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Benzimidazole Derivatives in Drug Design: Structure-Activity Relationships and Therapeutic Potential: A Review

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A B S T R A C T

Benzimidazole, a heterocyclic compound formed by the fusion of benzene and imidazole rings, has become a crucial scaffold in medicinal chemistry due to its versatile pharmacological properties. It plays a key role in the development of antiviral, anticancer, anti-inflammatory, and antiparasitic drugs. The benzimidazole ring is particularly effective in biological and clinical applications because its derivatives, as isosteres of natural nucleotides, can easily interact with biological macromolecules. This review explores the pharmacological activities of benzimidazole derivatives, emphasizing their structural modifications and the mechanisms that drive their therapeutic effects. It highlights their significant potential in modern medicine. Benzimidazole derivatives are known for their anticancer properties due to their resemblance to the nitrogenous base purine, which allows them to exhibit a broad spectrum of biological activities. Complexes of benzimidazole derivatives with copper and zinc, such as complex 1 and 11, respectively, have shown significant interactions with biomolecules, demonstrating nuclease activity and DNA-binding capabilities. Complex 1, in particular, has demonstrated potent cytotoxic activity against human cancer cells, including HepG2, HeLa, and MDA-MB 231, with results comparable to the standard drug, cisplatin. In addition to anticancer effects, benzimidazole derivatives have also shown antioxidant, analgesic, and anti-inflammatory properties. They have been particularly effective in conditions like acute respiratory distress syndrome by decreasing nitric oxide levels and inhibiting the activation of p38 MAPK and NF-κB. This review highlights the latest advancements in benzimidazole research, showcasing its emerging applications in treating protozoal infections, cancer, pain, viral infections, and inflammatory diseases, underscoring its significant role in drug development and its broad therapeutic potential.

Keywords: Benzimidazole derivatives, Drug design, Heterocyclic compounds, Antioxidants, Anti-inflammatory, Anticancer.

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INTRODUCTION

One of the fundamental organic elements used in the synthesis of various organic compounds, including pharmaceuticals, is heterocyclic compound. Because heterocyclic compounds have hetero atoms and a wide range of characteristics, they are among the most complex classes in chemistry (Gomez-Cabrera et al., 2008; Mohammed et al., 2023). Benzimidazole is the benzene derivative of imidazole or azapyrrole commonly known as 1,3-benzodiazole. It is a heterocyclic aromatic compound

containing 2 nitrogen atoms separated by a carbon atom (Ebenezer et al., 2023).

Structurally, benzimidazole consists of a fusion between benzene and imidazole rings (Figure 1), which allows for high affinity binding to biological targets. This versatile heterocyclic compound and its derivatives have found applications in various pharmaceutical areas (Alzhrani et al., 2022; Mahurkar et al., 2023). Due to their shown biological activity, including antiviral, anticancer, antifungal, antibacterial, anti-inflammatory, and analgesic properties, benzimidazole are heterocyclic compounds that have garnered a lot of attention in recent years (Ebenezer et al., 2023; Eswayah et al., 2017; Pathare and Bansode, 2021). Medicinal chemists looking for benzimidazole derivatives for anticancer drugs and also to study its effects on structure activity relationship (Ahmad et al., 2021).

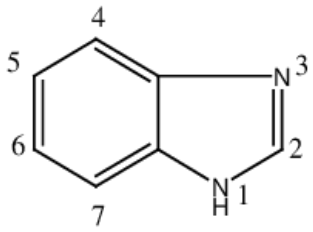


Figure 1: General Structure of Benzimidazole (Pullagura et al., 2016).

The benzimidazole chemical has attracted the interest of researchers over the past decades in research and application because of the unique features of the organic compounds formed from it, and because of its well-known biological applications and many essential medical properties. N-ribosyl-dimethyl benzimidazole is a major type of benzimidazole found in nature. It is the essential link that coordinates with the cobalt element in vitamin B12 (Walia et al., 2011).

Research continues to unveil new biological activities and therapeutic potential for benzimidazole derivatives, spurring further interest in the compound from both academia and industry. Understanding the chemistry and biology of benzimidazole is paramount for drug discovery and development initiatives aimed at overcoming emerging health challenges.

The objective of this review is to comprehensively explore the pharmacological activities of benzimidazole derivatives, their structural modifications, and the underlying mechanisms that contribute to their therapeutic effects. This review aims to synthesize current research findings to highlight the potential of benzimidazole derivatives in drug discovery and modern therapeutic applications.

DISCUSSION

Benzimidazole derivatives are very common in synthesis nowadays. this is because of their pharmacological activity. Their derivatives have anti-inflammatory and anticancer activity with antiprotozoal activity, antiviral and also antibacterial activity (Charlson, 1973; Cheng et al., 2005; Infante-Castillo et al., 2008; Walker et al., 1978). Thus, they should be given importance and must be kept in research so as to make their derivatives more prominent for pharmacological activity. These activities are discussed below:

Anti-viral

Benzimidazole derivative have showed strong antiviral activity (Chen et al., 2021; Marinescu, 2023). The flavonoid derivative of benzimidazole (4n) showed curative, protective and inactivation properties against Tobacco Mosaic Virus (TMV) (Chen et al., 2021). A novel series of 5-nitro-1H-benzimidazole derivatives substituted at position 1 by heterocyclic rings were shown to be the most promising compounds for their antiviral activity against rotavirus Wa strain (Aghaei Hakkak et al., 2024). Human respiratory syncytial virus (hRSV) is a highly contagious Paramyxovirus that is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year of age. A series of benzimidazole analogs have been identified that inhibit hRSV infection in vitro with high potency. The lead compound is SRI 29365 (1-[6-(2-furyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl]methyl-1H-benzimidazo le) having an EC50 of 66 lM (Mavrova et al., 2010).

A coumarin derivative, 7-(4-benzimidazole butoxy)-coumarin (BBC) (Figure 2), significantly declines SVCV-infected (Spring viraemia of carp) apoptosis and recovers caspase-3/8/9 activities. BBC results in a higher phosphorylation of PKCα/β that is involved in the activation of erythroid 2-related factor 2 (Nrf2) phosphorylation to favor Nrf2 translocation to nucleus at 24 and 48 h. In addition, BBC also up-regulates both antiviral responses,

heme oxygenase-1 (HO-1) expression and cellular IFN response. Therefore, treatment with BBC is effective in reducing SVCV infection and regulating SVCV-induced undesirable conditions (Andrzejewska et al., 2004; Mishra et al., 2020).

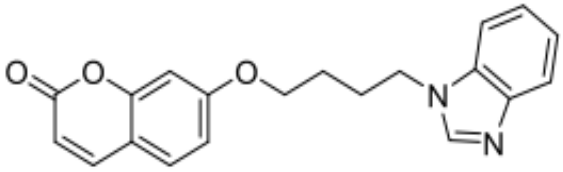


Figure 2: Structure of BBC (Andrzejewska et al., 2004).

A series of alkylated benzimidazole derivatives, 2-(5,6-dibromo-2-chloro-1H-benzimidazol-1-yl) ethan-1-ol (3a) showed anti-HIV and the compound 2b, 3-(2-chloro-5-nitro-1Hbenzimidazol-1-yl) propan-1-ol, showed excellent inhibitory property against the yellow fever virus (YFV) (Bukhari et al., 2016). Benzimidazole derivative 1-(2, 6-difluorobenzyl)-2-phenylbenzimidazole is an effective inhibitor of HIV-1 reverse transcriptase (RT) which is the causative agent of AIDS (Bantho, 2022; Chen et al., 2021).

Anti-cancer

Different derivatives of benzimidazole have been developed, which have demonstrated anticancer activity (Haider and Yar, 2022; Satija et al., 2022). Anticancer characteristics of benzimidazole derivatives are due to their resemblance to nitrogenous base, purine. Intercalation, alkylating agents, topoisomerases, DHFR enzymes, and tubulin inhibitors are all processes through which benzimidazole derivatives have anticancer effects (Akhtar et al., 2020).

Benzimidazole derivatives have anticancer properties, as these derivatives show a broad range of biological activities because they resemble a naturally occurring nitrogenous base i.e., purine. Benzimidazole derivatives have anticancer properties through multiple mechanisms such as intercalation, alkylating agents, topoisomerases, DHFR enzymes and tubulin inhibitors. The benzimidazole agents are effective in anticancer effects and their mechanisms are selective as they have structure activity relationships (Hernández-Ochoa et al., 2020; Mavvaji and Akkoc, 2023).

Benzimidazole hybrids are synthesized after substitution on triazene compound of triazene benzimidazole. On 60 human tumor cell it shows effectiveness after 1 to 5 doses. These compounds are also effective in inhibition of DHFR especially 6b is most effective in inhibiting DHFR and through molecular modeling studies stabilized interaction of 6b with enzyme's active site of DHFR is identified (Chikkula and Sundararajan, 2017).

A research was conducted in order to make effective anticancer compounds of benzimidazole in which it was substituted at 2 positions. These new compounds were tested in vitro anticancer screening and it was found that they all have anticancer effects against human hepatocellular carcinoma, human breast adenocarcinoma, and human colon carcinoma, cell lines (de la Torre et al., 2017).

UK-1 is a structurally unique bis (benzoxazole) natural product isolated from a strain of Streptomyces. UK-1 has been reported to possess anticancer activity but no activity against bacteria, yeast, or fungi (Ersan et al., 2022). Four classes of UK-1 analogues were synthesized and their cytotoxicity testing against human A-549, BFTC-905, RD, MES-SA, and HeLa carcinoma cell lines was determined. The results revealed that UK-1 and four of these analogues (15–18) are potent against the cancer cell lines. In particular, compound 16 is more potent than UK-1 against A-549 and HeLa cell lines, and compounds 15, 17, and 18 selectively exhibit potent cytotoxic activity against the BFTV-905 cells (IC50 9.6 lM), A-549 cells (IC50 6.6 lM), and MES-SA cells (IC50 9.2 lM), respectively (Di et al., 2020).

Benzimidazole ring is also effective in many biological and clinical applications because of its heterocyclic derivatives which are isosteres of natural nucleotides due to which they can easily interact with biological macromolecules having anticancer effects (dos Santos Nascimento et al., 2019). A new series of bis-benzimidazole clubbed with primary amine (3i-iii) and aromatic aldehydes (4i-ix) were design and synthesize with an intention to search an anticancer lead compound under microwave irradiation in good yields. Further, the spectral characterization of synthetic compounds was done with modern instrumental techniques such as FTIR, NMR (1 H and 13C), MS and elemental analysis. Anticancer activities of synthesized compounds were investigated at National Cancer Institute (NCI) against NCI 60 cell line panel, results showed good to notable

anticancer activity (Eswayah et al., 2017; Rashid, 2020).

The anticancer activity of some of the newly synthesized compounds was evaluated against HEPG2 (human liver carcinoma cell line) and PC12 (pheochromocytoma of the rat adrenal medulla) cells. Benzimidazole-2-isoxazole 5a derivative exhibited high potency against HEPG2 and PC12 cells. Benzimidazole chalcones 2c,e, benzimidazole mercapto acetohydrazide 14 and benzimidazole thiosemicarbazide 15a,b derivatives gave high potency against PC12 cells (Gaba et al., 2015).

The Cu complex with benzimidazole is studied as anticancer agents, and these compounds have cytotoxicity against A549 adenocarcinoma alveolar basal epithelial cells. This anticancer activity of benzimidazole derivatives is higher than any $CuCl_2.2H_2O$ or individual ligands. Electron paramagnetic resonance and UV-V spectroscopies were used to study the behavior of complexes, which shows two solvated species types in buffer and also coordinate and non-coordinate interaction and weak interactions with DNA. DNA studies using agarose gel electrophoresis results in strand cleavage by these complexes in the presence of ascorbate mediated by reactive oxygen species and ROS also result in damage of A549 (Nguyen et al., 2022; Revanasiddappa et al., 2023).

Benzimidazole are reacted with transition metal complexes Cu, Co, Zn with ligand and form three complexes 1,2 and 3, on examination with biomolecules i.e., calf thymus DNA. These complexes have nuclease activity against pBR322 DNA and this DNA cleavage pattern were studied in presence of radical scavengers, also these complexes 1 to 3 have cytotoxicity which were studied against 5 human cancer cell lines, i.e., HeLa, SK-MEL-1, HepG2, HT108, and MDA-MB 23. In vivo studies of complexes 1 to 3 are effective against anticancer cell lines and in vivo toxicities in mice is also studied (Kamat et al., 2021; Karaaslan, 2020).

Anti-protozoal

Benzimidazole derivatives have also showed strong antiprotozoal activity in various studies (Brishty et al., 2021; Moreno-Herrera et al., 2021). A series of twelve new 2-(methylthio)-1H-benzimidazole-5-carboxamide derivatives (1−12) were synthesized and their antiparasitic activity was tested in vitro against Giardia intestinalis, Trichomonasvaginalis and Entamoebahistolytica. Experimental evaluations showed IC50 values within the nanomolar range for all tested compounds, some showing higher activity than metronidazole and albendazole. A chemoinformatic study was used to compare the structure-activity relationship of the synthesized carboxamides with those of 91 previously studied benzimidazoles, and with some Nitazoxanide–N-methylbenzimidazole hybrids recently synthetized by our group (Figure 3). Compounds 1 and 3 were identified as prominent selective compounds against *T. vaginalis* and *G. intestinalis*, respectively, while compound 4 was found to be of broad spectrum against the three protozoans (Keurulainen, 2015).

Some thieno [2,3-d] pyrimidin-4(3H)-ones containing benzimidazol-2-yl-thioethyl- and benzimidazol-2-yl-methanethioethyl moiety in the second position of the pyrimidine ring were synthesized in order to determine their antitrichinellosis and antiprotozoal effects. The benzimidazole derivatives of thieno-[2,3-d] pyrimidin-4-(3H)-ones exhibited higher activity against *Trichinellaspiralis in vitro* in comparison to albendazole. The most active compound, 2-[2-(5-nitro-1H-benzimidazol-1-yl) ethyl]-5,6,7,8-tetrahydro [1] benzothieno[2,3-d] pyrimidin-4(3H)-one revealed 95% activity at a dosage of 5 mg/kg. The compound 2-[2-(5(6)-nitro-1H-benzimidazol-2-yl)thio]ethyl-5,6,7,8-tetrahydro[1]-benzothieno[2,3-d]pyrimidin-4(3H)-one exhibited 90% efficacy (Mavrova et al., 2010).

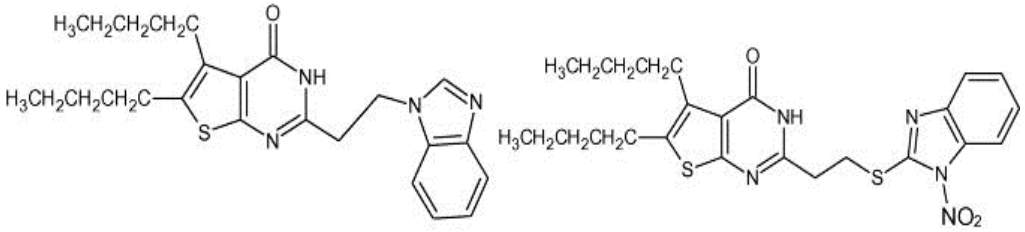
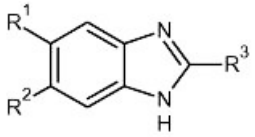


Figure 3: Structure of thieno-[2,3-d]pyrimidin-4-(3H)-ones and 2-[2-(5-nitro-1H-benzimidazol-1-yl)ethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (Mavrova et al., 2010).

Various 1-*H*-benzimidazoles have been synthesized and tested *in vitro* against the protozoa *G. lamblia*, *E.*

histolytica and the helminth *T. spiralis*. The compounds were also tested for the inhibition of rat brain tubulin polymerization and compared with standard drugs. Most of the compounds tested were more active as antiprotozoal agents than metronidazole and albendazole (Figure 4). None of the compounds was as active as albendazole against *T. spiralis* (Valdez et al., 2002). Some thio-alkylated and thio-arylated derivatives of c-substituted benzimidazole have been synthesized and evaluated as antiprotozoal activity against nosocomial strains of *S. maltophilia* using metronidazole as standard. One of the tested compounds, 4,6,-dichloro-2-(4-nitrobenzenethiol)-benzimidazole showed the most distinct antiprotozoal activity (Figure 5) (Andrzejewska et al., 2004; Gulati et al., 2022).



$R^1 = R^2 = H, Cl$ $R^3 = H, CH_3, NH_2, NHCO_2CH_3, SH, SCH_3$

Figure 4: Structure of 1-*H*-benzimidazoles (Salahuddin et al., 2017).

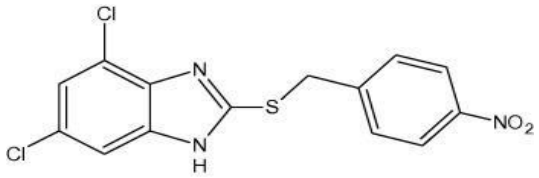


Figure 5: Structure of 4,6,-dichloro-2-(4-nitrobenzenethiol)-benzimidazole (Andrzejewska et al., 2004).

Diaz-Chiguer et al. prepared a new series of benzimidazole derivatives and evaluated in vitro (via the % of lysis of bloodstream) and in vivo for its trypanocidal activity against of *Trypanosoma Cruzi* (NINOA and INC5). In this series, compound 4a showed significant in vitro and in vivo [INC5: 68.4 (% lysis); NINOA: 46.4 (% lysis)] trypanocidal activity (Tahlan et al., 2019).

Kopanska et al. reported a series of 1*H*-benzimidazole analogues and assessed for its in vitro antiprotozoal activity against *Acanthamoeba Castellanii* and compared with chlorhexidine as reference. The screening results indicated that compounds 7a and 7b were found most efficient in reducing the figure of trophozoites and cysts (Kopańska et al., 2004).

A series of novel benzimidazole diamidines were prepared from the corresponding dicyano analogues either by applying Pinner methodology (5a–c, 10 and 13a) or by making amidoximes intermediates that were reduced to the corresponding amidines (15a–c). The new amidines were evaluated in vitro against the protozoan parasite Trypanosoma Brucei Rhodesiense (T. b. r.). The thiophene analogue 5b and the N-methyl compound 15a showed superior antitrypanosomal activity compared to that of the parent I (Abraham et al., 2018).

Torres-Gomez et al. reported some benzimidazole pentamidine compounds and assessed for their in vitro antiprotozoal activity against *L. Mexicana*, *E. histolytica*, *Giardia lamblia*, *T. vaginalis* and *Plasmodium berghei* using pentamidine and metronidazole (as reference drugs). Among the reported compounds, compound 15a showed good activity against *G. lamblia*, *E. histolytica*, *L. mexicana* and *T. vaginalis* and comparable to standard pentamidine (Díaz-Chiguer et al., 2012).

The novel benzimidazol-2-yl-fur-5-yl-(1,2,3)-triazolyldimeric series with aliphatic and aromatic central linkers was successfully prepared with the aim of assessing binding affinity to DNA/RNA and antitrypanosomal activity. UV-Visible spectroscopy, thermal denaturation showed interaction of heterocyclic bis-amidines with ctDNA. Circular dichroism studies indicated uniform orientation of heterocyclic bis-amidines along the chiral double helix axis, revealing minor groove binding as the dominant binding mode. The amidino fragment and 1,4-bis(oxymethylene)phenyl spacer were the main determinants of activity against Trypanosomabrucei. The bis-benzimidazole imidazole 15c, which had

antitrypanosomal potency in the submicromolar range and DNA interacting properties, emerged as a candidate for further structural optimization to obtain more effective agents to combat trypanosome infections (Bistrović et al., 2019; Popov et al., 2019).

It was previously demonstrated that CMC-20, a nitazoxanide and N-methyl-1H-benzimidazole hybrid molecule, had higher in vitro activity against Giardia intestinalis WB strain than metronidazole and albendazole and similar to nitazoxanide (Matadamas-Martínez et al., 2020).

Twelve novel benzimidazole derivatives were synthesized and their in vitro activities against epimastigotes of Trypanosoma Cruzi were evaluated. Two derivatives (6 and 7), which have 4-hydroxy-3-methoxyphenyl moiety in their structures, proved to be the most active in inhibiting the parasite growth. Compound 6 showed a trypanocidal activity higher than benznidazole (IC50 = 5 µM and 7.5 µM, respectively) and less than nifurtimox (IC50 = 3.6 µM). In addition, the ability of 6 and 7 to modify the redox homeostasis in T cruzi epimastigote was studied; cysteine and glutathione increased in parasites exposed to both compounds, whereas trypanothione only increased with 7 treatments. These results suggest that the decrease in viability of T. cruzi may be attributed to the change in cellular redox balance caused by compound 6 or 7 (de la Torre et al., 2017; Velázquez-López et al., 2016).

Albendazole is the most common benzimidazole drug and used as antiprotozoal (such as neurocysticercosis and hydatid disease) (Karaaslan, 2020; Reuter et al., 2000). Veliparib 2 is another potential benzimidazole anticancer drug appearing as a poly(ADP-ribose) polymerase (PARP) inhibitor and widely used in the curing of ovarian cancer, cell lung cancer and BRCA breast cancer (Keurulainen, 2015).

Anti-Inflammatory and Analgesic

The anti-inflammatory and analgesic activity of benzimidazole is also well established. (E)-N-Benzylidene-7-methyl-2-propyl-1H-benzo [d] imidazole-5-carbohydrazides were synthesized which were showing antioxidant properties and then evaluated for analgesic and anti-inflammatory actions which were also positive and further mocking studies were done to know its mechanism of action (Katikireddy et al., 2019).

A hyper-nociceptive and inflammatory induced mice was taken and given benzimidazole compound was given which proved to be reducing inflammation and also reduced pain in mice. The mechanism behind is by reducing the amounts of neutrophils (Rocha et al., 2019). The imidazole alkaloids were checked for anti-inflammatory activity using dendritic cells model they were analyzed, and it was observed that most of them tend to reduce the number of dendritic cells and thus secretion of inflammatory cytokine IL-12p40 (Di et al., 2020). Benzimidazole-thiazole hybrids linked to acetyl moiety 13, phenyl thiosemicarbazide 14, 1,3-thiazolines 15a-c and 4-thiazolidinone 16 exhibited significant COX-2 inhibition with significant COX-2 selectivity indices. Benzimidazole-thiazole hybrid 15b was the most potent dual COX-2) inhibitor. All active hybrids were subjected to docking simulation into active sites of COX-2 and 15-LOX enzymes to study the binding mode of these novel potent dual COX-2/15-LOX inhibitors (Maghraby et al., 2020).

Benzimidazole-containing tricyclic systems were synthesized to check antimicrobial activity. Results showed that the hydroxyl group at the fourth position on the aromatic ring has a substantial role in the biological activity. And this inhibits inflammation induced by the microbes (Alamgir et al., 2007; Kamat et al., 2021). Acetic acid induced writhing method was used to check analgesic activity of disubstituted benzimidazole derivatives. Mice were used for this experiment. They were fed normally and 12 hours before the experiment, the diet was stopped. Fifty mice were selected and divided into 10 groups each containing 5 mice. These mice were weighed and then given aceclofenac and acetic acid. Then after some time the number of squirms and writhings were counted and results showed that there was reduced pain in mice (Saha et al., 2020).

A new series of benzimidazole were checked for their anti-inflammatory actions for example compound like 1-[(5-substituted-1,3,4-oxadiazol-2-yl) methyl]-2-(morpholinomethyl)-1*H*-benzimidazoles. This activity was evaluated using carrageenan induced rat paw edema test.the compound showed maximum anti-inflammatory action with reduced ulcerogenic and lipid peroxidation profile and significant COX-2 inhibition (Rathore et al., 2017).

An epic N-acyl subbed indole-connected benzimidazoles and naphtha imidazoles were orchestrated. Their synthetic designs were affirmed utilizing spectroscopic instruments including 1H NMR, 13C NMR and CHN-natural investigations. Calming action for all objective mixtures was assessed in-vitro. The blended mixtures frustrate the biofilm arrangement and control the development of the microorganism, Staphylococcus epidermidis. Hostile to microbial action of the mixtures was thought about in contrast to both Gram negative and Gram-positive microorganisms, for example, Staphylococcus aureus (MTCC 2940), Pseudomonas aeruginosa (MTCC424),

Escherichia coli (MTCC 443) and Enterococcus faecalis (Abraham et al., 2018; Kavya and Sivan, 2022).

A progression of 5-methanesulfonamide benzimidazole subsidiaries were planned by consolidating the underlying highlights of clinically valuable mitigating drugs (nimesulide and rofecoxib) and antiulcer drugs (lansoprazole, omeprazole, and so forth) in view of physicochemical and 3D closeness considers. The mixtures were assessed for their mitigating movement in the carrageenan initiated rodent paw edema model accepting rofecoxib and indomethacin as standard medications. In vitro cancer prevention agent movement of the mixtures was surveyed by potassium ferricyanide decreasing force (PFRAP) measure. The mixtures 9, 10 and 11 showed calming action practically identical to the standard gathering and were likewise non-ulcerogenic at the test portions. Mixtures 6–11 displayed great cancer prevention agent impact in the focus range (1.0–50.0 µmol/ml. Fundamental hypothetical ADME profiling of the mixtures dependent on calculation of chosen physicochemical properties showed a great consistency with Lipinski's standard (Sharma et al., 2017).

As new biological activities and therapeutic potential for benzimidazole derivatives are discovered through research, this compound is gaining more attention from the academic and industrial sectors. Understanding the chemistry and biology of benzimidazole is crucial for medication development and discovery strategies targeting new health problems. The unique structural properties of benzimidazole derivatives make them intriguing prospects for future pharmaceutical breakthroughs, bringing promise for new, more effective treatments.

CONCLUSION

In conclusion, the broad-spectrum biological activities of benzimidazole and its derivatives, such as their antiviral, anticancer, antiparasitic, and anti-inflammatory qualities, have made them a focus in drug research. Benzimidazole is a promising scaffold for the development of novel therapeutic medicines due to its high affinity interactions with biological targets. These substances have a great deal of promise, according to current studies, especially when it comes to treating cancer, treating viral infections, and treating parasite infections. Because of its wide range of uses and simplicity in chemical modification, benzimidazole is a vital component in the creation of next-generation pharmaceuticals, which are in high demand due to the increasing need for innovative therapies. Subsequent investigations are anticipated to broaden its range of applications, providing new perspectives on enhancing its medicinal properties.

REFERENCES

Abraham, R., Prakash, P., Mahendran, K., Ramanathan, M., 2018. A novel series of N-acyl substituted indole-linked benzimidazoles and naphthoimidazoles as potential anti inflammatory, anti biofilm and anti microbial agents. Microbial pathogenesis 114, 409-413.

Aghaei Hakkak, R., Tiritiris, I., Schleid, T., 2024. Synthesis and Characterization of High-Energy Anti-Perovskite Compounds Cs3 X [B12H12] Based on Cesium Dodecahydro-Closo-Borate with Molecular Oxoanions (X−=[NO3]−,[ClO3]− and [ClO4]−). Molecules 29, 382.

Ahmad, N., Azad, M.I., Khan, A.R., Azad, I., 2021. Benzimidazole as a promising antiviral heterocyclic scaffold: a review. Journal of Science and Arts 21, 273-284.

Akhtar, M.J., Yar, M.S., Sharma, V.K., Khan, A.A., Ali, Z., Haider, M., Pathak, A., 2020. Recent progress of benzimidazole hybrids for anticancer potential. Current Medicinal Chemistry 27, 5970-6014.

Alamgir, M., Black, D.S.C., Kumar, N., 2007. Synthesis, reactivity and biological activity of benzimidazoles. Bioactive heterocycles III, 87-118.

Alzhrani, Z.M., Alam, M.M., Nazreen, S., 2022. Recent advancements on benzimidazole: A versatile scaffold in medicinal chemistry. Mini Reviews in Medicinal Chemistry 22, 365-386.

Andrzejewska, M., Yepez-Mulia, L., Tapia, A., Cedillo-Rivera, R., Laudy, A.E., Starościak, B.J., Kazimierczuk, Z., 2004. Synthesis, and antiprotozoal and antibacterial activities of S-substituted 4, 6-dibromo-and 4, 6-dichloro-2-mercaptobenzimidazoles. European journal of pharmaceutical sciences 21, 323-329.

Bantho, A.N., 2022. The synthesis, characterisation and antibacterial activity of benzimidazole-oxadiazole hybrids.

Bistrović, A., Stolić, I., Krstulović, L., Taylor, C.M., Kelly, M.J., Tomić, S., Bajić, M., Raić-Malić, S., 2019. Novel symmetric bis-benzimidazoles: synthesis, DNA/RNA binding and antitrypanosomal activity, 26. hrvatski skup kemičara i kemijskih inženjera (26HSKIKI); 4. simpozij Vladimir Prelog, pp. 145-145.

Brishty, S.R., Hossain, M.J., Khandaker, M.U., Faruque,

M.R.I., Osman, H., Rahman, S.A., 2021. A comprehensive account on recent progress in pharmacological activities of benzimidazole derivatives. Frontiers in pharmacology 12, 762807.

Bukhari, S.N.A., Lauro, G., Jantan, I., Fei Chee, C., Amjad, M.W., Bifulco, G., Sher, H., Abdullah, I., Rahman, N.A., 2016. Anti-inflammatory trends of new benzimidazole derivatives. Future medicinal chemistry 8, 1953-1967.

Charlson, A.J., 1973. The methanesulfonylation of 2-benzimidazolemethanol and α (2-benzimidazolyl) benzyl alcohol. Carbohydrate Research 29, 89-98.

Chen, M., Su, S., Zhou, Q., Tang, X., Liu, T., Peng, F., He, M., Luo, H., Xue, W., 2021. Antibacterial and antiviral activities and action mechanism of flavonoid derivatives with a benzimidazole moiety. Journal of Saudi Chemical Society 25, 101194.

Cheng, J., Xie, J., Luo, X., 2005. Synthesis and antiviral activity against Coxsackie virus B3 of some novel benzimidazole derivatives. Bioorganic & medicinal chemistry letters 15, 267-269.

Chikkula, K.V., Sundararajan, R., 2017. Analgesic, anti-inflammatory, and antimicrobial activities of novel isoxazole/pyrimidine/pyrazole substituted benzimidazole analogs. Medicinal chemistry research 26, 3026-3037.

de la Torre, S.M.-D., Vázquez, C., González-Chávez, Z., Yépez-Mulia, L., Nieto-Meneses, R., Jasso-Chávez, R., Saavedra, E., Hernández-Luis, F., 2017. Synthesis and biological evaluation of 2-methyl-1H-benzimidazole-5-carbohydrazides derivatives as modifiers of redox homeostasis of Trypanosoma cruzi. Bioorganic & Medicinal Chemistry Letters 27, 3403-3407.

Di, X., Wang, S., Oskarsson, J.T., Rouger, C., Tasdemir, D., Hardardottir, I., Freysdottir, J., Wang, X., Molinski, T.F., Omarsdottir, S., 2020. Bromotryptamine and imidazole alkaloids with anti-inflammatory activity from the bryozoan Flustra foliacea. Journal of Natural Products 83, 2854-2866.

Díaz-Chiguer, D.L., Márquez-Navarro, A., Nogueda-Torres, B., de la Luz León-Ávila, G., Pérez-Villanueva, J., Hernández-Campos, A., Castillo, R., Ambrosio, J.R., Nieto-Meneses, R., Yépez-Mulia, L., Hernández-Luis, F., 2012. In vitro and in vivo trypanocidal activity of some benzimidazole derivatives against two strains of Trypanosoma cruzi. Acta Tropica 122, 108-112.

dos Santos Nascimento, M.V.P., Munhoz, A.C.M., Facchin, B.M.D.C., Fratoni, E., Rossa, T.A., Sá, M.M., Campa, C.C., Ciraolo, E., Hirsch, E., Dalmarco, E.M., 2019. New pre-clinical evidence of anti-inflammatory effect and safety of a substituted fluorophenyl imidazole. Biomedicine & Pharmacotherapy 111, 1399-1407.

Ebenezer, O., Oyetunde-Joshua, F., Omotoso, O.D., Shapi, M., 2023. Benzimidazole and its derivatives: Recent Advances (2020–2022). Results in Chemistry 5, 100925.

Ersan, R.H., Alagoz, M.A., Dogen, A., Duran, N., Burmaoglu, S., Algul, O., 2022. Bisbenzoxazole derivatives: design, synthesis, in vitro antimicrobial, antiproliferative activity, and molecular docking studies. Polycyclic Aromatic Compounds 42, 3103-3123.

Eswayah, A., Khaliel, S., Saad, S., Shebani, N., Fhid, O., Belaid, A., Alsharif, T., Elforjane, H., Saadalla, Y., Baga, E., 2017. Synthesis and analgesic activity evaluation of some new benzimidazole derivatives. American Journal of Chemistry and Application 4, 30-35.

Gaba, M., Gaba, P., Uppal, D., Dhingra, N., Bahia, M.S., Silakari, O., Mohan, C., 2015. Benzimidazole derivatives: search for GI-friendly anti-inflammatory analgesic agents. Acta Pharmaceutica Sinica B 5, 337-342.

Gomez-Cabrera, M.-C., Domenech, E., Viña, J., 2008. Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. Free radical biology and medicine 44, 126-131.

Gulati, S., Singh, R., Sangwan, S., 2022. A Review on Green Synthesis and Biological Activities of Medicinally Important Nitrogen and Oxygen Containing Heterocycles. Current Organic Chemistry 26, 1848-1894.

Haider, K., Yar, M.S., 2022. Advances of benzimidazole derivatives as anticancer agents: bench to bedside. IntechOpen: London.

Hernández-Ochoa, B., Gómez-Manzo, S., Sánchez-Carrillo, A., Marcial-Quino, J., Rocha-Ramírez, L.M., Santos-Segura, A., Ramírez-Nava, E.J., Arreguin-Espinosa, R., Cuevas-Cruz, M., Méndez-Tenorio, A., 2020. Enhanced Antigiardial Effect of Omeprazole Analog Benzimidazole Compounds. Molecules 25, 3979.

Infante-Castillo, R., Rivera-Montalvo, L.A., Hernández-Rivera, S.P., 2008. Theoretical DFT, vibrational

and NMR studies of benzimidazole and alkyl derivatives. Journal of Molecular Structure 877, 10-19.

Kamat, V., Yallur, B.C., Poojary, B., Patil, V.B., Nayak, S.P., Krishna, P.M., Joshi, S.D., 2021. Synthesis, molecular docking, antibacterial, and anti-inflammatory activities of benzimidazole-containing tricyclic systems. Journal of the Chinese Chemical Society 68, 1055-1066.

Karaaslan, C., 2020. Synthesis and structure elucidation of new benzimidazole amidoxime derivatives. Turkish Journal of Pharmaceutical Sciences 17, 108.

Katikireddy, R., Kakkerla, R., Krishna, M.M., Durgaiah, G., Reddy, Y., Satyanarayana, M., 2019. Synthesis and Biological Evaluation of (E)-N'-Benzylidene-7-methyl-2-propyl-1 H-benzo [d] imidazole-5-carbohydrazides as Antioxidant, Anti-inflammatory and Analgesic agents. Heterocyclic Communications 25, 27-38.

Kavya, G., Sivan, A., 2022. Exploring the Versatility of Benzimidazole Scaffolds as Medicinal Agents: A Brief Update. Benzimidazole, 75.

Keurulainen, L., 2015. Synthesis and evaluation of antichlamydial, antileishmanial and antimalarial activity of benzimidazole and benzoxadiazole derivatives. University of Helsinki.

Kopańska, K., Najda, A., Żebrowska, J., Chomicz, L., Piekarczyk, J., Myjak, P., Bretner, M., 2004. Synthesis and activity of 1H-benzimidazole and 1H-benzotriazole derivatives as inhibitors of Acanthamoeba castellanii. Bioorganic & Medicinal Chemistry 12, 2617-2624.

Maghraby, M.T.-E., Abou-Ghadir, O.M., Abdel-Moty, S.G., Ali, A.Y., Salem, O.I., 2020. Novel class of benzimidazole-thiazole hybrids: The privileged scaffolds of potent anti-inflammatory activity with dual inhibition of cyclooxygenase and 15-lipoxygenase enzymes. Bioorganic & medicinal chemistry 28, 115403.

Mahurkar, N.D., Gawhale, N.D., Lokhande, M.N., Uke, S.J., Kodape, M.M., 2023. Benzimidazole: A Versatile Scaffold for Drug Discovery and Beyond-A Comprehensive Review of Synthetic Approaches and Recent Advancements in Medicinal Chemistry. Results in Chemistry, 101139.

Marinescu, M., 2023. Benzimidazole-triazole hybrids as antimicrobial and antiviral agents: A systematic review. Antibiotics 12, 1220.

Matadamas-Martínez, F., Nogueda-Torres, B., Castillo, R., Hernández-Campos, A., Barrera-Valdes, M.d.l.L., León-Ávila, G., Hernández, J.M., Yépez-Mulia, L., 2020. Characterisation of the in vitro activity of a Nitazoxanide-N-methyl-1H-benzimidazole hybrid molecule against albendazole and nitazoxanide susceptible and resistant strains of Giardia intestinalis and its in vivo giardicidal activity. Memórias do Instituto Oswaldo Cruz 115, e190348.

Mavrova, A.T., Vuchev, D., Anichina, K., Vassilev, N., 2010. Synthesis, antitrichinnellosis and antiprotozoal activity of some novel thieno [2, 3-d] pyrimidin-4 (3H)-ones containing benzimidazole ring. European journal of medicinal chemistry 45, 5856-5861.

Mavvaji, M., Akkoc, S., 2023. Recent advances in the anticancer applications of benzimidazole derivatives. ChemistrySelect 8, e202302561.

Mishra, S., Pandey, A., Manvati, S., 2020. Coumarin: An emerging antiviral agent. Heliyon 6.

Mohammed, L.A., Farhan, M.A., Dadoosh, S.A., Alheety, M.A., Majeed, A.H., Mahmood, A.S., Mahmoud, Z.H., 2023. A Review on Benzimidazole Heterocyclic Compounds: Synthesis and Their Medicinal Activity Applications. SynOpen 7, 652-673.

Moreno-Herrera, A., Cortez-Maya, S., Bocanegra-Garcia, V., Banik, B.K., Rivera, G., 2021. Recent advances in the development of broad-spectrum antiprotozoal agents. Current Medicinal Chemistry 28, 583-606.

Nguyen, V.-T., Huynh, T.-K.-C., Ho, G.-T.-T., Nguyen, T.-H.-A., Le Anh Nguyen, T., Dao, D.Q., Mai, T.V., Huynh, L.K., Hoang, T.-K.-D., 2022. Metal complexes of benzimidazole-derived as potential anti-cancer agents: Synthesis, characterization, combined experimental and computational studies. Royal Society Open Science 9, 220659.

Pathare, B., Bansode, T., 2021. biological active benzimidazole derivatives. Results in Chemistry 3, 100200.

Popov, A.B., Stolić, I., Krstulović, L., Taylor, M.C., Kelly, J.M., Tomić, S., Tumir, L., Bajić, M., Raić-Malić, S., 2019. Novel symmetric bis-benzimidazoles: Synthesis, DNA/RNA binding and antitrypanosomal activity. European journal of medicinal chemistry 173, 63-75.

Pullagura, M.K.P., Kanvinde, A., Raja, S., 2016. Potent biological agent benzimidazole-a review. Int. J. Pharm. Pharm. Sci 8, 22-33.

Rashid, M., 2020. Design, synthesis and ADMET prediction of bis-benzimidazole as anticancer agent. Bioorganic chemistry 96, 103576.

Rathore, A., Sudhakar, R., Ahsan, M.J., Ali, A., Subbarao, N., Jadav, S.S., Umar, S., Yar, M.S., 2017. In vivo anti-inflammatory activity and docking study of newly synthesized benzimidazole derivatives bearing oxadiazole and morpholine rings. Bioorganic Chemistry 70, 107-117.

Reuter, S., Jensen, B., Buttenschoen, K., Kratzer, W., Kern, P., 2000. Benzimidazoles in the treatment of alveolar echinococcosis: a comparative study and review of the literature. Journal of Antimicrobial Chemotherapy 46, 451-456.

Revanasiddappa, H., Shivamallu, C., Viswanath, P.M., Achar, R.R., Silina, E., Stupin, V., Manturova, N., Shati, A.A., Alfaifi, M.Y., Elbehairi, S.E.I., 2023. Novel benzimidazole derived imine ligand and its Co (III) and Cu (II) complexes as anticancer agents: chemical synthesis, DFT studies, in vitro and in vivo biological investigations. Pharmaceuticals 16, 125.

Rocha, T.M., Machado, N.J., de Sousa, J.A.C., Araujo, E.V.O., Guimaraes, M.A., Lima, D.F., Leite, J.R.d.S.d.A., Leal, L.K.A.M., 2019. Imidazole alkaloids inhibit the pro-inflammatory mechanisms of human neutrophil and exhibit anti-inflammatory properties in vivo. Journal of Pharmacy and Pharmacology 71, 849-859.

Saha, P., Brishty, S.R., Rahman, S.A., 2020. Synthesis and evaluation of disubstituted benzimidazole derivatives as potential analgesic and antidiarrheal agents. Indian J. Pharm. Sci 82, 222-229.

Salahuddin, Shaharyar, M., Mazumder, A., 2017. Benzimidazoles: A biologically active compounds. Arabian Journal of Chemistry 10, S157-S173.

Satija, G., Sharma, B., Madan, A., Iqubal, A., Shaquiquzzaman, M., Akhter, M., Parvez, S., Khan, M.A., Alam, M.M., 2022. Benzimidazole based derivatives as anticancer agents: Structure activity relationship analysis for various targets. Journal of Heterocyclic Chemistry 59, 22-66.

Sharma, R., Bali, A., Chaudhari, B.B., 2017. Synthesis of methanesulphonamido-benzimidazole derivatives as gastro-sparing antiinflammatory agents with antioxidant effect. Bioorganic & Medicinal Chemistry Letters 27, 3007-3013.

Tahlan, S., Kumar, S., Narasimhan, B., 2019. Pharmacological significance of heterocyclic 1H-benzimidazole scaffolds: a review. BMC Chemistry 13, 101.

Valdez, J., Cedillo, R., Hernandez-Campos, A., Yepez, L., Hernandez-Luis, F., Navarrete-Vazquez, G., Tapia, A., Cortes, R., Hernández, M., Castillo, R., 2002. Synthesis and antiparasitic activity of 1H-benzimidazole derivatives. Bioorganic & Medicinal Chemistry Letters 12, 2221-2224.

Velázquez-López, J.M., Hernández-Campos, A., Yépez-Mulia, L., Téllez-Valencia, A., Flores-Carrillo, P., Nieto-Meneses, R., Castillo, R., 2016. Synthesis and trypanocidal activity of novel benzimidazole derivatives. Bioorganic & Medicinal Chemistry Letters 26, 4377-4381.

Walia, R., Hedaitullah, M., Naaz, S.F., Iqbal, K., Lamba, H., 2011. Benzimidazole derivatives–an overview. Int. J. Res. Pharm. Chem 1, 565-574.

Walker, K.A., Braemer, A.C., Hitt, S., Jones, R.E., Matthews, T.R., 1978. 1-[4-(4-Chlorophenyl)-2-(2, 6-dichlorophenylthio)-n-butyl]-1H-imidazole nitrate, a new potent antifungal agent. Journal of Medicinal Chemistry 21, 840-843.