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Concise on Some Biologically Important 2-Substituted Benzimidazole Derivatives

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Abstract

Benzimidazole and its derivatives belong to a class of benzo fused heterocycles with two nitrogen atoms, are present in many drug molecules. This molecule is having wide ranging biological and pharmaceutical activities. This review summarizes pharmacological and medicinal activities of 2-substituted benzimidazole and its marketed drugs.

Keywords: Benzimidazole; Heterocycles; Drugs; Omeprazole; Pharmacophore

Introduction

Benzimidazole based mostly hybrids are of wide interest as a result of their miscellaneous biological activities. Benzimidazoles are ascertained as a capable category of bioactive heterocyclic compounds that exhibit a range of biological activities like anti- microbic, anti-oxidants, anti-cancer, anti-diabetic, anti-parasitic, anti-viral, anti-helminthic, anti-proliferative, anti-HIV, anti-convulsant, medication, anti-hypertensive, proton pump matter, anti-neoplastic and anti-trichinellosis [1-4]. Benzimidazoles exhibit important applications like potential swish muscle fiber propagation inhibitors, antineoplastic agents, as a treatment for viscus urinary tract infection and in different numerous areas of chemistry [5]. Many hybrids of benzimidazole are well according as thyroid receptor agonist gonadotropin-releasing secretion receptor antagonists, non-nucleoside HIV-1 reverse transcriptase inhibitors and apparently group benzimidazoles as modulators of metabotropic salt receptors [6]. The benzimidazole moiety is additionally gift in several natural merchandise and pharmacologically active agents [7]. Therefore, synthesis of novel derivatives of benzimidazole remains a determination of therapeutic investigation [8,9].

Benzimidazole substituted at 2 positions may be a important heterocyclic pharmacophore in drug discovery. Synthesis and biological analysis of assorted 2-substituted benzimidazole derivatives have resulted within the discovery of gastric antacid, acid, rabeprazole, and pantoprazole. In recent years, the synthesis of novel benzimidazole derivatives remains a spotlight of clinical analysis and notably attention has progressively been given to the synthesis of 2-substituted benzimidazole derivatives [10]. Current observations advocate that substituted benzimidazoles and heterocyclic, show straightforward interactions with the biopolymers, possess potential activity with lower toxicities at intervals the medical aid approach in humans and animals [11]. The 2-subtitued benzimidazole scaffold is useful for the development of recent motifs of pharmaceutical or biological interest [12]. The optimisation of benzimidazole-based structures has resulted in numerous medicines that area unit presently within the market, like gastric antacid (proton pump inhibitor), pimobendan (Ion dilator), and vermifuge, albendazole, flubendazole (anthelmintic) area unit shown in Figure 1 [13]. The spectrum of medicine activity exhibited by benzimidazoles has been reviewed by many researchers [14,15]. within the publications, many new strategies for the synthesis of benzimidazoles are discovered and reported; such work continues because of their wide selection of medicine activities and their industrial and artificial applications [16].

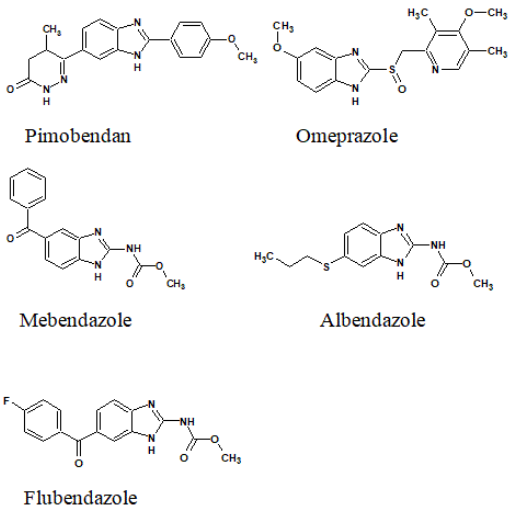


Figure 1: Representative 2-Substituted Benzimidazole derivatives as some marketed drugs for different therapeutic categories.

Chemistry of Benzimidazole

Benzimidazole is a connected aromatic imidazole ring system wherever a benzene ring is fused to an imidazole ring as indicated within the structure for benzimidazole (I) [17].

Benzimidazole possesses each acidic also as basic nature. The NH cluster present in benzimidazole is relatively powerfully acidic and frail basic extra characteristic of benzimidazole is that they need the capability to make salts (Figure 2). Benzimidazoles with unsubstituted

NH teams show quick prototrophic tautomerism that ends up in balance mixtures of asymmetrically substituted compounds. Benzimidazoles that embrace an atom connected to the nitrogen in the 1-position promptly tautomerize this could be delineating as follows [18,19].

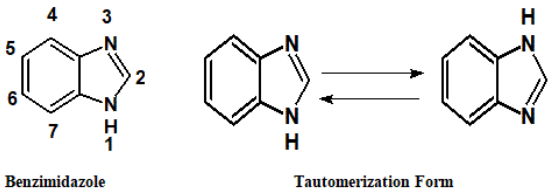


Figure 2: Benzimidazoles and an atom of Benzimidazoles, connected to the nitrogen in the 1-position promptly tautomerize.

Antimicrobial effects of 2-substituted benzimidazole

Literature survey shows that among the benzimidazole derivatives, 2-substituted ones are pharmacologically more potent and thence the planning and synthesis of 2-substituted benzimidazoles is that the prospective space of analysis [20]. Some wide used medicinal drug medicine like furacilin, furazolidone and ftivazide are known to contain this group. In past decades, hydrazones have received a lot of attention and lots of studies are reported because of their chemotherapeutical worth within the development of novel antimicrobial agents. A series of 1 and 2-disubstituted-1H-benzimidazole-N alkylated-5-carboxamidine derivatives are terribly potent medicinal drug agents against S. aureus and methicillin-resistant S. aureus. The study disclosed the best activity, with MIC values of 0.78-0.39 µg/ml against these species. numerous mono halogens and dihalogen substituted benzimidazole additionally possess antibacterial activities [21].

Synthesis, Reactions and Properties of 2-Substituted Benzimidazoles

Synthesis using cyanogen halides, cyanamide and cyanoguanidines

The Pierron process is one of the important procedures for the synthesis of several 2-amino benzimidazoles [22].

Reaction of hydrochloride salts of o-phenylenediamine with cyanamide and dimethyl cyanamide produces 2-Amino and 2-dimethylaminobenzimidazoles severally in low yields [23-25]. Synthesis of 2-acylamino and 2-alkoxycarbonyl amino benzimidazoles is feasible exploitation group or ethoxycarbonyl substituted cyanamide that is obtained by reaction of acyl chlorides and chlorocarbonic acid esters with cyanamide within the presence of hydroxide triethylamine or pyridine or with calcium cyanamide (Figure 3) [26-30].

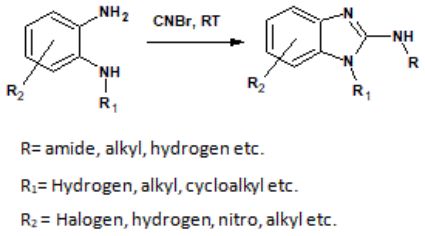


Figure 3: Preparation of 2-Amino Benzimidazoles using Cyanogen Halide.

The 2-alkoxycarbonyl aminobenzimidazole compounds find applications as fungicides and anthelminthic agents. 2-Aminobenzimidazole has also been synthesized from o-nitro chloro benzene and sodium cyanamide (Figures 4 and 5) [31].

The reaction of o-phenylenediamines with cyanoguanidines provides 2- amidinobenzimidazoles that are readily converted to 2-(cyanoamino) benzimidazoles [32,33]. The latter were additionally obtained from o-phenylenediamines and N- cyanodi(methylthio) imido carbonate within the presence of triethylamine electron donor substituents within the benzene nucleus were found to push the reaction, whereas negatron acceptor substituents hinder it [34,35].

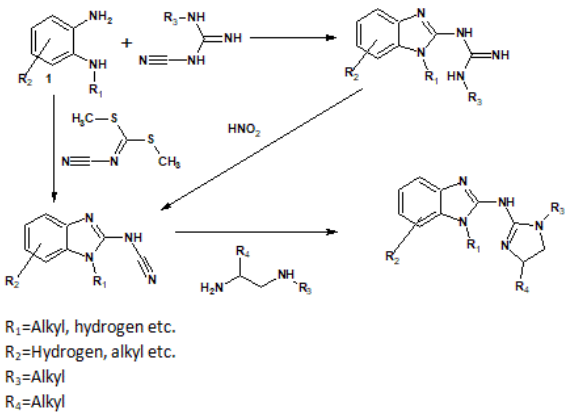
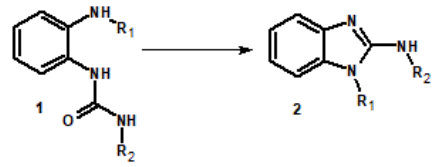


Figure 4: Preparation of 2-Amino Benzimidazoles using Cyanoguanidines and N- cyanodi(methylthio) imido carbonate.

Some 2-(hetero aryl amino) benzimidazoles can be prepared directly from o-phenylenediamines and hetero aryl cyanamides, whereas 2-(2-benzimidazolylamino)-4-hydroxypyrimidines have been synthesized by cyclization of 2-cyanamino-4-hydroxy-6-methylpyrimidine by substituted o-phenylenediamines [36].

Synthesis based on urea derivatives with aryl substituted guanidines

Heating of-(N-Phenacyl amino) phenyl urea (1) with phosphorus oxychloride, results in cyclization to 1-phenacyl-2-aminobenzimidazole (2) and refluxing of 1-(o-amino phenyl)-3-benzylurea in toluene in the presence of p-toluene sulfonic acid converts it to 2-benzylaminobenzimidazole (3) [37-39].

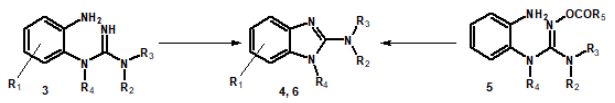


R_1= Hydrogen, alkyl, benzyl etc.

R_2 = Hydrogen, alkyl, benzyl etc.

Figure 5: Synthesis of 2-Amino Benzimidazoles using Urea Derivatives.

N-(o-Amino phenyl)-N-methyl-N',N"-disubstituted guanidines (3) cyclizedto aminobenzimidazole (4) when they are treated with CS2, CSC12, and HC(OC2H5)3 [40]. 2-Acyloxyguanidines (5) undergo decomposition to 2-dialkylaminobenzimidazoles (6) at room temperature [41]. It is supposed that the reaction, as in the case of the rearrangement of N-aryl-N-hydroxyamidines to benzimidazoles, proceeds through an imino nitrene intermediate (Figure 6) [42,43].



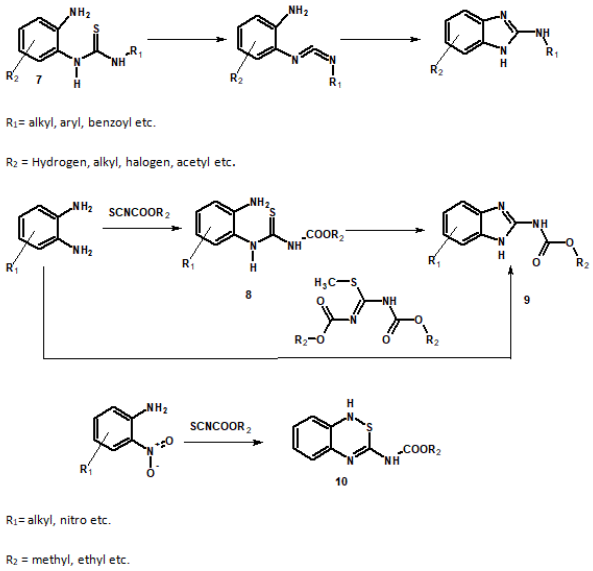
In **3, 4** R_1, R_2, R_3, R_4 = Hydrogen, alkyl etc.

In **5, 6** R_2, R_3, R_4 = Hydrogen, alkyl, benzyl, phenyl, phenyl amine etc.

Figure 6: Synthesis of 2-Amino Benzimidazoles using Aryl Substituted Guanidines.

Synthesis based on thiourea and similarly constructed compounds

Cyclization of 1-(2-amino-phenyl)thiourea (7) forms 2-Alkyl-2-aryl and 2-acylaminobenzimidazoles. It is understood that the reaction proceeds through carbodiimides intermediate (Figure 7) [44].



R_1= alkyl, aryl, benzoyl etc.

R_2 = Hydrogen, alkyl, halogen, acetyl etc.

R_1= alkyl, nitro etc.

R_2 = methyl, ethyl etc.

Figure 7: Synthesis of 2-Amino Benzimidazoles using Thiourea and Similarly Assembled Compounds.

The cyclization was initially carried out in lead oxide and mercuric oxide in dry chloroform [44]. Afterward, methyl iodide in ethanol Mercury (II) chloride and dimethyl sulphate were thereafter proposed as reagents [45-49]. Attempts to synthesize unsubstituted 2-aminobenzimidazole by cyclization of (o-aminophenyl) thiourea were unsuccessful and instead of the desired product they resulted in benzimidazole thione [50,51].

Reaction of o-phenylenediamines with alkyl esters of carbalkoxythiocarbamic and N-[alkoxy(methylthio)methylene] carbamic acids leads to the formation of 2-alkoxycarbonylaminobenzimidazole (9). The same compounds were also gained by heating benzothiadiazines (10), synthesized from substituted o-nitroanilines, in 2N HC1 and methanol [52-54]. Expedient method involving of the reaction of o-phenylenediamine with 1,3-bis(alkoxycarbonyl)-S-methylisothiourea was planned for the synthesis of carbamates (9) in 1934 by Murray and Dains, [55-61].

Replacement of a halogen atom by an amino group and an N-Heteroaryl group

Replacement of a chlorine atom by an amino group, was first described in 1912 and was continued as the most widely used method for the synthesis of 2-amino substituted benzimidazoles. This method has been used to obtain 2-aminobenzimidazole derivatives that have the most diverse substituents at one position of the benzimidazole ring, in the amino group, and in the benzene ring [62,63]. The reactivity of 2-chlorobenzimidazole with respect to piperidine is like the reactivity of p-nitro chlorobenzene but lower than that observed for 2-chlorobenzothiazole and 2-chlorobenzoxazole [64,65].

Besides the nucleophilic substitution of the chlorine atom, the intermediate 2-amino-l-acylmethyl-benzimidazoles (12) undergoes dehydration to give 1H-imidazo[1,2-a] benzimidazole derivatives (13) upon heating of 1-acylmethyl-2-chlorobenzimidazoles (11) with

ammonia or primary amines in lower alcohols or dimethylformamide at higher temperature (Figure 8) [66].

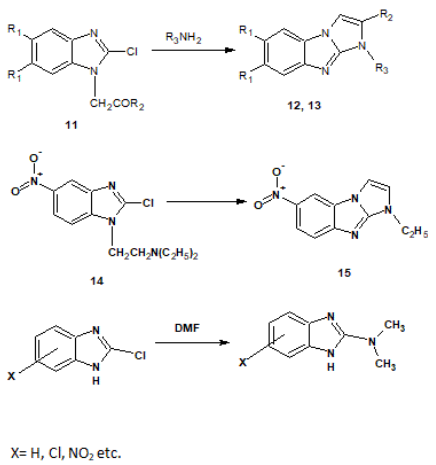


Figure 8: Replacement of Halogen Atom by Amino Group and an N-Heteroaryl Group.

An effort to exchange the chlorine in 1-diethylaminoethyl-2-chlorobenzimidazole (14) with a diethyl amino or aryl amino group led to the formation of 2,3-dihydroimidazo[1,2-a] benzimidazole (15), because the temperature at that bimolecular exchange is feasible is higher than the temperature at that building block cyclization takes place [67]. Benzimidazo (2, 1-b) quinazolin-12-one by-products (16 and 17) were obtained by the reaction of 2-chlorobenzimidazole and its 1-methyl-substituted derivative with esters of anthranilic and N-methyl-anthranilic acids respectively (Figures 9 and 10) [68].

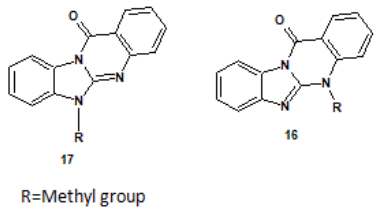


Figure 9: Benzimidazo [2, 1-b] quinazolin-12-one Derivatives.

To exchange the chlorine with a diphenyl amino using DMF, 2-Dimethylamino substituted derivatives were obtained in good yields rather than the expected 2-diphenylaminobenzimidazoles [69]. The reaction of 2-chlorobenzimidazole and urethane; resulted in the formation of cyclic benzimidazole trimer, rather than the specified product Benzimidazole-2-carbamic acid ester [70]. Fusion of 2-chlorobenzimidazoles with 5-membered heterocycles that contain an NH group in the rings results in the formation of 2-(N-heteroaryl) benzimidazoles. Benzimidazolyl pyridinium salts (18) are prepared by condensation of pyridine and its derivatives with 2-chlorobenzimidazoles. Heating of 2-chlorobenzimidazoles with excess pyridine or pyridine derivatives formed compounds (19) with a zwitterions structure [71-73].

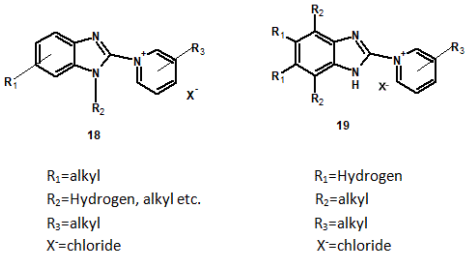


Figure 10: Benzimidazolyl pyridinium salts.

Replacement of sulphur-containing groups by an amino group

It is known that like halogens, sulfur containing groups in the 2-position of benzimidazole, can be replaced by amino groups, sometimes with even greater ease than in the case of halogens. Thus, for example, 2-dialkyl aminoethyl aminobenzimidazole (20) which cannot be synthesized from 2-chlorobenzimidazole, can be prepared by heating 2-methylsulfonylbenzimidazole and dialkyl amino ethyl amines (Figure 11) [74,75].

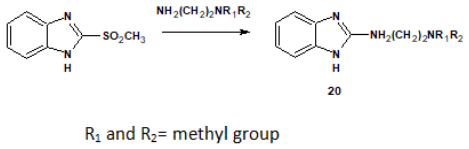


Figure 11: Replacement of Sulphur-Containing Groups by an Amino Group.

It has been recently shown that the sulphur group in benzimidazole-2-sulfonates is replaced by varied amino groups. The reaction takes place with extremely basic amines by heating the reactant in aqueous solutions. This technique has definite advantages over different ways, like simplicity within the execution of the syntheses and simple getting the starting compounds [76].

Chichibabin amination

Chichibabin amination reaction is widely used for the synthesis of 1-substituted, 2-amino benzimidazole, where nucleophilic substitution by radical of not only the atom in the 2-position of benzimidazole however also the alkyl, aryl alkyl, and aryl groups occur under the influence of sodium amide (Figure 12) [77,78].

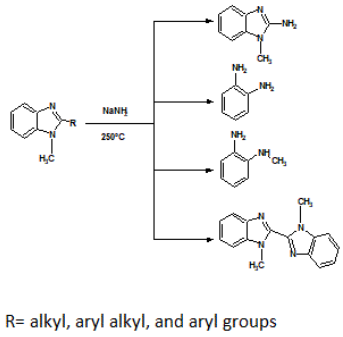


Figure 12: Chichibabin Reaction of 1-substituted Benzimidazoles.

2-Aminobenzimidazole with an unsubstituted NH group within the one position cannot be obtained by amination because of the N-anion that's formed by the action of sodium amide on benzimidazole is not capable of nucleophilic substitution reactions in the 2- position [79,80].

Cleavage of triazepines

N-Protective groups like benzyloxymethyl and alkoxy alkyl can simply be removed under acid hydrolysis conditions. Since the synthesis of 1-methoxymethyl-2-aminobenzimidazole by direct amination is not possible a replacement method has been developed for the preparation of 2-aminobenzimidazole; this methodology consists of cleavage of phenyl-(1-methoxymethyl-2-benzimidazolyl) triazene (22) with a mineral acid. during this case the methoxymethyl cluster is split out at the same time with cleavage of the triazene grouping (Figure 13) [81,82].

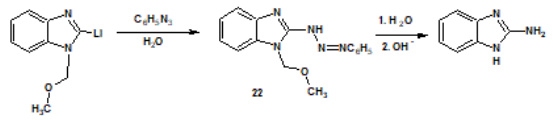


Figure 13: Cleavage of Triazepines of 1-substituted Benzimidazoles.

Different methods

An attempt to synthesize the corresponding amine derivative from 2-sodio-l-methyl benzimidazole and O-methylhydroxylamine was unsuccessful. However, the action of BrN(C2H5)2 on the 2-sodio by-product led to the formation of 2-diethylamino-l-methylbenzimidazole in low yield. N-Substituted carbon imidoyl dichloride (23) have application within the synthesis of 2-aminobenzimidazole derivatives. therefore 2-arylaminobenzimidazoles and 1-phenyl-2-anilinobenzimidazole were obtained in high yields within the reaction of N-aryl carbon imidoyl dichloride with o-phenylenediamine and N-Phenyl-o-phenylenediamine, many 2-Alkoxycarbonylaminobenzimidazoles were synthesized exploitation N-alkoxy carbonyl carbon imidoyl dichloride (Figure 14). The reactions proceed readily at room temperature within the presence of triethylamine, chloroform and dioxane [83,84].

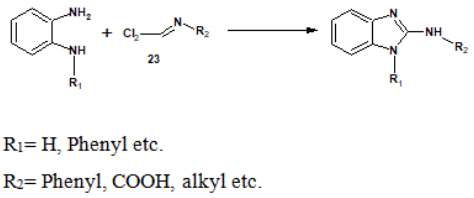


Figure 14: Synthesis of 2-amino Benzimidazoles using N-Substituted carbon imidoyl dichloride.

Some quinoxaline derivatives undergo photochemically initiated rearrangement to benzimidazole derivatives, the yields of which depend on the pH of the medium and the solvent (Figure 15). Hence, when 2-methoxycarbonylaminoquinoxaline N-oxide (24) is irradiated with UV light in dry acetonitrile, it undergoes swift rearrangement to 2-methoxycarbonylaminobenzimidazole (25) and its N-formyl derivative (26) [85,86].

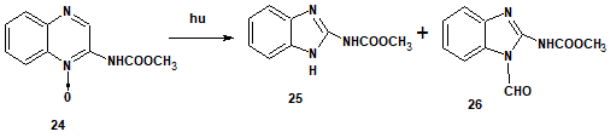


Figure 15: Synthesis of 2-amino Benzimidazoles using N-Substituted carbon imidoyl dichlorides.

Nucleophilic substitution in the imidazole ring

For unsubstituted 2-halobenzimidazole a contest exists between proton abstraction by the nucleophile at the one position with concomitant retardation of 2-substitution. consequently, chloride ion isn't displaced from 2-Chlorobenzimidazole by powerful nucleophiles, whereas 2-Chloro-1-methyl Benzimidazole reacts pronto with sodium methoxide or ethoxide (Figure 16) [87].

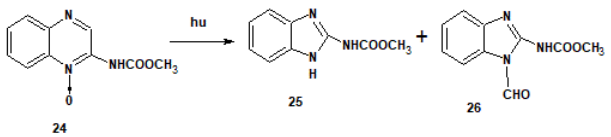


Figure 16: Nucleophilic substitution in the imidazole ring.

Electrophilic substitution reactions in the benzene ring

The bromination of 2-amino-1-methyl (ethyl) benzimidazole by using hydrobromic acid at room temperature ends up in the formation of a mixture of mono bromo substituted compound (31) through the intermediate formation of perbromides. just like the chemical element atom, the bromine atom is incorporated within the five and six positions, that are the foremost reactive positions in electrophilic substitution, 5,6-dibromo derivative (32) was obtained by exploitation of potassium bromate, while 4,5,6-tribromo derivative (33) was obtained under more severe conditions (Figure 17) [88].

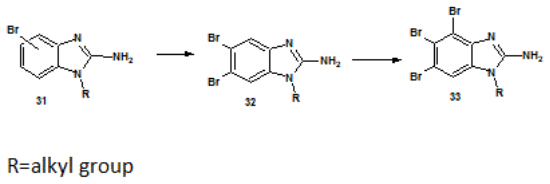


Figure 17: Structures of mono bromo substituted compound, 5,6-dibromo derivative, 4,5,6-tribromo derivative.

The nitration of 2-amino-l-methyl benzimidazole proceeds smoothly at -5°C with potassium nitrate (1 mol) in concentrated sulphuric acid to give a mixture of 5 and 6-substituted derivatives (34) in a ratio of 5:4. 5,6-Dinitro-2-amino-l-methyl benzimidazole (35) was obtained under the same conditions using 2 moles of potassium nitrate (Figure 18) [89].

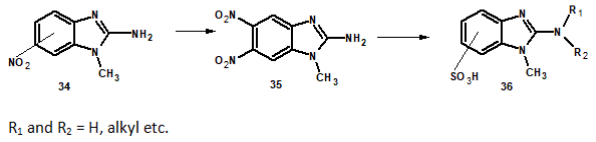


Figure 18: Structures of mixture of 5 and 6-substituted derivatives, 5,6-Dinitro-2-amino-l-methyl benzimidazole.

Biological Activities of Benzimidazole Based Marketed Drugs

The benzimidazole nucleus seems to be a part of the many medicine. Benzimidazole derivatives are of wide interest due to their numerous biological activities and clinical applications, they are remarkably effective compounds each with reference to their inhibitory activity and their favorable property quantitative relation. Specifically, this nucleus is a constituent of vitamin-B12 (Figure 19). Benzimidazole ring displays a crucial heterocyclic pharmacophore in drug discovery. Benzimidazoles are considered a promising class of bioactive heterocyclic compounds that exhibit a variety of biological activities like antiprotozoal, anthelmintic, anti-HIV, antiepileptic, anti-inflammatory, antiherpetic, antineoplastic, anti-allergic, anti-histaminic, vasodilative, a narcotic analgesic, medication, antifungal and antiulcer. Benzimidazole compounds area unit marketed for various therapeutic classes few of them are discussed below [90].

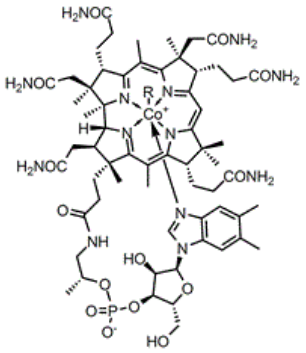


Figure 19: Structure of Vitamin-B12.

Anti-ulcer agents

These are the medicine that inhibit both basal and stimulated gastric acid secretion. Some drugs containing Benzimidazole nucleus are pantoprazole, rabeprazole, iansoprazole, antacid etc. (Figure 20) [91].

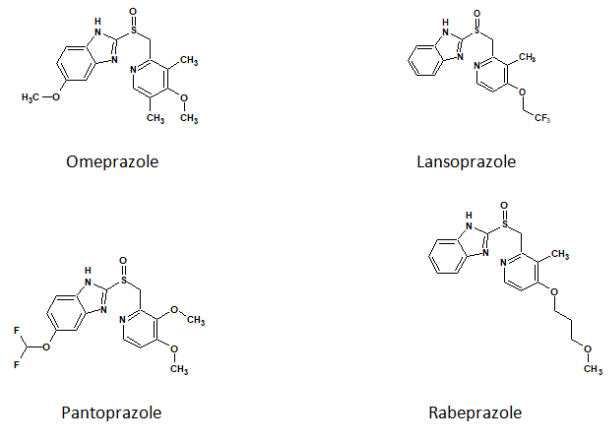


Figure 20: Structures of Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole.

Anti-psychotic agents

In psychopathy, thinking of the patient becomes illogical, off-the-wall and loosely organized. Patient has issue in understanding reality and their own conditions. In such cases some drugs containing benzimidazole nucleus like droperidol, pimozide, and benperidol are used (Figure 21) [1].

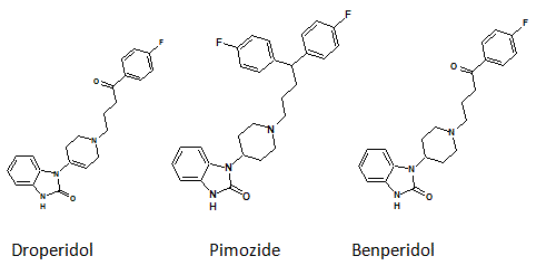


Figure 21: Structures of Droperidol, Pimozide, Benperidol.

Anthelmintic agents

These are the medicine that either kill or expel infesting helminthes. Some drugs containing benzimidazole nucleus are thiabendazole, mebendazole and albendazole etc. (Figure 22) [1].

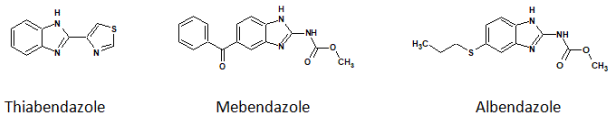


Figure 22: Structures of Thiabendazole, Mebendazole, Albendazole.

Antihistamine and antiallergic agents

Astemizole was a second-generation antihistamine and an antiallergic drug that features a long period of action. Astemizole was discovered by Janssen Pharmaceutical in 1977. It has been withdrawn from the market in most countries due to rare however probably fatal side effects (Figure 23) [1].

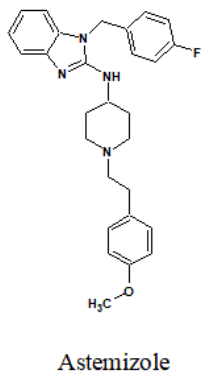


Figure 23: Structure of Astemizole.

Narcotic analgesic agents

These are the medicine used as anodyne. Clonitazene is an opioid analgesic having just about thrice the potency of morphine. It is related to Etonitazene, an opioid of considerably higher efficiency. Clonitazene is not presently marketed. It is a drug; in the united states it is a Schedule I Narcotic controlled substance with a Drug {enforcement Administration|Drug Enforcement Agency|DEA|law enforcement agency} (Drug Enforcement Administration) ACSCN (Administrative Controlled Substances Code Number) of 9612 (Figure 24) [1].

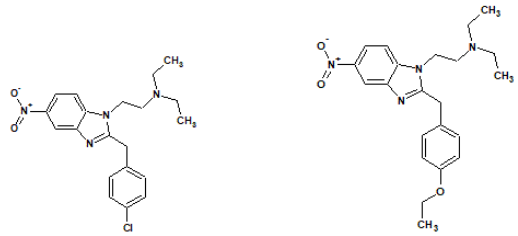


Figure 24: Structures of Clonitazene, Etonitazene.

Conclusion

The 2-substituted benzimidazoles has recognized to be a valuable pharmacophore in medicinal chemistry. Structural modification of benzimidazole moiety exhibits promising biological activities. 2-substituted benzimidazoles will provide an outstanding framework for the synthesis of small mofites for discovery based research and better quantity screening efforts. Besides, it needs better knowledge and skills on the mechanism of action in order to found balanced therapeutic tactics.

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