# A Review on Investigatigatary Apprach of the therapeutic potential of newly synthesized heterocyclic compounds

Pooja Choudhary and Neeraj Choudhary

Department of Science and Technology, Under Faculty of Education and Methodology

Jayoti Vidyapeeth woman's University Jaipur Rajasthan

Corresponding email: neeraj.ch1988@gmail.com

## Abstract:

In an organic chemistry, largest families of organic compounds are belonging in the heterocyclic compounds. In our daily life important of heterocyclic compounds are of very essential. It has broad range of application in medicinal chemistry and in agrochemicals products. Applications are also found in as developers, as corrosion inhibitors, sanitizers, as copolymers, antioxidants, dye stuff. There is always an important thing about an efficient methodology for synthesizing of new heterocycles moiety. Now in literature survey reveals that more than 85-95% new drugs containing heterocycles which has bright scientific insight in the biological system. In this review work, I mainly focus such type of heterocycle and their families which has main utility in medicinal chemistry. In the recent past developments of imidazole-based compounds in the wide range of medicinal chemistry such as antihypertensive, ant neuropathic, antitubercular, antiviral, anti-inflammatory, antibacterial, ant obesity, antiparasitic, antifungal, antihistaminic, anticancer, and other potential medicinal agents with their broad applications in pathology and diagnostics. Derivatives of imidazole have placed a unique position in the medicinal chemistry field. The involvement of the imidazole scaffold is a key of synthetic strategy in the drug discovery system. The imidazole moiety is a part of several important naturally occurring products, including histamine, purine, nucleic acid and histidine. It is expected that this brief review could be attractive for new thoughts from academia and pharmaceutical industries to designs of more biologically active and non-toxic imidazole-based drugs. The aims of this review work to the reported imidazole derivatives with pharmaceuticals activity.

Keyword: antifungal, anticancer, heterocycles

## 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 I mainly focused on imidazole heterocycle. 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.

## 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.

## 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.

**3.1. 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

1. Anti-analgesic activity and inflammatory activity
2. Anti-bacterial activity and Anti-fungal
3. Anti-depressant activity
4. Anti-tubercular activity
5. Anti-viral activity
6. Antileishmanial activity
7. Anti-cancer activity

3.2. 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 anticancer 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 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 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 in 2010, Hasanin ejad 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 initiate the formation of diamine intermediate to produced iso-imidazole followed by dehydration and finally to sigma topic rearrangement to produced imidazoles [32]. triflouroboronetherate. 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]

The synthesis and identification of heterocyclic compounds continue to be a vibrant and dynamic field of research with far-reaching implications. Various studies have been conducted on the synthesis and identification of various heterocyclic compounds using different precursors. These studies have not only expanded our understanding of the structural diversity and potential applications of heterocyclic compounds but have also contributed significantly to fields such as pharmaceuticals, materials science, and agriculture. Researchers have explored a wide range of

synthetic routes and reaction mechanisms to access these compounds, often focusing on improving yields, selectivity, and sustainability. Additionally, advancements in analytical techniques such as spectroscopy, chromatography, and crystallography have played a pivotal role in the accurate identification and characterization of these compounds.

Heterocyclic compounds frequently exhibit diverse biological activities due to their ability to interact with various biological targets. As a result, they have become key players in the discovery and design of therapeutic agents for various diseases including cancer, infectious diseases, and neurological disorders. The strategic modification of heterocyclic structures through rational design or high-throughput screening has led to the creation of more effective and selective drug candidates.

The reaction between various N-heterocyclic carbenes, a carbodiphosphorane, and bis(diphenylphosphino)ethane (DPPE) with $[BeX_2(OEt_2)_2]$ (X = Br or I). The results yielded diverse beryllium dihalide adduct complexes, all confirmed through crystallography. Attempts to reduce these compounds to lower oxidation state beryllium complexes using different reducing agents had limited success. Nevertheless, the reaction of $[(IPr)BeBr_2]$ with the aluminum(I) heterocycle [:Al(DipNacnac)] produced the adduct complex $[\{(IPr)(Br)Be(\mu\text{-}H)\}_2]$. Another outcome was the formation of the beryllium naphthalenediyl complex $[(IPr)Be(C_{10}H_8)]$ through the reduction of $[(IPr)BeBr_2]$ with potassium naphthalenide. Additionally, when $[\{(DPPE)BeI_2\}\infty]$ reacted with [:Al(DipNacnac)], the Al center of the heterocycle inserted into a Be–I bond, resulting in the formation of a rare Al–Be bonded complex [(DPPE)(I)Be–Al(I)(DipNacnac)] (19)

A study was conducted where they reacted a benzimidazolium salt containing a hydroxyethyl group, 1a, and a novel series of zwitterionic sulphonated benzimidazolium salts, 1b-e, with $Ag_2O$. This reaction yielded Ag(I)-N-heterocyclic carbene (NHC) complexes, specifically 2a-e. The synthesized silver(I)-N-heterocyclic carbene complexes were comprehensively characterized using methods including $^{1}H$ and $^{13}C$ NMR, elemental analysis, and HRMS spectroscopy. The research also encompassed assessing the anti-cancer potential of both the NHC salts and complexes. To determine their effectiveness, proliferation BrdU enzyme-linked immunosorbent assay (ELISA) was employed against HeLa (Human cervix carcinoma), HT29 (human adenocarcinoma), and L929 (mouse fibroblast) cell lines. The results of the study revealed that the $IC_{50}$ values, ranging from 11 ± 1 to 126 ± 3 μM, indicated substantial cytotoxic activity of the new

Ag(I)-NHC complexes, particularly complex 2b, against HeLa, HT29, and L929 cell lines. In contrast, the NHC salts 1a-e exhibited no significant activity against these cell lines. Notably, the higher $IC_{50}$ value of complex 2b against L929 cells suggested a heightened selectivity for healthy cells. This particular complex, due to its exceptional properties, was identified as a novel type of metallodrug with promising potential for further investigation in medical applications (34)

A novel isatinic hydrazone was introduced by schiff-base ligands: furan-2-carboxylic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide (L1), thiophene-2-carboxylic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide (L2), and 2-(pyridine-2-yl-hydrazono)-1,2-dihydro-indol-3-one (L3). These ligands were synthesized through the condensation of furan-2-carboxylic acid hydrazide (L1), thiophene-2-carboxylic acid hydrazide (L2), and 2-hydrazinopyridine (L3) with isatin. By reacting the corresponding metal chlorides with the ligands, monomeric complexes were formed. Characterization methods including FTIR, UV–Vis, $^{1}H$ and $^{13}C$ NMR spectroscopy, elemental analysis, metal content, magnetic measurement, and molar conductance were employed to analyze the ligands and their nine new complexes, denoted as $[M(Ln)_2]Cl_2$ [where M = Co(II), Zn(II), Cd(II); n = L1, L2, L3]. The studies unveiled the creation of distorted octahedral six-coordinate complexes with the metal atom. Biological assessments of the ligands and their metal complexes were carried out against the Gram-positive bacterial strain *Bacillus* (G+) and the Gram-negative bacteria *E. coli* (G−). The observed effects of the prepared compounds were dependent on the specific type of tested bacteria. The results highlighted the potential of both the ligands and their metal complexes to exhibit significant impact on both Gram-positive ($G^+$) and Gram-negative ($G^-$) bacterial strains (35)

Series of spiro quinoxaline-b-lactam based heterocyclic compounds (QL 1-QL 21) were synthesized and characterized by spectroscopic techniques like $^{1}H$-NMR, LC-MS, FT-IR spectroscopy and elemental analysis. The binding mode and binding strength between compounds and calf thymus-DNA were estimated by UV–visible spectroscopy, viscosity measurement and molecular docking studies. The compounds bind with the DNA through partial intercalation mode. In the absorption titration experiment, the $K_b$ values for all the synthesized compounds were found in the range of $0.24–0.64\times10^5$ $M^{-1}$. The protein binding studies of all the synthesized compounds were evaluated by absorption titration experiment, and the $K_b$ value for all the compounds was obtained in the range of $0.030–1.571\times10^4$ $M^{-1}$. The compounds were screened against two Gram

(+ve) and three Gram (–ve) bacteria for antimicrobial activity. The MIC values for all the synthesized compounds were found in 95–255 mM. The $LC_{50}$ values (cytotoxicity) of the synthesized compounds (QL 1–QL 21) were found in the range of 4.00–12.89 mg/mL. All the compounds were screened for anticancer activity against the human osteosarcoma (MG-63) cell line. The result shows that all the compounds exhibit effective anticancer activity (36).

The antiplatelet and anticoagulation activities of selected compounds and their mode of action were evaluated using human blood by impedance aggregometry and various aggregation inducers and inhibitors and compared to appropriate standards. Cytotoxicity was tested using breast adenocarcinoma cell cultures and potential anticoagulation activity was also determined. In total, four of 34 compounds tested were equally or more active than the standard antiplatelet drug Acetylsalicylic Acid (ASA). In contrast to ASA, all 4 active compounds decreased platelet aggregation triggered not only by collagen, but also partly by ADP. The major mechanism of action is based on antagonism at thromboxane receptors. In higher concentrations, inhibition of thromboxane synthase was also noted. The results concluded that the most active compound is 2-amino-4-(1H-indol-3-yl)-6-nitro-4H-chromene-3- carbonitrile (2-N) that is 4-5x times more potent than ASA and can be use as novel anti-platelet drugs (34).

Synthesis of a novel Schiff base macrocyclic ligand was conducted, which was subsequently subjected to characterization through UV-Visible, IR, NMR, and Mass spectra analyses. The gathered data for the complexes indicated a square planar geometry. When evaluating the antibacterial and antifungal properties of these complexes against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella typhimurium,* and *Candida albicans*, it was observed that the complexes displayed more potent biocidal activity compared to the ligands (37)

A comprehensive review on the expanding utilization of heterocyclic compounds was given within Medicinal Chemistry. These compounds have gained prominence due to their prevalence in biological materials. An example, benzimidazole, a fusion of benzene and imidazole, contains two nitrogen heteroatoms. Benzimidazole derivatives hold significant medicinal value and biochemical relevance. They find practical applications across diverse domains. These derivatives exhibit various pharmacological activities, including antihypertensive, anticancer, antiviral, antidiabetic, and antimicrobial effects. Given their effectiveness against microbial infections and other

biological activities, there's a drive to develop more potent drugs. Pharmacological investigations highlight the efficacy of these molecules against different microorganism strains (38).

## 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 posses 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 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.

## References

[1] A. Gomtsyan. Heterocycles in drugs and drug discovery. Chem. Heterocycl. Compd. 2012, 48: 7–10.

[2] H. B. Broughton, I. A. Watson. Selection of Heterocycles for drug design. J. Mol. Graph. Model. 2004, 23: 51–58.

[3] M. S. Salem, Sakr, S. I. El-Senousy, W. M. Madkour, H. M. F. Synthesis, Antibacterial, and Antiviral Evaluation of New Heterocycles Containing the Pyridine Moiety. Arch. Pharm. (Weinheim). 2013, 346: 766–773.

[4] N. M. A. El-salam, M. S. Mostafa, G. A. Ahmed, O. Y. Alothman. Synthesis and Antimicrobial Activities of Some New Heterocyclic Compounds Based on 6- Chloropyridazine-3 (2H) –thione. J. Chem. 2013, 13: 1–8.

[5] M. E. Azab, M. M. Youssef, E. A. El-Bordany. Synthesis and Antibacterial Evaluation of Novel Heterocyclic Compounds Containing a Sulfonamido Moiety. Molecules 2013, 18: 832– 844.

[6] E. R. El-Sawy, M. S. Ebaid, H. M. Abo-Salem, A. H. Al-Sehemi, A. G. Mandour. Synthesis, anti-inflammatory, analgesic and anticonvulsant activities of some new 4,6- dimethoxy-5-(heterocycles)benzofuran starting from naturally occurring visnagin. Arab. J. Chem. 2013, 7: 914–923.

[7] X. Cao, Z. Sun, Y. Cao, R. Wang, T. Cai, W. Chu, W. Hu, Y. Yang. Design, Synthesis, and Structure–Activity Relationship Studies of Novel Fused Heterocycles-Linked Triazoles with Good Activity and Water Solubility. J. Med. Chem. 2014, 57: 3687–3706.

[8] Y. Chen, K. Yu, N. Y. Tan, R. H. Qiu, W. Liu, N. L. Luo, L. Tong, C. T. Au, Z. Q. Luo, S. F. Yin. Synthesis, characterization and anti-proliferative activity of heterocyclic hypervalentorganoantimony compounds. Eur. J. Med. Chem. 2014, 79: 391–398.

9] E. R. El-Sawy, A. H. Mandour, El-Hallouty, S. M. Shaker, K. H. H. M. Abo-Salem. Arab. J. Chem. 2013, 6: 67–78.

[10] Mabkhot, Y. N. Barakat, A. Al-Majid, A. M. Alshahrani, S. Yousuf, M. I. S. Choudhary. Synthesis, reactions and biological activity of some new bis-heterocyclic ring compounds containing sulphur atom. Chem. Cent. J. 2013, 7: 112–120.

[11] D. A. Williams and T. L. Lemke. Foye's Principles of medicinal chemistry, Lippincott Williams and Wilkins, 2002, 5:36.

[12] S. N. PandeyaNath. A Text Book of medicinal chemistry. SG publisher, 2004, 1(3): 2-3.

[13] H. Singh and V. K. Kapoor. Medicinal and Pharmaceutical Chemistry. Vallabh Prakashan, 2008, 2: 1 -2.

[14] D. Lednicer, L. A. Mitscher. In Organic Chemistry of Drug Synthesis. Wiley IntersciencnewYork, 1997, 1: 226.

15] E. G. Brown. Ring Nitrogen and Key Biomolecules. Kluwer Academic Press, 1998.

[16] A. R. KatritzkyRees. Comprehensive Heterocyclic Chemistry, 1984, 5: 469-498.

[17] M. Grimmett, Ross. Imidazole and Benzimidazole Synthesis. Academic Press, 1997.

[18] A. F. Pozharskii, et al. Heterocycles in Life and Society. John Wiley & Sons, 1997.

[19] C. Congiu, M. T. Cocco and V. Onnis. Design, synthesis, and in vitro antitumor activity of new 1,4-diarylimidazole-2-ones and their 2-thione analogues. Bioorganic& Medicinal Chemistry Letters.2008, 18: 989–993.

[20] Heterocyclic Chemistry TL Gilchrist, the Bathpress 1985 ISBN 0-582-01421-2.

[21] A. M. Venkatesan, A. Agarwal, T. Abe, H. O. Ushirogochi, D. Santos, Z. Li, G. Francisco, Y. I. Lin, P. J. Peterson, Y. Yang, W. J. Weiss, D. M. Shales, T. S. Mansour. 2-(4-Chlorophen-yl)-4,5-diphenyl-1-(prop-2-en-1-yl)-1H-imidazole. Bioorg. Med. Chem. 2008, 16: 1890–1902.

[22] M. Su Han and D. H. Kim. Synthesis of Novel Imidazoles as Potent Antimicrobial Agents. Bioorganic & Medicinal Chemistry Letters. 2001, 11: 1425-1427.

[23] T. Nakamura, H. Kakinuma, H. Umemiya, H. Amada, N. Miyata, K. Taniguchi, K. Bando and M. Sato. Imidazole derivatives as new potent and selective 20-HETE synthase inhibitorsBioorganic& Medicinal Chemistry Letters. 2004, 14: 333–336.

[24] M. A. Bbizhayev, Life Sci., 2006, 78: 2343–2357.

[25] G. Roman, J. G. Riley, J. Z. Vlahakis, R. T. Kinobe, J. F. Brien, K. Nakatsu, W. A. Szarek. Hemeoxygenase inhibition by 2-oxy-substituted 1-(1H-imidazol-1-yl)-4-phenylbutanes: Effect of halogen substitution in the phenyl ring Bioorg. Med. Chem. 2007, 15: 3225–3234.

[26] J. L. Adams, J. C. Boehm, T. F. Gallagher, S. Kassis, E. F. Webb, Ralph Hall, Margaret Sorenson, Ravi Garigipati, Don E.Griswold and John C. Lee. Pyrimidinylimidazole inhibitors of p38: cyclic N-1 imidazole substituents enhance p38 kinase inhibition and oral activity. Bioorg. Med. Chem. Lett. 2001, 11: 2867-2870.

27] P. G. Nantermet, J. C. Barrow, S. R. Lindsley, M. Young, S. Mao, S. Carroll, C. Bailey, M. Bosserman, D. Colussi, D. R. McMasters, J. P. Vacca, H. G. Selnick. Imidazole acetic acid TAFIa

inhibitors: SAR studies centered around the basic P1′ group. Bioorg. Med. Chem. Lett. 2004, 14: 2141–2145.

[28] K. Bhandari, N. Srinivas, G. B. S. Keshava, P. K. Shukla. Tetrahydronaphthyl azole oxime ethers: The conformationally rigid analogues of oxiconazole as antibacterials. Eur. J. Med. Chem., 2009, 44: 437-447.

[29] S. Emami, A. Foroumadi, M. Falahati, E. Lotfali, S. Rajabalian, d S Ahmed Ebrahimi, S. Farahyarc and A. Shafiee. 2-Hydroxyphenacyl azoles and related azolium derivatives as antifungal agents. Bioorganic & Medicinal Chemistry Letters. 2008, 18: 141–146.

[30] R. K. Ujjinamatada, A. Baier, P. Borowski, R. S. Hosmane. An analogue of AICAR with dual inhibitory activity against WNV and HCV NTPase/helicase: Synthesis and in vitro screening of 4-carbamoyl-5-(4,6-diamino-2,5-dihydro-1,3,5-triazin-2-yl)imidazole-1-β-D-ribofuranoside. Bioorg. Med. Chem. Lett. 2007, 17: 2285–2288.

[31] R. V. Shingalapur, K. M. Hosamani, R. S. Keri. Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles. European Journal of Medicinal Chemistry. 2009, 44: 4244–4248.

[32] M. Kidwai, P. Mothsra, V. Bansal, R. K. Somvanshi, A. S. Ethayathulla, S. Dey and T. P. Singh. One-pot synthesis of highly substituted imidazoles using molecular iodine: A versatile catalyst. Journal of Molecular catalyst A. 2007, 265:177-182.

[33] S. Sharma, S. Gangal and A. Rauf. Convenient one-pot synthesis of novel 2-substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles and evaluation of their in vitro antibacterial and antifungal activities. European Journal of Medicinal Chemistry. 2009, 44: 1751-1757.

[34] J. Pandey, V. K. Tiwari, S. S. Verma, V. Chaturvedi, S. Bhatnagar, S. Sinha, A. N. Gaikwad and R. P. Tripathi. Synthesis and antitubercular screening of imidazole derivatives. European Journal of Medicinal Chemistry. 2009, 44: 3350-3355.

[35] A. Hasaninejad, A. Zare, M. Shekouhy and J. A. Rad. Catalyst-Free One-Pot Four Component Synthesis of PolysubstitutedImidazoles in Neutral Ionic Liquid 1-Butyl-3-methylimidazolium Bromide. J. Comb. Chem. 2010, 12: 844-849.

[36] C. Mukhopadhyay, P. K. Tapaswi and M. G. B. Drew. Room temperature synthesis of tri-, tetrasubstitutedimidazoles and bis-analogues by mercaptopropylsilica (MPS) in aqueous methanol: application to the synthesis of the drug trifenagrel. Tetrahedron Letters. 2010, 51: 3944-3950.

[37] H. R. ShaaterianandM. Ranjban. An environmentally friendly approach for the synthesis of highly substituted imidazoles using Brønsted acidic ionic liquid, N-methyl-2-pyrrolidonium hydrogen sulfate, as reusable catalyst. Journal of Molecular Liquids. 2011, 160: 40-49.

[38] Zhong-JianCai, Shun-Yi Wang and Shun-Jun Ji. CuI/BF3·Et2O Cocatalyzed Aerobic Dehydrogenative Reactions of Ketones with Benzylamines: Facile Synthesis of Substituted Imidazoles. Org. Lett. 2012, 14(23): 6068-6071.