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Exploring the Therapeutic Potential of 1,3-benzimidazole: An Auspicious Heterocyclic Framework

SHIVKANT PATEL[1]*, ASHIM KUMAR SEN[1], DHANYA B. SEN[1] and ASHISH SHAH[1]

[1]Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University,
At & Po. Piparia, Ta. Waghodia-391760, Vadodara, Gujarat, India.
*Corresponding author E-mail: shivapatel2609@gmail.com

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ABSTRACT

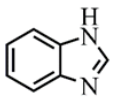
The scientific study of benzimidazole derivatives has advanced steadily due to its fascinating chemical structure with wide range of biological activities. This unique organic nitrogen bridged heterocyclic compounds have found applications in pharmaceuticals, organometallics, and natural products, establishing themselves as indispensable tools for medicinal chemists. To gather scientific insights, comprehensive searches were conducted across databases such as Google, PubMed, Scopus, Google Scholar, and others. This research highlights pharmacological profile of 1,3-Benzimidazole derivatives while examining their pharmacological characteristics and therapeutic potential, including antimicrobial, anticancer, antiviral, antidiabetic, antitubercular, antifungal, antimalarial, and anti-inflammatory effects. The 1,3-benzimidazole scaffold is a cornerstone in numerous natural and pharmaceutical products and serves as the basis for several clinically approved drugs, such as the antihistamine drug lerisetron, the antiviral agent maribavir, the proton pump inhibitor omeprazole, the anthelmintic triclabendazole, and the Anti-fungal chlormidazole. Recent developments in the pharmacological uses of 1,3-benzimidazole derivatives in a variety of therapeutic domains are explained in this thorough study. Furthermore, detailed molecular docking studies are included, providing medicinal chemists with valuable insights and a robust framework for future drug development efforts.

Keywords: Nitrogen-based heterocycle, 1,3 benzimidazole, Antimicrobial, Anticancer, Antiviral, Anti-diabetic, Anti-tuberculosis, Antifungal, Anti-Malarial, Anti-Inflammatory.

INTRODUCTION

The study of heterocycles forms the foundation of new drug discovery. Benzimidazole and its derivatives represent a significant class of synthetic compounds within heterocyclic systems[1]. A type of heterocyclic aromatic organic compounds known as benzimidazole is made up of benzene rings fused with imidazole rings at certain locations. The nitrogen atoms of its core structure found in many pharmacologically active compounds. It is known to have an array of biological effects, including as those on bacterial infections, TB, diabetes, inflammation, cancer, and viruses. Its ability to facilitate the synthesis of various therapeutic drugs underscores its versatility in medicinal chemistry[2]. For many bio heterocyclic molecules having a range of rationally active pharmacologic actions,

benzimidazole is a necessary pharmacophore. Benzimidazole's NH bunch is very acidic and somewhat basic[3]. Moreover, has the ability to create salts. Benzimidazole is a component that helps the pharmaceutical business grow. of novel compounds used in medicine. As a result, synthesis of different benzimidazole subsidiaries have been accounted for their medicinal properties[4].



1,3-benzimidazole

Fig. 1. Structure of 1,3-Benzimidazole[17]

The advancement of drugs derived from benzimidazole has resulted in several derivatives that are presently available for the treatment of various conditions. These include the antihistamine drug lerisetron, the antiviral agent maribavir[5], the proton pump inhibitor omeprazole[6], the anthelmintic triclabendazole[7], and the Antifungal chlormidazole[8], (Fig. 2). The versatility of benzimidazole scaffolds has captured the attention of numerous research groups. This review provides a comprehensive summary of recent studies (2019–2024) on the diverse medicinal applications of 1,3-benzimidazole compounds, including their roles as anti-tubercular[9], anticancer[10], antidiabetic[11], antifungal[12], antimicrobial[13], anti-inflammatory[14], antiviral[15], and antimalarial[16] agents. Medicinal chemists may clearly grasp therapeutic profile of these derivatives because to the presentation of detailed insights into SAR and molecular docking studies. For clarity and convenience, the benzimidazole derivatives have been systematically categorized based on their distinct chemotherapeutic properties, accompanied by concise summaries of key findings.

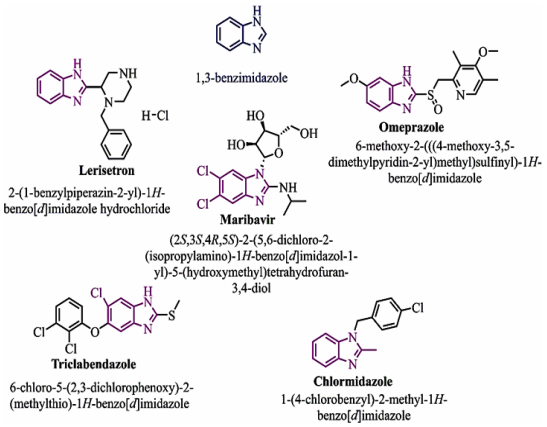


Fig. 2. 2D structures of 1,3-Benzimidazole based medlclnes[5-8]

Molecular Structure and Chemical properties of 1,3-Benzimidazole

Benzimidazole is the benzo subordinate of imidazole (Fig. 1), a set of aromatic bicyclic chemical compounds with six carbon atoms of benzene ring fused to 5 membered imidazole at 4th and 5th places of the imidazole ring. This was formerly known as glyoxalin. It is sometimes referred to as 1H-Benzo[d] imid- or 1H-1,3-Benzimidazole azole, with IUPAC name 1H-benzimidazole. It was first made by Hobrecker in 1872[17]. Numerous studies have been conducted on these derivatives, which show a broad variety of biological and chemical reactivity. They are essential pharmacophore with numerous biological acitivities[18]. Chemical formula of benzimidazole is $C_7H_6N_2$, and its molecular weight is 118 .14 g/mol^{-1}. Its M.P. is 170 to 172°C/1 mmHg[19], its boiling point is greater than 250°C/1 mmHg and its density at 20°C is 0.947 g/cm^3. By nature, it is a solid Its log P value is 0.90 (Fig. 3). It follows Lipinski rule of 5[20].

Physiocochemical Properties
Formula: $C_7H_6N_2$
Molecular weight: 118.14 g/mol
Number of heavy atoms: 9
Number of aromatic heavy atoms: 9
Fraction Csp^3: 0
Number of rotatable bonds: 0
Number of H-bond acceptors: 1
Num.ber of H-bond donors: 1
Molar Refractivity: 36.90
TPSA: 28.68 Å^2
Lipophilicity
Log $P_{o/w}$ (iLOGP): 0.90
Pharmacokinetics
GI absorption: High
BBB permeant: Yes
P-gp substrate: No
CYP1A2 inhibitor: Yes
CYP2C19 inhibitor: No
CYP2C9 inhibitor: No
CYP2D6 inhibitor: No
CYP3A4 inhibitor: No
Medicinal Chemistry
PAINS: 0 alert
Brenk: 0 alert
Leadlikeness: No; 1 violation: MW<250
Synthetic accessibility: 1.00

Fig. 3. Physlochemlcal Propertles of Benzimidazole[20]

Pharmacological activity of benzimidazole derivatives:

1,3-benzimidazole as anticancer agents

Cancer is a serious illness categorized by unchecked cell division that has the ability to spread to neighbouring tissues[21]. Since the majority of people with breast, lung, colon, or ovarian cancer present with metastatic progression, metastasis is responsible for around 90% of cancer related deaths[22]. Research by the American Cancer Society indicates that over twenty million new cancer cases were diagnosed worldwide in 2022, resulting in

9.7 million fatalities from the illness. By 2050, the global incidence of cancer is anticipated to reach 35 million cases. Cancer has emerged as a harsh reality in human lives, largely due to the resistance developed against available drugs. Consequently, the discovery of novel anticancer agents has become crucial. Benzimidazoles hold significant potential in the development of anticancer therapies, as they inhibit various enzymes implicated in cancer pathology, such as tyrosine kinase and raf kinase[23].

The search for innovative anticancer drugs has driven new strategies to overcome medication resistance and improve therapeutic outcomes. Padhy *et al.,*(2019) introduced one such strategy, focusing on the creation of hybrid molecules that merge structural features of Nbenzyl benzimidazole and pyrimidine derivatives. These compounds were then tested for their anticancer activity against the MDA-MB-231 cell line. Among them, compound 1 revealed the strongest anticancer activity with a GI_{50} value of 39.6 µM, while compound 2 followed with a GI_{50} value of 84.0 µM. These results shown compound 1 as a promising candidate for further optimization into more potent anticancer therapies[24]. Shinde *et al.,* (2020) reported a highly effective method for synthesizing benzimidazole nucleosides (3a to 3h), starting from the easily accessible Dglucose. After this they developed two distinct types of nucleosides. The first type, ribofuranosyl nucleosides (3a-3d), was created by incorporating different benzimidazole bases, while the second type (3e-3h) comprised deoxy-nucleosides. These newly developed compounds were tested for their anticancer potential against the MDA-MB-231 cell line. The findings indicated that the nucleosides with 3'-azide substitutions (3e-3h) exhibited greater potency compared to the ribofuranosyl series. Compound 3h, a C-3'-azido derivative, exhibited the highest anticancer activity (IC_{50} = 0.42 m) establishing potential candidate for new drug development comparable to etoposide[25] (0.36 µM). Anichina and colleagues (2021) described the production and structural analysis of fifteen benzimidazolyl-2-hydrazones, which were derived from -hydroxy, -fluoro and -methoxy substituted benzaldehydes[26]. These compounds were tested for the *in-vitro* cytotoxicity against MCF-7 breast cancer cells and 3T3 embryo mouse fibroblasts. Among them, compounds 4 and 5 showed IC_{50} values of 16.54 µg/mL and 17.40 µg/mL, respectively comparable to Nocodazole (1.54 µg/mL). These results indicate that the synthesized benzimidazole derivatives as potential cytotoxic agents[27]. Nguyen and colleagues (2022) reported the of 14 metal complexes incorporating Ag(I), Zn(II) and Cu(II) ions, using bis-benzimidazole derivatives. The successful incorporation of metals was confirmed via ICP optical emission spectrometry. The cytotoxic activity of the metal complexes was evaluated against cell lines: A549 (for lung), MDA-MB-231 (for breast), and PC3 (for prostate) cancer cells. Results indicated that the metal complexes displayed significantly enhanced antiproliferative activity compared to their metal ligands. Notably, Ag(I) and Zn(II) complexes showed the strongest cytotoxic effects, particularly against MDA-MB-231 breast cancerous cells. From the tested compounds, compound 6 exhibited remarkable multitarget anticancer activity, effectively inhibiting the growth of all 3 cancer cell lines with IC50 values below 10.4 µM. These results suggest that bis-benzimidazole-based metal complexes, particularly Zn(II) derivatives, hold promise as potential anticancer agents for further development[28]. Padhy *et al.,*(2023) emphasized the pressing need for novel anticancer agents to overcome the challenge of resistance to existing drugs. Both pyrazolines and benzimidazoles are known for their notable anticancer properties. To leverage this, the study adopted a hybrid strategy, adding the core structures of pyrazoline and benzimidazole into a one entity. The biological evaluation demonstrated the growth inhibitory effects of these compounds against the breast cancerous cell line MDA-MB-231. Among compounds tested, compounds 7 and 8 (GI_{50}: 26.13 µM and 12.27 µM) exhibited noteworthy anticancer activity. These results highlight the efficacy of benzimidazole pyrazoline hybrids as promising candidates for further advancement in anticancer drug development[29]. Chojnacka and colleagues (2024) developed an efficient approach for synthesizing new 4,5,6,7-tetrabromo-1Hbenzimidazole (TBBi) derivatives. These compounds showed notable cytotoxic effects against cancer cell lines, including MCF7 and CCRFCEM. Among the tested compounds, Compound 9 demonstrated the most potent cytotoxicity, with IC_{50} values of 5.30 µM and 6.80 µM for MCF-7 cells and CCRF-CEM cells, respectively. These results underscore the efficiency of these TBBi compounds for further exploration as anticancer agents[30] (Figure 4).

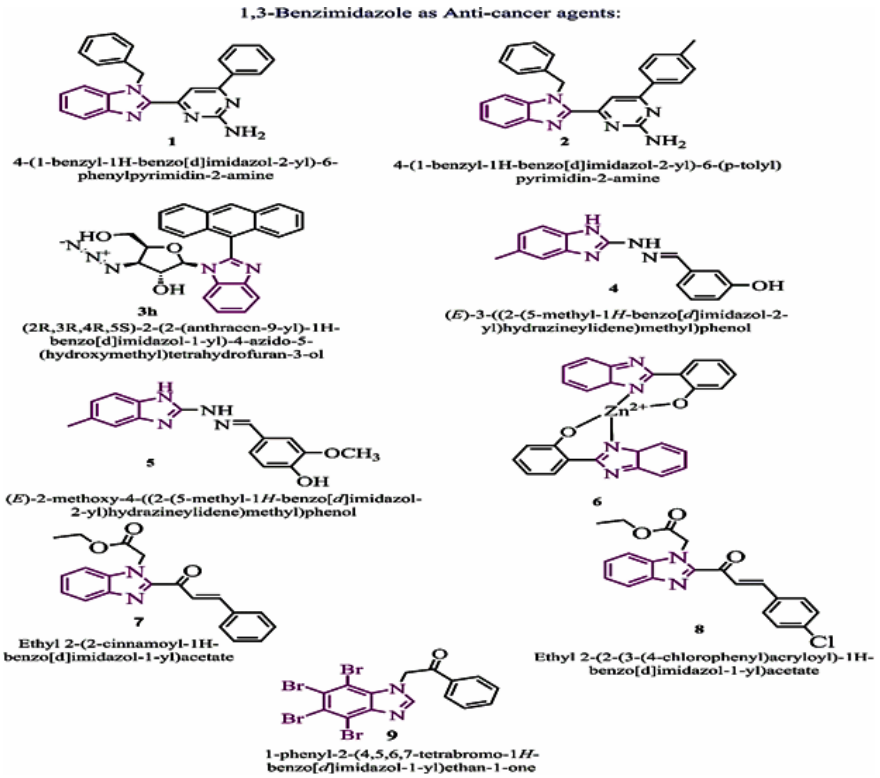


Fig. 4. 2D structures of 1,3-Benzimidazole as antl-cancer agents[24-30]

1,3-Benzimidazole as anti-microbial agents

Due to their ongoing development of resistance to several antimicrobial agents, bacteria, viruses, fungi, and parasites present serious threats to world health. Despite extensive efforts to address this issue, microbial resistance remains a critical concern[31]. The persistence and prevalence of these pathogens are driven by their ability to adapt, mutate, and evade the action of novel drugs, coupled with the potential toxicity and limited selectivity of certain therapeutic candidates. These infections adversely impact human health, livestock, and ecosystems, often resulting in significant morbidity and mortality. This ongoing threat underscores the urgent need to discover and develop new compounds with improved bioactive properties[32]. Among heterocyclic compounds, those containing N, O, S, atoms are particularly significant. Nitrogen-based heterocycles, such as imidazole and benzimidazole, serve as the core structures for numerous pharmacologically active compounds. Among these, benzimidazole derivatives are particularly notable for their strong interactions with biopolymers, making them valuable candidates in the growth of active molecules. Their structural resemblance to vitamin B12 analogues further enhances their therapeutic potential. These compounds exhibit an extensive range of biological activities, showing effectiveness against various human pathogens, including fungi, bacteria, and virus. This impressive versatility underscores their promise in addressing the urgent demand for new antimicrobial agents[33].

Fonkui and colleagues. (2019) described the successful synthesis of a range of Schiff base (10a–f). The antimicrobial activity of these Schiff bases was assessed against fourteen human pathogenic bacterial strains (comprising eight *Gram-negative* and six *Gram-positive* strains) using the microdilution method to determine their MIC. The consequences revealed that these Schiff bases possessed significant antimicrobial activity. In particular, compounds 10c and 10f demonstrated remarkable efficacy against gram-negative bacteria such as *E. coli*, and *K. pneumoniae* with MIC values as low as 7.8 µg/mL. These compounds exhibited stronger antibacterial activity comparable to nalidixic acid, which showed much higher MIC values

(64-512 µg/mL) against *E. coli* and *K. pneumoniae*. These findings underscore the credible of Schiff bases incorporating benzimidazole moieties as potential candidates for the growth of novel antimicrobial agents, especially for treating *Gram-negative* bacterial infections[34]. Marinescu *et al.,* (2020) reported the novel chiral Mannich base via a three-component reaction involving benzimidazole, various amines and 30% aqueous formaldehyde. The antibacterial properties of these compounds were assessed in vitro against three microbial strains using both qualitative and quantitative methods. Among the tested compounds, compound 11 displayed exceptional antimicrobial activity, with a MIC of 0.031 µg/mL against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*. This level of activity exceeded that of the erythromycin, which exhibited an MIC of 0.062 µg/mL against the same microorganisms. These results emphasize the chiral benzimidazole Mannich bases as auspicious antimicrobial agents[35]. Vlasov *et al.,* (2021) tackled the critical challenge of bacterial resistance to existing antibiotics by investigating novel antibacterial agents targeting previously unexplored mechanisms of action, specifically the inhibition of tRNA (Guanine37-N1) -methyltransferase (TrmD), a vital enzyme for bacterial survival. The study centered on designing and synthesizing heterocyclic hybrids that integrate thieno [2¸3d] pyrimidine and benzimidazole frameworks. Antimicrobial testing revealed that all synthesized compounds demonstrated activity against both *Gram-positive* and *Gram-negative* bacteria. Among them, compound 12 displayed the most noteworthy antimicrobial activity, producing the largest zone of inhibition, thereby highlighting its potential as a promising lead for developing new antibacterial therapies. The pursuit of antimicrobial agents capable of overcoming resistance to existing antibiotics remains a critical objective in medicinal chemistry[36]. Diaconu and colleagues. (2022) investigated two innovative groups of hybrids quinoline-benzimidazole derivatives QIBS salts and QIBC cycloadducts-for their antimicrobial potential. The compounds were synthesized through a straightforward and efficient four step process. The antibacterial properties of these hybrids were evaluated, yielding promising outcomes. Notably, among the hybrid QIBS salts, compounds 13, 14, and 15 demonstrated significant activity against *Gram-negative Escherichia coli*, with inhibition zone diameters reaching up to 20 mm. This performance considerably surpassed that of the standard antibiotic gentamicin, which produced inhibition zones of 8–12 mm. These outcomes highlight the potential of hybrid quinoline-benzimidazole derivatives as capable candidates for the development of novel antimicrobial agents. Their exceptional efficacy, particularly against *E. coli*, underscores their potential in addressing *Gram-negative* bacterial infections[37]. In the exploration for novel antimicrobial agents, Lungu and colleagues (2023) done a study focusing on the production and *in-vitro* evaluation of novel homodrimane sesquiterpenoids incorporating a benzimidazole moiety. Seven compounds were synthesized, categorized as 2-homodrimenyl-1¸3-benzimidazoles and N-homodrimenoyl-2-amino-1¸3-benzimidazoles, using a stepwise methodology. The antibacterial activity of these compounds was tested against *Pseudomonas aeruginosa* and *Bacillus* sp. Among the compounds, compound 16 exhibited remarkable antimicrobial activity, with MIC values of 0.05 µg/mL and 0.032 µg/mL, respectively. These MIC values were notably lower than those of reference antibiotics, including caspofungin (0.32 µg/mL) and kanamycin (2.0 µg/mL). This study underscores the potential of homodrimane sesquiterpenoids containing benzimidazole moieties as promising candidates for developing new antimicrobial agents, demonstrating superior efficacy compared to conventional antibiotics38. Samreen and colleagues (2024) created and produced fused tricyclic benzimidazole–thiazinone derivatives and evaluating their antimicrobial efficacy. Ten compounds were synthesized using a one-pot reaction. Among them, compound 17 stood out as the most promising, demonstrating notable inhibition of *Escherichia coli* and *Pseudomonas aeruginosa* at conc. of 512 µg/mL and 256 µg/mL respectively. Further analysis revealed that compound 17 exhibited a synergistic effect when combined with ciprofloxacin, indicating its potential in combination therapies. These finding highlights the use of fused tricyclic benzimidazole–thiazinone derivatives[39] (Figure 5).

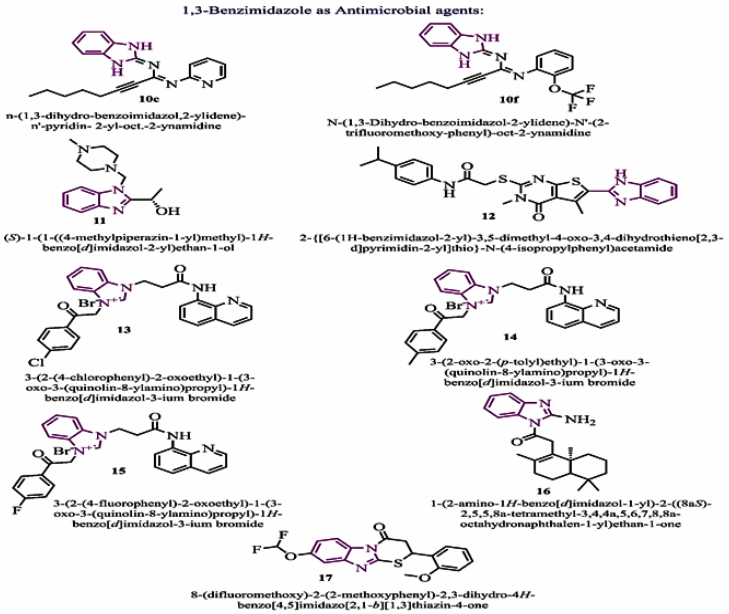


Fig. 5. 2D structures of 1,3-Benzimidazole as antImicroblal agents[34-39]

1,3-Benzimidazole as antitubercular agents

Tuberculosis introduced by the bacteria *M. tuberculosis*[40] is a significant global health concern. It ranks as the 13th leading cause of mortality worldwide. Antimicrobial medicines, including first-line treatments such as isoniazid, and pyrazinamide together with second-line medications like aminoglycosides and fluoroquinolones, constitute the cornerstone of tuberculosis treatment[41]. The rise of drug-resistant Mtb strains has significantly complicated sickness management. The emergence of multidrug-resistant TB has complicated and increased the cost of treatment efforts. This emphasizes how urgently new treatment medicines with a lower risk of resistance must be developed. It is thought that substituted benzimidazoles work by weakening the bacterial cell wall, which eventually causes the bacterium to die. According to a different generally recognized theory of how they work, benzimidazoles prevent the synthesis of vital proteins and nucleic acids needed for bacterial growth by interfering with purine metabolism[42]. Benzimidazoles are interesting options in the battle against bacterial infections because of these two processes. The logical creation and synthesis of such substances may pave the way for novel approaches to TB treatment, providing potent remedies that specifically target drug-resistant strains. Researchers may investigate a wide variety of alterations to find derivatives with better therapeutic potential and lower resistance risk by using the structural plasticity of the benzimidazole scaffold. This strategy is a vital step in tackling the increasing difficulties in treating tuberculosis[43].

The effectiveness of current antibiotic therapies is declining due to resistance, underscoring the urgent need for novel therapeutic agents with enhanced potency and specificity. Targeting Decaprenyl phosphoryl-β-D-ribose-2'-oxidase a key enzyme involved in Mtb cell wall biosynthesis, A study by Surineni *et al.,*(2019) explored this approach by designing and synthesizing new benzimidazole allylidene hydrazinyl methyl thiazole derivatives. Their method utilized a multicomponent molecular hybridization strategy, combining three important antitubercular pharmacophores-2-aminothiazole, benzimidazole, and substituted α,β-unsaturated ketones-into a single molecular structure through condensation reactions. These derivatives were then assessed for *in-vitro* antitubercular activity against the H37Ra strain of Mtb. Among the synthesized compounds, several demonstrated notable antitubercular activity, with compounds 18 and 19 showing the highest efficacy, achieving a MIC of 2.5 µg/mL. Compound 18 stood out due to its relatively low cytotoxicity. While the MIC values of these compounds were higher than rifampicin (0.25 µg/mL). This research highlights the value of molecular hybridization in drug design, particularly the integration of well-established pharmacophore scaffolds to improve biological

activity and pharmacological properties. The study underscores the probability of benzimidazole derivatives as promising candidates in the fight against drug-resistant TB, laying a foundation for future investigations into lead optimization and the development of more effective antitubercular agents[44]. Antoci *et al.,*(2020) explored a novel strategy for developing anti-TB agents by integrating three distinct benzimidazole, pharmacophores pyridine, and *p*-chlorobenzoyl moieties into a single molecular framework. Bis-pyridine benzimidazole derivatives were synthesized using a direct method involving two consecutive N-alkylation steps. Fifteen synthesized compounds were tested against H37Rv in an aerobic primary antimycobacterial assay. Among these, compound 20 exhibited remarkable activity against Mtb H37Rv. Subsequent secondary screening revealed its potency against both nonreplicating and replicating forms of Mtb, demonstrating greater efficacy than the reference drug metronidazole. Compound 20 also showed strong intracellular activity, effectiveness against drug-resistant Mtb strains. Furthermore, it displayed modest to strong activity against nontuberculous mycobacteria (NTM). Pharmacokinetic studies of compound 20 highlighted its excellent drug-like properties, including sustained duration of action extended half-life *in vivo*, low clearance rates, and minimal potential for drug-drug interactions. Importantly, the compound exhibited no cytotoxic effects on eukaryotic cells, such as THP-1 human monocytic cells and HepG2 hepatocyte cells. Compound 20 demonstrated an IC_{50} value of 17 μM, beating rifampicin IC_{50}>50 μM. These findings underscore the likely of compound 20 as a promising lead for future drug growth. Its potent antimycobacterial activity, favourable pharmacokinetic profile, and noncytotoxic nature position it as an excellent candidate for combating drug-resistant Mtb and advancing TB treatment strategies[45]. Haranahalli *et al.,* (2021) carried out comprehensive structure activity relationship studies to design and develop novel 2,5,6trisubstituted benzimidazoles as potential antitubercular agents. These compounds were specifically aimed at inhibiting the filamenting temperature sensitive protein of Mtb, a key protein essential for bacterial cell division. A new group of trisubstituted benzimidazoles was produced and evaluated against the Mtb-H37Rv strain. The compounds displayed MIC values ranging from 0.004 to 50 μg/mL. Among these, compound 21 demonstrated exceptional potency, with MIC values range between 0.004 and 0.08 μg/mL. Further evaluations identified compound 21 as the most promising candidate, achieving an MIC as low as 0.0039 μg/mL, underscoring its remarkable potential as an antitubercular agent. The SAR analysis, combined with 3D-QSAR modeling, identified compound 21 as the lead compound, emphasizing the significance of specific structural modifications at the 2-position in enhancing activity. The application of 3D-QSAR modeling proved instrumental in predicting and rationalizing the potency of the compounds, providing a valuable framework for designing highly effective antitubercular agents. This study highlights the potential of 2,5,6trisubstituted benzimidazoles as promising candidates in the fight against tuberculosis. The outstanding potency of compound 21 suggests its viability for further preclinical development. The ongoing emergence of drug-resistant Mtb strains underscores importance of identifying novel drug targets and developing compounds with selective and effective inhibitory properties. Strategies focusing on essential Mtb structures, including the cell wall, continue to be a focal point in overcoming drug resistance and advancing TB therapies[46]. Ersan *et al.,* (2022) evaluated the antitubercular potential of 23 benzimidazole derivatives to identify molecules with significant inhibitory activity against key *Mycobacterium tuberculosis* (Mtb) enzymes. Their investigation began with experimental assessments of the compounds' anti tubercular activity, followed by molecular docking studies targeting four essential enzymes: Filamentous Temperature Sensitive Protein Z, Arabinosyltransferase C, Protein Tyrosine Phosphatase B, and Decaprenylphosphoryl-β-D-ribose2'-oxidase. Among these, DprE1 was prioritized due to its critical role in synthesizing the arabinogalactan layer of the mycobacterial cell wall and its association with drug resistance, making it a promising target for novel antitubercular agents. Molecular docking tools, including AutoDock Vina and CDOCKER, were used to evaluate the binding affinities of the derivatives against DprE1. The docking studies revealed binding affinities below -8.0 kcal/mol, indicating strong interactions with the target enzyme. Among the 23 derivatives, compound 22 emerged as the most promising, displaying the maximum binding attraction and an MIC of 7.81 μg/mL. Although its MIC was higher than isoniazid (MIC = 0.97 μg/mL), compound 22 demonstrated notable potential as a lead molecule for further optimization and development[47]. Thapa and group in 2023 investigated the anti-TB likely of a series of small molecules derived from substituted benzimidazole scaffolds. In their

study, 12 benzimidazole derivatives were synthesized, incorporating various electron donating and electron withdrawing substituents to evaluate the impact of structural modifications on biological activity. The antitubercular activity of the derivatives was tested against MTB using the MABA. Among the tested compounds, derivatives 23 and 24 exhibited the most potent activity, with MIC values of 0.8 µg/mL, better than isoniazid. Further cytotoxicity assessments on the HCT-116 cell line revealed that both compounds were non-toxic, with IC_{50} values exceeding 250 µg/mL. The strong antitubercular activity and low cytotoxicity of compounds 23 and 24 position them as promising candidate's drug-resistant strains of MTB[48]. Almansour *et al.,* (2024) reported a sustainable and efficient method for synthesizing 2-(diethoxy methyl)-1-tosyl-1H-benzo[d]imidazole (compound 25) using an eco-friendly, ionic liquid based green protocol. This approach enabled the high yield synthesis of compound 25. Hirshfeld surface analysis revealed the primary intermolecular interactions contributing to the stability of the solid-state structure, highlighting H-C (21.6%), H-H (51.1%), O-H (18.9%), and N-H (6.3%) interactions. Key short contacts, including N2-H6 (2.55 Å), O3-H7 (2.55 Å), and H11C-H11C (1.96 Å), were found to play a critical role in crystal stability. Biological evaluation demonstrated that compound 25 exhibited important antitubercular activity against MTBH37Rv, with MIC of 3.12 µg/mL, comparable to ethambutol (MIC: 1.56 µg/mL). These findings feature the potential of compound 25 as a promising candidate for tuberculosis therapy, supported by both experimental and computational analyses[49](Figure 6).

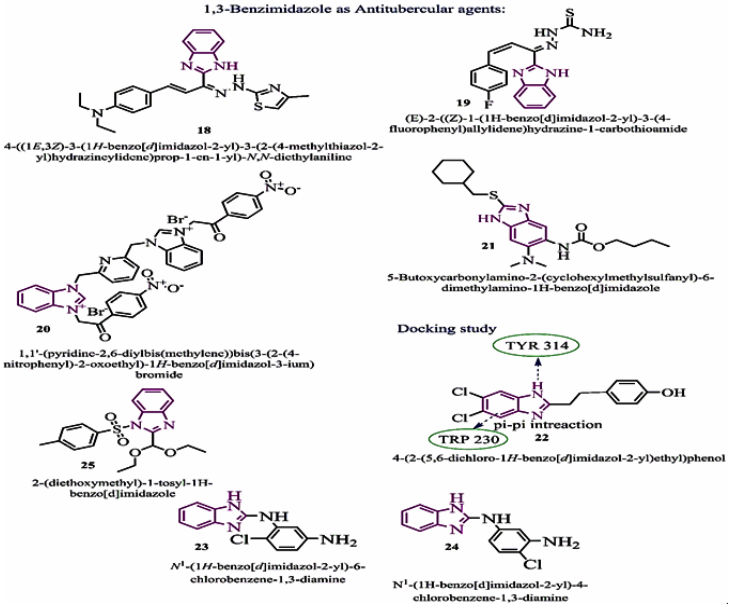


Fig. 6. 2D structure of 1,3-Benzimidazole as antItubercular agents[44-49]

1,3-Benzimidazole as anti-inflammatory agents

The body uses inflammation as a natural defence mechanism, playing a critical role in protecting against infectious agents and foreign substances. Additionally, it facilitates the healing process in various disease conditions. However, when the inflammatory response becomes dysregulated, it can cause significant harm rather than providing benefits. Excessive inflammation, or hyperinflammation, is a driving factor in the progression of numerous diseases[50]. Acute inflammation, on the other hand, often makes infectious disorders like COVID-19[51], dengue[52], and chikungunya[53] worse. Since anti-inflammatory drugs frequently have a variety of pharmacological effects and hyperinflammation plays a crucial role in disease pathology, it is crucial to continuously find and create new scaffolds with anti-inflammatory potential in order to advance them as bioactive therapeutic candidates. As a preferred structural framework, benzimidazole has been thoroughly investigated for its potential therapeutic uses in both infectious and noncommunicable disorders. Significant attempts have been made in recent years to create anti-inflammatory drugs based on benzimidazoles. Thus, in order to assess their potential as anti-inflammatory medicines, we synthesized novel benzimidazole derivatives[54].

Movahed *et al.,* (2019) introduced a new group of pyrazino[1¸2a] benzimidazole compounds, incorporating an SO_2Me pharmacophore at the para position of the C3 phenyl ring. They were created, manufactured, and tested for their ability to inhibit cyclooxygenase-2 (COX-2). *In vitro* investigations of COX1/COX2 inhibition revealed compound 26 as the most effective COX-2 inhibitor, exhibiting an IC_{50} value of 0.08 µM. Additionally, compound 27 had the greatest selectivity index (SI>909) with an IC_{50} value of 0.11 µM. The IC_{50} values of both compounds were similar to that of the conventional COX-2 inhibitor celecoxib (IC_{50} = 0.06 µM). These findings highlight the promise of both compounds 26 and 27 as viable candidates for selective COX-2 inhibition and its prospective therapeutic uses[53]. Maghraby *et al.,* (2020) investigated the creation and production of novel molecular hybrids of 2-methylthiobenzimidazole, incorporating various anti-inflammatory pharmacophores through a 2-aminothiazole linker. The study aimed to evaluate the effects of these structural modifications on the inhibition of cyclooxygenase, fifteen lipoxygenase enzymes and to assess their *in-vivo* anti-inflammatory potential. Among the hybrids, compounds 28 and 29 demonstrated notable COX-2 inhibitory activity, with IC_{50} values of 0.075 and 0.045 µM, respectively, and exhibited high COX-2 selectivity indices (SI = 142 for compound 28 and SI = 294 for compound 29). Both compounds also displayed solid inhibitory effects on the 15LOx enzyme, with IC_{50} of 2.98 µM for compound 28 and 1.67 µM for compound 29. Notably, hybrid compound 29 emerged as the most effective dual inhibitor, achieving COX-2 inhibition (SI = 294, IC_{50} = 0.045 µM,) comparable to celecoxib (SI = 327 IC_{50} = 0.045 µM,). Moreover, compound 29 exhibited twice the inhibitory action against 15LOx (IC_{50} :1.67 µM) compared to quercetin (IC_{50} = 3.34 µM). These findings feature the potential of both compounds 28 and 29 as promising dual inhibitors of 15Lox and COX-2, with significant implications for anti-inflammatory drug development[56]. In 2021, Kamat and team members. synthesized a range of novel tricyclic systems containing a benzimidazole scaffold and estimated their anti-inflammatory activity along with their haemolytic potential. The anti-inflammatory properties of these derivatives were tested in-vitro using the bovine serum albumin denaturation method, yielding IC_{50} ranging from 31.16 to 94.63 µg/mL. Among the derivatives, Compound 30 demonstrated the maximum potent activity, with an IC_{50} value of 31.26 µg/mL, comparable diclofenac sodium (IC_{50} = 31.37µg/ mL). The haemolytic activity of the analogues was also assessed at a concentration of 100 µg/mL, with haemolysis percentages varying between 1.14% and 52.8%. Importantly, Compound 30 exhibited minimal haemolysis (1.14%), indicating a favourable safety profile. These results suggest that benzimidazole-based tricyclic derivatives, particularly Compound 30, have significant potential as anti-inflammatory agents with low haemolytic toxicity, making them promising candidates for further development[57]. According to Moharana *et al.,* (2022), hyperinflammation plays a crucial part in aggravating the symptoms of both infectious and noncommunicable illnesses. With several effective benzimidazole based treatments serving as examples of its use in drug development, benzimidazole has become a favoured framework among other scaffolds. In respect to investigate the anti-inflammatory potential of three new small analogues, Moharana and associates synthesized, purified, and characterized them. These substances were tested for toxicity both *in vivo* (at 100 mg per kg in female Wistar rats detected for 48 h with no observed death) and in vitro (at 100µM for twenty-four hours against 3000 Vero cell/well). Interestingly, Compounds 31 and 32 showed strong anti-inflammatory properties. These results imply that benzimidazole derivatives, in particular Compounds 31 and 32, have potential for further research as anti-inflammatory drugs that target a variety of medical disorder[58]. An essential enzyme in the human antimicrobial defence system, myeloperoxidase (MPO) mainly oxidizes essential microbial compounds by generating hypochlorous acid (HOCl) within phagolysosomes (Saylam *et al.,* 2023). MPO is implicated as a local mediator in inflammatory processes because, when released extracellularly, it produces reactive intermediates that cause tissue damage. Numerous clinical disorders, including as multiple sclerosis, cardiovascular and neurological illnesses, and renal damage, have been connected to MPO-driven oxidative stress. The enzyme's potential as a therapeutic target is emphasized by these relationships. Saylam and colleagues (2023) designed and produced a group of isomeric 1¸3-dihydro-2H-benzo[d] imidazole-2-thione derivatives in order to address this possibility. These substances have groups of amides, hydrazide, and hydroxamic acid attached to either sulfur or nitrogen

atoms. These compounds' inhibitory properties were assessed for MPO's peroxidation and chlorination cycles. With IC_{50} values of 82.71 µM and 0.39 µM for the peroxidation cycles and chlorination respectively, Compound 33 was the most effective inhibitor among the produced compounds. In contrast, flufenamic acid, the reference medication, had IC_{50} values between 40 and 50 µM. These results demonstrate the substantial inhibitory activity of molecule 33 and its effectiveness as a lead molecule for the subsequent development of MPO inhibitors[59]. NSAIDs usually work by blocking the COX-1 and COX-2. Because COX-2 is essential for many pathological processes, there is a lot of interest in specifically targeting it (Bano and colleagues, 2024). In addition to COX enzymes, several molecular targets have been linked to inflammation and other disease processes, including aldose reductase, phospholipase A2, and aldo-ketoreductase family. This broad spectrum of targets illustrates how inflammatory illnesses may be effectively treated with multitargeting medications. By creating a number of 2-substituted benzimidazole compound and assessing their anti-inflammatory properties using extensive *in-vitro* and *in-vivo* tests, Bano *et al.,* (2024) investigated this idea. With IC_{50} values of 4.6, 2.4 and 5.4 µM, respectively, the evaluated compounds 34, 35, and 36 showed better *in-vitro* antiinflammatory action, exceeding the reference medication ibuprofen (IC_{50} = 11.2 µM) in the Luminol-enhanced chemiluminescence experiment. The carrageenan induced paw edema model was used to further evaluate the *in- vivo* anti-inflammatory effectiveness of compounds 34, 35, and 36, which shown the greatest in vitro activity. Both substances nearly matched the standard diclofenac sodium (69%), with a maximal inhibition of 65% at 4 hours. At the same time period, compound 34 showed significant action as well, with a maximum inhibition of 55%. These results highlight the possibility of 2-substituted benzimidazole derivatives as viable options for creating new anti-inflammatory drugs with many targets. More research into their mechanisms of action and optimization for therapeutic application are necessary in light of the shown *in-vitro* and *in-vivo* activity[60] (Figure 7)

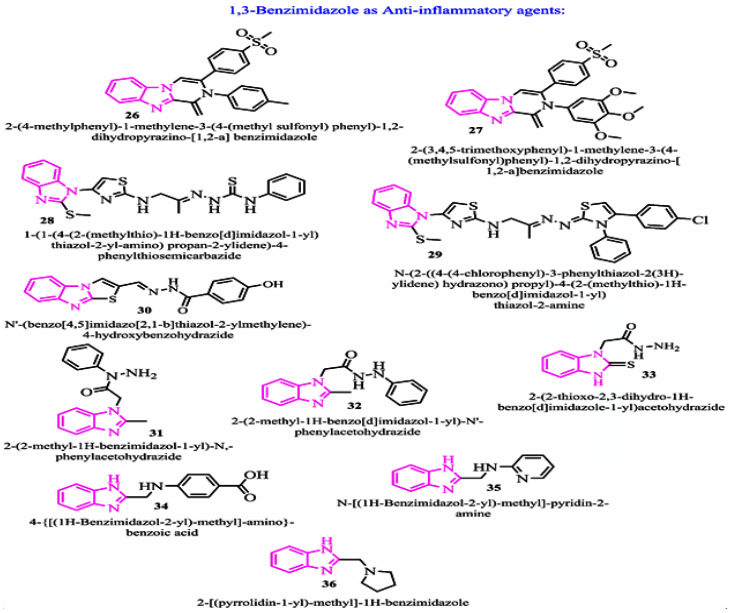


Fig. 7. 2D structures of 1¸3-Benzimidazole as antIInflammatory agents[53-60]

1¸3-Benzimidazole as anti-viral agents

Due in large part to issues like their growing variety and antibiotic resistance, bacterial infections have attracted a lot of interest from academics in recent decades. The search for new structures with antibacterial and antiviral qualities was heightened by the appearance and spread of SARS-CoV-2. A widespread variety of biological actions, including as antiviral, anticancer and anti-tubercular properties[61], have been established by benzimidazole, a structural isostere comprising indole and purine nuclei. Their biological actions are known to be greatly impacted by modifications made to the benzimidazole ring at positions 1¸ 2¸ 5¸ and 6 with

a different substitution, ranging from small groups to complex multicyclic moieties. Thus, one of the primary areas of interest in heterocyclic chemistry continues to be the investigation of structurally varied substituted benzimidazoles. Among them, antiviral benzimidazole derivatives are especially significant since several strong molecules have been found[62].

A new family of flavonoid derivatives containing benzimidazoles was produced and assessed for antiviral effects by Chen and colleagues (2020). Compound 37 showed significant antiviral effectiveness against tobacco mosaic virus among the compounds examined. According to the findings of the bioassay, compound 37 demonstrated inactivating, curative, and protective activities against TMV at 500 mg/mL, with effective doses of 54.1%, 57.6%, and 75.3%, respectively. These results either surpassed or were equal to those of the well-known antiviral drug ningnanmycin, which had analogous activity of 49.0%, 55.8%, and 82.7%. With a dissociation constant (Kd) of 1.049 ± 0.582 mmol/L, compound 37 demonstrated a significant binding affinity to the TMV coat protein (TMV-CP), according to further research using microscale thermophoresis (MST). This binding affinity (Kd = 1.058 ± 0.286 mmol/L) was marginally superior to that of ningnanmycin. These results highlight the potential of flavonoid compounds including benzimidazole as effective antiviral medicines for reducing TMV infections and maybe other related viruses[63]. The RSV, a major contributor to severe respiratory tract contaminations, was the subject of Huo *et al.,* (2021) investigation. The use of ribavirin, the only clinically licensed anti-RSV medication, is restricted to patients who are in critical condition due to its severe toxic side effects. A number of o-phenylenediamines and 1,4,3,6-dianhydro-D-fructose were used as starting materials to create a variety of benzimidazole derivatives in order to overcome this restriction. According to assessments of antiviral activity, compound 38 was the most effective, exceeding ribavirin with an EC_{50} of 18.53 μM and having a EC_{50} of 9.49 μM. According to mechanistic research, compound 38 suppresses RSV replication via altering the apoptotic and autophagic pathways. These results demonstrate the possibility of benzimidazole derivatives as less harmful and more efficient substitutes for ribavirin in the treatment of RSV[64]. In their study, Al-Humaidi colleagues. (2022) produced a group of 1,2,3-triazole compounds using benzimidazole precursors, and then used computational studies and *in-vitro* enzyme activity assays to assess the compounds' effectiveness against the Omicron spike proteins and SARS-CoV-2. Al-Humaidi reported on the persistent threat posed to global health by SARS-CoV-2 and its strains, particularly the Omicron variant. When compared to reference medications, the almost all synthesized compounds displayed encouraging binding affinities, according to the data. With an IC_{50} of 74.51 nM against the SARS-CoV-2 spike protein and 75.98 nM against the Omicron spike protein, compound 39 stood out as the most effective contender. IC_{50} values for Ceftazidime, the reference medication, were 80.10 nM and 80.01 nM, respectively, against the same targets. With an EC_{50} of 80.4 μg/mL and a CC_{50} of 1028.28 μg/mL, compound 39 safety and efficacy were validated by the test, which also produced a selectivity index of 12.78. These results highlight compound 39 potential as a safe and effective antiviral medication. Compound 39 demonstrated anti-inflammatory properties in addition to its antiviral action, which may help reduce the hyperinflammation brought on by viral infection. With docking scores of -8.66 and -7.27 against the Omicron spike proteins and SARS-CoV-2, respectively, molecular docking investigations provided further evidence of compound 39 greater binding affinity. Comparatively, Ceftazidime, the reference medication, obtained docking scores of -6.36 and -6.59 against the same proteins. The remarkable potential of benzimidazole-based triazoles, in particular compound 39, as dual-action therapeutic agents with anti-inflammatory and antiviral action is highlighted in the work by Al-Humaidi *et al.,*(2022). With implications for the treatment of COVID-19 and linked difficulties, our results help as a base for forthcoming study and the creation of novel medicines that target SARS-CoV-2 and its variations[65]. The LASV, the cause of Lassa fever, an acute viral haemorrhagic fever with high infectivity and mortality, is a serious concern, according to Chen *et al.,*(2023). Effective medicines are still unavailable despite the disease's severity, highlighting the urgent need for innovative therapeutic approaches. Compounds based on benzomidazoles have shown promise as inhibitors of the arenavirus envelope glycoprotein complex (GPC), which is essential for LASV viral entry. Chen *et al.,* created two groups of LASV inhibitors by taking benzimidazole structure as a base for their

investigation. Lentivral pseudotypes containing the LASV GPC were used to find possible inhibitors of virus entrance in order to assess the antiviral effectiveness of these substances. With IC_{50} values of 13.56 nM, 7.58 nM, and 11.87 nM, respectively, compounds 40, 41, and 42 showed remarkable antiviral activity among the produced inhibitors. In contrast, the IC_{50} of the conventional medication LHF-535 was 3.04 nM. Compounds 40, 41, and 42 also have selectivity indices (SI) greater than 1251, indicating their safety and efficacy. With an IC_{50} of 7.58 nM and a SI of 2496, compound 41 demonstrated the strongest antiviral activity and is a potential candidate for further lead development. The binding effectiveness of these compounds was further supported by SPR experiments, which showed that all three samples had substantial binding affinities with low KD constants (KD < 8.25×10^{-7}M). Derivatives with Oil loving character and bulky side chain tended to show superior antiviral activity and safety profiles, according to the SAR study. This discovery offers important new information on the structural characteristics required to maximize the safety and effectiveness of inhibitors based on benzimidazoles. Chen et al.'s study offers significant info for the growth of strong and targeted antiviral drugs that combat LASV. The SAR analysis and the discovery of compound 41 as a lead molecule provide a strong basis for the creation of upcoming treatments that target Lassa fever[66]. According to Hue *et al.,*(2024), quinazolinone and benzimidazole-based compounds were created and produced as possible inhibitors of the SARS-CoV-2 3CLpro, a crucial target in the development of coronavirus drugs. Three compounds that were synthesized using isatoic anhydride as the starting material comprised the unique series of quinazolinone-conjugated benzimidazoles that were the focus of the investigation. The inhibitory action of these compounds against the SARS-CoV-2 3CL protease was assessed. With an IC_{50} value of 10.73 μM, compound 43 showed the strongest dose-dependent anti-3CL enzymatic activity among the produced compounds. The mechanism behind this suppression was discovered by molecular docking experiments, which also highlighted important interactions between compound 43 and the 3CL protease's active site. In particular, hydrogen bonding was seen with essential amino acids that are vital to the protease's enzymatic activity, such as His41, Met49, and Glu166. The results of this investigation highlight the potential of quinazolinone-conjugated benzimidazoles as a novel scaffold for the inhibition of SARS-CoV-2 3CL pro. The discovery of compound 43 as a lead chemical opens the door for further investigation into anti-coronavirus treatments and the creation of new medications that specifically target 3CLpro[67] (Figure 8).

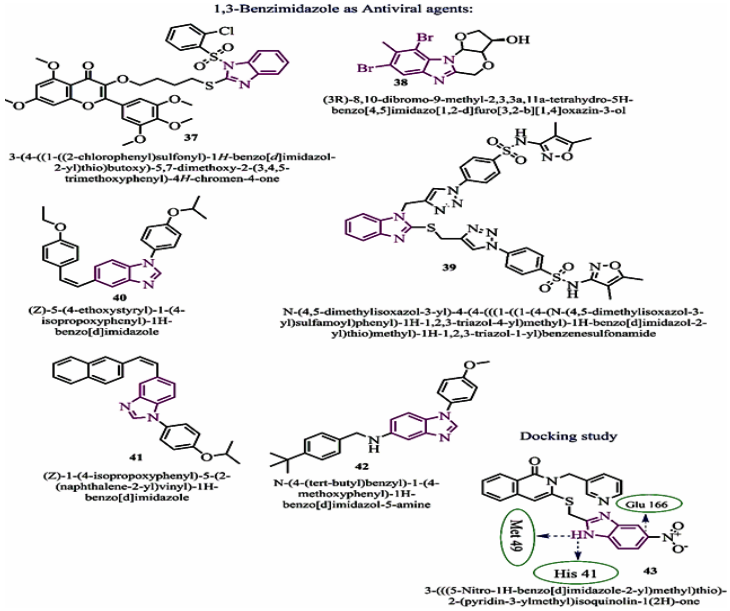


Fig. 8. 2D structures of 1,3-Benzimidazole as antIvIral agents[63-67]

1,3-Benzimidazole as antifungal agents

In recent decades, the prevalence of fungal infections has risen significantly, posing a persistent challenge to human hewalth[68]. For immunocompromised people, such those with AIDS, patients receiving anticancer chemotherapy, and organ transplant recipients, where the prevalence of fungal infections has significantly grown since the 1980s69, this problem is especially serious. *C. albicans*, *C. neoformans* and *A. niger*, are the main pathogens that cause fungal infections. Among all antifungal agents available, azole derivatives are the most extensively utilized and researched for antifungal therapy[70]. Despite the availability of numerous antifungal agents, current treatments often face limitations such as a limited spectrum of activity, drug resistance, and poor bioavailability, resulting in suboptimal outcomes for fungal infections[69]. These challenges have driven the continuous exploration and development of novel antifungal compounds. This need has motivated medicinal chemists to design and synthesize new molecules with enhanced antifungal efficacy. Benzimidazole derivatives have gained attention as a promising group of compounds due to their significant antifungal properties. Given the growing demand for effective antifungal agents, these heterocyclic compounds are receiving increased attention in ongoing research aimed at discovering potent and innovative treatments for fungal infections[72].

Shojaei and colleagues (2019) investigated the creation and production of a group of imidazole and benzimidazole compounds by a straightforward and effective two-step synthetic approach using readily accessible starting materials. The antifungal action of these derivatives was evaluated in vitro for fungal strains such as *M. gypseum*, *C. neoformans, A. niger*, and *C. albicans*. Some of the azole derivatives demonstrated significant antifungal properties, particularly against *A. niger* and *C. neoformans*. Among them, compound 44 showed remarkable efficacy, with MIC of 15.6 µg/mL against both *C. neoformans* and *A. niger*, comparable to the standard antifungal drug fluconazole, which exhibited similar MIC values for the same strains. Furthermore, a computational analysis was performed, revealing that the synthesized derivatives had low binding energy and strong affinity for cytochrome P-450, a key enzyme in antifungal therapy. The computational findings aligned with the experimental results, underscoring the potential of these imidazole and benzimidazole derivatives as promising antifungal agents[73]. In 2020, Abedin Emadi described the production and assessment of a group of Schiff bases containing a benzimidazole framework. Six novel derivatives are synthesized. Their biological activities were tested for antifungal and cytotoxic properties. Antifungal efficacy was evaluated against seven fungal strains, including five species of Aspergillus and two of Fusarium, using the microdilution method to determine MFC. Among the synthesized compounds, Schiff base 45 demonstrated the strongest antifungal action, with MFC values ranging from 7.8 to 15.6 µg/mL against *A. flavus* and *A. carbonarius*. The reference antifungal drug nystatin showed comparable MFC values (<8 µg/mL and <16 µg/mL) against these fungal strains. Compound 45 stood out for its potent antifungal activity combined with low cytotoxicity, indicating good biocompatibility with HeLa cells. These findings position compound 45 as a promising candidate for antifungal therapy, with potential applications as an antiparasitic agent. Further research into its effects on additional cell lines could provide a deeper understanding of its therapeutic potential. The study underscores the value of Schiff bases as potent antifungal agents, particularly against Aspergillus species, while emphasizing the need to balance efficacy with safety for therapeutic use[74]. Sun *et al.,* (2021) conducted a comprehensive study into the growth of new benzimidazole derivatives with enhanced antifungal properties. This research elaborates the design, synthesis, and estimation of a group of 2-(2-(alkylthio)-6-phenylpyrimidin-4-yl)-1H-benzimidazoles for their in vitro fungicidal action. Among the synthesized derivatives, compound 46 demonstrated exceptional effectiveness against two fungi, *S. sclerotiorum*, and *B. cinerea* with EC_{50} values of 4.65 µg/mL, and 0.14 µg/mL respectively. In comparison, the standard fungicide carbendazim exhibited EC_{50} values of 13.32 µg/mL for *S. sclerotiorum* and 0.21 µg/mL for *B. cinerea*, indicating the superior activity of compound 46. To elucidate the fungicidal mechanism of compound 46, computational analysis was executed to assess its interaction with β-tubulin protein. The results identified critical interactions contributing to its activity. The Amino group of the benzimidazole ring formed a H bond with the Gln-11 amino acid, while the -F atom on the benzene ring established a second H bond with the Tyr-208 amino acid. Additionally, a pi-pi interaction was observed between the benzene ring of compound 46 and the Tyr-222 amino acid. This study underscores the potential of compound 46 as a highly effective fungicidal agent[75]. Yang (2022) investigated the antifungal properties of benzimidazole analogues incorporating thioether and carbamate groups. A group of these compounds were produced and assessed for their *in vitro* antifungal activity using

the mycelium growth rate method. The study targeted fungal pathogens such as *V. daliae*, *P. infestans*, *G. zeae C. mandshurica*, *T. cucumeris*, and *B. cinerea*. The bio-assay results revealed that maximum synthesized derivatives displayed noteworthy antifungal activity. Notably, compound 47 emerged as the most effective, particularly against *V. daliae* and *P. infestans* at a conc. of 50 µg/mL. The inhibition rates for compound 47 were 75% and 70% against *P. infestans* and *V. daliae*, respectively, surpassing the performance of the reference antifungal agent albendazole, which achieved inhibition rates of 38% and 61% under identical conditions. This research represents a novel approach to synthesizing and evaluating benzimidazole derivatives featuring thioether and carbamate functionalities for antifungal applications[76]. Güzel *et al.,* (2023) addressed the escalating global challenge posed by offensive fungal contaminations, which contribute meaningfully to morbidity and mortality due to the lack of effectiveness of current antifungal drugs and the rise of drug-resistant strains. To combat this issue, the researchers synthesized a group of 12 benzimidazole-1,2,4-triazole compounds. The antifungal properties of the prepared compounds were tested in vitro against four fungal species: *C. krusei, C. parapsilopsis C. albicans,* and *C. glabrata*. The study revealed that the compounds displayed significant antifungal activity, with *C. glabrata* being particularly susceptible. Among the compounds, three (48, 49, and 50) showed remarkable efficacy, achieving MIC values of 0.97 µg/mL. These MIC values were notably higher to those of reference antifungal medicine voriconazole (MIC: 1.95 µg/mL) and fluconazole (MIC: 3.90 µg/mL). This research highlights the potential of benzimidazole-1,2,4-triazole compounds as powerful antifungal agents, particularly against drug-resistant fungal strains like *C. glabrata*. The findings emphasize the promise of these compounds as a foundation for developing new and more effective antifungal therapies[77]. Jin *et al.,* (2024) addressed the crucial requirement for innovative antifungal medicines by designing, synthesizing, and evaluating a of group of pyrazoles carboxamide compounds including a benzimidazole molecule. These compounds were tested for their antifungal activity, with results indicating strong efficacy against pathogenic fungi. Among them, compounds 52 and 51 stood out, demonstrating exceptional potency against Botrytis cinerea with EC_{50} values of 0.56 µg/mL and.79 µg/mL, respectively. These values were comparable to those of the standard antifungal medicine boscalid (EC_{50} = 0.60 µg/mL). To explore the mechanism underlying their antifungal activity, computational study was conducted. These analyses showed that compound 52 effectively binds to residues of key amino acid within the active site of SDH, an essential enzyme in fungal metabolism. This interaction offers valuable insights into the structural basis of its antifungal activity. The findings from Jin *et al.,* study contribute to the structural optimization and variation of potential SDH inhibitors. The research underscores the promise of pyrazole carboxamide derivatives as viable antifungal agents and provides a robust foundation for the growth of novel therapeutics targeting fungal infections[78] (Figure 9).

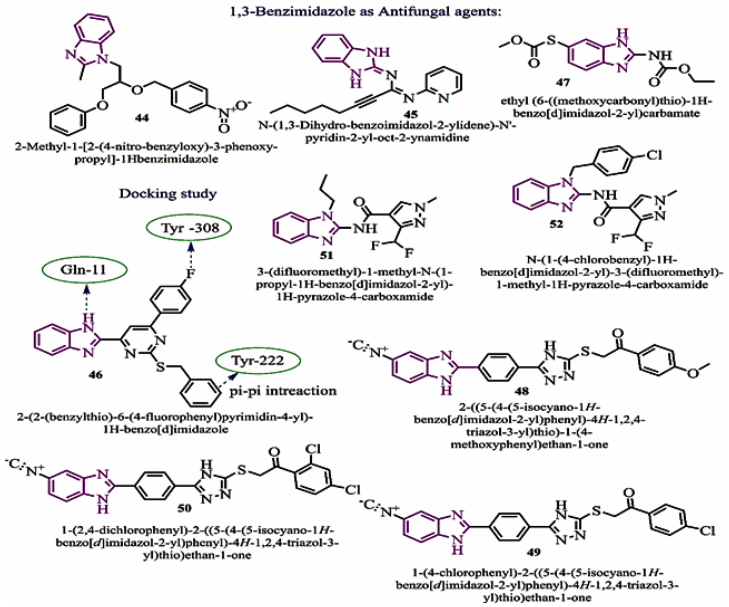


Fig. 9. 2D-structures of 1,3-Benzimidazole as antIfungal agents[73-78]

1,3-Benzimidazole as antimalarial agents

One of the most important parasite illnesses still impacting people is malaria, which has serious repercussions for both community well-being and economic growth, particularly in low-income areas[79]. The WHO assessments for 2023[80] indicate that there were 263 million cases of malaria worldwide and 597,000 fatalities related to the disease. Even while these numbers show improvements in malaria prevention over the previous 15 years, they are still quite high and point to a number of persistent issues. These include the growth of pesticide resistance in malaria vectors and decreased susceptibility to the WHO-recommended artemisinin-based combination treatments (ACTs)[81]. Furthermore, RTS, S, the only approved malaria vaccine, has only been used as an experimental program in a limited sub-Saharan African country to far, has limited efficacy[82], and offers no complete protection. These difficulties highlight the urgent need for novel treatment strategies. Despite significant efforts in recent decades to reduce malaria-related mortality and morbidity, the disease continues to burden public health systems and economies in developing nations. Furthermore, the rise of resistance to existing antimalarial drugs has intensified the demand for new and effective treatments. One promising avenue in medicinal chemistry involves the benzimidazole scaffold, a well-studied structural framework known for its ability to interact with diverse biological targets. Over the past 20-30 years, extensive research into benzimidazole derivatives has highlighted their versatility and potential. Several of these compounds have already been developed into therapeutic agents for various diseases. Benzimidazole derivatives could be promising candidates for antimalarial activity[83].

Okombo *et al.,* (2019) investigated a Novel group of pyrido[1,2-a] benzimidazole derivatives incorporating Mannich base side chains, along with their metabolites, for their antiplasmodial potential. These compounds were thoroughly assessed for in-vitro antiplasmodial action, microsomal metabolic constancy, and the creation of reactive metabolites (RMs). Notably, one derivative demonstrated remarkable *in vivo* antiplasmodial efficacy. When orally administered to Plasmodium berghei-infected mice at a dose of 4 × 50 mg per kg, it achieved a 95% reduction in parasitemia and extended the average survival time to 16 days. The *in-vivo* efficiency of synthesized compounds was primarily linked to their active metabolites. Among these metabolites, two exhibited potent *in-vitro* action for both chloroquine sensitive and multidrug resistant strains of *P. falciparum*. Specifically, compounds 54 and 53 demonstrated IC_{50} values of 0.89 μM and 0.11 μM, respectively, comparable to the chloroquine (IC_{50} = 0.02 μM). This study offers appreciated vision into the pharmacological point of view of pyrido[1,2-a] benzimidazole compounds, providing a solid foundation for the growth of novel antimalarial drugs[84]. Mueller and colleagues (2020) performed a high-throughput phenotypic analysis to recognize compounds effective against both the liver and asexual blood stages of *P. falciparum*. This analysis revealed a benzimidazole chemical series with notable antimalarial properties. Amongst the identified lead was the antiemetic medicine Lerisetron, which served as a structural template for further investigation. Building on this scaffold, approximately 60 analogues were synthesized and subjected to biological testing. Two lead compounds, 55 and 56, exhibited significant potency against both multidrug resistant (K1) and drug sensitive strains (NF54) of *P. falciparum*. Compound 55 demonstrated an IC_{50} of 0.098 μM against the NF54 strain, while compound 56 achieved IC_{50} values of 0.054 μM and 0.062 μM against the K1 and NF54 and strains, respectively. In vivo evaluations in mouse models infected with *P. berghei* and *P. falciparum* further confirmed the efficacy of these compounds, highlighting their potential as antimalarial candidates. Although the benzimidazole derivatives showed slightly lower potency compared to chloroquine, which had an IC_{50} of 0.016 μM against both NF54 and K1 strains, their activity against multidrug-resistant strains is noteworthy. However, addressing off-target cardiotoxic effects remains critical to advancing these compounds toward clinical application. The study underscores the significance of benzimidazole derivatives as promising antimalarial agents against *P. falciparum* resistance strain, including artemisinin-based combination treatments[85]. Devine *et al.,* (2021) detailed the development and assessment of a group of 2-aminobenzimidazole compounds as potential antimalarial agents. These compounds

were strategically designed to incorporate a phenol moiety essential to their pharmacophore. Among the synthesized derivatives, compounds 58 and 57 exhibited remarkable *in vitro* antimalarial efficacy, with IC_{50} values of 43 nM and 42 nM, respectively, against the *P. falciparum* 3D7 strain. Significantly, these compounds maintained potent activity against chloroquine-resistant (Dd2), inhibitor resistant (SJ557733) artemisinin-resistant (Cam3.IIC580Y). The standout derivatives, compound 59 achieved an IC_{50} value of 6.4 nM against the *P. falciparum* 3D7 strain, reflecting a 12-fold enhancement in potency compared to the established compound. The study emphasized the potential of 2-aminobenzimidazoles with N1-substituted phenols as an auspicious group of antimalarial agents. This research underscores the potential of 2-aminobenzimidazole derivatives as potent, selective, and pharmacologically promising antimalarial agents capable of addressing the challenge of drug resistance[86]. Escala *et al.,* (2023) concentrated on the synthesis and assessment of benzimidazole compounds. Thirty-six benzimidazole derivatives were created for the research, and their antiplasmodial efficacy against the Plasmodium falciparum HB3 strain was examined. Studies of the SAR were carried out to assess the effects of substituents on rings A and B, as well as their spatial or dimensional features and electron-donating or withdrawing capabilities. Many of the compounds were found to be quite hazardous, even though some had IC_{50} values in the mid-nanomolar range. Against *P. falciparum*, two lead compounds, 60 and 61, showed encouraging efficacy with strong selectivity indices (SI). While compound 61 had an IC_{50} of 0.85 µM, compound 60 showed an IC_{50} of 0.98 µM. In contrast, the IC_{50} of the common antimalarial drug chloroquine was 0.028 µM. Compounds 60 and 61 were notable for their very low toxicity and unique methods of action, even if chloroquine remained more effective. Mechanistic investigations identified a number of distinctive characteristics of compounds 60 and 61. In contrast to previous active but hazardous compounds, both exhibited little haemolytic activity and less membrane damage. Additionally, these substances varied in their capacity to alter the potential of the mitochondrial membrane and generate reactive. Interestingly, they had no effect on the crystallization of hemozoin, which is a recognized target of chloroquine. Compound 60's promise as a resistance-agnostic treatment was further supported by the fact that it maintained constant IC_{50} values even when tested against a chloroquine-resistant strain. Important structural elements that contribute to compounds 60 and 61's action were found by the SAR analysis. As an electron-donating substituent, compound 60 had a single methyl group on ring A, whereas compound 61 had two methyl groups. A non-substituted picolinamide fragment on ring B was present in both compounds and seemed to be essential for their antiplasmodial action. These results feature the promise of benzimidazole compounds as a new group of antimalarials and provide important information for improving these compounds. Escala *et al.,* work concludes by emphasizing the value of SAR-guided synthesis in finding and refining novel antimalarial drugs with desired pharmacological characteristics. Compounds 60 and 61 are strong prospects for further research and development due to their intriguing mode of action and encouraging activity. The investigation of new molecular frameworks with enhanced effectiveness has been prompted by the ongoing increase in resistance to conventional antimalarial treatments[87]. The production and pharmacological assessment of 7-chloro-4-aminoquinoline-benz imidazole hybrids as potent antimalarial drugs were reported by Krstulovic *et al.,* (2024). These hybrids' antiplasmodial efficacy was evaluated against two strains of *P. falciparum*: PfDd2 (resistant to chloroquine) and Pf3D7 (sensitive to it). Interestingly, the hybrids demonstrated strong anti-both strain action at nanomolar dosages. At 2.7 µM (Pf3D7), 3.3 µM (PfDd2), 2.6 µM (Pf3D7), and 4.8 µM (PfDd2), and 2.4 µM (Pf3D7) and 3.9 µM (PfDd2), respectively, compounds 62, 63, and 64 showed IC_{50} values. In contrast, the Pf3D7 strain showed an IC_{50} of 11.1 µM for the common antimalarial medication chloroquine. The hybrids' superior activity highlights their potential as next-generation antimalarial medicines, especially against the resistant PfDd2 strain. This work demonstrates how 7-chloro-4-aminoquinoline may be hybridized with benzimidazole scaffolds to provide strong antiplasmodial action. These results open the door for more structural refinement and preclinical testing of these hybrids as potential solutions to resistance-related problems in malaria therapy[88] (Figure 10).

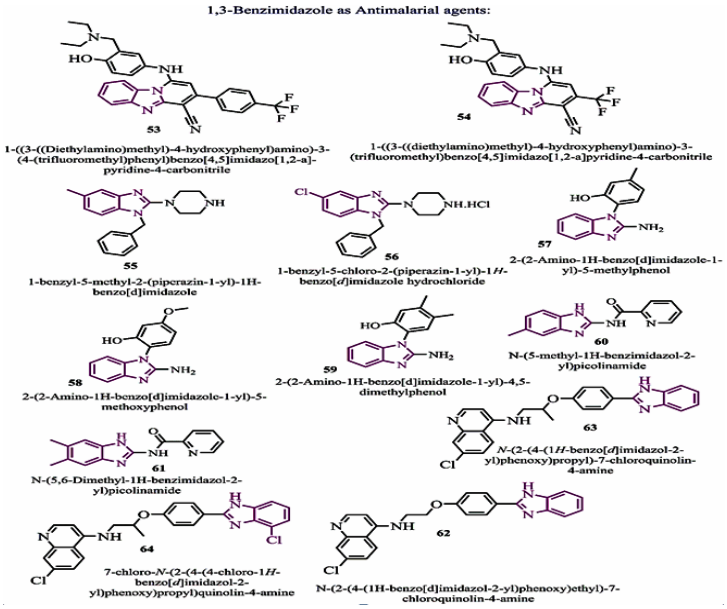


Fig. 10. 2D-structures of 1,3-Benzimidazole as antImalarlal agents[84-88]

1,3-Benzimidazole as antidibetic agents

One major worldwide health concern is diabetes mellitus (DM), a complex and common endocrine condition. It is characterized by hyperglycaemia, which causes many organs to malfunction and fail. This hyperglycaemic state results from either insufficient insulin production or disruptions in the insulin signalling pathway[89]. The etiology of diabetes mellitus is diverse, with the two primary types being Type 2 and Type 1 diabetes. Type 2 diabetes is primarily influenced through genetic predispositions that impair insulin secretion and contribute to insulin resistance. Additionally, environmental factors such as obesity, sedentary lifestyles, overeating, chronic stress, and aging exacerbate the risk. In contrast, an autoimmune disorder known as type-1 diabetes arises after the immune system targets the islet cells in the pancreas, resulting in a reduction in insulin production[90]. Over the last several decades, there has been a shocking rise in the rate of diabetes. Current estimations reveal that approximately 14% of the global population exceeding 800 million individuals live with diabetes, marking a doubling in prevalence since 1990. Projections by the International Diabetes Federation suggest that this number will climb to 783 million by 2045, a substantial increase from the 537 million cases reported in 2021[91]. In heterocyclic chemistry, benzimidazole and its analogues have gained a lot of interest in the search for novel therapeutic agents. Numerous studies have shown that benzimidazole and its analogues have an extensive variety of biological actions, including notable anticancer, antidiabetic action. This adaptability demonstrates the possibility of compounds based on benzimidazoles as viable options for the creation of innovative antidiabetic treatments[92].

Hernandez *et al.,* (2019) reported a simple and economical three-step synthesis process for making 1,3-thiazolidine-2,4-diones and benzimidazoles. Generally recognized safe hydroxybenzaldehyde's and 2-(chloromethyl)-1H-benzimidazole were used in a nucleophilic substitution (SN_2) reaction, which was tailed via a Knoevenagel condensation with thiazolidine-2,4-dione. Moderate quantities of the targeted chemicals were produced by the process, and they were carefully described using spectroscopic and analytical methods. Promising antidiabetic potential was found in the synthetic compounds' biological examination. Two important proteins, PPARγ and GLUT-4, are well-known therapeutic targets for the control of diabetes, and *in vitro* investigations on adipocytes showed that treatment with these drugs greatly raised their mRNA expression. These drugs' possible mode of action was further supported by in silico studies that shed light on their binding interactions with PPARγ. To verify the produced compounds' antihyperglycemic action, *in vivo* investigations were carried out. When injected at 100 mg per kg, the compounds significantly reduced blood glucose levels sixty minutes after glucose

administration (2 g per kg) in normoglycemic mice, according to an oral glucose tolerance test (OGTT). This was in contrast to the vehicle control (Tween-80, 10 percent), which exhibited peak hyperglycaemia at the one-hour mark. The compounds' (65, 66, and 67) effectiveness was further validated by the area under the curve (AUC) analysis, which showed that they decreased AUC values by almost 75% in comparison to the control. Crucially, in contrast to mice treated with the hypoglycaemic control medication glibenclamide, whose glucose levels fell below normal, the treated animals' glucose levels stayed within the normal range. This discovery emphasizes the drugs' antihyperglycemic action, which seems to be mediated via PPARγ activation-induced insulin sensitivity. All things considered, the research offers insightful information on the creation of new benzimidazole-thiazolidinedione hybrids with strong antidiabetic effects, establishing these substances as viable options for further medication development[93]. A novel series of benzimidazolyl-linked para-substituted-benzyl or methyl-based compounds containing 2,4-thiazolidinediones was designed, synthesized, and biologically estimated by Singh *et al.,* in 2020. Two derivatives, 68 and 69, had strong inhibitory action against α-glucosidase after the all derivatives were evaluated for antihyperglycemic action *in-vitro*. The IC_{50} values of 4.10 µM and 4.50 µM, respectively, for these substances were much lower than the IC_{50} of the common medication acarbose (15.4 µM). This suggests that the produced chemicals have a higher inhibitory potential than acarbose. With strong α-glucosidase inhibitory action, the research emphasizes the potential of N-methyl or benzyl substituted benzimidazolyl derivatives as viable candidates for the growth of innovative antihyperglycemic agents[94]. Hussain and colleagues (2021) explored the development of effective α-amylase inhibitors by synthesizing seventeen derivatives of 2-mercaptobenzimidazole functionalized with sulphonamide groups. These derivatives were tested for their α-amylase inhibitory activity. The inhibitory efficacy was benchmarked against acarbose, a standard drug, which exhibited an IC_{50} of 1.70 µM. Among the synthesized derivatives, compounds 70, 71, and 72 demonstrated the highest inhibitory potential, with IC_{50} values of 1.40, 1.30, and 0.90 µM, respectively, surpassing the activity of acarbose. The remaining derivatives also showed promising inhibition, underscoring the overall potential of the series as α-amylase inhibitors. This research emphasizes the promise of 2-mercaptobenzimidazole compounds containing sulfonamide groups as possible candidates for developing innovative α-amylase inhibitors[95]. In 2022, Hussain and colleagues described the synthesis and biological estimation of 17 hybrid compounds of benzimidazole featuring a thiazole moiety as potential twin inhibitor of α-amylase and α-glucosidase. The inhibitory activities of these compounds were evaluated against acarbose, which demonstrated IC_{50} values of 10.30 µM for α-amylase and 9.80 µM for α-glucosidase. The synthesized hybrids exhibited a broad range of inhibitory efficacy, with IC_{50} values spanning 1.31–38.60 µM against α-amylase and 2.71–42.31 µM against α-glucosidase. A detailed SAR analysis highlighted the critical influence of substitution patterns on rings B and C on the inhibitory activity. Compounds bearing smaller substituents such as fluorine (-F) or chlorine (-Cl), displayed significantly enhanced activity. Among these, analogues 73, 74, and 75 featuring meta, para, and ortho-fluoro substitutions, respectively showed the highest potency. Their IC_{50} values against α-amylase were 4.10 µM, 1.30 µM, and 1.90 µM, respectively, and against α-glucosidase were 5.60 µM, 2.70 µM, and 2.90 µM, outperforming acarbose in both cases. In contrast, derivatives with bulky substituents like -Br or groups unable to form hydrogen bonds, such as -CH3, exhibited reduced activity. This study underscores the potential of benzimidazole-thiazole hybrids as promising dual inhibitors for α-amylase and α-glucosidase, providing a basis for further development of novel antidiabetic agents[96] (Fig. 11). Aroua and colleagues (2023) synthesized and investigated a novel series of eight benzimidazole-urea compounds as potential antidiabetic agents. Their antidiabetic potential was evaluated using *in vitro* assays to measure inhibition of the α-amylase and α-glucosidase enzymes. The majority of the synthesized derivatives displayed reasonable inhibitory activity against target enzymes, with compounds 76, 77, and 78 demonstrating the most promising results. For α-amylase inhibition, compound 76 achieved an IC_{50} value of 18.65 µM, whereas derivatives 77 and 78 exhibited IC_{50} values of 20.70 µM and 22.33 µM, respectively, all of which were equivalent to the acarbose (IC_{50} = 14.21 µM). Similarly, the α-glucosidase inhibitory activity of these derivatives was noteworthy. Compound 76 recorded an IC_{50} value of 17.47 µM, while compounds 77 and 78 showed IC_{50} values of 21.97 µM and 23.01 µM, respectively, also aligning closely with acarbose (IC_{50} = 15.41 µM). These results feature the potential of benzimidazole-urea compounds as twin inhibitors of α-amylase and α-glucosidase, positioning

them as promising candidates for the growth of innovative antihyperglycemic agents[97]. Abbasi and colleagues (2024) described the production and biological assessment of benzimidazole-based thiazolidinone-bearing chalcone compounds as potential antidiabetic agents. These compounds were prepared through a four-step synthetic process. The synthesized derivatives demonstrated significant inhibitory activity against two key carbohydrate-metabolizing enzymes, α-amylase and α-glucosidase. The IC_{50} values for these derivatives are 25.0556.08 μM for α-amylase and 22.07 to 53.06 μM for α-glucosidase, compared to the standard glimepiride, which exhibited IC_{50} values of 18.05 μM and 15.02 μM, respectively. Among the synthesized derivatives, compounds 79 and 80 exhibited the maximum inhibitory activity. Compound 79 showed IC_{50} values of 25.05 μM against α-amylase and 22.07 μM against α-glucosidase, while compound 80 exhibited IC_{50} values of 25.75 μM and 22.80 μM against the respective enzymes[98]. These results suggest that the derivatives possess considerable potential as antidiabetic agents[99]. This study highlights the potential of benzimidazole-based thiazolidinone compounds as capable candidates for the growth of innovative therapies to manage diabetes mellitus[100] (Figure 12).

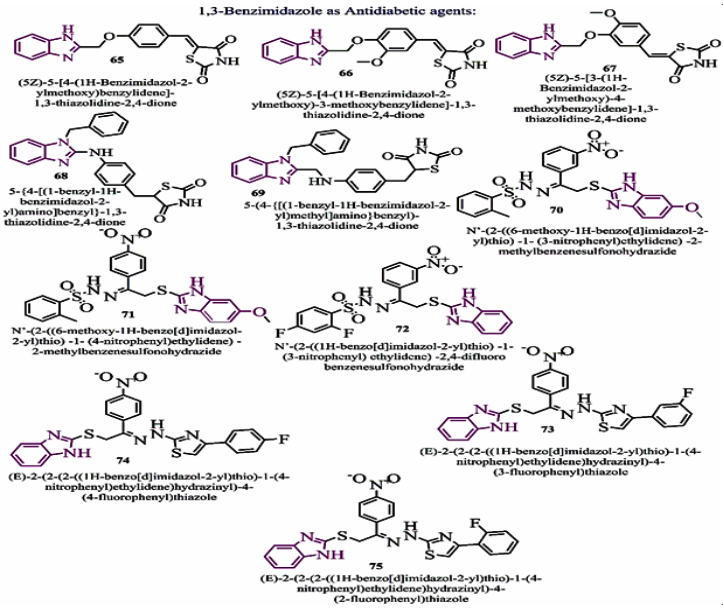


Fig. 11. 2D structures of 1,3-Benzimidazole as antIdlabetIc agents[93-96]

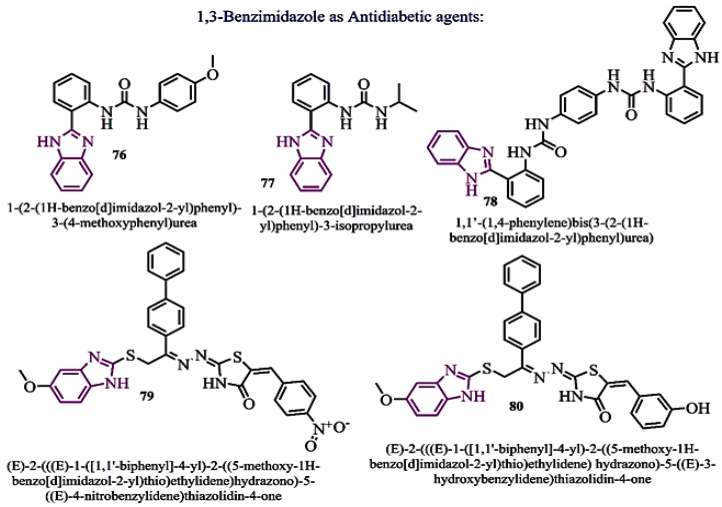


Fig. 12. 2D structures of 1,3-Benzimidazole as antIdlabetIc agents[97-100]

CONCLUSION

An important and adaptable class of chemicals are benzimidazole and its derivatives. that have made a significant impact on modern medicinal chemistry. Their distinctive structure, which combines an imidazole moiety with a benzene ring, facilitates the development of numerous novel compounds with an extensive variety of pharmacological actions. Extensive research into the therapeutic properties of benzothiazole derivatives has revealed their effectiveness in various areas, including antifungal, antituberculosis, antimalarial, antiviral, anti-inflammatory, antidiabetic, antimicrobial, and anticancer effects. This diverse variety of biological actions underscores the potential of benzimidazole compounds in drug discovery and development, making them a focal point of interest in pharmaceutical research. The continuous exploration of benzimidazole-based molecules in recent scientific literature not only reaffirms their promise as essential contributors to future medical advancements but also highlights the need for innovative approaches to fully exploit their therapeutic potential. Furthermore, ongoing research efforts are crucial for understanding the mechanisms underlying the diverse pharmacological properties of these compounds. This might result in the development of stronger drugs and the identification of new therapeutic targets. By leveraging the unique chemical properties of benzimidazole derivatives, researchers can pave the way for innovative treatments that address unmet medical needs and improve healthcare outcomes. This article features the significance of continued study and advancement in this exciting area, advocating for collaborative efforts among scientists, clinicians, and pharmaceutical companies to fully realize the medicinal potential of benzimidazole derivatives for the benefit of patients worldwide.

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Conflict of interest

Authors do not have any conflicts of interest to declare.

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