ejpmr, 2020,7(6), 177-185

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

BIOLOGICAL ACTIVITIES OF NITROGEN CONTAINING BENZIMIDAZOLE DERIVETIVES

Nidhi Dhama* and Dr. Nitin Kumar

*Assistant Professor, Department of Pharmacy, Swami Vivekanand Subharti University, Subhartipuram, NH-58, Delhi Haridwar Meerut Bypass Road, Meerut.

Dean, Department of Pharmacy, SMAS, KR Mangalam University, Sohna road, Gurgaon.

***Corresponding Author: Nidhi Dhama**

Assistant Professor, Department of Pharmacy, Swami Vivekanand Subharti University, Subhartipuram, NH-58, Delhi Haridwar Meerut Bypass Road, Meerut.

Article Received on 29/03/2020 **Article Revised on 19/04/2020** **Article Accepted on 09/05/2020**

ABSTRACT

Derivatives of Benzimidazole have been found to reveal assorted biological activities for example, anti-inflammatory, anti-fungal, anti-viral, antitumor and anti-hypertensive. Benzimidazole and its imitative have been showing promising activity in the treatment of many diseases. For these reasons, they have much interest as important pharmacophores and fortunate structure. Many benzimidazole based drugs have been broadly used in the treatment center to treat different types of diseases with high therapeutic potential. So this review article shows that the derivatives of benzimidazole are excellently effective compounds and a great number of reviews available for biochemical and biological studies conformed that their molecules are useful against a wide range of micro-organisms.

KEYWORDS: Benzimidazole, Anthelmintic activity, Anti-inflammatory activity.

1. INTRODUCTION

Benzimidazole is an example of heterocyclic aromatic organic compound. This is a bicyclic compound which consists of the fusion of benzene and imidazole. Heterocyclic compounds are occupied important place among different classes of aromatic organic compounds. Benzimidazole are having a variety of therapeutic uses including antitumor, antifungal, antiparasitic, analgesics, antiviral, antihistamine, as well as use in cardiovascular disease, neurology, endocrinology, and ophthalmology and antitubercular activity.[1] The adaptability of new generation benzimidazole would represent a profitable pharmacophores for further expansion of better medicinal agents. Many researchers have been fascinated to benzimidazole derivatives because of their wide range of biological activity. Over the past years, there is a considerable interest in the development and pharmacology of benzimidazole. They are of wide interest because of their diverse biological activity and clinical applications.[2] Benzimidazole moiety can also be extracted from naturally occurring compounds such as vitamin B12 and its derivatives, and it is similar to the structure of purins.[3]

1.1 Heterocyclic Compounds

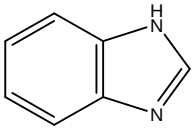
Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties, and applications of heterocycles. Heterocyclic derivatives can be divided into two wide categories: aromatic and non-aromatic. The non-aromatic generally consist of small (3- and 4-membered) and common (5 to 7 membered) ring systems. In comparison, the aromatic heterocyclic compounds are having a heteroatom in the ring and in some of their properties heterocyclic compounds act in a way parallel to benzene.

Table 1: Heterocyclic compounds with five-membered rings.

S. No.	Heteroatom	Compound
1.	Nitrogen	Pyrrole
2.	Oxygen	Furan
3.	Sulfur	Thiophene
4.	Nitrogen/nitrogen	Imidazole
5.	Nitrogen/oxygen	Oxazole
6.	Nitrogen/sulfur	Thiazole
7.	3 × Nitrogen	Triazoles
8.	2 × Nitrogen / 1 × oxygen	Furazan Oxadiazole
9.	2 × Nitrogen / 1 × sulphur	Thiadiazole

1.2 Benzimidazole

The most prominent benzimidazole compounds in nature are N-ribosyl-dimethylbenzimidazole, which act as an axial ligand for cobalt in vitamin B12 Benzimidazole is a heterocyclic aromatic organic compound. Benzimidazole is the fusion of benzene and imidazole moiety. Heterocyclic compounds are having important place between different classes of aromatic organic compounds. Benzimidazole are having a different varieties of therapeutic uses including antitumor, antifungal, antiparasitic, analgesics, antiviral, antihistamine, as well as use in cardiovascular disease, neurology, endocrinology, and ophthalmology and antitubercular activity.**(1)**



Benzimidazole

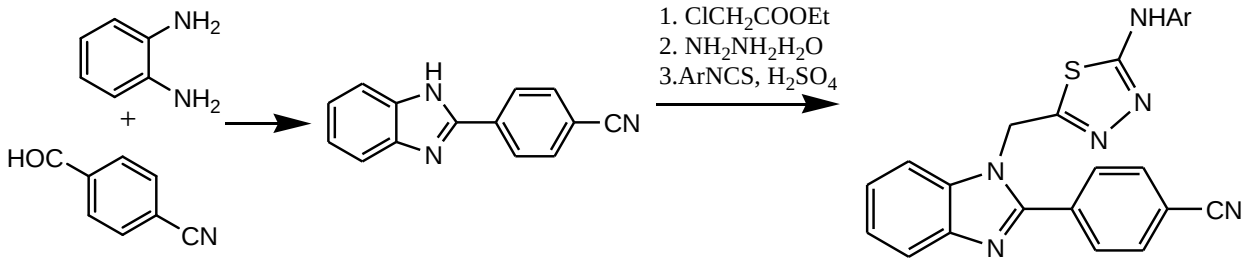
2. BIOLOGICAL IMPLICATIONS OF BENZIMIDAZOLE DERIVATIVES

Heterocycles have been found a key structural in medical chemistry. The largest and one of the classical divisions of organic chemistry is heterocycles. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a wide range of biological activities.[4] Their nucleus is a constituent of vitamin B12 and is present in numerous compounds possessing antioxidant,[5][6] antiparasitic,[7] anthelmintic,[8] antiproliferative,[9] anti-HIV,[10] anti-allergy,[11] anti-inflammatory,[12] antihypertensive,[13] antineoplastic[14] and antiulcer activity.[15]

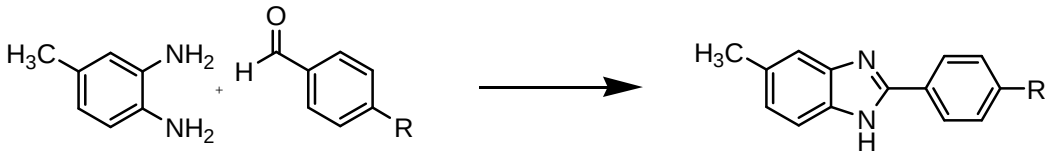
2.1 Antioxidant activity

Antioxidant activity is the ability of bioactive compounds to prevent, delay, and protect against oxidation of various substrates such as DNA and lipid materials, both in living organisms (e.g., humans) and in food products.

Kerimov I et al.[16] have synthesized new derivatives of benzimidazole which showed antioxidant activity.



Karmaker N et al.[17] have synthesized some novel benzimidazole derivatives which showed antioxidant activity. A series of 2-substituted-5-methylbenzimidazole derivatives (3a-e) were synthesized by reacting 4-methyl-1,2-phenylenediamine (1) with a number of p-substituted benzaldehydes (2a-e) in moderate yields (25.51-40.21%). The synthesized compounds (3a-e) were characterized by spectroscopic data and were evaluated for antioxidant activity using DPPH free radical scavenging assay. The compounds showed significant antioxidant activity having IC50 value of 1.054-19.05 µg/ml as compared to the standard BHT (26.96 µg/ml).



R = Cl, Br, F, OMe, NO_2

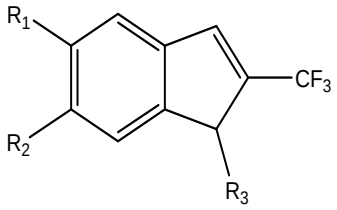
2.2 Antiparasitic activity

Antiparasitics are a class of medications which are indicated for the treatment of parasitic diseases, such as those caused by helminths, amoeba, ectoparasites, parasitic fungi, and protozoa, among others. Antiparasitics target the parasitic agents of the infections by destroying them or inhibiting their growth; they are usually effective against a limited number of parasites within a particular class. Antiparasitics are one of the antimicrobial drugs which include antibiotics that target bacteria, and antifungals that target fungi. They may be administered orally, intravenously or topically.

Alonso F. P. et al.[7] have synthesized new benzimidazole derivatives. 2-(Trifluoromethyl)-1Hbenzimidazole derivatives showed the most desirable in vitro antiparasitic profile against Giardia intestinalis, Entamoeba histolytica, Trichomonas vaginalis and

Trichinella spiralis The anthelmintic drugs derived from benzimidazole 2-carbamates, such as albendazole (ABZ) and mebendazole (MBZ), are used mainly to treat endoparasitic diseases in domestic animals and humans. These types of compounds are characterized by a high therapeutic index and low toxicity; however, they find little use in tissue-dwelling parasites mainly due to poor solubility and absorption problems.

Vazquez G N et al.[19] have synthesized 2-(Trifuoromethyl) - benzimidazole Derivatives showed antiparasitic activity. AbstractÐ2-(Trifuoromethyl) benzimidazole derivatives substituted at the 1-, 5-, and 6-positions have been synthesized and in vitro tested against the protozoa Giardia lamblia, Entamoeba histolytica, and the helminth Trichinella spiralis. Results indicate that all the compounds tested are more active as antiprotozoal agents than Albendazole and Metronidazole. One compound was as active as Albendazole against T. spiralis. These compounds were also tested for their effect on tubulin polymerization and none inhibited tubulin polymerization.

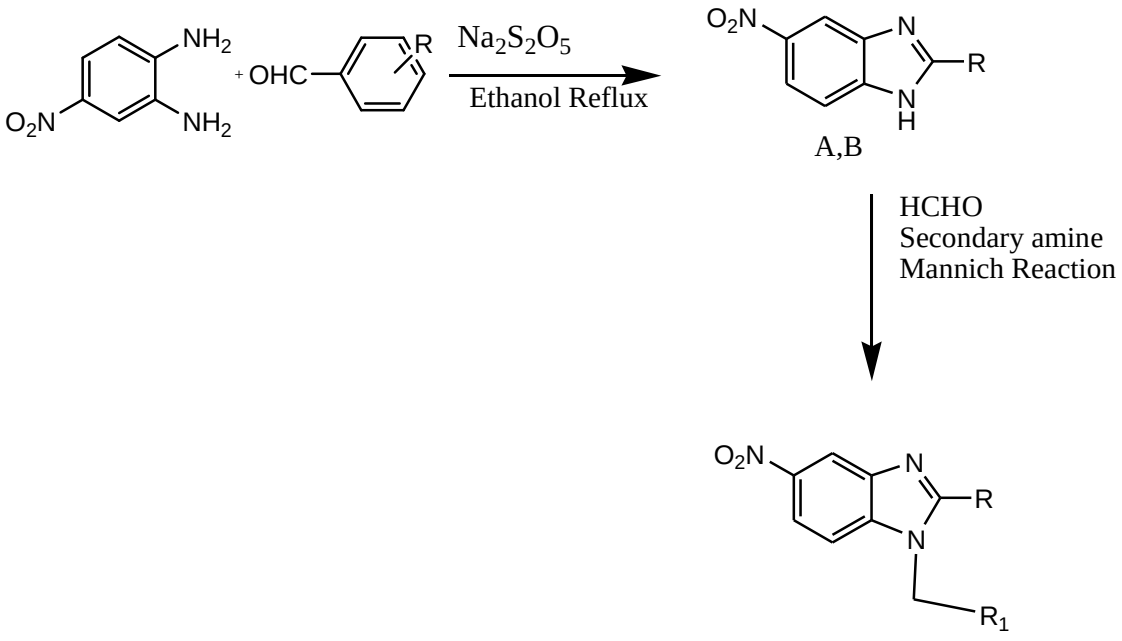


R_1	R_2	R_3
H	H	H
Cl	H	H
Cl	Cl	H
H	H	CH_3

2.3 Anthelmintic activity

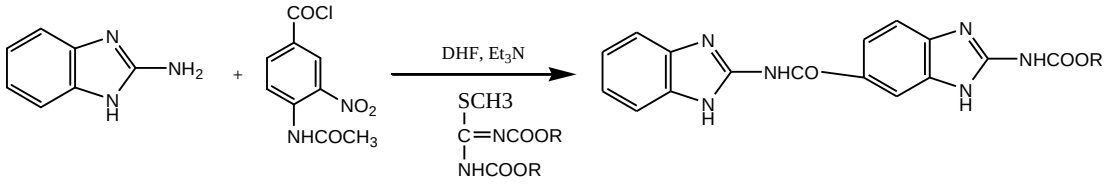
Anthelmintic or antihelminthic are a group of antiparasitic drugs that expel parasitic worms (helminths) and other internal parasites from the body by either stunning or killing them and without causing significant damage to the host. They may also be called vermifuges (those that stun) or vermicides (those that kill). Anthelmintics are used to treat people who are infected by helminths, a condition called helminthiasis. These drugs are also used to treat infected animals.

Pallab K et al.[18] have synthesized some novel derivatives of benzimidazole. This showed anthelmintic activity. The proposed substituted benzimidazole derivatives A [1-4] and B [1-4] were synthesized and evaluated for their antimicrobial and anthelmintic activity. All of the synthesized compounds were found to be active as anthelmintic and antimicrobial agent. Among all the title compounds, [A3] significantly showed very high anthelmintic activity.



Dubey R et al.[20] have synthesized 5-(6) –(Benzimidazole-2-yl Carbamoyl) and (4- substituted piperazin-1-yl) Benzimidazoles showed anthelmintic activity. When the compounds were tested for their anthelmintic activity against *Ancylostoma ceylanicum* in hamsters, *Hymenolepis nana* in rats, *Litomosoides cariniiin* cotton rats, and *Dipetalonema viteae* in *Mastomys natalensis* methyl 5(6)-(4-benzoylpiperazine-1-yl)benzimidazole-2-Carbamate, methyl 5(6)-[4-(2-furoyl)peprazin-1-yl] benzimidazole-2-Carbamate, methyl 5(6)-[4-[(diethylamino)carbonyl] piperazin-1-yl] benzimidazole-2-Carbamate showed 100% elimination of tapeworms *H.nana* at three oral doses of 100-250mg/kg. Compounds also killed the microfilariae and

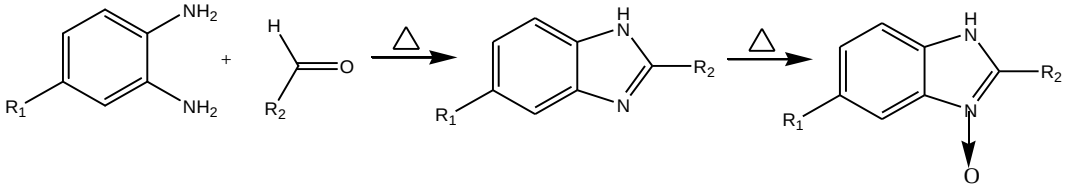
adult worms of *L.carinii* in cotton rats at an intraperitoneal dose of 30mg/kg given for 5 days.



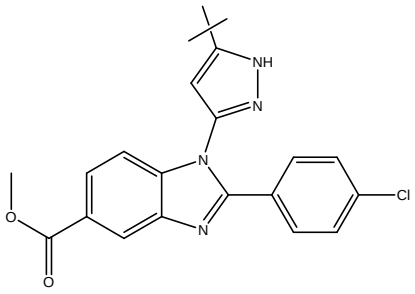
2.4 Antiproliferative activity

Antiproliferative activity is the ability of a compound to stop the growth of cells. This means that not allowing the cells to multiply rapidly. While cytotoxicity refers to causing harm to cells thereby killing them.

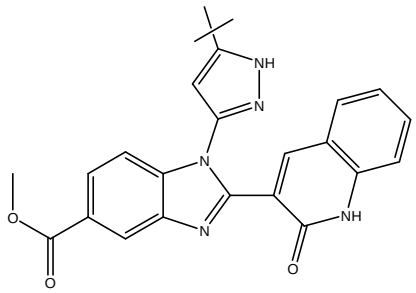
Swiatkiewicz K B et al.[21] have synthesized benzimidazole derivatives showed antiproliferative activity. Their effect of proliferation into selected tumor cell lines at normoxia and hypoxia conditions was determined by WST-1 test. Additionally, apoptosis test (caspase 3/7 assay) was used to check the mode caused by the agents of cell death. That compounds showed a very good antiproliferative effect.



Abonia R et al.[22] synthesized new derivatives of 1,2,5-trisubstituted benzimidazole and screened for their antiproliferative activity against the 60 human cancer cell lines (leukemia, melanoma, lung, colon, brain, ovary, breast and kidney carcinoma etc.) using SRB protein assay to estimate cell growth. Among the synthesized compounds, compound (A) and (B) displayed the utmost potency towards lung, melanoma and leukemia cancer cell lines (GI_{50} values 1.15–7.33 µM and 0.167–7.59 µM), respectively and LC_{50} values more than 100 µM.



(A)

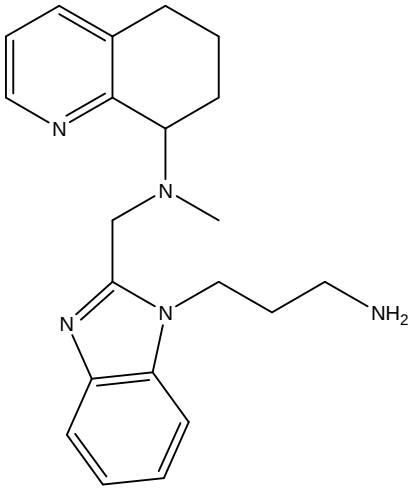


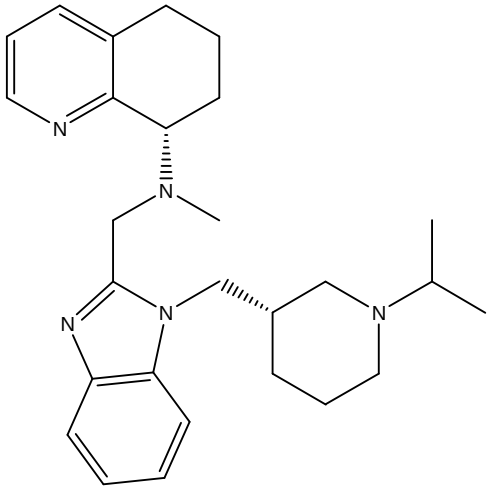
(B)

2.5 Anti-HIV activity

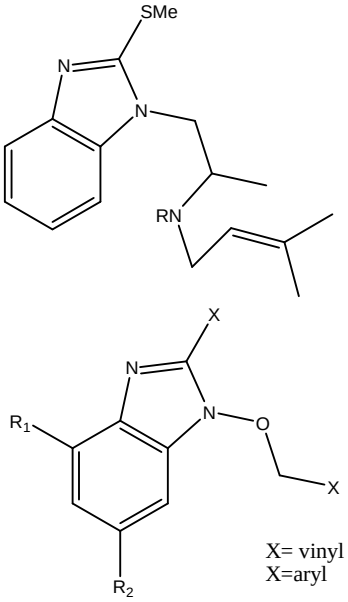
HIV is a virus spread through certain body fluids that attacks the body's immune system, specifically the CD4 cells, often called T cells. Over time, HIV can destroy so many of these cells that the body can't fight off infections and disease. These special cells help the immune system fight off infections.

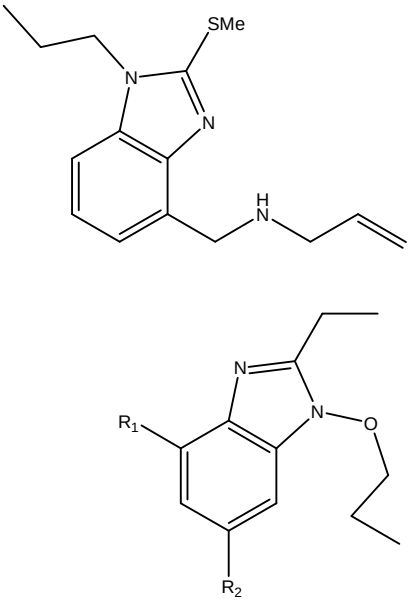
Filler J F et al.[23] have synthesized Novel N-substituted benzimidazole CXCR4 antagonists as potential anti-HIV agents. The lead optimization of a series of N-substituted benzimidazole CXCR4 antagonists is described. Side chain modifications and stereochemical optimization led to substantial improvements in potency and protein shift to afford compounds with low nanomolar anti-HIV activity.





Gardiner J M et al.[24] have synthesized novel benzimidazole derivatives and evaluated for inhibition of HIV-1 infectivity. The most active and selective compounds are a series of N-alkoxy-2-alkyl-benzimidazoles, several having EC50 < 10μM (one sub-micromolar at 600nM), and selectivity ratios of 10–167.

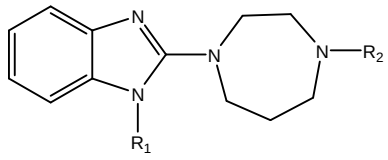


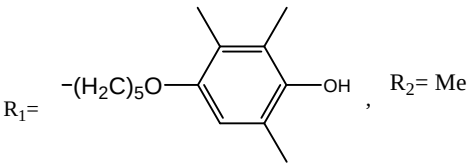


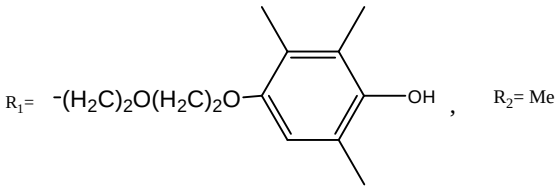
2.6 Anti-allergy activity

A condition in which the immune system reacts abnormally to a foreign substance. Allergies can cause a variety of symptoms such as a runny nose, sneezing, itching, rashes, swelling, or asthma. Allergies can range from minor to severe. Anaphylaxis is a severe reaction that can be life-threatening. Doctors use skin and blood tests to diagnose allergies. Treatments include medicines, allergy shots, and avoiding the substances that cause the reactions.

Nakano H et al.[25] have synthesized benzimidazole derivatives that have anti-allergy activity with 5-Lipoxygenase Inhibiting Action. Synthesized compounds suppress histamine release from mast cells, inhibit 5-lipoxygenase, and possess antioxidative action. Among the compounds synthesized, 1- [2 - [2 - (4 – hydroxyl - 2,3,5 - trimethylphenoxy) ethoxy] ethyl] – 2 - (4-methyl-1-homopiperazino)benzimidazole potently suppressed histamine release from rat peritoneal mast cells triggered by the antigen-antibody reaction, inhibited 5 lipoxygenase in rat basophilic leukemia-1 (RBL-1) cells, and prevented the NADPH-dependent lipid peroxidation induced by Fe31–ADP in rat liver microsomes, in addition to an antagonizing the contraction of guinea pig ileum caused by histamine.



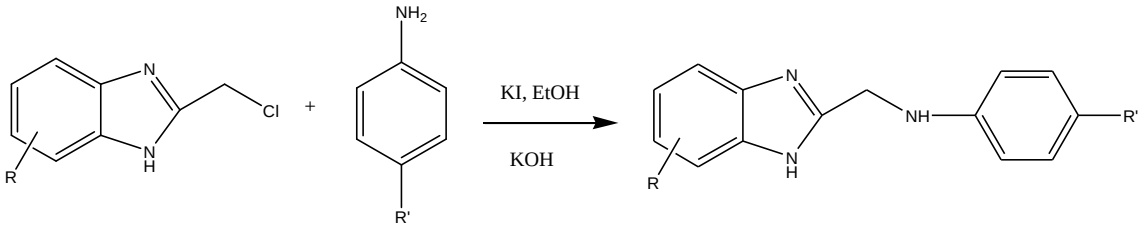




2.7 Anti-inflammatory activity

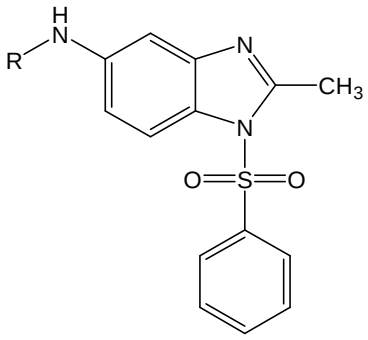
Inflammation is the body's first response to infection or injury and is critical for both innate and adaptive immunity. It can be considered as part of the complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells, or irritants.

Achar K C S et al.[26] have synthesized newly benzimidazole derivatives that have In-vivo analgesic and anti-inflammatory activities. A series of 2-methylaminobenzimidazole derivatives were synthesized by the reaction of 2-(chloromethyl)-1H-benzimidazole derivatives with primary aromatic amines. All these compounds were characterized by IR, 1H NMR, 13C NMR, GC-MS and elemental analysis. The newly synthesized compounds were screened for analgesic and anti-inflammatory activities on acetic acid induced writhing in mice and carrageenan induced paw oedema in rats.



Where, R= H, Br, NO_2
R'= H, Cl, Br, CH_3, OCH_3

Gaba M et al.[27] have synthesized and evaluated of novel 5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole derivatives as anti-inflammatory and analgesic agents. A series of novel 5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole derivatives have been synthesized. The structures of these compounds were established by IR, 1H NMR, 13C NMR, Mass spectral data and elemental analyses. Compounds were evaluated for their anti-infammatory and analgesic activity as well as gastric ulcerogenic effects.



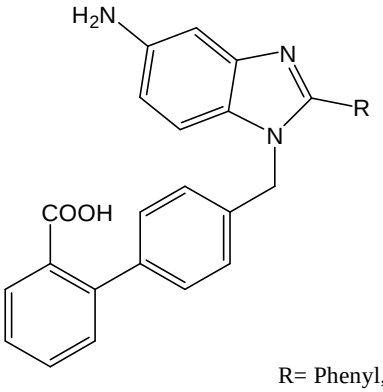
R= Sustituted alkyl/aryl

2.8 Antihypertensive activity

Antihypertensives are a class of drugs that are used to treat hypertension (high blood pressure). Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. There are many classes of antihypertensives, which lower blood pressure by different means. Among the most important and most widely used medications are thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists (ARBs), and beta blockers.

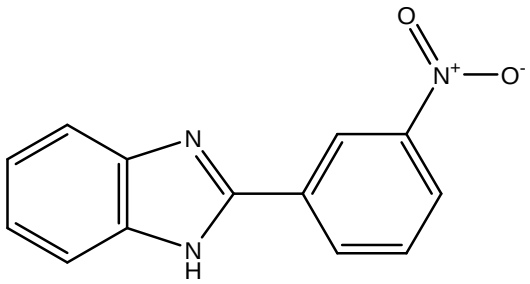
Kumar J R et al.[13] have synthesized benzimidazole derivatives that have antihypertensive activity. N-(biphenyl methyl) imidazoles e.g. 5-substituted (amino) -2- phenyl-1-(2'carboxy biphenyl-4-yl) benzimidazoles differ from the previously reported and related compounds in that they produce a potent hypertensive effect upon oral administration. The earlier series were generally active only when administered intravenously. It has been found that 2'-position of biphenyl is essential.

Only ortho substituted acid possess both high affinity for the AII receptor and oral anti-hypertensive potency.

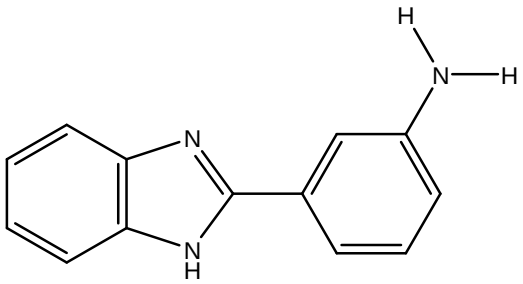


R= Phenyl, Ethyl

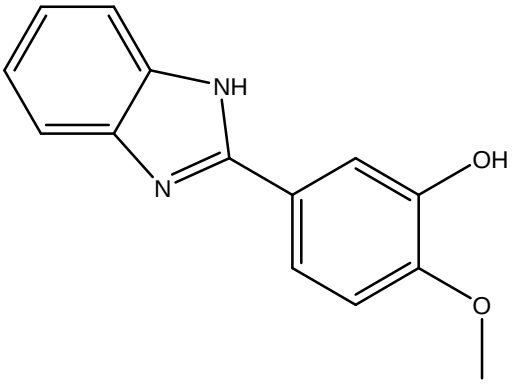
Khan M T et al.[28] have synthesized 2-phenyl substituted benzimidazoles that have antihypertensive activity. Synthesized 2-phenyl substituted benzimidazoles showed good antihypertensive activity by using None Invasive blood Pressure apparatus (NIBP). The present work was mainly intended to establish the moieties which are responsible for Angiotensin-II inhibition. Biological activity of synthesized compounds was carried out using spontaneous hypertensive rats (SHR) using None Invasive blood Pressure apparatus (NIBP).



(A)



(B)

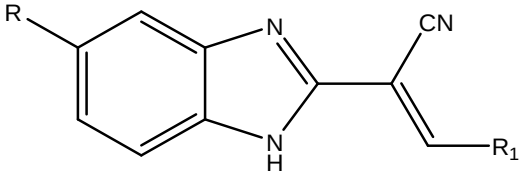


(C)

2.9 Antineoplastic activity

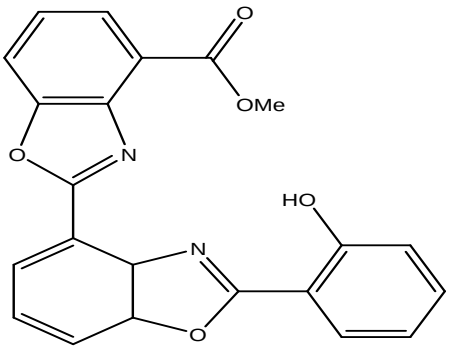
Antineoplastic drugs are medications used to treat cancer. Antineoplastic drugs are also called anticancer, chemotherapy, chemo, cytotoxic, or hazardous drugs. These drugs come in many forms. Some are liquids that are injected into the patient and some are pills that patients take.

Refaat H M et al.[29] have synthesized and evaluated anticancer activity some novel 2-substituted benzimidazole derivatives. Synthesized products were subjected to in vitro anticancer screening that revealed that all the tested compounds exhibited antitumor activity against human hepatocellular carcinoma (HEPG2), human breast adenocarcinoma (MCF7) and human colon carcinoma (HCT 116) cell lines, with IC50's < 10 µg/ml.



Kumar D et al.[30] have synthesized Benzimidazoles related to UK-1. Analogues of UK-1 were prepared and evaluated for anticancer and antibacterial activity. One analogue demonstrates selective anticancer activity

characteristic of UK-1 and also binds Mg2+-ions with affinity similar to UK-1. UK-1 is a structurally unique bis (benzoxazole) natural product isolated from a strain of *Streptomyces*. UK-1 has been reported to possess anticancer activity but no activity against bacteria, yeast, or fungi.

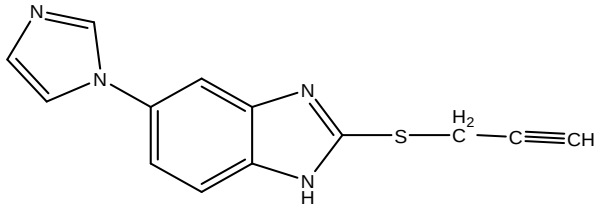


UK-1

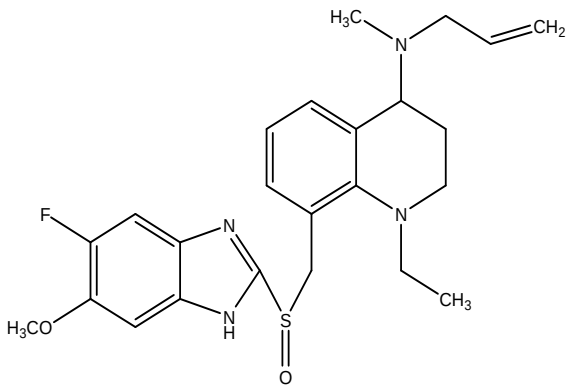
2.10 Antiulcer activity

Antiulcer drugs are a class of drugs, exclusive of the antibacterial agents, used to treat ulcers in the stomach and the upper part of the small intestine.

Nikole B et al.[31] reported the synthesis of 2-(thiopropyne) - 5- (imidazole -1-yl). Benzimidazole which exhibited moderate antiulcer activity against ulcer induced by anti inflammatory agents in rats orally.



The synthesis of 2-[[(1- ethyl, 4- N-methyl –N – (1 propene) 1,2,3,4 tetrahydro quinoline- 8 yl) methylsulfinyl] 5- fluro, 6- methoxy benzimidazole by Uchida M et al[32] showed high activity. It appears from these results that the presence of basic amino group may be an important contributing factor in activity of the molecule.



3. REFERENCES

1. Kale SC and Kale MK. (Synthesis and biological evaluation of benzimidazole derivatives as an antitubercular and antimicrobial agent). International Journal of Biomedical and Advance Research, 2018; 9(1): 37-44.
2. Brunton LL, Lazo JS, Parker KL and Graw-Hill MC. (The pharmacological basis of therapeutics). 11th ed., Occup Environ Med, 2007; 64(8).
3. Harkala KJ, Eppakayala L and Maringanti TC. (Synthesis and biological evaluation of benzimidazole-linked 1,2,3-triazole congeners as agents). Org Med Chem Lett., 2014; 4: 14.
4. Sawant R and Kawade D. (Synthesis and biological evaluation of some novel 2-phenyl benzimidazole-1-acetamide derivatives as potential anthelmintic agents). Acta Pharm, 2011; 61: 353–361.
5. Kus C, Kilcigil GA, Eke BC and Can MI. (Synthesis and antioxidant properties of some novel benzimidazole derivatives on lipid peroxidation in the rat liver). Arch. Pharm. Res., 2004; 27: 156–163.
6. Kus C, Kilcigil GA, Ozbey S and Kaynak FB. (Synthesis and antioxidant properties of novel N-methyl-1,3,4-thiadiazol-2-amine and 4-methyl-2H-1,2,4-triazole-3(4H)-thione derivatives of benzimidazole class). Bioorg. Med. Chem. Lett., 2008; 16: 4294–4303.
7. Alonso FP, Cook HJ, Villanueva JP, Piliado JC, Morales SR, Hernandez GP, Balbiaux NL, Campos AH, Castillo R and Luis FH. (Synthesis and in vitro cysticidal activity of new benzimidazole derivatives). Eur. J. Med. Chem., 2009; 44: 1794–1800.
8. Jasmer DP, Yao C, Rehman A and Johnson S. (Multiple lethal effects induced by a benzimidazole anthelmintic in the anterior intestine of the nematode Haemonchus contortus) .Mol. Biochem. Parasit., 2000; 105: 81–90.
9. Xiangming H, Huiqiang M and Yulu W. (p-TsOH catalyzed synthesis of 2-arylsubstituted benzimidazoles). ARKIVOC, 2007; 13: 150–154.
10. Ansari KF and Lal C. (Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents). Eur. J. Med. Chem., 2009; 44: 2294–2299.
11. Richards ML, Lio SC, Sinha A, Banie H, Thomas RJ, Major M, Tanji M and Sircar JC. (Substituted 2-phenyl-benzimidazole derivatives: novel compounds that suppress key markers of allergy). Eur. J. Med. Chem., 2006; 41: 950–969.
12. Kerimov I, Kilcigil GL, Caneke B, Altanlar N and Scan MM. (Synthesis, antifungal and antioxidant screening of some novel benzimidazole derivatives) J. Enz. Inhib. Med. Chem., 2007; 22: 696–701.
13. Kumar JR, Jawahar J and Pathak DP. (Synthesis of benzimidazole derivatives as anti-hypertensive agents). E-J. Chem., 2006; 3: 278–285.
14. Hranjec M, Starcevic K, Piantanida I, Kralj M, Marjanovic M, Hasani M, Westman G and Zamola GK. (Synthesis, antitumor evaluation and DNA

binding studies of novel amidino-benzimidazolyl substituted derivatives of furyl-phenyl- and thienyl-phenyl-acrylates, naphthofurans and naphthothiophenes). Eur. J. Med. Chem., 2008; 43: 2877–2890.
15. Mahajan SS and Nandre RG. (The synthesis of 2-mercapto-5-methoxybenzimidazole) Indian J. Chem., 2006; 45B: 1756–1758.
16. Kerimov I, Kilcigil GA, Can-Eke B, Altanlar N and Iscan M. (Synthesis, antifungal and antioxidant screening of some novel benzimidazole derivatives). Journal of Enzyme Inhibition and Medicinal Chemistry, 2007; 22.
17. Karmaker N, Lira DN, Das BK, Kumar U and Rouf ASS. (Synthesis and Antioxidant Activity of Some Novel Benzimidazole Derivatives). Dhaka University Journal of Pharmaceutical Sciences, 2017; 16.
18. Kalit P. (Synthesis, Antimicrobial and Anthelmintic Activity of Some Novel Benzimidazole Derivatives). International journal of drug research and technology, 2014; 4.
19. Zquez GN, Cedillo R, Campos AH, Yeapez L, Luis FH, Valdez J, Morales R, Cortea R and Castilloa R. (Synthesis and Antiparasitic Activity of 2-(Trifluoromethyl)- benzimidazole Derivatives). Bioorganic & Medicinal chemistry Letters, 2000.
20. Dubey R, Abuzar S, Sharma S, .Chatterjee RK and Katiyar JC. (Synthesis And Anthelmintic Activity of 5-(6) – (Benzimidazole-2-ylcarbamoyl) and (4-substituted Piperazin-1-yl) Benzimidazoles) Journal of Medicinal Chemistry, 1985; 28: 1748-1750.
21. Swiątkiewicz KB, Olszewska P and Olasik EM. (Antiproliferative activity of new benzimidazole derivatives). ABP Biocemica Polonica, 2013; 60: 427–433.
22. Abonia R, Cortes E, Insuasty B, Quiroga J, Nogueras M and Cobo J. (Synthesis of novel 1,2,5-trisubstituted benzimidazoles as potential antitumor agents). Eur J Med Chem., 2011; 46: 4062–4070.
23. Miller JF, Turner EM, Gudmundsson KS, Jenkinson S, Spaltenstein A, Thomson M and Wheelan P. (Novel N-substituted benzimidazole CXCR4 antagonists as potential anti-HIV agents). Bioorganic & Medicinal Chemistry Letters, 2010; 20: 2125-2128.
24. Gardiner JM, Loyns CR, Burke A, Khan A and Mahmood N. (Synthesis and HIV-1 inhibition of novel benzimidazole derivatives). Bioorganic & Medicinal Chemistry Letters, 1995; 5: 1251-1254.
25. Nakano H, Inoue T, Kawasaki N, Miyataka H, Matsumoto H, Taguchi T, Inagaki N, Nagai H and Satoh T. (Synthesis of Benzimidazole Derivatives as Antiallergic Agents with 5-Lipoxygenase Inhibiting Action) Chem. Pharm. Bull., 1999; 47(11): 1573-1578.
26. Kavitha, Kallappa CSA, Harisha MH and Reddy RS. (In-vivo analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives). European Journal of Medicinal Chemistry, 2010; 45(5): 2048-2054.
27. Gaba M, Singh D, Singh S, Sharma V and Gaba P. (Synthesis and pharmacological evaluation of novel 5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole derivatives as anti-inflammatory and analgesic agents). European Journal of Medicinal Chemistry, 2010; 45(6): 2245-2249.
28. Khan MT, Razi1 MT, Umer Jan S, Mukhtiar M, Gul R, Ullah I, Hussain A, Hashmi AM, Ahmad MT, Shahwani NA and Rabbani I. (Synthesis, characterization and antihypertensive activity of 2-phenyl substituted benzimidazoles). Pakistan journal of pharmaceutical sci., 2018; 31(3): 1067-1074.
29. Refaat HM. (Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives). European Journal of Medicinal Chemistry, 2010; 45(7): 2949-2956.
30. Kumar D, Jacob MR, Michael, Reynolds B and Kerwina SM. (Synthesis and evaluation of anticancer benzoxazoles and benzimidazoles related to UK-1). Bioorganic & Medicinal Chemistry, 2002; 10(12): 3997-4004.
31. Nicole B, Timur G, Jean L, Michele L and Marie TJ, Eur. Patent No. 385850 (1990).
32. Uchida M, Chihiro M, Morita S, Yamashita H, Chem. Pharm. Bull., 1990; 38(6): 1575-1586.