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Exploring the Versatility of Benzimidazole Scaffolds as Medicinal Agents: A Brief Update

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Abstract

Benzimidazole, one of the finest classes of heterocyclic aromatic compounds have the characteristic structure of benzene fused with a five-membered imidazole ring. Despite being made their first appearance in the late 1870s, they are considered as a 'privileged molecule'. The applications of this wonder molecule range from medicinal chemistry to material science. Benzimidazole being a potent inhibitor for various enzymes has got therapeutic effects like anticancer, antimicrobial, anthelmintic, anti-oxidant, anticonvulsant, antifungal, anti-inflammatory, antiviral, antihistaminic, antipsychotic, etc. It has also made its existence in various branches of medical science *viz* ophthalmology, neurology, cardiology and more. The applications of benzimidazole are not only limited to the biological field but also expanded to the field of material chemistry as well. This chapter summarizes the pharmacological properties of benzimidazole, illustrated on numerous derivatives since 2016.

Keywords: anti-cancer agent, Benzimidazole, biological activity, N-heterocycle, medicinal chemistry, pharmacophore

1. Introduction

The benzimidazole nucleus is fairly unique among heterocyclic ring systems because of its outstanding structural similarity with various naturally occurring nucleotides [1]. In 1872, Hoebrecker synthesized the first benzimidazole molecule by the reduction of 2-nitro-4-methylacetanilide [2]. The biological significance is because its structure is similar to purines, and the importance of the applications depends on their abundance in most of the biologically active molecules. The discovery of the structure of vitamin B₁₂ with 5, 6-dimethylbenzimidazole moiety in it, also elicited the search for benzimidazole - similar motifs for various pharmacological applications [3–5]. Following this, various research groups have outlined the synthesis and applications of benzimidazole [6, 7]. Benzene when fused with imidazole results in the formation of benzimidazole (1), which can readily undergo tautomerization as shown in **Figure 1**.

The greater reactivity of the 2nd position towards various electrophiles and nucleophiles is the outcome of tautomerization. Many drugs contain the benzimidazole

Figure 1.
Benzimidazole (compound 1) with its tautomeric forms.

Figure 2.
Drugs (compound 2, 3, 4, 5 and 6) based on benzimidazole core.

nucleus as a core unit and have a widespread application in the pharmaceutical field [8–14]. The presence of benzimidazole pharmacophore in the various branches of medical science is inexplicable. The therapeutic uses of benzimidazole include anti-cancer [15–20], antimicrobial [21–24], antiparasitic [25, 26], anti-inflammatory and analgesics [27–29], antiviral [30–32], and antiulcerative [33] activities and in fields like ophthalmology, neurology, endocrinology, etc. The first example of a benzimidazole that was clinically available was thiabendazole (2), which can be used as a fungicide and for antiparasitic purposes [34]. The 2, 6-disubstituted albendazole (3) and mebendazole (4) were used as anthelmintic or antiparasitic agents. The 1, 2-disubstituted benomyl (5) was shown to have antifungal and anticancer activities whereas 2-substituted lansoprazole (6) acted as a therapeutic agent for the reduced production of stomach acid and cardiac failures (**Figure 2**).

In this chapter, a plethora of benzimidazole analogs with different pharmacological properties such as anticancer, antibacterial, antifungal, antiviral, anticoagulant, anti-inflammatory, antiparasitic, anthelmintic activity, etc. has been discussed.

2. Benzimidazole and its pharmacological significance

Benzimidazoles were initially used as a plant fungicide and veterinary anthelmintic. After the discovery and use of thiabendazole (2), these benzimidazole motifs were used in human beings as well. Since then, a wide variety of molecules

having the core structure as (1) were synthesized and found their application in the medical world as well as in the material domain.

Various substituted derivatives of (1) were showcased diversified therapeutic properties such as antiparasitic, anticancer, anthelmintic, antiproliferative, antioxidants, antimicrobials, anti-inflammatory, antivirals, anticoagulants, antihypertensive, anticonvulsant, antidiabetic, lipid level modulators, anti-HIV, immunomodulators, hormone modulators, proton pump inhibitors and antidepressants. They have also used a building block for various other therapeutic agents. Let us have a peep at some of the innumerable reports of pharmacological activities of benzimidazole.

2.1 Anticancer activity

Cytotoxicity of benzimidazole derivatives is well known and, recently Noha et al. reported compounds of benzimidazole which are *N*-(benzimidazothiazolone) acetamides (7) [35]. In vitro analyses provided the cytotoxic activity of (7) over HCT-116 colon cancer cells. The further detailed study delivered the topoisomerase I- β (Topo I- β) and inhibiting activities against tubulin (**Figure 3**).

The role of benzimidazole analogs as potential metal-based DNA-sensor is unanimous. Fluorogenic differential/sequential Schiff base chemosensors which solely consists of benzimidazole derivatives (8), for detecting Cu^{2+} , CN^- , $\text{P}_2\text{O}_7^{4-}$, and Zn^{2+} ions in human cervical (HeLa) and breast cancer (MDA-MB-231 and MCF-7) cell lines were designed by Anbu et al. [36] (**Figure 3**).

Drug repurposing of benzimidazole compounds is generally considered for the reason that, it has antitumor activities. Florio and coworkers screened anthelmintics which are derivatives of benzimidazole [37]. Certain drugs like albendazole (3), flubendazole (9), oxibendazole (10) etc. are subjected to the evaluation of their pharmacokinetics and physicochemical properties (**Figure 3**). For the potential repurposing of the drugs in cancer therapy, a silico target prediction was used to access the pharmacology of these benzimidazole compounds.

Figure 3.
Benzimidazole derivatives (compound 7, 8, 9 and 10) acts as cytotoxic agents, chemosensors and repurposed drugs.

Figure 4.
N-substituted benzimidazole derivatives (compound **11**, **12**, **13**, **14** and **15**) with antiproliferative activity.

Figure 5.
Benzimidazole derivatives (compound **16** and **17**) for the inhibition of HSP90.

Synthesis of N-substituted benzimidazole analogues (**11–15**) with an alkyl chain and a nitrogen-containing 5- or 6-membered ring increased the anticancer effects on human ovarian carcinoma (OVCAR-3) and human breast adenocarcinoma (MCF-7) cell lines, were reported by Hsieh et al. [38]. (2*E*)-1-(1-(3-morpholinopropyl)-1*H*-benzimidazol-2-yl)-3-phenyl-2-propen-1-one (**11**) acts as the most potent antiproliferative drug and has got more advantages than the standard drug, cisplatin (**Figure 4**).

The stabilization of proteins in the cell is being coordinated by heat shock proteins (HSPs). HSP90 plays a major role in it. This can be reflected in cancer therapy. Neverdauskas et al. synthesized benzimidazole derivatives with resorcinol (**16**) and (**17**), as potential inhibitors for HSP90 (**Figure 5**) [39].

Benzimidazole is considered a privileged molecule in the medicinal world. Hernández-Romero et al. in 2021 synthesized first-row transition metal compounds which contain benzimidazole moieties (**18–21**) as ligands in them (**Figure 6**) [40]. The advancement of metallodrugs for the treatment of cancer has been rapidly evolving. The use of benzimidazole as mono-, di-, tri-, and tetradentate ligands with metals like Cu, Co, Zn, Ni, Mn, V, and Fe led to the formation of effective drugs for cancer therapy by increasing the cytotoxic and antiproliferative activity.

Bistrović et al. synthesized monocationic benzimidazoles (**22**) and (**23**), starting from *o*-phenylenediamines and benzaldehydes having 1,4-disubstituted-1,2,3-triazole

Figure 6.
Benzimidazole derivatives (compound 18, 19, 20 and 21) as metallodrugs.

motifs and studied its antiproliferative activities [41]. These compounds showed potent and selective activities that are cytostatic against non-small cell lung cancer (A549) in the low nM range and could be because of apoptosis and primary necrosis (Figure 7). Because of the presence of different amidino groups and aromatic substituents, these compounds showed a difference in their cytostatic activities in

Figure 7.
Benzimidazole derivatives (compound 22, 23, 24, 25 and 26) with potential inhibition for lung, colon, and breast cancer.

Western blot analysis. The enzyme p38 MAPK got inhibited by both the compounds as shown by *in silico* structural analysis.

The 1, 3-disubstituted benzimidazoles (24–26) were synthesized starting from *o*-diphenylamine and their interactions with cancer cells proteins were examined using molecular docking studies (Figure 7) [42]. The biochemical assay of the synthesized compounds were compared by doing theoretical calculations whereas its biological activity was tested against proteins such as colon cancer antigen (ID 2HQ6) and breast cancer (ID 2AR9) by using molecular docking studies. These benzimidazolyl halides were found to be better against the protein molecules studied and of which (26) was found to be more potent in action among the given three.

Synthesis of imidazo[1,2-*a*]pyrazine appended benzimidazoles (27) and (28) was done, starting from 1,3-dibromobenzene and evaluated its anticancer activities on the inhibition of growth of NCI-60 human cancer cell lines [43]. The antiproliferative activity of these molecules is attributed to causing damage to the DNA of such cells. The planar geometry of these compounds also enhanced the intercalated binding with cancer cells DNA. The cytotoxicity evaluation of the compounds was also done against the human normal cell line (Hek293) and found to be very low with higher LC₅₀ values (Figure 8).

Srouf et al. in 2020 reported the formation of a novel class of 2-thiazol linked benzimidazoles (29) and studied its inhibiting action against epidermal growth factor receptor (EGFR) (Figure 8). The *in vitro* studies of the synthesized compounds using erlotinib as a standard drug revealed its suppression activity against EGFR PK inhibitors, which targets human breast cancer (MCF-7) cells. They have also exhibited a

Figure 8.
Benzimidazole derivatives (compound 27, 28, 29 and 30) with NCI-60 cell line inhibition.

Figure 9.
Derivatives of benzimidazole (compound 31, 32 and 33) with anticancer activity against liver, lung, and gastric cancer cells.

very low suppression percentage among normal cells indicating its diminished side effects when used as an antiproliferative drug [44].

Benzimidazole-tethered pyrazoles (30) have been synthesized in multi-steps by the condensation of phenylhydrazine with acetylphenones followed by cyclization, Vilsmeier-Haack formylation and Knoevenagel reactions (Figure 8) [45]. A study of anti-inflammatory and antioxidant activities of the benzimidazoles showed a marked improvement when compared with diclofenac sodium and ascorbic acid as standards respectively. The anticancer activity was shown against human pancreatic cancer cell line AsPC1 (progenitor) and SW1990 (squamous) which was also visible in the better binding with B-cell lymphoma in docking studies.

Mn(I) and benzimidazole co-ligands (31) with potential photo-activated carbon monoxide releasing molecules (CORMs) were synthesized and their biological activities were studied (Figure 9) [46]. The CO releasing properties, as well as luminescence intensities of these complexes, differed with the extend of conjugation and with the degree of unsaturation present in the benzimidazole co-ligands. The bioimaging capabilities of these complexes were proved by the absorption of it by liver cancer cells (SK-Hep1) and human liver cells (HL-7702) under cellular fluorescence imaging tests. Complex (31) showed excellent anticancer activities among all the molecules synthesized.

Prosser et al. synthesized a Cu(II) complex of benzimidazole (32) and studied their anticancer properties [47]. This derivative that was revised at the non-coordinated nitrogen of the benzimidazole molecules, exhibited excellent cytotoxicity against A549 adenocarcinomic alveolar basal epithelial cells (Figure 9).

Research works concentrating on the effective therapeutic agent possessing antiproliferative activity for human gastric cancer paved the way to the discovery of yet another benzimidazole derivative (33) with quinoline copper-based complex (Figure 9) [48]. The complex ensures G2/M phase arrest, apoptosis, mitochondrial dysfunction etc. and thus provides effective cytotoxicity.

Aromatase inhibitors (AIs) are compounds that control estrogen-related diseases and hence breast cancer, as its concentration was found to be higher in such cases. Çevik et al. in 2020 synthesized some novel benzimidazole- triazolothiadiazine

Figure 10.

Benzimidazole derivatives (compound 34, 35, 36, 37, 38 and 39) provide inhibition against breast, lung, and prostate cancer cells.

libraries and examined its aromatase inhibition activities [49]. Initial screening of these compounds towards anticancer properties against breast cancer cell line (MCF-7) in humans, resulted in getting good results. Upon further subjecting it to *in vitro* aromatase enzyme inhibition studies, the compound (34).

among them was found to be almost equal in activity when compared with a reference drug letrozole (**Figure 10**).

The role of benzimidazole compounds in the treatment of breast cancer is exemplary. Gangrade et al. demonstrated the use of benzimidazole derivatives in the inhibition of Wnt/ β -catenin signaling [50]. The upregulation of Wnt/ β -catenin signaling in triple-negative breast cancer (TNBC), when compared to normal and other breast cancer subtypes, is inevitable. Benzimidazole compounds like SRI33576 (35) and SRI35889 (36) have a high cytotoxicity rate in TNBC cell lines. They are found to be active inhibitors of Wnt/ β -catenin signaling and have therapeutic properties for treating TNBC (**Figure 10**).

Cheong and co-workers designed and synthesized benzimidazole methylcarbamate analogue (37) with enhanced water solubility [51]. The existed drugs that account for the treatment of metastatic cancers are not suitably aiding the circumstances. Poorly soluble benzimidazole methylcarbamate drugs, which are effective anthelmintics are subjected to functionalization with oxetane or an amine group to improve the solubility and then used as an active therapeutic agent for the treatment of metastatic cancers. Cytotoxicity towards prostate, lung, and ovarian cancers is exhibited by the novel oxetanyl substituted compound (37) (**Figure 10**).

Liang and co-workers synthesized selenium-containing benzimidazole derivatives through condensation of peptide coupling reagents and irradiation of microwaves [52]. These selenediazole derivatives were recognized as potent anticancer agents

against MDA-MB-231 and MCF-7 breast cancer cell lines. Compounds (38) and (39) showed greater cytotoxic activity towards triple-negative breast cancer cell line MDA-MB-231 (**Figure 10**).

Husain et al. prepared various derivatives of furanone appended benzimidazoles, which effectively contribute to cancer therapy [53]. Compound (40) was found active against DU145 and MCF7 whereas compound (41) has got excellent activity against MCF7, A549, and DU145 cell lines (**Figure 11**). They are potential cytotoxic agents than the standard drug doxorubicin.

Compounds (42) and (43) are *bis*-benzimidazole analogs that have been synthesized to account for cancer therapy under microwave irradiation [54]. The anticancer activity was studied with the help of.

Figure 11.
Benzimidazole analogs (compound 40, 41, 42, 43, 44, 45, 46 and 47) with anticancer activities.

Molinspiration software and they possess high bioactivity scores. It was also found that they obey Lipinski's rule and could be emerged as a lead anticancer drug (**Figure 11**).

Shinde and co-workers used D-glucose as the precursor for the synthesis of ribofuranosyl nucleosides (**44**) and (**45**) (**Figure 11**). Evaluation of their anticancer activity was done using the MDA-MB-231 cell line [55].

Sireesha et al. designed and synthesized benzimidazole/benzoxazole-linked β -carboline (**46**) by the condensation of two various anti-cancer fragments (**Figure 11**) [56]. With the assistance of MTT assay, these compounds were subjected for the anti-cancer screening against Colo-205 (colon), MCF-7 (breast), A2780 (ovarian), and A549 (lung) and found that these exhibits maximum anti-cancer activity with the β -carboline hybrid.

Benzimidazole derivatives (**47**) with a pyrrolidine side chain can be effectively used to treat sorafenib resistance (SR) in hepatocellular carcinoma, was reported in 2019 [57]. Mode of action is through the inhibition of proliferation of SR cell lines by interrupting the phosphorylation of AKT, p70S6, and the downstream molecule RPS6 (**Figure 11**).

Synthesis of organoruthenium(II) complexes of benzimidazoles (**48**) and (**49**) was reported by Welsh and coworkers (**Figure 12**) [58]. Their anti-cancer activity was screened against triple-negative MDA-MB-231 and MCF-7 breast cancer cell lines, respectively. Among the synthesized compounds, (**48**) showed more potency and (**49**) showed comparable potency with the cisplatin, against the MCF-7 cell line.

2.2 Antibacterial and antifungal activity

Heterocyclic appended benzimidazoles were synthesized and their antibacterial and antifungal activities were tested [59]. The mechanism of action of these molecules was also examined by using docking studies with bacterial proteins such as DNA gyrase subunit B (DNAG) and penicillin-binding protein 1a (PBP1a). The compounds with thiazole and thiadiazole moieties (**50**) and (**51**) respectively, showed marked inhibitory activity against *Escherichia coli*, *Bacillus pumilus*, and *Staphylococcus aureus* bacteria (**Figure 13**).

Ajani et al. synthesized various *o*-substituted and 1, 2-disubstituted benzimidazoles and examined their antibacterial properties [60].

Figure 12. Organoruthenium benzimidazole derivatives (compound **48** and **49**) with inhibition against breast cancer cell lines.

Figure 13.
Benzimidazole derivatives (compound 50, 51, 52 and 53) with inhibitory activity against common bacteria.

Benzene-1,2- diamine undergoes condensation reactions with anthranilic acid, 3, 5- dinitrophenylbenzoic acid, and phenylacetic acid, catalyzed by NH_4Cl yielded the precursor molecules, which on reaction with electrophile-releasing agents produced the corresponding *o*-substituted and 1,2-disubstituted benzimidazoles (52) and (53), respectively (Figure 13). *In vitro* studies of these compounds showed a better activity with a low minimum inhibitory concentration (MIC) value.

1-aryl-substituted 1, 2, 3-triazole appended amidinobenzimidazoles linked *via* phoxymethylene units (54) and (55) were synthesized and their anti-bacterial as well as anti-trypanosomal activities and DNA/RNA binding affinities, were studied [61]. Compound (54) showed a remarked inhibition against gram-positive bacteria whereas compound (55) showed inhibition against gram-negative bacteria. These compounds also showed binding affinities towards ctDNA. Compound (56) with *N*-isopropylamidine and *p*-methoxyphenyl-1,2,3-triazole units exhibited enhanced anti-trypanosomal activities against *T. brucei* and reduced toxicity towards mammalian cells (Figure 14).

Figure 14.
Benzimidazole derivatives (compound 54, 55 and 56) with antibacterial and anti-trypanosomal activities.

A microwave-assisted, Ni(II) catalyzed novel preparation of 2,6-disubstituted and 1,2,6-trisubstituted benzimidazoles were achieved by Patel and his group (**Figure 15**) [62]. The *in-vitro* antimicrobial studies of the title compounds (**57**) against gram-positive and gram-negative bacteria and fungal strains showed an improved activity exhibited by them when compared with ampicillin, a standard drug. Certain compounds show potent anti-mycobacterium tuberculosis activity, antimalarial activity, antioxidant activity, etc. All these activities were supported by better molecular docking scores and their pharmacokinetics were also examined by ADME-Tox descriptors.

A comparative antimycobacterial activity study of 2,5-disubstituted and 1,2,5-trisubstituted benzimidazoles was reported in 2020 [63]. The *in vitro* studies against *Mycobacterium tuberculosis* H37Rv strain revealed an increased activity correlated with lipophilicity for disubstituted compounds (**58–60**) than for trisubstituted ones because of the addition of a long hydrocarbon chain at position 1 in the latter (**Figure 15**).

A library of mono and disubstituted benzimidazoles were synthesized by applying different methodologies, i.e., by using the microwave, ultrasound (US), infrared (IR), simultaneous application of US and IR, and by conventional heating [64]. The antimicrobial and antifungal activities of these benzimidazole derivatives were then evaluated. It was found that some compounds such as (**61**) and (**62**), were proved to be a better substitute than the standard drugs trimethoprim sulfamethoxazole and miconazole for antimicrobial and antifungal activities, respectively (**Figure 16**).

Very recently, Khan et al. designed and synthesized pyrimidine-benzimidazole hybrids (**63**) using the revised Biginelli reaction and evaluated its potential inhibition of SARS-CoV-2 main protease and spike glycoprotein [65]. Investigation about the pharmacological properties resulted in biological evidence like antimicrobial and antifungal properties. The derivatives developed possess more affinity in binding and anti-SARS-CoV-2 activity than presently approved drugs (**Figure 16**).

Zha et al. demonstrated benzimidazole derivatives (**64**) and (**65**) as potent antibacterial agents (**Figure 16**) [66]. Properties like enzyme inhibition, DNA binding, and having a synergistic effect with existing antibiotics makes benzimidazole an active warrior against methicillin-resistance *Staphylococcus aureus* (MRSA).

Figure 15.
Benzimidazole derivatives (compound **57**, **58**, **59** and **60**) with antibacterial and antimycobacterial activities.

Figure 16.
Potential benzimidazole-derived antibiotics (compound 61, 62, 63, 64 and 65).

Claisen-Schmidt condensation of 2-acetylbenzimidazole and aldehydes followed by a series of steps resulted in the synthesis of benzimidazole derivative (66) [67]. They exhibit exceptional anti-microbial and anti-bacterial activities. The grafting of certain functional groups and the presence of pyridine, pyrimidine, indole, etc. improves the anti-microbial activity (Figure 17).

Karaburun et al. described the multi-step synthesis of a series of benzimidazole-1,3,4-oxadiazole derivatives (67) which are prominent for their antifungal activities against *Candida* species [68]. The ergosterol inhibition power was proven *via* ergosterol quantification assay and the docking studies were performed on 14- α -sterol (Figure 17).

Figure 17.
Benzimidazole derivatives (compound 66, 67, 68 and 69) with antimicrobial, antifungal, and antibacterial activities.

Recently, Aroso and co-workers computationally designed benzimidazole derivatives through palladium-catalyzed reactions [69]. The reaction between 4-bromo-1,2-diaminobenzene and 2-nitrobenzaldehyde, followed by a couple of palladium-catalyzed Suzuki–Miyaura and Buchwald–Hartwig amination cross-coupling reactions resulted in the formation of (68) and (69) (**Figure 17**). The importance of these benzimidazoles is that it has an inhibitory effect on *E. coli* DNA gyrase B.

Chen et al. designed flavonoid analogs (70) which consist of benzimidazole derivatives like 4*H*-chromen-4-one, which provides a remarkable anti-bacterial resistance against members of *Xanthomonas* and *Ralstonia solanacearum* (**Figure 18**) [70]. Molecular docking studies showed the curative and protective activity for the *Tobacco mosaic virus* (TMV). The inhibition rate value is high for these analogs when compared with other anti-viral agents.

Compound (71) synthesized by Gençer and co-workers were tested against *Candida* species through microdilution methods [71]. MTT assay and other various microbiological studies provided the antifungal profile with good and effective *in vitro* cytotoxic effects along with inhibition on ergosterol biosynthesis (**Figure 18**).

Synthesis of benzimidazole derivatives like triazinane (72) and oxidiazinanes (73) through the process of amino methylation with the aid of different aryl-*N, N'* unsymmetrical thioureas were designed by Gullapelli and co-workers (**Figure 18**) [72]. The antibacterial activity was evaluated by using suitable gram-positive and negative bacterial strains.

Wang et al. reported the synthesis of a series of benzimidazole moieties (74–76) with quinolone analogs which exhibited antibacterial and antifungal properties (**Figure 19**) [73]. The bioactive assay proved that the 2-fluorobenzyl derivative has got remarkable antimicrobial activities against the *P. aeruginosa* and *C. tropicalis*.

A novel, one-pot synthesis of 2-substituted benzimidazoles and Mannich bases (77–80) with potent antimicrobial activity was reported by Marinescu et al. [74].

Qualitative and quantitative antimicrobial bioassay of these benzimidazole derivatives showed activity against a broad spectrum of gram-positive and negative bacterial strains both in planktonic and adherent states. The presence of nucleophilic groups like -OH or -CH₃ accounts for the microbicidal activity (**Figure 20**).

Figure 18. Derivatives of benzimidazoles (compound 70, 71, 72 and 73) with potential antibacterial, antifungal, and cytotoxic activities.

Figure 19.
Quinolone analogs of benzimidazole (compound 74, 75 and 76) with antibacterial and antifungal activities.

Figure 20.
Potent antimicrobial derivatives of benzimidazole (compound 77, 78, 79 and 80).

Benzimidazoles moieties linked with *N*-acyl substituted indole (81–86) were demonstrated by Abraham et al. [75]. The assessment of antimicrobial activity was done against gram-negative and gram-positive bacteria like *Pseudomonas aeruginosa* (MTCC424), *Staphylococcus aureus* (MTCC 2940), *Escherichia coli* (MTCC 443), and *Enterococcus faecalis*. These compounds also account for the hindering of biofilm formation and then the effective growth of *Staphylococcus epidermis* (Figure 21). Along with this, an HRBC membrane stabilization test was carried out for the evaluation of the anti-inflammatory activity.

Antoci and co-workers synthesized *bis*-(imidazole/benzimidazole)-pyridine derivatives (87) through *N*-alkylation (Figure 22) [76]. The anti-TB activity of the compound is good to excellent against both replicating and nonreplicating Mtb. The derivatives are effective against drug-resistant Mtb and some possess a bactericidal approach.

The synthesis of naphthyl-substituted benzimidazole derivatives (88) and (89) was reported by Ersan et al. in 2020 [77]. The antimicrobial activity was screened and was found that (89) showed maximum potency against all gram-positive and gram-negative bacteria. Also, (88) actively functions as an antifungal agent. These derivatives also interact with active sites of *E. coli* and can be accounted for inhibition of *E. coli* topoisomerase I (Figure 22).

Sirim et al. designed and synthesized benzimidazole-acrylonitrile hybrid derivatives from benzene-1, 2-phenyleneamine and ethyl cyanoacetate followed by reaction with piperazines [78]. All the derived compounds exhibited anti-mycobacterial activity against *M. tuberculosis* H37Rv strain by microplate alamar blue assay (MABA). Compound (90) was found to be more effective than standard drugs like isoniazid, ciprofloxacin, rifampicin, etc. (Figure 22).

Figure 21.
N-acyl substituted indole-linked benzimidazole derivatives (compound 81, 82, 83, 84, 85 and 86) as antimicrobial agents.

Figure 22.
Benzimidazole derivatives (compound 87, 88, 89 and 90) with antibacterial and anti-TB activities.

2.3 Antiparasitic activity

Taman et al. evaluated the antischistosomal activity of newly synthesized benzimidazole-related compounds like NBTP-OH (**91**) and NBTP-F (**92**) [79]. The Suzuki-Miyaura coupling reaction of 5-formyl thiophen-2-ylboronic acid and 1-bromo-4-hydroxy benzene or 1-bromo-4-fluoro benzene followed by a series of reactions resulted in the formation of compounds (**91**) and (**92**), respectively (**Figure 23**). To date, the treatment of schistosomiasis depended on Praziquantel (PZQ). The use of these two structurally related benzimidazole derivatives can be an alternative for PZQ. The *in vitro* schistosomicidal assay performed on adult worms gave the conclusion that they were considered dead through the destruction of tegument after two minutes of treatment with **91** and **92**.

Synthesis of 1, 3-disubstituted benzimidazol-2-ones (**93**) and (**94**) starting from *o*-phenylenediamine and urea, followed by the evaluation of its anti-trichinellosis efficacy was done [80]. It was found that the synthesized benzimidazole derivatives are more effective than the standard drug albendazole, which is the traditional drug used in the treatment against *Trichinella spiralis*. The estimation of antiparasitic activity was employed through the Campbell method. Selective binding of benzimidazole moiety with the β -tubulin of the parasite results in the destruction of the cell, followed by the death of the parasite. The *in vitro* activity of all the tested benzimidazole analogs increases with the concentration against the *Trichinella spiralis* (**Figure 23**).

Molecular docking studies and quantitative structure–activity relationship (QSAR) delivered that benzimidazole derivatives (**95–97**) can be used as cruzain inhibitors for the deadly Chagas disease [81]. The model compounds used displayed a high statistical consistency and a notable capability to predict the inhibiting sites (**Figure 24**). The scenario with Chagas disease is the unavailability of an effective treatment method. Clinical studies related to the Chagas disease and cruzain inhibitors have been on the

Figure 23.
Benzimidazole derivatives (compound **91**, **92**, **93** and **94**) with antischistosomal and anti-trichinellosis activities.

Figure 24.
Benzimidazole derivatives (compound 95, 96 and 97) as cruzain inhibitors for Chagas disease.

account of research scientists. In short, benzimidazole derivatives can be used as a lead in the drug discovery of Chagas disease by acting against the recombinant cruzain enzyme.

Tonelli et al. designed and synthesized benzimidazole derivatives from benzene-1,2-diamine and various acids followed by suitable functionalization and used it as a potent antileishmanial agent [82]. Benzimidazole derivatives were tested against *Leishmania tropica* and *L. infantum* and were found that compounds bearing the derivatives of 1-lupinyl were commonly more active than dialkylaminoalkyl derivatives and compounds (98) exhibited the highest potency among the synthesized compounds (Figure 25). The observed antileishmanial activity was a result of the interaction of benzimidazole derivatives with acidic components of the cell membrane leading to its destruction.

Exploration of the inhibitory activity of certain benzimidazole compounds like albendazole (3), ricobendazole (99), oxfendazole (100) etc. resulted in

Figure 25.
Compounds 98, 99 and 100 with antileishmanial and antiparasitic activities.

acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibition at nanomolar level [83]. This has got immense importance in therapy emerging for handling the resistance among anti-cholinergic factors and in antiparasitic treatment (**Figure 25**). The benzimidazole derivatives are selectively toxic towards helminths which are considered parasites. The inhibitive effect of benzimidazole derivatives on β -tubulin leads to disruption of function in helminths and results in its death.

2.4 Antiviral activity

Compound (**101**) has been synthesized in a multi-step process by Bessieres et al. in 2021 (**Figure 26**) [84]. A study about the inhibition of Ebola virus infection resulted in the design of a more potent and selective drug than the reference drug, Toremifene.

Ibba et al. demonstrated the role of benzimidazole derivatives (**102**) and (**103**), which are active inhibitory agents against *enterovirus* A71 (EV-A71), which is a major cause for foot-mouth disease (HFMD), herpangina, etc. [85]. Penetration and apoptosis assay concluded that the derivatives are capable to inhibit viral endocytosis through reduced viral attachment and penetration to the host cells (**Figure 26**).

Research for the inhibitory action of *chikungunya virus* (CHIKV) infection led to the discovery of benzimidazole-related antiviral agent which targets the nonstructural protein 4 (nsP4), was reported by Wada and co-workers [86]. One of the compounds (**104**), synthesized by them can effectively inhibit CHIKV by using M2295 residue in the nonstructural protein 4 (nsP4) and with the help of CHIKV replicons, it inhibits the RNA-dependent RNA-polymerase (RdRp) function of CHIKV (**Figure 26**).

Figure 26.
Potential antiviral derivatives of benzimidazole (compound **101**, **102**, **103** and **104**).

2.5 Other properties like antipsychotic, antidiabetic, anticoagulant activities, etc.

In vitro and *in vivo* characteristic studies of benzimidazole acetamide derivatives (**105**) in the ethanol-induced neuro-degeneration model was performed by.

Imran et al. in 2021 [87]. The derivatives lowered the neurodegeneration and inflammation of neurons by down-regulating inflammatory cascades caused by oxidative stress (**Figure 27**).

The prominence of benzimidazole in the field of medicine is exceptional. Etazene (**106**), a benzimidazole opioid that has got strong analgesic activity, is used as a new psychoactive substance (**Figure 27**) [88]. Misuse of certain benzimidazole derivatives can create social crises too.

Tantray and co-workers studied psychiatric disorders like depression and acknowledged the fact that glycogen synthase kinase-3 β (GSK-3 β) dysfunction is a potential implication [89]. They designed and synthesized several 1,3,4-oxadiazole carboxamides linked to benzimidazoles (**107**) and assessed their *in vitro* GSK-3 β inhibition. It was found that these molecules are having antidepressant activity (**Figure 27**).

Hussain et al. synthesized certain benzimidazole analogs (**108**) for the effective management of type-II diabetics [90]. The sulfonamide bearing 2-marcaptobenzimidazoles (**108**), possesses better *in vitro* α -amylase enzyme inhibitory activity while compared with the standard drug, acarbose (**Figure 27**).

Dabigatran is an effective drug having a benzimidazole core as the activity center and is used for the treatment of cardiovascular diseases because of its antithrombin as well as anticoagulant activities. Zhang et al. in 2020 enhanced the activity and bioavailability of dabigatran by adding methyl and methoxy groups into the benzene ring [91]. By studying the anticoagulant action and thrombin inhibition properties of compounds (**109**) in rats, proved the possibility of using these molecules as potential antithrombin drug candidates in the future (**Figure 27**).

Figure 27.

Benzimidazole derivatives (compound **105**, **106**, **107**, **108** and **109**) with antipsychotic, antidiabetic, and anticoagulant activities.

3. Conclusions

To sum up, benzimidazole is a chemical compound that belongs to the family of heterocyclic aromatic organic compounds. It is a potent biologically important molecule with a noticeable therapeutic activity. Applications of benzimidazole extend to medicinal chemistry. Several advanced research in this area also found out that the aforementioned compound has significant antimicrobial activities especially against many strains of viruses, fungus, bacteria, etc. It is also widely used in medicinal chemistry as an accepted drug against parasites and their allied infections. Benzimidazole is also used as an analgesic and anti-inflammatory agent. Recent studies have also created a lot of attention for the compound since it has an anti-carcinogenic activity like cytotoxicity and hence may become a viable cure for cancer in the future. The applications of benzimidazole cannot be marginalized. It has got a whole spectrum of medicinal agents. Benzimidazole has gained popularity in material science.

Apart from this, the multi-target capability of benzimidazole scaffolds has not been explored extensively. Being a versatile motif, benzimidazole could provide a plethora of novel multi-target ligands against various debilitated pathological conditions. The lack of comprehensive compilation about the SAR of many compounds and the various research reports stemmed the reason for less number of active benzimidazole compounds reaching the market. The existing design of benzimidazole derivatives can be further revised to accommodate potential multitargeting agents, thus enhancing and treating multifactorial disorders. This can be a breakthrough establishment in benzimidazole history.

In short, the importance of this imidazoline compound has been proved by the number of research papers getting published in a short period. This chapter is trying to narrate the formulation as well as execution of benzimidazoles in different fields of medicinal chemistry.

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