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A Review on Synthetic and Pharmacological Profile of Some Imidazole Derivatives

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ABSTRACT

Imidazoles have occupied a unique position in heterocyclic chemistry and derivatives of imidazole have attracted considerable interest in recent years for their different pharmacological properties. Imidazole is a nitrogen-containing heterocyclic ring which possesses biological and pharmaceutical importance. Thus, imidazole compounds have been an interesting source for researchers for more than a century. The imidazole ring is a constituent of many important natural products, including purine, histamine, histidine, and nucleic acid. Being a polar and ionizable aromatic compound, it improves pharmacokinetic characteristics of lead molecules and thus is used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble lead molecules. There are several methods used for the synthesis of imidazole-containing compounds and also their various structure reactions offer scope in the field of medicinal chemistry. The imidazole derivatives possess an extensive spectrum of biological activities such as antibacterial, anticancer, antitubercular, antifungal, analgesic, and anti-HIV activities. This paper aims to review the synthetic and pharmacological profile of imidazole during the past years.

1. INTRODUCTION

Heterocyclic compounds represent an important function in medicinal chemistry and serve as a key template for the devolvement of various chemotherapeutic agents. Most of the researcher has maintained their interest in nitrogen-containing heterocyclic compounds through decades of historical devolvement of medicinal synthesis. Heterocyclic form a major class of medicinal and organic chemistry and are used industrially and biologically. There is a wide range of therapeutic activity of synthetic heterocycles such as anticancer, antimicrobial, antidepressant, antimalarial, anticonvulsant, anthelmintic, and insecticidal agents. The explorations for the new biologically active heterocyclic compounds continue to be an area of major research in medicinal synthetic chemistry.[1]

Nitrogen-containing heterocycles are contributing to the devolvement of society from a pharmacological and industrial point of view as well as to improve quality of life.[2] Basic ideas for the development of biologically active synthesized compounds evoke from the consideration that active molecules binding to a protein or enzyme with a response in the form of certain pharmacological activity.[3] Rational drug discovery of small biologically active compounds form the basis of the practical compilation of chemical science with the life science discoveries of the target molecule and disease mechanism.[4] Moreover, synthetic compounds have been and will be an important source of new pharmaceuticals. The advances in molecular biology and functional genomics focus on tackling disorders through an understanding of drug targets.[5]

Drug discovery is the time consuming and inventive process of finding new molecules based on the biological target knowledge which involves small molecules that complementary structure, shape, charge to the biomolecular target with which they bind.[6]

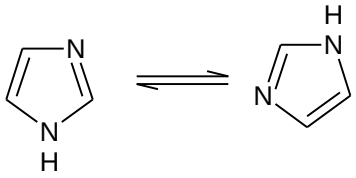
1.1 Imidazole

1.1.1 Introduction

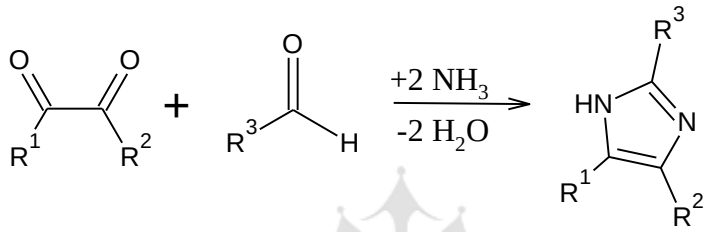
Imidazole is an entity that is synthesized in many of its derivative forms from the past few years and is a major source of interest for the researcher to explore its various biological activity potentials.

Imidazole (1, 3-diaza-2,4-cyclopentadiene) is a five-member planner ring system with 3C and 2N in 1 and 3 positions having molecular formula $C_3H_4N_2$. IUPAC name for the imidazole is

1, 3-diazole, one of the annular N bears an H atom and can be regarded as pyrrole type N. Imidazole is basic aromatic in nature, less basic than ammonia and more basic than pyridine. It exhibits tautomerism because the hydrogen atom that can be located on either of the two nitrogen atoms.[7]



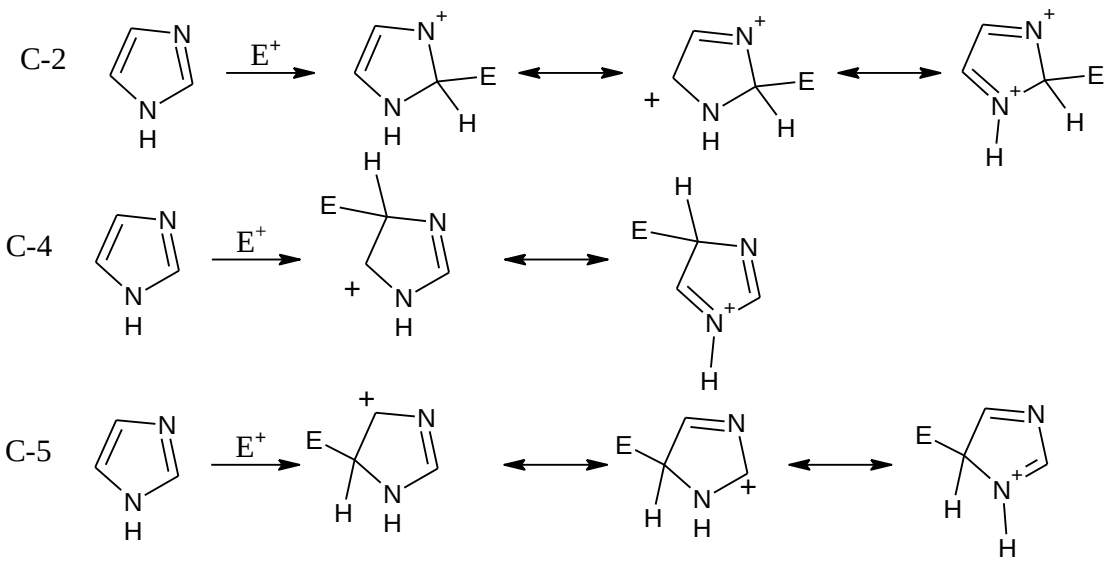
Imidazole was first synthesized by Heinrich Debus in 1958, but various imidazole derivatives had been reported as early as the 1840s. The synthesized imidazole shown below used formaldehyde and glyoxal in ammonia.[8]



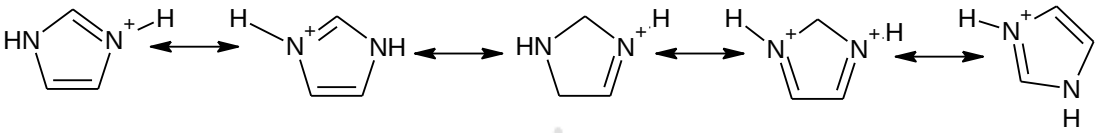
1.1.2 Chemistry

Amphoteric: Imidazole is amphoteric, i.e. acts as an acid and as a base. Acidic pKa is 14.5. N-1 is located as an acidic proton. The basic pKa of the conjugate is nearly 7. N-3 is the basic site. Protonation of the imidazole gives the imidazolium cation which is symmetrical.

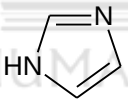
Electrophilic substitution: Imidazole is more favored to electrophilic attack than the pyrazole, thiazole, furan, and thiophene. The attack of electrophile takes place at the 4th and 5th position of the imidazole ring.



The resonance structure of the imidazole ring is shown below



1.1.3 Structure-Activity Relationship of Imidazole Ring [9-14]



SAR of imidazole had shown that ring-substituted only at position N-1 is most essential for the activity. Lipophilic substituents usually one or more with a five or six-membered ring system were attached for activity. The more potent antiviral, antidepressants, antimicrobial, anticancer imidazoles were reported with two or three aromatic substituents on the imidazole ring or annealing with imidazole ring which were with Halogen, Hydroxy, Methoxy substituents at positions 2, 4, 6.

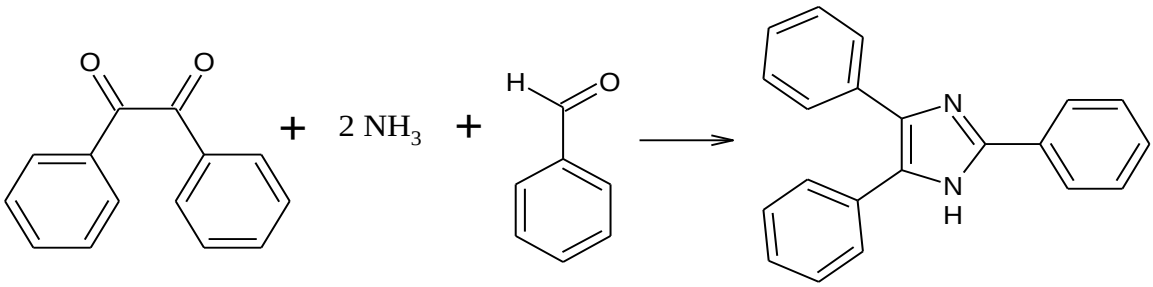
The addition of other alkyl substituents on the imidazole ring generally decreases the activity but imidazole's with N-substitutions on N-1 or N-3 position with methyl group results in nearly inactive agents. Substitutions with aliphatic amines result in decreasing the activity of the imidazole ring. Annealing of the imidazole ring with other heterocycles or aromatics results in pharmacologically active derivatives such as Benzodiazepine.

E.g. Imidazobenzodiazepine midazolam was popularly prescribed as potent anxiolytic agents.

GENERAL METHODS FOR SYNTHESIS OF IMIDAZOLE

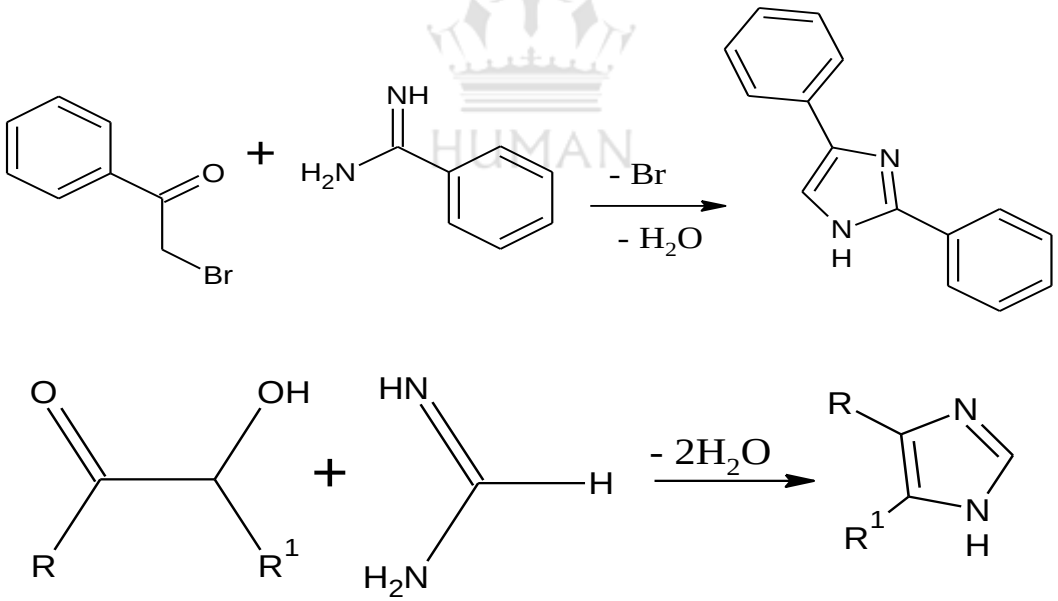
1.1.4.1 Radiszewski synthesis:

Radiszewski reported the synthesis of 2, 4, 5 -triphenyl-imidazole by the condensation of dicarbonyl compound and aldehydes in the presence of ammonia.[15]



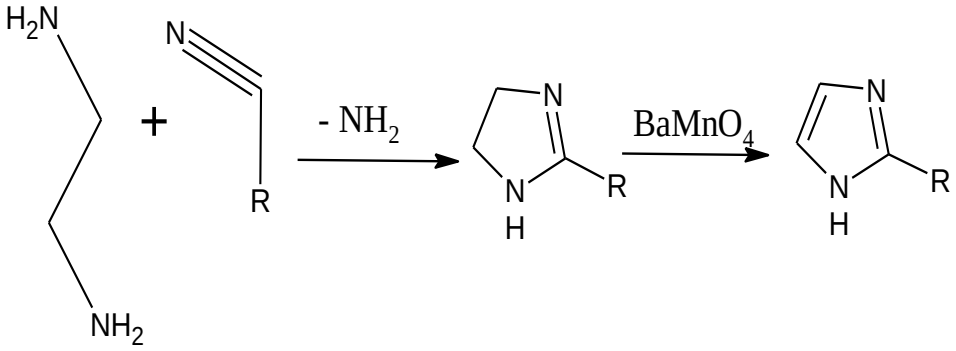
1.1.4.2 from α-haloketones:

This synthesis involves an interaction between an imidine and alpha ketones. This method is applicable for the synthesis of 2, 4 or 2, 5 biphenyl imidazole.[16]



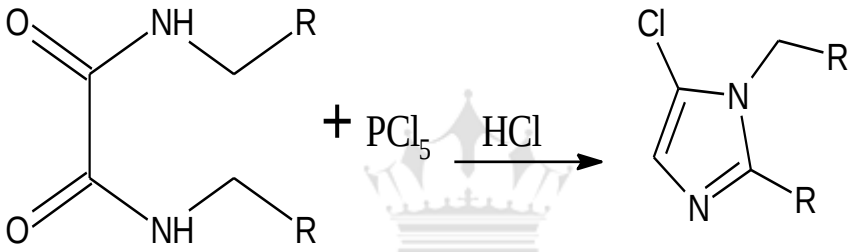
1.1.4.3 from Imidazoline:

Knapp had reported the conversion of imidazolines to imidazole in presence of sulfur with mild reagent barium manganate yields 2-substituted imidazoles.[17]



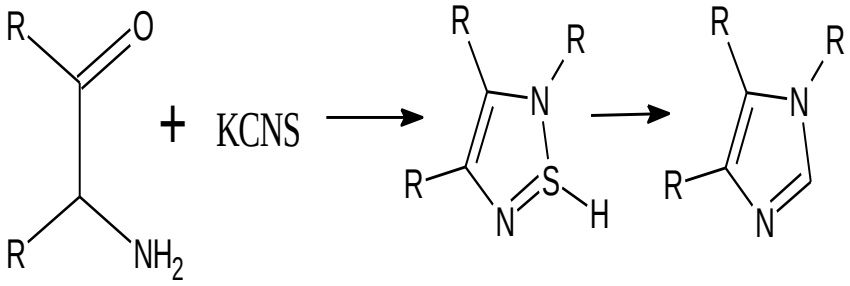
1.1.4.4 Wallach synthesis:

The reaction of N, N dimethylformamide with phosphorus pentachloride which is a chlorine-containing compound on reduction with hydroiodic acid gives N-methyl imidazole by using the same conditions N, N- dimethylformamide is converted to chlorine compound which on reduction gives 2-methyl-1-ethyl imidazole.[18]



1.1.4.5 Markwald synthesis:

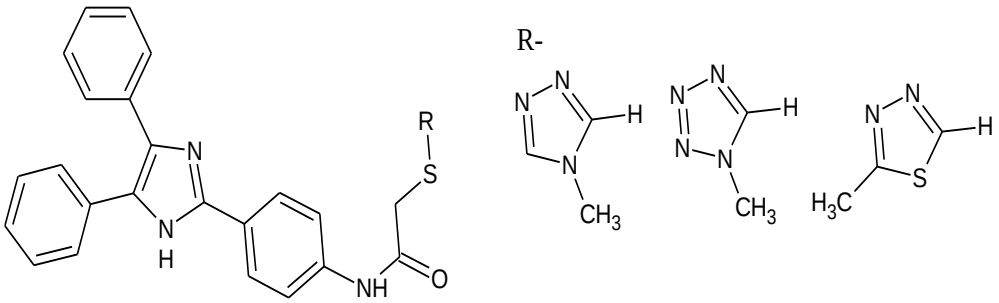
Markwald reported the synthesis of 2-mercaptoimidazoles from α-amino ketones or aldehydes and alkyl isothiocyanates which is a common method for the synthesis of imidazoles.[19]



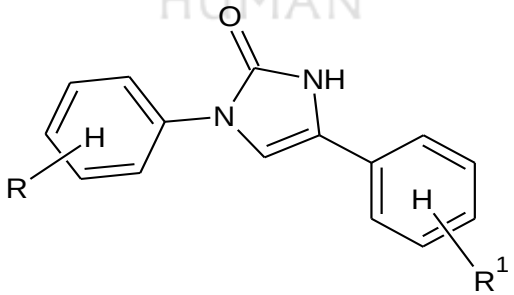
1.1.5 PHARMACOLOGICAL ACTIVITIES OF IMIDAZOLE:

1.1.5.1 Imidazole as anti-cancer agents:

Okay, *et al*. reported 18 novel imidazole piperazine derivatives. The structures of the synthesized agents were characterized by ^{1}HNMR, IR, and EI-MS spectral data. Among the synthesized compounds most of the compounds showed significant activity against carcinogenic cell lines.

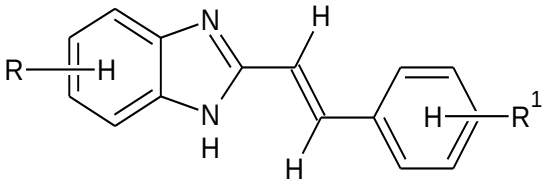


Congiu *et al*. had reported the synthesis of a series of 1, 4-diarylimidazole-2(3H)-one derivatives and evaluated them for in vitro anticancer activity. Compounds with a 3, 4, 5-trimethoxypheny ring attached to either N-1 or C-4 position of the imidazole ring showed anticancer activity against leukemic cell lines.[20]



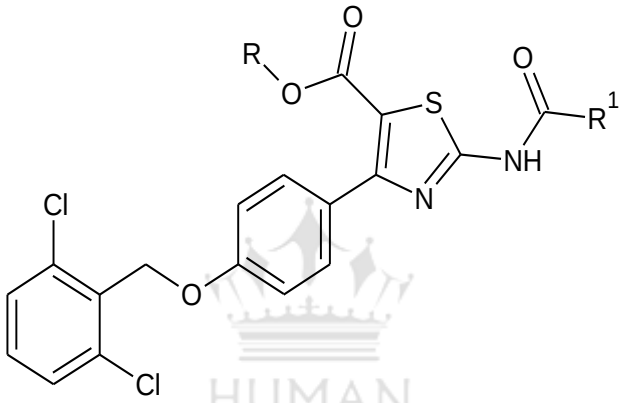
1.1.5.2 Imidazoles as anti-microbial agents:

Kallappa Hosamani *et al*. had reported the synthesis of a novel series of 5-(nitro/bromo) styryl-2-benzimidazoles by condensation of 5-(nitro/bromo)-o-phenylenediamine with trans-cinnamic acids. Synthesized compounds were evaluated for anti-tubercular activity against *Escherichia coli*, *Enterococcus faecalis*, and *Klebsiellapneumoniae* antibacterial strains and *Candida Albicans*, *Asperigillusfumigatus* antifungal strains were performed. Compounds showed significant activity against the group of all microorganisms.[21]



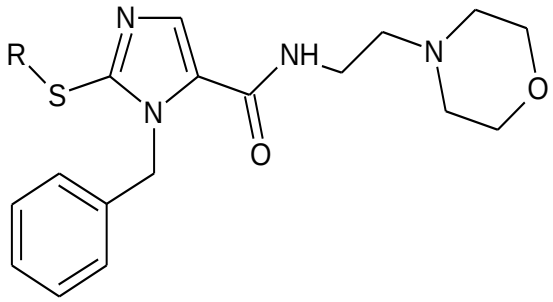
1.1.5.3 Imidazoles as anti-tubercular agents:

Qidong You *et al*. had reported the synthesis of 4-(2, 6-dichlorobenzyloxy) phenyl thiazole imidazole derivatives. Derivatives were evaluated for in vitro anti-tubercular activities against *Mycobacterium tuberculosis* H37Rv by the MicroplateAlamar Blue Assay (MABA). Compounds show good anti-tubercular activities with MIC values between 1μM and 61.2μM.[22]



1.1.5.4 Imidazoles as antidepressant agents:

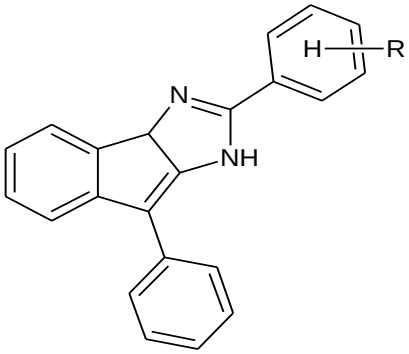
Kumarishalini had reported substituted imidazole with a moclobemide phenyl ring and evaluated them for antidepressant activity using a forced swimming test. Synthesized compounds show a more potent activity than moclobemide.[23]



R- CH_3, C_2H_5, $CH_2C_6H_5$

1.1.5.5 Imidazoles as anticonvulsant agents:

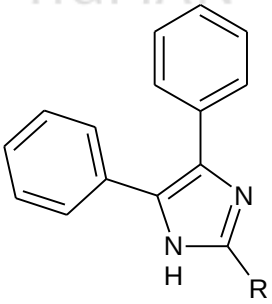
Bhragual *et al*. had reported imidazole derivatives with substitution of chloro and nitro group at 2nd position in the ring showed anticonvulsant activity without neurotoxicity.[24]



R- H, 2-Cl, 2-NO_2, 4-NO_2

1.1.5.6 Imidazoles as anti-inflammatory agents:

Mukeshdoble and A. Puratchikody had reported 2-substituted-4, 5-diphenyl-1*H*-imidazole derivatives and evaluated them for anti-inflammatory activity using the carrageenan-induced rat paw edema method. Derivatives having phenyl substitution with –F, -Cl, -NH_2, -OH, OCH_3, -$N(CH_3)_2$ at Para position showed maximum activity than the other substitutions.[25]



Also,imidazoles having potent antiviral[26], cardiotonic[27], antioxidant[28], anti-diabetic, antifungal[30], antinociceptive activity[31]. Given the above activities in present work we have synthesized 1, 2, 4, 5-tetra substituted imidazole derivatives and evaluated them for antibacterial and antifungal activity.

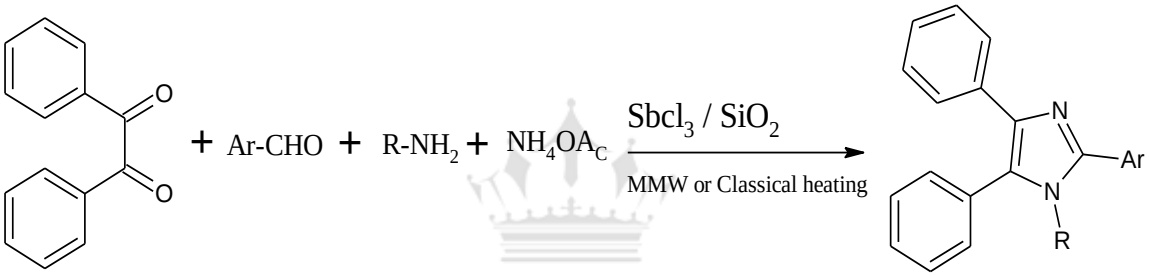
2. REVIEW OF LITERATURE

In the past few years 1, 2, 4, 5-tetra substituted imidazole compounds are being actively studied by the researchers. Various molecules having antimicrobial, antimalarial, anticancer,

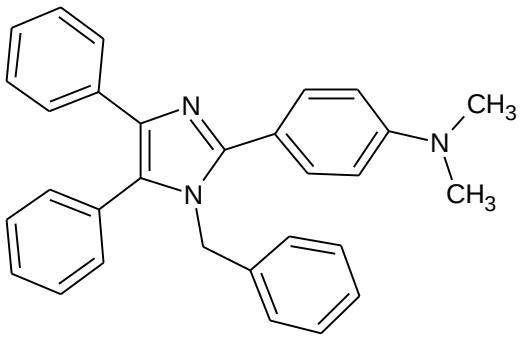
antidepressant activity are being designed and synthesized to study the effects of various substituents present on the target molecules. In the present work we have focused on the 1, 2, 4, 5-tetra substituted imidazole derivatives which have been identified as the new class of antimicrobial agents.

The extensive literature survey had been carried out about the synthesis and biological activity of 1, 2, 4, 5-tetra substituted imidazole derivatives by using books, peer-review journals, and internet sources.

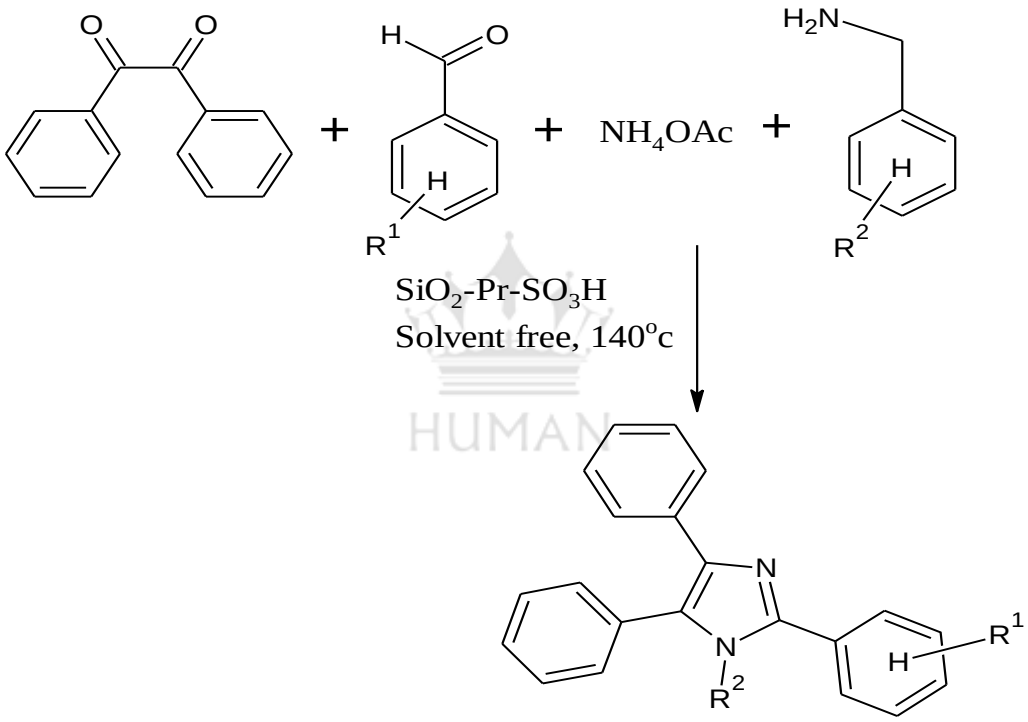
1. **Javad Safari *et al.***(2014) had synthesized 1, 2, 4, 5-tetra substituted imidazole derivatives by the one-pot cyclo condensation of aldehydes, benzil, ammonium acetate, and primary amines under microwave irradiation using silica-supported $SbCl_3$ as a catalyst. This method makes operational simplicity, applicability, and practicability to the previous methods of the synthesis.[32]



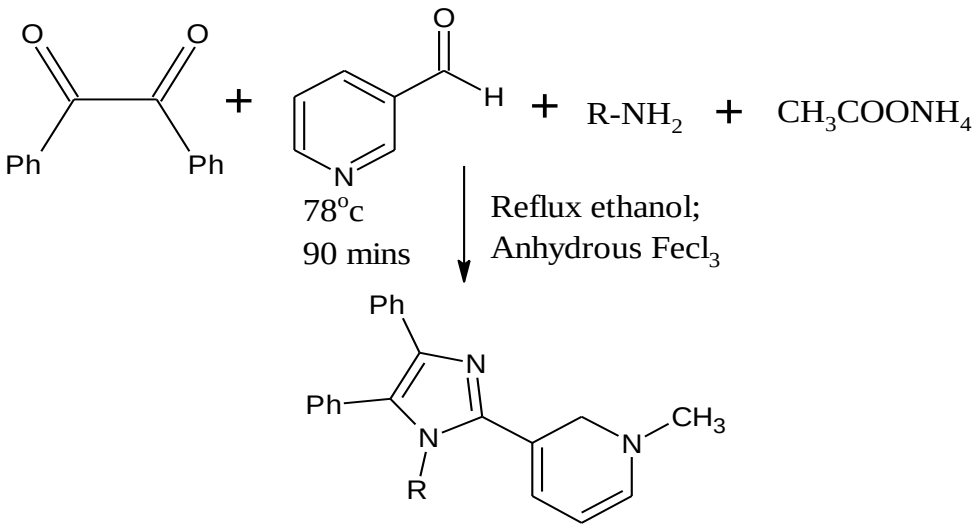
2. **Zong-Ze Zhang *et al.*** (2015) had synthesized 1, 2, 4, 5-tetrasubstituted imidazole derivatives using a one-pot reaction of 1, 2-diketones, ammonium acetate, aromatic aldehydes, and substituted aromatic amines. Synthesis had carried out using ß-cyclodextrin-propyl sulphonic acid as a catalyst under solvent-free medium and synthesized compounds were evaluated for local anesthetic activity. The local anesthetic activities of synthesized compounds were assessed in comparison to lidocaine as standard by using the rabbit corneal and mouse tail anesthesia model. Amongst the synthesized compounds 4-(1-benzyl-4, 5-diphenyl-1*H*-imidazole-2-yl)-N, N-dimethylaniline was reported most potent with minimum toxicity.[33]



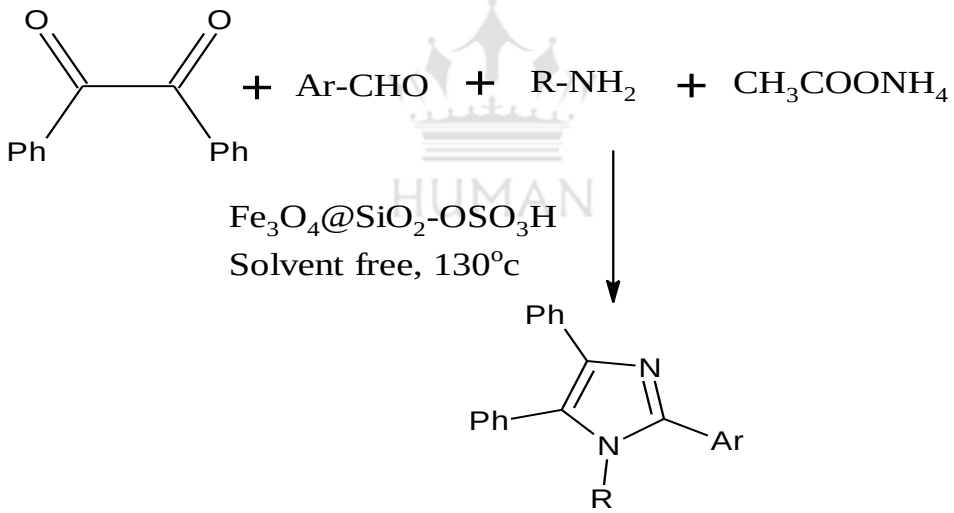
3. **Ghodsi Mohammadi Ziarani *et al.* (**2015) reported a one-pot four-component reaction between 1, 2-diketones, aromatic aldehydes, ammonium acetate, and substituted amines for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using sulfonic acid functionalized silica (SiO_2-Pr-SO_3H) as an efficient catalyst.[34]



4. **Manal Mohammed *et al.***(2014) had prepared series of 1-methyl-5-(1-substituted-4, 5-diphenyl-1*H*-imidazole-2-yl-1, 2, 5, 6-tetrahydropyrindine) derivatives by the refluxing mixture of benzil, arylamines, pyridine-3-carboxaldehyde, and ammonium acetate. Molecular docking study for the anti-inflammatory activity with the protein p38 MAP kinase showed a maximum binding affinity with the experimental values. Compounds were screened for anthelmintic and in vitro anti-inflammatory activity on comparison with standard Albendazole and standard diclofenac sodium respectively. All compounds showed significant activity with high practical yield.[35]



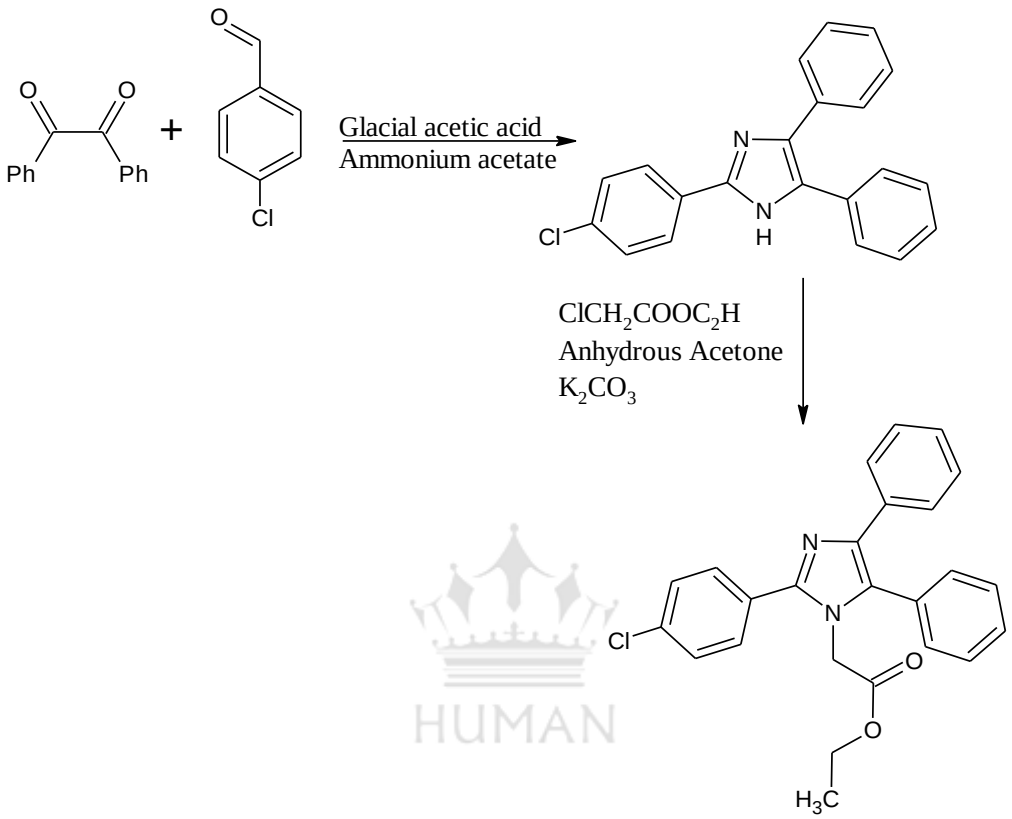
5. **Abolghasem Davoodina *et al.*** (2015) had synthesized 1,2,4,5-tetrasubstituted imidazole derivatives by one-pot four-component condensation of benzil, aromatic aldehydes, ammonium acetate, and primary amines using nano-Fe_3O_4 encapsulated-silica particles bearing sulfonic groups as a separable catalyst. Parameters like reaction temperature, catalyst loading, and solvent effect on synthesis reaction were also studied.[36]



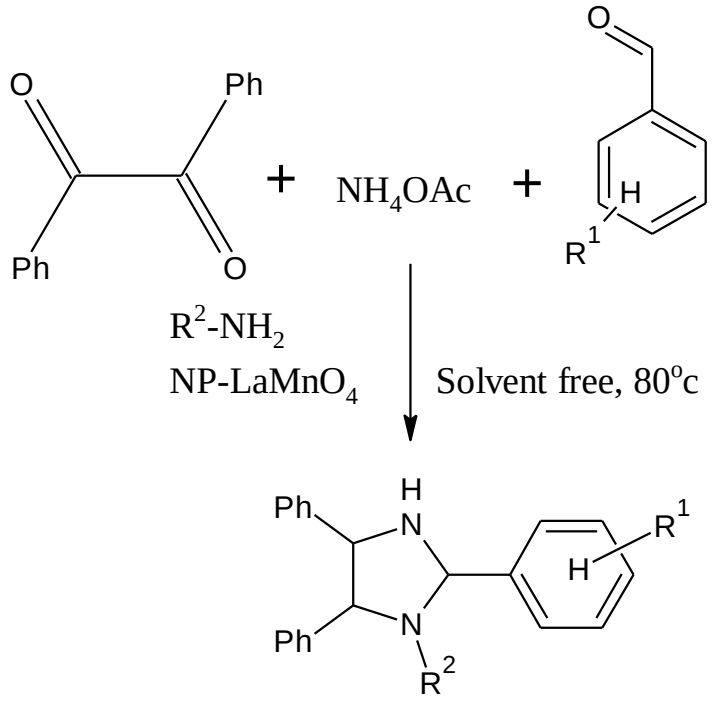
6. **Iftikhar Ahsan *et al.*** (2014) had synthesized imidazole derivatives from 2-(4-chlorophenyl)-4, 5-diphenyl-1*H*-imidazole-1-yl)-acetic acid hydrazide which being synthesized from benzil, 4-chlorobenzaldehydes, ammonium acetate. All derivatives were evaluated for anti-inflammatory and antimicrobial activity. Compounds bearing 4-fluoro, methyl, and fluorophenyl group showed maximum anti-inflammatory activity in comparison to standard indomethacin.

Antibacterial and antifungal activities were performed using the plate agar diffusion method by using ofloxacin as standard drug for antibacterial activity and Voriconazole as a standard

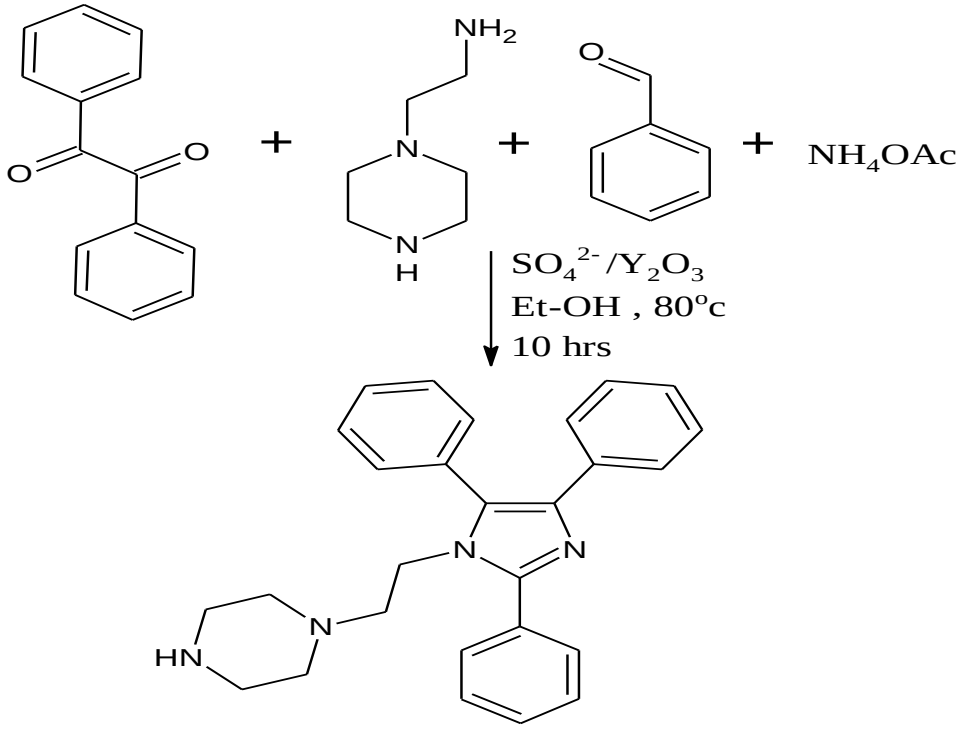
for antifungal activity. Compounds were evaluated against *E. coli, B. subtitles, S. aureus* in the nutrient agar medium for antibacterial activity, and *Candida albicans* in the Sabouraud's medium for antifungal activity. Compounds having 4-chlorophenyl, 4-methylphenyl group's shows the highest antibacterial activity and compounds with phenyl and 4-methoxyphenyl group showed the highest antifungal activity.[37]



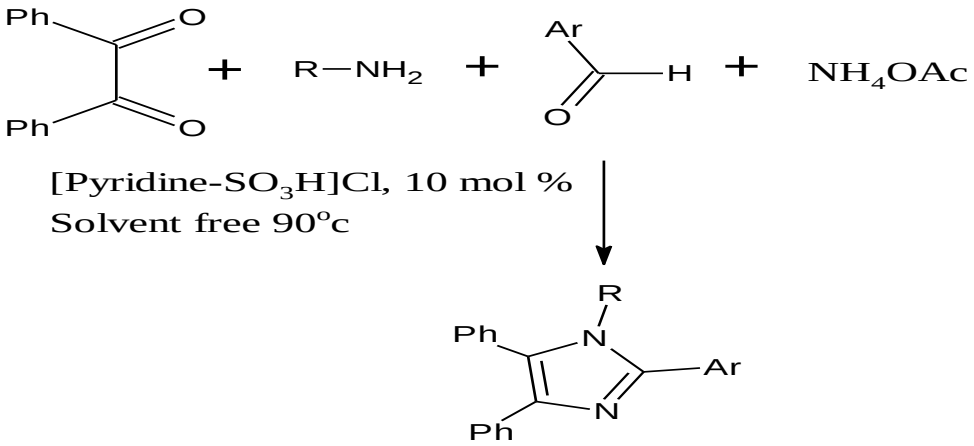
7. **Haleh Sanaeishoar *et al.***(2016) had prepared 1, 2, 4, 5-tetrasubstituted imidazole through one-pot condensation of amines, aldehydes, ammonium acetate, and 1,2-diketones using nano $LaMnO_3$perovskite type oxide as a catalyst under solvent-free conditions at 80^0 C. This method of synthesis overcomes the problem of previous methods of synthesis like catalyst recovery, high catalyst loading, poor yield, difficult workup, and reuse of catalyst.[38]



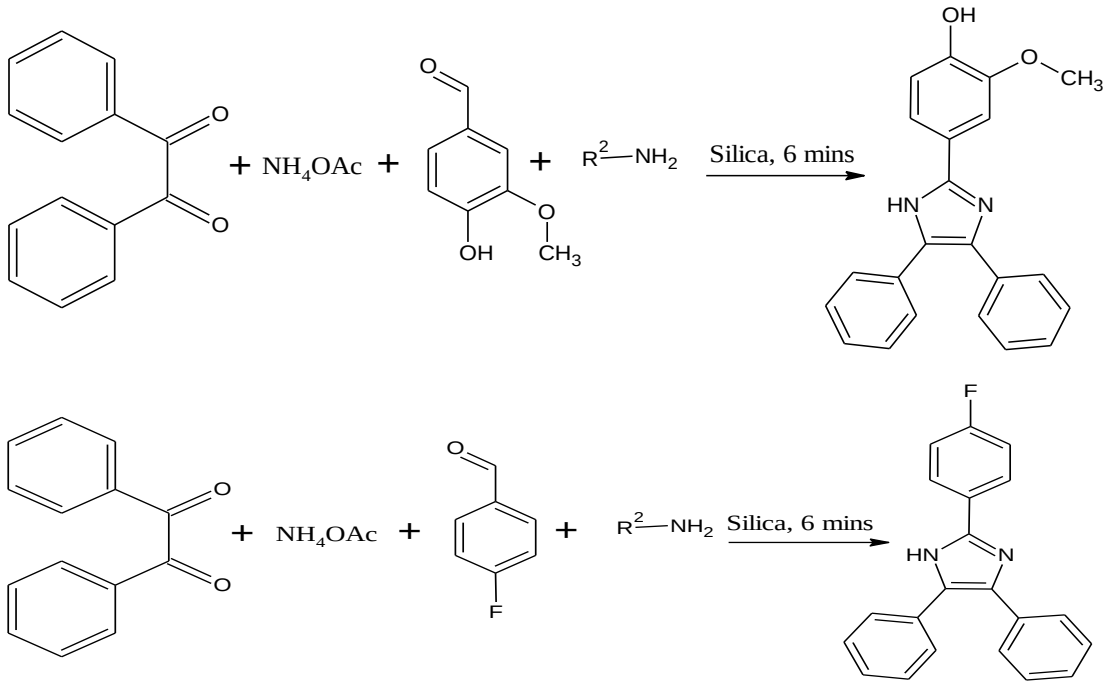
8. **Kuppusamy Krishnamy *et al.*** (2015) had devised a highly versatile, efficient, and simple method for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazole derivatives by the cyclo condensation of aminoethylpiperazine, an aromatic aldehyde, ammonium acetate, and benzil using sulfated yttria as a promising catalyst. This method of synthesis showed many advantages like high yield, simple operation, easy workup, low cost, catalyst recovery, and recyclability.[39]



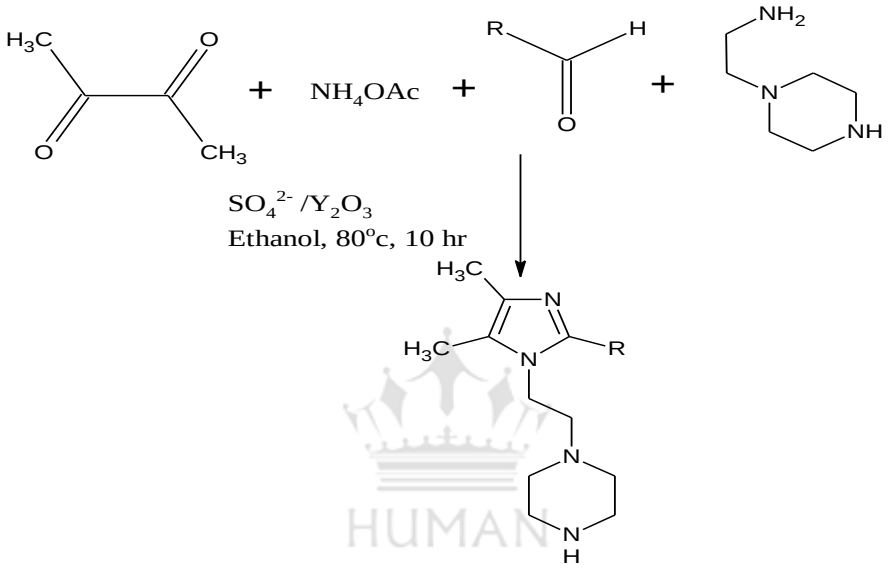
9. **A. R. Moosavi-Zare *et al.*** (2015) had reported an efficient and recyclable catalyst system of sulfonic acid-functionalized pyridinium chloride for the one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using benzil, ammonium acetate, aldehydes, and amines. This method of synthesis had shown advantages like short reaction time, efficiency, recyclability and easy preparation with good compliance with eco-friendly green chemistry protocol.[40]



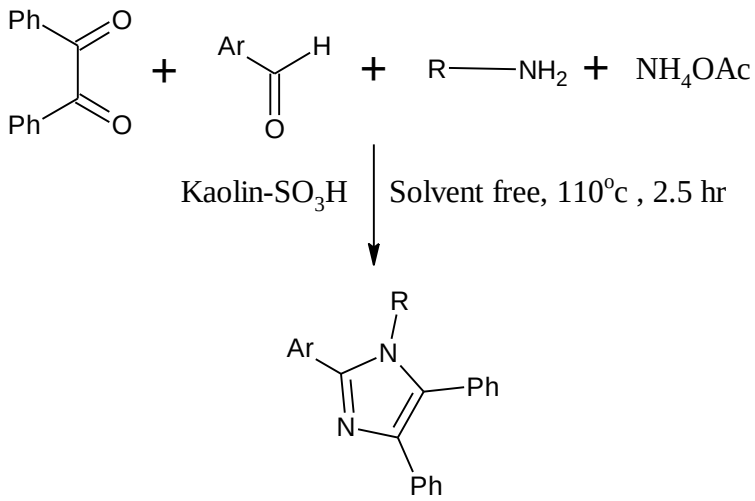
10. **Harsha Tripathy *et al.*** (2010) had synthesized 1, 2, 4, 5-tetra substituted imidazoles by the microwave-assisted parallel synthetic method in solid-phase with advantages like high yield, short reaction time, and purity. The synthesized compounds were confirmed by Mass, NMR, TLC, and IR. The synthesized compounds were screened for anti-inflammatory activity using the rat paw edema method. Amongst the all synthesized compounds, anti-inflammatory was found to be active orally with reduced in paw volume.[41]



11. **K. Krishnasamy*et al.*** (2014) had synthesized 1-[2-(4, 5-dimethyl-henyl-1H-imidazol-1-yl)-ethyl)-piperazine] derivatives by the cyclo condensation of aromatic aldehydes, ammonium acetate, diacetyl, and 2-(piperazine-1yl)-ethanamine in the presence of sulfated yttria. All the synthesized compounds were confirmed by MASS, NMR, IR and screened for antibacterial and antifungal activity. Amongst them, compounds having thiophene moiety with chlorine substitution showed excellent antibacterial activity against *E. coli*, *S. aureus*, *S. typhi*, and *P. aeruginosa* using ciprofloxacin as a standard. Excellent antifungal activities were shown by the compounds having chloro, fluoro, and 3-bromo, 4-fluoro substitution against *C. Albicans*, and *A. flavus*using amphotericin B as a standard.[42]



12. **Bibi Mirjalili *et al.*** (2015) had synthesized 1, 2, 4, 5-tetra substituted imidazole derivatives using Kaolin-SO_3H as an efficient catalyst by the reaction between benzyl, aromatic aldehydes, primary amines, and ammonium acetate. This method had shown key advantages over the other methods of synthesis including inexpensive, easy availability, high yields, and simple work-up.[43]



REFERENCES

1. Vijayta Gupta and Vinay Kant, Review on Biological Activity of Imidazole and Thiazole Moieties and their Derivatives, sciintl,2013:253-260.
2. Rajiv Dua, Suman Shrivastava, S.K. Sonwane and S.K. Srivastava, Pharmacological Significance of Synthetic Heterocycles Scaffold: A Review, Advances in Biological Research, 2011, Vol. 5 (3):120-144.
3. J.C. Espinoza-Hicks, A. Camacho-Dávila, and G.V. Nevarez-Moorillon, Structural modification of organic compounds by chemical synthesis to develop new antimicrobials, Amendez Vilas (Ed), 2011:169-175.
4. Smita Jain, I.G. Rathish, R. Sankaran, Review on current Industrial trends for synthesis of medicinal compounds, Int J Pharm Sci, 2013,Vol. 5(4):33-45.
5. Ashutosh Kar, Advanced Practical Medicinal Chemistry, New Age International Publishers.
6. Deniz Ekinci, Medicinal Chemistry and Drug Design Published By Intech.
7. Arunkumar S Suvarna, Imidazole and its derivatives and Importance in the Synthesis of Pharmaceuticals: A Review, Research Journal of Chemical Sciences, 2015, Vol. 5(10):67-72.
8. M. John Plater, The Crucial Early Contributions Of F. R. JAPP TO A General Synthesis Of Imidazole Derivatives, Bull. Hist. Chem., 2008, Vol. 33(2):76-81.
9. Katarzyna Gobis, Henryk Foks, Karolina Suchan, Novel 2-(2-phenalkyl)-1H-benzo[d]imidazoles as antitubercular agents, Synthesis, biological evaluation and structure–activity Relationship, Bioorganic & Medicinal Chemistry, 2015.
10. Sreekanth Ramachandran, Manoranjan Panda, Kakoli Mukherjee, Nilanjana Roy Choudhury, Synthesis and structure activity relationship of imidazo[1,2-a]pyridine-8-carboxamides as a novel antimycobacterial lead series, Bioorganic & Medicinal Chemistry Letters, 2013, Vol 23:4996–5001.
11. R. O. McCracken and K. B. Lipkowitz, Structure-Activity Relationships of Benzothiazole and Benzimidazole Anthelmintics: A Molecular Modeling Approach to In vivo Drug Efficacy, The Journal of Parasitology, 1990, Vol. 76(6):853-864.
12. Caliendol, G Cirino, G Greco, E Novellino, E Perissutti, Synthesis and structure-activity relationships of anti-inflammatory 1-methyl-2-(4-X-benzoyl)imidazole-5-acetic acids, Eur J Med Chem, 1994, Vol. 29:381-388.
13. Souad Mghazli, Abderrahim Jaouad, Mohamed Mansour, Didier Villemin, Driss Cherqaoui, Natural network studies: quantitative structure activity relationships of antifungal 1-[2-(substituted phenyl) allyl]imidazoles and related compounds, Chemosphere, 2001, Vol. 43:385-390.
14. Igor Tamm, Rostom Bablanian, Marjorie M. Nemes, Clifford H. Shunk, Franklin M. Robinson, Relationship between structure of Benzimidazole derivative and selective virus inhibitory activity, The Journal of experimental medicine, 1961, Vol. 113 (4):625-654.
15. Anshul Chawla, Ashu Sharma and Anil Kumar Sharma, Review: A convenient approach for the synthesis of imidazole derivatives using microwaves, Der Pharma Chemica, 2012, Vol.4 (1): 116-140.
16. Bhatnagar A., Sharma P. K., Kumar N., A Review on "Imidazoles": Their Chemistry and Pharmacological Potentials, International Journal of Pharm Tech Research, 2011, Vol. 3(1):268-282.
17. Alka Pradhan, Nazish Khan, Harshita Goyal, A Convenient Approach for the Synthesis of Ingenous Imidazole Derivatives Using Microwaves, Chemical and Process Engineering Research, 2015, Vol.35:128-134.
18. Deepak Chaudhury, Janmajoy Banerjee, Niraj Sharma, Nomi Shrestha, Routes of synthesis and biological significances of Imidazole derivatives: Review, World J Pharm Sci, 2015, Vol. 3(8):1668-1681.
19. Arunkumar S Suvarna, Imidazole and its derivatives and Importance in the Synthesis of Pharmaceuticals: A Review, Research Journal of Chemical Sciences, 2015, Vol. 5(10):67-72.
20. Sanchita Baroniya, Zaihra Anwer, Pramod K. Sharma, Rupesh Dudhe, Nitin Kumar, Recent advancement in imidazole as anti-cancer agents: A review, Der Pharmacia Sinica, 2010, Vol. 1 (3): 172-182.
21. Ramya V. Shingalapur, Kallappa M. Hosamani, Rangappa S. Keri, Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles, European Journal of Medicinal Chemistry, 2009, Vol.4:4244–4248.
22. Xiaoyun Lu, Xiaobo Liu, Baojie Wan, Scott G. Franzblau, Lili Chen, Changlin Zhou, Qidong You, Synthesis and evaluation of anti-tubercular and antibacterial activities of new 4-(2, 6-dichlorobenzyloxy) phenyl thiazole, oxazole and imidazole derivatives, Part 2, European Journal of Medicinal Chemistry, 2012, Vol.49:164-171.

23. Kumari Shalini, Pramod Kumar Sharma, Nitin Kumar, Imidazole and its biological activities: A review, Der Chemica Sinica, 2010, Vol.1 (3): 36-47.
24. Anupam, Supriya Maity, Shamim Ahmad, Sudha Singh and Gopalji Baranwal, Imidazole-A New Profile Of Various Pharmacological Activities, European Journal Of Pharmaceutical And Medical Research, 2017, Vol.4 (2), 322-334.
25. A. Puratchikody and Mukesh Doble, Antinociceptive and anti-inflammatory activities and QSAR studies on 2-substituted-4, 5-diphenyl-1H-imidazoles, Bioorganic & Medicinal Chemistry, 2007, Vol. 15:1083–1090.
26. Deepika Sharma, Balasubramanian Narasimhan, Pradeep Kumar, Vikramjeet Judge, Rakesh Narang, Erik De Clercq, Jan Balzarini, Synthesis, antimicrobial and antiviral evaluation of substituted imidazole derivatives, European Journal of Medicinal Chemistry, 2009, Vol. 44: 2347–2353.
27. Jat Rakesh Kumar, Review Of Imidazole Heterocyclic Ring Containing Compounds With Their Biological Activity, Pharmacophore2010, Vol. 1 (3):167-177.
28. Mark. A. Babizhayev, Yann Courbebaisse, Jean-Francois Nicolay and Yuri. A Semiletov, Design and Biological activity of imidazole containing peptidomimetics with a broad spectrum anti-oxidant activity, Letters in peptide science, 1998, Vol. 5:163-169.
29. GE. Suhasini, M. Nirmala, DR. Archanagiri, V. Varalaksmi and B. Solomon sunder Raj, Antidiabetic Activity Of New Imidazole Derivative (2-(2-benzylidenehydrazinyl)-5,5-diphenyl-1,5- dihydro-4H-imidazol 4-one($C_{22}H_{17}N_4OCl$), IJPCBS 2013, Vol. 3(4), 1293-1304.
30. B. Nandhaa, L. V. G. Nargund, S. L. Nargund and H. Kuntal, Design and synthesis of imidazolylmethyl substituted fluorobenzimidazoles for antitubercular and antifungal activity, Journal of Chemical and Pharmaceutical Research, 2014, Vol. 6(1):530-539.
31. Delia Hernandez Romero, Victor E. Torres Heredia, Oscar Garcia-Barradas, Ma. Elizabeth Marquez Lopez1 & Esmeralda Sanchez Pavon, Synthesis of Imidazole Derivatives and Their Biological Activities, Journal of Chemistry and Biochemistry, 2014, Vol. 2(2): 45-83.
32. Javad Safari, Simin Naseh, Zohre Zarnegar, Zahra Akbari, Applications of microwave technology to rapid synthesis of substituted imidazoles on silica-supported $SbCl_3$ as an efficient heterogeneous catalyst, Journal of Taibah University for Science, 2014, Vol. 8:323–330.
33. Yan Ran, Ming Li,and Zong-Ze Zhang, ß-Cyclodextrin–Propyl Sulfonic Acid Catalysed One-Pot Synthesis of 1, 2, 4, 5-Tetrasubstituted Imidazoles as Local Anesthetic Agents, Molecules 2015, Vol.20, 20286–20296.
34. Ghodsi Mohammadi Ziarani, Zeinab Dashtianeh, Monireh Shakiba Nahad, Alireza Badiei, One-pot synthesis of 1, 2, 4, 5-tetra substituted imidazoles using sulfonic acid functionalized silica (SiO_2-Pr-SO_3H), Arabian Journal of Chemistry, 2015, Vol.8:692–697.
35. Manal Mohammed, K Arul, Anjana A K, Remya K, Synthesis, Docking Studies And Pharmacological Evaluation of Imidazole Analogues of Arecoline, Int J Curr Pharm Res, Vol 6(1), Issue 1, 22-26.
36. Sepideh Yadegarian, Abolghasem Davoodnia and Ahmad Nakhaei, Solvent-Free Synthesis of 1, 2, 4, 5-Tetrasubstituted Imidazoles Using Nano Fe_3O_4@SiO_2 –OSO_3 H as a Stable and Magnetically Recyclable Heterogeneous Catalyst, Oriental Journal of Chemistry, 2015, Vol. 31 (1):573-579
37. Iftikhar Ahsan, K. K. Sharma, Arun Sharma, Suroor Ahmed Khan and Uzma Khan, Design and synthesis of some imidazole derivatives containing 2-(4-chlorophenyl)-4, 5-diphenyl imidazole moiety as anti-inflammatory and antimicrobial agents, Der PharmaChemica, 2014, 6(3):320-325.
38. Haleh Sanaeishoar, Haman Tavakkoli, Mahsa Asareh, Fouad Mohave, One-pot synthesis of tri- and tetrasubstituted imidazoles using nano-$LaMnO_3$perovskite-type oxide as heterogeneous catalyst in solvent-free condition, Iranian Journal of Catalysis 6(2), 2016.
39. Rathinam Rajkumar, Arisiyappan Kamaraj, Kuppusamy Krishnasamy, Multicomponent, one-pot synthesis and spectroscopic studies of 1-(2-(2,4,5-triphenyl-1*H*-imidazol-1-yl)ethyl)piperazine derivatives, Journal of Taibah University for Science, 2015, (9): 498–507.
40. A.R. Moosavi-Zare, Zh. Asgari, A. Zare, and M.A. Zolfigol, One-pot multicomponent synthesis of 1,2,4,5-tetrasubstituted imidazoles using sulfonic acid-functionalized pyridinium chloride as an efficient and recyclable catalyst, ScientiaIranica C, 2015, Vol.22(6), 2254-2261.
41. Harsha Tripathy, Krishnanand ST, Laxmi Adhikary, Chandrashekar J, Parallel Synthesis of Tetra Substituted Imidazoles by Microwave Irradiation and Evaluation of their Anti-inflammatory Activity, RJPBCS 1(4):31-44.

42. R. Rajkumar, A. Kamaraj, K. Krishnasamy, Synthesis, spectral characterization and biological evaluation of novel 1-(2-(4,5-dimethyl-2-phenyl-1H-imidazol-1-yl)ethyl)piperazine derivatives, Journal of Saudi Chemical Society, 2014, Vol. 18: 735–743.
43. Bibi Fatemeh Mirjalili, Hamidreza Akrami, Kaolin-SO_3H as an efficient catalyst for one-pot synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles, Iranian Journal of Catalysis, 201, Vol. 5(2):129-134.