

SYNTHESIS AND BENZIMIDAZOLE DERIVATIVES POTENTIAL ACTIVITY AS ANTI-ULCER AGENTS

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ABSTRACT

The present work aimed to study the therapeutic significance of various substituted benzimidazole derivatives in the treatment of peptic ulcers. Benzimidazoles represent a privileged heterocyclic scaffold of significant importance in medicinal chemistry due to their broad spectrum of biological activities. This review highlights the therapeutic applications of benzimidazole and its derivatives, focusing on their roles as potential agents in the treatment of diverse diseases. Benzimidazole is a recognized nitrogenous heterocycle renowned for its many pharmacological and biological properties. In medicinal chemistry, its core structure is a privileged scaffold, and many of its derivatives have promising therapeutic applications. This review presents a comprehensive analysis of biological activities, physicochemical characteristics, and synthetic approaches of benzimidazole and its derivatives, and their anticancer, antimicrobial, anti-inflammatory, antioxidant, antiparasitic, antiviral, antihypertensive, antidiabetic, and neuroprotective activities are reported. This article also reviews recent industrial applications, with special reference to hydrogen storage and environmental sustainability. molecular docking, and molecular dynamics simulation, are particularly emphasized because they can be instrumental in understanding structure–activity relationships and rational drug design. In summary, the present review describes the importance of new benzimidazole derivatives, which are considered a different class of multitarget agents in medicinal chemistry and computational drug design.

KEYWORDS: heterocyclic compounds; benzimidazoles; biological activity; molecular docking.

1. INTRODUCTION

The benzimidazole moiety sparked popular interest in 1944 when Woolley's research revealed that it shared structural similarities with biotin and purines, meaning it could function similarly to purines in inducing certain biological reactions. However, Brink later identified 5, 6-dimethylbenzimidazole as a vitamin B12 degradation product and discovered that several of its derivatives had activity similar to that of vitamin B12. Despite this breakthrough, it was not taken seriously. Certain compounds of substituted benzimidazoles have notable antifungal activity,^[1] according to a 1952 study by Jerchel, et al. Due to its structural similarities to several moieties found in vitamins, proteins and nucleic acids,

the benzimidazole structure has drawn and continues to draw a great deal of interest from medicinal chemists. Benzimidazoles have a significant role in both synthetic and biological medicinal chemistry approaches. Periodically, a number of review publications on the benzimidazole moiety and its many biological actions are released.^[2]

The disorders Zollinger-ellison syndrome, duodenal ulcer, gastric ulcer, gastroesophageal reflux disease and peptic ulcer are becoming more common worldwide, especially in poorer nations. Approximately 10% of the global population is impacted and a survey conducted in 2015 revealed 267,500 deaths.^[3]

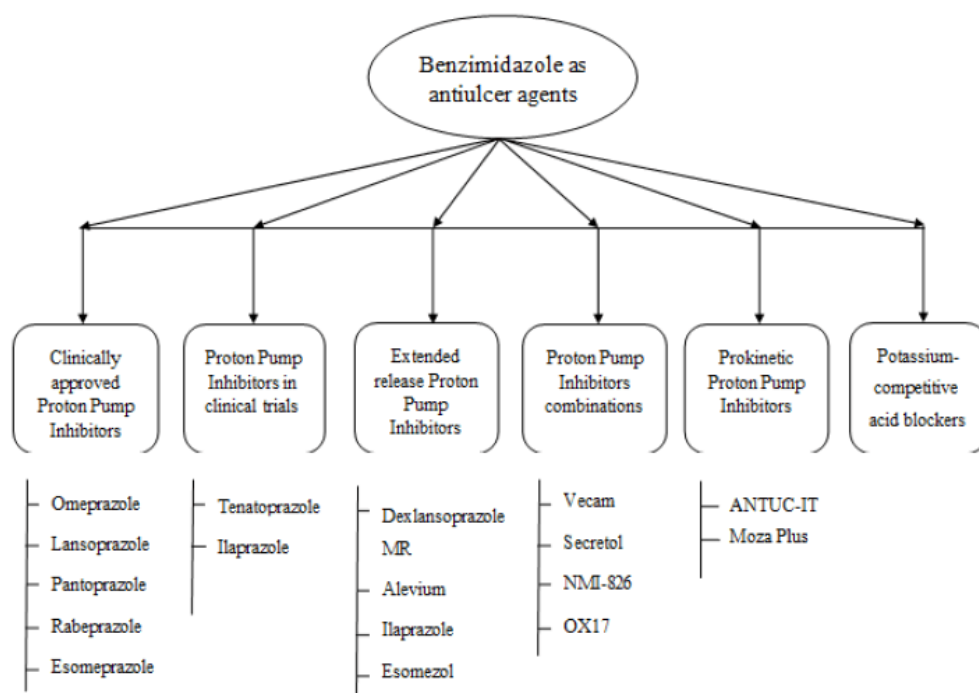


Figure 1: Benzimidazole derivatives as antiulcer agents.

A class of heterocyclic, aromatic chemicals known as benzoimidazole shares a basic structural feature: Six-membered benzene fused to a five-membered imidazole.

It contains hydrogen bound to nitrogen at the 1-position, which causes hydrogen to tautomerise in benzimidazole.^[4]

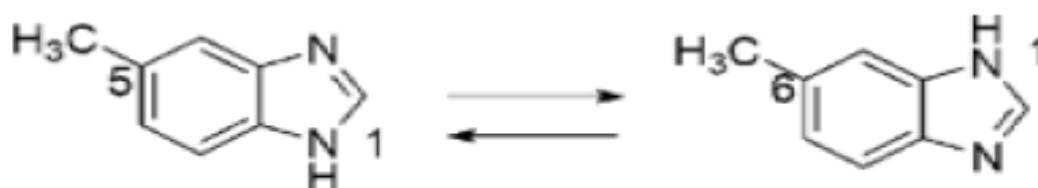


Figure 2: Benzimidazole as tautomers.

These two are tautomers even though they appear to be isomers. A tautomer of 6- methylbenzimidazole is 5-methylbenzimidazole. Ring nitrogens are important because they use a range of forces to interact with different types of receptors and enzymes in biological systems. In benzimidazole, the NH group at position 1 has a weak basicity and is comparatively strongly acidic.^[5]

2. Chemistry of Benzimidazole

Benzimidazole is a heterocycle formed by fusing a benzene ring with an imidazole ring (Figure 2).^[6] Benzimidazole derivatives are an important class of drugs because of their characteristic chemical and biological properties. They have been the centre of interest for medicinal chemists and pharmacologists. These derivatives are the basis of a vast array of drug compounds that can be used to fight a wide variety of

diseases, from things like bacterial and fungal infections to long-term and complex diseases like cancer and high blood pressure. These are structurally versatile molecules with wide-ranging biochemical activity that makes them capable of interacting efficiently with many biological systems, allowing them to serve as multitarget drugs.^[7]

3. Benzimidazole derivatives SAR

The majority of benzoimidazole derivatives with antiulcer properties are in the class of proton pump inhibitors. In the realm of antiulcer medications, PPIs offer a novel strategy for the efficient suppression of stomach acid production. The first was omeprazole, which was released in 1988. With their SAR study, pantoprazole 5, rabeprazole 6, lansoprazole 3 and omeprazole 4 are now well-established proton pump inhibitors.^[8]

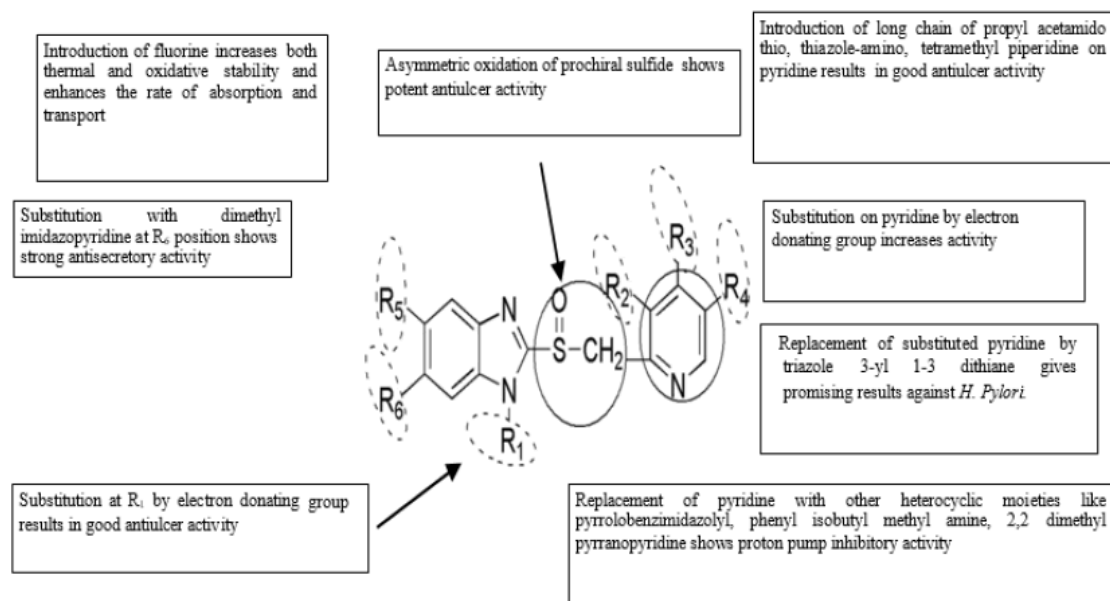


Figure 3: Benzimidazoles as clinically approved Proton Pump Inhibitors (PPIs) with their SAR study.

According to the structure-activity relationship study, strong antiulcer agents have been produced by substituting different substituents at positions 1, 2, 5 and 6 of the benzimidazole nucleus. On the other hand, the nucleus's positions 3, 4 and 7 are empty Benzimidazole's 1-position can be left unsubstituted or can have aryl or heteroaryl moieties suitably substituted with groups that donate electrons. Similarly, good antiulcer activity is obtained by introducing a long chain of propyl, acetamido, thio, thiazole-amino and tetramethyl piperidine on the pyridine ring at position 2. PPI activity is observed when pyridine is substituted with other heterocyclic compounds such as pyrrolobenzimidazolyl or phenyl isobutyl methylamine. Dimethylimidazopyridine has a potent antisecretory effect. The nucleus's 5 or 6 positions may be unsubstituted or substituents may come from functional groups like halogens. Omeprazole^[9] was a breakthrough drug discovered in 1979. It was reported to be the most

potent substance and did not cause any significant side effects in the initial animal repeat-dose toxicity studies. Its effectiveness in humans was initially documented in 1983. Literature review shows that in an acidic environment, omeprazole is converted to its sulfenic acid and sulfenamide derivatives, which then form a covalent disulfide bond with the Cys 813 sulfhydryl group. Additionally, it was discovered to be beneficial in the management of persistent Zollinger-Ellison syndrome. The most promising antiulcer drug, lansoprazole 4, was discovered by Kubo, et al. in 1990. It possesses cytoprotective, antisecretory and antiulcer properties that outperform those of omeprazole. The drug pantoprazole^[10] was produced by substituting certain functional groups on the pyridine ring, such as methyl and trifluoroalkoxy with methoxy. This resulted in a drug with increased stability and potency comparable to omeprazole 3 and lansoprazole.^[11]

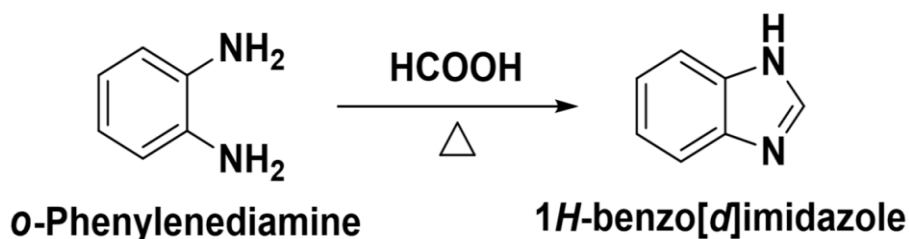


Figure 4^[12]

4. Methods for Preparing Benzimidazole Derivatives^[13]

Several approaches have been reported for the synthesis of benzimidazole analogues, which have demonstrated potency towards the targeted compounds at a higher degree of purity. The most direct method is the condensation of a monomer such as *o*-phenylenediamine and formic acid, as demonstrated in Scheme 1.^[14] Building on this, innovative synthetic techniques have emerged that address many of the limitations associated with traditional methods, offering improved efficiency,

milder reaction conditions, and greater selectivity. Such advancements have paved the way for the development of diverse benzimidazole derivatives, each tailored for specific biological activities or pharmaceutical applications. In the following subsections, we will delve into some of the most notable synthetic strategies, detailing their mechanisms and advantages, and highlighting recent advancements that have significantly streamlined the preparation of these valuable heterocycles.^[15]

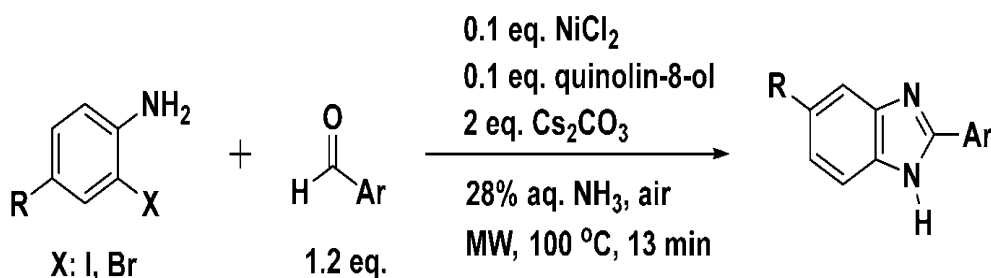


Scheme 1 Synthesis of benzimidazole.

4.1 Synthesis of Benzimidazole from 2-Haloanilines^[16]

Efficient and convenient one-pot synthesis of *N*-substituted benzimidazoles using a nickel catalyst was developed. This approach involves the condensation of 2-haloanilines with different aldehydes with the aid of

ammonia as the source of nitrogen. The reaction is catalysed by nickel, and C-N bond construction is efficiently realized, affording the corresponding benzimidazole compounds in good to high yields (Scheme 2).^[17]



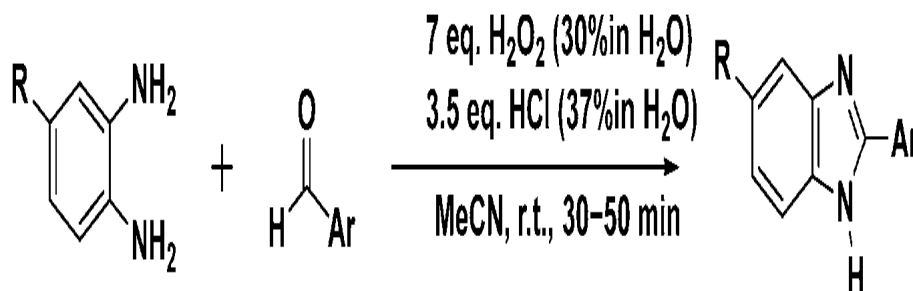
Scheme 2 Synthesis of benzimidazole derivatives from 2-haloanilines.

4.2 Synthesis of Benzimidazole from *o*-Phenylenediamine^[18]

4.2.1. Reaction with Aldehydes^[18]

The synthesis of benzimidazole derivatives was achieved in a one-pot manner from *o*-phenylenediamines and various aryl aldehydes using H₂O₂/HCl as catalysts under

solvent-free conditions at room temperature, or in acetonitrile via single-step condensation. This process affords a range of benzimidazole products with rapid reaction kinetics, easy workup, and high yields (Scheme 3).^[19]

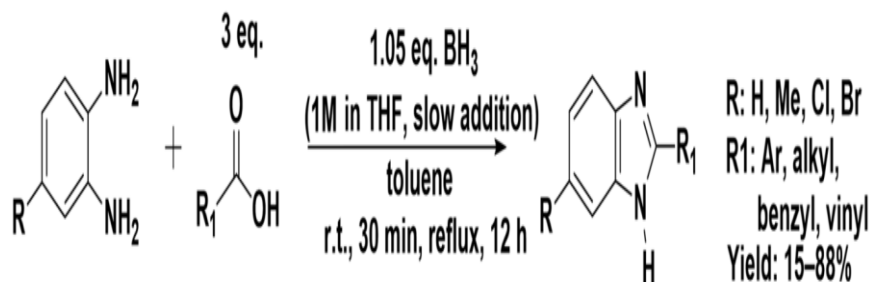


Scheme. 3: General one –post condensation of *O*-phenylenediamine with substituted aryl aldehydes to afford a series of benzimidazole derivatives Synthesis of benzimidazole

4.2.2. Reaction with Carboxylic Acids^[20]

Some reports in the literature showed that benzimidazoles and their derivatives can be prepared by

the condensation of various carboxylic acids and *o*-phenylenediamine or its derivatives (**Scheme 4**).^[21]



Scheme 4. Condensation of *O*-phenylenediamines with carboxylic acids to prepare benzimidazoles.

5. Green Synthesis^[22]

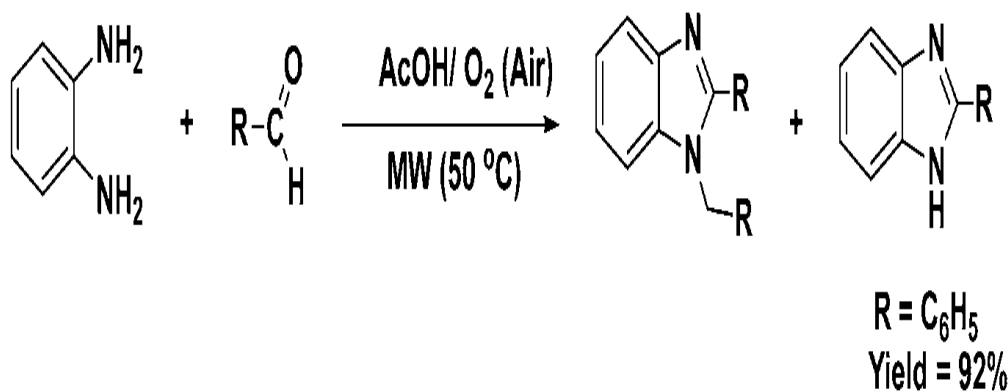
With the rapid development of green chemistry, designing processes that reduce the use of environmentally harmful substances has become one of the main goals of scientific research in the modern era. These principles were established in the 1990s as sustainable solutions aimed at reducing the risks associated with conventional chemical processes, which contribute to environmental pollution through toxic gases and difficult-to-treat secondary waste. Thus, the methods of manufacturing chemicals have been reconsidered to achieve a balance between industrial development and environmental protection. In this context, a set of alternative technologies has been adopted to prepare organic compounds, which are essentially based on improving the quality of products and reducing the resulting waste, in addition to saving energy in chemical processes. Among these advanced technologies, the following have shown great effectiveness.^[23]

Microwave technology, which is used to accelerate chemical reactions and save time and energy.

Photochemical reactions, which are catalysed by light and allow for improved productivity in safer environments; Reactions in aqueous medium, which is an environmentally friendly solvent, instead of toxic materials;

Ultrasound methods, which are used to accelerate organic reactions and make them more efficient; Catalytic reactions, which rely on chemical catalysts to increase the reaction rate and reduce the need for additional materials.

The use of microwave technology is among the most efficient modern methods for preparing benzimidazole derivatives. This technique has proven highly effective in accelerating condensation reactions between *ortho*-phenylenediamine and aldehydes in the presence of acetic acid as a catalyst (**Scheme 5**).^[24] This method is characterized by its rapid reaction time and the use of non-toxic solvents, making it environmentally friendly. It also contributes to a significant increase in the reaction yield, reflecting its simultaneous economic and environmental efficiency. A catalyst-free synthetic route has also been discussed, in which *o*-phenylenediamine reacts with aldehydes under thermal conditions without any added catalyst, producing benzimidazole derivatives with good yields and minimal waste generation. These modern methods for preparing organic compounds represent an important and advanced step toward achieving the goals of green chemistry, given their prominent role in improving traditional chemical processes while preserving the environment and reducing negative impacts.^[26]



Scheme 5: preparation of benzimidazole using the microwave technique.

6. Molecular Docking Techniques^[27]

Molecular docking is an essential tool for investigating the interaction mechanism between small molecules (ligands) and target proteins. This method estimates, by simulating the binding energy between the molecule and the protein active site, how a molecule binds to a protein active site.^[28]

Applications of Molecular Docking in Benzimidazole Derivatives^[29]

Molecular docking is one of the useful computational approaches for the prediction of how benzimidazole derivatives interact with target proteins, including EGFR and HER2. It has been reported that derivatives can block the signals that promote the growth of tumours for

cancer treatment. Calculations performed by means of the molecular docking technique led us to deduce that derivatives bearing functional groups, ketones or amines, possess an ability to interact strongly with target proteins; they achieve very low binding energies, displaying the stability of the interaction with the active site of the protein. This stability within the interaction is one of the crucial aspects making the compound effective in terms of its interference with cancer-related biological processes.^[30] Some of the benzimidazole derivatives have been reported to be promising anticancer drug candidates via molecular docking studies. reports the interactions of these derivatives with the active sites of target proteins.^[31]

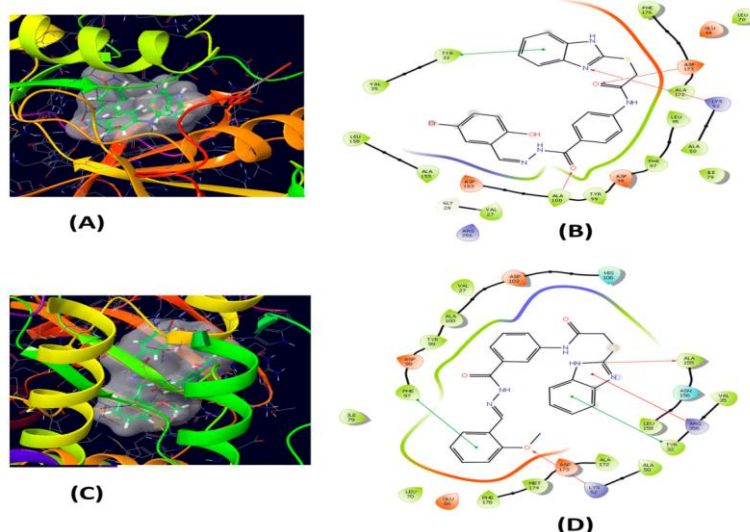


Figure 5: Molecular interactions of benzimidazole derivatives: (A,B) show ((E)-2-((1H-benzo[d]imidazol-2-yl)thio)-N-(4-(2-(5-bromo-2-hydroxybenzylidene)hydrazine-1-carbonyl)phenyl)acetamide) while (C,D) show ((E)-2-((1H-benzo[d]imidazol-2-yl)thio)-N-(4-(2-(2-methoxybenzylidene)hydrazine-1-carbonyl)phenyl)acetamide) interacting with the active sites of target proteins.^[32]

his work emphasizes the potential of designed benzimidazole derivatives to form stable and effective molecular interactions that, in turn, can be promising in the development of cancer therapeutics.^[33] In addition, molecular docking has been employed to assist in designing new inhibitors from these compounds, where the molecular structures could be modified through the introduction of functional groups, increasing the selectivity of the target protein and thus enhancing the therapeutic effects. Toxicity is minimized by the discovery of compounds that interact more favourably with the biological targets without affecting healthy tissues. In that sense, molecular docking provides an excellent roadmap for the prospective design and development of new and safer drugs that can more accurately pinpoint cancerous cells or other biological targets.^[34]

7. Biological Activity of Benzimidazole Derivatives^[35]

Since their first preparation, benzimidazole derivatives have been associated with a wide range of biological

applications, owing to their high efficiency proven by scientific research over the years.^[36,37,38] The following are the most important biological applications in which benzimidazole derivatives have been used as basic components.^[39]

8. Benzimidazole antiulcer agent^[40]

Created new substituted benzimidazole derivatives and used pharmacological screening to look for H⁺ K⁺ ATPase inhibitors and antiulcer properties. Comparing certain compounds to the standard drug, such as 12c (74.03%), 12f (72.87%) and 12i (75.15%), they demonstrated highly significant antiulcer activity; similarly, compound 12c (88.88%), 12d (91.03%), 12f (86.48%) and 12g (84.21%) demonstrated highly significant antisecretory activity. Khan, et al., synthesized the 2-mercaptobenzimidazole amino acid conjugates and assessed them biologically. Compounds 13f and 13j demonstrated a noteworthy anti-ulcer effect, while compounds 13g and 13k demonstrated an anti-secretory effect. Analogs of benzimidazole piperazine

conjugated compounds were reported and their in vivo antiulcer activity was evaluated. Out of all the synthesized analogs, compound 24 exhibited the strongest antiulcer properties. To determine the function of various functional groups accountable for increased activity, SAR research was also conducted. It was revealed that the activity of the 4-methoxy phenyl substituted for piperazine and attached to the benzimidazole moiety was caused by its electron-donating property. A group of 3,4,5-trimethoxybenzylbenzimidazole derivatives with anti *H. pylori* activity were reported by Chang, et al. Compound 2-fluorophenyl-5-methyl-1-(3,4,5-trimethoxybenzyl)benzimidazole 25, the most potent of the series, was found. Additionally, an in vitro investigation revealed its mode of action, which involved FMTMB preventing *H. pylori* from adhering to and invading gastric epithelial cells.^[41] By inhibiting stomach H^+ / K^+ ATPase, derivatives made from pyrimidine and benzimidazoles were assessed for their antiulcer and antisecretory properties. The control dose was acetylsalicylic acid. When compared to the standard medication pentaprazole, sulfoxides 26(a-d) demonstrated good antiulcer activity with lower toxicity and compound 26(c,d) demonstrated good antisecretory activity. reported and screened a series of 2-[(2-pyridylmethyl)sulfinyl]benzimidazole derivatives for H^+ / K^+ ATP enzyme inhibitors in 2011. Compound 27 showed notable in vitro activity within the series, with an IC₅₀ value within the range of 1.6×10^{-5} M when compared to the reference medication, omeprazole.^[42]

9. Proton pump inhibitors^[43]

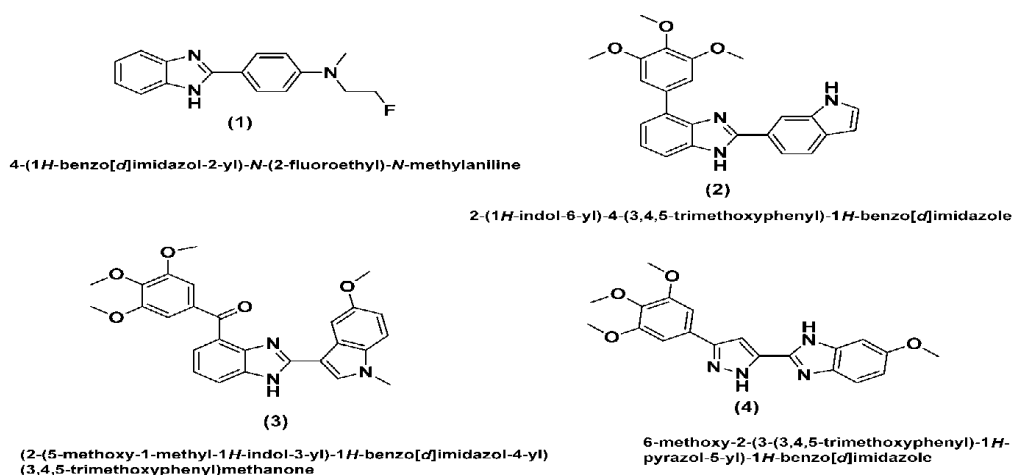
The controlled and prolonged drug release of these PPI formulations with extended release makes them popular. Takeda pharmaceuticals sells the dual delayed-release formulation of dexlansoprazole (the R-enantiomer of lansoprazole), known as dexlansoprazole MR 8. The medication comes in capsule form, each containing two different kinds of granules with a coating that dissolves at a different pH of 6.8 and 5.5, respectively. Unlike

other delayed PPIs, it can be taken without consideration for meals.^[44] The omeprazole prodrug AGN201904-Z (Alevium) 9 is acid-stable. It therefore has a long plasma half-life and does not need an enteric coating to protect itself from acid. It is quickly hydrolyzed to omeprazole in vivo. Ilaprazole: Ilaprazole 10, also known as compound IY-81149, shares chemical similarities with lansoprazole and omeprazole. It undergoes extensive metabolism to produce ilaprazole sulfone as the main metabolite. The patent license for ilaprazole in China (license ID: CN 1121714 A) is held by Livzon Pharmaceutical Group Inc. (China), who is currently developing the drug after Il-Yang (South Korea) synthesizes it.^[45]

10. Anticancer Activity^[46]

Cancer is the second leading cause of death worldwide, prompting scientists to develop effective compounds to be applied as anticancer drugs. To be effective, these compounds must have high selectivity and target only cancer cells without harming healthy cells. Although many previously developed anticancer drugs have shown efficacy against cancer cells, they have caused significant damage to normal cells as well. The challenge of the toxic side effects of chemotherapy has aroused the interest of researchers to find safer and less harmful alternatives. In this context, heterocyclic compounds, including benzimidazole derivatives, have proven to be promising options because of their ability to balance high selectivity with limited side effects, making them a priority in pharmaceutical research.^[47]

A series of hydrogenated and fluorinated alkyl derivatives was synthesized to assess their anticancer potential. Among them, compound designated 4-(1*H*-benzo[d]imidazol-2-yl)-*N*-(2-fluoroethyl)-*N*-methylaniline, exhibited outstanding anticancer activity. This enhanced performance is attributed largely to the fluoroethyl substituent, which is well recognized for improving cellular permeability, as well as its pharmacokinetic and pharmacodynamic properties.^[48]



Figur 6: Representative chemical structures of benzimidazole derivative compounds.

synthesized a series of benzimidazole derivatives containing hydrogenated or fluorinated alkyl substituents to evaluate their anticancer properties. Among these, compound identified as 4-(1*H*-benzo[d]imidazol-2-yl)-*N*-(2-fluoroethyl)-*N*-methylaniline, demonstrated remarkable anticancer activity, particularly due to the presence of the fluoroethyl moiety, which is known to enhance cell permeability and pharmacodynamic behaviour. In another study, researchers introduced novel benzimidazole conjugates as inhibitors of tubulin, the main component of microtubule proteins that are partly involved in cancer cell division, to facilitate the diversification activity and formation of these compounds. For instance, Lu et al.^[49] designed and prepared compound which showed a high ability to inhibit tubulin protein, leading to the disruption of microtubule functions and preventing cell division. The GI₅₀ value of this compound was 30 nM, thus exhibiting good metabolic stability in human liver microsomes, enhancing its potential as an anticancer compound. In a related context, Wang et al. prepared a series of 1-benzoyl-2-(1-methylindole-3-yl)-benzimidazole derivatives, where compound showed prominent activity against cancer cells by inhibiting tubulin protein, with GI₅₀ values reaching 2.4, 3.8, and 5.1 μ M against the A549 (lung cancer), HepG2 (liver cancer), and MCF-7 (breast cancer) cancer cell lines, reflecting its promising efficacy in disrupting the malignant cell division cycle. Kamal et al. prepared compound from a group of 20 derivatives of benzimidazole linked to aryl pyrazole. This compound exhibited inhibitory activity against tubulin protein, which led to the prevention of microtubule polymerization through its association with the colchicine site. Although it lacks direct structural similarity to colchicine, it clearly inhibits cancer cell division.^[50]

Conversely, the data indicates that benzimidazole derivatives are promising anticancer agents because of their high effectiveness and targeted action. This section's anticancer research clearly outlines structure-activity relationships (SARs). Substituents at the 2-position and the addition of bulky aromatic or electron-withdrawing groups consistently improve tubulin inhibition and cytotoxic strength. Molecules that bind at the colchicine site show better activity, suggesting that benzimidazole scaffolds can effectively mimic or interfere with microtubule dynamics, even with limited structural similarity to colchicine. These results collectively position benzimidazoles as promising anticancer candidates with customizable pharmacological profiles, making them suitable for further drug development. Notably, there was considerable variation in cytotoxic responses across different cell lines.^[51]

11. Antifungal

The antifungal activity of the synthesized benzimidazole hybrid was screened against three different types of fungal strains namely, *C. albicans*, *A. clavatus* and *A.*

niger. Among the evaluated compounds, 28c, 28e, and 28i (MIC values = 250 μ g/mL) showed good results against *C. albicans* strain compared with the control (griseofulvin). The remaining tested compound showed unfavored activity against the three strains (Fig. 36). Two strains of fungi (*C. albicans* and *C. parapsilosis*) were used to determine the antifungal activity of the synthesized compounds 29.^[59] The results from the assay demonstrated that almost all the targeted compounds had insignificant activity against the tested fungi strains. However, the compounds bearing 6-chlorosubstituted and aliphatic linkers (29b and 29e) exhibited moderate activity against *C. parapsilosis* (MIC = 15.62 μ g/mL) compared to the control (fluconazole). The introduction of 4-aminophenyl and *N*-phenylamino moieties (R1 = 4-NH₂Ph, R = -NHPh) on C2 and C5 positions of the unsubstituted benzimidazole hybrids 32b strongly enhanced the antifungal activity. Which is superior to the control (miconazole) with zone inhibition.^[52]

12. Anti-Alzheimer

The inhibition effects of four new benzimidazole derivatives bearing amide bonds 78a, 78b, 79a, and 79b against acetylcholinesterase (AChE) and human erythrocyte carbonic anhydrase I (CA-I) and II (CAII) have been reported. The activities of hCA-I and hCA-II isoenzymes were performed using esterase activity measurement protocol and AChE activity in inhibition studies was performed according to the spectrophotometric approach. Besides, in the concentration gating of memory retention, synaptic alteration, and signal processing; carbonic anhydrase has been reported to play a critical role.^[84] Thus, it is an important pharmacological target for the treatment of cognitive disorders such as mental retardation, Alzheimer's disease, and aging. The reference compounds include acetazolamide (AZA) and taurine (TAC). The results showed excellent IC₅₀ values for AChE of 78a, 78b, 79a, and 79b (0.94 μ M, 7.63 μ M, 10.43 μ M, and 17.07 μ M, respectively). Compounds 78b, 79a, and 79b exhibited inferior activity compared to TAC, while compound 78a (0.94 μ M) was comparable to.^[53]

13. CONCLUSIONS

When compared to the standard medication pentapazole, demonstrated good antiulcer activity with lower toxicity and compound demonstrated good antisecretory activity. reported and screened a series of 2-[(2-pyridylmethyl)sulfinyl]benzimidazole derivatives for H⁺ + /K⁺ ATP enzyme inhibitors. Benzimidazole derivatives are one of the most important classes of organic compounds as they have a very significant biological role and are nowadays frequently used in the preparation of a large number of. These derivatives have shown impressive development in medicinal and industrial chemistry as they are very effective in the treatment of several refractory and chronic diseases, such as cancer, convulsions, and diseases of the nervous system. These derivatives have contributed to the

development of better drug treatments, and their range of medical uses has broadened to include the struggle against parasites and viral diseases, in addition to other illnesses such as tuberculosis and Alzheimer's disease. The development of classical and modern techniques for the preparation of benzimidazole derivatives, as a basic consideration, has made the process easier, minimizing the experimental workup and providing impressive results. Techniques based on microwave irradiation are one of the most reported approaches providing high reaction efficiency and decreasing chemical waste generation. Theoretical studies have played a crucial role in understanding the scientific basis of the molecular architecture of these derivatives, using computational tools like molecular docking, molecular dynamics simulation, and density functional theoretical parameters, thereby making a path towards the design of more potent and efficacious drugs. Besides their extensive use as drug molecules, these derivatives are well addressed in other fields of research for fighting environmental pollution and green chemistry. Benzimidazole derivatives, due to their biological activities and eco-friendly properties, are considered potential therapeutic agents for use in green chemistry and green medicine research. In conclusion, benzimidazole analogues continue to be a convenient model for research in both chemistry and medicine, providing new answers to untreatable and persistent health problems, as well as offering new drugs that are more efficient and safer, underscoring their crucial role in human health and welfare.

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