Chapter 1

Recent Developments in Benzimidazole Derivatives (2023)

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Abstract

Because of their peculiar properties, heterocyclic compounds have become important in the design of pharmaceuticals. It's superior quality. Specifically, because nitrogen-based heterocyclic group atoms are beneficial in multiple ways, these compounds are the pharmaceutical industry is finding new treatments for diseases. Numerous studies have been conducted on creating and utilizing novel bioactive compounds. Even though many types of active compounds have been identified, it is still important to know that benzimidazole stents are still popular. Conversely, research on hybridization has a significant role in the literature and contributes to the diversification of pharmaceutical activity. After the investigation, studying the structure-activity relationships (SAR) of recently created molecules is useful for further research. Based on the information listed above, this chapter discusses the recent accomplishments in synthesizing benzimidazoles and their pharmacological properties. Synthesis methods, structural studies, and significant findings in the pharmaceutical field of research and the analysis of new compounds synthesized by humans show how these methods are different from one another. As a result, it's significant in the literature as a source for researchers who want to acquire the latest information on this topic quickly.

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1. INTRODUCTION

Nitrogen-containing heterocycles have been described for their medical importance. An important class of heterocyclic benzimidazoles or benzoclolines consists of fused benzene and imidazole. Benzimidazoles, also known as cyclic analogs of amidines; exist in two equivalent tautomeric forms in which the hydrogen atom can be placed on either of the two nitrogen atoms **(Figure 1)** [1-4].

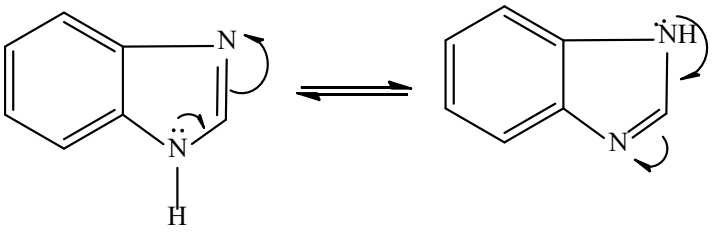
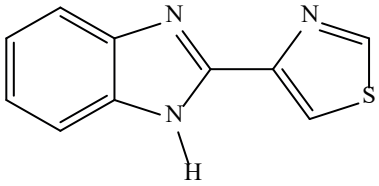
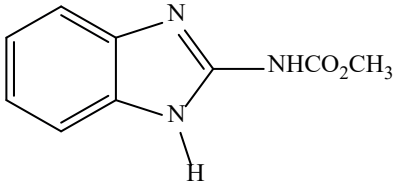
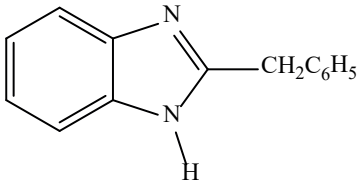
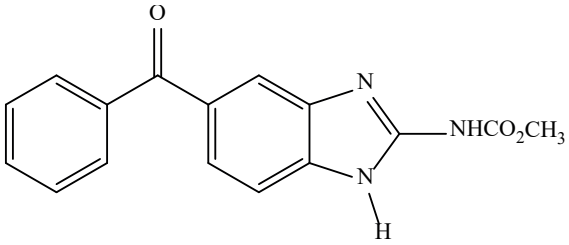
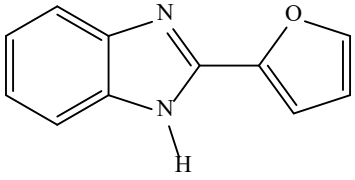
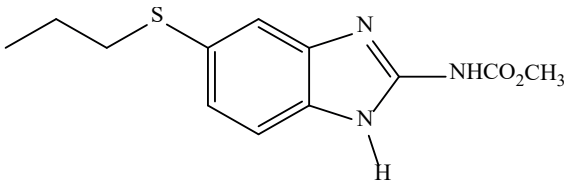
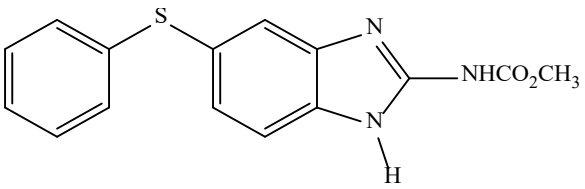
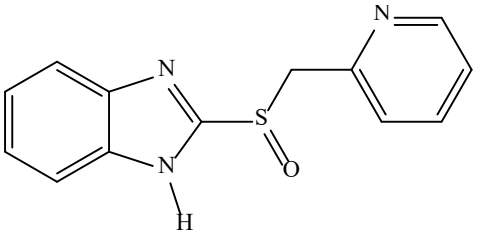


Figure 1: Structure of Benzimidazole.

Benzimidazole is a fundamental structure for medicinal chemists because its derivatives have antioxidant [5], anti-hepatitis [6], antimicrobial [7], antihypertensive [8], antiulcer [9], anti-inflammatory [10], anticonvulsant [11], analgesic [12], antiprotozoal [13], antifungal [14], and anticancer activity [15]. Benzimidazole with a wide range of pharmacological activity; it is one of the oldest and best-studied nitrogen heterocycles. In addition, several benzimidazole derivatives have also been used in sunburns as a means to protect the skin by absorbing ultraviolet radiation. Clinically approved benzimidazole drugs include dibazole, mebendazole, timoprazol, fuberidazole, albendazole, fenbendazole, thiabendazole, and, carbendazim **(Table 1)** [16].

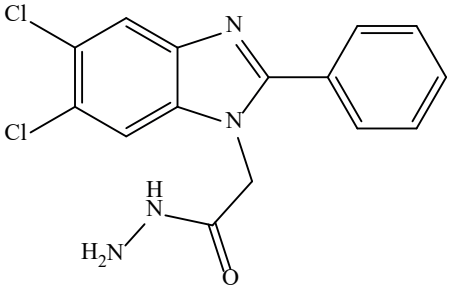
Table 1. Some benzimidazole drugs.

Compound	**Structure**	**Ref.**
Thiabendazole		[17]
Carbendazim		[18]
Dibazole		[19]
Mebendazole		[20]
Fuberidazole		[21]
Albendazole		[22]

Fenbendazole		[23]
Timoprazol		[24]

2. PHARMACOLOGICAL ACTIVITIES

In the study conducted by Albay *et al.* (2023), new benzimidazole derivatives were synthesized, and their enzyme inhibition and antioxidant activities were investigated. Methods such as DPPH free radical scavenging and iron-reducing power activities were used to determine elastase inhibition capacities in enzyme inhibition tests and two different antioxidant capacities in antioxidant tests. One of the synthesized compounds showed the highest elastase inhibition and antioxidant activity with iron reduction power. Another of the synthesized compounds showed the highest antioxidant activity with DPPH. These two compounds are shown below [25].



2-(5,6-dichloro-2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide

Antielastase IC_{50} (μM): 0.007 ± 0.0430

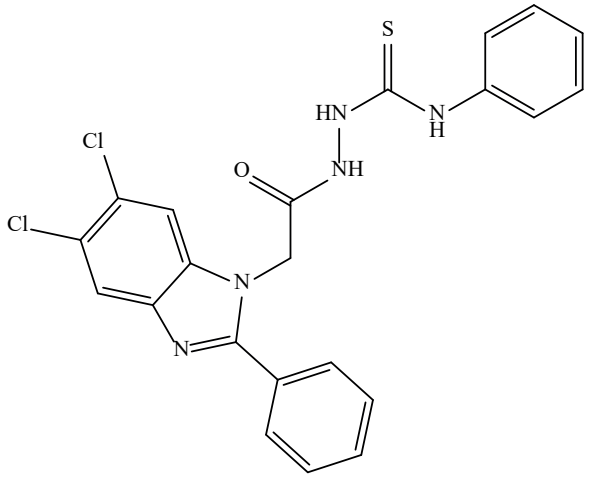
Reducing power absorbancea:

0.249 ± 0.0573

0.249 ± 0.0707

0.395 ± 0.0339

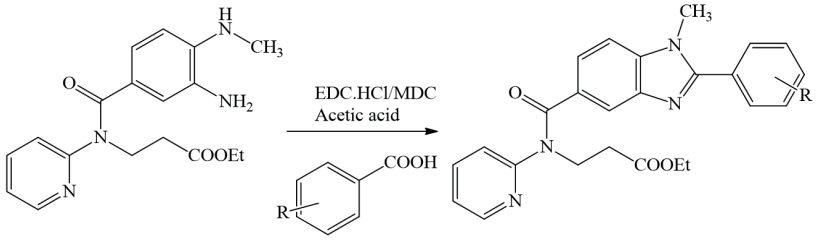
0.517 ± 0.0297



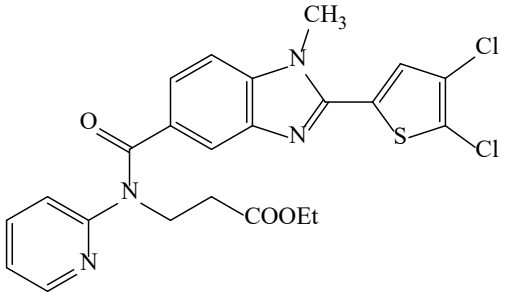
2-(2-(5,6-dichloro-2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)acetyl)-*N*-phenylhydrazinecarbothioamide

DPPH SC_{50} (μM): 407.21 ± 33.998

Shinde *et al.* (2023) synthesized a number of novel benzimidazole compounds with high yields. The reaction with various aromatic carboxylic acids was initiated with compound ethyl 3-(3-amino-4-(methylamino)-*N*-(pyridin-2-yl)benzamido)propanoate, EDC.HCl, a starting agent, and a small amount of DMAP. The compounds obtained as a result of this process were evaluated for cancer prevention in vitro. This study revealed that the benzimidazole compound, to which the 2-chloro thiophene-5-carboxylic acid group is attached, has the strongest *in vivo* anti-cancer capacity [26].



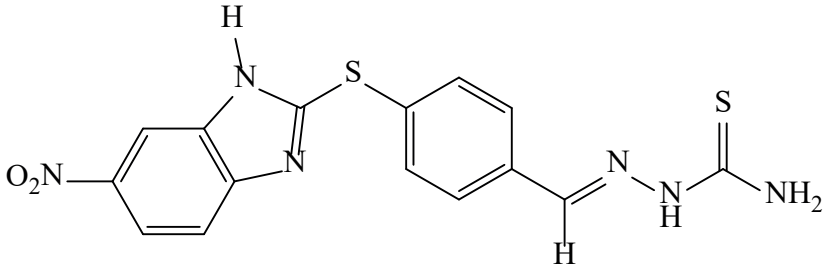
R: Benzoic Acid, 2-(4-cyanophenyl) amino acetic acid, 3-Bromo Benzoic acid, Phenyl acetic acid, Thiophene-2-Carboxylic acid, *o*-Toluic acid, 3,5-Dichloro Benzoic acid, and 3-Nitro Benzoic acid



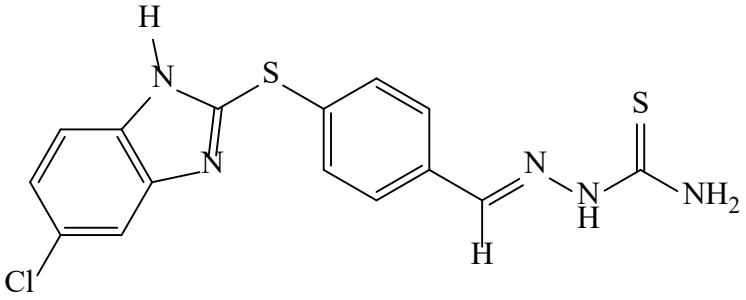
ethyl 3-(2-(4,5-dichlorothiophen-2-yl)-1-methyl-*N*-(pyridin-2-yl)-1*H*-benzo[*d*]imidazole-5-carboxamido)propanoate

Anticancer IC_{50} (μM): HepG2 (12.02 ± 0.11), MCF-7 (9.14 ± 0.09), HCT116 (4.96 ± 0.06)

Champa *et al.* (2023) synthesized six benzimidazole derivatives and considered the quantum chemical properties of compounds to understand the concept of structural activity. To evaluate all synthesized compounds in terms of antioxidant activity, cytotoxicity, and DPPH scavenging activity using MTT test and Ferrous-Ion Chelating Assay were used. All of the tested compounds showed anti-inflammatory, antioxidant, and toxic potential. Of all the compounds, only two compounds were found to have the highest potency. These compounds are shown below. The agar diffusion method was used to perform antibacterial and antifungal tests with bacteria and fungi. Although there are no compounds that are effective against isolated fungal species, some have been found to have a weak antibacterial effect. Furthermore, the benzimidazole compound at the 5-chloro position was found to have a significantly greater effect on all bacterial species (*E. coli, S. aureus, Bacillus cereus, and Acetobacter sp*.). In addition, the *in vitro* anticancer properties of the designed compounds have been documented using in silico molecular placement simulation studies [27].

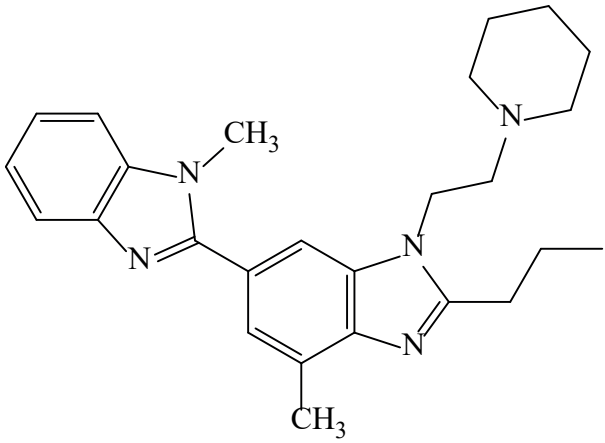


(*E*)-2-(4-((6-nitro-1*H*-benzo[*d*]imidazol-2-yl)thio)benzylidene)hydrazinecarbothioamide



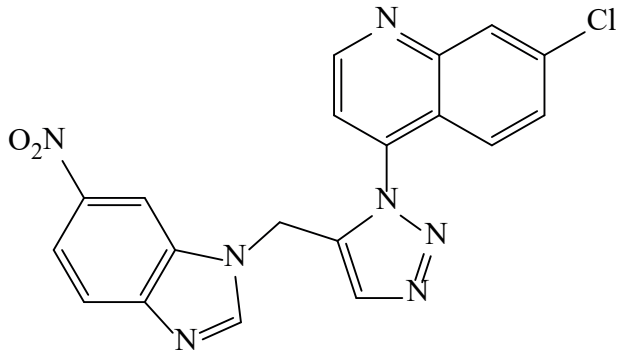
(*E*)-2-(4-((5-chloro-1*H*-benzo[*d*]imidazol-2-yl)thio)benzylidene)hydrazinecarbothioamide

Rajagopal *et al.* (2023) were synthesized using bis-benzimidazole using simple and environmentally friendly reactions. The antibacterial activities of bis-benzimidazole oils of all synthesized images were tested against Gram-positive properties (*Bacillus subtilis, Staphylococcus aureus*), Gram-negative properties (*Escherichia coli, Serratia sp.)* and fungal pathogen *Candida albicans*. According to the natural substances obtained, 1,7'-dimethyl-3'-(2-(piperidin-1-yl)ethyl)-2'-propyl-1*H*,3'*H*-2,5'-bibenzo[*d*]imidazole had strong activity against *C. albicans* [28].



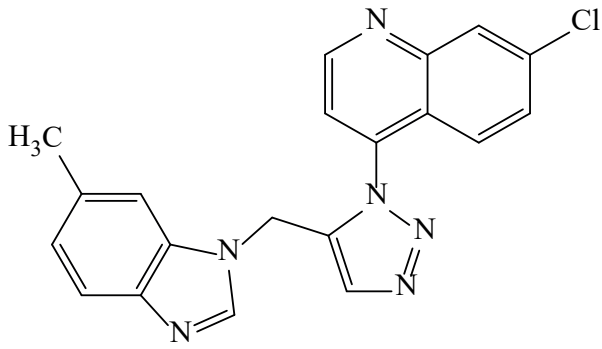
Minimum inhibitory concentration (MIC): 16 μg/ml

Novel benzimidazole-1,2,3-triazole-quinoline derivatives were synthesized by Nyoni *et al.* (2023) with high yield. An *in vitro* assessment of antimycobacterial activity against the H37Rv strain of *Mycobacterial tuberculosis* was performed on all synthesized compounds. The hybrid compounds showed potent MIC_{90} activities ranging from 1.07 to 8.66 μM, showing more effective than the first-line reference drug ethambutol (MIC_{90}=9.54 μM). Three of the synthesized compounds showed excellent MIC_{90} activities (between 1.49 and 2.08 μM) compared to the other compounds [29].



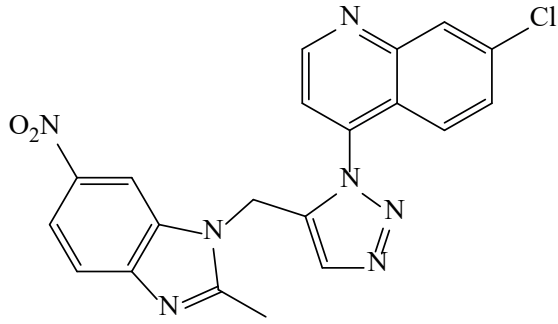
7-chloro-4-(5-((6-nitro-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)quinoline

(H37Rv) MIC_{90} (μM): 1.54



7-chloro-4-(5-((6-methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)quinoline

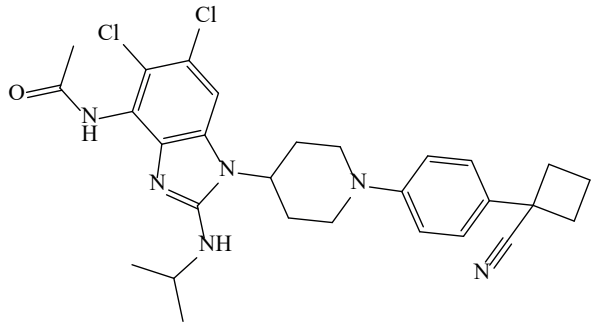
(H37Rv) MIC_{90} (μM): 2.08



7-chloro-4-(5-((2-methyl-6-nitro-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)quinoline

(H37Rv) MIC_{90} (μM): 1.49

Ai *et al.* (2023) synthesized novel derivatives of benzimidazole and found that the compounds showed significant inhibition activity against TRPV4 current. According to the findings, the group of compounds containing cyanocyclobutyl was found to be a new and highly potent TRPV4 antagonist. In addition, evaluations of this compound for drug-like properties are ongoing [30].



N-(5,6-dichloro-1-(1-(4-(1-cyanocyclobutyl)phenyl)piperidin-4-yl)-2-(isopropylamino)-1*H*-benzo[*d*]imidazol-4-yl)acetamide

IC_{50}: 22.65 nM and IR at 1 μM: 79.85%

References

[1] N. Jeelan. Basha, and N. M. Goudgaon, "A Comprehensive Review on Pyrimidine Analogs-Versatile Scaffold with Medicinal and Biological Potential," *Journal of Molecular Structure 1246* (2021): 131168.

[2] B. S. Mathada, N. G. Yernale, J. N. Basha, and J. Badiger, "An Insight into the Advanced Synthetic Recipes to Access Ubiquitous Indole Heterocycles," *Tetrahedron Letters 85* (2021): 153458.

[3] M. S. Vasava, M. N. Bhoi, S. K. Rathwa, D. J. Jethava, P. T. Acharya, D. B. Patel, and H. D. Patel, "Benzimidazole: A Milestone in the Field of Medicinal Chemistry," *Mini Reviews in Medicinal Chemistry 20*, no. 7 (2020): 532–65.

[4] J. B. Wright, "The Chemistry of the Benzimidazoles," *Chemical Reviews 48*, no. 3 (1951): 397–541.

[5] Gurer-Orhan, H., Orhan, H., Suzen, S., Orhan Püsküllü, M., & Buyukbingol, E. (2006). Synthesis and evaluation of in vitro antioxidant capacities of some benzimidazole derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry, 21*(2), 241-247.

[6] Li, Y. F., Wang, G. F., He, P. L., Huang, W. G., Zhu, F. H., Gao, H. Y., ... & Zuo, J. P. (2006). Synthesis and anti-hepatitis B virus activity of novel benzimidazole derivatives. *Journal of Medicinal Chemistry, 49*(15), 4790-4794.

[7] Özkay, Y., Tunalı, Y., Karaca, H., & Işıkdağ, İ. (2010). Antimicrobial activity and a SAR study of some novel benzimidazole derivatives bearing hydrazone moiety. *European Journal of Medicinal Chemistry, 45*(8), 3293-3298.

[8] Kumar, J. R., Jawahar L, J., & Pathak, D. P. (2006). Synthesis of benzimidazole derivatives: as anti-hypertensive agents. *Journal of Chemistry, 3*(4), 278-285.

[9] Cho, S. Y., Kang, S. K., Kim, S. S., Cheon, H. G., Choi, J. K., & Yum, E. K. (2001). Synthesis and SAR of Benzimidazole Derivatives Containing Oxycyclic Pyridine as a Gastric ATPase Inhibitors. *Bulletin-Korean Chemical Society*, *22*(11), 1217-1223.

[10] Lazer, E. S., Matteo, M. R., & Possanza, G. J. (1987). Benzimidazole derivatives with atypical antiinflammatory activity. *Journal of Medicinal Chemistry, 30*(4), 726-729.

[11] Shingalapur, R. V., Hosamani, K. M., Keri, R. S., & Hugar, M. H. (2010). Derivatives of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. *European Journal of Medicinal Chemistry, 45*(5), 1753-1759.

[12] Rathore, A., Sudhakar, R., Ahsan, M. J., Ali, A., Subbarao, N., Jadav, S. S., ... & Yar, M. S. (2017). In vivo anti-inflammatory activity and docking

study of newly synthesized benzimidazole derivatives bearing oxadiazole and morpholine rings. *Bioorganic Chemistry*, 70, 107-117.

[13] Katiyar, S. K., Gordon, V. R., McLaughlin, G. L., & Edlind, T. D. (1994). Antiprotozoal activities of benzimidazoles and correlations with beta-tubulin sequence. *Antimicrobial Agents and Chemotherapy, 38*(9), 2086-2090.

[14] Podunavac-Kuzmanović, S. O., Barna, D. J., & Cvetković, D. D. (2007). Quantitative structure-activity relationship of some 1-benzylbenzimidazole derivatives as antifungal agents. *Acta Periodica Technologica*, (38), 139-147.

[15] Nofal, Z. M., Soliman, E. A., Abd El-Karim, S. S., El Zahar, M. I., Srour, A. M., Sethumadhavan, S., & Maher, T. J. (2011). Novel benzimidazole derivatives as expected anticancer agents. *Acta Pol Pharm*, 68, 519-534.

[16] Ebenezer, O., Oyetunde-Joshua, F., Omotoso, O. D., & Shapi, M. (2023). Benzimidazole and its derivatives: Recent Advances (2020-2022). *Results in Chemistry,* 100925.

[17] Martin, F., Dube, F., Karlsson Lindsjö, O., Eydal, M., Höglund, J., Bergström, T. F., & Tydén, E. (2020). Transcriptional responses in Parascaris univalens after in vitro exposure to ivermectin, pyrantel citrate, and thiabendazole. *Parasites & Vectors,* 13, 1-14.

[18] Goyal, K., Sharma, A., Arya, R., Sharma, R., Gupta, G. K., & Sharma, A. K. (2018). Double edge sword behavior of carbendazim: a potent fungicide with anticancer therapeutic properties. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, *18*(1), 38-45.

[19] Boggu, P., Venkateswararao, E., Manickam, M., Kim, Y., & Jung, S. H. (2017). Exploration of SAR for novel 2-benzylbenzimidazole analogs as inhibitor of transcription factor NF-κB. *Archives of pharmacal research*, *40*, 469-479.

[20] Elayapillai, S., Ramraj, S., Benbrook, D. M., Bieniasz, M., Wang, L., Pathuri, G., ... & Gunderson, C. C. (2021). Potential and mechanism of mebendazole for treatment and maintenance of ovarian cancer. *Gynecologic oncology*, *160*(1), 302-311.

[21] K. N. Wei, G. X. Song, S. Z. Huang, Q. Tang, J. H. Hu, Z. Tao, and Y. Huang, "Lab-on-a-Molecule Probe:Multitarget Detection of Five Aromatic Pesticides Using a Supramolecular Probe under Single Wavelength Excitation," *Journal of Agricultural and Food Chemistry 70, no.* 19 (2022): 5784–93.

[22] Alavi, S. E., & Shahmabadi, H. E. (2021). Anthelmintics for drug repurposing: Opportunities and challenges. *Saudi Pharmaceutical Journal*, *29*(5), 434-445.

[23] De Oliveira, H. C., Joffe, L. S., Simon, K. S., Castelli, R. F., Reis, F. C., Bryan, A. M., ... & Rodrigues, M. L. (2020). Fenbendazole controls in vitro growth, virulence potential, and animal infection in the Cryptococcus model. *Antimicrobial Agents and Chemotherapy, 64*(6), 10-1128.

[24] Jana, K., Bandyopadhyay, T., & Ganguly, B. (2016). Revealing the mechanistic pathway of acid activation of proton pump inhibitors to inhibit the gastric proton pump: A DFT study. *The Journal of Physical Chemistry B, 120*(51), 13031-13038.

[25] Albay, C., & Tekbaş, G. (2023). Desing, synthesis, and characterization of some 5, 6-dichloro benzimidazole derivatives with investigation of their antioxidant and elastase inhibitory activities. *Journal of Heterocyclic Chemistry*.

[26] Shinde, R. B., Pansare, D. N., Shelke, R. N., Sarkate, A. P., Tiwari, S. V., Bangal, M. N., ... & Zine, A. M. (2023). A facile Synthesis and characterization of some novel benzimidazole derivatives. *Results in Chemistry,* 101134.

[27] Champa, R., Vishnumurthy, K. A., Bodke, Y. D., Naik, H. B., Pushpavathi, I., Meghana, P., & Kadam, P. R. (2023). Synthesis, characterization, and biological investigations of potentially bioactive heterocyclic compounds containing benzimidazole nucleus. *Results in Chemistry,* 101018.

[28] Rajagopal, K., Dhandayutham, S., Nandhagopal, M., & Narayanasamy, M. (2023). Study on new series of bis-benzimidazole derivatives synthesis, characterization, single crystal XRD, biological activity, and molecular docking. *Journal of Molecular Structure, 1283*, 135253.

[29] Nyoni, N. T., Ncube, N. B., Kubheka, M. X., Mkhwanazi, N. P., Senzani, S., Singh, T., & Tukulula, M. (2023). Synthesis, characterization, *in vitro* antimycobacterial and cytotoxicity evaluation, DFT calculations, molecular docking and ADME studies of new isomeric benzimidazole-1,2,3-triazole-quinoline hybrid mixtures. *Bioorganic Chemistry, 141*, 106904.

[30] Ai, C., Wang, Z., Li, P., Wang, M., Zhang, W., Song, H., ... & Zheng, Z. (2023). Discovery and pharmacological characterization of a novel benzimidazole TRPV4 antagonist with cyanocyclobutyl moiety. *European Journal of Medicinal Chemistry, 249*, 115137.