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A Brief Review on History Synthesis Mechanism of Action of Benzimidazole

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Abstract: *In the last 2-3 decades, the broad research in the application of benzimidazole derivatives made it important for mankind. Benzimidazole, a fused heterocycle bearing benzene and imidazole has gained considerable attention in the field of contemporary medicinal chemistry. benzimidazole and its derivatives have evolved as vibrant heterocyclic systems due to their potency in a wide range of bioactive compounds like analgesics, antifungals, anti-inflammatory, antihypertensives, proton pump inhibitors, anti-HIV, antiviral and so on. Benzimidazole is considered a privileged moiety for the development of molecules with therapeutic potential. Over the years several drugs viz: albendazole, pantoprazole, astemizole, telmisartan, thiabendazole, and benomyl have been developed by optimizing benzimidazole-based structures. In the present study, a series of novel benzimidazole derivatives containing chrysanthemum acid moieties was designed and synthesized. A series of benzimidazole derivatives was developed and its chemical scafolds were authenticated By NMR, IR, elemental analyses and physicochemical properties. The synthesized compounds were screened for their Antimicrobial activity.*

Keywords: Benzimidazole, Biological activity, History Mechanism of action

I. INTRODUCTION

The natural use of benzimidazole core is found way back in 1944 when Woolley hypothesized that benzimidazoles look like purinelike construction and evoke some organic application. [2]. A preferred IUPAC name is 1H-1,3 Benzimidazole.The utilization of Benzimidazole began numerous years back in 1990 ahead, and countless benzimidazole analogs amalgamation were accounted for, Which brought about expanded strength, bioavailability, and huge natural action. recent years, benzimidazole compounds have emerged as a hot research topic due to their varied biological activities.Benzimidazole derivatives have developed a considerable interest in the medical field due to their therapeutic action as antimicrobial , antitumor , antihelmintic , antihistaminic , proton pump inhibitors,anti-inflammatory , anticancer,antioxidant, and antihypertensive drugs.

History of Benzimidazole

Year	Biological activity reported
Year	Goodman and Nancy Hart published the first paper on antibacterial properties of benzimidazole Biological Activity
1944	Woolley published their work on benzimidazoles He also reported the antibacterial activity of synthesized benzimidazoles against E. coli and Streptococcus lactic.
1950	CIBA pharmaceutical (now Novartis) were discovered benzimidazole derivative opioid agonist etonitazene.
1960	Fort et al. reported the discovery of benzimidazole derivatives as proton pump inhibitors .
1965	Burton et al. Reported 2-trifluoro benzimidazoles are potent decouplers of oxidative phosphorylation in mitochondria. They are also inhibitors of photosynthesis, and some exhibit appreciable herbicidal activity.
1971	Mebendazole was discovered by Janssen pharmaceutical in Belgium.

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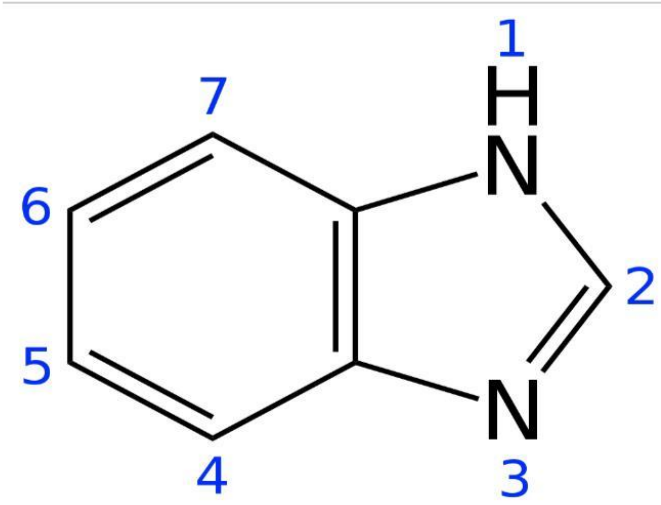
1975	Albendazole was invented by Robert J. Gyurik and Vassilios J. Theodorides and assigned to SmithKline Corporation.
1977	Astemizole was discovered by Janssen pharmaceutical .

Physical and chemical properties



Molecular Formula: C7H6N2
Molar mass: 118.14 g/mol
Classification: Organic compound
Melting point: 170 to 172 °C (338 to 342 °F; 443 to 445 K)
Form :Crystalline Powder or Crystals
Pka : 5.532(at 25℃)
Color : Beige to brown
Water Solubility : sparingly soluble

Chemistry

Benzimidazole is a six-membered bicyclic heteroaromatic compound in which Benzene ring is fused to the 4- and 5-positions of the imidazole ring.

Material and Methods

Preparation. Benzimidazole is produced by condensation of o-phenylenediamine with formic acid, or the equivalent trymethyl orthoformate

$C6H4(NH2)2 + HC(OCH3)3 \rightarrow C6H4N(NH)CH + 3\ CH3OH$

2-Substituted derivatives are obtained when the condensation is conducted with aldehydes in place of formic acid, followed by oxidation .

Procedure:

Dissolve 27gm ef o-phenylenediamine in a round boomed flask of 250m and add 17.5gm of formic acid.Heat the mixture on a water bath at 100°c for 2 hrs Cool and add 10% sodium hydroxide solution slowly, with constant rotation of the fask, and the mixture is just alkaline to litmus. Filter off the synthesized crude Benzimidazole by using the pump, wash with ice cold water, drain well and wash again with 25ml at cold water.

Recrystallization with dissolve the synthesized product in 400ml of boiling water. Add 2gm of decolorizing carbon and digest for 15min. filter rapidly through a preheated Buchner funnel and a flask at the pump Cool the filtrate tio about

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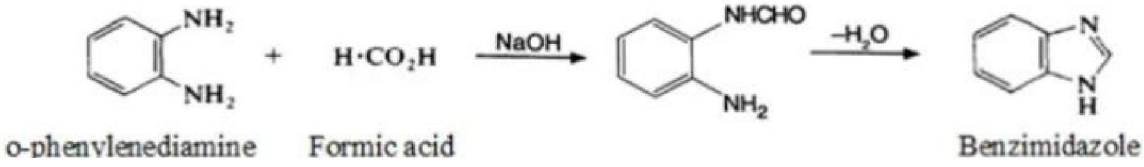
100°c filter off the Benzimidazole, wash with 25ml of cold water and dry at 100°c The yield of pure Benzimidazole, is 25g M.P. points 171 – 172°c.

Reaction



Mechanism of Action of Benzimidazole

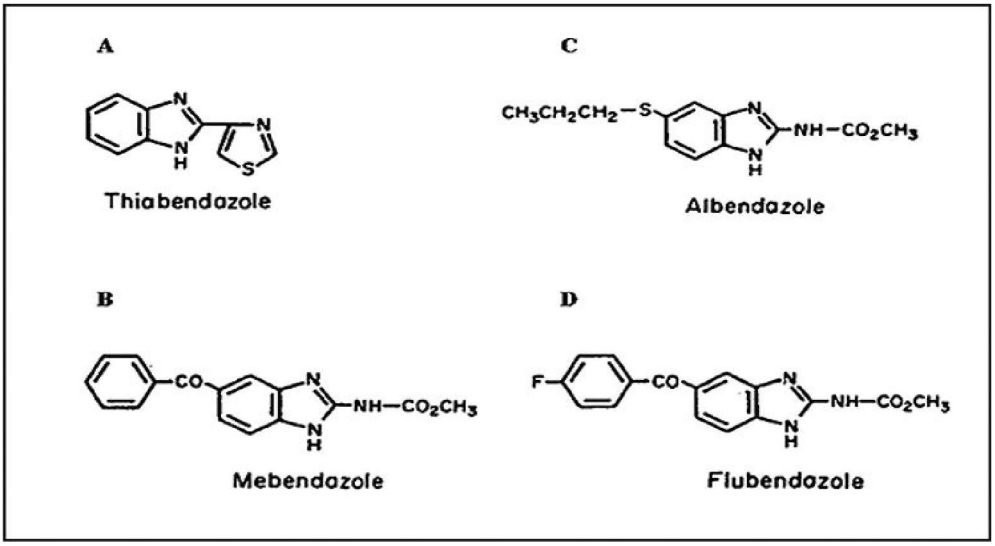
Thiabendazole was the first benzimidazole anthelmintic agent produced. Since the introduction of thiabendazole in 1961, a number of benzimidazoles with improved efficacy and extended spectrum of action have been developed.These include mebendazole, albendazole and flubendazole. The initial mode of action of benzimidazoles was thought to be inhibition of various parasite metabolic enzymes including fumarate reductase and malate dehydrogenas. However, it is now established that benzimidazoles selectively bind with high affinity to parasite β-tubulin and inhibit microtubule polymerization. This results in the destruction of cell structure and consequent death of the parasite.

Biological activity of Benzimidazole

Anticancer Activity

Among the anticancer drugs discovered in the recent years,Different benzimidazole derivatives occupy an important place.The current review accounts the anticancer activity of Benzimidazoles reported after 2013. The benzimidazole Derivatives with anticancer. A series of substituted benzimidazole derivatives were Evaluated for in vitro anticancer activity in human lung Adenocarcinoma A549 cell line at normoxic and hypoxic Conditions. Compound 230 was found to be the most Cytotoxic agent with hypoxia/normoxia cytotoxic coefficient of 4.75, compared to standard tirapazamine. The benzimidazole-thiazole. Derivatives 231–232 showed notable anticancer effect against human liver carcinoma cell line (HepG2: IC50 0.518 and 0.578 mM) and pheochromocytoma of the rat adrenal medulla Cell line (PC12: IC50 0.309 and 0.298 mM).

Antiviral Activity



The antiviral properties of benzimidazole derivatives have been tested against different viral strains; human immunodeficiency Virus (HIV), hepatitis B and C virus (HBV and HCV), Enteroviruses, respiratory syncytial virus

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(RSV), human Cytomegalovirus (HCMV), bovine viral diarrhea virus (BVDV) and herpes simplex virus-1 (HSV-1) are some to Mention (Abu-Bakr et al., 2012). This section focuses on the recent studies involving varied antiviral properties of Different benzimidazole derivatives.

Benzimidazole Against HIV

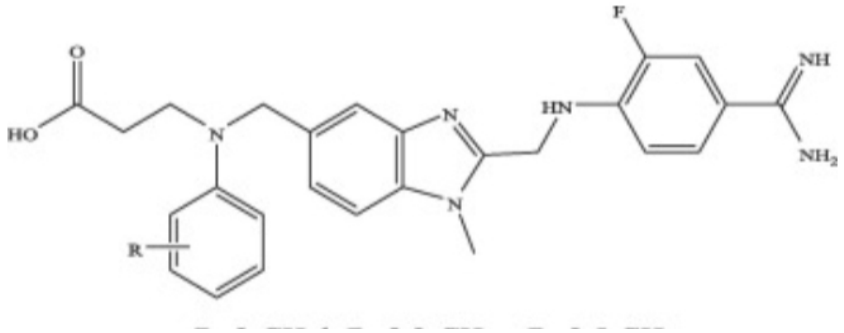
A number of substituted benzimidazole derivatives were Synthesized as reverse transcriptase inhibitors (RTIs) against HIV-1 replication, among them compounds 97–98 showed Notable antiviral activity against laboratory-adapted strains HIV-1IIIB and HIV-1Ada5 (EC50 15.4–40 µM) and primary Isolates of HIV-1UG07O and HIV-1VB59 strains (EC50 5.28–31.86 µM) (Singh et al., 2015). Besides, Ferro et al. (Ferro Et al., 2017) synthesized two series of N1-aryl-benzimidazol-2-One derivatives as non-nucleoside reverse transcriptase Inhibitors (NNRTIs) against HIV-1, where the compounds 99–100 were more potent than the standard drug nevirapine (IC50: 1.3 and 0.79 vs. 1.55 µM). The sulfone derivatives, synthesized by the same research group were also Found to be potent HIV-1 NNRTIs with IC50 values of 47 and 50 nM, respectively. The substitution at C-4 position of the Arylacetamide portion of the compounds might have Contributed for their notable activity against HIV-1IIIB Strain in cell-based assays (Monforte et al., 2018). Finally,Srivastava et al. (Srivastava et al., 2020) has recently reported Promising anti-HIV benzimidazole derivative 103 with a low IC50 value of 0.386 × 10–5 µM.

Anticoagulants

Anticoagulants are used to prevent the formation of blood clots. Conditions and diseases like heart attack, stroke, atrial fibrillation, pulmonary embolism and deep venous thrombosis requires anticoagulant treatment to reduce the risk of blood clots.

Yang Haoran et al.were synthesized 1,2,5-trisubstituted benzimidazole fluorinated derivatives and tested for anticoagulant activity. Compounds (34a, 34b and 34c) with IC50 values of (2.26 ± 0.38), (1.54 ± 0.09) and (3.35 ± 0.87) nmol/L, respectively exhibited better anticoagulant activity than argatroban, of which the IC50 values was (9.88 ± 2.26) nmol/L. It is observed that methyl substituent at the ortho position of the benzene ring is beneficial for anticoagulant activity.

II. CONCLUSION



Benzimidazole is an important heterocyclic Pharmacophoric moiety for the discovery of new drugs. A number of research Work is going in the development of benzimidazole containing bioactive molecules. This article highlights the History Synthesis and Mechanisms of Action of Benzimidazole .

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