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Review Article

Benzimidazole, A Versatile Analogue- A Review

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Abstract

The Benzimidazole has been an important pharmacophore, played a very significant role in the development of theory in heterocyclic chemistry and also extensively in organic synthesis and privileged structure in medicinal chemistry. Benzimidazole derivates play vital role in biological field such as antimicrobial, antiviral, antidiabetic, anticancer activity, inhibitors of type I DNA topoisomerases, antihelmintic, anti-allergic etc. Benzimidazoles are remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms. This review is summarized to know about the chemistry of different derivatives of substituted Benzimidazoles along with their pharmacological activities.

Keywords: - Benzimidazole, pharmacophore, biological activities

Introduction

Nowadays Infectious microbial diseases are causing problems world-wide, because of resistance to number of antimicrobial agents (β-lactam antibiotics, macrolides, quinolones, and vancomycin). A variety of clinically significant species of microorganisms has become an important health problem globally [1]. One way to fight with this challenge is the appropriate usage of the available marketed antibiotics the other is the development of novel anti-microbial agents [2]. In the past few decades, Benzimidazole and its derivatives have received much attention due to their chemotherapeutic values. Benzimidazoles are an important group of heterocyclic compounds that are biologically active and of significant importance in medicinal chemistry. Benzimidazole is a bicyclic compound having imidazole ring containing two nitrogen atoms at nonadjacent positions, fused to benzene [3]. Benzimidazole is a structural isosters of naturally occurring nucleotide, due to which it interact easily with the biopolymers of living system[4]. This character is responsible for its numerous biological activities and functions like anti-inflammatory [5], diuretic [6], antimicrobial [7], antiviral [8], antitumor [9], antiulcer [10], antioxidants [11], antiasthmatic [12] analgesic [13].

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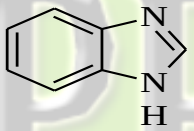


1*H*-benzimidazole

Chemistry

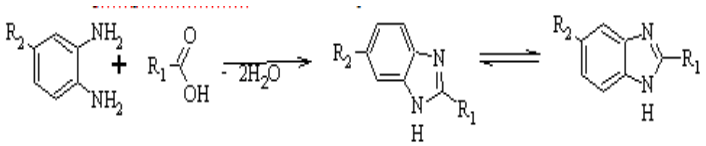
The UV and 13C-NMR spectra of Benzimidazole show the following characteristics:

UV (ethanol)	13C-NMR (methanol-d4)
λ(nm) €	δ(ppm)
244 (3.74), 248 (3.73), 266 (3.69), 272(3.71), 279(3.73) 137.9	C-2: 141.5, C-4: 115.4, C-5: 122.9, C-6: 122.9 C-7: 115.4, C-3a: 137.9, C-7a:

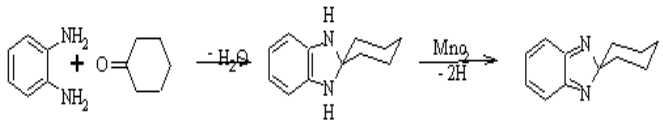
Benzimidazole is a white slightly being solid melting at 172 °C and boil at 360 °C,flash point at143 °C, autoignition at 538 °C, specific gravity 1,slightly soluble in water and soluble in ethanol. Stable under normal temperatures and condition. Molecular formula $C_7H_6N_2$ and mol. Wt 188.14 . [14]

General method of synthesis

The standard synthesis for Benzimidazoles is the cyclocondensation of o-phenylenediamine or substituted o-phenylenediamines with carboxylic acids or their derivatives.



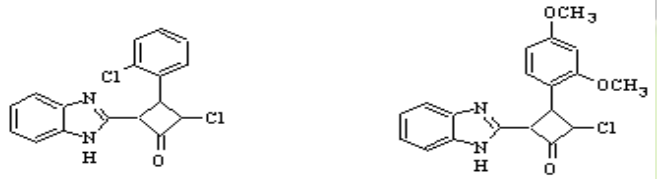
o-Phenylendiamine reacts with formic acid at 100°C to give Benzimidazole in a yield of over 80%. N-Monosubstituted o-phenylenediamines react with other carboxylic acids more slowly, necessitating the addition of hydrochloric or phosphoric acid. A mixture of trifluoromethanesulfonic acid anhydride and triphenylphosphane oxide in dichloromethane is a very efficient dehydrating agent [15].



o-phenylenediamine reacts with cyclohexanone under mild conditions (in hot water) to give l,3-dihydro-2H-Benzimidazole-2-spirocyclohexane 3, which can be oxidized with active manganese dioxide to yield Benzimidazole-2-spirocyclohexane 4.[16]

Cytotoxic activity

Cytotoxic activity of 3-chloro-1-(1-methyl-1hbenzimidazol-2-yl)-(4'-substituted)-phenylazetidin-2-one was reported by malleshappa noolvi et al[17] the four-membered b-lactam ring was introduced by the cycloaddition and chloroacetyl chloride in the presence of triethylamine catalyst to give 3-chloro-1-(1-methyl-1hbenzimidazol- 2-yl)-(4'-substituted)-phenylazetidin-2-one (a–g) and 5f, 5g shown good cytotoxic activity in vitro



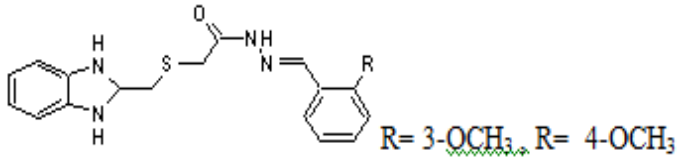
Compound f Compound g

f) 2-(1*H*-benzimidazol-2-yl)-4-chloro-3-(2-chloro phenyl) cyclobutanone

g) 2-(1*H*-benzimidazol-2-yl)-4-chloro-3-(2,4-dime thoxy phenyl)cyclob

Anti-inflamatory activity

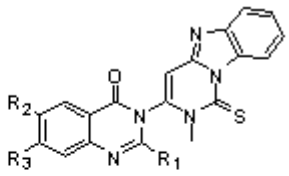
Synthesis and anti –inflamatory activity of 2-substituted Benzimidazoles derivatives (a-g) was reported by S.Manjula et al[18].Compounds a - g were screened for anti-inflamatory activity and compounds d and f shown high potency in terms of % inhibition and are moderately potent to that of standard drug diclofenac (20 mg/kg body weight).



R= 3-OCH$_3$, R= 4-OCH$_3$

Diuretic Activity

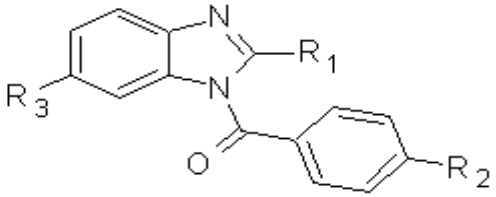
Synthesis of 3-(2-methyl-1,2-dihydropyrimido (1,2-c)Benzimidazole-1-thionyl)-6,8-dibromo-2-substituted-3*H*-quinazolin-4-one was reported by Srinivasan *et al* [19]. Compound (2a) and (2b) showed moderate diuretic activity.



Compound	2a	2b
	R_1 – CH_3,	Br
	R_2- C_6H_5,	H
	R_3- H,	Br

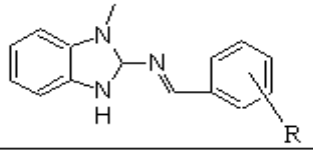
Antmicrobial activity

Synthesis and antimicrobial activity of 3-benzoylBenzimidazole derivatives (1-4) was reported by Rathe P.S. et al [20].Compounds 1-4 were screened for Antmicrobial activity and compounds 3 and 4 shown maximum potency against *C.albican*. 1 and 4 shown maximum activity against A.fumigates.



S.NO	R_1	R_2	R_3
1.	CH_3	NO_2	H
2.	CH_3	H	OH
3.	$CH_2C_6H_5NO_2$	NO_2	H
4.	$CH_2C_6H_5$	H	OH

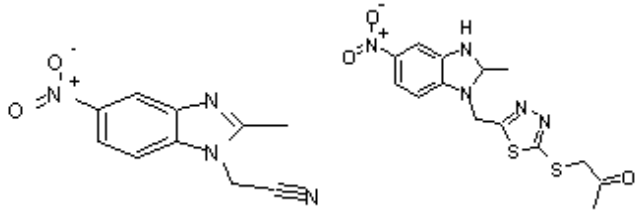
Synthesis of series of 1-methyl-N-[(substituted-phenylmethylidene)-1 H-benzimidazol-2-amine (4a–4g) were reported by Malleshappa Noolvi. *et al* [21] Among the chemicals tested 4a, 4b, exhibited good antimicrobial l activity.



4a	4-Chloro
4b	4-Nitro
4c	2-Nitro
4d	3-Nitro
4e	N,N-dimethyl amino
4f	2, 5 dimetoxy
4g	2-Chloro

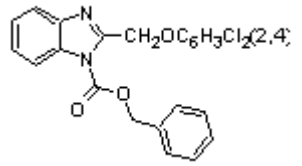
Antitumor Activiy

Some new 2-methyl-5(6)-nitro-1H-Benzimidazole substituted at 1-position were synthesized and reported by Mostafa M. Ramla et al[22] . The antitumor effect of compounds 1, 2, 2a, 4, 5, 7, 8, 9a, 10, 13, 14a, 15, 16, and 18c was studied against breast cancer (MCF7) and compounds 2 [IC50 = 4.52 lg] and 7 [IC50 = 8.29 lg] were found to more active.

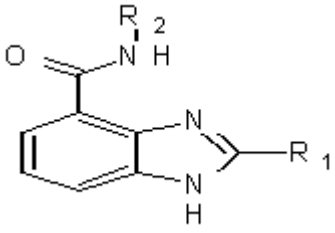


Antiviral activity

H.C. Gupta et al [23] reported to antiviral properties against PRSV (Papaya ring spot virus) developed on chenopodium amranticolor by petriplate technique at 3000, 2000, 1000 ppm concentration of compound. The most active compound of our investigation was having 2-4 Di-chloro substituent on phenoxy groups.



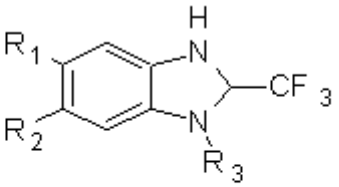
Fei Xue, Xianjin Luo *et al*[24] reported 40 series of novel Benzimidazole derivatives were designed, synthesized, and evaluated for their activities against four Kinds of enteroviruses, i.e., Coxsackie virus A16, B3, B6 and Enteroviruses 71 in VERO cells. The most Promising compound was (L)-2-(pyridin-2-yl)-*N*-(2-(4-nitrophenyl) pentan-3- yl)-1*H*-Benzimidazole-4-carboxamide, with a high antiviral potency (IC50 = 1.76 µg/mL) and a remarkable selectivity index (328).



Antiparasitic activity

The anthelmintic drugs derived from Benzimidazole 2-carbamates, such as albendazole (ABZ) and mebendazole (MBZ), are used mainly to treat endoparasitic diseases in domestic animals and humans. These types of compounds are characterized by a high therapeutic index and low toxicity; however, they find little use in tissue-dwelling parasites mainly due to poor solubility and absorption problems. [25].

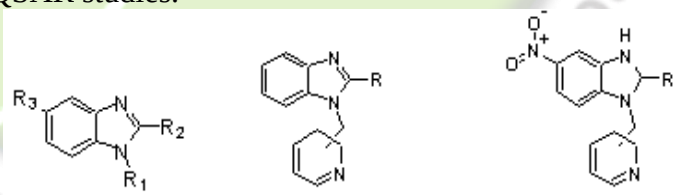
Hernández-Luis F *et al* reported 2-(Trifluoromethyl)-1*H*Benzimidazole derivatives showed the most desirable *in vitro* antiparasitic profile against *Giardia intestinalis*, *Entamoeba histolytica*, *Trichomonas vaginalis* and *Trichinella spiralis*. [26]



1 b R_1= 2,3 $Cl_2C_6H_3O$ R_2= H R_3=CH_3
1 c R_1= H ,R_2=2,3-$Cl_2C_6H_3O$ R_3= CH
1 e R_1=$C_{10}H_7O$ R_2=Cl_2 R_3=H

Anti convulsant Agents

Some potential anticonvulsant compounds have been synthesized, a series of 1, 2, 5-trisubstituted Benzimidazoles derivatives has been reported by Singh J, Grover P *et al* [27].The results of QSAR investigation and the study of various physicochemical properties indicates that the change in linker at position one (R1) does not change the activity of the synthesized compounds and optimum chain length at position two (R2) is responsible for the anticonvulsant activity. The results also showed that the synthesized compounds with electron withdrawing group such as nitro at position five (R3) have been reported to possess better anti-convulsant activity as predicted by QSAR studies.

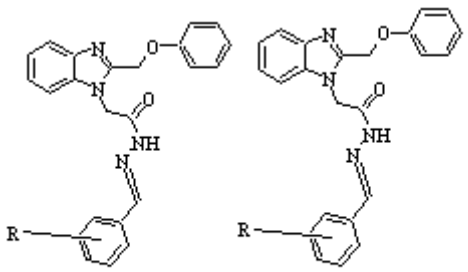


R_1=Picoline,
R_2=varyin
R_3=NO_2

STR II, R=H,CH_3,C_2H_5,C_3H_7,C_4H_9

STR III, R=H,CH_3,C_2H_5,C_3H_7,C_4H_9, alkyl chain

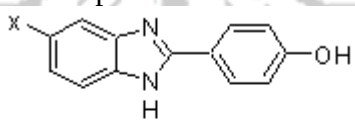
Mohammad Shaharyar *et al*[28] reported Various derivatives of 2-[2-(phenoxymethyl)-1H-benzimidazol-1-yl]-N0-[(Z)-phenylmethylidene] acetohydrazide and some compounds containing oxadiazole bearing Benzimidazole were synthesized. Two compounds 7g and j were found to be potent in both the screens and their protective index was found to be better than standard drugs used(phenytoin, ethosuximide).



(R=4-F) R=NO_2

Topoisomerase I inhibitor

A. Selcen Alpan1 *et a l* [29] reported three 1*H*-Benzimidazole derivatives with different electronic characteristics at position 5-, namely 5-chloro-4-(1*H*-Benzimidazole-2-yl)phenol (Cpd I), 5-methyl-4-(1*H*-Benzimidazole- 2-yl)phenol (Cpd II) and 4-(1*H*-Benzimidazole-2-yl)phenol (Cpd III), were synthesized and evaluated for their effects on mammalian type I DNA topoisomerase activity using quantitative *in vitro* plasmid supercoil relaxation assays. Among the compounds, 5-methyl-4-(1*H*-Benzimidazole-2-yl)phenol (Cpd II) manifested relatively potent topoisomerase I inhibition

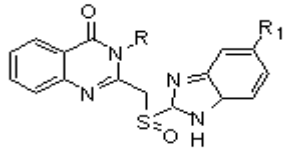


Sr. NO	X
Cpd 1	Cl
Cpd 2	CH_3
Cpd 3	H

Antiulcer activity

Dubey PK et al [30] reported Substituted Benzimidazoles are potent inhibitors of Parietal cell proton pump, the H+/K+ ATPase, the substituted Benzimidazoles are capable of blocking gastric acid secretion in response to some stimuli. For the activity sulfoxide group, methylene group with hetercycles is important for activity.

Avinash Patil et al [31] reported 2-[5-substituted-1-H-benzo(d)imidazol-2-yl sulfinyl]methyl-3-substituted quinazoline-4- (3H)-one derivatives(a –o) and tested for antiulcer activity against pylorus ligation-induced, aspirin induced and ethanol induced ulcer in rat model .among which compounds k and n showed higher activity than omeprazole used as standard.

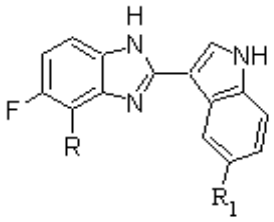


(R_1=$OCHF_2$ R=3,4-dimethoxyphenyl)
(R_1=$OCHF_2$ R= 2-pyrazine)

Antioxidant activity

Anisimova VA et al [32] reported Some compounds possessing dihydrochlorides have also been reported possessing antioxidant activity, these salts also possess mild platelet and erythrocyte antiaggregant activity. Nikano H et al[18] reported In another approach it was found out that using trimethyl group with Benzimidazole also adds antioxidative property by 5-lipoxygenase inhibitory action.

ZA Alagoz *et al* [33] reported Synthesis of some 6-flouro-5-substituted Benzimidazole 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 (e) showed strong super scavenging effect on superoxide anion at 10-3 M concentration.

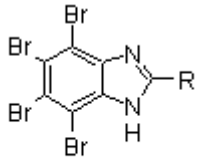


	R	R_1
a.	4-$CH_3C_5H_{10}N$	
b.	4-$CH_3C_5H_{10}N$	
c.	4-$C_6H_5C_4H_9N_2$	
d.	4-$C_6H_5C_4H_9N_2$	Br
e.	4-$C_6H_5C_4H_9N_2$	OCH_3

Protein Kinase Ck2 Inhibitors

Protein kinase CK2 is a highly pleiotropic enzyme whose high constitutive activity is suspected to be instrumental to the enhancement of the tumour phenotype and to the propagation of infectious diseases . Mario A. Pagano *et al*[34] reported a novel compound, 2-dimethylamino- 4,5,6,7-tetrabromo-1H-Benzimidazole (DMAT), which is superior to the commonly used specific CK2 inhibitor 4,5,6,7-tetrabromobenzotriazole (TBB) in several respects. DMAT displays the lowest Ki value ever reported for a CK2 inhibitor (40nM); it is cell permeable and its efficacy on cultured cells, both in terms of endogenous CK2 inhibition and induction of apoptosis, is several fold higher than that of TBB .

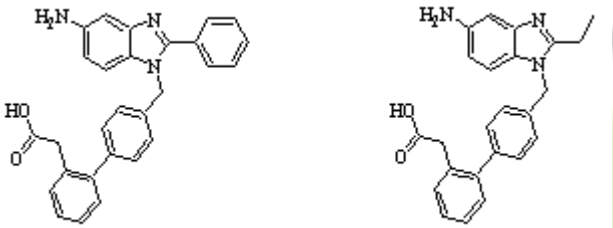
QSAR studies were carried out on 4,5,6,7 tetra-bromo Benzimidazole derivatives by Tripathi *et al* [35] and having the inhibitory activity data (IC50) and the values converted in to –log IC50 (μM), compound 10a (0.797), 10b (0.177), 10c (0.607), by these values compound 10b shown effective inhibitory concentration



R=NH_2, Br, $NHCH_3$

Anti hypertensive Activity

A new series of non peptide angiotensin(A-II) receptor antagonist has been prepared. N-(biphenyl methyl) imidazoles. (A) 5-phenyl-1-(2'carboxy biphenyl-4-yl, (B)5-ethyl-1-(2'carboxy biphenyl-4-yl. Benzimidazoles reported by B. Anil reddy [36] and they produce a potent hypertensive effect upon oral administration.



Conclusion.

Present studies reflect that benzimidazole is a nucleous that can be explored in medicine and drug discovery area as it has numerous biological activities. Moreover reported literature reveal that benzimidazole based derivatives can act as alternate medicine to circumvent problem like resistance associated with currently available drugs. Therefore this substrate has a tremendous scope for the discovery of new, better, safe and more potent chemotherapeutic agents.

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