Research Article

Imidazole: Having Versatile Biological Activities

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Imidazoles have occupied a unique position in heterocyclic chemistry, and its derivatives have attracted considerable interests in recent years for their versatile properties in chemistry and pharmacology. Imidazole is 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 several important natural products, including purine, histamine, histidine, and nucleic acid. Being a polar and ionisable 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 enormous scope in the field of medicinal chemistry. The imidazole derivatives possess extensive spectrum of biological activities such as antibacterial, anticancer, antitubercular, antifungal, analgesic, and anti-HIV activities. This paper aims to review the biological activities of imidazole during the past years.

1. Introduction

Imidazole nucleus forms the main structure of some well-known components of human organisms, that is, the amino acid histidine, Vit-B12, a component of DNA base structure and purines, histamine, and biotin. It is also present in the structure of many natural or synthetic drug molecules, that is, cimetidine, azomycin, and metronidazole. Imidazole-containing drugs have a broaden scope in remedying various dispositions in clinical medicine [1]. Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives had been discovered as early as the 1840s. His synthesis used glyoxal and formaldehyde in ammonia to form imidazole [2]. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles (see Scheme 1).

Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents. It exists in two equivalent tautomeric forms because the hydrogen atom 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, and is entirely soluble in water. Imidazole is amphoteric; that

is, it can function as both an acid and a base. 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 in Scheme 2.

Medicinal chemistry concerns with the discovery, development, interpretation, and identification of the mechanism of action of biologically active compounds at the molecular level [3].

2. Pharmacological Activities

Imidazoles are well-known heterocyclic compounds which are common and have an important feature of a variety of medicinal agents. On the basis of various literature surveys, imidazole derivatives show various pharmacological activities:

- (i) antibacterial activity;
- (ii) anticancer activity;

SCHEME 1

SCHEME 2

1a	2,4-Dichlorophenyl
1b	2,5-Dichlorothiophene
1c	4-SCH ₃ -C ₆ H ₄
1d	4-CH ₃ -C ₆ H ₄

	Ar	X
2a	4-SCH ₃ -C ₆ H ₄	H
2b	2,4-Dichlorophenyl	H
2c	Biphenyl	H
2d	4-CH ₃ -C ₆ H ₄	H
2e	2,5-Dichlorothiophene	H
2f	4-SCH ₃ -C ₆ H ₄	Br
2g	2,4-Dichlorophenyl	Br
2h	Biphenyl	Br
2i	4-CH ₃ -C ₆ H ₄	Br
2j	2,5-Dichlorothiophene	Br

SCHEME 3

- (iii) antitubercular activity;
- (iv) antifungal;
- (v) analgesic activity;
- (vi) anti-HIV activity.

3. Antibacterial Activity

Vijesh et al. carried out the *in vitro* antibacterial activity of newly synthesized compounds 1a–d and 2a–j. *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhimvrium*, *Clostridium perfringens*, and *Pseudomonas*

aeruginosa were used to investigate the activity. The antibacterial screening revealed that some of the tested compounds showed good inhibition against various tested microbial strains. 1c showed excellent activity against *P. aeruginosa* and *C. perfringens* compared to standard drug streptomycin [4] (see Scheme 3).

A series of substituted 4-(2,6-dichlorobenzoyloxy)phenyl thiazole, oxazole, and imidazole derivatives (3a–f, 4a–e) were synthesized by Lu et al. The derivatives were screened for *in vitro* antibacterial activity against *S. aureus*, *E. coli*, *S. pneumonia*, and penicillin-resistant *S. pneumonia* [5] (see Scheme 4).

SCHEME 4

SCHEME 5

Compounds	R	R ₁	R ₂	R ₃
6	H	H	CH ₃	H
7	H	H	CH ₃	H
8	H	H	CH(CH ₃) ₂	H
9	H	H	CH ₃	CH ₃
10	F	H	CH ₃	CH ₃
11	H	OCH ₃	CH ₃	CH ₃
12	F	H	CH ₃	CH ₃
13	H	F	CH ₃	CH ₃
14	H	OCH ₃	CH ₃	CH ₃
15	H	F	CH ₂ CH ₃	H

SCHEME 6

Jain et al. synthesize 2-substituted-4,5-diphenyl-N-alkyl imidazole derivatives, and evaluate their antibacterial activity. All the synthesized compounds were evaluated for antibacterial activity against *S. aureus*, *B. subtilis*, and *E. coli*. Out of 5a-e only 5a and 5b showed some short of activity but none of them had considerable activity compared with that of the standard [6] (see Scheme 5).

Ramachandran et al. synthesized imidazole/benzotriazole substituted piperidin-4-one derivatives. Compounds 6-15 were screened for their *in vitro* antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhi*, *Escherichia coli*, and *Klebsiella pneumonia*. Among the compounds, 7 and 10 against *B. subtilis*, 9 against *S. aureus*, 8 and 13 against *K. pneumonia*, and 15 against *E. coli* did not

SCHEME 7

SCHEME 8

SCHEME 9

SCHEME 10

show any inhibitory activity even at maximum concentration. However, piperidine ring containing compounds 8 against *B. subtilis* and 9 against *E. coli* explored good inhibitory activity. Compound 13 increased the growth inhibition activity against *E. coli*. And compound 15 showed superior inhibition activity against *B. subtilis* [7] (see Scheme 6).

Padmavathi et al. synthesized amido linked imidazoles derivatives and screened antibacterial activity; it was seen that 16c and 18c were more effective against *Pseudomonas aeruginosa*. Amongst bis heterocyclic compounds, the aromatized bis heterocycle 18 was effective than the corresponding nonaromatized compound 17. The compounds 16c and 18c

SCHEME 11

SCHEME 12

displayed excellent activity particularly against *P. chrysogenum*, almost equivalent to the standard drug Ketoconazole. Amongst the tested compounds, chlorosubstituted imidazolyl cinnamamide 16c showed strong antibacterial activity against *B. subtilis* [8] (see Scheme 7).

4. Anticancer Activities

Yang et al. synthesised series of novel hybrid compounds between 2-phenylbenzofuran and imidazole have been prepared and results suggest that substitution of the imidazolyl-3-position with a naphthylacyl or bromophenacyl group, was vital for modulating cytotoxic activity. Compound 21 was the most active compound which displayed similar cytotoxic activity *in vitro* compared with DDP. Compared with alkyl substituent imidazolium salt derivatives 20–23, hybrid compounds 24–30 with phenacyl substituent at position-3 of imidazole ring exhibited higher cytotoxic activity. Compounds 28, 29, and 30 displayed similar cytotoxic activity *in vitro* compared with DDP [9] (see Scheme 8).

Alkahtani et al. synthesized and evaluated benzo[d]imidazole derivatives as potential anticancer agents. 5,6-Dichloro-1-cyclopentyl-1H-benzo[d]imidazoles 31, 32, and 33 possessed potent antiproliferative activity in cancer cell lines [10] (see Scheme 9).

Ozkay et al. synthesized 2-substituted-N-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl] acetamide derivatives and evaluated anticancer activity. The 35, 38, 39, 40, and 41 are the most cytotoxic compounds in the series. Cytotoxicity of the 43 was lower than that of the 34. The compounds 36, 37, and 42 showed approximate cytotoxic activity to the 34. Compounds 44 and 45 revealed greater cytotoxic activity than the 34. However, when concentrations were raised, cytotoxic activity of the 34 increased significantly

	R ₁	R ₂		R ₁
89a	2,4-Dichloro	H	90a	2,4-Dichloro
89b	2,4-Dichloro	Br	90b	2,4-Difluoro
89c	2,4-Dichloro	Br	90c	4-F
89d	4-F	Br	90d	4-Cl
89e	4-Cl	Br	90e	4-NO ₂
89f	4-NO ₂	Br	90f	4-Phenyl
89g	H	Br	90g	H
89h	2,4-Dimethyl	Br	90h	2,4-Dimethyl

SCHEME 13

SCHEME 14

SCHEME 15

SCHEME 16

SCHEME 17

SCHEME 18

SCHEME 19

SCHEME 20

SCHEME 21

SCHEME 22

SCHEME 23

SCHEME 24

and seemed as higher than those of the 44 and 45 [11] (see Scheme 10).

Wang et al. evaluated the cytotoxic potential of all newly synthesized hybrid compounds. 2-Benzylbenzofurane imidazole hybrids 47–49 lacked activities against all tumor cell lines. In terms of the imidazole ring (imidazole, 2-methyl-imidazole or 2-ethyl-imidazole, and benzimidazole), imidazolium salt hybrids 50–59 with imidazole ring displayed weak cytotoxic activities. Only compounds 55 and 58 showed medium cytotoxic activities, and compound 59 with a naphthylacetyl substituent at position-3 of the imidazole ring displayed higher cytotoxic activity *in vitro*. Imidazolium salt hybrids 60–68 with 2-methyl-imidazole ring and 69–77 with 2-ethyl-imidazole ring exhibited medium cytotoxic activities. However, imidazolium salt hybrids 78–87 with benzimidazole ring exhibited powerful cytotoxic activities. Among them, compounds 86 and 87 showed potent cytotoxic activities [12] (see Scheme 11).

5. Antitubercular Activity

Lu et al. synthesised a series of substituted 4-(2,6-dichlorobenzoyloxy)phenyl thiazole, oxazole and imidazole derivatives. The derivatives were screened for *in vitro* antitubercular activities against *Mycobacterium tuberculosis* H37Rv [13] (see Scheme 12).

Lee et al. synthesised monocyclic nitroimidazole derivatives, and the antitubercular activity of the synthesized compounds against Mtb H37Rv was determined by the microdilution Alamar blue assay. Compounds 89a, 89b, and 89d were moderately active. In case of 90a, 90d, 90e, and 90g, the activity was increased 4-fold, compared with 89b, 89e, 89f, and 89g, respectively. While 90c and 90h were 8-fold more active than 89d and 89h, respectively, 90b was 16-fold more active than 90c [14] (see Scheme 13).

Alegaon et al. synthesized imidazo[2,1-b][1,3,4]thiadiazole derivatives, and the antitubercular activities have been assessed against *M. tuberculosis* H37Rv (ATCC 27294) and found that compounds (91, 92a, 92b, 92c, 92d, 93a, 93b, 93c, 93d, and 93e) are active against *M. tuberculosis* [15] (see Scheme 14).

According to Fassihi et al. a series of 4-substituted imidazolyl-2,6-dimethyl-N3,N5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides (94a–j) were prepared and tested *in vitro* against *M. tuberculosis* H37RV strain ATCC 27294 which is susceptible to rifampicin and isoniazid [16] (see Scheme 15).

According to Zampieri et al. a series of 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole and 1-[(1-aralkyl)-3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl]-1H-imidazole derivatives were synthesized and evaluated for antimycobacterial activities. Compounds 95a–t were tested against a strain of

SCHEME 25

SCHEME 26

M. tuberculosis H37Rv and showed a good antimycobacterial activity [17] (see Scheme 16).

Imidazo[2,1-b][1,3,4]thiadiazole derivatives were synthesised by Patel et al. and evaluated for *in vitro* antitubercular activity against *M. tuberculosis* strain H37Rv. Among the imidazo[2,1-b][1,3,4]thiadiazole series the compounds 96a–f exhibited significant antitubercular activities but not as good as that of the nitro phenyl substituent 96e [18] (see Scheme 17).

Pandey et al. synthesized and screened a series of imidazole-based compounds (97–116) for their antitubercular efficacy against *M. tuberculosis* [19] (see Scheme 18).

6. Antifungal Activities

Yang et al. synthesized various N-cyano-1H-imidazole-4-carboxamides derivatives, and the fungicidal activities were screened against six kinds of fungi, *Fusarium oxysporum*, *Rhizoctonia solani*, *Botrytis cinerea* Pers, *Gibberella zeae*, *Dothiorella gregaria*, and *Colletotrichum gossypii*, at a concentration of 50 lg/mL. The newly synthesized compounds have good antifungal activity selectively against *Rhizoctonia solani* among the six fungi tested. Particularly, compound 117h was identified as the most promising candidate with an EC₅₀ of 2.63 lg/mL against *R. Solani* [20] (see Scheme 19).

The *in vitro* antifungal activity of imidazole derivatives 118a–c, 119a–d, 120a, 121a–c, 122b–c, 123a–c, and 124c was evaluated by Vita et al. against four strains of *C. albicans*

and seven strains of nonalbicans *Candida* species [21] (see Scheme 20).

Ramachandran et al. synthesised various imidazole derivatives and evaluated fungicidal activity against *A. niger*, *C. neoformans*, *Rhizopus* sp., *C. albicans*, and *A. flavus* [7] (see Scheme 21).

Desai et al. synthesised N-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)(aryl) amides (135a–l). The compounds were tested for antifungal activity in six sets against *C. albicans*, *Aspergillus niger* and *A. clavatus* at various concentrations. Among these compounds 135c, 135d, 135f, 135h, and 135j showed significant potency against different microbial strains [22] (see Scheme 22).

Vijesh et al. synthesized and screened compounds 136a–d and 137a–j for their antifungal activity against *Aspergillus flavus*, *Aspergillus niger*, *Candida albicans*, *Microsporum gypseum*, and *Trichophyton rubrum*. Among the tested compounds, the compound 136c has emerged as active against *T. rubrum* compared with standard, fluconazole [4] (see Scheme 23).

7. Analgesic Activity

Ucucu et al. reported the synthesis of some 1-benzyl-2-substituted-4,5-diphenyl-1H-imidazole derivatives. Swiss albino mice were used to carry out analgesic activity of both sexes weighing 23–36 g. All derivatives show poor response; only compounds 138 and 139 exhibited a moderate activity, and compounds 140 and 141 ranged not far from morphine [23] (see Scheme 24).

According to Kankala et al. synthesis of isoxazole-mercaptobenzimidazole hybrids and the analgesic activity of the synthesized compounds (142a–l) was assessed by hot plate method. Almost all the compounds have shown very potent analgesic activity when compared with standard drug pentazocine. Amongst all the compounds, 142e and 142f with potent analgesic activity, the compounds 142k and 142l have shown moderate activity and were found to be more potent than the standard pentazocine. The remaining

SCHEME 27

compounds 142a–d and 142g–j had shown poor activity [24] (see Scheme 25).

A series of novel 5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole derivatives have been synthesized and evaluated for analgesic activity. Derivatives 143a–c exhibited moderate to good analgesic activity [25] (see Scheme 26).

8. Anti-HIV Evaluation

A series of 2-(1-aryl-1H-imidazol-2-ylthio)acetamide [imidazole thioacetanilide (ITA)] derivatives were synthesized and evaluated as potent inhibitors of human immunodeficiency virus type-1 (HIV-1). All of the newly synthesized imidazole thioacetanilides were first evaluated for their anti-HIV activity. The most potent HIV-1 inhibitors were 148 and 145. Other compounds, 146, 147, 149, and 144, also showed higher anti-HIV-1 potency [26] (see Scheme 27).

9. Conclusion

The above study about various imidazole derivatives is the significant class of heterocyclic compounds, showed promising results in most of the pharmacological activities, and also has fascinating results including antibacterial, anticancer, antitubercular, antifungal, analgesic, and anti-HIV activities. It has been noticed so far that modifications on imidazole nucleus displayed promising biological activities. It will be interesting to observe that in the future many new pharmacological profiles will be added to it as it is still unrevealed and can be taken as a lead for future development to get safer and more effective compounds.

Conflicts of Interests

Authors declare that there is no conflict of interests regarding the publication of this article.

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