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Valuable Insight Into Recent Biological Activities of Different Benzimidazoles

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Abstract **Review Article**

Benzimidazole nucleus plays an important role in several categories of clinical agents such as antimicrobials, antivirals, antiparasitic, anticancer, anti-inflammatory, antioxidants, proton pump inhibitors, antihypertensives, anticoagulants, immunomodulators, hormone modulators, CNS depressants, and antidiabetics, etc. Many researchers coin it as a crucial moiety for the development of innovative therapeutic agents. Wide-ranging substituents on the benzimidazole nucleus show a varied spectrum of biological activities. In order to understand the current position of the benzimidazole nucleus in medicinal chemistry research, this review summarized the chemistry as well as pharmacological activities of benzimidazole scaffold. This discussion will further help in the development of novel benzimidazole compounds.

Keywords: Benzimidazole, Anticancer, Antihypertensive, Antioxidant, Anti-inflammatory, Analgesic.

INTRODUCTION

Benzimidazoles are the heterocyclic molecule which contains benzene ring attached to an imidazole ring. These compounds are developed to design the new building blocks for several more bioactive molecules. Over the past years, the existence of benzimidazole scaffold established lots of therapeutic active modifications. Several biological activities also have been found for benzimidazole derivatives such as cytotoxic, antiretroviral, antihypertensive, antioxidant, anti-inflammatory *et al.* [1]. It is also known that planer fused benzimidazole has the potential to insert in DNA base pairs and cleavage them. Benzimidazoles are fused with many other moieties to increase its activity spectrum or to find a new activity [2]. From the literature survey, a researcher revealed that when benzimidazole moiety is combined with other heterocyclic or cyclic rings it exhibits innumerable activities such as 2-aryl benzimidazole [3], 2-thiohalogenonitrophenyl benzimidazole [4], ferrocenyl and cyrhetrenyl benzimidazole [5] corresponds to α-amylase inhibitory response, antifungal activity, and antiparasitic activity respectively. Along with utilizing of traditional approach, structure-activity relationship (SAR) strategy and computer-aided drug design is the faster and smarter way to design new chemical entity and by using the approach in initial phase of drug discovery and development leads to decrease the chances of failure in final steps and also reduces the cost of drug development [6,7]. To facilitate the discovery of new drugs computer-aided drug design (CADD) methods include especially the quantitative structure-activity relationship (3D-QSAR) method as prominent applications of chemometrics, provides valuable information for design and synthesis of novel antimicrobials, which interacts with specific receptors. Two most successful tools comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) are used widely. In addition to Docking and molecular dynamics, QSAR was carried out to get a deep insight in silico studies and to search out possible binding modes of these new antimicrobials [8, 9]. Due to the limited option available for the treatment of different diseases like Alzheimer, Hepatitis c, liver cirrhosis, etc. It increases interest in the use of benzimidazole as a lead compound to develop a new drug to combat these diseases [10,11]. The nonnucleoside inhibitors (NNI'S) series of benzimidazoles represent a promising group of compounds which merit computational investigations. To illustrate the binding mode of these inhibitors at an allosteric site of the enzyme, molecular docking simulations were performed using the X-ray crystallographic structure of the complex of NS5B with tetracyclic indole inhibitor, so here analysis helps in predicting the activity [12-14].

CHEMISTRY

Benzimidazole derivatives are getting popular for their numerous clinical uses. Benzimidazole is a

heterocyclic ring system consists of a benzene ring fused to Imidazole at 4th and 5th position. Benzimidazole has been synthesized from o-phenylenediamine by reacting with different reagents (Figure 1).

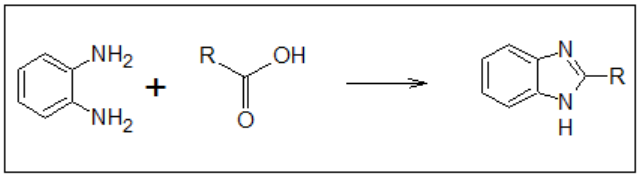
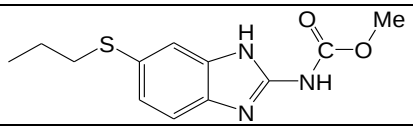
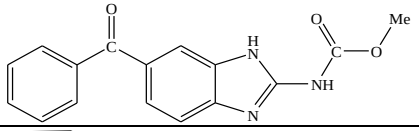
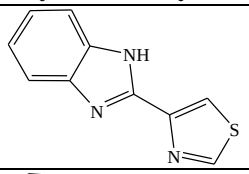
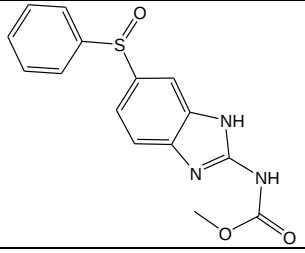
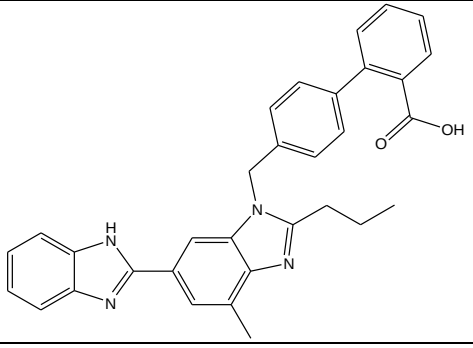
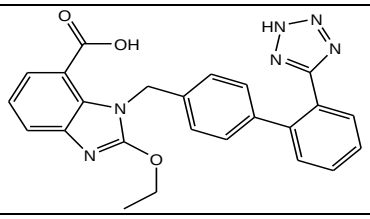
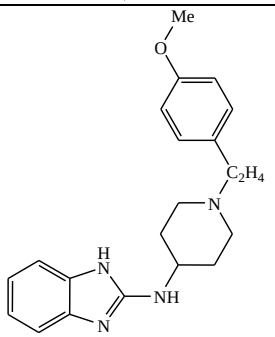
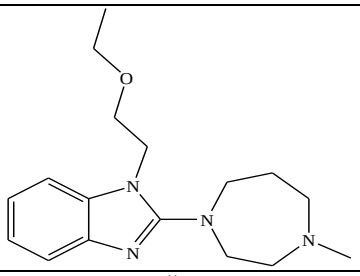
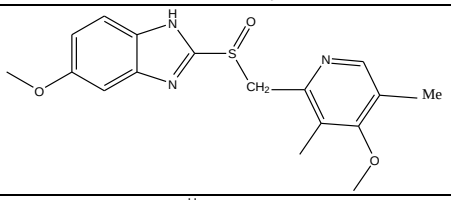
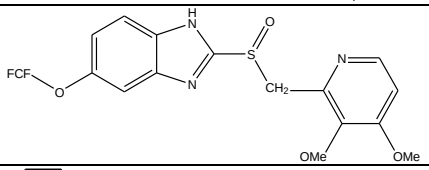
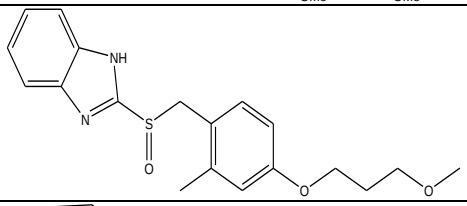
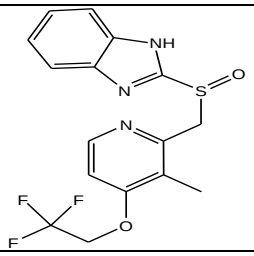


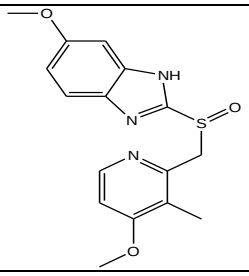
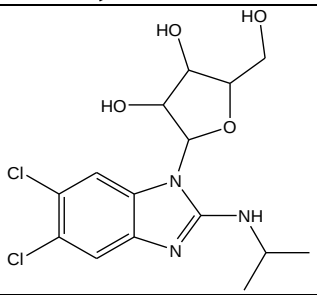
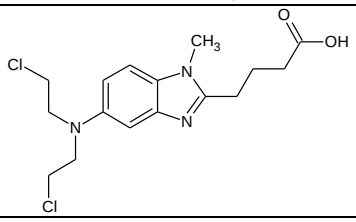
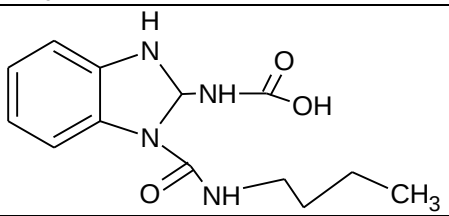
Fig-1: Synthesis of benzimidazole

Benzo derivatives of imidazole ring are also known as Benziminazoles and 1,3-benzodiazoles [15,16]. Along with the other derivatives reported, recently different catalyst and reagents like $Na_2S_2O_4$, $ZrCl_4$, sulfamic acid, $VOSO_4$ [17], DMF and $CuFe_2O_4$ have been reported for the synthesis of benzimidazoles [18] Benzimidazole moiety is considered as one of the most important nitrogen-containing fused organic compound [19]. It is a very formidable heterocyclic pharmacophore in drug discovery. Benzimidazole derivatives are associated with various pharmacokinetics and pharmacodynamic properties and are a prominent heterocyclic moiety having various biological activities [4]. The modification to the structural chemistry of benzimidazole has given rise to various potent clinical agents such as albendazole, omeprazole, mebendazole, thiabendazole, bendamustine, etc. Which are used in a horde of diseases conditions [20] (Table 1).

Table-1: Marketed drugs containing Benzimidazole moiety [21–25]

Serial no.	Drug name	Structure	Clinical Use
1	Albendazole (Tablet, Suspension)		Anthelmintic
2	Mebendazole (Tablet, Suspension)		Anthelmintic
3	Thiabendazole (Tablet, Ointment)		Anthelmintic
4	Oxfendazole (Tablet, oral suspension)		Anthelmintic (for veterinary use)
5	Telmisartan (Tablet)		Antihypertensive

6	Candesartan (Tablet)		Antihypertensive
7	Astemizole (Tablet)		Antihistaminic
8	Emedastine (Capsule, tablet, eye drop)		Antihistaminic
9	Omeprazole (Tablet, enteric coated capsule, injection-IV)		Antiulcer
10	Pantoprazole (Tablet, enteric coated capsule, injection-IV)		Antiulcer
	Rabeprazole (Tablet, enteric coated capsule, injection-IV)		Antiulcer
12	Lansoprazole (Tablet, enteric coated capsule, injection-IV)		Antiulcer

13	Esomeprazole (Tablet, enteric coated capsule, injection-IV)		Antiulcer
14	Maribavir (Injection-IV)		Antiviral
15	Bendamustine (Injection-IV)		Anticancer
16	Benomyl (wettable powder)		Antifungal

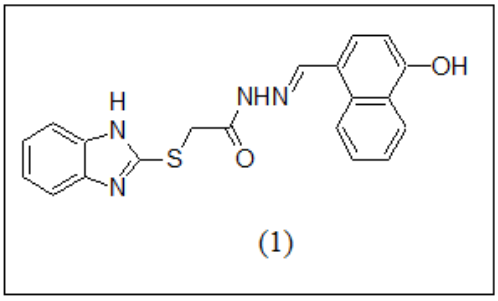
Along with all these drugs, there are others which have been approved for various clinical uses, and many more are in clinical pipelines.

Pharmacological activity of benzimidazoles

Benzimidazole is a heterocyclic moiety pulling the interest of modern researchers in recent times. It is a flexible heterocyclic as it contains imidazole and shows a versatile range of biological activities

Benzimidazole derivatives acting as anticancer agents

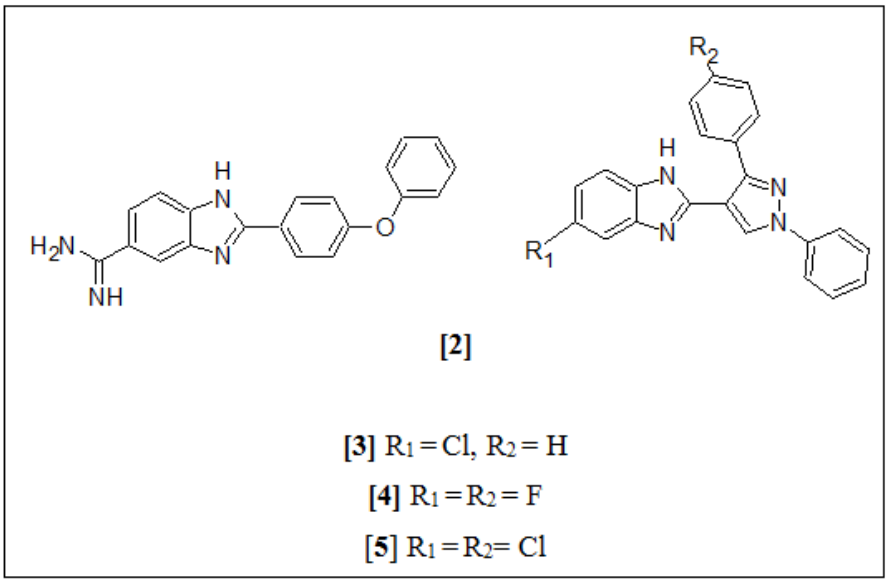
Cancer is a major community health disease in the major parts of the world. According to US survey reports the prevalence of this disease is more in female than in the male. As the severity of the problem increasing day by day, researchers are trying to develop new moieties for the treatment of this disease. However, the main problem with the currently existing drug is their cytotoxicity. It becomes necessary to develop new candidates with potent activity against cancer cells and less cytotoxicity to normal cell [26,27]. Thus, in order to cure cancer, Yadav *et al.* synthesized series of benzimidazole compounds which displayed promising results as anticancer agents. *In vitro* cytotoxicity testing of synthesized compounds has been checked on MCF-7 cell line by use of assay (Sulforhodamine-B). From the whole series, compound [1] (IC50=0.0013mM) was found to be the most active compound carrying high toxicity against MCF-7 cell line comparing to 5-fluorouracil (IC50=0.0461mM). Most of the compounds were more active than standard drug (carboplatin) with IC50=0.2694mM [28].



(1)

Alp *et al*. synthesized 2-(4-phenoxy phenol)-1H-benzimidazole derivatives and were examined for anticancer activity. Among all the synthesized derivatives, compound (2) showed good cytotoxicity against K562 cells (IC50=20.65mM) [29].

In continuation in the development of anticancer drugs, Reddy *et al*. synthesized 1,3-Diphenylpyrazolo-1H-benzimidazoles and screened for their anticancer activity on MCF-7 cell lines and compound (3-5) reported maximum inhibition of growth of MCF-7 cell lines having IC50 values 0.83, 0.95, and 1.17 mM respectively [29].



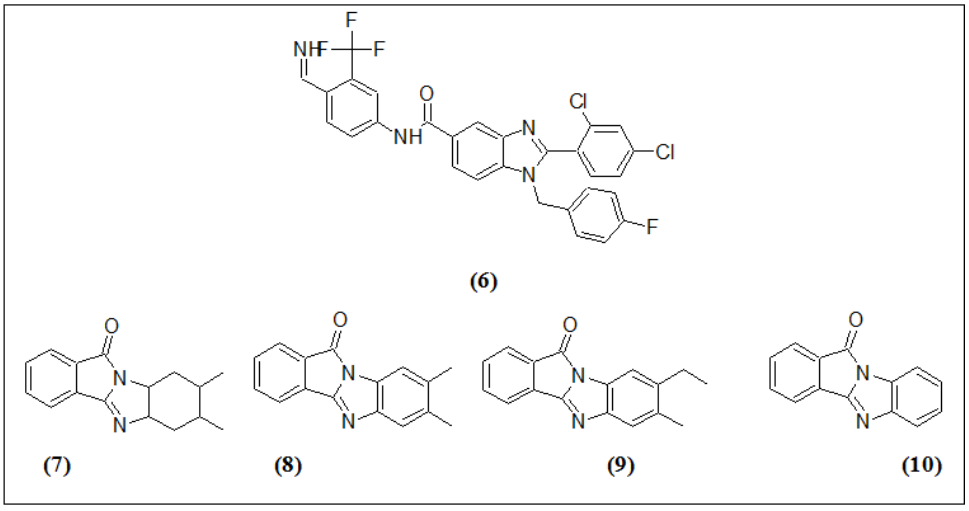
[2]

[3] $R_1 = Cl$, $R_2 = H$

[4] $R_1 = R_2 = F$

[5] $R_1 = R_2 = Cl$

Thimmegowda *et al.* synthesized a novel series of trisubstituted benzimidazole derivatives and were evaluated for inhibitory activity against MDA-MB-231 breast cancer cell proliferation. The compound [6]. N-[4-cyano-3-(trifluoromethyl) phenyl]-4-fluoro-3-nitrobenzamide has been obtained as a potent inhibitor [30]. Sondhi *et al*. synthesized various heterocyclic benzimidazole derivatives [7-10] by condensation of succinic acid, homophthalic acid and pyrazinedicarboxlic acid with variously substituted diamines using microwave irradiation. Anticancer activity of these compounds was evaluated against ovary (IGR-OV-1), breast (MCF-7), CNS(SF-295) human cancer cell lines. All compounds have shown good anticancer activity [4].



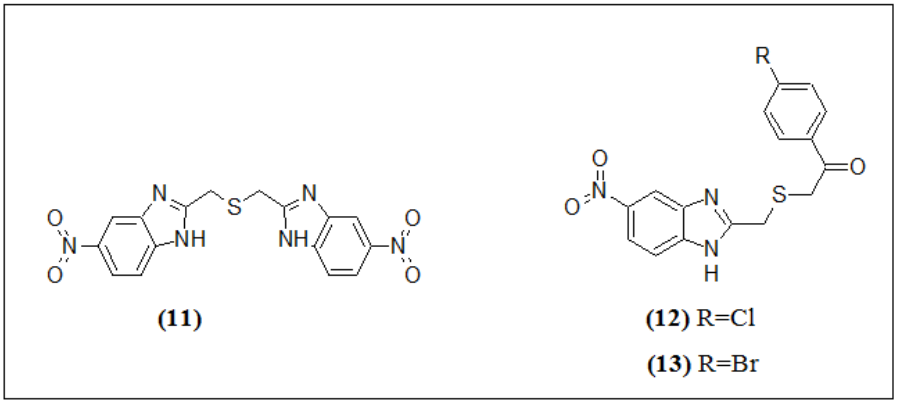
(6)

(7) **(8)** **(9)** **(10)**

Gohary *et al*. synthesized new benzimidazole derivatives and were tested against liver (HepG2), colon (HCT-116) and breast (MCF-7) cancer cell lines employing MTT assay. The compounds (11-13) were found to be the most potent anticancer derivatives with respective IC50 values given in Table 2 [31].

Table-2: IC50 Values of compound [11-13]

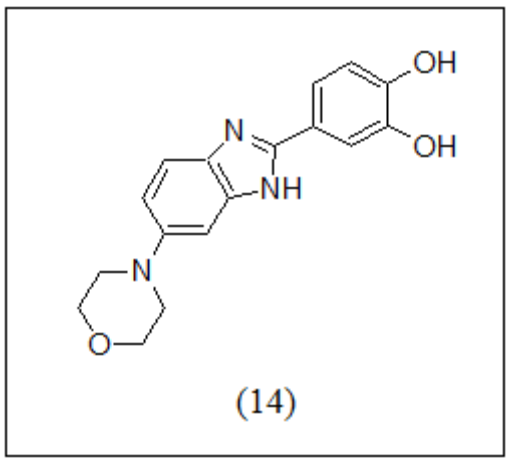
Compound no.	IC50(µM)		
	HepG2	MCF-7	HCT-116
11.	2.25	1.74	2.41
12.	2.65	2.80	2.23
13.	2.01	1.55	1.78



Benzimidazole derivatives acting as antioxidant agents

Oxidative stress is a phenomenon occurs due to an imbalance production and growth of oxygen reactive species (ROS) in cells and tissues and the capacity of a biological system to detoxify these responsive products. A large body of indications displays that oxidative stress can be responsible, with various degrees of importance, in the onset and/or development of numerous diseases (i.e. Cancer, diabetes, metabolic disorders, atherosclerosis, and cardiovascular diseases) Few antioxidants have been discovered in recent years for their actual or supposed advantageous effect against oxidative stress. Many scientists are working in search of effective antioxidant moieties to reduce the danger of various diseases development [32–35].

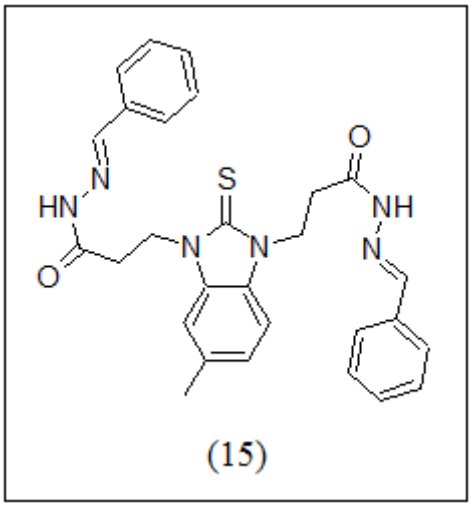
A new series of 2-(aryl)-6-morpholine-4-yl(or 4-methyl piperazine-1-yl)-1*H*-benzimidazole derivatives were synthesized from 5morpholine-4-yl(or 4-methylpiperazin-1-yl)-2-nitroaniline with a variety of aldehydes and were preliminarily screened for *in vitro* antioxidant activities by Ozil *et al*. These derivatives were discovered by using a rapid 'one-pot' nitro reductive cyclization reaction with sodium hydrosulfite as a reagent. Antioxidant activities of the synthesized derivatives were evaluated by *in vitro* antioxidant assays together with Cupric Reducing Antioxidant Capacity (CUPRAC, ranging from 5.511 to 19.703 mM Trolox / mg compound) along with Ferric Reducing Antioxidant Power (FRAP) (1.141-12.943 mM FeSO4.7H2O / mg compound) assays. Also, the radical scavenging activities of these products were assayed using ABTS•+ and DPPH• methods. Compound (14) has been found to be the most potent antioxidant molecule from the whole series [36].



Anastassova *et al*. synthesized a new series of N,N'-disubstituted benzimidazole-2-thione by incorporation of hydrazone moiety in the side chains. The toxicological prospective of studied compounds

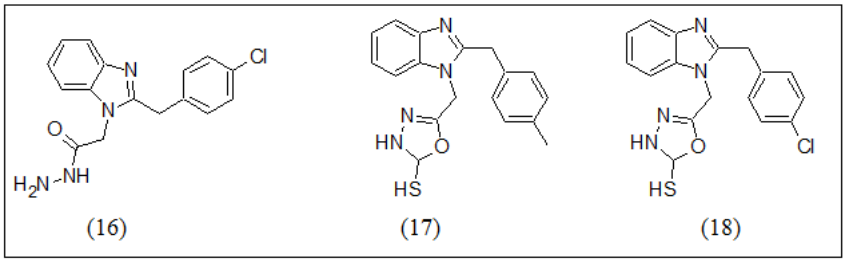
were checked by monitoring the cell viability along with levels of lactate dehydrogenase, glutathione, and malonaldehyde in isolated rat hepatocytes.

The antioxidant characteristics of the compounds with the low toxicity were evaluated by means of oxidative stress induced by *tert*-butyl hydroperoxide (*tert*-BOOH) on rat hepatocytes. Their study reported that compound (15) has demonstrated the highest protection effect in both tested systems [37].



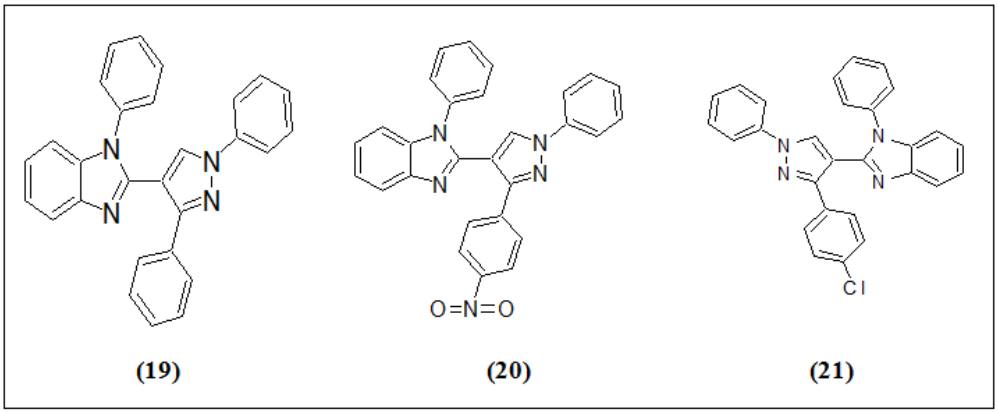
(15)

Usta *et al.* synthesized some benzimidazole derivatives containing salicyl, oxadiazole, thiosemicarbazide and 1, 2, 4-triazole molecules and evaluate their antioxidant activities. Antioxidant activities of the synthesized compounds were tested with DPPH and ABTS•+ radical cation decolorization assays. Compounds (16), (17) and (18) showed very good scavenging activity[38].



(16) (17) (18)

A chain of new *N*-substituted pyrazole-bearing benzimidazoles was synthesized by Bellam *et al*. from 1,2-diaminobenzene and pyrazole-4-carbaldehyde and antioxidant activity of all synthesized compounds have been checked by using 2,2-diphenyl-1-picrylhydrazyl and hydrogen peroxide assays. Some derivatives (19-21) bearing benzyl moiety as a substituent on imidazole nitrogen showed potent activity [39].

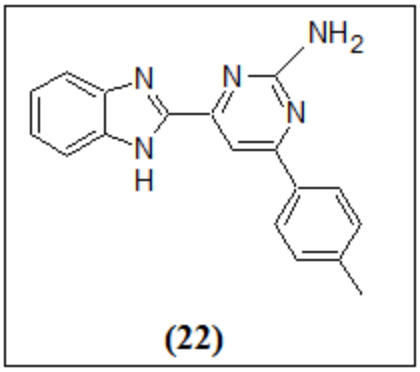


(19) **(20)** **(21)**

Benzimidazole derivatives acting as antimicrobial agents

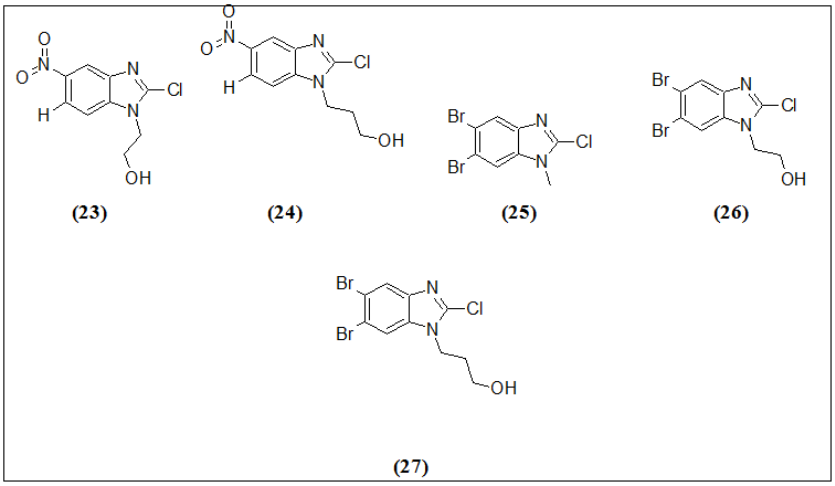
Antimicrobials, particularly antibiotics have been a backbone of modern medical therapy for the last eight decades. In recent years, a significant improvement in life expectation and access to antimicrobials were there but increasing pathogen resistance to antimicrobials threatens leads to roll back this progress. Resistant organisms in health-care and community settings pose a threat to survival rates from serious infections, including neonatal sepsis and health-care-associated infections, and limit the potential health benefits from surgeries, transplants, and cancer treatment. The increasing challenge for health care is to overcome antimicrobial resistance and the subsequent absence of access to effective antimicrobials. To deal with the risk to human health and biosecurity from antimicrobial resistance it becomes necessary to design and synthesize potential antimicrobial agents [40–42].

So, in this viewpoint, Liu *et al*. designed and synthesized a series of novel aminopyrimidine benzimidazoles as highly acting antimicrobial agents and were characterized by IR, NMR, and HRMS spectra. Their biological assessment *in vitro* study revealed that few of the target compounds exerted superior antibacterial activity over the reference drugs (chloromycetin, norfloxacin, and fluconazole). Particularly, compound (22) displayed potentially inhibit the growth of *A. flavus*, *E. coli.* Further investigation found that pyrimidine derivative (22) has a bactericidal mode of action against both Gram-positive and Gram-negative bacteria [43].



(22)

A new class of 2-Cl-benzimidazole derivatives has been synthesized by Srivastava *et al*. and investigated all prepared derivatives for antibacterial activity. Their result showed that compounds (23), (24) and (25) carries potential activity against *B. cereus*, *S. aureus* and *P. aeruginosa* (MIC: 6.2 µg/mL) along with great efficacy against *E. coli* (MIC: 3.1µg/mL). Particularly compounds (26) and (27) has been found to be promised superior activity (MIC: 3.1 µg/mL) than the reference drugs chloramphenicol and cycloheximide in opposition to gram-positive and gram-negative bacterial strains [44].

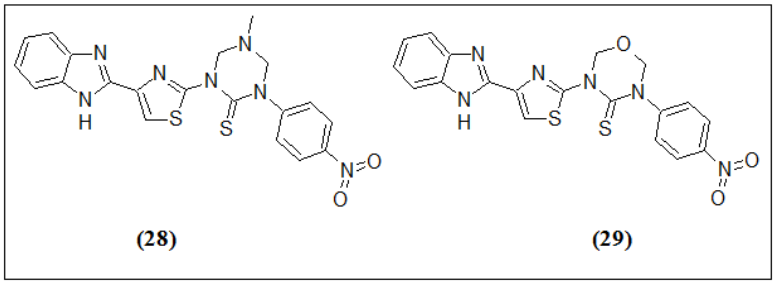


(23) **(24)** **(25)** **(26)**

(27)

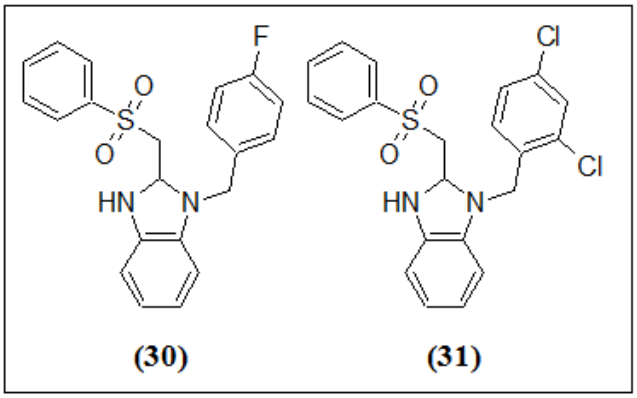
Gullapelli *et al*. synthesized a series of novel analogs of benzimidazole fused heterocyclic compounds such as triazinane and oxadiazines by conventional amino methylation through diverse aryl-N, N-O unsymmetrical thioureas. The antibacterial activity of triazinane and oxadiazinane has been evaluated by means of the zone of inhibition by well diffusion method against *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, *E. coli*, *Klebsiella pneumonia*, and *Salmonella typhi*. The synthesized compounds were

subjected to molecular docking studies with two proteins, named as topoisomerase II (PDB ID: 1JIJ) and DNA gyrase subunit b (PDB ID: 1KZN). The docking outcomes of the formed compounds (28) and (29) exhibited strong binding energy with topoisomerase II as well as with DNA gyrase subunit b [45].



(28) **(29)**

In objective to find out new antimicrobial agents Zhang *et al*. designed and synthesized a novel series of benzimidazole-integrated sulfonamide analogs. Compound (30) exhibited powerful activities against Gram-positive bacteria and fungi, along with 2,4-dichlorobenzyl derivative (31) results in potent activity against Gram-negative bacteria. The two active molecules (30) and (31) (MIC values ranging from 4 to 32 µg/mL) might obstruct DNA replication and showed their potent antimicrobial activity. Molecular docking study indicated that compounds (30) and (31) might insert inside base-pairs of DNA hexamer duplex by the construction of hydrogen bonds with guanine of DNA.



(30) **(31)**

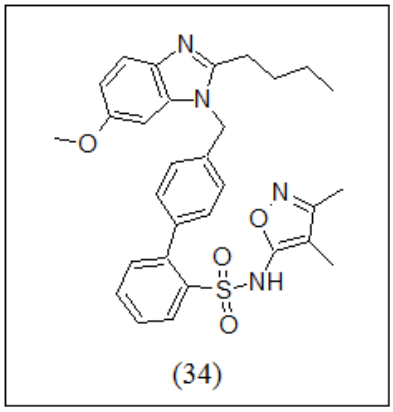
A range of nine 2-chloromethyl-benzimidazole derivatives was synthesized Zhang *et al.* and evaluated for their activity against *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive) and *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative). All the synthesized compounds showed good antimicrobial spectrum as compared to the standard drug (streptomycin) [46].

Benzimidazoles as antihypertensive agents

Extensive progress has been made to understand the epidemiology, pathophysiology, and risk accompanying hypertension, and numerous evidence exist to explain that lowering blood pressure (BP) can significantly reduce premature morbidity and mortality. Globally, high blood pressure (BP) affects over 40% of adults above 25 years and is the foremost universal risk factor for death or disability. Numerous, well managed, and healthy lifestyle and drug treatment approaches can achieve a reduction in hypertension. But still, BP control rates persists poor worldwide. Consequently, hypertension stands as the chief preventable cause of the cardiovascular disease (CVD) and all-cause death globally. With the goal of improving the prevention and management of hypertension, various potent agents have been discovered and still, the research is going on [47,48]. Kini *et al*. performed docking experiments on twenty novel 5-nitro benzimidazoles using VLife MDS3.5 software via GRIP batch docking method taking AT-2 receptor model with bovine rhodopsin crystal structure as a target. Based on docking scores of the designed molecules from (-14.39 to -36.16), the 5-nitrobenzimidazole derivatives were synthesized by utilizing 4-nitro-1,2-phenylenediamine in dimethoxyethane along with different substituted aromatic aldehydes in the existence of sodium metabisulphite as an oxidizing agent. The resulted derivatives were characterized by using TLC, melting point, UV, IR, 1H NMR, and mass spectroscopy. All the compounds were checked for vasorelaxant activity in rat aorta rings pre-contracted with phenylephrine and among all derivatives (32,33) exhibited great vasorelaxant activity (EC50<30 µM) [49–51].

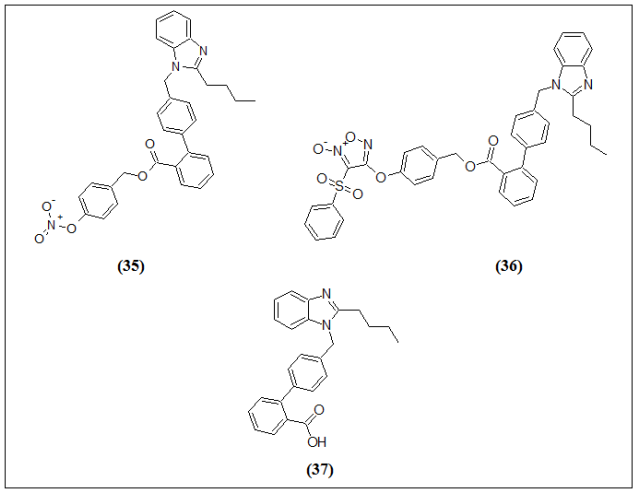
(32) (33)

In order to found new biological active compounds, a series of 40-[(benzimidazole-1-yl)methyl]biphenyl-2-sulfonamide derivatives were synthesized by Bai *et al*. promising antihypertensive activity was found in compound (34) which antagonized both Ang II AT_1 and endothelin ET_A receptors (AT_1 IC50 = 8.5, ET_A IC50 = 8.9 nM). Additionally, it was found as a more potent compound when compared to losartan in RHRs with nearly no side effect on heart rate [52].



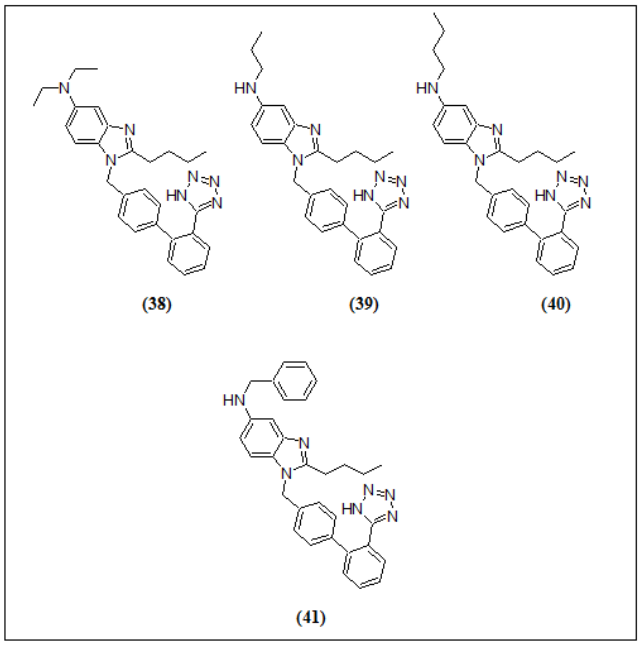
(34)

Zhang *et al.* designed and synthesized two series of innovative NO-releasing benzimidazole derivatives by combining nitro ester and furoxan NO-donor molecules with benzimidazole biphenyl skeleton. All the compounds had a different level of NO liberating capabilities and also the Ang II encouraged vasoconstriction antagonism ability has been evaluated by isolated organ assay (rat aortic strips). It was found that pA_2 values of compounds (35) and (36) were dominant over that of lead compound (37) and comparable to that of the positive control Losartan. Results of their research suggested that NO-releasing hybrids may afford an auspicious approach for the finding of new antihypertensive agents [53].



(35) (36) (37)

Jain *et al*. designed and synthesized a series of 5-substituted benzimidazoles as well as evaluated there in vivo antihypertensive activity by acute renal hypertension on a guinea pig. All the derivatives of this series produced remarkable activity when compared to the reference drug (losartan). The activity was found to be relatively better in four compounds (38-41) substituted alkylamino group at 5-position of benzimidazole [54].

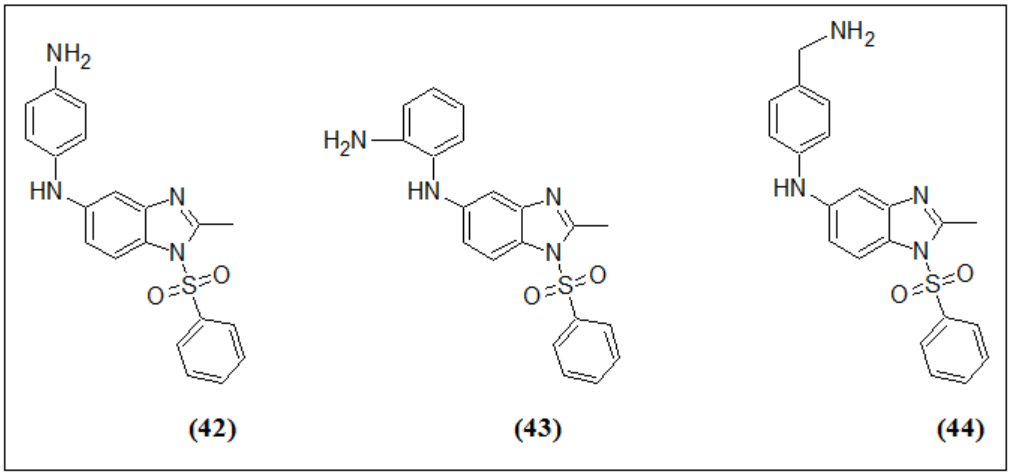


Benzimidazole derivatives as analgesics and anti-inflammatory agents

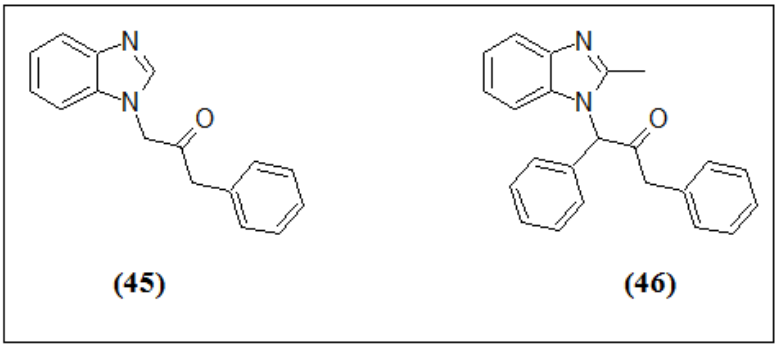
There are many novel pathways to discover selective analgesic agents which act via different ways related to pain receptor activation. In order to overcome the challenges of serious side effects on renal, hepatic and cardiovascular system of existing NSAID's there is an urgency to find out new agents as an analgesic and anti-inflammatory. From past work (1980-1985) it has been showed that various benzimidazole derivatives carry the potential for anti-inflammatory and analgesic activity in animal models of inflammation and pain [55–59].

1-(1-Alkyl-6-substituted-1H-benzimidazole-2-yl)-naphthalene-2-ols were synthesized by Dixit et al. by the reaction of o-phenylenediamine and naphthaldehyde utilizing sodium hydride and THF as a catalyst. The synthesized compounds were checked for the analgesic activity by tail flick method in rats. These prepared derivatives are then observed in tail flick model that identify the amplification of the pain threshold expressively after 0, 30, 60, 90, and 120 min by administering the dose of 50 mg/kg. The study showed that different derivatives elicited time-dependent activity in all the experimental models [60].

Gaba *et al*. synthesized a new chain of 5-substituted-1-(phenylsulfonyl)-2-methyl benzimidazole derivatives. The compounds were characterized by IR, 1H NMR, 13C NMR, Mass spectral data and elemental analyses. All synthesized derivatives were checked for their anti-inflammatory and analgesic activity along with gastric ulcerogenic effects. Compounds (42-44) showed modest to good anti-inflammatory and analgesic activity in carrageenan-induced rat paw edema and acetic acid-induced writhing in mice, correspondingly, with low ulcerogenicity related to reference drug indomethacin [61].

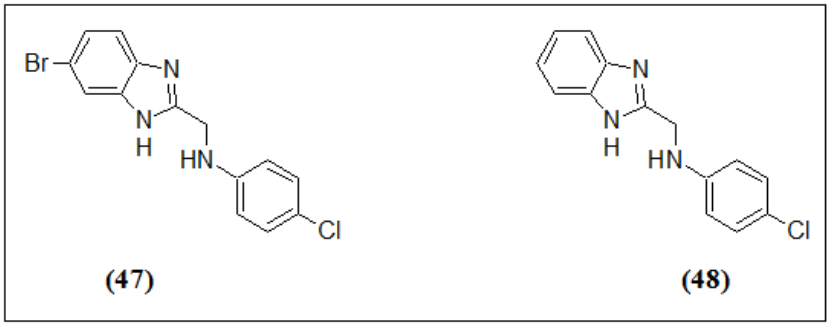


Kumar *et al*. synthesized a series of new mannich bases of 2-substituted benzimidazoles by the reaction of 2-substituted benzimidazoles with different aldehyde and acetophenones. All the synthesized compounds were characterized by elemental analysis, IR, 1HNMR, 13C-NMR, and LCMS. The derivatives were checked for *in vivo* analgesic and *in vivo* anti-inflammatory activities by a tail flick method and carrageenan-induced rat paw edema test. Compound (45) and (46) showed noteworthy analgesic and anti-inflammatory activities among the synthesized compounds [62].



(45) **(46)**

In order to discover some new analgesic and anti-inflammatory agents, Achar *et al*. synthesized a series of 2-methylamino benzimidazole derivatives by the reaction of 2-(chloromethyl)-1H-benzimidazole derivatives with primary aromatic amines. All these derivatives were characterized by using IR, 1H NMR, 13C NMR, GC-MS, and elemental analysis. The novel compounds were evaluated for analgesic and anti-inflammatory activities on acetic acid-induced writhing in mice and carrageenan-induced paw edema in rats. Among all of these, Compounds [47] and [48] carried a strong analgesic (89% at 100 mg/kg b.w) as well as anti-inflammatory (100% at 100 mg/kg b.w) activities equated with reference drug Nimesulide (100% at 50 mg/kg b.w) [63].



(47) **(48)**

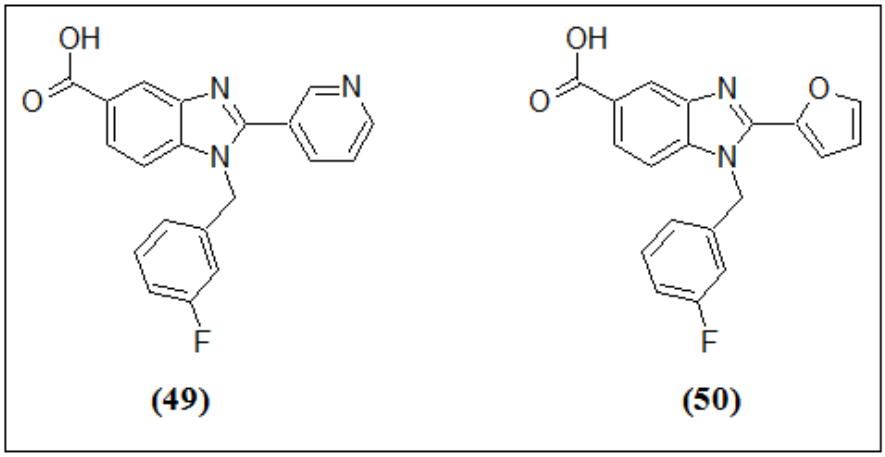
Miscellaneous biological activities of benzimidazoles

Anxiolytic

A novel chain of benzimidazole derivatives was synthesized by Bairam et al. using the reaction of *o*-phenylenediamine with diverse aromatic aldehydes in the presence of ammonium chloride NH4Cl, as an effective catalyst at room temperature. All synthesized derivatives were identified by utilizing LCMS, IR and NMR spectroscopy. The synthesized derivatives were evaluated for chronic anti-anxiety activity in albino rats by means of Light and Dark box model and showed potent anti-anxiety effect [64].

Human DHODH inhibitors

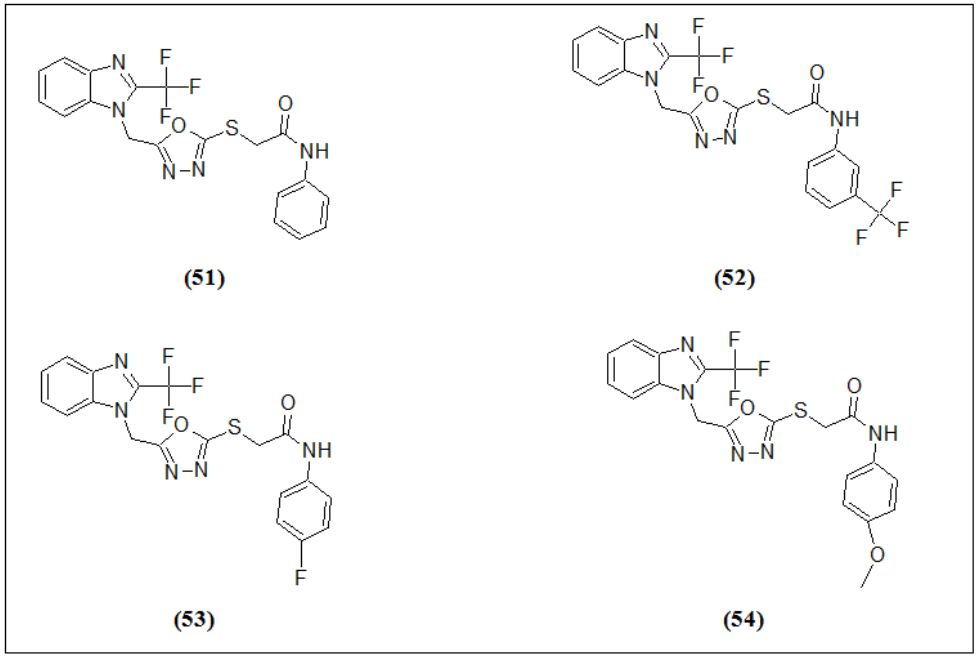
Liquid phase combinatorial synthetic technique is a well known equivalent method to perform solution-phase chemistry utilizing support-bound chemicals to eliminate impurities or added reagents from the solutions [65]. Applying this technique Sitwala et al. synthesized a series of 1,2,5-trisubstituted benzimidazole derivatives by using soluble polymer assisted support (PEG5000). All derivatives were identified by ESI-MS, FTIR, 1H NM, and 13C NMR. Along with that, these compounds were also docked into the binding site of human dihydroorotate dehydrogenase (hDHODH). The synthesized derivatives were evaluated for hDHODH enzyme inhibition assay using reference drug Brequinar [66]. Dihydroorotate dehydrogenase (DHODH) is an enzyme essential in de novo pyrimidine biosynthesis and it catalyzes the conversion of dihydroorotate (DHO) to orotate (ORO) with the reduction of ubiquinone. The targeted compounds showed comparative biological activity and among all, compounds (49) and (50) demonstrated an IC50 value of 81 ± 2 nM and 97 ± 2 nM, correspondingly [67,68].



Antidepressant

Glycogen synthase kinase-3 (GSK-3) is a protein kinase enzyme which acts as a mediator for the addition of phosphate molecules onto serine and threonine amino acid residues and is occur in two major isoforms as GSK-3a and GSK-3b, exist in all over the body. The possible relationship between disturbed inhibitory GSK-3 regulation and depression has been well-known by multiple pharmacological and molecular approaches [69-71].

Tantray *et al*. synthesized a series of benzimidazole linked-1,3,4-oxadiazole carboxamides and checked them for *in vitro* GSK-3b inhibition. The synthesized compounds were found to be active *in vivo* antidepressant activity in Wistar rats. Along with that docking study of all active compounds was also investigated. Some derivatives [51-54] displayed noteworthy effectiveness against GSK-3b in sub-micromolar range with IC50 values of 0.13 lM, 0.14 lM, 0.20 lM, 0.22 lM respectively. From the results of the docking study, these compounds may serve as valuable candidates for further expansion of effective drugs as an antidepressant and related disorders [72].



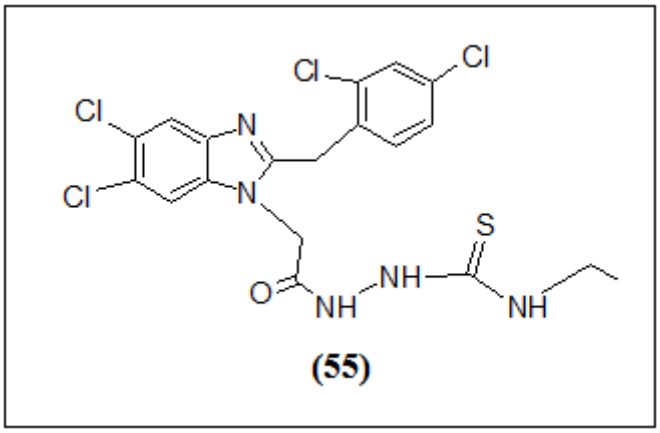
Anticonvulsant

Shaharyar *et al*. synthesized various derivatives of 2-[2-(phenoxymethyl)-1H-benzimidazol-1-yl]-N0-[(Z)-phenylmethylidene] acetohydrazide. Along with that, some compounds comprising oxadiazole bearing benzimidazole derivatives were prepared by utilizing several aromatic aldehydes, cyanogen bromide and carbon disulfide/potassium hydroxide. All synthesized compounds were characterized by IR, NMR and elemental analysis and they're *in vivo* anticonvulsant evaluation was achieved using MES and scPTZ. Some of the compounds were

found potent comparing with the standard drug (phenytoin and ethosuximide) [73].

Anti-Urease

Karaali *et al*. synthesized a series of new 5,6-dichlorobenzimidazole derivatives and further, their structure was determined by FT-IR, 1H NMR, 13C NMR, and elemental analysis spectroscopic methods. All the synthesized compounds were checked for anti-urease activity. Urease is an enzyme that catalyzes the hydrolysis of urea into carbon dioxide and ammonia. Among these derivatives, compound (55) showed the greatest inhibitory effect against urease with IC50 2.52 µg/mL [74].



(55)

Benzimidazole derivatives have various biological activities. However, some adverse effects are also associated with different derivatives. The heterocyclic substituted benzimidazoles do not undergo much change during metabolism but still, there are some side effects like dizziness, anorexia, nausea & vomiting caused to the body [75–76]. Therefore, scientists should take their research forward to next level to minimize the toxic effects caused be this valuable benzimidazole moiety

CONCLUSION

Numerous compounds have been synthesized from the benzimidazole nucleus for the treatment of many diseases. This literature reports various benzimidazole derivatives to have potent anticancer, antimicrobial, antioxidant and some other therapeutic activities. However, despite these active, exhaustive and target-based research on the development of many compounds from benzimidazole core as anti-inflammatory, immunomodulatory, lipid modulators, etc. no molecule has made its way to the market and clinic. It can be probably due to incomplete research reports and some adverse effects. In order to reduce side effects, new derivatives need to be properly designed and synthesized with a target-oriented approach using computer-aided drug design as an important tool.

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