Faculty of Medical and Health Sciences, University of Poonch Rawalakot
Journal of Pharma and Biomedics
ISSN: 3007-1984(online), 3007-1976 (Print)
https://www.jpbsci.com/index.php/jpbs

2-Mercaptobenzimidazoles as Privileged Scaffolds: Synthetic Techniques, Docking Analysis, and Biological Evaluation. A Mini Review

[a]Abu Sulman, [b]Muhammad Kashif, [c]Hajira Kanwal, [a]Muhammad Muneeb Ayub, [a]Maria Shafaqat, [a]Muhammad Hammad, [d]Mobeen Ahmad, [a]Tuba Ameen, [a]Aleeha Afzal, [a]Hadiqa Arif, [a]Hafsa Sehar, [a]Waleed Maqbool, [a]Hafiz Aamir Ali Kharl*

[a] Faculty of Health & Pharmaceutical Sciences, Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan.
[b] Hamdard Institute of Pharmaceutical Sciences, Hamdard University Islamabad Campus, Pakistan.
[c] Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan.
[d] Atta-Ur-Rehman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan, Pakistan.

Received: November 21, 2024; *Revised: December 29, 2024;* *Accepted: December 30, 2024*

A B S T R A C T

2-mercaptobenzimidazole derivatives are Sulphur containing heterocyclic compounds with diverse pharmacological properties. This review discusses structural modifications, reactivity, traditional to advanced synthetic methods, chemical properties, biological studies, and structure-activity relationship of these derivatives. Traditional methods are used commonly for their synthesis, but green approaches and nanomaterial-based technology offer better pathways with environmental-friendly properties. Nanotechnology also improves the delivery of drug molecules to specific biological targets. In-vitro molecular docking studies of the derivatives also discussed which demonstrate their affinity towards biological targets and predict their better therapeutic activity against various pathological conditions. By compiling recent developments in synthetic strategies, structure–activity relationships (SAR), and in silico screening results, this review highlights the therapeutic potential and future prospects of 2-mercaptobenzimidazole-based compounds in drug discovery and development. However, these derivatives have some issues related to metabolic stability, bioavailability, and toxicity, they can be proved novel therapeutic molecules with better activities by overcoming these problems.

Keywords: 2-mercaptobenzimidazoles, Heterocyclic compounds, Molecular docking, Structure-activity relationship, Nanomaterial-technology, Green chemistry.

Corresponding Author: Hafiz Aamir Ali Kharl
Email: hafiz.kharl@uaf.edu.pk

INTRODUCTION

Heterocyclics are those cyclic organic compounds that also contain an atom other than carbon i-e nitrogen, Sulphur or oxygen, incorporated in their ring structure. Medicinal chemists are using these compounds in treatment of different diseases to achieve desired therapeutic effects because of their ability to use hydrogen atoms which interact with enzymes and have high biological protection profile (Joule *et al*., 2020; Romine *et al*., 2011). Example of heterocyclic compounds are those compounds containing oxadiazole ring in their structure. They are well known for their anti-inflammatory, analgesic and antirhinoviral characteristics (Gutierréz-Hernández *et al*., 2019; Sheikha *et al*., 2018; Youssif *et al*., 2019; Abd El-Hameed *et al*., 2021; Diana *et al*., 1994; Mohamed *et al*., 2020).

Another example of heterocyclic compounds are

benzimidazoles, which are heterocyclic compounds in which benzene ring and imidazole ring are fused together. They are very important compounds in medicinal chemistry due to their large spectrum of pharmacological properties (Tahlan *et al*., 2019; Shaharyar *et al*., 2017; Sharaf *et al.*, 2025; Wright *et al.,* 1951; García-Valverde *et al.,* 2005; Obaid *et al*., 2023). They are used in treatment of various pathological conditions such as infections due to bacteria (Kulkarni *et al.,* 2016; Tahlan *et al*., 2019; Negi *et al.,* 2017), fungi (Si *et al*., 2015) or viruses (Francesconi *et al*., 2020; Gigante *et al.,* 1999) as well as in diabetes (Enumula *et al.,* 2014), leishmania (Tonelli *et al*., 2018), hyperlipidemia (Sheikha *et al*., 2018), oxidative stress (Ali *et al*., 2018), inflammation (Sethi *et al*., 2018) and malaria (Camacho *et al.,* 2011). They are also used as diuretics (Wang *et al.*, 2007) and antimycobacterial agents (Pathak *et al*., 2010).

Benzimidazole rings allow substitution at different positions of the ring that considerably affect their therapeutic activity e.g. substitution of different groups such as thiol, halogen etc at position 2 of the ring structure influences their pharmacodynamic and pharmacokinetic properties (Figure 1) (Brishty *et al*., 2021; Lgaz *et al.,* 2021). 2-mercaptobenzimidazole are heterocyclic compounds containing sulfur functional group at position-2 which highly influence its activities and make it important in the field of drug discovery and development (Poonam *et al*., 2022; Martínez-Pascual *et al*., 2025). As an important nucleophilic center 2-mercapto group of these compounds facilitates bonding with hydrogen and metal ions which enhance its enzyme inhibition, antibiotic and anti-cancer characteristics. Hydrogen bond formation, participating in enzyme inhibitory mechanism and acting as biomolecular moiety, is an important property of 2-MBI which makes its derivatives effective against cancer, infections and oxidative stress (de Sousa Couto and Guerra *et al.,* 2021). Its pharmacological activities are also influenced by the presence of a 2-mercapto group that react with biological macromolecules (Badgujar *et al*., 2024).

Due to their significance researchers are studying their possible synthesis processes and explore advanced ones that can give better results with less drawbacks. Computational techniques such as molecular docking are frequently used to explain their mechanism and interaction with biological targets at molecular level (Heckenlively *et al.,* 2022; Sahu *et al.,* 2023). Structure-activity relation analysis suggests improvements in their selectivity and efficacy. Some studies overclaimed their characteristics but they have bioavailability, toxicity and stability issues yet. The aim of this study is to overcome these flaws via advanced synthesis process and structure modifications to make them better drug candidates, and it also covers chemical properties, synthesis and biological activities of 2-mercaptobeznimidazoles (Figure 2) (Vaishnav *et al*., 2025; de Sousa Couto & Guerra *et al*., 2021).

Chemical Properties and Structural Characteristics

As discussed earlier, the primary reactivity of 2-BMI is due to thiol group because as nucleophilic atom it reacts with electrophilic centers of various species including ions of metals, organic electrophiles and biological targets such as enzymes and make strong bond due to polarizability of Sulphur atom. This property makes it significant in coordination chemistry where Sulphur atom as ligand, make complexes with metals having properties like metalloenzyme inhibition. Lone pair of Sulphur is responsible for its nucleophilicity and eventually nucleophilic substitution reactions. It has importance in metal-based drug formulation due to its capability of metal-Sulphur complexes (Osuofa *et al.,* 2023; Andrés *et al*., 2023; Santos *et al*., 2022; Ebenso *et al*., 2021; Zhu *et al*., 2022).

It has dual solubility (hydrophobic nature of benzimidazole ring and hydrophilic nature of thiol group) character and hence possesses improved pharmacokinetic (solubility in various solvents) and pharmacodynamic (drug delivery system) properties (Kumari *et al.,* 2023).

Methods of synthesis

Traditional method

Disulfide method is the most common traditional method of its synthesis in which o-phenylenediamine reacts with carbon disulfide to produce 2-mercaptobenzimidazole. This reaction is significant at industrial scale due to high yield, but it has limitations such as it is energy consuming as it requires prolonged elevated temperature and the solvents (DFM and DMSO) which are used in reaction, have environmental safety risks. It also produces Sulphur containing by-products which are difficult to dispose of. So, the interest of researchers is growing towards more eco-friendly methods (Jakeria *et al.,* 2022; Poonam *et al.,* 2022; Ahamed *et al.,* 2013; Tejaswini *et al*., 2021; Vidal *et al*., 2021).

Green synthesis

Researchers have developed methods that are eco-friendly and reduce the risks related to environmental crises (Ying *et al*., 2022). Amon them microwave-assisted method is most common method in which o-phenylenediamine reacts with carbon disulfide in ethyl alcohol using radiations of microwaves. This method has advantages over traditional

synthesis such as low time and energy consumption, higher yield and possibility of solvent-free mechanism (Chung *et al.,* 2023). Solvent-free technique is an emerging option for large scale production as it eliminates the need for toxic solvents and hence harmful waste (Langsdorf *et al*., 2021).

Advancement in synthetic processes

Several advanced techniques are being used for 2-mercaptobenzimidazole synthesis. One of them is nanomaterial-assisted synthesis in which nanoparticles or nanocatalysts are used in reaction that improves the efficacy of reaction and stability of product (Bin Rashid *et al.,* 2023; Abbas *et al.,* 2024). Another method is biocatalysis in which enzymes or microorganisms are used as catalysts and reaction occurs on normal conditions of pH and temperature that helps to conserve energy, and this method is also regioselective hence, selective derivatives can be obtained easily which is impossible in other old methods (Bell *et al*., 2021).

Mohammed et al. proposed a new efficient synthesis method of the 2-(thiophen-2-yl)-1H-benzo[d]imidazole 9, by reacting orthophenyl- enediamine 7 with thiophene-2-carbaldehyde 8 in equimolar quantities, in the presence of a catalytic quantity of zinc oxide (nanoparticles) in ethanol at 70 °C for 15 minutes (Scheme 1) (El-Alami *et al*., 2024).

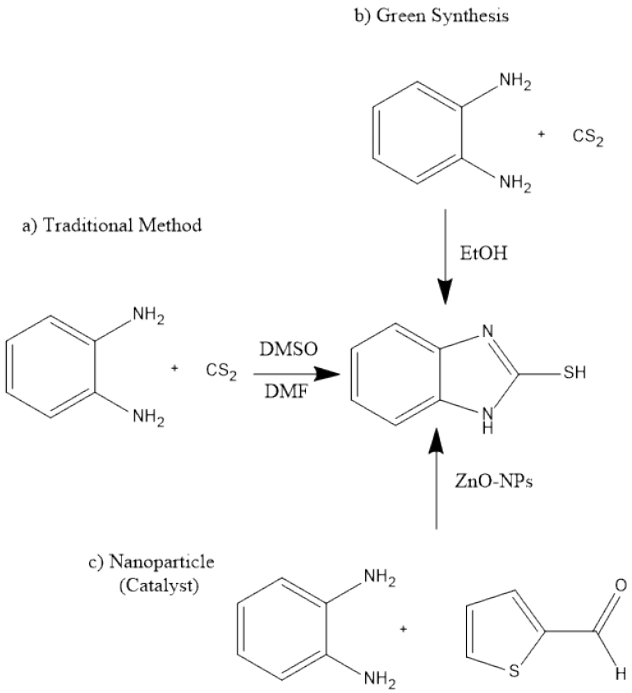


Figure 1: Different ways to synthesize 2-Mercaptobenzimidazole a) Traditional method by utilizing solvents (DMSO, DMF) b) Green Synthesis method by utilizing Microwave radiations c) Nanoparticle (Catalyst) driven synthesis.

Significance in Medicinal Chemistry

Therapeutic Potential

Modification of side chains and substitutions at different sites of 2-mercaptobenzimidazole ring capable it to interact with various biological targets hance it has broad range of therapeutic activities in several pathological conditions (Parthiban *et al.,* 2024; Ngoepe & Clayton *et al.,* 2021).

Drug Delivery system

Stable complexes of 2-MBI with metals, nanoparticles, liposomes and micelles influence their bioavailability and make them capable of developing nanocarriers to target specific biological targets such as enzymes and tumors and hence alleviate systemic toxicity and increase therapeutic efficacy (Ezike *et al.,* 2023).

Enzyme Inhibition

The thiol group of 2-MBI interacts with the metal ions of active sites of enzymes and disrupts them hence causes enzyme inhibition. For example, some 2-MBI derivatives inhibit matrix metalloproteinases (MMPs) enzymes that are involved in remodeling tissues and hence inhibit cancer. Another example is carbonic anhydrase enzyme inhibition. As this enzyme involves regulation of pH and transport of carbon dioxide hance show activity in glaucoma and cancer (Lee *et al*., 2023). Schiff derivatives, including 5-(2-hydroxy-4-methoxybenzylideneamino)-2-mercaptobenzimidazole and 5-(4-hydroxy-3-

methoxybenzylideneamino)-2-mercaptobenzimidazole ere synthesized to assess their glutathione-S-transferase inhibitory activity by using spectroscopy and molecular docking techniques (by using Chimera and AutoDock Vina). The second derivative showed greater inhibitory potential (Figure 3) (Aras *et al*., 2022).

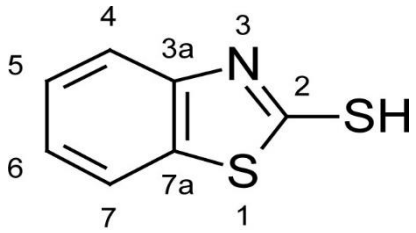


Figure 1: Structure of 2-Mercaptobenzimidazole.

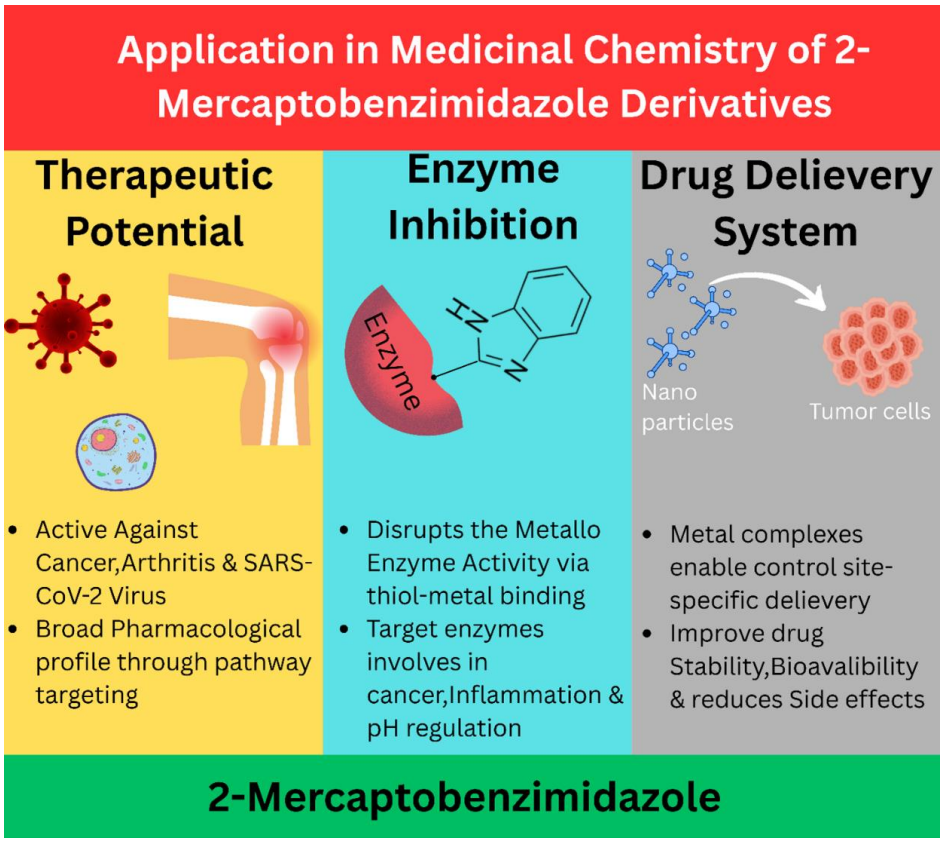


Figure 2: Therapeutic applications of 2-MBI derivatives.

Biological Activities of 2-Mercaptobenzimidazole

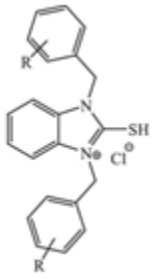
Antimicrobial Activity

Research has revealed that 2-MBI derivatives have potent antimicrobial activity against certain multidrug-resistant strains of microbes and can play pivotal role against drug resistance (Dad *et al*., 2023). Combined derivatives with sugars such as mannose, arabinose, glucose as well as aldehydes show good activity against gram positive and gram-negative bacterial species (Hosamani *et al*., 2011). For example, antimicrobial activity of 2-mercaptobenzimidazole derivatives having 50, 100 and 200 microgram per milliliter concentration, was determined against *E. coli* ATCC3750 and *B. subtilis* 6633 at Haffkine institute of Mumbai through paper disc method and compared their activity against standard drug, Ciprofloxacin (Yaseen *et al*., 2010). Poonam *et al*., (2022) also investigated 2-MBI derivatives against gram positive and negative bacterial species and results showed even better activity than standard drug, Ciprofloxacin proving them equivalent even superior antimicrobial drug candidates. 2-mercaptobenzimidazoles derivatives also showed antifungal

activity by interacting with biosynthesis and functionality of fungal cell membranes. Attachment of electron withdrawing groups (EWGs) with phenyl ring increases its activity against target fungi, hence improves efficacy (Poonam *et al.,* 2022). For instance, benzimidazole, levamisole, closantel and ivermectin have been extensively used in Asia and worldwide to treat worm infections (Qamar & Alkheraije 2023).

Anticancer Activity

2-MBI derivatives show anticancer activity by arresting cell cycle and induction of apoptosis, inhibition of DNA replication and protein synthesis. Researchers are working on the selectivity of these derivatives for target cells so that they show their only against cancer cells but not normal human body cells (Gousias *et al*., 2022). Mavvaji *et al.*, (2025) synthesized a series of 2-mercaptobenzimidazole derivative **1** compounds and tested them against three human cell lines; colon (DLD-1), lung (A549) and liver (HepG2) to check their cytotoxic activity. Results showed that all synthesized derivatives had cytotoxic activity with low or high minimum inhibitory concentration (minimum concentration of compound required for inhibitory effect) values (Mavvaji *et al.,* 2025).

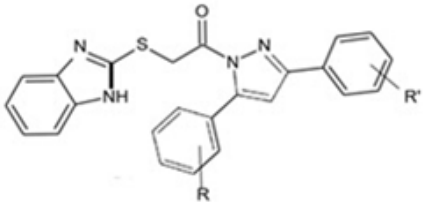


1

In a study by Tahlan *et al.,* (2020) novel compounds, azomethine of 2-mercaptobenzimidazoles were synthesized and characterized by Fourier transform-infrared spectroscopy (FT-IR), proton and carbon-nuclear magnetic resonance ($^{1}H/^{13}C$-NMR), mass spectroscopy (MS) and carbon, hydrogen, nitrogen analysis. The in-vitro anticancer activity of these synthesized derivatives was investigated against human colorectal carcinoma cancer cell line (HCT-116) by using 5-Fluorouracil (5-FU) as reference drug. All derivatives contained anticancer property and one of them showed potent activity (Tahlan *et al*., 2020).

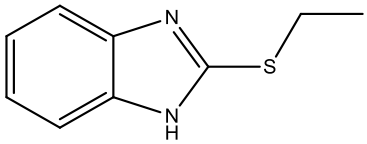
Antioxidant Activity

Antioxidant activity of 2-MBI derivatives is also reported and they can play a role in the treatment of cardiovascular diseases, neurodegenerative diseases, and diabetes (Lee *et al*., 2023). Kharl *et al*., (2020) reported the scavenging activity of 2-MBI derivatives **2** on DPPH and results showed that they have equivalent, even superior activity as compared to standard drug, ascorbic acid. This activity makes them capable of taking part in the treatment of diseases in which oxidative stress is cause of progression (Ali Kharl *et al*., 2025).



2

These derivatives have also shown tyrosine inhibitory activity and can be used as anti-browning agent in the food industry. Kinetic analysis and docking studies were used to explain the inhibitory activity of these derivatives. It is also proved that the thiol group is responsible for this activity and in the absence of thiol group antioxidant activity is not shown (Figure 4) (Lee *et al*., 2023). A series of thirty-four derivatives of 2-mercaptobenzimidazoles **3** were synthesized and explored their antioxidant acidity by Ata *et al.,* (2023). These compounds were tested for 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals scavenging and urease inhibition activities. Results showed that all compounds had potent to moderate antioxidant activity (Ata *et al.,* 2023).



3

Anti-inflammatory and Anti-Arthritic activity

They show anti-inflammatory activity in some diseases such as arthritis by blocking the production of pro-inflammatory cytokines e.g., TNF-α (Tumor necrosis factor-alpha) and IL-6 (Interleukin-6) which are principal mediators of autoimmune diseases. So, they can be used in the treatment of chronic inflammatory diseases like rheumatoid arthritis and osteoarthritis (Figure 5) (Moudgil and Venkatesha et al., 2022; Direito et al., 2021). Mobashir *et al.,* (2025) studied 2-MBI derivatives and their efficacy in inflammatory and autoimmune disorders was determined. Symptoms of rheumatoid arthritis were diminished due to reduction in production of pro-inflammatory markers. The level of prostaglandin E_2 was also lowered. One of the reasons for anti-inflammatory activity is autocoid suppression which is evident by carrageenan model of inflammation (Mobashir *et al.,* 2025).

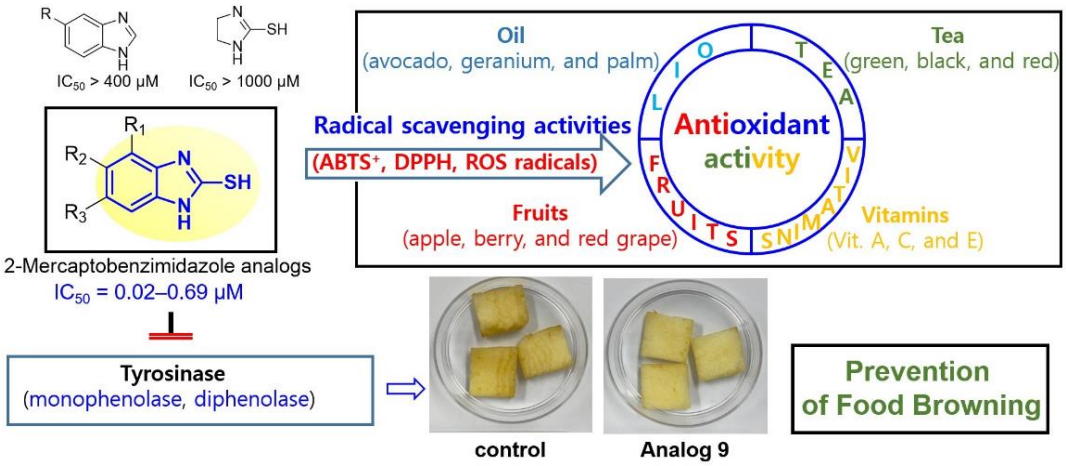


Figure 4: Anti-browning activity of 2-MBI derivatives in fruits.

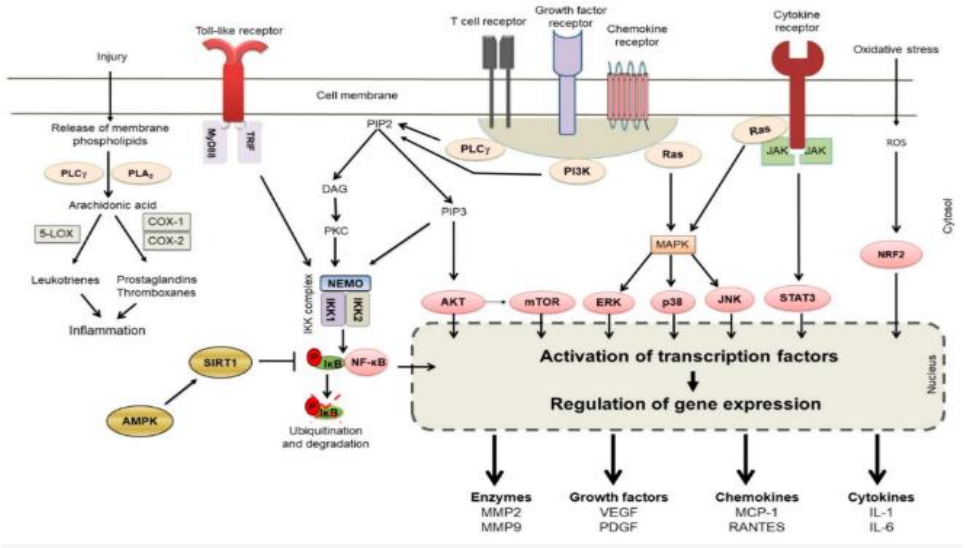


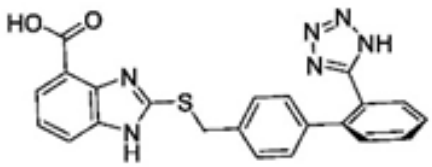
Figure 5: Mechanism of Anti-Inflammatory and Immunomodulatory Activities.

Activity against COVID-19

Recent studies have discovered the activity of 2-MBI derivatives against SARS CoV-2. The study was done on sixty-one 2-MBI derivatives out of which twenty-two compounds were eliminated from the experiment due to having insufficient pharmacokinetic properties. Binding affinities with target sites of remaining thirty-nine derivatives were studied by molecular docking. Results showed that they bind with spikes proteins of virus even with greater strength than standard drugs, Remdesivir and Umifenovir and hence block their entry in human body cells. Former standard drug is only available medication for the treatment of new coronavirus but it is very costly due to having complex structure So novel synthesized 2-MBI derivatives can be proved economical treatment. As they also have anti-inflammatory activity so they can play a role against cytokine storms in severe COVID-19 infection (Porto *et al.*, 2022).

Anti-hypertensive Activity

Although less data is reported, some 2-mercaptobenzimidazole derivatives 4 showed blood pressure lowering activity due to their vasodilatory effect and can play role in cardiovascular diseases (Gutierrez-Hernandez *et al.*, 2024).



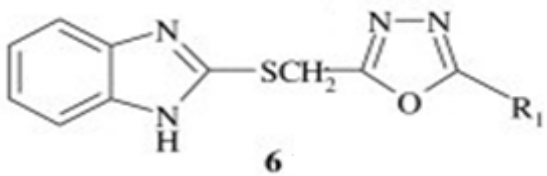
4

Antihyperlipidemic Activity

2-MBI derivatives **5** showed antihyperlipidemic effect by increasing the metabolism of lipids in the body. Molecular docking studies also confirmed their strong binding with lipid-modulating enzymes (Sharaf *et al.*, 2024).

α- Glucosidase Inhibitory Activity

Anticonvulsant and antidiabetic activities of a new series of 2-MBI derivatives **6** were investigated by using Maximal electric shock model and oral glucose tolerance test respectively. One derivative showed potent antidiabetic activity (Figure 6) (Shingalapur *et al.*, 2010; Rosales Hernández *et al*., 2024).



6

***In-silico* Docking Studies and Binding Affinities**

In silico docking studies suggested the binding affinity of 2-MBI derivatives with different biological targets and active sites of various enzymes e.g. binding with metalloenzymes and spikes proteins of corona virus. It also showed the resulting effects of modifications of thiol group or benzimidazole ring (Mohapatra *et al.*, 2023; Ni *et al*., 2025). Several derivatives substituted by alkyl group of carbons, were investigated by using *in-vitro* molecular docking and it was found that some of them had potent antioxidant property at several concentrations.

The results also showed the significant inhibitory action on α-glucosidase enzyme is even greater than standard drug, acarbose and hence indicated as novel drug molecules for antidiabetic activity (Ali *et al*., 2018). A series of S-substituted 2-mercaptobenzimidazole derivatives was synthesized and investigated for urease inhibitory and DPPH radicals scavenging activities. All compounds showed good activity but some of them even showed better results as compared to standard drug, thiourea. Molecular docking showed binding affinities between synthesized derivatives and active site of target enzymes and predicted some compounds as novel therapeutic agents having antioxidant and urease inhibitory properties (Figure 7) (Ata *et al.*, 2023).

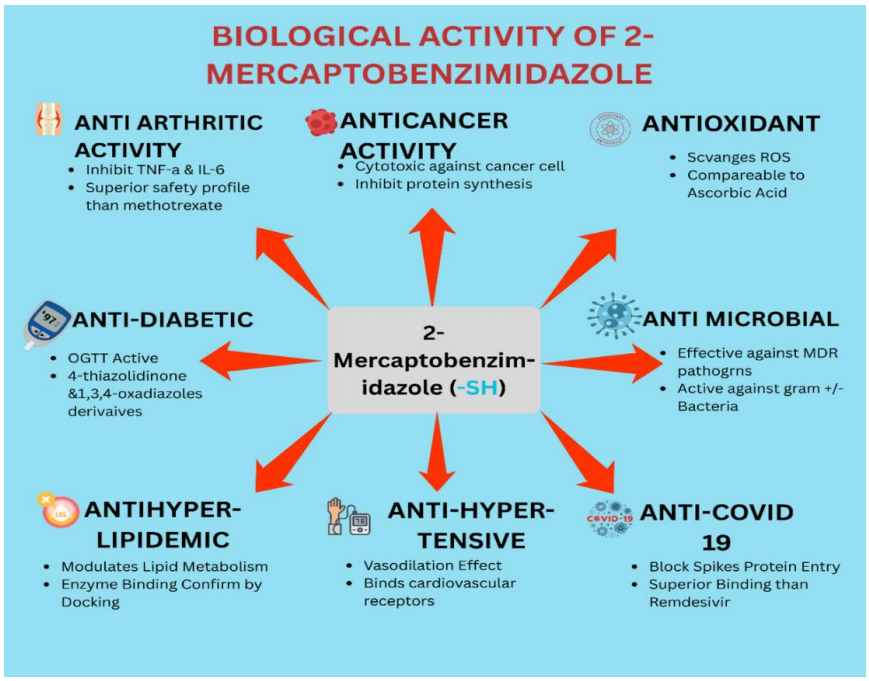


Figure 6: Biological Activities of 2-MBIs.

A series of novel N, N-disubstituted-2-mercaptobenzimidazolium salts were synthesized in conjugation with two novel benzimidazolium chlorides and investigated through nuclear magnetic resonance (NMR) and liquid chromatography-mass spectroscopy (LC-MS) techniques. Binding affinities of relative active compounds with topo2α (topoisomerase II alpha) were determined by molecular docking. According to docking studies some of

these compounds had cytotoxic effect against cancer cell lines (Figure 8) (Mavvaji et al., 2025).

Structure Activity Relationship (SAR) Study

Structure-activity relationship of 2-mercaptobenzimidazole derivatives show the possible effects of modification at different sites of imidazole ring and thiol group. Khan *et al.*, (2023) synthesized various derivatives of 2-MBI with substitutions at distinct positions of benzimidazole ring and mercapto group and showed that substitution has prominent effect on the therapeutic activity of these compounds (Hassan & Khan *et al*., 2021; Satija *et al*., 2022).

Modification at Benzimidazole ring

Modification at different sites of ring highly affects its therapeutic characteristics. For example: Substitution at 5-position: Substitution of electron withdrawing groups at position 5 of the ring increases its electrophilicity towards nucleophilic center of bacterial enzymes and hence enhances its antimicrobial activity but substitution of electron donating groups at position 5 of the ring influences its anticancer activity (Kurishiba *et al*., 2024). Substitution at 6-position: Substitution at position 6 of the ring enhances its cytotoxic and enzyme inhibitory activity (Huang *et al*., 2024).

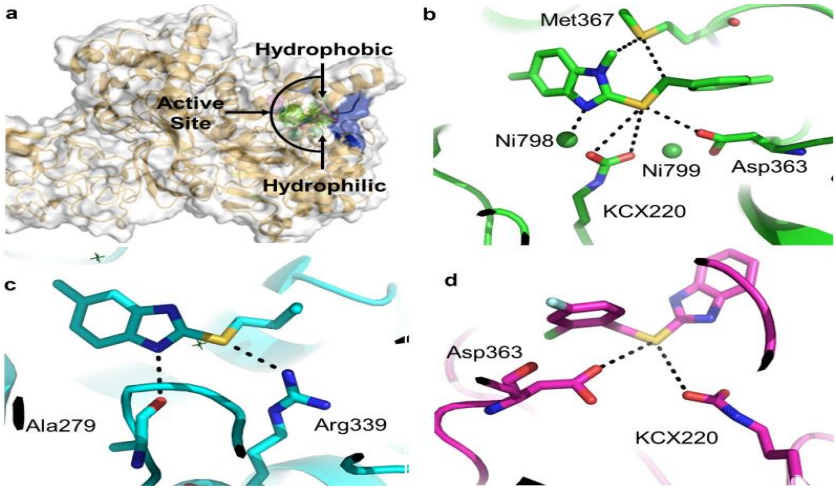


Figure 7: Molecular docking against specific protein to predict the biological activity of 2-MBIs.

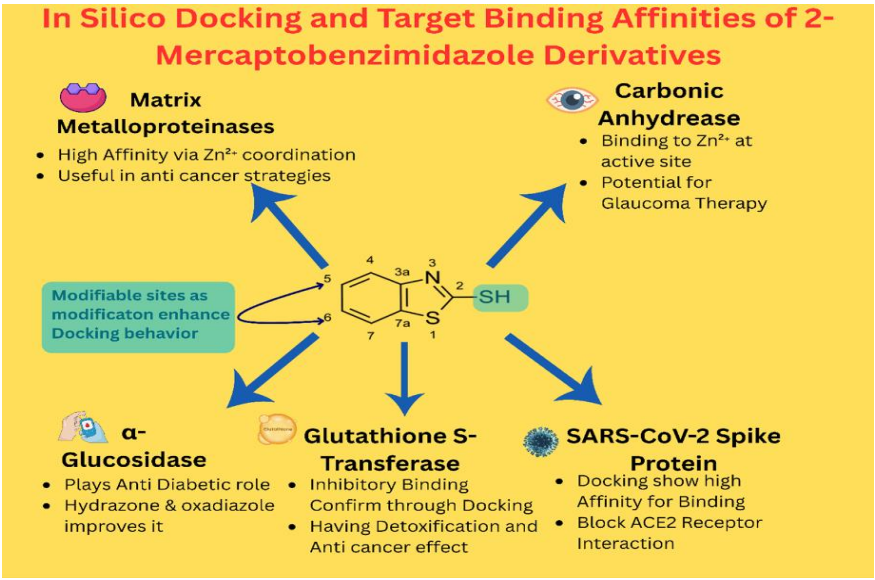


Figure 3: In-silico docking and target binding affinities of 2-Mercaptobenzimidazole Derivatives.

Modification to the Mercapto group

Mercapto group present at position-2 of 2-mercaptobenzimidazole ring highly affects its activity. For example: Electron-withdrawing substitution: Substitution of

electron withdrawing groups at mercapto group increases its nucleophilicity against electrophilic centers of biological targets and hence influences it anticancer activity and enzyme inhibitory activity of those containing iron containing active sites (Mlostoń *et al*., 2024).

Electron-donating group substitution: Substitution of electron donating groups at mercapto group of 2-MBI ring reduces its anticancer activity by decreasing nucleophilicity, but antioxidant property is increased (Zhang and Fang *et al*., 2024). So, the researchers can develop derivatives having more potency and selectivity by refining these modifications (Figure 9).

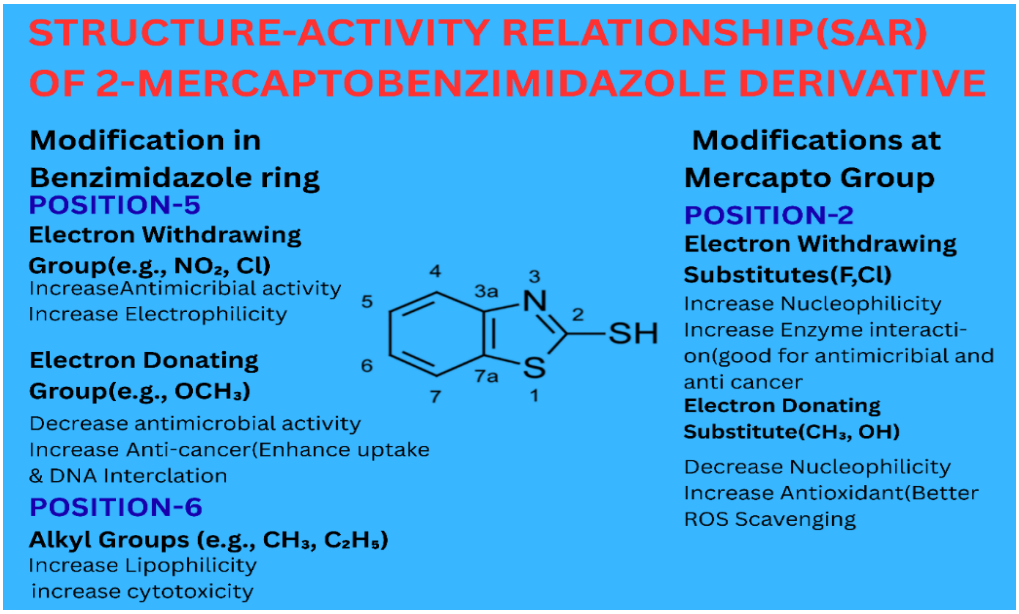


Figure 4: Structure Activity Relationship (SAR) of 2-MBI derivatives.

CONCLUSION

2-Mercaptobenzimidazoles represent a crucial class of heterocyclic compounds with diverse chemical, pharmacological, and therapeutic potential. Their unique structural framework featuring both benzimidazole and thiol functionalities allows for extensive chemical modification and broad-spectrum biological activities, including antimicrobial, anticancer, anti-inflammatory, antiviral, and antioxidant properties. Recent advances in synthesis strategies, including green and efficient routes, have improved the accessibility of various derivatives. Usually, traditional methods are used on an industrial scale for synthesis of these compounds, but nanotechnology opened the doors towards environmental-friendly synthesis and improved the delivery of synthesized compounds to desired biological targets. As they have potent antiviral and anti-inflammatory properties, molecular docking studies of these compounds predict that these molecules can be proved effective against severe inflammatory diseases and HIV (human immunodeficiency virus).Moreover, the integration of molecular docking and in silico screening has greatly enhanced the understanding of structure activity relationships (SARs), enabling the rational design of more potent and selective therapeutic candidates. The combined insights from synthetic chemistry and computational modeling support the growing significance of 2-mercaptobenzimidazoles as lead scaffolds in drug discovery. However, further in vivo validation, pharmacokinetic profiling, and toxicity assessments are essential to translate these promising compounds into clinically viable drugs. Overall, this review highlights the versatility and biomedical relevance of 2-mercaptobenzimidazoles and provides a foundation for future research in medicinal chemistry, especially in the context of rational drug design and targeted therapeutic development. So further research on pharmacokinetic and structural properties of 2-mercaptobenzimidazole derivatives can provide novel therapeutic drug candidates with superior biological activities than standard drugs and treatment of some unmet medical needs.

REFERENCES

Abbas, A., Hussain, S., Asad, M., Khatoon, A., Raza, A.

and Xu, S. Pickering emulsion-derived nano/microreactors for unconventional interfacial catalysis: state-of-the-art advances and perspectives in green reactions. Green Chemistry, 26(6). 2024, pp.3039-3057.

Abd El-Hameed, R.H., Mahgoub, S., El-Shanbaky, H.M., Mohamed, M.S. and Ali, S.A. Utility of novel 2-furanones in synthesis of other heterocyclic compounds having anti-inflammatory activity with dual COX2/LOX inhibition. Journal of Enzyme Inhibition and Medicinal Chemistry, 36(1).2021, pp.977-986.

Ahamed, M.R., Narren, S.F. and Sadiq, A.S. Synthesis of 2-mercaptobenzimidazole and some of its derivatives. Al-Nahrain Journal of Science, 16(2). 2013, pp.77-83.

Ali Kharl, H.A., Nadeem, H., Khan, A.U., Mehreen, A., Afzal, A., Mehdi, S.M.Q., Adamova, U. and Fozilova, S. Synthesis, Molecular Docking, and Investigation of Enzyme Inhibition Activities of Benzimidazole-Pyrazole Hybrids. J. Vis. 2025 Exp(1).

Ali, M., Ali, S., Khan, M., Rashid, U., Ahmad, M., Khan, A., ... & Latif, A. Synthesis, biological activities, and molecular docking studies of 2-mercaptobenzimidazole based derivatives. Bioorganic chemistry. 2018, 80, 472-479.

Aras, A. Synthesis of two novel mercaptobenzimidazole derivative Schiff bases and their in vitro antioxidant and enzyme inhibitory effects. Journal of the Indian Chemical Society, 99(7). 2022, p.100553.

Ata, A., Khan, K.M., Lateef, M., Salar, U., Anwar, A., Wadood, A., Ur Rehman, A., Hameed, S., Zafar, F., Taha, M. and Perveen, S. Evaluation of S-substituted-2-mercaptobenzimidazole analogs for urease inhibitory and DPPH radical scavenging potential: synthesis, bioactivity, and molecular docking study. Journal of the Iranian Chemical Society, 20(1). 2023, pp.175-191.

Badgujar, N.D., Dsouza, M.D., Nagargoje, G.R., Kadam, P.D., Momin, K.I., Bondge, A.S., Panchgalle, S.P. and More, V.S. Recent advances in medicinal chemistry with benzothiazole-based compounds: An in-depth review. Journal of Chemical Reviews, 6(2). 2024, pp.202-236.

Bell, E.L., Finnigan, W., France, S.P., Green, A.P., Hayes, M.A., Hepworth, L.J., Lovelock, S.L., Niikura, H., Osuna, S., Romero, E. and Ryan, K.S. Biocatalysis. Nature Reviews Methods Primers, 1(1). 2021, p.46.

Bin Rashid, A. Utilization of nanotechnology and nanomaterials in biodiesel production and property enhancement. Journal of nanomaterials, 2023(1). 2023, p.7054045.

Brishty, S.R., Hossain, M.J., Khandaker, M.U., Faruque, M.R.I., Osman, H. and Rahman, S.A., 2021. A comprehensive account on recent progress in pharmacological activities of benzimidazole derivatives. Frontiers in pharmacology, 12, p.762807.

Camacho, J., Barazarte, A., Gamboa, N., Rodrigues, J., Rojas, R., Vaisberg, A., Gilman, R. and Charris, J. Synthesis and biological evaluation of benzimidazole-5-carbohydrazide derivatives as antimalarial, cytotoxic and antitubercular agents. Bioorganic & medicinal chemistry, 19(6). 2011, pp.2023-2029.

Chung, N.T., Dung, V.C. and Duc, D.X. Recent achievements in the synthesis of benzimidazole derivatives. RSC advances, 13(46). 2023, pp.32734-32771.

Curieses Andrés, C.M., Pérez de Lastra, J.M., Andrés Juan, C., Plou Gasca, F.J. and Pérez-Lebeña, E. Chemistry of Hydrogen Sulfide—Pathological and Physiological Functions in Mammalian Cells., 2023.

Dad, O., Umar, M.N., Khan, M.F.F. and Rome, S., 2023. Design and Synthesis of Oxadiazole Derivatives Based on 2-Mercaptobenzimidazole. International Journal of Novel Research and Development, IJNRD, 8(2).

de Sousa Couto, R.A. and Guerra, M.V.N.Q.G., 2021. Development and Application of an Innovative Disposable Sensor for Novel Psychoactive Substances Based on Electrochemistry (Doctoral dissertation, Universidade do Porto (Portugal)).

Diana, G.D., Volkots, D.L., Nitz, T.J., Bailey, T.R., Long, M.A., Vescio, N., Aldous, S., Pevear, D.C. and Dutko, F.J. Oxadiazoles as ester bioisosteric replacements in compounds related to disoxaril. Antirhinovirus activity. Journal of medicinal chemistry, 37(15). 1994, pp.2421-2436.

Direito, R., Rocha, J., Sepodes, B. and Eduardo-Figueira, M. Phenolic compounds impact on rheumatoid arthritis, inflammatory bowel disease and

microbiota modulation. Pharmaceutics. 2021, 13(2), p.145.

Ebenso, E.E., Verma, C., Olasunkanmi, L.O., Akpan, E.D., Verma, D.K., Lgaz, H., Guo, L., Kaya, S. and Quraishi, M.A. Molecular modelling of compounds used for corrosion inhibition studies: a review. Physical Chemistry Chemical Physics, 23(36). 2021, pp.19987-20027.

El Alami, A., Sdassi, H., & Bouzikri, S. (2024). Review of synthesis process of benzimidazole-heterocycle hybrid compounds. Synthetic Communications, 54(8), 613-635.

Enumula, S., Pangal, A., Gazge, M., Shaikh, J.A. and Ahmed, K., 2014. Diverse pharmacological aspects of benzimidazole derivatives: A review. Research Journal of Chemical Sciences, ISSN, 2231, p.606X.

Ezike, T.C., Okpala, U.S., Onoja, U.L., Nwike, C.P., Ezeako, E.C., Okpara, O.J., Okoroafor, C.C., Eze, S.C., Kalu, O.L., Odoh, E.C. and Nwadike, U.G., 2023. Advances in drug delivery systems, challenges and future directions. Heliyon, 9(6).

Francesconi, V., Cichero, E., Schenone, S., Naesens, L. and Tonelli, M. Synthesis and biological evaluation of novel (thio) semicarbazone-based benzimidazoles as antiviral agents against human respiratory viruses. Molecules, 25(7). 2020, p.1487.

García-Valverde, M. and Torroba, T. Sulfur-nitrogen heterocycles. Molecules, 10(2). 2005 pp.318-320.

Gigante, B., Roseiro, J.C. and Marcelo-Curto, M.J. Antimicrobial activity of diterpene resin acid derivatives. Journal of microbiological methods, 35(3). 1999, pp.201-206.

Gousias, K., Theocharous, T. and Simon, M. Mechanisms of cell cycle arrest and apoptosis in glioblastoma. Biomedicines, 10(3). 2022, p.564.

Gutierrez-Hernandez, A., Estrada-Soto, S., Martinez-Conde, C., Gaona-Tovar, E., Medina-Franco, J.L., Hernandez-Nunez, E., Hidalgo-Figueroa, S., Castro-Moreno, P., Ibarra-Barajas, M. and Navarrete-Vazquez, G., 2024. Synthesis, biosimulation and pharmacological evaluation of benzimidazole derivatives with antihypertensive multitarget effect. Bioorganic & Medicinal Chemistry Letters, 110, p.129879.

Gutierréz-Hernández, A., Galván-Ciprés, Y., Domínguez-Mendoza, E.A., Aguirre-Vidal, Y., Estrada-Soto, S., Almanza-Pérez, J.C. and Navarrete-Vázquez, G., 2019. Design, Synthesis, Antihyperglycemic Studies, and Docking Simulations of Benzimidazole-Thiazolidinedione Hybrids. Journal of Chemistry, 2019(1), p.1650145.

Hassan, A. and Khan, N. A novel acyl hydrazone Schiffs bases of benzimidazole-2-thiol. J Anal Pharm Res, 10(4). 2021, p.151155.

Heckenlively, C., 2022. Impact of a Mentorship Training Course on the Prevalence of Burnout in Nurse Leaders Working in a Regional Healthcare System. Available at SSRN 4190536.

Hosamani, K.M. and Shingalapur, R.V. Synthesis of 2-mercaptobenzimidazole derivatives as potential anti-microbial and cytotoxic agents. Archiv der Pharmazie, 344(5). 2011, pp.311-319.

Huang, H., Alvarez-Hernandez, J.L., Hazari, N., Mercado, B.Q. and Uehling, M.R. Effect of 6, 6′-Substituents on bipyridine-ligated Ni catalysts for cross-electrophile coupling. ACS catalysis, 14(9). 2024, pp.6897-6914.

Jakeria, M.R., Toh, R.J., Chen, X.B. and Cole, I.S. Evolution and stability of 2-mercaptobenzimidazole inhibitor film upon Al alloy 6061. Journal of Applied Electrochemistry, 52(6). 2022, pp.1021-1044.

Joule, J.A. Heterocyclic chemistry. 2022, CRC Press.

Kulkarni, K.M., Jadhav, S.A., Patil, P.B., Dhole, V.R. and Patil, S.S. Synthesis and antimicrobial screening of 2-mercaptobenzimidazole derivatives. Der Pharma Chemica, 8(4). 2016, pp.1-5.

Kumari, L., Choudhari, Y., Patel, P., Gupta, G.D., Singh, D., Rosenholm, J.M., Bansal, K.K. and Kurmi, B.D. Advancement in solubilization approaches: A step towards bioavailability enhancement of poorly soluble drugs. Life, 13(5). 2023, p.1099.

Kurishiba, Y., Oguri, A., Yamamoto, D., Homma, C., Goseki, R. and Ishizone, T. Living Anionic Polymerization of 5-Substituted 2-Vinylthiophenes. Macromolecules, 57(17). 2024, pp.8601-8609.

Langsdorf, A., Volkmar, M., Holtmann, D. and Ulber, R. Material utilization of green waste: a review on potential valorization methods. Bioresources and Bioprocessing, 8(1). 2021, pp.1-26.

Lee, J., Park, H.S., Jung, H.J., Park, Y.J., Kang, M.K., Kim, H.J., Yoon, D., Ullah, S., Kang, D., Park, Y. and Chun, P. Anti-Browning Effect of 2-Mercaptobenzo [d] imidazole Analogs with Antioxidant Activity on Freshly-Cut Apple Slices and Their Highly Potent Tyrosinase Inhibitory

Activity. Antioxidants, 12(10). 2023, p.1814.

Lehnert, N., Kim, E., Dong, H.T., Harland, J.B., Hunt, A.P., Manickas, E.C., Oakley, K.M., Pham, J., Reed, G.C. and Alfaro, V.S. The biologically relevant coordination chemistry of iron and nitric oxide: electronic structure and reactivity. Chemical reviews, 121(24). 2021, pp.14682-14905.

Lgaz, H. and Lee, H.S., 2021. The effect of heterocyclization of 2-mercaptobenzimidazole on its strength of coordination to iron: A dispersion-corrected DFT study. Applied Surface Science, 567, p.150819.

Martínez-Pascual, R., Valera-Zaragoza, M., Fernández-Bolaños, J.G. and López, Ó. Exploring the Chemistry and Applications of Thio-, Seleno-, and Tellurosugars. Molecules, 30(9). 2025, p.2053.

Mavvaji, M., Muhammed, M.T., Onem, E., Aslan, H.G., Alhag, S.K. and Akkoc, S. Synthesis, Cytotoxic Activity, Antiquorum Sensing Effect, Docking and Md Simulation of Novel 1, 3-Disubstituted 2-Mercapto-1H-Benzo [D] Imidazolium Chlorides. Journal of Biochemical and Molecular Toxicology, 39(4). 2025, p.e70248.

Mlostoń, G., Celeda, M., Kowalczyk, M., Oliver, G.A. and Werz, D.B. Ring-Opening Reactions of Donor-Acceptor Cyclopropanes with Enolizable 5-Mercapto-1H-tetrazoles. European Journal of Organic Chemistry, 27(46). 2024, p.e202400831.

Mobashar, A., Akbar, Z., Barkat, K., Hussain, K., Nadeem, H., Kharl, H.A.A. and Basri, M.A., 2025. Evaluation of anti-inflammatory and anti-arthritic activities of Benzimidazole derivative 2-((1H-benzo [d] imiadazol-2-yl) thio)-1-3, 5-diphenyl-1h-pyrazol-1-yl) ethanone. Atlantic Journal of Life Sciences, 2025(1).

Mohamed, M.F., Marzouk, A.A., Nafady, A., El-Gamal, D.A., Allam, R.M., Abuo-Rahma, G.E.D.A., El Subbagh, H.I. and Moustafa, A.H., 2020. Design, synthesis and molecular modeling of novel aryl carboximidamides and 3-aryl-1, 2, 4-oxadiazoles derived from indomethacin as potent anti-inflammatory iNOS/PGE2 inhibitors. Bioorganic chemistry, 105, p.104439.

Mohapatra, R.K., Mahal, A., Ansari, A., Kumar, M., Guru, J.P., Sarangi, A.K., Abdou, A., Mishra, S., Aljeldah, M., AlShehail, B.M. and Alissa, M. Comparison of the binding energies of approved mpox drugs and phytochemicals through molecular docking, molecular dynamics simulation, and ADMET studies: An in silico approach. Journal of Biosafety and Biosecurity, 5(3). 2023, pp.118-132.

Moudgil, K.D. and Venkatesha, S.H. The anti-inflammatory and immunomodulatory activities of natural products to control autoimmune inflammation. International journal of molecular sciences, 24(1). 2022, p.95.

Negi, D.S., Kumar, G., Singh, M. and Singh, N., 2017. Antibacterial activity of benzimidazole derivatives: A mini review. Research & Reviews: Journal of Chemistry, 6, pp.18-28.

Ngoepe, M.P. and Clayton, H.S. Metal complexes as DNA synthesis and/or repair inhibitors: anticancer and antimicrobial agents. Pharmaceutical Fronts, 3(04). 2021, pp.e164-e182.

Ni, X., Luo, X., Jiang, X., Chen, W. and Bai, R. Small-Molecule Tyrosinase Inhibitors for Treatment of Hyperpigmentation. Molecules, 30(4). 2025, p.788.

Obaid, R.J. New benzimidazole derivatives: Design, synthesis, docking, and biological evaluation. Arabian Journal of Chemistry, 16(2). 2023, p.104505.

Osuofa, J.O., 2023. Protein A and Multimodal Anion-Exchange Membrane Adsorbers for Downstream Purification of Therapeutic Biomolecules (Doctoral dissertation, Clemson University).

Parthiban, D., Kuppusamy, M.R., Vanitha, C., Gomathi, A. and Suraksha, D., 2024. Mangrove tree aerial root extract mediated green synthesis of Ag/Fe3O4/GO nanocomposite and its application as a catalyst for one pot synthesis of 7-phenyl-6H, 7H-benzo [4, 5] imidazo [2, 1-b] chromeno [4, 3-d][1, 3] thiazin-6-one derivatives.

Pathak, D., Siddiqui, N., Bhrigu, B., Ahsan, W. and Alam, M.S. Benzimidazoles: a new profile of biological activities. Der Pharmacia Lettre, 2(2). 2010, pp.27-34.

Poonam, D., Mohammad, S. and Prasad, D.N. Recent overview on synthesis of 2-mercaptobenzimidazole derivatives and its activities. Journal of Drug Delivery & Therapeutics, 12(1). 2022, pp.203-207.

Porto, R.S., de Lima Costa, L.F. and Porto, V.A., 2022. Identification of Synthetic 2-Mercaptobenzimidazole Derivatives as Inhibitors of Spike Protein of SARS-CoV-2 by Virtual Screening.

Qamar, W., & Alkheraije, K. A. (2023). Anthelmintic Resistance in Haemonchus contortus of Sheep and Goats from Asia--A Review of In Vitro and In

Vivo Studies. Pakistan Veterinary Journal, 43(3).

Romine, J.L., St. Laurent, D.R., Leet, J.E., Martin, S.W., Serrano-Wu, M.H., Yang, F., Gao, M., O'Boyle, D.R., Lemm, J.A., Sun, J.H. and Nower, P.T. Inhibitors of HCV NS5A: from iminothiazolidinones to symmetrical stilbenes. ACS Medicinal Chemistry Letters, 2(3). 2011, pp.224-229.

Rosales Hernández, M.C., Olvera-Valdez, M., Velazquez Toledano, J., Mendieta Wejebe, J.E., Fragoso Morales, L.G. and Cruz, A. Exploring the Benzazoles Derivatives as Pharmacophores for AChE, BACE1, and as Anti-Aβ Aggregation to Find Multitarget Compounds against Alzheimer's Disease. Molecules, 29(19). 2024, p.4780.

Sahu, B.C., 2023. Organic corrosion inhibitors. In Introduction to corrosion-Basics and advances. IntechOpen.

Santos, A.C., Monteiro, L.P., Gomes, A.C., Martel, F., Santos, T.M. and Ferreira, B.J.L. NSAID-based coordination compounds for biomedical applications: recent advances and developments. International journal of molecular sciences, 23(5). 2022, p.2855.

Satija, G., Sharma, B., Madan, A., Iqubal, A., Shaquiquzzaman, M., Akhter, M., Parvez, S., Khan, M.A. and Alam, M.M. Benzimidazole based derivatives as anticancer agents: Structure activity relationship analysis for various targets. Journal of Heterocyclic Chemistry, 59(1). 2022, pp.22-66.

Seo, H., Prosser, K.E., Kalaj, M., Karges, J., Dick, B.L. and Cohen, S.M. Evaluating Metal–Ligand Interactions of Metal-Binding Isosteres Using Model Complexes. Inorganic chemistry, 60(22). 2021, pp.17161-17172.

Sethi, P., Bansal, Y. and Bansal, G. Synthesis and PASS-assisted evaluation of coumarin–benzimidazole derivatives as potential anti-inflammatory and anthelmintic agents. Medicinal chemistry research, 27(1). 2018, pp.61-71.

Shaharyar, M. and Mazumder, A., 2017. Benzimidazoles: A biologically active compounds. Arabian Journal of Chemistry, 10, pp.S157-S173.

Sharaf, M., Moustafa, A.H., Obaid, R.J., Alzahrani, A.Y., Aboelez, M.O., Elkady, H., Alenazi, N.A., Mohamed, M.A., Al-Fahemi, J.H., Moussa, Z. and Omran, O.A., 2024. Design, synthesis, molecular docking, ADMET studies, and biological activity evaluation of new 2-({[3-aryl-1, 2, 4-oxadiazol-5-yl) methyl] thio}-1H-benzimidazoles and 6-amino-6-aryl-5, 6-dihydro [1, 6, 2, 4] oxathiadiazocino [4, 5-a] benzimidazol-3 (2H)-ones. Journal of Molecular Structure, 1295, p.136708.

Sheikha, G.A., Bkhaitan, M.M., Kalloush, H., Hamadneh, L., Khalaf, R.A., Al-Qirim, T. and Al-Hiari, Y. Synthesis of novel benzimidazole-2-carboxamide derivatives and in vivo antihyperlipidemic activity evaluation. Chemical and Pharmaceutical Bulletin, 66(4). 2018, pp.423-426.

Shingalapur, R.V., Hosamani, K.M., Keri, R.S. and Hugar, M.H. Derivatives of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. European journal of medicinal chemistry, 45(5). 2010, pp.1753-1759.

Si, W., Zhang, T., Li, Y., She, D., Pan, W., Gao, Z., Ning, J. and Mei, X. Synthesis and biological activity of novel benzimidazole derivatives as potential antifungal agents. Journal of Pesticide Science, 41(1). 2015, pp.15-19.

Tahlan, S., Kumar, S. and Narasimhan, B. Antimicrobial potential of 1 H-benzo [d] imidazole scaffold: a review. BMC chemistry, 13(1). 2019, p.18.

Tahlan, S., Narasimhan, B., Lim, S.M., Ramasamy, K., Mani, V. and Shah, S.A. Design, synthesis, SAR study, antimicrobial and anticancer evaluation of novel 2-mercaptobenzimidazole azomethine derivatives. Mini Reviews in Medicinal Chemistry, 20(15). 2020, pp.1559-1571.

Tejaswini, D.P., 2021. Design, in silico analysis, synthesis, and evaluation of novel benzofused nitrogen-containing heterocyclic N-substituted mercaptobenzimidazole derivatives as potential antimicrobial agent. International Journal of Green Pharmacy (IJGP), 15(3).

Tonelli, M., Gabriele, E., Piazza, F., Basilico, N., Parapini, S., Tasso, B., Loddo, R., Sparatore, F. and Sparatore, A. Benzimidazole derivatives endowed with potent antileishmanial activity. Journal of Enzyme Inhibition and Medicinal Chemistry, 33(1). 2018, pp.210-226.

Vaishnav, Y., Verma, S. and Mishra, A. The Role of Structure-Activity Relationship (SAR) In Drug Discovery. Indian Journal of Pharmaceutical Chemistry and Analytical Techniques (IJPCAT). 2025, pp.67-83.

Vidal, R., Alberola-Borràs, J.A., Habisreutinger, S.N., Gimeno-Molina, J.L., Moore, D.T., Schloemer,

T.H., Mora-Seró, I., Berry, J.J. and Luther, J.M. Assessing health and environmental impacts of solvents for producing perovskite solar cells. Nature Sustainability, 4(3). 2021, pp.277-285.

Wang, M.L. and Liu, B.L. Synthesis of 2-mercaptobenzimidazole from the reaction of o-phenylene diamine and carbon disulfide in the presence of potassium hydroxide. Journal of the Chinese Institute of Chemical Engineers, 38(2). 2007, pp.161-167.

Wright, J.B. The chemistry of the benzimidazoles. Chemical reviews, 48(3). 1951, pp.397-541.

Yaseen, G. and Sudhakar, J. Design, synthesis and antimicrobial activity of 2-mercaptobenzimidazole derivatives. International Journal of Pharma and Bio Sciences, 1(4). 2010, pp.281-286.

Ying, S., Guan, Z., Ofoegbu, P.C., Clubb, P., Rico, C., He, F. and Hong, J., 2022. Green synthesis of nanoparticles: Current developments and limitations. Environmental technology & innovation, 26, p.102336.

Youssif, B.G., Mohamed, M.F., Al-Sanea, M.M., Moustafa, A.H., Abdelhamid, A.A. and Gomaa, H.A., 2019. Novel aryl carboximidamide and 3-aryl-1, 2, 4-oxadiazole analogues of naproxen as dual selective COX-2/15-LOX inhibitors: Design, synthesis and docking studies. Bioorganic chemistry, 85, pp.577-584.

Zhang, Z. and Fang, H., 2024. Control of sulfur-containing hydrogen bonding interaction and novel thiol-type ESIPT behavior by different functional groups: A TD-DFT study. Journal of Molecular Structure, 1303, p.137546.

Zhu, W.R., Su, Q., Deng, X.Y., Liu, J.S., Zhong, T., Meng, S.S., Yi, J.T., Weng, J. and Lu, G. Organocatalytic enantioselective SN 1-type dehydrative nucleophilic substitution: access to bis (indolyl) methanes bearing quaternary carbon stereocenters. Chemical Science, 13(1). 2022, pp.170-177.