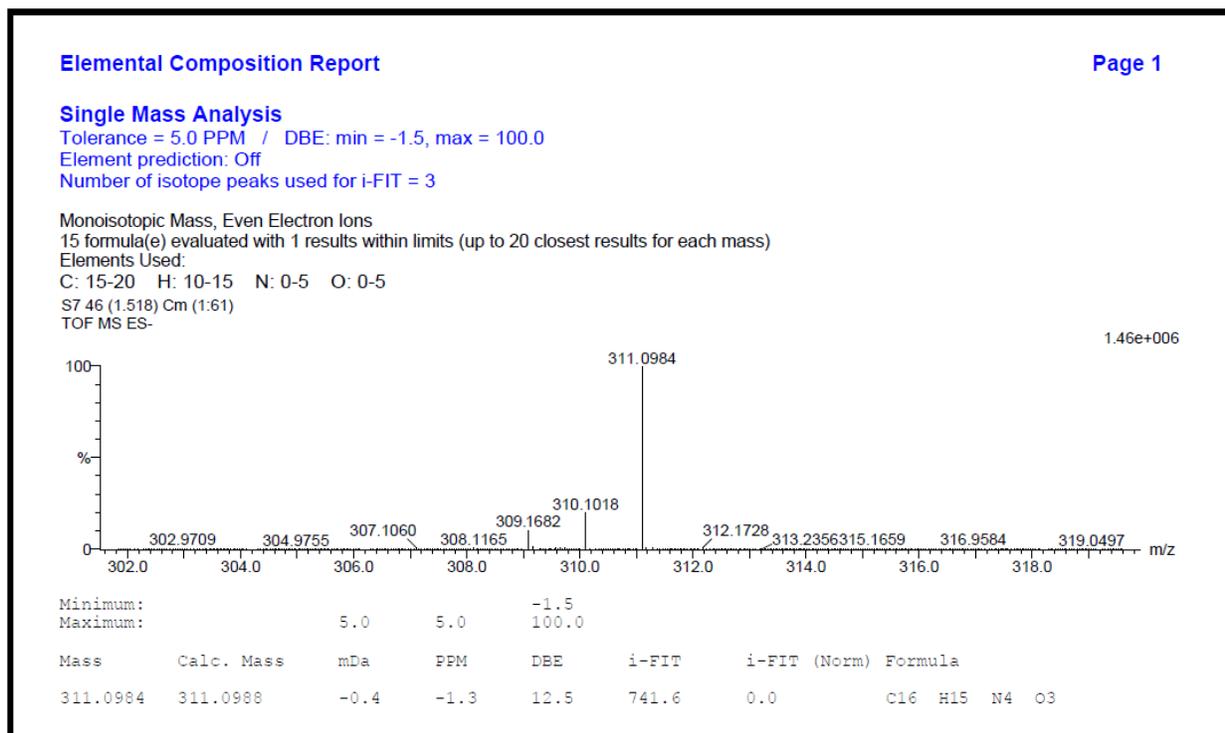
^1H NMR spectra of compound **5i**



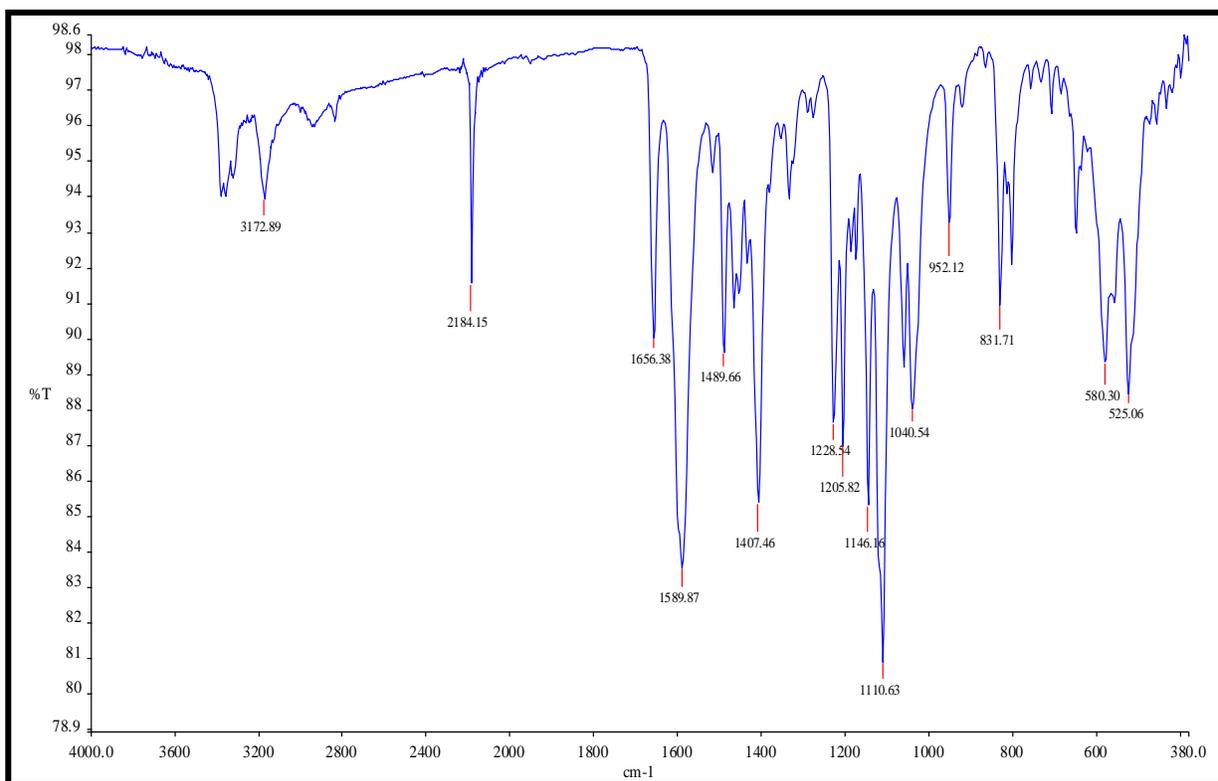
^{15}N NMR spectra of compound **5i**



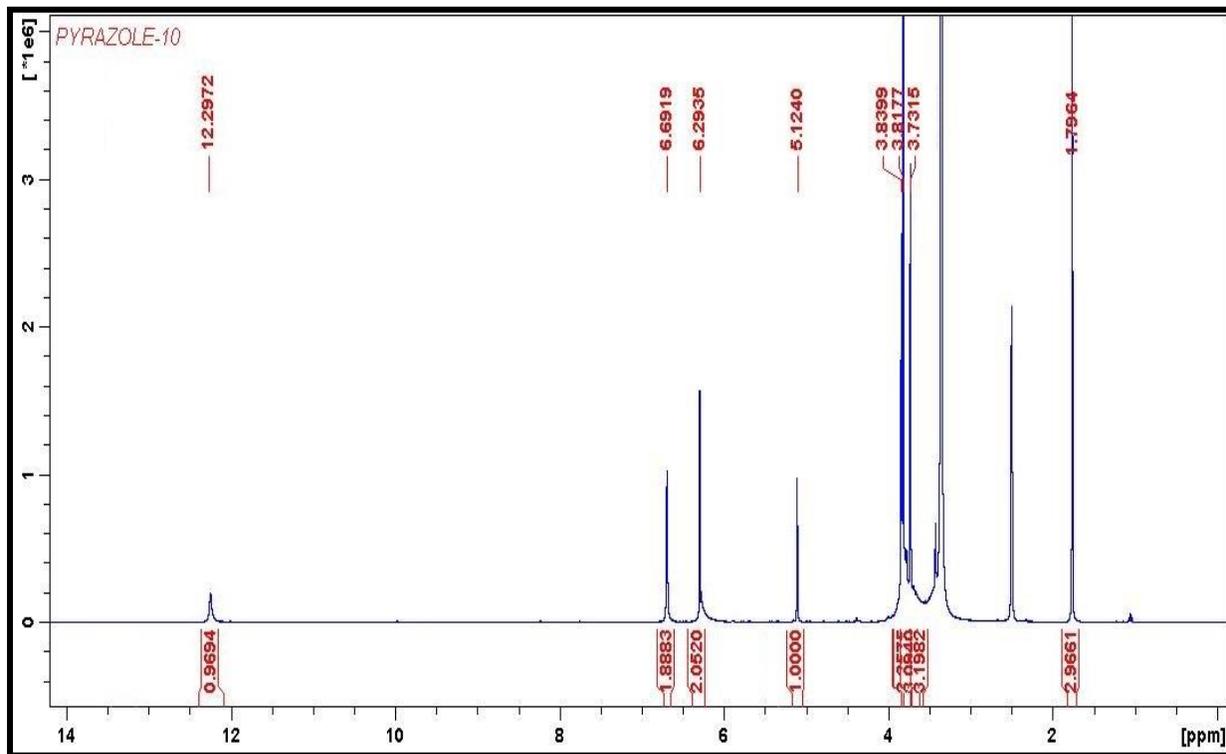
¹³C NMR spectra of compound **5i**



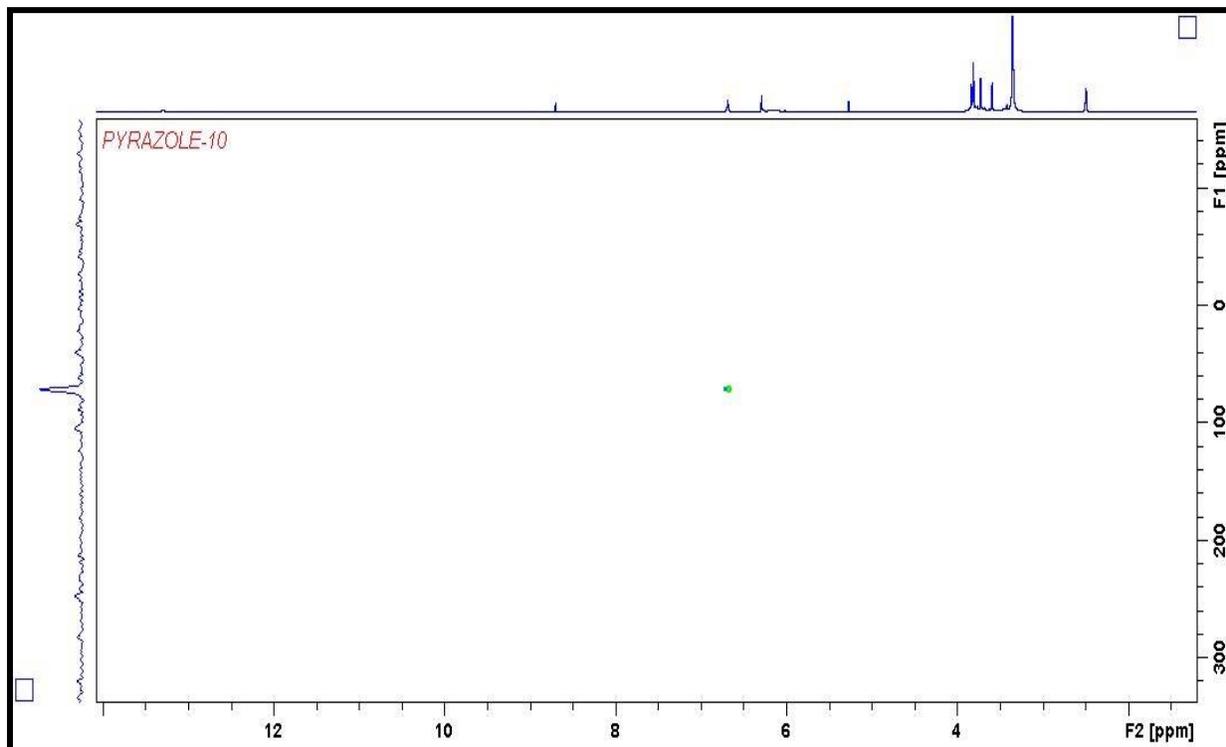
HR-MS spectra of compound **5i**



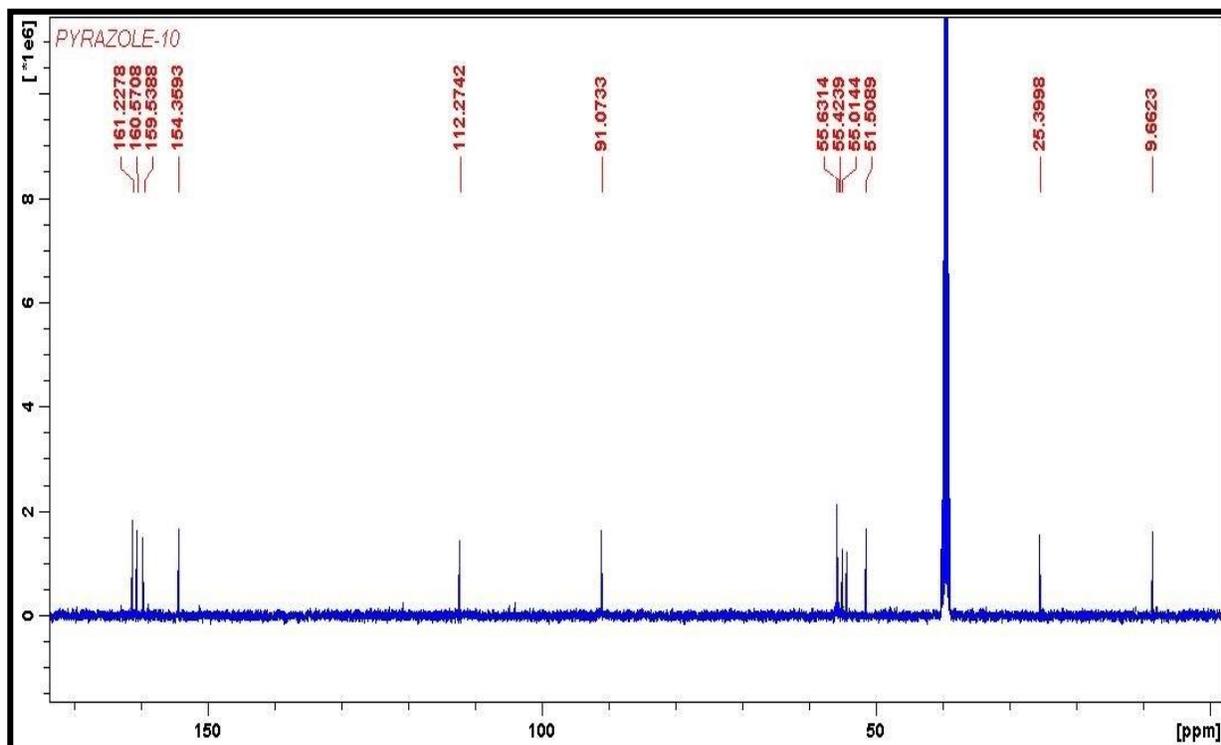
FT-IR spectra of compound **5i**



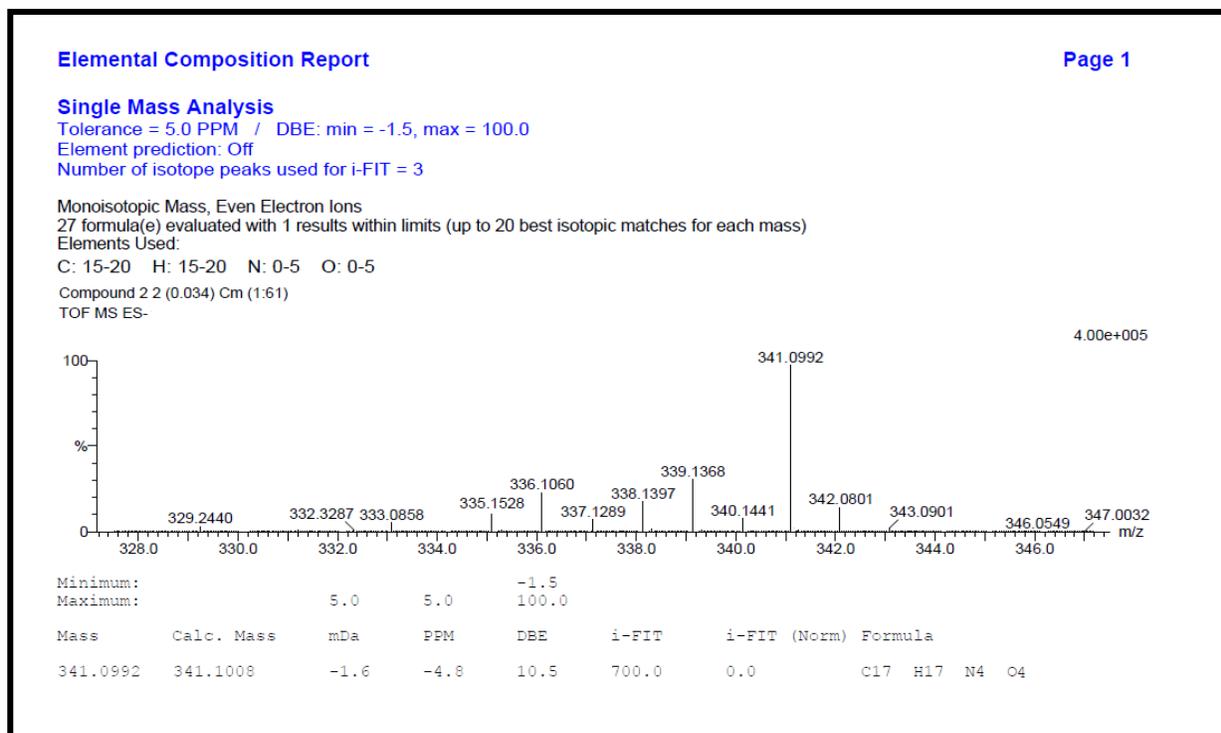
^1H NMR spectra of compound **5j**



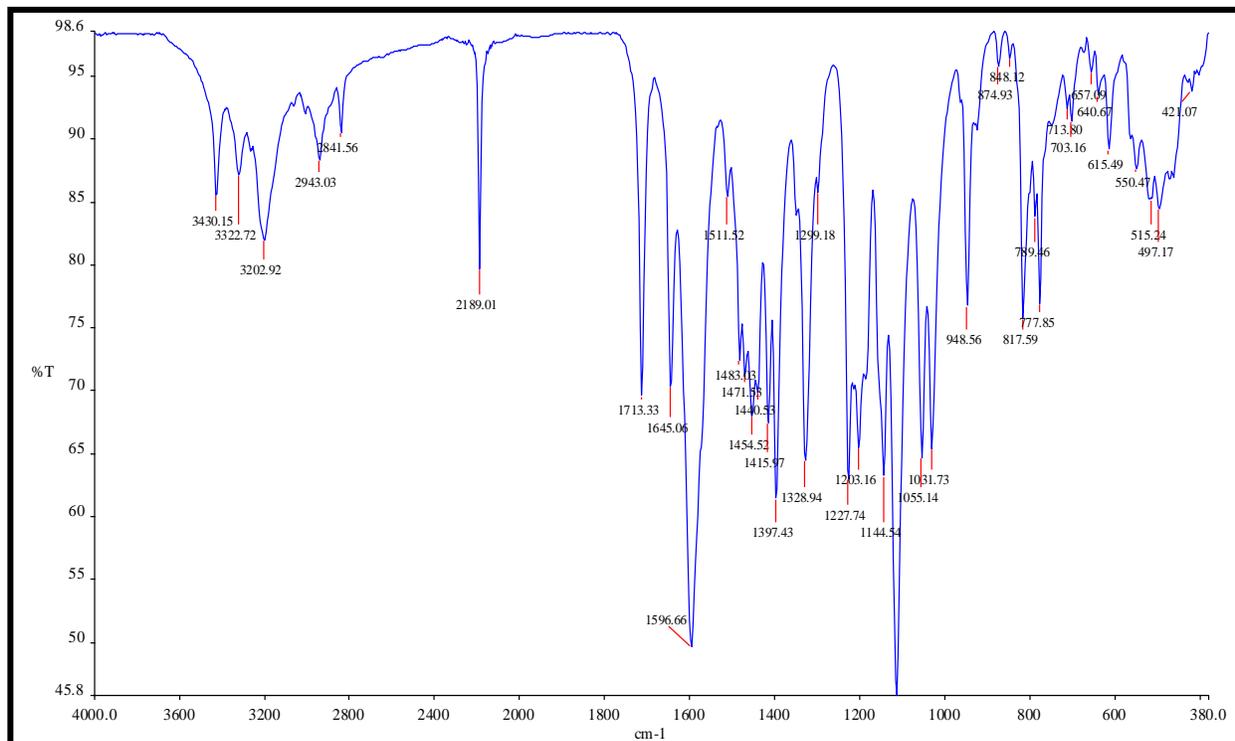
^{15}N NMR spectra of compound **5j**



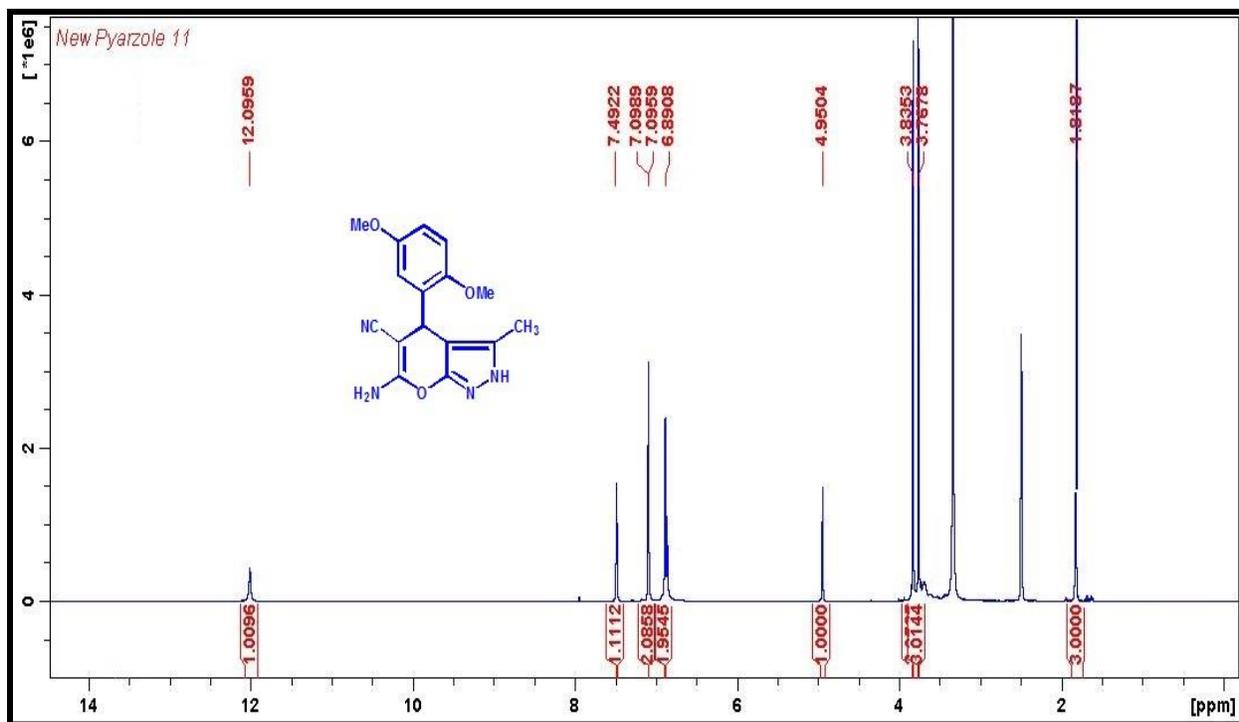
¹³C NMR spectra of compound **5j**



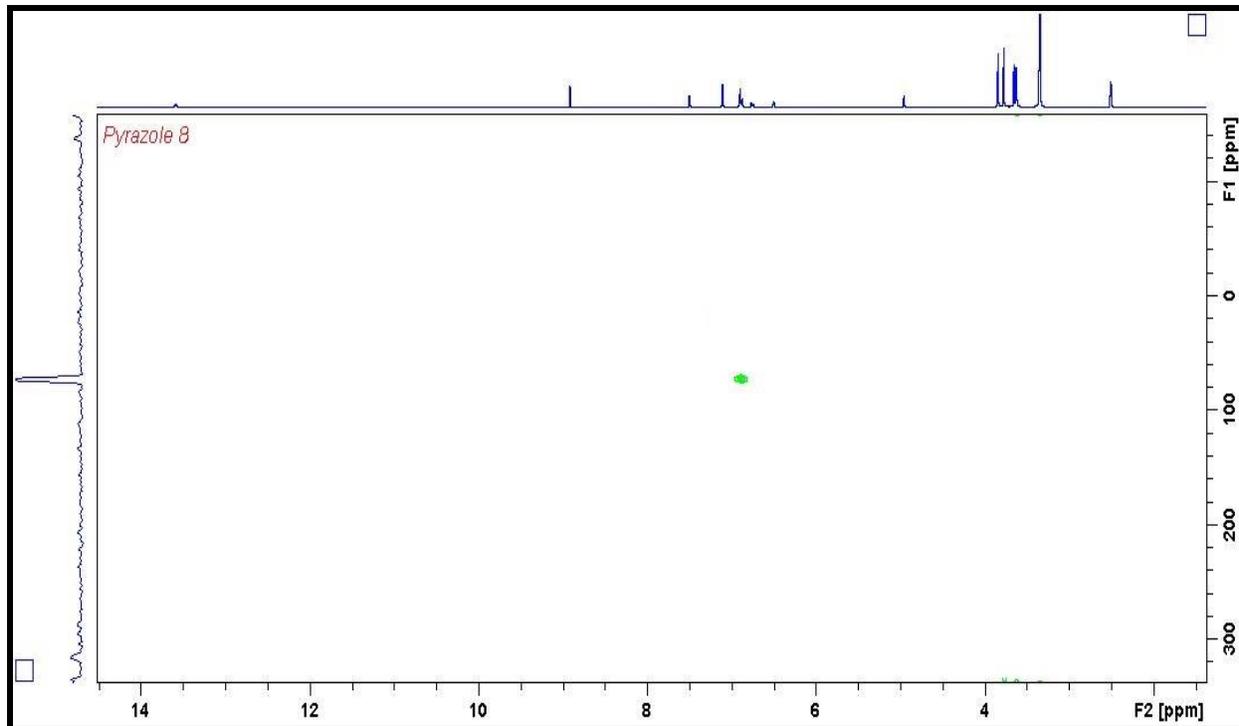
HR-MS spectra of compound **5j**



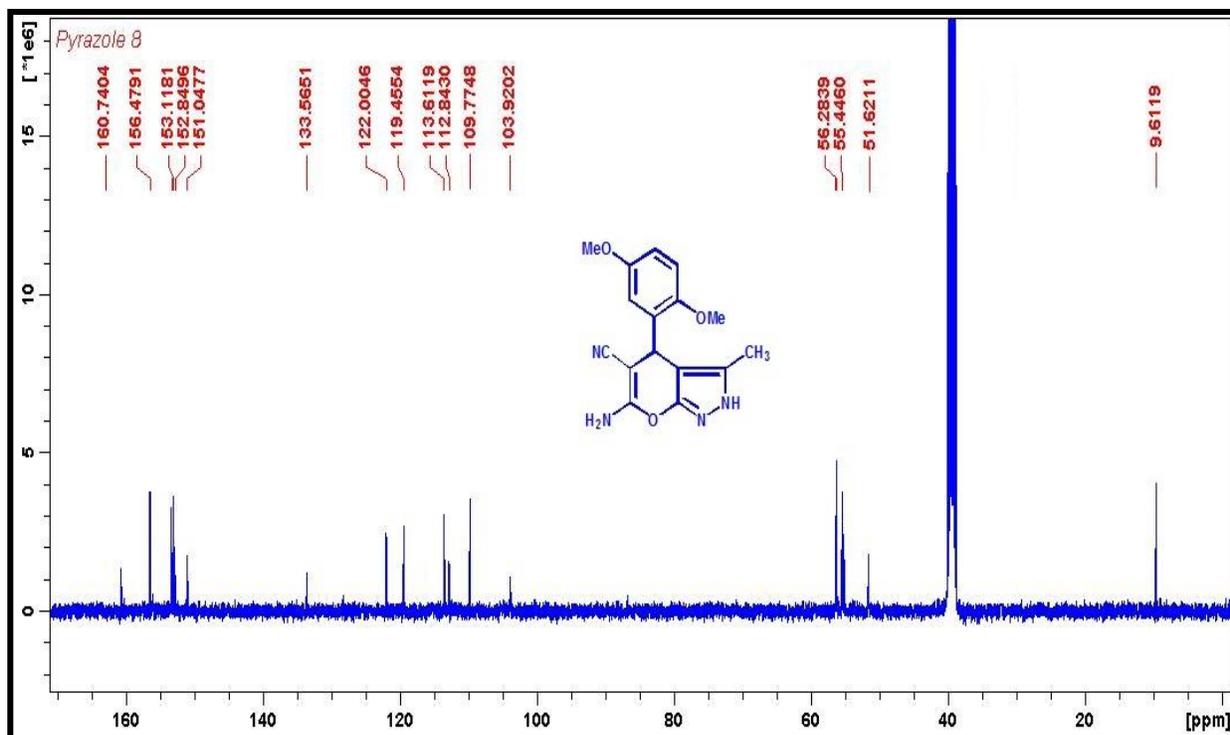
FT-IR spectra of compound 5j



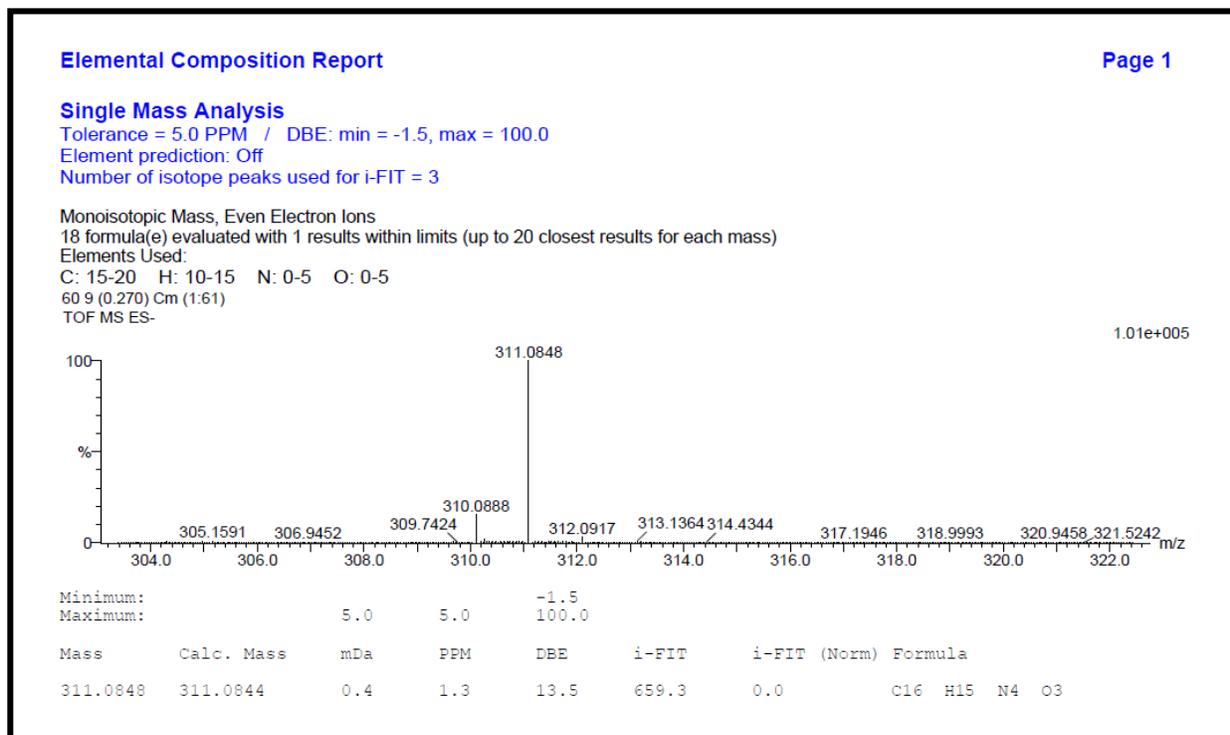
^1H NMR spectra of compound **5k**



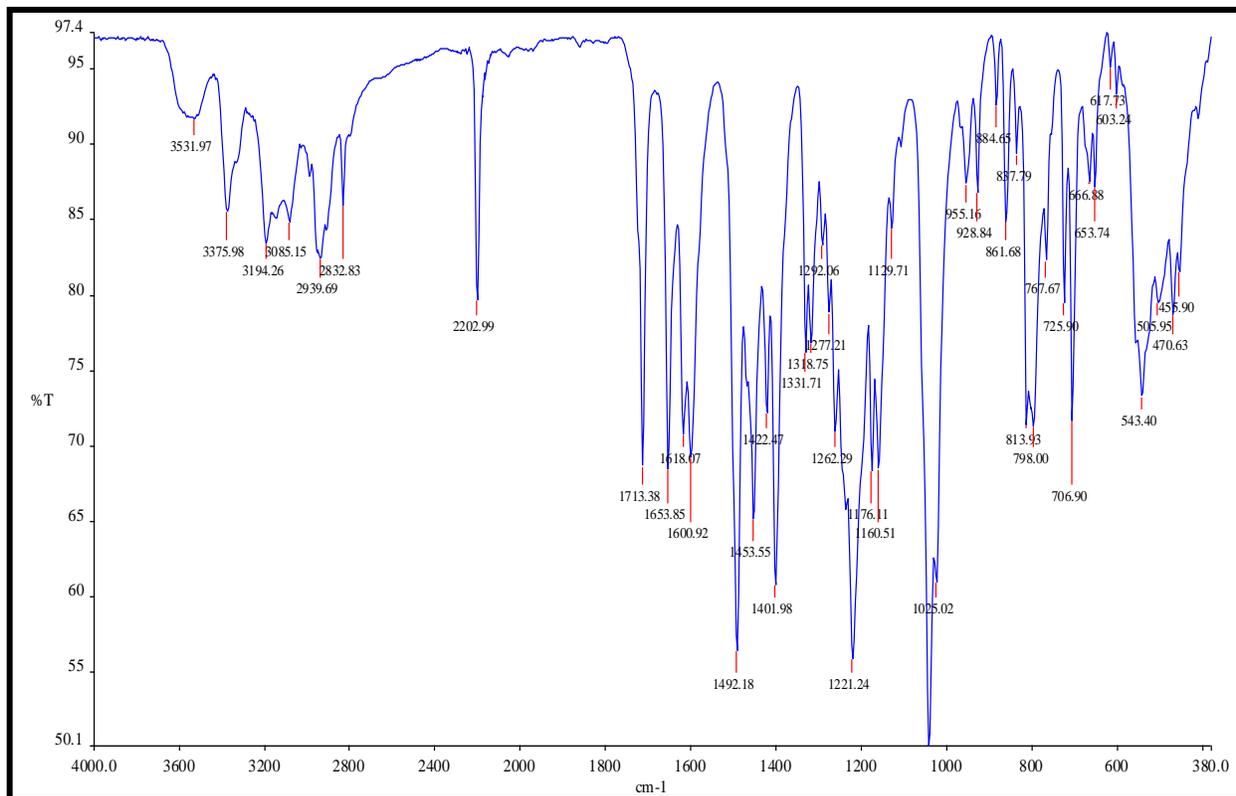
^{15}N NMR spectra of compound **5k**



¹³C NMR spectra of compound **5k**



HR-MS spectra of compound **5k**



FT-IR spectra of compound 5k

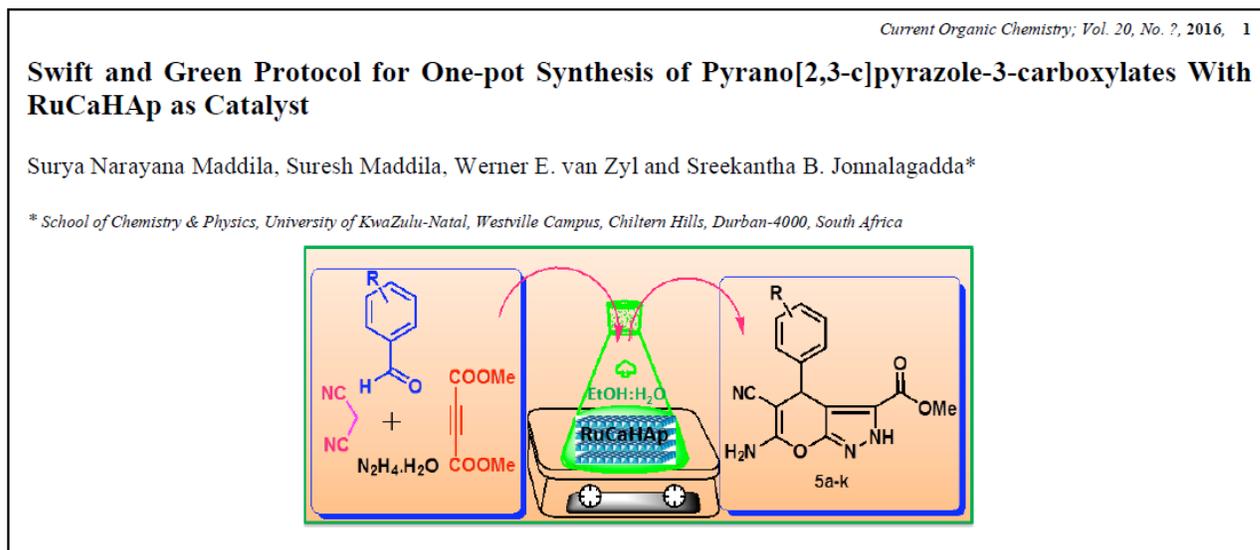
CHAPTER-6

Swift and green protocol for one-pot synthesis of pyrano[2,3-c]pyrazole-3-carboxylates with RuCaHAp as catalyst

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School of Chemistry and Physics, University of Kwa-Zulu Natal, Westville Campus, Private Bag X 54001, Durban, 4000, South Africa.

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This chapter is published in the **Current Organic Chemistry** and has been structured according to the journal's format.

Swift and green protocol for one-pot synthesis of pyrano[2,3-c]pyrazole-3-carboxylates with RuCaHAp as catalyst

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Abstract

An efficient, atom-economical, four-component one-pot reaction method was developed for pyrano[2,3-c]pyrazole-3-carboxylates using dimethylacetylenedicarboxylate, hydrazine hydrate, malononitrile and aromatic aldehydes, using a RuCaHAp catalyst. Ten new substituted pyrano[2,3-c]pyrazole-3-carboxylate derivatives (**5a-k**) were synthesized in good to excellent yields (88 to 97%), at room temperature with short reaction times (\approx 30 min) using the green solvent aqueous ethanol. RuCaHAp was prepared and characterized by various techniques including SEM, TEM, P-XRD and BET spectroscopy. The proposed heterogeneous catalyst can be easily synthesized, is inexpensive and stable with good reusability (at least 6 times) showing marginal loss of activity. The suggested environmentally benign protocol offers high yields, clean reaction profiles, operational simplicity and no need for chromatographic separations.

Keywords: Green protocol, Multicomponent reaction, Heterogeneous catalyst; Ru hydroxyapatite, pyrano[2,3-c]pyrazoles; Recyclable.

6.1. Introduction

The improvement of many efficient and eco-friendly methods used extensively in synthetic and medicinal chemistry from readily available reagents is a major challenge for chemists [1,2]. Multicomponent reactions (MCRs) have opened up new opportunities in the synthesis of varied heterocyclic moieties minimizing the steps, solvents and separations involved in the process [3-5]. Furthermore, MCRs also facilitate simple processes with higher yields and provide prospects to negotiate for more environmentally benign procedures and solvents [4,5], but further improvement and demand for discovery of new MCRs is ongoing.

Heterogeneous catalysts is very useful in heterocyclic synthetic methodology because of several advantages including reusability, environmental compatibility, non-corrosiveness, and ease of separation by making processes more cost effective [6,7]. To substitute conventional methods which require toxic stoichiometric reagents, with atom-efficient green alternatives is the way forward for sustainable chemistry [8]. Heterogeneous catalysis offer many benefits in this regard such as thermal stability, long life, recyclability and high selectivity through specific surface ensemble sites within a regular arrangement [7-9].

Hydroxyapatites (HAPs) possess M^{2+} sites surrounded by PO_4^{3-} tetrahedra parallel to the hexagonal axis. HAP materials have both acidic and basic sites in the crystal lattice and it is thus anticipated to perform both acidic and basic catalytic reactions [10]. The high sorption capacity for heavy metals, low water solubility, high chemical stability, good affinity, availability and low cost makes HAPs a perfect candidate for support material [11] and these characteristics also have made HAPs better contenders to be used as biomaterials, adsorbents and ion exchangers [12-14]. HAPs have been used in removal of heavy and toxic metals from contaminated soils [15], fertilizer production [16], water purification [17], organic synthesis [18] and medical treatment as targeted and controlled drug delivery carriers [19]. In this communication, we report the preparation and characterization of modified hydroxyapatites loaded with transition metals and tested their performance as catalysts for the synthesis of heterocyclic molecules and carbon-carbon bond-forming reactions.

Heterocyclic molecules have played a very important role in the development of medicines and pesticides in recent years and have become a new trend [20]. Nitrogen-containing pyranopyrazole heterocycles are essential components of many biologically active compounds and interesting templates for use in medicinal and pharmaceutical chemistry [21,22]. Due to their

potential as anti-cancer, anti-inflammatory, antimicrobial, anti-viral, antipyretic, anti-anxiety agents, the pyranopyrazoles have drawn significant attention from various research spheres [23-27]. Pyranopyrazoles have also been used as ingredients in biodegradable agrochemicals [28,29]. Although pyranopyrazole derivatives form an important class of heterocyclics, not many processes have been reported for their synthesis [21]. Literature surveys show that only three methods have been reported for synthesis of various pyrano[2,3-c]pyrazole-3-carboxylate derivatives. Those protocols employed Δ /reflux [30], Δ /CH₃COOH [31] and SnO₂ [32]. These methods used acidic or basic conditions, costly reagents, tedious handling processes, strict reaction conditions and obtained the product yield (<80%) after long reaction times (1.5 to 3.0 h). Thus, an improved greener protocol with an efficient and less expensive catalyst with shorter reaction times would be welcomed.

Our studies focused on the design and improvement of practical and environmentally friendly techniques for synthesis of biologically active molecules with either antimicrobial, insecticidal, anti-inflammatory and/or antioxidant activities. Previously, we have reported efficient protocols for synthesis of 1,2,4-triazoles, triazoles, 1,3,4-thiadiazoles, benzothiazoles [20, 33-35], tetrazole linked triazole [36], fused 1,2,4-triazolo-[3,4-b][1,3,4]-thiadiazole [37], thieno[2,3-d]pyrimidine, pyrimidinesulfamoyls [38,39], pyrazole-4-carbonitriles [5], pyrano[2,3-d]-pyrimidines [6], isoxazole-5(4*H*)-ones [40], pyrazolo-pyranopyrimidines [41], multifunctionalized benzenes [42] and pyranoquinolines [43], all derivatives using various heterogeneous catalysts by multicomponent reactions. Here we report on the applicability of a novel recyclable heterogeneous solid catalyst Ru supported hydroxyapatites (RuCaHAp) for efficient, convenient and facile green synthesis of pyrano[2,3-c]pyrazole-3-carboxylate derivatives through the one-pot reaction of dimethyl acetylenedicarboxylate, hydrazine hydrate, malononitrile and aldehyde under aqueous ethanol solvent condition and at room temperature. We are not aware of any reports on the use of any heterogeneous catalysts for this conversion.

6.2 Experimental section

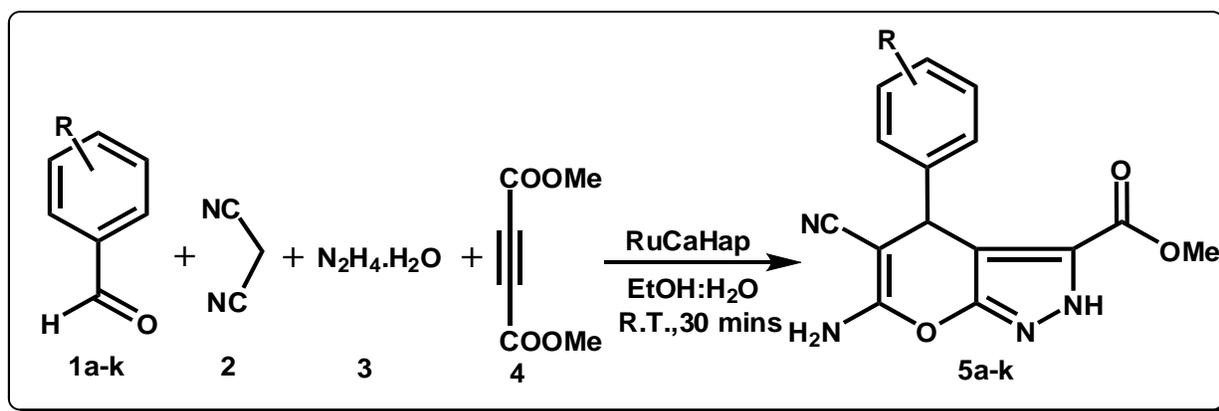
6.2.1 Preparation of the catalyst

Ca-hydroxyapatite (HAp) was synthesised using a co-precipitation method [44]. A solution of diammonium hydrogen orthophosphate, (NH₄)₂HPO₄ (5.6 g), (1.00 mol) (Merck, 98.5 %) was adjusted to pH 11.0 using a dilute ammonia solution and then diluted to 250 mL with double distilled water. Similarly, a calcium nitrate tetrahydrate, Ca(NO₃)₂.4H₂O (23.7 g),

(0.167 mol) (Merck, 99 %) solution was prepared and the pH adjusted to 11.0 and this solution was then diluted to 250 mL using double distilled water. The $(\text{NH}_4)_2\text{HPO}_4$ solution was added drop-wise to the $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ solution with constant and vigorous stirring at room temperature over a period of 1 h. The pH of the mixture was maintained at 11 throughout, using diluted ammonia. The resultant precipitate was heated to and maintained at 85 °C for 1.5 h and then allowed to cool to room temperature. Thereafter, the precipitate was filtered under vacuum and washed repeatedly until the pH of the filtrate was neutral, thus having ensured the removal of excess diluted ammonia. The HAp was then dried overnight in an oven at 120 °C and thereafter calcined at 500 °C for 6 hours. Supported catalysts were synthesised by adding the HAp to a solution of ruthenium(III) chloride hydrate ($\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (Aldrich, 99.98 %)) to afford the weight percentage of 1.0 wt% of RuO_2 . The catalyst materials were dried overnight at 120 °C. The powdered form of the catalyst material was calcined at 500 °C for 6 h.

6.2.2. General procedure for the synthesis of pyrano[2,3-c]pyrazole-3-carboxylates

To a mixture of dimethyl acetylenedicarboxylate (1.0 mmol), aldehydes (1.0 mmol), malononitrile (1.1 mmol) and hydrazine hydrate (1 mmol) in 1:1 water/ethanol (10 mL), Ru-CaHAp (30 mg) was added and the reaction was allowed to proceed for 30 min under stirred conditions at room temperature (RT) (**Scheme 1**). The progress of the reaction was followed by thin-layer chromatography (TLC) and the solid residue obtained at the end of the reaction was dissolved in hot ethanol and the catalyst was recovered by filtration. The filtrate was concentrated to afford the solid pure product (**5a-k**).



Scheme 1. Synthesis of pyrano[2,3-c]pyrazoles-3-carboxylate derivatives

6.3. Results and discussion

In our primary study to identify a suitable solvent system for the four-component one-pot reaction for the synthesis of pyrano[2,3-c]pyrazole-3-carboxylate derivatives, dimethyl acetylenedicarboxylate, hydrazine hydrate, malononitrile and 2-methoxybenzaldehyde were chosen as starting materials and RuHAp as catalyst as model reaction. The model reaction was investigated under varied solvent conditions (**Table 1**). The results showed that nonpolar solvents, like acetonitrile (CH₃CN), toluene and hexane, gave insignificant yields even after prolonged reaction times (Table 1, entries 1-3). Reaction under solvent-free conditions was not successful (Table 1, entry 4). However, the polar solvents EtOH or water at room temperature gave good yields (Table 1, entries 5 & 6). Further, the reaction was studied in different aqueous and ethanol mixtures. When the reaction was performed in EtOH–H₂O (1:3, 1:1 and 3:1 v/v) the yields were 73, 97 and 85 %, respectively (Table 1, entries 7-9). Thus EtOH–H₂O (1:1 v/v) proved most suitable solvent for this condensation in terms of yield and reaction time (Table 1, entry 8).

Table 1: Optimization of various solvent condition for the synthesis of pyrano[2,3-c]pyrazole-3-carboxylate derivatives by Ru-CaHAp catalyst

Entry	Catalyst	Solvent	Yield (%)
1	Ru-CaHAp	CH ₃ CN	12
2	Ru-CaHAp	Toluene	15
3	Ru-CaHAp	n-Hexane	09
4	Ru-CaHAp	No solvent	0
5	Ru-CaHAp	Ethanol	51
6	Ru-CaHAp	H ₂ O	48
7	Ru-CaHAp	EtOH–H ₂ O (2.5:7.0)	66
8	Ru-CaHAp	EtOH–H ₂ O (7.5:2.5)	70
9	Ru-CaHAp	EtOH–H ₂ O (1.0:1.0)	97

The impact of various parameters on the yield of model reaction was further investigated. In the absence of a catalyst under room temperature even after 8 h, the reaction proceeded with trace yields (Table 2, entries 1). The same reaction was tried under reflux conditions to achieve a lesser yield of product (Table 2, entries 2). 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 acidic catalysts such as SiO₂, CeO₂, Fe₂O₃ and TiO₂ at RT in aqueous ethanolic media and gave low yields (Table 2, entries 3-6). The use of inorganic basic catalysts, NaOH and K₂CO₃ in the same media exhibited slight catalytic activity, but gave only low yield of

product (Table 2, entries 7&8). When the reaction was examined using several organic basic catalysts such as TEA, pyridine and piperidine, the anticipated product improved with 45-54% yields (Table 2, entry 9-11). Thereafter, the reaction was performed in the presence of ionic liquids such as (Bmim)BF₄, L-proline, but yields were moderate at RT conditions (Table 2, entry 12 & 13). Furthermore, screening the reactivities of various hydroxyapatites, CaHAp, BaHAp SrHAp as catalysts, the reaction was repeated and after 50 min reaction time, yields were moderate (62-76%) (Table 2, entry 14-16). To further improve the quality of the reaction, Ru supported on CaHAp was used as catalyst, a reaction completed with an impressive 97% yield of pyrano[2,3-c]pyrazole-3-carboxylate derivative at RT and within 30 min reaction time (Table 2, entry 17). The efficiency of the catalyst system was compared with two other Ru supported HAp under similar conditions. The use of Ru-BaHAp and Ru-SrHAp gave marginally less yield (Table 2, entry 18 & 19).

Table 2: Optimization for the synthesis of pyrano[2,3-c]pyrazole-3-carboxylate by Ru-CaHAp catalyst^a

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%) ^b
1	--	EtOH:H ₂ O	RT	10	11
2	--	EtOH:H ₂ O	Reflux	8.0	17
3	SiO ₂	EtOH:H ₂ O	RT	4.0	22
4	CeO ₂	EtOH:H ₂ O	RT	3.5	39
5	Fe ₂ O ₃	EtOH:H ₂ O	RT	4.5	33
6	TiO ₂	EtOH:H ₂ O	RT	6.0	23
7	NaOH	EtOH:H ₂ O	RT	3.0	29
8	K ₂ CO ₃	EtOH:H ₂ O	RT	3.5	32
9	TEA	EtOH:H ₂ O	RT	3.5	45
10	Pyridine	EtOH:H ₂ O	RT	4.0	51
11	Piperidine	EtOH:H ₂ O	RT	5.0	54
12	(Bmim)BF ₄	EtOH:H ₂ O	RT	3.5	50
13	L-proline	EtOH:H ₂ O	RT	3.0	47
14	CaHAp	EtOH:H ₂ O	RT	1.0	76
15	BaHAp	EtOH:H ₂ O	RT	1.5	71
16	SrHAp	EtOH:H ₂ O	RT	2.0	62
17	Ru-CaHAp	EtOH:H ₂ O	RT	0.30	97
18	Ru-BaHAp	EtOH:H ₂ O	RT	0.30	93
19	Ru-SrHAp	EtOH:H ₂ O	RT	0.30	91

^a All products were characterised by IR, ¹H NMR, ¹³C NMR, ¹⁵N NMR & HRMS spectral analysis.

^b Isolated yields; -- No reaction

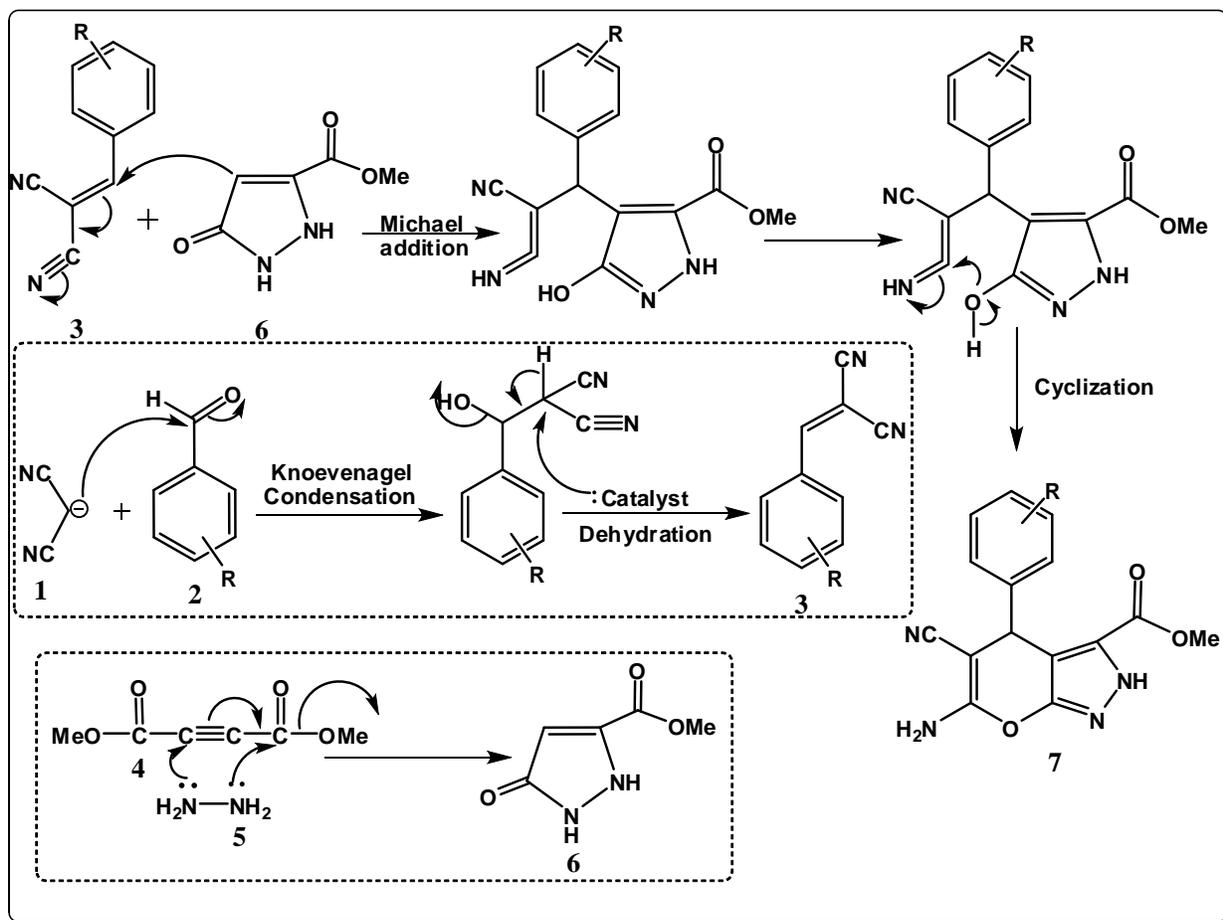
We next examined the amount of Ru-CaHAp needed for optimum performance of the model reaction under otherwise similar conditions. As illustrated in Table 3, the best results were achieved by use of 30 mg Ru-CaHAp and further increase in the amount of the catalyst gave no additional advantage. The yield decreased when the amount of catalyst was reduced to 10 mg (Table 3, entry 1-5), and prolonged the reaction time with impact on yield. Therefore, 30 mg of Ru CaHAp at RT with aqueous ethanol as solvent was identified as optimal condition for the model reaction giving 97% yield in 30 minutes.

Table 3: Optimization of the amount of 1% Ru-CaHAp as catalyst in the reaction

Entry	Catalyst (mg)	Time (min)	Yield (%)
1	Ru-CaHAp (10 mg)	90	85
2	Ru-CaHAp (20 mg)	55	88
3	Ru-CaHAp (30 mg)	30	97
4	Ru-CaHAp (40 mg)	30	95
5	Ru-CaHAp (50 mg)	30	95

Calcium hydroxyapatite exhibited better catalytic activity than strontium and barium hydroxyapatites. This may be due to the higher surface area of the ruthenium supported on calcium hydroxyapatite catalyst. This arrangement may depend on the nature of cations such as their electronegativity, ionic radius etc. These factors influence the crystal structure of hydroxyapatite and thus lead to difference in the surface properties of the material.

According to our results, the possible mechanism to account for the reaction was proposed (**Scheme 2**). The reaction mechanism shows the tandem sequence of base-catalyzed reactions proposed to explain formation of the pyrano[2,3-c]pyrazole-3-carboxylate. In the first step, 2-arylidene malonitrile (**3**) is formed by a fast Knoevenagel condensation of malonitrile (**1**) with arylaldehyde (**2**) catalyzed by the RuCa-HAp. The second step involves formation of 1*H*-pyrazol-3-carboxylate (**6**) by reaction of hydrazine hydrate (**5**) with ethyl acetoacetate (**4**). In the third step, a Michael addition of **3** to **7** in the presence of the mild basic catalyst produces the intermediate. Intramolecular cyclization and subsequently tautomerization afford the desired pyranopyrazolecarboxylate.



Scheme 2. Proposed Reaction Mechanism

Employing the above optimised reaction conditions the versatility of the protocol was evaluated for the synthesis of other pyrano[2,3-*c*]pyrazole-3-carboxylate derivatives using various aromatic aldehydes. The RuHAp heterogeneous catalyst facilitated the facile one-pot synthesis of pyrano[2,3-*c*]pyrazole-3-carboxylate derivatives with good to excellent yields. All the reaction products with corresponding details are shown in Table 4. Interestingly, the substrates used and reaction yields obtained shows that the reaction using several electron-withdrawing and electron donating substrates in ortho-, meta- and para- positions of the aromatic ring have also contributed positively to obtain the desired pyrano[2,3-*c*]pyrazole-3-carboxylate derivatives (Table 4). Structures of all the products (**5a-k**) were established and confirmed on the basis of their spectral data, ^1H NMR, ^{13}C NMR, ^{15}N NMR (GHSQC), FTIR and HRMS. Some of the details of the product characterization are presented in the Electronic Supporting Information (ESI-II).

Table 4: Synthesis of pyrano[2,3-c]pyrazole-3-carboxylate derivatives catalyzed by Ru-CaHAp catalyst

Entry	R	Product	Yield (%)	Mp °C	Lit Mp °C
1	2-OMe	5a	97	249-251	--
2	4-OMe	5b	92	236-237	--
3	4-Br	5c	88	246-247	247-248
4	2-Cl	5d	93	258-260	--
5	2,3-(OMe) ₂	5e	90	224-225	--
6	2,5-(OMe) ₂	5f	88	255-256	--
7	3,4-(OMe) ₂	5g	95	241-243	--
8	2,4,6-(OMe)	5h	91	238-240	--
9	2-F	5i	90	251-252	--
10	3-OH	5j	89	217-218	--
11	4-Cl	5k	94	213-215	--

-- New compounds/no literature available.

6-Amino-5-cyano-4-(2-methoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate

(5a): ¹H NMR (400 MHz, DMSO-d₆): δ 3.58 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃), 5.01 (s, 1H, CH), 6.83 (d, *J* = 7.36 Hz, 1H, ArH), 6.86 (s, 2H, NH₂), 6.92 - 6.95 (m, 2H, ArH), 7.17 (t, *J* = 7.32 Hz, 1H, ArH), 13.57 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): 31.83, 51.56, 55.59, 56.63, 104.11, 111.50, 120.24, 120.34, 127.92, 129.00, 132.32, 156.67, 158.51, 160.69; ¹⁵N NMR (40.55 MHz, DMSO-d₆) δ 6.86 (s, 2H, NH₂); FT-IR: 3386, 3321, 3202, 2196, 1715, 1652, 1467, 1247; HRMS of [C₁₆H₁₄N₄O₄ - H] (m/z): 325.0929; Calcd: 325.0937.

6-Amino-5-cyano-4-(4-methoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate

(5b): ¹H NMR (400 MHz, DMSO-d₆): δ 3.65 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃), 4.68 (s, 1H, CH), 6.83 (d, *J* = 8.52 Hz, 2H, ArH), 6.99 (s, 2H, NH₂), 7.03 (t, *J* = 8.88 Hz, 2H, ArH), 13.69 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): 36.19, 51.71, 54.92, 11.53, 128.34, 129.93, 137.03, 157.85, 160.02, 160.44; ¹⁵N NMR (40.55 MHz, DMSO-d₆): δ 6.99 (s, 2H, NH₂); FT-IR: 3461, 3331, 3164, 2201, 1722, 1632, 1486, 1390, 1228.

6-Amino-5-cyano-4-(4-bromoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate

(5c): ¹H NMR (400 MHz, DMSO-d₆): δ 3.64 (s, 3H, OCH₃), 4.75 (s, 1H, CH), 7.08 (s, 2H, NH₂), 7.47 (d, *J* = 8.28 Hz, 2H, ArH), 7.72 (d, *J* = 8.36 Hz, 1H, ArH), 7.82 (d, *J* = 8.48 Hz, 1H, ArH), 13.77 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): 32.23, 51.62, 55.44, 56.28, 103.35, 109.77, 115.35, 119.45, 122.00, 133.56, 151.11, 156.47, 160.74; ¹⁵N NMR (40.55 MHz, DMSO-d₆): δ

7.08 (s, 2H, NH₂); FT-IR: 3293, 3155, 2196, 1739, 1637, 1449, 1397, 1227; HRMS of [C₁₅H₁₁BrN₄O₃ - H] (m/z): 372.9942; Calcd: 372.9936.

6-Amino-5-cyano-4-(2-chloroxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate

(5d): ¹H NMR (400 MHz, DMSO-d₆): 3.57 (s, 3H, OCH₃), 5.26 (s, 1H, CH), 7.05 (s, 2H, NH₂), 7.21 – 7.25 (m, 2H, ArH), 7.37 – 7.39 (m, 1H, ArH), 7.56 – 7.59 (m, 2H, ArH), 13.76 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): 32.71, 51.62, 55.48, 56.86, 104.21, 114.45, 120.53, 121.24, 123.23, 128.45, 137.25, 146.39, 152.25, 155.82, 158.46, 160.52; ¹⁵N NMR (40.55 MHz, DMSO-d₆): δ 7.05 (s, 2H, NH₂); FT-IR: 3422, 3291, 3177, 2199 1722, 1602, 1489, 1316, 1186; HRMS of [C₁₅H₁₁ClN₄O₃ - H] (m/z): 329.0434; Calcd: 329.0441.

6-Amino-5-cyano-4-(2,3-dimethoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-

carboxylate (5e): ¹H NMR (400 MHz, DMSO-d₆): δ 3.55 (s, 3H, OCH₃), 3.61 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 4.91 (s, 1H, CH), 6.60 (d, *J* = 7.08 Hz, 1H, ArH), 6.68 (d, *J* = 7.08 Hz, 1H, ArH), 6.93 (s, 2H, NH₂), 6.95 (d, *J* = 8 Hz, 1H, ArH), 13.58 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): 32.71, 51.59, 55.48, 56.86, 59.70, 104.21, 114.45, 120.53, 121.24, 123.23, 128.45, 137.25, 146.39, 152.25, 158.46; ¹⁵N NMR (40.55 MHz, DMSO-d₆): δ 6.93 (s, 2H, NH₂); FT-IR: 3426, 3289, 3154, 2186, 1732, 1606, 1479, 1396, 1266; HRMS of [C₁₇H₁₆N₄O₅ - H] (m/z): 355.1042; Calcd: 355.1042.

6-Amino-5-cyano-4-(2,5-dimethoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-

carboxylate (5f): ¹H NMR (400 MHz, DMSO-d₆): δ 3.64 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 4.95 (s, 1H, CH), 6.89 (s, 2H, NH₂), 7.09 (d, *J* = 1.2 Hz, 2H, ArH), 7.49 (s, 1H, ArH), 13.54 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): 51.62, 55.44, 56.28, 56.46, 109.7, 111.81, 115.35, 119.45, 120.38, 122.00, 133.56, 151.04, 153.33, 158.49, 160.74; ¹⁵N NMR (40.55 MHz, DMSO-d₆): δ 6.89 (s, 2H, NH₂); FT-IR: 3531, 3375, 3194, 2939, 2202, 1713, 1600, 1492, 1221.

6-Amino-5-cyano-4-(3,4-dimethoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-

carboxylate (5g): ¹H NMR (400 MHz, DMSO-d₆): δ 3.62 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 4.54 (s, 1H, CH), 6.69 (d, *J* = 1.96 Hz, 1H, ArH), 6.75 (d, *J* = 1.96 Hz, 1H, ArH), 6.80 (s, 2H, NH₂), 6.90 (d, *J* = 8.28 Hz, 1H, ArH), 13.58 (s, 1H, NH). ¹³C NMR (100 MHz, CDCl₃): 35.79, 51.59, 55.41, 57.42, 59.70, 97.67, 111.19, 111.72, 119.46, 120.81, 135.63, 136.86, 147.53, 148.51, 154.68, 160.72; ¹⁵N NMR (40.55 MHz, DMSO-d₆): δ 6.80 (s, 2H, NH₂); FT-IR: 3294, 3003, 2930, 2222, 1730, 1579, 1507, 1420, 1269.

6-Amino-5-cyano-4-(2,4,6-trimethoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5h): ^1H NMR (400 MHz, DMSO- d_6): δ 3.59 (s, 3H, OCH $_3$), 3.73 (s, 3H, OCH $_3$), 3.81 (s, 3H, OCH $_3$), 3.83 (s, 3H, OCH $_3$), 5.27 (s, 1H, CH), 6.29 (s, 2H, ArH), 6.69 (s, 2H, NH $_2$), 13.29 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl $_3$): 25.39, 51.50, 55.01, 55.42, 55.63, 91.07, 112.27, 154.35, 159.53, 160.57, 161.22; ^{15}N NMR (40.55 MHz, DMSO- d_6): δ 6.69 (s, 2H, NH $_2$); FT-IR: 3430, 3322, 3202, 2189, 1713, 1596, 1397, 1227; HRMS of [C $_{18}$ H $_{18}$ N $_4$ O $_6$ - H] (m/z): 385.1161; Calcd: 385.1148.

6-Amino-5-cyano-4-(2-fluorophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5i): ^1H NMR (400 MHz, DMSO- d_6): δ 3.61 (s, 3H, OCH $_3$), 5.01 (s, 1H, CH), 7.06 (s, 2H, NH $_2$), 7.10 - 7.12 (m, 3H, ArH), 7.24 (t, J = 1.96 Hz, 1H, ArH), 13.76 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl $_3$): 31.13, 51.58, 56.08, 102.95, 124.32, 128.75, 129.99, 158.28; ^{15}N NMR (40.55 MHz, DMSO- d_6): δ 7.06 (s, 2H, NH $_2$); FT-IR: 3321, 3379, 3201, 2202, 1720, 1655, 1442, 1224; HRMS of [C $_{15}$ H $_{11}$ FN $_4$ O $_3$ - H] (m/z): 313.0734; Calcd: 313.0737.

6-Amino-5-cyano-4-(3-hydroxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5j): ^1H NMR (400 MHz, DMSO- d_6): 3.61 (s, 3H, OCH $_3$), 4.63 (s, 1H, CH), 6.53 (s, 1H, ArH), 6.59 - 6.62 (m, 2H, ArH), 6.83 (s, 2H, NH $_2$), 7.10 (t, J = 7.8 Hz, 1H, ArH), 9.31 (s, 1H, OH), 13.24 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl $_3$): 36.14, 57.26, 97.66, 113.80, 114.10, 118.15, 120.77, 129.23, 135.53, 145.93, 154.39, 157.39, 160.80; ^{15}N NMR (40.55 MHz, DMSO- d_6): δ 6.83 (s, 2H, NH $_2$); FT-IR: 3422, 3178, 2188, 1712, 1633, 1490, 1397, 1207; HRMS of [C $_{15}$ H $_{12}$ N $_4$ O $_4$ - H] (m/z): 311.0984; Calcd: 311.0988.

6-Amino-5-cyano-4-(4-chloroxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5k): ^1H NMR (400 MHz, DMSO- d_6): 3.66 (s, 3H, OCH $_3$), 4.78 (s, 1H, CH), 7.06 (s, 2H, NH $_2$), 7.15 (d, J = 5.68 Hz, 2H, ArH), 7.34 (d, J = 5.52 Hz, 2H, ArH), 13.78 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl $_3$): 36.89, 52.23, 57.88, 104.11, 120.57, 128.69, 129.77, 144.32, 155.78, 158.78, 160.67; ^{15}N NMR (40.55 MHz, DMSO- d_6): δ 7.06 (s, 2H, NH $_2$); FT-IR: 3433, 3161, 2197, 1741, 1635, 1482, 1386, 1228.

6.3.1. Powder X-ray diffraction

Figure 1 displays powder X-ray diffraction patterns of calcined Ru loaded CaHAp. The catalyst diffraction peak values 2θ of 25.78°, 31.91°, 32.74°, 33.97°, 39.82°, 46.66°, 49.34° and 53.12°, were assigned to CaHAp. All these diffraction peaks agree with the international standards files (JCPDS file no. 09-0432). Ru supported on CaHAp sample showed diffraction

peaks at a 2θ angles of 28.21° , 35.11° , 54.34° and 69.70° corresponding to the RuO_2 (JCPDS # 40-1290). The peaks identified in the diffractogram shows the polycrystalline nature of the materials. The average crystallite size of this sample was obtained to be 6.8 nm using the Scherrer equation based on the highest intensity diffraction peaks of Ru-CaHAp.

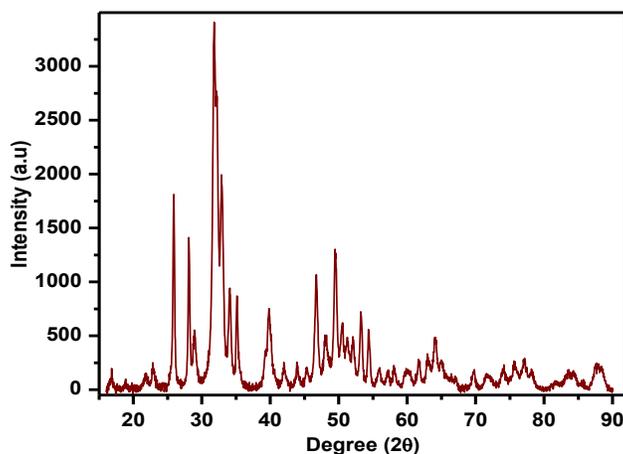


Figure 1. XRD spectrum of Ru-CaHAp catalyst

6.3.2. SEM analysis

Figure 2 shows an illustrative SEM surface morphology micrograph of the sample Ru on CaHAp catalyst. The morphologies of the synthesized Ru-CaHAp seem to be similar with considerable agglomeration of Hap particles. The catalyst material exhibited irregular spherical shapes and agglomeration with inter-granular micropores, as shown in image **Figure 2**. This micrograph reveals the aggregation state of the HAp particles and its uniform distribution. The micrographs of SEM-EDX confirmed the uniform distribution of ruthenium on the hydroxyapatite surface. The SEM-EDX agrees with the data from ICP elemental analysis. Furthermore, the morphology of the catalyst as per the SEM images noticeably point to the crystallinity and homogeneity of the sample.

6.3.3. TEM analysis

The TEM micrograph confirms more structural information of the catalyst. **Figure 3** shows a distinctive TEM image of Ru supported on HAp, from which it can be seen that the Ru particles revealed square-like shapes and particle dimension ranging between 20 and 50 nm and hydroxyapatite appearing as rod-like particles. No drastic change was noticed in the morphology of the used catalyst.

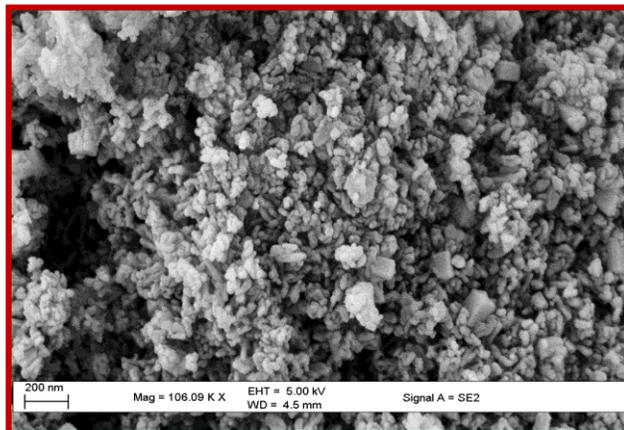


Figure 2. SEM micrograph of Ru-CaHAp catalyst

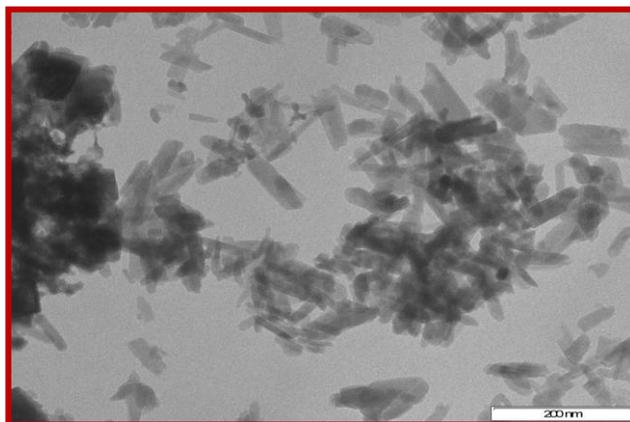


Figure 3. TEM micrograph of Ru-CaHAp catalyst

6.3.4. BET surface area (BET) and elemental (ICP) analysis

The N_2 adsorption–desorption isotherms of the prepared Ru loaded CaHAp material are shown in **Figure 4**. The figure shows the nitrogen adsorption isotherms and pore size distribution of RuCaHAp catalyst. As per the IUPAC classification, the sample displays type-VI isotherms and a typical H1-hysteresis loop, representing the mesoporous nature of the materials. The BJH pore size distribution designates a mesoporous (pore of 3–50 nm) texture for the sample, and the isotherms p/p_0 range was 0.82-0.95. The Brunauer–Emmett–Teller (BET) surface area was determined at $46 \text{ m}^2 \text{ g}^{-1}$ with a pore volume of 0.218 cc g^{-1} . As anticipated, the ICP analysis results showed the presence of a nominal amount of Ru in the catalyst (0.98 mol %).

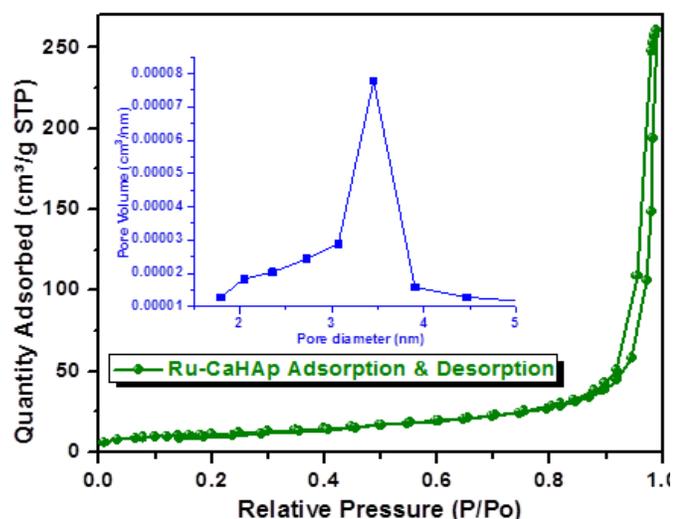


Figure 4. N₂ adsorption & desorption spectra of Ru-CaHAp catalysts

6.3.5. Reusability of the catalyst

The reusability of any heterogeneous catalyst is a significant factor to consider for potential commercial adaptation. After each reaction the catalyst was filtered and the recovered catalyst was washed with hot ethanol (2 x 10 mL) and was dried at 100 °C under reduced pressure for 2-3 h. The recycled catalyst was used for the subsequent runs repeating the same procedure. The reusability of the catalyst was evaluated in the synthesis of pyrano[2,3-*c*]pyrazole-3-carboxylate derivatives (**Figure 5**). The recovered catalyst was employed in five consecutive runs, and the decrease in activity was marginal.

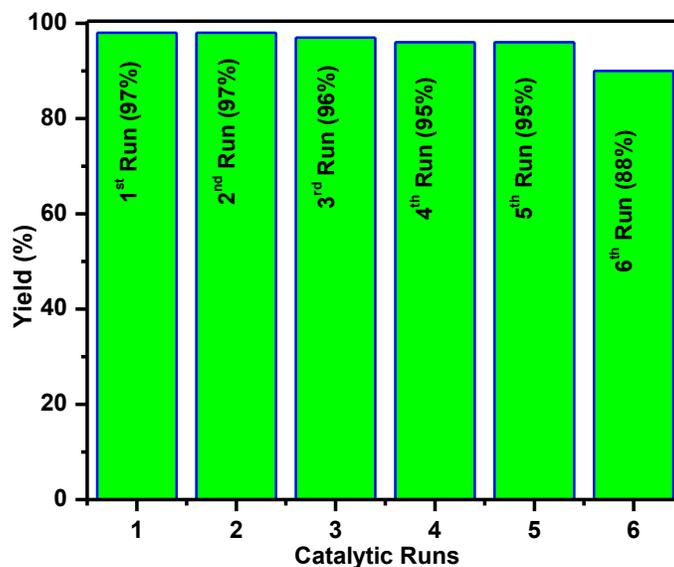


Figure 5. Recyclability of Ru-CaHAp catalyst

3.4. Conclusion

We designed and utilized an extremely capable and green protocol using a recyclable Ru on CaHAp catalyst for the synthesis of pyrano[2,3-c]pyrazole-3-carboxylate derivatives in an unprecedented multicomponent reaction. The reaction proceeded at room temperature and required short reaction times (< 30 min) in excellent yields. The catalyst material used for this process is cost effective, and easy to prepare and handle and separate with marginal decrease in activity during replicate runs.

6.5. References:

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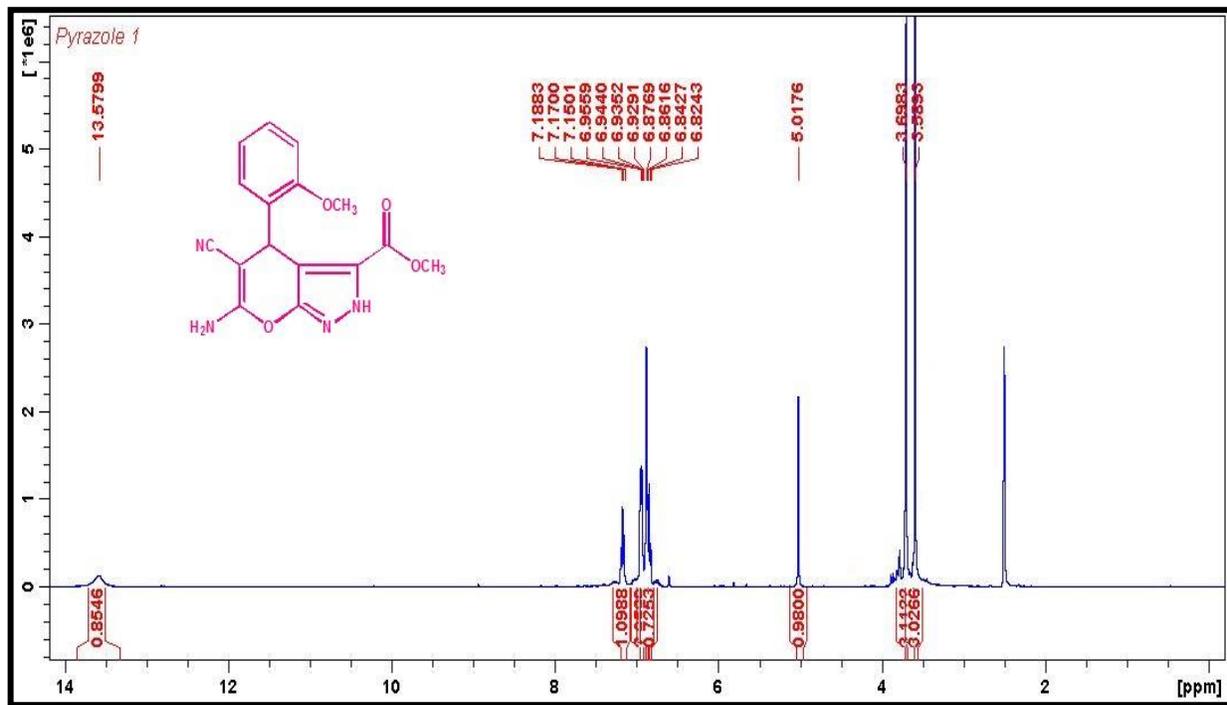
6.6. Supplementary material data

6.6.1. Catalyst characterization

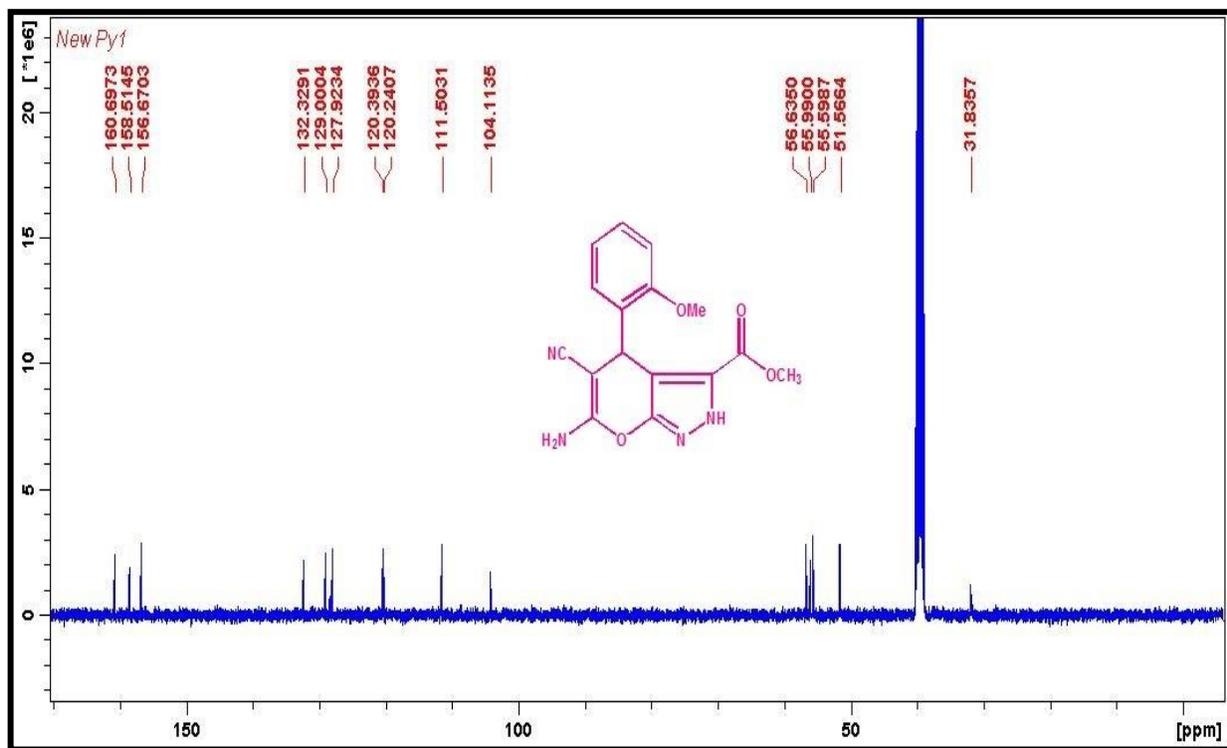
Micromeritics Tristar-II porosity and surface area analyzer was used to determine the values of surface area, pore size and pore volume of the catalyst material. The catalyst sample was degassed overnight using N₂ flow at 200 °C. The BJH adsorption-desorption curves were generated at -196 °C and were used to assess the catalyst's particulate properties. Employing a Bruker D8 Advance instrument (Cu K radiation source with a wave length of 1.5406 Å), the X-ray diffraction data related the structural phases of the catalyst were acquired. Using a Jeol JEM-1010 electron microscope and JEOL JSM-6100 microscope, the TEM and SEM analysis data was recorded. iTEM software was used analyze the TEM data and images. Employing the X-ray analyzer (energy-dispersive), EDX-analysis on the SEM images was conducted. To confirm the elemental composition catalyst materials Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES) (Optima 5300 DV) was used.

6.6.2. Materials, methods and instruments

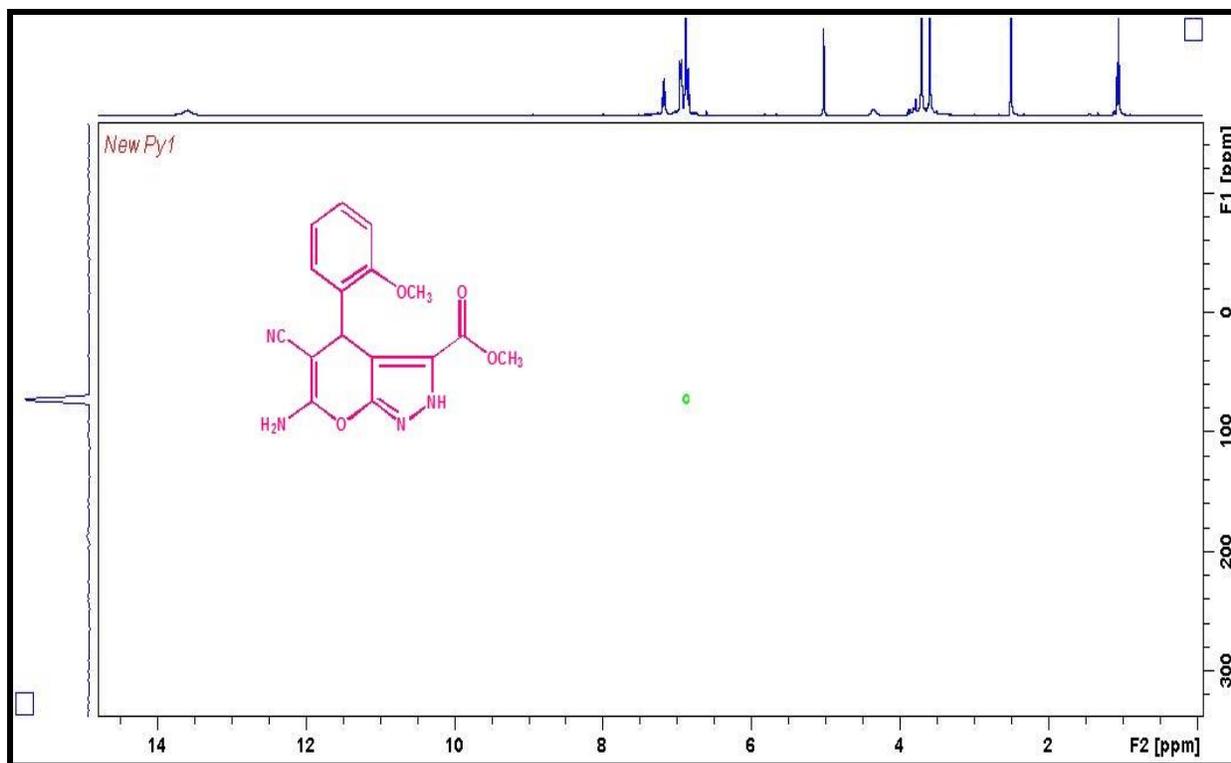
All chemicals and reagents required for the reaction were of analytical grade and were used without any further purification. Bruker AMX 400 MHz NMR spectrometer was used to record the ¹H NMR, ¹³C NMR and ¹⁵N NMR spectral values. High-resolution mass data were obtained using a Bruker micro TOF-Q II ESI instrument operating at ambient temperature. The DMSO-d₆ solution was utilized for this while TMS served as the internal standard. TMS was further used as an internal standard for reporting the all chemical shifts in δ (ppm). The FT-IR spectrum for the samples was established using a Perkin Elmer Precisely 100 FT-IR spectrometer at the 400-4000 cm⁻¹ area. Purity of all the reaction products was confirmed by TLC using aluminum plates coated with silica gel (Merck Kieselgel 60 F254).



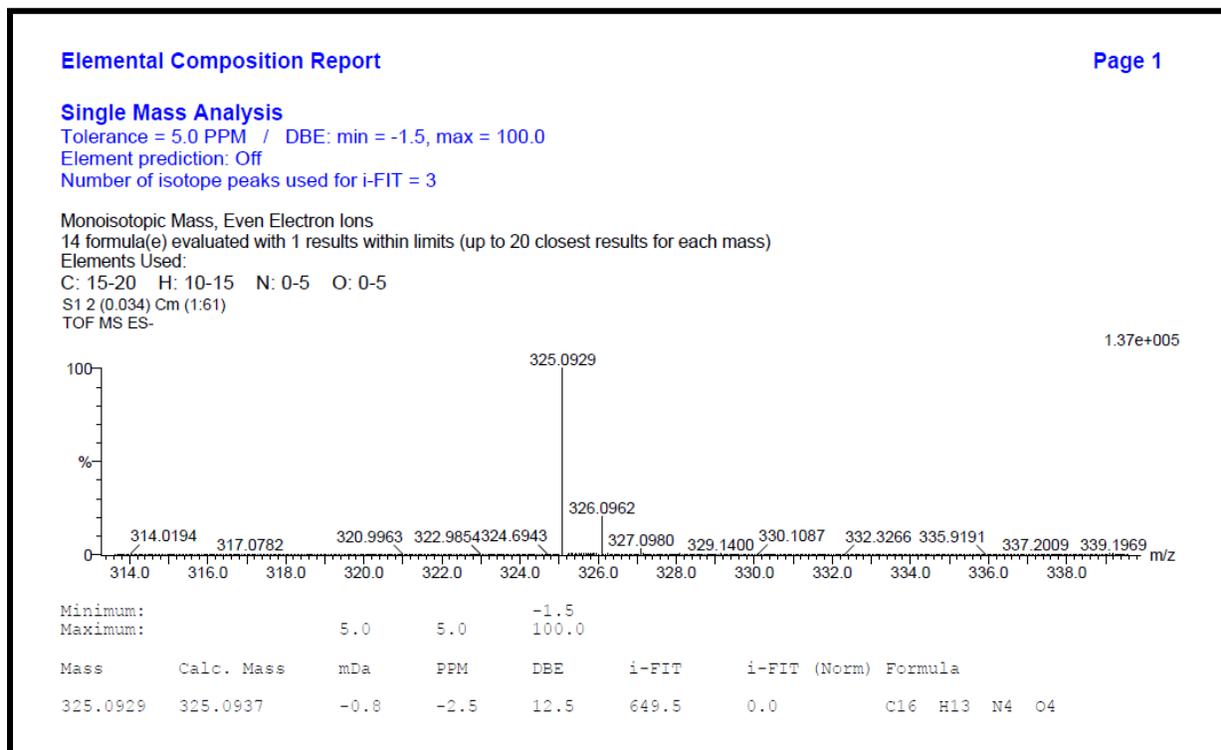
^1H NMR spectra of compound 5a



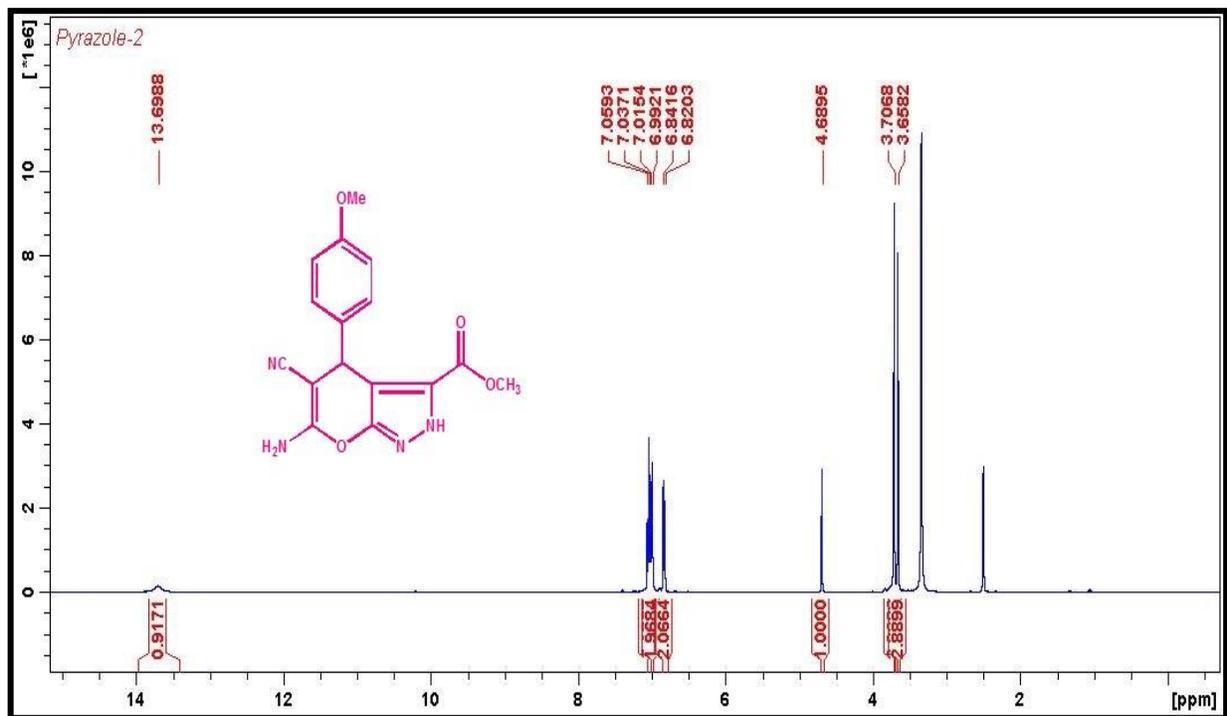
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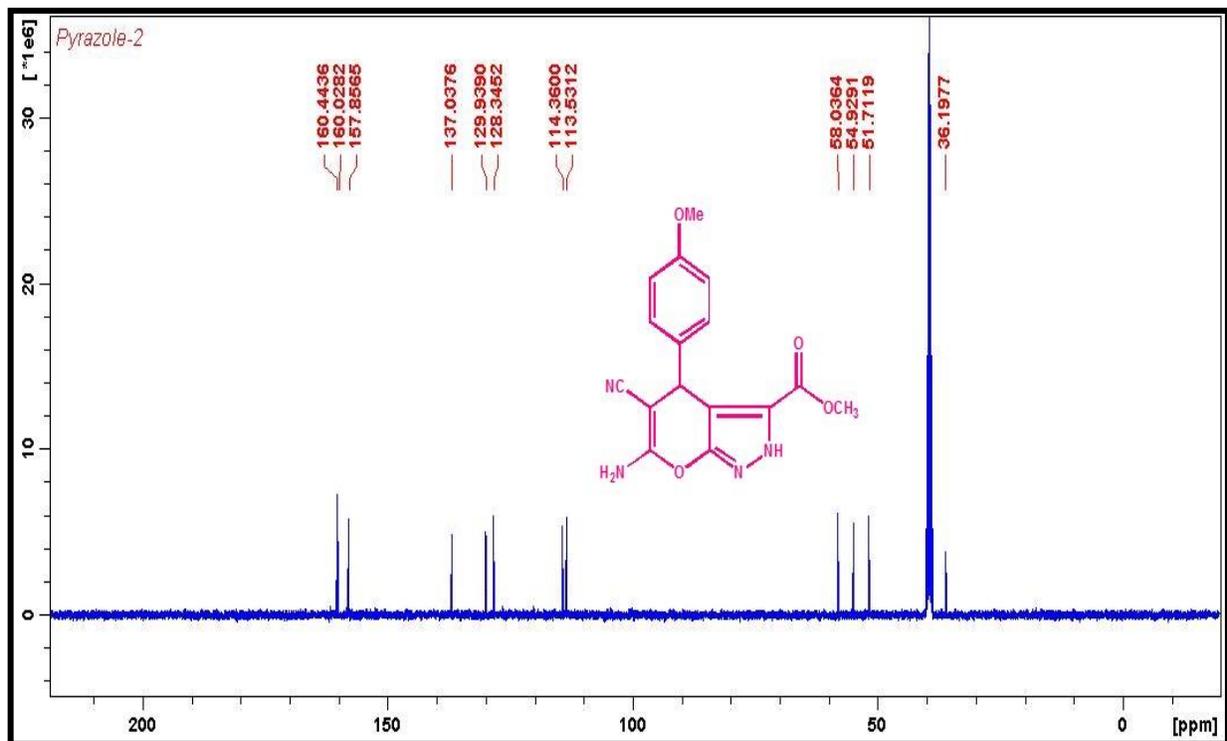
^{15}N NMR spectra of compound 5a



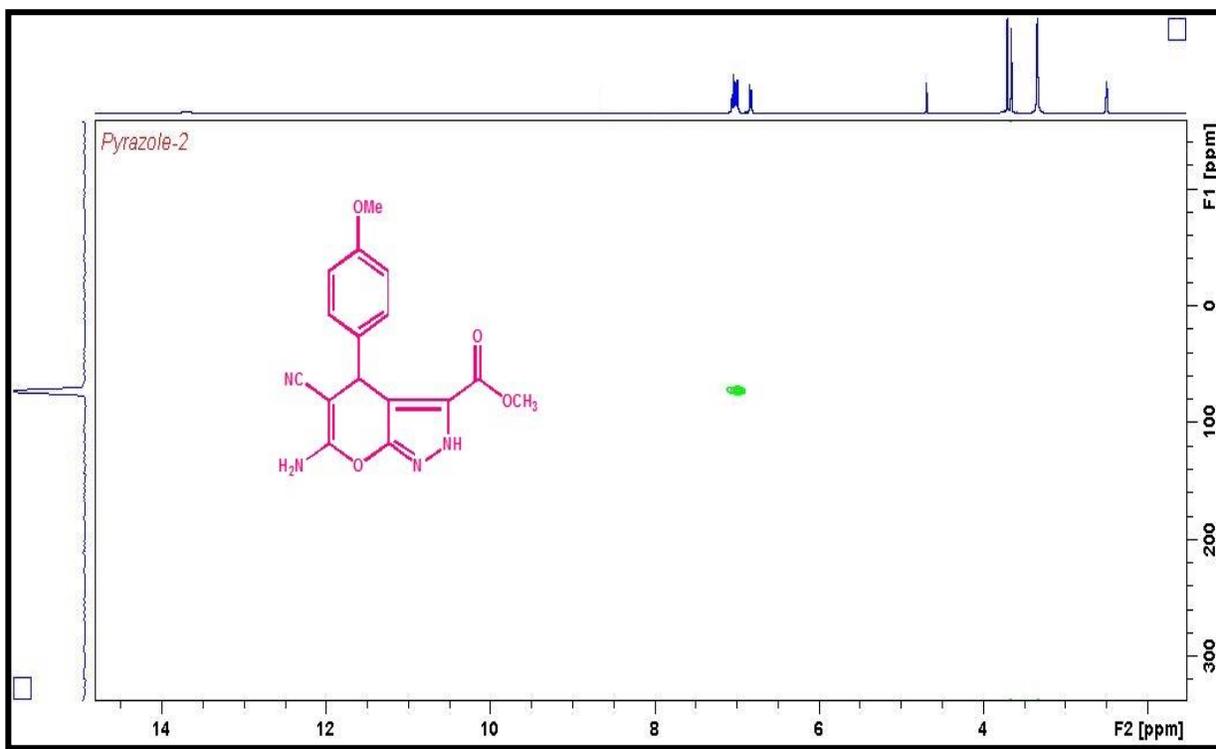
HRMS spectra of compound 5a



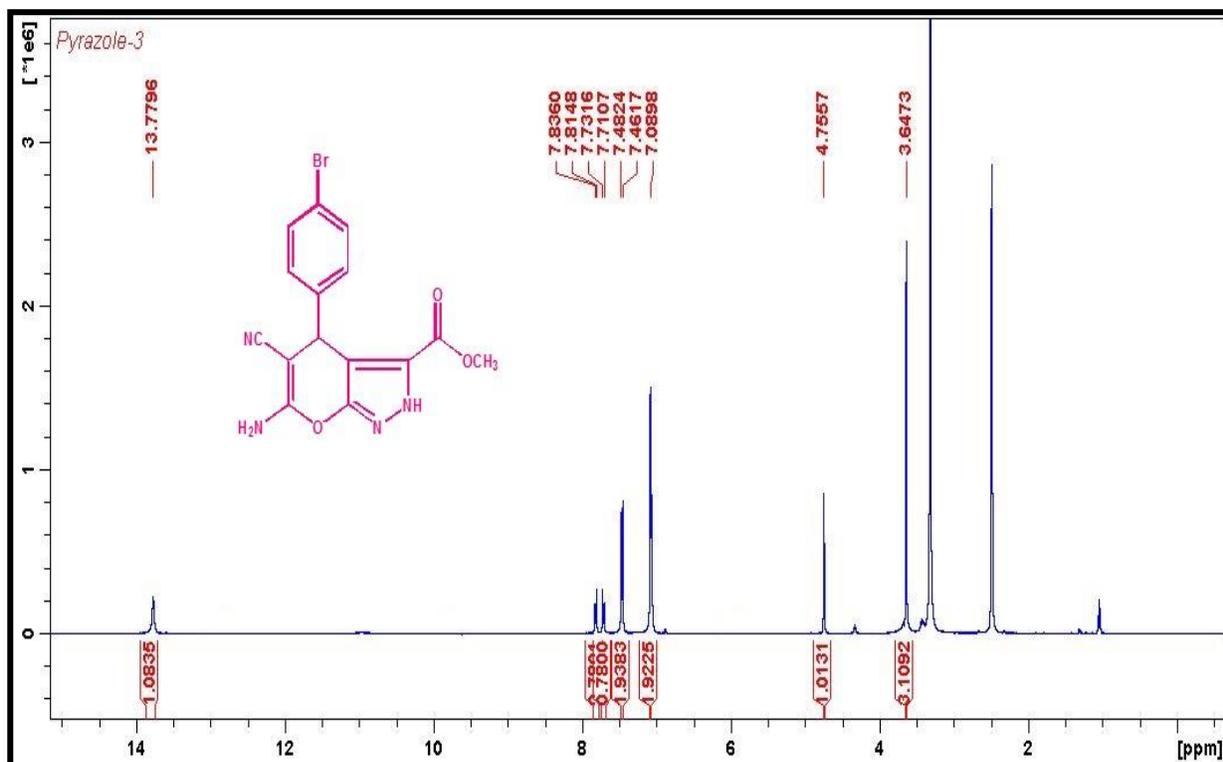
^1H NMR spectra of compound **5b**



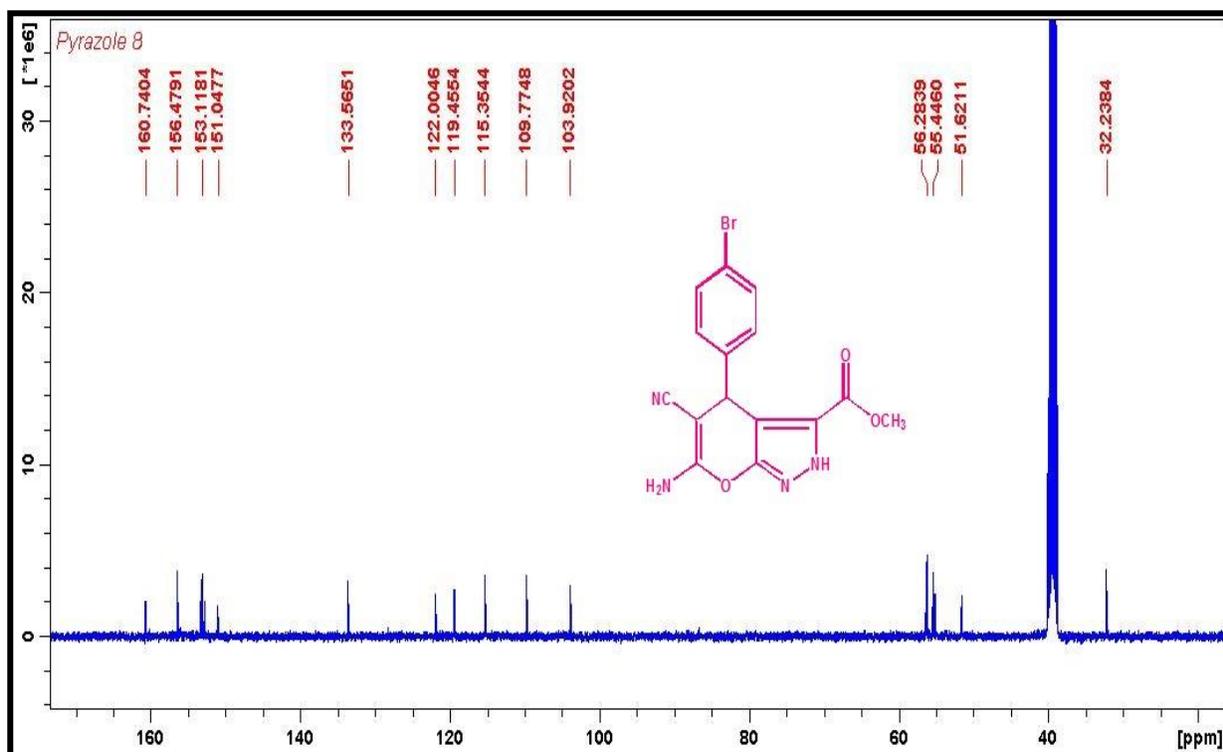
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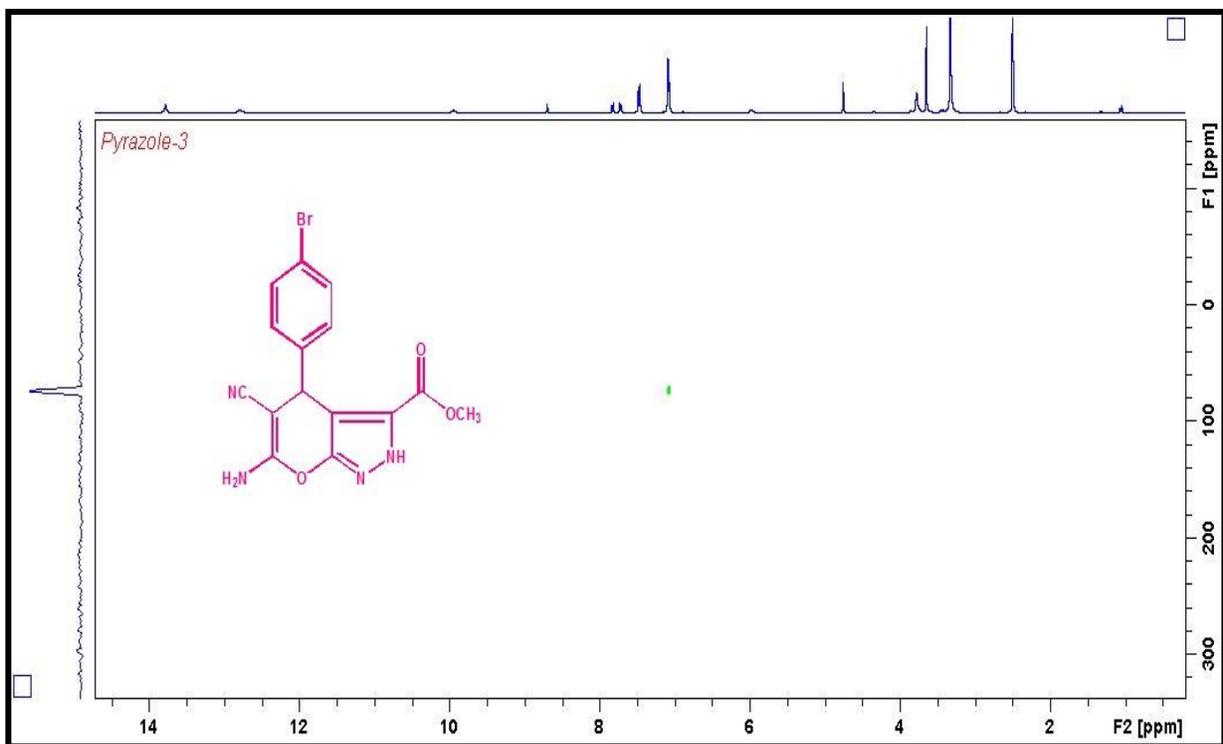
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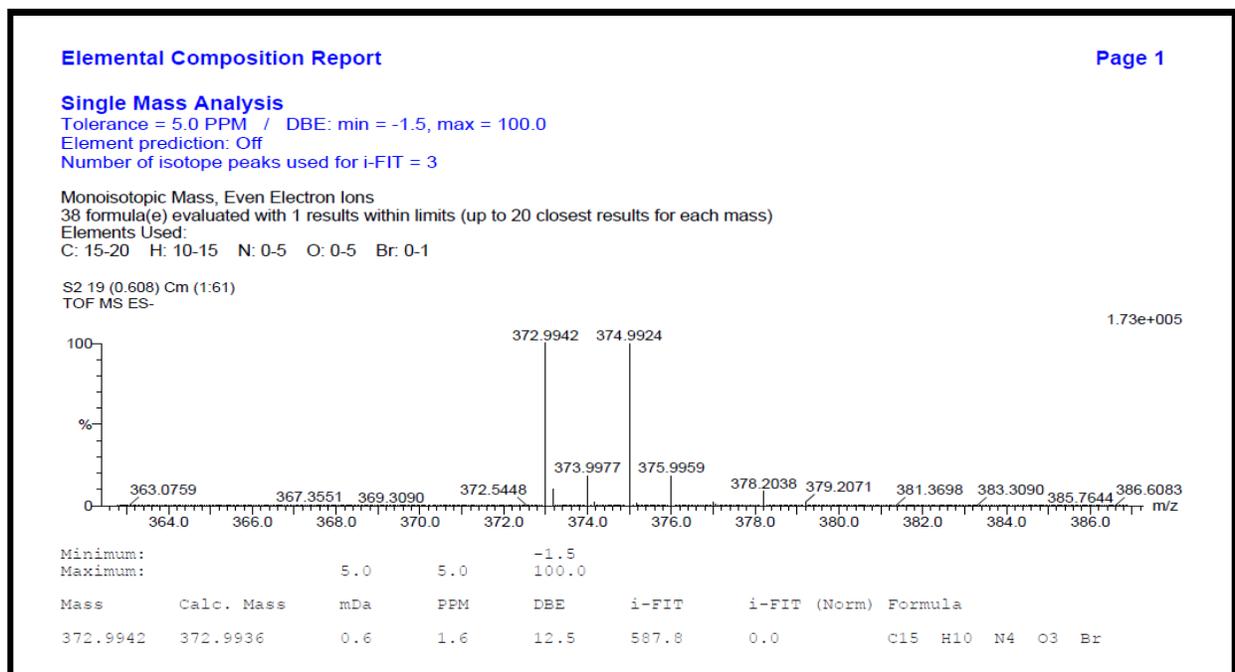
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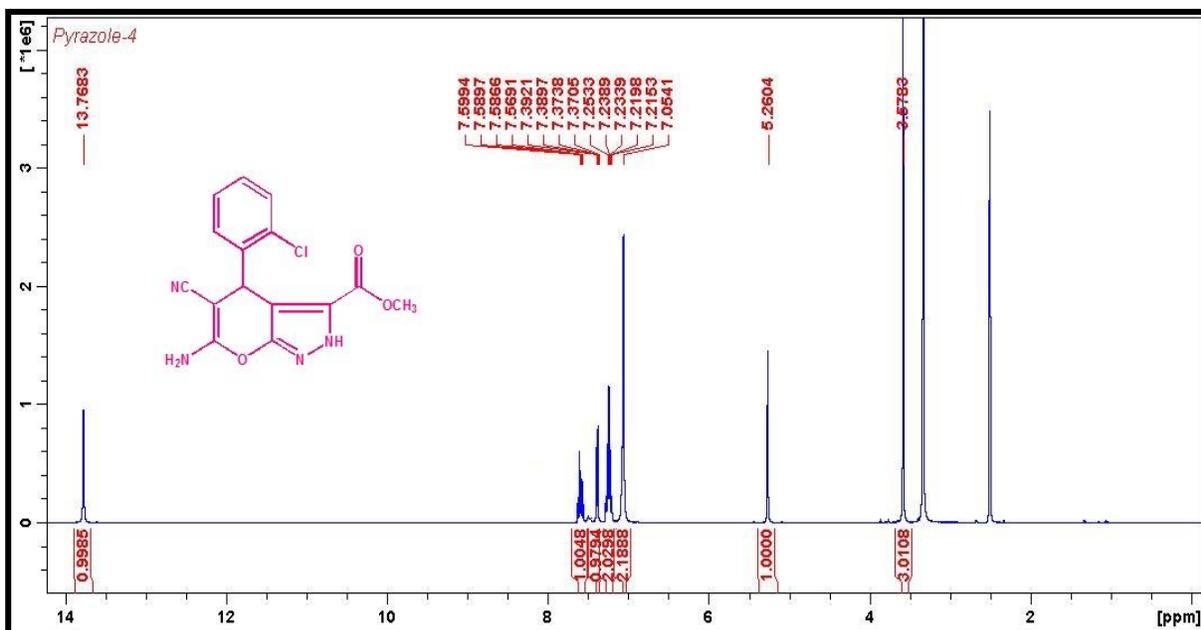
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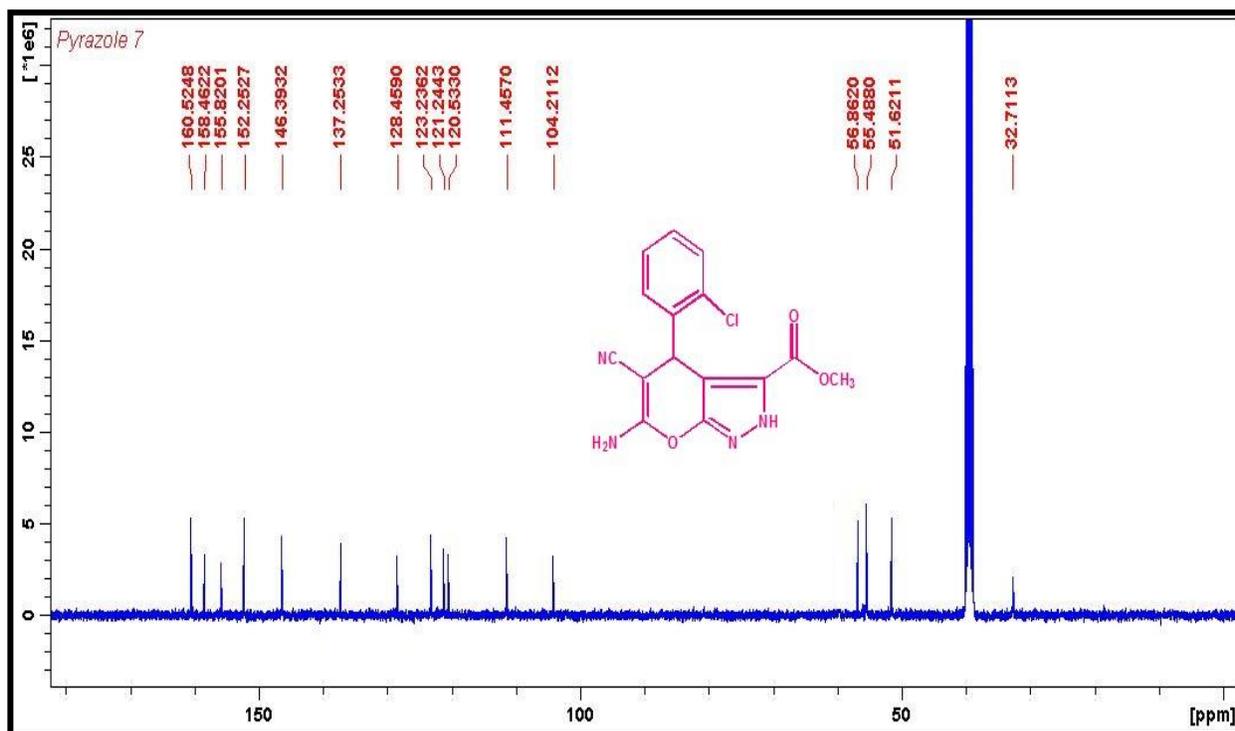
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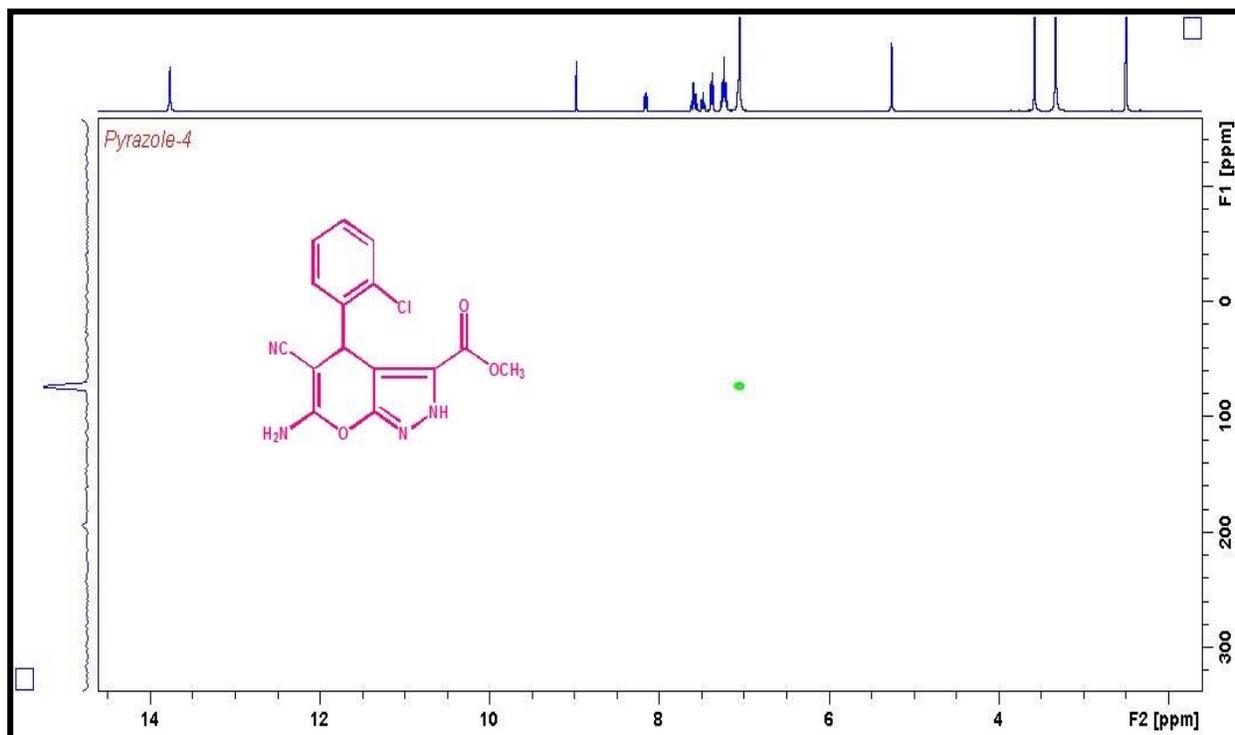
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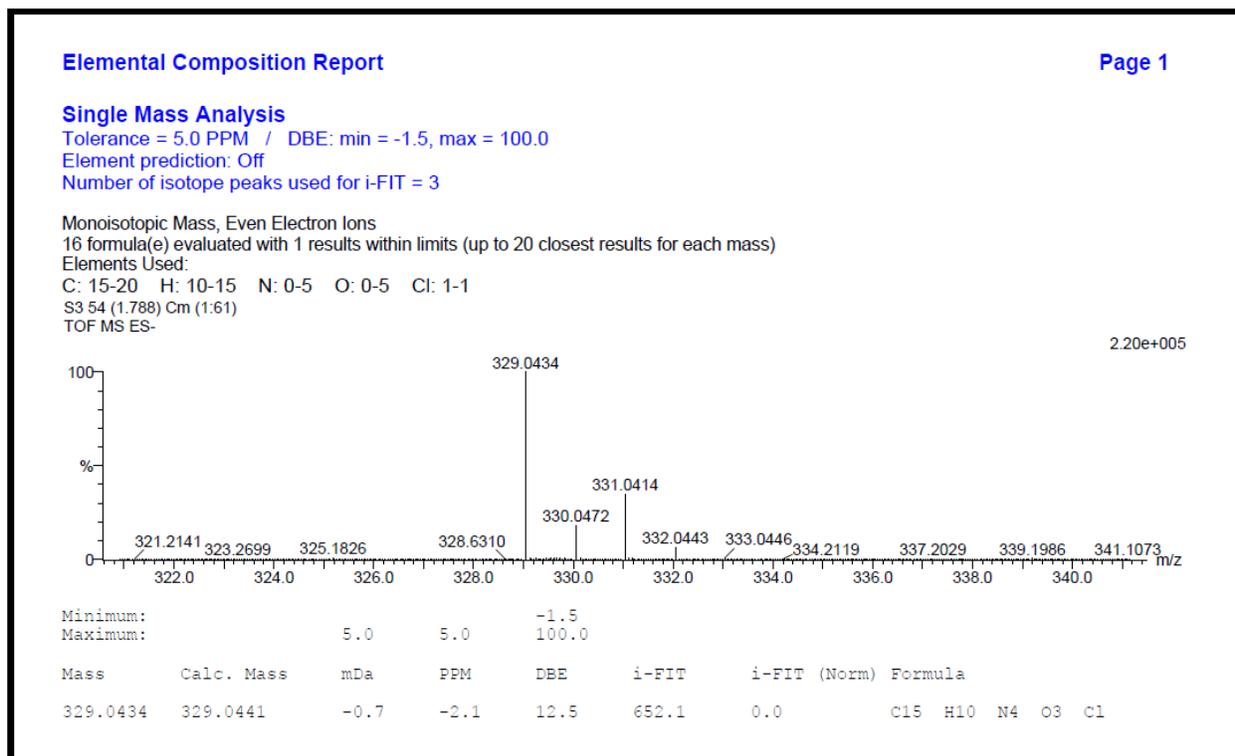
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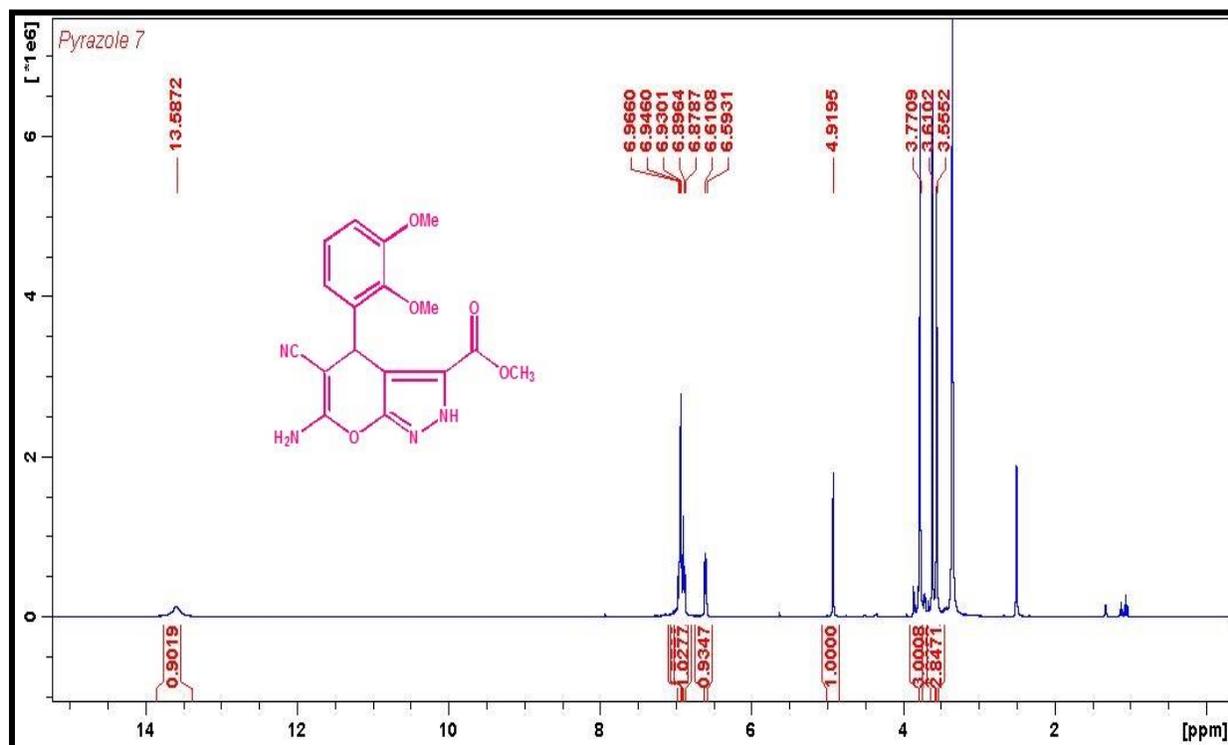
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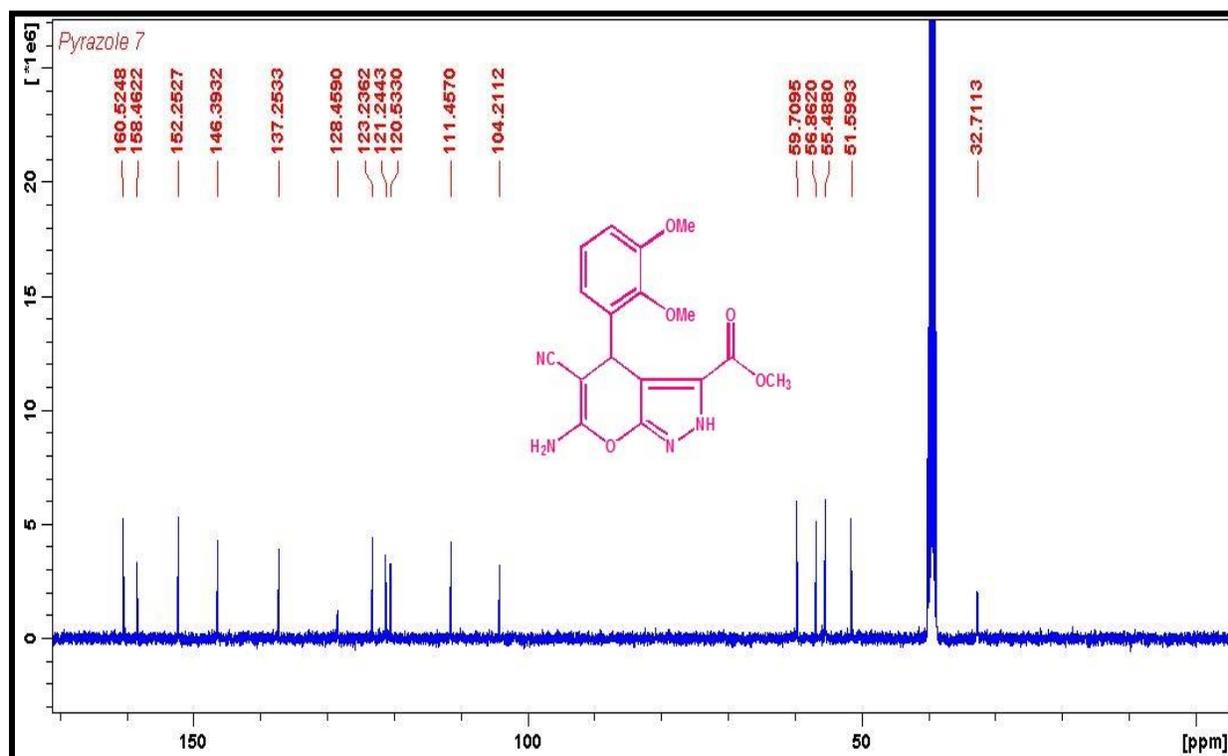
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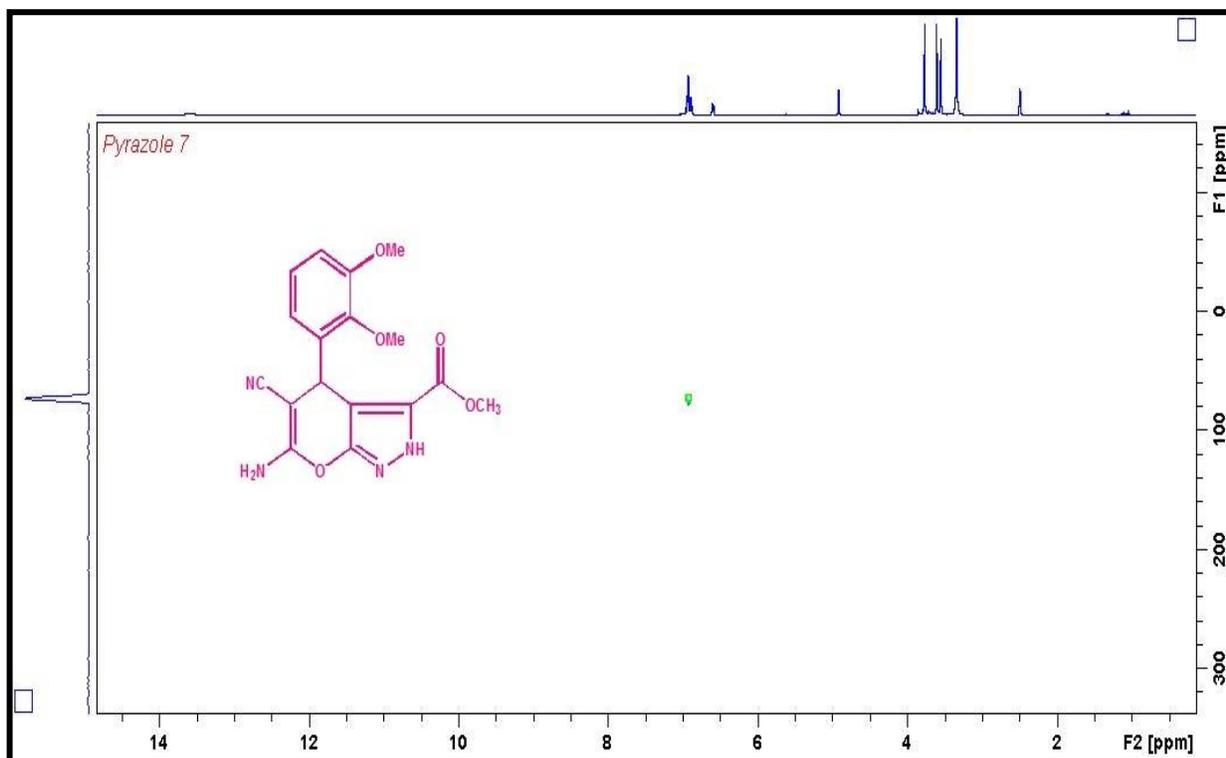
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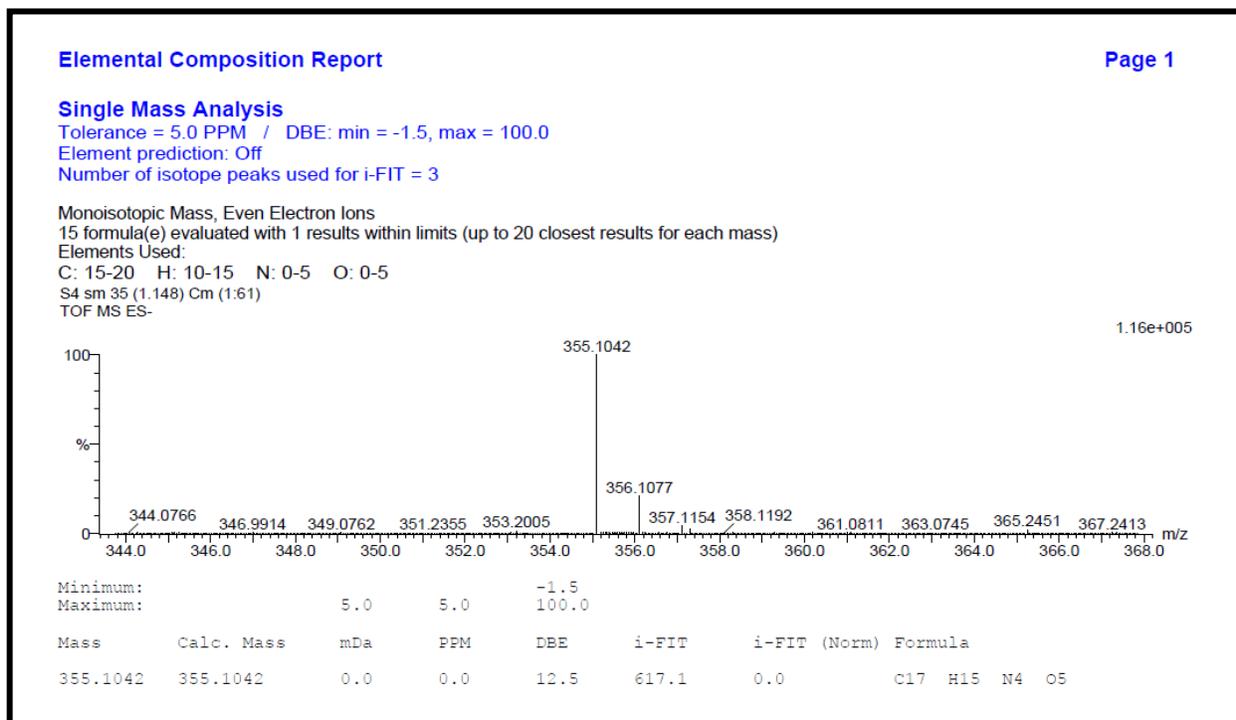
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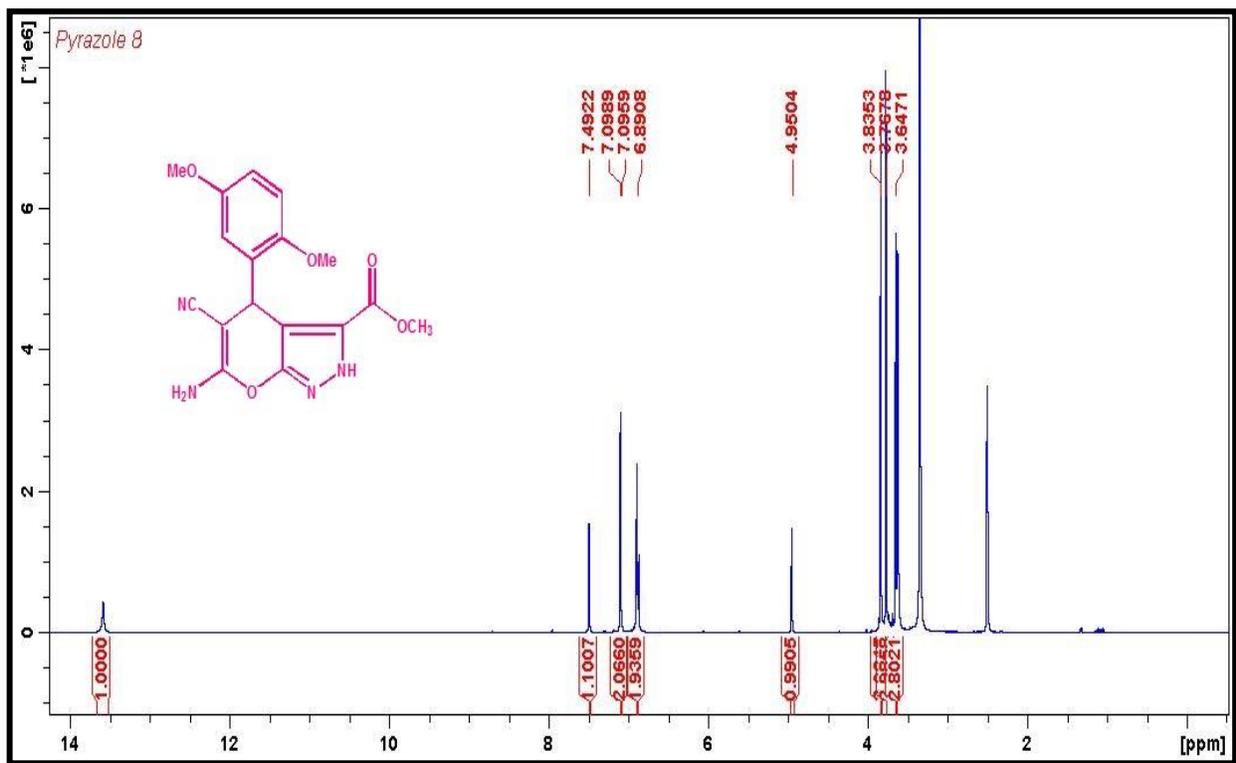
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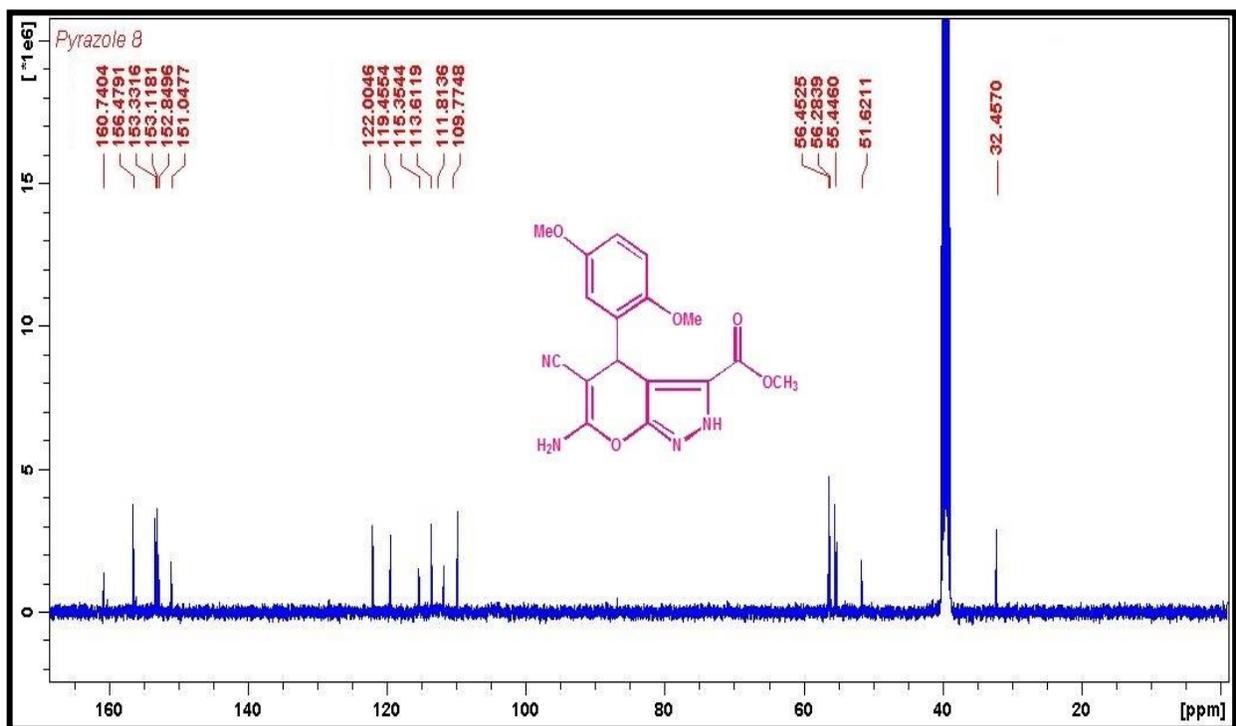
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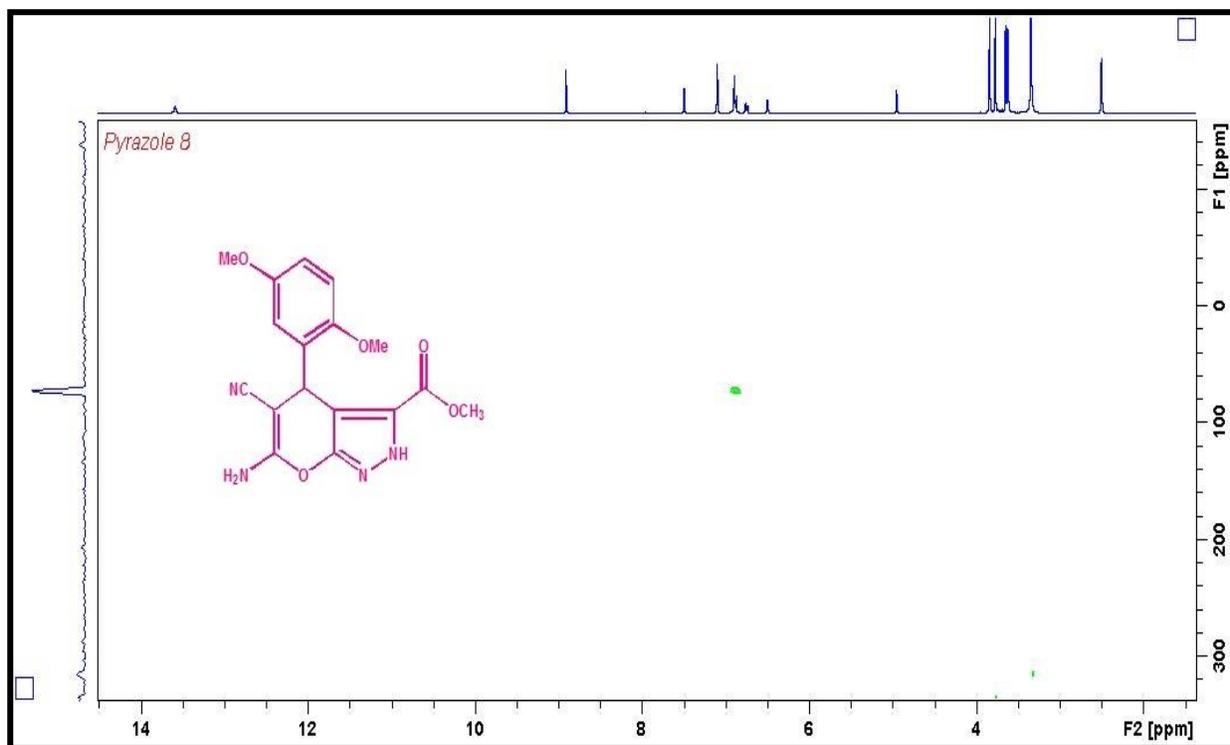
HRMS spectra of compound **5e**



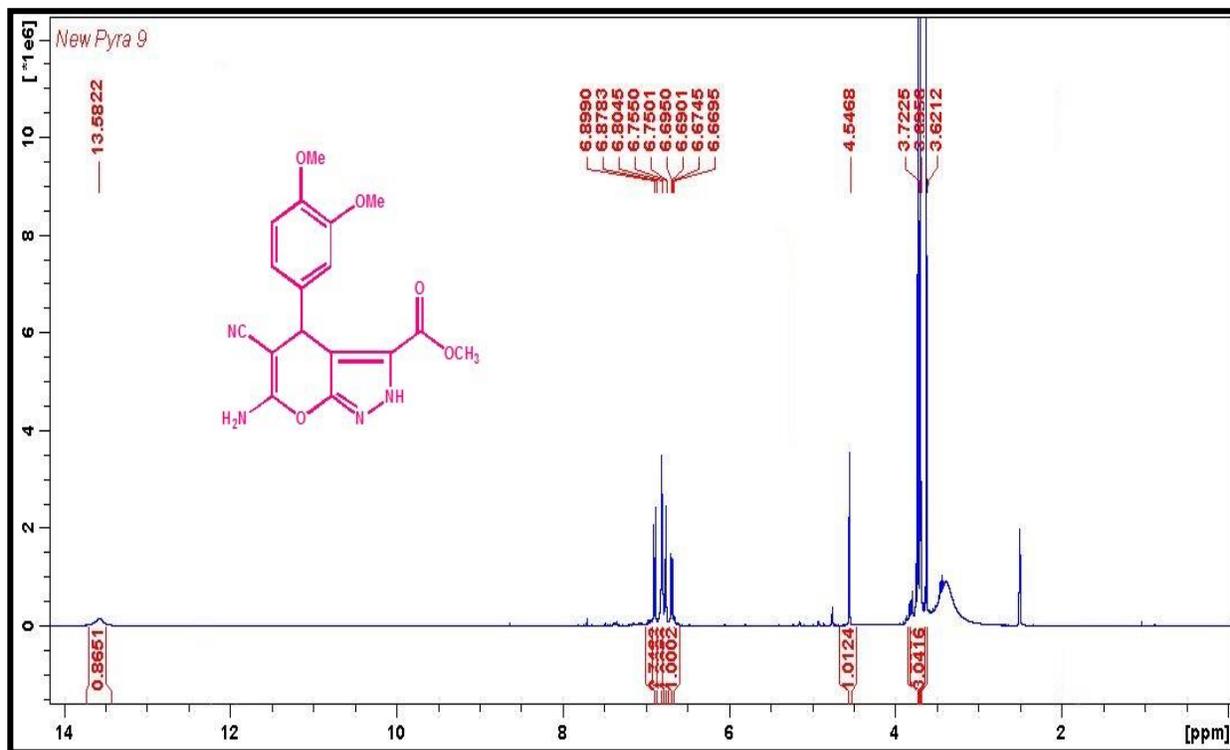
^1H NMR spectra of compound 5f



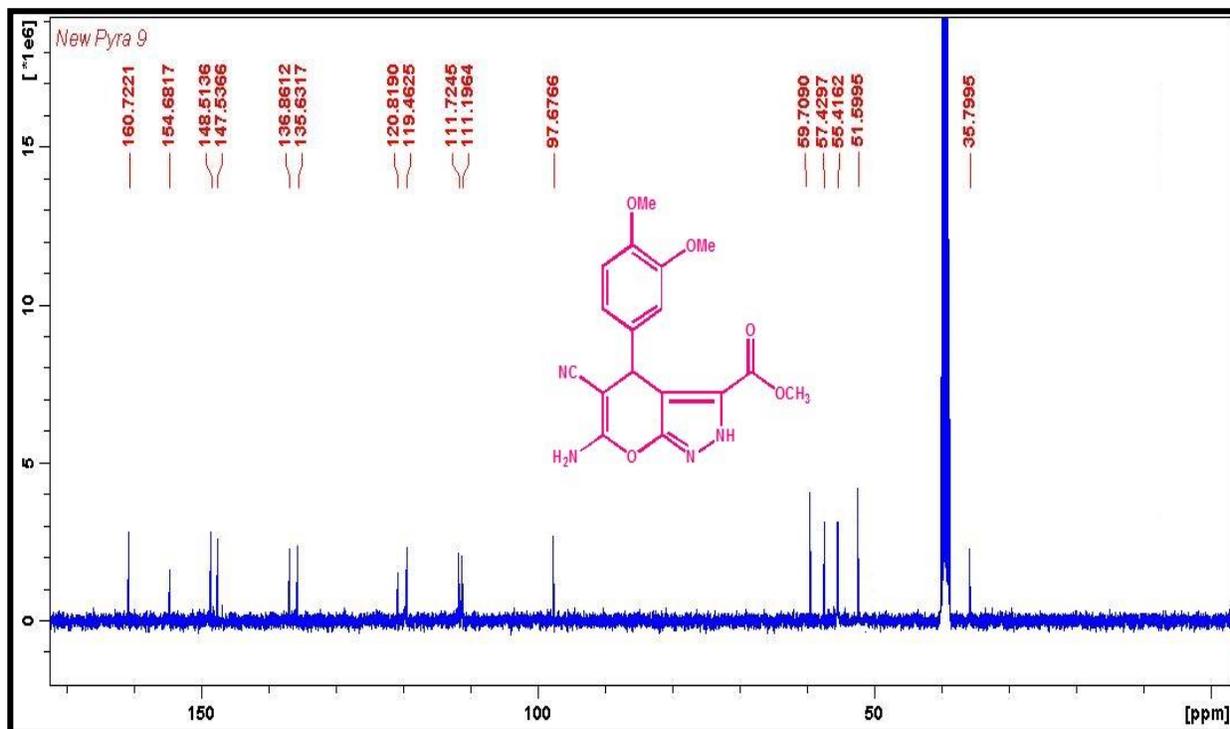
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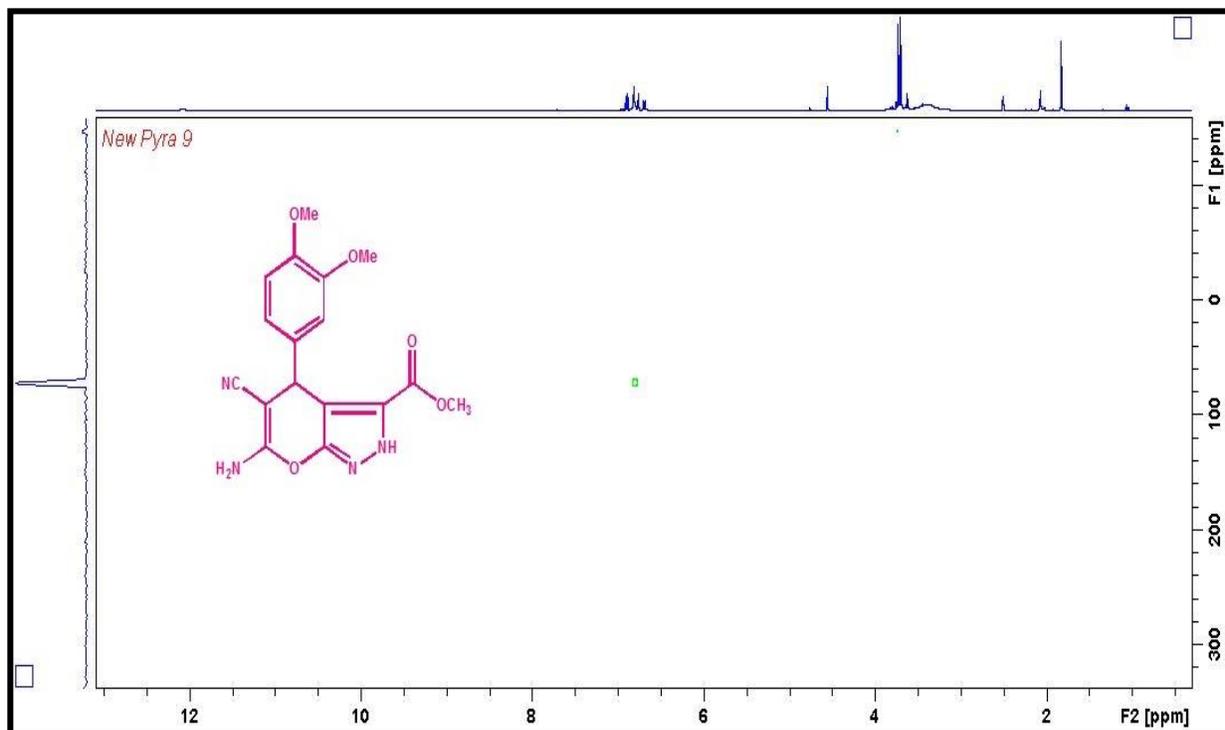
^{15}N NMR spectra of compound **5f**



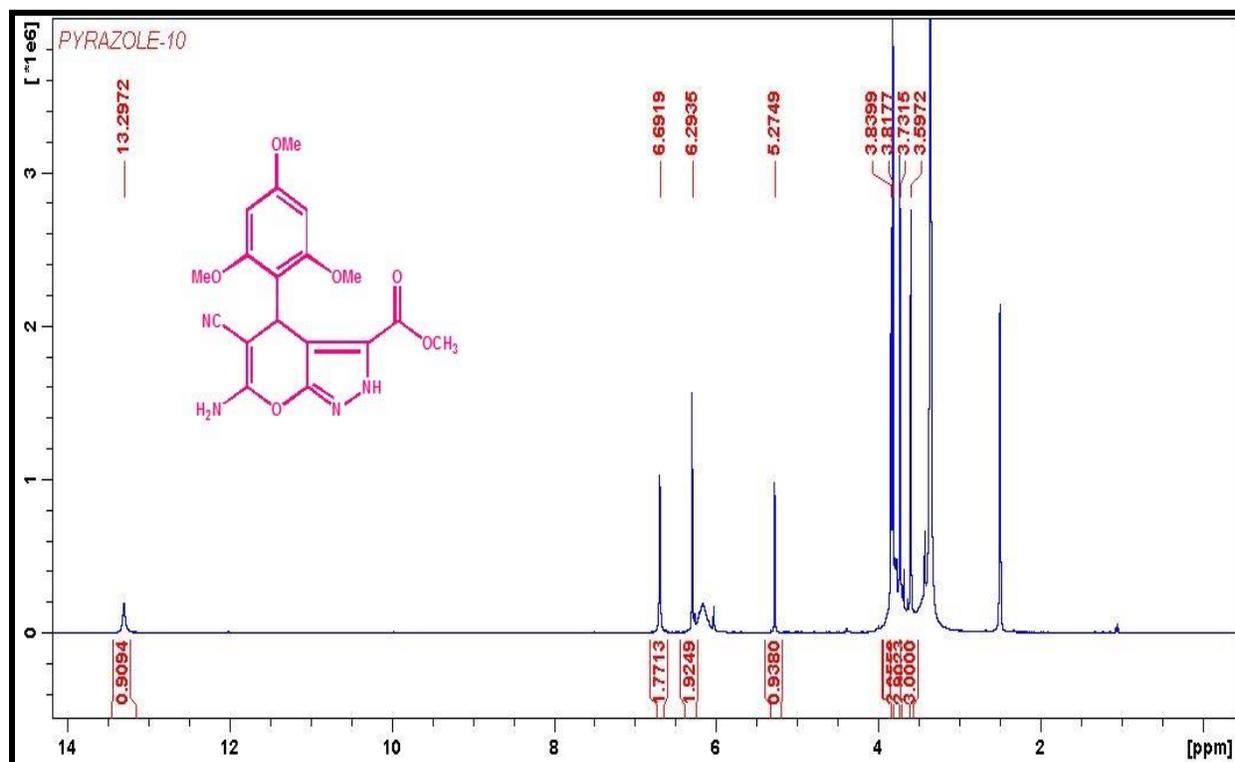
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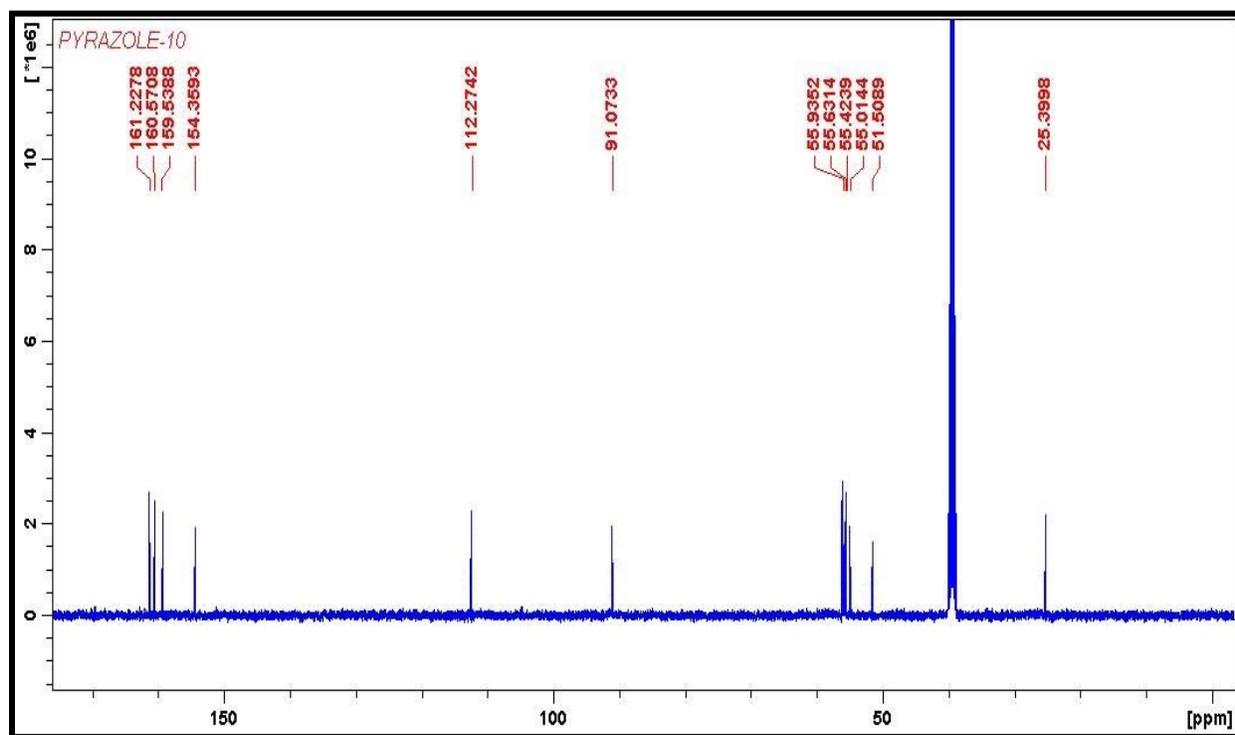
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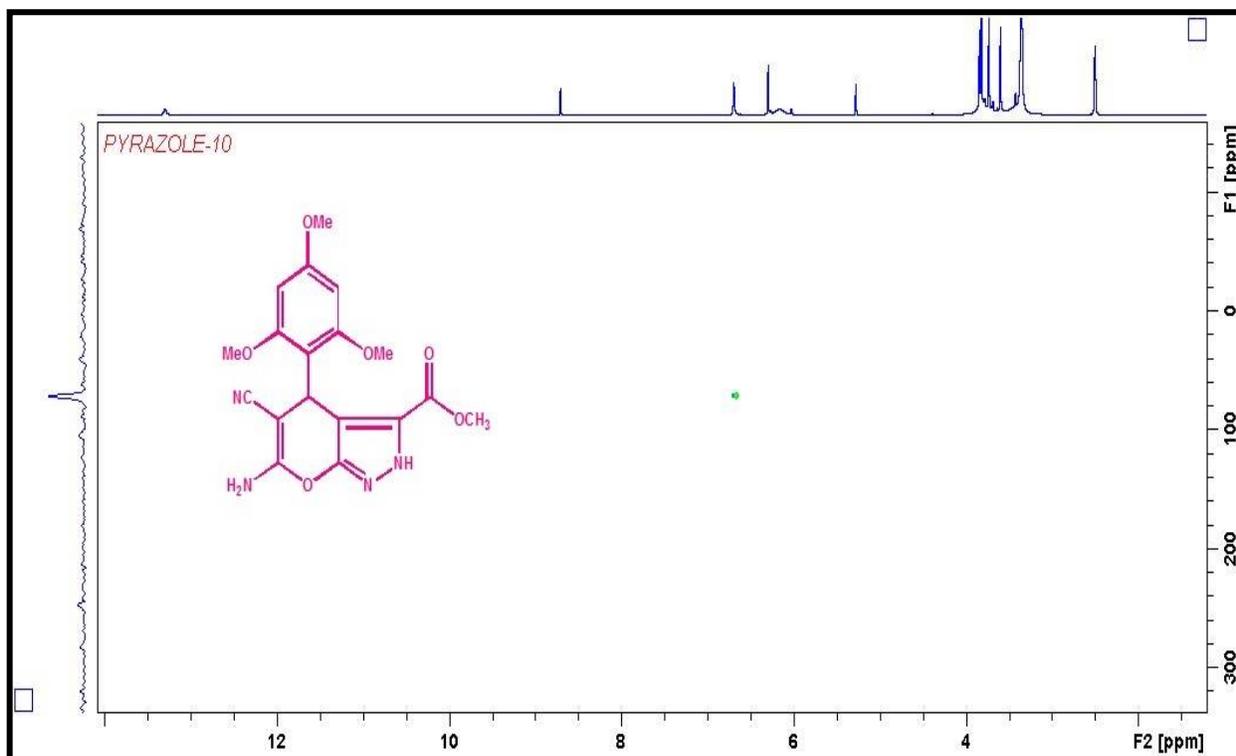
^{15}N NMR spectra of compound **5g**



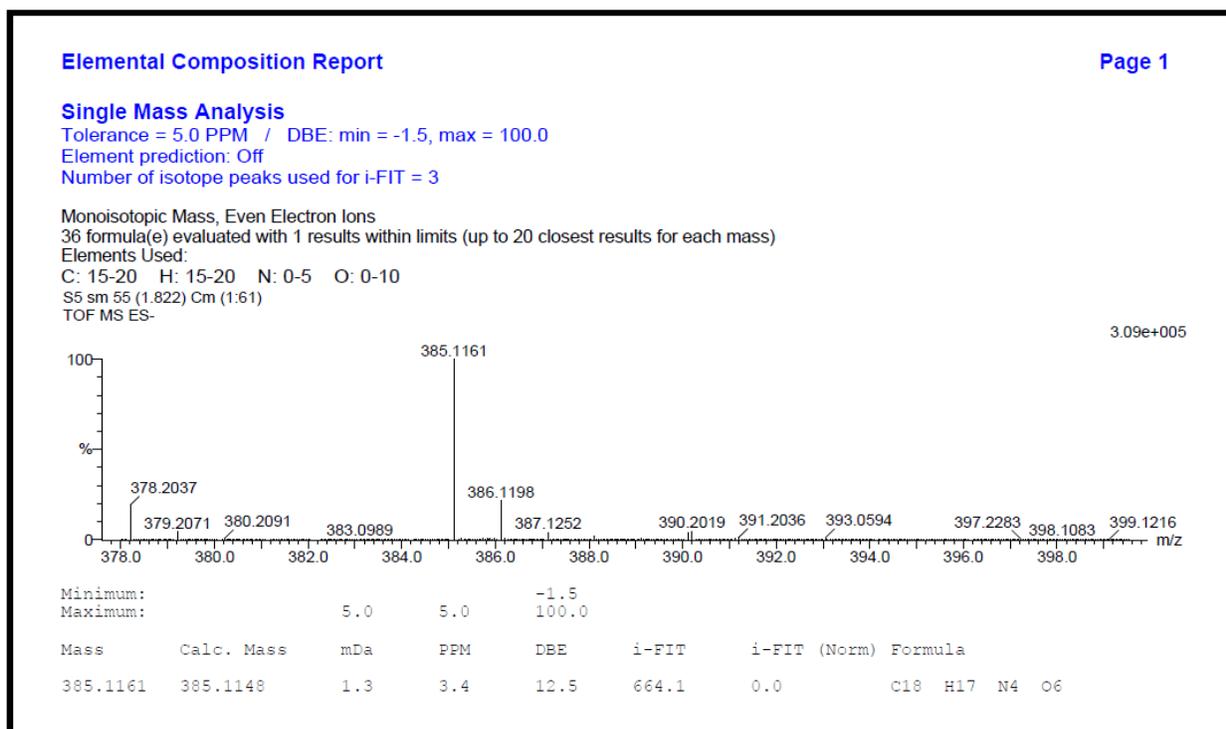
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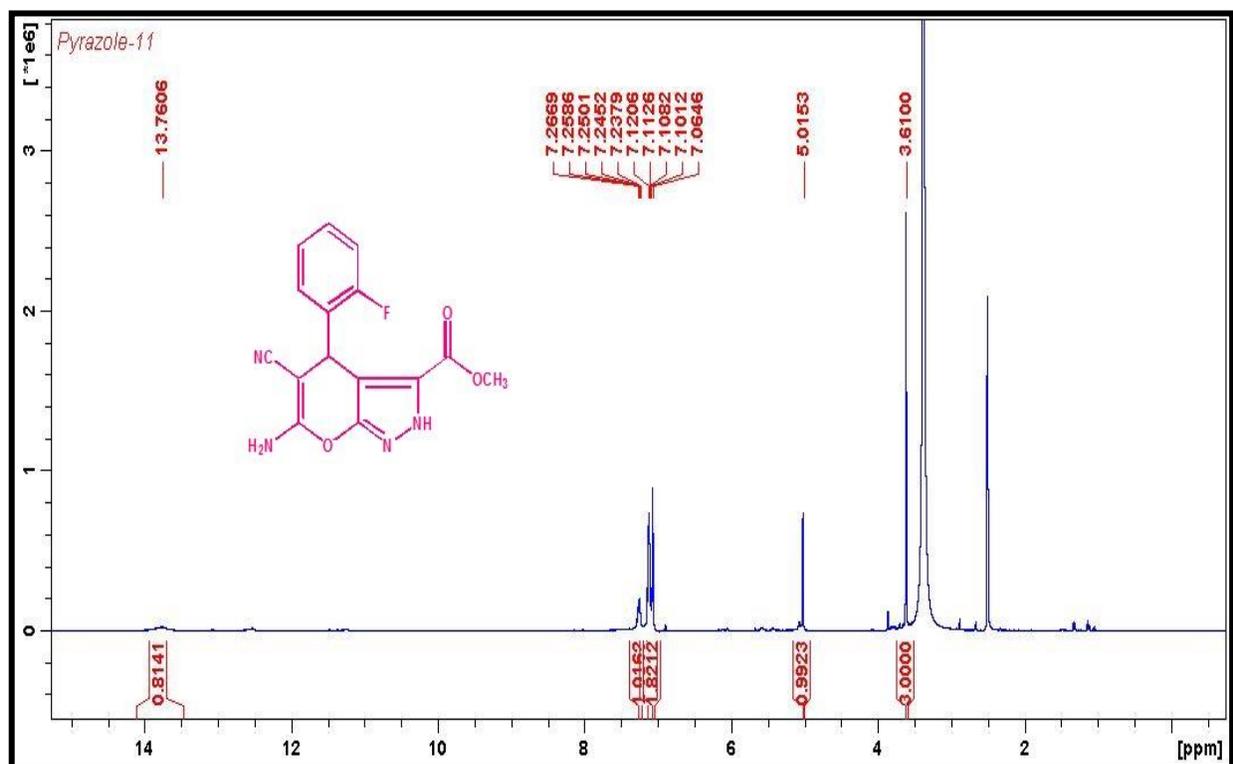
^{13}C NMR spectra of compound **5h**



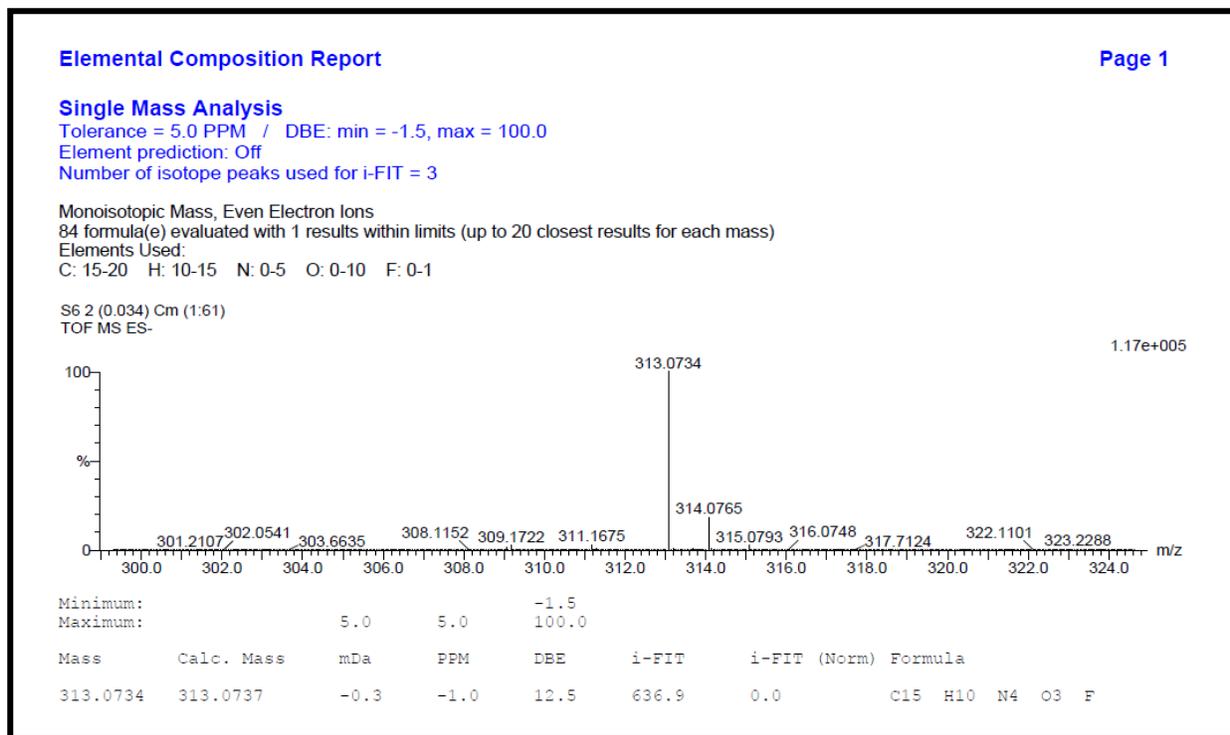
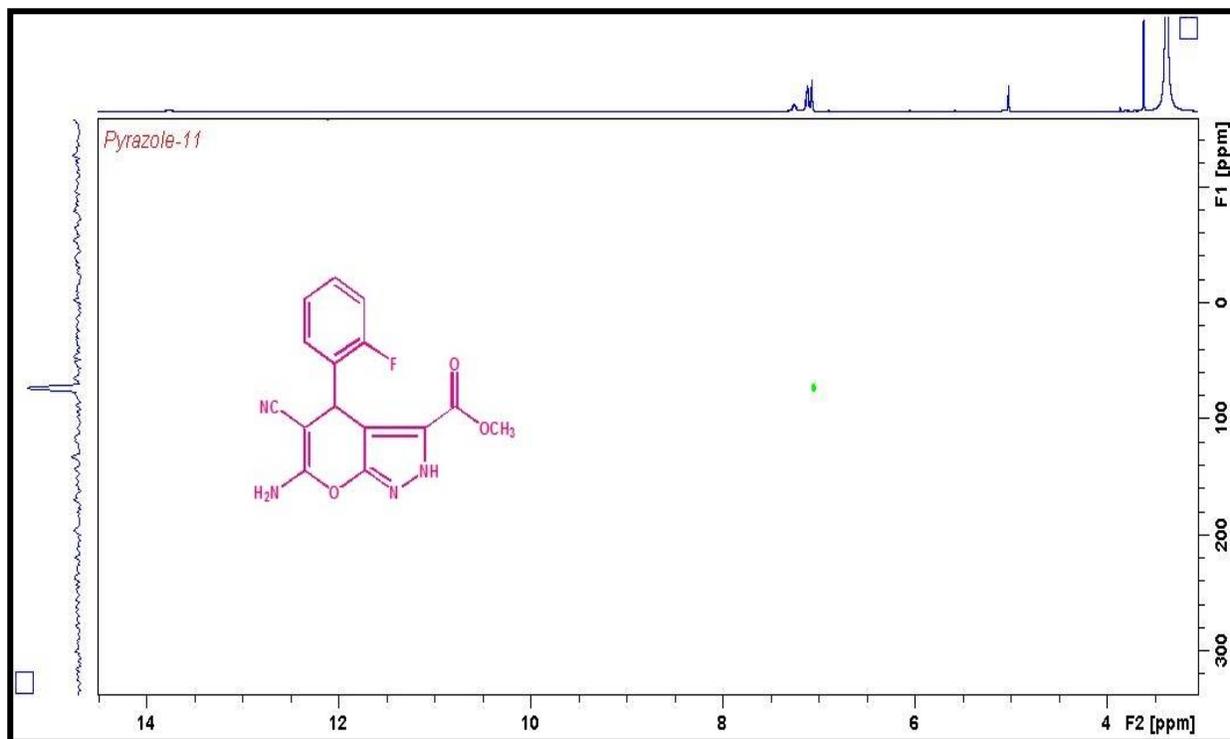
^{15}N NMR spectra of compound **5h**



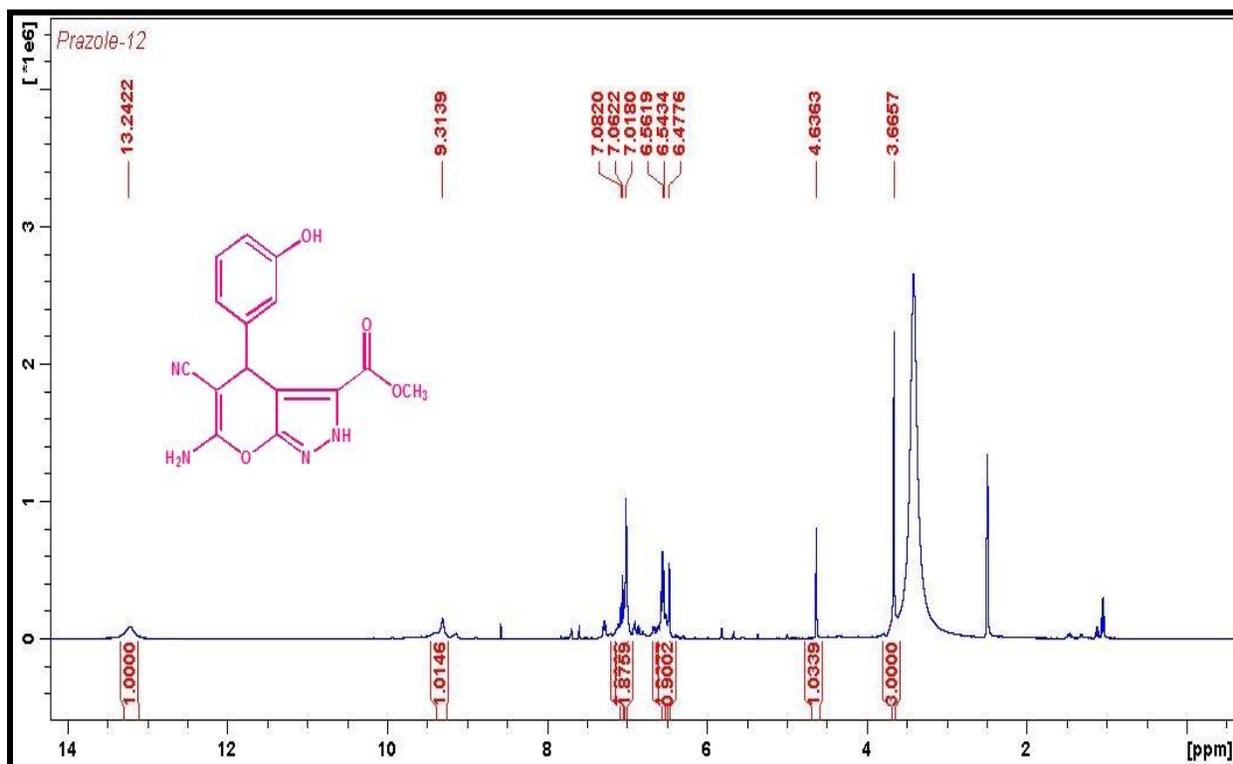
HRMS spectra of compound **5h**



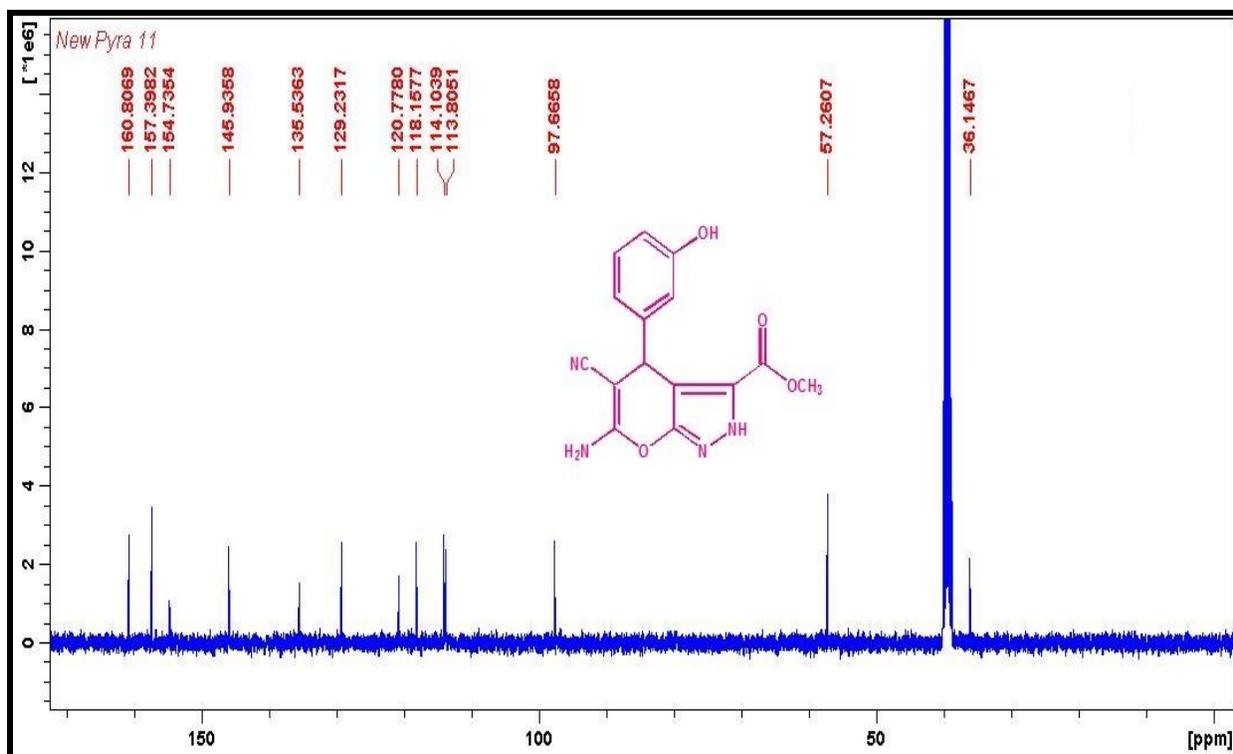
^1H NMR spectra of compound **5i**



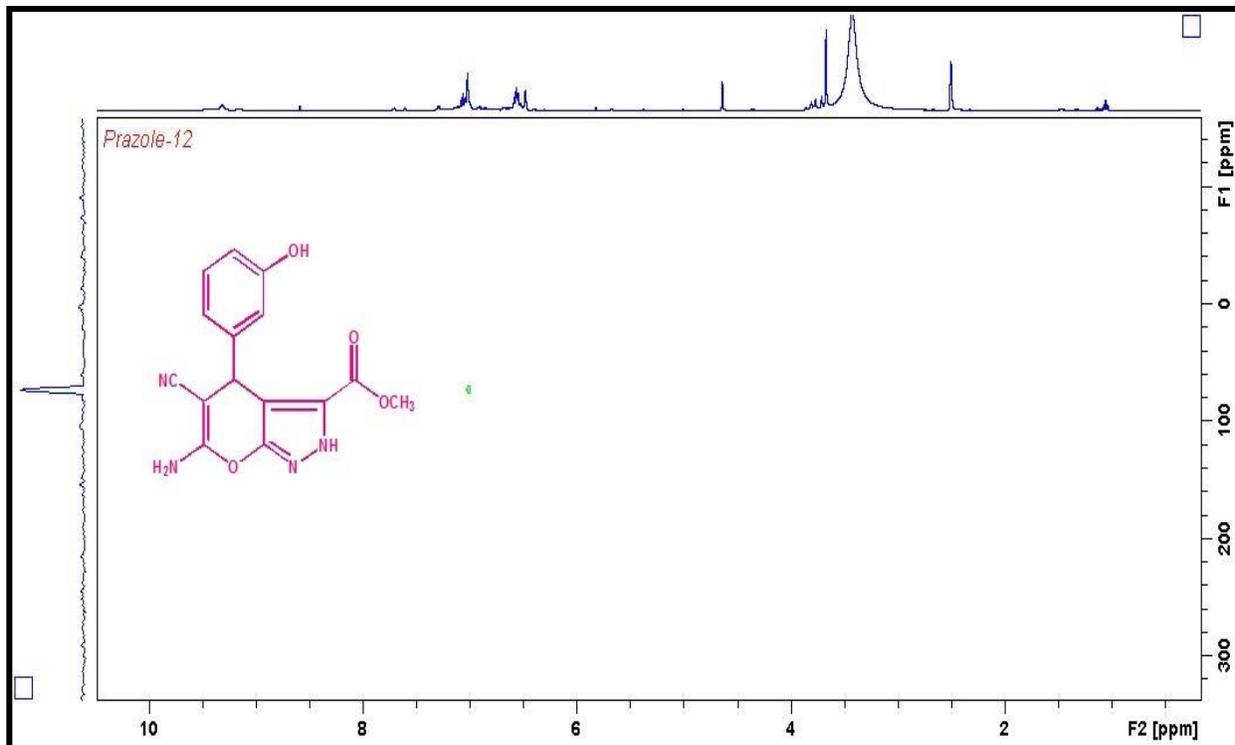
HRMS spectra of compound **5i**



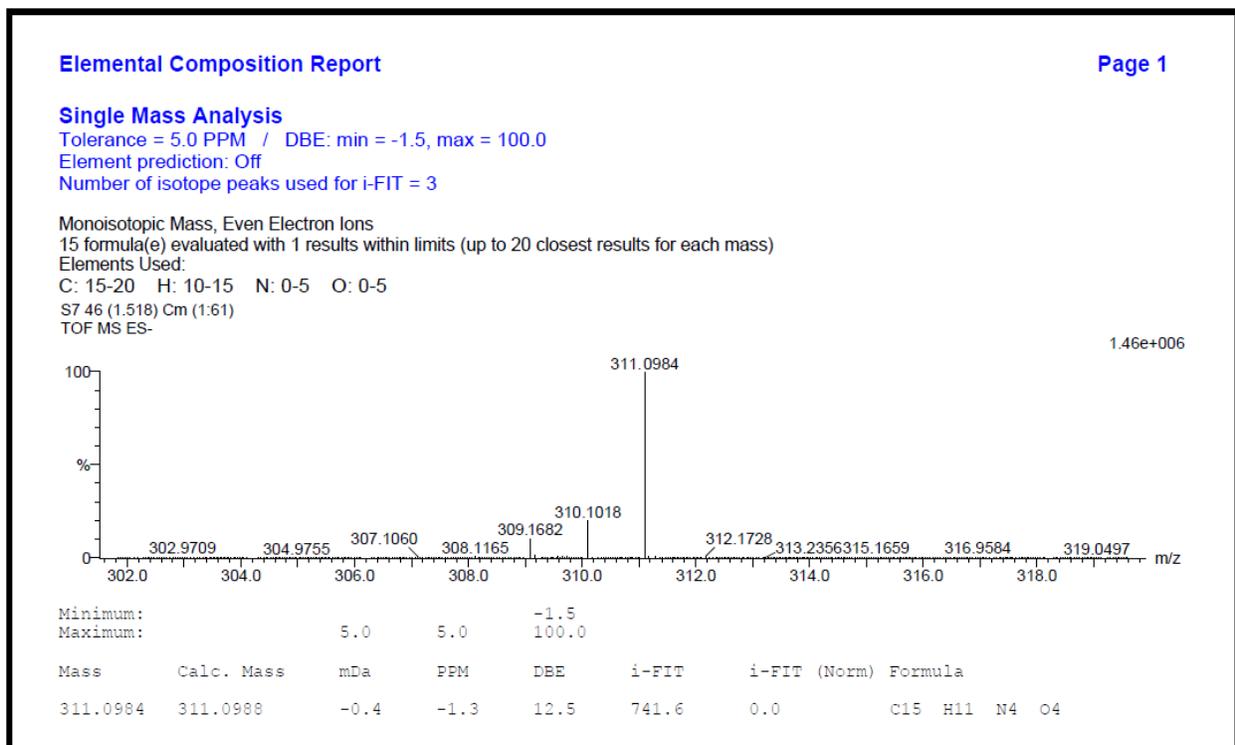
^1H NMR spectra of compound **5j**



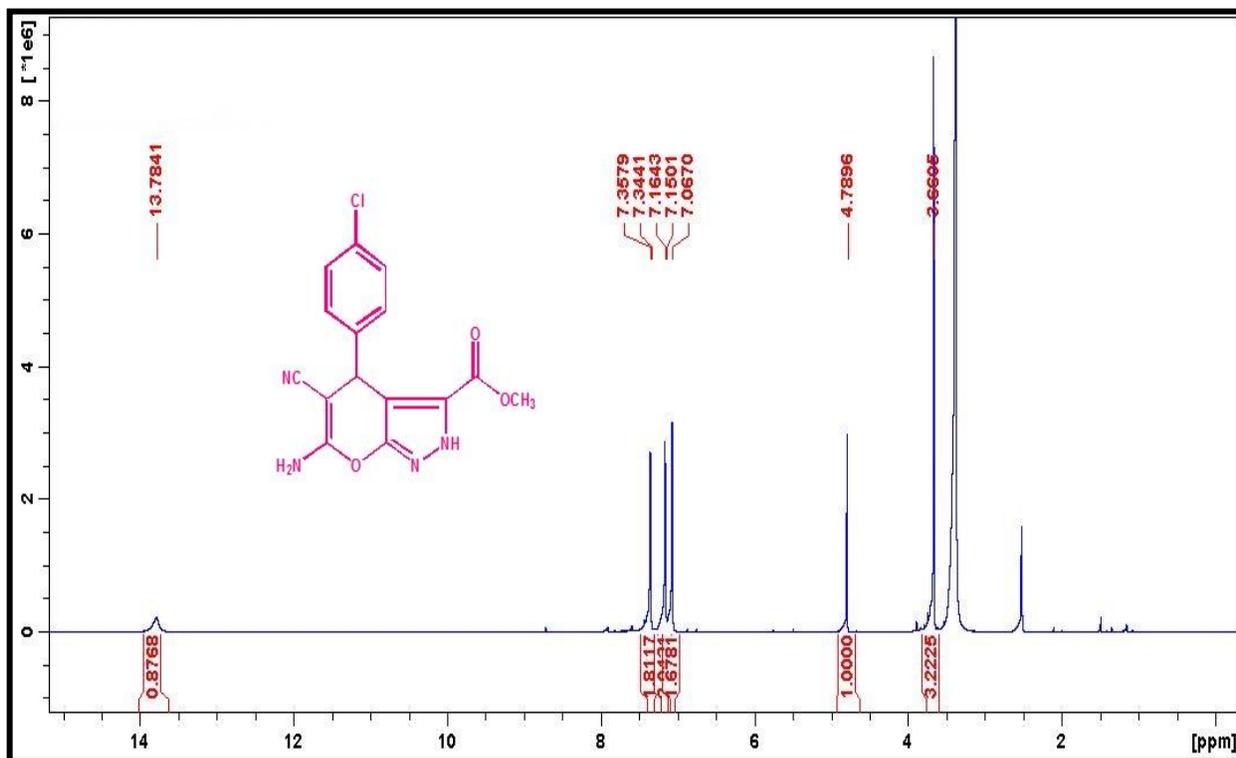
^{13}C NMR spectra of compound **5j**



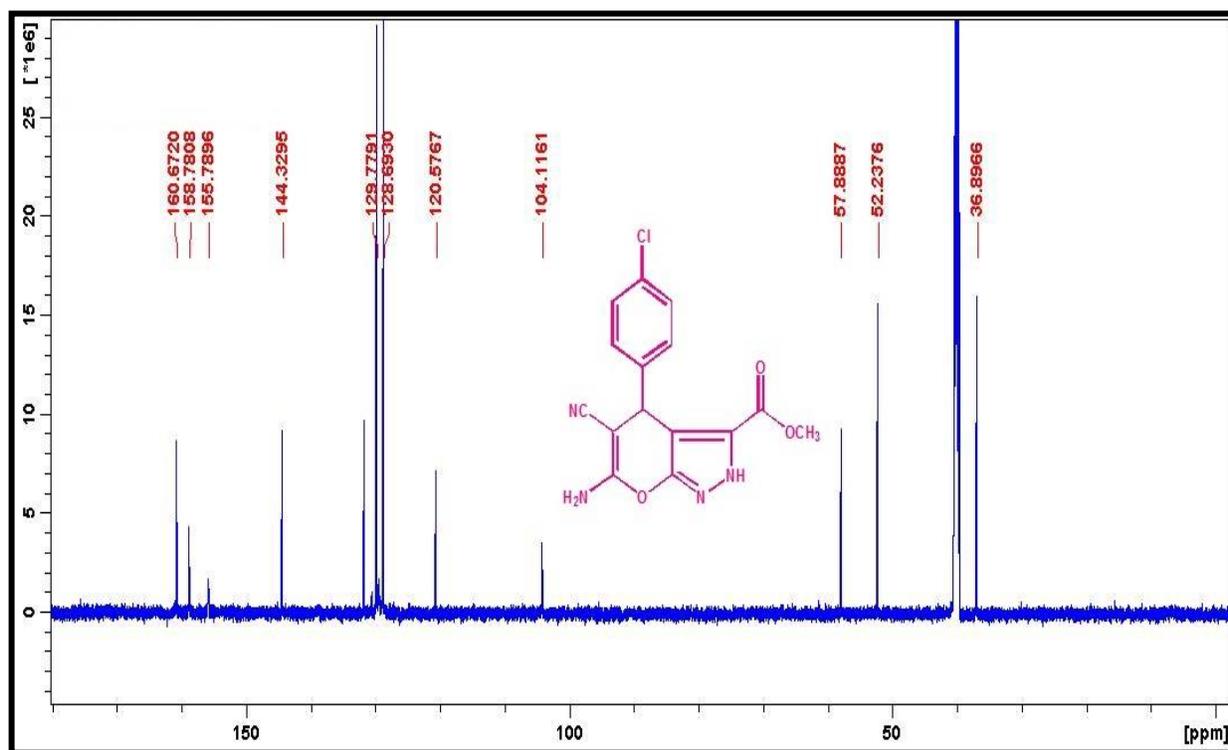
¹⁵N NMR spectra of compound **5j**



HRMS spectra of compound **5j**



¹H NMR spectra of compound **5k**



¹³C NMR spectra of compound **5k**

CHAPTER-7

CeO₂/ZrO₂ as Green catalyst for the one-pot synthesis of novel pyrano[2,3-*c*]-pyrazoles

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Res Chem Intermed
DOI 10.1007/s11164-017-2878-7



CeO₂/ZrO₂ as green catalyst for one-pot synthesis of new pyrano[2,3-*c*]-pyrazoles

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Received: 21 September 2016 / Accepted: 19 January 2017
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CeO₂/ZrO₂ as Green catalyst for the one-pot synthesis of novel pyrano[2,3-c]-pyrazoles

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Abstract

The ceria doped zirconia (CeO₂/ZrO₂) catalysed synthesis of pyrano[2,3-c]-pyrazoles via the four-component reaction of malononitrile, hydrazine hydrate, ethyl acetoacetate and substituted aldehydes is described. The catalytic material, CeO₂/ZrO₂ was prepared and characterized by different techniques including P-XRD, SEM, TEM and BET analysis. Twelve novel pyrano[2,3-c]-pyrazole derivatives (5a-l) were synthesized giving good to excellent yields (89 to 98%) and their structures were established and confirmed by different spectroscopic methods (¹H NMR, ¹³C NMR, ¹⁵N NMR and HRMS). The environmental benefits of the process includes excellent yield, short reaction time, simple work-up, elimination of toxic solvents and avoidance of chromatographic separations. The CeO₂/ZrO₂ catalyst follows a facile synthesis procedure, is inexpensive and has good reusability (at least 6 times).

Keywords: Multicomponent reaction; Green Synthesis; Pyrazoles; One-pot reaction; CeO₂

7.1. Introduction

Multicomponent Reactions (MCRs) are assimilation reactions, in which three or more starting materials react with each other simultaneously to form wanted product [1]. This approach is identified as a potent method in drug discovery due to the generation of essential target compounds [1-3]. MCR approaches have numerous significant benefits over the classic stepwise procedures, leading to the formation of several bonds in a single step without the need for intermediate separations and purifications [4]. Thus, MCRs accomplish their goals in an efficient, fast and environmentally benign manner with substantial savings in time and costs [2,3].

The development of heterogeneous catalysts for heterocyclic compounds synthesis has grown into a key issue for researchers [5]. Heterogeneous materials as catalyst in green organic reactions contribute to both environmental and fiscal benefits. Many such materials are easy to recover and recycle, which make their use appealing [6-8]. These recyclable catalysts have numerous benefits such being amenable to separation from the reaction without any heavy workups, but also offer long life, stability, recyclability and high selectivity. This circumvents waste production, whilst giving high yield products in short reaction times through a green procedures [9].

Zirconia (ZrO_2) is an eco-friendly and widely available plus low-cost material [6]. It stands out amongst other metal oxides due to its excellent stability and mechanical properties, which can promote the activity of the supported metal catalysts [9,10]. It has been commonly used for its substantial chemical and thermal stability, inertness, and high surface area [9-11]. The use of pure zirconia and its composites (with other metals) as catalysts for various organic transformations has been reported in the literature [12,13]. Cerium salts are generally used as dopants and advantages include ease of handling, low-cost, high stability and non-hazardous properties [14]. Cerium salts as dopant material are thus an appropriate choice for green organic conversions and has played a major role in green catalysis.

Heterocyclics play a vital role in drug discovery, pharmaceutical, agrochemical and computational fields. Heterocyclic compounds are the main precursors in various clinical applications and play a pivotal role in generating diverse biological activities [15,16].

Pyranopyrazoles and their derivatives are important heterocyclic compounds exhibiting remarkable biological properties acting as antibacterial, antifungal, antiviral, antitumor, anti-HIV, anti-convulsant, anti-inflammatory and antioxidants [17-23]. Many pyranopyrazoles are also used as herbicidal and insecticidal agents [24]. Literature reports on the synthesis protocols using catalysts for substituted pyranopyrazole derivatives include [ChCl][ZnCl₂]₂ [25], Amberlyst A₂1 [26], Per-6-ABCD [27], [(CH₂)₄SO₃HMIM][HSO₄] [28], [DBU][Ac] [29], silicotungstic acid [30], NaOH/microwave [30], [Dsim]AlCl₄ [31], L-Proline [32], TEABr [33] and FeNi₃/SiO₂/HPGMNP [34], to mention a few. Many of these reports have some limitations and weaknesses, such as use of severe reaction conditions, hazardous organic solvents, costly reagents and catalysts, non-reusability, long reaction times and low product yields, which confine their scope in practical applications. Hence, the development of green protocols for heterocyclic synthesis involving facile and environment-friendly methods (using green solvents in reaction and/or in workup method) would be worthy and well desired.

In our pursuit for developing efficient, environmentally benign and green approaches for synthesis of different heterocyclic compounds [35-37], we have recently reported varied synthetic methods for several biologically interesting products [38-42]. Here, we report a novel approach using highly efficient CeO₂/ZrO₂ as reusable catalyst for synthesis of a series of novel pyranopyrazole derivatives by the reaction of aromatic aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate at room temperature with ethanol as solvent.

7.2. Experimental section

7.2.1. Catalyst preparation

A range of supported catalysts with weight percentages Ce/ZrO₂ (1, 5, & 10 wt%), were synthesized using the wet-impregnation procedure [4,6]. The heterogeneous catalyst was prepared from a mixture of zirconia (ZrO₂, 3 g, catalyst support, Alfa Aesar) and an appropriate amount (wt%) of cerium nitrate [Ce(NO₃)₃·6H₂O (Alfa Aesar)] in distilled water (50 mL). The reaction mixture was stirred at room temperature (R.T) for 10 h. The resulting slurry was filtered under vacuum and dried in an oven at 110–120 °C for 5 h and calcined in the presence of air, at 450 °C for 5 h to form (1, 5 & 10 wt%) of Ce/ZrO₂ catalysts.

7.2.2. General procedure for the synthesis of pyranopyrazole derivatives

In a typical reaction, to equimolar ratios of aldehydes (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol) and ethyl acetoacetate (1 mmol) were dissolved in ethanol (10 ml) at

R.T followed by addition of CeO₂/ZrO₂ (50 mg) as catalyst. The reaction mixture was stirred continuously for 15 min at R.T, (Scheme 1) using a magnetic stirrer. The progress of the reaction was monitored by TLC. The reaction mixture was then filtered, and the filtrate was subsequently extracted with ethyl acetate and evaporated under reduced pressure to obtain the crude product. The crude product was then purified with ethanol to afford pure products (**5a-k**). The reaction products were identified and validated by various spectral techniques (¹H-NMR, ¹⁵N NMR, ¹³C-NMR and HRMS). All the spectral instrumentation details are incorporated in the supplementary information (SI-II). Details of some of the compounds were included in the supplementary information (SI-II).

6-Amino-4-(2,4,6-trimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5a): ¹H NMR (400 MHz, DMSO-d₆) δ = 1.79 (s, 3H, CH₃), 3.73 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 5.12 (s, 1H, CH), 6.259 (s, 2H, ArH), 6.69 (s, 2H, NH₂), 12.29 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): 9.66, 25.39, 51.50, 55.01, 55.42, 55.63, 91.07, 112.27, 154.35, 159.53, 160.57, 161.22; HRMS of [C₁₇H₁₈N₄O₃ + H]⁺ (m/z): 343.1141; Calcd.: 343.1141.

6-Amino-4-(2-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5b): ¹H NMR (400 MHz, DMSO-d₆) δ = 1.76 (s, 3H, CH₃), 5.06 (s, 1H, CH), 6.91 (s, 2H, NH₂), 7.05 (t, *J* = 8 Hz, 1H, ArH), 7.25 – 7.31 (m, 2H, ArH), 7.41 (dd, *J* = 7.8 Hz, 1.08 Hz, 1H, ArH) 12.11 (s, 1H, NH); ¹³C NMR (400 MHz, DMSO-d₆): 161.12, 154.95, 152.15, 146.19, 137.29, 135.09, 123.98, 120.97, 120.72, 111.06, 97.75, 60.22, 56.66, 55.48, 30.32, 9.42; HRMS of [C₁₄H₁₁ClN₄O₃ + H]⁺ (m/z): 287.1340; Calcd.: 287.1344.

6-Amino-4-(2-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5c): ¹H NMR (400 MHz, DMSO-d₆) δ = 1.79 (s, 3H, CH₃), 4.86 (s, 1H, CH), 6.90 (s, 2H, NH₂), 6.90 – 7.29 (m, 4H, ArH), 12.10 (s, 1H, NH); ¹³C NMR (400 MHz, DMSO-d₆): 9.35, 30.02, 55.53, 96.59, 115.37, 120.53, 124.69, 128.87, 129.76, 130.76, 135.72, 154.87, 158.69, 161.28; HRMS of [C₁₄H₁₁FN₄O₃ + H]⁺ (m/z): 271.0623; Calcd.: 271.0626.

6-Amino-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5d): ¹H NMR (400 MHz, DMSO-d₆) δ = 1.81 (s, 3H, CH₃), 3.70 (s, 3H, OCH₃), 4.49 (s, 1H, CH), 6.55 (dd, *J* = 8.12 Hz, 1.84 Hz, 1H, ArH), , 6.71 (t, *J* = 108.8 Hz, 2H, ArH), 6.76 (s, 2H, NH₂), 8.82 (s, 1H, OH), 12.03 (s, 1H, NH); ¹³C NMR (400 MHz, DMSO-d₆): 9.79,

35.79, 55.41, 57.42, 97.67, 111.19, 111.72, 119.46, 120.81, 135.63, 136.86, 147.53, 148.51, 154.68, 160.72; HRMS of $[C_{15}H_{14}N_4O_3 + H]^+$ (m/z): 299.0786; Calcd.: 299.0800.

6-Amino-4-(3-hydroxy-4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5e): 1H NMR (400 MHz, DMSO- d_6) δ = 1.80 (s, 3H, CH₃), 3.72 (s, 3H, OCH₃), 4.42 (s, 1H, CH), 6.52 (s, 1H, ArH), 6.58 – 6.60 (m, 1H ArH), 6.76 (s, 2H, NH₂), 6.82 (d, J = 8.2 Hz, 1H, ArH), 8.88 (s, 1H, OH), 12.04 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO- d_6): 9.70, 35.63, 57.70, 97.70, 111.80, 114.45, 118.05, 120.80, 135.54, 137.08, 146.45, 154.71, 160.60; HRMS of $[C_{15}H_{14}N_4O_3 + H]^+$ (m/z): 299.0732; Calcd.: 299.0732.

6-Amino-4-(4-ethylphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5f): 1H NMR (400 MHz, DMSO- d_6) δ = 1.16 (t, J = 7.6 Hz, 3H, CH₃), 1.78 (s, 3H, CH₃), 2.58 (dd, J = 15.24 Hz, 7.56 Hz, 2H, CH₂), 4.54 (s, 1H, CH), 6.59 (dd, J = 7.52 Hz, 1.28 Hz, 1H, ArH), 6.80 (s, 2H, NH₂), 6.89 (d, J = 6.8 Hz, 1H, ArH), 6.99 (t, J = 7.96 Hz, 1H, ArH), 11.99 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO- d_6): 9.73, 15.39, 27.68, 35.81, 57.33, 97.72, 120.82, 127.05, 127.31, 127.73, 128.31, 128.38, 135.50, 141.72, 141.96, 154.72, 160.78; HRMS of $[C_{16}H_{16}N_4O + H]^+$ (m/z): 281.1040; Calcd.: 281.1039.

6-Amino-4-(4-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5g): 1H NMR (400 MHz, DMSO- d_6) δ = 1.78 (s, 3H, CH₃), 4.62 (s, 1H, CH), 6.86 (s, 2H, NH₂), 7.13 – 7.19 (m, 4H, ArH), 12.10 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO- d_6): 9.67, 35.41, 57.10, 97.46, 115.01, 115.22, 129.25, 129.33, 135.59, 160.79; HRMS of $[C_{14}H_{11}FN_4O + H]^+$ (m/z): 271.0835; Calcd.: 271.0839.

6-Amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5h): 1H NMR (400 MHz, DMSO- d_6) δ = 1.78 (s, 3H, CH₃), 4.46 (s, 1H, CH), 6.68 (d, J = 8.4 Hz, 2H, ArH), 6.74 (s, 2H, NH₂), 6.94 (d, J = 8.4 Hz, 2H, ArH), 9.26 (s, 1H, OH), 12.02 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO- d_6): 9.70, 35.45, 57.81, 98.03, 115.07, 120.84, 128.38, 134.72, 135.49, 154.72, 155.97, 160.59; HRMS of $[C_{14}H_{12}N_4O_2 + H]^+$ (m/z): 269.0835; Calcd.: 269.0839.

6-Amino-4-(4-(dimethylamino)phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5i): 1H NMR (400 MHz, DMSO- d_6) δ = 1.78 (s, 3H, CH₃), 2.85 (s, 6H, N(CH₃)₂), 4.45 (s, 1H, CH), 6.65 (d, J = 8.56 Hz, 2H, ArH), 6.73 (s, 2H, NH₂), 6.96 (d, J = 8.56 Hz, 2H, ArH), 12.02 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO- d_6): 9.74, 35.34, 57.98, 98.15, 112.28, 120.92, 127.98, 129.45, 132.01, 135.44, 149.19, 154.76, 160.52.

6-Amino-4-(2,3-dimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-

carbonitrile (5j): ^1H NMR (400 MHz, DMSO- d_6) δ = 1.76 (s, 3H, CH₃), 3.64 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 4.82 (s, 1H, CH), 6.59 (dd, J = 7.52 Hz, 1.28 Hz, 1H, ArH), 6.80 (s, 2H, NH₂), 6.89 (d, J = 6.8 Hz, 1H, ArH), 6.99 (t, J = 7.96 Hz, 1H, ArH), 11.99 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO- d_6): 9.42, 30.32, 55.48, 56.66, 60.22, 97.75, 111.06, 120.97, 123.98, 135.09, 137.29, 146.19, 152.15, 154.95, 161.12.

6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-

carbonitrile (5k): ^1H NMR (400 MHz, DMSO- d_6) δ = 1.82 (s, 3H, CH₃), 3.69 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 4.54 (s, 1H, CH), 6.69 (dd, J = 7.52 Hz, 1.96 Hz, 1H, ArH), 6.75 (d, J = 1.96 Hz, 1H, ArH), 6.80 (s, 1H, NH₂), 6.88 (d, J = 8.28 Hz, 1H, ArH), 12.07 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO- d_6): 9.79, 35.79, 55.41, 57.42, 97.67, 111.19, 111.72, 119.46, 120.81, 135.86, 147.53, 148.51, 154.68, 160.72; HRMS of $[\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_3 + \text{H}]^+$ (m/z): 313.0952; Calcd.: 313.0957.

6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5l): ^1H NMR (400 MHz, DMSO- d_6) δ = 1.77 (s, 3H, CH₃), 4.58 (s, 1H, CH), 6.84 (s, 2H, NH₂), 7.15 – 7.23 (m, 5H, ArH), 12.09 (s, 1H, NH); ^{13}C NMR (400 MHz, DMSO- d_6): 9.69, 36.22, 57.22, 97.61, 126.69, 127.42, 127.65, 128.39, 135.57, 144.40, 154.73, 160.84; HRMS of $[\text{C}_{14}\text{H}_{14}\text{N}_4\text{O} + \text{H}]^+$ (m/z): 253.0953; Calcd.: 299.0953.

7.3. Results and discussion

7.3.1. BET surface area (BET) and elemental (ICP) analysis

The porosity of the synthesized catalyst was determined by N₂ adsorption and desorption analysis. The N₂ physisorption isotherms were determined for the 5% ceria supported on zirconia catalyst. The N₂ adsorption-desorption isotherms showed a characteristic hysteresis loop of a type-IV adsorption isotherm representing the mesoporous nature of the catalysts (**Figure 1**). The mesoporous structure was confirmed by the pore size values, which exhibited values located in the mesoporous region for the samples (3 nm < pore size < 50 nm) and the isotherms p/p⁰ range is 0.76-0.94. The prepared catalyst showed a surface area of 56 m² g⁻¹ with a pore volume of 0.212 cc g⁻¹. The ICP analysis results showed the presence of a anticipated amount of Ce in the catalyst (4.96 mol %).

7.3.2. TEM analysis

The TEM micrograph provides more structural information of the catalyst. **Figure 2** shows a distinctive TEM image of CeO₂ supported on ZrO₂, from which it can be seen that the ceria particles were revealed as black irregular cube like shapes and zirconia shown as white globular shape particles. No drastic change was noticed in the morphology of the used catalyst.

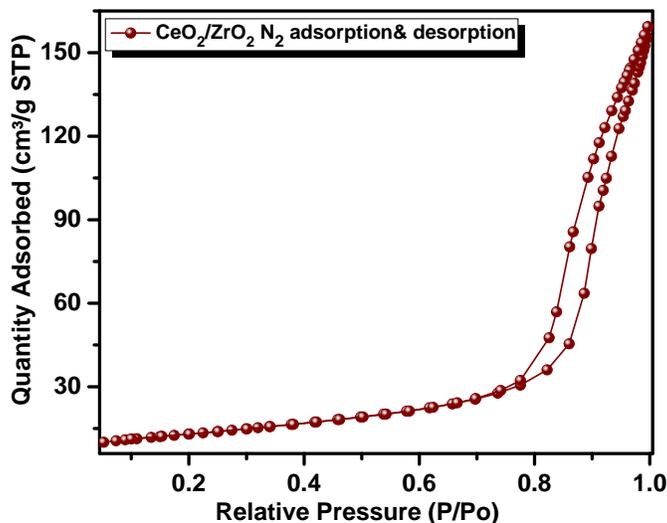


Figure 1: BET surface area of 5% CeO₂/ZrO₂ catalyst

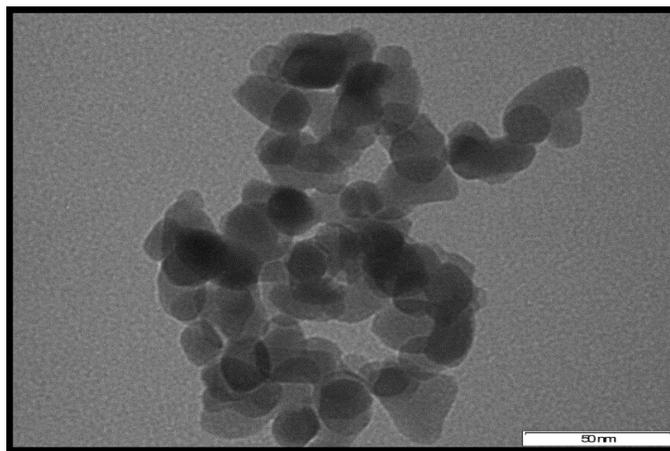


Figure 2: TEM micrograph of 5% CeO₂/ZrO₂ catalyst

7.3.3. SEM analysis

Figure 3a exhibits a representative SEM surface morphology micrograph of the sample CeO₂ on ZrO₂. A few large cubic sheet asymmetrical silhouettes were observed from the SEM image of CeO₂/ZrO₂. It reveals that the aggregation state of the zirconia particles with ceria. The

micrographs of SEM–EDX confirmed the uniform distribution of ceria on the zirconia surface (**Figure 3b**). The SEM-EDX agreed well with the data from ICP elemental analysis. Furthermore, the morphology of the catalyst as per the SEM images noticeably point to the crystallinity and homogeneity of the sample.

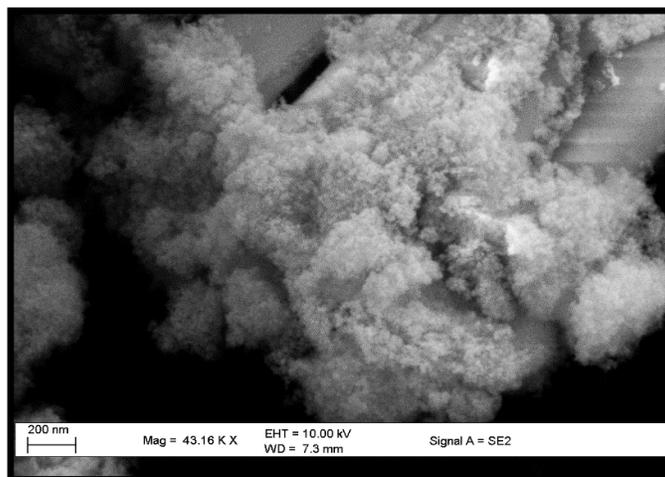


Figure 3(a): SEM micrograph of 5% CeO₂/ZrO₂ catalyst

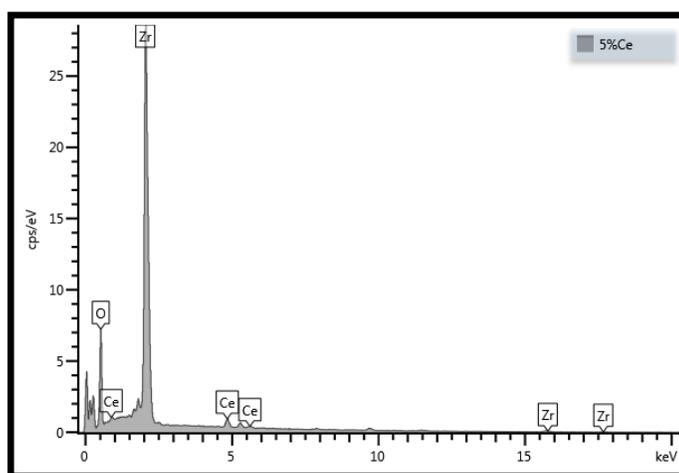


Figure 3(b): SEM-EDX micrograph of 5% CeO₂/ZrO₂ catalyst

7.3.4. Powder X-ray diffractogram (XRD) analysis

The powdered XRD arrangements of calcined ceria doped zirconia are shown in **Figure 4**. The diffraction peak values 2θ of 28.7°, 33.2°, 47.5°, 56.3°, 59.3°, 69.8°, 76.6° and 79.4° were assigned to ceria. All these diffraction peaks agreed with the International Centre for Diffraction Data (JCPDS file No. 43-1002). 5% CeO₂ loaded on ZrO₂ sample exhibited diffraction peaks at a

2θ angles of 24.7° , 28.8° , 31.8° , 34.6° , 41.4° , 50.9° and 60.5° corresponding to the ZrO_2 (JCPDS file No. 01-089-9066). The peaks identified in the diffractogram confirm the polycrystalline nature of the materials. The average crystallite size of the sample was about 6.9 nm, based on the highest intensity diffraction peaks of $\text{CeO}_2/\text{ZrO}_2$ by using the Scherrer equation.

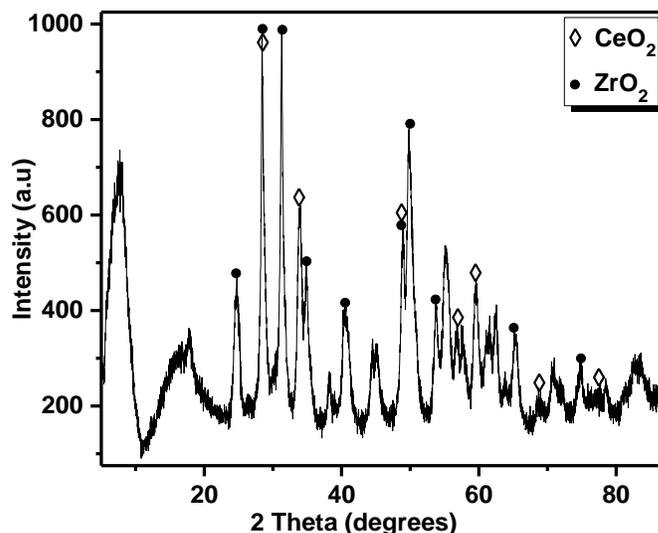


Figure 4: Powder X-ray diffractogram of 5% $\text{CeO}_2/\text{ZrO}_2$ catalyst

7.3.5. Optimization procedure

The model reaction containing benzaldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1.2 mmol) and ethyl acetoacetate (1 mmol) as reactants was investigated in detail as function of varied conditions, i.e. in the absence and presence of different catalysts and using varied solvents and temperature conditions. First, the reaction was studied without a catalyst or solvent at both R.T and reflux conditions and there was no reaction, even after 10 h (Table 1, entry 1 and 2). When the reaction was carried out with the various basic catalysts such as TEA, Na_2CO_3 , pyridine and Na_2S and with ethanol as solvent, yield of product was low, even after 6 h (Table 1, entry 3-6). Next, the reaction was tried in the presence of ionic liquids, L-proline or $(\text{Bmim})\text{BF}_4$ and the product yield was moderate at R.T conditions (Table 1, entry 7 and 8). Further, when pure oxide catalysts, such as Al_2O_3 , SiO_2 and ZrO_2 were employed using the same solvent and RT., the reaction revealed moderate to good yields after 1.5-3.0 h reaction time (Table 1, entries 9-11). After noticing encouraging result with ZrO_2 , to enhance the reaction efficiency it was used as support to dope with different metal oxides. As such, $\text{Fe}_2\text{O}_3/\text{ZrO}_2$, V/ZrO_2 , and Ce/ZrO_2 composites were prepared and screened for activity. The mixed oxide catalytic reactions afforded very good to excellent yields (84-98%) within 45 min in ethanol and

at R.T (Table 1, entry 12-14). In particular, CeO₂ doped ZrO₂ as catalyst, recorded an excellent yield (98%) of pyranopyrazoles in 15 min time. Assessing the impressive results, CeO₂ doped ZrO₂ was chosen as ideal catalyst for the further studies.

Table 1: Optimal conditions for the synthesis of model reaction by 5% CeO₂/ZrO₂ catalyst^a

Entry	Catalyst	Temperature	Time (h)	Yield (%) ^b
1	--	RT	10	--
2	--	Reflux	10	--
3	TEA	RT	8.0	19
4	Na ₂ CO ₃	RT	6.0	27
5	Pyridine	RT	7.0	23
6	Na ₂ S	RT	7.5	20
7	L-proline	RT	4.5	39
8	(Bmim)BF ₄	RT	5.0	48
9	Al ₂ O ₃	RT	3.0	51
10	SiO ₂	RT	2.5	59
11	ZrO ₂	RT	1.5	70
16	5% Fe ₂ O ₃ /ZrO ₂	RT	0.75	84
17	5% V ₂ O ₅ /ZrO ₂	RT	0.50	89
18	5% CeO ₂ /ZrO ₂	RT	0.25	98

^a All products were characterised by ¹H NMR, ¹³C NMR, ¹⁵N NMR & HRMS spectral analysis.

^b Isolated yields.

-- No reaction

Table 2: Optimization of the amount of 5% CeO₂/ZrO₂ as catalyst in the model reaction^a

Entry	Catalyst (mg)	Time (min)	Yield (%)
1	10	45	88
2	30	35	92
3	50	15	98
4	70	20	97
5	90	15	94

^aReaction conditions: ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1.1 mmol), benzaldehyde (1 mmol), catalyst and ethanol (10 mL) solvent were stirred at room temperature.

Next, to evaluate the influence of quantity of catalyst on the synthesis of pyrano[2,3-c]pyrazoles, the reaction of hydrazine hydrate, malononitrile, ethyl acetoacetate and

benzaldehyde was studied using variable amounts of CeO₂/ZrO₂ (10, 30, 50, 70, 90) mg. The 50 mg amount of catalyst proved opt to complete the reaction in terms of yield and reaction time. Any further amount of the catalyst did not improve either the yield or reaction time (Table 2). However, the decrease in quantity of the catalyst used to < 50 mg, affected the product yield by reducing it to 88% (Table 2). Thus, 50 mg of CeO₂/ZrO₂ at R.T with ethanol as solvent was preferred as optimum reaction condition.

When the efficiency of different polar and non-polar solvents as solvent were investigated ethanol as solvent was found crucial for the reaction (Table 3). Under otherwise comparable conditions, the CeO₂/ZrO₂ catalyzed reaction in presence of relatively non-polar solvents like n-hexane, 1,4-dioxane and toluene gave trivial yields even after protracted reaction times (Table 3 entries 1-3). Even with polar aprotic solvents such as CH₃CN and DMF, the reaction yield was low (Table 3, Entry 4 and 5). Although, good results were obtained when polar solvents, CH₃OH, C₂H₅OH and isopropanol were used as solvents (Table 3, entries 6-8), based on the criteria such as reaction time, green nature, cost-effective and excellent yields, ethanol proved to be superior and best solvent for the reaction.

Table 3: Optimization of various solvent condition for the synthesis of pyrano[2,3-c]pyrazoles derivatives by 5% CeO₂/ZrO₂ catalyst

Entry	Solvent	Yield (%)
1	n-Hexane	09
2	Toluene	13
3	1,4-Dioxane	10
4	CH ₃ CN	34
5	DMF	37
6	Ethanol	78
7	Methanol	69
8	isopropanol	71

^aReaction conditions: ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1.1 mmol), benzaldehyde (1 mmol), catalyst (50 mg) and solvent (10 mL) solvent were stirred at room temperature.

The CeO₂/ZrO₂ catalyst could catalyze the facile one-pot synthesis reactions of pyrano[2,3-c]pyrazoles derivatives with excellent yields. Under the optimal reaction conditions, the flexibility and applicability of the protocol was confirmed by using variety of other aromatic aldehydes instead of benzaldehyde. Convincingly, irrespective of aldehydes possessing different

electron-withdrawing or electron releasing substituents in ortho, meta and/or para positions on the aryl ring, all the reactions gave impressive results, producing respective pyrano[2,3-c]pyrazole derivatives in very good to excellent yields (Table 4). All of the reaction products were characterized and structures were confirmed by ¹H NMR, ¹⁵N NMR, ¹³C NMR and HRMS spectral data (Electronic Supplementary Information).

Table 4: Synthesis of pyrano[2,3-c]pyrazoles catalyzed by 5% CeO₂/ZrO₂ catalyst

Entry	R	Product	Yield (%)	Mp °C	Lit Mp °C
1	2,4,6-(OMe) ₃	5a	92	227-228	--
2	2-Cl	5e	90	145-147	145-146 [27]
3	2-F	5f	91	258-260	--
4	3-OMe, 4-OH	5d	90	236-237	--
5	3-OH, 4-OMe	5e	93	209-211	--
6	4-Et	5f	95	241-243	--
7	4-F	5g	89	171-172	--
8	4-OH	5h	92	210-212	210-211 [27]
9	NN-(Me) ₂	5i	89	162-165	--
10	2,3-(OMe) ₂	5j	94	215-216	--
11	3,4-(OMe) ₂	5k	92	192-193	--
12	H	5l	98	167-168	167-169 [27]

-- New compounds/no literature available.

7.3.6. Reusability of catalyst

The reusability of the synthesized heterogeneous catalysts is an important requirement from the environmental and economic point of view. In heterogeneous catalysis, poisoning of the catalyst and leaching of metal are the main limitations, which impact on activity of catalyst for further reuse. To examine the stability of the catalyst, recycling experiments were performed. After each run, the catalyst was separated by filtration. The recovered catalyst was subjected to washing with dichloromethane, dried, and then reused for up to six cycles. No significant loss was observed in the first five cycles. The catalytic activity of the CeO₂/ZrO₂ decreased by 4%, when the recovered catalytic system was reused in the 6th cycle (Figure 5).

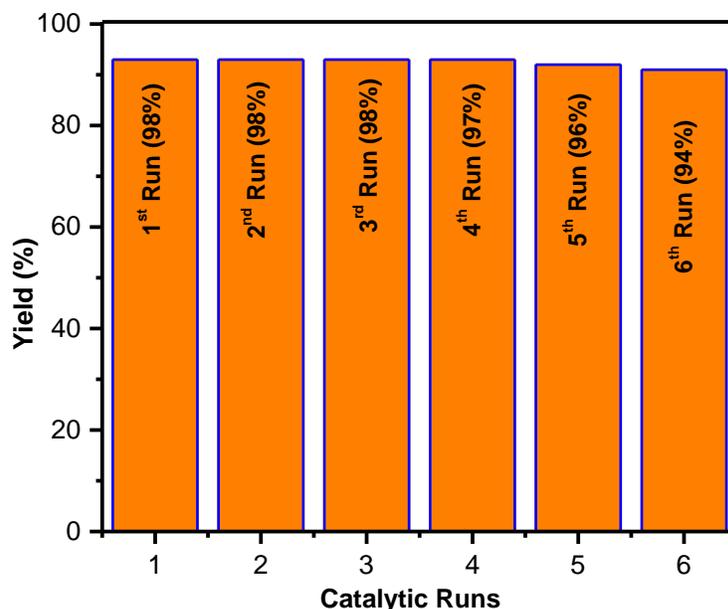


Figure 5: Recyclability of CeO₂/ZrO₂ catalyst

7.4. Conclusion

In summary, a simple, robust, efficient and green multicomponent one-pot method is designed for the syntheses of pyrano[2,3-c]pyrazole derivatives in good to excellent yields using CeO₂/ZrO₂ as catalyst at RT. The catalyst proved effective and recyclable for the MCR protocol. The advantages of the approach are excellent yields, cost-effectiveness, easy work up, environment friendly reaction conditions, short reaction times, green solvent and reusable catalyst. This procedure is promising for diversity oriented synthesis of potentially bioactive heterocycles.

7.5. 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.

7.6. References

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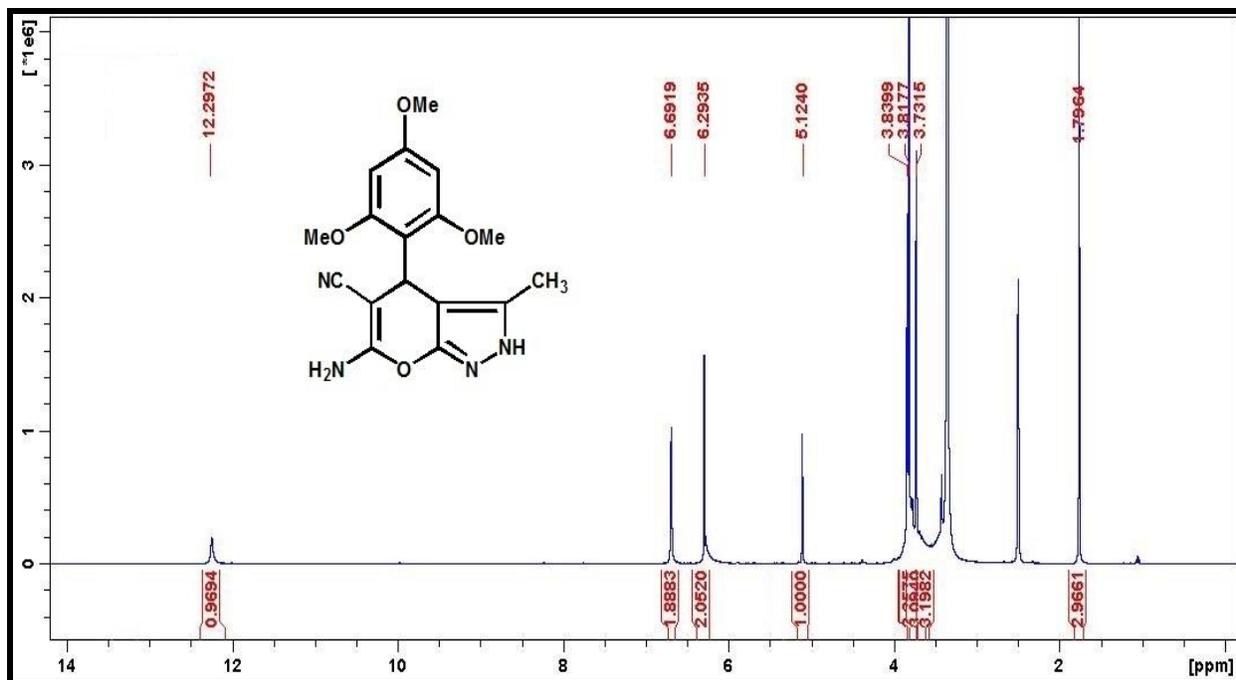
7.7. Supplementary material data

7.7.1. Catalyst instrumentation details

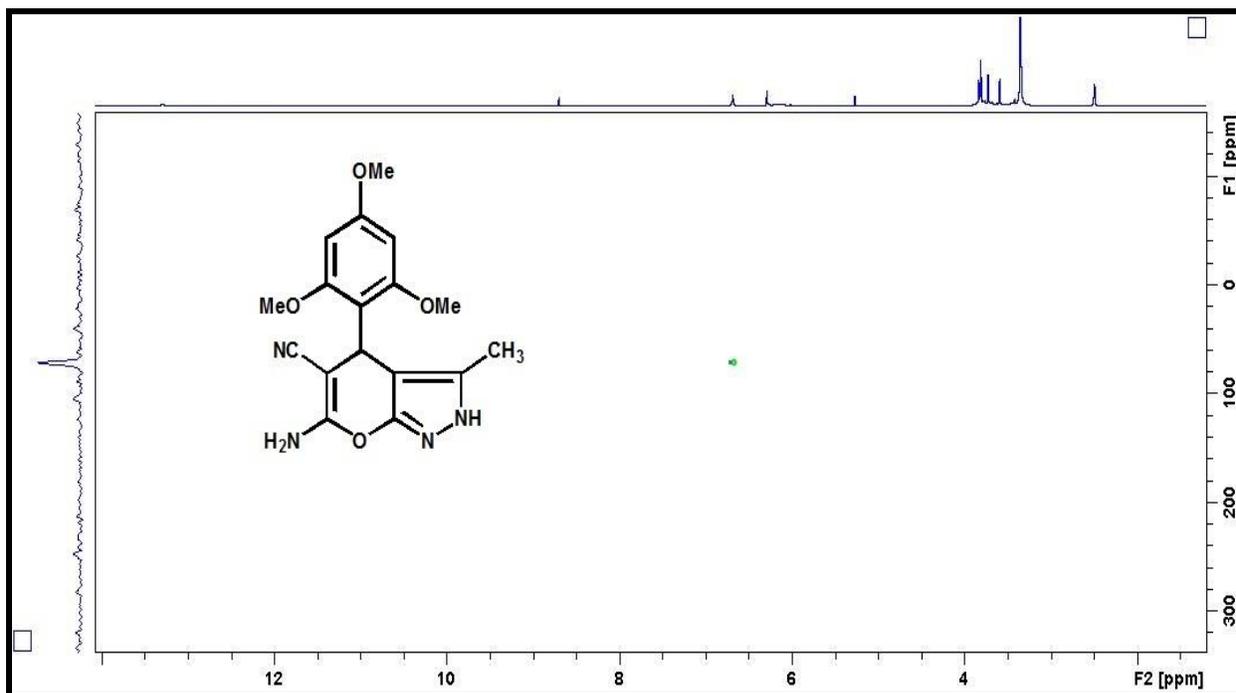
Employing a Bruker D8 Advance instrument (Cu K radiation source with a wave length of 1.5406 Å), the X-ray diffraction data related the structural phases of the catalyst were acquired. Using a Jeol JEM-1010 electron microscope and JEOL JSM-6100 microscope, the TEM and SEM analysis data was recorded. iTEM software was used analyze the TEM data and images. Employing the X-ray analyzer (energy-dispersive), EDX-analysis on the SEM images was conducted.

7.7.2. Experimental section:

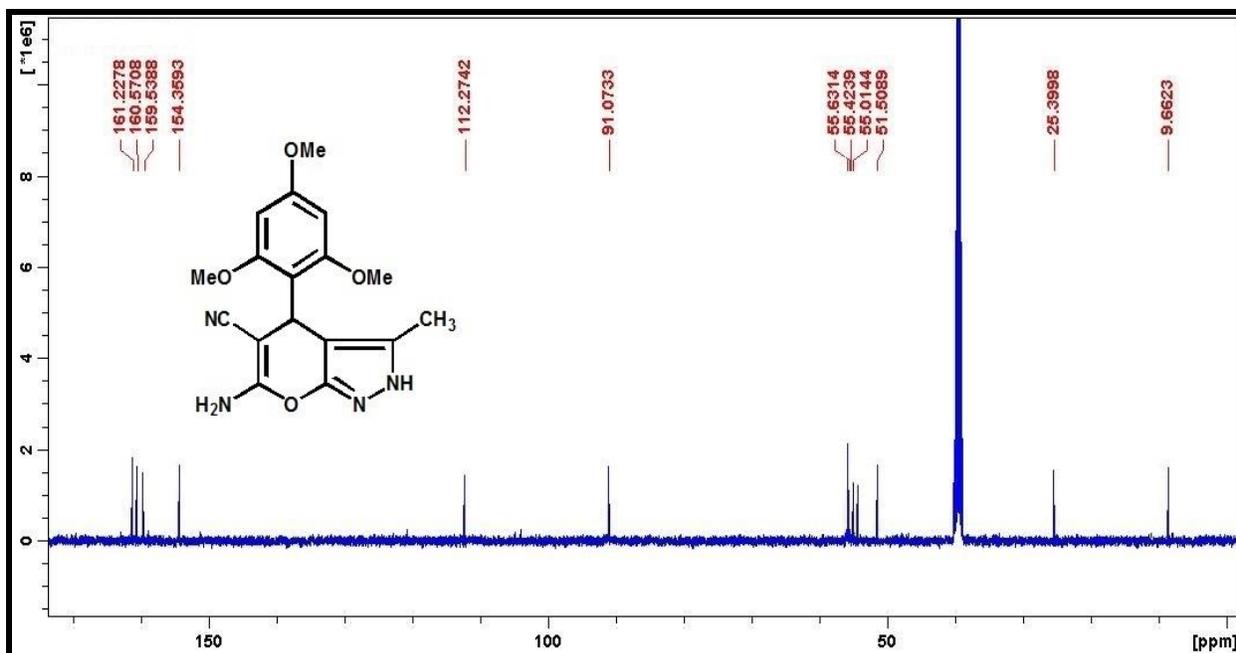
All chemicals and reagents required for the reaction were of analytical grade and were used without any further purification. Bruker AMX 400 MHz NMR spectrometer was used to record the ¹H NMR, ¹³C NMR and ¹⁵N NMR spectral values. High-resolution mass data were obtained using a Bruker micro TOF-Q II ESI instrument operating at ambient temperature. The DMSO-d₆ solution was utilized for this while TMS served as the internal standard. TMS was further used as an internal standard for reporting the all chemical shifts in δ (ppm). Purity of all the reaction products was confirmed by TLC using aluminum plates coated with silica gel (Merck Kieselgel 60 F254).



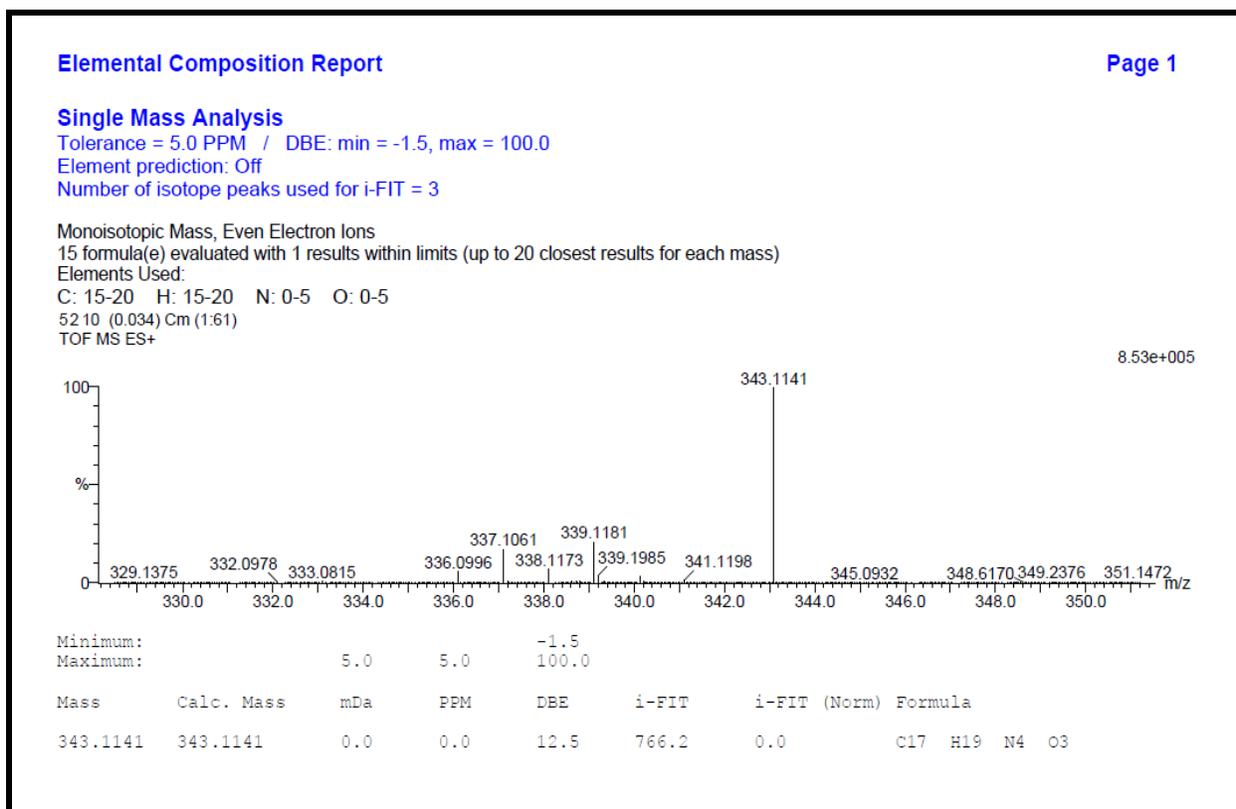
^1H NMR spectra of compound **5a**



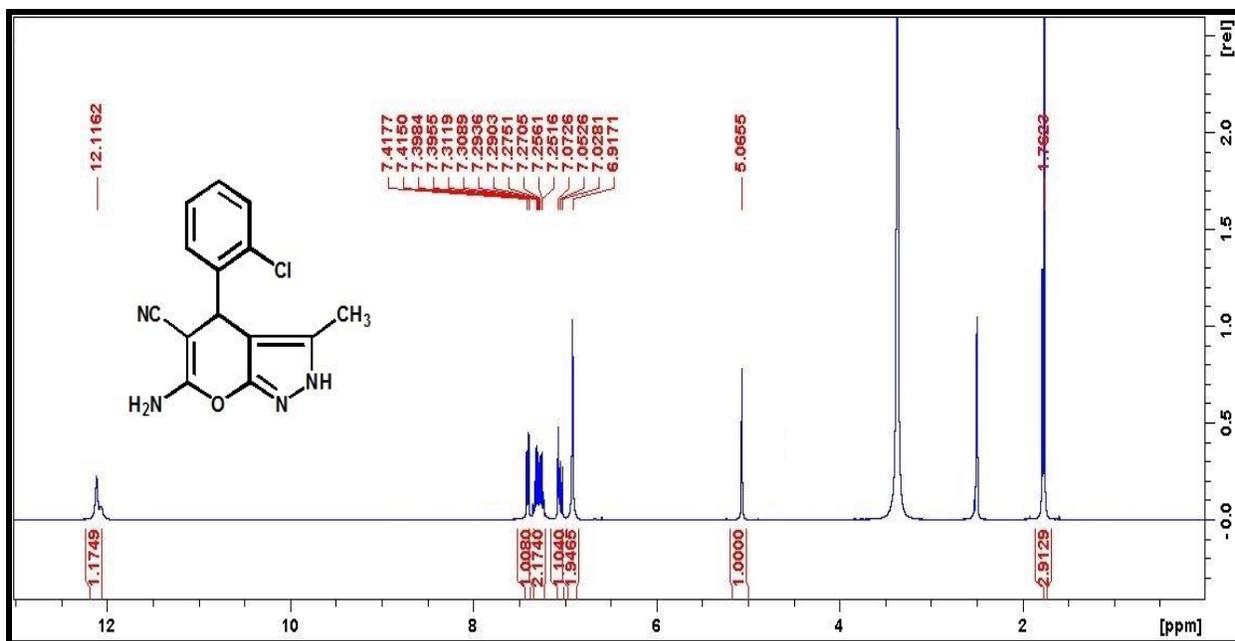
^{15}N NMR spectra of compound **5a**



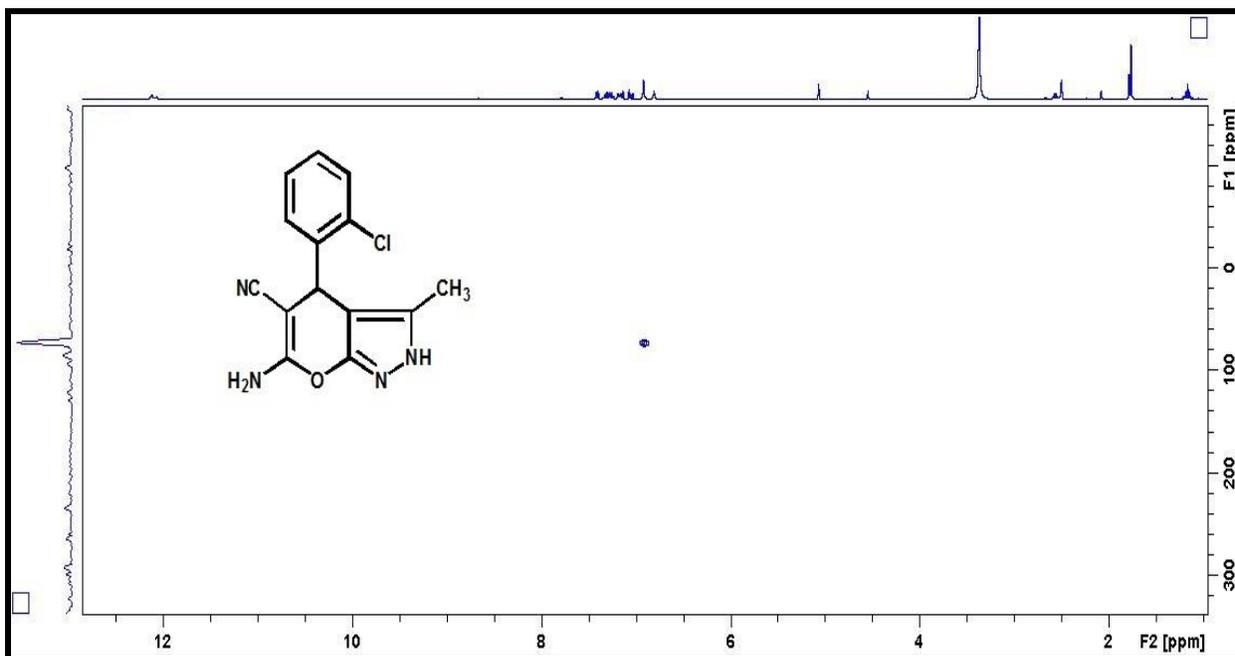
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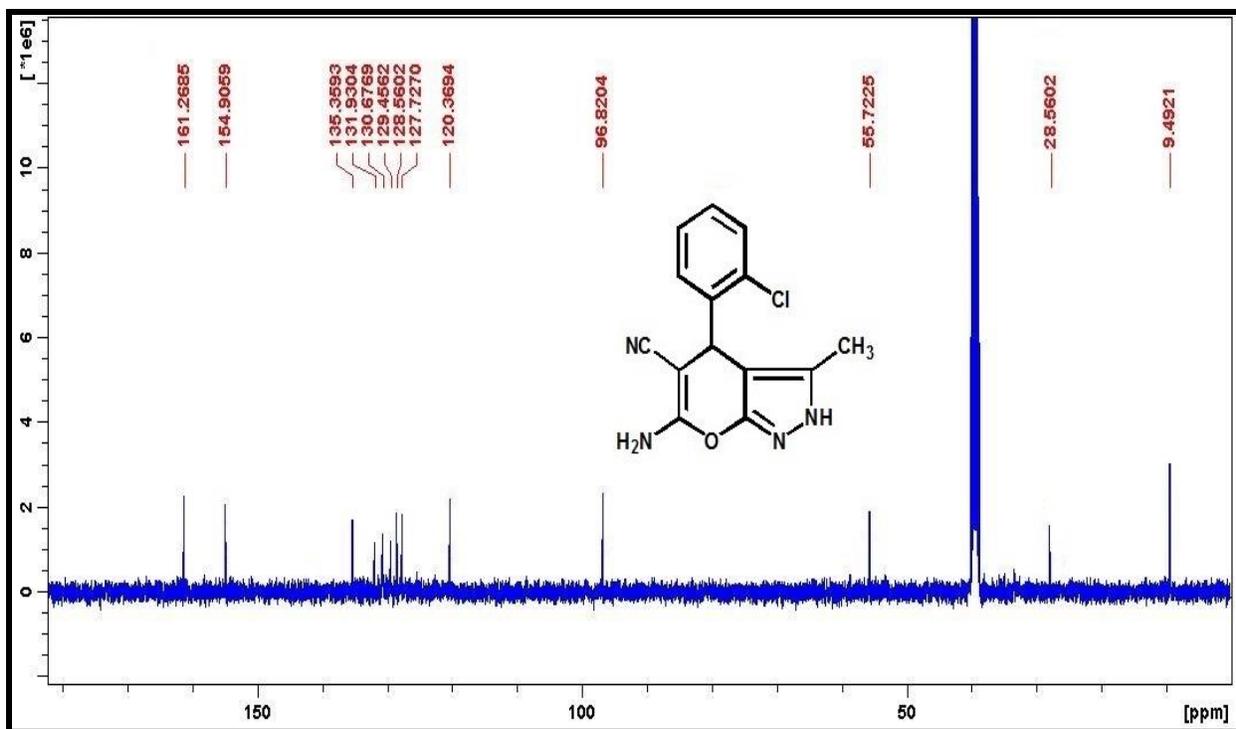
HR-MS spectra of compound **5a**



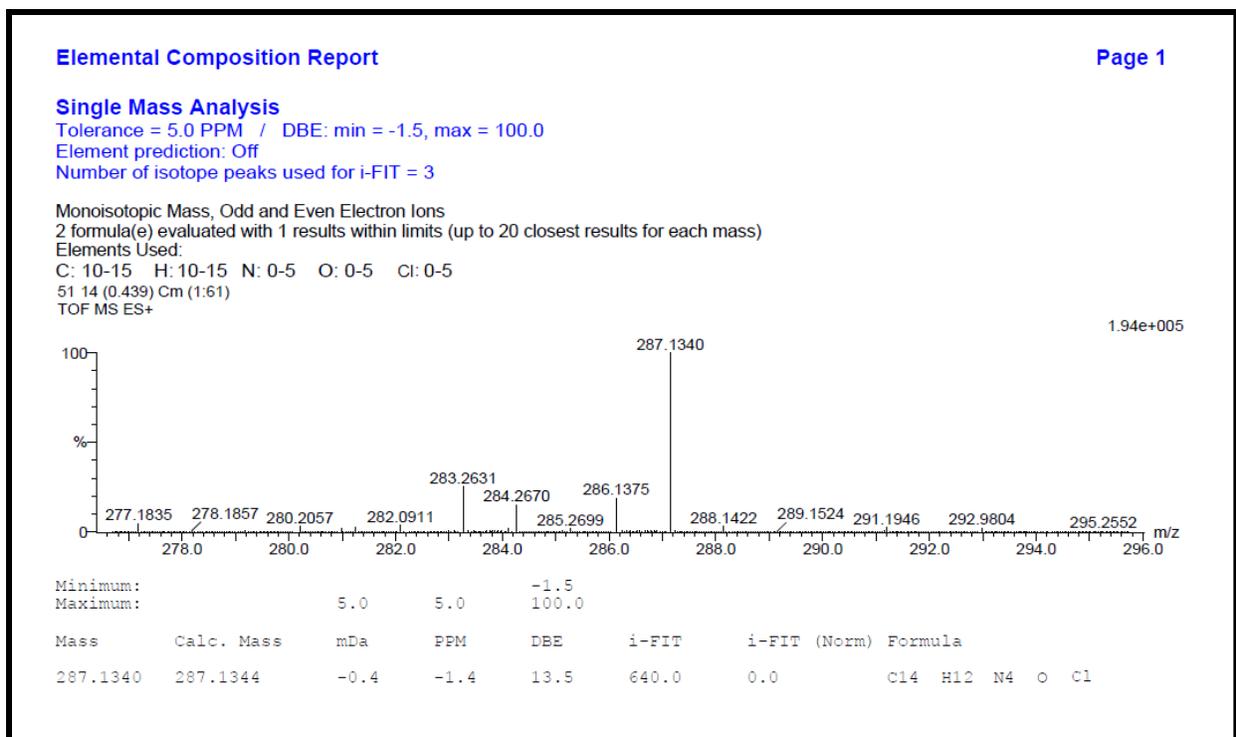
^1H NMR spectra of compound **5b**



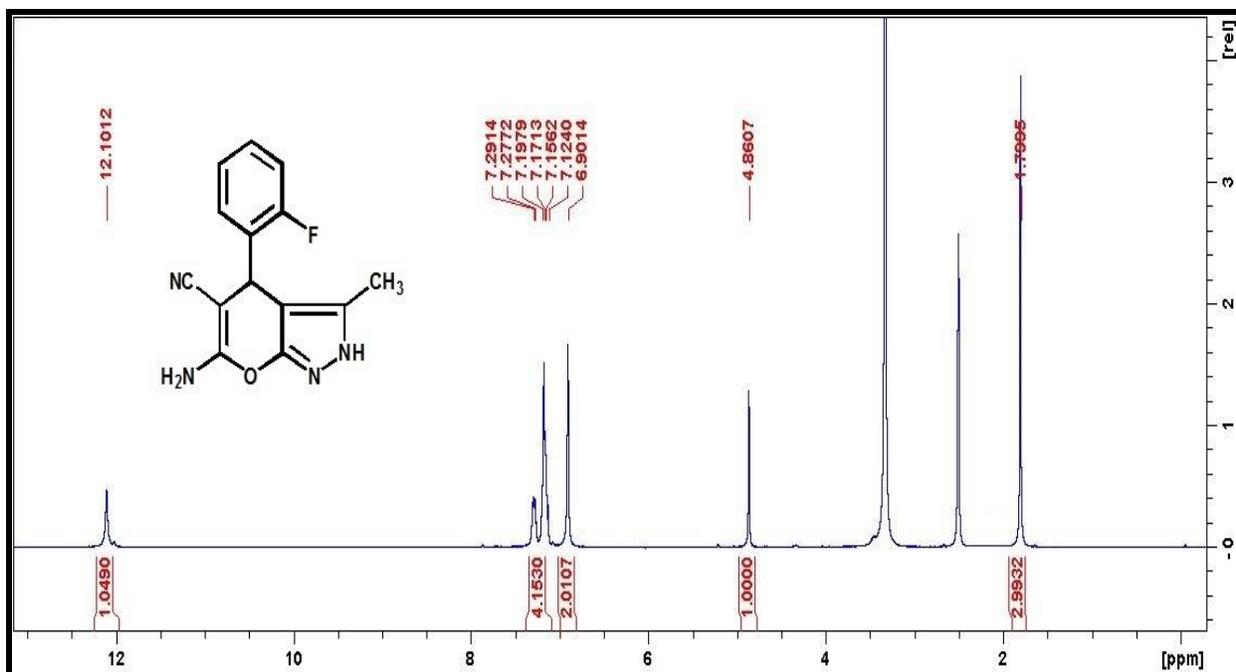
^{15}N NMR spectra of compound **5b**



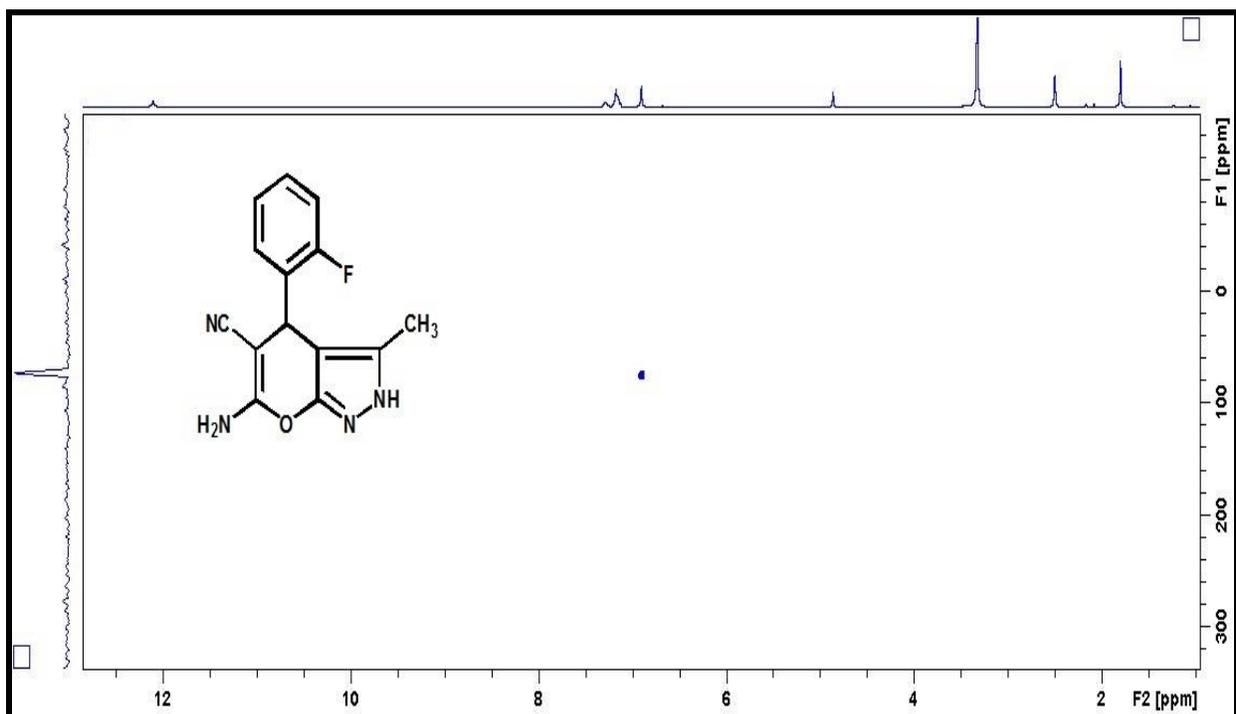
¹³C NMR spectra of compound **5b**



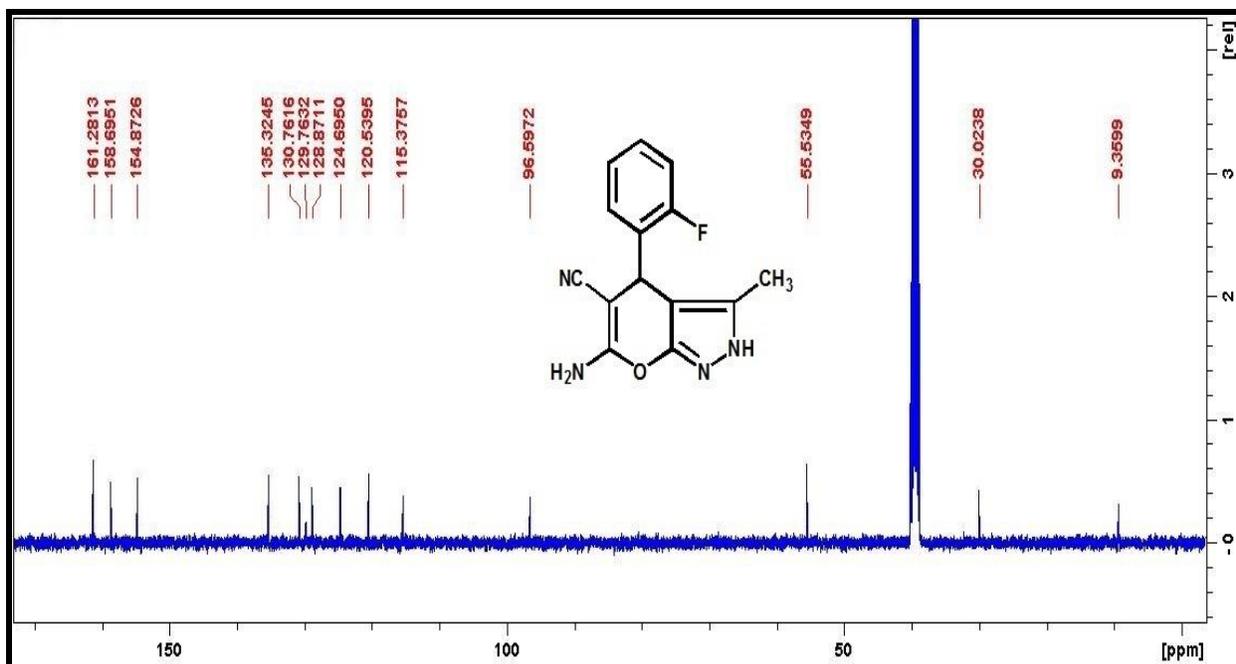
HR-MS spectra of compound **5b**



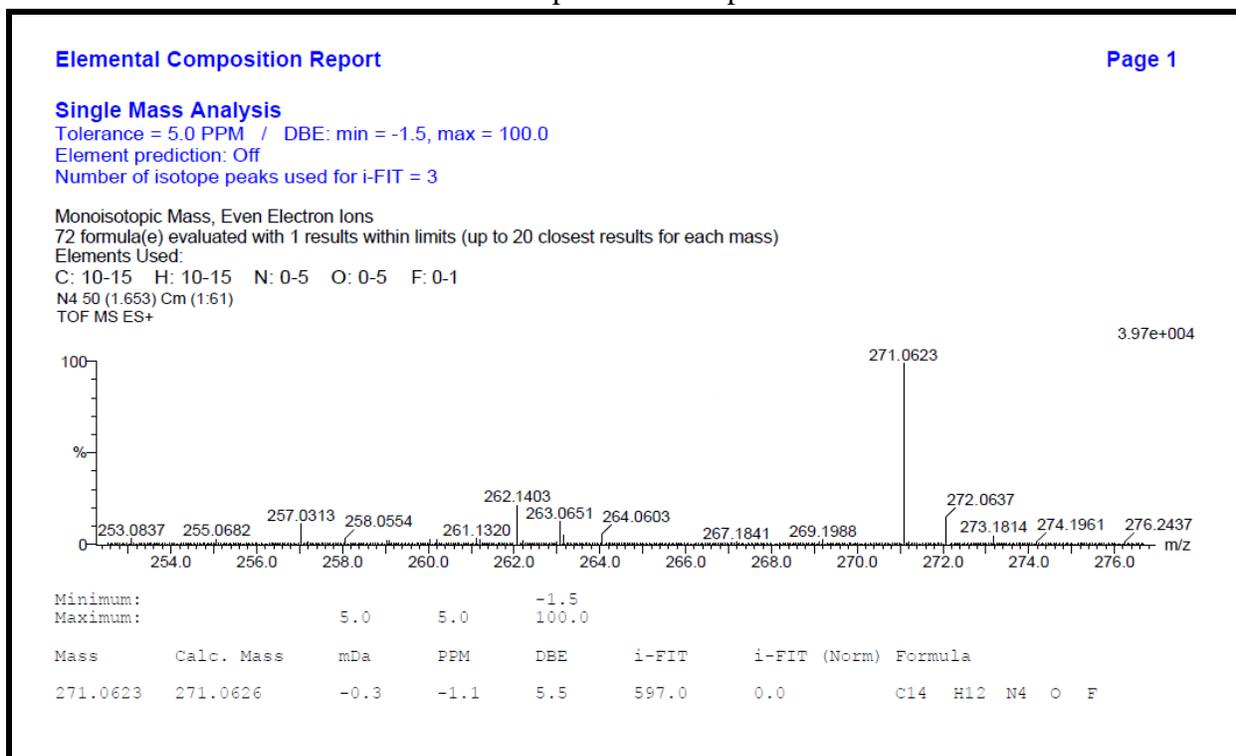
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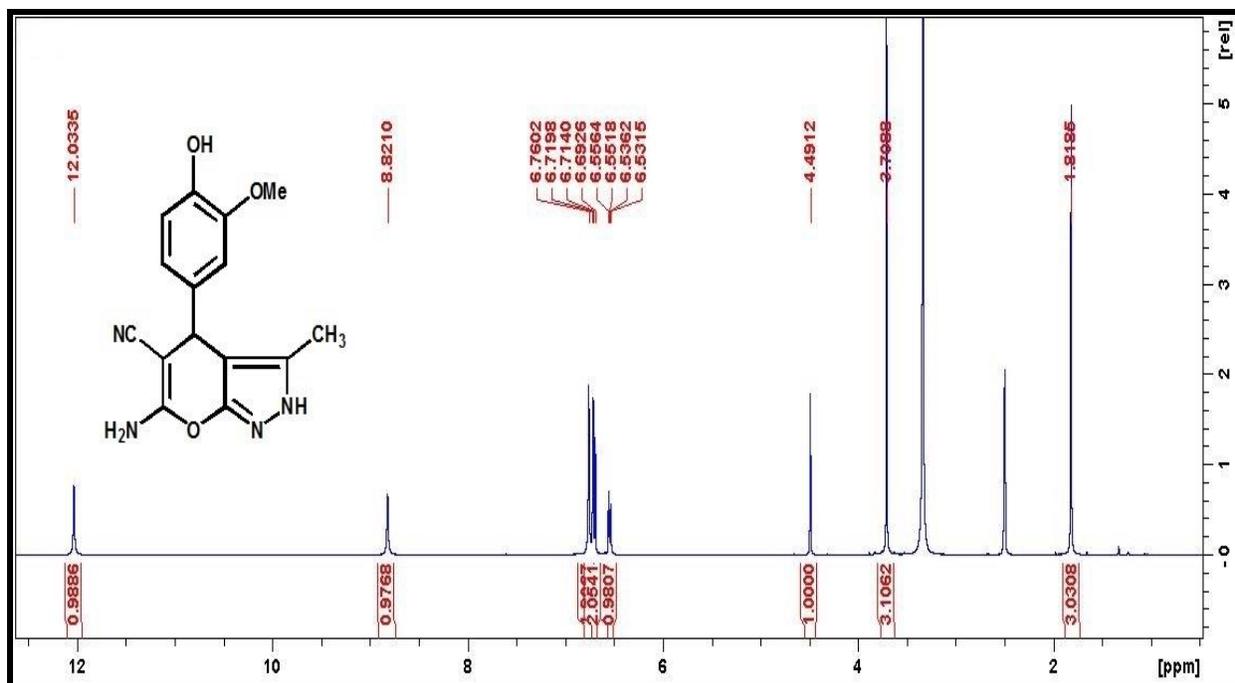
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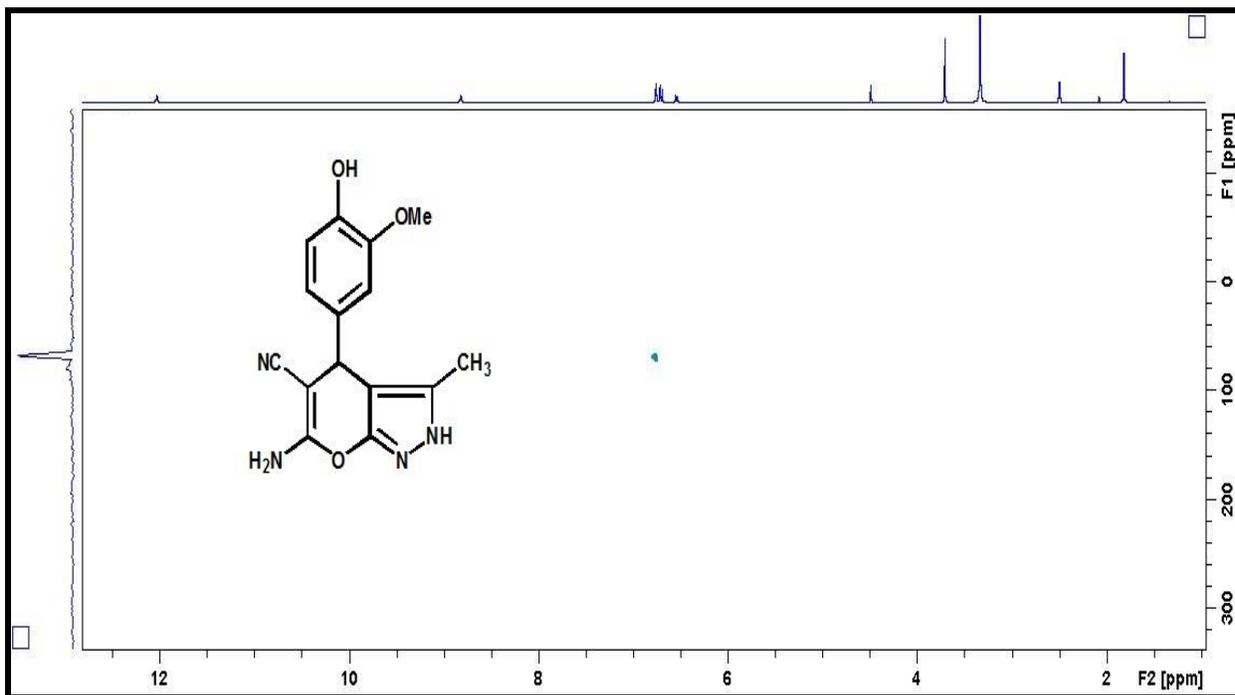
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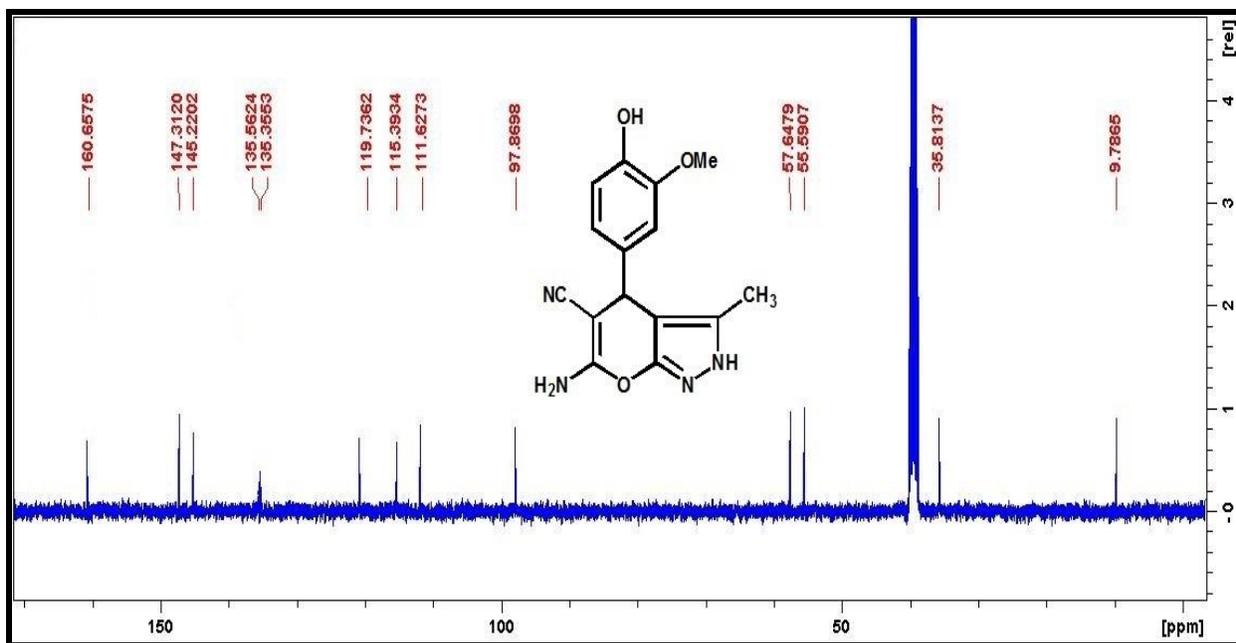
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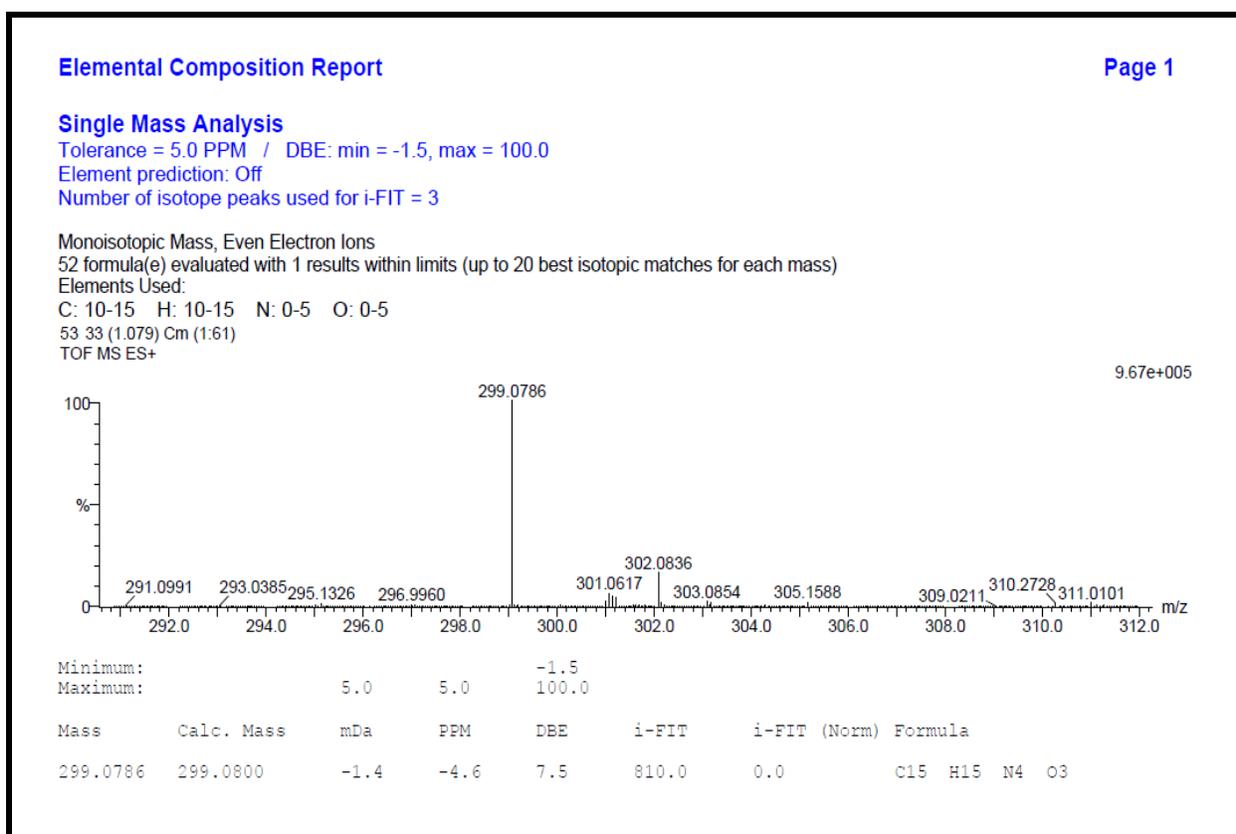
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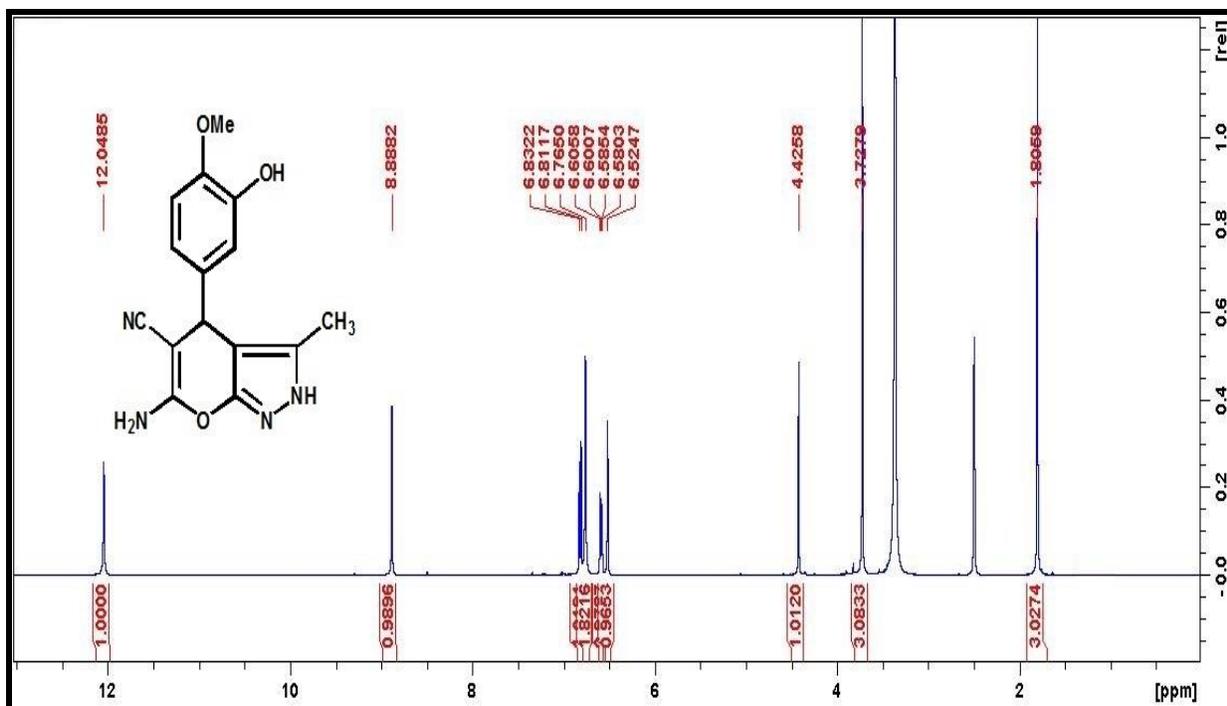
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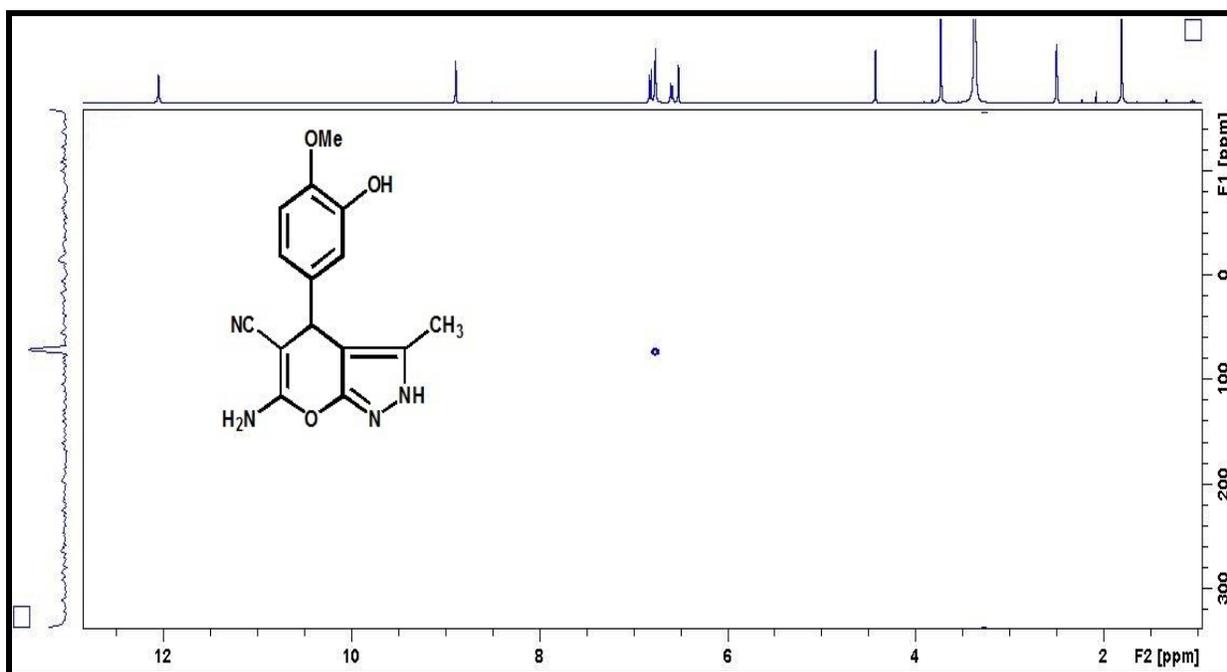
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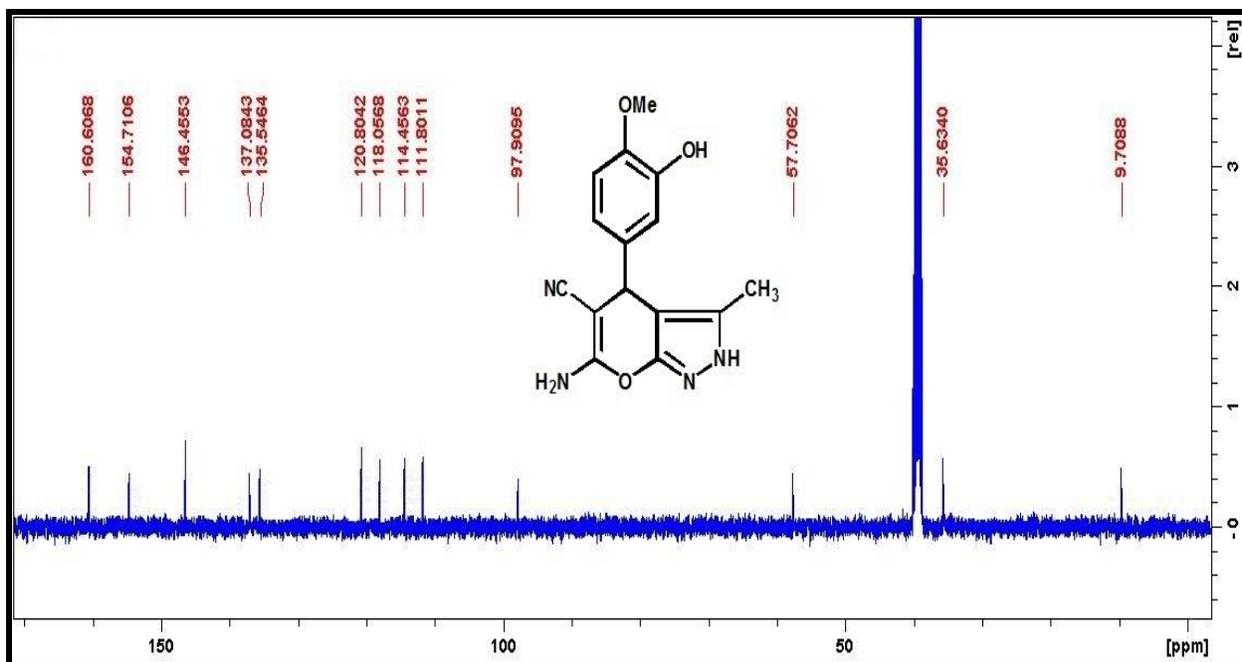
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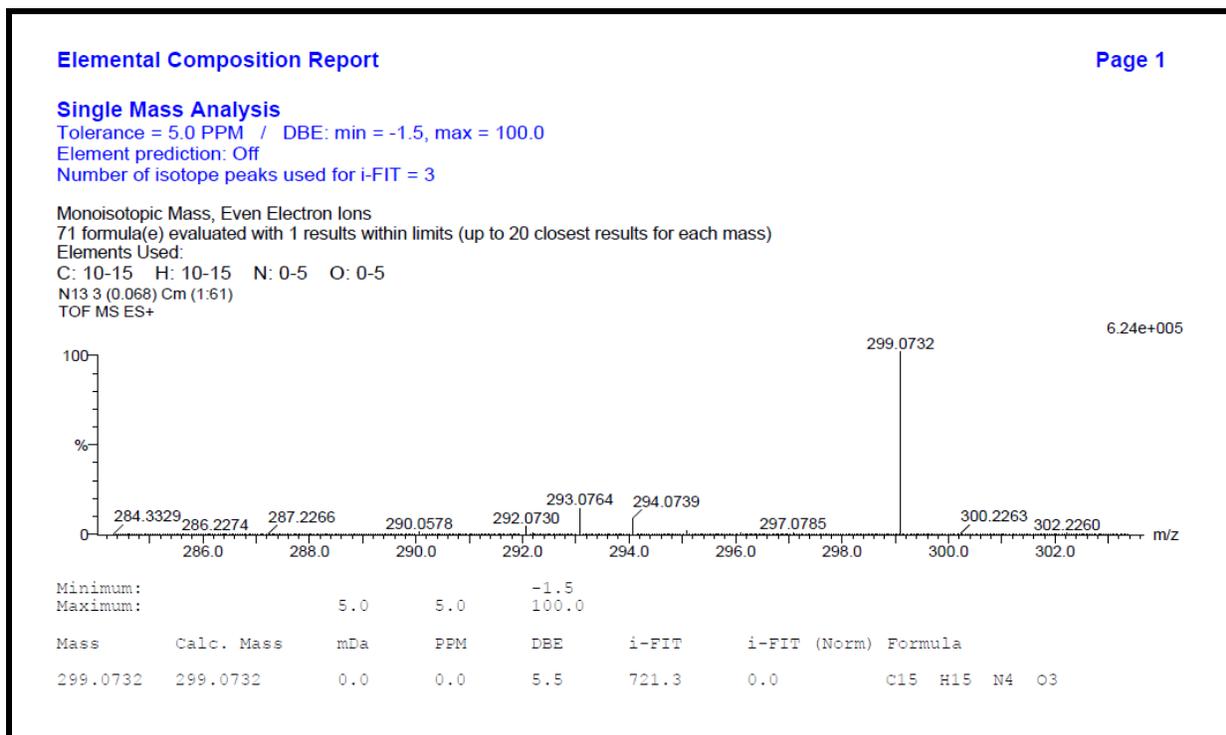
^1H NMR spectra of compound **5e**



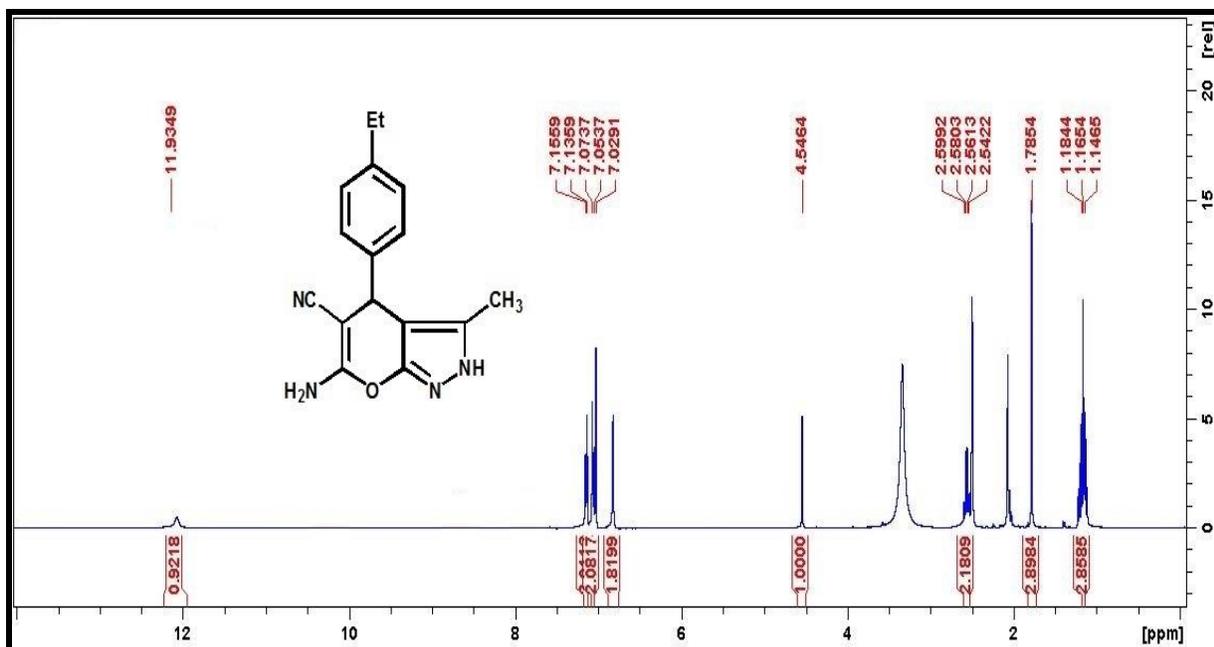
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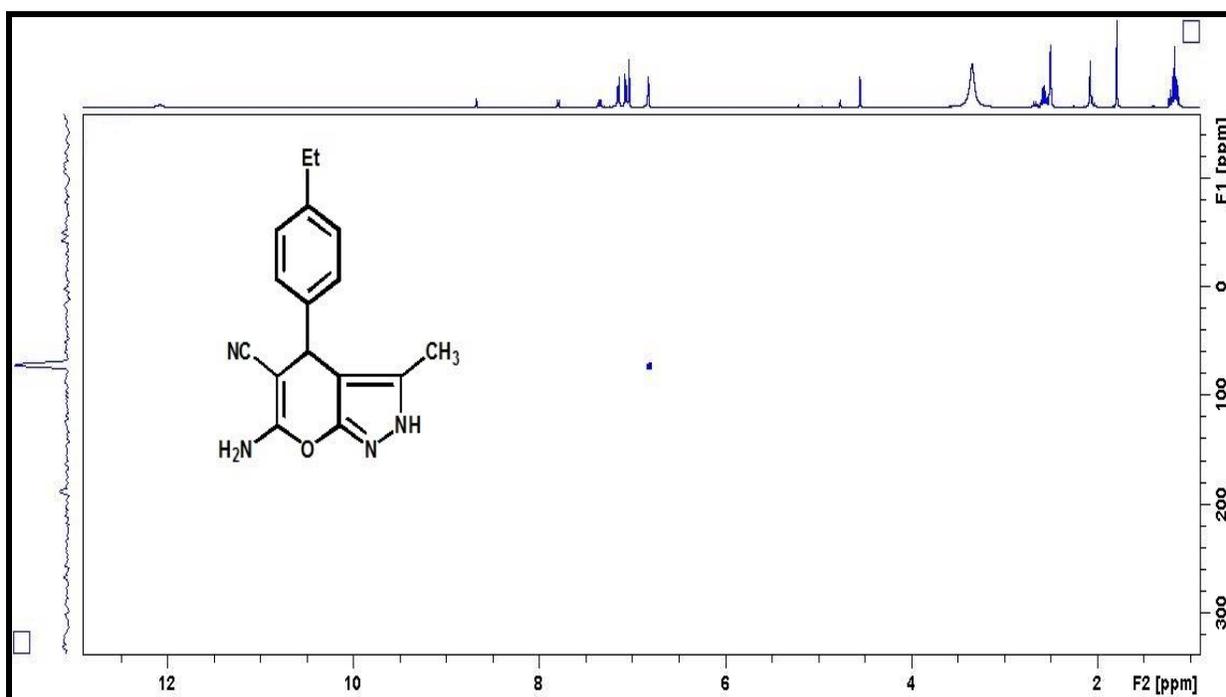
^{13}C NMR spectra of compound **5e**



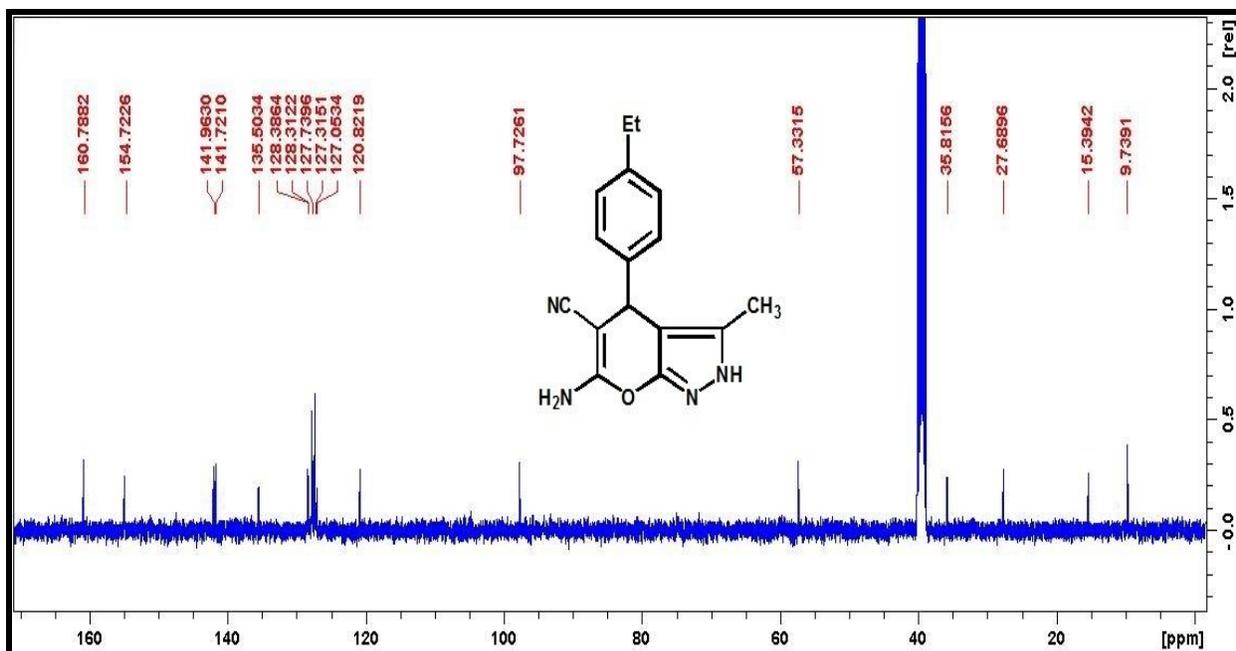
HR-MS spectra of compound **5e**



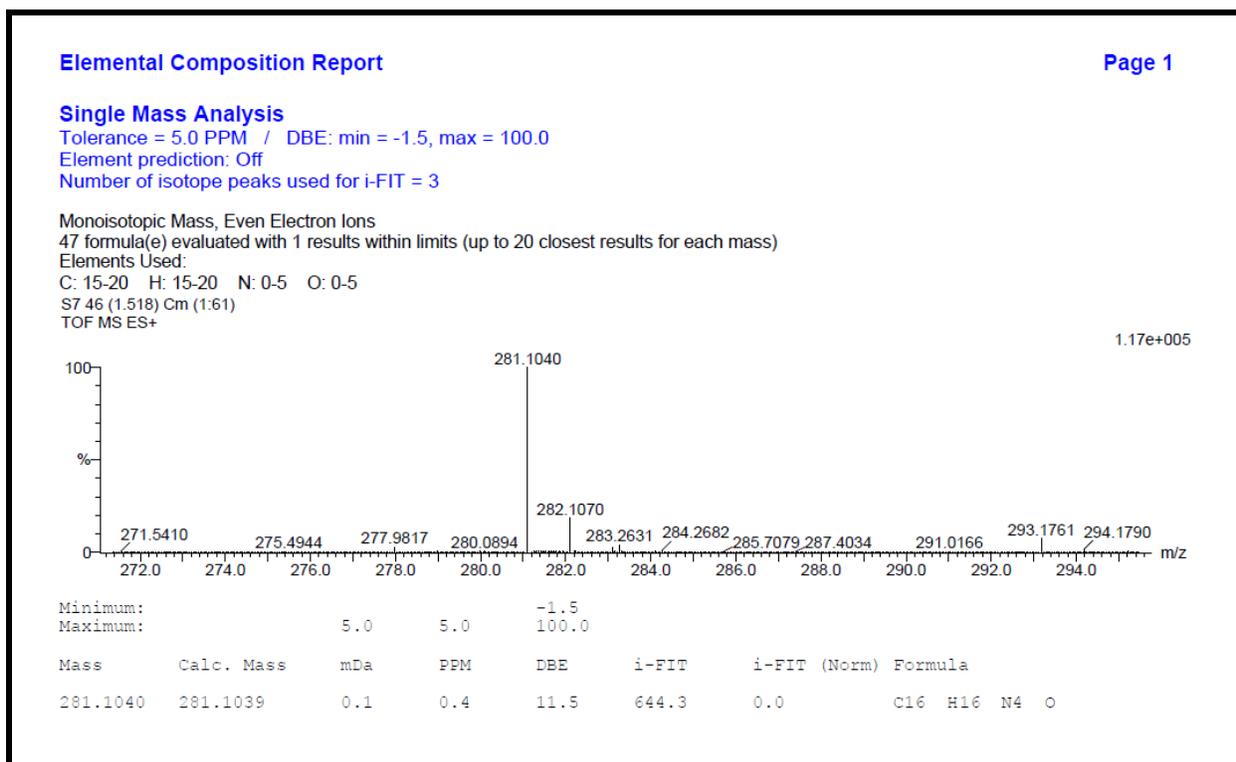
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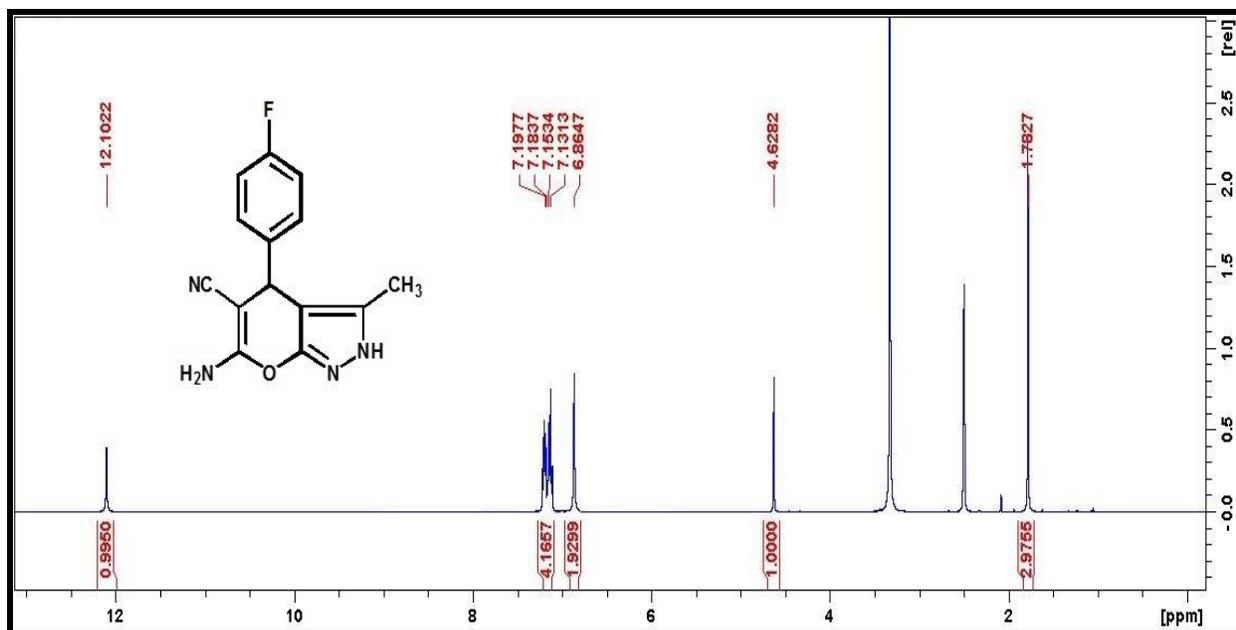
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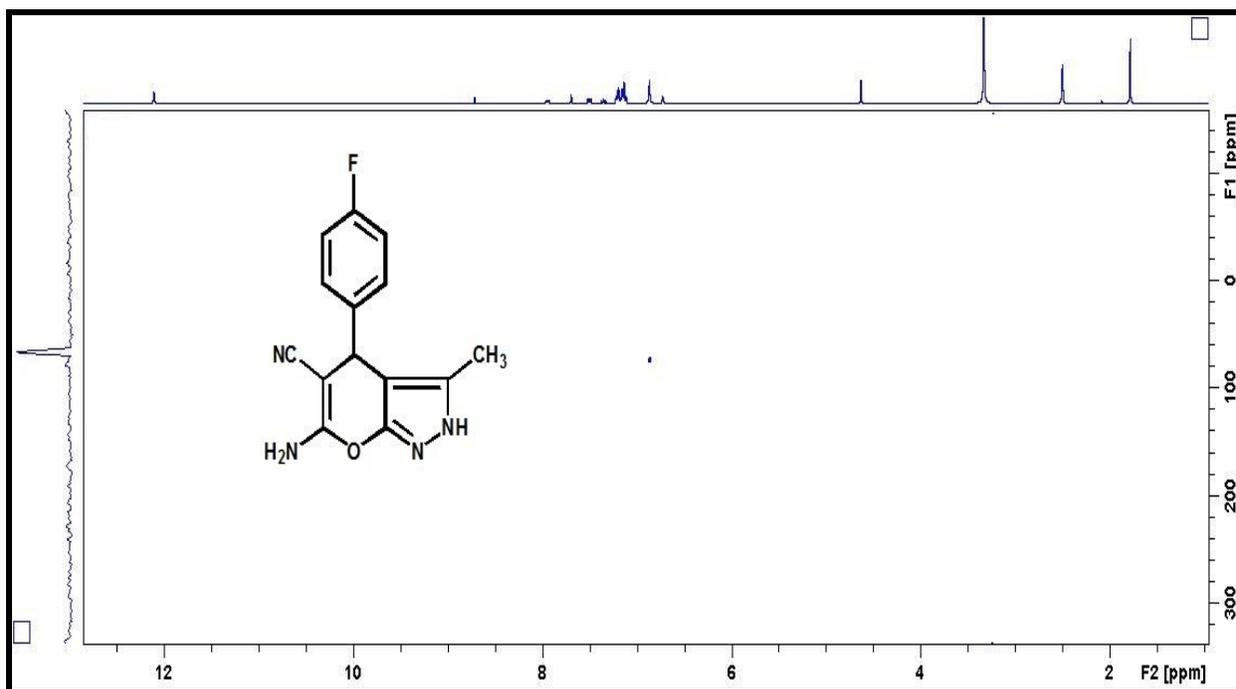
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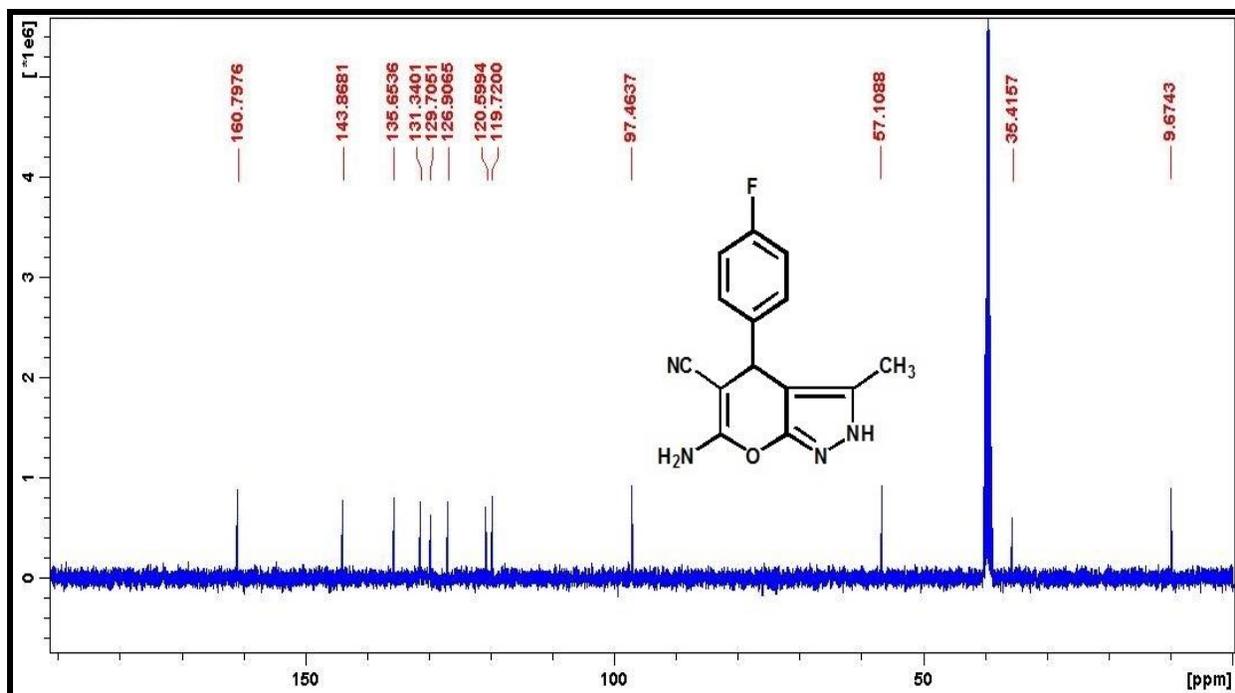
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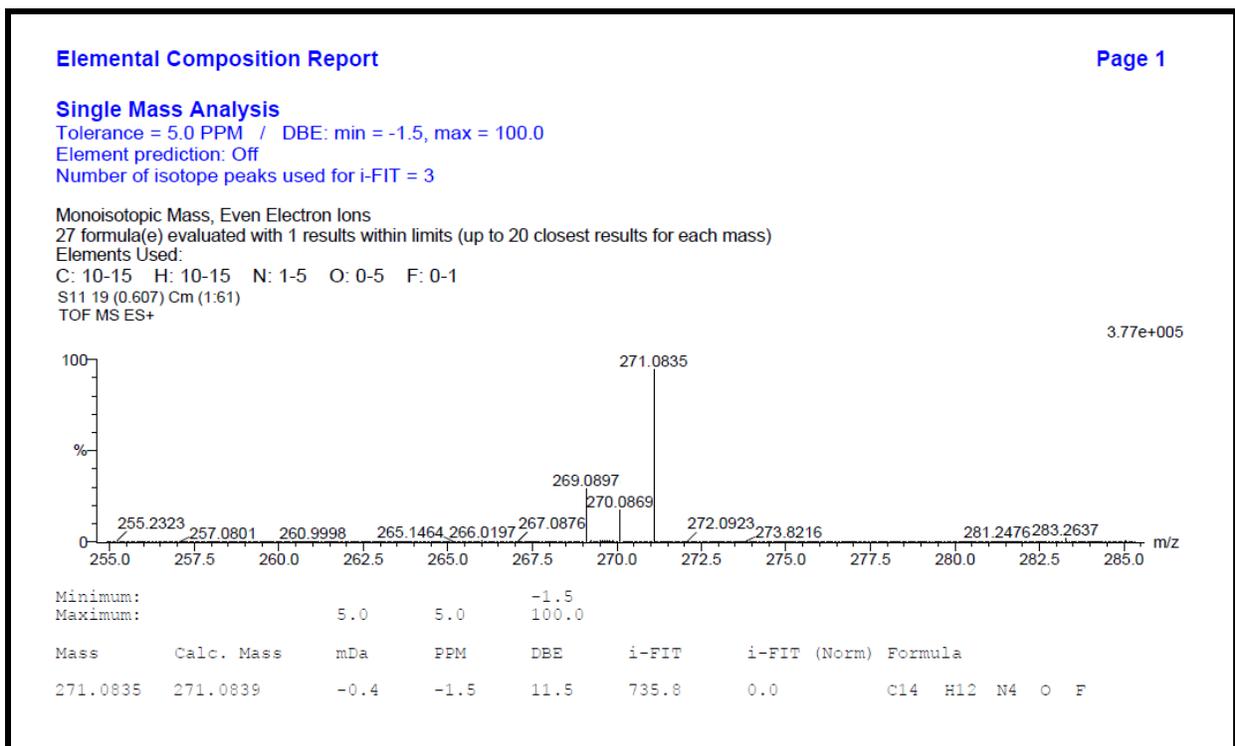
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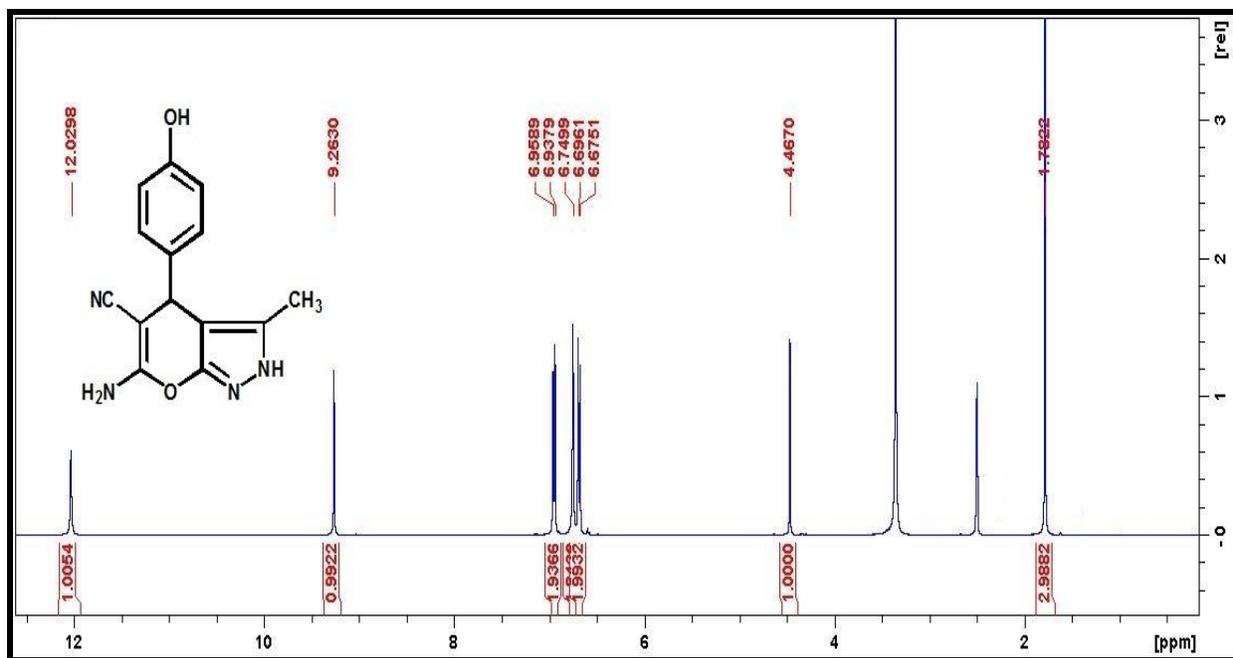
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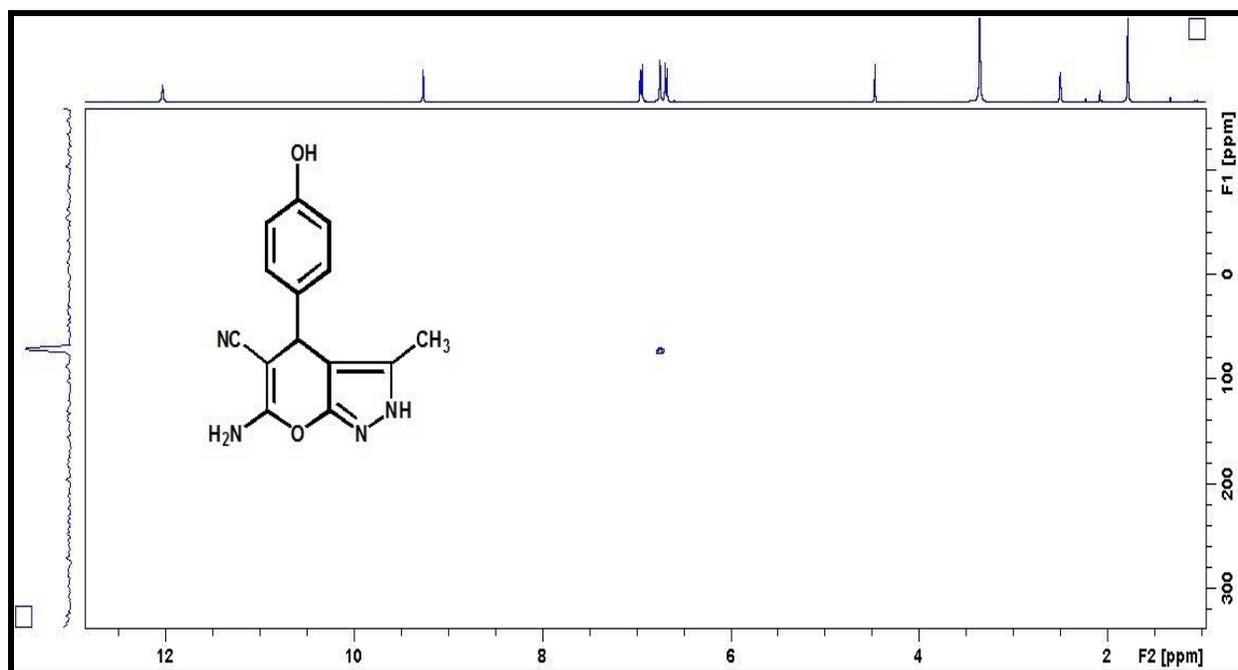
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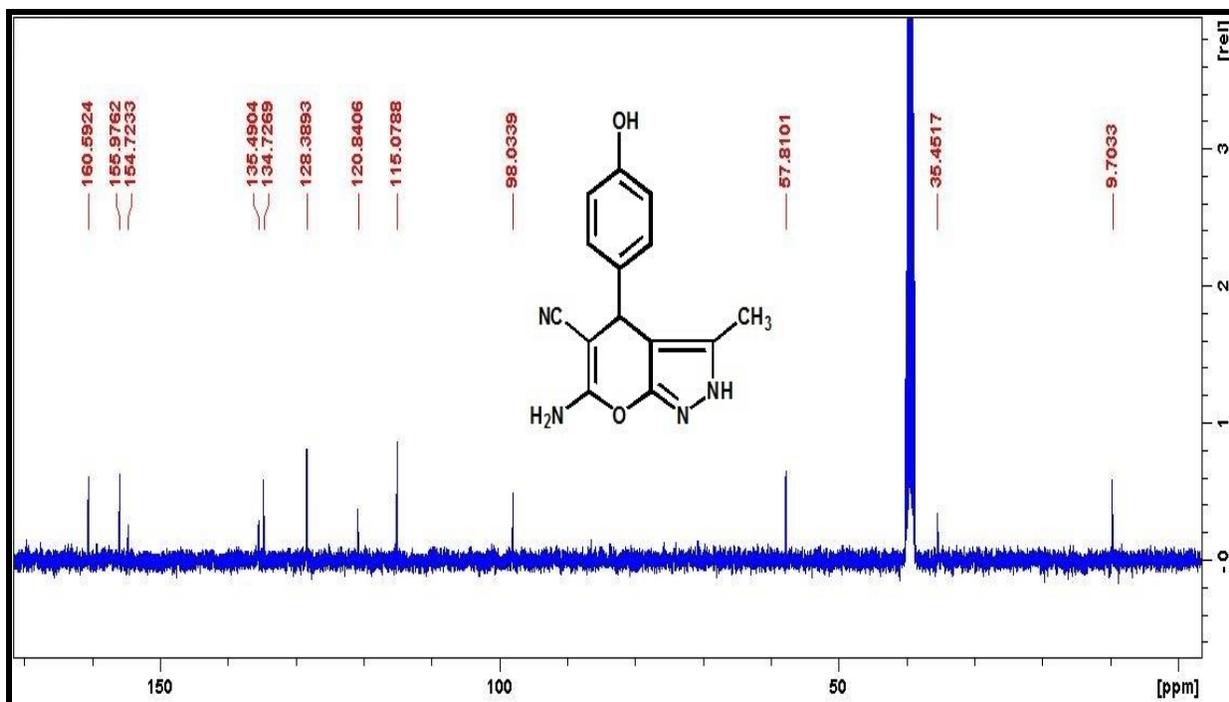
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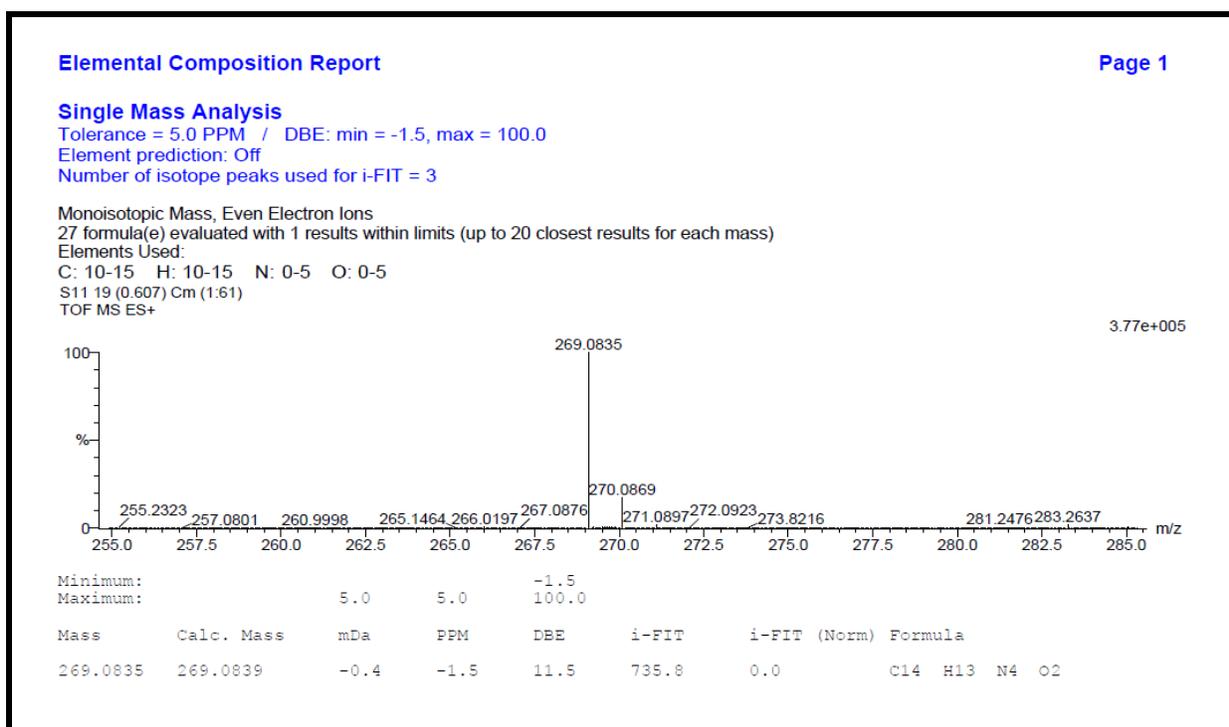
¹H NMR spectra of compound 5h



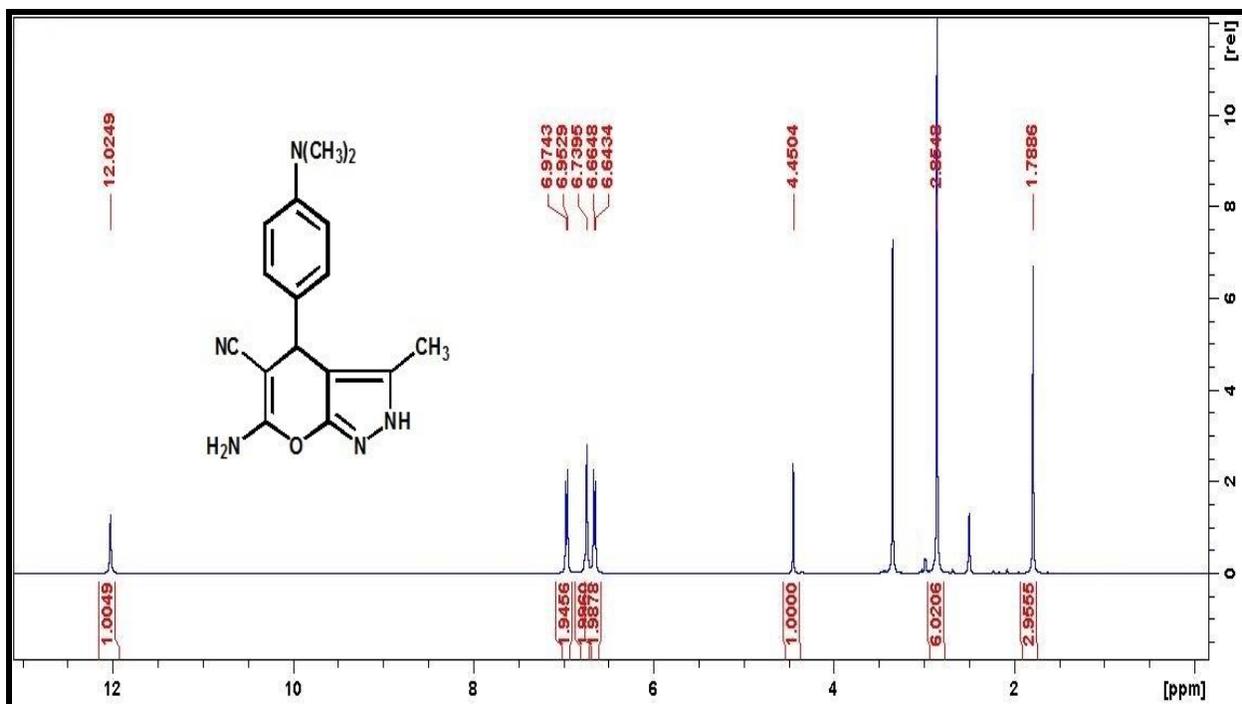
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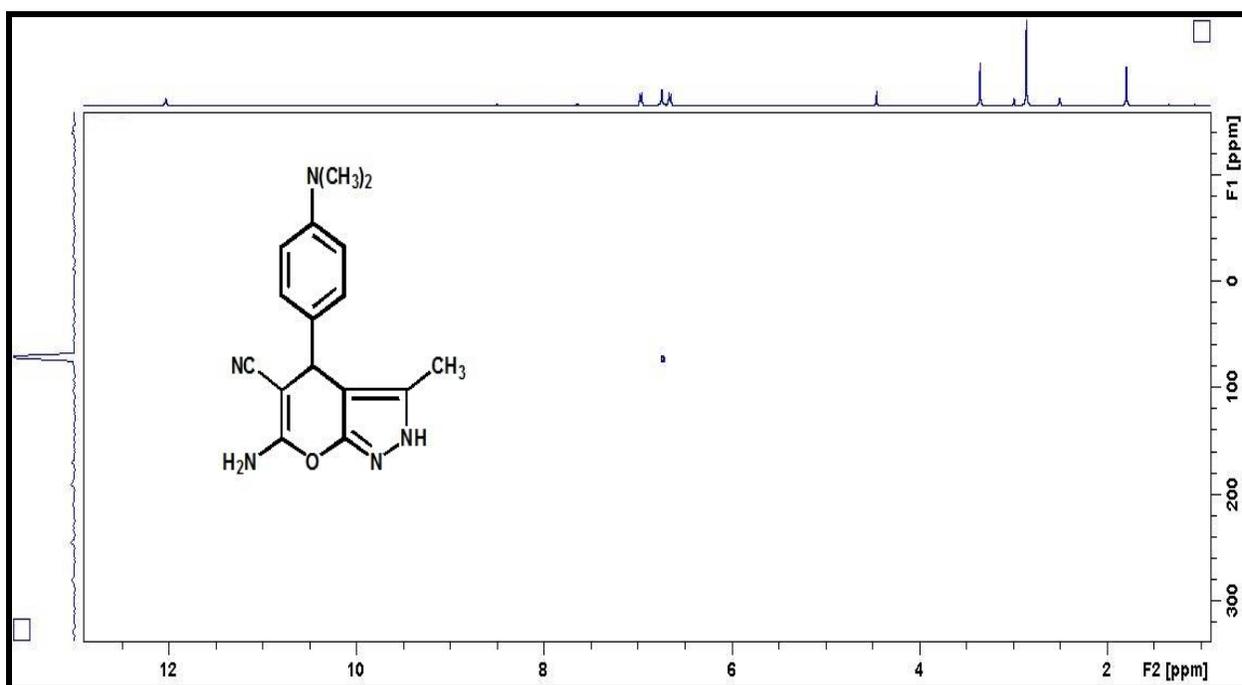
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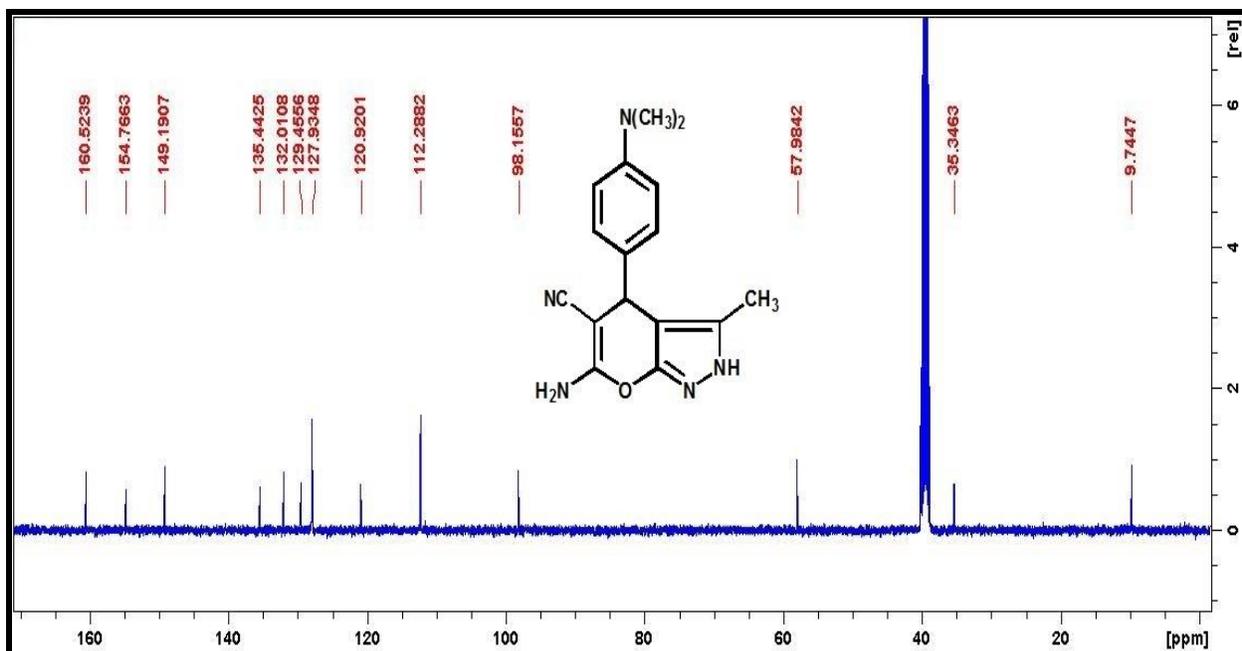
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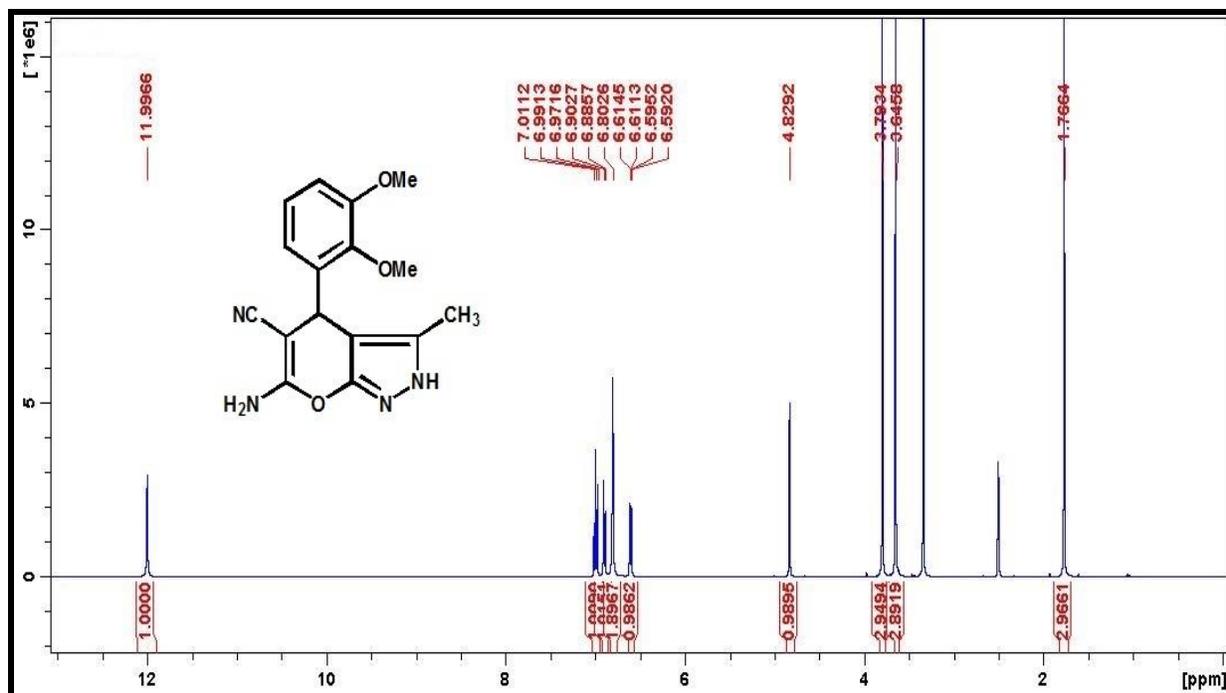
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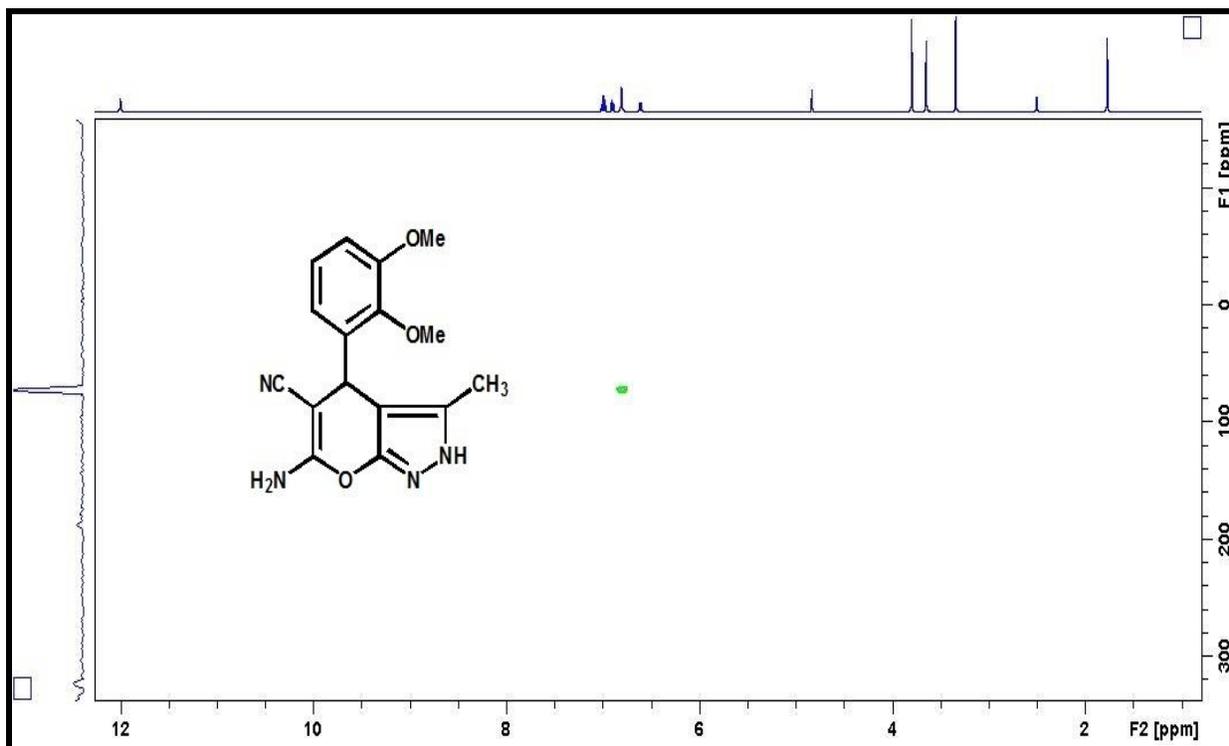
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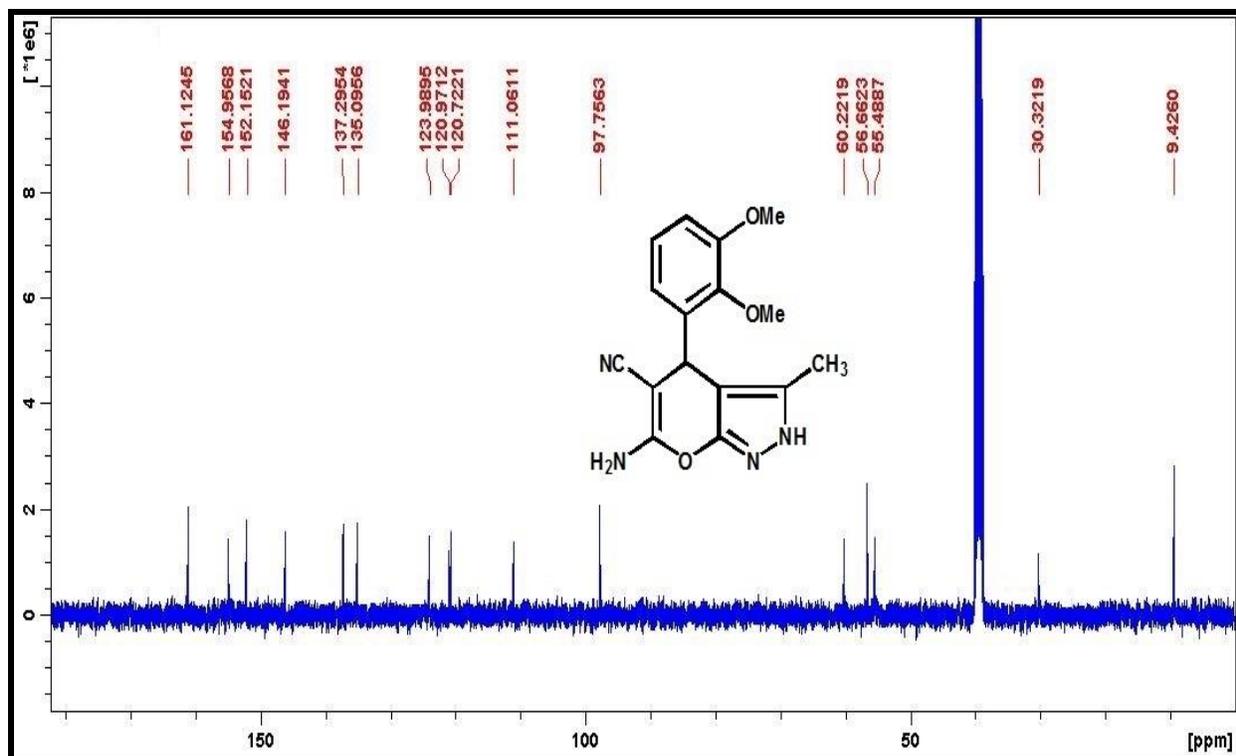
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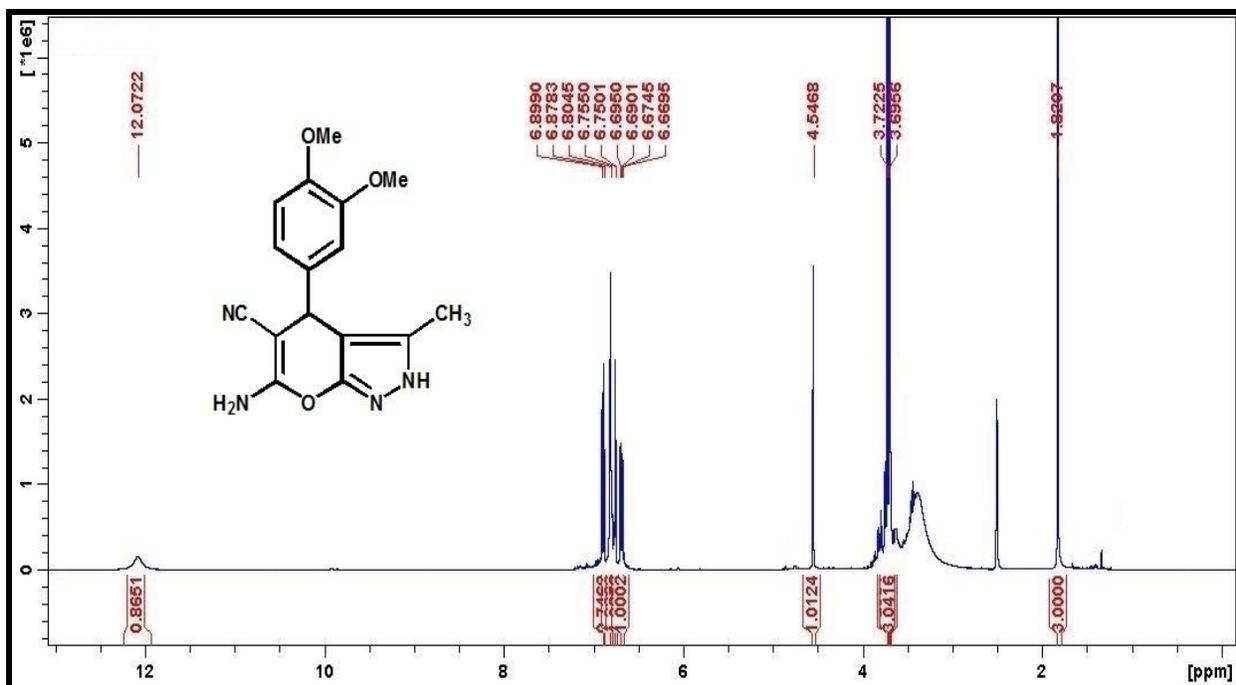
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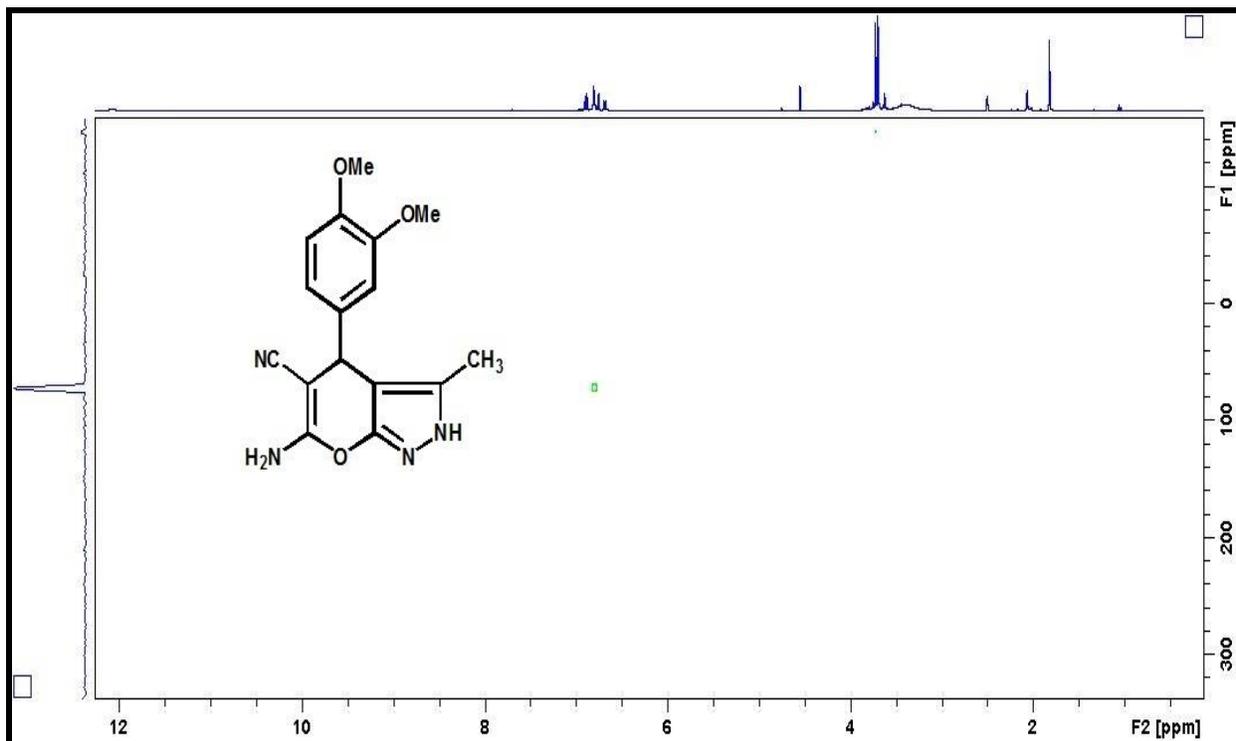
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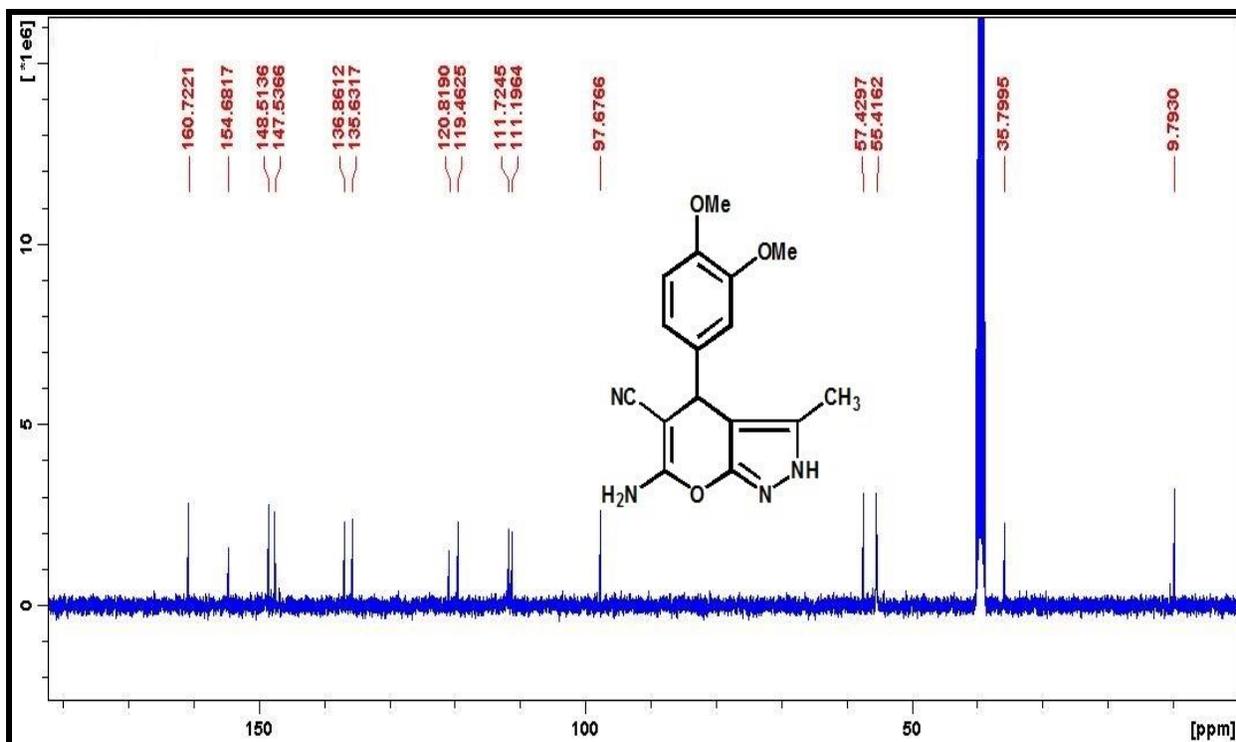
^{13}C NMR spectra of compound **5j**



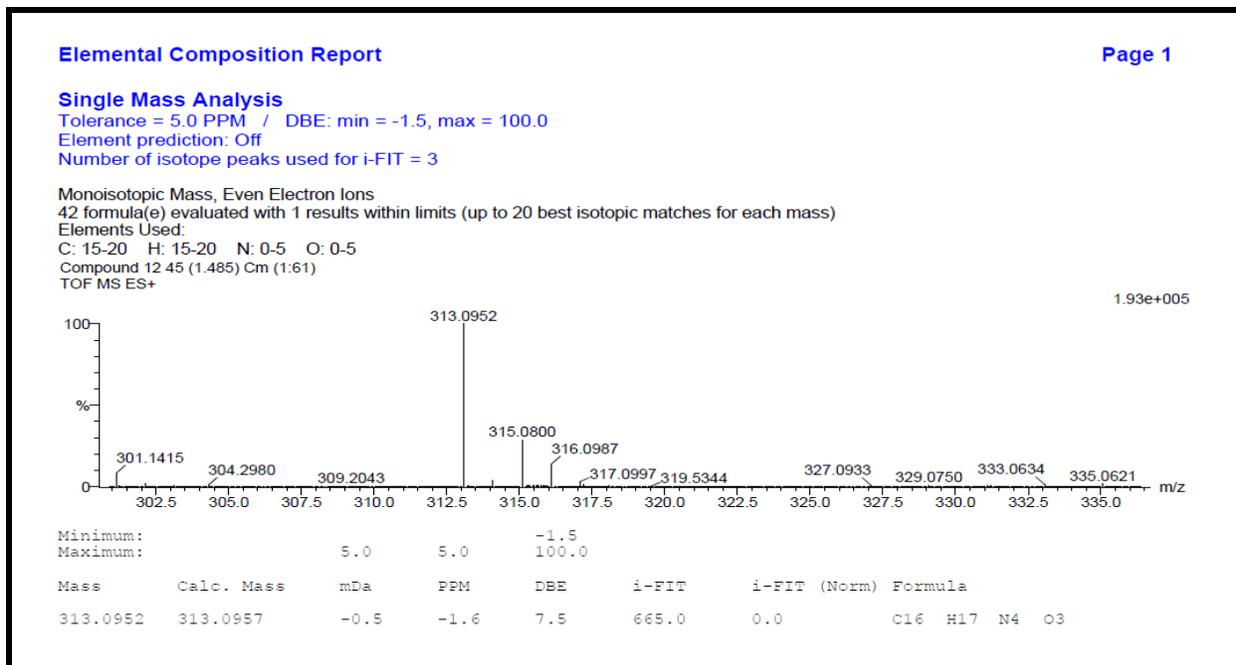
^1H NMR spectra of compound **5k**



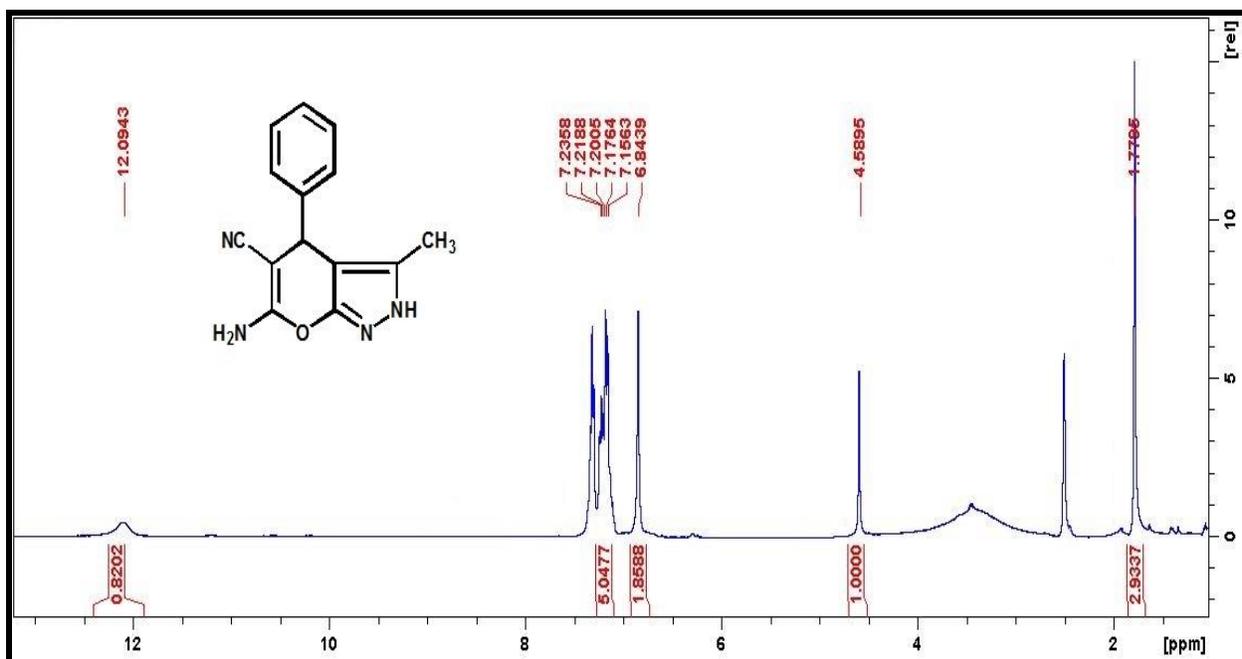
^{15}N NMR spectra of compound **5k**



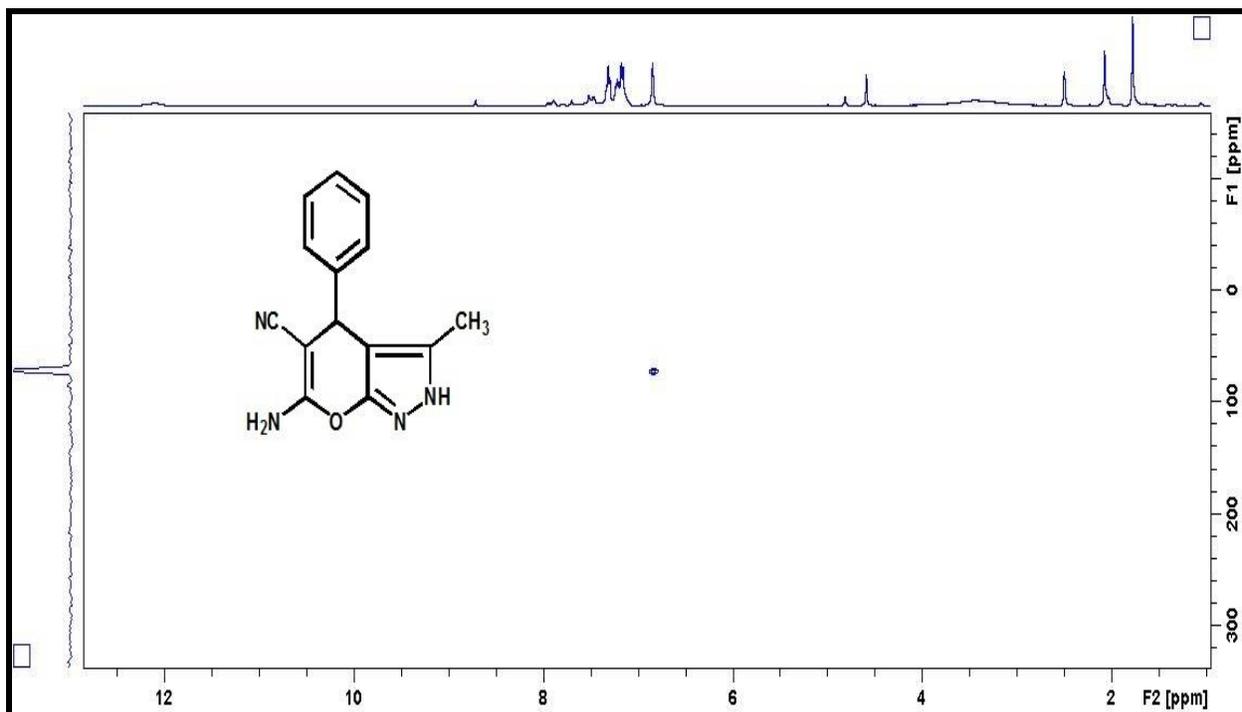
¹³C NMR spectra of compound 5k



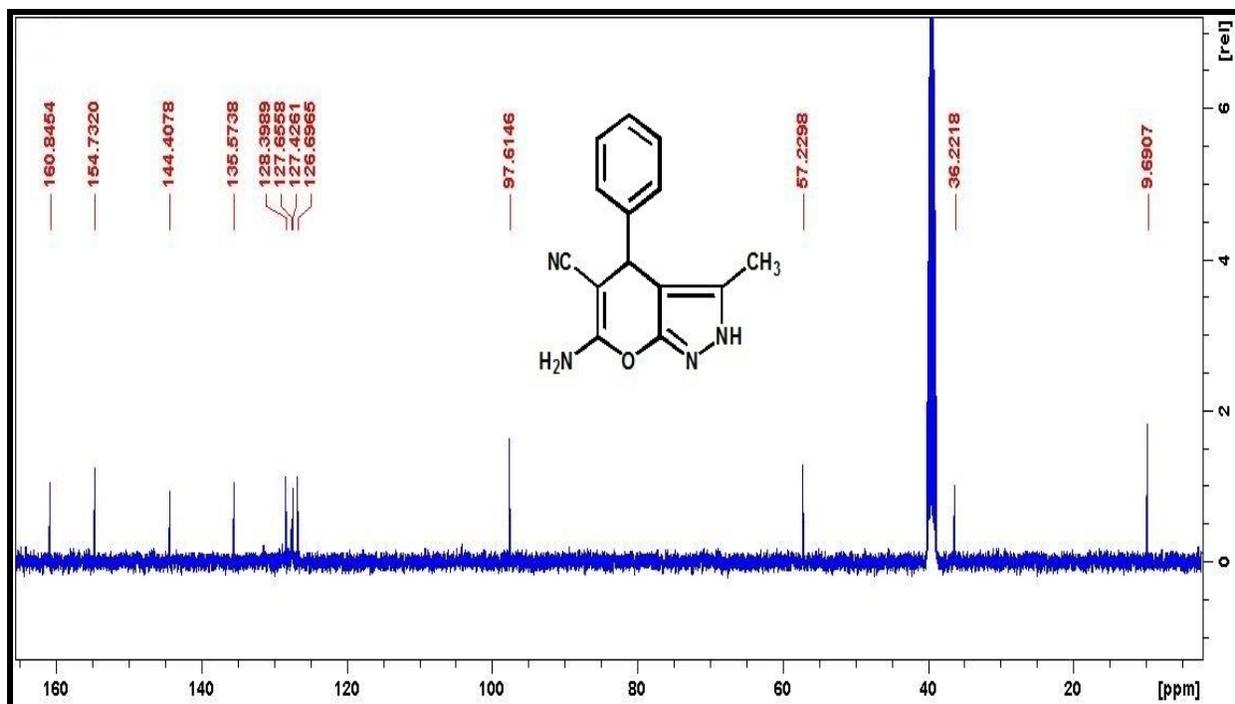
HR-MS spectra of compound 5k



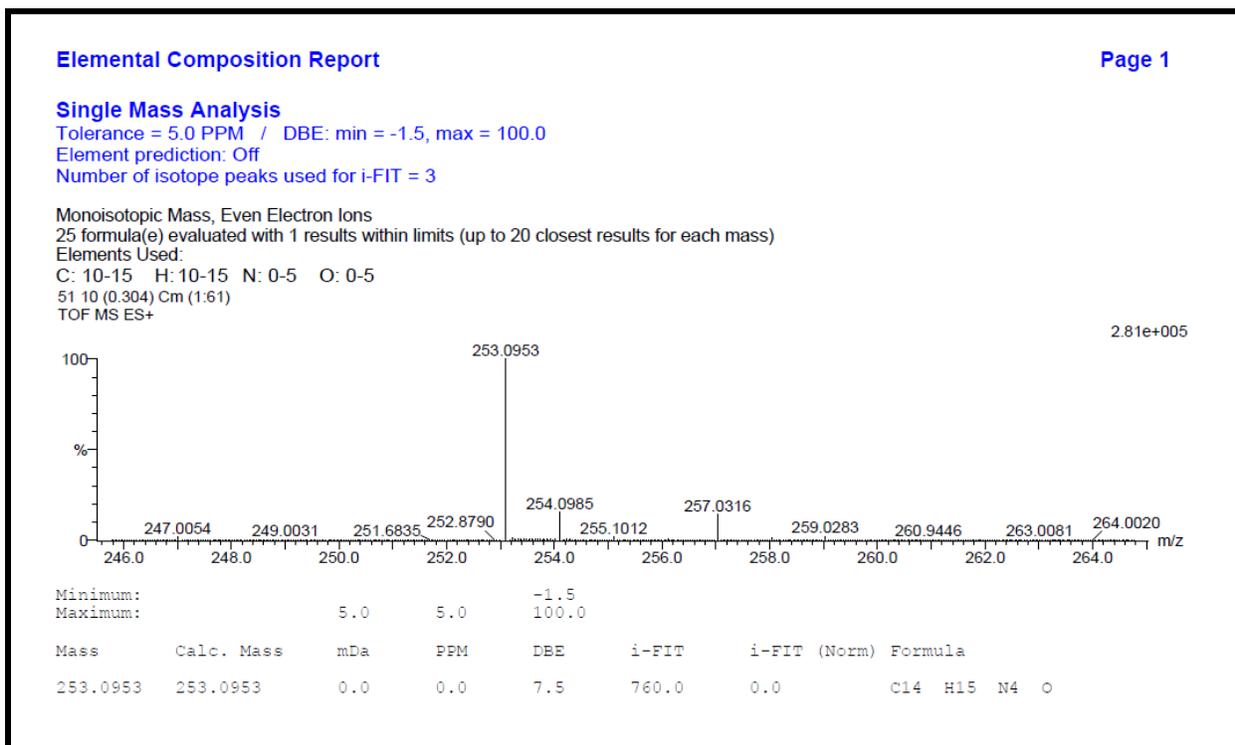
^1H NMR spectra of compound **51**



^{15}N NMR spectra of compound **51**



^{13}C NMR spectra of compound **5I**



HR-MS spectra of compound **5I**

CHAPTER-8

CONCLUSIONS

In this thesis, new heterogeneous mixed metal oxides and their modified analogues were developed; and their potential applications as catalysts for synthesis of varied heterocyclic molecules and their derivatives were evaluated. The major conclusions drawn based on the studies are presented below:

In chapter 1, a review of various mixed oxide catalysts is presented, emphasizing the significance of preparation, reusability and activity of heterogeneous catalysts and compiled the recent developments, breakthroughs, trends and unsolved problems in this area. This overview prepared ground to synthesize novel mixed oxide catalysts (typical supports used are CaHAp, SiO₂ and ZrO₂ and while oxides of Ag, Ce, Mn, Ru and V) as active components, and evaluate their catalytic performance in selected reactions. The mixed oxide materials are used as efficient catalysts for synthesis of structurally diverse heterocyclic derivatives. The improvement in surface area, morphology of metal oxides, mesoporosity, acidic and basicity etc., are the important factors, which positively contribute to the catalytic activity of this material. Compared to literature reported methods, the catalytic protocol developed in this work, were found to be advantageous in terms of recyclability, exclusion of toxic solvents, high yields and purity of the products. More importantly, considering the wider uses of mixed oxide catalysts in heterocyclic synthesis, the results and findings presented in the study would open new applications in “green” chemistry involving the recycling of such catalysts.

In the chapter 2, the challenging task was to prepare mesoporous silica with a highly ordered hexagonal structure and to manage the preservation of this organized structure after silver oxide incorporation. Thus, the study describes the successful synthesis of well-ordered mesoporous silica and AgO-modified silica in a simple, versatile, and reproducible process carried out by a bottom-up approach through a simple wet-impregnation method. The spectroscopic investigations on the material growth and formation mechanism revealed that the mixed oxide abilities of silver oxide with silica centers are the key factor, leading to successful well-ordered assembly process. The synthesis allowed the formation of well-organized active materials with large specific surface area and total pore volumes, as well as uniform and narrow

average pore size distribution. Interestingly, the presence of uniform mesoporous network with well-arranged circular pores with newly prepared materials, was illustrated by TEM micrographs. AgO greatly enhanced Lewis acidity of the supports, and Si-O-Ag-O species were mainly formed on the surface as illustrated with XRD and SEM-EDX analysis. The Ag doped silica material was used as an efficient catalyst for synthesis of structurally diverse 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives derivatives. The catalytic protocol developed in this work will be advantageous in terms of preclusion of toxic solvent, cost-effectiveness, high yield (88-93%) and purity of the products. The catalyst was easily separated from the reaction medium and recycled for six cycles with only a slight decrease of activity and small leaching of silver, when aldehydes, hydroxylamine and ethylacetoacetate were chosen as model substrates.

In chapter 3, the method for synthesis of novel class of manganese doped zirconia (Mn/ZrO₂) mixed oxide materials was developed. The constrained interlayer space (~ 5 nm) and high surface area (~168.47 m²/g) of Mn was used effectively to trap the ZrO₂ moieties in the adjacent space. The ZrO₂ moieties in the MnO₂ interlayer exhibit good thermal stability and resistance to condensation. Structurally diverse pyrano[2,3-*d*]-pyrimidines were synthesized by multicomponent one pot condensation of dimethylbarbituric acid, aromatic aldehyde and malononitrile compounds using aqueous ethanol as solvent and Mn/ZrO₂ as heterogeneous catalyst. The observed catalytic activity can be explained in terms of the presence of two types of acidic sites with different acid strength distribution, from the metal oxides, manganese dioxide and zirconia. The size of ionic Mn²⁺ is small when compared to Zr²⁺ ion. By introducing extrinsic dopant Mn, the defect environment is changed, whether the Mn atom substitutes the zirconia atom or it occupies the interstitial site. It clearly indicates that impregnated MnO₂ had a strong influence on the acidic properties of the ZrO₂, evident by increased activity, which due to the high surface area and good dispersion of MnO₂ on the surface of the support. Further, avoiding the use of toxic solvents, minimizing the amount of waste for each organic transformation, reasonable reaction times, easy purification, aqueous conditions, efficiency, green, inexpensive, mild, and economic availability of the heterogeneous catalyst are the other noticeable features of this method.

In chapter 4, a novel class of ceria and vanadia loaded silica mixed oxide (Ce-V/SiO₂) material containing surface acidic-basic bifunctional groups was synthesized employing cerium nitrate, vanadyl sulfate as metal salts and silica as support. This could be attributed to the property of Ce-V/SiO₂ where the high surface area presumably enhanced the accessibility of the substrate to the anchored acidic and basic groups on the catalyst surface. The optimal distribution of the acidic and basic sites on SiO₂ possibly contributed to its enhanced catalytic efficiency, which is evident from the high yield, selectivity and speed of the reaction achieved in the title reaction. The Ce-V/SiO₂ catalytic system efficiently catalyzes the synthesis of 2-amino-3-cyano-4*H*-pyrans by one pot condensation of 5,5-dimethylcyclohexane-1,3-dione, aromatic aldehyde and malononitrile. The synergistic effect between the acidic sites of the silica lattice and the basic sites of the metal is responsible for synthesis of structurally diverse pyrans in good to excellent yield under mild conditions.

For chapter 5, the study reports a new one-pot methodology for the preparation of the ruthenia doped hydroxyapatite (Ru-HAp) and its efficacy as catalyst in highly efficient synthesis of pyranopyrazoles with a single annealing step. This synthesis strategy was simple, fast and cost-effective, and offers access to Ru-HAp with better features and higher synthesis yields (87-95%) compared to other approaches. These enhanced properties including textural (larger surface area) and highly dispersed active surface sites led to improved target molecule. They are also accompanied by intrinsic Lewis basicity of HAp functions, which are capable of bonding with carbonyl oxygen of the substrates assisting in generation of ionic intermediates through activation of reactants. Therefore, these results are very promising towards opening up future opportunities for robust heterogeneous catalysts design as well as towards large-scale pyranopyrazole applications.

For the first time, Ru doped hydroxyapatite (Ru-HAp) was utilized in synthesis of pyrano[2,3-*c*]pyrazole-3-carboxylate derivatives on at room temperatures in this study. Chapter 6 detailed these results. The mixed oxide Ru-HAp catalyst displayed excellent catalytic activity, because of the larger surface areas associated with nano-sized particles provide more accessible active sites. The synthesized catalysts possess a large BET surface area in the range of 146-200 m²/g and a mesoporous pore size in the range of 80-110 Å. Ca series catalysts display stronger basicity (H = 10.0 -15.0). All these excellent physico-chemical properties resulted in a very high

catalytic activity of synthesized catalysts. Recycling experiments showed that the catalyst could be used without a significant yield drop for 6 cycles.

In chapter 7, the high surface area and mesoporosity of zirconia was effectively utilized for supporting ceria oxide particles and ceria loaded zirconia was developed as effective catalyst. The ZrO₂ supported Ce metal particles exhibited efficient condensation activity for synthesis pyrano[2,3-*c*]-pyrazoles under ethanol solvent and mild condition. Zirconia is more acidic than ceria, and the insertion of ceria into the zirconia lattice leads to a decrease in the acid strength of selective sites. The acidic centers of the zirconia provides adsorption sites for the compounds whereas the ceria metal is responsible for the condensation activity. Furthermore, it is noticeable that as the ceria content gets higher, the particles size increases and the surface area marginally decreases.

Optimization

Optimising the novel reaction conditions revealed that green solvents such as water, ethanol and aqueous ethanol are quite appropriate for the synthesis of various heterocyclic compounds like pyranopyrazoles, pyrano[2,3-*c*]pyrazole-3-carboxylates, 2-amino-3-cyano-4*H*-pyrans, pyrano[2,3-*d*]-pyrimidines and isoxazoles derivatives. A highly polar solvent, ethanol, which dissipates heat faster may provide optimum conditions for formation of intermediates, and their conversion to final products on the catalyst surface. Ethanol has proved ideal solvent for the preparation of the various heterocyclic derivatives in this study. Polar solvents such as water and ethanol gave excellent yields. This effect can be explained by a simple acid-base bi-functional catalysis mechanism facilitated by the strong hydrogen bond interaction at the organic–aqueous ethanol interface, which stabilizes the reaction intermediate.

Current studies showed that the scope of green principles for synthesis varied heterocyclic moieties and their derivatives at moderate reaction conditions using selective reusable heterogeneous catalysts with high efficiency. All the reactions for the synthesis of these compounds were optimized in terms of solvent, catalyst amount and reaction temperatures in order to achieve the preferred product in good to excellent yields in very short reaction times. This thesis described six protocols for successful synthesis of series of novel isoxazoles, pyrano[2,3-*d*]-pyrimidines, 2-amino-3-cyano-4*H*-pyrans, pyranopyrazoles and pyrano[2,3-

c]pyrazole-3-carboxylate derivatives tetrahydropyrazolopyridine and dihydropyranopyrazole derivatives under green solvent conditions in the presence of suitable heterogeneous catalysts at room temperature in short reaction times in good to excellent yields.

Future work

- Study the multicomponent reaction products for their further synthesis of fused heterocyclic compounds.
- To investigate the biological activities (anticancer, anti-oxidant and anti-microbial) of the synthesized products
- To examine the application of the new heterogeneous materials as catalysts in other fields, such as catalysed and photocatalysed degradation of organic pollutants in water systems.