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Benzimidazole scaffold as a versatile biophore in drug discovery: A review

Prakash Prajapat,[a]*, Monika Kumawat,[b] Ganpat L. Talesara,[b] Priyanka Kalal,[b] Shikha Agarwal[b] and Chandra Shekhar Kapoor[c]

[a]*Department of Chemistry, Ganpat University, Mehesana-384012, Gujarat, India*
[b]*Department of Chemistry, M. L. S University, Udaipur-313001, Rajasthan, India*
[C]*Department of Environment Studies, Pacific University, Udaipur-313001, Rajasthan, India*
E-mail: prajapatprakash11@yahoo.in, psp04@ganpatuniversity.ac.in
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Abstract: Heterocyclic molecules are pervasive in several areas of life sciences. These molecules perform numerous significant functions in nature, medicine, and technology. Nitrogen-containing heterocycles specially azoles family are the subject of continuous interest in organic synthesis owing to the fact that they occur ubiquitously in pharmacologically active natural products, multipurpose oriented functional materials as well as highly potent pharmaceuticals and agrochemicals. Benzimidazole has been a popular heterocycle in medicinal and pharmaceutical chemistry allowing the construction of structurally different molecules with diverse bioactivities *viz*. anticancer, anti-inflammatory, antimicrobial, antimalarial, anticonvulsant, antiviral, analgesic, antiparasitic *etc.* This review article is an effort to compile the literature of several synthetic approaches and bio-evaluation of benzimidazole analogues. This review helps in the further development of novel benzimidazoles for future drug discovery.

Keywords: Drug discovery, Pharmacophore, Benzimidazole, Synthesis, Biological activity

Introduction

Drug design is a creative science, a special technology, and an art all in one. Design of highly proficient chemical reaction sequences that give functionalized bioactive heterocyclic motifs with interesting pharmacophoric properties is a major challenge of recent drug discovery. Organic synthetic and medicinal chemists are screening a large number of newer molecules in the lab but very few can pass through the vigorous journey of drug discovery pipeline from lab to market. The pipeline of drug discovery from idea to market consists of seven basic pathways: disease selection, target selection, lead molecule identification, lead optimization, preclinical trial testing, clinical trial testing and pharmacogenomic optimization (**figure 1)**. In present academia, biochemical, and pharmaceutical industry all

contribute to drug discovery. The important for the pharmaceutical and biochemical industry to discover breakthrough drugs is matched by the increasing number of first-in-class drugs approved in recent years and reflects the impact of modern drug discovery, methods, technologies, and genomics[1-7].

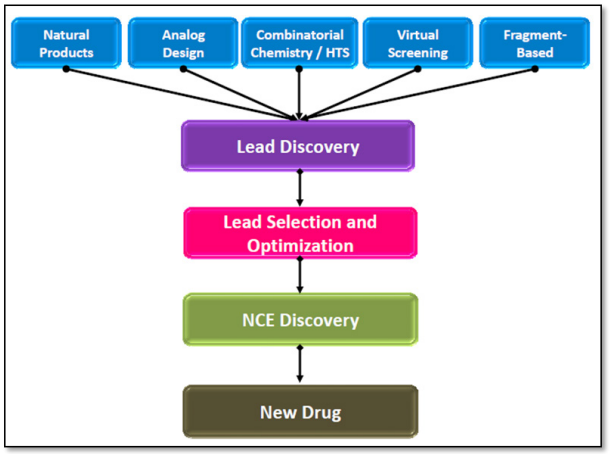


Figure 1. Drug discovery process

In current scenario, the area of synthesizing new bioactive heterocyclic molecules, their designing, development and application is the most focused and challenging task for the researchers. Organic molecules bearing different heterocyclic ring systems have attracted a great deal of attention in nowadays, both in chemical and medicinal research that could be attributed to their different pharmacological applications. Synthetically produced heterocycles designed by organic chemists are used for instance as pharmaceuticals, dyestuff, agrochemicals and are of increasing importance in many other areas including adhesives, molecular engineering, polymers etc. Naturally occurring heterocyclic moieties played a vital role in biological processes. They are broadly found in naturally in plant alkaloids, nucleic acids, anthocyanins and flavones as well as in haem and chlorophyll. Additionally several proteins, hormones, vitamins contain aromatic heterocyclic ring system[8-10].

Heterocycles act as drugs because they have specific chemical reactivity and they provide convenient building blocks to which pharmacologically active substituents can be attached. Thus, we needed the development of innovative methodology for bioactive heterocycles in synthetic organic and medicinal chemistry with some advantages including its simplicity of operation, greener approach, easy workup procedure, selectivity, higher yields, and high-atom economic[11].

Benzimidazole biophore **(figure 2)** is a benzannulated ring where benzene ring fused with imidazole ring system contain hetero atom at 1 and 3 positions. It is also known as 1*H*-benzimidazole or 1, 3-benzodiazoles or benzoglyoxalines. These were also named as derivatives of o-phenylenediamine. Benzimidazole ring possessing the hydrogen atom at N-1 position, there actually exists a readily exchange between the –NH and =N- nitrogen atoms, which is responsible for isomerisation **(1, 2)** in derived compounds[12] **(figure 3)**. Structurally, benzimidazole contains two aromatic N-heterocycles that can bind to enzymes or receptors *via* hydrogen bonds coordinated with metal ions or hydrophobic interactions. The most prominent benzimidazole molecule found in nature in the form of N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12} **(3)**. Five membered imidazole ring system has been found in some naturally occupying molecules which consist of the α-amino acid histidine, a normal constituent of most proteins, purine , biotin and histamine.

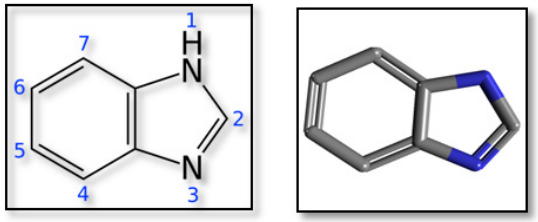


Figure 2. Benzimidazole Pharmacophore

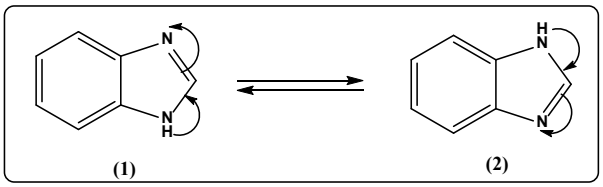
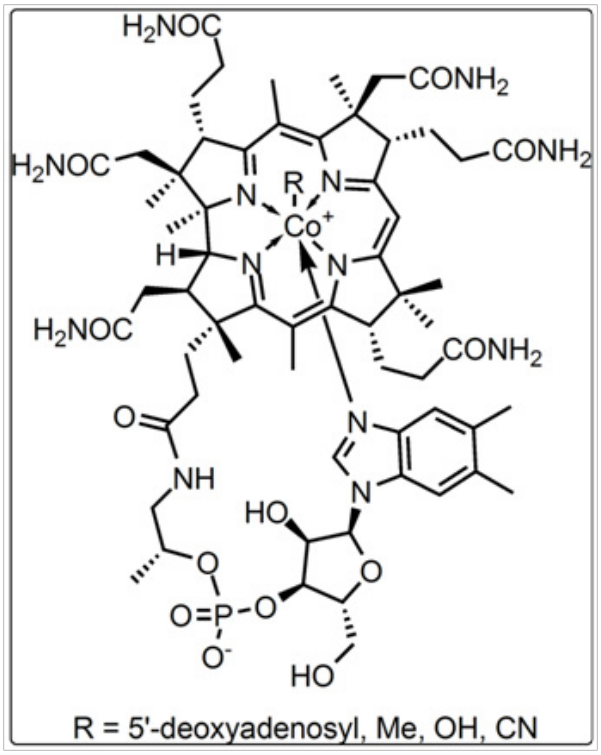


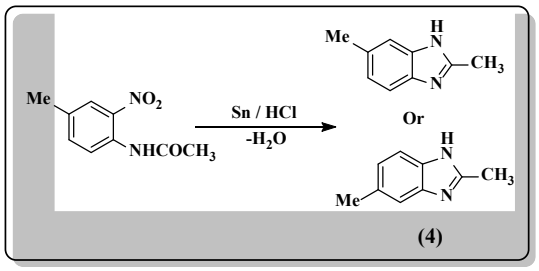
Figure 3. Isomerisation of Benzimidazole

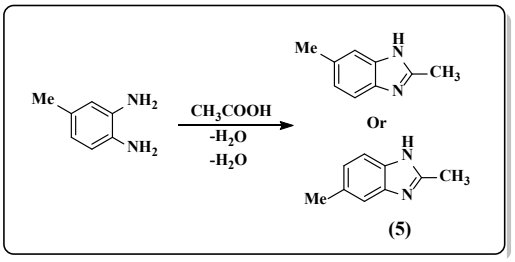


(3)

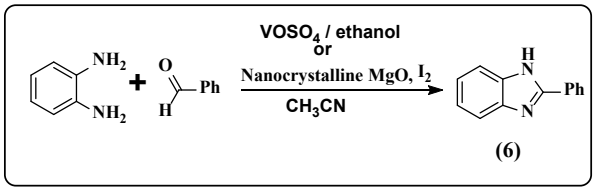
SYNTHETIC ASPECTS

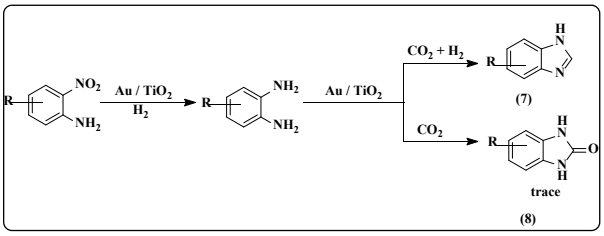
The continuously accelerating rate of research and development in heterocyclic chemistry suggested that large numbers of heterocyclic systems are well known and this number is increasing very rapidly. Benzimidazole moiety as a versatile pharmacophore for the generation of newer chemical entities in diverse therapeutic areas, the formation of these privileged classes of molecules has generated interest to introduce new synthetic methods. Chemistry of benzimidazole revealed that the first benzimidazole (2,5-dimethylbenzimidazole or 2,6-dimethylbenzimidazole) was prepared in 1872 by Hoebrecker through reduction of 2-nitro-4-methylacetanilide molecule **(4)**. After several years Ladenburg obtained the similar molecule **(5)** by refluxing 3,4-diamino toluene with acetic acid. Benzimidazole and its analogues are mainly synthesized *via* cyclocondensation reactions in between 1,2-diaminobenzenes with formic acid or its derivatives (imidates, orthoesters, esters, or nitriles) under strong acidic conditions at high temperatures[13] or under microwave irradiation[14].



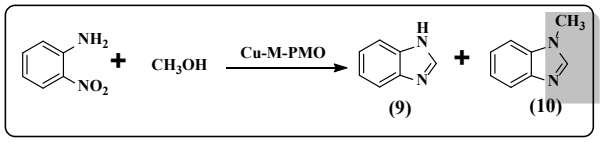


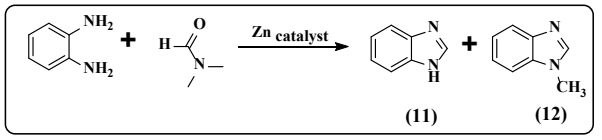
Naeimi *et al.*[15] reported an efficient synthesis of 2-substituted benzimidazole derivatives (6) by nanocrystalline magnesium oxide as solid base catalyst under acetonitrile solvent at room temperature. Recently, eco-friendly protocols were described[16] for the synthesis of benzimidazole derivatives using $VOSO_4$ as a catalyst in ethanol. The gold-catalyzed preparation of benzimidazoles **(7, 8)** from 2-nitroanilines and CO_2 in the presence of H_2 under mild conditions has been reported[17].

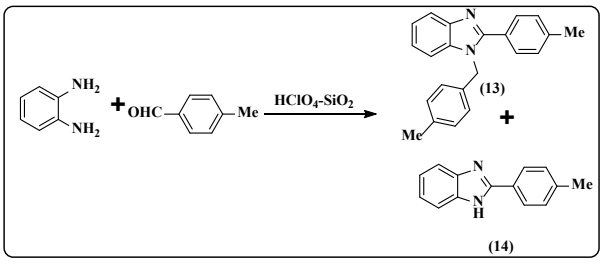




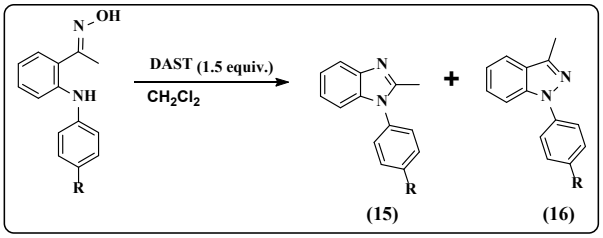
A greener approach reported[18] for the synthesis of benzimidazoles **(9, 10)** from 2-nitroanilines by heating starting moiety in the presence of supercritical MeOH that acts both as solvent and reagent by use of copper-doped porous metal oxides (Cu-PMOs). The synthesis of benzimidazole derivatives **(11, 12)** in the presence of metal zinc catalyst under solvent-free conditions have been performed by Nale *et al.*[19] Similarly, Chakraborti and co-workers[20] described a efficient method for synthesis of 1,2-disubstituted benzimidazole derivatives **(13, 14)** by using solid supported protic acids catalyst like $HClO_4$–SiO_2.

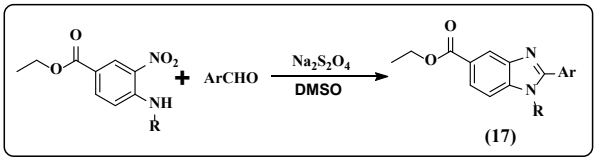




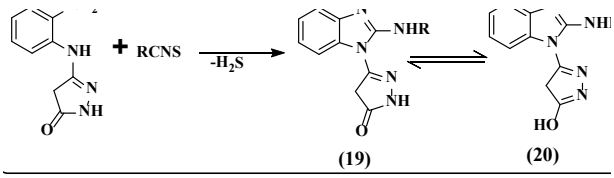


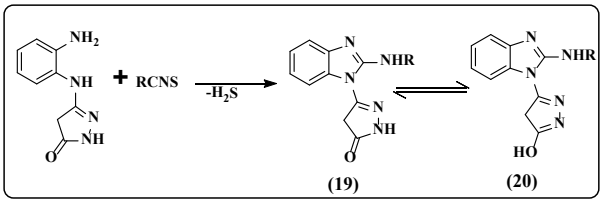
Xingqi Li *et al.*[21] developed a protocol as the first DAST-promoted Beckmann rearrangement/ intramolecular cyclization reaction of acyclic ketoximes, which represented a effective route to benzimidazoles **(15, 16)**. A series of new 1,2-disubstituted benzimidazole-5-carboxylate derivatives **(17)** obtained by the one-pot nitro-reductive cyclization reaction by use of sodium dithionite and also its effect on N-debenzylation have been described[22].

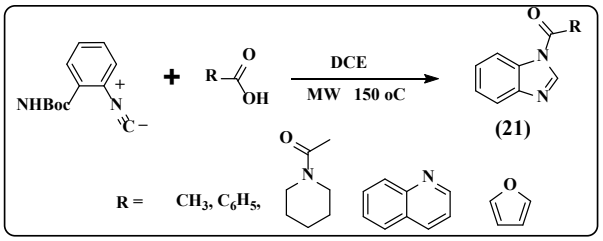




One-pot cyclocondensation reaction reported for the synthesis of various benzimidazole derivatives **(18)** in between o-phenylenediamines and aryl aldehydes by using urea hydrogen peroxide (UHP) and iodine in DMSO with good yields. El-Nassan and co-workers[23] described the reaction of pyrazolone containing benzimidazole derivatives **(19, 20)** by the treatment of substituted o-phenylinediamine with isothiocyanates. Similarly, benzimidazole nucleus **(21)** can also be synthesized by treating of 2-(*N*-Boc-amino)phenylisocyanide (Boc: *tert*-butoxycarbonyl) with carboxylic acids under microwave irradiation[24].





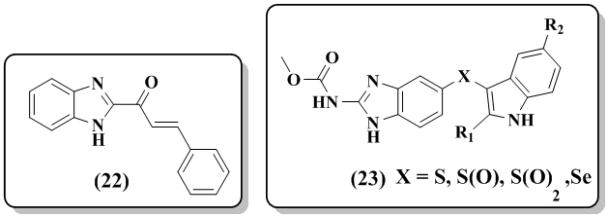


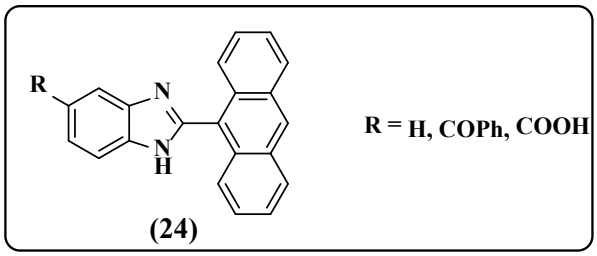
PHARMACOLOGICAL ASPECTS

Benzimidazole derivatives have evoked considerable attention in current years as these are endowed with various important biological activities. Benzimidazole is a structural isostere of naturally occurring nucleotides; hence, it has been extensively used as a drug candidate in the pharmaceutical and medicinal chemistry. Benzimidazoles are a group of heterocyclic organic compounds that display multiple bioactivities *viz.* antimalarial[25], anticancer[26], anti-inflammatory[27], antimicrobial[28], anticonvulsant[29], Hv1 proton channel inhibitor[30], antiviral[31], anti-parasitic[32] etc. Several promising antitumour agents were found to contain the benzimidazole ring system. They were found to exert their anti-tumour activity by acting mainly as topoisomerases inhibitors[33-35], anti-angiogenic agents[36-38], and alkylating agents[39-41].

Among the large family of N-heterocycles, the benzimidazole motif is particularly attractive as it has been integrated in a number of commercial drugs such as Chlormidazole (antifungal), Enviradine (antiviral), Omeprazole (proton pump inhibitor), Astemizole (antihistaminic), Telmisartan (antihypertensive), Pimobendan (Ionodilator), Benzitramide (analgesic) **figure 3**.

A number of benzimidazole-2-subsituted phenyl or pyridine propyl ketene derivatives **(22)** have been synthesized and assayed for their antiproliferative activity against HCT116, MCF-7 and HepG2 cell lines *in vitro*[42]. Benzimidazole carbamates **(23)** bearing indole moiety with sulphur or selenium atoms connecting the aromatic rings have been also reported[43] for their antiproliferative activities against three human cancer cell lines (SGC-7901, A-549 and HT-1080) using an MTT assay. Similarly, 2-anthryl benzimidazole derivatives **(24)** were prepared and screened for anti-cancer activity against MCF-7 and HL-60 cell lines[44].





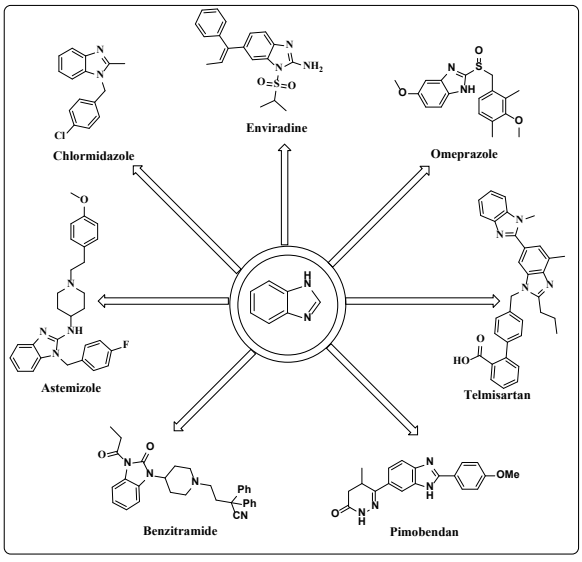
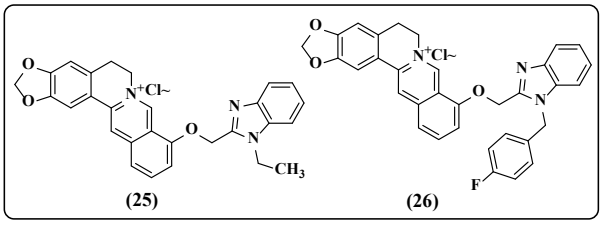
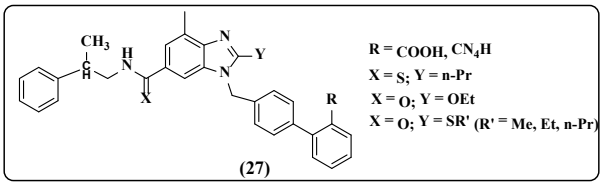


Figure 3. Several drugs containing benzimidazole ring as a core moiety

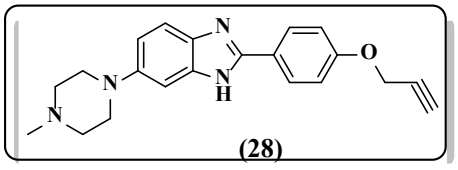
The synthesis and anti-microbial studies with pET-28a (*E. coli* DNA), calf thymus DNA, human serum albumin and molecular docking

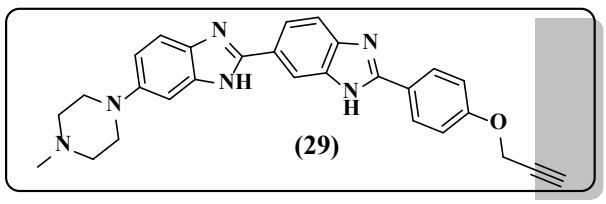
simulation of berberine-benzimidazole hybrids **(25, 26)** have been peformed[45]. Recently, angiotensin II receptor type 1 (AT1) blockers bearing 6-substituted carbamoyl benzimidazole derivatives **(27)** with a chiral center have been reported[46] as antihypertensive agents.

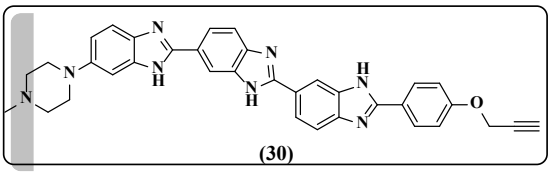


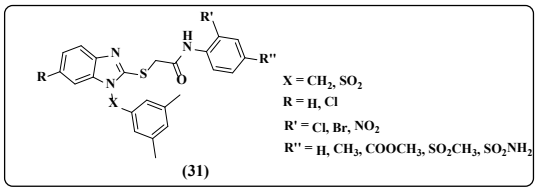


Tsodikova and coworkers[47] studied the synthesis and antifungal activities of 18 alkylated mono-, bis-, and tris-benzimidazole derivatives, **(28, 29, 30)** their toxicities against mammalian cells and also their ability to induce reactive oxygen species (ROS) in yeast cells. Chimirri *et al.*[48] reported the efficient synthesis of N-1-aryl-2-arylthioacetamido-benzimidazole analogues **(31)** as HIV-1 non-nucleoside reverse transcriptase inhibitors and found that some of derivatives effectively inhibit the HIV-1 replication at submicromolar and nanomolar concentration which acted as HIV-1 non-nucleoside RT inhibitors (NNRTIs), with low cytotoxicity.

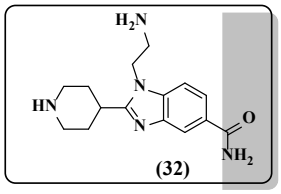








A variety of 1,2-disubstituted benzimidazole-5-carboxamide derivatives **(32)** studied[49] their inhibitory activities against all four Janus kinase (JAK) isozymes. This JAK inhibition modulates cytokine-mediated effects. Selective inhibition of JAK1 or JAK3 provides an efficient therapeutic agent for the treatment of inflammatory diseases, with minimized side effects. One of the derivatives, 1-(2-aminoethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole-5-carboxamide showed significant JAK1 selectivity (63-fold vs JAK2, 25-fold vs JAK3,and 74-fold vs Tyk2) as depicted in **figure 4**.



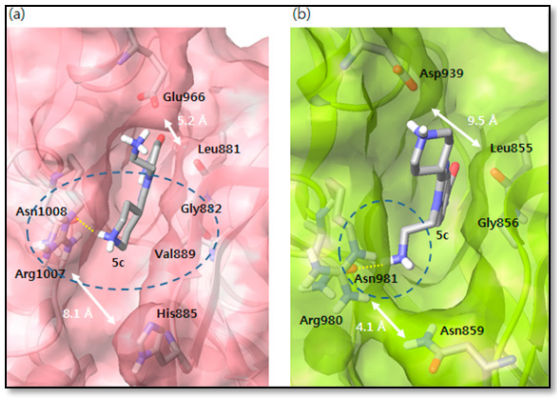
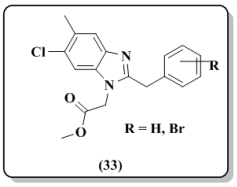
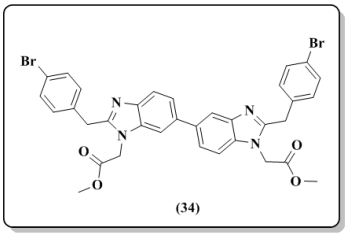
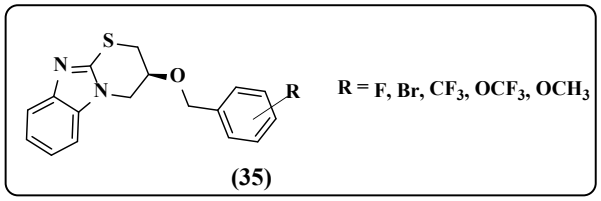


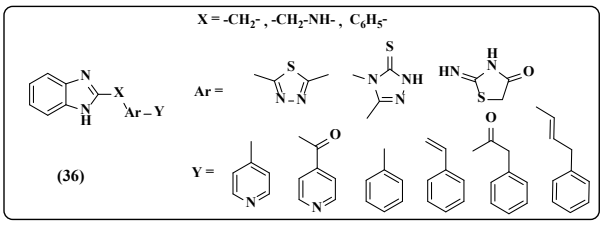
Figure 4. Docked structures of derivative **32**

Microwave-assisted method of benzimidazole derivatives **(33, 34)** with lipase inhibition activity has been reported[50]. Recently, synthesis of fused thiazino[3,2-a]benzimidazole derivatives **(35)** and their anti-tuberculosis activity was investigated by Gong *et al*[51]. A number of benzimidazoles bearing different five membered heterocyclic rings (1,3,4-thiadiazole; 1,2,4-triazole-5-thione and 1,3-thiazolan-4-one) **(36)** have been reported[52] for their antimicrobial activity against diverse bacterial and fungal microorganisms.

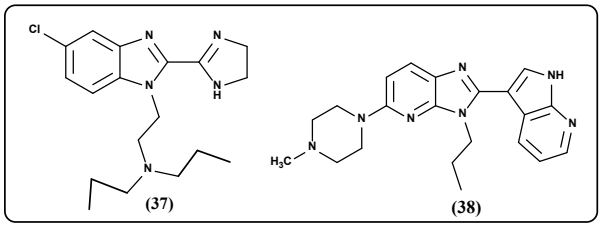


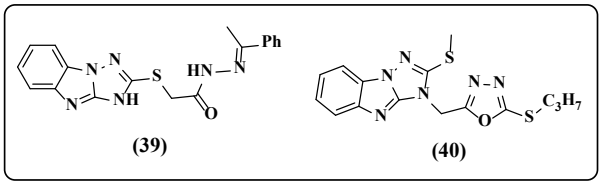






A series of benzimidazole and imidazopyridine derivatives **(37, 38)** studied[53] for their anti-inflammatory activities, and the imidazopyridine series showed excellent inhibition of inflammatory cytokines in LPS-stimulated macrophages. Similarly, synthesis of benzimidazole derivatives bearing different heterocyclic rings as oxadiazole, thiadiazole, triazole have been reported[54] for their activities against *Coxsackie virus* B3 and B6 in Vero cells. Similarly, analgesic and anti-inflammatory activities of 1, 2, 4-triazolobenzimidazol-3-yl acetohydrazide derivatives **(39, 40)** have been investigated by Mohammed *et al.*[55] Synthesis and biological screening of analogues of the pan class I phosphatidylinositol 3-kinase (PI3K) inhibitor 2-(difluoromethyl)-1-[4,6-di(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (ZSTK474) **(41)** have been tested by Rewcastle and co-workers[56].





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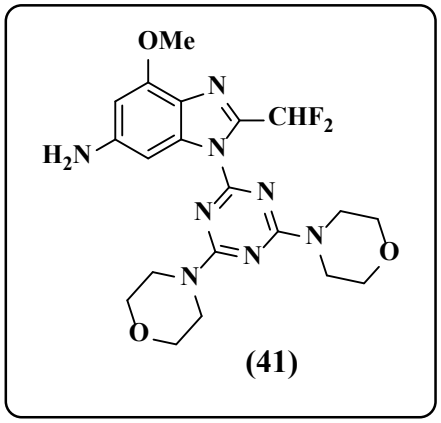
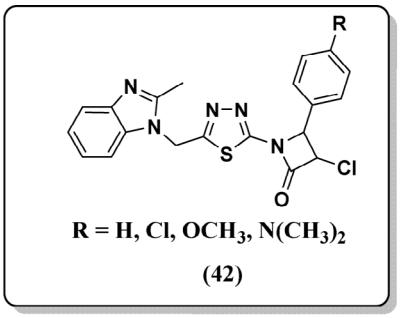
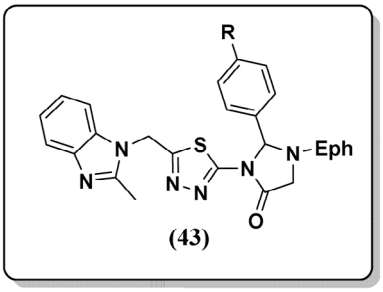
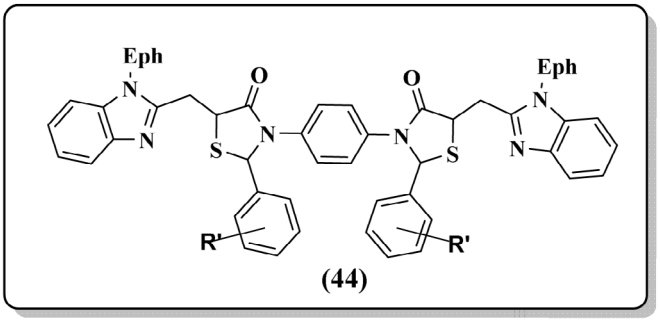


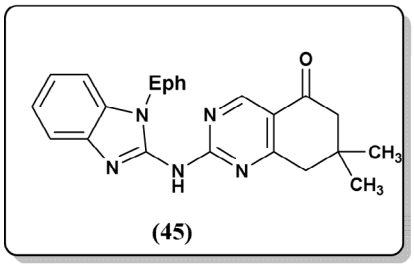
Kumawat *et al.*[57] described the synthesis of ethoxyphthalimido derivatized thiadizole assembled imidazolidinone **(42)** and chloroazetidinone **(43)** systems from common intermediate schiff's bases and tested their antibacterial activity. Synthesis and antiviral screening against cytomegalovirus (CMV) and varicella virus (VZV) in human embryonic lung (HEL) cells of thiazolidinone derivatives **(44)** of benzimidazole have been examined by

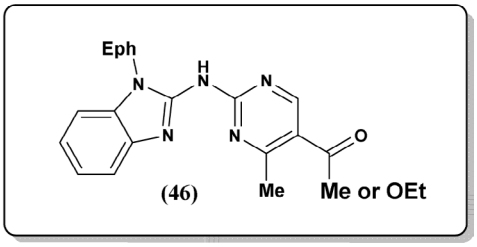
Hussain and co-workers[58]. Recently, i*n-vivo* anti-inflammatory activity against carrageenan-induced rat paw edema method and *in-vitro* antimicrobial screening of mono- and bis-ethoxyphthalimide clubbed benzimidazoles **(45-49)** have been studied by Prajapat *et al.*[59-61]

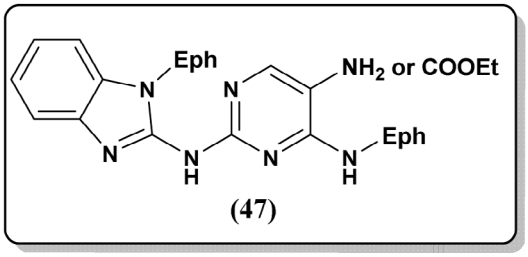


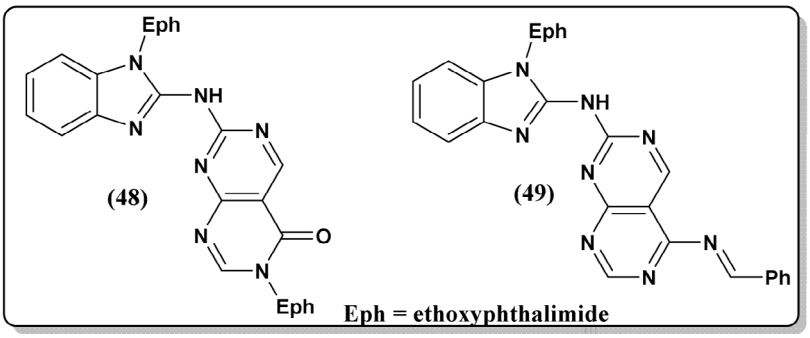












Conclusion

Benzimidazole derivatives are very useful for the development of drug leads and molecules of pharmaceutical and agrochemical interests. Owing to the great synthetic and medicnal importance of this heterocyclic core, synthesis of benzimidazole derivatives has long been an area of intense development, and still constitutes an active domain from academic and industrial points of view. The idea of this work is to collect the literature reported by researchers on benzimidazole for its diverse bioactivities and also report present efforts made on this motif. Finally, this review helps to find potential future directions on the development of new effective and specific analogues of azoles family for different biological targets.

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