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BENZIMIDAZOLE SCAFFOLD: A PRIVILEGED CORE FOR DIVERSE PHARMACOLOGICAL ACTIVITIES

Chander Shekhar Sharma, Mukesh Kumar Gupta, Shikha Sharma

ABSTRACT

Microbes have a substantial role in the spread of dangerous infections, and how they spread to humans presents an increasing challenge to public health. The effective management of these types of infections and the mitigation of antimicrobial resistance can be accomplished using novel pharmaceuticals, which are essential to ongoing research within the scientific community. The strategic use of current antimicrobial alternatives alongside novel drug regimens warrants investigation to address the significant issue of drug resistance. Extended research in antimicrobial drugs has shown that, among various targets, targeting proteins is the most effective approach for developing robust treatments. Despite considerable progress in antibiotic therapies and the availability of various inhibitors for drug-resistant bacterial strains, there remains a critical necessity to develop new compounds that possess a favourable safety profile to tackle this issue. In immunocompromised individuals, severe diseases resulting from pathogenic fungi are frequently observed. Fungal infections are common, yet treatment options remain limited; thus, the development of new antifungal agents is crucial for community members.

Key words: Benzimidazole, Pharmacological activity, Bioactive scaffold, Drug design, Therapeutic agents, Heterocyclic compounds.

1 INTRODUCTION

It is the most diverse family of organic molecules, and it has received attention because of its ubiquitous use in natural substances and pharmaceuticals. More than 50 per cent of the 50 million documented organic molecules are heterocyclic in nature, and the number is continually growing.[1-5] Heterocyclic chemistry addresses compounds that include either one or more elements apart from carbon and are referred to as hetero-atoms.[6-9] Because it is so essential in pharmaceutical sciences, advances in synthesis methods that offer fast access to a varied variety of altered heterocyclic compounds are critical for developing useful drugs.[10-15] Five and six-membered heterocyclic compounds are now attracting a lot of scientific attention due to their important applications in medicinal, commercial, and synthetic chemistry.[16-20] Numerous fused heterocyclic compounds (hybrids) have been identified as effective and efficient new drugs employing empirical assessment, structural chemistry, and rational drug design.[21-26] Nitrogen-containing heterocyclic categories, such as imidazole, are critical in developing novel medicines with potential pharmacological properties.[27-32]

Most of the hetero atoms are sulphur, nitrogen, and oxygen atoms. The heterocyclic ring constitutes the active nucleus or active pharmacophore.[33] Azoles are the 5-membered ring category with oxygen, nitrogen or sulfur atoms that are believed to be derived from the pyrrole, furan, and thiophene.[34] If azole is present, oxygen is termed as oxazole, sulphur is termed as thiazole, and nitrogen is referred to as pyrazole, imidazole, or imidazolines. In search of efficient compounds,

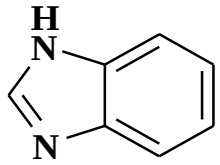
Numerous types of heterocyclic molecules have been recognized.[35-36] Nitrogen-containing heterocyclic categories, such as the azoles, are particularly important in the development of newer drugs that have potential biological activities.[37-41]

1.1 Introduction to Benzimidazole

Benzimidazole is one of the renowned nitrogen-containing heterocyclic scaffolds, having been synthesized initially by Hoebrecker in 1872.[42] It is a fully symmetrical ring configuration with a ring of benzene attached to the fourth and fifth places within the imidazole nucleus. Imidazole is a 5-membered framework containing an imino unit (N-H) and a tertiary N. It is also concluded that benzimidazole is particularly useful for molecular and synthetic methods for comprehending the medicinal chemistry. [43] This nucleus is present in a variety of bioactive compounds, namely purine bases, histidine, and is an essential component of Vitamin-B12, thus, its analogues may effectively interact with living body macromolecules.[44] In addition, the integration of this framework with other heterocycles produces hybrids with improved biological activity. This moiety's anticancer potential has been well identified and defined, and various benzimidazole-based drugs are now being studied in clinical trials.[45–47] Because of its steric and electrical properties, benzimidazole is exceedingly flexible, capable of stimulating and establishing interactions with a broad variety of biological processes involved in the uncontrolled growth of cancer cells.[48] In the current scenario, there has been an increased interest in benzimidazole analogues because they have a variety of pharmacological activities such as antibacterial, antifungal, anticancer, anti-inflammatory, antitubercular, antiviral, antihypertensive, antioxidant, anthelmintic, anti-Alzheimer, antipsychotic, H1 receptor antagonist, antidiabetic, and anticonvulsant.[49-63] Numerous marketed drugs contain this nucleus, including pimobendan, omeprazole, dovitinib, albendazole, candesartan, flubendazole, bendamustine, Clopimozide, astemizole, enviradene, and bezitramide. In the pharmaceutical domain, benzimidazole and its related compounds are a key class of bioactive chemicals for generating next-generation dominating medications.[65-66]

Benzimidazole is extremely important in both biological and synthetic ways to the chemistry of medicines.[67] The structures depict the systematic counting of the benzimidazole nucleus. Although it has the proton at the N1 position, there is a fast exchange among the -NH and N atoms, and the benzimidazole molecule can be drawn into two tautomeric forms. Tautomerism is caused by an intermolecular process that involves more than one benzimidazole nucleus, or by interactions with protic solvents such as water.[68]

1.1.1 Properties of Benzimidazole



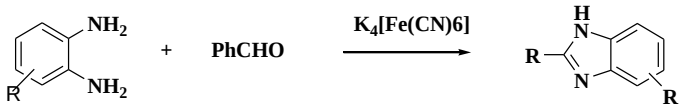
Structure of benzimidazole

Benzimidazole is a bicyclic aromatic heterocycle composed of a fused benzene and imidazole ring system **01**. It is a white to off-white crystalline solid with a molecular formula of $C_7H_6N_2$ and a molar mass of 118.14 g/mol. The compound has a melting point ranging between 170°C and 175°C and typically decomposes before boiling. Benzimidazole is only slightly soluble in water but shows good solubility in organic solvents such as ethanol, dimethyl sulfoxide (DMSO), chloroform, and acetone. It exhibits weak basicity, with a pKa value around 5.5 due to the presence of the NH group, which also enables hydrogen bonding. Benzimidazole displays strong ultraviolet absorption near 290–300 nm, attributed to its conjugated aromatic system. As a chemically stable and aromatic compound, benzimidazole serves as a versatile scaffold in medicinal chemistry, known for its ability to interact with biological targets through π-π stacking, hydrogen bonding, and coordination with metal ions.

1.2 Synthetic Approaches Towards Benzimidazole

1.2.1 Solvent-free synthesis

Benzimidazoles were synthesized in great yield by the reaction of 1, 2 diamine with aldehyde derivatives using K4[Fe (CN)6] metal complex as a catalyst.[68-69]



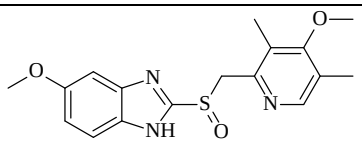
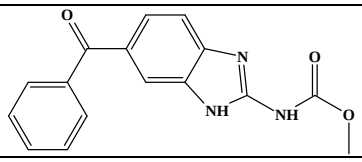
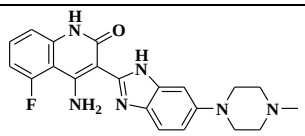
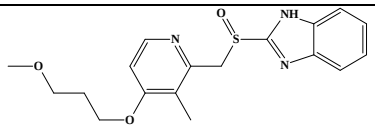
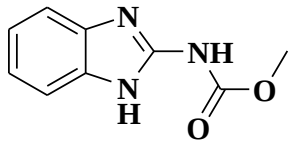
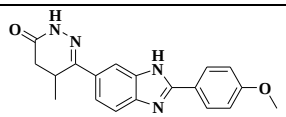
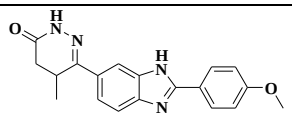
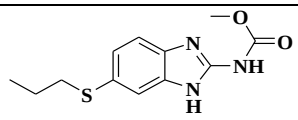
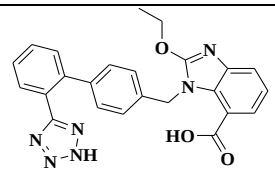
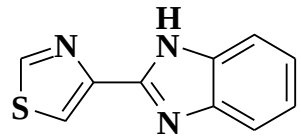
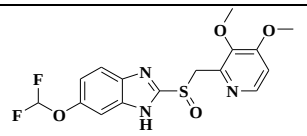
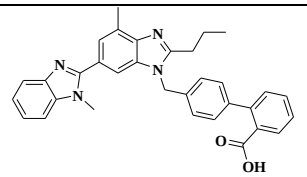
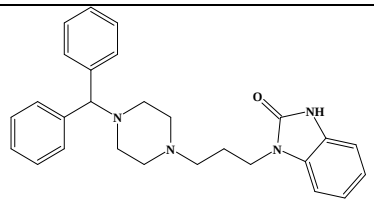
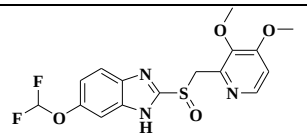
1.2.2 From phenylene diamines

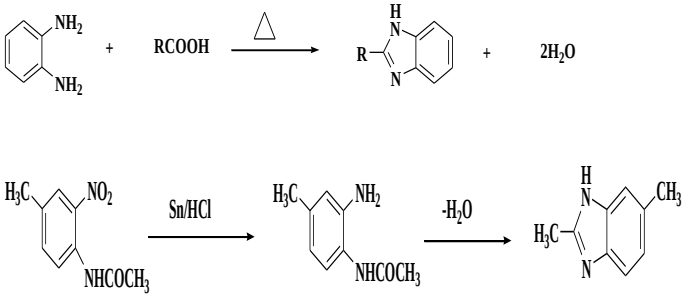
Preparation of benzimidazole compounds may practically start with the reaction of ortho-phenylenediamines (OPD) with saturated carboxylic acids to produce 2-substituted benzimidazole derivatives in excellent yield. This reaction is typically carried out by heating both reactants collectively on a water bath, under reflux, or at a high temperature.[70]

1.2.3 Hoebrecker synthesis

Benzimidazole was first prepared by Hoebrecker using an acetanilide derivative as a starting material. Reduction of substituted acetanilide in the presence of Sn/HCl yielded 2-amino-4-methyl acetanilide. Further on, dehydration produces 2,5-dimethylbenzimidazole.[71]

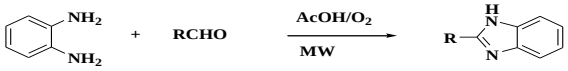
Table 1: FDA-approved drugs containing the benzimidazole nucleus

S. No	Structure	Drug Name	Uses
1		**Omeprazole**	Proton-pump inhibitor
2		**Mebendazole**	Antiparasitic
3		**Dovitinib**	Anticancer
4		**Rabeprazole**	Proton pump inhibitor
5		**Carbendazim**	Fungicidal
6		**Pimobendan**	Cardiotonic vasodilator
7		**Flubendazole**	Antifungal
8		**Albendazole**	Anthelmintic
9		**Condesartan**	Antihypertensive
10		**Thiabendazole**	Fungicidal
11		**Pantoprazole**	Proton-pump inhibitor
12		**Telmisartan**	Antihypertensive
13		**Oxatomide**	: Antiallergic/ antihistaminic
14		**Bendamustine**	Anticancer



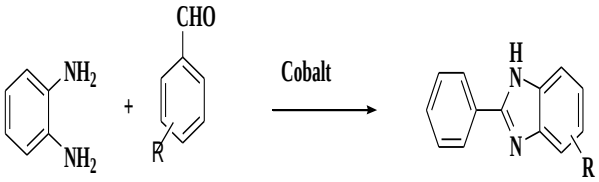
1.2.4 Microwave-assisted benzimidazole synthesis

Benzimidazoles can be yielded by the condensation of o-phenylenediamine with acetic acid in a microwave in the presence of ethanol at 50˚C. Alternatively, it may be obtained by refluxing both reactants at 80˚C.[72]



1.2.5 Synthesis from aromatic aldehydes

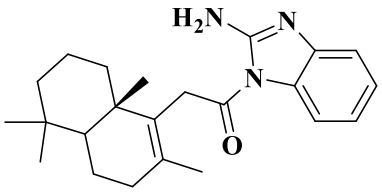
Rajabi et al. stated one-pot benzimidazole synthesis for analogues using cobalt adhered on mesoporous silica via the oxidative condensation of aromatic aldehyde compounds using ortho-phenylenediamine under mild conditions.[73]



2 BIOLOGICAL ACTIVITY

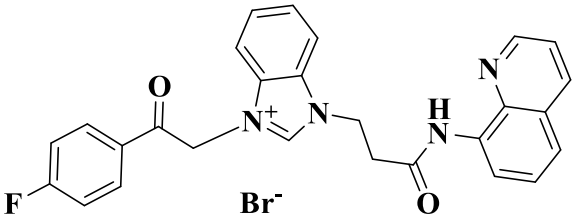
2.1 Antimicrobial Activity

Lungu and coworkers created new benzimidazoles and tested their antibacterial activity. X-ray diffraction was used to extensively confirm the molecular makeup of these derivatives. In vitro activity was tested against several varieties of fungi (A. niger, A. alternata, and P. chrysogenum) and bacterial strains (Bacillus sp., P. aeruginosa). The obtained MIC values revealed that analogue **1** exhibited excellent action (MIC values 0.06 and 0.052 µg/ml), greater than the reference medications, caspofungin and kanamycin (with MIC of 0.35 and 2.2 µg/ml, respectively). The apparent presence of unsubstituted amines was presumably accountable for the appealing findings of benzimidazoles.[74]



1

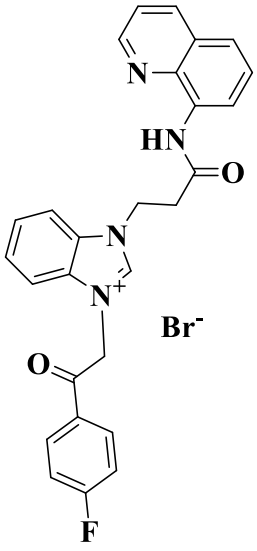
Diaconu et al. synthesized two classes of benzimidazole-quinoline hybrids to assess their antibacterial properties. The disc diffusion technique was used in vitro to test the potency over distinct strains. Gentamicin and Nystatin were used as reference medicines to evaluate antibacterial and antifungal activity, while the results were reported as inhibitory zone (in mm). Analogue **2** showed exceptional action exclusively against *E. coli*, with a zone of 24 mm (for Gentamicin: 12 mm). SAR revealed intriguing results that the presence of a benzimidazole promoted potency, and the inclusion of F considerably increases the potency.[75]



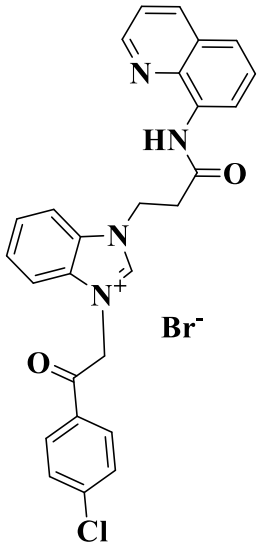
2

Onicius et al. developed and synthesized two series of hybrid benzimidazole analogues and evaluated their antibacterial attributes towards E. coli and S. aureus. The antibacterial assay indicated that two derivatives, **3a** and **3b** showed an excellent profile against bacterial strains (higher than the reference drug Gentamicin). Compound **3a** had the greatest inhibition zone of 24 mm against *E. coli.*[76]

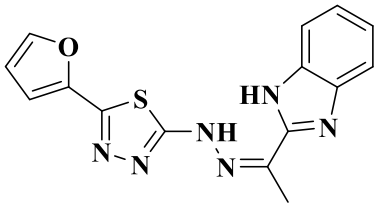
Acetyl benzimidazole was used as an initial material for synthesizing newer benzimidazole analogues and tested in vitro for antibacterial activities against bacterial and fungal strains. Compound **4** had high efficacy towards the tested bacterial strains, with zone of inhibition of 17, 19, and 18.25 mm over distinct strains, and activity indexes of 91.40%, 75.14%, and 79.02%, when compared to the standard medicine gentamicin (19-25 mm). Docking studies were also undertaken to test their effectiveness and learn more about the processes involved. Virtual assessment of active compounds was performed over two bacterial proteins: DNAG and the protein that binds to penicillin (PBP). It also had a lower binding free energy to DNAG and PBP (-7.85 and -8.31 kcal/mol, respectively) compared to the standard agonist (-9.38 and -7.21 kcal/mol).[77]



3a



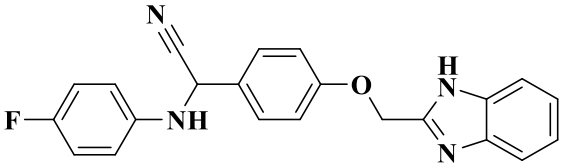
3b



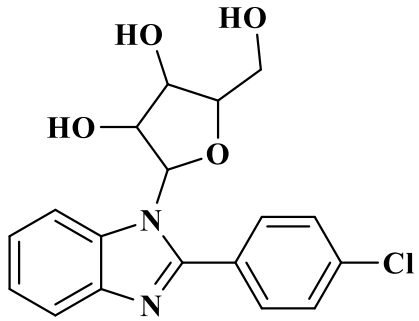
4

Shaikh et al. used the Strecker process to create novel α-aminonitrile benzimidazoles and tested their antibacterial properties in vitro. The MIC of these substances was measured using the broth-dilution technique against bacterial and fungal strains. Derivative **5** demonstrated strong efficacy against specific bacterial strains with MIC concentrations from 3.85-7.85 μg/ml, comparable to the reference medication tetracycline. Furthermore, **5** demonstrated equipotent antifungal activities towards *C. albicans* with an MIC of 3.92 μg/ml (fluconazole <3.95 μg/ml). SAR: The addition of F immediately attached to a phenyl significantly changed the behaviour of molecule **5**.[78]

Using in silico methods, a class of novel ribo-furanosyl benzimidazole analogues were developed as potent antimicrobials by Chaurasia et al. 2021. The molecules were tested for antifungal and antibacterial properties. The broth microdilution method was used for antibacterial examination, and several molecules exhibited great inhibitory activities (MIC value 50-1.56 μg/mL) against various micro-organisms as well as drug-resistant strains (DRS) of *E. coli*. The MIC data acquired through various procedures of the combination approach suggested 4- 128 fold greater potency than derivatives tested alone. Antifungal testing was carried out using two distinct approaches, which demonstrated that molecules were potentially effective against several fungal species, like *A. flavus*, and *A. niger*. Chloramphenicol, kanamycin, and ketoconazole were utilized as std. drugs for antimicrobial activity. The MIC values for antibacterial activity were as: **6a** was active against *B. cereus* and *S. aureus* with conc. 3.12 μg/ml while 6.25 μg/ml against *B. subtilis*. Derivative **6b** possessed a MIC value 3.12 μg/ml for *E. coli* and *P. aeruginosa*. Furthermore, derivative **6c** showed excellent potency against three fungi stains: *A. flavus, A. niger,* and *C. albicans* carrying MIC 1.56, 0.78, 0.78 μg/ml respectively.[79]

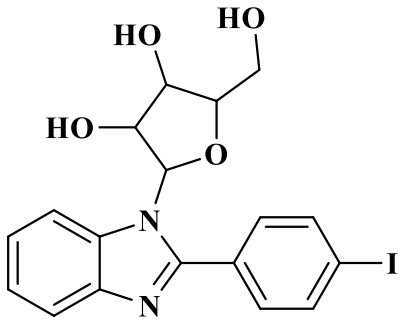


5

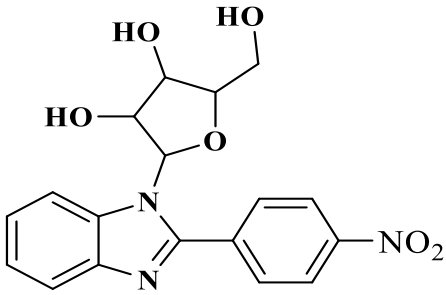


6a

Acetyl benzimidazole was employed for designing a newer sequence of benzimidazole derivatives by Motaal et al. 2020. Most of the synthesized molecules were determined *in vitro* for antimicrobial efficacy over *S. aureus, E. coli, and B. pumilus*, as well as antifungal properties against *Saccharomyces cerevisiae*. With no antifungal inhibition, analogue **7** possessed the great strong inhibitory effect against all tested bacteria.

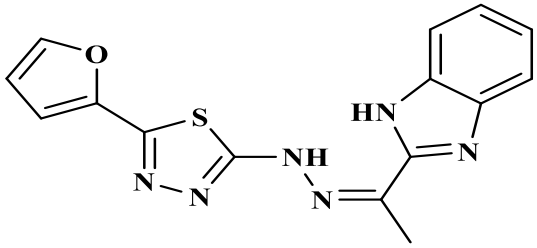


6b



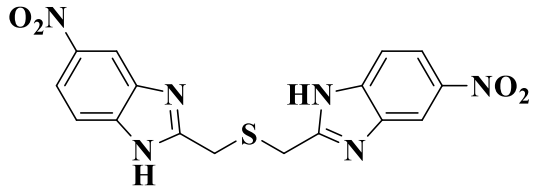
6c

Furthermore, docking analyses were carried out for the molecules to assess their efficacy as antibacterial agents. Derivative **7** showed a remarkable inhibition zone 17.33, 18.96, 18.20 mm over distinct strains, as that of gentamycin. On the other hand, it showed an excellent inhibition zone of 19.25mm against *Saccharomyces cerevisiae* (Standard drug ketoconazole: 20.25mm).[80]



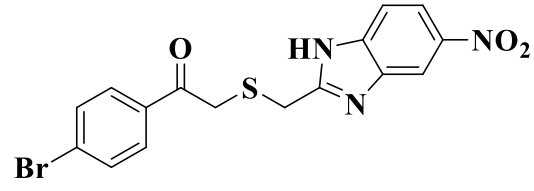
7

The antimicrobial efficacy of novel analogues of benzimidazole was assessed over numerous strains after the design and synthesis by Gohari and Shabaan 2017. Compound **8a** demonstrated potent and broad-spectrum antimicrobial activity. Furthermore, **8b and 8c** demonstrated outstanding antimicrobial activity against *S. aureus, B. cereus, and A. fumigatus*. Moreover, **8d** showed intriguing antifungal potential in order with *C. albicans*. Derivative 8 showed MIC 156.25 µg/ml against *E. coli*. Furthermore, **8b** and **8c** exhibited MIC values 312.5 and 78.125 µg/ml against *B. cereus* and *S. aureus* accordingly (reference drug: ampicillin). Also, analogue **8d** had MIC value 156.30 µg/ml opposite to *C. albicans.*[81]

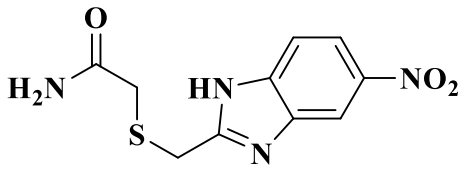


8a

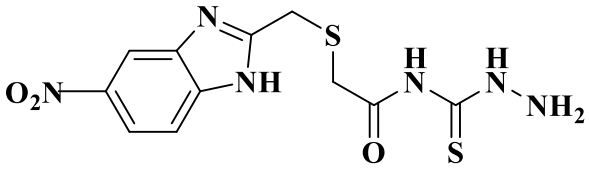
Ranjith and co-workers 2013 synthesized two new classes of benzimidazole analogues and examined them *in vitro* for antimicrobial activity against different strains. Among all, four derivatives were exposed as efficient against the bacterial and fungal strains tested. Furthermore, derivative **9** demonstrated significant effectiveness against the MTB H37Rv strain. SAR. studies exposed that the halogen-substituted derivatives showed improved lipophilic nature When methyl and methoxy-substituted compounds act as electron donors.[82]



8b



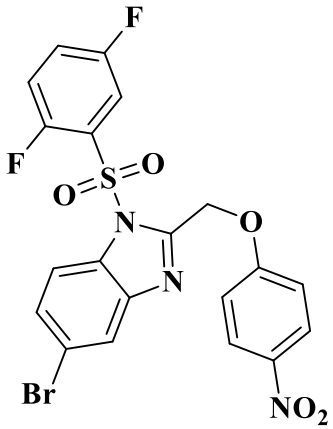
8c



8d

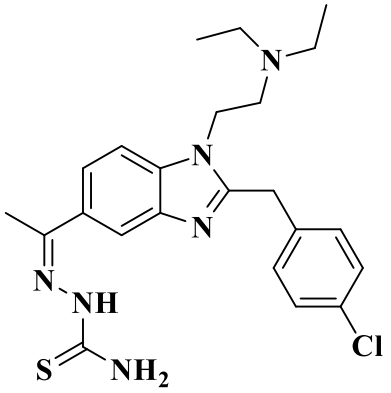
2.2 Antiviral Activity

In the present literature, Francescony *et al.* 2020 investigated two series of benzimidazoles by derivatizing 5-acetyl benzimidazoles and evaluated them for antiviral activity. Two derivatives, **10a, 10b** with benzyl rings on the core framework of benzimidazoles inhibited both the influenza A virus and human coronavirus.



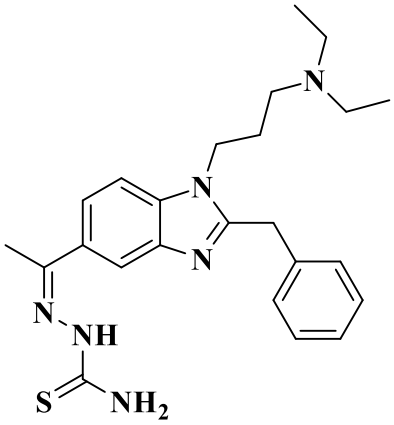
9

Furthermore, another derivative exposes remarkable activity against the respiratory syncytial virus (RSV). These compounds were demonstrated pronounced efficiency as compared to most potent antiviral agents, with potency profiles comparable to the licensed drug ribavirin. Derivative **10a** possessed an EC_{50} 81 µm over influenza A virus, while **10b** showed potency over coronavirus with EC_{50} 38 µm.[83]



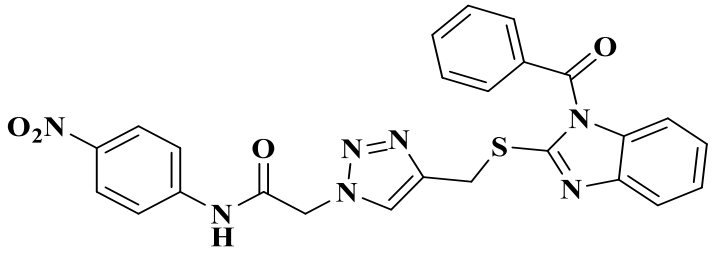
10a

New 2-thiobenzimidazole derivatives products with the triazole scaffold were developed, characterized, and examined for their anti-viral properties in opposite to hepatitis B and C viruses *in vitro* by Youssif et al, 2016. The decline in the counting of viable cells determined their cytotoxicity. Not all the synthesized molecules were not so active over HBV, while others showed significant activity. Two derivatives unveiled significant activity: **11a** and **11b**. The findings concluded the significance of the benzimidazole substituent in position 2 for HCV inhibition. According to the findings, the 50% effective conc. (EC_{50}) of HCV restriction for compounds **11a** and **11b** were 7.8, 7.9 µmol/L, respectively, also 50% cytotoxic conc. (CC_{50}) were 17.1 µmol/L and 21.25 µmol/L, producing SI of 2 to 3.[84]



10b

50 benzimidazole analogues were developed, and efficiency was examined over Zika virus (ZV) by Hue *et al.* Some compounds were active over the African ZV with a selectivity index of 10-38. Importantly, the compounds suppressed ZV in human neural cells, like microcephaly. In hepatoma and neural cells, derivative **12** displayed efficacy as that of drug mycophenolate acid.[85]



11a

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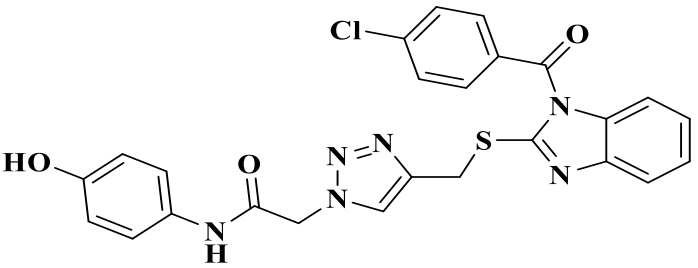
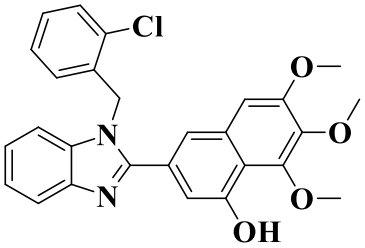
2.3 Antimalarial Activity

Devine et al. developed a series of benzimidazoles, including a phenol, and tested them for antimalarial properties. 2 powerful compounds demonstrated high IC_{50} values against different strains and demonstrated little cytotoxicity (IC_{50}> 55 nM). Compound **12a** had a remarkable IC_{50} of 6.5 nM over the falciparum strain, which was twelvefold more potent than the lead molecule and outperformed the reference medication chloroquine (IC50 16 nm).



11b

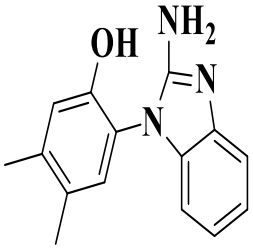


12

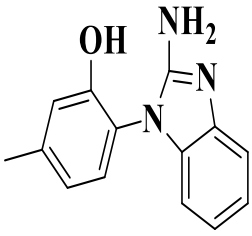
Furthermore, derivative **12b** performed well against different strains, with IC_{50} values of 13.51 and 31.70 nM. Cytotoxicity tests were conducted at 50 nM; no analogues were deadly to the cells. Indeed, **12a** demonstrated >1050-fold specificity, suggesting a favourable safety profile. These derivatives were synthesized with favourable physicochemical properties such as low MW, high solubility, and binding effectiveness. The substitution of -CH3 allowed molecules **12a** and **12b** to investigate excellent binding contacts with energies of 0.059 kcal/mol.[86]

A series of pyrido-benzimidazoles containing Mannich bases as side chains were created and tested for antiplasmodial properties *in vitro*, both CQ-sensitive and multi drug-resistant plasmodium strains. The compounds were also tested *in vivo*, where **13a** demonstrated high action, with IC_{50} concentrations of 0.11 and 0.182 μM across CQ-different strains at a dosage of 50mg/kg. Compound **13b** showed equipotency against both strains *in vitro*, with an IC_{50} of 0.07 μM.[87]

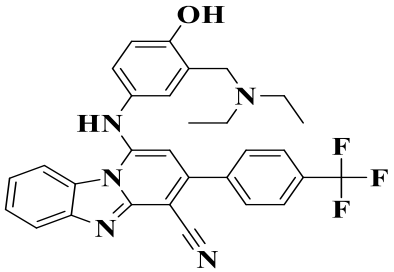
Sharma and co-workers developed a series of eighteen title compounds and examined them for antimalarial activity. The findings were favorable, with derivative **14** showing the highest efficacy with an IC_{50} of 0.69 μM. It had been demonstrated to be cytotoxic within tolerable ranges. Analogue **14** binds to FP-2 with a good IC50 value of 2.21 μM, indicating possible inhibition. Fluorescence tests were conducted to evaluate this.



12a



12b



13a

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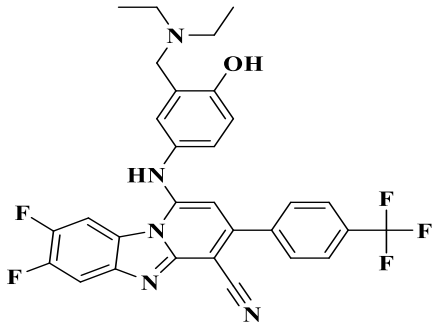

13b

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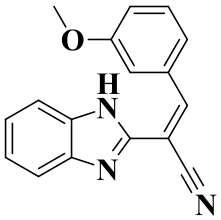
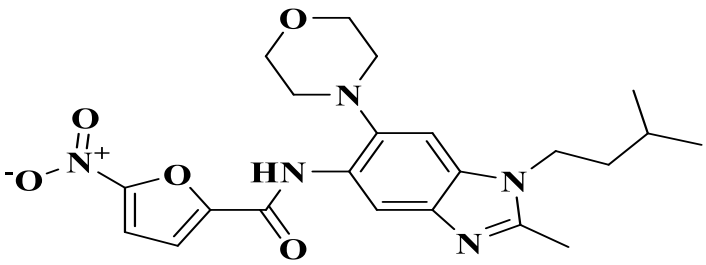


14

2.4 Antimycobacterial Activity

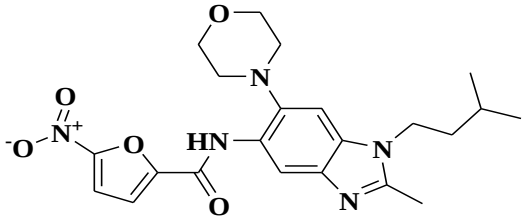
The development and SAR of a sequence of molecules with potential in oppose to *M. tuberculosis* (Mtb) in multiplication, physiologically-induced and non-replicating (both states) was performed by Gong et al. Multiple derivatives showed considerable activity as well as appropriate selectivity indices (SI) because they shared a 5-nitrofuranyl moiety. Compound **15** (MIC_{90} 0.049 mg/mL, SI > 512), showed the

excellent activity. As per SOS assay, **15** unveiled a low mutagenic potential, making this class of molecules suitable for further investigation.[89]



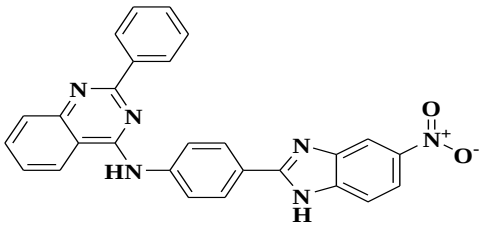
15

A newer library of analogues was synthesized and examined for efficacy over the Mtb-H37Rv strain as part of continuing SAR investigation on tri-substituted compounds as antitubercular by Haranahalli *et al.* The newly developed library of substituted benzimidazoles had MIC from 0.004 to 50 µg/mL. The growth inhibitory activities of four derivatives with varying ranges from 0.004 to 0.082 µg/ml. The SAR studies resulted in the identification of a remarkably potent derivative **16** (MIC value 0.039 and normal MIC was 0.015 µg/ml). The three-dimensional QSAR approaches anticipated that the most effective compound in the library would be this molecule.[90]

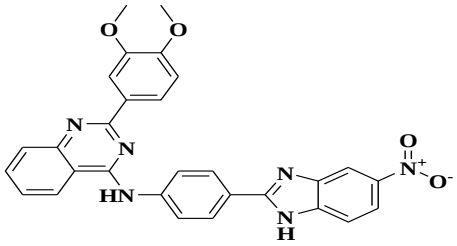


16

Malasala and colleagues synthesized 15 novel benzimidazole-quinazoline hybrids and investigated individual's contrary to a set of *M. tuberculosis* (H37Rv) and other mycobacterial types in this study. Among the analogues evaluated, three molecules, **17a, 17b,** and **17c,** displayed inhibitory effects against various mycobacterium species. Although the molecules were found not harmful for cell lines (CC50 40->100 g/ml), and displayed a significant selectivity index (SI > 25). In a separate study, the compounds **17a, 17b,** and **17c** were discovered to exhibit potent anti-tubercular. action with MIC 8 to 16 µg/ml. These three derivatives demonstrated MIC values of 8, 8, 16 µg/ml compared with the reference isoniazid and rifampicin 1µg/ml.[91]

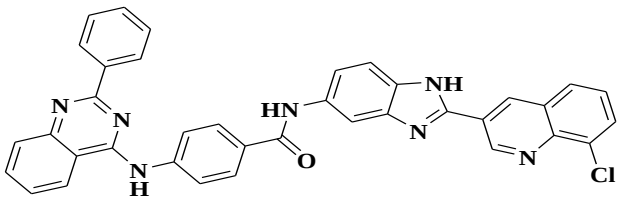


17a

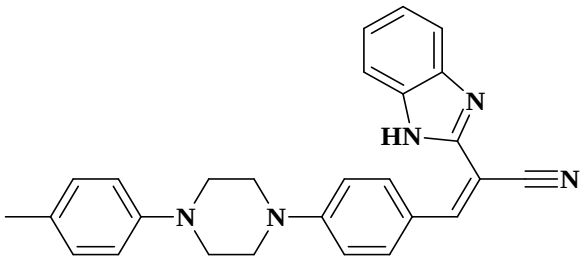


17b

This literature describes the assessment of benzimidazoles associated with acrylonitrile hybrid analogues for antimycobacterial property in oppose to M. tuberculosis (H37Rv strain) established by Sirim and co-workers *in vitro*.



17c



18

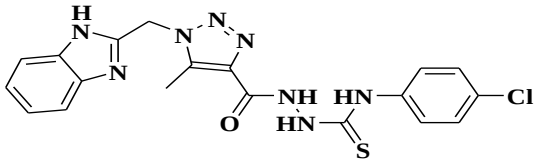
This literature describes the assessment of benzimidazoles associated with acrylonitrile hybrid analogues for antimycobacterial property in oppose to M. tuberculosis (H37Rv strain) established by Sirim and co-workers *in vitro*. Among all the molecules tested, **18** was discovered as a potent derivative against the mentioned strain, having an MIC of 0.78 µg/ml. When

compared with ethambutol (1.60 µg/ml), this is quite a good activity. Furthermore, **18** demonstrated a 2.8 times suppression in bacterial counting of inactive forms of mycobacteria, making it more effective than antiTB agents' isoniazid, rifampicin. With activities against the active and inactive variants of *M. tuberculosis*, **18** could be an intriguing option for the development of newer tubercular agents.[92]

2.5 Anticancer Activity

Two novel classes of benzimidazole-containing compounds were investigated for anticancer potential as EGFR, Topo II, and VEGFR-2 inhibitors by Othman and co-workers. Molecules **19a** and **19b** were shown to be the most effective derivatives against 4 cell lines. Compound **19a** was found to be an improved EGFR, topo II, and VEGFR-2 inhibitor with IC_{50} of 0.086, 0.107, and 2.52 µM than the drug Gefitinib (0.052 µM), Sorafenib (0.0482 µM), and Doxorubicin (3.62 µM).[93]

Using a molecular hybridised approach, a novel sequence of pyrrole-3-carboxamide-benzimidazole analogues was created and assessed for antiproliferative potency *in vitro* (Rasal *et al.***)** on melanoma, colon, and breast tumor with an individual dose of 10 µM. Some conjugates developed displayed promising activity, while analogue **20** demonstrated pronounced antiproliferative properties against MDA-MB cancer cells. Compound **20** demonstrated significant activity against the melanoma cell line with 62.46% growth inhibition (GI), colon cancer cell lines (GI: 69%) and breast cell line (GI: 40.24%). ADME study confirmed its crucial pharmacokinetic and drug-like attributes.[94]



19a

The mentioned literature covers the research objective of benzimidazole molecules developed by Atmaca *et al.* Research emphasis on fundamental molecular attachment mechanisms for inhibition of cell proliferation and apoptosis consequences with oppose to a group of human embryonic kidney cells (HEK-293). All the derivatives had a substantial cytotoxicity effect on cancerous cells, (with IC_{50} ranging from 9.2 to 166.1 µg/ml). Derivative **21** demonstrated noteworthy cytotoxic properties against HEK with remarkable IC_{50} values >100 µM/ml. According to the findings, compound **21** substantially inhibited specimen cells. This chloro-derivative demonstrated its greatest cytotoxic potential, inducing G2/M arrest in the cell-cycle and cell suicide in diverse human cancer cells.[95]

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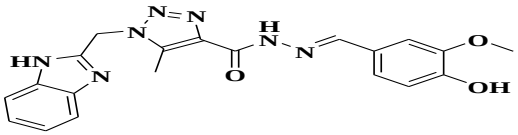
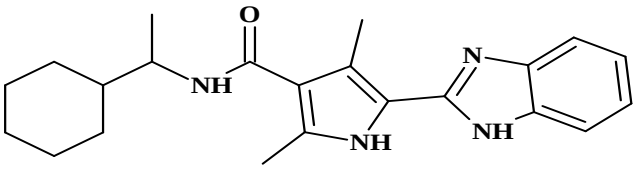


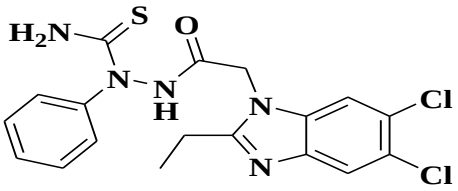
19b

Through a multi-component reaction in pure alcohol, a series of benzimidazole-linked pyrazole analogues was synthesized, and evaluated by Akhtar and colleagues. These compounds were examined for antiproliferative activity (EGFR receptor inhibitory activity) *in vitro* against five cancerous cell lines: liver, breast, lungs, and HaCaT.

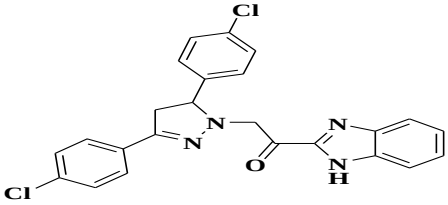


20

Most of the analogues revealed potent antiproliferative properties over distinct cancer cell lines tested. Derivative **22** demonstrated potent activity against lungs and breast-cancer cells (IC_{50} 2.2 and 9.6 µM respectively) Taking 5-FU as standard drug (IC_{50} 1.16 and 7.12 µM). Also, **22** showed promising EGFR binding affinity (IC_{50} 0.97 µM) as that of the standard drug gefitinib (IC_{50}: 0.011 µM).[96]



21

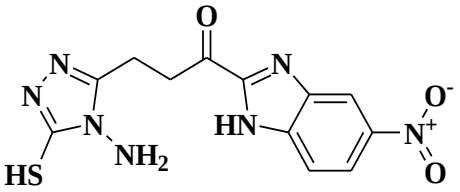


22

Three classes of benzimidazole bearing thiadiazole, oxadiazole and piperazine were created and examined for anticancer properties against lungs (code: A549) and colorectal cancer (code: HCT116) cells, as well as inhibitors of VEGFR-2 and c-Met (Ibrahim *et al.*). The selected analogues showed good to amazing inhibitory activity for the enzyme, with analogue **23** fitting like the original ligands and interacting perfectly with VEGFR-2 and. **23**'s docking findings were related to weak inhibition of the enzyme against VEGFR-2 and strong inhibition against c-Met (29 and 71.66% action, respectively). This compound showed significant IC_{50} values of 2.25

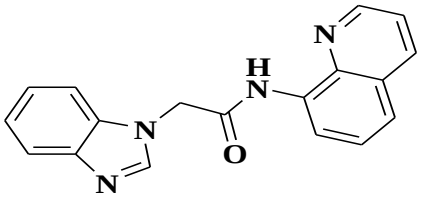
and 11.00 µM over different cells, as of the reference medication 5-FU.[97]

Mantu and co-workers developed, synthesized, structured, and examined novel benzimidazoles and assessed for anticancer action *in vitro*. Several new synthesized molecules were also examined for solubility. These hybrids showed magnificent solubility in the biological medium, making them potent in terms of pharmacological characteristics. **24** (with an 8-aminoquinoline and benzimidazole) was one of the hybrids that demonstrated excellent antitumor attributes over kidney and breast cells. It showed excellent inhibition of growth with values of 53 and 57% activity.[98]



23

Swiatkiewicz and colleagues established and validated the stability of a novel sequence of heterocyclic compounds, i.e., benzimidazole-diones in the literature. These derivatives were created as potential anticancer agents that could be activated under hypoxic conditions. Following that, active molecules were investigated in vitro for anticancer potential. Four molecules demonstrated very good antiproliferative effects, and three of them were hypoxia-specific. Molecule **25a** explores hypoxia/normoxia compared with tirapazamine, and was précised between the concentrations of mitomycin C and miconazole. Furthermore, derivative **25b** was more potent against hypoxic cells with IC_{50} concentrations of 116.0 and 500.6 µM, accordingly. Although **25b** possessed the same activity as the previously mentioned molecule.[99]

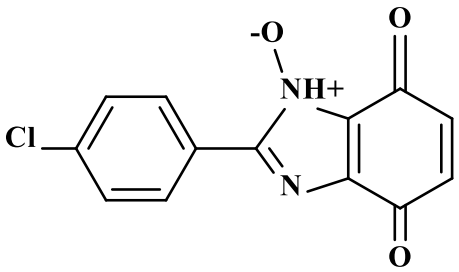


24

2.6 Anti-Inflammatory Activity

The present literature covers the synthesis of novel benzimidazole derivatives by Mohrana et al. These analogues were assessed for anti-inflammatory properties *in vitro* and *in vivo*. Two compounds, **26a** and **26b** explored the maximum activity *in vitro* at 100 µM conc. and *in vivo* at a conc. of 100mg/kg. All analogues proved no adverse consequences on Vero cell survival, with an optimal survivability of 95%. This finding showed that the compounds were safe, which was corroborated by in vivo investigations for acute oral toxicity.[100]

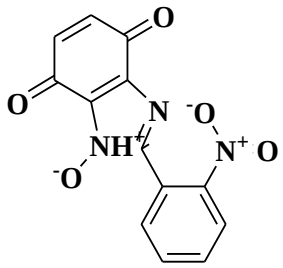
The literature study involves the design, development of novel molecule hybrids of 2-methyl thio benzimidazole, performed by Maghraby *et al.* for exploring anti-inflammatory scaffolds for estimating molecular variations on the inhibition of 15-lipoxygenase and cyclooxygenase enzymes (*in vivo* activity). Three hybrid scaffolds inhibited COX-2 considerably (with IC_{50} 0.045 - 0.075 µM) and had noteworthy SI towards COX-2. These hybrids inhibited 15-LOX effectively (IC_{50} ranging from 1.70-6.50 µM). Analogue **27a** was promising COX-2 inhibitor (possessing IC_{50} 0.04 µM and SI of 294) that showed equipotency to the drug celecoxib (with IC_{50} value 0.045 µM and SI 327), twice the activity



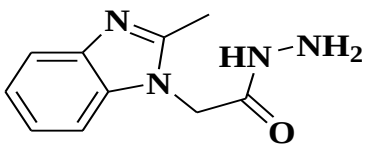
25a

as opposed to enzyme 15-LOX (IC_{50} value 1.60 µM) as reference drug quercetin (with IC_{50} 3.34 µM). The analogues were chosen for *in vivo* evaluation with the carrageenan-induced oedema procedure. Derivative **27b** inhibited oedema the most at 3 and 4h intervals (119 and 102% as drug indomethacin, respectively). Ulcerogenic outcomes of **27b** was calculated in comparison to indomethacin, which revealed an enhanced safety profile.[101]

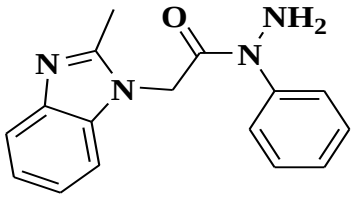
Herein reported the synthesis and anti-inflammation attributes of a novel series of morpholino ethyl-benzimidazoles with the objective of potential therapeutics for inflammatory conditions are reported by Rathore and co-workers. The compounds' activity was examined by using a carrageenan-induced oedema method in rats' paws. In this oedema test, certain derivatives demonstrated excellent anti-inflammatory activity. While **28a** demonstrated the greatest anti-inflammatory activity (75% inhibition) with a decreased ulcerogenic and lipid peroxidation profile, as well as noteworthy suppression of COX-2 (IC_{50} values 8.00 µM). Furthermore, two molecules, **28b** and **28c,** were discovered to be effective COX 2 inhibitors (IC_{50} value 11.4 and 13.7 µM respectively).[102]



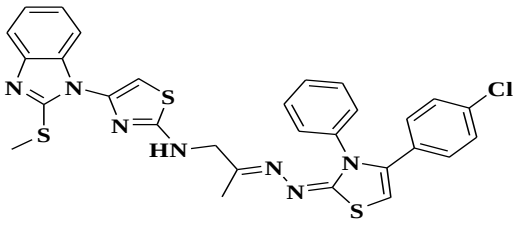
25b



26a



26b



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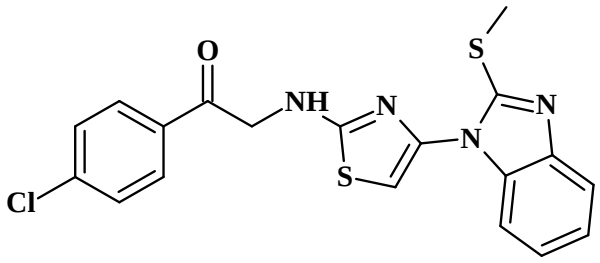
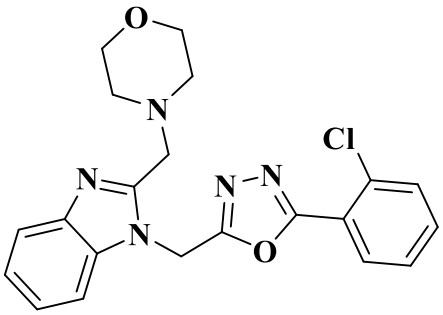


27b

As anti-inflammatory drugs, a sequence of benzimidazoles was developed by Moneer *et al.* The newly synthesised compounds' cyclooxygenase inhibitory activity was investigated. All the compounds inhibited COX-1 and 2 non-selectively, as indicated by their docking results. 5 compounds unveiled enhanced COX-2 inhibiting activities and were chosen for further in *vivo* studies as anti-inflammatory agents against

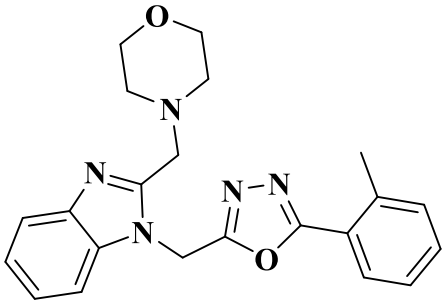
diclofenac. One of the tested molecules **29** demonstrated strong activity equivalent to diclofenac while having a lower ulcerogenic effect than indomethacin. Derivative **29** inhibited oedema by 61%, after 4 hours of administration (diclofenac inhibited by 64%).[103]



28a

2.7 Antihypertensive Activity

Wu and colleagues developed a new series of fluoro-substituted benzimidazoles and tested them for antihypertensive efficacy. Few drugs showed nanomolar affinity for AT1 and significantly reduced blood pressure in unilaterally hypertensive animals. Compound **31** displayed notable selectivity for the AT1 receptor, having an IC_{50} of 0.8 nM and an inhibitory constant (Ki) of 0.6 nM, outperforming telmisartan and losartan (IC_{50} of 2.85 and 10.5 nM, respectively). Some compounds were then tested *in vivo* for their effects on systolic and diastolic BP in hypertensive rats. Furthermore, 31 showed the strongest reaction to a drop in normal bp and the effect lasted 24 hours. Derivatives bearing the benzimidazole structure at the 6-position on benzimidazole might bind more easily, indicating a clear sensitivity to receptor binding sites. In radio ligand binding experiments, carboxylic acid analogues outperformed other acidic derivatives. According to studies, analogue **30** had greater affinities than telmisartan, showing that including F into aliphatic chains might increase hydrophobic interaction with the AT1 receptor, as-CH2CH2CF3 was determined to be the best lipophilic substitution.[104]



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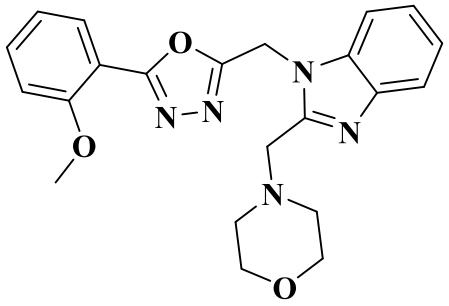

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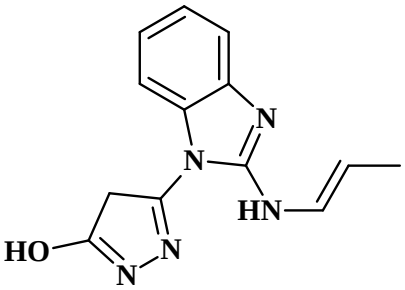
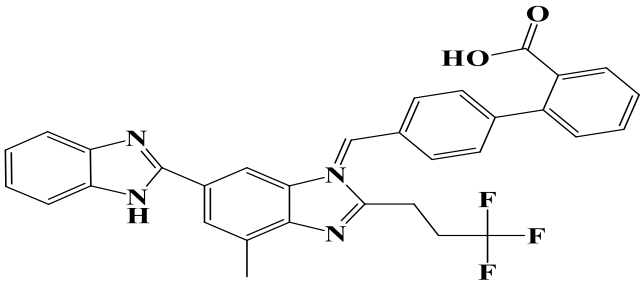


29

NO is a messenger with a variety of physiological features that regulates arterial pressure, inhibits platelet aggregation, suppresses blood vessel smooth muscle cell growth, and protects against ischemia damage. Zhang et al. synthesized two sequences of new NO-releasing analogues by including NO-donor groups. NO-releasing Griess assays demonstrated that all substances had variable levels of their releasing capacity. Furthermore, an isolated tissue evaluation was performed to test the ability to prevent Ang-II-induced vasoconstriction. Derivative **31** demonstrated greater suppression of Ang II-induced hypertensive responses, releasing the most NO (0.77 μmol/l) and comparable to the standard medication Losartan. Although the active region had been obscured by the NO-donating group, the active molecule reduced the Ang-II-induced pressure response soon after injection.[105]



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Zhu and colleagues discovered a unique class of benzimidazole-endowed disubstituted compounds. These drugs were evaluated using radioligand binding tests on spontaneously hypertensive and kidney hypertensive rats. In vitro findings showed that derivative **32** had enhanced efficacy for the AT1 receptor, with an IC50 of 1.03 nM. Furthermore, *in vivo* compound **32** caused a substantial drop in mean blood pressure in an excellent way. 10 mg/kg, and the effect lasted 24 hours longer than Losartan. A tailored drug profile was constructed, with disubstituted indole interacting with the L2 lipophilic pockets and the compound interacting to the AT1 receptor through binding sites. SAR: The presence of a butyl chain in the second position on benzimidazole was required for maximal activity because an aliphatic chain of sufficient length could bind quicker and more securely with the L1 lipophilic area.[106]

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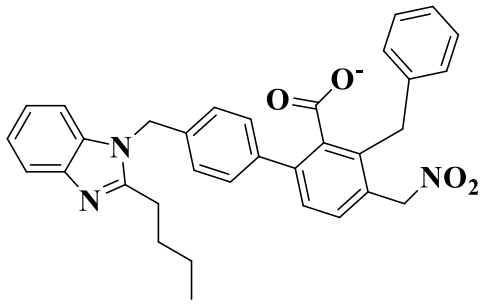

31

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2.8 Antipsychotic Activity

A benzimidazole-based carbohydrazide series and thiadiazole hybrids were created and assessed for glycogen synthase-kinase inhibition and antidepressant properties by Khan et al. Among the twenty-five hybrids developed, five derivatives were determined as potent GSK-3 inhibitors *in vitro*. When compared with fluoxetine, an acknowledged antidepressant medicine *in vivo*, compound **33** was found to exhibit noteworthy antidepressant actions at 50 mg/Kg. The docking investigations suggested various interactions of hydrogen bonds between the developed molecules and several amino acid residues at the GSK-3 receptor site.[107]

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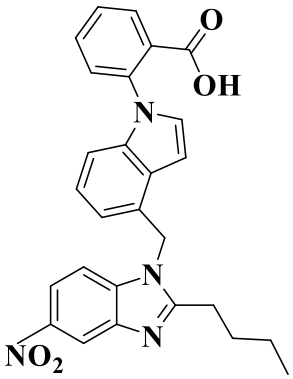
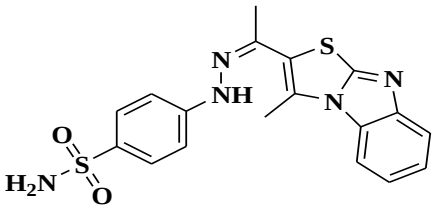


32

2.9 Antidiabetic Activity

A reaction between 2-substituted 1-H benzimidazole and *in situ* the compound azide yielded some novel benzimidazole endowed 1,2,3triazole analogues (4a-r). Spectroscopic studies (nuclear magnetic resonance, high-resolution mass spectra, FT infrared) confirmed the structures of compounds (Deshwal et al.). Anti-diabetic properties of the synthesized compounds had been investigated. Compounds **34a, 34b** and **34c** inhibited amylase and glucosidase good to moderately, with IC_{50} varying from 0.041 to 0.0916 mol/ml and 0.0146 to 0.0732 mol/ml, respectively.[108]



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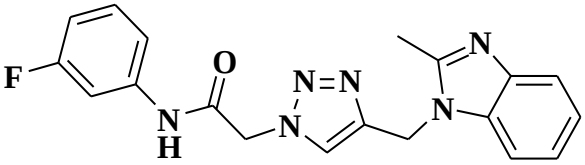
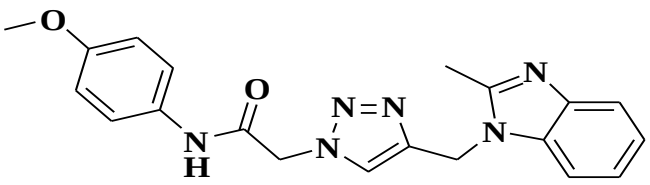
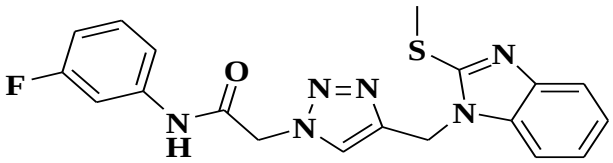


34a

The α-glucosidase enzyme inhibitory effect for novel benzimidazole analogues was assessed by Zawawi et al. When compared to standard acarbose, these derivatives displayed a range of α-glucosidase inhibition, with IC_{50} values that ranged from 8.45 to 179.80 µM as that of acarbose (with IC_{50} 774.5 ± 1.94 µM). In this test, seven molecules outperformed the rest of the benzimidazole series in terms of inhibitory activity.

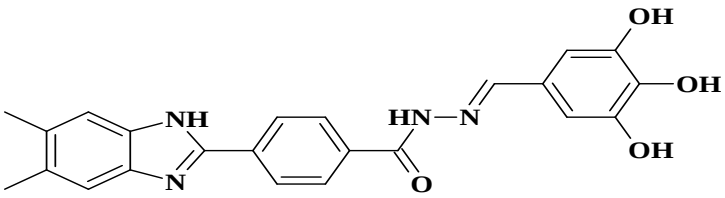


34b



34c

All the molecules were adequately characterized using various spectroscopic methods. Derivative **35** contains three OH groups at meta and para position, showing potent inhibitory activity with IC_{50} 8.40±0.76 µM.[109]

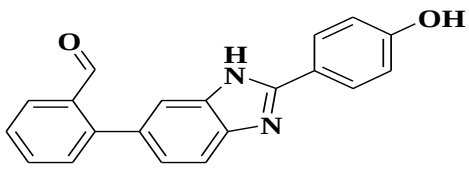


35

Aroua and colleagues synthesized a series of benzimidazoles and evaluated these analogues for *in vitro* use as competitive inhibitors for different enzymes. Antidiabetic assays indicate that most explored molecules showed good to outstanding efficacy. Derivative **36** with a hydroxyl group at the p-phenyl displayed greatest efficacy towards α-amylase (IC_{50} value 12 µM) and α-glucosidase (IC_{50} value 11 µM), as acarbose (with IC_{50} values 10.07 and 9.18 µM, respectively).[110]

2.10 Anticonvulsant Activity

A novel sequence of twenty-eight benzimidazole derivetives was established by Jain et al. to make them ligands for $GABA_A$ receptors. The quantitative relationship between binding capacity and structural characteristics was investigated employing an Array of the different tested steric, electronic, physicochemical, and thermodynamic descriptors. All the nitro-benzimidazole compounds were active against tonic seizures in mice provoked by chemical and electrical stimuli. Analogue **37a** and **37b** revealed promising results against PTZ and MES-induced convulsions.[111]



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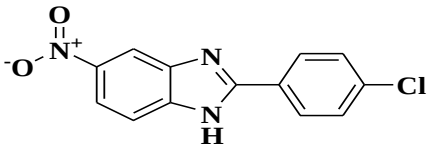
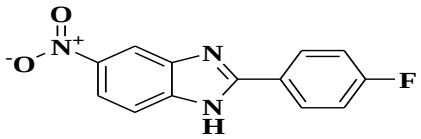


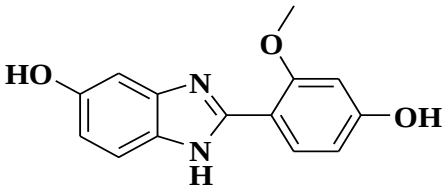
37a

2.11 Antioxidant Activity

Zhou and co-workers developed novel benzimidazole compounds with phenyl in the second position and examined their antioxidant activities. The results showed that molecules with hydroxyl groups at the 5-position of the benzimidazole nucleus had antioxidant properties compared to or superior better that reference antioxidant drug tert-butylhydroquinone (TBHQ). Compound **38** demonstrated the greatest HO• and DPPH scavenging activity with EC_{50} of 46 and 27 µM in comparison to standard drug TBHQ (EC_{50} 65 and 36 µM respectively).[112]

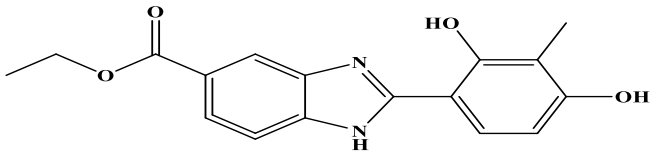


37b



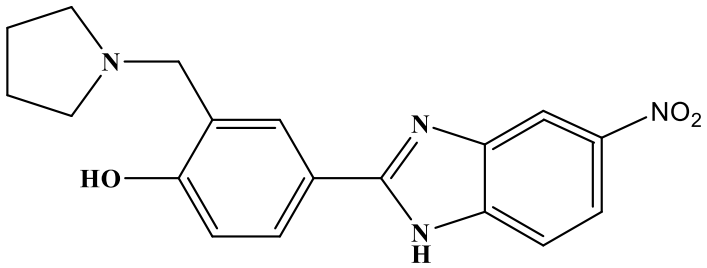
38

The current literature examines Matysiak and colleagues' efforts to generate a new family of benzimidazole derivatives. The compounds were tested for antioxidant activities in vitro utilizing the radical absorbing capability of persisting DPPH radicals and rutin as a reference. The chemicals studied showed dose-dependent inhibition of DPPH, with derivative **39** (IC_{50} 0.125 µM) outperforming the medication rutin (IC_{50} 0.087 µM) in terms of radical scavenging. SAR: The replacement of an ester group at the benzimidazole pharmacophore and two OH groups on the phenyl ring increased biological activity.[113]



39

Alpan et al. constructed and created an archive of benzimidazole analogues with a phenol group to test their antioxidant characteristics. This study relied on the observation that FeCl2 and Ascorbic acid promote in vitro lipid peroxidation and protein oxidation. Similarly, activity was assessed in vitro using FeCl2/vitamin C-induced damage from oxidation in the rat brain, and few derivatives were effective radical scavengers when compared to the reference medication tert-butyl hydroquinone (tBHQ). Targeted compounds reduced the peroxidation of lipids in brain homogenate in a dose-dependent manner. All compounds had a larger inhibitory impact on ROS formation, but derivative 40 showed the strongest efficacy with 53% suppression at a concentration of 10^{-6} µM, comparable to tBHQ.[114]



40

3 CONCLUSIONS

Benzimidazole is recognized as one of the most important heterocyclic scaffolds exhibiting potent anticancer activity, largely attributed to its structural similarity to nucleosides. In this review, we summarize benzimidazole-based hybrids and metal complexes with reported antiproliferative activity from 2016 to 2025. The examples discussed highlight various mechanisms of action through which benzimidazole derivatives exert their anticancer effects. We also emphasize the rationale behind combining the benzimidazole core with other active pharmacophores or utilizing metal complexation strategies to design multitarget anticancer agents. Overall, benzimidazoles can function as hydrogen bond donors or acceptors and effectively interact with multiple biological targets, making them promising scaffolds for the development of novel anticancer agents with favorable drug-like properties. This approach represents a future direction for the design of innovative therapeutic molecules and the advancement of benzimidazole-based anticancer drug candidates.

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