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A Review On Benzimidazole Derivatives

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Abstract

Benzimidazole is aheterocyclic aromatic organic compound. Benzimidazole is also known as 1H-benzimidazole. It is a bicyclic compound. It is formed by fusing the benzene ring with an imidazole ring that contains two nitrogen atoms.They are widely distributed, both natural and synthetic molecules. Benzimidazoles, known for their significant medical benefits against various diseases, have gained significant interest due to recent advancements in synthetic methods. Recent advancements in synthetic methodologies and drug design have facilitated the development of novel benzimidazole derivatives with improved potency and reduced side effects. Benzimidazole and its derivatives play amajor role in treating various diseases, like anti-cancer, anti-inflammatory, anti-oxidant, anti-coagulant, anti-microbial, anti-viral, anti-bacterial, antidiabetic, neuroprotective, analgesic, anti-protozoal, hypertensive, anti-ulcer, anti-convulsant, anti-HIV, analgesic, anti-parasitic, proton pump inhibitors,etc.Benzimidazole and its derivatives are prepared in different ways,including condensation of o-phenylenediamine with carbonyl compounds or carboxylic acids and their derivatives. The benzimidazole can beprepared by rearranging other heterocyclic compounds,including quinoxaline derivatives, triazole derivatives, etc. In recent years, benzimidazoles have been prepared by using green methods like microwaves, ultrasound, ecofriendly catalysts, and photochemical reactions. This review focuses on the benzimidazole and their derivatives,the methods used to preparethem, as well as their biological applications in our daily lives.

Key words:benzimidazole derivatives, greenmethod,activity, and o-phenylenediamine

Figure 1. Diverse biological activities of benzimidazole derivatives

Introduction:

Benzimidazole is a heterocyclic compound formed from a benzene ring with an imidazole ring that contains nitrogen, oxygen,and sulfur.[1][2]Its derivatives are of wide interest because of their inhibitory activity and their suitable selective ratio.[3]Benzimidazole is also known as 1H-benzimidazole or 1,3-benothiazole.[4]Benzimidazoles are formed by the condensation reaction of 1,2-phenylenediamine with carboxaldehyde and carboxylic.[5][6]Benzimidazole is a class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbial(omeprazole and metronidazole), anti-viral(ribavirin and acyclovir), anti-diabetic(metformin and thiazolidinediones), anti-cancer(vincristine and vinblastine), anti-oxidants (2-aryl-1H-benzimidazole), anti-parasitic, anthelmintics(Albendazole and mebendazole), anti-proliferative, anti-HIV, anti-convulsant (Clobazam and clemizole),anti-inflammatory (ranitidine), anti-hypertensive(captopril and benazepril),anti-ulcer(esomeprazole), anti-neoplastic, and proton pump inhibitors(lansoprazole and pantoprazole). Benzimidazoles exhibit significant activity as potential antitumor agents.[6][7][8]

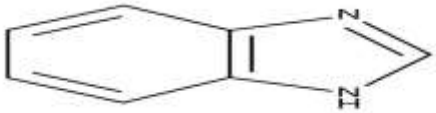


Figure 2.Benzimidazole

Anti-cancer activity:

Hanan M. REFAAT etal.The benzimidazole ring system isa crucial pharmacophore in medicinal chemistry and modern drug discovery. 2-substitued benzimidazoles have potential anti-cancer activity. methyl-2-benzimidazole carbamate is a potent anticancer agent that promotes apoptosis of cancer cells.[9]

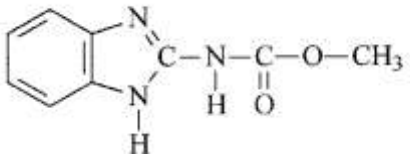


Fig 3. Methyl-2- benzimidazole carbamate

W. M.ELDEHNAet al. The new series of oxindole-thiazolo[3,2-a] benzimidazole scaffolds uses non-rigid. Hydrazine spacers 6 and 7 as potential anticancer CDK2 inhibitors have been reported. The newly synthesized ISATIN-TBI was tested forantiproliferation properties against two cancer cell lines, MDA-MD-231 and MCF-7.[10]

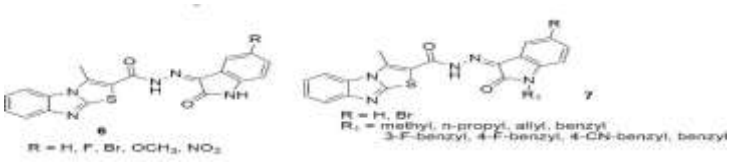
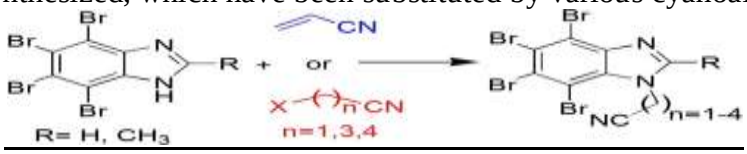


Figure 4. Potent anti-cancer benzimidazole derivatives

EDYTA LUKOWSKAN et al. The benzimidazole derivatives are used to treat cancer. They inhibit the protein kinase CK2 with anticancer and proapoptotic activity. A series of polybrominated benzimidazole derivatives have been synthesized, which have been substituted by various cyanoalkyl groups.[11]



Anti-bacterial activity:S.B. KORRAPATI et al. Spirobenzimidazole-quinolines derivatives have significant DNA gyrase inhibitors that have been synthesized and evaluated for their bacterial inhibitory activity. The synthesized hybrids selectively slow down the gram-positive pathogens. The synthesized compounds 27a,27b, and27c show good antibacterial activity. [12]

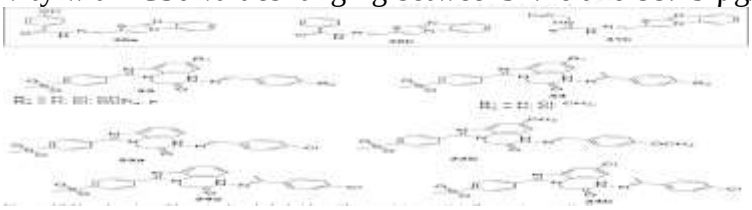
Figure 5.Potentanti-bacterial benzimidazole derivatives

JOAO. B. MOREIRA ET AL.the benzimidazole derivatives have potential antibacterial activity. The symmetric bis-benzimidazole conjugates show activity against a range of Gram-positive and Gram-negative bacteria. Para-substituted ethoxy, amino, and methoxy derivatives show potent bacteriostatic activity.[13]

VALENTINA REP et al.A series of tetrahydropyramidinyl-substituted benzimidazoles were synthesized to study their antibacterial activities against gram-positive and gram-negative bacteria. The type of substituted at the C-3 and C-4 positions improved anti-bacterial potency, with benzoyl substitute benzimidazole derivatives 15a being the most active.[14]

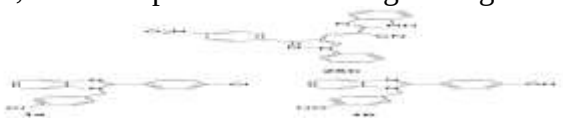
Anti-Inflammatory activity:

V.KAMAT, ET AL.A novel series of benzimidazole derivatives plays a significant role to treating inflammation. Kamat's novel series of benzimidazoleswerefor their in vitro anti-inflammatory effect using protein denaturation protocol. Diclofenac sodium as the reference compound.The percentage inhibition was observed using varying 20-100µg/ml concentrations from the results, compounds **30a,30b, and 31c** displayed good activity with IC50 values ranging between31.16 and 88.49 µg/ml. [15]

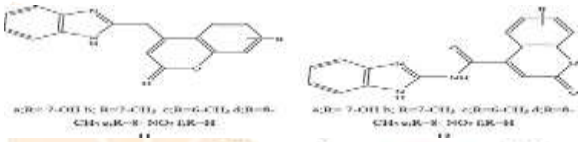


MOHAMED A.SA BADAWY ET AL., non-steroidal anti-inflammatory drugs are used to treat a wide range of inflammatory diseases, such as pain, fever, and arthritis. NSAIDS are capable of reducing the production of key pro-inflammatory mediator's prostaglandins by the inhibition of constitutive [COX-1] and [COX-2] isoenzymes. The non-selective NSAIDS effectively inhibit both cox-1 and cox-2. Indomethacin, as a potent non-selective NSAIDS, has medical applications in the treatment of inflammation diseases including osteoarthritis, rheumatoid, etc. Clinical trials have shown that selective cox-2 inhibitors such as celecoxib have a significantly better safety profile. According to SAR studies,selective cox-2 inhibitors are diaryl heterocyclic compounds bearing SO_2NH_2 or SO_2NH_3 groups.[16]

S.C.RAKA et al., and R. SIVARAMAKARTHIKEYAN et al., The protein denaturation method was used to assess the anti-inflammatory activity of benzimidazole-tethered pyrazoles. The synthesized compound 26b with a nitro substituent shows good activity. The activity of synthesized derivatives was evaluated for acute inflammation using carrageenan- induced rat hind paw oedema.Results showed that compounds 1a and 1b at 100 mg/kg demonstrated significant anti-inflammatory activity against carrageenan induced paw oedema, with compounds 1a showing the highest inhibition.[17][18]

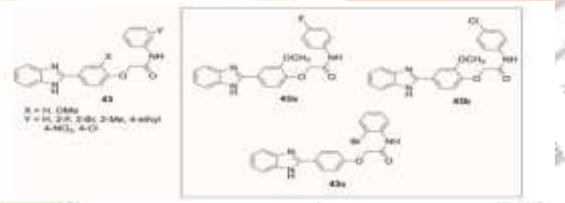


PURVA SETHI et al. synthesized new benzimidazole derivatives from coumarin and benzimidazole nuclei, showing maximum anti-inflammatory activity. The synthesized compounds show maximum activity.[19]



Anti-diabetic activity:

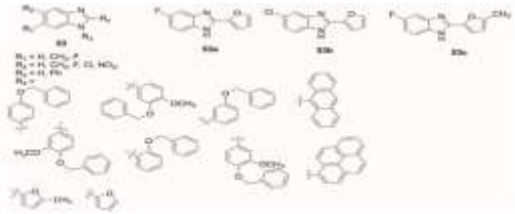
SHAYEGAN ET AL. reported the benzimidazole derivatives have antidiabetic activity. Benzimidazole-bearing Phenoxyacetamide products were screened for their antidiabetic activities. The in vitro α-amylase inhibition was tested. The targeted compounds demonstrated IC50 values ranging from 99.6 ± 3.1 to >750µM in comparison to the control. Compound **43a** bearing the Fluoro substituent at the para position shows significant inhibitory activity, while compound **43b** bearing chloro and methoxy also displayed good activity. The results of the α-amylase inhibitory activities indicated that compounds**43c** and **43a** demonstrated excellent inhibition.[20]



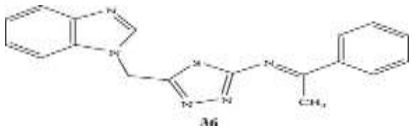
SINGH ET AL. designed and synthesized a new library of N-methyl/benzimidazolyl para substituted benzyl-conjugated compounds. The α-glucosidase inhibition of the novel synthesized molecules was screened. All tested compounds showed potent α-glucosidase inhibitory activity with IC50 values ranging between 4.10±0.01 and 31.5 ±1.01 µm.[21]

Benzimidazole derivatives with promising anti-diabetic activity

AKANDE ET AL., designed and synthesized different series of substituted benzimidazoles 53. The α-amylase inhibitory activity of the targeted compounds was screened using acarbose as a control. Compounds **53a, 53b and 53c** good exhibited inhibitory activity with IC50 values of 1.91 ± 0.02, 1.89 ± 0.25 and 1.86 ± 0.08 µm. against the α-amylase enzymes.[22]



SANDHYA MJ NAIR et al. synthesized novel N-[(2-amino-5-methylene)-1,3,4-thiadiazole]-2-methyl benzimidazole analogues selected for in vitro antidiabetic activity, showing 49.25% inhibition compared to acarbose's 68.61% inhibition.[23]

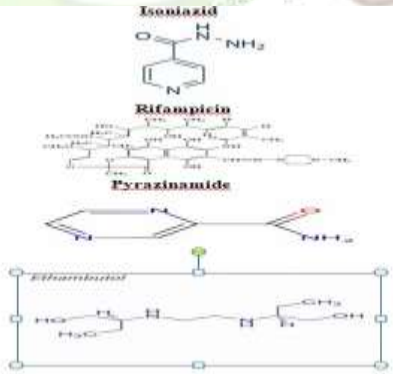


Anti-urease and anti- mycobacterial activity:

EMRE MENTASE ET AL., the non-redox metalloenzyme urease is a nickel-containing enzyme located in the body structure of many organisms like plants, algae, fungi, and various microorganisms. Urease enzymes cause diseases such as duodenal ulcer, chronic gastritis, andpyelonephritis. control the urease activity by using urease inhibitors. A novel series of 5,6-dichloro-2-methyl-1H-benzimidazole derivatives used as potent anti-urease activity. The benzimidazole derivatives such as omeprazole, thiabendazole,albendazole,mebendazole.[24]

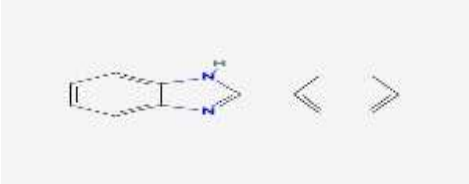
Emrementaseet al., A new series of benzimidazole compounds, including hydrazine carbothioamide,1,2,4-triazole,1,3,4-oxadiazole and imine function, were synthesized starting from 5,6-dichloro-2-cyclopropyl-1H benzimidazole All benzimidazole derivatives exhibited good urease inhibitor activity.[25]

YEONG KENG YOON ET AL., The novel series of benzimidazole derivatives shows their activity against M. tuberculosis $H_{37}RV$ and 1NH resistant. The introduction of first line drugs like streptomycin, Para-amino salicylic acid, and isoniazid for treatment with a four-first-line drug regimen comprising mainly isoniazid, rifampicin, pyrazinamide, and ethambutol for a period of at least 6 months currently treated with a four first line drug to cure the active TB.[26]



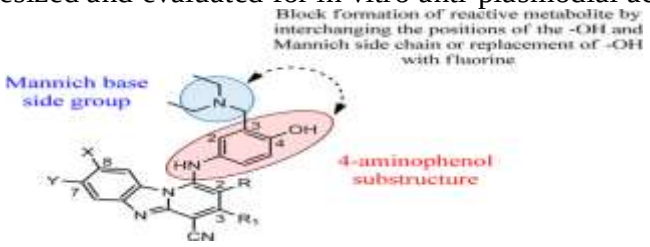
Anti-plasmodial activity:

NEREA ESCALA ET AL., malaria cases and deathskeep being excessively highevery year**.** The benzimidazole skeleton plays a major role to treating malaria. The benzimidazole derivatives have potential antimalarial activity. 2-phenyl-1H-benzimidazole derivatives exhibited good activity in vitro against plasmodium falciparum,with IC50 values of the most potent compounds ranging from 18nM to 1.30µm.[27]



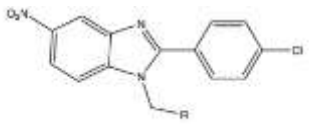
2-phenyl-1H-benzimidazole

OKOMBO ET AL.,A novel series of pyrido[1,2-a] benzimidazoles bearing Mannich base side chains and their metabolites were synthesized and evaluated for in vitro anti-plasmodial activity.[28]

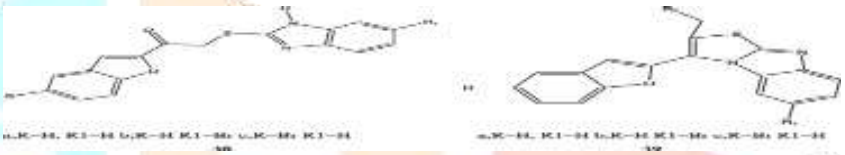


Anthelmintic activity:

FARUK ALAM et al. synthesized 1 and 2-substituted-5-nitrobenzimidazole derivatives. shows anthelmintic activity against adult Indian earth worms, all compounds showed potential anthelmintic activity, with the compound 2-(4- chlorophenyl)-5-nitro-1-(piperidin-1-ylmethyl)-1H-benzimidazoles.[29]



R.KENCHAPPA et al. synthesized the thiazolo[3,2-a] benzimidazole derivatives containing benzofuran nucleus and conducted their anthelmintic activity against earthworms. The tested compounds show anthelmintic activity.[30]



CONCLUSION:

The benzimidazoles are the most important classes of synthetic organic compounds. Benzimidazole derivatives have emerged as a promising class of compounds with diverse pharmacological activities, including anti-cancer activity, anti-bacterial activity, anti-inflammatory activity, anti-diabetic activity, anti-urease activity and anti-mycobacterial activity, anti-malarial activity.

REFERENCES:

1. Ebenzer, Oluwakemi, Funsho Oyetunde-Joshua, Oluwadamilare D. Omotoso, and Micheal Shapi. ‘‘benzimidazole and its derivatives’’: Recent advances (2020-2022). Results in chemistry 5(2023):100925.
2. Singh, Namrata, Annamalai, Pandurangan,Kavita rana, Preeti Anand. Arsad Ahamad, and Amit kumar Tiwari. Benzimidazole: short review of their antimicrobial Activite. Int. current pharm.j.1.no.5(2012):119-127.
3. Vitaku, Edon, David T.smith, and Jon T. Njardarson. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceutical: Miniperspective. Journal of medical chemistry 57, no 24(2014):10257-10274.
4. Wright, J.B. The chemistry of the benzimidazoles chemical reviews,48,no.3(1951):397-541
5. Atyam, VSSS Gupta, Ch Sarva Raidu, D. T. Nannapaneni, and M. I. Reddy. “Synthesis, characterization, and biological Evaluation of benzimidazole derivatives as potential anxiolytics. “Journal of young Pharmacists 2, no. 3(2010): 273-279.
6. Debsharma,Kingshuk, Sunanda Dey, Soumya Jyoti Ghosh, Suvendu Maity, and Chittaranjan Sinha. "Synthesis of benzimidazole derivatives via reaction between aromatic amines and aldehydes: Structure determination and theoretical insights." Journal of the Indian Chemical Society 100, no. 2 (2023): 100878.
7. Mohammed, Leqaa A., Mohammed Alwan Farhan, Safaa A. Dadoosh, Mustafa A. Alheety, Abdulwahhab H. Majeed, Ali Saadon Mahmood, and Zaid H. Mahmoud. "A Review on Benzimidazole Heterocyclic Compounds: Synthesis and Their Medicinal Activity Applications." SynOpen 7, no. 04 (2023): 652-673.
8. Pathare, Balasaheb, andTanaji Bansode."biological active benzimidazole derivatives." Results in Chemistry 3 (2021): 100200.

9. Refaat, Hanan M. "Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives." European journal of medicinal chemistry 45, no. 7 (2010): 2949-2956.

10. Eldehna, Wagdy M., Mahmoud A. El Hassab, Mahmoud F. Abo-Ashour, Tarfah Al-Warhi, Mahmoud M. Elaasser, Nesreen A. Safwat, Howayda Suliman et al. "Development of isatin-thiazolo [3, 2-a] benzimidazole hybrids as novel CDK2 inhibitors with potent in vitro apoptotic anti-proliferative activity: Synthesis, biological and molecular dynamics investigations." Bioorganic Chemistry 110 (2021): 104748.

11. Łukowska-Chojnacka, Edyta, Patrycja Wińska, Monika Wielechowska, Martyna Poprzeczko, and Maria Bretner. "Synthesis of novel polybrominated benzimidazole derivatives—potential CK2 inhibitors with anticancer and proapoptotic activity." Bioorganic & Medicinal Chemistry 24, no. 4 (2016): 735-741.

12. Korrapati, Suresh Babu, Poornachandra Yedla, Girinath G. Pillai, Faruq Mohammad, Venkata Ramana Reddy Ch, Pranav Bhamidipati, Ramars Amanchy, Riyaz Syed, and Ahmed Kamal. "In-silico driven design and development of spirobenzimidazo-quinazolines as potential DNA gyrase inhibitors." Biomedicine & Pharmacotherapy 134 (2021): 111132.

13. Moreira, Joao B., John Mann, Stephen Neidle, Timothy D. McHugh, and Peter W. Taylor. "Antibacterial activity of head-to-head bis-benzimidazoles." International journal of antimicrobial agents 42, no. 4 (2013): 361-366

14. Rep, Valentina, Rebeka Štulić, Sanja Koštrun, Bojan Kuridža, Ivo Crnolatac, Marijana Radić Stojković, Hana Čipčić Paljetak, Mihaela Perić, Mario Matijašić, and Silvana Raić-Malić. "Novel tetrahydropyrimidinyl-substituted benzimidazoles and benzothiazoles: synthesis, antibacterial activity, DNA interactions and ADME profiling." RSC Medicinal Chemistry 13, no. 12 (2022): 1504-1525.

15. Kamat, Vinuta, Basappa C. Yallur, Boja Poojary, Veerabhadragouda B. Patil, Suresh P. Nayak, Panchangam Murali Krishna, and Shrinivas D. Joshi. "Synthesis, molecular docking, antibacterial, and anti-inflammatory activities of benzimidazole-containing tricyclic systems." Journal of the Chinese Chemical Society 68, no. 6 (2021): 1055-1066.

16. Badawy, Mohamed AS, Eman KA Abdelall, EL-Nahass EL-Shaymaa, Khaled RA Abdellatif, and Hamdy M. Abdel-Rahman. "Design, synthesis, biological assessment and in silico ADME prediction of new 2-(4-(methylsulfonyl) phenyl) benzimidazoles as selective cyclooxygenase-2 inhibitors." RSC advances 11, no. 44 (2021): 27659-27673.

17. Raka, Sabreena Chowdhury, Arifur Rahman, Fahad Hussain, and SM Abdur Rahman. "Synthesis, characterization and in vitro, in vivo, in silico biological evaluations of substituted benzimidazole derivatives." Saudi Journal of Biological Sciences 29, no. 1 (2022): 239-250.

18. Sivaramakarthikeyan, Ramar, Shunmugam Iniyaval, Vadivel Saravanan, Wei-Meng Lim, Chun-Wai Mai, and Chennan Ramalingan. "Molecular hybrids integrated with benzimidazole and pyrazole structural motifs: Design, synthesis, biological evaluation, and molecular docking studies." ACS omega 5, no. 17 (2020): 10089-10098.

19. Sethi, Purva, Yogita Bansal, and Gulshan Bansal. "Synthesis and PASS-assisted evaluation of coumarin–benzimidazole derivatives as potential anti-inflammatory and anthelmintic agents." Medicinal chemistry research 27 (2018): 61-71.

20. Nair, S. M., J. Beevi, M. Nj, B. D. Emmanuel, S. S. Dharan, and R. Cr. "Insilico Design, Synthesis and In Vitro Antidiabetic and Anti-inflammatory Activities of 1, 3, 4-Thiadiazole Substituted 2-Methyl Benzimidazole Derivatives." J. Pharm. Res. Clin. Pract 6 (2016): 27-

21. Singh, Vigyasa, Rahul Singh Hada, Ravi Jain, Manu Vashistha, Geeta Kumari, Snigdha Singh, Neha Sharma et al. "Designing and development of phthalimides as potent anti-tubulin hybrid molecules against malaria." European Journal of Medicinal Chemistry 239 (2022): 114534.

22. Akande, Akinsola Adegboye, Uzma Salar, Khalid Mohammed Khan, Shazia Syed, Sherifat Adeyinka Aboaba, Sridevi Chigurupati, Abdul Wadood et al. "Substituted benzimidazole analogues as potential α-amylase inhibitors and radical scavengers." ACS omega 6, no. 35 (2021): 22726-22739.

23. Nair, S. M., J. Beevi, M. Nj, B. D. Emmanuel, S. S. Dharan, and R. Cr. "Insilico Design, Synthesis and In Vitro Antidiabetic and Anti-inflammatory Activities of 1, 3, 4-Thiadiazole Substituted 2-Methyl Benzimidazole Derivatives." J. Pharm. Res. Clin. Pract 6 (2016): 27-36

24. Menteşe, E., Emirik, M. and Sökmen, B.B., 2019. Design, molecular docking and synthesis of novel 5, 6-dichloro-2-methyl-1H-benzimidazole derivatives as potential urease enzyme inhibitors. Bioorganic Chemistry, 86, pp.151-158.

25. Menteşe, Emre, Hakan Bektaş, Bahar Bilgin Sokmen, Mustafa Emirik, Demet Çakır, and Bahittin Kahveci. "Synthesis and molecular docking study of some 5, 6-dichloro-2-cyclopropyl-1H-

benzimidazole derivatives bearing triazole, oxadiazole, and imine functionalities as potent inhibitors of urease." Bioorganic & medicinal chemistry letters 27, no. 13 (2017): 3014-3018.

26. Keng Yoon, Yeong, Mohamed Ashraf Ali, Tan Soo Choon, Rusli Ismail, Ang Chee Wei, Raju Suresh Kumar, Hasnah Osman, and Farzana Beevi. "Antituberculosis: synthesis and antimycobacterial activity of novel benzimidazole derivatives." BioMed research international 2013, no. 1 (2013): 926309.

27. Escala, Nerea, Laura M. Pineda, Michelle G. Ng, Lorena M. Coronado, Carmenza Spadafora, and Esther Del Olmo. "Antiplasmodial activity, structure–activity relationship and studies on the action of novel benzimidazole derivatives." Scientific Reports 13, no. 1 (2023): 285.

28. Okombo, John, Christel Brunschwig, Kawaljit Singh, Godwin Akpeko Dziwornu, Linley Barnard, Mathew Njoroge, Sergio Wittlin, and Kelly Chibale. "Antimalarial pyrido [1, 2-a] benzimidazole derivatives with Mannich base side chains: synthesis, pharmacological evaluation, and reactive metabolite trapping studies." ACS infectious diseases 5, no. 3 (2019): 372-384.

29. Faruk, A., K. D. Biplab, and K. Sharma. "Synthesis, antimicrobial and anthelmintic activity of some novel benzimidazole derivatives." International Journal of Drug Research and Technology 4 (2014): 31-38.

30. Kenchappa, R., Yadav D. Bodke, Sandeep Telkar, and M. Aruna Sindhe. "Antifungal and anthelmintic activity of novel benzofuran derivatives containing thiazolo benzimidazole nucleus: an in vitro evaluation." Journal of Chemical Biology 10 (2017): 11-23.