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BENZIMIDAZOLE: A PROPITIOUS SCAFFOLD WITH MULTIFARIOUS THERAPEUTIC POTENTIAL

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ABSTRACT
Most of the drugs and pharmacologically active moieties possess heterocyclic ring structure and presence of hetero atoms or groupings evinces privileged specificities in their pharmacological targets. Among the heterocyclic compounds, benzimidazole has emerged as cardinal construction motif, which plays pivotal role in drug development. Benzimidazole scaffold is known to possess some prime pharmacological activities like anti-mycobacterial, antimicrobial, anti-viral, anti-oxidant, anti-inflammatory, anti-hypertensive, etc. This broad spectrum of biological and biochemical activities has been further assisted by the synthetic flexibility of benzimidazole, which permits development of large no of structurally diverse derivatives. Therefore, it is necessary to compile the latest information along with earlier information to understand present status of benzimidazole nucleus in drug discovery. In the present review, various derivatives of benzimidazole possessing anti-mycobacterial, antimicrobial, analgesic and anti-inflammatory potential are brought into limelight and their activity has been elucidated in accordance with structure activity relationship studies.

KEYWORDS: Benzimidazole, Anti-mycobacterial, Anti-Microbial, Analgesic, Anti-inflammatory.

INTRODUCTION
Benzimidazole has been an overriding pharmacophore and privileged structure in medicinal chemistry. Benzimidazole derivatives have versatile pharmacological properties based on their presence in both clinical medicines and compounds with broad range of biological functions. In addition, they are important intermidiates in many organic reactions and act as ligands to transition metals for modelling biological system. In 1872, Hobrecker reported the first ever benzimidazole synthesis of 2,5-dimethylbenzimidazole and 2,6-dimethylbenzimidazole through reduction of 4-methyl-2-nitroacetanilide.[1] The therapeutic potential of benzimidazole nucleus came into limelight when Woolley suggested that benzimidazole can act similar to purines to elicit biological responses.[2] In 1949, Brink identified 5,6-dimethylbenzimidazole as a degradation product of vitamin B_{12}.[3] These incipient reports encouraged the active research to explore the variety of possible biological activities that benzimidazole may possess. After years of active research, benzimidazole and its derivatives have evolved as privileged structures in medicinal chemistry possessing wide range of biological activities summarised in (Fig.1), including antiparasitic, anti-cancer, anti-emetic, anti-ulcer, anti-hypertensive, anti-histaminic, anti-viral and many other therapeutic uses.

Thus, interest has been developed in multi-target drug discovery based on benzimidazole core. In this review, we have attempted to limelight and compile published reports on benzimidazole derivatives which may possibly help medicinal chemist in development of potent and safe analogues bearing benzimidazole scaffold.

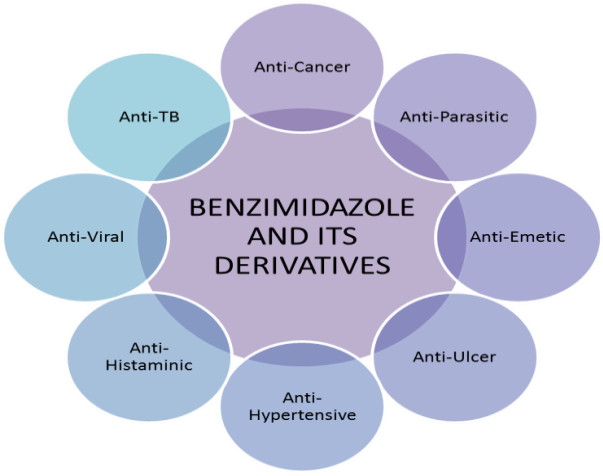


Fig. 1: Activity spectrum of benzimidazole and its derivatives.

Benzimidazole: Chemistry

Medicinal organic chemistry is an emerging research field as unique heterocycle based organic derivatives offer potentials for design of new drug candidates. Benzimidazole (Fig.2) is one of the thoroughly studied nitrogen-based benzo-fused heterocyclic system.

Benzimidazole is an aromatic and planar molecule, systematic numbering of benzimidazole core depicted in (Fig.2). Similar to that of imidazole, a rapid conversion between the –NH– and =N– modules leads to the formation of two tautomers, depicted in (Fig.3). Tautomerism occurs in benzimidazole through either an intermolecular route involving two or more benzimidazole molecules or through interactions with polar solvent such as water.[1]

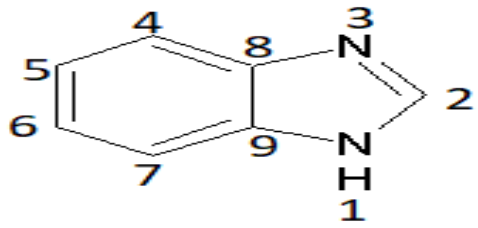


Fig. 2: Chemical structure and Numbering of benzimidazole.

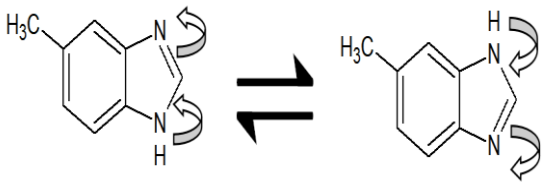


Fig. 3: Tautomerism in benzimidazole.

Physical properties of benzmidazoles

Benzimidazoles are weakly basic, somewhat less basic than imidazole. Thus, they are soluble in dilute acids. Benzimidazoles are also sufficiently acidic and are generally soluble in aqueous alkali and form *N*-metallic compounds. The acidic properties of benzimidazoles are similar to that of imidazoles, seem to be due to stabilisation of ion by resonance.

Benzimidazoles with imide nitrogen are usually more soluble in polar solvents and less soluble in organic solvents. Introduction of non-polar substituents in various positions of benzimidazole ring leads to increased solubility in non-polar solvents. Conversely, introduction of polar groups in molecule increases aqueous solubility. Introduction of substituent in 1-position lowers the melting point. This appears to be due to fact that benzimidazoles containing hydrogen in the 1-position are associated. Melting points of few simpler benzimidazoles are listed in (Fig.4).[1]

Table 4: Melting points of benzimidazoles.

Sr. No.	Benzimidazole	Melting point (^{0}C)
1	Benzimidazole	170
2	1-methylbenzimidazole	61
3	2-methylbenzimidazole	176
4	2-phenylbenzimidazole	294
5	1, 2-diphenylbenzimidazole	112
6	2, 5-dimethylbenzimidazole	203
7	5-methyl-2-phenylbenzimidazole	239
8	2(3*H*)-benzimidazolone	308
9	2(3*H*)-benzimidazolethione	292-293

Chemical properties of benzimidazoles

Benzimidazole ring possess high degree of stability. It is not affected by concentrated sulphuric acid when heated under pressure to 270^{0}C., nor by vigorous treatment with hot hydrochloric acid. It is not affected by treatment with alkalies. Benzimidazole scaffold is quite resistant to reduction; however, benzene ring of benzimidazole may be reduced with the aid of catalytic reduction under certain conditions. Oxidation cleaves the benzene ring of benzimidazole under specific conditions.[1]

Biological Activities

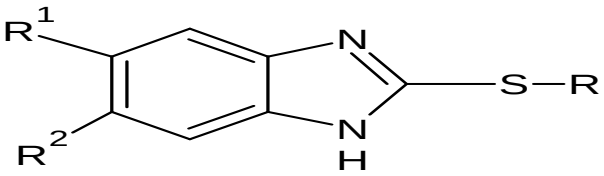
Benzimidazole scaffold is an important core in many entities acting at different targets to elicit variety of pharmacological effects. Benzimidazoles elicit their biological actions through different mechanisms like receptor mediated mechanism, oxidative stress, enzymatic action, etc. Structure activity relationship studies revealed that substitution of various groups on the ring imparts different activities. All seven positions in benzimidazole nucleus can be substituted with variety of substituents; however, most of the biologically active benzimidazole based compounds bear substituents at 1, 2 and/or 5 or 6 positions. In the present review variety of benzimidazole based compounds have been categorised with respect to their biological activities.

1) Antimycobacterial activity

Tuberculosis (TB), is one of the world's deadliest communicable diseases. The bacterium responsible for TB, called Mycobacterium tuberculosis (Mtb), is transmitted by people infected with pulmonary TB who release Mtb into the air through coughing, sneezing or spitting. Approximately 1/3rd of the world's population carry the disease but don't have any symptoms, known as latent infection; however approximately 10% of these people will likely develop active disease during their lifetime and become capable of transmitting the bacterium. Anti-tuberculosis drug resistance is a major obstacle that threatens progress made in tuberculosis care and control worldwide. Drug resistance arises due to improper use of antibiotics in chemotherapy.[4]

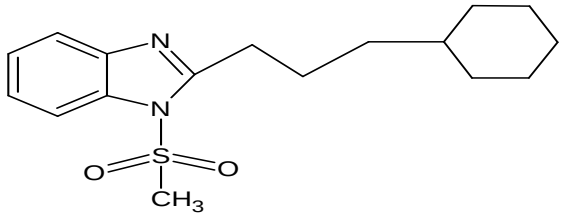
1.1- Benzimidazole derivatives for treatment of tuberculosis

The literature investigation reveals that the derivatives anchored on simple benzimidazole core evidenced a crucial role for the treatment of tuberculosis. Gorska et al. reported the synthesis and evaluation of marcpto-benzimidazole derivatives as antiTB candidates and revealed that the compounds with 5-nitro- and 5,6-dichloro-2-mercapto- benzimidazole**(1:a-d)**, respectively showed considerable antimycobacterial activity.[5] Foks et al.synthesised 2-Substituted benzimidazoles derivatives and evaluated them for antiTB activity, The compounds with cyclohexylethyl or cyclohexylpropyl **(2)** substituents in position C-2 of the benzimidazole increased the antiTB potential, while the presence of the sulfomethyl group at the nitrogen atom doesn't have significant effect on overall activity.[6]



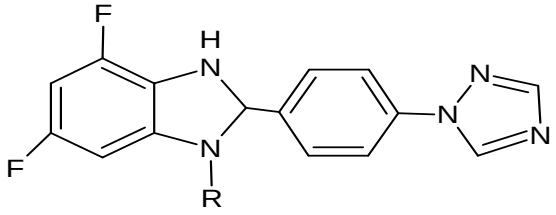
structure (1:a-d)

a) R= 4-nitrobenzyl, R_1=NO_2, R_2=H
b) R= 3,5-dinitrobenzyl, R_1=NO_2, R_2=H
c) R=2,4-dinitrobenzyl, R_1= R_2=Cl
d) R=2,5-dinitrobenzyl, , R_1= R_2=Cl



Structure 2.

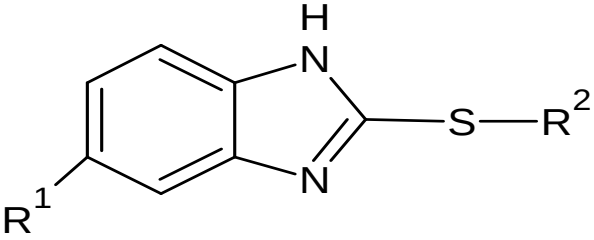
Jadhav et al. synthesised a series of novel fluorobenzimidazoles fused with [1,2,4]-triazoles and were subjected to evalution of their antimycobacterial activity against H37Rv strain. The compounds having electronegative substituents such as fluorine and chlorines **(3:a-c)** exhibited potent activity.[7]



Structure (3:a-c)

a) R= $CH_2(3\text{-}FC_6H_5)$
b) R=$CH_2(3\text{-}ClC_6H_5)$
c) R=$CH_2(4\text{-}FC_6H_5)$

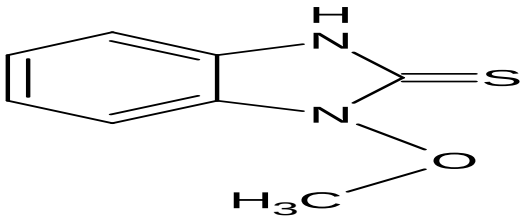
Kazimierczuk et. al. synthesised 2-substituted halobenzimidazoles and evaluated them of antimycobacterial activity, 5-halogeno **(4:a–c)**, 4,6-dihalogeno **(4:d)** and 3,5-dinitro benzimidazoles showed good antiTB activity. From SAR study, 3,5-dinitrobenzylsulfanylbenzimidazoles halogenated at 5-position with a halogen substituent **(4:a–c)** showed considerable activity against Mtb and the two M. kansasii strains used, but only a moderate activity against M. avium. Introduction of additional chlorine or bromine atom onto benzene part of the benzimidazole core did not improve the antimycobacterial activity.[8]



Structure (4:a-d)

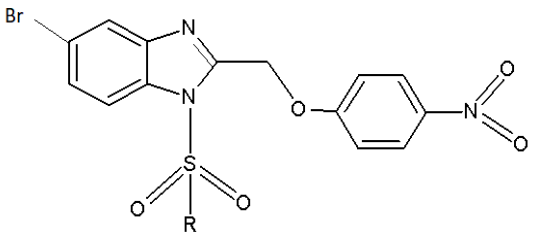
a) R_1= 5-Cl, R_2= 3,5-dinitrobenzyl
b) R_1= 5-Br, R_2= 3,5-dinitrobenzyl
c) R_1= 5-I, R_2= 3,5-dinitrobenzyl
d) R_1= 4, 6-Br, R_2= 4-nitrobenzyl

Vasan et al., have designed and synthesized a 2-thione substituted benzimidazole derivative **(5)** as the most promising Mtb inhibitor. SAR investigations reveals the H-bond donor capacity of the NH and also the 2-thionegroup in **(5)** is important for activity.[9]



Structure 5.

Ranjith et al. designed and synthesised 5 and 6-bromo-1-[(phenyl)sulfonyl]-2-[(4-nitrophenoxy)methyl]-1H-benzimidazoles and evaluated them for antimycobacterial activity. SAR investigations of these compounds suggested that, 5-bromo substituted isomers **(6)** are comparatively more active than 6-bromo substituted isomers of benzimidazoles. Bromine at 5th or 6th position of central benzimidazole is essential element for biological activity.[10]



Structure. 6.

1.2- Structural requirements for antiTB activity

Benzimidazole nucleus substituted at 1, 2, 5 and 6-position with variety of substituents have yielded utilitarian entities with antiTB activity. 4th and 7th position of the nucleus must be unsubstituted for antiTB activity.The 1-position of benzimidazole nucleus was generally substituted with a range of alkyl, aryl, aryl-alkyl or phenyl sulfonyl groups, and cycloalkanes to heteroaryl moieties that were suitably substituted with alkyl or heterocyclic groups; however benzimidazole with sulfonyl at 2-position shows considerable antiTB activity. 2-position can be substituted with a range of alkyl or bulky lipophilic aryl/heteroaryl substituents withalkyl or heterocyclic groups in order to have favorable steric and electronic properties of the molecule. 5 and 6-positions either be unsubstituted or substituted with range of substituents like halogens, nitro, amino, methyl, hydroxyl, sulfonyl, etc. (Fig.5).[11]

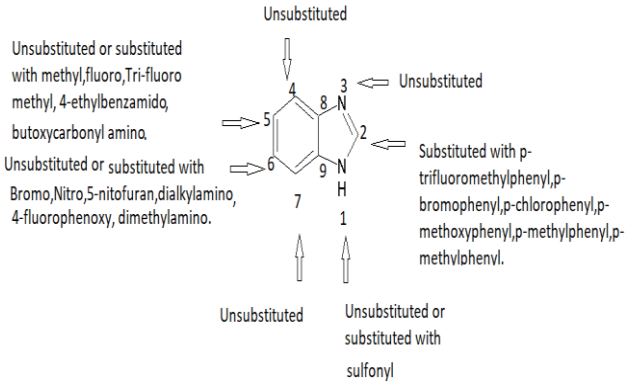
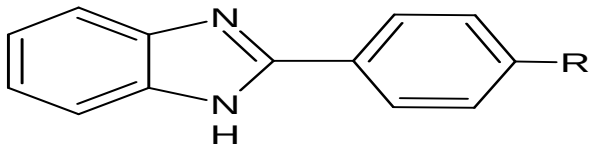


Fig. 5: Structural requirements around benzimidazole scaffold for anti-TB potential.

2) Antimicrobial activity

Microbial drug resistance is a serious issue, especially as increasing numbers of strains are becoming resistant to multiple antimicrobial agents, with some bacteria now being resistant to all available antibiotics. There is thus a critical need to develop new drugs with novel mechanisms of action. Antimicrobial agents constitute a diverse group of chemical entities acting against varied kinds of microbes including bacteria, protozoa, helminths (worms), fungi and viruses. In the present review, compounds having antibacterial and antifungal activities are discussed collectivelyunder the heading of antimicrobials. Molecules with benzimidazole core are attractive targets for synthesis of antimicrobials.

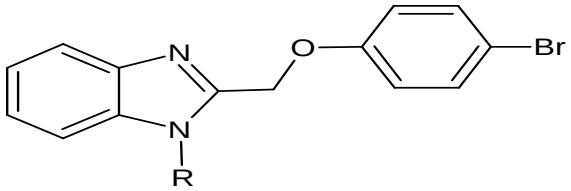
K. Shrikanth kumar et. al. carried out the synthesis and evaluation of 2-aryl substituted benzimidazoles and evaluated these compounds for anti-bacterial activity against both gram-positive and gram-negative bacterial species. Compound **(7:b)** shows good activity against B. *subtilis* while compounds **(7:b, d)** shown good activity against S. *aureus*. SAR of these studies reveal that 4-fluorophenyl moiety in 2-position of benzimidazole core is crucial for anti-bacterial activity.[12]



Structure (7:a-e)

R=a) 4-NO_2
b) 4-F
c) 4-OH
d) 4-OCH_3
e) 4- CH_3

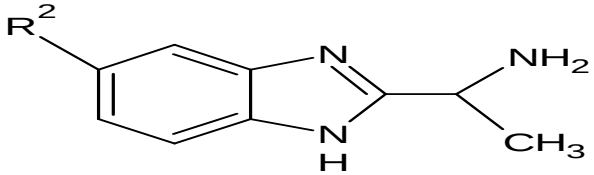
G. Dnyandev and V. Sanjay reported the synthesis of N-substituted 2-(4-bromo-phenoxymethyl)-1*H*-benzimidazole derivatives and evaluated them for antimicrobial activity. Compounds having carbonyl **(8:c, d)** and sulphonyl **(8:a, b)** functionalities were found to have promising antibacterial activity against E. *coli* whereas all compounds were highly active against S. *aureus.*[13]



Structure (8:a-h)

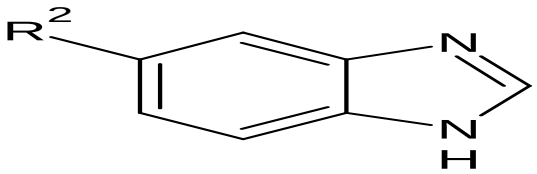
a) R= Trifluoromethanesulphonyl
b) R= 4-tolunesulphonyl
c) R= Methoxy carbonyl
d) R= Ethoxy carbonyl
e) R= methyl
f) R= ethyl
g) R= benzyl
h) R= butyl
i) R= iso-butyl

Alasmary et. al. synthesised benzimidazole derivatives and evaluated them as potential antimicrobial agents. Their studies revealed that some derivatives of benzimidazole offer significant possibilities for development of new broad spectrum antimicrobial agents. SAR investigations suggested that benzimidazoles substituted with halogen functionality in 5-position provides promising antimicrobial activity (9, 10, 11).[14]



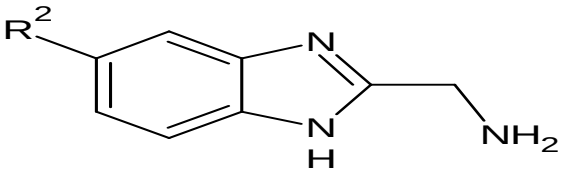
Structure 9.

R_2= 1) Cl
R_2= 2) Br



Structure 10.

$R_{2=}$ Br



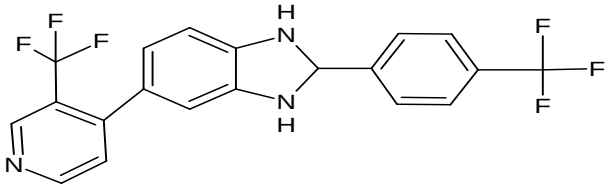
Structure 11.

R_2= Cl
R_2= F
R_2= NO_2

3) Analgesic and anti-inflammatory activity

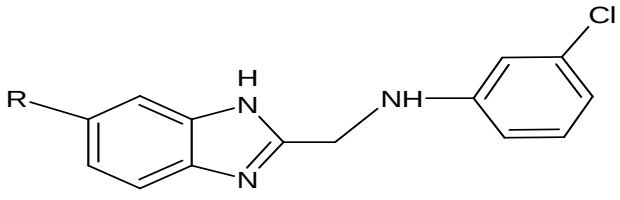
A number of reports reveal that the benzimidazole and its derivatives can be used actively on different clinically approved therapeutic targets for treatment of pain and inflammation.

Fletcher et. al. reported the synthesis of benzimidazole derivatives with potent affinity for hTRPV-1 receptors. SAR studies reveal that modification of compound **(12)** i.e. replacement of 4-trifluoromethyl group with tert. butyl, methyl or fluoro substituents leads to decrease in activity.[15]



Structure 12.

Achar et. al. carried synthesis of novel 2-substituted benzimidazole derivatives and evaluated them with aid of carrageenan-induced paw edema model. Introduction of bromo substituent in 5-position subsequently leads to increase in the activity(13:b).[16]



Structure (13:a-b).

R= H and R= Br

3.1- Structural requirements for analgesic and anti-inflammatory acitivity: Benzimidazole nucleus substituted at 1, 2, 5 and 6-position with different functionalities provides potent analgesic and anti-inflammatory agents. 4 and 7-position must be unsubstituted for compound to possess analgesic and anti-inflammatory potential. The position 1st of benzimidazole either be unsubstituted or may be substituted with methyl, phenylsulfonyl, cycloalkane, aryl/heteroaryl moieties. 2-position may be substituted with alkyl, aryl, heteroaryl or heterocyclic moieties. 5 or 6-position of benzimidazole core may be unsubstituted or substituted with halogens, nitro, hydroxyl, alkoxy, aryl or heteroaryl groups(Fig.6).[17]

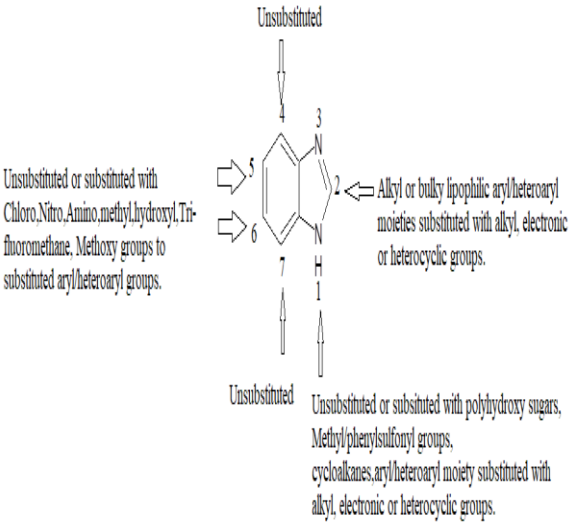


Fig. 6: Structural requirements for analgesic and anti-inflammatory activity.

CONCLUSION

Numerous studies in the field of pharmaceutical medicinal chemistry has revealed that benzimidazole derivatives can act on variety of targets and are capable of fostering therapeutic effects. This fact has drawn the attention of many researchers and benzimidazole derivatives are being intensively investigated for their potential therapeutic properties. Benzimidazole has emerged as promising bioactive heterocyclic compound that will bestow exemplary results in the nearest scientific future. The present review is expected to be helpful to researchers and acadamicians while exploring therapeutic potential of benzimidazole and its derivatives.

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