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Benzimidazoles: A New Profile of Biological Activities

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Abstract

Benzimidazole and its derivatives are used in organic synthesis and they are used in evaluating new product that possesses different biological activities. This review article covers the most active benzimidazole derivatives that have shown considerable biological actions such as antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radioprotective and anti-leishmanial. This review also discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing benzimidazole moiety that could be better agents in terms of efficacy and safety.

Keywords: Benzimidazoles, synthesis, biological activities.

INTRODUCTION

Benzimidazole is a bicyclic compound having imidazole ring containing two nitrogen atoms at nonadjacent positions, fused to benzene. Benzimidazoles are an important group of heterocyclic compounds that are biologically active and of significant importance in medicinal chemistry.

In light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as privileged 'sub-structures' for drug dosing. The incorporation of the nucleus is an important synthetic strategy in studies of antimicrobial drug discovery. In the past few decades, benzimidazole and its derivatives have received much attention due to their chemotherapeutic values.

Anti-inflammatory Activity

Synthesis and anti-inflammatory activity of phenyl benzimidazole (**1**) was reported by Leonardo *et al* [1]. Compounds 1a, 1b, 1c and 1d were screened for anti-inflammatory activity and they

showed percent inhibition (22.1%, 52.2%, 54.6% and 49.6%) at 50 mg/kg each doses. By these values the compound (1c) showed maximum (54.6%) inhibition of edema at doses of 50 mg/kg.

Diuretic Activity

Synthesis of 3-(2-methyl-1,2-dihydropyrimido (1,2-c)benzimidazole-1-thionyl)-6,8-dibromo-2-substituted-3*H*-quinazolin-4-one (**2**) was reported by Srinivasan *et al* [2]. Compound (2a) and (2b) showed moderate diuretic activity.

Antimicrobial Activity

Synthesis of benzimidazole as 1-(substituted-methyl)-2-(substituted-phenyl)benzimidazole (**3**) was reported by Leonardo *et al* [1]. Compounds 3a, 3b and 3c were screened for their antibacterial activity against *S. aureus*, *B. pumillus* and *P. Aeurugenosa*. Compound (3a) showed MIC (6.25) at 100 µM/mL and exhibited good antibacterial activity. Synthesis of 2,3,4,-trisubstituted-1,2-dihydropyrimido[1,2-*a*]benzimidazole derivatives (**4**) were reported by Deshmukh *et al* [3]. The compounds were tested for their fungicidal activities against *Aspergillus niger* MTCC-2255 and *Penicillium chrysogenum*-NCIM-723 using Greiseofulvin as control. The efficient synthesis of novel 3-chloro-1-5-(2-methyl-1*H*-bezimidazol-2-yl)-4-(substituted)phenylazetidin-2-one (**5**) were reported by Ansari *et al* [4]. Compounds were screened for antimicrobial activity against *B. substilis* and *E. coli* and compound 5a, 5b and 5c shown MIC at 100 µg/mL, 100 µg/mL and 200 µg/mL doses.

Antiviral Activity

Synthesis of 2-(benzylthio)-5,6-dichloro-1-(*β-D*-ribofuranosyl)benzimidazoles (**6**) was reported by Devivar *et al* [5]. Compounds 6a, 6b and 6c performed antiviral activity against HSV-1 and HCMV and compound 6c shown maximum activity at 90% inhibitory concentration (µM).

Antitumor Activity

Some new benzimidazole-4,7-diones substituted at 2-position (**7**) were synthesized and reported by Gellis *et al* [6]. Compounds 7a, 7b and 7c (10µM, 8µM and 3µM) among three of them (7c) perform 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).

Antiprotozoal Activity

Synthesis and anti-protozoal activity of 2-(trifluoromethyl)-1*H*-benzimidazole (**8**) were reported by Vazquez *et al* [7]. A series of 2-(triflouromethyl)-1*H*-benzimidazole derivatives with 5 and 6 position bio isosteric 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* compared with Albendazole and Metronidazole, have $IC_{50} < 1$ µM and compound (6), was more active than Albendazole against *T. vulgaris* and also showed moderate antimalarial activity against W2 and D6 strains of *Plasmodium falciparum.*

Antiulcer Activity

Series of novel pyrimidyl-thio-methyl- benzimidazole **9(a)** pyrimidyl-sulfinyl-methylbenzimidazole **9(b)** synthesized and reported by Bariwal *et al* [8]. Compounds evaluated for the antiulcer activity. Compound 9a and 9b at 10 and 30 mg/kg doses reduced the ulcer formation significantly comparable to standard (Omeprazole) and 9b (sulfinyl derivative) compound was more effective than 9a (thio derivative).

Protein Kinase Ck2 Inhibitors

QSAR studies were carried out on 4,5,6,7 tetra-bromo benzimidazole (**10**) derivatives by Tripathi *et al* [9] and having the inhibitory activity data (IC_{50}) and the values converted in to –log IC_{50} (µM), compound 10a (0.797), 10b (0.177), 10c (0.607), by these values compound 10b shown effective inhibitory concentration.

Antioxidant Activity

Synthesis of some 6-flouro-5-substituted benzimidazole (**11**) reported by Alagoz *et al* [10] in which indole and 1,4,4,4-tetramethyl-1,2,3,4-tetrahydro naphthalene groups were attached to the 2-position ring were synthesized and tested for antioxidant activity and compound (11e) showed strong super scavenging effect on superoxide anion at 10^{-3} M concentration.

Anti-Asthmatic Activity

Syntheses of novel and functionalized benzimidazole derivatives (**12**) were reported by Kumar *et al*. [11]. Compounds were tested against PDE-1V for potential anti-asthmatic effect, compound 12a, 12b and 12c shown inhibitory activity (3.40%, 13.52% and 8.91%) at 1µm doses. The 12b compound showed potential anti-asthmatic activity.

Anti-Diabetic Activity

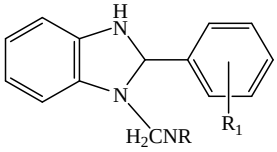
Syntheses of a series of novel and functionalized benzimidazole derivatives (**13**) were reported by Kumar *et al* [11]. Compounds shown anti-diabetic activity against DPP-IV and PTP-IB. compound 13a and 13b shown inhibitory activity against PTP-IB (1.64 %, 2.42 %) at 30µM doses and 13c shown inhibitory activity against DPP-IV (3%) at 0.3 µM doses.

Cysticidal Activity

Synthesis of novel benzimidazole derivatives (**14**) was reported by Alonso *et al* [12]. Compounds 14a, 14b and 14c had shown their invitro activity against *Taenia crassiceps* of WFU strain (22.6%, 9.3% and 5.0%) cysts's mortality percentage. Among three of them compound, 14c having good mortality rate.

5-HT_3 Receptor Antagonist Activity

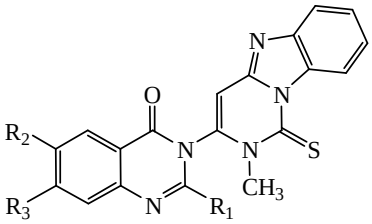
Synthesis of novel benzimidazole-2-carboxylic acid amides and esters (**15**) were reported by Orjales *et al* [13] with a quinolidine or a tropane moiety and evaluated for in vitro affinity for the 5-HT_3 receptor. Synthesized compounds 15a, 15b, 15c having 5-HT_3 receptor antagonist activity (12.7, 18.4, 24.4) with ED_{50} values of (10.6-19.1) mg/kg i.v. among these compound 15a having higher affinity for 5-HT_3 receptor



R= morpholine,diphenylamine,dimethylamine,imidazole

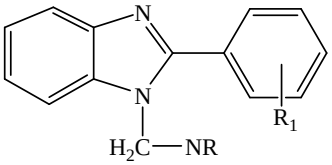
R_1= Cl

(1)



R_1 = CH_3, Br, R_2 = C_6H_5, H, R_3 = H, Br

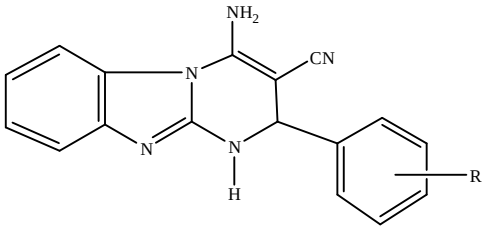
(2)



R= piperazine, dimethylamine, diethylamine

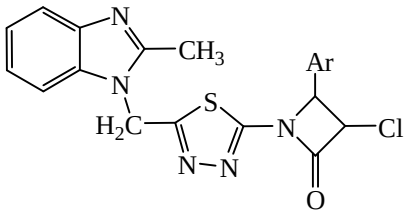
R_1= Cl

(3)



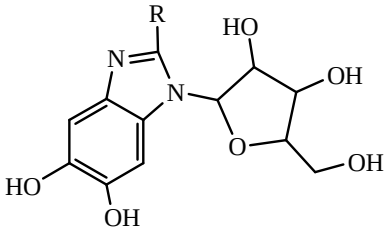
R = $-OCH_3$, -OH

(4)



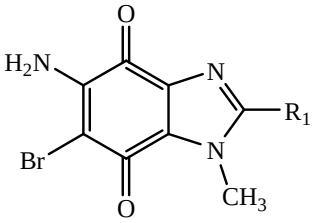
Ar = 2-C_6H_5Cl, 2-C_6H_5OH

(5)



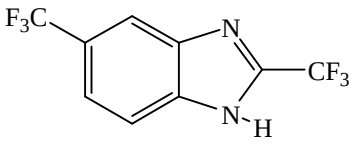
R = SCH_3, SO_2CH_3, $SO_2C_6H_5$

(6)

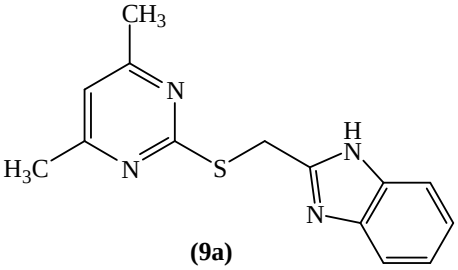


R_1 = $-CH=CH_2(CH_3)_2$, $-CH_2-CH(CH_3)_2NO_2$

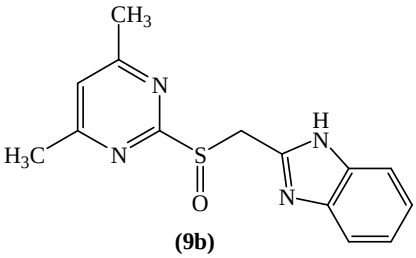
(7)



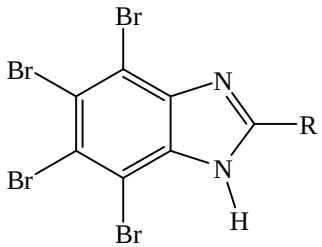
(8)



(9a)

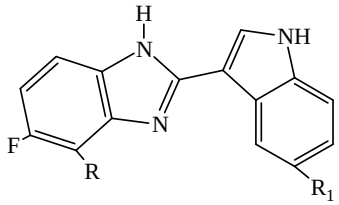


(9b)



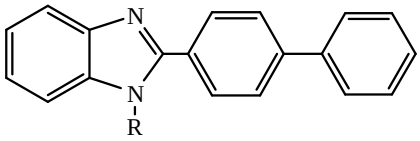
R = NH_2, Br, $NHCH_3$

(10)



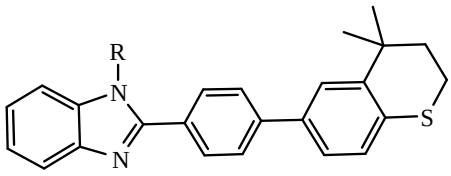
	R	R_1
a	4-$CH_3C_5H_{10}N$	–
b	4-$CH_3C_5H_{10}N$	–
c	4-$C_6H_5C_4H_9N_2$	–
d	4-$C_6H_5C_4H_9N_2$	Br
e	4-$C_6H_5C_4H_9N_2$	OCH_3

(11a-e)



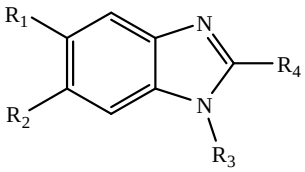
R= H, C_2H_5, $CH_2CH_2CH_3$

(12)



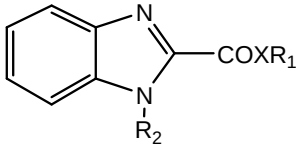
R= H, $CH_2CH_2CH_2CH_3$

(13)



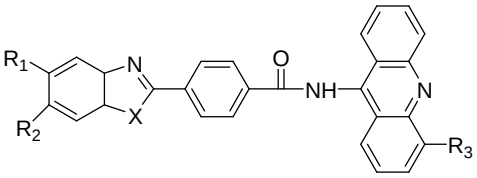
R_1= 4-nitrobenzyl formate, 4-piperidine-carbaldehyde, -Cl
R_2=R_3= H, R_4= $NHCOOCH_3$

(14)



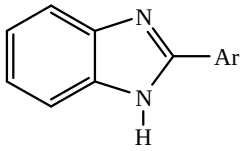
R_1= 7-methyl-7aza-bicyclo heptan-2-amine
R_2=isopropyl, benzyl

(15)



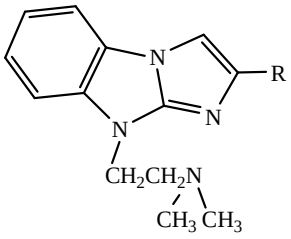
R1= Cl,NO_2,CH_3,H; R_2 = H,CH_3; R_3 = H,OCH_3;
X= NH,O

(16)



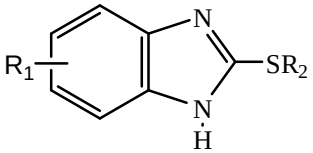
Ar = $C_6H_5COC_2H_5$, 4-OH-3-$OCH_3C_6H_5$,
2,3,4 -trimethoxybenzene

(17)



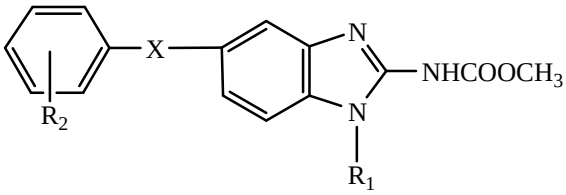
R= 1-4 dihydroxymethylbenzene,
1-3 dihydroxymethylbenzene,

(18)



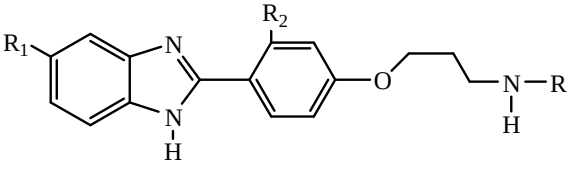
R_1= Cl, Br
R_2= methylnitrobenzene,C_4F_9

(19)



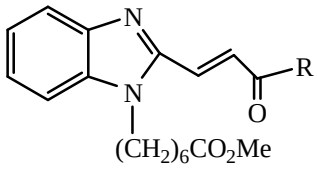
R_1= $COOCH_2CH_2OCH_3$, $CONHCH_2CH_2COOCH_3$
R_2= H, X= S

(20)



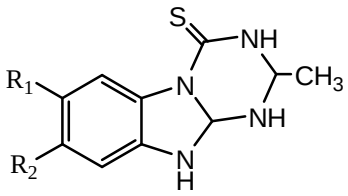
R = methylpiperazine, dimethylpyrrolidin-3-amine,
1-5diazocanemethylamine
R_1= Cl

(21)



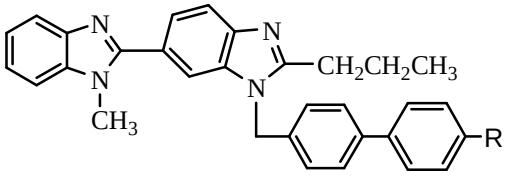
R= cyclopropylheptan-1-ol,
cyclopropylheptan-1-one

(22)



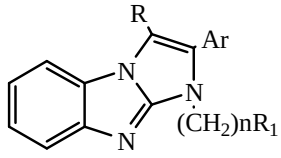
R_1= CH_3,COOH, R_2= CH_3, H

(23)



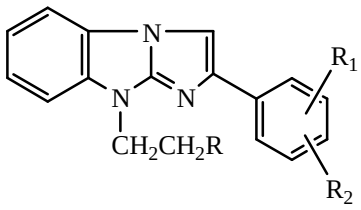
R= imidazole ,4-chloro-imidazole

(24)



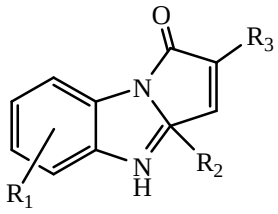
R= H, Ar= 4-$OCH_3C_6H_5$, 3-$OCH_3C_6H_5$, 4-OHC_6H_5
R_1= diethylamine, ethylamine, ethoxyethylethanamine

(25)



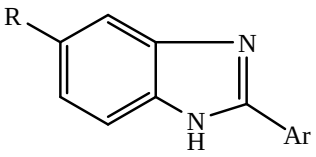
R= diethylamine, ethoxyethylethanamine
R_1= OH, R_2= H

(26)



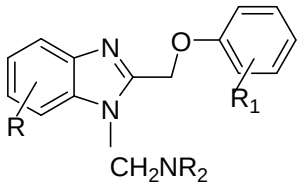
R_1= Cl, F, H, R_2= C_6H_5,CH_3, R_3= H

(27)



R= H, CH_3,
Ar= dichlorophenylbenzenamine,
isobutylmethylbenzene

(28)



R = H,Cl,F; R_1= H,CH_3,C_2H_5;
R_2 = H, C_6H_5

(29)

Analgesic Activity

Syntheses of a series of *N*-(acridin-9-yl)-4-(benzo[d]imidazol/oxazol-2-yl)benzamides (**16**) have been reported by Sondhi *et al* [14]. Compound containing R_1 = NO_2, R_2 = H, R_3 = H, X = NH showed significant *in vitro* activity against CDK-5 (IC_{50} = 4.6 lM) and CDK-1(IC_{50} = 7.4 lM) and compound having R_1 = Cl, R_2 = H, R_3 = H, X = NH showed moderate CDK-5 inhibitory activity (IC_{50} = 7.5 lM). The other compounds showed moderate anti-inflammatory and analgesic activities.

Spasmolytic Activity

Synthesis of 2-(aryloxyaryl)-1*H*-benzimidazole derivatives (**17**) was reported by Vazquez *et al* [7]. Compounds 17a, 17b and 17c showed significant antispasmodic effect in a concentration dependent manner, IC_{50} 1.94 µM, 1.19 µM and 1.8 µM, compound 17c shown potent relaxant smooth muscle activity.

Hypotensive Activity

Synthesis of 9-dialkylaminomethyl-2-oxy(dioxy)phenylimidazo[1,2-*a*] benzimidazole (**18**) were reported by Anisimova *et al* [15] compounds 18a, 18b and 18c possessed hypotensive 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 18c exceeded the reference drugs (Dibazole and Apressin) (ED_{50}: 22.1, 4.0) with respect to both the degree of the hypotensive action (ED_{50}) and the conditional therapeutic index (LD_{50}/ED_{50}).

Antimycobacterial Activity
Synthesis of substituted 2-polyfluroalkyl and 2-nitrobenzyl sufanyl benzimiazole (**19**) were reported by Kazimierczuk *et al* [16]. Compounds were evaluated for their activity against mycobacterium strains and compounds which showed appreciable antimycobacterial activity compound 19a, 19b and 19c shown their MIC values 2 µmol L^{-1}, 2 µmol L^{-1} and 4 µmol L^{-1}.

Anthelmintic Activity
Synthesis of 2-benzimidazole carbamic acid methyl ester derivatives (**20**) were reported by Solominova *et al* [17]. Compounds 20a and 20b shown anthelmintic activity against *Nippostrongilus*, *Ankilostoma* and *Haemonhus* larvae that exceeded 65% upon per oral administration in animals (rats, sheep, dogs) at a dose of 2.5-50 mg/kg. In another group of animal inhibition action is below 40% upon per oral administration in a dose of 50-100 mg/kg.

Histamine H_4-Receptor Antagonist
Synthesis of 2-arylbenzimidazole derivatives (**21**) were reported by Dutra *et al* [18] and found to bind with high affinity to the human histamine H_4 receptor. Compounds 21a, 21b and 21c shown their antihistaminic activity, among three of them 21a showed moderate affinity for H_4 receptor (K_i = 124 nM) and others (K_i = 65, 95).

Prostaglandin Analogs
Syntheses of 2-(1-2-methylene-3-methylene-3-hydroxyoctyl)-*N*-(6-methoxy carbonylhexyl) benzimidazole (**22**) derivatives were reported by Bespalov *et al* [19]. Synthesized compounds 22a and 22b shown comparable results with $F_{2\alpha}$ prostaglandin preparation Enzaprost and spasmogenic action of these compounds significantly lower (4-6 times) than Enzaprost.

Anti-Amoebic Activity
Synthesis of pyrimido[1,6-*a*]benzimidazole derivatives (**23**) were reported by Sondhi *et al* [20]. Compounds 23a and 23b were carried out in-vitro against *E. histolytica* and IC_{50} values obtained (1.82 µM, 2.62 µM) compared with the reference drug Metronidazole had 50% inhibitory concentration (IC_{50}) of 1.22 µM and the best IC_{50} value shown by 23a compound.

Angiotensin II Receptor Antagonist
Synthesis of benzimidazole derivatives (**25**) were reported by Guo *et al* [21]. Compounds 25a, 25b were evaluated for angiotensin II antagonist activity. Compound 25a showed good binding affinity (IC_{50} = 2.9nM) and 25b showed moderate binding affinity (IC_{50} = 6.2nM) when compared with reference drug Losartan (1.6 nM).

Antiarrhythmic Activity
Syntheses of 9-dialkylaminoethyl-2-oxy (dioxy)phenylimidazo[1,2-a]benzimidazole derivatives (26) were reported by Anisimova *et al* [15]. Compounds exhibited the antiarrhythmic activity. Compound 26a, 26b and 26c were evaluated the activity in minimum effective concentration (MIC mole/L) 2.9×10^{-4}m/L, 2.3×10^{-4} m/L, 2.1×10^{-4} m/L with reference to Quinidine (3.1×10^{-4} m/L). Hence the 26a MIC value was close to the reference drug. Concentrations but the values showed no significant result.

Anticonvulsant Activity
In this synthesis of novel 1-*H* pyrrolo(1,2-a)benzimidazole-1-one derivative (**27**) were reported by Chimrri *et al* [22]. Compounds 27a, 27b and 27c showed (84 %, 67% and 69 %) by maximal electroshock method, at dose level 25 mg/kg orally. The compound 27a showed maximum anticonvulsant activity.

Shukla *et al*. [23] synthesized a series of 1-heterocyclic amino/iminomethyl-2-substituted benzimidazoles (**29**) and were screened for their neuropharmacological and monoamine-oxidase inhibitory properties. A number of such compounds showed CNS stimulant, anticonvulsant and mono amine oxidase inhibitory activities.

CONCLUSION

This has been noticed so far, that modifications on benzimidazole moiety displayed valuable biological activities. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. The biological profiles of these new generations of benzimidazole would represent a fruitful matrix for further development of better medicinal agents.

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