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Studies on Imidazole and its Derivatives with Particular Emphasis on Their Chemical/biological Applications as Bioactive Molecules/Intermediated to Bioactive Molecule

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Abstract

Imidazoles are heterocycles with five-member ring structure heterocyclic compounds have gained very remarkable place in recent years because of their exceptional pharmacological activities. The imidazole nucleus is a main synthetic strategy in drug discovery. Imidazole is a planar five-member ring system having N atom at 1 and 3 positions. The systemic name for the compound is 1, 3 diazoles, one of the N bear an H atom and other to be termed as a pyrrole type N. Imidazole was first named as glyoxaline. It is amphoteric in nature, and it has susceptibility to be attacked by electrophile and nucleophile. It is a constituent of the purine nucleus and histidine amino acid, 4-amino imidazole-5- carboxamide found naturally as a riboside. This interesting group of heterocyclic compounds has wide range biological activities such as, analgesic, anti-inflammatory anticancer, antiviral, anthelmintic, anticonvulsant, antiulcer, antimicrobial, anti-allergic activity etc. Various methods employed for the synthesis of imidazole's and their chemical structure reactions offer enormous scope in the field of medicinal chemistry.

Keywords: Imidazole; Heterocyclic; Aromatic; Anti-convulsant; Anti-ulcer; Anti-allergic; Anti-viral

Introduction

Imidazole is a five-member heterocyclic aromatic compound in which two Nitrogen atoms are present both Nitrogen atom are sp^2 hybridized. Imidazole ring contains two types of lone-pair one is delocalized and second is non-delocalized (Non-Huckle-lone pair) due to this both Nitrogen has different pka. The Nitrogen has delocalized lone-pair has pka=7 and other nitrogen which has non- delocalized lone- pair has pka=14.9. Hence Imidazole is amphoteric in nature i.e., it work as both acid and base, susceptible to nucleophilic and electrophilic attack [1]. Imidazole generally is colourless or pale yellow solid, has amine like order, it is an aromatic heterocycle, categorized as a diazole and as an alkaloid. It is water soluble and other polar solvents. It occurs in two equivalent tautomericn forms because the hydrogen atom can be located on either of the two nitrogen atoms. The melting point imidazole is 88.9°C and the boiling point is 267.8°C. Imidazole is polar in nature and its dipole moment is 4.8 Debye, The molecular formula is $C_3H_4N_2$ and the structural formula is as shown in Figure 1 [2,3]. Imidazoles are a class of heterocycles with five-member ring structure, but variable substituents. This ring system is present in significant biological skeleton, like histidine and the associated hormone histamine. Imidazole can serve as a weak acid as well as base. Many drugs have an imidazole ring, like Nitro imidazole and anti-fungal drugs [4]. Heterocyclic compounds are also having utility in agriculture and pharmacy. Analysis of research manuscript in the last ten decades exposed that there is an overall trend in research for novel drugs involving modified of existing biologically vigorous matrices and molecular strategy of the structures of compounds. The imidazoles nucleus is a significant synthetic technique in drug discovery. Imidazole derivatives show anti-inflammatory, anticancer, antimicrobial, analgesic, and anti-tubercular activity. One of the most vital features of imidazole derivatives is their use as material for action of denture stomatities. The high beneficial properties of the imidazole associated drugs have encouraged the medicinal chemists to prepare a large number of new chemotherapeutic materials. Imidazole drugs have wide scope in pharmaceutical field. Medicinal characteristics of imidazoles include anti-coagulants, anti-cancer, anti-fungal, anti-inflammatory, anti-bacterial, anti-viral, anti-diabetic, anti-malarial and anti-tubercular [5-9]. Imidazole derivatives are reported to be pharmacologically and physiologically active and it is used in the treatment of several diseases. Imidazoles as constituent are found in component in a large number of natural products and clinical active molecules i.e., a large numbers of drug contain the imidazole ring, containing ketoconazole which have application to treat, bacterial infections, gastric ulcers and fungal infections. Due to their significance, it has become a suitable target for the synthetic and clinical. There are many techniques that have been established for assembling and modifying the imidazole ring with different functional groups [10]. The basic site is N-3. Synthesis Several types of 2-imidazolines are pharmaceutically and biologically very indispensable, since many imidazoline derivatives have antidiabetic, anti-inflammatory and antihypertensive, action. Its application for medicinal purpose it also has many applications in pharmaceutical

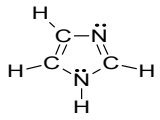

Figure 1: Structural formula of $C_3H_4N_2$.

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industries. Imidazolines are synthetically indispensable due to their use as a synthetic intermediates, catalysts, chiral catalysts, chiral auxiliaries, and ligands for asymmetric catalysis in different synthetic reactions. There are several synthetic methods for 2-imidazolines from ethylenediamine and aldehydes with NBS Some methods of synthesis from acids carboxylic nitriles, ortho-esters, esters, mono or di-substituted chloro-di-cyano vinyl benzene and hydroxy-amides [11-15]. Imidazole is an IUPAC name and synonyms of this compound are below which are also suggested by IUPAC system.

(1) 1,3 – diazo – 2,4 – cyclo pentadiene.

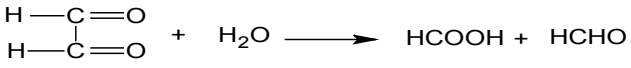
(2) 1,3 – diazole.

(3) Glyoxalin.

(4) Miazole.

Since Imidazole first time synthesized by glyoxal and ammonia so it's first named as glyoxaline.

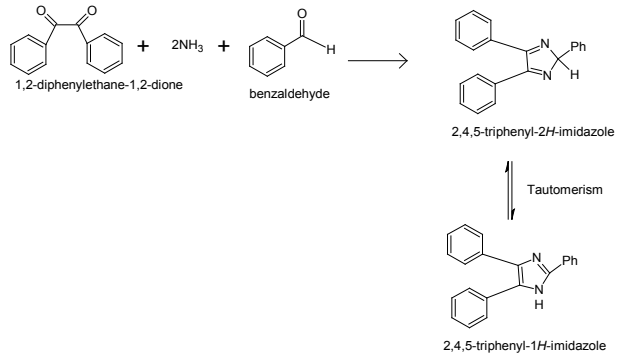
The mechanism of the preparation of glyoxaline from glyoxal and ammonia was uncertain. But according to suggested mechanism, first of all the molecules of glyoxal break down into formaldehyde and formic acid, after the formation of aldehyde, glyoxalin is prepared by following reaction:



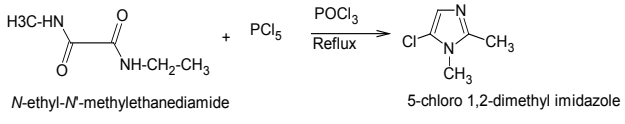
Imidazole ring is present as a constituent in several natural products like: Histidine, histamine, purine and nucleic acid etc. Some important natural product with their structure is given below in which imidazole ring is present as a constituent [16] and Natural product [17-20].

Synthesis of imidazole and their derivatives

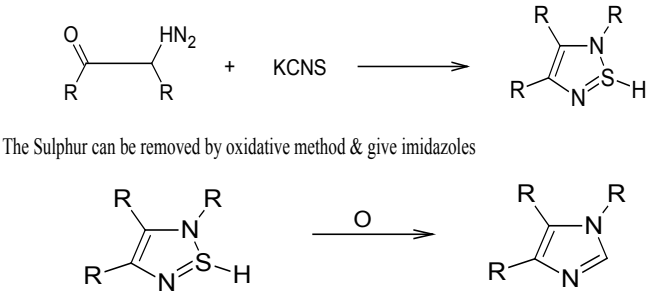
Reserchers, all over the reputed labs across the world, have investigated biological and physiological action of imidazole by synthesizing its derivatives. First time imidazole was prepared in 1858. Now-a-days several methods of sythesis of imidazoles are available some of these are given below in Schemes 1-9 [20-29].



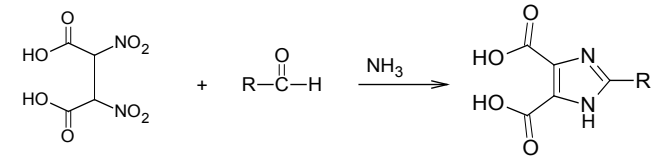
Scheme 1: Re-Diszewski synthesis [20-22].



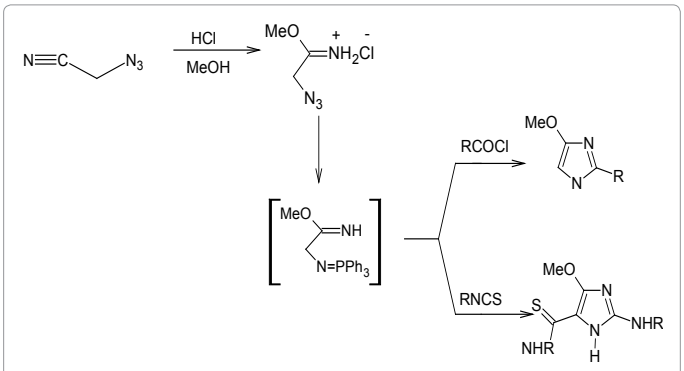
Scheme 2: Wallach synthesis [23-26].



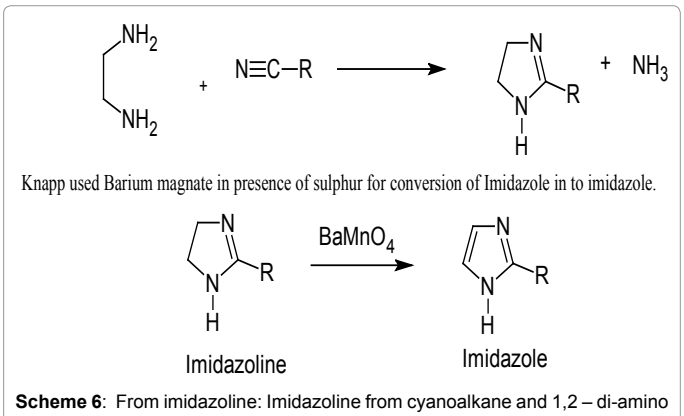
Scheme 3: Markwald synthesis [23].



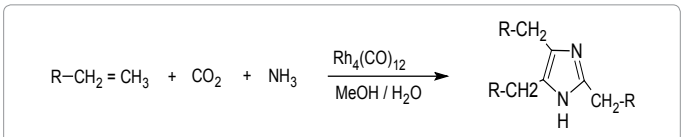
Scheme 4: Maquenne synthesis [27].



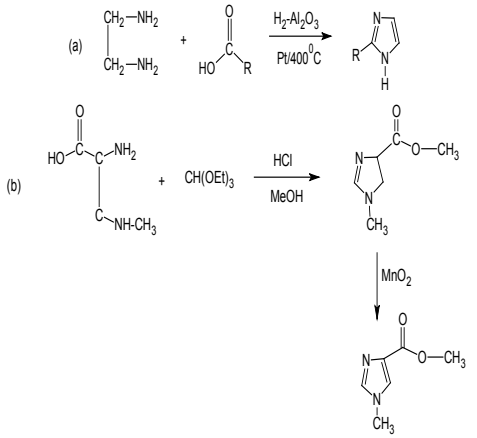
Scheme 5: Pinner salt method [23].



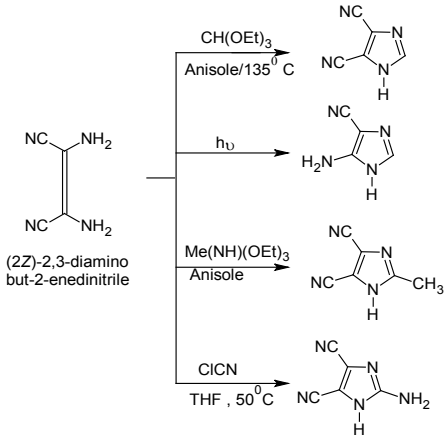
Scheme 6: From imidazoline: Imidazoline from cyanoalkane and 1,2 – di-amino ethane.



Scheme 7: From alkene, carbon monoxide and ammonia [25].



Scheme 8: From 1,2-diaminoalkanes [27].



Scheme 9: From di-amino maleonitrile (DAMN) [28,29].

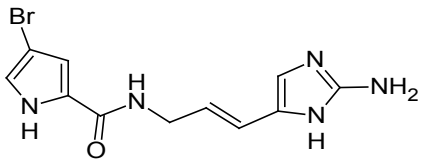
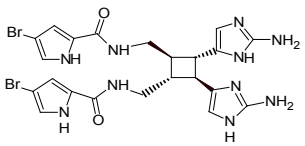
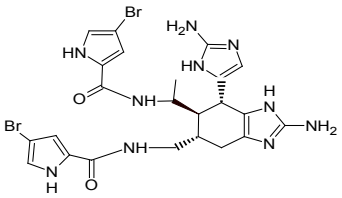
Biological action of imidazole containing compounds

There are so many Imidazole ring containing compounds that manifest various types of physiological,biological and pharmaological activities such as: Anti-carcinogen, anti-bacterial, anti-fungal, anti- viral, anti-HIV agents, anti- ulcer agent, anti-leishmanial, anti-microbial, anti-convulsant, anti-protozoal, anti-allergic, anti-inflammatory, analgesic, anxiolytic, anti-diabetic activities and etc.

Imidazole has wide range of biological activities. The drugs which contain of imidazole act on different type of receptors. For example, dopamine receptor, histaminic receptor, adreno-receptor, etc. The pharmacogical activity of some important imidazole contaning compounds with their particular biological action, structure and name are given below in Tables 1 and 2 [30-54].

Discussion

Heterocyclic compounds have gained very remarkable place in recent years because of their exceptional pharmacological activities. The imidazole nucleus is an imain synthetic strategy in drug. Imidazole is the heterocyclic aromatic compound, out of which three are carbon and therest of two are nitrogen, located at 1 and 3 positions. It is the part of several natural compounds like histamine, histidine, biotin, alkaloids, nucleic acid are very significant class among the medicinal compounds. Imidazole moiety have been most frequently studied, many of its parallel compounds are active against various pathologens, which are presented in brief in this article. Imidazole is less penetrating in extra duodenal parasites particularly, intravascular and intestinal dwelling parasites than stomach parasites. This member of class 2-alkyl benzimidazole are thought to be the most effective ones, has been originate to remove numerous species of nematodes and trematodes from diverse hosts thus various compounds have been synthesized custody 2-alkyl benzimidazole as basic moiety. One of the other possible actions which are presented in this manuscript is anti-inflammatory action; amino acids are supposed to be powerful for any sort of annoyances or edema allied with it. A Study is done in regard to

S. No	Name of the compound	Structures
1	Oroidin	
2	Sceptrin	
3	Ageliferin	

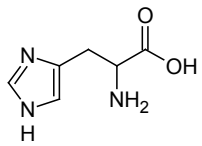
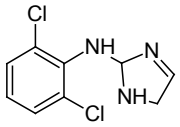
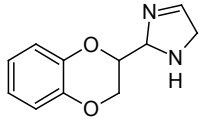
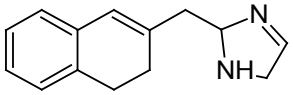
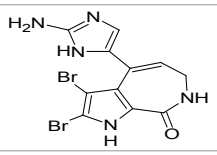
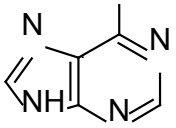
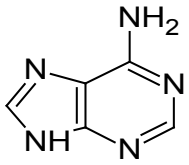
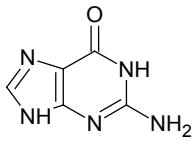
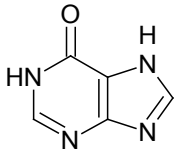
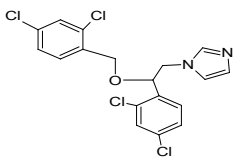
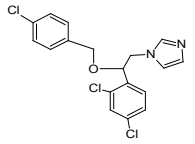
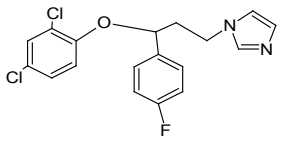
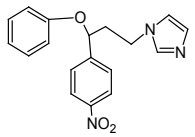
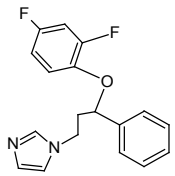
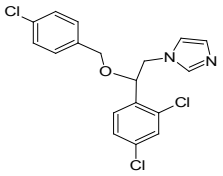
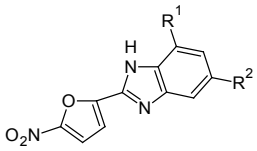
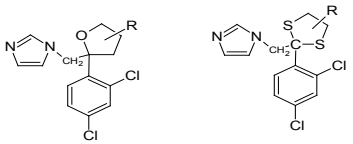
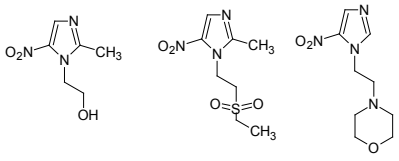
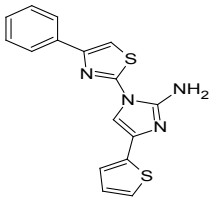
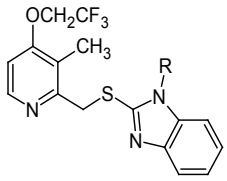
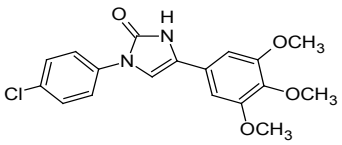
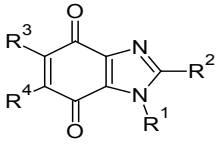
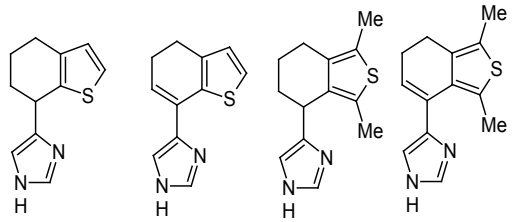
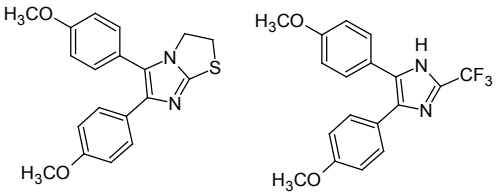
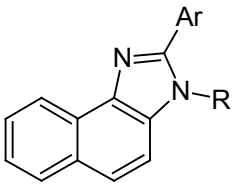
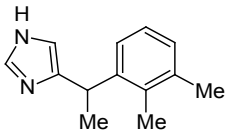
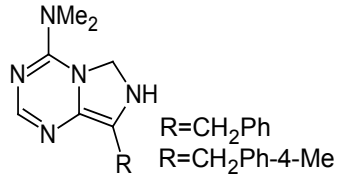
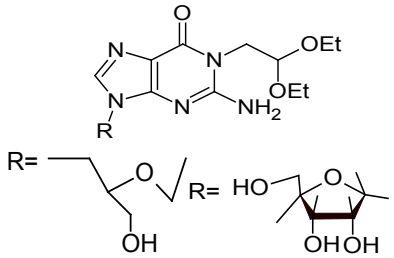
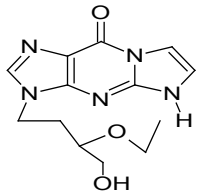
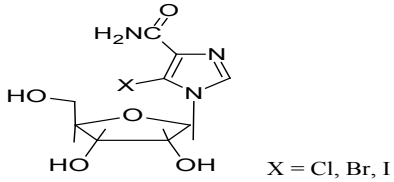
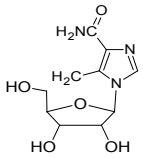
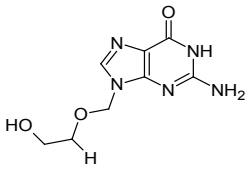
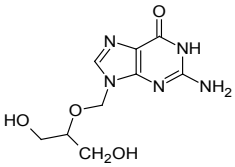
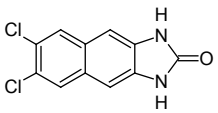
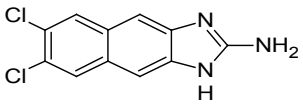
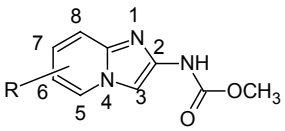
4	Histidine	
5	Clonidine	
6	Idazoxan	
7	Napamazole	
8	Stevensine	
9	Xanthine	
10	Adenine	
11	Guanine	
12	Hypoxanthine	

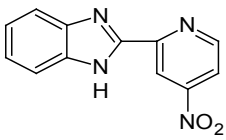
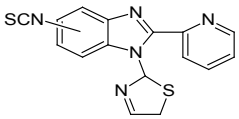
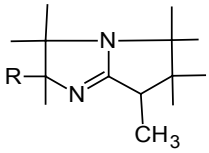
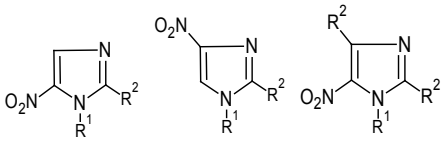
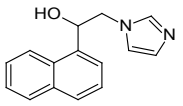
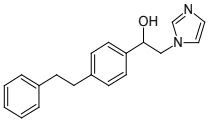
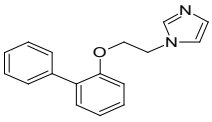
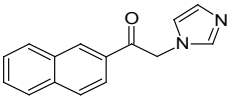
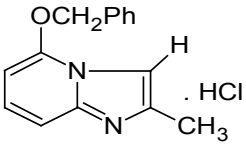
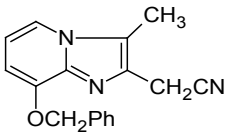
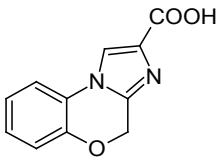
Table 1: The chemical structure profile of compounds.

S. No	Structure of compounds	Name of compounds	Uses
1	[30] 	1-{2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1H-imidazole	Antimicrobial agent [Active against *C. albicans, C. tropicalis*]

2	[31]		1-{2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole	Antimicrobial agent [Active against *Penicillium* species]
3	[31]		1-[3-(2,4-dichlorophenoxy)-3-(4-fluorophenyl) propyl]-1*H*-imidazole	Anti-microbial agent [Active against *C. albicans*]
4	[30]		1-[3-(4-nitrophenyl)-3-phenoxypropyl]-1*H*-imidazole	Antimicrobial agent [Active against *C. albicans*]
5	[31]		1-[3-(2,4-difluorophenoxy)-3-phenylpropyl]-1*H*-imidazole	Antimicrobial agent [Active against *C. albicans*]
6	[32]		-{2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole (Econazole) an imidazole derivative as an antifungal agent.	Antimicrobial agent [Active against *M. pusillus, penicillium* species]
7	[33]		--	Anti-microbial agent [Active against *E. coli* , *S. aureus*]
8	[34]		--	Antimicrobial agent [Active against *C. albicans*]
9	[35]		--	Anti-microbial agent [active against *E. coli*]
10	[36]		--	Anticancer agent [Active against P 388 leukemic cell]

11	[37]		--	Anti-cancer agent [Active against Human leukemia cell lines, K562 and CEM]
12	[38]		1-(4-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2*H*-imidazol-2-one	Anticancer agent [Active against NCI Human cancer cell]
13	[39]		--	Anticancer agent [Active against P 388 leukemia
14	[40]		(A) 4-(4,5,6,7-tetrahydro-1-benzothiophen-7-yl)-1*H*imidazole (B) 4-(4,5-dihydro-1-benzothiophen-7-yl)-1*H*imidazole (C) 4-(1,3-dimethyl-4,5,6,7-tetrahydro-2-benzothiophen-4-yl)-1*H*-imidazole (D) 4-(1,3-dimethyl-6,7-dihydro-2-benzothiophen-4-yl)-1*H*-imidazole	Act as anti-inflammatory agent and analgesic
15	[41]		A) 5,6-bis(4-methoxyphenyl)-2,3-dihydroimidazo[2,1-*b*][1,3]thiazole B) 4,5-bis(4-methoxyphenyl)-2-(trifluoromethyl)-1*H*-imidazole	Act as anti-inflammatory agent and analgesic
16	[42]		3-alkyl-2-aryl-3*H*-naphtho [1,2-*d*]imidazole	Act as anti-inflammatory agent and analgesic
17	[43]		4-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole	Act as anti-inflammatory agent and analgesic
18	[44]		8-alkyl-*N*,*N*-dimethyl-6,7-dihydroimidazo[1,5-*a*][1,3,5]triazin-4-amine	Act as antiviral Active against influenza A virus, respiratory syncytial virus

19	[44]		--	Act as antiviral [Active against DNA viruses , including herpes simplex virus (HSV – 1 , HSV – 2) , Cytomegalo virus]
20	[45]		3-(3-ethoxy-4-hydroxybutyl)-3,5-dihydro-9*H*-imidazo[1,2-*a*]purin-9-one	Act as antiviral [Active against DNA viruses , including herpes simplex virus (HSV – 1 , HSV – 2) , Cytomegalo virus]
21	[46]		--	Act as antiviral [Active against rhino virus, herpes virus,vaccina virus, parainfluenza virus]
22	[47]		--	Act as antiviral [Active against Vesicular stomatitis virus and herpes simplex virus type-1 (HSV-1)]
23	[48]		2-amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one	Act as antiviral [Active against HSV-1 and HSV-2]
24	[48]		2-amino-9-{[(1,3-dihydroxypropan-2-yl)oxy] methyl}-1,9-dihydro-6*H*-purin-6-one	Act as antiviral [Active against HSV-1 and HSV-2]
25	[49]		6,7-dichloro-1,3-dihydro-2*H*-naphtho[2,3-*d*] imidazol-2-one	Act as antiviral [Active against Human Cytomegalovirus (HCMV)]
26	[49]		6,7-dichloro-1*H*-naphtho[2,3-*d*]imidazol-2-amine	Act as antiviral [Active against Human Cytomegalovirus (HCMV)]
27	[50]		--	Act as Anti-helmintic Agent & antitrichomonal agent

28	[51]		2-(4-nitropyridin-2-yl)-1*H*-benzimidazole	A CT as Anti-helmintic agent and anti-trichomonal agent
29	[51]		1-(2,5-dihydro-1,3-thiazol-2-yl)-2-(pyridin-2-yl)-1*H*-benzimidazole	Act as anti-helmintic Agent and Antitrichomonal Agent
30	[52]		--	Act as anti-helmintic Agent and Anti-trichomonal Agent
31	[53]		2-(1*H*-imidazol-1-yl)-1-(naphthalen-1-yl) ethanol	Act as anti-convulsant agent
32	[53]		2-(1*H*-imidazol-1-yl)-1-(naphthalen-1-yl) ethanol	Act as anticonvulsant agent
33	[54]		-- 2-(1*H*-imidazol-1-yl)-1-[4-(2-phenylethyl) phenyl]ethanol	Act as anticonvulsant agent
34	[55]		1-[2-(biphenyl-2-yloxy)ethyl]-1*H*-imidazole	Act as anticonvulsant agent
35	[52]		2-(1*H*-imidazol-1-yl)-1-(naphthalen-2-yl) ethanone	Act as anticonvulsant agent
36	[53]		5-(benzyloxy)-2-methylimidazo [1,2-*a*]pyridine	Act as antiulcer agent and agonists gastrointestinal disorder
37	[53]		[8-(benzyloxy)-3-methylimidazo[1,2-*a*]pyridin- 2-yl]acetonitrile	Act as antiulcer agent and agonists gastrointestinal disorder
38	[54]		4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2- carboxylic acid	Act as anti-allergic agent

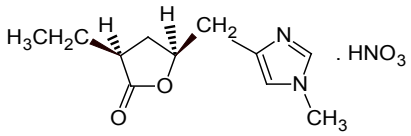
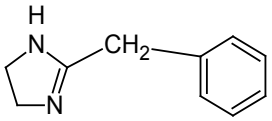
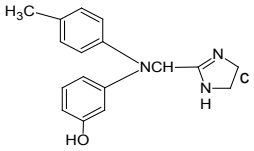
39	[2]		Pilocarpine nitrate	Parasympathomimetic agent
40	[15]		Tolazoline	It exhibits a sympathomimetic effect To stimulate the heart
41	[20]		Phentolamine	It use for treatment of shock or heart failure

Table 2: The privileged compounds with respect to their activity.

developing imidazole substituents having both amino and carboxylic group.

Conclusion

Various compounds have been developed, which are tested clinically to check their efficacy, a detailed review is present on such compounds, with help to compare review and available research articles. Anti-fungal activity is also being discussed, imidazole and triazoles are the main areas where substituted compounds have been developed and synthesized. Here we present certain of the compounds prepared with these moieties as their physical back bone. Thus can say imidazole is a moiety which had been exploited in the past for preparing various compounds having diverse pharmacological activities, and still it can be further exploited for future potential against numerous compulsive conditions and other uses.

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