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Review Article

Review on: Benzimidazole derivatives as potent biological agent.

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ABSTRACT
Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a restricted structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Benzimidazole and its derivatives are used in organic synthesis and they are used in evaluating new product that possesses different pharmacological activities. It can act as an important tool for medicinal chemists to develop newer compounds possessing benzimidazole moiety that could be better agents in terms of efficacy and safety. This review article is précised to know about the chemistry of different derivatives of substituted benzimidazoles along with their pharmacological activities.

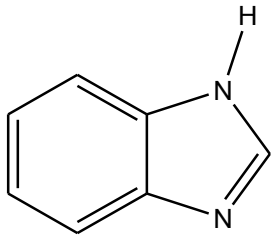
KEYWORDS
Benzimidazole Derivatives, Pharmacological activities.

1. INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years due to the pharmacological activities. They have important applications in organic synthesis as organocatalysts, synthetic intermediates, chiral auxiliaries, and metal ligands in asymmetric catalysis. Therefore, the development of new efficient methods to synthesize heterocyclic is of considerable interest. Benzimidazole is a bicyclic compound having imidazole ring containing two nitrogen atoms at nonadjacent positions, fused to benzene. Benzimidazole is a biologically important framework and it is a useful structural theme for the development of molecules of pharmaceutical or biological interest. Appropriately substituted benzimidazole derivatives have found diverse therapeutic applications. It has earned an important place as a pharmacophore in chemotherapeutic agents of pharmacological activities.

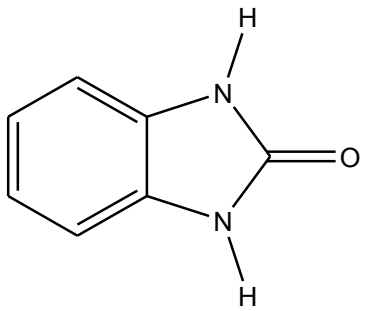
Chemistry of Benzimidazoles:

The benzimidazoles contain a phenyl ring fused to an imidazole ring, as indicated in the structure for benzimidazole (1).



Benzimidazole (1)

The benzimidazoles are also known as benzimidazole or benzoglyoxalines. They have been named also as derivatives of *o*-phenylenediamine, especially in the early literature. Thus, benzimidazole according to this nomenclature would be called methenyl-*o*-phenylenediamine and 2-methylbenzimidazole would be called ethenyl-*o*-phenylenediamine. Also, they have been named as derivatives of the grouping composing the imidazole portion of the ring. Thus, for example, benzimidazole has also been called *o*-phenyleneformamidine and 2 (3H) - benzimidazolone (2) and 2 (3H) benzimidazolethione (3) are known also as *o*-phenyleneurea and *o*-phenylenethiourea, respectively.



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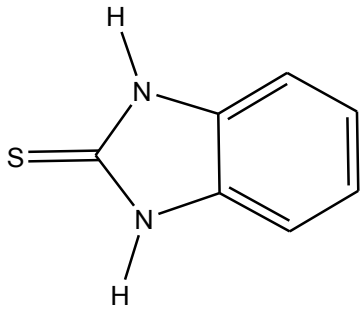
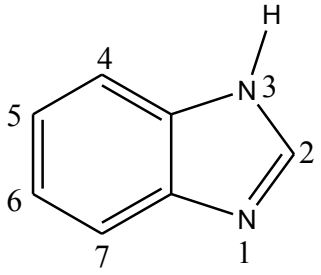


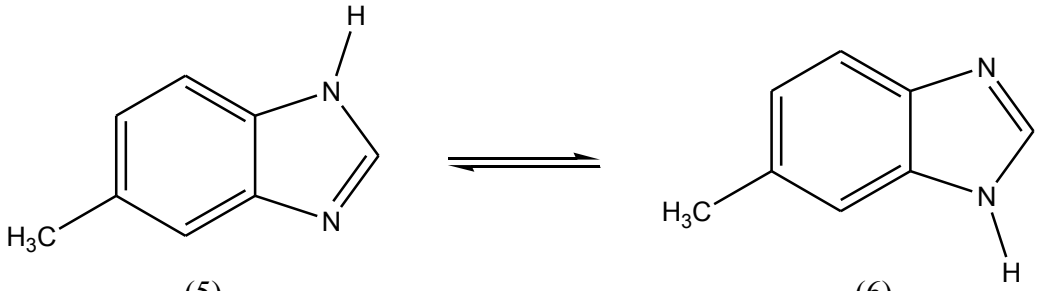
(3)

The numbering system for the benzimidazoles is as follows: Occasionally, the 2-position is designated as the μ-position.



(4)

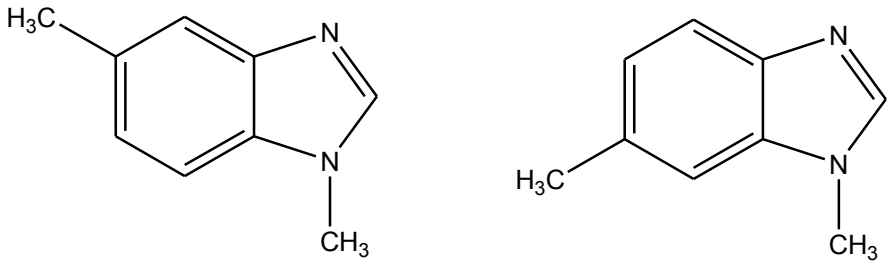
Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerize. This tautomerism is analogous to that found in the imidazoles and amidines. The benzimidazoles, in fact, may be considered as cyclic analogs of the amidines. Because of this tautomerism in benzimidazoles certain derivatives which appear at first to be isomers are in reality tautomers; although two non-equivalent structures can be written, only one compound is known. This may be illustrated with 5(or 6)-methylbenzimidazole.



(5) (6)

Thus, 5 methylbenzimidazole (5) is a tautomer of 6-methylbenzimidazole (6) and both structures (4 and 5) represent the same compound. In designating such tautomeric compounds two numbers or sets of numbers are usually given designating the positions of the substituent group (or groups), the second number or group of numbers being placed in parentheses.

When the group attached to the nitrogen in the l-position is larger than hydrogen, such tautomerism is not indicated and isomeric forms exist. Thus, 1, 5-dimethylbenzimidazole (7) and 1, 6-dimethylbenzimidazole (8) are separate and distinct compounds.

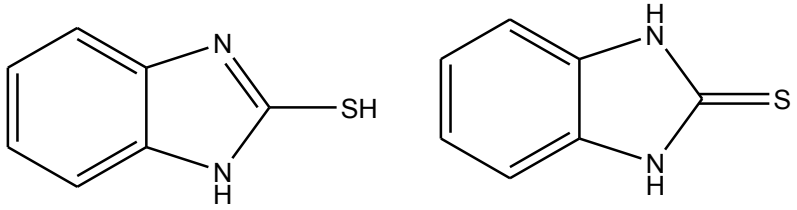


(7) (8)

The benzimidazoles are predominantly basic compounds having the ability to form salts with acids. Benzimidazole (pK α 5.5) is a basic considerably weaker than the imidazole (pK α7.0). This difference in the basic strength is a reflection of the conjugation between the imidazole and benzene rings. Conjugation increases the number of contributing states in the resonance sense, thus enhancing the chemical stability of the molecule.

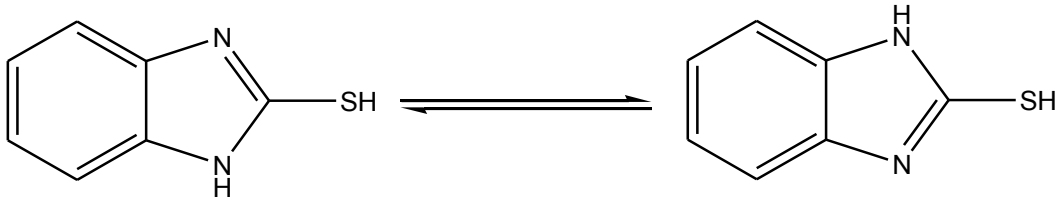
Benzimidazoline-2-thiones:

A number of benzimidazoline 2-thiones have been synthesized by the general method described by Van allan and Deacon. The 2-mercapto benzimidazole (9) and benzimidazole -2-thione (10) are depicted as under.



(9) (10)

2-mercapto-benzimidazole which contain a hydrogen atom attached to nitrogen in the 1-position readily tautamerised. This may be depicted as follows.



Spectral properties of benzimidazoles:

1. Infra-red (IR) spectroscopy: The absorption spectra of benzimidazole near the 2850Å indicates the presence of the aryl ring , absorption near the 3107Å indicates the presence of N-H stretch and 1690Å indicates the presence of C-N stretch.
2. Nuclear magnetic resonance (NMR) spectroscopy: An important feature of this work is that the protonation parameters derived from simple five and six membered heterocycles can be used to predict chemical shift changes resulting from nitrogen protonation and deprotonation in more complex molecules.δ7-9 values shows multiplet indicates the presence of benzimidazole aryl ring.
3. ^{13}Carbon NMR: The spectra shows different carbon peaks at range of δ0-200 compared to TMS. For benzimidazoles the range starts from δ115-144.Overlapping is easily confirmed by triplet, doublet peaks obtained. Low intensity peaks show the presence of proton less carbons. So carbonyl group at which position is recognized.
4. Mass spectroscopy: The fragmentation pathways of simple benzimidazoles are similar to those of imidazoles. The spectrum of benzimidazole indicates a sequential loss of two molecules of hydrogen cyanide from the molecular ion, the first of which is nonspecific as evidenced by deuterium labeling procedures. A characteristic feature in the fragmentation of 2-n-propylbenzimidazole is the elimination of ethylene from the molecular ion, 2-

acylthiophenes, 2-acyl and 2- benzoylbenzimidazoles are characterized by loss of carbon monoxide from the molecular ion

Physical Properties of Benzimidazole:

The melting point of number of the benzimidazoles indicated that the introduction of a substituent into 1-position in general lowers the melting point. Benzimidazoles with the imide nitrogen are usually soluble in polar solvents and less soluble in organic solvents.

With introduction of other non-polar substituents in various positions of the benzimidazole ring, the solubility in nonpolar solvents is increased. Benzimidazole distills unchanged above 300℃. Benzimidazoles are weakly basic, being somewhat less basic than the imidazoles and are in general soluble in dilute acids. Benzimidazoles are also sufficiently acidic to be generally soluble in aqueous alkali and form N-metallic compounds. The acidic properties of the benzimidazoles, like those of the imidazoles, seem to be due to stabilization of ion by resonance. The more acidic benzimidazoles may be soluble in less basic solution, such as potassium carbonate solution.

Hunter and Marriot determined the molecular weight of a number of benzimidazoles from freezing point data in naphthalene solution over a range of concentrations. Evidence was obtained indicating molecular association through N-H-N bonds in those compounds possessing an unsubstituted NH grouping. The strength of this bond is evidently enhanced by resonance of the benzimidazole nucleus. The dipole moment of benzimidazole has been determined, the values that have been obtained being 3.93-4.08 D (in dioxane).

Chemical Properties of Benzimidazole:

A) Scheme for the synthesis of Benzimidazole:

1) Reaction with carboxylicacids:

a) Monobasic acids:

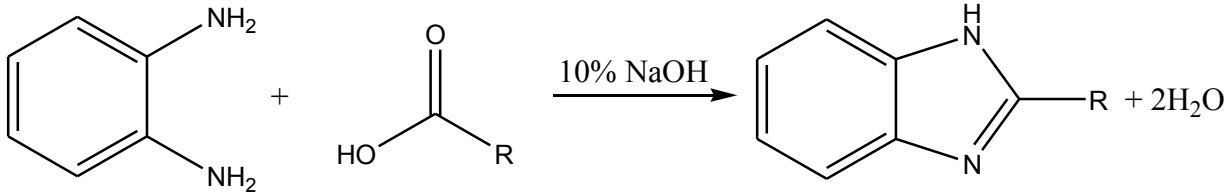
Conventional method:

A mixture of *o*-Phenylene diamine and carboxylic acids was refluxed thermally. The reaction mixture was cooled and sodium hydroxide solution was added and then the crude product, benzimidazole was washed with ice cold water and dissolved in boiling water for recrystallization, filtered and dried. Benzimidazole may be prepared in 83-85 % yield by using 90 % formicacid.

Microwave method:

A mixture of *o*-Phenylene diamine and carboxylic acids was placed in a domestic microwave oven. The reaction mixture was cooled and sodium hydroxide solution was added. The crude product was washed with ice cold water, dissolved in boiling water for recrystallization, filtered and dried.

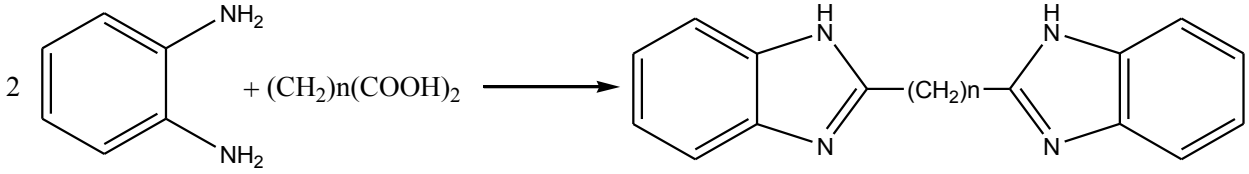
Reaction:



o-Phenylene diamine Carboxylic acid Benzimidazole

b) Dibasic acids:

When dibasic acids are caused to react with o-phenylene diamines the product formed depend on the mole ratio of the reactant and the experimental conditions. When two or more moles of o-phenylene diamines are heated with one mole of the dibasic acid, the products in most cases are bis benzimidazoles.

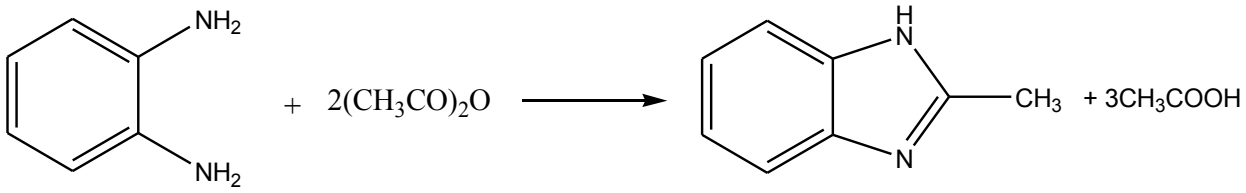


O-phenylene diamine Bis-Benzimidazole

2) By reaction with acid anhydrides:

a) Anhydrides of mono basic acids:

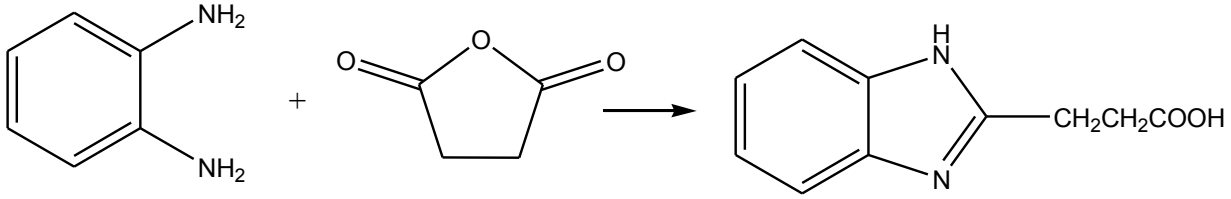
The reaction of acid anhydrides and o-phenylene diamines will lead to benzimidazole or N N'diacylphenylenediamines depending on the condition employed. It was formerly thought that o-phenylenediamine yield benzimidazole with acids and diacyl derivatives with acid anhydrides. Practically the acid anhydride that has been used in the preparation of benzimidazole has been acetic anhydride. However mixed formic-acetic anhydride and benzoic anhydride have also been used successfully6. And the example is as under, o-phenylene diamine when heated under reflux for several hours with acetic anhydride is completely converted to 2-methyl benzimidazole.



O-Phenylene diamine Acetic anhydride 2-methyle benzimidazole

b) **Anhydrides of mono basic acids:**

The anhydrides of dibasic acids reacts as monobasic acids for example succinic anhydride with O-phenylene diamine gives β-(2-benzimidazole) propionic acid and with phthalic anhydride gives o-(2-benzimidazole) benzoic acid.

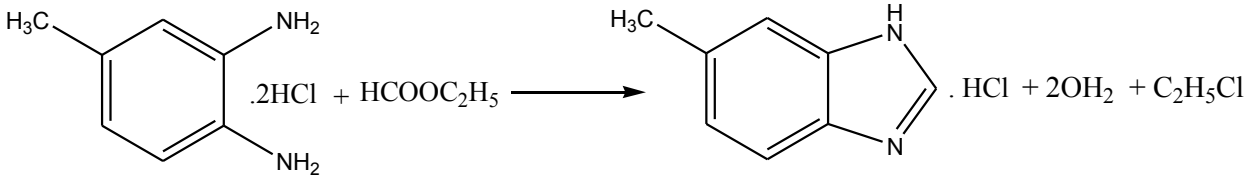


Beta-(2-benzimidazole) propionic acid

3) By reaction with ester:

Von Neimentowski first investigated the reaction of esters and o-phenylene diamines to give benzimidazole. Equimolar amounts of 3, 4-diamino toluene dihydrochloride and ethyl formate

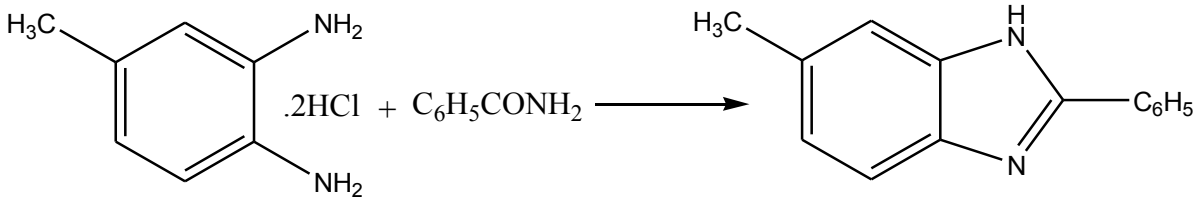
when heated in a sealed tube for 3 hrs, at 225^{0}C give 84% of 5 or 6-methyl benzimidazole hydrochloride.



4) By reaction with amides:

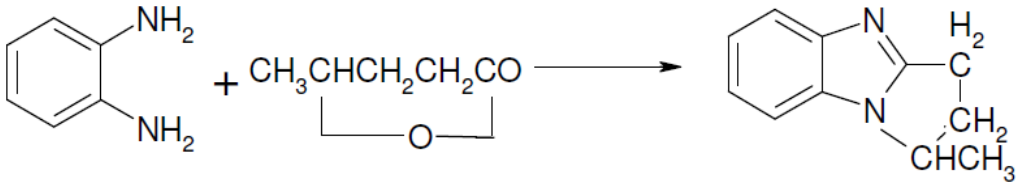
Relatively few amides have been used for the synthesis of benzimidazole. However good yields have been obtained in most cases.

Equimolar amounts of 3, 4-diamino toluene dihydrochloride and benzamides. When heated to 240-250^{0}C give an almost quantitative yield of 2-phenyl 5-methyl benzimidazole.



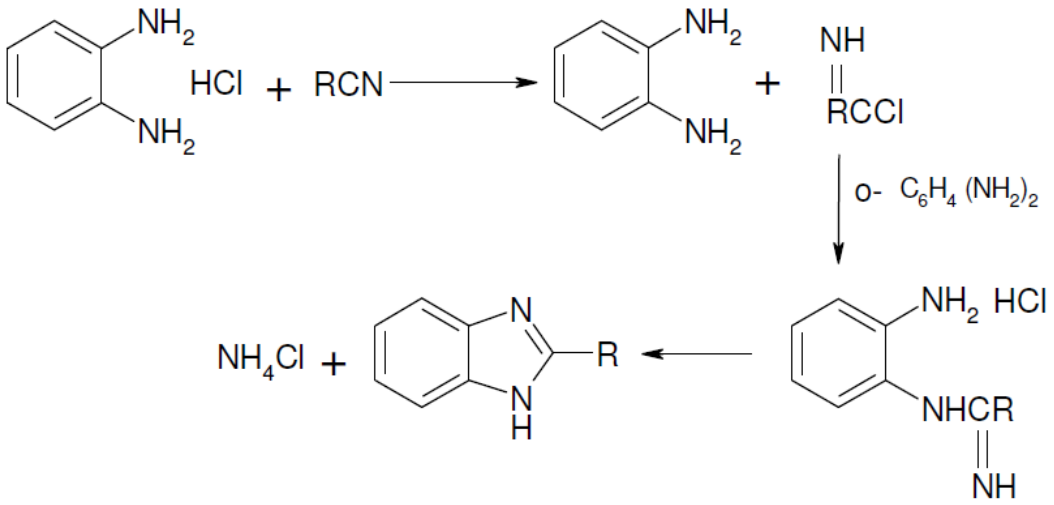
5) By reaction with lactones:

The reaction of lactones with o-phenylene diamines was first studied by Bistrzycki and Schmutz, who investigated several γ- lactones of alcohol acids and phenol acids. Velerolactone when refluxed with o-phenylene diamine gives only a small yield of 1, 2-(1'- methyl tri methylene) benzimidazole.



6) By reaction with nitriles:

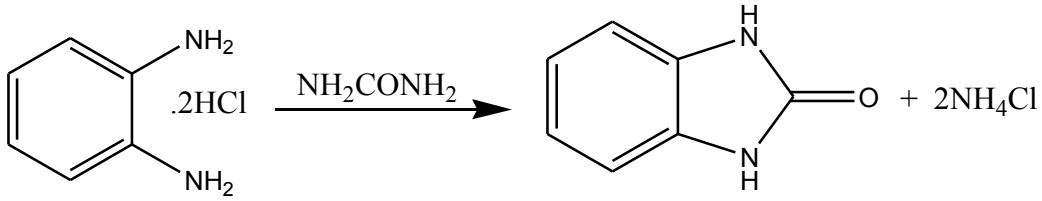
Nitriles when heated with o-phenylene diamine hydrochloride give 2-substituted benzimidazoles. This reaction has been studied by Holljes and Wagner, who find that the reaction proceeds under acid condition and probably involves hydrogen ion catalysis. The mechanism of the reaction is as under,



The reaction is carried out usually at about 2000C at this temperature ammonium chloride will undergo decomposition to regenerate additional hydrogen chloride and cause the reaction to proceed further. The reaction proceeds further under anhydrous condition and is not due to the generation of acid or amide in situ. The first step in the reaction appears to be the rate determining step.

7) By reaction with urea:

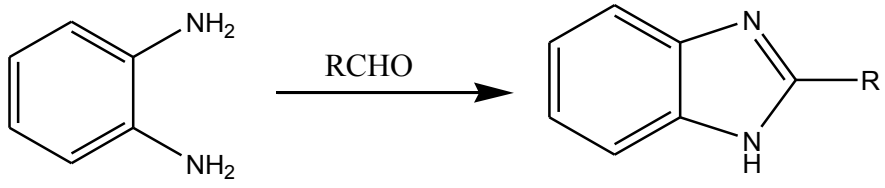
O-phenylenediamine dihidrochloride when heated with urea at 130^{o}C gives 2(3H)-benzimidazolone.



o-phenylene diamine

8) By reaction with aldehydes:

Under the correct conditions aldehydes may reacted with o-phenylenediamines to yield 2-substituted benzimidazoles. Due improvement of oxidation reaction was best carried out under oxidative conditions.

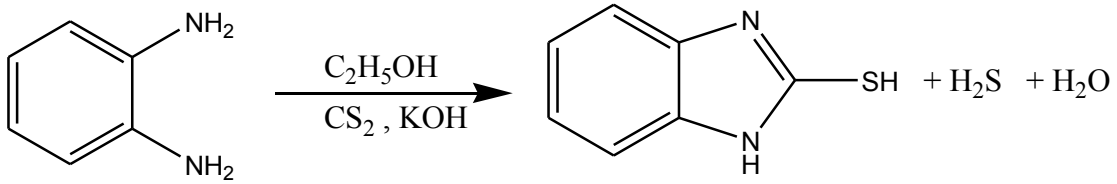


o-phenylene diamine Benzimidazole

B) Synthesis of benzimidazoline 2- thione:

Preparation of 2-mercapto benzimidazole:

A mixture of o-phenylenediamine, potassium hydroxide and carbon disulfide reacted in presence of 95% ethanol and water in a round bottom flask heated under reflux for three hours. After 3 hrs Charcoal is added cautiously and the mixture is heated at the reflux for 10 minutes the charcoal is removed by filtration. The filtrate is heated to 60- 70^{o}C, warm water is added, and then acidified with acetic acid. The product separated as glistening white crystals, and the mixture is placed in a refrigerator for three hours to complete the crystallization. The product is recrystallized from ethanol. Melting point is 300- 305^{o}C.

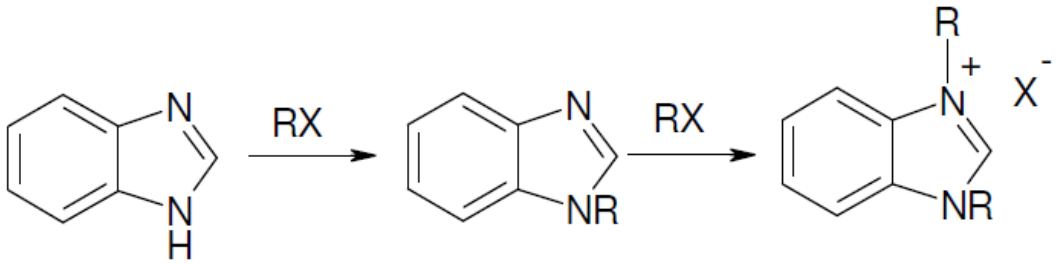


o-phenylene diamine Mercaptobenzimidazole

C) Reaction of Benzimidazoles:

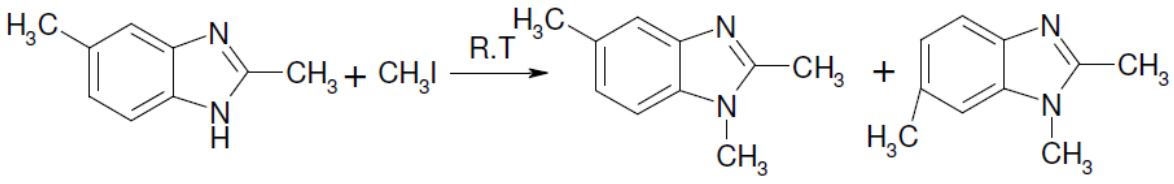
1) Alkylation:

Benzimidazoles upon alkylation with alkyl halides yields 1-alkylbenzimidazoles and under more vigorous conditions 1, 3-dialylbenzimidazolium halides.



The alkylation of benzimidazoles has been extensively studied especially by O. Fisher the alkylation is carried out by various alkyl and aryl alkyl groups the reaction is carried out usually by heating the benzimidazole with an excess oh alkyl halide in methanol under pressure at a temperature of about 110-150^{0}C. Alkyl iodides are used usually and in some cases periodides are obtained as by product or as exclusive product.

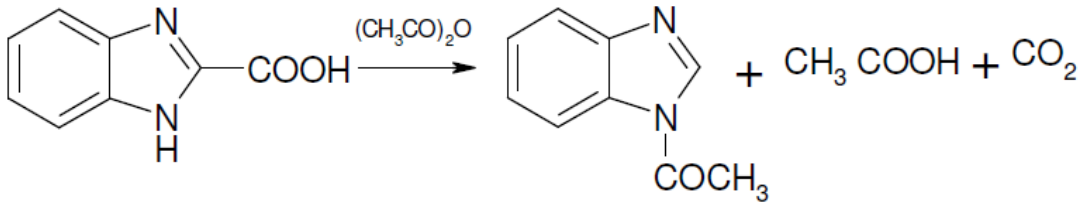
When alkylation reaction is carried out at lower temperature with one equivalent of alkyl halide 1-alkyl benzimidazole may be the main product. Thus equimolar amounts of benzimidazole and methyl iodide in methanol at 90-100^{0}C give mostly 1- methyl benzimidazole. Example is given as under,



2) Acylation:

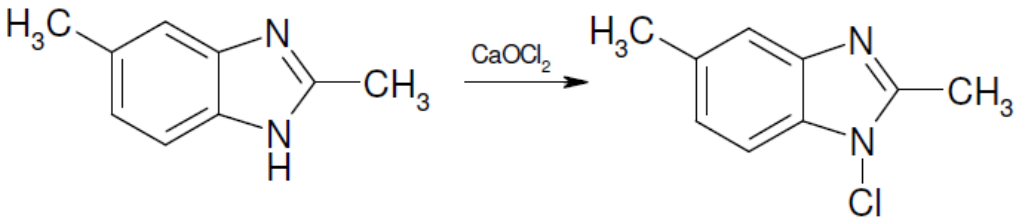
N-acyl benzimidazoles may be prepared by the action of acid chlorides or anhydrides on benzimidazoles. The reaction is usually carried out in the absence of water. In the presence of water and especially in the alkaline solution cleavage of imidazole ring may occur.

1-acetyl benzimidazole has been prepared by heating 2-benzimidazole carboxylic acid with acetic anhydride decarboxylation occurs and forms the product.

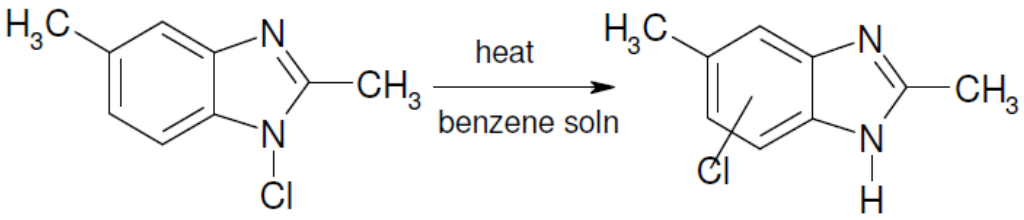


3) Halogenation:

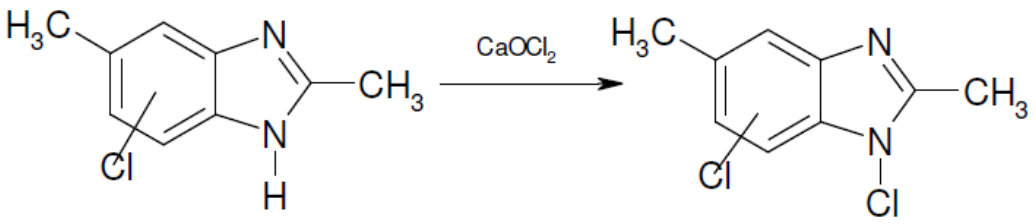
When 2, 5 or 2, 6-dimethyl benzimidazole in an aqueous acid solution is treated with the saturated solution of bleaching powder at 0-5^{0}C 1-chloro 2, 5- or 2, 6-dimethyl benzimidazole is obtained.



The N-chloro compound loses chlorine quite readily, even at relatively low temperature. When heated under reflux in benzene solution a rearrangement of the chlorine atom to the benzene ring takes place.



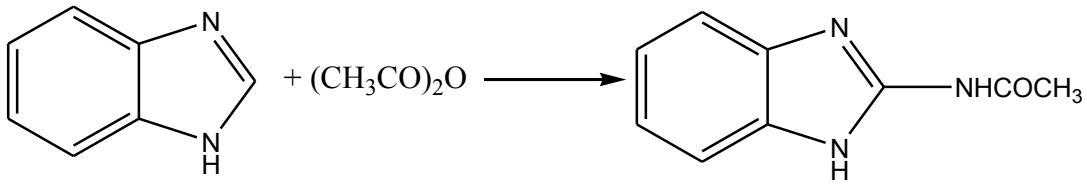
The N-chloro derivative of this compound may then be prepared by treatment again with bleaching powder.



Treatment of the later compound by refluxing in benzene solution rearranges the N-chlorine atom again into the ring. This process may be repeated until the totally chlorinated compound (1, 4, 5, 6-tetrachloro-2, 5-dimethyl benzimidazole) is obtained.

4) Oxidation:

Benzimidazoles are stable to oxidation. By vigorous conditions of oxidation (potassium permanganate in hot alkaline solution) it is partially possible to oxidize benzimidazoles to obtain a small amount of imidazoledicarboxylic acid.

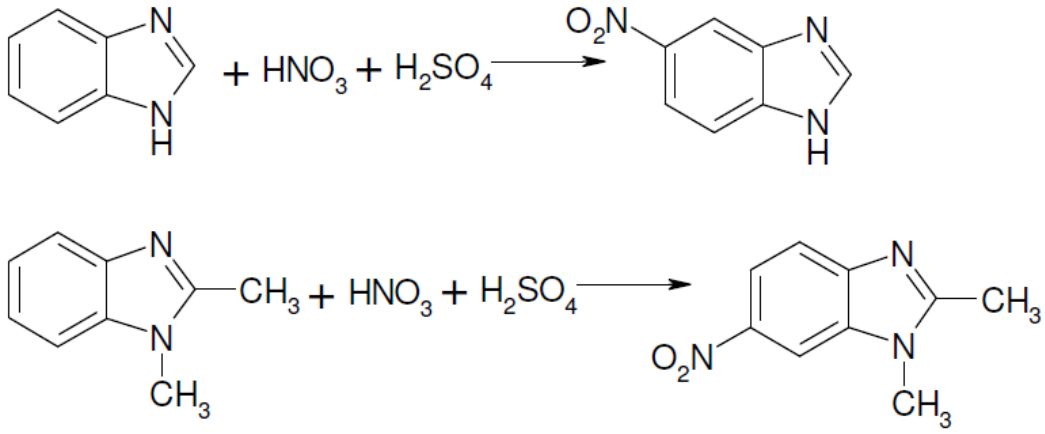


Because of the stability of the benzimidazoles ring to oxidation it is possible to oxidize substituent group without affecting the ring. By the oxidation of the substituent groups a variety of benzimidazolecarboxylic acids have been prepare.

5) Nitration:

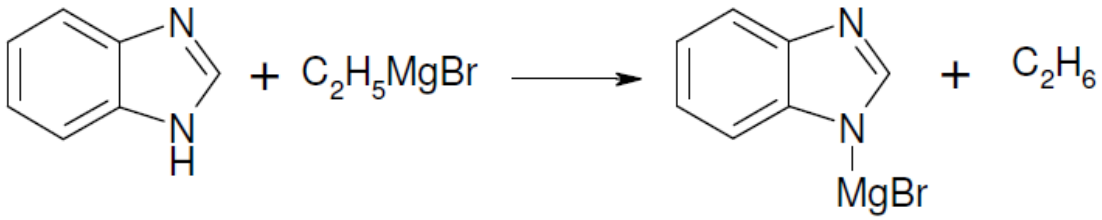
The nitration of benzimidazole proceeds readily. In most cases nitration appears to take place preferentially in the 5 or 6 place. However the nitro group may also enter 4 or 7- position, especially if 5 or 6 positions are blocked.

Nitro benzimidazoles that have been obtained by the nitration of benzimidazoles example is as under,

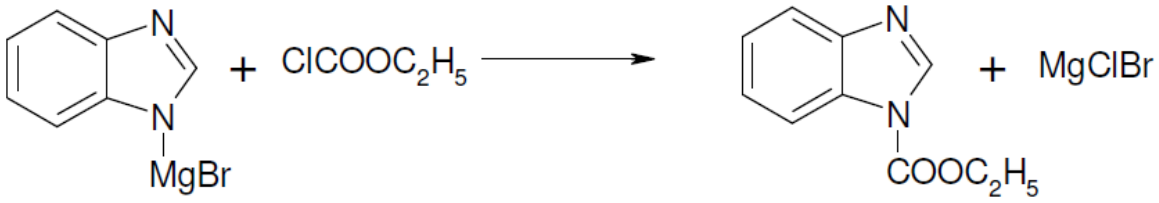


6) The action of Grignard reagents on benzimidazoles:

Grignard reagent reacts with the active hydrogen in the 1-position of benzimidazole.



Benzimidazole-1-magnesium bromide reacts with aliphatic acid chloride or anhydrides to yield 1-acyl benzimidazole with ethyl chloroformate, 1-carbethoxy benzimidazole is obtained.

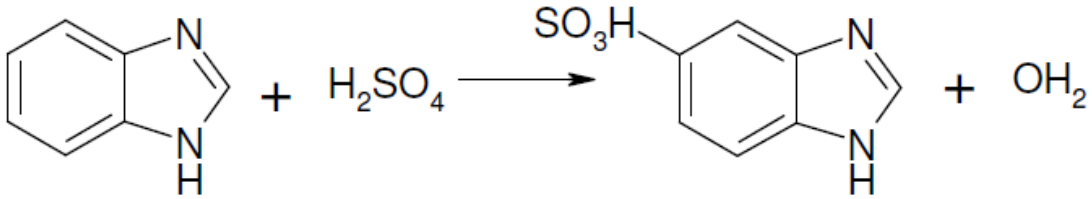


7) Cleavage of the imidazole ring:

The imidazole ring of benzimidazoles may be cleaved by one of the several methods by reacting with pseudobases, acid anhydrides and halide.

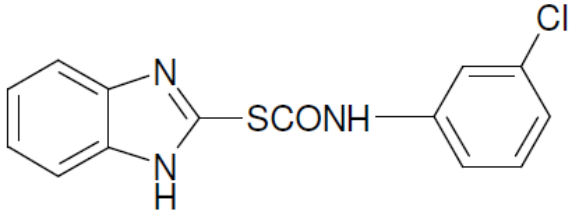
8) Miscellaneous reaction:

Sulfonated benzimidazoles are obtained by the sulfonation of benzimidazoles with either sulfuric acid or chloro sulfonic acid. Treatment of benzimidazole with concentrated sulfuric acid gives 5-benzimidazole sulfonic acid.



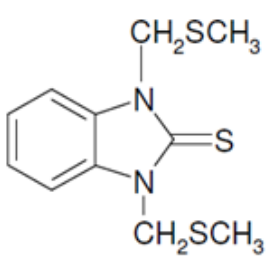
D) Reactions of benzimidazoline 2- thione:

The majority of data on benzimidazoline 2- thione relates to S-alkylation and closely related processes are the synthesis of 2-thiocyanatobenzimidazoles from the reaction of benzimidazoline 2- thione with cynogen chloride or bromide and 2- benzimidazolyl thiocarbamates (VIII) from addition of the 2-thione to aryl isocyanates.

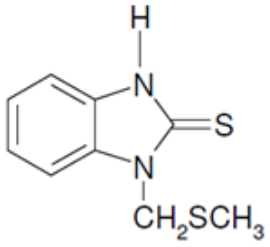


VIII

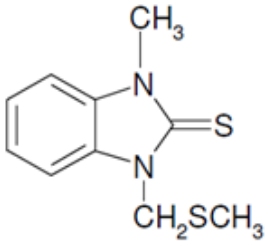
Other routine procedures are the oxidation of 2-thiones to bis benzimidazolyl disulfides and benzimidazole 2-sulfonic acids by hydrogen peroxide. The varieties of compounds are obtained and are as under (IX, X, XI, XII).



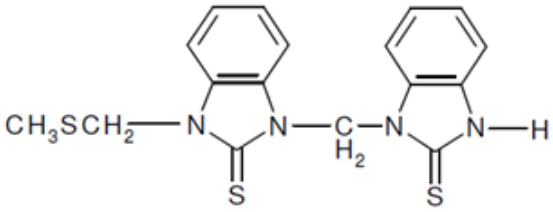
IX



X

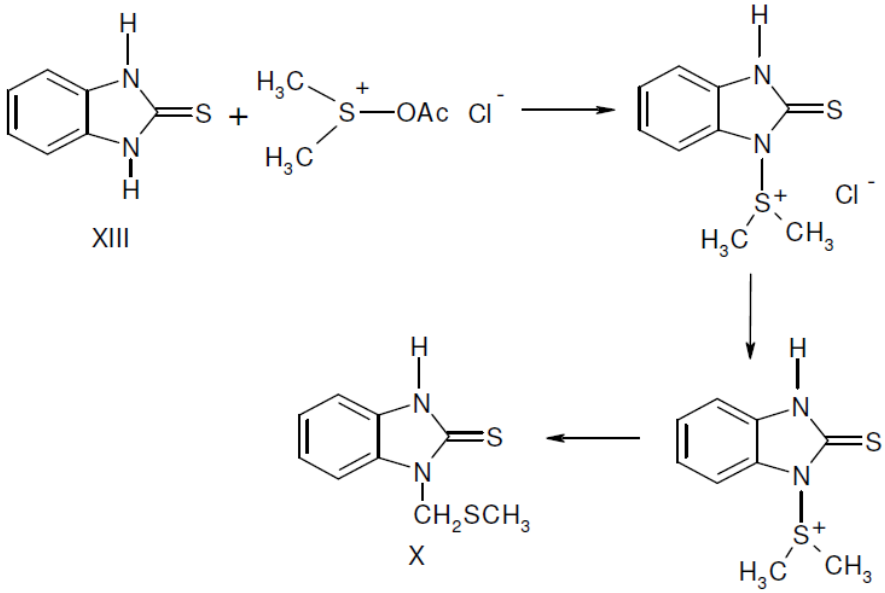


XI



XII

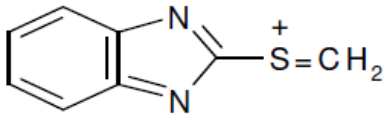
When benzimidazoline 2-thione (X) is allowed to react with a mixture of dimethylsulfoxide and acetyl chloride at 50-60^{0}C the formation of these products can be satisfactorily rationalized in term of displacement reactions by the thione (XIII) on an intermediate sulfonium acetate.



XIII

X

Interestingly if this reaction is carried out below 300C the reaction product includes the compound and also the novel 2-(methylene sulfonium) benzimidazolide in 20% yield (XIV).



XIV

Structural modifications and their biological actions:

Benzimidazole is a heterocyclic aromaticorganic compound. It is an importantpharmacophore and a privileged structure inmedicinal chemistry. This compound isbicyclic in nature which consists of the fusionof benzene and imidazole. Nowadays is amoiety of choice which possesses manypharmacological properties. The mostprominent benzimidazole compound in natureis *N*-ribosyl-dimethylbenzimidazole, whichserves as an axial ligand for cobalt in vitaminB_{12}.

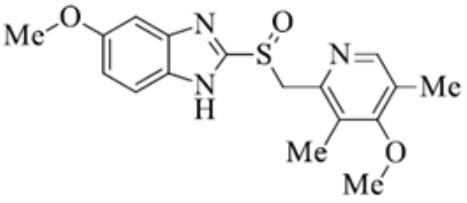
Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications. They are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio. Looking at the importance of benzimidazole and oxadiazole nucleus, it was thought that it would be worthwhile to design and synthesize some new benzimidazole derivatives bearing oxadiazole moiety and screen them for potential biological activities. Resistance to number of anti-microbial agents (β-lactam antibiotics, macrolides, quinolones, and vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly important global problem. In particular, increasing drug resistance among Gram-positive bacterium such as staphylococci, enterococci, and streptococci is a significant health matter. Benzimidazole ring displays an important heterocyclic pharmacophore in drug discovery. These compounds carrying different substituent's in the benzimidazole structure are associated with a wide range of biological activities including anti-cancer, anti-viral, anti-bacterial, anti-fungal, anti-helmintic, anti-inflammatory, anti-histaminic, proton pump inhibitor, anti-oxidant, Anti-hypertensive, Antidiabetic, anti-coagulant agents etc.

Reported Pharmacological Activities of Benzimidazole and Benzimidazole-2- thiones:

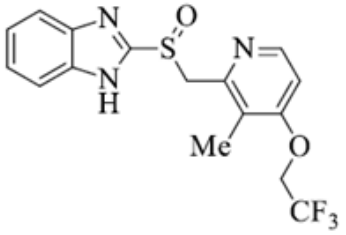
Benzimidazole and various derivatives of benzimidazoles possess a variety of pharmacological activities. Benzimidazole, 2-methyl benzimidazole, benzimidazole-2- thione studied pharmacologically by Aurmann. The few selected activity reported as under.

a. Antiulcer agents:

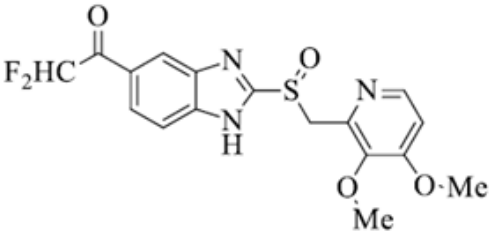
The presence of acid is a fundamental factor in the pathogenesis of gastric and duodenal ulcers, reflux-oesophagitis and nonsteroidal anti-inflammatory drug-induced lesions. In human body many tissues are responsible for the imbalance between aggressive factors (like acid, pepsin, H. pylori infection) and local mucosa defense (secretion of bicarbonates, mucus and prostaglandin) results in acid-peptic and duodenal ulcer, gastroesophageal reflux disease, Zolinger-ellision syndrome and gastritis. This disease seems to have very prominent share in health disorder in current scenario of globalization.



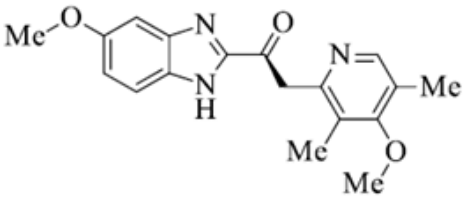
Omeprazole



Lansoprazole



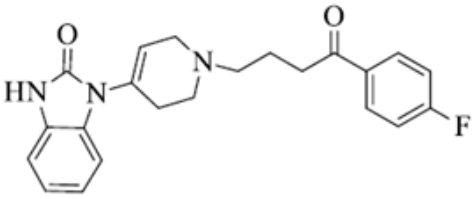
Pantoprazole



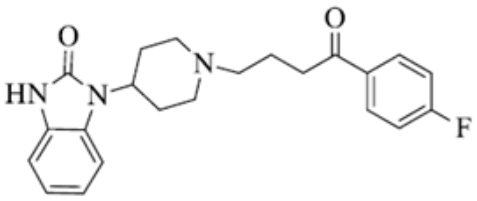
Esomeprazole

b. Antipsychotic agents:

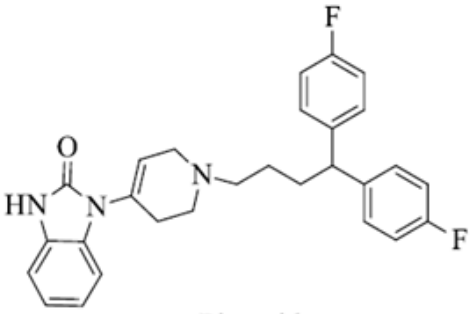
Benzimidazoles containing piperdinyl moiety are useful as antipsychotic agents and as analgesic.



Droperidol



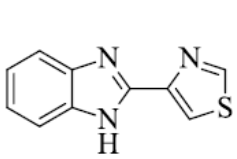
Benperidol



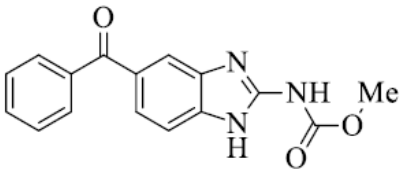
Pimozide

c. Antihelmintic drugs:

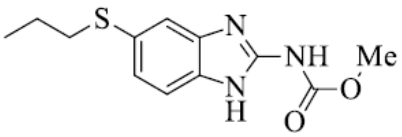
Benzimidazolesare most promising drugs as antihelmintic agents. Thiabendazole and mebendazoleare highly effective asbroad-spectrum antihelmintic agents. They are used for the treatment of nematode infestations and treatment of proto myxzoa infestations. Albendazole is effective against roundworms, tapeworm and flukes of domestic animals and human.



Thiabendazole



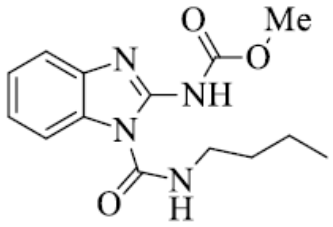
Mebendazole



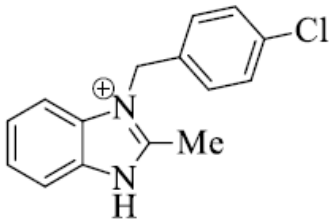
Albendazole

d. Antimicrobial and fungicidal drugs:

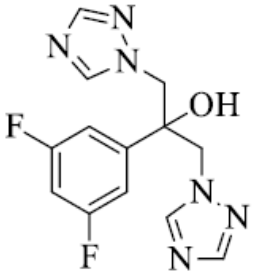
Infectious diseases have been serious and growing threatens to human health duringthe past few decades. Several research groups are working in this direction with afocus to prepare or invent new class of drugs which can withstand to bacterialresistance strains. Fluconazole is the first line of triazole based antifungal drugrecommended by WHO duo to its pharmacokinetics characteristics. Tri halogenbenzimidazoles exhibited the most potent antibacterial activity with MIC 3.12 µg/mlagainst S.aureus.Number of benzimidazole derivatives havecommercial application for fungal infections.



Benomyl



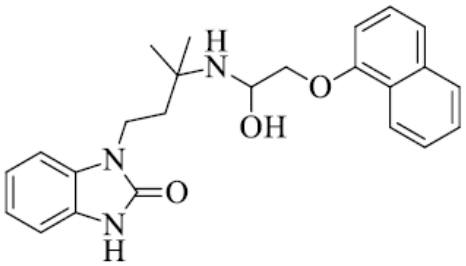
Chlormidazole



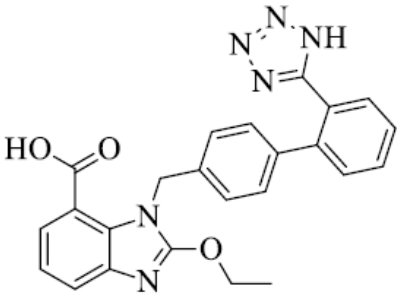
Fluconazole

e. Anti-hypertensive drugs:

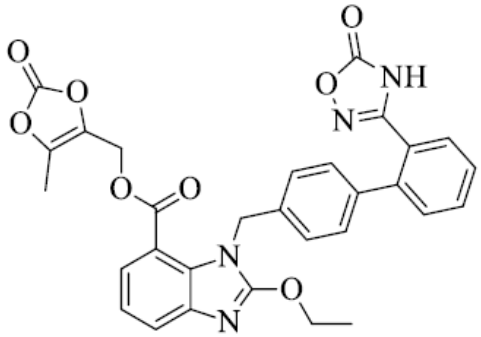
Benzimidazoles are considered as promising as anti-hypertensive drugs. Adimol is an anti-hypertensive agent which acts as anon selective α1-, α2-, β- adrenergic receptor antagonist. Azilsartan medoxomil and Candesartan are acts as angiotension-II receptor antagonist, which are benzimidazole nucleus containing compounds.



Adimolol



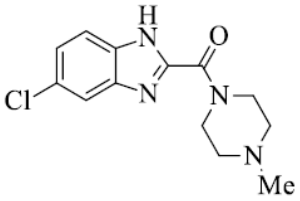
Candesartan



Azisartan medoxomil

f. Anti-inflammatory drugs:

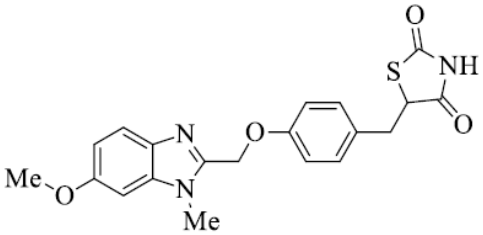
Some of the benzimidazole derivatives act as anti-inflammatory agents, like VUF- 6002 a potent and selective antagonist at the histamine H4 receptor. It has anti-inflammatory and analgesic effects in animal studies of acute inflammation.



VUF-6002

g. Antidiabetic drugs:

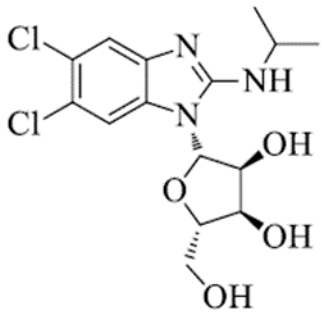
Rivoglitazone is a thiazolidine dione which contain benzimidazole nucleus was under the research for the use in the treatment of type-II diabetes.



Rivoglitazone

h. Antiviral drugs:

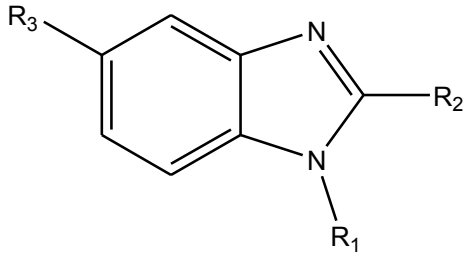
Maribavir is an oral anti-viral drug which is the benzimidazole derivative; it is used for the prevention and treatment of human cytomeglo virus (HCMV) disease in hematopoietic stem cell/ bone marrow transplant patients. The mechanism by which inhibits HCMV replication is by inhibition of an HCMV encoded protein kinase enzyme called UL97 or pUL.



Maribavir

i. Anti convulsant Agents:

Some potential anticonvulsant compounds have beensynthesized, a series of 1, 2, 5-trisubstituted benzimidazoles derivatives has been reported. The results of QSAR investigation and the study of various physicochemical properties indicates that the change in linker at position one (R1) does not change the activity of the synthesized compounds and optimum chain length at position two (R2) is responsible for the anticonvulsant activity. The results also showed that the synthesized compounds with electron withdrawing group such as nitro at position five (R3) have been reported to possess better anti-convulsant activity as predicted by QSAR studies.



1,2,5-trisubstituted benzimidazole

Where, R_1 = Picoline, R_2= Varying alkyl chain, $R_3 = NO_2$.

2. REFERENCES

1. Ramanpreet Walia (2011). "Benzimidazole derivatives – an overview." Int. J. Res. Pharma. Chem. 1(3): 565-570.

2. J. B. Wright (1951). The chemistry of benzimidazoles. Chemical Reviews. 48: 397- 541.

3. Goswami babita (2012). "Pharmacological activities of benzimidazole derivatives – an overview." Inter. J.Sci. Inn. Disc. 2 (1), 121-136.

4. E.C. Wanger, W.H. Millett (1943). Synthesis of Benzimidazole. Org. Syn. (2): 65.

5. N.S. Habib, R. Soliman, F. A. Ashour (1997). Synthesis and antimicrobial testing of novel oxadiazole benzimidazole derivatives. Die Pharmazie. 52(10): 746–749.

6. Y. Bansal (2012). The therapeutic journey of benzimidazoles: A review. Bioorganic and med. chem. 20 (21): 6208-6236.

7. R. V. Shingalapur, K. M. Hosamani (2010). Derivatives of benzimidazole pharmacophore: synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. Eur J Med Chem.45: 1753-1759.

8. E.L.Sayed (2016). "Synthesis and crystal structures of benzimidazole-2-thione derivatives by alkylation reactions." Mole. 21, 12; doi: 10.3390.

9. S. Gurrala (2011). Symmetrical coupling of 2- mercapto benzimidazole derivatives and theirantimicrobial activity. IJPPS. 3(2): 217-220.

10. Gulhan Turan-Zitouni, Sqeref Demirayak (2003). "Synthesis of some 2-[(benzazole-2-yl) thioacetylamino] thiazole derivatives and their antimicrobial activity and toxicity." Eur. J. Med. Chem. 39: 267–272.

11. D. Pathak (2010). Benzimidazoles: A New Profile of Biological Activities. SRL. Der Pharmacia Lettre. 2(2): 27-34.

12. Meral Tuncbilek, Tulug Kiper, Nurten Altanlar (2009). "Synthesis and in vitro antimicrobial activity of some novel substituted benzimidazole derivatives having potent activity against MRSA." Eur. J. Med. Chem. 44: 1024–1033.

13. N. Nassir, Al-Mohammed (2013). Synthesis and antibacterial evaluation of some novel imidazole and benzimidazole sulfonamides. Mole. 18: 11978-11995.

14. R. Mohammad, Ahmad, H. Athraa, Ahmad (2014). "Synthesis and characterization of some New Derivatives from 2- Mercaptobenzothiazole." Ira. J. Sci. 2 (55): 319-333.

15. R.V. Heralagi (2012). Synthesis of some novel bis type 2-mercapto benzimidazole derivatives. RJPBS. 3(2): 407-414.

16. P. Pratik, Maske, G. Sachin G Lokapure (2012). "Synthesis and antiprotozoal activity of nitro and halogeno substituted some novel mercaptobenzimidazole derivatives." Der. Pharma. Chemica. 4 (3):1283-1287.

17. Meeta, Pradeep kumar, Balasubramanian narasimhan (2014). "Synthesis, antimicrobial evaluation and QSAR studies of p-amino benzoic acid derivatives." J. Pharma. Tech. Res. Mang. 1 (2): 87-104.

18. R.M. Kim, J. Chang (2008) Discovery of potent, orally active benzimidazole glucagon receptor antagonists. Bioorg Med Chem Lett 18: 3701-3705.