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A REVIEW ON BENZIMIDAZOLE AND ITS BIOLOGICAL ACTIVITY

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ABSTRACT

This review paper provides a comprehensive overview of the biological and pharmacological properties of benzimidazole and its compounds, emphasizing their significance in medicinal chemistry. Benzimidazole, a heterocyclic compound containing an imidazole ring, forms the backbone of various natural products and pharmaceuticals, including histidine and histamine. The paper highlights the historical context of benzimidazole discovery and its composition of the structure. It categorizes the diverse pharmacological profiles of benzimidazole derivatives, which exhibit a range of biological activity, including antiviral, anticancer, anti-inflammatory, analgesic, and antibacterial qualities. The evaluation of multiple synthesized benzimidazole compounds demonstrates their effectiveness against various pathogens and conditions, including drug-resistant bacterial strains and tuberculosis. The paper also discusses the mechanisms underlying these activities, including COX-2 inhibition and antioxidant effects, while stressing the potential for new therapeutic agents derived from benzimidazole scaffolds. Overall, the findings emphasize how crucial benzimidazole is as a versatile pharmacophore in the development of novel drugs targeting a wide array of diseases.

KEYWORDS: Benzimidazole, Anti-inflammatory, Analgesic, Antiviral, Anticancer, Tuberculosis activity.

INTRODUCTION

Imidazole is a heterocyclic ring structure with five members that includes a tertiary nitrogen and an imino group. Among the natural compounds that contain imidazole skeletons are

histamine, purines, biotin, and the amino acid histidine, which is a common component of most proteins.[1] Hoebrecker first synthesized benzomidazole in 1872, and Ladenberg and Wundt followed suit in 1878, making it one of the first nitrogen heterocycles ever discovered.[2] The heterocyclic aromatic system known as the benzimidazole nucleus is created when a benzene ring is attached to the fourth and fifth positions of an imidazole. It plays a significant part in medical chemistry and can be found in a wide variety of naturally occurring chemicals.[3] When a benzene ring is joined to the fourth and fifth places of an imidazole, a heterocyclic aromatic system called the benzimidazole nucleus is formed. It is present in many different naturally occurring compounds and has an important role in medical chemistry.[4] The adaptable pharmacophore benzoimidazole produces a wide range of biological actions, such as anti-inflammatory, analgesic, anti-ulcer, anti-microbial, anthelmintic, anti-cancer, anti-asthmatic, anti-diabetic, anti-tubercular, antiprotozoal, and antiviral qualities. Benzimidazole-derived drugs that are often used in therapeutic settings include omeprazole and rabeprazole for gastric ulcers, telmisartan and candesartan for hypertension, astemizole and mizolastine for allergic rhinitis, and albendazole, oxibendazole, and mebendazole for parasitosis. In general, benzimidazoles have been investigated for a variety of biological functions and have emerged as a significant pharmacophore and substructure in drug creation.[3]

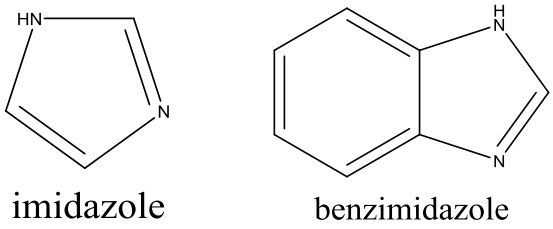


Figure 1: General structure of imidazole and benzimidazoles.

MATERIALS AND METHODS

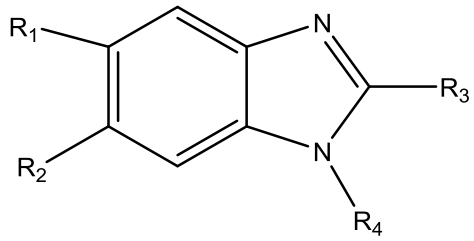
Biological/Pharmacological activities of the benzimidazole analogs

Many medicinally used medications contain benzomidazole and its analogs, which are significant pharmacophores and desirable structures in medical chemistry. The various pharmacological profiles that benzimidazoles exhibit can be categorized into the following groups. a) antimicrobial; b) anti-inflammatory and analgesic; c) antitubercular; d) antidiabetic and anticonvulsant; e) antioxidant; f) antiprotozoal and antitrichinellosis; g) anticancer; h) antiviral; i) antiulcer; j) antihypertensive; k) antiparasitic agents; l) diuretic; m) antimalarial

activity; n) acetylcholinesterase inhibitors (Alzheimer's disease); and o) agonists/antagonists of enzymes and receptors.[2]

1) Antimicrobial Agent

14 new benzimidazole compounds were evaluated for antibacterial activity by Özkay et al. in 2011. P. vulgaris, S. thyphimurium, K. pneumoniae, L. monocytogenes, S. aureus, E. faecalis, B. subtilis, E. Coli 35218, E. Coli 25922, and P. vulgaris were one of the nine strains of bacteria they used.[6] The compounds' in vitro antimicrobial effectiveness was assessed using fluconazole, a common antifungal drug, and amoxicillin, a common antibiotic that fights bacteria. against Gram-positive bacteria (Bacillus cereus and Staphylococcus aureus), Gram-negative bacteria (Escherichia coli), and dangerous fungi (Candida albicans and Aspergillus fumigatus 293).[7] 31 novel benzimidazole derivatives (3, 5, 8, 9, 12–14, 18–41) were evaluated for their antibacterial qualities against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Candida albicans, and methicillin-resistant S. aureus (MRSA, standard and clinical isolates).



2,5,6-trihalogenobenzimidazole analogues, and 5,6-dichloro-2-amino derivative (13),Among these, 5,6-dichloro-2-(4-fluoro/chlorophenyl) Five-chloro-2-(4-benzyloxyphenyl) benzimidazole and -1-nonsubstituted (24–26) (35) showed exceptional activity against S. aureus with a MIC of 3.12 mg/ml. Compounds 24–26, which do not include substitution at the N1 position, were somewhat more effective against MRSA standard and MRSA clinical isolate than compounds 8, 12, 13, and 35. Additionally, these versions outperformed the standards in terms of effectiveness. (sultamicillin, ampicillin, and ciprofloxacin) against both germs that are resistant to drugs. The dichlorinated compounds 13, 24, and 26 demonstrated a moderate level of activity against B. subtilis, with a MIC value of 6.25 mg/ml. (ciprofloxacin, ampicillin, and sultamicillin) against both drug-resistant bacteria. With a MIC value of 6.25 mg/ml, the dichlorinated compounds 13, 24, and 26 showed a modest level of activity against B. subtilis.

2. Inflammatory-Reduction Action

In Vivo Anti-Inflammatory activity

Millions of patients around the world still take non-steroidal anti-inflammatory medicines (NSAIDs) on a daily basis since they have been effectively utilized in the past to reduce pain and inflammation. However, NSAID-related gastrointestinal (GI) toxicity is a significant medical and financial issue. To investigate the anti-inflammatory qualities of the test compounds, 0.1 mL of a 1.0% carrageenan solution was employed as the phlogistic agent in the carrageenan-induced rat paw edema model. SD rats of either sex were randomly assigned to standard, vehicle control, and other test groups, each consisting of six rats. The conventional medication, indomethacin, was given at a dosage of 50 mg per kilogram of body weight., whereas the vehicle control was 2% sodium carboxymethylcellulose (CMC). 30 minutes prior to the phlogistic agent injection, the test compounds were given intraperitoneally (p.o.) as a suspension in 2% sodium CMC at a dose level of 100 mg/kg body weight. Using a plethysmograph, the mercury displacement method was used to measure the volume of paw edema at 0 and 3 hours after the carrageenan injection.

The % anti-inflammatory activity was estimated according to the formula as shown below:

Edema (%) is equal to 100 - (1-Vt / Vc) × 100 (1).

Edema reduction (%) = (1 - Vt / Vc) × 100 (2)

The edema volume in the drug-treated and control groups is denoted by Vt and Vc, respectively.

The results of 3a–i, which ranged from 23.88% to 37.31%, showed encouraging anti-inflammatory effectiveness. When given After three hours, it was discovered that the examined compounds 3d, 3e, 3f, and 3i considerably reduced edema at doses of 100 mg/kg p.o. (31.34%, 32.84%, 34.33%, and 37.31%, respectively).[9,10]

In Vitro Anti-Inflammatory activity

COX-2 inhibitory test in vitro Following testing against The IC50 of the compound being studied was determined for COX-1 and COX-2. Furthermore, the SI of the basic medication indomethacin was compared with the COX-2 The resulting selectivity indices (SI) are IC50 (COX- 1)/IC50 (COX- 2). The findings demonstrated that all of the investigated substances inhibited the COX-1 isozyme at higher concentrations (IC50= 2.56–9.35 µM), suggesting that they are less efficient against the enzyme than the standard medication indomethacin

(IC50= 1.56 µM) and may be safer as a result. The IC50 inhibitory range for COX-2, however, was 0.13–0.27 µM for compounds 4a, 4b, 5, 6, and 9, which is more potent than indomethacin (IC50 = 0.41 µ). Comparing the SI to indomethacin (SI=4), the results showed that compounds 4a, 4b, 5, 6, and 9 had high selectivity (SI range of 22.83–71.92), with compound 6 being the most selective of all (SI= 71.92).[11]

3. The Analgesic Effect

The synthetic chemicals' analgesic efficacy was evaluated using a writhing model generated by acetic acid. Five groups of six Swiss albino mice, each weighing 20–25 g b.w., were used. A 0.6% acetic acid injection (dose ¼ 10 ml/Kg) was given intraperitoneally. After injecting each animal with acetic acid for five minutes, the number of writhes was tallied for twenty minutes. As a control, this measurement was used. The following day, the analgesic impact was tested on mice in the same groups. The produced chemicals were given orally to each group. One hour prior to the acetic acid injection, an animal A dosage of 100 mg/kg was given. Acetic acid injections were given to mice for five minutes. and then they were watched for writhing for twenty minutes. The mean value for each group was calculated and compared to the control. Mesulide was the benchmark drug used to compare analgesic activity. The percentage of protection was calculated using the formula below:

$$(1\text{-}Vc/Vt) \times 100$$

Where the mean number of writhings in the test animals is denoted by Vt, and the mean number in the control group by Vc.[12]

4. Antioxidant properties

Applying the 2,2-diphenyl-1-picryl hydrazyl (DPPH) reduction method the antioxidant capacity of each molecule was assessed in terms of its ability to scavenge free radicals in vitro. 10 milliliters of methanol were used to dissolve 10 milligrams of DPPH. This stock solution was diluted to yield concentrations of 10, 20, 30, and 40 µg/mL. Regarding these dilutions The absorption was measured at 516 ηm. The highest absorbance was 0.903 at a concentration of 30 µg/ml. Ten milliliters of methanol were used to dissolve ten milligrams of ascorbic acid. Dilutions were made from this stock solution to reach 10, 20, 30, and 40 µg/mL concentrations.1 mL of DPPH solution (300 µg/mL concentration) was added to 1 mL of each of these solutions to achieve a volume of 10 mL. It had been collected in different volumetric flasks. The absorbance for these dilutions was measured at 516 ηm after 30 minutes. The test answers were prepared in the same way as regular ascorbic acid, and the

absorbance at 516 nm was measured 30 minutes later. All of the compounds exhibited moderate antioxidant activity, regardless of substitution.; however, the molecule containing pyridyl substituted oxadiazole exhibited good antioxidant activity.[13] When assessing antioxidant potential, the 2,2-diphenyl-1-picrylhydrazyl (DPPH) technique was used to measure radical scavenging capacity. Since DPPH is made up of unstable free radicals, it absorbs any radicals that the test compound produces and changes its color visibly from violet to pale yellow to colorless. Antioxidant potential is the amount of change in absorbance relative to control. Because of the DPPH method's non-linear relationship, probit regression was used, and BLeSq software was used to determine the EC50 values. It is discovered that series 5a–e is more powerful than series 4a–e as shown. The most powerful compounds were Having corresponding EC50 values of 13.92±1.4 µmol/L and 1.2±0.1 µmol/L, respectively, identified as 4d and 5a. The study found that electron withdrawing groups improve the antioxidant potential, possibly as a result of the increased positive charge on the amide's -NH associated with the negative inductive action of these groups. Free radical quenching could result from the strengthening of the positive charge. Furthermore In and of itself, electron-withdrawing groups are powerful free radical quenchers. Conversely, it was shown that substituting electron-releasing groups reduced the radical scavenging potential, presumably as a result of their beneficial inductive action.[14]

5. Anticancer activity

1, 3-diarylpyrazinobenzimidazole derivatives have been studied and synthesized for their anticancer properties. This was accomplished by reacting 2-bromoacetophenones in acetone with 2-aryloylbenzimidazole derivatives to produce 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles. The resultant compound was reacted with ammonium acetate in acetic acid to produce the chemical. According to reports, microwave irradiation technology was used to perform the aforementioned treatment. Another reported approach is the synthesis and evaluation of 1-(4-methoxyphenethyl)-1H-benzimidazole-5- carboxylic acid derivatives. The compound that killed the most leukemic cells was methyl 1-(4-methoxyphenethyl)-2-(4-fluoro-3-nitrophenyl)-1H-benzimidazole-5-carboxylate, with an IC (50) value of 3 microM.[15,16]

6. Anti-hypertensive Agents

Because they are more readily available when taken orally, biphenyl benzimidazoles have a stronger antihypertensive effect than their predecessors. The activity depends on the

biphenyl's location. It has been demonstrated that substituted aryl or alkyl carboxamide derivatives exhibit angiotensin-II AT1 receptor antagonistic action, rendering them potent antihypertensive medications.[14]

7. Antitubercular activity

TB, a contagious infection caused by Mycobacterium tuberculosis (MTB), continues to be the most prevalent infectious disease that kills people globally. According to WHO estimates, between 2002 and 2020, around one billion people will contract TB, over 150 million will become ill, and 36 million will pass away. There is an urgent need for new medications that can target multidrug-resistant strains of tuberculosis and shorten this lengthy treatment duration. The following is a discussion of benzoimidazole and its derivatives, which show a variety of TB actions.[2] Mycobacterium tuberculosis (Mtb) is the bacterium that causes tuberculosis (TB), an infectious disease that can spread from person to person through coughing, sneezing, or other respiratory fluids that are carried by the air to other parts of the body. White plaque, another name for tuberculosis, is caused by infection with Mtb complex members. In 1882, Robert Koch became the first scientist to isolate Mtb bacterium, and he was awarded the Nobel Prize for this groundbreaking discovery. The Mtb bacteria typically causes lung disease, which can then migrate to other parts of the body and cause more harm. TB was virtually nonexistent in the industrialized world, but it has recently been making a comeback, while being widespread and fatal in developing nations. Since the recovery rate for patients with immune disorders like AIDS and many others is comparatively lower than that of healthy individuals, this spreads very quickly among them. The majority of Mtb infections are silent latent TB infections (LTBI), and the primary source of infection is patients with active pulmonary TB.[17] Excellent antitubercular capabilities have been reported for compounds with heterocyclic moieties, including pyrrole, imidazole, and benzimidazole. The scientists' goal has been to create new antitubercular medicines using the benzoimidazole scaffold. several variants of benzimidazoles that have antitubercular properties.[18]

8. Antiviral activity

Research shows that benzoimidazoles that are N- and 2-substituted are effective against tobacco mosaic virus38 since they have been shown to have antiviral characteristics against enterovirus, poliovirus, and picornavirus. Creating Hetercycles of Benzimidazole with an amidino group at position C-5 was another method that was documented. new benzimidazole

derivatives were created, manufactured, and tested for their ability to inhibit four different types of enteroviruses in VERO cells: Coxsackie virus A16, B3, B6, and Enterovirus. (L)- 2-(pyridin-2-yl)-N-(2-(4-nitrophenyl) pentan-3- yl) was the most promising chemical. -1H-benzimidazole-4-carboxamide, which has a remarkable selectivity index (328) and a high antiviral efficacy (IC50 = 1.76 µg/mL).[14]

9. Anti-Ulcer Activity

In response to specific stimuli, substituted benzimidazoles can restrict the release of stomach acid because they are strong inhibitors of the parietal cell proton pump and the H+/K+ ATPase. Methylene groups with heterocycles are crucial for the activation of sulfoxide groups.[14]

10. Anticonvulsant activity

Maximal electroshock seizure test (MES)

Oral administration of each chemical was carried out at dose levels of 30, 60, and 100 mg/kg body weight. Rats were given 60 Hz, 150 mA electrical stimulation using ear clip electrodes for 0.2 s to induce the maximal electroshock convulsions. The five phases of MES-convulsions are as follows:(a)Clonic convulsion, (b) tonic flexion, and (c)tonic extensor (d) insomnia (e) recuperation or demise. The animal's duration in each convulsion phase was recorded in seconds. If a compound lessens or eliminates the hind limb tonic extensor phase of MES convulsions, it is said to have anticonvulsant properties.

scPTZ

test for induced seizures Pentylenetetrazole is used in rats given a dosage of 70 mg/kg in the scPTZ test. This results in clonic seizures that continue for at least five seconds. The length of the seizure and the amount of time required for the development of limb-related clonic seizure activity were meticulously recorded. A one-hour seizure-free interval was regarded as protective. A percentage of protection was computed by counting the number of animals in each group that were protected.

Neurotoxicity screening (NT)

The rotorod test was used to gauge the rats' minimum motor impairment. The 100ñ250 g albino rats were trained to remain on a rotorod that revolved at 10 rpm and had a diameter of 3.2 cm. Rats that could remain on the rotating rod for at least a minute were the only ones chosen for the test. The test chemicals were administered intraperitoneally (i.p.) to trained

animals at doses of 100 mg/kg. The animal's failure to stay in equilibrium on the rod for at least a minute was a sign of neurotoxicity.[19,20]

RESULTS AND DISCUSSION

In this review, we explored the multifaceted biological and pharmacological properties of benzimidazole and its derivatives, revealing their significant role in medicinal chemistry. Below, we summarize the key findings that emerged from our analysis of the literature.

1. Antimicrobial Activity

Benzimidazole derivatives demonstrated a robust antimicrobial profile, with several compounds exhibiting potent activity against a range of pathogens, including both gram-positive and gram-negative bacteria. Notably, certain derivatives showed effectiveness against drug-resistant strains, highlighting their potential as alternatives in an era of rising antibiotic resistance. For instance, compounds like albendazole and mebendazole have been pivotal in treating parasitic infections, showcasing their broad-spectrum efficacy.

2. Anti-inflammatory and Analgesic Effects

Numerous studies indicated that benzimidazole compounds possess significant anti-inflammatory and analgesic properties. Mechanistic evaluations revealed that these compounds could inhibit cyclooxygenase-2 (COX-2), a key player in inflammatory processes. This inhibition correlates with reduced pain and inflammation in various models, suggesting that benzimidazole derivatives could be developed into effective therapeutic agents for chronic pain and inflammatory conditions.

3. Antitubercular Activity

The review highlighted the promising antitubercular activity of several benzimidazole derivatives. Compounds were identified that not only inhibited Mycobacterium tuberculosis but also showed synergy when combined with existing antitubercular drugs. This synergy could pave the way for more effective treatment regimens, particularly for patients with multidrug-resistant tuberculosis, a growing global health concern.

4. Anticancer Potential

Many benzimidazole derivatives demonstrated anticancer properties across various cancer cell lines. The compounds were found to induce apoptosis and inhibit cell proliferation through multiple pathways, including cell cycle arrest. For example, certain derivatives have

shown promise against breast and lung cancer cell lines, suggesting their potential role as lead compounds in cancer therapy.

5. Antioxidant Properties

The antioxidant activity of benzimidazole compounds was another significant finding. These compounds exhibited the ability to scavenge free radicals and reduce oxidative stress, which is linked to various diseases, including cancer and neurodegenerative disorders. This property underscores the therapeutic potential of benzimidazole in protecting cellular integrity and promoting overall health.

6. Other Pharmacological Actions

Beyond the primary activities mentioned, benzimidazole derivatives have also been explored for their antidiabetic, antiviral, and antihypertensive properties. The diversity of their biological activities points to the versatility of the benzimidazole scaffold in medicinal chemistry. For instance, compounds have been effective in managing hypertension, showcasing their potential as dual-action agents.

CONCLUSION

In conclusion, the Nucleus of benzimidazole plays a crucial role in medical chemistry and is found in various natural substances. It possesses a variety of biological properties, including as analgesic, antibacterial, and anti-inflammatory. antioxidant, anticancer, antihypertensive, antitubercular, antiviral, antiulcer, antiparasitic, antidiabetic, and anticonvulsant properties, making it significant in drug development. Research has shown promising results for benzimidazole derivatives in various pharmacological profiles, such as their effectiveness against bacterial and fungal strains, their anti-inflammatory properties, and their potential as antioxidants and anticancer agents. These findings highlight the multifaceted potential of benzimidazole and its analogs in addressing a wide range of health-related challenges.

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