



Routes of synthesis and biological significances of Imidazole derivatives: Review

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ABSTRACT

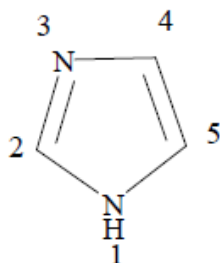
Imidazole is a five membered, heterocyclic ring containing two hetero (nitrogen) atoms and two double bonds. Many imidazoles molecules are synthesized either through fusion or substituting various functional groups in the lead moiety. Several methods of synthesis were reported till date. Imidazole has already been reported to possess many biological activities like anticancer, analgesic, anti-inflammatory, antiviral, antihelmintic, anticonvulsant, aniallergic, antiulcer etc. the article here focus on various synthetic procedures and biological properties chemistry and major reactions of various imidazole derivatives in a comprehensive manner.

Keywords: imidazole, anticancer, analgesic, antiinflammatory, antiviral, antihelmintic, anticonvulsant, aniallergic, antiulcer

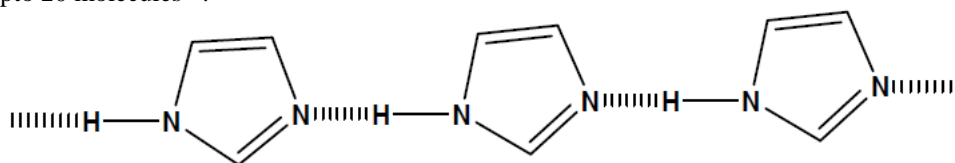


INTRODUCTION

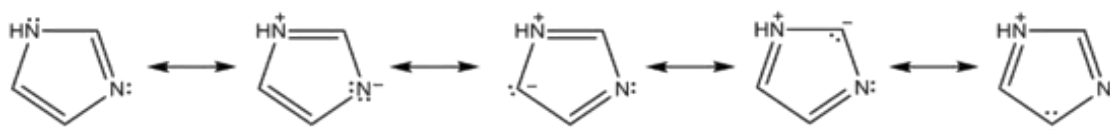
Imidazole is a five-member heterocyclic ring with three Carbon and two Nitrogen atom and the position of N is in 1st and 3rd positions of the molecule. Being a major constituent of various natural products, including purine, histamine, histidine and nucleic acid, Imidazole derivatives have occupied a unique place in the field of medicinal chemistry, thus incorporation of the imidazole nucleus to prepare or synthesis novel imidazole derivatives has always carried the attention of many medicinal chemist and hence proved to be a vital synthetic strategy in drug discovery. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents^[1]. Numerous methods for the synthesis of imidazole and also their various structure reactions offer enormous scope in the field of medicinal chemistry



Imidazole is a colourless organic compound having melting point 89-91 °C and boiling point is 256° C. It has high boiling point as compared all other five membered heterocyclic compounds, the boiling point of 1-methylimidazole is comparatively low because the hydrogen bonding exists in imidazole ring and may consists upto 20 molecules^[2].



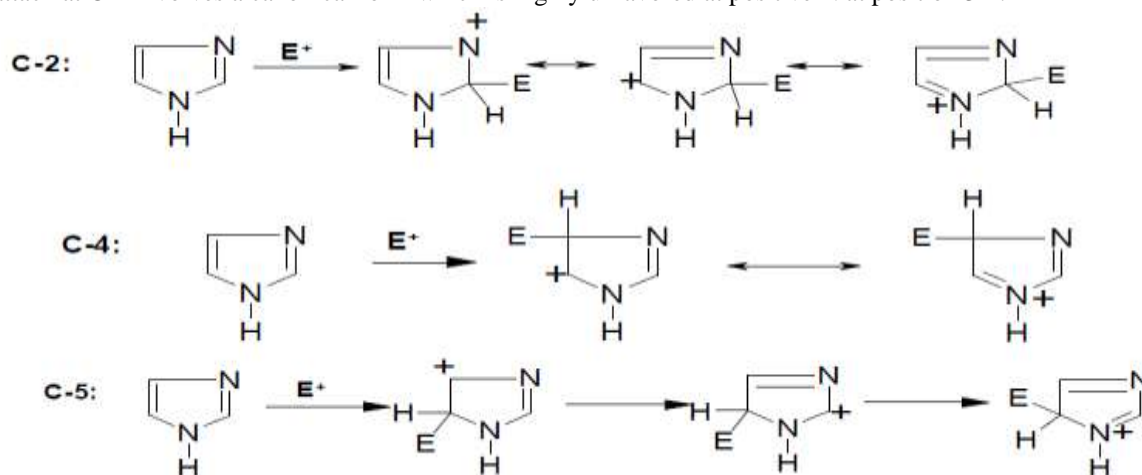
Imidazole exists in two equivalent tautomeric forms, because the proton can be located on either of the two nitrogen atoms. Imidazole is a highly polar compound, calculated dipole of 3.61D, making it more soluble in water. The compound is classified as aromatic due to the presence of a sextet of π -electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring^[3]. Some resonance structures of imidazole are shown below:



CHEMISTRY

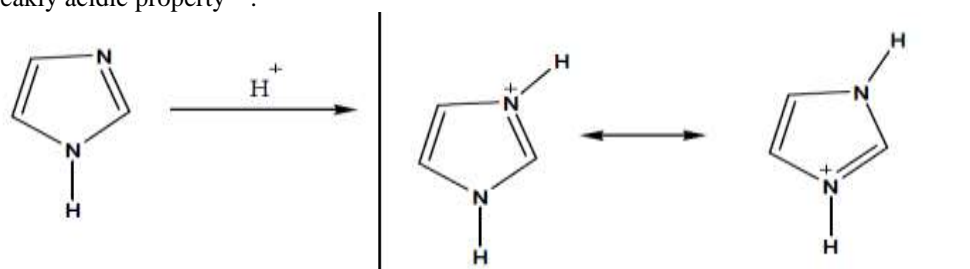
Amphoterism: Imidazole is amphoteric in nature i.e acts as acid and as a base. Acidic pKa is 14.5. The acidic proton is located on N-1. Basic pKa of the conjugate acid is approximately 7, The basic site is N-3. Protonation gives the imidazolium cation, symmetrical in nature^[4].

Electrophilic substitution: Imidazole is more susceptible to electrophilic attack than pyrazole, thiazole, furan and thiophene. The attack of electrophile takes place at the 4th and 5th position in imidazole ring. The attack at C-2 involves a canonical form which is highly unfavored at positive N at position 3^[4].

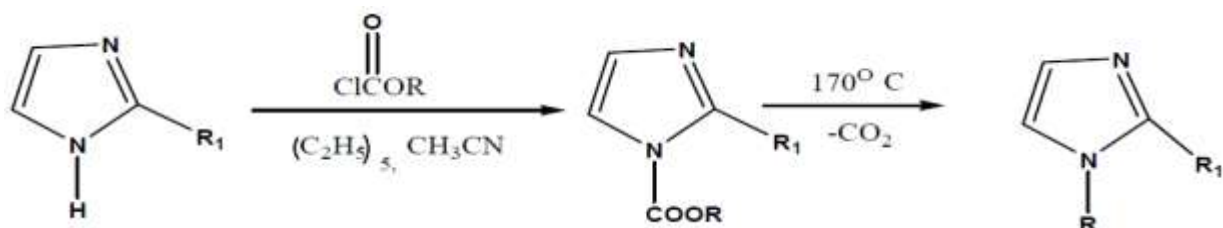


CHEMICAL PROPERTIES

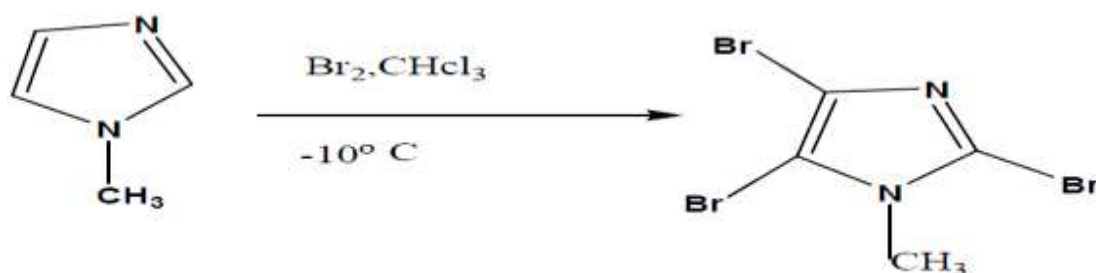
1) **Reaction with acids:** Imidazole is a mono acidic base. It forms crystalline salts with acids and also possesses weakly acidic property^[5].



2) **Quaternization:** Quaternization of the nitrogen atom of the imidazole is normally achieved by the reaction of alkyl halides or dialkyl sulfates in an organic solvent under strongly basic conditions. Alkylation of imidazoles is achieved by heating 1-carboethoxyimidazoles^[5,6].

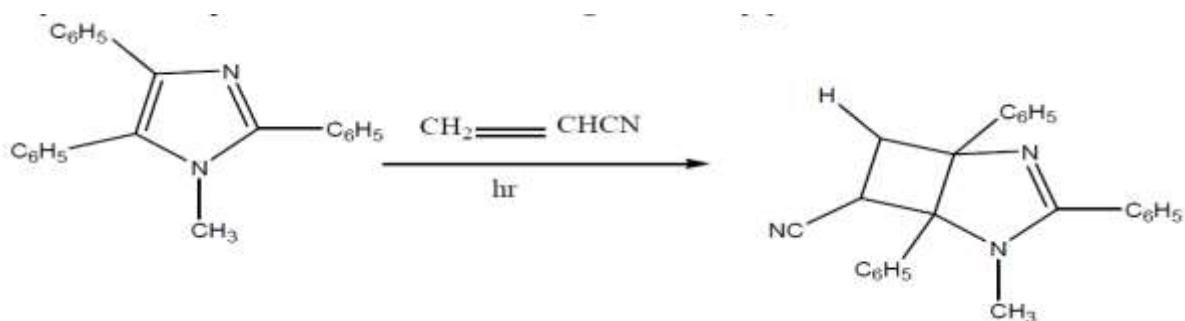


3) **Halogenation:** Halogenation of imidazole is a bit complicated reaction and depends on the substrate, reagents and reaction conditions. Direct chlorination gives undefined products. Bromination yields 2,4,5-tribromo derivative. Iodination takes place in alkaline conditions to give 2,4,5-triiodoimidazole^[5].



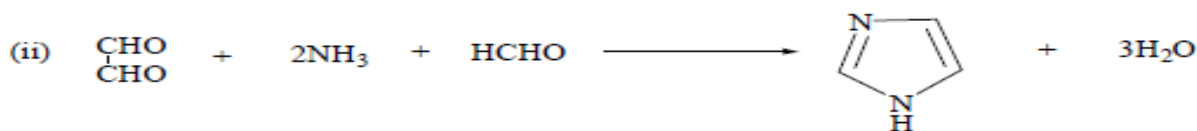
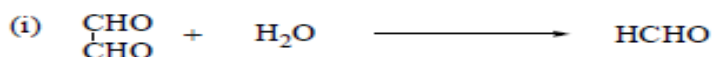
4) **Reaction with Oxidizing and Reducing Agents:** Imidazole shows stability for autoxidation. Oxygen in the presence of sensitizer reacts to give an imidazole derivative. Imidazolium Dichromate, a mild oxidizing agent which is employed for the oxidation of allylic and benzylic alcohols^[5].

5) **Cycloaddition Reactions:** Imidazoles give addition across the carbon-carbon double bond. This kind of reaction is performed under photochemical conditions. The reaction of imidazole with acrylonitrile is representative from the reaction given below^[5].

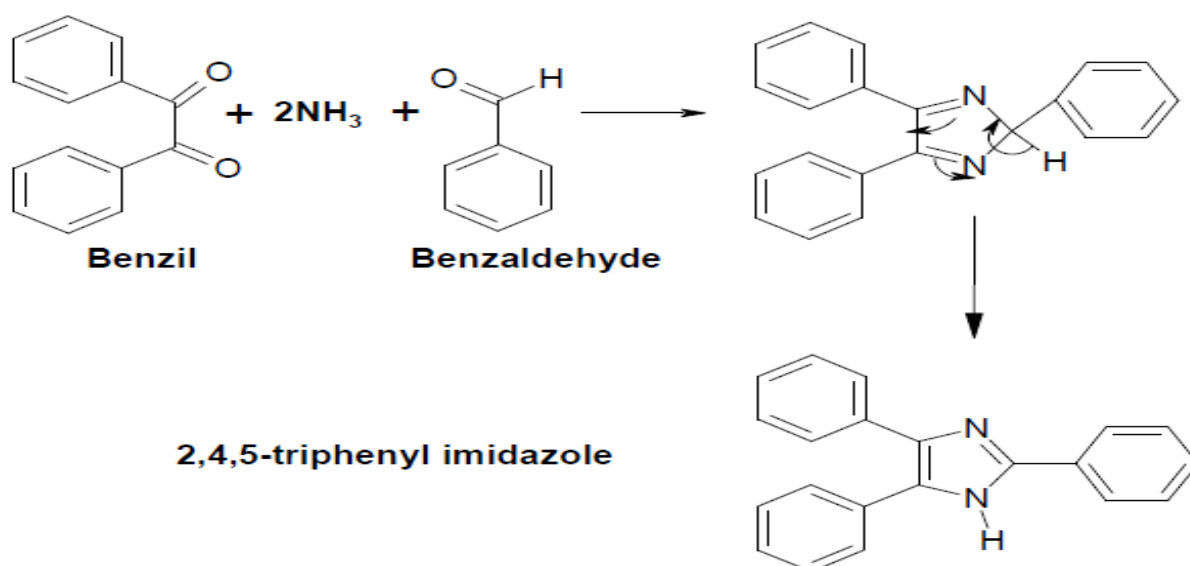


GENERAL SYNTHESIS OF IMIDAZOLE

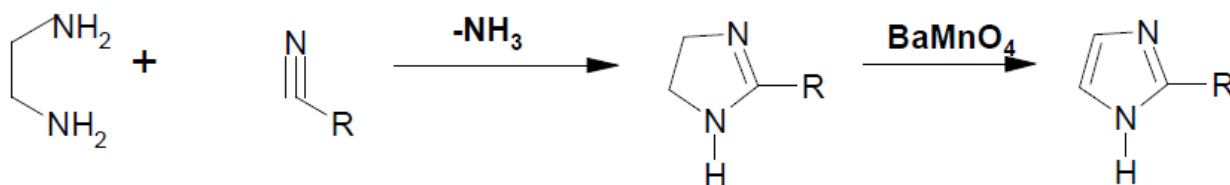
Imidazoles were prepared in 1858 from glyoxal and ammonia, glyoxal breaks down into formic acid & formaldehyde, and then the latter reacts as follows^[7]

**1) RADISZEWSKI SYNTHESIS**

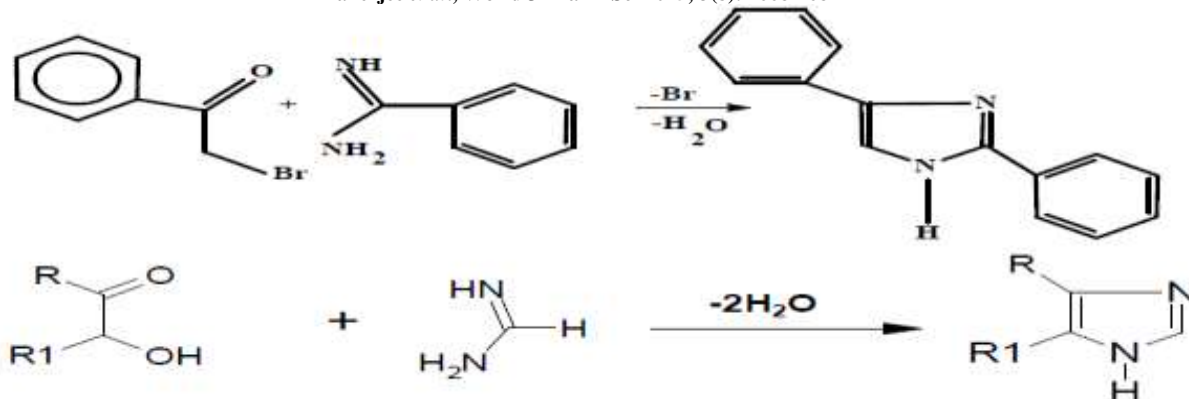
The synthesis denotes condensing a dicarbonyl compound such as glyoxal, α -keto aldehyde or α -diketones with an aldehyde in the presence of ammonia, with benzaldehyde and two molecules of ammonia react to yield 2,4,5-triphenylimidazole. Formamide often proves a convenient substitute for ammonia^[8,9,10]. In recent studies it was found that urea is also a better substitute for ammonia as a source of nitrogen.

**2) DEHYDROGENATION OF IMIDAZOLINE**

Knapp and coworkers have reported a milder reagent barium manganate for the conversion of imidazolines to imidazoles in presence of sulphur. Imidazolines obtained from alkyl nitriles and 1,2-ethanediamine on reaction with BaMnO₄ yield 2-substituted imidazoles^[11].

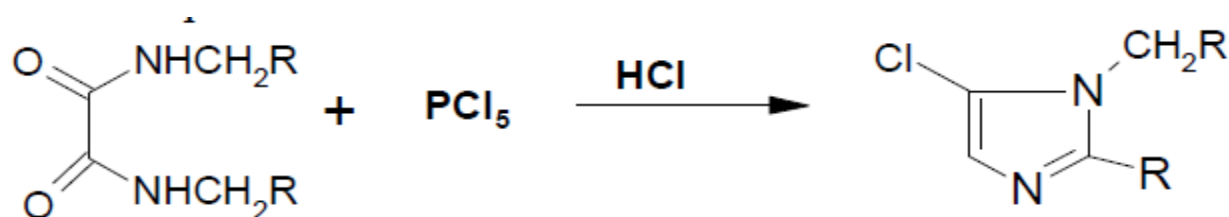
**3) FROM α -HALO KETONE**

This reaction involves an interaction between an imidine and α -halo ketones. This method was applied successfully for the synthesis of 2,4- or 2,5-biphenyl imidazole phenacyl bromide and benzimidazole according to this method afford 2,4-diphenyl imidazole. Similarly, amidine reacts with acylon or α -halo ketones to yield imidazoles^[11].



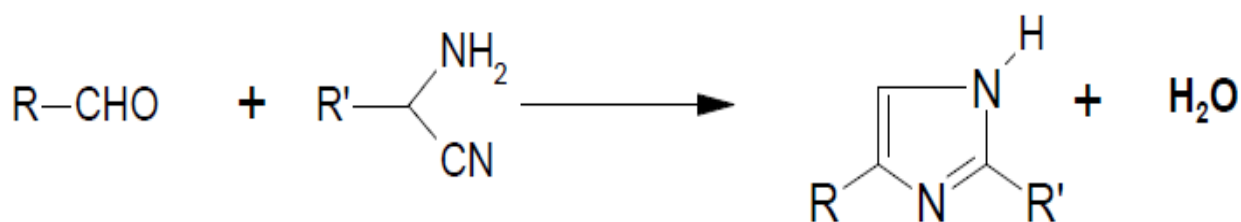
4) WALLACH SYNTHESIS

The synthesis denotes that when N, N' -dimethyloxamide is reacted with phosphorus pentachloride, a chlorine containing compound is obtained which on reduction with hydroiodic acid give N- methyl imidazole. Under the same condition N, N' -diethyloxamide is converted to a chlorine compound, which on reduction gives 1- ethyl – 2- methyl imidazole. The chlorine compound has been shown to be 5- chloral imidazole^[11-15].



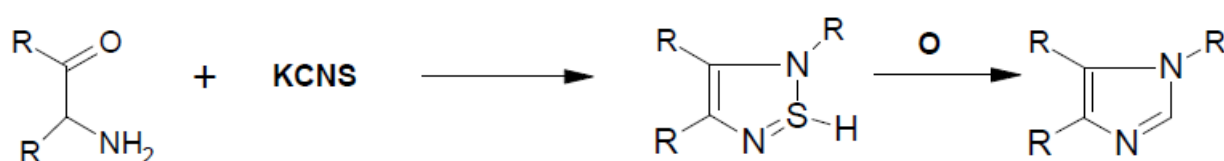
5) FROM AMINONITRILE AND ALDEHYDE

Mixture of an aldehyde and aminonitrile both condensed under suitable reaction condition to give substituted imidazole^[11].



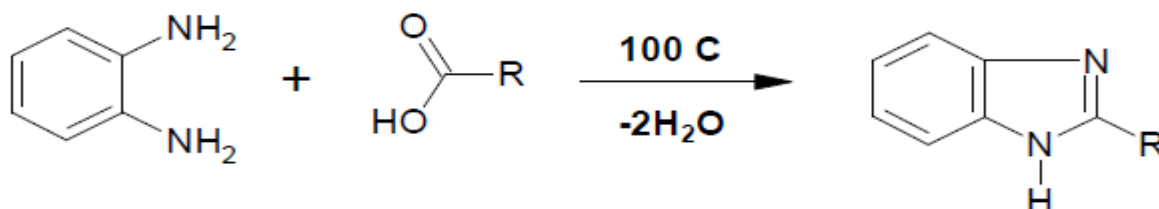
6) MARKWALD SYNTHESIS

The preparation of 2- mercaptoimidazoles from α- amino ketones or aldehyde and potassium thiocyanate or alkyl isothiocyanates is a common method for the synthesis of imidazoles. The sulfur is easily removed by a variety of oxidative methods to give the desired imidazoles.^[11].

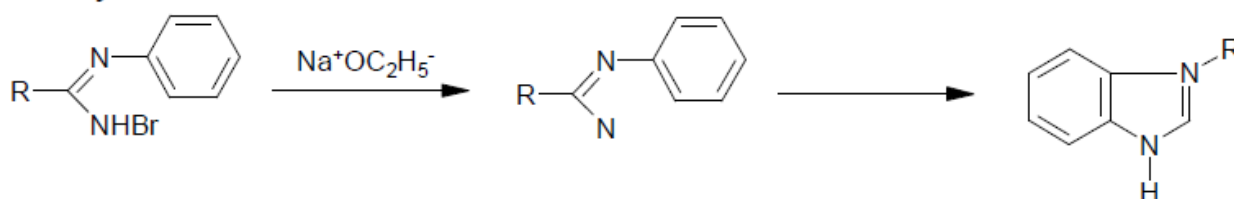


Some other methods by which imidazole and its derivatives can be synthesized

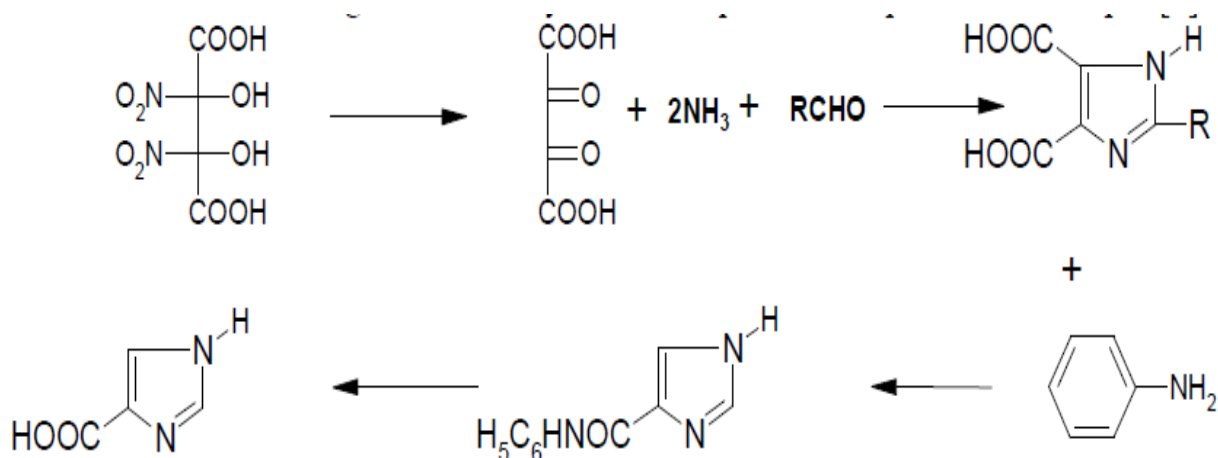
7) Benzimidazole a derivatives of imidazole is more important than imidazole as the former occur in Vit B12 and has been prepared by a number of methods, 1, 2-diaminobenzene condenses with a carboxylic acid on heating in an acidic medium to give benzimidazole



The cyclization of N-haloamidines with sodium ethoxide forms benzimidazoles (imidazole derivative) through a nitrene intermediate. ^[16]

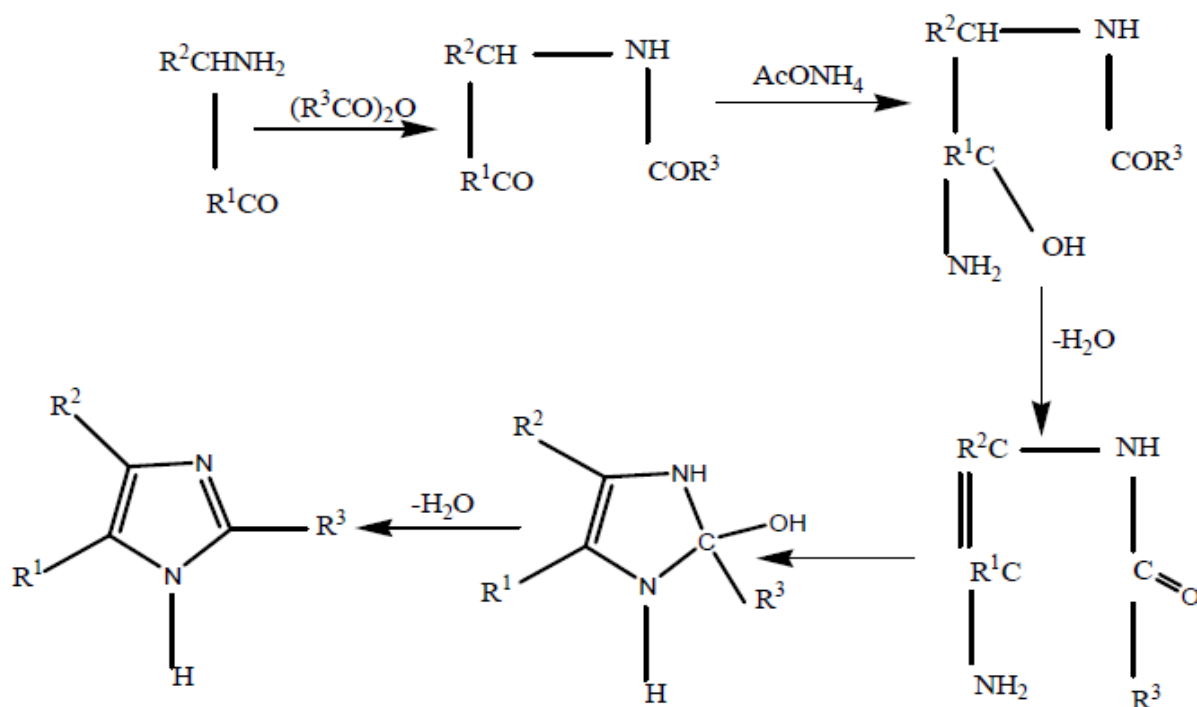


8) Imidazole can be prepared itself by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and then heating the dicarboxylic acid in quinoline in presence of copper ^[16]

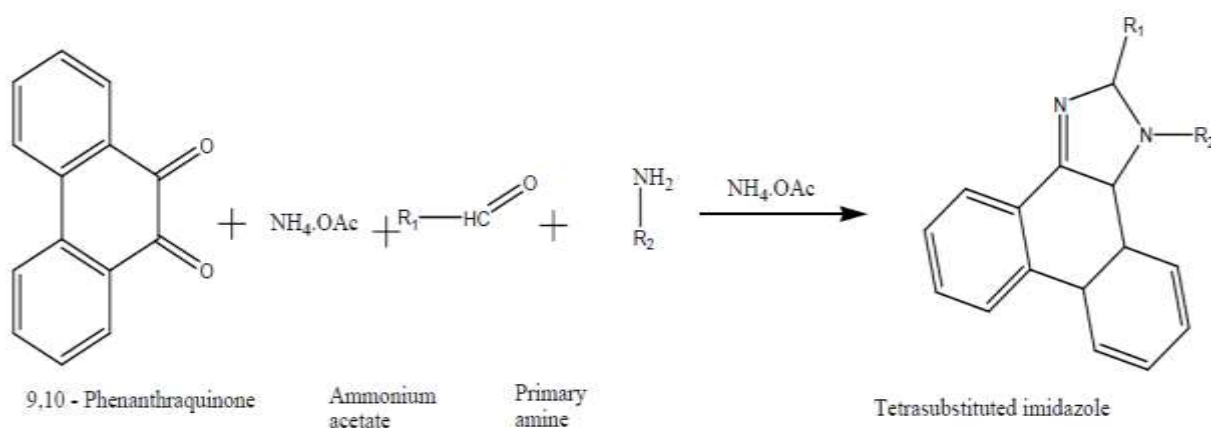


9) CYCLIZATION OF α -ACYLAMINOKETONES

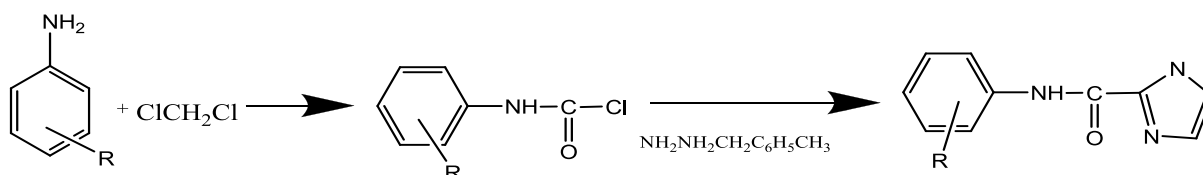
α -acylamino ketones, also behave as 1, 4-diketo compounds. This compound undergoes ready cyclization, in the presence of anhydride and ammonium acetate^[17].



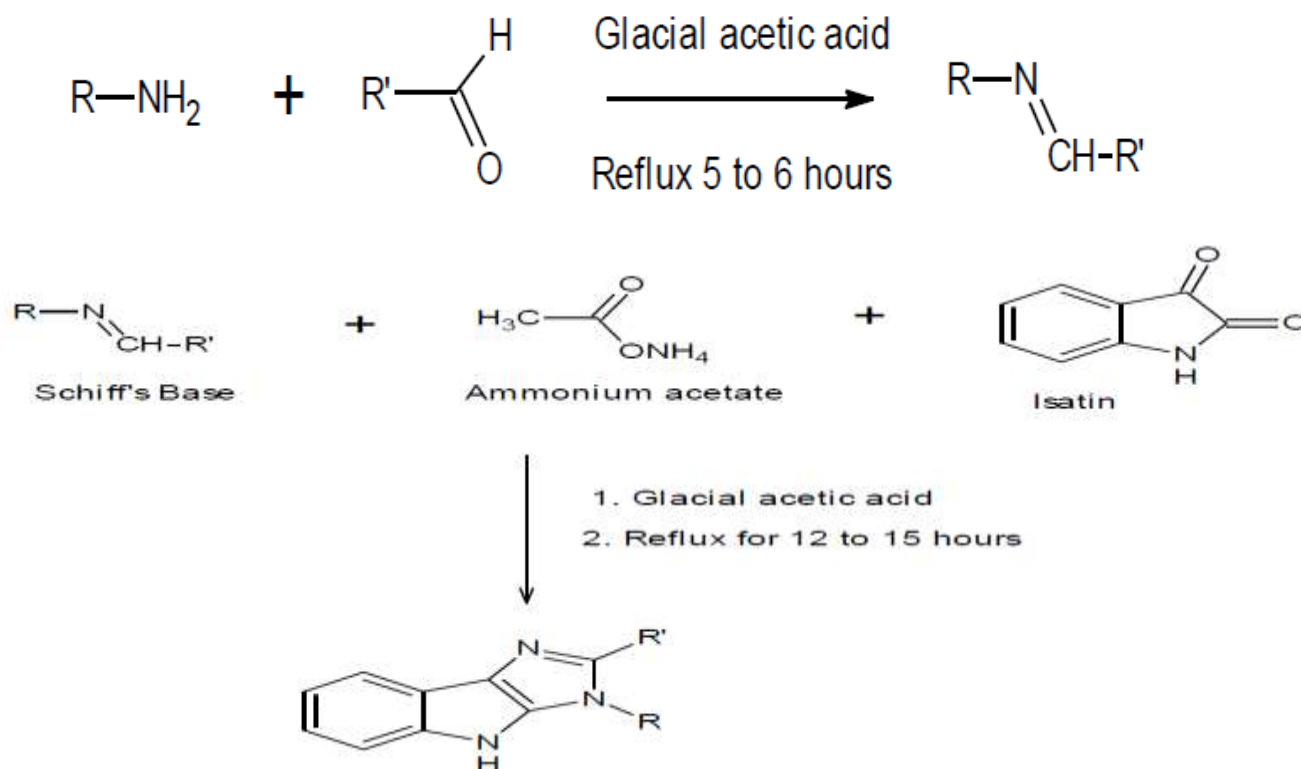
10) In this scheme, the synthesis of imidazole is carried out by refluxing 9, 10-phenanthraquinone with aryl aldehyde, primary amines and ammonium acetate in the presence of glacial acetic acid in round bottom flask for 3 hrs. Completion of reaction is checked out by TLC. ^[18]



11). In this scheme the intermediate 2-chloro-N substituted phenyl acetamide is prepared by reacting substituted aromatic amines with chloro acetyl chloride. The final product is synthesized by treating intermediate with ethylenediamine in presence of Toluene and Sulphur^[19].



12) Aryl imidazole derivatives are prepared by the condensation of compounds containing primary aromatic amine (Sulphanilamide, Sulphacetamide sodium, Sulphamethoxazole, Para-amino benzoic acid and 2-amino pyridine) with aryl aldehydes to give respective Schiff's bases, which were further treated with ammonium acetate and isatin in the presence of glacial acetic acid^[20].



BIOLOGICAL ACTIVITY

Imidazoles are considered as an important pharmacophore in medicinal chemistry encompassing wide spectrum of biological activities. On the basis of various literature surveys Imidazole derivatives shows various pharmacological activities:

- Anti fungal and Anti-bacterial activity
- Antihelmintic activity
- Anti inflammatory activity and analgesic activity
- Anti tubercular activity
- Anti depressant activity
- Anti cancer activity
- Anti viral activity
- Anticonvulsant activity
- Anti allergic activity

➤ Anti ulcer and Gastrointestinal disorder.

Table 1: Imidazole as Antifungal and Antibacterial Agent

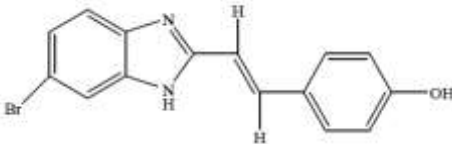
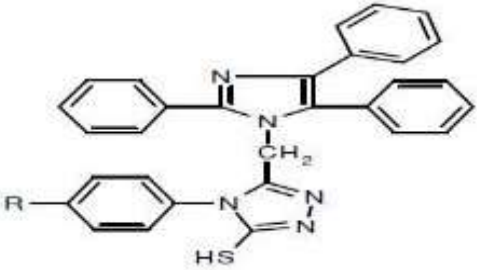
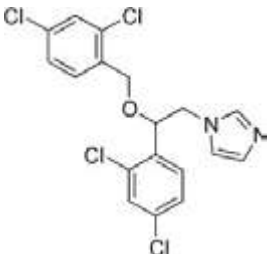
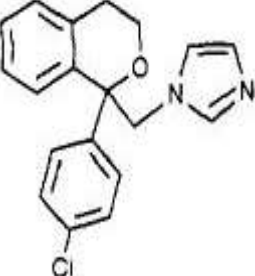
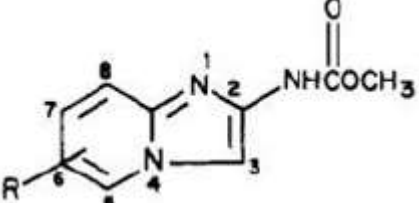
Name of Author	Structure/Compound	Active against strains
Ramya v <i>et al</i> ^[21]		Antibacterial activity against Staphylococcus aureus, Escherichia coli, Enterococcus faecalis, and Klebsiella pneumonia Enterococcus faecalis, and anti fungal activity against Candida albicans and Aspergillus fumigates.
Mohd Amir <i>et al</i> ^[22]		S. aureus, E. coli, B. subtilis, C. Albicans
Dennis Dixon <i>et al</i> ^[23]		C. albicans , C. tropicalis, C. parapsilosis.
Raymond G. Lovey <i>et al</i> ^[24] .		C. albicans C. tropicalis E. floccosum. etc.

Table 2: Imidazole as Antihelmintic agent

Name of author	Structure	Activity against
Richard J. Bochis <i>et al</i> ^[25] .		<i>pheritima posthuma</i> (earthworm)

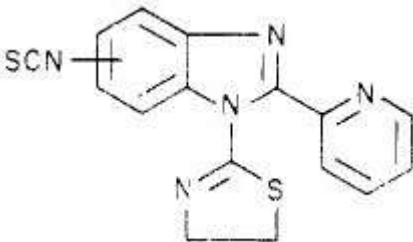
R. D. Haugwitz <i>et al.</i> ^[26]		Earthworm of <i>Eudrilis SP</i> by Garg's method.
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Table 3: Imidazole as Antiviral agent

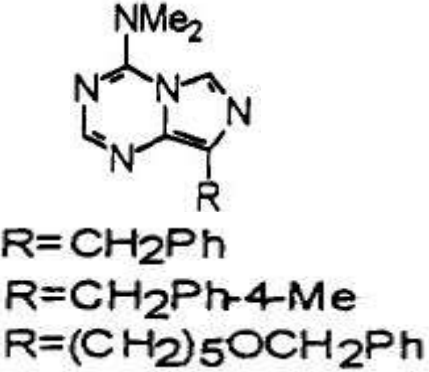
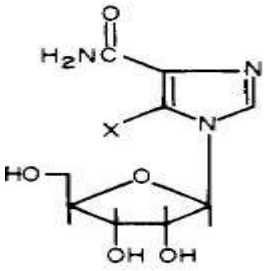
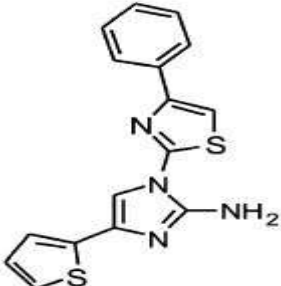
Name of autor	Structure	Activity against virus
Bozena Golankiewicz <i>et al.</i> ^[27]		VIRUS: Influenza A virus, respiratory syncytial virus.
Prem C. Srivastava <i>et al.</i> ^[28]	 <p>X = Cl X = Br X = I</p>	VIRUS: Herpes virus, rhino virus, parainfluenza virus, vaccinia virus.

Table 4: Imidazole as Anticancer agent

Name of autor	Structure	Activit against specific cellines
Wen-Tai Li <i>et al.</i> ^[29]		P 388 leukemic cells

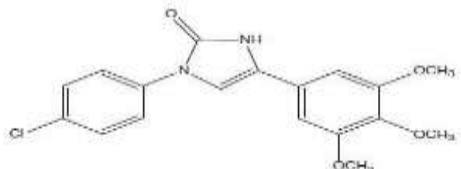
Balasubramanian Narasimhan <i>et al</i> ^[30]		NCI human cancer cell
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Table 5: Imidazole as Antituercular agent

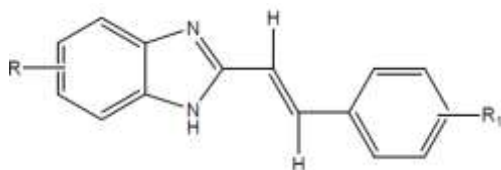
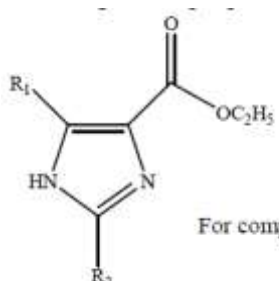
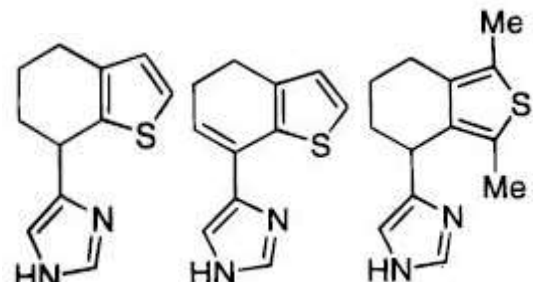
Name of author	Structure	Activity against strains
Ramya V <i>et al</i> ^[31]	 <p>For This compound A R=Br, R1=H B R=Br, R1=3,4-OCH3 C R=Br, R1=4-CH3 D R=Br, R1=2,4-Cl</p>	<i>Mycobacterium tuberculosis</i>
Preeti Gupta <i>et al</i> ^[32]	 <p>For compound 2f=R₁=R₂=c-C₅H₉ 2h=R₁=R₂=C₆H₁₁</p>	<i>M. tuberculosis</i> strains.

Table 6: Imidazole as Anti inflammatory activity and analgesic agent

Name of author	Structure
Tina M. Ross <i>et al</i> ^[33]	

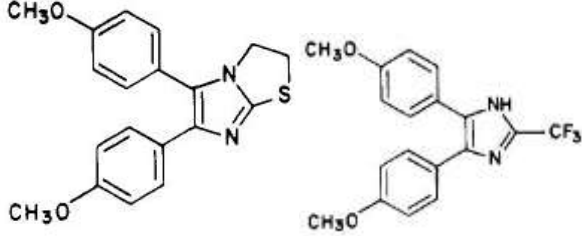
<p>Paul E. Bender <i>et al</i>^[34]</p>	
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Table 7: Imidazole as Anticonvulsant agent

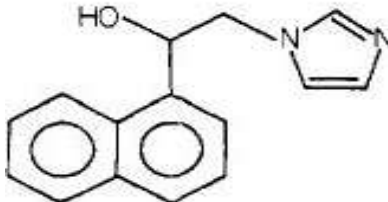
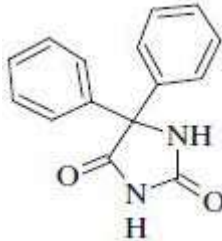
Name of Author	Structure
<p>Keith A. M. Walker <i>et al</i>^[35]</p>	
<p>Rahul Mishra <i>et al</i>^[36]</p>	

Table 8: Imidazole as Antiallergic agent

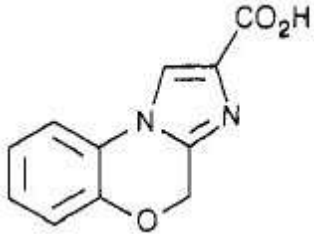
Name of Author	Structure
<p>Ian R. Ager <i>et al</i>^[37]</p>	

Table 9: Imidazole as Antiulcer agent

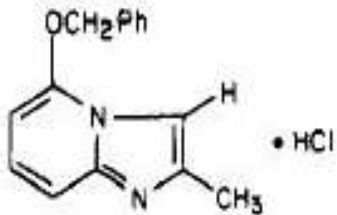
Name of author	Structure
James J. Kaminski <i>et al</i> ^[38]	

Table 10: Imidazole as Antidepressant agent

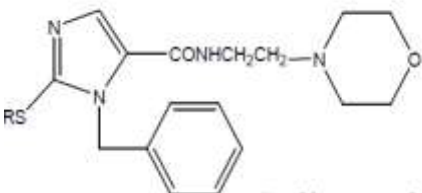
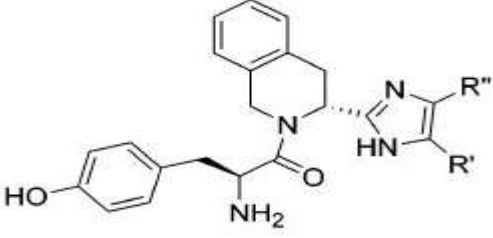
Name of author	Structure
Farzin Hadizadeh <i>et al</i> ^[39]	

Table 11: Imidazole as Gastrointestinal disorder agent

Name of author	Structure
Henry J. Breslin <i>et al</i> ^[40]	 <p>R'=Me; R''=Ph R'=Me; R''=n-Pr</p>

CONCLUSION

This article aims to review the works reported, their chemistry and biological activities of imidazole during past years. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. Having structural similarity with histidine imidazole compound can bind with protein molecules with ease compared to the some other heterocyclic moieties. Thus imidazole offers to some extent better biological and pharmacological characteristics in comparison to other heterocycles.

REFERENCES

1. Shalini K, Sharma PK, Kumar N. A review on Imidazole and its biological activities. *Der Chemica Sinica* 2010;1 (3):36-47
2. Baroniya S, Anwer Z, Sharma PK, Dudhe R, Kumar N. A review on recent advancement in imidazole as anticancer agents. *Der Pharmacia Sinica* 2010; 1 (3): 172-182
3. Ghosh R, Biplab De. Review on: Synthesis, Chemistry and Therapeutic Approaches of Imidazole Derivatives. *Int. J. Pharm. Sci. Rev. Res.*, Nov – Dec 2013,23(2), 41, 237-246, ISSN 0976 – 044X
4. Bhatnagar A, Sharma PK, Kumar N. A review on Imidazoles; Their chemistry and pharmacological potentials, *International Journal of Pharm Tech Research* 2001,3(1)268-282.
5. R. J. Bansal; *Heterocyclic Chemistry*, New Age Publishers, 2006
6. H. J. J. Loozen, J. J. M. Droven, O. Piepers. *J. Org. Chem* 1975, 40, 3279.
7. I.L. Finar. *Organic chemistry, stereochemistry and the chemistry of natural products*,5(2), ELBS longman Group Ltd., London, 2009, 614-615

8. Lunt E, Newton C.G, Smith C, Stevens G.P, Stevens M.F, Straw C.G, Walsh R.J, Warren P.J, Fizames C, Lavelle F. J. Med. Chem Feb 1987, 30 (2), 357- 66.
9. Hoffman K. Imidazoles and its derivatives. Interscience , New york ,1953, 143-145
10. Bredereck H., Gompper R., Hayer D. Chem. Ber 1959, 92, 338.
11. Robert C, Elderfield, 5- membered heterocycles combining two heteroatoms & their benzo derivatives, heterocyclic compound 1957, V-5, 744.
12. Wallach & Schuelze, Ber., 1881, 14,420-423.
13. Wallach , Ber., 1876, 184,33-35.
14. Wallach , Ber .1881, 14,735, Wallach 7 Stricker , Ber, 1880,13,51, Wallach & Schulze , Ber , 1880, 13,1514 .
15. Sarasin & Weymann, Helv. Chim, Acta, 1924, 7,720.
16. Bhatnagar A.1, Sharma P. K, Kumar N, International Journal of PharmTech Research, CODEN (USA): IJPRIF ISSN : 0974-4304
17. Finar I.L., stereochemistry and chemistry of natural products, Organic chemistry,vol 2, V thedition,622, 629.
18. Jawaharml, Lamba HS, Narwal S, Singh G, Saini ,ApramdeepKaur, Sumit DR, Narwal. Indo Global Journal of Pharmaceutical Sciences, 2012,2(2), 147-156, ISSN 2249- 1023
19. Mariapan G, Alam S, sutharsan L, Haldar PK and Shyammellendu Nath, Indian Journal of chemistry, April 213,vol 52(B) , 568-572
20. M.Prabhu, R.Radha,Asain Journal of Pharmaceutical and Clinical Research, Vol 5, Suppl 4, 2012, ISSN - 0974-2441
21. Shingalapur RV, Hosamani KM, Keri RS, European Journal of Medicinal Chemistry 2009, 44, 4244-4248.
22. Amir M, Ahsan I, Akhter W, Khan SA, Ali I. Indian Journal of Chemistry 2011,50(B),207-213.
23. Dixon D,Shadomy HJ,Espinel-Ingroff A, Kerkering TM, Comparison of the in vitro Antifungal Activities of Miconazole and a new Imidazole, R41,400,The Journal of Infectious Disease.
24. Lovey RG, Elliott AJ, Kaminski JJ, Loebenberg D, Parmegiani RM, Rane DF, Girijavallabhan VM, Pike RE, Guzik H, Antonacci B, Tomainet TY, Isobenzofurans as conformationally constrained miconazole analogues with improved antifungal potency, Journal of Medicinal Chemistry, 35, 1992, 4221-4229.
25. Bochis RJ, Olen LE, Fisher MH, Reamer RA. Isomeric phenylthioimidazo [1,2-a] pyridines as anthelmintics. Journal of Medicinal Chemistry 1981,24,1483-1487
26. Haugwitz RD, Maurer BV, Jacobs GA, Narayanan VL, Antiparasitic agents. 3. Synthesis and anthelmintic activities of novel 2-P yridinyl-5-isothiocyanatobenzimidazoles. Journal of Medicinal Chemistry 1979,22(9),1113-1118.
27. Golankiewicz B, Januszczyk SP, Ikeda S, Balzarini J, Clercq ED. Synthesis and antiviral activity of benzyl-substituted imidazo[1,5a]-1,3,5-triazine(5,8-Diaza-7,9-dideazapurine)derivatives. Journal of Medicinal Chemistry 1995,38,3558-3565.
28. Srivastava PC, Streeter DG, Matthews TR, Allen LB, Sidwell RW, Robins RK. Synthesis and antiviral and antimicrobial activity of certain 1-β-D-Ribofuranosyl-4,5-Disubstituted imidazoles. Journal of Medicinal Chemistry, 1976,19(8), 1020-1026.
29. Li WT, Hwang DR, Song JS, Chen CP, Chen TW, Lin CH, Chuu JJ, Lien TW, Hsu TA, Huang CL, Tseng H, Lin CC, Lin HL, Chang CM, Chao YS, Chen CT. Synthesis and biological evaluation of 2-amino-1-thiazolyl imidazoles as orally active anticancer agents, Invest New Drugs 2012,30, 164-175.
30. Narasimhan B, Sharma D, Kumar P. Biological importance of imidazole nucleus in the new millennium. Medicinal Chemistry Research 2011, 20, 1119-1140.
31. R. V. Shingalapur, K. M. Hosamani, R.S. Keri. European Journal of Medicinal Chemistry 2009,44,4244-4248
32. P. Gupta, S. Hameed, R. Jain, European Journal of Medicinal Chemistry.,2004,39,805-814
33. Ross TM, Jetter MC, McDonnell ME, Boyd RE, Connelly CD, Martinez RP, Lewis MA, EE, Raffa RB, Reitz AB.Journal of Medicinal Chemistry. 2000,43, 1423-1426.
34. Bender PE, Hill DT, Offen PH, Razgaitis K, Lavanchy P, Stringer OD, Sutton BM, Griswold DE, DiMartino M, Walz DT, Lantos I, Laddo CB-, Journal of Medicinal Chemistry, 1985,28, 1169-1177.
35. Walker KAM,Wallach MB, Hirschfeld DR, Journal of Medicinal Chemistry,1981,24,67-74
36. Mishra R, Ganguly S. Imidazole as an anti-epileptic: an overview. Medicinal Chemistry Research 2012, 12, 3929-3939
37. Ager IR, Barnes AC, Danswan GW, Hairsine PW, Kay DP, Kennewell PD, Matharu SS, Miller P, Robson P, Rowlands DA, Tully WR, Westwood R. Journal of Medicinal Chemistry 1988,31,1098-111
38. Kaminski JJ, Perkins DG, Frantz JD, Solomon DM, Elliott AJ, Chiu PJS, Long JF. Antiulcer agents. 3. structure- activity-toxicity relationships of substituted imidazo[1,2 a] pyridines and a related imidazo [1,2-a] pyrazine. Journal of Medicinal Chemistry 1987,30,2047-2051.
39. Hadizadeh F, Hosseinzadeh H, Sadat V, Motamed-Shariaty, M. Seifi and S. Kazemi, Iranian Journal of Pharmaceutical Research 2008, 7(1), 29-33.
40. Breslin HJ, Miskowski TA, Rafferty BM, Coutinho SV, Palmer JM,Wallace NH, Schneider CR, Kimball ES, Zhang SP, Li J, Colburn RW, Stone DJ, Martinez RP, He W. Rationale, design, and synthesis of novel phenyl imidazoles as opioid receptor agonists for gastrointestinal disorders.Journal of Medicinal Chemistry 2004,47,5009-5020.