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RECENT ADVANCES IN BENZIMIDAZOLE DERIVATIVES: CHEMISTRY AND BIOLOGICAL ACTIVITIES

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ABSTRACT

Benzimidazole is a privileged heterocyclic scaffold, which has long been recognized for its significant pharmacological potential. This review focuses on the chemistry, structure, and recent developments in the biological activities of benzimidazole derivatives, which include anticancer, anti-parasitic, antioxidant, anti-fungal, analgesic, and anti-inflammatory activities. The benzimidazole core, which is constructed by linking a benzene ring with an imidazole ring, acts as a platform for structural modifications, which in turn help in designing derivatives with superior activity and selectivity. Structure-activity relationship studies indicate that the type and position of functional groups, especially electron-withdrawing and electron-donating groups, significantly influence their activities. Hybridization with other pharmacophores and the presence of heterocyclic groups enhance their pharmacological activities. Besides, these derivatives show multiple mechanisms of action, which include enzyme inhibition, free radical scavenging, and interference with cell processes. This review emphasizes the significance of structural modifications in optimizing their therapeutic potential and their potential in drug discovery.

KEYWORDS: Anticancer, Antioxidant, Antiparasitic, Analgesic, Benzimidazole.

INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound with a bicyclic structure made by the fusion of benzene and imidazole rings. It usually appears as a white crystalline solid and often forms tabular crystals.

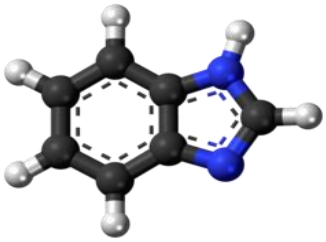

Fig 1: 3D of benzimidazole.

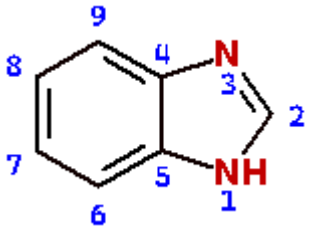

Fig 2: 2D of benzimidazole.

It serves as a basic structure for many derivatives with various biological activities, including anthelmintic, antimicrobial, antitumor, and antioxidant effects. It was first introduced in the 1950s as a plant fungicide and later developed for use in veterinary and human medicine.[5,9]

Table 1: properties of benzimidazole moiety.

IUPAC Name	1H-Benzimidazole
Molecular Formula	$C_7H_6N_2$
Molecular Weight	118.14 g/mol
Boiling Point	360–365 °C
Synonyms	Benzimidazol,o-Phenylenimidazole, 1H-1,3-Benzodiazole, Benzoglyoxaline
Melting Point	170–172 °C

PREPARATION

Benzimidazole was first identified as a result of research into vitamin B12. It was found to be a stable structure on which drugs could be developed. Benzimidazole can be made by the condensation of o-phenylenediamine with formic acid.

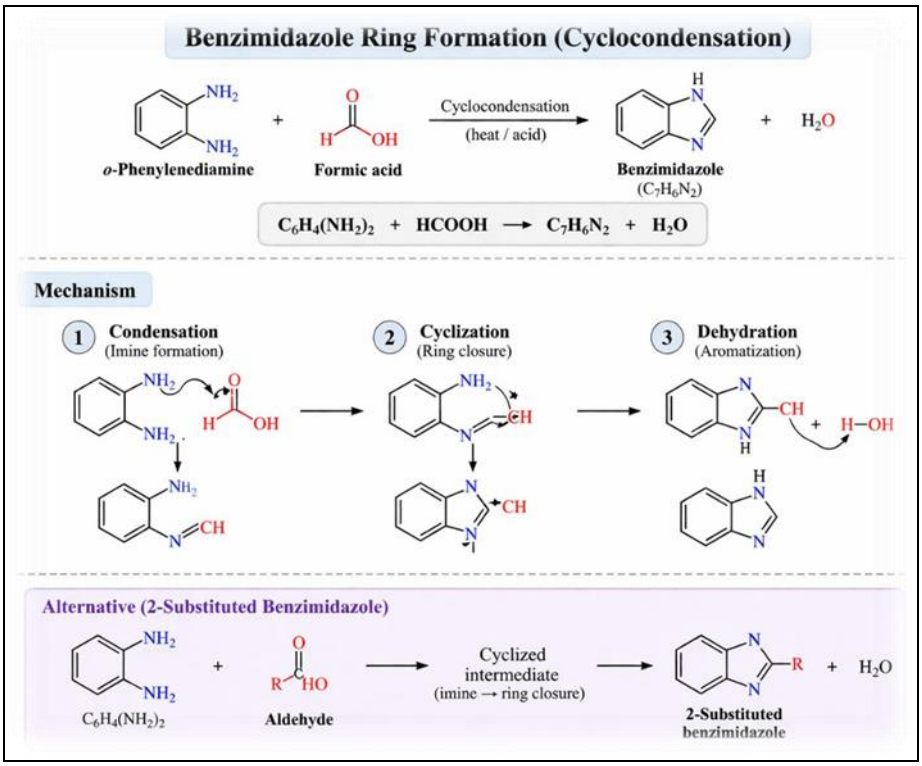

Fig. 3: Mechanism of bezimidazole ring formation.

REACTIONS

Benzimidazole reacts as a base:

$$C_6H_4N(NH)CH + H^+ \rightarrow [C_6H_4(NH_2)\ CH]^+$$

It can also be deprotonated with strong bases:

$$C_6H_4N(NH)CH + LiH \rightarrow Li[C_6H_4N_2CH] + H_2$$

The imine group can be alkylated and also acts as a ligand in coordination chemistry. The most well-known coordination compound of benzimidazole contains the ligand N-ribosyl-dimethylbenzimidazole, as found in vitamin B.

MARKETEDLY AVAILABLE DRUGS CONTAINING BENZIMIDAZOLE MOIETY

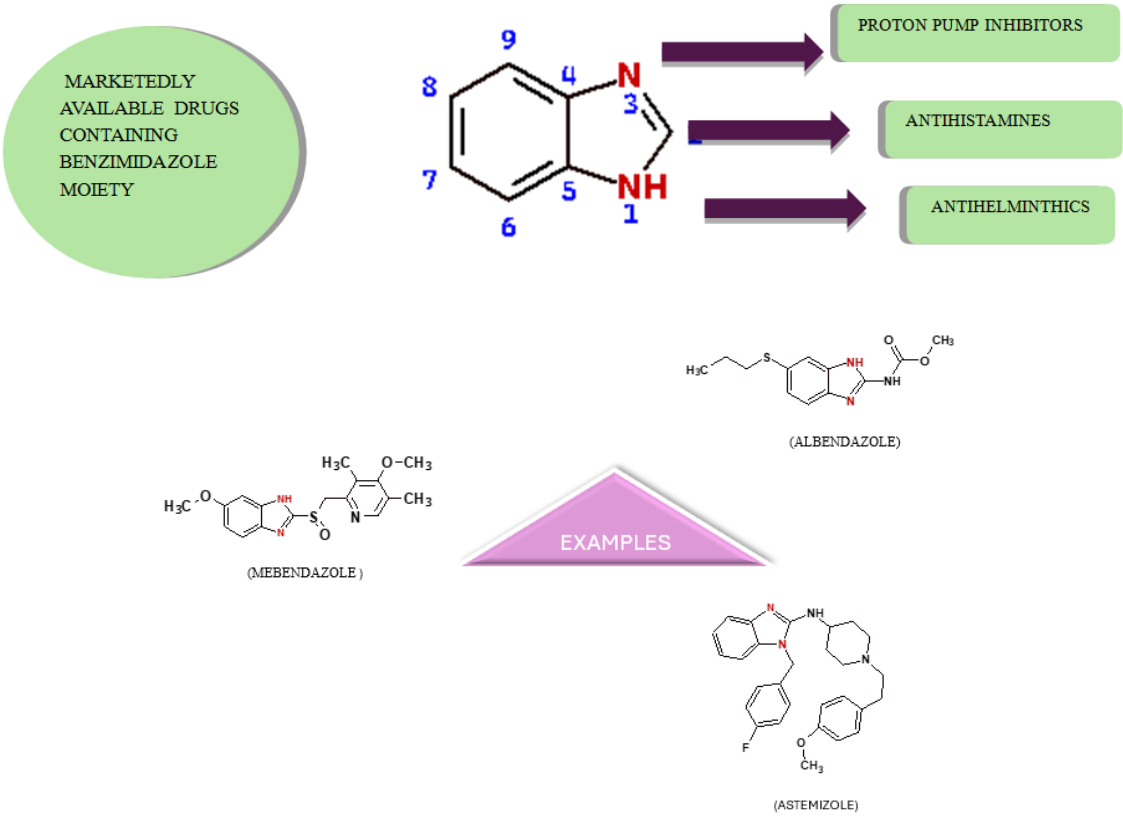

Fig. 4: examples of drug contains benzimidazole moiety.

BIOTIC EFFECT

Anticancer activity

Benzimidazole is a fused heterocyclic compound, which consists of a benzene ring and an imidazole ring. It is well accepted as a privileged structure with significant medicinal activities, especially for cancer. The unique electronic characteristics of the benzimidazole core make it an effective compound for the development of cancer therapeutics. Recently, various benzimidazole derivatives have been synthesized and screened for their anticancer activities on different cancer cell lines, such as leukemia, breast cancer, lung cancer, prostate cancer, and colon cancer. The significant cytotoxic activities of these compounds make them promising for cancer therapeutics.[1]

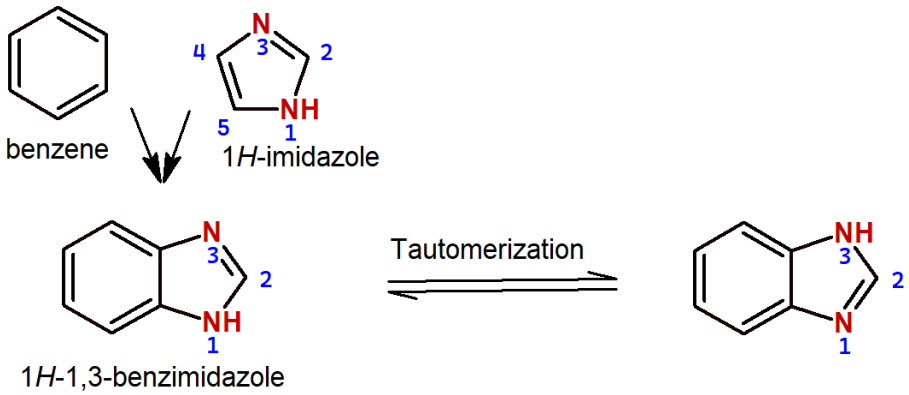

Fig. 5: tautomerized form of benzimidazole.

The anticancer potential of benzimidazole derivatives can be attributed to their capability to target cancer cells through multiple mechanisms. They have the potential to target crucial enzymes like *topoisomerases* and *tyrosine kinases*, thereby affecting DNA replication and signal transmission, which are crucial for cancer cell survival. In addition, benzimidazole derivatives have shown the potential to induce cell cycle arrest, especially during the G2/M phase. This mechanism prevents cancer cell division and proliferation. Furthermore, benzimidazole derivatives have shown anticancer potential by activating the mitochondrial pathway of apoptosis. This process involves the upregulation of pro-apoptotic proteins like Bax and caspases, whereas anti-apoptotic proteins like Bcl-2 are down regulated. In addition, benzimidazole derivatives induce the formation of reactive oxygen species, thereby resulting in oxidative stress, which leads to cancer cell death. Furthermore, benzimidazole derivatives have shown the potential to target microtubule dynamics, thereby affecting mitotic spindle formation and resulting in apoptosis.[2]

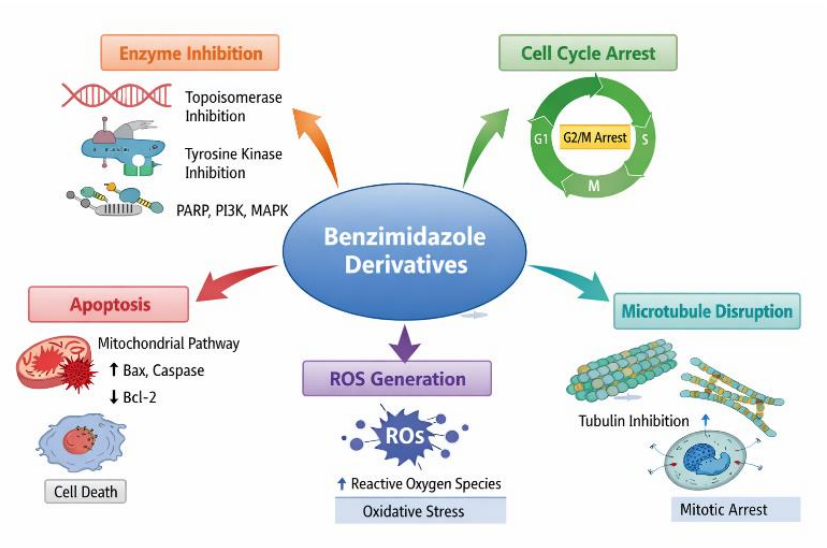

Fig. 6: Anticancer mechanism.

From the studies on structure-activity relationships, it has been observed that the biological activities of benzimidazole derivatives are significantly influenced by the nature and position of substituents on the benzimidazole ring system. For instance, the presence of electron-withdrawing groups such as nitro and chloro has shown to improve anticancer activities through enhanced binding affinity to target proteins. On the other hand, electron-donating groups can

influence pharmacokinetics and electronic effects. Hybridization of benzimidazole with other pharmacophores has shown to improve activities.

Some studies have found that benzimidazole derivatives exhibit promising results against different types of cancer cell lines. For example, some derivatives have exhibited strong inhibitory effects against leukemia cells via targeting specific oncogene products, such as BCR-ABL. In addition, they have been found to exhibit apoptosis and cell cycle arrest effects. Other derivatives have been found to exhibit strong inhibitory effects against breast cancer cells (MCF-7), lung cancer cells (A549), and prostate cancer cells (PC-3). Most importantly, some derivatives have been found to exhibit selective toxicity against cancer cells without affecting normal cells, which is a key requirement for developing new anti-cancer agents.[7]

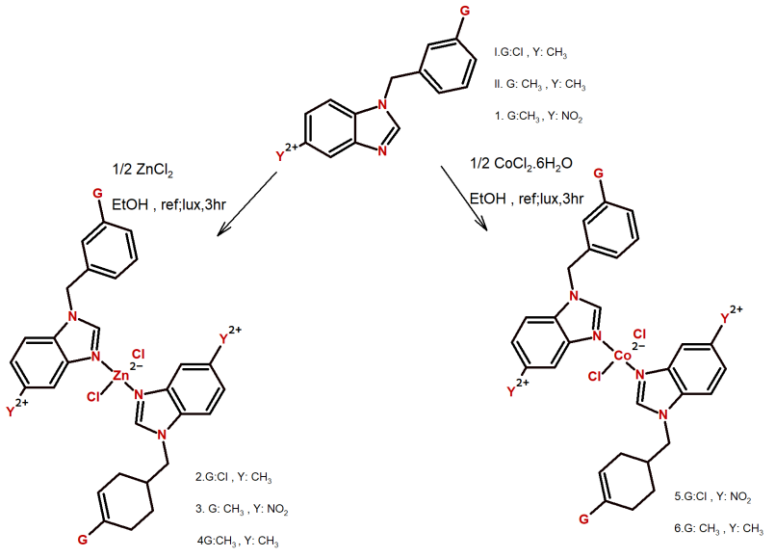

Fig. 7: benzimidazole derivatives.

Recent research activities have concentrated on developing novel benzimidazole derivatives with high efficacy, selectivity, and safety. Techniques such as green chemistry techniques, molecular docking techniques, and structure-based drug design are increasingly being used to improve benzimidazole derivatives. To conclude, benzimidazole derivatives are still considered to be one of the promising compounds for anticancer research because of its multiple targets and flexibility to be further improved.

Antiparasitic activity

Benzimidazole derivatives are an important group of antiparasitic drugs with activity against protozoa and helminths.

In the current study, a number of 1H-benzimidazole derivatives (1-18) were tested for their in vitro activity against Giardia lamblia, Entamoeba histolytica, and Trichinella spiralis. It was observed that most of the synthesized compounds showed significantly higher antiprotozoal activity than standard drugs such as metronidazole, with some of the compounds showing higher activity, such as those with simple substitution, such as the unsubstituted benzimidazole (compound 6) and thioether-containing compounds (such as compound 11) to the C-2 of the 1H-benzimidazole. In contrast, carbamate derivatives (compounds 3, 9, and 15), which structurally resemble albendazole, were linked with inhibition of tubulin polymerization, which is one of the major mechanisms of action of anthelmintics. However, they

were not the most active antiprotozoal agents. Substitution at the C-5 and C-6 positions, especially with chlorine, was also linked with increased activity in some cases, whereas bulky groups were associated with reduced activity. A remarkable point is that no direct correlation was found between inhibition of tubulin polymerization and antiprotozoal activity. This indicates that distinct mechanisms of action were involved. To conclude, structural modifications on the benzimidazole ring system, especially at the C-2 and aromatic ring positions, were linked with significant antiparasitic activity. Therefore, benzimidazole derivatives have been recognized as promising candidates for the development of new antiparasitic agents.

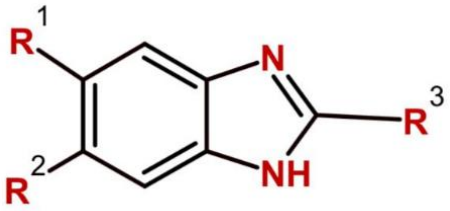

Fig. 8: novel benzimidazole derivative.

Table 2: substitutions in R1, R2, R3.

COMPOUND	R1	R2	R3
3	H	H	$NHCO_2CH_3$
9	Cl	H	$NHCO_2CH_3$
11	Cl	H	SCH_3
15	Cl	Cl	$NHC0_2CH_3$

Antioxidant activity

Benzimidazole derivatives have shown promise as antioxidant compounds, as they are capable of scavenging free radicals and alleviating oxidative stress. In the study, a number of benzimidazole derivatives, including salicyl, oxadiazole, thiosemicarbazide, and 1,2,4-triazole groups, were synthesized and examined for antioxidant activity by DPPH and ABTS free radical scavenging assays. The results showed that all of the synthesized compounds possessed significant antioxidant activity.

The findings indicated that some of these compounds, especially those in the thiosemicarbazide series (7a and 7b), possess excellent scavenging activities comparable to those of the standard antioxidant BHT. These findings highlight the role of sulfur atoms in enhancing free radical scavenging activities. In addition, some of these compounds, such as 4b, 6a, 6b, and 8a, possess excellent activities in scavenging free radicals in an ABTS assay, with some compounds being more efficient than the standard antioxidant. From the analysis of the structure-activity relationship, it is evident that the presence of electron-donating groups and heterocycles enhances hydrogen donation and free radical stabilization.

From the above findings, it can be concluded that structural modifications of the benzimidazole ring, especially with the incorporation of various heterocyclic/sulfur-containing moieties, are of significant importance in order to improve antioxidant activity, thus making the derivatives promising candidates for the treatment of various oxidative stress-related diseases.[24]

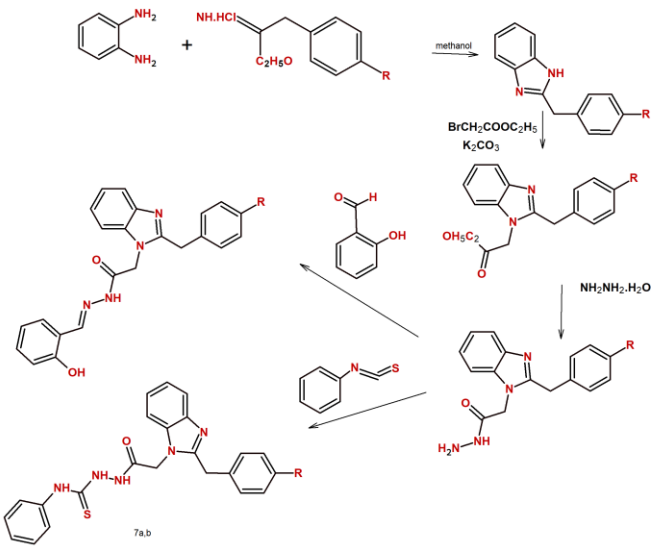

Fig. 9: Benzimidazole derivatives.

Antifungal activity

Derivatives of benzimidazole have shown promise as a new generation of antifungal compounds because of the flexible nature of the compound and its potential for interaction with a number of targets. Current studies have shown that these compounds have shown promise against a number of pathogenic fungi, such as *Candida albicans, Aspergillus niger, and Cryptococcus neoformans,* and are a solution to the rising problem of antifungal drug resistance. The antifungal potential of benzimidazole derivatives is highly dependent on structural variations, especially substitution of the C-2 position and the presence of electron-withdrawing groups, such as nitro and halogen groups, in the C-5 and C-6 positions.

In addition, hybrids of the benzimidazole core with other heterocyclic pharmacophores such as triazoles and thiazoles have also demonstrated an improvement in potency and activity. From a mechanistic perspective, these compounds are known to inhibit lanosterol 14α-demethylase (CYP51), which in turn disrupts ergosterol biosynthesis, cell membrane function, and ultimately leads to cell death in fungi. In addition, some of these compounds are known to display membrane-disrupting activities and interactions with fungal enzyme systems, which also contribute to their overall mechanism of action. In conclusion, the benzimidazole core represents an interesting core for developing novel antifungal compounds, with SAR investigations being key in developing potent and selective compounds in this area.[4]

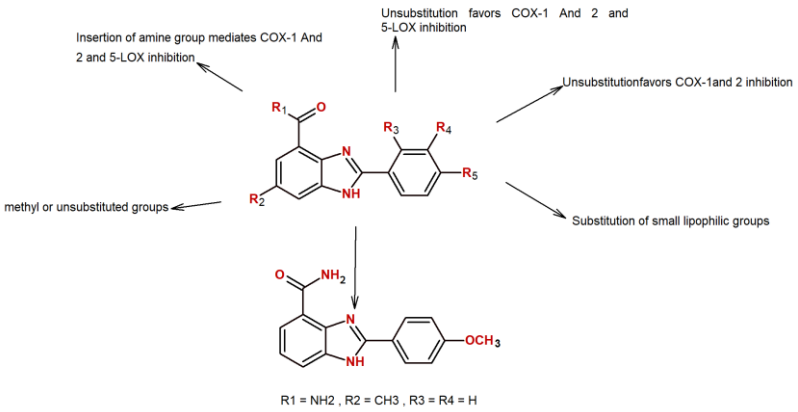

Fig. 10: SAR of benzimidazole and structural modifications.

Analgesic and anti-inflammatory activity

The benzimidazole derivatives that are used in the analgesic and anti-inflammatory activities are based on the 2-substituted benzimidazole ring system, with the compound 2-(chloromethyl)-1H-benzimidazole undergoing condensation reactions with substituted aromatic amine derivatives to yield the 2-methylaminobenzimidazole class of compounds (1-11). The general structure of these benzimidazole-based compounds consists of the benzimidazole ring fused with the –CH_2–NH– bridge and the aryl ring of the aniline derivative. The presence of Br, Cl, and NO_2 groups in the benzimidazole ring and the presence of Cl, Br, CH_3, and OCH_3 groups in the aniline ring are important in modulating the biological activities.

The analgesic activity of the benzimidazole derivatives was assessed using the acetic acid-induced writhing test, in which most of the compounds showed potent analgesic activity. From the structural activity relationship, it was observed that the presence of halogen substitution in the form of bromo and chloro groups on both the benzimidazole and aniline rings was responsible for potent analgesic activity. For instance, the compound with the highest analgesic activity, namely, N-[(5-bromo-1H-benzimidazol-2-yl)methyl]-3-chloroaniline (compound 7), was shown to possess approximately 89% analgesic activity, thus proving that electron-withdrawing groups enhance analgesic activity. The presence of functional groups on the aromatic ring enhances the interaction of analgesic drugs.

The anti-inflammatory activity of these compounds was evaluated by carrageenan-induced paw oedema in rats, and some of these compounds have shown comparable activity to standard drugs. From the structural point of view, unsubstituted benzimidazole derivatives and those with chloro substituents on the aniline ring, such as compounds 1 and 2, are found to possess potent activity. This indicates that moderate electron-withdrawing groups are beneficial for anti-inflammatory activity, which may be due to inhibition of *cyclooxygenase* enzymes and thereby preventing the formation of prostaglandins. On the other hand, sterically hindered compounds are found to possess low activity.

In general terms, the analgesic and anti-inflammatory activities of benzimidazole derivatives are significantly influenced by the structure of the compound, including the substituent groups attached to the benzimidazole and the aromatic ring. The presence of halogen substituents such as Br and Cl and the nitro group significantly contributes to the analgesic and anti-inflammatory activities. The methoxy and methyl groups moderately contribute to the activities by increasing the lipophilicity and membrane permeability. The presence of the –CH_2–NH– linker between the benzimidazole and the aryl group is important for the analgesic and anti-inflammatory activities. The linker offers flexibility in the structure that is important for the interaction with the receptor.

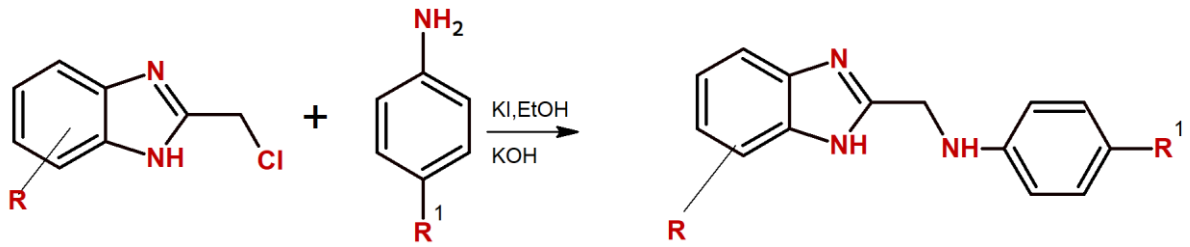

Fig. 11: Novel derivatives of benzimidazole.

Table 3: Substitutions in R and R1.

COMPOUMD	R	R^1
1	H	H
2	H	Cl
7	Br	Cl

CONCLUSION

Benzimidazole derivatives are still of significant interest in medicinal chemistry, especially in terms of their broad spectrum of biological activities. The presence of a functional benzimidazole nucleus enables wide-ranging structural optimization, which has led to the discovery of derivatives with improved pharmacological properties. From studies discussed in this review, it is evident that substitution on the benzimidazole nucleus and associated functional groups is critical in defining their biological activities, which include anticancer, anti-parasitic, antioxidant, anti-fungal, analgesic, and anti-inflammatory activities, among others. Advances in synthetic methodologies and drug design have enabled the discovery of potent and selective benzimidazole derivatives with improved pharmacological properties. However, there is still a lot to be done in this field in order to enhance their safety, selectivity, and clinical utility. In conclusion, benzimidazole derivatives are still a promising class of compounds with potential in the discovery of new therapeutic agents for a wide variety of conditions.

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