Review Article

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# BENZIMIDAZOLE: AN OVERVIEW

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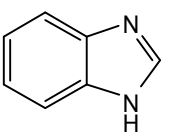
**ABSTRACT**

Benzimidazole derivatives are versatile nitrogen containing heterocyclic compounds which have long been known as a promising class of biologically active compounds possessing wide variety of biological and pharmacological activities like antibacterial, anti-inflammatory, anti-ulcer, anti-diabetic etc. Scientists have elucidated that Benzimidazole system possesses the variable sites like position 2 and 5 which can be suitably modified to yield potent therapeutic agents.The present review covers the chemistry and pharmacological activities of substituted bezimidazoles.

**Keywords:** Benzimidazole, anti-fungal, anti-histaminic, anti-convulsant, anti-inflammatory, analgesic, anti-viral, anti-oxidant, anti-cancer and anti-ulcerative.

## INTRODUCTION

Benzimidazole is as aromatic heterocyclic organic compound. The synthesis of benzimidazole based polyheterocycles draw the attention of pharmacists from last few decades as it functions as an important pharmacophore in medicinal chemistry and pharmacology. Basically, benzimidazole is a bicyclic compound consisting of the fusion of benzene with imidazole which ultimately gives a privileged structure. This magical moiety possesses many pharmacological properties. Till now the most prominent benzimidazolemoiety is *N*-ribosyl-dimethylbenzimidazole present in nature and it serves as the axial ligand for cobalt in vitamin $B_{12}$.[1]




Benzimidazole

Benzimidazolepossess many biological activities such as anti-microbial, anti-fungal, anti-histaminic, anti-inflammatory, anti-viral, anti-oxidant, anti-cancer, anti-ulcerative etc., that's why benzimidazole derivatives are considered as an important moiety for the development of molecules of pharmaceutical interest.[2,3]

There is biological relevance of many heterocyclic building blocks is due to the structural similarity to purine nucleobase and as benzimidazole derivative also which selectively inhibits the endothelial cell growth and then suppresses the process of angiogenesis in vitro as well as in vivo.[3]

In addition to this activity, substituted benzimidazoles plays the role of potent inhibitors of parietal cell $H^+/K^+$ ATPase (proton pump).[4]

Moreover, a benzimidazole when substituted with proline bis-amide, it is helpful in curing insomnia and promotes sleep; it acts as a potent orexin inhibitor which was found from high throughput screening. Orexins plays a wide range of functions in CNS which includes regulation of normal sleep-wake cycle and feeding behaviors. Patients of narcolepsy have seen with a disfunctioning of neurons responsible for orexin production.[5]

Benzimidazoles when substituted with aminothio carbamoyl hydrazine carbonyl, 1,3,4-thiadiazole and 4H-1,2,4-triazole at 1st position via a methyl chain and the 2nd position is substituted with phenyl, *p*-chlorophenyl, *p*-methoxyphenyl and pyridinyl rings then the derivatives of benzimidazolemoiety shows potent antioxidant properties.[6]

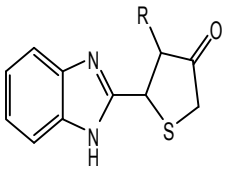
The planar chromophoric ability of benzoannulatedbenzimidazole such as benzimidazo [1,2-a]quinolines or benzimidazo[1,2-a]quinazolines have the ability to get inserted between adjacent base pairs of DNA molecule in the intercalation process and also they can be used as fluorescent probes in assays(homogeneous) of biological molecules.[7]

Some reports suggested that benzimidazoles substituted with hydrogen at 1st position were found active against E.histolytica.[8]

## PHARMACOLOGICAL ACTIVITIES

### Anti-inflammatory activity

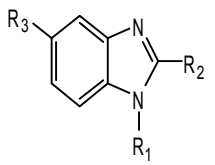
**Suresh** *et al.,* (2011) synthesized derivatives having thiophene nuclei bind with benzimidazole moiety **1**. Newly synthesized compounds were then screened for anti-inflammatory activity and showed significant effect when compared with standard Diclofenac sodium.[9]



R= cinnamaldehyde, m-nitrobenzaldehyde, m-methoxy benzaldehyde

(1)

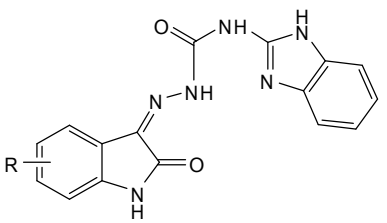
**Thakurdesai** *et al.,* (2007) synthesized benzimidazole-2-carboxylic acid derivatives **2**. They were tested for acute anti-inflammatory activity and found to be potent anti-inflammatory agent.[10]



$R_1$= H, $CH_2$-Ar
$R_2$= COOH, $CH_2COOH$, $CH_2CH_2COOH$
$R_3$= H, $NO_2$, Cl, $OCH_3$, $OC_2H_5$

(2)

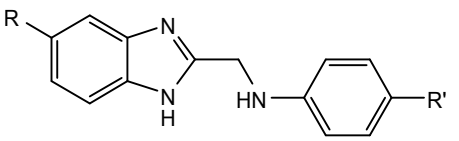
**Babu** *et al.,* (2010) synthesized novel *N*-(1*H*-Benzimidazol-2-yl)-2-Isatinylidene-Hydrazinecarboxamide Derivatives **3**. These agents were then evaluated for anti-inflammatory effect and found to be potent.[11]



R= 5-$CH_3$, 5-$NO_2$, 7-COOH, 7-Br, 7-Cl

(3)

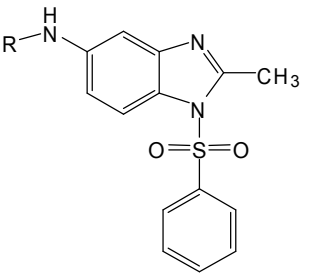
**Achar** *et al.,* (2010) have synthesized a series of 2-methylaminobenzimidazole derivatives**4**. The newly synthesized compounds were screened for analgesic and anti-inflammatory activities. Compounds 2 and 7 showed a potent analgesic (89% at 100 mg/kg b.w.) and anti-inflammatory (100% at 100 mg/kg b.w.) activities.[12]



R= H, Br
R'= Cl

(4)

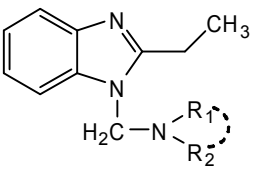
**Gaba** *et al.,* (2010) synthesized a series ofnovel 5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole derivatives**5**. These compounds were screened for anti-inflammatory and analgesic activity as well as gastric ulcerogenic effects. These derivatives showed good activity.[13]



a= *p*-$NH_2C_6H_4$
b= *o*-$NH_2C_6H_4$
c= *p*-$NH_2C_7H_6$

(5)

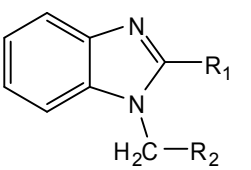
**Mariappan** *et al.,* (2011) have synthesized a new series of [1-(*N*-substituted amino) methyl]-2-ethyl benzimidazole derivatives**6**. These derivatives were screened for analgesic and anti-inflammatory activity. These derivatives were showed excellent activity.[14]



$-NR_1R_2$
Piperidino
3,4-dichloroanilino
4-flouroanilino
4-bromoanilino

(6)

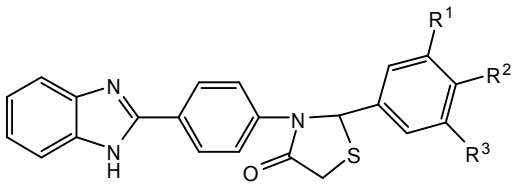
**Jesudason** *et al.,* (2009) have synthesized a novel series of *N*-Mannich bases of benzimidazole derivatives**7**. These compounds were screened for analgesic, anti-inflammatory and *in-vitro* bovine corneal permeability activities. Compounds **7** was found to have potent activity.[15]



$R_1$= -CH=$CHC_6H_5$
$R_2$= $-N(C_2H_5)_2$, $-NC_5H_5$

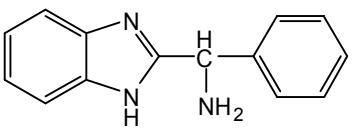
(7)

**Shanmugapandiyan** *et al.,* (2010) synthesized A new series of 2-[4-(azetidin-2-one)-3-chloro-4-phenyl]-1*H*-Phenylbenzimidazole and 2-(thiazolidin-4-one)-phenyl-1*H*-Phenylbenzimidazole**8**. These derivatives were screened for antibacterial and anti-inflammatory activity. Compounds $8_1$ and $8_3$ were showed good analgesic and anti-inflammatory activity.[16]



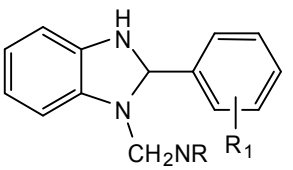
$R^1$= H
$R^2$= H, OH
$R^3$= H
(8)

**Reddy** (2010) has synthesized 1,2-disubstituted benzimidazole derivatives**9**. These derivatives were screened for anti-inflammatory activity. Compound showed potent activity.[17]



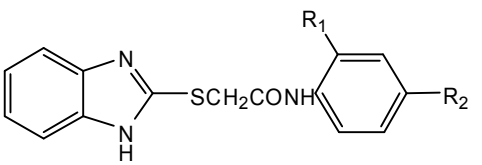
(9)

**Leonard** *et al.,* (2006) have synthesized some new Phenyl benzimidazole derivatives**10**. These derivatives were screened for anti-inflammatory activity. The compound 1c was showed maximum (54.6%) inhibition of edema at doses of 50 mg/kg.[18]



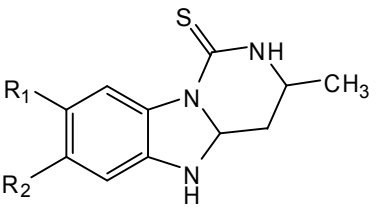
(1c; R=dimethylamine, $R_1$=Cl)
(10)

**Gaud** *et al.,* (2011) have synthesized a new series of substituted benzimidazole derivatives**11**. These compounds were screened for analgesic and anti-inflammatory activities by biological evaluation method and also for other possible pharmacological activities including antibacterial activity. These derivatives were showed potent analgesic and anti-inflammatory activity.[19]



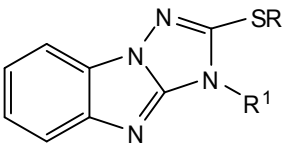
$R_1$= $CH_3$, Cl
$R_2$= OH, $NH_2$
(11)

**Sondhi** *et al.,* (2002) have synthesized some novel pyrimido[1,6-a]benzimidazole derivatives**12**. These derivatives were screened for anti-inflammatory, analgesic and anti-amoebic activity. Compound **12c** was showed good activity.[20]



$R_1$= $NO_2$
$R_2$= H
(12)

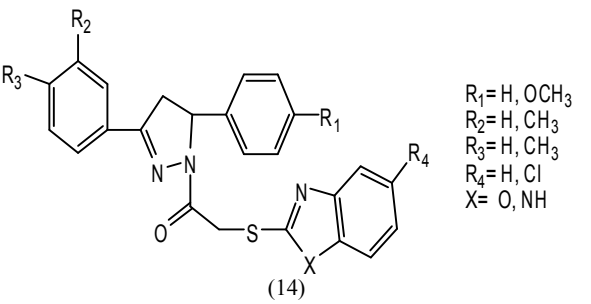
**Mohamed** *et al.,* (2006) have synthesized some new derivatives of 1,2,4-triazolo[2,3-a]benzimidazoles**13**. These derivatives were screened for antifungal, analgesic and anti-inflammatory activity. The compound **13d** was found to be most potent.[21]



R=$CH(CH_3)_2$
$R^1$=*p*-$ClC_6H_4CO$)
(13)

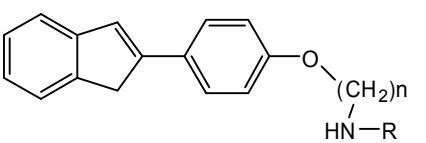
**Analgesic activity**

**Kaplancikli** *et al.,* (2008) synthesized 1-[(Benzoxazole/benzimidazole-2-yl)thioacetyl]pyrazoline derivatives **14** which then screened for analgesic activity and the synthesized compounds were found to be potent.[22]



$R_1$= H, $OCH_3$
$R_2$= H, $CH_3$
$R_3$= H, $CH_3$
$R_4$= H, Cl
X= O, NH
(14)

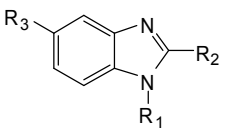
**Shukla A.** (2012) synthesized benzimidazoles derivative involves subsequent synthesis of 4-(2-chloro-ethoxy)-benzaldehyde, 4-methyl benzaldehyde followed by benzimidazoles derivative **15**. The synthesized benzimidazole compounds were screened for analgesic and anticonvulsant activity and some compounds showed significant analgesic activities.[23]



R= N methyl cyclo hexyl amine,
di propyl amine, 1-phenyl piperazine,
N methyl piperazine
(15)

**Anti-convulsant activity**

**Singh** *et al.,* (2010) synthesized a series of 1, 2, 5-trisubstituted benzimidazoles derivatives **16a-c**. The compounds with optimum chain length at position two ($R_2$) and electron withdrawing group at position five ($R_3$) showed better anticonvulsant activity.[24]



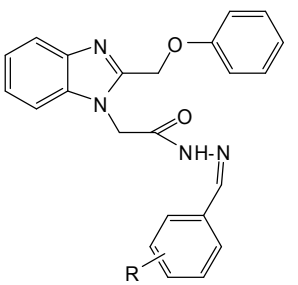
(a)
$R_1$= 1-picoline
$R_2$= H, $CH_3$, $C_2H_5$, $C_3H_7$
$R_3$= H, $NO_2$

(b)
$R_1$= 2-picoline
$R_2$= H, $CH_3$, $C_2H_5$, $C_3H_7$
$R_3$= H, $NO_2$

(c)
$R_1$= 3-picoline
$R_2$= H, $CH_3$, $C_2H_5$, $C_3H_7$
$R_3$= H, $NO_2$

(16)

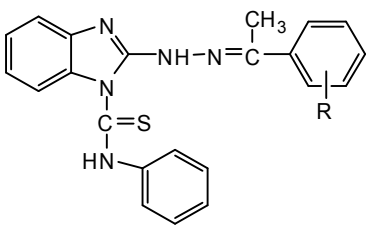
**Shaharyar** *et al.,* (2011) synthesized various derivative of 2-[2-(phenoxymethyl)-1*H*- benzimidazole-1-yl]-*N'*-[(*Z*)-phenylmethylidene]acetohydrazide and some compounds containing oxadiazole bearing benzimidazole**17**. Compoundwas found to have better protective index than standard drugs used.[25]



R= 4-F, $NO_2$

(17)

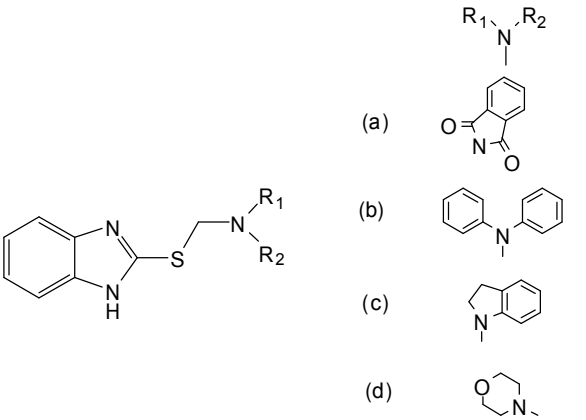
**Bhrigu** *et al.,* (2012) synthesized a series of new 2-[(1-substituted phelylethylidine) hydrazine]-*N*-phenyl-1*H*-benzo[*d*]imidazole-1-carbothioamides **18** which were then screened for anticonvulsant activity. Some of the compounds exhibited anticonvulsant activity.[26]



R= 4-Br, 4-F, 2-Cl, 4-$NO_2$, 4-Cl

(18)

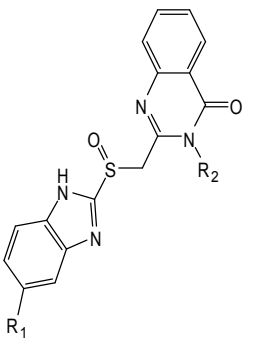
**Anandarajagopal** *et al.,* (2010) synthesized a series of 2-mercaptobenzimidazole derivatives **19**. Anticonvulsant activity was evaluated for newly synthesized derivatives. Most of the synthesized compounds exhibited anticonvulsant activity.[27]



(19)

**Anti-ulcer activity**

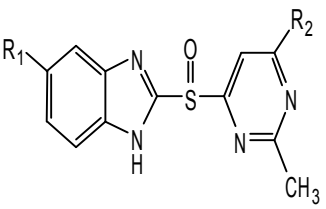
**Patil** *et al.,* (2010) synthesized 2-[5-substituted-1-*H*-benzo(*d*)imidazolyl-2-ylsulfinyl] methyl 3-substituted quinozoline-4-(3*H*) derivative**20** was synthesized and tested for anti-ulcer activity. Compound **20a** and **20b** showed higher activity than omeprazole used as standard.[28]



| | $R_1$ | $R_2$ |
|---|---|---|
| (a) | 3,4 dimethoxy phenyl | $OCHF_2$ |
| (b) | 2 pyrazine | $OCHF_2$ |

(20)

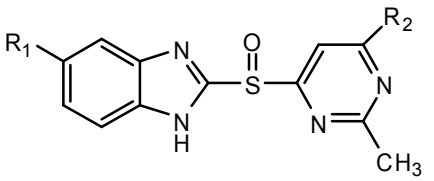
**Nadeem** and **Khan** (2011) studied to investigate the effect of 2-(pyrimidinylsulfinyl) benzimidazole derivative **21** and the compound was found to have good antiulcer activity.[29]



2-[(2-methyl, 6- alkyl pyrimidin-4-yl)sulfinyl]-5-alkyl-1-H- benzimidazole

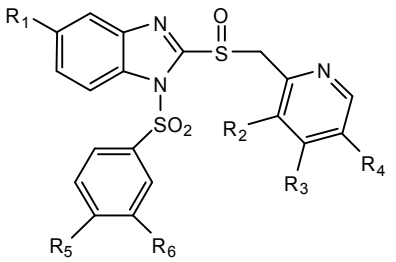
(21)

**Thakare** and **Asnani** (2011) synthesized a series of all new substituted 2-(pyrimidinylsulfinyl) benzimidazole**22**. All compounds were tested for antiulcer and anti-secretary activity and found to be potent.[30]



(22)

**Shin** *et al.,* (2009) synthesized new aryl sulfonyl proton pump inhibitor (PPI) **23** prodrug forms. These prodrugs provided longer residence time of an effective PPI plasma concentration, resulting in better gastric acid inhibition.[31]



$R_1$= H, 5MeO, 6MeO, $5CF_2HO$, $6CF_2HO$
$R_2$= Me, MeO
$R_3$= $MeOCH_2CH_2CH_2O$, $CF_3CH_2O$, MeO
$R_4$= H, Me
$R_5$= H, $NH_2CONH$, Cl
$R_6$= H

(23)

## CONCLUSION

The review has concluded with the key pharmacological activities of the Benzimidazole. This moiety has shown a wide range of therapeutic value. This paper comprises of the major pharmacological activities[32] of Benzimidazole and it can be used for further researches. Substituted benzimidazole moiety (specially at the 2nd position) are reported to possess a number of interesting biological activities such as anti-inflammatory, analgesic, anti-convulsant and anti-ulcer activity.[33]

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