We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

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 activities 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 amphoteric 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 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, mibefradil using as anti-hypertensive 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 envirodine, samatasvir, and maribavir using as antiviral agents (**Figures 2**) [13–17].

Figure 1.
Chemistry of benzimidazole [1].

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 $4.53 \mu M$ 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 $4.12 \mu M$ against the human colorectal carcinoma cell line (HCT116) [18], same year few authors reported the synthesis, 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 $5 \pm 2 \mu M$ against the melanoma (A375) cells [19], Mohamed et al., reported the compound **4** (**Figure 3**) showed best activity at IC_{50} value of $80, 35, 72 \mu g/ml$ 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 $0.022, 0.014, 0.015 \mu M$ 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 $25.72 \pm 3.95 \mu M$ against MFC cells [22] and Yadav et al., reported the anti cancer activity of synthesized the 2-(1*H*-benzo[d]imidazol-2-ylthio)acetamides, the compound **7, 8** (**Figure 3**) showed significant activity at IC_{50} value of $0.00005, 0.00012 \mu M/ml$ 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 $0.98 \pm 0.02 \mu M$ against human T-lymphoblastic leukemia (CEM) cells [24].

In 2015 few authors worked on synthesis of benzimidazole and evaluated the anti-cancer activity, the Gao et al., reported the compound **10** (**Figure 3**) showed good activity at IC_{50} value of $2.68 \mu M$ 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 $1.8 \mu M$ against

Figure 2.
 Structures of marketing drugs containing benzimidazole moiety [13–17].

Figure 3.
Structures of effective anticancer compounds.

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 IC₅₀ values of 1.81, 0.83, 1.76, 1.13, 0.95, 1.57 µM against lung (A549), breast (MCF-7), cervical (HeLa) 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 carcinoma75 [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 IC₅₀ value of 49.63, 46.33, 62.43, 42.30 µM 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 derivatives, the compound **19** (**Figure 4**) showed significant activity at IC₅₀ value range of 0.006 to 1.774 µM 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 a percentage growth of 36.23, 47.56 against Breast cancer (MDA-MB-468), Melanoma (SK-MEL-28) cells [33], Paul et al., reported the compound **21** (**Figure 4**) found to be good anticancer activity at GI₅₀ values of 0.34, 0.31 µM against colon cancer cell lines, prostate cancer cell lines [34], Madabushi et al., reported the compound **22** (**Figure 4**) showed best anticancer activity at IC₅₀ values of 5.2, 9.8, 12.3, 11.1 µM 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 IC₅₀ values of 0.098, 0.15, 0.13 µM against SGC-7901, A-549, 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 GI₅₀ 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 IC₅₀ value of 0.0390 µM 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 IC₅₀ values of 4.73, 0.96, 3.24, 1.67 µM against HeLa, WI38 cell lines [40].

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 IC₅₀ value of 0.386×10^{-5} µM 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 IC₅₀ value of 0.09 µg/mL against HIV-1 [41], Yadav et al., reported the anti HIV activity of synthesized benzimidazole derivatives, in all the synthesized

Figure 4.
Structures of effective anticancer compounds.

derivatives the compounds **31–34** (**Figure 5**) found to be best active compounds with more than 50% of RT inhibition at concentration of 20 μ 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_{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_{50} 1.15 μ g/mL against HIV-1 and HIV-2 [44].

Figure 5.
 Structures of effective anti-HIV compounds.

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

Figure 6.
Structures of effective anti-leishmanial compounds.

significant inhibition of promastigotes, amastigotes of *Leishmania tropica*, *Leishmania infantum* at IC₅₀ values of 0.19, 0.34, 0.31 μ M and compound **39** (Figure 6) inhibited promastigotes of *Leishmani infantum* at IC₅₀ value of 3.70, 4.76 μ M [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 μ M [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 μ g/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 μ M/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 μ g/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-benzimidazole derivatives, the compounds **54–60** (Figures 7 and 8) showed best activity at MIC value of 3.125 μ g/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 μ M 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 7.
Structures of effective anti-tubercular compounds.

Figure 8.
Structures of effective anti-tubercular compounds.

Figure 9.
 Structures of effective anti-tubercular compounds.

(**Figure 8**) found to be best activity at MIC value of 0.20, 0.049 $\mu\text{g/mL}$ 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 μM 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 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ against *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 $\mu\text{g/mL}$ 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 compound **72** (**Figure 9**) showed best activity at MIC value of 12.5 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ against *Mycobacterium tuberculosis* strains of H37Rv [61],

Figure 10.
Structures of effective anti-tubercular compounds.

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, rifampicin [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 benzimidazoles, 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 MIC values of 1.0 µM, 1.0 µM against *Mycobacterium tuberculosis* strains of H37Rv, W210, NHN 20, NHN335, NHN382, 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].

3. Conclusions

The benzimidazole plays an important role in the field of medicinal chemistry, many of the marketed drugs contain benzimidazole moiety are used to treat 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 requirements. The present literature may be helpful to researchers, medicinal chemists, pharmacologists to design, to synthesize, to develop pharmacologically active benzimidazole derivatives with low toxicity in the future.

Acknowledgements

All the authors are thankful to managements of respective colleges for providing facilities to carry out the work.

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.

Funding

No funding applicable.

Conflict of interest

The authors declare no conflict of interest.

Author details

Mahender Thatikayala^{1*}, Anil Kumar Garige² and Hemalatha Gadegoni³

1 Avanthi Institute of Pharmaceutical Sciences, Hyderabad, Telangana, India

2 Jayamukhi Institute of Pharmaceutical Sciences, Warangal, Telangana, India

3 Pathfinder Institute of Pharmacy Education and Research, Warangal, Telangana, India

*Address all correspondence to: mahenderpharma395@gmail.com

IntechOpen

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Singh VK, Parle A. The intriguing benzimidazole: A review. *International Journal of Pharmaceutical Sciences and Research*. 2019;**10**(4):1540-1552. DOI: 10.13040/IJPSR.0975-8232.10(4).1540-52
- [2] Chaves S, Hiremathad A, Tomas D, Keri RS, Piemontese L, Santos MA. Exploring the chelating capacity of 2-hydroxyphenyl-benzimidazole based hybrids with multi-target ability as anti-Alzheimer's agent. *New Journal of Chemistry*. 2018;**42**(20):16503-16515. DOI: 10.1039/c8nj00117k
- [3] Marinescu M. Synthesis of antimicrobial benzimidazole-pyrazole compounds and their biological activities. *Antibiotics*. 2021;**10**(1002):1-29
- [4] Tahlan S, Ramasamy K, Lim SM, Shah SAA, Mani V, Narasimhan B. 4-(2-(1*H*-Benzo[d]imidazol-2-ylthio)acetamido)-*N*-(substituted phenyl) benzamides: Design, synthesis and biological evaluation. *BMC Chemistry*. 2019;**13**(1):1-16. DOI: 10.1186/s13065-019-0533-7
- [5] Aboul-Enein HY, Rashedy AAE. Benzimidazole derivatives as antidiabetic agents. *Medicinal Chemistry*. 2015;**5**(7):318-325. DOI: 10.4172/2161-0444.1000280
- [6] Si W, Zhang T, Li Y, She D, Pan W, Gao Z, et al. Synthesis and biological activity of novel benzimidazole derivatives as potential antifungal agents. *Journal of Pesticide Science*. 2016;**41**(1):15-19. DOI: 10.1584/jpestics.D15-037
- [7] Srivastava R, Gupta SK, Naaz F, SenGupta PS, Yadav M, Singh VK, et al. Alkylated benzimidazoles: Design, synthesis, docking, DFT analysis, ADMET property, molecular dynamics and activity against HIV and YFV. *Computational Biology and Chemistry*. 2020;**89**:1-16. DOI: 10.1016/j.compbiolchem.2020.107400
- [8] Tonelli M, Gabriele E, Piazza F, Basilico N, Parapini S, Tasso B, et al. Benzimidazole derivatives endowed with potent antileishmanial activity. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2017;**33**(1): 210-226. DOI: 10.1080/14756366.2017.1410480
- [9] Gaba M, Singh S, Mohan C. Benzimidazole: An emerging scaffold for analgesic and anti-inflammatory agents. *European Journal of Medicinal Chemistry*. 2014;**76**:494-505. DOI: 10.1016/j.ejmech.2014.01.030
- [10] Farahat AA, Ismail MA, Kumar A, Wenzler T, Brun R, Paul A, et al. Indole and benzimidazole bichalcophenes: Synthesis, DNA binding and antiparasitic activity. *European Journal of Medicinal Chemistry*. 2018;**143**: 1590-1596. DOI: 10.1016/j.ejmech.2017.10.056
- [11] Marinescu M, Tudorache GD, Marton GI, Zalaru CM, Popa M, Chifiriuc MC, et al. Density functional theory molecular modeling, chemical synthesis, and antimicrobial behavior of selected benzimidazole derivatives. *Journal of Molecular Structure*. 2017;**1130**:463-471. DOI: 10.1016/j.molstruc.2016.10.066
- [12] Manivannan S. Substituted benzimidazoles: A novel class of anti-tubercular agents. *International Journal of Pharmaceutical Chemistry and Analysis*. 2019;**6**(1):10-13. DOI: 10.18231/j.ijpca.2019.003

- [13] Bansal Y, Silakari O. The therapeutic journey of benzimidazoles: A review. *European Journal of Medicinal Chemistry*. 2012;**20**(21):6208-6236. DOI: 10.1016/j.bmc.2012.09.013
- [14] Njar VC, Brodie AM. Discovery and development of galeterone (TOK-001 or VN/124-1) for the treatment of all stages of prostate cancer. *Journal of Medicinal Chemistry*. 2015;**58**(5):2077-2087. DOI: 10.1021/jm501239f
- [15] Moniruzzaman RS, Mahmud T. Quantum chemical and pharmacokinetic studies of some proton pump inhibitor drugs. *American Journal of Biomedical Sciences and Research*. 2019;**2**(1):3-8. DOI: 10.34297/AJBSR.2019.02.000562
- [16] Scholten WK, Christensen AE, Olesen AE, Drewes AM. Quantifying the adequacy of opioid analgesic consumption globally: An updated method and early findings. *American Journal of Public Health*. 2019;**109**(1): 52-57. DOI: 10.2105/AJPH.2018.304753
- [17] Tahlan S, Kumar S, Ramasamy K, Lim SM, Shah SAA, Mani V, et al. Design, synthesis and biological profile of heterocyclic benzimidazole analogues as prospective antimicrobial and antiproliferative agents. *BMC Chemistry*. 2019;**13**(50):1-15. DOI: 10.1186/s13065-019-0567-x
- [18] Tahlan S, Ramasamy K, Lim SM, Shah SAA, Mani V, Narasimhan B. Design, synthesis and therapeutic potential of 3-(2-(1*H*-benzo[d]imidazol-2-ylthio)acetamido)-*N*-(substituted phenyl)benzamide analogues. *Chemistry Central Journal*. 2018;**12**(1):1-12. DOI: 10.1186/s13065-018-0513-3
- [19] Aikman B, Wenzel M, MóscA A, de Almeida A, Klooster W, Coles S, et al. Gold(III) pyridine-benzimidazole complexes as aquaglyceroporin inhibitors and antiproliferative agents. *Inorganics*. 2018;**6**(4):1-16. DOI: 10.3390/inorganics6040123
- [20] Mohamed LW, Taher AT, Rady GS, Ali MM, Mahmoud AE. Synthesis and biological evaluation of certain new benzimidazole derivatives as cytotoxic agents new cytotoxic benzimidazoles. *Der Pharma Chemicalia*. 2018;**10**(5): 112-120
- [21] El-Gohary NS, Shaaban MI. Synthesis and biological evaluation of a new series of benzimidazole derivatives as antimicrobial, antiquorum-sensing and antitumor agents. *European Journal of Medicinal Chemistry*. 2017;**131**:1-29. DOI: 10.1016/j.ejmech.2017.03.018
- [22] Wang Z, Deng X, Xion S, Xiong R, Liu J, Zou L, et al. Design, synthesis and biological evaluation of chrysin benzimidazole derivatives as potential anticancer agents. *Natural Product Research*. 2017;**32**(24):1-10. DOI: 10.1080/14786419.2017.1389940
- [23] Yadav S, Narasimhan B, Lim SM, Ramasamy K, Vasudevan M, Shah SAA, et al. Synthesis, characterization, biological evaluation and molecular docking studies of 2-(1*H*-benzo[d]imidazol-2-ylthio)-*N*-(substituted 4-oxothiazolidin-3-yl) acetamides. *Chemistry Central Journal*. 2017;**11**(1): 1-12. DOI: 10.1186/s13065-017-0361-6
- [24] Onnis V, Demurtas M, Deplano A, Balboni G, Baldisserotto A, Manfredini S, et al. Design, synthesis and evaluation of antiproliferative activity of new benzimidazolehydrazones. *Molecules*. 2016;**21**(5):1-9. DOI: 10.3390/molecules21050579
- [25] Gao C, Li B, Zhang B, Sun Q, Li L, Li X, et al. Synthesis and biological evaluation of benzimidazole acridine derivatives as potential DNA-binding

and apoptosis-inducing agents.

Bioorganic and Medicinal Chemistry. 2015;**23**(8):1800-1807. DOI: 10.1016/j.bmc.2015.02.036

[26] Kamal A, Reddy TS, Vishnuvardhan MVPS, Nimbarte VD, Subba Rao AV, Srinivasulu V, et al. Synthesis of 2-aryl-1,2,4-oxadiazolo-benzimidazoles: Tubulin polymerization inhibitors and apoptosis inducing agents. Bioorganic and Medicinal Chemistry. 2015;**23**(15):4608-4623. DOI: 10.1016/j.bmc.2015.05.060

[27] Reddy TS, Kulhari H, Reddy VG, Bansal V, Kamal A, Shukla R. Design, synthesis and biological evaluation of 1,3-diphenyl-1*H*-pyrazole derivatives containing benzimidazole skeleton as potential anticancer and apoptosis inducing agents. European Journal of Medicinal Chemistry. 2015;**101**:790-805. DOI: 10.1016/j.ejmech.2015.07.031

[28] Rodionov AN, Zhrebker KY, Snegur LV, Korlyukov AA, Arhipov DE, Peregodov AS, et al. Synthesis, structure and enantiomeric resolution of ferrocenylalkyl mercaptoazoles. Antitumor activity in vivo. Journal of Organometallic Chemistry. 2015;**783**: 83-91. DOI: 10.1016/j.jorganchem.2015.01.031

[29] Sharma A, Luxami V, Paul K. Purine-benzimidazole hybrids: Synthesis, single crystal determination and in vitro evaluation of antitumor activities. European Journal of Medicinal Chemistry. 2015;**93**:414-422. DOI: 10.1016/j.ejmech.2015.02.036

[30] Wang YT, Qin YJ, Yang N, Zhang YL, Liu CH, Zhu HL. Synthesis, biological evaluation, and molecular docking studies of novel 1-benzene acyl-2-(1-methylindol-3-yl)-benzimidazole derivatives as potential tubulin polymerization inhibitors. European Journal of Medicinal

Chemistry. 2015;**99**:125-137. DOI: 10.1016/j.ejmech.2015.05.021

[31] Yoon YK, Ali MA, Wei AC, Choon TS, Osma H, Parang K, et al. Synthesis and evaluation of novel benzimidazole derivatives as sirtuin inhibitors with antitumor activities. Bioorganic & Medicinal Chemistry. 2014;**22**(2):703-710. DOI: 10.1016/j.bmc.2013.12.029

[32] Wang W, Kong D, Cheng H, Tan L, Zhang Z, Zhuang X, et al. New benzimidazole-2-urea derivatives as tubulin inhibitors. Bioorganic & Medicinal Chemistry Letters. 2014;**24**(17):4250-4253. DOI: 10.1016/j.bmcl.2014.07.035

[33] Salahuddin, Shaharyar M, Mazumder A, Ahsan MJ. Synthesis, characterization and anticancer evaluation of 2-(naphthalen-1-ylmethyl/naphthalen-2-yloxymethyl)-1-[5-(substituted phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1*H*-benzimidazole. Arabian Journal of Chemistry. 2014;**7**(4):418-424. DOI: 10.1016/j.arabjc.2013.02.001

[34] Paul K, Sharma A, Luxami V. Synthesis and in vitro antitumor evaluation of primary amine substituted quinazoline linked benzimidazole. Bioorganic and Medicinal Chemistry Letters. 2014;**24**(2):624-629. DOI: 10.1016/j.bmcl.2013.12.005

[35] Madabhushi S, Mallu KKR, Vangipuram VS, Kurva S, Poornachandra Y, Ganesh KC. Synthesis of novel benzimidazole functionalized chiral thioureas and evaluation of their antibacterial and anticancer activities. Bioorganic and Medicinal Chemistry Letters. 2014;**24**(20):4822-4825. DOI: 10.1016/j.bmcl.2014.08.064

[36] Guan Q, Han C, Zuo D, Zhai M, Li Z, Zhang Q, et al. Synthesis and

evaluation of benzimidazole carbamates bearing indole moieties for antiproliferative and antitubulin activities. *European Journal of Medicinal Chemistry*. 2014;**87**:306-315. DOI: 10.1016/j.ejmech.2014.09.071

[37] Sharma A, Luxami V, Paul K. Synthesis, single crystal and antitumor activities of benzi midazole quinazoline hybrids. *Bioorganic and Medicinal Chemistry Letters*. 2013;**23**(11): 3288-3294. DOI: 10.1016/j.bmcl.2013.03.107

[38] Husain A, Rashid M, Shaharyar M, Siddiqui AA, Mishra R. Benzimidazole clubbed with triazolo-thiadiazoles and triazolo-thiadiazines: New anticancer agents. *European Journal of Medicinal Chemistry*. 2013;**62**:785-798. DOI: 10.1016/j.ejmech.2012.07.011

[39] El-Nassan HB. Synthesis, antitumor activity and SAR study of novel [1,2,4] triazino[4,5-a]benzimidazole derivatives. *European Journal of Medicinal Chemistry*. 2012;**53**:22-27. DOI: 10.1016/j.ejmech.2012.03.028

[40] Hranjec M, Starcevic K, Pavelic SK, Lucin P, Pavelic K, Karminski ZG. Synthesis, spectroscopic characterization and antiproliferative evaluation in vitro of novel Schiff bases related to benzimidazoles. *European Journal of Medicinal Chemistry*. 2011;**46**(6): 2274-2279. DOI: 10.1016/j.ejmech.2011.03.00

[41] Iannazzo D, Pistone A, Ferro S, DeLuca L, Monforte AM, Romeo R, et al. Graphene quantum dots based systems as HIV inhibitors. *Bioconjugate Chemistry*. 2018;**29**(9):1-38. DOI: 10.1021/acs.bioconjchem.8b00448

[42] Yadav G, Ganguly S, Murugesan S, Dev A. Synthesis, anti-HIV, antimicrobial evaluation and

structure activity relationship studies of some novel benzimidazole derivatives. *Anti Infective Agents*. 2015; **13**(1):65-77

[43] Pan T, He X, Chen B, Chen H, Geng G, Luo H, et al. Development of benzimidazole derivatives to inhibit HIV-1 replication through protecting APOBEC3G protein. *European Journal of Medicinal Chemistry*. 2015;**95**:500-513. DOI: 10.1016/j.ejmech.2015.03.050

[44] Al-Masoudi NA, Jafar NNA, Abbas LJ, Baqir SJ, Pannecouque C. Synthesis and anti-HIV activity of new benzimidazole, benzothiazole and carbohyrazide derivatives of the anti-inflammatory drug indomethacin. *Zeitschrift für Naturforschung*. 2011;**66**: 953-960

[45] Oh S, Kim S, Kong S, Yang G, Lee N, Han D, et al. Synthesis and biological evaluation of 2,3-dihydroimidazo[1,2-a] benzimidazole derivatives against *Leishmania donovani* and *Trypanosoma cruzi*. *European Journal of Medicinal Chemistry*. 2014;**84**:395-403. DOI: 10.1016/j.ejmech.2014.07.038

[46] Mohanty SK, Khuntia A, Yellsubbaiah N, Ayyanna C, Naga Sudha B, Harika MS. Design, synthesis of novel azo derivatives of benzimidazole as potent antibacterial and anti tubercular agents. *Beni-Suef University Journal of Basic and Applied Sciences*. 2018;**7**(4):1-6. DOI: 10.1016/j.bjbas.2018.07.009

[47] Yadav S, Narasimhan B, Lim SM, Ramasamy K, Vasudevan M, SAA S, et al. Synthesis and evaluation of antimicrobial, antitubercular and anticancer activities of benzimidazole derivatives. *Egyptian Journal of Basic and Applied Sciences*. 2018;**5**(1): 100-109. DOI: 10.1016/j.ejbas.2017.11.001

- [48] Ramprasad J, Nayak N, Dalimba U, Yogeeswari P, Sriram D, Peethambar SK, et al. Synthesis and biological evaluation of new imidazo [2,1-b][1,3,4] thiadiazole-benzimidazole derivatives. *European Journal of Medicinal Chemistry*. 2015;**95**:49-63. DOI: 10.1016/j.ejmech.2013.06.025
- [49] Ramprasad J, Nayak N, Dalimba U, Yogeeswari P, Sriram D, Peethambar SK, et al. Synthesis and biological evaluation of new imidazo[2,1-b][1,3,4]thiadiazole-benzimidazole derivatives. *European Journal of Medicinal Chemistry*. 2015;**95**: 49-63. DOI: 10.1016/j.ejmech.2015.03.024
- [50] Gong Y, Karakaya SS, Guo X, Zheng P, Gold B, Ma Y, et al. Benzimidazole-based compounds kill *Mycobacterium tuberculosis*. *European Journal of Medicinal Chemistry*. 2014;**75**: 336-353. DOI: 10.1016/j.ejmech.2014.01.039
- [51] Hameed PS, Raichurkar A, Madhavapeddi P, Menasinakai S, Sharma S, Kaur P, et al. Benzimidazoles: Novel mycobacterial gyrase inhibitors from scaffold morphing. *ACS Medicinal Chemistry Letters*. 2014;**5**(7):820-825. DOI: 10.1021/ml5001728
- [52] Kalalbandi VKA, Seetharamappa J, Katrahalli U, Bhat KG. Synthesis, crystal studies, anti-tuberculosis and cytotoxic studies of 1-[(2E)-3-phenylprop-2-enoyl]-1*H*-benzimidazole derivatives. *European Journal of Medicinal Chemistry*. 2014;**79**:194-202. DOI: 10.1016/j.ejmech.2014.04.017
- [53] Park B, Awasthi D, Chowdhury SR, Melief EH, Kumar K, Knudson SE, et al. Design, synthesis and evaluation of novel 2,5,6-trisubstituted benzimidazoles targeting FtsZ as antitubercular agents. *Bioorganic and Medicinal Chemistry*. 2014;**22**(9): 2602-2612. DOI: 10.1016/j.bmc.2014.03.035
- [54] Gobis K, Foks H, Serocki M, Augustynowicz-Kopeć E, Napiórkowska A. Synthesis and evaluation of in vitro antimycobacterial activity of novel 1*H*-benzo[d]imidazole derivatives and analogues. *European Journal of Medicinal Chemistry*. 2015;**89**:13-20. DOI: 10.1016/j.ejmech.2014.10.031
- [55] Nandha B, Nargund LVG, Nargund SL, Nandha B. Design and synthesis of some new imidazole and 1,2,4-triazole substituted fluorobenzimidazoles for antitubercular and antifungal activity. *Der Pharma Chemica*. 2013; **5**(6):317-327
- [56] Birajdara SS, Girish D, Ashish PK, Kamble VM. Synthesis and biological evaluation of amino alcohol derivatives of 2-methylbenzimidazole as antitubercular and antibacterial agents. *Journal of Chemical and Pharmaceutical Research*. 2013;**5**(11):583-589
- [57] Anand N, Ramakrishna KKG, Gupta MP, Chaturvedi V, Singh S, Srivastava KK, et al. Identification of 1-[4-(benzyloxyphenyl)-but-3-enyl]-1*H*-azoles as new class of anti tubercular and antimicrobial agents. *ACS Medicinal Chemistry Letters*. 2013;**4**(10):958-963. DOI: 10.1021/ml4002248
- [58] Awasthi D, Kumar K, Knudson SE, Slayden RA, Ojima I. SAR studies on trisubstituted benzimidazoles as inhibitors of Mtb FtsZ for the development of novel antitubercular agents. *Journal of Medicinal Chemistry*. 2013;**56**(23):9756-9770. DOI: 10.1021/jm401468w
- [59] Keng Yoon Y, Ashraf Ali M, Choon TS, Ismail R, Chee WA, Suresh

Kumar R, et al. Antituberculosis: Synthesis and antimycobacterial activity of novel benzimidazole derivatives. *BioMed Research International*. 2013; **2013**:1-6. DOI: 10.1155/2013/926309

[60] Ranjith PK, Rajeesh P, Haridas KR, Susanta NK, Guru Row TN, Rishikesan R, et al. Design and synthesis of positional isomers of 5 and 6-bromo-1-[(phenyl)sulfonyl]-2-[(4-nitrophenoxy)methyl]-1*H*-benzimidazoles as possible antimicrobial and antitubercular agents. *Bioorganic and Medicinal Chemistry Letters*. 2013;**23**(18):5228-5234. DOI: 10.1016/j.bmcl.2013.06.072

[61] Patel RV, Patel PK, Kumari P, Rajani DP, Chikhalia KH. Synthesis of benzimidazolyl-1,3,4-oxadiazol-2-ylthio-*N*-phenyl (benzothiazolyl) acetamides as antibacterial, antifungal and antituberculosis agents. *European Journal of Medicinal Chemistry*. 2012;**53**: 41-51. DOI: 10.1016/j.ejmech. 2012.03.033

[62] Sangani CB, Jardosh HH, Patel MP, Patel RG. Microwave-assisted synthesis of pyrido [1,2-*a*]benzimidazole derivatives of β -aryloxyquinoline and their antimicrobial and anti tuberculosis activities. *Medicinal Chemistry Research*. 2012;**22**(6):3035-3047. DOI: 10.1007/s00044-012-0322-5

[63] Gobis K, Foks H, Bojanowski K, Augustynowicz-Kopec E, Napiórkowska A. Synthesis of novel 3-cyclohexylpropanoic acid-derived nitrogen heterocyclic compounds and their evaluation for tuberculostatic activity. *Bioorganic & Medicinal Chemistry*. 2012;**20**(1):137-144. DOI: 10.1016/j.bmc.2011.11.020

[64] Saleshier FM, Suresh S, Anitha N, Karim J, Divakar MC. Design, docking and synthesis of some 6-benzimidazolyl pyrans and screening of their anti

tubercular activity. *European Journal of Experimental Biology*. 2011;**1**(2):150-159

[65] Camacho J, Barazarte A, Gamboa N, Rodrigues J, Rojas R, Vaisberg A, et al. Synthesis and biological evaluation of benzimidazole-5-carbohydrazide derivatives as antimalarial, cytotoxic and antitubercular agents. *Bioorganic and Medicinal Chemistry*. 2011;**19**(6): 2023-2029. DOI: 10.1016/j.bmc. 2011.01.050

[66] Kumar K, Awasthi D, Lee SY, Zanardi I, Ruzsicska B, Knudson S, et al. Novel trisubstituted benzimidazoles, targeting *mtbfts*, as a new class of antitubercular agents. *Journal of Medicinal Chemistry*. 2011;**54**(1): 374-381. DOI: 10.1021/jm1012006

[67] Pieroni M, Tipparaju SK, Lun S, Song Y, Sturm AW, Bishai WR, et al. Pyrido[1,2-*a*]benzimidazole-based agents active against tuberculosis (TB), multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB. *ChemMedChem*. 2011;**6**(2):334-342. DOI: 10.1002/cmdc.201000490