INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Review Article

A REVIEW ON CHEMISTRY OF BENZIMIDAZOLE NUCLEUS AND ITS BIOLOGICAL SIGNIFICANCE

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ABSTRACT

Benzimidazole could be a heterocyclic aromatic chemical compound. it's a crucial pharmacophore and privileged structure in medicative chemistry. It plays a awfully vital role with lots of helpful therapeutic activities such as: antiulcers, antihypertensives, analgesic, medication, anti-virals, antifungals, anticancers, and antihistaminics. The review of the literature shows that the benzimidazole derivatives square measure effective compound and range of reviews on the market for organic chemistry and medical specialty studies conformed that their molecules square measure helpful against a good style of micro-organisms. Due to their importance, the strategies for its synthesis became attention of artificial Organic Chemists. Thus within the gift review we have a tendency to tried to compile the chemistry numerous by product of substituted benzimidazole further as various medical specialty activities.

Keywords: Benzimidazole, pharmacophore, anti-viral,anti-bacterial

1. INTRODUCTION

Because of their various biological activity and clinical applications benzimidazole derivatives square measure of wide interest, with relevance their restrictive activity and their favorable property magnitude relation they're remarkably effective compounds. Staring at the importance of benzimidazole, for potential biological activities it had been thought that it might be worthy to style and synthesize some new benzimidazole derivatives bearing oxadiazole moiety and screen them. In drug discovery benzimidazole ring displays a crucial heterocyclic pharmacophore. These compounds possess totally different substituent's within the benzimidazole structure square measure related to a large vary of biological activities as well as anti-bacterial, anti-cancer, anti-viral, medicine, anti-oxidant, anti-fungal, anti-helmintic, anti-histaminic, nucleon pump substance, anti-coagulant properties and anti-hypertensive. In fashionable drug discovery the benzimidazole ring is a crucial pharmacophore. In In healthful analysis the synthesis of novel benzimidazole derivatives remains a main focus. [1-3]

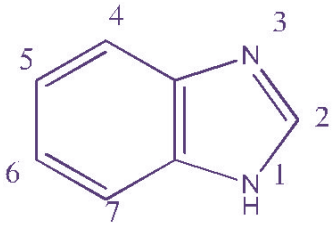

Fig: 1H-Benzimidazole

1.1 Spectral properties of benzimidazoles[4]

1.1.2 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.

1.1.3 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.

1.1.4 Nuclear magnetic resonance (NMR) spectroscopy

An important feature of this work is that the protonationparameters 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.

1.1.5 13Carbon NMR

The spectra shows different carbon peaks at range of δ0-200 compared to TMS. Forbenzimidazoles 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.

2.0 Physical properties of benzimidazoles[5]

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 . Conversely, the introduction of polar groupings into the molecule increases solubility in polar solvents . Benzimidazole distills unchanged above 300 C̊. 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.

3.0 Chemical properties of benzimidazole[6]

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 except under certain considerations.

3.1 Alkylations

Benzimidazoles, undergoes alkylation with alkyl halides, yielding 1-alkylbenzimidazoles and undermore vigorous conditions, 1,3-dialkylbenzimidazolium halides. Benzimidazoles also react with acylating, Grignard reagents and metal. The benzimidazole also forms mannich bases by reacting formaldehyde and piperidne.

Fig: Alkylation of benzimidazole

Fig. 2: shows the alkylation of benzimidazole

3.2 Hydrogenation and dehydrogenation reactions: Until very recently it was thought that benzimidazole ring wasstable to reduction. Catalytic reduction of benzimidazole even under high pressure with nickel as the catalyst is reported to give negative results. 2-Phenylbenzimidazole gives only 2-cyclohexylbenzimidazole. Hydrogenation of 2-(p-dimethylaminostyryl) benzimidazole with nickel at atmospheric pressure saturates only the olefinic linkage in the 2-positions.

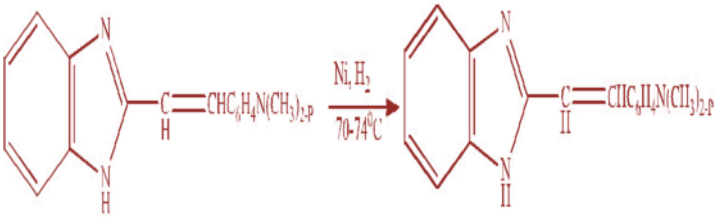

Fig. 3: shows the Hydrogenation reaction of benzimidazole

4.0 Biological significance

4.1 Antimalarial activity[7-9]

Malaria caused 350-500 million clinical episodes annually and end in over one thousand thousand deaths, most ofthat have an effect on youngsters underneath five years recent in sub Saharan Africa. protozoal infection is that

the fifth explanation for death from infectious diseases worldwide Recent estimates in order that as several asthree.3 billion folks sleep in areas in danger of protozoal infection in 109 countries. additionally to its health toll,protozoal infection puts an important economic burden on endemic countries and contributes to the cycle offinancial condition folks face
in several countries. protozoal
infection mortality and morbidity began to extendwithin the Nineteen Eighties thanks to a mixture of things like increase in parasite and vector resistance to thisanti-malarial medicine and pesticides, the weakening of ancient protozoal
infection management programs, fastdecentraliz ation and integration into deteriorating primary health service, and also the development of humanitarian crisis things in several malaria-endemic areas. This dramatic increase diode to a compelling and imperative necessity for brand new protozoal infection, with mechanisms of action totally different from the present ones, and to spot new drug targets. Cloroquine has recently been shown to inhibit hemozoin formation inside the parasite food cavity. This method is additionally thought to be the molecular target of different quinoline anti-malarial. Hemozoin was originally thought-about to be shaped by the chemical change of hematin, however has currentlybeen i ncontestable to be a crystalline cyclic variable resistor of ferriprotoporphyrin IX. Thus, hemozoin synthesis, amethod distinctive to the sporozoan, offers a logical and valuable potential target for brand new anti-malarial drug development. New medicine that attack an equivalent very important target
of antimalarial however that aren'tsubject to an equivalent resistance mechanism would be extremely fascinating.

4.2 Antifungal activity[10]

Irresistible sicknesses have been not kidding and developing debilitates to human wellbeing amid the previous couple of decades. The diminishing of sensibility to hostile to microbial operators in current use has likewise been expanding for an extraordinary assortment of pathogens and the imperviousness to various medications is increasingly common for a few microorganisms, particularly for Gram-positive microscopic organisms and some obstinate parasites. Their inhibitory properties as respect agent organisms have been widely misused. Particularly, it is qualified to note that Fluconazole, the primary line triazol hostile to parasitic medication Recommended by World Health Organization (WHO) has built up an outstanding restorative record for Candida contaminations, and turn into the principal decision in the treatment of diseases by Candida albicans and Cryptococcus neoformans because of its powerful action, great wellbeing profile, and positive pharmacokinetic attributes. Be that as it may, Fluconazole is not successful against obtrusive aspergillosis and is not fungicidal. Likewise, broad clinical utilization of Fluconazole has brought about the expanding Fluconazole-safe C. albicans detaches reported combination of a progression of novel spiro [indolethiazolidinones and screened in vitro for hostile to contagious movement against Rhizoctoniasolani, Fusariumoxysporum and Collectotrichum.

4.3 Antiviral activity[11]

Chronic infection with the hepatitis C virus (HCV) could be a major risk issue for developing liver disease and carcinoma close to third of the worldwide population is inveterately infected with HCV. A preventive vaccine has not been developed and limits of current medical specialty embody serious aspect effects
and medical aid typically lasting forty eight weeks with solely a five hundredth sustained medicine response rate. A recent major advance wasthe event of AN infectious virus system supported the transfection of human malignant hepatoma cells with genomic HCV ribonucleic acid (JFH1) isolated from a patient with sudden liver disease. This cell culture model permits all stages of the HCV life cycle to be studied. Antiviral properties of varied benzimidazole derivatives are reportable in an exceedingly style
of studies exploitation completely different virus strains, like human herpes virus (HCMV), human immune deficiencyvirus, and viral hepatitis and C virus. Also, amidino-substituted benzimidazoles, like bis(5-amidino-2-benzimidazolyl) paraffin (BABIM), showed ability to dam metastasis syncytial (RS) virus evoked cell fusion.Additionally, introducing amidino moiety to benzimidazole ring was shown to possess potent antimicrobial and anti-protozoal activity.

4.4 Antiproliferative activity[12]

A novel Schiff bases, the derivatives of 2-aminobenzimidazole and substituted aromatic aldehydes, has been reported. The Compounds were reduced by NaBH4 fashioned 2-benzylaminobenzimidazoles that were acylated

by cinnamoyl chloride gave 2-(o-bromo-benzylamino)-1-cinnamoylbenzimidazo autoimmune disease. The compounds were evaluated for antiproliferative activity in vitro.

4.5 Antitumor activity[13]

Several new nitrobenzimidazoles are rumored to possess cytotoxic activity against carcinoma. within the rumoured analysis it absolutely was conjointly acknowledged that the compounds like thiadiazole, tetrazole, triazines and imidazoles conjointly possess the activity.

4.6 Anti-inflammatory activity[14]

A series of 2- methylaminobenzimidazole derivatives were synthesized and reported by the reaction. The new synthesized compounds were screened for analgesic and anti-inflammatory activities by the writhing in mice and carrageenan induced paw oedema in rats. Another research was carried out indicating that benzimidazole on combination with iodole Skelton give potent anti inflammatory action similar to indomethacin.

4.7 Antioxidant activity[15]

Some compounds possessing dihydrochlorides have also been reported possessing antioxidant activity, these salts also possess mild platelet and erythrocyte antiaggregant activity. In another approach it was found out that using trimethyl group with benzimidazole also adds antioxidative property by 5-lipoxygenase inhibitory action.

4.8Antiprotozoal activity[16]

Another benzimidazole derivatives reported are 5, 6 dinitro and thioalkyl or thioaryl substituted compounds .These active compounds reported to possess activity against Stenotrophomonasmalthophilia. These compounds have activity related to metronidazole against gram positive and gram negative bacteria. Substituted 2-trifluorobenzimidazoles have been reported. Earlier it have reported anti-giardial activity. One of another research involves the synthesis of series of 2-(trifluoromethyl)- 1H-Benzimidazole derivatives by using Phillips cyclocondensation of a substituted 1, 2-phenylenediamine and trifluoroacetic acid. The compounds were evaluated in vitro against various protozoan parasitesnaming Giardia intestinalis, Entamoebahistolytica, Trichomonasvaginalis and Leishmaniamexicana, and they showed nanomolar activities against some of the above mentioned protozoa. The compounds were also tested in vitro and in vivo against the nematode Trichinellaspiralis.

4.9 Androgen Receptor antagonist[16-18]

Another benzimidazole derivatives are 5, 6 dichloride benzimidazole derivatives.It was found out that trifluoromethyl group greatly enhances prostrate antagonistic activity. Bicalutamide is a non steroidalantiandrogen which is prominent antiandrogen for the treatment of androgen dependantprostrate cancer.

4.10Anti cancer activity [19-21]

The syntheses of 1, 3-diarylpyrazinobenzimidazole derivatives have been reported and the investigated for their anticancer activities. For this, 2-aryloylbenzimidazole derivatives were reacted with 2-bromoacetophenones in acetone to give 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles. The resulting material was reacted with ammonium acetate in acetic acid to obtain the compound. The above process was reported to be carried out by microwave irradiation method. Another approach reported is the synthesis and evaluation of 1-(4-methoxyphenethyl)-1H-benzimidazole-5-carboxylic acid derivatives .The compound methyl 1-(4-methoxyphenethyl)-2-(4-fluoro-3-nitrophenyl)-1H-benzimidazole-5-carboxylate induced maximum cell death in leukemic cells with an IC(50) value of 3 microM.

4.11 Anti convulsant Agents[22-23]

Some potential anticonvulsant compounds have been synthesized, a series of 1, 2, 5-trisubstituted benzimidazolesderivatives 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.

CONCLUSION

Benzimidazoles are thought to be a promising category of bioactive heterocyclic compounds that exhibit a variety of biological activities like anti-microbial, anti-viral, anti-inflammatory and anti-cancer activity. This comprehensive summary summarizes the chemistry of various spinoff of substituted

benzimidazole together with their biological activities.

ACKNOWLEDGEMENT
The authors are thankful to management of Vignan Pharmacy College, Vadlamudi for providing
facilities to do this tiny research work.

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