Chapter

Benzimidazole: Pharmacological Profile

Mahender Thatikayala, Anil Kumar Garige and Hemalatha Gadegoni

Abstract

Benzimidazole is a bicyclic heterocyclic aromatic compound in which benzene fused to imidazole moiety. Benzimidazole holds a vital role in the field of medicinal chemistry which possesses wide variety of pharmacological activities like antibacterial, anti cancer, antifungal, antileishmanial, anti tubercular, anti viral and anti malarial respectively, hence the benzimidazole moiety attracting the medicinal chemist to synthesize the different benzimidazole derivatives with wide variety of pharmacological activities. The book chapter mainly discussed the anti cancer, anti HIV, antileishmanial and anti tubercular activites of recently synthesized benzimidazole derivatives.

Keywords: benzimidazole, anti cancer, anti HIV, antileishmanial, anti tubercular

1. Introduction

Benzimidazole is bicyclic heterocyclic aromatic compound in which benzene ring fused to 4 and 5 position of imidazole ring, it contain two nitrogen atoms at 1 and 3 position exhibit both acidic and basic nature called amphotericin nature and exists in two equivalent tautomeric forms, when the hydrogen present at first position nitrogen atom possess acidic nature, when the hydrogen present at third position nitrogen atom possess basic nature (Figures 1) [1]. Benzimidazole is a very important important pharmacophore among all the heterocyclic compounds due to its important pharmacological activities like anti-Alzheimer [2], antibacterial [3], anti cancer [4], anti-diabetic [5], antifungal [6], anti HIV [7], anti leishmanial [8], anti inflammatory [9], analgesic [9], anti malarial [10], anti microbial [11] and anti tubercular [12] activity, there are many benzimidazole derivatives are using to treat many diseases, few presently marketing drugs contain benzimidazole moiety are the bezitramide using as an analgesic, ridinilazole sing as antibacterial, the candesartan, mibebradil using as antihypertensive drugs, mebendazole, albendazole, thiabendazole, and flubendazole using as antihelminthics, astemizole, bilastine using as antihistamines, pantoprazole, lansoprazole, esomeprazole, ilaprazole using as proton pump inhibitors, bendamustine, selumetinib, galeterone, pracinostat using as antitumor agents and enviradine, samatasvir, and maribavir using as antiviral agents (Figures 2) [13–17].
2. Pharmacological profile of benzimidazole derivatives

2.1 Anti cancer activity

In the year of 2019 Tahlan et al., reported the synthesis and anti cancer activity of the new benzimidazole derivatives, among all the derivatives the compound 1 ([Figure 3](#)) found to be best activity at IC$_{50}$ value of 4.53 μM against the human colorectal cancer cell line [4], same authors in 2018 reported the compound 2 ([Figure 3](#)) showed best activity at IC$_{50}$ value of 4.12 μM against the human colorectal carcinoma cell line (HCT116) [18], same year few authors reported the synthesis, anti anti cancer activity of the new benzimidazole derivatives, Aikman et al., reported the compound 3 ([Figure 3](#)) found to be best active compound at EC$_{50}$ value of 5/C6 2 μM against the melanoma (A375) cells [19], Mohamed et al., reported the compound 4 ([Figure 3](#)) showed best activity at IC$_{50}$ value of 80,35, 72 μg/ml against the against human breast adenocarcinoma (MCF-7), human lung carcinoma (A549), human epitheloid cervix carcinoma (HELA) [20], Gohary et al., reported the compound 5 ([Figure 3](#)) showed significant activity at IC$_{50}$value of 0.022, 0.014, 0.015 μM against the against liver cancer (HepG2), colon cancer (HCT-116), breast cancer (MCF-7) cells [21], in 2017 Wang et al., reported the synthesis, anti-cancer activity of the chrysin benzimidazole derivatives, the compound 6 ([Figure 3](#)) showed significant activity at IC$_{50}$ values of 25.72 ± 3.95 μM against MFC cells [22] and Yadav et al., reported the anti cancer activity of synthesized the 2-(1H-benzo[d]imidazol-2-ylthio)acetami do)-N-(substituted-4-oxothiazolidin-3-yl)acetamides, the compound 7, 8 ([Figure 3](#)) showed significant activity at IC$_{50}$ value of 0.00005, 0.00012 μM/ml against HCT116 cell line [23], Onnis et al., reported the anti cancer activity of benzimidazolehydrazones, the compound 9 ([Figure 3](#)) showed excellent activity at IC$_{50}$ value of 0.98 ± 0.02 μM against human T-lymphoblastic leukemia (CEM) cells [24].

In 2015 few authors worked on synthesis of benzimidazole and evaluated the anti-cancer activit, the Gao et al., reported the compound 10 ([Figure 3](#)) showed good activity at IC$_{50}$ value of 2.68 μM against K562 and HepG-2 cells [25], Kamal et al., reported the compound 11 ([Figure 3](#)) found to be best at IC$_{50}$ value of 1.8 μM against most of the tumor cell lines [26], T.S. Reddy et al., reported the compounds 12, 13 ([Figure 3](#)) showed best anti-cancer activity with IC$_{50}$ values of 1.81, 0.83, 1.76, 1.13, 0.95, 1.57 μM against lung (A549), breast (MCF-7), cervical (HeLa)
Figure 2.
Structures of marketing drugs containing benzimidazole moiety [13–17].
Figure 3. 
Structures of effective anticancer compounds.
human tumor cell lines [27], Rodionov et al., reported the compound 14 (Figure 3) found to be good activity with 87% tumor growth inhibition against carcinoma [28], Sharma et al., reported the Compound 15 (Figure 3) showed maximum activity at GI₅₀ values of 3.16, 2, 1.36 μM against colon cancer, CNS cancer and ovarian cancer [29] and Wang et al., reported the compound 16 (Figure 3) showed excellent activity at GI₅₀ values of 2.4, 3.8, 5.1 μM against human lung adenocarcinoma cells (A549), human liver hepatocellular carcinoma (HepG2), human breast carcinoma cells (MCF-7) [30].

In 2014 Yoon et al., evaluated the anti cancer activity of synthesized novel benzimidazole derivatives, the compounds 17 (Figure 3) 18 (Figure 4) found to be
good at IC\textsubscript{50} value of 49.63, 46.33, 62.43, 42.30 \textmu M against breast cancer cells (MCF-7), triple-negative breast cancer cells (MDA-MB-468) [31], same year Wang et al., reported anticancer activity of benzimidazole-2-urea derivates, the compound 19 (Figure 4) showed significant activity at IC\textsubscript{50} value range of 0.006 to 1.774 \textmu M against the K562, A431, HepG2, Hela, MDA-MB-435S cancer cells [32], Salahuddin et al., reported the compound 20 (Figure 4) showed best anti cancer activity at GI\textsubscript{50} values of 0.34, 0.31 \textmu M against colon cancer cell lines, prostate cancer cell lines [34], Madabushi et al., reported the compound 22 (Figure 4) showed best anticancer activity at GI\textsubscript{50} values of 5.2, 9.8, 12.3, 11.1 \textmu M against A549, MCF7, DU145, HeLa human cancer cell lines [35] and Guan et al., reported the compound 23 (Figure 4) showed significant anticancer activity with IC\textsubscript{50} values of 0.098, 0.15, 0.13 \textmu M against SGC-7901, A549, HT-1080 human cancer cell lines [36].

In 2013 Sharma et al., reported the anti cancer activity of synthesized the benzimidazole quinazoline hybrids, the compound 24 (Figure 4) found to be activity with percentage growth of inhibition of 98, 94.2, 94.3, 97.5 against leukemia (K-562, SR), colon (HT29), melanoma (LOX IMVI) human cancer cell lines [37], in the same year Husain et al., reported the synthesis and the anti cancer activity of benzimidazole clubbed with triazolo-thiadiazoles and triazolo-thiadiazines, the compound 25 (Figure 4) found to be maximum activity with growth inhibition with GI\textsubscript{50} values ranging from 0.20 to 2.58 mM against leukemia cell lines [38], Nassan et al., reported the anti cancer activity of synthesized novel 1,2,3,4 tetrahydro[1,2,4]triazino[4,5-a]benzimidazoles, the compound 26 (Figure 4) showed excellent activity at IC\textsubscript{50} value of 0.0390 \textmu M against human breast adenocarcinoma cell line (MCF7) [39] and Hranjec et al., reported the anti cancer activity of synthesized the novel benzimidazole schiff bases, the compound 27, 28 (Figure 4) found to be significant activity at IC\textsubscript{50} values of 4.73, 0.96, 3.24, 1.67 \textmu M against HIV-1 [40], same year Pan et al., evaluated the anti HIV activity of synthesized benzimidazoles, the compounds 35, 36 (Figure 5) found to be significant activity with IC\textsubscript{50} values of 3.45, 58.03 nM against HIV-1 [43], Masoudi et al., synthesized the new benzimidazole derivatives, evaluated the anti HIV activity, among all the synthesized derivatives, compounds 37 (Figure 5) found to be significant activity at EC\textsubscript{50} 1.15 \mu g/mL against HIV-1 and HIV-2 [44].

2.2 Anti HIV activity

In the year of 2020 Srivastava et al., reported the synthesis and anti HIV activity of the new benzimidazole derivatives, among all the derivatives the compound 29 (Figure 5) found to be best activity at IC\textsubscript{50} value of 0.386 \times 10^{-5} \textmu M against HIV-1 [7], Iannazzo et al., reported the synthesis and anti HIV activity of the new benzimidazole derivatives, among all the derivatives the compound 30 (Figure 5) showed best activity at IC\textsubscript{50} value of 0.09 \mu g/mL against HIV-1 [41], Yadav et al., reported the anti HIV activity of synthesized benzimidazole derivatives, in all the synthesized derivatives the compounds 31–34 (Figure 5) found to be best active compounds with more than 50% of RT inhibition at concentration of 20 \textmu M against HIV-1 [42], same year Pan et al., evaluated the anti HIV activity of synthesized benzimidazoles, the compounds 35, 36 (Figure 5) found to be significant activity with IC\textsubscript{50} values of 3.45, 58.03 nM against HIV-1 [43], Masoudi et al., synthesized the new benzimidazole derivatives, evaluated the anti HIV activity, among all the synthesized derivatives, compounds 37 (Figure 5) found to be significant activity at EC\textsubscript{50} 1.15 \mu g/mL against HIV-1 and HIV-2 [44].

2.3 Anti leishmanial activity

M. Tonelli et al., reported the antileishmanial activity of newly synthesized benzimidazole derivatives, among all the derivatives compound 38 (Figure 6)
found to be significant inhibition of promastigotes, amastigotes of *Leishmania tropica*, *Leishmania infantum* at IC50 values of 0.19, 0.34, 0.31 μM and compound 39 (Figure 6) inhibited promastigotes of *Leishmania infantum* at IC50 value of 3.70, 4.76 μM [8], Oh et al., reported the antileishmanial activity of newly synthesized benzimidazole derivatives, among all the derivatives compound 40, 41 (Figure 6) found to be most active against promastigotes, amastigotes of *Leishmania donavani* at EC50 values of 1.25, 3.05, 1.48 5.29 μM [45].
2.4 Anti tubercular activity

In the year of 2019 S. Manivannan et al., reported the synthesis anti tubercular activity of benzimidazole derivatives, among all the derivatives compound 42, 43 (Figure 7) showed best anti tubercular activity with MIC values of 6.5, 6.5, 12.5, 6.5, 12.5, 6.5 μg/mL against *Mycobacterium tuberculosis* H37Rv, drug-resistant, drug-susceptible strains [12], previous year Mohanty et al., reported the anti tubercular activity of synthesized the novel azo derivatives of benzimidazoles, in all the derivatives the compounds 44 (Figure 7) showed best activity at IC50 value of 0.119 μM/mL against *Mycobacterium tuberculosis* [46], before previous year Yadav et al., synthesized the benzimidazole derivatives, reported the anti tubercular activity the compounds 45–53 (Figure 7) at MIC value of 12.5 μg/mL against *Mycobacterium tuberculosis* strains of H37Rv [47]. In the year of 2015 Ramprasad et al., reported the synthesis, anti tubercular activity of the imidazo[2,1-b][1,3,4]thiadiazole-benimidazole derivatives, the compounds 54–60 (Figures 7 and 8) showed best activity at MIC value of 3.125 μg/mL against *Mycobacterium tuberculosis* strains of H37Rv, Species192, Specis210 [48], same year Yoon et al., evaluated the anti tubercular activity of synthesized the new benzimidazole aminoesters, the compound 61 (Figure 8) showed best activity with IC50 value of 11.52 μM against *Mycobacterium tuberculosis* strains of H37Rv [49].

In the year of 2014 many authors reported the anti tubercular activity of synthesized the new benzimidazole derivatives, Gong et al., reported the compound 62 (Figure 8) found to be best activity at MIC value of 0.20, 0.049 μg/mL against non-replicating *Mycobacterium tuberculosis* and replicating *Mycobacterium tuberculosis* [50], Hameed et al., reported the compound the compounds 63 (Figure 8) showed significant activity at MIC value of 0.19 μg/mL against fluoroquinolone-resistant strains of *Mycobacterium tuberculosis* [51], Kalalbandi et al., reported the compounds 64–66 (Figure 8) showed good activity at MIC value of 3.12, 3.12, 1.6 μg/mL against *Mycobacterium tuberculosis* strains of H37Rv [52], Park et al., reported the compounds 67 (Figure 8) showed excellent activity at MIC value of 0.63 μg/mL against
Figure 7.
Structures of effective anti-tubercular compounds.
Mycobacterium tuberculosis strains of H37Rv [53] and Gobis et al., reported the compounds 68–71 (Figure 8) found to be better activity at MIC value of 0.75 μg/mL against Mycobacterium tuberculosis strains of H37Rv, Spec. 192, Spec. 210 [54].

In the year of 2013 also many authors evaluated the anti-tubercular activity of newly synthesized benzimidazole derivatives, Nandha et al., reported the

\[ \text{Figure 8. Structures of effective anti-tubercular compounds.} \]
compound 72 (Figure 9) showed best activity at MIC value of 12.5 μg/mL against *Mycobacterium tuberculosis* strains of H37Rv [55], Birajdara et al., reported the compound 73, 74 (Figure 9) showed good activity at MIC value of 6.25 μg/mL against *Mycobacterium tuberculosis* strains of H37Rv [56], Anand et al., reported the
compounds 75, 76 (Figure 9) found to be significant activity at MIC value of 1.56 μg/mL against Mycobacterium tuberculosis strains of H37Rv [57], Awasthi et al., reported the compound 77 (Figure 9) showed better activity at MIC value of 0.06 μg/mL against Mycobacterium tuberculosis strains of H37Rv [58], Yoon et al., reported the compound 78 (Figure 9) showed best activity at MIC value of 0.115, 6.12 μM against Mycobacterium tuberculosis H37Rv and INH-resistant Mycobacterium tuberculosis [59] and Ranjith et al., reported the compounds 79–83 (Figure 9) showed excellent activity at MIC value of 1 μg/mL against Mycobacterium tuberculosis H37Rv [60].

In 2012 Patel et al., reported the anti tubercular activity of synthesized the benzimidazolyl-1,3,4-oxadiazol-2ylthio-N-phenyl(benzothiazolyl)acetamides, among all the synthesized derivatives, the compounds 84–86 (Figure 9) showed best activity at MIC value of 12.5 μg/mL against Mycobacterium tuberculosis strains of H37Rv [61], Sangani et al., reported the synthesis and anti tubercular activity of pyrido[1,2-a]benzimidazole derivatives of beta-aryloxyquinoline, among all the derivative, the compound 87 (Figure 9) found to be best active compound at MIC value of 6.25 μg/mL against Mycobacterium tuberculosis strains of H37Rv compared with isoniazid, refampicin [62] and Gobis et al., reported the anti tubercular activity of new benzimidazoles, the compound 88 (Figure 10) showed best activity at MIC value of 3.1, 1.5, 3.1 μg/mL against Mycobacterium tuberculosis strains of H37Rv, Species 192, Species 210 [63].

In 2011 few authors reported the anti tubercular activity of synthesized benzimidaoles, Saleshier et al., reported the compounds 89–91 (Figure 10) found to be best activity at 10, 100mcg/ml concentrations against Mycobacterium tuberculosis [64], Camacho et al., reported the compound 92 (Figure 6) showed best activity with MIC values of 12.5 μg/mL, 6.25 μg/mL against multidrug-resistant MDR, MTB strains [65], Kumar et al., reported the compound 93 (Figure 6) found to be better activity at MIC99values of 1.0 μM, 1.0 μM against Mycobacterium tuberculosis strains of H37Rv, W210, NHH 20, NHH335, NHH382, TN587 [66] and Pieroni et al., reported the compound 94 (Figure 10) showed excellent activity at MIC values of 0.5 μg/mL, 1.0 μg/mL, 8.0 μg/mL against Mycobacterium tuberculosis strains of H37Rv [67].

Figure 10. Structures of effective anti-tubercular compounds.
3. Conclusions

The benimidazole plays an important role in the field of medicinal chemistry, many of the marketing drugs contain benzimidazole moiety are using to illness. In recent medicinal chemistry research the benzimidazole derivatives are in continuous development with many pharmacological activities such as anti-cancer, anti-HIV, anti-leishmanial, anti-tubercular, anti-malarial, anti-inflammatory, anti-diabetic, and so on, to meet pharmacological requirement. The present literature may helpful to researcher, medicinal chemist, pharmacologist to design, to synthesize, to develop pharmacologically active benzimidazole derivatives with low toxicity in future.

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Author contribution

Mahender Thatikayala contributed the chemistry, anti cancer, anti leishmanial and anti tubercular activity of benzimidazoles. Anil Kumar Garige, Hemalatha Gadegoni contributed the chemistry and anti HIV activity of benzimidazoles.

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Conflict of interest

The authors declare no conflict of interest.
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