Review Article

Review on: Synthesis, Chemistry and Therapeutic Approaches of Imidazole Derivatives

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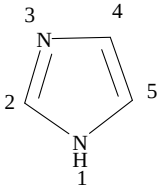
ABSTRACT

Imidazole is a planar, five membered heteroaromatic molecule with pyrrole type and pyridine type annular nitrogens. Several approaches are available for synthesis of imidazoles from alpha halo ketones, aminonitrile, aldehyde etc. Reactivity of imidazole and benzimidazole is referred from sets of resonance structure in which the dipolar contributors have finite importance. Electrophilic substitution takes place at the 2nd , 4th and 5th position in the imidazole ring, it is much less likely to become involved in nucleophilic substitution reaction unless there is a strongly electron withdrawing substituents elsewhere in the ring. This interesting group of heterocyclic compound has diverse biological activities such as antimicrobial, anticancer, analgesic, anti-inflammatory, antiviral, anthelmintic, anticonvulsant, antiulcer, anti-allergic activity etc. In the present article we review the various synthetic approaches, chemistry and biological activities reported by researchers throughout the world on imidazole.

Keywords: Imidazole, Electrophilic Substitution, Antimicrobial, Analgesic- anti-inflammatory, Antiviral.

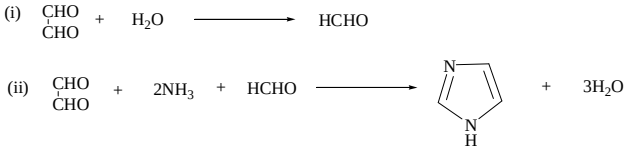
INTRODUCTION

Imidazole is a planar five-membered ring system with three (3) carbon and two (2) nitrogen atom in 1 and 3 positions. Imidazole was first named as glyoxaline. It is amphoteric in nature, susceptible to electrophilic and nucleophilic attack. It also occurs in the purine nucleus & amino acid histidine; 4-amino-imidazole-5-carboxamide occurs naturally as a riboside (or, ribotide).[1]



SYNTHESIS OF IMIDAZOLES

Imidazole may be prepared by the reaction of ammonia on glyoxal. The mechanism of this reaction was uncertain, but one suggestion had been given that one molecule of glyoxal breaks down into formic acid & formaldehyde, and then the latter reacts as follows[1]:



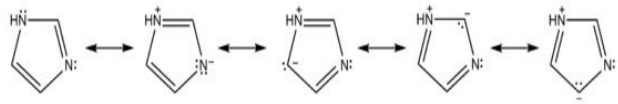
Radziszewsky explained a general method for preparing imidazoles by reaction of an α-dicarbonyl compound, ammonia & an aldehyde.[1] This method was improved by Bredereck *et al.,* who heated α-diketones with formamide & formaldehyde (or other aldehydes) at 180-200°C. Imidazole itself was best prepared by the action of ammonia on a mixture of formaldehyde & tartaric acid dinitrate (dinitrotartaric acid), and then heating the dicarboxylic acid in quinolone in the presence of copper.

All these imidazole synthesizing methods were limited in scope. So the most general method was the reaction of potassium thiocyanate on α-amino aldehydes of ketones (as hydrochlorides) & an imidazoline thione, was desulphurized with Raney nickel or by oxidation with nitric acid.[1] Another route had been developed by researchers with α-bromoketone & an amidine. Afterwards, another general method was developed to synthesize imidazole by the cyclization of α-acylaminoketones (behave as 1, 4-diketo compounds).[1] D. S. Ermolat'ev *et al*. reported one-pot microwave-assisted protocol for the synthesis of substituted 2-amino-1*H*-imidazoles.[2] Michael A. Schmidt and Martin D. Eastgate reported regioselective synthesis of 1,4-disubstituted imidazoles.[3] Zahra Rezaei *et al*. reported design, synthesis and antifungal activity of some new imidazole and triazole derivatives.[4] V. A. Chornous *et al*. mentioned 2-Aryl-4-chloro-1-methyl(aryl)-1H-imidazole-5-carbaldehydes synthesis.[5] V. A. Chornous along with A. N. Grozav and M. V. Vovk, reported synthesis of polyfunctional imidazoles;1-aryl-2,4-dihalo-1H-imidazole-5-carboxylic acids and their derivatives.[6] Biswanath das *et al*. reported synthesis of 5-substituted 2,3-diphenyl and 5-substituted 1-aryl-2,3-diphenyl imidazoles using polyethylene glycol.[7] Cheng-he zhou *et al*. prepared a series of ether bis-imidazoles and their derivatives.[8] Majid M. Heravi *et al*. reported acidic ionic liquid {$[(CH_2)_4SO_3HMIM][HSO_4]$} a green media for the simple and straight forward synthesis of 2,4,5-trisubstituted imidazoles.[9] Even Majid M. Heravi *et al*. mentioned efficient and reusable catalyst for the synthesis of 2,4,5-trisubstituted imidazoles under solvent-free conditions.[10] Sidhanath V. Bhosale *et al*. reported one-pot synthesis of 2,4,5-trisubstituted imidazoles using MoO_3/SiO_2, an efficient and recyclable catalyst.[11] Ahmad Shaabani *et al*. mentioned 1,1,3,3-N,N,N′,N′-tetramethylguanidiniumtrifluoroacetate ionic liquid–

promoted efficient one-pot synthesis of trisubstituted imidazoles.[12] Mohammad R. Mohammadizadeh *et al.* reported trifluoroacetic acid as an efficient catalyst for one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles under microwave-assisted solvent-free condition.[13]

CHEMISTRY OF IMIDAZOLE[14,15]

Imidazole is having properties similar to both pyrrole and pyridine. The electrophilic reagent would attack the unshared electron pair on N-3, but not on the 'pyrrole' nitrogen since it is the part of the aromatic sextet. Imidazole ring is susceptible to electrophilic attack on an annular carbon, it is much less likely to become involved in nucleophilic substitution reaction unless there is a strongly electron withdrawing substituents elsewhere in the ring. In the absence of such activation the position most prone to nucleophilic attack is C-2. The fused benzene ring in benzimidazoles provides sufficient electron withdrawal to allow a variety of nucleophilic substitution reaction at C-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, as evidenced by a calculated dipole of 3.61D. It is highly 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. Some resonance structures of imidazole are shown below:



Amphotericity

Imidazole is amphoteric. That is, it can function as both an acid and as a base. As an acid, the pK_a of imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is located on N-1. As a base, the pK_a of the conjugate acid is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is N-3. Protonation gives the imidazolium cation, which is symmetrical.

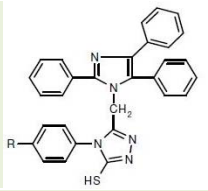
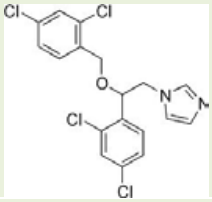
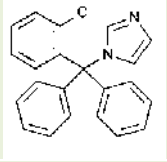
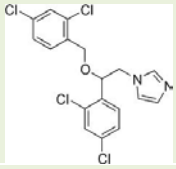
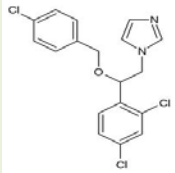
Electrophillic substitution

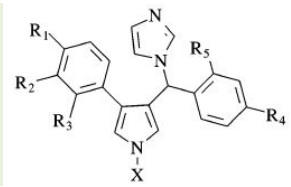
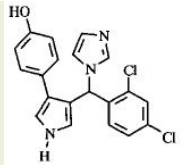
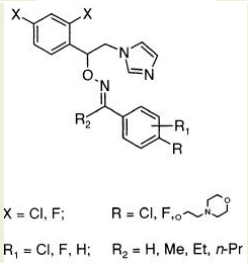
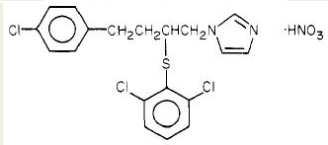
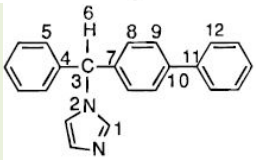
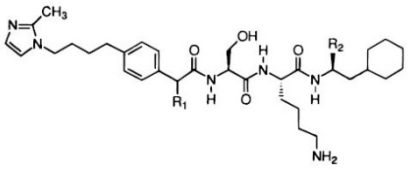
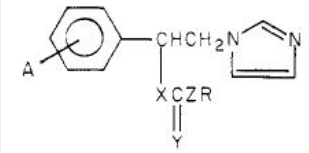
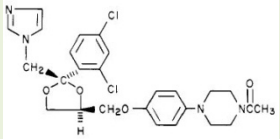
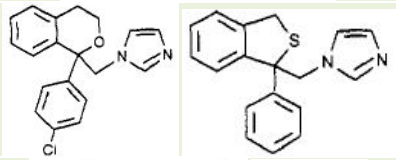
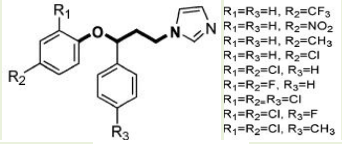
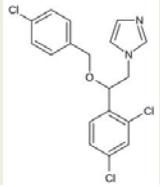
Imidazole possess increased reactivity towards electrophillic attack. It is more susceptible to electrophillic attack than pyrazole or thiazole and more so than from furan and thiophene also. It is evident that the attack takes place at the 4th and 5th position in imidazole ring. It may be noticed that the attack at C-2 involves a canonical form which is highly unfavored at positive N at position 3.

BIOLOGICAL ACTIVITY OF IMIDAZOLE

Imidazole and its derivatives could be considered as possible antimicrobial, anticancer, analgesic, antiinflammatory, antiviral, anthelmintic, anticonvulsant, antiulcer, antiallergic activity etc. This paper includes different biological activities of imidazole and its derivatives.

Table 1: Imidazole as Antimicrobial agent

Name of author	Structure / Compound	Active against strains
Mohd Amir *et al.*[16]		*S. aureus, E. coli, B. subtilis, C. albicans*.
Dennis Dixon *et al.*[17]	 Comparison of the in Vitro Antifungal Activities of Miconazole and a New Imidazole.	*C. albicans , C. tropicalis, C. parapsilosis*.
R. F. Cosgrove *et al.* [18]	  Amphotericin B in Combination with the Imidazole Antifungal Compounds Clotrimazole and Miconazole	*S. cerevisiae*
R. Wyler *et al.*[19]	 An Imidazole Derivative (Econazole) as an Antifungal Agent in Cell Culture Systems	*A fumigatus ,C albicans M pusillus, Penicillium* sp.

Roberto Di Santo *et al.*[20]		*C. albicans*
Andrea Tafi *et al.*[21]		*C. albicans*, *C. glabrata*, *C. krusei*
Armando Rossello *et al.*[22]		*C. albicans*
Keith A. M. Walker *et al.*[23]		*C. albicans*
Andrea Tafi *et al.*[24]		*C. albicans*.
Balekudru Devadas *et al.*[25]		*C. albicans*, *C. neoformans*.
Keith A. M. Walker *et al.*[26]		*M. audouini* ,*M. gypseum* *C. albicans* ,*C. neoformans* *S. aureus* ,*C. acne* etc.
J. Heeres *et al.*[27]		*M. canis*,*C. neoformans* *C. tropicalis*,*C. albicans* *P. verrucosa*, *E. insidiosa*
Raymond G. Lovey *et al.*[28]		*C. albicans* *C. tropicalis* *E. floccosum.* etc.
Romano Silvestri *et al.*[29]		*C. albicans*
R. Wyler *et al.*[30]		*A. fumigatus* *C. albicans* *Penicillium sp*.

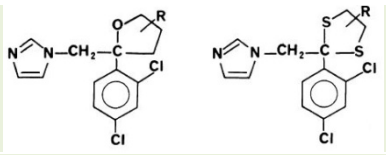
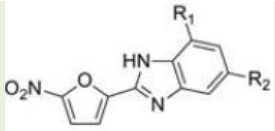
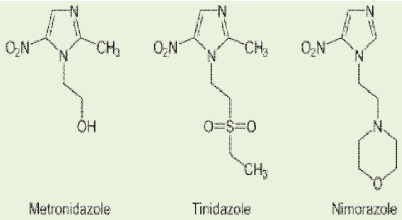
K. Richardson *et al.* [31]		*C. albicans*
Andreas Schaffne *et al.* [32]	Ketoconazole	*Aspergillus fumigatus* *A. flavus, A. niger*
Garrett C Moraski [33]		*E. coli* *P. aeruginosa* *S. aureus*
R. J. Knox[34]	 Metronidazole Tinidazole Nimorazole	*E. coli*

Table 2: Imidazole as anticancer agent

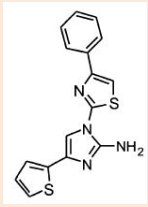
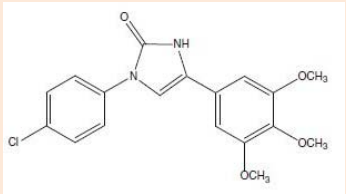
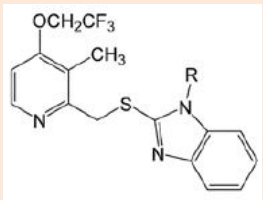
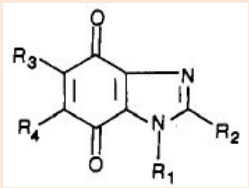
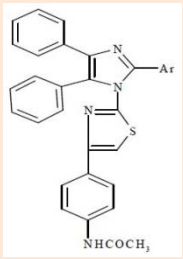
Name of author	Structure / Compound	Active against specific celllines
B.K. Keppler *et al.* [35]	Bis(imidazolium) (Imidazole)pentachlorouthenate	P 388 Leukemia
Wen-Tai Li *et al.*[36]		P 388 leukemic cells
Balasubramanian Narasimhan *et al.*[37]		NCI human cancer cell
S. R. Ranganatha *et al.*[38]		Human leukemia cell lines, K562 and CEM
Ippolito Antonini *et al.* [39]		P 388 leukemia
Gyanendra Kumar Sharma *et al.* [40]		DLA cells and EAC cells

Table 3: Imidazole as Analgesic & Anti-inflammatory agent

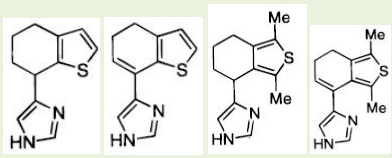
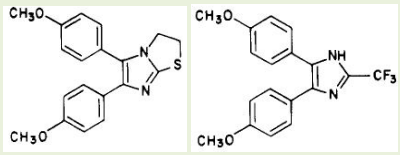
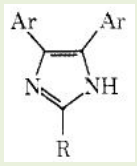
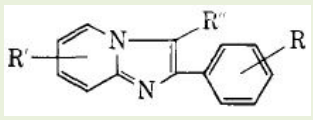
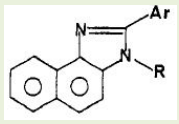
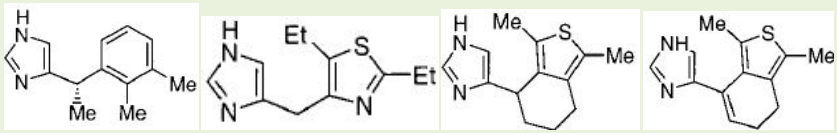
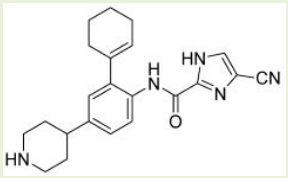
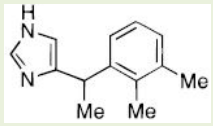
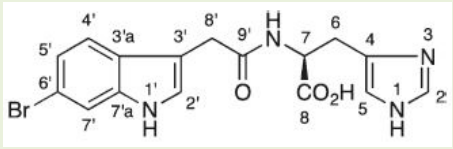
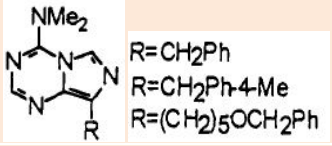
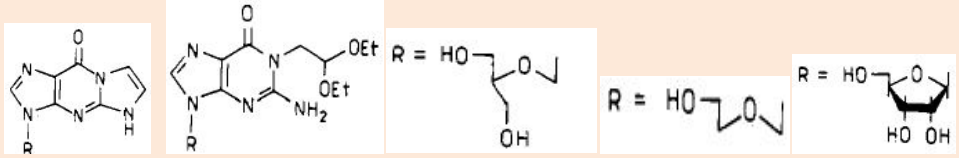
Name of author	Structure
Tina M. Ross *et al.* [41]	
Paul E. Bender *et al.*[42]	
Joseph G. Lombardino *et al.*[43]	
Luigi Almirante *et al.* [44]	
Emilio Toja *et al.* [45]	
Robert E. Boyd *et al.* [46]	
Carl R. Illig *et al.* [47]	
Robert E. Boyd *et al.*[48]	
Andre J. Zaharenko *et al*[49]	

Table 4: Imidazole as Antiviral agent

Name of author	Structure; Activity against virus
Bozenna Golankiewicz *et al.* [50]	 VIRUS: Influenza **A** virus, respiratory syncytial virus.
Jerzy Boryski *et al.*[51]	 VIRUS: DNA viruses including herpes simplex virus (HSV-1 , HSV-2) ,vaccinia virus,varicella-zoster virus, cytomegalo virus.

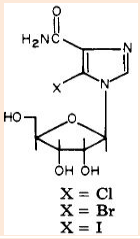
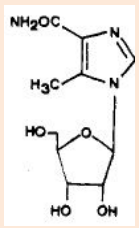
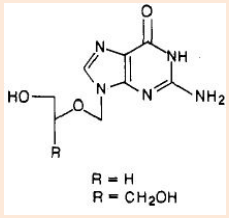
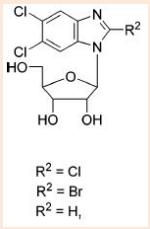
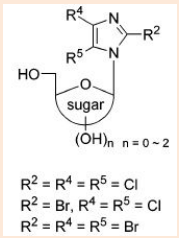
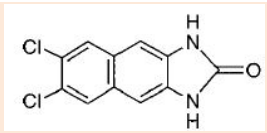
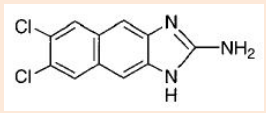
Prem C. Srivastava *et al.*[52]	 X = Cl X = Br X = I	VIRUS: Herpes virus, rhino virus, parainfluenza virus, vaccinia virus.
Rosario Alonso *et al.* [53]		VIRUS: Herpes simplex virus type 1 (HSV-1) and vesicular stomatitis virus.
Jerzy Boryski *et al.* [54]	 R = H R = CH_2OH	VIRUS: HSV-1 and HSV-2
Tun-Cheng Chien *et al.*[55]	 R^2 = Cl R^2 = Br R^2 = H,  $R^2 = R^4 = R^5$ = Cl R^2 = Br, $R^4 = R^5$ = Cl $R^2 = R^4 = R^5$ = Br	VIRUS: Herpes simplex virus type-1(HSV-1), human cytomegalovirus (HCMV).
Zhijian Zhu *et al.* [56]	  VIRUS:Human cytomegalovirus (HCMV)	

Table 5: Imidazole as Anthelmintic Agent[57-59] & Antitrichomonal Agent[60]

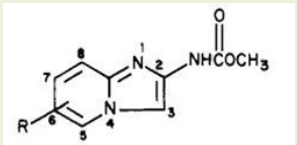
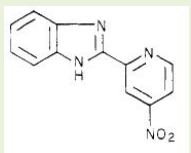
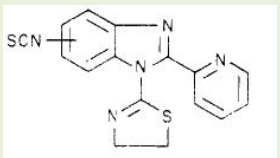
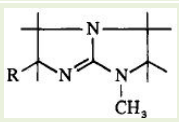
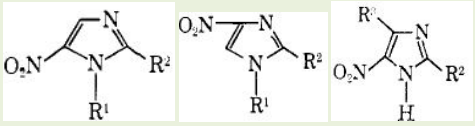
Name of author	Structure
Richard J. Bochis *et al.* [57]	
R. D. Haugwitz *et al.*[58]	 
Laird F. Miller *et al.*[59]	
K. Butler *et al.*[60]	

Table 6: Imidazole as Anticonvulsant Agent

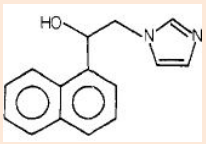
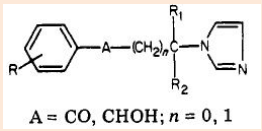
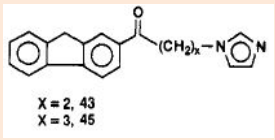
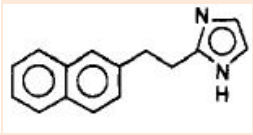
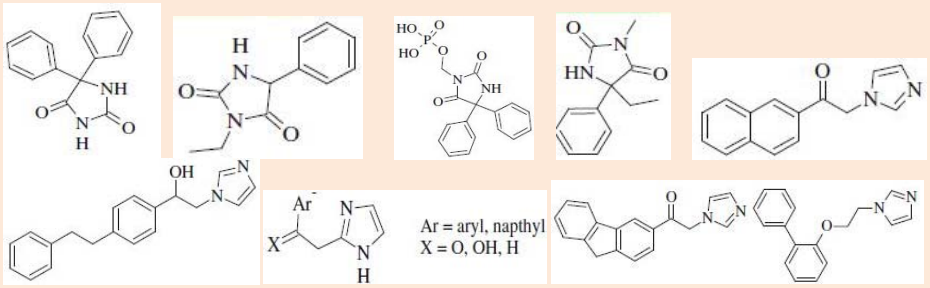
Name of author	Structure
Keith A. M. Walker *et al.* [61]	
Dante Nardi *et al.*[62]	
David W. Robertson *et al.*[63]	 
Rahul Mishra *et al.* [64]	

Table 7: Imidazole as Antiulcer Agent [65] & Agonists for Gastrointestinal Disorders [66]

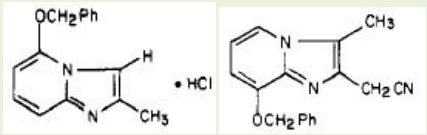
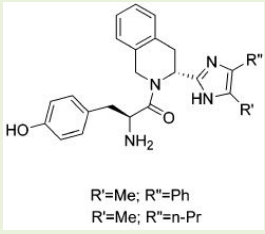
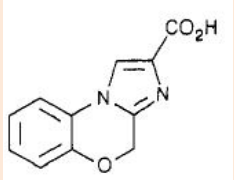
Name of author	Structure
James J. Kaminski *et al.*[65]	
Henry J. Breslin *et al.*[66]	

Table 8: Imidazole as Antiallergic Agent

Name of author	Structure
Ian R. Ager *et al.* [67]	

CONCLUSION

Imidazole is a five membered heterocyclic compound. There were so many different conventional methods to synthesize imidazole and its derivatives by researchers, where dicarbonyl compound, ammonia & aldehyde were found to be good starting materials for the synthesis of imidazole; even microwave assisted synthesis, regioselective synthesis were well documented. On the basis of the literature it was found that imidazole was synthesized under solvent free condition with the help of efficient and reusable catalyst & good yield was achieved using ammonium acetate along with polyethylene glycol. Imidazole is a base in nature due to nitrogen atom. It under goes electrophilic substitution but nucleophilic substitution is rare one. From the extensive literature

survey it was found that it has antimicrobial, anticancer, analgesic , antiinflammatory, anticonvulsant, antiviral, anthelmintic, antiulcer, antiallergic activity etc. So from the above discussion it can be concluded that imidazole is a therapeutically active versatile moiety, which had been exploited in the past years for synthesizing various compounds having diverse pharmacological activities, and still imidazole can be further utilized for the future prospective against various diseases or disorders.

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