ISSN (Print 0974-2115) (Online 2349-8552)
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

Benzimidazole: Multifunctional Nucleus with Diverse Biological Activities

Prafulla Sabale[1], Lata Potey*[2], Dhanashree Wasu[2], Tabssum Bano[2]
[1]Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur-440033 M.S. India
[2]School of Pharmacy, G. H. Raisoni University, Saikheda, 480106, MP. India.
***Corresponding Author: E-Mail: lata.potey@ghru.edu.in**

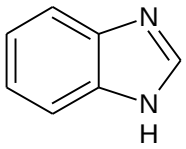
ABSTRACT

Benzimidazole is the fused heterocyclic compound which is the fusion of benzene and imidazole ring containing nitrogen atom that has attracted much attention due to their diverse biological activity and clinical applications. Benzimidazole is well known as a capable class of biologically active fused heterocyclic compounds that can show a range of biological activities like anti-tuberculosis, anti-microbial, anti-protozoal, anti-cancer, anti-inflammatory, anti-hypertensive, anti-oxidant, anti-ulcer, anti-viral, anti-proliferative, anti-hypertensive, proton pump inhibitors, etc. In addition, several compounds containing benzimidazole moiety have found industrial applications as wetting, emulsifying, foaming, or softening agents or as dispersants for use in dyeing. For this reason the main focus of the researchers is the synthesis of novel benzimidazole derivatives. The present review article is concerned about the general introduction about benzimidazole and its synthesis with special emphasis on drug available in the market having benzimidazole nucleus with its mechanism, therapeutic uses, side effects and also highlighted research work of many researchers reported in the literature for diverse pharmacological activities on synthesized benzimidazole.

KEY WORDS: Benzimidazole, Bicyclic heterocyclic, anti-tuberculosis, anti-microbial, anti-protozoal, anti-cancer, anti-inflammatory, anti-hypertensive, anti-oxidant, anti-ulcer.

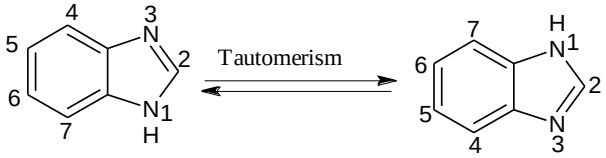
1. INTRODUCTION

Benzimidazole (I) is a bicyclic heterocyclic organic compound that consists of benzene rings fused with Imidazole ring which is also known as benzoglyoxalines. The most famous benzimidazole naturally occurs is *N-ribosyl-dimethyl benzimidazole*, which act as an axial ligand for cobalt metal in vitamin B_{12} (Barker, 1960). This important group of substances has found practical applications in many fields. Recently the attention in benzimidazole chemistry has been revised somewhat through the discovery that, the 5,6-dimethylbenzimidazole moiety is a fraction of the chemical construction of vitamin B_{12}.



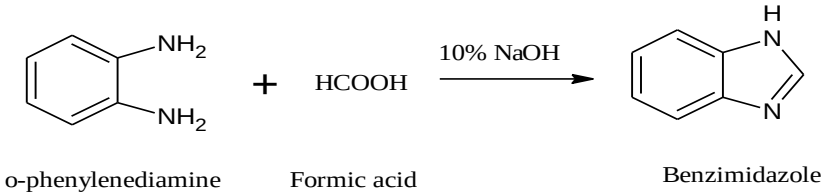
(I)

In History, the first time, benzimidazole was synthesized by Hoebrecker in 1872 who was obtained 2, 5, or (2, 6) dimethyl benzimidazole via the reduction of 2-nitro-4-methyl acetanilide. More than a few years later Ladenburg prepared the similar compound via refluxing of 3, 4-diamine toluene with Glacial acetic acid. Benzimidazole can be formed by condensation reaction between of *o*-Phenylenediamine and formic acid, or the equivalent trimethyl orthoformate. Since compounds of this category can be produced by the loss of water molecule, they called as "anhydrobases". It was then showed that "anhydrobases" of this category was formed only by analogs in which the nitrogen-containing substituents are ortho position to each other. The ring produced was an imidazole ring as reported by certain reactions of benzimidazoles, such as the fact that, imidazole dicarboxylic acid may be obtained, although in small yield, by the oxidation of benzimidazole (Verma, 2021). Benzimidazole possesses acidic as well as basic properties. The –NH group present in the benzimidazole nucleus is comparatively strongly acidic as well as weakly basic also. One more property of benzimidazole is that it can form salts. Benzimidazole with unsubstituted –NH groups exhibits fast prototrophic tautomer formation which form the equilibrium mixture of asymmetrically substituted analogs.



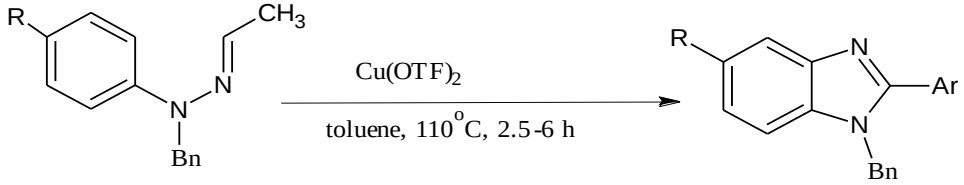
Thus, the benzimidazole nucleus is becomes target for the structural modification in the development of novel molecules of pharmacological or biological concern. Rightly substituted benzimidazole derivatives have seen diverse therapeutic purposes such as anti-ulcer, anti-hypertensive, anti-viral, anti-fungal, anti-cancer, anti-oxidant, anti-microbial, anthelmintic, anti-inflammatory, and anti-tuberculosis activity (Bansal and Silakari, 2012).

Synthesis of Benzimidazole:



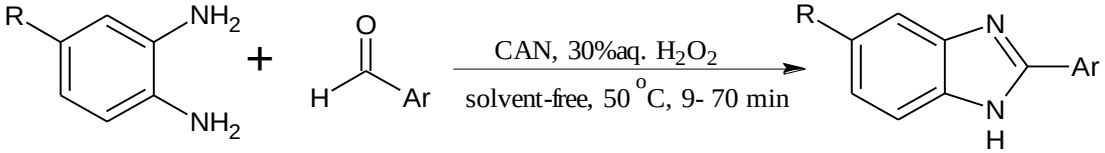
Scheme 1

The traditional approach of synthesis of benzimidazole involves the condensation of O-phenylenediamine and formic acid in 10% sodium hydroxide, while with acetic acid, it yields 2-methyl benzimidazole having m.p 173-174ºC (Brian, 2010).



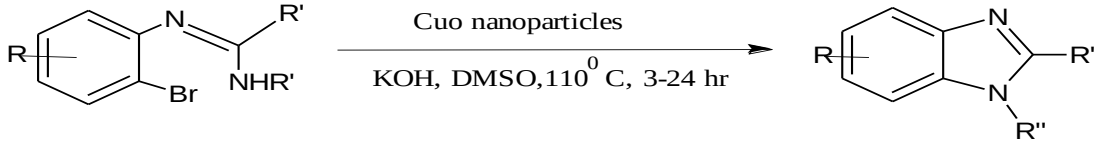
Scheme 2

An adequate method for the transformation of *N*-benzyl bisarylhydrazones and bisaryloxime ethers to functionalized 2-aryl-*N*-benzylbenzimidazoles comprises copper (II)-mediated cascade like cupric trifluoromethane sulfonate (Cu $(OTf)_2$), where C-H functionalization/C-N/C-O bond formation occur under neutral conditions. Compounds substituted with either electron-donating group or electron-withdrawing group experience the cyclization at moderate temperature (Murali, 2012).



Scheme 3

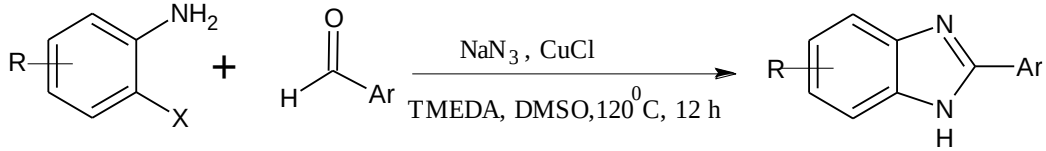
The synthesis of 2-substituted benzimidazole derivatives from the substituted *o*-phenylenediamine and various aldehyde in presence of cerium ammonium nitrate (CAN), allows short reaction times, large-scale synthesis, easy and quick isolation of the products, excellent chemoselectivity, and great yield are the major benefits of this reaction. (Katikireddy and Kakkerla, 2021).



R= H, Br,Cl
R'= Me, Ph
R''=Bn, Ar,alkyl

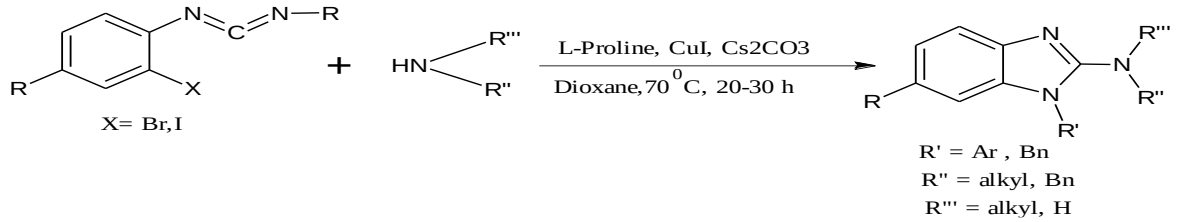
Scheme 4

2-aminobenzimidazoles through intramolecular cyclization of *o*-bromoaryl derivatives is catalyzed by copper (II) oxide nanoparticles in DMSO under air is an experimentally simple, common, efficient, and ligand-free synthesis of substituted benzimidazole. The heterogeneous catalyst can be well gain and reuse without any loss of activity (Prasenjit, 2009).



Scheme 5

A synthesis of benzimidazole in excellent yields is facilitated by the reaction of 2-haloanilines, aldehydes, and sodium azide using catalytic amounts of Copper chloride and tetramethylethylenediamine (TMEDA) in DMSO at 120°C for 12 h. The reaction can tolerate many functional groups like ester, nitro, and chloro, etc. (Kim, 2011).

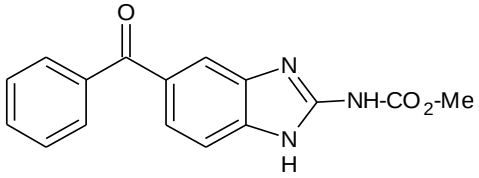


Scheme 6

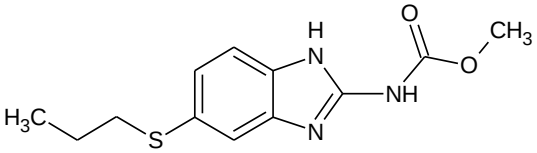
The well-organized copper (I)-catalyzed cascade intermolecular addition/intramolecular C-N coupling reaction enables the synthesis of a ample range of 2-heterobenzimidazoles from *o*-haloarylcarbodiimide.

Drug available in the market having benzimidazole nucleus:

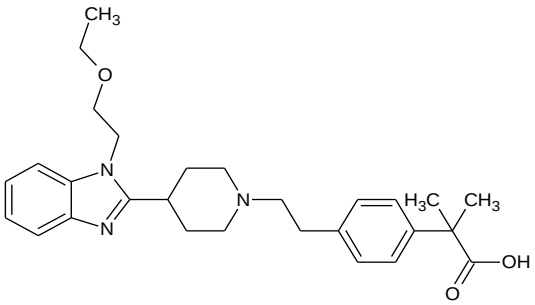
Anthelmintic drug: Mebendazole: Mebendazole is a profoundly effective, broad-spectrum anthelmintic drug dispense for the treatment of nematode infection, including roundworm, whipworm, threadworm, and hookworm. It is also effective for the healing of protozoan infection. Mebendazole inhibit the synthesis of microtubules in parasitic worms, and destroy extant cytoplasmic microtubules in their intestinal cells, and block the uptake of glucose and other nutrients, which result in the slow immobilization and final death of the helminths. It is comparatively free of deadly side effects or adverse reactions, although patients may disapprove of temporary abdominal pain, diarrhoea, minor headache, fever, faintness, exanthema, urticaria, and angioedema (Heath, 1975).



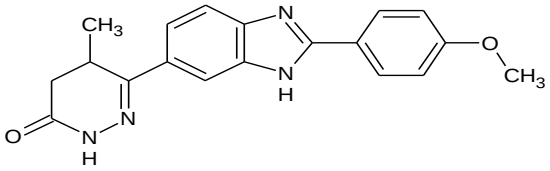
Albendazole: Albendazole having benzimidazole nucleus is marketed as Abenzer, Albenza, Eskazole, Zentel, Andazol, and Alworm for the cure of various parasitic worm infestations. It is a broad-spectrum anthelmintic, valuable against roundworm, tapeworm, and flukes of tame animals and humans. Albendazole causes degenerative modifications in the intestinal cells of the worm by binding to the colchicine-sensitive site of β- tubulin, thus restraining its polymerization or assembly into microtubules. The decline of the cytoplasmic microtubules leads to undermined uptake of glucose by the larval and adult stages of the susceptible parasites and consumes their glycogen stores (Theodorides and Gyurik, 1976). Albendazole may let abdominal ache, faintness, nausea, headache, fever, vomiting, or provisional hair loss. In unique cases, it may cause unwavering painful throat, harsh headache, seizures, visualization troubles, dark urine, yellowing eyes or skin, stomach ache, easy bruising, changes in mental/mood, very rigid neck, or variations in the amount of urine.



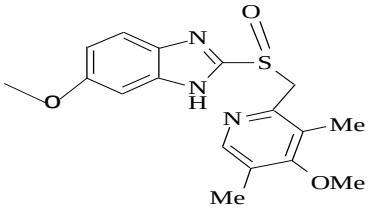
Anti-histamine drug: Bilastine: Bilastine is sold as a Bilaxten brand, which is an antihistamine drug used for the healing of allergic rhino conjunctivitis and urticaria (hives). It exerts its effect as a selective histamine H_1-receptor antagonist. Bilastine has been effective in the remedy of ocular symptoms and diseases of allergies, including rhino conjunctivitis (Jauregui, 2011). Additionally, bilastine has been conferred to improve quality of life, and all nose and ear related symptoms associated with allergic rhinitis. Bilastine can potentially binds to cerebellar histamine H_1-receptors (ki=44 nm) and human recombinant histamine H_1-receptors (ki=64 nM) of guinea-pig with an affinity equivalent to that of Astemizole and Diphenhydramine, and outstanding than that of Cetirizine and Fexofenadine by three-fold and five-fold respectively. Bilastine has been shown to have no adverse cardiac side effects and does not affect driving ability, cardiac conduction, or attentiveness (Bousquate, 2012).



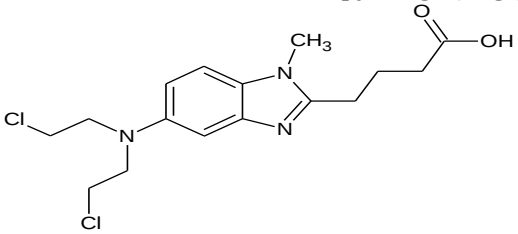
Vasodilator: Pimobendan: Pimobendan is a calcium sensitizing agent have positive inotropic as well as vasodilator property. It is also a selective inhibitor of phosphodiesterase-III (PDE3). Pimobendan increases endurance time and improves the quality of life in patients with congestive heart failure, secondary to mitral valve disease when compared with benazepril, an angiotensin-converting enzyme (ACE) inhibitor (Haggstrom, 2008). Pimobendan is a positive inotrope. It refines and strengthens the binding efficiency of cardiac troponin in the myofibril to the calcium ions that are already present without increasing the consumption of oxygen and energy. Pimobendan also causes peripheral vasodilation by restraining the function of phosphodiesterase-III. This results in diminished pressure, translating into smaller cardiac preload and afterload (decreases the failing heart's workload).



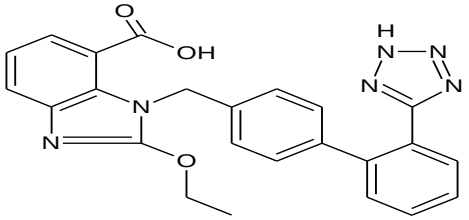
Anti-ulcer: Omeprazole: Omeprazole is used in the remedy of dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD/GERD), laryngopharyngeal reflux (LPR), and zollinger–ellison syndrome as a proton pump inhibitor (McGowan, 1994). Its act by suppressing gastric acid secretion by inhibiting the H^+/K^+ ATPase pump in the gastric parietal cell (Jai Moo and George, 2008). Some of the most prevalent side effects of omeprazole (experienced by over 1% of those taking the drug) are headache, diarrhea, abdominal pain, nausea, dizziness, trouble awakening, and sleep deprivation, although other side effects may include iron and vitamin B_{12} deficiency.



Anticancer: Bendamustine: Bendamustine (Brand names Ribomustine, Treakisym, Levact and Treanda, also called as SDX-105) is nitrogen mustard applied in the healing of chronic lymphocytic leukemia and lymphomas (Kath, 2001). It pertains to the class of drugs called alkylating agents which serve by conflicting with the function of DNA & RNA. It is also being studied for the healing of sarcoma (Bagchi, 2007). East German investigators noticed that it is applied for healing Hodgkin's disease, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, lung cancer and multiple myeloma. Bendamustine are used together as single therapy and in combination therapy with other agents like Etoposide, Fludarabine, Mitoxantrone, Methotrexate, Prednisone, Rituximab, and Vincristine and 90Y-Ibritumomab Tiuxetan. Common adverse effects are fatigue, nausea, vomiting, diarrhoea, fever, constipation, cough, loss of appetite, headache, meaningless weight loss, complexity in breathing, rashes, stomatitis, as well as immunosuppression, anemia, and short platelet counts. Reputably, this drug has a small occurrence of hair loss (alopecia) distinct from other chemotherapy drugs (Tageja and Nagi, 2010).

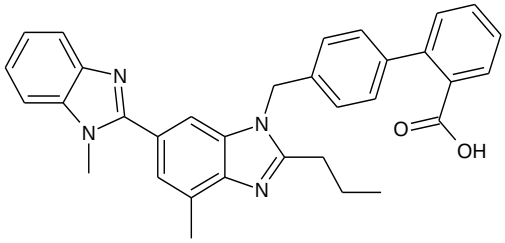


Antihypertensive: Candesartan: Candesartan is a blocker of Angiotensin II receptor used chiefly for the remedy of hypertension. The prodrug of Candesartan is Cilexetil is sold under the brand names Blopress, Ratacand Amias, Atacand. It is generally given in combination with an ACE inhibitor to achieve improved fatality and morbidity in a patient with Congestive heart failure (CHF) and additionally is an option in patients who develop intolerance of ACE inhibitor therapy. Candesartan is also accessible in a combine therapy with a low dose of thiazide diuretic, invariably Hydrochlorothiazide, to attain potential hypotensive result (Ezequiel, 2002).



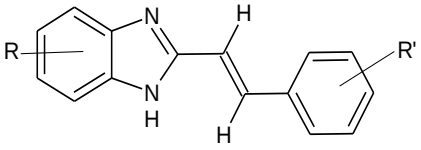
Telmisartan: Telmisartan is an antagonist of angiotensin II receptor useful in managing essential hypertension. It shows high binding affinity to the angiotensin II receptor type 1 (AT_1), with a binding affinity 3000 times superior for AT1 than AT_2. It has the longest half-life of 24 h. and the largest volume of distribution 500 liters. In addition to blocking the RAS, Telmisartan acts as a selective modulator of Peroxisome Proliferator-activated receptor-gamma (PPAR-γ), a central regulator of metabolism of insulin and glucose. It is thought that Telmisartan have dual mode of action which provide protective benefits against the vascular and renal damage caused by Diabetes and Cardiovascular disease (CVD). Telmisartan activity at the PPAR-γ receptor has promote theory just about its potential as a sports doping agent as an option to GW 501516 (Gosse, 2006).

Telmisartan activates PPAR δ receptor in more than a few tissues (Zhiming, 2013). Adverse effects are like to another angiotensin II receptor blockers and include Tachycardia and Bradycardia (fast or slow heartbeat), Hypotension (low blood pressure), Edema and different allergic reactions.



Recent trends in Benzimidazole nucleus:

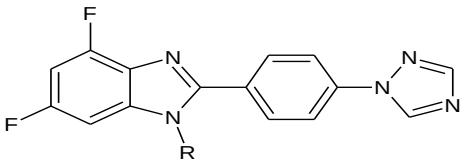
Anti-tubercular activity: Hosamani and Shingalapur (2009), were reported a synthesis and anti-tubercular activity of a new series of novel 5-(nitro/bromo)-stryl-2-benzimidazole derivatives obtained by reacting 5-(nitro/bromo)-o-phenylenediamine with trans-cinnamic acids in ethylene glycol. The synthesized compounds were chosen for *in-vitro* Anti-tubercular activity against Mycobacterium Tuberculosis $H_{37}R_V$ strain in BACTEC 12B medium. Following two compounds (1a &b) were documented as the most promising candidate with the Minimum Inhibitory Concentration (MIC) of 45 μM and 54 μM respectively.



1a: R= -NO_2, R'=2,4 -CL
1b: R= -Br, R'=3,4- OCH_3

(1)

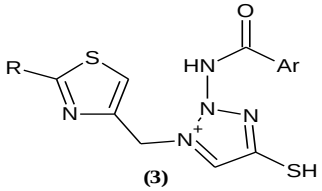
Gill (2009), reported a series of new clubbed 2-[4-(1H-[1,2,4]-triazol-1-yl)phenyl]-1- substituted-4,6-difluoro-1H-benzo[d]imidazole derivatives and evaluated them for their antitubercular efficacy against M.Tb H37Rv. Among all, two derivatives (2 a & b) have shown prominent potency of MIC 0.36 μg/mL and 0.58 μg/mL respectively.



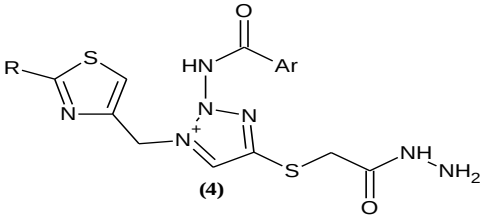
Compound	R	MIC
2a	-CH_2(3-FC_6H_5)	0.36
2b	-CH_2(3-ClC_6H_5)	0.58

(2)

Shridhar (2007), reported the synthesis of N-{4-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substituted amide derivatives and clinically tested for their in-vitro antitubercular activity against M. Tuberculosis strain $H_{37}Rv$. Especially compounds (3a & 4a) contain Schiff base have shown the highest activity, due to increased lipophilicity with MIC of 0.39 and 0.78 μm respectively.



(3)



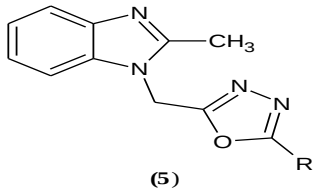
(4)

3a: R= - $NHCOCH_3$, Ar= -3$NO_2C_6H_4$

4a: R= -$NHCOC_6H_5$, Ar= -3$NO_2C_6H_4$

Anti-microbial activity: Ansari and Lal (2009), were reported a synthesis and anti-microbial activity of a new derivatives of 2-substituted-1-*H* benzimidazole compounds (5a-h) determined as potent anti-microbial agents against Gram-positive bacteria including *Staphylococcus aureus*, *Bacillus subtilis*, and *Streptococcus mutan*ts and

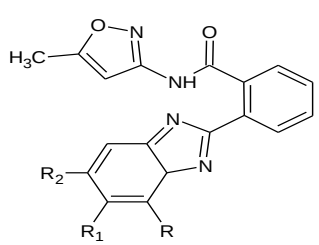
Gram-negative bacteria including *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella typhi* and compound (5e) gave potent antifungal activity against *A. flavus*.



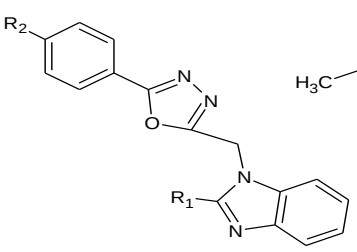
(5)

Compound	R	Compound	R
5a	CH_3	**5e**	$4\text{-}ClC_6H_4$
5b	C_2H_5	**5f**	$4\text{-}OHC_6H_4$
5c	CH_2CH_2Cl	**5g**	$2\text{-}OCH_3C_6H_4$
5d	C_6H_5	**5h**	$4\text{-}OCH_3C_6H_4$

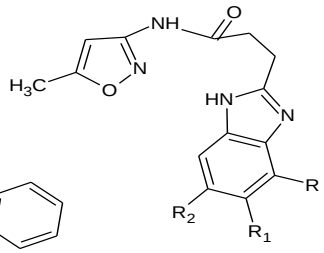
Rajanarendar (2008), were reported a synthesis and anti-microbial activity of benzimidazole as novel 2/3 (1H-benzoimidazole-2-yl)-N-(5-methyl-3-isoxazolyl) benzamides, acrylamides, propionamides. Compounds (6a, 7a & 8a) were clinically tested for antibacterial potency against two gram-negative bacteria *Escherichia coli* and *Proteus Vulgaris*, and two Gram-positive bacteria *Bacillus mycoides* and *Staphylococcus aureus* at 600 and 900 µg/ml concentration and for their antifungal activity against two plant pathogens like *Fusarium oxysporum* and *Drescherla halides* at 160 µg, 320 µg, 480 µg, and 640 µg concentration.



(6)



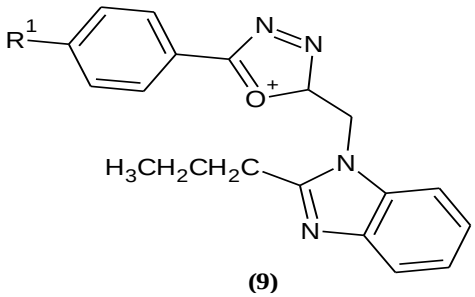
(7)



(8)

Compound	R	R_1	R_2
6a :	H	H	H
7a :	NO_2	H	H
8a :	H	Cl	Cl

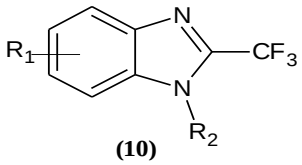
Gowda (2010), were reported a synthesis and antibacterial activity of a new series of 2-substituted-1-[(5-substituted phenyl-1,3,4-oxadiazol-2-yl)methyl]-1H-benzimidazole. Compounds (9a-e) were tested for the *in-vitro* antibacterial activity against the common bacterial strains like *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and the antifungal activity was carried out against four different fungi namely *Penicillium marneffei*, *Trichophytonm entagrophytes*, *Aspergillus flavus and Aspergillus fumigatus*.



(9)

Compound	R_1
9a	H
9b	Cl
9c	Br
9d	Me
9e	OMe

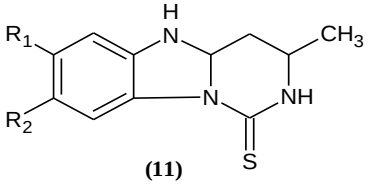
Anti-protozoal activity: Vazquez (2009), reported the synthesis and anti-protozoal activity of a 2-(trifluoromethyl)-1H-benzimidazole derivatives with various 5th and 6th position bio isosteric substituents. All the compounds were evaluated *in-vitro* against the protozoa *Giardia intestinalis* and *Trichomonas vaginalis* in comparison with Albendazole and Metronidazole. Quite a few analogs had IC_{50} values < 1 µM against both species, which build them considerably extra potent than standard. Compound (10a) [2,5(6)-bis(trifluoromethyl)-1H-benzimidazole], was 14 times more active than albendazole against *T. vaginalis*.



(10)

10a : $R_1 = CF_3$, $R_2 = H$

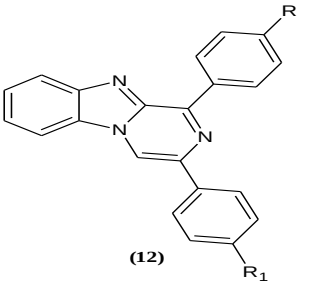
Saeed (2010), synthesized a pyrimidobenzimidazole derivative which shows a potent anti-protozoal activity. The anti-protozoal activity was done by micro dilution method against *Entamoeba histolytica* (strain HM1: IMSS). The compounds (11a, b, c, & d) were found to be most active.



(11)

11a : $R_1 = H$, $R_2 = H$
11 b: $R_1 = H$, $R_2 = CH_3$
11c: $R_1 = COOH$, $R_2 = H$
11d : $R_1 = CH_3$, $R_2 = CH_3$

Anti-cancer activity: Demirayak and Kayagil (2015), carried out the microwave-supported synthesis and anti-cancer activity of 1,3-diarylpyrazino[1,2-a] benzimidazole derivatives. The anticancer and/or cell growth inhibitory effects of the compounds (12a-j) were evaluated *in-vitro* against approximately sixty human tumor cell lines obtained from nine cancerous diseases.

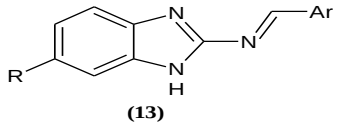


(12)

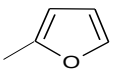
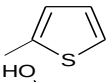
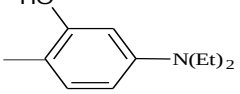
Compound	R	R_1
12a	H	H
12b	H	CH_3
12c	H	F
12d	H	Cl
12e	OCH_3	H

Compound	R	R_1
12f	OCH_3	CH_3
12g	OCH_3	Cl
12h	Cl	H
12i	Cl	F
12j	Cl	Cl

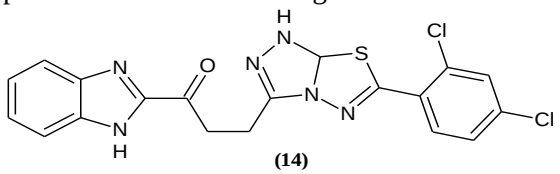
Marijana (2011), reported synthesis and antiproliferative activity of new benzimidazole substituted Schiff Bases. The compounds (13a-f) were showed the strongest non-specific anti-proliferative activity on all cell lines and shown a concentration dependent effect on HeLa and MCF-7 cell lines at micromolar concentrations but simultaneously remain greatly cytotoxic on human fibroblasts also.



(13)

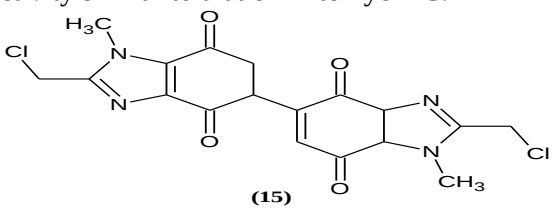
Compound	R	Ar
13a	CN	
13b	CH_3	
13c	CN	
13d	NO_2	
13e	CN	
13f	CH_3	

Husain (2013), were reported two series, triazolo-thiadiazoles and triazolo-thiadiazines of benzimidazole clubbed to produce capable anticancer agents. *In-vitro* anticancer activities of synthesized compounds was analysed at the National Cancer Institute (NCI) against NCI 60 cell line panel, results have shown good to moderate anticancer activity. Amongst them, the compound (14) (NCS: 760452, 1-(1H-benzo [d] imidazol-2-yl)-3-(6-(2,4-dichlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl) propan-1-one) shown major growth inhibition with GI_{50} values ranging from 0.20 to 2.58 µM and shown better selectivity for the leukemia cell lines and further tested at 10-fold dilutions of five different concentrations (0.01, 0.1, 1, 10 and 100 µM). The compound (14) may be a lead compound for the development of new anticancer agents.



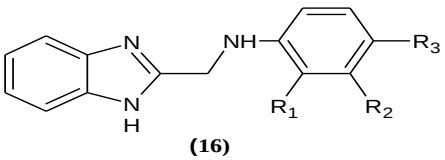
(14)

Gellis (2008), were reported synthesis of new benzimidazole-4, 7-diones substituted analogues at 2nd position through a microwave-assisted synthesis by using 2-chloromethyl-1,5,6-trimethyl-1H-benzimidazole-4,7-dione. Cytotoxicity was tested against the colon, breast, and lung cancer cell lines. The dimer (15) was shown to possess outstanding cytotoxicity activity similar to that of Mitomycin C.



(15)

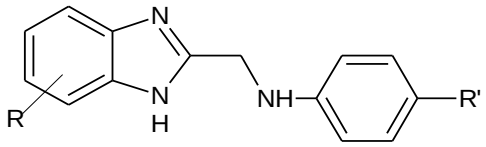
Anti-inflammatory activity: Mariappan (2011), were reported a synthesis and anti-inflammatory activity of a new series of 2-substituted benzimidazole derivatives prepared from 2-chloromethyl benzimidazole with substituted primary aromatic amines. The compounds (16b, c, d, & e) showed profound analgesic activity which was carried out by Tail-flick method using Swiss albino mice, and the compounds (16a, b, c & e) showed potent anti-inflammatory activity which was evaluated by carrageenan-induced rat paw edema model.



(16)

Compound	R_1	R_2	R_3
16a	Cl	Cl	H
16b	H	H	NO_2
16c	Cl	H	NO_2
16d	H	H	SO_2NH_2
16e	H	H	I

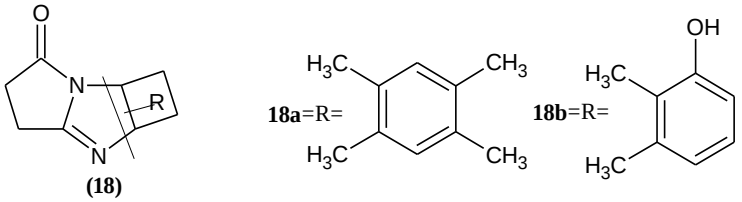
Kavitha (2010), were reported synthesis and analgesic and anti-inflammatory activity of 2-methyl amino benzimidazole derivatives by acetic acid-induced writhing in mice and carrageenan-induced paw edema in rats. Compounds (17a & b) showed potent analgesic and anti-inflammatory activities compared with standard drug Nimesulide (100% at 50 mg/kg b.w.) respectively.



(17)

17a : R = H, R' = Cl
17b : R = Br, R' = B

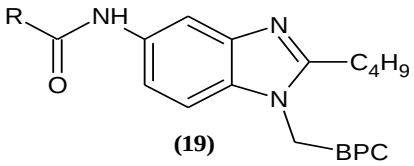
Sondhi (2010), synthesized heterocyclic benzimidazole derivatives by condensation reaction of homophthalic acid, succinic acid, and 2, 3-pyrazinedicarboxlic acid with different diamines with microwave synthesis method in better yields. All derivatives were analyzed for Anti-inflammatory activity at a dose of 50 mg/kg p.o. Compounds (18a) (39.4%) and (18b) (39.2%) demonstrated good to moderate anti-inflammatory activity, compared to standard Ibuprofen which have shown 39% activity at 50 mg/kg p.o.



(18)

18a=R= **18b**=R=

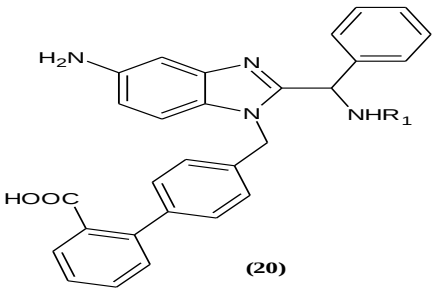
Anti-hypertensive activity: Dhvanit (2008), were synthesized a series of 5-(alkyl and aryl) carboxamido benzimidazole derivatives. Compounds (19a-g) were clinically tested for *in-vitro* angiotensin II - AT1 receptor blocking activity and *in-vivo* anti-hypertensive activity. Compounds with fewer alkyl groups at 5th position of benzimidazole ring has demonstrated potent anti-hypertensive activity.



(19)

Compound	R
19a	CH_3
19b	CH_2CH_3
19c	n-C_3H_7
19d	n-C_4H_9
19e	C_6H_5
19f	(2-Cl)C_6H_4
19g	(4-Cl)C_6H_4

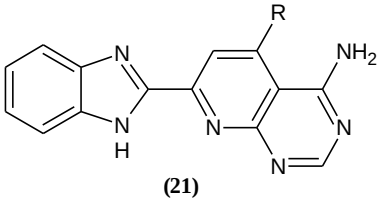
Sharma (2010), has reported the method for the synthesis of a new series of 4'-{5-amino-2-[2-substituted-phenylamino)-phenyl-methyl]-benzimidazol-1-ylmethyl}-biphenyl-2-carboxylic acid derivatives were synthesized by converting 2-(α- hydroxy benzyl) benzimidazole to 2-(α-bromo benzyl) benzimidazole by reacting with HBr and anhydrous $ZnCl_2$. All compounds (20a-d) were clinically tested by tail-cuff method for the antihypertensive activity and direct method analysis of blood pressure. All the derivatives have shows the potent anti-hypertensive effect.



(20)

20a : R = 4-NO_2
20b : R = 2-NO_2
20c : R = 4-Cl
20d : R = 3-Cl

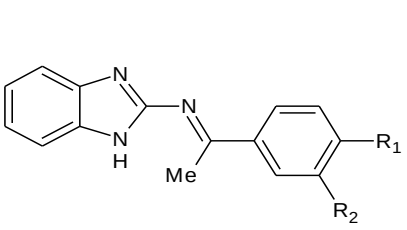
Anti-oxidant activity: Mavrova (2013), reported the synthesis and anti-oxidant activity of novel series of 7-(1H-benzimidazol-2-yl)-5-(substituted phenyl) pyrido [2, 3-d] pyrimidin-4-amine. The compounds (21a & b) showed good antioxidant activity with an IC_{50} value of 10μg/mL compared to the standard ascorbic acid and screened by *in-vitro* free radical scavenging activity using DPPH (2, 2-diphenyl-1picryl hydrazyl) reduction method.



(21)

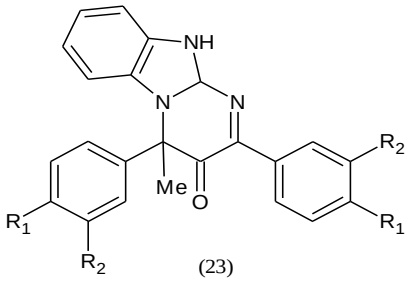
Compound	R	Compound	R
21a	C_6H_5	**21d**	$Br_2C_6H_2Cl$
21b	FC_6H_4	**21e**	OHC_6H_4
21c	ClC_6H_4	**21f**	$OCH_3C_6H_4$

Constantinos and Tryfon (2011), have demonstrated the method for the synthesis of several benzimidazole Schiff base and 3-oxo-pyrimido [1,2-a] benzimidazoles in superb yields by a one-step reaction from 2-aminobenzimidazole under green chemistry conditions. The anti-oxidant activity can be evaluated by inhibitors of lipoxygenase (LOX) and lipid peroxidation (LPO). All the tested compounds (22a-b & 23a-c), showed inhibition of lipid peroxidation, whereas most compounds have higher activation than the reference compound Trolox.



(22)

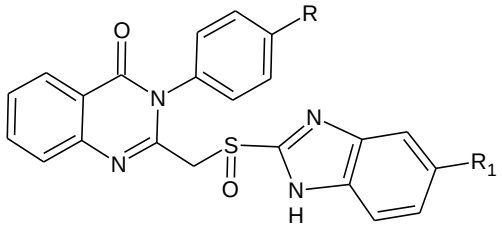
	R_1	R_2
(22a) :	H	OMe
(22b) :	H	Br



(23)

	R_1	R_2
(23a)	H	OMe
(23b)	H	Br
(23c)	Cl	H

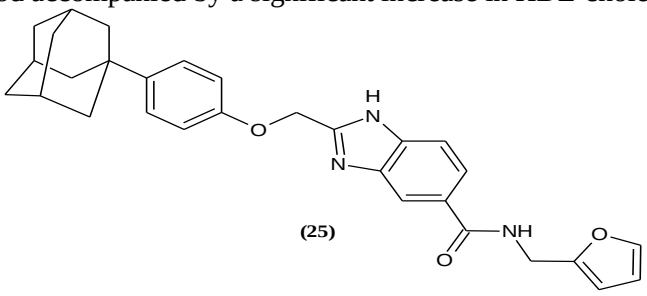
Anti-ulcer activity: Rajesh (2017), reported a synthesis and anti-ulcer activity of 2-[{5-substituted-1H-benzo(d)imidazol-2-yl sulfinyl} methyl]-3-substituted phenyl quinazoline-4(3H)-one derivatives. The compounds (24a-f) have shown potent anti-ulcer activity which was studied by pylorus ligation induced ulcer models in rats.



(24)

Compound	R	R_1
24a	H	OCH_3
24b	CH_3	OCH_3
24c	H	$OCHF_2$
24d	CH_3	$OCHF_2$
24e	OCH_3	$OCHF_2$
24f	OC_2H_5	$OCHF_2$

Antihyperlipidemic agents: Lee (2012), were prepared new run of benzimidazole derivatives and tested for diacylglycerol acyltransferase (DGAT) inhibitory activity using microsome from rat liver. Among the newly synthesized compounds, furfurylamine containing benzimidazole carboxamide (25) shown the most potent DGAT inhibitory activity (IC_{50} = 4.4 lM) and inhibited triglyceride formation in HepG2 cells. Furthermore, compound **(25)** reduced body weight gain of mice on a high-fat diet and decreased levels of total triglyceride, total cholesterol, and LDL-cholesterol in the blood accompanied by a significant increase in HDL-cholesterol level.



(25)

2. CONCLUSION

This article emphasized on drug available in the market having benzimidazole nucleus with its mechanism, therapeutic uses, and adverse effects and also highlighted research work of many researchers reported in the literature for different pharmacological activities like anti-tuberculosis, anti-microbial, anti-protozoal, anti-cancer, anti-inflammatory, anti-hypertensive, anti-oxidant, anti-ulcer and anti-hyperlipidemic agent. The broad and potent activity of benzimidazole and their derivative has established them as pharmacologically meaningful scaffolds.

Declaration of competing interests: The authors have reported no conflict of interest.

3. ACKNOWLEDGEMENT

The authors are grateful to all the team of G. H. Raisoni University, Saikheda M.P., and Rashtrasant Tukdoji Maharaj Nagpur, University Nagpur, MS for giving support for the completion of this review article.

Availability of data and materials: The datasets used during the current study are available from the corresponding author on reasonable request.

REFERENCES

Ansari KF, Lal C, Synthesis, physicochemical properties and antimicrobial activity of some new benzimidazole derivatives, Eur. J. Med. Chem., 44 (10), 2009, 4028–4033.

Bagchi S, Combination therapy of an afucosylated CD20 antibody with bendamustine, Lancet Oncol., 8, 2007, 674.

Bansal Y, Silakari O, The therapeutic journey of benzimidazoles: a review, Bio. Org. Med. Chem., 20 (21), 2012, 6208-6236.

Barker H, Smyth RD, Weissbach H, Toohey JI, Ladd JN, Isolation and properties of crystalline cobamide coenzymes containing benzimidazole or 5, 6-dimethylbenzimidazole, J. Bio. Chem., 235, 1960, 480–488.

Bousquet J, Ansotegui I, Canonica, Zuberbier G.W, Baena T.C, Bachert C.E, Cruz C, Gonzalez, Role of bilastine in the management of allergic rhinitis and urticaria: An Asia- Pacific consensus statement, Curr. Med. Res. and Opinion, 11, 2012, 31–39.

Brian SF, Hannaford AJ, Smith PWG, Tatchell AR, Vogel's Textbook of practical organic chemistry, 5th edition, 2010, 1162.

Constantinos GN, Tryfon ZT, ChemInform Abstract: One-Pot Microwave Assisted Synthesis under Green Chemistry Conditions, Antioxidant Screening, and Cytotoxicity Assessments of Benzimidazole Schiff Bases and Pyrimido[1,2-a]benzimidazol-3(4H)-ones, Eur. J. Med. Chem., 46 (1), 2011, 297-306.

Demirayak S, Kayagil I, QSAR Studies on Anticancer Activities of Some Imidazole and Imidazo [1,2-a] Pyrazine Derivatives, The Journal of Graduate School of Natural and Applied Sciences of Mehmet Akif Ersoy University, 6 (2), 2015, 65-73.

Dhvanit I, Shah, Sharma M, Bansal Y, Bansal G, Angiotensin II – AT1 receptor antagonists: Design, synthesis and evaluation of substituted carboxamido benzimidazole derivatives, Eur. J. Med. Chem., 43 (9), 2008, 1808-1812.

Ezequiel B, Candesartan cilexetil plus hydrochlorothiazide combination: a review of its use in hypertension, Drugs, 62 (5), 2002, 787-816.

Gellis A, Kovacic H, Boufatah N, Synthesis and cytotoxicity evaluation of some benzimidazole-4,7-diones as bio reductive anticancer agents, Eur. J. Med. Chem., 43 (9), 2008, 1858-1864.

Gill CH, Jadhav GR, Shaikh MU, Shridhkar MR, SAR study of clubbed [1,2,4]-triazolyl with fluoro benzimidazoles as antimicrobial and antituberculosis agents, Eur. J. Med. Chem., 44 (10), 2009, 2930-2935.

Gosse P, A Review of Telmisartan in the Treatment of Hypertension: Blood Pressure Control in the Early Morning Hours, Vasc. Health Risk Manag., 2 (3), 2006, 195-201.

Gowda J, Khadar AM, Kalluraya B, Suchetha NK, Microwave assisted synthesis of 1,3,4-oxadiazole carrying benzimidazole moiety and their antimicrobial activity, Ind. J. Chem., 49B, 2010, 1130-1134.

Haggstrom J, Boswood A, Grady O, Effect of Pimobendan or Benazepril Hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study, J. Veterinary Inter. Med., 22, 2008, 1124.

Heath DD, Christie MJ, Chevis RA, The lethal effect of mebendazole on secondary Echinococcus granulosus, cysticerci of Taenia pisiformis and tetrathyridia of Mesocestoides corti, Parasitology, 70 (2), 1975, 273-85.

Hosamani KP, Shingalapur RV, Synthesis and evaluation of in vitro anti-microbial and anti-tubercular activity of 2-styryl benzimidazoles, Eur. J. Med. Chem., 44 (10), 2009, 4244-4248.

Husain A, Rashid M, Shaharyar M, Siddiqui AA, Mishra R, Benzimidazole clubbed with triazolo-thiadiazoles and triazolo-thiadiazines: new anticancer agents, Eur. J. Med. Chem., 62, 2013, 785-798.

Jai Moo S, George S, The gastric HK-ATPase: Structure, function, and inhibition, European Journal of Physiology, 457 (3), 2008, 609–622.

Jauregui I, Bartra J, Cuvillo AD, Davila I, Ferrer M, Montoro J, Mullol J, Effect of Bilastine Upon Nasal Obstruction, J. Investing, Allergol Clin. Immunol, 21, 2011, 16–23.

Kath R, Blumenstengel K, Fricke HJ, Hoffken K, Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia, Journal of cancer research and clinical oncology, 127 (1), 2001, 48–54.

Kavitha CS Achar, Hosamani KM, Harisha SR, In-vivo analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives, Eur. J. Med. Chem., 45 (5), 2010, 2048–2054.

Kim Y, Manian RK, Park N, Heo Y, Lee S, Copper-Catalyzed, One-Pot, Three-Component Synthesis of Benzimidazoles by Condensation and C-N Bond Formation, J. Org. Chem., 76, 2011, 9577–9583.

Lee K, Goo JI, Jung HY, Kim M, Boovanahalli SK, Park HR, Kim MO, Kim DH, Lee HS, Choi Y, Discovery of a novel series of benzimidazole derivatives as diacylglycerol acyl transferase inhibitors, Bioorganic & Medicinal Chemistry Letters, 22, 2012, 7456-7460.

Mariappan G, Hazarika R, Faruk A, Synthesis and biological evaluation of 2-substituted benzimidazole derivatives, Ara. J. Chem., 2011, 1-5.

Marijana H, Kristina S, Pavelic SK, Synthesis, spectroscopic characterization and antiproliferative evaluation in vitro of novel Schiff bases related to benzimidazoles, Eur. J. Med. Chem., 46 (6), 2011, 2274-2279.

Mavrova A, Antioxidant activity of some benzimidazole derivatives to definite tumor cell lines, Journal of cancer research and therapy, 1 (2), 2013, 87-89.

McGowan CC, Cover TL, Blaser MJ, The proton pump inhibitor omeprazole inhibits acid survival of Helicobacter pylori by a urease-independent mechanism, Gastroenterology, 107 (5), 1994, 1573-1578.

Murali MG, Ashif AM, Tharmalingam P, Copper(II)-Catalyzed Aerobic Oxidative Synthesis of Substituted 1,2,3- and 1,2,4-Triazoles from Bisaryl hydrazones via C–H Functionalization/C–C/N–N/C–N Bonds Formation, The Journal of Organic Chemistry, 77 (11), 2012, 5295-5308.

Prasenjit S, Tamminana R, Ashif AM, Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles, and Benzoxazoles, J. Org. Chem., 74, 2009, 8719-8725.

Rajanarendar E, Ramu K, Siva RR, Firoz PS, Synthesis and in vitro study of novel isoxazolyl benzoimidazolyl benzamides, acrylamides, propionamides as antimicrobial agents, Ind. J. Chem., 47B, 2008, 1284-1290.

Rajesh R, Manikandan A, Sivakumar A, C Ramasubbu, Substituted methoxybenzyl-sulfonyl-1H-benzo[d] imidazoles evaluated as effective H+/K+-ATPase inhibitors and anti-ulcer therapeutics, European Journal of Medicinal Chemistry, 139, 2017, 454-460.

Saeed S, Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents, Eur. J. Med. Chem., 45 (4), 2010, 1323-1331.

Sharma M, Dharm VK, Smita S, Synthesis and biological evaluation of some new benzimidazoles derivatives 4'-{5- amino-2-(2-substituted-phenylamino)-phenyl-methyl)-benzimidazol-1 ylmethyl}- biphenyl-2-carboxylic acid: Nonpeptide angiotensin II receptor antagonists, Inter. J. Drug Delivery, 2 (3), 2010, 265-277.

Shridhar MR, Murahari KK, Gangadasu HR, Kalyan CA, Synthesis of new S-derivatives of clubbed triazolyl thiazole as anti-Mycobacterium tuberculosis agents, Bio. Med. Chem., 15, 2007, 3997-4008.

Sondhi SM, Rani R, Singh J, Agrawal SK, Solvent free synthesis, anti-inflammatory and anticancer activity evaluation of tricyclic and tetracyclic benzimidazole derivatives, Bio. Org. Med. Chem. Lett., 20 (7), 2010, 2306-2310.

Tageja N, Nagi J, Bendamustine: Something old, something new Cancer Chemo, Pharmacol., 66, 2010, 413-423.

Theodorides VJ, Gyurik RJ, Comparative Disposition Kinetics of Albendazole in Sheep, Experientia, 32, 1976, 702–703.

Vazquez P, Synthesis and antiprotozoal activity of novel 1-methylbenzimidazole derivatives, Bioorganic & Medicinal Chemistry, 17 (4), 2009, 1724-1730.

Verma R, Gupta C, Ganie AM, Kumar V, Chemistry of benzimidazole and their derivatives: mini review, International Journal of Modern Pharmaceutical Research, 5 (3), 2021, 167-197.

Zhiming Z, Telmisartan Improves Insulin Resistance of Skeletal Muscle through Peroxisome Proliferator–Activated Receptor-δ Activation, Diabetes, 62 (3), 2013, 762-774.