INTERNATIONAL JOURNAL OF ADVANCE RESEARCH, IDEAS AND INNOVATIONS IN TECHNOLOGY

ISSN: 2454-132X
Impact Factor: 6.078
(Volume 11, Issue 3 - V11I3-1182)
Available online at: https://www.ijariit.com

Synthesis of Newer Benzotriazol Derivatives for Antibacterial and Antioxidant Potential

Sheevendra Singh Sibbu
sheevendrasingh2@gmail.com
Oriental College of Pharmacy, Bhopal, Madhya Pradesh

ABSTRACT

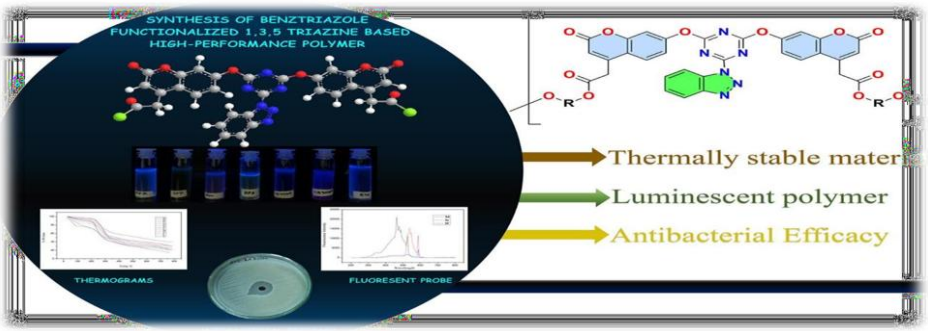
In response to pandemics and microbial resistance, novel heterocyclic compound spotent biological activity are needed. A series of (E)-2-(2-((5-(1H-benzo[d][1,2,3]triazol-1-yl)-3- methyl-1-phenyl-1
H-pyrazol-4-methylene(hydrazinyl)-4-(aryl) thiazole derivatives were synthesized via a three- component reaction involving pyrazole-4-carbaldehyde, thio semicarbazide, and substituted phenacyl bromides for antibacterial and antifungal study. Recent health research focuses on multifunctional compounds that interact with multiple biological targets, streamlining multidrug therapies and enhancing patient adherence. This study aimed to develop novel multifunctional chemical entities incorporating a benzothiazole nucleus, a structure widely recognized for its diverse biological activities. Benzothiazole has gained attention due to its role as a scaffold in various multifunctional drugs, making it a promising candidate for innovative therapeutic applications that improve treatment efficacy and simplify pharmaceutical regimens.

To combat the growing threat of multi-resistant bacteria, scientists synthesized four benzotriazole and three benzimidazole derivatives using two distinct methods, recognizing the vital role of heterocyclic compounds in medicinal chemistry. These newly developed compounds were then docked with two protein targets, DNA gyrase (PDB ID: 2XCT and 3ILW), to evaluate their binding potential. The effectiveness of these derivatives was compared with standard antibacterial drugs, sparfloxacin and ciprofloxacin. This study aims to identify promising candidates for overcoming bacterial resistance, providing valuable insights into new drug development strategies targeting resistant bacterial strains through advanced molecular docking techniques.

Antimicrobial resistance (AMR) is a global health challenge, leading to higher mortality, morbidity, and treatment costs. The World Health Organization (WHO) reported in 2019 that only six out of 32 antibiotics in clinical trials featured innovative novel moieties, while the rest were based on existing compounds. This highlights the urgent need for new antibiotic development to combat resistance. Among promising candidates, benzothiazole derivatives stand out due to their broad spectrum of biological activities and significant medicinal applications. Their potential in drug discovery has gained attention for addressing resistance issues, reinforcing the necessity of developing novel compounds. Advancing research in benzothiazole derivatives may pave the way for effective antimicrobial agents to tackle evolving resistance problems and improve global healthcare outcomes.

Keywords: *Benzothiazole Derivatives, Antimicrobial Resistance (AMR), Heterocyclic Compounds, Molecular Docking, Multifunctional Drug Development*

GRAPHICAL ABSTRACT



INTRODUCTION

Multifactorial diseases pose significant challenges in medicinal chemistry due to their complex causes, ranging from environmental influences to genetic mutations. These conditions, which include Alzheimer's, atherosclerosis, CNS disorders, rheumatoid arthritis, asthma, and cancer, affect multiple biological targets, making treatment difficult.

Traditional approaches relying on single-drug therapies targeting specific molecular sites have proven inefficient and often lead to drug resistance. As a result, combination therapies—where multiple drugs from different therapeutic classes are used—have become the norm. However, these "drug cocktails" come with challenges, such as drug–drug interactions, varying pharmacokinetics, toxicity, bioavailability concerns, and high costs, prompting the search for better alternatives.

A promising approach is the development of multifunctional drugs—single molecules capable of acting on multiple biological targets simultaneously. These drugs aim to reduce side effects, improve therapeutic efficacy, and enhance patient adherence by offering a more streamlined treatment with fewer complications.

Skin cancer, a prime example of a multifactorial disease, remains one of the most prevalent malignancies worldwide, with over 2 million new cases diagnosed annually. Given that one- third of all cancer diagnoses involve skin cancer, its incidence continues to rise. While UV exposure, sunburn history, phenotype, and genetics remain primary risk factors, environmental issues, such as ozone layer depletion, exacerbate the problem.

Given these challenges, research focuses on innovative therapeutic solutions that can simultaneously target multiple pathways while improving safety and effectiveness in treatment. The ultimate goal is to develop more efficient, less toxic, and highly accessible therapies to combat complex diseases like skin cancer.

Excessive or improper exposure to UV rays can lead to oxidative stress, resulting from an accumulation of reactive oxygen species (ROS) that exceed the body's antioxidant defenses. This imbalance is considered a major factor in both melanoma and non-melanoma skin cancers. Studies have shown a notable increase in antioxidant enzymes—such as copper-zinc superoxide dismutase, manganese superoxide dismutase, and catalase—in human melanoma biopsies compared to surrounding non-cancerous tissue.

While existing sunscreens are widely recognized for their ability to prevent certain skin cancers, they often fail to counteract the side effects of UV exposure, particularly the free radical production triggered by UVA rays. There remains a challenge in formulating sunscreen filters that not only shield against UVA and UVB radiation but also neutralize the formation of ROS and other damaging free radicals.

Type 2 diabetes mellitus (T2DM) is a widespread metabolic and endocrine disorder, affecting around 370 million individuals globally. It results from insulin resistance or insufficient insulin secretion and is classified as non-insulin-dependent diabetes. Beyond elevated blood glucose levels, T2DM can lead to serious complications such as cardiovascular disease, hyperlipidemia, and hyperuricemia, and, in severe cases, may even result in death.

To manage diabetes, various medications have been developed, including inhibitors of α- amylase and α-glucosidase, such as acarbose. These enzymes play a critical role in regulating blood glucose levels by breaking down starch into glucose. Inhibitors of α-amylase and α- glucosidase slow this process, thereby reducing glucose absorption and helping to control post- meal blood sugar levels in diabetic patients. By limiting the rapid rise in blood glucose after meals, these inhibitors contribute to improved metabolic control, lowering the risk of long-term complications associated with diabetes. As research continues, advancements in therapeutic approaches aim to provide better management options, enhancing quality of life for those affected by this chronic condition.

Molecular hybridization is an emerging strategy in medicinal chemistry and drug development, closely resembling conventional combination therapy. By merging two or more bioactive pharmacophores, this approach allows the creation of molecular frameworks with improved biological activity. Among various hybrid structures, clubbed azoles have gained significant interest as promising antibacterial lead compounds due to their diverse structures and notable biological properties.

Owing to their potential antimicrobial effects, heterocyclic frameworks such as pyrazole- triazole, thiazole-pyrazole, and thiazole-triazole have garnered considerable attention. The pyrazole-triazole hybrid exhibits antifungal, antimycobacterial, and anticancer properties. Similarly, the thiazole-pyrazole combination has demonstrated antibacterial, anti- inflammatory, and antitubercular activities. Meanwhile, the thiazolyl-triazole hybrid has shown antitumor, anti-inflammatory, and anticonvulsant effects. These findings highlight the therapeutic potential of molecular hybridization in drug development, paving the way for further exploration of structurally diverse compounds with enhanced pharmacological benefits.

Benzotriazole derivatives marks a significant milestone in medicinal chemistry. These newly developed compounds have demonstrated notable bioactivity against various organisms, indicating their potential as effective antimicrobial agents. The molecular docking studies further reinforce this potential by revealing that the synthesized compounds possess relatively low binding energy when compared to the standard drug used in treatment, as well as previously reported compounds. This lower binding energy suggests a stronger and more stable interaction with the target protein, which is crucial for effective drug action.

A strong binding affinity to the protein's active site enhances the efficacy of these compounds, allowing them to disrupt bacterial pathways more efficiently. This property is particularly valuable in addressing the growing challenge of multidrug-resistant bacteria, which have become a major public health concern. With many bacterial strains developing resistance to existing antibiotics, novel therapeutic strategies are urgently required. The promising interaction characteristics of benzotriazole derivatives make them viable candidates for further investigation.

Additionally, their structural properties contribute to their potential pharmacological benefits. By optimizing their design and functional groups, these compounds may offer improved bioavailability and reduced toxicity compared to conventional treatments. This not only increases their therapeutic potential but also minimizes side effects, making them more suitable for clinical applications.

The findings of this research highlight the importance of continuous exploration and innovation in drug development. While the preliminary data suggest strong antimicrobial activity, further in-depth studies, including in vitro and in vivo assessments, are essential to fully understand their mechanisms and validate their effectiveness. Investigating their pharmacokinetics, toxicity profiles, and possible side effects will be crucial in determining their viability as new drug candidates.

Moreover, expanding the scope of this research by synthesizing additional benzotriazole-based derivatives could provide a broader range of bioactive compounds, enhancing the possibility of discovering a highly potent antimicrobial agent. Computational modeling and advanced molecular docking techniques could further refine their development, allowing researchers to design compounds with optimized properties.

In conclusion, the successful synthesis and promising bioactivity of benzotriazole derivatives underscore their potential in combating multidrug-resistant bacteria. The lower binding energy observed in docking studies suggests enhanced protein interaction, which may translate into increased therapeutic efficacy. With further research and refinement, these compounds could pave the way for novel antimicrobial drugs, addressing the urgent need for innovative solutions in bacterial resistance management.

The discovery of free radicals in biological materials was first reported approximately 70 years ago, leading to extensive scientific research and the development of free radical science. Today, free radicals are recognized as by-products of enzymatic reactions occurring within organisms. They are generated through endogenous processes such as cellular respiration, phagocytosis, biosynthesis, catalysis, and biotransformation. In addition to internal production, they can also arise from external sources, including radiation, sunlight, exposure to heavy metals, and interactions with bacteria, fungi, protozoa, and viruses.

Excessive generation of free radicals disrupts physiological balance, contributing to oxidative stress (OS) and accelerating aging processes. Furthermore, an overabundance of free radicals is implicated in the development of numerous diseases, including cancer, rheumatoid arthritis, neurodegenerative disorders such as Alzheimer's and Parkinson's, pulmonary diseases, atherosclerosis, and DNA damage. As a result, maintaining equilibrium between free radical formation and neutralization is vital for preserving overall health.

Compounds with antioxidant properties play a crucial role in counteracting the harmful effects of free radicals. Natural antioxidants, including flavonoids, carotenoids, and vitamins, aid in stabilizing reactive molecules, preventing cellular damage, and reducing disease risk. Alongside naturally occurring antioxidants, synthetic antioxidants have garnered significant scientific interest due to their potential therapeutic applications.

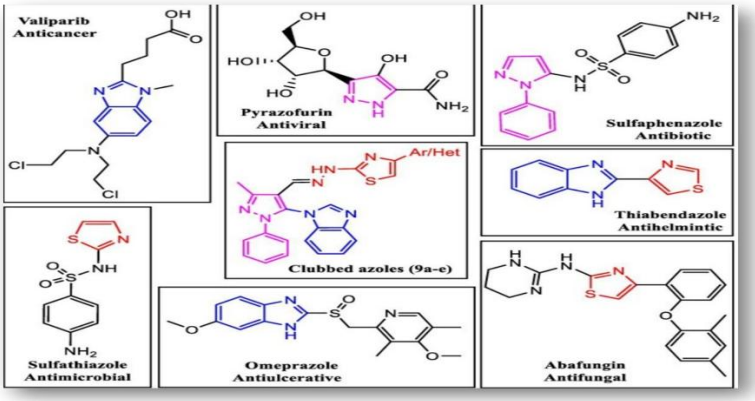
Among synthetic antioxidant compounds, 1,2,4-triazoles and their derivatives stand out for their promising biological activities. These heterocyclic compounds, characterized by three nitrogen atoms in their structure, have been studied extensively in medicinal chemistry. They exhibit a broad spectrum of biological functions, making them valuable in drug development. Over the years, researchers have explored the pharmacological properties of 1,2,4-triazoles, and some derivatives have already been incorporated into pharmaceutical treatments.

Given their significant antioxidant potential, discovering and synthesizing novel 1,2,4-triazole- based compounds has become an important objective in medicinal chemistry. The development of synthetic antioxidants within this class may provide new opportunities for combating oxidative stress-related diseases. By further investigating their molecular structures and optimizing their bioactivity, researchers aim to enhance their effectiveness in neutralizing free radicals and protecting against cellular damage.

In conclusion, free radicals play a critical role in various biological processes, yet their excessive accumulation can contribute to the progression of aging and disease. Maintaining a balance between free radical production and antioxidant defense mechanisms is essential for sustaining health. While natural antioxidants provide protection, synthetic compounds such as 1,2,4-triazoles offer promising therapeutic potential. Ongoing research continues to explore their efficacy, with the goal of developing advanced antioxidant agents that can effectively mitigate oxidative stress and support disease prevention efforts.

Natural polyphenols, a subgroup of flavonoids found in various plants, have been reported to offer notable skin-protective benefits, including antioxidant, anti-inflammatory, and anti- carcinogenic properties. Additionally, their molecular structure—characterized by hydroxyl and aromatic groups—enables them to absorb UV rays across a broad wavelength spectrum, making them mild UV filters. Emerging research suggests that polyphenols may effectively protect the skin from UV radiation damage. Both topical application and dietary consumption of polyphenols have been linked to reduced UVB-induced skin inflammation and sunburn.

MATERIAL & METHODS



Chemicals and instrumentations

The chemicals (Make-Sigma-Aldrich and Avra synthesis) were purchased from Virion Enterprizes, Mumbai. Merck TLC Plates, Silica Gel 60 F254 were used to monitor the reaction. NMR experiments were performed on 400 MHz FT-NMR Spectrometer, Model: JNM-ECZ 400S (SAIF, Dharwad, India and FTIR was recorded on Spectrometer 4600, JASCO (Jaysingpur College, Maharashtra, India)

Synthesis methods

The synthesis of 5-(1H-benzoimidazol-1-yl)-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde and 1H-benzoimidazol-1-yl)-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazineyl)-4- (aryl) thiazole derivatives, derivatives is depicted in scheme 1& scheme 2 respectively.

Procedure for the synthesis of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde

As per previously reported method compounds 3 and 4 were synthesized. The reaction of ethyl acetoacetate 0.2 mol) and phenyl hydrazene 0.2 mol) in 30 mL ethanol at 60–70 ℃ to give 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one. The DMF (0.3 mol) was cooled and to this, POCl3 (0.7 mol) was added very slowly. To this ice-cold solution 5-methyl-2-phenyl-2,4- dihydro-3H-pyrazol-3-one 0.1 mol) was added and resulting reaction mass was refluxed until formation of desired product (checked by TLC). The reaction mass was then poured onto ice- cold water. The crude product was filtered, dried and recrystallized to give white crystals of 5- chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde

Procedure for the 5-(1H-benzo[d]imidazol-1-yl)-3-methyl-1-phenyl-1H-pyrazole-4- carbaldehyde

5-(1H-benzo[d]imidazol-1-yl)-3-methyl -1-phenyl-1H-pyrazole- 4-carbaldehyde was synthesized as per previous report . In a 50 mL round bottom flask with mechanical stirrer and condenser, 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde 0.1 mol), 1H- benzo[d]imidazole 0.12 mol), and anhydrous Potassium carbonate (0.2 mol) were added in dimethyl formamide (50 mL). The reaction mixture was refluxed until formation of the product (checked by TLC). After the reaction was completed, the reaction mixture was cooled to room temperature and poured into ice cold water with continuous stirring, followed by neutralisation with 1 N HCl until pH 7 was reached. 5-(1H-benzo[d]imidazol-1-yl)-3-methyl- 1-phenyl-1H-pyrazole-4-carbaldehyde was separated, washed completely with water, dried, and recrystallized from hot ethanol.

General procedure synthesis of (E)-2-(2-((5-(1H-benzo[d]imidazol-1-yl)-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylenehydrazineyl)-4-(aryl)thiazole derivatives

An equimolar mixture 5-(1H-benzo[d]imidazol-1-yl)-3-methyl-1-phenyl-1H-pyrazole-4- carbaldehyde (6, 0.01 mol) and Thio semi carbazine 7, 0.01 mol) were taken in conical flask containing 10 mL ethanol and 2–3 drops of acetic acid were added to it. The reaction mixture was stirred at 60–70 °C for 30 min. Then, a compound (8a-e, 0.01 mol) was added over period of 5 min, and the product was precipitated immediately. The formation of the product (9a-e) was checked by TLC. The reaction mass was allowed to cool at room temperature, filtered, washed with cold ethanol and dried.

Spectral data of the synthesized compounds

5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (4)

Disk diffusion assay

The antimicrobial (antibacterial and antifungal) potential of (E)-2-(2-((5-(1H-benzotriazol-1- yl)-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazineyl)-4-aryl/heteroarylthiazoles were evaluated using Kirby-Bauer disk diffusion method. Briefly, each sterile disk (Himedia

Pvt. Ltd. Mumbai) loaded with synthesized compounds 50 µL (1 mg/ mL) and dried. Each disk was then placed on the surface of the sterile solidified Muller Hilton agar and potato dextrose agar for bacterial (E. coli (MTCC 40), B. subtilis (MTCC 441), B. megaterium (MTCC 2412), and S.aureus (MTCC3166)and

fungal A.niger (MTCC281), A.oryzae (MTCC1122) Rhizophus spp. (MTCC262), and C.albicans (MTCC 183) strains respectively and standard (1 mg/ mL). The plates were kept in refrigerator for diffusion for 1 h and then transferred to the incubator at 37 °C for 24– 48 h. After incubation, the zones around the discs were measured by the zone scale (Himedia Pvt. Ltd. Mumbai).

Resazurin microtiter assay (REMA)

The REMA plate assay was carried out as described elsewhere Briefly, 100 µL of Middle brook broth medium was dispensed in each well of a sterile flat-bottom 96-well plate, and serial twofold dilutions of each thiazole derivative were prepared directly in the plate. 50 µL of inoculums was added to each well. Sterile cold water was added to all perimeter wells to avoid evaporation during the incubation. The plate was covered, sealed with the sterile plastic bag, and incubated at 37 °C for 24 hrs. After 24 hrs of incubation, 30 µL of resazurin solution (0.01 % in sterile deionized water) was added to each well, and the plate was re-incubated for 12 h. A change in color from blue to pink indicated the growth of bacteria, and the MIC was defined as the lowest concentration of drug that prevented this change in color. The drug concentration ranges used were as follows: for newly synthesized compounds and standards 0.97–500 µg/mL.

2,2-diphenyl-1-picrylhydrazyl radical (DPPH) scavenging assa Free radical damage is one of the important aspects in the tuberculosis management. DPPH is stable reagent used in this spectrophotometric assay Briefly, the assay was performed by mixing of equal quantity of DPPH solution and the newly synthesized compounds, so that the final volume is made up to 3ml. The absorbance of incubated sample for 20 min, is measured at 517 nm using UV-Vis spectrophotometer (Shimadzu). Ascorbic acid (1

mm) and α-tocopherol (1 mm) were used as reference. Percent inhibition was calculated using following formula: %radical scavenging activity=1-T/C×100

Hydroxyl radical assay

The OH radical scavenging activity was demonstrated with Fenton Briefly, the typical reaction mixture contained 60 µL of FeCl2 (1 mm), 90 µL of 1–10 phenanthroline (1 mm), and 2.4 ml of phosphate buffer (0.2 M, pH 7.8), 150 µL of H2O2 (0.17 M) and 1.5 ml newly synthesized compounds, (1 mg/ml). The reaction was started by adding H2O2. After 5 min incubation at room temperature, the absorbance was read at 560 nm. Ascorbic acid (1 mm) and α-tocopherol (1 mm) were used as reference. % radical scavenging activity =1- T/C×100

Hemolytic activity

The hemolytic activities of the newly synthesized compounds, were determined using human red blood cells. Initially, 5 mL of human blood was collected in tubes containing 1 mg of EDTA (anti-coagulant). The erythrocytes were harvested by centrifugation for 10 min at 2000 x g at 20 °C. The collected pellet was washed thrice with Phosphate-buffered saline (PBS). Then 10 % (v/v) erythrocytes/PBS suspension was made using PBS. From this 10 % suspension, 1:10 dilution was achieved by using PBS and this was used for assay. The protocol involves addition of the 100 µl of erythrocytes suspension to each tube containing different synthesized compounds 100 µl (500 µg/ml). Triton X 100 at 0.001 N used as reference. The tubes were incubated for 1 hr. at 37 °C and centrifuged at same conditions mentioned above. From supernatant fluid, 150 µl was transferred to flat bottom 96 well microtiter plate (BD falcon, USA), and the absorbance was measured at 540 nm by using Thermo make automated micro plate reader. Percent hemolysis was calculated using following equation.

RESULT

Antioxidant-

About 70 years ago, researchers first identified the presence of free radicals in biological materials. Since then, extensive scientific studies have helped establish the field of free radical science. Today, we understand that free radicals are natural by-products of enzymatic reactions within the body. They are generated through various endogenous processes such as cellular respiration, phagocytosis, biosynthesis, catalysis, and biotransformation. Additionally, external factors—including radiation, sunlight, heavy metals, bacteria, fungi, protozoa, and viruses— can also contribute to their production.

An excessive buildup of free radicals plays a significant role in aging and oxidative stress, as well as the development of numerous diseases. These include cancer, rheumatoid arthritis, neurodegenerative disorders like Alzheimer's and Parkinson's, pulmonary conditions, atherosclerosis, and DNA damage.

Antioxidants are crucial in maintaining balance within the body, helping to neutralize free radicals before they cause harm. Natural antioxidants, such as flavonoids, carotenoids, and vitamins, play a vital role in this process. However, synthetic antioxidants are also valuable. Among these synthetic compounds, 1,2,4-triazoles and their derivatives have attracted significant scientific interest due to their broad spectrum of biological activity. These nitrogen- containing heterocyclic compounds have been studied for years, with some already being used as pharmaceutical drugs. The search for new synthetic triazole-based antioxidants remains a key focus in medicinal chemistry.

Antibacterial

In conclusion, the newly synthesized compounds were evaluated for their antibacterial activity against selected human pathogens, including Gram-positive and Gram-negative bacteria. The results demonstrated that certain derivatives exhibited promising inhibitory effects, with some

surpassing the activity of reference antibiotics. Specifically, compound 18g showed the highest potency against Listeria monocytogenes, likely due to its unique structural features. The study also highlighted the impact of specific functional groups and molecular arrangements on antibacterial efficacy, contributing to the understanding of structure-activity relationships (SAR). These findings suggest that structural modifications, such as linker variations and functional group adjustments, can significantly influence antibacterial performance, paving the way for further optimization and in silico studies.

ACKNOWLEDGMENT

We would like to express our sincere gratitude to Oriental College of Pharmacy Bhopal M.P. (462022) for providing us with the the opportunity and resources to carry out this project.

We extend our hearfelt thanks to our mentor and faculty members for their continuos guidance [ms. Sonam Pal] and support throughtout our research work.

We also aknowlegde the collective effort and collaration for all team member Sheevendra Singh Sibbu (enrolment no. 0145PY211098) for their dedication and contributions towards the successful completion for this project.

REFERENCE

[1] Gangurde, K. B., More, R. A., Adole, V. A., & Ghotekar, D. S. (2024). Design, synthesis and biological evaluation of new series of benzotriazole-pyrazole clubbed thiazole hybrids as bioactive heterocycles: Antibacterial, antifungal, antioxidant, cytotoxicity study. Journal of Molecular Structure, 1299, 136760.

[2] Barbari, R., Tupini, C., Durini, E., Gallerani, E., Nicoli, F., Lampronti, I., ... & Manfredini, S. (2022). Design, Synthesis and Evaluation of New Multifunctional Benzothiazoles as Photoprotective, Antioxidant and Antiproliferative Agents. Molecules, 28(1), 287.

[3] Jimoh, T. A., Oyewale, A. O., Ibrahim, H., Habila, J. D., & Arthur, D. E. (2022). Biological evaluation and docking study of synthesized derivatives of benzotriazole and benzimidazole as antibacterial agents. Chemistry Africa, 5(3), 509-523.

[4] Seboletswe, P., Kumar, G., Gcabashe, N., Olofinsan, K., Islam, S., Idris, A., & Singh,

[5] P. (2025). Benzylidenehydrazine Derivatives: Synthesis, Antidiabetic Evaluation, Antioxidation, Mode of Inhibition, DFT and Molecular Docking Studies. Chemistry & Biodiversity, 22(3), e202401556.

[6] Gupta, K., Sirbaiya, A. K., Kumar, V., & Rahman, M. A. (2022). Current perspective of synthesis of medicinally relevant benzothiazole based molecules: Potential for antimicrobial and anti-inflammatory activities. Mini Reviews in Medicinal Chemistry, 22(14), 1895-1935.

[7] Aleksandrova, Y. R., Nikolaeva, N. S., Shagina, I. A., Smirnova, K. D., Zubishina, A. A., Khlopotinin, A. I., ... & Neganova, M. E. (2024). N-Aryl Benzimidazole and Benzotriazole Derivatives and Their Hybrids as Cytotoxic Agents: Design, Synthesis and Structure–Activity Relationship Studies. Molecules, 29(22), 5360.

[8] Kashyap, P., Verma, S., Gupta, P., Narang, R., Lal, S., & Devgun, M. (2023). Recent insights into antibacterial potential of benzothiazole derivatives. Medicinal Chemistry Research, 32(8), 1543-1573.

[9] Pachuta-Stec, A. (2022). Antioxidant activity of 1, 2, 4-triazole and its derivatives: A mini-review. Mini reviews in medicinal chemistry, 22(7), 1081-1094.

[10] Mirjafary, Z., Mohammad Karbasi, M., Hesamzadeh, P., Shaker, H. R., Amiri, A., & Saeidian, H. (2022). Novel 1, 2, 3-triazole-based benzothiazole derivatives: Efficient synthesis, DFT, molecular docking, and ADMET studies. Molecules, 27(23), 8555.

[11] Wang, X., Du, J., Zhou, T., Fang, X., & Yang, H. (2023). Novel benzotriazole- benzimidazole metal complexes: structure-activity relationship, synthesis, characterization, and antidiabetic activity. Journal of Molecular Structure, 1292, 136141.

[12] Yadav, R. K., Kumar, R., Singh, H., Mazumdar, A., Salahuddin, Chauhan, B., & Abdullah, M. M. (2023). Recent insights on synthetic methods and pharmacological potential in relation with structure of benzothiazoles. Medicinal Chemistry, 19(4), 325- 360.

[13] Beč, A., Persoons, L., Daelemans, D., Starčević, K., Vianello, R., & Hranjec, M. (2024). Biological activity and computational analysis of novel acrylonitrile derived benzazoles as potent antiproliferative agents for pancreatic adenocarcinoma with antioxidative properties. Bioorganic chemistry, 147, 107326.

[14] Küçükbay, H., Gönül, Z., Küçükbay, F. Z., Angeli, A., Bartolucci, G., & Supuran, C. T. (2020). Preparation, carbonic anhydrase enzyme inhibition and antioxidant activity of novel 7-amino-3, 4-dihydroquinolin-2 (1H)-one derivatives incorporating mono or dipeptide moiety. Journal of Enzyme Inhibition and Medicinal Chemistry, 35(1), 1021-1026.

[15] Gopi, C., Sastry, V. G., & Dhanaraju, M. D. (2016). Investigation of Anti-Oxidant and Anti-Microbial Activity of Bio-Active Molecules of Some 4-((5-((1 H-Benzo [D][1, 2, 3] Triazol-Y) Methyl)-1, 3, 4 Thiadiazol-2yl) Diazenyl Derivatives. Middle- East Journal of Scientific Research, 24(3), 728-733.

[16] Al-Majedy, Y. K., Ibraheem, H. H., Issa, A. A., Jabir, M. S., Hasoon, B. A., Al- Shmgani, H. S., & Sulaiman, G. M. (2024). Synthesis, biomedical activities, and molecular docking study of novel chromone derivatives. Journal of Molecular Structure, 1295, 136647.

[17] Gondru, R., Li, Y., & Banothu, J. (2022). Coumarin–benzimidazole hybrids: A review of developments in medicinal chemistry. European Journal of Medicinal Chemistry, 227, 113921.