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Review Article

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Benzimidazole: A plethro of biological load

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ABSTRACT

All the heterocyclic compounds are of great interest in Pharmaceutical Chemistry. Out of these heterocyclic compounds the benzfused heterocyclic compound, i.e. benzimidazole is an important pharmacophore and privileged structure in medicinal chemistry. Recently many benzimidazole drugs like antiparasitic, thiabendazole, mebendazole and albendazole, antihistaminic norastemizole and mizolastine, as well as antihypertensive telmisartan etc. have been successfully developed and extensively used in clinic. The wide spectrum of biological activities associated with benzimidazole has been of huge interest and its derivatives have wide variety of biological activities like antihelminthic, antiulcer, diuretic, anticonvulsant, analgesic, antiulcer, antihypertensive, anticoagulant, anticancer, antiinflammatory, antimicrobial, antiviral, antiparasitic and antioxidant. This review is summarized different derivatives of substituted benzimidazoles along with their pharmacological activities. This has attracted increasing interest to investigate the possible applications of benzimidazole derivatives in other medicinal aspects.

Keywords: Benzimidazole, antiviral, antimicrobial, review, Chemistry.

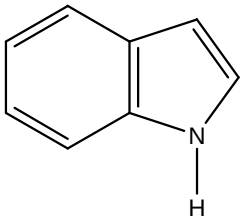
INTRODUCTION

The benzimidazole scaffold is a useful structural modification for the development of molecules of pharmaceutical or biological interest [1]. The benzimidazole heterocycle is represented in nature as an integral part of the structure of vitamin B12 and has been incorporated into Pharmaceutical agents to form enzyme inhibitors and DNA intercalators [2]. Benzimidazoles are very useful intermediates/subunits for the development of molecules of Pharmaceutical or biological interest [3]. Appropriately substituted benzimidazole derivatives have found diverse therapeutic applications such as in antimicrobial & antiprotozoal, antibacterial effects [4], antiallergic activity [5], HIV inhibtors, antiviral effect [6], antiparasitic effect [7], antihypertensive agents [8], cardiotonic activity [9], antiulcer activity [10], antiproliferative activity [11], anti-inflammatory activity [12], analgesic activity [13], antioxidant activity [14], antiprotozoal activity [15], antidiabetic activity[16], diuretic activity [17], androgen receptor antagonist [18], anticonvulsant agents [19], antinflammatory [20], DNA binding properties, bovine DHFR, antitumor [21, anticoagulant [22]. Optimization of benzimidazole-based structures has resulted in various drugs.

CHEMISTRY OF BENZIMIDAZOLE

Benzimidazoles (1) are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin-B12. Benzimidazole is a fused aromatic imidazole ring system where a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Benzimidazole is 1, 3-benzodiazole, It is also called as azindole, benzoglyoxaline, NCS759, N, N'-methyl-o-phenylenediamine, 1, 3-diazaindene, 1-*H*-benzimidazole, *o*-benzimidazole, BZI, 3-azaidole [23]. They possess both acidic and basic characteristics. The NH group present in benzimidazole is relatively strongly acidic and also weakly basic. Another

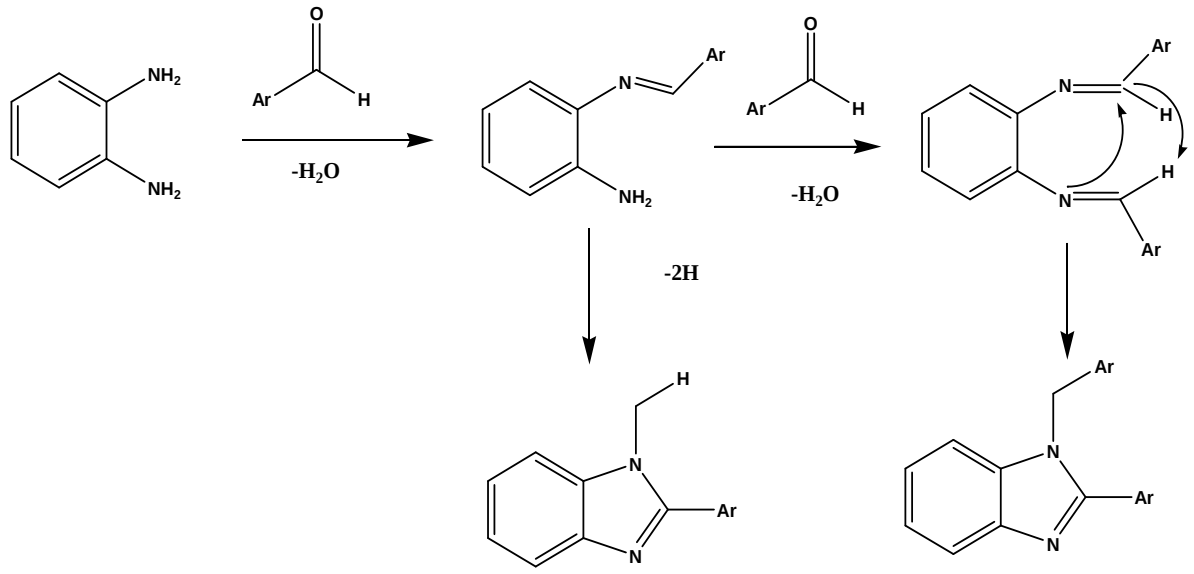
characteristic of benzimidazole is that they have the capacity to form salts. Benzimidazole with unsubstituted NH groups, exhibit fast prototropic tautomerism which leads to equilibrium mixture of asymmetrically substituted compounds [24].



(1) Benzimidazole

Mechanism of Benzimidazole ring formation

The first step of this mechanism involves nucleophilic attack of one NH_2 to the carbonyl carbon of the aldehyde. Following the loss of water, the Schiff base intermediate is formed. Because excess aldehyde was used, two routes are possible for the consumption of intermediate. The first route is the nucleophilic attack of the second NH_2 on the second aldehyde molecule resulting into intermediate. This intermediate then undergoes intramolecular ring closure followed by 1, 3- hydride transfer, subsequently resulting into the formation of the required 2-aryl-1-arylmethyl-1*H*-benzimidazole. Alternatively, intermediate can undergo intramolecular cyclisation by the attack of the second NH_2 into the imine carbon (2). 2-substituted-1*H*-benzimidazole is from this process [25].

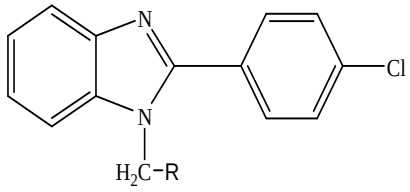


Mechanism of 1& 2 substituted benzimidazole ring formation (2)

STUDY ON STRUCTURAL MODIFICATIONS AND THEIR PHARMACOLOGICAL ACTIONS

Anti-inflammatory activity

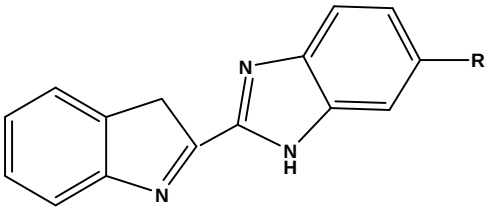
Benzimidazole moiety with carboxylic acid substitution at 2^{nd} position fulfills the minimum and desirable structural requirements that are common in most of the marketed anti-inflammatory drugs. Thakurdesai et al. synthesized some benzimidazole-2-carboxylic acid and tested for acute anti-inflammatory activity against carrageenan induced rat paw edema model. The test compounds were found to be safe upto 2000 mg/kg, p.o. doses and exhibited good anti-inflammatory activity at 100 mg/kg p.o. and higher doses. Their activity largely depends on substituents at position 5 and chain length at position 2 of benzimidazole moiety. With 1-benzyl substitution, activity was found to be increase [26]. Synthesis and anti-inflammatory activity of various substituted phenyl benzimidazoles were reported by Leonard et al. Compounds 3a, 3b and 3c were screened for anti-inflammatory activity and showed 22.1%, 52.2% and 54.6% inhibition respectively at 50 mg/kg. Compound (3c) showed maximum i.e., 54.6% inhibition of edema at doses of 50 mg/kg [27].



(3)
R = morphilono (3a), diphenylamine (3b), dimethylamine (3c)

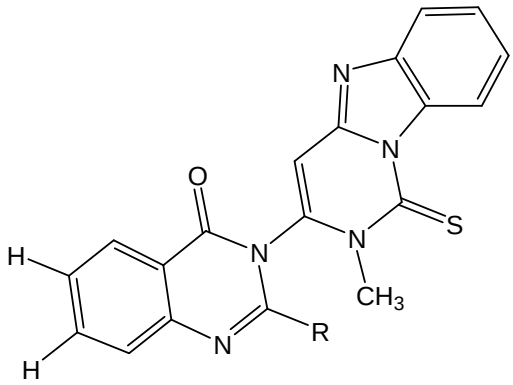
Diuretic activity

Diuretic activity of indolyl benzimidazoles (4) was carried out by Vittal Rao et al. Compounds 4a, 4b and 4c showed significant increase in urine volume (LV=2) and also urinary excretion of Na^+ and K^+ [28].



(4)
R= NO_2 (4a), Cl (4b), Br (4c)

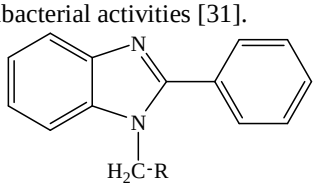
Srinivasan et al. carried out synthesis of 3-(2-methyl-1, 2-dihydropyrimido (1, 2-c) benzimidazole-1-thionyl)-6, 8-dibromo-2-substituted-3*H* quinazolin-4-one (5) and reported synthesized compound 5a and 5b showed moderate diuretic activity [29].



(5)
R = CH_3 (5a), Br (5b)

Antibacterial activity

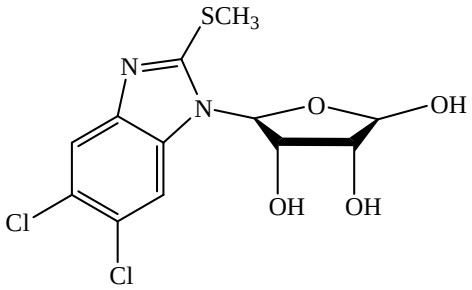
Goker et al. synthesized a series of 1, 2-disubstituted-1Hbenzimidazole-N alkylated- 5-carboxamidine derivatives and evaluated antibacterial activities against *S. aureus* and methicillin resistant *S. aureus*. The study revealed the best activity, with MIC values of 0.78 - 0.39µg/mL against these species [30]. Mohamed et al. synthesized benzimidazoles as 1-(substituted-methyl)-2(substituted-phenyl) benzimidazoles (6) and compounds 6a, 6b and 6c were screened for their antibacterial activity against *S. aureus*, *B. pumillus* and *P. aeurugenosa.* Compound 6a showed MIC (6.25) at 100 µm/ML and exhibited good antibacterial activity. Various Chloro and dichloro substituted benzimidazole also possess antibacterial activities [31].



(6)
R= Diethylamine (6a), Dimethylamine (6b), Morphilono(6c)

Antiviral activity:

Tetrahydro-imidazo[4,5,lJ.k][1,4]-benzodiazepin-2 (1H)one (TIBO) is a non competitive non nucleotide antiretroviral drug with a specific allosteric binding site of HIV-1 RT. TIBO derivatives have proved to be potent, highly selective and specific inhibitors of HIV-1 replication in vitro. The reverse transcriptase (RT) of HIV-1, but not HIV-2, is inhibited by the TIBO compounds. Several compounds other than TIBO have recently been reported to specifically inhibit HIV-1 replication. In a research it was investigated that some novel benzimidazole derivatives, bearing analogy to TIBO, have been synthesized, and were evaluated for inhibition of HIV-1 infectivity. The most active and elective compounds are a series of N-alkoxy-2-alkyl-benzimidazoles, several having EC50 < 10Mm (one sub-micromolar at 600nM) and selectivity ratios of 10–167.The selective benzimidazoles, show modest RT inhibition. Ramanpreet et al determined antiviral activity of series of 2-(alkylthio)-5, 6-dichloro-1-(*β-D*-ribofuranosyl) benzimidazoles (7). Compounds 7a, 7b and 7c were performed for antiviral activity against HSV-1 and HCMV and compound 7c shown maximum activity at 90% inhibitory concentration (µM) [32].

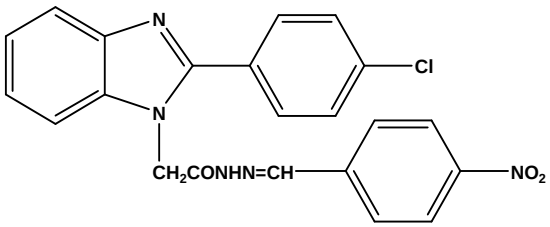


(7)

R= SCH_3 (7a), SO_2 CH_3 (7b), $SO_2CH_2C_6H_5$ (7c)

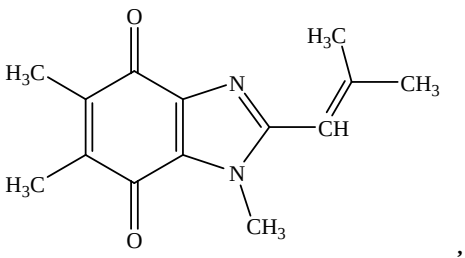
Antitumor activity

Balram Soni et al. synthesized a series of benzimidazole derivatives and screened for their in vitro cytotoxic activity. From the cytotoxic activity study, it was observed that compound with the presence of a 2-chloro on aromatic ring and 2-NO_2 on benzylidene amino group (compound 8) in most cases gives better cytotoxic activity against human K-562 cell line [33].



(8)

Some new benzimidazole-4, 7-diones substituted at 2-position were synthesized and reported by Gellis et al. In synthesized compounds 9a, 9b and 9c (10µM, 8µM and 3µM) among three of them 9c exhibited excellent cytotoxic activity against colon (HT29), breast (T47D) and lung (A549) cancer cell lines and shown lowest IC_{50} values in µM i.e., (3µM) [34].



(9a)

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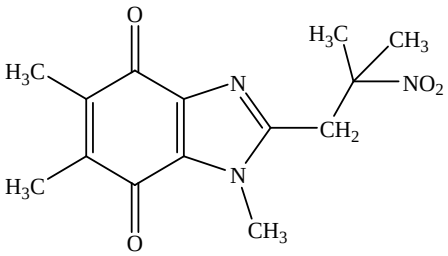
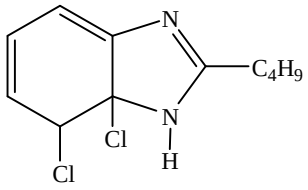


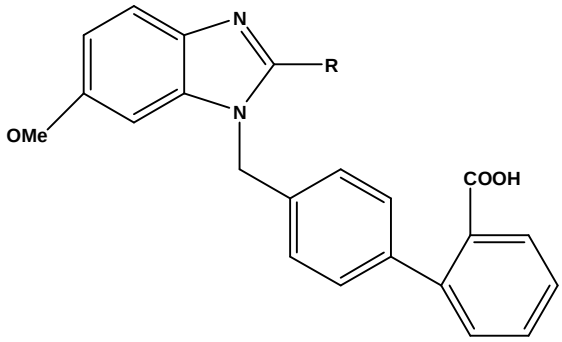
(9b)



(9c)

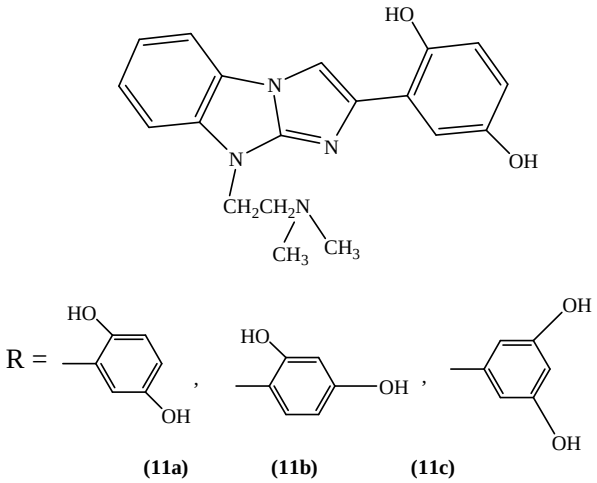
Antihypertensive activity

A series of 4'-(6-Methoxy-2-substituted-benzimidazole-1-ylmethyl)-biphenyl-2-carboxylic acid (10) were synthesized by kohli et al. expeditiously in good yields from 4-methoxy-1, 2-phenylenediamine and different substituted carboxylic acids in the presence of BF3·OEt2 as a catalyst with biphenyl carboxylic acid have been confirmed by IR, 1H, NMR, MS and elemental analysis. The title compounds have been evaluated for antihypertensive activity by direct and indirect methods. Some of these compounds (10a, 10b, 10c, 10d and 10e) have been found to exhibit excellent antihypertensive activity [35].



(10)
R = Cl (10a), Br (10b), NO_2 (10c), CH_3 (10d), C_2H_5 (10e)

Anisimova et al. synthesized 9-dialkylaminomethyl-2-oxy (dioxy) phenylimidazo[1,2-*a*] benzimidazole, compounds 11a, 11b and 11c possessed antihypertensive activity (ED_{50}: 2.8mg/kg, 0.8mg/kg, 0.13mg/kg) , (LD_{50}: 121.0mg/kg, 182mg/kg, 143mg/kg) and (LD_{50}/ED_{50} : 43.2, 227.5, 1100), the most active compound out of these was 11c exceeded the reference drugs (Dibazole-ED_{50}: 4.0) with respect to both the degree of the hypotensive action (ED_{50}) and the conditional therapeutic index (LD_{50}/ED_{50}) [36].

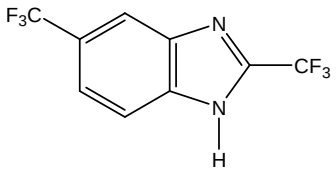


(11a) **(11b)** **(11c)**

Antiprotozoal activity

Vazquez et al. synthesized and determined anti-protozoal activity of 2-(trifluoromethyl)-1*H*-benzimidazole. A series of 2-(triflouromethyl)-1*H* benzimidazole derivatives (12) with 5 and 6 position bioisosteric substituent (-Cl, -F, -

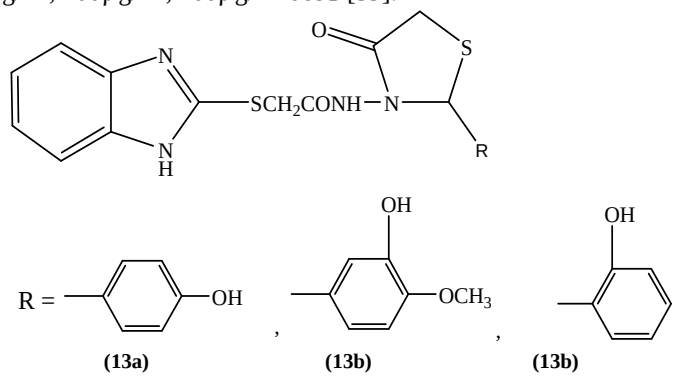
CF_3, -CN) were prepared by using short synthetic route. Analogues were tested *in-vitro* against the protozoa *Giardia intestinals* and *Trichomonas vaginalis* compare with albendazole and metronidazole, having IC_{50} < 1 µM and compound 12 was found to be more active than albendazole against *T. vulgaris* and also showed moderate antimalarial activity against W2 and D6 strains of *Plasmodium falciparum* [37].



(12)

Antimicrobial activity

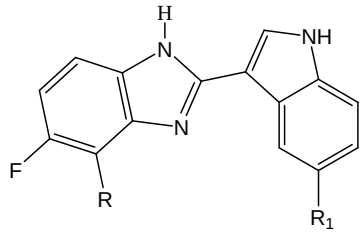
Ranjit et al. determined antimicrobial activity of 1,4-dihydropyrimido[1,2-a]benzimidazoles is based on the Biginelli like cyclocondensation of aromatic aldehydes and acetoacetic acid derivatives with 2-amino benzimidazole containing a guanidine fragment and synthesized compounds were evaluated for antimicrobial activity against *Escherichia coli*, *Streptococcus pneumoniae* and *Staphylococcus aureus* [38]. The efficient synthesis of novel 3-chloro-1-5-(2-methyl-1*H*-bezimidazol-2-yl)-4-(substituted) phenylazetidin-2-one were reported by Ansari et al. and synthesized compounds were screened for antimicrobial activity against *B.substilis* and *E.coli*, compound 13a and 13b showed MIC at 100µg/ml, 100µg/ml, 200µg/ml doses [39].

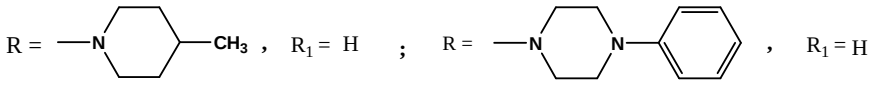


(13a) **(13b)** **(13b)**

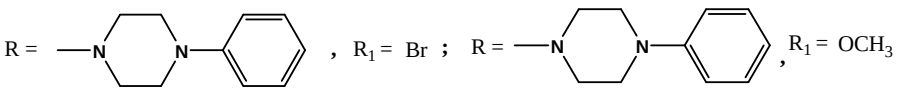
Anticonvulsant activity

Stables et al. synthesized 2-substituted benzimidazole derivatives (14). Synthesized compounds 14a and 14b shown anticonvulsant activity and having percentage of the activity (88%, 76% and 84%), thus the compound 14a showed maximum percentage against maximal electroshock therapy [40].





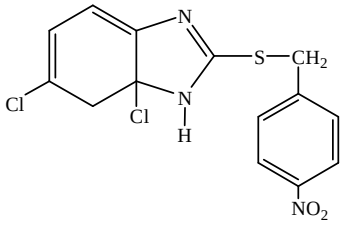
(14 a) (14 b)



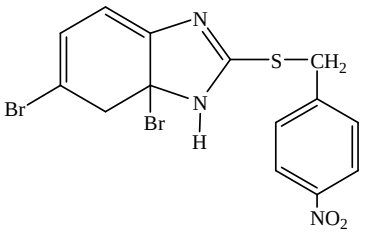
(14 c) (14 d)

Antimycobacterial activity

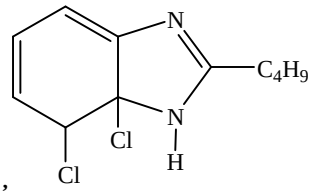
Synthesis of substituted 2-polyfluroalkyl and 4-nitrobenzyl sufanyl benzimiazole were reported by Kazimierczuk et al. and synthesized compounds were evaluated for their activity against mycobacterium strains, compound showed appreciable antimycobacterial activity. Compounds 15a, 15b and 15c showed their MIC values 2µmol l^{-1}, 2µmol l^{-1} and 4µmol l^{-1} respectively [41].



(15a)



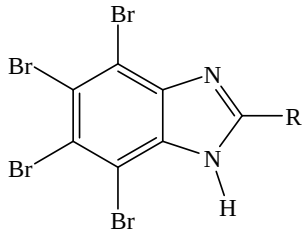
(15b)



(15c)

Protein kinase CK2 inhibitors

Protein kinase CK2 inhibitory activity were carried out on 4,5,6,7 tetra-bromo benzimidazole (16) derivatives by Tripathi et al. and compound 16a and 16b were found to posses –log IC_{50} (µM) 0.797, 0.177, 0.607 and it was found that compound 16b has shown the effective inhibitory concentration [42].

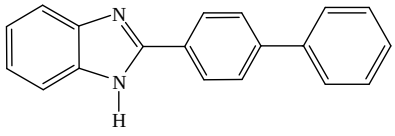


(16)

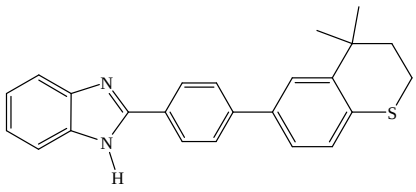
R = Br (16a), -NH-CH_3 (16b)

Antidiabetic activity

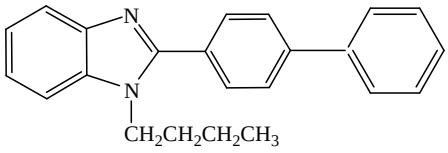
Synthesis of a series of novel and functionalized benzimidazole derivatives were reported by Kumar et al. Synthesized compounds exhibited antidiabetic activity against DPP-IV and PTP-IB. compound 17a and 17b shown inhibitory activity against PTP-IB (1.64 %, 2.42 %) at 30µM doses and 17c showed inhibitory activity against DPP-IV (3 %) at 0.3 µM doses [43].



(17a)



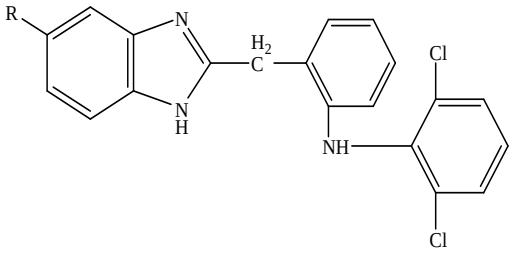
(17b)



(17c)

Analgesic activity

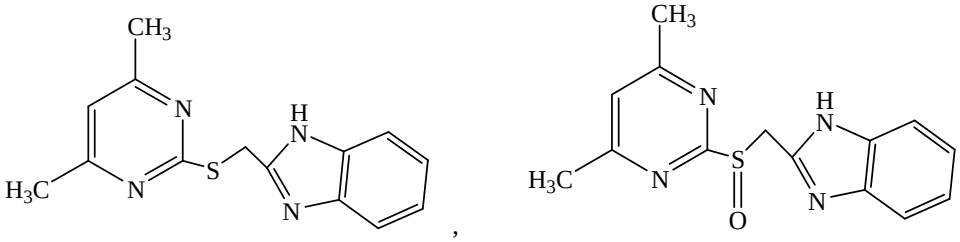
Syntheses of 2-substituted benzimidazoles (18) were reported by Sravanthi et al. All the Synthesized compounds were tested for analgesic activity by tail flick method at 25 mg/kg doses orally and compared with indomethacin, compounds 18a, 18b and 18c showed analgesic activity (86%, 85% and 74%) [44].



(18)
R = NO_2 (18a), Br (18b), Cl (18c)

Antiulcer activity

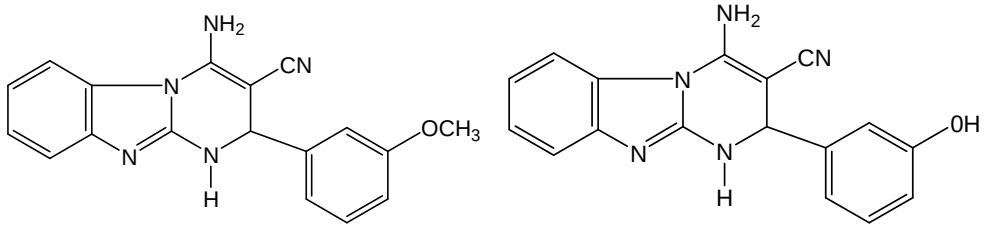
Bariwal et al. synthesized and reported evaluated antiulcer activity of compound 19a and 19b. Compound 19a and 19b at 10 and 30 mg/kg doses reduced the ulcer formation significantly, comparable to standard (Omeprazole) and it was found that compound 19a (sulfinyl derivative) was more effective than (thio derivative) [45].



(19a) , **(19b)**

Antifungal activity

Deshmukh et al. synthesized 2, 3, 4,-trisubstituted 1, 2-dihydropyrimido [1, 2-*a*] benzimidazole derivative. The compounds 20a and 20b were tested for their fungicidal activities against *Aspergillus niger*-MTCC-2255 and *Penicillium chrysogenum*-NCIM-723 using greseofulvin as control [46].



(20a) , **(20b)**

CONCLUSION

A vast majority of procedures and evaluation for pharmacological activity have been reported in various literatures for benzimidazole and its derivatives. Based on the above literature survey it is concluded that substituted benzimidazole is an important pharmacophore for wide range of pharmacological activity in modern drug discovery. The knowledge gained by various research has suggested that substituted benzimidazole interact easily with the biopolymers; possess pharmacological activity with lower toxicities. So in future trend designing more potent benzimidazole derivatives having wide diverse of biological activity with lower toxicity profile would be important resource for medicinal research.

Acknowledgement

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