SOLVENT FREE SYNTHESIS OF SOME HETEROCYCLES AND THEIR APPLICATIONS

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In

Chemistry

By

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November, 2017

Dedicated

TO

My Parents

&

Family Members

DECLARATION

I declare that the thesis entitled **SOLVENT FREE SYNTHESIS OF SOME HETEROCYCLES AND THEIR APPLICATIONS** has been prepared by me under the guidance of Dr. Ashis Kumar Nanda, Associate Professor of Chemistry, University of North Bengal. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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ABSTRACT

The toxicity and volatile nature of some organic solvents, basically chlorinated hydrocarbons that are generally used in immense amounts for organic reactions have created hazardous for the environment. Thus, propose of solvent-free multi-component reaction has received spectacular attention in recent times in the area of green synthesis. It was with the objective of judgment cheaper, easier and efficient method for synthesis of compounds with potential pharmacological and industrial demand that the efforts culminated into this study. Besides the choices from microwaves to ultrasonication, we narrowed down to the utility of thermal methods for unfolding our solvent-free protocols because of its simplicity and its possibility for up-scaling in this technique.

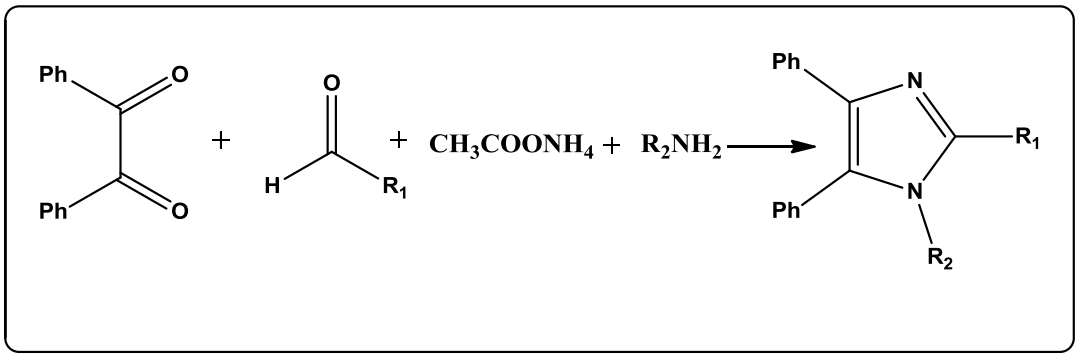
The dissertation entitled **SOLVENT FREE SYNTHESIS OF SOME HETEROCYCLES AND THEIR APPLICATIONS** is designed at developing a benign synthetic approach for the syntheses of a variety of biologically and synthetically important compounds. The whole work concentrates on multi-component solvent-free synthesis via thermochemical activation. The synthetic procedures of the reaction mixtures are accompanied by thermal analysis to optimize the reaction conditions for carrying out the whole reaction under solvent-free conditions. The novelty of these methodologies stands out in respect of very short reaction time, its high yields and the challenge to avoid so far as possible the use of solvents.

In the process of generating a condensed phase for reactions, the work culminated with a variety of synthesis of a great number of Imidazole and its derivatives, chlorination on imidazole, acetoxylation on imidazole and synthesis of quinazoline derivatives and its solubility increases via inclusion complexes by cyclodextrin. The work has resulted in the synthesis of a huge number of metal complexes via a solvent-free multi-component approach. This work initiated in March 2013 as UGC-BSR- JRF. The reflection has been organized in three chapters.

Chapter I includes a brief review on heterocycles especially imidazole and quinazoline and their some bioactive compounds, Solvent-free reactions and Multi-component synthesis and finally a small introduction to Thermal analysis, with help of these principles design the methodology.

Chapter II is the main text of the thesis i.e. the results and discussion of the work.

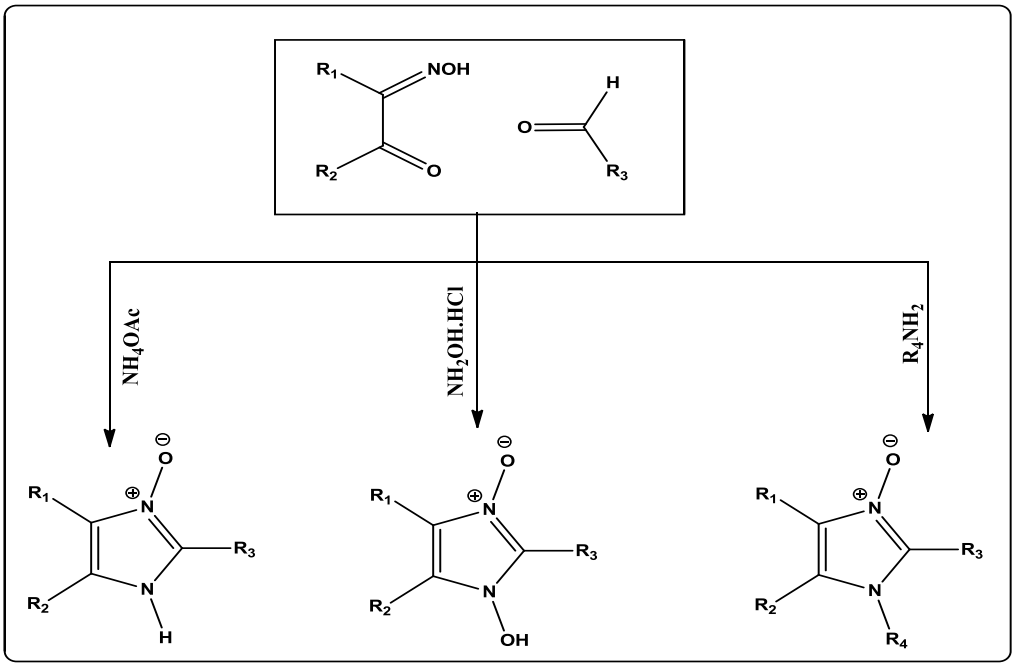
In the first section A, application of our protocol of this work was extended to the multi-component reaction leading to a multipurpose heterocycle, the Imidazole and its derivatives. Also the reaction was studied in condensed phase and mechanistically insights were described through the optimization process.



Using of HPLC was found to be very helpful technology for efficient calculation representing the presence of the reaction intermediates of the HPLC trace from the peak areas and of rate constants. Interestingly, kinetic only seldom of the solid –state reactions has been studies with the help of HPLC. As compared to any other method, kinetic studies of the present work exposed that the non-catalytic process was successful method for its synthetic preparation if it is carried out to some extent at a higher temperature (optimized through HPLC studies). Product formation in this optimized temperature up to 99% within 2-4 minutes.

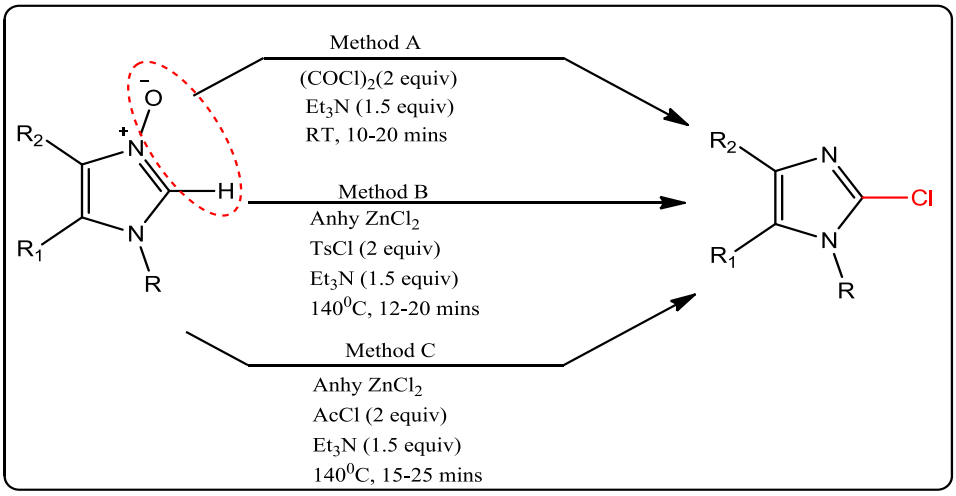
In the condensed phase this observation led us to suggest that carbonyl groups could be activated by self catalytic effect. This was explained by quantum mechanical chemistry PM3 calculations which were supported to agree with the spectroscopic and experimental results.

To further proof our rationale of self-catalytic activation of carbonyl groups in the condensed phase, this work was further extended to the synthesis of the Hydroxy Imidazole *N*-oxides, *N*-substituted imidazole *N*-oxide and Imidazole N-oxides. The synthesis of *N*-substituted Imidazole *N*-oxide has to be needed the use of an amine compound instead of ammonium acetate while synthesis of 1-hydroxyImidazole-3-oxide warrants hydroxylamine hydrochloride. All syntheses were carried out under solvent-less conditions with a priori DSC, STA and as well as TGA studies.

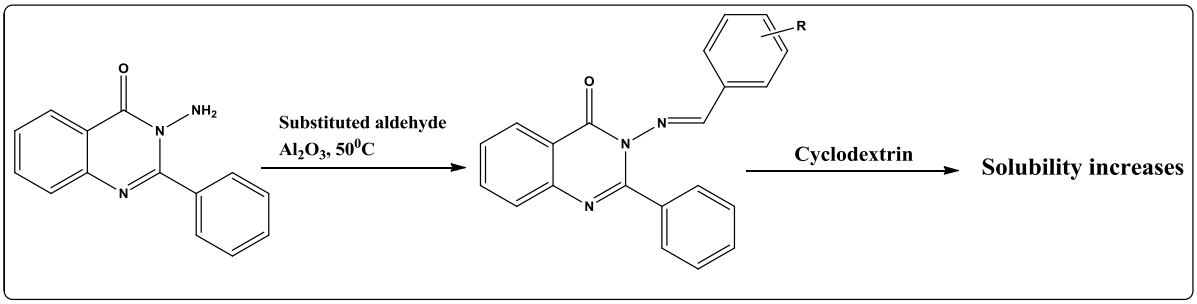


All the derivatives are suitably formed in an excellent yield within 10 minutes at a much lower temperature of the reaction as compared to 3- 6 hours of the reported time with solvent based methods, even in without added catalysts. Thus, a conclusion in the condensed phase of these synthetic experiments was drawn that the reaction rates in the all cases, synthesis of Imidazoles are very prominent not just because of the catalytic activity of the added catalysts or in *situ* catalysts generated like acetic acid but also because of the self catalytic activity of carbonyl groups.

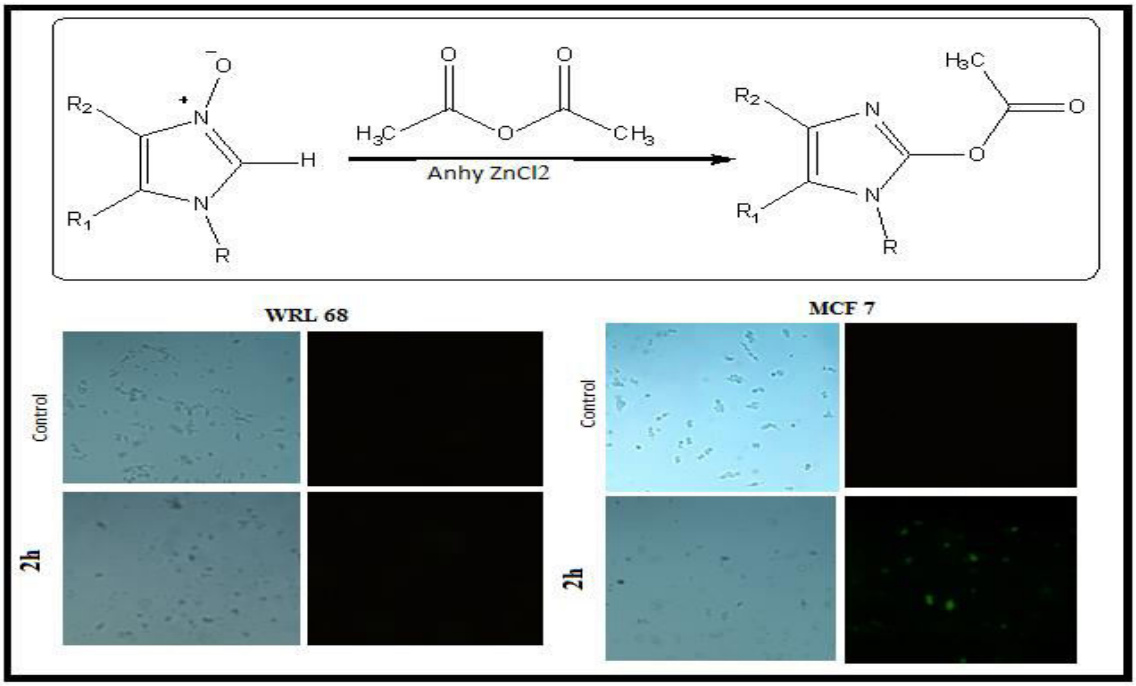
In the second section B, diversity of chlorination at the C-2 position of imidazole *N*-oxides using various chlorinating agents under solvent-free condition. Among the whole chlorinating reagent such as oxalyl chloride, tosyl chloride and acetyl chloride, oxalyl chloride gave the best output to conversion of substituted 2-chloroimidazoles from imidazole *N*-oxide. This reaction is very expeditious under solvent-free condition at a room temperature, conversion of the desired yields up to 95%. The biological study such as antimicrobial activity of the substituted 2-chloroimidazoles has been studies in both gram positive and gram negative bacteria. MIC (µg/ml) values of the corresponding all chloroimidazole compounds were discussed in the result discussion portion. The MIC value was found at 75µg/ml in gram positive bacteria.

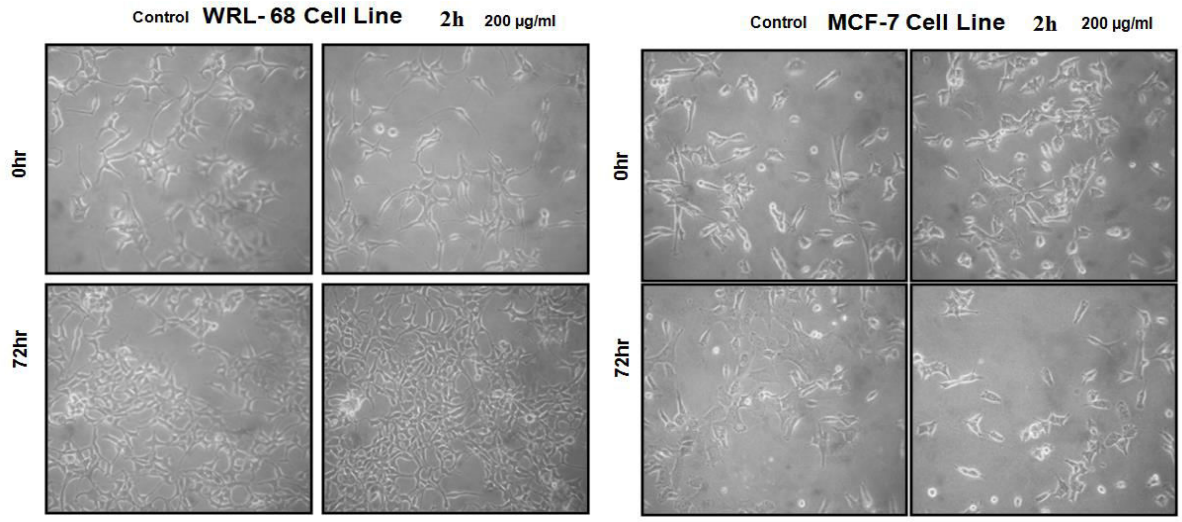


In the third section C, synthesis of substituted bioactive quinazoline derivatives from 3-amino-2-phenylquinazolin-4(3*H*)-one using alumina under solvent-free condition at 50^{0}C, product conversion is almost above 90%. In reported method, all substituted quinazoline derivatives showed antibacterial activity in a good immense. One drawback of these compounds has shown their insolubility property in water. Here we tried to solve this problem with the help of inclusion in β-cyclodextrin. After inclusion its solubility increases due to some weak interaction with β-cyclodextrin.



In the fourth section D, further functionalized of imidazole *N*-oxide to acetoxyimidazole at 2-position by using acetic anhydride in presence of a lewis acid. To find out utility of these acetoxyimidazole we have investigated its biological application. In these series all compounds showed cytotoxicity. Finally we investigated three compounds that can be treated as a drug through in vitro, bioimformatics and in vivo analysis. One compound 2h (1-benzyl-4,5-dimethyl-1*H*-imidazol-2-yl acetate) is totally different that showed activity only in cancerous cell. No such activity found in normal cell this evidence drawn from fluorescent microscope. Ecotoxicity test has performed in different way in normal mice.





The final part of the thesis work described **in the section E,** synthesis of a variety of metal complexes with efficient preparation of the 2-(4, 5-disubstituted 1H-imidazol-2-yl) phenol. A variety substitution on the diketone and changing the number of metal salts leads to formation of Imidazole metal complexes.

This remarkable diversity and importance of using solvent-free reactions to prepare a variety of compounds demonstrates that these methodologies have a quite important place in the toolbox for Green chemistry.

PREFACE

The still increasing demand for efficient synthetic chemistry of novel and biologically active organic compounds remains the major focus for the progress of efficient and new greener methodologies and their biological activity. The development of solvent-free processes in organic syntheses methodologies has picked up a speedy in sense of green chemistry. This entitled work is focussed on towards fulfilling our objective to syntheses newly bio-active novel hetero-molecules. Finally, we observed that thermal analysis study for a particular reaction is of quite immense help while designing another reaction conditions.

The present research work has design to syntheses of a variety of heterocyclic compounds and their application and some metal binding complexes under solvent-free condition. This thesis begins with **Chapter I,** which describe a brief review on heterocycles especially imidazole and quinazoline, Solvent-free reactions, about Green Chemistry and its principles, and Multi-component syntheses. **Chapter II,** in this chapter there are five sectional parts, In **section A**, deals with mainly synthesis of variety type imidazole compounds, *N*-substituted imidazole *N*-oxide, *N*-hydroxyimidazole *N*-oxide and finally imidazole *N*-oxide with mechanistically approach towards with and without catalyst in condensed phase reaction**. In section B,** mainly deals with preparation of the substituted 2-chloroimidazoles from imidazole *N*-oxides and their antimicrobial activity. **In section C,** general outline to syntheses of reported antibacterial activity of quinazoline derivatives from 3-amino-2-phenylquinazolin-4(3*H*)-one and their solubility increases using inclusion technique in β-cyclodextrin. **In section D,** preparation of acetoxyimidazoles through acetoxylation at C-2 position of imidazole *N*-oxide and their anticancer activity, showed by in vitro, bioinformatics and in vivo analysis. Finally **In section E,** further utility of substituted imidazole to produce imidazoles metal complexes using variety of metal salt.

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Patent and List of publications

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Oral presentations & poster presentations

Patent:

1. "Novel 2-acetoxyimidazole derivatives a potent cancer drug to combat multiple cancers and their preparation thereof" **Mossaraf Hossain**.
   Patent Application Number- 201731038374

List of Publications (Thesis Related):

1. "An expeditious synthetic protocol for chlorination of imidazole N-oxide: Synthesis of 2-chloroimidazoles" **Mossaraf Hossain**, Kiran Pradhan and Ashis Kumar Nanda. *Tetrahedron Letters*, 2017, 58, 3772-3776.
2. "A mechanistic study of carbonyl activation under solvent-free conditions: evidence drawn from the synthesis of imidazoles" Kiran Pradhan, Bipransh Kumar Tiwary, **Mossaraf Hossain**, Ranadhir Chakraborty and Ashis Kumar Nanda. *RSC Adv*., 2016, 6, 10743.
3. "Design, Synthesis and biological evaluation of novel 2-acetoxyimidazole derivatives as multidrug resistance in cancer therapy and their molecular docking studies" **Mossaraf Hossain**, Anoop Kumar, Indrani Sarkar, Tilak Saha, Vivek Kumar Ranjan, kiran Pradhan, Ranadhir Chakraborty, Arnab Sen, Ashis Kumar Nanda. (Communicated)
4. "Alumina catalyst: Synthesis of novel quinazoline derivatives and their inclusion complexes" **Mossaraf Hossain**, Ashis Kumar Nanda (Manuscript under process of submission).
5. "Investigation of reactive and spectroscopic properties of imidazole derivatives: Combined spectroscopic, DFT, MD and docking study" **Mossaraf Hossain**, Y.Sheena Mary, C.Yohannan Panicker, Ashis Kumar Nanda, Stevan Armakovic, Sanja J.Armakovic, C.Van Alsenoy. Journal of Molecular Structure. (Communicated)
6. Synthesis, crystal structure, molecular dynamics and molecular docking, study of 1-hydroxy-2-(4-methoxyphenyl)-4,5-dimethyl-imidazole-3-oxide.
   Mossaraf Hossain, Kiran Pradhan, Dhiraj Brahman, Bipransh Kumar Tiwary (Communicated).

7. One-pot solvent-free synthesis to Metal-Imidazole complexes with analgesic properties.
Mossaraf Hossain, Kiran Pradhan , Bipransh K. Tiwary, Ranadhir Chakraborty, Ashis K. Nanda (Communicated).

(Non Thesis Publication):

8. "Radical Scavenging Activities of Lagerstroemia speciosa (L.) Pers. Petal Extracts and its hepato-protection in CCl_4 intoxicated mice" Bipransh Kumar Tiwary, Somit Dutta, Priyankar Dey, **Mossaraf Hossain**, Anoop Kumar, Sony Bihani, Ashis Kumar Nanda, Tapas Kumar Chaudhuri and Ranadhir Chakraborty. BMC *Complementary and Alternative Medicine*, 2017, 17:55.
DOI 10.1186/s12906-016-1495-0.

Oral Presentations

1. "A mechanistic insight for the preparation of Imidazole and Imidazole-N-oxide and further its functionalization at C-2 position under solvent free condition." in the National Seminar "Frontier in Chemistry –2017" organized by the Department of Chemistry, NBU and funded by UGC and SAP (DRS–III), held at University of North Bengal, Darjeeling, India, February 20-21, 2017.
2. "Solvent-free strategy: Chlorination at C-2 position of Imidazoles Scaffold from Imidazole *N*-oxides and their antimicrobial activities" in the National Seminar on "Frontiers in Chemistry –2017-18" organized by the Department of Chemistry, NBU and funded by UGC held at University of North Bengal, Darjeeling, India, September 14, 2017.

Poster Presentations

1." Petal extract of *Lagerstroemia speciosa* possess free radical scavenging activities supporting hepato-protection in CCl_4 intoxicated mice" **Mossaraf Hossain**, Bipransh Kumar Tiwary, Somit Dutta, Priyankar Dey, Anoop Kumar, Ashis Kumar Nanda, Tapas Kumar Chaudhuri and Ranadhir Chakraborty in 19th CRSI National Symposium in Chemistry, held at University of North Bengal, Darjeeling, India, July 13–16, 2016.

LIST OF ABBREVIATIONS

Ac	Acetyl
B.M.	Bohr magneton
^{o}C	Degree Celsius
ca.	constant agitation
d	Doublet
dd	Doublet of a doublet
DCM	dichloromethane
DFT	Density functional theory
DMSO	dimethyl sulphoxide
DOS	Diversity oriented synthesis
DSC	Differential Scanning Calorimetry
DTA	Differential Thermal Analysis
EGFR	Epidermal growth factor receptor
Et	Ethyl
FAAH	fatty acid amide hydrolase
h	hour/hours
HPLC	High Performance Liquid Chromatography
HRMS	High resolution mass spectrometry
IR	Infra red
Litt.	Literature
m	multiplet
MAOS	Microwave Assisted Organic Synthesis
MCR	multi-component reactin
Me	Methyl
MeOH	Methanol
MHz	Mega Hertz
min	minute
mmol	millimole
mol%	Mole percent
MW	Microwave
NaOAc	sodium acetate
nm	nanometers
NMR	Nuclear magnetic resonance
Ph	Phenyl
q	Quartet
QSAR	Quantitative structure activity relationship
RT	Room Temperature
s	Singlet
STA	Simultaneous Thermal Analysis
t	Triplet
TGA	Thermogravimetric Analysis
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

TMS	Tetra methyl silane
T.S	Transition state

CHAPTER-I

A brief review on synthesis and functionalization of some heterocycles and their application in medicinal chemistry and about solvent-free reaction, multi-component reaction and thermal analysis

CHAPTER-I

I. Introduction

Heterocyclic compounds are of mainly interest in medicinal chemistry. The most complex branches of chemistry are normally heterocyclic chemistry. It is equally contributed in interesting for the industrial and physiological significances and for its diversity of its synthetic procedure as well as its theoretical implication. Synthetic heterocyclic chemistry has not only played an important role in every place of human life and also found their application in diverse field as agriculture, medicine, polymer and various industries. Most of the synthetic heterocyclic compounds act as a drug is used as anticonvulsants, hypnotics, antineoplastics, antiseptics, antihistaminics, antiviral, anti-tumor etc. In every year large number of heterocyclic drugs is being introduced in pharmacopeias. The size and type of ring structures, together with the effective substituent groups of the mother scaffold, showed strongly their physicochemical properties.[1,2]Among the various medical applications, heterocyclic compounds have a significant active role as anti-viral [3], anti-bacterial [4,5], anti-inflammatory [6], anti-fungal [7], and anti-tumor drugs[8–10]. Heterocycle's general applications are as immense as they are various and are not extensively encompassed in the scope of this brief review. The alkaloids form a most important group of naturally occurring heterocyclic compounds having wide-ranging biological activity. Most of the alkaloids contain basic nitrogen atoms. Here we have mainly focused on two heterocycles that is imidazole and quinazoline. Recent developing organic synthetic methodologies on heterocyclic chemistry are more successful pathways for the chemists to prepare useful bulk chemicals and fine. This is not only their strategies are influenced by economical aspects, expressed in enhancement of reaction yield and purity, but the environmental aspect is gaining additional importance as well. As the reducing of using hazardous solvents and reagents is one of the major reasons why this work regarding the design of the reaction conditions was performed in the absence of any solvent, this chapter will start with a brief introduction of imidazole and quinazoline moiety with a focus on solvent–free multi-component reactions.

I. Literature Overview

I.1. History of Heterocyclic Chemistry

The history of the heterocyclic chemistry began in 1800s, in step with the improvement of organic chemistry. Some noteworthy developments-

1818: From uric acid, Brugnatelli isolates alloxan.

1832: Dobereiner produces furfural (a furan) by mixing starch with sulfuric acid.

1834: Runge isolates pyrrole ("fiery oil") by bones dry distillation.

1906: Friedlander discovered indigo dye, allowing synthetic chemistry methodologies to displace a large number of agricultural industry.

1936: Treibs syntheses chlorophyl derivatives from crude oil, explaining the biological source of petroleum.

1951: Chargaff's rules are explained, importance the role of heterocyclic compounds (pyrimidines and purines base) in the genetic code.

I.1.A. Brief review on Imidazole

Medicinal chemistry is the discipline anxious with determing the manipulate of chemical structure in biological field to determine activity and in the practice of medicinal chemistry unfolded from an empirical one connecting organic synthesis of new compound based mainly on the modification of structure and then find out their biological activity .[11, 12] Medicinal chemistry concerns with the development, discovery, interpretation and the identification of mechanism path way of biologically active compounds at molecular level. [13] Synthetic biologically active compounds have mainly five-membered nitrogen-containing heterocyclic ring structures. [14] Structural frameworks have been explained as privileged structures and in particular, N-containing polycyclic hetero structures have been reported to be linked with a broad range of biological activity. In the field of heterocyclic five membered ring structures imidazole nucleus shows diverse properties. The elevated therapeutic behaviors of the imidazole moiety connected drugs have encouraged in the medicinal field to chemists to synthesize a bulky number of novel chemotherapeutic agents. The drugs containing imidazole ring have broadened scope in remedying a mixture of dispositions in clinical medicines. In the medicinal field imidazoles properties include 20HETE (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, anticancer, b-lactamase inhibitors, carboxypeptidase inhibitors, antiaging agents, hemeoxygenase inhibitors, anticoagulants, antibacterial, anti-inflammatory, antiviral, antifungal, antidiabetic,

antitubercular and antimalarial. [15-28] At high concentrations, some imidazole drugs, could apply direct inhibitory action on membranes, without interference by way of sterols and sterol esters. [29, 30] Infectious microbial disease creates worldwide problem, because microbes have protected therapy or prophylaxis longer than any other form of life. In recent decades, troubles of multidrug-resistant microorganisms have attained an alarming level in many countries in the world. Resistance of anti-microbial agents such as macrolides, β-lactam antibiotics, vancomycin and quinolones etc. and unlike species of bacteria causes increased significant global problem.[31] In the literature overview, imidazole and its derivatives have pharmacologically and physiologically active and find applications in the treatment of numerous diseases.

I.1.A.1. Structure and pharmacological activities of Imdazole

Imidazoles are very important heterocyclic compounds which have important feature of various medicinal agents. Imidazole is a 5-membered planar ring compound, which is soluble in polar solvents water. It exists in two canonical tautomeric forms because the hydrogen atom can be situated on either of the two nitrogen atoms. It is very much polar compound, as evidenced by a calculated 3.61D dipole moment. Imidazole compound is treated as aromatic due to the presence of sextet of π-electrons, consisting of a pair of electrons on the nitrogen atom. Imidazole is amphoteric, i.e. it can acts as a both base and an acid.

Imidazole derivatives shows diverse pharmacological activities on the basis of a variety of literature surveys

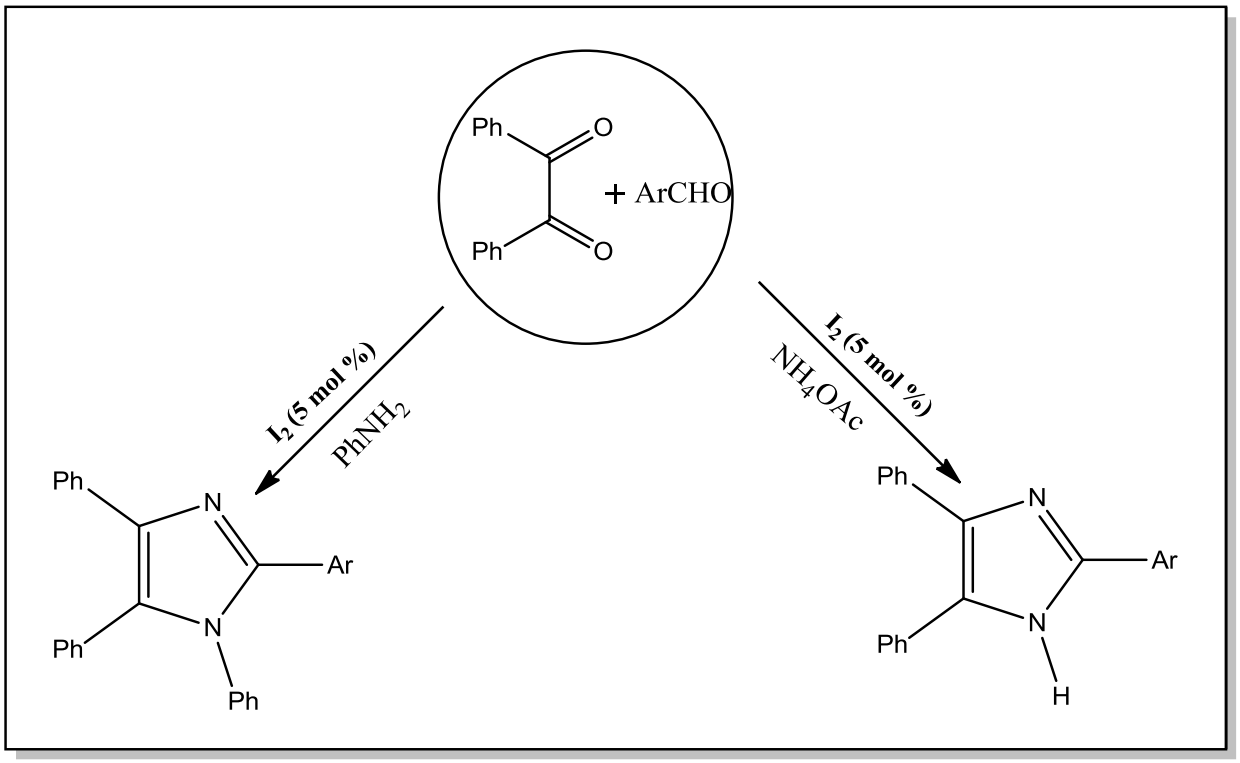
- Anti analgesic activity and inflammatory activity
- Anti-bacterial activity and Anti fungal
- Anti depressant activity
- Anti tubercular activity
- Anti viral activity
- Antileishmanial activity
- Anti cancer activity

I.1.A.2. Development of the Synthesis of Imidazoles:

Imidazoles are very omnipotent class of drug due its wide-ranging antimalarial, antibacterial, antifungal, anti-inflammatory, antiviral, antitubercular and finally anti cancer

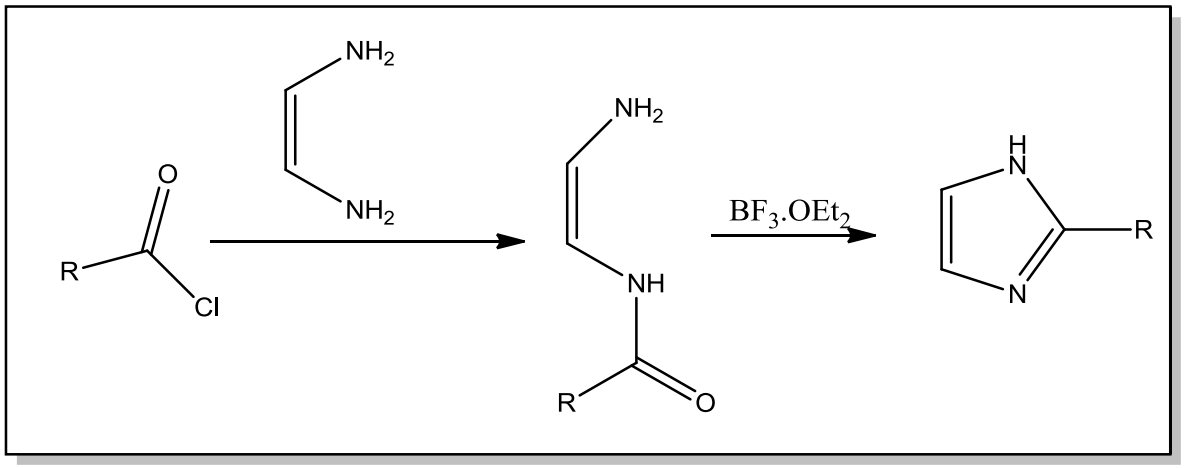
activity. The development of synthesis of imidazoles moiety as well as its functionalisation at various position is still going on to raise its activity. Generally, these procedures involve harsh condition, various name reaction, multicomponent reaction, multi-step strategy, and use of lewis base and lewis acid, metal free condition, costly transition metal catalyst or in solvent and solvent-free condition. In this literature survey, we mainly focus on the different route of synthesis part of imidazoles and functionalisation at its various positions.

In 2007, M. Kidwai and co-workers, syntheses one pot multicomponent tri- and tetra-substituted imidazole using molecular iodine as a catalyst with diketo system, substituted aldehyde and ammonium acetate and substituted amine as a source of nitrogen. They proposed a mechanism where iodine not only acts as a mild lewis acid catalyst to activate the carbonyl system of the parent diketo compound as well as initiate the formation of diamine intermediate to produced iso-imidazole followed by dehydration and finally to sigma topic rearrangement to produced imidazoles.[32]



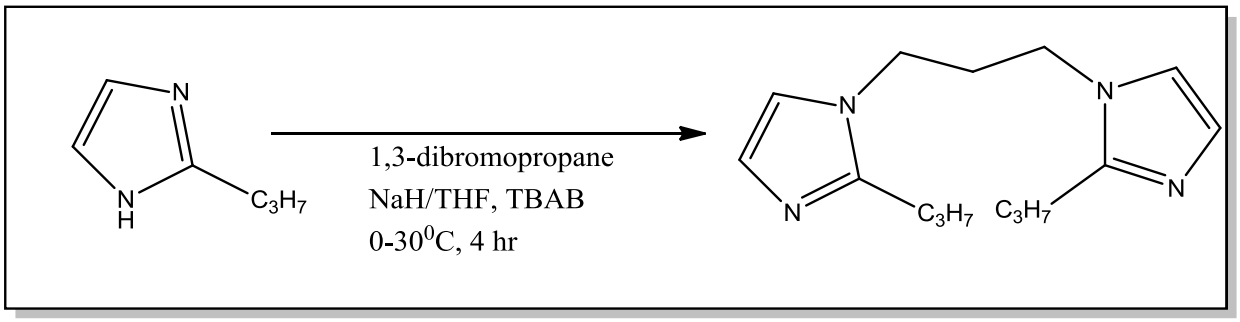
Scheme I.1: Synthesis of substituted imidazoles catalyzed by molecular iodine.

In 2008, S. Sharma and coworkers, typically syntheses substituted imidazole from acid chloride and ethylenediamine at 0°C in non polar solvent, dry dioxane and stirring at room temperature to furnish the N-acyl-1,2-ethylenediamine derivatives followed by the addition of strong lewis acid triflouroboron etherate. They used acid chloride containing long-chain at the alkyl group is not available in the commercial source. This was synthesized from hydroxyl olifinic and olifinic long acids chain in situ preparation.[33]



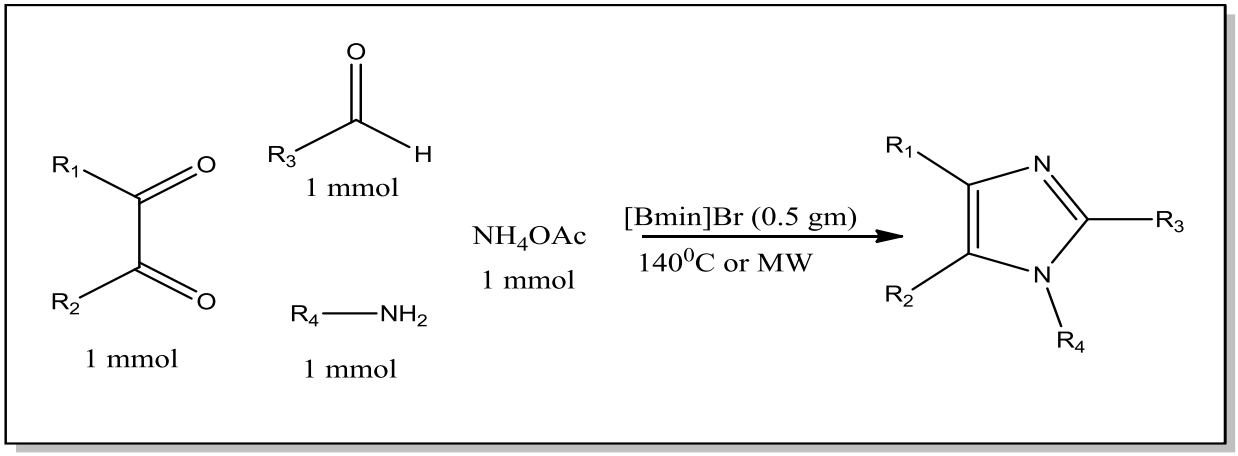
Scheme I.2: Preparation of 2-substituted imidazoles using lewis acid.

In 2009, J.pandey et al. described the synthesis of 1,3-bis-(2-propyl-imidazol-1-yl) propane from the reaction between 2-propyl imidazole and 1,3-dibromopropropane in presence of NaH in polar aprotic solvent at 0-30° C for 4 hrs. Using this synthetic pathway it is possible to synthesis the several substituted imidazoles and their multi coupling products. Among the whole compounds, 1,3-bis-(2-propyl-imidazol-1-yl) propane serve as a better antitubercular activity.[34]



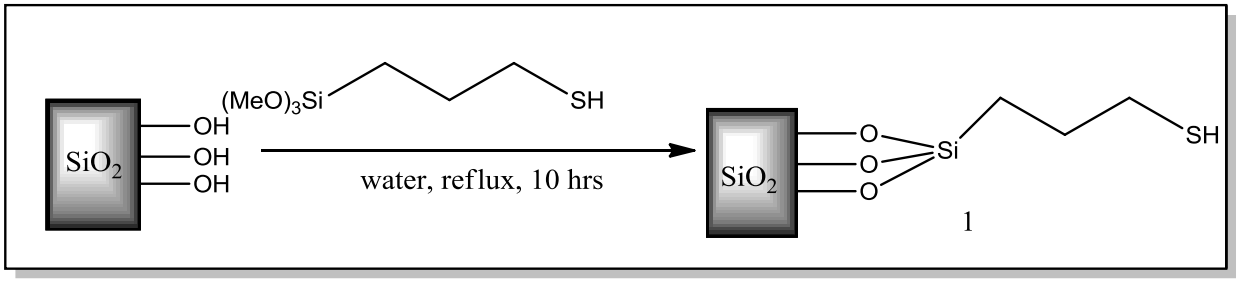
Scheme I.3: Preparation of antitubercular active compound from 2-propyl imidazole.

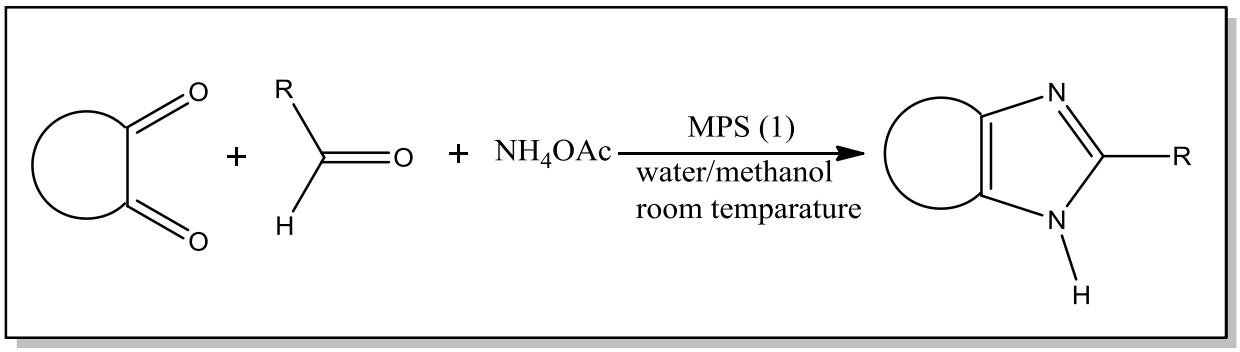
In 2010, Hasaninejad et al. reported the multi-component catalyst free polysubstituted imidazole in presence of neutral ionic liquid. This methodology has several advantages as compared to other method due to in this procedure reaction has carried out under microwave one pot multi-component condition as well as catalyst free. Finally using of ionic liquid it is more facile to accept a greener process.[35]



Scheme I.4: Preparation of polysubstituted imidazole using ionic liquid.

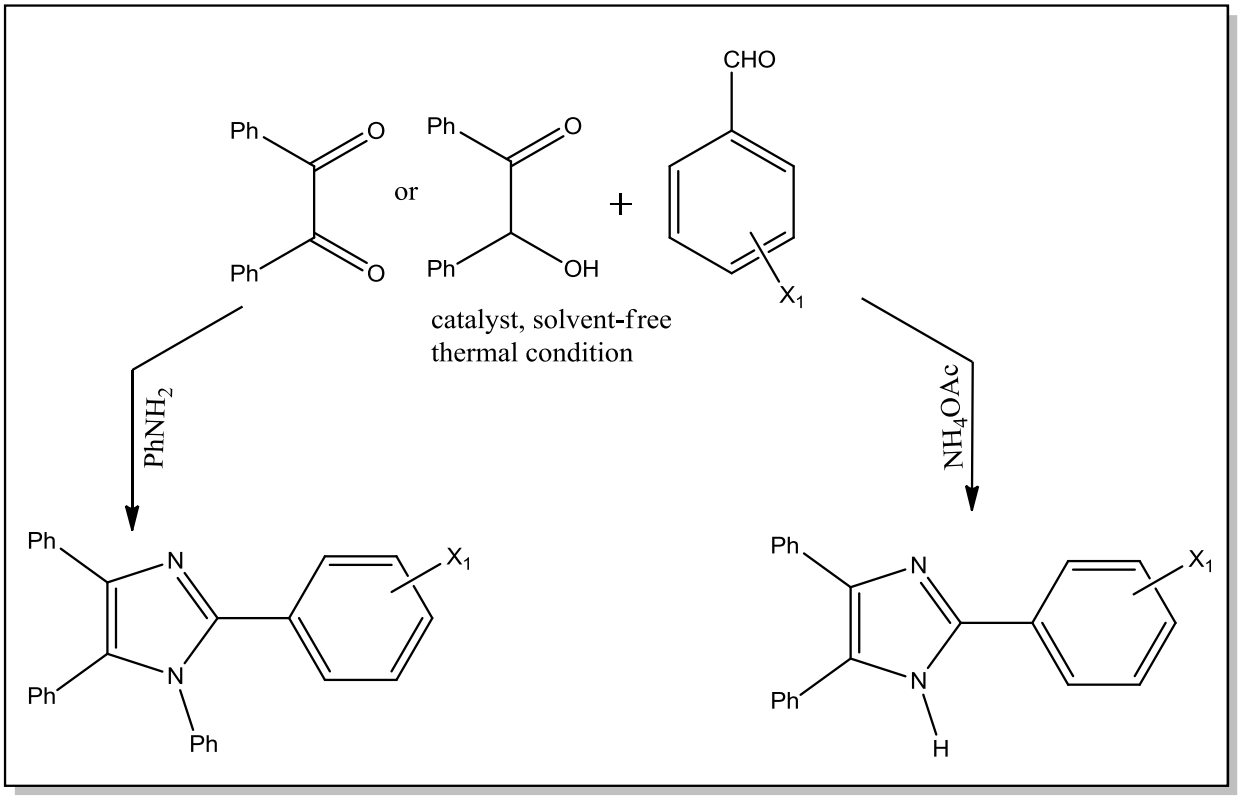
In 2010, there is another important work to synthesis of substituted imidaole, C. Mukhopadhyay et al. at first syntheses the mercaptopropylsilica in water medium. It is a very efficient catalyst to synthesis the imidazole derivatives because of its large surface area which increases the binding ability as a catalyst. C. Mukhopadhyay et al. reported the synthesis of polysubstituted imidazole using this catalyst in water/ethanol mixture (1:1) at room temperature. One scheme is reported as follow.[36]





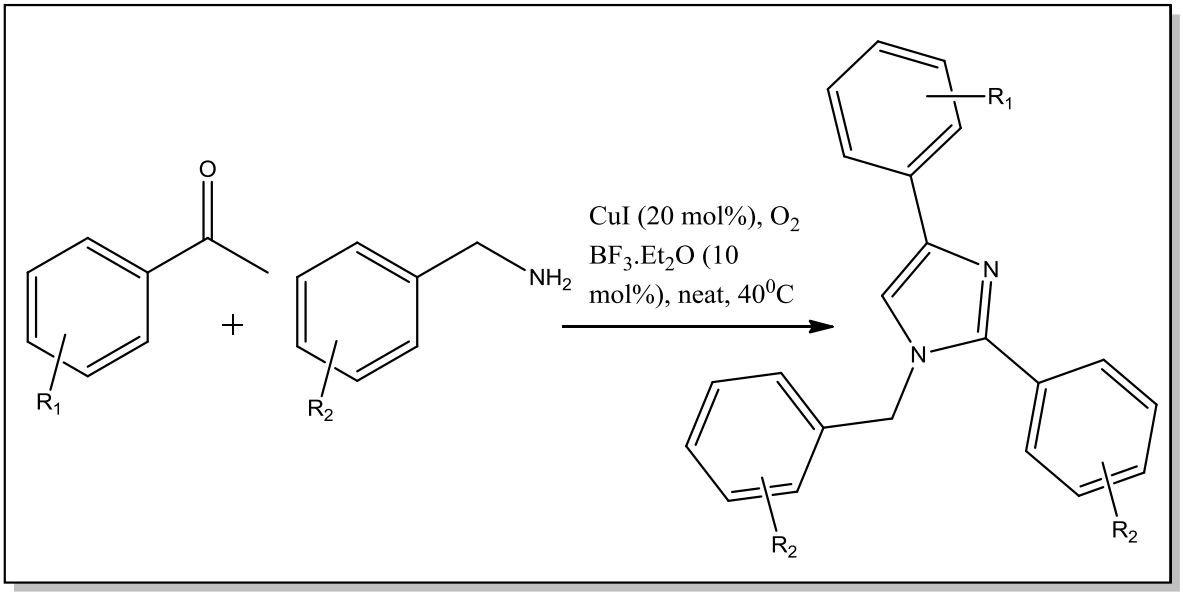
Scheme I.5: Synthesis of polysubstituted imidazole using MPS as a catalyst.

In 2011, H.R. Shaterian, M. Ranjbar reported the synthesis of tri- and tetra-substituted imidazoles from benzyl or benzoin and substituted aldehyde and substituted aniline or ammonium acetate as a source of nitrogen in presence of Bronsted acidic ionic liquid, N-methyl-2-pyrrolidonium hydrogen sulfate under solvent-free thermal condition.[37]



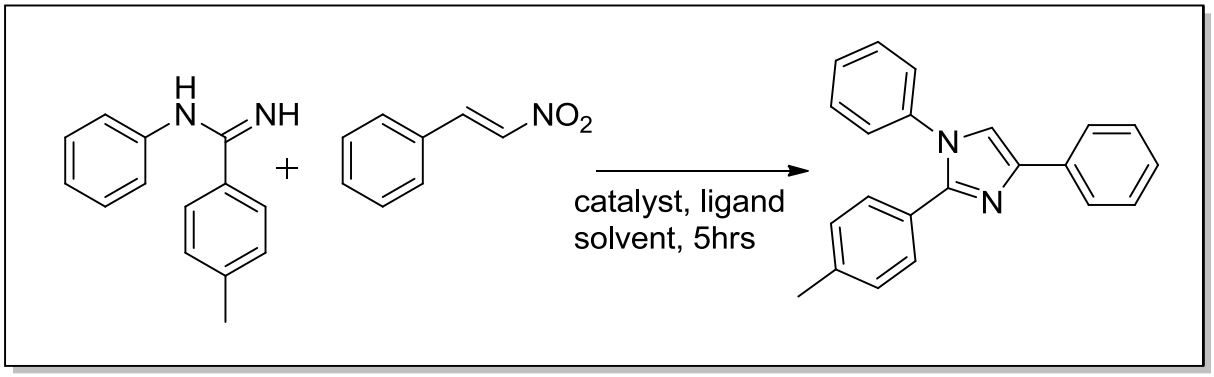
Scheme I.6: Preparation of tri- and tetra-substituted imidazoles using Bronsted acidic ionic liquid.

In 2012, Shun-Jun Ji and co-workers reported a novel method of preparation of highly substituted imidazoles with ketones and benzylamines using CuI/BF_3.Et_2O cocatalyzed aerobic oxidative in the presence of O_2 through aerobic oxidation. In presence of CuI, co-catalyst activity of BF_3.Et_2O is much more increased.[38]



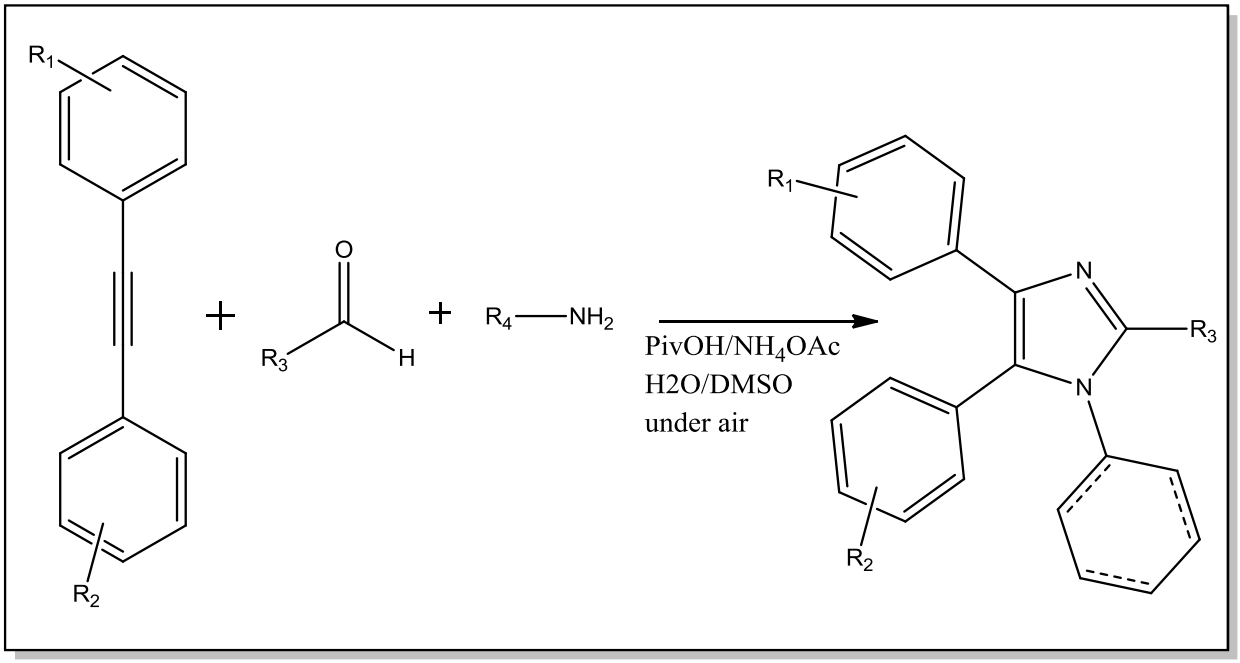
Scheme I.7: CuI/BF_3.Et_2O cocatalyzed synthesis of tri-substituted imidazoles.

In 2013, Bao-Hua Chen et al. reported the multisubstituted imidazole via copper catalyzed cycloadditions reaction. The preparation of multisubstituted imidazoles from 4-methyl-N-phenylbenzamidine and 1-(2-nitrovinyl)benzene using 2,2-bipyridyl (bipy) as the ligand and CuI as the catalyst in DMF at 90 °C under air conditions. In this case Cu^I was primarily oxidized to Cu^{II} in presence of oxygen atmosphere. Finally a copper catalyzed cycloaddition reaction to formation of substituted imidazoles was developed.[39]



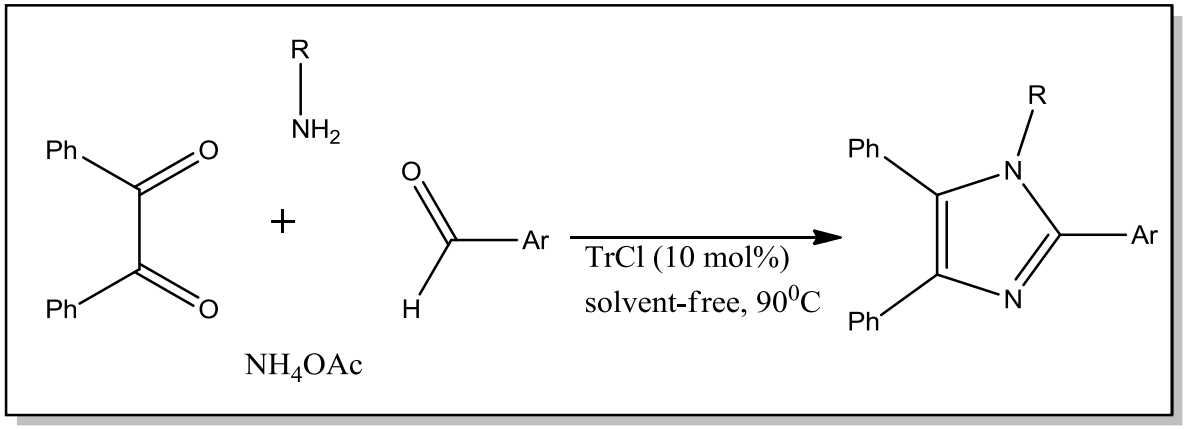
Scheme I.8: Copper catalysed synthesis of multisubstituted imidazoles via cycloadditions.

In 2013, Jeh-Jeng Wang and co-workers reported a metal free multicomponent acid catalyst synthesis of substituted imidazoles with diphenylacetylene and benzaldehyde using various additives, oxidants, solvent and temperature to produced tri-substituted imidazole and derivatives of aniline used for tetra-substituted imidazoles.[40]



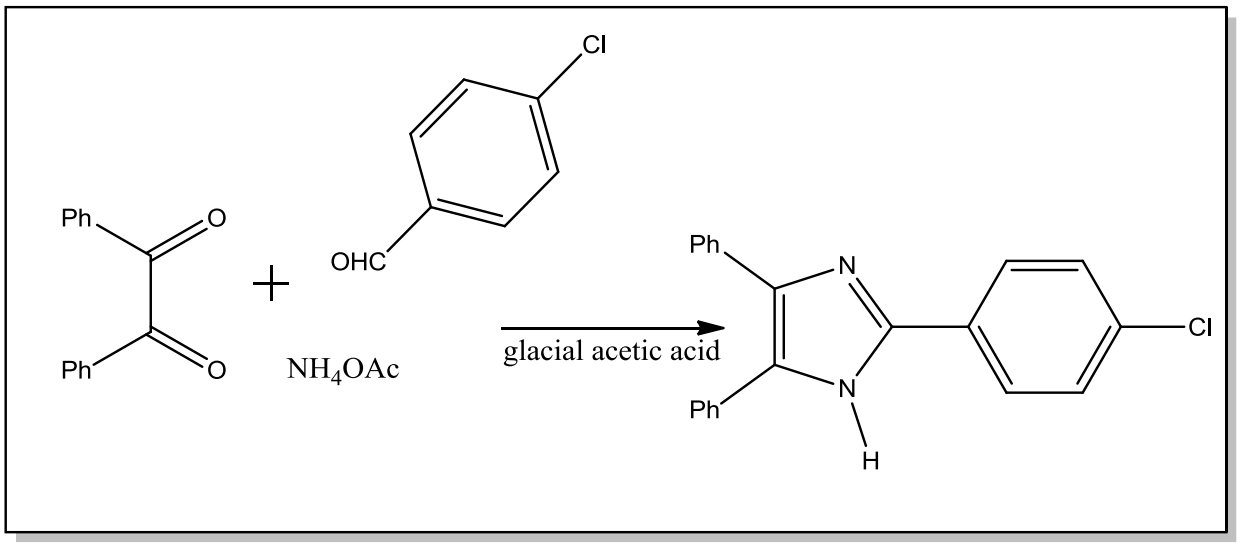
Scheme I.9: Synthesis of imidazole derivatives via multi-component acid catalyzed reactions.

In 2014, Ahmad Reza Moosavi-Zare and co-workers demonstrated one pot synthesis of tetra-substituted imidazole using trityl chloride (TrCl or Ph_3CCl) with benzyl, derivatives of aldehydes, ammonium acetates and finally substituted aniline under solvent-free condition at 90°C. This methodology furnished the more efficient products. Using the all reagents in this method is eco-friendly so it's denoted as a greener process.[41]



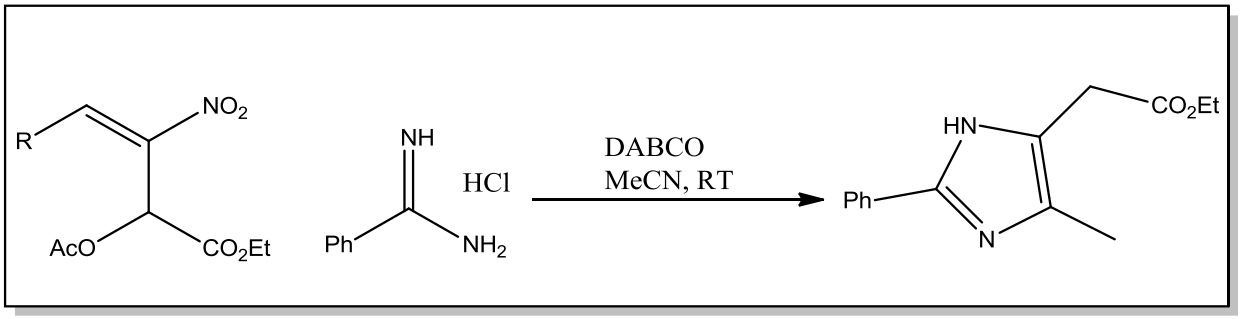
Scheme I.10: Trityl chloride catalyzed synthesis of tetra-substituted imidazole.

In 2014, Iftikhar Ahsan et al described an efficient strategy for the synthesis of derivatives of imidazole containing 2-(4-chlorophenyl)-4, 5-diphenyl imidazole ring as antimicrobial and anti-inflammatory agents with benzyl and chlorobenzaldehyde and ammonium acetate under glacial acetic acid condition. Further, the 2-(4-chlorophenyl)-4, 5-diphenyl imidazole was converted by the corresponding substituent at NH- position to give biological active compound that showed anti-inflammatory and antimicrobial activity.[42]



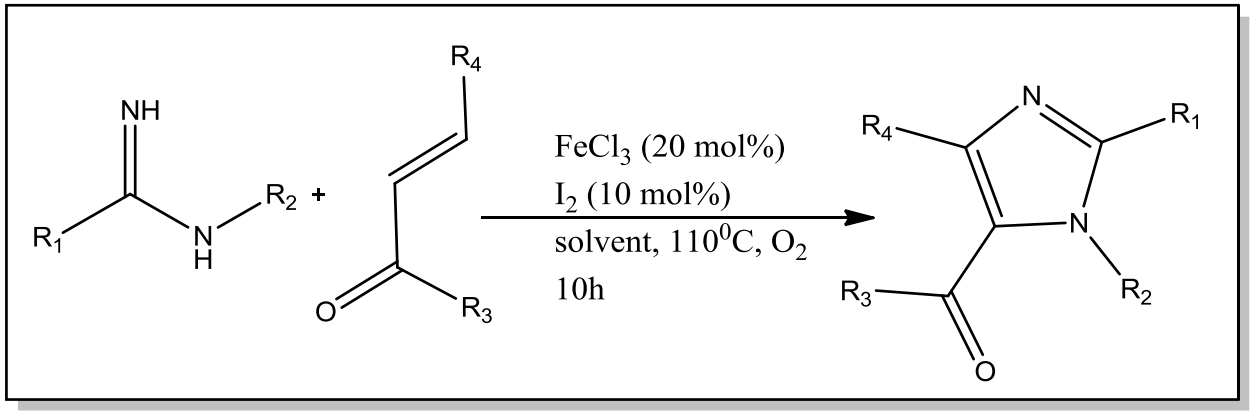
Scheme I.11: Preparation of 2-(4-chlorophenyl)-4, 5-diphenyl imidazole from benzyl in presence of glacial acidic acid.

In 2015, Irishi N. N. Namboothiri et al. envisioned a one-pot reaction to synthesis of highly substituted and bioactive imidazoles ring connecting of Morita-Baylis-Hillman (MBH) acetates of nitroalkenes and amidines under mild conditions. The significant 1,2- and 1,3-bielectrophilic character of nitroallylic acetates and 1,3-binucleophile such as amidine has leads the reaction to produce substituted imidazole with a efficient conversion in presence of a base, DABCO at room temparature.[43]



Scheme I.12: Synthesis of substituted imidazole from MBH acetates having Trypanocidal activity.

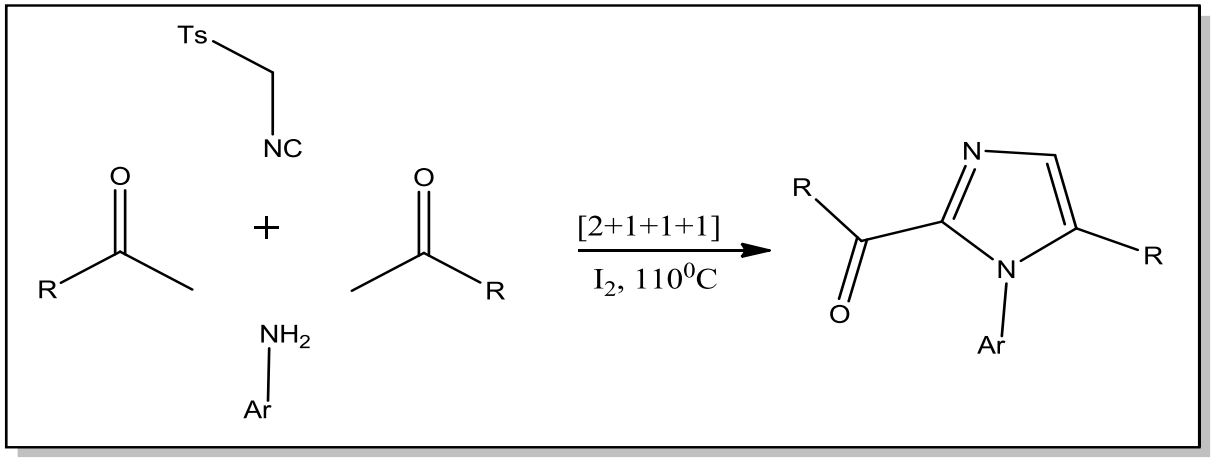
In 2015, Jianli Li and co-workers demonstrated here an efficient and facile route for the preparation of tetrasubstituted imidazoles with amidines and chalcones through $FeCl_3$/ I_2-catalyzed from aerobic oxidative coupling reaction has been developed. This reaction is highly regioselective and more functional groups tolerance as well as mild reaction conditions.[44]



Scheme I.13: Formation of tetrasubstituted imidazole from amidines and chalcones.

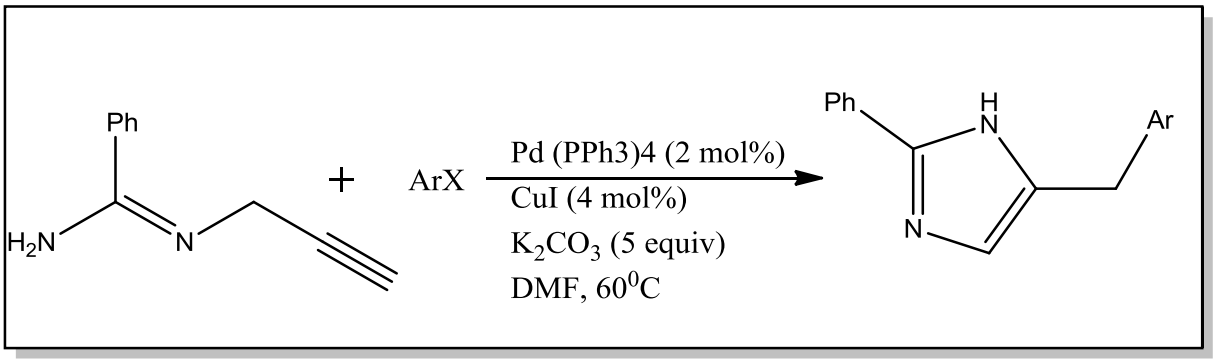
In 2016, Anxin Wu and team reported 1,2,5-trisubstituted imidazole via a formal (2+1+1+1) type annulations through Radziszewski-type reaction in presence of molecular

iodine catalyzed mediated with methyl ketones, tosylmethyl isocyanide and anilines has been unfolded. It is the first time reported example where methyl ketones act as the α-dicarbonyl compounds and aldehydes act in Radziszewski-type reactions. Discussing the mechanistically the reaction may be proceeds by way of a key C-acylimine intermediate and I_2 plays a significant role in the self-sorting tandem reaction.[45]



Scheme I.14: Radziszewski-type synthesis of 1,2,5-trisubstituted imidazole reaction catalyzed by molecular Iodine.

Very recently, Esmail vessally and co-workers revels that synthesis of imidazole derivatives from N-propargyl-benzamidines and aryl halides via a tandem aminopalladation or reductive elimination or isomerization process involving $Pd(PPh_3)_4$ as a catalyst and CuI act as a co-catalyst and in presence of a base, K_2CO_3 in anhydrous DMF medium. The role of co-catalyst is very crucial for the success of this reaction. Even in found that in absence of co-catalyst, reaction will proceed at a longer time and low yield.[46]

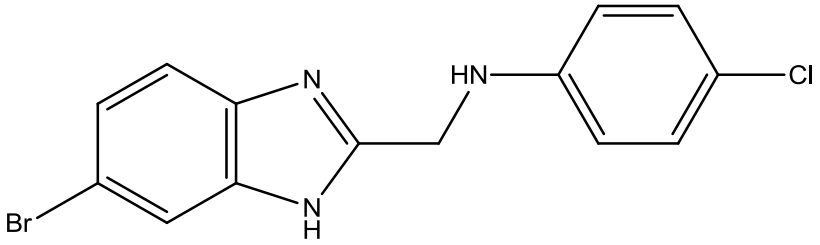


Scheme I.15: Synthesis of substituted imidazoles from N-propargyl-benzimidines via palladium catalyzed.

I.1.A.3. Pharmacological activities of some imidazole moiety:

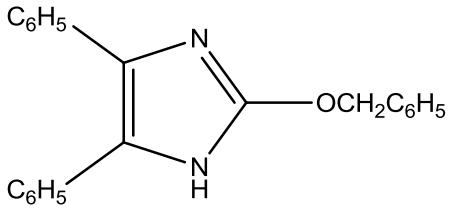
Anti analgesic activity and inflammatory activity:

Kavitha C.S.et al reported a series of derivatives of 2-methylaminibenzimidazole and newly synthesized drugs were screened for inflammatory and anti- analgesic activities. Analgesic activity of this compouds compared with the standard nimesulide drug.[47]



N-((6-bromo-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-chloroaniline

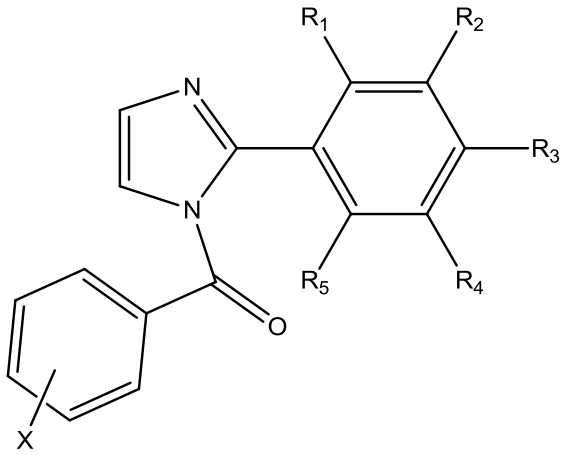
Puratchikody A.et al reported 2-substituted-4, 5-diphenyl-1H-imidazoles and their anti-inflammatory activity of this compound were examined by using Carrageenan-induced paw edema method. Finally found the maximum activity of this compound with reference as an indomethacin drug.[48]



2-(benzyloxy)-4,5-diphenyl-1*H*-imidazole

Anti-bacterial activity and Anti fungal:

Deepika Sharma et al have described [2-(substituted phenyl)-imidazol-1-yl]-menthanone and 2-(substituted phenyl)-1H-imidazole analogues and tested for their antimicrobial activity against Gram negative, gram positive and fungal species. Norfloxacin used as a reference drug.[49]



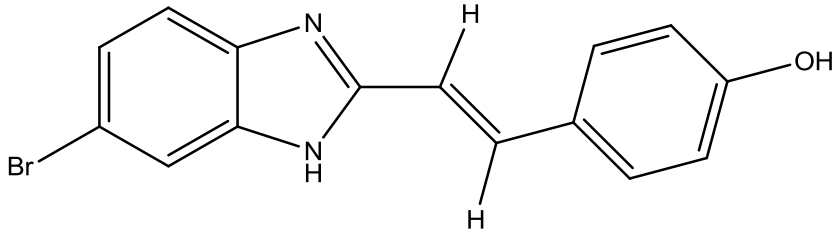
1 R_1=Cl, R_2=H, R_3=H, R_4=H, R_5=H, X=4-NO_2

2 R_1=COOH, R_2=H, R_3=H, R_4=H, R_5=H, X=4-NO_2

3 R_1=H, R_2=H, R_3=Cl, R_4=H, R_5=H, X=2-Br

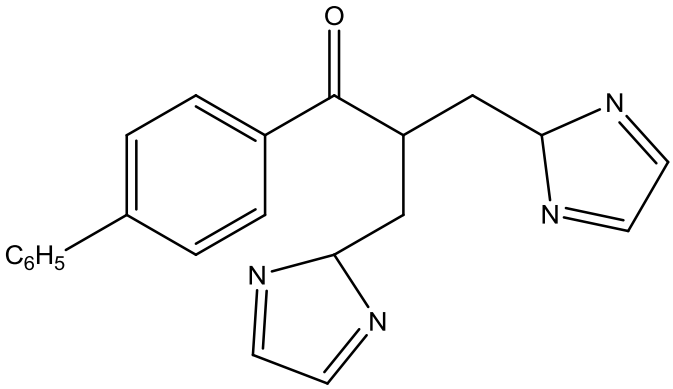
4 R_1=H, R_2=H, R_3=NO2, R_4=H, R_5=H, X=2-Br

Ramya v et al reported a novel series of 5-(nitro/bromo)-styryl-2-benzimidazole derivatives and studies for the anti-bacterial activity against Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae and Enterococcus faecalis and anti-fungal activity against Aspergillus fumigates and Candida albicans. This was compared with ciprofloxacin as reference drug.[50]



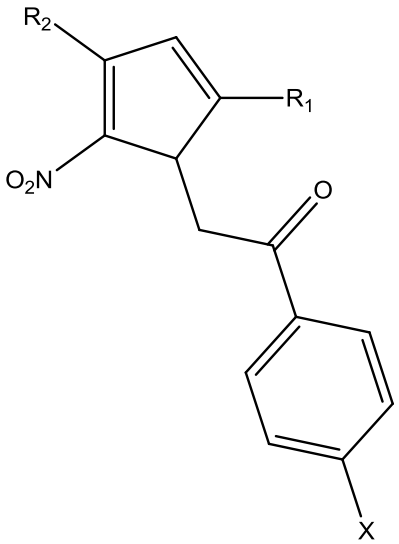
(*E*)-4-(2-(6-bromo-1*H*-benzo[*d*]imidazol-2-yl)vinyl)phenol

Daniele Zampieri et al reported bis-imidazole derivatives and tested for anti mycobacterial and antifungal activity. All compounds have moderate to good activity against Candida glabrata and Candidaalbicans. Miconazole used as a standard reference drug.[51]



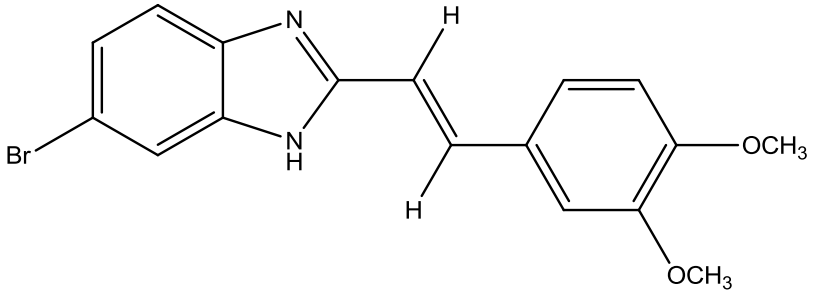
2-((2*H*-imidazol-2-yl)methyl)-1-([1,1'-biphenyl]-4-yl)-3-(2*H*-imidazol-2-yl)propan-1-one

Dorota Olender et al reported nitroimidazole derivatives and studies for their antifungal activity against sclerophoma pityophila using the standard nutrient method. After successfully examined, finally found more potent fungistatic activity of this compound.[52]



1 R_1=H, R_2=Morpholine, X=H

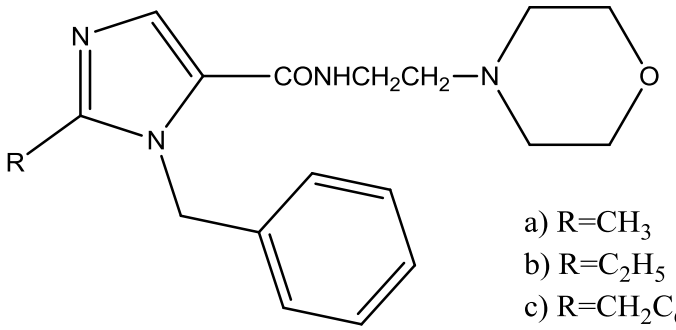
2 R_1=CH_3, R_2=Piperidine methyl, X=Cl



(*E*)-6-bromo-2-(3,4-dimethoxystyryl)-1*H*-benzo[*d*]imidazole

Anti depressant activity:

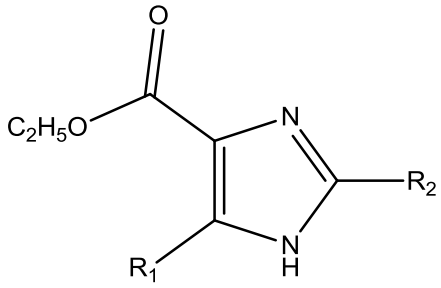
Farzin Hadizadeh et al reported moclobemide analogues by changing moclobemide phenyl ring with derivative of imidazole and tested for the antidepressant activity of this compound using forced swimming test. Compounds 7a-c was found to be more potent as a drug than moclobemide.[53]



a) R=CH_3
b) R=C_2H_5
c) R=$CH_2C_6H_5$

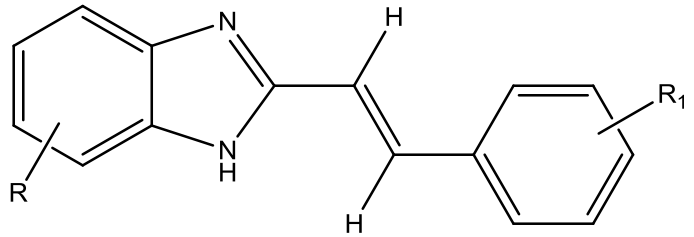
Anti tubercular activity:

Preeti Gupta et al illustrate anti-mycobacterium tuberculosis activities of 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives and substituted ring -1H-imidazole-4-carboxylic acid derivatives against durg-resistent and durg-sensetive M. tuberculosis strains. The compounds 2f and 2h were found most potent as a drug.[54]



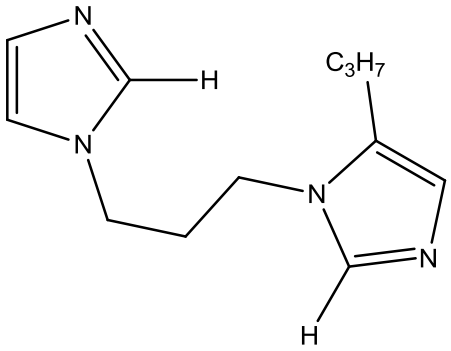
2f=R_1=R_2=C_5H_9
2h=R_1=R_2=C_6H_{11}

Ramya V et al developed a novel series of 5-(nitro/bromo)-styryl-2-benzimidazoles (1–12) derivatives and tested for in vitro anti-tubercular activity of these series against Mycobacterium tuberculosis and all these compounds responded good anti-tubercular activities. Streptomycin was used as a standard reference drug.[50]



For this compound A R=Br, R_1=H
B R=Br, R_1=3,4-OCH_3
C R=Br, R_1=4-CH_3
D R=Br, R_1=2,4-Cl

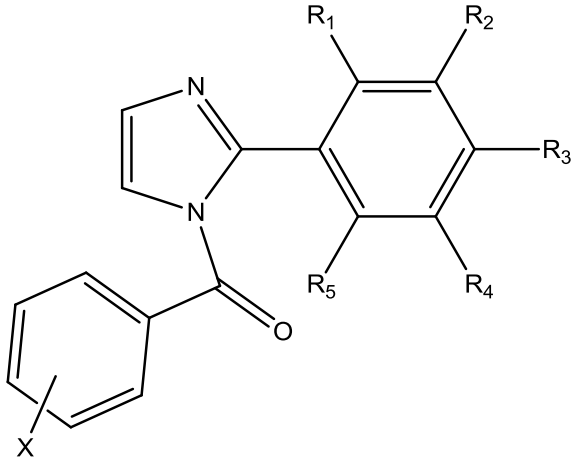
Jyoti Pandey et al reported a series of substituted imidazole derivatives and compounds were tested against M .tuberculosis where this compound showed excellent anti-tubercular activity.[55]



1-(3-(1*H*-imidazol-1-yl)propyl)-5-propyl-1*H*-imidazole

Anti viral activity:

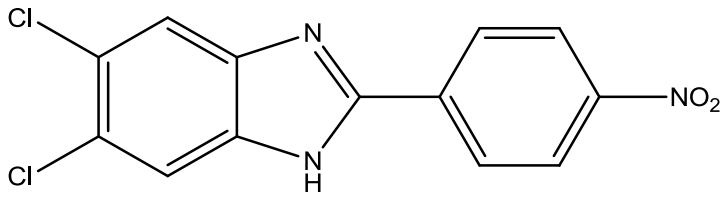
Deepika Sharma et al reported derivatives of imidazole and their antiviral activity against viral strains, testing of (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones analogous indicated that compounds A and B showed as the most potent antiviral agents. Ribavirin was used as standard reference drug.[49]



A R_1=H, R_2=H, R_3=Cl, R_4=H, R_5=H, X=4-NO_2

B R_1=H, R_2=H, R_3=NO2, R_4=H, R_5=H, X=4-NO_2

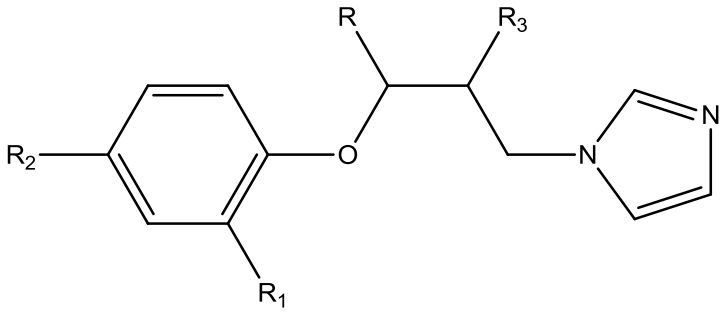
Michele Tonelli et al reported seventy six 2-phenylbenzimidazole derivatives and invented their cytotoxicity and anti-viral activity against a DNA and RNA viruses. Compound ([56-dichloro-2-(4-nitrophenyl) benzimidazole]) showed a high activity as a more potent drug than reference drugs 6-azauridine and smycophenolic acid.[56]



5,6-dichloro-2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole

Anti leishmanial activity:

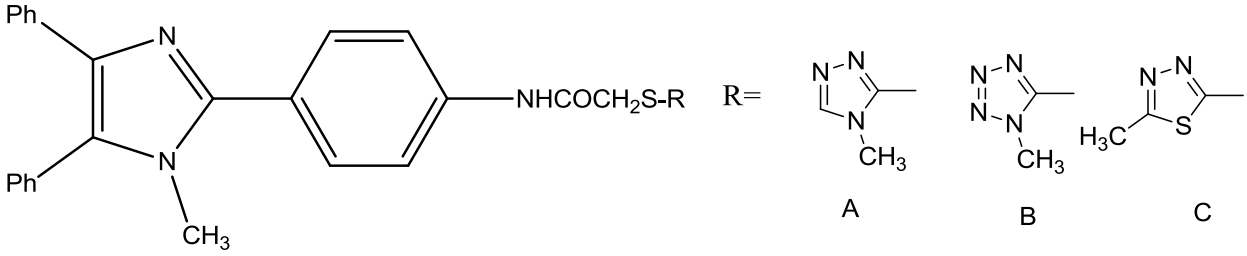
Kalpana bhandari et al reported a novel series of substituted aryloxy aryl alkyl and aryloxy alkyl imidazole and evaluated for their anti-leishmanial activity against Leshmania donovani in vitro process. Most of the compounds showed 94–100% inhibition.[57]



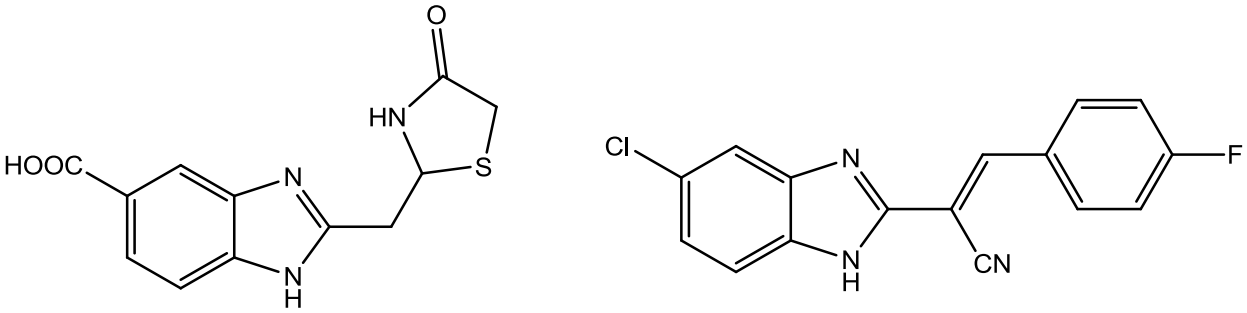
For compound	R	R_1	R_2	R_3
A	=Ph,	H,	CF3,	H
B	$=CH_3$,	H,	CF_3,	H
C	$=CH_3$,	H,	NO_2,	H
D	$=CF_3$,	F,	NO_2,	H
E	$=CH_3$,	NO_2,	H,	H
F	$=CH_3$,	CH_3,	NO_2,	H

Anti cancer activity:

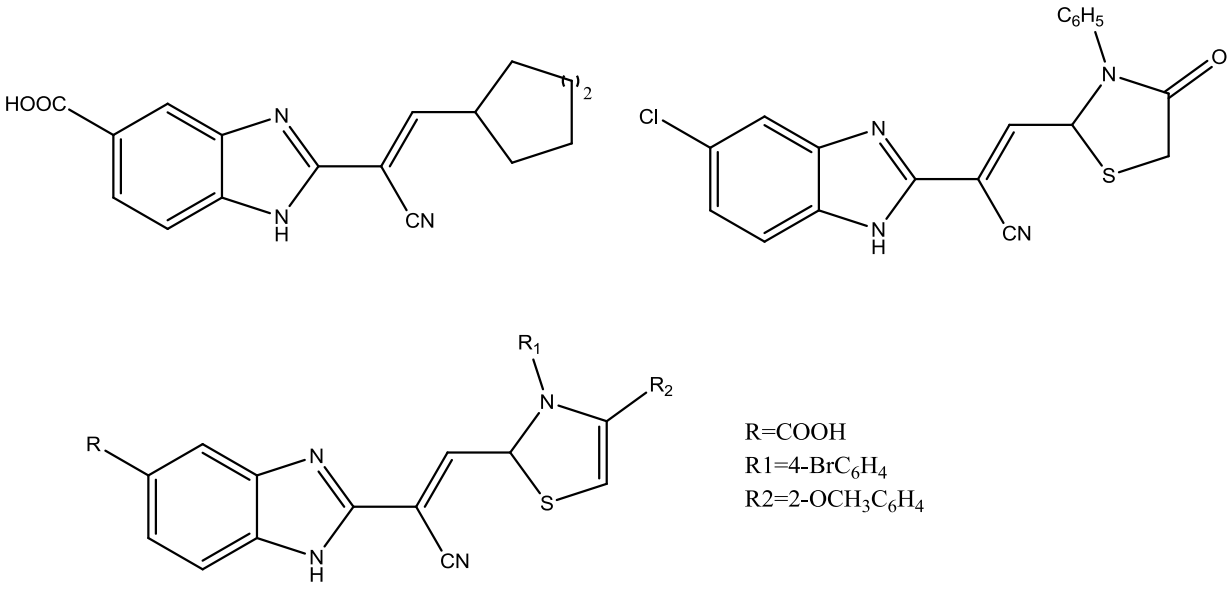
Yusuf Ozkay et al reported so many novel imidazole-(Benz) azole and derivatives of imidazole epiperazine with the purpose of study of anticancer activity. Anticancer activity showing results exposed that these were the most anticancer active compounds in these series. Cisplatin was used as a standard reference drug.[58]



Hanan M. Refaat et al developed various type of 2-substituted benzimidazole. Several of the unfolded products were subjected for anticancer testing which exposed that all the tested compounds displayed antitumor activity against breast adenocarcinoma, human hepatocellular carcinoma and human colon carcinoma. The following two compounds exhibited the maximum potency resistant to human hepatocellular carcinoma.[59]



Antitumor activity against human hepatocellular carcinoma

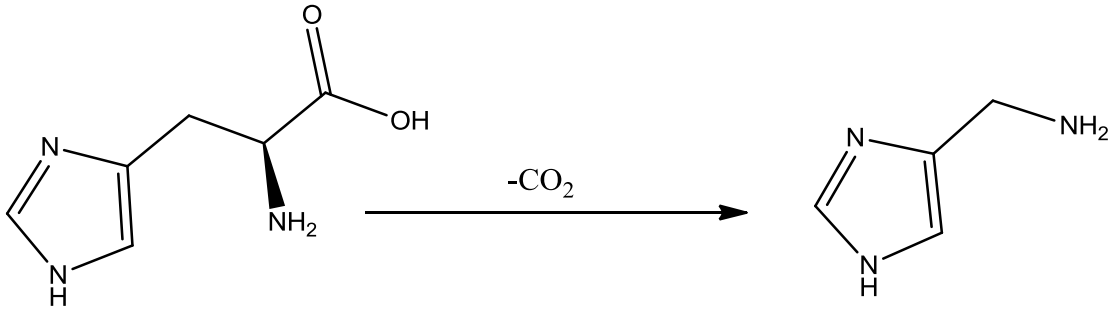


Most active against human breast adenocarcinoma and moderately against human colon carcinoma

I.1.A.4. Biological significance of imidazole:

Imidazole is built-in into many significant biological molecules. The most essential is the amino acid histidine, which has an imidazole ring side chain. Histidine is present in many

enzymes and proteins play a fundamental role in the structure and hemoglobin binding functions. Histidine can also be decarboxylated to histamine, which is also a familiar biological compound. It is a part of the toxin that sources urticaria, i.e. allergic. The decarboxylation of histidine to histamine are shown below



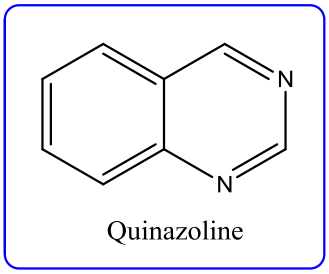
Scheme I.16: Synthesis of histamine from histidine uder decarboxylation.

I.1.A.5. Conclusion:

The above mentions information about imidazole ring containing compounds has clearly shown that the structurally simple imidazole moiety plays a significant role in medicinal chemistry and the related research has been being unusually active subjects. A large amount of work has been reported toward imidazole-based a highly biological activity in medicinal chemistry. Numerous outstanding achievements exposed that imidazole moiety containing compounds possess widely potential application as medicinal drugs, pathologic probes and diagnostic agents. In particular, a huge number of imidazole-based compounds as clinical antibacterial, anticancer, antifungal, antihypertensive, antineuropathic, antiparasitic, antihistaminic agents and so on have been successfully expanded, marketed and widely used in the clinic in preventing and treating different types of diseases with high bioavailability, low toxicity, good biocompatibility and curative effects. An expanding attempt from all over the universe has been directly focusing on imidazole moiety containing compounds for potential clinical application in the diagnosis and treatment of diverse types of diseases. Excitingly, a growing number of derivatives of imidazole have been becoming scientific drug candidates in actively constant research and developments. All these have powerfully suggested the infinite potentiality application of imidazole derivatives in the field of medicine.

I.1.B. Brief review on Quinazoline:

Quinazoline molecules are family of fused heterocycles that are of significant interest because of their various pharmacological profile.[60] Quinazoline catch the attention of the scientists since 1888, with the innovation of the first natural demonstrated - (+)-peganine (vasicine).[61] Quinazoline has become a popular topic up of two fused ring containing aromaticity, a benzene ring and a pyrimidine ring due to its multiple uses.



Quinazoline

Many quinazoline-based compounds have been found to have a wide spectrum of pharmacological activities, which enhanced the research activity in this field. Various substituted derivatives of quinazoline possess an broad range of biological activity for example antimalarial, anticancer, antifungal, anticonvulsant, antiviral, antimicrobial, anti-protozoan, anti-inflammatory, muscle relaxant, diuretic, weedicide, antidepressant, acaricidal, anti-tubercular, and lots of other pharmacological activities.[62-64] Quinazoline compounds are also used in the preparation of a mixture of functional diversity for synthetic medicinal chemistry and also present in several drugs molecules. The synthetic work on quinazolines are showed in huge potentiality and resolved on a variety of pharmacological activities of quinazolines.[65] Quinazolinones are one of derivative of quinazoline which is also very active compound like quinazoline. Quinazolinones will be divided into the following categories, based on the substitution positions in the ring system.[66] (a) 3-Substituted-4(3H)-quinazolinones (b) 2-Substituted-4(3H)-quinazolinones, (c) 2,3-disubstituted-4(3H)-quinazolinones, (d) 2,4-disubstituted-4(3H)-quinazolinones (e) 4-Substituted-quinazolines. Depending upon the nature of arrangement of the keto or oxo group, these lead compounds may be three forms of categories of which, 4-(3H)-quinazolinones are most common, either as natural products or as intermediates in several projected biosynthetic pathways.[67]

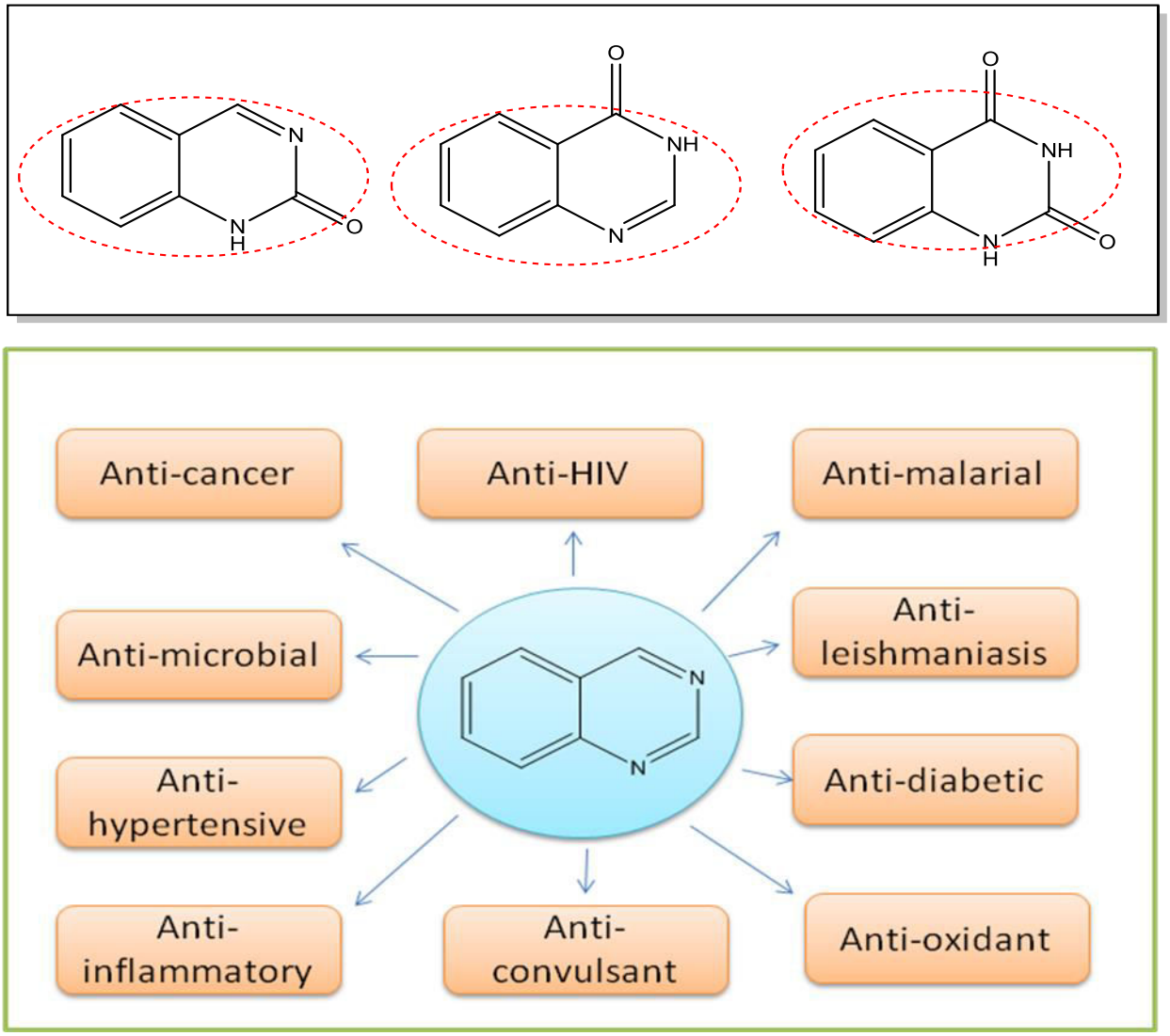


Figure I.1: Biological activity of quinazoline scaffold.

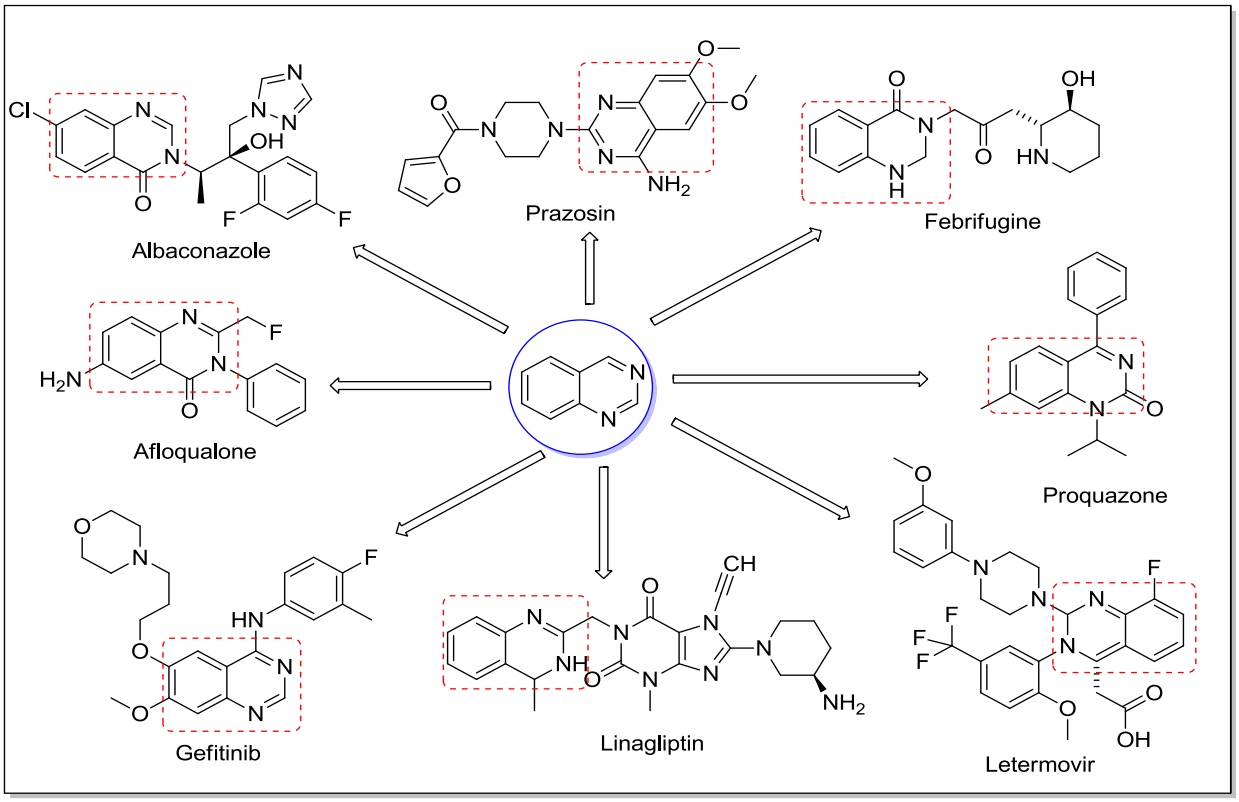


Figure I.2: Quinazoline moiety containing marketed drugs.

I.1.B.1. Importance of quinazoline nucleus in biological field:

Quinazoline as Anticancer:

A main difficulty about healthiness which concerns medical society is cancer disease throughout the world. The extensive progress in various aspects of cancer research come about in researcher, cancer chemotherapy is extremely insufficient.[68] Abdel Gawad et al.(2010), reported the quinazolin-4(3H)-one derivatives compounds are very well-known in industrial interest, medical and technological. A variety of new 3,4-dihydro-quinazolin-2(1H)-one and 3-substituted quinazolin-4(3H)-ones derivatives are demonstrated that compounds 3-(4-chlorophenyl)-2-[2(4methoxyphenyl)-2-oxo-ethylthio] quinazolin-4(3H)-one (1) and 2-[2-(4-chlorophenyl)-2-oxo-ethylthio]-3-(4-methoxyphenyl) quinazolin-4(3H) one as wide-ranging anti-tumor confirm effectiveness toward various cell lines that belong to indivisual tumor subpanels.[69]A novel series containing thiosemicarbazide moiety quinazoline derivatives (2) and evaluate the biological activity as an antitumor agents by He et al. (2012).[70] Fernandes et al. (2007) reported a series of novel quinazoline derivatives (3) were investigated for their function as EGFR inhibitors by

using radio iodination. All quinazoline containing compounds were further investigated for their potential SPECT activity for breast cancer molecular imaging.[71] Noolvi et al. (2013) demonstrated a novel series quinazoline derivatives (4) were investigated for the biological response against tyrosine kinase (EGFR).[72] The 3-(pyrimidin2-yl)-2 styrylquinazolin-4(3H)ones (5) and 3-(3-methylisoxazol-5-yl) were arranged by refluxing in acetic acid corresponding 2-methylquinazolinones followed by the benzoic aldehyde and examined for their anti-leukemic activity in vitro against K-562 (human chronic myelogenous leukemia), HL-60 (human leukemia) and L-1210 (murine leukaemia) cell lines screening in a few cases good activity by Raffa et al. (2004).[73] In 2008, Chinigo and co-workers reported 2,3-dihydro-2-arylquinazolin-4-ones (6) and activity evaluation found to have potent fluorescent tubulin inhibition with anticancer. In 2010, Tian and co-workers reported a series of novel 5, 8 disubstituted quinazolines (7) and were found to have antitumor activity. In 2010, Sirisoma and co-workers reported N-methyl-4-(4-methoxy anilino) quinazolines (8) and mentioned that all these compounds induced apoptosis. Krishnan et al.(2011) reported a series of novel 3-(benzylideneamino)-2-phenyl quinazoline-4(3H)-ones (9) from 3-amino-2-phenyl-3H-quinazoline-4-one with a variety of carbonyls compounds and evaluated cytotoxic activity.[74] In this study, a novel series 7 or 8-substituted-4-morpholinequinazoline derivatives (10) was proposed and synthesized. Their anti-proliferative activities, PI3Kα inhibitory activities against few cancer cell lines, namely, DU145, PC-3, U937, BT474, MCF-7, A431, and SK-BR-3 were investigated in vitro by Tu et al.(2015). Most active compound showed to be a potential drug with high PI3Kα inhibition activity (IC = 4.2 μM) and excellent anti-proliferative activity. Active compound was also analyst for its inhibitory activities against new kinases, such as PI3Kβ, PI3Kδ, mTOR and PI3Kγ its outcome on p-Akt (S473) and cell cycle. These results indicated that compound could considerably inhibit the mTOR/ Akt/PI3K pathway as a potent anticancer agent and PI3K inhibitor.[75]

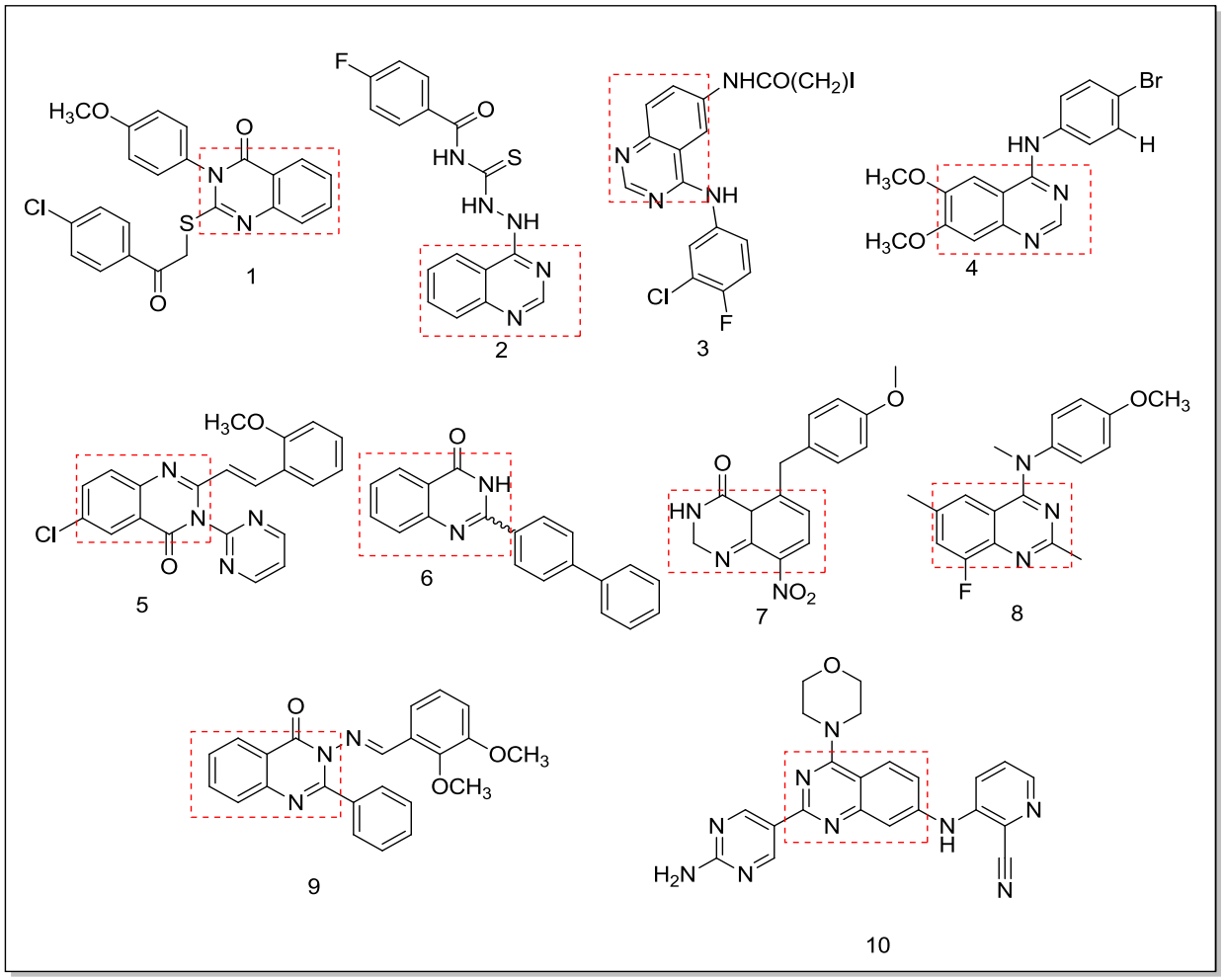


Figure I.3: Quinazoline nucleus containing anticancer drugs.

Quinazoline as Anticonvulsant

A neurological condition, Epilepsy, which is universally upsetting almost 0.5 to 1% of the global population annually [45 to 100 million people], is a relation of neurological disorder, which if kept untreated, can affect the human brain and lead to other neurological deficits. Patients with epilepsy, in severe cases, retain a normal life by the use of antiepileptic drugs (AEDs), and others continue for the management of epilepsy, which can provide control or total gross relief of the seizures.[76] Aly et.al in 2010, synthesized a compound, named 3-aryl-4(3H)-quinazolinone-2 carboxaldehydes (11), thio-semicarbazone derivatives and their corresponding Schiff's Base and reported these compounds as anticonvusants.[77]Mukherjee et.al. in 2014,[78]

synthesized a compound named 2, 4-dichloroquinazoline (12) which was made to react with different N-substituted piperazines and a series of compounds were obtained [6(A-G)]. All the compounds synthesized were characterized by spectral data, and it was found that these showed anticonvulant activity. Ibrahim et. Al. In 1998 studied the anticonvulsant activity[79] of a series of 3-substituted-6,8-dichloro-2-phenyl-4(3H)-quinazolines (13) and he was successful in his operation. Jatav et. Al. In the year 2008, prepared a series of 3-[5-substituted 1, 3, 4-thiadiazole-2-yl]-2styryl quinazoline-4(3H)-ones derivatives (14) and evaluated their activity for their use as antidepressant agents.[80] Many 1-(4-substitutedphenyl)-3-(4oxo-2-phenyl/ethyl4H-quinazolin-3-yl)-urea derivatives (15) have been examined for their anticonvulsant activity (16) by MES and Kashaw et. Al. In 2009[81] were found to be active in the scPTZ screen after testing them on mice.

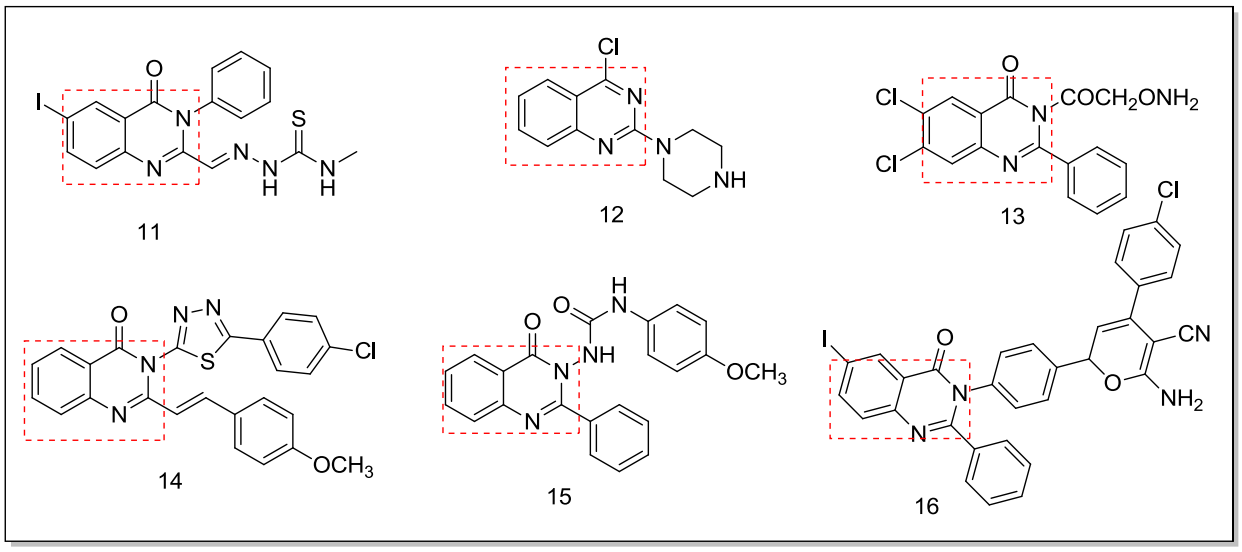


Figure I.4: Quinazoline nucleus containing anticonvulsant drugs.

Quinazoline as Anti-inflammatory and Analgesic

Anti-inflammatory drugs (NSAIDs) which are Non-steroidal such as acetylsalicylic acid (ASA) majorly contributed in the management of inflammation and pain. Cycloxygenase (COX), the essential enzyme in prostaglandin biosynthesis, exists in 2 forms, constitutive COX-1 (responsible for physiological functions) and inducible COX-2 (involved in inflammation). Inhibition COX described both the beneficial effects (inhibition of COX-2) and adverse effects (inhibition of COX-1) of non-steroidal anti-inflammatory drugs (NSAIDs).[82]

Mohamed et al successfully synthesised two series of 2-phenyl-4(3H) quinazolinone derivatives (17).As far as indomethacin was considered as the reference drug,[83] most of the tested quinazolinone derivatives showed considerable potent anti-inflammatory and analgesic activity of superior GIT safety profile in experimental rats. In addition, some compounds surpassed the work of indomethacin as the reference drug and were the most potent antiinflammatory in experimental rats. Baja kumar et al. (2010) synthesized a series of novel 8/10 trifluoromethyl-substituted-imidazo [1, 2-c] quinazolines (18) and evaluated in vivo (rat paw edema) for their anti-inflammatory activity and in silico (docking studies) to recognize the hypothetical binding motif with the Cycloxygenase enzymes (COX-1 and COX-2) employing GOLD (CCDC, 4.0.1 version) software and found that compounds shows good anti-inflammatory activity against standard: indomethacin.[84] Alafeefy et al.(2010) synthesized quinazoline derivatives (19) which showed potent analgesic and antiinflammatory activity. The reference compound indomethacin was found to be highly inferior as compared to the potent activity of these compounds as anti-inflammatory analgesic.[85] Hemlatha et al.(2011) synthesized a series of some novel 2, 3disubstituted quinazolinone derivatives (20) by condensing 2-methyl/ 2-phenyl/6-bromo-2-methyl/6-bromo-2phenyl/6, 8-dibromo-2-methyl/ 6, 8-dibromo-2-phenyl benzoxazines with compounds containing amino group were confirmed by IR, C-NMR and Mass spectral data and evaluated for their analgesic activity. The report was that this compound (21) showed promising analgesic activity compared to standard drug diclofenac sodium.[86]

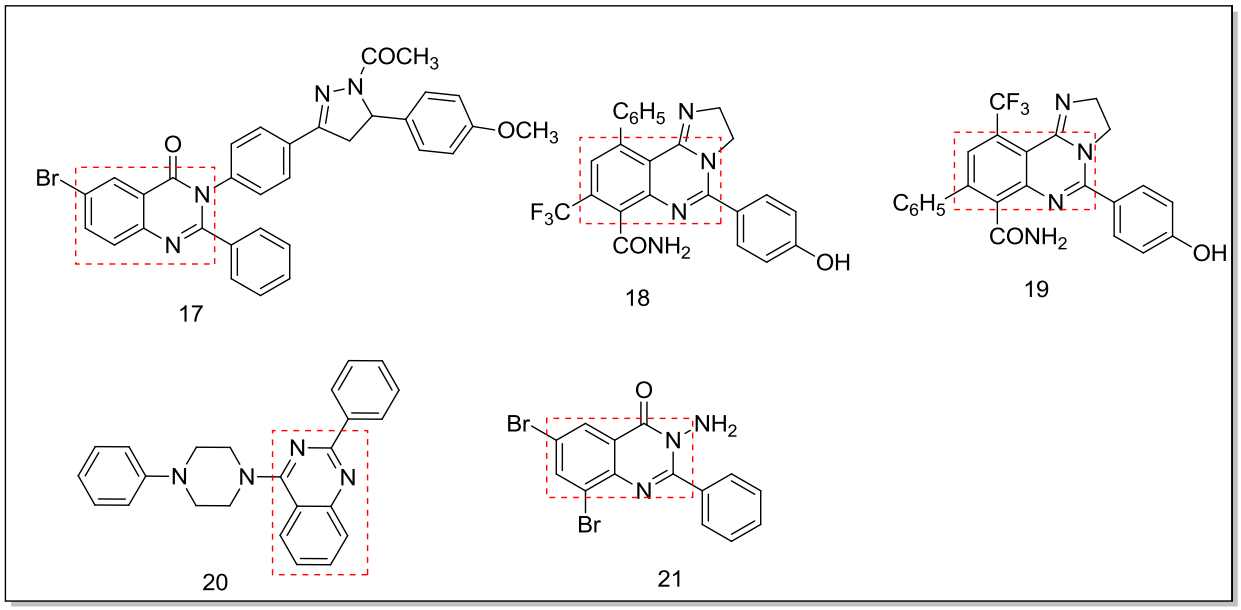


Figure I.5: Quinazoline nucleus containing anti-inflammatory and anti-analgesic drugs.

Quinazoline as Antimicrobial

Diseases caused by the multi-drug resistant bacteria are life threatening. Their quantity has reached a high shocking level in many countries or precisely more or less, the entire world. At this moment, SARS (or, Severe Acute Respiratory Syndrome) that is caused by the Corona virus SARS-CoV and bird flu, that is caused by the H5N1 (or avian influenza) virus have come forward to become the two most important contagious diseases, when thought about their epidemic perspective. These infections have crossed the hurdle of species to get itself transmitted to humans.[87] Patel et. Al. In 2011, had synthesised 2-[2-(2,6-dichlorophenyl) amino] phenyl methyl-3-[(5-substitutedphenyl)1,5-dihydro H-pyrazol-3-yl-amino]-6-iodoquinazolin-4(3H) ones (22), a new series of compound. This was prepared by mixing 2-[2-(2,6-dichlorophenyl)amino] phenyl methyl-3-1substituted phenyl acryl amido-6-iodoquinazolin-4(3H)-ones along with hydrazine hydrate, and this was done in the presence of acetic acid [glacial]. The compounds that were synthesized, were then tested for their antibacterial activity. This was done in vitro, by measuring a zone of inhibition (in mm) by a cup plate method and was texted against two different strains like two Gram positive bacteria such as Bacillus subtilis, Staphylcoccus aureus and two Gram negative bacteria such as Certium, Escherichia coli. This work was conducted under two different concentrations, 100 µg/mL and 50 µg /mL.[88] Gautam et. Al. In 2012

synthesized some 4, 6-disubstituted derivatives (23) and tested these for their anti microbial activity that started from anthracitic acid derivatives by normal conventional methods. At the initial level, acylation was followed by cyclisation. Then, benzoxazinones were obtained, which when treated further with ammonia. This reaction yielded the crucial intermediate, 2-substited, benzamide. Then the product was subsequently cyclised to obtain quinazoline, which on chlorination yielded various 4,6-disubstituted quinazoline derivatives.[89] Jatav et. Al. In 2008 prepared 3-[5-(4-substituted phenyl)-1,3,4-thiadiazole-2yl]-2-styryl quinazoline-4(3H)-ones (24) and reported that these showed anti-fungal and anti-bacterial activity.[90] All these compounds showed antifungal activity in good amounts, especially those which had a wide spectrum of values that ranged from 8.3 to 64.2 μg/mL. Of bioactivity ; it shows potent inhibitory activity on the growth of most of the fungi with EC50 values ranging from 8.3 to 46.2 µg/ml. Octahydroquinazoline (25) was found on modification of the Biginelli reaction with phenacyl bromide and bromomalononitrile for furnishing thiazolo [2,3-b] quinazoline and it was found that the interaction of the compound with formamide, formic acid, and phenyl isothiocyanate had yielded the corresponding pyrimidine thiazolo [2,3-b] quinazolines(26) and that revealed antifungal activity against Candida albicans by Ghorab et al. in the year 2000.[91]

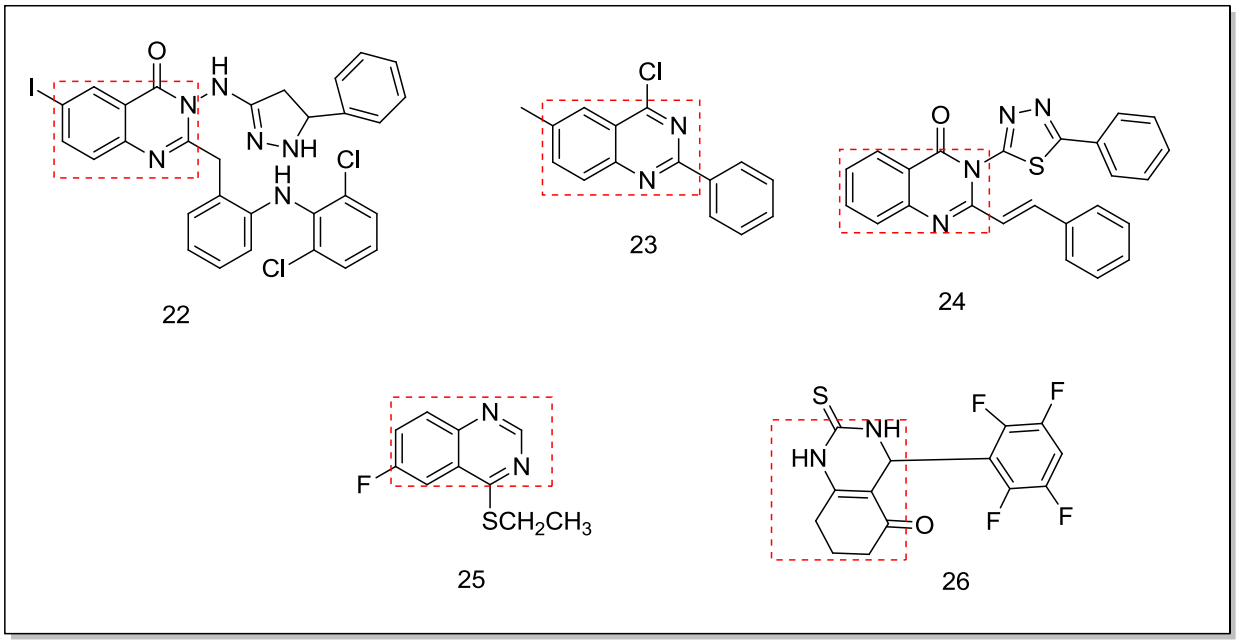


Figure I.6: Quinazoline nucleus containing antimicrobial drugs.

Quinazoline as Anti-malarial

Malaria is the most well known protozoan disease. Malaria infects about 300-600 million people and kills about 3 million in a year. While the most influential weapon against malaria would actually be a lifelong vaccine, there has been a failure of various vaccine developments indicating that extremely active vaccine is extended way from certainty. The rising incidents of several drug resistant strains in the malaria prevalent field have extensively reduced the efficacy of current anti-malarial drugs for prophylaxis and the management of this ailment. Therefore, drugs based on new mode of working are compulsory to overcome the coming out of resistance as well as to manage the ever increasing figure of the epidemic that is caused by the malaria parasite.[92] Mohammed et al. (2015) synthesised six 3-aryl-2(substituted styryl)-4(3H)-quinazolinone derivatives (27) by the treatment of 3-aryl-2-methyl 4(3H)-quinazolinone (intermediate species) with a various types of substituted aromatic aldehydes. Their structures were finally confirmed by IR, HNMR, CNMR spectroscopic procedures and several elemental microanalyses. The synthesized compounds were then evaluated for their corresponding in vivo anti-malarial activity against a strain called P. berghei. Four of the produced compounds possessed the activity against the parasite. One of them was found to be the most active one amongst them. Results of the acute toxicity study had shown that oral administration of the synthesized drugs in single doses (100, 250 and 500 mg/kg) had no adverse effects thus indicating that the compounds have very high safety margin and their corresponding LD50 is much higher than 500 mg/kg. As a whole, this study thus indicates that 4(3H)-quinazolinone derivatives are effective sources of lead compounds for anti-malarial drugs.[93] Sen et al.[94] (2010) prepared a series of 2-substituted and 2,3-substituted quinazolin-4(3H)-one derivatives (28) depending on the structure of febrifugine. The in vivo biological activity results indicated that these compounds exhibited anti malarial activities by Werbel et al. (1987) against P. berghei in mice, at a dose of 5 mg/kg. As compared to Chloroquine or Artemisinin, these compounds have the advantages of a shorter synthetic route and consequently they are highly cost effective in nature. Werbel et al. (1987) synthesized a variety of similar 2, 4-diamino-6-[(aryl) thio] quinazolines (29) with well known anti-malarial properties where the 4-amino group was substituted by hydroxyamino and hydrazino moieties and it was found that such changes reduced

remarkably the anti-malarial properties of this series. The compound was again tested against a normal drug-sensitive strain of P. berghei in mice by the parental route.[95]

Quinazoline as Anti-oxidant

Selvam et al. (2010), synthesized a number of novel thiazolo quinazoline derivatives(30) by reaction of various aromatic aldehydes with 4-nitro aniline and the chemical structures of the compounds were finally confirmed by IR, H-NMR, mass spectroscopy and elemental analyses and was screened for the antioxidant activity by nitric oxide scavenging activity, DPPH radical assay and the Hydrogen Peroxide scavenging activity and it was reported that compound was found to exhibit the most effective anti-oxidant activity.[96]Al-Omar et al. 2006[97] synthesized a completely new series of 6-iodo-2-propyl-4(3H)-quinazolinone (31) and its condensed heterocyclic and was screened for their antioxidant activity. Selvam et al.(2010) synthesized some compounds which inhibited aldehyde oxidase effectively by more than 98%. A series of novel thiazolo quinazoline derivatives (32) by reaction of various aromatic aldehydes with 4-nitro aniline are screened for their antioxidant activity by nitric oxide scavenging activity, DPPH radical assay and hydrogen peroxide scavenging activity and it was reported that the synthesized compounds were found to possess the most efficient antioxidant activity.[98]

Quinazoline as Anti-leishmanial

Sinha et al. (2013) synthesized a series of compounds 4-(substituted benzyl dine)-2-substituted-3,4,5,6tetrahydrobenzo[h]quinazolinefrom2-(substituted-benzyl dine)tetralone-1 (33) and several other substituted guanidine sulphates and were evaluated for their in vitro anti-leishmanial activity and it was reported that the compounds showed significant amount of anti-leishmanial activity against the parasite Leishmania donovani.[99] Agarwal et al. (2009) synthesized 4-(Substitutedbenzylidine)-2-substituted-5, 6 dihydrobenzo[h]quinazoline and 4-(substituted benzylidine)-2-substituted-3, 4, 5, 6 tetrahydrobenzo[h]quinazoline (34) using 2-(substituted-benzylidine) tetralone-1 and other substituted guanidine sulphates and then evaluated their in-vitro anti-leishmanial activity and then reported that the compounds showed high amounts of anti-leishmanial activity against Leishmania donovani.[100]

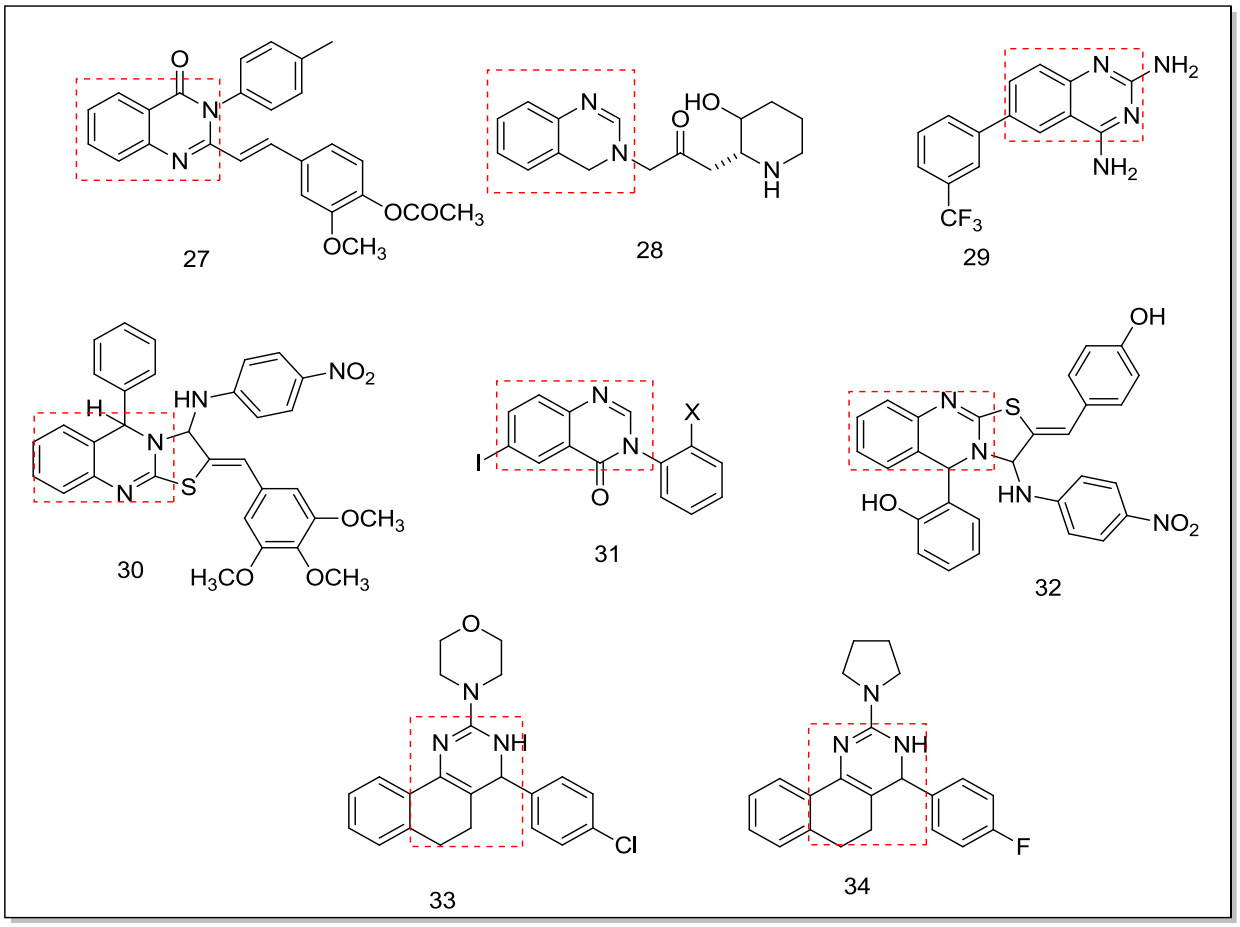


Figure I.7: Quinazoline nucleus containing anti-malarial, anti-oxidant and anti-leishmanial drugs.

Quinazoline as Antihypertensive

Patel et al.(2013)[101] synthesized an entirely new Quinazoline derivative (35) in three steps and then screened for the α1-adrenergic receptor blocking activity. Alagarsamy et al.(2007) synthesised a new series of 3-benzyl-2 substituted-3H-[1,2 ,4]triazolo[5,1-b]quinazolin-9-ones (36) by the cyclo condensation of 3-amino-2-benzylamino-3H-quinazolin-4-one. The compounds were then evaluated in vivo anti-hypertensive activity. All the compounds showed significant amounts of antihypertensive activity. The compound 3-benzyl-2-methyl-3H-[1, 2,4]triazolo[5,1-b] quinazolin-9-one showed antihypertensive activity much more than the conventional drug prazocine.[102]

Quinazoline as Anti HIV

Pandeya et al. (1999) synthesized a new quinazolinone which showed Anti-HIV activity where the compound 3amino-2-methyl mercaptoquinazolin-4(3H)-one (37) was prepared by the condensation of the acidic amino group of isatin with formaldehyde and secondary amines and were evaluated for anti-HIV activity against HIV-1 III B in MT-4 cells.[103] Yahia et al.(2012)[104] synthesized a new series of dihydrobenzo[h]quinazoline derivatives (38) from aryl ethylenethiopyrimidine and 2-(4-(thiophen-2-yl)-5,6-dihydrobenzo[h]quinazolin-2-ylthio) acetic acid as the starting materials. The biological screening then showed that several of these compounds have high amounts of anticancer and antiviral activities. In the year (2004), anti-HIV activities by some 2,3- substituted quinazolin-4(3 H)-ones were being reported by Agarsamy et al., who synthesized the compound 2-mercapto-3-[(benzimidazol-1--methylamine]-quinazolin4-(3H)-one (39) which exhibited maximum 31% and 25% protection against HIV-1. Especially, 2-mercapto-3[(pyridine-2-yl)-methylamino]-inazolin-4-(3H)-one showed 27% protection against HIV-2.

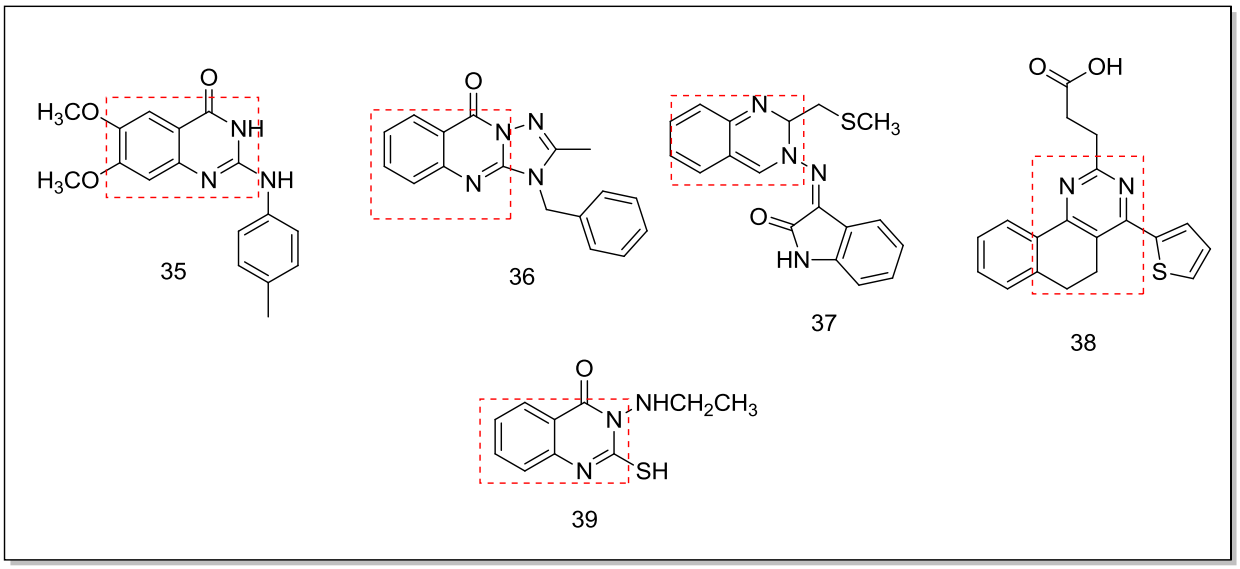


Figure I.8: Quinazoline nucleus containing anti-hypertensive and anti-HIV drugs.

I.1.C. Conclusion:

Quinazoline rings have been studied extensively; the variety in the structural modifications surrounding the ring system subsequently gives a measure of their effectiveness

for the treatment of various pathophysiological conditions. Quinazoline, being an important body of pharmacephore, has various types of groups and substituents attached to it. The results of the diverse literature survey conclude that Quinazoline shows various types of biological activities. Thus, it can be concluded that the above mentioned work will bestow with the diverse and novel drug synthesis and enhancements for an improved efficiency and lowered toxicity.

I.1.D. Benign Methods in Organic Synthesis

I.1.D.1. Solventless Reactions

Normally the assumption with regard to organic reactions is that the reactions are performed in a solvent medium. The reason behind this concept is quite simple. The interactions of the reactants in the solvent medium is effective, in homogenous solutions, facilitating the shaking, stirring or other different ways of agitation. The reactant molecules can hence come together, continuously and rapidly. In addition to this, if uniform cooling or heating of the mixture is required, would be easy to carry out in a solvent-inclusive reaction medium. Hence, the solvent's role in an organic reaction is much more complex, than we think of, let alone providing a homogenous medium for conduction of a larger number of collisions of the reactants taking place. A solvent can work hand and gloves with the process of the organic reaction through the solvation of the products and reactants, the transition state or any other species that intervene in the course of reaction. Despite such a strong involvement, the product does not usually include the solvent [which is the case in solvolysis reactions], and is recovered in an unchanged condition after the completion of the reaction. Hence, we normally do not envisage or plan for performing a particular reaction in the solvent's absence.

Any liquid can act as a solvent by principle. But there is a restriction in a number of commonly used solvents. Chlorinated hydrocarbons, esters, a few hydrocarbons, a few ethers, sulphoxides, amide derivatives, alcohols, water, CS_2, liq. Ammonia, etc. are in frequent use for carrying out an organic synthesis. The choice one makes about a solvent depends on many factors. If an experienced investigator or researcher has to make selections for a solvent for a particular new synthesis, he would keep in mind its physical and chemical properties. Sometimes, the reactant, if liquid would itself act as a solvent. Considering every case, we can never overlook its use in any particular reaction. It has been reported by GlaxoSmithKline [GSK]

that in a pharmaceutical process,[105] 80-90% of the mass intensity is typically constituted by the solvent, and this fact was validated by a benchmarking exercise conducted by a pharmaceutical industry in 2007 which involved seven inventor pharmaceutical companies. After careful conduction and assessment conducted over many years over pharmaceutical batch reactions, the biggest mass contributor to the processes as found were the solvents and this was confirmed by GSK. The organic solvents are normally volatile liquids that are difficult to store, as they are employed on huge amounts, and hence contribute to be on the list of the chemicals which get damaged easily.

Even now, the basis of our chemical operations is mostly organic, and contains various environmental and health concerns and their source continue to be petroleum. Though they are recycled as and when possible but this is not the case always, since this process is rarely accomplished which an efficiency of unity. This however means that some chemicals would escape from the reaction vessel and would severely pollute the environment. Hence Green Chemistry comes into existence. This area of research involves the replacement of hazardous solvents with their eco-friendly counterparts which stops the pollution of the environment. Therefore the best way to curb this problem would be to stop the use of solvents and make the reaction medium solvent-free.[106] This, in recent times, has led to increase in vigorous research activity and also reinvestigation of reactions which are known, so that that we could achieve an organic synthesis under solvent-free conditions.

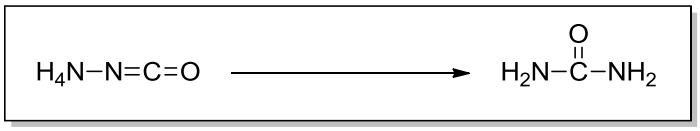
But, we still observe that some chemists even at this day carry out their reactions in the solution phase, when they know that the reason behind the use of solvents cannot be found until this day. This can be because a reaction which is carried out without the use of a solvent, or in a solid state, was generally thought to be less feasible or inefficient with respect to the reactions which use solvents, even though, organic reactions that are solid state reactions have been known to exist. The fact of the matter today is that organic chemists are trying to choose solvent free media over solvents, although many modern solvents, such as ionic liquids, water and fluorous media are gaining prominence, but still we can say that not using a solvent is a better option over the others.

Reactions that are performed under solvent-free conditions have many advantages. Since the requirement of a solvent is nil, hence the process would be economical too, as it saves the money that would be required in the buying of a solvent. The rates of the reactions too are high owing to the fact that the reactants are of higher concentrations. At the end, since we do not require removing the solvents after the reaction is complete, hence the workup decreases. During industrial production, these would gain special importance, and the environment too would be benefited as well.[107]

A process that is solvent-free or solvent-less, may be carried out by incorporating the reactants in zeolites, clays, alumina, silica, other matrices etc. or can also be carried out using the reactants alone. Ultrasound, irradiation with UV, microwave or thermal processes can gain employment during the course of reaction. While there are many advantages, the researcher must be careful to conduct the mixing of the reactants in a homogenous system, which is problematic, because the system has high viscosity. To add to this, this methodology becomes unsuitable for reactions that are solvent assisted.

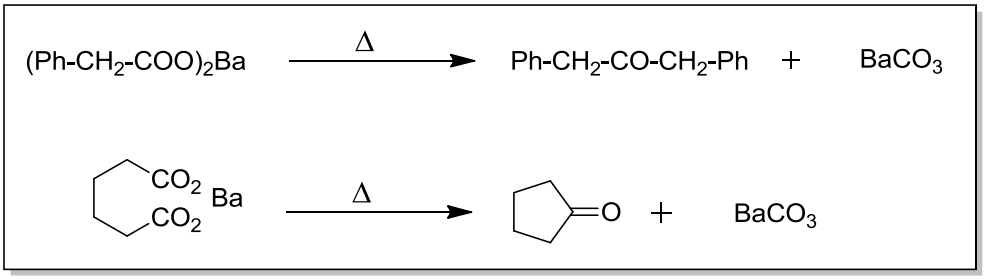
I.1.D.2. Developments in Solvent-less Synthesis

There are of path an enormous many reactions that can be happened in the absence of a solvent. Solid state reactions are very well known process. Its application can also be found in undergraduate text books. In fact, first organic synthesis by Wohler of urea achieved in 1828 belongs to this family are the historically significant (Scheme 1).[108]



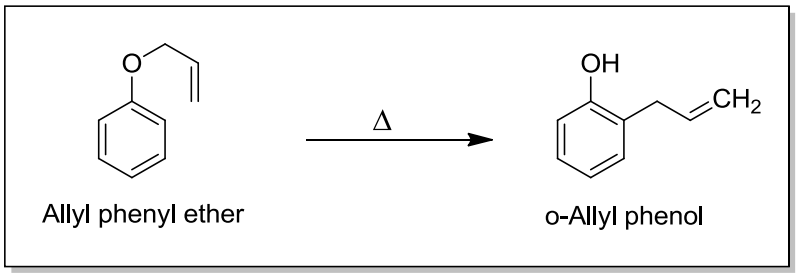
Scheme I.17: Wohler's synthesis of urea

Pyrolytic distillation to prepare ketones of calcium or barium salts of carboxylic acids is even now a usually used procedure (Scheme 2).[109]



Scheme I.18: Pyrolytic distillation of Barium dicarboxylates

In the earlier there is another record of a synthetic organic reaction is the Claisen rearrangement to produce *o*-allyl phenol from allyl phenyl ether in dry state (Scheme 3).[110]

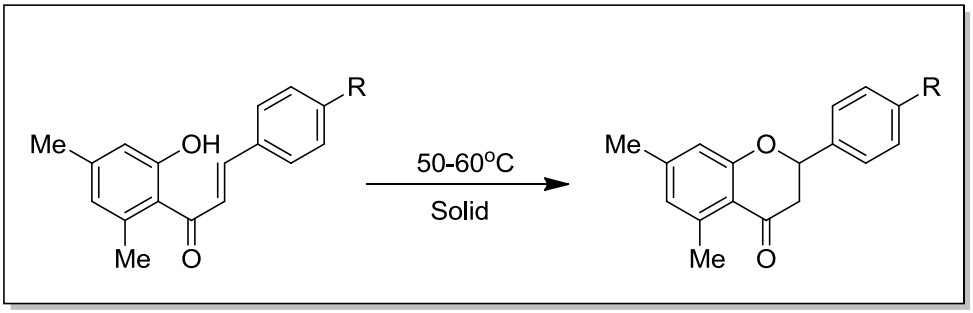


Scheme I.19: Claisen Rearrangement

Nevertheless, in recent times the mentioning examples focus on the organic reactions studied under solvent-free condition with the particular purpose. However, it should be noted that most of the organic reactions are being carried out in organic solvent. Solvent-free reaction procedures used in the synthetic condensation reactions such as Michael and Aldol reactions are speedy becoming the most excellent synthetic approaches. New reactions designed exclusively for such processes, both in industrial process and in research laboratory intensification, have led to an understanding of solvent-free protocols of the synthetic potential that afford close to quantitative yields with no or little waste.

Michael Addition

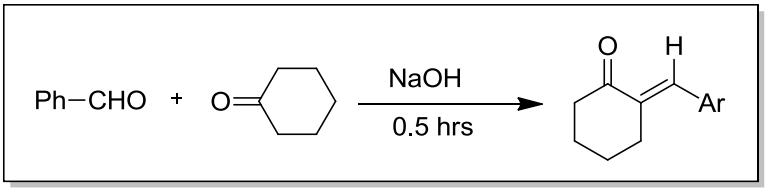
The attack of a nucleophile to a double bond with a strong electron-withdrawing substituent at vinylic position is commonly known as Michael addition. A series of 2'-hydroxy-4', 6' -dimethyl chalcones go through an intramolecular Michael type solid state addition to yield the respective flavonones (Scheme 4).[111]



Scheme I.20: Solventless Michael Addition

Aldol Reaction

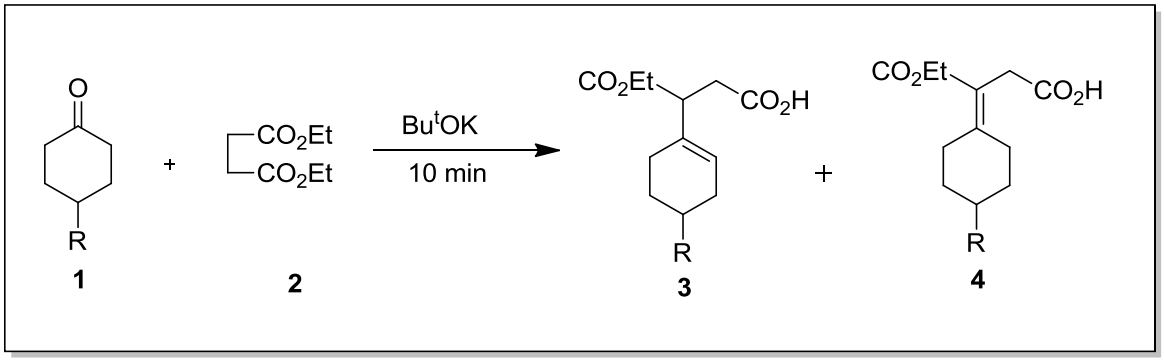
The addition of an enolate ion or enol of a ketone or an aldehyde to the carbonyl group of a ketone or an aldehyde is aldol condensation or aldol addition, if water is eliminated in a successive step to produce α, β-unsaturated ketone or aldehyde. A few aldol condensations have been found to continue more stereoselectively and efficiently in the absence of solvents than in the solution.[112] Aldol reactions may be occurred simply by grinding the solid reagents in the presence of NaOH. No organic solvent (unless recrystallisation is required of product) is used in the reaction and the only small amount of acidic aqueous waste is produced (Scheme 5). In case of crossed aldol condensation high yield products are produced even in reactions where a chance to produce a mixture products. These reactions are extremely atom and energy efficient and also are extremely chemoselective.[113]



Scheme I.21: Solventless Aldol Condensation

Stobbe condensation

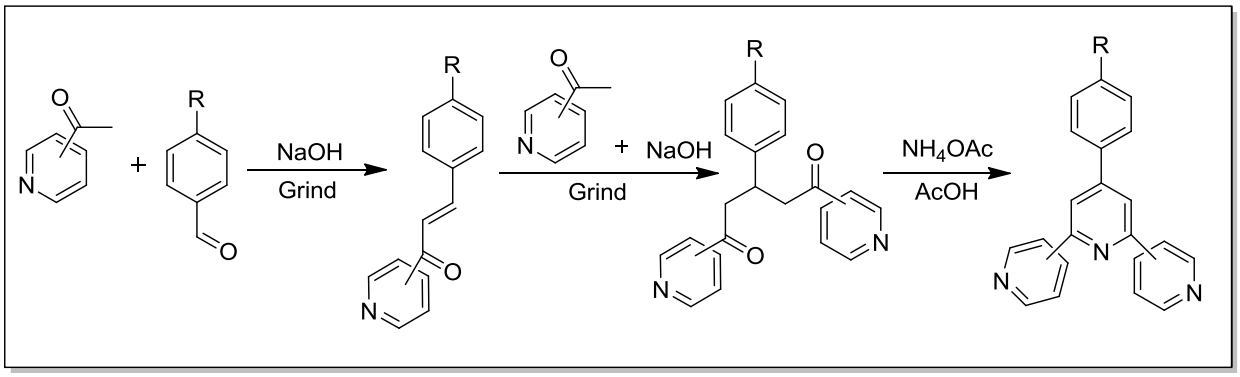
Stobbe condensation reactions under solvent-free condition from cyclohexanone (**1**) and diethyl succinate (**2**) at room temperature in the presence of ^{t}BuOK and at 80 °C produced cyclohexenylsuccinic acid (**3**) and cyclohexlidenesuccinic acid (**4**), respectively (Scheme 7). The reactions were also established to proceed more selectively and more efficiently than those in solution state.[114]



Scheme I.22: Solvent-free Stobbe Condensation

Sequential Aldol and Michael addition reactions

Generally aldol condensation followed by Michael addition of Krohnke type pyridines under solvent-less condition involving solid NaOH followed by ammonium acetate in acetic acid are readily accessible to produce required products as a one pot reaction, which facilitates both the symmetrical or unsymmetrical 2,6-bisaryl derivatives of pyridines to be isolated in good yield (Scheme 8).[115]

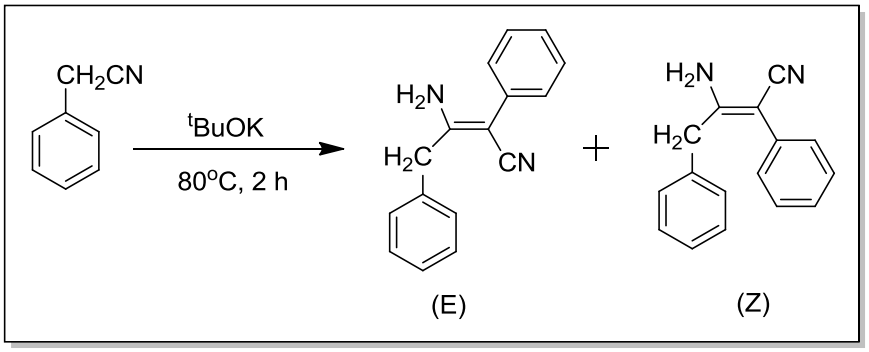


Scheme I.23: Solventless sequential Aldol and Michael addition reaction

Thorpe Reaction

The dinitriles cyclization via intramolecular and nitriles dimerization via intermolecular, which are generally known as Thorpe reactions, have been established to proceed extremely efficiently under solvent-less conditions.[116] The solid reaction product can be isolated just by washing with water of the reaction mixture. The solvent-free protocol in Thorpe reactions is expensive not only for economical and ecological aspects but also for straightforwardness in

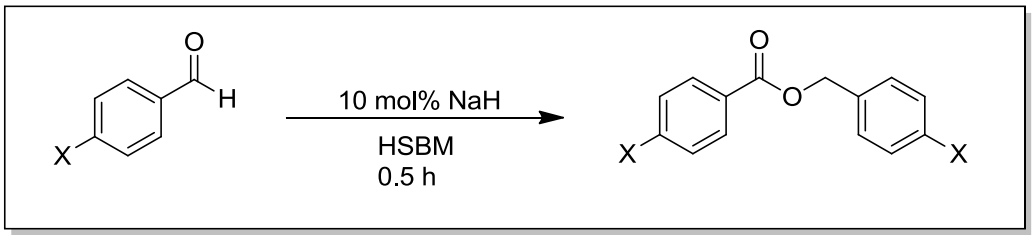
protocol and for the excellent yields of the products. The solvent-less Thorpe reaction of benzyl cyanide gives a mixture of (*E*) - and (*Z*)-enamines at 4:1 in 73% yields within 3 hours at 80 °C (Scheme 9).



Scheme I.24: Solvent-free Thorpe Reaction

Tischenko reaction

The formation of dimeric esters of the corresponding aldehydes, commonly known as Tischenko reaction has been well-known for over a hundred years. This reaction is greatly used in industry and it is environmentally benign process since it uses catalytic conditions. Waddell *et al.* illustrated that the solvent-less Tishchenko reaction by ball milling process could be carried out for aryl aldehydes in excellent yields in 0.5 hours with high speed ball milling in presence of sodium hydride as a catalyst (Scheme 10).[117]

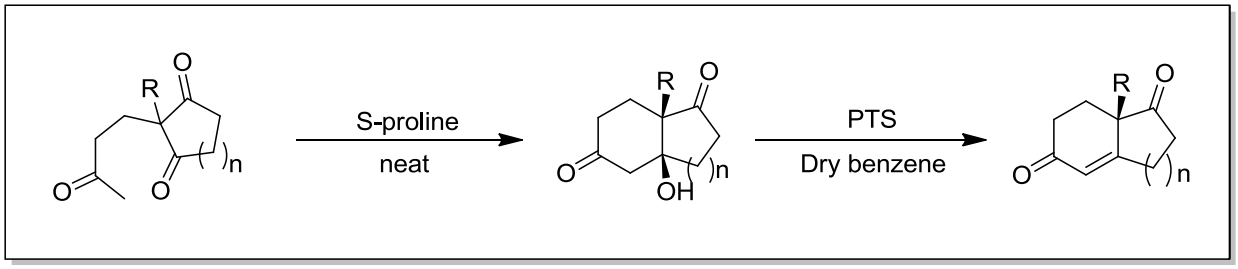


Scheme I.25: Solventless Tischenko reaction

Robinson Annulation

A tandem reaction combination of a Michael addition step and an aldol condensation to make a cyclic compound is known as Robinson annulation. A series of such reactions have been successfully performed under solvent-less condition. The involving of (S)-proline in the reaction

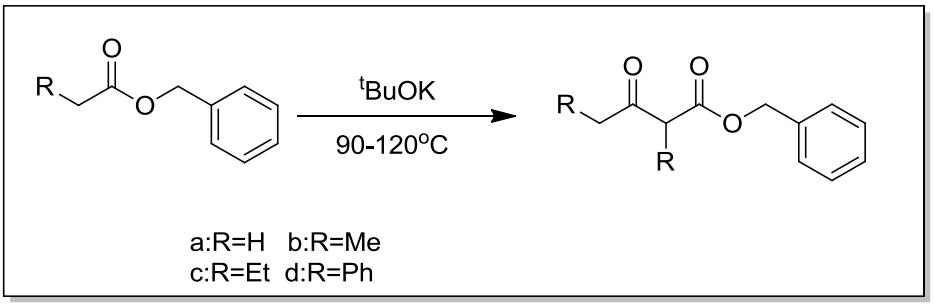
protocols a chiral intermediate that finally one enantiomer are produced at high percentage of yields. (Scheme 11).[118]



Scheme I.26: Solventless Robinson annulations

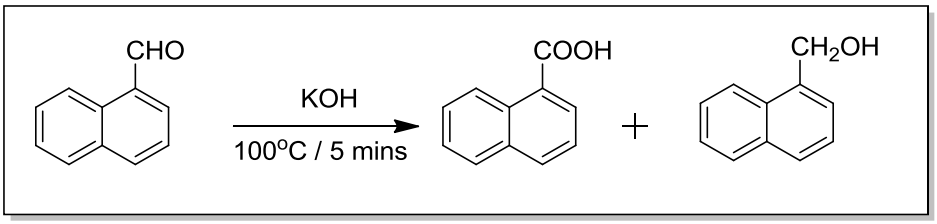
Cannizzaro and Claisen reactions

Cannizzaro and Claisen reactions were found to carry on efficiently under solvent-less conditions.[119]The solvent-less Claisen reactions was especially efficient for the ester, substituted with sterically hindered bulky groups, which does not react in solution state. (Scheme 12)



Scheme I.27: Claisen reaction under solvent-free condition

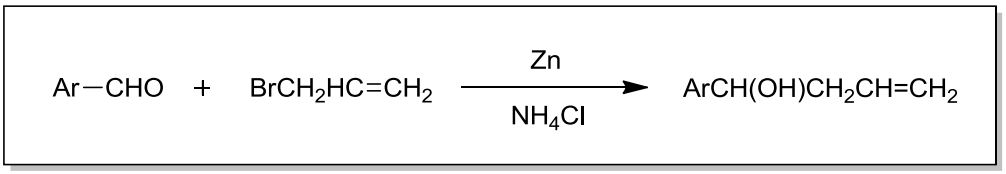
The solvent-less Cannizzaro reaction has several advantages. In addition to cleanness and simplicity of the procedure, the solvent-less reaction proceeds much more rapidly than a solution reaction. Cannizzaro reactions were found to carry on under solvent-less condition efficiently even in milder conditions and the products were formed in moderate yields by a simple separation procedure. (Scheme 13)



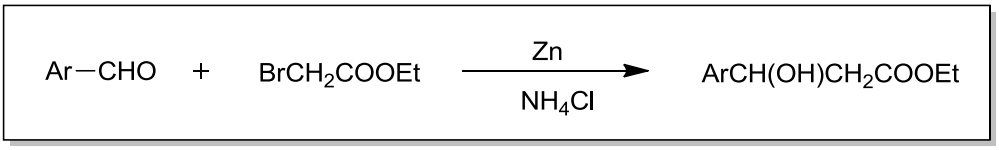
Scheme I.28: Cannizzaro reaction under solvent-free condition

Reformatsky and Luche Reaction

Tanaka *et al.* described Luche (Scheme 15) and Reformatsky reactions (Scheme 14) with Zn give more economical C-C bond formation protocols with more expensive Mg metal[120] than Grignard reactions. However, it was pointed out that in the absence of any solvent, the reactions proceed efficiently. The non-solvent Luche and Reformatsky reactions can be performed by a very effortless procedure and give products in higher percentage of yield than with solvent.



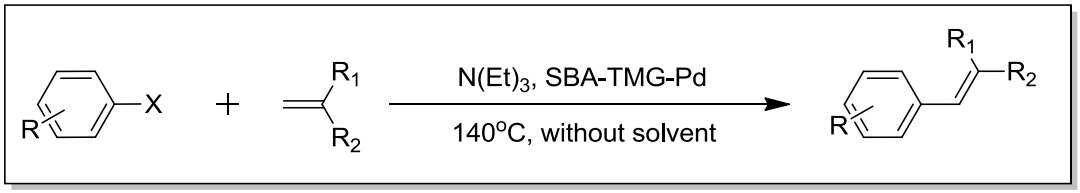
Scheme I.29: Solventless Luche Reaction



Scheme I.30: Solventless Reformatsky Reaction

Heck Reaction

Coupling reactions of olefins with vinyl or aryl halides catalyzed by palladium, known as the Heck reaction. In the modern synthetic chemistry, Heck reaction is the most attractive protocols to form a new carbon–carbon double bond. The solvent-less Heck reaction catalyzed by recyclable Pd catalyst based on SBA-15 through an ionic liquid. (Scheme 16)[121]



Scheme I.31: Heck reaction under solvent-free condition

Apart from the some famous reactions that have been pointed out above the solvent-free reaction protocol has been used in various other cases such as the synthesis of

Dihydropyrimidinones, [122] chalcones,[123] Bis-*N*-Boc Protection of Adenosine, 3-carboxycoumarins,[124] Guanosine and Cytidine derivatives,[125] manufacture of Polycarbonate and Polypropylene,[126] synthesis of primary imines,[127] the preparation of bis-imine Schiff bases,[128] and so on. The above examples show that a mixture of organic reactions, which are traditionally handled in solvent media, can be performed more profitably without solvents. To be an organic chemist our effort would certainly be to carry on bringing more and more organic reactions into a single umbrella of the solvent-less synthetic methodology.

The examples of diverse thermal and photochemical organic reactions under solvent-less conditions are only the glimpse of the vast possibilities of such reactions in organic synthetic chemistry. We may not be capable of totally keep away from organic solvents, but nonstop attempts have to be completed to explore and devise synthetic protocols in this direction. It is the required of the hour to put away the environment and remove costs of production. In one direction of achieving this is to remain the solvents away whenever it is necessary. It is satisfying to note that numerous Indian scientists are still working in this area. At this point of view it becomes essential, to get an improved understanding on a molecular level reactions without any media and how, if at all, the mechanisms of reaction vary from those in additional conventional media.

I.1.E. Multi-component Reactions

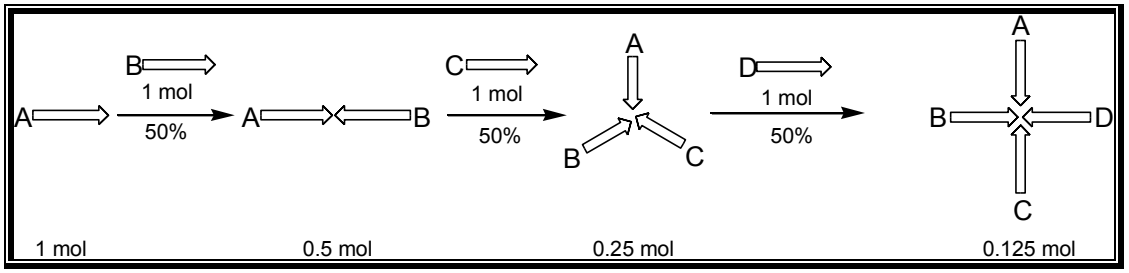
The efforts that are made to increase the efficiency of a certain process, serves to minimise the impact this has on the environment from the chemical industry, that encompasses everything, viz. Ceramics, polymers, paints, drugs, textiles, pharmaceuticals, beverages, fossil fuels, food and all other non-renewable source of energy. In the recent years, though implementation of new strategies has been done in almost all chemical companies, still, the amount of waste that results from highly optimised synthesis has not found much signs of reduction. Significant changes are encountered in lieu of the fact that old processes and methodologies are redesigned and we are moving towards a goal of conducting an ideal synthesis. This would refer to a process, that would be safe, eco-friendly, selective, high yielding, based on readily available starting materials, and highly diverse. In addition to the fact,

the criteria of selectivity, has to be matched with ecological aspects and also with the economical significance.

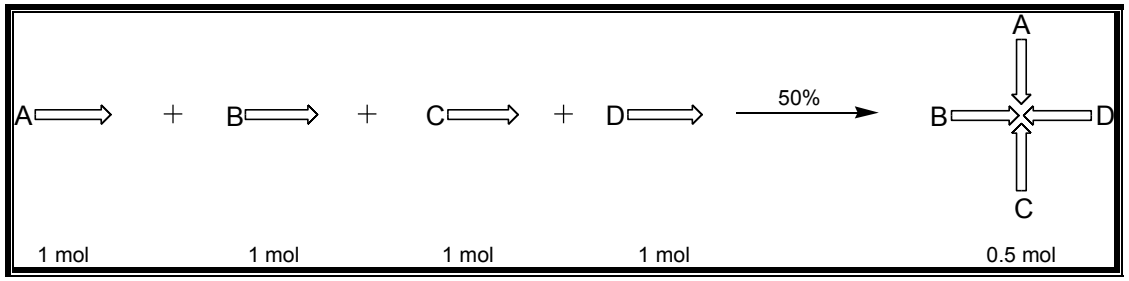
The initiation of green Chemistry or sustainable Chemistry has put a major jump on the above aspects which in the recent times calculates the efficiency of a chemical reaction not only by considering parameters such as over all yield and selectivity but also by its time, human resources, raw materials and energy requirements. Toxicity and hazardousness of the chemicals are also the protocols that are involved. Designing a Chemical synthesis on the basis of the Green Chemistry protocol it certainly addressing many issues but getting due and outright acceptance from the Chemical Industry is still far away. Deviation from the use of conventional procedures and choosing the path of sustainable Chemistry, diverse eco friendly protocols which range from systems that are efficient in energy such as microwave, ultrasound, micro-reactors etc. to alternative media, organocatalytic systems[129] and solvent-less methodology come into active use.

Leave alone catalytic reactions, multi-catalyst reactions in the form of one-pot reactions, multistep and micro reactors, and the one-pot multi-component condensations have now become a versatile tool for the conduction for clean and efficient transformations. The multicomponent coupling reactions (MCRs) now form a highly valuable and synthetic tool for the efficient construction of complex and novel structures of molecules, by using a minimum number of synthetic steps. It therefore is a process where multiple components that are easily accessible are together combined to conduct a single reaction in a vessel such as to produce a final product that would contain a significant portion from the reactants[130], and if considering the ideal view, then all reactants. Jieping Zhu in his book *Multicomponent Reactions* puts forward a definition of MCR which states that, "Multicomponent reactions (MCRs) are processes involving sequential reactions among three or more reactant components that co-exist in the same reaction mixture. In order to be efficient, MCRs rely on components that are compatible with each other and do no undergo alternative irreversible reactions to form other products or by-products." Since the MCRs have the ability to build a single product in a single operation from multiple reactant molecules, with multiple bond-forming efficiency and high atom efficiency, MCRs therefore provide a well established approach to reach the goal of idealist.

A MCR is a domino process, involving a sequence of elementary steps which is determined by conduction of subsequent transformations and the products produced in the step before. Hence they are also sometimes referred to as domino or tandem reactions. These reactions are advantageous over the normal conventional techniques because these involve lower costs, higher degrees of atom economy, shorter time for completion of the reaction, the possibility for combinatorial surveillance of variations in structure and eco-friendliness. Conventional techniques require greater time and money to advance starting materials towards targets that are complex.



On the other hand, the multicomponent reactions decrease the cost in the form of material and time and by generating complex targets in a single convergent step. This also avoids the consumption of time during the isolation and purification of the intermediates.



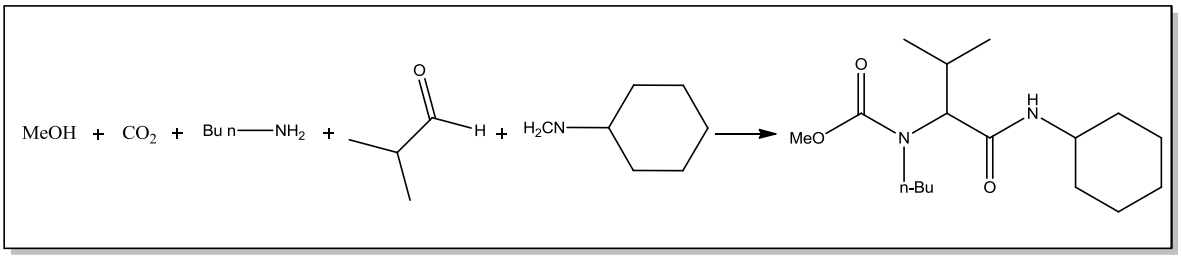
Although the most conducted applications lie in the line of library synthesis, the high amount of convergence between these reactions also provide an efficient, quick, and low-cost alternative to the current conventional syntheses. Since multicomponent reactions are one-pot reactions, these are easy to carry out as compared to multistep syntheses and these also provide fast access to large libraries of organic chemicals and their diverse patterns of substitutions. As compared to the conventional reactions, conduction of a low-yielding multicomponent reaction is

not as costly as we think it to be. As we reduce the number of reaction steps, and start the reactions by using simple, inexpensive starting materials, the money required for construction of the higly diverse and complex small molecules is automatically reduced. Most MCRs contain a broad substrate scope which can tolerate diverse functionalities as well as reactive centers. This can set up MCR products so that these can be used for conductions of further cascade transformations.[131]

I.1.E.1. Recent Developments in Multi-component Synthesis

In spite of the tremendous useful features of MCRs in modern organic chemistry and their capability of creating large compound libraries, the reactions remained of limited interests in the early stages for as long as fifty years. Although the multicomponent reactions have accompanied organic chemistry in its early days, especially in the field of heterocyclic chemistry, but it was not considered as a fundamental principle until Ugi's significant extension of the Passerini reaction and the conclusions that he obtained from it. With this groundbreaking discovery, Ivar Ugi had already recognized as early as in 1961 that MCR is capable of obtaining the structure-reactivity relationships through the synthesis of a "large variety of compounds", which are now recognized as libraries. But, in the past few decades, with the utilization of high-throughput biological screening, this strategy was a vital development in the discovery of drugs in the field of rapid identification and purification of biologically active lead compounds. By using a very small set of starting substances, a large number of libraries can be created in a very short span of time, which can be easily utilized for research purposes on medicinal substances. This growing interest has received a boost by significant therapeutic potential of various heterocyclic compounds.

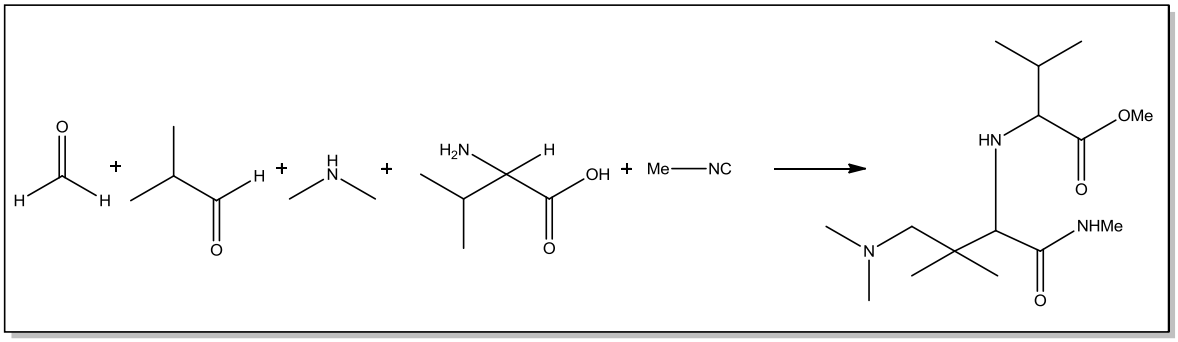
With the passage of time, there has been tremendous development in the MCRs and nowadays they are used for the condensing of 3, 4,5,6,7 and even 8 reactants in a single reaction container. An example of the five-component reaction as reported by Haslinger et al is as shown below (Scheme 36).[132]



Scheme I.32: A typical five-component reaction

A current example involves the highly efficient synthesis of tetrahydropyridines via a one pot, five component reaction.[133]

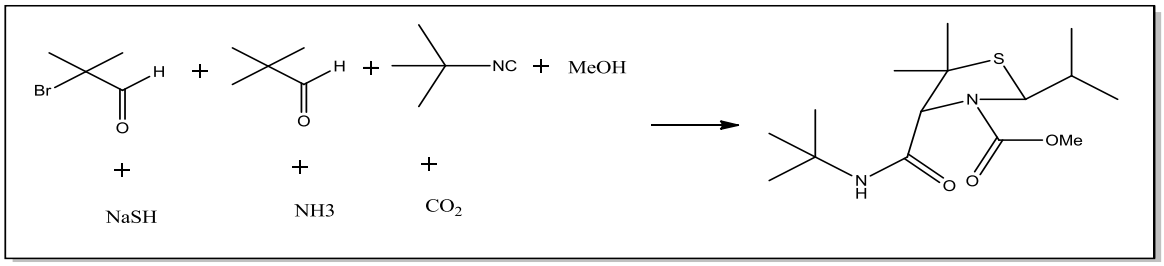
An example of a six-component (seven–centre) reaction was reported by Mannich-Ugi (Scheme 37). [134]



Scheme I.33: A typical six-component reaction

Recently Bonfield et al. has also reported a highly efficient method for the synthesis of the isoindoline mechanism through a six component, tandem double A3-coupling and [2+2+2]-cycloaddition reaction .[135]

About 10 years ago Asinger-Ugi had reported a seven-component reaction (Scheme 38).[136]



Scheme I.34: A typical seven-component reaction

Very recently, Brauch et al. have extended MCRs to seven components by taking help of the various chemo selectivities of the Ugi-Mumm and the Ugi-Smiles reaction.[137]

In the recent developments in MCRs,[138] a one-pot reaction consisting of eight components has been developed by the Orru group that includes nine new bond formations and a total of eleven points of diversity.[139]

In addition to these, most of the work in MCRs over the past few decades has been done to extend the applicability of the classical MCRs to the newer systems. [140] Among all these efforts there have been two fields which have stood apart from the others and have gained a lot of attention in the past decade and they are- MCRs carried under solvent free conditions and their applicability in DOS (diversity oriented synthesis). MCR strategies can be planned effectively under *solvent free conditions*. In addition to this, the ease with which a large number of compounds can be can be synthesized using MCRs makes them suitable for any *Diversity Oriented Synthesis*. Thus we can easily relate its significance in *drug discovery* efforts. All the three topics will be discussed briefly.

I.1.E.2. Solvent-free Multi-Component Reactions

There has been a significant growth in the literature of MCRs over the past few decades and its applicability in solvent free conditions has expanded exponentially which makes it very difficult to keep record of the research done in this field. These solvent-free, eco-friendly MCRs has opened up various possibilities for carrying out organic synthesis rapidly and is very useful for efficient functional group transformations. This the major reason why solvent-free approach has been developed for almost all kinds of classical MCRs like Strecker,[141] Hantzsch,[142] Biginelli,[143] Mannich,[144] Passerini,[145] Ugi,[146] Gewald,[147] Petasis,[148] Radziwenski etc,. The

creation of chemo-, stereo-, or regioselective methods for synthesizing high-value chemical species and the simultaneous generation of libraries of small molecules will highly add on to expansion of multi-component solvent-free reactions in the days to come. A highly efficient and thorough review on the recent advancements of the various solvent-free MCRs has exposed the scope and the tremendous significance of these methods in the modern day organic synthesis. [149]

I.1.E.3. Multi-component reactions for Diversity Oriented Synthesis

MCRs performs a vital role in the library synthesis as they provide a direct access to the compounds of the library and also act as the starting points for DOS (Diversity Oriented Synthesis).[150] DOS involves the generation of relatively smaller libraries of organic compounds which are more complex structurally and have a higher variety of core structures. It attempts at maximizing the total number of scaffolds and structures that are produced from a particular synthetic reaction scheme. It is, in some way, opposite to that of natural product synthesis, where all efforts are given to produce one molecule at a time. Unlike the traditional target-oriented synthesis (TOS) methods, the DOS procedure enables a chemist to synthesize the libraries of complex and structurally diverse small molecules in an efficient manner in a small number of synthetic steps. Since the only way to identify the biologically active molecules is the proper screening of these small-molecule libraries, the major point of interest is to enhance the basic diversity of the compound libraries for the biological screening. The continuous and rapid decline in successful drug discoveries basically points out to the deficiencies in the current collection of compounds. Mainly, these collections are comprised of a very large number of structurally similar compounds. However, it is much more important to have a small and diverse library (on structural and functional grounds) rather a large one consisting of similar type of compounds. Diversity-oriented synthesis (DOS) basically aims at generating such structural diversity in a highly efficient manner.

The main advantages for utilizing an MCR for DOS are as follows :- (i) MCRs can provide the maximum number of compounds using the least synthetic effort. A 3CR can provide about 1000 compounds when 10 variants of each type of component are used in an entire matrix of combinations. Secondly, MCRs can provide SAR (structure activity relationship) information for a screening library by providing a set of compounds with similar core structures. Third,

'screening positives' or 'hits' that emerges from MCRs can provide a highly valuable starting point for the follow-up as the quick preparation of highly 'focused' libraries and the scale up is ensured. In spite of the possible advantages, the use of MCRs for the synthesis of diverse libraries may carry a highly potential liability of having one core structure that is repeatedly represented over the entire collection. The basic diversity of a library of the MCR products is, on some level, restricted by the structures of the appendages that are reattached to the core substances. This limitation is addressed by the new variants of conventional MCR that results in fundamentally different structures. Moreover, the use of MCRs as a starting point for the subsequent reactions that defines the basic connectivity of the components is a highly powerful method of achieving diversity with efficiency. Many current examples of DOS in which MCRs play vital roles was been given by Schreiber in his recent review.[151]

Recently, the diversity in the products has increased by both versatile MCRs and the consecutive reactions like domino reactions and post-condensation-cyclization (PCCs).[152] This can also be obtained by an enhancement of the number of components, as in 5CR, [153] 7CR, [154] and 8CR, transition metal catalyzed MCRs[155] and the evolutionary chemistry aided MCRs.[156] Several recent diversity related review demonstrates the innovation and creativity in the seminal field of chemistry.

I.1.E.4. Multi-component reactions in Drug discovery

In the past decade, the pharmaceutical companies have invested significantly for the development of robotics and the miniaturization of the biological screening processes. These efforts have resulted in a significant improvement in drug discovery by enhancing the ability of the biologists to perform in vitro high-throughput screening of chemicals. [157]The major drawback of this new screening technology is that it causes the chemists to provide the biologists with a large number and diversity of products. Conventionally, drug discovery methods involve the optimization of the lead structures, which are mostly obtained from the biological sources, through a series of steps involving synthesis and screening. The method is extremely expensive as each substance has to be synthesized individually in the solution by a synthetic chemist. With the current advances in the robotic screening that enables the testing of thousands of products per year, the pharmaceutical companies are have to examine MCR synthetic procedure with DOS

methods combined with the combinatorial synthetic strategies as means of accelerating drug discoveries and also enhancing the chemical diversity of their compound libraries. The chemists from academia are at present conscious and tremendous efforts are being made in to meet the ever increasing requirements of the high-throughput biologically screening technology. That is why the use of MCR along with DOS approach is preferred over combinatorial synthetic approach and it highly enhances the diversity of the synthetic libraries.

By their very nature, MCRs are not restricted to a particular application, but they can be used very easily in any domain of modern chemistry-based technology. In the recent years, asymmetric MCRs have been employed to the total synthesis of variety of commercial drugs enantiopure and natural products, thereby reducing the number of reaction steps significantly.[158]

Current applications of MCRs which are not related to drugs include biocompatible materials, EPR-spin labeling, e.g. polymers with novel properties, for artificial eye lenses, natural product synthesis, chiral phases for HPLC, peptide-nucleic acids and agrochemicals. Many groups have received advantages in their projects on natural product total synthesis with the help of MCR, e.g. Jouille, Ugi, Fukuyama, Hofheinz, Semple, Banfi, Armstrong, Hatanaka, Schmidt, etc. The only restriction in total synthesis is that the higher is the number of components that an MCR employs, the higher is the complexity of the target that it generates. With increase in the complexity of the target, the applicability in the total synthesis decreases.

The library of the known MCRs is far from complete. New combinations of the existing reactions are always possible and a complete understanding of the reaction mechanism can lead to the discovery of noble modes of reactivity. The most obvious advantage of MCR is that it can be extended into combinatorial, solid phase synthesis thereby promising a large number of opportunities for the development of novel lead structures of catalysts, active agents and also novel molecule-based substances.

I.1.E.5. Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) is a method in which the energy required to maintain a temperature difference of zero between the sample and reference substance is plotted as function of time or temperature. Thus, during an endothermic transition, the energy that is

absorbed by the sample is neutralized by an enhanced energy input to the sample to maintain a temperature difference of zero Kelvin. As the energy intake is almost equivalent to the energy that is absorbed during the transition, the balancing energy will give a measure of the energy transition via calorimetric measurement.

Differential Scanning Calorimetric (DSC) and the thermo gravimetric analysis (TGA) methods, which were used to determine the thermal stability of polymers, are also being employed for the evaluation of the thermal properties of a large number of bio-composites that are mainly used in the packaging industry.[159]DSC is very much useful to obtain the thermal properties of substances plotted as a function of temperature. The thermal-temperature dependent nature of substances can provide a lot of vital information regarding their structure, properties and also the thermo-mechanical history. A typical DSC curve shows the variation of heat capacity against temperature, and hence the thermal events which actually do not involve an enthalpy change like the transition of a glass can also be detected. These changes mainly appear as a change in the position of the baseline or a change in the slope or gradient.

DSC provides a very rapid but a highly reliable procedure to determine the purity of materials. Melting point of a substance can be obtained through DSC technique as the substance is heated through its melting point. The presence of impurities reduces the temperature for the melting point and the curve gets broader near the melting range. The plot of DSC involves the entire melting curve as well as the latent heat of fusion (ΔH_f) of the material.

I.1.F. References

References are given in BIBLIOGRAPHY under Chapter I (pp 259-266).

CHAPTER-II

(SECTION A)

A mechanistic insight of carbonyl activation under solvent-free strategy: evidence drawn from the synthesis of imidazole derivatives

II.A.A. Introduction

In the past two decades successful solvent-free procedures for various types of reactions like rearrangements, condensations and oxidative couplings have been createdd apart from the various name reactions like the Claisen,[1]aldol,[2] Knoevenagel condensations,[3] Stobbe,[4] Thorpe,[5] Reformatsky, [6] Luche reactions,[7] Baeyer–Villiger oxidation,[8] pinacol rearrangement[9] and Tischenko just to name a few. The use of a solvent-free synthetic procedure for organic compounds that were traditionally synthesized in the presence of a solvent has become common in recent years.[10] Thus a large number of well-known organic reactions have been found to occur in solvent-free conditions and are more efficient than the reactions in solution. Such solvent free procedures serve as a tool to expand the chemistry including Green Chemistry reactions. Green chemistry has turned into the realm of chemistry which is more efficient and sustainable one and it can be been realized in several ways; reactions in aqueous media or ionic liquids and neat reactions, microwave reactions, among others. Mechano-chemistry has no doubt become an integral part of the green chemistry reactions and has helped in advancing and strengthening the solvent-free reaction methods further, either by including mechanochemical or thermochemical excitation. Moreover, metal-template reactions, multi-component reactions, one pot-synthesis and DOS have widened the scope for solvent-free protocol. Solvent-free methods have already been developed for almost all kinds of traditional multi-component reactions like Biginelli,[11] Strecker,[12] Passerini,[13] Hantzsch,[14] Mannich,[15] Petasis,[16] Ugi,[17] Radziwenski synthesis,[18] Gewald,[19] and so on. And to impart a higher reactivity to the reactants and the reagents, these synthetic protocols have been wisely exploited in the use of transition metal catalysts and the various organocatalysts. They are now being successfully used as a versatile route to biologically active motifs and have attracted considerable attention in the recent years. Thus, we can find ample scope and opportunity in the development of similar methods to synthesize a wide range of compounds. Lewis acids and many organocatalysts have also been shown to be efficient catalysts for C–C bond forming reactions, and through the carbonyl activation provide effective opportunities for upgrading classical MCRs. In particular, close attention must be paid to condensation reaction mechanism that includes the activation of carbonyl-containing electrophiles. The large number of investigations associated with chemical transformations mediated by organocatalysts[20] or by the Lewis acids in anhydrous organic media,[21] aqueous media[22] and in the absence of any media[23] has given a fundamental understanding of the internal dynamics of the adduct formation between the acid and the

carbonyl moieties and has shed light upon the role of these adducts in accelerating catalytic transformations.

II.A.B. Present work: Background and Objective

A well known example is the significant increase in the reaction rates for the Radziwenski synthesis which is attained by the excitation of a carbonyl group by a Lewis base center[24] or a Lewis acid center[23] or through the formation of the adducts. This chapter thus specifies recent advancements in solvent-free synthesis of a very vital biologically active part of a heterocyclic compound, the Imidazoles. In addition to the cleanness and simplicity of the procedure, the absence of any medium has been found to lead to various uncommon reactivities. The syntheses of imidazoles and their derivatives have also allowed us to draw evidences for the mechanistic study of excitation of carbonyls in solvent-free syntheses.

We have always tried to stick to a solvent-free non-catalytic approach by using simple heating. It focuses on the use of grinding to carry out reactions between solid reactants followed by heating of the mixture to form a melt. Though sometimes it was found that some reactions do not essentially go to completion on simple mechano-chemical activation, or even if it happens, it usually takes a longer time. Despite of this fact, mechanochemistry has been highly used for the synthesis of a large number of compounds. It has been found that providing a little additional heat to the mechanochemically shaken mixture gives promising results. The products were formed in a much lesser time, comparable to the microwave assisted reactions. And according to the arguments given in the literature, they could also be regarded as being more efficient (less time consuming), and thus being green. It could be stated as efficient because a fast reaction performed at a high temperature (Arrhenius equation) is likely to require very less energy when compared to a reaction that requires significantly longer reaction times at a lower temperature. However, as it is known that excess heat always has a tendency of charring the reaction mixture and also since there are certain possibilities of runaway reactions it becomes imperative that the shaken mixtures were heated to an optimum temperature to get the very best results. One of the best ways of highly optimizing the reaction conditions was done by carrying out the thermal analysis of the powdered mixture of the reactants. Thus, initially the optimization of the reaction conditions of the representative reactions were done using Thermal analysis techniques like the DSC. Subsequently the reaction optimization for the Imidazole synthesis was carried out by using HPLC where thermal reactions in solvent-free conditions were observed and

optimized by running HPLC of the reaction mixtures at various temperatures. The HPLC analysis of the reaction mixture at various time intervals also led to the determination of reaction kinetics.

II.A.C. Present work: Result and Discussion

II.A.C.1. Substituted Imidazoles

Imidazoles are heterocyclic compounds that are part of a vast number of highly significant biomolecules like the essential amino acid histidine and other related compounds, biotin and imidazole alkaloids.[25] Synthetic imidazoles are present in various fungicides and herbicides[26] and also in antiprotozoal, antihypertensive medications and antifungal.[27] Imidazole drugs have a broad application in several areas of clinical medicine.[28] The imidazole moiety is also present in various histaminergic ligands for histamine H1, H2 and H3 receptors as well as in various FTase inhibitors.[29] The vital therapeutic properties of imidazole drugs have been exploited by the medicinal chemists to synthesize and test a huge number of novel molecules. Several 5-lipoxygenase, 'P38' MAP and B-Raf Kinase inhibitors carrying the imidazole moiety have been synthesized.[30] Some substituted triarylimidazoles are efficient antagonists of the glucagon receptor[31] and inhibitors of Tie-2 and IL-1 biosynthesis.[32] The potency and wide applicability of the imidazole pharmacophore is attributed to its hydrogen bond donor–acceptor capability as well to its high affinity for metals, which are present in most of the protein active sites (e.g., Fe, Zn, and Mg). Thus, the synthesis reactions and biological properties of substituted imidazoles constitute an important part of the modern heterocyclic chemistry. Recent advancements in green chemistry and the organometallic chemistry have widely extended the boundaries of imidazoles to the synthesis and applications of a huge class of imidazoles as ionic liquids[33] and imidazole related N-heterocyclic carbenes.[34] In industry, imidazoles have been used widely as a corrosion inhibitor on several transition metals, such as copper.[35]

II.A.C.2. Synthesis of substituted Imidazoles

In the continuation of our studies for the development of synthetic procedures, and to study the mechanistic aspects of the solvent-free reactions, the synthetic route to Imidazoles and its derivatives were also investigated. Synthetic route to Imidazole, both tri- and tetra-substituted and their other derivatives like Imidazole N-oxides and 1-Hydroxy Imidazole N-oxides were also investigated for a few reasons; first of all they were easy to investigate

without a need to synthesize complex starting materials (easily available starting materials like benzil, glyoxal, dimethyl glyoxime etc were used); secondly it was highly challenging to come up with a new protocol (as simple as the thermo-chemical activation) which could compete with the recent technologies, in terms of their yield, reaction time, scalability and the greenness of reaction; and thirdly, the Imidazoles and compounds containing the imidazole ring have many pharmacological characteristics and play significant roles in biochemical processes, the reaction protocol could further be extended for syntheses of metal complexes. Metal complexes of many heterocyclic compounds have been found to show higher biological activities and catalytic activities then their simple ligand predecessors.

The artificial approach to the Imidazoles has been constantly redesigned over the past few years, some have resulted in better yields while others have looked for the greener catalysts to improve the yields and lower the reaction time. Modern organic synthesis mainly relies on the rapid development of efficient approaches to the chemically and biologically vital products from easily available inexpensive starting materials.[36] Historically, the first synthesis of imidazole core, starting from 1, 2-dicarbonyl compounds, aldehydes and ammonia, was first reported by Debus in 1858. Radziszewski and Japp later on fully developed the procedure in the year 1882.[37] Although, classical methods were obtained from this early success, the reaction suffered from low yields, mixtures of products and longer reaction times. Since then, the imidazole nucleus has over the years initiated the development of new and improved methodologies.

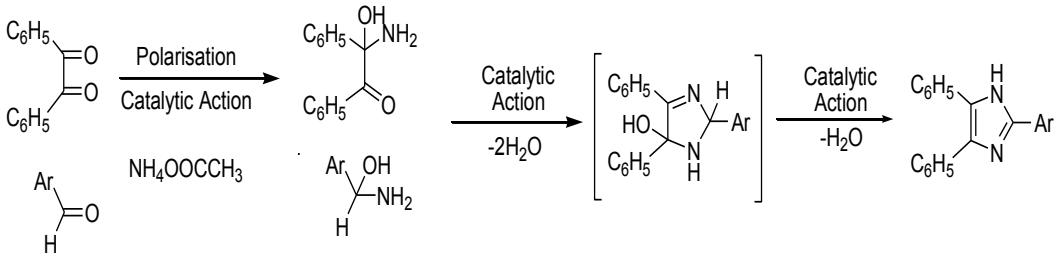
The literature has a large number of methods that can be given for the synthesis of 2, 4, 5-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles. While 2, 4, 5-trisubstituted imidazoles are synthesized by the three component cyclocondensation of 1, 2-diketone, α-hydroxyketone or α -ketomonoxime with aldehyde and ammonium acetate, the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles are mainly carried out by the four-component condensation of a 1, 2-diketone, α -hydroxyketone or α -ketomonoxime with an aldehyde, primary amine and ammonium acetate. Syntheses of Tri-and tetra-substituted imidazoles have been done using zeolites, HY/silica gel,[38] iodine,[39] L-proline,[40] ceric ammonium nitrate,[41] sulphanilic acid,[42] NaHSO3,[43] silica sulphuric acid,[44] and some common Lewis acids such as $LaCl_3$, $Yb(OTf)_3$, $NbCl_3$, $FeCl_3$, $AlCl_3$[45] or by traditionally refluxing in acetic acid.[46] To add to this, there are a few microwave (MW) assisted syntheses of imidazoles from 1, 2- diketones and aldehydes in the absence of any solvent[47] or in the presence of variety of catalysts like silica-

gel, Al_2O_3,[48] silica-gel/HY, $ZrCl_4$,[49] acetic acid,[50] $NiCl_2.6H_2O$,[51] ionic liquid[52] and DMF. Kidwai *et al* reported that during the MAOS of tri- and tetra substituted derivatives they became sticky solid which indicated that, it was not a cleaner approach[53] Ultrasound-promoted synthesis of imidazoles catalyzed by $Zr(acac)_4$,[54] and the perpetual flow of micro reactor system [55] are some recent techniques that have been added to the book of Imidazole synthetic methodologies.

The methods given above for the Imidazole synthesis have their own merits and demerits. While some of the methods suffer by the limitations of poor yield, longer reaction time, laborious work-up and effluent pollution, other methods use drastic reaction conditions, hazardous and very often expensive acid catalysts. Moreover, sometimes the products that are formed needs a very tedious purification. It is found that the synthesis of these heterocycles has been carried out in polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. The preparations of some catalysts require highly expensive reagents, harsh reaction conditions, and sometimes tedious workup using toxic reagents or solvents. Therefore, the creation of a new non-catalytic method with an efficient and environmentally friendly protocol could overcome these drawbacks.

II.A.D. Optimization of reaction conditions for Imidazole synthesis with HPLC studies

The optimization of the reaction for Imidazole syntheses was the initial step to be carried out in our study. For this, a representative 2-(4-methoxyphenyl)-4,5-diphenylimidazole **[2]** was initially synthesized by a three-component reaction using the benzil, anisaldehyde, and ammonium acetate through a solvent-free catalyst-free procedure according to **Scheme II.A.1**.



Scheme II.A.1: A plausible solvent-free mechanism for the synthesis of Tri-substituted Imidazoles

Thus, in order to optimize the reaction reaction time and the temperature the reaction was carried out under solvent-free procedure for 20 minutes at various temperatures and the peak areas found from HPLC were plotted against temperature (^{o}C). As shown in the figure 22, at the beginning ammonia addition starts at relatively lower temperature, but the product (imidazole) formation begins at a much later stage and it was quite sensitive to temperature variation. The optimum temperature was found to be 125-135^{o}C.

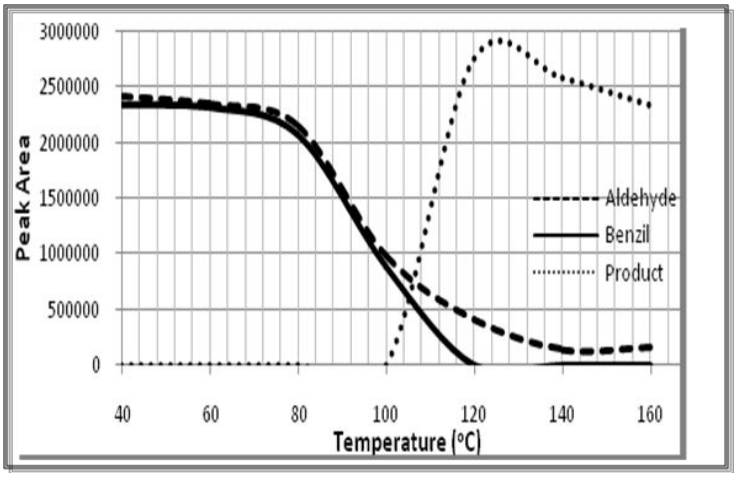


Figure II.A.1: HPLC Peak Area vs Temp. after 20 mins of reaction (Compound **[2]** in **Scheme II.A.1**).

In the view of the above understanding of the optimized conditions we then tried to obtain the mechanistic insights. The main objective was to look for the intermediate ammonia addition product using HPLC. Initially, HPLC (at 259 nm with methanol as eluent, a C-18 column and flow rate of 0.5ml/min) of pure benzil and the imidazole **[2]** were recorded to locate the retention time of the substrates. It was found that pure benzil gave a peak with retention time of 5.872 minutes (**Figure II.A.2**) while the pure recrystallised product **[2]** which was previously prepared, gave a peak with retention time of 6.092 minutes (**Figure II.A.3**).

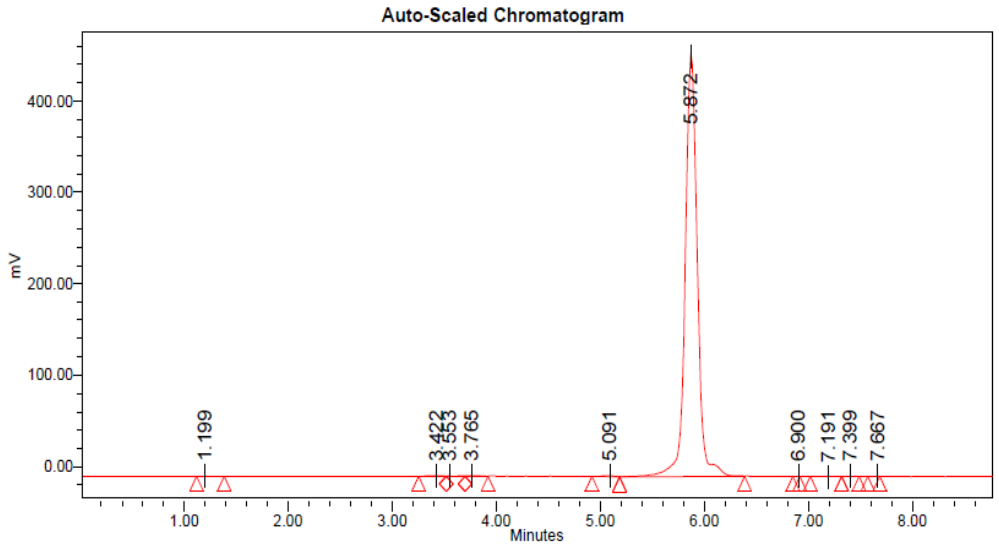


Figure II.A.2: HPLC chromatogram of pure benzil

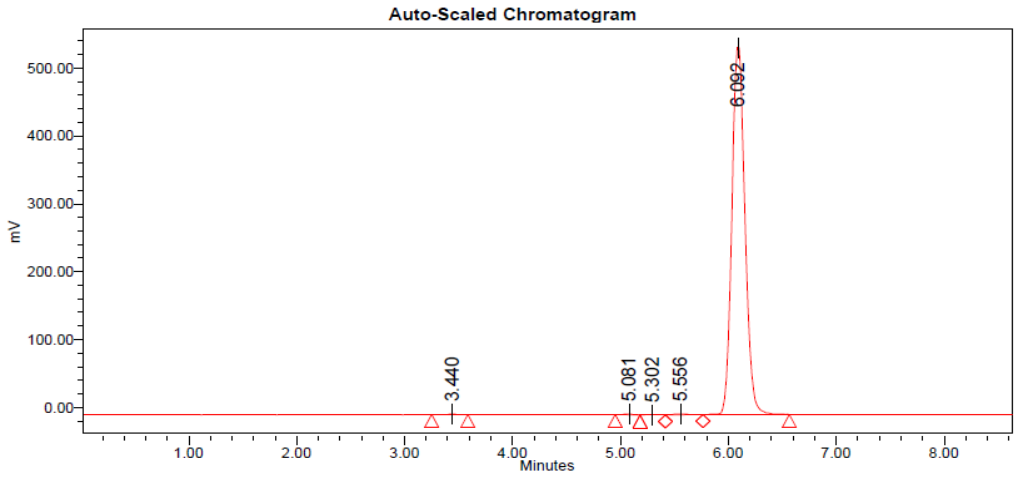


Figure II.A.3: HPLC chromatogram of the pure product 2-(4-methoxyphenyl)-4,5-diphenylimidazole **[2]**

Since the accepted mechanism for the synthesis Imidazole considers a benzyl-ammonia addition product as the intermediate, we tried to investigate a little further. 5 mili-moles of NH_4OAc was mixed with 1 mmole of benzil and then heated to 120^oC and was kept for 5 minutes. After 5 minutes, the reaction mixture was frozen in ice cold methanol and the HPLC chromatograms were obtained. The benzil and the NH_3 mixture show a major peak at 5.801 which is due to benzil (**Figure II.A.4**). A new peak was also observed at retention time of 8.075 indicating the benzil-ammonia addition product.

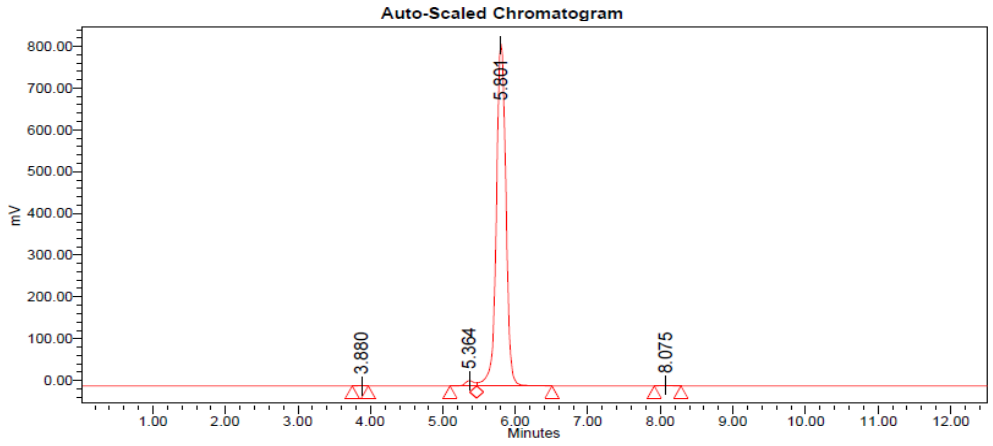


Figure II.A.4: HPLC chromatogram of benzil and ammonium acetate.

It is also highly significant to note that the peak at 8.075 is not observed in HPLC chromatogram of pure benzil (**Figure II.A.4**) but it is observable in chromatogram obtained from HPLC run of the reaction mixture leading to the formation of Imidazole, **[2]** (**Figure II.A.5**). It is also apparent from the chromatogram of the entire reaction mixture, the presence of the intermediate at 8.045 along with presence of Imidazole, **[2]** peak at 5.926, anisaldehyde peak at 5.543and the peak for benzil at 5.789.

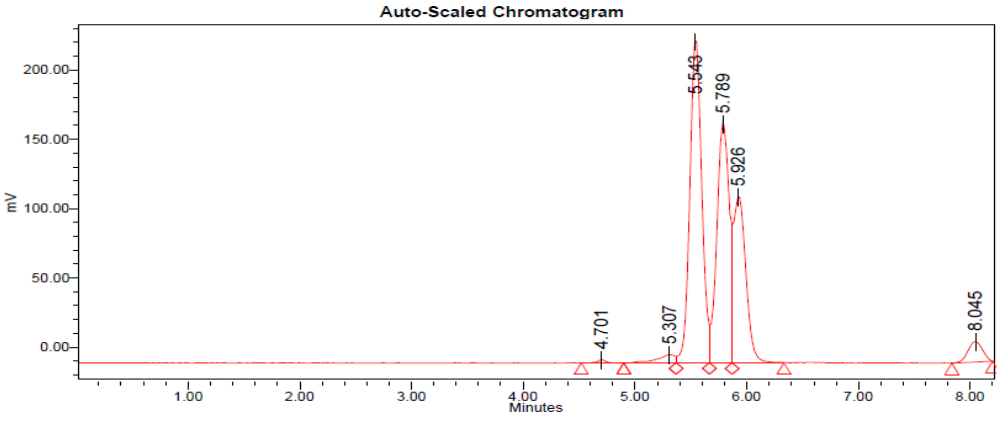


Figure II.A.5: HPLC chromatogram of reaction mixture of benzil, anisaldehyde and ammonium acetate after 15 minutes at 120^{o}C.

To authenticate our proposal, an HPLC chromatogram of the aldehyde and ammonia was carried out as been carried out with benzil and ammonia. The HPLC chromatogram of the aldehyde (anisaldehyde) when treated with ammonia under similar conditions showed no peak at a higher retention time than the aldehyde itself which shows only a single peak at retention time of 5.549 (**Figure II.A.6**).

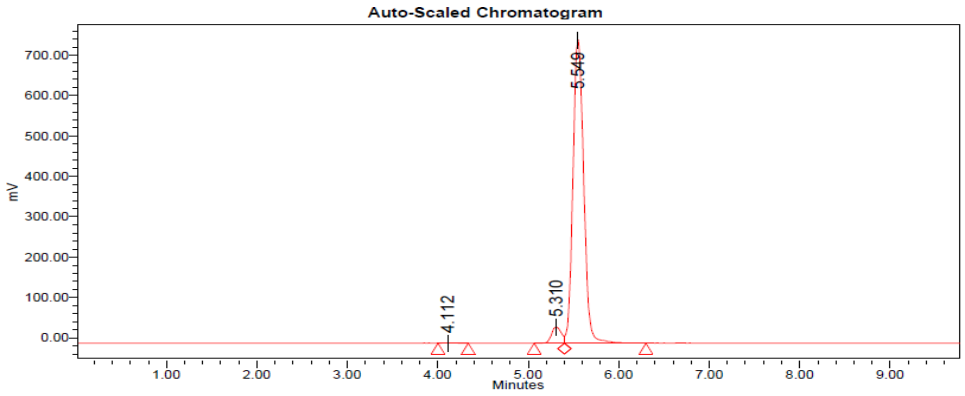


Figure II.A.6: HPLC chromatogram of Anisaldehyde and ammonium acetate.

Instead, a peak is observed at a retention time of 5.310 which was observed in chromatogram of the reaction mixture (**Figure II.A.6**).Of all the possibilities, this peak may be due to the aldehyde-ammonia addition product.

To start with, the kinetics of imidazoles 1b and 1c were thoroughly studied through HPLC monitoring of benzil and aldehyde (reactants) consumption along with the product (imidazoles) formation. When the ordinary logarithm values (-ve for reactants and +ve for products) of the peak area was plotted against time, a good linear relationship was observed in each case. The first order rate constant and half life ($t^{1/2}$) was determined from the slope of this curve using the first order rate equation given below:

$$dC/dt = (+/-)\ kC$$

$$C \ \alpha \ I$$

$$C = I*X$$

$$\pm \ln I = (+/-)\ kt + \text{integration constant}$$

Figure II.A.7: shows the observed dependence of reactants' concentrations (logarithm) and product formation with the variation of time (at reaction temperature 125^{o}C, temperature optimized for maximum conversion). It was found that the product peak in HPLC was not much prominent within the first 10 minutes.

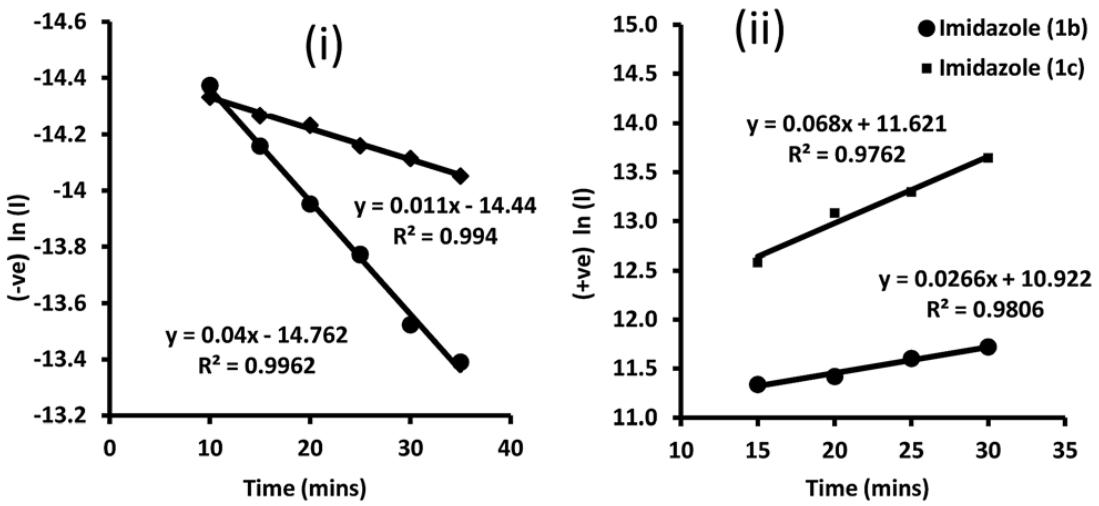


Figure II.A.8: (_ve)/(+ve) ln(I) vs. time (mins) of [i] benzil during formation of imidazoles (1b) and (1c); [ii] rate curve of the product imidazoles (1b) and (1c) formation; I = peak area.

The catalytic effect of some metal salts (5 mol%) at the same reaction temperature (125°C) was also compared. The corresponding rate constant and half life values are shown in **Table II.A.1**.

Table II.A.1: Rate constants and half lifes of reactant consumption and products formation at 125°C under solvent-free conditions.

Catalyst	Rate of benzil consumption ($t_{1/2}$)[a]	Rate of aldehyde consumption ($t_{1/2}$)	Rate of product formation ($t_{1/2}$)
Solvent-free (no catalyst)	0.011 (63.01)	0.008 (86.64)	0.026 (26.66)
$Sm(NO_3)_3.6H_2O$	0.012 (57.76)	0.008 (86.64)	0.023 (30.13)
$Yb(SO_3CF_3)_3$	0.033 (21.00)	0.009 (77.02)	0.115 (6.03)
$ZrO(NO_3)_2$	0.058 (11.95)	0.017 (40.77)	0.034 (20.38)
$(NH_4)_2Ce(NO_3)_6$	0.035 (19.80)	0.024 (28.88)	0.112 (6.19)
$NiCl_2.6H_2O$	0.032 (21.66)	0.021 (33.00)	0.041 (16.90)

[a] Note: Half-life ($t_{1/2}$) in minutes

The organized results indicated that the catalysts acted at various stages of the reaction steps of the MCR reaction. A representative case of ytterbium triftate, a threefold increase in the rate of benzil consumption and five time increase in imidazole formation as against the catalyst free reaction was observed. Considering that in a reaction, catalysts are used in very small proportions. Thus only a small mole fraction of the reactant would have the chance to get associated with the catalyst and hence the possibility of the substrate taking part in the adduct formation would be further reduced. Hence with only trace amounts of a catalyst (5 mol% in the above case) added to a reaction, the rate should have been hardly affected as only a few molecules would have engaged in activated complex in comparison to the large number of un-associated molecules in the reaction media. We have also studied the reactions at various elevated temperatures and found that at the temperature range 150–160°C, almost quantitative products were formed in a very short period of time of 4 minutes; and that too without using any kind of catalyst. This is a landmark record in the imidazole synthesis (ESI†).

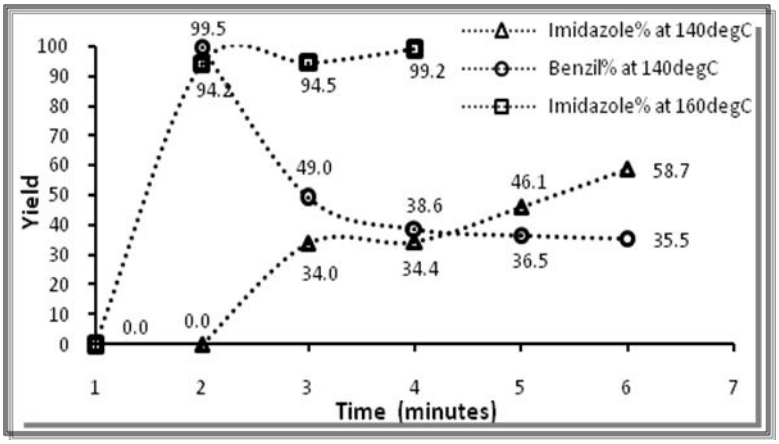


Figure II.A.9: Comparison of percentage yield of Imidazole, **[2]** at 140°C, 160°C and benzil consumption at 140°C versus time (mins).

Since, it was well known that the aldehydes have been frequently reacted with ammonium acetate to prepare 1, 2-diaminoethanes,[56] it was an initial assumption that the multi component reaction of the aldehydes with ammonium acetate and benzil under thermo chemical activation may not give quantitative results. Under these conditions, it has also been revealed that in the reaction hydrobenzamide is also formed in the initial stage which in turn gets transformed into amarine (*cis*-triphenylimidazoline). The compound further reacted with another molecule of aldehyde and through a series of intermediates formed the benzylidene benzoyl derivative. Contrary to what was expected, several other reported methods like

microwave, ultrasonication and catalytic methods, have been found to yield the Imidazoles efficiently. A possible reasoning may be that the presence of benzil actually hinders the formation of the said intermediates.

II.A.E. Optimization of reaction conditions for the synthesis of Imidazole derivatives with Thermal Analysis

Differential Scanning Calorimetry (DSC), one of the various methods for thermal analysis was used for the optimization of the reaction conditions for the synthesis of an Imidazole N-oxide. The study was carried out using diacetyl monoxime, p-hydroxy benzaldehyde and p-amino benzoic acid as the starting materials for their one-pot multicomponent synthesis of the corresponding Imidazole N-oxide as the model reaction. A DSC analysis of a powdered mixture containing equimolar amounts of each reactant for the synthesis of 1-substituted Imidazole N-oxides has shown that the reaction is highly exothermic. A detailed look at the DSC plot shows an exotherm at 112^{o}C which thereby indicates the onset of the reaction and the product formation probably begins at this temperature (**Figure II.A.10**).

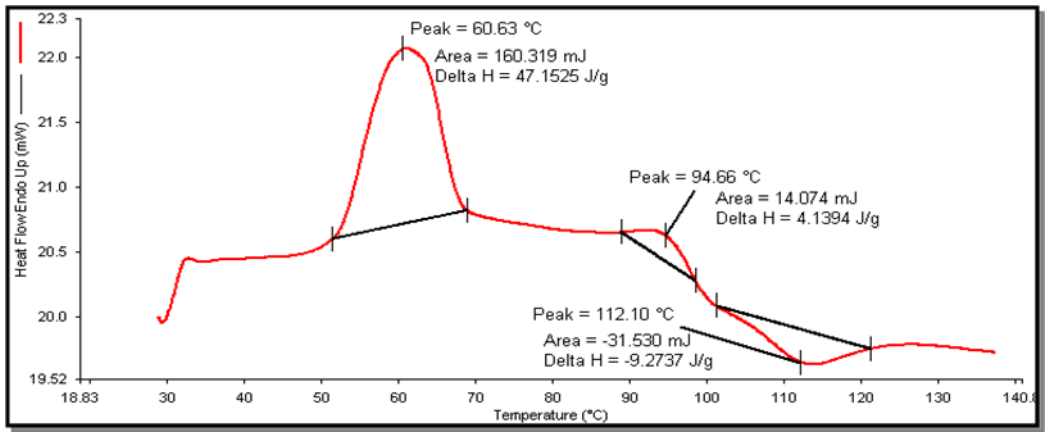


Figure II.A.10: DSC plot of a mixture of diacetyl monoxime, p-hydroxy benzaldehyde and p-amino benzoic acid

For 1-hydroxy 2, 4, 5-trisubstituted imidazole-3-oxides synthesis the DSC and TGA results gave more interesting results for the study. For the refinement of the present study, the DSC plots of the three systems were compared. The DSC trace of the ground mixture of diacetyl monoxime and m-nitrobenzaldehyde monoxime (**Figure II.A.11**) has shown two high peaks at 60^{o}C (sharp) and 222^{o}C. These two peaks correspond to m.p of diacetyl monoxime and the product m.p. respectively. There are also two broader humps at around

97°C and 125°C which corresponds to the sublimation of diacetyl monoxime and the m.p. of m-nitrobenzaldehyde monoxime (Litt. M.p.122-123°C) respectively.

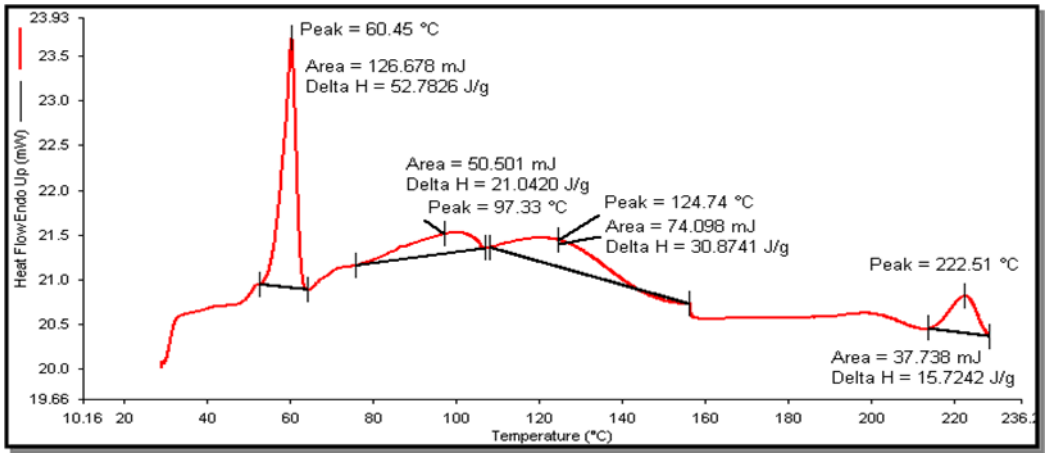


Figure II.A.11: DSC trace of a mixture of diacetyl monoxime and m-nitrobenzaldehyde monoxime

A Simultaneous Thermal Analysis (STA) was also been carried out to have some insight of the reaction scheme. It suffered from a serious technical disadvantage of being carried out only in an open sample holder. Since one of the reactants, diacetyl monoxime underwent through sublimation; a correct picture about the loss of water molecule cannot be obtained. Inspite of this, the TGA trace obtained from the STA of the reaction mixture of diacetyl monoxime and m-nitrobenzaldehyde oxime indicates the increase in temperature at around 90°C. Moreover, the m.p. peak of the product at 222-225°C cannot be observed in the DSC trace (**Figure II.A.12**).

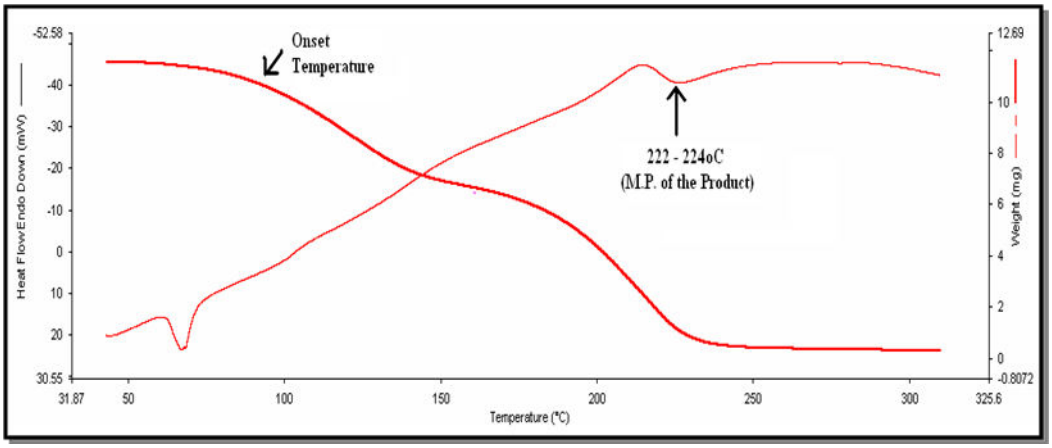


Figure II.A.12: STA of the mixture of diacetyl monoxime and m-nitrobenzaldehyde oxime

A second DSC analysis of the mixture of m-nitrobenzaldehyde and dimethyl glyoxime was also done (**Figure II.A.13**). The DSC plot shows around three peaks at 58°C, 60°C and 202°C corresponding to m.p. of m-nitrobenzaldehyde (Litt. m.p. 55-58°C), diacetyl monoxime (Litt. m.p. 75-78°C) and the product (Observed m.p. 225-227°C) respectively.

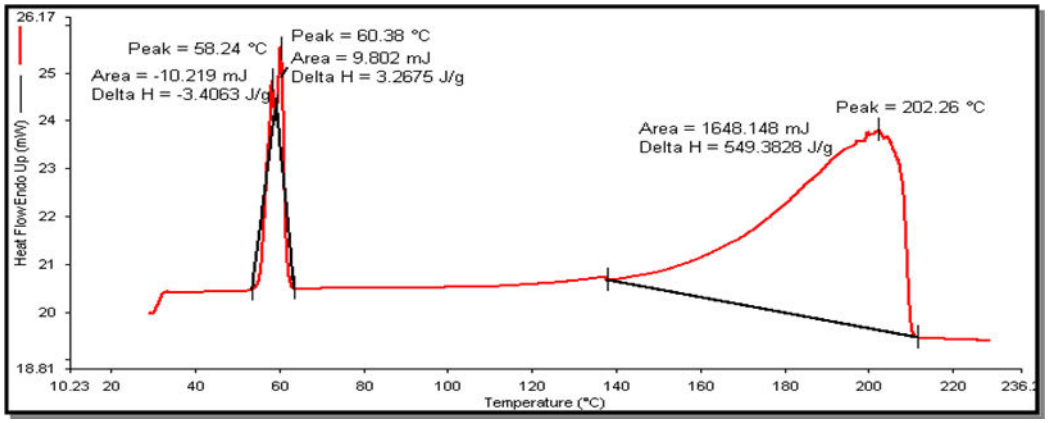


Figure II.A.13: DSC trace of a mixture of dimethyl glyoxime and m-nitrobenzaldehyde

Interestingly, the appearance of the at around peak at 60°C for the m.p of diacetyl monoxime in the second DSC curve, even in its absence as a starting material, suggests that there could be some mechanism involved wherein the dioxime at first gets transformed to the monoxime by the exchange of the oxime group between aldehyde and dioxime, a mechanism which was earlier proposed by John B. Wright[57] but not yet been verified. It is highly possible that the reaction then proceeds via a monoxime to yield the corresponding products. A DSC trace for the pure dimethyl glyoxime for comparison was also obtained (**Figure II.A.14**). No peak was actually seen at the m.p. of diacetyl monoxime or at 60°C as was actually observed earlier, when it was thoroughly mixed with the m-nitrobenzaldehyde. It can be concluded that the peak observed at 60°C arises only in the presence of aldehyde and is due to the diacetyl monoxime which always tends to melt at that high temperature in the mixture.

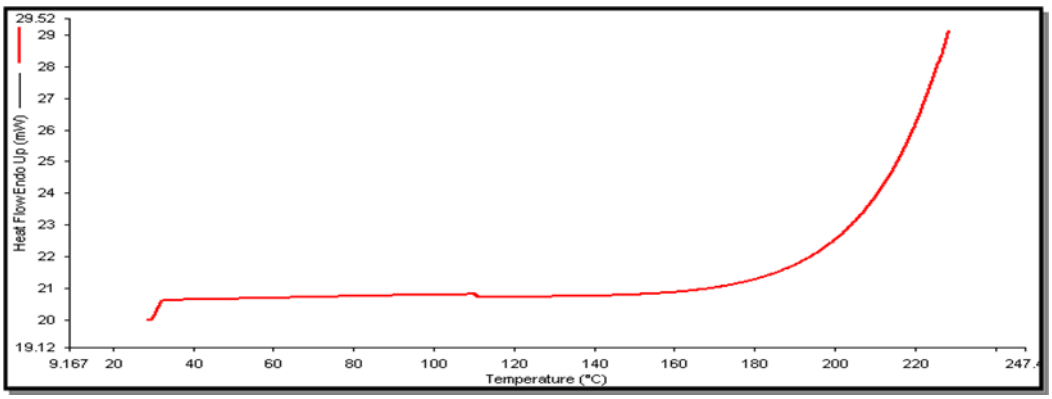


Figure II.A.14: DSC trace for pure dimethyl glyoxime

In the DSC trace of the pure diacetyl monoxime two peaks were observed. The peak at around 76^{o}C is for the m.p. of diacetyl monoxime while the second peak at around 153^{o}C actually confirms the appearance of the endotherm for sublimation of diacetyl monoxime (**Figure II.A.15**).

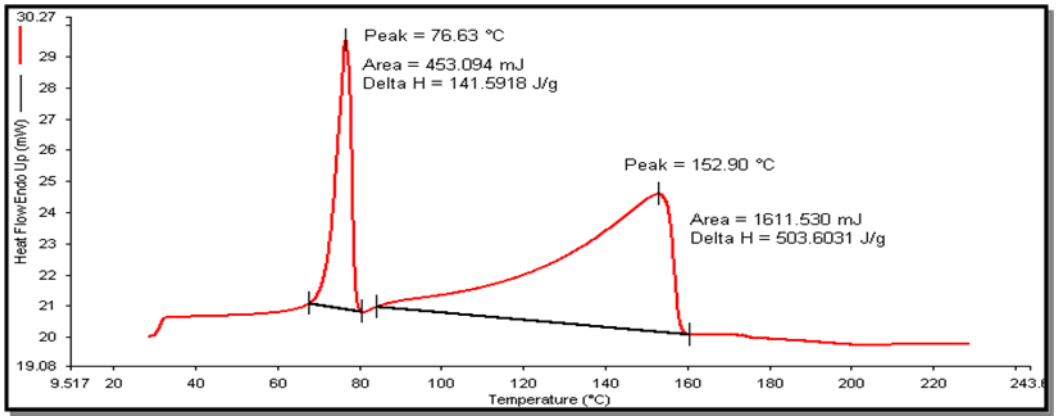


Figure II.A.15: DSC trace of pure diacetyl monoxime

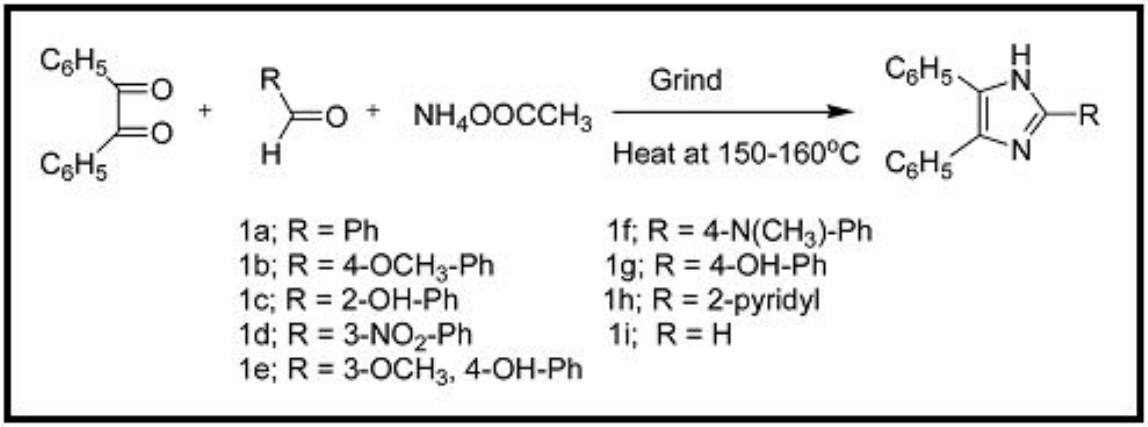
The peak at around 153^{o}C in the above shown DSC curve corresponds to the sublimation of the pure diacetyl monoxime, which in the above case is at a much higher temperature compared to the actual peak at 125^{o}C and is attributed for the same as in the case of the reaction mixture shown in **Figure II.A.15**. The depression by 28^{o}C in the sublimation peak which is observed in the reaction mixture could be due to the presence of some other compounds in the reaction mixture, which is quite similar to the observed depression of melting point of the diacetyl monoxime from 76^{o}C in the pure form to about 60^{o}C in the

reaction mixture. Overall, it may be concluded that the reaction actually proceeds via some monoxime in all the three cases. Whatever maybe the functionality of the substrate, the synthon in all the three reactions was found to be α-(hydroxyimino) ketones.

II.A.F. Solvent-free multi-component synthesis of Tri- and tetra-substituted Imidazoles

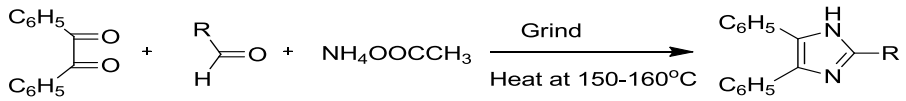
According to exixting literature Debus-Radziszewski imidazole synthesis in the solution state would take about 24 hrs to get a yield of good quantity.[58] Heather to,while the two most reported efficient syntheses are under the conditions of microwave irradiation where reactants are being irradiated at 180^{o}C in for 5 minutes in acetic acid[50] (Wolkenberg et al) and for 3-5 minutes at 120^{o}C [47] (Zhou et al) in the absence of catalyst. Both cases having yields which are almost quantitative. The reaction in first case was catalyzed by acetic acid while focused heating of microwave in the solvent-free condition helped in second case. It is seen that solvent-free condition is being responsible for mostly the self-catalytic effect. basic chemistry in all cases remains the same; changes in polarizability and electrophilicity of carbonyl group has an influence on rate of reaction. Quantitative yields of under four minutes are obtained even in solvent free thermal conditions without the presence of catalyst. Reactions based on thermal heating might be more practical to use out in the scaled up syntheses.

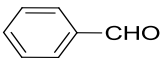
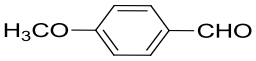
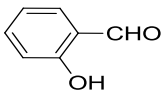
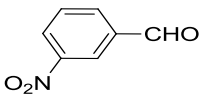
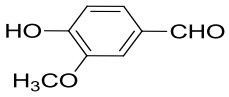
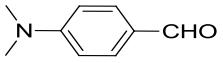
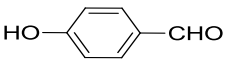
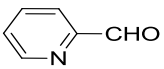
We examined variety of aldehydes (both aliphatic and aromatic) with different substituents for establishing catalyst-free solvent-free protocol for the following reaction (**Scheme II.A.2**). A variety of *ortho*-, *meta*-, and *para*-substituted aromatic aldehydes undergo this one-pot multi-component synthesis with the 1, 2-diketones and ammonium acetate to give, 4, 5-trisubstituted imidazoles in good quantitative yields (**Table II.A.2**). For all cases, it was observed that reaction profile was very clean with no side-products. The imidazoles synthesized have all been characterized with the basis of elemental and spectral studies.



Scheme II.A.2: R-I synthesis of tri-substituted imidazoles **.**

Table II.A.2. Solvent free synthesis of 2,4,5-trisubstituted Imidazoles.



Entry	Aldehyde (R-CHO)	Product	Melting Point / °C	Reaction Time	Reported Time [a]
1		**[1]**	274-276	4 min	8.3 h[7]
2		**[2]**	226-228	4 min	9 h[7]
3		**[3]**	202-203	4 min	9.1 h[7]
4		**[4]**	> 300	4 min	8.5 h[7]
5		**[5]**	165-168	4 min	
6		**[6]**	256-258	4 min	10 h[5]
7		**[7]**	260-261	4 min	8.4 h[7]
8		**[8]**	240-242	4 min	
9		**[9]**	225-226	4 min	12 h[7]

Near Quantitative yields of above 98% was obtained in all cases. [a]Time reported in presence of catalyst and in solvents. In absence of any catalyst the reaction time is 24 hours to get 10% yield. [7]

Along the usual methods of spectroscopy for structure determination, we used single crystal X-ray diffraction (Sc-XRD) data of 1 of the representative compounds: 4,5-diphenyl-1Himidazole, **9**, to confirm its structure. Single crystals of compound suitable for Sc-XRD were formed by slow evaporation from the methanol/hexane mixture. This compound crystallizes in a monoclinic crystal system with space group $P2_1/c$ (Hall group - P_{2ybc}); a= 11.0471(4) A°, b = 9.2483(3) A°, c = 11.5780(4) A°, α = 90°, β = 93.921(3)°, γ = 90°, Z = 4, μ = 0.577 mm^{-1}, F_{000} = 468.0 and Kα = 1.54184 °A. The ORTEP diagram has been presented in **Figure II.A.16**. Its heterocyclic ring has been seen as planar. An interesting thing in the following diagram is attachment of a proton in every nitrogen atom reflecting an overall excess of a proton. The N_7–C_{11} and N_9–C_{10} bond lengths are identical (1.380 A° and 1.3799 A° respectively), Also N_7–C_8 and N_9–C_8 bond lengths are close as well (1.3157 A° and 1.3462 A° respectively); also the N7 and N9 centered bond angles are quite close (107.83° and 105.91°). Intermolecular transfer rate of extra proton in imidazole has been reported in order of 0.3 $\times 10^{-12}$ second[31] but no such data is there for intramolecular N to N transfer of proton due to shift of N–C double bond in the imidazole; thus it's difficult to tell the process would be faster than the X-ray diffraction time (10^{-18} second). However, bond lengths are between C–N single bond (1.47 A°) and double bond (1.25 A°). As both nitrogen atoms are similar, and on basis of probability the Hydrogen atoms might have been added to both atoms during the computation. This extra proton is not being originated from imidazolinium salt as in such case the counter ion would have been in the unit cell; and also non equivalence of nitrogen atoms would be observed.

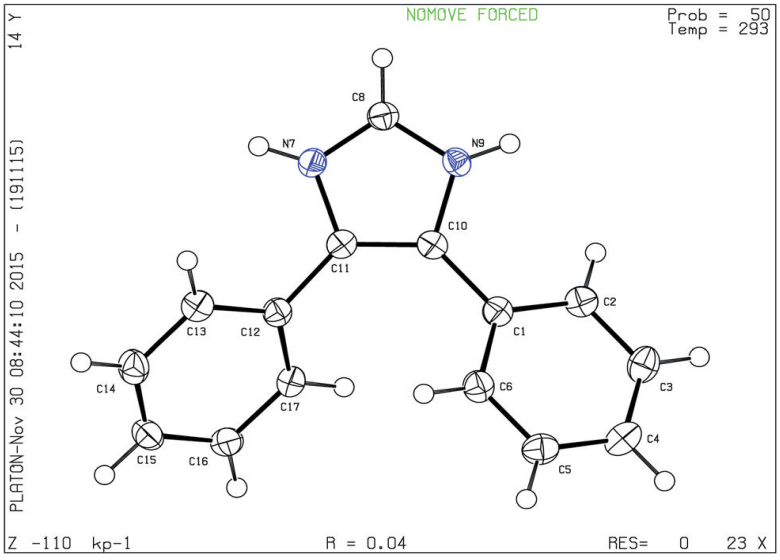
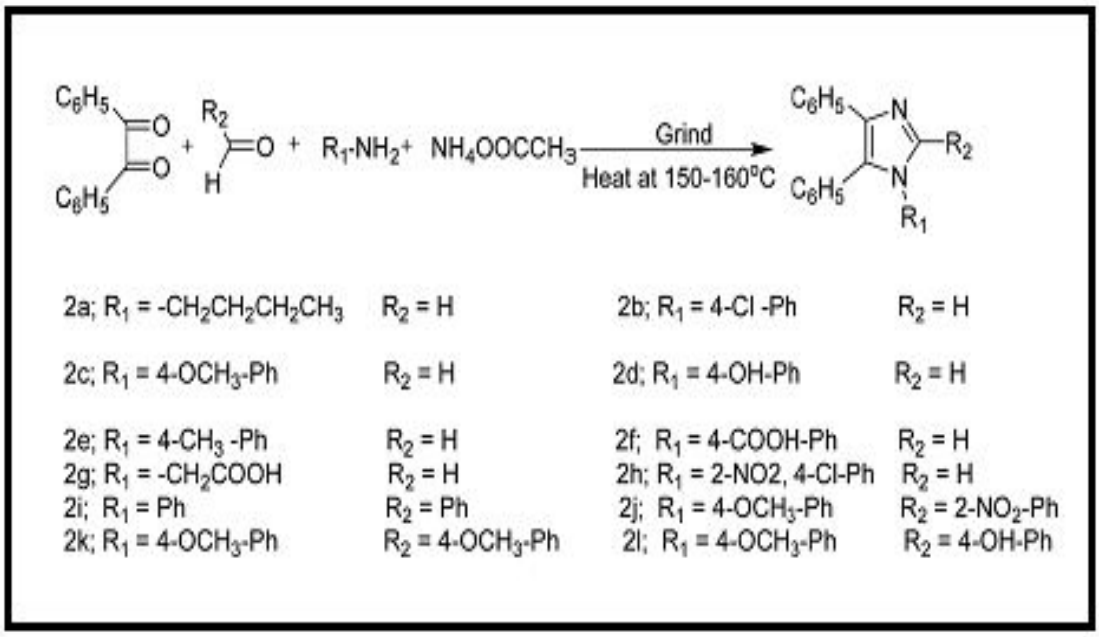


Figure II.A.16: ORTEP diagram of **9** derived from single crystal data

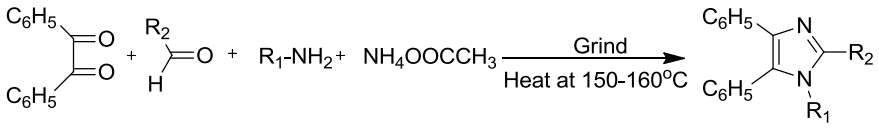
The reaction woukld be extended under same conditions to synthesize of 1, 2, 4, 5-tetrasubstituted imidazoles via a one-pot, four-component condensation of benzil (1mmol), a primary amine (1mmol), an aldehyde (1mmol), and ammonium acetate (5mmol) as is shown in **Scheme II.A.3**.

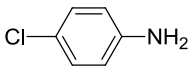
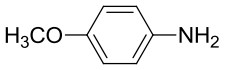
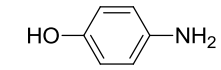
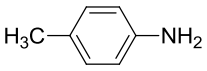
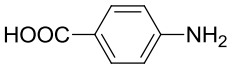
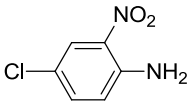
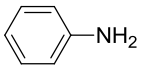
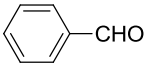
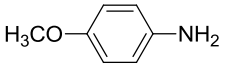
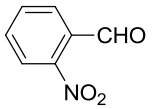
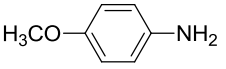
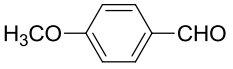
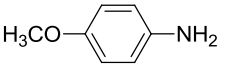
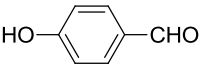


Scheme II.A.3: R-I synthesis of tetra-substituted imidazoles.

The tetra-substituted Imidazoles can be synthesized in the quantitative yields in very short time and also with minimal product purification procedures (**Table II.A.3**). It's also found that aromatic and aliphatic amines also along with aromatic and aliphatic aldehydes can be subjected to the following protocol successfully.

Table II.A.3: Solvent free synthesis of 1,2,4,5-tetrasubstituted Imidazoles



Entry	Amine (R_1-NH_2)	Aldehyde (R_2-CHO)	Product	Melting Point / °C	Reaction Time
1	$CH_3CH_2CH_2CH_2NH_2$		**[10]**	78-80	4 min
2			**[11]**	209-211	4 min
3			**[12]**	180-182	4 min
4			**[13]**	218-220	4 min
5			**[14]**	170-172	4 min
6			**[15]**	>270	4 min
7	NH_2CH_2COOH		**[16]**	173-175	4 min
8			**[17]**	206-208	4 min
9			**[18]**	78-80	4 min
10			**[19]**	209-211	4 min
11			**[20]**	180-182	4 min
12			**[21]**	218-220	4 min

Near Quantitative yields of above 98% was obtained in all cases.

II.A.G. Imidazole N-Oxides and 1-hydroxy Imidazole 3-oxide

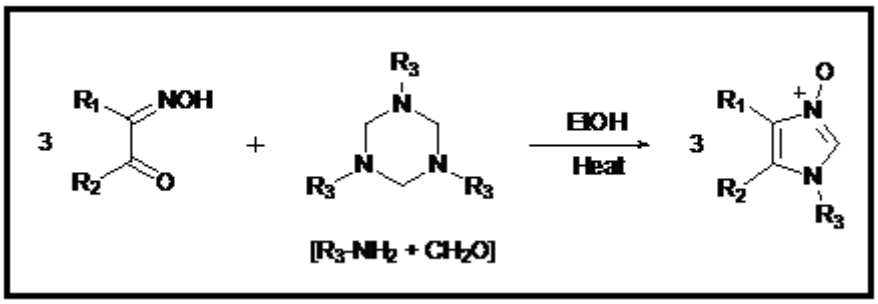
Substituted heterocycles having an imidazole backbone are frequently found to have some interesting biological activities. Imidazole N-oxides having oxide functionality at N-3 position and the 1-Hydroxy Imidazole-3-oxides with hydroxy function at N-1 and oxide functionality at N-3 positions are also no exceptions. These heterocycles with bioactivity with

an imidazole ring system, being a part of the large number of very significant biomolecules, have a lot of pharmacological properties along with playing significant some roles in the biochemical processes. Further, it's observed that there's a well-known *N*-oxide group effect leading to a significant change in the reactivity of heteroaromatic *N*-oxides, compared to their unoxidized analogues, thus activating them to nucleophilic, electrophilic and radical agents.[59] Presence of an N-oxide group, or an N- hydroxy group in the ring of imidazole is thought to alter the properties of diazole compound.

Imidazole N-oxides and the 1-hydroxy imidazole-3-oxides currently are of interest as they can be building blocks for chosen transformations of the diverse imidazole derivatives, including the enantiomerically pure compounds.[60]Also, they have been found to possess various biological activities.[61]Heterocyclic aromatic N-oxides, or dioxides in specific are antitumor agents exhibiting DNA-damaging properties.[62] Further, presence of supplementary hydroxyl substituent in the imidazole framework in 1-hydroxy imidazole N-oxides has been used frequently for preparing 1-hydroxy imidazoles by selective reduction,[63] as 1-hydroxyimidazoles [64] are useful intermediates to prepare pharmaceuticals and agricultural chemicals. Nowadays they are some of the most widely produced compounds in organic synthesis to serve as precursors for a class of various alternative media, [65] where *N*-bulky substituted imidazole 3-oxides act as attractive starting material to synthesize new and stable nucleophilic carbenes (NHC) through three step deoxygenation-quaternization-elimination process.[66] Apart from synthetic and pharmacological utilities, 1-hydroxyimidazole-3-*N*-oxides are found to be acting as effective inhibitors of aluminum corrosion.[67]

II.A.H. Synthesis of Imidazole N-Oxides and 1-hydroxy Imidazole 3-oxide

Normally, imidazole *N*-oxides can't be prepared through direct oxidation of parent compound. Still, preparation of 1-methylimidazole *N*-oxide by the treatment of 1-methyl-1*H*-imidazole in THF along with H_2O_2 at room temperature is described recently.[68] 2-unsubstituted imidazole *N*-oxides are conveniently synthesized by the condensation of the *α*-(hydroxyimino) ketones with *in situ* generated formimides,[69] of *α*-amino oximes with orthoformates,[70] and of diimines with formaldoxime.[71] However, the method of choice for their preparation is via the condensation of α-(hydroxyimino) ketones with aldehyde and a corresponding primary amine. The reaction can be carried out either by refluxing in alcohol or in presence of acetic acid (**Scheme II.A.4**). The amines are converted into formaldimines (monomeric forms) or hexahydro-1, 3, 5-triazine using either paraformaldehyde or formalin.



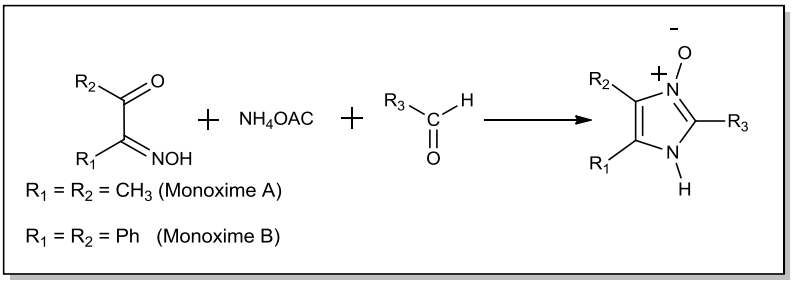
Scheme II.A.4: Conventional synthesis of Imidazole N-oxides

Just like above, 1-hydroxyimidazole-N-oxides could be prepared through condensation of either α-(hydroxyimino) ketones and aldehyde monoximes or through condensation of dioximes with aldehydes. Still, here also the method of choice for the preparation has been three-component cyclization of 1, 2-diketone, an aldehyde, and hydroxylamine.[63] Drawback of the begining two procedures was that they are very time consuming while given third procedure includes an elaborate process extending over 24 hours.

Keeping the view of the general uses of N-oxides and 1-hydroxy imidazole-3-oxides in the synthetic biology and organic chemistry, an one-pot, solvent-free path for synthesis of derivatives of imidazole would provide simple yet environmentally friendly alternative to the previous reported methods. In published papers that deal with preparation of Imidazole N-oxides and 1-hydroxy imidazole-3-oxides, the solvent free processes have not yet been explored and their mechanistic investigations have still not been dealt. While elaboration of simple yet efficient procedures of their synthesis is a real challenge, it becomes more interesting and also significant when scope of this study extends positively with even more newer findings. A simple and versatile process to synthesize Imidazole N-oxides and 1-hydroxyimidazole-3-oxides in a good yield has already been demonstrated in this section of work. This study investigates the processes of synthesis and characterization of these compounds (some of which were unpublished earlier) through a solvent-free method. There's been no report published on solvent-free method of synthesis of such heterocyclic compounds till date.

II.A.I. Solvent-free multicomponent synthesis of Imidazole N-oxides and 1-hydroxyimidazole-3-oxides

It is to be kept in mind that the traditional methods for the preparation of the Imidazole N-oxide using refluxing conditions for as long as 3-6 hours. It implied that the above method brings about a considerable reduction in the reaction time. A variety of Imidazole N-oxides were further synthesized under the highly optimized reaction conditions using a diverse range of aliphatic/aromatic aldehydes and ammonium acetate instead of amine component according to **Scheme II.A.5**.

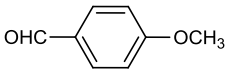
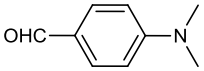
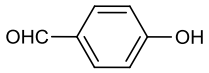
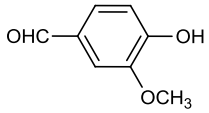
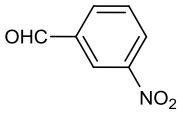
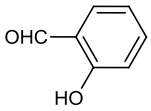
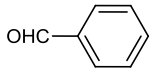
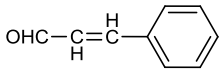
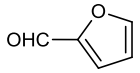
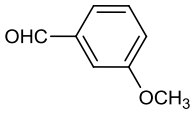
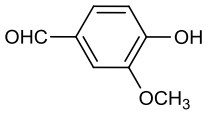
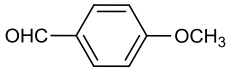
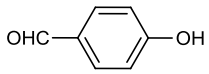
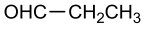


Scheme II.A.5: One-pot solvent free method for synthesis of Imidazole N-oxides

In a reaction 1 mili mole of each of the monoxime and the aldehyde was finely grinded with 5 mili mole of ammonium acetate and the thorough mixture was heated to 115-120^{o}C for about 10 minutes. It was then cooled until a black sticky precipitate resulted. To the black precipitate was then added a very small volume of diethyl ether until a brown precipitate got separated. The precipitate was evenly washed with ethyl acetate to produce the pure products. The black precipitates got dissolved in ethanol and then water was added gradually a hazy solution was formed. The milkiness disappeared on heating. Creamy colored precipitates were obtained after cooling.

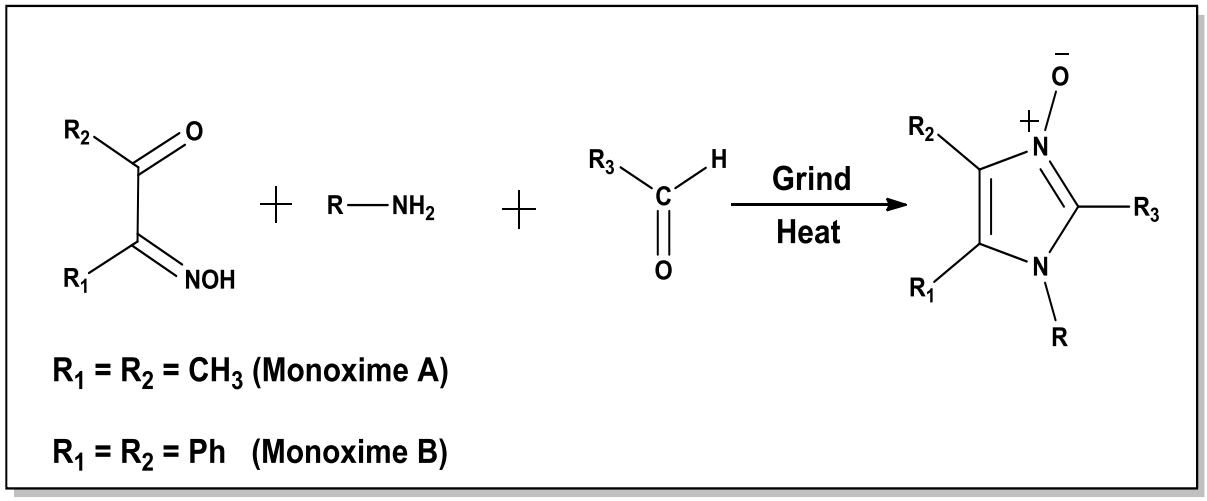
A wide variety of Imidazole N-oxides can actually be prepared by employing a diverse range of aliphatic and aromatic aldehydes. Various monoximes can also be taken, the methods worked well with all kinds of substitution on monoxime. The reaction was found to proceed smoothly to give quantitative yields of the products and the results are briefly summarized in **Table II.A.4**.

Table II.A.4: Synthesis of Imidazole N-oxides under catalyst-free and solvent-free conditions

Entry	Monoxime	Aldehyde	Product	Melting Point (^{o}C)
1	A		**[22]**	138-140
2	A		**[23]**	233-235
3	A		**[24]**	>260-270
4	A		**[25]**	258-259
5	A		**[26]**	172-174
6	A		**[27]**	233-235
7	A		**[28]**	125-127
8	A		**[29]**	116-118
9	A		**[30]**	95-97
10	A		**[31]**	118-120
11	B		**[32]**	197-199
12	B		**[33]**	95-96
13	B		**[34]**	230-232
14	B		**[35]**	72-74
15	B		**[36]**	88-90

Initial one-pot reaction of α-(hydroxyimino) ketones using a wide range of aromatic/ aliphatic aldehydes and aliphatic/aromatic amines were also carried out. The products, N-

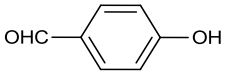
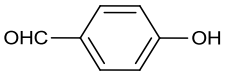
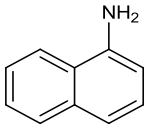
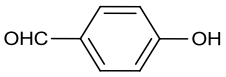
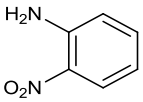
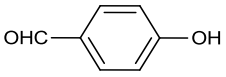
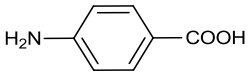
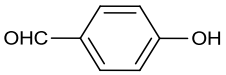
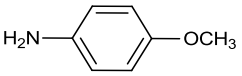
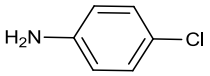
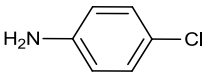
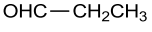
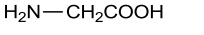
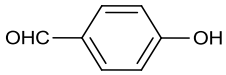
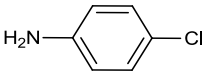
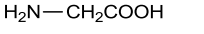
substituted imidazole N-oxides were actually formed in quantitative yields at an optimized temperature of 115-120^{o}C within 10 minutes. The yield of the product was actually not affected by the structure of amine. An overview of the synthetic details has been summarized in **Scheme II.A.6**.



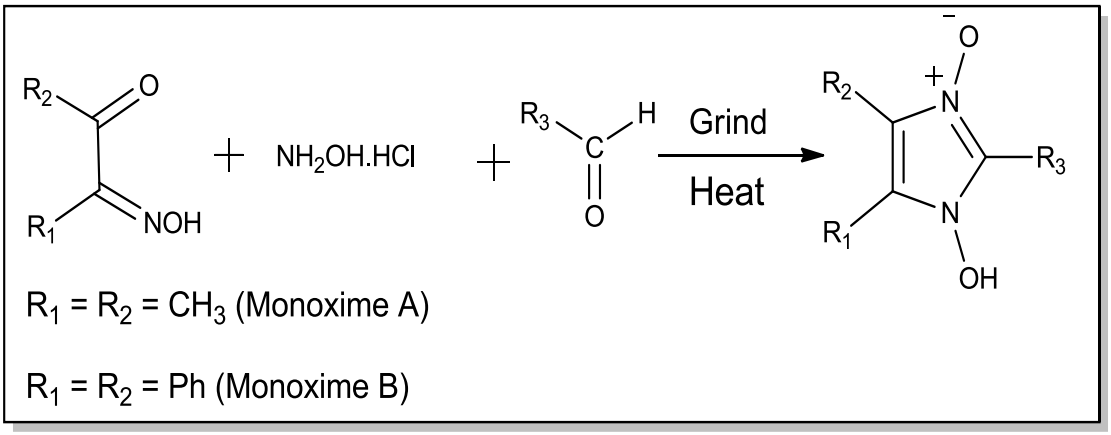
Scheme II.A.6: One-pot solvent free method for synthesis of N-substituted Imidazole N-oxides

In a typical reaction, 1 mili mole each of monoxime and the aldehyde was mixed with 1.5 mmole of the amine and was heated. The completion of the reaction was indicated through TLC. The product formed was thoroughly washed with a very little amount of ether and further by heated ethyl acetate. A little excess of the amine was actually used as a stoichiometric amount resulted in only 75% yield and the reactant spots were clearly visible in the TLC only after 10 minutes of the reaction. When 1.5 mili mole of amine was used, within 10 minutes, a single spot of the product was observed and the reactant spots actually disappeared. With this approach ten imidazole N-oxides were actually prepared in high quantitative yields and were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectra.

Table II.A.5: Synthesis of N-substituted Imidazole N-oxides under catalyst-free and solvent-free conditions

Entry	Monoxime	Aldehyde	Primary amine	Product	Melting Point
1	A		$CH_3CH_2CH_2CH_2NH_2$	**[37]**	128-130
2	A			**[38]**	232-235
3	A			**[39]**	272-273
4	A			**[40]**	210-213
5	A			**[41]**	205-207
6	A			**[42]**	238-240
7	B			**[43]**	170-172
8	B			**[44]**	>260
9	B			**[45]**	182-184
10	B			**[46]**	248-250

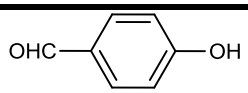
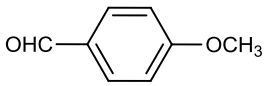
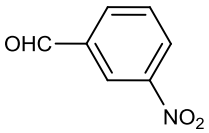
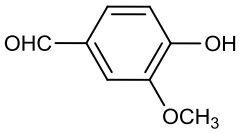
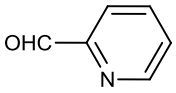
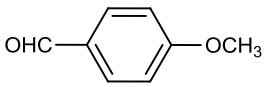
When the same approach was extended to the synthesis of 1-hydroxy Imidazole-3-oxides, it was actually found to be even more successful as it highly reduces the reaction time from 24 hours (traditional method) to 10 minutes. Usually in the optimized solvent-free preparation of 1-hydroxyimidazole-N-oxides, usual grinding of equi-molar amounts of monoxime and the aldehyde and an excess amount of hydroxylamine hydrochloride using a mortar pestle over a period of ca. 3 min was done. Subsequent heating for another 7 mins at about 110-120^{o}C (**Scheme II.A.7**) gave the products in near quantitative yield. The products mainly remained as eutectic melt on cooling and then immediately precipitate out on adding a liitle amount of ether. It was further washed with water and ethyl acetate.



Scheme II.A.7: One-pot solvent free method for synthesis of 1-hydroxyImidazole-3-oxides

A appreciable observation that deserves actual mentioning is that including only the mechanochemical process of grinding the representative reaction including benzil monoxime, anisaldehyde and an excess amount of hydroxylamine hydrochloride at room temperature took about 8 days to yield the products which precipitated from water and could be re-crystallized to get very pure crystals. The solvent-free method produced the product in just 10 minutes. Analysis of the product by ^{1}H and ^{13}C NMR has shown only the pure products. The 1-hydroxy 2,4,5-trisubstituted imidazole-3-oxides were prepared at an optimized temperature in excellent yields without requiring any extensive workup or purification and that too in a very short period of time (**Table II.A.6**). Apart from the lower reaction times (energy saving), the other advantage of using this solvent-free approach is that the product obtained is of high purity. Single crystals of the product could also be obtained for characterization purposes.

Table II.A.6: Synthesis of 1-hydroxyImidazole-3-oxides under catalyst-free and solvent-free conditions

Entry	Monoxime	Aldehyde	Product	Melting Point
1	A		**[47]**	165-168
2	A		**[48]**	196-198
3	A		**[49]**	209-211
4	A		**[50]**	201-203
5	A		**[51]**	hygroscopic
6	A		**[52]**	136-137
7	B		**[53]**	233-235

This is the initial report of the solvent-free condensed phase protocol for the oxide and hydroxyl oxide derivatives of the imidazoles. The advantages of the above mentioned method are many:

- The synthetic strategy is highly facile, leading to the higher yields and is susceptible to up-scaling.
- It is operationally simple, efficient and a very green route to synthesize biologically important imidazole N-oxides and 1-hydroxyimidazole-3-oxides.
- The high yields and low waste generation of this procedure gives it highly attractive green chemistry metrics, not to mention its remarkable versatility.
- The approach actually avoids the use of those organic solvents and the extensive work-up and thus makes it highly attractive and practical for the library synthesis of such compounds.

The useful synthesis of the N-substituted imidazole N-oxides and 1-hydroxyimidazole-3-oxides within the 10 minutes of reaction was actually also based on the same synthetic procedure as with the Imidazoles. The synthesis also proves that acetic acid, generated in the reaction, is not the only catalyzing factor for increasing the reaction rates under the solvent-free conditions. The synthesis of N-substituted Imidazole N-oxide requires the use of an amine compound instead of ammonium acetate while hydroxylamine hydrochloride is actually used during the preparation of the 1-hydroxyImidazole-3-oxide.

II.A.J. Evidences for Carbonyl activation in Solvent-free reactions

We have seen in the preceding sections that solvent-free procedures involving the carbonyl moiety in the substrate undergo mechano-chemical activation very easily. The reaction tends to proceed even faster than in solvents. Therefore, it becomes imperative on our part to investigate, in order to understand, at least partially, why these reactions proceed so efficiently under solvent-free conditions. To this purpose, a combination of methods viz., reactivity, spectroscopy and computational studies have been used.

II.A.J.1. Infrared studies

In order to contemplate the cause behind the efficacy in solvent-free procedure, the IR-spectra of pure benzil in thin film as well as that with catalyst was studied. A thin solid film of benzil was prepared and its IR spectra taken. Subsequently, a thin film of a mixture of benzil with the catalyst ytterbium triflate was also taken. The carbonyl region of the benzil thin film and that with 5 mmol% of ytterbium triflate has been presented in **Figure II.A.17**.

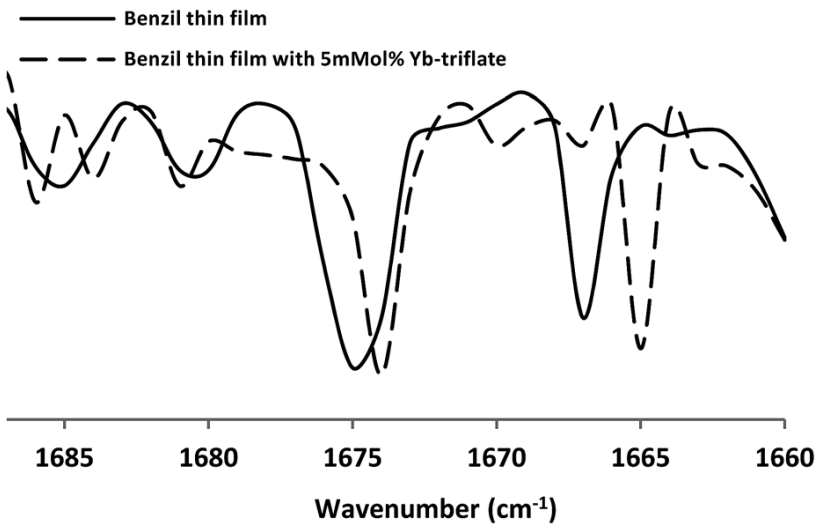


Figure II.A.17: IR spectra of benzil thin film, with and without a catalyst.

It can be seen that the free carbonyl band (with catalyst) at 1676 cm^{-1} has apparently increased in intensity with simultaneous shifting to lower frequency compared to the corresponding band for benzil. It was earlier reported[72] that the C=O stretching band of benzil appears at 1676 cm^{-1} in the crystalline state and at 1685 cm^{-1} in solution. The red-shift and the enhancement in intensity of the peak have obviously been brought about by the presence of the catalyst. Hence we could consider this phenomenon as a marker of catalytic effect. Alike shift of carbonyl stretching frequency in TiO_2 surface for benzophenone has already been reported.[73] The difference in stretching frequency (9 cm^{-1}; red-shift) indicates a greater degree of single bond character in the C=O bond (polarisation enhancement) in the solid state compared to that in the solution state for benzil. The shifting of carbonyl stretching manifested as a sharp peak provides an indication of bulk polarization of benzil in the solid state. Since a similar effect is also observed with catalysts in the solid state, it is highly indicative of polarizations occurring in bulk, rather than being partial.

To substantiate, the study was extended further to be carried out in solution. The extent of the shift caused by the presence of trace amounts of ytterbium triflate and zirconyl nitrate on benzil carbonyl stretching frequency in hexane solution was also studied. The IR spectra in the carbonyl range have been presented in **Figure II.A.18**. As is apparent from the figure, in the presence of a catalyst the free carbonyl peak of benzil at 1685 cm^{-1} and all other associated peaks are shifted to lower frequencies. In addition to this, the intensity of the free carbonyl peaks (particularly the peak at 1680 cm^{-1}) is seen to be diminished while the intensities of some other peaks are found to increase at lower frequencies in the presence of traces of catalyst.

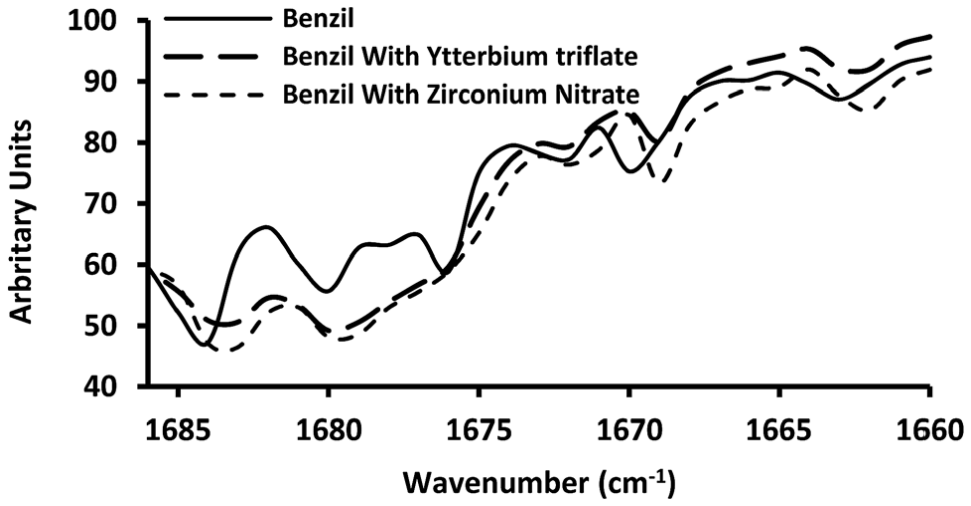


Figure II.A.18: Solution IR spectra in the carbonyl range of benzil in hexane.

Apparently the catalyst, zirconyl nitrate, is found to polarize benzil to a greater extent than ytterbium triflate. A quick perusal of Table 1 also points to the fact that the catalytic effect of zirconyl nitrate is a better for benzil consumption rate as well. It is observed that in both the solution as well as in the solid state there is a noticeable enhancement of the band at 1680 cm^{-1} in the presence of catalyst. The peak at 1680 cm^{-1} has been described as another C=O stretching band associated with a different symmetry of the molecule.[74] Enhancement of the band near 1680 cm^{-1} in presence of catalyst suggests that the catalysts not only polarize the carbonyl but also influence the conformation of benzil. The IR spectroscopic investigation thus strongly provides evidences for bulk polarization of the C=O moiety in the condensed phase. This in turn may lead to a marginal increase of the electrophilicity of the carbonyl carbon. The above observation suggests that catalysts bind to the carbonyl oxygen and the weak interaction activates the carbonyl group with the enhancement of polarization.

II.A.J.2. Computational studies

Since the IR spectroscopic results hinted at bulk polarization of the substrate molecules, it was thought that quantum mechanical calculations carried out on simple molecules bearing the same functionality i.e., the C=O group could provide more insight to the study. Therefore, CBS-QB3 model chemistry calculations of a HCHO monomer and trimer were performed. We carried out a geometry optimization for a linear arrangement of the trimer (**Figure II.A.19**).

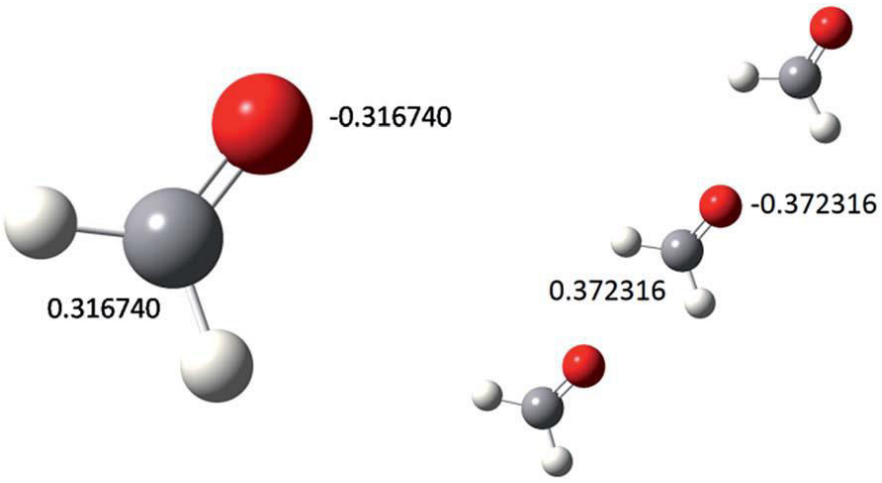


Figure II.A.19: Minimum energy models with partial charges.

It is expected that a number of minimum energy conformations with different geometries could be feasible when molecules remain in association. To serve our purpose, we searched for minimum energy that would result when the molecules are arranged linearly. The calculations terminated on convergence to such minima. A quick comparison of the partial charges on the carbon and oxygen atoms of the monomer and trimer showed that it was enhanced in the case of the trimer where the molecules were associated. It was found that the dipole moment of the associated monomer was also enhanced in the trimer as compared to the monomer (**Table II.A.7**).

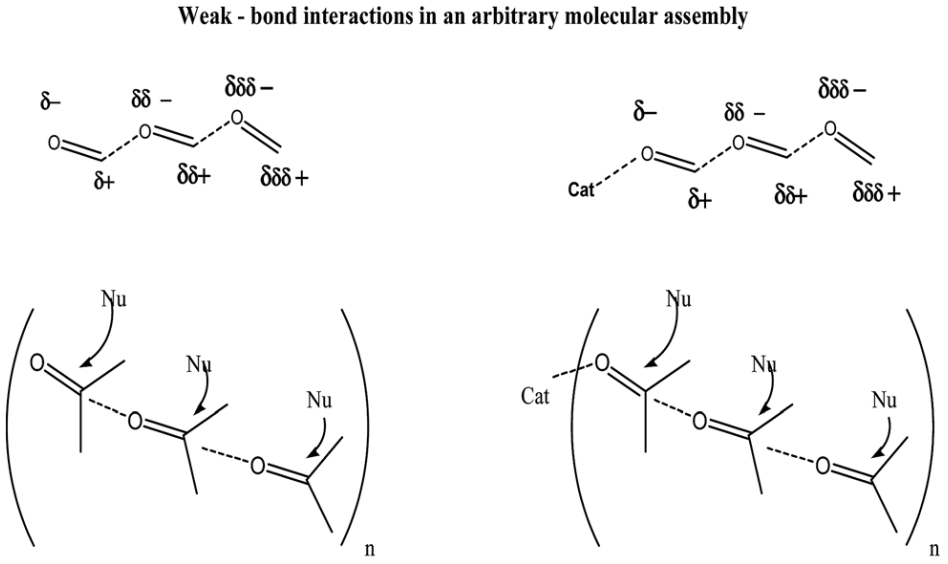
Table II.A.7: Mulliken atomic charges, dipole moment and C–O bond distances in monomers and trimer from the CBS-QB3 model

Parameter	Monomer	Trimer
Mulliken charge at C (au)[a]	0.316740	0.372316
Mulliken charge at O (au)[a]	-0.316740	-0.372316
Dipole moment (Debye)	2.8542	3.2133[b]
C–O bond distance (°A)	1.20001	1.20259
Symmetry	C_{2v}	C_1

Note: [a] atomic charges with hydrogens summed into heavy atoms; [b]average value.

As is evident from the results, there is a sizeable increase in the atomic charges in the associated monomers than those in the isolated free monomer. It implies that on association there is sizeable charge reorganization in such molecular assemblies. These may be interpreted as atomic expressions of sizeable cooperative effects. As a consequence, the charge reorganization brings about enhanced polarization in the carbonyl groups in such environment due to the increase of partial charges in each atom. The possibility of a dipole–dipole type of intermolecular interaction and the absence of H-bond (or a small possibility) in formaldehyde itself has also been previously reported.[75] It indirectly convinced us that the electrophilic behavior of the carbonyl group was enhanced under solvent-free condition. It is the result of the cooperative effect of very weak forces that bulk of carbonyl groups gets

activated. Therefore, the activation of the C=O group can be attributed to a unique spatial organization of the carbonyl moieties. We, thus propose that in reactions occurring under solvent-free conditions, an arbitrary molecular assembly comes into play, where polarization transfer through a non-covalent bond (weak bond interactions) as shown in **Scheme II.A.8**.



Scheme II.A.8: Polarization transfer through a non-covalent bond without and with a catalyst.

In this proposed supramolecular assembly a pseudo-conjugated pi-system makes the system more chemically soft (more polarizable). Thus, with respect to a free carbonyl, we observe better reactivity in solvent free reaction media. It can also be envisaged that in such an assembly, a set of reacting molecules participates in a cycle making the process faster. This self-activating effect will continue to work even if some oxyphilic substance were present in catalytic amounts. When the catalyst is bonded to the terminal carbonyl oxygen it further activates the trail of carbonyls and thereby brings about a further enhancement in the catalytic effect (**Scheme II.A.8**).

The study focuses on unearthing the challenge of using weak forces as a design tool for studying new properties and performance in molecules and materials. The present work has utilised the concept of constitutional dynamic chemistry (CDC) as propagated by Prof. Lehn. With the help of CDC we are hopeful of resolving the existing paradox in the process of catalysis (involving carbonyl activation). CDC hints at supramolecular entities being

assembled entities of discrete number of molecular sub-units held together reversibly through weak interactions (non-covalent interactions).[76] If we extend the concept to the carbonyl system, we could think of the carbonyl molecular sub-units to be held together through similar type of weak interactions, since they are inherently polar. This is true for all the catalytic effects on carbonyls in solution state as well as in solvent-free molten state. The un-catalyzed Radziwenski synthesis of imidazole and the syntheses of Imidazole oxides and hydroxy imidazole-N-oxides under solvent-free conditions as described in the previous sections could be taken as evidences. In all the above syntheses, it was found that the reaction took less time than when they were carried out in solvents. The reason being, that in polar solvents, since there are stronger solute-solvent interactions the weak but favorable conformation of the carbonyl cluster breaks. Thus solvents may be adversely affecting the self-catalytic effect which is pronounced under solvent-free conditions.

The higher reaction rates of such reactions may be possible due to ***self-activation*** of the carbonyl group in the appropriate condensed phase. A proper understanding of the genesis of the catalytic effect in such condensed-phase reactions thus becomes highly significant. In order to understand, why these reactions proceed so efficiently under solvent-free conditions, a combination of the methods viz., reactivity, spectroscopy and theories have been used.

II.A.K. Conclusion

The polarizability of organized carbonyl functionalities in condensed phase contributes for the observed self-catalysis. High yields of many different imidazoles were obtained from the simply mechanical grinding and heating of MCR starting materials, even in the absence of Lewis acid catalysts. The very weak dipole of carbonyls can induce polarization in bulk because the carbonyl bonds are very much polarisable and the net result is the enhancement of electrophilicity of carbonyls. In polar solvents, the weak but favorable conformation of the carbonyl cluster expectedly breaks due to stronger solute– solvent interactions. Thus solvents act adversely to the self catalytic effect. This phenomenon can be well utilized to generate a self-catalytic effect without using any catalytic substance.

II.B.L. References

References are given in BIBLIOGRAPHY under Chapter II, Section A (pp 268-272).

CHAPTER-II

(SECTION B)

Solvent-free strategy: An expeditious synthetic protocol for Chlorination at C-2 position of Imidazoles Scaffold from Imidazole N-oxide and their anti-microbial activity

II.B.A. Introduction

Over the years, synthetic organic chemistry and particularly heterocyclic chemistry has taken quantum leaps in basic organic chemistry research. The multitude of manipulations of functional groups that can be achieved around a simple skeletal system can lead to new drug scaffolds. Moreover, if the routes to these pharmacologically active molecules come with a facile and greener protocol, it will, undoubtedly serve to be very rewarding for an environmental friendly and waste-free world. Heterocyclic compounds, due to its wide assortment of biological and pharmacological properties are exclusive organic molecules. Hence, the exploration of novel and benign routes to a broad range of heterocycles are being carried out globally. Imidazole derivatives are biologically active compounds that play an important role in various biochemical processes.[1] Imidazole fragment is therefore often used as a building block in the development of new drugs.[2] (**Figure II.B.1**). Synthetic imidazoles have been incorporated in many antifungal,[3] antibacterial,[4,5] antiprotozoal, anti-inflammatory,[6] antihypertensive[7] and of late, anti-cancer medications.[8]

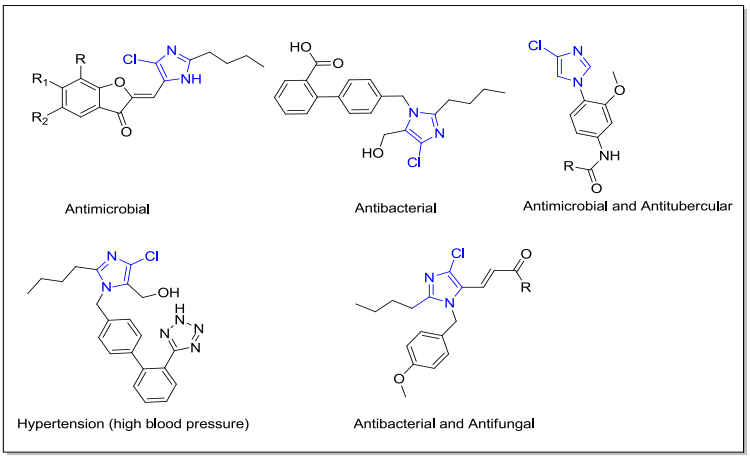
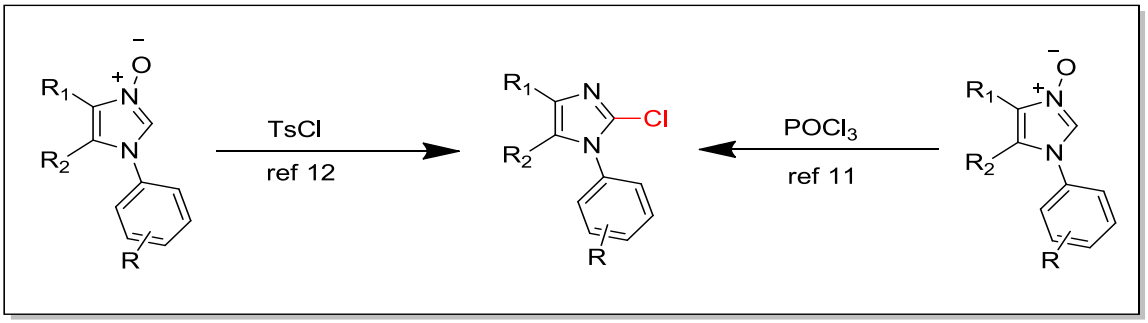


Figure II.B.1. Representative molecules containing chloroimidazole moiety with pharmacological activities.

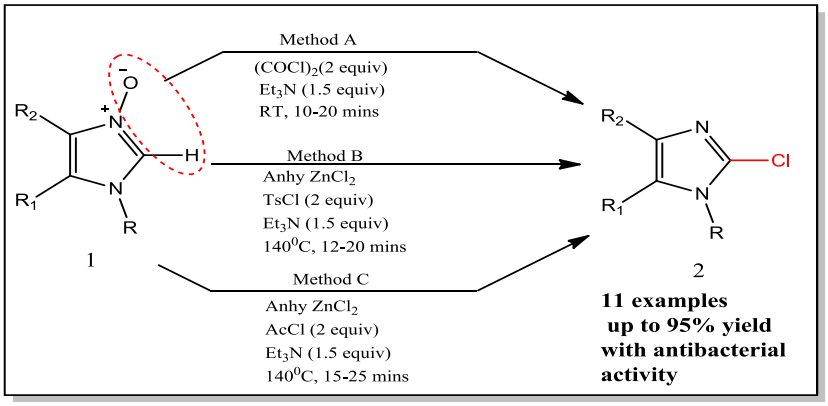
II.B.B. Present work: Background and Objective

Further applications of this moiety are found in coordination chemistry, organometallic chemistry and asymmetric synthesis.[9] 2-Chloroimidazole also represents a valuable synthetic precursor for further functionalizations under metal-free conditions. For example, simple nucleophilic substitution with thiolate anion leads to the formation of 2-sulfenylimidazole derivatives, which serve as important candidates as anti-inflammatory drugs.[10] A literature search for preparative methods for chlorination of imidazole reveals that

the reaction could be achieved from imidazole *N*-oxide using $POCl_3$[11] or tosyl chloride.[12] However, both procedures suffer from one or more disadvantages from green chemistry point of views. While $POCl_3$ is toxic and expensive, use of tosyl chloride requires high temperature, refluxing in anhydrous solvents like $CHCl_3$ or THF. Therefore, the development of mild and greener conditions for regioselective chlorination of imidazoles is of importance.



In continuation of our interest in the use of mild and greener conditions in imidazole chemistry, we have developed an expeditious, a new, solvent-free and room temperature condition for nearly quantitative conversion of imidazole-N-oxide to 2-Chloroimidazole in excellent yields. (**Scheme II.B.1**) The starting compounds imidazole *N*-oxides are easily prepared following our previously reported protocol.[13] The solvent-free protocol is greener and less time-consuming as it only requires mixing of the imidazole-N-oxide and various chlorinating agents in a mortar and pestle in open air in the presence of a base triethylamine (1.5 equivalent of the starting *N*-oxide) and subsequently isolating the desired product by column chromatography. To the best of our literature survey knowledge, no such work has been well filled before. Finally we have investigated the anti-microbial activity of substituted 2-chloroimidazole.



Scheme II.B.1. Different routes of chlorination for the synthesis of 2-chloroimidazole derivative.

II.B.C. Present work: Result and Discussion

Using imidazole *N*-oxide, a variety of chlorinating agent combinations such as oxalyl chloride, tosyl chloride and acetyl chloride were investigated for selective C-2 chlorination (Scheme II.B.1). Here we have explored the reactivity of both electron withdrawing and electron donating group as well as aliphatic and biaryl system also. After treatment of various chlorinating agent here we compared the isolated yield at different conditions. An expeditious synthetic protocol finally found to good to excellent conversions were isolated using $(COCl)_2$ in presence of strong base like, triethylamine at rt stirring for 10 mins.

Method A

In general, the reaction was carried out by intimately mixing the reactants, the imidazole *N*-oxide (1 mmol), oxalyl chloride (2 mmol) and triethylamine (1.5 mmol) in an agate mortar and pestle. Continuous mixing of the reactants at room temperature for 10–20 minutes resulted into complete conversion and the product was isolated by column chromatography over silica gel in 83-95% yields.[14]All compounds were characterized by NMR, FT-IR and mass spectrometry.[15] In the study, a model reaction was conducted for the formation of **2h**. The reaction was optimized with regards to the amounts of the substrate, the base and the time for the reaction which has been summarized in **Table II.B.1**.

Table II.B.1. Optimized conditions for chlorination of imidazole *N*-oxide[a] by oxalyl chloride

Entry	$(COCl)_2$ (mmol)	Base (1.5 equiv)	Temp (ºC)	Time (min)	(2h)Yield (%)[b]
1	1	triethylamine	RT	30	70
2	1.5	-	RT	30	90
3	**2**	**-**	**RT**	**10**	**95[c]**
6	2	pyridine	RT	10	79
7	2	no base	RT	10	67

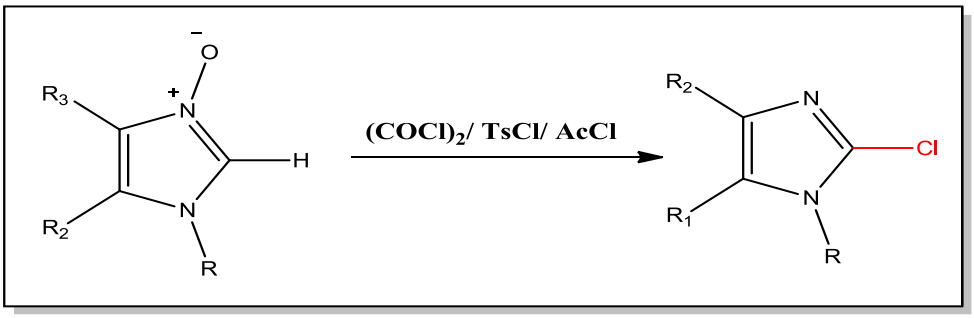
[a]Reagent (1 mmol) [b]Isolated Yield [c]Optimized reaction condition

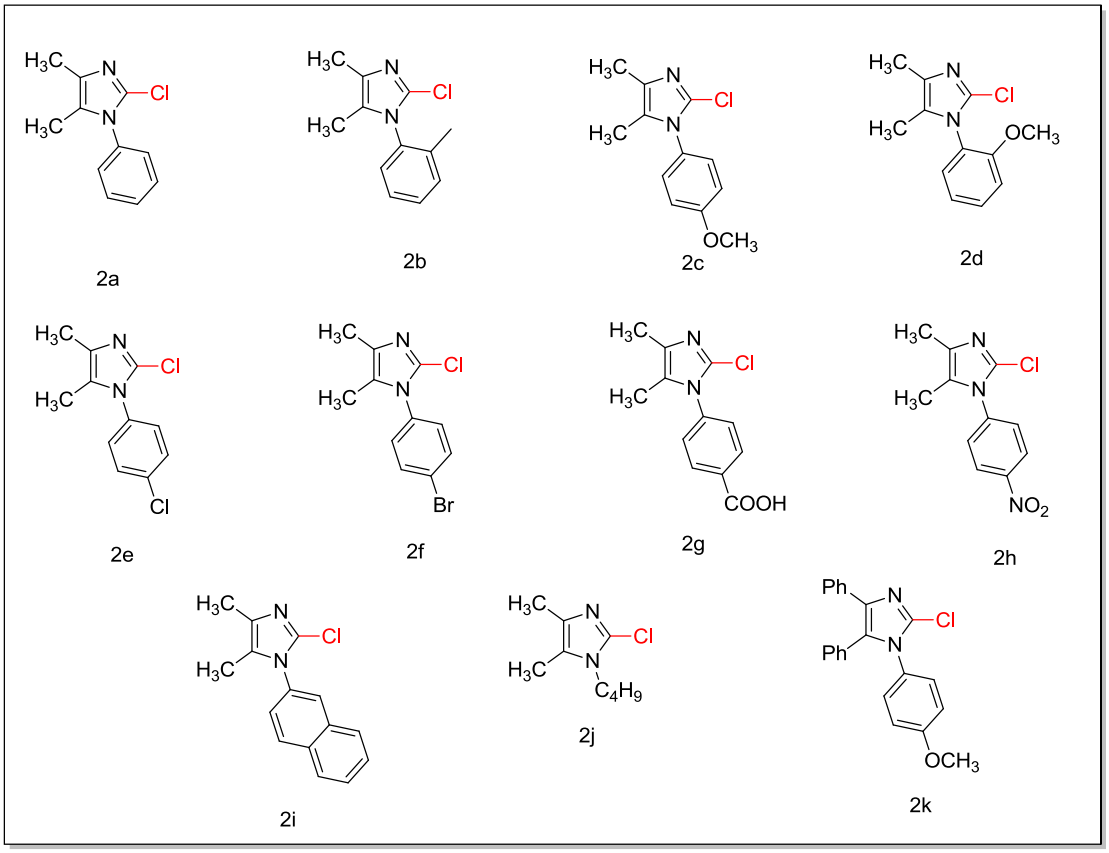
We started optimization of the reaction conditions with a mixture of imidazole *N*-oxide and oxalyl chloride (1:1 ratios) in the presence triethylamine (1.5 equiv). After mixing in a mortar (15 min.), the TLC of the reaction mixture showed the presence of starting *N*-oxide. Further continuation for another 15 min. did not show much improvement. After column chromatography, we were able to isolate the desired product in 70% yield (**Table II.B.1, entry 1**). Increasing the quantity of oxalyl chroride up to 2 equiv and stirring for only

10 min at room temperature showed complete disappearance of the starting *N*-oxide (on TLC) and isolated the 2-chloroimidazole in 95% yield (**Table II.B.1, entry 3**). Changing the base with pyridine or without using any base afforded the product in relatively lower yields (**Table II.B.1, entries 4 and 5**). It is evident that the best conversion (95% yields) is achieved with 2 equivalents of oxalyl chloride with respect to 1 equiv. of imidazole *N*-oxide in the presence of 1.5 equiv. of base, and stirring for 10 minutes at room temperatures. The presence of triethylamine promotes the reactions, since its absence the reaction proceeds with moderate yields (67%).

Based on the above optimization, a variety of 2-chloroimidazoles were synthesized using the solvent-free protocol (**Table II.B.2**). It was observed that the presence of electron-donating groups such as –Me, –OMe, at various position of the *N*-phenyl ring afforded the product in 83-89% (**Table II.B.2, entries 2a, 2b, 2c**). On the other hand, the presence of electron-withdrawing groups such as –Cl, –Br, –COOH and $–NO_2$ gave slightly better yields and in the range of 91-95% yields (**Table II.B.2, entries 2d, 2e, 2f, 2g, 2h**). The results however could be explained on the basis of electrophilicity at the C-2 position of the imidazole ring system, which is increased by the presence of electron-withdrawing groups thereby facilitating attack by a nucleophile. We also carried out the reaction with imidazole *N*-oxide bearing a bulky naphthalene ring, which also afforded excellent conversion (**Table II.B.2, entry 2i**). Further extension of the protocol was examined with *n*-butyl group (an aliphatic substituent), which worked quite smoothly but afforded the desired product in relatively lower yield (85%; **Table II.B.2, entry 2j**). The reaction worked efficiently also from benzil monoxime yielding the desired 2-chloroimidazole with two phenyl groups at 4 and 5 positions (95%; **Table II.B.2, entry 2k**). However, glyoxal monoxime did not result in the formation of desired 2-chloroimidazole derivative.

Table II.B.2: Substrate scope for chlorination using various chlorinating agents





All reactions were carried out using 1 mmol of various substituted imidazole *N*-oxide and 2 mmol of respective chlorinating reagents.

In due course of the methodology development, chlorination was carried out with tosyl chloride and acetyl chloride for **2h** formation, as well. The chlorination's, however, required anhydrous $ZnCl_2$ to catalyze the reactions and as expected, to get optimum results, the reactions had to be carried out at higher temperatures. Optimized condition for chlorination with TsCl [**Method B**] and acetyl chloride [**Method C**] under solvent free conditions required heating at 140°C of the ground mixture containing imidazole N-oxide, with $ZnCl_2$ and 1.5 equivalents of the base, triethylamine for 10 minutes to give yields of

upto 90%. While [**Method B**] required only 2 equivalent of the chlorinating agent TsCl, [**Method C**] required 2 equivalents of acetyl chloride to get maximum yield of 87%. As the substituent's variation for all three method of chlorination are same so further explanation of the substituent's effect for below two methods are negligible.

Method B

In the previous work[12], they used tosyl chloride for chlorination at C-2 position using THF as solvent give max 80% yield with BF_3 as a lewis acid. Initially we trying to synthesize the chlorinated compound without using the lewis acid, the isolated product yield are not too good as that of with lewis acid. Here we used excess anhydrous $ZnCl_2$ instead of $AlCl_3$, $FeCl_3$ and BF_3, despite being milder lewis acid, it activate the sulpher centre to producing the chloride ion easily as well as avoided the side reaction of imidazole N-oxide under solvent-free condition, excellent yield are isolated. Here we have also used different substituent to understanding the progress of the reaction. After attack by nucheophile at C-2 position of the substituted imidazole motifs, base can easily picked up acidic hydrogen to give desired product. In case of para nitro substituent (**Table II.B.2, entry 2h**), that increases the electroplilic character at C-2 position with the help of electron withdrawing nitro group and isolated yield is maximum but in case of others substituent at different positions, product yield is low this is because of groups effect. After optimized, here we found that 2 equivalent of tosyl chloride at 140^0C for 10 mins gives the maximum yield, 90% (**Table II.B.3**).

Table II.B.3. Optimized conditions for chlorination of imidazole *N*-oxide[a] by Tosyl chloride

Entry	Equiv (m mol)	Base (1.5 equiv)	Temp (°C)	Time (min)	Tield (%)[b]
1	1	triethylamine	RT	10	NR
2	1	-	60	10	47
3	1	-	100	10	67
4	1.5	-	100	10	77
5	2	-	100	10	83
6	2	-	120	10	85
7	**2**	**-**	**140**	**10**	**90[c]**
8	2	pyridine	140	10	78
9	2	no base	140	10	67

[a]Reagent (1 mmol) [b]Isolated Yield [c]Optimized reaction condition

We stated our journey with the mixture of *N*-oxide and tosyl chloride (1:1 ratios) in presence triethylamine as a base (1.5 equivalents) at rt, reaction does not proceed. But when

temperature is increases, product conversion is also increases. Further testing the product yield, we varied chlorinating reagent's concentration keeping temperature fixed, product yield continuously increases. To know more temperature and reagent increasing simultaneously, product also increases. After a certain limit the reaction did not show to further improvement. It is evident that the best conversion (95% yields) is achieved with 2 equivalent of tosyl chloride with respect to imidazole *N*-oxide in the presence of 1.5 equivalents of base, and stirring for 10 minutes at room temperatures. The presence of triethylamine promotes the reactions, since it its absence the reaction proceeds with moderate yields (67%). When the reaction was carried out in pyridine, the yield of the product increased to about 80%. Triethylamine was thus found to give the best result.

Method C

In this method we have used acetyl chloride for chlorination. Electrophilicity of carbonyl carbon of acetyl chloride increases using milder lewis acid such as anhydrous zinc chloride. After reaction with imidazole *N*-oxide corresponding nucleophile, Cl^-, is easily produced for further reaction at C-2 position of imidazole moiety. But here the product comparison with respect to others is low due to the lower polarity of –C-Cl bond. We have used same substituent as that of previous to comparing the isolated product. In this case, we got the highest conversion of desired product (**Table II.B.4, entry 2h**). Here we optimized the reaction condition using 2 equivalent of acetyl chloride and 1.5 equivalent of base at 140^0C for 10 mins to yielding 87% of required product.

Table II.B.4. Optimized conditions for chlorination of imidazole *N*-oxide[a] by Acetyl chloride

Entry	Equiv (m mol)	Base (1.5 equiv)	Temp (°C)	Time (min)	Yield (%)[b]
1	1	triethylamine	RT	10	NR
2	1	-	50	10	23
3	1	-	90	10	58
4	1.5	-	120	10	67
5	**2**	**-**	**140**	**10**	**87[c]**
6	2	-	140	10	87
7	2	pyridine	140	10	71
8	2	no base	140	10	66

[a]Reagent (1 mmol) [b]Isolated Yield [c]Optimized reaction condition

In the study, a model reaction was conducted for the formation of **2h**. The reaction was optimized with regards to the amounts of the substrate, the base and the temparature for the reaction which has been summarized in **Table II.B.4**. It is evident that the best conversion (87% yield) is achieved with 2 equivalent of acetyl chloride with respect to imidazole *N*-

oxide in the presence of 1.5 equivalent of base, and stirring for 10 minutes at room temperatures. The presence of triethylamine promotes the reactions, since it its absence the reaction proceeds with moderate yields (67%). When the reaction was carried out in pyridine, the yield of the product increased to about 80%. Triethylamine was thus found to give the best result.

The results of all the reactions have been summarized in **Table II.B.5** vis-a-vis the results of other two reported methods. It is quite apparent that oxalyl chloride serves as the best chlorinating agent for the preparation of 2-chloroimidazoles.

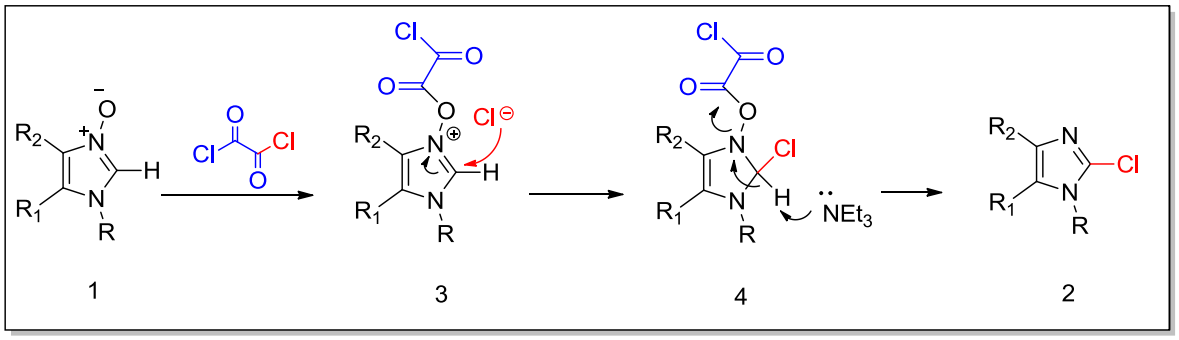
Table II.B.5: Scope of chlorination on imidazole *N*-oxides using several chlorinating agents.

Compounds	Oxalyl Chloride			Tosyl Chloride			Acetyl Chloride		
	Temp (°C)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
2a	RT	15	93	140	15	85	140	15	76
2b	RT	20	83	140	20	78	140	20	70
2c	RT	15	89	140	15	81	140	15	73
2d	RT	20	85	140	20	78	140	20	70
2e	**RT**	**10**	**93**	**140**	**10**	**90**	**140**	**10**	**87**
2f	RT	10	91	140	10	83	140	10	75
2g	RT	10	93	140	10	89	140	10	81
2h	RT	10	95	140	10	90	140	10	87
2i	RT	10	93	140	10	88	140	10	79
2j	RT	20	85	140	20	77	140	20	69
2k	RT	15	95	140	15	88	140	15	84

II.B.D. Mechanism

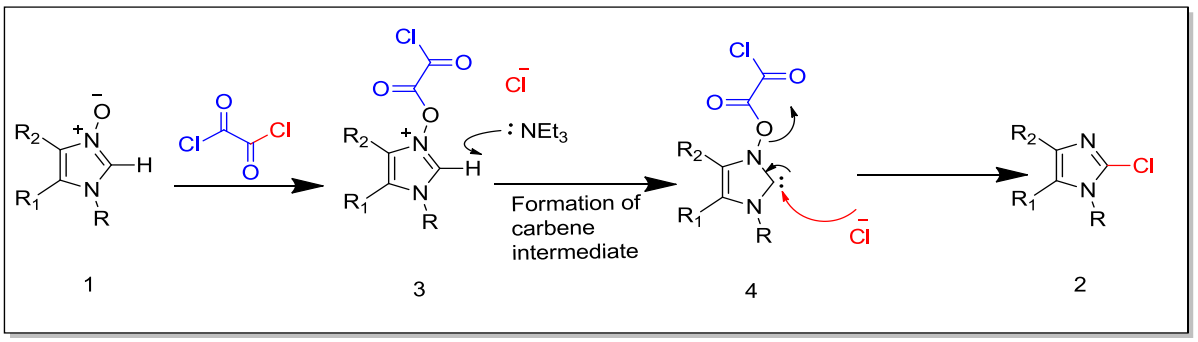
Literature reveals two plausible mechanistic pathways that can be drawn for the chlorination of Imidazole N-oxides to 2-chloroimidazoles. We have extended the same to chlorination using oxalyl chloride as these are analogous reactions.

On the basis of the experimental observations, a plausible mechanism of cine substitution,[12] is presumed to be operative (**Scheme II.B.2**). Thus, initially the imidazole *N*-oxide (**1**) is activated by oxalyl chloride to form the imidazolium chloride (**3**), which is then converted to the intermediate (**4**). The hydrogen atom at the C-2 position, being now more acidic, is trapped by the base NEt_3 to yield the desired product **2**.



Scheme II.B.2. Plausible mechanisms for solvent-free synthesis of substituted 2-chloroimidazole.

Based on the above experimental results, a simplistic mechanism can be predicted in which the *N*-oxide (1) is initially activated by oxalyl chloride and then acidic proton at C-2 position in the resulting imidazolium chloride (3) is picked up by triethylamine to generate a highly reactive and unstable electrophilic species such as a carbene intermediate. The presence of electro-deficient centre may also suggest the observed regioselectivity. Halide ion can act as nucleophiles in very rapidly to form desired substituted 2-chloroimidazole (**Scheme II.B.3**).



Scheme II.B.3. Plausible mechanisms for solvent-free synthesis of substituted 2-chloroimidazole through carbene intermediate.

II.B.E. Anti-microbial study of substituted 2-chloroimidazoles

In our biological studies, we have found the antimicrobial activities against gram negative (*E.coli K12* MTCC1265 and *Pseudomonas fluorescencs* MTCC 103) or gram positive (*Staphylococcus Aureus* MTCC1144, and *Bacillus Subtilis* MTCC1305) bacteria. Eight compounds out of total chloroimidazole compounds exhibited potential antimicrobial activities against gram negative or gram positive bacteria. 2a compound showed

antimicrobial activity against three bacterial strain in both gram positive and gram negative bacteria. Whereas 2b and 2c compounds showed antimicrobial activity against four bacterial strain in both gram positive and gram negative bacteria. But here one compound (2e) showed the exceptionally more sensitive bacterial strain against *Staphylococcus Aureus* (MTCC1144) and have lewest MIC (µg/ml) i.e. 75 µg/ml . Compound 2f is also quite sensitive against *Staphylococcus Aureus* (MTCC1144). Compounds 2d and 2k does not respond any bacterial property against the used bacteria. All MIC (µg/ml) values of the entire compounds are shown in **Table 6**.

Table II.B.6: MIC (µg/ml) values of the substituted 2-chloroimidazole compounds

Compounds Code	*Bacillus Subtilis* (MTCC1305)	*Staphylococcus Aureus* (MTCC1144)	*Pseudomonas fluorescencs* (MTCC 103)	*E.coli K12* (MTCC1265)
2a	100	200	---	750
2b	750	700	400	800
2c	400	200	400	1000
2d	---	---	---	---
2e	**---**	**75**	**---**	**---**
2f	---	100	---	---
2g	---	---	---	1000
2h	---	200	200	---
2i	1000	100	---	---
2j	750	---	500	---
2k	---	---	---	---

II.B.F. Conclusion

In summary, we have unfolded a highly regioselective, expeditious and efficient synthetic route for chlorination at C-2 position of imidazole *N*-oxide under solvent-free condition with excellent yields and that too, in a very short span, which are very challenging for Synthesis. The protocol has been examined with diversely substituted *N*-phenyl group. In all cases, the yields are too good, although the electron-withdrawing groups' presence at the ring system favors the reaction over electron-donating substituents. 2-chlorinated imidazole derivatives compounds are very useful intermediates and sub-units of numerous pharmacologically important compounds. This straightforward setup and facile protocol could be attractive to the synthetic organic chemists from academia and pharmaceutical industries. We have also reported the biological activity such as anti-bacterial activity, of all chloroimidazole compounds.

II.B.G. References

References are given in BIBLIOGRAPHY under Chapter II, Section B (pp 273).

CHAPTER-II

(SECTION C)

Alumina catalyst: Synthesis of novel quinazoline derivatives and their solubility increases through inclusion with β-Cyclodextrin

II.C.A. Introduction

Quinazoline-4-(3H)-one moieties have gained wide-ranging research interest due to their broad spectrum range of biological activity. Quinazoline is an important studied moieties in medicinal field.[1-2] At the beginning researches in the medicinal field started the febrifugine (3) discovery on the quinazoline scaffold which is a quinazolinone alkaloid, has immense anti-malarial activity, from the plant aseru (Dichroa febrifuga Lour). [3-4] In addition the anti-malarial activity,[5] the derivatives of quinazoline demonstrate a broad range of biological activities including antibacterial,[6] anticancer,[8-9] antihypertensive,[10] anti-inflammatory,[11-13] activities and so on (Figure II.C.1). Even though their immense medicinal value to come out as successful drugs, water solubility is one of the key factors.[14]

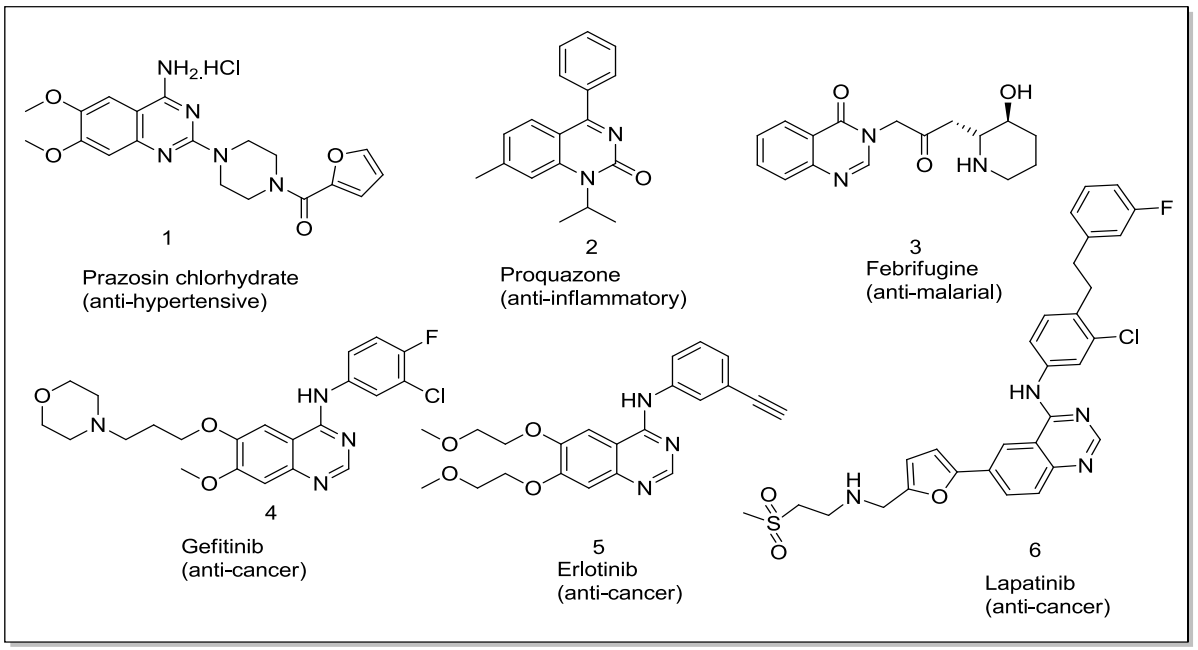


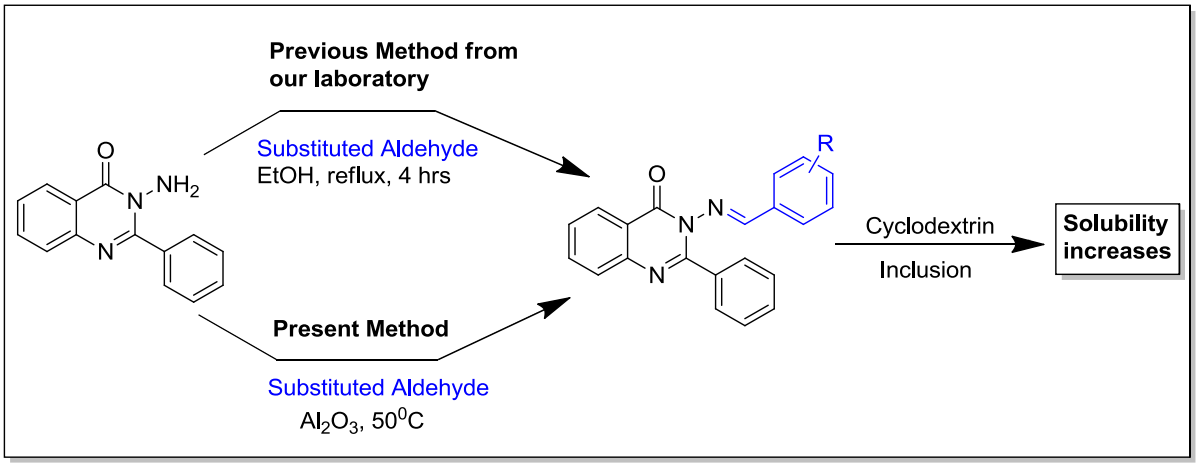
Figure II.C.1: Representative some bioactive molecules containing quinazoline scaffold.

II.C.B. Present work: Background and Objective

In 2007, this work[15] reported from our laboratory under refluxing condition in ethanol solution to formation of a substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one and reported their anti-bacterial activity with QSAR studies. Now further more investigating a new methodology, we have synthesized this series of bioactive quinazoline moieties in a very easier greener technique under solvent-free protocol at 50°C for 20 min using alumina as a catalyst that enhances the electrophilicity character of the carbonyl of respective aldehyde upto the product formation 90%. But one drawback of these series of compounds is fully water insoluble, despite their immense medicinal property to come out as successful

drugs. Water solubility is one of the key factors to enhance the biological activity. Here we tried to solve this problem through inclusion with β-cyclodextrin. Cyclodextrins (CDs) are homochiral, cyclic oligosaccharides belonging the family of 6, 7, or 8 member α-1, 4-linkage D-glucopyranose units (namely α, β, and γ cyclodextrins), fully water-soluble and have cavity sizes ranging from 4.9 to 7.9 Å.[16-19] Interior the hydrophobic nature of its cavity with an exterior hydrophilic part activated β-CD to encapsulate molecules which are hydrophobic in nature to form thermodynamically more stable molecular microcapsules, commonly name as host–guest complexes or inclusion complexes. Due to this behaviour of CDs, molecules binds with some weak interaction such as H-bonding, vander waals interaction, hydrophobic interaction, etc. This binding chemistry between the host β -CDs and guest molecules is not permanent interaction, but rather remained in a dynamic equilibrium. The binding strength mainly depends on selective local interactions between the exterior atoms and extent of how ‘‘host–guest’’ complex interaction fits together.

Most recently, this technique of complexion with Cyclodextrins has been repeatedly used to develop oral bioavailability.[20-22] In this technique some drugs expand shelf life[23] to a certain extent, and furthermore it contributes to control drug release rate, progressed organoleptic properties and maximized tolerance in gastrointestinal.[24] Thus, increased drugs solubility plays a very significant role in absorption, which in due course affects its bioavailability.[25] Therefore it is very important to develop protocols to improve the efficiency of complexation of drug–Cyclodextrins.



Scheme II.C.1: Synthesis of substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using alumina as a catalyst.

II.C.B.1. Present work: Result and Discussion

In general, we begun our journey with the intimately mixing the reactants, the 3-amino-2-phenylquinazolin-4(3H)-one (1), which were easily prepared from our previously reported protocol[15], substituted aldehyde and the lewis acid, alumina in an agate mortar and pestle. Continuous mixing of the reactants at room temperature and then heated on an oil bath for 20–30 minutes at 50°C resulted into excellent conversion and isolation of the products with the help of washing technique with high yields up to 90%.

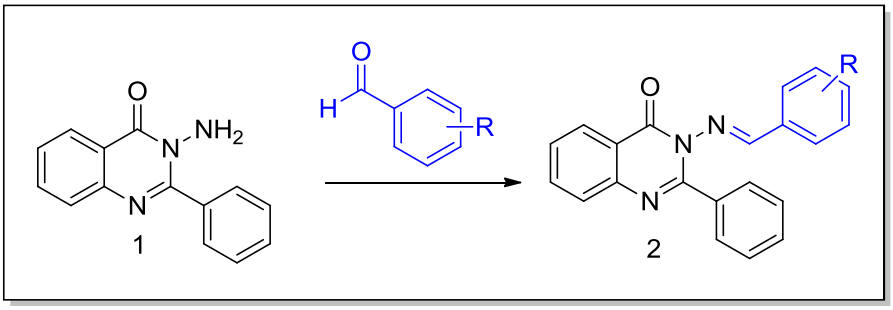
All the compounds were characterized by NMR, FT-IR and mass spectrometry. In the study of optimization, a model reaction was conducted for the formation of **2j**. The reaction was optimized with regards to the amounts of the lewis acid, temparature and the time for the reaction which has been summarized in **Table II.C.1**.

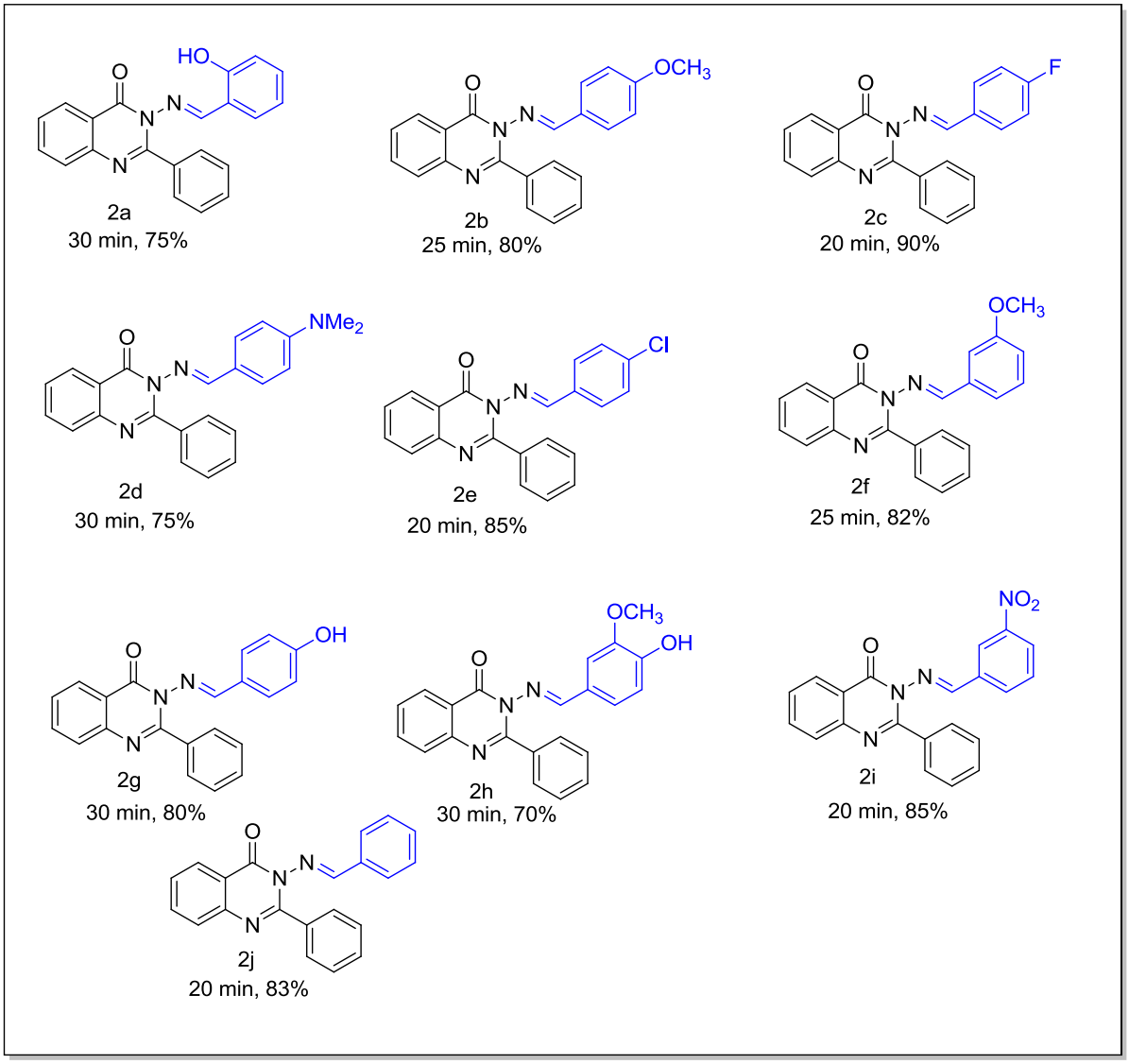
To investigate the reaction optimization, we stated our journey with equivalent mixture of the 3-amino-2-phenylquinazolin-4(3H)-one and benzaldehyde at RT for 20 min but we could not find out any formation of a new spot (on TLC). Then with constant time to increase temperature at 50°C reaction did response to about 30% (table II.C.1, entry 2). For futher justification we used alumina (2 equiv w.r.t substrates) as a catalyst at same condition, conversion is about 60% (table II.C.1, entry 3). To continuing increases alumina's concentration remaining all other condition same, product conversion is also increases to such an extent. After a certain amount of alumina reaction did not response to further yield conversion. So here we found the reaction optimized condition with 4 equivalents of alumina w.r.t substrates at 50°C for 20 min to best conversion upto 83% (table II.C.1, entry 5).

Table II.C.1: Optimized table for formation of 3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using Alumina as a catalyst.

Entry	Alumina (equiv)	Time (min)	Temp (°C)	Yield (%)
1	__	20	RT	NR
2	__	20	50	30
3	2	20	50	60
4	3	20	50	77
5	**4**	**20**	**50**	**83**
6	5	20	50	83

Scheme II.C.2: Substrate scope of alumina catalyst substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one.



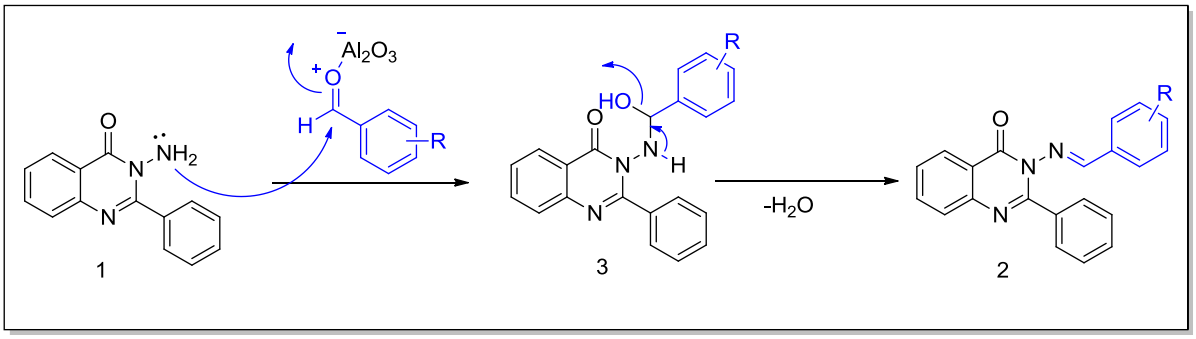


With the help of this optimization in our hand, we varied the reaction in various substrates for more diversity (Scheme II.C.2). To continue our interest, we varied mainly nature of the

substituent that is electron withdrawing and electron donating effect. Both type of substituent were performed very well in this reaction condition. In case of electron withdrawing substituent such as –F, -Cl, -NO_2, in all cases conversion of the reaction is too good. This is because mainly increasing the electrophilicity character of the carbonyl carbon of the corresponding aldehyde. When 4-fluorobenzaldehyde reacts with 3-amino-2-phenylquinazolin-4(3H)-one (1:1 ratios), conversion upto 90% (Scheme II.C.2, entry 2c) due to high electronegativity of fluorine atom withdraw electron through inductive effect directly, increases the electrophilicity at the carbonyl carbon to improve the reaction yield. But in case of –Cl (85%, Scheme II.C.2, entry 2e) and –NO_2 (85%, Scheme II.C.2, entry 2i), yields are slightly lower as compared to –F because of chlorine showed the low inductive effect and as nitro group is present in meta position it can't show resonance effect, only pulls electron through inductive effect. For the electron donating substituent such as –OCH_3, -NMe_2, -OH, product conversion is slightly reduced due to increases the electron availability in the carbonyl carbon of aldehyde group. When these groups are directly connected in ortho or para position w.r.t aldehyde group, conversion of the desired products yield excellent to moderate. When in the meta position, product conversion is enhanced to further extent upto 82% (Scheme II.C.2, entry 2f). Very interestingly, when reaction takes place only with benzaldehyde that is no substituent are incorporated in the aryl ring still product conversion 83% (Scheme II.C.2, entry 2j) due to aryl ring shows inductive as well as resonance effect both. For this behaviour, it converted the reaction yield upto 83% in between donating and withdrawing substituent.

II.C.C. Mechanism

Using alumina as a catalyst not only enhances the carbonyl character through electrophilicity but also act as a powerful desiccant (dehydrating agent) that improved the reaction towards forward direction by forcing dehydration to produce desired product. Alumina binds with carbonyl to activate the centre facilitate the nucleophilic attack for formation of intermediate (3). Finally a molecule of water eliminated from the system to give desired product (2).

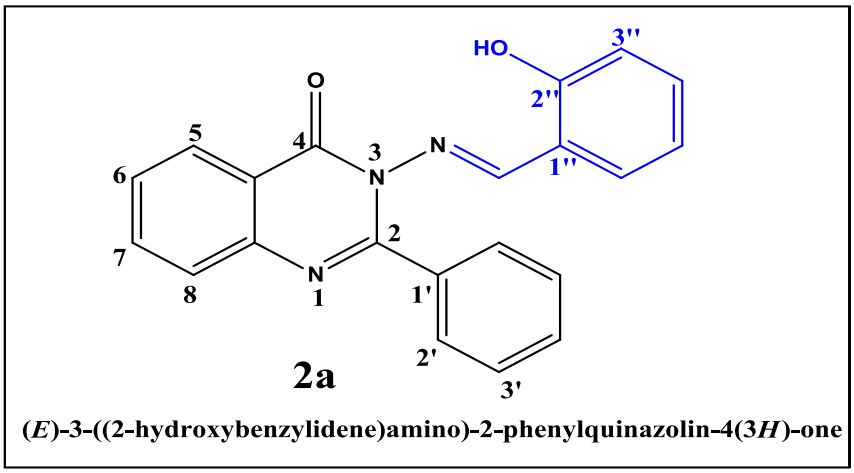


Scheme II.C.3. Plausible mechanisms for solvent-free synthesis of substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using alumina.

II.C.D. Inclusion Technique

II.C.D.1. Formation of complexes

In this portion, the complex is formed by the kneaded protocol and is characterized by UV, IR and DSC technique. It is examined that the effects of complex formation by β-CD showing improvement solubility of the compound in aqueous medium. We developed different protocols for the complex formation and screened most suitable protocol of its preparation. We worked only with compound **2a** for complexation.



- **Preparation of Physical mixture (PM)**

The physical mixture of the compound 3-{[(2-Hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one and β-CD [1:1 molar ratio] were prepared by mixing simultaneously in a mortar and pestle.

- **Complex formation by Kneading method (KN)**

The physical mixture (PM) was triturated in a mortar with water-ethanol solution with small volume. The slurry was kneaded for 45 min and dried over at 40°C. This dried mass was crushed and sieved through 100 micron mesh.

- **Complex formation by Co-evaporation method (COE)**

The aqueous solution of β-cyclodextrin (CD) was mixed to an alcoholic solution of 3-{[(2-Hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one. Then the mixture was stirred for 1 hr and was evaporated to dryness at 45°C. The dried mass was crushed and sieved through 100 micron mesh.

- **Complex formation by Freeze–Drying Method (FD)**

The physical mixtures (PM) were taken in 500 ml double distilled water and stirred for 5 days. The resulting suspension was freeze-dried and freeze-dried complex, thus formed was crushed and sieved through 100 micron mesh.

The inclusion complexes made by different protocols were primarily illustrated by the degree of transparency of the drug of the solution prepared in water. In distilled water (5 ml), β- CD (34 mg) solubilized to form clear solution, the physical mixture [3.34 mg said compound + 17 mg β- CD (3 mM : 3 mM)] made a turbid suspension and the complex [3.34 mg said compound + 17 mg β- CD (3 mM : 3 mM)] was made to be faintly turbid as shown in Figure. II.C.2 (A, B, & C respectively). A comparative study was done on silica-gel plates (TLC) using the eluent [ethyl acetate: butanol (5:4 v/v)]. The spots of β- CD and the compound was observable with slight trailing of spot of the compound for the physical mixture (PM) while in the complex a concentrated bulk trailing was examined with faint spot compared of the free compound. The appearance of the faint trailing spot indicated that of slow diffusion of the compound in TLC study in the used eluent.

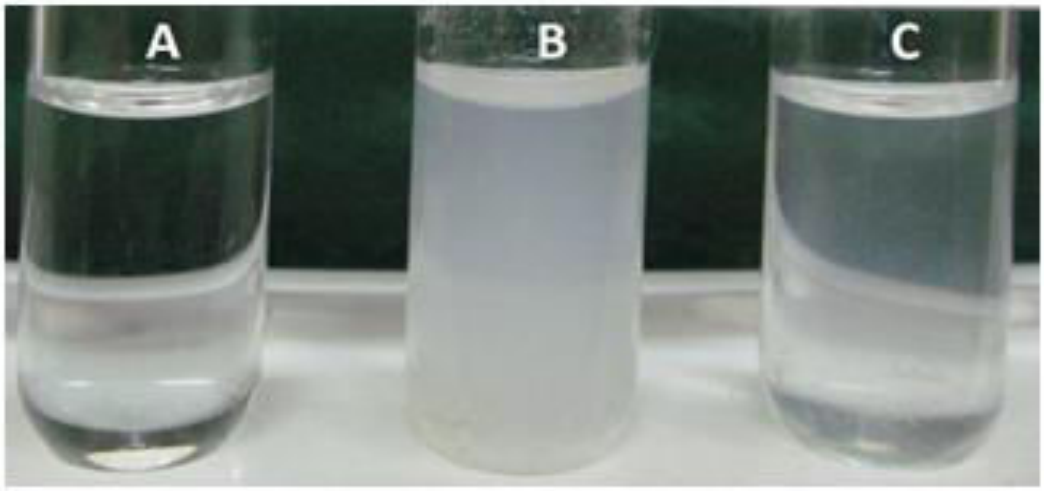


Figure II.C.2: Water solution of A) β-CD. B) Physical Mixture. C) Complex.

II.C.D.1.1. Ultra Violet Studies

From the UV spectra, the corresponding absorbance of the compound was varied due to the formation of complex as shown in Figure 2. In the complex formed through physical mixtures without addition of water are very slow as compared to complex formed from Kneading method which contained water during crushing. The study demonstrates that the dissolution rate of 3-{[(2-Hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one was increased to such an extent using kneading method for complex formation as compared to other methods.

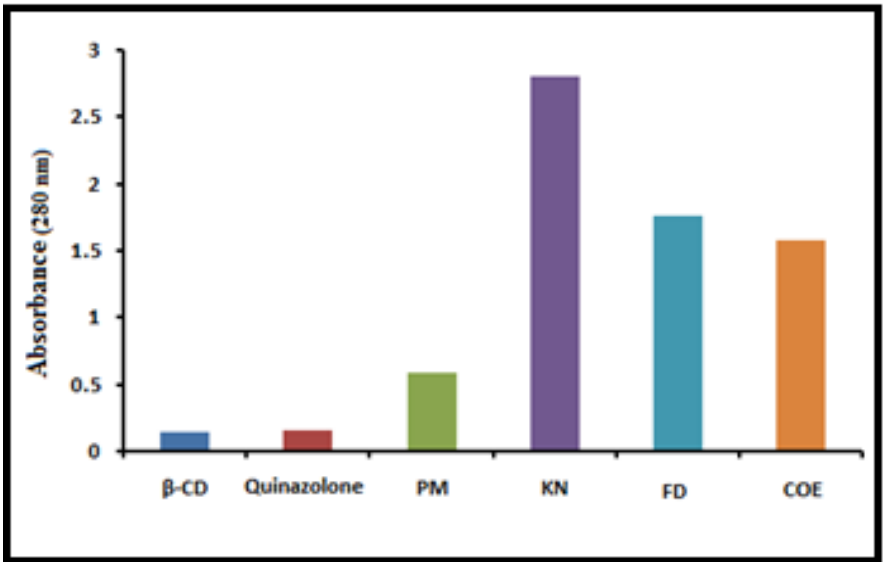


Figure II.C.3: Efficiency of diverse methods for the complex formation.

To best of our knowledge to design the most excellent formulation of inclusion complexes, a little volume of warm water was mixed with β cyclodextrin to make slurry and then reserved at the 50°C for 12 h. The slurry was observed for 12 h with infrequent mauling. After 12 h, equivalent amount of the 3-{[(2-Hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one and the β cyclodextrin was mixed by triturating in a mortar and pestle with a small volume of water-ethanol mixture to form a slurry. The slurry was grinded for 45 min and dried at 50°C. The crushing time was varied for the complex preparation as follows: 0min, 20 min, 30min, 40 min, 60min. The mixture of β-cyclodextrin and compounds (1:1) was applied in every preparation. The dried mass was sieved through 100 micron mesh. It was found that optimization of the formation of product after 40 min crushing. It is examined that crushing time has played also an important role in the complex formation. With increasing crushing time during formation a PM, the absorbance of that mixture is also increases. This indicates to be a very simple and basic novel experiment that demonstrates how the crushing time is very important for complex formation. After 40 minutes of crushing time of the drug with β-CD, it showed a plateau which indicated that the optimum condition (**Fig. II.C.4**).

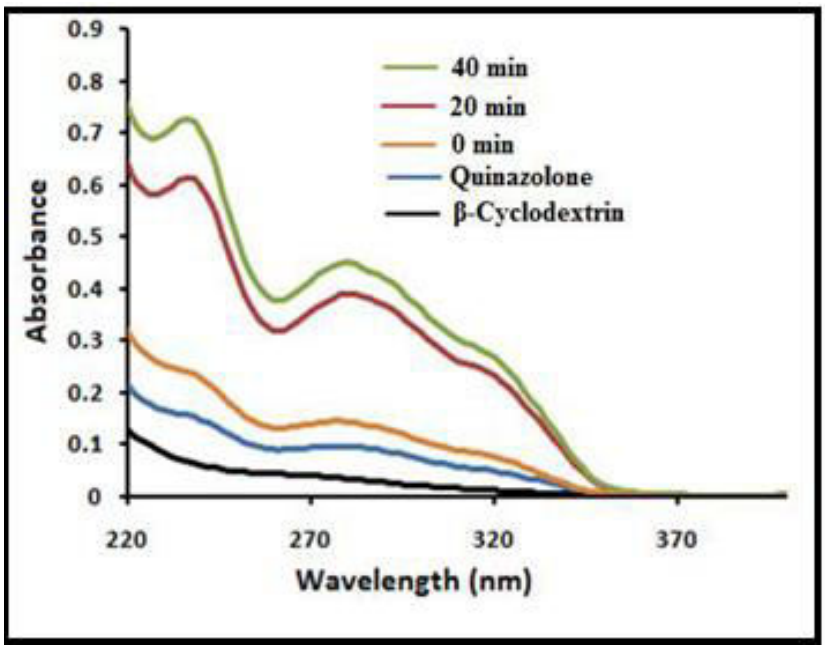


Figure II.C.4: UV Spectrum of Complex formation in various crushing time.

II.C.D.1.2. Infra Red Studies

The IR spectrum of β-CD, 3-{[(2-Hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one (2a), physical mixture of 2a and β-CD (1:1 molar ratios) as well as the complex formation under Kneaded method are shown in below (Figure 5). In our drug compound, the essential bands are carbonyl (-C=O), imine (-C=N), amine (-C-N), aromatic –C-H (stretching & out of plane, bent), alcoholic –OH (H-bonding) and finally aromatic –C=C group. Analysis of the IR spectrum of the both a physical mixture and inclusion complexes are observed in a changing frequency or hidden or lower the intensity of the spectrum band. Normally the carbonyl frequency appears at 1700-1650 cm^{-1} regions, mentioning drug response at ~1651 cm^{-1} which is fully disappeared in complex. The essential band imine (-C=N) appears at 1604 cm^{-1}, the amine vibration band (-C-N) appears at ~1280 cm^{-1}, aromatic –C=C skeleton vibrations band appears at ~1530 cm^{-1}, aromatic –C-H band (out of plane, bent) appears at ~758 and ~702 cm^{-1} regions, all of these band are totally disappeared in inclusion compound but in physical mixture lower the intensity of peak was observed. Not only this even in the aromatic –C-H stretching band regions appears at 3064 cm^{-1} are shifted towards at shorter wave number as well as some disappeared was also observed in case of –OH band which is appears at ~3216 cm^{-1} (may be H-bonding, normally –OH band appears at 3400-3600 cm^{-1} regions). The shape or intensity or shift or disappearance of these bands varied dramatically for the complex as compared to those for pure drug and physical mixture. These pointed out that the bending and vibrating of the guest molecule **[**3-{[(2-Hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one**]** was restricted owing to the formation of a complex, hence from this point of view we can comment that the molecule must be inserted into the β-CD cavity.

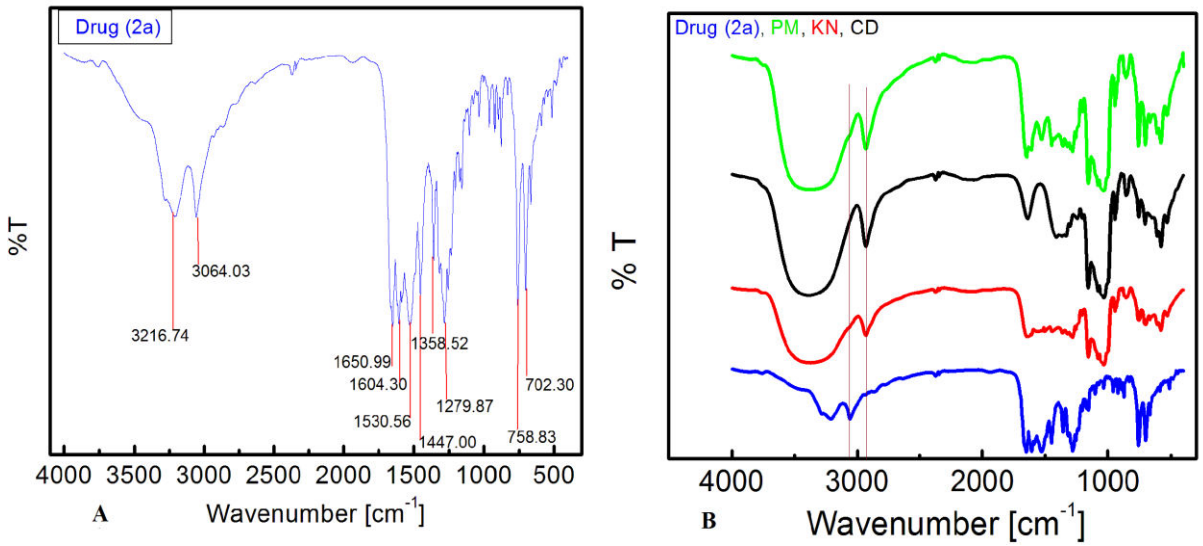


Figure II.C.5: IR Spectrum of A) Drug (2a) and B) Drug (2a), Cyclodextrin (CD), Physical mixtiure (PM) and complex (KN).

[blue line=drug; red line=complex; black line=CD; green line=PM]

II.C.D.1.3. Differential Scanning Calorimetry studies

The DSC thermograms of drug (2a), CD, Physical mixtures of CD/drug (1:1) and complex (1:1) are shown in Figure 6. Drug was characterized by a single, sharp melting endotherm at 234.6°C (ΔH=88.71 J/g) in the time of DSC analysis and a broad endothermic thermogram of CD are observed at a maximum around 97°C respectively, reason due to release of a molecule of water.[22] In case of complex, the drug endotherm are almost disappeared along with shifting at 231.6°C and the peak arises from CD are shifted to 104°C approximate. No such changes are observed in case of physical mixture as that of complex as it showing some peak intensity. But peak intensity is reduced and slight shifting arises towards lower temperature in with physical mixture. The shape or intensity or shift or disappearance of these bands varied dramatically for the complex as compared to those for pure drug and physical mixture. This observation indicating that for the complex formation, the molecule must be encapsulation inside the cavity of β-CD.

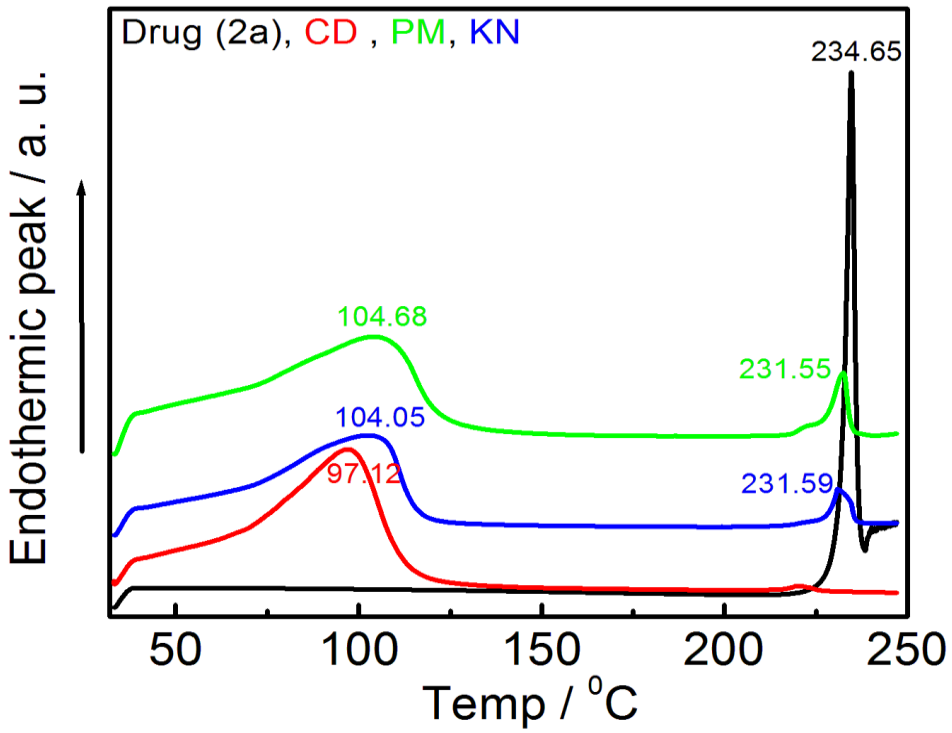


Figure II.C.6: DSC thermograms of CD, PM, Drug (2a) and complex. **[Mentioning with respective colour]**

II.C.E. Conclusion

In summary, we have developed a new synthetic route for the synthesis of substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using a greener reagent in a very short span under solvent free condition to excellent yield. In the previously reported all these compounds are biologically active but low solubility in water medium. Here we have tried to develop the solubility in aqueous medium of this synthesized molecule. Finally we have unfolded the solubility problem through inclusion with β-cyclodextrin. For preparing a complex with β-cyclodextrin to increase solubility, Kneaded method is the best method among the all other mentioned method. Increasing the bioavailability of the drug molecule, pharmaceutical potential is also increases.

II.C.F. References

References are given in BIBLIOGRAPHY under Chapter II, Section C (pp 274-275).

CHAPTER-II

(SECTION D)

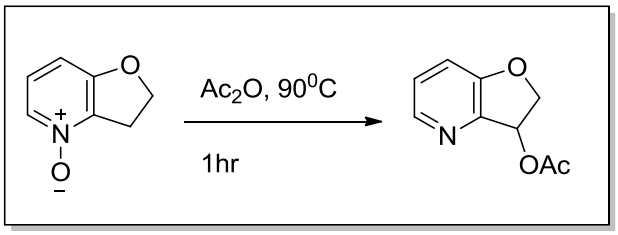
Design, Synthesis and biological evaluation of novel 2-acetoxyimidazole derivatives as multidrug resistance in cancer therapy and their molecular docking studies

II.D.A. Introduction

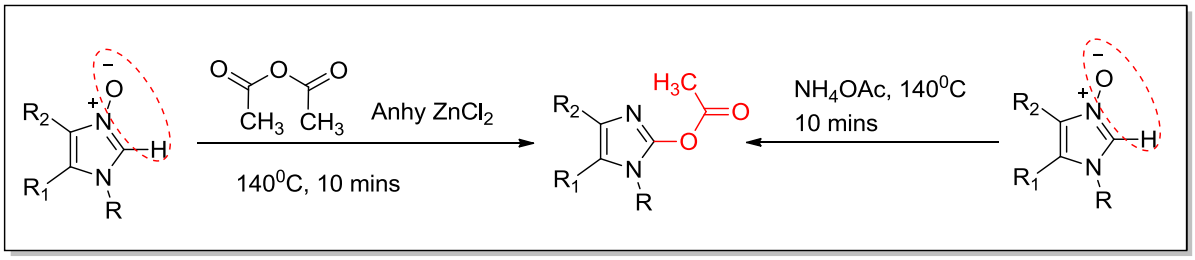
The acetoxylation of a C–H bond converted into a C–O bond in directly has attracted significantly attention in recent years because of its industrially important roles of ester or phenol compounds.[1]For examples, both of them are used as key structural motifs in various drugs, natural products and carbohydrates. C–H bond activation by transition metal-catalyzed is a recent strategy for the step-economical organic synthesis. In numerous biologically important molecules, it can be applied for the direct modification without prefunctionalization.[2]In 2004, Sanford and co-workers reported acetoxylation of pyridine-directed of the C–H bond by Pd-catalyzed was first demonstrated.[3] In a while, Yu et al.[4] reported a variety of acetoxylations of ortho-aryl C–H bonds by Cu-mediated, which showed good efficiency and high regioselectivity. Thereafter, C–H bond activation of several directing groups such as amine,[6] pyridine,[5] carbonyl[8] and oxime[7] have been used to catalyst by transition-metal. A broad range of metal act as catalysts, including Rh, Ru, Fe, Pd, and so on have been greatly explored for this purpose.[3] Last few years a series of aromatic ortho-acetoxylation of C-H bonds have been unfolded. In 2010, Yu and coworkers reported triflate ortho C-H acetoxylation protected phenethyl- and phenpropylamines by Pd (II)-catalyzed using tert-butyl peroxyacetate as the source of acetate.[5] Kim group synthesized ortho-acetoxylation of phosphoric and phosphonic monoacids by Pd (II) catalyzed using PhI(OAc)2 as the oxidant and acetate reagent.[6]

II.D.B. Present work: Background and Objective

Literature survey reveals that there is a one and only work on pyridine *N*-oxide has been reported by S Shiotani and co-workers. [12] No such works yet to be done on imidazole *N*-oxide for acetoxylation. In 1997, S Shiotani and co-workers reported acetoxylation on pyridine N-oxide using acetic anhydride by varying time at refluxing condition at various position of the substituted pyridine N-oxide.



In continuation of our curiosity in the use of greener and mild conditions in imidazole chemistry, we have unfolded a first time reported newly synthetic route and solvent-free condition for almost quantitative conversion of imidazole *N*-oxide to 2-Acetoxyimidazole in excellent yields.(**Scheme II.D.1**) The initial compounds imidazole *N*-oxides are easily synthesized by our previously reported method.[13] The solvent-less protocol is less time-consuming and greener as it only requires only mixing of the imidazole *N*-oxide and acetic anhydride in a mortar and pestle in the presence of a lewis acid, anhydrous Zinc chloride in excess. We have applied for another protocol to synthesis acetoxyimidazole by using ammonium acetate heated in an oil bath for 10 mins to get desired product by using column chromatoghaphy. After successfully synthesized of these series of acetoxyimidazole compounds we have tested the biological activity such as anti-microbial and anti-cancer. Anti-microbial activity of these series of compounds does not show good results against both gram positive and gram negative bacteria but anti-cancer activity reveals that near about all compounds showed cytotoxicity against different cancer cell lines. In vitro analysis of these compounds against HEK 293, MCF 7, cancer cell lines in comparison with nomal WRL 68 cell lines, compound **2h** showed a excellent results as compared to others compound that only showing activity in cancerous cell upto 65% cytotoxicity but no such effect found in normal cell lines. The result was confirmed by fluorescence microscope. To knowing further, we have done molecular docking studies of all relevant compounds that indicates the good binding ability upto -7.2 binding affinity with various amino acid of the respective cell line with help of some weak interaction such as H-bonding, vander-waals attractive force, hydrophobic interaction and etc. The bioinformatics studies told that compounds 2c, 2d and 2h can be treated as a drug for various cancer therapies such as lung, breast, liver, kindey, overian. Receptor tyrosine-protein kinase **erbB-2** is the cell target where the compounds bind mainly.



Scheme II.D.1. Different routes of acetoxylation for the synthesis of 2-acetoxyimidazole derivative.

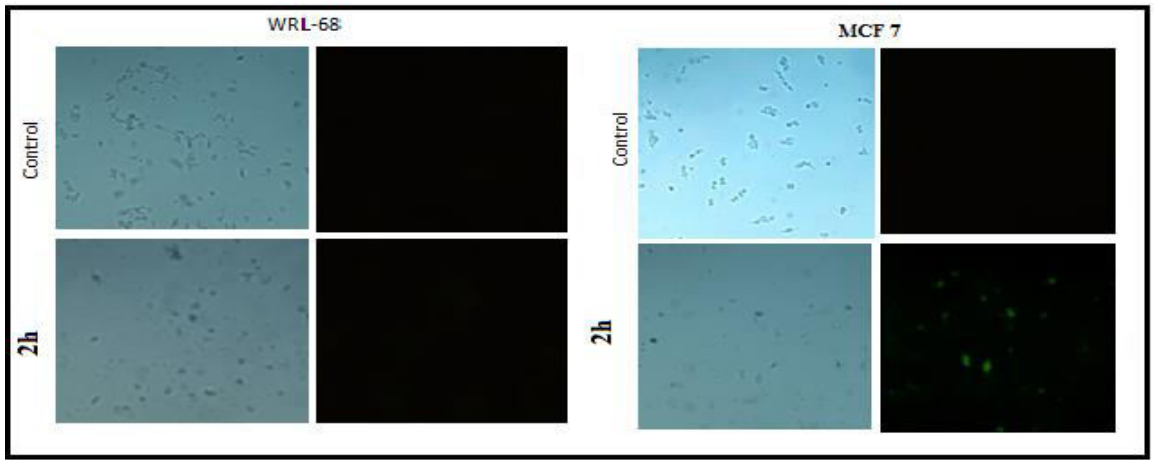


Figure II.D.1: Fluorescence microscope of compound 2h comparison between cancer cell line (MCF 7) and normal cell line (WRL 68).

II.D.C. Chemistry studies:

II.D.C.1. Present work: Result and Discussion

In general, we started our journey with the intimately mixing the reactants, the imidazole *N*-oxide, acetic anhydride and the lewis acid, anhydrous Zinc chloride in an agate mortar and pestle. The precursors, imidazole *N*-oxides were prepared *via* our previously reported procedures under solvent-free conditions. Continuous mixing of the reactants at room temperature and then heated on an oil bath for 10–20 minutes at 140°C resulted into good conversion and isolation of the products with the help of column chromatoghaphy with high yields up to 81%.

All the compounds were characterized by NMR, FT-IR and mass spectrometry. In the study of optimization, a model reaction was conducted for the formation of **2e**. The reaction was optimized with regards to the amounts of the substrate, temparature and the time for the reaction which has been summarized in **Table II.D.1**.

We optimized the reaction condition, initially we took the imidazole *N*-oxide and acetic anhydrate at equivalent ratios (1:1) at room temperature for 30 mins, the reaction does not show any response. The temperature and time remaining constant, we varied only concentration of corresponding substrate, reaction showed slightly improvement (27%, table II.D.1, entry 2). With constant reagent concentration with changing time, the reaction yields are continuously increases even in decreasing reaction time. After a certain time, reaction did

not show much more improvement then we once again varied reagent concentration with increasing temperature with constant timing, eventually reaction yields conversion increases with reaction condition (77%, table II.D.1, entry 7). Then for further optimization, we increased the temperature at 140°C with same reagent concentration in lowering the reaction time, it was found that best conversion of this reaction upto 81% (table II.D.1, entry 8) only in 10 mins. It was confirmed by further increasing reagent concentration remaining the other parameter same, reaction did not show any improvement. It is evident that the best conversion (81% yield) is achieved with 4 equivalent of acetic anhydride with respect to imidazole *N*-oxide in the presence of slight excess of Zinc chloride and stirring for 10 minutes at 140°C temperatures. The presence of anhydrous Zinc chloride promotes the reactions, since its absence the reaction proceeds with moderate yields (69%). Anhydrous Zinc chloride acting as a lewis acid to serve as a catalyst to bind with carbonyl oxygen that enhance the electrophilic character of carbonyl carbon of acetic anhydride to facilitate the attack by oxide of imidazole *N*-oxide to produce acetate ion in the reaction intermediate. That acetate ion acted as a nucleophile to attack the corresponding C-2 position of imidazole *N*-oxide being an electron deficient centre.

Table II.D.1: Optimized table for acetoxylation of imidazole *N*-oxide[a](2e) by acetic anhydride

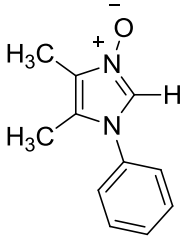
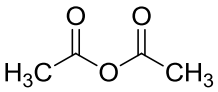
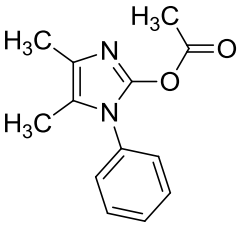
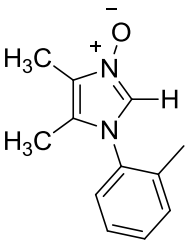
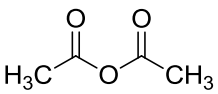
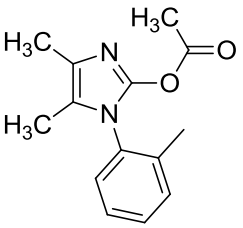
Entry	Reagent(equiv)	Temp (°C)	Time (min)	Yield (%)[b]
1	1	RT	30	ND
2	2	RT	30	27
3	2	50	20	49
4	2	80	20	57
5	3	80	20	67
6	4	80	20	72
7	4	120	20	77
8	**4**	**140**	**10**	**81**[c]
9	5	140	10	81

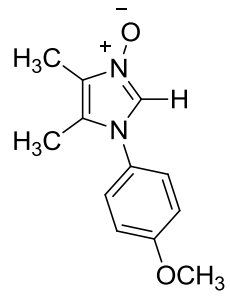
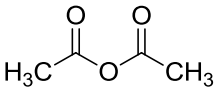
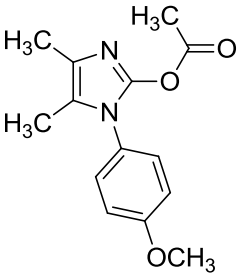
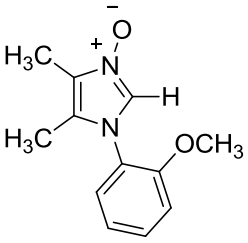
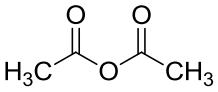
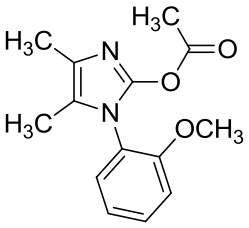
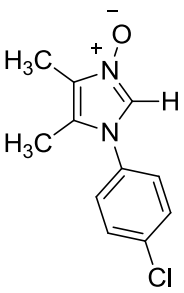
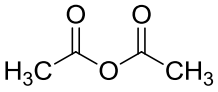
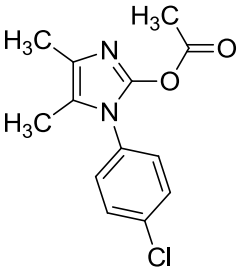
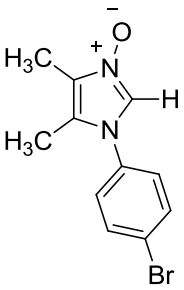
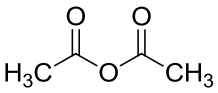
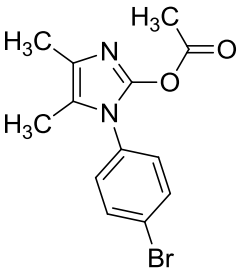
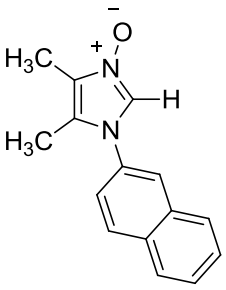
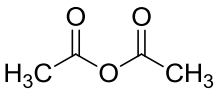
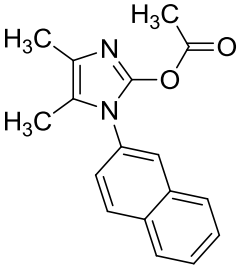
[a]Reactant (1 mmol), [b]Isolated Yield, [c]Optimized reaction condition

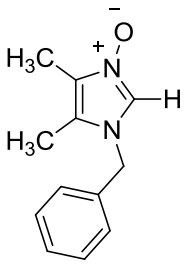
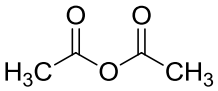
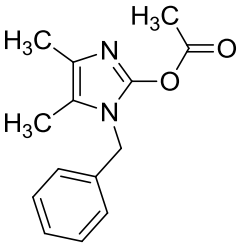
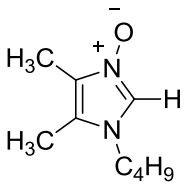
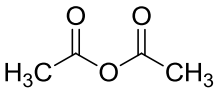
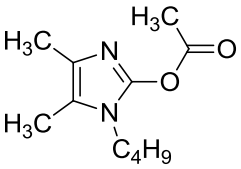
After achieving the optimization, the scope of variation of substrates was examined. At first, we applied these optimized reaction conditions to the various functionalized aryl ring and aliphatic system as well as fused ring also, a variety of 2-acetoxyimidazoles derivatives were synthesized using acetic anhydride under solvent-free protocol (**Table II.D.2**). It was examined that the presence of electron- donating groups such as –Me, –OMe, at different

position of the *N*-phenyl ring afforded the product in 69-75% (**Table II.D.2, entries 2b, 2c, 2d**). Alternatively, the presence of electron-withdrawing groups such as –Cl and –Br, gave slightly better yields and in the range of 78-81% yields (**Table II.D.2, entries 2e, 2f**). However, the results could be discussed on the basis of electron deficiency (electrophilicity) at the C-2 position of the imidazole ring system. In the presence of electron-withdrawing groups at the imidazole ring system, eletrophilicity increases rapidly that facile the nucleophilic attack at the C-2 position. We also continued the reaction with a bulky naphthalene ring in the imidazole *N*-oxide, which also afforded a good to excellent conversion (81%, **Table II.D.2, entry 2g**). Further derived a diverse application of this protocol was carried out with benzyl group, which worked quite slightly but afforded the required product in relatively lower yield (69%, **Table II.D.2, entry 2h**). The reaction was also carried out efficiently with n-butyl group (an aliphatic substituent) yielding the desired 2-acetoxyimidazole (65%, **Table II.D.2, entry 2i**).

Table II.D.2: Scope of various imidazole *N*-oxide in the synthesis of substituted 2-acetoxyimidazole[a] by varying time

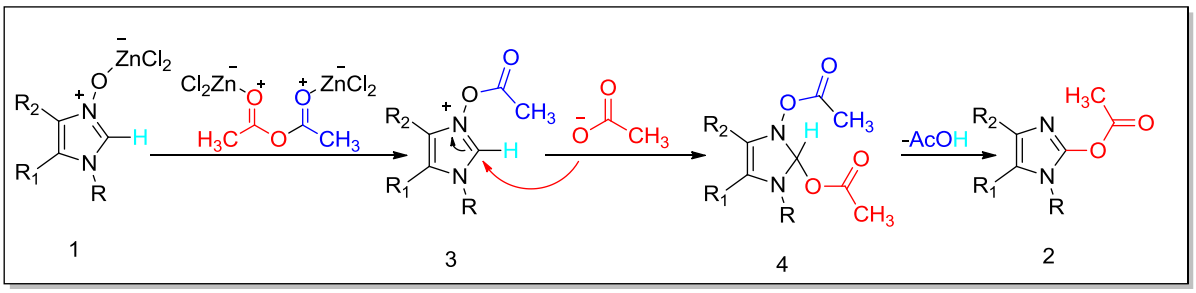
Entry	Imidazole *N*-oxide (1)	Acetic Anhydride	Temp (°C)	Time (min)	Product (2)	Yield (%)
1			140°C	10	 2a	79
2			140°C	15	 2b	73

3			140°C	15	 2c	75
4			140°C	20	 2d	69
5			140°C	10	 2e	81
6			140°C	10	 2f	78
7			140°C	10	 2g	81

8			140°C	10	 2h	69
9			140°C	15	 2i	65

II.D.C.2. Mechanism

Here we proposed the plausible mechanism analogous to that of cine substitution, initially imidazole *N*-oxide activated to binds with Zinc chloride to lowering the polarity reacts with carbonyl carbon of acetic anhydride which is also activated by Zinc chloride to form *N*-acetate imidazolium species (3). Being activated the C-2 position of *N*-substituted imidazolium species (3), the acetate ion which is produced during reaction attacks as a nucleophile to the C-2 position formation of a reactive intermediate (4). The hydrogen atom at C-2 position, being now more acidic which is easily eliminated along with acetate group to produces derivatives of 2-acetoxyimidazole as a desired product (2).



Scheme II.D.2. Plausible mechanisms for solvent-free synthesis of substituted 2-acetoxyimidazole.

II.D.D. Biological Studies:

II.D.D.1. Anti-microbial study of substituted 2-acetoxyimidazoles

In our anti-bacterial studies, we have found the antimicrobial activities against gram negative (*E.coli K12* MTCC1265 and *Pseudomonas fluorescencs* MTCC 103) or gram positive (*Staphylococcus Aureus* MTCC1144, and *Bacillus Subtilis* MTCC1305) bacteria. Seven compounds out of total acetoxyimidazole compounds exhibited antimicrobial activities against gram negative or gram positive bacteria, especially E.coli K12 (gram negative) and Staphylococcus Aureus (gram positive) bacteria. 2a and 2g compounds do not respond any antimicrobial activity. Compound 2d, 2f and 2i are also quite sensitive against E.coli K12 (gram negative) bacteria. All MIC (µg/ml) values of the entire compounds are shown in **Table II.D.3**.

Table II.D.3: MIC (µg/ml) values of the substituted 2-actoxyimidazole compounds

Compounds Code	*Bacillus Subtilis* (MTCC1305)	*Staphylococcus Aureus* (MTCC1144)	*Pseudomonas fluorescencs* (MTCC 103)	*E.coli K12* (MTCC1265)
2a	---	---	---	---
2b	---	---	---	1000
2c	---	1000	---	750
2d	---	1000	---	500
2e	---	---	---	1000
2f	---	1000	---	500
2g	---	---	---	---
2h	---	800	---	800
2i	---	---	---	500

II.D.D.1.2. In-vitro Results and Discussion

In biological system, drug availability at the target site is very important and longer time stay in the cell affect viability. However, excretion is also important for any drug. So, we have chosen normal human liver cell line (WRL-68) for our experiments because all drugs will pass through to liver to spread in human body. We were also interested to see the effect on compounds on cancerous cell i.e. we have taken human breast adenocarcinoma cell line (MCF-7) because this is an important cancer disease nowadays.

Till date, the various studies by using various combinations of drugs have been tested on only the cancerous cells. Similar work on any normal cells has not been yet reported. The

treatment bears quite satisfactory results for cancer cells but its effect on normal cells are not known. With such combination treatments the normal cells are expected to suffer more than the cancerous cells. So we wanted to make a comparative analysis using both cancer cells on one hand and normal cells on the other.

Firstly we wanted to check the effects of chemical compunds on both the cancer and normal cells at various cellular levels, such as mitochondria, lysosomes, DNA, protein, reproductive viability and also whether compound is toxic to the cells or not. We treated both the cells (cancer and normal) with chemical compounds by increasing the concentration of complexes from 50 to 250µg/ml. Then, firstly performed the MTT assay to see the effect of synthetic compounds on the viability of cells. It is known that mitochondria are responsible for the production of ATP in cells, which is responsible for the cellular metabolism. So we wanted to assess the effect of 2a to 2i series at the mitochondrial level.

MTT assay measures the reduction of yellow 3-(4,5-dimethythiazol-2-yl)-2,5- diphenyl tetrazolium bromide (MTT) by the enzyme mitochondrial succinate dehydrogenase. The MTT enters the cells and passes into the mitochondria where it is reduced to an insoluble, coloured (dark purple) formazan product. The cells are then solubilised with an organic solvent and the released, solubilised formazan reagent is measured. Since reduction of MTT can only occur in metabolically active cells, thus the level of activity of the mitochondria can be measured by this assay.

We observed the differences in the level of activity of the mitochondria of the overall cells (cumulative effects) with respect to the normal cells. We observed that after treating with 2a to 2i the cytoxicity increase in both normal as well as cancer cell, the level of toxicity increase in the MCF-7 cell lines and also affect the WRL-68 cell lines (Figure II.D.2).

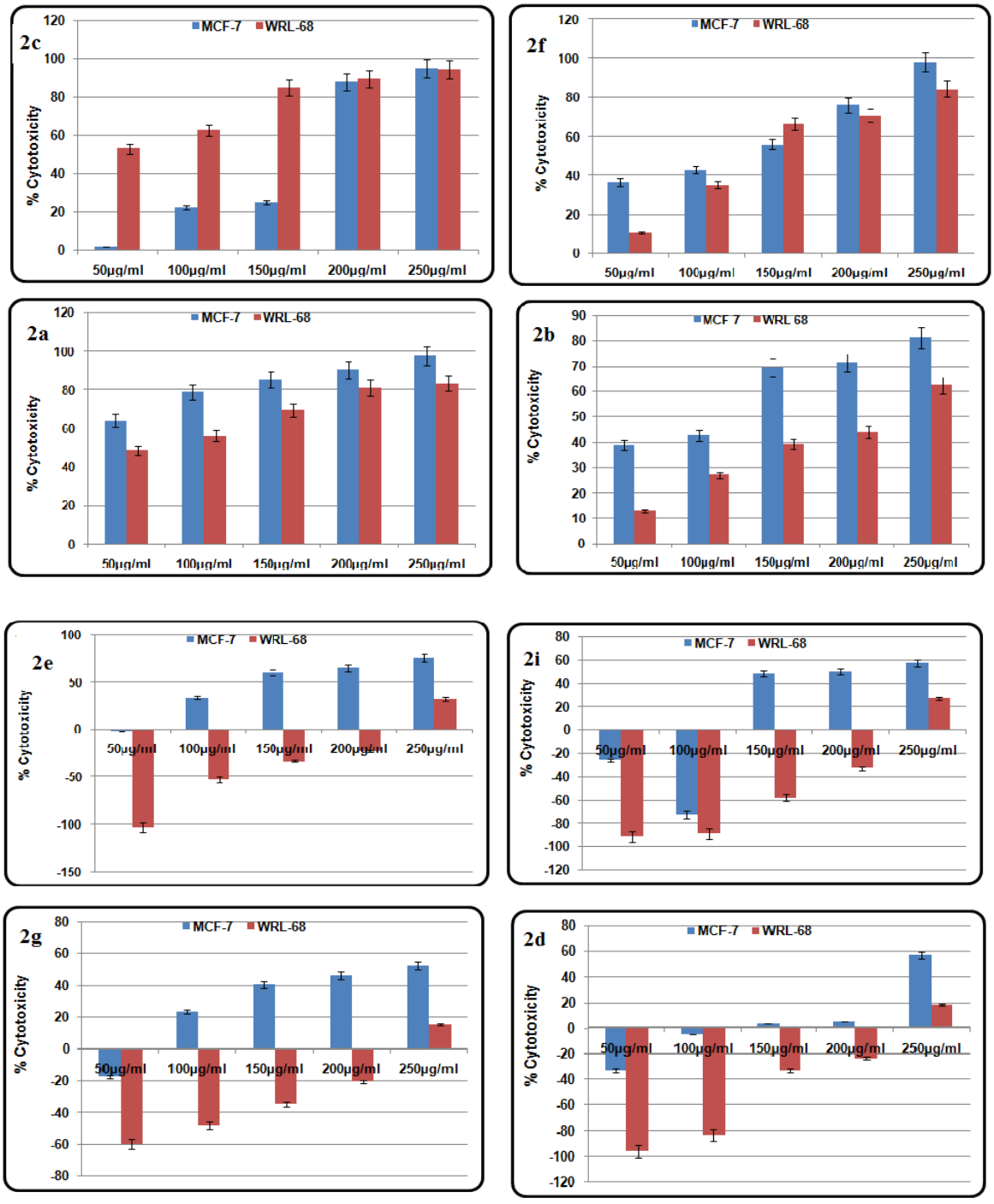
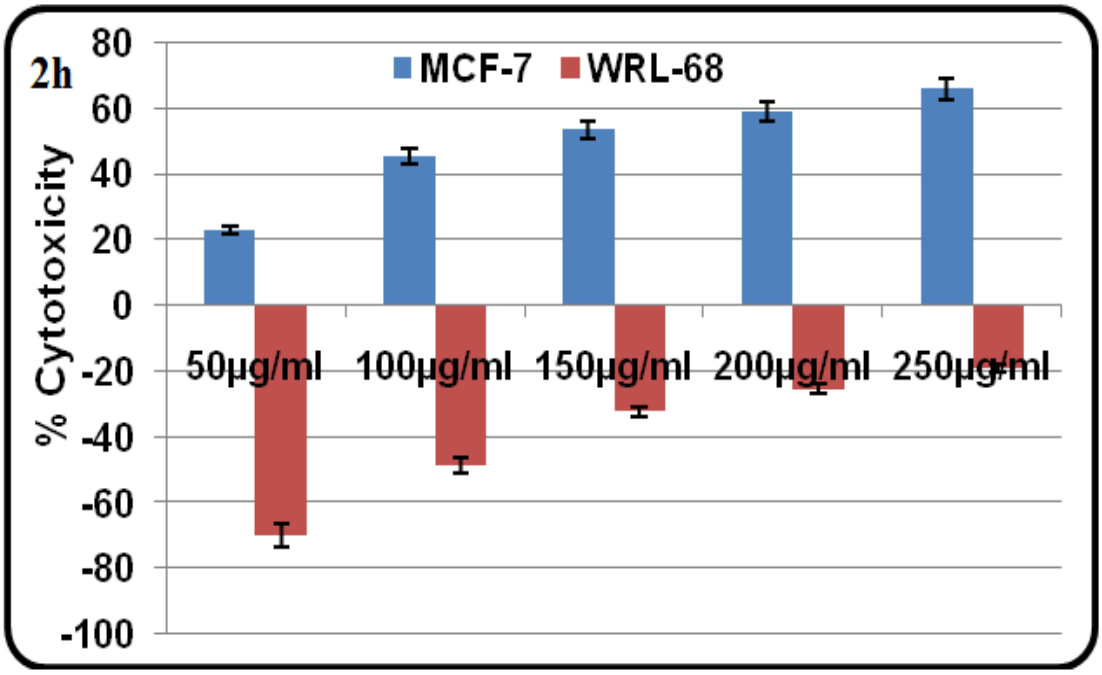


Figure II.D.2. Effect of chemical compounds on cell viability in respect of diluent DMSO. MTT assay were performed with MCF 7 and WRL-68 cells with increasing concentration of compounds. Percentage of cytotoxicity was calculated in respect of DMSO treated cells. Bar graph representations cell cytotoxicity data as determined by MTT assay.

Indicating that due to the increasing concentration of complex in the cells, the normal cells try to adapt and the environment upto certain level and produce more energy for the cellular metabolism which is required for their survivality whereas the cancer cells also try to survive but the activity of mitochondrial enzyme is decreasing may be due to the occurrence of mitophagy, which is also a survival strategy adopted by cells in response to any stress. We observed that **2h** did not show any toxicity to normal cell lines.



It was interesting result, so, we further studied mother compound to understand the effect of mother compound and its derivatives. We have not found any cytotoxicity in mother componds and its derivatives.

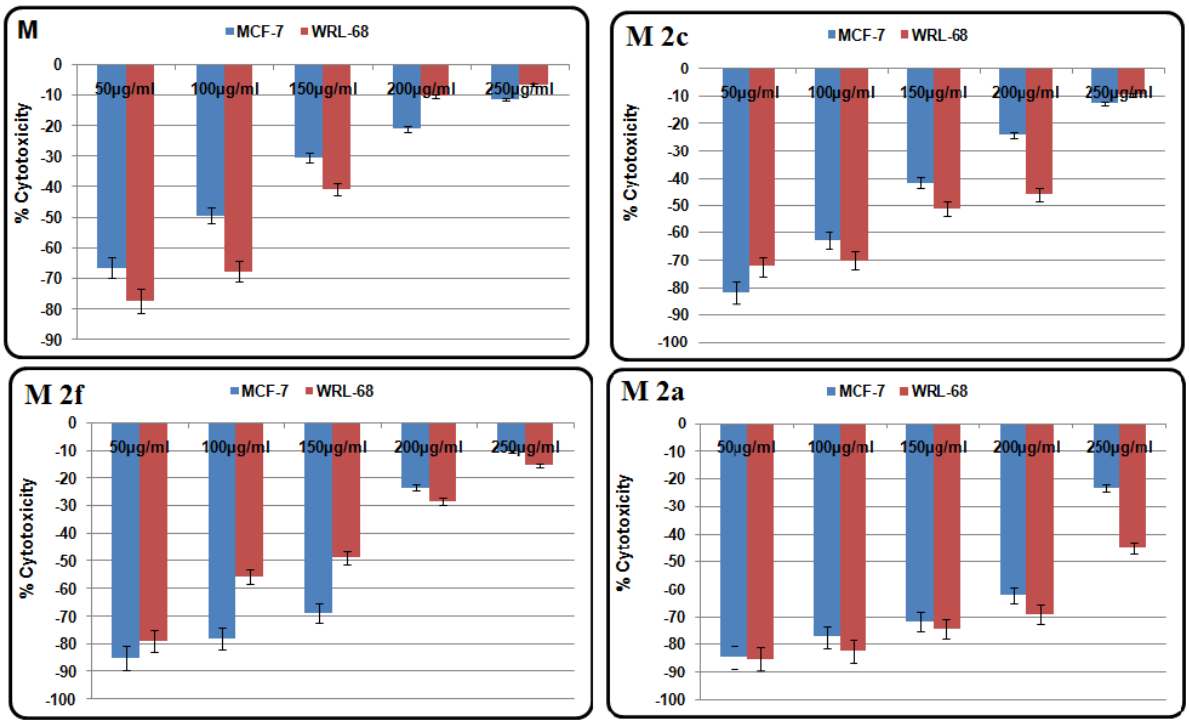


Figure II.D.2. Effect of chemical compounds on cell viability in respect of diluent DMSO. MTT assay were performed with MCF 7 and WRL-68 cells with increasing concentration of compounds. Percentage of cytotoxicity was calculated in respect of DMSO treated cells. Bar graph representations cell cytotoxicity data as determined by MTT assay.

It was surprising result and raised questions in our mind than why **2h** compound could have cytotoxcity only to cancerous cells. So, we have performed fluorescence based assay because **2h** compound have fluorescence property and give emission spectra. Results were according to our expectation it did not enter in the normal cell because of highly active membrane whereas **2h** compound enter in cancerous cell because of high speed proliferation and uptake **2h** compound easily. There was no fluorescence in WRL-68 cell line whereas green colour fluorescence observed in MCF-7 cell line.

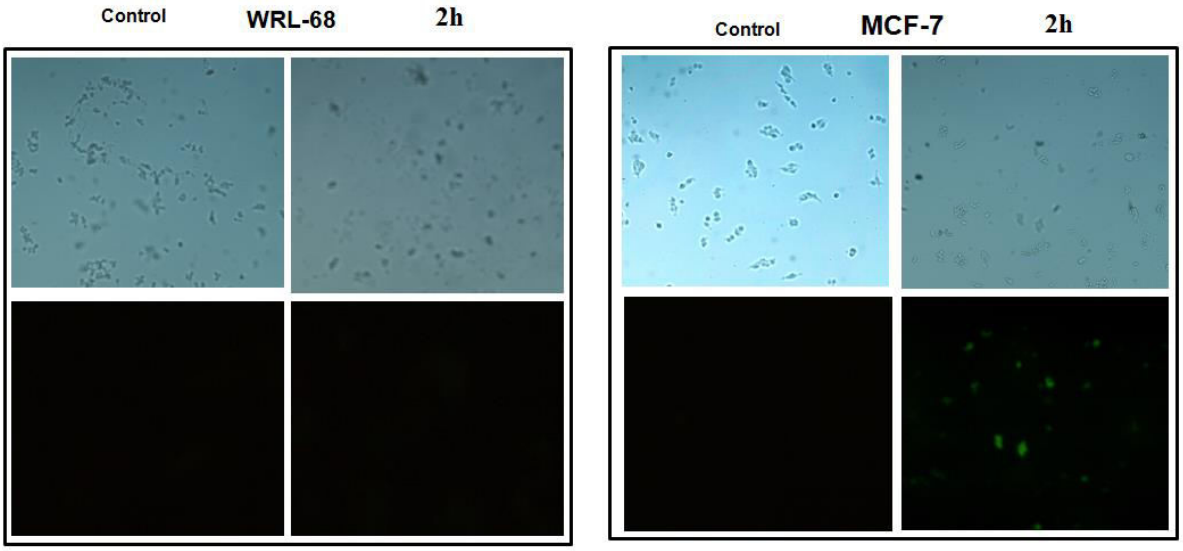


Figure II.D.3. Membrane invading property of chemical compound wad observed by Fluorescence property:- Fluorescent image of MCF 7 and WRL-68 cells were seen in the presence of compounds under fluorescence microscope, 10X magnification. There was no fluorescence measured in WRL-68 cells.

Cellular metabolism is also responsible for production of toxin when comes in contact of foreign particles which takes part in cell proliferation, cell activation. This mechanism also affects cell shape, size, and attachment to the surface in case of adherent cells. Cellular responses were measured in **2h** treated cells by morphological assessment assay and compared it with untreated cells. Cells were healthy and in proper shape and size like control shown in Figure II.D.4. Cells were properly attached to substratum and vacuoles were in normal in size. The numbers of cells were increased as compared to control which indicated non toxic effect of **2h** on WRL-68 cell proliferation whereas it affects proliferation of cancerous cells MCF-7.

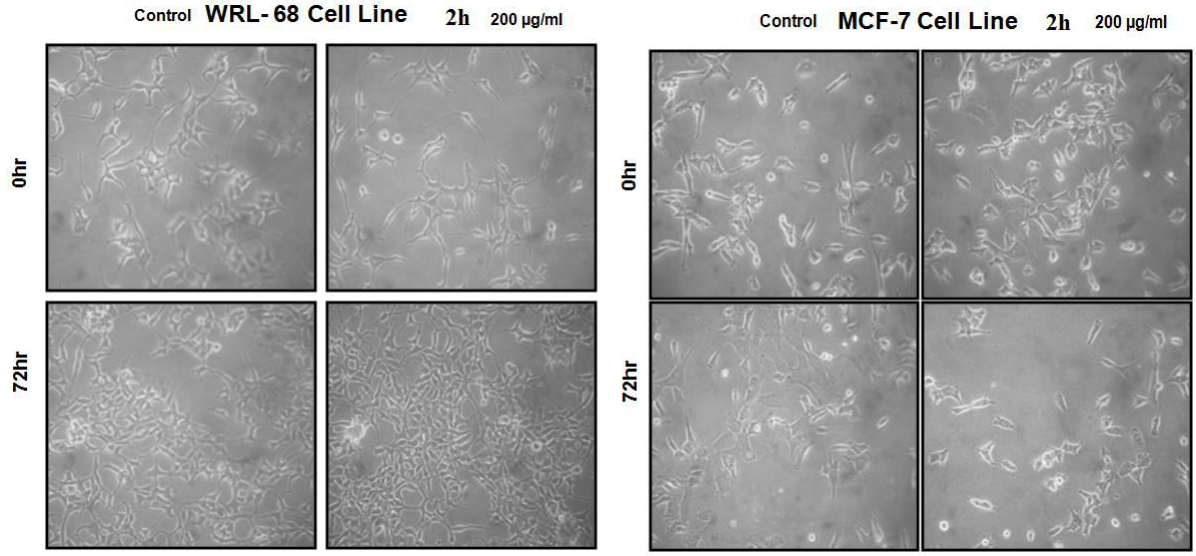


Figure II.D.4:- Morphological assessment Assay:- Observation effect of **2h** compound on cellular metabolism in human breast cancer cell line (MCF-7) and comparison with hepato cellular cell line (WRL-68).

Here, we used 2 cell lines- MCF-7 (cancer) cell lines and wrl-68 (normal) cell lines. **MCF-7** is a well differentiated breast carcinoma cell line. The MCF-7 cell line is an immortal cell line, tumorigenic cells, and are adherent in nature. The doubling time is approximately 36 hours. **WRL 68** - the human hepatic cell line WRL 68 exhibits a morphology similar to MCF-7 and hepatic primary cultures. It is epithelial-like and are adherent in nature. Firstly we intended to see the effect of synthetic compunds on both normal and cancer cell lines at various cellular levels**. MTT assay** was done to see the effect of compounds at the mitochondrial level. We observed the activity of the mitochondrial enzyme-succinate dehydrogenase, thus observing the activity of the mitochondria. Any effect on the morphology of the cells were also analysed by the **morphological assessment assay**.

We observed that the effect of this **2h** only on the cancer cell and normal cell lines are almost similar. **2h** has been presented as excellent synthetic compound. The cytotoxicity profile of the compound measured via Cell culture, MTT assay in normal human hepato cell line (WRL-68) showed that the particles are nontoxic and have toxic effect on MCF-7 and may be useful for pertinent drug delivery and other biomedical applications. So, it's better to explore

more and more about **2h** compound and keep it for future cancer therapeutics. This is expected to increase the drug efficacy by more study. This will hopefully provide a future direction for using the non-toxic synthetics products for the cancer therapeutics rather than the previously existing treatment.

II.D.D.1.3. Bioinformatics Results and Discussion

On the basis of our in-vitro studies, we have chosen the best five compounds for bioinformatics study to knowing the binding pattern as well as for cell target and want to see the compared study with various cancer cell proteins. However, 2f compound failed to bind with most of the cancer specific proteins. Docking studies of five selected compounds with receptors predicted from Swiss Target Prediction server showed that, most of the trans-membrane proteins are acting as good receptor for our ligand compounds. The drug ability nature of our studied compound was found out by using Lipinski rule which is summaries in table II.D.4.

Table II.D.4: Physio-chemical properties of all the five compounds abide by the Lipinski Rule of Five.

ligand	Molecular mass (Dalton)	Hydrogen bond donor	Hydrogen bond acceptors	logP	Molar Refractivity
2c	260	0	4	2.613640	71.061989
2f	310	0	3	1.810780	64.207993
2a	230	0	3	2.605040	64.509987
2b	244	0	3	2.913460	69.246986
2h	244	0	3	2.473540	68.553986

This all molecules followed the Lipinski rule of five and thus can be used as drug for medicinal purpose. The binding energies of five compounds with different target proteins were found out using various techniques (table II.D.5a, 5b).

Table II.D.5a: Binding affinities with cancer proteins.

Molecules	Binding Affinity (Kcal/mol)					
	3U9U (Breast cancer protein)	**4J96 (Cervical cancer protein)**	**4DD8 (Liver cancer protein)**	**1X2R (Lung cancer protein)**	**2NS2 (Ovarian cancer protein)**	**1GS4 (Prostate cancer protein)**
2c	-6.2	-6.4	-4.4	-4.8	-4.3	-5.0
2f	-4.4	-3.3	-3.8	-5.0	-4.7	-4.9
2a	-6.8	-7.2	-6.6	-6.5	-5.6	-6.5
2b	-6.7	-6.3	-5.6	-6.8	-5.9	-5.9
2h	-6.6	-5.2	-5.3	-7.2	-6.5	-6.2

Table II.D.5b: Binding affinities with predicted receptor proteins.

Ligand molecule	Predicted Receptor molecule	PDB id	Binding affinity (kcal/mol)
2c	Cytochrome P450	1og2	-5.0
	Fatty-acid amide hydrolase 1	3qj8	-5.0
	Microtubule associated protein tau	4tqe	-5.1
2f	Fatty-acid amide hydrolase 1	3qj8	-5.3
2a	Dual specificity protein kinase CLK1	5j1v	-6.5
	Dual specificity protein kinase CLK2	3nr9	-5.5
	Fatty-acid amide hydrolase 1	3qj8	-6.1
2b	Microtubule associated protein tau	4tqe	-6.1
	Cannabinoid receptor 1	5tgz	-6.0
	Fatty-acid amide hydrolase 1	3qj8	-5.8
2h	**Receptor tyrosine-protein kinase erbB-2**	**2a91**	**-7.1**
	ERBB4 intracellular domain	3u7u	-6.1
	Sodium-dependent serotonin transporter	5i6z	-6.2

Table II.D.5a clearly reveals that, 2c, 2a, 2b and 2h have good binding affinities against breast, liver, lung, prostrate, ovarian and cervical cancer proteins.

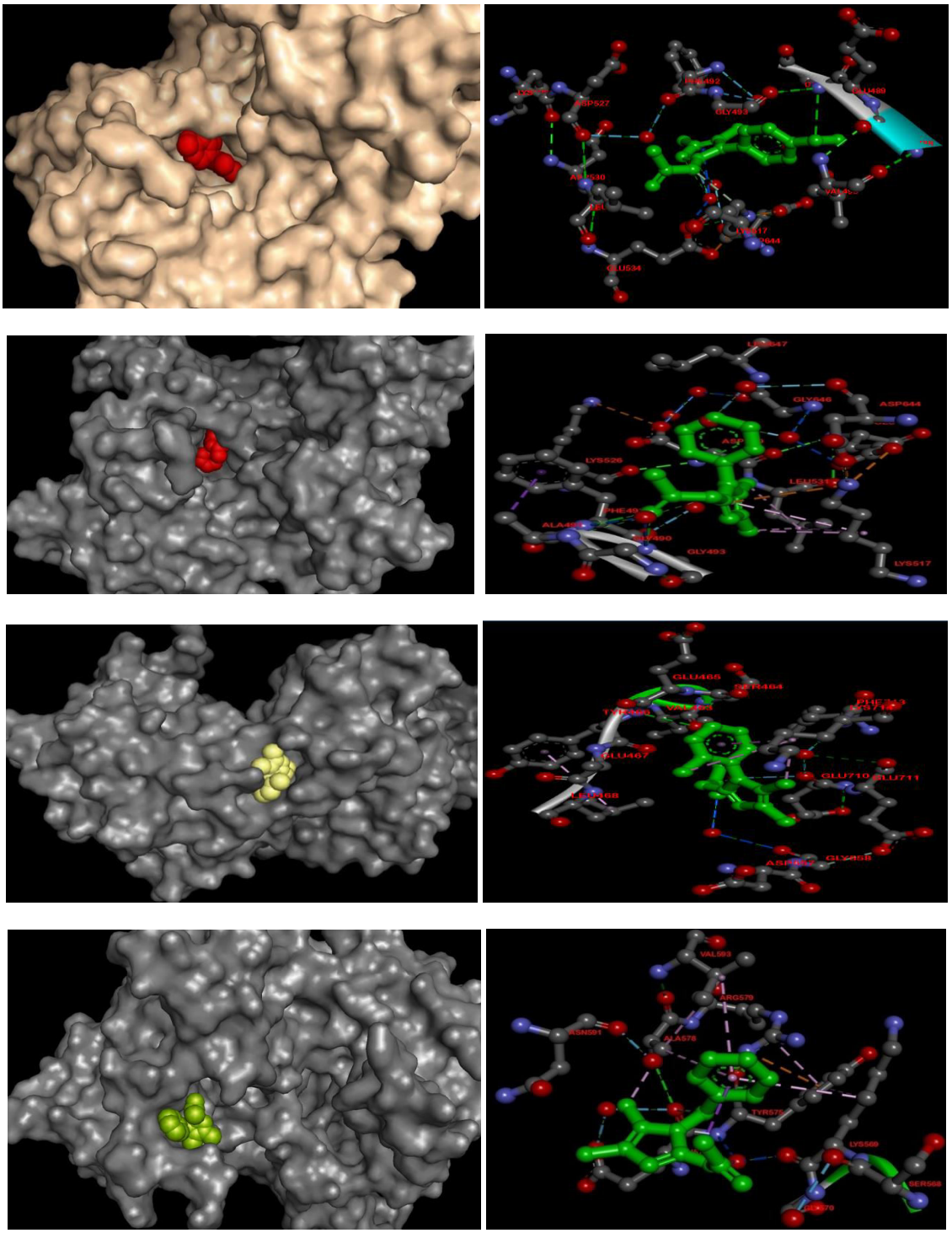


Figure II.D.5: Docking of 2c, 2a, 2b, 2h (top to bottom) with cervical cancer protein and their interaction with amino acids.

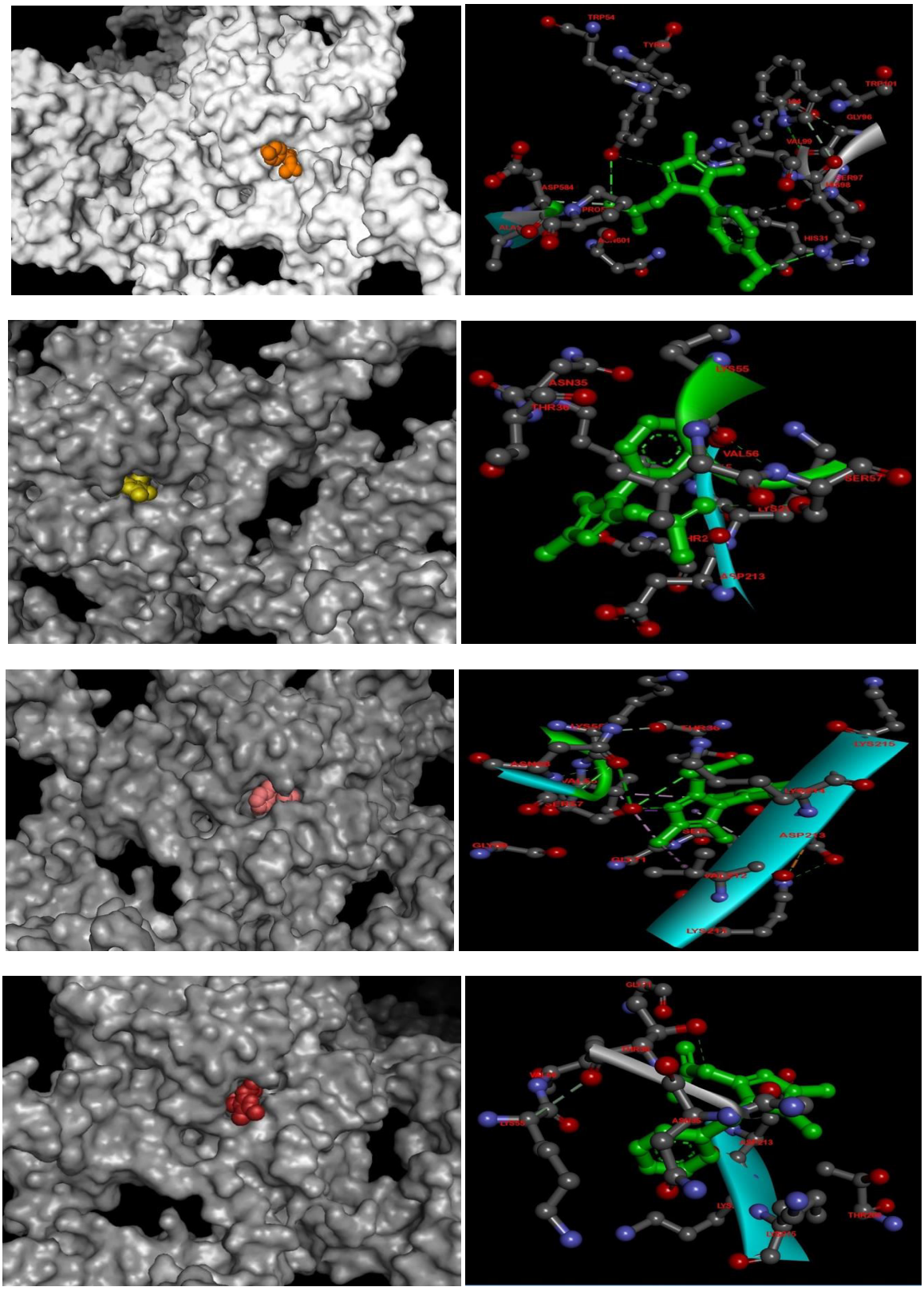


Figure II.D.6: Docking of 2c, 2a, 2b, 2h (top to bottom) with breast cancer protein and their interaction with amino acids.

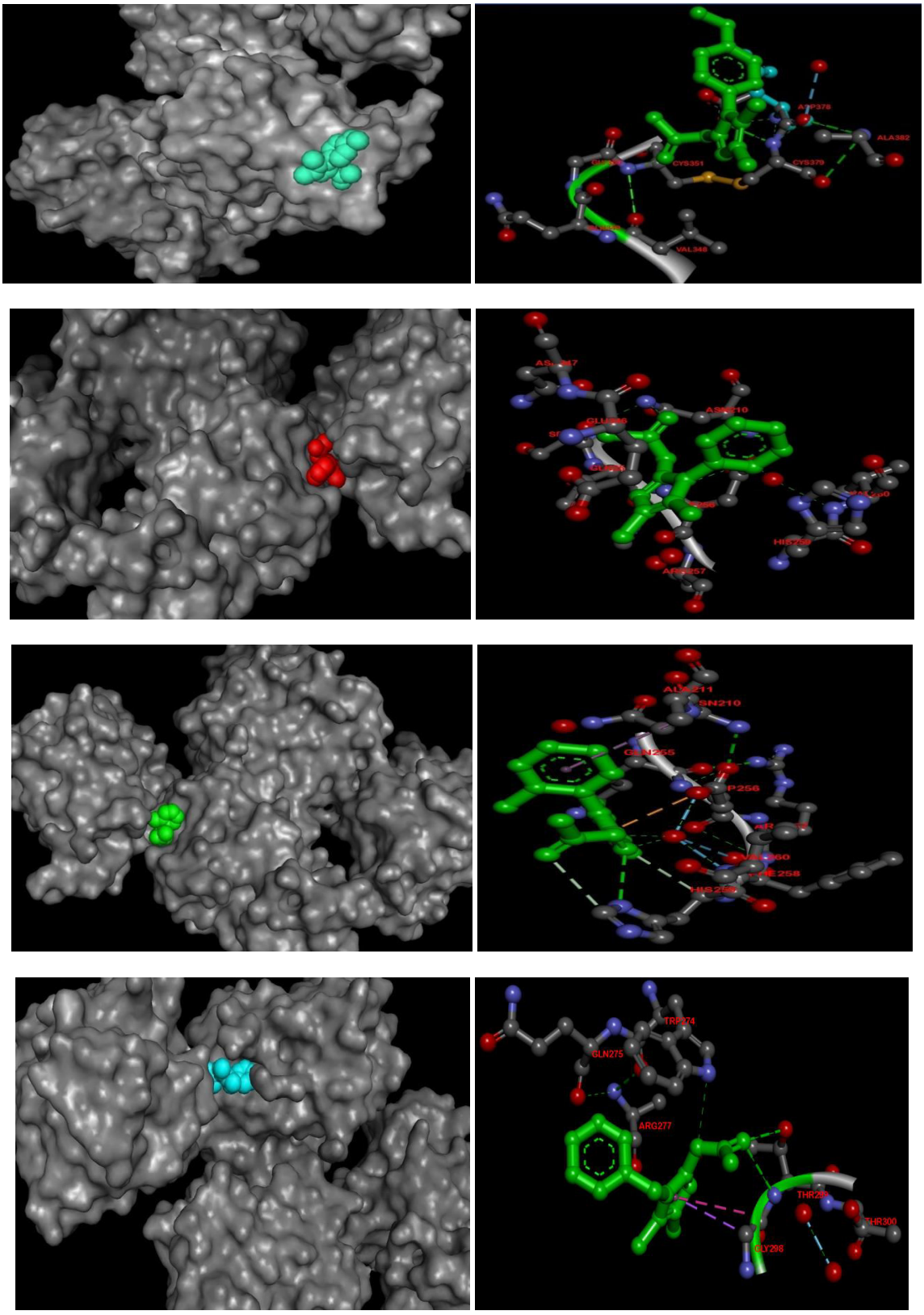


Figure II.D.7: Docking of 2c, 2a, 2b, 2h (top to bottom) with liver cancer protein and their interaction with amino acids.

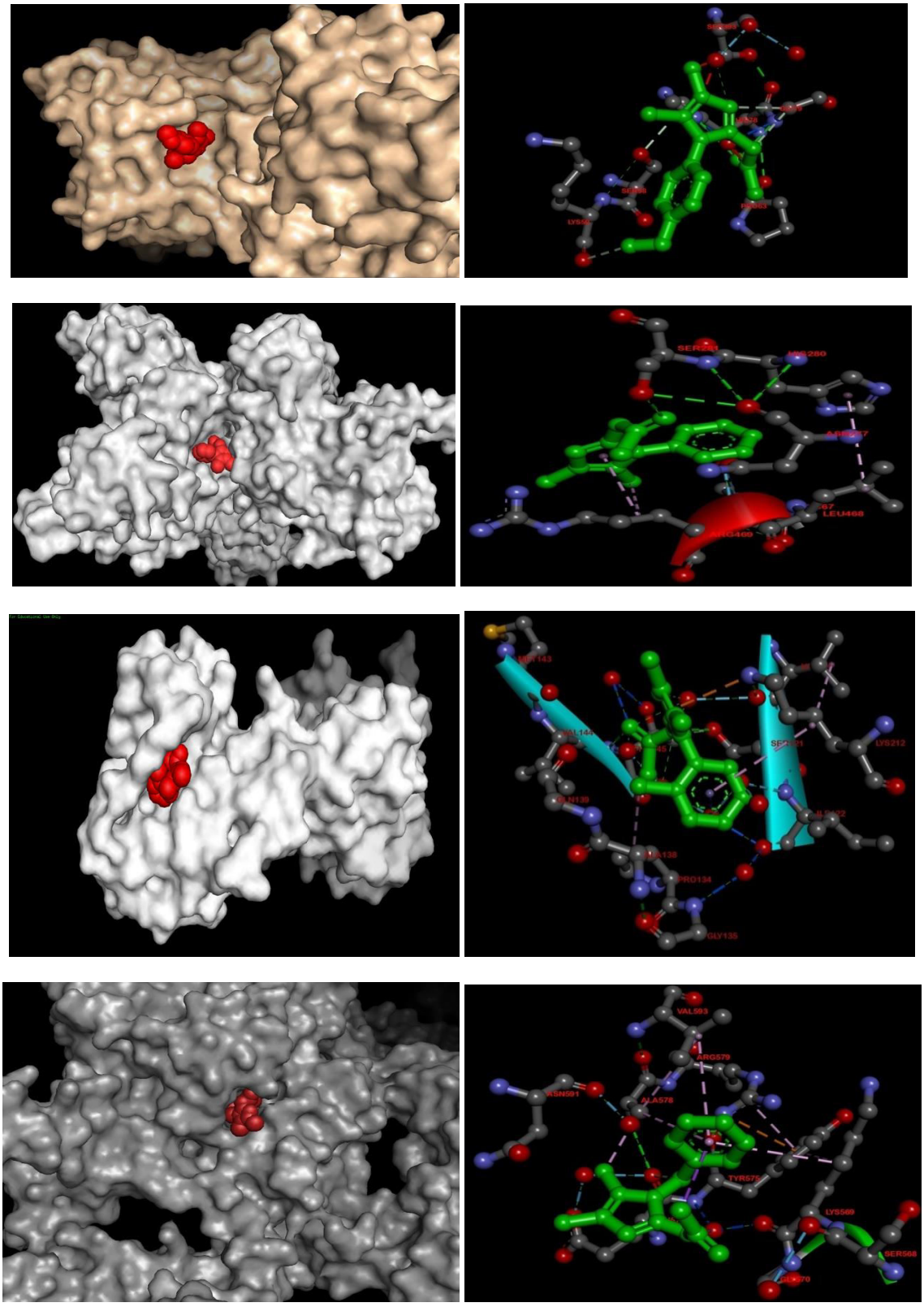


Figure II.D.8: Docking of 2c, 2a, 2b, 2h (top to bottom) with lung cancer protein and their interaction with amino acids.

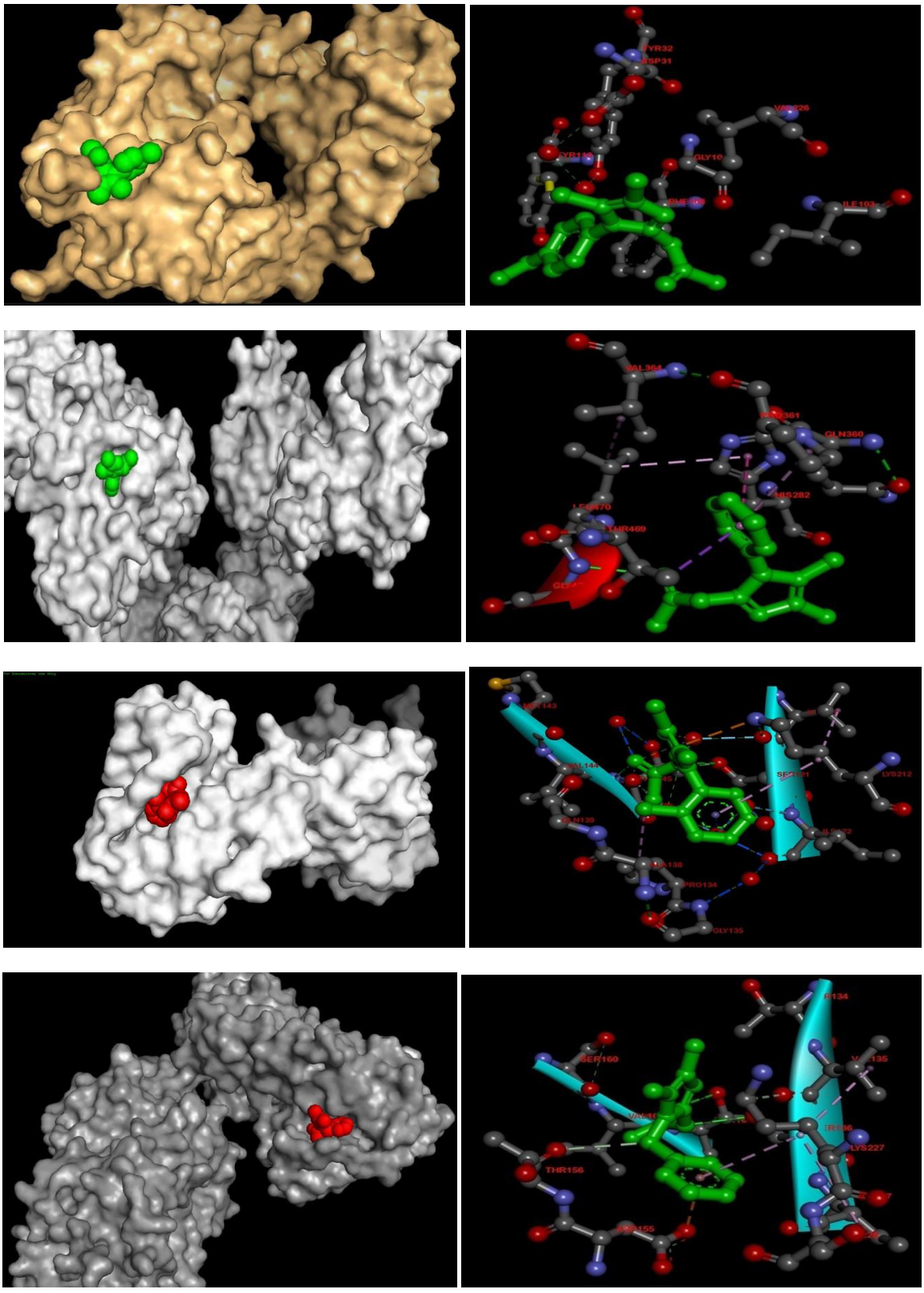


Figure II.D.9: Docking of 2c, 2a, 2b, 2h (top to bottom) with ovarian cancer protein and their interaction with amino acids.

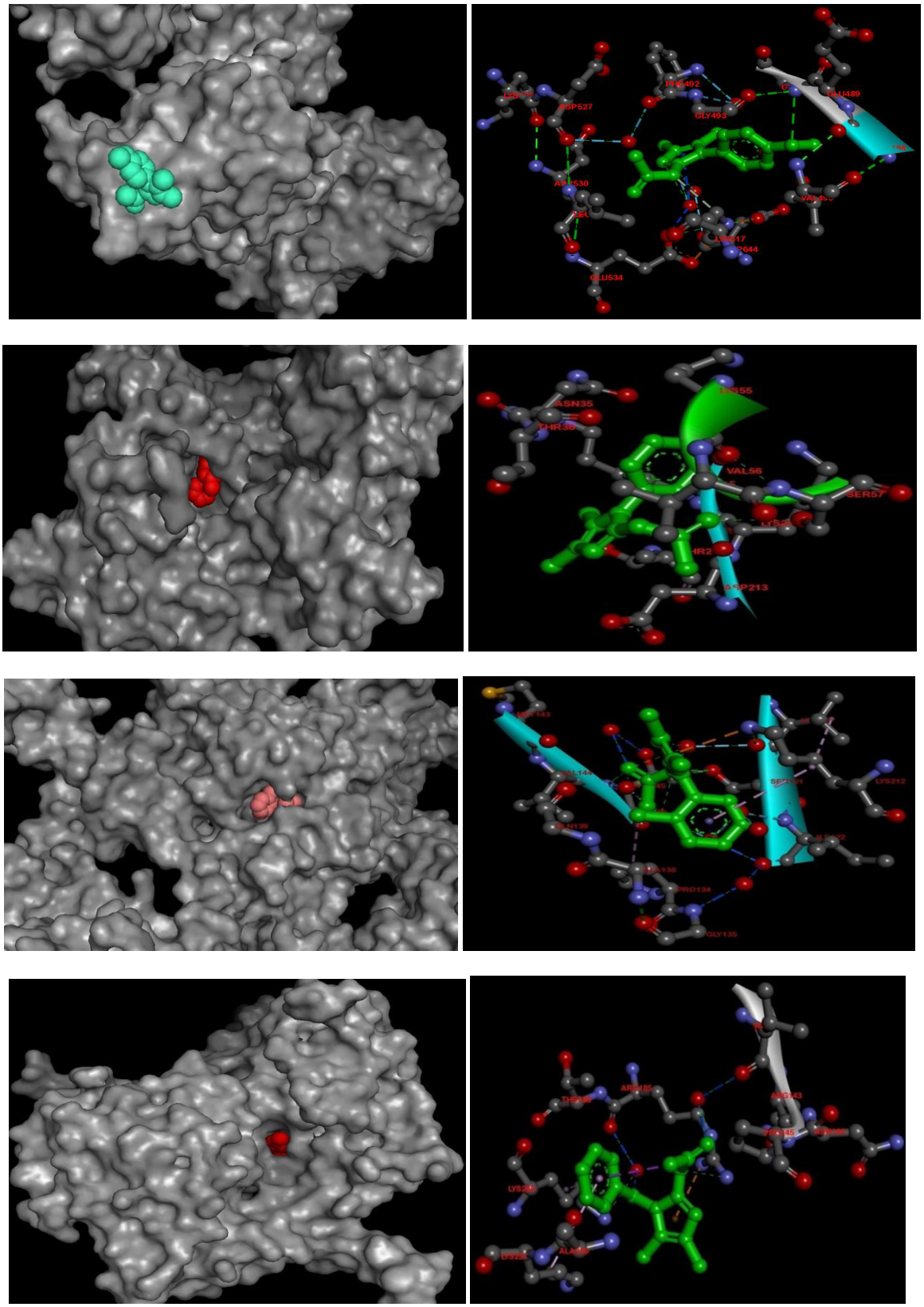
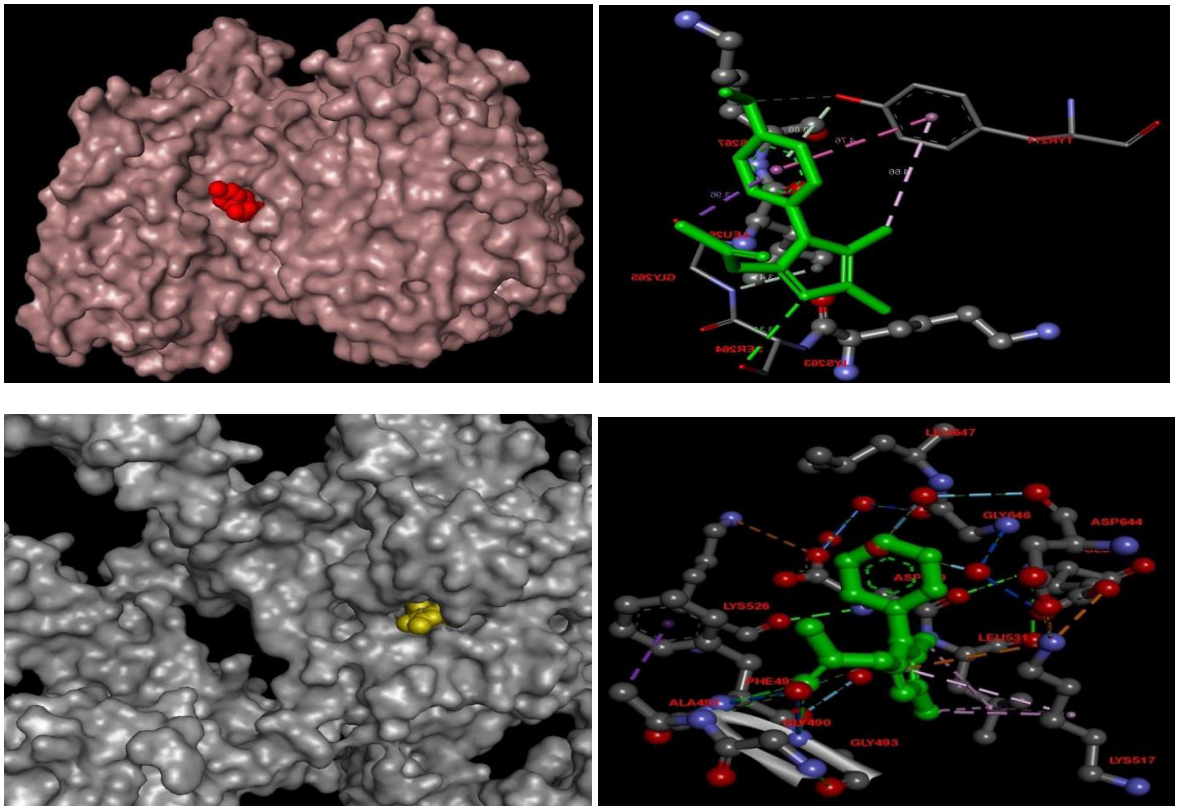


Figure II.D.10: Docking of 2c, 2a, 2b, 2h (top to bottom) with prostrate cancer protein and their interaction with amino acids.

It has been revealed that, fatty acid amide hydrolase (FAAH) is an important protein having good binding affinity to most of the compounds. This particular protein is very important for endo-cannabinoid signaling system. Previous studies have proved that FAAH protein expression markedly varies between the prostate cancer cell and normal prostate cells.[14] In prostrate cancer cells (LNCaP,DU-145,PC-3) the level of FAAH elevates than normal. Furthermore, the elevation of FAAH among different prostate cancer cell line varied. For instance, in LNCaP the FAAH level was more than that of DU-145 and PC-3. Interestingly, PC-3 and DU-145 cells after treatment with anandamide undergo apoptosis whereas LNCaP cells are resistant to suchtreatment. This may be due to the higher rate of FAAH induced anandamide hydrolysis.[15] Thus, we may hypothesise that, regulation of FAAH can control the onset of prostate or other tissue specific cancer and can also trigger the treatment induced apoptosis. Since, most of our synthetic compounds have shown good binding affinities with FAAH protein, we may say that, these compounds have some regulatory role on the aforementioned protein.



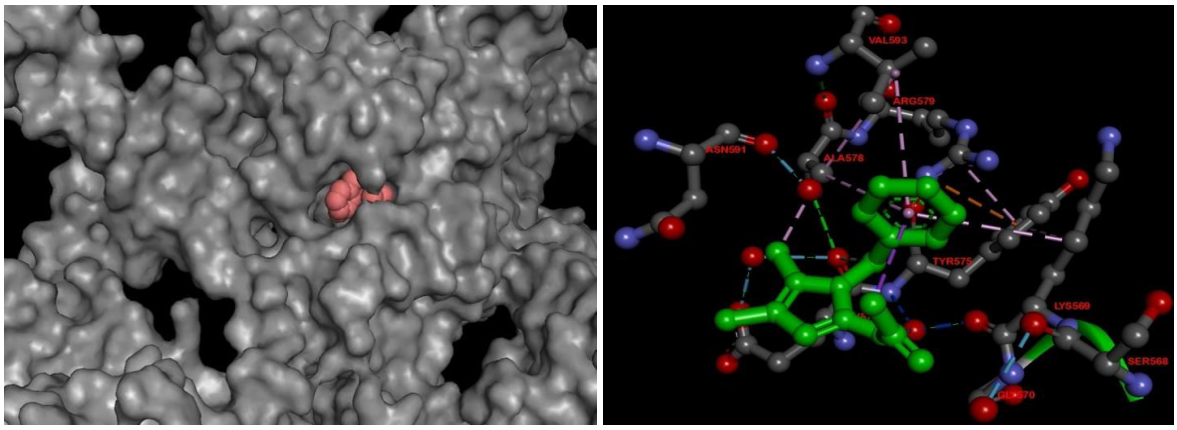


Figure II.D.11: Docking of 2c, 2a, 2h (top to bottom) with fatty acid amide hydrolase protein and their interaction with amino acids.

Another important receptor protein for our compounds was microtubule associated protein tau. This protein is also very important in prostate cancer and breast cancer physiology. It has been proved that, sensitivity of breast cancerous cells towards paclitaxel (a drug) increase with down regulation of tau protein.[16] Actually, low tau level renders microtubule more vulnerable to paclitaxel. Hence, breast cancer cells become hypersensitive to this drug. The low expression of tau protein can thus be used as a marker for paclitaxel sensitivity in breast cancer.[17] In our study, we have found that, 2c and 2b both have can bind to tau protein with considerable affinity and except 2f, all other compound bound to the breast cancer protein with permissible binding affinity. Hence, we may say that, our compounds can regulate the expression of tau protein and make the cancer cells sensitive to medicinal treatment. Similarly, elevated expression of cannabinoid receptors (with this receptor 2b showed considerable binding score) remains associated with pro-oncogenic signaling and breast cancer. They can be used as a biomarker with prognostic value in breast cancer or tumors. Regulation of these receptors may help in treatment strategy of cancer.[18]

Another important receptor with which **2h** showed good dock score was receptor tyrosine kinase ErbB2 and ErbB4. Mutation in ErbBr and epidermal growth factor receptor may induce many types of cancer and also lead to its progression. They do so by interacting with multiple signaling pathways. These receptors have been reported to play a pivotal role in breast and lung cancer.[19] Thus, **2h** having considerable binding affinities with tissue specific cancer proteins and with ErbB receptors may be used as a therapeutic agent against cancer.

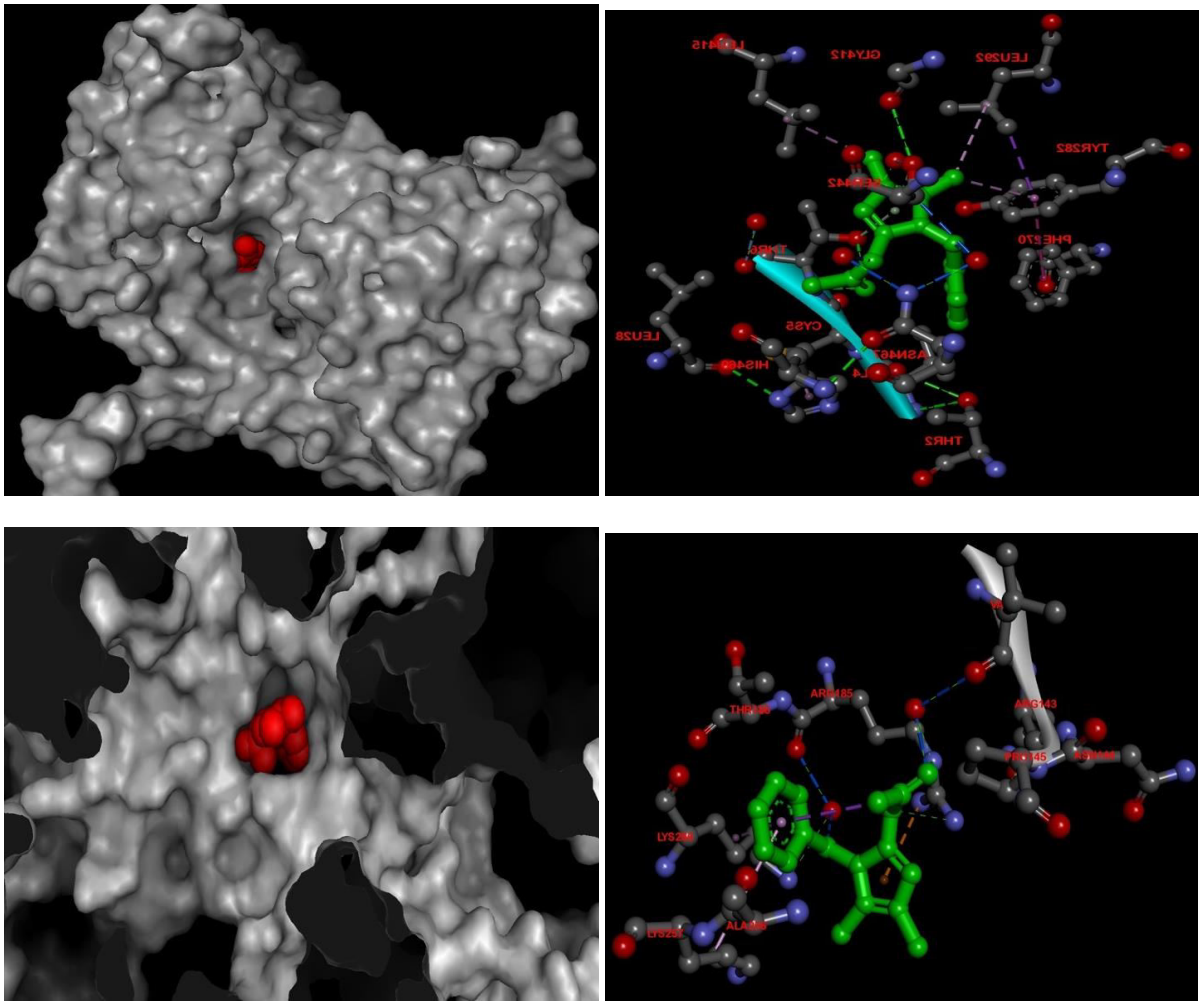


Figure II.D.12: Docking of **2h** with erbB2 and erbB4 (top to bottom) proteins and their interaction with amino acids.

Thus, the these synthetic compounds under investigation revealed substantial binding affinities with tissue specific cancer proteins (breast cancer, lung cancer, liver cancer, ovarian cancer, cervical cancer and prostate cancer) along with some other predicted receptor molecules which are important in cancer induction and progression. Furthermore, the drug ability score of all these five compounds also abide by the Lipinski rule of five. Hence, we hypothesise that, these five compounds have a potentiality to combat with cancer cells and cure the disease through several means. Their anti-cancer roles have been further evaluated through some experiments and validation.

II.D.D.1.4. In-vivo toxicity assay of 2h

In-vivo acute toxicity of compound **2h** was studied following standard methods[20] with appropriate modifications. Mice were divided into four groups (n = 6) and fasted overnight prior to the experiment. Compound **2h** was administered orally at 50, 100, 150 and 200 mg/kg body weight (bw) dose. The experimental mice were carefully observed for development of any clinical or toxicological symptoms at different time-period, 0.5, 2, 4, 8, 24 and 48 h.

Observation

In the experimental mice, no signs of mortality were observed up to 200 mg compound **2h** /kg BW (highest dose used in this study). So, a dosage of 100 mg/kg (low dose) was selected for in-vivo experiments.

II.D.E. Conclusion

In summary, we have developed an eco-friendly diverse synthetic protocol for the synthesis of a series of novel 2-acetoxyimidazole derivatives under solvent-free condition in very short span to excellent yield which are shows a potent anti-cancer activity in multiple cancers. In this work, we have studied with several biological processes such as in-vitro, bioinformatics as well as in-vivo for knowing the activity of that series of compounds. Anti-bacterial activity reveals that all of these compounds do not show any significant activity against gram positive and gram negative bacteria. Among the series of compounds, here we observed that the effect of the **2h** compound only on the cancer cell and normal cell lines are almost similar. **2h** compound has been presented as excellent synthetic compound. So, it's better to explore more and more about **2h** compound and keep it for future cancer therapeutics. This is expected to increase the drug efficacy by more study. This will hopefully provide a future direction for using the non-toxic synthetics products for the cancer therapeutics rather than the previously existing treatment.

This is my Patent work. Patent Application Number- 201731038374

II.D.F. References

References are given in BIBLIOGRAPHY under Chapter II, Section D (pp 275-276).

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CHAPTER-II

(SECTION E)

Metallo-Imidazoles Complexes

II.E.A. INTRODUCTION

The present day medicinal chemistry has been found to focus on small molecular weight scaffolds with heterocyclic moieties leading to a diverse range of pro-drug candidates. Extensive literary works are available to prove beyond doubt that heterocyclic cores containing metal ions exhibit profound pharmacological properties. Yet, very few delve into metal template-based multi-component reactions as tools of drug discovery-oriented synthetic organic chemistry. We have recently also reported one such scaffold adding to the large volume of literature already present.[1] As the presence of these metal ions in such heterocyclic cores becomes really significant it was thought that a metal template based MCR would be indeed very helpful in synthesizing a diverse range of molecules incorporating metal ions via a simple one-pot procedures.

To this effect, it was thought best to employ the Imidazole scaffolds which have been readily prepared by our one-pot solvent-free strategy. The Imidazole scaffold was chosen since there was comparatively very less literature related to the synthesis of their metal complexes and studies on their biological activities although the chemistry of Imidazole and its derivatives have attracted steady interest over the years. Imidazoles have been found to show wide range of applicabilities and their presence in many biological systems provide a potential binding site for metal ions.[2] A review of literature has shown that some novel complexes of transition metals with Imidazole have been found not only to display DNA binding ability. [3] but have also been found to interact with DNA by intercalation.[4]The metal-imidazole complexes show some catalytic effects too apart from the biological activities. Imidazole-containing cyclophosphazene metal complexes have been found to show high catalytic specificity in phosphoester hydrolysis.[5] Methylaluminoxane activated Ni-Imidazole complexes have been found to show good catalytic effects in norbornene polymerization.[6]

II.E.B. Present work: Background and Objective

Though, of significant applications the metal imidazoles have not been investigated much as is evident from the available literature. It is extensively on the varied synthetic approaches to this heterocycle while the metal complexes have been ignored. Literature reveals that the metal

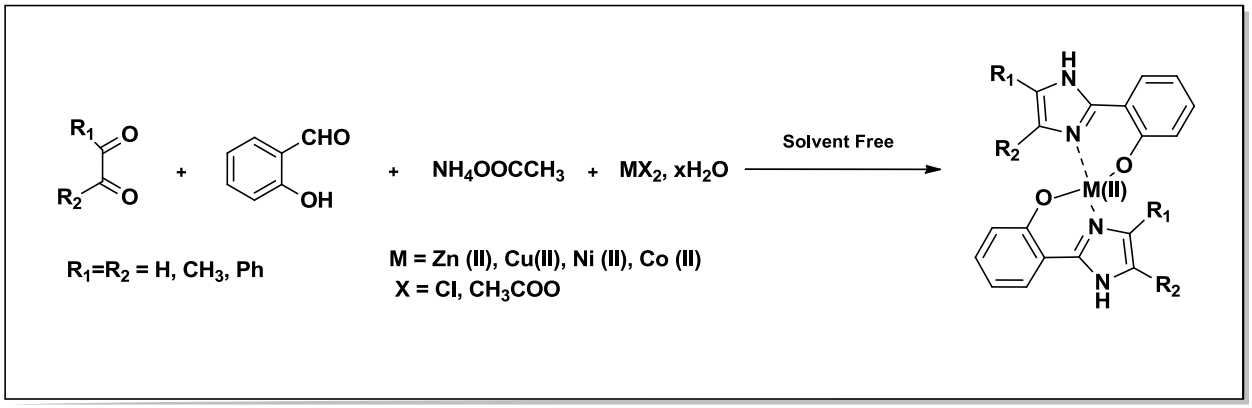
complexes of imidazoles are conventionally prepared by a two step process. This involves the initial preparation of the imidazole ligand and the final complexation with metal ions. The Imidazole ligand is generally prepared by refluxing the reactants for a few hours in glacial acetic acid. Refluxing the ligand with the metal salts in alcohol for another two hours completes the metallation process.[7]

Till date, a one-pot solvent-free strategy or a sequential multi-component neat reaction has not been carried out for the preparation of the Imidazole metal complexes. Recent reviews have focused on multiple reasons to think upon the diverse aspects of the solvent-free multicomponent protocol if extended to metal complexations. The review highlights the benefits of being able to access a wide range of complexes using solvent-free techniques, with diverse structures incorporating a variety of metal ions, ligand types and dimensionalities. It was also noted that not a single synthesis of metal-imidazole complex incorporated a multicomponent synthetic strategy under solvent-free conditions. Therefore, the synthesis of metal-imidazole complexes via a solvent-free multicomponent protocol becomes all the more important. Before proceeding with the actual synthesis, it was felt that the reaction conditions should be optimized. It was done with the help of High Performance Liquid Chromatography (HPLC).

II.E.C. Present work: Result and Discussion

II.E.C.1. Solvent-free synthesis of Metallo-Imidazole complexes

In extension to our previous studies on metal complexation,[8] the chosen synthetic procedure was also applied to gain access to various Imidazole metal complexes via the solvent-less mechanochemical activation, which hitherto has not been done. A four-component one-pot strategy for preparing these complexes (**Scheme II.E.1**) was found to be immensely successful and met three basic criteria: it was cheaper and greener; and was applicable in large scale and yielded the products in quantitative yields.



Scheme II.E.1. An efficient one-pot synthesis of metal Imidazole complexes under solvent-free conditions.

In a typical experiment, the metal imidazole complex is formed in near quantitative yield by grinding two molar equivalents each of the diketone and salicyldehyde and one molar equivalent of the metal acetate or chloride along with an excess of ammonium acetate (20 mmole) using a pestle and mortar over a period of ca. 5 minutes. Heating the reaction mixture in an oil bath for further 20 minutes is followed by formation of the product as colored solids. After this simple functional synthetic route to the metal complexes was found, several possible diversifications were possible. Using the optimized conditions, a library synthesis was set up combining three different diketones and four different metal salts. Thus eleven metal complexes were prepared in a very short time (**Table II.E.1**).

Table II.E.1: Analytical and spectral data of Imidazole Metal complexes

Entry	Compound	Compound Colour	M.P (^oC)	Λ_M ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff} BM	U.V. λ_{max} (nm)(DMSO)
1	Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Zn **(1)**	Yellow	>300^{o}C	3.57	-	208,231, 295
2	Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Ni **(2)**	Orange	>300^{o}C	6.25	-	321, 400
3	Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Co **(3)**	Pink	>300^{o}C	4.65	2.69	330, 415
4	Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Cu **(4)**	Violet	>300^{o}C	14.56	2.09	264, 342

5	Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Ni **(5)**	Brown		7.15	-	322, 400
6	Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Zn **(6)**	Yellow		4.03	-	270, 327
7	Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Cu **(7)**	Green		11.56	1.48	267, 334
8	Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Co **(8)**	Brown		5.62	2.2	
9	Bis{1H-imidazol-2-yl)phenoxy}Ni **(9)**	Brown		5.86	-	322, 399
10	Bis{1H-imidazol-2-yl)phenoxy}Cu **(10)**	Green	255-257	13.58	1.41	353
11	Bis{1H-imidazol-2-yl)phenoxy}Co **(11)**	Brown	285-286	4.69	2.49	355

When the protocol was extended further to involve a five–component reaction of the diketone, salicylaldehyde, primary amine, ammonium acetate and the metal salt to give a tetra-aryl imidazole metal complex, the one-pot synthesis predominantly yielded the metal complex of the triaryl imidazole and the metal complex of the Schiff base rather than the tetra-aryl imidazole metal complex. The results did confirm reports that alkylation of 1H-imidazoles did not necessarily produce the anticipated push of electron density to the donor nitrogen, rather the substituent on the 4, 5-carbon of the imidazole rings is more important for tuning the donor attributes of the imidazole base. Otherwise, the expected N-alkyl substituted metal complex (tetra-aryl imidazole metal complex) would have been selectively and predominantly formed rather than the tri-aryl imidazole metal complex.[9]

II.E.C.2. Optimization of Imidazole metal complex synthesis using HPLC

Before proceeding towards the actual synthesis it was imperative to optimize the reaction conditions for metal complexation reactions of the imidazoles. For this purpose, as a reference the 2-(4,5-diphenyl 1H-imidazol-2-yl phenol **[3, section A]** was taken. With the inputs benzil, salicylaldehyde, Ni (II) chloride hexahydrate and ammonium acetate the reaction was carried out to yield the nickel complex of the Imidazole **[3, section A]**. The optimum temperature and the

reaction time were determined using HPLC for this four component reaction under solvent-free conditions.

To get a general idea about the position of appearance of the peak for the ligand, an initial run involving the three components benzil, salicylaldehyde and ammonium acetate was carried out. The product 2-(4,5-diphenyl 1H-imidazol-2-yl) phenol, **[3, section A]** showed a peak with retention time 7.203. The HPLC plot of the reaction mixture after 20 minutes is shown in Figure II.E.1 where the peak at 5.7 for benzil can also be seen.

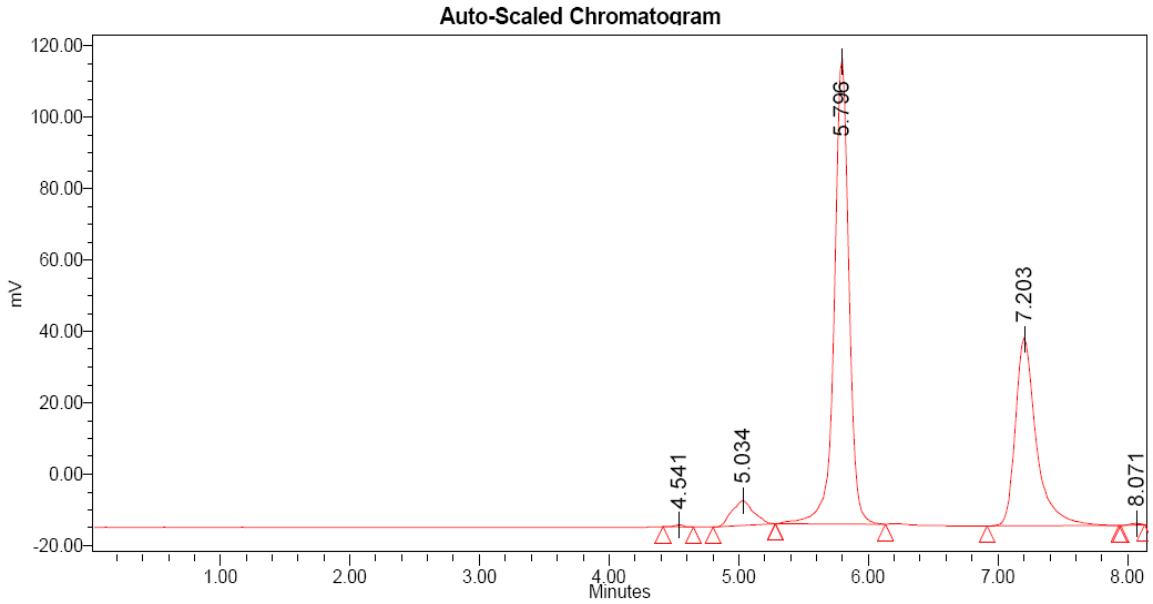


Figure II.E.1. HPLC trace for formation of 2-(4, 5-diphenyl 1H-imidazol-2-yl) phenol, **[3, section A]**

The metal complexation reaction with the Imidazole was then carried out at 100^{o}C. The reaction mixture was freezed and HPLC was done with the aliquot. At this temperature, the product peak appeared only after 10 minutes of reaction with retention time at 6.242 as shown in Figure II.E.2. The peak for the Imidazole **[3, section A]** ligand was observed at 7.151.

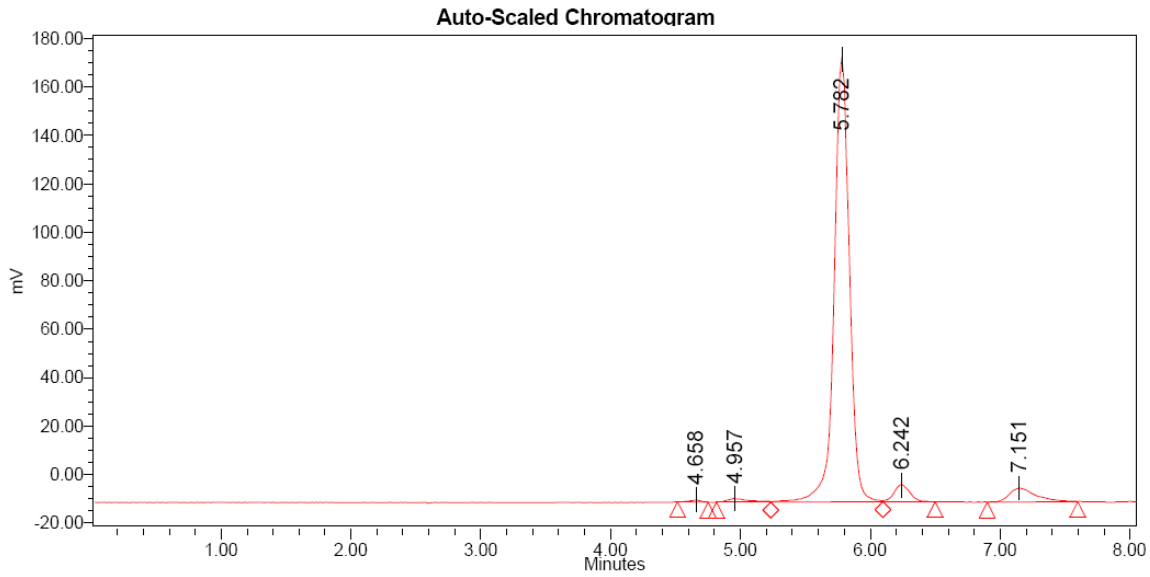


Figure II.E.2 HPLC trace for formation of 2-(4, 5-diphenyl 1H-imidazol-2-yl) phenol, **[3]** at 100 ^{o}C

The reaction temperature was increased to 120^{o}C, and the appearance of the product peak was checked in the HPLC. As expected the peak for the Imidazole product appeared immediately after 5 minutes of reaction at a retention time of 6.238. This indicated that with the increase in temperature, the product was formed at a faster rate (Figure II.E.3). The peak at 7.147 is for the imidazole ligand.

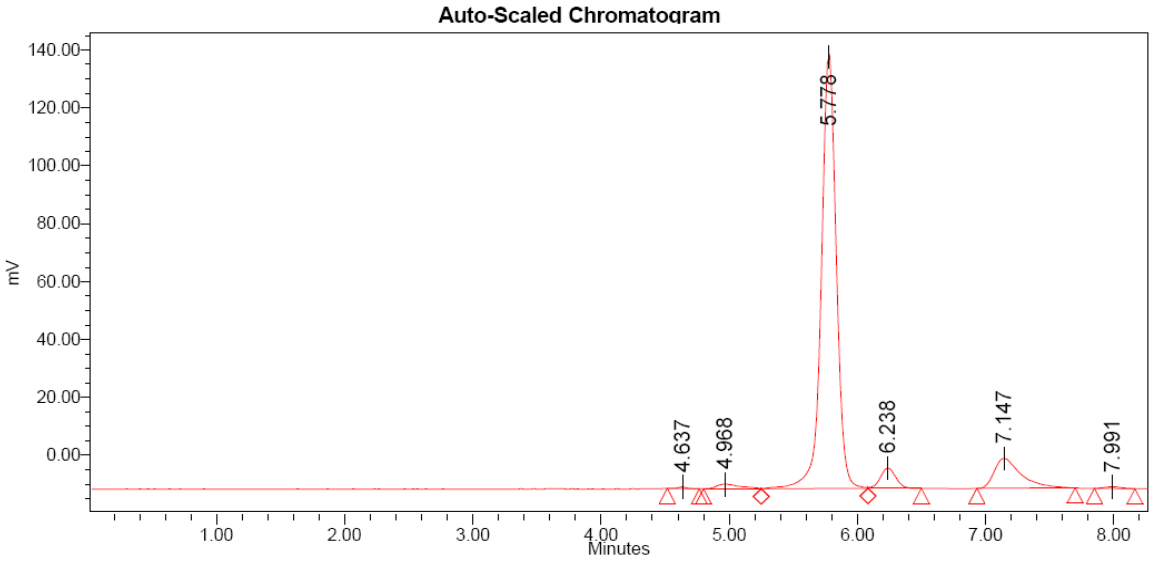


Figure II.E.3. HPLC trace for formation of 2-(4, 5-diphenyl 1H-imidazol-2-yl) phenol, **[3, section A]** at 120 ^{o}C

On increasing the temperature of the reaction further to 140°C the product peak area increased substantively within 5 minutes and appears with retention time of 6.285 (Figure II.E.4). Interestingly the imidazole ligand peak was found to disappear completely.

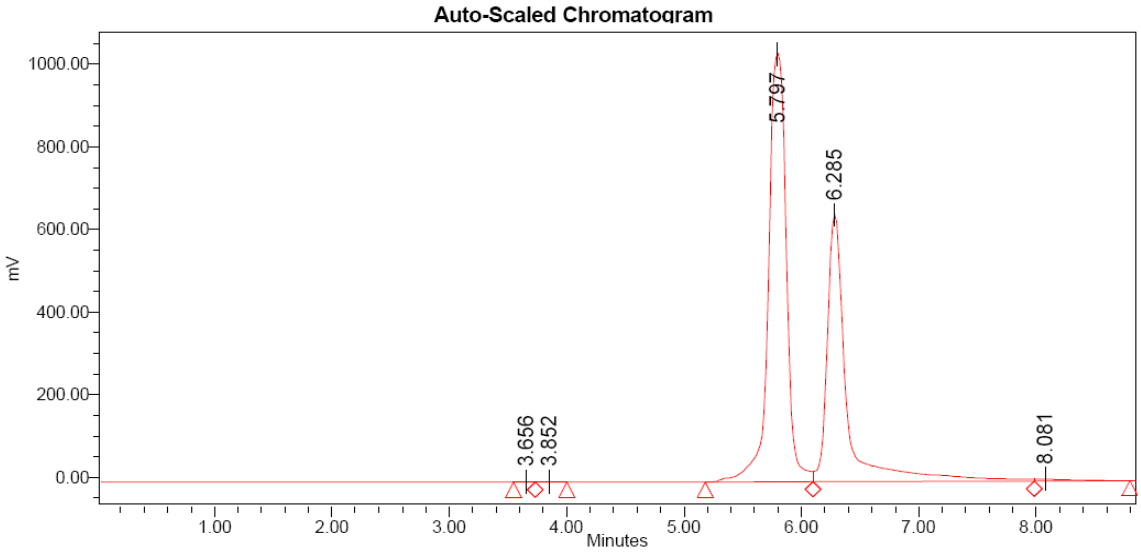


Figure II.E.4. HPLC trace for formation of 2-(4, 5-diphenyl 1H-imidazol-2-yl) phenol, **[3, section A]** at 140 °C

From the HPLC study, it could be concluded that the product formation started in as early as 5 minutes. The reaction of Ni (II) salt, benzil, and salicyldehyde was taken as a representative reaction using molar proportions to monitor the kinetics. It was found that within the first 5 minutes more than 90% yield (at 140°C) was observed (Figure II.E.5). But the reaction had to be carried out for a further 20 minutes to obtain quantitative yield.

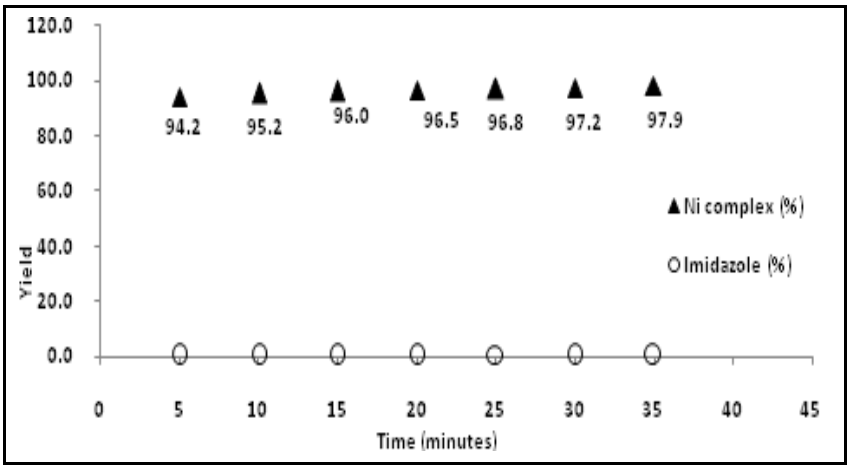


Figure II.E.5. Yield (%) of the nickel imidazole complex and Imidazole **[3, section A]** vs time (mins).

A quantitative analysis of the percentage conversion to the products could be obtained from the peak areas of the HPLC plot. It was found that the highest conversions took place at 140^{o}C when the reactions were performed at three different temperatures (100, 120 and 140^{o}C). Not only the Ni (II) complex but the Zn (II), Co (II) and the Cu (II) complexes could also be formed in similarly at the same rate. While the synthesis of the complexes of Cu-II and Zn-II) have been reported in solvent medium,[7]this is the first report of the synthesis of the Ni-complex via a solvent-free multicomponent strategy. The reactions carried out in solvents resort to a two stage preparation. The first stage is the synthesis of the imidazole ligand which takes 2 hours for the reaction to complete. The second stage is the complex formation stage which requires another 1hr. The solvent-free strategy is much better as is evident from the reduction of time taken for the reaction to complete. It is very plausible that a two stage acceleration of the reactions take place in solvent-free medium to make it faster. The absence of the solvent itself maybe one reason for the reaction to proceed at a faster rate while there could be a further augmentation of the catalytic process in the presence of metal ions.

In an MCR, a product is said to be assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product.[10] The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side

products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance while designing for a DOS. Hence, we envisaged that employing a number of appropriate metal salts and different diketones instead of N-alkylations using different amines would be better and a large number of metal complexes could be added to the library.

II.E.D. Conclusion

To summarize we may say that, on performing the MCR via metal template synthesis, good yields of the metal complexes in comparable time was achieved, probably because of the metal ions playing a pivotal role in catalyzing the reactions. The multiple component approach is especially appealing in view of the fact that products are formed in one-pot, and the diversity can be readily achieved simply by varying the reacting components. Additionally, there are distinct advantages of these solvent-free protocols since they provide reduction or elimination of solvents thereby preventing pollution in organic synthesis ‘‘at source’’.

II.E.E. References

References are given in BIBLIOGRAPHY under Chapter II, Section E (pp 277).

CHAPTER-III

EXPERIMENTAL SECTION

III. Experimental Section

Chemistry Portion

III.A. General Remarks

The commercially available all reagents used here such as aldehydes, ketones, amines, etc needed for molecules and ligand synthesis were used further without purification and the metal salts were obtained from Merck. Other reagents used in this work were purchased from the different companies Sigma-Aldrich, Acros, Thomas and Baker Merck and were used as received except otherwise stated. The employed glassware was proceeding to reaction flame-dried or oven and cooled.

^{1}H-NMR (300 MHz) spectra and ^{13}C-NMR (75 MHz) spectra were recorded on a *Bruker Avance* 300 spectrometer. Chemical shifts (δ) are given in ppm unit relative to reference as tetramethylsilane (TMS, δ 0.00 ppm). Coupling patterns are expressed by the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Solvents are varied in each case. Infrared (IR) spectra were recorded on a *Schimadzu* FTIR-8300 spectrometer in the 4000 – 400 cm^{-1} region as in KBr pellets or neat or solution. Only respective absorption bands are informed. Absorptions are given in unit, wave numbers (cm^{-1}); abbreviations: strong = s, medium = m, weak =w, broad =b. UV/VIS spectra were recorded on a JASCO V-530 spectrophotometer. The electron-spray mass spectra were taken on a MICROMASS QUATTRO II triple quadruple mass spectrometer. The FAB MS analyses were taken on a Jeol SX 102/Da-600 mass spectrometer, Data System using Argon/Xenon (6kv, 10mA) as the FAB gas. 10kV was the accelerating voltage and spectra were taken at room temperature. For the metal complexes, Magnetic susceptibilities were recorded at room temperature on a Magway MSB Mk1 (Sherwood Scientific) using Hg [Co $(SCN)_4$] as the calibrant, magnetic susceptibility balance and diamagnetic corrections have been completed accordingly. Cyclic voltammetric measurement was done in a BAS CV-27 cyclic voltammeter. HPLC grade dimethylsulfoxide (DMSO) and Baker Analyzed KCl were used. Tetra-n-butyl ammonium perchlorate (TBAP) as Southwestern Analytical's (Austin, Texas) electrometric grade was used as a helping electrolyte after ventilation on a vacuum line overnight. Melting points were recorded in open glass capillaries using concentrated Sulphuric acid bath and are uncorrected. Thin-layer chromatography (TLC) was carried out using TLC silica gel 60 F254, Merck. HPLC was carried out on a Waters –2487 Dual

Lambda absorber using RP-18 (Symmetry Shield) column. The solvent methanol used here with a flow rate of 0.5 ml/min. In all experiments was done in the same flow rate and same column. DSC studies were recorded in a Perkin Elmer Pyris 6. Temperature heating range and heating rate was done in the 30 - 250 ^{o}C and 5-10^{o}C per min. 2-5 mg of sample was packed in aluminium pans.

Calculations of quantum mechanical chemistry have been carried out on an Intel Pentium IV Core 2 Duo processor containing Desk Top PC. The semi empirical work package MOPAC 2000 (Fujitsu) program, in Chem 3D Ultra 8.0 and 12.0 with Graphic interface in CambridgeSoft software Chem Office Ultra was manipulated for visualization. Computations for some compound in this work were carried out through the PM3 method. The semi-empirical (MOPAC) technique for the quantum mechanical calculations was selected since it is not as much of desirable computationally instead of ab initio methods and is most excellent for medium-sized systems. However, this is less rigorous instead of ab initio methods, they are able of calculating excited states and transition states using experimentally calculated empirical parameters. While slight information exists about the limitations of PM3, it is a different improvement than AM1 and overall errors in ΔH_f are decreased by regarding 40% relative to AM1. Molecular geometries were entirely optimized without forcing any symmetry relations or idealizations. In all case, it was confirmed that every Eigen values were positive for the ultimate structure. The molecular structures found in this way were applied in a dipole moments calculation, configurational interaction, electronic transition energies and bond orders.

Biology Portion

III.B. Anti-bacterial: Material and method

Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial that will inhibit the growth of a microorganism after overnight incubation. MIC determination of 12 series compounds by employing a tube dilution method (most commonly method) in Mueller- Hinton broth, in accordance with the recommendations contained in the CLSI guidelines. Four bacterial strain two gram positive (*Staphylococcus Aureus* MTCC1144, and *Bacillus Subtilis* MTCC1305) and two gram negative (E.coli K12 MTCC1265 and Pseudomonas fluorescencs MTCC 103) were used. For MIC determination 3ml Mueller-Hinton broth distributed in test tube and different concentration of compound which was dissolved in ethanol (10mg/ml) added in test tube, with positive and negative control. 1%

Overnight growth bacterial culture was added in each test tube and incubated overnight at 37^0 c (MTCC1265, MTCC1305, MTCC1144) and 25^0 c (MTCC103) for overnight . Bacterial growth was detected by optical density at 600 OD. MIC values were defined as the lowest concentration of each chemical compound, which completely inhibited microbial growth. The results were expressed in micrograms per milliliters.[1]

III.C. In-vitro Analysis

MAMMALIAN CELL CULTURE MAINTENANCE:

Mammalian cell lines were cultured and maintained for cell biology experiments in sterile condition. The cells were grown in 100mm polyvinyl coated plates in Dulbeco's modified Eagle's medium (DMEM) with 10% FCS at 37ºC in a humidify atmosphere containing 5% CO_2. The medium were supplemented with 10U/ml PenicillinG and 100µg/ml Streptomycin. Splitting were performed by trypsinizing cells with 1X Trypsin-EDTA when cells were reached appropriate confluency (80%-90%) with prior washing of cells by 1X PBS. The cells were treated with 1X Trypsin- EDTA solution for 2-3 minutes in CO_2 incubator at 37°C and 5% CO_2. After incubation the cells were detached from the plate surface. The trypsin-EDTA solution was neutralized by adding 1.0ml of complete DMEM medium; cells were centrifuged and resuspended in the complete media. Equal numbers of cells were added to fresh plates and were allow to grow till they became confluent.

PRESERVATION OF CELL LINES:

Mammalian cells were preserved by cryoperservation method. Cells were harvested at confluent stage and after trypsinization, the cells were collected in a 15 ml falcon. The cells were centrifuged at 2,000rpm for 2 minutes at room temperature followed by washing with 1X PBS solution and were recentrifuged at 2,000 rpm for 2min at room temperature. The PBS solution was decant, and the cell pellet were resuspended in the preservation solution 90% FCS (Fetal Calf Serum) and 10% DMSO (Dimethyl sulphoxide). The cells were immediately transferred in liquid nitrogen cylinder to maintained -196° C temperature.

REVIVAL OF MAMMALIAN CELL LINES:

Cells were taken out from the liquid nitrogen cylinder and were thawed to 37ºC. The cells were collected in a 15ml falcon, which would have had 1.0ml of complete DMEM media. The cells were centrifuged at 1000rpm for 1 minute, supernatant were discarded and cell

pellet were wash with 1X PBS solution and recentrifugation as before. Finally, pellets were homogenized and resuspended in 1ml of complete media and were plated in 35mm or 60mm petriplates. These cells were used for further experiments.

Cytotoxicity study:

The human breast adenocarcinoma cell line (MCF-7), and human hepato cell line (WRL-68) were obtained from National Centre for Cell Science, Pune, India. All cell lines were cultured in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% fetal bovine serum (FBS), 100 units/ml penicillin, 100 mg/ml Streptomycin, 0.14% Sodium bicarbonate and 0.1mM sodium pyruvate. The cell lines were maintained in CO_2 incubator (N-Biotech) at 37°C in a 5% CO2 atmosphere with 95% humidity.

The dry chemical compounds were redissolved in dimethyl sulfoxide (DMSO, Hi-Media), and 10mg/ml stock was prepared for tetrazolium- dye (MTT)[2] cytotoxicity assays. The MTT colorimetric assay developed by Denizot[3] with modification was used to screen for cytotoxic activity of all the synthesized compounds. Each compound was screened initially for its cytotoxicity against all cancerous cell lines at the concentration of 50 µg/ml and 250µg/ml. The potential candidates which showed more than or equivalent to 50% cytotoxcity were further assessed for their IC_{50} (concentration that inhibits cell growth by 50%) values at the concentration range of 50µg, 100µg, 150µg, 200µg, and 250µg.

Briefly, the cells were seeded in 96-well plates at a density of $5x10^3$ cells/well in 200 µl culture medium. Following 24hrs incubation and attachment, the cells were treated with different concentrations of chemicals and similar concentration of diluents (DMSO) for 24 hr. After treatment, media was replaced with MTT solution (10µl of 5mg/ml per well) prepared in PBS and incubated further for 3hrs at 37°C in a humidified incubator with 5% CO2. The yellow MTT dye was reduced by succinic dehydrogenase in the mitochondria of viable cells to purple formazan crystals. Then 50µl of isopropanol was added to the each well to solubilize the formazan crystals. The plates were gently shaken for 1 min and absorbance was scanned at 500-690 nm by micro titer plate reader (Spectrostar^{nano}BMG LABTECH, Germany). The percentage of cytotoxicity was calculated as (Y-X)/Y x 100, where Y is the mean optical density of control (DMSO treated cells) and X is the mean optical density of treated cells with chemical compounds. The all experiments were repeated three times independently.

Morphological assessment of cancerous cells:

Cells were seeded in 35mm polyvinyl coated cell culture plates and incubated it at 37^{o}C for 24hrs. Following, day cells were treated with 200µg/ml chemical compounds. Cells were then incubated in CO_2 incubator with diluents (DMSO) treated cells as control and morphological changes of cancerous cells treated with chemical and with diluents (DMSO) were observed under phase contrast inverted microscope (Olympus, CK40-SLP), at 200X magnification and photographed at every 8, 16, and 24hr interval.

Fluorescence imaging:

MCF 7 and WRL-68 cells were seeded at 2×10^5 cells on coverslips in 35 mm glass petri plate culture dishes and left for 24h at 37 °C with 5% CO_2. Chemical compound was added to the cells (to achieve a final concentration of 100µg/ml) and left to incubate for 24-72hr. Cells were washed with 1X PBS and imaged immediately, using a LED based fluorescence microscope, Magnus MLXi microscope. The cells were excited at 480nm using LED cassettes and emission was collected using a long pass filter. Cells were observed immediately after PBS washing under 10X magnification and images were captured by digital SLR Olympus camera mounted on head for high resolution image.

III.D. Bioinformatics Analysis:

Materials and Method

The *in silico* analysis was done for predicting the activities of five synthetic compounds namely 11a, 11b, 11c, 11d and 11j on different tissue specific cancer proteins. First of all we evaluated some of the physio-chemical properties of these compounds to ensure that they can be used as drug for treatment purpose. Swiss target prediction server (http://www.swisstargetprediction.ch/) was used to predict the probable receptor molecules of each compound. The PDB structures of those proteins along with some tissue specific cancer proteins like breast cancer, lung cancer, liver cancer, ovarian cancer, cervical cancer and prostate cancer were downloaded from PDB database (Table 1).

Table 1: List of all the receptor molecules with PDB Ids used for docking.

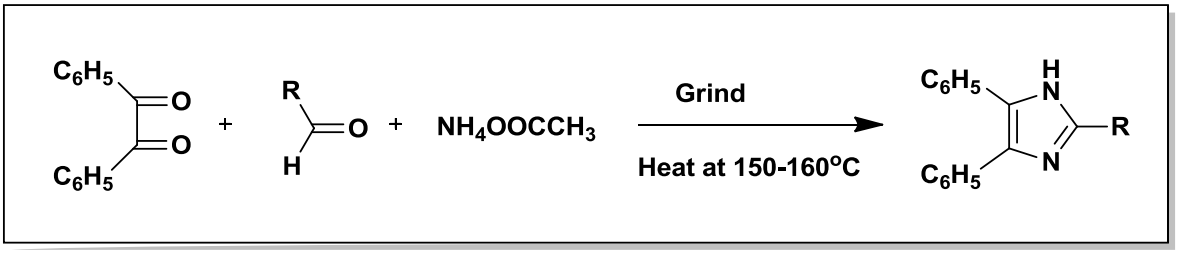
Receptor molecule	PDB ID
Breast cancer protein	3U9U
Cervical cancer protein	4J96
Liver cancer protein	4DD8
Cytochrome P450	1og2
Fatty-acid amide hydrolase 1	3qj8
Microtubule associated protein tau	4tqe
Fatty-acid amide hydrolase 1	3qj8
Dual specificity protein kinase CLK1	5j1v
Dual specificity protein kinase CLK2	3nr9
Fatty-acid amide hydrolase 1	3qj8

These proteins were prepared for docking after deletion of water and addition of polar hydrogen. Gasteiger charge was calculated for each protein. Grid box was prepared suitably. Finally, the PDB structure was saved in pdbqt format. Structures of the synthetic compounds were drawn via Chemdraw online version. The mol version was converted to pdb format through SMILES server which was further converted to pdbqt format. AutodockVina software was used for docking study and the binding energy was obtained in kcal/mol. Amino acids with which the ligands were interacting were visualized by Discovery Studio viewer.

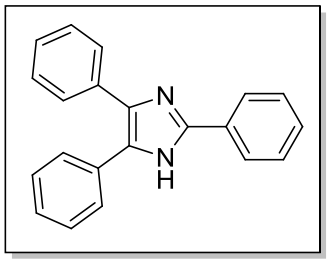
III.E. Synthetic Procedures, physical characteristics and spectral data.

III.E.1. Preparation of 2, 4, 5-trisubstituted Imidazoles via multi-component reaction:

Benzyl (1 mmole), corresponding aldehyde (1 mmole) and ammonium acetate (10 mmole) were taken in an agate mortar and pestle. The mixture was then thoroughly grinded under solvent-free condition. The contents were converted to a test tube and heated it in an oil bath at 150-160^{o}C for 4 minutes. The reaction mixtures were cooled and water was added to this mixture and filtered. The required product was recrystallised from pure ethanol. Completion of reaction was checked by TLC plate.

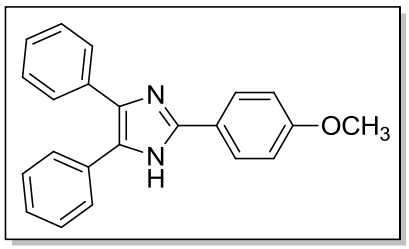


2, 4, 5-Triphenylimidazole [1, section A]:



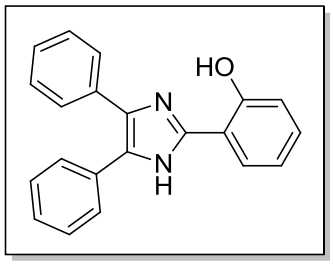
M.P. 274-276°C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.30-8.12 (m, $3C_6H_5$); ^{13}C NMR (75 MHz, DMSO-d_6): 145.94 ; 130.83; 129.13; 128.87; 128.68; 128.36; 128.15; 127.73; 125.66. IR (KBr, cm^{-1}): 3424 (N-H), 3050 (C-H), 1603 (C=C), 1480 (C=N). m/z found for ($C_{21}H_{18}N_2$): 299.2 (M+1)

2-(4-methoxyphenyl)-4, 5-diphenylimidazole [2, section A]:



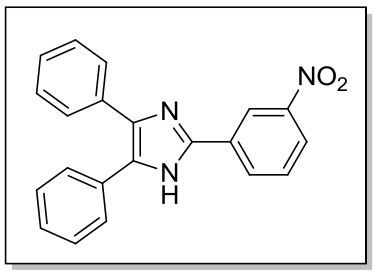
M.P. 226-228°C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.813(s, OCH_3); δ 7.05 (d, 2H); δ 7.03-7.54 (m, 10H, Ph); δ 8.03 (d, 2H): ^{13}C NMR (75 MHz, DMSO-d_6): 158.93, 145.07, 127.95, 126.73, 126.22, 122.61, 113.61, and 54.72. IR (KBr, cm^{-1}): 3409(N-H), 3057(C-H), 1616(C=C), 1493(C=N). m/z found for ($C_{22}H_{20}N_2O$): 329.6(M+1)

2-(4,5-diphenyl 1H-imidazol-2-yl) phenol [3, section A]:



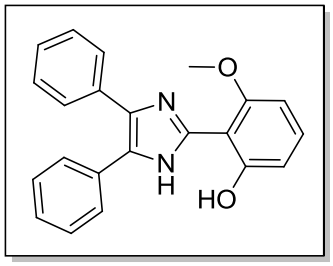
M.P. 202-203°C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.40-7.66 (m,5H); δ 7.21-7.24 (d,1H); 6.96-6.99 (dd, 1H); δ 6.75-6.77 (dd, 1-H); δ 6.66-6.89 (d, 1H); δ 6.05 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 165.7, 154.2, 134.6, 130.6, 127.8, 127.3, 126.6, 126.0, 117.8, 114.6. IR (KBr, cm^{-1}): 3278(N-H), 3058 (C-H), 1603 (C=C), 1485(C=N), 1074, 696. m/z found for ($C_{21}H_{18}N_2O$): 315.5 (M+1).

2-(3-nitrophenyl)-4,5-diphenylimidazole [4, section A]:



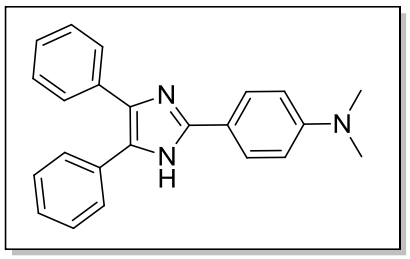
M.P. >300°C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.10 (s, 1H); δ 8.95 (s,1H); δ 8.52 (d, 1H); δ 8.20 (d, 1H); δ 7.77 (d, 1H); δ 7.55-7.39 (m,10H); ^{13}C NMR (75 MHz, DMSO-d_6): 147.9, 142.8, 131.4, 130.7, 129.9, 127.9, 127.2, 122.1, 118.9. IR (KBr, cm^{-1}): 3398(N-H), 3059(C-H), 1603(C=C), 1529(C=N), 1345, 1070, 694. m/z found for ($C_{21}H_{17}N_3O_2$): 344.2(M+1).

2-(4,5-diphenyl 1H-imidazol-2-yl)-3-methoxy phenol [5, section A]:



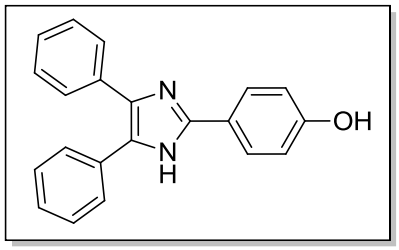
M.P. 165-168°C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (s,3H); δ 6.85-6.88 (m, 3H); δ 7.26-7.36 (m, 5-H); δ 7.39-7.64 (m, 5H); δ 12.5 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 147.2, 146.7, 145.4, 132.6, 127.9, 127.3, 126.6, 121.1, 118.0, 115.1, 108.9, 55.4. IR (KBr, cm^{-1}): 3503(N-H), 3412 (O-H), 3047 (C-H), 1603 (C=C), 1494(C=N).
m/z found for ($C_{22}H_{20}N_2O_2$): 345.8 (M+1).

{4-(4,5-diphenyl1H-imidazol-2-yl)phenyl}–dimethylamine [6, section A]:



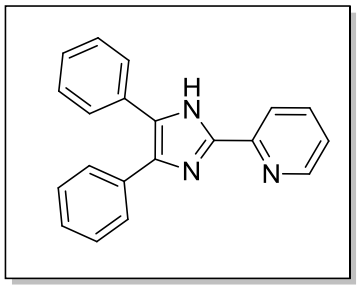
M.P. 256-258^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.89 (d, 1H); δ 7.52 (d,1H); δ 7.28-7.35 (m, 10H); δ 6.80 (d, 1H); δ 3.52 (s, 3H): ^{13}C NMR (75 MHz, DMSO-d_6): 149.8, 145.9, 127.8, 126.3, 125.8, 117.8, 111.4, 39.8. IR (KBr, cm^{-1}): 3350(N-H), 3067(C-H), 1614(C=C), 1502(C=N), 1070. m/z found for ($C_{23}H_{23}N_3$): 342.8(M+1).

2-(4-hydroxyphenyl)-4, 5-diphenylimidazole [7, section A]:



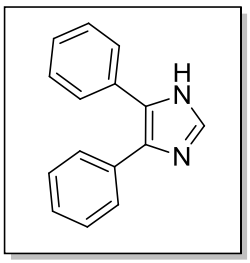
M.P. 260-261^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.30-7.51 (m, 10H); δ 6.85-6.88 (d, 2H); δ 7.89-7.92(d, 2H); δ 12.58(s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 158.23 ; 146.53; 135.85; 131.79; 129.04; 128.66; 127.55; 127.32; 126.84; 122.07; and 115.86. IR (KBr, cm^{-1}): 3200 (N-H), 3050 (C-H), 1610 (C=C), 1490 (C=N). m/z found for ($C_{21}H_{18}N_2O$): 315.2(M+1).

2-(4,5-diphenyl 1H-imidazol-2-yl) pyridine [8, section A]:



M.P. 240-242^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.66 (d,1H); δ 8.14 (d,1H); δ 8.11 (dd, 1H); δ 8.09 (d, 1-H); δ 7.50- 7.29 (m, 2C_6H_5); ^{13}CNMR (75 MHz, DMSO-d_6): 149.46, 149.21, 145.92, 137.67, 130.84, 129.14, 128.87, 128.78, 128.37, 127.58, 125.67, 123.63, 120.39. IR (KBr, cm^{-1}): 3420(N-H), 3058 (C-H), 1602 (C=C), 1489(C=N), 1070, 694. m/z found for ($C_{20}H_{17}N_3$): 300.8 (M+1).

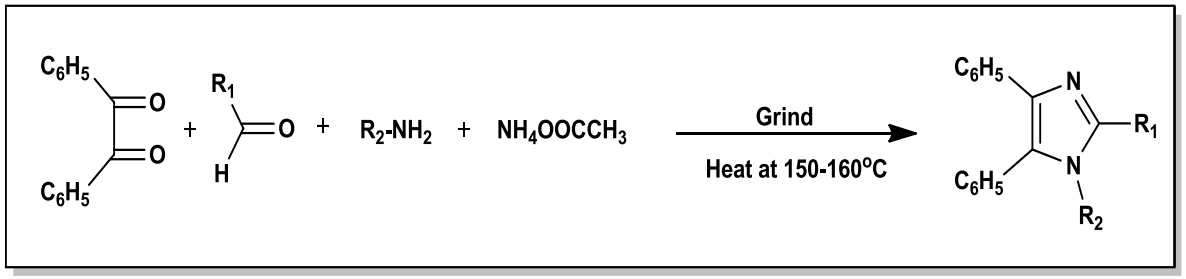
4, 5-diphenyl-1-H imidazole [9, section A]:



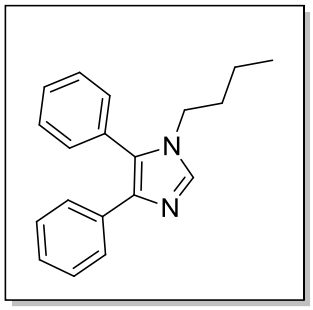
M.P. 225-226^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (s,1H); δ 7.50- δ 7.26 (m, $2C_6H_5$); ^{13}C NMR (75 MHz, DMSO): 134.54, 132.26, 131.55, 128.66, 127.85, 129.14, 127.64. IR (KBr, cm^{-1}): 3380 (N-H), 3066 (Ar C-H), 2810 (Al C-H), 1602 (C=C), 1512 (C=N), 1452, 1070, 698. m/z found for ($C_{15}H_{12}N_2$): 220.10 (M+1).

III.E.2. General procedure for the preparation of 1, 2, 4, 5-tetrasubstituted Imidazoles:

Benzyl (1 mmole), aldehyde (1 mmole), primary amine (1 mmole) and ammonium acetate (5 mmole) were taken in an agate mortar and pestle.the mixture was then thoroughly grinded under solvent-free condition. The mixtures were transferred to a test tube and heated iun an oil bath at 150-160^{o}C for 4 minutes. The mixtures were cooled and water was added into the test tube and filtered. The desired product was recrystallised from pure ethanol. Completion of reaction was checked by TLC plate.

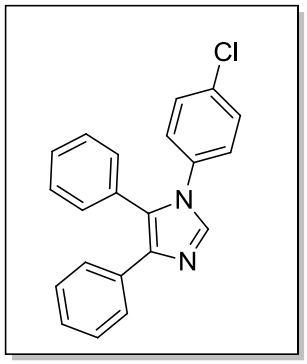


1-butyl-4,5-diphenyl-1-H imidazole [10, section A].



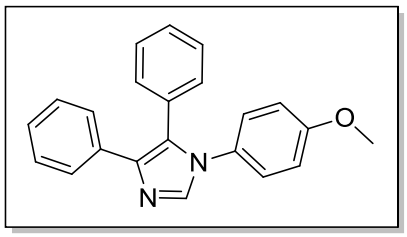
M.P. 78-80°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s,1H); δ 7.43-δ 7.20 (m, $2C_6H_5$); δ 3.78 (t,1H); δ 1.56 (m,1H); δ 1.24 (m,1H); δ 0.82 (t,1H); ^{13}C NMR (75 MHz, $CDCl_3$): 138.0, 136.62, 134.69, 130.97, 130.85, 129.04, 128.65, 128.50, 128.09, 127.78, 126.55, 126.20. IR (KBr, cm^{-1}): 3060 (Ar C-H), 2872 (Al C-H), 1601 (C=C), 1506 (C=N), 1448, 1242, 1071, 704. m/z found for ($C_{19}H_{20}N_2$): 276.2 (M+1).

1-(4-chlorophenyl)-4,5-diphenyl-1-H imidazole [11, section A].



M.P. 209-211°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (s,1H); δ 7.55-δ 7.03 (m, $3C_6H_5$); ^{13}C NMR (75 MHz, $CDCl_3$): 138.86, 137.08, 134.82, 133.99, 133.84, 130.77, 129.61, 129.50, 128.79, 128.58, 128.43, 128.27, 127.25, 126.93. IR (KBr, cm^{-1}): 3045 (Ar C-H), 1599 (C=C), 1497 (C=N), 1440, 1248, 1091, 698. m/z found for ($C_{21}H_{15}ClN_2$): 330.2 (M+1).

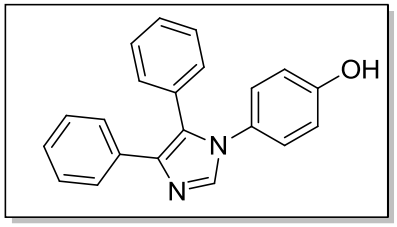
1-(4-methoxyphenyl)-4,5-diphenyl-1-H imidazole [12, section A].



M.P.180-182°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (s,1H); δ 7.76- δ 6.81 (m, $3C_6H_5$); δ 3.79 (s,3H); ^{13}C NMR (75 MHz, $CDCl_3$): 138.33, 137.42, 134.21, 130.81, 130.03, 129.22, 128.96, 128.56, 128.20, 128.10, 127.21, 127.13, 126.69. IR

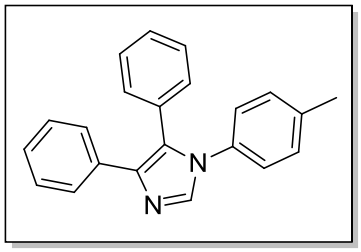
(KBr, cm^{-1}): 3047 (Ar C-H), 2837 (Al C-H), 1600 (C=C), 1515 (C=N), 1440, 1251, 1070, 698. m/z found for ($C_{22}H_{18}N_2O$): 326.8 (M+1).

4-(4,5-diphenyl-1H-imidazol-1-yl)phenol [13, section A]:



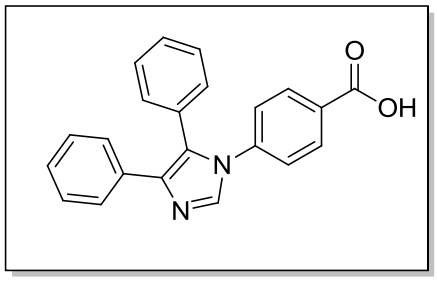
M.P. 218-220°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (s,1H); δ 7.50-δ 7.26 (m, $3C_6H_5$); δ 4.30 (s,1H); ^{13}C NMR (75 MHz, $CDCl_3$): 134.65, 132.45, 131.62, 128.64, 127.82, 127.55. IR (KBr, cm^{-1}): 3057 (Ar C-H), 1602 (C=C), 1512 (C=N), 1442, 1248, 1070, 698. m/z found for ($C_{21}H_{16}ON_2$): 312.1 (M+1).

4,5-diphenyl-1-p-tolyl-1H-imidazole [14, section A]:



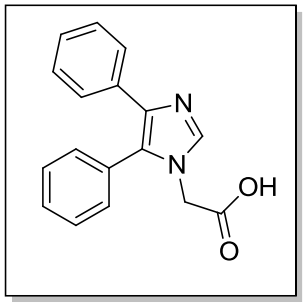
M.P.170-172°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (s,1H); δ 7.56-δ 6.98 (m, $3C_6H_5$); δ 2.34 (s,3H); ^{13}C NMR (75 MHz, $CDCl_3$): 138.44, 138.04, 137.30, 134.13, 133.76, 130.80, 130.01, 129.80, 128.74, 128.57, 128.21, 128.12, 127.24, 126.73, 125.58. IR (KBr, cm^{-1}): 3105 (Ar C-H), 1600 (C=C), 1515 (C=N), 1440, 1242, 1070, 698. m/z found for ($C_{22}H_{18}N_2$): 310.3 (M+1).

4-(4,5-diphenyl-1H-imidazol-1-yl)benzoic acid [15, section A]:



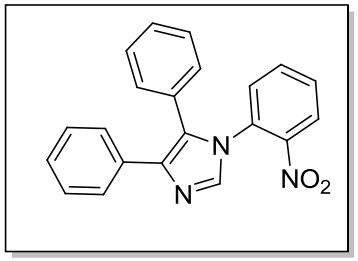
M.P. >270°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, 2H); δ 7.48 (s, 1H); δ 7.34-δ 7.18 (m, $2C_6H_5$); δ 3.42 (s,1H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.21, 130.84, 130.68, 128.84, 128.26, 127.19, 125.23. IR (KBr, cm^{-1}): 3057 (Ar C-H), 2852, 2551, 1683, 1604 (C=C), 1506 (C=N), 1430, 1292, 1070, 696. m/z found for ($C_{22}H_{16}N_2O_2$): 340.4 (M+1).

2-(4,5-diphenyl-1H-imidazol-1-yl)acetic acid [16, section A]:



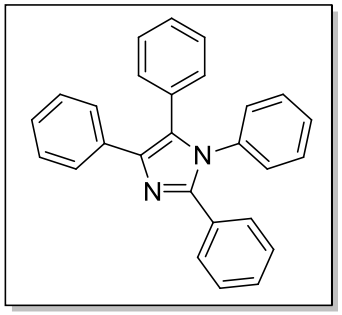
M.P. 173-175°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (s,1H); δ 7.56-δ 7.34 (m, $2C_6H_5$); δ 4.30 (s,1H); δ 3.50 (s,2H); ^{13}C NMR (75 MHz, $CDCl_3$): 148.77, 138.46, 131.08, 130.06, 129.33, 129.23, 128.90, 128.76, 128.46, 127.92, 127.41, 126.35. IR (KBr, cm^{-1}): 3055 (Ar C-H), 2825 (Al C-H), 1686, 1602 (C=C), 1506 (C=N), 1393, 1211, 1072, 696. m/z found for ($C_{17}H_{14}N_2O_2$): 278.5 (M+1).

1-(2-nitrophenyl)-4,5-diphenyl-1H-imidazole [17, section A]:



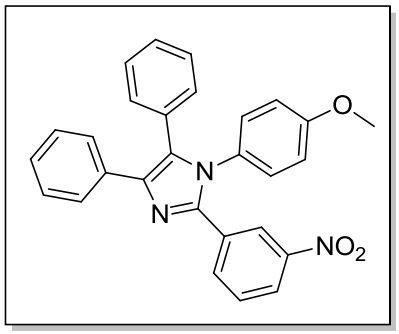
M.P. 206-208°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (s,1H); δ 7.46-δ 7.28 (m, 14H). IR (KBr, cm^{-1}): 3060(Ar C-H), 1652, 1602 (C=C), 1510 (C=N), 1442, 1070. m/z found for ($C_{21}H_{15}N_3O_2$): 341.8 (M+1).

1,2,4,5-tetraphenyl-1H-imidazole [18, section A]:



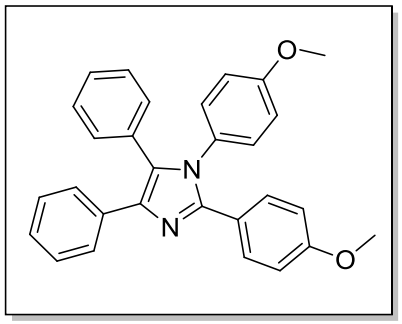
M.P. 215-217°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-δ 7.07 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): 146.91, 138.20, 137.04, 134.33, 131.10, 130.83, 130.57, 130.41, 129.02, 128.96, 128.40, 128.33, 12.28, 128.15, 128.09, 127.96, 127.41, 126.62. IR (KBr, cm^{-1}): 3057(Ar C-H), 1652, 1599(C=C), 1497 (C=N), 1442, 1074, 694. m/z found for ($C_{27}H_{20}N_2$): 372.4 (M+1).

1-(4-methoxyphenyl)-2-(3-nitrophenyl)-4,5-diphenyl-1H-imidazole [19, section A]:



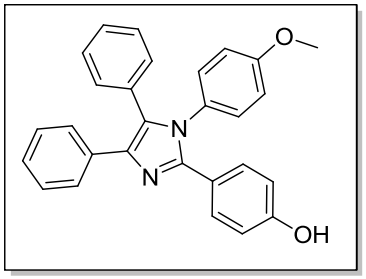
M.P.278-280°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s,1H); δ 8.12 (d, 1H); δ 7.88 (d, 1H); δ 7.59 (d, 2H); δ 7.49 (t, 1H); δ 7.26 (m, 9H); δ 7.02 (d, 2H); δ 6.83 (d, 2H); δ 3.79 (s,3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.79, 148.08, 1144.33, 134.40, 132.18, 131.09, 130.01, 129.92, 129.34, 129.19, 128.53, 128.38, 128.30, 127.36, 127.05, 123.49, 122.89, 114.76, 55.51. IR (KBr, cm^{-1}): 3057(Ar C-H), 1604(C=C),1527 (C=N), 1442, 1348, 1070, 698. m/z found for ($C_{28}H_{21}N_3O_3$): 447.1 (M+1)

1,2-bis(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole [20, section A]:



M.P. 158-160°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 - δ 6.74 (m,18H); δ 3.77 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.54, 159.03, 146.99, 137.73, 134.47, 131.13, 130.78, 130.67, 130.28, 129.92, 129.46, 128.31, 128.12, 127.82, 127.39, 126.49, 123.07. IR (KBr, cm^{-1}): 3057(Ar C-H), 2935 (Al C-H), 1608(C=C), 1512 (C=N), 1440, 698. m/z found for ($C_{29}H_{24}N_2O_2$): 432.4 (M+1).

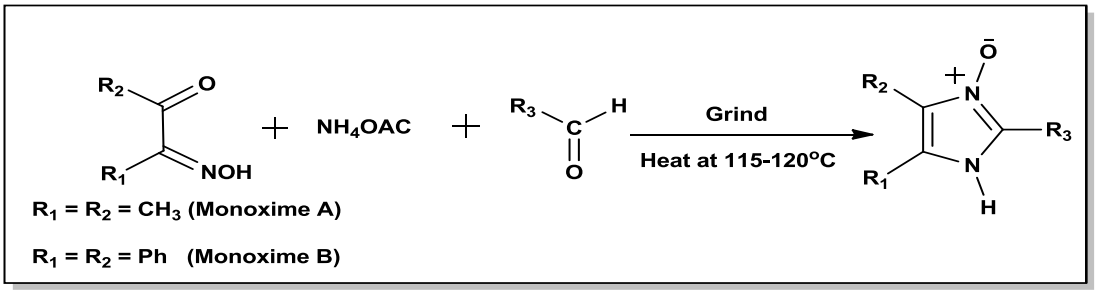
4-(1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-2-yl)phenol [21, section A]:



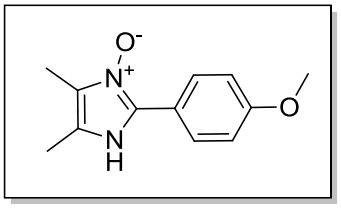
M.P. >280°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 - δ 6.76 (m, 19H); δ 3.80 (s, 3H). IR (KBr, cm^{-1}): 3037(Ar C-H), 1610(C=C), 1510 (C=N), 1442, 1070, 694. m/z found for ($C_{28}H_{22}N_2O_2$): 418.6 (M+1).

III.E.3. General procedure for the preparation of Imidazole N-oxide:

Monoxime (1 mmole), aldehyde (1 mmole) and ammonium acetate (5 mmole) were grinded into an intimate agate mortar and pestle under solvent-free condition. The mixture was then heated in an oil bath at 115-120^{o}C with constant shaking. A black solution obtained which was cooled until a black sticky precipitate formed; a small volume of diethyl ether was then added to this black precipitate when a brown precipitate formed. The precipitate was either thoroughly dissolved in ethanol or washed with ethyl acetate and pure product obtained through crystallization by the addition of water.

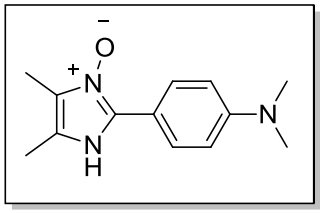


2-(4-methoxy phenyl)-4,5-dimethyl Imidazole N-oxide [22, section A]:



M.P. 138-140 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.35 (d, 2H); δ 6.96 (d, 2H); δ 3.77 (s, 1H); δ 2.05 (s, 4H); δ 1.79 (s, 2H): ^{13}C NMR (75 MHz, DMSO-d_6): 158.43, 127.08, 122.56, 122.06, 113.52, 55.03, 12.15, 7.50. IR (KBr, cm^{-1}): 3409 (N-H), 3152 (Ar C-H), 2921 (Al C-H), 1614 (C=C), 1507 (C=N), 1384, 1262, 1031. m/z found for ($C_{12}H_{14}N_2O_2$): 218.2 (M+1).

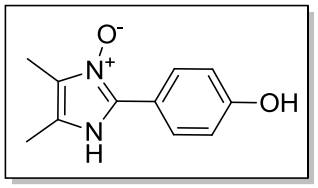
2-(4-N,N-dimethylphenyl)-4,5-dimethyl Imidazole N-oxide [23, section A]:



M.P. 233-235 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.01 (d, 2H); δ 7.26(s, 1H); δ 6.48 (d, 2H); δ 2.88 (s, 6H); δ 1.90 (s, 6H): ^{13}C NMR (75 MHz, DMSO-d_6): 150.54 ; 135.29; 127.73; 124.27; 119.69; 112.32; 111.38; 40.03, 9.56, 7.13. IR (KBr, cm^{-1}):

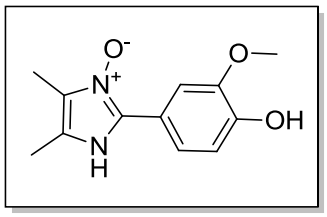
3390(N-H), 3050 (Ar C-H), 2921 (Al C-H), 1611 (C=C), 1508 (C=N), 1366, 1205, 1096 cm^{-1}; m/z found for ($C_{13}H_{17}N_3O$): 232.4 (M+1).

2-(4-hydroxy phenyl)-4,5-dimethyl Imidazole N-oxide [24, section A]:



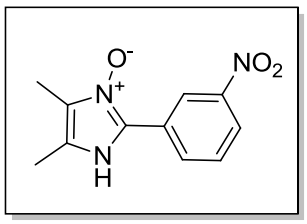
M.P. >260 ^oC, ^1H NMR (300 MHz, DMSO-d_6): δ 7.89 (d, 2H); δ 6.77 (d, 2H); δ 2.03 (s, 3H); δ 1.98 (s, 3H): ^{13}C NMR (75 MHz, DMSO-d_6): 157.18 ; 135.49; 127.21; 123.50; 122.66; 119.36; 114.92; 11.52, 7.28. IR (KBr): 3409(N-H), 3059 (Ar C-H), 2923 (Al C-H), 1654, 1614 (C=C), 1512 (C=N), 1380, 1286, 1095 cm^{-1}. m/z found for ($C_{11}H_{12}N_2O_2$): 204.1 (M+1).

2-(4-hydroxy-3-methoxyphenyl)-4,5-dimethyl Imidazole N-oxide [25, section A]:



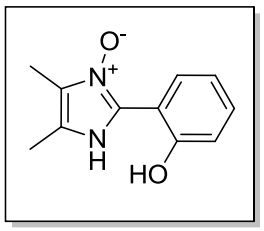
M.P.258-259^oC, ^1H NMR (300 MHz, DMSO-d_6): δ 7.76 (s, 1H); δ 7.55 (d, 2H); δ 6.75 (d, 2H); δ 2.03 (s, 3H); δ 1.96 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 147.04 ; 146.06; 135.25; 122.92; 120.41; 118.56; 114.96; 109.75, 55.31, 11.60; 7.36. IR (KBr, cm^{-1}): 3418(N-H), 3057 (Ar C-H), 2923 (Al C-H), 1648 (C=C), 1507 (C=N), 1438, 1279, 1038. m/z found for ($C_{12}H_{14}N_2O_3$): 234.5 (M+1).

2-(3-nitrophenyl)-4,5-dimethyl Imidazole N-oxide [26, section A]:



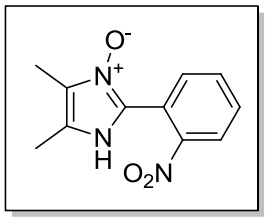
M.P.172-174 ^oC, ^1H NMR (300 MHz, DMSO-d_6): δ 8.01 (d, 2H); δ 8.81 (s, 1H); δ 8.20 (d, 1H); δ 7.86 (d, 1H); δ 7.50 (d, 1H) δ 1.96 (s, 3H); δ 1.90 (s, 3H);: ^{13}C NMR (75 MHz, DMSO-d_6): 147.49 ; 130.69; 129.35; 128.78; 127.37; 123.94; 118.84; 118.38, 12.07, 7.27. IR (KBr, cm^{-1}): 3390(N-H), 3076 (Ar C-H), 2732 (Al C-H), 1646 (C=C), 1523 (C=N), 1347, 1230, 1071 cm^{-1}. m/z found for ($C_{11}H_{11}N_3O_3$): 233.2 (M+1).

2-(2-hydroxyphenyl)-4,5-dimethyl Imidazole N-oxide [27, section A]:



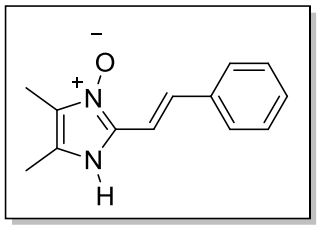
M.P.233-235 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52(d, 1H); δ 7.26(t, 1H); δ 6.88 (d, 2H); δ 2.15 (s, 3H); δ 2.06 (s, 3H); δ 1.77 (s, 1H): ^{13}C NMR (75 MHz, DMSO-d_6): 157.39 ; 134.28; 130.67; 127.37; 123.24; 123.10; 119.02; 118.21, 114.19, 10.16, 7.03. IR (KBr, cm^{-1}): 3400(N-H), 3047 (Ar C-H), 2904 (Al C-H), 1649, 1602 (C=C), 1496(C=N), 1305, 1269, 1154, 1087. m/z found for ($C_{11}H_{12}N_2O_2$): 204.1 (M+1).

2-(2-nitrophenyl)-4,5-dimethyl Imidazole N-oxide [28, section A]:



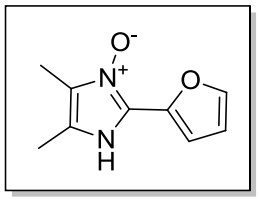
M.P.125-127 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.15 (d, 1H); δ 7.40 (t, 2H); δ 7.30 (t, 2H); δ 2.09 (s, 3H); δ 2.06 (s, 3H): ^{13}C NMR (75 MHz, DMSO-d_6): 135.32 ; 128.87; 128.14; 127.28; 125.57, 125.01, 123.63; 11.73; 7.40. IR (KBr, cm^{-1}): 3390(N-H), 3050 (Ar C-H), 2921 (Al C-H), 1611 (C=C), 1508 (C=N), 1366, 1205, 1096. m/z found for ($C_{11}H_{12}N_2O$): 188.1 (M+1).

(E)-4,5-dimethyl-2-styryl-1H-imidazole 3-oxide [29, section A]:



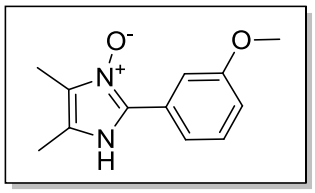
M.P. 116-118^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.90 (s, 1H); δ 8.45 (d, 2H); δ 8.20 (d, 2H); δ 7.30 (d, 1H); δ 7.22 (d, 1H): δ 2.24 (s, 3H); δ 2.14 (s, 3H). IR (KBr, cm^{-1}): 3419 (N-H), 3040 (Ar C-H), 2921 (Al C-H), 1652 (C=C), 1554 (C=N), 1407, 1234, 1143, 968, 833. m/z found for ($C_{13}H_{14}N_2O$): 214.6 (M+1).

2-(2-furyl)-4,5-dimethyl Imidazole N-oxide [30, section A]:



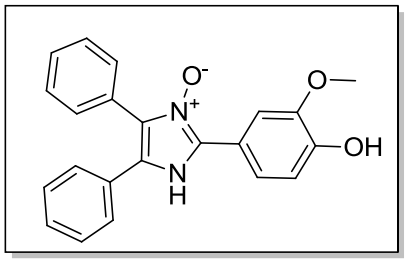
M.P. 95-97 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70 (d, 1H); δ 7.00 (t, 1H); δ 6.60 (d, 1H); δ 2.06 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 142.07 ; 124.89; 123.22; 111.54; 107.91; 11.49; 7.08. IR (KBr, cm^{-1}): 3466(N-H), 3085 (Ar C-H), 1559 (C=C), 1528 (C=N), 1400, 1280, 1005. m/z found for ($C_9H_{10}N_2O_2$): 178.5 (M+1).

2-(3-methoxyphenyl)-4,5-dimethyl Imidazole N-oxide [31, section A]:



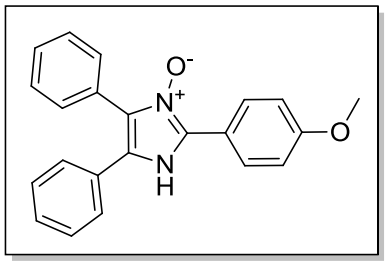
M.P.118-120 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78 (s, 1H); δ 7.65 (d, 1H); δ 7.30 (t, 1H); δ 6.85 (d, 1H); δ 3.70 (s, 3H); δ 2.08 (s, 3H); δ 2.08 (s, 3H): ^{13}C NMR (75 MHz, DMSO-d_6): 159.02 ; 134.19; 129.41; 128.90; 124.31; 123.96; 117.83; 113.61, 110.69, 54.97, 11.03, 7.19. IR (KBr, cm^{-1}): 3418 (N-H), 3076 (Ar C-H), 1603 (C=C), 1559 (C=N), 1404, 1238, 1108, 1034. m/z found for ($C_{12}H_{14}N_2O_2$): 218.2 (M+1).

2-(4-hydroxy-3-methoxyphenyl)-4,5-diphenyl Imidazole N-oxide [32, section A]:



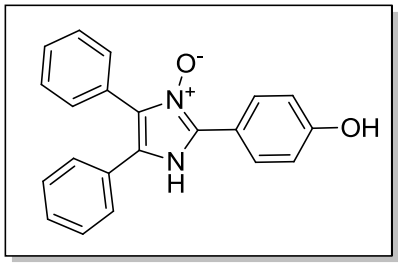
M.P.197-199 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.01 (s, 1H); δ 7.22-7.48 (m, 10H); δ 6.92, δ 6.80, δ 6.62, δ 5.08, δ 3.42 (s, 3H). IR (KBr, cm^{-1}): 3494 (N-H), 3050 (Ar C-H), 2939 (Al C-H), 1600 (C=C), 1496 (C=N), 1267, 1226, 1029. m/z found for ($C_{22}H_{18}N_2O_3$): 358.1 (M+1).

2-(4-methoxyphenyl)-4,5-diphenyl Imidazole N-oxide [33, section A]:



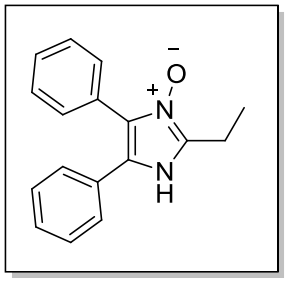
M.P. 95-96 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.11 (s, 1H), δ 7.20-7.53 (m, 10H), δ 7.06, δ 6.78, δ 6.32, δ 6.19, δ 5.54, 3.09 (s, 3H). IR (KBr, cm^{-1}): 3419 (N-H), 3057 (Ar C-H), 2829 (Al C-H), 1608 (C=C), 1494 (C=N), 1298, 1253, 1028, 835, 696. m/z found for ($C_{22}H_{18}N_2O_2$): 342.4 (M+1).

2-(4-hydroxyphenyl)-4, 5-diphenyl Imidazole N-oxide [34, section A]:



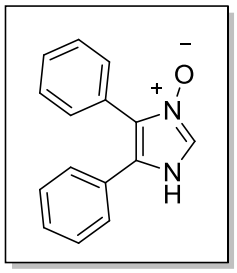
M.P.230-233 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.89 (s, 1H); δ 7.26-7.56 (m, 10H); δ 7.11, δ 6.48, δ 6.32, δ 6.12, δ 5.67 (s, 1H). IR (KBr, cm^{-1}): 3409 (N-H), 3045 (Ar C-H), 2790 (Al C-H), 1610 (C=C), 1492 (C=N), 1285, 1173, 836, 696. m/z found for ($C_{21}H_{16}N_2O_2$): 328.1 (M+1).

2-(2-ethyl)-4,5-diphenyl Imidazole N-oxide [35, section A]:



M.P.72-74 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.01 (s, 1H); δ 7.86-δ 7.48 (m, 10H); δ 2.59 (q, 2H); δ 1.24 (t, 3H): ^{13}C NMR (75 MHz, DMSO-d_6): 136.54 ; 129.29; 128.50; 127.27; 19.56, 17.13. IR (KBr, cm^{-1}): 3431 (N-H), 3062 (Ar C-H), 2921 (Al C-H), 1609 (C=C), 1488 (C=N), 1276, 834, 657. m/z found for ($C_{17}H_{16}N_2O$): 264.2 (M+1).

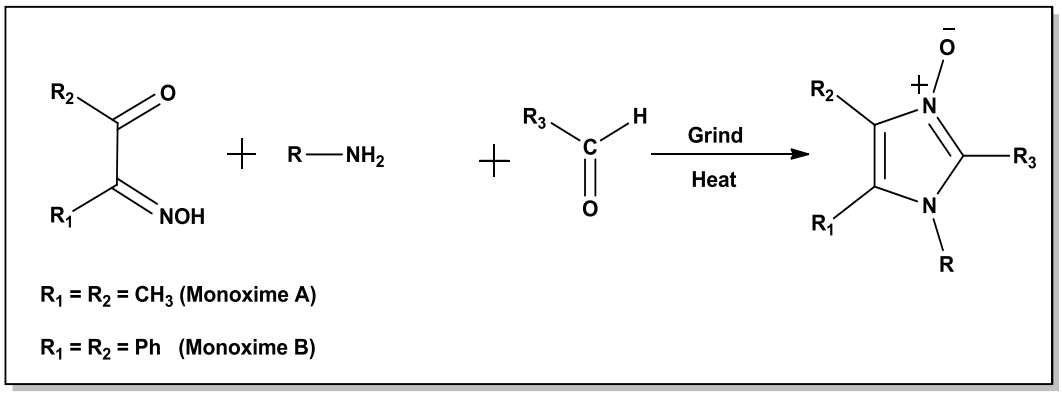
4,5-diphenyl-1H-Imidazole N-oxide [36, section A]:



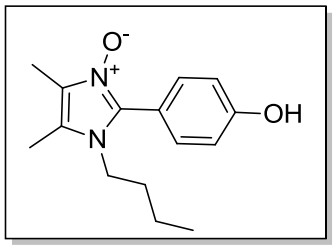
M.P.88-90 ^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (s,1H); δ 7.66- δ 7.34 (m, 10H); ^{13}C NMR (75 MHz, DMSO-d_6): 134.54, 132.26, 131.55, 128.66, 127.85, 129.14, 127.64. IR (KBr, cm^{-1}): 3487 (N-H), 3057 (Ar C-H), 1602 (C=C), 1512 (C=N), 1452, 1070, 698. m/z found for ($C_{15}H_{12}N_2O$): 236.0 (M+1).

III.E.4. General procedure for the preparation of *N*-substituted Imidazole-1-oxide:

Monoxime (1 mmole), aldehyde (1 mmole) and amine (1.5 mmole) were grinded for 2 minutes and followed by heated at 115-120^{o}C in an oil bath under solvent-free condition, when a melt is formed. After an additional 8 minutes of heating, the completion of reaction was checked by TLC plate. On cooling the melt slowly solidifies and to the product so formed was added a little amount of ether whereby a precipitate is obtained. The precipitate is further washed with hot ethyl acetate. Recrystallization from ethanol gave products with the same melting points.

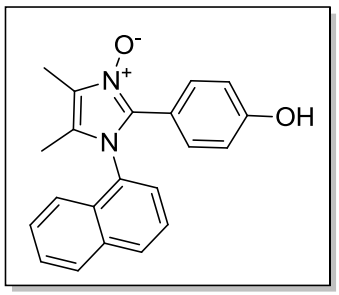


N-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide [37, section A]:



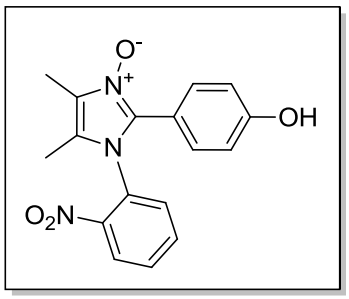
M.P. 128-130°C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.45(d, 2H); δ 6.85 (d, 2H); δ 3.84 (t, 2H); δ 2.22 (s, 3H); δ 2.06 (s, 3H) δ 1.43 (m, 2H); δ 1.06 (m, 2H); δ 0.71 (t, 3H): ^{13}C NMR (75 MHz, DMSO-d_6): 131.20, 124.16, 119.84, 115.35, 31.59, 18.91, 13.20, 8.53, 7.39. IR (KBr, cm^{-1}): 3047 (Ar C-H), 2958 (Al C-H), 1602(C=C), 1544(C=N), 1454, 1340, 1282, 1168, 839. m/z found for ($C_{15}H_{20}N_2O_2$): 260.15 (M+1).

N-napthyl-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide [38, section A]:



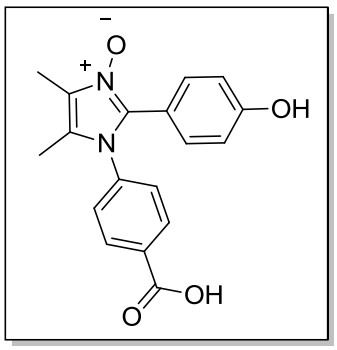
M.P.232-235 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.62 - δ 7.95 (m, 11H); δ 2.00 (t, 6H). IR (KBr, cm^{-1}): 3058(Ar C-H), 2925 (Al C-H), 1587(C=C), 1560(C=N), 1510, 1454, 1388, 1245, 1170, 839. m/z found for $C_{21}H_{18}N_2O_2$): 330.14 (M+1).

N-(2-nitrophenyl)-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide [39, section A]:



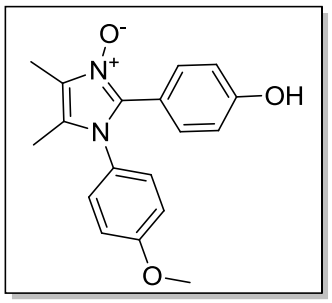
M.P. 272-273 °C, IR (KBr, cm^{-1}): 3200(Ar C-H), 2929 (Al C-H), 1593(C=C), 1510(C=N), 1438, 1350, 1259, 1172, 1105, 837. m/z found for ($C_{17}H_{15}N_3O_4$): 325.32 (M+1).

1-(4-carboxyphenyl)-2-(4-hydroxyphenyl)-4,5-dimethyl-1H-imidazole 3-oxide [40, section A]:



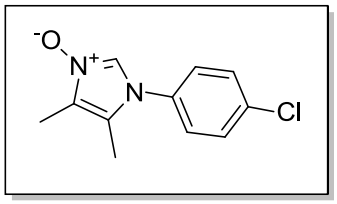
M.P. 210-213 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.86 (s, 1H); δ 6.55 - δ 8.10 (m, 8H); δ 4.06 (s, 1H) δ 1.95 (s, 3H); δ 1.76 (s, 3H): ^{13}C NMR (75 MHz, DMSO-d_6): 196.85, 155.08, 132.10, 131.18, 112.49, 59.80, 24.82, 20.72, 7.91. IR (KBr, cm^{-1}): 3219, 2808, 1685, 1605, 1440, 1377, 1280, 1172, 1010, 837. m/z found for ($C_{18}H_{16}N_2O_4$): 324.5 (M+1).

N-(4-methoxyphenyl)-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide [41, section A]:



M.P. 205-207 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.20 (d, 2H); δ 6.95 (d, 2H); δ 6.56 (d, 4H); δ 3.73 (s, 3H) δ 2.10 (s, 3H); δ 1.92 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 159.15, 130.61, 129.44, 124.67, 115.05, 114.63, 59.79, 55.34, 14.02, 9.08, 7.47. IR (KBr, cm^{-1}): 3170 (Ar C-H), 2929 (Al C-H), 1608(C=C), 1512(C=N), 1461, 1251,1172, 1031, 833. m/z found for ($C_{13}H_{17}N_3O$): 310.2 (M+1).

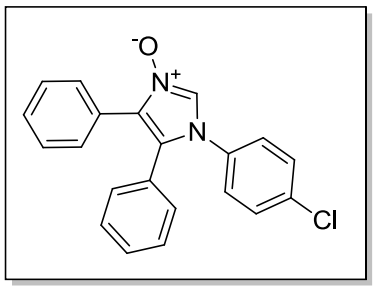
1-(4-chlorophenyl)-4,5-dimethyl -1H- Imidazole 3-oxide [42, section A]:



M.P. 238-240 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50 (d, 2H); δ 7.32 (d, 2H); δ 1.92 (s, 3H); δ 1.80 (s, 3H): ^{13}C NMR (75 MHz, DMSO-d_6): 152.33, 134.36,

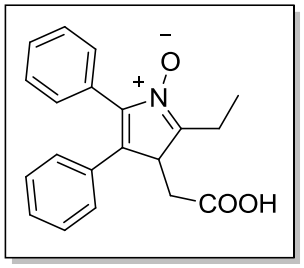
131.13, 128.78, 128.32, 112.94, 112.82, 9.02. IR (KBr, cm^{-1}): 3037 (Ar C-H), 2881 (Al C-H), 1676, 1595 (C=C), 1497 (C=N), 1444, 1394, 1240, 1089, 829. m/z found for ($C_{11}H_{11}N_2OCl$): 222.3 (M+1).

1-(4-chlorophenyl)-4,5-diphenyl -1H- Imidazole 3-oxide [43, section A]:



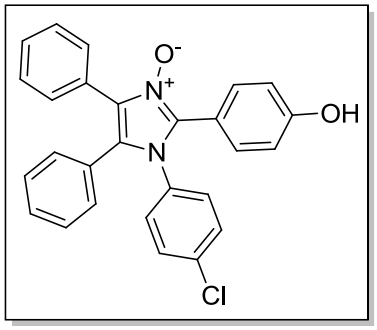
M.P. 170-172°C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.42-7.22 (m, 2H); δ 7.12 (t, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 136.23, 134.31, 130.53, 129.78, 128.32, 127.94. IR (KBr, cm^{-1}): 3064 (Ar C-H), 2956 (Al C-H), 1679, 1596 (C=C), 1498 (C=N), 1446, 1367, 1228, 1097, 908. m/z found for ($C_{21}H_{15}N_2OCl$): 346.1 (M+1).

1-(glycinato)-2-ethyl-4,5-diphenyl Imidazole 3-oxide [44, section A]:



M.P. >260 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.01 (s, 1H); δ 7.48, δ 7.32, δ 7.13 , δ 4.67, δ 2.87, δ 1.25. IR (KBr, cm^{-1}): 3105(Ar C-H), 2952 (Al C-H), 1625, 1595 (C=C), 1498 (C=N), 1436, 1394, 1334, 1126, 1043, 929. m/z found for ($C_{19}H_{18}N_2O_3$): 322.5 (M+1).

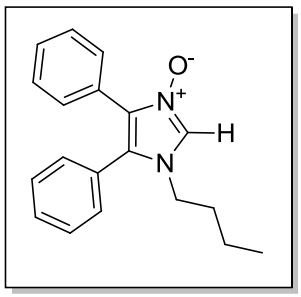
1-(4-chlorophenyl)-2-(4-hydroxyphenyl)-4,5-diphenyl Imidazole 3-oxide [45, section A]:



M.P. 182-184 °C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50 - δ 7.20 (m, ArH); δ 6.65 (d, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 157.89, 136.65, 134.13,

130.78, 129.10, 128.94, 127.43, 116.76. IR (KBr, cm^{-1}): 3057 (Ar C-H), 2885 (Al C-H), 1602, 1573 (C=C), 1485 (C=N), 1442, 1388, 1284, 1161, 1101, 1008, 902, 835. m/z found for ($C_{27}H_{19}N_2O_2Cl$): 438.7 (M+1).

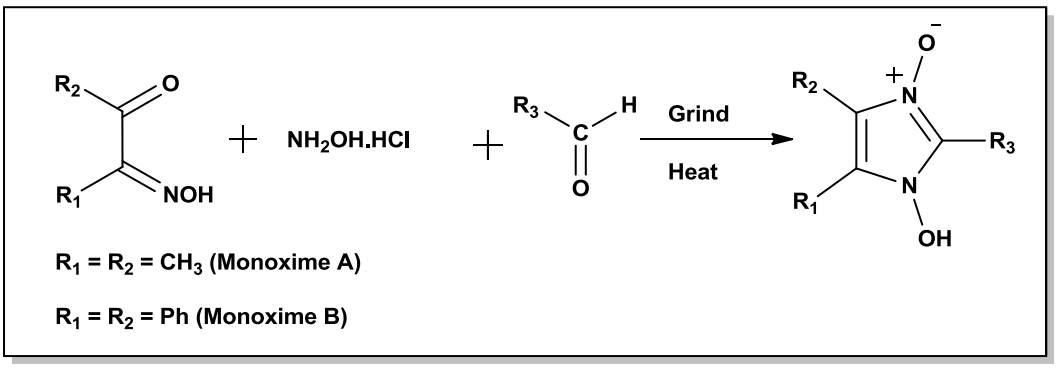
1-butyl-4,5-diphenyl-1H-imidazole 3-oxide [46, section A]:



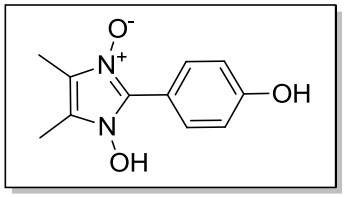
M.P. 248-250 ^oC, ^1H NMR (300 MHz, DMSO-d_6): δ 7.50 -δ 7.12 (m, ArH); δ 6.79 (d, 2H); δ 3.73, δ 1.77 δ 1.25 δ 1.02. IR (KBr, cm^{-1}): 3051(Ar C-H), 2931 (Al C-H), 1606, 1487 (C=C), 1458 (C=N), 1400, 1340, 1286, 1172, 837. m/z found for ($C_{25}H_{24}N_2O_2$): 384.2 (M+1).

III.E.5. General procedure for the preparation of 1-hydroxy Imidazole-3-oxide:

Monoxime (2 mmole) and aldehyde (2mmole) are thoroughly grinded with hydroxylamine hydrochloride (10 mmole) in an intimate mixture agate mortar and pestle under solvent-free condition for a period of 3 minutes throughout which it melts and then gets hardened gradually. The mixture is then converted to a test tube and heated at 110-120^oC in an oil bath when it starts to melt. Constant shaking for further 7 minutes gives the desired product which stays on in the melt form yet at room temperature. On completion of reaction, checked by TLC plate, addition of 5 ml of ethyl acetate or 5 ml of diethyl ether precipitates the product. The products which are insoluble in water are then separated by washing with ethyl acetate and water to get the desired pure products. The products which are soluble in water **[48]** are washed with ethyl acetate and D.E.E and then the products are dissolved in water and slight warmed. The pure product is crystallized slowly on cooling on ice. The pure products **[51]** and **[52]** are appeared by dissolving the precipitated in alcohol followed by addition of ethyl acetate.

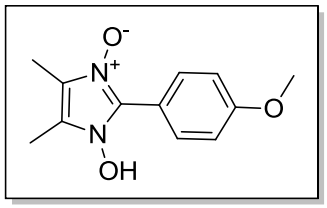


1-hydroxy-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide [47, section A]:



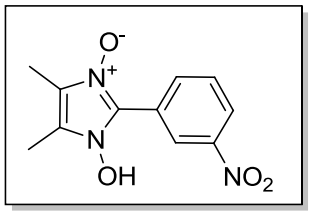
M.P. 165-168 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.86 (d, 2H); δ 7.04 (d, 2H); δ 2.27 (s, 6H), δ 2.19 (s, 1H): ^{13}C NMR (75 MHz, DMSO-d_6): 160.83, 135.26, 131.83, 122.09, 116.06, 110.68, 7.64. IR (KBr, cm^{-1}): 3400, 3000 (Ar C-H), 2671 (Al C-H), 1611, 1560 (C=C), 1446 (C=N), 1385, 1252, 1178, 1087, 1000, 837 cm^{-1}. m/z found for ($C_{11}H_{12}N_2O_3$): 220.0 (M+1)

1-hydroxy-2-(4-methoxyphenyl)-4,5-dimethyl Imidazole 3-oxide [48, section A]:



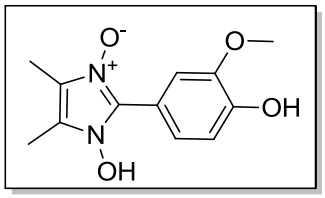
M.P. 196-198 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.12 (d, 2H); δ 6.93 (d, 2H); δ 3.78 (s, 3H), δ 1.83 (s, 6H): ^{13}C NMR (75 MHz, DMSO-d_6): 159.10, 129.10, 119.11, 113.21, 55.49, 7.41. IR (KBr, cm^{-1}): 3418, 3003 (Ar C-H), 2929 (Al C-H), 1610, 1541 (C=C), 1444(C=N), 1380, 1296, 1256, 1182, 1026, 837 cm^{-1}. m/z found for ($C_{12}H_{14}N_2O_3$): 234.1 (M+1).

1-hydroxy-2-(3-nitrophenyl)-4,5-dimethyl Imidazole 3-oxide [49, section A]:



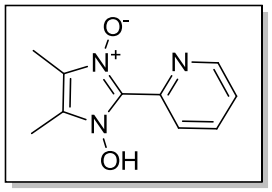
M.P. 209-211 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.22 (s, 1H); δ 8.72 (d, 1H); δ 8.05 (d, 1H), δ 7.58 (t, 1H), δ 1.91. IR (KBr, cm^{-1}): 3428, 3088 (Ar C-H), 2927 (Al C-H), 2580, 1634, 1530(C=C), 1435(C=N), 1355, 1284, 1248, 812 cm^{-1}. m/z found for ($C_{11}H_{11}N_3O_4$): 249.1 (M+1).

1-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4,5-dimethyl Imidazole 3-oxide [50, section A]:



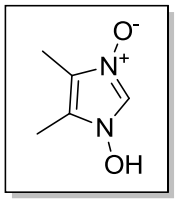
M.P. 201-203 ^{o}C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.52 (s, 1H); δ 8.19 (d, 2H); δ 6.65 (d, 2H), δ 3.66 (s, 3H), δ 2.02. IR (KBr, cm^{-1}): 3390, 3076 (Ar C-H), 2928 (Al C-H), 1636, 1596 (C=C), 1493(C=N), 1388, 1279, 1205, 1177, 1031, 856 cm^{-1}. m/z found for ($C_{12}H_{14}N_2O_4$): 250.1 (M+1).

1-hydroxy-2-(2-pyridyl)-4, 5-dimethyl Imidazole 3-oxide [51, section A]:



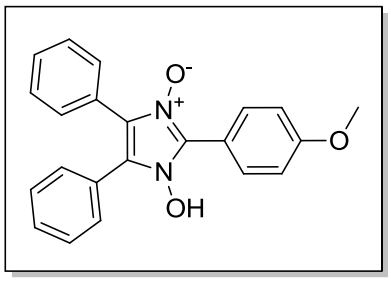
Hygroscopic. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.71 (d, 1H); δ 8.28 (t, 1H); δ 8.06 (t, 1H), δ 7.76 (d, 1H), δ 2.26; ^{13}C NMR (75 MHz, DMSO-d_6): 148.30, 145.34, 144.92, 143.10, 126.18, 123.48, 122.91, 7.59. IR (KBr, cm^{-1}): 3400, 3085 (Ar C-H), 2667 (Al C-H), 1621, 1578 (C=C), 1456(C=N), 1404, 1287, 1194, 1158, 1088, 998, 779 cm^{-1}. m/z found for ($C_{10}H_{11}N_3O_2$): 205.9 (M+1).

1-hydroxy-4, 5-dimethyl-1H-Imidazole 3-oxide [52, section A]:



M.P. 136-137 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.21 (s, 1H); δ 1.96 (s, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): 122.67, 7.32. IR (KBr, cm^{-1}): 3300, 3085 (Ar C-H), 2667 (Al C-H), 1886, 1573 (C=C), 1474(C=N), 1404, 1194, 1164, 1091, 997 cm^{-1}. m/z found for ($C_5H_8N_2O_2$): 128.6 (M+1).

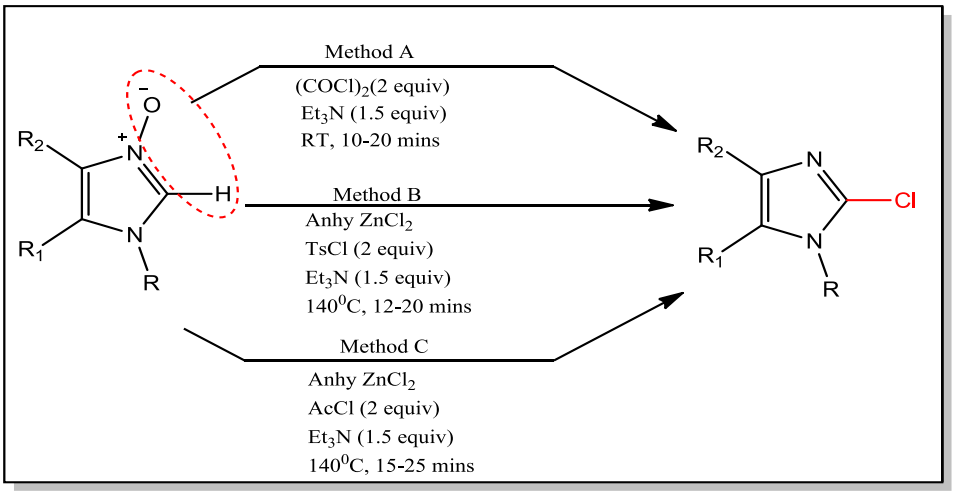
1-hydroxy-2-(4-methoxyphenyl)-4,5-diphenyl Imidazole 3-oxide [53, section A]:



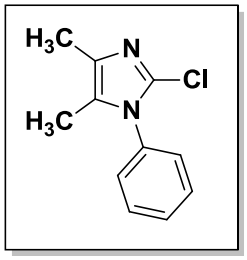
M.P. 233-235 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.82, δ 7.48, δ 7.27, δ 6.90, δ 3.36 (s, 3H). IR (KBr, cm^{-1}): 3431, 3055 (Ar C-H), 2835 (Al C-H), 1608, 1575 (C=C), 1488(C=N), 1442, 1394, 1301, 1255, 1087, 1029 cm^{-1}. m/z found for ($C_{22}H_{18}N_2O_3$): 358.3 (M+1).

III.E.6. General procedure for chlorination at C-2 position of substituted imidazole:

Imidazole *N*-oxide (1 mmol), oxalyl chloride (2 mmol) and triethylamine (1.5 mmol) were mixed intimately in an agate mortar and pestle for a period of 10-20 min under solvent-free condition. The reaction mixture was then dissolved in dichloromethane (2 ml), washed with water and finally dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the residue, which was chromatographed over silica gel column and elution with petroleum ether/ethyl acetate mixture to furnish the desired 2-chloroimidazole.

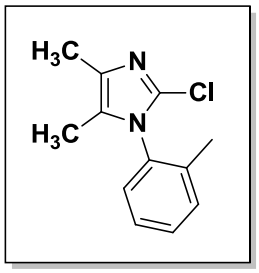


2-chloro-4, 5-dimethyl-1-phenyl-1H-imidazole [2a, section B]:



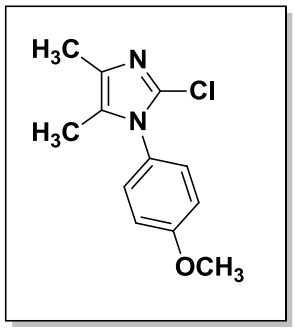
Yield 93%, white solid, mp 53-56 °C, IR (KBr, cm^{-1}): 3049, 2916, 1601, 1490, 1461, 1392, 1279, 989, 756, 697. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.60-7.53 (3H, m, Ar-H), 7.39-7.35 (2H, m, Ar-H), 2.09 (3H, s, -CH_3), 1.92 (3H, s, -CH_3). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 135.5, 132.7, 130.1, 129.7, 128.3, 128.2, 126.1, 12.9 and 9.8. ESI MS (m/z) $[M+H]^+$: 207.

2-chloro-4, 5-dimethyl-1-*o*-tolyl-1H-imidazole [2b, section B]:



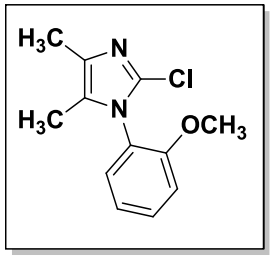
Yield 83%, white solid, mp 67-70 °C, IR (KBr, cm^{-1}): 3054, 2921, 1717, 1496, 1459, 1388, 1314, 1154, 1039, 758. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.50-7.27 (4H, m, Ar-H), 2.08 (3H, s, -CH_3), 1.96 (3H, s, -CH_3), 1.83 (3H, s, -CH_3). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 135.7, 133.8, 131.9, 131.1, 130.0, 128.3, 127.7, 127.3, 125.5, 16.6, 12.3 and 8.9. ESI MS (m/z) $[M+H]^+$: 221.

2-chloro-1-(4-methoxyphenyl)-4,5-dimethyl-1H imidazole [2c, section B]:



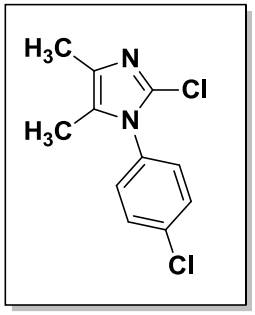
Yield 89%, yellowish white solid, mp 76-80 °C, IR (neat, cm^{-1}): 2921, 1606, 1510, 1459, 1383, 1252, 1174, 1036, 837. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.29 (2H, d, *J* = 9 Hz, Ar-H), 7.09 (2H, d, *J* = 9 Hz, Ar-H), 3.83 (3H, s, $-OCH_3$), 2.08 (3H, s, $-CH_3$), 1.93 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 159.9, 132.8, 129.8, 128.8, 128.2, 125.8, 114.6, 55.5, 12.7 and 9.7. ESI MS (m/z) $[M+H]^+$: 237.

2-chloro-1-(2-methoxyphenyl)-4,5-dimethyl-1H-imidazole [2d, section B]:



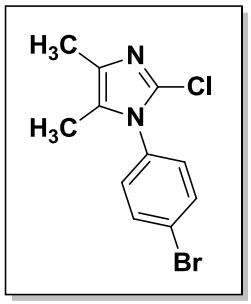
Yield 85%, yellowish white solid, mp 76-80 °C, IR (neat, cm^{-1}): 2926, 1719, 1599, 1505, 1464, 1392, 1272, 1021, 753. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.40 (2H, t, Ar-H), 7.07 (1H, d, *J* = 7.8 Hz, Ar-H), 6.98 (1H, d, *J* = 6.6 Hz, Ar-H), 3.71 (3H, s, $-CH_3$), 2.11 (3H, s, $-CH_3$), 1.83 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 155.6, 132.7, 131.3, 130.1, 129.8, 126.4, 124.3, 121.1, 112.6, 56.1, 12.9 and 9.6. ESI MS (m/z) $[M+H]^+$: 237.

2-chloro-1-(4-chlorophenyl)-4, 5-dimethyl-1H-imidazole [2e, section B]:



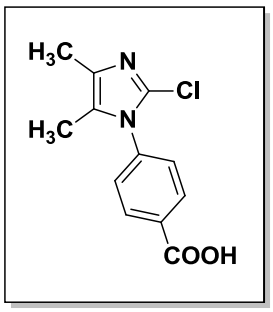
Yield 93%, yellowish white solid, mp 82-85 °C, IR (KBr, cm^{-1}): 3059, 2921, 1496, 1459, 1378, 1272, 1085, 987, 842, 650. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.49 (2H, d, *J* = 8.4 Hz, Ar-H), 1.18 (2H, d, *J* = 8.4 Hz, Ar-H), 2.20 (3H, s, $-CH_3$), 1.96 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 135.5, 134.2, 133.7, 130.0, 129.2, 127.5, 125.6, 12.9 and 9.9. ESI MS (m/z) $[M+H]^+$: 241.

1-(4-bromophenyl)-2-chloro-4, 5-dimethyl-1H-imidazole [2f, section B]:



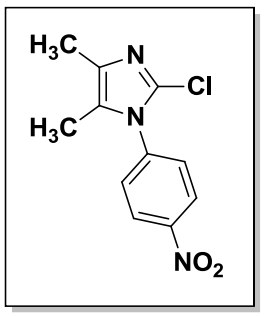
Yield 91%, yellow solid, mp 117-120 °C, IR (KBr, cm^{-1}): 3049, 2921, 1604, 1491, 1459, 1380, 1270, 1068, 984, 842. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.761 (2H, d, *J* = 1.8 Hz, Ar-H), 7.38 (2H, d, *J* = 4.5 Hz, Ar-H), 2.08 (3H, s, -CH_3), 1.92 (3H, s, -CH_3). ^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 134.7, 133.1, 132.9, 130.4, 128.3, 126.1, 123.0, 12.9 and 9.8. ESI MS (m/z) $[M+H]^+$: 287.

4-(2-chloro-4, 5-dimethyl-1H-imidazol-1-yl) benzoic acid [2g, section B]:



Yield 93%, white solid, mp 49-53 °C, IR (neat, cm^{-1}): 3423, 3024, 2923, 2862, 1489, 1181, 1080, 1016, 803, 485. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.39 (2H, d, *J* = 8.1 Hz, Ar-H), 7.10 (2H, d, *J* = 7.8 Hz, Ar-H), 2.32 (3H, s, -CH_3), 1.40 (3H, s, -CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 169.5, 149.0, 138.5, 138.0, 134.5, 134.0, 129.8, 128.6, 29.9 and 21.0. ESI MS (m/z) $[M+H]^+$: 251.

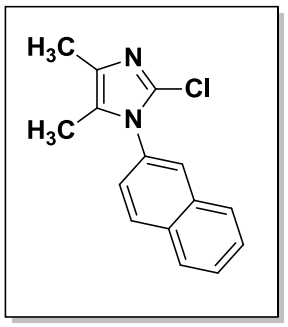
2-chloro-4, 5-dimethyl-1-(4-nitrophenyl)-1H-imidazole [2h, section B]:



Yield 95%, yellow solid, mp 132-135 ^{o}C, IR (KBr, cm^{-1}): 3369, 3135, 2921, 1628, 1596, 1474, 1299, 1110, 837. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 7.76 (2H, d, *J* = 8.4 Hz, Ar-H), 7.50 (2H, d, *J* = 8.1 Hz, Ar-H), 2.50 (3H, s, -CH_3), 2.42 (3H, s, -CH_3).

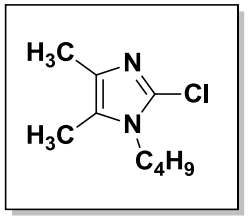
^{13}C NMR (75 MHz, DMSO-d_6), δ, ppm: 148.5, 144.9, 132.3, 130.1, 128.0, 127.5, 125.4, 24.4 and 21.1. ESI MS (m/z) $[M+H]^+$: 251.

2-chloro-4,5-dimethyl-1-(napththalen-2-yl)-1H-imidazole [2i, section B]:



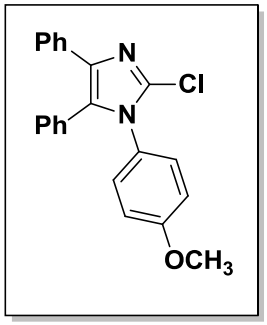
Yield 93%, yellow solid, mp 68-73 °C, IR (neat, cm^{-1}): 3060, 2921, 1717, 1599, 1456, 1395, 1279, 1031, 820, 751, 662. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.92-7.20 (7H, m, Ar-H), 2.17 (3H, s, -CH_3), 1.92 (3H, s, -CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 133.5, 133.4, 133.0, 132.8, 130.0, 129.8, 128.5, 128.2, 127.7, 127.6, 127.0, 126.2, 125.2, 12.7 and 10.0. ESI MS (m/z) $[M+H]^+$: 256.

1-butyl-2-chloro-4, 5-dimethyl-1H-imidazole [2j, section B]:



Yield 85%, liquid, IR (neat, cm^{-1}): 2965, 2926, 1702, 1474, 1447, 1380, 1134, 805, 665. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 3.79 (2H, t, -CH_2-), 2.1 (6H, s, -CH_3), 1.63 (2H), 1.4 (2H), 0.95 (3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 133.0, 129.1, 124.1, 44.6, 32.5, 20.2, 14.0, 12.9 and 9.6. ESI MS (m/z) $[M+H]^+$: 187.

2-chloro-1-(4-methoxyphenylphenyl)-4,5-diphenyl-1H-imidazole [2k, section B]:

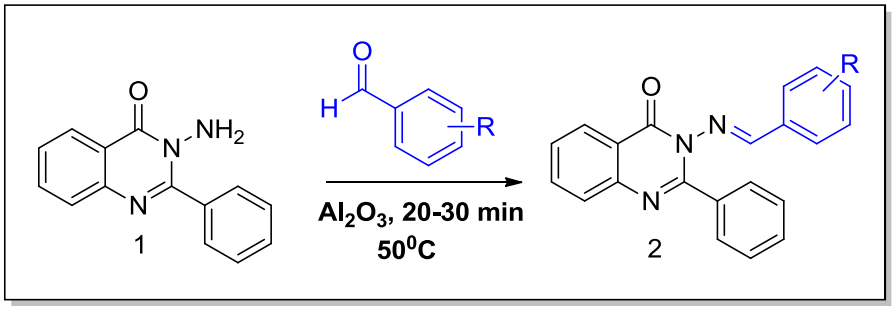


Yield 95%, white solid, mp 195-200 ºC, IR (KBr, cm^{-1}), 3049, 2960, 1596, 1496, 1478, 1392, 1252, 1174, 1029, 837, 776, 697. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 7.51-6.85 (14H, m, Ar-H), 3.80 (3H, s, -OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm:

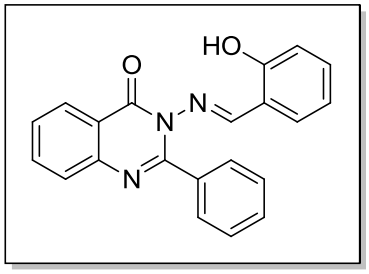
159.6, 137.4, 133.6, 130.7, 129.9, 129.2, 128.5, 128.1, 127.0, 126.8, 114.2 and 55.4. ESI MS (m/z) $[M+H]^+$: 360.

III.E.7. General procedure for substituted-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one using alumina as a catalyst:

A mixture of 3-amino-2-phenylquinazolin-4(3H)-one (1 mmol), substituted aromatic aldehyde (1 mmol) and alumina (4 equiv w.r.t. stating substance) were mixed intimately in an agate mortar and pestle for a period of 20-30 min under solvent-free condition. Then the mixture was heated in an oil bath at 50°C. To this mixture, a few ml of water was added, filtered and dried the mass in an oven until to dryness. Then dried mass was dissolved in ethanol and collect the filtrate and evaporation of the solvent afforded the residue as a pure product. Purity of the product was cheeked by TLC on TLC plate.

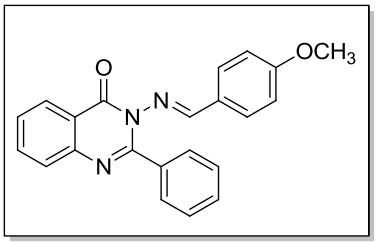


3-{[(2-Hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2a, section C]:



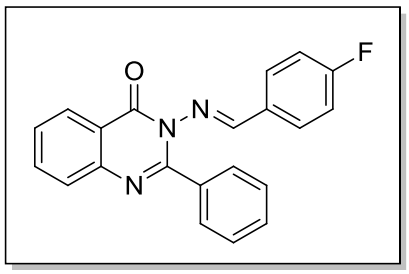
Yield 75%; mp 233°C; IR (cm^{-1}): 3200-3100, 1681, 1604, 1467; ^{1}H-NMR: 6.69-8.36 (13H, m, Ar-H), 9.19 (1H, s, H-C=N), 9.99 (OH, H-bonded), ^{13}C-NMR: 116.4, 117.5, 119.7, 121.5, 127.3, 127.4, 128.0, 128.9, 130.3, 132.5, 133.3, 134.2, 134.8, 146.4, 153.6, 159.1, 159.7, 164.7, Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89%; H, 4.45%; N, 12.31%; found: C, 74.10%; H, 4.45%; N, 12.28%. FAB MS (m/z): 342 (M+1).

3-{[(4-Methoxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2b,section C]:



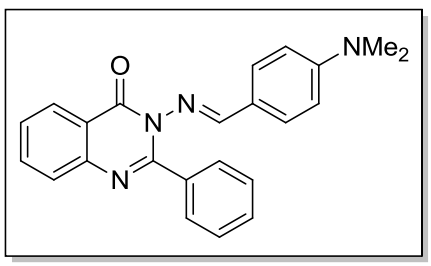
Yield 80%; m.p. 210°C; IR (cm^{-1}): 1679, 1602, 1448, 1494, 1257, 1170; ^{1}HNMR: 3.84 (3H, s, -OCH_3), 7.37-8.36 (13H, m, Ar-H), 8.87 (1H, s, H-C=N-N); ^{13}C-NMR: 55.4, 114.3, 121.5, 125.9, 126.9, 127.3, 127.7, 127.9, 129.9, 129.9, 130.7, 134.4, 134.7, 146.5, 159.4, 163.0, 164.0, 166.5, Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35%, H, 4.82%, N, 11.82%; found: C, 74.40%, H, 4.90%, N, 11.78%. FAB MS (m/z): 356(M+1).

3-{[(4-Fluorophenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2c, section C]:



Yield 90%; m.p. >200°C; IR (cm^{-1}): 1674, 1614, 1593, 1554, 1537, 1469, 1373, 1184; ^{1}H-NMR: 7.10-8.70 (13H, m, Ar-H), 9.04 (1H, s, H-C=N); ^{13}C-NMR: 166.3, 164.8, 153.9, 153.9, 146.6, 134.5, 134.1, 131.0, 130.9, 130.5, 129.3, 128.9, 127.7, 127.2, 126.8, 121.5, 116.3; Anal. Calcd. for $C_{21}H_{14}N_3OF$: C, 73.46%, H, 4.11%, N, 12.24%; found: C, 73.50%, H, 4.10%, N, 12.18%. FAB MS (m/z): 344(M+1).

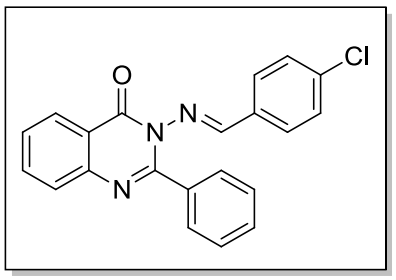
3-{[4-Dimethylaminophenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2d, section C]:



Yield 75%; m.p. 240°C; IR (cm^{-1}): 1681, 1589, 1556, 1508, 1456, 1375, 1328, 1313; ^{1}H-NMR: 3.04 (-N-CH3), 6.68-8.70 (13H, m, Ar-H), 8.67 (1H, s, H-C=N); ^{13}C-NMR: 187.6, 159.8, 154.0, 153.0, 146.7, 134.8, 134.1, 130.7, 129.7, 129.3, 127.9, 127.7, 127.2, 126.8, 121.6, 120.3, 111.5, 40.1; Anal. Calcd. for $C_{23}H_{20}N_4O$: C,

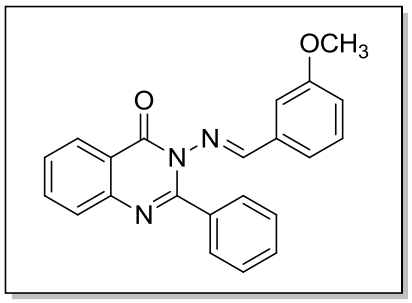
74.98%, H, 5.47%, N, 15.2%; found: C, 74.99%, H, 5.50%, N, 15.13%. FAB MS (m/z): 344(M+1).

3-{[4-Chloroyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2e, section C]:



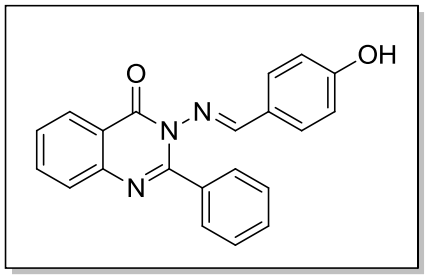
Yield 85%; m.p. 196°C; IR (cm^{-1}): 1679, 1591, 1554, 1377; ^{1}H-NMR: 7.37-8.36 (13H, m, Ar-H), 9.10 (1H, s, H-C=N); ^{13}C-NMR: 121.5, 127.1, 127.3, 127.9, 127.9, 129.2, 129.8, 129.9, 130.0, 131.7, 134.4, 134.8, 138.5, 146.5, 154.0, 159.2, 164.4; Anal. Calcd. for $C_{21}H_{14}N_3OCl$: C, 70.10%; H, 3.92%; N, 11.68%; found: C, 70.20%; H, 4.10%; N, 11.62%. FAB MS (m/z): 360(M+1).

3-{[3-Methoxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2f, section C]:



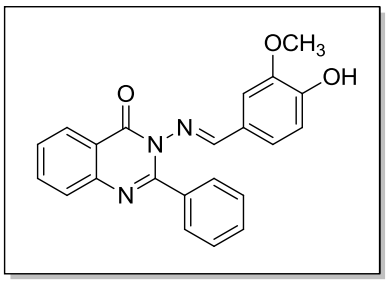
Yield 82%; m.p. 234°C; IR (cm^{-1}): 1679, 1575, 1465, 1367, 1317, 1276; ^{1}HNMR: 3.74 (3H, s, -OCH_3), 7.30-8.37 (13H, m, Ar-H), 9.09 (1H, s, H-C=N-N); ^{13}C-NMR: 111.7, 119.1, 121.7, 121.8, 122.3, 127.0, 127.3, 127.9, 128.1, 128.2, 129.8, 134.2, 134.5, 134.9, 146.5, 154.1, 159.3, 159.9, 165.5; Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35%; H, 4.28%; N, 11.82%; found: C, 74.45%; H, 4.35%; N, 11.78%. FAB MS (m/z): 356(M+1).

3-{[(4-Hydroxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2g, section C]:



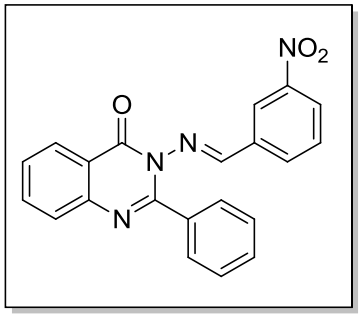
Yield 80%; m.p. 233°C; IR (cm^{-1}): 3307, 3213, 1668, 1645, 1604, 1554, 1375, 1338; ^{1}H-NMR: 5.03 (-OH), 7.42-8.29 (13H, m, Ar-H), 9.16 (1H, s, H-C=N-N); ^{13}C-NMR: 110.0, 120.1, 126.6, 127.0, 127.8, 128.2, 129.2, 130.3, 133.9, 134.5, 134.5, 143.1, 149.0, 149.9, 155.0, 161.5; Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89%; H, 4.43%; N, 12.31%; found: C, 73.99%; H, 4.49%; N, 12.30%. FAB MS (m/z): 342(M+1).

3-{[(4-Hydroxy-3-methoxyphenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2h, section C]:



Yield 70%; m.p. >240°C; IR (cm^{-1}): 3305, 3215, 1749, 1712, 1664, 1575, 1467, 1377; ^{1}H-NMR: 3.81 (3H, s, -OCH_3), 5.03 (-OH), 6.92-8.30 (12H, m, Ar-H), 8.90 (1H, s, H-C=N-N); ^{13}C-NMR: 55.9, 108.7, 114.5, 125.4, 126.4, 126.6, 127.0, 127.3, 127.8, 128.2, 129.3, 129.9, 130.3, 134.5, 143.2, 146.7, 147.3, 154.4, 159.8; Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15%; H, 4.61%; N, 11.31%; found: C, 71.25%; H, 4.65%; N, 11.26%. FAB MS (m/z) : 372 (M+1).

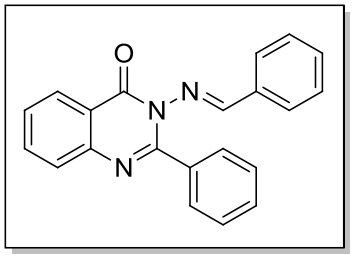
3-{[(3-Nitrophenyl)methylene]amino}-2-phenylquinazolin-4(3H)-one [2i, section C]:



Yield 85%; m.p. 248°C; IR (cm^{-1}): 1674, 1641, 1500, 1456, 1344; ^{1}H-NMR ($CDCl_3$ + DMSO-d6): 7.22-8.54 (12H, m, Ar-H), 9.58 (1H, s, Ar-H), 8.59 (1H, s, H-C=N); ^{13}C-NMR ($CDCl_3$ + DMSO-d6): 118.3, 120.6, 122.3, 122.3, 126.9, 127.3, 127.9, 128.1, 128.9, 130.0, 131.5, 132.4, 133.5, 134.0, 139.8, 161.6, 164.9, 165.5; Anal.

Calcd. for $C_{21}H_{14}N_4O_3$: C, 68.10%; H, 3.84%; N, 15.15%; found: C, 68.15%; H, 3.81%; N, 15.13%. FAB MS (m/z): 371(M+1).

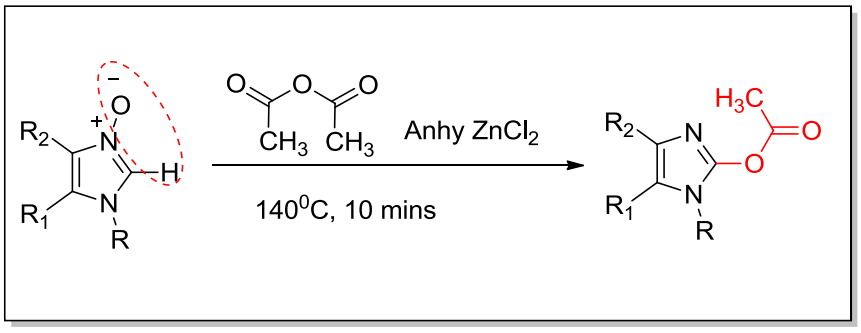
3-{[(Pheny)lmethylene]amino}-2-phenylquinazolin-4(3H)-one [2j, section C]:



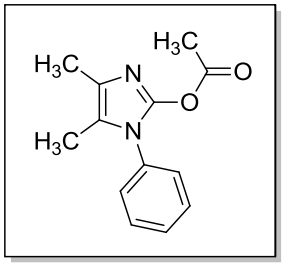
Yield 83%; m.p. 196°C; IR (cm^{-1}): 1662, 1647, 1645, 1556, 1454; ^{1}H-NMR ($CDCl_3$ + DMSO-d6): 6.98-8.62 (14H, m, Ar-H), 8.47 (1H, s, H-C=N); ^{13}C-NMR ($CDCl_3$ + DMSO-d6): 119.8, 121.6, 122.8, 127.5, 127.7, 127.8, 128.7, 128.8, 130.6, 132.1, 132.7, 133.6, 134.3, 139.8, 15.0, 165.8, 166.0; Anal. Calcd. for $C_{21}H_{15}N_3O$: C, 77.52%; H, 4.65%; N, 12.91%; found: C, 77.54%; H, 4.71%; N, 12.85%. FAB MS (m/z): 326(M+1).

III.E.8. General procedure for acetoxylation at C-2 position of substituted imidazole:

Imidazole *N*-oxide (1 mmol), acetic anhydride (4 mmol) and anhydrous Zinc chloride were mixed intimately in an agate mortar and pestle for a period of 10-20 min under solvent-free condition. The reaction mixture was then converted to a round bottle and heated in an oil bath for a period of 10 mins at 140°C. The reaction mixture was then dissolved in dichloromethane (2 ml), washed with water and finally dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the residue, which was chromatographed over silica gel column and elution with petroleum ether/ethyl acetate mixture to furnish the desired 2-acetoxyimidazole.

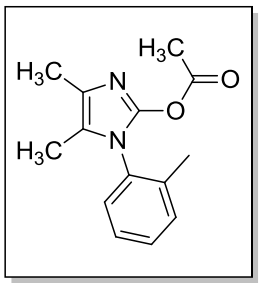


4,5-dimethyl-1-phenyl-1H-imidazol-2-yl acetate [2a, section D]:



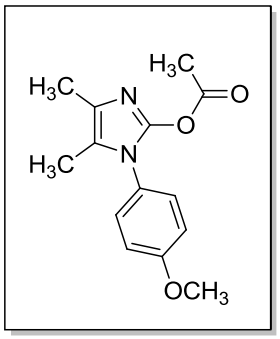
Yield 79%, yellow solid, mp 138 °C, IR (neat, cm^{-1}): ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.42-7.17 (5H, m, Ar-H), 2.59 (3H, s, -CH3), 2.25 (3H, s, $-CH_3$), 1.76 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 171.0, 152.1, 134.2, 129.4, 128.3, 127.7, 118.1, 114.5, 26.2, 12.0 and 9.0. ESI MS (m/z) $[M+H]^+$: 231.

4,5-dimethyl-1-(o-tolyl)-1H-imidazol-2-yl acetate [2b, section D]:



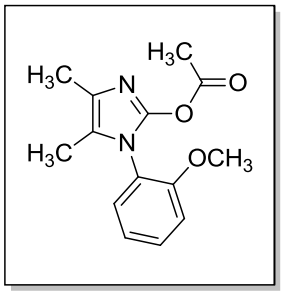
Yield 73%, white solid, mp 142 °C, IR (neat, cm^{-1}): ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.27-7.04 (4H, m, Ar-H), 2.55 (3H, s, $-CH_3$), 2.37 (3H, s, $-CH_3$), 2.10 (3H, s, $-CH_3$), 1.64 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 171.1, 166.0, 137.0, 133.1, 131.1, 128.9, 127, 118.4, 114.3, 26.2, 17.6, 12.1 and 8.7. ESI MS (m/z) $[M+H]^+$: 245.

1-(4-methoxyphenyl)-4,5-dimethyl-1H-imidazol-2-yl acetate [2c, section D]:



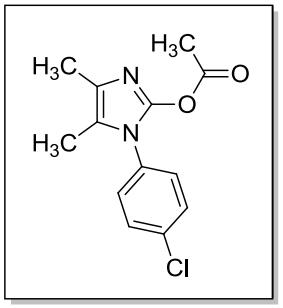
Yield 75%, yellowish white solid, mp 134 °C, IR (neat, cm^{-1}): ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.09 (1H, d, J = 8.7 Hz, Ar-H), 6.89 (1H, d, J = 8.7 Hz, Ar-H), 3.75 (3H, s, $-OCH_3$), 2.59 (3H, s, $-CH_3$), 2.41 (3H, s, $-CH_3$), 1.73 (3H, s, $-CH_3$), 1.18 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 171.1, 159.4, 152.7, 129.0, 126.8, 118.5, 114.6, 114.1, 55.5, 26.2, 12.0 and 9.0. ESI MS (m/z) $[M+H]^+$: 261.

1-(2-methoxyphenyl)-4,5-dimethyl-1H-imidazol-2-yl acetate [2d, section D]:



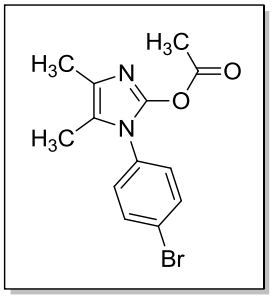
Yield 69%, light yellowish white solid, mp 134 °C, IR (neat, cm^{-1}): ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.32 (1H, d, *J* = 15.6, 7.14 (1H, *J* = 7.8, Ar-H), 6.95 (2H, 2, Ar-H), 3.74 (3H, s, $-OCH_3$), 2.59 (3H, s, $-CH_3$), 2.25 (3H, s, $-CH_3$), 1.65 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 171.1, 155.9, 152.0, 130.4, 130.4, 122.7, 121.0, 119.3, 113.8, 112.0, 55.7, 26.2, 12.1 and 8.4. ESI MS (m/z) $[M+H]^+$: 261.

1-(4-chlorophenyl)-4,5-dimethyl-1H-imidazol-2-yl acetate [2e, section D]:



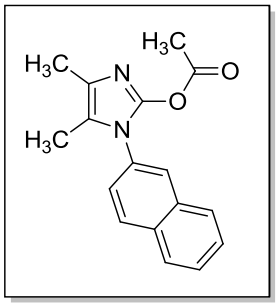
Yield 81%, white solid, mp 140 °C, IR (neat, cm^{-1}): ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.37 (1H, d, *J* = 5.4 Hz, Ar-H), 7.16 (1H, d, *J* = 10.8 Hz, Ar-H), 2.59 (3H, s, $-CH_3$), 2.25 (3H, s, $-CH_3$), 1.77 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 170.9, 152.0, 134.1, 132.8, 129.6, 128.9, 117.7, 115.0, 26.2, 12.0 and 9.1. ESI MS (m/z) $[M+H]^+$: 265.

1-(4-bromophenyl)-4,5-dimethyl-1H-imidazol-2-yl acetate [2f, section D]:



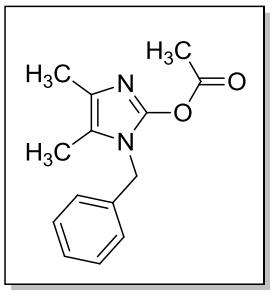
Yield 78%, yellowish white solid, mp 142 °C, IR (neat, cm^{-1}): ^1H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.52 (1H, *J* = 8.7 Hz, Ar-H), 7.07 (1H, d, *J* = 8.7 Hz, Ar-H), 2.59 (3H, s, $-CH_3$), 2.21 (3H, s, $-CH_3$), 1.72 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 170.9, 151.9, 133.3, 132.6, 129.2, 122.1, 117.7, 115.0, 26.2, 12.0 and 9.1. ESI MS (m/z) $[M+H]^+$: 309.

4,5-dimethyl-1-(naphthalen-2-yl)-1H-imidazol-2-yl acetate [2g, section D]:



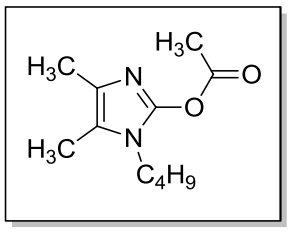
Yield 81%, Pinkish white solid, mp 140 °C, IR (neat, cm^{-1}): ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.86-7.25 (7H, m, Ar-H), 2.61 (3H, s, $-CH_3$), 2.27 (3H, s, $-CH_3$), 1.79 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 171.0, 152.3, 133.4, 132.7, 131.6, 129.4, 128.0, 127.8, 126.8, 126.8, 126.6, 125.3, 118.3, 114.7, 26.3, 12.1 and 9.2. ESI MS (m/z) $[M+H]^+$: 281.

1-benzyl-4,5-dimethyl-1H-imidazol-2-yl acetate [2h, section D]:



Yield 69%, white solid, mp 78 °C, IR (neat, cm^{-1}): ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.28-7.13 (5H, m, Ar-H), 4.72 (2H, s, $-CH_2$), 2.61 (3H, s, $-CH_3$), 2.17 (3H, s, $-CH_3$), 1.79 (3H, s, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 170.0, 151.7, 135.8, 127.8, 126.5, 125.9, 116.8, 112.8, 43.4, 25.2, 10.8 and 7.4. ESI MS (m/z) $[M+H]^+$: 245.

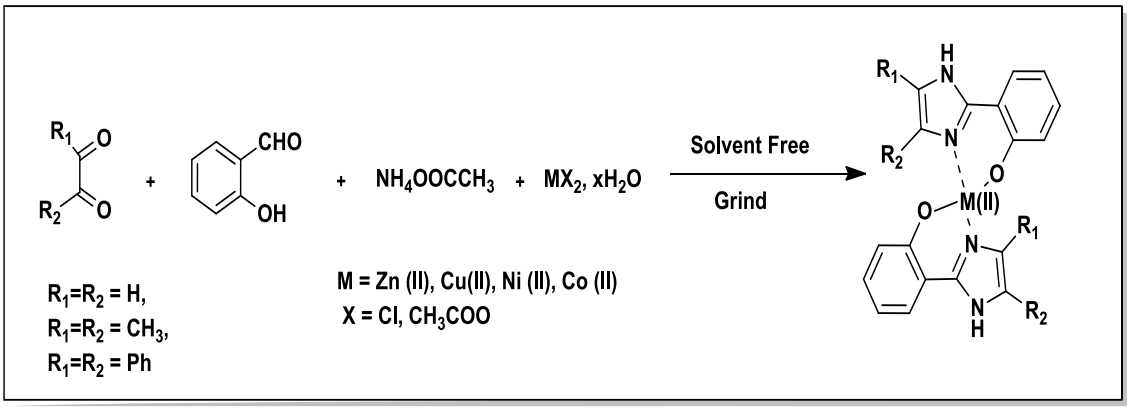
1-butyl-4,5-dimethyl-1H-imidazol-2-yl acetate [2i, section D]:



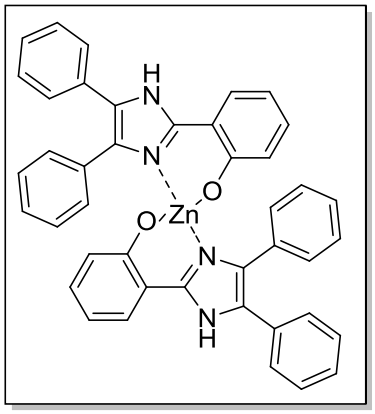
Yield 65%, Yellow liquid, IR (neat, cm^{-1}): ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 3.79 (2H, t, $-CH_2-$), 2.1 (6H, s, $-CH_3$), 1.63 (2H), 1.4 (2H), 0.95 (3H), 0.85 (3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 171.4, 152.7, 118.0, 113.8, 41.2, 31.9, 26.5, 20.4, 14.1, 12.2 and 8.5. ESI MS (m/z) $[M+H]^+$: 211.

III.E.9. General procedure for the preparation of Metal Imidazole complexes:

Diketone (2 mmole) and salicyldehyde (2 mmole) are grinded with metal acetate or chloride (1 mmole) along with ammonium acetate (20 mmole) using a mortar and pestle more than a period of ca. 5 minutes under solvent-free condition. The reaction mixtures are heated for further 20 minutes in an oil bath to form the pure products. Addition of water to the mixtures of the test tube gives the product as colored solids. It is further purified by washing with a little amount of methanol.

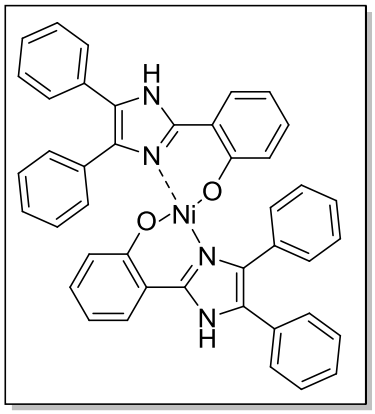


Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Zn [1, section E]:



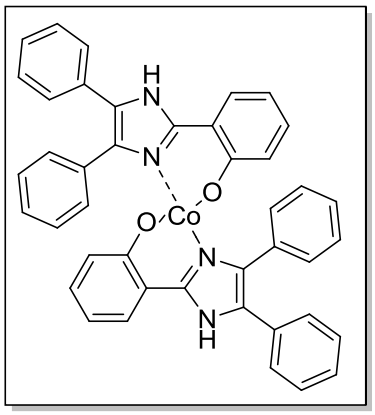
M.P.>300°C, **IR (KBr, cm^{-1}):** 3455, 3055 (Ar C-H), 1608, 1565 (C=C), 1532 (m), 1364, 1301, 1255, 694. **m/z found for ($C_{42}H_{30}N_4O_2Zn$):** 686.53 (M+1). **Anal.Calcd for ($C_{42}H_{30}N_4O_2Ni$):** C, 73.31; H, 4.39; N, 8.14. Found: C, 73.74; H, 4.63; N, 7.11.

Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Ni [2, section E]:



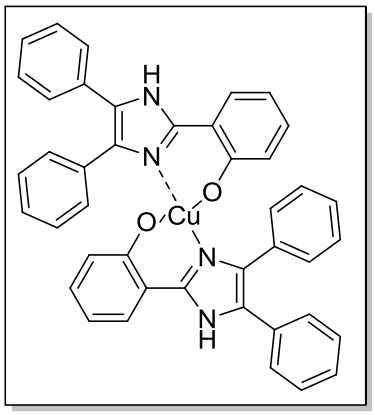
M.P. >300^{o}C, **IR (KBr, cm^{-1}):** 3506, 3062 (Ar C-H), 1611, 1581 (C=C), 1511(C=N), 1356, 1304, 1263, 687. **m/z found for $C_{42}H_{30}N_4O_2Ni$):** 680.3 (M+1). **Anal.Calcd for ($C_{42}H_{30}N_4O_2Ni$):** C, 74.03; H, 4.44; N, 8.22. Found: C, 74.68; H, 4.13; N, 8.62.

Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Co [3, section E]:



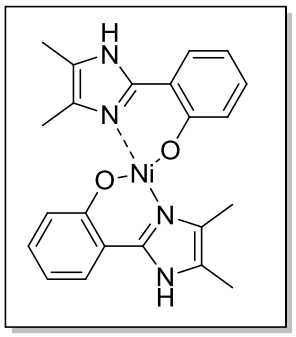
M.P. >300^{o}C, **IR (KBr, cm^{-1}):** 3386, 3050 (Ar C-H), 1601, 1565 (C=C), 1506(C=N), 1352, 1314, 1283, 687. **m/z found for ($C_{42}H_{30}N_4O_2Co$):** 681.3 (M+1). **Anal.Calcd for ($C_{42}H_{30}N_4O_2Co$):** C, 74.00; H, 4.44; N, 8.22. Found: C, 74.96; H, 4.56; N, 7.26.

Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Cu [4, section E]:



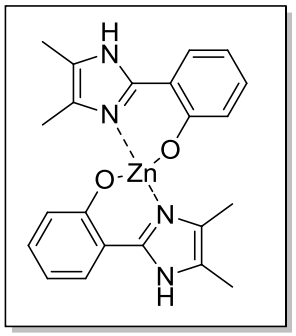
M.P. >300^{o}C, **IR (KBr, cm^{-1}):** 3421, 3072(Ar C-H), 1605, 1582 (C=C), 1497 (C=N), 1350, 1306, 1275, 672. **m/z found for ($C_{42}H_{30}N_4O_2Cu$):** 685.8 (M+1). **Anal.Calcd for ($C_{42}H_{30}N_4O_2Cu$):** C, 73.51; H, 4.41; N, 8.16. Found: C, 73.02; H, 4.87; N, 8.42.

Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Ni [5, section E]:



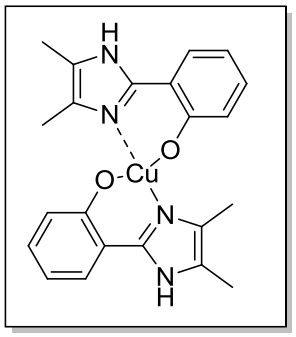
M.P. 285-286 ^{o}C, **IR (KBr, cm^{-1}):** 3405, 3047 (Ar C-H), 2921 (Al C-H), 1635, 1601, 1498(C=N), 1311, 1080. **m/z found for ($C_{22}H_{22}NiN_4O_2$):** 432.4 (M+1). **Anal. Calcd for ($C_{22}H_{22}NiN_4O_2$):** C, 61.01; H, 5.12; N, 12.94. Found: C, 60.88; H, 5.76; N, 12.46.

Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Zn [6, section E]:



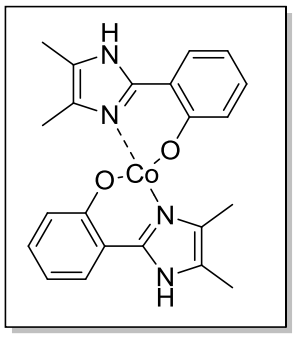
M.P. 285-286 ^{o}C, **IR (KBr, cm^{-1}):** 3448, 3032 (Ar C-H), 2921 (Al C-H), 1611, 1564 (C=C), 1478(C=N), 1262, 1080. **m/z found for ($C_{22}H_{22}ZnN_4O_2$):** 438.9 (M+1). **Anal. Calcd for ($C_{22}H_{22}ZnN_4O_2$):** C, 60.08; H, 5.04; N, 12.74. Found: C, 60.55; H, 5.96; N, 11.56.

Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Cu [7, section E]:



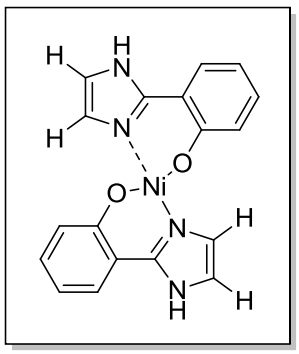
M.P. 285-286 ^{o}C, **IR (KBr, cm^{-1}):** 3364, 3065 (Ar C-H), 2912 (Al C-H), 1615, 1474(C=N), 1342, 1160, 1072 1394 **m/z found for ($C_{22}H_{22}CuN_4O_2$):** 437.2 (M+1). **Anal.Calcd for ($C_{22}H_{22}CuN_4O_2$):** C, 60.33; H, 5.06; N, 12.79. Found: C, 59.64; H, 5.96; N, 12.87.

Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Co [8, section E]:



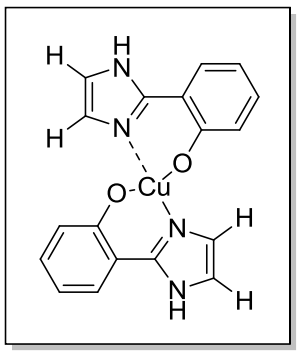
M.P. 285-286 ^{o}C, **IR (KBr, cm^{-1}):** 3388, 3043(Ar C-H), 2936 (Al C-H), 1655, 1600, 1562 (C=C), 1448(C=N), 1087. **m/z found for ($C_{22}H_{22}CoN_4O_2$):** 433.6 (M+1). **Anal. Calcd for ($C_{22}H_{22}CoN_4O_2$):** C, 60.97; H, 5.12; N, 13.60. Found: C, 60.17; H, 5.46; N, 13.89.

Bis{1H-imidazol-2-yl)phenoxy}Ni [9, section E]:



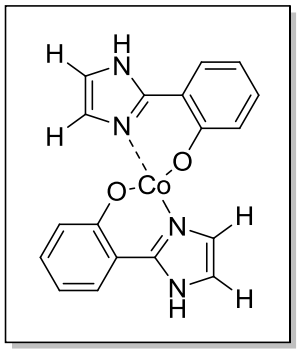
M.P. 285-286 ^{o}C, **IR (KBr, cm^{-1}):** 3390, 3148, 3066 (Ar C-H), 1606, 1558, 1448, 1400, 1272, 1151, 1035, 754. **m/z found for ($C_{18}H_{14}NiN_4O_2$):** 376.2 (M+1). **Anal. Calcd for ($C_{18}H_{14}NiN_4O_2$):** C, 57.34; H, 3.74; N, 14.86. Found: C, 57.12; H, 3.26; N, 15.24.

Bis{1H-imidazol-2-yl)phenoxy}Cu [10, section E]:



M.P. 255-257^{o}C, **IR (KBr, cm^{-1}):** 3410, 3061 (Ar C-H), 1608, 1562 (C=C), 1451, 1412, 1301, 1123, 1032, 750. **m/z found for ($C_{18}H_{14}CuN_4O_2$):** 381.7 (M+1). **Anal.Calcd for ($C_{18}H_{14}CuN_4O_2$):** C, 56.61; H, 3.70; N, 14.67. Found: C, 56.02; H, 3.95; N, 14.52.

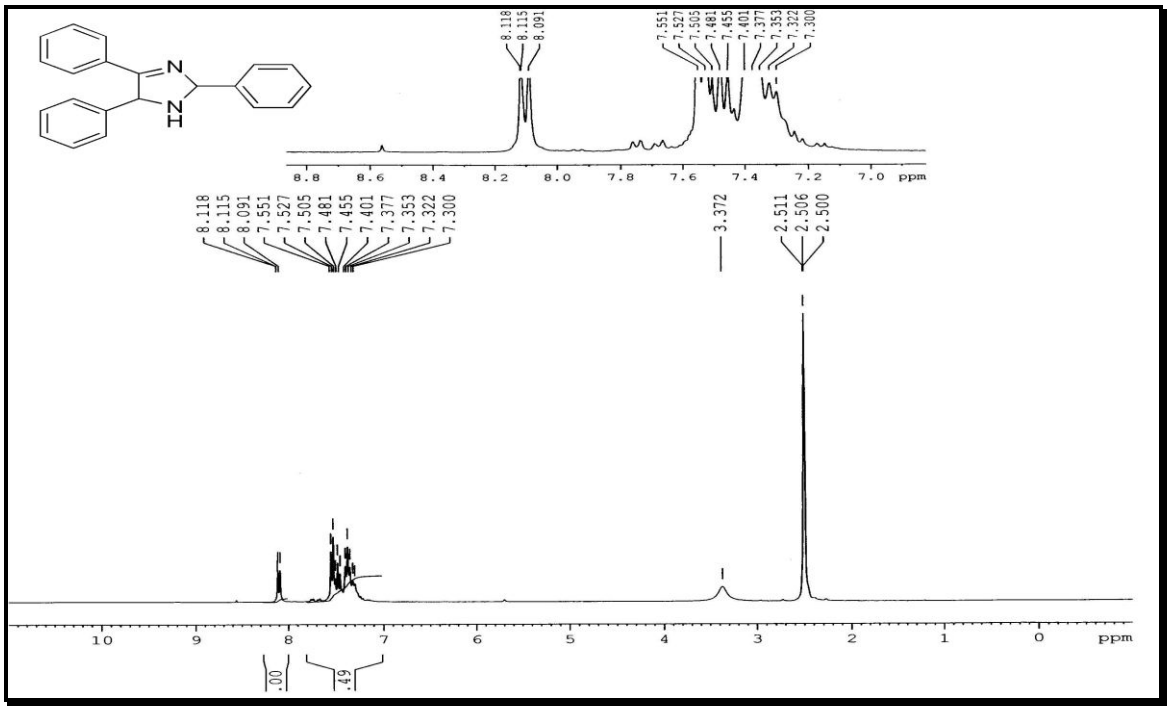
Bis{1H-imidazol-2-yl)phenoxy}Co [11, section E]:



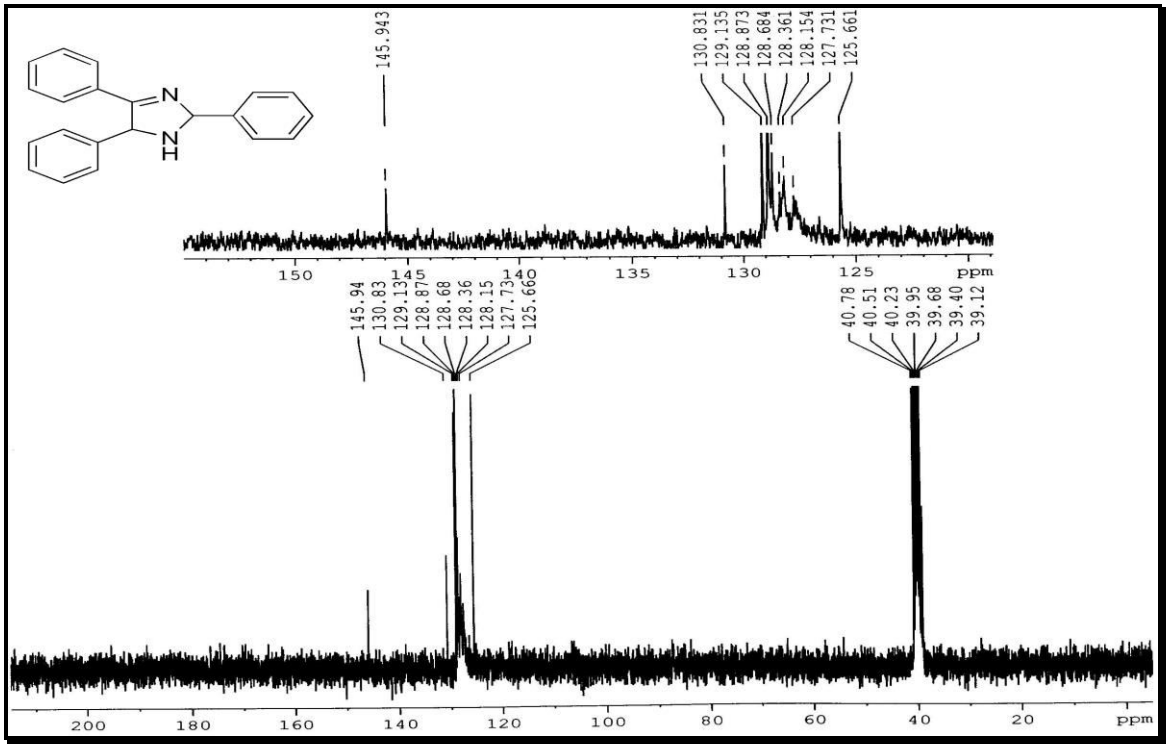
M.P. 285-286 ^{o}C, **IR (KBr, cm^{-1}):** 3465, 3069 (Ar C-H), 1611, 1563 (C=C), 1475, 1418, 1284, 1150, 1052, 745. **m/z found for ($C_{18}H_{14}CoN_4O_2$):** 377.8 (M+1). **Anal. Calcd for ($C_{18}H_{14}CoN_4O_2$):** C, 57.31; H, 3.74; N, 14.85. Found: C, 57.89; H, 3.85; N, 13.78.

III.F. Selected Spectra

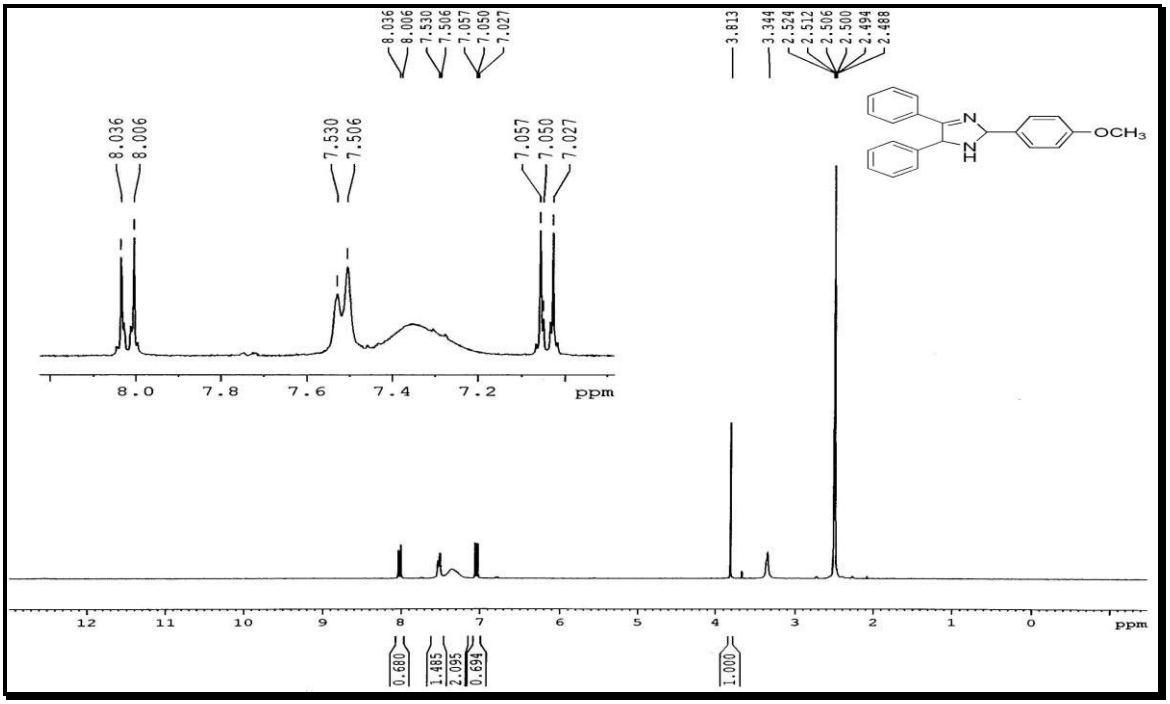
[1]HNMR - 2, 4, 5-Triphenylimidazole



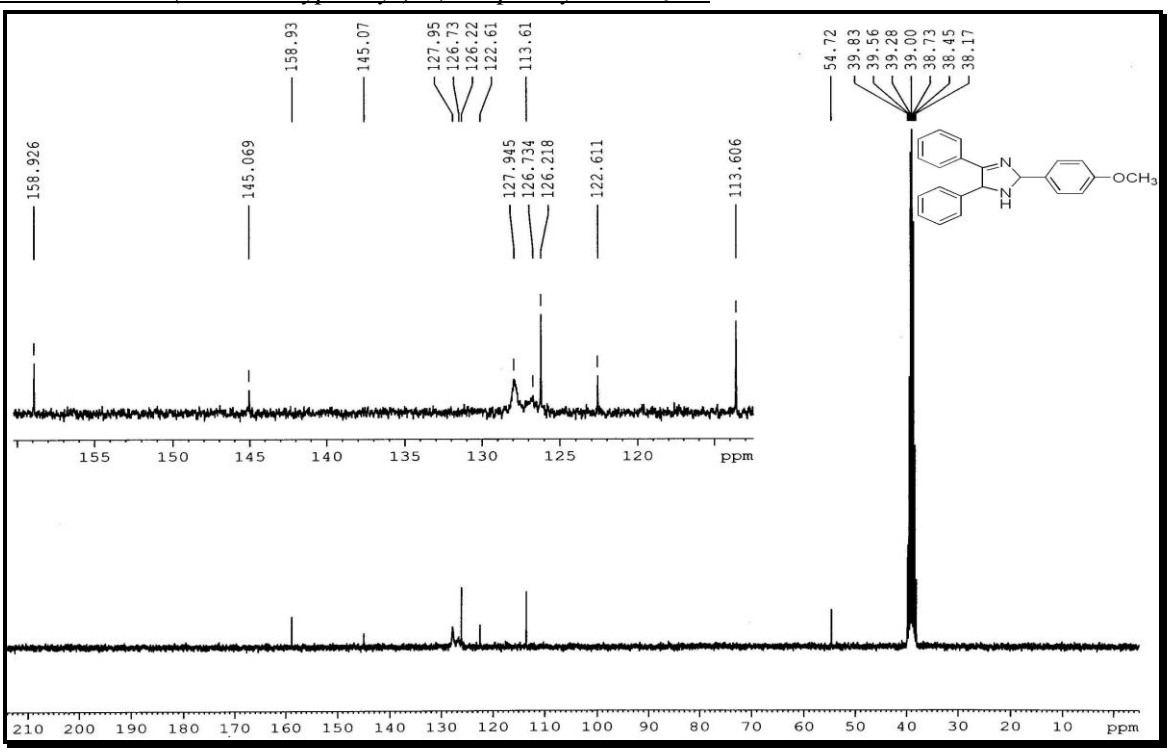
[13]CNMR - 2, 4, 5-Triphenylimidazole



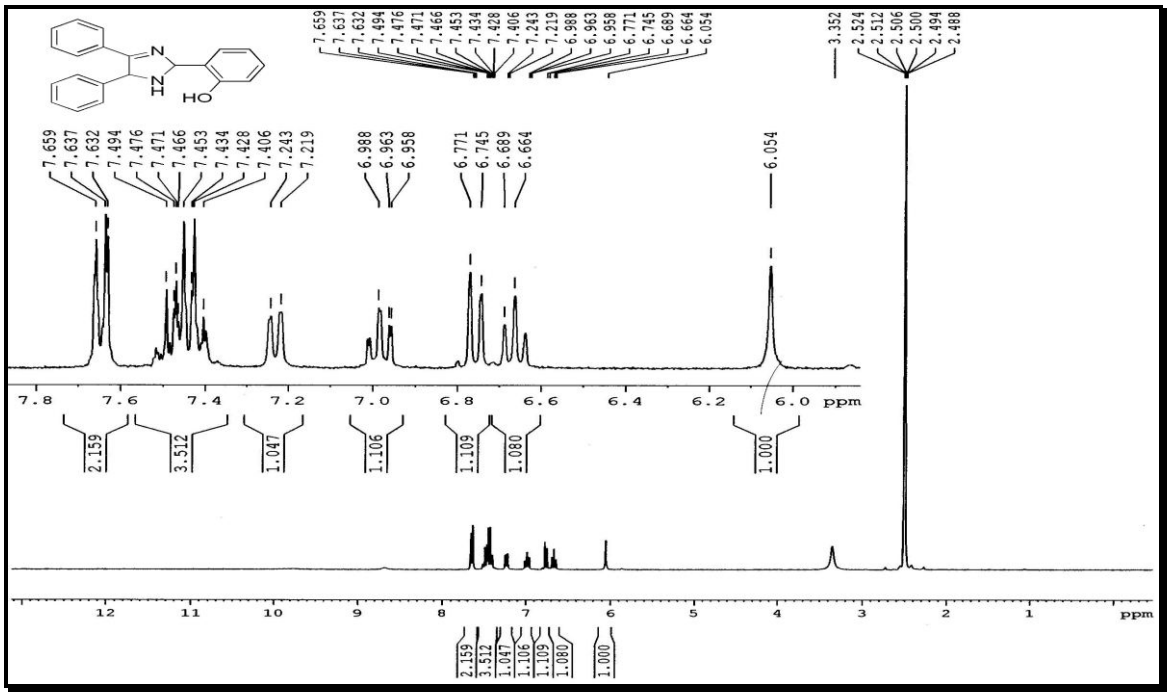
[1]HNMR - 2-(4-methoxyphenyl)-4,5-diphenylimidazole



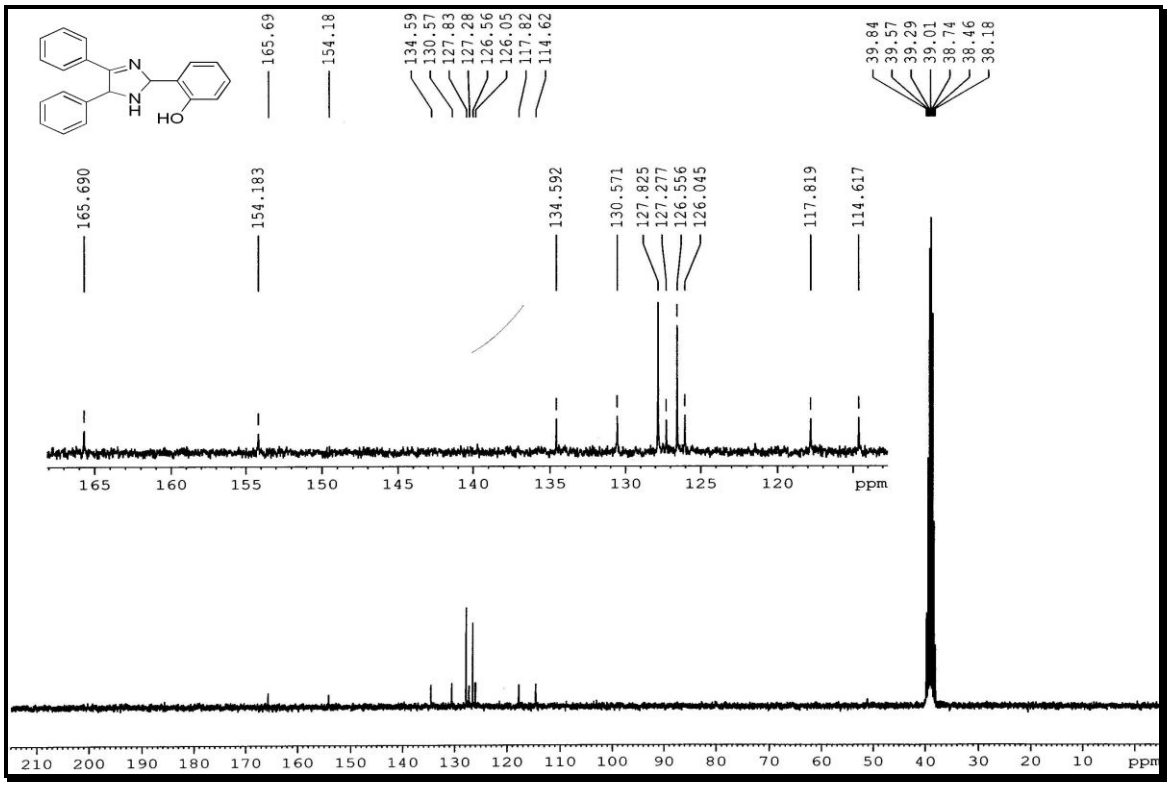
[13]CNMR-- 2-(4-methoxyphenyl)-4,5-diphenylimidazole



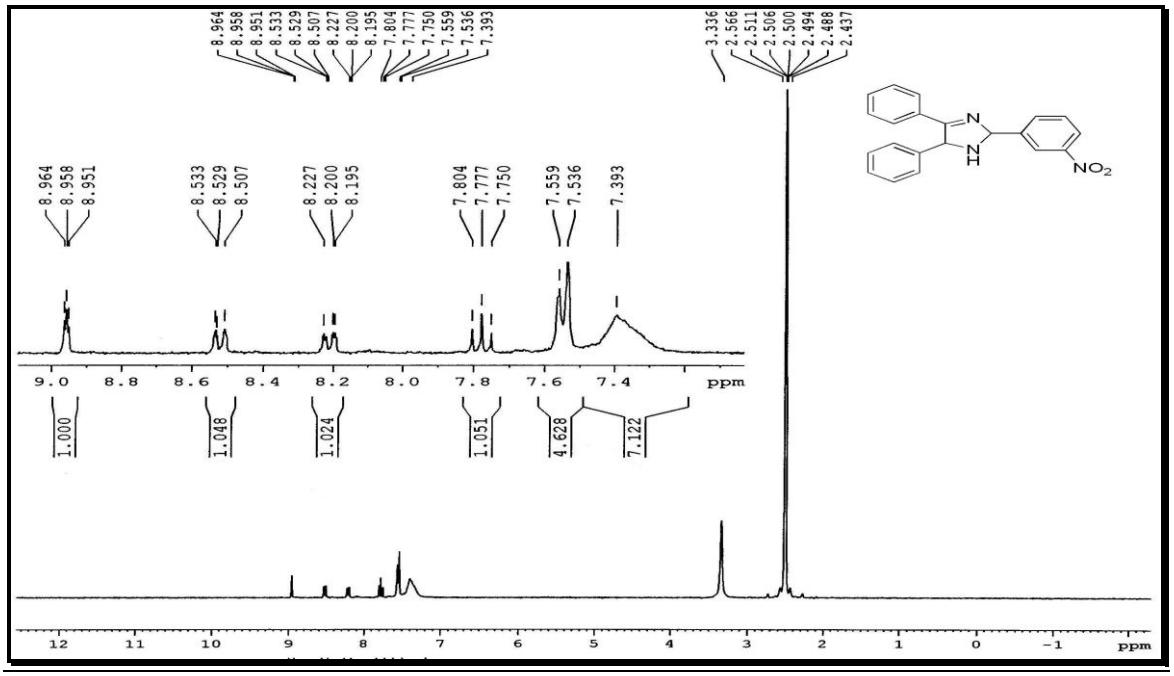
[1]HNMR-2-(4,5-diphenyl 1H-imidazol-2-yl) phenol



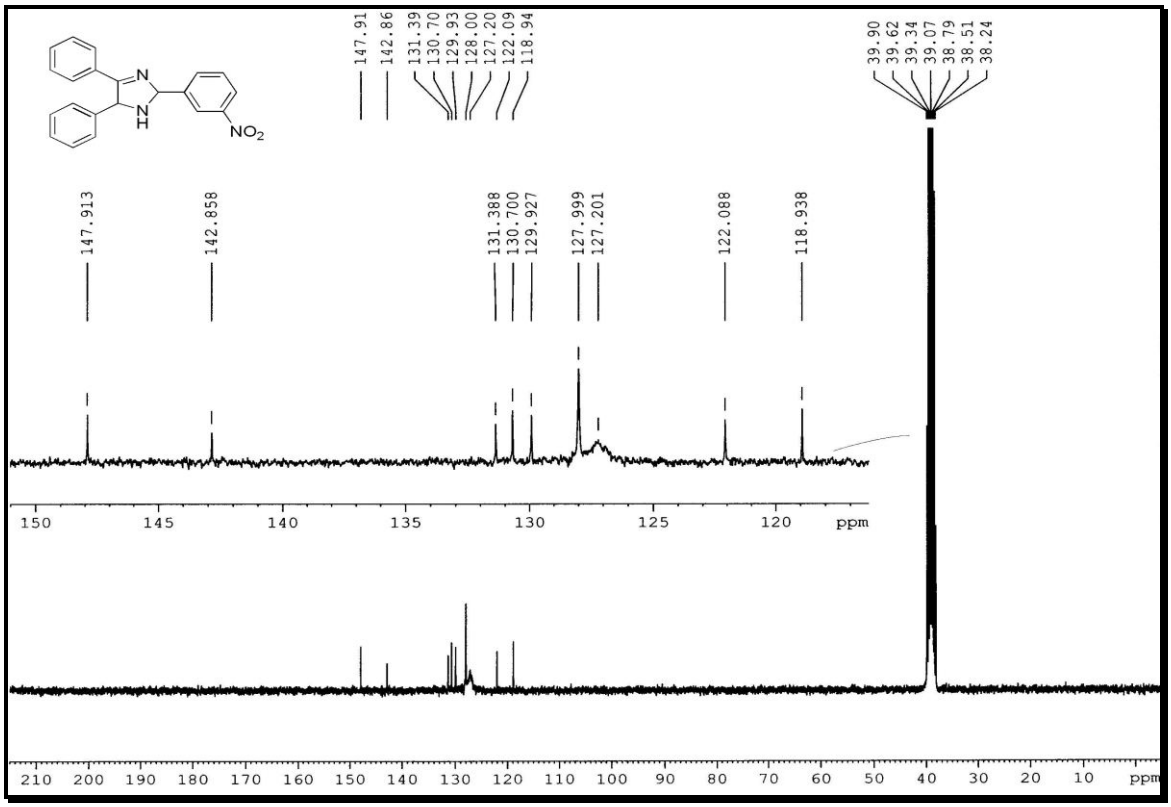
[13]CNMR-2-(4,5-diphenyl 1H-imidazol-2-yl) phenol



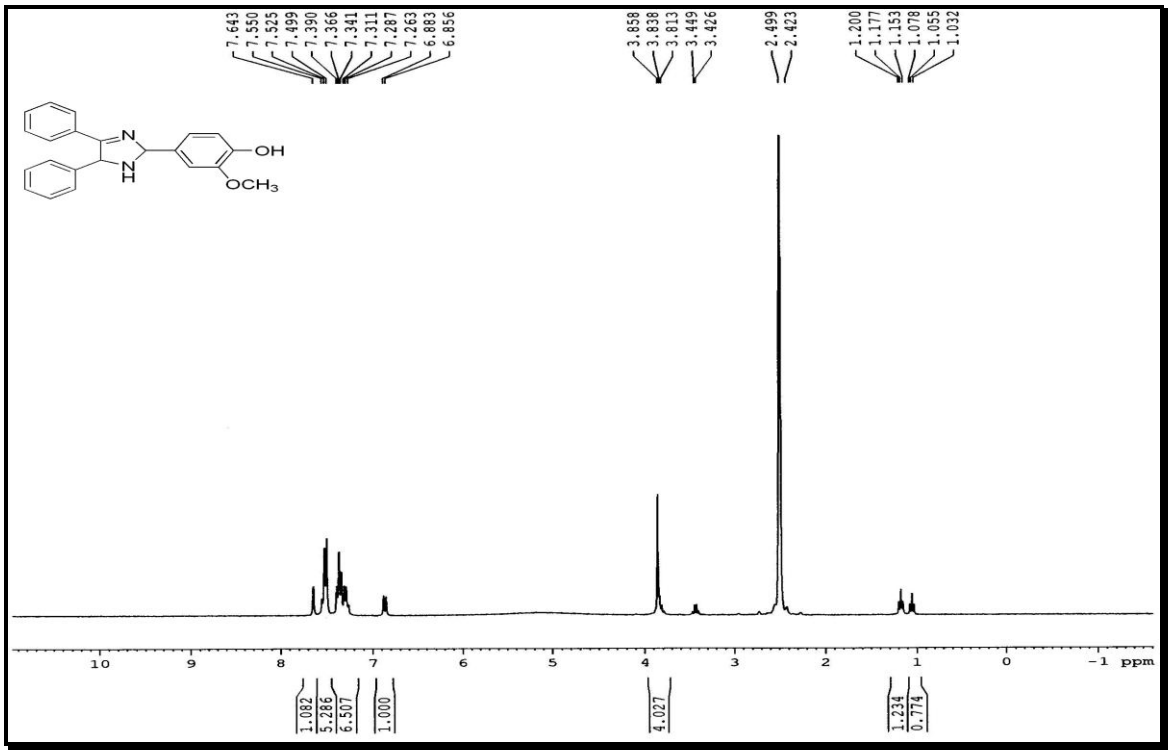
[1]HNMR - 2-(3-nitrophenyl)-4,5-diphenylimidazole



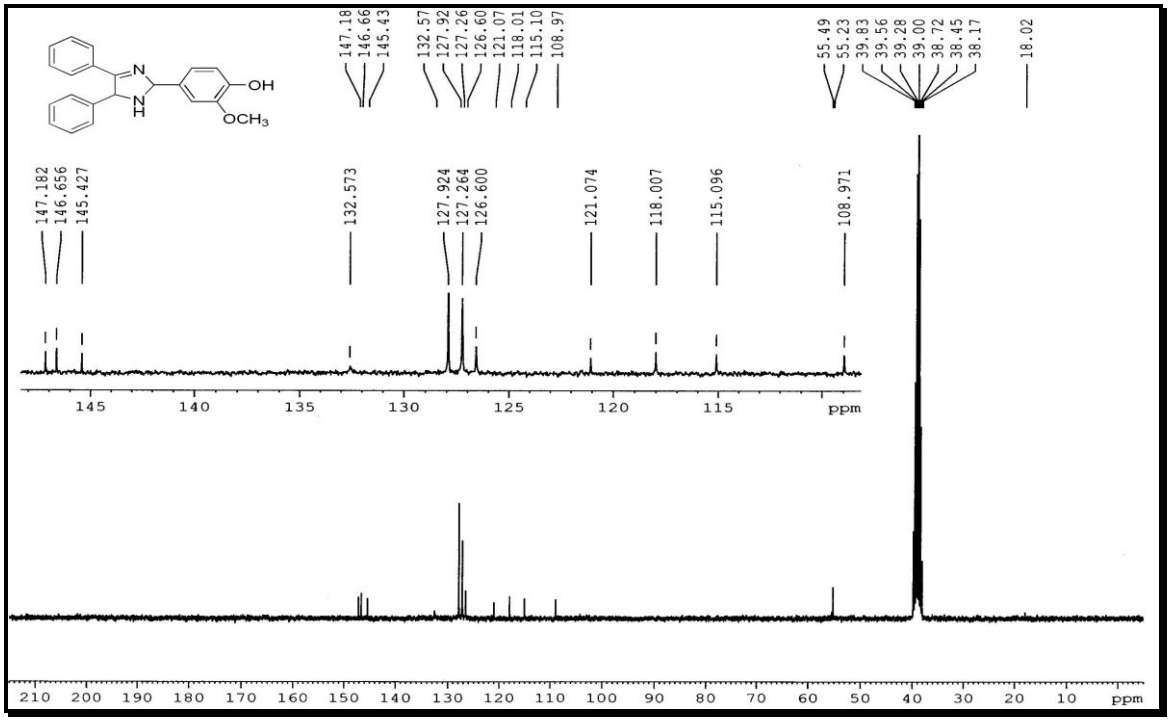
[13]CNMR - 2-(3-nitrophenyl)-4,5-diphenylimidazole



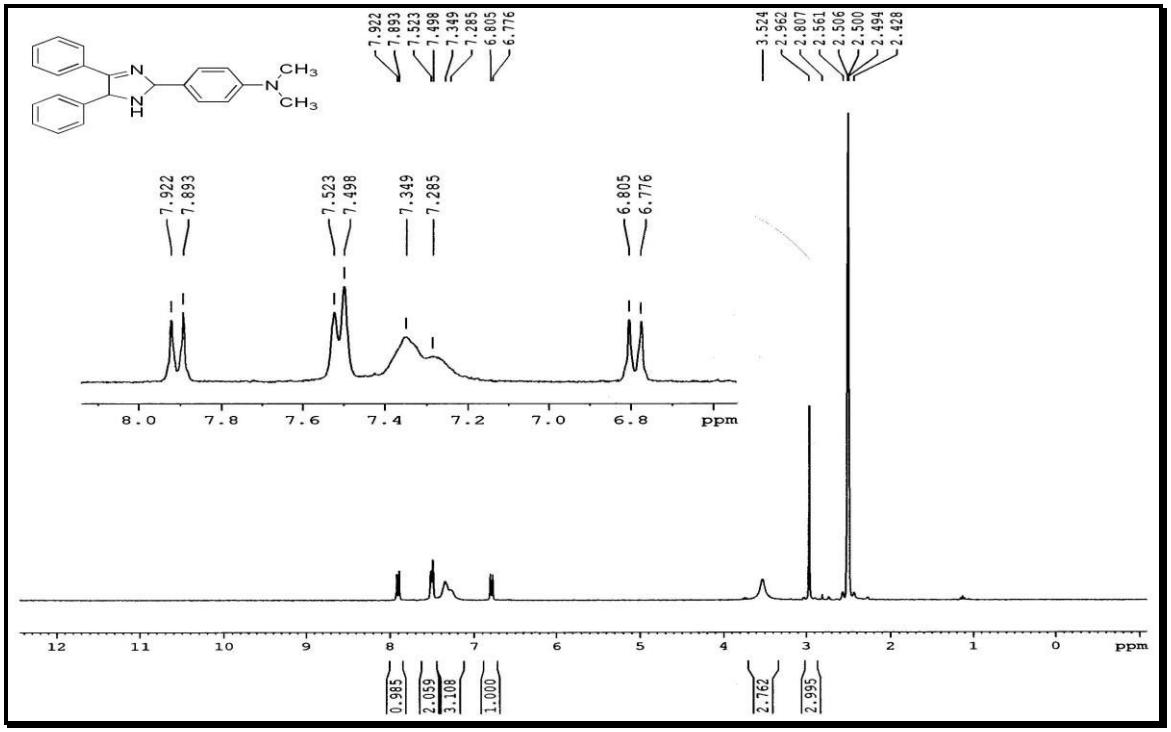
[1]HNMR - 2-(4,5-diphenyl 1H-imidazol-2-yl)-3-methoxy phenol



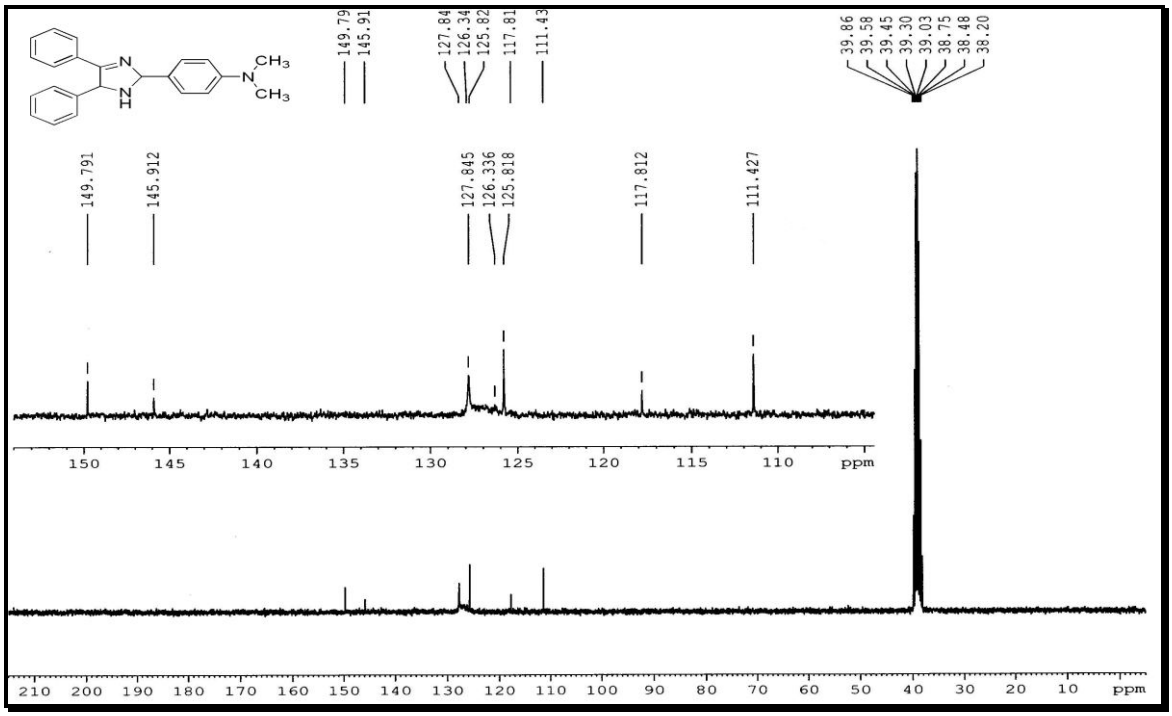
[13]CNMR - 2-(4,5-diphenyl 1H-imidazol-2-yl)-3-methoxy phenol



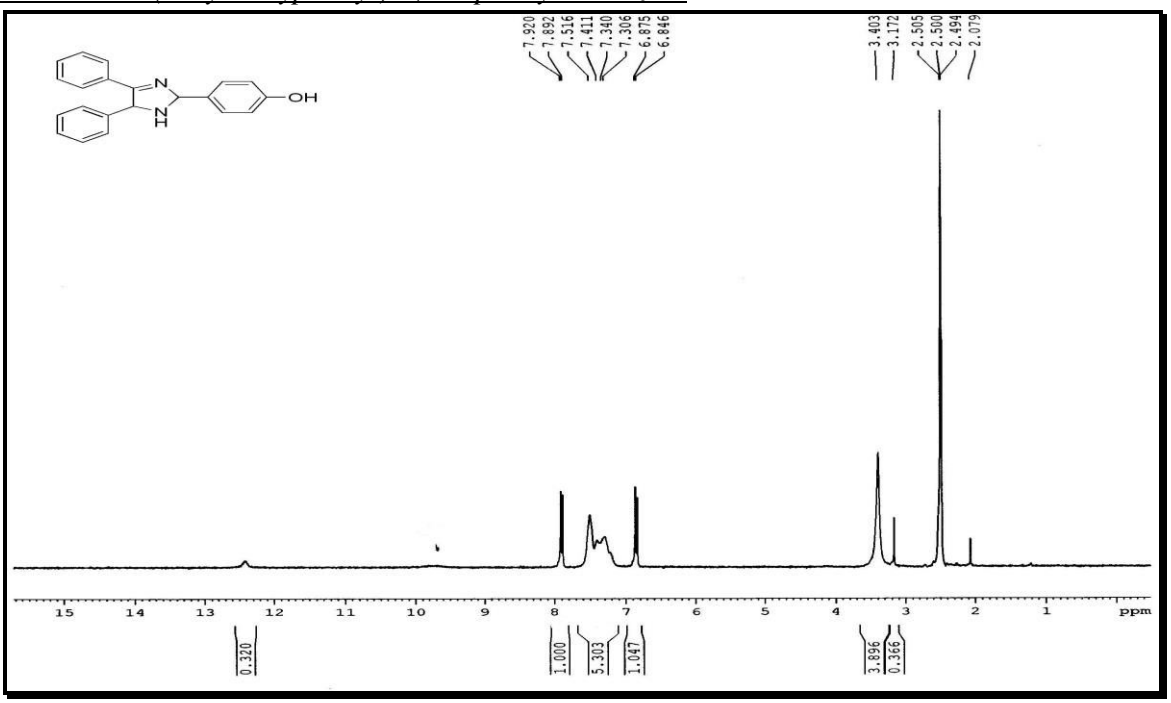
[1]HNMR - {4-(4,5-diphenyl1H-imidazol-2-yl)phenyl}–dimethylamine



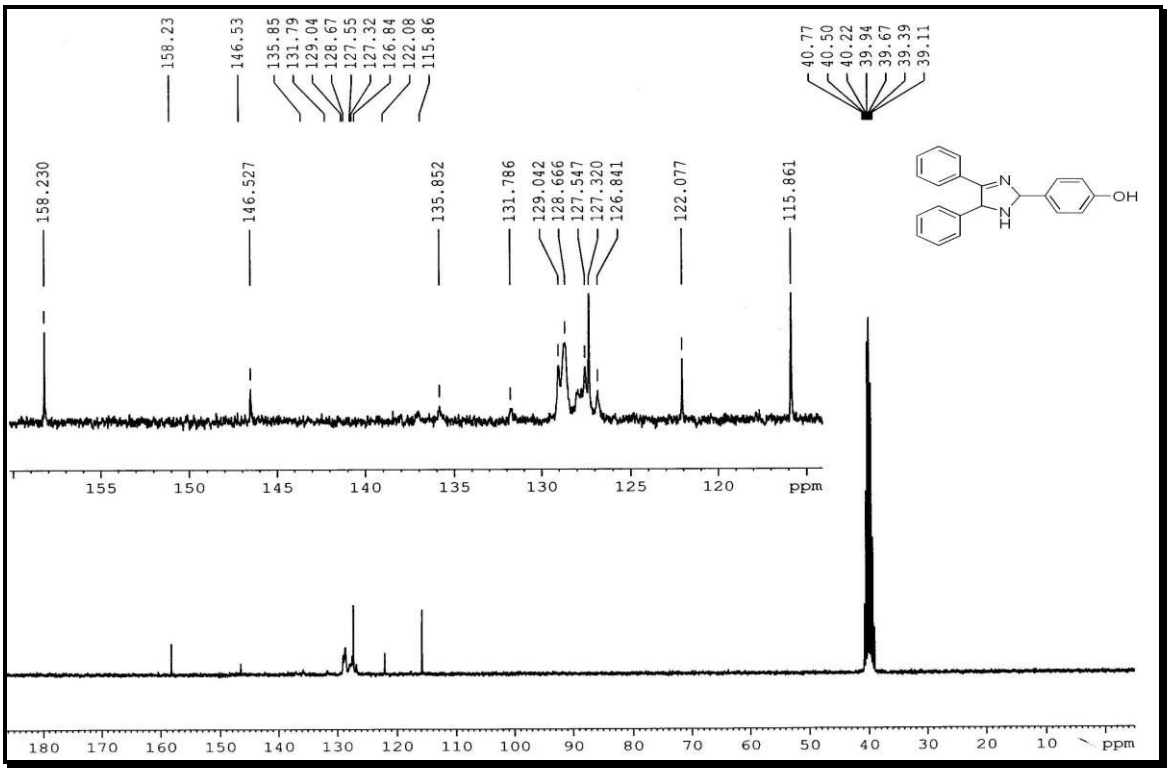
[13]CNMR - {4-(4,5-diphenyl1H-imidazol-2-yl)phenyl}–dimethylamine



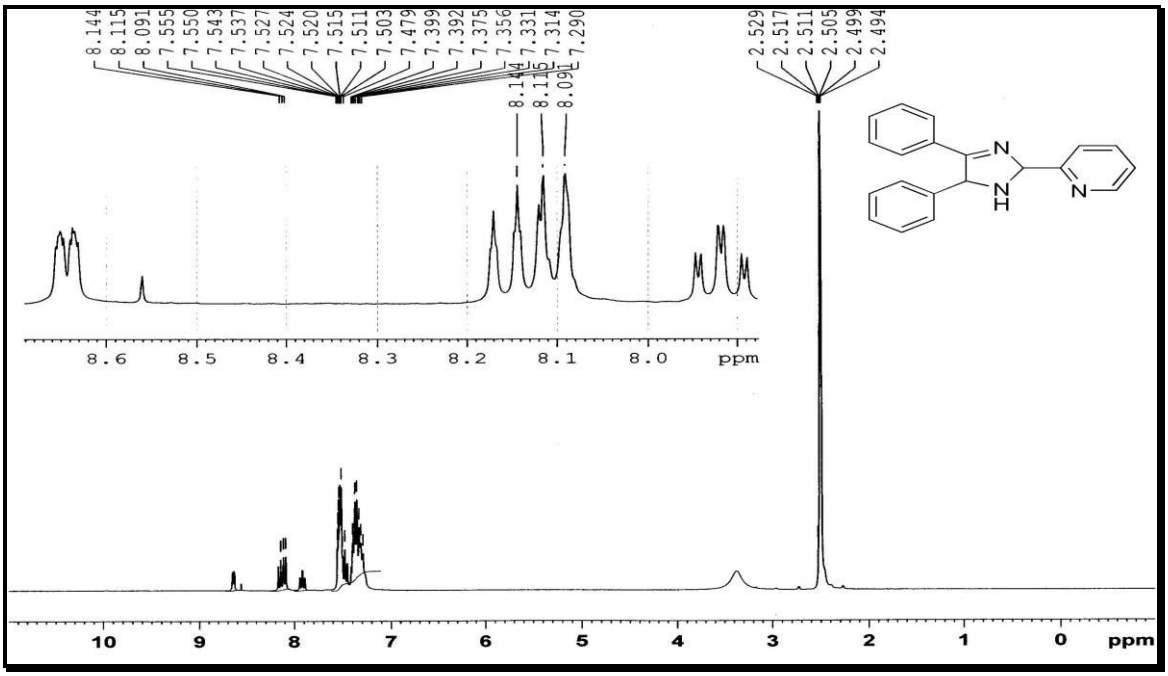
[1]HNMR - 2-(4-hydroxyphenyl)-4,5-diphenylimidazole



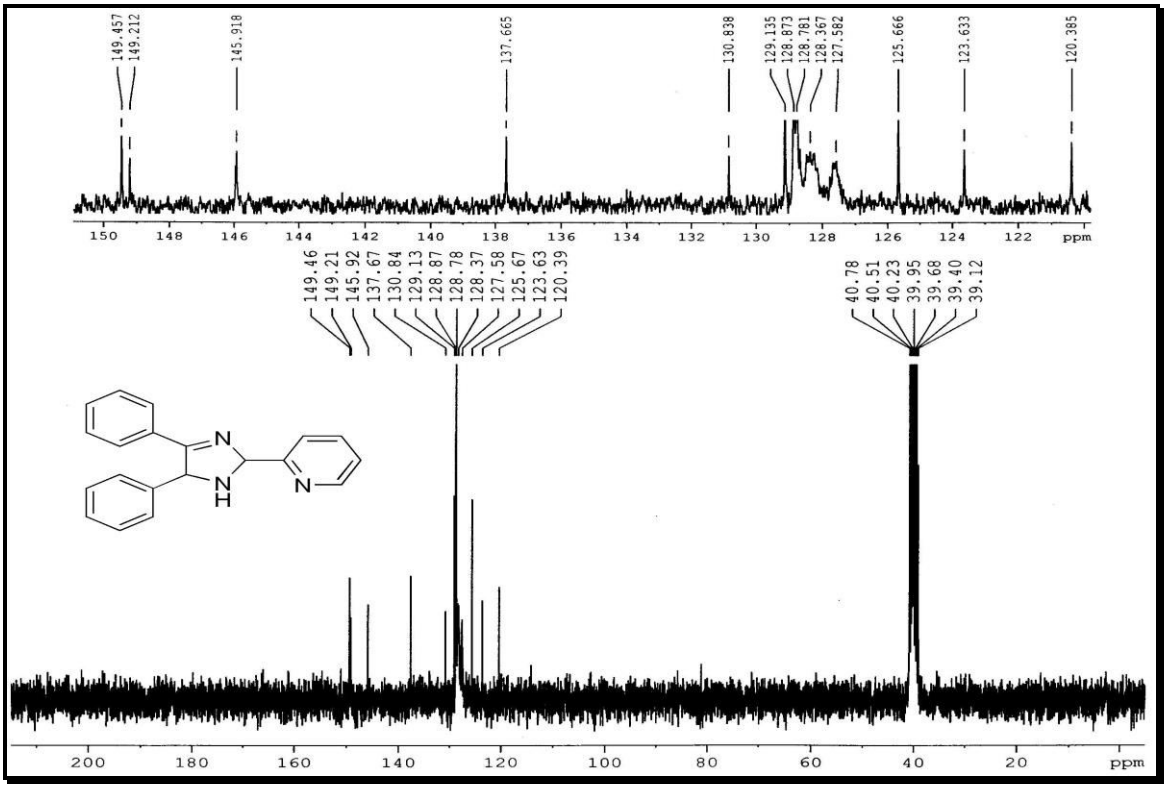
[13]CNMR - 2-(4-hydroxyphenyl)-4,5-diphenylimidazole



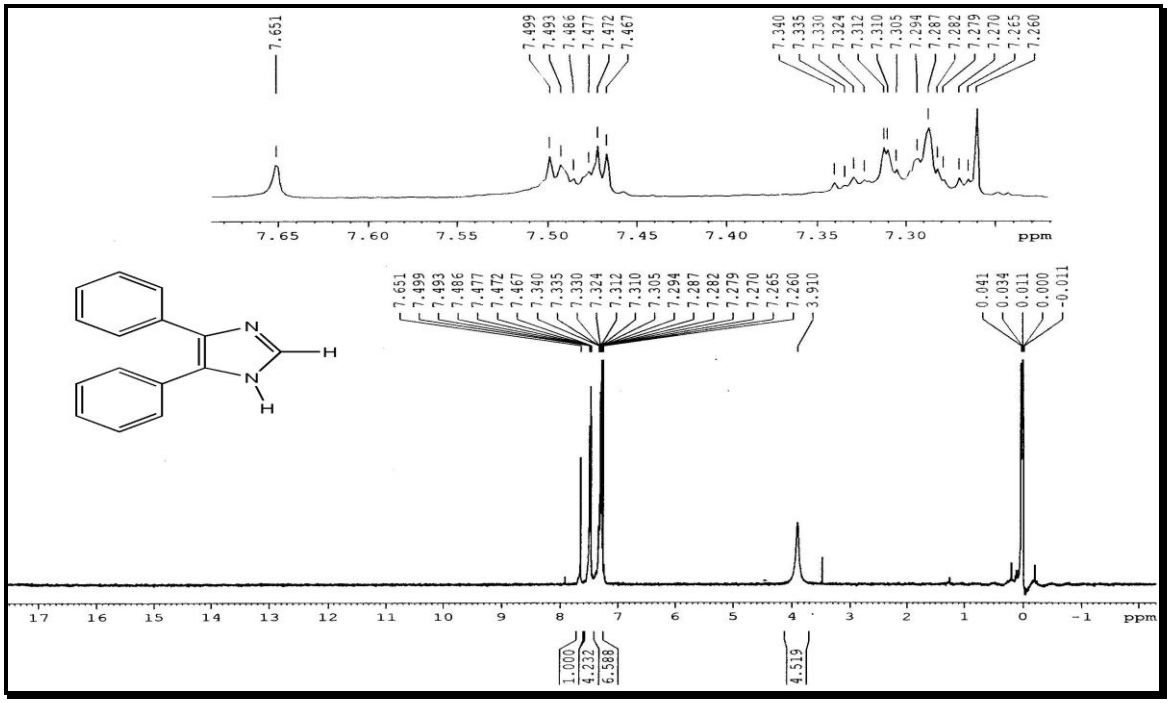
[1]HNMR - 2-(4,5-diphenyl 1H-imidazol-2-yl) pyridine



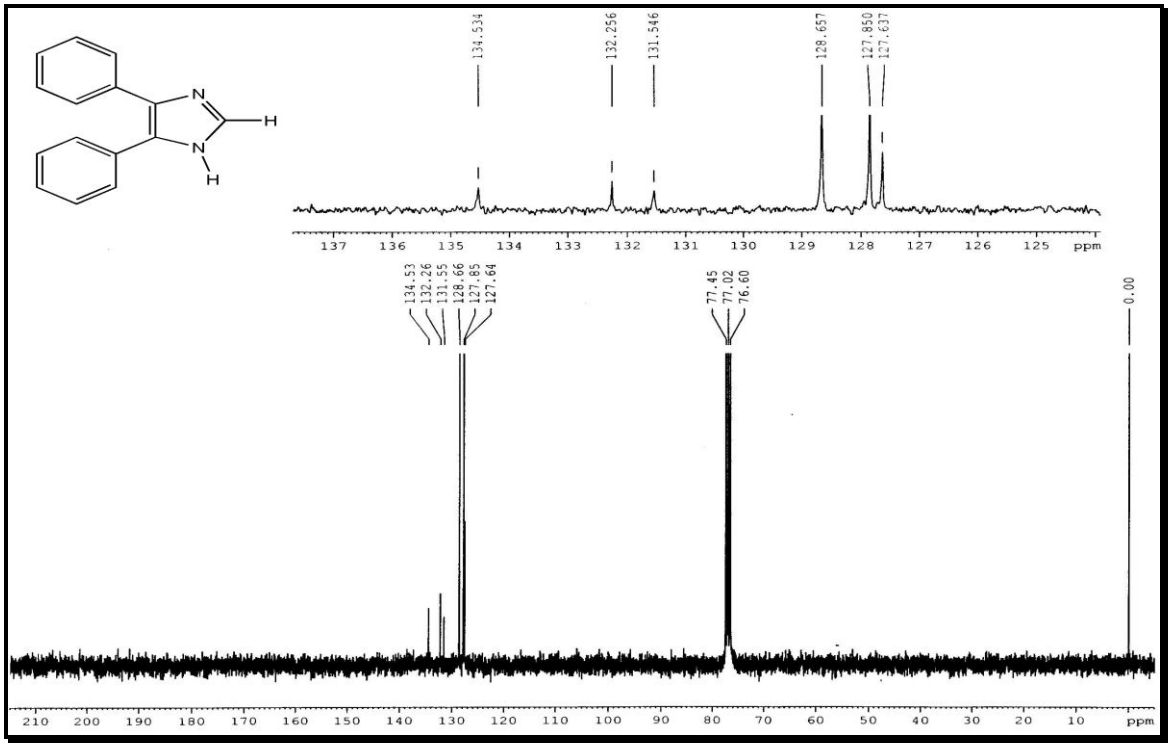
[13]CNMR - 2-(4,5-diphenyl 1H-imidazol-2-yl) pyridine



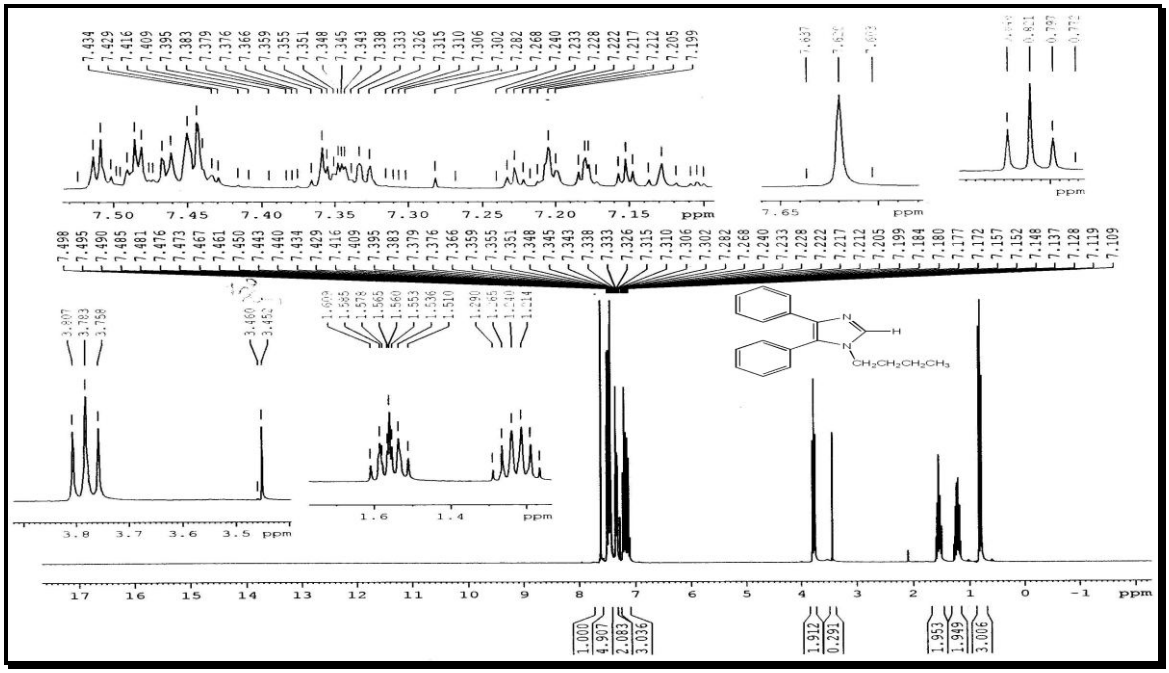
[1]HNMR -4, 5-diphenyl-1-H imidazole



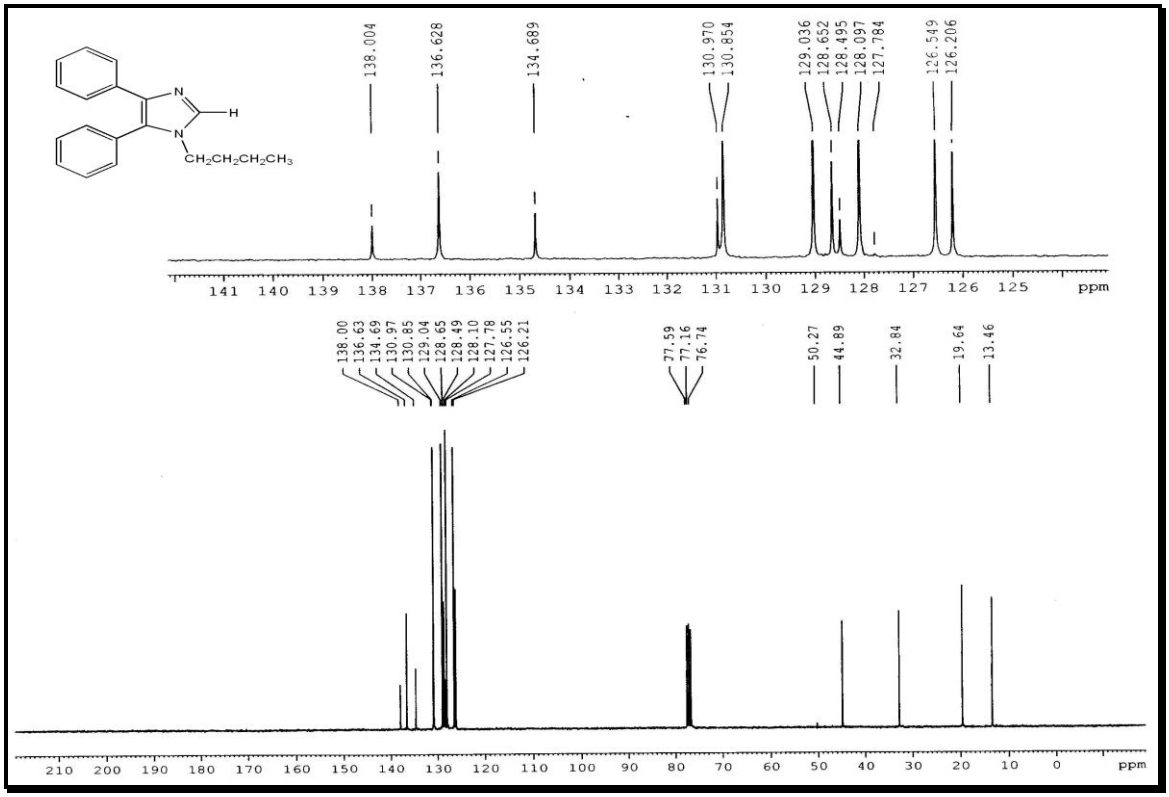
[13]CNMR - 4, 5-diphenyl-1-H imidazole



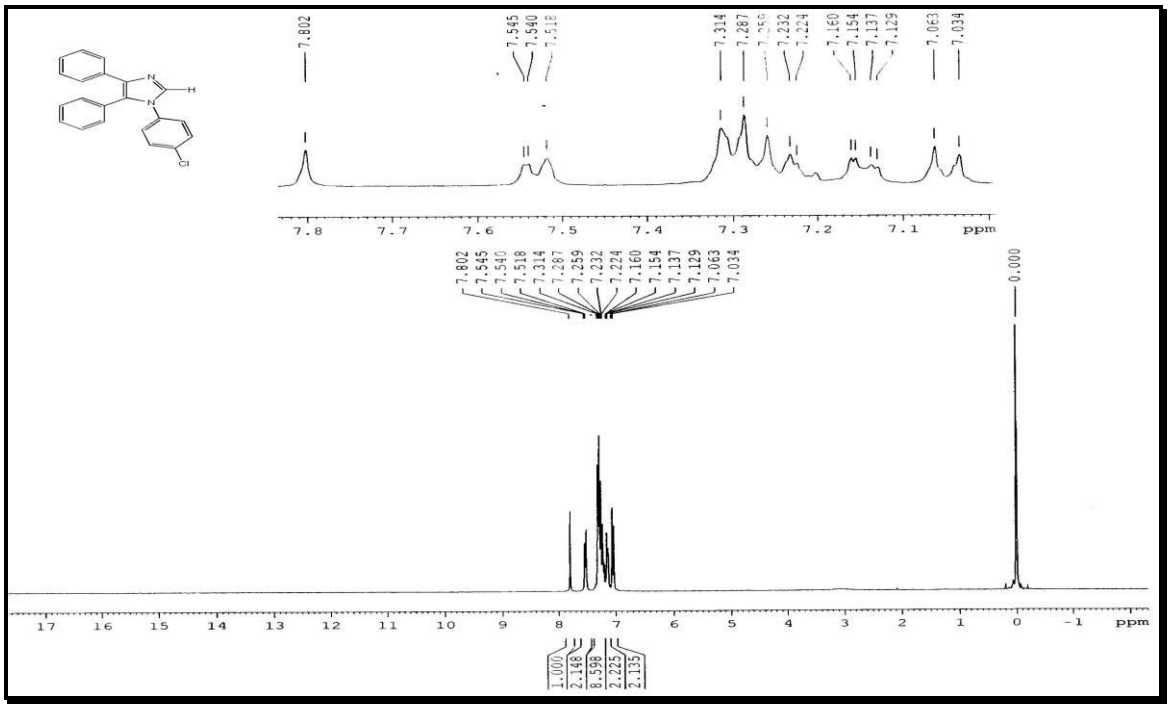
[1]HNMR - 1-butyl-4,5-diphenyl-1-H imidazole



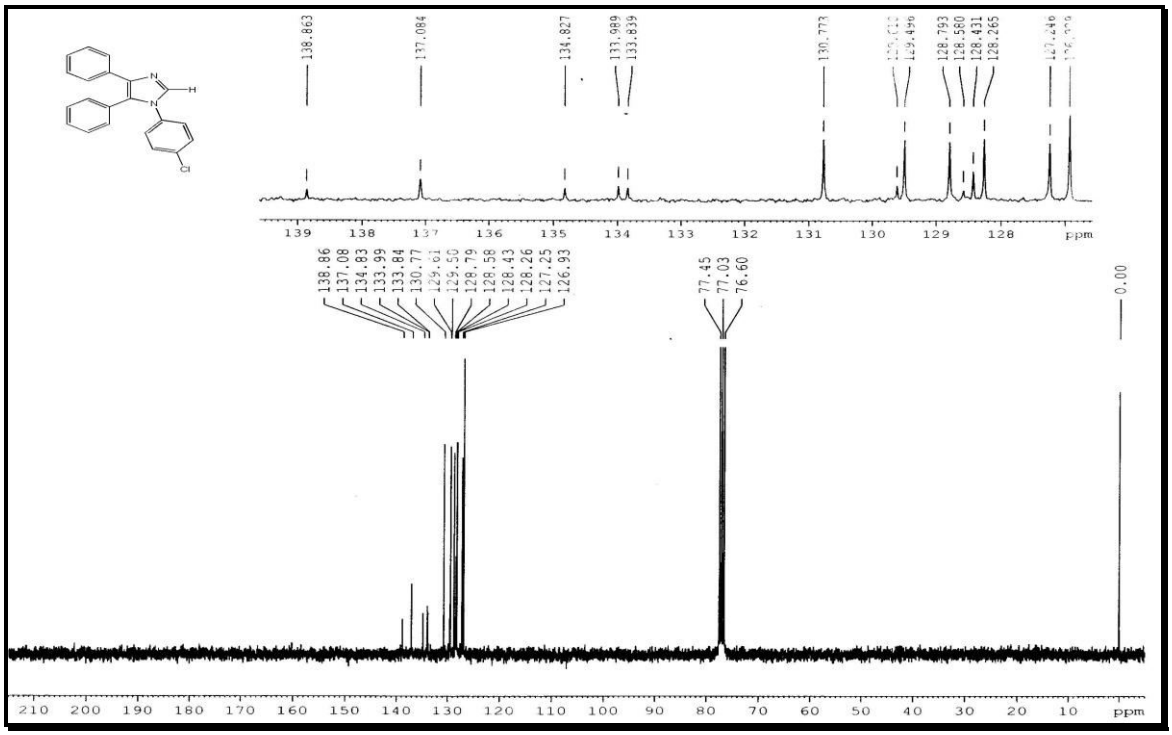
[13]CNMR - 1-butyl-4,5-diphenyl-1-H imidazole



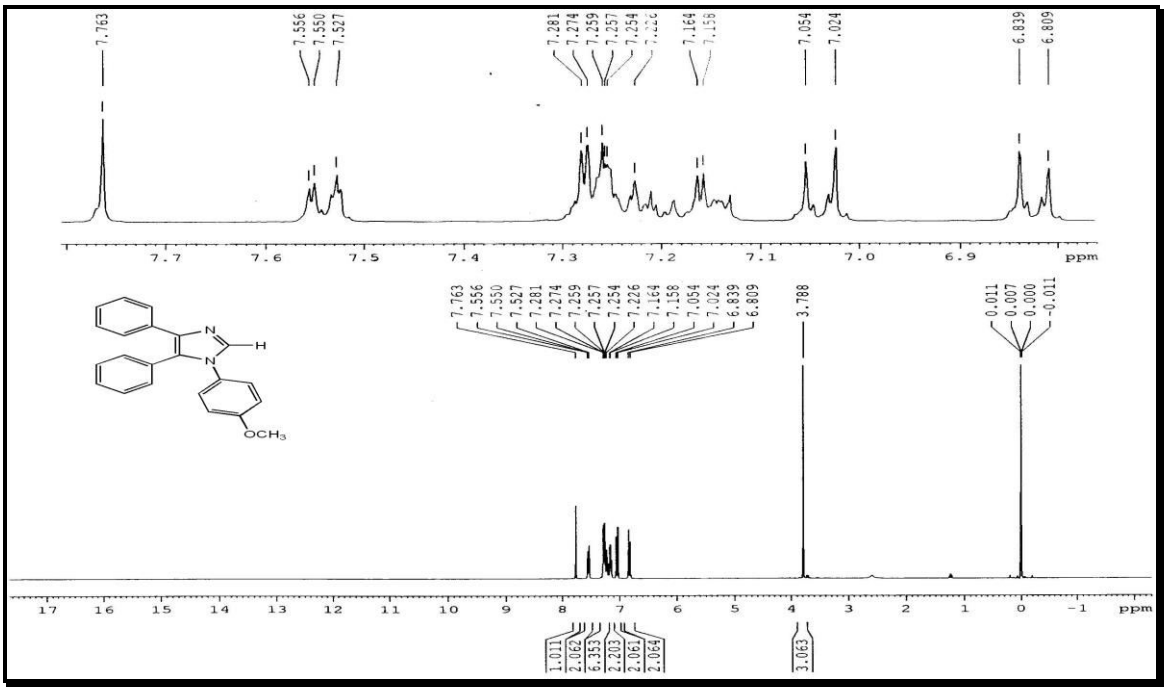
[1]HNMR - 1-(4-chlorophenyl)-4,5-diphenyl-1-H imidazole



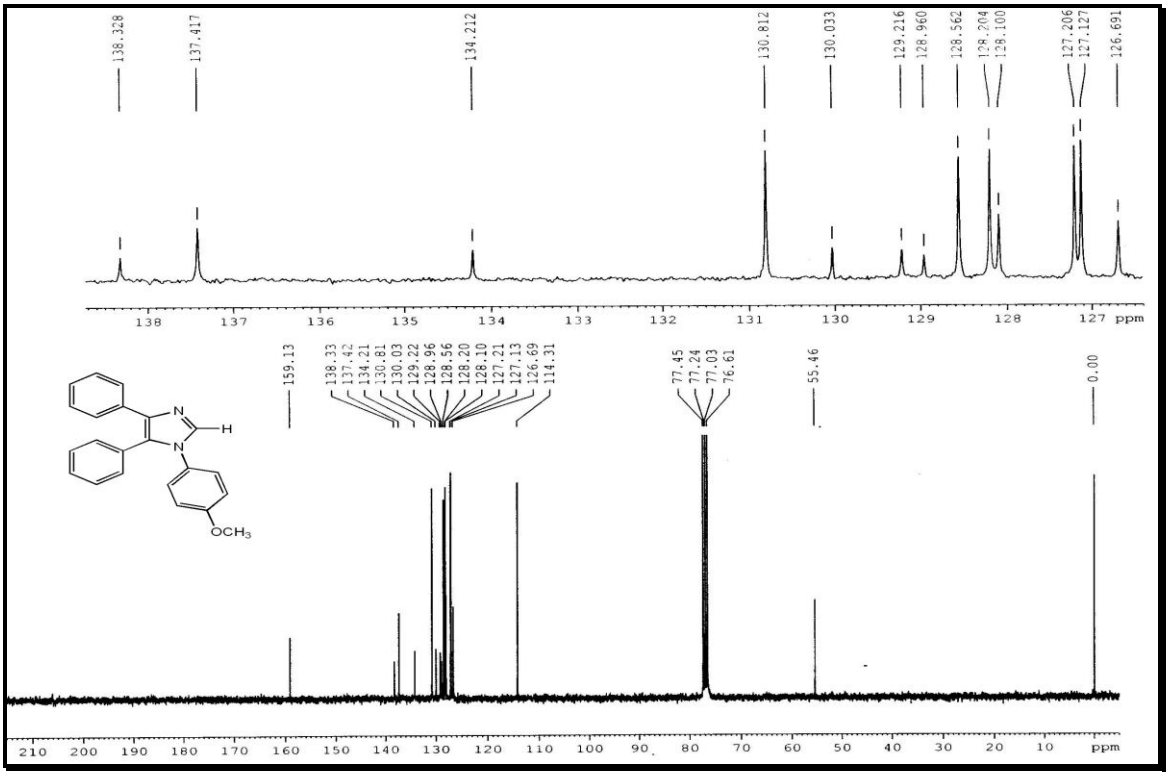
[13]CNMR - 1-(4-chlorophenyl)-4,5-diphenyl-1-H imidazole



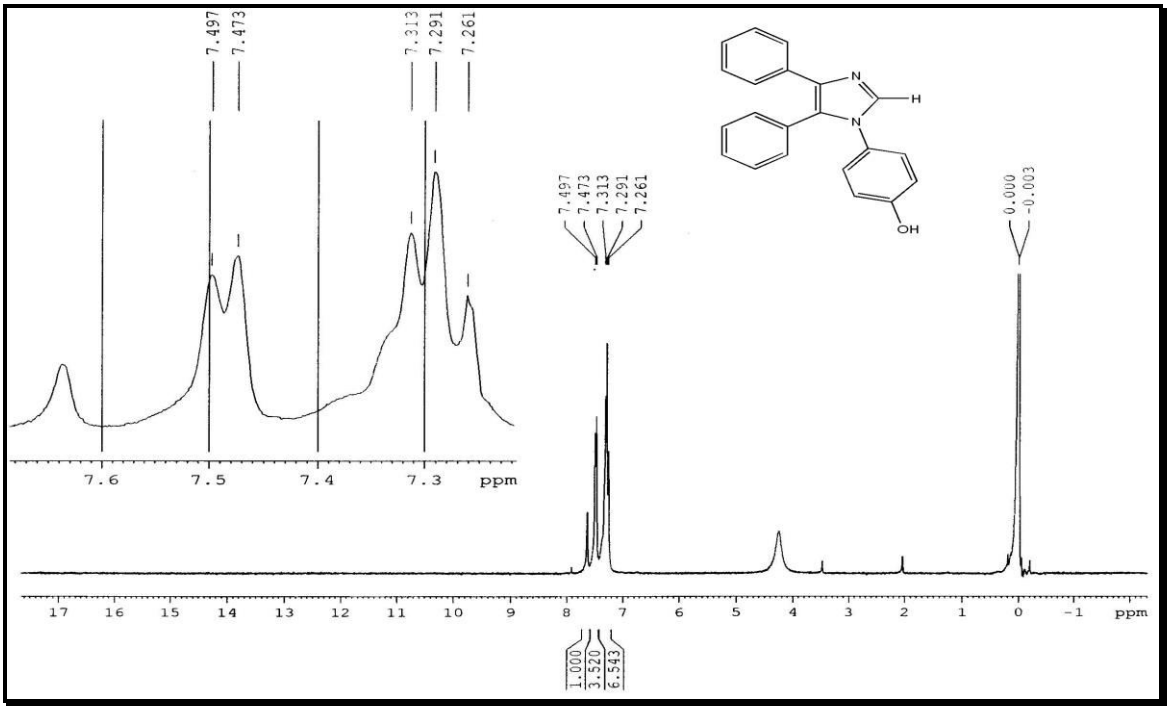
[1]HNMR - 1-(4-methoxyphenyl)-4,5-diphenyl-1-H imidazole



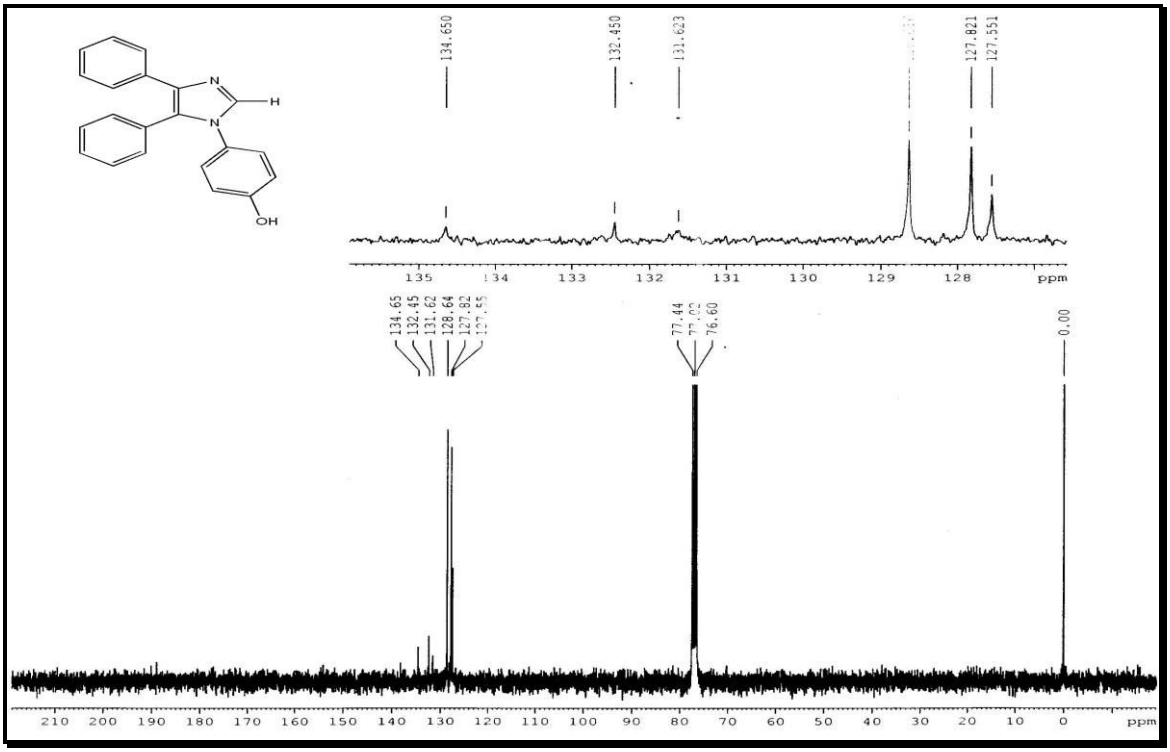
[13]CNMR - 1-(4-methoxyphenyl)-4,5-diphenyl-1-H imidazole



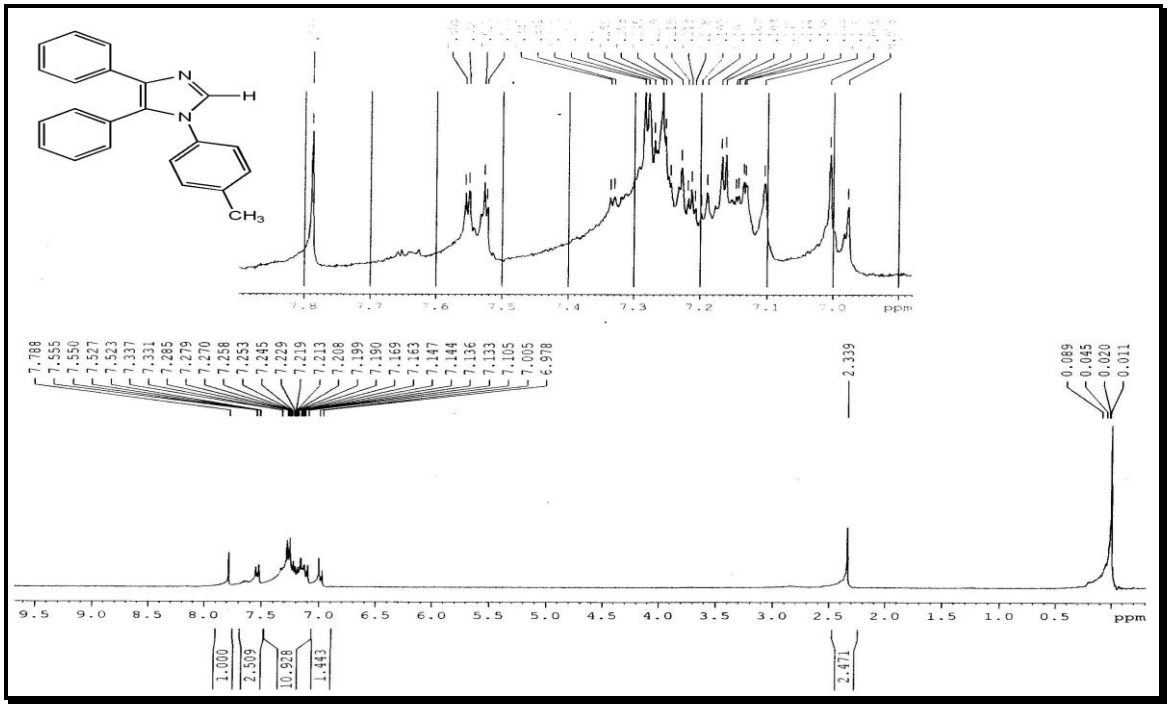
[1]HNMR - 4-(4,5-diphenyl-1H-imidazol-1-yl)phenol



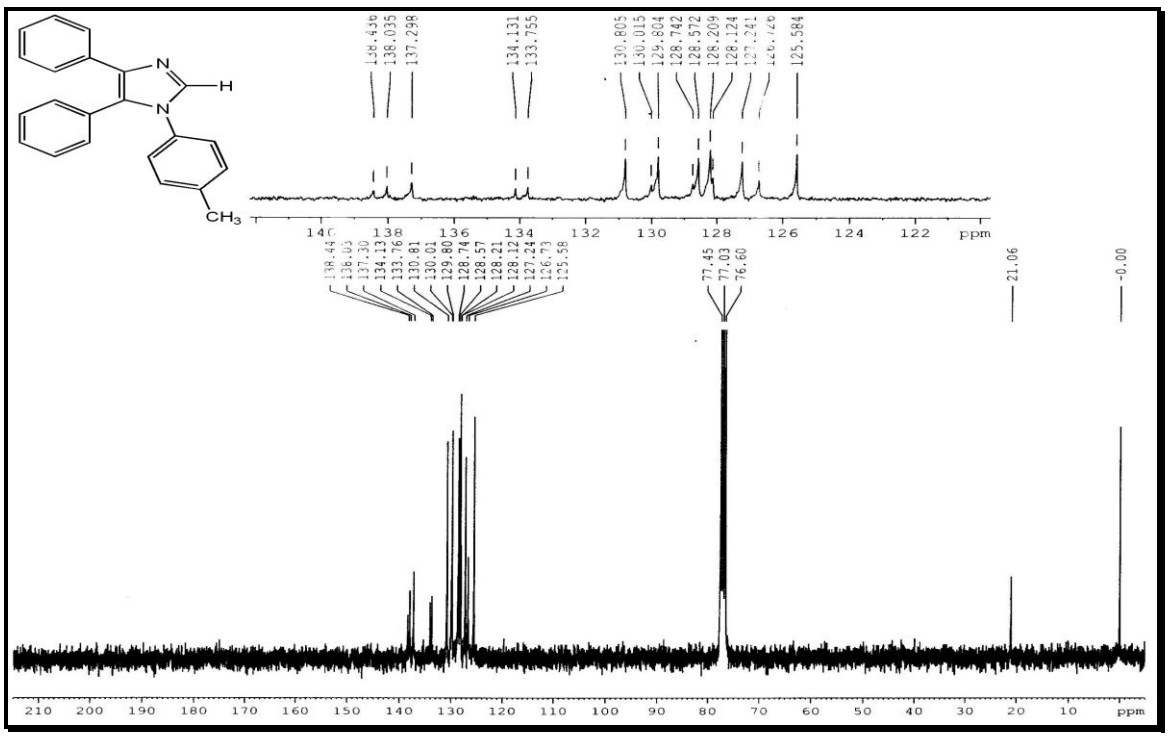
[13]CNMR - 4-(4,5-diphenyl-1H-imidazol-1-yl)phenol



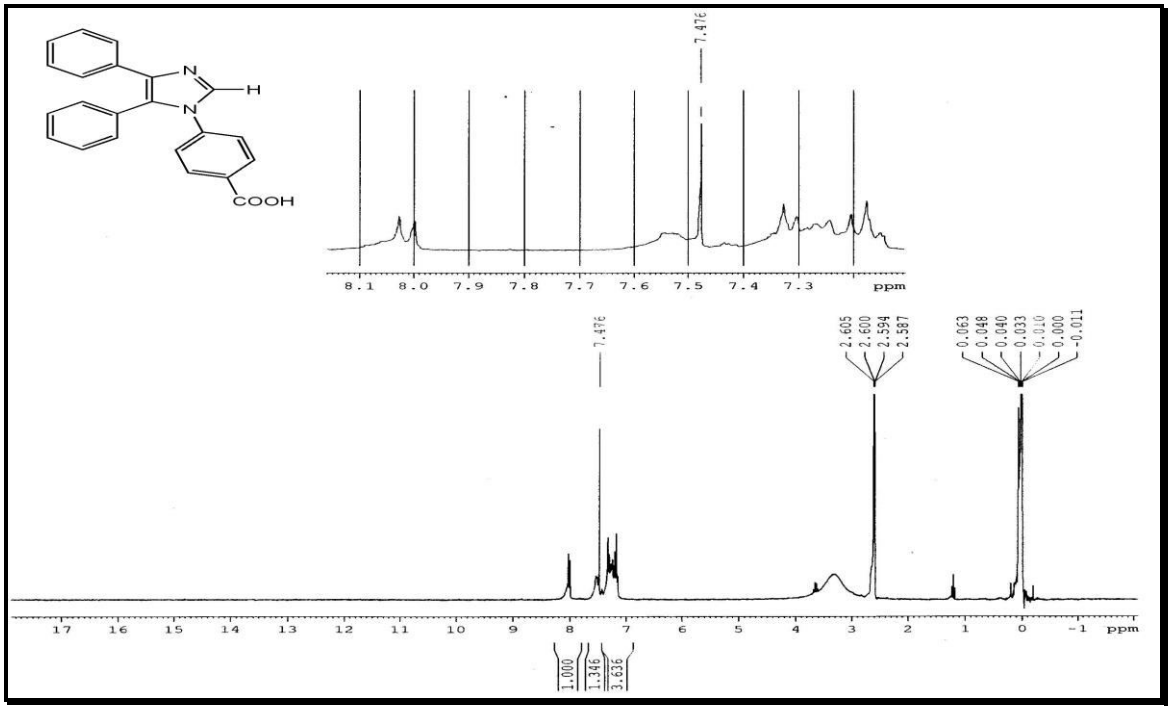
[1]HNMR - 4,5-diphenyl-1-p-tolyl-1H-imidazole



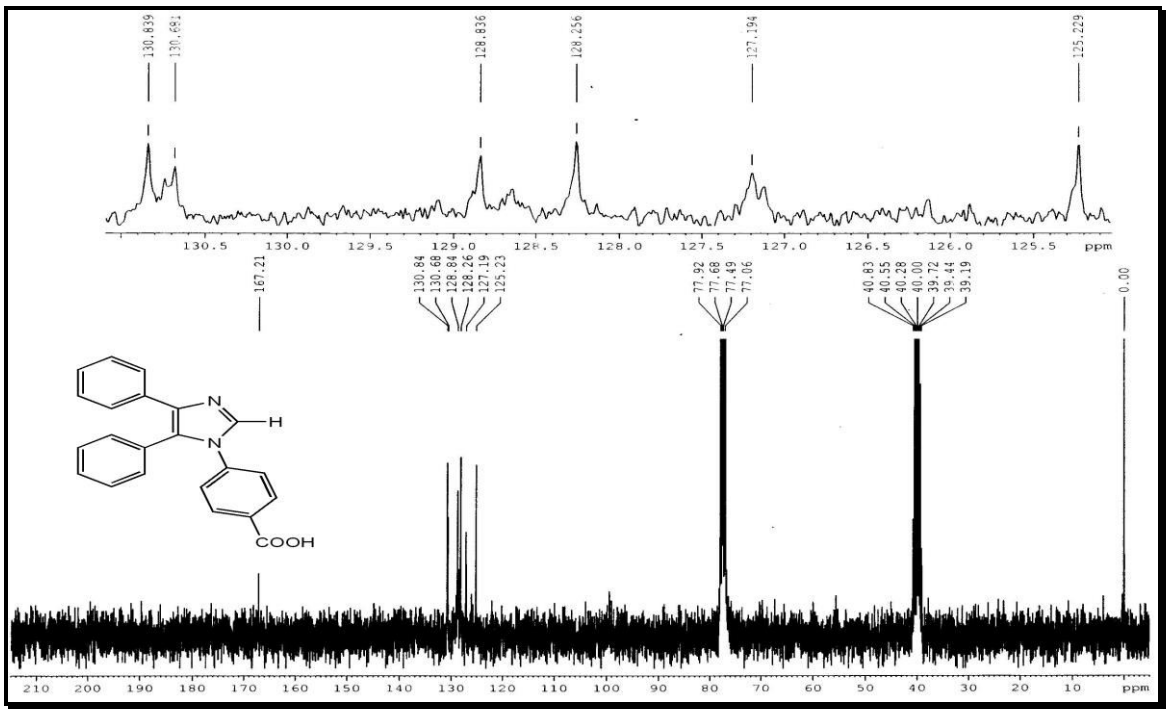
[13]CNMR - 4,5-diphenyl-1-p-tolyl-1H-imidazole



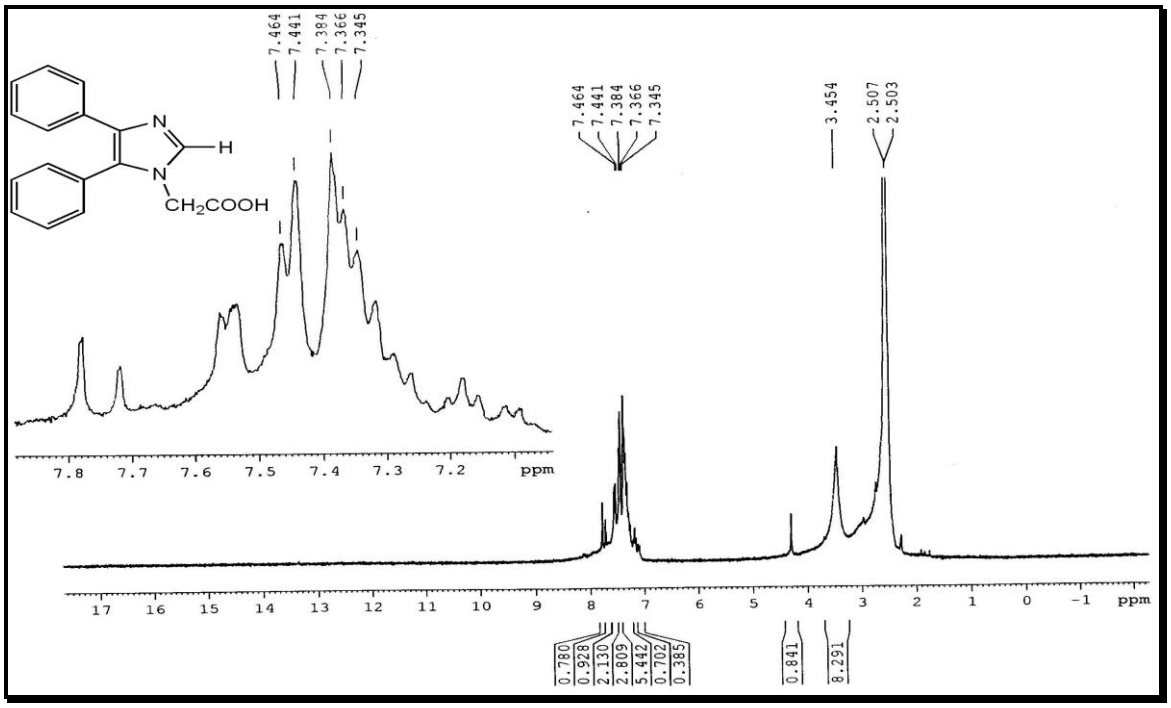
[1]HNMR - 4-(4,5-diphenyl-1H-imidazol-1-yl)benzoic acid



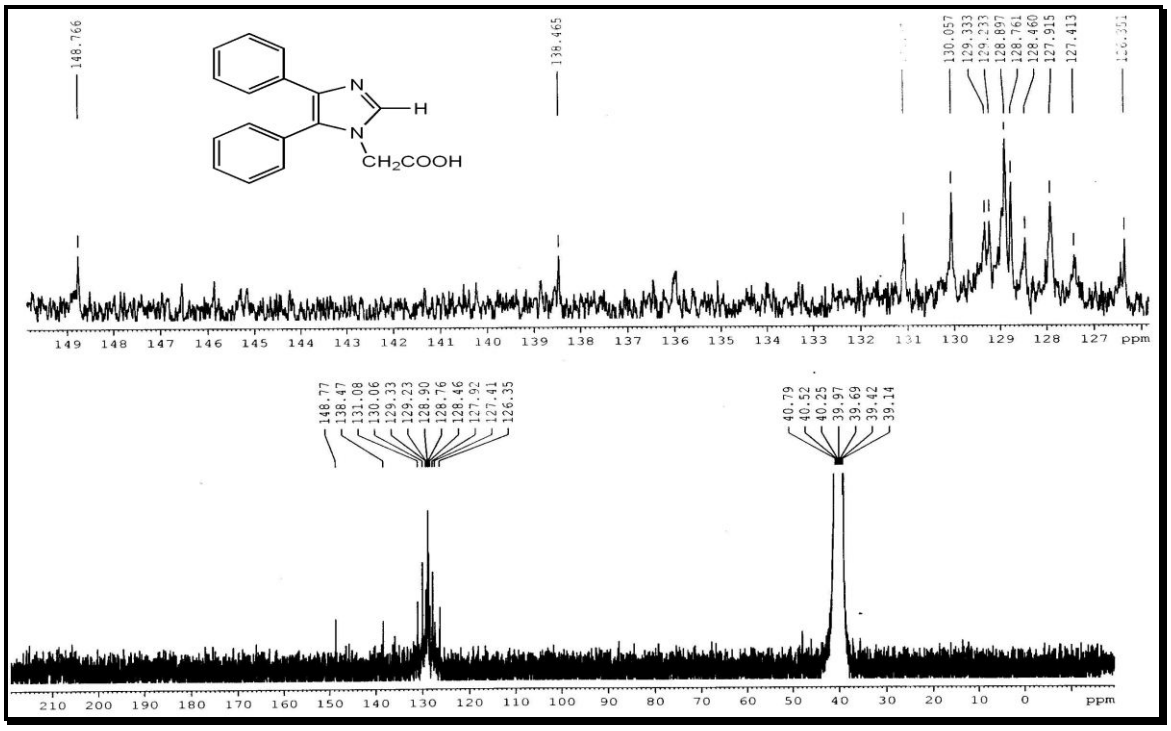
[13]CNMR - 4-(4,5-diphenyl-1H-imidazol-1-yl)benzoic acid



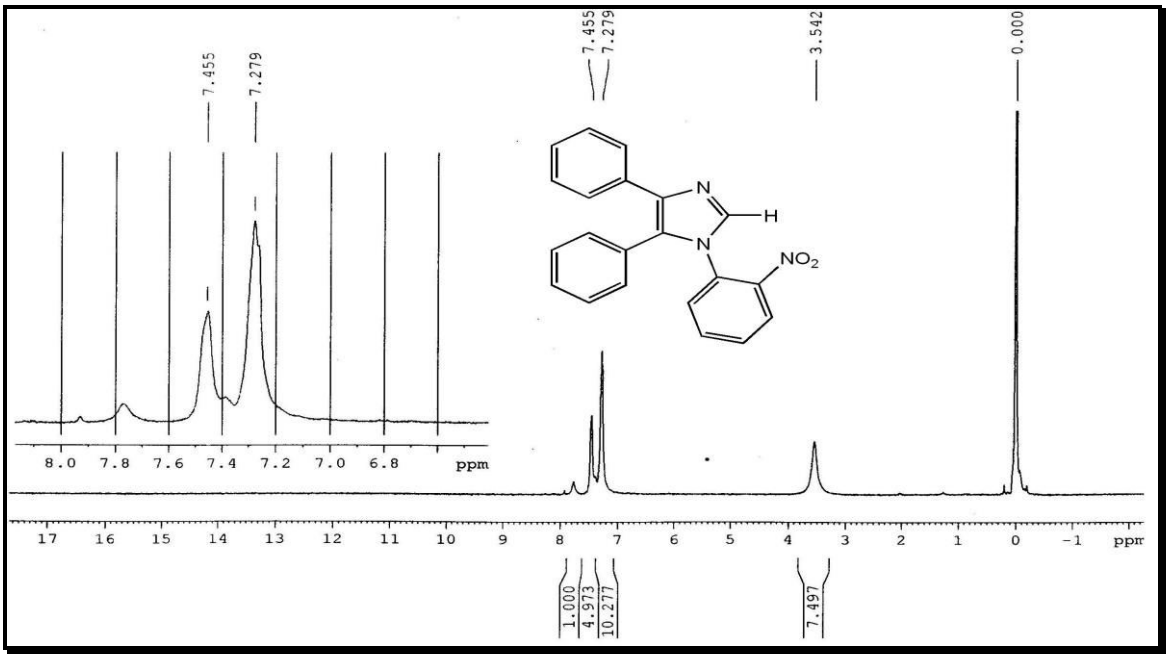
[1]HNMR - 2-(4,5-diphenyl-1H-imidazol-1-yl)acetic acid



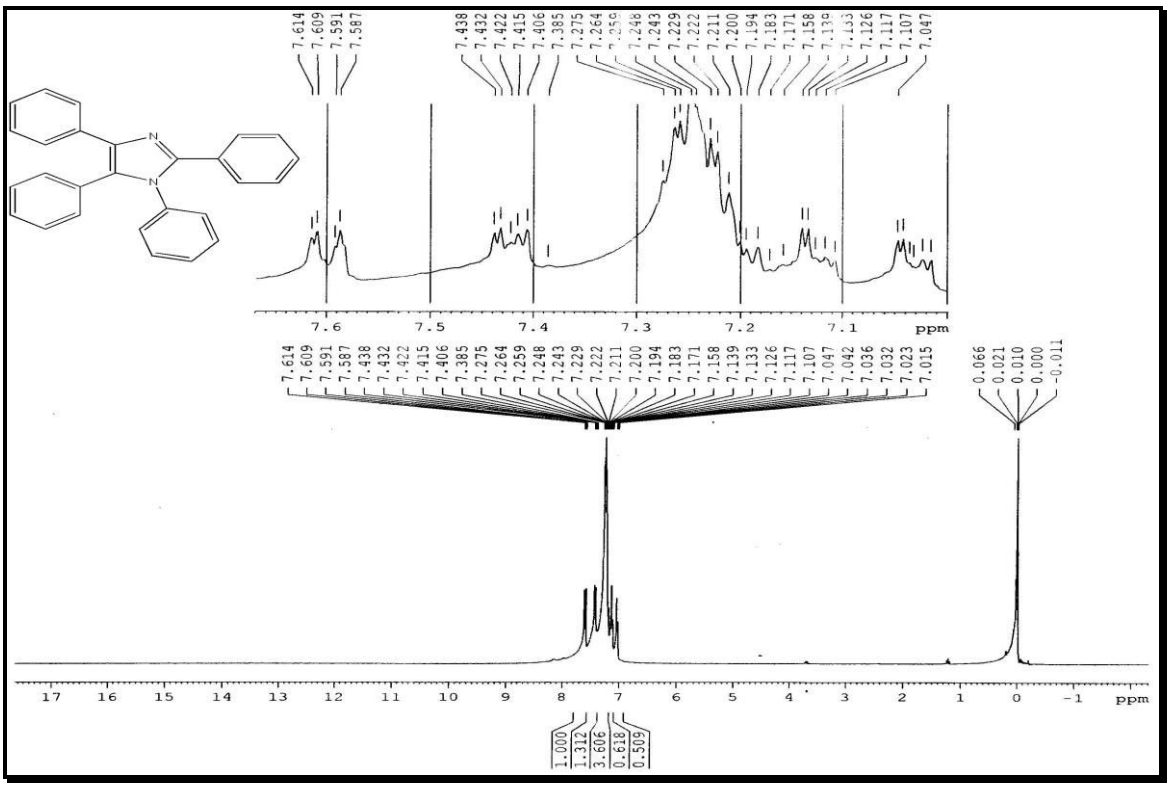
[13]CNMR - 2-(4,5-diphenyl-1H-imidazol-1-yl)acetic acid



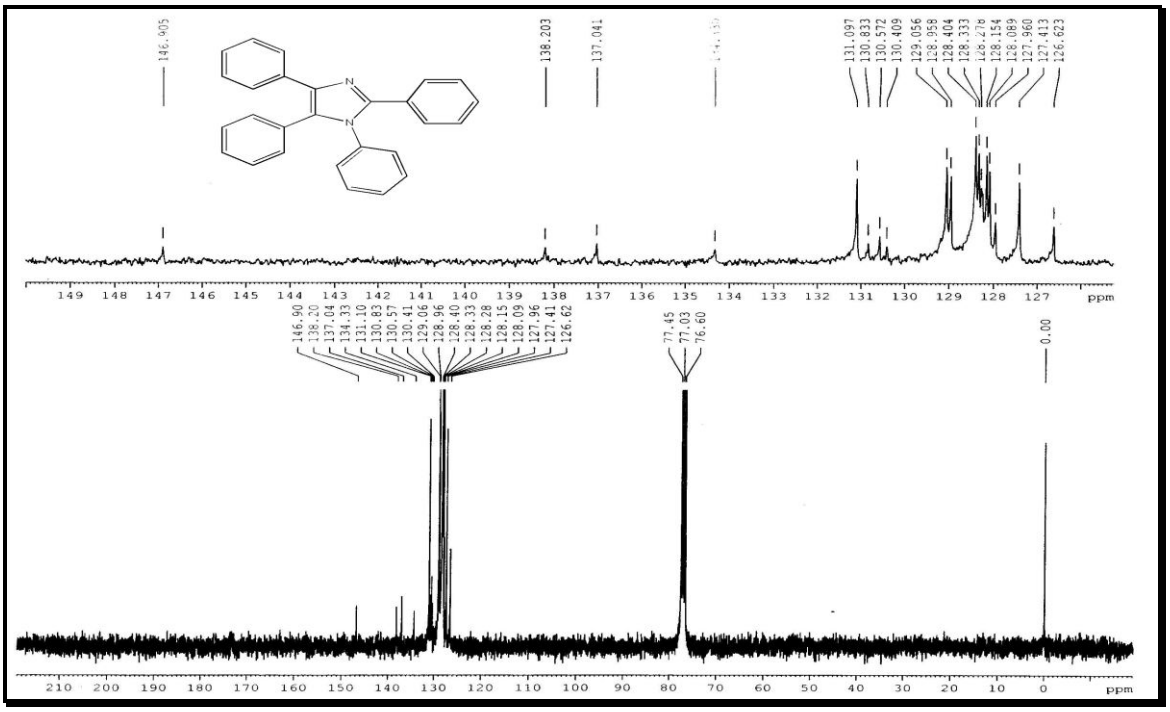
[1]HNMR - 1-(2-nitrophenyl)-4,5-diphenyl-1H-imidazole



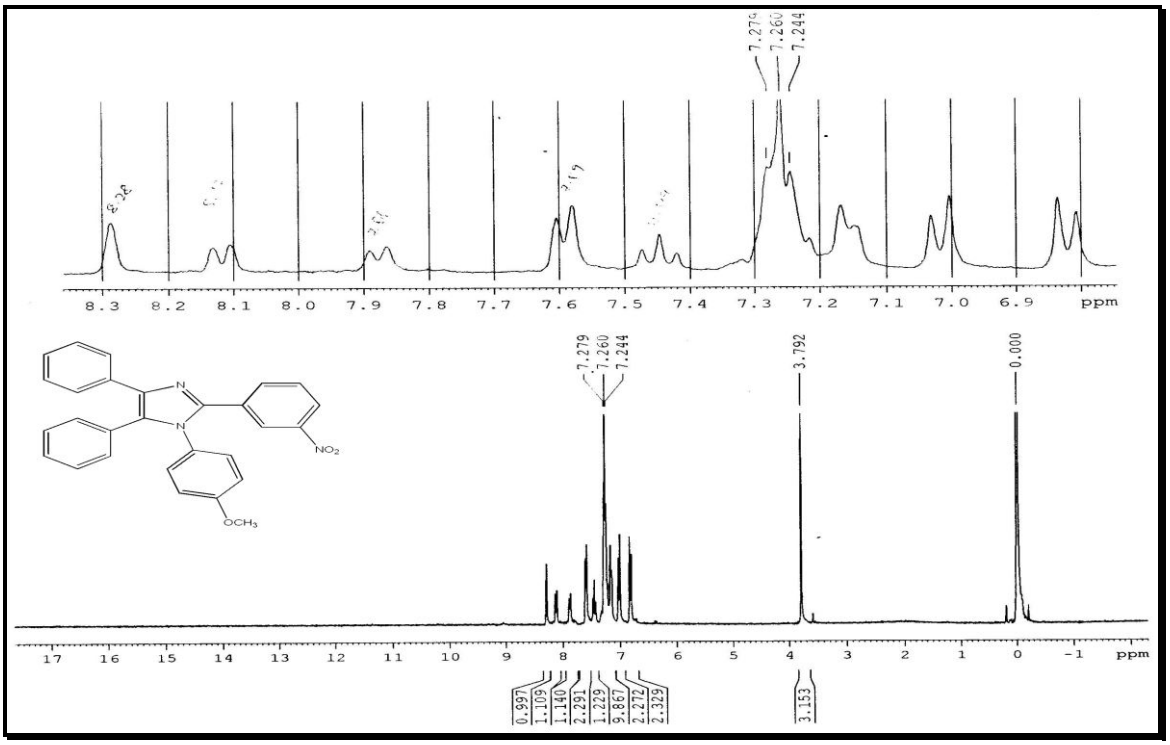
[1]HNMR- 1,2,4,5-tetraphenyl-1H-imidazole



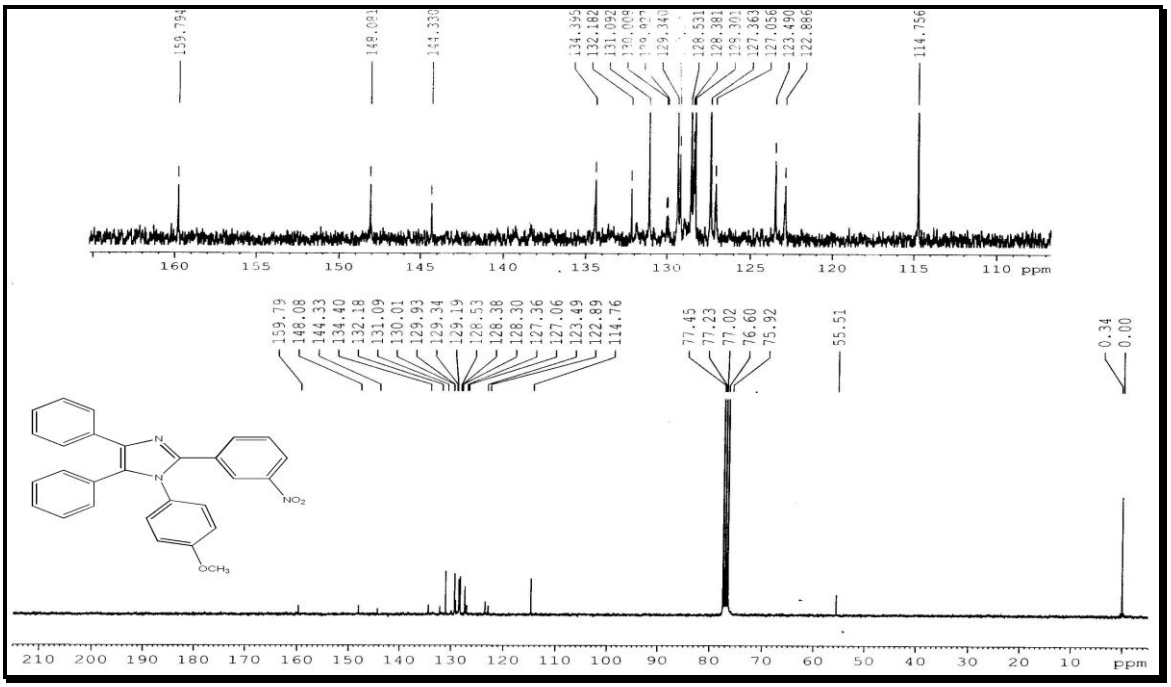
[13]CNMR - 1,2,4,5-tetraphenyl-1H-imidazole



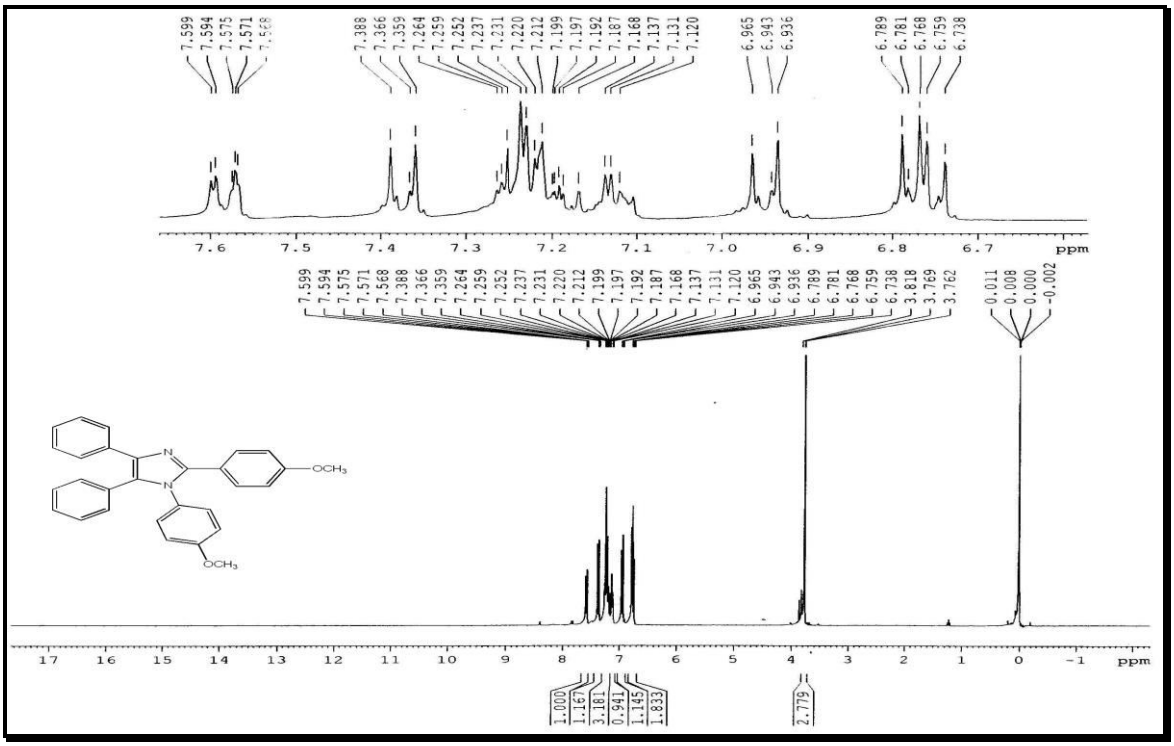
[1]HNMR - 1-(4-methoxyphenyl)-2-(3-nitrophenyl)-4,5-diphenyl-1H-imidazole



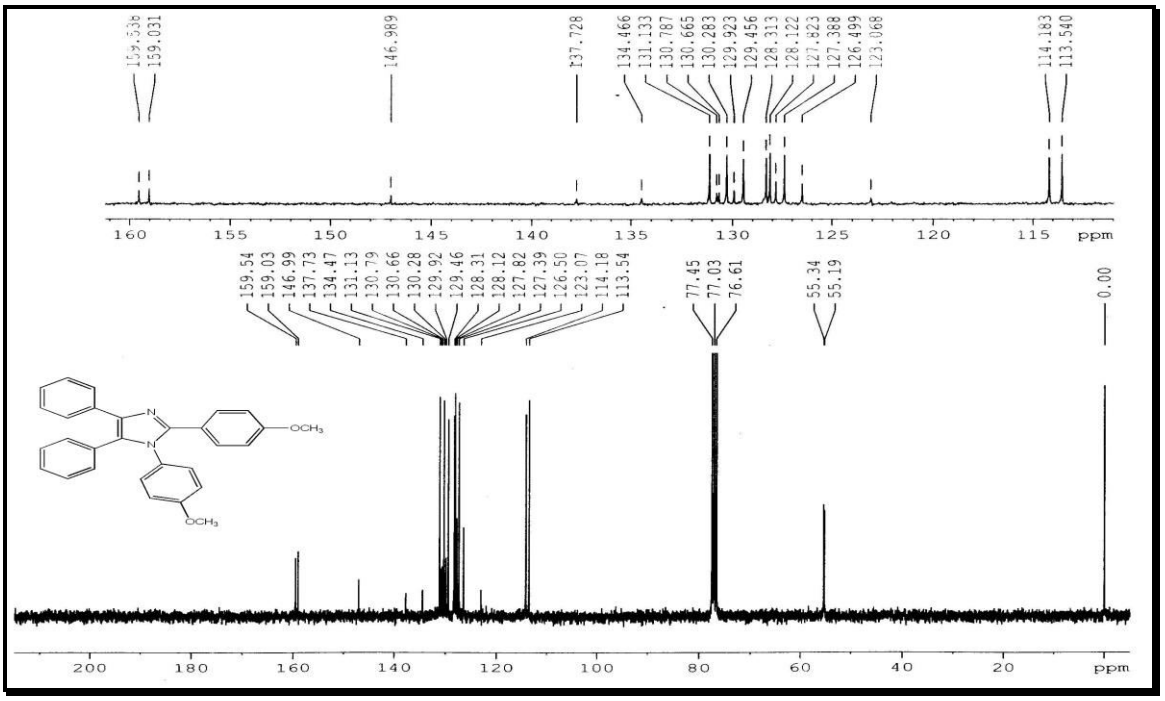
[13]CNMR - 1-(4-methoxyphenyl)-2-(3-nitrophenyl)-4,5-diphenyl-1H-imidazole



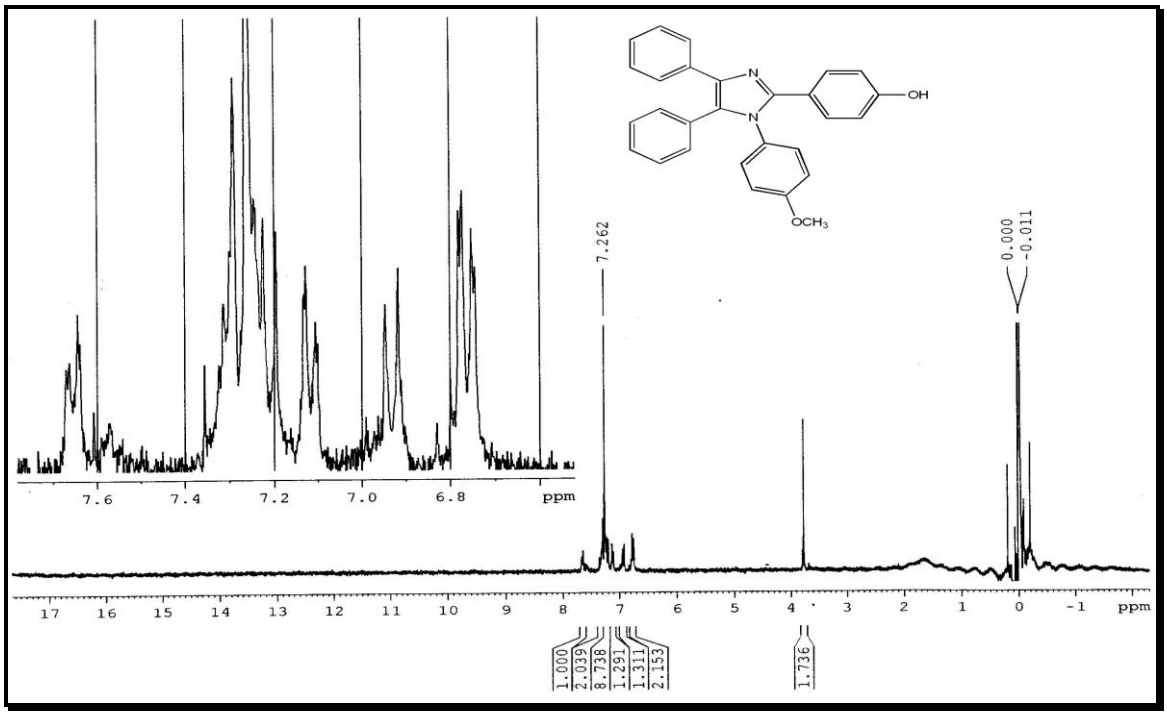
[1]HNMR - 1,2-bis(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole



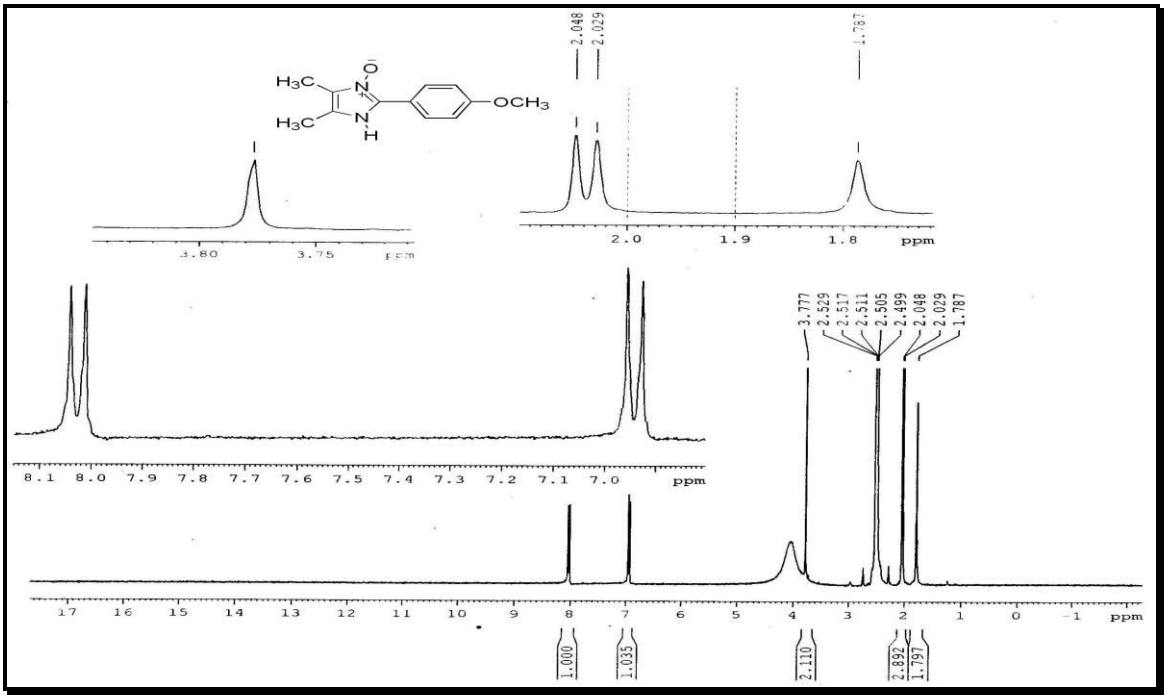
[13]CNMR - 1,2-bis(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole



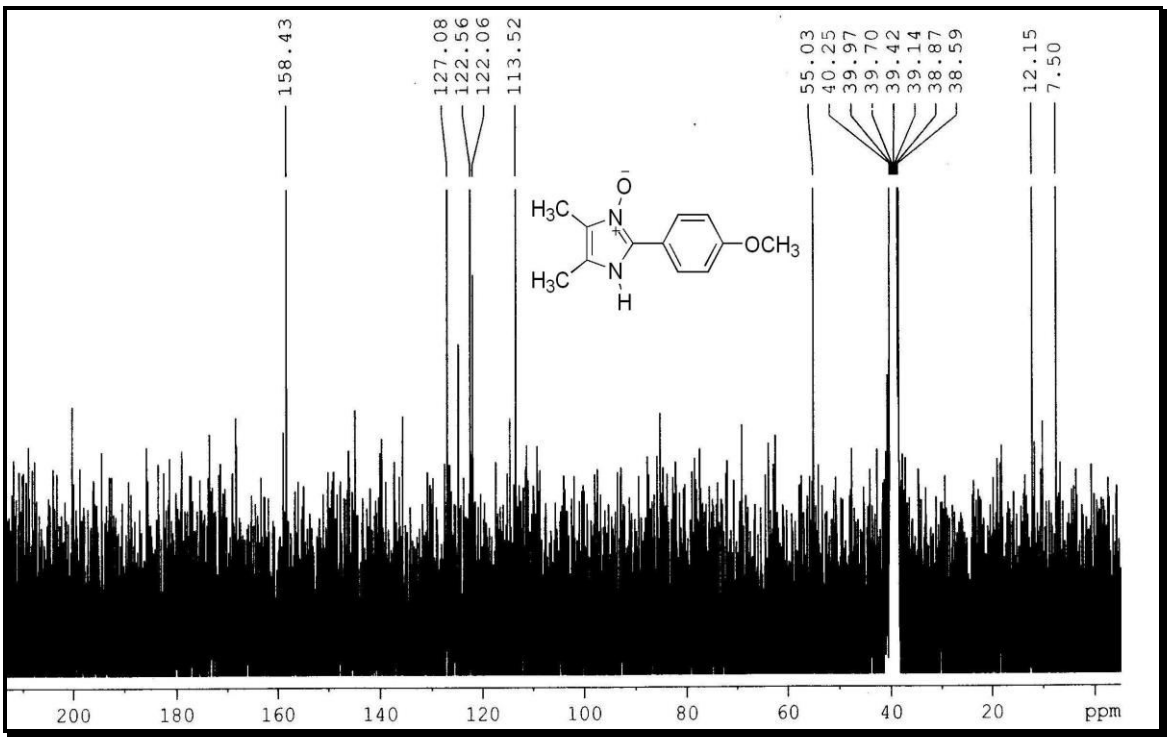
[1]HNMR - 4-(1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-2-yl)phenol



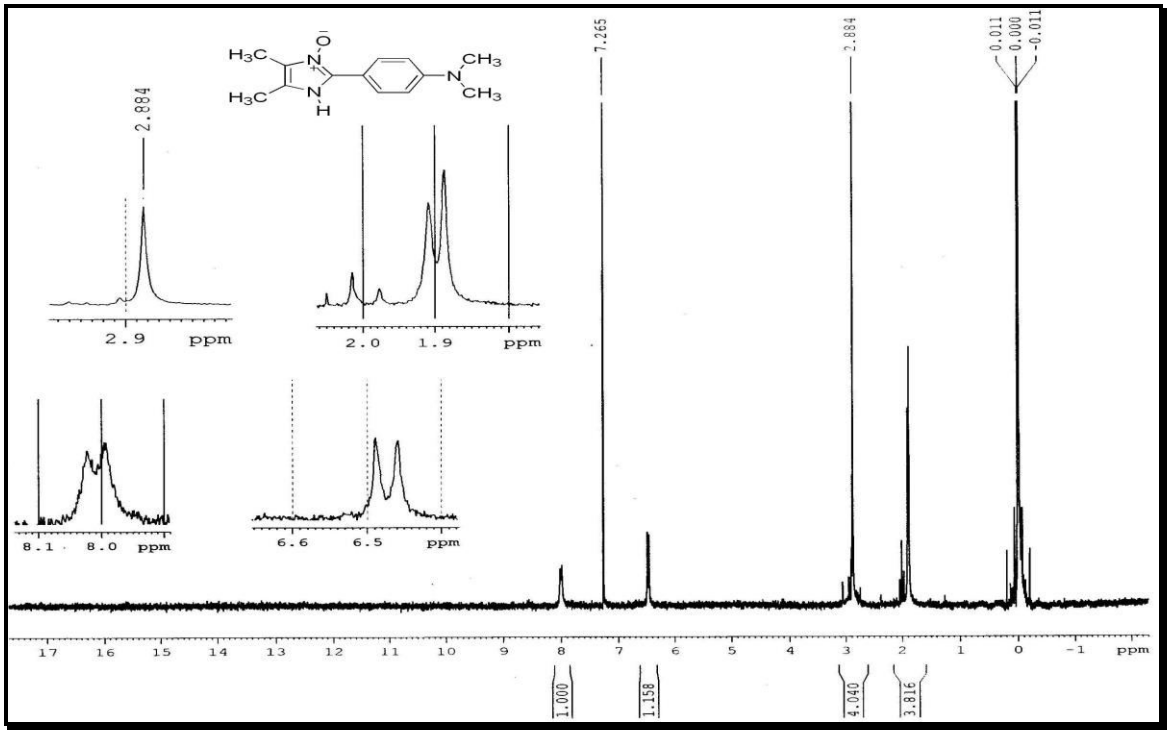
[1]HNMR - 2-(4-methoxy phenyl)-4,5-dimethyl Imidazole N-oxide



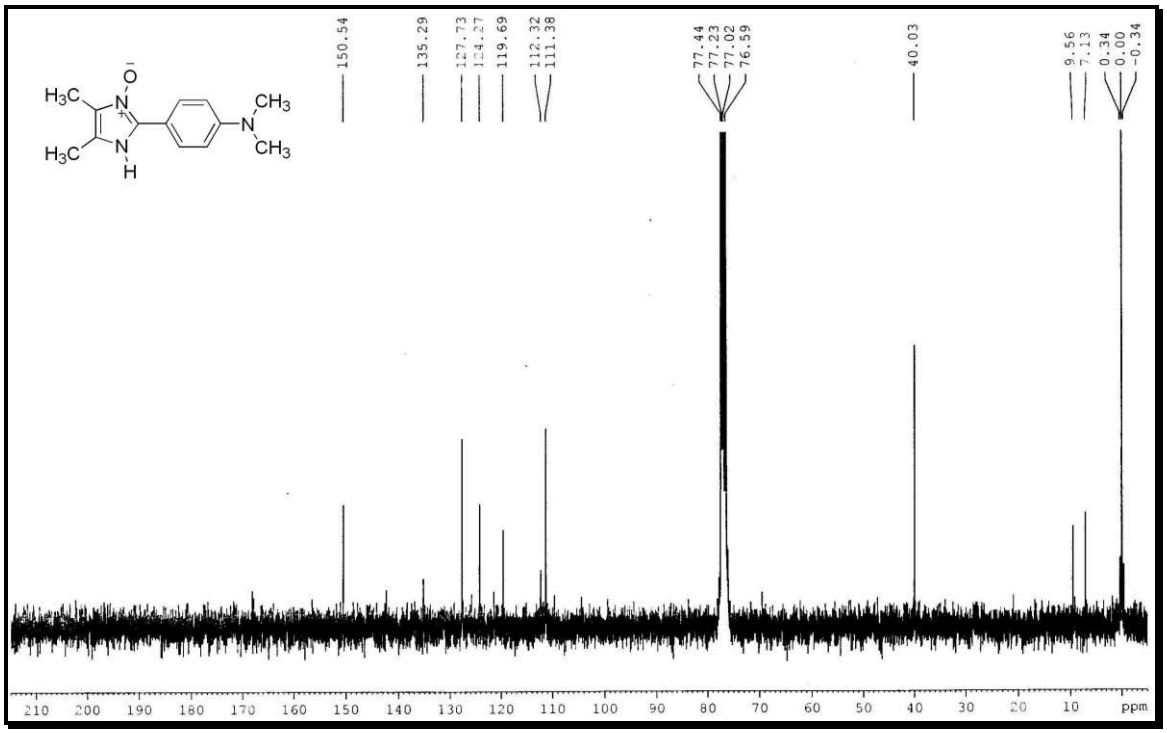
[13]CNMR - 2-(4-methoxy phenyl)-4,5-dimethyl Imidazole N-oxide



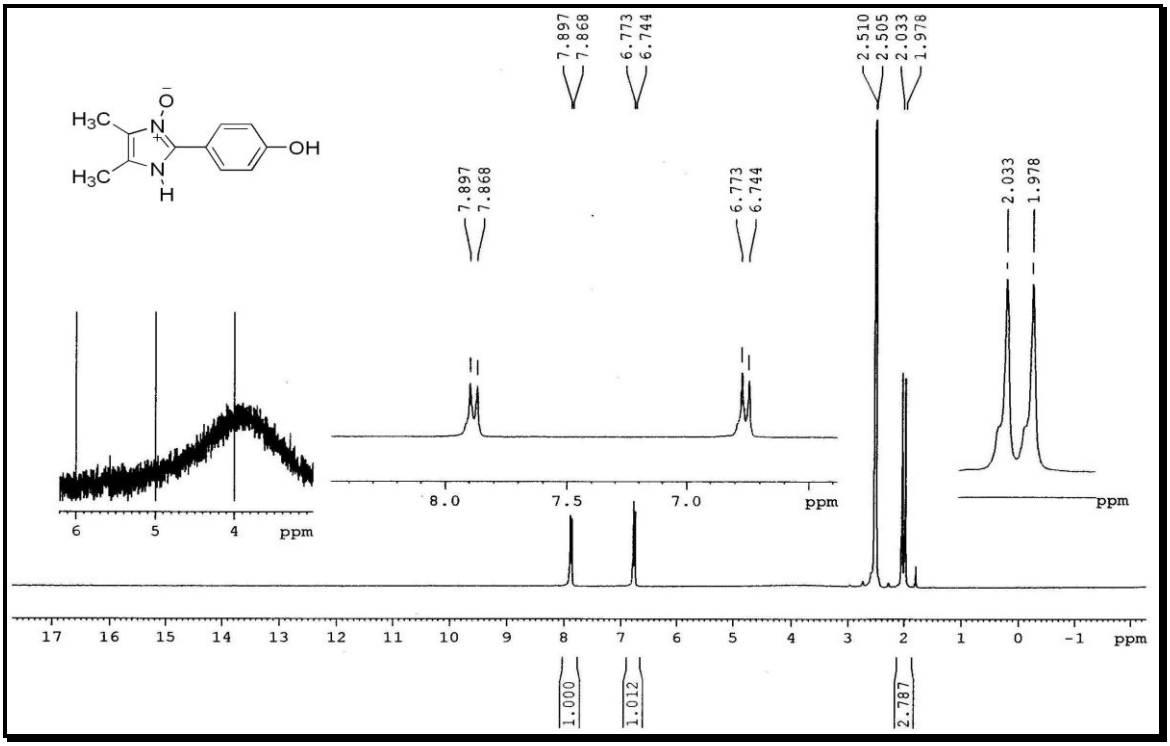
[1]HNMR - 2-(4-N,N-dimethylphenyl)-4,5-dimethyl Imidazole N-oxide



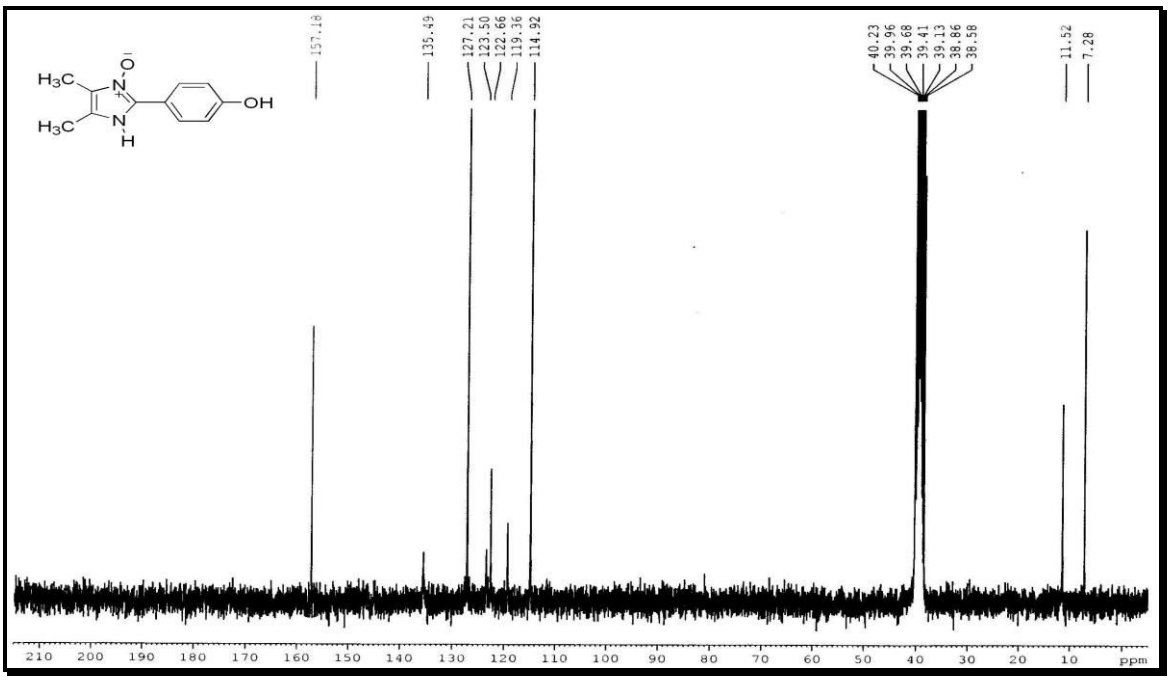
[13]CNMR - 2-(4-N,N-dimethylphenyl)-4,5-dimethyl Imidazole N-oxide



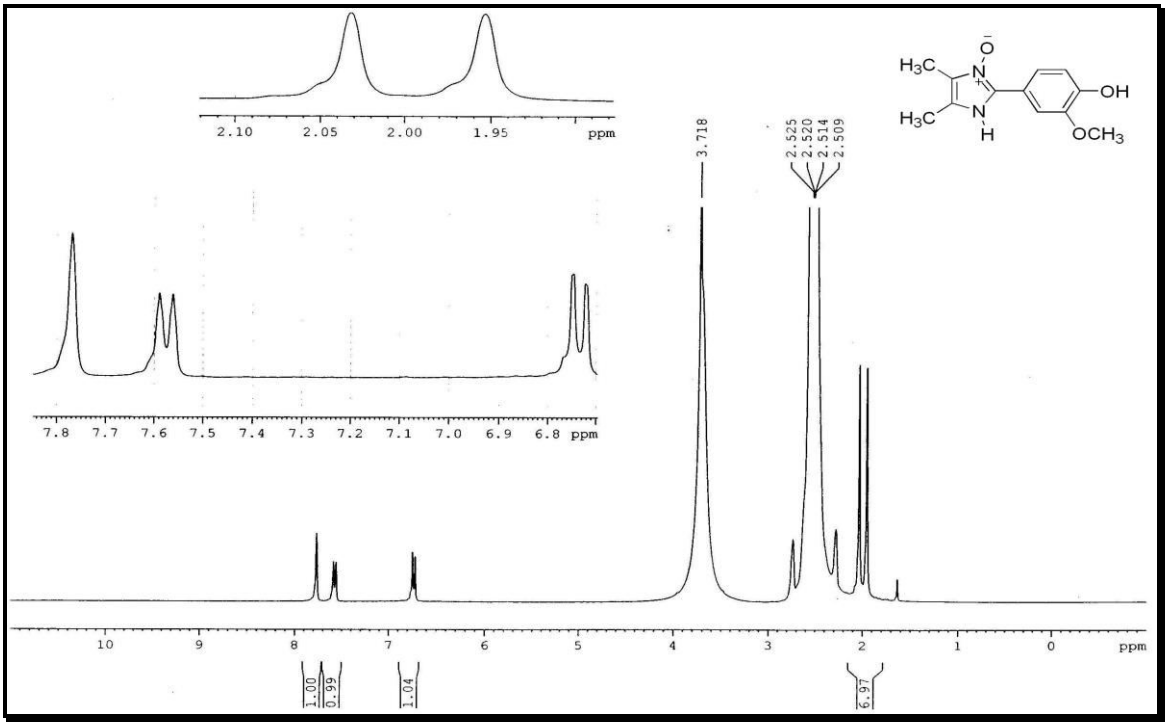
[1]HNMR - 2-(4-hydroxy phenyl)-4,5-dimethyl Imidazole N-oxide



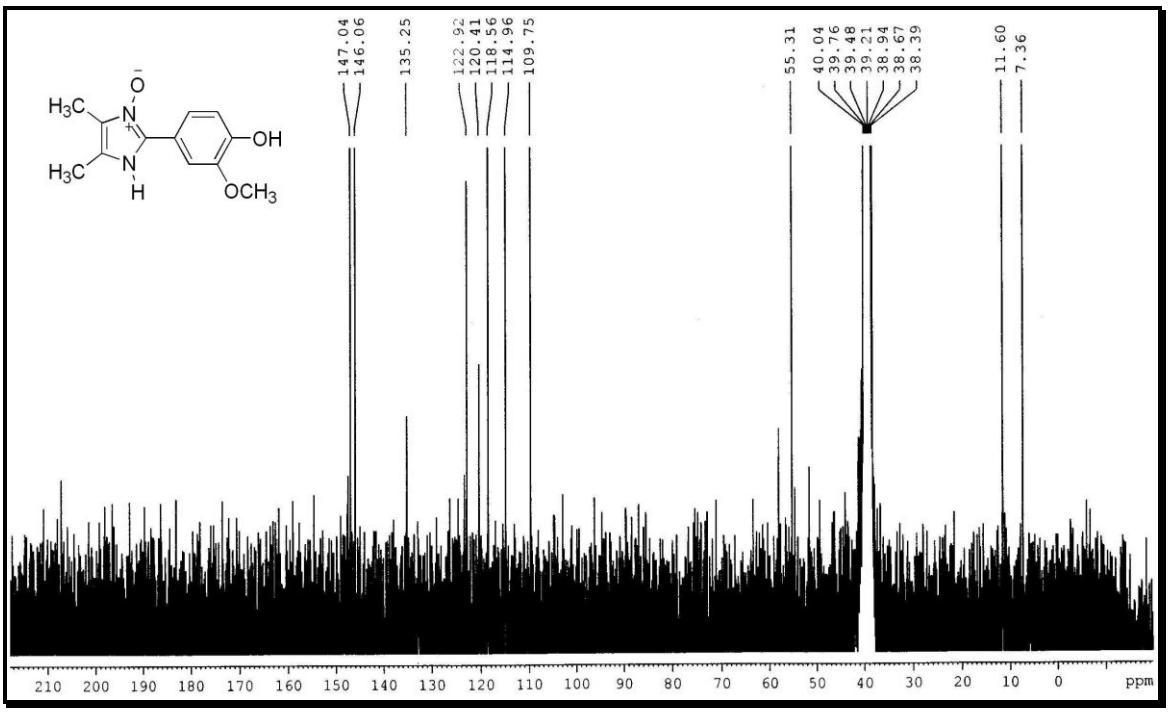
[13]CNMR - 2-(4-hydroxy phenyl)-4,5-dimethyl Imidazole N-oxide



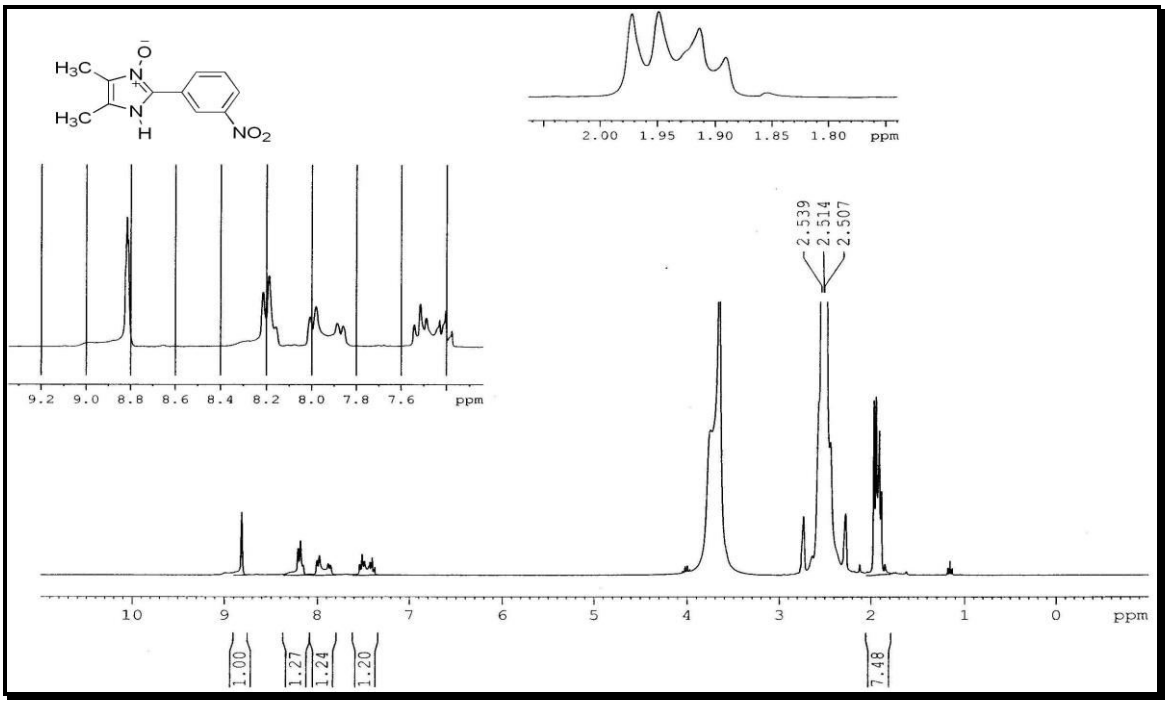
[1]HNMR - 2-(4-hydroxy -3-methoxyphenyl)-4,5-dimethyl Imidazole N-oxide



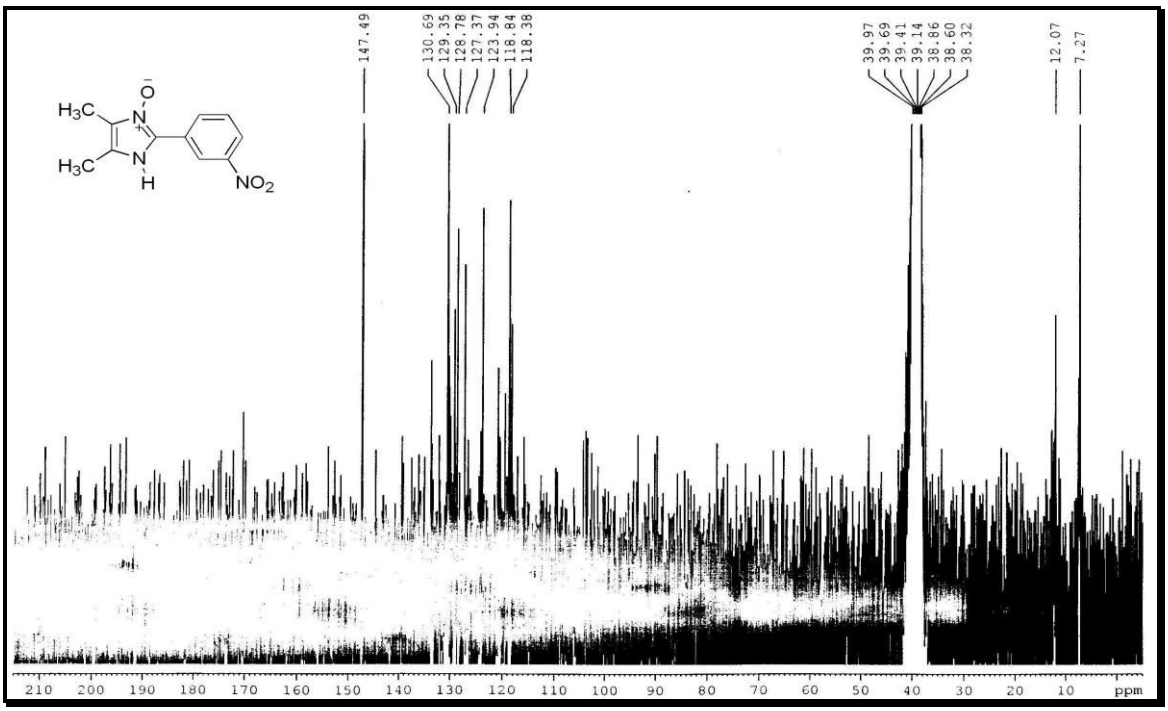
[13]CNMR - 2-(4-hydroxy -3-methoxyphenyl)-4,5-dimethyl Imidazole N-oxide



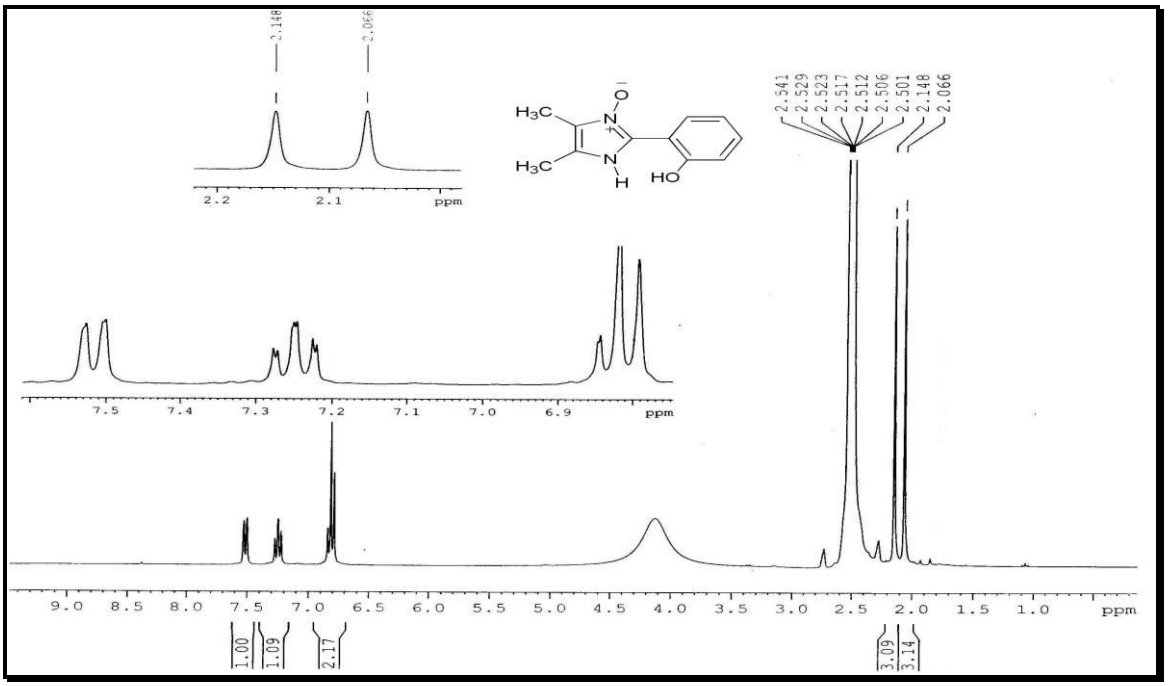
[1]HNMR - 2-(3-nitrophenyl)-4,5-dimethyl Imidazole N-oxide



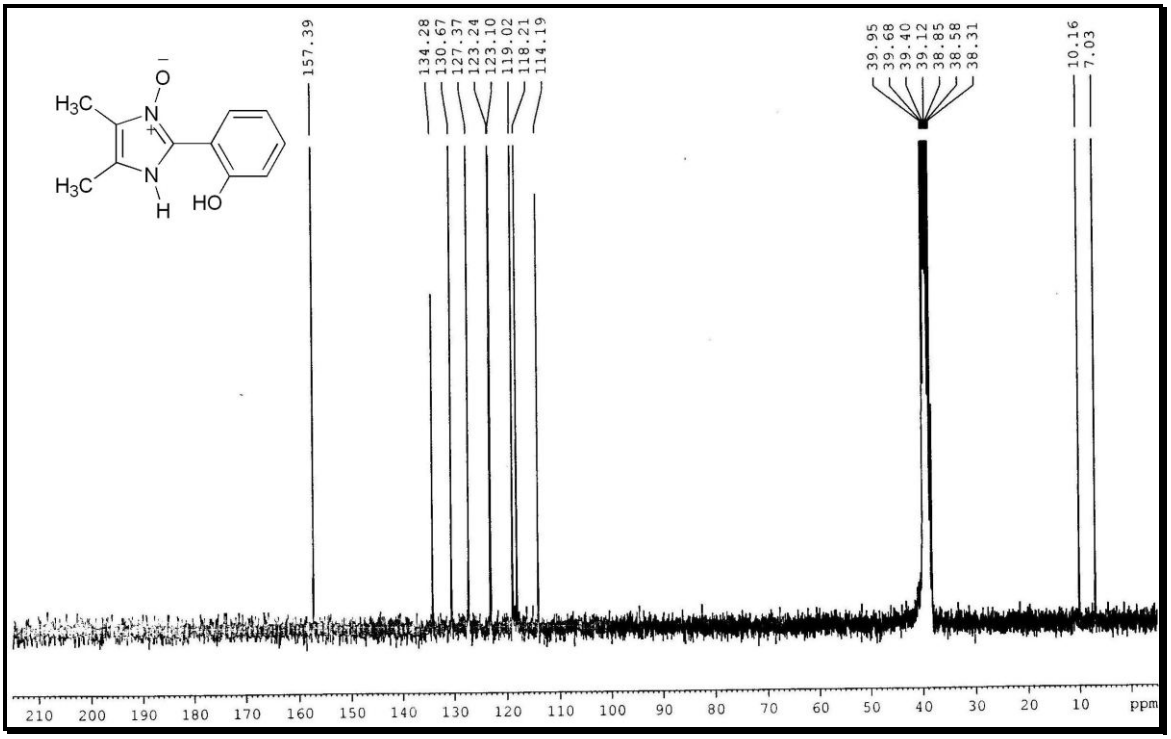
[13]CNMR - 2-(3-nitrophenyl)-4,5-dimethyl Imidazole N-oxide



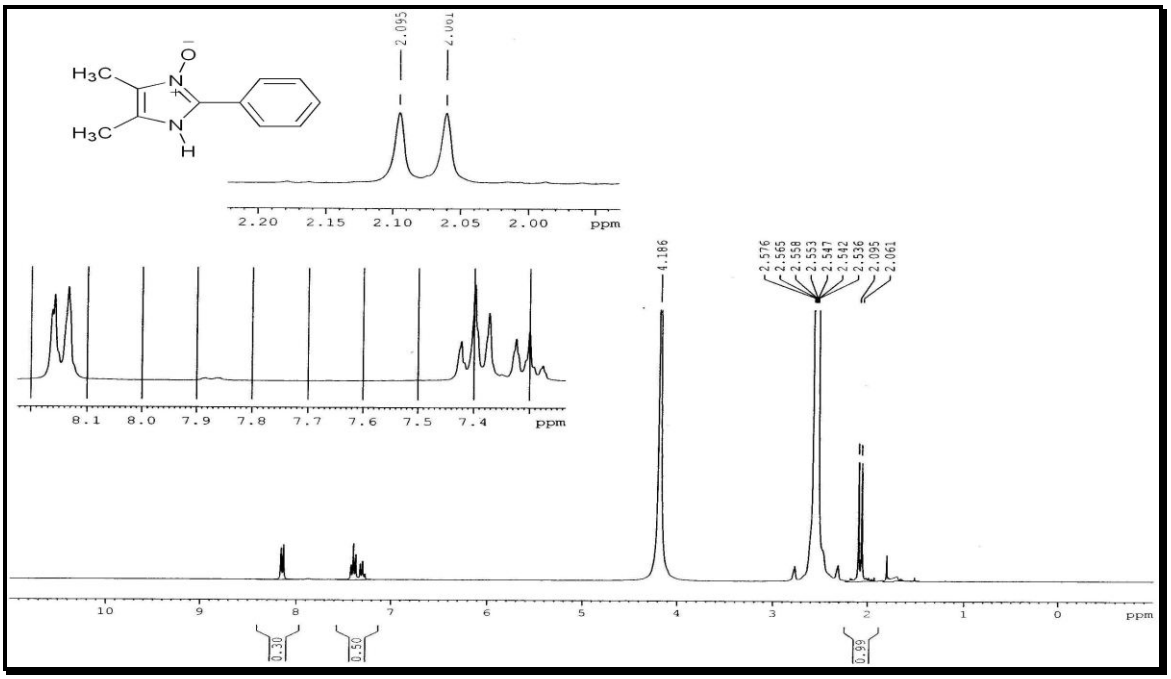
[1]HNMR - 2-(2-hydroxyphenyl)-4,5-dimethyl Imidazole N-oxide



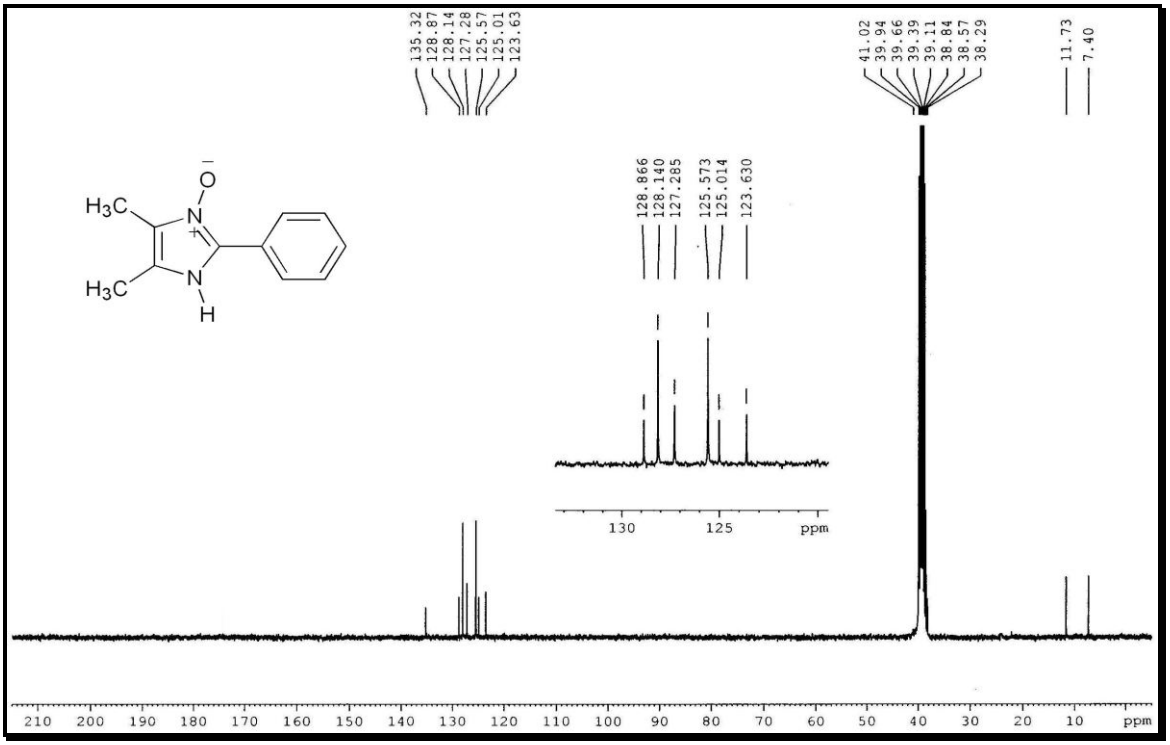
[13]CNMR - 2-(2-hydroxyphenyl)-4,5-dimethyl Imidazole N-oxide



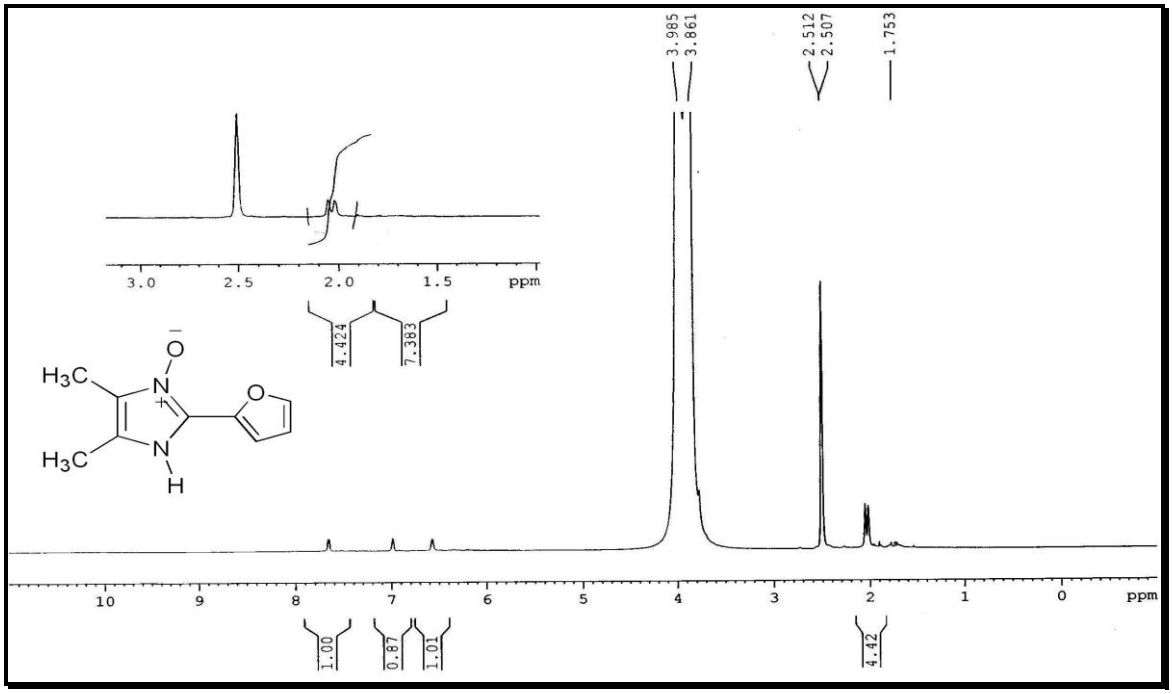
[1]HNMR - 2-(2-phenyl)-4,5-dimethyl Imidazole N-oxide



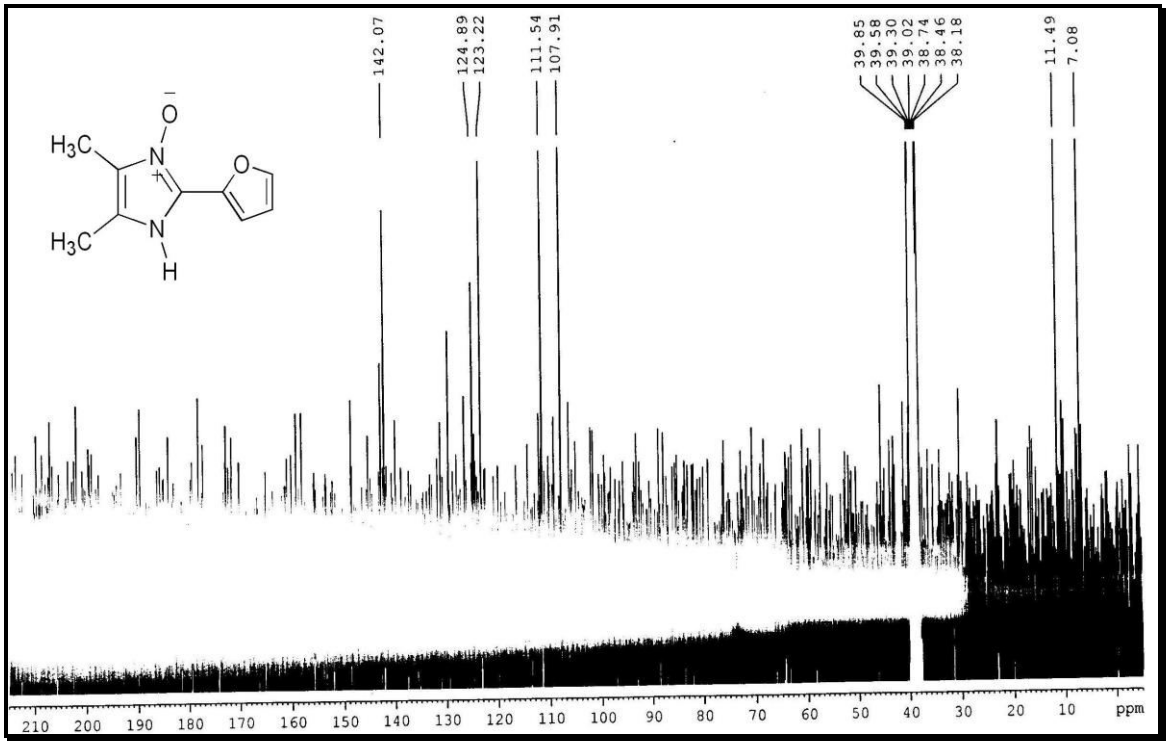
[13]CNMR - 2-(2-phenyl)-4,5-dimethyl Imidazole N-oxide



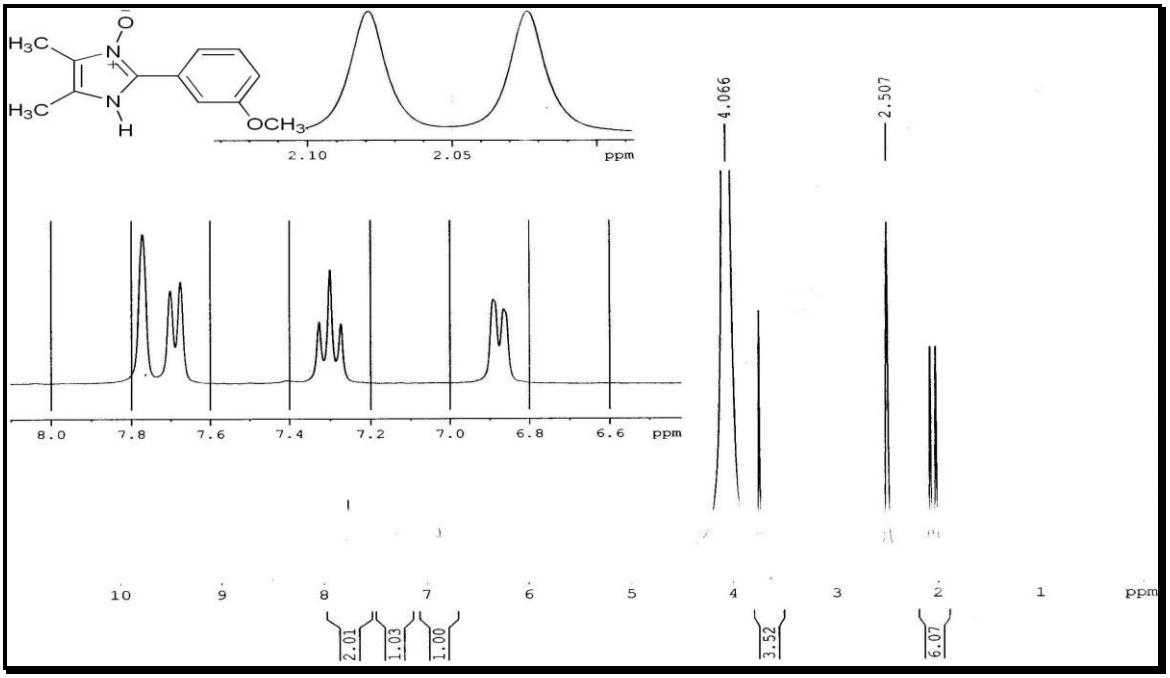
[1]HNMR - 2-(2-furyl)-4,5-dimethyl Imidazole N-oxide



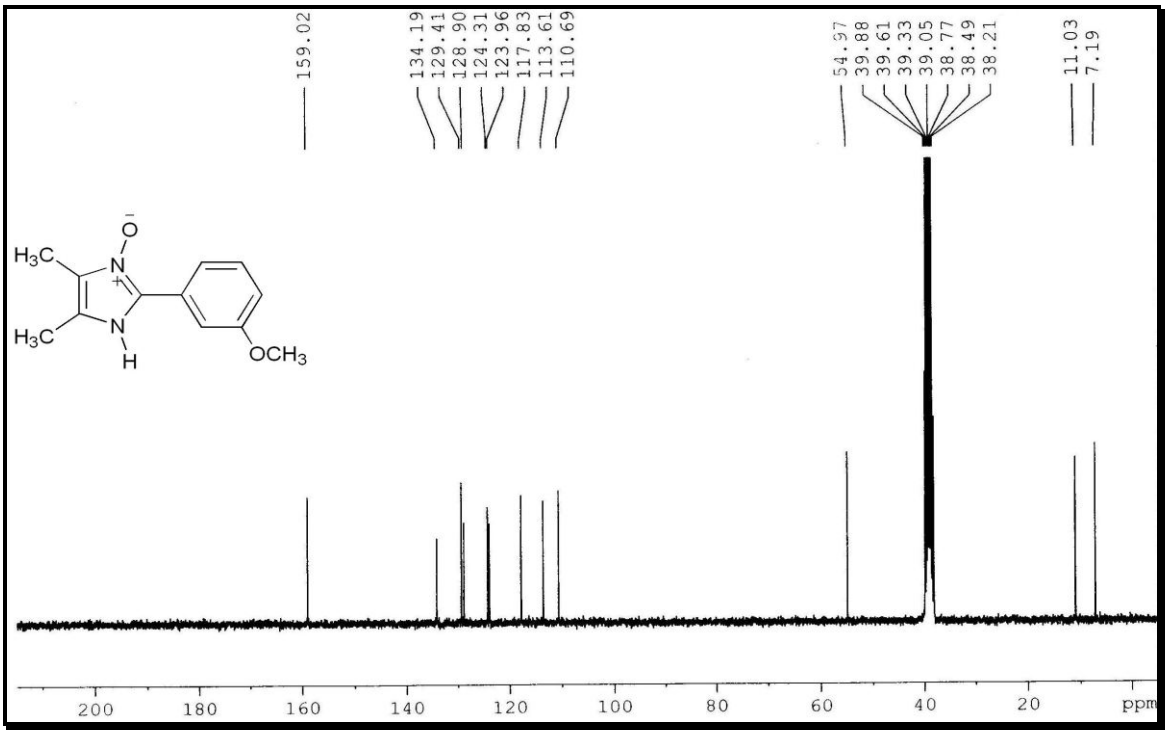
[13]CNMR - 2-(2-furyl)-4,5-dimethyl Imidazole N-oxide



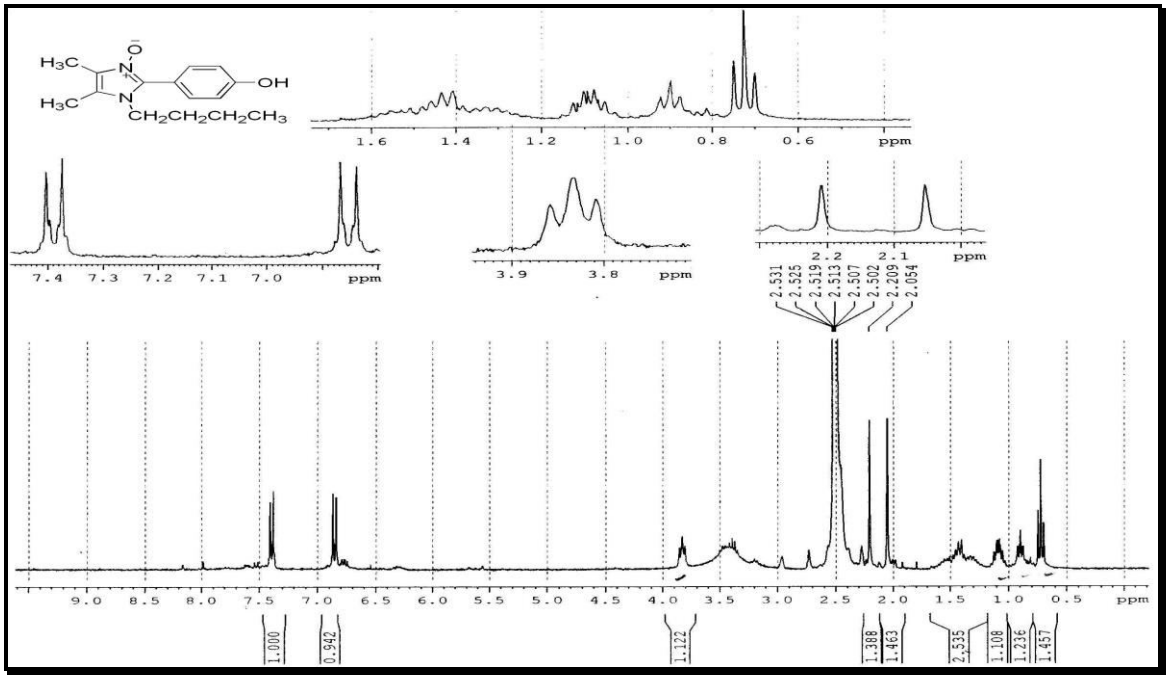
[1]HNMR - 2-(3-methoxyphenyl)-4, 5-dimethyl Imidazole N-oxide



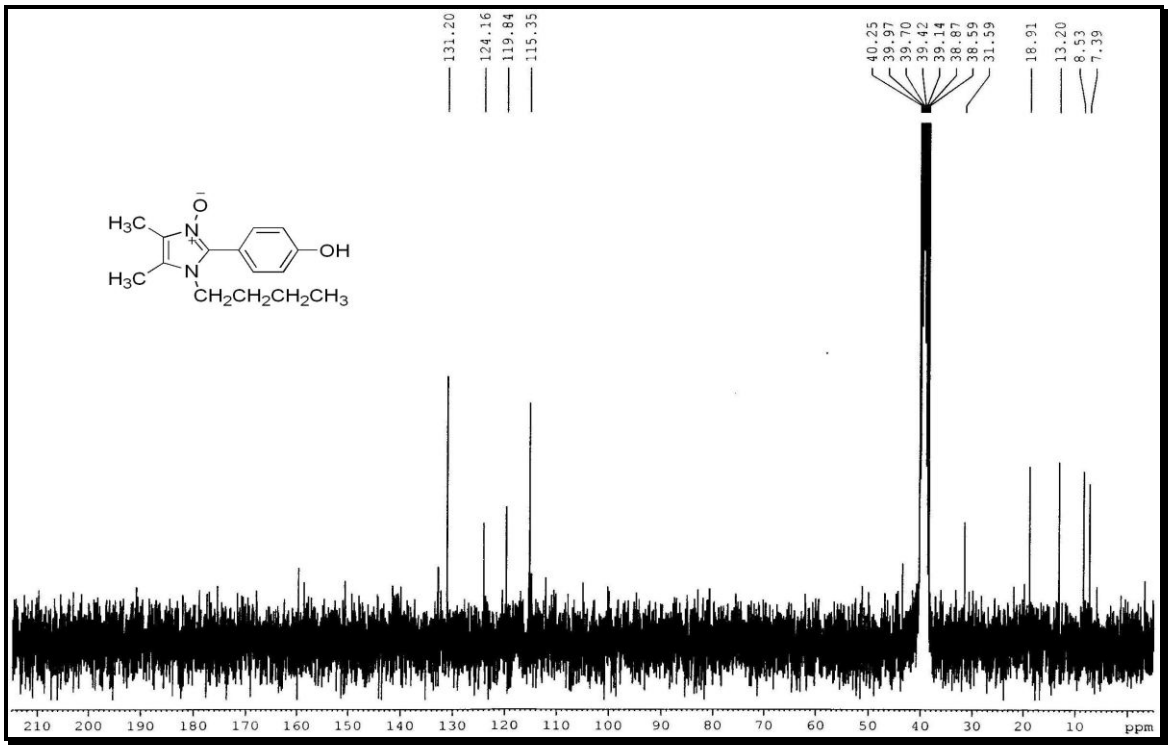
[13]CNMR - 2-(3-methoxyphenyl)-4,5-dimethyl Imidazole N-oxide



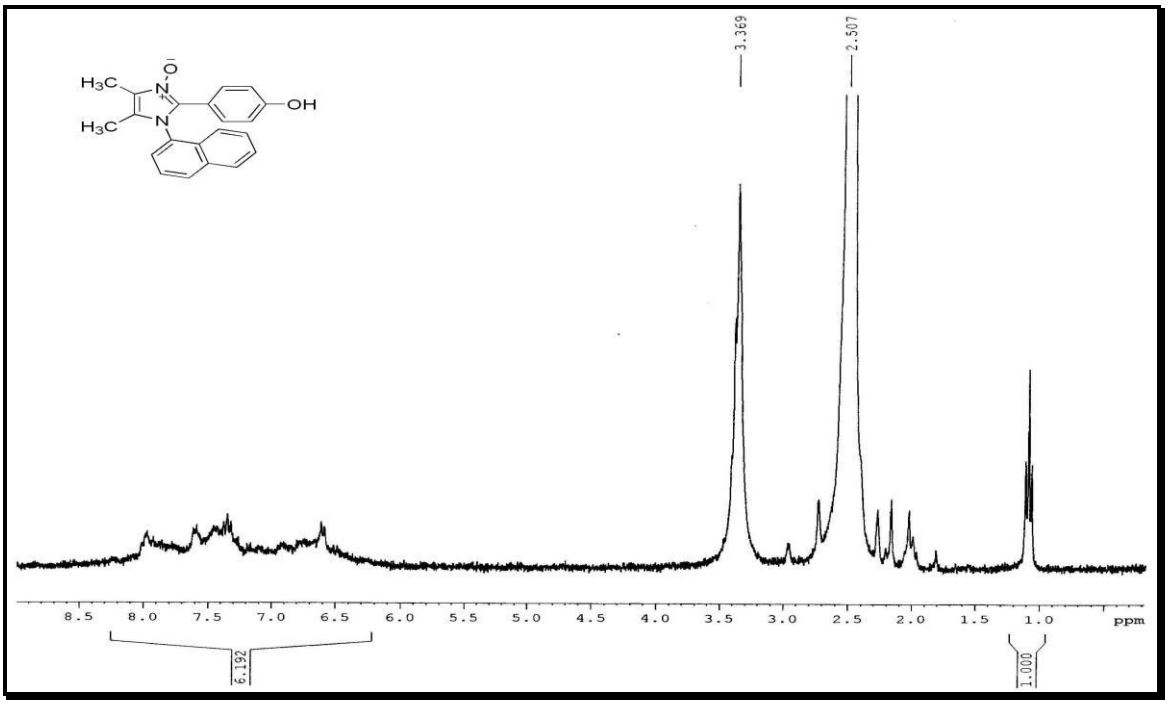
[1]HNMR - N-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide



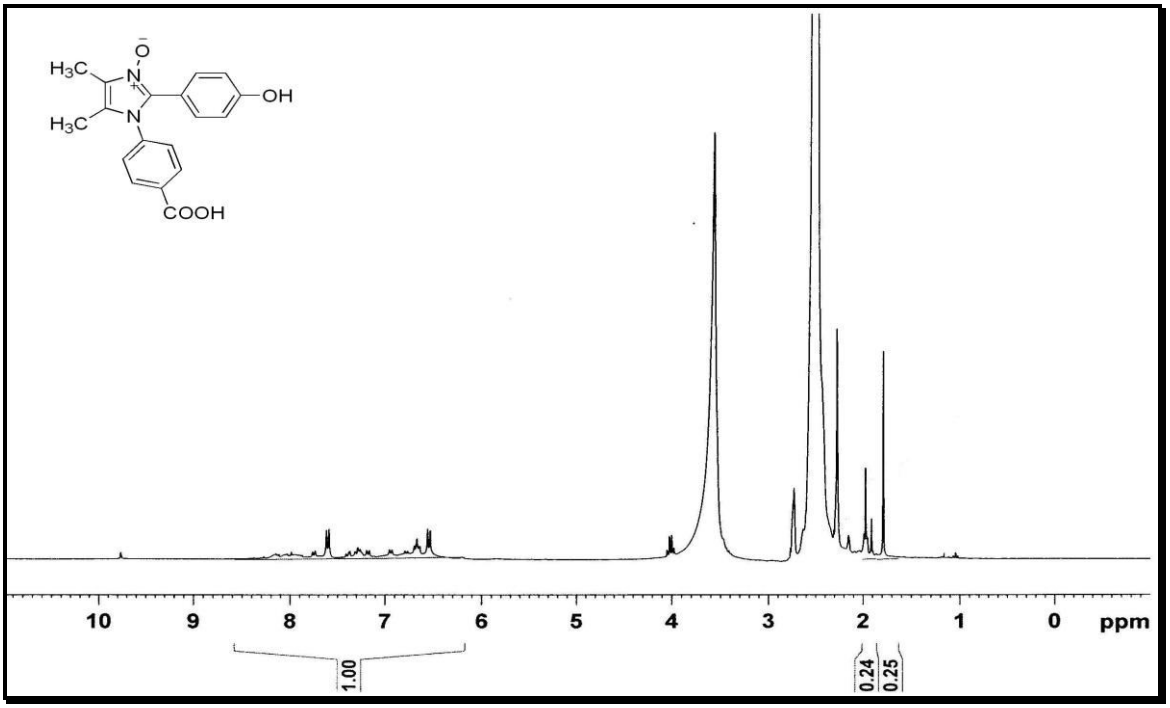
[13]CNMR - N-butyl-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide



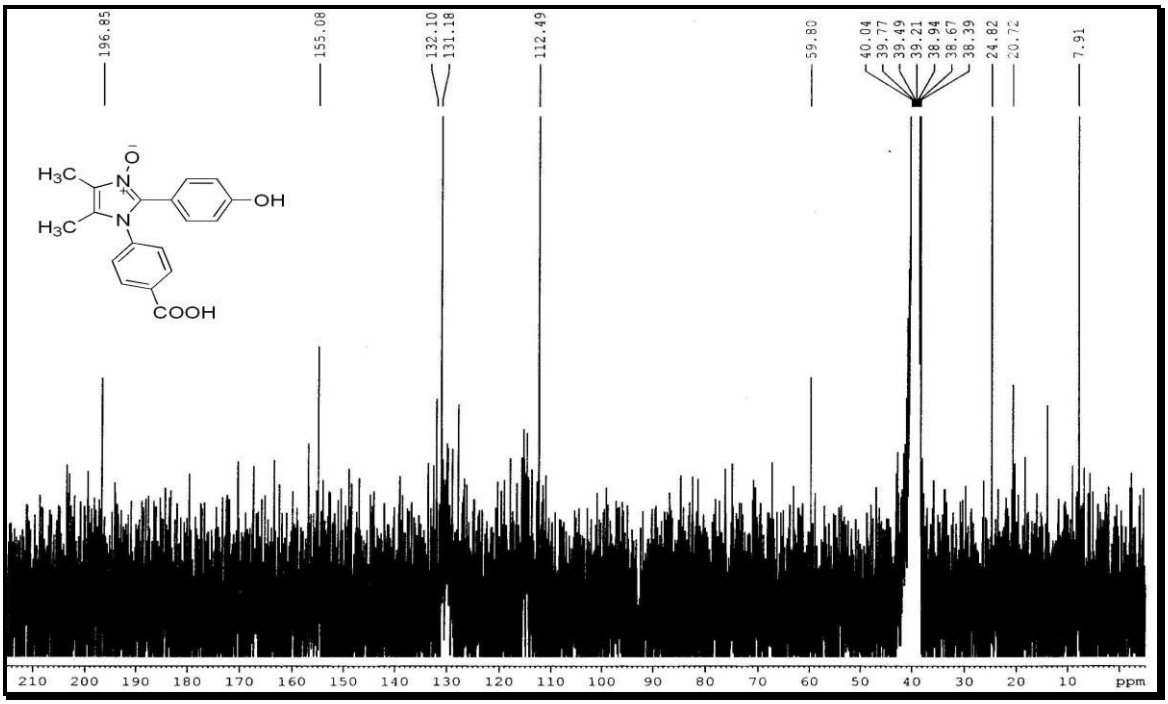
[1]HNMR - N-napthyl-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide



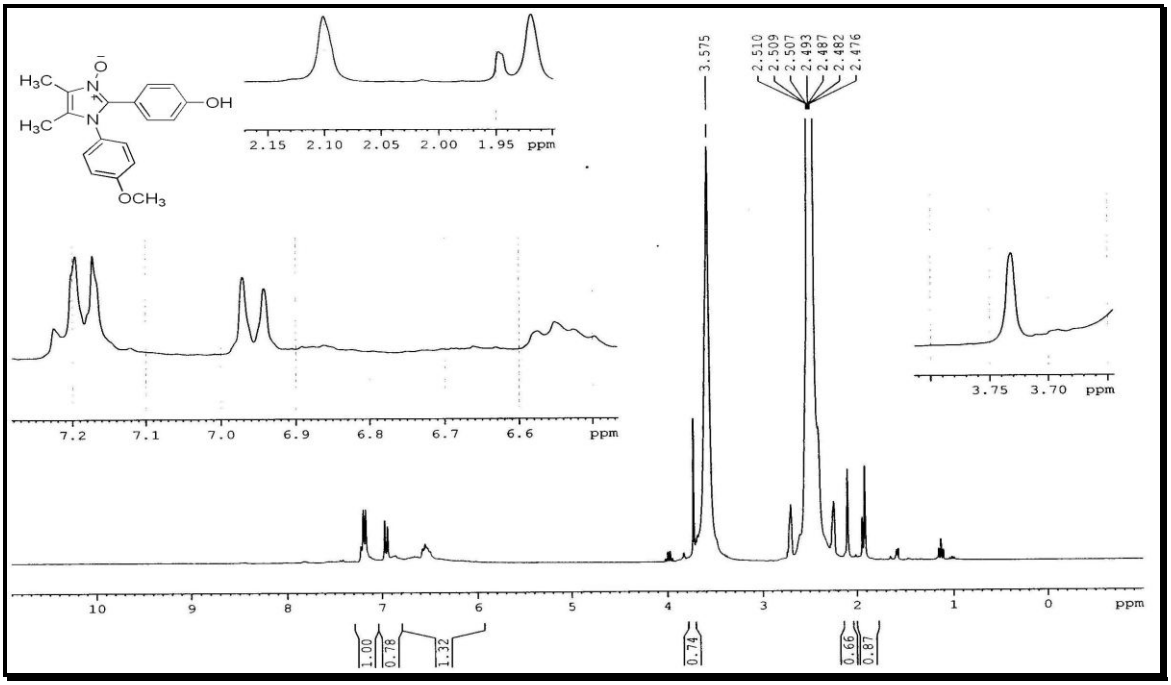
[1]HNMR - 4-{2-(4-hydroxyphenyl)-4,5-dimethyl imidazol-1-oxo} benzoic acid



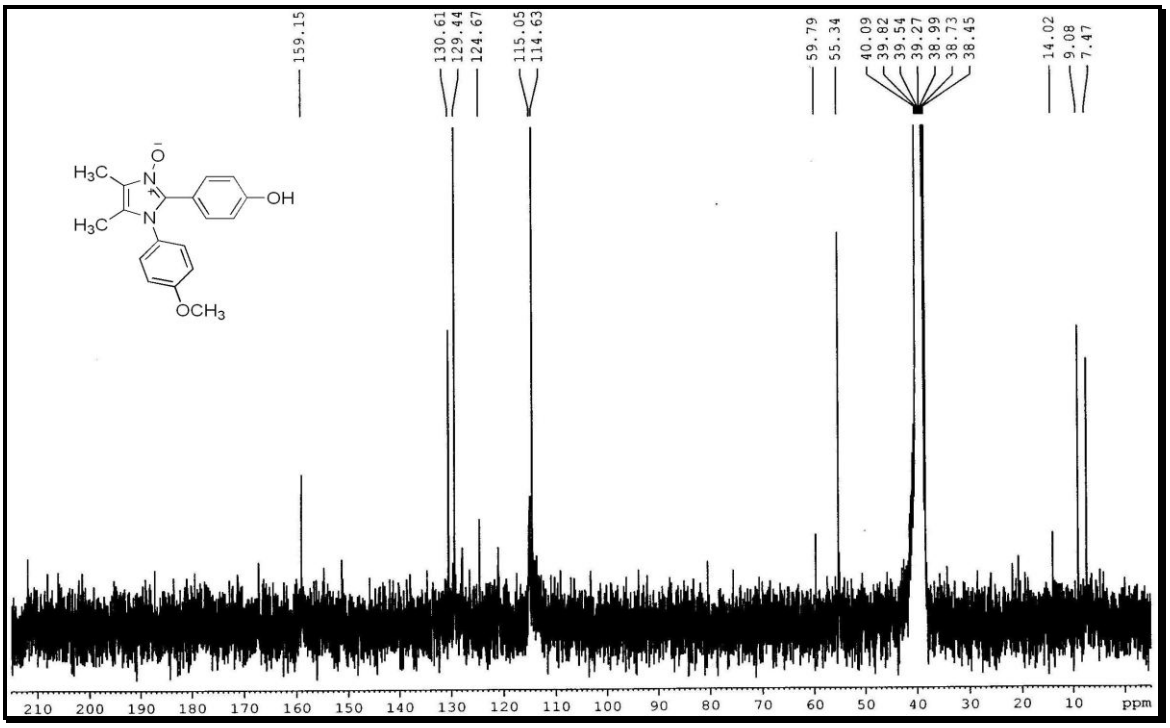
[13]CNMR - 4-{2-(4-hydroxyphenyl)-4,5-dimethyl imidazol-1-oxo} benzoic acid



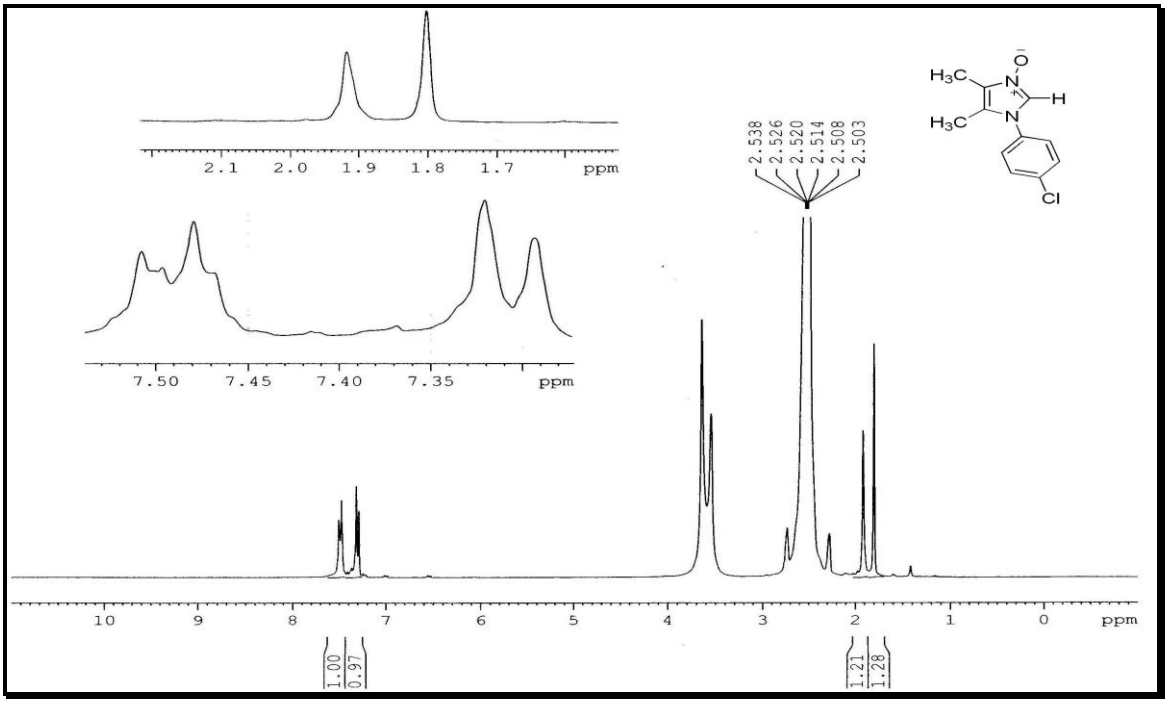
[1]HNMR - N-(4-methoxyphenyl)-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide



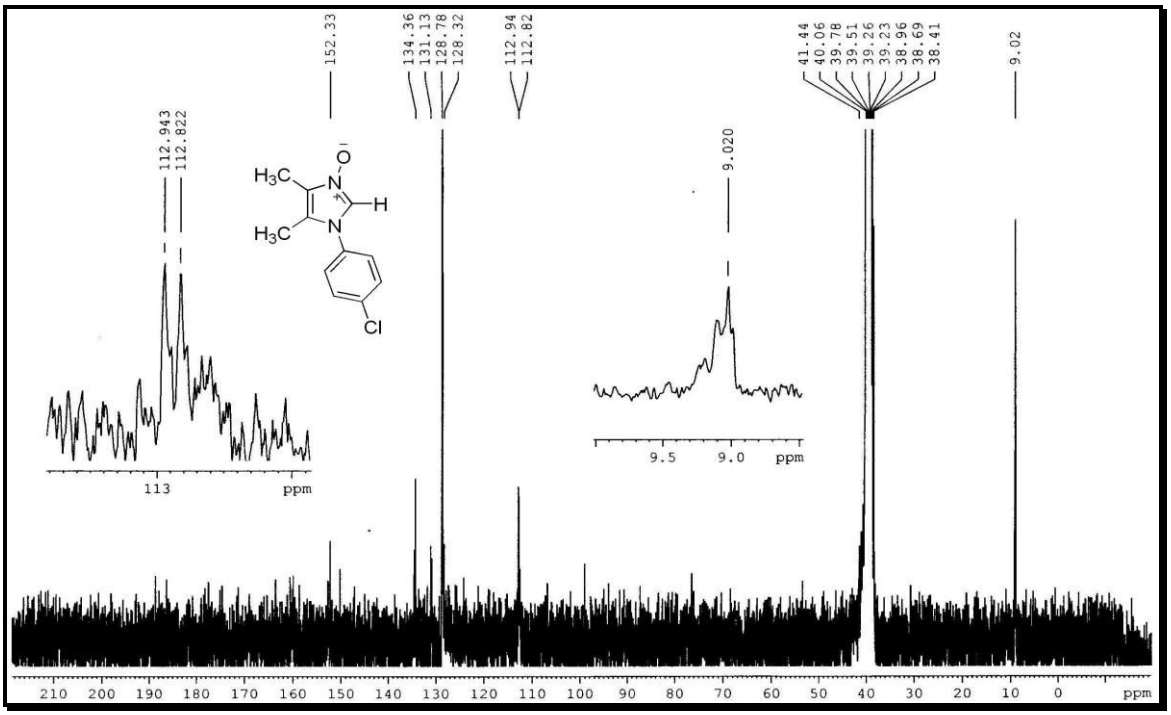
[13]CNMR - N-(4-methoxyphenyl)-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide



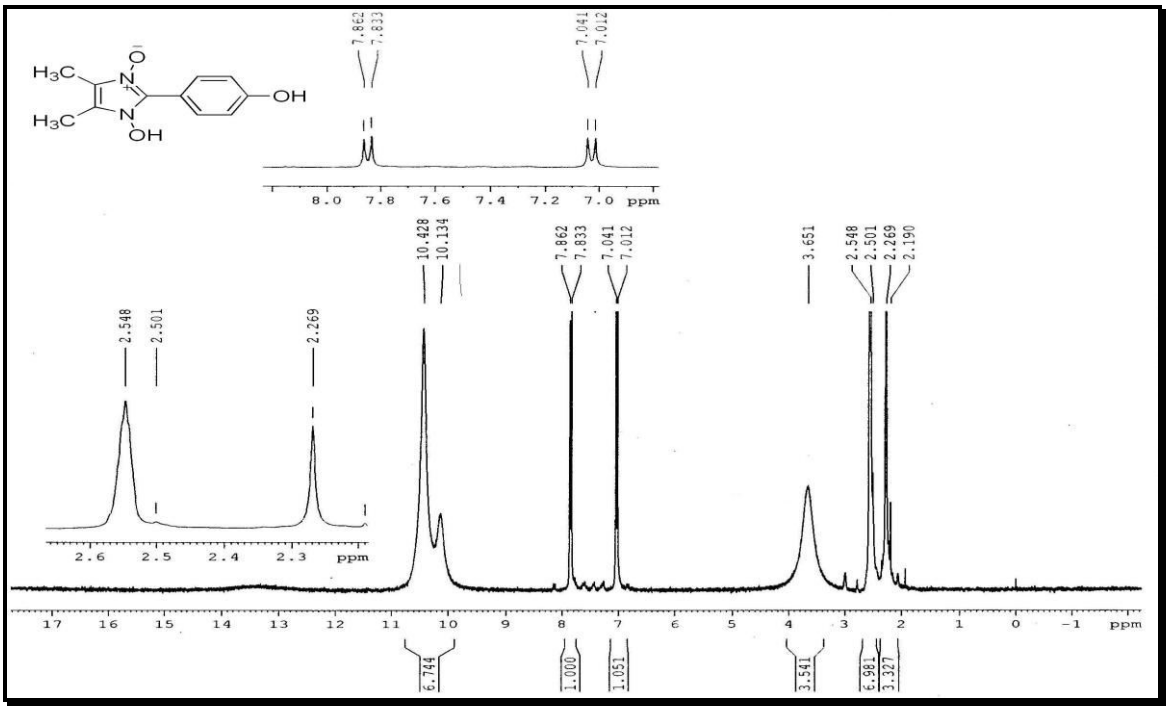
[1]HNMR - 1-(4-chlorophenyl)-4, 5-dimethyl -1H- Imidazole 3-oxide



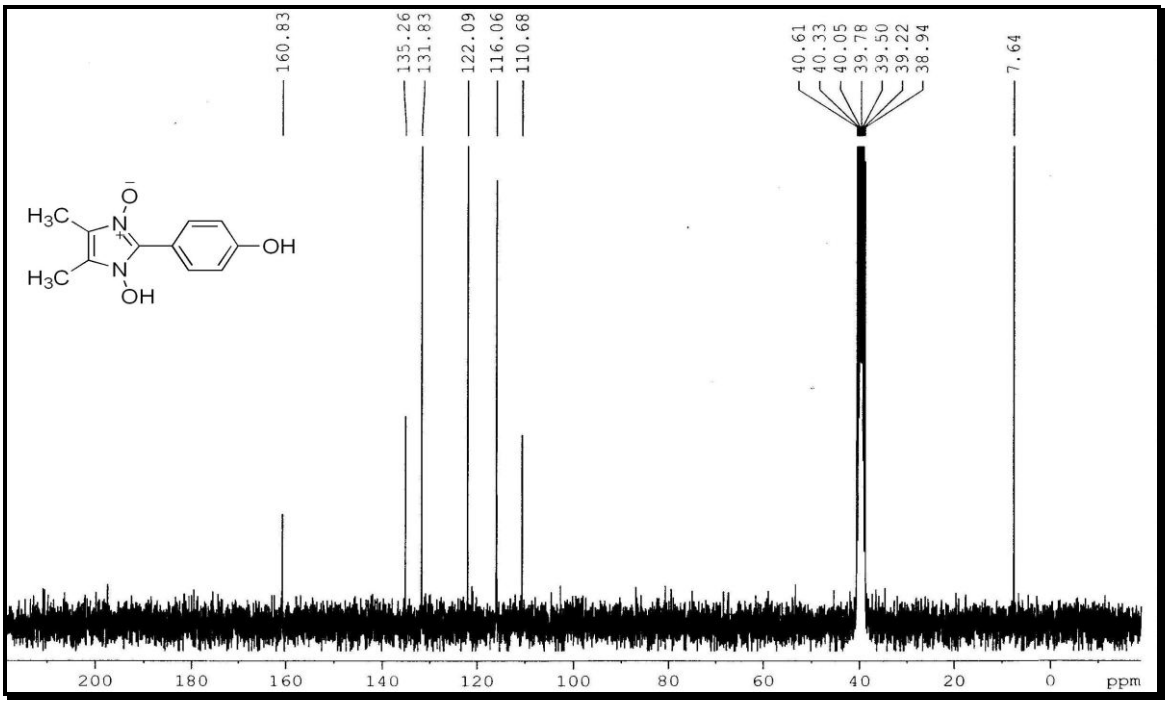
[13]CNMR - 1-(4-chlorophenyl)-4, 5-dimethyl -1H- Imidazole 3-oxide



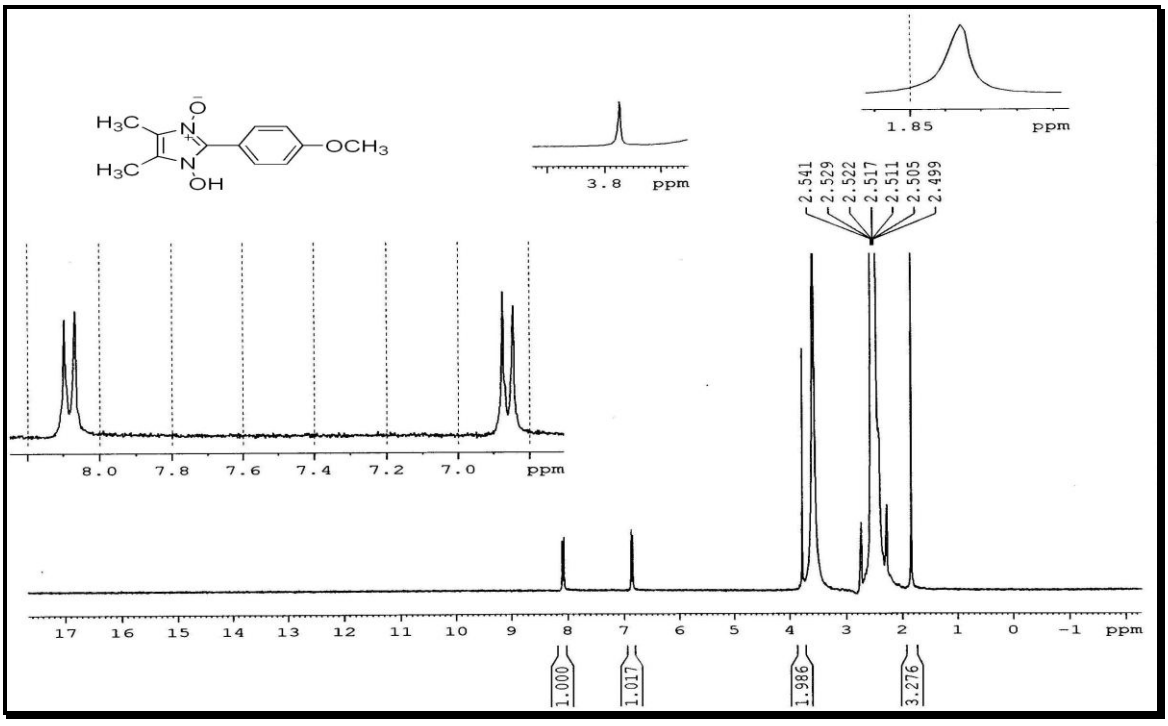
[1]HNMR - 1-hydroxy-2-(4-hydroxyphenyl)-4, 5-dimethyl Imidazole 3-oxide



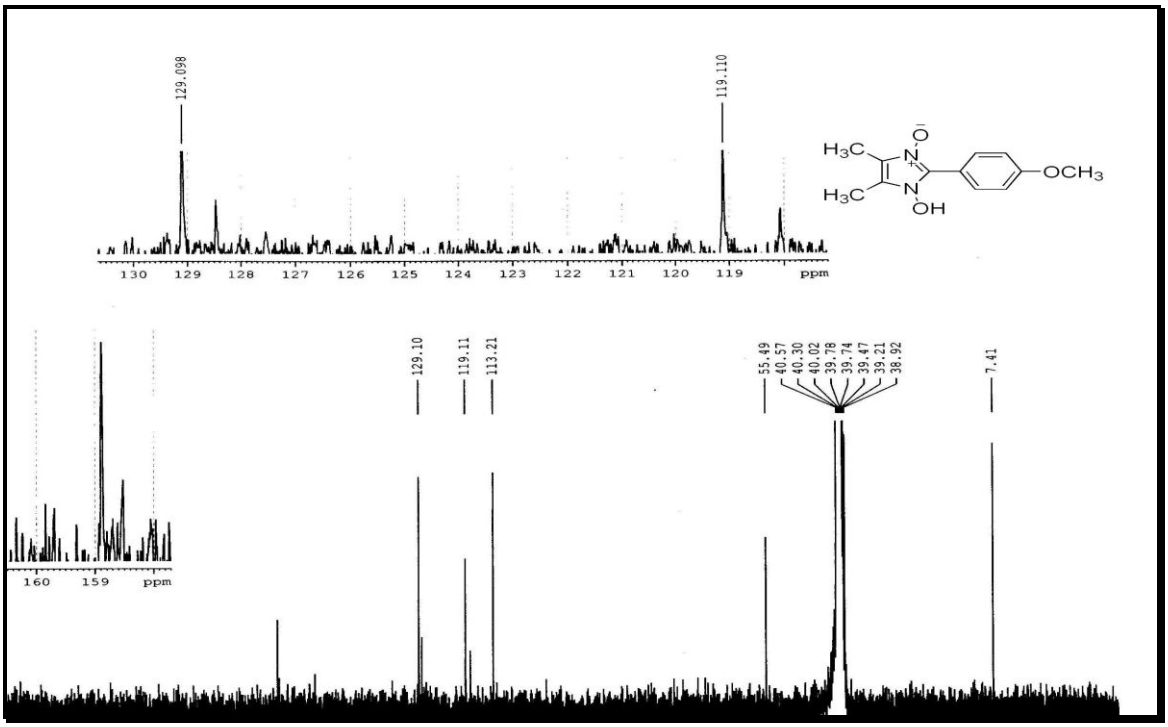
[13]CNMR - 1-hydroxy-2-(4-hydroxyphenyl)-4,5-dimethyl Imidazole 3-oxide



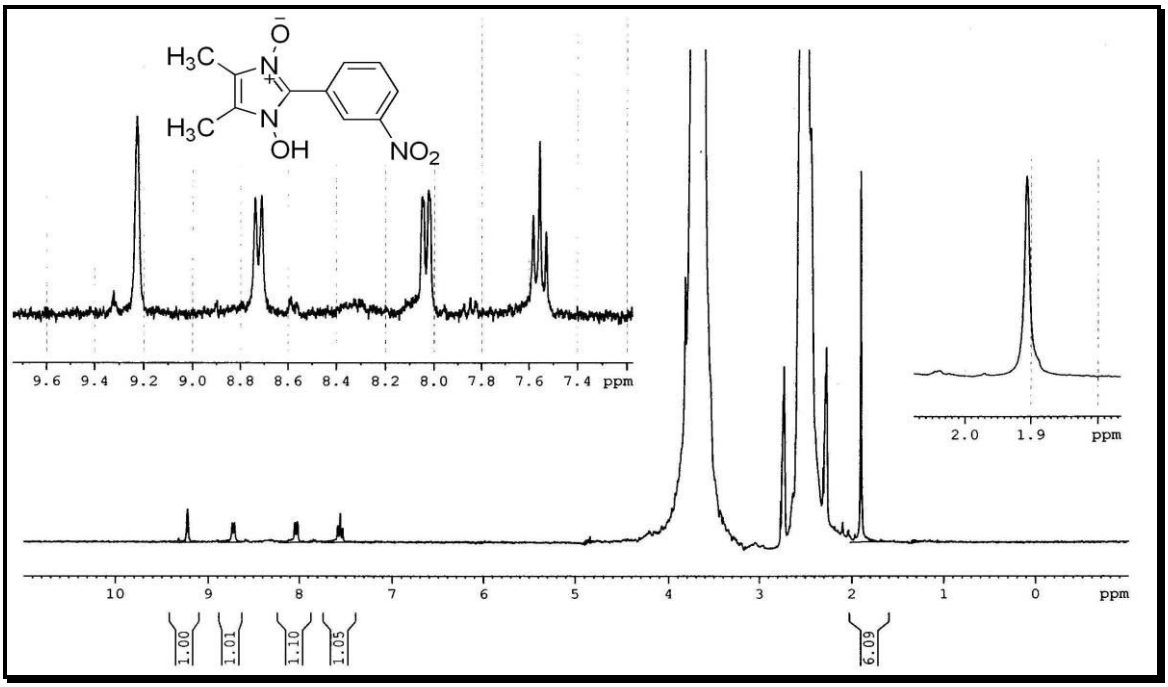
[1]HNMR - 1-hydroxy-2-(4-methoxyphenyl)-4,5-dimethyl Imidazole 3-oxide



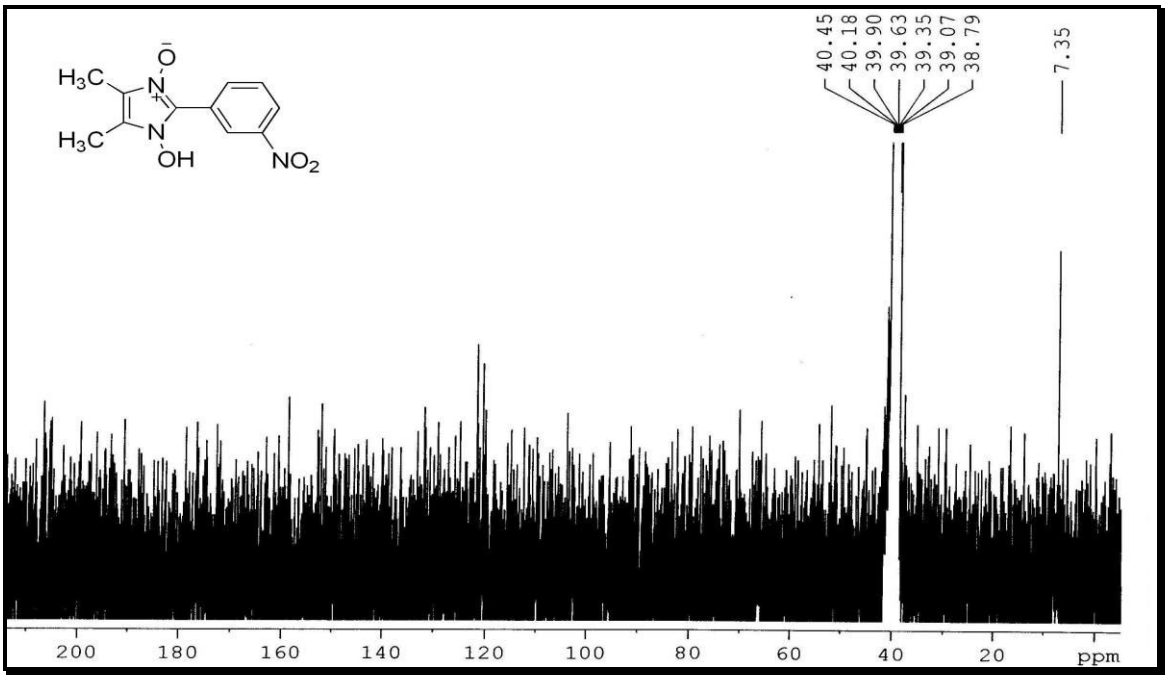
[13]CNMR - 1-hydroxy-2-(4-methoxyphenyl)-4,5-dimethyl Imidazole 3-oxide



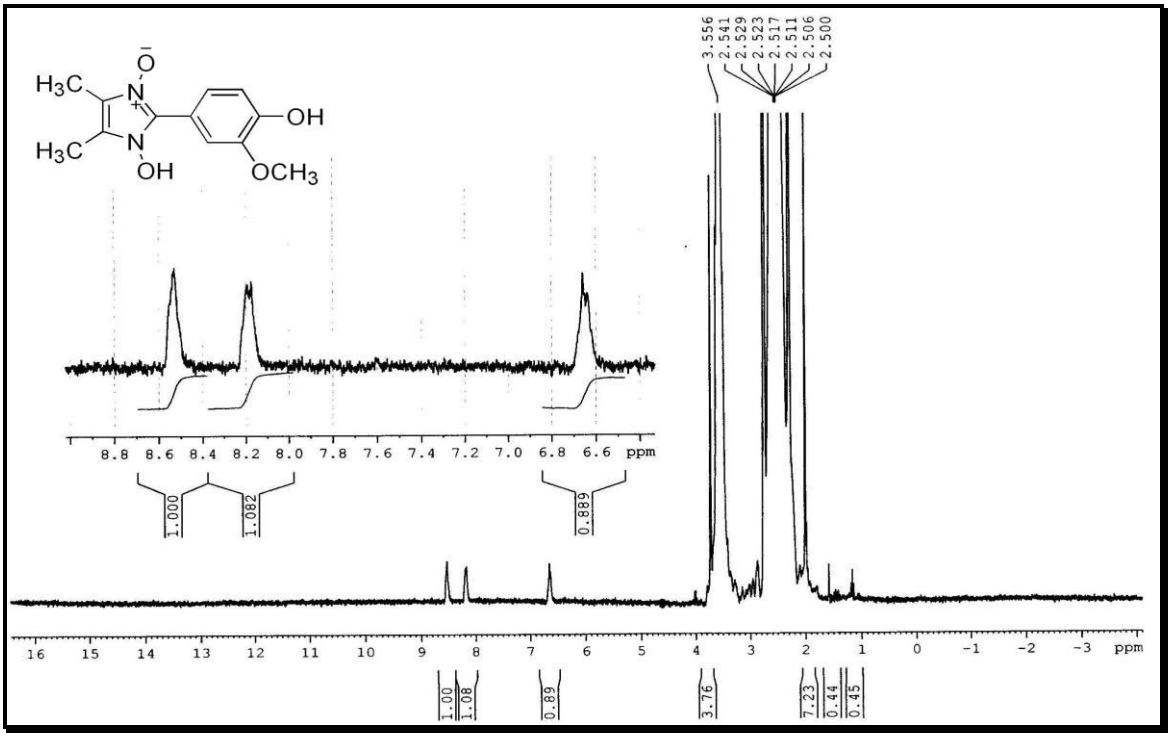
[1]HNMR - 1-hydroxy-2-(3-nitrophenyl)-4,5-dimethyl Imidazole 3-oxide



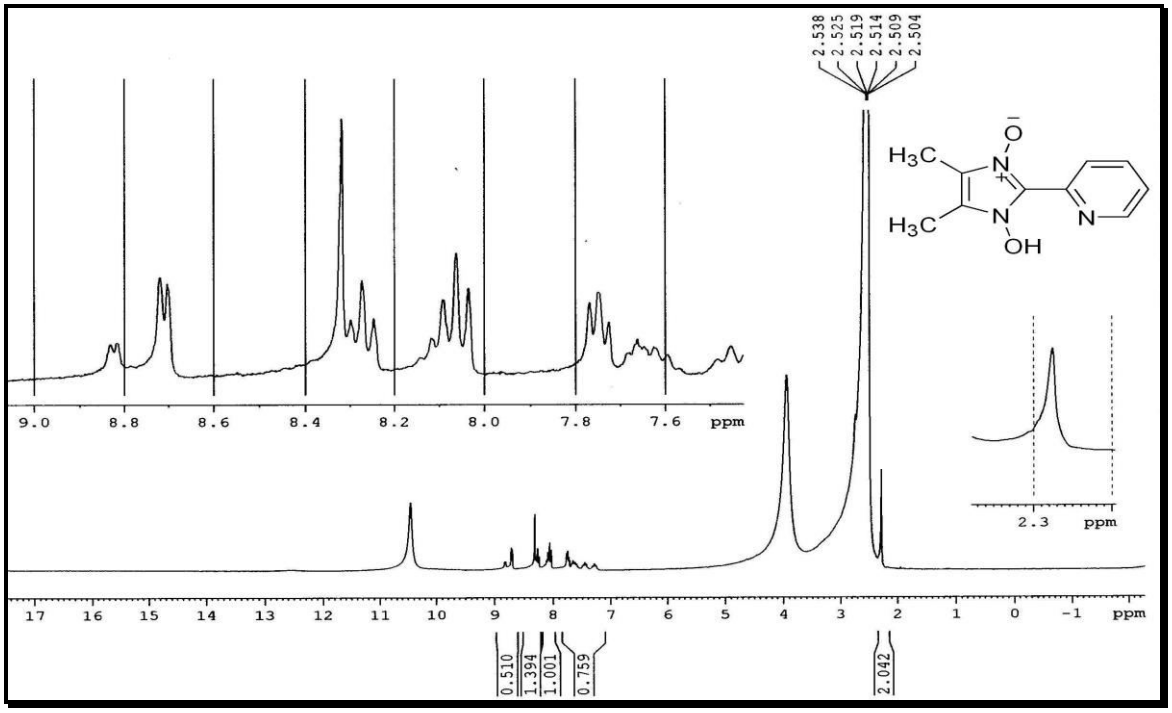
[13]CNMR - 1-hydroxy-2-(3-nitrophenyl)-4,5-dimethyl Imidazole 3-oxide



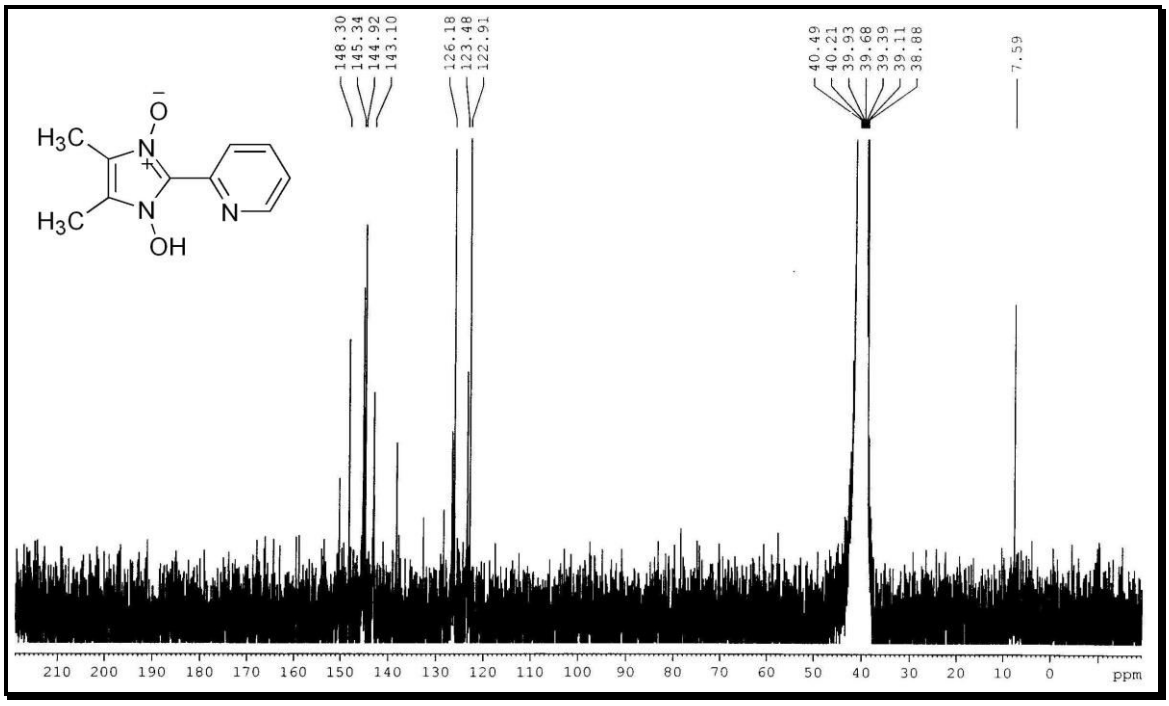
[1]HNMR - 1-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4,5-dimethyl Imidazole 3-oxide



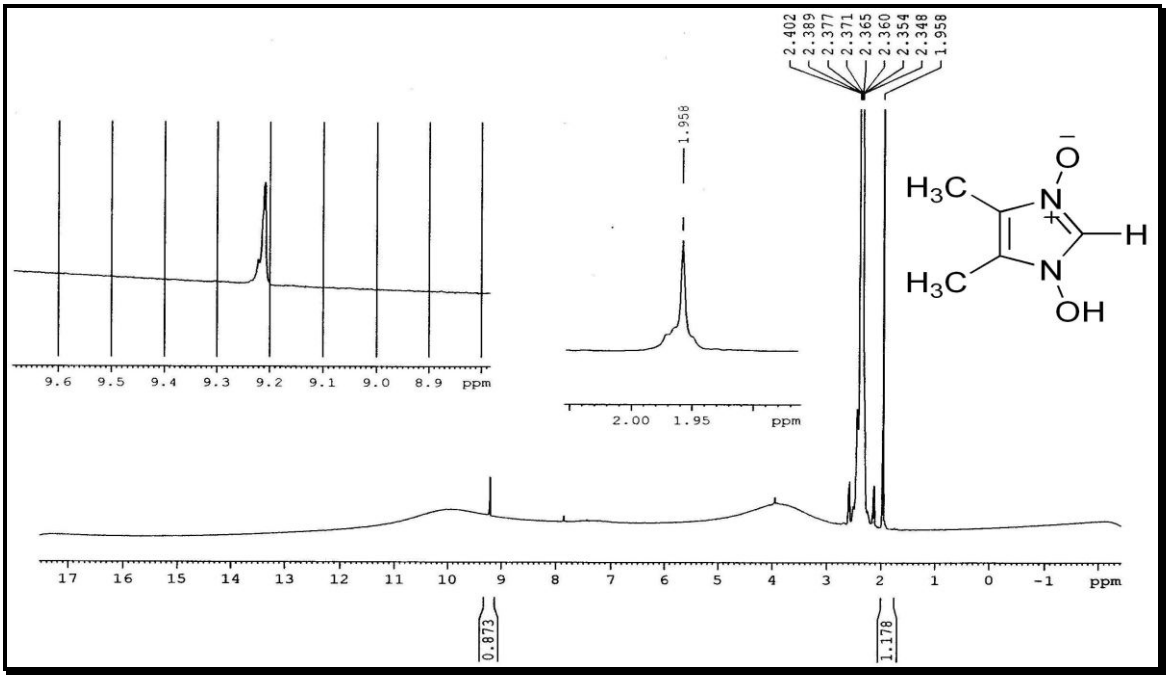
[1]HNMR - 1-hydroxy-2-(2-pyridyl)-4,5-dimethyl Imidazole 3-oxide



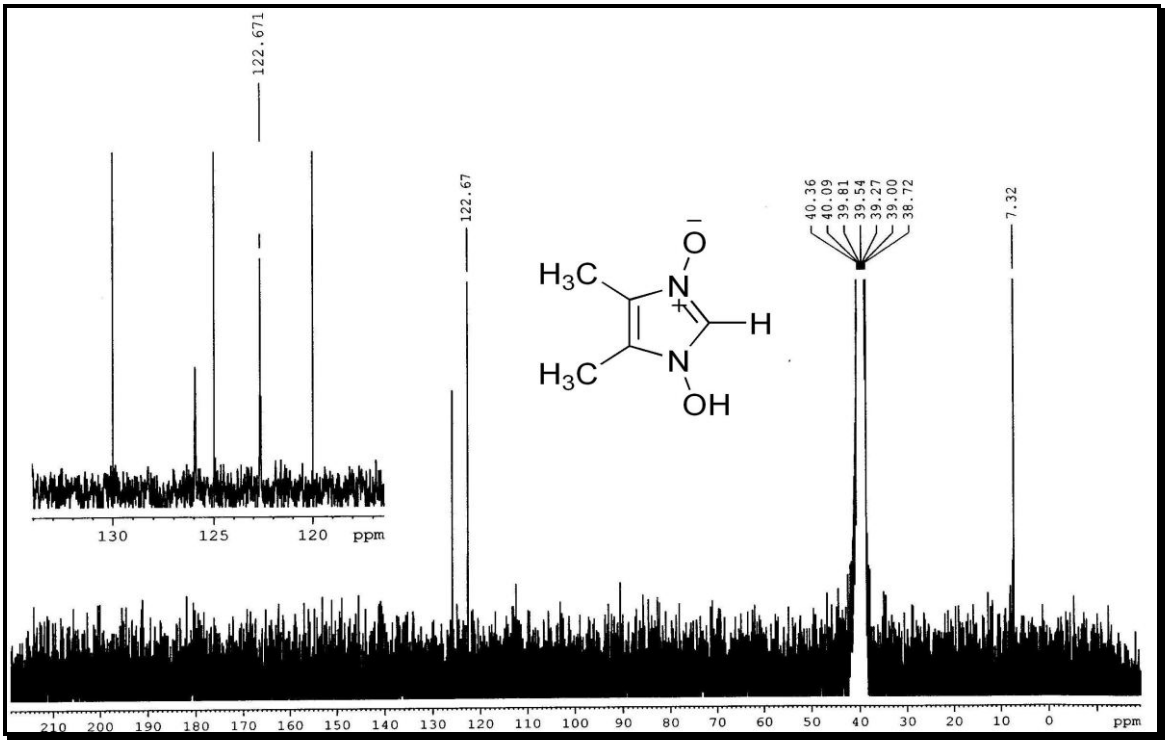
[13]CNMR - 1-hydroxy-2-(2-pyridyl)-4,5-dimethyl Imidazole 3-oxide



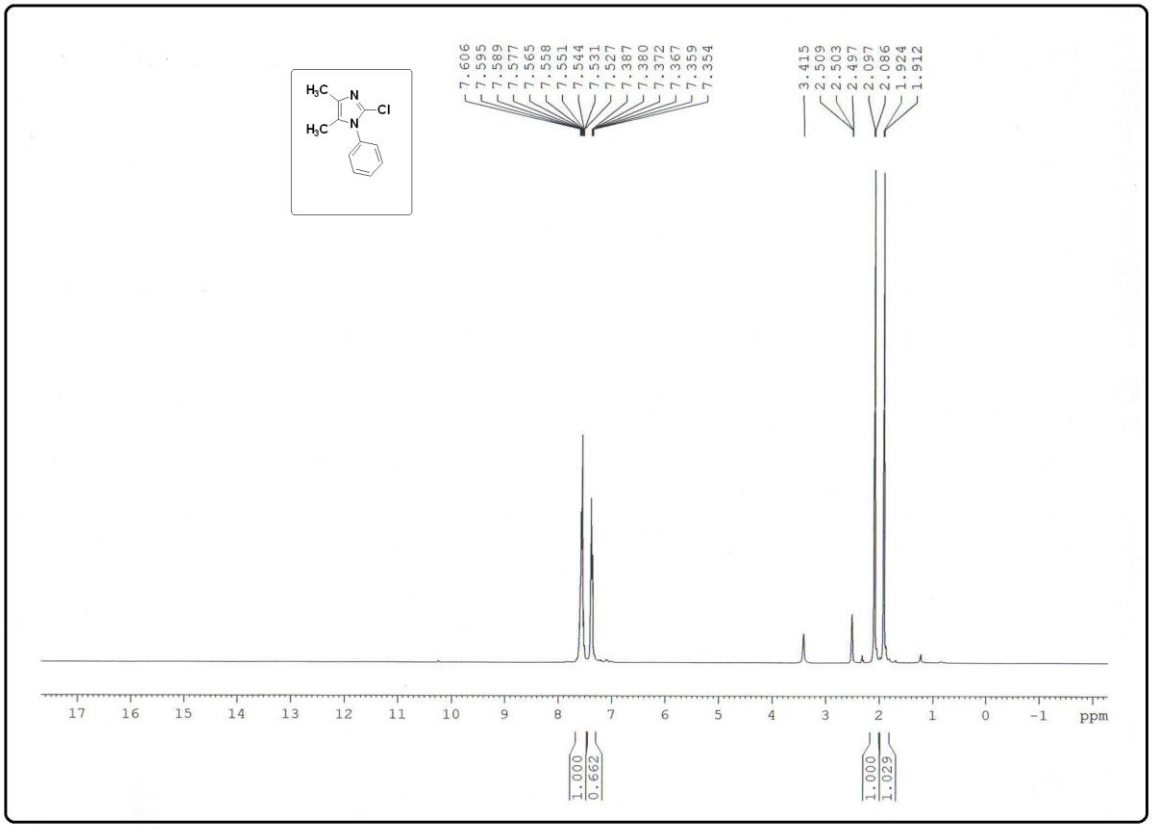
[1]HNMR - 1-hydroxy-4,5-dimethyl, 1H Imidazole 3-oxide



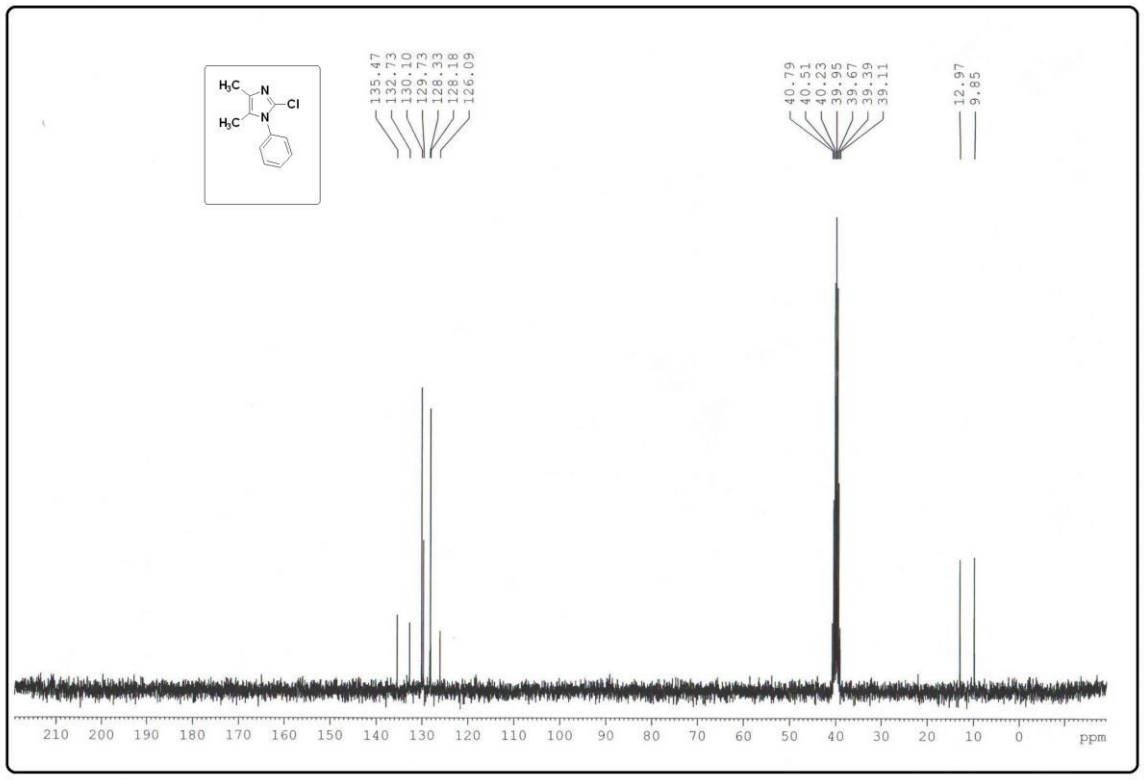
[13]CNMR - 1-hydroxy-4,5-dimethyl, 1H Imidazole 3-oxide



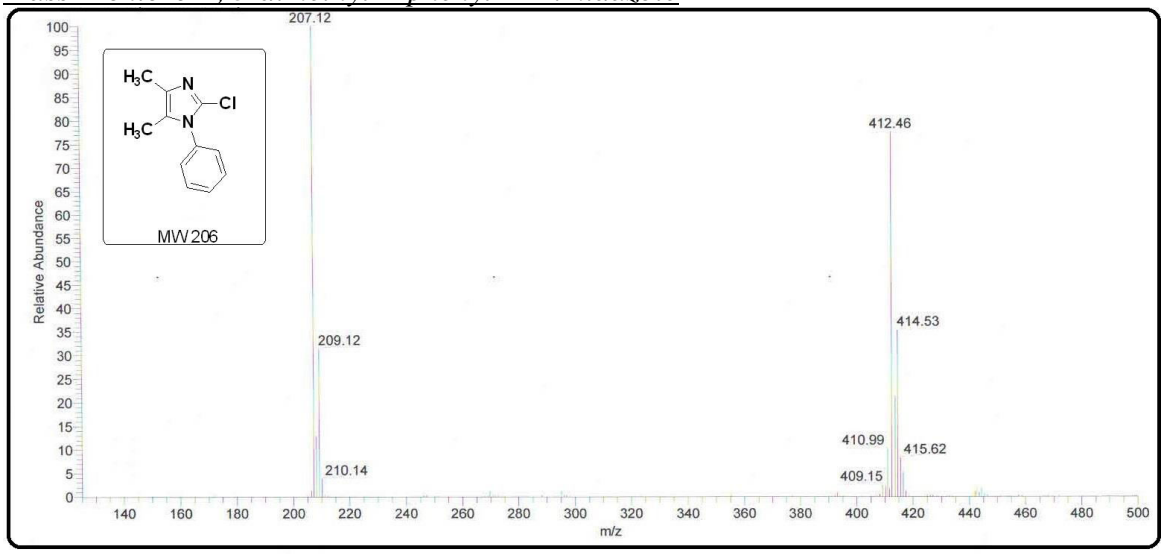
[1]HNMR-2-chloro-4, 5-dimethyl-1-phenyl-1H-imidazole



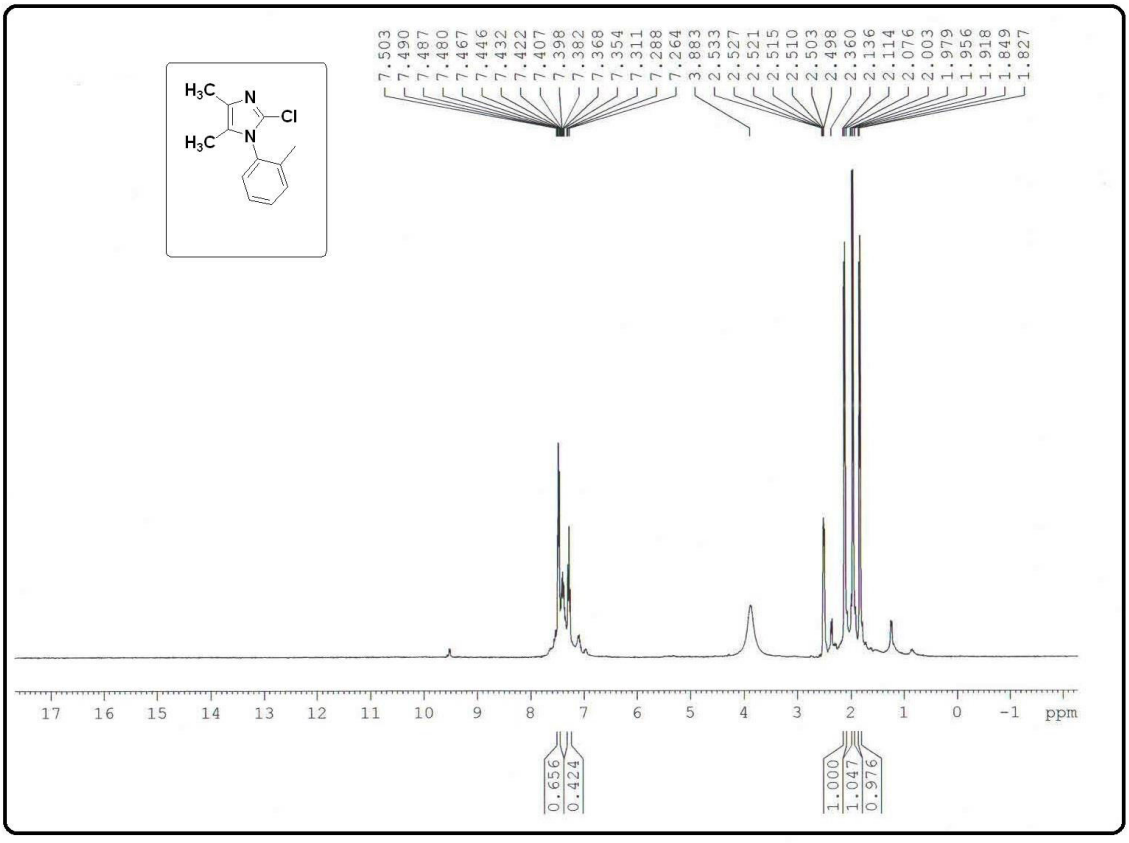
[13]CNMR-2-chloro-4, 5-dimethyl-1-phenyl-1H-imidazole



Mass-2-chloro-4, 5-dimethyl-1-phenyl-1H-imidazole



^{1}HNMR-2-chloro-4, 5-dimethyl-1-o-tolyl-1H-imidazole



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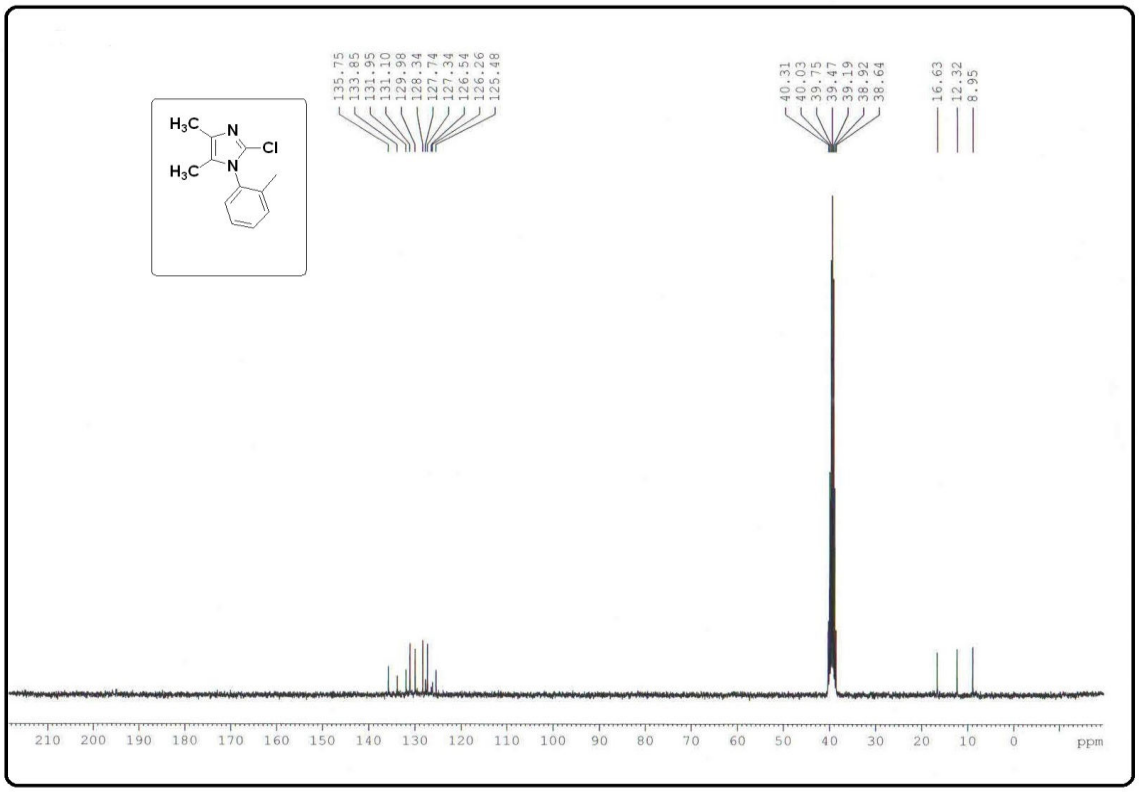
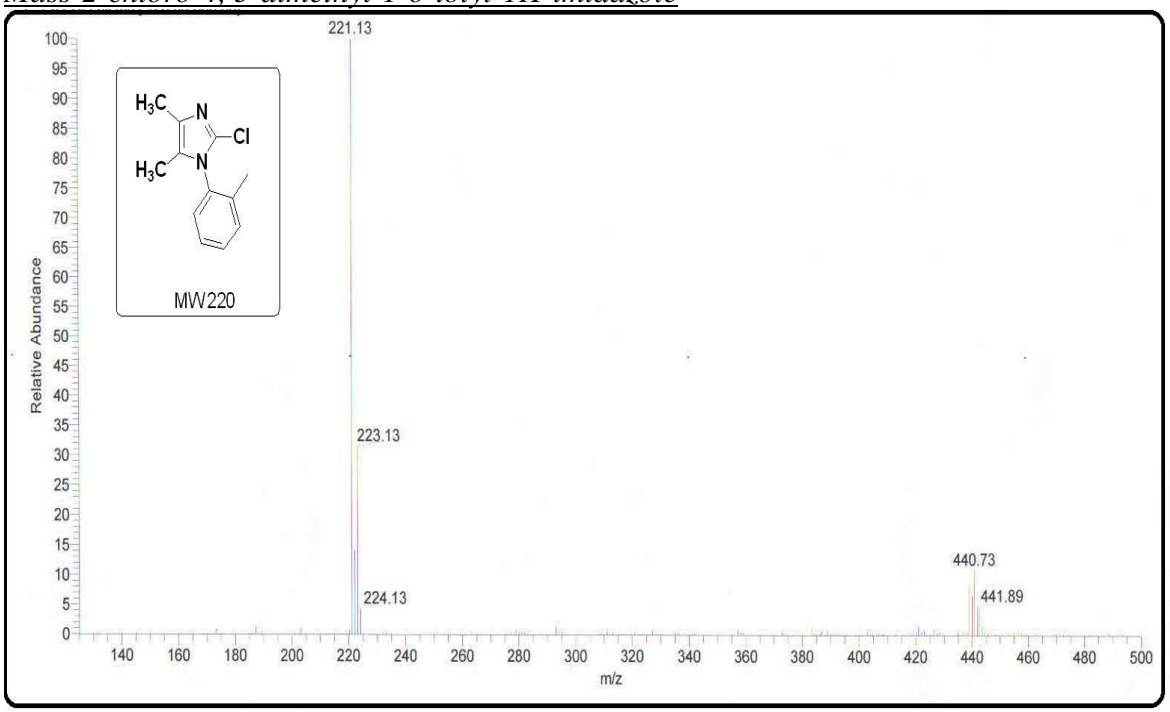
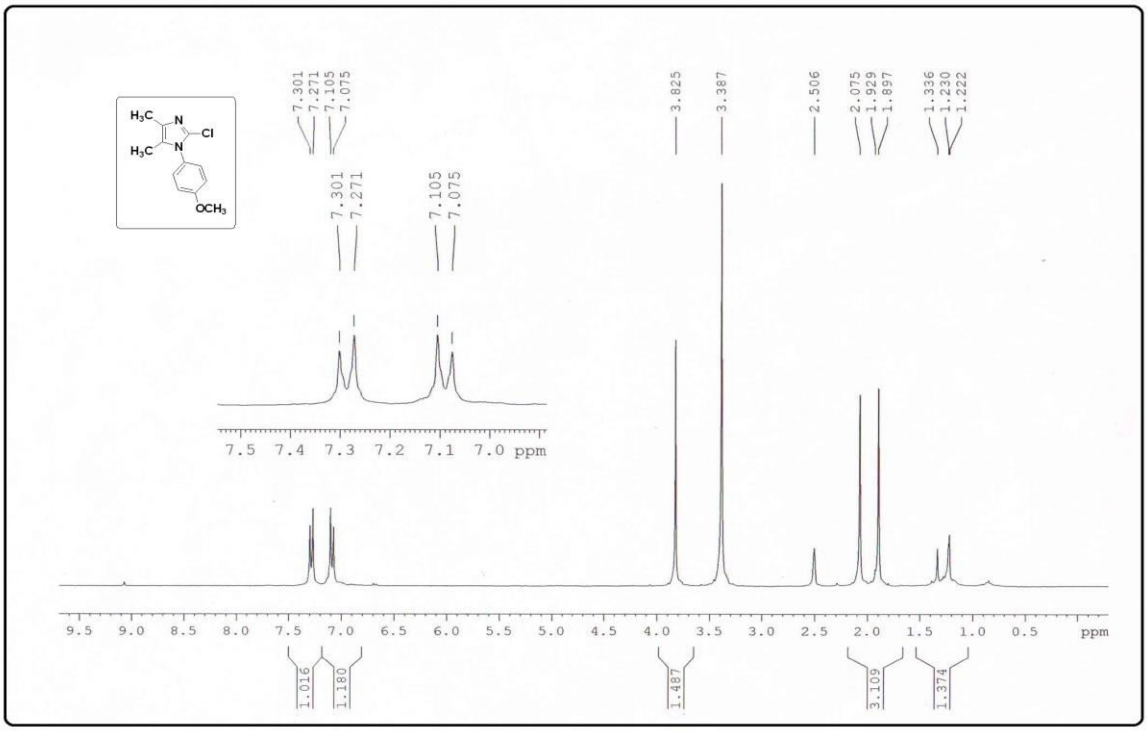


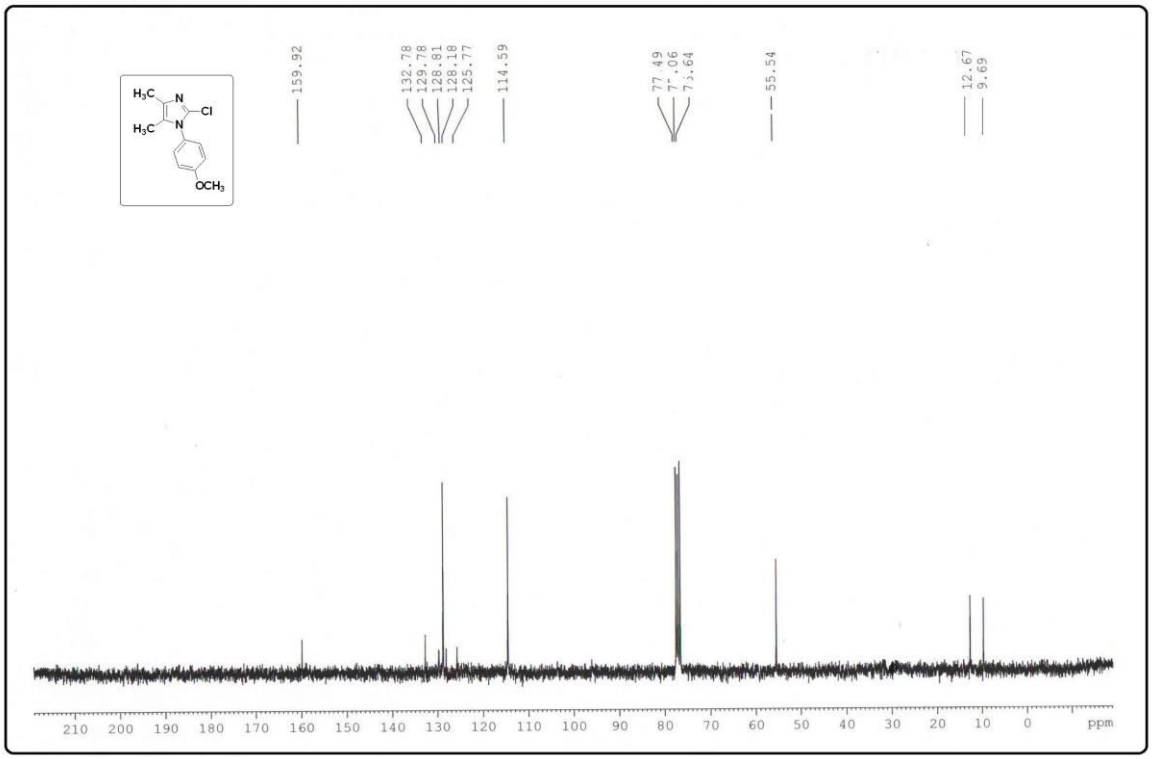
Mass-2-chloro-4, 5-dimethyl-1-o-tolyl-1H-imidazole



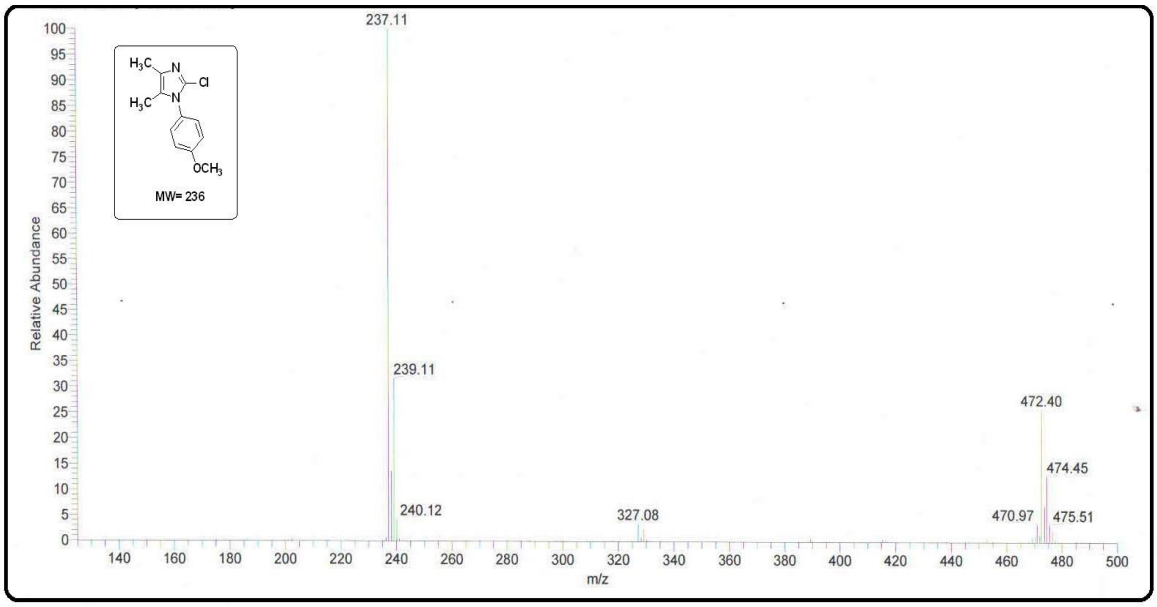
[1]HNMR-2-chloro-1-(4-methoxyphenyl)-4,5-dimethyl-1H imidazole



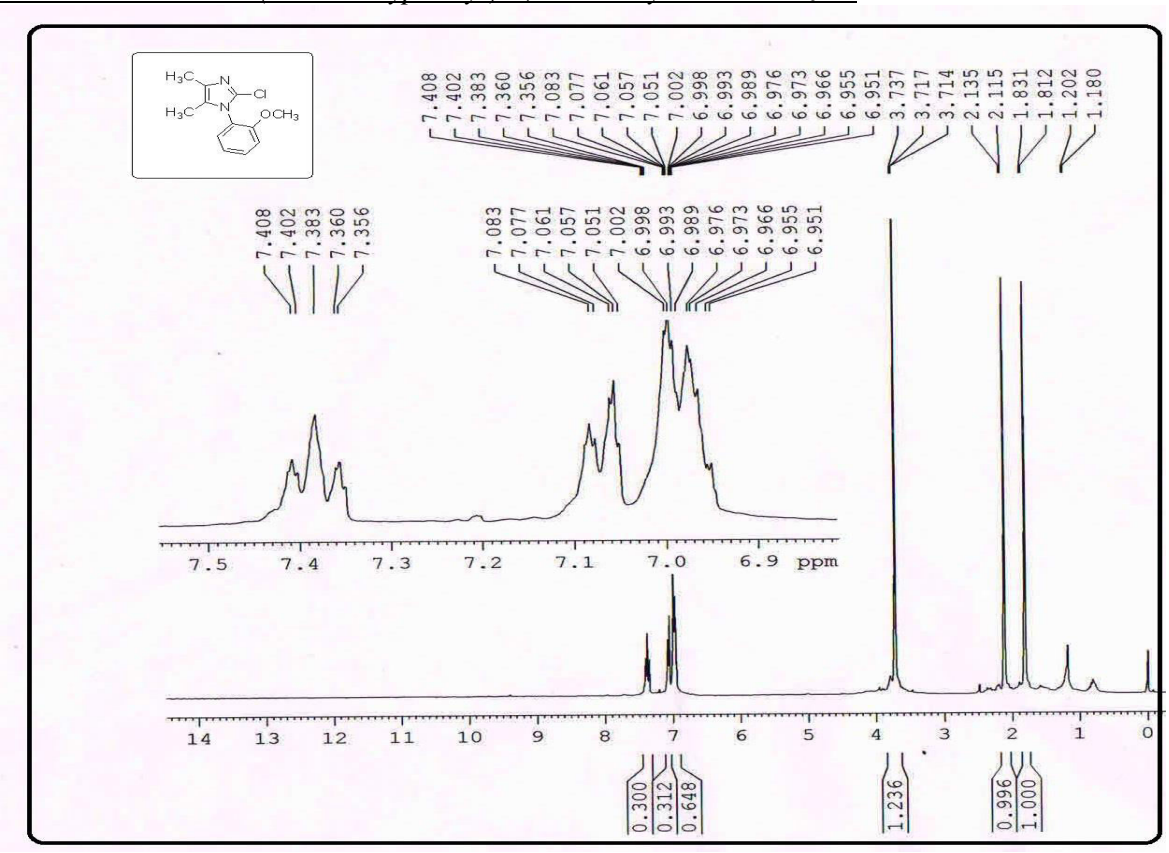
[13]CNMR-2-chloro-1-(4-methoxyphenyl)-4,5-dimethyl-1H imidazole



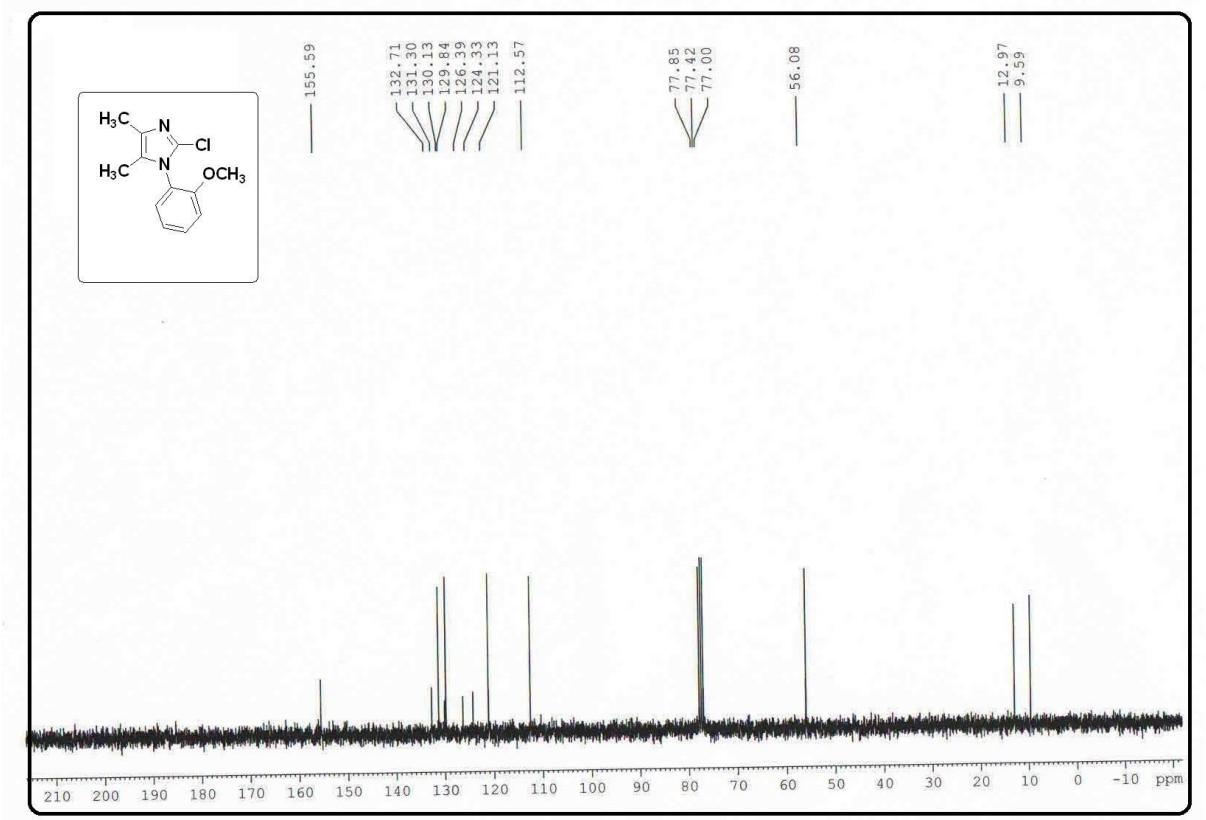
Mass-2-chloro-1-(4-methoxyphenyl)-4,5-dimethyl-1H imidazole



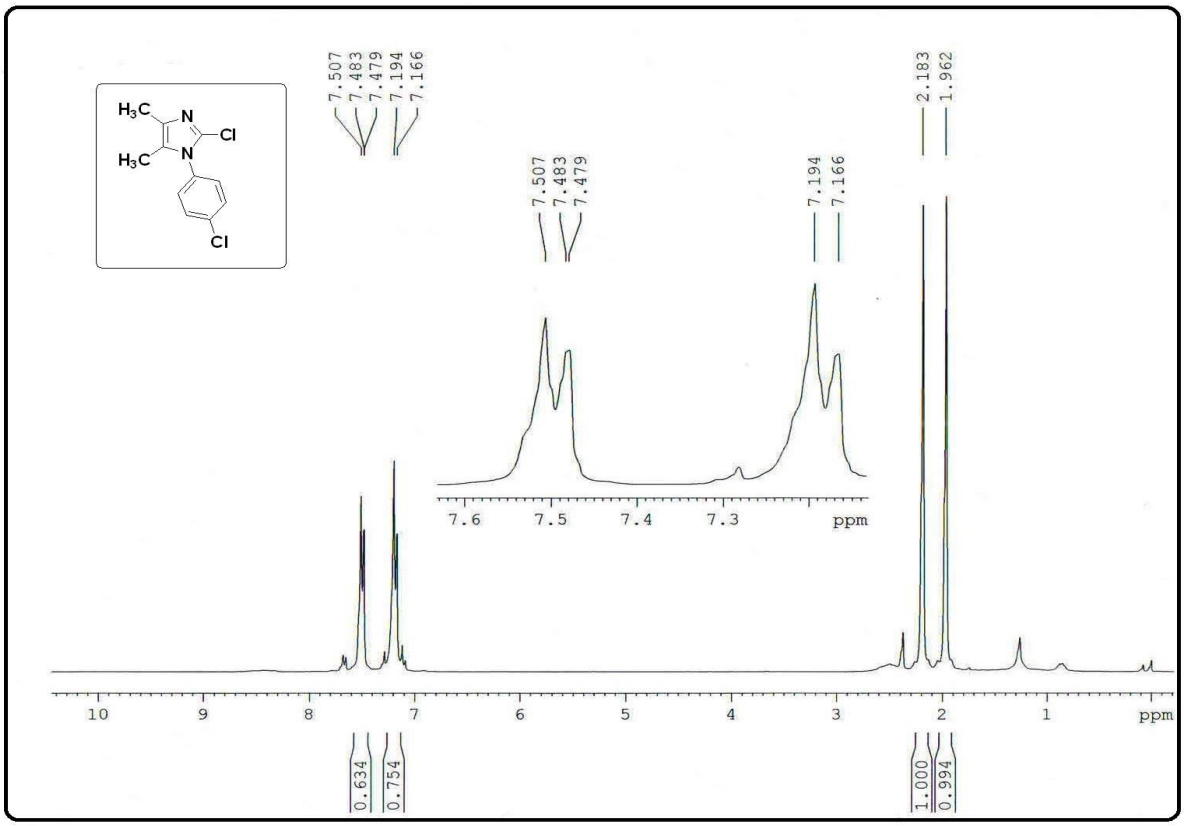
[1]HNMR-2-chloro-1-(2-methoxyphenyl)-4,5-dimethyl-1H-imidazole



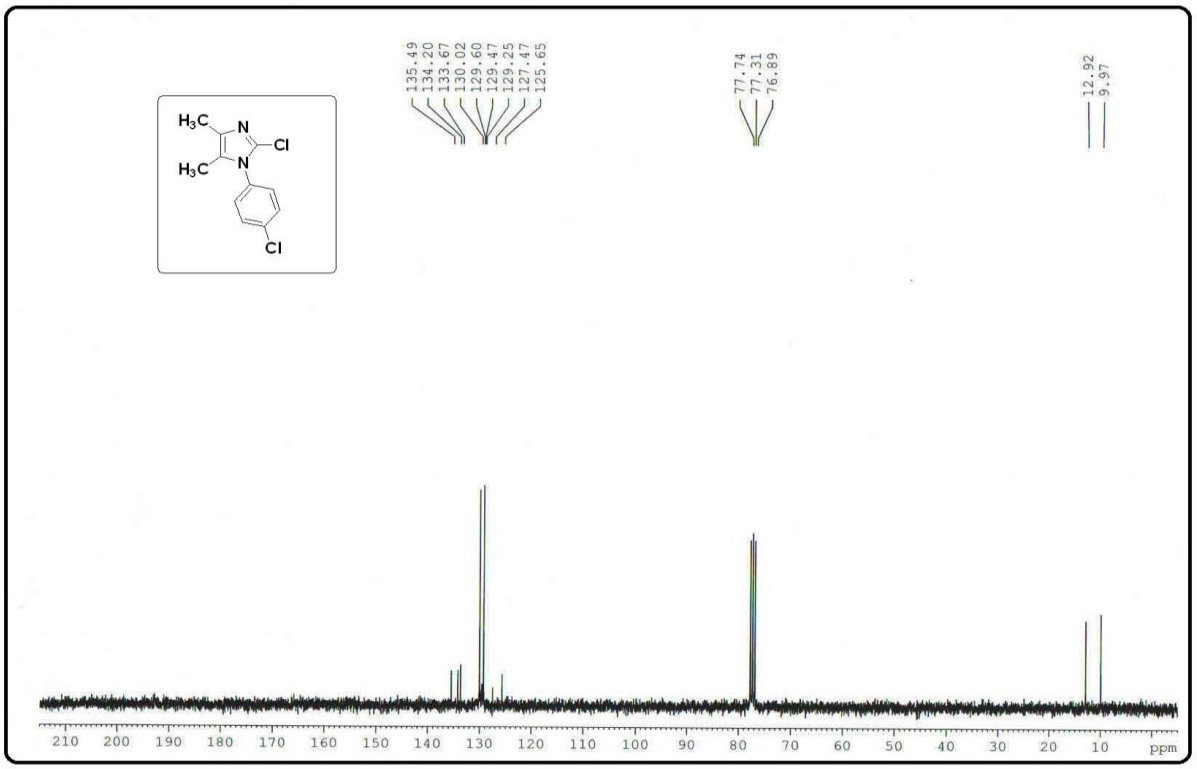
[13]CNMR-2-chloro-1-(2-methoxyphenyl)-4,5-dimethyl-1H-imidazole



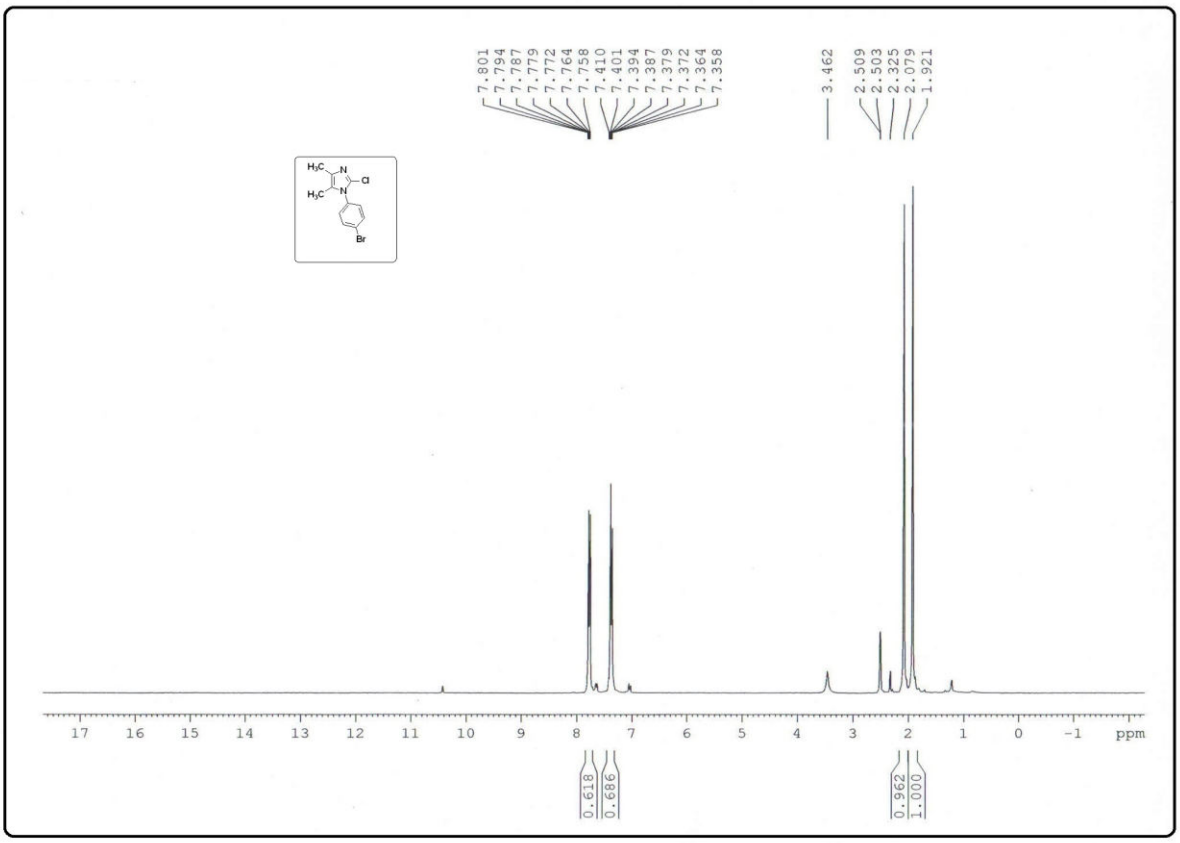
[1]HNMR-2-chloro-1-(4-chlorophenyl)-4, 5-dimethyl-1H-imidazole



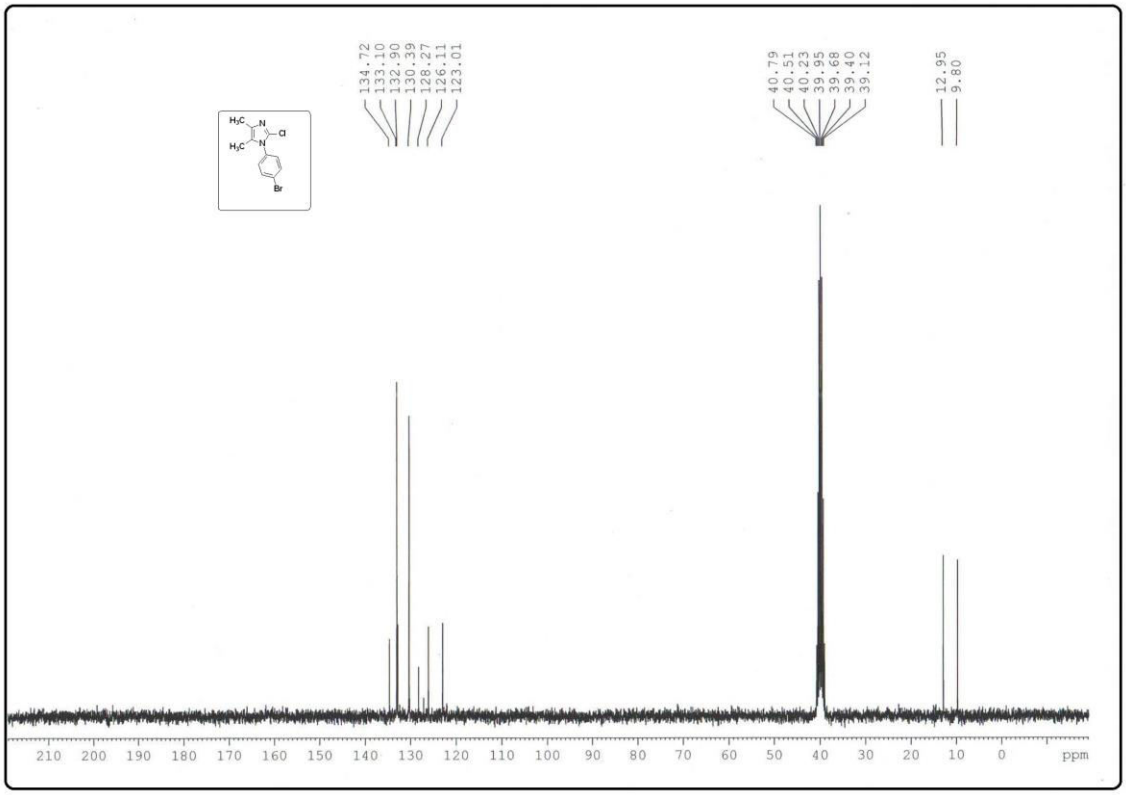
[13]CNMR-2-chloro-1-(4-chlorophenyl)-4, 5-dimethyl-1H-imidazole



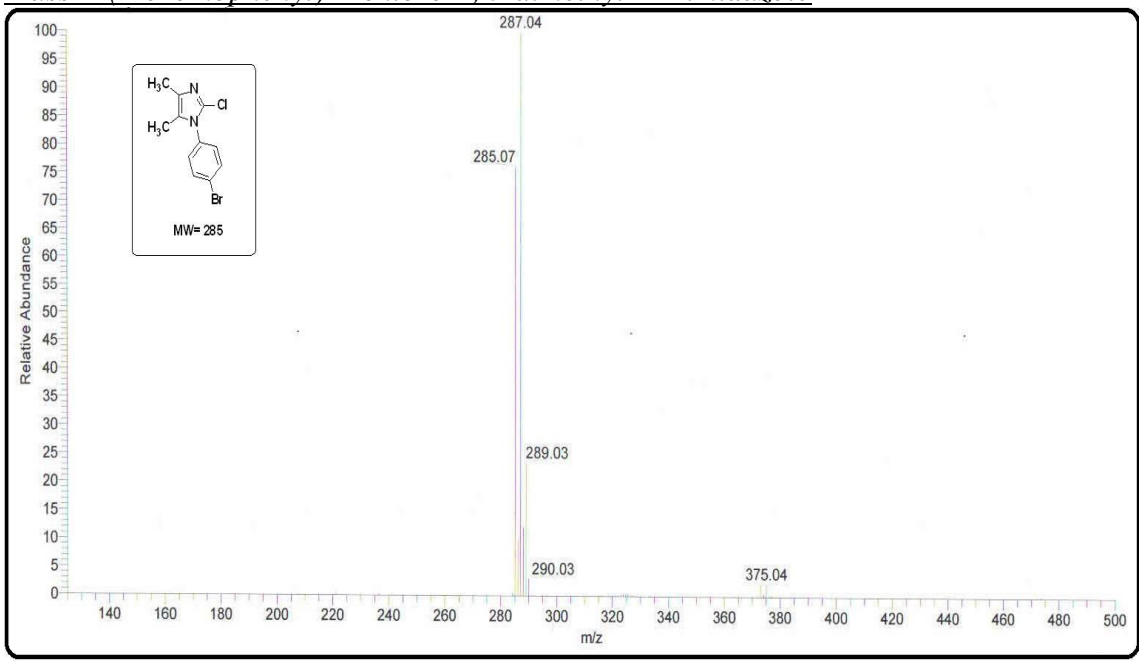
[1]HNMR-1-(4-bromophenyl)-2-chloro-4, 5-dimethyl-1H-imidazole



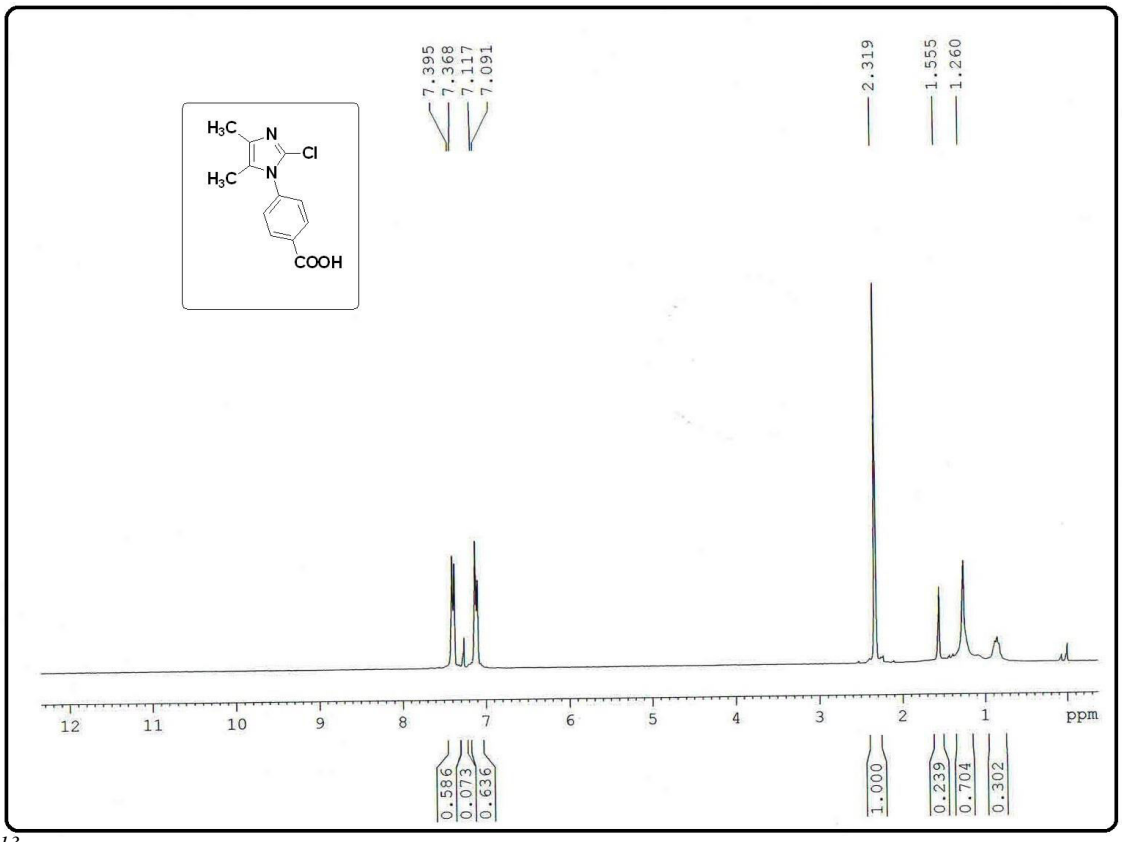
[13]CNMR-1-(4-bromophenyl)-2-chloro-4, 5-dimethyl-1H-imidazole



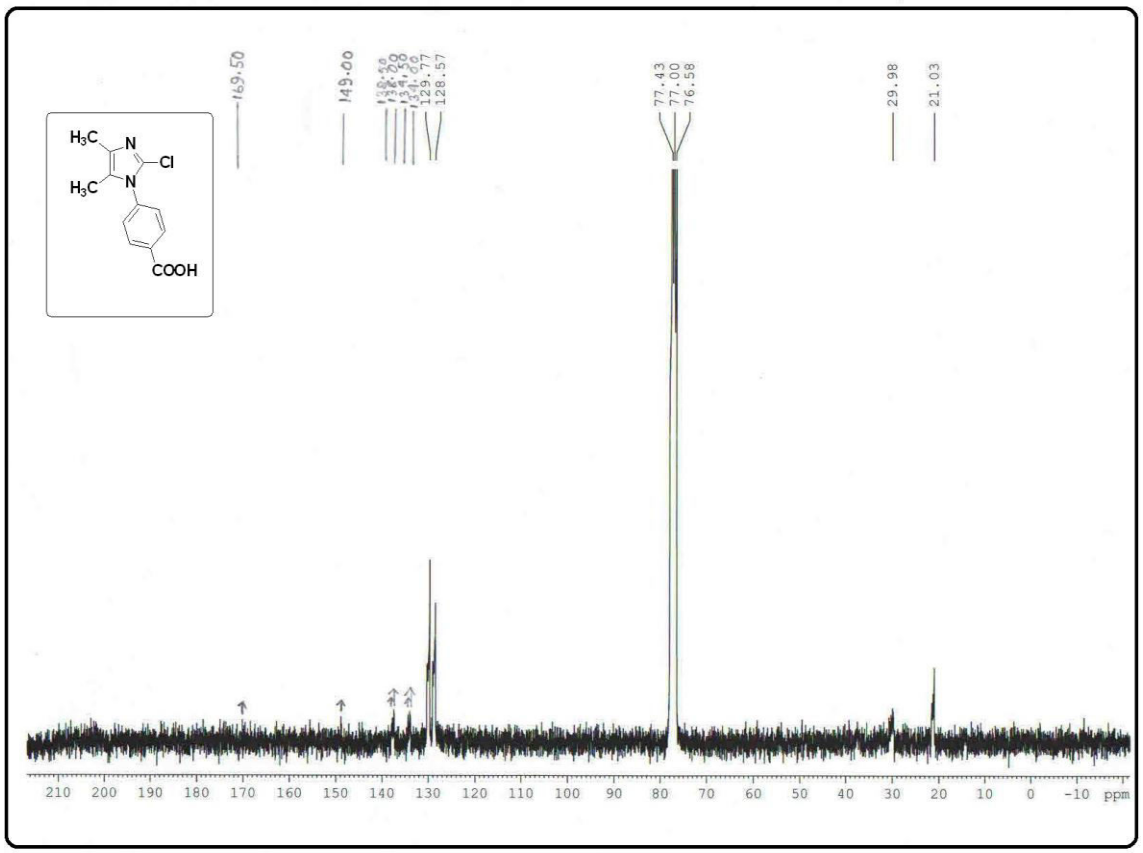
Mass-1-(4-bromophenyl)-2-chloro-4, 5-dimethyl-1H-imidazole



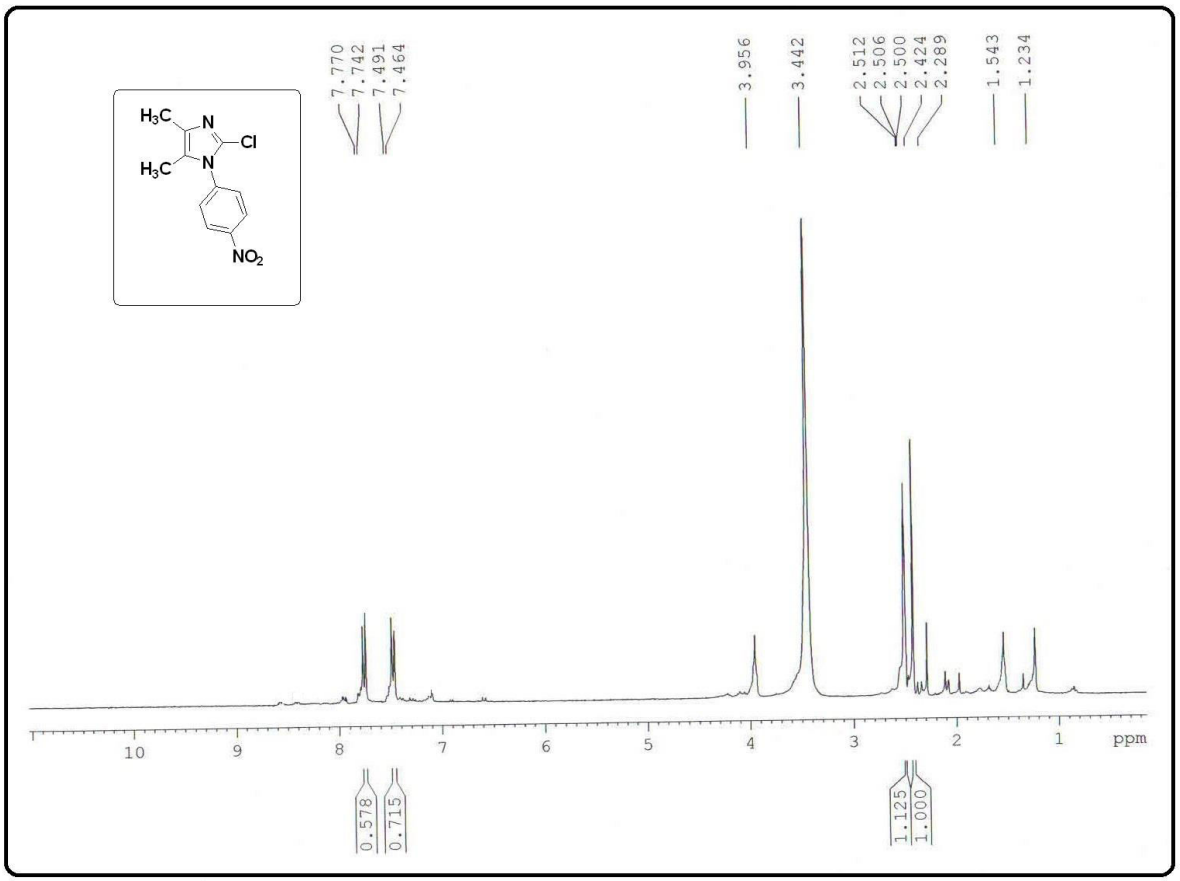
[1]HNMR-4-(2-chloro-4, 5-dimethyl-1H-imidazol-1-yl) benzoic acid



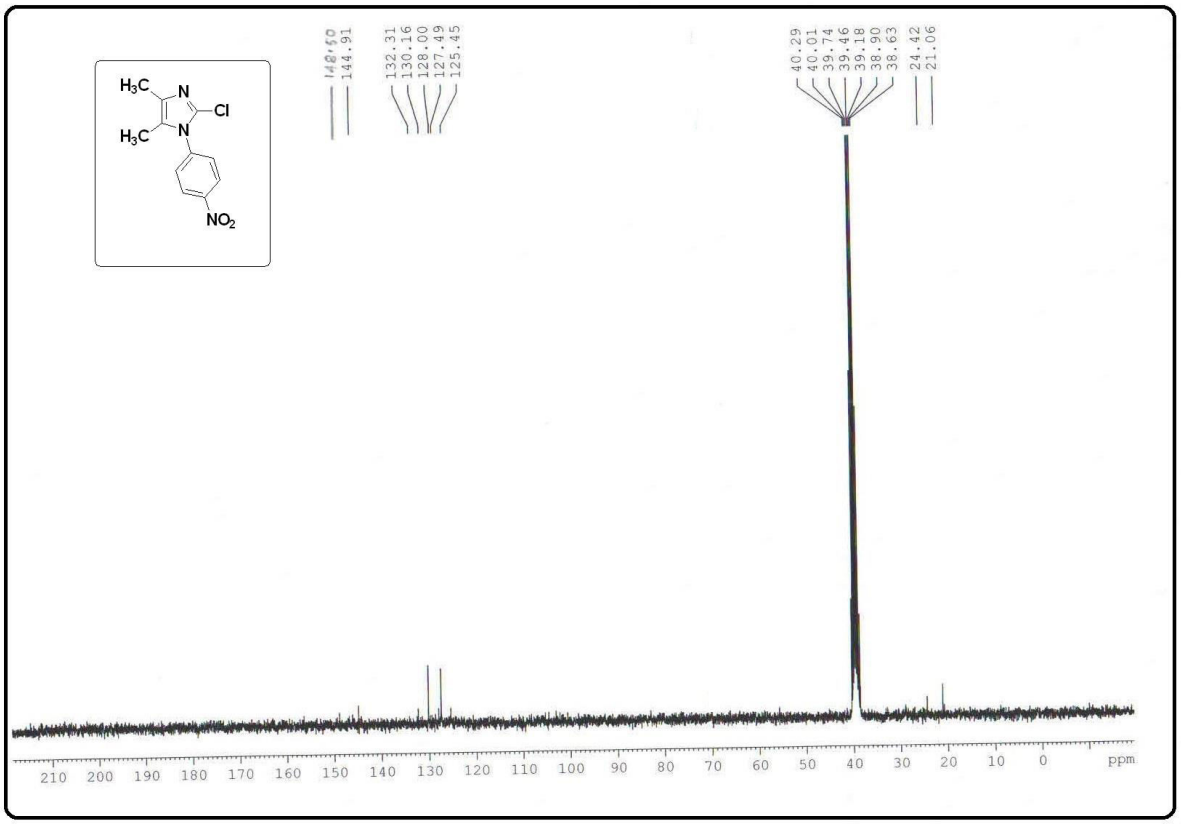
[13]CNMR-4-(2-chloro-4, 5-dimethyl-1H-imidazol-1-yl) benzoic acid



[1]HNMR-2-chloro-4, 5-dimethyl-1-(4-nitrophenyl)-1H-imidazole



[13]CNMR-2-chloro-4, 5-dimethyl-1-(4-nitrophenyl)-1H-imidazole



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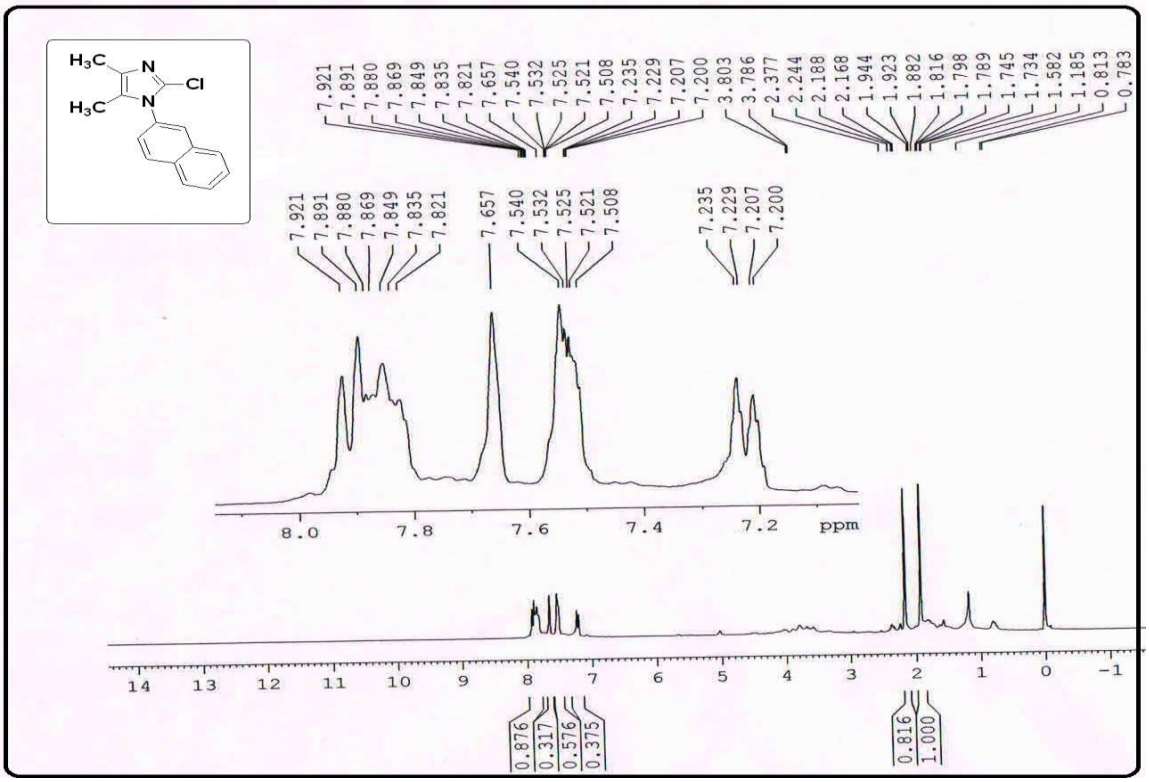

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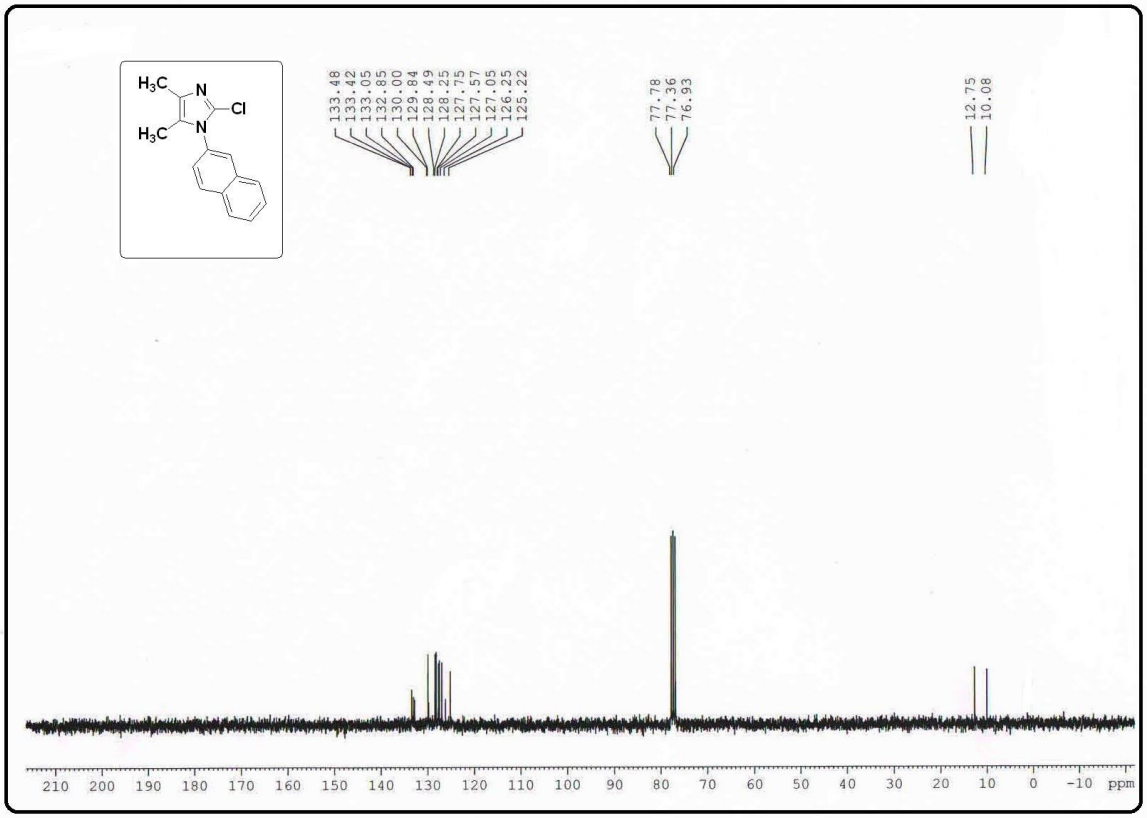

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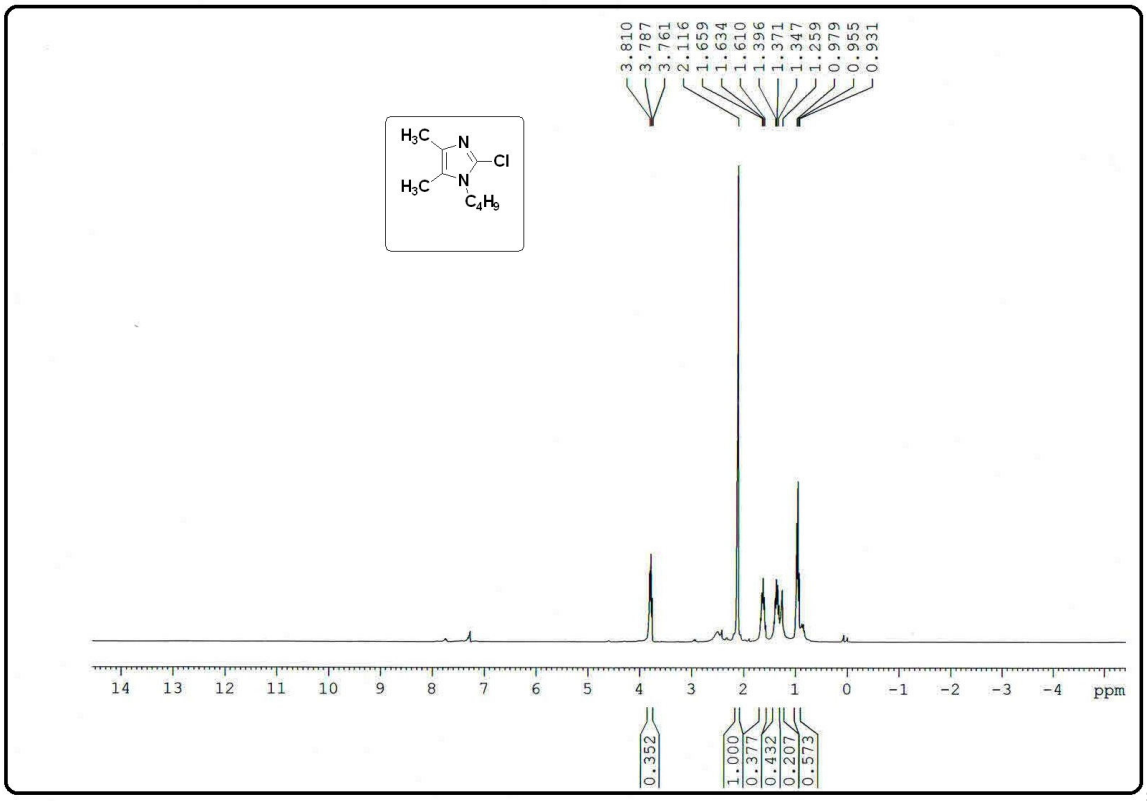

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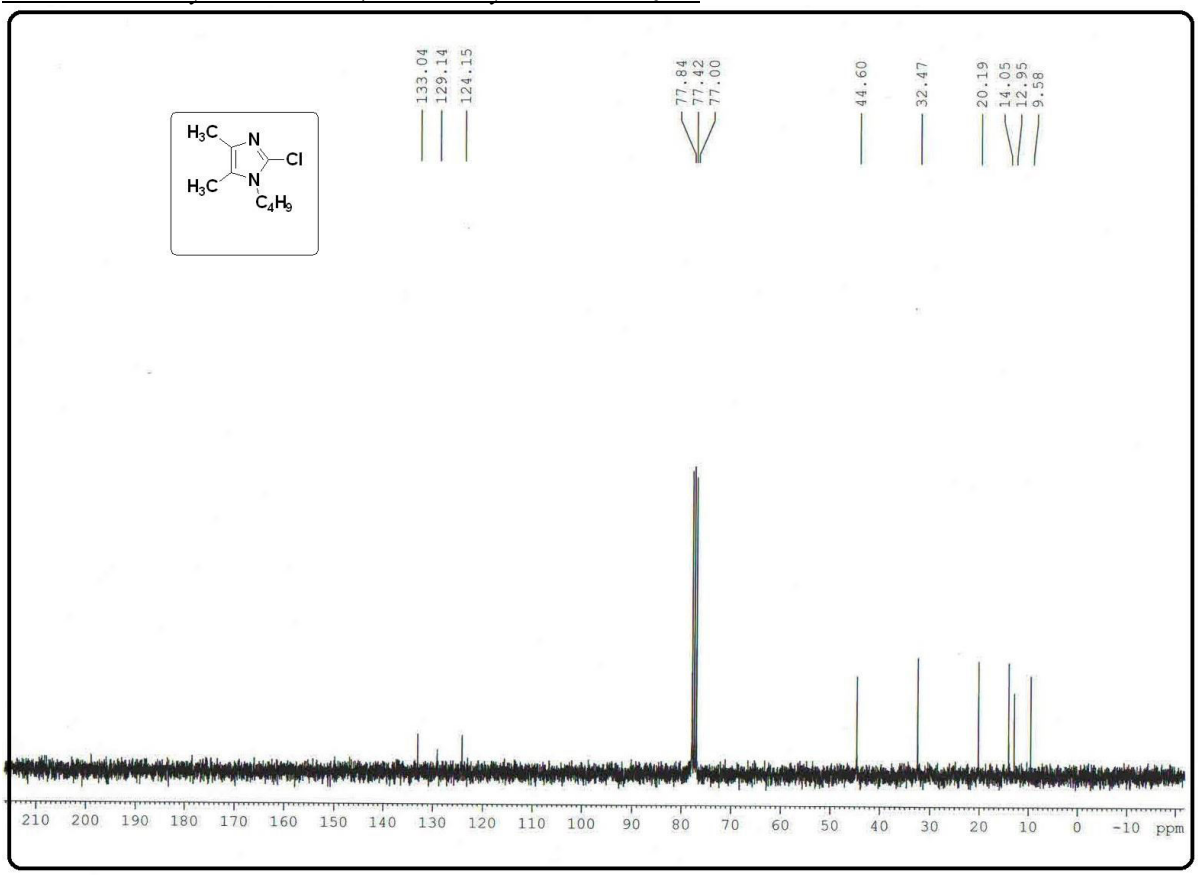
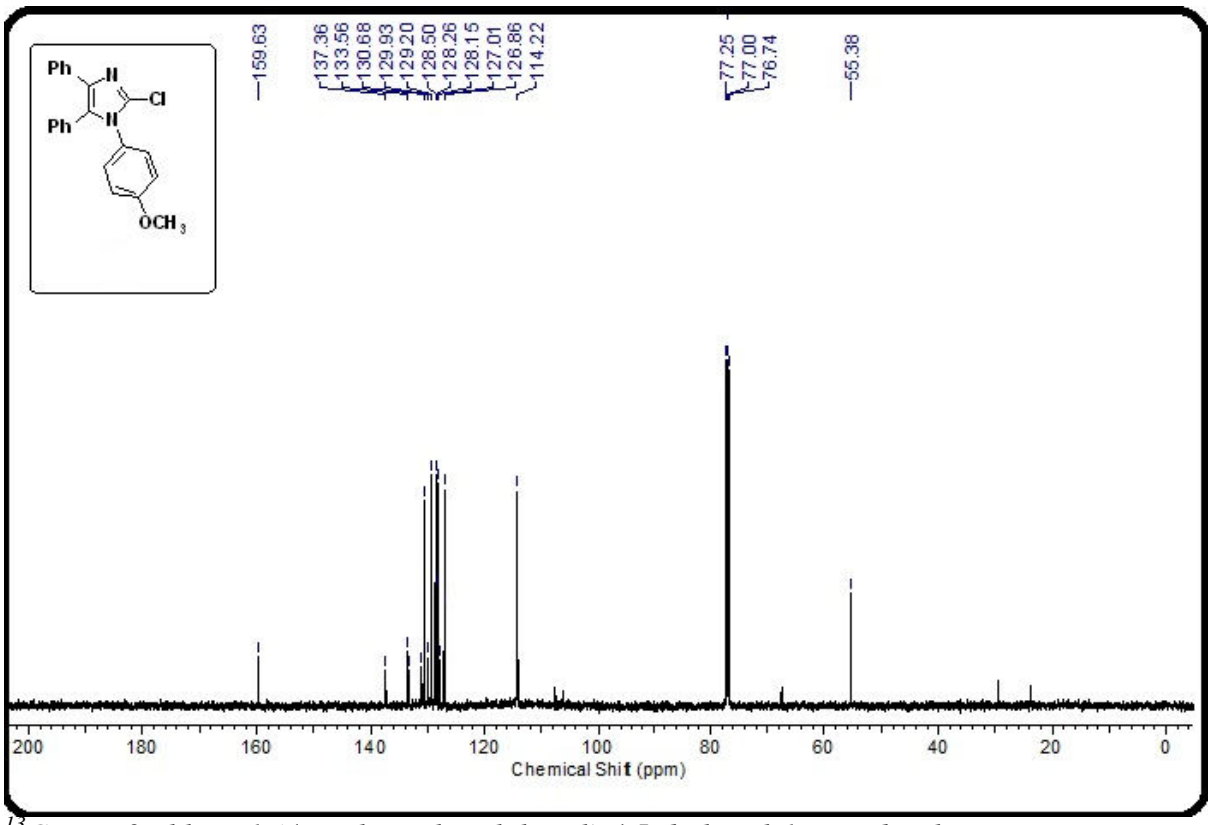
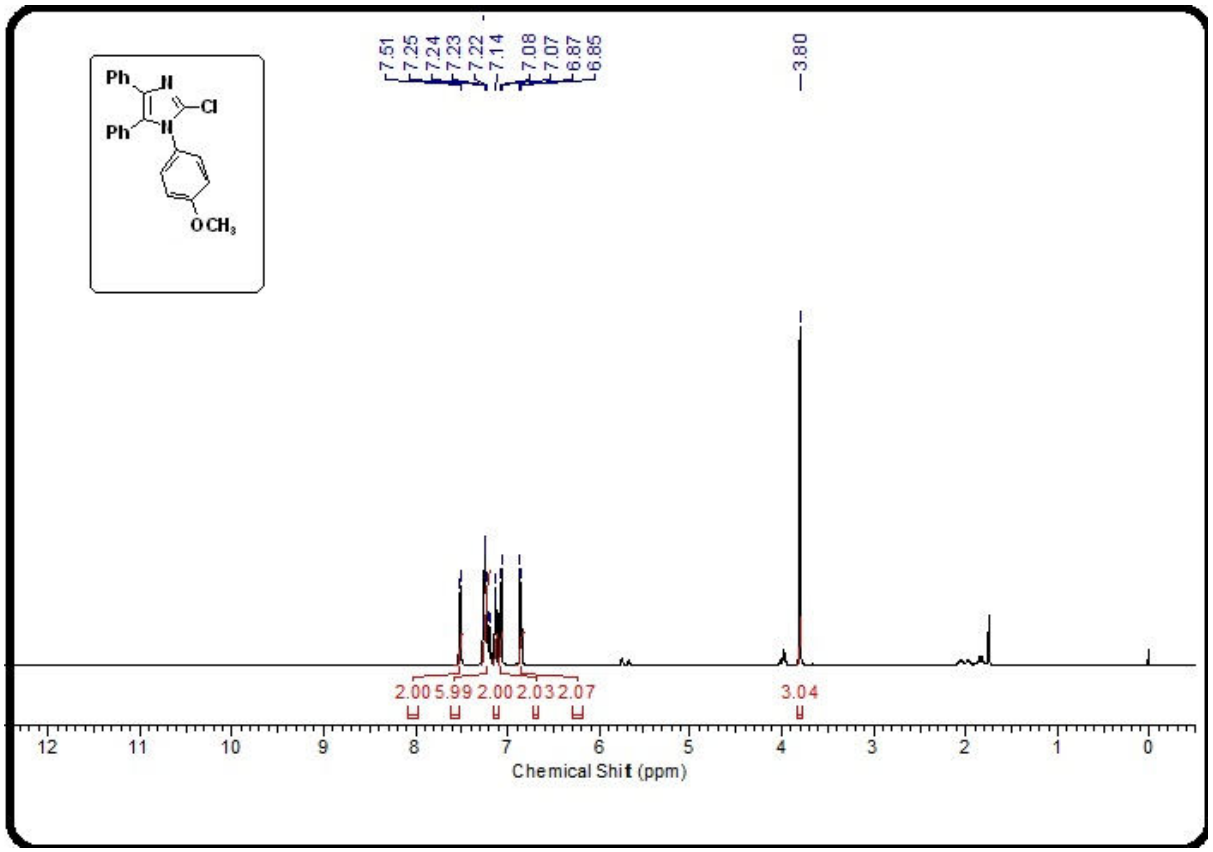
[13]CNMR-1-butyl-2-chloro-4, 5-dimethyl-1H-imidazole



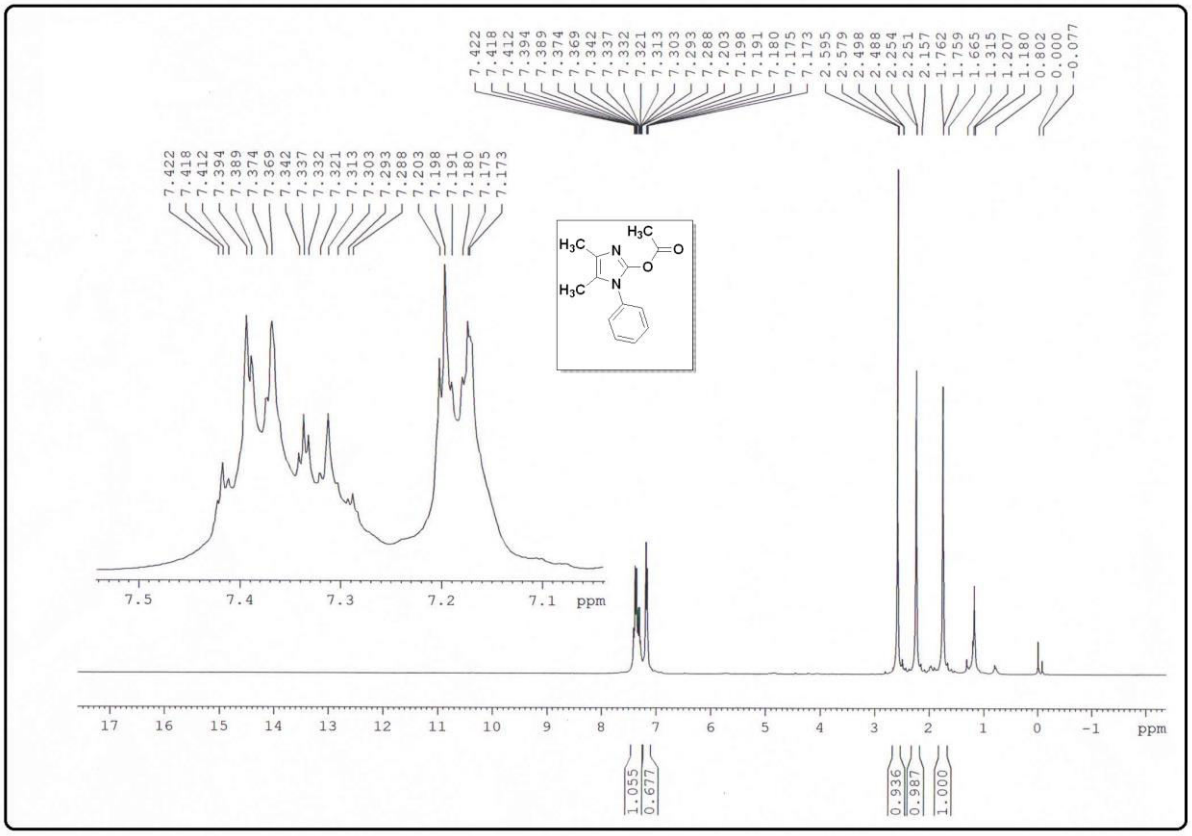
[1]HNMR-2-chloro-1-(4-methoxyphenylphenyl)-4,5-diphenyl-1H-imidazole



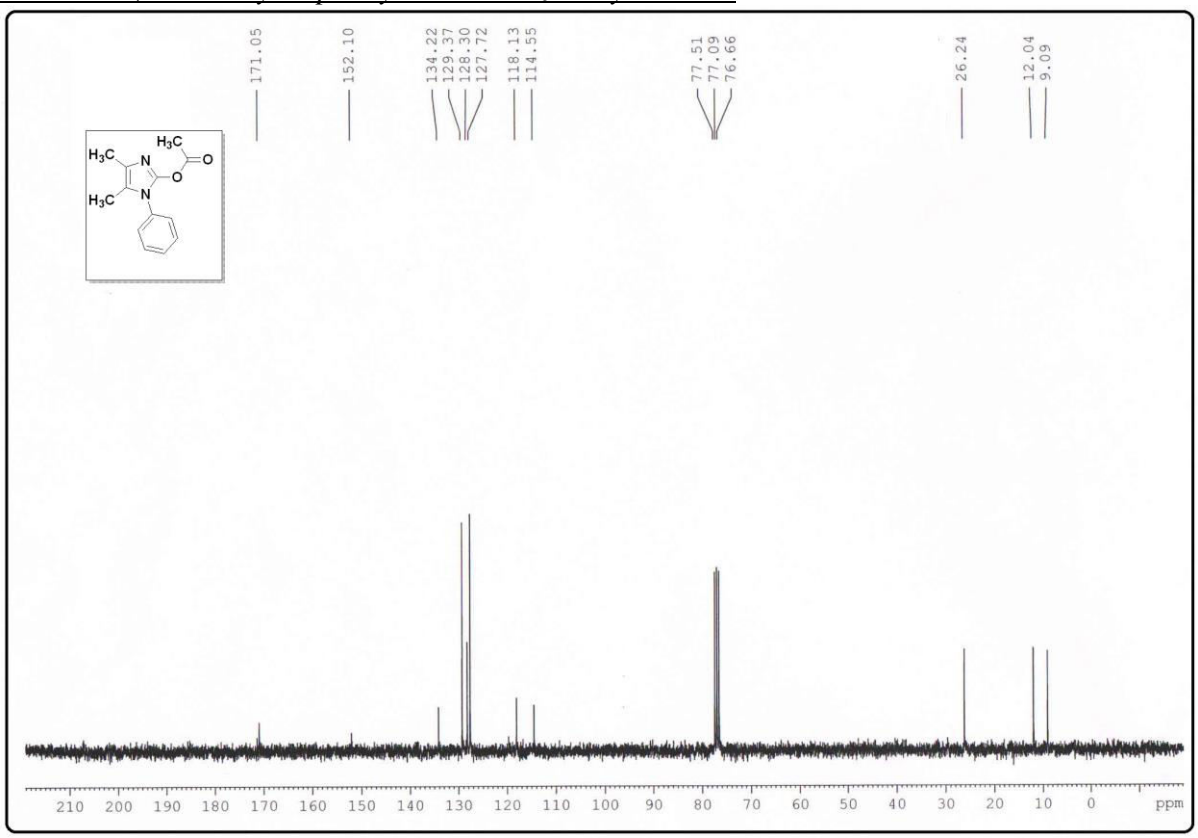
[13]CNMR-2-chloro-1-(4-methoxyphenylphenyl)-4,5-diphenyl-1H-imidazole



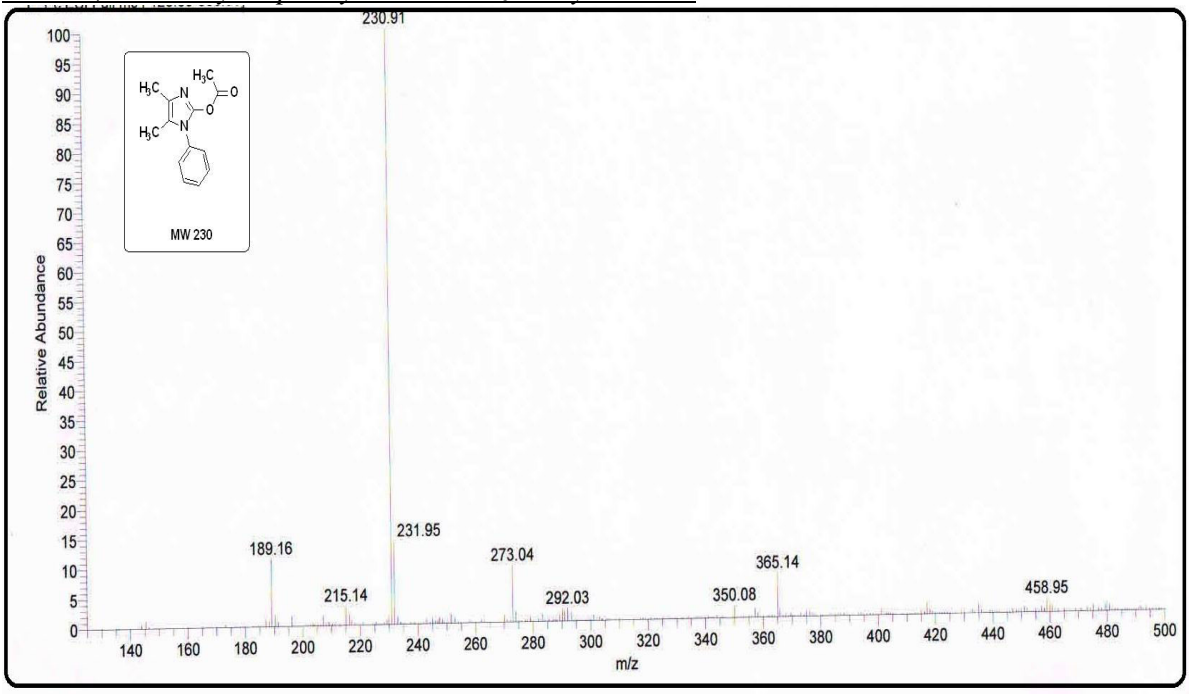
[1]HNMR-4,5-dimethyl-1-phenyl-1H-imidazol-2-yl acetate



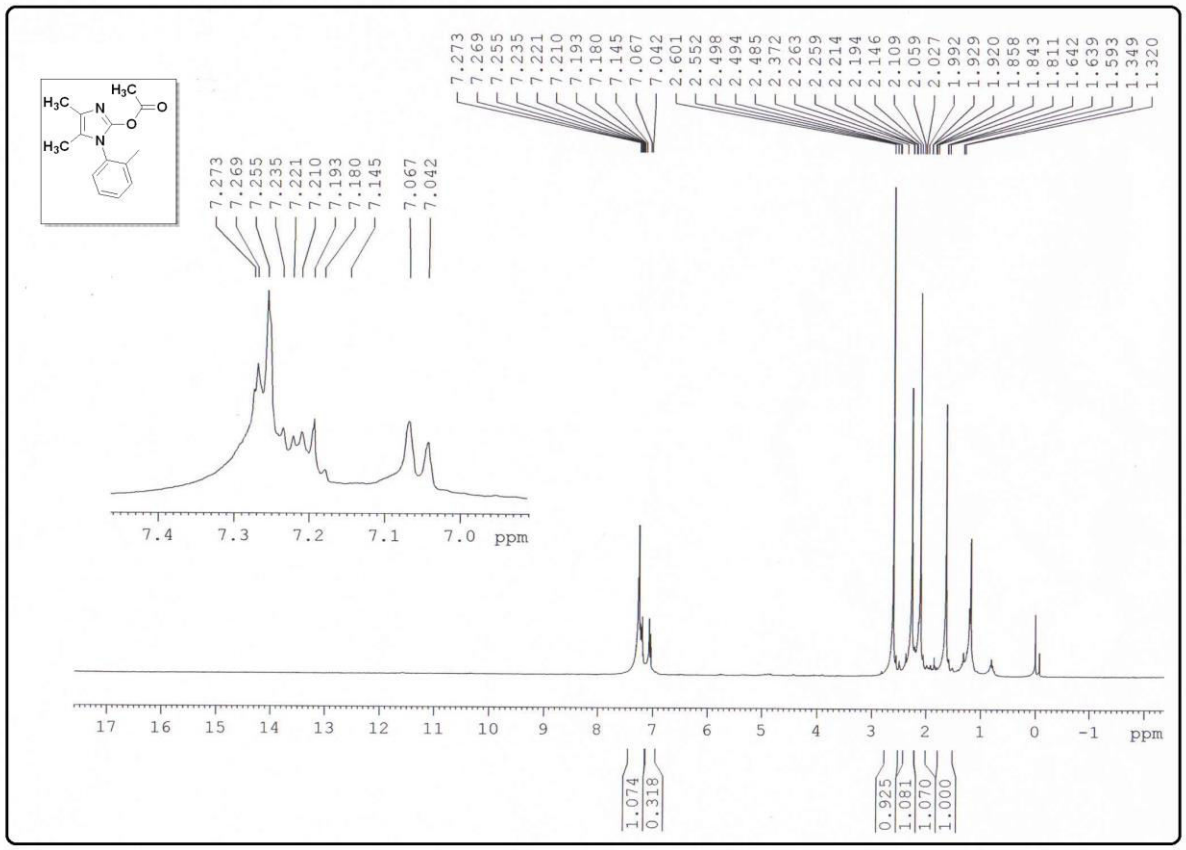
[13]CNMR-4,5-dimethyl-1-phenyl-1H-imidazol-2-yl acetate



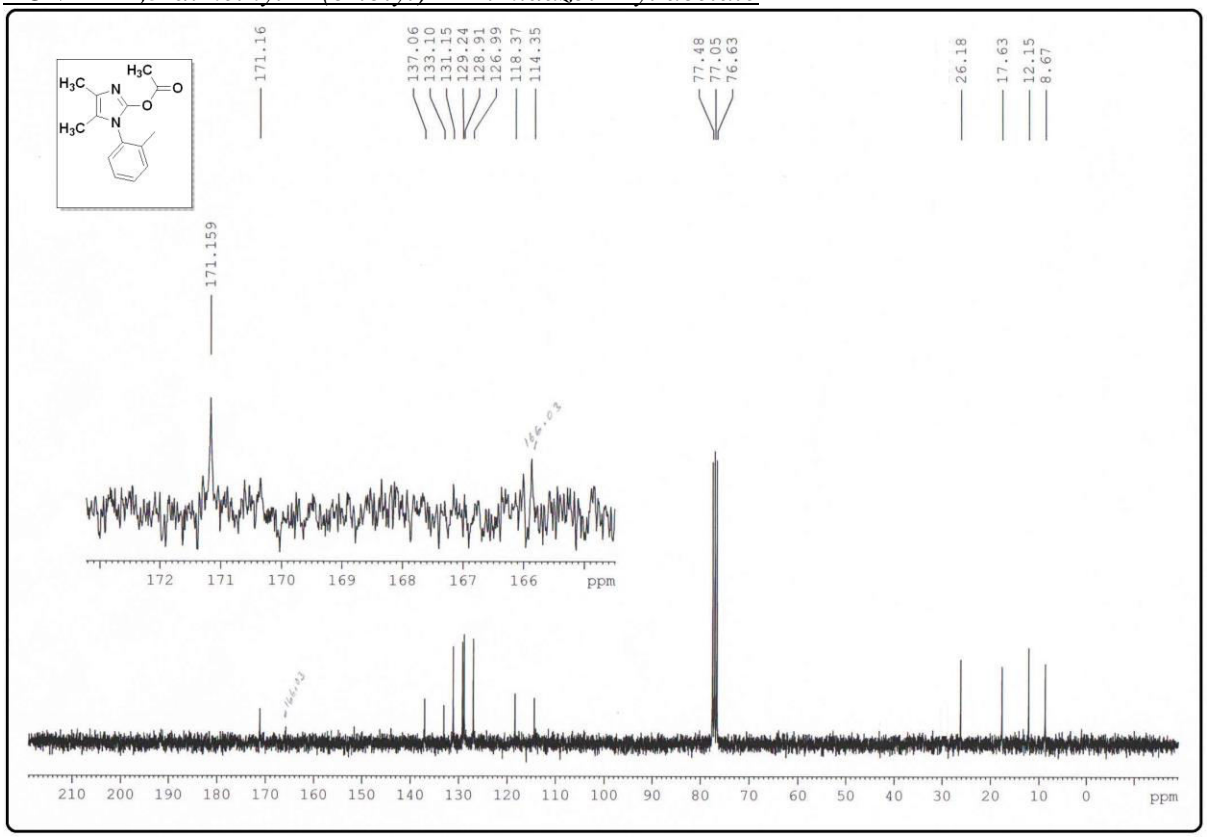
Mass-4,5-dimethyl-1-phenyl-1H-imidazol-2-yl acetate



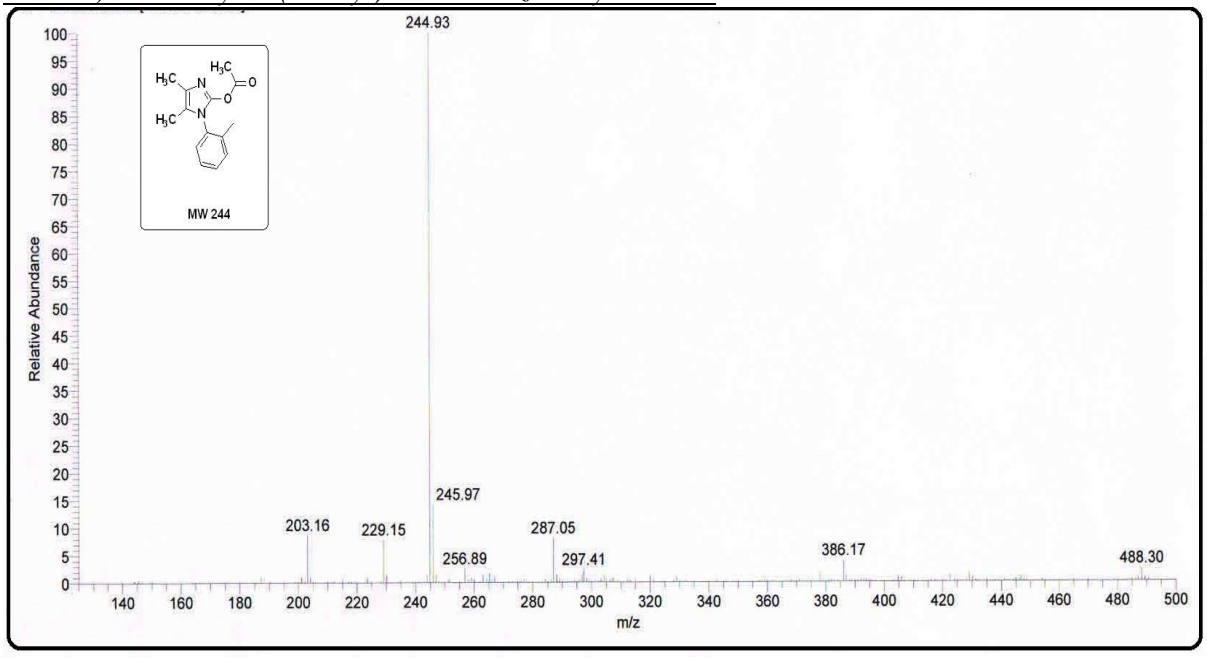
^{1}HNMR-4,5-dimethyl-1-(o-tolyl)-1H-imidazol-2-yl acetate



[13]CNMR-4,5-dimethyl-1-(o-tolyl)-1H-imidazol-2-yl acetate



Mass-4,5-dimethyl-1-(o-tolyl)-1H-imidazol-2-yl acetate



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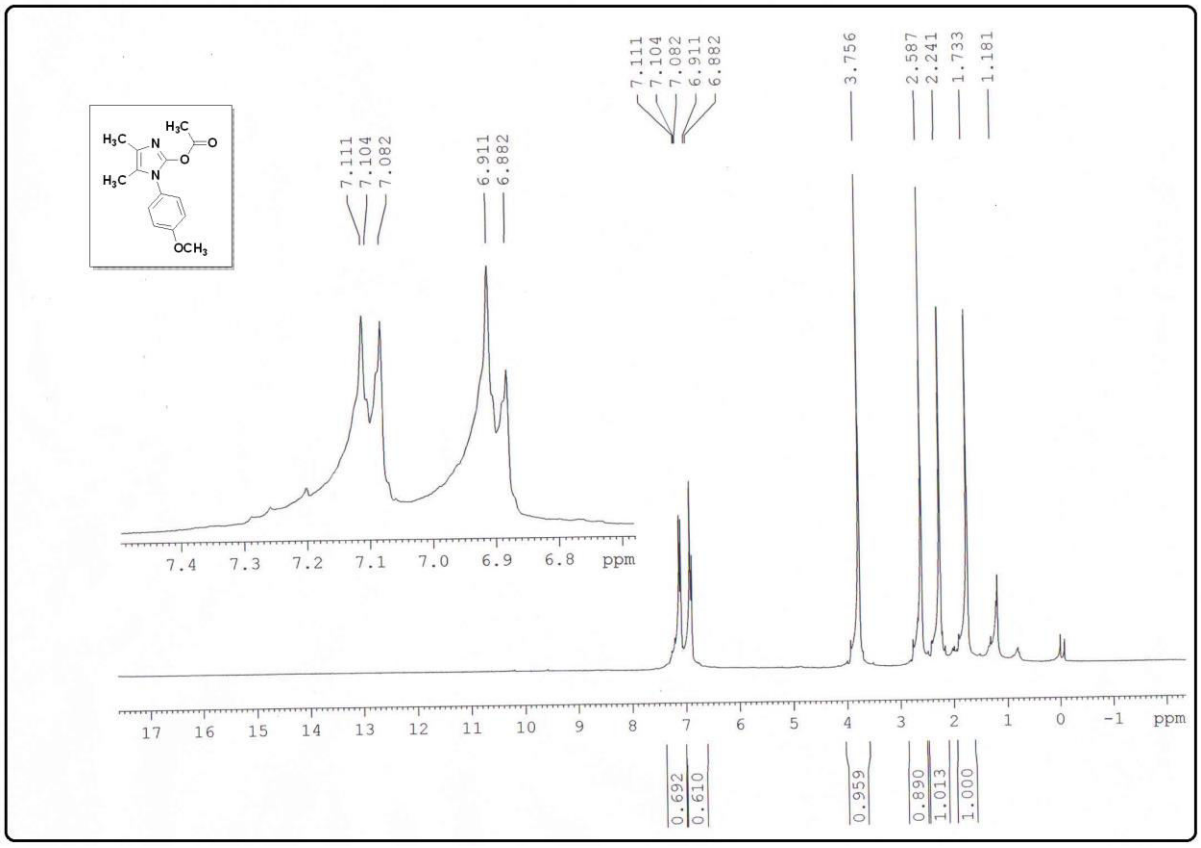

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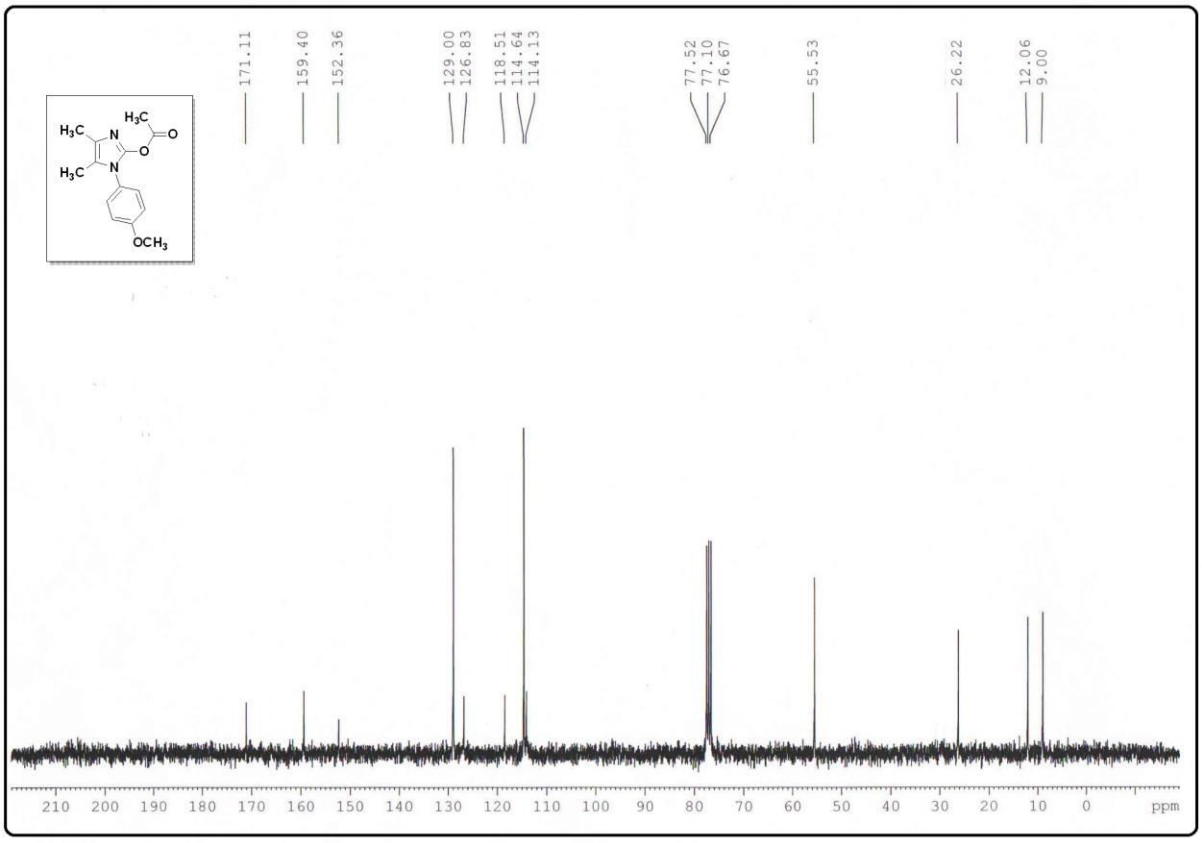
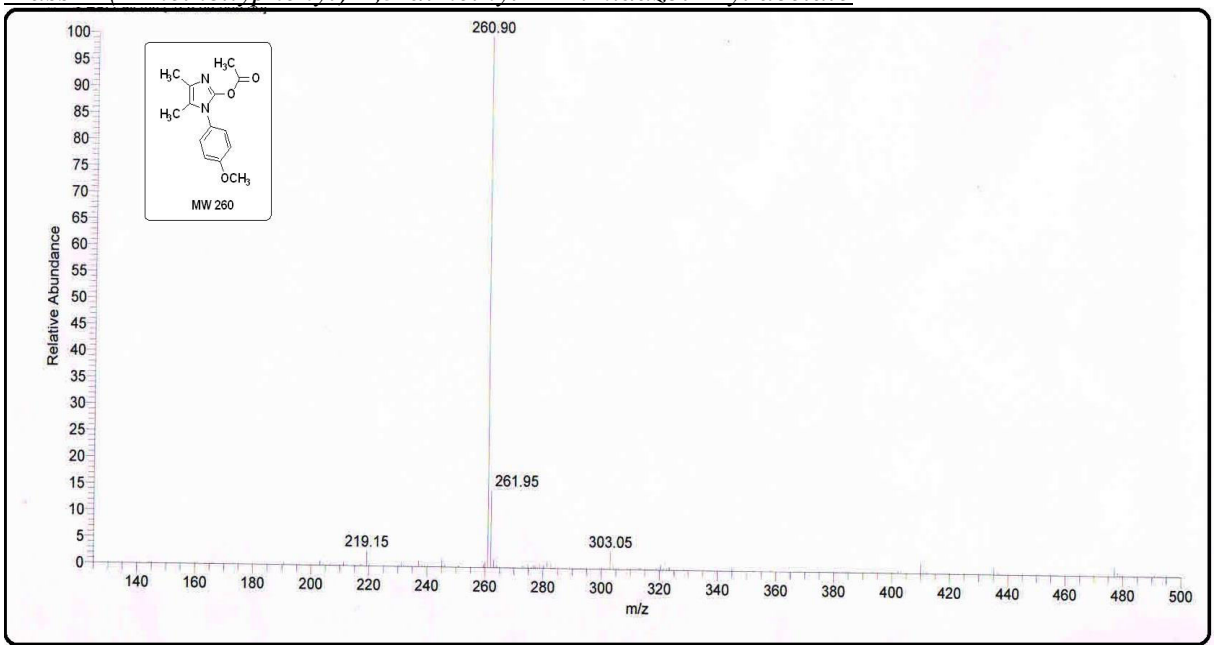


Mass-1-(4-methoxyphenyl)-4,5-dimethyl-1H-imidazol-2-yl acetate



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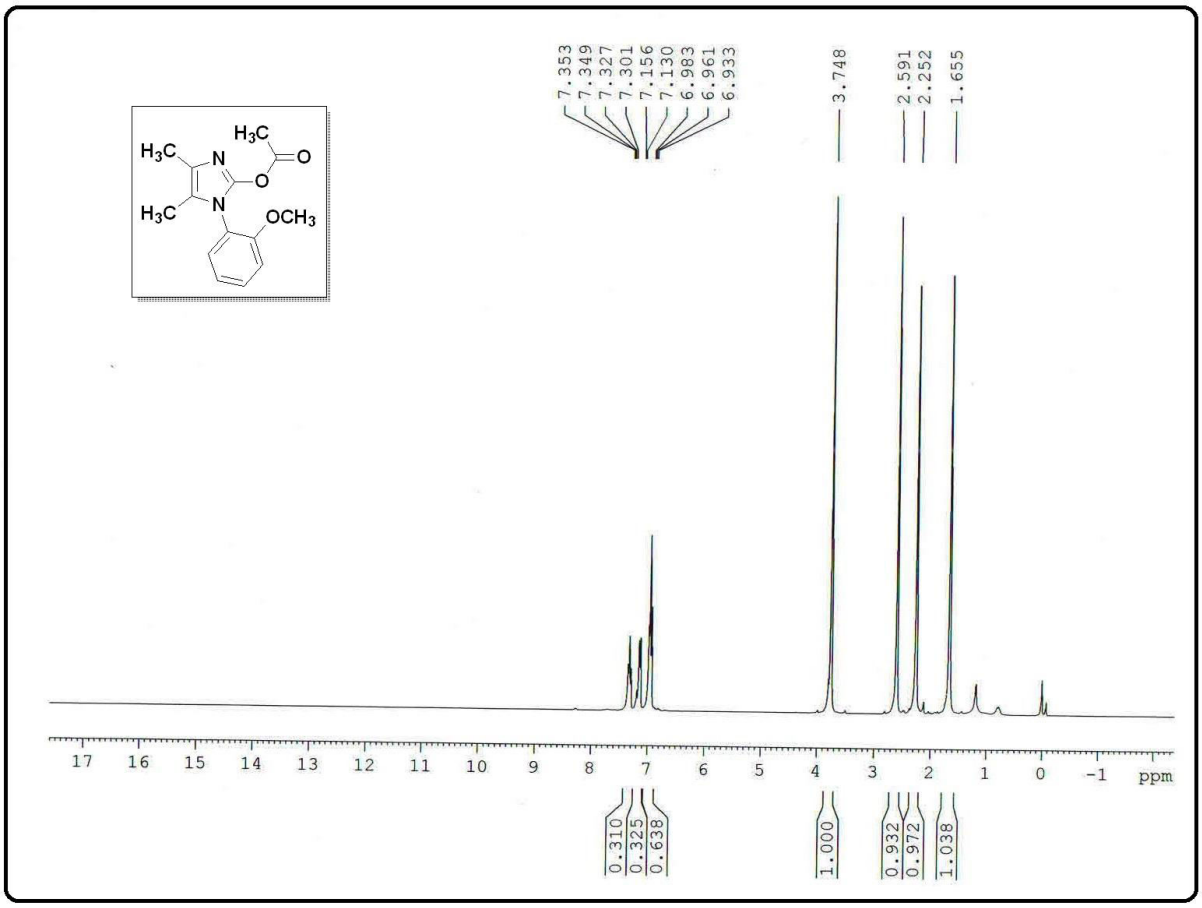

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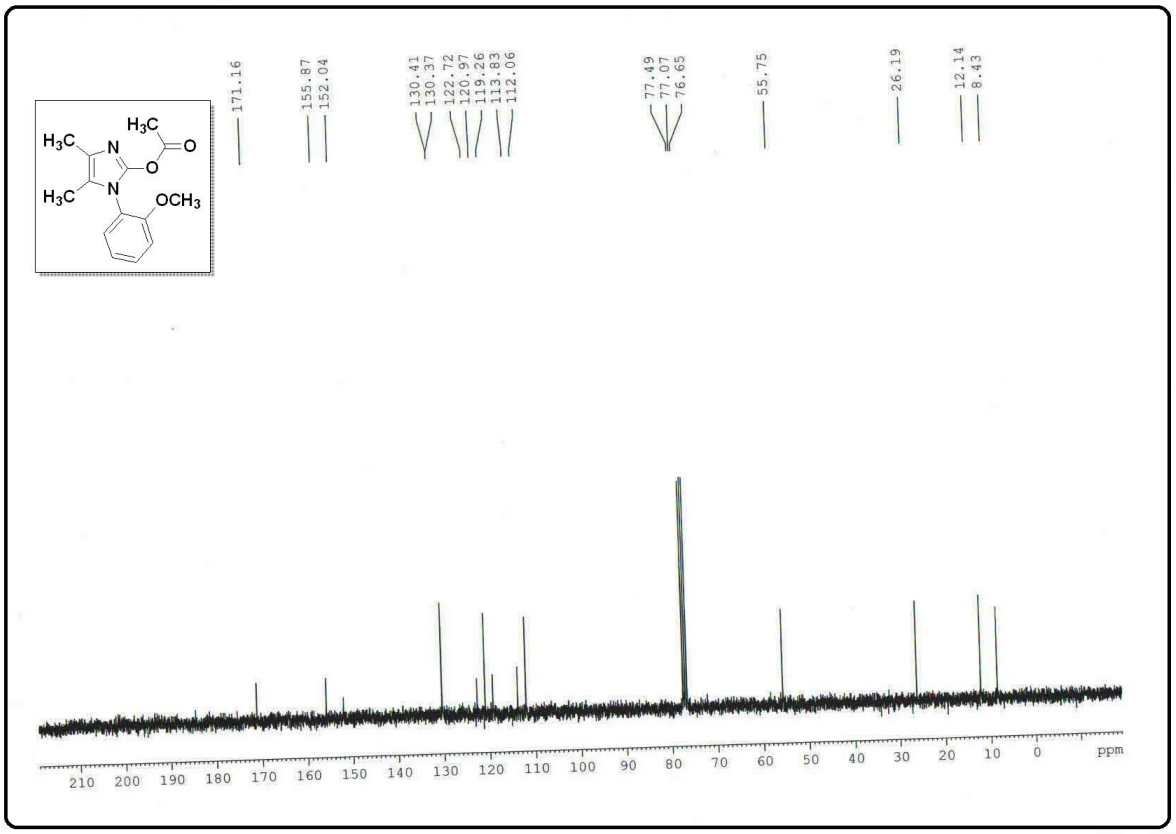
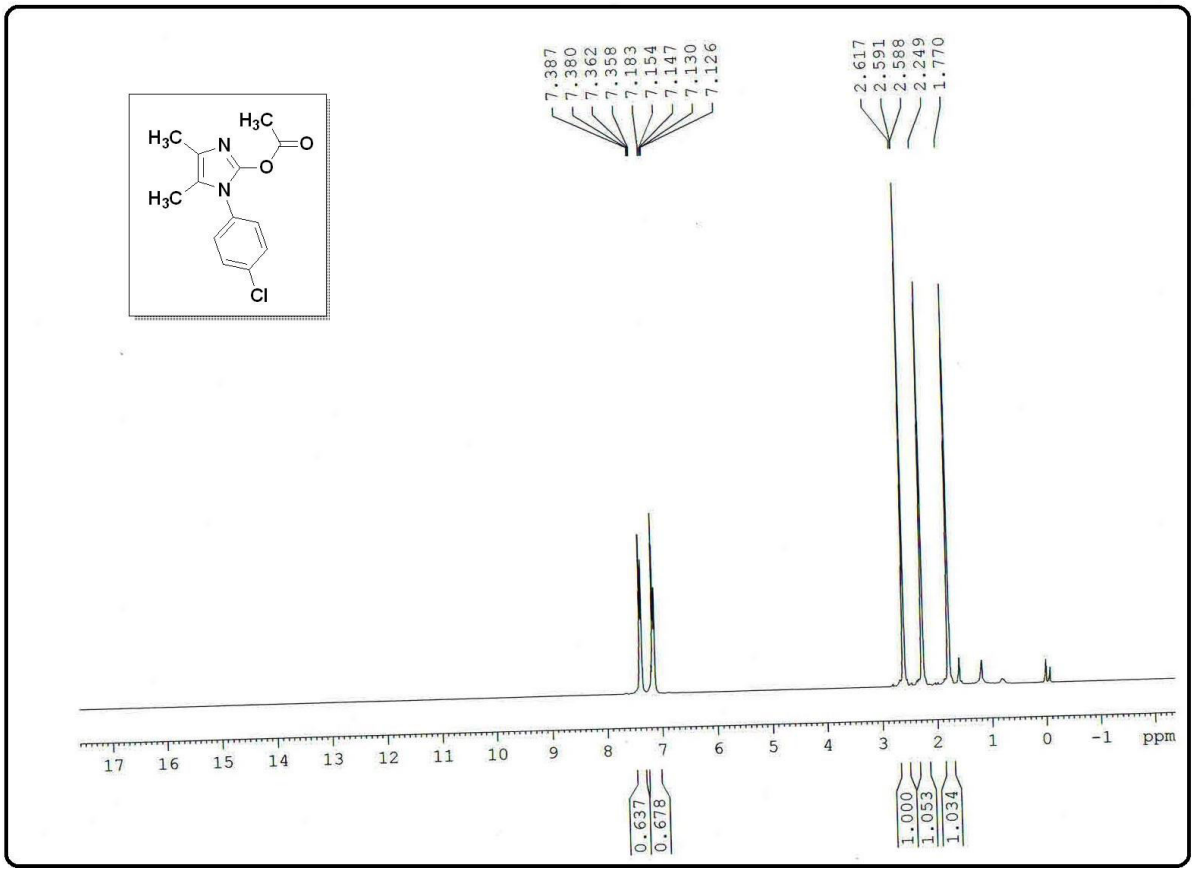
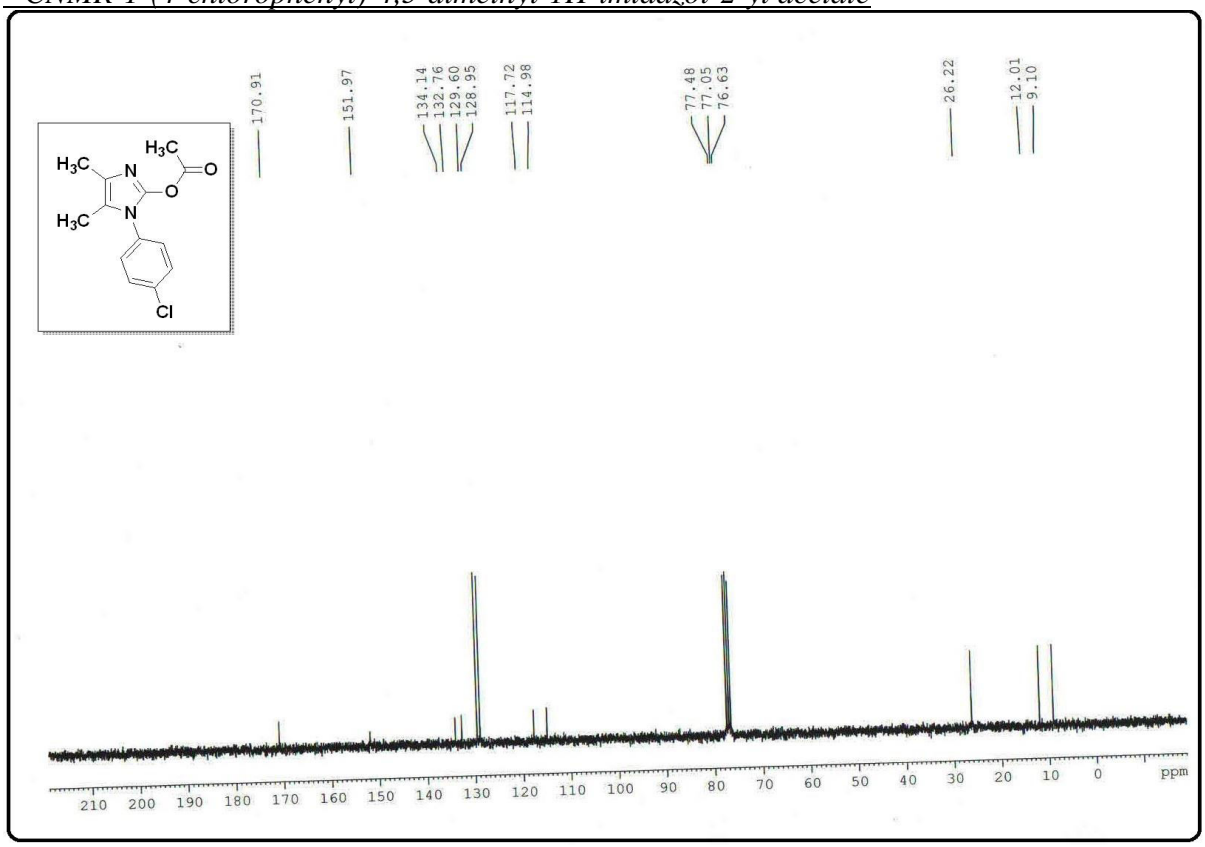


[1]HNMR-1-(4-chlorophenyl)-4,5-dimethyl-1H-imidazol-2-yl acetate



[13]CNMR-1-(4-chlorophenyl)-4,5-dimethyl-1H-imidazol-2-yl acetate



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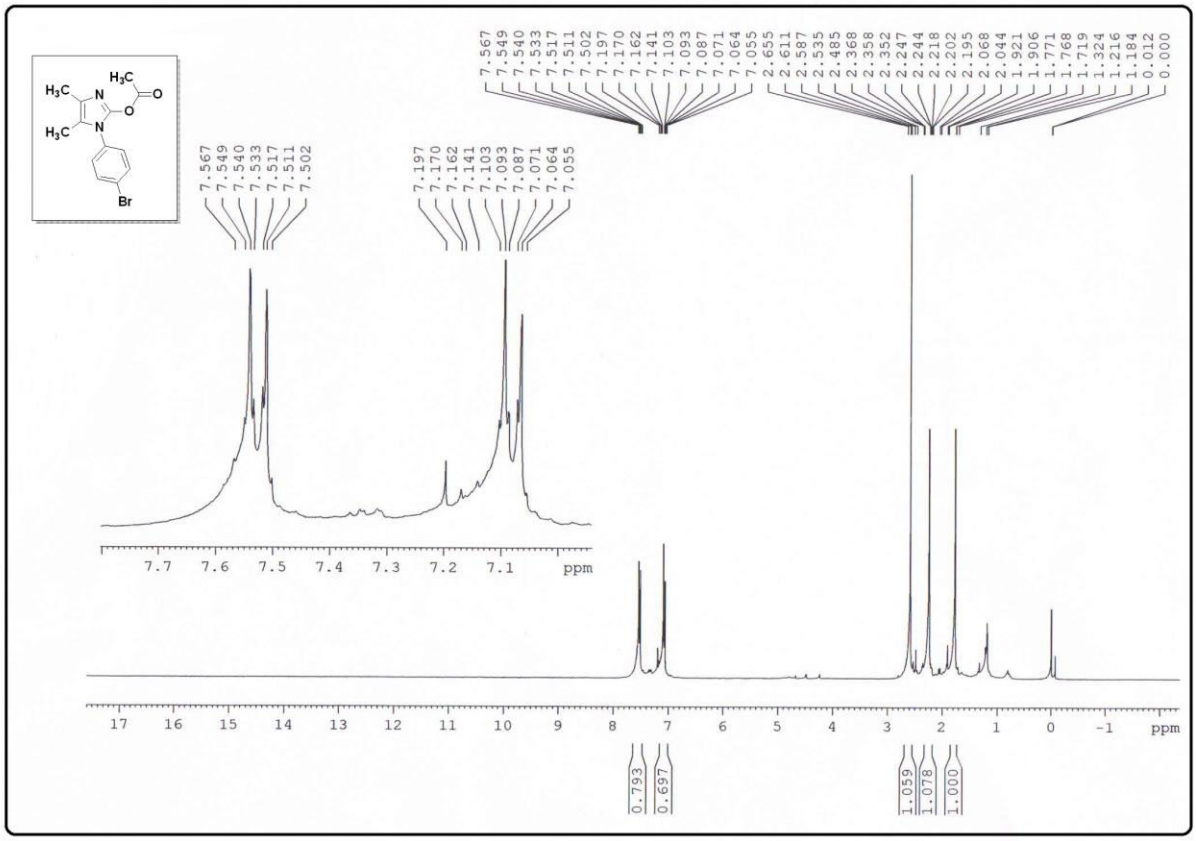

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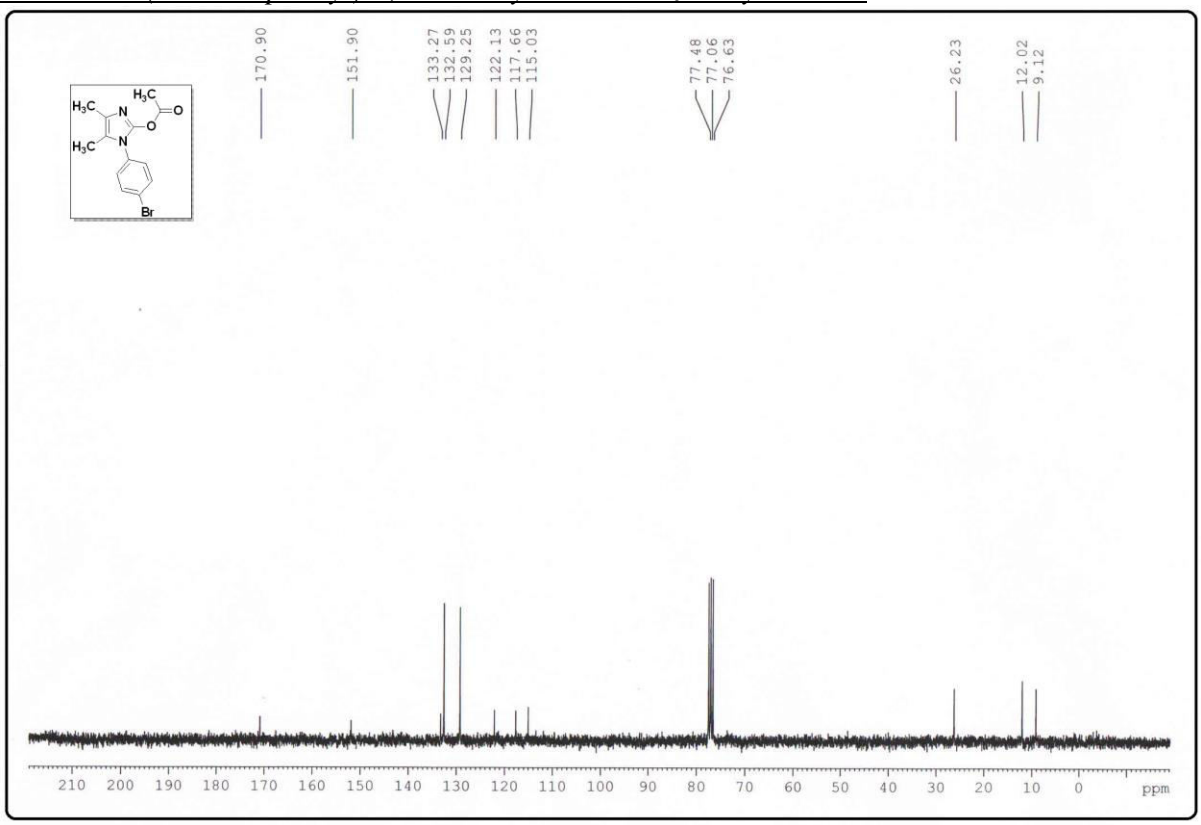
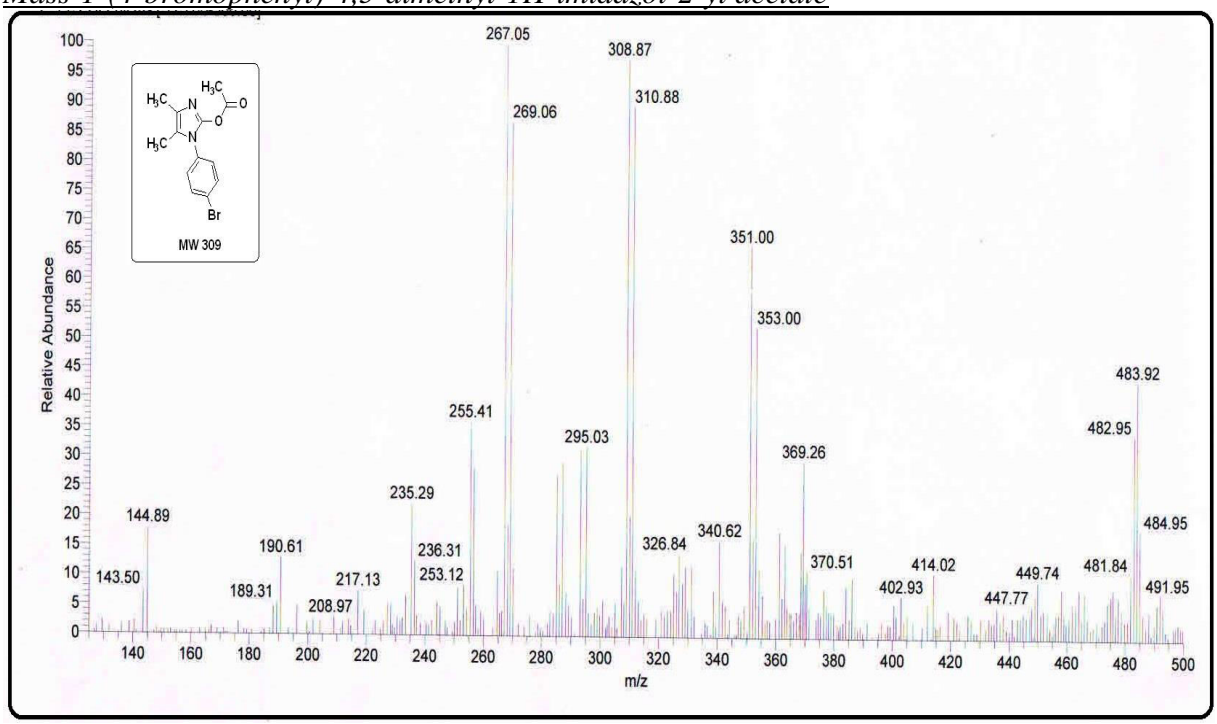


Mass-1-(4-bromophenyl)-4,5-dimethyl-1H-imidazol-2-yl acetate



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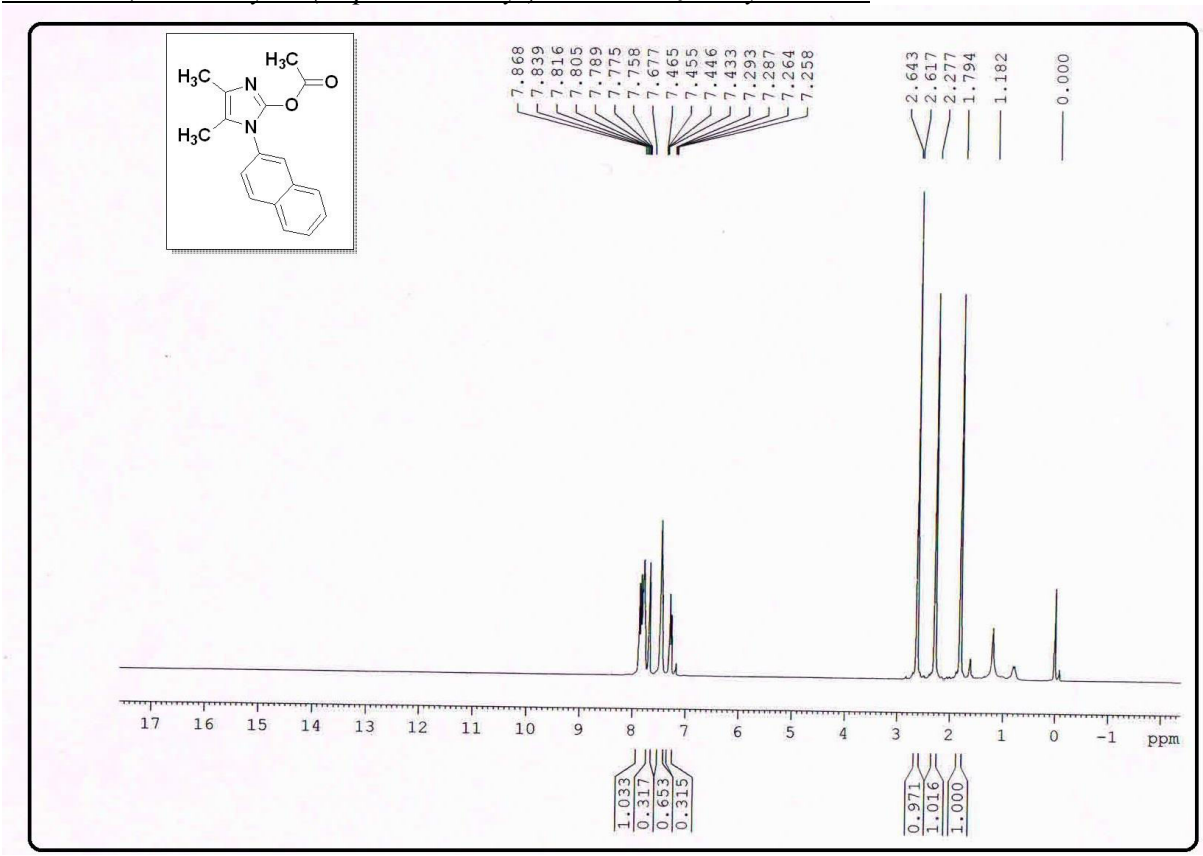
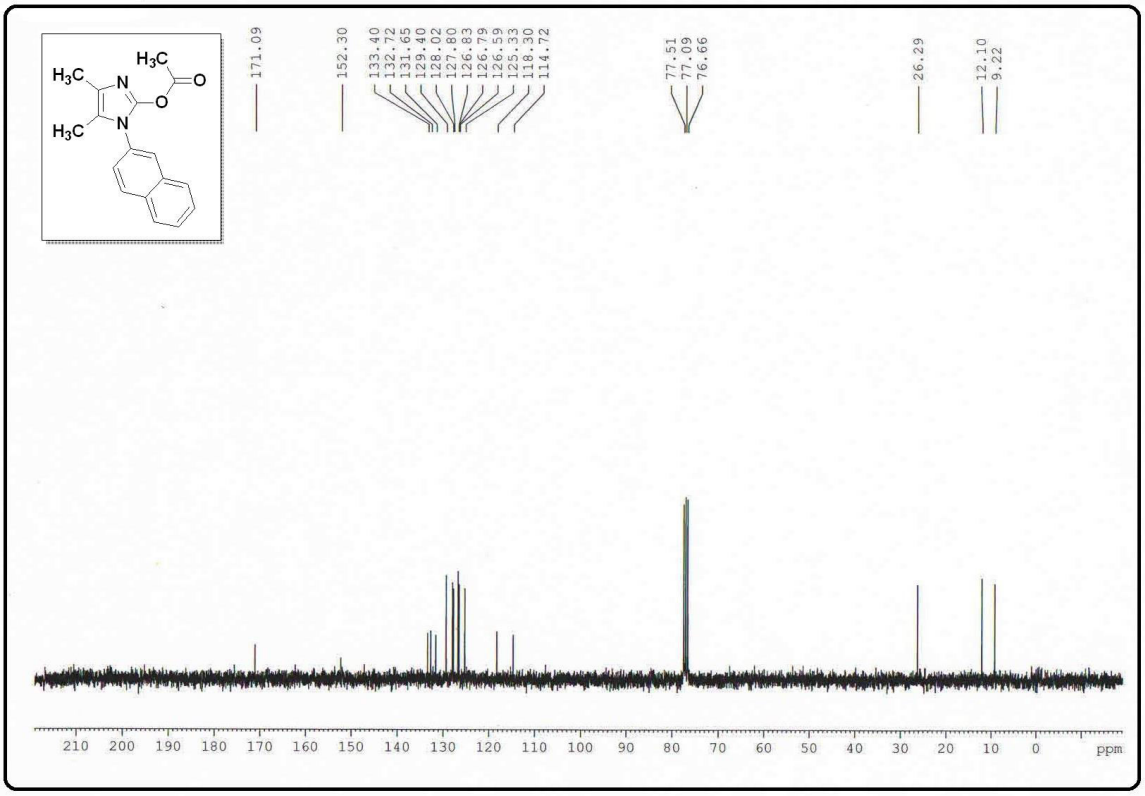
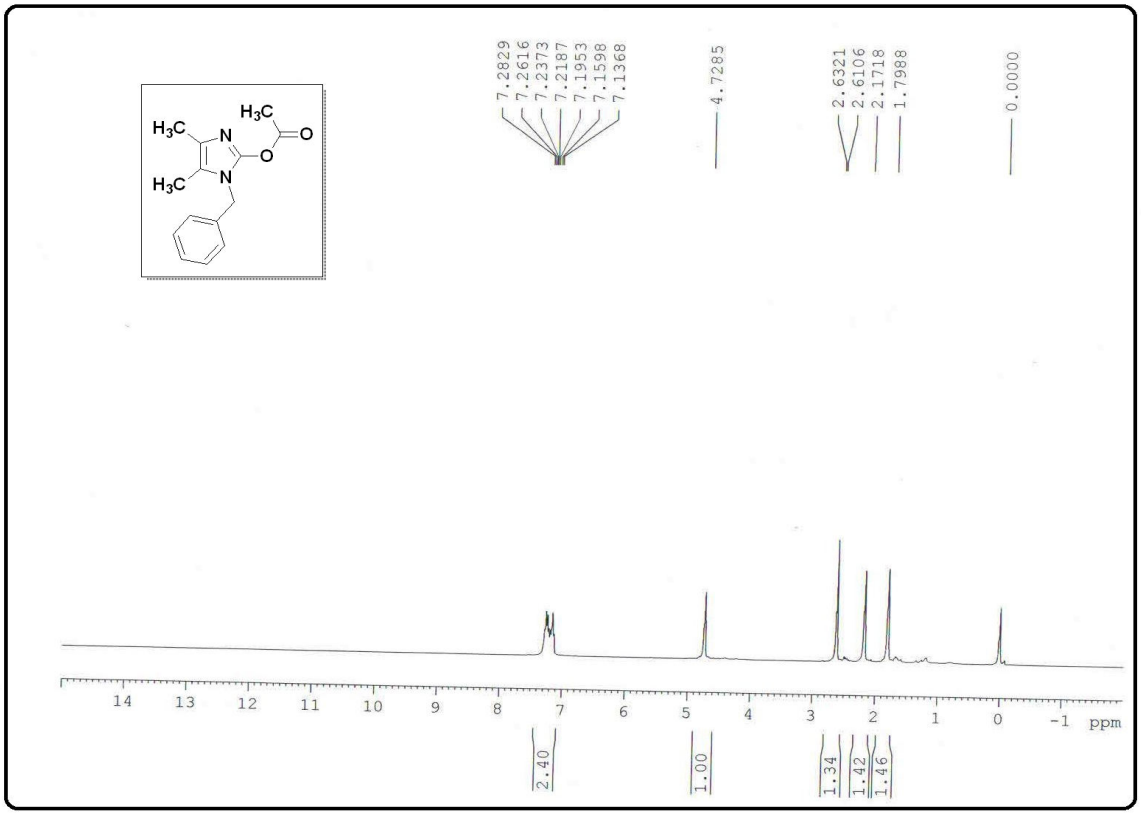


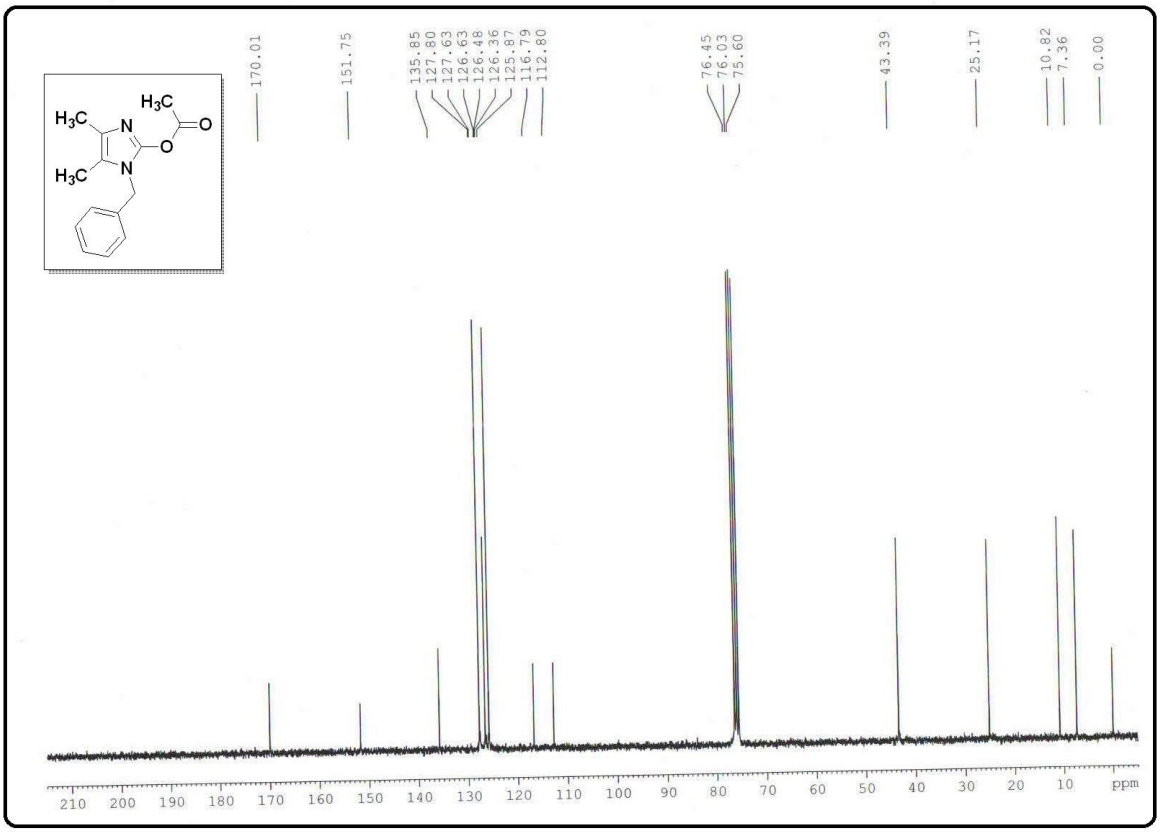
[13]CNMR-4,5-dimethyl-1-(naphthalen-2-yl)-1H-imidazol-2-yl acetate



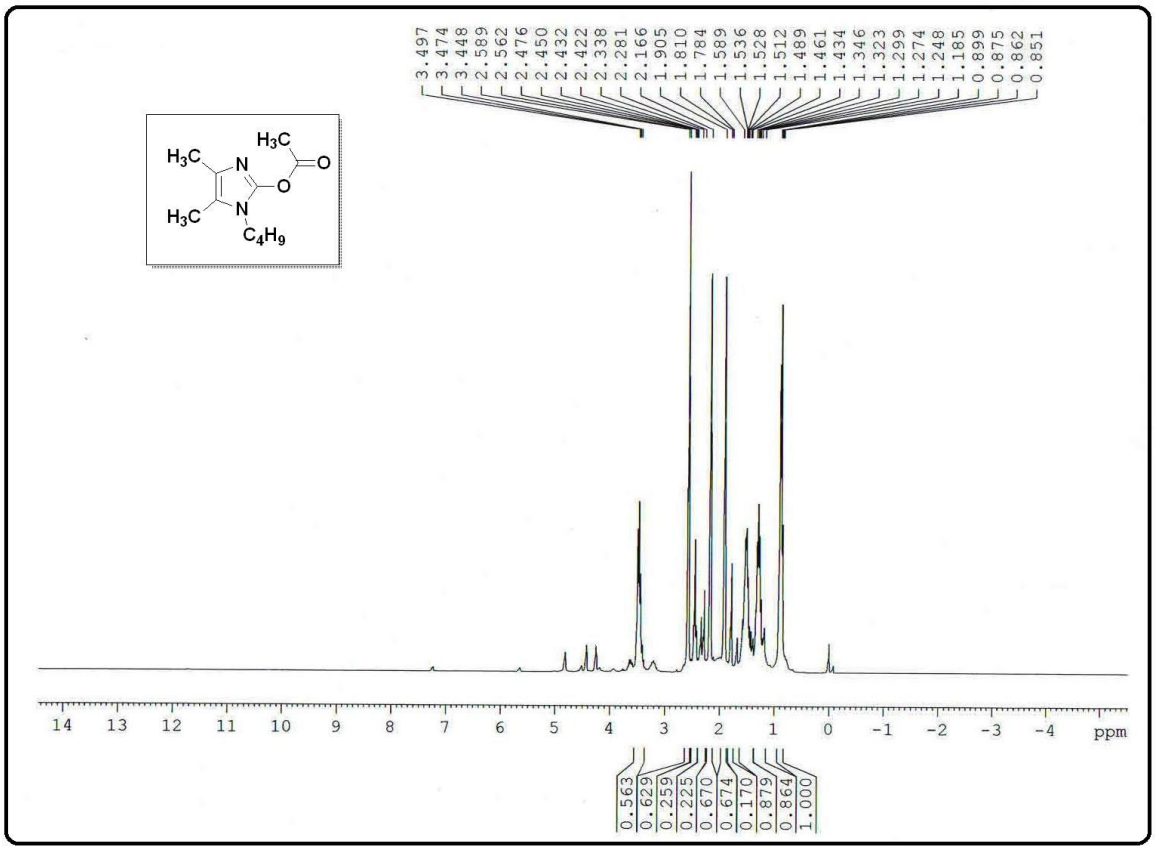
[1]HNMR-1-benzyl-4,5-dimethyl-1H-imidazol-2-yl acetate



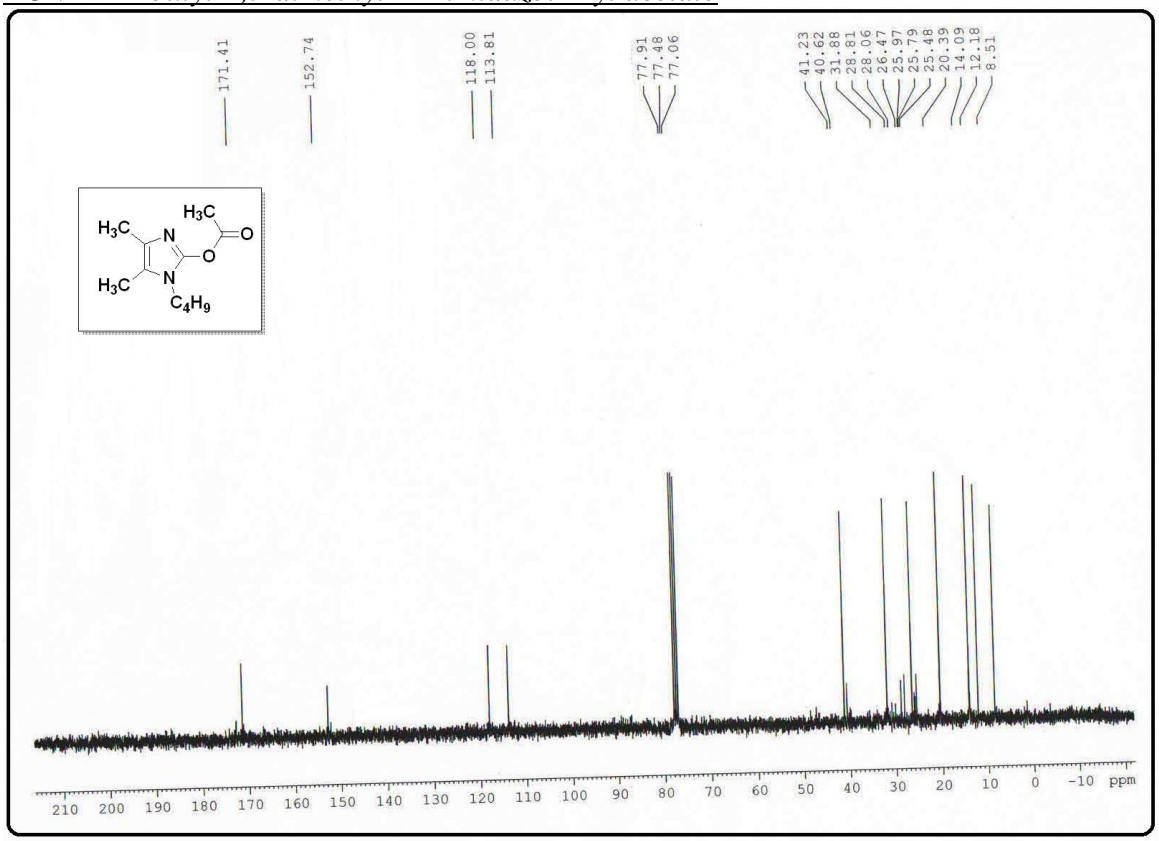
[13]CNMR-1-benzyl-4,5-dimethyl-1H-imidazol-2-yl acetate



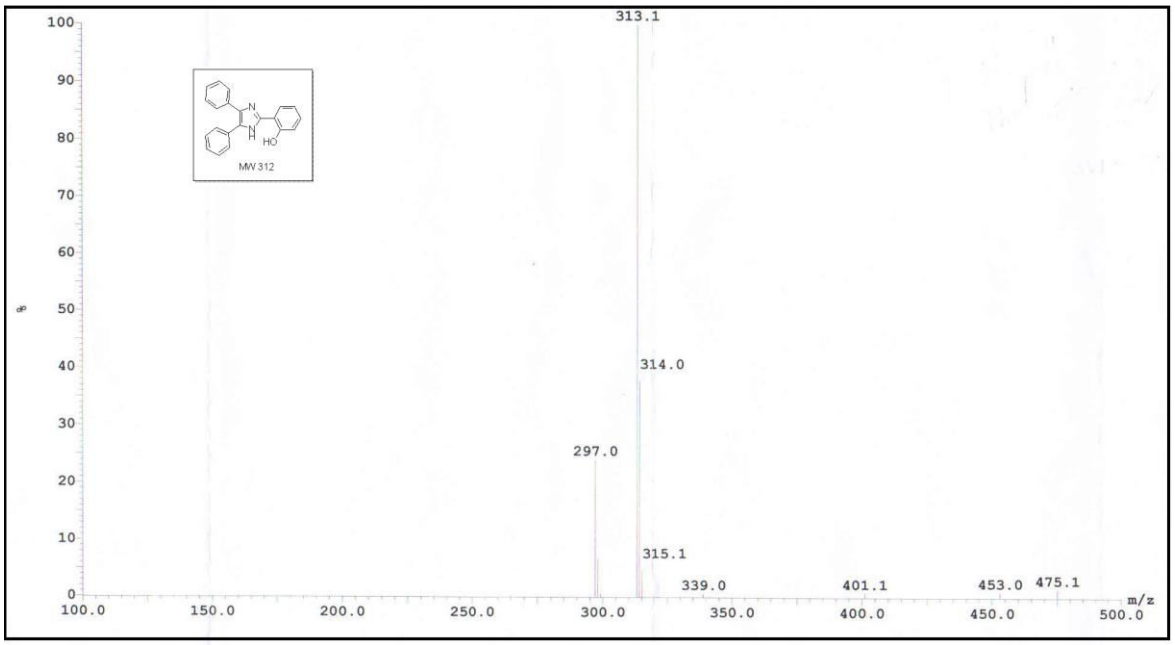
[1]HNMR-1-butyl-4,5-dimethyl-1H-imidazol-2-yl acetate



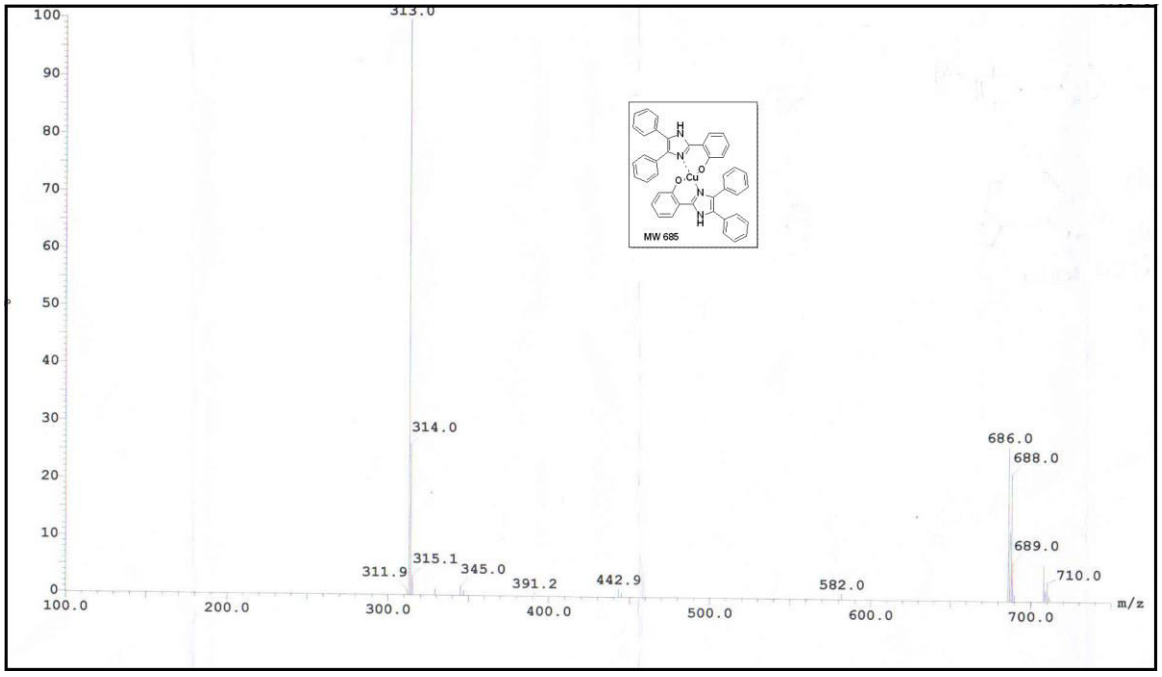
[13]CNMR-1-butyl-4,5-dimethyl-1H-imidazol-2-yl acetate



Mass-2-(4,5-diphenyl-1H-imidazol-2-yl)phenol



Mass- Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Cu



III.G. References

References are given in BIBLIOGRAPHY under Chapter III (pp 279).

CHAPTER-I (LITERATURE OVERVIEW)

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CHAPTER-II (SECTION D)

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CHAPTER-III (EXPERIMENTAL)

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An expeditious synthetic protocol for chlorination of imidazole *N*-oxide: Synthesis of 2-chloroimidazoles

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ABSTRACT

An expeditious, one-pot and room temperature protocol is reported for the synthesis of 2-chloroimidazoles from imidazole *N*-oxide. Simple mixing of the imidazole *N*-oxide, derived easily from diacetyl monoxime via three-component reaction, with oxalyl chloride in an agate mortar and pestle in open air affords the desired products in excellent yields. In view of versatile applications of 2-chloroimidazoles and only two other methods are known in the literatures that suffer from certain drawbacks, the present protocol could be of importance.

Introduction

Functionalized imidazoles are important scaffolds in many biologically active compounds.[1] For example, chloroimidazoles are subunits of different bioactive molecules exhibiting antifungal,[2] antibacterial,[3,4] antiprotozoal, anti-inflammatory,[5] antihypertensive,[6] and of late, anti-cancer medications.[7] Chloroimidazole moiety is often used as a building block in the development of new drugs.[8]

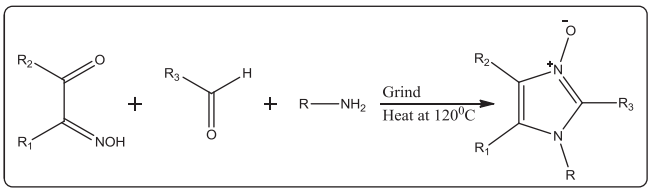
Further applications of this moiety are found in coordination chemistry, organometallic chemistry and asymmetric synthesis.[9] 2-Chloroimidazole also represents a valuable synthetic precursor for further functionalizations under metal-free conditions. For example, simple nucleophilic substitution with thiolate anion leads to the formation of 2-sulfenylimidazole derivatives, which serve as important candidates as anti-inflammatory drugs.[10] A literature search for preparative methods for chlorination of imidazole reveals that the reaction could be achieved from imidazole *N*-oxide using $POCl_3$[11] or tosyl chloride.[12] However, both procedures suffer from one or more disadvantages from green chemistry point of views. While $POCl_3$ is toxic and expensive, use of tosyl chloride requires high temperature, refluxing in anhydrous solvents like $CHCl_3$ or THF. Therefore, the development of mild and greener conditions for regioselective chlorination of imidazoles is of importance.

We report herein an expeditious, one-pot and room temperature protocol under solvent-less for the synthesis of 2-chloroimidazoles from imidazole *N*-oxide in excellent yields. The starting compounds imidazole *N*-oxides are easily prepared following our previously reported protocol[13] (Scheme 1).

The present procedure simply involves mixing of the imidazole *N*-oxide with oxalyl chloride (1:2 ratios) in an agate mortar and pestle in open air in the presence of triethylamine (1.5 equivalent of the starting *N*-oxide). It may be noted that oxalyl chloride has been used for chlorination of pyridine *N*-oxide.[14] Subsequently, isolating the desired product[15] by column chromatography. A comparison of previous synthetic protocols and our method are schematically shown in Scheme 2.

Results and discussion

We started optimization of the reaction conditions with a mixture of imidazole *N*-oxide and oxalyl chloride (1:1 ratios) in the



Scheme 1. Synthesis of substituted imidazole *N*-oxides.

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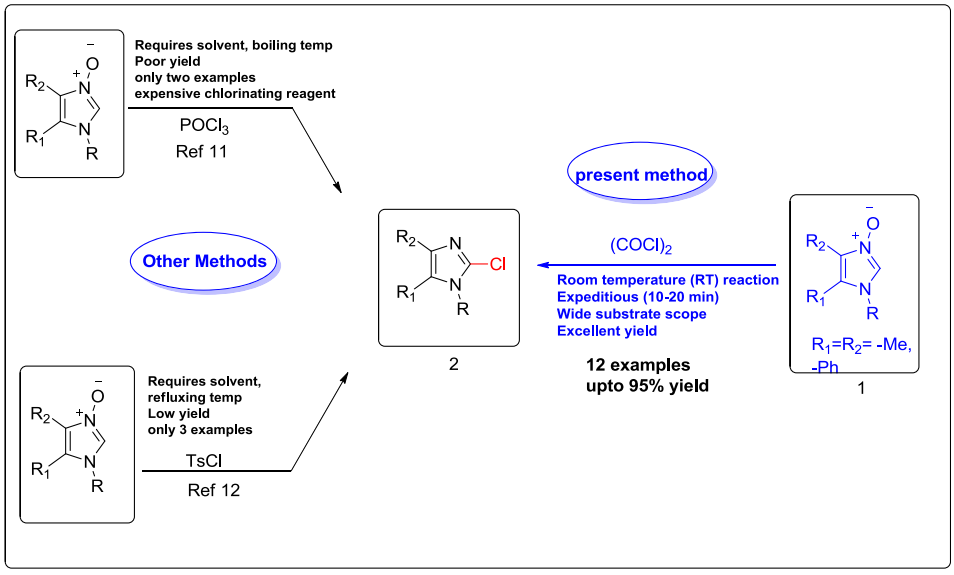
E-mail address: hossainmossaraf@gmail.com (M. Hossain).

http://dx.doi.org/10.1016/j.tetlet.2017.08.047
0040-4039/



Scheme 2. Different routes of chlorination for the synthesis of 2-chloroimidazole derivative.

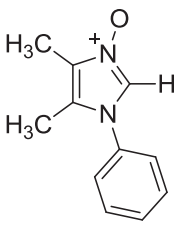
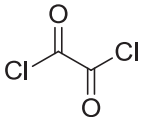
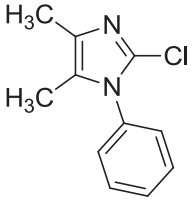
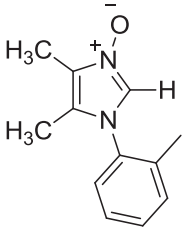
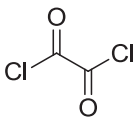
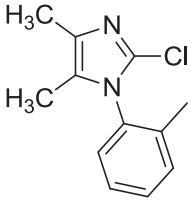
Table 1
Optimized conditions for chlorination of imidazole *N*-oxide[a] by oxalyl chloride.

Entry	$(COCl)_2$ (mmol)	Base (1.5 equiv)	Temp (°C)	Time (min)	(2 h) Yield (%)[b]
1	1	Triethylamine	RT	30	70
2	1.5	–	RT	30	90
3	**2**	**–**	**RT**	**10**	**95**[c]
4	2	Pyridine	RT	10	79
5	2	No base	RT	10	67

[a] Reactant (1 mmol).
[b] Isolated yield.
[c] Optimized reaction condition.

presence triethylamine (1.5 equiv). After mixing in a mortar (15 min.), the TLC of the reaction mixture showed the presence of starting *N*-oxide. Further continuation for another 15 min. did not show much improvement. After column chromatography, we were able to isolate the desired product in 70% yield (Table 1, entry 1). Increasing the quantity of oxalyl chloride up to 2 equiv and stirring for only 10 min at room temperature showed complete disappearance of the starting *N*-oxide (on TLC) and isolated the 2-chloroimidazole in 95% yield (Table 1, entry 3). Changing the base with pyridine or without using any base afforded the product in relatively lower yields (Table 1, entries 4 and 5). It is evident that the best conversion (95% yields) is achieved with 2 equivalents of oxalyl chloride with respect to 1 equiv. of imidazole *N*-oxide in the presence of 1.5 equiv. of base, and stirring for 10 min at room

Table 2
Scope of various imidazole *N*-oxide in the synthesis of substituted 2-chloroimidazole[a] by varying time.

Entry	Imidazole *N*-oxide	Oxalyl Chloride	Temp (°C)	Time (min)	Product (2)	Yield (%)[b]
1			RT	15	 2a	93
2			RT	20	 2b	83

(*continued on next page*)

Table 2 (*continued*)

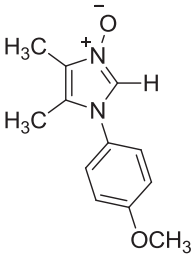
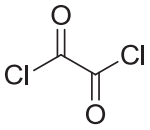
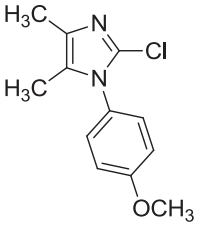
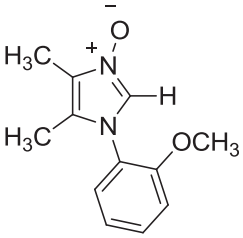
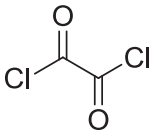
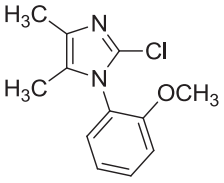
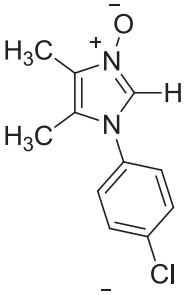
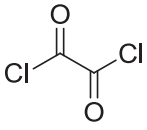
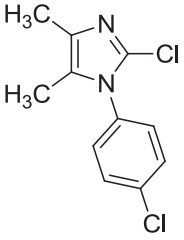
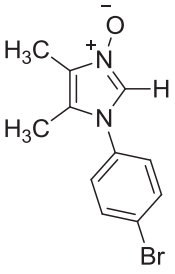
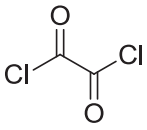
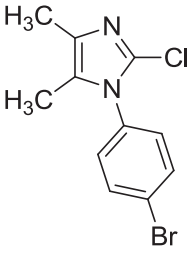
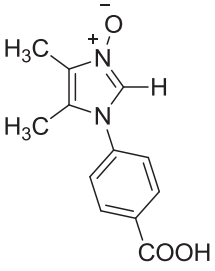
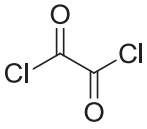
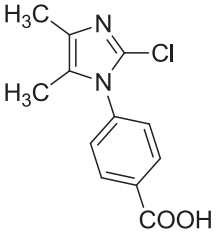
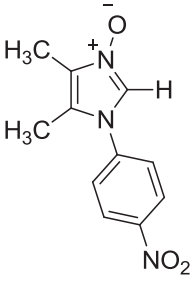
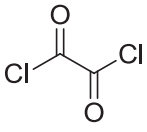
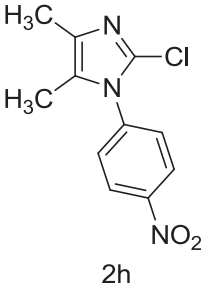
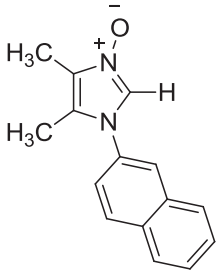
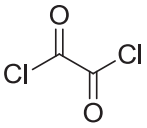
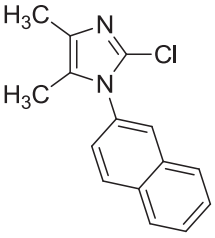
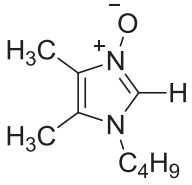
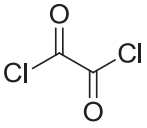
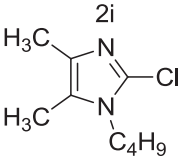
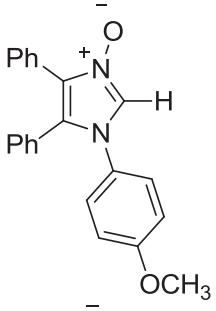
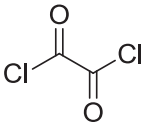
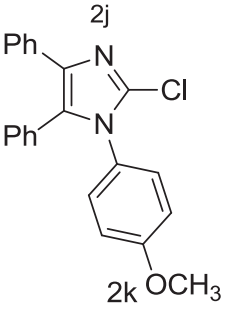
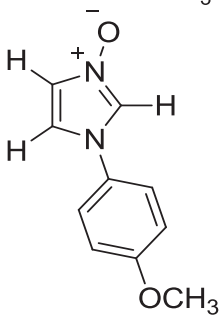
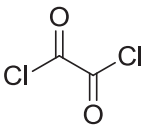
Entry	Imidazole *N*-oxide	Oxalyl Chloride	Temp (°C)	Time (min)	Product (2)	Yield (%)[b]
3			RT	15	 2c	89
4			RT	20	 2d	85
5			RT	10	 2e	93
6			RT	10	 2f	91
7			RT	10	 2g	93
8			RT	10	 2h	95

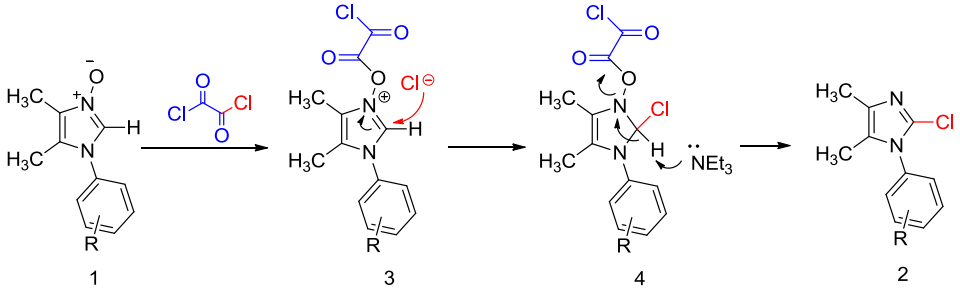
Table 2 (*continued*)

Entry	Imidazole *N*-oxide	Oxalyl Chloride	Temp (°C)	Time (min)	Product (2)	Yield (%)[b]
9			RT	10		93
10			RT	20	 2i	85
11			RT	15	 2j 2k	95
12			RT	15	No desired product	–

[a] Imidazole *N*-oxide (1 mmol), Oxalyl Chloride (2 mmol), Triethylamine (1.5 equiv) were ground and stirred at room temperature.
[b] Isolated yield from column chromatography.

temperatures. The presence of triethylamine promotes the reactions, since its absence the reaction proceeds with moderate yields (67%).

Based on the above optimization, a variety of 2-chloroimidazoles were synthesized using the solvent-free protocol (Table 2). It was observed that the presence of electron- donating groups such as –Me, –OMe, at various position of the *N*-phenyl ring afforded the product in 83–89% (Table 2, entries 2–4). On the other hand, the presence of electron-withdrawing groups such as –Cl, –Br, –COOH and $-NO_2$ gave slightly better yields and in the range of 91–95% yields (Table 2, entries 5–8). The results however could be explained on the basis of electrophilicity at the C-2 position of the imidazole ring system, which is increased by the presence of electron-withdrawing groups thereby facilitating attack by a nucleophile. We also carried out the reaction with imidazole *N*-oxide bearing a bulky naphthalene ring, which also afforded



Scheme 3. Plausible mechanisms for solvent-free synthesis of substituted 2-chloroimidazole.

excellent conversion (Table 2, entry 9). Further extension of the protocol was examined with *n*-butyl group (an aliphatic substituent), which worked quite smoothly but afforded the desired product in relatively lower yield (85%; Table 2, entry 10). The reaction worked efficiently also from benzil monoxime yielding the desired 2-chloroimidazole with two phenyl groups at 4 and 5 positions (95%; Table 2, entry 11). However, glyoxal monoxime did not result in the formation of desired 2-chloroimidazole derivative (entry 12).

On the basis of the experimental observations, a plausible mechanism of cine substitution,[12] is presumed to be operative (Scheme 3). Thus, initially the imidazole *N*-oxide (**1**) is activated by oxalyl chloride to form the imidazolium chloride (**3**), which is then converted to the intermediate (**4**). The hydrogen atom at the C-2 position, being now more acidic, is trapped by the base NEt_3 to yield the desired product **2**.

Conclusions

In summary, we have developed an expeditious and mild synthetic route for the chlorination at C-2 position of imidazole *N*-oxide under solvent-free conditions leading to the formation of 2-chloroimidazole. The protocol has been tested with diversely substituted *N*-phenyl group. In all cases, the yields are excellent, though the presence of electron-withdrawing groups favors the reaction over electron-donating substituents. 2-chlorinated imidazole derivatives are useful intermediates and subunits of several pharmacologically important compounds. This simple setup and facile method could be attractive to the synthetic chemists from academia and pharmaceutical industries. Further application of this protocol in other heterocyclic systems is underway in this laboratory.

Acknowledgements

The author (MH) thanks UGC, New Delhi, for the award of the fellowship under UGC-BSR Scheme. The author also acknowledges CDRI, Lucknow for mass spectra.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.08.047.

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15. *General experimental procedure for the chlorination of Imidazole N-oxides:* Imidazole *N*-oxide (1 mmol), oxalyl chloride (2 mmol) and triethylamine (1.5 mmol) were mixed intimately in an agate mortar and pestle for a period of 10–20 min under solvent-less condition. The reaction mixture was then dissolved in dichloromethane (2 mL), washed with water and finally dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the residue, which was chromatographed over silica gel column and elution with petroleum ether/ethyl acetate mixture to furnish the desired 2-chloroimidazole.

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A mechanistic study of carbonyl activation under solvent-free conditions: evidence drawn from the synthesis of imidazoles†

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Syntheses of various imidazoles and their derivatives, imidazole *N*-oxides and 1-hydroxyimidazole 3-oxides, from sterically different dicarbonyl moieties provided insights into the self-catalytic effect of the condensed phase reactions of carbonyl compounds. The self-catalytic activity in solvent-free multi-component syntheses was investigated using a combination of methods *viz.*, reactivity, spectroscopy and theory. While IR spectroscopic studies revealed that reacting molecules were polarised in bulk, quantum mechanical calculations of associated HCHO monomers suggest an increase in the average dipole moment of each monomer and provide evidence for the presence of cooperative effects. A comparative study of the kinetics of un-catalysed and catalysed reactions with the help of HPLC provided insights into the mechanism.

1 Introduction

The application of a solvent-free synthetic methodology for organic compounds that were conventionally synthesized in a solvent medium has become more common in recent years.[1] Thus, well-known organic reactions such as the aldol,[2] Claisen,[3] Stobbe[4] and Knoevenagel condensations,[5] the Thorpe,[6] Tischenko,[7] Reformatsky and Luche reactions,[8] the Baeyer–Villiger oxidation,[9] the pinacol rearrangement[10] and the oxidative coupling of phenols,[11] just to name a few, have been found not only to occur under solvent-free conditions but are more efficient than reactions in solution. In addition to the simplicity and cleanness of the procedure, the absence of any media has been found to lead to uncommon reactivities. Apart from these efforts, over the past two decades organic synthesis has been devoted to extending the scope of solvent free reactions, notably for newer multi-component reaction (MCR) strategies.[12] Solvent-free protocols have already been developed for almost all the classical multi-component reactions namely the Strecker,[13] Hantzsch,[14] Biginelli,[15] Mannich,[16] Passerini,[17] Ugi,[18] Gewald,[19] Petasis,[20] Radziwenski synthesis,[21] and so on. And to impart greater reactivity to the substrates and the reagents, these synthetic protocols have constructively exploited the use of transition metal catalysts and the very recent organocatalysts.

Lewis acids and organocatalysts have been shown to be excellent catalysts for C–C bond forming reactions, and through carbonyl activation provide effective avenues for upgrading classical MCRs. In particular, close attention has to be paid to condensation reaction mechanisms that involve the activation of carbonyl-containing electrophiles. The vast number of investigations related to chemical transformation mediated by organocatalysts[22] or by Lewis acids in anhydrous organic media,[23] aqueous media[24] and in the absence of any media[25] has provided a basic understanding of the intricate dynamics of adduct formation between the acid and the carbonyl moieties and has shed light on the role that these adducts have in accelerating catalytic transformations. A noteworthy example is the dramatic increase in reaction rates for the Radziwenski synthesis attained by the activation of a carbonyl group by a Lewis acid center[25] or by a Lewis base center[26] through the formation of adducts.

In the present study we have attempted to explore in some details the mechanistic insight for better reaction under solvent-free condition compared to reactions in solution. Here we have chosen a well-studied method for imidazole synthesis.

2 Experimental

The compounds **1a–1i**, **2a–2l**, **3a–3g**, **4a–4g** and **5a–5e** were all prepared under solvent-free conditions. All other reagents are commercially available and were used as purchased from the supplier. Grinding experiments were performed with an agate mortar and pestle, which was acetone rinsed and dried prior to use. The yield of the reaction was determined by the product peak area count in HPLC analysis with respect to the purified

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5ra16386b

product. NMR spectra were recorded on Bruker Avance 300 spectrometer chemical shifts (δ in ppm) were referenced to external $SiMe_4$. IR spectra were recorded on a FTIR-8300 SHIMADZU spectrophotometer. Analytical thin-layer chromatography was performed using silica gel aluminium sheets (Merck, TLC silica gel 60 F254). HPLC was performed on a Waters-2487 Dual Lambda absorber with a RP-18 (Symmetry Shield) column. The solvent used was methanol with a flow rate of 0.5 ml min^{-1}. In all experiments the same column and same flow rate was maintained. The electrospray mass spectra were recorded on a MICROMASS QUATTRO II triple quadruple mass spectrometer. The ESI capillary was set at 3.5 kV and cone voltage was 40 V. X-Ray diffraction data was collected on a Bruker APEX CCD-II diffractometer at 293 K. The structure was solved by a direct method using the program SHELXS-97.[27]

2.1 Computational details

The optimized geometry and the energy of each monomer were calculated using the CBS-QB3 model chemistry. The CBS-QB3 model chemistry[28] was employed for the calculation of the molecular structures since this method is known to predict thermochemical parameters with high accuracy.[29] Molecular geometry was fully optimized and harmonic vibrational frequencies were calculated using the analytic second derivatives to confirm the convergence to minima on the potential surface. All the calculations were carried out using the Gaussian 98 suite of programs.[30]

2.2 General procedure for the synthesis of 2,4,5-trisubstituted imidazoles (1a–1i)

210 mg (1 mmol) of benzil, 1 mmol of the corresponding aldehyde and 770 mg (10 mmol) of ammonium acetate was taken in an agate mortar and thoroughly ground. The contents were transferred to a test tube and heated to 150–160 °C for 4 minutes. The contents were cooled and water was added to the test tube and filtered. The product was recrystallised from ethanol. Completion of the reaction was checked by TLC.

2.3 General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (2a–2l)

210 mg (1 mmol) of benzil, 1 mmol of aldehyde, 1 mmol of primary amine and 385 mg (5 mmol) of ammonium acetate was taken in an agate mortar and thoroughly ground. The contents were transferred to a test tube and heated to 150–160 °C for 4 minutes. The contents were cooled and water was added to the test tube and filtered. The product was recrystallised from ethanol. Completion of the reaction was checked by TLC.

2.4 General procedure for the synthesis of imidazole *N*-oxide (3a–3g)

1 mmol of the monoxime, 1 mmol of the aldehyde and 385 mg (5 mmol) of ammonium acetate was ground into an intimate mixture in an agate mortar and pestle. The mixture was then heated to 115–120 °C in an oil bath with constant shaking. A black solution resulted which was cooled when a black sticky precipitate formed. To the black precipitate was then added a small volume of diethyl ether when a brown precipitate separated. The precipitate was then thoroughly washed with ethyl acetate, dissolved in ethanol and crystallized by addition of water to yield pure products.

2.5 General procedure for the synthesis of *N*-substituted imidazole-1-oxide (4a–4g)

1 mmol of the monoxime, 1 mmol of the aldehyde and 1.5 mmol of the amine was ground for 2 minutes and subsequently heated in an oil bath at 115–120 °C, when a melt was formed. After a further 8 minutes of heating, the completion of the reaction was indicated by TLC. On cooling the melt slowly solidified and to the product so formed was added a little amount of ether whereby a precipitate was obtained. The precipitate was further washed with hot ethyl acetate. Recrystallization from ethanol gave products with the same melting points.

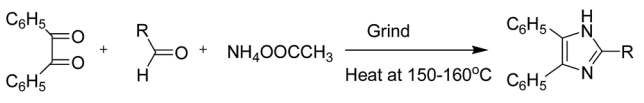
2.6 General procedure for the synthesis of 1-hydroxy imidazole-3-oxide (5a–5e)

2 mmol each of the monoxime and the aldehyde was thoroughly ground with 695 mg (10 mmol) of hydroxylamine hydrochloride in an agate mortar and pestle for a period of *ca.* 3 minutes during which it melts and then gets hardened slowly. The mixture was then transferred to a test tube and heated in an oil bath maintained at 110–120 °C when it started to melt. Constant shaking for another 7 minutes gave the product which remained in the melt form even at room temperature. On completion of the reaction, checked by TLC, addition of 5 ml of diethyl ether or 5 ml of ethyl acetate precipitated the product. The water insoluble products were then washed with water and ethyl acetate to get the pure products.

3 Results and discussion

The Radziwenski Imidazole (R-I) synthesis is a very useful preparative method for imidazole and its derivatives. The manifold utilizes a diketone, an aldehyde and ammonium acetate as the ammonia source (Scheme 1). The pure products have been synthesized in quantitative yields in 4 minutes at the given temperature by heating in an oil bath under solvent-free conditions. The temperature conditions and product yield were optimised by HPLC studies (ESI†).

Besides usual spectroscopic methods for determining the structure, we have used single crystal X-ray diffraction (Sc-XRD)



1a; R = Ph
1b; R = 4-OCH_3-Ph
1c; R = 2-OH-Ph
1d; R = 3-NO_2-Ph
1e; R = 3-OCH_3, 4-OH-Ph
1f; R = 4-N(CH_3)-Ph
1g; R = 4-OH-Ph
1h; R = 2-pyridyl
1i; R = H

Scheme 1 R-I synthesis of tri-substituted imidazoles (1a–1i).

data of one of the representative compounds, 4,5-diphenyl-1*H*-imidazole, **1i**, to confirm the structure. The single crystals of the compound suitable for Sc-XRD were obtained by the slow evaporation from methanol/hexane mixture. The compound crystallizes in a monoclinic crystal system with the space group $P2_1/c$ (Hall group $-P_{2ybc}$); $a = 11.0471(4)$ Å, $b = 9.2483(3)$ Å, $c = 11.5780(4)$ Å, $\alpha = 90°$, $\beta = 93.921(3)°$, $\gamma = 90°$, $Z = 4$, $\mu = 0.577$ mm^{-1}, $F_{000} = 468.0$ and K$\alpha = 1.54184$ Å. The ORTEP diagram is presented in Fig. 1. The heterocyclic ring is planar. One interesting point in the diagram is the attachment of one proton in each nitrogen atom which reflects overall an excess of one proton. The N_7–C_{11} and N_9–C_{10} bond distances are identical (1.380 Å and 1.3799 Å respectively), similarly N_7–C_8 and N_9–C_8 bond distances are also close (1.3157 Å and 1.3462 Å respectively); corresponding N7 and N9 centered bond angles are also close (107.83° and 105.91°).

Intermolecular extra proton transfer rate in imidazole is reported in the order of 0.3×10^{-12} second[31] but there is no such data for intramolecular N to N proton transfer due to the shift of N–C double bond in imidazole; intuitively it is difficult to say that the process could be faster than X-ray diffraction time (10^{-18} second). However, the bond lengths are in between C–N single bond (1.47 Å) and double bond (1.25 Å). Since both the nitrogen atoms are identical, and on probability basis H atoms might have added to both the atoms during computation. The extra proton does not originate from the imidazolinium salt because in such case the counter ion should be in the unit cell; and non equivalence of the nitrogen atoms would have been observed.

However, these reactions are not very efficient in solution, and the yield of product is not very high. Existing literature reveals that the Debus–Radziszewski imidazole synthesis in solution state takes around 24 h to achieve moderate to good yield.[25] By contrast, solvent-free reactions proceed efficiently under much simpler conditions to give products in quantitative yield (Scheme 2).

Interestingly, very similar solvent-free reactions of various ammonia derivatives and alkyl/aryl monoximes at 115–120 °C

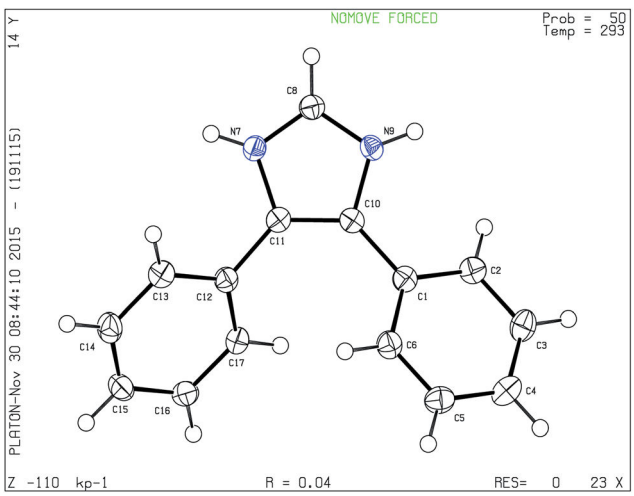
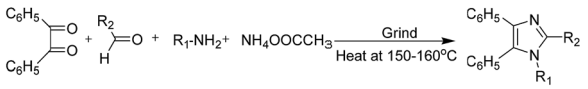


Fig. 1 ORTEP diagram of **1i** derived from single crystal data.



2a; R_1 = -$CH_2CH_2CH_2CH_3$ R_2 = H
2b; R_1 = 4-Cl -Ph R_2 = H
2c; R_1 = 4-OCH_3-Ph R_2 = H
2d; R_1 = 4-OH-Ph R_2 = H
2e; R_1 = 4-CH_3 -Ph R_2 = H
2f; R_1 = 4-COOH-Ph R_2 = H
2g; R_1 = -CH_2COOH R_2 = H
2h; R_1 = 2-NO2, 4-Cl-Ph R_2 = H
2i; R_1 = Ph R_2 = Ph
2j; R_1 = 4-OCH_3-Ph R_2 = 2-NO_2-Ph
2k; R_1 = 4-OCH_3-Ph R_2 = 4-OCH_3-Ph
2l; R_1 = 4-OCH_3-Ph R_2 = 4-OH-Ph

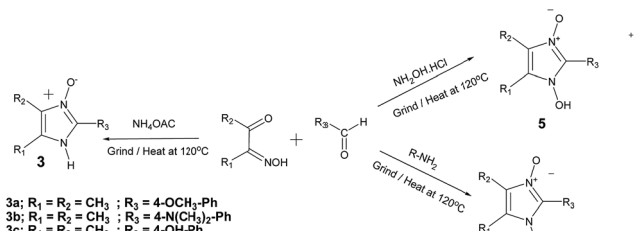
Scheme 2 R-I synthesis of tetra-substituted imidazoles (**2a–2l**).

for 10 min also gave the corresponding imidazole *N*-oxides (**3a–3g**), *N*-substituted imidazole *N*-oxides (**4a–4g**) and 1-hydroxy imidazole 3-oxide derivatives (**5a–5e**) in quantitative yields (Scheme 3). This is the first report of a solvent-free condensed phase protocol for the oxide and hydroxyl oxide derivatives of imidazoles. Apart from the usual characterizations of the compounds, further spectroscopic investigations, vibrational assignments, HOMO–LUMO, NBO and MEP analysis of two of the synthesized compounds **3a**[32] and **3c**[33] have already been done and reported. The syntheses also proves that acetic acid, generated *in situ* in the reaction, is not the only catalysing factor for enhancing the reaction rates under solvent-free conditions.

In order to understand, at least partially, why these reactions proceed so efficiently under solvent-free conditions, a combination of methods *viz.*, reactivity, spectroscopy and theory have been used.

3.1 Kinetic studies

Firstly, the reaction kinetics of imidazoles **1b** and **1c** were studied through HPLC monitoring of benzil and aldehyde (reactants) consumption along with product (imidazoles) formation. A good linearity was observed in each case with the plots of natural logarithm values (−ve for the reactants and +ve for the products) of peak area against time. From the slope of these curves the first order rate constants and half lives ($t_{1/2}$) were determined. The observed dependence of reactants' concentrations (logarithm) and product formation with the



3a; $R_1 = R_2 = CH_3$; R_3 = 4-OCH_3-Ph
3b; $R_1 = R_2 = CH_3$; R_3 = 4-$N(CH_3)_2$-Ph
3c; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph
3d; $R_1 = R_2 = CH_3$; R_3 = 3-NO_2-Ph
3e; $R_1 = R_2$ = Ph ; R_3 = 3-OCH_3, 4-OH-Ph
3f; $R_1 = R_2$ = Ph ; R_3 = 4-OCH_3-Ph
3g; $R_1 = R_2$ = Ph ; R_3 = 4-OH-Ph

5a; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph
5b; $R_1 = R_2 = CH_3$; R_3 = 4-OCH_3-Ph
5c; $R_1 = R_2 = CH_3$; R_3 = 3-NO_2-Ph
5d; $R_1 = R_2 = CH_3$; R_3 = H
5e; $R_1 = R_2$ = Ph ; R_3 = 4-OCH_3-Ph

4a; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph ; R = n-butyl
4b; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph ; R = α-napthyl
4c; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph ; R = 2-NO_2-Ph
4d; $R_1 = R_2 = CH_3$; R_3 = 4-OH-Ph ; R = 4-OCH_3-Ph
4e; $R_1 = R_2$ = Ph ; R_3 = H ; R = 4-Cl-Ph
4f; $R_1 = R_2$ = Ph ; R_3 = ethyl; R = -CH_2COOH
4g; $R_1 = R_2$ = Ph ; R_3 = 4-OH-Ph ; R = 4-Cl-Ph

Scheme 3 Analogous R-I synthesis of imidazole *N*-oxides (**3a–3g**), *N*-substituted imidazole *N*-oxides (**4a–4g**) and 1-hydroxy imidazole 3-oxides (**5a–5e**).

variation of time (at reaction temperature 125 °C, temperature optimised for maximum conversion) is shown in Fig. 2. The product peak in HPLC was not much prominent within the first 10 minutes. This information helps to understand more about the sequences of reactions which manifest together as a multi-component reaction.

The catalytic effect of some metal salts (5 mol%) at the same reaction temperature (125 °C) was also compared. The corresponding rate constant and half life values are shown in Table 1.

The general catalytic process at the molecular level maybe represented as in Scheme 4.

The compiled results indicate that the catalysts acted at different stages of the reaction sequences of the MCR reaction. To cite a representative case of ytterbium triflate, a threefold increase in the rate of benzil consumption and fivefold increase in imidazole formation as against the catalyst free reaction was observed. Considering that in a reaction, catalysts in general, are used in very small proportions. Therefore only a small mole-fraction of the substrate would have the chance to be associated with the catalyst and thus the probability of the substrate taking part in adduct formation would be further reduced. Hence with only traces of a catalyst (5 mol% in the present case) added to a reaction, its rate should have hardly been affected as only a few molecules would engage in the activated complex in comparison to the vast number of un-associated molecules in the reaction media. We also studied the reactions at different elevated temperatures and found that at the temperature range 150–160 °C, almost quantitative products formed in a very short time of 4 minutes; and that too without using any catalyst. This is a landmark record in imidazole synthesis (ESI†).

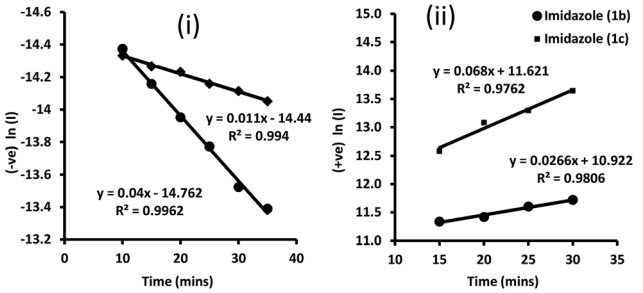
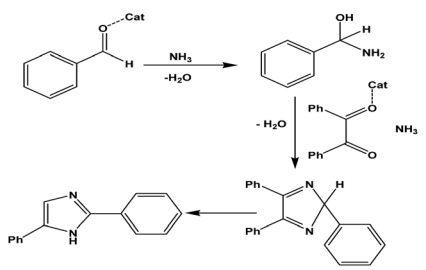


Fig. 2 (−ve)/(+ve) ln(*I*) *vs.* time (mins) of [i] benzil during formation of imidazoles (**1b**) and (**1c**); [ii] rate curve of the product imidazoles (**1b**) and (**1c**) formation; *I* = peak area.

Table 1 Rate constants and half lives of reactant consumption and product formation at 125 °C under solvent-free conditions

Catalyst	Rate of benzil consumption ($t_{1/2}$)[a]	Rate of aldehyde consumption ($t_{1/2}$)	Rate of product formation ($t_{1/2}$)
Solvent-free (no catalyst)	0.011 (63.01)	0.008 (86.64)	0.026 (26.66)
$Sm(NO_3)_3 \cdot 6H_2O$	0.012 (57.76)	0.008 (86.64)	0.023 (30.13)
$Yb(SO_3CF_3)_3$	0.033 (21.00)	0.009 (77.02)	0.115 (6.03)
$ZrO(NO_3)_2$	0.058 (11.95)	0.017 (40.77)	0.034 (20.38)
$(NH_4)_2Ce(NO_3)_6$	0.035 (19.80)	0.024 (28.88)	0.112 (6.19)
$NiCl_2 \cdot 6H_2O$	0.032 (21.66)	0.021 (33.00)	0.041 (16.90)

[a] Note: half-life ($t_{1/2}$) in minutes.



Scheme 4 Mechanism of the R-I synthesis.

3.2 Infrared studies

In order to contemplate the cause behind the efficacy in solvent-free procedure; we studied the IR-spectra of pure benzil in thin film as well as that with catalyst. The carbonyl region of a benzil thin film and that with 5 mmol% of ytterbium triflate has been presented in Fig. 3. It was observed that the free carbonyl band (with catalyst) at 1676 cm^{-1} has apparently increased in intensity with concomitant shift to lower frequency compared to the corresponding band for benzil. It was earlier reported[34] that C═O stretching band of benzil appears at 1676 cm^{-1} in the crystalline state and at 1685 cm^{-1} in solution.

As the catalyst caused a red-shift and brought about enhancement in intensity, we have considered this phenomenon as a marker of catalytic effect. Similar shift of carbonyl stretching frequency for benzophenone in TiO_2 surface has also been reported.[35] The difference in stretching frequency (9 cm^{-1} red-shift) indicates a greater degree of single bond character in the C═O bond (polarisation enhancement) in the solid state compared to that in the solution state for benzil. The red-shift of carbonyl stretching provides an indication of bulk polarization of benzil in the solid state and similar effect is also observed with catalysts in the solid state.

The extent of the shift caused by the presence of trace amounts of zirconyl nitrate and ytterbium triflate on benzil

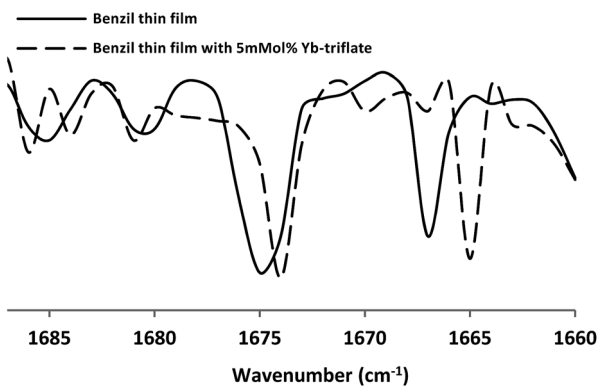


Fig. 3 IR spectra of benzil thin film, with and without a catalyst.

carbonyl stretching frequency in hexane solution was also studied. The IR spectra in the carbonyl range have been presented in Fig. 4.

It was found that in the solution spectra, the free carbonyl peak at 1685 cm^{-1} and all other associated peaks showed a little amount of red-shift in the presence of a catalyst. In addition to this, there was concomitant diminishing of the intensity of the free carbonyl peak with increasing intensities of some other peaks at lower frequencies (particularly the peak at 1680 cm^{-1}) in the presence of traces of catalyst. It is also apparent that the catalyst, zirconyl nitrate, caused a little bit more polarization than that with ytterbium triflate. Notably we have found that the catalytic effect of zirconyl nitrate is a bit greater for benzil consumption rate as well (Table 1). The conspicuous enhancement of the band at 1680 cm^{-1} in the presence of catalyst in both solution state and in solid state is observed. The peak at 1680 cm^{-1} has been described as another C=O stretching band associated with the different symmetry of the molecule.[36] Enhancement of the band near 1680 cm^{-1} in presence of catalyst suggests that the catalysts not only polarize the carbonyl but also influence the conformation of benzil. The IR spectroscopic investigation thus strongly provides evidences in favour of bulk polarization in the condensed phase which consequently leads to the enhancement of the electrophilicity of the carbonyl carbon. The above observation suggests that catalysts bind to the carbonyl oxygen and the weak interaction activates the carbonyl group with the enhancement of polarization.

3.3 Computational studies

As further proof of concept, the CBS-QB3 model chemistry calculations of a HCHO monomer and trimer were performed. Geometry optimization for a linear arrangement of the trimer was done as shown in Fig. 5. In molecular association a number of minimum energy conformations with different geometries are feasible, we searched for minimum energy in linear arrangement and our calculation terminated on convergence to such minima.

The partial charges on the carbon and the oxygen atom and the dipole moment of the associated monomer are found to be enhanced as we move from the monomer to the trimer (Table 2).

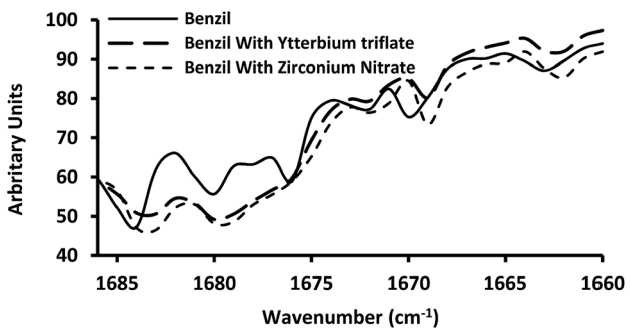


Fig. 4 Solution IR spectra in the carbonyl range of benzil in hexane.

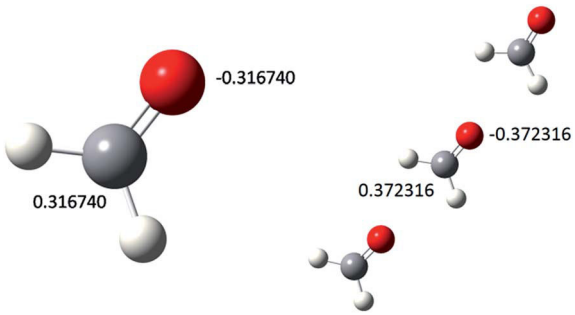


Fig. 5 Minimum energy models with partial charges.

Table 2 Mulliken atomic charges, dipole moment and C–O bond distances in monomers and trimer from the CBS-QB3 model[a]

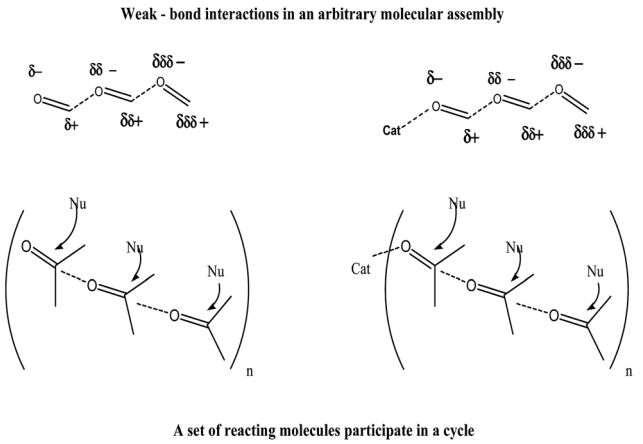
Parameter	Monomer	Trimer
Mulliken charge at C (au)[a]	0.316740	0.372316
Mulliken charge at O (au)[a]	−0.316740	−0.372316
Dipole moment (Debye)	2.8542	3.2133[b]
C–O bond distance (Å)	1.20001	1.20259
Symmetry	C_{2v}	C_1

[a] Note: [a]atomic charges with hydrogens summed into heavy atoms; [b]average value.

It is evident that the atomic charges in the associated monomers are different to those in the isolated free monomer, indicating a sizeable charge reorganisation due to the association. These may be interpreted as atomic expressions of sizeable cooperative effects. This charge reorganization in the carbonyls, as a consequence, brings about enhanced polarization in the carbonyl groups in their environment as the partial charges increase in each atom. A seminal report has already established the possibility of a dipole–dipole type of intermolecular interaction and the occurrence of little or no H-bond in formaldehyde itself.[37]

The theoretical *ab initio* calculation of conformationally similar formaldehyde dimer was done by Smith *et al.*,[38] whereby they have shown that an excess electron can attach to the system forming a dipole bound anion. This work indirectly supports our proposition as well, to the cause of enhancement in electrophilic behavior of the carbonyl group under solvent-free condition. The theoretical results also suggest that, as a result of the cooperative effect of very weak forces a bulk amount of carbonyl groups get activated. Therefore, the activation can be attributed to a unique spatial organization of the carbonyl moieties. This would be best understood if we consider an arbitrary molecular assembly where polarization transfer through a non-covalent bond (weak bond interactions) could well be conceived of as shown in Scheme 5.

This pseudo-conjugated pi-system in the proposed supramolecular assembly makes the system more chemically soft (more polarizable) compared to a free carbonyl which is also responsible for better reactivity in solvent free reaction media. Hence, considerable catalytic action became viable in condensed phase. Since, in such an assembly a set of reacting



Scheme 5 Polarization transfer through a non-covalent bond without and with a catalyst.

molecules participates in a cycle, the process undoubtedly becomes faster. In addition to this self-activating effect, if some oxyphilic substance were present in catalytic amount it bonded to the terminal carbonyl oxygen affecting further activation of the trail of carbonyls and thereby resulting in further enhancement of the catalytic effect (Scheme 5). The present work emphasizes on meeting this challenge of using weak forces as a design tool for imparting new properties and performance in molecules and materials.

The present work incorporates the concept of constitutional dynamic chemistry to resolve the existing paradox in the process of catalysis (involving carbonyl activation). According to Prof. Lehn, supramolecular entities are assembled entities of discrete number of molecular sub-units held together reversibly through weak interactions (non-covalent interactions).[39] When extended to the carbonyl system, one could conceive the carbonyl molecular sub-units to be held together through similar type of weak interactions, by virtue of it being polar. In our opinion this hypothesis unequivocally embraces all the catalytic effects on carbonyls in solution state as well as in solvent-free molten state. As a proof of concept, we have reported herein the un-catalyzed Radziwenski synthesis of imidazole and its derivatives under solvent-free conditions employing a multicomponent protocol.

4 Conclusions

The polarizability of organized carbonyl functionalities in condensed phase contributes for the observed self-catalysis. High yields of many different imidazoles were obtained from the simply mechanical grinding and heating of MCR starting materials, even in the absence of Lewis acid catalysts. The very weak dipole of carbonyls can induce polarization in bulk because the carbonyl bonds are very much polarisable and the net result is the enhancement of electrophilicity of carbonyls. In polar solvents, the weak but favorable conformation of the carbonyl cluster expectedly breaks due to stronger solute–solvent interactions. Thus solvents act adversely to the self-catalytic effect. This phenomenon can be well utilized to generate a self-catalytic effect without using any catalytic substance.

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