STUDY ON MEDICINAL CHEMISTRY OF EMERGING BENZIMIDAZOLE NUCLEUS

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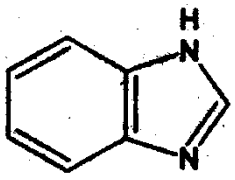
Abstract : In drugh discovery benzimidazole ring displays a crucial role of heterocyclic pharmacophore. Benzimidazole has privileged structure with meditative chemistry. Its derivatives play important role in medical field with so many pharmacological activities such as antimicrobial, antiviral, analgesic, antidiabetic, antihistaminics, anticancers and anti-hypertensive. Due to versatile importance, the strategies for their synthesis became aattention to chemists. Scientists have elucidated that Benzimidazole system possesses the variable sites likes position 2 and 5 which can be suitably modified to yield important therapeutic agents. This review is mainly summarized the research work reported in the recent scientific literature on different derivatives of substituted benzimidazoles along with their pharmacological activities.

Keyword : Benzimidazole derivatives, Antimicrobial activity, Antiviral drugs, pharmacophor.

I. INTRODUCTION

Benzimidazoles are promising category of bioactive hetercyclic compounds. Benzimidazole is bicyclic compound consists of the fusion of benzene and imidazole. It is present in numerous cellular components. Nowadays is a moiety of choice which possesses many pharmacological properties. The most prominent benzimicazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin-B_{12}. Besides their significance in biomedical research, benimidazoles also have a prominent place in other branches of chemistry due to their molecular arrangement: the imidazole may be precursor to N-heterocycliec compounds; and benzene ring provides a part on which additional functionalizations and modifications may be easily incorporated to change subsequently the electronic characteristics of benzijmidazole derivative. This rationalized fact undoubtedly progressed to the study of benzimidazoles and its derivatives.



1-H Benzimidazole

The nitrogen containing hetercyclic organic molecules are potential medicinally active chromohore. Extensive biochemical and pharmacological studies have confirmend that these molecules are effective against various strains of microorganisms. Benzimidazole derivatives are potential drugs used for the treatment of antibacterial, antiviral, anti-inflammatory, antihistaminic, analgesic, antitumor, antidabetic, anticancer, anti-HIV, antihypertensive as well as various other diseases. It is well established fact that meditional activity of organic molecule is enhanced radically on incorporation of suitable metal ions. In 1990 various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cyclized compound which resulted in compounds with increased stability,

bioavailability and significant biological activity. Metal complexes of biologically important ligands are more effective than free ones[5].

A large numbers of therapeutic agents are synthesized with the help of benzimdazole nucleus. During recent years there have been some interesting developments in the biological activities of benzimidazole derivatives. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities.

II. VARIOUS PHARMACOLOGICAL ACTIVITIES OF BENZIMIDAZOLE

1.1 Antimicrobial

In present day antibacterial and antifungal diseases are very common in the world. Currently used antimicrobial agents are not effective due to the resistance developed by the microbes and therefore it is an ongoing effort to synthesize new antimicrobial agents. Efficient syntheses of some novel potent compounds are the target to overcome problem of multi-drug resistant (MDR) bacteria and fungi resulting from the widespread use and misuse of classical anti-microbial agents. The antibacterial activity of derivatives of benzimidazoles was explained by the competitive inhibition for the synthesis of bacterial nucleic acids and proteins.

Viswanthetal[11] reported 4(1H-benzimidazol-2yl) benzene-1, 2-diol, 2(4-chlorophenyl)1H-benzimidazole and 4(1H-benzimidazol-2yl) benzene-1, 2-diolwith anti bacterial activity. Metal complexes of the ligand 2-amino acetate, 6-chloro benzothiazole with some metalions Ni(II), Cu(II), Zn(II), Cd(II) and Sn(II) were synthesized and evaluated for their anti-bacterial activities against Gram-positive and Gram-negative pathogenic bacteria were investigated using disc diffusion method, and appreciate activity were obsserve.

The benzimidazole substituted quinoline derivatives showed appreciable antibacterial activity against the organisms. Synthesis of benzimidazole as 1-(substituted-methyl)-2-(substituted-phenyl) benzimidazole was reported by Leonardo et. al. These compounds show antibacterial activity against S. aureus, B. pumillus and P. Aeurugenosa. Another efficient synthesis of novel 3-chloro-1-5-(2-methyl-1H-bezimidazole-2-yl)-4-(substituted) phenylazetidin was screened for antimicrobial activity against B. Substilis and E. coli. Reports showed that 1, 2-disubstituted-1H-benzimidazole-N alkylated-5-carboxamidine derivatives are very potent antibacterial activities against S. aureus and methicillin resistant S. aureus.

1.1.1 Antifungal

Fungal infections are termed mycoses and in divided in to superficial infections (skin, nails, and scalp) and systemic infe tions (deeper tisssues and organs) some conditions are blastomycosis, histoplasmosis, antifungal condidiasis, coccibiomycosis etc.

Two series of novel benzimidazole derivatives ewer synthesized. The first one comprise of 2-methyl, the second one comprise of 2-phenyl substitution on benzimidazole moiety. Severalnovel benizimdazole derivatives were synthesized successfully in appreciable yields and characterized physic-chemically, some of the synthesized compounds showed appreciable antifungal activity.

Synthesis of 2,3,4, -trusubstituted-1, 2-dihydropyrimido were tested for their fungicidal activities against Aspergillusniger and Penicilliumchrysogenum.

1.1.2 Antiprotozoal

These are the drugs which are used to treat theamoebiasis caused by E. histolytica. they exert cytotoxicity by damaging DNA and result in DNA belix destabilization starand breakage. The antiprotozoal drugs containing benzimidazole nucleus are metronidazole, benzidazole.

Synthesis and anti-protozol activity of 2-(trifluoromethyl)- 1H-Benzimidazole derivatives by using Phillips cyclocondensation were reported by Vazquez et. al. The com,pounds were evaluated *in vitro* against various protozoan parasitesnaming *Giardia intestinalis, Entamoebahistolytica, trichomonasvaginalisand Leishmaniamexicana,* and they showed nanomolar activities against some of the above mentioned protozoa. The compounds were also tested *in vitro* and *in vivo* against nematode *Trichinellaspiralis.*

1.1.3 Anti-Hepatitis B and C Virus

Hepatitis B virus (HBV) infection is one of the leading causes of lethal infectious diseases worldwide. There are approximately 400 million people with chronic HBV infection, with aglobal death toll of 4 million per year. Thiazolylbenzimidazole derivatives was synthesized and evaluated for their anti-hepatitis B virus (HBV) activity and cytotoxicity. Recently a large body of work reported that a set of heterocyclic benzimidazole derivatives showed promising anti-HCV activity.

Synthesis of 2-(benzylthio)-5, 6-dichloro-1-(β-D-ribofuranosyl) benzimidazoles was reported by Devivar et. al which performed antiviral activity against HSV-1 and HCMV.

1.2 Anti-inflammatory and Analgesic

It has been reported that 2-(Substituted pyridynyl) benzimidazole possess anti-inflammatory activity with reduced toxicity that of ibuprofen. Pyrazole derivatives of benzimidazole were showed excellent significant analgesic as well as anti-inflammatory activity. A novel seris of pyrazole derivatives of benzimidaole like 2-[5-(4-chloro-phenyl-2H-pyrazol-3-yl]-1H-benzimidazole was synthesized and reported.

Anti-inflammatory activity of phenyl benzimidazole was reported by Leonardo et. al. A series of N-(acridin-9-yl)-4-(benzoimidazol/oxazol-2-yl) benzamides have been reported withsignificant in vitro activit. A series of novel 2-phenylhydrazinomethyl and 2-(2-bydroxyphenyl)-benzimidazole derivatives substituted at the N1- position of benzimidazole nucleus were synthesized as well as screened for analgesic activity.

1.3 Antiulcer

These drugs inhibit both basal and stimulated gastric acid secretion. Some drugs containing benzimidazole nucleus are Pantoprazole, Rabeprazole, Lansoprozole, Omeprazole etc. substituted benzimidazoles are potent inhibitors of Parietal cell proton pump, the H^+/K^+ ATPase, the substituted benzimidazolewss are capable of blocking gastric acid secretion in response to some stimuli. Sulfoxide group, methylene group with heterocycles is important for above activity. Series of novel pyrimidyl-thio-methyl-benzimidazole and pyrimidyl-sulfinyl-methylbenzimidazole were synthesized and reported with antiulcer activity.

Patil et.al synthesized 2-[5-substituted-1-Hbenzo(d) imidazolyl-2-ylsulfinyl] methyl 3-substututed quinozoline-4-(3H) derivative was synthesized and tested for anti-ulcer activity.

1.4 Antioxidant

Some benzimidazole derivatives possessing dihydrochlorides have 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.

Synthesis of some 6-flouro-5-substituted benzimidazole were reported by Alagozet et.al, in which indole and 1,4,4,4-tetramethyl-1,2,3,4-tetrahydro naphthalene groups were attached to the 2-position ring and tested for antioxidant activity. These compounds showed strong super scavenging effect on superoxide anion at 10^{-3}M concentration.

1.5 Anticonvulsantand Antidiabetic

Some potential anticonvulsant compounds with benzimidazole nucleus have bewen synthesized. A series of 4-thiazolidinones and 1,3,4-oxadiazoles containing 2-mercaptobenzimidazole derivatives were synthesized and screened for in vivo anticonvulsant activvity. By maximal Electroshock (MES) model and antidiabetic activity using OralGlucose Tolerance Test (OGTT). Synthesis of a series of novel and functionalized benzimidazolew derivatives was reported by Kumar et.al shown anti-diabetic activities. Efforts are still going on in the search of new benzimidazole derivatives that are pharmacologically effective and safe as anti-diabetic agents.

1.6 Anti-Asthmatic

Kumar et. al were reported some benzimidazole derivatives with potential anti-asthmatic activity. Compounds were tested against PDE-IV for potential anti-asthmatic effect. Recently N-substituted 2-(4-styrylphenyl)-1H-benzimidazole were synthesized and screened for their potential anti-bacterial, anti-asthmatic and anti-diabetic properties.

1.7 Anthelmintic

These are the drugs that either kill or expel infesting helminthes. Some drugs containing benzimidazole nucleus are Thibendazole, Mebendazole, and Albendazole etc. these may also be called as vermifuges (stunning) or vermicides (Killing). Studies showed 2-phenylbenzimidazole has potential anthelminitic activity. In literature 2-benzimidazole carbamic acid methyl ester dervatives were peproted with anthelmintic activity against *Nippostrongilus*, *Ankilostoma* and *Haemonhus*.

1.8 Anti-Psychotic Agents

In psychosis thinking of patient becomes illogical, bizarre and loosely organized. Patienthas difficulty in understanding reality and theirown conditions. Some antihypertensive drugs containing benzimidazole nucleus are droperidol, pimozide and benperidol. A series of novel benzimidazole-based 1,3,4-oxadiazole-1,2,3,-triazole conjugates has been synthesized and evaluated for GSK-3β inhibitory antidepressant activity *in vitro*. Compounds exhibited significant inhibition.

1.9 Anticancer

A dose of anticancer drugsufficient to kill tumour cells is often toxic to thenormal tissue and leads to many side effects, which in turn, limits its treatment efficacy. In recent years, there has been a concerned search for the discovery and development of novel selective antitumoragents. On the basis of exhaustive literature review, it has been found that benzothiazole derivatives have good potential to exhibit anticancer activity.

A series of new 2,6-disubstitued benzothiazol derivatives were synthesized and their anti-cancer activities were reported.

III. CONCLUSION

The comprehensive summary indicates a wide spectrum of pharmacological activities exhibited by Benzimidazole nucleus. The knowledge gained by various researches has suggested that substituted

benzimidazoles, which are the structural isosterses of nucleotides, allow them to interact easily with the biopolymers, possess pharmacological activity with lower toxicities. With proper designing and structure activity relationship studies of known benimidazole, prospective compounds can be designed and synthesized with diverse of biological activity.

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