Benzimidazole: An Attractive Pharmacophore in Medicinal Chemistry

R. Sivakumar1*, R. Pradeepchandran2, K. N. Jayaveera3, P. Kumarnallasivan1, P.R.Vijaianand1, R. Venkatnarayanan1

1 Department of Pharmaceutical Chemistry, RVS College of Pharmaceutical Sciences, Sulur, Coimbatore- 641 402, Tamilnadu. India.
2 Department of Pharmacy, Narayana College of Pharmacy, Nellore, Andrapradesh. India.
3 Jawaharlal Nehru Technological University of college of Engineering, Anantapur-515 002, Andrapradesh. India.

*Corresponding Author: E-mail: andrilan@rediffmail.com, Mobile: +919791903606

Received: 24/07/2010, Revised: 29/09/2010, Accepted: 01/11/2010

ABSTRACT
Benzimidazoles exhibit broad range of biological activities. Several benzimidazoles are used in therapy such as albendazole, mebendazole, flubendazole, fenbendazole, Omeprazole, Lansoprazole, Clofazone. Benzimidazole derivatives play vital role in biological field such as antimicrobial, antiviral, anti diabetic, antiulcer and anticancer activity. The present review highlights the recently synthesized benzimidazoles possessing important potential biological activities.

KEYWORDS: benzimidazole, antimicrobial, anti-ulcer, biological activity.

INTRODUCTION
Benzimidazole is also called as benziminazole, 3-benzodiazole, azindole, benzoglyoxaline, 3-azaindole, 1,3-diazaindene with melting point of 170-172°C and occurs as white crystals. It is used as muscle relaxant [1]. A group of therapeutic agents are based on the benzimidazole nucleus; this heterocyclic system provides a unifying theme for the subset of anthelmintic compound [2]. Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio [3].

IMPORTANCE OF BENZIMIDAZOLE IN MEDICINAL CHEMISTRY
Benzimidazoles 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 [1]. Several benzimidazoles are commercially available as pharmaceuticals. Benzimidazoles are most widely studied drugs as anthelmintic. Recent studies have established that benzimidazole carbamates such as Albendazole (1), mebendazole (2), flubendazole (3), and fenbendazole (4) inhibit the in vitro growth of Trichomonas vaginalis [4] and G. lamblia [5, 6]. Clinical reports have shown that albendazole is as effective as metronidazole, the choice drug for the treatment of giardiasis. Benzimidazole carbamates, well known therapeutic agents used mainly as anthelmintics, have a broad antiparasitic spectrum of activity, low toxicity and have been used successfully to treat gastrointestinal helminthic infections.

Another area of important use of benzimidazole has recently been as proton pump inhibitor. Omeprazole (5) is appeared for the treatment and reduction of risk of recurrence of duodenal ulcer, gastric ulcer and pathological
hypersecretory conditions. Lansoprazole (6) is used for the treatment of duodenal ulcer, and Zollinger-Ellison syndrome.

\[
\text{Omeprazole (5)}
\]

\[
\text{Lansoprazole (6)}
\]

Another benzimidazole containing drug Clofazone (7) exhibits antidepressant activity.

\[
\text{Clofazone (7)}
\]

**COX inhibitors**

A series of 2-[(2-alkoxy-6-pentadecylphenyl) methyl] thio]-1H-benzimidazoles/benzothiazoles and benzoazoles (8) from anacardic acid and investigated their ability to inhibit human cyclooxygenase-2 enzyme (COX-2). The active compounds were screened for cyclooxygenase-1 (COX-1) inhibition. Compound 13 is 384-fold and 19 is more than 470-fold selective towards COX-2 compared to COX-1. Thus, this class of compounds may serve as excellent candidates for selective COX-2 inhibition [7].

\[
\text{Antiviral activity}
\]

A serious of 2-pyridyl-1H-benzimidazole-4-(N-carboximide) derivatives (9-10) are reported as antiviral activity against COX Sackie virus B3, a non-enveloped single positive-strand RNA virus belonging to the picornaviridae family, which is the major cause of virus-induced human myocarditis [8].

\[
\text{Ashish kumar Tewari et al synthesized two series of N-substituted -2- substituted benzimidazole derivatives , viz. 1-benzyl-2- substituted benzimidazole 11 (a-e) and 1- (p- chlorophenyl )-2- substituted benzimidazole 11 (f-j) and tested for their anti-viral activities. These compounds have been screen for Tobacco mosaic viruses and Sunhemp rosette viruses and showed significant activities [9].}
\]

11a R= CH₂CH₂COOH, R’= -CH₂C₆H₅
11b R= CH₂CH₂COOH, R’= -C₆H₅Cl
11c R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11d R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11e R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11f R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11g R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11h R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11i R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11j R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11k R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11l R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11m R= CH₂CH₂OH (O), R’= -C₆H₅Cl
11n R= CH₂CH₂OH (O), R’= -C₆H₅Cl
Angiotensin-II Antagonist

5-Nitro and 5-amine benzimidazole derivatives with varying substitutions at 2-position of benzimidazole and compounds (12 a-c) have been reported as good angiotensin II antagonistic activity [10].

Another series of benzimidazoles have been synthesized (13-14) and shown to be angiotensin II receptor antagonists. The SAR of these new antagonists has been explored. The benzimidazole antagonists displaced angiotensin II in binding studies in vitro with IC₅₀ values in the range 10⁻⁵-10⁻⁷ M and antagonized the hypertensive effects of angiotensin II in vivo with ED₅₀ values in the range of 5-20 mg/kg [11].

Antimicrobial activity and anti protozoal activity

Ilkay oren et al synthesized some new 2,5-and/or 6 substituted benzimidazole derivatives and tested them for antimicrobial activity against gram positive, gram negative bacterial strains and antifungal activity towards C. albicans. From this study, the compounds were moderately active against different strains of bacteria and fungus. Significant activity was observed in compound (17) 5-chloro-2-(2cyclohexylethyl) benzimidazole [13].

Khalafi-Nezhad et al synthesized benzimidazole and imidazole chloroaryloxyalkyl derivatives. The compounds were screened for antimicrobial activity against S. aureus, S. typhi. Compound (18) showed considerable in vitro antibacterial activities against both bacteria [14].

Andrzejewska et al has synthesized 5-substituted 4, 6-dibromo and 4, 6-dichloro-2-mercapto benzimidazoles (19 a-b). All the compounds were screened for antimicrobial activity against E.coli, Proteus vulgaris, Bordetella bronchiseptica, pseudomonas aeriginoa, Stenotrophomonas maltophilia, staphylococcus aureus, Enterococcus faecalis, Bacillus stearothermophilus, Bacillus substilis, and
**Bacillus cereus.** The results of this confirmed that gram positive bacteria were more susceptible to all examined 4, 6-dihalogenated 6-substituted-2-mercapto benzimidazoles. The most active agents were (19a-b) when compared with reference agent nitrofurantoin [15].

![Diagram](19_a-b)

\(a = R, R_1 = \text{Cl}, R_3 = \text{CH}_2\text{-CH}_2\text{(C}_6\text{H}_4\text{)}\text{-P-NO}_2\)  
\(b = R, R_1 = \text{Br}, R_3 = \text{CH}_2\text{-CH}_2\text{(C}_6\text{H}_5\text{)}\)

Shelar et al synthesized some alkyl thio aryl substituted benzimidazole derivatives. The synthesized compounds have been screened for *in vitro* antibacterial activity against *Klebsiella*, *E.coli* and *E.fecalis*. The compounds (20) have shown varying degree of antibacterial activity [16].

![Diagram](20)

(a) \(R_1 = \text{Cl}, R_2 = \text{H}, R_3 = \text{Cl}\)  
(b) \(R_1 = \text{Cl}, R_2 = \text{Cl}, R_3 = \text{Cl}\)  
(c) \(R_1 = \text{Cl}, R_2 = \text{NO}_2, R_3 = \text{Cl}\)

Anelia et al synthesized some new thiazolo [3,2-a] benzimidazole derivatives. The effectiveness of compounds (21) and (22) in the intestinal phase of *Trichinellosis spiralis* was 100% and in the muscle phase were 88% and 80% at a concentration of 100mg/kg [17].

![Diagram](21)

![Diagram](22)

Ilkay Yildiz-Oren synthesized a series of multisubstituted benzoazoles, benzimidazoles and benzthiazoles (23-25) as non-nucleoside fused isosteric heterocyclic compounds and tested for their anti-bacterial against various gram-positive and gram-negative bacteria and anti-fungal activity against the fungus *Candida albicans*. In these sets of non-nucleoside fused heterocyclic compounds electron withdrawing groups at position 5 of the benzazoles increased the activity against *C. albicans* [18].

![Diagram](23)

![Diagram](24)

![Diagram](25)

Seckin Ozden et al synthesized a series of benzimidazole-5-carboxylic acid alkyl ester derivatives carrying amide or amidine substituted methyl or phenyl groups at the position C-2 and evaluated for antibacterial and anti-fungal activities against *S.aureus*, methicillin resistant *S.aureus* (MRSA), *S.faecalis*, methicillin resistant *S.epidermidis* (MRSE) *E.coli* and *C.albicans*. Aromatic amidines derivatives 26-28 exhibited the best inhibitory activity [19].

![Diagram](26)

![Diagram](27)

![Diagram](28)
Shipra Parmar et al synthesized 1-methyl [(N-alkyl phthalyl)-(benzimidazo)-3'-chloro-4'-substituted azetidin-2-ones (29-30) which shown promising antimicrobial activity against *salmonella typhimurium* [20].

Sivakumar et al synthesized some novel 2-(6-fluorochroman-2-yl)-1-alkyl / acyl / aroyl-1H-benzimidazoles. Some compounds (31) exhibited promising antibacterial activity against *salmonella typhimurium* [21].

Yun He et al synthesized a series of 2-piperidin-4-yl benzimidazoles (32-34) and evaluated for antibacterial activities against both gram positive and gram negative bacteria of clinical importance, particularly *enterococci* [22].
Yun He and et al synthesized a series of novel benzimidazole derivatives via parallel solution phase chemistry. Many of these compounds (35) were found to inhibit the growth of *Staphylococcus aureus* and *E.coli* [23].

Some benzimidazole derivative containing oxadiazole like, 1-[(5-(alkyl/aryl)-1, 3, 4-oxadiazol-2-yl) methyl]-2-alkyl-1H-benzimidazoles (36) are synthesized for their antimicrobial activities. To evaluate the activity of synthesized compounds against bacteria minimum inhibitory concentrations (MICs) were determined and for yeast and fungi zone of inhibition was determined. Known antibiotics like ciprofloxacin and ampicillin and amphotericin B were used for comparison [24].

Antimicrobial activity of nitro- and halogeno-substituted benzimidazole derivatives were synthesized (37 a-d) and showed both antimicrobial and antiprotozoal activity. Sulfur derivatives are more active towards protozoal and others are more active towards microbes. The antibacterial activity of the benzimidazole derivatives was first tested by the agar disc-diffusion method against Gram-positive and Gram-negative bacteria. For the testing of anti protozoal activity mebendazole is taken as reference compounds [25].

Antifungal activity

Canan KUS prepared the synthesis and structure elucidation of methyl 5(6) - flouro- 6(5) - substituted -1H benzimidazole carbamate derivatives (39) and their antifungal activities evaluated against *Candida albicans* [27].

(R=H or CH₃)
(R = -CH₃, -C₆H₅, -CH₂Cl, -CH₂CH₂Cl, -C₆H₅₂, 2-Cl C₆H₄, 4-Cl C₆H₄, 2-OH C₆H₄, 4-OH C₆H₄, 2-OC H₂ C₆H₄, 4-OCH₃C₆H₄
Anti diabetic and anti-asthmatic activity

A series of novel substituted benzimidazole derivatives (40-42) were synthesized and screened for their potential anti-asthmatic and anti-diabetic properties. All the compounds showed anti-diabetic activity against DPP-IV and PTP-IB. Compound 40 (a-d) shown inhibitory activity against PTP-IB (1.64 %, 2.42 %) at 30 μM doses and shown inhibitory activity against DPP-IV (3%) at 0.3 μM doses. Compounds were tested against PDE-1V for potential anti-asthmatic effect, compound 41 and 42 shown inhibitory activities (3.40%, 13.52% and 8.91%) at 1μM doses. The compound 42 showed potential anti-asthmatic activity [28].

Some new benzimidazole containing thiazolidinone (43, 44) were also reported for anti-diabetic activity. Both the compounds were found to be more potent both in hyperglycemic and normoglycemic models at a dose level of 50 mg/kg [29].

Anxiolytic agents

Alfanzo D. Jordan synthesized a series of pyrido[1,2-a] benzimidazole (PBIs) (45) with substitution on the N1-nitrogen and found to possess high affinity for the benzimidazole site on the GABA-A receptor. The compounds evaluated include those bearing a hetero alkyl group and heterocyclic rings [30].

Antiproliferative activity

Laure Garuti synthesized a series of benzimidazole-4,7-diones bearing at the 2-position the thio methyl group or the 2-pyridyl moiety and tested in vitro on three tumour cell lines. Compounds (46 a) and (46 b) are more active. Compounds (46 a) is non toxic at all concentrations used in the anti-proliferative assay and (46 b) is toxic only at high concentrations [31].
Anti allergic agents
Hiroyuki Nakano, conducted synthesis on novel benzimidazole derivatives that suppress histamine release from mast cells, inhibit 5-lipoxygenase and possess anti-oxidant activity. Among the compounds synthesized, 1-[2-[2-(4-hydroxy-2,3,5-trimethylphenoxy)ethoxy]ethyl]-2-(4-methyl-1-homopiperazino) benzimidazole (47) potently suppressed histamine release [32].

Non-peptide thrombin inhibitors
Nobert H. Hauel et al proved that the clinical syndromes of thromboembolism are evoked by an excess stimulation of the coagulation cascade. In this context, the serine protease thrombin plays a key role. They designed a new structural class of nonpeptide inhibitors employing a 1,2,5-trisubstituted benzimidazole as the central scaffold. This zwitterionic molecule was converted into the double-prodrug (48) (BIBR 1048), which showed strong oral activity in different animal species [33].

Antiparasitic Activity
Valdez et al synthesized 18 compounds and tested in-vitro against the protozoa Giardia lamblia, Entamoeba histolytica and the helminth Trichinella spiralis. Inhibition of rat brain tubulin polymerization was also measured and compared for each compound. Compounds 49, 50 and 51 (2-methoxy carbonyl amino derivatives) were most potent [34].

DNA Topoisomerase I inhibitors
Selcen Alpan were reported three 1H-benzimidazole derivatives with different electronic characteristics at position namely 5-chloro-4(1H-benzimidazole-2-yl) phenol, 5-methyl-4(1H-benzimidazole-2-yl) phenyl and 4-(1H-benzimidazole-2-yl) phenol were synthesized and evaluated for their effects on mammalian type I DNA topoisomerase activity using quantitative in-vitro plasmid super coil relaxation assays. Among the compounds 5-methyl 4-(1H-benzimidazole-2-yl) phenol (52) manifested relatively potent topoisomerase inhibition [35].
Anti cancer and anti HIV activity
Seref Demirayak et al synthesized some 1- methylene-2,3- diaryl -1,2- dihydro pyrazino [1,2-a] benzimidazole derivatives (53) were synthesized. It was also observed that the compounds were more potent against leukemia cell lines [36].

![Image of compound 53]

Anti tumour activity
Imadul Islam et al described herein studies of new anti-tumour agents based on the pyrrolo [1,2-a] benzimidazole (PBI) ring system. These compounds were designed as new DNA cross-linkers mimicking the mitomycin anti-tumour agents. The best anti tumour agent studied is 6-N-aziridinyl-3-hydroxy-7-methyl-2,3-dihydro-1H pyrrolo [1,2-α] benzimidazole-5,8-dione-3-acetate (54) (PBI-A) against various human ovarian and colon cancer cell lines [37].

![Image of compound 54]

R.Suthakaran synthesized 4'-aryl-211-D-aldosugar disubstituted bis-benzoimidazoles (55) and screened for in vivo anti tumour activity, most of them showed significant activity [38].

![Image of compound 55]

Siyaram synthesized a series of methyl and ethy-5-(alkoxy carbonyl)-1H benzimidazole-2-carbamates and methyl 5-carbamoyl-1H-benzimidazole-2-carbamates (56). Compounds 56 (a-e) demonstrated significant growth inhibitions associated with mitotic spindle poisoning [39].

![Image of compounds 56 a-e]

56a, R= -C(=O)OCH3, 56b, R=(CH3)2CHOC(=O)-, 56c, R= -COOH, 56d, R= CH3CH2NH-C(=O)-, 56e, R=(CH3)2CHNHC(=O)-

Anti-convulsion Activity
Chimirri et al synthesized a series of 2,3,3a,4- tetrahydro-1H- pyrrolo [1,2-a] benzimidazole-1-ones (57) and evaluated for anticonvulsant activity in DBA/2 mice against sound- induced seizures and in rats against maximal electro shock induced seizures [40].

![Image of compound 57]

H3 Receptor antagonist activity
Marco Turconi et al synthesized a series of 2,3- dihydro-2-oxo-1H- benzimidazole-1- carboxylic acid esters and amides, a basic azacyclo or azabicycloalkyl moiety and their modeling study showed that compound (58), was a recently proposed pharamacophoric model for 5-HT3 antagonistic activity [41].

![Image of compound 58]

Rivara et al developed a novel series of non-imidazole H3-receptor antagonists. The greatest H3-receptor affinity was obtained for the piperidine substituted compounds. It was possible to get good H3-antagonist potencies with 2-aminobenzimidazoles (59) having a tertiary amino group at appropriate distance [42].
Marco Mor et al reported the design, synthesis, QSPR and QSAR of a new class of H3- antagonists, having a 2-aminobenzimidazole moiety connected to the 4(5) position of an imidazole ring through di or tri methylene chains (60). Compound lipophilicity (log P), basicity (pKa) and H3-receptor affinity and antagonist potency were determined and submitted to QSPR and QSAR investigations. When a three-methylene spacer was inserted between the imidazole ring and the 2-aminobenzimidazole nucleus, very potent compounds were obtained [43].

Shin-ichi et al reported the synthesis of 2-[(4-methoxy, 6,7,8,9-tetrahydro-5H-cyclo hepta (b) pyridine – 9-yl) sulfinyl] 1H benzimidazole sodium salt (63) which showed promising anti-ulcer activity and stability on isolated H+/K+-ATPase of rabbit gastric mucosa. Introduction of a rigid ring system was expected to influence a process of chemical transformation in acidic medium to biologically active sulfonamide from parent compound [46].

The synthesis of 2-[(4-dimethyl amino, 5 carboxylate 2 pyrimidinyl) methyl sulfinyl] benzimidazole in which the pyridine nucleus of omeprazole is replaced by ethyl 4- dimethyl amino-5- pyrimidine carboxylate (64) reported by Shimamura et al showed good antiulcer, gastroprotective and anti-secretory activity [47].

Robert J. Ife et al synthesized benzimidazole sulfoxide class of anti-secretory H'/K+ ATPase inhibitors. 2-[[3-chloro-4-morpholino-2-pyridyl]methyl]sulfinyl]-5- methoxy-(1H)-benzimidazole (65) was chosen for further development [48].

Anti-ulcer activity

Brumagniez et al reported the synthesis of 2-(thiopropyne) - 5- (imidazole -1-yl.) benzimidazole (61) which exhibited moderate anti-ulcer activity against ulcer induced by anti inflammatory agents in rats orally [44].

Shrinivasulu et al reported the synthesis of 2- n propyl, 5 (N methyl 3, 4 cyclo hexane, 4 amino piperidine) keto-6- ethoxy, benzimidazole (62) which exhibited good antiulcer activity [45].

5-HT1A/ 5-HT3 antagonist

Rodriguez et al synthesized a series of new benzimidazole-arylpiperazine derivatives III and evaluated for
binding affinity at serotoninergic 5-HT1A and 5-HT3 receptors. Compound (66) was identified as a novel mixed 5-HT1A and 5-HT3 ligand with high affinity for both serotonin receptor and excellent selectivity over α-adrenergic and dopamine D2 receptors [49].

\[ \text{(66)} \]

Rodriguez et al synthesized a series of mixed benzimidazole–arylpiperazine derivatives and evaluated for binding affinity at both serotoninergic receptors. Among them, analogue (67) was selected for further activity at 5-HT1A and 5-HT3 receptors and behavioral effects in anxiety and cognitive dysfunction models [50].

\[ \text{(67)} \]

Antioxidant

Benay Can- Eke et al synthesized seven benzimidazole compounds and their in-vitro effects on rat liver, lung and kidney microsomal NADPH-dependent lipid peroxidation (LP) levels were determined. The compound 4 at 10^{-4} and 10^{-3} M concentrations inhibited the hepatic microsomal ethoxyresorufin O-deethylase (EROD) (37% and 65%) and pentoxyresorufin O-depentylase (PROD) (14 and 62%) enzyme activities significantly. In lung and kidney the compound (68) at 10^{-4} concentration significantly increased EROD (44 and 19%) and PROD (103 and 86%) enzyme activities [51].

\[ \text{(68)} \]

R1 = -CH2-Ph, -CH2-O-Ph, -CH2CH2COOH, -CH2-p-NH2Ph, -CH2CH2CH2COOH
R2 = H, -COOH

Canan Kus synthesized some benzimidazole derivatives namely 1-[(substituted thiocarbanoyl)hydrazine carbonyl][methyl]-2-phenyl-1H-benzimidazoles (69) and 5-(2-phenyl benzimidazol-1-yl)-methyl)-4 substituted phenyl-4H-1,2,4-triazole-3-thiones (70) and their in-vitro effects on the rat liver microsomal NADPH-dependent lipid peroxidation (LP) levels were determined [52].

\[ \text{(69)} \]

\[ \text{(70)} \]

Analgesic Activity

Synthesis of a series of N-(acridin-9-yl)-4-(benzimidazol/oxazol-2-yl) benzamides (71) has been reported by Sondhi et al. Compound containing R1 = NO2, R2 = H, R3 = H, X = NH showed significant in vitro activity against CDK-5 (IC50 = 4.6 μM) and CDK-1 (IC50 = 7.4 μM) and compound having R1 = Cl, R2 = H, R3 = H, X = NH showed moderate CDK-5 inhibitory activity (IC50 = 7.5 μM). The other compounds showed moderate anti-inflammatory and analgesic activities [53].

\[ \text{(71)} \]

R1 = Cl, NO2, CH3, H; R2 = H, CH3; R3 = H, OCH3; X = NH, O

Spasmolytic Activity

Synthesis of 2-(aryloxyaryl)-1H-benzimidazole derivatives (72) was reported by Vezquez et al. Compounds 73a, 73b and 73c showed significant antispasmodic effect in a concentration dependent manner, IC50 1.94 μM, 1.19 μM and 1.8 μM, compound 73 c shown potent relaxant smooth muscle activity [54].

\[ \text{(72)} \]

R1 = C6H5COC2H5, 72b, Ar = 4-OH-3-OCH3C6H5, 72c, Ar = 2, 3, 4–trimethoxybenzene

CONCLUSION

The benzimidazole ring is an important pharmacophore in modern drug discovery. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. There is still scope for more research work to be done in this field to find a novel agent. The versatility of new generation benzimidazole would represent a fruitful pharmacophore for further development of better medicinal agents. Since now, researchers have been attracted toward designing more potent benzimidazole derivatives having wide range of biological activity.

REFERENCE
31. Garuti, L.; Roberti, M.; Malagobi, M.; Rossi, T.; Castelli, M. Synthesis and antiproliferative activity of


