Review Article

An Overview on Chemical Characterizations and Anti-Microbial Activities of Some Benzimidazole Derivatives

Mohammad Asif

Department of Pharmacy, GRD (PG) Institute of Management & Technology, 248009, Dehradun, (Uttarakhand), India

*Corresponding Author
Mohammad Asif
Department of Pharmacy, GRD (PG) Institute of Management & Technology, 248009, Dehradun, (Uttarakhand), India
E-mail: aasif321@gmail.com

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Abstract

Benzimidazoles are play an important role in medical field with so many pharmacological activities such as like anti-microbial, anti-viral, anti-diabetic, anti-cancer, antioxidant, anti-parasitic, antihelmintics, antiproliferative, anti-HIV, anticonvulsant, analgesic, antiinflammatory, antihypertensive, antineoplastic, proton pump inhibitor, antitrichinellosis and other pharmacological activities. Benzimidazoles are remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms. Different substituted benzimidazoles having anti-microbial activities. These activities encouraged the development of some more potent and significant compounds.

1. Introduction

Benzimidazole derivatives having wide interest because of their diverse biological activities and clinical applications. They are remarkably effective compounds with respect to their activity [1-3]. The importance of benzimidazole nucleus, it would be worthwhile to design and synthesize some benzimidazole derivatives and screen them for potential biological activities. Resistance to various antimicrobial drugs (β-lactam antibiotics, macrolides, quinolones, and vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly important problems. Increasing drug resistance is a significant health matter. Benzimidazole ring displays an important heterocyclic pharmacophore in drug discovery, these compounds carrying different substituent in the benzimidazole structure are connected with a wide range of pharmacological activities such as anti-cancer, antiviral, antibacterial, antifungal, antihelminthic, antiinflammatory, antihistaminic, analgesic, proton pump inhibitor, antioxidant, antihypertensive, anticoagulant and other properties [4]. The different substituted benzimidazole derivatives are exhibited proton pump inhibitor actions, such as omeprazole, lansoprazole, rabeprazole, and pantoprazole [5]. In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocyclic, show easy interactions with the biopolymers, possess potential activity with lower toxicities in the chemotherapeutic approach in man [6].

2. Benzimidazole

The benzimidazoles contain a phenyl ring fused to an imidazole ring as indicated below (1).

![Benzimidazole (1)]
problem. A matter of concern in the treatment of microbial infections is the limited number of efficacious antimicrobial drugs. Many of the currently available drugs are toxic, enable recurrence because they are bacteriostatic or fungistatic and not bactericidal or fungicidal or lead to the development of resistance due in part to the prolonged periods of administration. There is a real perceived need for the discovery of new compounds that are endowed with antimicrobial activities, possibly acting through mechanisms of action, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant. It is therefore critical to realize that antimicrobial drug effectiveness, widely accepted as a common good, its increasing resistance cannot be taken for granted. Thus, an urgent need for new potent classes of antibiotics with novel modes of action persists [11]. The biological activity of the compounds is mainly dependent on their molecular structures [12]. Heterocyclic compounds are acquiring more importance in recent years as these can be found in a large number of compounds which display biological activity [13]. Heterocyclic compounds particularly five and six member heterocycles have attracted the attention of pharmaceutical community over the years due to their therapeutic value [14]. Polyfunctionalized heterocyclic compounds containing Nitrogen, sulphur, oxygen as heteroatoms play important roles in the drug discovery process [15]. Analysis of drugs in late development stages or in the market shows that 68% of them are heterocycles [16]. Therefore, it is not surprising that during past decades, compounds bearing heterocyclic nuclei have received much attention due to their chemotherapeutic value in the development of novel antimicrobials and anthelminthics [17]. Therefore, these heterocyclic compounds are being synthesized in terms of operational simplicity, non-toxicity, reusability, environment and economical acceptability.

4. Biological activities of benzimidazole derivatives:

Despite of the availability of a number of antimicrobial agents the main matter of concern in the treatment of microbial infections is the limited number of efficacious antimicrobial drugs [17]. Infectious microbial diseases remain pressing problems world-wide, because resistance to a number of antimicrobial agents among variety of clinically significant species of microorganisms has become an important global health problem. One way to battle with this challenge is the conscious usage of the currently marketed antibiotics; the other is the development of novel antimicrobial agents. Hence, there will always be a vital need to discover new therapeutic agents to avert the emergence of resistance and ideally shorten the time duration of therapy [18]. The outcome of numerous attempts to new structural prototype in the search for effective antimicrobials indicates that the benzimidazoles still remain as one of the most versatile class of compounds against microbes [19]. Compounds bearing benzimidazoles moiety are reported to possess various interesting biological activities such as antitubercular, anticaner, antihelminthic, antiallergic, antioxidant, antihistaminic and antimicrobial [20]. In recent years benzimidazoles have been reported to act as topoisomerase-I inhibitors, selective neuropeptide YY1 receptor antagonists, angiotensin-II inhibitors, 5-HT3 antagonist, in the treatment of interstitial cystitis and as a factor Xa inhibitors [21].

4.1 Benzimidazoles as Antimicrobials:

The increase in bacterial resistance has attracted considerable interest in the discovery and development of new classes of anti-bacterial agents. The new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents. Actinonin was first isolated from a Malayan strain of Actinomyces and found to show a weak inhibitory activity against Gram-positive and Gram-negative bacteria. However, recently actinonin has been proven to have anti-proliferative effects on human tumor cells. The action mechanism of actinonin is believed to be the inhibition of the peptide deformylase that is a new class of metal-loenzyme which is essential for bacterial survival. The hydroxamate group of actinonin, which can complex with the metal ion in the active pocket of the peptide deformylase, is necessary for its activity. Nevertheless, actinonin lacks in vivo efficacy, due to the poor bioavailability [22]. Second-generation macrolides such as clarithromycin (CAM) and azithromycin (AZM) have enjoyed widespread clinical use for the treatment of upper and lower respiratory tract infections as well as genital infections due to their superior anti-bacterial activity, pharmacokinetic properties and fewer gastrointestinal side (GI) effects compared with first generation macrolides such as erythromycin (EMA) which is its acid instability, leading to consequential degradation products responsible for its poor pharmacokinetic profile and GI side effects. Their mechanism of action has been elucidated that the macrolides bind reversibly to the nucleotide A2058 in domain V of the 23S RNA in the ribosomal 50S subunit and block protein synthesis. However, the therapeutic Utility of the macrolides has been severely compromised by the emergence of widespread bacterial resistance which has become a serious medical problem worldwide [23].

A series of 1-methyl-N-[(substituted-phenylmethylidene)-H-benzimidazole]-2-amines (1) showed antibacterial and cytotoxic properties for Gram positive bacteria (S.aureus, B. pumillus) and Gram negative bacteria (E.coli) [24]. Some thieno[2,3-d]pyrimidin-4(3H)-ones (2) containing benzimidazol-2-yl-thioethyl and benzimidazol-2-yl-methanethioethyl moiety in second position of pyrimidine ring were exhibited anticholine llosis and antiprotosal effects [25].

In vitro antibacterial evaluation against Gram positive bacteria (B. thuringienis) and Gram negative bacteria (E.coli) of various series including 2-substituted-3a,4,9a-tetrahydro-4,9-benzeno-benz(f)isoindole-1,3-diones: benzimidazoles (3) acetybenz-imidazole (4) [26]. A amine derived bis-benzimidazole (5) showed antibacterial efficiency against Cabbiconis, B.proteus, which were designed by the systematical structural modification of Flucnazole [27]. A series of 2-substituted benzimidazoles analogues (6) having potent activity against Gram positive bacteria (B.subtilis), Gram negative bacteria (E.coli) and antifungal activity for Twirdae [28]. A series of 5-(nitro/bromo)-styril-2-benzimidazoles (7) are synthesized showing antitubercular activity against Bacterium tuberculosis, anti-bacterial activity against Saureus [29].

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(Gram positive) and E.coli (Gram negative) [30]. Some 1-{[5-(alkyl/aryl)-1,3,4-oxadiazol-2-yl](methyl)-2-allyl-1H-benimidazoles (9) showing potent activity against Gram positive bacteria (S.aureus ATCC29213). (J.mutans MTCC 890) with Gram negative (E.coli) and antifungal activity (A. niger) [31].

The 2-(Amino-/isopropylamino-/chloro-/bromo-)benzimidazoles analogues (10) having potent activity against methicillin-resistant staphylococcus [32]. The 2-alkene substituted benzimidazoles, tetrahydrobenzimidazoles (11). A series 2-(substituted phenyl)-1H-benimidazoles (12) [33].

The 1-(4-(1H-benz[d]imidazol-1-yl)phenyl)-3-chloro-4-phenyl azetidin-2-one (13) [34]. A series of phenyl and benzimidazoles substituted benzyl ethers (14) were tested for antibacterial (S.aureus, E.coli) and antifungal activities (C.albicans, C.krusei) [35].

Substituted 5-{2-(2-methylbenimidazole-1-yl)ethyl}-3-diethylaminoethyl (15) were tested against one strain of Gram +ve bacteria (Bacillus cereus), Gram -ve bacteria (E.coli) [36]. A series of Schiff bases of 4-(4-aminophenyl)-morphone (16) were tested for antibacterial (S. aureus, S. epidermis) and antifungal (C. albicans, A. niger) [37].

Various N-alkyl and N-acyl derivatives of 2-(4-thiazolyl)-1H-benimidazole (17) were screened for their antifungal and antibacterial activity (2004) [38]. Some 2-substituted-phenyl-1H-benz-imidazoles-5-carbonitril (18) with their potent activity against Candida species was reported [39]. Synthesis and antiparasitic activity of 1H-benimidazole derivatives (19) were tested against protozoa Giardia lamblia, Entamoeba hystolytica [40].

5. Other Compounds:

Some 2-{[6-fluorochroman-2-yl]-1-alkyl/acyl/aroyl-1H-benimidazoles (20) exhibited anti-bacterial activity against Salmonella typhimurium [41].

A series of functionalized benzimidazole derivatives by the condensation of OPDA with 4-bromobenzoic acid (21) were tested for their potential anti-bacterial [42]. A series of actinonin derivatives containing a benzimidazole heterocyclic linked as amide isosteres (22) were evaluated in vitro against S. aureus, K. pneumonia, and Sarcina lutea [22]. The 0-benzimidazolyl clarithromycin derivatives (23) were tested for their in vitro anti-bacterial activities [23].

5.1 Antifungal activity:

Infectious diseases have been serious and growing threats to human health during the past few decades. The decrease of sensibility to anti-microbial agents in current use has also been increasing for a great variety of pathogens and the resistance to multiple drugs is more and more prevalent for several microorganisms, especially for Gram-positive bacteria and some intractable fungi. Their inhibitory properties as regard representative fungi have been extensively exploited. Especially, it is worthy to note that Fluconazole, the first-line triazole-anti-fungal drug has established an exceptional therapeutic record for Candida infections, and become the first choice in the treatment of infections by C. albicans and Cryptococcus neoformans due to its potent activity, excellent safety profile, and favorable pharmacokinetic characteristics. However, Fluconazole is not effective against invasive aspergillosis and is not fungicidal. In addition, extensive clinical use of Fluconazole has resulted in the increasing Fluconazole-resistant Candida and C. albicans isolates [43].

A series of novel spiro [indole-thiazolidinones (24) were tested in vitro for anti-fungal activity against Rhizoctonia solani, Fusarium oxysporum and Collectotrichum [44]. A series of 2'-arylsulphonyl-substituted-1H,10H-[2,5]-bisbenzimidazolyl-5-carboxamidines (25) were evaluated for their anti-fungal activity [45].

A series of novel 2-substituted benzimidazoles (26), tetrahydrobenzimidazoles and imidazoles and screened there in vitro anti-bacterial anti-fungal activities [46]. A series of novel benzimidazole derivatives (27) were evaluated for anti-fungal activity [47].

Lipophilicity and anti-fungal activity of some 2-substituted benzimidazole derivatives (28) tested against yeast Saccharomyces cerevisiae [48].
Anti-bacterial and Anti-fungal Activities of Benimidazole and Benzoazole Derivatives (28a-c) against standard strains and 59 clinical Isolate and compound 28a and 28b is active [49].

\[ \text{28a-c} \]

5.2 Antiviral activity:

Chronic infection with the hepatitis C virus (HCV) is a major risk factor for developing cirrhosis and hepatocellular carcinoma. About 3% of the worldwide population is chronically infected with HCV. A preventive vaccine has not been developed and limits of current therapeutics include serious side effects and therapy usually lasting 48 weeks with only a 50% sustained virologic response rate. A recent major advance was the development of an infectious virus system based on the transfection of human hepatoma cells with genomic HCV RNA (JFH1) isolated from a patient with fulminant hepatitis. This cell culture model also allows all stages of the HCV life cycle to be studied [50]. Antiviral properties of various benimidazole derivatives have been reported in a variety of studies using different virus strains, such as human cytomegalovirus (HCMV), human immunodefi ciency virus, and hepatitis B and C virus. Also, amidino-substituted benimidazoles, such as bis(5-amidino-2-benimidazolyl) methane (BABIM), showed ability to block respiratory syncytial (RS) virus induced cell fusion. In addition, introducing amidino moiety to benimidazole ring was shown to possess potent antimicrobial and anti-protozoal activity.

Major progress has been made in developing infectious HCV cell culture systems and these systems have been useful in identifying novel HCV anti-viral [50]. A set of heterocyclic benimidazole derivatives (29) bearing amidino substituent at C-5 of benimidazole ring, by introducing various hetero-cyclic nuclei (pyridine, N-methylpyrrole or imida-zole) at C-2, and evaluated their anti-tumor and anti-viral activities [51]. A series of 4-(1-(substituted aryl/alkyl carbonyl)-benzoimidazol-2-yl)-benzene sulphonic acids (30,31) were tested for anti-fungal activity and compounds 4-(1-(4-Nitrophenyl)-1H-benzoimidazol-2-yl) benzene sulfonic acid (32) and 4-(1-octade-9-enoyl-1H-benzoimidazol-2-yl)-benzenesulfonic acid (33) was found to be the most active ones [52]. Some benimidazoles (34) synthesized by refluxing o-phenyldiamine with corresponding carbo-sylic acids and evaluated for anti-viral activity against PRSV on plant Chenopodium amaranticolor [53]. A series of 2-arylbenimidazoles (35) were evaluated them for anti-viral activity as well as anti-proliferative. Compounds were tested in cell-based assays against viruses’ representative of: i) two of the three genera of the Flaviviridae family, i.e. Flaviviruses and Flaviviruses; ii) other RNA virus families, such as Retroviridae, Picornaviridae, Paramyxoviridae, Raboviridae and Reoviridae; iii) two DNA virus families (Herpesviridae and Poxviridae). Compounds resulted moderate activity only against Yellow Fever Virus [54]. Water-soluble benimidazole-2-one derivatives (36) with anti-viral activity in vivo in the cotton rat model of RSV infection following administration as a small parti-cle aerosol. The acidic compounds demonstrated potent anti-viral activity in cell culture [55]. A series of benimidazole derivatives (37) and substituted benimidazole β-L- and β-D-2-deoxyribonucleosides and evaluated for anti-viral activity against selected RNA and DNA viruses including HIV-1, BVDV, YFV, DENV-2, WNV, HBV, HCV and human RSV [56].

\[ \text{29, 30, 31} \]

5.3 Antimalarial activity:

Malaria caused 350-500 million clinical episodes annually and result in over one million deaths, most of which affect children under 5 years old in sub-Saharan Africa. Malaria is the fifth cause of death from infectious diseases globally (after respiratory infections, HIV/AIDS, diarrheal diseases and tuberculosis). In addition to its health toll, malaria puts a heavy economic burden on endemic countries and contributes to the cycle of poverty people face in many countries. Malaria mortality and morbidity began to increase in the 1980s due to a combination of factors such as increase in parasite and vector resistance to the current anti-malarial drugs and insecticides, the weakening of traditional malaria control programs, rapid decentralization and integration into deteriorating primary health service, and the development of humanitarian crisis situations in many malaria-endemic areas. This dramatic increase led to a compelling and urgent necessity for new malarial, with mechanisms of action different from the existing ones, and to identify new drug targets. Chloroquine has recently been shown to inhibit hemozoin formation within the parasite food vacuole. This process is also thought to be the molecular target of other quinoline anti-malarial. Hemozoin was originally considered to be formed by the polymerization of heme, but has now been demonstrated to be a crystalline cyclic dimer of ferriprotoporphyrin IX. Thus, hemozoin synthesis, a process unique to the malaria parasite, offers a logical and valuable potential target for new anti-malarial drug development. New drugs that attack the same vital target of chloroquine but that are not subject to the same resistance mechanism would be highly desirable [57].

The activity of N1-(7-chloro-4-quinoyl)-1H-benzimidazole derivative (38) against a chloroquine-resistant strain of Plasmodium falciparum in which compound is active showing promising therapeutic properties. A series of ten novel hybrids from benimidazole (40) tested in vitro against the protozoa Trichomonas vaginalis, Giardia lamblia, Entamoeba histolytica, Leishmania mexicana, and Plasmodium berghei showed good anti-malarial activity [59]. Vázquez et al. (2006) substituted a series of 2-(trifluoromethyl)-1H-Benzimidazole derivatives (41) was shows good anti-malarial activity [60]. Several series of imidazo[2,1-a] isoindol-5-ol derivatives (42) evaluated against Plasmodium falciparum [61].
6. Physical properties of benzimidazoles

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°C. 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. Evidence was obtained indicating molecular association through N-H-N bonds in those compounds possessing an unsubstituted NH group. The strength of this bond is evidently enhanced by resonance of the benzimidazole nucleus. The dipole moment of benzimidazole, the values that have been obtain being 3.93-4.08 D (in dioxane) [64].

7. Chemical properties of benzimidazoles [65-69]

Reactions of the benzimidazole ring: The benzimidazole ring possesses a high degree of stability. Benzimidazole is not affected by concentrated sulfuric acid, hot hydrochloric acid as well as alkalis. Oxidation cleaves the benzene ring of benzimidazole only under vigorous conditions. The benzimidazole ring is also quite resistant to reduction but under certain conditions the tetrahydro and hexahydrobenzimidazoles may be prepared by catalytic reduction.

Reactions involving 1 and 3-positions: Benzimidazoles form salts e.g. with acids readily forms monohydrochloride, mononitrate, monopicrate, monoacetate. Alkylation: Benzimidazoles, undergoes alkylation with alkyl halides, yielding 1-alkylbenzimidazoles and under more vigorous conditions, 1,3-diallylbenzimidazolium halides.

Benzimidazoles also react with acylating, Grignard reagents and metal. The benzimidazole also forms manich bases by reacting formaldehyde and piperidine.

Hydrogenation and dehydrogenation reactions: It was thought that benzimidazole ring was stable to reduction. Catalytic reduction of benzimidazole even under high pressure with nickel as the catalyst is reported to give negative results. 2-Phenylobenzimidazole gives only 2-cyclohexylbenzimidazole. Hydrogenation of 2-(p-dimethylaminostyryl) benzimidazole with nickel at atmospheric pressure saturates only the olefinic linkage in the 2-positions (fig 2.4).

A number of hydrogenated benzimidazoles have been prepared also by chemical methods. Hexahydro-2(3H)-benzimidazolone may be obtained by the reaction between hexahydro-o-phenylenediamine and phosgene in sodium hydroxide solution. Attempted dehydrogenation of tetrahydrobenzimidazoles with palladium sponge does not give the corresponding benzimidazole but instead a compound of high molecular weight.

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.

Halogenation: When 2,5(or 2,6)-dimethylbenzimidazole is an aqueous acid solution on treatment with saturated solution of bleaching powder at 0-5°C. 1-chloro-2,5(or 2,6)-dimethyl benzimidazole is obtained (fig 2.5).

Reactions involving the 2-methyl or methylene group: The methyl group of 2-methylbenzimidazoles is comparable in its activity to the methyl group of α-picoline, quinaldine, or methyl ketones and shows most of the same reactions of these compounds. The benzimidazoles ring, like the pyridine and quinoline ring, because of its electron attracting nature imparts a positive character to the carbon atom of the 2-methyl group. 2-Methylbenzimidazoles, for example, react with aromatic aldehydes in aldol type condensations in a manner analogous to α-picoline quinaldine.

Nitrification: The nitration of benzimidazoles proceeds readily. In most cases nitrification appears to take place preferentially at the 5 or 6 position. However, the nitro group may also enter the 4 or 7 position, especially if the 5 or 6 position is blocked.

Reactions involving substituent groups: The various useful transformations can be successfully carried out various substitutents in benzimidazoles. Some of the conversions are discussed below (fig 2.6).

Reactions of 2-benzimidazolecabonylic acids: Benzimidazoles containing a carboxyl group in the 2-positions readily undergo decarboxylation on heating. 2-benzimidazolecabonylic acid on heating above its melting point, for example, yields benzimidazoles (fig 2.7).

Reactions of 2-(α-haloalkyl)benzimidazoles: 2-(α-Chloroisopropyl) benzimidazole when refluxed in dry alcoholic solution in the presence of pyridine gives a good yield of 2-(α-ethoxisopropyl)benzimidazoles and hence reacts in a manner analogous to tritylchloride (triphenylmethyl chloride) (fig 2.8).

Reactions of 2-(3H)-Benzimidazolones: 2(3H)-Benzimidazolones (or 2-hydroxybenzimidazoles) are extremely stable treatment of substances 2(3H)-benzimidazolone is not split by treatment with benzyl chloride in alkaline solution. 2(3H)-benzimidazolones show...
many of the reactions of 2-hydroxypyridines and 2-hydroxyquinolines; for example, 2(3H)-benzimidazolone with phosphorous oxychloride or phosphorous pentachloride yields the 2-chloro-derivative.

2(3H)-Benzimidazolethiones: 2(3H)-Benzimidazolethiones or 2-mercaptobenzimidazoles are generally stable substances and are soluble in dilute alkali. Alkylation occurs readily with replacement of the mercapto hydrogen to yield S-alkylated derivatives, and a number of these derivatives have been prepared.

2-Aminobenzimidazoles: 2-Aminobenzimidazole with acetic anhydride gives 2-acetylaminobenzimidazole.

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 imidazidicarbonylic 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 prepared.

8. Methods for synthesis of benzimidazoles:

All synthesis of benzimidazoles starts with benzene derivatives possessing nitrogen-containing functional group at position ortho. Various strategies for the synthesis of benzimidazoles are discussed below.

From o-phenylenediamines

By reaction of carboxylic acid and carboxylic acid derivatives: The o-phenylenediamines react readily with most carboxylic acids to give 2-substituted benzimidazoles. Also, o-phenylene-diamines and their dihydrochlorides also react with various carboxylic acid derivatives like anhydrides, ester, amides and acid chlorides to give the corresponding benzimidazoles.

By reaction with lactones: Valerolactone when refluxed with o-phenylenediamines gives only a small amount of 1, 2-{1-methyltrimethylene} benzimidazoles.

By reaction with nitriles: Cyanogen bromide reacts with o-phenylenediamines to give 2-amino-benzimidazoles. The reaction is carried out by mixing equimolecular amounts of the reactants in aqueous suspensions.

By reaction with aldehydes: Under the correct conditions aldehydes may reacted with o-phenylene-diamines to give 2-substituted benzimidazoles. Due improvement of oxidation reaction was best carried out under oxidative conditions.

By reaction with ketones: The reaction with a number of ketones, the direct elimination of the alkyl group and of hydrogen (as R-H) may be assumed to be due to the gain in resonance stabilization on conversion to the benzimidazoles.

By reaction with imino-ethers and imino-thioethers: The synthesis of benzimidazoles from imino ethers or imino thioethers and o-phenylenediamines had been investigated. This reaction was illustrated by the preparation of 2-phenylbenzimidazole from o-phenylenediamine and benzimino methyl ether.

By reaction with amidines and guanidines: Diphenylformamidine gives an 85.5 per cent yield of benzimidazoles when heated at a about 125°C with o-phenylenediamine.

By reaction with urea: o-phenylenediamine dihydrochloride when heated with urea at 130°C gives 2(3H)-benzimidazolone.

By reaction with carbon disulfide: The reaction was carried out generally by heating the reactants in alcoholic solutions with or without the addition of alkali to the reaction mix and led to the synthesis of 2(3H)-Benzimidazolethionone.

By reaction with thiophosgene: The 2(3H)-benzimidazolothione and 5-methyl-2(3H)-benz-imidazothione by the reaction of thiophosgene on o-phenylenediamine and 3,4-diaminotoulene, respectively. The 3,4-Diaminobenzenearsenic acid thiophosgene gave 2(3H)-benzimidazolethione-5-arsenic acid.

By reaction of 2-aminobenzimidazoles: 2-Arylamidobenzimidazoles were formed by the action of diarylcarbodimides on o-phenylenediamines.

From monoacetyl- and diacetyl-o-phenylenediamines: Triacetylaminobenzene on ring closure gave 2-methyl-4(or 7)-acetylaminobenzimidazole.

By reduction of acetylated o-nitroanilines: N-substituted acetylated o-nitroanilines lead to 1-substituted benzimidazoles. N-methyl-2-nitro-o-methylacetanilide on reduction gives 1,2,5-trimethylbenzimidazole.
From \(\text{o-aminooazol compounds:}\) The \(\text{o-aminooazol compounds react with aldehydes to form schiff bases. The resulting schiff bases were undergo isomerization (boiling acetic acid) with the shifting of a hydrogen atom to form N-arylinobenzimidazoles.}

From phenyurethans: \(\text{2(3\text{H})-Benenzimidazazole was prepared by heating o-aminophenyl-urethan above its melting point [16].}

Advanced methods of synthesis of benzimidazoles: The synthesis of various benzimidazoles using a catalytic amount of \(\text{TiCl}_4\) and silica sulfuric acid under mild solvent free conditions and synthesis of 2-substituted benzimidazoles by microwave in the presence of alumina-methane sulfonic acid [70-72].

9. Conclusion

Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Benzimidazole is the heterocyclic compound formed from benzene and imidazole ring containing nitrogen, oxygen sulphur and its 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 favourable selectivity ratio. Benzimidazole nucleus is a constituent of vitamin-B12. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbial, anti-viral, anti-diabetic, anti-cancer, anti-oxidant, anti-parasitic, anti-helminthic, anti-proliferative, anti-HIV, anti-convulsant, anti-inflammatory, anti-hypertensive, anti-neoplastic, proton pump inhibitor and anti-trichinellosis. Benzimidazoles exhibit significant activity as potential antitumor agents, smooth muscle cell proliferation inhibitors, a treatment for intestinal cystitis, and in diverse area of chemistry. Some of the important benzimidazole derivatives have been reported as thyroid receptor agonist gonadotropin releasing hormone receptor antagonists, non-nucleoside HIV-1 reverse transcriptase inhibitors and interestingly allylbenzimidazoles as modulators of metabotropic glutamate receptors. The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. This comprehensive overview summarizes the chemistry of different derivative of substituted benzimidazole along with their anti-microbial activity containing anti-malarial anti-fungal, anti-bacterial, anti-viral activity. This comprehensive overview summarizes the chemistry of different derivative of substituted benzimidazole along with their anti-microbial activity.

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