Review Article

A review on the multifaceted pharmacological aspects of benzimidazole derivatives

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Abstract

Benzimidazoles have emerged as multifaceted scaffold among the various heterocyclic compounds, exhibiting wide range of pharmacological activities like anticancer, antibacterial, anhelminthic, anti-HIV, anti-inflammatory, anxiolytic, anti-allergic, coagulant, anticoagulant, anti-oxidant and anti-diabetic activities and is gaining much more importance amongst the medicinal chemist to design, synthesize and discover newer benzimiazole derivatives for its diverse pharmacological activities. In the present review, we highlight the importance of benzimidazole scaffold as an important pharmacophore with various applications.

Keywords: Benzimidazole, Benzimidazole derivatives, Chemotherapeutic activities

Introduction

Among the various heterocyclic compounds benzimidazoles have gained much importance, because of their flexible structure, which can bind to different receptors and proteins exhibiting varied biological activities with high efficiency, low toxicity. Previously benzimidazoles were used as antimalarial, antihelminthic agents, etc but recently benzimidazoles have gained much importance as anticancer agents, acting by various mechanism of actions [1-2]. Various benzimidazole derivatives like benimetinib are under phase 3 clinical trials (NCT01849874). Benzimidazole is a six membered heterocyclic compound, in which benzene is fused to imidazole ring at 4- and 5- positions. Benzimidazole and its derivatives has gained much alertness in the recent years because of its diverse range of pharmacological activities.

Literature review:

Anti-Cancer activity:

Shinde et al. Synthesized benzimidazole nucleosides and evaluated for their anti-cancer activity. In vitro cytotoxicity of the nucleosides was tested against the MDA-MB-231 cell lines and concluded that among the synthesized series the compound with C-3′-azido analog I having anthryl group at 2-position of nucleobase showed almost similar potency as that of standard etoposide, with further studies ongoing to know anticancer mechanism and structural optimization [3].

Ren et al, synthesized a series of novel indazole and benzimidazole analogues as tubulin inhibitors with potent antiproliferative activities. Among the series the compound II exhibited strongest inhibitory action on cancer cells with average IC50 value of 50 nM, slightly better than colchicine. It also displayed significant invivo antitumor activity in a melanoma tumor model with tumor growth inhibition rates of 78.70% (15 mg/kg) and 84.32% (30 mg/kg), indicating that II is a promising lead compound deserving further investigation as a potential anticancer agent [4].

Akhtar et al. Synthesized a series of benzimidazole linked pyrazole derivatives and tested their anticancer activity against five human cancer cell lines including MCF-7, HaCaT, MDA-MB231, A549 and HepG2. Among the series Compound III showed the most effective activity against the lungs cancer cell lines (IC50 = 2.2 µM) and EGFR binding affinity (IC50 = 0.97 µM), molecular docking studies showed that the

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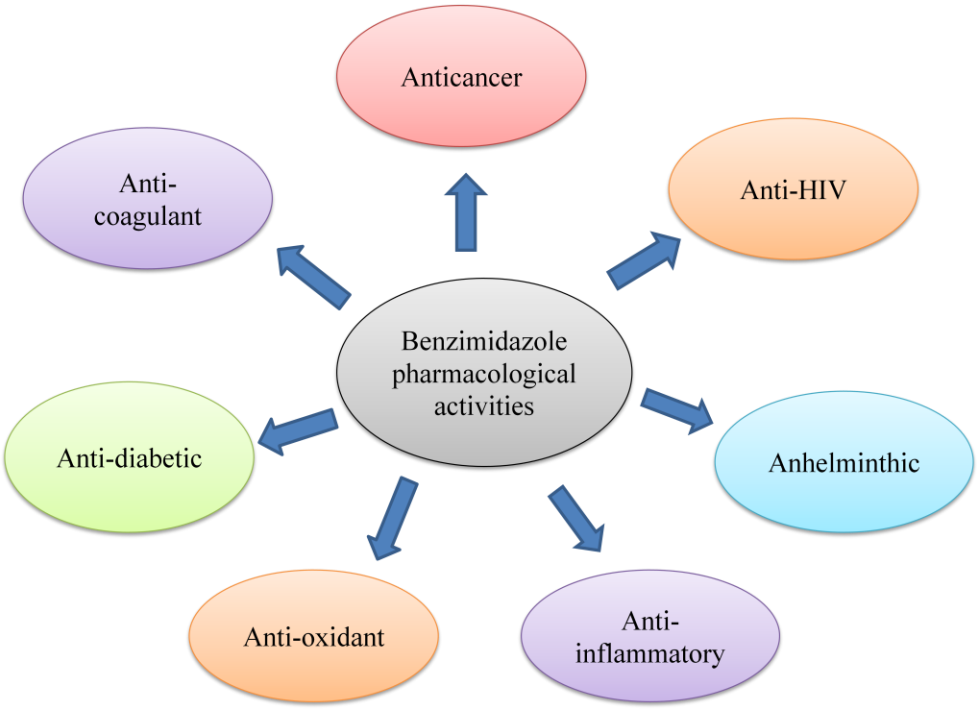
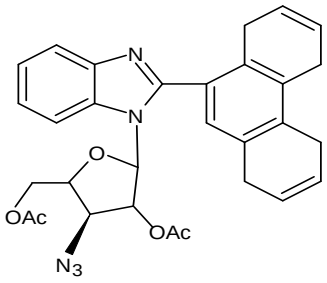
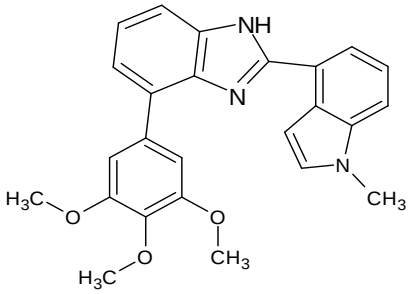




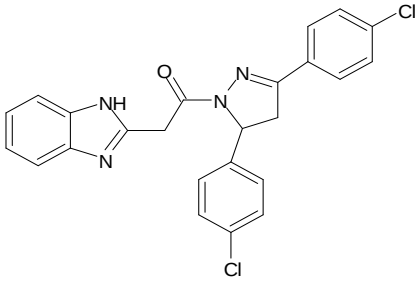
2-Anthryl-1-(2′ ,5′ -dihydroxyl-3′ -azido-3′ -deoxy-β-D-xylofuranose) benz-imidazole

I



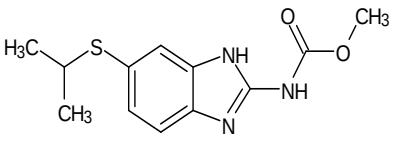
2-(1-Methyl-1H-indole-4-yl)-4-(3,4,5-trimethoxyphenyl)-1H-benzimidazole

II



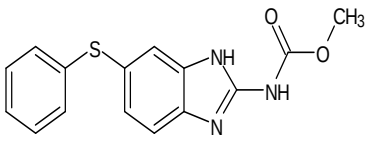
2-(1H-benzo[d]imidazol-2-yl)-1-(3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone

III



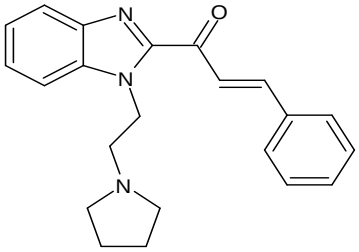
methyl N-(6-propan-2-ylsulfanyl-1H-benzimidazol-2-yl)carbamate

IV



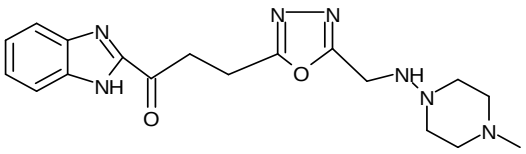
methyl N-(6-phenylsulfanyl-1H-benzimidazol-2-yl)carbamate

V



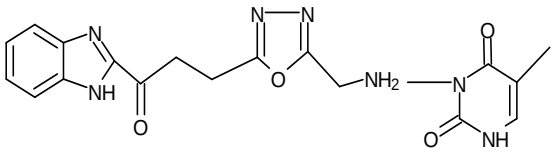
N-ethylpyrolidine-2-(3-phenylprop-2-en-1-one)-1H-benzo[d]imidazolyl

VI



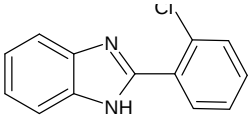
[1-(1H-benzo[d]imidazol-2-yl)-3-(5-((4-methylpiperazin-1-yl)methyl)-1,3,4-oxadiazol-2-yl) propan-1-one]

VII



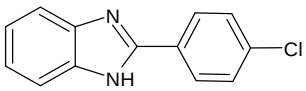
[3-((5-(3-(1H-benzo[d]imidazol-2-yl)-3-oxopropyl)-1, 3, 4-oxadiazol-2-yl) methyl)-5-methylpyrimidine-2,4(1H, 3H)-dione]

VIII



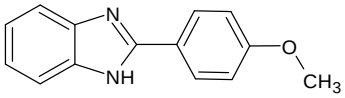
2-[2-Chlorophenyl] Bemzimidazole

IX



2-[4-Chlorophenyl] Benzimidazole

X



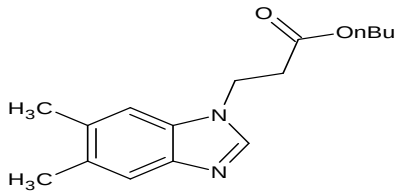
2-[4-Methoxyphenyl] Benzimidazole

XI

compound III was bound to the active pocket of the EGFR (PDB 1M17) with five key hydrogen bonds and two π-π interaction with best binding energy, indicating that benzimidazole linked pyrazoles can serve as potent compounds for developing anticancer agents [5].

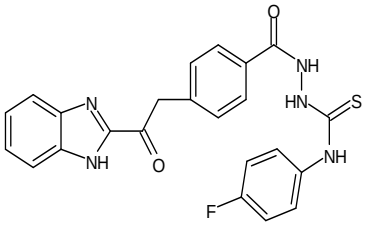
Shimomura screened a total of 1271 small molecules against KRAS-mutant and wild-type lung cancer cell lines and found that the Treatment with two benzimidazole derivatives, IV and V yielded significant suppression of the RAS-related signaling pathways in KRAS-mutated cells, suggesting that benzimidazole derivatives with tyrosine kinase inhibitors, especially trametinib, may offer a novel therapeutic strategy for cancer treatment [6].

Fat-Moon Suk et al. Synthesized a series of benzimidazole derivative and reported that the compound VI bearing a pyrrolidine side chain on benzimidazole, inhibited the proliferation of sorafenib resistance cells by blocking the phosphorylation of AKT, p70S6 and the downstream molecule RPS6, indicating that the compound VI can be a novel therapeutic agent for treating patients with sorafenib resistance [7].



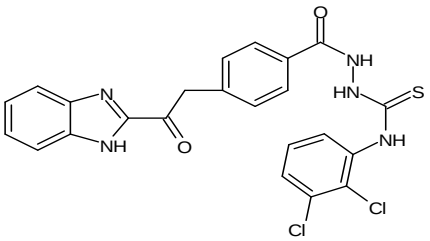
Butyl-3-(5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)propanoatemz imidazole

XII



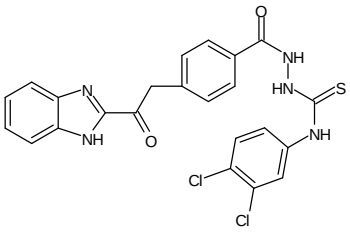
2-(4-(((1H-benzo[d]imidazol-2-yl)thio)methyl)benzoyl)-N-(4-fluoro phenyl)hydrazine-1-carbothioamide

XIII



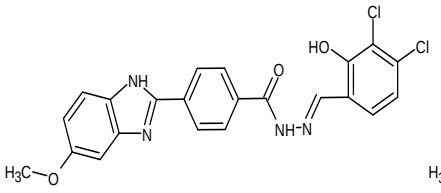
2-(4-(((1H-benzo[d]imidazol-2-yl)thio)methyl)benzoyl)-N-(2,3-dichlorophenyl) hydrazine-1-carbothioamide

XIV



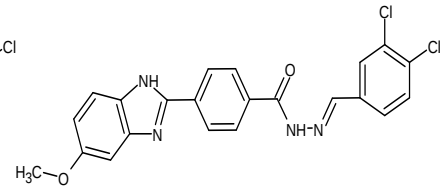
2-(4-(((1H-benzo[d]imidazol-2-yl)thio)methyl)benzoyl)-N-(3,4-dichlorophenyl)hydrazine-1-carbothioamide

XV



N′-(3,4-dichloro-2-hydroxybenzylidene)-4-(5-methoxy-1H-benzo[d]imidazol-2-yl) benzohydrazide

XVI



N'-(3,4-dichlorobenzylidene)-4-(5-methoxy-1H-benzo[d]imidazol-2-yl)benzohydrazide

XVII

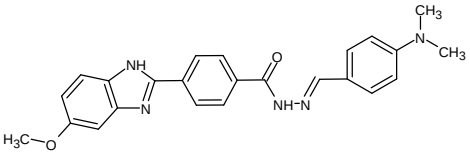
Rashid et al. synthesized a series of benzimidazole with oxadiazole ring and evaluated for antiproliferative activity, amongst the series the compound VII and VIII exhibited highest drug score and emerged as lead compounds and motivates for further development of more effective and safer compounds [8].

Verma et al. synthesized a series of 2-substituted benzimidazole derivatives, and evaluated their antimicrobial activity by filter paper disc method at conc 100 µg/ml and concluded that the compounds IX, X and XI exhibited good activity against gram-positive bacteria *staphylococcus aureus* and gram –negative bacteria *Escherichia coli* [9].

Wen et al, synthesized a series of benzimidazole derivatives and evaluated their antimicrobial activity against *Bacillus subtilis* and *Bacillus proteus*. Among the series the compound XII showed excellent activity with MIC of 16 µg/mL against *Bacillus subtilis* and MIC of 8 µg/mL against *Bacillus proteus*, than standard chloromycin indicating that benimidazole scaffolds can be a potential bioactive compounds with further investigation [10].

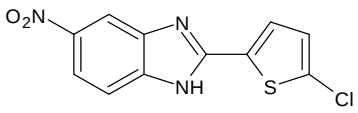
Anti-Alzheimers Activity:

Adalat et al, synthesized a series of Benzimidazole thiosemicarbazide and benzimidazole-based Schiff bases derivatives and evaluated their invitro anti-Alzheimer's activity and concluded that from series 1 (benzimidazole thiosemicarbazide derivatives), the compounds XIII, XIV and XV, showed excellent anticholinesterase with IC50 values of 1.30±0.10, 1.60±0.50 and 2.40±0.10µM respectively and butylcholinesterase activity with IC50 values of 2.40±0.10, 1.50±0.10 and 2.40±0.10µM respectively. And compounds from series 2, (benzimidazole-based Schiff bases) the compounds XVI, XVII and XVIII exhibited excellent anticholinesterase activity with IC50 values of 1.50±0.10, 0.60±0.50 and 0.90±0.05µM and butylcholinesterase activity with IC50 values of 4.10±0.10, 2.20±0.10 and 2.20±0.30µM [11].



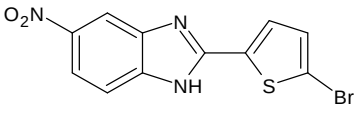
2-(5-chlorothiophenyl)-5-nitro-1H-benzimidazole

XIX



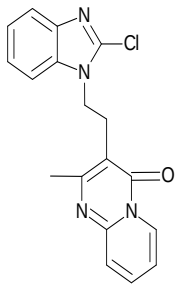
2-(5-bromothiophenyl)-5-nitro-1H-benzimidazole

XX



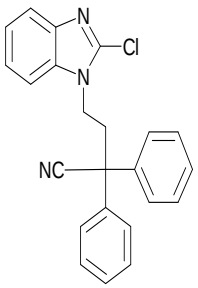
2-(3′ -Nitrophenyl)-5-chlorobenzimidazole

XXI



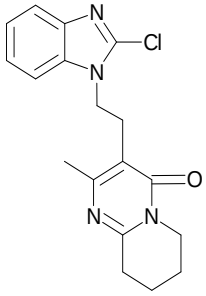
3-[2-(2-Chloro-benzimidazole-1-yl) -ethyl]-2-methyl-pyrido [1,2-a]pyrimidine-4-one

XXII



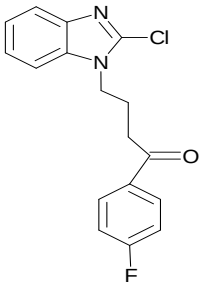
4-(2-Chloro-benzimidazole-1-yl)-2, 2-diphenyl-butyronitrile

XXIII



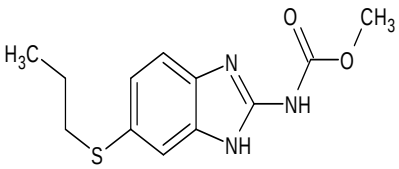
3-[2-(2-Chloro-benzimidazole-1-yl)-ethyl]-2-methyl-6,7,8,9-tetrahydro-pyrido[1,2-a]pyrimidine-4-one

XXIV



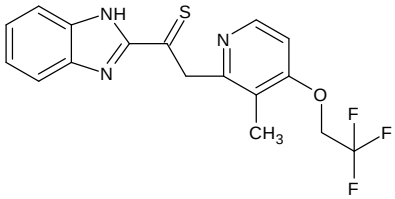
4-(2-Chloro-benzimidazole-1-yl)-1-(4-fluoro-phenyl) –butan-1-one

XXV



methyl (6-(propylsulfonyl)-1H-benzo[d]imidazol-2-yl)carbamate

XXVI



(RS)-2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl] methylsulfinyl)-1H-benzo[d]imidazole

XXVII

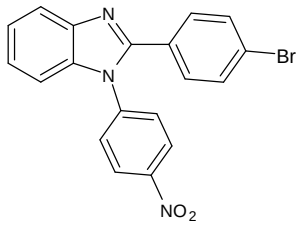
Jimenez-Juarez et al, Synthesized a series of 2,5 disubstuted and 1,2,5-trisubstituted benzimidazole derivatives and evaluated for their invitro antimycobacterial activity against M. *tuberculosis* H37Rv, and reported that the among the series disubstiuted compounds XIX, XX, and XXI effectively inhibited the growth of M. *tuberculosis* with MIC values of 89.6, 19.4, and 22.9nM respectively. Suggesting that antimycobacterial activity of 2,5-disubstituted benzimidazoles can be further evaluated for in vivo studies to determine their potential for treating tuberculosis [12].

Antifungal Activity:

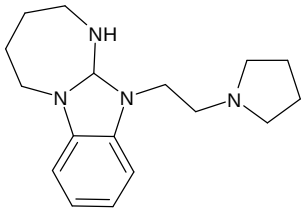
Radhu et al. synthesized N-substituted 2-chloro-1H-benzimidazole derivatives, compounds XXIII, XXV were found to possess high activity against *Escherichia coli* whereas compound XXII and XXV exerted very good activity against *Streptococcus pyogenes* when compared to the standard ampicillin. The compound XXIV and XXV exhibited good antifungal activity [13].

Anti-diabetic activity:

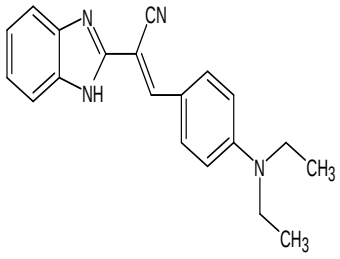
Dik et al, conducted type 2 diabetic mellitus experiment using benzimidazole derivatives like albendazole (XXVI) and lansoprazole (XXVII) on Wistar albino rats, and concluded that albendazole and lansoprazole can be potential drug in combination with other antidiabetic drugs for developing effective benzimidazole scaffold [14].



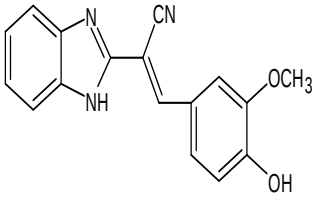
2-(4-bromophenyl)-1-(4-nitrophenyl)-1H-benzo[d]imidazole
XXVIII



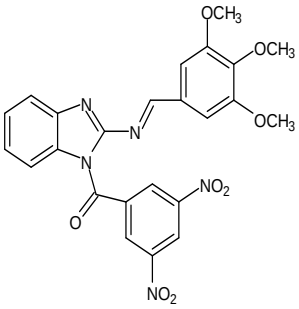
11-[(2-Pyrrolidin-1-yl)ethyl]-2,3,4,5-tetrahydro[1,3]diazepino [1,2-a]benzimidazole dihydrochloride
XXIX



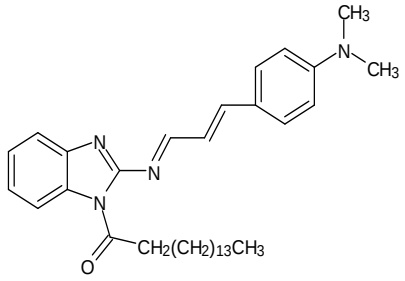
2-(1H-benzimidazol-2-yl)-3-(4-diethylaminophenyl)acrylonitrile
XXX



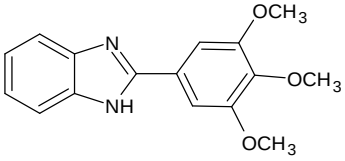
2-(1H-benzimidazol-2-yl)-3-(4-hydroxy-3-methoxyphenyl) acrylonitrile
XXXI



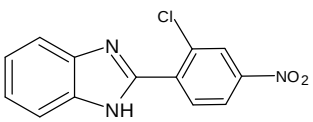
(E)-(3,5-Dinitrophenyl)(2-((3,4,5-trimethoxybenzylidene)amino)-1H-benzo[d]imidazol-1-yl)methanone
XXXII



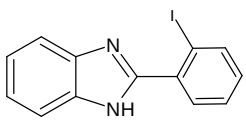
(E)-1-(2-((4-(Dimethylamino)benzylidene)amino)-1H-benzo[d]imidazol-1-yl)hexadecan-1-one
XXXIII



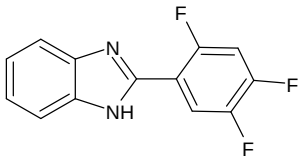
2-(3,4,5-trimethoxyphenyl)-1H-1,3-benzodiazole
XXXIV



2-(2-chloro-4-nitrophenyl)-1H-1,3- benzodiazole
XXXV

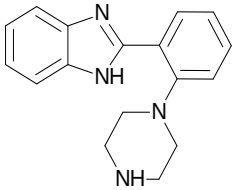


2- (2-iodophenyl)-1H-1, 3-benzodiazole
XXXVI



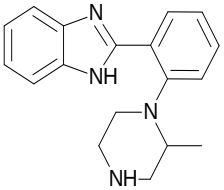
2- (2, 4, 5-trifluorophenyl)-1H-1,3- benz odiazole

XXXVII



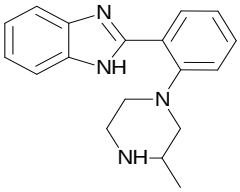
2-(2-(piperazin-1-yl)phenyl)-1H-benzo[d]imidazole

XXXVIII



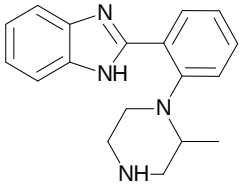
2-(2-(2-methyl piperazin-1-yl)phenyl)-1H-benzo[d]imidazole

XXXIX



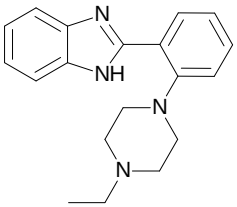
2-(2-(3-Methyl piperazin-1-yl)phenyl)-1H-benzo[d]imidazole

XXXX



2-(2-(2-ethyl piperazin-1-yl)phenyl)-1H-benzo[d]imidazole

XXXXI



2-(2-(4-ethyl piperazin-1-yl)phenyl)-1H-benzo[d]imidazole

XXXXII

Anti-inflammatory activity:

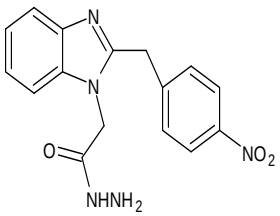
Garcia-Arandaa et al, synthesized a series of 1,2-diphenylbenzimidazoles derivatives and evaluated their anti-inflammatory activity, for COX and NO synthase. Among the series the compound XXVIII exhibited the best inhibitory activity against COX-2 with additional, significant anti-inflammatory activity in vivo when given orally [15].

Anti-anxiolytic activity:

Maltsev et al, Performed anxiolytic study with new 11-dialkylaminoethyl-2,3,4,5-tetrahydrodiazepino [1,2-a]benzimidazole derivatives. The screening was done invivo using elevated plus maze (EPM) and concluded that compound XXIX was found to be the most active compound than diazepam with less toxicity. Indicating that 11-dialkylaminomethyl-2,3,4,5-tetrahydrodiazepino[1,2-a]benzimidazoles derivatives can be potential promising compounds in search of new effective anxiolytics [16].

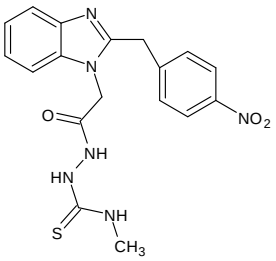
Anti- HIV:

Ting et al, synthesized a series of benzimidazole derivatives and evaluated their anti-HIV activity and concluded that the compounds XXX and XXXI exhibited the, best anti-HIV-1 activity with IC50 values of 3.45 nM and 58.03 nM respectively in anti-HIV-1 replication assay conducted in H9 cells with low acute toxicity profiles indicating that these compounds can be further developed as new anti-HIV-1 leads [17].



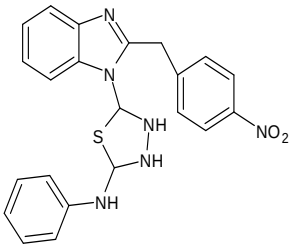
2-[2-(4-nitrobenzyl)-1H-benzimidazol-1-yl]acetohydrazide

XXXXIII



N-methyl-2-{(2-(4-nitrobenzyl)-1H-benzimidazol-1-yl]acetyl}hydrazine carbothioamide

XXXXIV



5-{[2-(4-Nitrobenzyl)-1H-benzimidazol-1-yl]methyl}-N-phenyl-1,3,4-thiadiazol-2-amine

XXXXV

Miscellaneous:

Vashist et al, Synthesized a series of benzimidazole derivatives and evaluated their antibacterial, antifungal and anticancer activities and concluded that compound 1 exhibited good antimicrobial activity against E. coli (MICec = 5.4 μM) and B. subtilis (MICbs = 10.7 μM), on other hand compound XXXII exhibited potent antifungal activity against A. niger (MICan = 3.1 μM) compared to standard fluconazole (MIC = 5.0 μM), and can act as lead for further development as potent antifungal agents. On other hand compounds like XXXIII exhibited potent anti-cancer activity against MCF7 (ATCC HTB-22) with a (IC50 = 5.5 μM, respectively) when compared to standard drug 5-fluorouracil, indicating that these compounds can act as leads for discovery of new anticancer agents [18].

Anand and Wakode, synthesized and characterized a series of benzimidaole derivatives and evaluated their anti-bacterial anti-oxidant and anti-fungal activities, and concluded that, the compound XXXIV and XXXV were comparitively more active than other compounds against standard cefodoxamine, while the compounds XXXVI and XXXVII exhibited more antifungal activity against *candida albicans* than other compounds at the same time showed best scavenging activity than the standard ascorbic acid, which states that benzimidazole exhibits high potential and can be further developed for finding potent inhibitors [19].

Bhardwaj et al. synthesized a series of novel 2-(2-(substituted piperazin-1-yl)-phenyl)-1H-benzo[d] imidazoles and evaluated their Antibacterial, Antifungal and Anticancer activity. The compounds XXXX was found to be active against Escherichia coli and Pseudomonas aeruginosa, XXXXI was active against Bacillus subtilis and Staphylococcus aureus, XXXXII was active against Candida albicans and Aspergillus niger, compounds XXXVIII and XXXIX, showed significant anticancer activity, indicating that benzimidazole derivatives can prove to potent chemotherapeutic agents [20].

Karaali et al. synthesized and characterized a new series of 2-(4-nitrobenyl)-1H-benzimidazole derivatives containing 1-substituted moieties at the 1st position of benzimidazole ring and screened for their antioxidant, antiurease and anti-xanthine oxidase activities. Compound XXXXIII, posses antioxidant effect (CUPRAC Antioxidant activity assay), XXXXIV, exhibited the best inhibitory effect against urease with an IC50 value of 13.04±0.89μg/ml, XXXXV displayed the best inhibitory effect against xanthine oxidase with an IC50 value of 12.30±0.33μg/ml [21].

Conclusion

Therapeutic drugs containing benzimidazole scaffold are used in raising drugs that set out to be an active area of research. Owing to its number of pharmacological properties, this scaffold is of superior interest in designing and synthesis of novel therapeutic compounds. Therefore, in the present literature survey, we endeavour to discuss various derivatives of benzimidazole scaffold with various pharmacological activities. The literature survey shows the pharmacological activities of the reported synthesized benzimidazole derivatives in medicinal domain. The present survey based on reported heterocyclic benzimidazole derivatives which displayed the significant biological potentials in medicinal chemistry. Benzimidazole moiety is the key building block for several heterocyclic scaffolds that play central role in the biologically functioning of essential molecules.

Conflict of Interest

The authors proclaim no conflict of interest.

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