SYNTHESIS OF PYRIDINES BY USING METAL OXIDES ON ZIRCONIA SUPPORT AS CATALYSTS

by

SEBENZILE BEAUTY SHABALALA

UNIVERSITY OF KWAZULU-NATAL

Submitted in fulfillment of the academic requirements for the degree of

Master of Science in the Chemistry, School of Chemistry & Physics

College of Agriculture, Engineering and Science

University of KwaZulu-Natal

Durban

May 2017

As the candidate's supervisor I have approved this thesis for submission

Supervisor: **Prof. Sreenkantha Jonnalagadda**

Signed:…….. Date: …….

Co-Supervisor: **Prof. Werner Van Zyl**

Signed:…….. Date: ……

ABSTRACT

In recent years, there has been a concern for the development and design of sustainable chemical routes, which resulted in Green Chemistry, a concept that became popularized in the 1990s with the intention to reduce pollution. It encouraged the planning of chemical processes to attain a final product that would, amongst other things, use the same amount of input materials, the use of green solvents as well as the use of environmentally friendly materials, which are non-toxic.

Multicomponent reactions (MCRs) have become very attractive subjects in organic synthesis due to the formation of C-C and C-hetero atoms in a one-pot synthesis. They have emerged as processes with considerable ecological interest as they address the fundamental principles of synthetic efficiency and reaction design. This arises from minimization of waste, time, energy, and cost. In this study, heterogeneous catalysts with an increased activity have been synthesized and applied as easily recoverable catalysts, and focused on the effect of heterogeneous catalysts reaction's parameters on the catalytic activity and selectivity of 1, 4-dihydropyridines synthesis.

Heterocyclic structures are commonly useful templates for the design and improvement of potent and specific biologically active agents. Pyridines and their derivatives form an important class of heterocyclic compounds and owing to their properties are desired in many different fields, such as natural products, pharmaceuticals, and functionalized materials. They also show a wide range of biological properties, such as antibacterial, antioxidant, antiviral, anticancer, anticonvulsant and antihypertension activity. Pyridines are also known for their anti-inflammatory activity and can act as antagonist's inhibitors.

This study is based on the development efficient and environmental-friendly techniques and routes for the synthesis of heterocyclic compounds (pyridines), in the presence of variety of reusable catalysts.

The synthesis of functionalized 1,4-dihydropyridine derivatives by the incorporation of dimethylacetylenedicarboxylate, 4-fluoroaniline, malononitrile with various substituted

benzaldehydes using Sm_2O_3/ZrO_2 as catalyst with ethanol as solvent and at room temperature has been achieved with (87-96%) yields.

A CeO_2/ZrO_2 heterogeneous catalyst was employed for the synthesis of pyridine derivatives *via* a one-vessel, four-component reaction consisting of substituted benzaldehyde, malononitrile, dimethylacetylenedicarboxylate and dimethylaniline. Eleven compounds were synthesized giving yield of (87-95%).

An efficient four component/one-pot protocol was developed for synthesis of functionalized pyridine derivatives by reacting dimethylacetylenedicarboxylate, 4-bromoaniline, malononitrile with various substituted benzaldehydes in the presence of Y_2O_3/ZrO_2 as catalyst. Excellent yield of (88-95%) were obtained.

The noteworthy advantages of this basic method are the use of ethanol as a solvent, excellent yields and shorter reaction times. Most catalysts were reusable for up to seven cycles. Powder X-ray diffraction, TEM, SEM and N_2 adsorption/desorption analysis techniques were employed for the structural interpretation of the catalysts. The identity of target products were established and confirmed by diverse spectral (^{1}H NMR, ^{13}C NMR, ^{15}N NMR, FT-IR and HRMS) techniques.

DECLARATIONS

DECLARATION 1 - PLAGIARISM

I, **Sebenzile Beauty Shabalala,** declare that

1. The research reported in this thesis, except where otherwise indicated is my original research.
2. This thesis has not been submitted for any degree or examination at any other university.
3. This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
4. This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

a. Their words have been re-written but the general information attributed to them has been referenced

b. Where their exact words have been used, then their writing has been placed in italics and inside quotation marks, and referenced.

5. This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the References sections.

Signed: ……

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. **Sebenzile Shabalala**, Suresh Maddila, Werner E. van Zyl and Sreekantha B Jonnalagadda, A facile, efficacious and reusable Sm_2O_3/ZrO_2 catalyst for the synthesis of functionalized 1,4- dihydropyridine derivatives. **Catalysis Communications,** (79) 21–25, 2016. http://dx.doi.org/10.1016/j.catcom.2016.02.017

   My contribution: All the pyridines and derivatives were synthesized and characterized by me under the supervision of Prof. Jonnalagadda (Supervisor), Prof van Zyl (Co-author) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article.

2. **Sebenzile Shabalala**, Suresh Maddila, Werner E. van Zyl and Sreekantha B Jonnalagadda, Sustainable CeO_2/ZrO_2 catalyst for the green synthesis of highly functionalized 1,4-dihydropyridine-2,3-dicarboxylate derivatives. *(Revised manuscript submitted to Current Organic Synthesis)*

   My contribution: Synthesis and characterization of all compounds and derivatives were done by me under the supervision of Prof. Jonnalagadda (Supervisor) Prof van Zyl (Co-author) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article.

3. **Sebenzile Shabalala**, Suresh Maddila, Werner E. van Zyl and Sreekantha B Jonnalagadda, An innovative and simple protocol for the synthesis of 1,4-Dihydropyrines using a highly stable and efficient Y_2O_3/ZrO_2 catalyst *(submitted to a journal for publication)*

   My contribution: Synthesis of all compounds and their derivatives as well as the characterization were done by me under the supervision of Prof. Jonnalagadda (Supervisor) Prof van Zyl (Co-author) and Dr. S. Maddila (Postdoctoral fellow working under Prof. Jonnalagadda) and drafted the article.

Signed:……....

ACKNOWLEDGEMENTS

I would first like to thank the Sovereign God Jesus Christ for keeping and humbling me until this day and the scripture, which kept me going Mattew 6:33 "But seek ye first the kingdom of God, and his righteousness; and all these things shall be added unto you".

I thank my supervisors Professors S.B. Jonnalagadda and W.E. van Zyl for the opportunity and guidance that they gave me throughout the research and write up. I really appreciate it.

The University of KwaZulu-Natal, I acknowledge it for the platform it has given me to do the research as well as Prof. S.B. Jonnalagadda, for bursary given from his NRF grant holder funds. It was not going to be easy without that bursary.

I would like to convey my warmest gratitude to Dr Suresh Maddila, who has guided me from day one until the end. He has been such a wonderful research adviser; he assisted in every possible means one could offer.

This one goes to my research group members Gracious Shabalala, who did not only share a lab with me but also became a loving and caring sister to me. Surya Narayana Maddila, who assisted me in various ways, as well as the rest of the research group members, Vuyolwethu Ndabankulu, Bhekumuzi Gumbi and Mlungisi Sithole.

Special thanks to my parents, Pheneas Shabalala and Gugu Shabalala, as well as my fiancé Siyabonga Mbatha. They have been supporting me emotionally, financially and mentally. They were there through all the hardships and challenges I went through. Thank you

CONFERENCE PARTICIPATION

1. **Sebenzile Shabalala**, Suresh Maddila, Werner E. van Zyl and Sreekantha B Jonnalagadda "A facile, efficacious and reusable Sm/ZrO_2 catalyst for the synthesis of functionalized 1,4-dihydropyridine derivatives". (Oral presentation at the **42nd National Convention of the South African Chemical Institute Conference** 29 Nov. - 4th December, 2015 at ***Elangeni Hotel, Durban***

2. **Sebenzile Shabalala**, Suresh Maddila, Werner E. van Zyl and Sreekantha B Jonnalagadda "Sustainable CeO_2/ZrO_2 catalyst for the green synthesis of highly functionalized 1,4-dihydropyridine-2,3-dicarboxylate derivatives" (Poster presentation at the **College of Agriculture, Engineering and Science Research** day, 29th November 2016, ***Howard Campus, UKZN***.

LIST OF ABBREVIATIONS

Abbreviations

3-CR	Three component reaction
^{1}HNMR	Proton Nuclear Magnetic Resonance
^{13}CNMR	Carbon-13 Nuclear Magnetic Resonance
°C	Degrees Celcius
ArH	Aromatic ring proton
BET	Brunauer-Emmett-Teller
Calcd	Calculated
C-C	Carbon-Carbon bond
$CDCl_3$	Deuterated Chloroform
COSY	Correlation spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMSO-d_6-	Deuterated-dimethyl sulfoxide
Dd	Doublet of doublet
D	Doublet
Dt	Doublet of triplet
Et_3N	Triethyl amine
EtOH	Ethanol
Eq	Equivalent
FT-IR	Fourier Transform Infrared Spectroscopy
HIV	Human Immunodeficiency Virus
HMBC	Heteronuclear Multiple Bond Coherence
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
HRMS	High Resolution Mass Spectrometry
H_2PO_3	Dihydrogen Phosphite
IL	Ionic Liquids
IMCRs	Isocyanide-based Multicomponent Reactions

MCRs	Multicomponent reactions
MHz	Mega Hertz
M	Multiplet
MNP	t-nitrosobutane
MOF	Metal-organic frameworks
PEG 600	Poly (ethylene glycol) 600
Ppm	Parts Per Million
REE	Rare earth element
RT	Room temperature
S	Singlet
S_8	Elemental Sulfur
TEA	Triethanolamine
TEM	Transmission electron microscopy
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TOF	Turn over frequency
T	Triplet
VOC	Volatile organic compounds

TABLE OF CONTENTS

Chapter 1

The objective of this study is to design and develop bimetallic mixed oxides using zirconia as support and rare earth metals as potential active materials to be used as recyclable heterogeneous catalysts in valued added organic conversions, with focus on synthesis of varied pyridine derivatives. The chapter mainly describes the importance and applications of various heterogeneous catalysts, multicomponent reactions and chemistry of heterocyclic compounds. The chapter also interprets the role of zirconia as support material for the various active metals and their efficacy in the value added organic transformations. Numerous heterocyclic compounds and their syntheses are described to appreciate the scope and viability of Multi-Component Reactions (MCRs). The literature survey on pyridine moieties and their syntheses in different operating conditions are described.

1. Introduction

A catalyst is a constituent of a reaction, which accelerates the rate, without being consumed in the reaction. Catalysts are widely utilized in industry, laboratory and research fields. Attention to catalyst materials has been prompted by the central problem of how to adapt comparatively economical feedstocks into molecules of enhanced value [1-3]. Catalysts play a vital role, as part of industrial processes, in the formation of simple molecules into new composite fragments (e.g., from ethylene into methanol) [3-5]. Solid catalysts possess catalytically active sites on their surface [6], and in the reaction process, the reactant molecules come in contact with active sites on the surface [6-8]. The conversion of N_2 to NH_3, using a heterogeneous catalyst was one of the greatest successes in manufacturing procedures, with over 150 million tons of NH_3 manufactured per annum globally [9-11]. The transition metal oxides are the most explored materials as a heterogeneous catalysts for different organic conversions [12-14]. Varied inorganic catalysts have been employed in the synthesis of new organic chemicals and petroleum products of value, like pharmaceuticals, polymers, petrochemicals and fuels [15-17]. Catalyst also plays a key role in providing a cleaner environment, via the elimination of pollutants and through the development of cleaner industrial processes with lesser production of by-products [18-20]. Mixed metal oxides are a noteworthy class of heterogeneous catalysts because of their high stability, simple separation, chemo-

selectivity, environmental compatibility, highly active, simplicity of operation and are cost-effective [21].

Catalysts can broadly be divided into homogeneous and heterogeneous [22] and bio-catalysis is often seen as a separate category [23]. A homogeneous catalyst is distributed on the molecular level within the reactants, which are most frequently in the liquid state [24]. Catalysis of the conversion of organic molecules by acids or bases denotes one of the best known types of homogeneously catalysed reactions [25]. In addition, the catalysis of organic reactions by metal complexes in solution has grown rapidly with both scientific and industrial importance [26]. Heterogeneous catalysts remain mostly in solid phase, while reactants exist in liquid and/or vapour phases heteroatom catalysis [27], whereas in homogeneous catalysis the reactants and the catalyst are in the same phase [28].

This study is focused on heterogeneous catalysts. In order for the reaction to occur, one or more of the reactants must diffuse to the catalyst surface and adsorb onto it. After the reaction, the products must desorb from the surface and diffuse away from the solid surface [29]. Transport phenomena and surface chemistry is an important aspect of heterogeneous catalysis research [30]. A simple model for heterogeneous catalysis involves the catalyst providing a surface on which the reactants temporarily become adsorbed [31]. Bonds in the substrate become sufficiently weakened for new bonds to be created. The bonds between the products and the catalyst are weaker, so the products are released. Several heterogeneous catalysts used in petrochemical and refinery applications are reused multiple times therefore saving energy and they also are eco-friendly [32-34]. Furthermore, it provides the opportunity for simple separation and recycling of the catalyst and easy product purification [34]. In recent years, there have been an improvement in using recyclable heterogeneous catalysts for varied chemical conversions, owing to their associated cost-effectiveness and environmental benefits [34-36]. Mainly, reactions catalysed by these materials have modernized the field of organic synthesis due to easy work up, higher yields and reduction in waste production [35-38]. In that sense, a demand to improve heterogeneous catalyst with excellent yields and shorter reaction times, without using a hazardous materials have been investigated [39,40]. One of the main aims of green chemistry is to improve environmentally appropriate routes to important organic molecules. Thus, there is great demand

for designing and development of newer materials as the preferred catalysts in the industry, academic research and industry to achieve variety of objectives.

1.1. Metal and rare earth elements

Rare earths, a collection of sixteen naturally occurring chemical elements [41] that contain unique properties, make them ideal for the high technology industry. They are applicable in permanent magnets, lasers, automotive catalytic converters, superconductors, and alloys as well as in catalysis [42]. The first application of these chemicals dates to the 1880 and they have shown significant applications over the years. They are used in alloys to prevent corrosion and impart strength, hardness and inertness to structural material, in the ceramic industry and in catalysis [43].

The use of lanthanides in many applications to explore its complexity using techniques such as gravimetric, volumetric, voltammetry, potentiometry and spectrometry. Lanthanides form a major component of the rare earth elements, which are critical components of many higher valued products for petroleum refining catalysis, as well as phosphors in colour television [46].

Ninety percent of lanthanides found globally are used in the U.S.A. and most of it is imported from China. Lanthanides possess flexible coordinative saturated metal centers and they exhibit a high thermal stability [47]. Because of the properties, they have various physical, chemical and biological applications [48-50]. There is lack of information on the potential effects of lanthanides when exposed to humans. [51,52].

1.1.1. Samarium metal

Samarium, a member of the lanthanide series, is a very hard and silvery-white metal. It ignites in air at high temperatures. In nature, samarium occurs as seven isotopes, of which three are radioactive with extremely long half-lives [51-54]. It is also applicable in catalysis and decomposition reactions. Its radioactive isotopes are used in cancer cell treatment, nuclear reactors, x-ray lasers and in the determination of age and origin of rocks [55].

Samarium is found in a variety of minerals such as monazite, bastnasite, cerite, gadolinite, and samarskite. These minerals contain different mixes of rare earth metals, ranging the elements from lanthanum through to lutetium in the periodic table. Currently, it is mainly

used as an alloy together with cobalt in super strong permanent magnets and as an active metal in catalysis. Samarium has two stable oxidation states, +2 and +3, where the latter is the most stable. This property makes samarium a good lanthanide for catalytic activity [56, 57]. The coordination chemistry of samarium and together with other lanthanides as well is not as predictable as for the d-block elements.

1.1.2. Cerium metal

This lanthanide element is found in oxide form as ceria. Ceria is recognised for its excellent catalytic activities. It is normally used with other materials to alter the overall properties for example in the Oxygen Reduction Reactions (ORR). It is mixed with gold for improved catalytic activity and that is referred to as a synergistic effect. It can also be mixed with other metals to enhance the redox properties [58]. Ceria can be recovered from several industrial wastes. It is used as a promoter/additive in hydrogenation reaction as it contains excellent promoting effects [59]. It has unique and various application such as polishing material, electrochemical device as well as in catalysis on oxidation and partial oxidation of hydrocarbons.

It basically acts as an oxygen sink for the reactions that occur on its surface of it or at the surface of supported ceria [60]. A variety of methods are used in the preparation of ceria which includes sol-gel, co-precipitation and a hydrothermal solid-solid reaction procedure. It can release and absorb large quantities of oxygen (oxidation state conversion). Ceria allows the formation of oxygen vacancies, whose concentration is directly proportional to the catalytic activity. It normally increases the surface area of the catalyst, therefore enhancing the catalytic activity [61]. Silver supported ceria is active in the gas-phase catalytic combustion of volatile organic compounds (VOCs) and is economically reasonable viable due to the utilization of small amounts of oxides [62].

1.1.3. Yttrium metal

Yttrium plays a huge role in catalysis as it increases the oxygen mobility. It modifies the catalytic activity by enhancing the reducibility of the catalyst [63, 64].

Yttrium is used as a catalyst in ethylene polymerization. The effect of yttrium on the activity of the Ru catalyst for carbon dioxide hydrogenation is significant. In comparison to Ru/sepiolite, the Ru-Y/sepiolite catalyst presents higher CO_2 conversion under comparable

condition. This indicates that yttrium can play an important role by aiding the increase of the catalytic activity of Ru/sepiolite. It is well known that the catalytic activity of a catalyst can be related to its surface properties.[65] The presence of yttrium in the Ru/sepiolite catalyst obviously increases the number of active sites in this catalyst and improves the dispersion of ruthenium over the support. Thus, the increase in CO_2 conversion due to the presence of yttrium can be related to the change of surface properties of this catalyst [66. 67].

1.1.4. Zirconia oxide

Zirconia is an intensively used compound because of its acidic properties and is prominently used in heterogeneous catalysis doped with other metals [68, 69]. It has high calcining temperatures, resulting to a decrease in the surface area, thereby forming an individual crystalline phase [70-72].

Acidic zirconia catalysts contains transition metals such as nickel, cerium and chromium and are preferably prepared by the sol gel method [73-75]. Since it introduces homogeneity and controls the morphology and the overall textural properties [76]. Zirconia holds many advantages, including strong acidity, stability, excellent activity and it can be recovered easily after use. It improves the yield of the desired product [76-78]. Furthermore, zirconia has been considered because of its thermal, mechanical, and chemical stability. It retains its form under harsh reaction conditions for example high temperature, high pressure, and a strong oxidizing agent, in acidic and basic aqueous media [79-81].

1.2. Preparation of Zirconia

The different methods to get synthetic sulfated zirconia could usually be classified into two synthesis routes [82-86]. The first route is by the synthesis of mesoporous sulfated zirconia. Many researchers were devoted to synthesizing mesoporous zirconia with uniform pore structure by using various templates as the pore-directing agents. Cetyl trimethyl ammonium bromide, neutral amine and the triblock copolymer were used in the first step before using sulfate impregnation in the second step [87]. However, the amorphous pore wall of surfactant-templated mesoporous zirconia would often suffer from the collapse of the porous structure after high temperature calcination. Here, an alternative strategy was to load sulfated zirconia on the pores of heat stable mesoporous materials. Great effort have been made on obtaining sulfated zirconia

loaded mesoporous silica materials through a direct synthesis or post-synthesis impregnating methods [88]. However, as the blocking of pores would be observed as enhancing the loading amount of metal oxides, it would result in a serious degeneration of the catalytic activities due to the difficulty caused in mass transfer. The second approach was by synthesizing the sulfated zirconia nanoparticles. In this approach, a conventional two-step technique included the precipitation of zirconium hydroxide followed by the impregnation of zirconium hydroxide with sulfate ions, which was used for the preparation of sulfated zirconia nanoparticles. Several zirconium precursors such as zirconium nitrate, zirconium chloride, zirconium oxychloride, zirconium isopropoxide and zirconium acetylacetonate were at first employed to form zirconium hydroxide precipitated by alkaline agents. Then, common sulfonating agents, such as H_2SO_4 and $(NH_4)_2SO_4$, were used for the impregnation of zirconium hydroxide. In the two approaches, the one-step synthesis approach has attracted more attention because of its advantage in avoiding the impregnation step, which would simplify the synthesis procedure of sulfated zirconia nanoparticles [86-89]. In fact, both monoclinic and tetragonal sulfated zirconia with high surface area had been prepared by a novel one-step hydrothermal method. Stichert et al. [88] also reported a one-step liquid-crystal template route to synthesize nano-sized sulfated zirconia with coexisted mixed phases of tetragonal and monoclinic zirconia. It was noted that zirconia with a combination of tetragonal and monoclinic phases, however, exhibited less catalytic activity than that with pure tetragonal phase. This proves that the tetragonal sulfated zirconia is active, but the monoclinic is nearly inactive. Reddy et al., also found that sulfated zirconia required for the formation of active sites after high-temperature calcination was accompanied by the transformation of tetragonal into monoclinic zirconia, which resulted in a decrease in catalyst activity [89-90]. Therefore, it deserves to search for a procedure that synthesizes stable and high active sulfated tetragonal zirconia. There were no reports in the literature to synthesize sulfated tetragonal zirconia catalyst with a one-pot vapor controlled synthesis method [90]. Some of the studies reported with different active materials doped on zirconia support used as catalysts are detailed below.

1.2.1. Nickel-Zirconia

Nizio et al. reported the use of metals supported on zirconia for the methanation process. It represents both a feasible approach contributing to the reduction of the emissions of CO_2 and a way of transforming hydrogen into a conventional energy carrier [91]. Though many different porous materials containing metal have been used to catalyze the methanation process, zirconia doped nickel showed excellent catalytic effect, achieving considerable methanation rates. The interaction between the metal and support also plays a very important role in catalyst performance and a key role in the active site dispersion, stability and activity [92].

Chu *et al.* evaluated CO_2 methanation activity of Ni-ceria-zirconia and revealed that Ni-ceria-zirconia exhibited excellent catalytic activity and stability. Exceptional performance was due to the high oxygen storage capacity of ceria zirconia oxides together with the presence of highly dispersed nickel [93]. Other studies claimed that CO_2 methanation activity on Ni-ceria-zirconia was related to the particular interaction between nickel cations and the ceria-zirconia support [94].

1.2.2. Copper-Zirconia

Researchers investigated the sustainable development for methanol synthesis via CO_2 hydrogenation. Amongst different additives such as ZnO, Al_2O_3, ZrO_2, Ga_2O_3, Y_2O_3, TiO_2 and SiO_2 used, zirconia has shown an outstanding performance [95]. The ZrO_2-supported copper catalyst has been reported to be more selective and stable than the other catalysts for methanol synthesis from CO_2 hydrogenation because of the high thermal stability and the high surface basicity of ZrO_2 [96]. Therefore, ZrO_2 was suggested as a structural stabilizer to prevent the sintering of Cu nanoparticles. In addition, the surface basicity of ZrO_2 provides more active sites for CO_2 adsorption. Reddy and Patil reported that the methanol selectivity linearly increased with strong basic site on the catalyst surface [97].

Sreethawong et al. reported that Cu doped m-ZrO_2 exhibited a higher concentration and basicity of hydroxyl group as well as the stronger Zr^{4+}/O_2 pairs compared to t-ZrO_2, resulting in superior CO_2 adsorption capacity. The work reported that the phase of ZrO_2 affected activity and selectivity for the synthesis of higher alcohols and isobutene, butane isomerization, ethanol dehydration and the water gas shift reaction [97-99]. However, a few studies have investigated the effect of the zirconia phase on methanol synthesis from CO_2 hydrogenation. However, the

roles of ZrO_2 phases in the determination of structure and catalytic activity of Cu/ZrO_2 catalysts are not yet fully understood. The effects of ZrO_2 polymorphs including amorphous (-m), tetragonal (-t) and monoclinic (-m) phase on the structure of copper, $Cu–ZrO_2$ interaction and adsorption–desorption of H_2 and CO_2 were systematically investigated. The catalytic performance in terms of activity, selectivity and normalization of the copper site specific activity (TOF) of the Cu/a-ZrO_2, Cu/t-ZrO_2 and Cu/m-ZrO_2 catalysts is discussed based on their structure and adsorption–desorption properties [100-102].

1.2.3 Tungsten-Zirconia (WO_x-Zr)

The stability of WO_x-ZrO_2 is attributed to the strong interaction between the WO over layer species and the ZrO_2 support [103]. Further studies found promising catalytic activity of WO_x-ZrO_2 in the liquid phase Beckmann rearrangement, dehydration, hydrolysis, hydrogenolysis, hydration of cyclohexene, selective catalytic reduction of NO and esterification. WZr catalysts are conventionally prepared by impregnating a $Zr(OH)_4$ support with a W precursor. The material is subsequently subjected to calcination temperatures [104]. Variation of WO_3 content and calcination temperature enables the control of the population of WOx species on the support, which is frequently expressed by the theoretical W surface density (W-SD) [105]. The W-SD has a significant impact on the catalytic performance of WZr and the value of W-SD producing the optimal activity has been discussed controversially [106]. Optimum catalytic activities were proposed for W-SD forming a 2D-monolayer coverage of polymeric tungstate species. Above monolayer coverage, WO_3 nanoparticles (WO_3-NPs) start to develop on the surface of ZrO_2 causing a decline in activity [107].

Furthermore, Wachs et al., have carried out extensive studies on the WO surface states over metal oxide supports, particularly ZrO_2. Okuhara et al., found evidence for the presence of sub-nanometre Zr-WOx clusters responsible for high catalytic activity in the Friedel–Crafts alkylation. Moreover, other reports showed that the formation of crystalline WO_3-NPs on a level slightly above monolayer coverage can still give a positive effect in catalysis [108-110].

1.3. Multicomponent Reactions

Chemical conversions utilizing three or more reactants to form products are typically referred to as multicomponent reactions (MCRs) [111]. It can be revealed as a subclass of domino progressions as they are frequently accomplished by putting all substrates in one pot under parallel reaction conditions, where the compounds undergo the transformations in a time-resolved mode [112]. Since several substrates are put together, it is not only the molecular complexity that is built up very rapidly; indeed, there is also the possibility of generating manifold analogues. Specifically, MCRs provide products with the diversity needed for the discovery of new lead compounds [113]. This diversity and easy accessibility to a large number of compounds, combined with high throughput screening techniques, makes MCRs a very important tool in modern drug discovery processes [114].

MCRs supports a large variety of reactions based on the combination of simple and flexible construction blocks in time-saving one-pot procedures [115]. Owing to their characteristic simple investigational techniques and their one-pot character, they are clearly appropriate for automated synthesis [116]. Therefore, MCRs have attracted significant interest due to their unique synthetic efficacy [115]. The structure of the reaction product can simply be prolonged by systematic divergence and the reactants are either commercially accessible or easy to prepare. The bond forming efficiency, that is the number of bonds that are formed in single process, is a significant part to determine the benefit of MCRs [117].

In MCRs, numerous starting materials combine to generate composite products. Model multicomponent synthesis approves the concurrent addition of all reactants and catalysts in a single step process in which all reactants combine in a distinctively systematic mode under the same reaction circumstances [118]. Thus, a model MCR is an arrangement of mono and bimolecular events that profits consecutively until an irreversible final step traps the product. All these processes are highly efficient for creating molecular complexity by generating more than two chemical bonds per operation [119]. Hundreds of MCRs have been used over the years. However, the finding of novel MCRs was a consistent theme during the past decade [115]. With the occurrence of high-throughput showing in chemical industry, researchers and chemists are confronting the challenges to conceiving huge collections of new molecules [112]. By virtue of its intrinsic high tentative power, research on MCRs has positively become a field of interest for

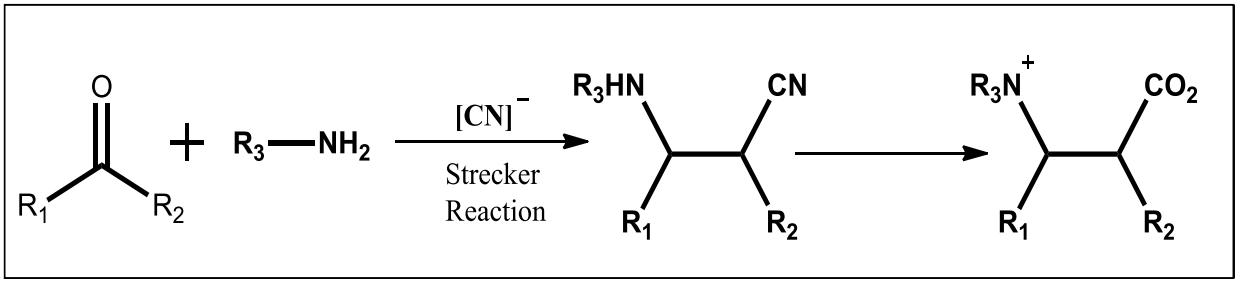
both academic and industrial researchers [119-121]. It is therefore not surprising that many efforts are currently being devoted to this area of exploration.

1.4. Types of Multi-component reactions

1.4.1. Strecker multicomponent reaction

The Strecker multicomponent reaction was first reported in 1850. This is one of the oldest multicomponent reactions, which have proven to be straightforward and an efficient route for the synthesis of α-amino acids which are applicable in the pharmaceutical industry [122]. Strecker is a valuable multicomponent reaction because of the formation of C-C bonds as well as its richness in the chemistry of the nitrile function groups [122-124].

This is a three-component type of MCR, which includes a carbonyl compound, an amine and either an alkaline metal cyanide or hydrogen cyanide coupled together to produce an amino nitrile [125]. This reaction involves condensation of an aldehyde, ammonia as well as a cyanide source. A subsequent hydrolysis of the resulting amino nitrile follows thereafter (Scheme 1). After 167 years of discovery, the Strecker reaction is still practical and efficient. It is applicable in both the laboratory and technical scale, which adds to its advantages. It form amino nitriles, which are very useful precursors for synthesis of amino acids and other nitrogen containing heterocycles [123]. This reaction is catalyzed by both acidic and basic catalysts, for example lithium perchlorate, zinc halide, ruthenium, depending on the conditions of the reaction. These reactions are tedious, producing a lot of waste, therefore modifications had been made using cyanating agents e.g. diethyl phosphorocyanidate, α-trimethylsiloxy nitrile tri-n-butyltin cyanide and so forth [126].

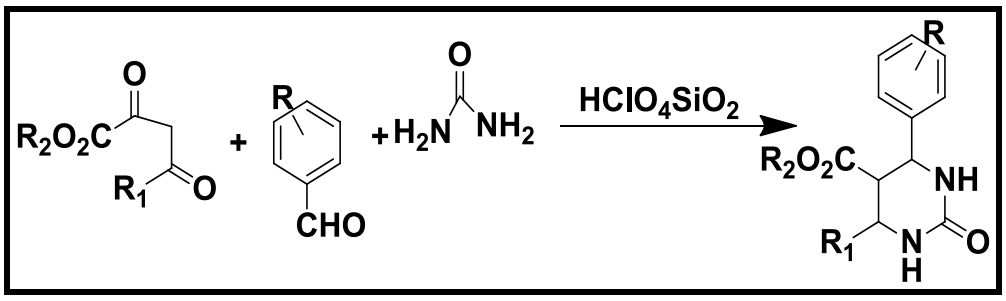


Scheme 1: The synthesis of α-amino nitrile through Strecker reaction.

1.4.2. Biginelli multicomponent reaction

The Biginelli multicomponent reaction demonstrates one of the fundamental strategies involving a three-component condensation [127]. It was discovered in 1893 and it involves a one-pot condensation of an aldehyde, α, β-ketoester, and urea/thiourea under strong acidic conditions (scheme 2) [128]. This is an important route to produce multi-functionalized-3,4-dihydropyridin-2-(1H-thionesdihydropyridines (DHPs). These DHPs have been receiving considerable attention because they exhibit a wide range of biological and pharmacological properties, for example, antiviral, antibacterial, antitumor, anticancer, anti-hypertention [128-130].

The Biginelli type of reaction is related to the innovation of dihydropyridines based calcium channel modulator such as nifedipine drugs used in cardiovascular diseases [131]. This type of MCR has some drawbacks such as harsh acidic conditions, longer reaction time as well as low yield particularly when subjected to aromatic aldehydes. However, appropriate catalysts have been used for example ionic liquids, SiO_2-H_2SO_4, PEG-SO_3H, SiO_2-H_2PO_3 to overcome these [129-131].

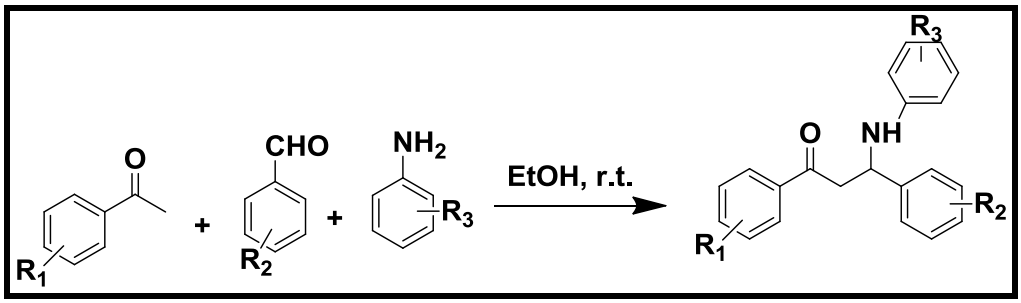


Scheme 2: Preparation of dihydropyridinones through the Biginelli condensation.

1.4.3. Mannich multicomponent reaction

Mannich multicomponent reaction is one of the most general and suitable route for the synthesis of nitrogen-containing building blocks [132]. It is used in the preparation of secondary and tertiary amino derivatives. These reactions result in asymmetric and racemic products, therefore making them a special area of research [133]. It is amongst the most widely used three component systems, utilizing a non-enolizable aldehyde, a primary/secondary amine as well as an enolizable carbonyl compound (Scheme 3). The resulting β-amino carbonyl compounds are valuable in the synthesis of pharmaceutical and natural products and act as synthetic

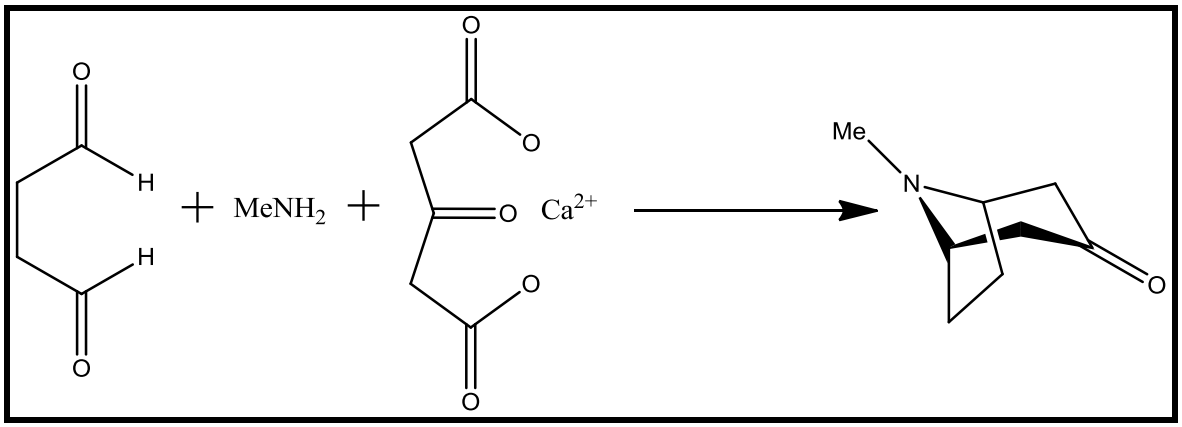
intermediates in organic synthesis [134,135]. They are also applicable effectively in amino ketones generation, synthesis of amino alcohols, sugar derivatives and alkaloids [133]. Carbon-carbon and carbon-nitrogen bonds are formed, which are crucial in pharmaceutical and natural products and makes these reaction highly versatile. Modification of the reaction was been done to overcome the drawbacks such as purification procedure, production of waste and complex work-up [132-135].



Scheme 3: Three-component Mannich multicomponent reaction.

1.4.4. Robinson multicomponent reaction

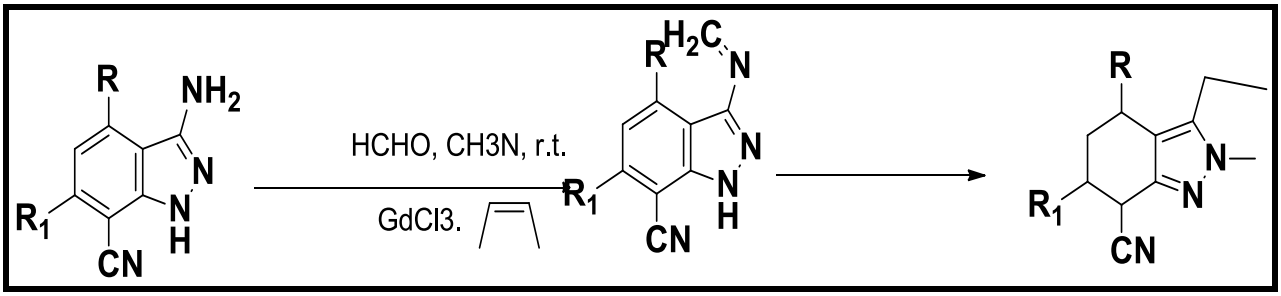
The Robinson reaction is amongst the oldest and most powerful means for the synthesis of the alkaloid tropinone heterocycles and was initially carried out in 1917 [136]. The leading central application of Robinson MCRs is in natural product chemistry [137]. This type of reaction involves a coupling of succinic dialdehyde, calcium salt of acetonedicarboxylic acid as well as methylamine (Scheme 4) [138].



Scheme 4: Robinson three-component multicomponent reaction.

1.4.5. Passerini multicomponent reaction

Passerini multicomponent reaction is a three-component system [139]. It is a dominant tool for combinatory chemistry as well as heterocyclic chemistry, which has been used for over 80 years [139]. This type of reaction involves the synthesis of a diverse library of potentially bioactive and densely functionalized molecules [140]. The Passerini reaction has found much utility in the drug discovery field as well as biological natural product synthesis [140-142]. The Passerini reaction is an efficient way for the synthesis of α-acyloxycarboxamides, after BOC deprotection and acyl migration by using carboxylic acid, aldehyde as well as isocyanide (Scheme 5) [143]. This type of reaction gives the desired product that constitutes a stereogenic center, which contains ester and amide linkage functionalities which are very advantageous [144]. The other advantage includes better yield, variability of conditions that they proceed in for example aqueous solvent, solvent free and ionic liquid.



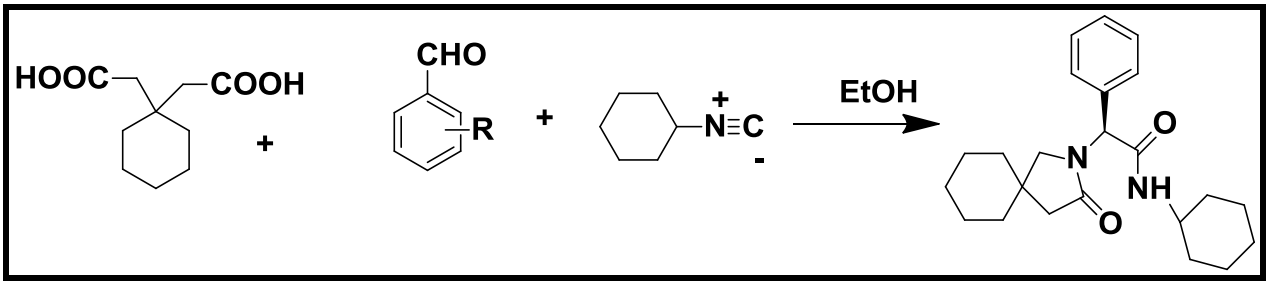
Scheme 5: The Passerini three component reaction.

1.4.6. Ugi multicomponent reaction

Ugi firstly described the concept of a four component reaction system in 1959 used in the synthesis of new compounds that are effective against infectious diseases [145]. The Ugi reaction is one of the developmental foundations of isocyanides based multicomponent reactions [146,147]. It is a reaction methodology used for the synthesis of peptides by using monomers that contains biocompatible side groups [148]. This is a one-pot four component system which is efficacious for the synthesis of di-amide scaffolds by reacting an aldehyde/ ketone, amine, carboxylic acid and an isocyanide [149].

The Ugi multicomponent reaction is easy to perform and it tolerates a wide range of functional groups. It is also a very rapid access to structural complex compounds. It has a greater diversity of ligands as it increases the scaffold diversity and application of novel affinity adsorbents [150]. It has amazing simplicity since it produces a linear peptide either than the

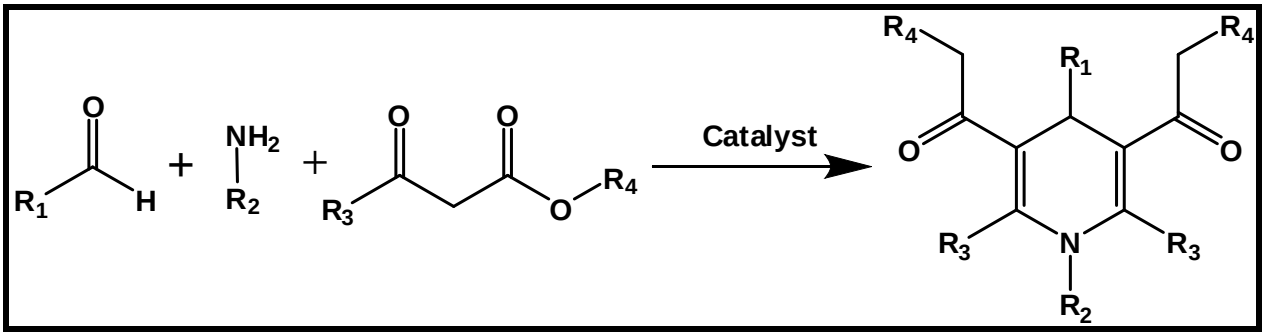
heterocyclic ring [151]. There is also a modified version of Ugi MCR, where only three-components an aldehyde, acid and isocyanide (Scheme 6) are used as starting materials [149-151].



Scheme 6: Ugi three-component multicomponent reaction.

1.4.7. Hantzsch multicomponent reaction

1,4-Dihydropyridine derivatives (1,4-DHPs) are a significant class of biological active molecules and also work as biomimetic reducing agents. These classes of compounds are generally accessible by use of the Hantzsch reaction, which was reported in 1882 [152]. This multicomponent reaction consists of an aldehyde, ethylacetoacetate and ammonium acetate to form dihydropyridine, which oxidises to form a pyridine derivative (Scheme 7).

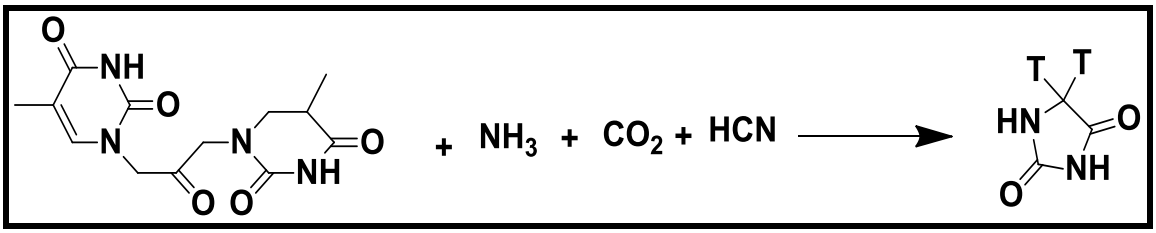


Scheme 7: General scheme for the Hantzsch reaction

A reaction of aromatic aldehydes, methyl acetoacetate and ammonium acetate was used for the one-pot multicomponent synthesis of functionalized 1,4-dihydropyridines (Scheme 8). The reaction was catalysed by Mn and Ce oxides under solvent-free conditions. The yields were good (69-87%) in the case of the benzaldehyde, as they have both electron-withdrawing and electron donating groups [153].

1.4.8. Bucherer-Bergs hydantoin multicomponent reaction

This four-component system was discovered in 1929. It was first synthesized by Bucherer- Bergs and it was carried out by reacting cyanohydrins, which include the addition products of cyanide anion to a ketones/aldehyde with ammonium carbonate (Scheme 8) [154]. The reaction mechanism involved is associated with the Strecker synthesis, because of the α-aminonitriles involvement as intermediates [155]. It is considered to be appropriate for the formation of amino acid because it is prone to succeed over the Strecker synthesis in a CO_2-rich atmosphere [156]. The conversion of *N*-carbamoylamino acids to amino acid N-carboxyanhydrides potentially produces peptides [154].



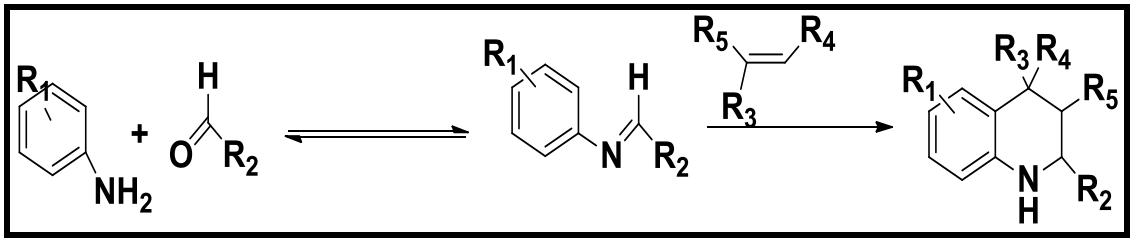
Scheme 8: Bucherer-Bergs hydantoin multicomponent reaction.

1.4.9. Aza-Diels-Alder multicomponent reaction

Aza-Diels-Alder multicomponent reaction is an efficient synthesis method in the assembly of six membered rings of the heterocycles [157]. These are normally important in the biological synthesis field [158]. It ensures excellent atom-economy of the reaction [159]. Both types of Aza-Diels-Alder involve an *in-situ* generation of either the diene or the dienophile, which still need to be explored further. It is basically a synthesis of complex annulated quinolines as well as optically active dihydropyridines [160]. These have a rich synthetic diversity, excellent regio-diastereo and enantio selective power [161].

These reactions deals with a combination of an electron rich olefin with an *N*-arylimines for the synthesis of tetrahydroquinolines (Scheme 9). Tetrahydroquinolines are an area of interest as the moiety exhibits wide-range of biological properties, including anti-allergic, anti-inflammatory, astrogen and psychotropic activities ideal for pharmaceutical applications [162]. Further, the synthesized quinolines are also vital because of their variable oxidation states [163]. This reaction requires an organic solvent as well as catalysts or additives, which is the major

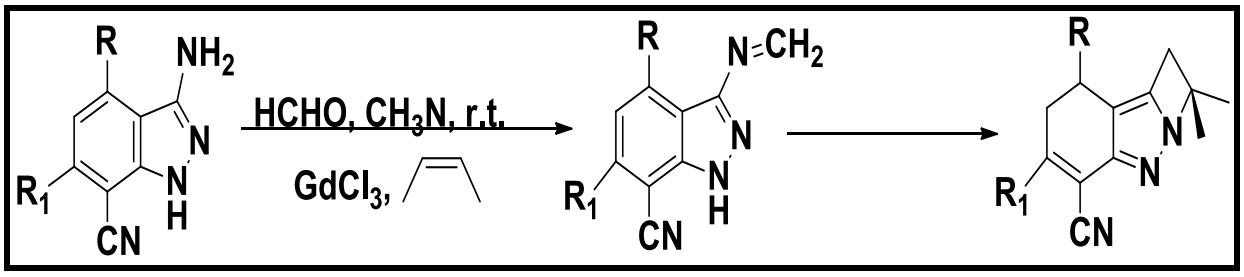
drawback. These reactions have been modified using mild and water tolerant Lewis acid and protic acid catalysts [164].



Scheme 9: Synthesis of tetrahydroquinolines via Aza-Diels-Alder reaction [165].

1.4.10. Grieco multicomponent reaction

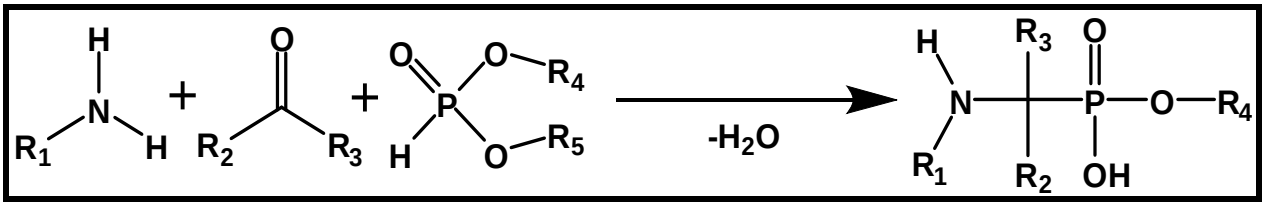
This is a type of multicomponent reaction was first reported by Grieco and Bhasas in 1988 [166]. It is a three-component reaction, which was termed the Grieco condensation [166-168]. This reaction is fairly new compared to other multicomponent reactions, but has a dominant application in the medical and pharmaceutical field [169]. It deals with the coupling of an amine together with an aldehyde to form a tetrahydroquinoline (Scheme 10).



Scheme 10: Grieco multicomponent reaction to form a tetrahydroquinoline [170]

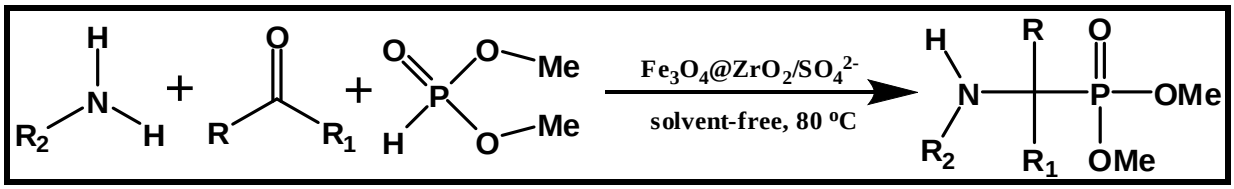
1.4.11. Kabachnik-Fileds reaction

The Kabachanik reaction is a multicomponent reaction between an amine, a carbonyl compound and dialkyl phosphonate to form α-amino phosphonate (Scheme 11). This reaction was discovered by Kabachnik and Fields in 1952 and is used in the synthesis of anti-inflammatory drugs [171].



Scheme 11: General scheme for the Kabachnik-Fields reaction

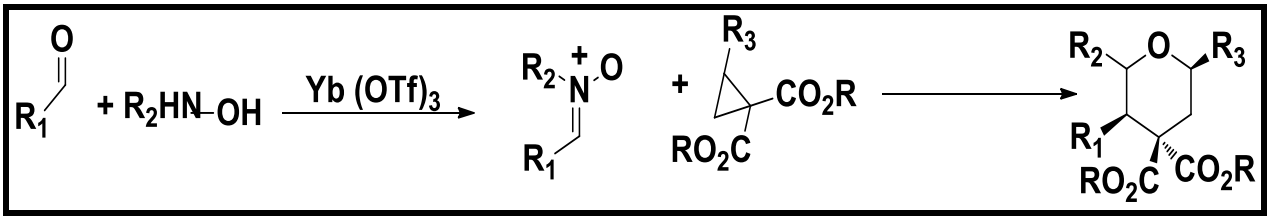
Recently, Ghafuri et al. reported a nanomagnetic sulfated zirconia catalysed Kabachnik reaction of α-aminophosphonates using aromatic aldehydes, anilines and dimethyl phosphite carried out in absence of solvent at 80 °C (Scheme 12). Like many other heterogeneous catalysts, Nano-$Fe_3O_4ZrO_2/SO_4^{2-}$, an acidic catalyst offers many benefits including easy workup, short reaction times, high activity and yields, in addition to easy separation and reusability and requires environmentally benign reaction conditions [172].



Scheme 12: Synthesis of the substituted α-aminophosphonates

1.4.12. Dipolar Cycloaddition reaction

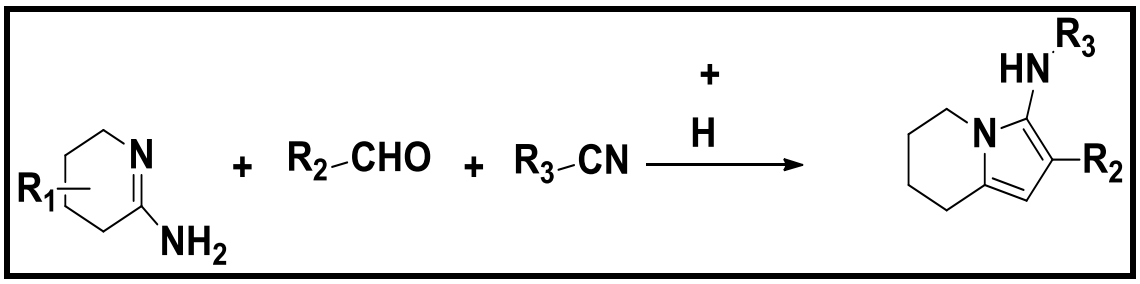
Dipolar cycloadditions are a two-component system of multicomponent reaction [173]. It is still innovative as compared to other multicomponent reactions and is also applicable in both the medicinal and pharmaceutical fields [174]. It is basically, a reaction for the synthesis of 1,3-dipoles, followed by a reacting the 1,3-dipole with an appropriate dipolarophile (Scheme 13) [175].



Scheme 13: 1,3 Dipolar cycloadditions multicomponent reaction.

1.4.13. Grobcke-Blackburn-Bienayme reaction

Grobcke-Blackburn-Bienayme reaction [176,177] is basically a three-component system, which proceeds by coupling an aldehyde to an isonitrile as well as α-aminoazine (Scheme 14) [178].



Scheme 14: The Grobcke-Blackburn-Bienayme multicomponent reaction.

1.5. Synthesis of heterocyclic molecules

Nitrogen in heterocyclic compounds have drawn significant attention owing to their wide range of pharmacological and physicochemical properties. Heterocyclic molecules offer a high degree of structural variety and are proven to be useful as therapeutic agents [179]. Traditional approaches for the synthesis of heterocycles are always being updated and replaced by new, effective and viable synthetic methods [180]. An improvement of eco-friendly and vastly cost-effective methods for the synthesis of heterocyclic compounds continues to be a challenging area for organic chemists [181,182]. One-pot synthetic pathways are advantageous to access diverse functionalized molecules which are useful as fine chemicals, chiral catalysts, ligands, drug candidates and drug intermediates [180-182]. 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 [183]. Transition metal catalysed one-pot reactions are well-established methods for the synthesis of heterocyclic compounds [184-186]. This will certainly increase the interest of heterogeneous catalyzed one-pot reactions in the near future.

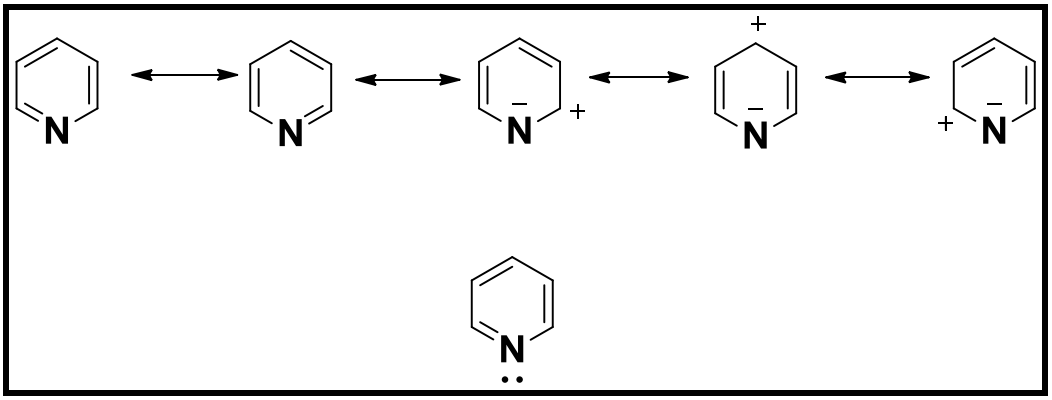
Heterocyclic chemistry, which forms the major division of conventional organic chemistry, is a challenging and interesting field [187], as a huge number of alkaloids derived from heterocyclic molecules are used as drugs [188]. Consequently, pharmaceutical and agrochemical industries have made rapid and significant progress to develop suitable heterocyclic compounds for the advantage of mankind [182]. The attractive feature of heterocyclic chemistry is the scope and provision to vary the core scaffold with innovative substitutions and variations [189]. 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 [190]. 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 various pyridine moieties in particular [191].

1.6. Pyridines

The finding of the pyridine basis (Pyr, means fire in Greek, and idine, suffix used for aromatic bases) is related to a peculiar study conducted in 1846 by Anderson, who was really investigating the pyrolysis of bones and was able to separate picoline as the first known pyridine [192]. The correct structure of pyridine core was improved by Korner (1869) and Dewar (1871), and other pyridines such as monopyridines, bipyridines, or terpyridines have also been reported [193-195]. The reactivity of heterocycles is different and they enhance their selectivity/reactivity in terms of the compounds they react with (nucleophile and electrophile).

The pyridine six-membered ring is reactive towards an electrophile due to the partial positive carbonyls on the ring while the nitrogen is partially negative as shown in Scheme 14.



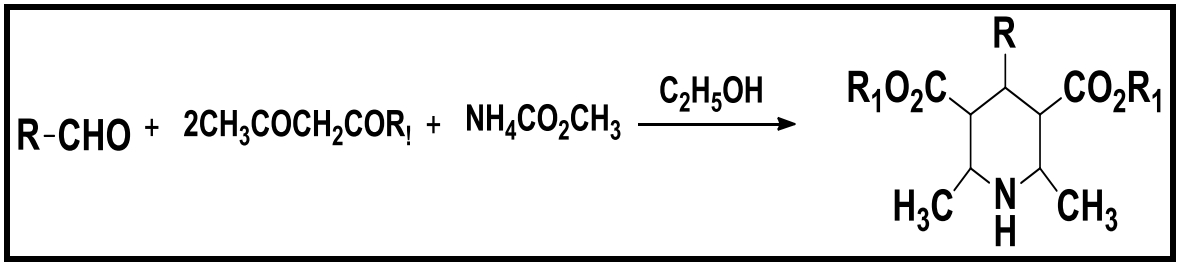
Scheme 14: Reactivity of a pyridine six membered ring

Pyridines can be utilized to chelate metallic ions as *N*-donor ligands, giving effective organometallic catalysts [196]. These are also used in many applications like material science [197], polymers [198], supra-molecules [199] and organo-catalysis [200]. Pyridines have fascinated scientists for their biological and pharmaceutical characteristics, as they play a central role in the biological activity of natural substances containing nicotine, vitamin B6, and oxido-reductive NADP−NADPH coenzymes [201]. Pyridine-containing complex natural products also

exist in the sesquiterpene, alkaloid, enediyne, or polypeptide families. Several other bioactive enlarged pyridines have been prepared consequential in various interesting effects like antiviral, antiprotozoal, antiheroes, anti-apoptotic, anti-inflammatory, anti-asthmatic, antidepressant, anti-malarial, antitumor, antibacterial, anti-fungal, and antioxidant activities [202]. On the other hand, pyridines are also exploited in agrochemical for their herbicide and insecticide properties [201-205]. They basically act as the main building block in organic chemistry because of their predominant domination/display over a range of therapeutic activity classes. Due to the biological properties within the pyridine class their development is growing significantly with different methodologies and approaches [201-205]. Specifically, 1,4-dihydropyridines are a significant class, as they are used in the treatment of cardio vascular diseases (hypertension, arrhythmia, angina). They exhibit a calcium channel modulating property [206].

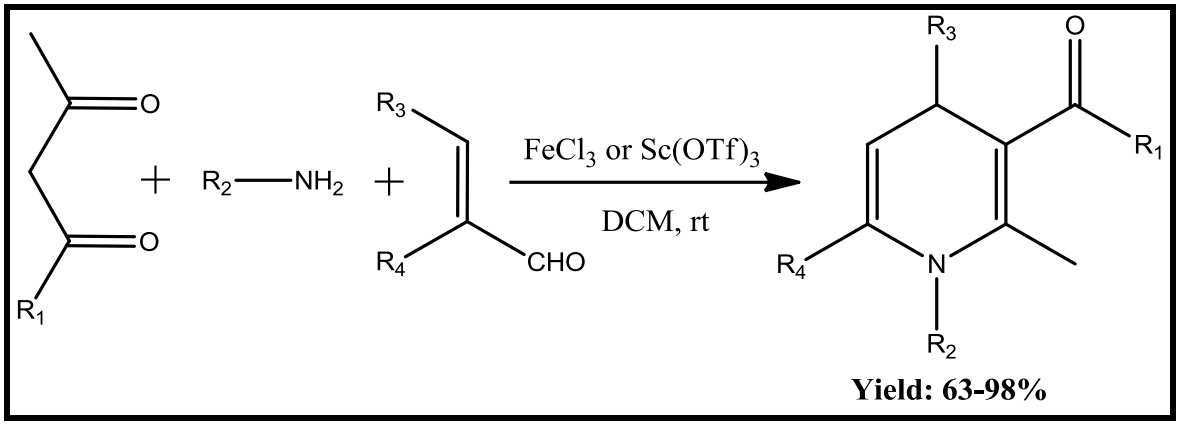
1.6.1. Synthesis of aryl-1,4-dihydropyridines via Hantzch reaction

The conventional methods for the preparation of Hantzsch 1,4-dihydro-pyridines from various aliphatic and aromatic aldehydes, β-keto ester and ammonia reported by earlier workers involved prolonged reaction times under refluxing conditions and moderate yields [20, 208]. This class of compounds have gained growing importance as they exhibit biological activities, like antihypertensive treatment of benign prostatic hyperplasia, and overcoming multidrug resistance encountered in cancer chemotherapy [209]. The reaction of equal ratio of ethyl acetoacetate, ammonium acetate and aldehyde in ethanol was subjected to microwave irradiation for 45 second in a domestic microwave oven with a pulse of 15 second each. The reaction product obtained is a light yellow solid in 96% yield (Scheme 15). Other substituted aldehydes were also synthesized [210].



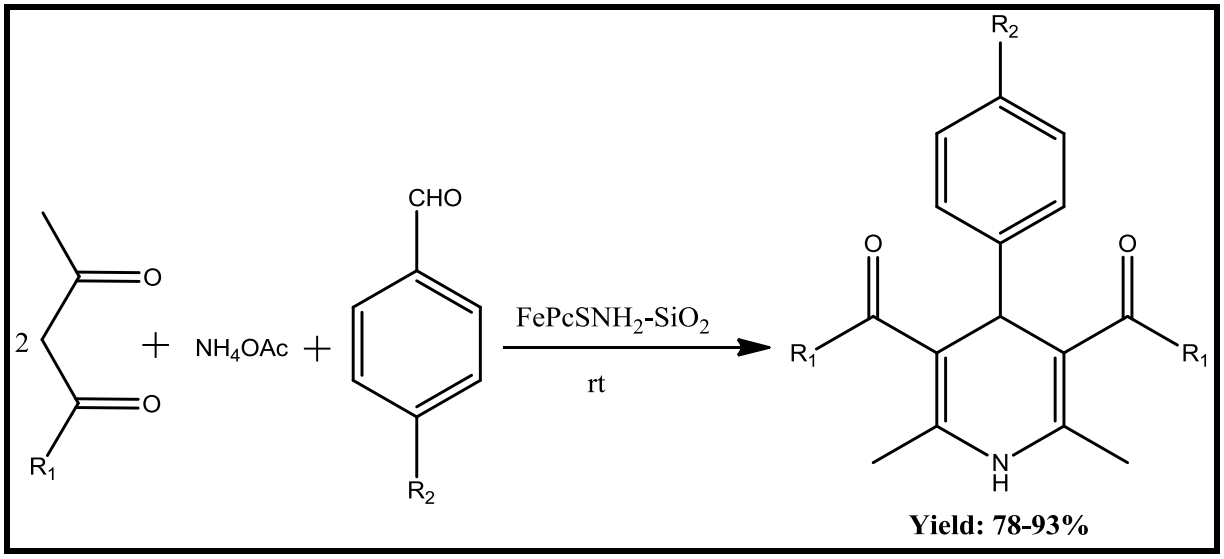
Scheme 15: Synthesis of 4-aryl-1,4-dihydropyridines

Renaud and co-workers have reported good yields in the synthesis of dihydropyridine compounds namely, 1,4-dihydropyridines by a one-pot multi-component reaction, employing aldehyde, 1,3-dicarbonyl compounds and amines in the presence of a Lewis acid as a catalyst, for the transformation into the desired product at room temperature under DCM conditions (Scheme 16) [211].



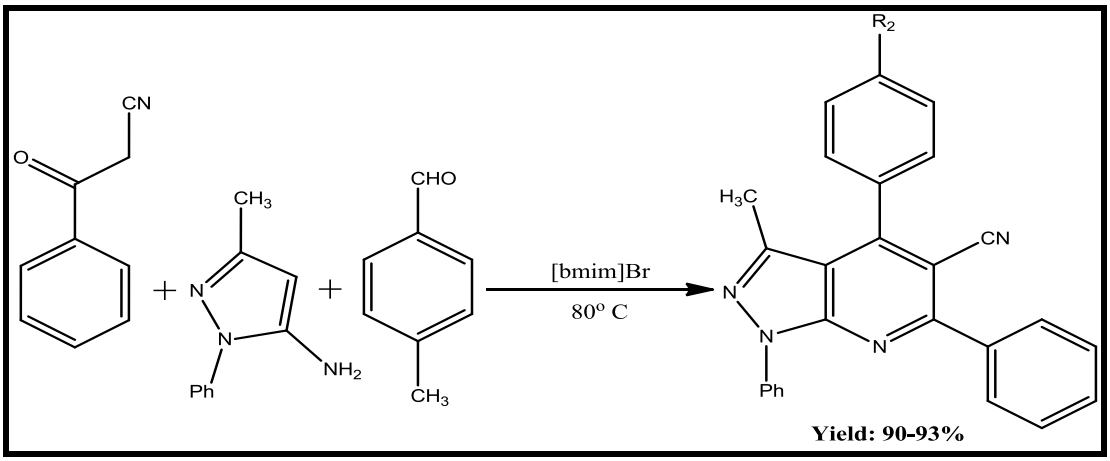
Scheme 16: Lewis acid-catalyzed synthesis of substituted dihydropyridines

Villa et al., synthesized 1,4- and 1,2-phenylpyridine compounds, by using immobilized metallic phthalocyanines as a heterogeneous reusable catalyst in the reaction of an aldehyde, methyl acetoacetate and ammonium acetate in acetonitrile at room temperature In that study, catalyst particles with its unique viscoelastic properties facilitated the reaction (Scheme 17) [212].



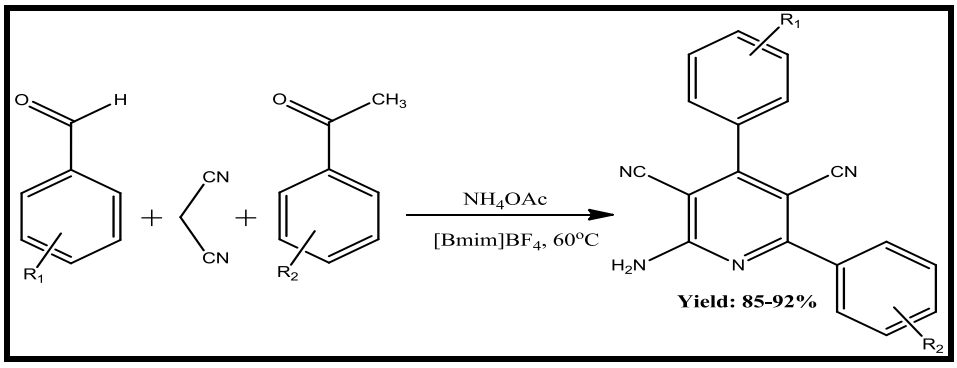
Scheme 17: Synthesis 1,2-phenylpyridines by Hantzsch reaction over $FePcSNH_2$-SiO_2

Shi and co-workers have synthesized fused pyridine derivatives like pyrazolo[3,4-b]pyridine and pyrido[2,3-d]pyrimidine using [bmim]Br ionic liquid as the catalyst the reaction was environmentally friendly, higher yields were obtained over shorter reaction times, and convenient operation. They synthesized the pharmaceutically relevant and easily work-up synthesis of pyrazolo[3,4-b]pyridine derivatives with aromatic aldehyde, acyl acetonitrile and electron-rich amino heterocycles in the presence of ionic liquid as catalyst and solvent medium under reflux conditions (Scheme 18) [213].



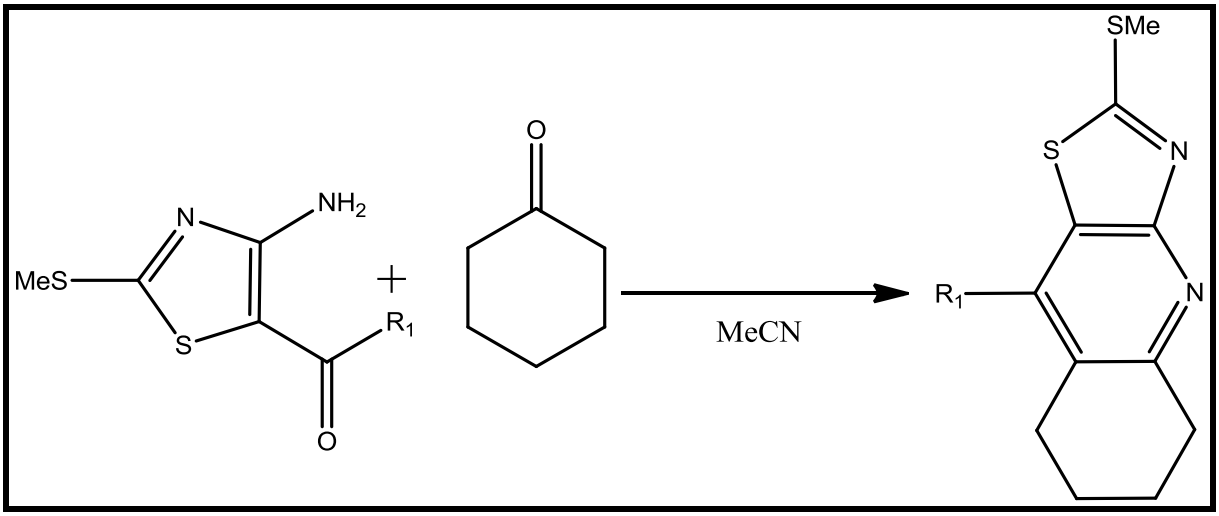
Scheme 18: Synthesis of Fused Pyridine Derivatives in Ionic Liquid [bmim]Br

Mansoor et al.,[214] have focused on the synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives using [Bmim]BF_4 as a ionic liquid catalyst and simultaneously as a promoting solvent at 60°C. In the proposed mechanism, it was suggested that an intermediate arylidenemalononitrile formed, underwent Michael addition to form the desired product through an environmentally benign procedure (Scheme 19).



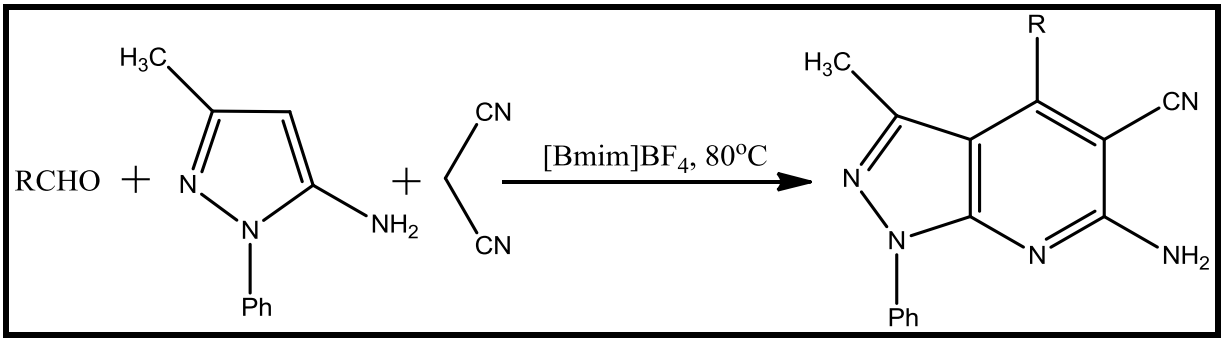
Scheme 19: One-pot synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile.

Lee and co-workers showed a unique Friedlander reaction procedure for the preparation of medicinally viable thiazolo[4,5-b]pyridine, with solid supported cyanocarbonimidodithioate as the catalyst. This approach, based on an efficient solution-phase sequence, allows for a ready access to a large library and is potentially applicable to the preparation of other drug-like fused-thiazole ring systems (Scheme 20) [215].



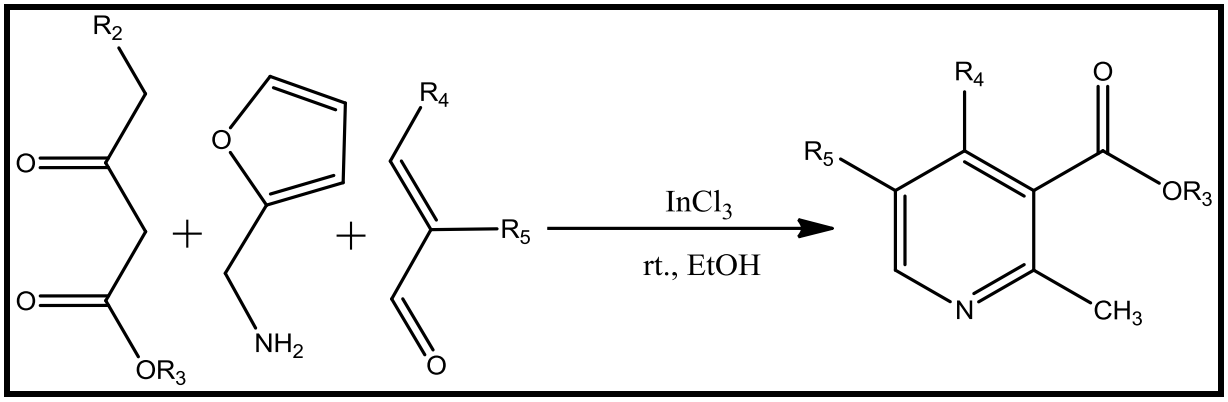
Scheme 20: Synthesis of Thiazolo[4,5-b]pyridine under the Friedlander reaction

Zhang et al., have described the synthesis of pyrazolo[3,4-b]pyridine using an efficient [Bmim]BF_4 as a ionic liquid catalyst. The mixture ethylacetoacetatee, benzaldehyde, malononitrile and 5-amino-3-methyl-1-phenylpyrazole were reacted at 80° C under [Bmim]BF_4 as a solvent. The protocol proposed here is an environmentally friendly procedure with mild conditions, high yields, easy recovery and reusability (Scheme 21) [216].



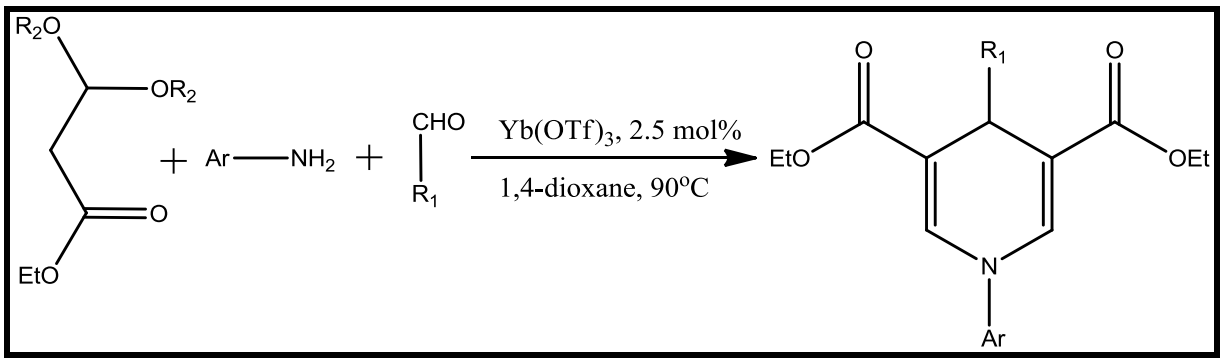
Scheme 21: Synthesis of the pyrazolo[3,4-b]-pyridin-6-one in [bmim][BF_4]

Raja and co-authors have developed a convenient, a heavy metal and oxidant-free, one-pot synthesis of pyridines and fused pyridine derivatives starting with aromatic aldehyde, 2-furfurylamine, β-dicarbonyl compounds and using $InCl_3$ as heterogeneous catalyst. The catalyst offers benefits such as non-toxicity, ready availability and recyclability. The study revealed that 5 mol% of $InCl_3$ is efficient to achieve the desired outcome (Scheme 22) [217].



Scheme 22: Synthesis of the polysubstituted pyridines

Sueki et al., formed an efficient Lewis acidic $Yb(OTf)_3$ catalyst and its catalytic behavior was validated with the preparation of β-ester acetal initiated synthesis of 1,4-DHPs containing organic compounds. The authors synthesized 1,4-DHP derivatives through a one-pot, multi-component condensation of acetal, aldehydes and aromatic amine compounds in the presence of the catalyst. The used acidic catalyst was separated with help of temperature-dependent phase-separation catalytic field and re-used with no loss of catalytic activity (Scheme 23) [218].



Scheme 23: β-ester acetal initiated synthesis of 1,4-DHPs

Bazgir et al., have investigated the preparation of spiro[diindeno[1,2-b:2′,1′-e]pyridine-11,3′-indoline]-trione derivatives employing a novel functionalized basic, p-TSA (para toluene

sulfonic acid). The best condition for the synthesis of spiro[diindeno[1,2-b:2′,1′-e]pyridine-11,3′-indoline]-triones with good yields was reported to be with equal ratio of 1,3-indandione, aniline and isatin in the presence of 20% catalyst at reflux in the presence of acetonitrile as a solvent (Scheme 24) [219].

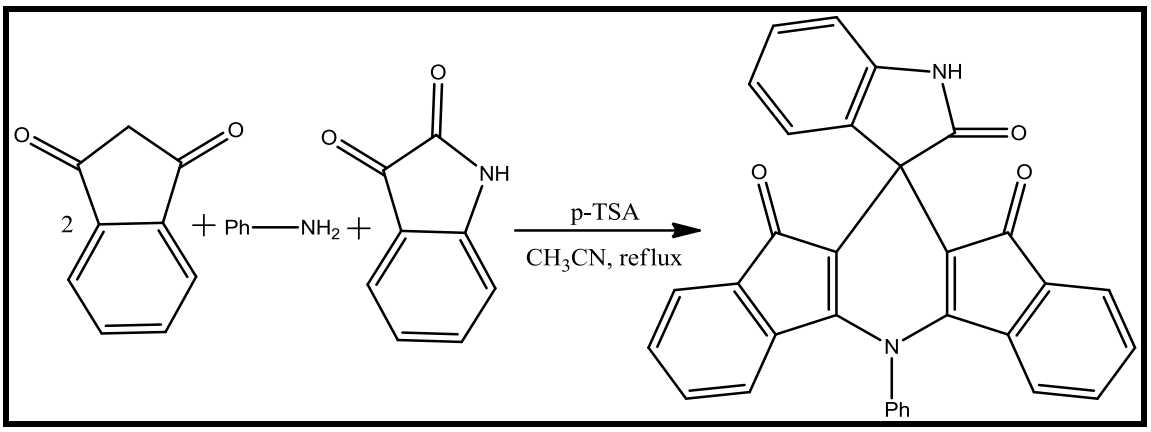
Shang et al., prepared polysubstituted pyridin derivatives by using acidic $FeCl_3$, as heterogeneous catalyst under ambient conditions using an equal proportion of aromatic aldehyde, malononitrile, ethyl acetoacetate and aniline. The study showed that 5 mol% catalyst was optimum for the reaction in order to achieve 94% yield of the final product in 1 h reaction time (Scheme 25) [220].

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 a mixture of arylaldehyde, malononitrile and (R)-1-(1-phenylethyl)tetrahydro-4(1*H*)-pyridinone within short period of time to get the 4(H)-pyrans in good yield under solvent-free conditions (Scheme 26) [221].

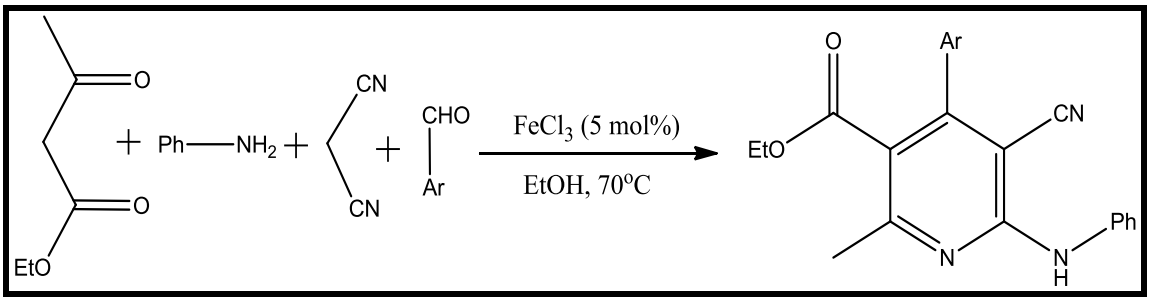
Alinezhad et al., have prepared substituted new indeno[1,2- b]pyridine derivatives through one-pot, four-component condensation of propiophenone, 1,3- indandione, aromatic aldehydes and ammonium acetate compounds in aqueous ethanol solvent at rt by using Cu doped

ZnO nano crystalline powder as a green catalyst. In compliance with the green chemistry principles and optimum reaction conditions were reported with green solvent and catalyst (10 mol%), where the anticipated product was obtained in good to high yields within a short reaction time (Scheme 27) [222].

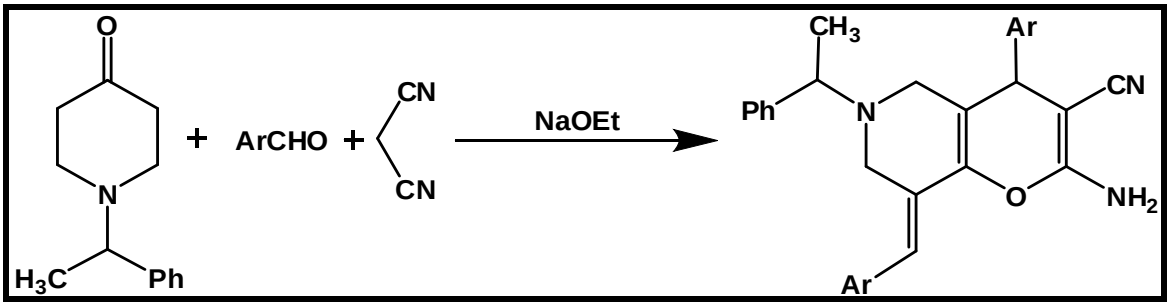
Zhao and co-workers have demonstrated the catalytic activity of Zn(II) and Cd(II) metal–organic frameworks (MOFs) towards the preparation of f 2-amino-3,5-dicarbonitrile-6-thio-pyridines derivatives from a one-pot, multi-component reaction of aromatic aldehydes, malononitrile and thiophenols. The authors proposed metal–organic framework catalysts for the organic transformations. This process offers many benefits including mild, environmental friendly green conditions and good to high yields in short reaction times. Moreover, the product did not necessitate separation via extraction and column chromatography (Scheme 28) [223].



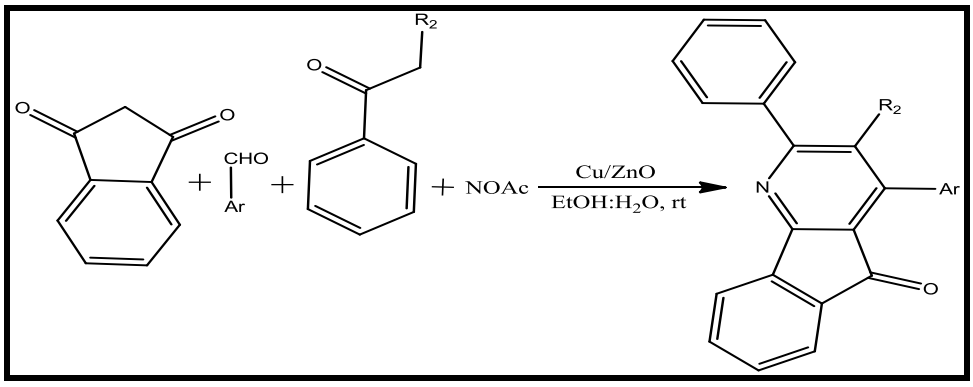
Scheme 24: Synthesis of Spiro-[diindenopyridine-indoline]-triones



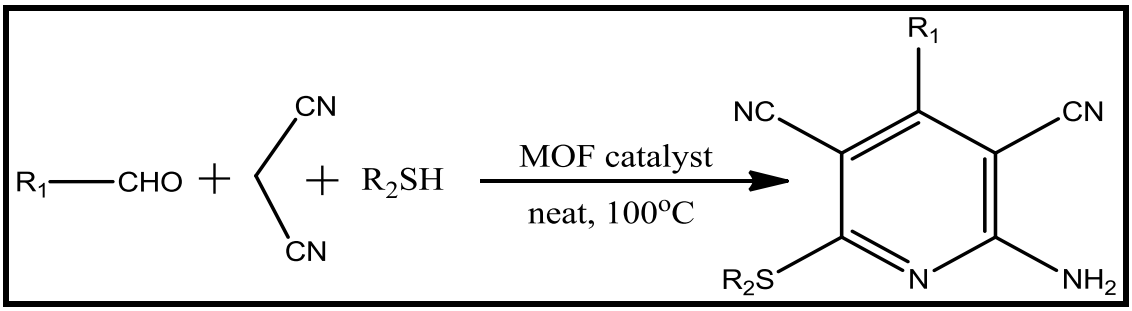
Scheme 25: Synthesis of Polysubstituted Pyridines via a $FeCl_3$ Catalst



Scheme 26: Synthesis of biologically active 4(H)-pyran derivatives



Scheme 27: Synthesis of indenopyridines using Cu/ZnO catalyst



Scheme 28: Multi-component synthesis of 2-amino-6-thiopyridine-3,5-dicarbonitriles catalyzed by Zn-MOF and Cd-MOF

1.7. Objectives of the study

Aim of the study is to develop new materials as potential heterogeneous catalysts to improve the efficiency of one-pot Hantzsch multicomponent protocols for synthesis of multi-substituted heterocyclic moieties, and to design the facile methods with improved efficiency by employing environmentally benign solvents at moderate conditions. The studies are focused on the development of novel heterogeneous catalyst materials and also their characterization.

The study involved the preparation of three new catalyst materials namely, ceria, samaria and yttria loaded on zirconia support and their characterization, plus the validation of their efficacy as reusable hydrogenous catalysts in the syntheses of three series of varied pyridine derivatives, namely

a) Synthesis of novel dimethyl 6-amino-5-cyano-1-(4-fluorophenyl)-4-(substitutedphenyl)-1,4-dihydropyridine-2,3-dicarboxylates (11 new compounds)
b) Synthesis of novel dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(substituted phenyl)-1,4-dihydropyridine-2,3-dicarboxylate-1,4-dihydropyridines (9 new compounds)
c) Synthesis of novel dimethyl 6-amino-5-cyano-1-(4-bromo-3-chlorophenyl)-4-(substitutedphenyl)-1,4-dihydropyridine-2,3-dicarboxylate derivatives (10 new compounds)

1.8. References

[1]. I.W.C.E. Arends, R.A. Sheldon, Activities and stabilities of heterogeneous catalysts in selective liquid phase oxidations: Recent developments. Appl. Catal. A: Gen. 2001, 212, 175–187.

[2]. P.T. Anastas, L.B. Bartlett, M.M. Kirchhoff, T.C. Williamson, The role of catalysis in the design, development, and implementation of green chemistry. Catal. Today. 2000, 55, 11–22.

[3]. T.P. Vispute, H. Zhang, A. Sanna, R. Xiao, G.W. Huber, Renewable chemical commodity feedstocks from integrated catalytic processing of pyrolysis oils. Science. 2010, 330, 1222-1227.

[4]. M.G. Kulkarni, R. Gopinath, L.C. Meher, A.K. Dalai, Solid acid catalyzed biodiesel production by simultaneous esterification and transesterification. Green Chem. 2006, 8, 1056-1062.

[5]. J.H. Clark, Green chemistry: challenges and opportunities. Green Chem. 1999, 1, 1-8.

[6]. H. Hattori. Solid base catalysts: generation of basic sites and application to organic synthesis. Appl. Catal. A: Gen. 2001, 222, 247–259.

[7]. K. Yamaguchi, K. Ebitani, T. Yoshida, H. Yoshida, K. Kaneda. Mg−Al mixed oxides as highly active acid−base catalysts for cycloaddition of carbon dioxide to epoxides. J. Am. Chem. Soc. 1999, 121, 4526–4527.

[8]. J.H. Clark, D.J. Macquarrie. Environmentally friendly catalytic methods. Chem. Soc. Rev. 1996, 25, 303-310.

[9]. J.N. Galloway, The global nitrogen cycle: changes and consequences. Environ. Pollut. 1998, 102, 15-24.

[10]. J.M. Thomas, R. Raja, Catalytically active centres in porous oxides: design and performance of highly selective new catalysts. Chem. Commun. 2001, 675-687.

[11]. D.E. De Vos, M. Dams, B.F. Sels, P. A. Jacobs, Ordered mesoporous and microporous molecular sieves functionalized with transition metal complexes as catalysts for selective organic transformations. Chem. Rev. 2002, 102, 3615–3640.

[12]. F. Zaera, Nanostructured materials for applications in heterogeneous catalysis. Chem. Soc. Rev. 2013, 42, 2746-2762.

[13]. M.B. Gawande, R.K. Pandey, R.V. Jayaram, Role of mixed metal oxides in catalysis science—versatile applications in organic synthesis. Catal. Sci. Technol. 2012, 2, 1113-1125.

[14]. R.B.N. Baig, R.S. Varma, Magnetically retrievable catalysts for organic synthesis. Chem. Commun. 2013, 49, 752-770.

[15]. K.H. Kim, S.K. Ihm, Heterogeneous catalytic wet air oxidation of refractory organic pollutants in industrial wastewaters: A review. J. Hazard. Mater. 2011, 186, 16–34.

[16]. A.A. Kiss, A.C. Dimian, G. Rothenberg, solid acid catalysts for biodiesel production –towards sustainable energy. Adv. Syn. & Catal. 2006, 348, 75–81.

[17]. M. Klavarioti, D. Mantzavinos, D. Kassinos, Removal of residual pharmaceuticals from aqueous systems by advanced oxidation processes. Environ. Inter. 2009, 35, 402–417.

[18]. C. Descorme, P. Gallezot, C. Geantet, C. George, Heterogeneous catalysis: a key tool toward sustainability. ChemCatChem. 2012, 4, 1897–1906.

[19]. C.J. Pereira, Environmentally friendly processes, Chem. Eng. Sci. 1999, 54, 1959-1973.

[20]. L. Brennan, P. Owende, Biofuels from microalgae—A review of technologies for production, processing, and extractions of biofuels and co-products. Ren. Sus. Ene.rgy Rev. 2010, 14, 557–577.

[21]. B.M. Reddy, A. Khan, Recent advances on tio_2-zro_2 mixed oxides as catalysts and catalyst supports. Catal. Rev. 2005, 47, 257-296.

[22]. P. McMorn, G.J. Hutchings, Heterogeneous enantioselective catalysts: strategies for the immobilisation of homogeneous catalysts. Chem. Soc. Rev. 2004, 33, 108-122.

[23]. F. Rantwijk, R.A. Sheldon, Biocatalysis in Ionic Liquids. Chem. Rev. 2007, 107, 2757–2785.

[24]. H.O. Bourbigou, L. Magna1, D. Morvan, Ionic liquids and catalysis: Recent progress from knowledge to applications. Appl. Catal. A: Gen. 2010, 373, 1–56.

[25]. R.G. Pearson, J. Songstad, Application of the principle of hard and soft acids and bases to organic chemistry. J. Am. Chem. Soc. 1967, 89, 1827–1836.

[26]. C.K. Prier, D.A. Rankic, D.W.C. MacMillan, Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. Chem. Rev. 2013, 113, 5322–5363.

[27]. J.K. Nørskov, T. Bligaard, B. Hvolbæk, F. Abild-Pedersen, I. Chorkendorff, C.H. Christensen, The nature of the active site in heterogeneous metal catalysis. Chem. Soc. Rev. 2008, 37, 2163-2171.

[28]. B. Cornils, W.A. Herrmann, Concepts in homogeneous catalysis: the industrial view. J. Catal. 2003, 216, 23–31.

[29]. N. Mizuno, M. Misono, Heterogeneous catalysis. Chem. Rev. 1998, 98, 199–218.

[30]. C. Baleizão, A. Corma, H. Garcia, A. Leyva, oxime carbapalladacycle covalently anchored to high surface area inorganic supports or polymers as heterogeneous green catalysts for the suzuki reaction in water. J. Org. Chem. 2004, 69, 439–446.

[31]. J.V. Lauritsen, F. Besenbacher, model catalyst surfaces investigated by scanning tunneling microscopy. Adv. Catal. 2006, 50, 97–147.

[32]. P.S. Nigam, A. Singh, Production of liquid biofuels from renewable resources. Prog. Ener. Combust. 2011, 37, 52–68.

[33]. Z. Zhang, K. Deng, Recent advances in the catalytic synthesis of 2,5-furandicarboxylic acid and its derivatives. ACS Catal. 2015, 5, 6529–6544.

[34]. K. Pirkanniemia, M. Sillanpaa, Heterogeneous water phase catalysis as an environmental application: a review. Chemosphere. 2002, 48, 1047–1060.

[35]. G.A. Olah, A. Goeppert, G. K.S. Prakash, Chemical recycling of carbon dioxide to methanol and dimethyl ether: from greenhouse gas to renewable, environmentally carbon neutral fuels and synthetic hydrocarbons. J. Org. Chem. 2009, 74, 487–498.

[36]. J.A. Melero, J. Iglesias, G. Morales, Heterogeneous acid catalysts for biodiesel production: current status and future challenges. Green Chem. 2009, 11, 1285-1308.

[37]. J.M. Thomas, R. Raja, The advantages and future potential of single-site heterogeneous catalysts. Top. Catal. 2006, 40, 3–17.

[38]. C. Baleizao, H.Garcia, chiral salen complexes: an overview to recoverable and reusable homogeneous and heterogeneous catalysts. Chem. Rev. 2006, 106, 3987–4043.

[39]. R.A. Sheldon, R.S. Downing, Heterogeneous catalytic transformations for environmentally friendly production. Appl. Catal. A: Gen. 1999, 189, 163–183.

[40]. K. Tanabe, W.F. Hölderich, Industrial application of solid acid–base catalysts. Appl. Catal. A: Gen. 1999, 181, 399–434.

[41]. K. Matharu, S.K. Mittal, S.K.A. Kumar, S.K. Sahoo, Selectivity enhancement of Arsenazo(III) reagent towards heavier lanthanides using polyaminocarboxylic acids: a spectrophotometric study. Spectrochim. Acta. A. 2015, 145, 165-169.

[42]. G. Trautwein, B.E. Bakkali, J.A. Monge, B. Artetxe, S. Reinoso, J.M. Gutierrez-Zorrilla. Dimeric assemblies of lanthanide-stabilised dilacunary Keggin tungstogermanates: A new class of catalysts for the selective oxidation of aniline. J. Catal. 2015, 331, 110.

[43]. L. Ling, N.H L. Wang, Ligand-assisted elution chromatography for separation of lanthanides. J. Chromatogr. A. 2015, 1389, 28-38.

[44]. M.R. Kubli, A.K. Yatsimirsky, Phosphodiester cleavage by trivalent lanthanides in the presence of native cyclodextrins. Inorg. Chim. Acta. 2016, 440, 9-15.

[45]. X. Beaudoux, M. Virot, T. Chave, G. Leturcq, N. Clavier, N. Dacheux, S.I. Nikitenko, Catalytic dissolution of ceria–lanthanide mixed oxides provides environmentally friendly partitioning of lanthanides and platinum. Hydrometallurgy. 2015, 151, 107-115.

[46]. F.T. Edelmann, Lanthanides and actinides: Annual survey of their organometallic chemistry covering the year 2013. Coord. Chem. Rev. 2015, 284, 124-205.

[47]. Y. Ren, J.Lu, O. Jiang, X. Cheng, Amine-grafted on lanthanide metal-organic frameworks: Three solid base catalysts for Knoevenagel condensation reaction. J. Chen, Chinese Journal of Catalysis. 2015, 3, 1949-1956.

[48]. H. Zhao, J. Hong, X. Yu, X. Zhao, L. Sheng, Y. Ze, X. Sang, S. Gui, Q. Sun, L. Wang, F. Hong, Oxidative stress in the kidney injury of mice following exposure to lanthanides trichloride. Chemosphere. 2013, 93, 875-884.

[49]. S. Tan, S.N. Paglieri, D. Li, Nano-scale sulfur-tolerant lanthanide oxysulfide/oxysulfate catalysts for water–gas-shift reaction in a novel reactor configuration. Catal. Commun. 2016, 73, 16-21.

[50]. X. Yu, J. K. Clegg, Y. Q. Zhang, S. F. Xue, Z. Tao, Q. J. Zhu, L. F. Lindoy, G. Wei, Adducts of aqua complexes of Ln^{3+} with ortho-tetramethyl substituted cucurbituril: Potential applications for isolation of heavier lanthanides. Polyhedron. 2015, 91, 150-154.

[51]. H.Y. Wua, H.B. Wang, X.H. Liua, J.H. Lia, M.H. Yanga, C.J. Huanga, W.Z. Wenga, H. L. Wana, Samarium-modified vanadium phosphate catalyst for the selective oxidation of n-butane to maleic anhydride. Appl. Sur. Sci. 2015, 351, 243-249.

[52]. G. Paolucci, A. Zanella, M. Bortoluzzi, S. Sostero, P. Longoc, M. Napoli, New constrained geometry catalysts-type yttrium, samarium and neodymium derivatives in olefin polymerization. J. Mol. Catal. A: Chem. 2007, 272, 258-264.

[53]. M. Bellardita, A.D. Paolaa, L. Palmisanoa, F. Parrinoa, G. Buscarinob, R. Amadellic, Preparation and photoactivity of samarium loaded anatase, brookite and rutile catalysts. Appl. Catal. B-Environ. 2011, 104, 291-299.

[54]. M. Martincic, C. Frontera, E. Pach, B. Ballesteros, G. Tobias, Synthesis of dry SmCl3 from Sm2O3 revisited. Implications for the encapsulation of samarium compounds into carbon nanotubes. Polyhedron. 2016, DOI: 10.1016/j.poly.2016.03.045

[55]. Y. Hanifehpour, B. Soltania, A. Reza A. Ghadima, B. Hedayatia, B. Khomamic, S.W. Joo, Synthesis and characterization of samarium-doped ZnS nanoparticles: A novel visible light responsive photocatalyst. Mater. Res. Bull. 2016, 76, 411-421.

[56]. I. Rossettia, J. Lassoa, V. Nicheleb, M. Signorettob, E. Finocchioc, G. Ramisc, A.D. Micheled, Silica and zirconia supported catalysts for the low-temperature ethanol steam reforming. Appl. Catal. B-Environ. 2014, 150, 257-267.

[57]. I. Reyero, A. Moral, F. Bimbela, J. Radosevic, O. Sanz, M. Montes, L. M. Gandía, Metallic monolithic catalysts based on calcium and cerium for the production of biodiesel. Fuel. 2016, 182, 668-676.

[58]. L. Wei, S. Cui, H. Guo, X. Ma, L. Zhang, DRIFT and DFT study of cerium addition on SO2 of Manganese-based Catalysts for low temperature SCR. J. Mol. Catal. A-Chem. 2016, 421, 102-108.

[59]. W. Wattanathana, N. Nootsuwan, C. Veranitisagul, N. Koonsaeng, N. Laosiripoja, A. Laobuthee, Simple cerium-triethanolamine complex: Synthesis, characterization, thermal decomposition and its application to prepare ceria support for platinum catalysts used in methane steam reforming. J. Mol. Struct. 2015, 1089, 9-15.

[60]. T.R. Reina, S. Ivanova, V. Idakiev, T. Tabakova, M.A. Centeno, Q.F. Deng, Z.Y. Yuan, J. A. Odriozola, Nanogold mesoporous iron promoted ceria catalysts for total and preferential CO oxidation reactions. J. Mol. Cat. A: Chemical. 2016, 414, 62-71.

[61]. X.K. Phan, J.C. Walmsley, H.B. Davijanya, R. Myrstad, P. Pfeifer, H. Venvika, A. Holmena, Pd/CeO2 catalysts as powder in a fixed-bed reactor and as coating in a stacked foil microreactor for the methanol synthesis. Catal. Today. 2016, 273, 25-33.

[62]. F. Hayashi, M. Tanaka, D. Lin, M. Iwamoto, Surface structure of yttrium-modified ceria catalysts and reaction pathways from ethanol to propene. J. Catal. 2014, 316, 112-120.

[63]. Y. Cao, X. Feng, H. Xua, L. Lana, M. Gong, Y. Chen, Novel promotional effect of yttrium on Cu–SAPO-34 monolith catalyst for selective catalytic reduction of NOx by NH3 (NH3-SCR). Catal. Commun. 2016, 76, 33-36.

[64]. A.A. Fakhrabadi, R. Saravanan, M. Jamshidijam, R.V. Mangalaraja, M.A. Gracia, Preparation of nanosized yttrium doped CeO2 catalyst used for photocatalytic application. J. Saud. Chem. Soc. 2015, 19, 505-510.

[65]. F. Wang, J.L. Fan, Y. Zhao, W.X. Zhang, Y. Liang, J. Q. Lu, M.F. Luo, Y.J. Wang, Effects of yttrium-doping on the performance of Cr_2O_3 catalysts for vapor phase fluorination of 1,1,2,3-tetrachloropropene. J. Fluorin. Chem. 2014, 166, 78-83.

[66]. B. Xua, Q. Zhanga, S. Yuana, M. Zhanga, T. Ohno, Synthesis and photocatalytic performance of yttrium-doped CeO2 with a porous broom-like hierarchical structure. Appl. Catal. B: Env. 2016, 183, 361-370.

[67]. I. Kumar, N. A. Mir, P. Ramarajua and B.P. Wakhlooc, Organocatalytic Mannich/cyclization/aromatization sequence: direct synthesis of substituted pyrrole-3-carboxaldehydes. RSC Adv. 2012, 2, 8922-8925.

[68]. M. Sadiqa, M. Ilyas, Exploring the Catalytic Activity of Zirconia, Zirconia Supported Metals and Metal Oxides for Oxidation of Phenol. Modern Res. Catal. 2012, 1, 23-27.

[69]. M. Pudukudya, Z. Yaakobb, Catalytic aspects of ceria zirconia solid solution: Part-II An overview on recent developments in the heterogeneous catalytic applications of metal loaded ceria-zirconia solid solution. Der Pharma Chem. 2014, 6, 224-240.

[70]. H. Muthu, V.S. Selvabala, T.K. Varathachary, D.K. Selvaraj, J. Nandagopal, S. Subramanian, Synthesis of biodiesel from neem oil using sulfated zirconia via tranesterification. Braz. J. Chem. Eng. 2010, 27, 601-608.

[71]. P.T. Patil, K.M. Malshe, P. Kumar, M.K. Dongare, E. Kemnitz, Benzoylation of anisole over borate zirconia solid acid catalyst. Catal. Commun. 2002, 3, 411-416.

[72]. S.H. Cho, S.B.T. Nguyen, J. T. Hupp, The interface between heterogeneous and homogeneous catalysis. Top. Catal. 2005, 34, 1-4.

[73]. J. Houghton, 10th Scientific Bases for the Preparation of Heterogeneous Catalysts. Platin. Met. Rev. 2011, 55, 28-32.

[74]. I. Fatimah, D. Rubiyanto, T. Huda. Effect of Sulfation on Zirconia-Pillared Montmorillonite to the Catalytic Activity in Microwave-Assisted Citronellal Conversion. Int. J. Chem.Eng. 2014, 1-7.

[75]. E. Gaignaux, D.E.D, Vos, P. Grange, P.A. Jacobs, J.A. Martens, P. Ruiz, G. Poncelet. Scientific Basis for the Preparation of Heterogeneous Catalysts. 2002, 803.

[76]. E. Moretti, L. Storaro, A. Talon, S. Chitsazan, G. Garbarino, G. Busca, E. Finocchio. Ceria–zirconia based catalysts for ethanol steam reforming. Fuel. 2015, 153, 166.

[77]. A. Song, G. Lu, Selective oxidation of methylamine over zirconia supported Pt-Ru, Pt and Ru catalysts. Chin. J. Chem. Eng. 2015, 23, 1206-1213.

[78]. I. U. Din, M.S. Shaharun, D. Subbarao, A. Naeem, Synthesis, characterization and activity pattern of carbon nanofibers based copper/zirconia catalysts for carbon dioxide hydrogenation to methanol: Influence of calcination temperature. J. Power Sources. 2015, 274, 619-628.

[79]. N. Nikolaou, C.E. Papadopoulos, I.A. Gaglias, K.G. Pitarakis, A new non-linear calculation method of isomerisation gasoline research octane number based on gas chromatographic data. Fuel. 2004, 83, 517-523.

[80]. A. Dömling, Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry, Chem. Rev. 2006, 106, 17–89.

[81]. E.S. Elshazly, O.A.A. Abdelal, Nickel stabilized zirconia for SOFCs: synthesis and characterization. Int. J. Metall. Eng. 2012, 1(6), 130-134.

[82]. S. Chakharia, M.K. Younesa, A. Rivesb, A. Ghorbel, Effect of the doping agent nature on the characteristic and catalytic properties of aerogel zirconia catalysts doped with sulfate groups or heteropolytungstic acid. Mater. Res. Bull. 2015, 72, 35-42.

[83]. G.D. Hobson, Modern Petroleum Technology 1984, 2, 786.

[84]. P.B. Weisz, P.W. Eley, Advances in Catalysis and Related Subjects. 1963, 13, 157.

[85]. N. Nikolaou, C.E. Papadopoulos, I.A. Gaglias, K.G. Pitarakis, A new non-linear calculation method of isomerisation gasoline research octane number based on gas chromatographic data. Fuel. 2004, 83, 517-523.

[86]. G. Shi, F. Yu, Y. Wang, D. Pan, H. Wang, R. Li, A novel one-pot synthesis of tetragonal sulfated zirconia catalyst with high activity for biodiesel production from the transesterification of soybean oil. Renew. Energ. 2016, 92, 22-29.

[87]. D.F. Srcaiu, J.Q. Li, S. Cameron, Preparation of sulfated zirconia catalysts with improved control of sulfur content II. Effect of sulfur content on physical properties and catalytic activity. Appl. Catal. A: Gen. 1997, 154, 173-184.

[88]. W. Stichert, F. Schuth, S. Kuba, H. Knozinger, Monoclinic and Tetragonal High Surface Area Sulfated Zirconias in Butane Isomerization: CO Adsorption and Catalytic Results. J. Catal. 2001,198, 277–285.

[89]. X. Qi, M. Watanabe, T.M. Aida, R.L. Smith, Jr. Sulfated zirconia as a solid acid catalyst for the dehydration of fructose to 5-hydroxymethylfurfural. Catal. Commun. 2009, 10, 1771.

[90]. G. A. Moldoveanu, V.G. Papangelakis, Effects of thermal pre-treatment and ore dryness on the recovery of lanthanides from ion-adsorption clays. Hydrometallurgy. 2015, 158, 180-185.

[91]. N. Nikolaou, C.E. Papadopoulos, I.A. Gaglias, K.G. Pitarakis, A new non-linear calculation method of isomerisation gasoline research octane number based on gas chromatographic data. Fuel. 2004, 83, 517-523.

[92]. B.A. Dar, S. Khalid, T. A. Wani, M.A. Mir, M. Farooqui, Ceria-Based Mixed Oxide Supported CuO: An Efficient Heterogeneous Catalyst for Conversion of Cellulose to Sorbitol. Green Sus. Chem. 2015, 5, 15-24.

[93]. W. Chu, T. Echizen, Y. Kamiy, T. Okuhara, Gas-phase hydration of ethene over tungstena–zirconia. Appl. Catal. A: Gen. 2004, 259, 199–205.

[94]. M.A. Mironov, Design of multi-component reactions: from libraries of compounds to libraries of reactions. QSAR & Combinatorial Science: Multicomponent Reactions. 2006, 25, 423-431.

[95]. H. Purnama, F. Girgsdies, T. Ressler, J.H. Schattka, R.A. Caruso, R. Schomäcker, R. Schlogl. Catal. Lett. 2004, 94, 61.

[96]. A.M. Hengne, C.V. Rode, Cu–ZrO_2 nanocomposite catalyst for selective hydrogenation of levulinic acid and its ester to γ-valerolactone. Green Chem. 2012, 14, 1064–1072.

[97]. C.O. Kappe, 4-Aryldihydropyrimidines via the Biginelli Condensation: Aza-Analogs of Nifedipine-Type Calcium Channel Modulators. Molecules. 1998, 3, 1 – 9.

[98]. T. Sreethawong, S. Ngamsinlapasathian, S. Yoshikawa, Synthesis of crystalline mesoporous-assembled ZrO_2 nanoparticles via a facile surfactant-aided sol–gel process and their photocatalytic dye degradation activity. Chem. Eng. J. 2013, 228, 256–262.

[99]. A. Miko, A.L. Demirel, M. Somer, Vertically oriented hexagonal mesoporous zirconia thin films by block copolymer templating. J. Mater. Chem. 2012, 22, 3705–3707.

[100]. S. Esposito, M. Turco, G. Bagnasco, C. Cammarano, P. Pernice, A. Aronne, Highly dispersed sol–gel synthesized Cu–ZrO_2 materials as catalysts for oxidative steam reforming of methanol. Appl. Catal. A: Gen. 2010, 372, 48–57.

[101]. X. Guo, D. Mao, G. Lu, S. Wang, G. Wu, The influence of La doping on the catalytic behavior of Cu/ZrO_2 for methanol synthesis from CO_2 hydrogenation. J. Mol. Catal. A-Chem. 2011, 345, 60– 68.

[102]. Y. Bai, D. He, S. Ge, H. Liu, J. Liu, W. Huang, Influences of preparation methods of ZrO_2 support and treatment conditions of Cu/ZrO_2 catalysts on synthesis of methanol via CO hydrogenation. Catal. Today. 2010 111–116.

[103]. W. Ciptonugroho, M.G. Al-Shaal, J.B. Mensah, R. Palkovits, One pot synthesis of WOx/mesoporous-ZrO2 catalysts for the production of levulinic-acid esters. J. Catal. 2016, 340, 17–29.

[104]. L. Chen, J. Li, M. Ge, Promotional Effect of Ce-doped V2O5-WO3/TiO2 with Low Vanadium Loadings for Selective Catalytic Reduction of NOx by NH3. J. Phys. Chem. C. 2009, 113, 21177–21184.

[105]. M.A. Cortés-Jácome, J.A. Toledo, C. Angeles-Chavez, Influence of Synthesis Methods on Tungsten Dispersion, Structural Deformation, and Surface Acidity in Binary WO3−ZrO2 System. J. Phys. Chem. B. 2005, 109, 22730–22739.

[106]. L. Xiaowei, S. Mingmin, H. Xi, Z. Haiyang, G. Fei, K. Yan, D. Lin, C. Yi, Dispersion and Reduction of Copper Oxide Supported on WO3-Modified Ce0.5Zr0.5O2 Solid Solution. J. Phys. Chem. B. 2005, 109, 3949–3955.

[107]. M.A. Cortés-Jácome, C.A. Chavez, E.L. Salinas, J. Navarrete, P. Toribio, J.A. Toledo, Migration and oxidation of tungsten species at the origin of acidity and catalytic activity on WO3-ZrO2 catalysts. Appl. Catal. A: Gen. 2007, 318, 178–189.

[108]. W. Chu, T. Echizen, Y. Kamiy, T. Okuhara, Gas-phase hydration of ethene over tungstena–zirconia. Appl. Catal. A: Gen. 2004, 259, Pages 199–205.

[109]. S. Ramu, N. Lingaiah, B.L.A.P. Devi, R.B.N. Prasad, I. Suryanarayana, P.S.S. Prasad, Esterification of palmitic acid with methanol over tungsten oxide supported on zirconia solid acid catalysts: effect of method of preparation of the catalyst on its structural stability and reactivity. Appl. Catal. A: Gen. 2004, 276, 163–168.

[110]. C.D. Baertsch, S.L. Soled, E. Iglesia, Isotopic and Chemical Titration of Acid Sites in Tungsten Oxide Domains Supported on Zirconia. J. Phys. Chem. B, 2001, 105, 1320–1330.

[111]. I. N, M.M.S. Duquek, J. Plaquevent, Y. Genisson, J. Rodriguez, T. Constantieuxl, Multicomponent reactions and ionic liquids: a perfect synergy for eco-compatible heterocyclic synthesis. Chem. Soc. Rev. 2011, 40, 1347-1357.

[112]. C. Graaff, E. Ruijter, R.V.A. Orru, Recent developments in asymmetric multicomponent reactions. Chem. Soc. Rev. 2012, 41, 3969-4009.

[113]. A. Domling, W. Wang, K. Wang, Chemistry and biology of multicomponent reactions. Chem. Rev. 2012, 112, 3083-3135.

[114]. P. Slobbe, E. Ruijter, R.V.A. Orru, Recent applications of multicomponent reactions in medicinal chemistry. Med. Chem. Commun. 2012, 3, 1189-1218.

[115]. B.H. Rotstein, S. Zaretsky, V. Rai, A.K. Yudin, Small heterocycles in multicomponent reactions. Chem. Rev. 2014, 114, 8323-8359.

[116]. S. Brauch, S.S. Berkel, W. Westermann, Higher-order multicomponent reactions: beyond four reactants. Chem. Soc. Rev. 2013, 42, 4948-4962.

[117]. M.B. Gawande, V.D.B. Bonifacio, R. Luque, P.S. Branco, R.S. Varma, Benign by design: catalyst-free in-water, on-water green chemical methodologies in organic synthesis. Chem. Soc. Rev. 2013, 42, 5522-5551.

[118]. C.C. Razvan, E. Ruijter, R.V.A. Orru, Multicomponent reactions: Advanced tools for sustainable organic synthesis. Green Chem. 2014, 16, 2958-2975.

[119]. G. Silvia, P. Stefano, B. Andrea, Toward a green atom economy: development of a sustainable multicomponent reaction. Synthesis. 2015, 47, 2385-2390

[120]. M.A. Mironov, Design of multi-component reactions: from libraries of compounds to libraries of reactions. QSAR & Comb.Sci. 2006, 25, 423-431.

[121]. M.S. Singh, S. Chowdhury, Recent developments in solvent-free multicomponent reactions: a perfect synergy for eco-compatible organic synthesis. RSC Adv. 2012, 2, 4547-4592.

[122]. A.A. Strecker. Chem. Pharm. 1850. 75. 27.

[123]. H. Ishitani, S.Y. Komiyama, Y. Hasegawa, S.J. Kobayashi. J. Am. Chem. Soc. 2000, 122, 762.

[124]. R. Martínez, D.J. Ramón, M. Yus, Catalyst-free multicomponent Strecker reaction in acetonitrile. Tetrahedron Lett. 2005, 46, 8471–8474.

[125]. S.S. Mansoor, K. Aswin, K. Logaiya, S.P.N. Sudhan, An efficient one-pot three-component synthesis of α-amino nitriles via Strecker reaction catalysed by bismuth(III) nitrate. J. Saud. Chem. Soc. 2016, 20,202–210.

[126]. M. Shiri, Indoles in Multicomponent Processes (MCPs), Chem. Rev. 2012, 112, 3508–3549.

[127]. P. Biginelli. Derivati aldeidureidici degli eteri acetil-ed ossalacetico. Gazz. Chim. Ital. 1893, 23, 360-413.

[128]. C.O. Kappe, The Generation of Dihydropyrimidine Libraries Utilizing Biginelli Multicomponent Chemistry. Mol. Inform. 2003, 22, 630–645.

[129]. C.O. Kappe, Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. Acc. Chem. Res. 2000, 33, 879–888.

[130]. A. Stadler, C.O. Kappe, Automated Library Generation Using Sequential Microwave-Assisted Chemistry. Application toward the Biginelli Multicomponent Condensation. J. Comb. Chem. 2001, 3, 624–630.

[131]. C.O. Kappe, 4-Aryldihydropyrimidines via the Biginelli Condensation: Aza-Analogs of Nifedipine-Type Calcium Channel Modulators. Molecules. 1998, 3, 1 – 9.

[132]. C. Mannich. Eine Synthese von β-Ketonbasen. Arch. Pharm. 1917, 255, 261– 276.

[133]. B.B. Toure, D.G. Hall, Natural Product Synthesis Using Multicomponent Reaction Strategies. Chem. Rev. 2009, 109, 4439–4486.

[134]. M.J. Climent, A. Corma, S. Iborra, Homogeneous and heterogeneous catalysts for multicomponent reactions. RSC Adv. 2012, 2, 16-58.

[135]. N. Azizi , L. Torkiyan, M.R. Saidi, Highly Efficient One-Pot Three-Component Mannich Reaction in Water Catalyzed by Heteropoly Acids. Org. Lett. 2006, 8, 2079–2082.

[136]. R. Robinson. LXXV. A theory of the mechanism of the phytochemical synthesis of certain alkaloids. J. Chem. Soc. 1917, 111, 876– 899.

[137]. G.H. Posner, Multicomponent one-pot annulations forming 3 to 6 bonds. Chem. Rev. 1986, 86, 831–844.

[138]. A.J. Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing, M. Beller, multicomponent coupling reactions for organic synthesis: chemoselective reactions with amide–aldehyde mixtures. Chem. A. Eur. J. 2003, 9, 4286–4294.

[139]. M. Passerini. New progresses of multicomponent reactions based on isocyanides Gazzetta Chimica Italiana. 1921, 51, 126– 129.

[140]. M. Adib, E.Sheikhi, M. Azimzadeh, A new modification of the Passerini reaction: A one-pot synthesis of a-acyloxyamides via sequential kornblum oxidation/passerini reaction. Tetrahedron Lette. 2015, 56, 1933–1936.

[141]. A. Dömling, Recent advances in isocyanide-based multicomponent chemistry, Curr. Opi. Chem. Bio. 2002, 6, 306–313.

[142]. E. Ruijter, R.V.A. Orru, Multicomponent reactions – opportunities for the pharmaceutical industry. Drug Discov. Today-Technol. 2013, 10, 15–20.

[143]. R.K. Ali, R. Ali, Synthetic Applications of Passerini Reaction, Source: Curr. Org. Chem. 2012, 16, 418-450.

[144]. L.E. Kaïm, M. Gizolme, L. Grimaud, J. Oble, Smiles Rearrangements in Ugi- and Passerini-Type Couplings: New Multicomponent Access to O- and N-Arylamides. J. Org. Chem. 2007, 72, 4169–4180.

[145]. I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner. Versuche mit isonitrilen. Angew. Chemie. 1959, 71, 386–388.

[146]. I. Ugi, C. Steinbruckner, Uber ein neues kondensations-prinzip. Angew. Chem. 1960 ,72, 267–268.

[147]. A. Domling, I. Ugi, Multicomponent reactions with isocyanides. Angew. Chem. Int. Ed. 2000, 39, 3169–3210.

[148]. A. Golebiowski, J. Jozwik , S.R. Klopfenstein, A.O. Colson, A.L. Grieb, A.F. Russell, V. L. Rastogi, C.F. Diven, D.E. Portlock, J.J. Chen, Solid-Supported Synthesis of Putative Peptide β-Turn Mimetics via Ugi Reaction for Diketopiperazine Formation. J. Comb. Chem., 2002, 4, 584–590.

[149]. D. Yuan, Z. Duan, Y. Rao, M.W. Ding, New efficient synthesis of isoquinoline-1,3(2H,4H)-diones and isoindolin-1-ones via sequential ugi/cyclization reaction. Tetrahedron. 2016, 72, 338– 346.

[150]. J.M. Haigh, A. Hussain, M.L. Mimmack, C.R. Lowe, Affinity ligands for immunoglobulins based on the multicomponent Ugi reaction. J.Chromatogr-B. 2009, 877, 1440–1452.

[151]. G.E. Khoury, L.A. Rowe, C. R. Lowe, Biomimetic Affinity Ligands for Immunoglobulins Based on the Multicomponent Ugi Reaction. Chem. Genom. Proteomi. 2011, 800, 57-74.

[152]. A. Hantzsch, Ueber die Synthese pyridinartiger Verbindungen aus Acetessigäther und Aldehydammoniak. Justus Liebigs Annalen der Chemie. 1882, 215, 1– 82.

[153]. O.D. Alessandro, Á.G. Sathicq, J.E. Sambeth, H.J. Thomas, G.P. Romanelli. A study of the temperature effect on Hantzsch reaction selectivity using Mn and Ce oxides under solvent-free conditions. Catal. Commun. 2015, 60, 65–69.

[154]. R.G. Murray, D.M. Whitehead, F.L. Strat, S. J. Conway, Facile one-pot synthesis of 5-substituted hydantoins. Org. biomol. Chem. 2008, 6, 988-991.

[155]. K. Tanak, H. Iwabuchl, H. Sawanlshl,, Synthesis of homochiral 4-amino-4-carboxy-2-phosphonomethylpyrrolidines via a diastereoselective bucherer-bergs reaction of 4-oxopyrrolidine derivative: Novel conformationally restricted AP 5 analogues. Tetrahedron-Asymmetr. 1995, 6, 2271-2279.

[156]. C. Montagne, J. J. Shiers, M. Shipman, Rapid generation of molecular complexity using “sequenced” multi-component reactions: one-pot synthesis of 5,5′-disubstituted hydantoins from methyleneaziridines. Tetrahedron Lett. 2006, 47, 9207-9209.

[157]. R.G. Murray, D.M. Whitehead, F.L. Strat, S. J. Conway, Facile one-pot synthesis of 5-substituted hydantoins, Org. biomol. Chem. 2008, 6, 988-991.

[158]. E. Rajanarendar, M.R. Nagi, K.R. Govardhan, S.K. Rama, l-Proline catalyzed efficient one-pot three-component aza-Diels–Alder reactions on nitrostyrylisoxazoles: a facile synthesis of new isoxazolyl tetrahydroquinolines and isoxazolo[2,3-a]pyrimidines. Tetrahedron Lett. 2012, 53, 2909-2913.

[159] M. M. Sarmah, R. Sarma, D. Prajapati, W. Huc, Efficient synthesis of dihydropyrido[4,3-*d*]pyrimidines by microwave-promoted three-component aza-Diels–Alder reaction. Tetrahedron Lett. 2013, 54, 267-271.

[160]. Z. Q. Liu, Y. J. Hu, X.Y. Chen, Q. Wu, X.F. Lin, Enzymatic multicomponent reaction for simultaneous synthesis of two important scaffolds, pyridin-2-ones and a-alkylated nitriles. Tetrahedron. 2015, 71, 663-668.

[161]. M. Daryabari, S. Khaksar, Green synthesis of highly substituted pyridines via the one-pot multi-component reaction in 2,2,2-trifluoroethanol. J. Mol. Liq. 2014, 198, 263-266.

[162]. E. Rajanarendar, M.R. Nagi, K.R. Govardhan, S.K. Rama, l-Proline catalyzed efficient one-pot three-component aza-Diels–Alder reactions on nitrostyrylisoxazoles: a facile synthesis of new isoxazolyl tetrahydroquinolines and isoxazolo[2,3-a]pyrimidines. Tetrahedron Lett. 2012, 53, 2909-2913.

[163]. D. A. Powell, R.A. Batey, Lanthanide(III)-catalyzed multi-component aza-Diels–Alder reaction of aliphatic N-arylaldimines with cyclopentadiene. Tetrahedron Lett. 2003, 44, 7569.

[164]. J. Kajanus, I. Jacobson, A. Astrand, R.I. Olsson, U. Gran, A. Björe, O. Fjellström, O. Davidsson, H. Emtenas, A. Dahlen, B. Lofberg, Z.Q. Yuan, J. Sundell, J.Cassel, J. Gyll, T. Iliefski, A. Hogberg, E. Lindhardt, J. Malmberg, Isoindolinone compounds active as Kv1.5 blockers identified using a multicomponent reaction approach. Bioorg. Med. Chem. Lett. 2016, 26, 2023-2029.

[165]. D. Bhuyan, R. Sarma, D. Prajapati, Microwave-assisted efficient synthesis of spiroquinoline derivatives via a catalyst- and solvent-free aza-Diels–Alder reaction. Tetrahedron Lett. 2012, 53, 6460-6463.

[166]. M. Daryabari, S. Khaksar. Green synthesis of highly substituted pyridines via the one-pot multi-component reaction in 2,2,2-trifluoroethanol, J. Mol. Liq. 2014, 198, 263-266.

[167]. T. Yakaiah, B.P.V. Lingaiah, B. Narsaiah, K.P.Kumar, U.S.N. Murthy, GdCl3 catalysed Grieco condensation: A facile approach for the synthesis of novel pyrimidine and annulated pyrimidine fused indazole derivatives in single pot under mild conditions and their anti-microbial activity. Eur. J. Med.Chem. 2008, 43, 341-347.

[168]. P.W.S. Werner, G.H.C. Woo, C.R.J. Stephenson, M.A.A. Walczak, C.M. Coleman, L.A. Twining, Application of divergent multi-component reactions in the synthesis of a library

of peptidomimetics based on γ-amino-α,β-cyclopropyl acids. Tetrahedron. 2005, 61, 11488-11500.

[169]. A. Ouach, S. Gmouh, M. Pucheault, M. Vaultier, Onium salt supported organic synthesis in water: application to Grieco's multicomponent reaction. Tetrahedron. 2008, 64, 1962-1970.

[170]. M. Adib, E.Sheikhi, M. Azimzadeh, A new modification of the Passerini reaction: A one-pot synthesis of a-acyloxyamides via sequential kornblum oxidation/passerini reaction. Tetrahedron Lett. 2015, 56, 1933–1936.

[171]. E.K. Fields, The Synthesis of Esters of Substituted Amino Phosphonic Acids. J. Ame. Chem. Soc. 1952, 74, 1528-1531.

[172]. H. Ghafuri, A. Rashidizadeh, H.E. Zand, Highly efficient solvent free synthesis of a aminophosphonates catalysed by recyclable nanomagnetic sulfated zirconia (Fe_3O_4@ZrO_2/SO_4). RSC Adv. 2016, 6, 16046–16054.

[173]. Z.N. Tisseh, M. Dabiri, M. Nobahar, H.R. Khavasi, A. Bazgir, Catalyst-free, aqueous and highly diastereoselective synthesis of new 5-substituted 1H-tetrazoles via a multi-component domino Knoevenagel condensation/1,3 dipolar cycloaddition reaction. Tetrahedron. 2012, 68, 1769-1773.

[174]. J.M. Aracil, C.N._Ajera, L.M. Castell, J.M. Sansano, O. Naga, A.C. Ozar, F.P. Cossío, Regio and diastereoselective multicomponent 1,3-dipolar cycloadditions between prolinate hydrochlorides, aldehydes and dipolarophiles for the direct synthesis of pyrrolizidines. Tetrahedron. 2015, 71, 9645-9661.

[175]. B. Jones, M. Proud, V. Sridharan, Synthesis of oxetane/azetidine containing spirocycles via the 1,3-dipolar cycloaddition reaction. Tetrahedron Lett. 2016, 57, 2811-2813.

[176]. N. Devi, R.K. Rawal, V. Singh, Diversity-oriented synthesis of fused-imidazole derivatives via Groebke–Blackburn–Bienayme reaction: a review. Tetrahedron. 2015, 71, 183-232.

[177]. G.M.M. Ayaz, F. Medda, C. Hulme,, Synthesis of diverse nitrogen-enriched heterocyclic scaffolds using a suite of tunable one-pot multicomponent reactions, J. Org. Chem. 2014, 79, 5153– 5162.

[178]. T. Yakaiah, B.P.V. Lingaiah, B. Narsaiah, K.P. Kumar, S.N. Murthy, European Journal of Medicinal Chemistry. GdCl3 catalysed Grieco condensation: A facile approach for the synthesis of novel pyrimidine and annulated pyrimidine fused indazole derivatives in single pot under mild conditions and their anti-microbial activity. 2008, 43, 341-347.

[179]. M. Kidwai, R. Venktaramanan, R. Mohan, P. Sapra, Cancer Chemotherapy and Heterocyclic Compounds. Curr. Med. Chem. 2002, 9, 1209-1228.

[180]. N.T. Patil, Y. Yamamoto, Coinage Metal-Assisted Synthesis of Heterocycles. Chem. Rev. 2008, 108, 3395–3442.

[181]. G. Brahmachar, B. Banerjee, Facile and One-Pot Access to Diverse and Densely Functionalized 2-Amino-3-cyano-4H-pyrans and Pyran-Annulated Heterocyclic Scaffolds via an Eco-Friendly Multicomponent Reaction at Room Temperature Using Urea as a Novel Organo-Catalyst. ACS Sus. Chem. Eng. 2014, 2, 411–422.

[182]. S.M. Prajapati, K.D. Patel, R.H. Vekariya, S.N. Panchal, H.D. Patel, Recent advances in the synthesis of quinolines: a review. RSC Adv. 2014, 4, 24463-24476.

[183]. R.N. Patel, Synthesis of chiral pharmaceutical intermediates by biocatalysis. Coord. Chem. Rev. 2008, 252, 659–701.

[184]. B.M. Trost, A.J. Frontier, Atom Economical Syntheses of Oxygen Heterocycles via Tandem Palladium-Catalyzed Reactions. J. Am. Chem. Soc. 2000, 122, 11727–11728.

[185]. D.M. D'Souzaa, T.J.J. Müller, Multi-component syntheses of heterocycles by transition-metal catalysis. Chem. Soc. Rev. 2007,36, 1095-1108.

[186]. I. Nakamura, Y. Yamamoto, Transition-Metal-Catalyzed Reactions in Heterocyclic Synthesis. Chem. Rev. 2004, 104 , 2127–2198.

[187]. C. Liu, H. Zhang, W. Shi, A. Lei, Bond Formations between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions. Chem. Rev. 2011, 111, 1780–1824.

[188]. J.H. Clark, Solid Acids for Green Chemistry. Acc. Chem. Res. 2002, 35, 791–797.

[189]. V.V. Kouznetsov, Recent synthetic developments in a powerful imino Diels–Alder reaction (Povarov reaction): application to the synthesis of N-polyheterocycles and related alkaloids. Tetrahedron. 65, 14, 2721–2750.

[190]. A. Dömling, Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. Chem. Rev. 2006, 106, 17–89.

[191]. A.L. Boreen, W.A. Arnold, K. McNeill, Photochemical Fate of Sulfa Drugs in the Aquatic Environment: Sulfa Drugs Containing Five-Membered Heterocyclic Groups. Environ. Sci. Technol. 2004, 38, 3933–3940.

[192]. B. Jones, M. Proud, V. Sridharan, Synthesis of oxetane/azetidine containing spirocycles via the 1,3-dipolar cycloaddition reaction. Tetrahedron Lett. 2016, 57, 2811-2813.

[193]. D. Bora, B. Deb, A.L. Fuller, A.M.Z. Slawin, J.D. Woollins, DK. Dutta, Dicarbonyliridium(I) complexes of pyridine ester ligands and their reactivity towards various electrophiles. Inorg. Chim. Acta 2010, 363, 1539-1546.

[194]. M. Zhou, K.R. Jain, A. Günyar, P.N.W. Baxter, E. Herdtweck, F,E. Kühn, Bidentate Lewis Base Adducts of Methyltrioxidorhenium(VII): Ligand Influence on Catalytic Performance and Stability. Eur. J. Inorg. Chem. 2009, 2907-2914.

[195]. Y.T. Chan, C.N. Moorefield, M. Soler, G.R. Newkome, Unexpected Isolation of a Pentameric Metallomacrocycle from the FeII-Mediated Complexation of 120° Juxtaposed 2,2′:6′,2″-Terpyridine Ligands. Chem. Eur. J. 2010, 16, 1768-1771.

[196]. K. Shibatomi, T. Muto, Y. Sumikawa, A. Narayama, S. Iwasa, Development of a new chiral spiro oxazolinylpyridine ligand (Spymox) for asymmetric catalysis. Synlett 2009, 24. DOI: 10.1055/s-0028-1087675

[197]. R. Makiura, S. Motoyama, Y. Umemura, H. Yamanaka, O. Sakata, H. Kitagawa, Surface nano-architecture of a metal–organic framework. Nat. Mater. 2010, 9, 565-571.

[198]. N.G. Kang, M. Changez, J.S. Lee, Living Anionic Polymerization of the Amphiphilic Monomer 2-(4-Vinylphenyl)pyridine. Macromolecules 2007, 40, 8553-8559.

[199]. H. Hofmeier, U.S. Schubert, Combination of orthogonal supramolecular interactions in polymeric architectures. Chem. Commun. 2005, 2423-2432.

[200]. Fu, G. C. Acc. Asymmetric catalysis with “planar-chiral” derivatives of 4-(dimethylamino) pyridine. Chem. Res. 2004, 37, 542.

[201]. A.T. Khan, M. Lal, S. Ali, M.M. Khan, One-pot three-component reaction for the synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst. Tetrahedron Lett. 2011, 52, 5327.

[202]. J. P. Wana, D. Hua, Y. Liu, L. Li, C. Wen, Copper-catalyzed intramolecular oxidative amination of enaminone C–H bond for the synthesis of imidazo [1, 2-a] pyridines. Tetrahedron Lett. 2016, 57, 2880.

[203]. A. Z. Halimehjani, J. Martens, T. Schleuter, A one-pot three-component synthesis of dithiocarbamates starting from vinyl pyridines and vinyl pyrazine under solvent-and catalyst-free conditions. Tetrahedron. 2016, 72, 3958.

[204]. D. Srinivas, H. P. Upadhyaya, Chlorine atom formation dynamics in the dissociation of halogenated pyridines after photoexcitation at 235 nm: A resonance enhanced multiphoton ionization-time of flight (REMPI-TOF) study. Chem. Phy. 2016, 472, 208.

[205]. P. Thapa, T.M. Kadayat, S. Park, S. Shin, T.B.T. Magar, G. Bist, A. Shrestha, Y. Na, Y. Kwon, E.S. Lee, Synthesis and biological evaluation of 2-phenol-4-chlorophenyl-6-aryl pyridines as topoisomerase II inhibitors and cytotoxic agents. Bioorg. Chem. 2016, 66, 145.

[206]. S. Lai, X. Ren, J. Zhao, Z. Tang, G. Li, Simple Brønsted acid catalyzed C–H functionalization: efficient access to poly-substituted pyridines. Tetrahedron Lett. 2016, 57, 2957.

[207]. T. Onnagawa, Y. Shima, T. Yoshimura, J. Matsuo, Formal [4+ 2] cycloaddition of quinolines, pyridines, and isoquinolines with 3-ethoxycyclobutanones. Tetrahedron Lett. 2016, 57, 3050.

[208]. T. Katoh, Y. Tomata, T. Tsukamoto, Y. Nakada, Double Michael addition/aza-cyclization: a valuable sequence for the construction of symmetrical and unsymmetrical spirobarbiturate-pyridines. Tetrahedron Lett. 2015, 56, 6043.

[209]. L. De Crescentini, O.A. Attanasi, L.A. Campisi, G. Favi, S. Lillini, F. Ursini, F. Mantellini, Double Michael addition/aza-cyclization: a valuable sequence for the construction of symmetrical and unsymmetrical spirobarbiturate-pyridines. Tetrahedron. 2015, 71, 7282-7292.

[210]. T. M. Kadayat, C. Song, Y. Kwon, E. S. Lee, Modified 2, 4-diaryl-5H-indeno [1, 2-b] pyridines with hydroxyl and chlorine moiety: Synthesis, anticancer activity, and structure–activity relationship study. Bioorg. Chem. 2015, 62, 30-40.

[211]. R. K.Vohra, C. Bruneau, J.L. Renaud, Lewis acid-catalyzed sequential transformations: Straightforward preparation of functional dihydropyridines. Adv. Synth. Catal. 2006, 348, 2571–2574.

[212]. L.M. Sanchez, A.G. Sathicq, G.P. Romanelli, L.M. Gonzalez, A.L. Villa, Activity of immobilized metallic phthalocyanines in the multicomponent synthesis of

dihydropyridine derivatives and their subsequent aromatization. Mol. Catal. 2017, 435, 1–12.

[213]. Z. Huang, Y. Hu, Y. Zhou, D. Shi, Efficient One-Pot Three-Component Synthesis of Fused Pyridine Derivatives in Ionic Liquid. ACS Comb. Sci. 2011, 13, 45–49.

[214]. S.S. Mansoor, K. Aswin, K. Logaiya, S.P.N. Sudhan, [Bmim]BF_4 ionic liquid: An efficient reaction medium for the one-pot multi-component synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives. J. Saudi. Chem. Soc. 2016, 20, 517–522.

[215]. T, Lee, D, Lee, Y. Lee, Y.D. Gong, Solid-Phase Synthesis of Thiazolo[4,5-b]pyridine Derivatives Using Friedlander Reaction. J. Comb. Chem. 2010, 12, 95–99

[216]. X.Y. Zhang, X. Y. Li, X.S. Fan, X.W. Wang, G.R. Qu, A novel synthesis of pyrazolo[3,4-b]pyridine derivatives through multi-component reaction in ionic liquid. Chin. Chem. Lett. 2008, 19, 153–156.

[217]. V.P. A. Raja, G. Tenti, S. Perumal, J.C. Menendez, A heavy metal- and oxidant-free, one-pot synthesis of pyridines and fused pyridines based on a Lewis acid-catalyzed multicomponent reaction. Chem. Commun. 2014, 50, 12270—12272.

[218]. S. Sueki, R. Takei, J. Abe, I. Shimizu. Tetrahedron Lett. 2011, 52, 4473–4477.

[219]. R. Ghahremanzadeh, G.I. Shakibaei, S. Ahadi, A. Bazgir, One-Pot, Pseudo Four-Component Synthesis of a Spiro[diindeno[1,2-b:2′,1′-e]pyridine-11,3′-indoline]-trione Library. J. Comb. Chem. 2010, 12, 191–194.

[220]. X. He, Y. Shang, Z. Yu, M. Fang, Y. Zhou, G. Han, F. Wu, $FeCl_3$-Catalyzed Four-Component Nucleophilic Addition/Intermolecular Cyclization Yielding Polysubstituted Pyridine Derivatives. J. Org. Chem. 2014, 79, 8882–8888.

[221]. A.I. Almansour, R.S. Kumar, N. Arumugam, D. Sriram, A solvent free, four-component synthesis and 1,3-dipolar cycloaddition of 4(H)- pyrans with nitrile oxides: synthesis and discovery of anti-mycobacterial activity of enantiomerically pure 1,2,4-oxadiazoles, Eur. J. Med. Chem. 2012, 53, 416–423.

[222]. H. Alinezhad, S.M. Tavakkoli, P. Biparva, Cu-doped ZnO nanocrystalline powder catalyzed one-pot synthesis of fully substituted new indeno[1,2-b]pyridines at room temperature by a multi-component reaction. Chin. J. of Catal. 2014, 35, 560-564.

[223]. M. Thimmaiah, P. Li, S. Regati, B. Chen, J.G. Zhao, Multi-component synthesis of 2-amino-6-(alkylthio)pyridine-3,5-dicarbonitriles using Zn(II) and Cd(II) metal–organic

frameworks (MOFs) under solvent free conditions. Tetrahedron Lett. 2012, 53, 4870–4872.

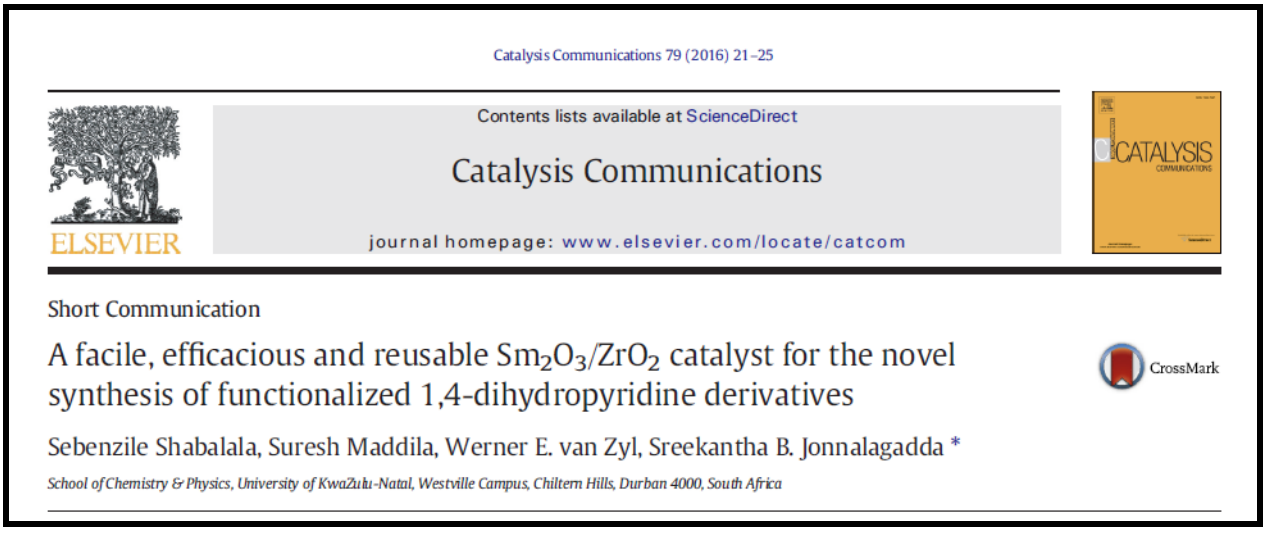
Chapter 2

A facile, efficacious and reusable Sm_2O_3/ZrO_2 catalyst for the synthesis of functionalized 1,4-dihydropyridine derivatives

Sebenzile Shabalala, Suresh Maddila, Werner E. van Zyl and Sreekantha B Jonnalagadda**

*School of Chemistry & Physics, University of KwaZulu-Natal, Westville Campus, Chiltern Hills, Durban-4000, South Africa

E-mail address: **jonnalagaddas@ukzn.ac.za**



Catalysis Communications 79 (2016) 21–25

Contents lists available at ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Short Communication

A facile, efficacious and reusable Sm_2O_3/ZrO_2 catalyst for the novel synthesis of functionalized 1,4-dihydropyridine derivatives

Sebenzile Shabalala, Suresh Maddila, Werner E. van Zyl, Sreekantha B. Jonnalagadda *

School of Chemistry & Physics, University of KwaZulu-Natal, Westville Campus, Chiltern Hills, Durban 4000, South Africa

Abstract

An efficient four component/one-pot protocol is developed for synthesis of functionalized 1,4-dihydropyridine derivatives by a reaction incorporating dimethylacetylenedicarboxylate, arylamine, malononitrile with various substituted aldehydes using Sm on ZrO_2 as catalyst with ethanol as solvent and at room temperature. The reactions completed in < 20 min. The structures of all the eleven new compounds were identified and confirmed by 1H NMR, 15N NMR, 13C NMR, FT-IR and HR-MS spectral data. The catalyst Sm_2O_3/ZrO_2 was synthesized and fully characterised by various techniques including P-XRD, BET, SEM-EDX and TEM analysis. The key advantages of this process are good to high yields (87 to 96%), short reaction times, easy work-up, reusability of the catalyst and no chromatographic purifications.

Keywords: Green synthesis; Functionalized pyridines; Multicomponent reactions; Heterogeneous catalyst; Recyclability; Sm_2O_3/ZrO_2, Mixed oxide catalyst.

2.1. Introduction

Any further improvement of an existing efficient and environmentally benign technique extensively used for synthesis of compounds, will be a challenge for all researchers.[1] One of the effective tools used to merge fiscal and environmental benefits is the multicomponent reaction (MCR) strategy; which comprises of two or more synthesis steps that are carried out without isolation of any intermediates, thus enhancing cost-effectiveness and energy saving.[2,3] MCRs have proved to be very powerful and efficient bond-forming techniques in heterocyclic and medicinal chemistry in the context of green approaches.[4,5] These protocols are also very flexible and atom economic in nature, and proceed through a sequence of reaction equilibria forming targeted products in high yields.[6,7] Among other reaction conditions, the nature of the catalyst is very important in determining yield, selectivity, solvents and general applicability.[6,7] Thus, the development of less inexpensive, mild, reusable, and specific catalysts for MCRs remains a task and matter of interest.

One of the promising green chemistry approaches is to replace conservative procedures which demand toxic and/or hazardous reagents, with atom-efficient benign alternatives. [8] Many of the conventional synthesis reactions are time consuming. Therefore, catalysts are sought to make them more efficient and to reduce the reaction times. Heterogeneous catalysis refers to

processes, where the catalyst and reactants are in different phases. [9] Heterogeneous catalysts offer a number of benefits such as thermal stability, long life, recyclability and high selectivity. Moreover, heterogeneous catalysts have also attracted a lot of attention in heterocyclic synthesis because of numerous advantages which include easy handling, environmental compatibility, non-corrosiveness, saving energy, and ease of product separation compared with typical hazardous and corrosive homogeneous counterparts. [8-9] The surface properties of a catalyst become crucial to enhance its effectiveness in selectivity. [10]

Heterocyclic structures are commonly used vital templates for the design and improvement of potent and specific biologically active agents.[11,12] Pyridines and their derivatives, in particular form an important class of heterocyclic compounds, owing to their properties desired in many fields such as natural products, pharmaceuticals and functional materials.[13] They show a wide range of biological properties, such as antibacterial, antioxidant, antiviral, anticancer, anticonvulsant and antihypertension activity.[14-19] Pyridines are also known for their anti-inflammatory activity.[20,21] Furthermore, many pyridine derivatives is used as herbicides and insecticidal agents.[22,23] Literature survey reveals that only four synthetic methods have been reported for different 1,4-dihydropyridine derivatives. Those protocols employed TEA, NaOH, PEG-600 or microwave irradiation to facilitate the reactions.[24-27] These procedures demanded acidic or basic conditions, costly reagents, tedious handling processes, high temperature and harsh reaction conditions. The product yields were < 92 %, while involving reaction times that ranged between 1.5 to 10.0 h. Thus, development of improved green protocols for their synthesis and evaluation of the novel class of *N*-containing heterocyclic molecules has been our area of focus. We are not aware of reports on the use of Sm_2O_3/ZrO_2 as catalyst for the synthesis of functionalized 1,4-dihydropyridines.

In continuation of our research toward the improvement of new green routes for the synthesis of heterocyclic compounds using green reaction methods with reusable catalysts.[28-30] we have reported various heterocyclic molecules with biologically active potential.[31-34] Here we report on the applicability of a novel recyclable heterogeneous solid catalyst using Sm supported zirconia (Sm_2O_3/ZrO_2) for efficient, convenient and facile green synthesis of highly functionalized 1,4-dihydropyridines derivatives through the one-pot reaction of dimethyl acetylenedicarboxylate, arylamine, malononitrile and aldehyde under ethanol solvent condition and at room temperature.

2.2 Experimental Section

2.2.1. Preparation of Catalyst

A sequence of supported catalysts, weight percentage Sm_2O_3/ZrO_2 (1, 2 & 4 wt%), were prepared using the wet-impregnation technique [1]. The heterogeneous catalyst was obtained from mixture of 2 g zirconia (ZrO_2, Catalyst support, Alfa Aesar) and an appropriate wt% amount of samarium nitrate [$Sm(NO_3)_3 \cdot$ ***6***H_2O (Alfa Aesar)] in (50 mL) dissolved in water. The mixture was stirred at room temperature for 12 h after which the resulting slurry was filtered under vacuum. Further, it was dried in an oven at 110–130 °C for 12 h and calcined in the presence of air, at 450 °C for 5 h to acquire (1, 2 & 4 wt%) of Sm_2O_3/ZrO_2 catalysts.

2.2.2. Catalyst instrumentation details

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 relating 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 spectroscopy using an (ICP-OES) Optima 5300 DV was conducted.

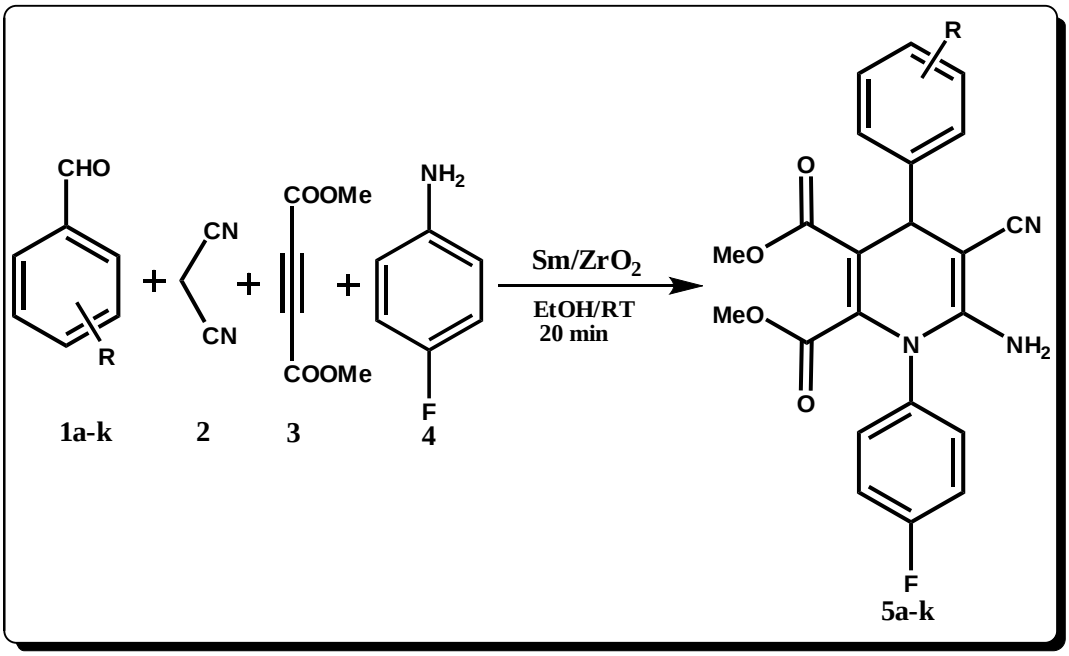
2.2.3. Instrumentation

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 ^{1}H 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 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).

2.2.4. General synthesis of functionalized 1,4-dihydropyridine derivatives (5a-k)

Initially an absolute ethanol (5 mL) solution of substituted aldehyde (1.0 mmol), malononitrile (1.1 mmol) and Sm_2O_3/ZrO_2 catalyst (30 mg) was stirred at room temperature for 5 minutes. Subsequently a solution of dimethylacetylenedicarboxylate (1.0 mmol) and arylamine (1.0 mmol) and in absolute ethanol (5 mL) was added to this mixture and stirred at room temperature for another 15 minutes. The reaction progress was monitored by TLC. After completion of the reaction, catalyst was filtered, and the solvent was evaporated to obtain the pure product **(Scheme 1)**. After the reaction, the used catalyst was recovered by filtering the catalyst, washing with ethanol and heated at 120 - 150 °C under reduced pressure. The recovered catalyst was reused six times in consecutive reactions, with no change in its catalytic efficiency.



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

2.2.5. Products characterization data

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(2-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.96 (s, 2H, NH_2), 5.10 (s, 1H, CH), 6.92 – 6.98 (m, 2H, ArH), 7.16 (t, *J* = 8.12 Hz, 2H, ArH), 7.23 (t, *J* = 10.12 Hz, 2H, ArH), 7.32 – 7.35 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 32.16, 52.05, 52.69, 55.77, 63.06, 104.83, 111.41, 117.08, 120.89, 127.73, 128.30, 131.34, 131.37, 132.31, 132.40, 132.55, 142.54, 149.98, 156.77, 161.89, 163.78, 164.39, 165.85; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 3.96 (s, 2H, NH_2); FT-IR: 1229, 1504, 1650, 1706, 2175, 2950, 3214, 3342, 3461; HRMS of [$C_{23}H_{20}FN_3O_5$ + H] (m/z): 438.1461; Calcd: 438.1465.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.06 (s, 2H, NH_2), 4.60 (s, 1H, CH), 6.89 (d, *J* = 8.64 Hz, 2H, ArH), 7.17 (t, *J* = 8 Hz, 2H, ArH), 7.26 (t, *J* = 4.48 Hz, 2H, ArH), 7.32 – 7.36 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 37.67, 52.07, 52.69, 55.28, 63.61, 105.36, 114.22, 116.92, 117.15, 120.38, 128.07, 131.09, 132.31, 132.39, 137.07, 141.34, 149.31, 158.76, 161.96, 163.58,164.47, 165.76; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 4.06 (s, 2H, NH_2); FT-IR: 1245, 1506, 1648, 1746, 2188, 3301, 3445, 3634; HRMS of [$C_{23}H_{20}FN_3O_5$ + H] (m/z): 438.1474; Calcd: 438.1465.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(2-chlorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 4.06 (s, 2H, NH_2), 5.26 (s, 1H, CH), 7.19 (d, *J* = 8.44 Hz, 3H, ArH), 7.27 – 7.31 (m, 1H, ArH), 7.36 – 7.40 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 35.93, 52.05, 52.74, 62.27, 104.61, 1116.97, 117.21, 119.88, 127.47, 128.44, 129.89, 130.08, 132.46, 132.55, 132.78, 141.89, 142.37, 149.69 162.03, 163.40, 164.55, 165.50; ^{15}N NMR (40.55 MHz, CDCl3) δ 4.06 (s, 2H, NH_2); FT-IR**:** 1253, 1507, 1650, 1702, 2189, 2949, 3326, 3479; HRMS of [$C_{22}H_{17}ClFN_3O_4$ − H] (m/z): 440.0818; Calcd: 440.0813.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(2-bromophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 4.14 (s, 2H, NH_2), 5.30 (s, 1H, CH), 7.19 (t, *J* = 8.04 Hz, 4H, ArH), 7.35 – 7.42 (m, 3H, ArH), 7.57 (dd, *J* = 8 Hz, 0.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 37.92, 52.02, 52.74, 62.33,

105.01, 117.18, 119.86, 122.78, 128.23, 128.66, 129.90, 130.82, 132.43, 132.53, 133.20, 142.27, 143.99, 149.65, 162.02, 163.38, 164.53, 165.52; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 4.14 (s, 2H, NH_2); FT-IR**:** 1251, 1508, 1649, 1706, 2176, 2956, 3301, 3461; HRMS of [$C_{22}H_{17}BrFN_3O_4$ − H] (m/z): 484.0314; Calcd: 484.0308.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(4-chlorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 4.17 (s, 2H, NH_2), 4.64 (s, 1H, CH), 7.18 (t, *J* = 8.04 Hz, 2H, ArH), 7.28 (d, *J* = 8.4 Hz, 2H, ArH), 7.32 – 7.36 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 38.04, 52.14, 52.77, 62.72, 105.13, 117.01, 117.21, 128.39, 129.03, 132.30, 132.39, 133.02, 141.83, 143.17, 149.61, 162.03, 163.36, 164.54, 165.46; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 4.17 (s, 2H, NH_2); FT-IR**:** 1253, 1572, 1656, 1705, 2480, 2949, 3353, 3454.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(4-bromophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 4.12 (s, 2H, NH_2), 4.63 (s, 1H, CH), 7.15 – 7.23 (m, 4H, ArH), 7.32 – 7.35 (m, 2H, ArH) 7.49 (d, *J* = 8.36 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 38.10, 52.16, 52.77, 62.73, 105.05, 117.03, 117.25, 120.07, 121.19, 128.74, 130.82, 131.99, 141.86, 143.65, 149.56, 162.03, 163.33, 164.55, 165.44; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 4.12 (s, 2H, NH_2); FT-IR**:** 1251, 1507, 1654, 1702, 2194, 2949, 3226, 3319, 3474.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(2,3-dimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.02 (s, 2H, NH_2), 4.99 (s, 1H, CH), 6.89 (d, *J* = 8.08 Hz, 3H, ArH), 7.17 (t, *J* = 8.08 Hz, 2H, ArH), 7.31 – 7.34 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 33.87, 51.96, 52.63, 55.71, 61.31, 63.02, 105.29, 111.51, 115.80, 116.85, 123.98, 132.47, 137.66, 141.96, 147.03, 149.73, 152.85, 161.92, 163.70, 165.87, 169.94; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 4.02 (s, 2H, NH_2); FT-IR**:** 1215, 1574, 1650, 1708, 2185, 2953, 3228, 3336, 3476; HRMS of [$C_{24}H_{22}FN_3O_6$ + H] (m/z): 468.1578; Calcd: 468.1571.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5h): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.03 (s, 2H, NH_2), 4.61 (s, 1H, CH), 6.89 (d, *J* = 8.08 Hz, 3H, ArH), 7.17 (t, *J* = 8.08 Hz, 2H, ArH), 7.31 – 7.34 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 37.91, 51.22, 52.09, 52.71, 55.91, 63.70, 105.67, 110.46, 111.61, 116.96, 117.19, 118.76, 132.22, 132.31, 137.43, 141.49, 148.22, 149.27, 161.96, 163.55, 164.47, 165.73; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 4.03 (s, 2H, NH_2); FT-IR**:** 1248, 1509, 1655, 1700, 2190, 2954, 3227, 3322, 3434.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(2,5-dimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5i): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.98 (s, 2H, NH_2), 5.05 (s, 1H, CH), 6.76 (dd, *J* = 8.84 Hz, 3.04 Hz, 1H, ArH), 6.82 (d, *J* = 3.04 Hz, 1H, ArH), 6.86 (d, *J* = 8.84 Hz, 1H, ArH), 7.16 (t, *J* = 8.12 Hz, 2H, ArH), 7.32 – 7.35 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 32.44, 52.06, 52.68, 55.59, 56.60, 63.02, 104.74, 112.09, 112.62, 114.57, 116.87, 117.09, 132.40, 113.89, 142.51, 149.89, 151.13, 153.84, 161.89, 163.70, 164.40, 165.76; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 3.98 (s, 2H, NH_2); FT-IR**:** 1234, 1498, 1659, 1703, 2183, 2838, 3227, 3318, 3415.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(2-fluorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5j): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 4.08 (s, 2H, NH_2), 4.85 (s, 1H, CH), 7.05 – 7.10 (m, 1H, ArH), 7.12 – 7.14 (m, 1H, ArH), 7.16 – 7.20 (m, 2H, ArH), 7.22 – 7.24 (m, 1H, ArH), 7.29 – 7.33(m, 1H, ArH), 7.39 – 7.42 (m, 2H ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 34.69, 52.04, 52.69, 61.35, 103.75, 116.07, 116.29, 116.92, 117.15, 120.14, 124.27, 124.31, 129.05, 129.13, 129.88, 129.92, 130.92, 131.01, 131.05, 132.51, 132.60, 142.25, 150.14, 160.31, 162.02, 162.77 163.47, 164.53, 165.56; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 4.08 (s, 2H, NH_2); FT-IR**:** 1219, 1413, 1576, 1646, 1712, 2183, 2953, 3378, 3481; HRMS of [$C_{22}H_{17}F_2N_3O_4$ − H] (m/z): 424.1101; Calcd: 424.1109.

Dimethyl-6-amino-5-cyano-1-(4-fluorophenyl)-4-(4-ethylphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5k): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.64 Hz, 3H, CH_3), 2.61 - 2.67 (m, 2H, CH_2), 3.47 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 4.06 (s, 2H, NH_2), 4.61 (s, 1H, CH), 7.14 (d, *J* = 2 Hz, 1H, ArH), 7.18 (t, *J* = 6.84 Hz, 3H, ArH), 7.26 (t, *J* = 2.24 Hz, 2H, ArH), 7.32 – 7.35

(m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 15.41, 28.48, 37.99, 52.08, 52.69, 63.52, 105.79, 116.92, 117.15, 120.40, 126.87, 128.35, 131.11, 131.15, 132.31, 132.40, 141.88, 143.11, 149.45, 161.96, 163.59, 164.47, 165.75; ^{15}N NMR (40.55 MHz, $CDCl_3$) δ 4.06 (s, 2H, NH_2); FT-IR**:** 1212, 1576, 1647, 1708, 2186, 2966, 3216, 3314, 3455; HRMS of [$C_{24}H_{22}FN_3O_4$ − H] (m/z): 434.1530; Calcd: 434.1516.

2.3. Results and Discussion

2.3.1. BET surface area and ICP analysis

The texture of the prepared catalysts was determined by physisorption analysis. Figure 1 shows an isotherm of 2 Sm_2O_3/ZrO_2 catalyst in an N_2 adsorption-desorption study and all synthesized samples exhibited type IV isotherms. The Type IV isotherm is related to the mesoporous structure of the prepared catalysts and structural mesopores play a significant role on the supported metal dispersion and its activity. The prepared catalyst showed a surface area of 145 m^2 g^{-1} with a pore volume of 0.24 cc g^{-1}. The elemental analysis showed the presence of a anticipated amount of Sm (1.98 wt %) in the catalyst.

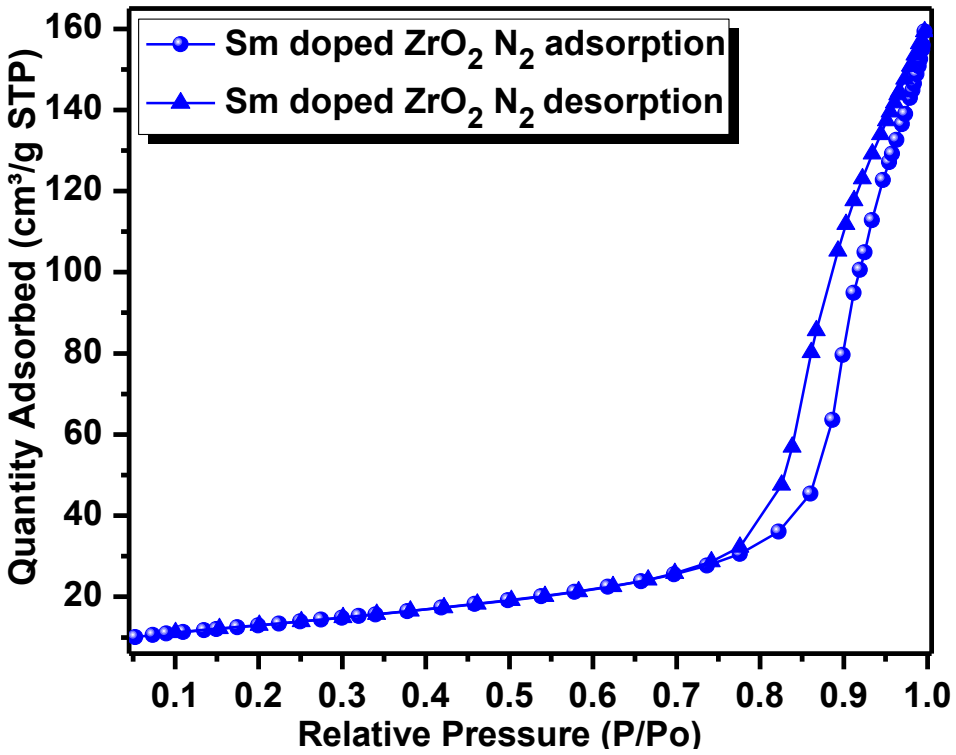


Figure 1. N_2 adsorption-desorption isotherms of 2% Sm_2O_3/ZrO_2 catalyst

2.3.2. Electron Microscopy (SEM & TEM analysis)

Figure 2a displays a SEM image of the 2% Sm_2O_3/ZrO_2 catalyst. It illustrates randomly distributed spherical, oval and elongated stick or rod shaped metal oxide particles. Agglomeration of particles leading to formation of larger particles as a result was observed. The figure also reveals that the catalyst has a consistent morphology and clusters of metal particles on the support surface. The rod-like particles of Sm_2O_3 of approximately 50-150 nm in length and <20 nm in width and were observed on the zirconia surface. SEM-EDX spectrum (Figure. 2b) shows the presence of Sm and Zr on the surface of catalyst.

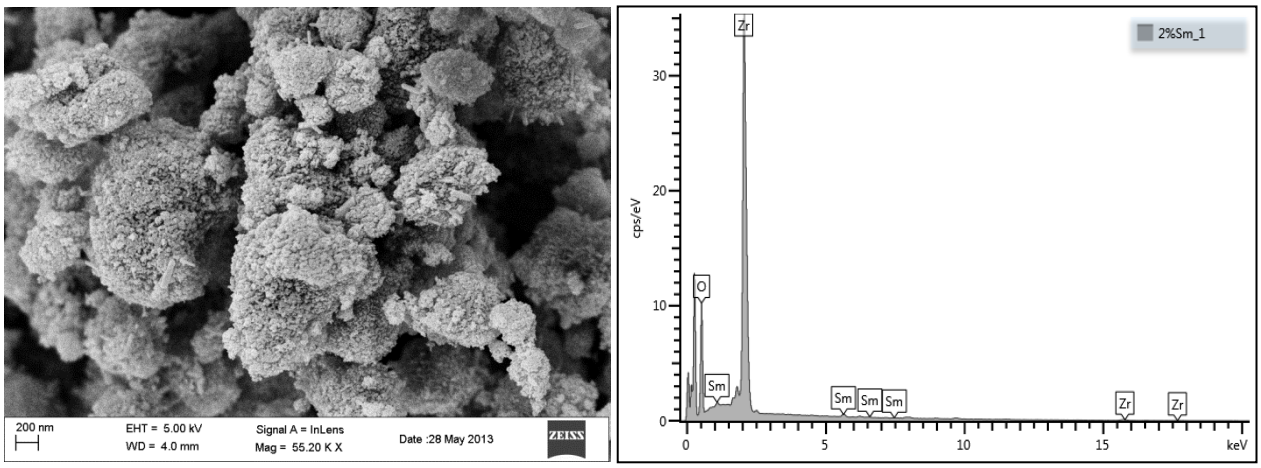


Figure 2. (a) SEM image and (b) EDX spectrum of 2% Sm_2O_3/ZrO_2 catalyst

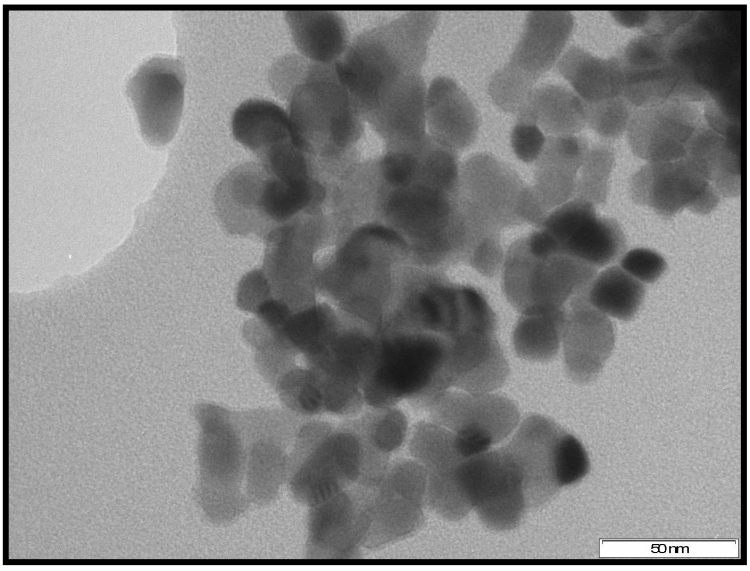


Figure 3. TEM image of 2% Sm_2O_3/ZrO_2 catalyst

TEM results showed the presence of differently shaped metal oxide particles (Figure. 3). This indicates all particles are well distributed throughout the sample. The TEM micrograph showed that the catalyst prepared on a ZrO_2 support has good dispersion of Sm_2O_3 with the average particle size distribution in the range of 20-40 nm.

2.3.3. XRD study

An X-ray diffractogram of the prepared catalyst is depicted in Figure. 4. The XRD study reveals the presence of crystalline ZrO_2 phase (JCPDS 37-1484) with Sm_2O_3 phase (JCPDS 42-1461). The intense and sharp peak at 28° corresponds to (222) plane of Sm_2O_3 and also assigned to the ZrO_2 phase, due to more quantity of crystalline oxide support in the catalyst. Other peaks of Sm_2O_3 phase were observed at 47° and 55°. Formation of pure ZrO_2 has been confirmed from peaks obtained at its characteristics 2Θ value as shown in diffractogram.

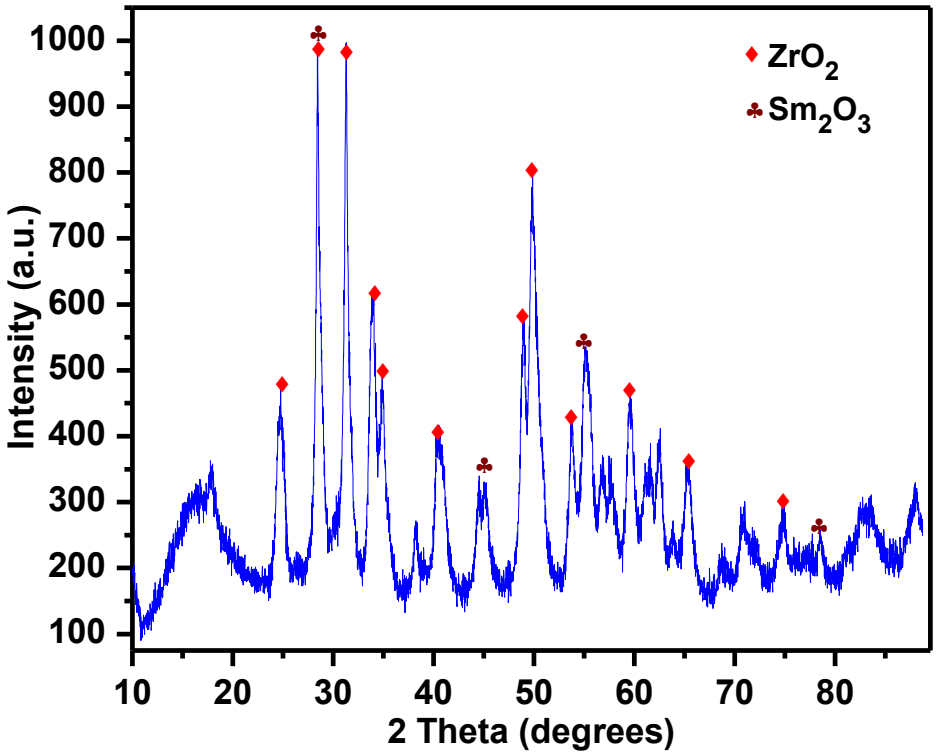


Figure 4. Powder X-ray diffractogram of 2% Sm_2O_3/ZrO_2 catalyst

2.3.4. Results and discussion

The proposed method describes the synthesis of functionalized 1,4-dihydropyridines using substituted aldehydes (1 mmol), malononitrile (1.1 mmol), dimethylacetylenedicarboxylate (1.0 mmol) and arylamine (1.0 mmol) in the presence of Sm_2O_3/ZrO_2 (30 mg) as a catalyst and ethanol as solvent at room temperature for 20 min (Scheme 1). The structures of functionalized 1,4-dihydropyridines were characterized ^{1}H NMR, ^{13}C NMR, ^{15}N NMR, FT-IR and HR-MS (Supplementary data).

Preliminary investigations were conducted with a model reaction of substituted aldehyde (4-methoxybenzaldehyde), malononitrile, dimethylacetylenedicarboxylate and arylamine under varied conditions. No product was obtained when the reaction was carried out in solvent free and catalyst free conditions (Table 1, entry 1). When the reaction was performed in the absence of any catalyst in ethanol at RT, no product formed even after 12 h. The same reaction was conducted under reflux conditions for 12 h, but the reaction failed to provide the desired product (Table 1, entry 2 & 3). To explore the scope of homogeneous catalysis to facilitate the reaction, the reaction was then performed in the presence of different organic and inorganic basic catalysts such as triethylamine, piperidine, NaOH, $NaHCO_3$ and K_2CO_3 in EtOH for 6-10h at RT, but the product yield was moderate (Table 1, entries 4-8). The reaction was repeated in the presence of ionic liquids [Bmim]OH, DABCO, but yields were again low at RT (Table 1, entry 9 & 10). When pure oxides, such as SiO_2, Al_2O_3, ZrO_2 and Fe_2O_3 were employed as catalysts at RT with ethanol as solvent, the reaction gave moderate to good yields after 1.5-3.0 h reaction time (Table 1, entries 11-14). Based on the promising results obtained with zirconia, reactivity for various metal oxides supported ZrO_2 catalysts, such as MnO_2/ZrO_2 and CuO/ZrO_2 were screened. Those mixed oxide catalyzed reactions gave good yields (70-79%) after 40 min reaction time (Table 1, entry 15 & 16). Excitingly, when Sm_2O_3/ZrO_2 was used as catalyst, a reaction progressed impressively recording an excellent 96% yield of functionalized 1,4-dihydropyridines at RT within 20 min reaction time (Table 1, entry 17).

We next examined the amount of catalyst needed for optimum performance of the model reaction. The amount of catalyst used was varied from 10 mg to 50 mg. When amount was decreased from 30 to 10 mg, the yield of the reaction decreased from 96 to 75 % (Table 2, entry 1-3), while increase in amount from 30 mg to 50 mg, showed no significant changes in the yield

(Table 2, entry 3-5) or reaction times. The usage 30 mg of Sm_2O_3/ZrO_2 which gave 96 % yield was assumed optimal to promote the reaction.

Table 1: Optimization of the model reaction conditions[a]

Entry	Catalyst	Time (h)	Yield (%)[b]
1	--	24	--
2	--	12	--
3	--	12	--
4	TEA	10	43
5	Piperidine	10	39
6	NaOH	7.0	40
7	$NaHCO_3$	8.5	48
8	K_2CO_3	6.0	41
9	[Bmim]OH	12	15
10	DABCO	12	21
11	SiO_2	2.5	55
12	Al_2O_3	3.0	51
13	ZrO_2	1.5	67
14	Fe_2O_3	2.0	60
15	MnO_2/ZrO_2	0.4	79
16	CuO/ZrO_2	0.4	70
17	1% Sm_2O_3/ZrO_2	0.35	87
18	2% Sm_2O_3/ZrO_2	0.25	96
19	4% Sm_2O_3/ZrO_2	0.25	94

[a]Reaction conditions: dimethylacetylenedicarboxylate (1 mmol), 4-fluoroanilene (1 mmol), malononitrile (1.1 mmol), 2-methoxybenzaldehyde (1 mmol) and catalyst.

[b]Isolated yields; -- No reaction

We then assed the scope of other solvents under varying conditions on the model reaction, it was investigated under varied solvent conditions (Table 3). The effect of different protic, aprotic and non-polar solvents was examined. Under solvent free conditions, the reaction, even in presence of catalyst (Sm_2O_3/ZrO_2) did not take place even after prolonged reaction time (Table 3, entry 1). In non-polar solvents such as n-hexane, 1,4-dioxane, and toluene, the reaction did not proceed (Table 3, entries 2-4), whereas in the case of polar aprotic solvents such as tetrahydrofuran (THF) and dimethylformamide (DMF), the reaction occurred, but the yield was low (Table 3, entries 5 & 6). In the case of polar protic solvents such as methanol, ethanol and isopropyl alcohol (Table 3, entries 7-9), the yield of the desired product was good to excellent. In

view of the nature, cost, and yields plus the reaction times, we observed ethanol as the most suitable solvent for the synthesis (Table 3, entry 8).

Table 2: Optimization of the amount of 2% Sm_2O_3/ZrO_2 as catalyst in the model reaction[a]

Entry	Catalyst (mg)	Time (min)	Yield (%)
1	10	60	75
2	20	35	84
3	30	15	96
4	40	15	96
5	50	20	95

[a]Reaction conditions: dimethylacetylenedicarboxylate (1 mmol), 4-fluoroanilene (1 mmol), malononitrile (1.1 mmol), 2-methoxybenzaldehyde (1 mmol), catalyst and ethanol (10 mL) solvent were stirred at room temperature.

Using the optimised reaction conditions, the latitude and efficiency of this protocol was examined for the synthesis of a wide variety of substituted functionalized 1,4-dihydropyridines. Fascinatingly, a variety of aryl aldehydes bearing both electron-releasing and electron-withdrawing (ortho, meta, and para functional) groups have apparently, no obvious effect on the yields obtained and the reaction time under the optimal conditions, and afforded the functionalized 1,4-dihydropyridine derivatives in good to excellent yield in all the cases (Table 4). Conferring to our results, a plausible mechanism for the synthesis of functionalized 1,4-dihydropyridine using a heterogeneous catalyst is shown in Scheme 2. In the first step, 2-arylidenemalononitrile (3) is formed by a fast Knoevenagel condensation of malononitrile (1) with arylaldehyde (2) catalyzed by the Sm_2O_3/ZrO_2. The next step involves formation of a 1,3-dipole intermediate compound (6) by reaction of amine (5) with dimethylacetylenedicarboxylate (4). In the third step, a Michael addition of 3 to 7 in the presence of catalyst produces the intermediate. Finally, an intramolecular cyclization affords the desired functionalized 1,4-dihydropyridines.

Table 3: Optimization of various solvent condition for the model reaction by 2%Sm_2O_3/ZrO_2 catalyst[a]

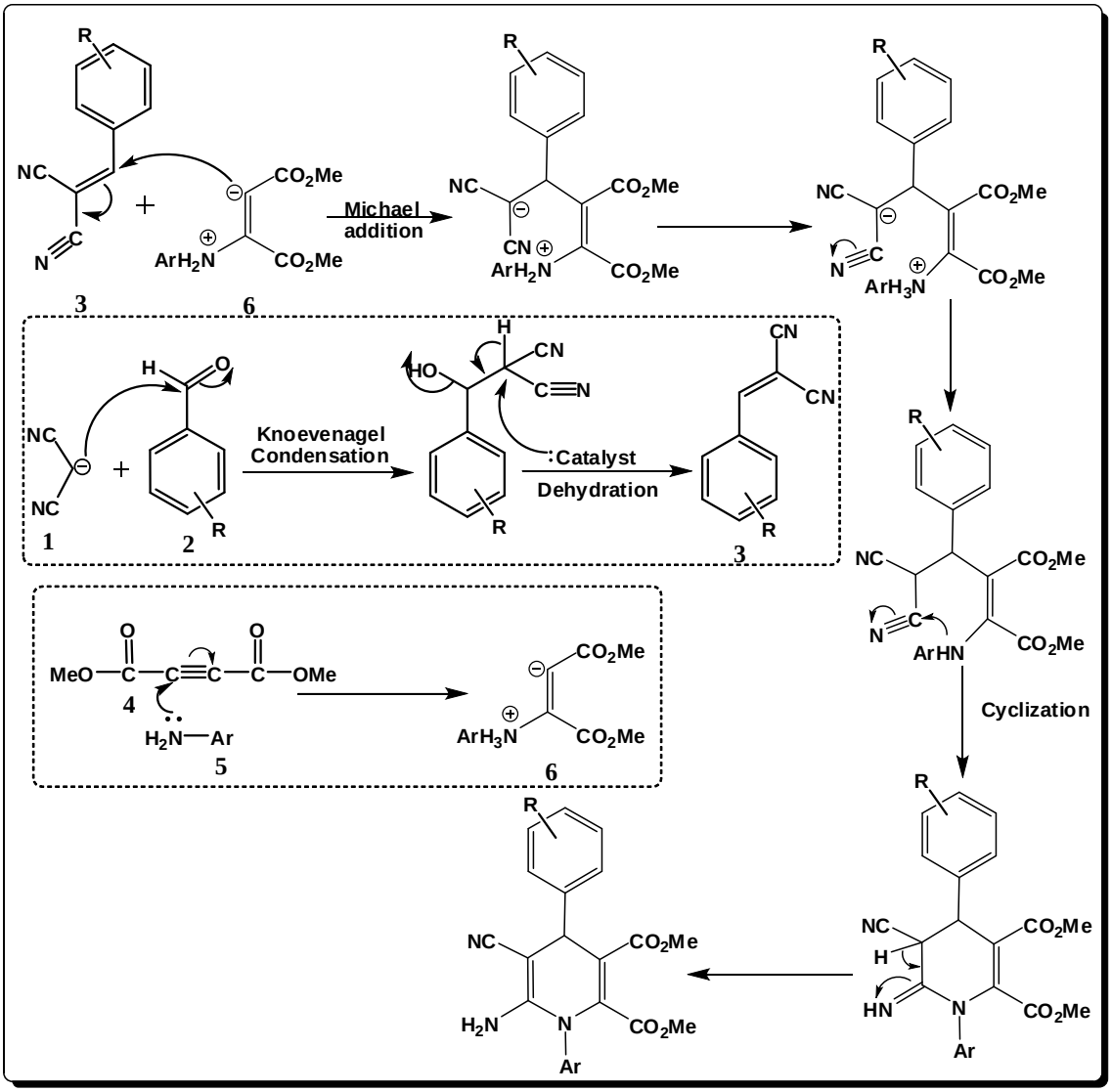
Entry	Solvent	Yield (%)
1	No solvent	0
2	n-hexane	0
3	1,4-dioxane	0
4	toluene	0
5	THF	27
6	DMF	19
7	MeOH	77
8	EtOH	96
9	isopropyl alcohol	69

[a]Reaction conditions: dimethylacetylenedicarboxylate (1 mmol), 4-fluoroanilene (1 mmol), malononitrile (1.1 mmol), 2-methoxybenzaldehyde (1 mmol), catalyst (30 mg) and solvent (10 mL) were stirred at room temperature.

Table 4: Synthesis of functionalized 1,4-dihydropyridines by 2% Sm_2O_3/ZrO_2 catalyst[a*]

Entry	R	Product	Yield (%)	Mp °C
1	2-OMe	5a	96	242-243
2	4-OMe	5b	93	220-221
3	2-Cl	5c	90	247-248
4	2-Br	5d	87	258-260
5	4-Cl	5e	94	224-225
6	4-Br	5f	92	252-253
7	2,3-$(OMe)_2$	5g	95	241-243
8	3,4-$(OMe)_2$	5h	92	231–234
9	2,5-$(OMe)_2$	5i	90	256–257
10	2-F	5j	89	237-238
11	4-Et	5k	94	196-198

[a]Reaction conditions: dimethylacetylenedicarboxylate (1 mmol), 4-fluoroanilene (1 mmol), malononitrile (1.1 mmol), substituted benzaldehyde (1 mmol), catalyst (30 mg) and ethanol solvent (10 mL) were stirred at room temperature; * All the compounds are new;
R = substituted benzaldehydes



Scheme 2. Proposed reaction mechanism

2.4. Reusability of the catalyst

The recyclability of the heterogeneous catalyst Sm_2O_3/ZrO_2 was also examined, and was found to be reusable without significant loss of catalytic activity. After completion of the reaction, the catalyst was filtered and recovered catalyst was washed with ethanol and dried at 120-150 °C under reduced pressures for 2 h. The recycled catalyst was then reused for the subsequent reactions. In a representative experiment, the Sm_2O_3/ZrO_2 was reused for seven consecutive runs, and the decrease in activity was marginal.

2.5. Conclusion

We have improved a protocol for the synthesis of functionalized 1,4-dihydropyridine derivatives via a four-component facile one-pot condensation reaction. Substituted aldehyde, malononitrile, dimethylacetylenedicarboxylate and arylamine in the presence of Sm_2O_3/ZrO_2 heterogeneous catalyst was used under green solvent conditions. The Sm_2O_3/ZrO_2 catalyst is simple, highly efficient and recyclable for MCR protocol at RT. This green and straightforward method offers numerous benefits such as operative simplicity, cleaner reactions, facile workup, excellent product yields, and short reaction times, as well as a reusable catalyst, and is a promising eco-friendly strategy.

2.6. 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.

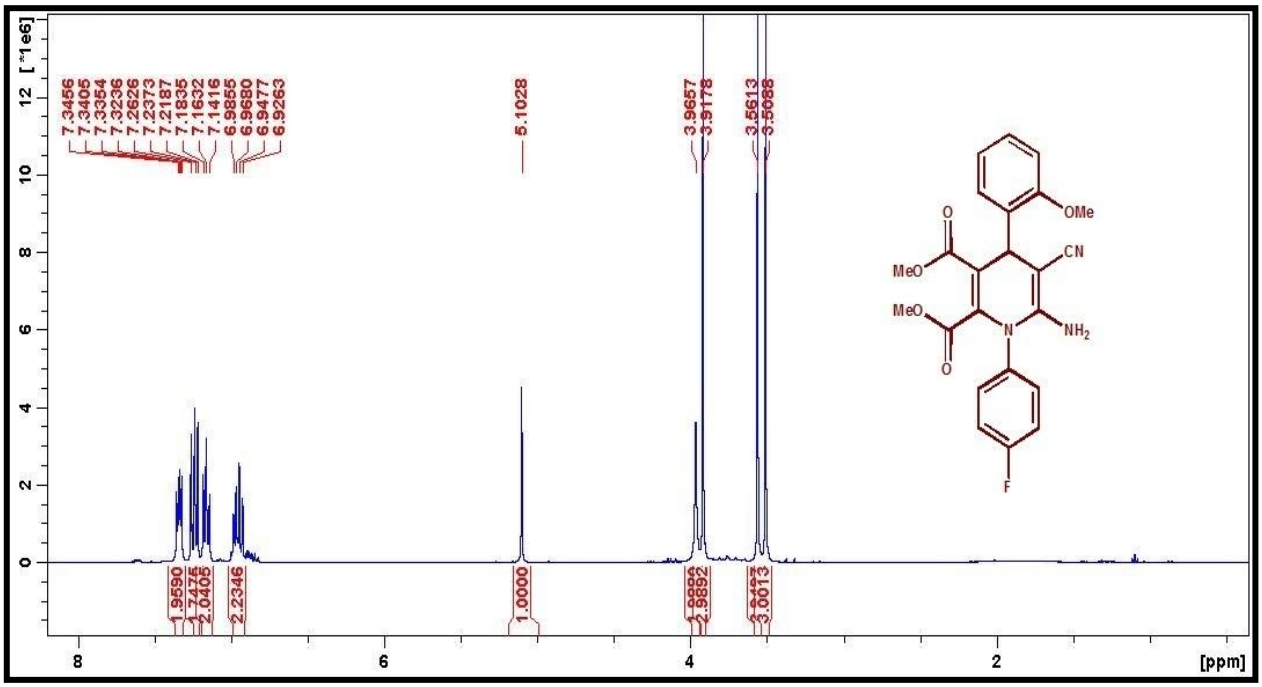
2.7. References

1. B. G. Manoj, D. B. B. Vasco, L. Rafael, S. B.Paula and S. V. Rajender. *Chemical Society Reviews.* **2013**, *42*, 5522.
2. S. Maddila, S. Rana, R. Pagadala, S. Kankala, S. N. Maddila and S. B. Jonnalagadda. *Catalysis Communications*. **2015**, *61*, 26.
3. S. N. Maddila, Maddila, S, W. E. van Zyl, and S. B. Jonnalagadda. *Royal Society of Chemistry Advances*. **2015**, *5*, 37360.
4. R. Pagadala, S. Maddila, S. Rana and S. B. Jonnalagadda. *Current Organic Synthesis*. **2015**, *12(2)*, 163.
5. B. B. Toure and D. G. Hall. *Chemical Reviews*. **2009**, *109*, 4439.
6. D. Reinhardt, F. Ilgen, D. Kralisch, B, Konig and G. Kreisel. *Green Chemistry*. **2008**, *10*, 1170.
7. Y. Gu, and F. Jerome. *Green Chemistry*. **2010**, *12*, 1127.
8. T. A. Paul and M. K. Mary. *Accounts of Chemical Research*. **2002**, *35(9)*, 686.
9. B. M. Reddy and A. Khan. *Catalysis Reveiws*. **2005**, *47*, 257.
10. A. Dandia, V. Parewa, A. K. Jain and K.S. Rathore. *Green Chemistry*. **2011**, *13*, 2135.

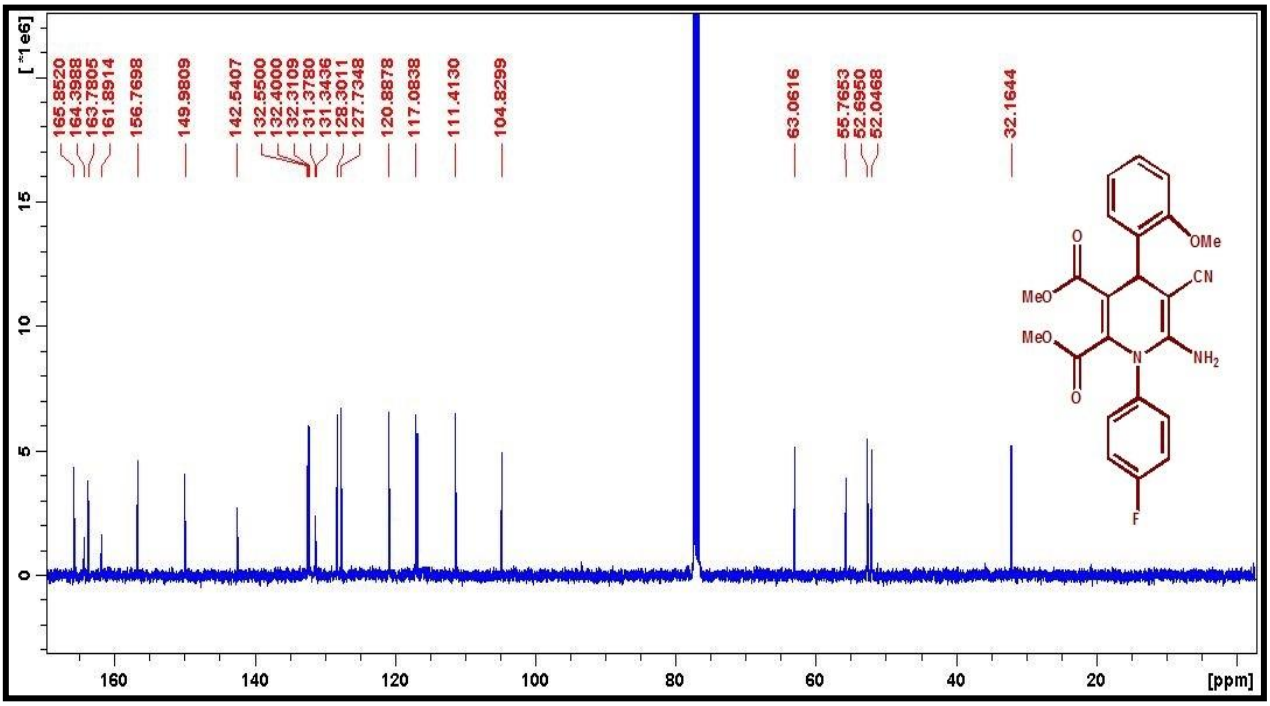
11. S. Maddila, R. Pagadala and S. B. Jonnalagadda. *Letters in Organic Chemistry*. **2013**, *10(10)*, 693.
12. S. Maddila, R, Pagadala and S. B. Jonnalagadda. *Journal of Heterocyclic Chemistry*. **2015**, *52(2)*, 487.
13. J. Sun, E. Y. Xia, Q. Wu and C. Y. Yan. *Organic Letters*. **2010**, *12*, 3678.
14. S. Kalam, B. Darna, A. Garlapati and M. R. Vanga. *European Journal of Medicinal Chemistry*. **2011**, *46(5)*, 1564.
15. K. Atul, A. M. Ram, S. Siddharth, K, Mukesh and B. Gitika. *European Journal of Medicinal Chemistry*. **2010**, *45(2)*, 501.
16. D. M. Stout. *Chemical Reviews*. **1982**, *82*, 223.
17. M. Kawase, A. Shah, H. Gaveriya, H, N, Motohashi, H. Sakagami and A.Varga. J. *Bioorganic & Medicinal Chemistry **2002**, 10, 1051*.
18. G. Prasanthi, K. V. S. R. G. Prasad and K. Bharathi. *European Journal of Medicinal Chemistry.* **2014**, *73*, 97.
19. D. J. Triggle, D. D. Langs and R. A. Janis. *Medical Care Research and Review*. **1989**, *9*, 123.
20. J. El Bakali, P. Gilleron, M. Body-Malapel, R. Mansouri, G. G. Muccioli, M. Djouina, A. Barczyk, F. Klupsch, V. Andrzejak, E. Lipka, C. Furman, D. M. Lambert, P. Chavatte, P. Desreumaux and R. Millet. *Journal of Medicinal Chemistry*. **2012**, *55(20)*, 8948.
21. M. Iman, A. Davood, A. R. Nematollahi, A. R. Dehpoor and A. Shafiee. *Archives of Pharmacal Research*. **2011**, *34(9)*, 1417.
22. L. Gangyue, Q. Xuhong, C. Jingnan, H. Qingchun, Z. Rong and G. Huai. *Journal of Agricultural and Food Chemistry*. **2006**, *54(1)*, 125.
23. D. Xudong, L. Yingqian, Yanqing, Y. Xiangyang, X. T. Xuan and G. Rong. *Pesticide Biochemistry and Physiology*. **2007**, *89(1)*, 81.
24. S. Jing, X. Er-Yan, W. Qun, and Y. Chao-Guo. *Organic Letters.* **2010**, *12(16)*, 3678.
25. P. Suman, H. C. Lokman, and P. Tasneem. *Synthetic Communications*. **2013**, *43*, 986.
26. P. Suman, S. Vandana, D. Prolay and H. C. Lokman. *Bioorganic & Medicinal Chemistry*. **2013**, *48*, 8.
27. K. Atul and S. Siddharth. *Green Chemistry.* **2011**, *13*, 2017.

28. S. N. Maddila, S. Maddila, W. E. van Zyl, and S. B. Jonnalagadda. *Chemistry Open* **2015,** DOI: 10.1002/open.201500159.
29. S. Rana, S. Maddila, K. Yalagala, S. N. Maddila, and S. B. Jonnalagadda. *Chemistry Open.* **2015**, DOI: 10.1002/open.201500121.
30. R. Pagadala, S. Maddila, V. Moodley, W. E. van Zyl, and S. B. Jonnalagadda. *Tetrahedron Letters.* **2014**, *55*, 4006.
31. S. Maddila, S. Gorle, M. Singh, P. Lavanya, and S. B. Jonnalagadda. *Letters in Drug Design & Discovery*. **2013**, *10(10)*, 977.
32. S. Maddila and S. B. Jonnalagadda. *Letters in Organic Chem*istry **2013**, *10*, 374.
33. S. Maddila and S. B. Jonnagadda. *Pharmaceutical Chemistry. J*. **2013**, *46(11)*, 1.
34. S. Maddila and S.B. Jonnalagadda. *Archiv der Pharmazie*. **2012**, *345*, 163.
35. S. Maddila, V. D. B. C. Dasireddy and S. B. Jonnalagadda. *Applied Catalysis B: Environmental*. **2014**, 150-151, 305.
36. E. C. Chetty, S. Maddila, C. Southway, and S.B. Jonnalagadda. *Industrial & Engineering Chemistry Research*. **2012**, *51*, 2864.

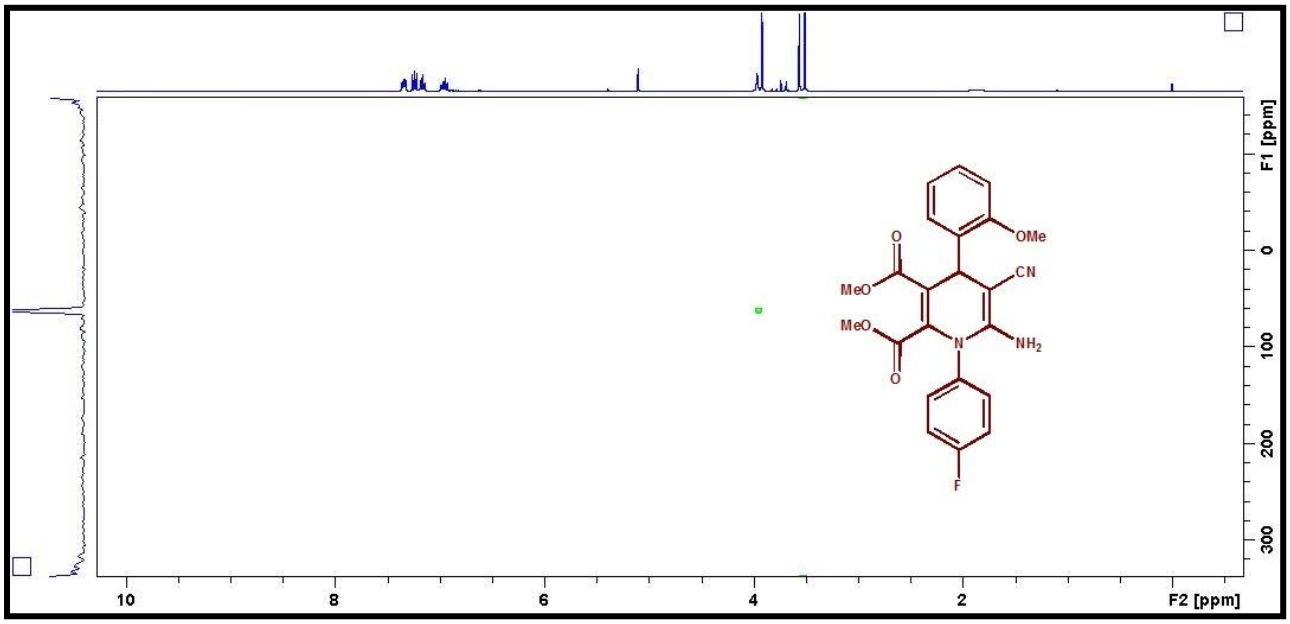
2.8. Supporting Information (Product Analysis)



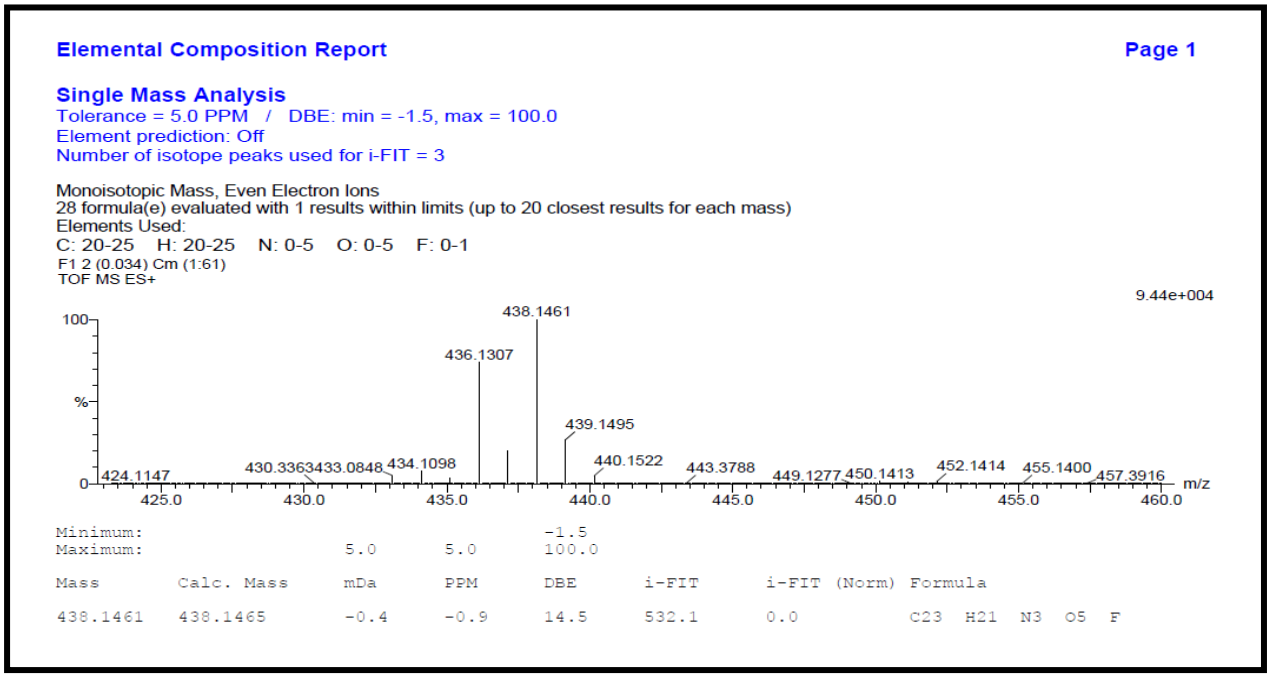
^{1}H NMR spectra of compound 5a



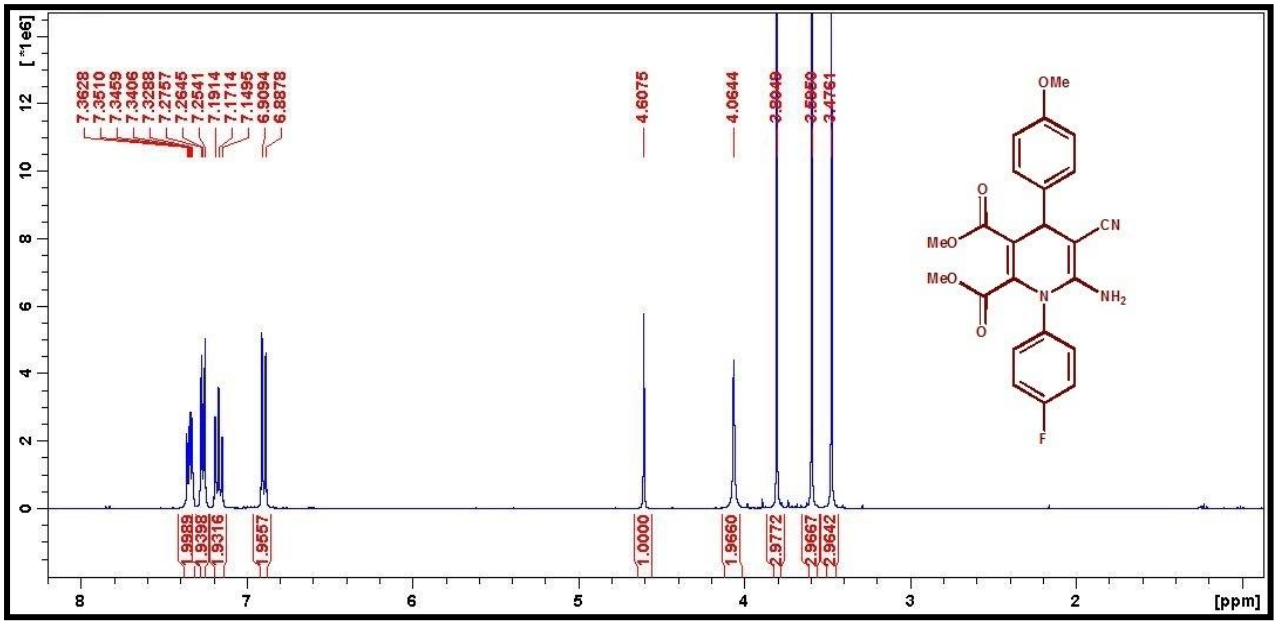
^{13}C NMR spectra of compound **5a**



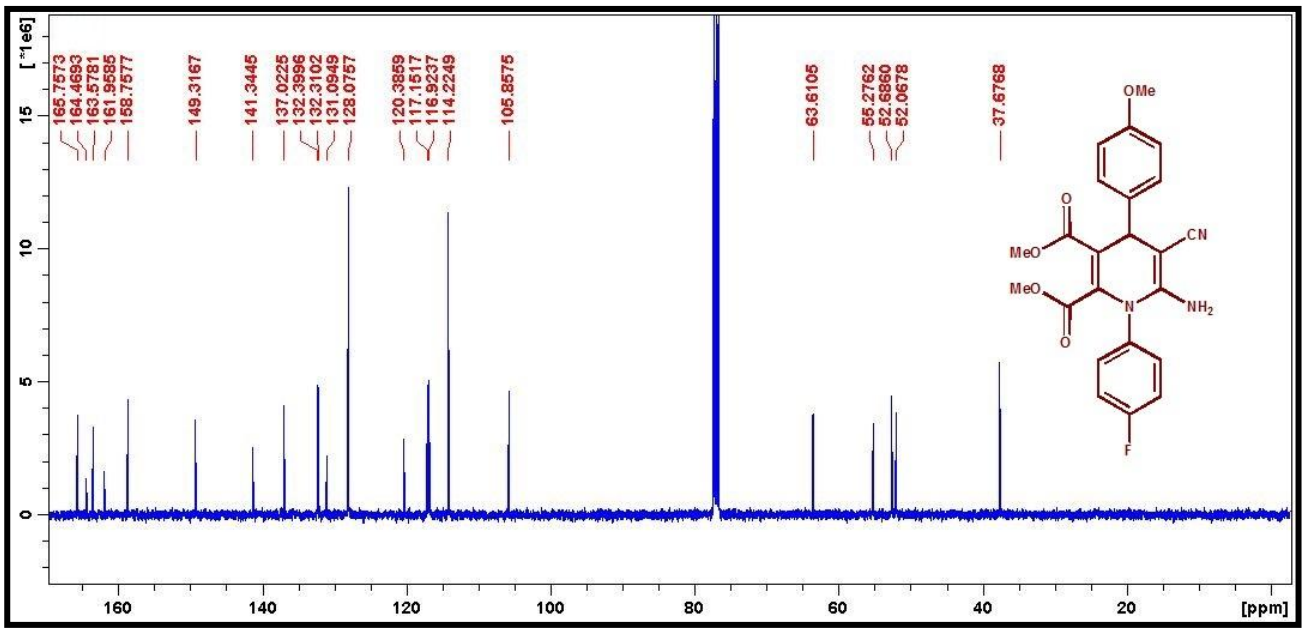
^{15}N NMR spectra of compound **5a**



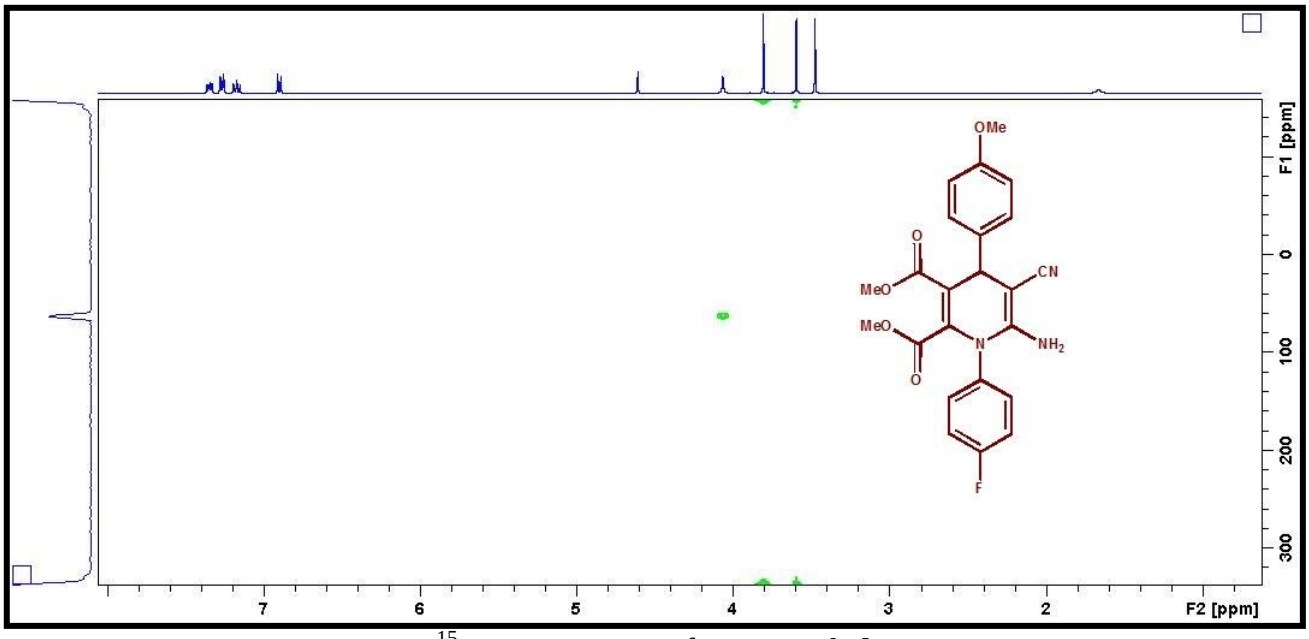
HRMS spectra of compound **5a**



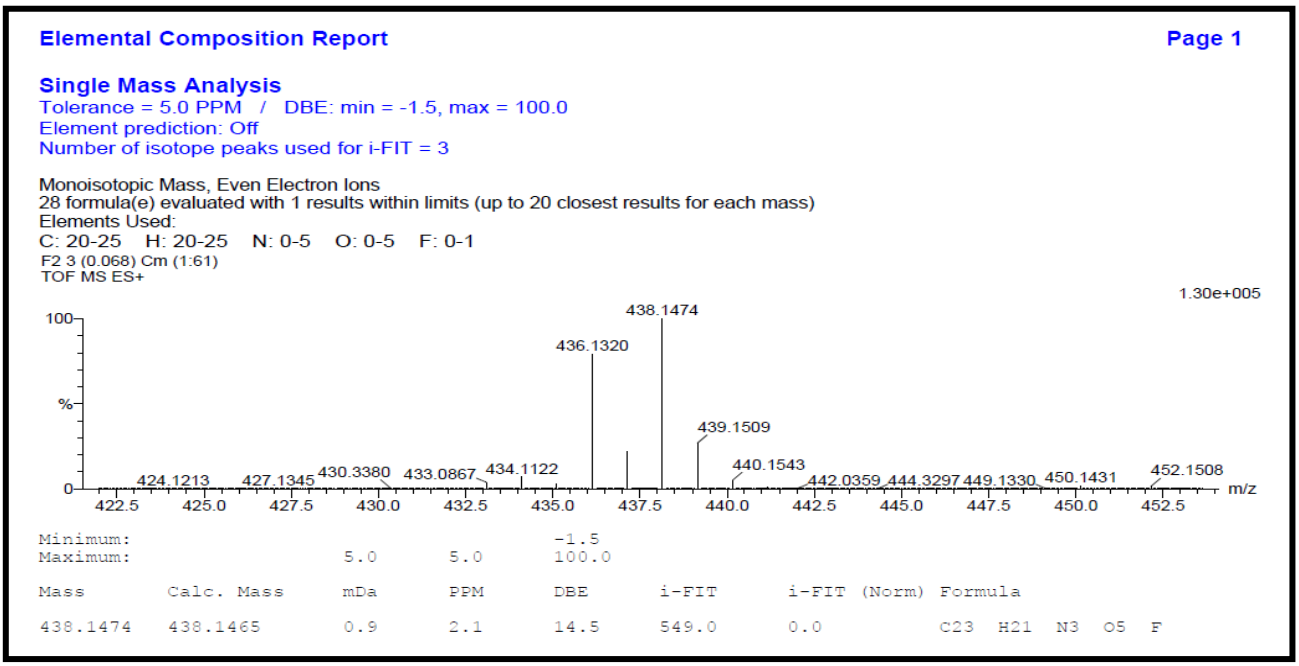
^{1}H NMR spectra of compound **5b**



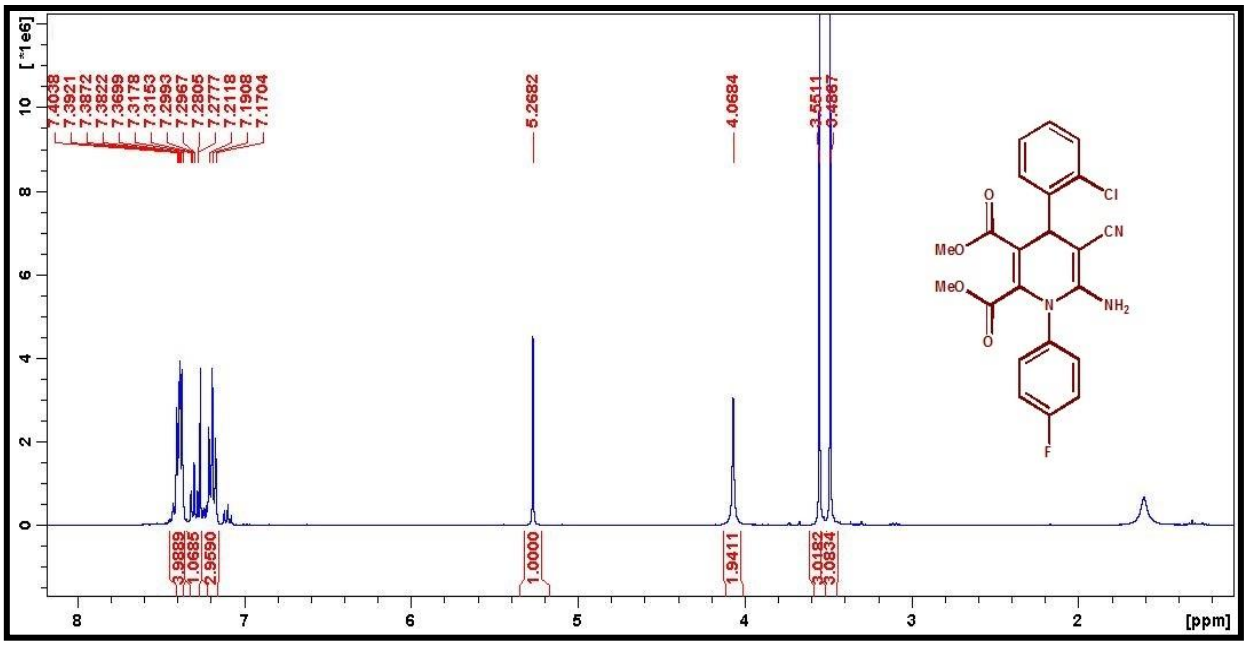
^{13}C NMR spectra of compound **5b**



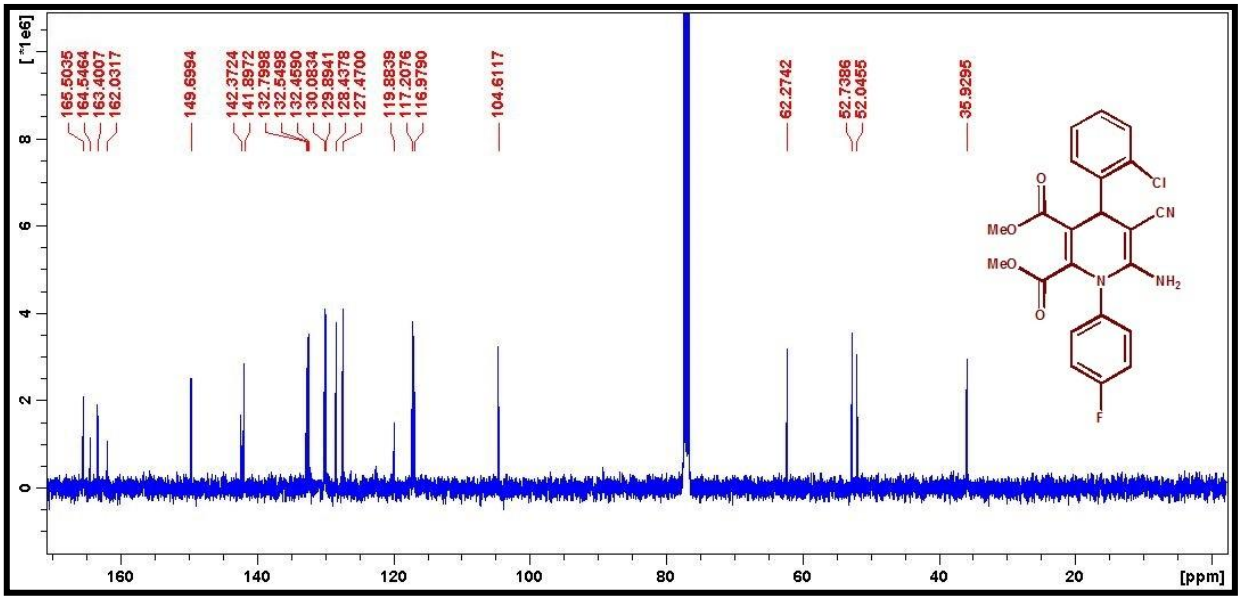
^{15}N NMR spectra of compound **5b**



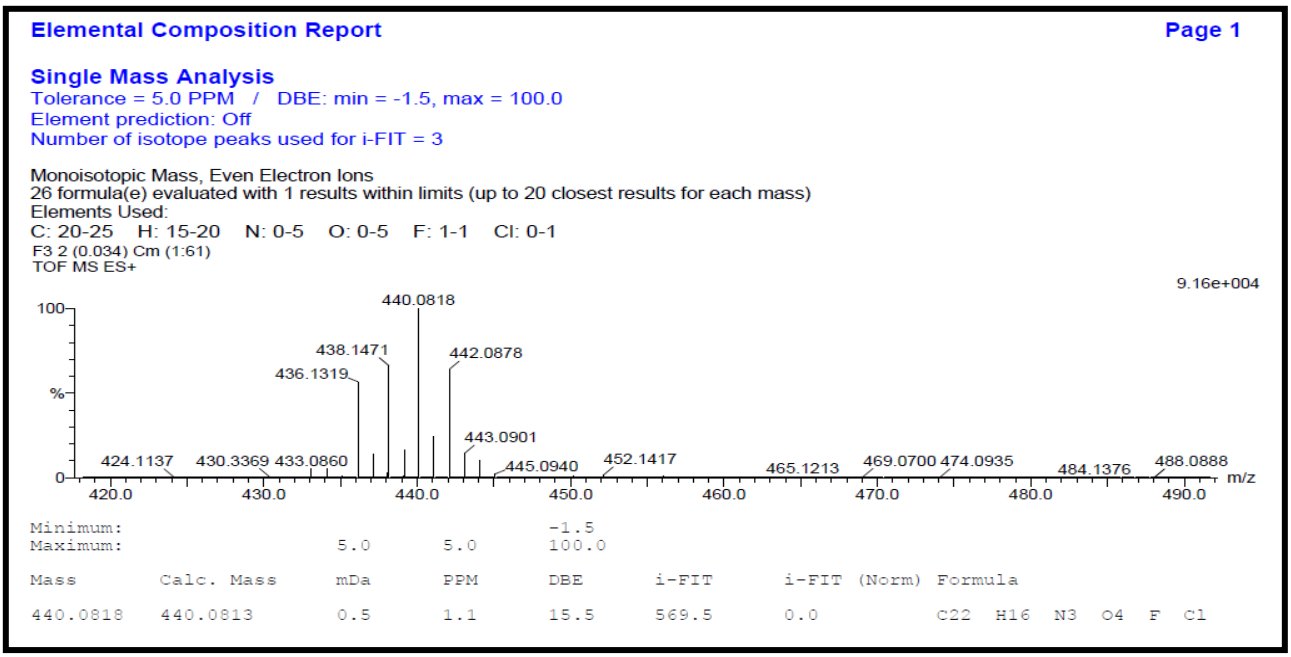
HRMS spectra of compound **5b**



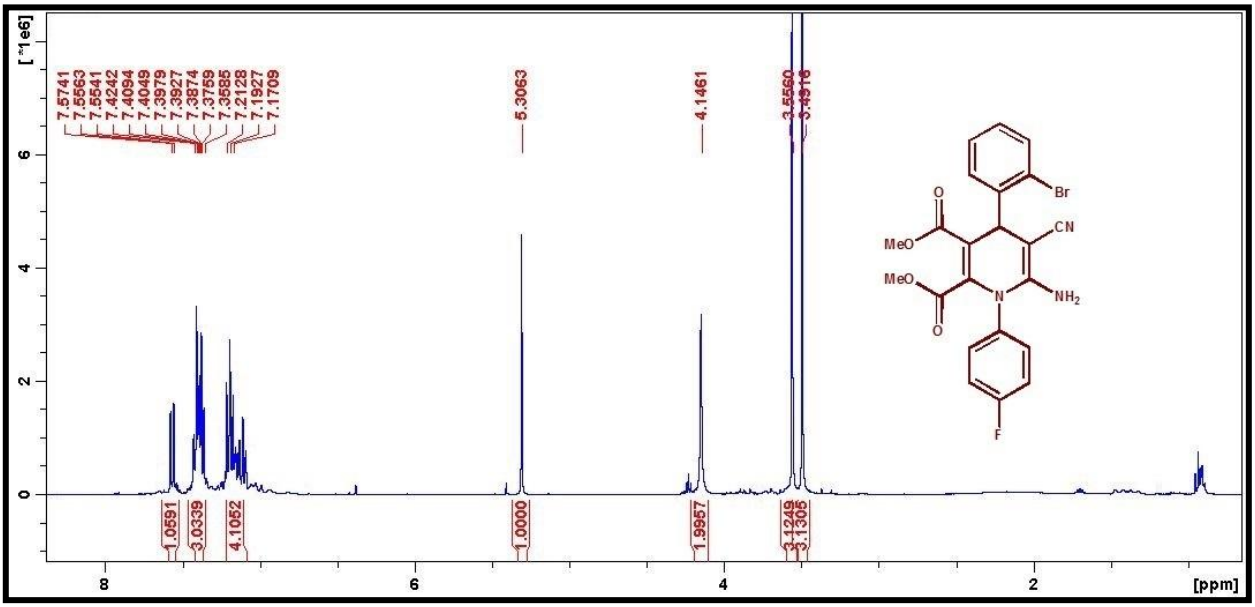
^{1}H NMR spectra of compound **5c**



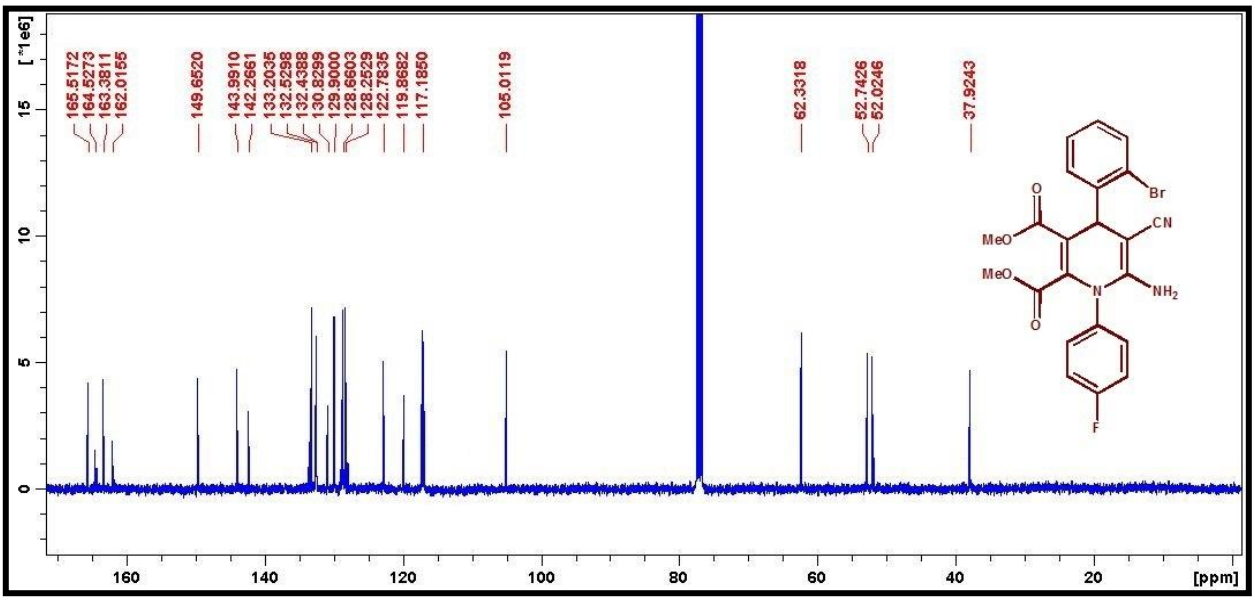
^{13}C NMR spectra of compound **5c**



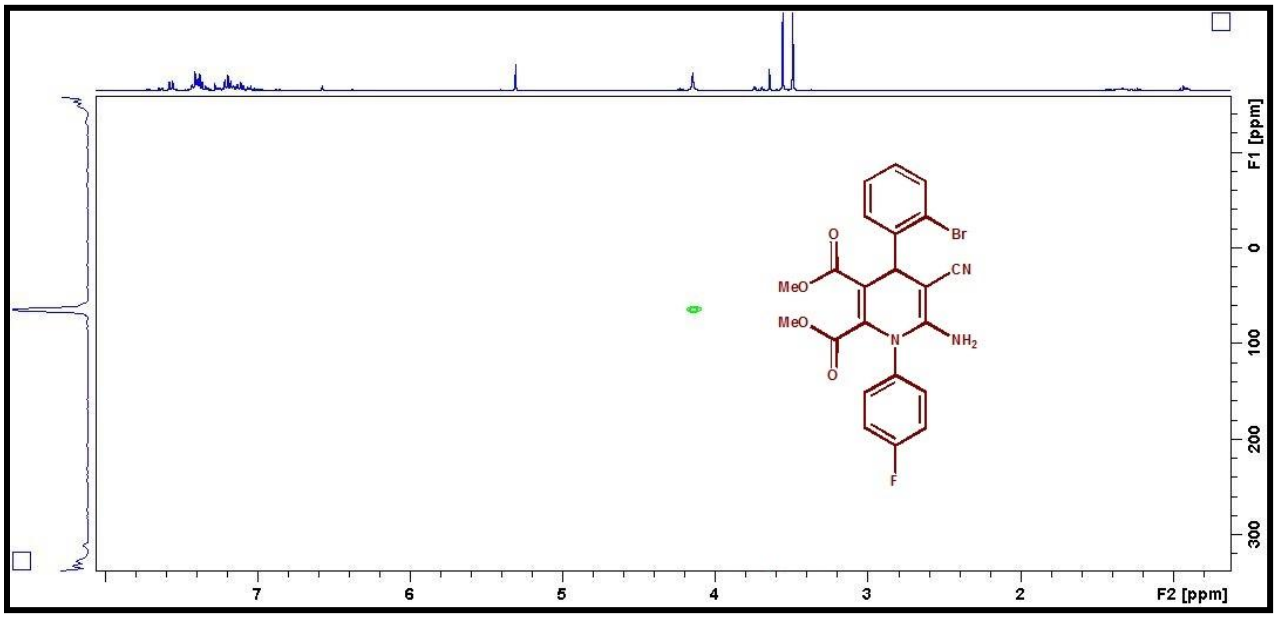
HRMS spectra of compound **5c**



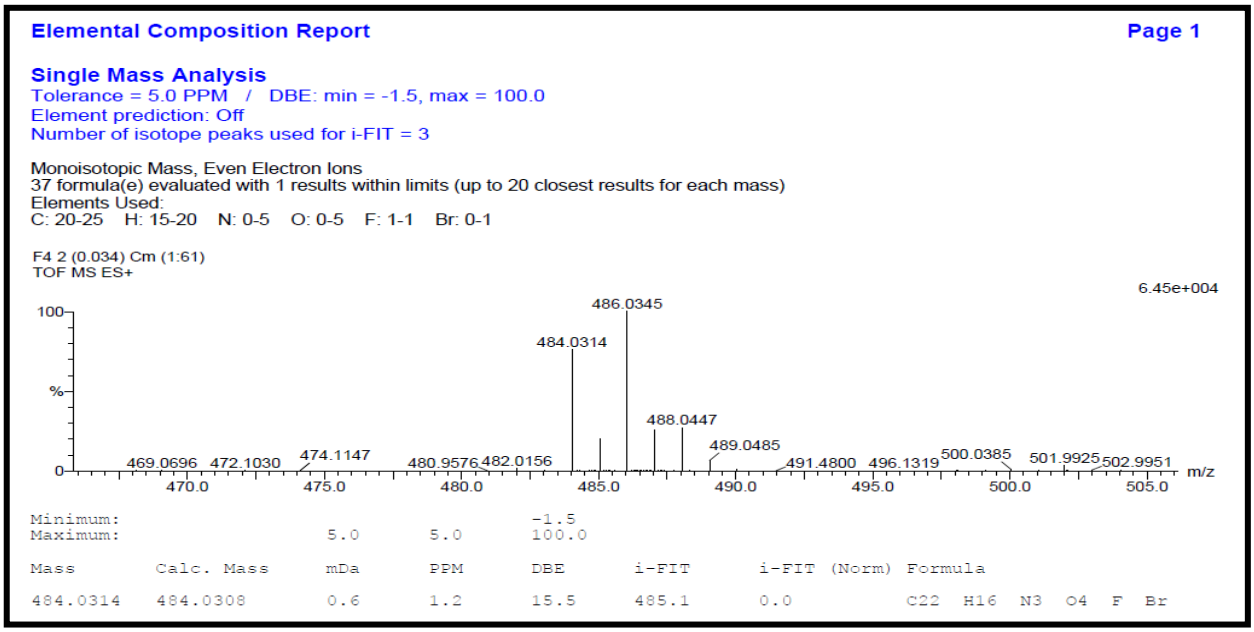
^{1}H NMR spectra of compound **5d**



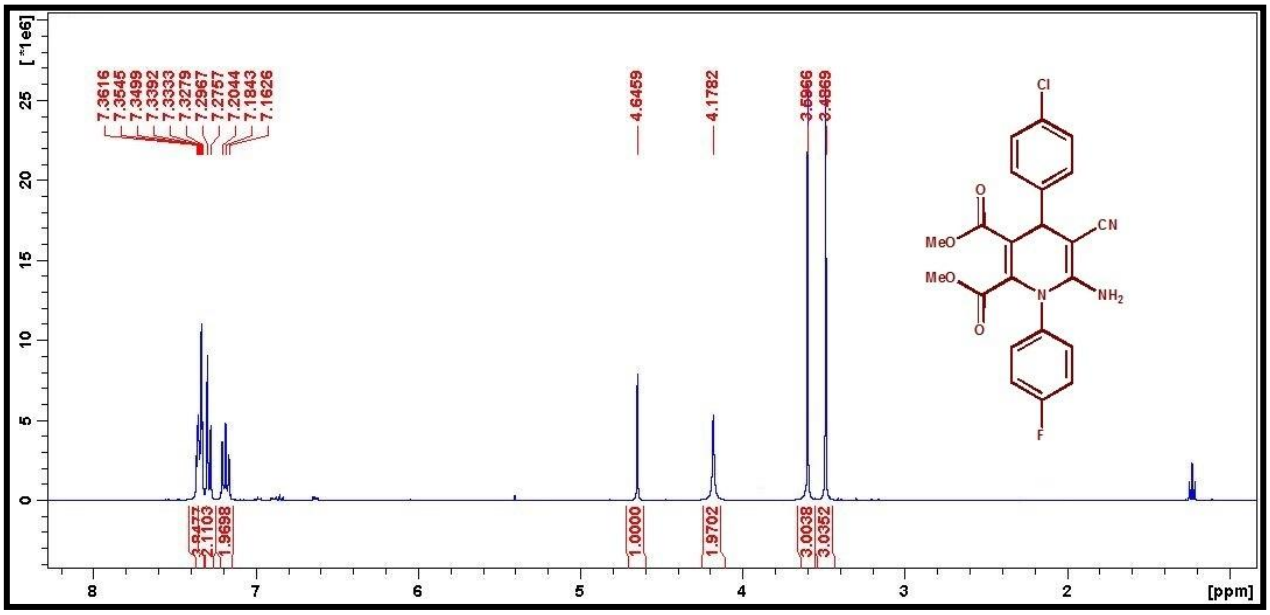
^{13}C NMR spectra of compound **5d**



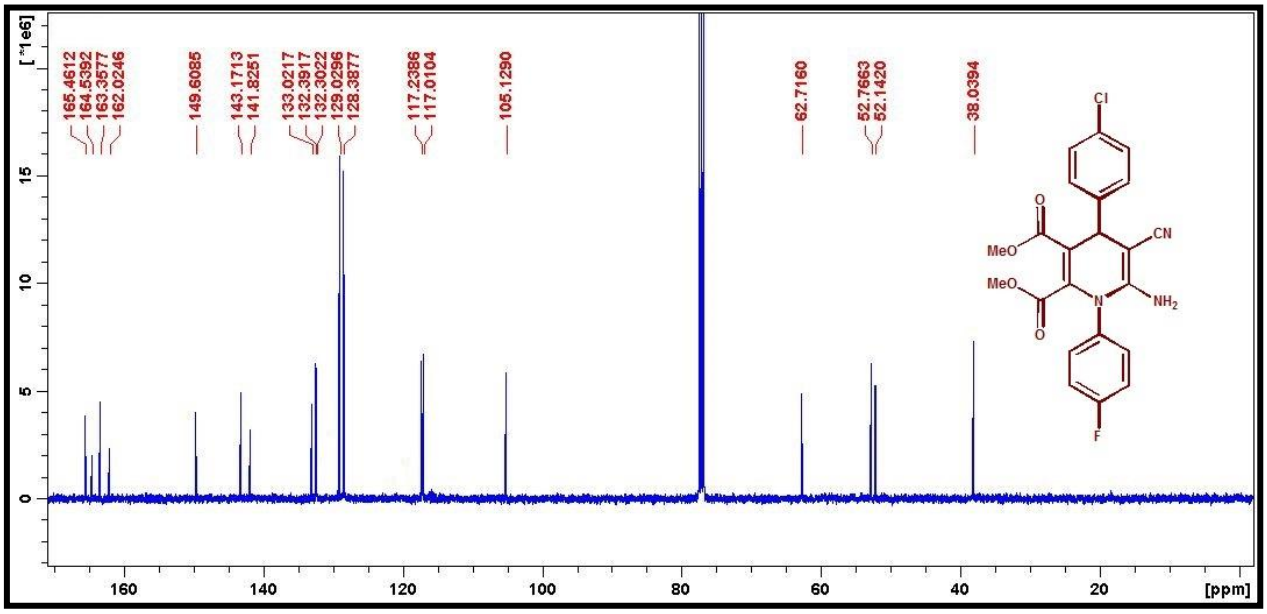
^{15}N NMR spectra of compound **5d**



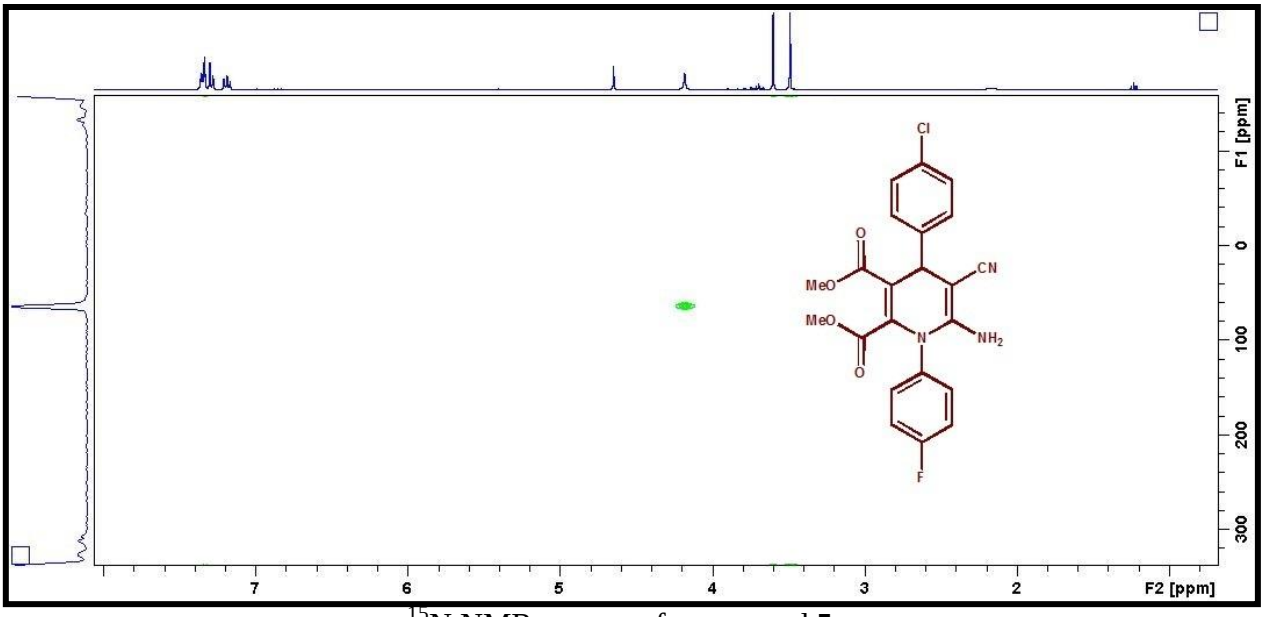
HRMS spectra of compound **5d**



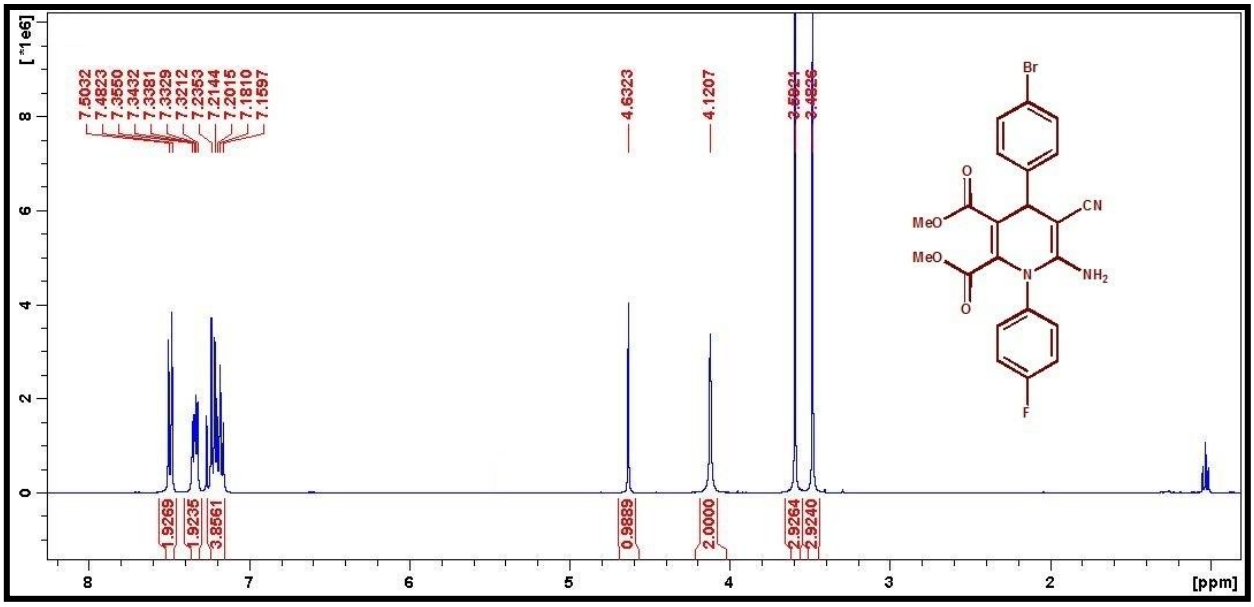
^{1}H NMR spectra of compound **5e**



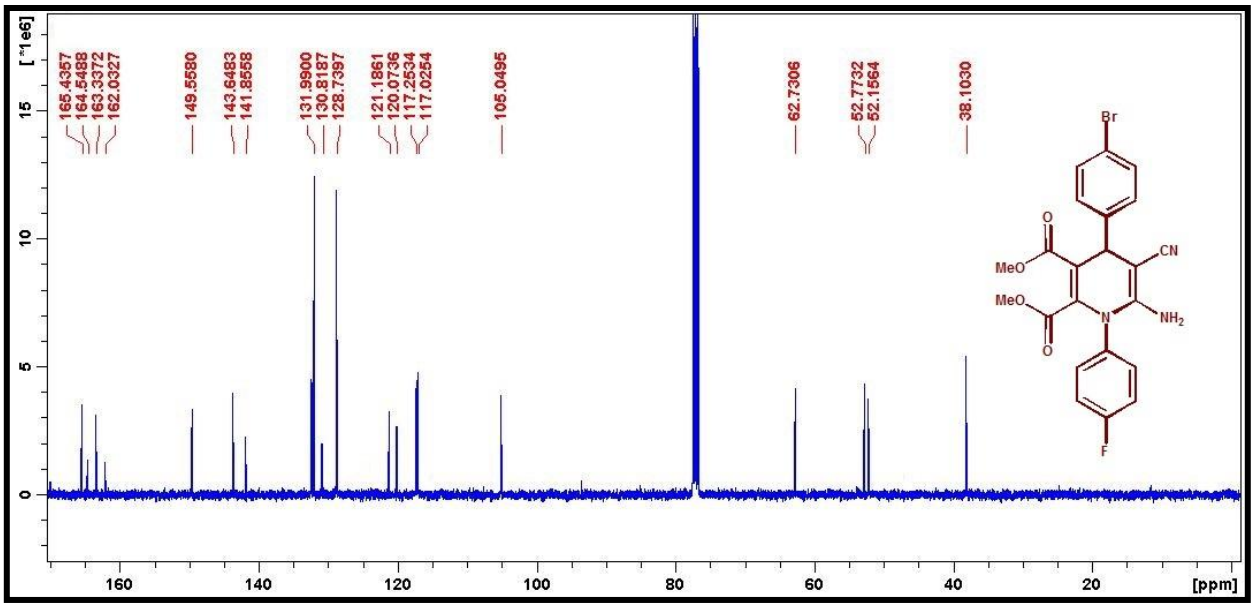
^{13}C NMR spectra of compound **5e**



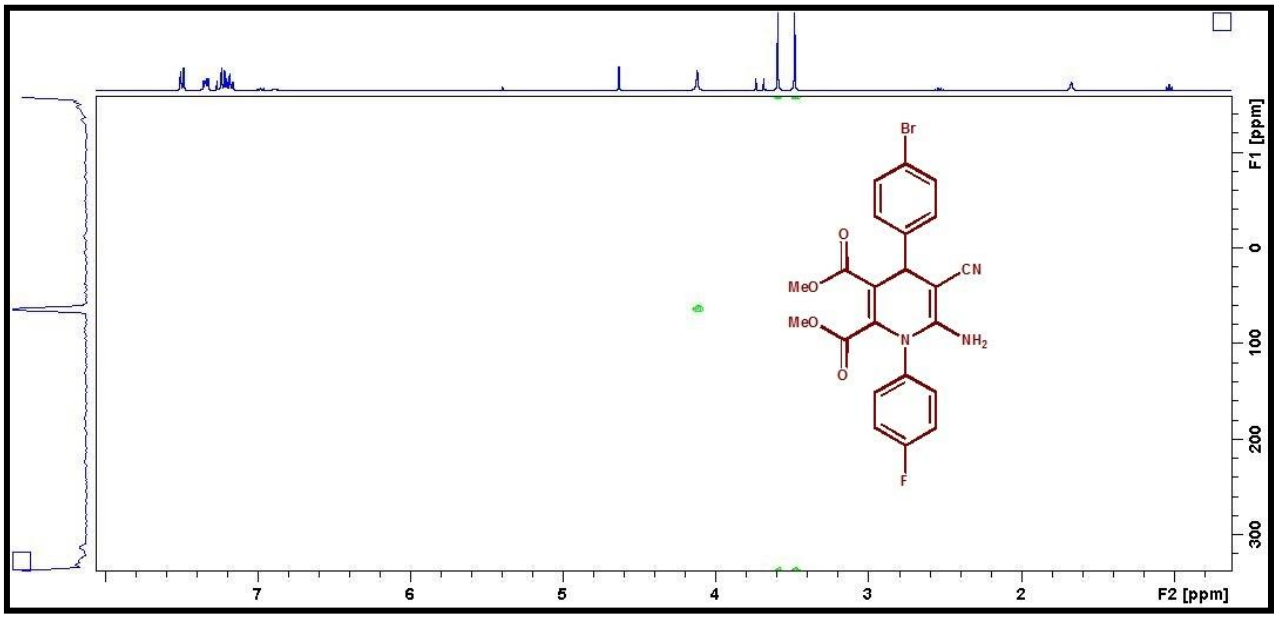
^{15}N NMR spectra of compound **5e**



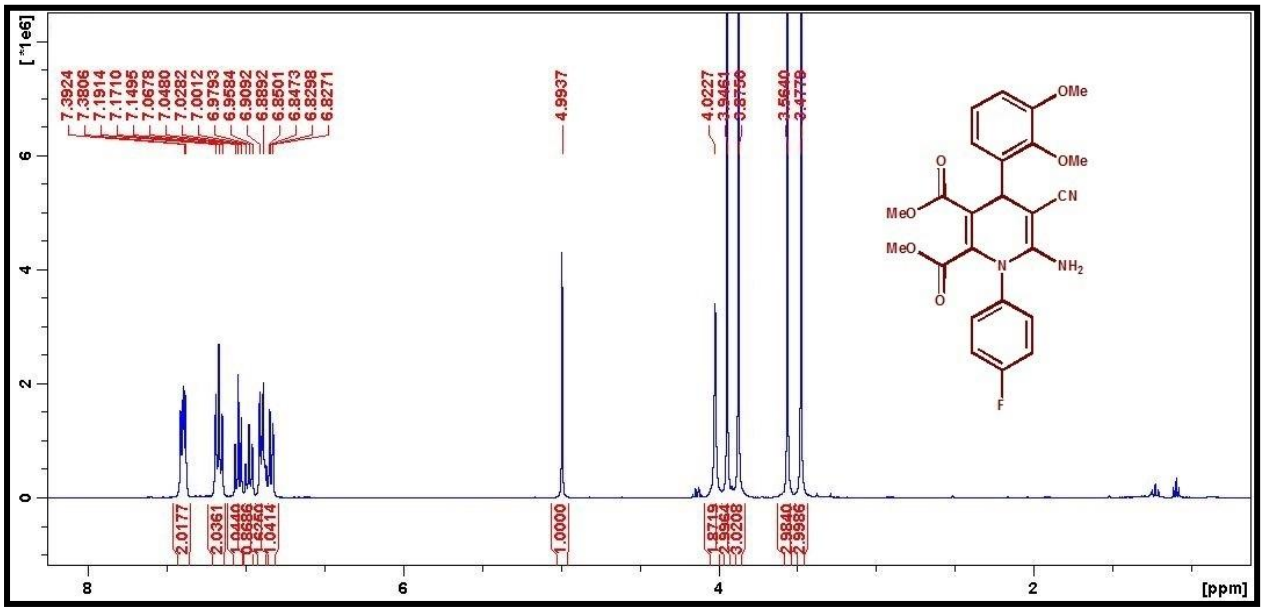
^{1}H NMR spectra of compound **5f**



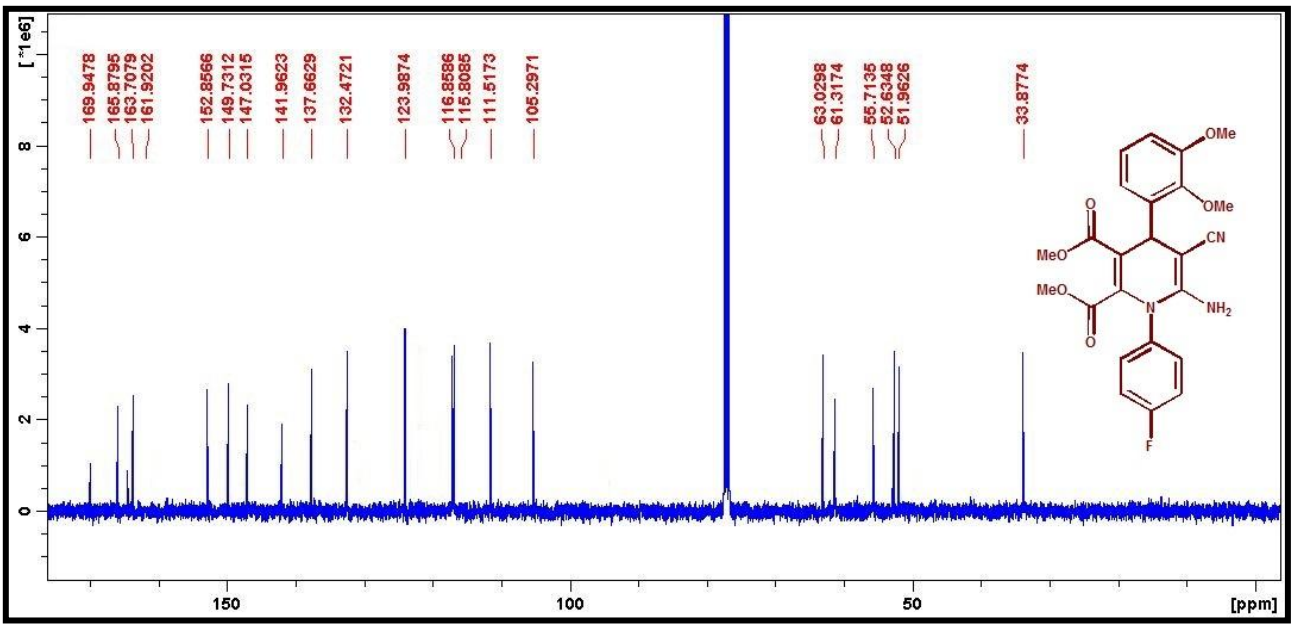
^{13}C NMR spectra of compound **5f**



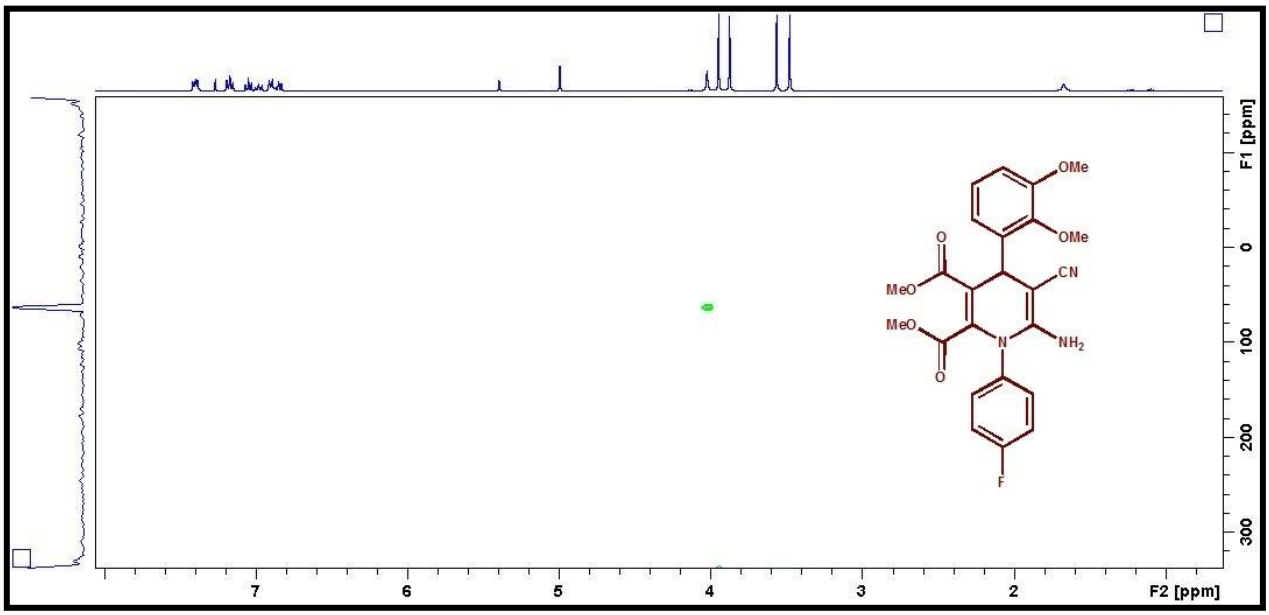
^{15}N NMR spectra of compound **5f**



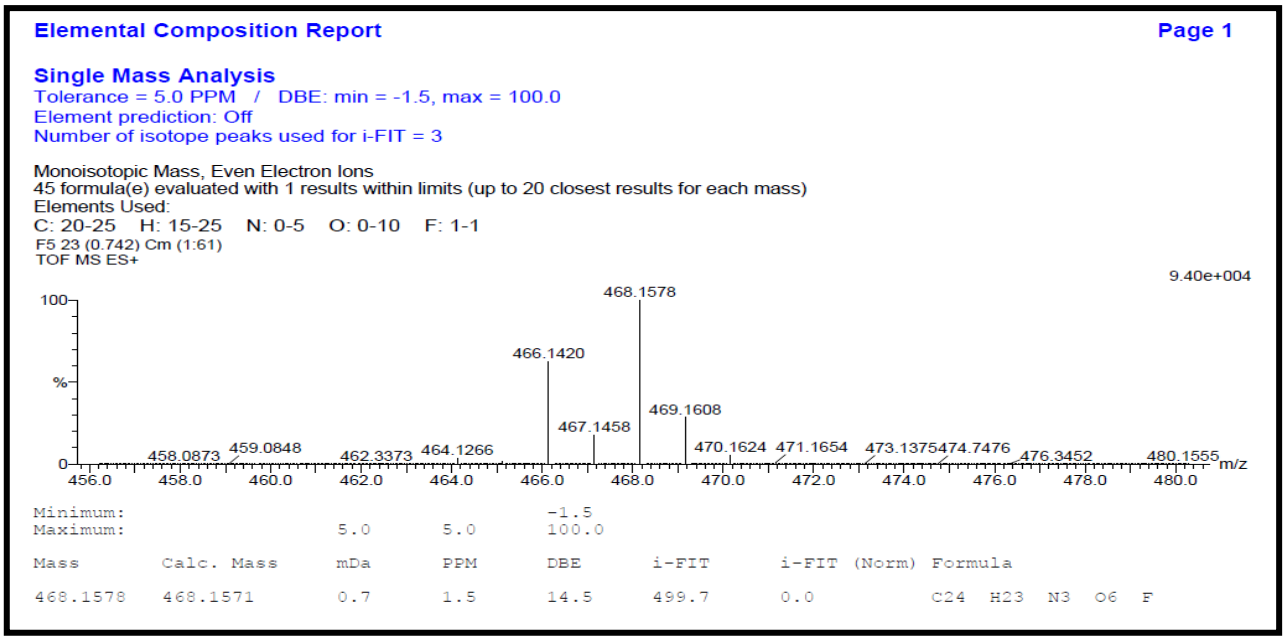
^{1}H NMR spectra of compound **5g**



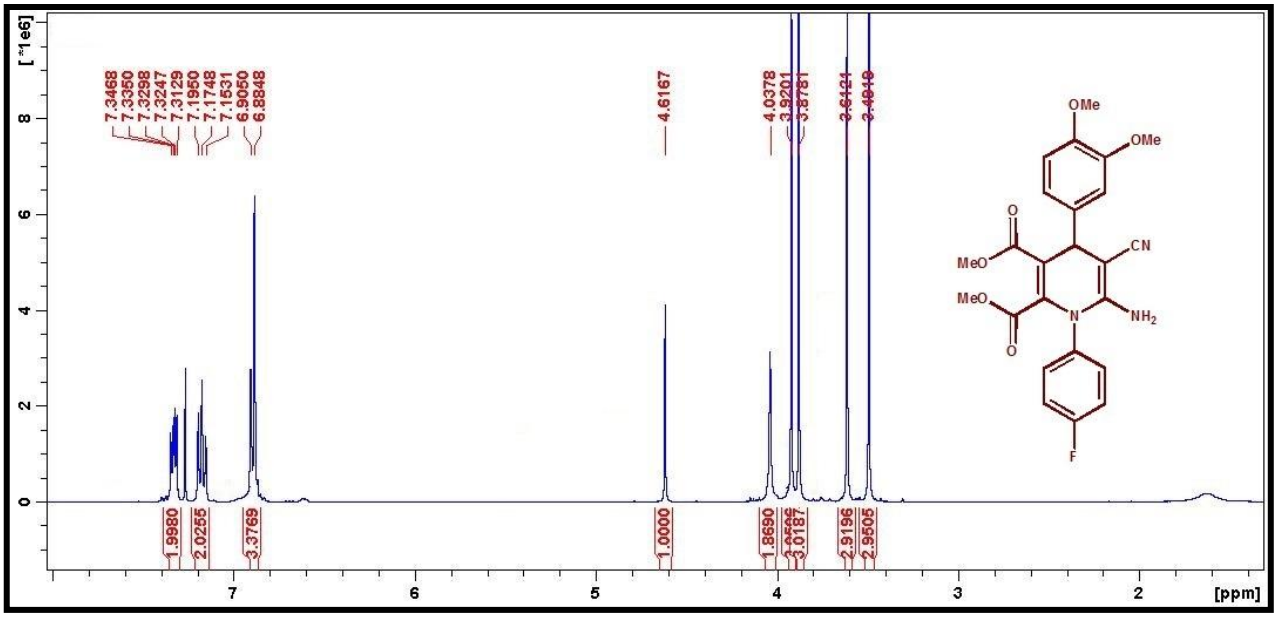
^{13}C NMR spectra of compound **5g**



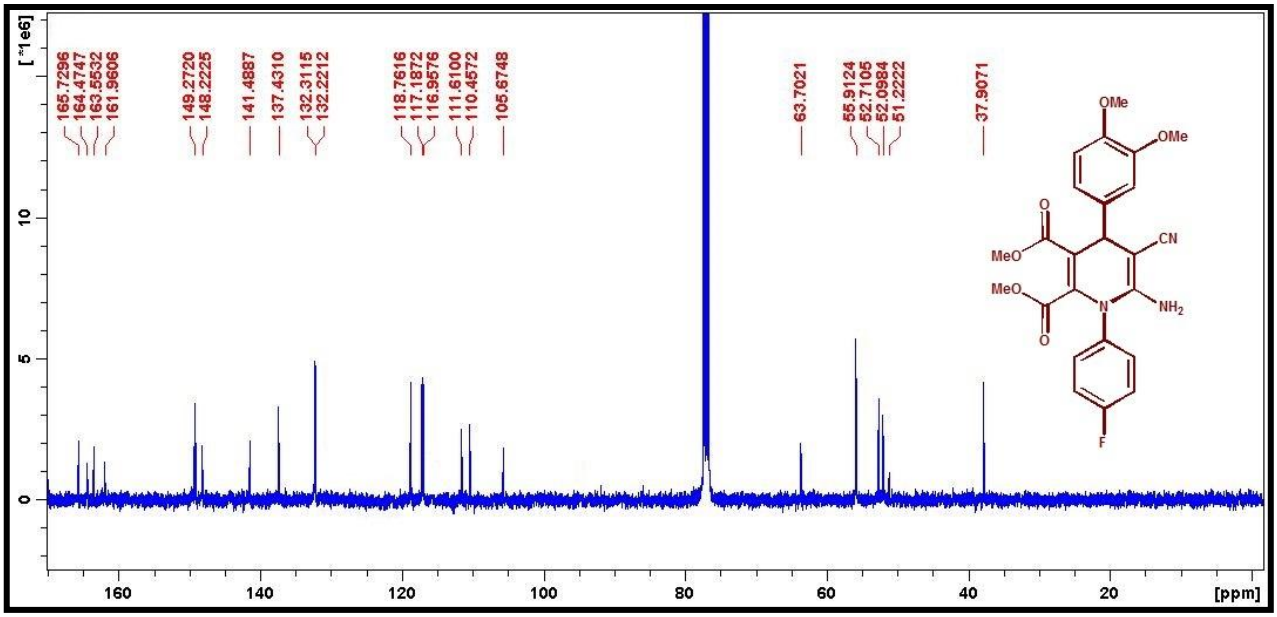
^{15}N NMR spectra of compound **5g**



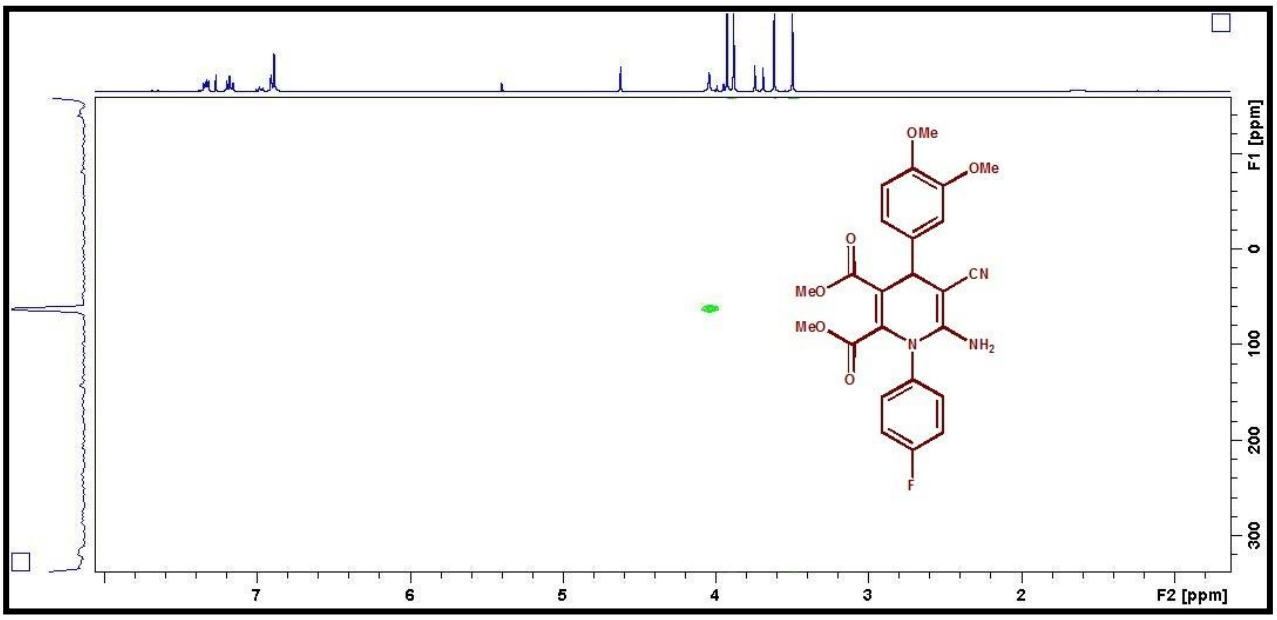
HRMS spectra of compound **5g**



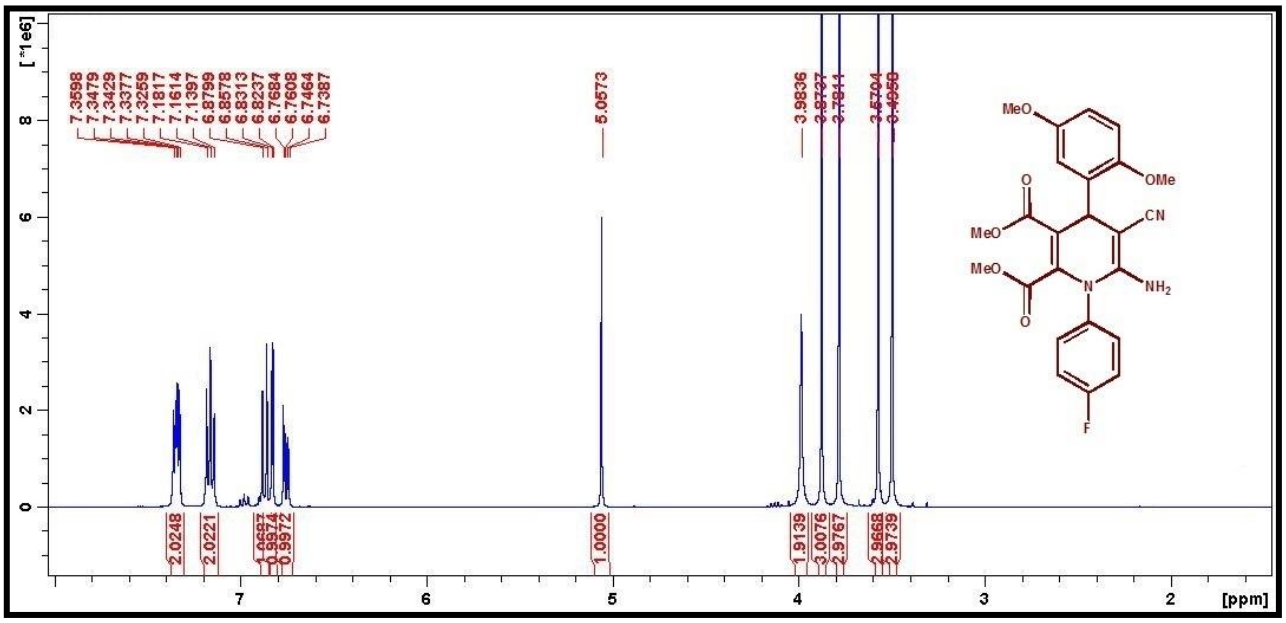
^{1}H NMR spectra of compound **5h**



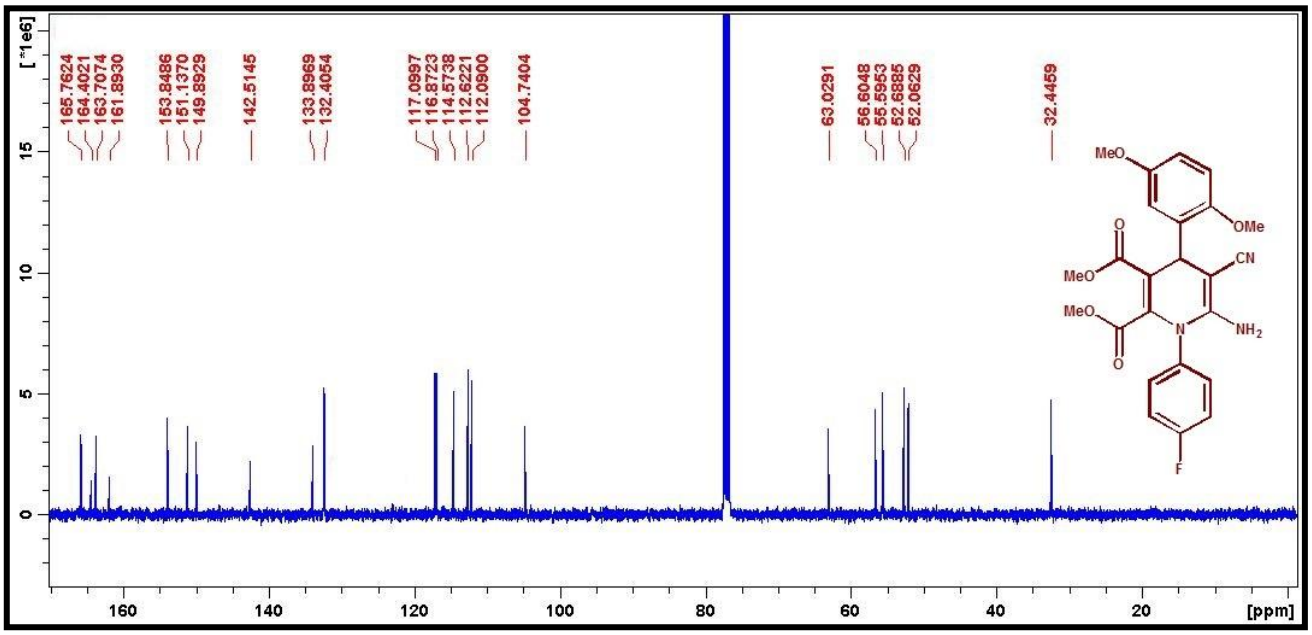
^{13}C NMR spectra of compound **5h**



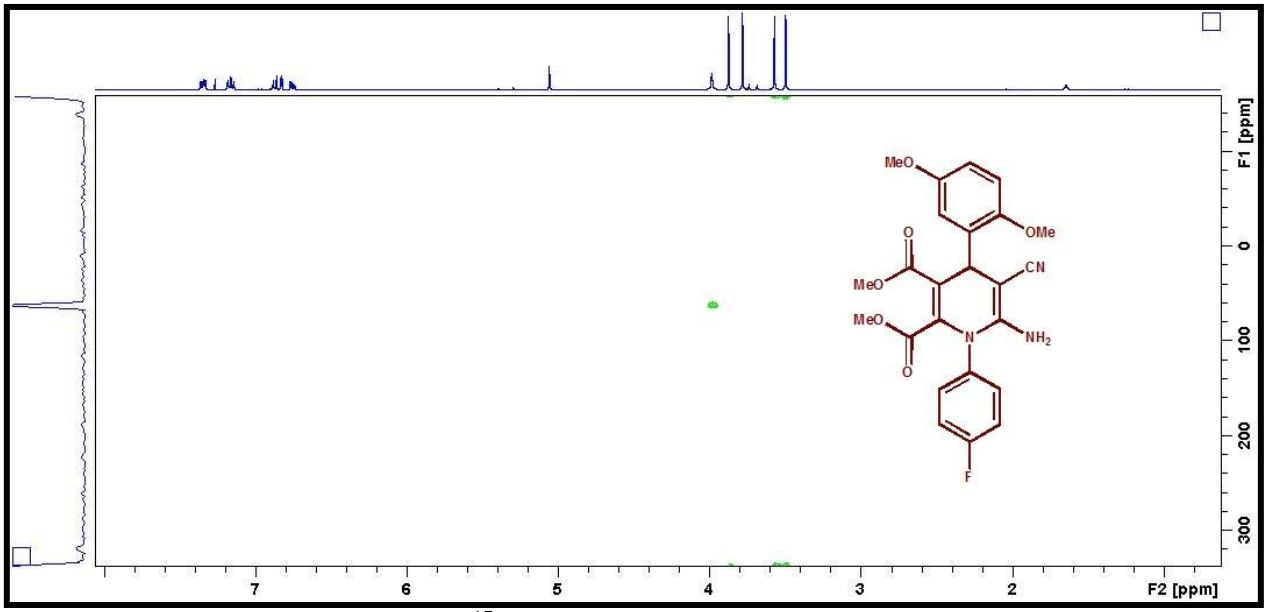
^{15}N NMR spectra of compound **5h**



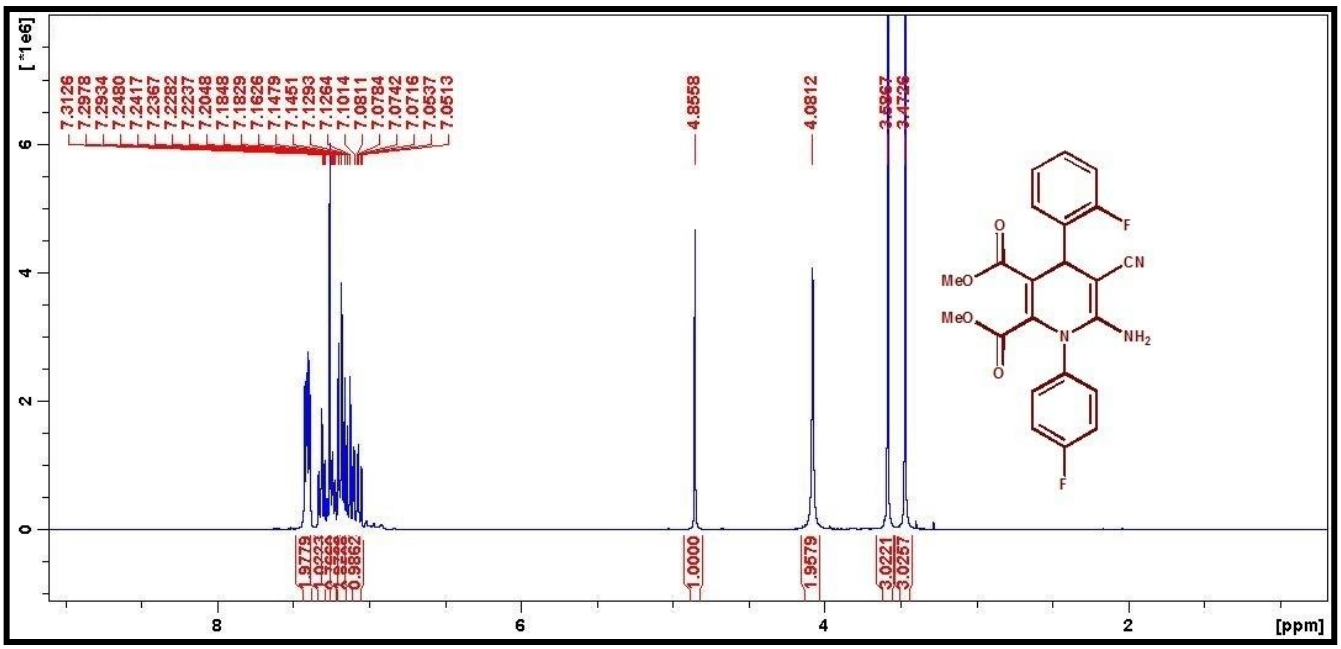
^{1}H NMR spectra of compound **5i**



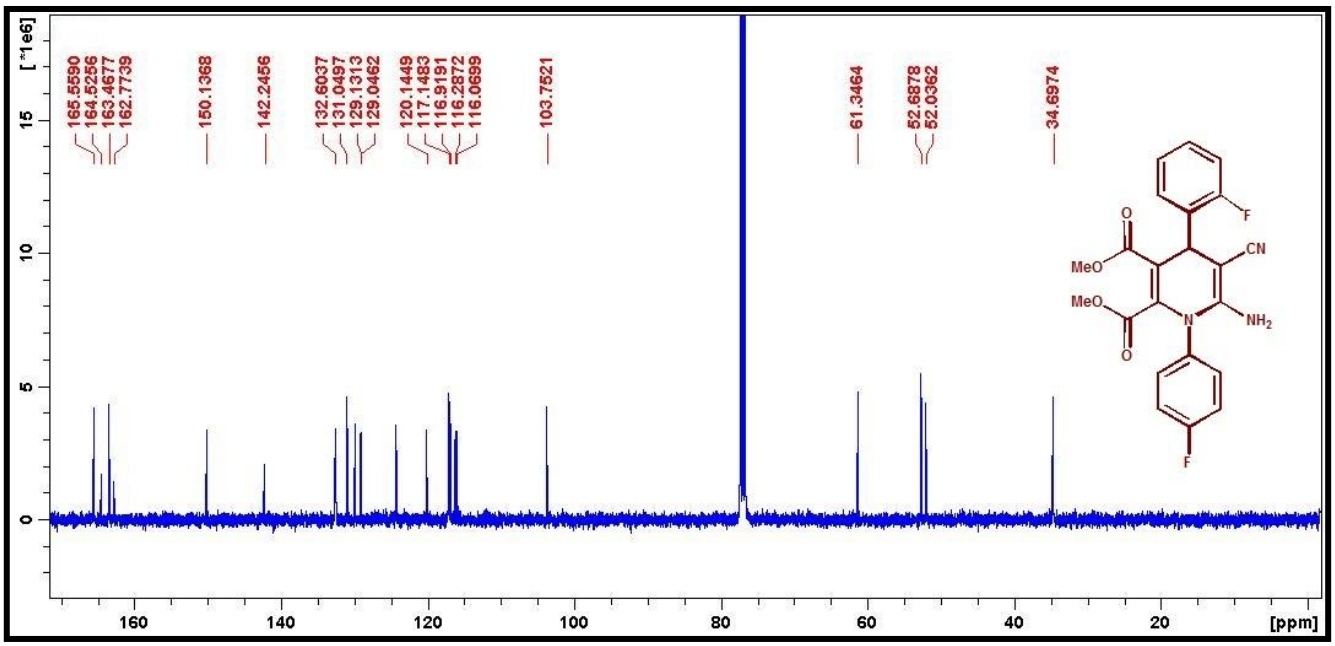
^{13}C NMR spectra of compound **5i**



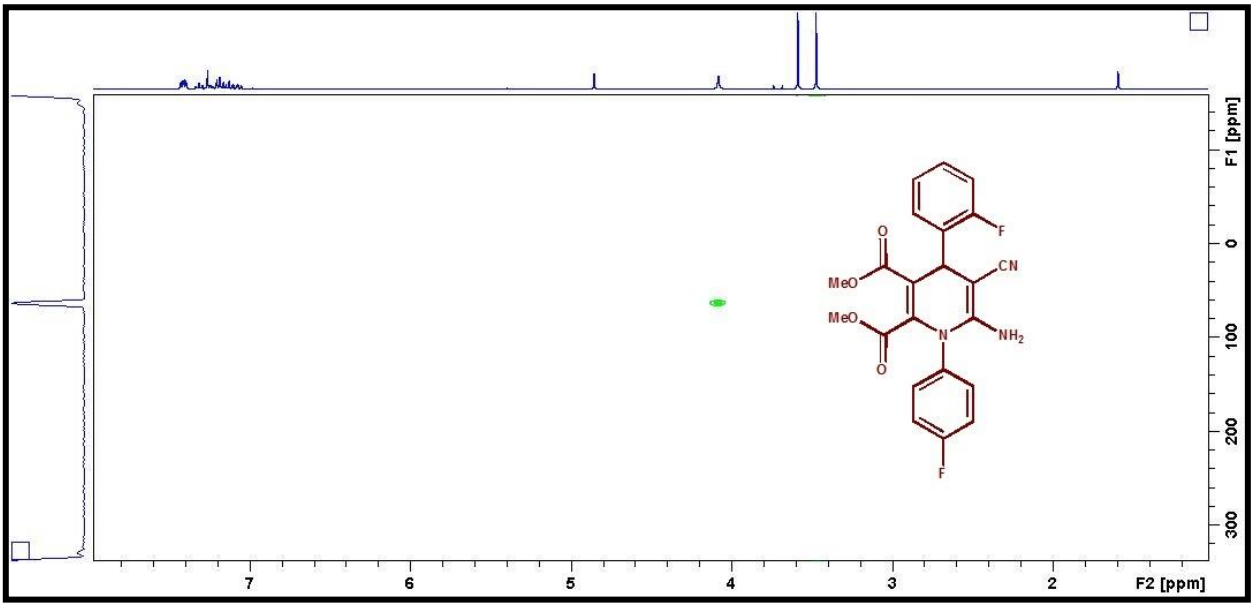
^{15}N NMR spectra of compound **5i**



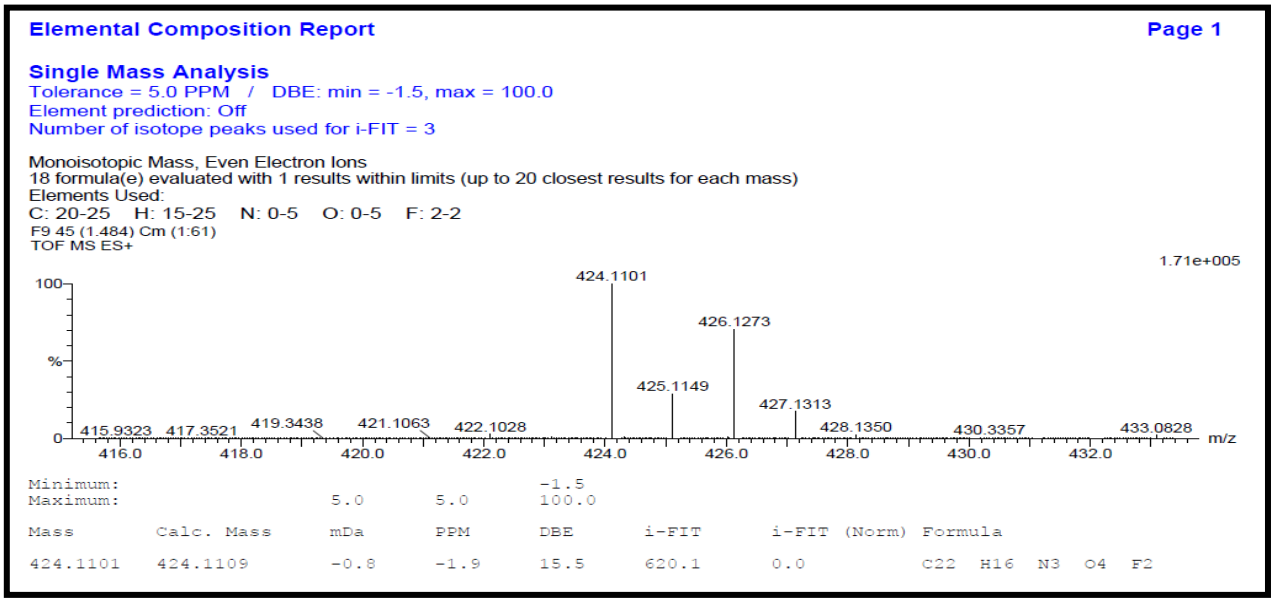
^{1}H NMR spectra of compound **5j**



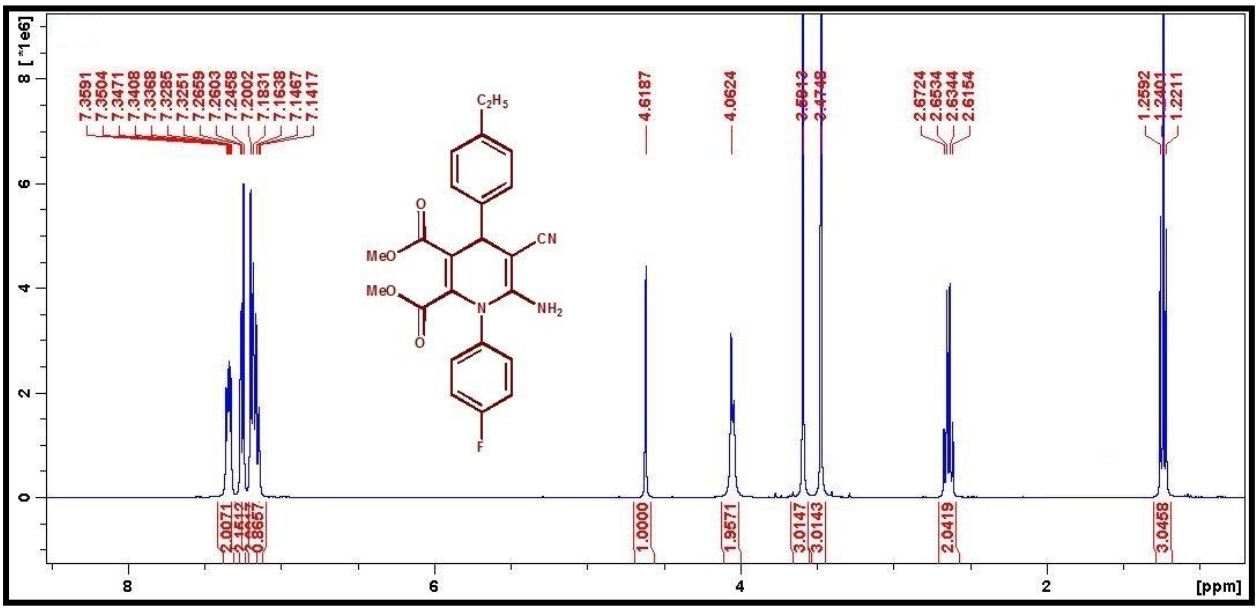
^{13}C NMR spectra of compound **5j**



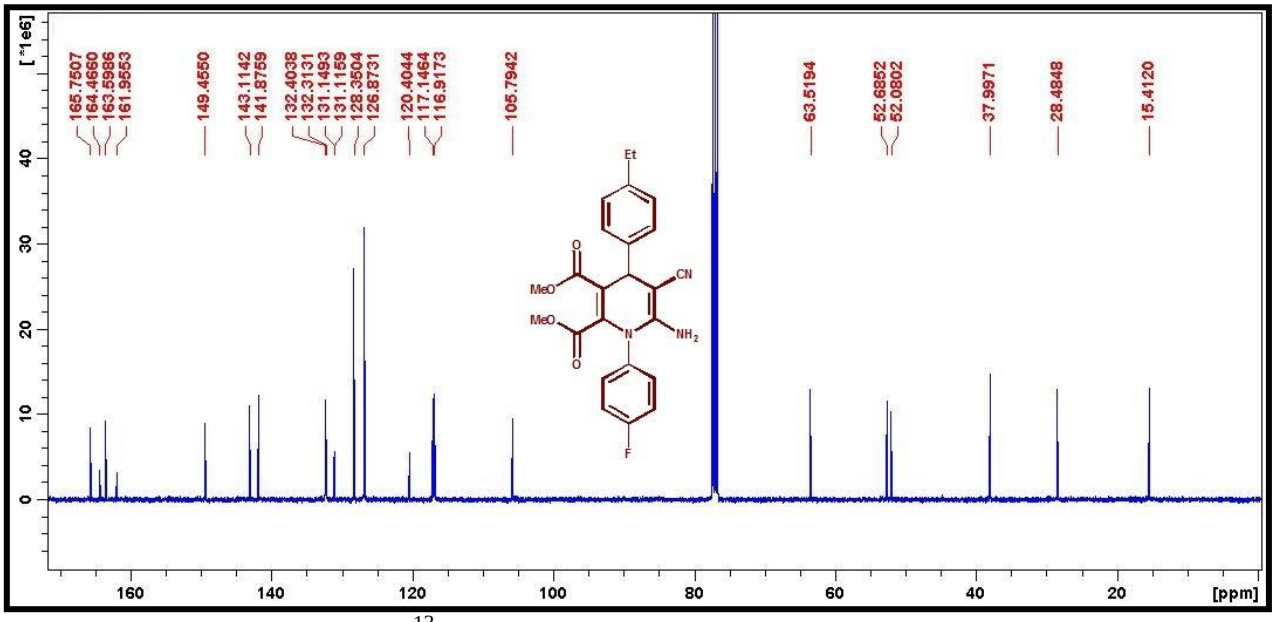
^{15}N NMR spectra of compound **5j**



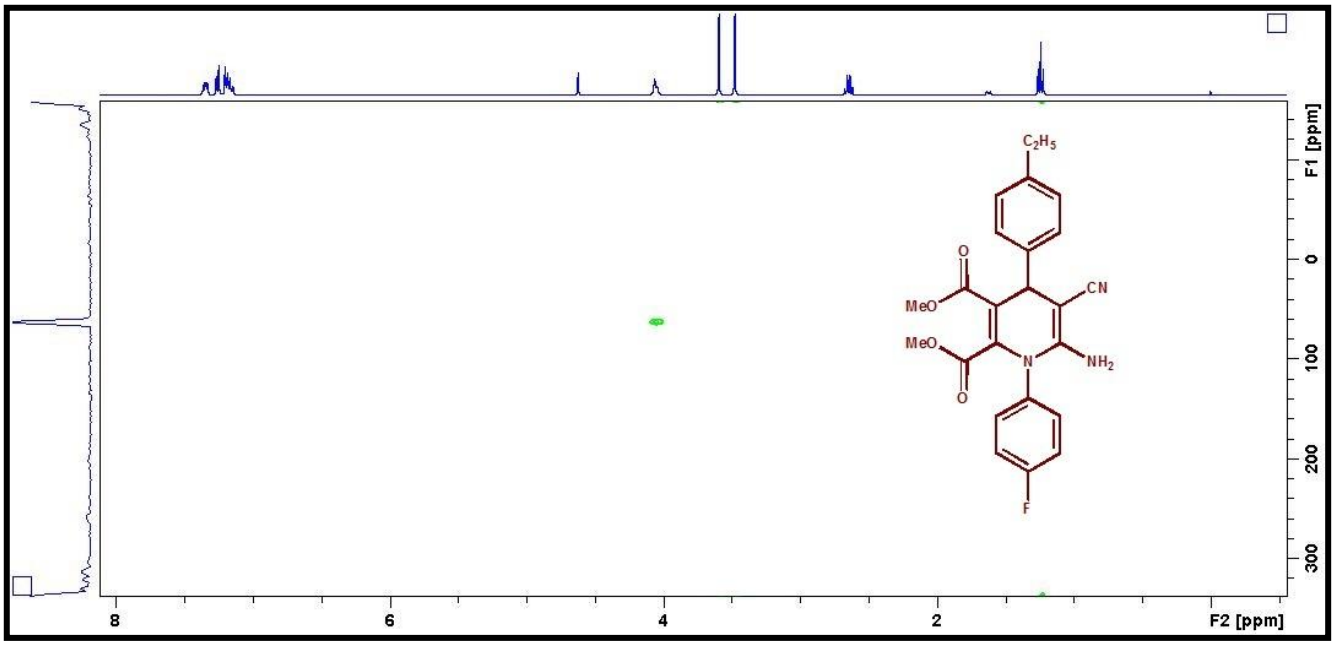
HRMS spectra of compound **5j**



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



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



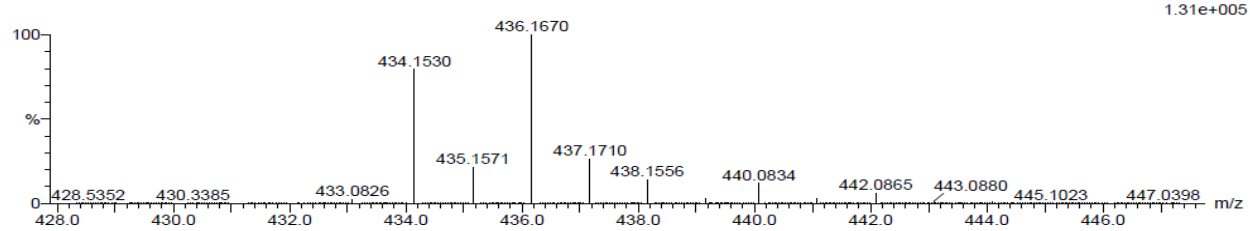
^{15}N NMR spectra of compound **5k**

Elemental Composition Report Page 1

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

Monoisotopic Mass, Even Electron Ions
38 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 15-25 N: 0-5 O: 0-5 F: 0-1
F10 10 (0.304) Cm (1:61)
TOF MS ES+

1.31e+005



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
434.1530	434.1516	1.4	3.2	15.5	550.9	0.0	C24 H21 N3 O4 F

HRMS spectra of compound **5k**

Chapter 3

Sustainable CeO_2/ZrO_2 catalyst for the green synthesis of highly functionalized 1,4-dihydropyridine-2,3-dicarboxylate derivatives

Sebenzile Shabalala, Suresh Maddila, Werner E. van Zyl and Sreekantha B Jonnalagadda*****

*School of Chemistry & Physics, University of KwaZulu-Natal, Westville Campus, Chiltern Hills, Durban-4000, South Africa.

***Corresponding Author:** Prof. Sreekantha B. Jonnalagadda
School of Chemistry & Physics,
University of KwaZulu-Natal,
Durban 4000, South Africa.
Tel.: +27 31 2607325,
Fax: +27 31 2603091
E-mail address: **jonnalagaddas@ukzn.ac.za**

Abstract

CeO_2/ZrO_2 was employed as a heterogeneous catalyst for the synthesis of pyridine derivatives *via* a one-vessel, four-component reaction consisting of a substituted aldehyde, malononitrile, dimethylacetylenedicarboxylate and dimethylaniline with good to excellent product yields (87 to 95%). The noteworthy advantages of the facile method with ethanol as solvent are excellent yields with short reaction times. The catalyst is reusable with little loss of activity up to six cycles. While, powder X-ray diffraction, TEM, SEM and N_2 adsorption/desorption analysis techniques were employed for the structural interpretation of CeO_2/ZrO_2, the identity of target products were established and confirmed by diverse spectral (^{1}H NMR, ^{13}C NMR, ^{15}N NMR, FT-IR and HRMS) techniques.

Keywords: Green synthesis, CeO_2/ZrO_2, Heterogeneous catalysis, One-pot synthesis, Pyridines, Multicomponent reaction.

1.1. Introduction

The multicomponent reaction (MCR) is one of many efficient routes of making optimum use of resources and saving time in the fields of synthetic and medicinal chemistry. [1,2] MCR refers to a synthetic process where the reactants are added in a one-pot procedure to ideally give only one desired product without isolation of the intermediates.[1-3] These reactions have gained a lot of attention because of their clear benefits such as excellent atom efficiency, amenability, simplicity in performance (whilst generating a complex reaction) and maximum diversity.[4-6] MCRs are generally faster and therefore essential in the drug discovery and pharmaceutical fields.[7] The improvement of heterogeneous catalysts for heterocyclic synthesis has grown into a major topic of research.[7,8] Heterogeneous materials as catalyst in organic reactions enjoy both conservational and fiscal benefits and such materials are easily recoverable and recyclable, which make their use more attractive.[8,9] Heterogeneous catalysts have many advantages such being amenable to filtration after completion of the reaction, thermal stability, long life, high selectivity and recyclability. This prevents any waste production whilst obtaining the high yield products after a short period of time through a green procedure.[10]

Ceria metals are commonly used as doped catalysts and their usefulness is demonstrated through ease of handling, low-cost, high stability and non-hazardous properties.[11] Although

their use in stoichiometric quantities is frequently thwarted by unwanted environmental and economic features. Hence, the use of a heterogenized version of cerium salts is a desirable choice for green organic conversions. Zirconium is a metal oxide that has been known for use as a gem from ancient times.[12] Zirconia (ZrO_2) stands out amongst other metal oxides due to its excellent stability and mechanical properties.[13] It readily promote the activity of the supported metal catalysts. Crystalline zirconia contains three different temperature-dependent (in the absence of dopants) polymorphic phases which are transformed from a cubic to a tetragonal to a monoclinic phase.[14] and are highly dependent on the sintering temperature. ZrO_2 has been mainly used because of its significant chemical and thermal stability, high surface area and inertness. Therefore, it has played a major role in catalysis.

A wide range and variety of heterocyclic compounds have been synthesized and utilized in the medicinal and pharmaceutical chemistry arenas.[15,16] The pyridine entity is one of the most significant heterocycles, found in several natural products. [17] These classes are very important because they exhibit a wide and diverse window of biological activities.[18-22] In addition, heterocycles are found in the synthetic derivatives of pyridines, which represents the *N*-heterocycles class. [23] Literature reveals that very few reports are available for the synthesis of pyridine derivatives. The described methods employed TEA, PEG-600, meglumine and NaOH as catalysts to facilitate the reactions, which also involve costly reagents, high temperature, long reaction times, tedious handling processes and harsh reaction conditions, but low yields.[24-26]

Focused on developing efficient and environmental-friendly techniques for the synthesis of heterocyclic compounds, in the recent year we reported the robustness of variety of reusable catalysts.[27, 28] and novel heterocyclic compounds with different biological activities.[29-32] Here, we report an efficacious and facile green synthesis of novel functionalized 1,4-dihydropyridine-2,3-dicarboxylates through a four-component, one-pot reaction of substituted aldehydes, malononitrile, dimethylacetylenedicarboxylate and dimethylaniline with ethanol as solvent at room temperature using ceria on zirconia as a reusable catalyst.

3.2. Experimental Section

3.2.1 Preparation of Catalyst

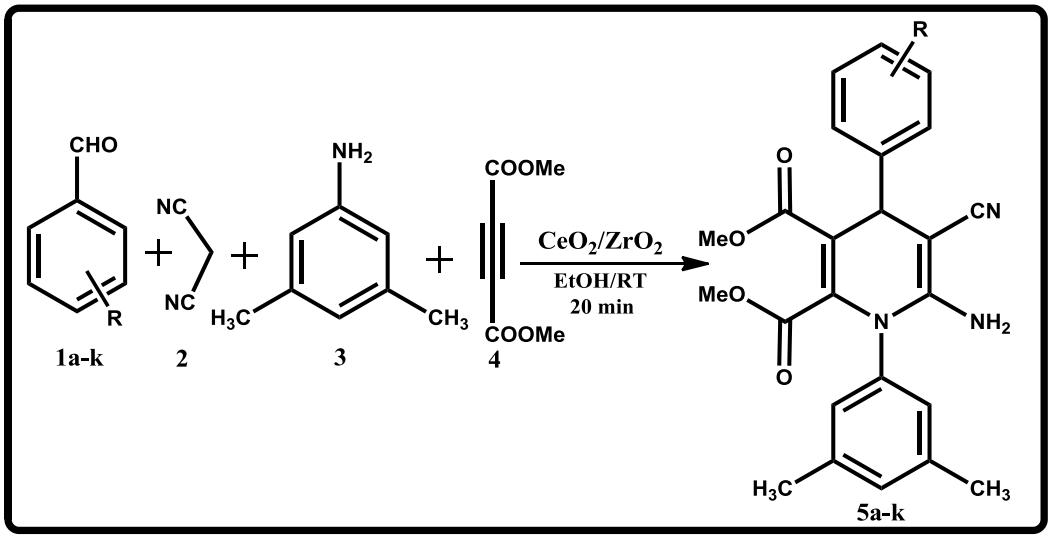
A sequence of supported catalysts, weight percentage CeO_2/ZrO_2 (1, 2.5 & 5 wt%), were prepared using the wet-impregnation procedure. The heterogeneous catalyst was achieved from mixture of zirconia (ZrO_2, 2 g, Catalyst support, Alfa Aesar) and an appropriate wt% amount of cerium nitrate [$Ce(NO_3)_3 \cdot 6H_2O$ (Alfa Aesar)] in (60 mL) dissolved in distilled water. The mixture was stirred at room temperature for 12 h after which the resulting slurry was filtered under vacuum. Further, it was dried in an oven at 120–130 °C for 6 h and calcined in the presence of air, at 450 °C for 5 h to acquire (1, 2.5 & 5 wt%) of CeO_2/ZrO_2 catalysts.

3.2.2. Catalyst instrumentation details

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.

3.2.3. General synthesis of functionalized 1,4-dihydropyridine-2,3-dicarboxylates (5a-l)

A mixture of substituted aldehyde (1 mmol), malononitrile (1.1 mmol), dimethylacetylenedicarboxylate (1.0 mmol), dimethylaniline (1 mmol) and CeO_2/ZrO_2 (30 mg) in 10 mL ethanol was taken a round-bottom flask and stirred at room temperature (RT). The progress and completion of reaction was checked by TLC. Upon completion, the crude solid was collected by filtration and followed by two washings with ethanol, it was further purified by recrystallization to afford pure products (Scheme 1). The molecular structures of the resulting products were established based on their physical properties and spectral data.



Scheme 1. Synthesis of functionalized 1,4-dihydropyridine-2,3-dicarboxylate derivatives

3.2.4. Products characterization data

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5a): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.25 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.09 (s, 1H, CH), 5.31 (s, 2H, NH_2), 6.95-7.03 (m, 2H, ArH), 7.06 (s, 1H, ArH), 7.18-7.21 (m, 4H, ArH), 7.29 (t, J = 7.52 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 17.32, 17.80, 31.12, 51.66, 52.15, 55.74, 58.58, 103.03, 111.56, 120.76, 120.90, 127.91, 128.83, 130.08, 132.96, 134.34, 135.37, 138.85, 138.89, 142.00, 149.59, 155.78, 162.77, 165.31, 169.14; FT-IR: 3309, 2180, 1705, 1650, 1573, 1494, 1344, 1202; HRMS of $[C_{25}H_{25}N_3O_5 + Na]^+$ (m/z): 470.0338; Calcd: 470.0331.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2-fluorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5b): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 6H, $(CH_3)_2$), 3.36 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 4.77 (s, 1H, CH), 5.55 (s, 2H, NH_2), 6.90 (s, 2H, ArH), 7.14-7.25 (m, 1H, ArH), 7.27-7.35 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.59, 33.11, 51.86, 52.25, 58.06, 102.32, 115.55, 115.77, 120.71, 124.88, 127.33, 128.97, 129.05, 129.20, 129.24, 131.39, 131.87, 132.01, 134.86, 139.00, 142.73, 151.03, 158.46, 160.90, 162.81, 164.89; FT-IR: 3378, 2949, 2180, 1706, 1652, 1566, 1433, 1343, 1231; HRMS of $[C_{24}H_{22}FN_3O_4 + H]^+$ (m/z): 436.1474; Calcd: 436.1465.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2-chlorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5c): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 6H, $(CH_3)_2$), 3.36 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 5.08 (s, 1H, CH), 5.53 (s, 2H, NH_2), 6.94 (s, 2H, ArH), 7.14 (s, 1H, ArH), 7.25-7.29 (m, 1H, ArH), 7.41-7.44 (m, 3H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.58, 35.30, 51.83, 52.26, 58.58, 103.12, 120.46, 127.35, 128.15, 128.57, 129.42, 129.46, 131.21, 131.43, 134.76, 139.03, 142.79, 142.87, 150.81, 162.77, 164.86; FT-IR: 3377, 2950, 2181, 1706, 1652, 1566, 1514, 1433, 1377, 1230; HRMS of $[C_{24}H_{22}ClN_3O_4 + H]^+$ (m/z): 452.1087; Calcd: 452.1085.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2-bromophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5d): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 6H, $(CH_3)_2$), 3.35 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 4.49 (s, 1H, CH), 5.58 (s, 2H, NH_2), 6.88 (s, 2H, ArH), 7.13 (s, 1H, ArH), 7.19-7.24 (m, 2H, ArH), 7.30-7.34 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 8.55, 20.54, 37.87, 51.87, 52.25, 59.27, 104.09, 115.39, 105.60, 117.64, 120.89, 127.25, 128.53, 128.61, 131.37, 134.87, 138.42, 139.03, 141.83, 150.74, 159.94, 162.35, 162.86, 165.03, 168.56; FT-IR: 3376, 2950, 2180, 1736, 1651, 1567, 1433, 1343, 1230.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(4-chlorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5e): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 6H, $(CH_3)_2$), 3.36 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 4.49 (s, 1H, CH), 5.62 (s, 2H, NH_2), 6.89 (s, 2H, ArH), 7.13 (s, 1H, ArH), 7.31 (d, J = 8.44 Hz, 2H, ArH), 7.47 (d, J = 8.44 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.55, 38.06, 5.90, 52.27, 58.95, 103.77, 120.81, 127.26, 128.56, 128.76, 131.39, 131.56, 134.82, 139.03, 142.01, 144.37, 150.81, 162.80, 164.96; FT-IR: 3461, 3377, 2951, 2181, 1749, 1650, 1566, 1443, 1376, 1230; HRMS of $[C_{24}H_{22}ClN_3O_4 + H]^+$ (m/z): 452.1432; Calcd: 452.1437.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(4-bromophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5f): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 6H, $(CH_3)_2$), 3.36 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 4.47 (s, 1H, CH), 5.63 (s, 2H, NH_2), 6.89 (s, 2H, ArH), 7.13 (s, 1H, ArH), 7.25 (d, J = 8.40 Hz, 2H, ArH), 7.60 (d, J = 8.36 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.54, 20.75, 38.15, 51.89, 52.26, 58.89, 103.70, 117.64, 119.32, 120.07, 120.80, 125.49, 126.12, 127.26, 128.94, 131.68, 134.81, 138.41, 139.04, 142.03, 144.79, 147.50, 150.81, 162.79,

164.50, 164.95, 168.56; FT-IR: 3381, 2951, 2181, 1736, 1707, 1655, 1565, 1443, 1342, 1230; HRMS of $[C_{24}H_{22}BrN_3O_4 + 2H]^+$ (m/z): 497.2487; Calcd: 497.2485.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2,3-dimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5g): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 6H, $(CH_3)_2$), 3.46 (s, 6H, $(OCH_3)_2$) , 3.80 (s, 6H, $(OCH_3)_2$), 4.84 (s, 1H, CH), 5.41 (s, 2H, NH_2), 6.85 (dd, J = 7.76 Hz, 1H, ArH), 6.85 (dd, J = 1.16 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 6.81 (s, 2H, ArH), 6.94 (dd, J = 8.24 Hz, 1H, ArH), 6.94 (dd, J = 1.32 Hz, 1H, ArH), 7.09 (d, J = 7.92 Hz, 1H, ArH), 7.13 (d, J = 4.44 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.59, 20.76, 32.55, 51.72, 52, 17, 55.52, 56.02, 59.53, 103.87, 111.39, 117.66, 119.80, 120.98, 124.16, 127.25, 131.25, 135.16, 138.33, 138.95, 142.40, 145.56, 150.82, 152.23, 163.03, 165.15; FT-IR: 3378, 2951, 2181, 1736, 1653, 1566, 1443, 1376, 1230.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5h): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 6H, $(CH_3)_2$), 3.46 (s, 6H, $(OCH_3)_2$), 3.80 (s, 6H, $(OCH_3)_2$), 4.84 (s, 1H, CH), 5.41 (s, 2H, NH_2), 6.85 (dd, J = 7.76 Hz, 1H, ArH), 6.85 (dd, J = 1.16 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 6.81 (s, 2H, ArH), 6.94 (dd, J = 8.24 Hz, 1H, ArH), 6.94 (dd, J = 1.32 Hz, 1H, ArH), 7.09 (d, J = 7.92 Hz, 1H, ArH), 7.13 (d, J = 4.44 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.75, 20.84, 34.36, 51.03, 52.89, 55.36, 55.32, 59.70, 111.52, 111.93, 114.09, 115.58, 118.92, 121.07, 125.48, 129.73, 138.39, 139.76, 147.49, 147.91, 148.41, 149.69, 153.43, 164.49, 168.55; FT-IR: 3377, 2950, 2181, 1736, 1652, 1566, 1433, 1231.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2,5-dimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5i): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 6H, $(CH_3)_2$), 3.49 (s, 6H, $(OCH_3)_2$), 3.70 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.82 (s, 1H, CH), 5.43 (s, 2H, NH_2), 6.71 (d, J = 3.04 Hz, 1H, ArH), 6.81 (s, 3H, ArH), 6.97 (d, J = 8.8 Hz, 1H, ArH), 7.12 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 18.42, 20.59, 30.62, 31.88, 51.86, 52.29, 56.02, 56.34, 59.48, 103.54, 111.83, 112.91, 113.53, 120.79, 127.12, 131.15, 134.13, 135.37, 138.93, 142.82, 150.34, 151.24, 153.31, 163.10, 164.05; FT-IR: 3377, 2950, 2181, 1706, 1652, 1566, 1433, 1377, 1231; HRMS of $[C_{26}H_{27}N_3O_6 + Na]^+$ (m/z): 500.2573; Calcd: 500.2559.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(4-fluorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5j): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 6H, $(CH_3)_2$), 3.35 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 5.08 (s, 1H, CH), 5.52 (s, 2H, NH_2), 6.95 (s, 2H, ArH), 7.14-7.20 (m, 2H, ArH), 7.44 (dd, J = 7.76 Hz, 1H, ArH), 7.44 (dd, J = 1.72 Hz, 1H, ArH), 7.47-7.51 (m, 1H, ArH), 7.59 (dd, J = 7.96 Hz, 1H, ArH) 7.59 (dd, J = 1.00 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.57, 37.60, 51.80, 52.26, 58.84, 103.46, 120.32, 121.74, 127.34, 128.85, 129.58, 131.45, 132.61, 134.72, 139.04, 142.65, 144.78, 150.66, 162.76, 164.89; FT-IR: 3470, 3310, 3217, 2950, 2192, 1714, 1650, 1569, 1415, 1310, 1262; HRMS of $[C_{24}H_{22}FN_3O_4 + H]^+$ (m/z): 436.1461; Calcd: 436.1465.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2,4,6-trimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate (5k): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 6H, $(CH_3)_2$), 3.46 (s, 6H, $(OCH_3)_2$), 3.80 (s, 6H, $(OCH_3)_2$), 4.84 (s, 1H, CH), 5.41 (s, 2H, NH_2), 6.85 (dd, J = 7.76 Hz, 1H, ArH), 6.85 (dd, J = 1.16 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 6.81 (s, 2H, ArH), 6.94 (dd, J = 8.24 Hz, 1H, ArH), 6.94 (dd, J = 1.32 Hz, 1H, ArH), 7.09 (d, J = 7.92 Hz, 1H, ArH), 7.13 (d, J = 4.44 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.74, 30.60, 51.04, 52.90, 55.63, 55.95, 56.08, 91.02, 92.53, 103.66, 113.85, 116.39, 117.62, 125.49, 138.41, 139.76, 147.49, 150.78, 161.39, 164.50, 167.41, 168.55; FT-IR: 3378, 2950, 2180, 1706, 1652, 1566, 1433, 1342, 1231; HRMS of $[C_{27}H_{29}N_3O_7 + Na]^+$ (m/z): 530.2393; Calcd: 530.2409.

Dimethyl-6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5l): ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 6H, $(CH_3)_2$), 3.64 (s, 6H, $(OCH_3)_2$), 3.87 (s, 3H, OCH_3), 5.21 (s, 1H, CH), 6.50 (s, 2H, NH_2), 6.70 (s, 1H, ArH), 7.12 (d, J = 8.56 Hz, 2H, ArH), 7.43 (dd, J = 8.52 Hz, 2H, ArH), 7.43 (dd, J = 2.16 Hz, 2H, ArH), 7.51 (s, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.73, 30.56, 51.02, 52.87, 55.90, 112.07, 113.85, 114.89, 115.21, 117.63, 124.24, 125.47, 126.39, 138.39, 139.75, 146.85, 147.50, 153.81, 160.59, 164.47, 168.56; FT-IR: 3461, 3380, 3316, 2181, 2230, 1748, 1655, 1566, 1408, 1343.

3.3 Results and discussion

3.3.1 Powder X-ray Diffraction

The powder X-ray diffraction patterns of calcined ceria loaded zirconia are shown in Figure 1. The catalyst diffraction peak values 2θ of 28.7°, 33.1°, 47.6°, 56.2°, 59.2°, 69.78, 76.7° and 79.3° were assigned to CeO_2. All these diffraction peaks agree with the international standards files (JCPDS file No. 43-1002). In addition, the sample showed diffraction patterns at 2θ angles of 24.8°, 28.6°, 31.9°, 34.7°, 41.3°, 50.8° and 60.4° corresponding to the ZrO_2 (JCPDS file No. 01-089-9066). The peaks identified in the diffractogram shows the polycrystalline nature of the materials. The average crystallite size of this sample was obtained to be 7.2 nm using the Scherrer equation based on the highest intensity diffraction peaks of 2.5% CeO_2/ZrO_2.

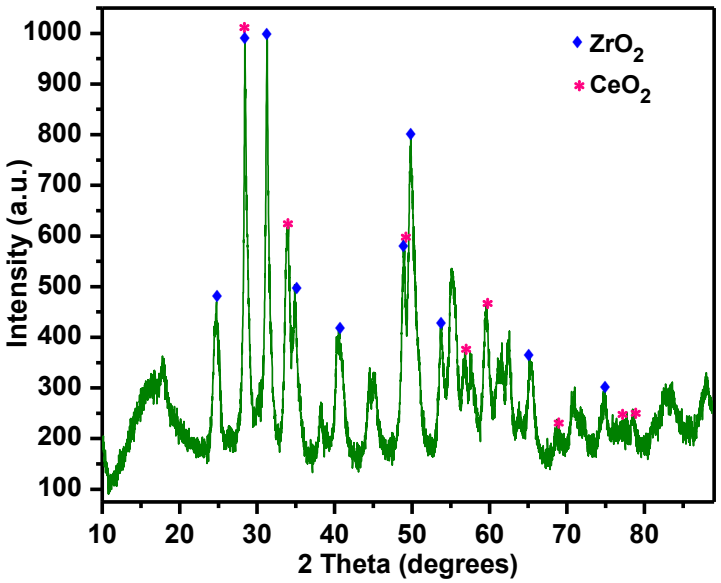


Figure 1. Powder XRD spectra of 2.5% ceria doped zirconia catalyst

3.3.2. SEM analysis

A demonstrative SEM surface morphology micrograph of the sample ceria on zirconia catalyst is shown in Figure 2. A number of large, white and irregular shapes are observed from the SEM image of 2.5% CeO_2/ZrO_2. The micrographs of SEM–EDX confirmed the uniform distribution of ceria on the zirconia surface. The SEM-EDX confirms the data from ICP elemental analysis. Furthermore, the morphology of the catalyst from the SEM images noticeably point to the crystallinity and homogeneity of the sample.

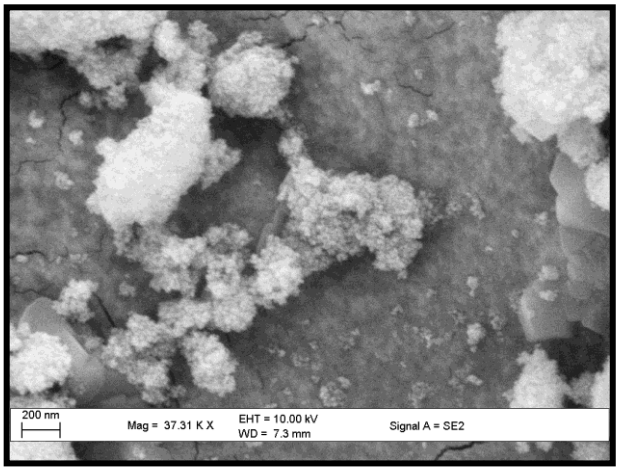


Figure 2.SEM micrograph of 2.5% CeO_2/ZrO_2 catalyst

3.3.3. TEM analysis

The TEM image provides more structural information of the catalyst. A distinct TEM image of 2.5% CeO2/ZrO2 is shown in Figure 3. It can be seen that the ceria particles are shown as black irregular oval-like shapes and particle dimension ranging between 13 to 35 nm and zirconia shown as white bulbous shape particles. No drastic change was noticed in the morphology of the used catalyst

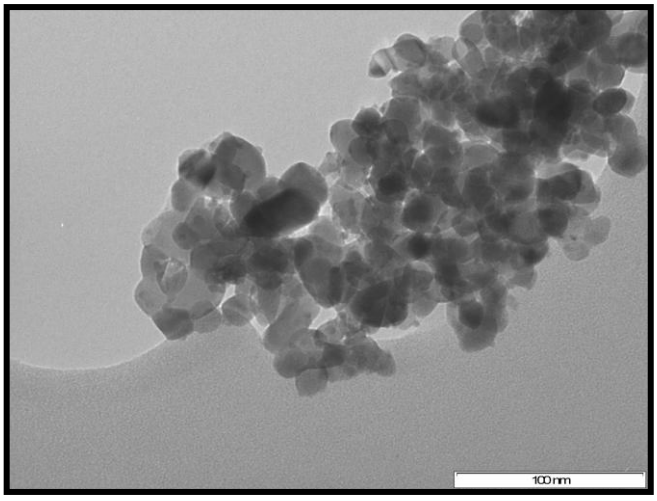


Figure 3. TEM micrograph of 2.5% CeO_2/ZrO_2 catalyst

3.3.4. BET surface area analysis

The N_2 isotherms of the prepared ceria loaded zirconia material are shown in Figure 4. The figure shows the nitrogen adsorption isotherms and pore size distribution of 2.5% CeO_2/ZrO_2 catalyst. As per the IUPAC classification, the sample displays type-IV isotherms and a typical H1-hysteresis loop, demonstrating the mesoporous nature of the materials. The BJH pore size distribution designates a mesoporous (pore of 4–55 nm) texture for the sample, and the isotherms p/po range was 0.75-0.90. The Brunauer–Emmett–Teller (BET) surface area was determined at 52 $m^2\ g^{-1}$ with a pore volume of 0.226 $cm^3\ g^{-1}$. As anticipated, the ICP analysis results showed the presence of a nominal amount of cerium in the catalyst (2.46 wt %).

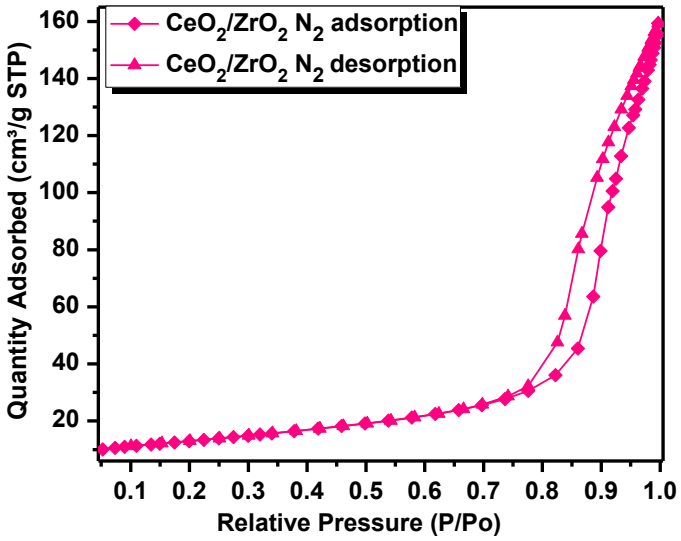


Figure 4. N_2 adsorption & desorption spectra of 2.5% CeO_2/ZrO_2 catalyst

3.4. Optimization Procedure

In the first instance, optimal conditions were sought by a model reaction which was accomplished by applying various types of catalysts, solvents and also solvent-free conditions, with the anticipation to reduce the reaction time and increase product yield. When the reaction of substituted aldehyde (1 mmol), malononitrile (1.1 mmol), dimethylacetylenedicarboxylate (1.0 mmol) and dimethylaniline (1 mmol) were stirred together, no product formation took place in the presence of catalyst-free and solvent-free condition at RT, even after 12 h of reaction (Table

1, entry 1). The same reaction was then carried out in ethanol solvent under catalyst-free condition at RT and it was observed that no product was formed even after 12 h. The same reaction was conducted under reflux conditions, but the reaction did not afford the desired product (Table 1, entry 2 & 3). Subsequently the reaction was performed in the presence of different acidic catalysts, such as acetic acid (AcOH), $FeCl_3$ and H_3BO_3 for their efficiency in catalyzing the reaction at RT but no reaction occured (Table 1, entries 4–6). Further, the same reaction was evaluated using base catalysts (inorganic or organic) such as NH_4OAc, K_2CO_3, NaOH, TEA, DABCO, and piperidine, and low yield of product was obtained in the presence of these bases after 6 h (Table 1, entries 7–12). This was followed by pure oxide catalysts, such as Al_2O_3, SiO_2 and ZrO_2 which were performed in an ethanol solvent system at RT, the reaction showed moderate to good yields after 2.0-3.5 h reaction time (Table 1, entries 13-15). After having this positive result using zirconia oxide, we wanted to optimize the reaction condition by doping with various metal oxides, such as 2.5% Cu/ZrO_2, Mn/ZrO_2, and Ce/ZrO_2 was screened in ethanol solvent at RT Those mixed oxide catalytic reactions afforded very good to excellent yields (82-95%) within 30 min reaction time (Table 1, entry 16-18). Remarkably, when CeO_2/ZrO_2 was used as catalyst, a reaction progressed impressively recording an excellent yield (95%) of functionalized 1,4-dihydropyridine-2,3-dicarboxylates at RT, within 20 min reaction time. Based on the evaluation of positive results, it is noticeably that ceria on zirconia catalyst revealed high surface areas which have most active sites showing more catalytic activity over other catalysts. Therefore, this study focused on one-pot, four-component reactions to achieve excellent yields. Mixed oxides offer greater surface area, smaller particle sizes and greater generation of catalytic active sites than the corresponding oxide homologues. [33] These aspects are of extreme importance since higher surface area favors adsorption of reaction molecules, while the small particle size is advantageous for minimal internal dispersion resistance of molecules in this manner increasing the catalytic activity.

We further investigated the effect of solvent in this reaction, because solvents can play a deciding outcome for many important multi-component reactions. [34] Attempts to optimize the solvent-system indicated that the activity of CeO_2/ZrO_2 was greatly affected by the solvent in which the reaction was performed (Table 2). The reaction proceeded efficiently in polar solvents such as methanol, ethanol and isopropyl alcohol, but not in non-polar solvents such as acetonitrile, DMF, n-hexane and toluene. EtOH solvent, which can disperse temperature

promptly, affords an optimum environment for formation of intermediates on the catalyst surface, and their consequent transformation to target products. In view of the green nature, short reaction and excellent yields, EtOH demonstrated to be the ideal solvent for the present procedure.

Table 1: This table shows the yield of the different catalysts for the model reaction

Entry	Catalyst	Temperature	Time (h)	Yield (%)[b]
1	--	R.T.	12	--
2	--	R.T.	12	--
3	--	Reflux	12	--
4	AcOH	R.T.	12	--
5	$FeCl_3$	R.T.	12	--
6	H_3BO_3	R.T.	12	--
7	NH_4OAc	R.T.	8.0	27
8	K_2CO_3	R.T.	6.2	34
9	NaOH	R.T.	6.5	25
10	TEA	R.T.	7.0	24
11	DABCO	R.T.	7.5	19
12	piperidine	R.T.	7.0	22
13	Al_2O_3	R.T.	3.5	51
14	SiO_2	R.T.	2.5	60
15	ZrO_2	R.T.	2.0	76
16	2.5% CuO/ZrO_2	R.T.	0.5	82
17	2.5% MnO_2/Zr_2	R.T.	0.4	89
18	2.5% CeO_2/Zr_2	R.T.	0.33	95

[a]**Reaction conditions:** dimethylacetylenedicarboxylate (1 mmol), dimethylaniline (1 mmol), malononitrile (1.1 mmol), 2-methoxybenzaldehyde (1 mmol) and catalyst.
[b]Isolated yields; -- No reaction

Furthermore, we examined the amount of catalyst needed for reaction, because this has a major effect on the reactant transformation to product. When we increased the amount of catalyst 10 to 30 mg, the yield of the product continuously increased from 79 to 95% and further increase of the catalyst quantity did not increase the reaction yield of the product (Table 3). The outcome of the above promising result suggests that 30 mg of Ce/ZrO_2 is most suitable for this reaction.

Table 2: Optimization of various solvent condition for the model reaction by 2.5% Ce/ZrO_2 catalyst[a]

Entry	Solvent	Yield (%)
1	CH_3CN	15
2	DMF	19
3	n-hexane	--
4	Toluene	--
5	MeOH	75
6	EtOH	95
7	isopropyl alcohol	68

[a]Reaction conditions: dimethylacetylenedicarboxylate (1 mmol), dimethylaniline (1 mmol), malononitrile (1.1 mmol), 2-methoxybenzaldehyde (1 mmol), catalyst (30 mg) and solvent (10 mL) were stirred at room temperature.

Table 3: Optimization of the amount of 2.5% Ce/ZrO_2 as catalyst in the model reaction[a]

Entry	Catalyst (mg)	Time (min)	Yield (%)
1	10	45	75
2	20	35	84
3	30	20	95
4	40	20	95
5	50	15	94

[a]Reaction conditions: dimethylacetylenedicarboxylate (1 mmol), dimethylaniline (1 mmol), malononitrile (1.1 mmol), 2-methoxybenzaldehyde (1 mmol), catalyst and ethanol (10 mL) solvent were stirred at room temperature.

To demonstrate the robustness of the new protocol, reactions with numerous aromatic aldehydes substituted with diverse electron-withdrawing or electron-releasing groups were assessed and obtained; the results are summarized in (Table 4). In all cases, all the substituted aromatic aldehydes, irrespective of electron-donating or electron-withdrawing groups showed exceptional reactivity in forming the respective pyridine derivatives in good to high yields. Structures of all the isolated products 5a–l were deducted and validated by physical and spectroscopic data including IR, ^{1}H NMR, ^{15}N NMR, ^{13}C NMR and HR-MS spectral analysis. Some of the compounds details are showed in supplementary information.

Table 4: Synthesis of functionalized 1,4-dihydropyridine-2,3-dicarboxylates by 2.5% Ce/ZrO_2 catalyst[a*]

Entry	R	Product	Yield (%)	Mp °C
1	2-OMe	5a	95	215-216
2	2-F	5b	87	206-208
3	2-Cl	5c	90	220-221
4	2-Br	5d	88	239-240
5	4-Cl	5e	94	221-222
6	4-Br	5f	92	249-250
7	$2,3\text{-}(OMe)_2$	5g	91	201-203
8	$3,4\text{-}(OMe)_2$	5h	93	233–235
9	$2,5\text{-}(OMe)_2$	5i	92	246–247
10	4-F	5j	87	227-228
11	$2,4,6\text{-}(OMe)_3$	5k	89	186-188
12	4-MeO	5l	92	206-208

[a]Reaction conditions: dimethylacetylenedicarboxylate (1 mmol), dimethyl aniline (1 mmol), malononitrile (1.1 mmol), substituted benzaldehyde (1 mmol), catalyst (30 mg) and ethanol solvent (10 mL) were stirred at room temperature.

* All the compounds are new; R = substituted benzaldehydes

3.5. Reusability of the catalyst

Commercial application for any catalyst can be realized if reusability thereof becomes a demonstrated advantage and we thus investigated the recovery and reusability of the CeO_2/ZrO_2 catalyst. The reusability of the catalyst was tested by separating the CeO_2/ZrO_2 from the reaction mixture by simple filtration under vacuum, washed with acetone, and drying in a vacuum oven at 80 °C for 4 h to reuse in consequent reactions. The recovered catalyst can be reused at least six runs in successive reactions without significant loss in product yield.

3.6. Conclusion

In this study, we report on a green and efficient one-pot protocol for the synthesis of functionalized 1,4-dihydropyridine-2,3-dicarboxylate derivatives through a four-component reaction between malononitrile, dimethylacetylenedicarboxylate, dimethylaniline and substituted aldehydes using 2.5% CeO_2/ZrO_2 as a catalyst in EtOH and at room temperature. This methodology has several advantages such as short reaction times (< 30 min), high product yields

(87-95%), ease of handling, facile and green work-up. The easy recoverable and reusable catalyst meets the industrial and environmental requirements and is versatile and cost effective.

3.7. 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.

3.8. References

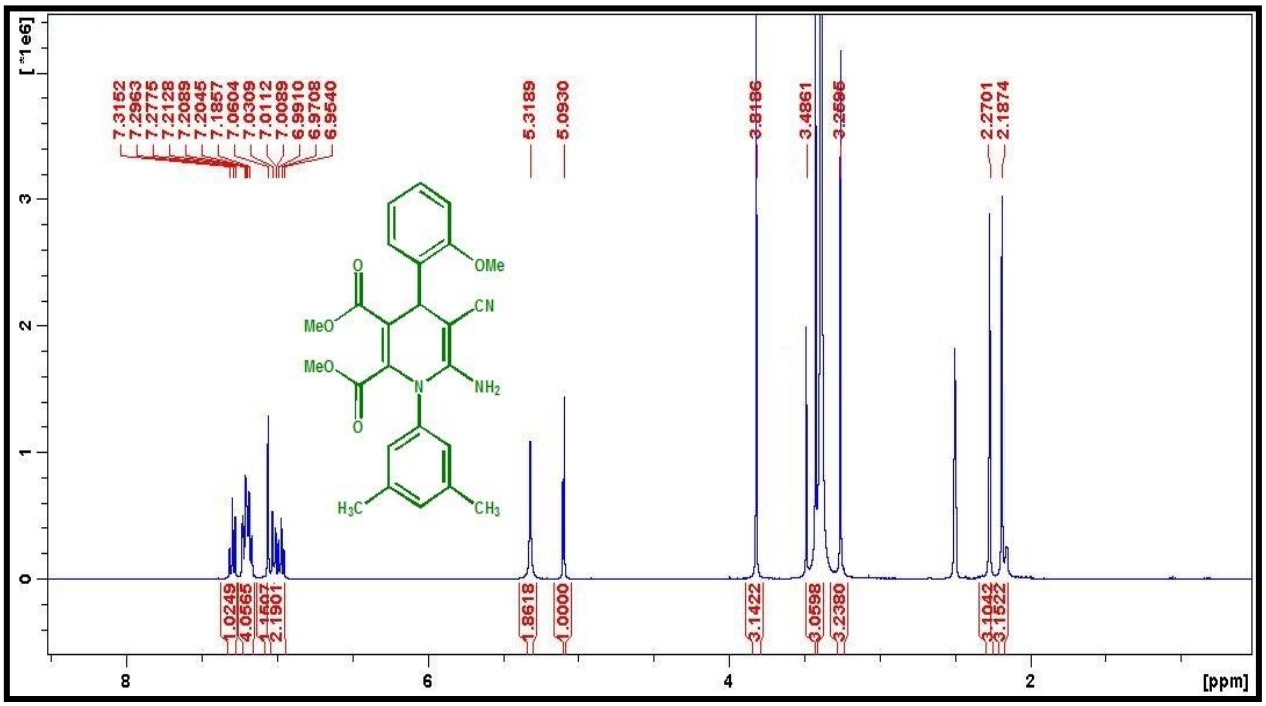
1. A. Domling. *Chemical Reviews.* **2006**, *106,* 17.
2. S. N. Maddila, S. Maddila, W. E. Van Zyl and S. B. Jonnalagadda. *Chemistry Open.* **2016**, *5*, 38.
3. S. Brauch, S. S. van Berkel and B. Westermann. *Chemical Society Reviews.* **2013**, *42,* 4948.
4. S. Maddila, S. Rana, R. Pagadala and S. B. Jonnalagadda. *Research on Chemical*. **2015**, *41*, 8269.
5. S. N. Maddila, S. Maddila, W. E. van Zyl and S. B. Jonnalagadda. *RSC Advances.* **2015,** *5*3, 7360.
6. S. Maddila, S. N. Maddila, S. B. Jonnalagadda and L. Palakondu, *Journal of Heterocyclic Chemistry.* **2016**, *53,* 658.
7. P. Salehi, D. I. MaGee, M. Dabiri, L. Torkian and J. Donahue. *Molecular Diversity.* **2012,** *16,* 231.
8. Y. Zhangand and S. N. Riduan. *Chemical Society Reviews.* **2012,** *41,* 2083.
9. R. Pagadala, S. Maddila, S. Rana and S. B. Jonnalagadda. *RSC Advances.* **2014,** *4,* 6602.
10. S. Maddila, S. Rana, R. Pagadala, S. Kankala, S. N. Maddila and S. B. Jonnalagadda. *Catalysis Communication.* **2015,** *61,* 26.
11. M. Pudukudya and Z. Yaakob. *Der Pharma Chemica.* **2014**, *6(1),* 188.
12. C. Piconi and G. Maccaur. *Biomaterials.* **1999**, *20,* 1.
13. S. A. Moom, C. Osojnik and P. Albin. *Catalysis Communications.* **2014,** *52,* 10
14. O. Y. Kurapova and V. G. Konakov. *Reviews on Advanced Materials Science.* **2014,** *36,* 177.

15. S. Maddila, S. Gorle, M. Singh, L. Palakondu and S. B. Jonnalagadda. *Letters in Drug Design & Discovery.* **2013,** *109,* 77.
16. S. Maddila and S. B. Jonnalagadda. *Archiv der Pharmazie.* **2012**, *34, 5*163.
17. M. Baumann and I. R. Baxendale. *Beilstein Journal of Organic Chemistry.* **2013**, *9*, 2265.
18. S. Maddila, L. Palakondu, C. V. Rao. *Arabian Journal of Chemistry.* **2016**, *9*, 136.
19. G. Prasanthi, K. V. Prasad and K. Bharathi. *European Journal of Medicinal Chemistry.* **2014**, *73,* 97.
20. N. Y. Wang, W. Q. Zuo, Y. Xu, C. Gao, X. X. Zeng, L. D. Zhang, X. Y. You, C. T. Peng, Y. Shen, S. Y. Yang, Y. Q. Wei and L. T. Yu. *Bioorgonic of Medicinal Chemistry Letters.* **2014**, *24,* 1581.
21. J. El Bakali, P. Gilleron, M. Body-Malapel, R. Mansouri, G. G. Muccioli, M. Djouina, A. Barczyk, F. Klupsch, V. Andrzejak, E. Lipka, C. Furman, D. M. Lambert, P. Chavatte, P. Desreumaux and R. Millet. *Journal of Medicinal Chemistry.* **2012**, *55,* 8948.
22. K. Atul, A. M. Ram, S. Siddharth, K. Mukesh and B. Gitika. *European Journal of Medicinal Chemistry.* **2010**, *4, 5*501.
23. P. C. Gros and Y. Fort. *European Journal of Medicinal Chemistry.* **200,** *25,* 4199.
24. P. Suman, H. C. Lokman and P. Tasneem. *Synthesis Communications.* **2013**, *43,* 986.
25. P. Suman, S. Vandana, D. Prolay and H. C. Lokman. *Bioorganic Chemistry.* **2013**, *4, 8*8.
26. C. Hong-Shuo and G. Rui-Yun. *Monatshefte Fur Chemie.* **2015,** *146,* 1355.
27. R. Pagadala, S. Maddila, V. Moodley, W. E. van Zyl and S. B. Jonnalagadda. *Tetrahedron Letters.* **2014,** *55,* 4006.
28. S. N. Maddila, S. Maddila, W. E. Van Zyl and S. B. Jonnalagadda. *Research on Chemical Intermediates.* **2016**, *42,* 2553.
29. S. Maddila, K. Naicker, M. Momin, S. Rana, S. Gorle, S. N. Maddila, K. Yalagala, M. Singh and S. B. Jonnalagadda. *Medicinal Chemistry Research.* **2016**, *25,* 283.
30. S. Maddila, R. Pagadala and S. B. Jonnalagadda. *Letters in Organic Chemistry.* **2013,** *10,* 693.
31. S. Maddila, R. Pagadala and S. B. Jonnalagadda. *Journal of Heterocyclic Chemistry.* **2015**, *52,* 487.
32. S. Maddila and S. B. Jonnalagadda. *Letters in Organic Chemistry.* **2013,** *10*, 374.

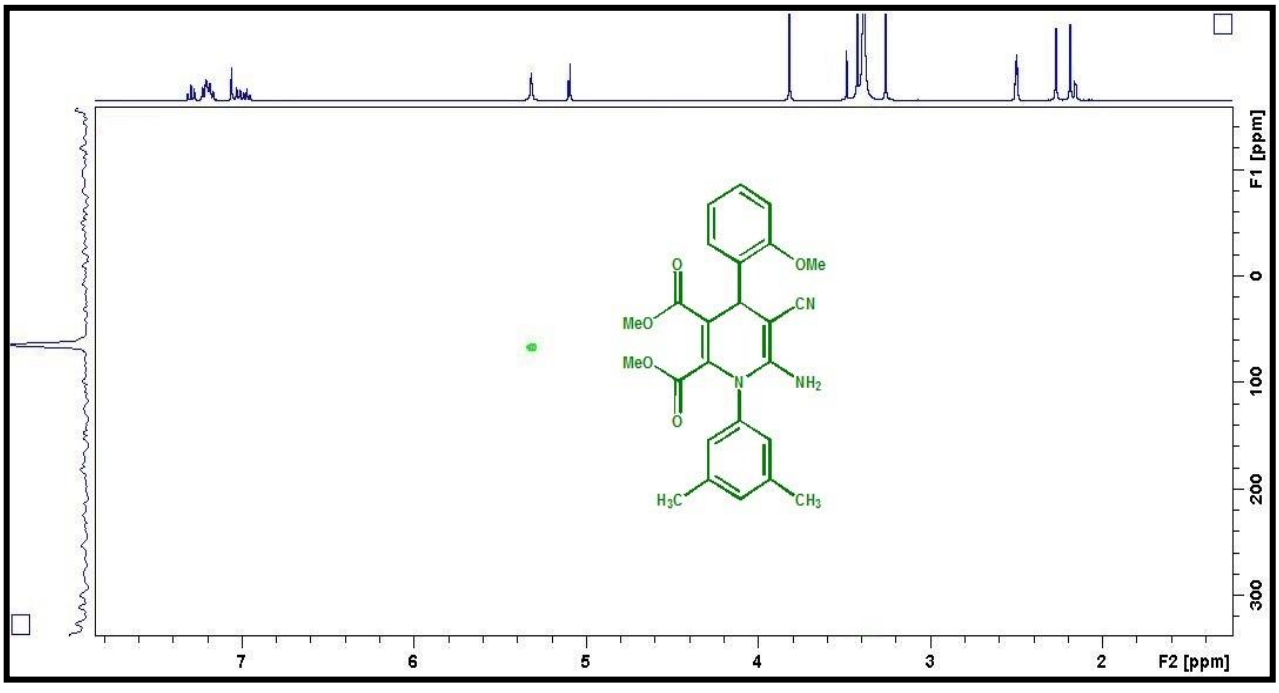
33. H. Kaper, K. Bouchmella, P. H. Mutin and F. Goettmann. *Chem Cat Chem.* DOI: 10.1002/cctc.201200175

34. M. B. Gawande, V. D. B. Bonifacio, R. Luque, P. S. Brancoa and R. S. Varma. *Chemical Society Reviews.* **2013**, *42*, 5522.

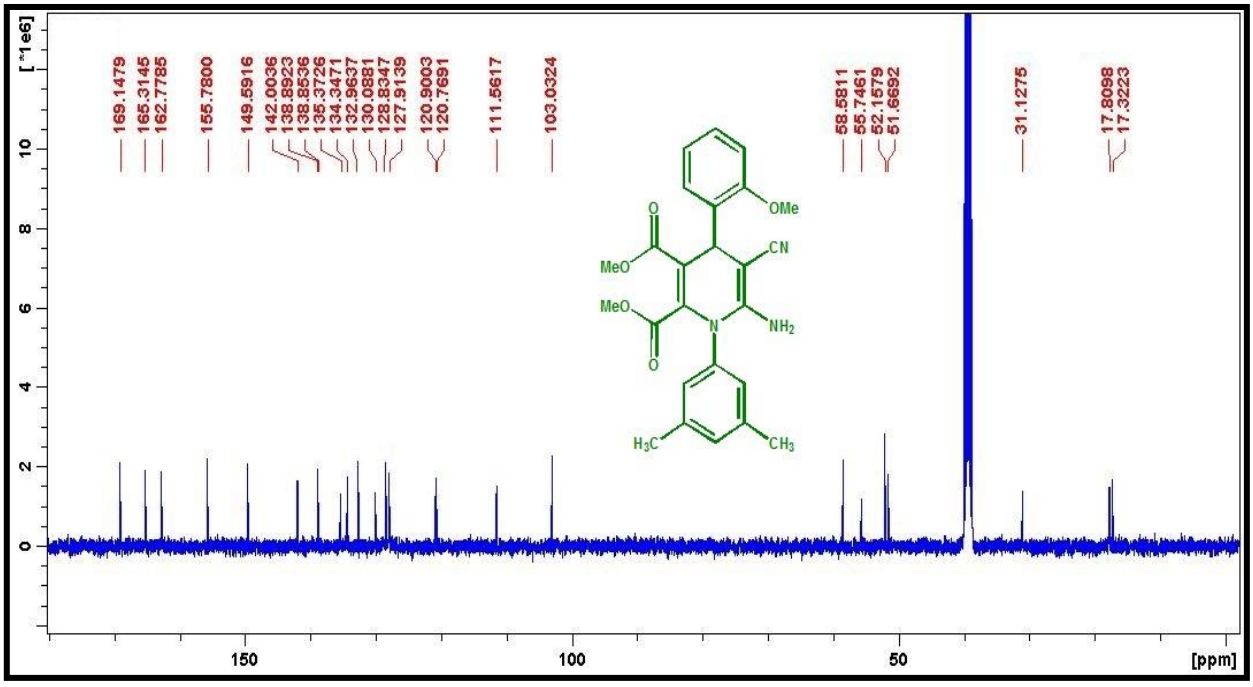
3.9. Supporting Information – I:



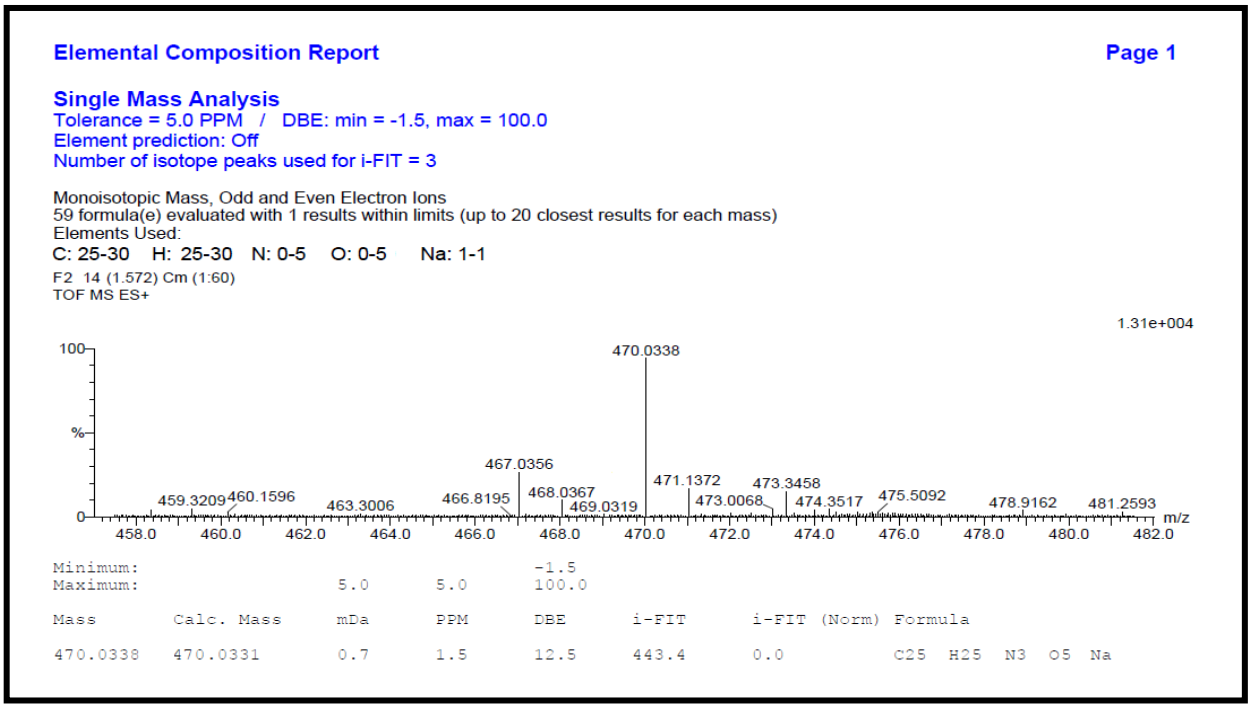
^{1}H NMR spectra of compound **5a**



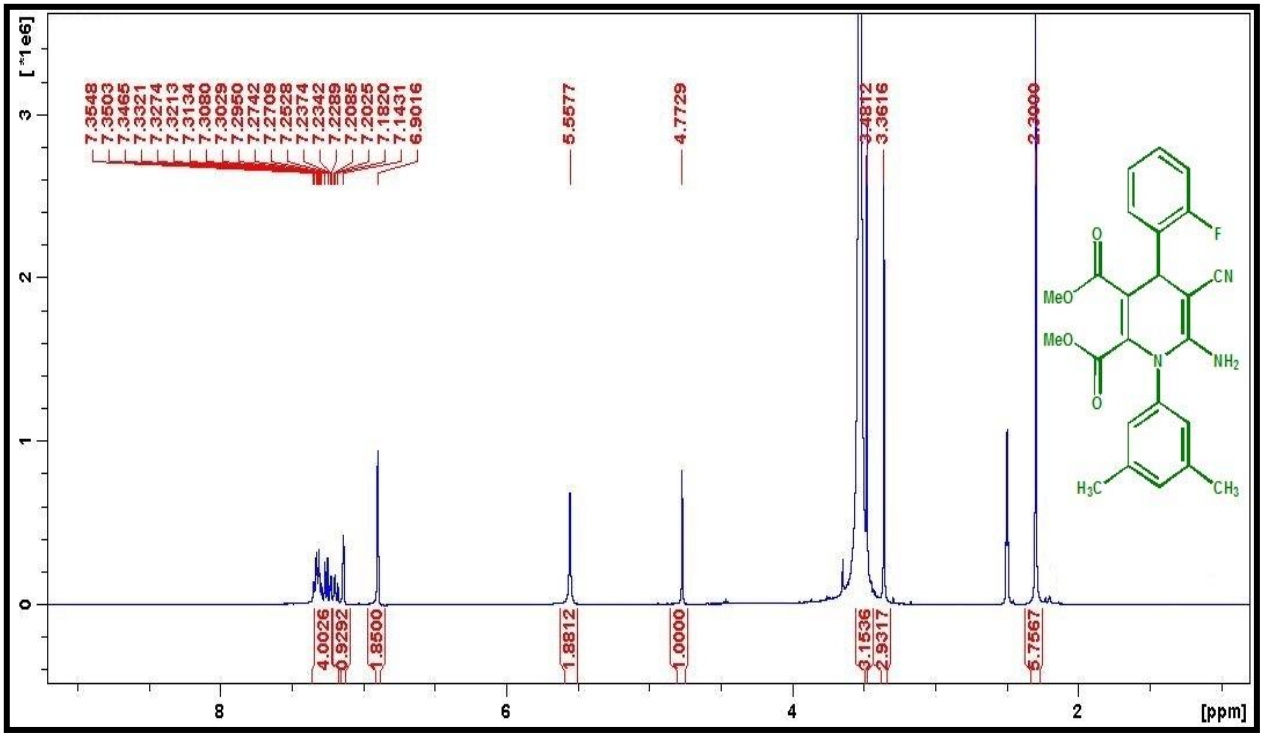
^{15}N NMR spectra of compound **5a**



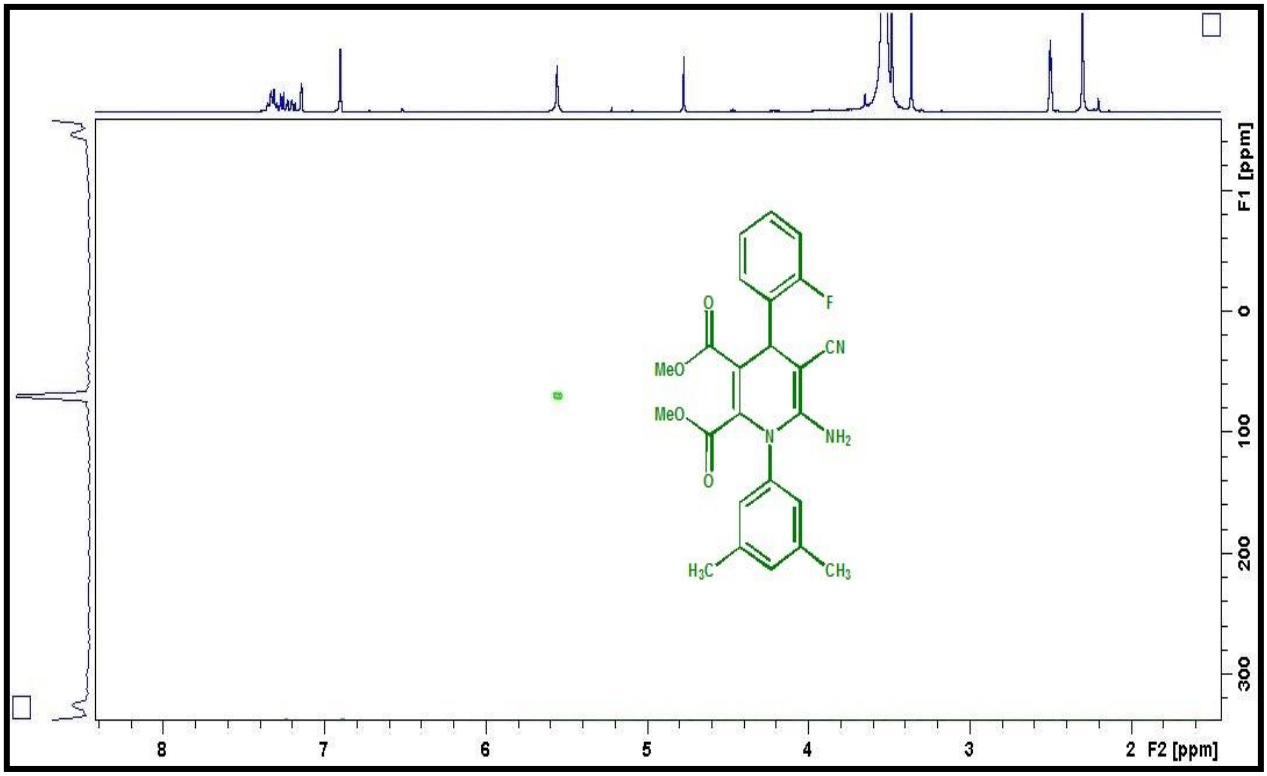
^{13}C NMR spectra of compound **5a**



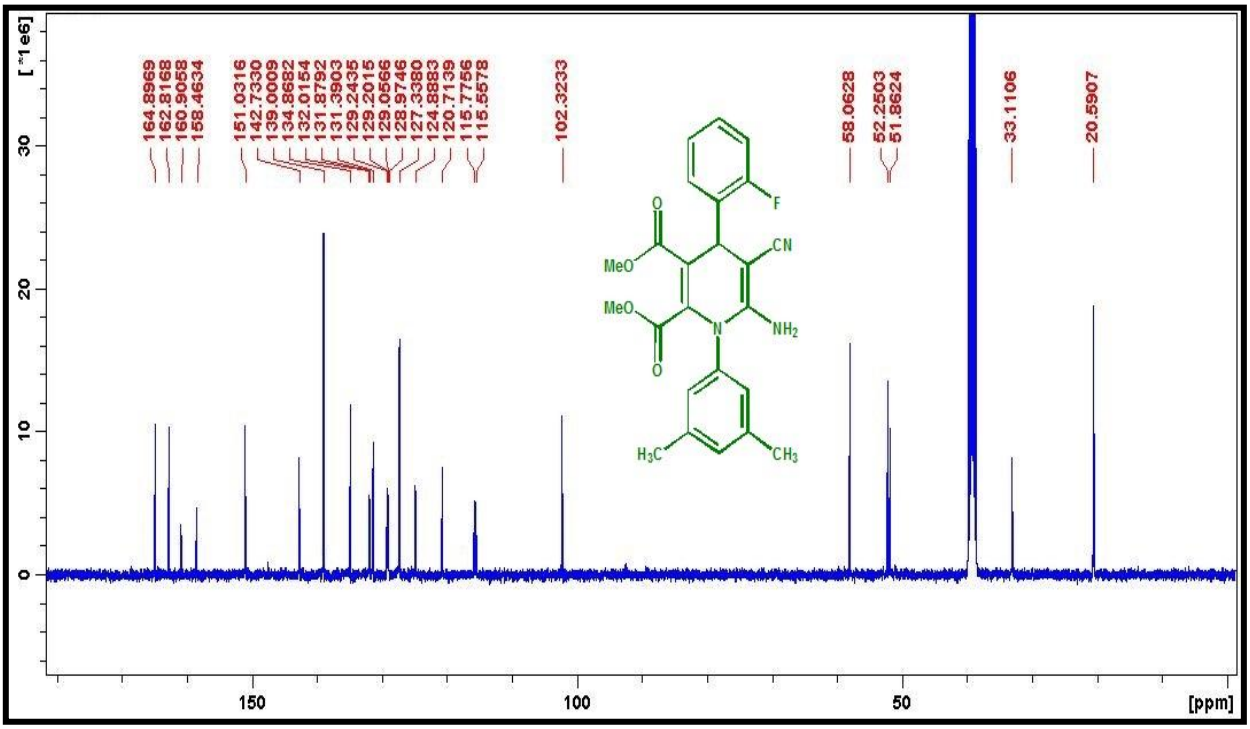
HR-MS spectra of compound **5a**



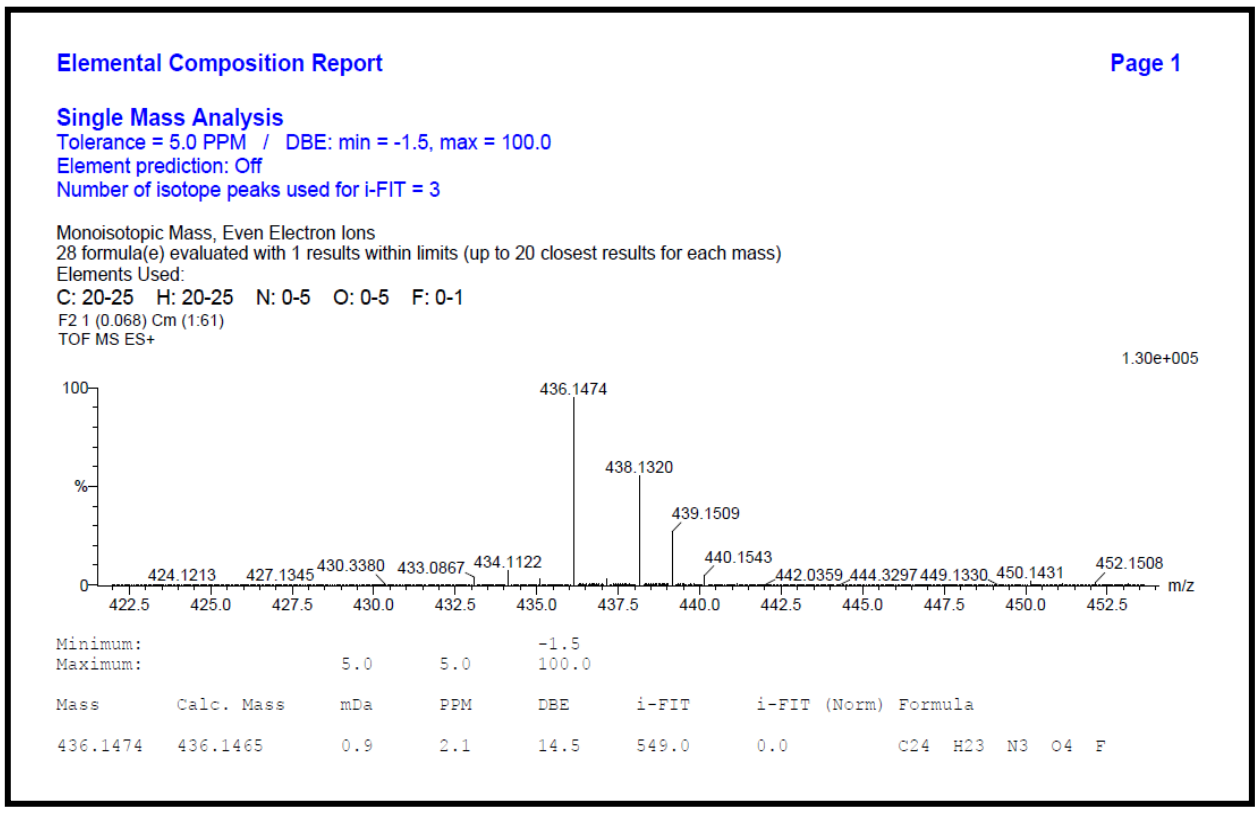
^{1}H NMR spectra of compound **5b**



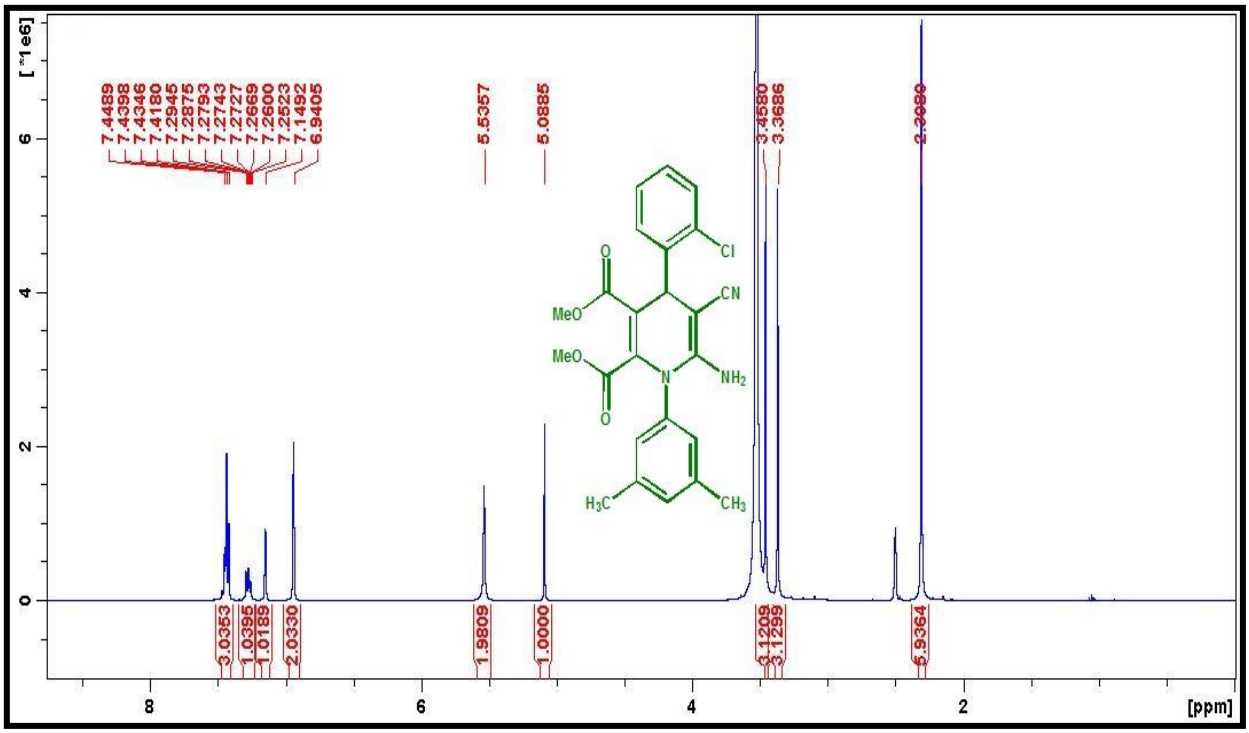
^{15}N NMR spectra of compound **5b**



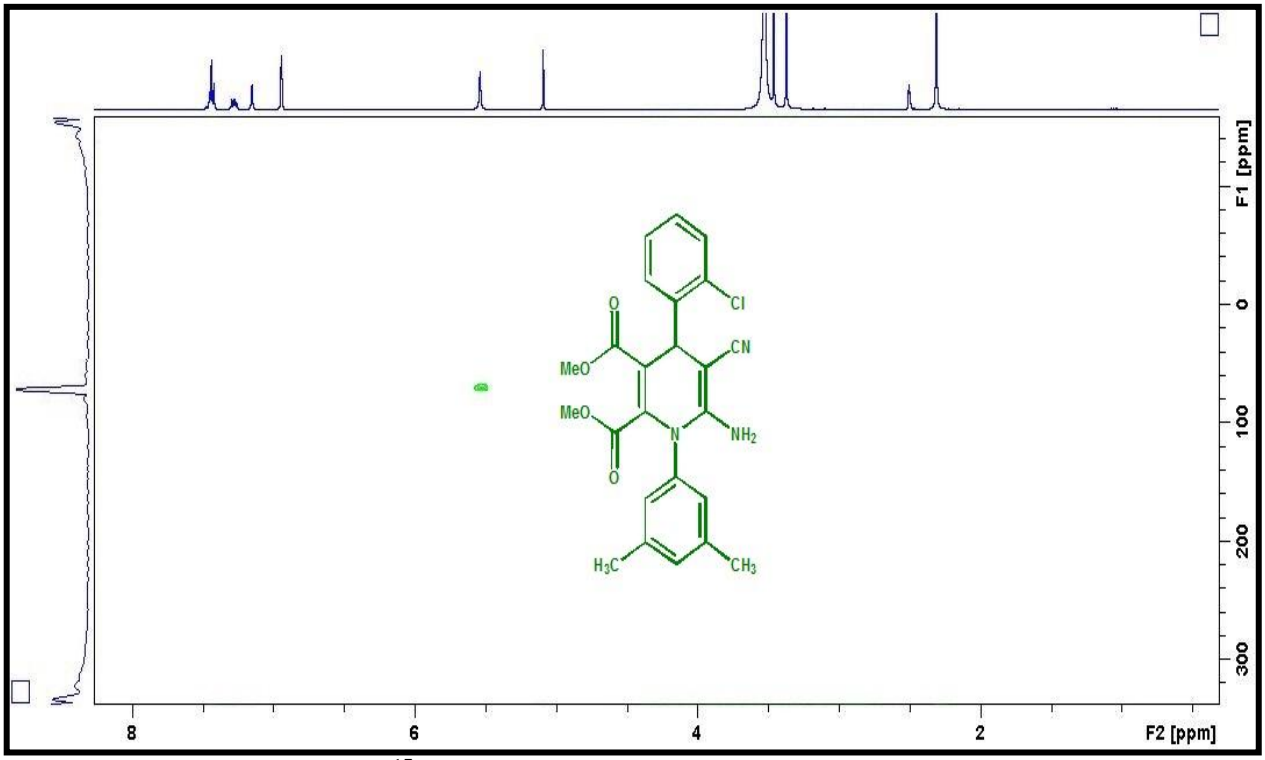
^{13}C NMR spectra of compound **5b**



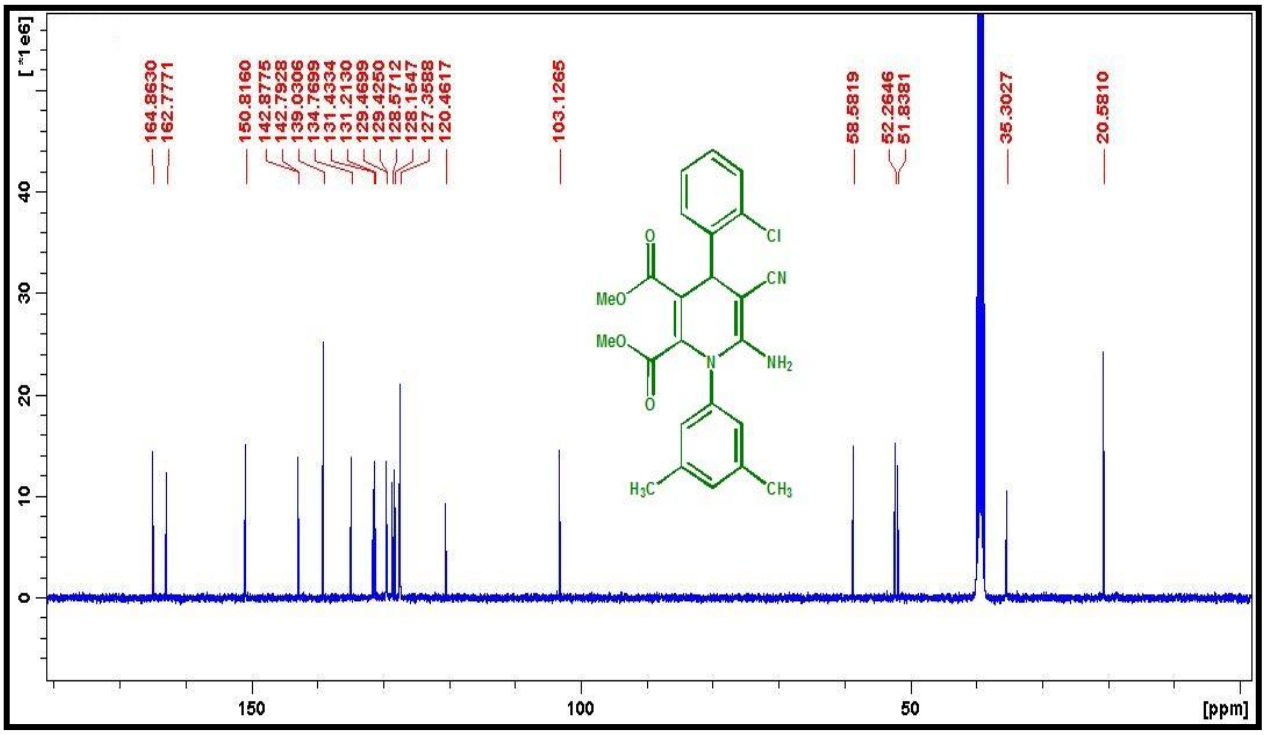
HR-MS spectra of compound **5b**



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



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

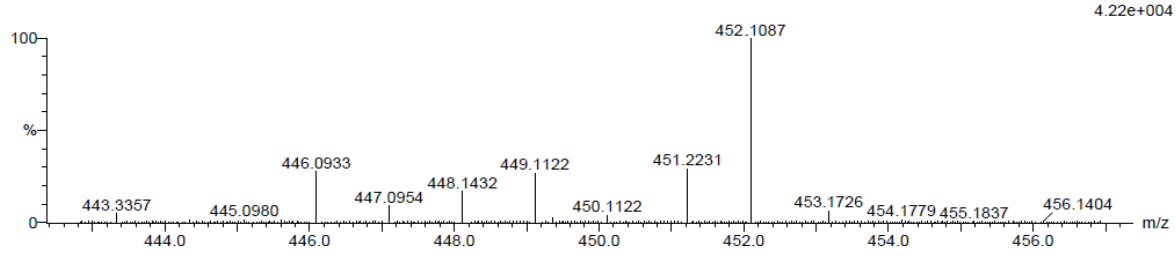


^{13}C NMR spectra of compound **5c**

Elemental Composition Report **Page 1**

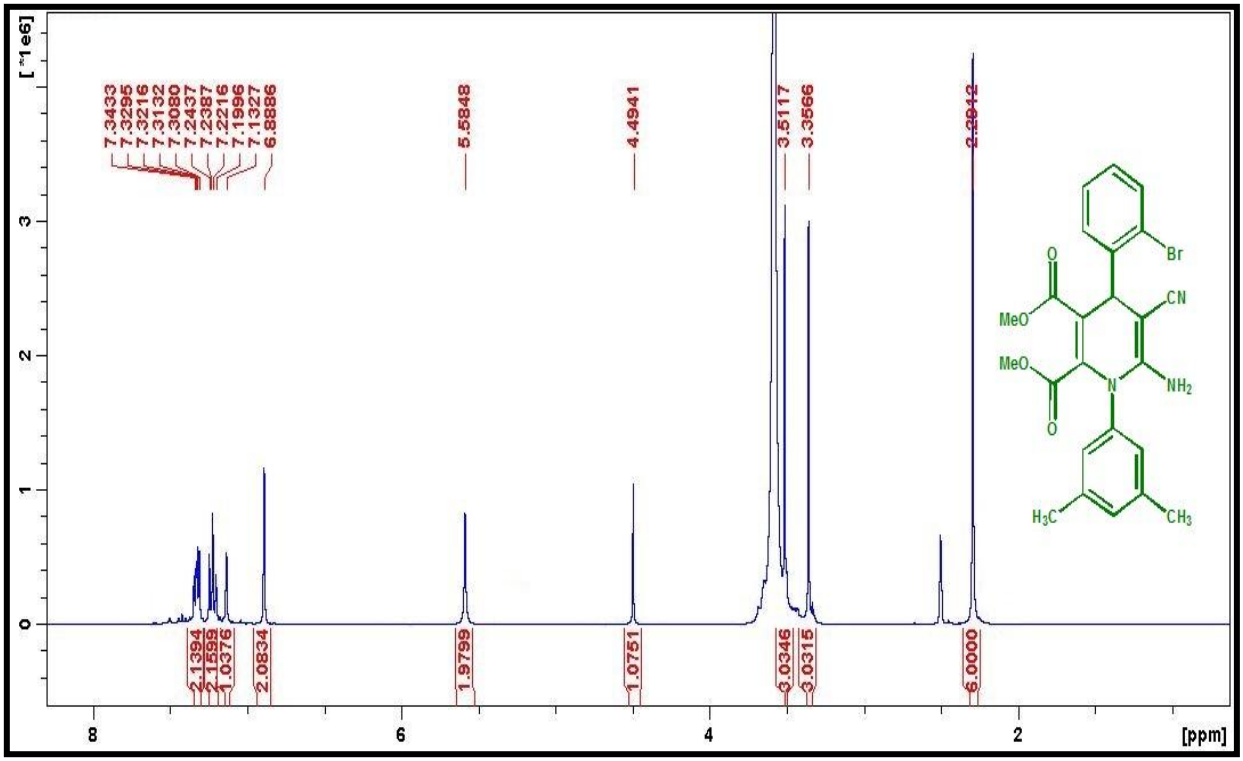
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
47 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 Cl: 1-1
F2 6 (2.025) Cm (1:61)
TOF MS ES+

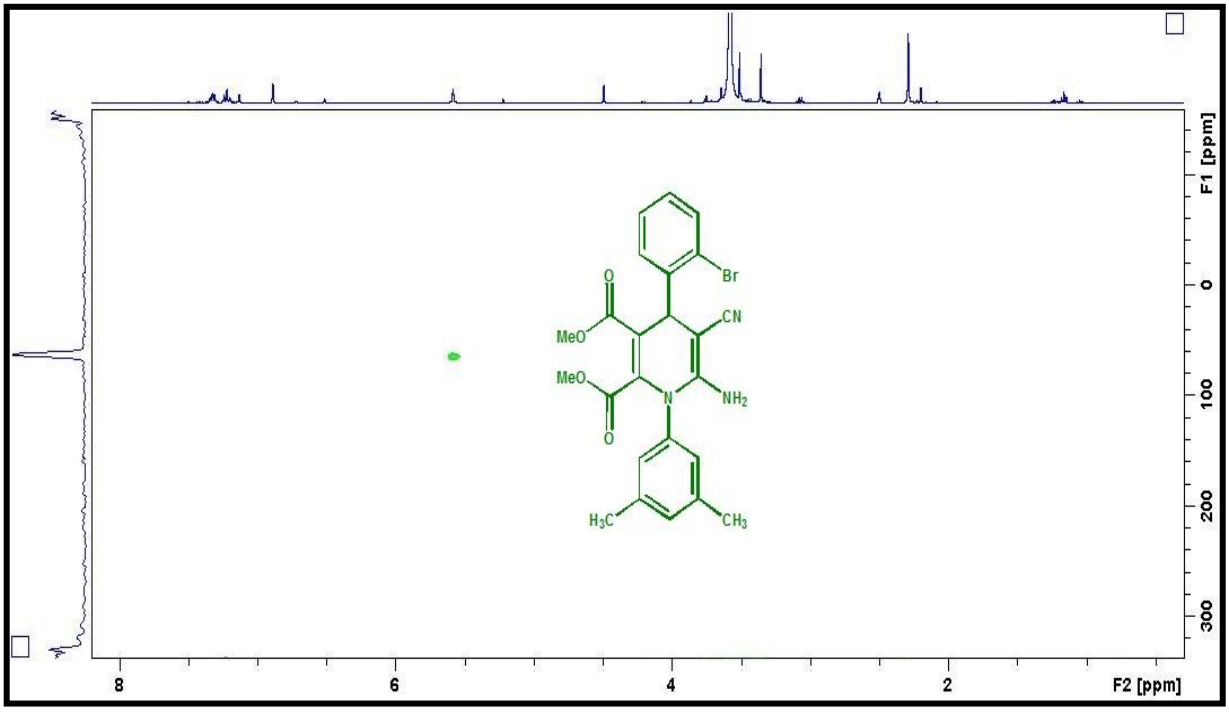


Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
452.1087	452.1085	0.2	0.4	14.5	482.1	0.0	C24 H23 N3 O4 Cl

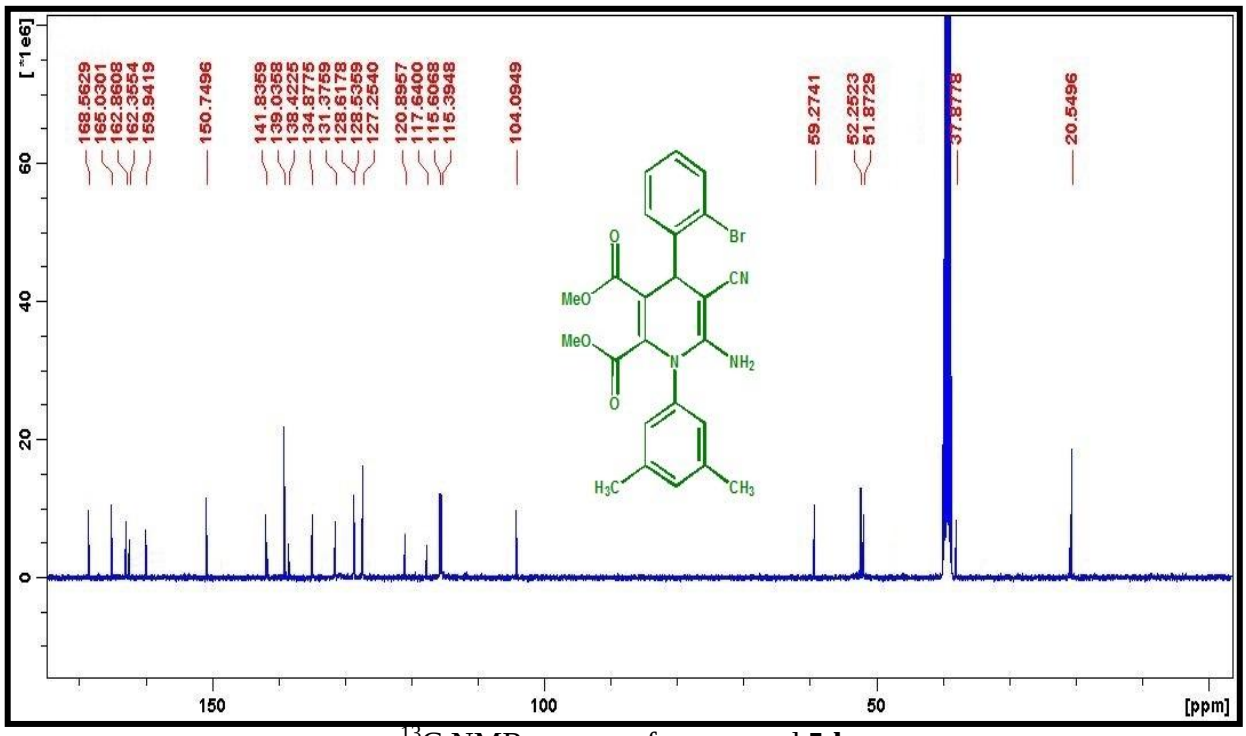
HR-MS spectra of compound **5c**



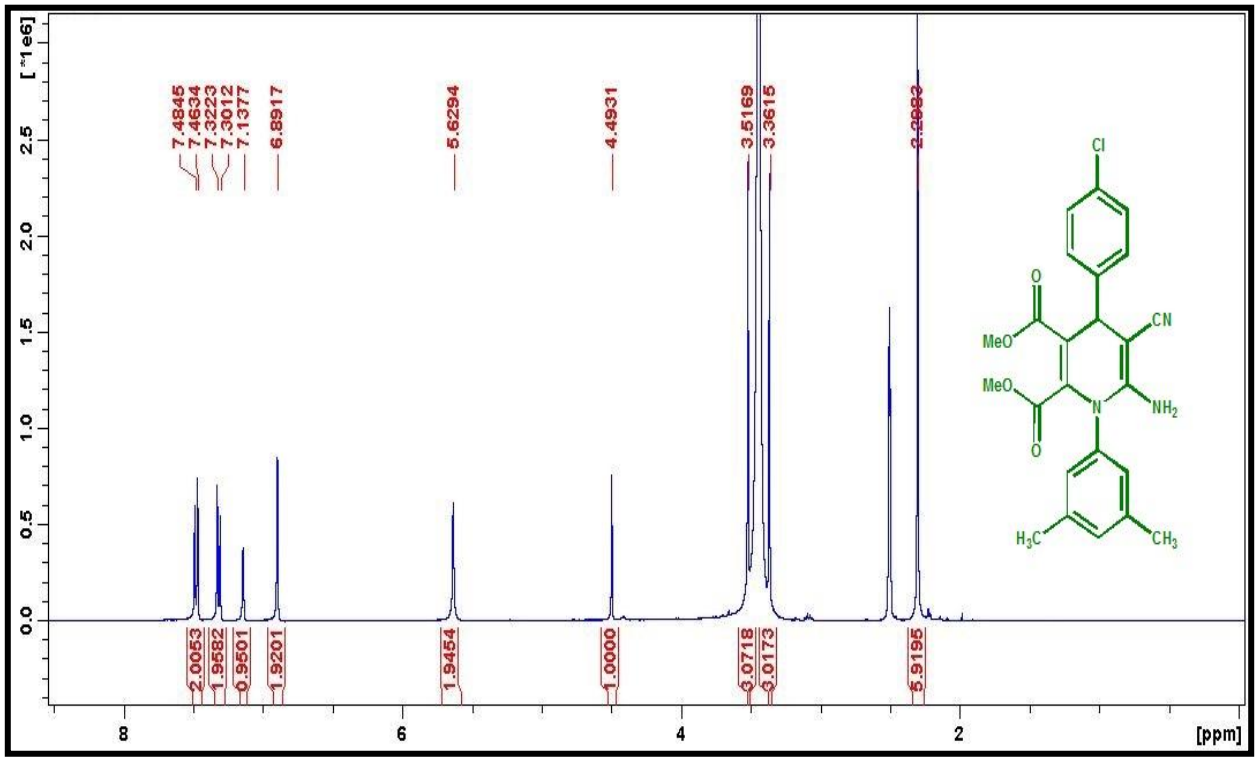
^{1}H NMR spectra of compound **5d**



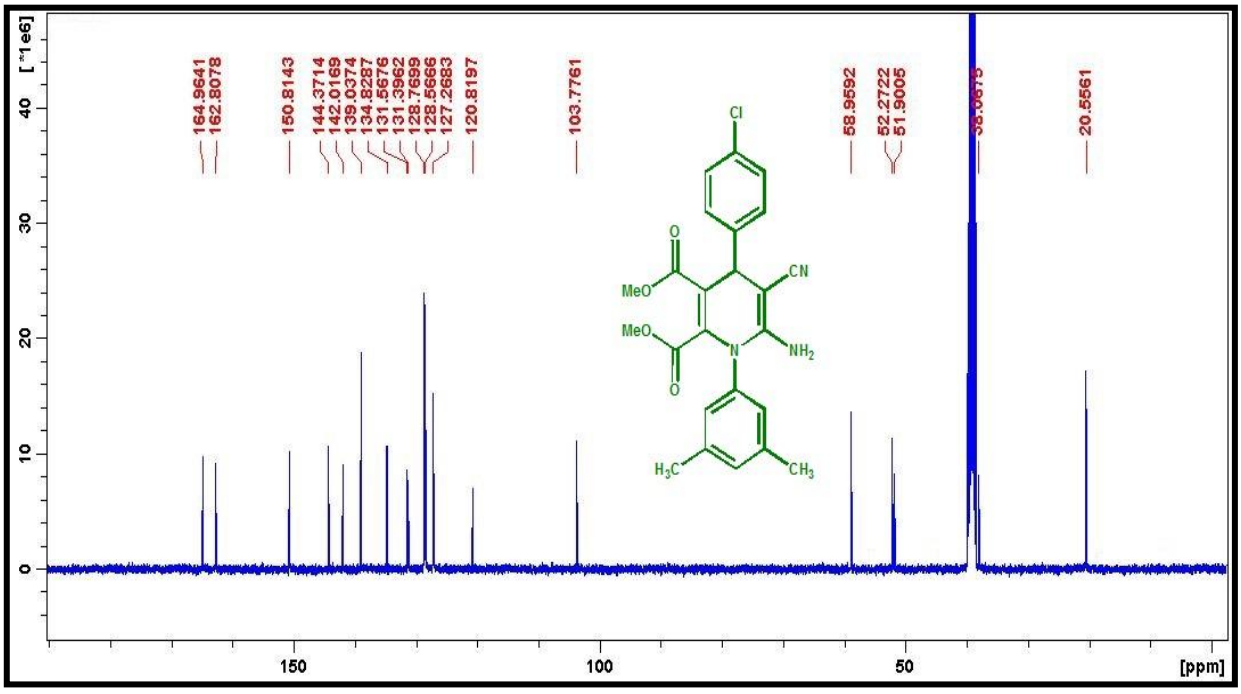
^{15}N NMR spectra of compound **5d**



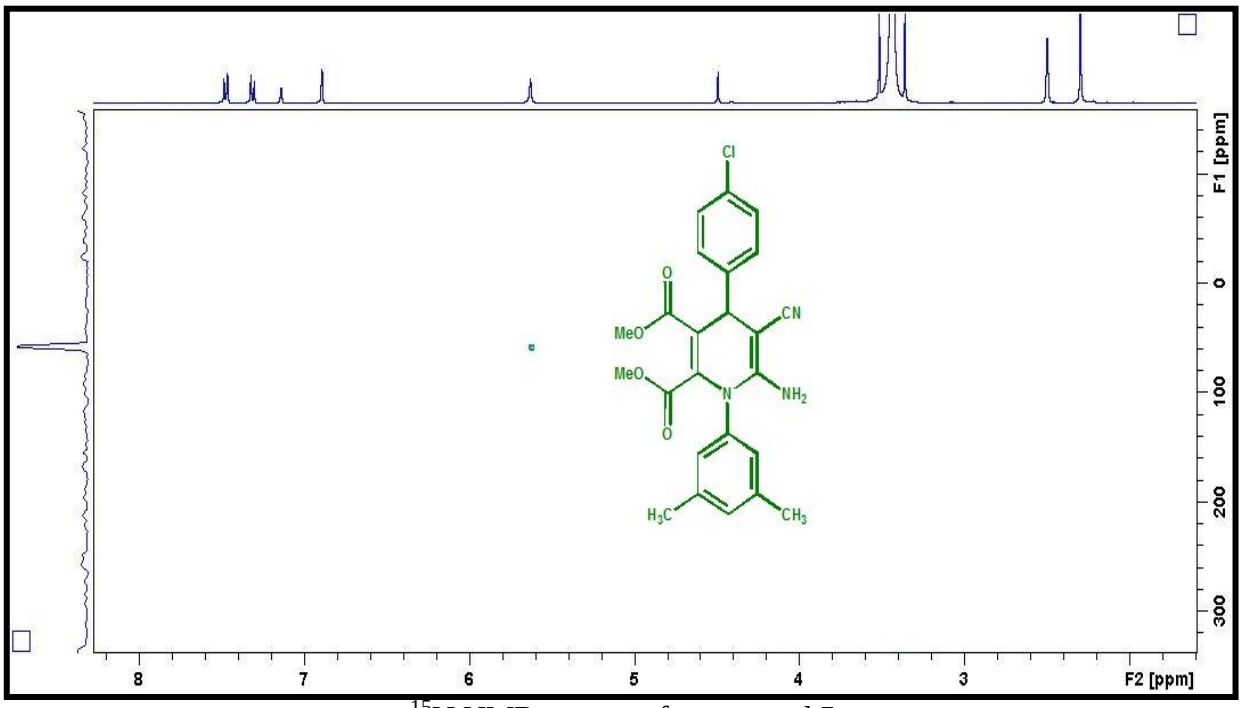
^{13}C NMR spectra of compound **5d**



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



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



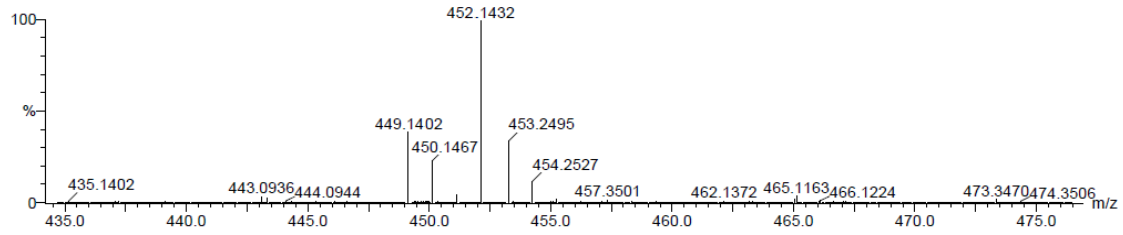
^{15}N NMR spectra of compound **5e**

Elemental Composition Report Page 1

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

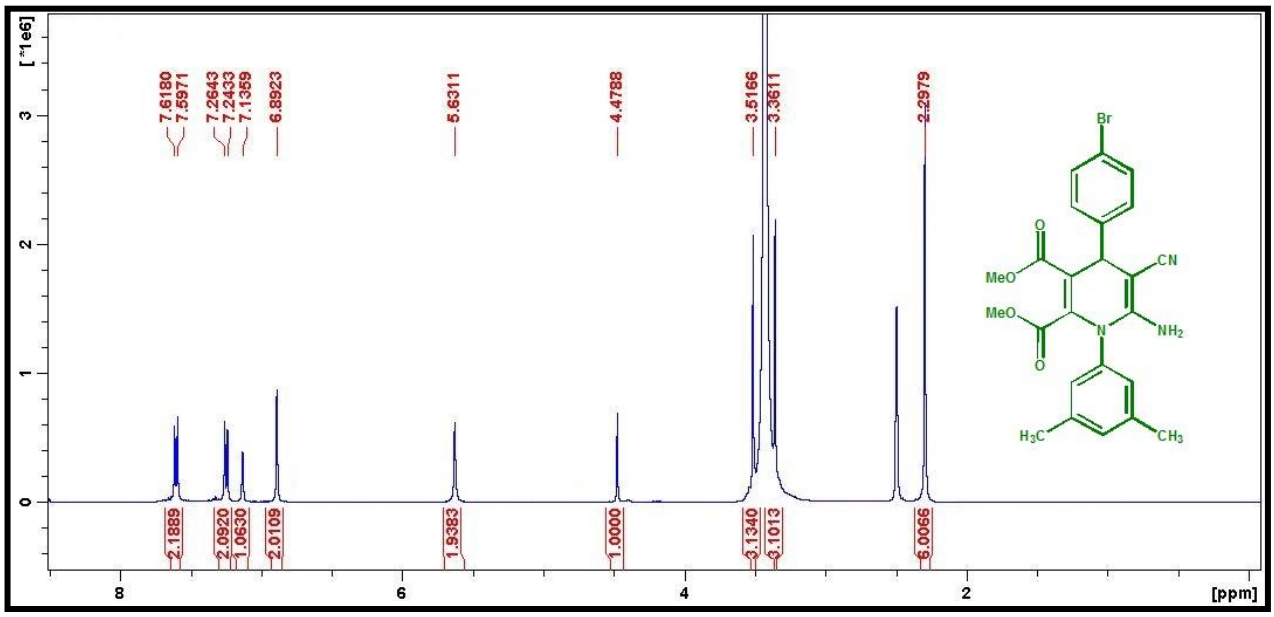
Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 20-25 N: 0-5 O: 0-5 Cl: 1-1
F2 3 (0.070) Cm (1:58)
TOF MS ES+

1.27e+005

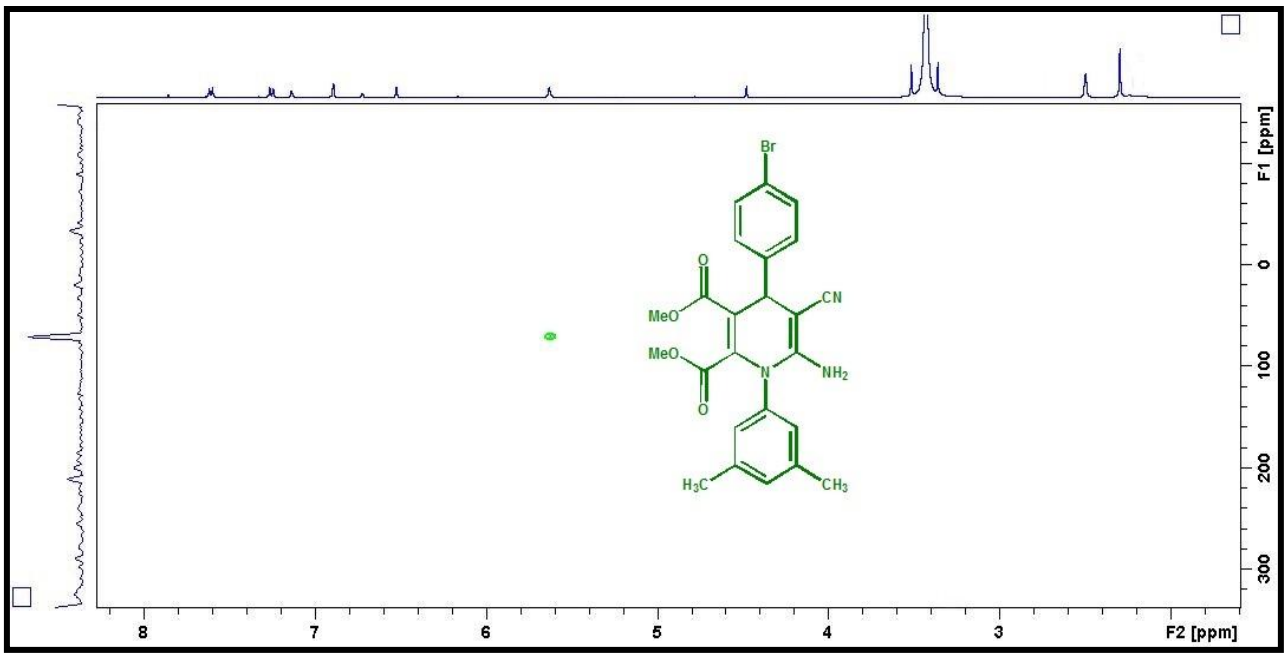


Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
452.1432	452.1437	-0.5	-1.1	12.5	516.0	0.0	C24 H23 N3 O4 Cl

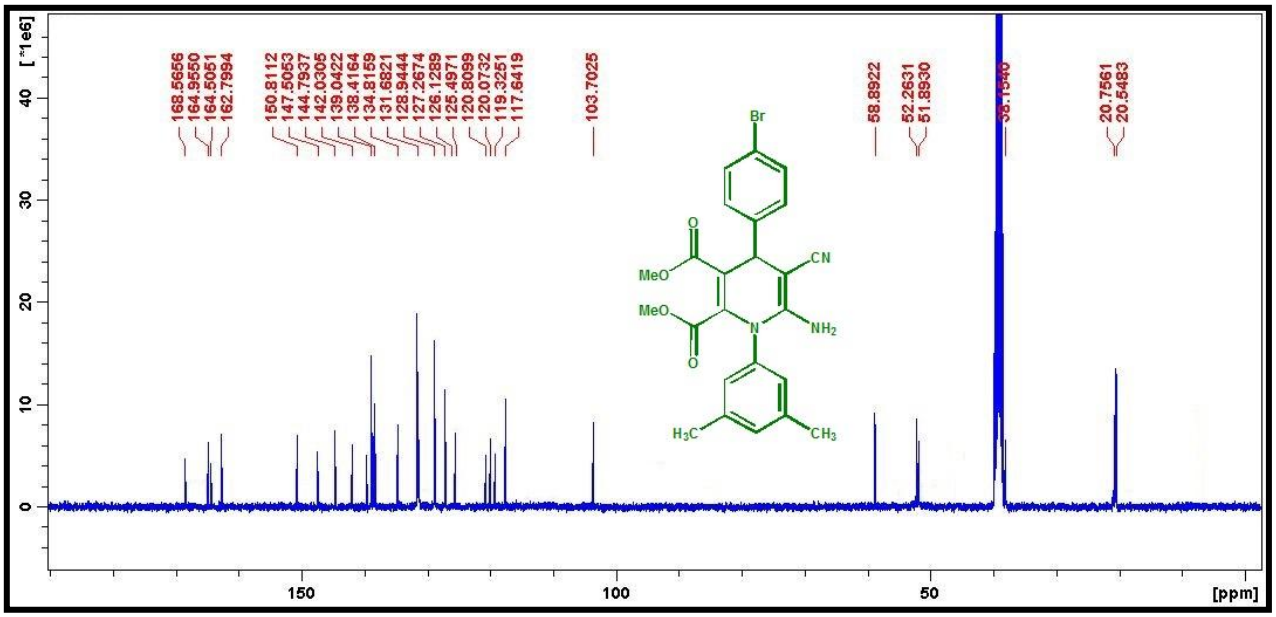
HR-MS spectra of compound **5e**



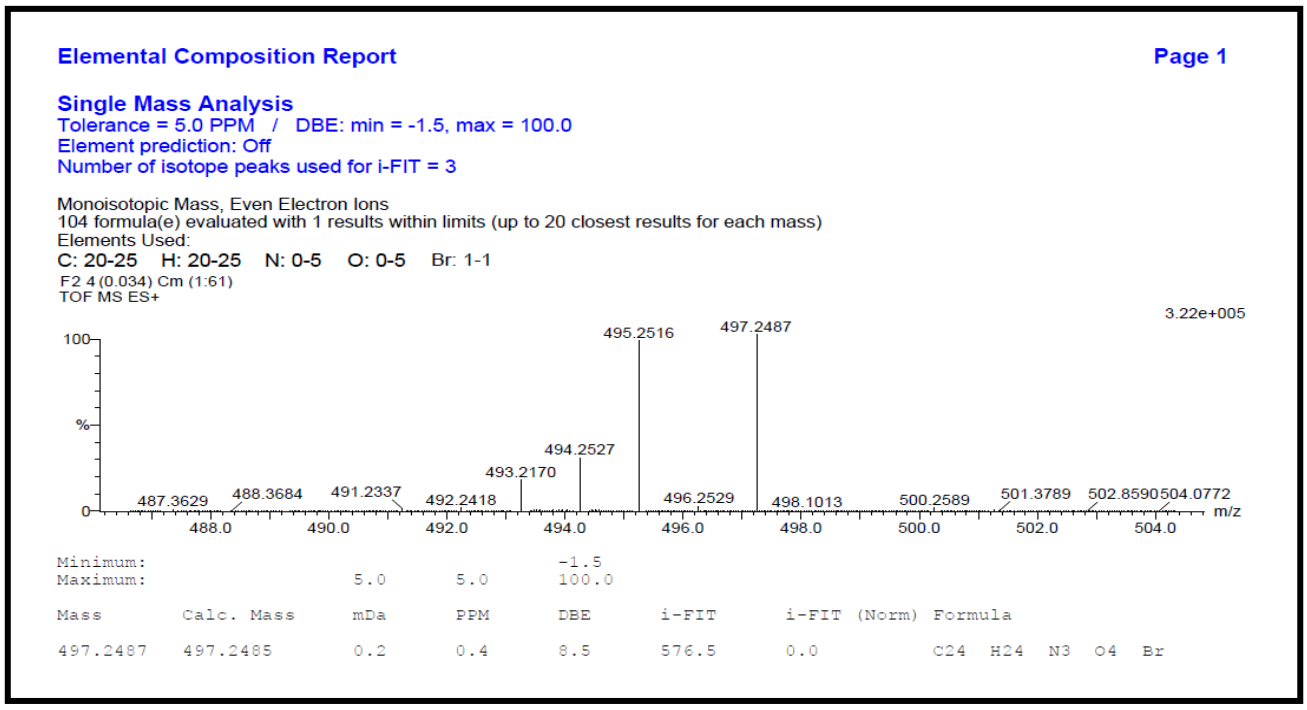
^{1}H NMR spectra of compound **5f**



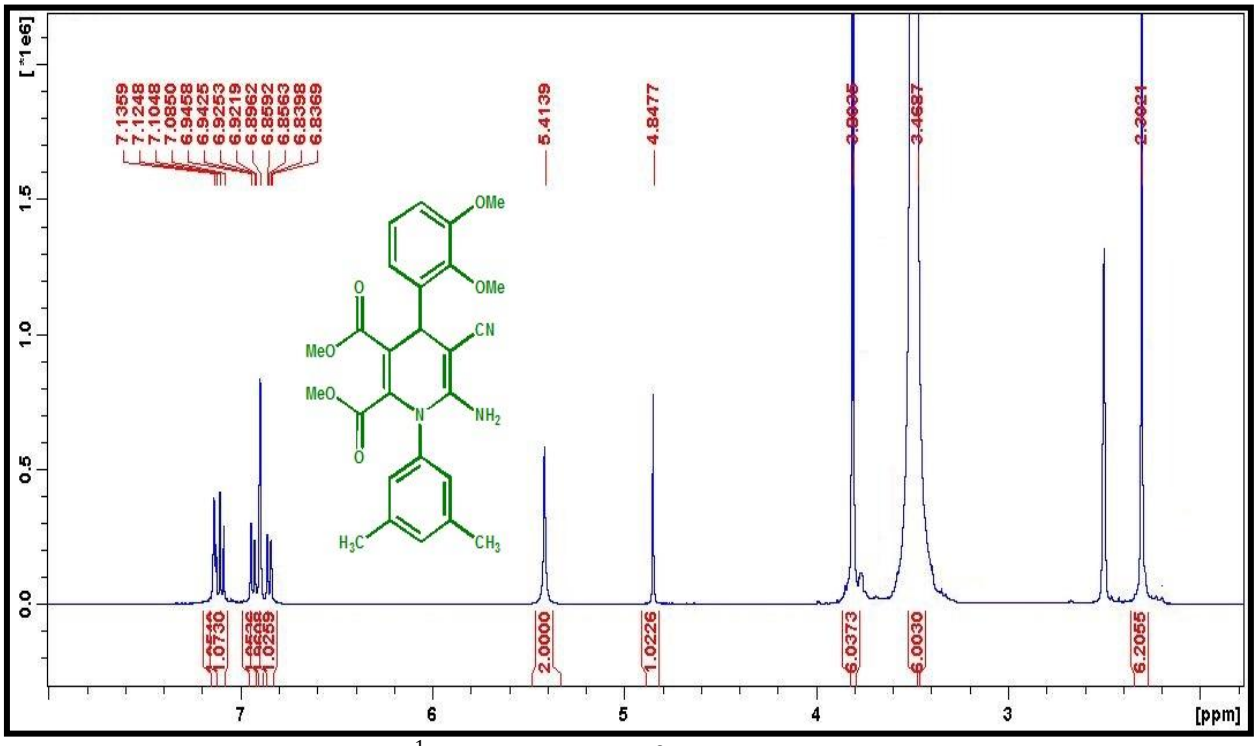
^{15}N NMR spectra of compound **5f**



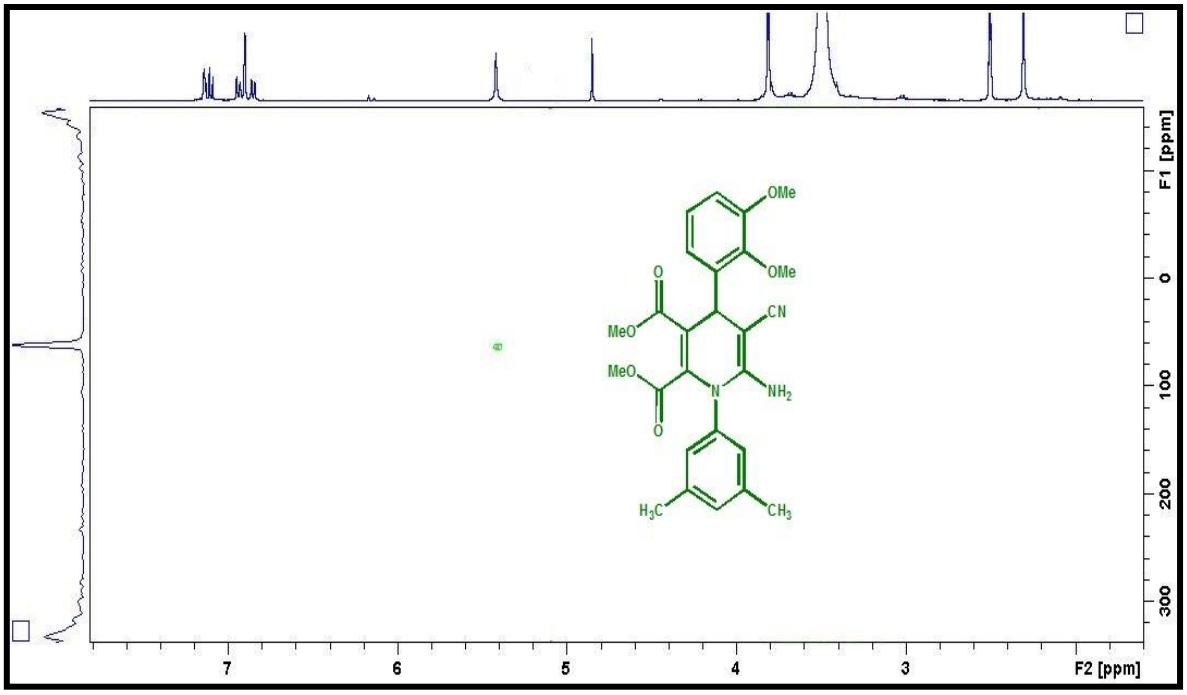
^{13}C NMR spectra of compound **5f**



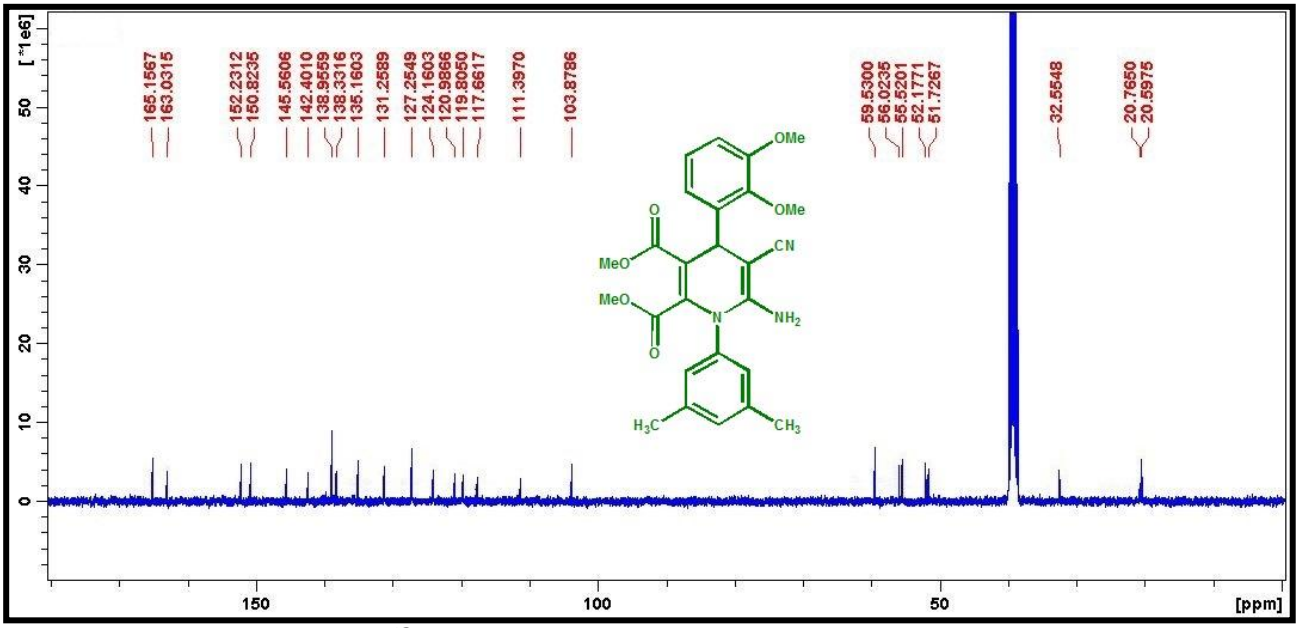
HR-MS spectra of compound **5f**



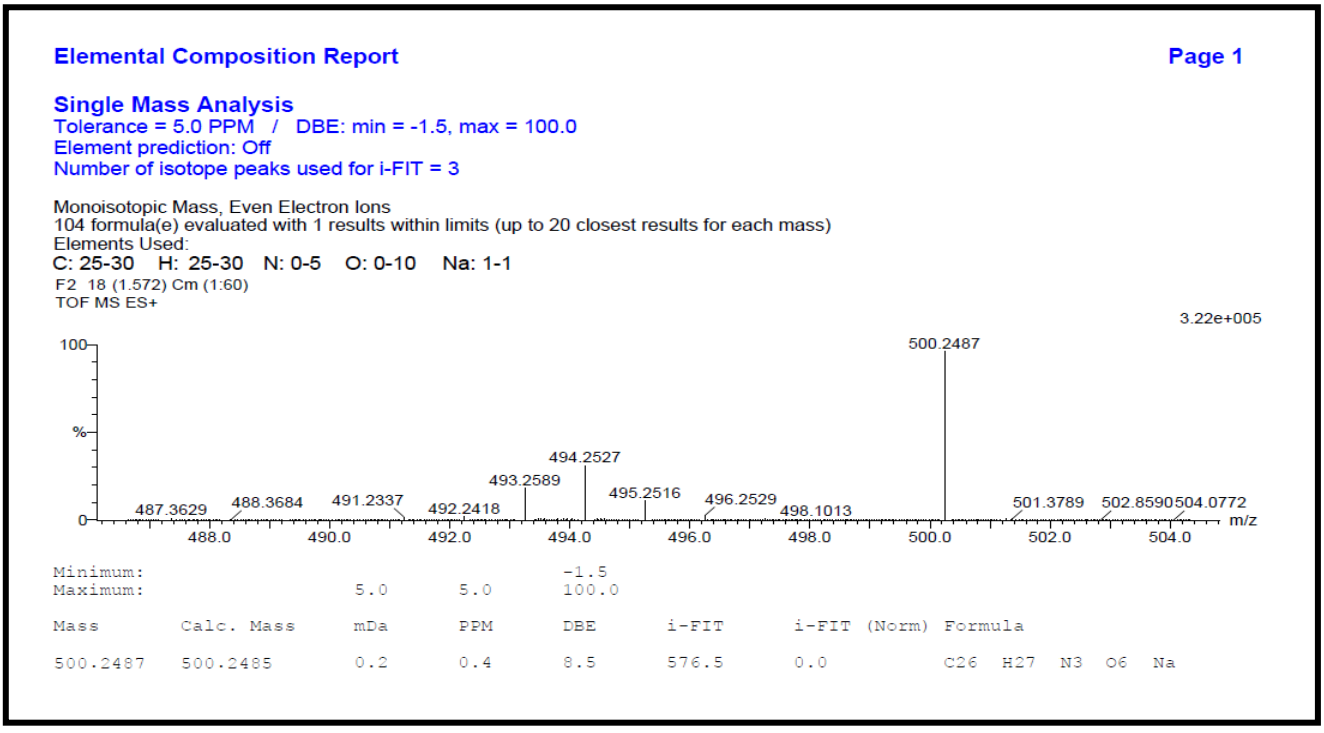
^{1}H NMR spectra of compound **5g**



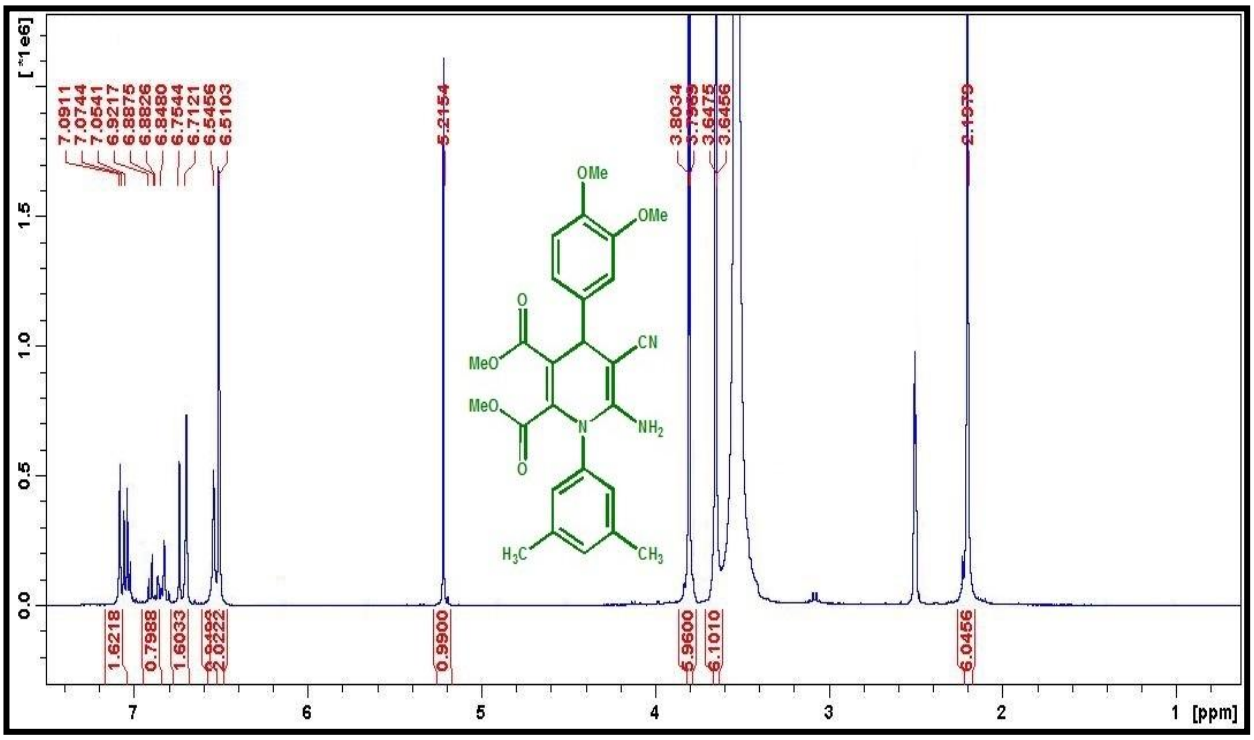
^{15}N NMR spectra of compound **5g**



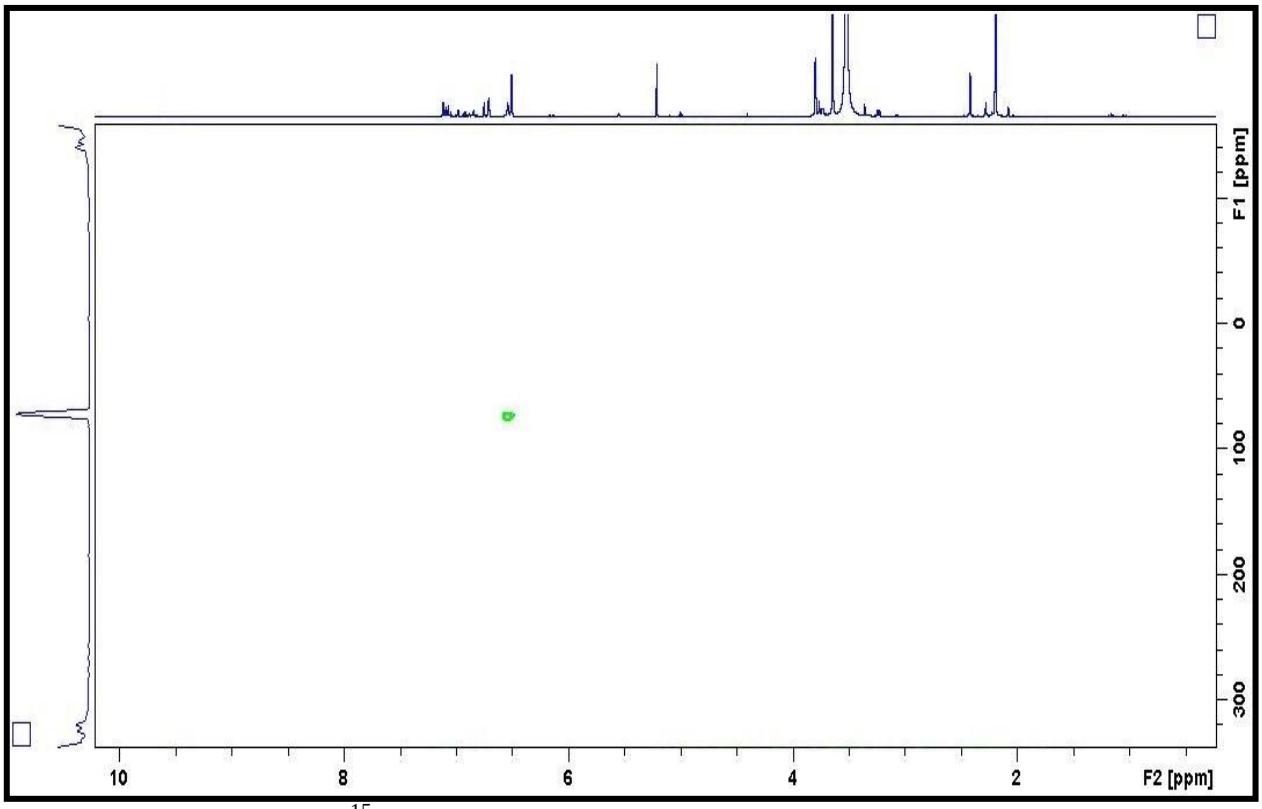
^{13}C NMR spectra of compound **5g**



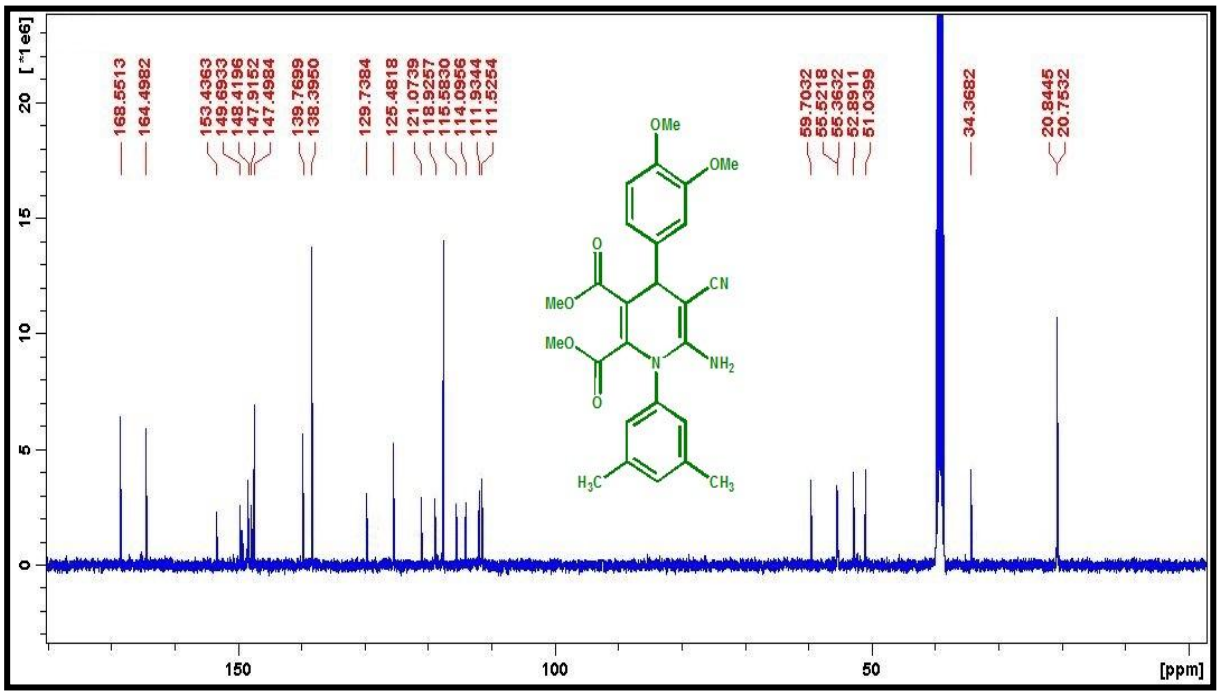
HR-MS spectra of compound **5g**



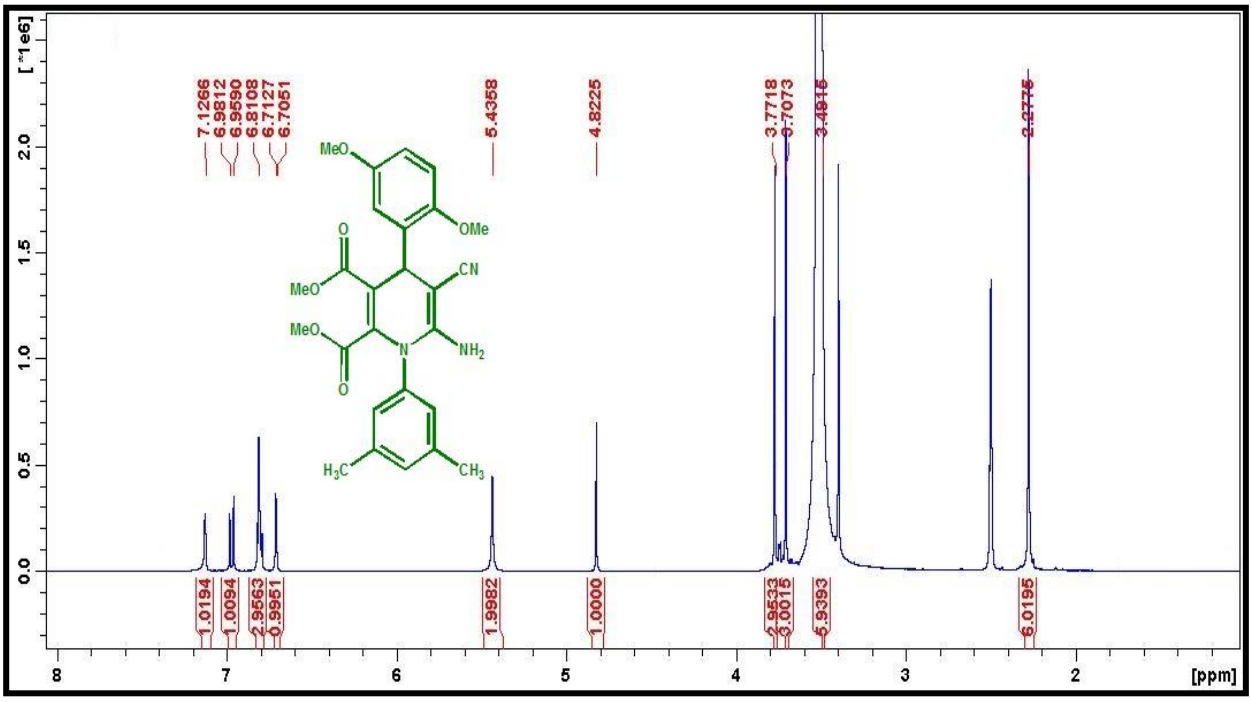
^{1}H NMR spectra of compound **5h**



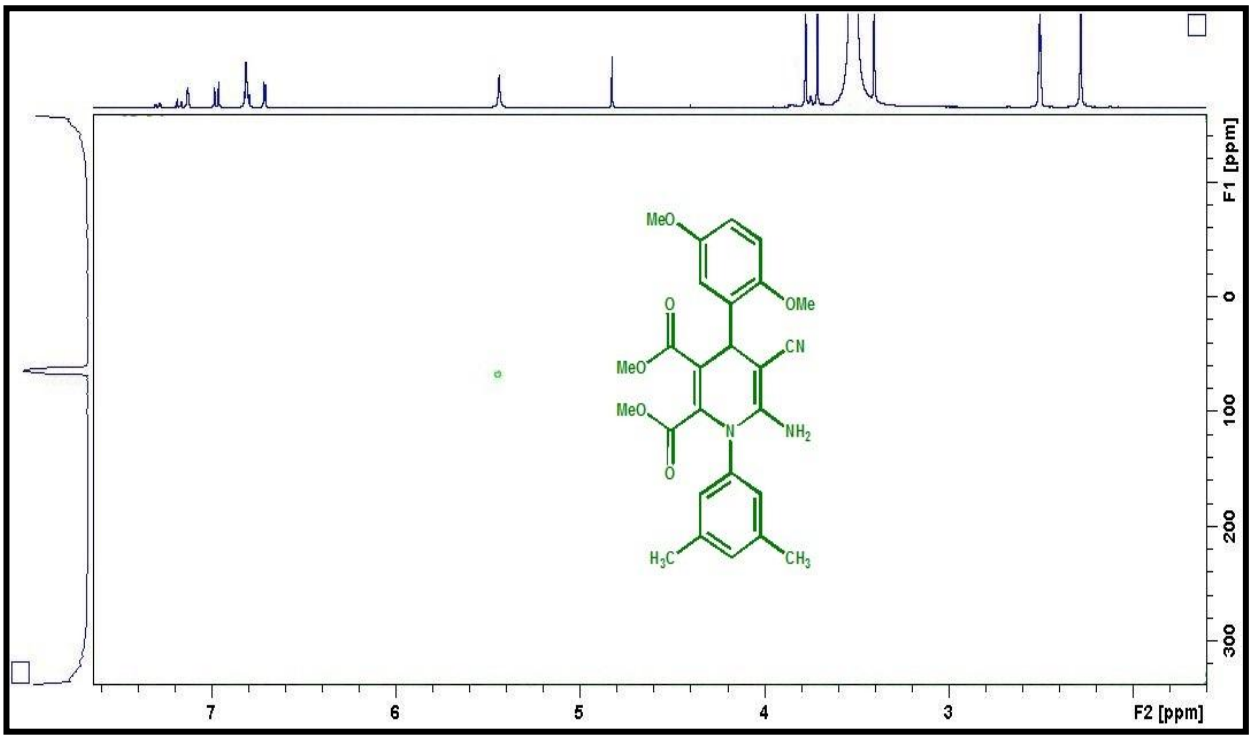
^{15}N NMR spectra of compound **5h**



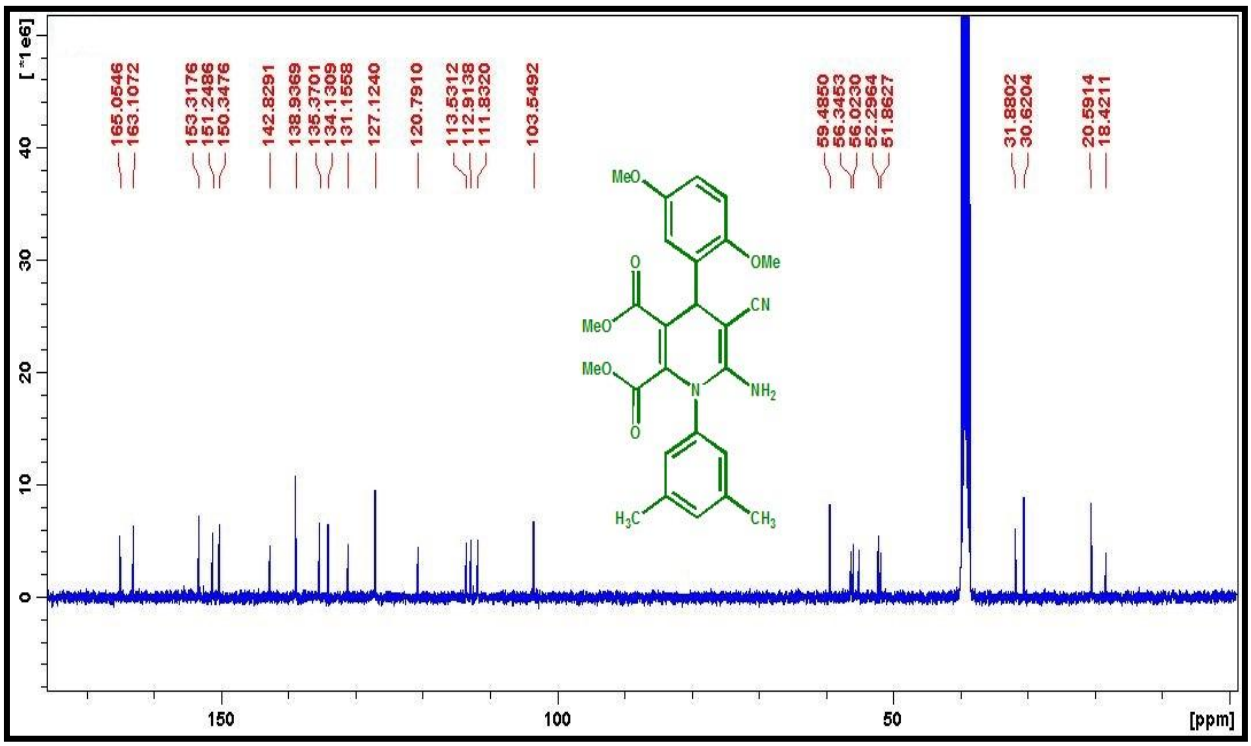
^{13}C NMR spectra of compound **5h**



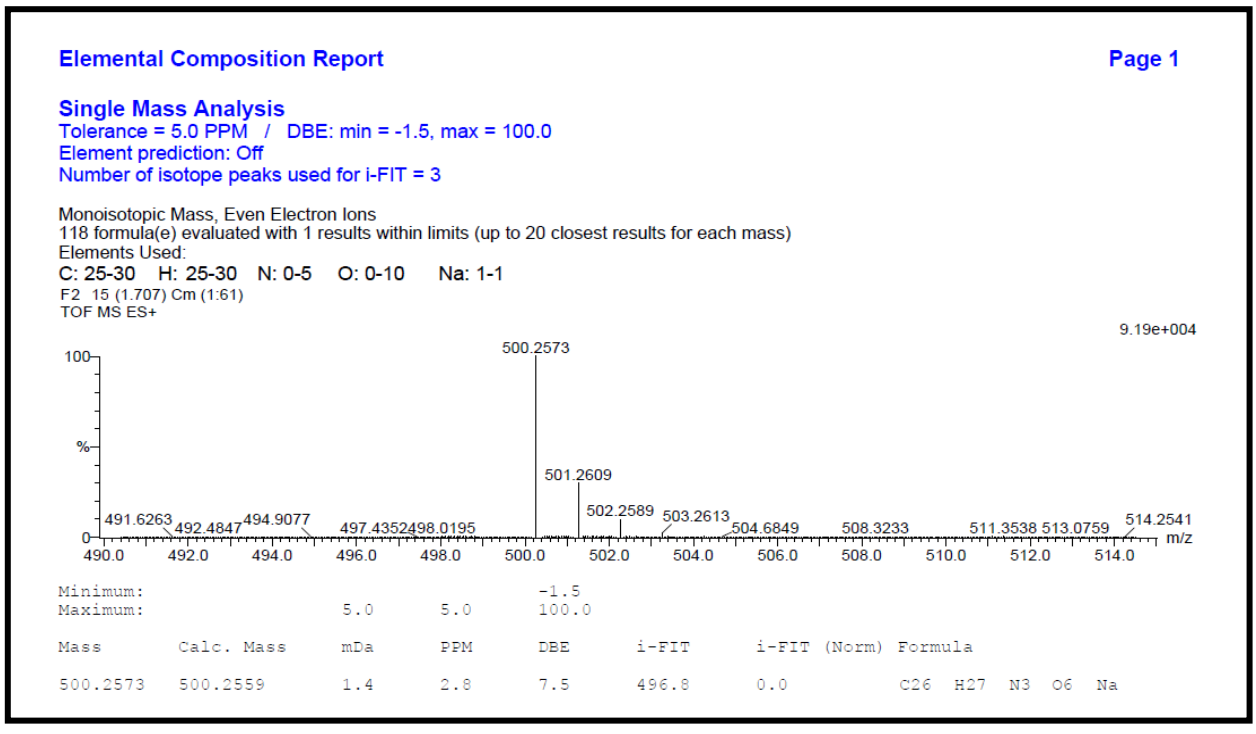
^{1}H NMR spectra of compound **5i**



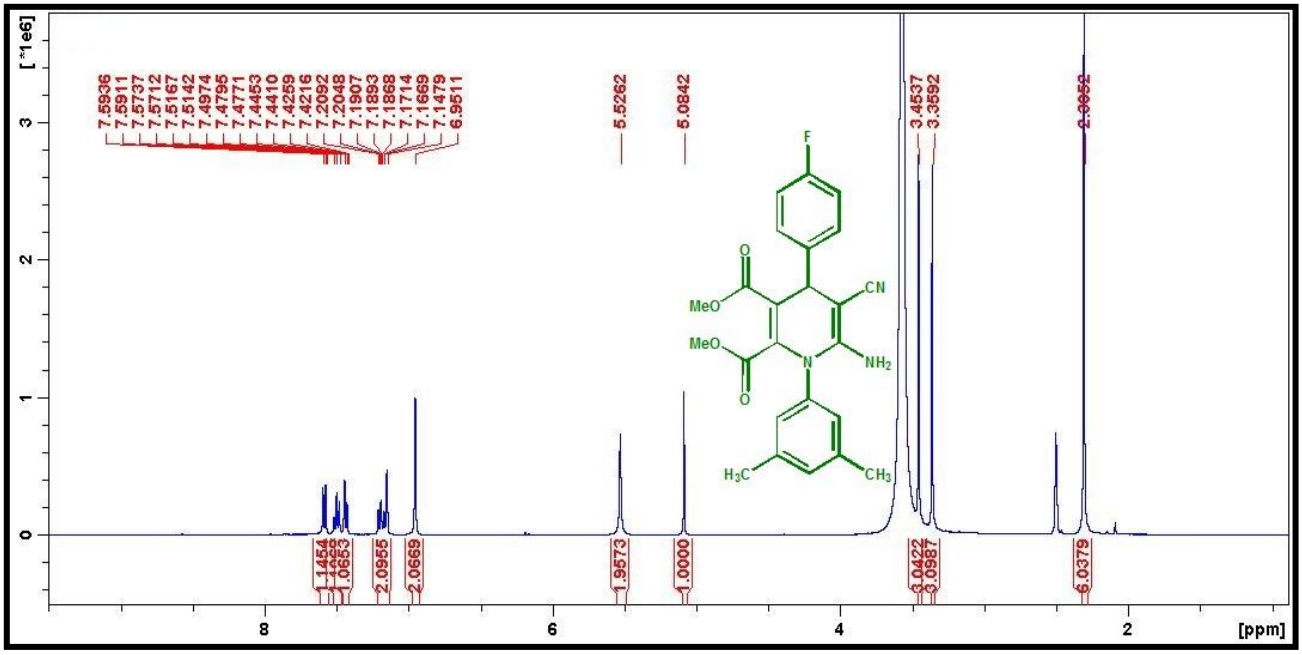
^{15}N NMR spectra of compound **5i**



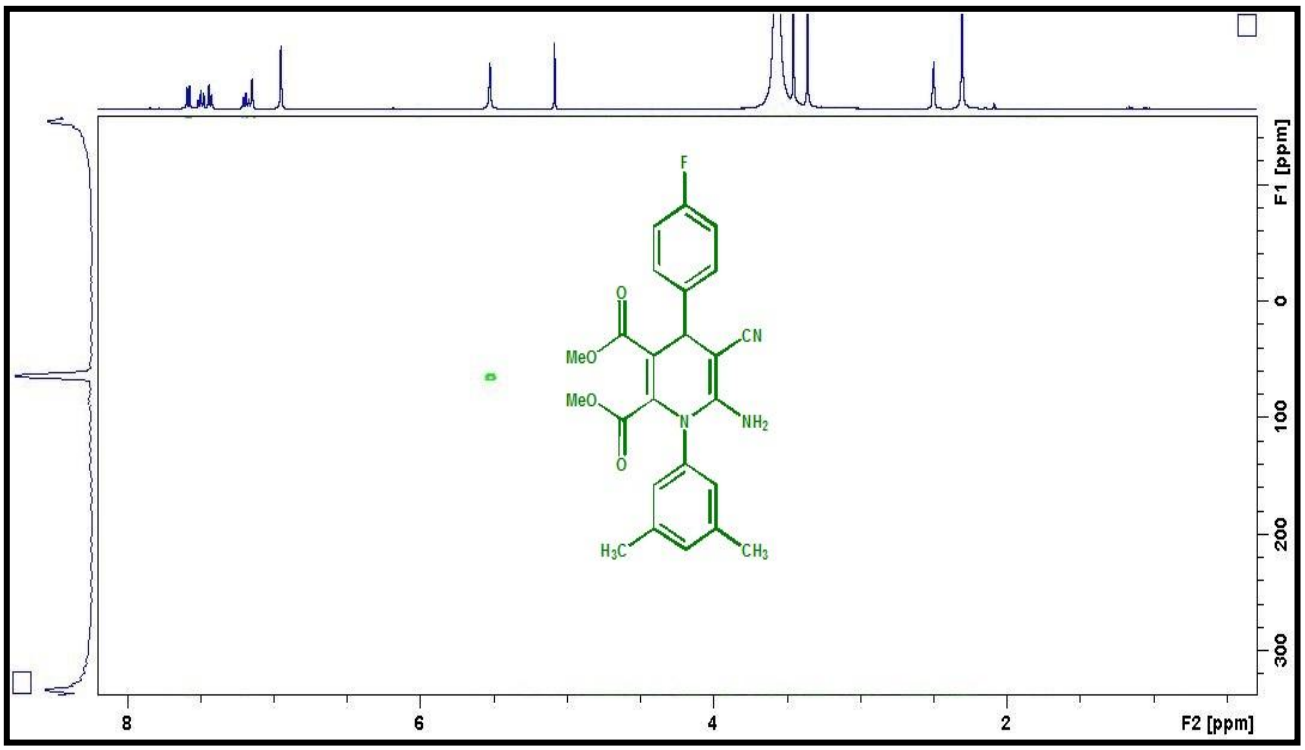
^{13}C NMR spectra of compound **5i**



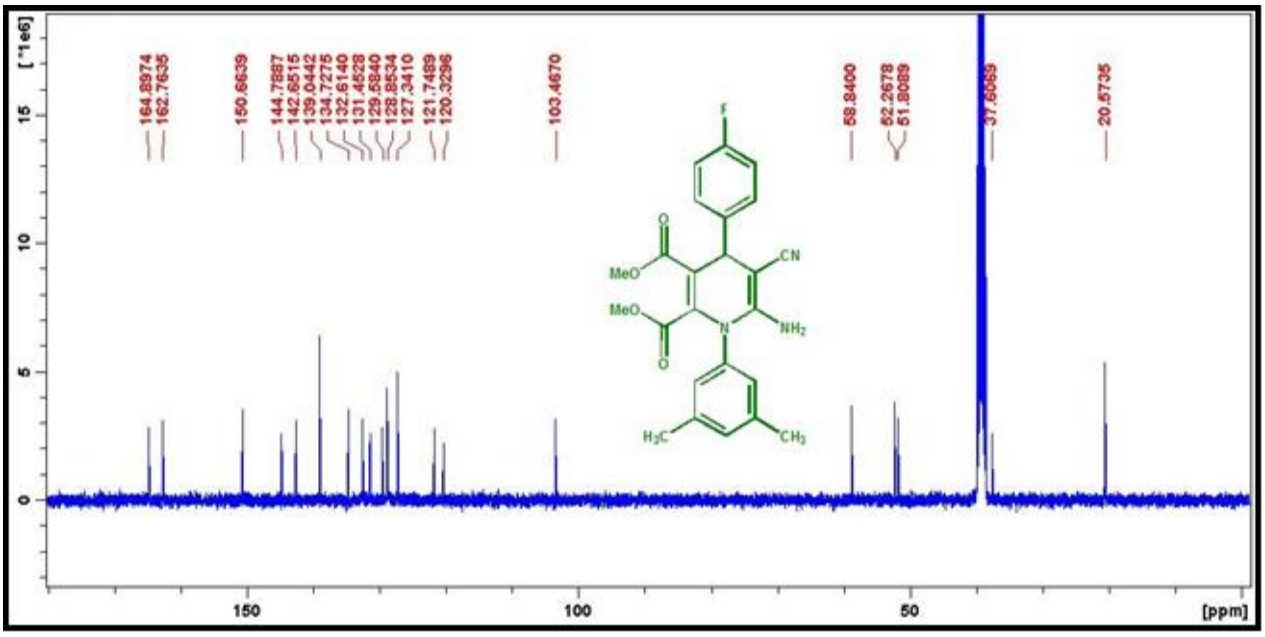
HR-MS spectra of compound **5i**



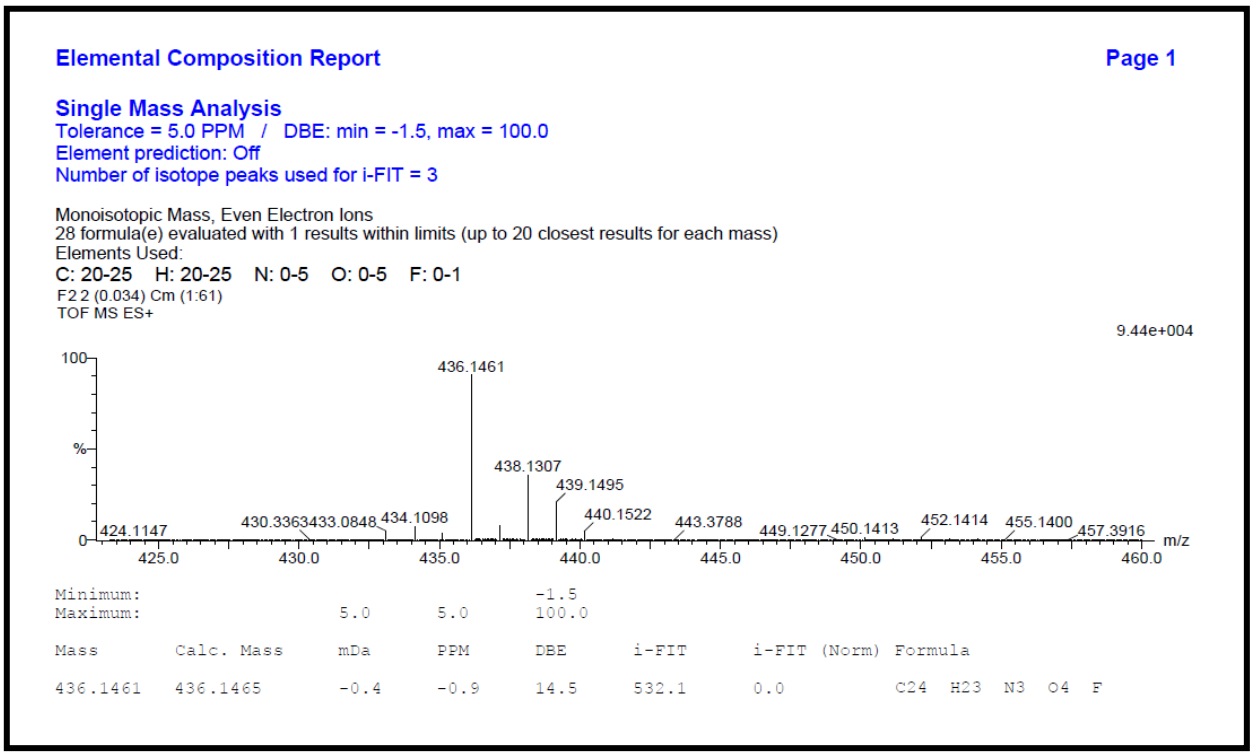
^{1}H NMR spectra of compound **5j**



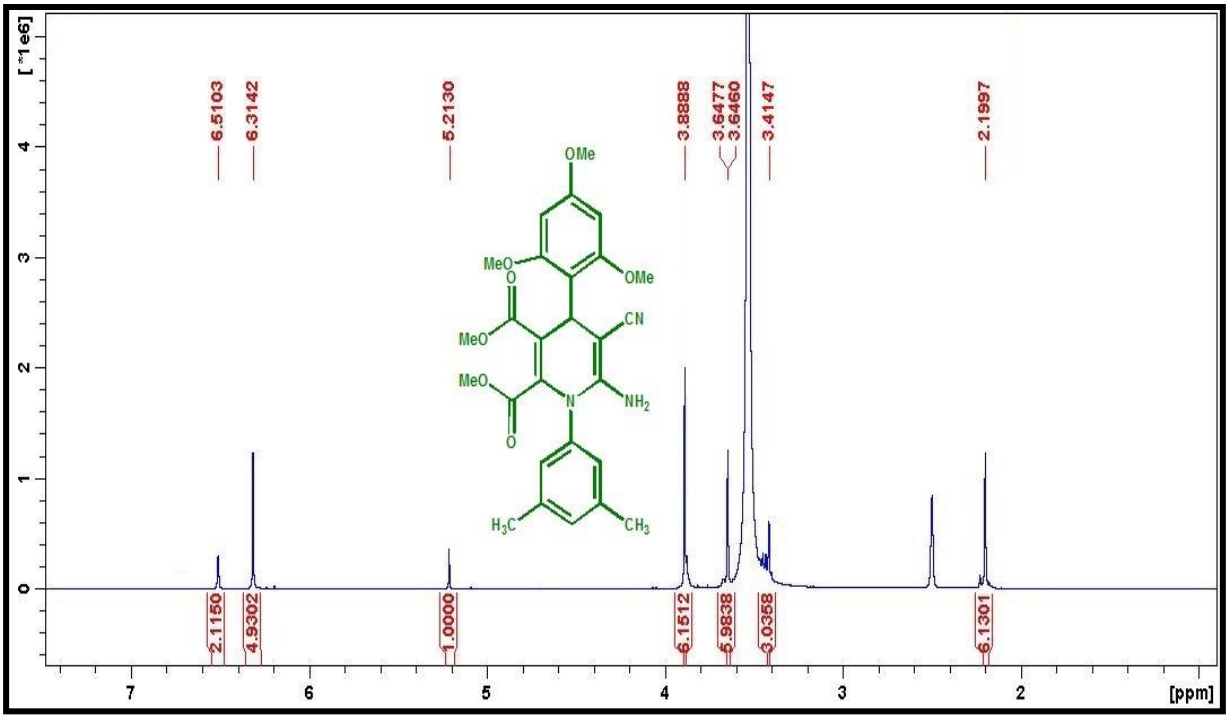
^{15}N NMR spectra of compound **5j**



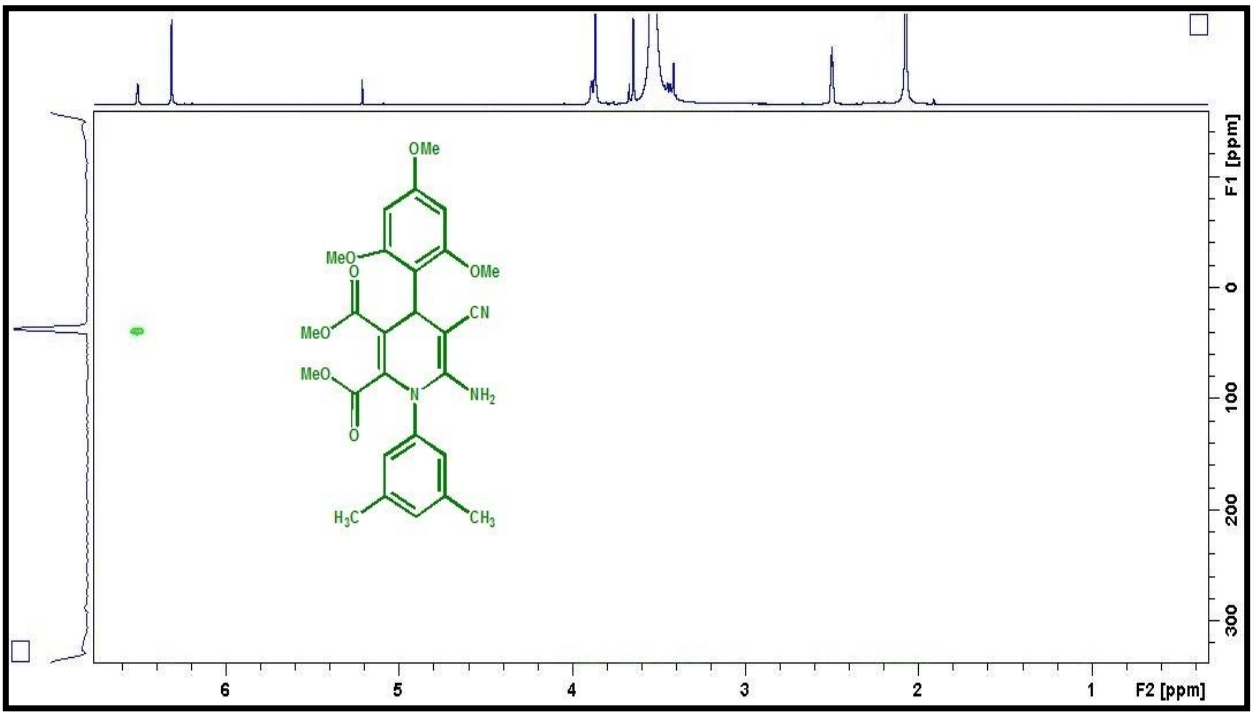
^{13}C NMR spectra of compound **5j**



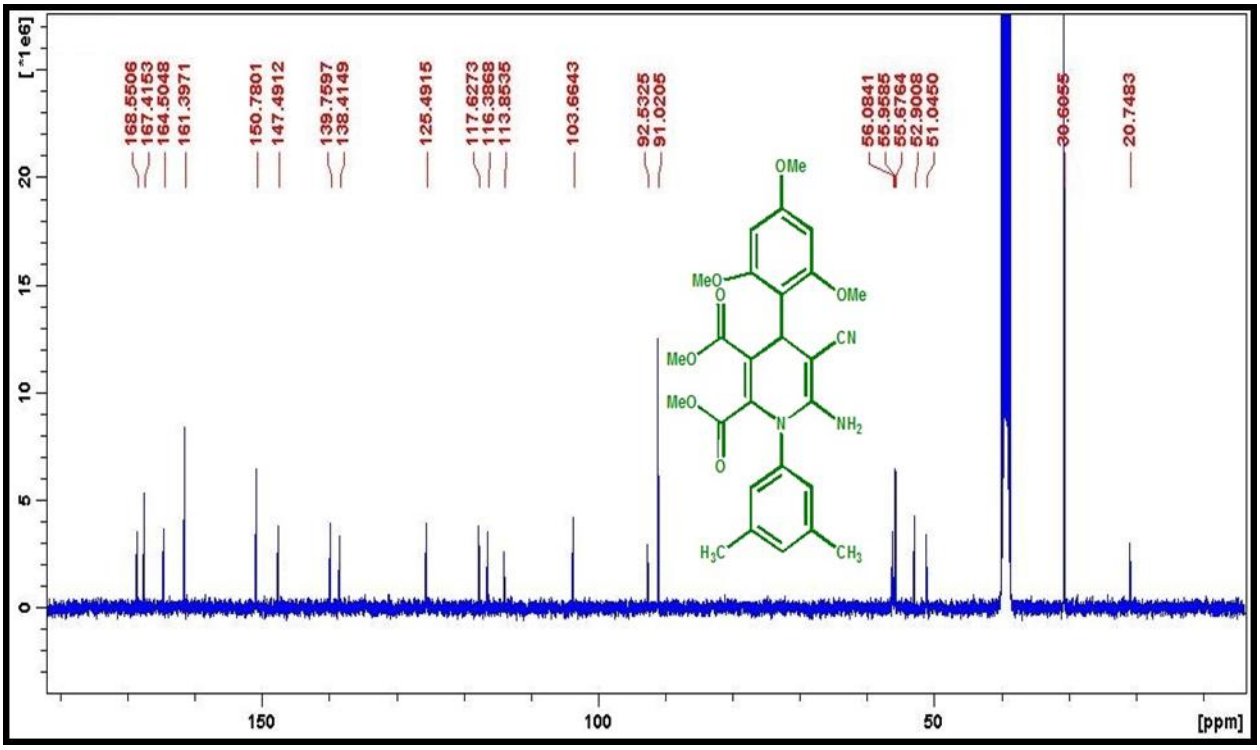
HR-MS spectra of compound **5j**



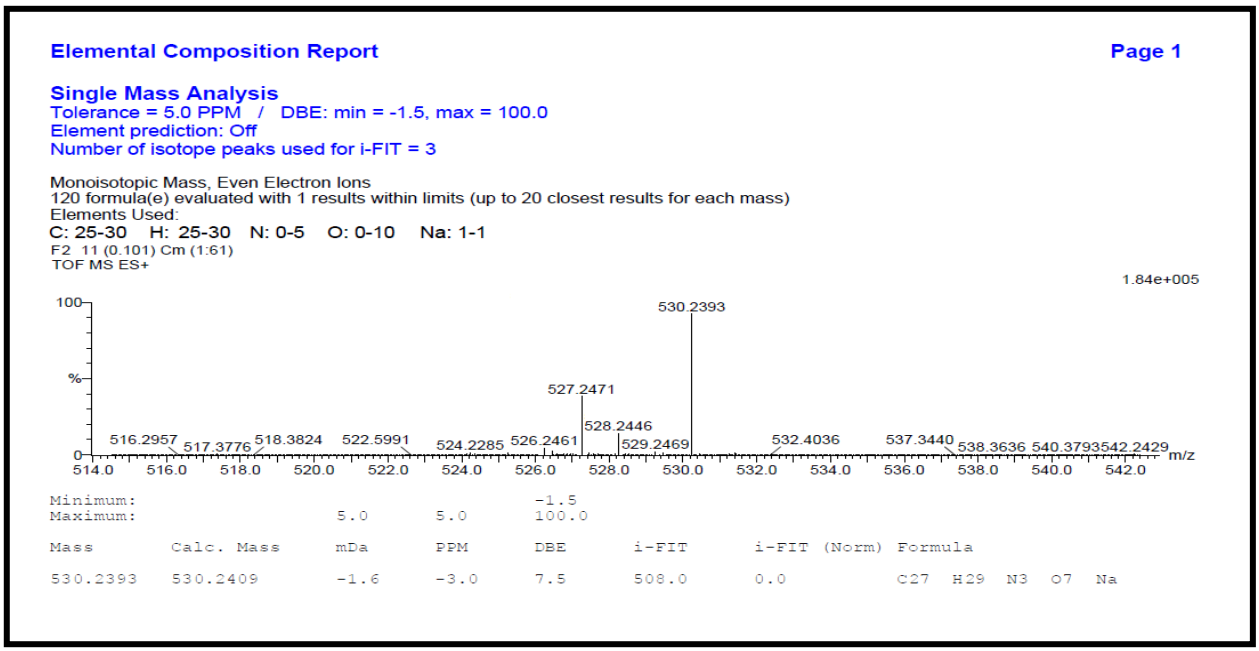
^{1}H spectra of compound **5k**



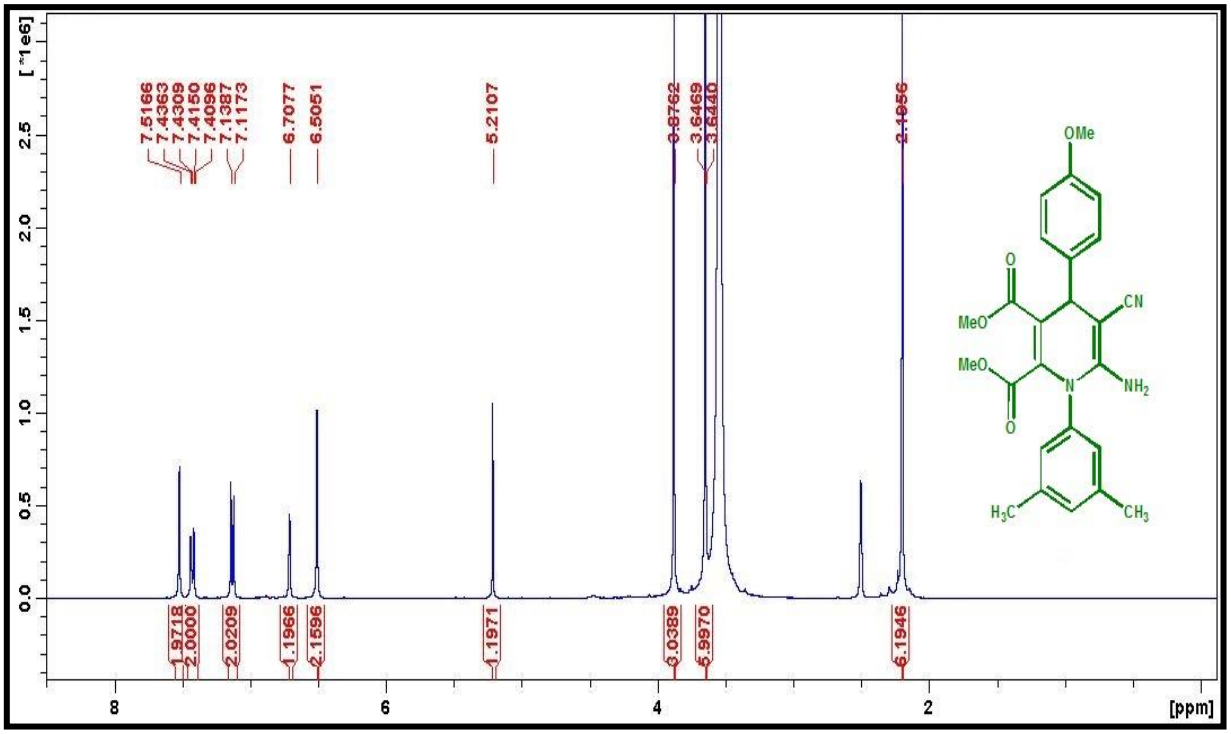
^{15}N spectra of compound **5k**



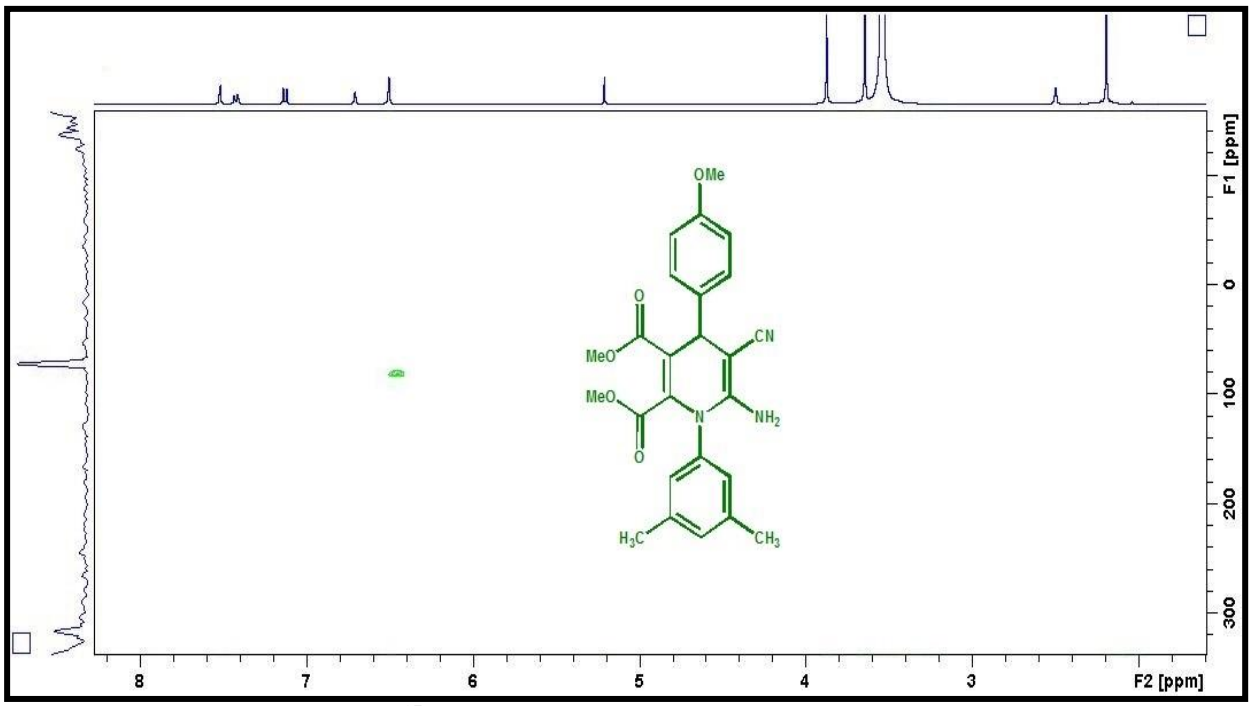
^{13}C NMR spectra of compound **5k**



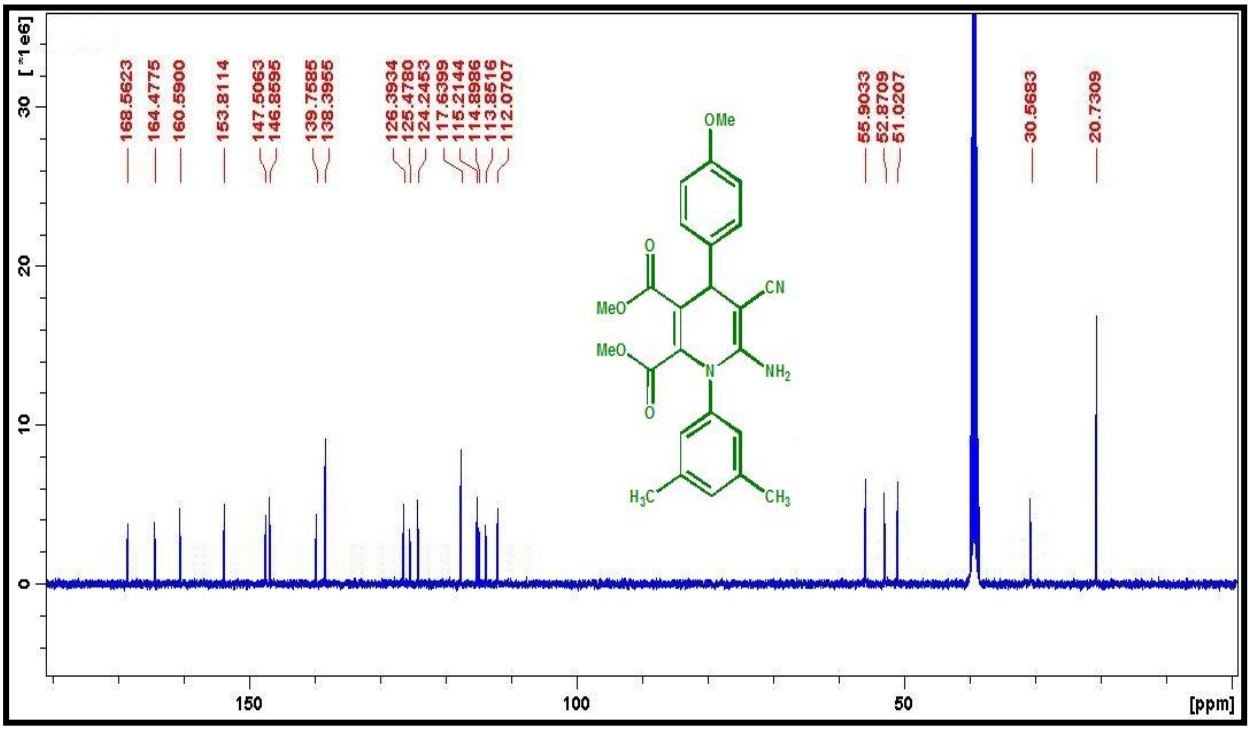
HR-MS spectra of compound **5k**



^{1}H NMR spectra of compound **5l**



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



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

Chapter 4

An efficient method for the synthesis of 1,4-dihydropyridines using Y_2O_3/ZrO_2 as a reusable catalyst

Sebenzile Shabalala, Suresh Maddila, Werner E. van Zyl and Sreekantha B Jonnalagadda*

*School of Chemistry & Physics, University of KwaZulu-Natal, Westville Campus, Chiltern Hills, Durban-4000, South Africa.

***Corresponding Author:** Prof. Sreekantha B. Jonnalagadda
School of Chemistry & Physics,
University of KwaZulu-Natal,
Durban 4000, South Africa.
Tel.: +27 31 2607325,
Fax: +27 31 2603091
E-mail address: **jonnalagaddas@ukzn.ac.za**

Abstract

In this study a highly efficient protocol is reported to synthesize 1,4-dihydropyridine derivatives using 2.5% Y_2O_3/ZrO_2 as a heterogeneous catalyst. The one-pot four component reaction involves substituted aldehyde, malononitrile, 4-bromoaniline and dimethylacetylenedicarboxylate in green solvent ethanol. The new catalyst material is characterized by powder X-ray diffraction, TEM, SEM and nitrogen adsorption/desorption analysis techniques. The key benefits of this novel approach are easy work-up, green solvent, short reaction times (< 20 min), energy efficient reaction conditions and no chromatographic separation techniques plus excellent yields (88-95%).

Keywords: Multicomponent reaction, Heterogeneous catalysis, Pyridines, Sustainability, Efficient protocol, Y_2O_3/ZrO_3.

4.1. Introduction

Green chemistry refers to design of chemical reactions and products that minimize or eliminate the use or generation of hazardous compounds.[1] It is basically concerned with the efficient use resources, averting of the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical compounds.[2] It is focused on the use of green principles in organic synthesis and on the industrial scale processes in chemical industry in general and pharmaceutical industry in particular.[3] with objective to develop the optimal methods to minimize energy consumption for the production of desired products.[4,5]

Multicomponent reaction (MCR) put together several reactant molecules to form a product.[5] It is one of the most important protocols in organic synthesis and medicinal chemistry.[6] The benefits of one-pot reactions are rapid access to diverse highly functionalized organic molecules with efficiency, and cost effectiveness.[7] MCR approach is of central interest in the construction of combinatorial libraries and optimization in drug discovery process.[8] MCRs are the cornerstones in the diversity oriented construction of molecular complexity due to their atom efficiency and ability to incorporate the reactants into product molecule in a fast and efficient manner.[9-10] These are highly selective, simple workup, operate under mild conditions with atom economy and high yields, and main need no chromatographic separations.[11-12]

Heterogeneous catalysis plays an important role in both the research laboratory and in the chemical and pharmaceutical industries.[13] These are the key technology used in varies catalytic fields.[14] They generate high purity products without any need to purify the obtained products and also it can be separated easily from the product.[15,16] Their cost is low, wide availability, environmental friendly and reusable.[17] They exhibit very high activity and selectivity for a large range of reactions.[18] Hence, there is always demand for good recyclable heterogeneous catalyst with high selectivity and good activity. [17-19]

Zirconium oxide (ZrO_2) has received great attention, both as catalyst and catalyst support,[20] owing to its amphoteric nature. It has the presence of both acidic and basic sites and can act as bi-functional catalytic material.[21] It's high specific surface area, better flexibility, active metal centres and thermal stability, make it appropriate over wide-ranging temperatures.[22] Rare-earth elements, including yttrium possess large surface area and stable at high temperatures making them ideal as catalyst materials.[23] The combination of zirconia with yttrium shows even better properties than their individual components.[24] The exceptional activity of the mixed oxides is described by ultrahigh vacuum surface experiments.[23-25] The structure of yttrium doped zirconia strengthens the interaction between these two components, and because of its dispersion on zirconia enhance its catalytic activity.

Literature survey shows various methodologies for the synthesis of different heterocyclic compounds with unique biological properties.[26] Such methods constitute the largest of the classic division of organic chemistry in terms of number of new compounds synthesized.[27] Many of the new molecules played important role in the discovery of new drugs and bioactive compounds, including anti-tumor, anti-bacteria and ant-virulence agents.[28] Several naturally occurring organic compounds with nitrogen containing heterocyclic moieties are reported to exhibit remarkable biological activities.[29] Pyridines and their derivatives are useful structural motifs possessing interesting biological and pharmaceutical properties.[30] Generally, these derivatives are used as antimicrobial,[31] anticancer,[32] antioxidant,[33] antimalarial,[34] anti-inflammatory,[35] anti-^{HIV}[36] and anti-ulcer activity.[37] Owing to their importance and relevance, several procedures have been reported in literature for synthesis of various dihydropyridine derivatives. The Hantzsch synthesis is one of the distinguished techniques for the preparation of 1,4-dihydropyridines.[38,39] Some of such processes employed TMSI,[40] PEG-600,[41] Et_3N,[42]

I_2,[43], etc., as catalysts. Some of those reactions demand expensive reagents, tedious handling procedures, high temperatures and harsh reaction conditions, while the others suffer with low yields and time-consuming reactions. Consequently, new approches with better features for the synthesis of 1,4-dihydropyridine derivatives is paramount.

Encouraged by a promising results in evolving synthetic methodologies for varied heterocyclic molecules,[44-49] we recently have reported various procedures for viable synthesis of various biological interesting heterocyclic protocols in good yeilds.[50-54] In this communication, in continued pursuit for developing efficient materials, we report a new heterogeneous catalyst, yttrium doped zirconia (Y_2O_3/ZrO_2) and its characterization. Its superior selectivity and activity for the syntheses of series of novel functionalized 1,4-dihydropyridine derivatives using one-pot four-component reaction at room temperature with ethanol as solvent is also detailed. To the best of our knowledge, this is the first application of this type of heterogeneous catalyst in one-pot reactions and for the synthesis of 1,4-dihydropyridine scaffolds.

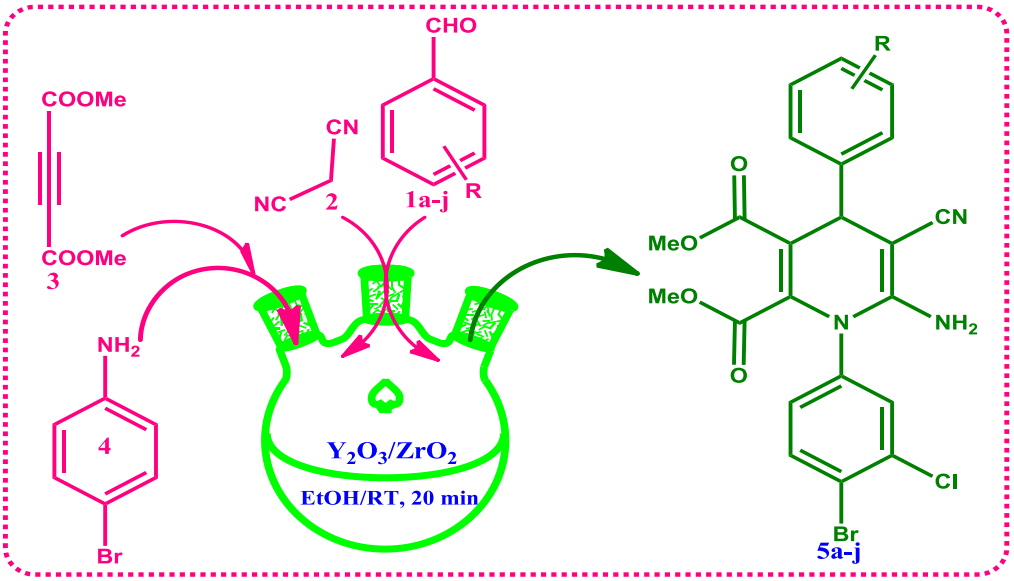
4.2. Experimental section

4.2.1. Catalyst preparation

A wet-impregnation process was used to prepare a series of supported catalysts Y_2O_3/ZrO_2 of weight percentage (1%, 2.5% & 5 wt%). The heterogeneous catalyst was achieved from mixture of zirconia (ZrO_2, 2 g, Catalyst support, Alfa Aesar) and an appropriate wt% amount of yittrium carbonate [$Y_2(CO_3)_3 \cdot 6H_2O$ (Alfa Aesar)] in (60 mL) dissolved in distillated water. The mixture was stirred at room temperature for 6 h after which the resulting slurry was filtered under vacuum. Further, it was dried in an oven at 120–130 °C for 6 h and calcined in the presence of air, at 450 °C for 5 h to acquire of corresponding Y_2O_3/ZrO_2 catalysts.

4.2.2. General synthesis of functionalized 1,4-dihydropyridine-2,3-dicarboxylates (5a-l)

Substituted benzyaldehyde (1 mmol), dimethylacetylenedicarboxylate (1.0 mmol), malononitrile (1.1 mmol), 4-bromoanaline (1 mmol) and Y_2O_3/ZrO_2 (30 mg) in 10 mL ethanol were reacted a round-bottom flask, and stirred at room temperature. TLC plate was used to check the progress of the reaction and its completion. The solid product formed was then collected by filtration, and washed with ethyl acetate. It was further recrystallized to purify the crude product. The structures of obtained products were further confirmed with ^{1}H NMR, ^{13}C NMR, ^{15}N NMR and HR-MS and the related spectra details are assimilated to the supplementary information file.



Scheme 1. Synthesis of functionalized 1,4-dihydropyridine derivatives

4.3. Results and discussion

4.3.1. SEM analysis

The yttrium/zirconia material morphology was observed using SEM micrographs (Fig. 1). The mixture of Y_2O_3/ZrO_2 catalyst particles agglomerates has no specific/particular shape uniformity. The dispersal size of the agglomerate particles is in a nano-metric scale as can be seen. Their scale contributes onto the catalytic activity as they are very crystalline and homogenized. This implies that even the active site is dominant leading to the catalysts to be more effective.

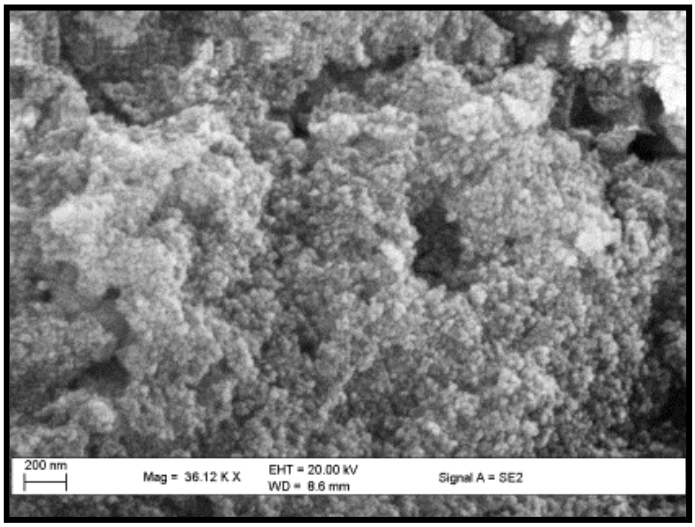


Figure 1: SEM micrograph of 2.5% Y_2O_3/ZrO_2 catalyst

4.3.2. TEM analysis

The method used in this study to determine the size and size distribution of particle of interest is TEM. Figure 2 shows the pattern and size distribution of 2.5% Y_2O_3/ZrO_2. It basically shows clusters in oval shapes of about 12 nm. The zirconia seen to be lighter compared to the yttrium oxides, which are seen to be darker. This is shown in some part of the given image bearing in mind that in most part, it is just the combination/mixture of both Y_2O_3/ZrO_2.

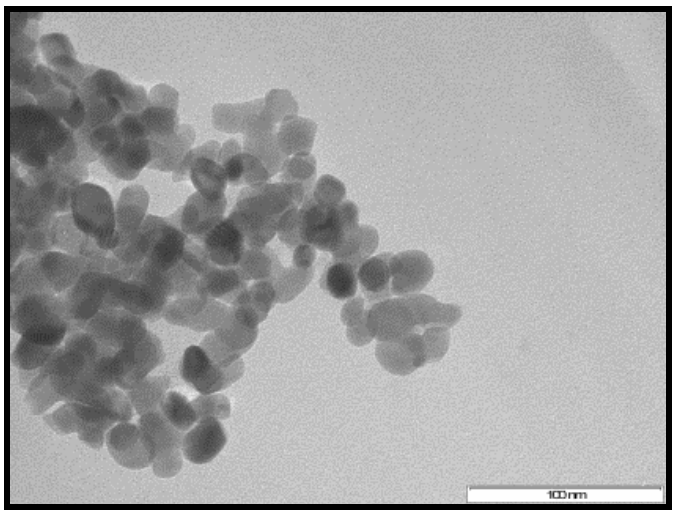


Figure 2: TEM micrograph of 2.5% Y_2O_3/ZrO_2 catalyst

4.3.3. Powder X-ray Diffraction

Figure 3 shows 2.5 wt% Y_2O_3/ZrO_2 powdered X-ray diffraction patterns. Yttrium oxide is temperature dependent therefore it is calcined at higher temperature of 450 °C so that oxide can be obtained. It confirms diffraction peaks 2θ values at 28.4°, 32.6°, 49.7°, 56.2°, 62.1°, 70.0° and 79.2° are assigned to Y_2O_3. Their higher intensity confirms that indeed they are yttrium oxide without any water remaining after calcinations. The obtained XRD peaks are in correspondence with the standard Y_2O_3 [(JCPDS) 25-1200]. In addition, the sample showed diffraction patterns at 2θ angles of 23.9°, 28.8°, 33.9°, 33.6°, 44.1°, 53.4° and 60.1° that corresponds to ZrO_2 (JCPDS file No. 01-089-9066). The average crystallite size of the sample was calculated using with Scherrer equation. It was about 9.3 nm, based on the maximum intensity diffraction peaks of Y_2O_3/ZrO_2 catalyst.

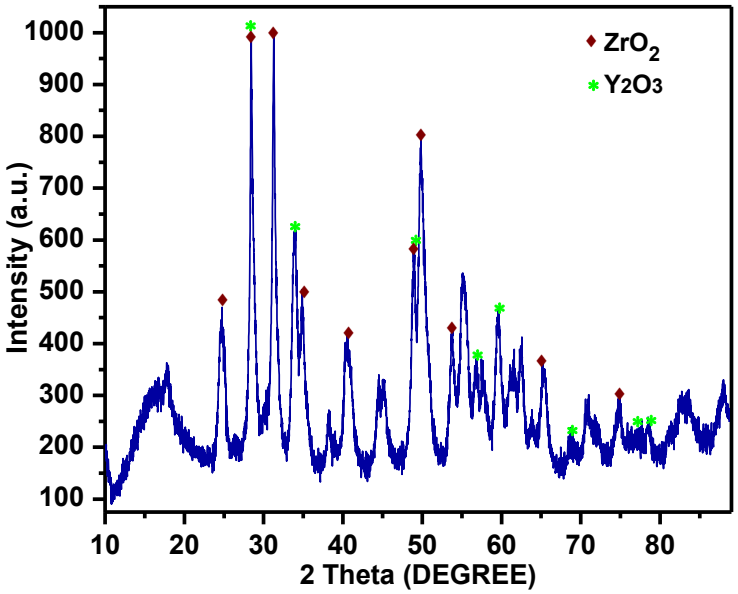


Figure 3. Powder XRD spectra of 2.5% Y_2O_3/ZrO_2 catalyst

4.3.4. BET surface area analysis

Figure 4 depicts N_2 adsorption/desorption isotherms. This basically illustrates the pore size distribution of 2.5% Y_2O_3/ZrO_2 catalyst. The pore size distribution assign a mesoporous pore size of 98.12 Å texture for the sample, and the isotherms P/Po range was found to be 0.68-0.83. The surface area was given to be 68 $m^2\ g^{-1}$ with a pore volume of 0.312 $cm^3\ g^{-1}$. As seen from the figure, this 2.5% Y_2O_3/ZrO_2 catalyst describes type-IV adsorption isotherms which signifies a mesoporous material.

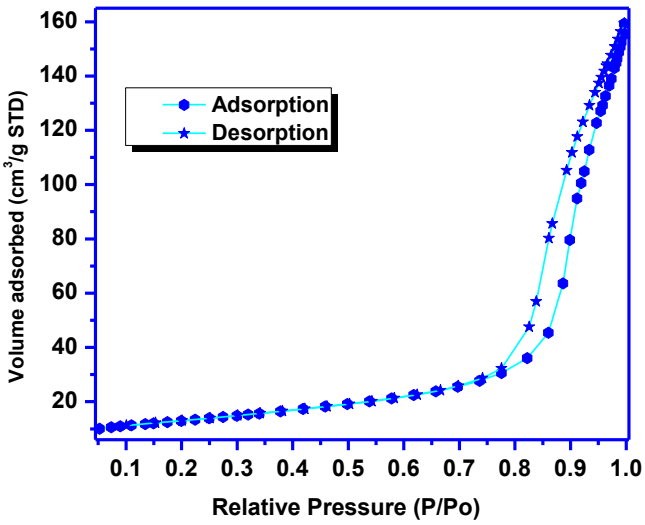


Figure 4. N_2 adsorption & desorption isotherms of a 2.5% Y_2O_3/ZrO_2 catalyst

4.4. Optimization

The model reaction was conducted by a one-pot, four-component reaction of 2-methoxybenzaldehyde (1 mmol), dimethylacetylenedicarboxylate (1.0 mmol), malononitrile (1.0 mmol), and dimethylaniline (1 mmol) in 10 ml ethanol. Different reaction conditions were tested on this model reaction. Varied catalysts and solvents were assessed at the different temperature conditions. Initially, in the absence of any catalyst or solvent, even after 12 h stirring of the reaction mixture, no product was observed, both at RT and reflux conditions (Table 1, entries 1 & 2). Then, the reaction was tried in ethanol in absence of any catalyst and at both temperature conditions and no product was noticed (Table 1, entries 3 & 4). Thereafter, different catalysts were tested, starting with acidic catalysts such as acetic acid (AcOH), $FeCl_3$ and H_3BO_3 to assess the efficiency of the catalyst. No product was observed at RT in all the runs (Table 1, entries 5-7). A trace amount of product was obtained after 8 h reaction by using ionic liquids like DABCO or (Bmim)BF_4 as a catalysts (Table 1, entries 8 & 9). When the reaction was attempted with different basic catalysts, such as KOH, Na_2CO_3, pyridine and TEA in ethanol, at RT the yield was low (Table 1, entry 10 & 13). Further, the pure oxide catalysts like alumina (Al_2O_3), silica (SiO_2) and zirconia (ZrO_2) were examined, and those oxides proved effective giving the desired product in 52 to 69% yields at RT after 3 h (Table 1, entries 14-16). Among the chosen oxide catalysts, zirconia gave relatively higher yield (Table 1, entries 16). Hence, using zirconia as support, bimetallic mixed oxides 2.5% CeO_2/ZrO_2, MnO_2/ZrO_2, and Y_2O_3/ZrO_2 were prepared and their activity was tested. Impressive yields (82-95%) were obtained within 20 min reaction time in ethanol and at RT, by using the mixed oxide catalysts (Table 1, entry 17-19). Among the three catalysts investigated, Y_2O_3/ZrO_2 showed better results, giving the target functionalized 1,4-dihydropyridines in 95% yield in 20 min reaction time under RT conditions.

Table 1: Optimal conditions for the synthesis of model reaction by 2.5% Y_2O_3/ZrO_2 catalyst[a]

Entry	Catalyst	Solvent	Temperature	Time (hr)	Yield (%)[b]
1	--	--	RT	12	--
2	--	--	Reflux	12	--
3	--	EtOH	RT	12	--
4	--	EtOH	Reflux	12	--
5	AcOH	EtOH	RT	12	--
6	$FeCl_3$	EtOH	RT	12	--
7	H_3BO_3	EtOH	RT	12	--
8	DABCO	EtOH	RT	8.0	10
9	$(Bmim)BF_4$	EtOH	RT	8.0	08
10	KOH	EtOH	RT	7.0	19
11	Na_2CO_3	EtOH	RT	7.5	23
12	pyridine	EtOH	RT	8.0	27
13	TEA	EtOH	RT	7.0	25
14	Al_2O_3	EtOH	RT	5.5	53
15	SiO_2	EtOH	RT	4.5	59
16	ZrO_2	EtOH	RT	3.5	69
17	2.5% CeO_2/ZrO_2	EtOH	RT	1.5	82
18	2.5% MnO_2/ZrO_2	EtOH	RT	2.0	74
19	2.5% Y_2O_3/ZrO_2	EtOH	RT	0.30	95

Solvent plays major role in the stability and solubility of the reactants and reaction mechanism. The solvent optimization was performed to examine the scope for improving reaction yield and selectivity. The title reaction was studied in the presence of non-polar solvents like DMF, acetonitrile, toluene and n-hexane (Table 2, entries 1-4), but yields were poor. The product yields were good to excellent, when the reaction was carried with polar solvents such as ethanol, methanol and isopropyl alcohol respectively (Table 2, entries 5-7). Highest yield (95%) was afforded with ethanol as solvent. Due to the hydrophobicity of the catalyst and organic reactant materials, ethanol as solvent might promotes better interactions with each other facilitating the formation of the desired product selectively.

Table 2: Optimization of various solvent condition for the synthesis of functionalized 1,4-dihydropyridines by 2.5% Y_2O_3/ZrO_2 catalyst[a]

Entry	Solvent	Time (minutes)	Yield (%)
1	DMF		48
2	acetonitrile		38
3	toluene		35
4	n-hexane		--
5	MeOH		76
6	EtOH		95
7	isopropyl alcohol		67

When amount of catalyst needed for optimum activity was also probed, while in the absence of a catalyst, no product was formed (Table 3, entry 1); when, the catalyst amount was increased from 10 to 30 mg, the product yield constantly increased from 74 to 95% (Table 3, entries 2-4). Using higher than 30 mg of catalyst, neither improved the yield nor the reaction time (Table 3, entries 5-7). The results suggest that 30 mg of Y_2O_3/ZrO_2 catalyst is ideal amount for the chosen reaction conditions.

Table 3: Optimization of the amount of by 2.5% Y_2O_3/ZrO_2 catalyst[a] in the reaction

Entry	Catalyst (mg)	Time (min)	Yield (%)
1	--	120	--
2	10	45	74
3	20	30	82
4	30	15	95
5	40	15	95
6	50	15	95
7	60	15	95

To widen the effectiveness and an excellence of the new synthetic procedure, reactions were studied using varied benzaldehyde derivatives substituted with different electron-withdrawing and electron-donating groups. All the ten reactions investigated gave good to excellent yields in short reaction times (Table 4, entries 1-10). The structures of all the newly synthesized compounds characterized and confirmed positively by employing ^{1}H NMR, ^{15}N NMR, ^{13}C NMR and HR-MS spectral analysis.

Table 4: Synthesis of functionalized 1,4-dihydropyridines catalyzed by 2.5%Y_2O_3/ZrO_2 catalyst[a]

Entry	R	Product	Yield (%)	Mp °C	Lit Mp °C
1	2-OMe	**5a**	93	239-241	--
2	4-OMe	**5b**	91	222-224	--
3	2-Cl	**5c**	89	231-232	--
4	4-Br	**5d**	87	258-260	--
5	4-Cl	**5e**	76	239-241	--
6	4-F	**5f**	78	274-276	--
7	2,5-$(OMe)_2$	**5g**	87	240-242	--
8	2-F	**5h**	92	209–211	--
9	4-Et	**5i**	90	250–252	--
10	2-Br	**5j**	89	198-200	--

-- New compounds/no literature available

4.5. Spectral data

Dimethyl-6-amino-1-(4-bromophenyll)-5-cyano-4-(2-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5a): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.39 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.88 (s, 1H, CH), 5.53 (s, 2H, NH_2), 7.01 (t, *J* = 8.00 Hz, 2H, ArH), 7.15 (dd, *J* = 7.52, 1.44 Hz, 1H, ArH), 7.20 (d, *J* = 8.60 Hz, 3H, ArH), 7.68 (d, *J* = 8.60 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 31.92, 51.88, 52.50, 55.73, 59.64, 104.05, 111.74, 120.82, 123.27, 127.25, 128.24, 132.85, 134.82, 142.21, 150.96, 156.19, 163.14, 165.13; FT-IR: 3820, 2466, 1675, 1480, 1343, 1244, 1184, 1082; HRMS of $[C_{23}H_{20}BrN_3O_5 + H]^+$ (m/z): 498.0644; Calcd: 498.0665.

Dimethyl-6-amino-1-(4-bromophenyll)-5-cyano-4-(4-methoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5b): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.42 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.89 (s, 1H, CH), 5.58 (s, 2H, NH_2), 6.96-7.04 (m, 2H, ArH), 7.15 (dd, *J* = 7.68, 1.26 Hz, 1H, ArH), 7.19-7.23 (m, 3H, ArH), 7.70 (d, *J* = 8.44 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 31.92, 51.85, 55.74, 59.76, 104.05, 111.74, 120.78, 120.82, 123.17, 127.23, 128.14, 132.20, 132.62, 132.99, 134.46, 142.27, 150.95, 156.20, 165.08; FT-IR: 3866, 2342, 1644, 1586, 1573, 1288, 1134, 1054; HRMS of $[C_{23}H_{20}BrN_3O_5 + H]^+$ (m/z): 498.0674; Calcd: 498.0665.

Dimethyl-6-amino-1-(4-bromophenyl)-5-cyano-4-(2-chlorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5c): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.38 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3),

4.37 (s, 1H, CH), 5.67 (s, 2H, NH_2), 6.90 (d, *J* = 1.44 Hz. 2H, ArH), 7.02-7.18 (m, 2H, ArH), 7.23 (d, *J* = 8.68 Hz, 2H, ArH), 7.69 (d, *J* = 8.64 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 30.63, 45.72, 51.91, 52.46, 59.88, 104.78, 113.49, 114.04, 115.73, 117.21, 120.87, 123.31, 129.64, 131.27, 132.26, 132.62, 134.27, 141.34, 146.69, 148.02, 150.55, 157.66, 162.96, 165.04; FT-IR: 3844, 2466, 1456, 1367, 1422, 1210, 1108, 1088; HRMS of $[C_{22}H_{17}BrClN_3O_4 + H]^+$ (m/z): 502.0148; Calcd: 502.0169.

Dimethyl-6-amino-1-(4-bromophenyll)-5-cyano-4-(4-bromophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5d): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.39 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 4.78 (s, 1H, CH), 5.78 (s, 2H, NH_2), 7.25-7.34 (m, 6H, ArH), 7.71 (d, *J* = 8.60 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 8.62, 30.64, 33.35, 45.75, 51.91, 52.48, 58.32, 102.81, 115.73, 115.78, 120.57, 123.40, 124.83, 129.04, 129.34, 131.83, 131.83, 131.96, 132.64, 134.62, 142.34, 150.89, 158.59, 161.04, 162.81, 164.79; FT-IR: 3829, 2480, 1505, 1450, 1399, 1394, 1224, 1100.

Dimethyl-6-amino-1-(4-bromophenyll)-5-cyano-4-(4-chlorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5e): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.37 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 4.49 (s, 1H, CH), 5.75 (s, 2H, NH_2), 7.25-7.31 (m, 4H, ArH), 7.43 (d, *J* = 8.44 Hz, 2H, ArH). 7.69 (d, *J* = 8.68 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 18.31, 38.08, 51.98, 52.54, 56.08, 59.27, 104.31, 115.86, 120.69, 123.49, 128.61, 128.76, 131.64, 132.27, 132.68, 134.43, 141.36, 144.19, 150.64, 162.84, 164.91; FT-IR: 3822, 2455, 1688, 1544, 1520, 1422, 1065, 1006; HRMS of $[C_{22}H_{17}BrClN_3O_4 + H]^+$ (m/z): 502.2573; Calcd: 502.2559.

Dimethyl-6-amino-1-(4-bromophenyll)-5-cyano-4-(2-fluorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5f): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.39 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 4.51 (s, 1H, CH), 5.78 (s, 2H, NH_2), 7.18-7.34 (m, 6H, ArH), 7.70 (d, *J* = 8.64 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 37.97, 51.93, 52.49, 59.64, 104.56, 115.39, 115.60, 120.73, 123.39, 128.57, 128.66, 132.34, 132.62, 134.62, 141.48, 150.57, 159.94, 162.35, 162.85, 164.93; FT-IR: 3798, 2455, 1644, 1424, 1398, 1255, 1248, 1097; HRMS of $[C_{22}H_{17}BrFN_3O_4 + H]^+$ (m/z): 486.0483; Calcd: 486.0465.

Dimethyl-6-amino-1-(4-bromophenyll)-5-cyano-4-(2,5-dimethoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5g): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.42 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.84 (s, 1H, CH), 5.61 (s, 2H, NH_2), 6.68 (d, *J* = 3.18 Hz, 1H, ArH), 6.80 (dd, *J* = 8.68, 3.08 Hz, 1H, ArH), 6.98 (d, *J* = 8.92 Hz, 1H, ArH), 7.16 (d, *J* = 8.71 Hz, 2H, ArH), 7.71 (d, *J* = 9.04 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 13.37, 30.63, 32.26, 45.77, 51.87, 52.51, 55.17, 56.43, 59.63, 62.59, 103.84, 111.80, 113.01, 113.70, 120.67, 121.46, 123.18, 132.07, 132.68, 134.18, 134.95, 142.37, 150.48, 150.95, 153.34, 163.08, 165.01; FT-IR: 3809, 2480, 1405, 1350, 1273, 1194, 1044, 1002; HRMS of $[C_{24}H_{22}BrN_3O_6 + H]^+$ (m/z): 528.0775; Calcd: 528.0770.

Dimethyl-6-amino-1-(4-bromophenyll)-5-cyano-4-(4-fluorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5h): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.39 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 4.36 (s, 1H, CH), 5.68 (s, 2H, NH_2), 6.76 (d, *J* = 8 48 Hz, 6H, ArH), 7.08 (d, *J* = 8.48 Hz, 2H, ArH), 7.24 (d, *J* = 8.60 Hz, 2H, ArH), 7.69 (d, *J* = 8.64 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 8.79, 37.67, 45.67, 51.84, 52.43, 60.32, 105.28, 115.41, 120.97, 123.26, 127.78, 131.27, 132.27, 132.60, 134.84, 135.82, 140.88, 150.39, 156.35, 163.02, 165.16; FT-IR: 3811, 2462, 1605, 1520, 1313, 1294, 1224, 1034.

Dimethyl-6-amino-1-(4-bromophenyll)-5-cyano-4-(2-ethylphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5i): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06 (t, *J* = 6.96 Hz, 3H, CH_3), 3.39 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2), 4.50 (s, 1H, CH), 5.81 (s, 2H, NH_2), 7.25-7.29 (m, 4H, ArH), 7.59 (d, *J* = 8.40 Hz, 2H, ArH), 7.70 (d, *J* = 8.64 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 18.48, 30.61, 38.24, 45.79, 51.94, 52.50, 55.00, 56.03, 59.24, 104.18, 120.66, 123.45, 128.98, 131.68, 132.35, 132.63, 134.55, 141.68, 144.71, 150.65, 162.79, 164.86; FT-IR: 3869, 2477, 1466, 1480, 1312, 1244, 1145, 1066.

Dimethyl-6-amino-1-(4-bromophenyll)-5-cyano-4-(2-bromophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (5j): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.37 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 4.48 (s, 1H, CH), 5.76 (s, 2H, NH_2), 7.24 (t, *J* = 8.92 Hz, 4H, ArH), 7.55 (d, *J* = 8.24 Hz, 2H, ArH), 7.68 (d, *J* = 8.59 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 18.34, 51.98, 52.53, 56.07, 59.19, 89.74, 104.22, 115.84, 120.12, 120.68, 123.48, 128.99, 131.69, 132.28, 132.67, 134.44, 141.59, 144.63, 150.64, 162.82, 164.89; FT-IR: 3866, 2324, 1420, 1344, 1234, 1122, 1066, 1024; HRMS of $[C_{22}H_{16}Br_2N_3O_4 + 2H]^+$ (m/z): 547.9636; Calcd: 547.9644.

4.6. Reusability of the catalyst

For cost effectiveness, recyclability and reusability of the material is of esteemed benefit in heterogeneous catalytic processes. In this work, the reusability of Y_2O_3/ZrO_2 in the synthesis of 1,4-dihydropyridines was examined under optimum reaction conditions. After completion of the reaction, the reaction mixture was filtered under vacuum and washed with ethyl acetate followed by drying in a vacuum oven at 110°C for 3 h. Then, the recovered catalyst was reused for a consequent fresh batch of the reaction and it can be used at least six runs without any minor loss in the yield of the desired product.

4.7. Conclusion

In summary, this study shows a highly efficient 2.5% Y_2O_3/ZrO_2 heterogeneous catalyst, which is used in synthesis of ten novel 1,4-dihydropyridine derivatives under green solvent conditions in excellent yields (88-95%). This novel procedure offers numerous advantages such as simple workup, cleaner reactions, green solvent, reduced reaction times, high yields, reusable catalyst and an eco-friendly approach. We assume this approach will find widespread applications in the fields of medicinal, combinatorial and drug discovery syntheses.

4.8. 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.

4.9. References

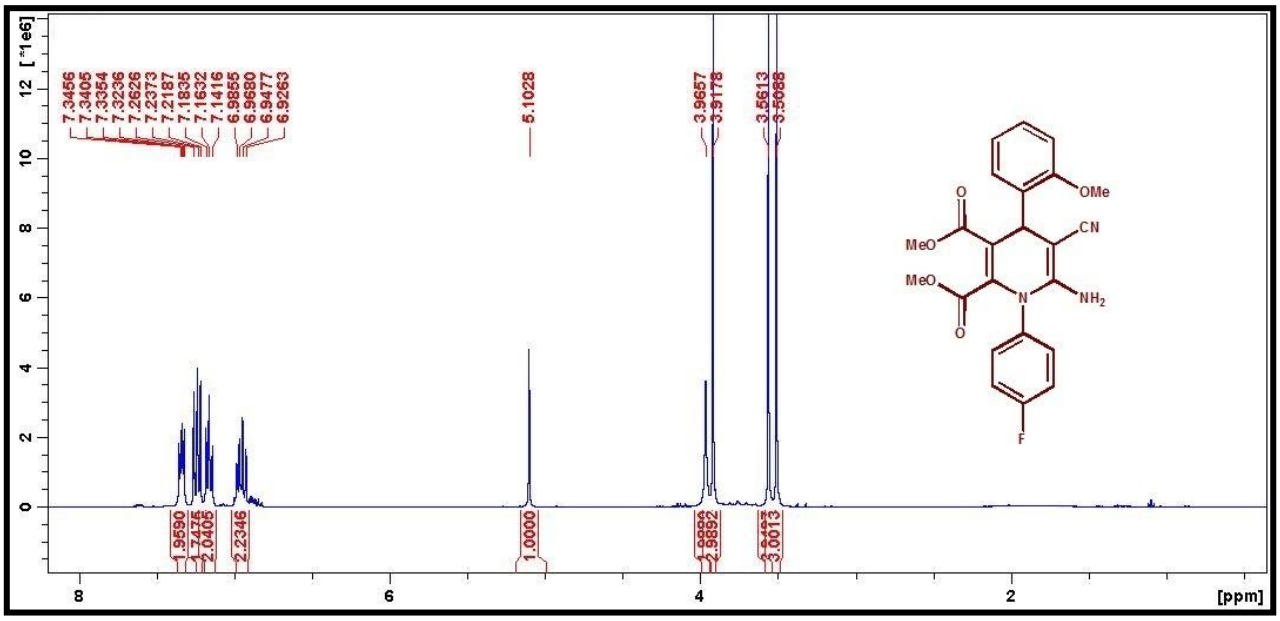
1. P. Anastas and N. Eghbali. *Chemical Society Reviews.* **2010**, *39*, 301.
2. R. A. Sheldon. *Journal of Molecular Catalysis.* **2016**, *422*, 3.
3. P. T. Anastas and M. M. Kirchhoff. *Accounts of Chemical Research***. 2002**, *35*, 686.
4. S. N. Maddila, S. Maddila, K. K. Gangu, W. E. van Zyl and S. B. Jonnalagadda. *Journal of Fluorine Chemistry.* **2017**, *195*, 79,
5. S. Maddila, K. K. Gangu, S. N. Maddila and S. B. Jonnalagadda. *Molecular Diversity.* **2017**, *21*, 247.
6. P. Slobbe, E. Ruijter and R. V. A. Orru. *Medicinal Chemistry Communication.* **2012,** *3*, 1189.

7. K. K. Gangu, S. Maddila, S. N. Maddila and S. B. Jonnalagadda. *RSC Advances.* **2016**, *6*, 58226.
8. L. Weber. *Drug Discovery Today*. **2002**, *7*, 143.
9. B. Ganem. *Accounts of Chemical Reserch.* **2009**, *42(3)*, 463.
10. E. Marsault, and M. L. Peterson. *Journal of Medicinal Chemistry*, **2011**, *54* (7), 1961.
11. S. N. Maddila, S. Maddila, W. E. Van Zyl and S. B. Jonnalagadda. *Current Organic Chemistry*. **2016**, *20(20)*, 2125.
12. K. K. Gangu, S. Maddila, S. N. Maddila and S. B. Jonnalagadda. *RSC Advances.* **2016,** *21*, 1281.
13. A. H. M. Elwahy, and M. R. Shaaban. *RSC Advances.* **2015**, *5*, 75659.
14. A. H. Chughtai, N. Ahmad, H. A. Younus, A. Laypkov and F. Verpoort, *Chemical Society Reviews.* **2015**, *44*, 6804.
15. A. Dhakshinamoorthy, A. M. Asiri and H. Garcia. *Chemical Society Reviews*. **2015**, *44*, 1922.
16. M. B. Gawande, P. S. Branco and R. S. Varma. *Chemical Society Reviews*. **2013**, *42*, 3371.
17. S. N. Maddila, S. Maddila, W. Van Zyl and S. B. Jonnalagadda. *Current Organic Synthesis.* **2016**, *13(6)*, 893.
18. S. N. Maddila, S. Maddila, W. Van Zyl and S. B. Jonnalagadda *Chemistry Open.* **2016**, *5*, 38,
19. S. Maddila, S. Rana, R. Pagadala, and S. B. Jonnalagadda. *Research on Chemical Intermediates.* **2015**, *41*, 8269.
20. R. Chorghade, C. Battilocchio, J. M. Hawkins, and S. V. Ley. *Organic Letters*. **2013**, *15(22)*, 5698.
21. M.E. Borges and L. *Renewable and Sustainable Energy Reviews.* **2012**, *16*, 2839.
22. W. Morris, B. Volosskiy, S. Demir, F. Gandara, P. L. McGrier, H. Furukawa, D. Cascio, J. F. Stoddart, and O. M. Yaghi. *Inorganic Chemistry*. **2012**, *51(12)*, 6443.
23. M. Mamak, N. Coombs, and G. Ozin. *Chemical Society*. **2000**, *122 (37)*, 8932.
24. J. Y. Chane-Ching, F. Cobo, D. Aubert,m H. G. Harvey, M. Airiau and A. Corma. *Chemistry A European Journal*. **2005**, *11*, 979.

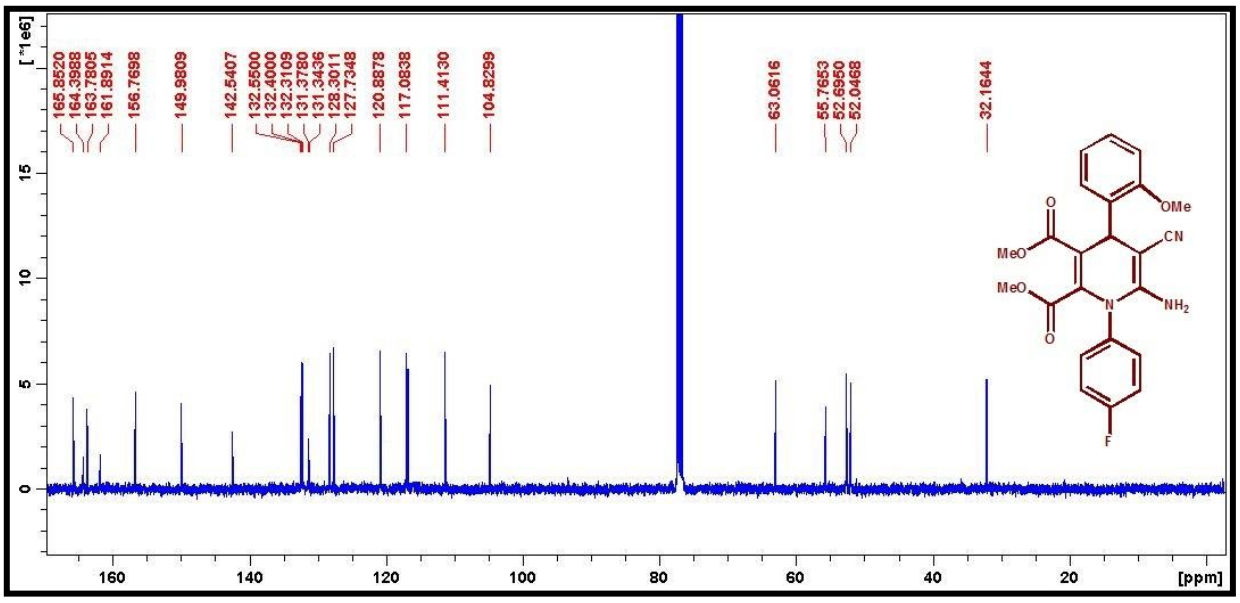
25. R. Craciun, B. Nentwick, K. Hadjiivanov and H. Knözinger. *Applied Catalysis A: General.* **2003**, *243*, 67.
26. Y. G. Zheng, J. Su, C. Y. Gao, P. Jiang, L. An, Y. S. Xue, J. Gao and Y. Liu. *European Journal of Medicinal Chemistry.* **2017**, *130*, 393.
27. S. Maddila, K. Naicker, S. Gorle, S. Rana, K. Yalagala, S. N. Maddila, M. Singh, P. Singh and S. B Jonnalagadda. *Anti-Cancer Agents in Medicinal Chemistry.* **2016,** *16(8),* 1031.
28. S. Maddila, R. Pagadala and S. B. Jonnalagadda. *Letters in Organic Chemistry*. **2013,** *10(10),* 693.
29. J. Akhtar, A. A. Khan, Z. Ali, R. Haider and Y. M. Shahar. *European Journal of Medicinal Chemistry*. **2017**, *125*, 143.
30. O. Delgado, F. Delgado, J. A. Vega and A. A. Trabanco, *European Journal of Medicinal Chemistry*, **2015**, *97*, 71.
31. S. M. Nkosi, K. Anand, S. Anandakumar, S. Singh A. A. Chuturgoon and R. M. Gengan. *Journal of Photochem Photobiol B.* **2016**, *165*, 266.
32. J. Dam, Z. Ismail, T. Kurebwa, N. Gangat, L. Harmse, H. M. Marques, A. Lemmerer and M. L. Bode. *European Journal of Medicinal Chemistry*. **2017**, *126*, 353.
33. W. E. Santana, C. V. Nunez and M. D. Moya. *Natural Product Communications.* **2015**, *11(182),* 1.
34. R. M. Ribeiro-Viana, A. P. Butera, E. S. Santos, C. A. Tischer, R. B. Alves, R. Pereira de Freitas, L. Guimaraes, F. P. Varotti and G. H. Viana. *International Journal of Chemical Modeling.* **2016**, *56(3),* 571.
35. E. M. Kirwen, T. Batra, C. Karthikeyan, G. D. Singh, V. Rathore, C. Mulakayala, N. Mulakayala, A. C. Nusbaum, J. Chen, H. Amawi, K. McIntosh, B. Sahabjada, N. Shivnath, D. Chowarsia, N. Sharma, M. Arshad, P. Trivedi and A. K. Tiwari. *Acta Pharmaceutica Sinica B.* **2017**, *7(1),* 73.
36. J. Yang, W. Chen, D. Kang, X. Lu, X. Li, Z. Liu and B. Huang. *European Journal of Medicinal Chemistry.* **2016**, *109*, 294.
37. N N.E. El-Sayed, M. A. Abdelaziz, W. W. Wardakhan and R. M. Mohareb. *Steroids.* **2016,** *107*, 98.
38. D. S. Rekunge, C. K. Khatri and G. U. Chaturbhuj. *Tetrahedron Letters,* **2017,** *58(12),* 1240.

39. Q. Zhong, Q. Fan and H. Yan. *Tetrahedron Letters,* **2017,** *58(13),* 1292.
40. G. Sabitha, G. S. K. K. Reddy and C. S. Reddy and J. S. Yadav. *Tetrahedron Letters.* **2003,** *44(21),* 4129.
41. S. Pal, V. Singh, P. Das and L. H. Choudhury. *Bioorganic Chemistry.* **2013**, *48*, 8-15.
42. J. Sun, E.Y. Xia, Q. Wu and C.G. Yan. *Organic Letters.* **2010,** *12,* 3678.
43. S. Ko, M.N.V. Sastry, C. Lin and C. F. Yao. *Tetrahedron Letters*. **2005**, *46*, 5771.
44. K. K. Gangu, S. Maddila and S. B. Jonnalagadda. *ACS-Industrial & Engineering Chemistry Research.* **2017**, *56,* 2917.
45. N. Shabalala, S. Maddila and S. B. Jonnalagadda. *New Journal of Chemistry.* **2016,** *40,* 5107.
46. S. Maddila, M. Momin, P. Lavanya and C. V. Rao. *Journal of Saudi Chemical Society.* **2016**, *20,* 173.
47. S. N. Maddila, S. Maddila, W. Van Zyl and S. B. Jonnalagadda. *Chemistry Open.* **2016**, *5*, 38.
48. S. Maddila, S. N. Maddila, S. B. Jonnalagadda and P. Lavanya. *Journal of Heterocyclic Chemistry.* **2016,** *53,* 658.
49. S. Maddila, P. Lavanya and S. B. Jonnalagadda. *Arabian Journal of Chemistry.* **2016** *9(6),* 891.
50. S. Maddila, S. Gorle, N. Seshadri, P. Lavanya and S. B. Jonnalagadda. *Arabian Journal of Chemistry.* **2016**, *9,* 681.
51. S. Maddila, S. Gorle, M. Singh, P. Lavanya and S. B. Jonnalagadda. *Letters in Drug Design & Discovery*. **2013,** 10(10), 977.
52. S. Maddila, R. Pagadala and S. B. Jonnalagadda. *Journal of Heterocyclic Chemistry.* **2015**, *52(2),* 487.
53. S. Gorle, S. Maddila, S. N. Maddila, K. Naicker, M. Singh, P. Singh and S. B. Jonnalagadda. Synthesis. *Anti-Cancer Agents in Medicinal Chemistry.* **2017**, *17,* 464.
54. S. Maddila, K. Naicker, M. Momin, S. Rana, S. Gorle, S. N. Maddila, K. Yalagala, M. Singh and S. B Jonnalagadda. *Medicinal Chemistry Research.* **2016**, *25*, 283.

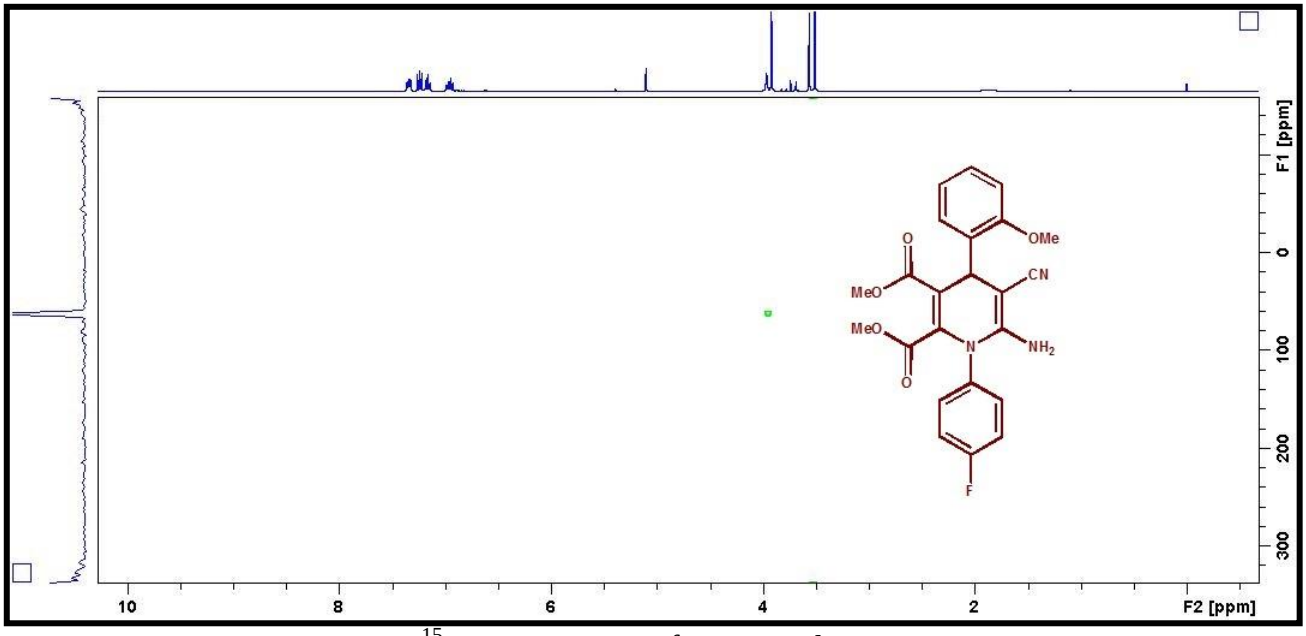
4.10. Supporting information



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



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

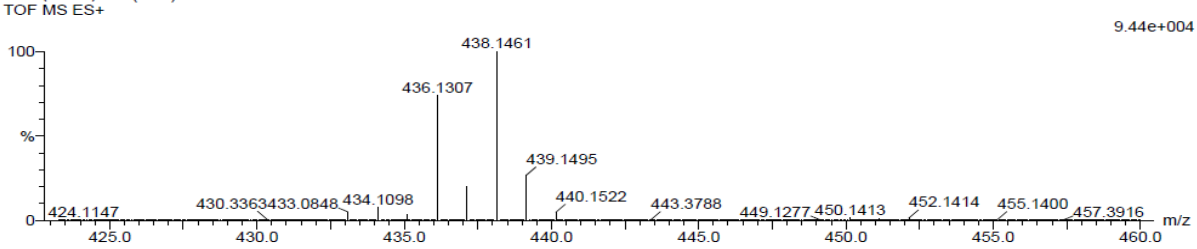


^{15}N NMR spectra of compound **5a**

Elemental Composition Report **Page 1**

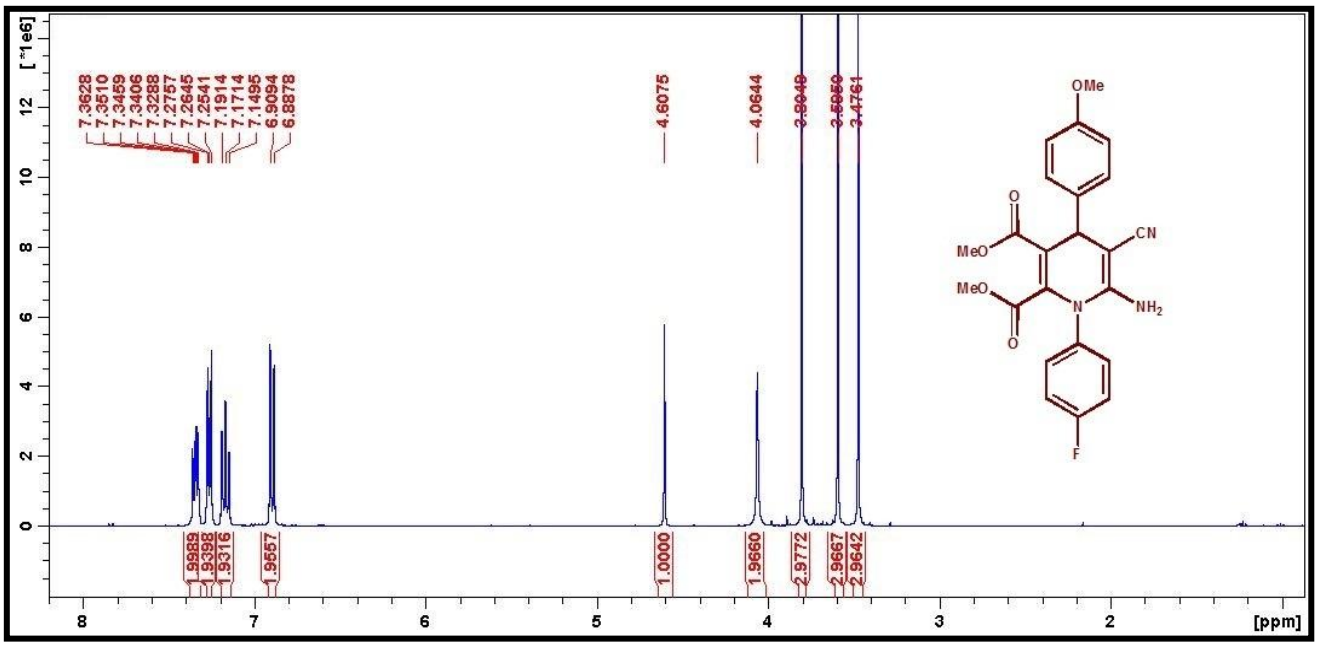
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

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

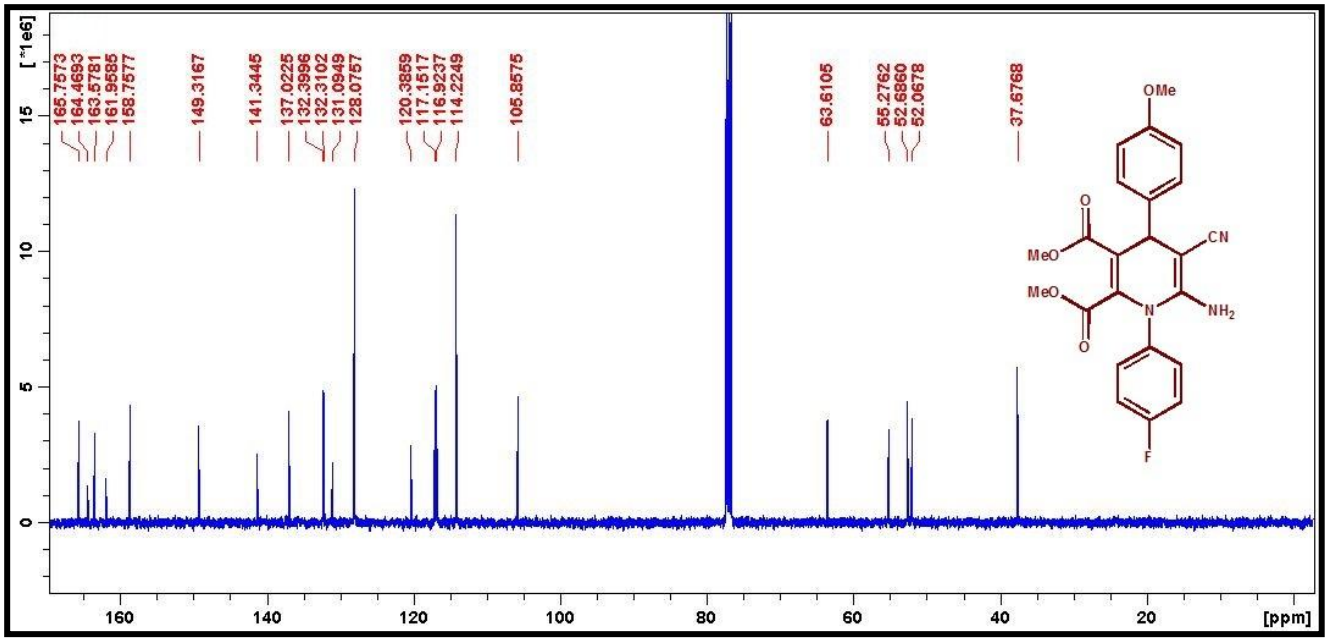


Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
438.1461	438.1465	-0.4	-0.9	14.5	532.1	0.0	C23 H21 N3 O5 F

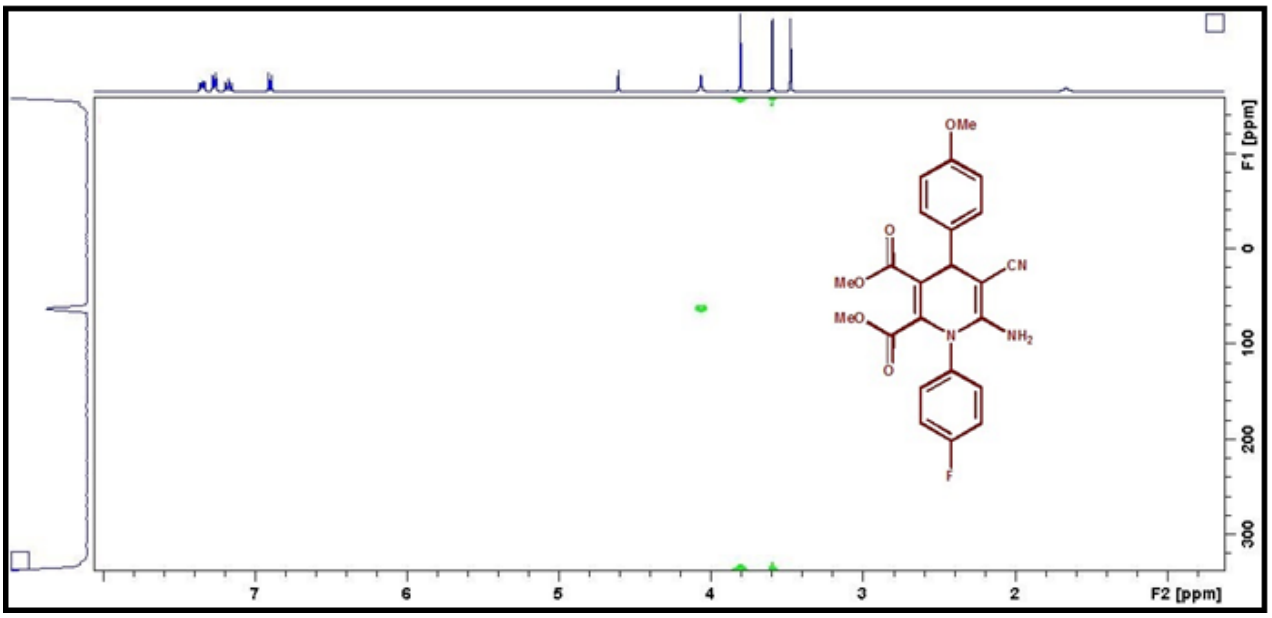
HRMS spectra of compound **5a**



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



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

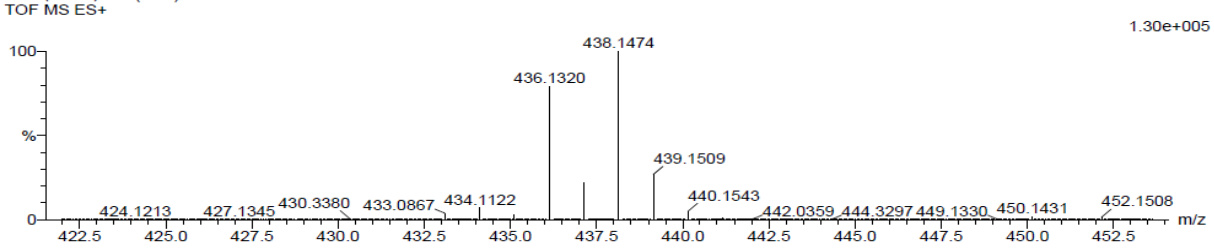


^{15}N NMR spectra of compound **5b**

Elemental Composition Report Page 1

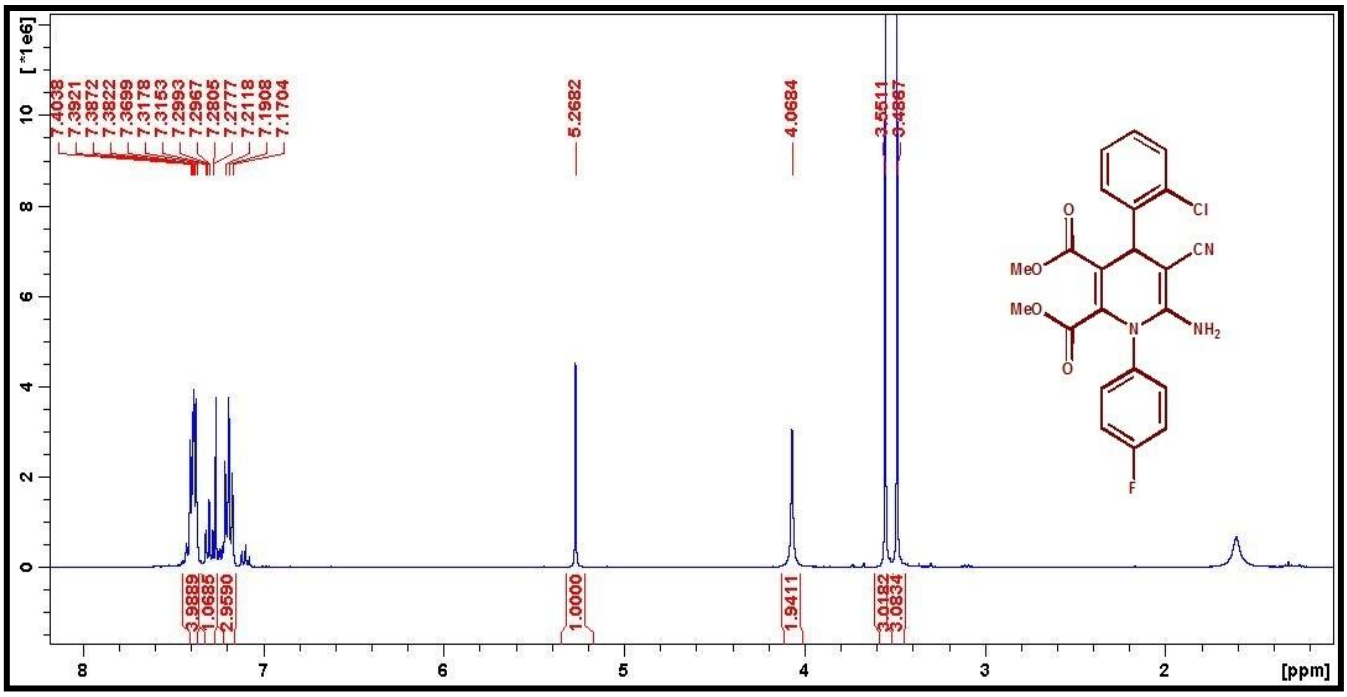
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
28 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 20-25 N: 0-5 O: 0-5 F: 0-1
F2 3 (0.068) Cm (1:61)
TOF MS ES+

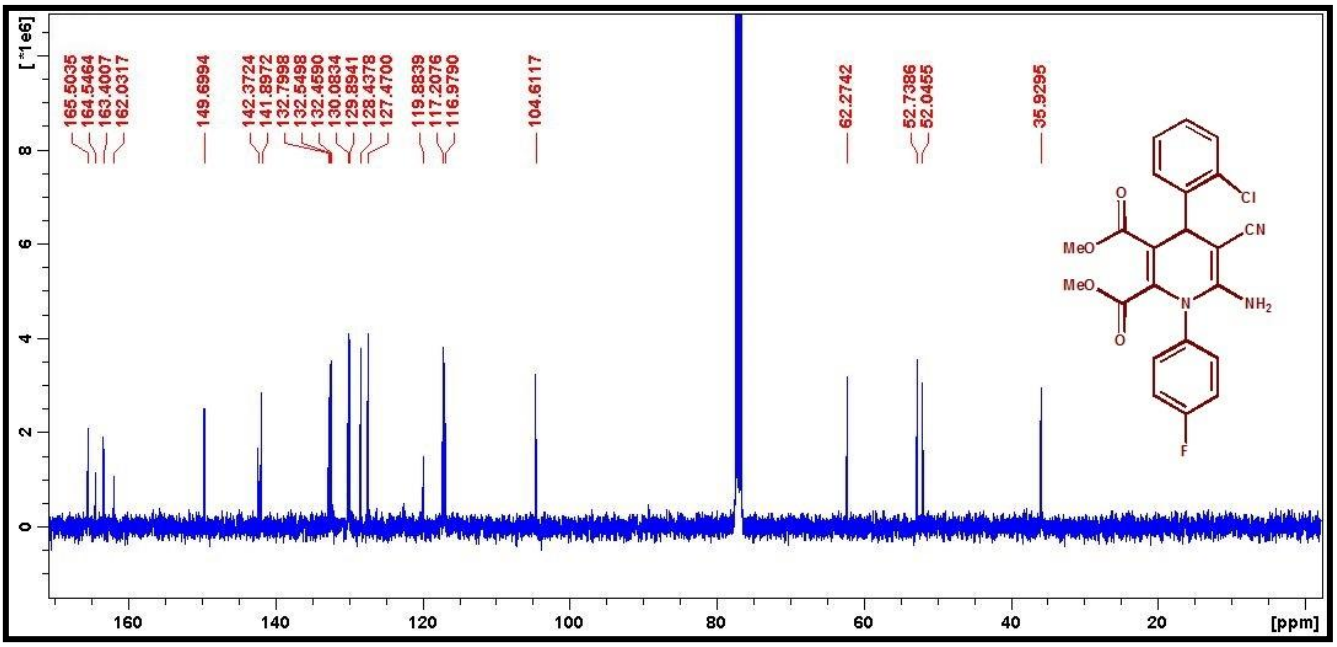


Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
438.1474	438.1465	0.9	2.1	14.5	549.0	0.0	C23 H21 N3 O5 F

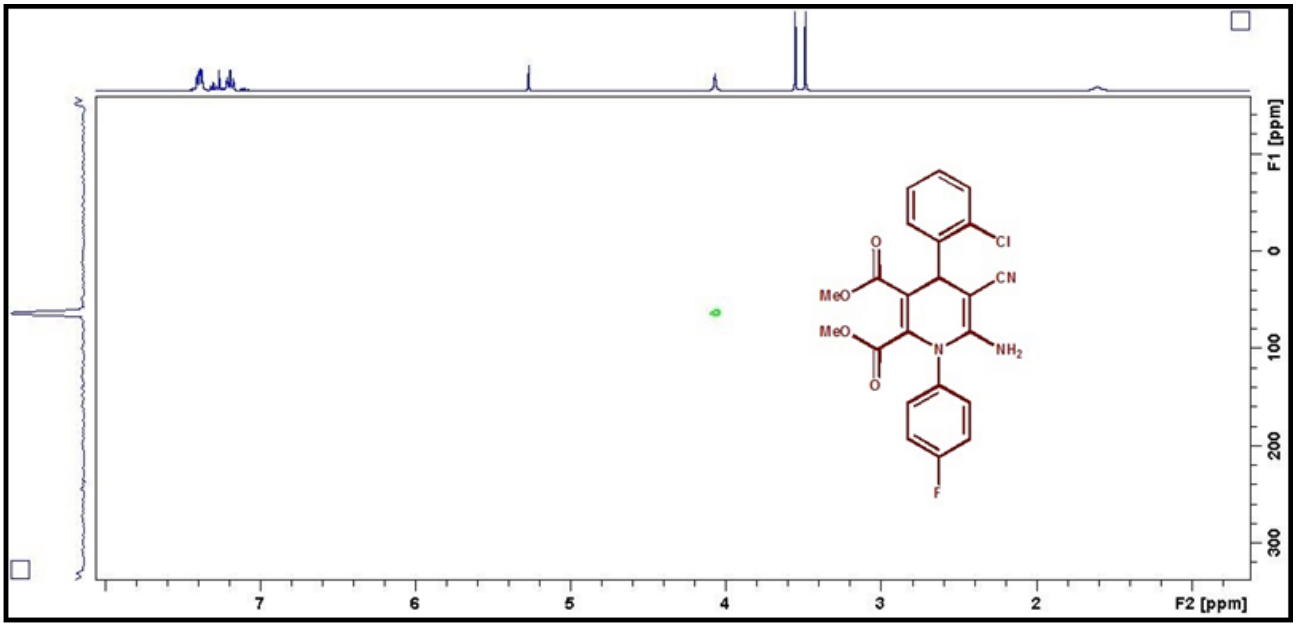
HRMS spectra of compound **5b**



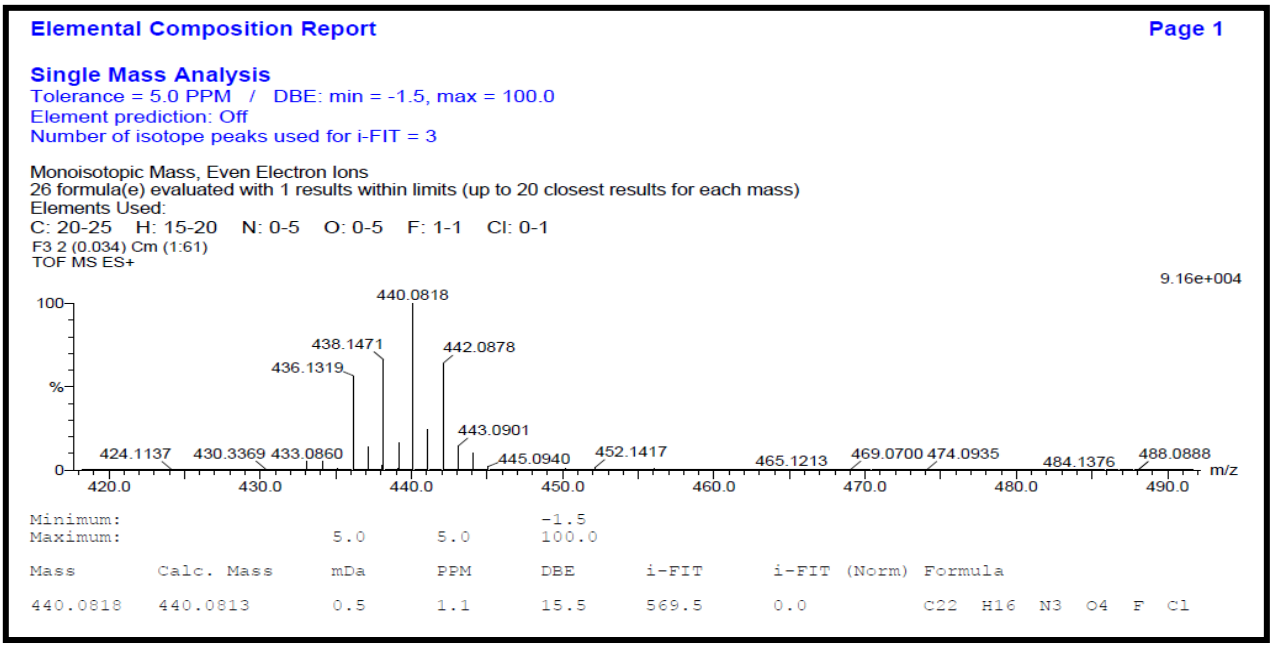
^{1}H NMR spectra of compound **5c**



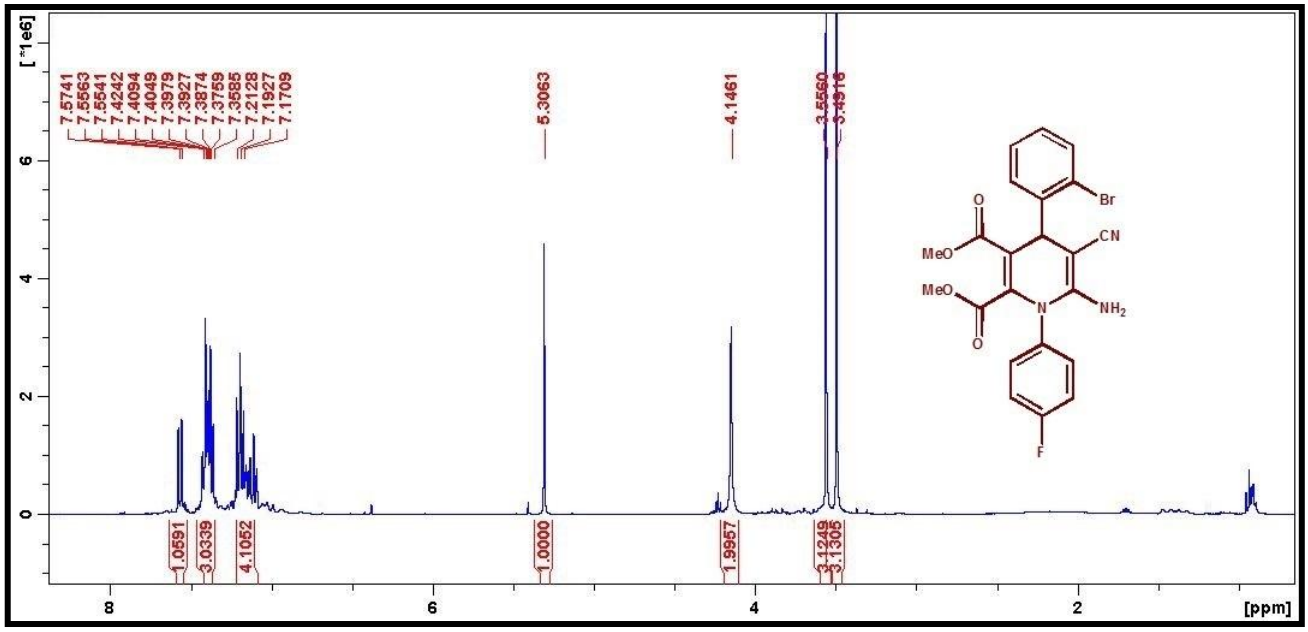
^{13}C NMR spectra of compound **5c**



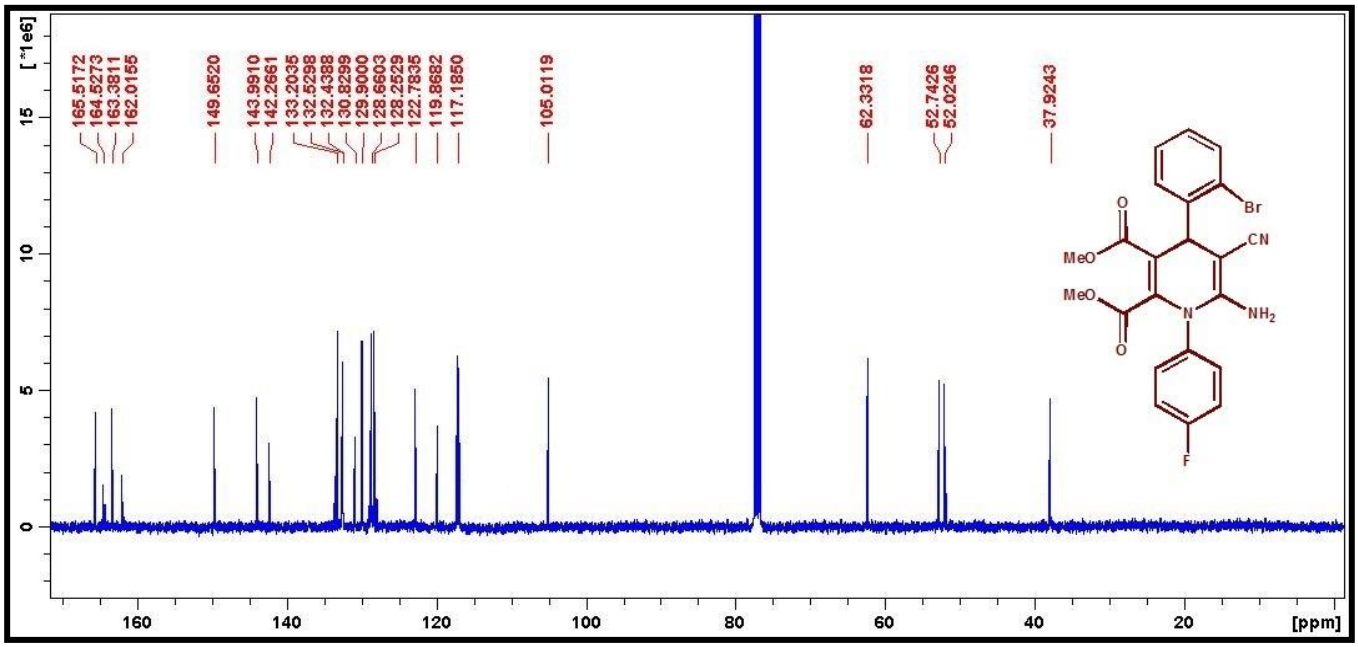
^{15}N NMR spectra of compound **5c**



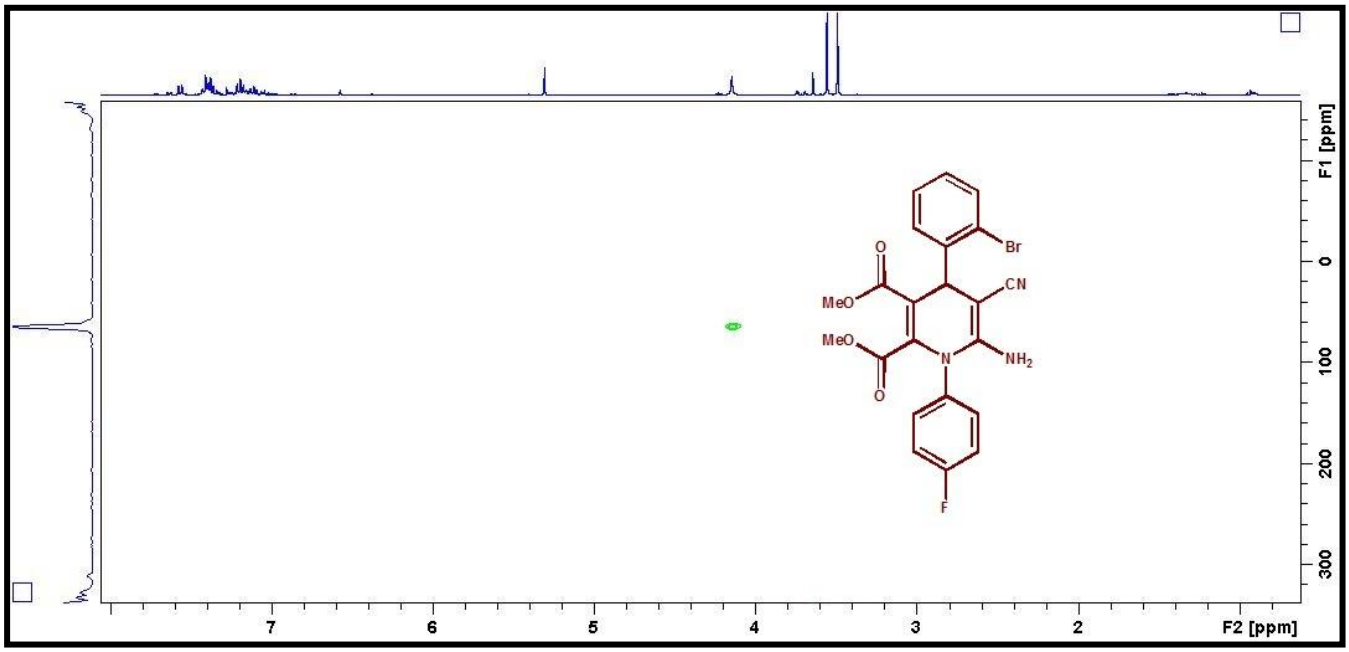
HRMS spectra of compound **5c**



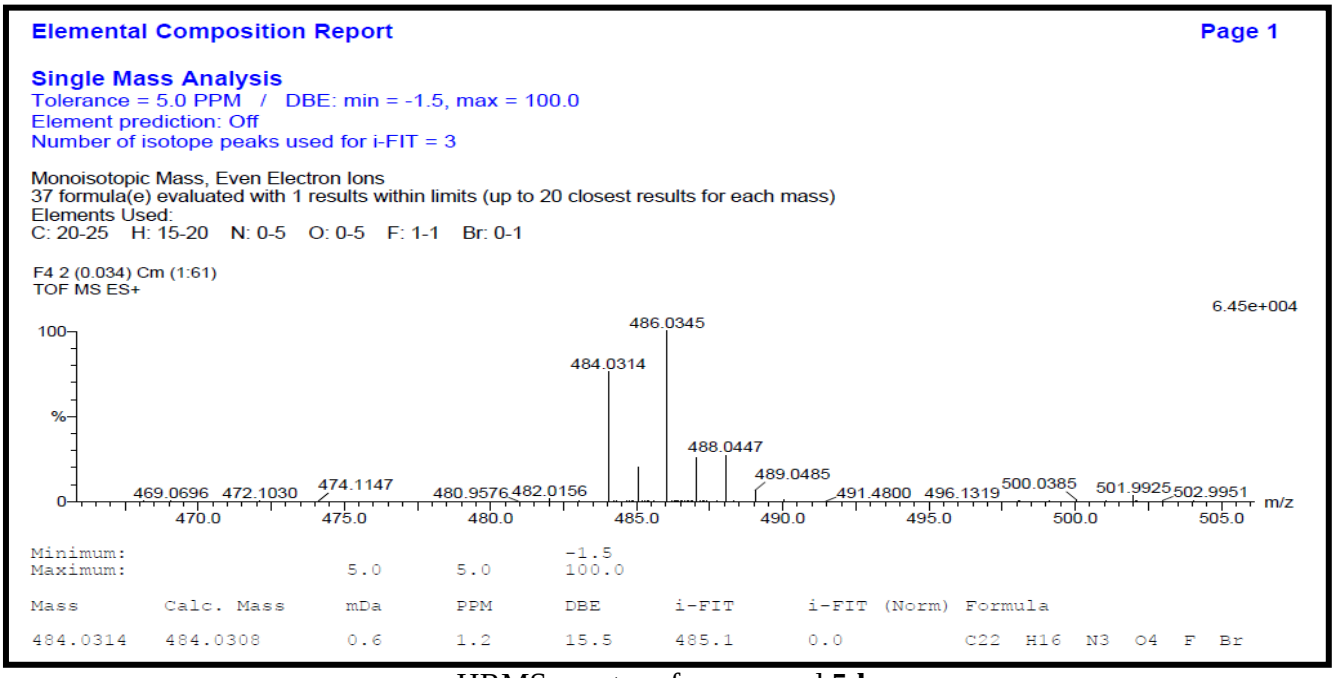
^{1}H NMR spectra of compound **5d**



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



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



Elemental Composition Report Page 1

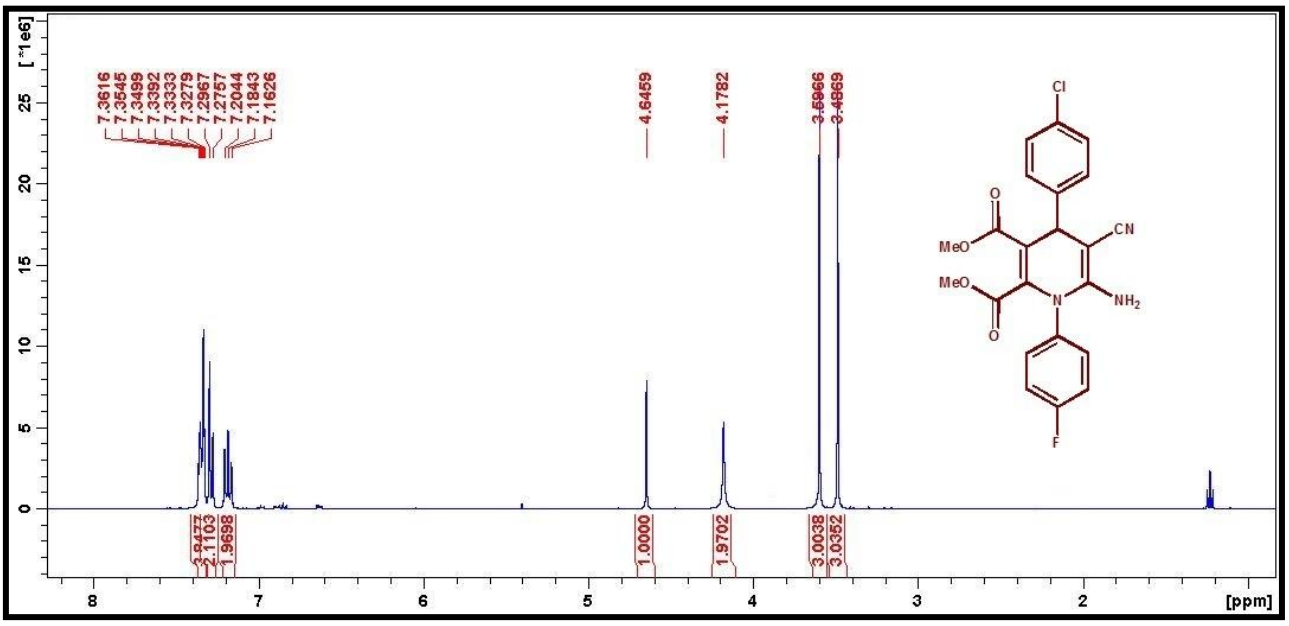
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
37 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 15-20 N: 0-5 O: 0-5 F: 1-1 Br: 0-1

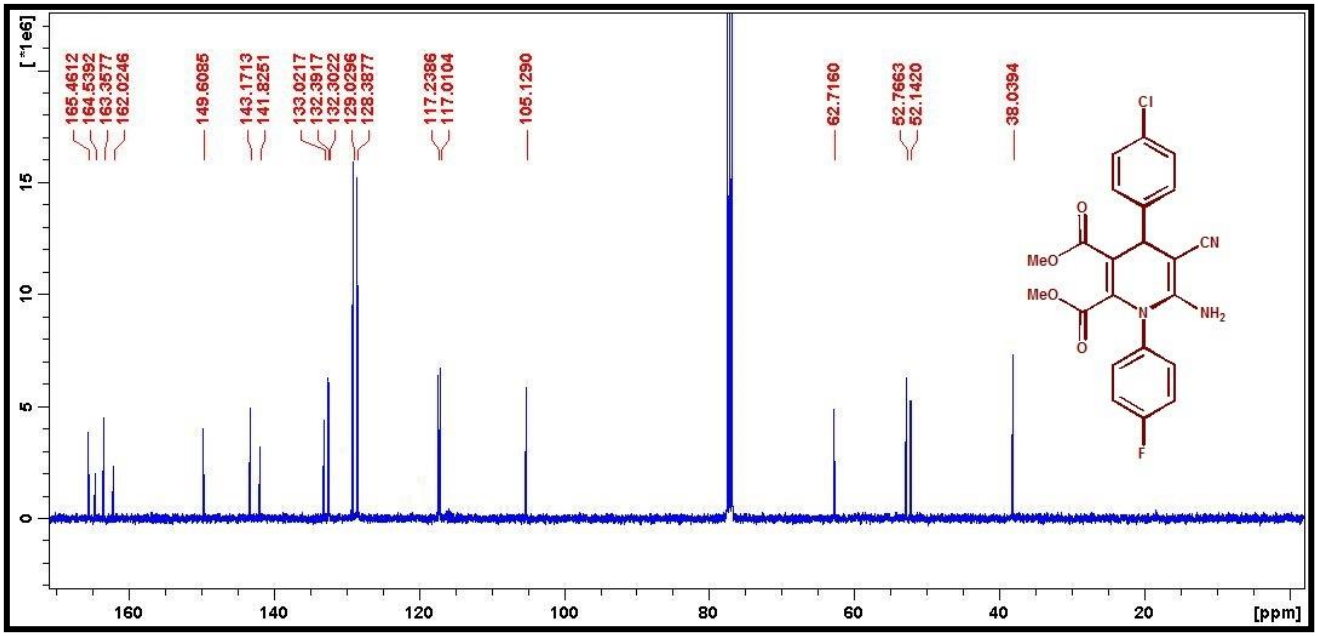
F4 2 (0.034) Cm (1:61)
TOF MS ES+
6.45e+004

Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
484.0314	484.0308	0.6	1.2	15.5	485.1	0.0	C22 H16 N3 O4 F Br

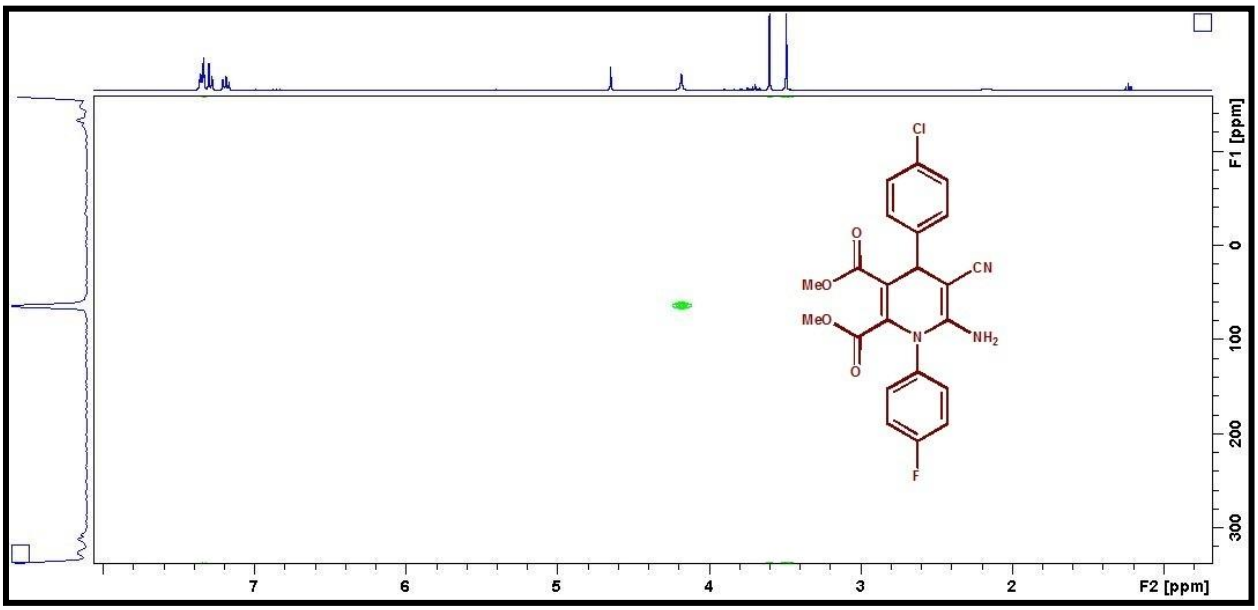
HRMS spectra of compound **5d**



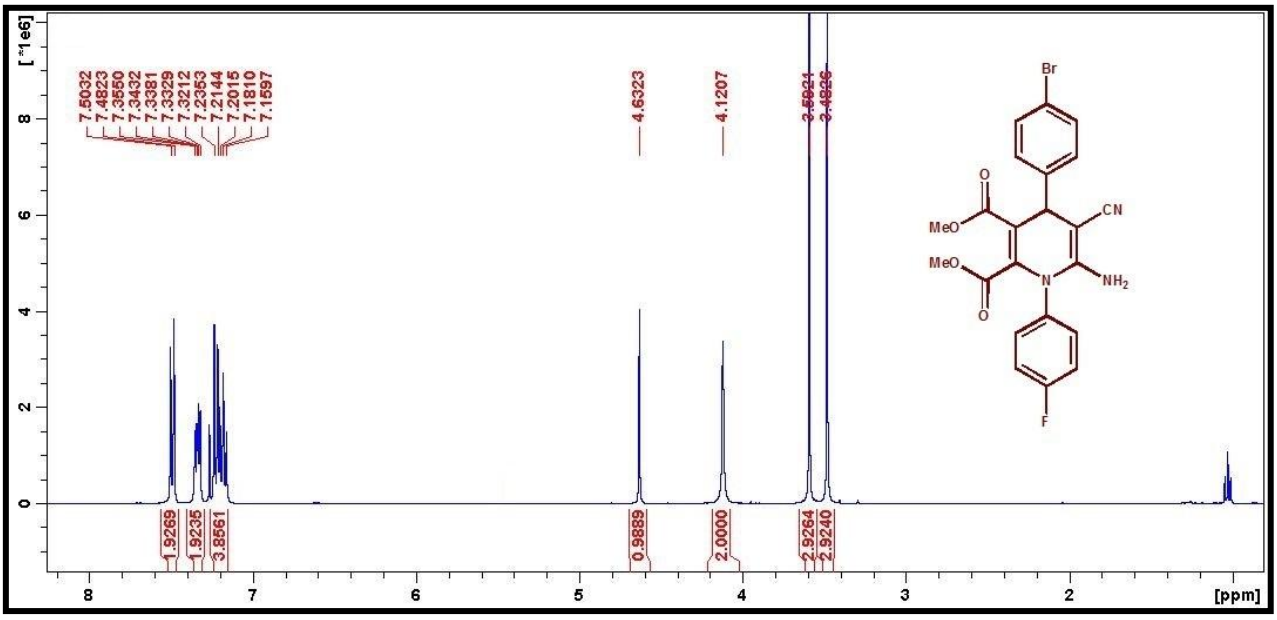
^{1}H NMR spectra of compound **5e**



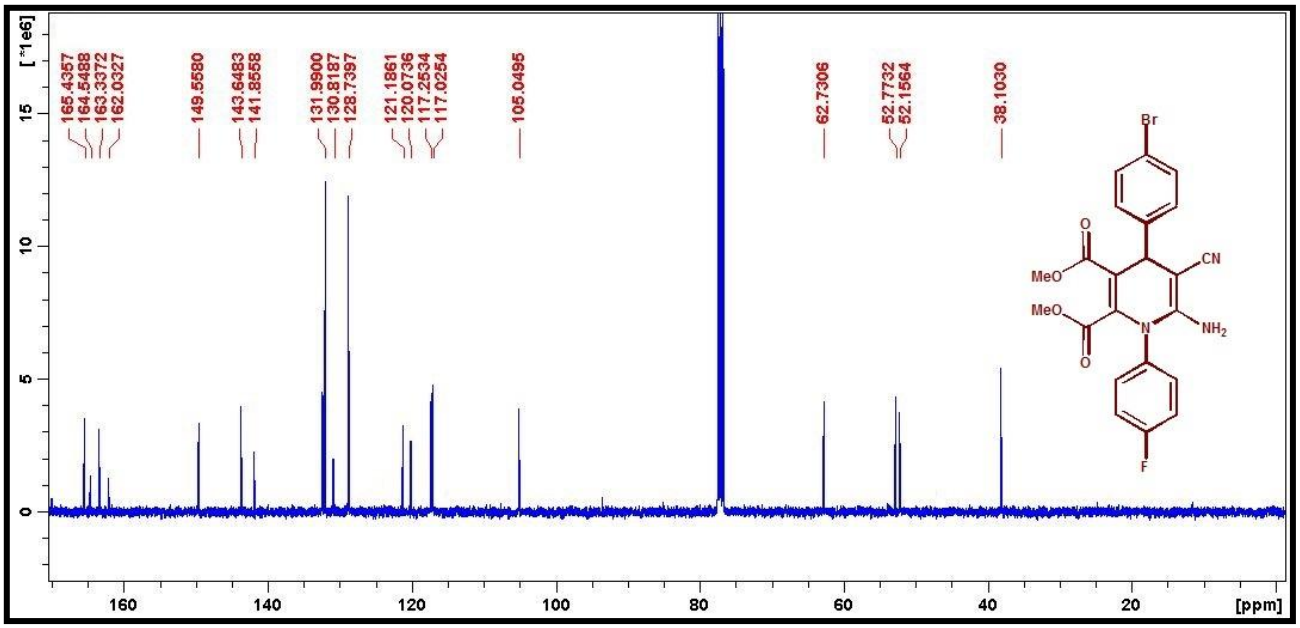
^{13}C NMR spectra of compound **5e**



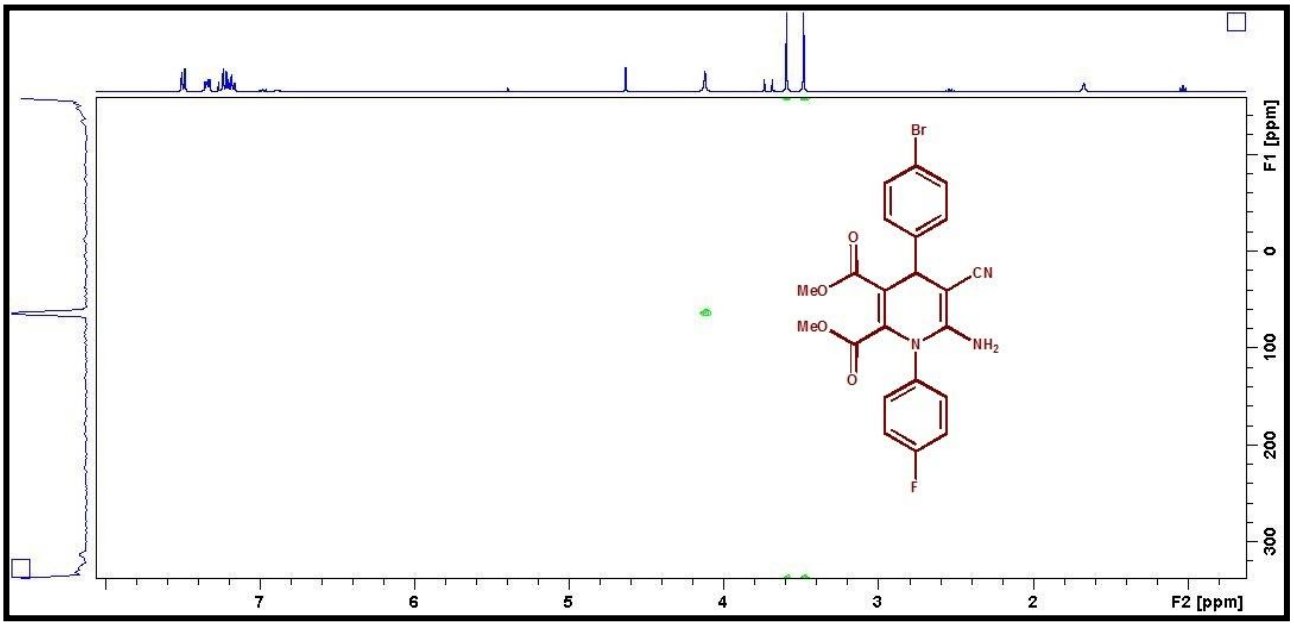
^{15}N NMR spectra of compound **5e**



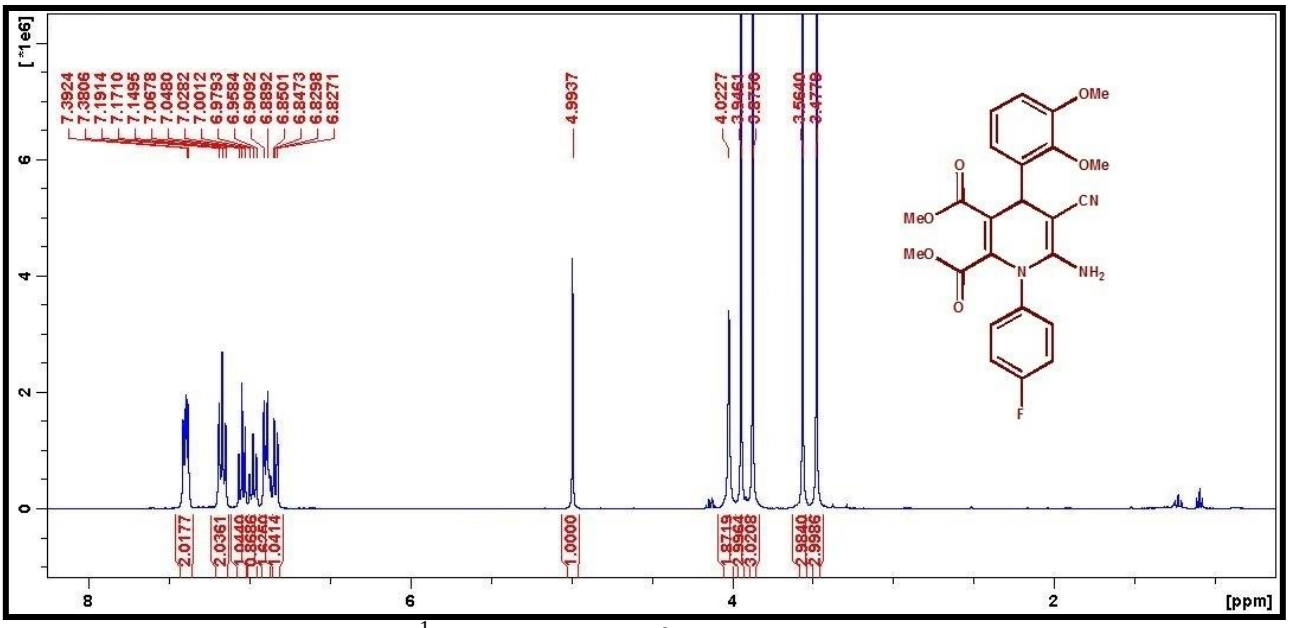
^{1}H NMR spectra of compound **5f**



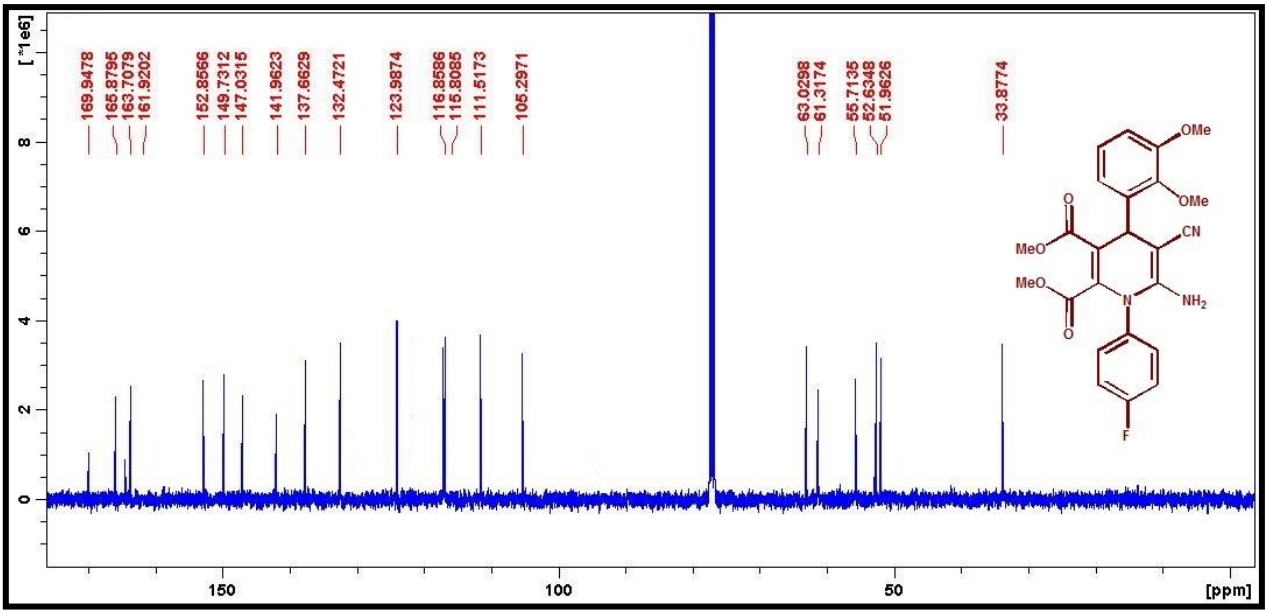
^{13}C NMR spectra of compound **5f**



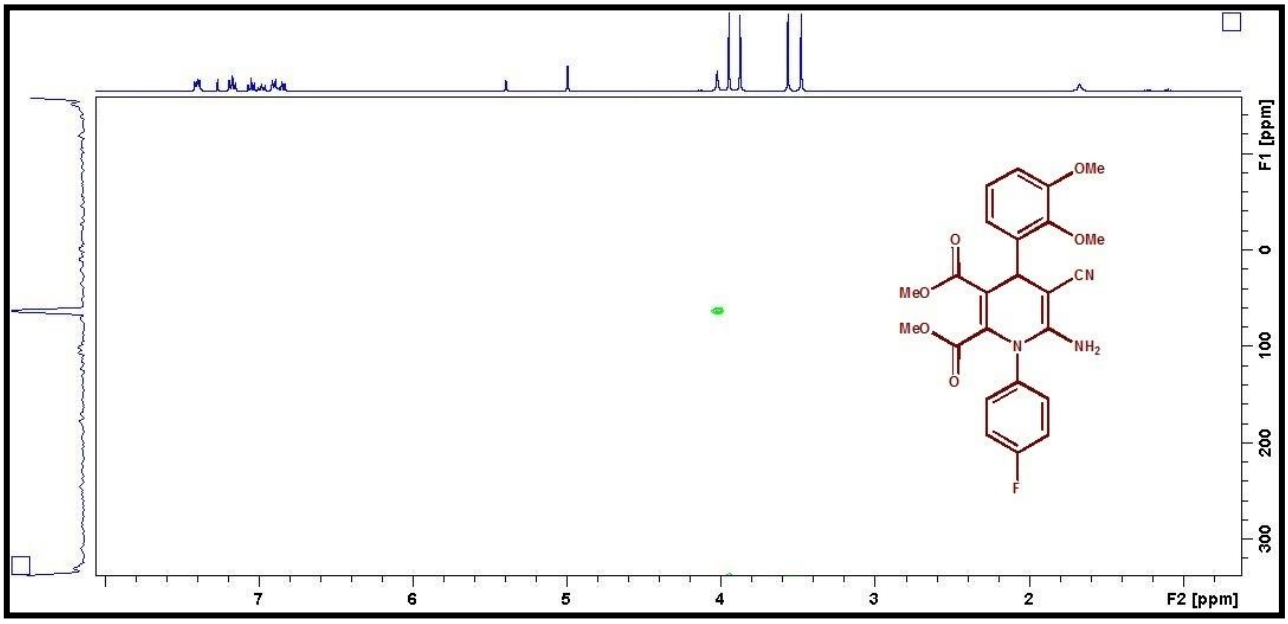
^{15}N NMR spectra of compound **5f**



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



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

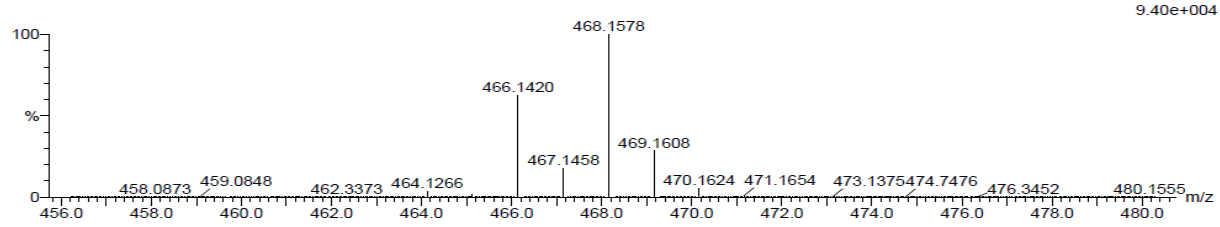


^{15}N NMR spectra of compound **5g**

Elemental Composition Report **Page 1**

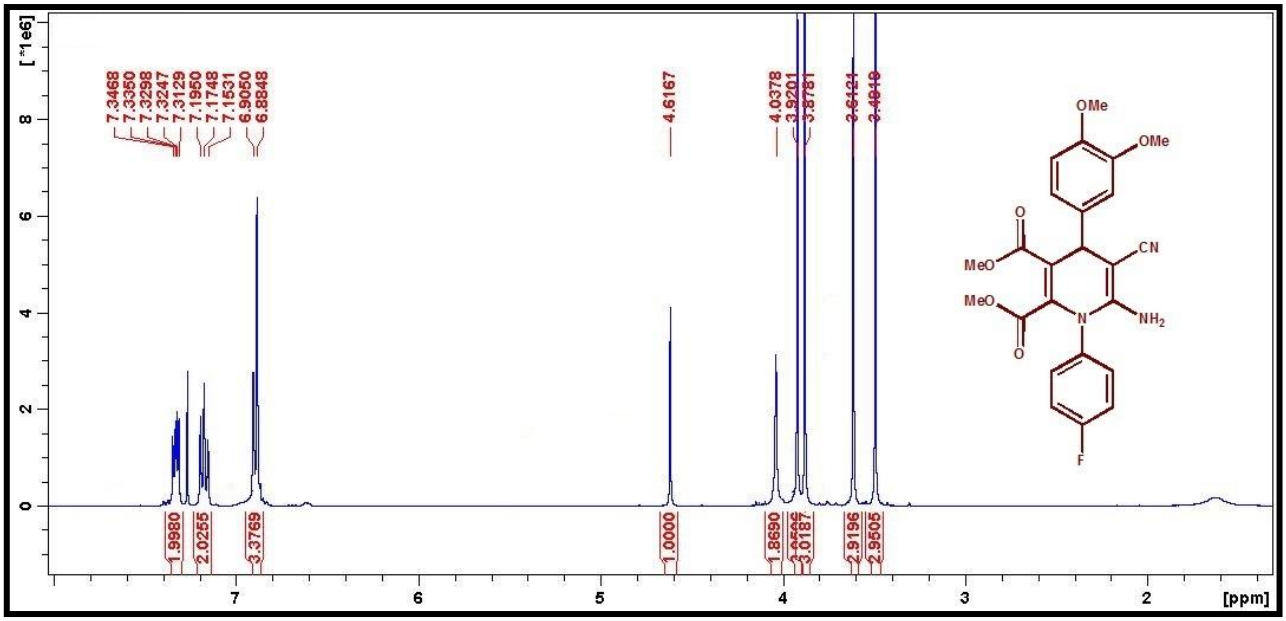
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

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

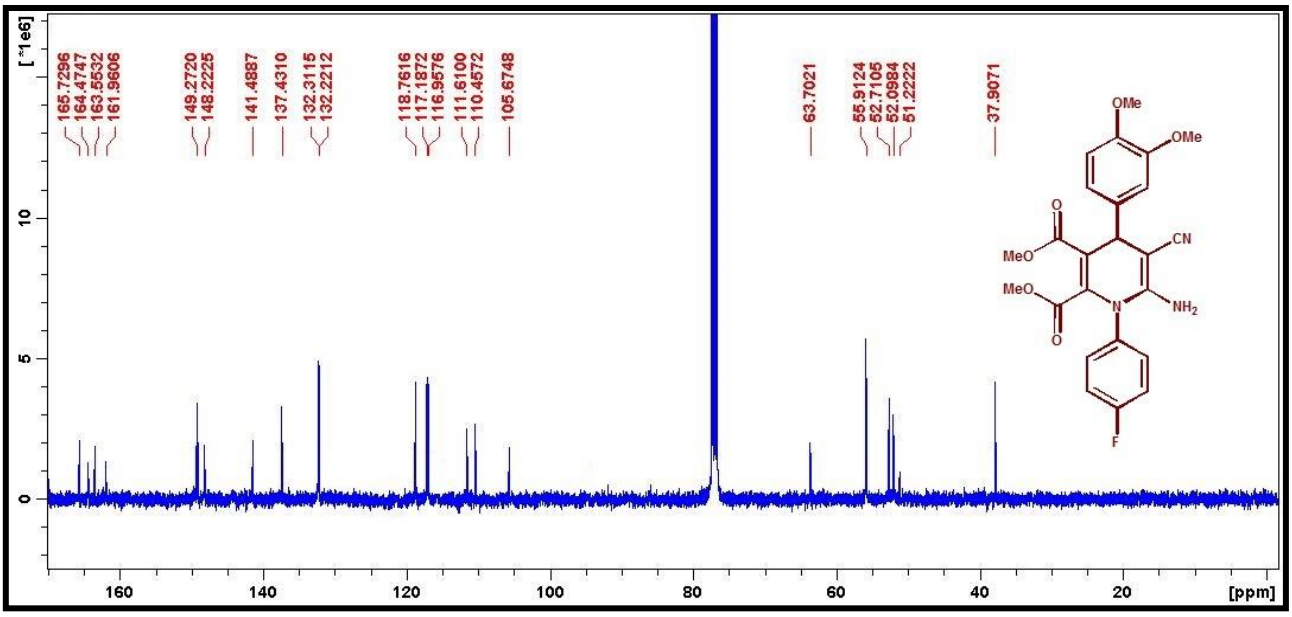


Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
468.1578	468.1571	0.7	1.5	14.5	499.7	0.0	C24 H23 N3 O6 F

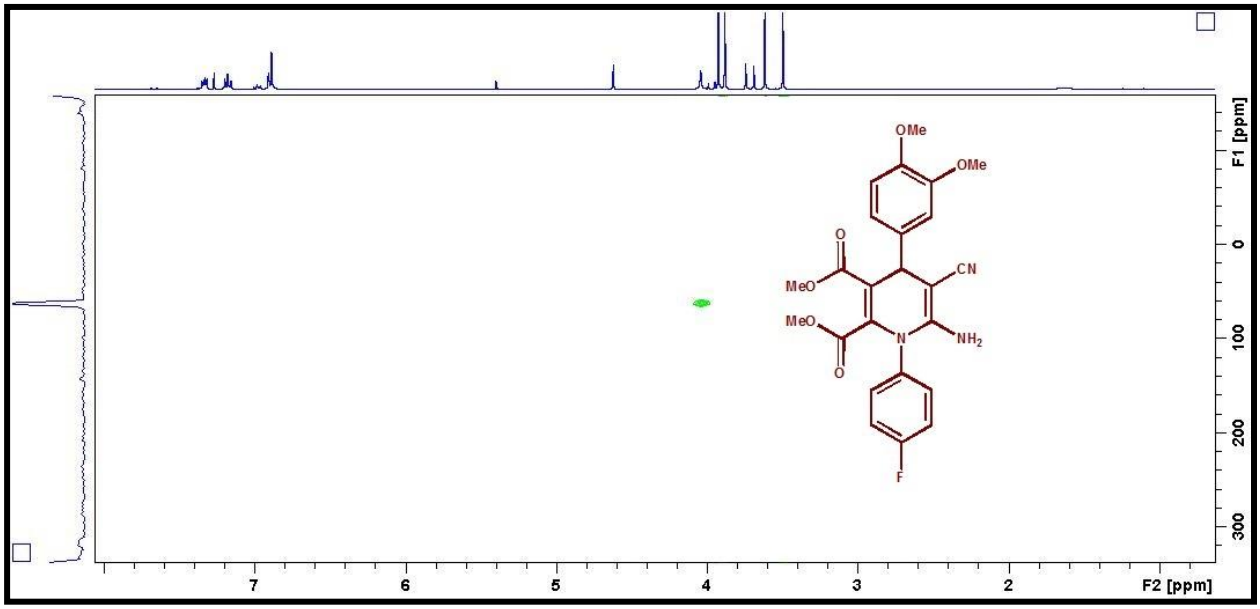
HRMS spectra of compound **5g**



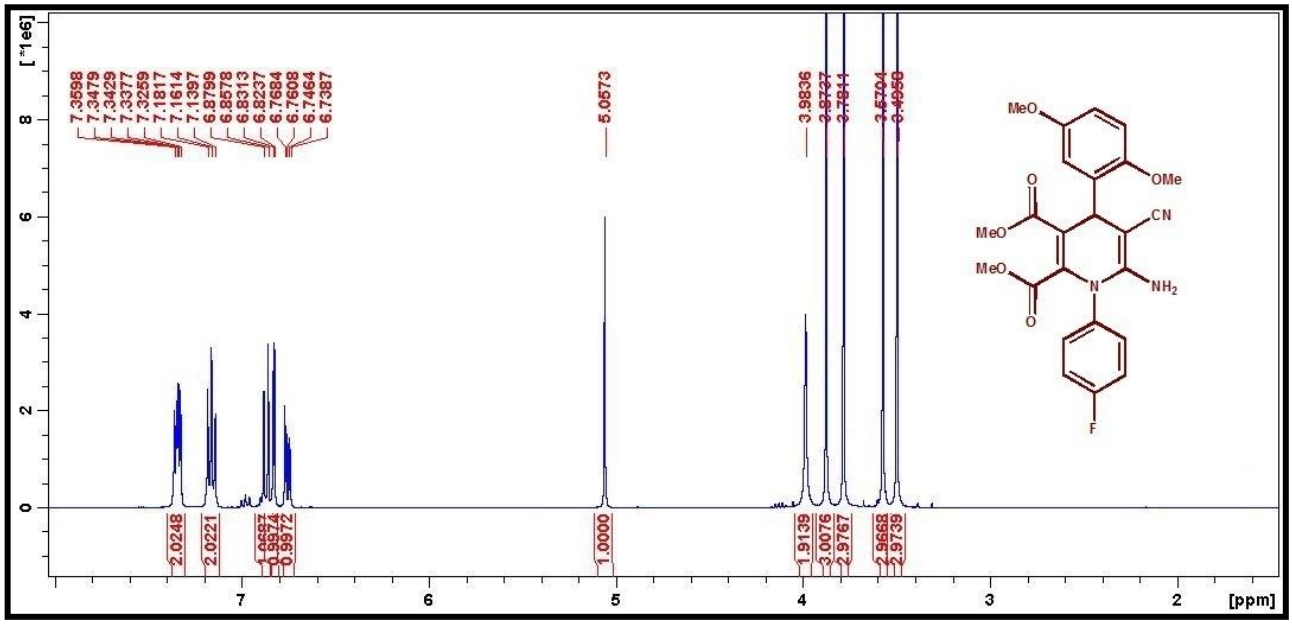
^{1}H NMR spectra of compound **5h**



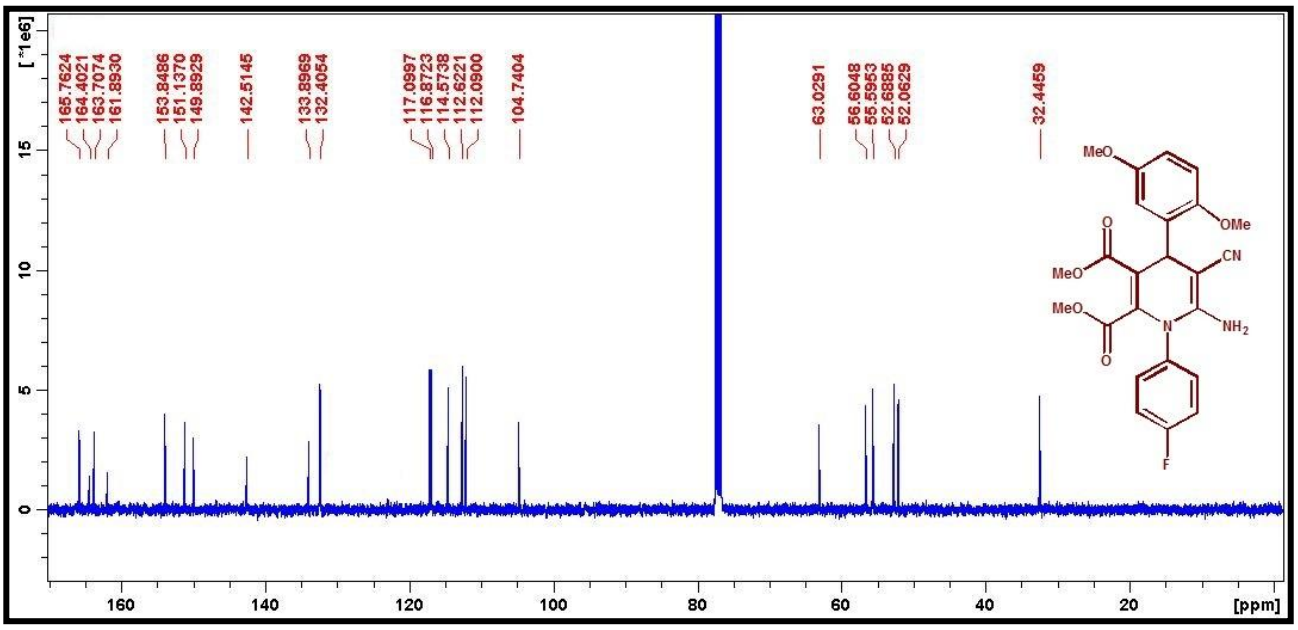
^{13}C NMR spectra of compound **5h**



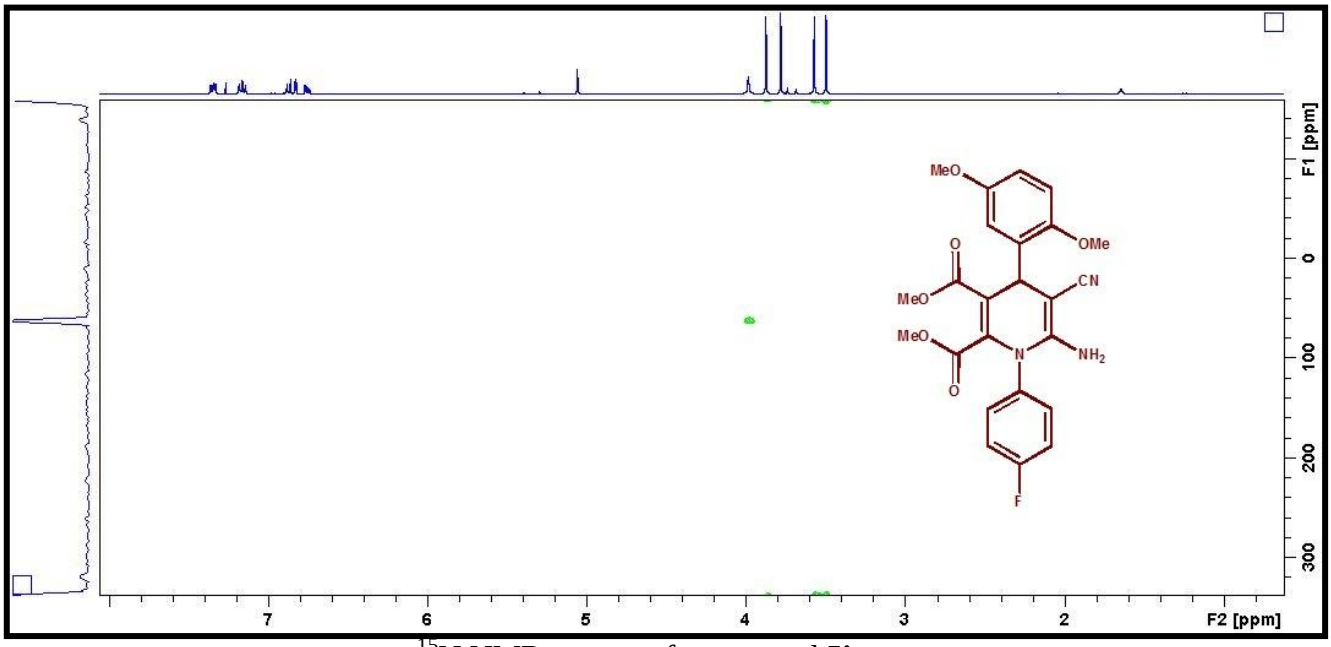
^{15}N NMR spectra of compound **5h**



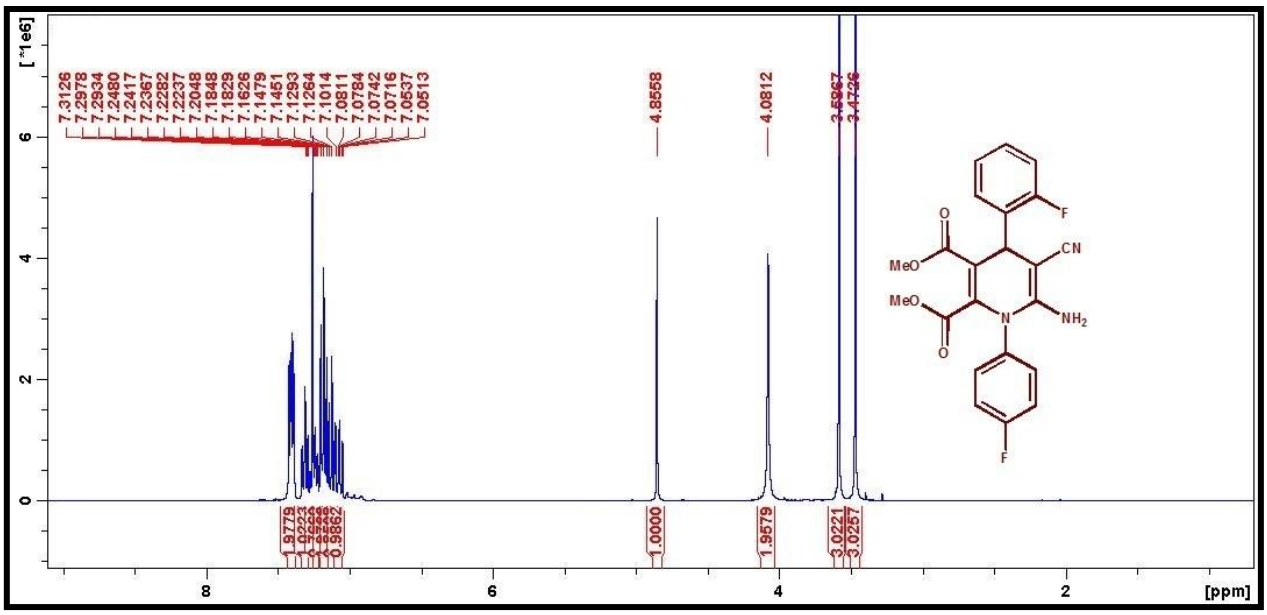
^{1}H NMR spectra of compound **5i**



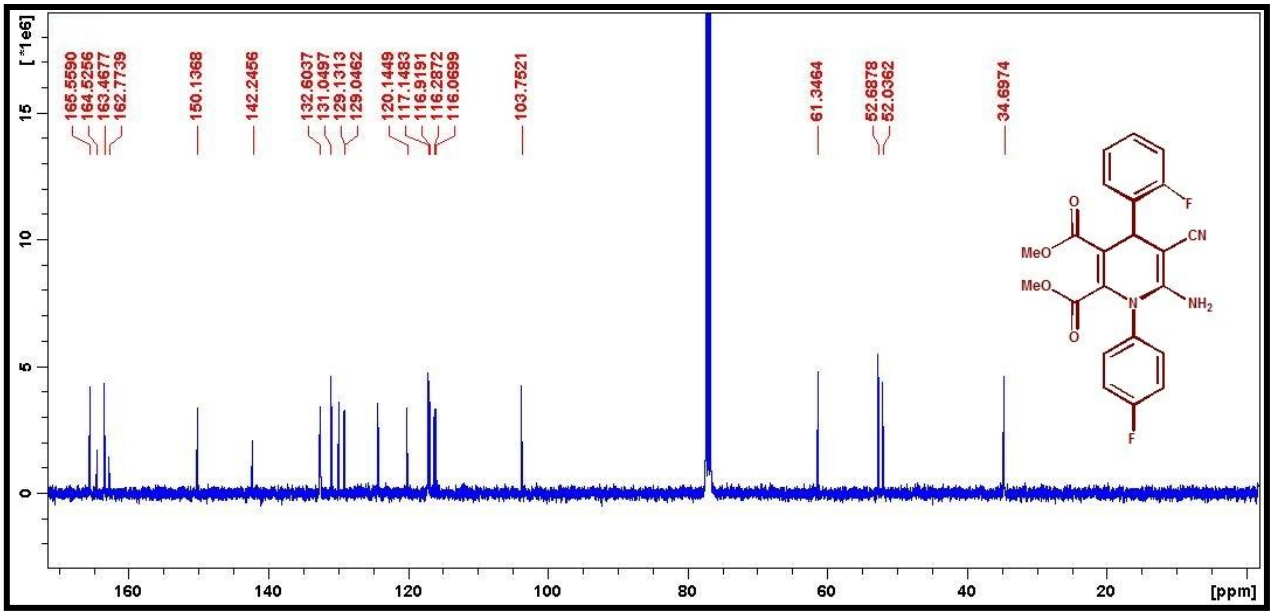
^{13}C NMR spectra of compound **5i**



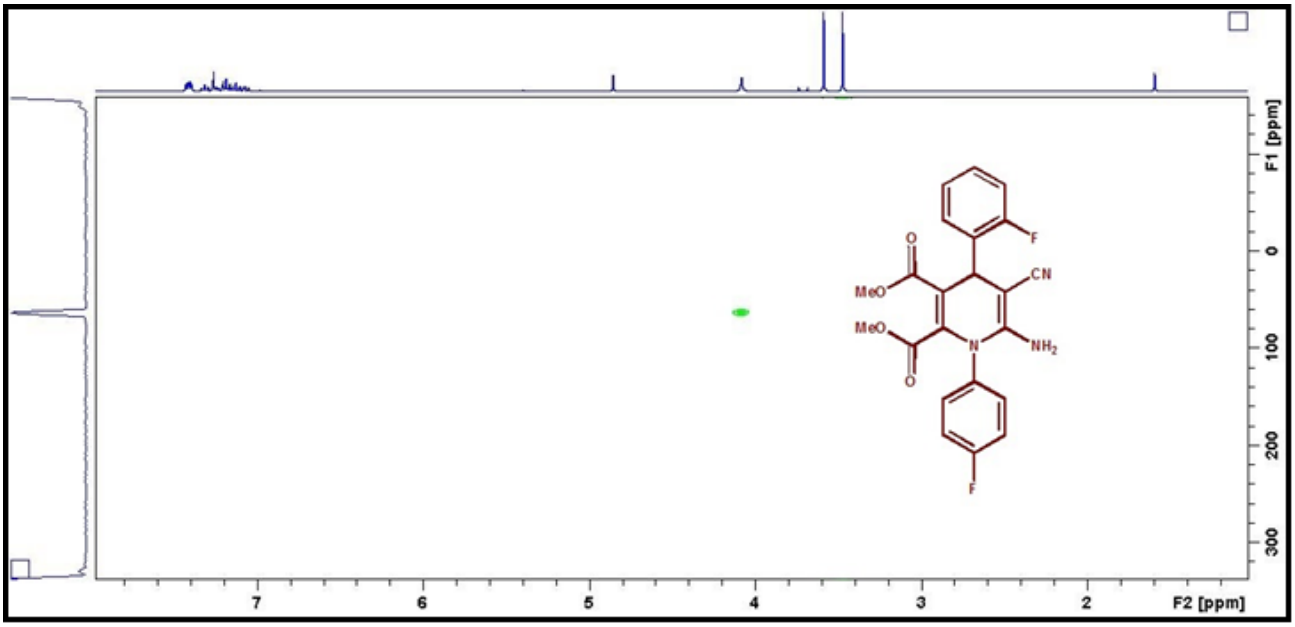
^{15}N NMR spectra of compound **5i**



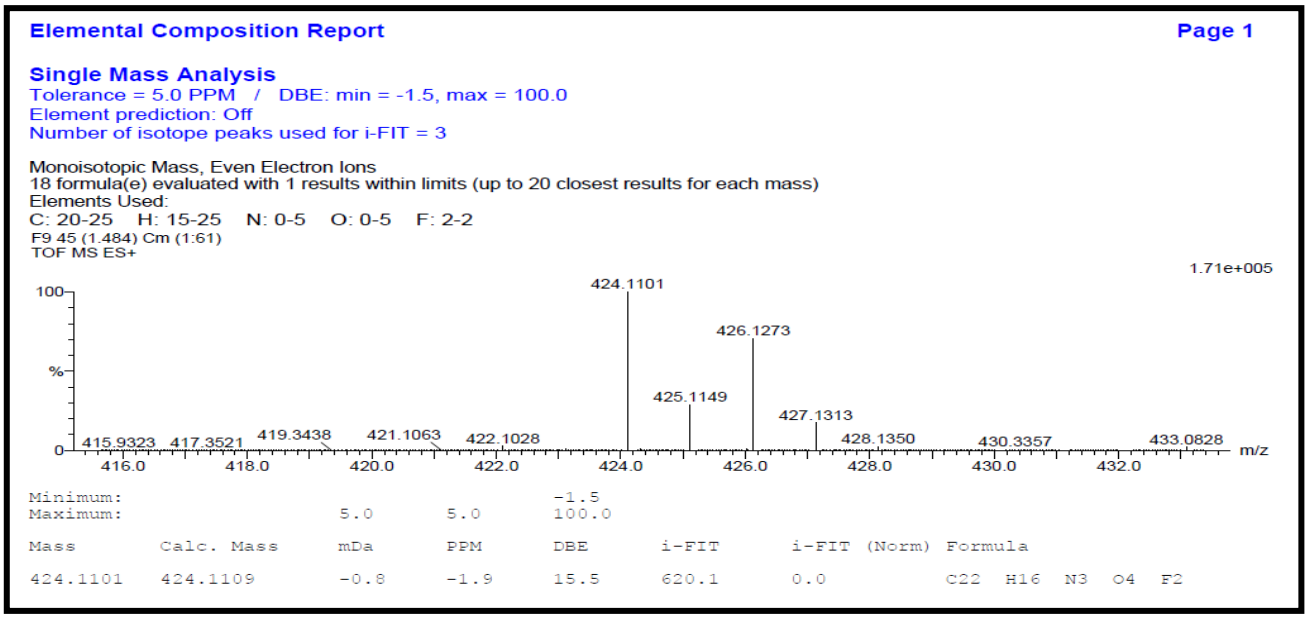
^{1}H NMR spectra of compound **5j**



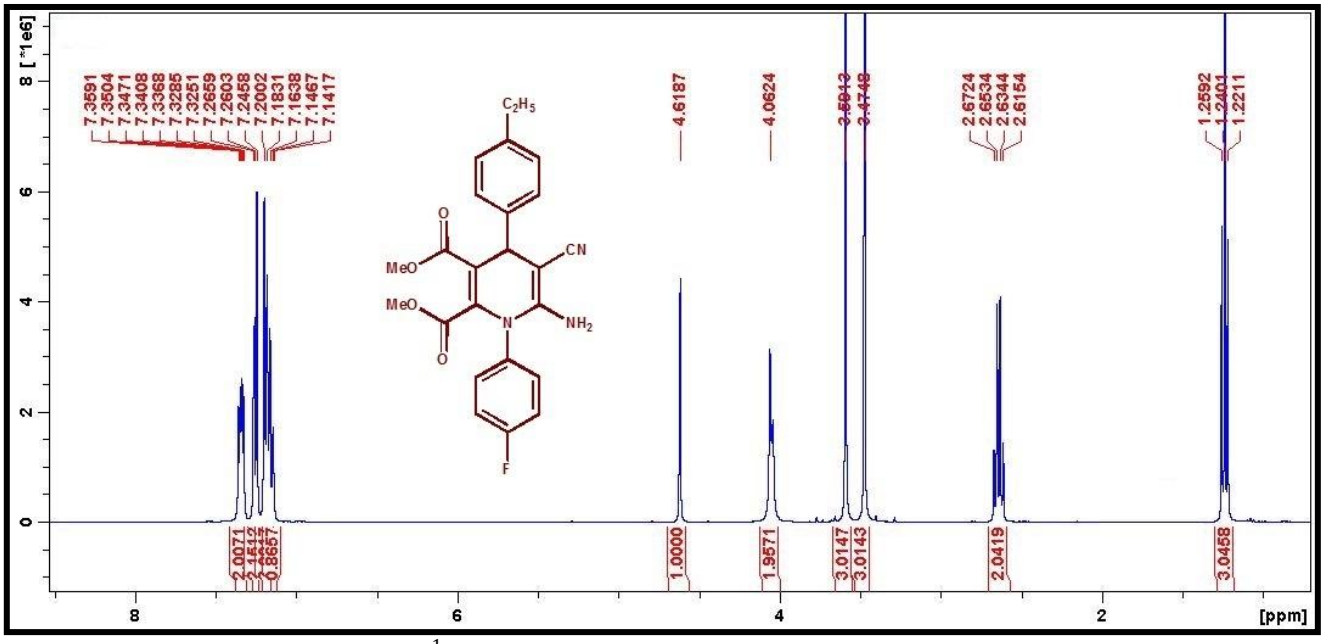
^{13}C NMR spectra of compound **5j**



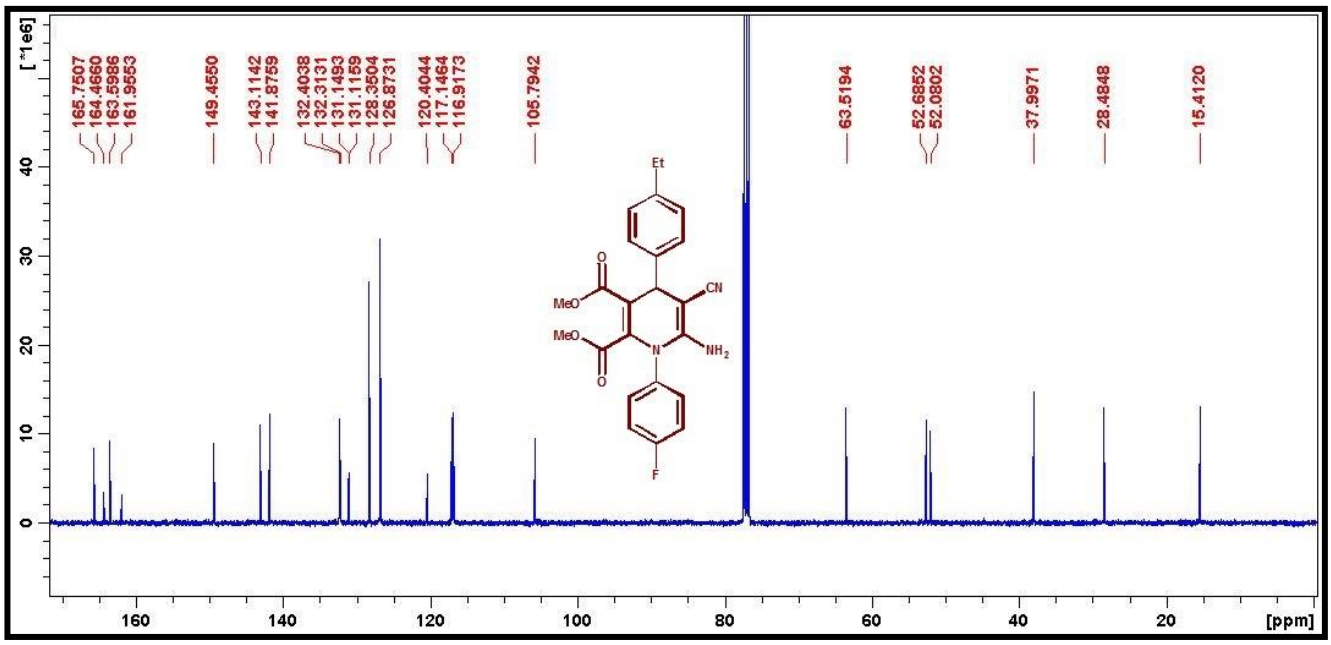
^{15}N NMR spectra of compound **5j**



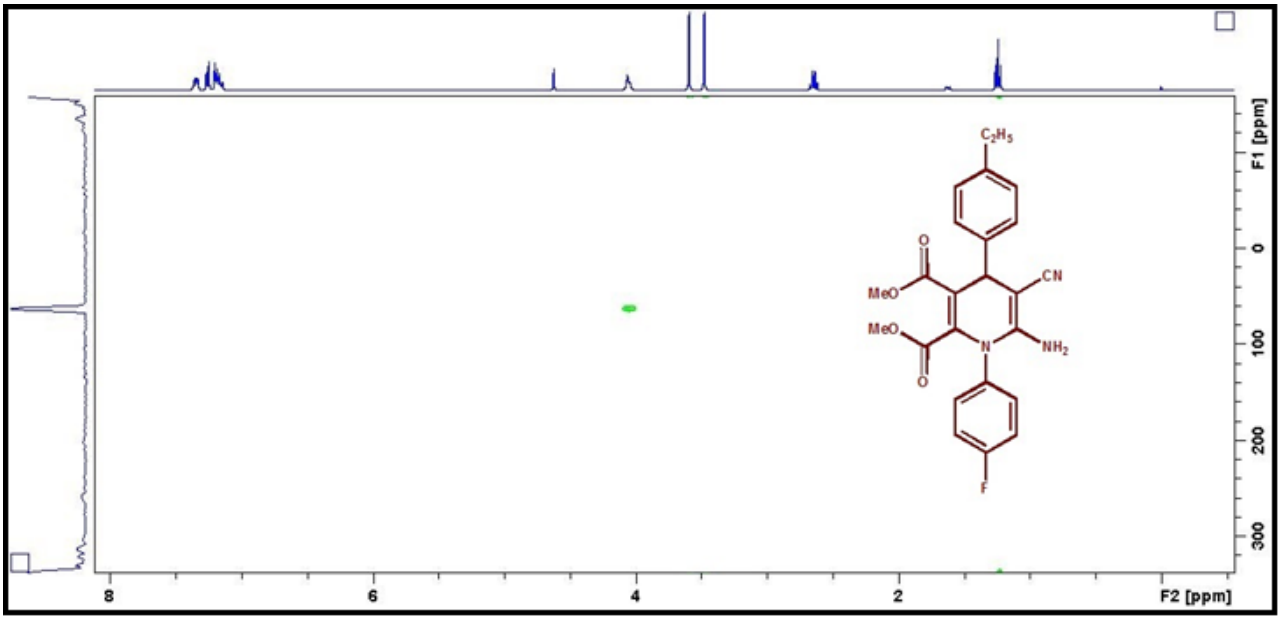
HRMS spectra of compound **5j**



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



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



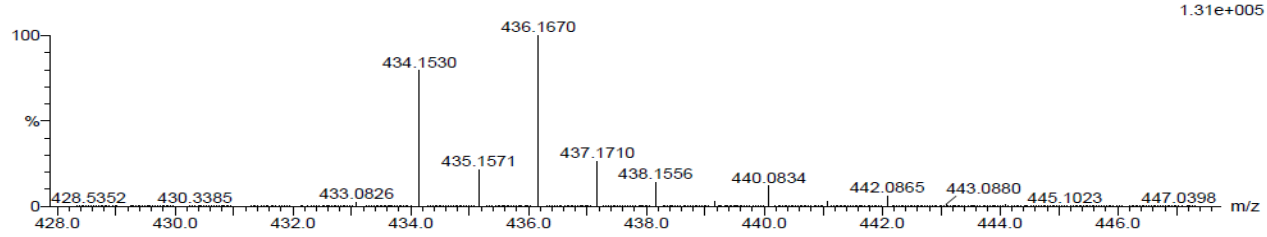
^{15}N NMR spectra of compound **5k**

Elemental Composition Report Page 1

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

Monoisotopic Mass, Even Electron Ions
38 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 20-25 H: 15-25 N: 0-5 O: 0-5 F: 0-1
F10 10 (0.304) Cm (1:61)
TOF MS ES+

1.31e+005



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
434.1530	434.1516	1.4	3.2	15.5	550.9	0.0	C24 H21 N3 O4 F

HRMS spectra of compound **5k**

Chapter 5

5.1. Conclusion

The aim of this study was to synthesize pyridine derivatives under reflux conditions and using different reusable catalysts that are easily recovered. Three series of pyridines derivatives were successfully synthesized. These derivatives are different 1,4-dihydropyridine-2,3-dicarboxylates, which were synthesized following three different reactions.

- In the first reaction, 1,4-dihydropyridine-2,3-dicarboxylate derivatives were successfully synthesized using Sm_2O_3/ZrO_2 as catalyst in ethanol solvent at room temperature to assist the reaction of dimethylacetylenedicarboxylate, dimethylaniline, malononitrile with various substituted aldehydes. The advantage of this method includes excellent yields (87-96%), simple work-up, reusability of the catalyst and shortened reaction time.
- In the second reaction, 1,4-dihydropyridine-2,3-dicarboxylate derivatives were successfully synthesized following the use of CeO_2/ZrO_2 as catalyst in ethanol at room temperature to facilitate the reaction between malononitrile, dimethylacetylenedicarboxylate, dimethylaniline and substituted aldehydes. This protocol offers short reaction times (< 30 min), high product yields (87-95%)
- In the third reaction, 1,4-dihydropyridine-2,3-dicarboxylate derivatives were successfully synthesized following the use of Y_2O_3/ZrO_2 heterogeneous catalyst, which was used to help the reaction between substituted benzaldehydes, dimethylacetylenedicarboxylate, malononitrile and 4-bromoanaline. This methodology has advantages, which include short reaction times (< 20 min), high product yields (88-95%),
- All catalysts used facilitated the formation of the products to reactions with excellent selectivity, even with reactants that would not otherwise give products, because of functional group hindrance. All different substituents of benzaldehyde investigated gave the expected products in good to excellent yields.
- All three catalyst are selective in their respective reactions as reported.
- The reactions are easy to handle, facile and environmentally friendly.
- By varying the aniline substrate, new 1,4-dihydropyridine were synthesized

- The reaction time of the reactions are shortened, the yields are excellent and the catalysts are reusable

Future work

- The synthesized will be tested for biological activities.
- The three different synthesized catalysts will be incorporated together to check for even better results.
- Electronegative substituents of benzaldehyde did not hinder the products from forming, so the selectivity of the catalysts used will also be studied.