



An Overview of Thiazole Derivatives and its Biological Activities

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ABSTRACT

Thiazole, one of the most common five-membered heterocyclic compounds, has a nitrogen atom at position 3 and a sulfur atom at position 1, and many of its natural and synthetic derivatives exhibit different biological behaviour. Thiazole ring substituents are modified for drug discovery and development to create new molecules with potent biological activity. To assist other researchers in developing new molecules of thiazole derivatives with more potent biological activity, this review article describes thiazole chemistry, thiazole synthesis pathways, and their biological activities. This review article aims to define the structural and biological importance of thiazoles in drug development and discovery, with recent publications on various compounds containing thiazole rings and their diverse biological activities. In particular, attention has been paid to heterocyclic scaffolds, which belong to a class of compounds with proven utility in medicinal chemistry.

Keywords: Thiazole, Heterocyclic Compound, Biological Activity, Medicinal Chemistry.

INTRODUCTION

Nearly 75% of FDA-approved small-molecule drugs contain one or more nitrogen-based heterocycles, making nitrogen-containing heterocyclic compounds essential in the drug discovery process. Thiazole, also known as 1,3 - thiazole, belongs to the group of compounds known as azoles and has sulphur and nitrogen atoms in positions 1 and 3, respectively. One of the extensively studied heterocycles, the thiazole nucleus plays a crucial role in many biologically active compounds. 1,3 - thiazole is an essential component of numerous drug structures. Some examples of thiazole-bearing products include tiazofurin and dasatinib (anti-neoplastic agents), ritonavir (anti-HIV medication), ravuconazole (antifungal agent), nitazoxanide (antiparasitic agent), fanetizole, meloxicam and fentiazac (anti-inflammatory agents), nizatidine (antiulcer agent), and thiameth.¹

With a focus on recent publications about various compounds containing thiazole rings and their various biological activities, this review aims to define the structural and biological importance of thiazoles in drug design and discovery.²

Designing, synthesizing, and developing molecules with the potential to be used as medicines for humans is one of the main goals of organic and medicinal chemistry. Combinatorial chemistry has made it possible to access chemical libraries based on privileged structures over the past ten years, with heterocyclic scaffolds receiving special attention because they are a class of compounds with established medicinal chemistry applications. There are many five-membered rings with two heteroatoms, biologically active molecules.³

One of these rings is the thiazole ring. Due to its numerous pharmaceutical uses, thiazole makes a good pharmacophore nucleus. Many biological activities,

including antioxidant, analgesic, antibacterial, anticancer, antiallergic, antihypertensive, anti-inflammatory, anti-malarial, antifungal, and antipsychotic, are exhibited by its derivatives.⁴

More than 18 FDA-approved drugs contain the thiazole scaffold. When no other option is available, this thiazole derivative was found to be effective against a variety of multi-drug resistant Gram-negative bacteria, including *Pseudomonas aeruginosa* (*P. aeruginosa*). It is used to treat complicated urinary tract infections. Alpelisib, sold under the brand name Pigray, is a different thiazole-based medication that was once again authorized in 2019 for the treatment of specific types of breast cancer. Breast cancer is one of the most prevalent serious illnesses in the world and the second leading cause of cancer death, primarily in less developed nations.⁵

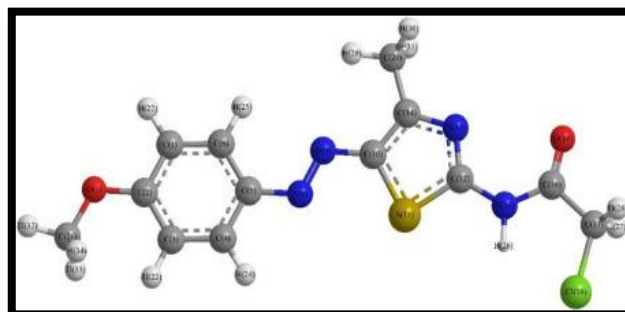


Figure 1: 3D Structure of Thiazole

Structural Characteristics

With the molecular formula C_3H_3NS , thiazole, also known as 1,3-thiazole, is a clear to pale yellow flammable liquid with a pyridine-like odour. It is a five-membered ring with two nitrogen- and sulfur-containing vertices and three carbon-containing members. The numeration scheme for naming thiazole derivatives is displayed below.⁶



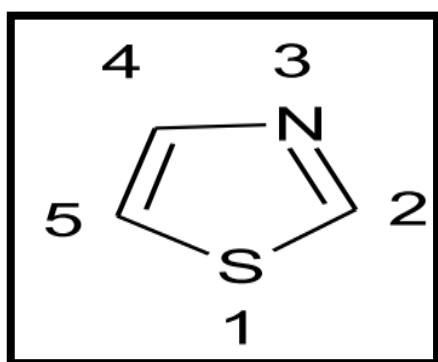


Figure 2: The Structure of thiazole

Chemistry of thiazole

A stable heterocyclic compound is produced by thiazole by using both an electron-donating group (-S-) and an electron-accepting group (C=N). The important class of heterocycles known as thiazoles and their analogues, including oxazole, are thought to have a variety of biological properties. The azole compound isothiazole, which contains the same atoms (nitrogen and sulphur) but in a different position, is isomeric with the thiazole compound. Thiazole is soluble in alcohol and ether but only moderately soluble in water. It has a boiling point between 116 and 118 °C and is a clear, pale yellow liquid. Thiazole is a heterocyclic ring that has six delocalized electrons from the sulphur atom's lone pair of electrons, according to Huckel's rule.^{7,8}

Due to their planar and aromatic structure, which shows greater -electron delocalization than oxazole, thiazole derivatives are desirable model compounds for chemistry research. By spotting the chemical shift of the protons between 7.27 and 8.77 ppm in ¹H NMR spectroscopy, the aromatic behaviour of the thiazole ring was confirmed. Due to the addition of various substituents at the C-2, C-4, and C-5 positions, the reactivity of the thiazole derivatives ring was strained, which may require further structural consideration. For instance, the methyl group (electron donating group) substituent had a noticeable effect on the thiazole ring's basicity and nucleophilicity when it was positioned at any position on the ring.^{9,10}

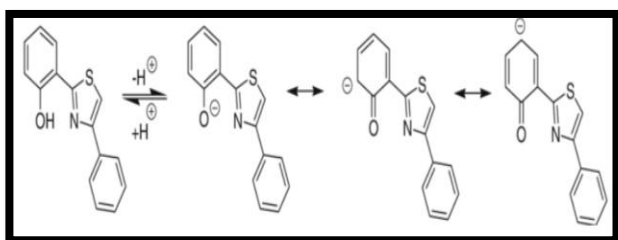


Figure 3: Resonates Structure of thiazole

However, when a potent electron-withdrawing group, like a nitro group, was incorporated into the molecule, the basicity and nucleophilicity reductions take place. Thiazole's versatile building blocks as bioactive substances give rise to a peculiar molecular structure. According to numerous studies, the thiazole ring can be found in the

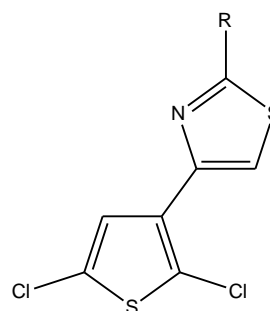
majority of synthetic and natural products with a wide variety of biological properties. One of the examples is vitamin B1, also known as thiamine, which plays a part in the synthesis of acetylcholine and thus naturally supports the nervous system. The fact that thiazole derivatives contained both hydrophobic (lipophilic) and hydrophilic (lipophobic) components gave them an amphiphilic quality as well.¹¹

This quality increases its ability to easily diffuse into the bacterial cell membrane for inhibition activity. Compounds can effectively inhibit Gram-negative and Gram-positive bacteria with both hydrophilic and lipophilic sections by penetrating the bacteria's cell membrane. This penetration causes cytoplasmic material leakage, disruption of the cell's physiology, and apoptosis.¹²

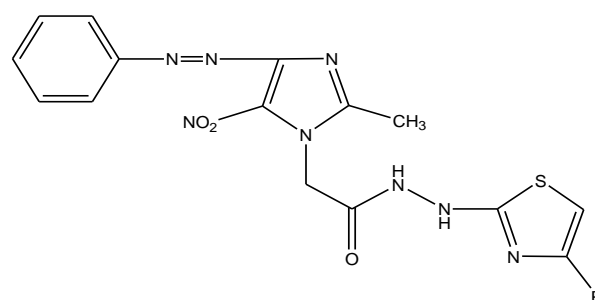
Biological Activities of thiazole derivatives:

Antimicrobial activity

Cris O. et al. synthesized a new series of 2,5-dichloro thienyl-substituted thiazoles and their minimum inhibitory concentration (MIC) values against bacterial strains and fungal strains, including *Aspergillus fumigatus*, *Aspergillus flavus*, *Penicillium marneffeii*, and *Trichophyton mentagrophytes*. Increased antibacterial activity was observed in compounds having MIC values between 6.25 and 12.5 µg/mL.¹³



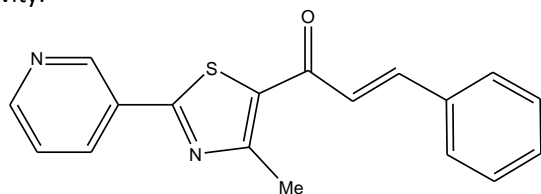
Qureshi A. et al. synthesized a compounds containing thiazole and imidazole moieties and screened for the antimicrobial properties. The antimicrobial activity of novel compounds was evaluated by cup plate method. A synthesized compounds showed good antimicrobial activity when compared with standard.¹⁴



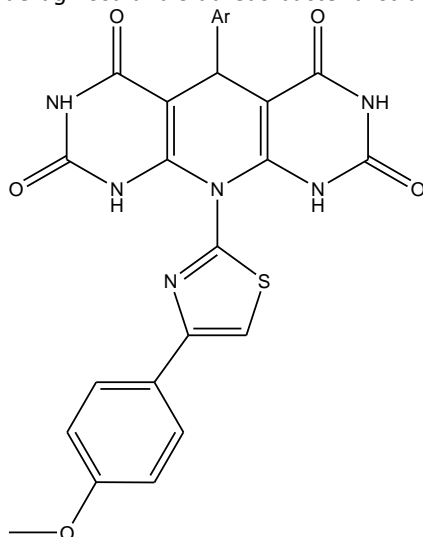
Antibacterial activity

Mohanty P. et al. synthesized a series of 2-(3-pyridyl)-4,5-disubstituted thiazole derivatives that were tested for antibacterial activity against various microorganisms. When compared to the reference

drugs, the compounds showed significant antibacterial activity.¹⁵

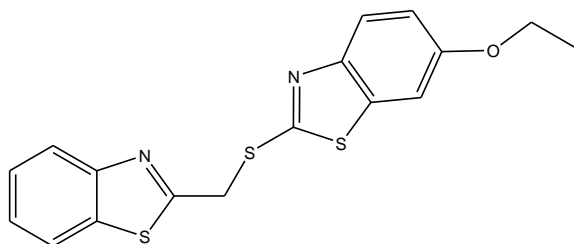


Koka I. et al. synthesized a novel thiazole hybrid molecule that has a 1,4-dihydropyridine moiety, the antibacterial activity of which has been tested against *E. coli*, *M. luteus*, *P. aeruginosa* and *S. aureus* bacterial strains.¹⁶

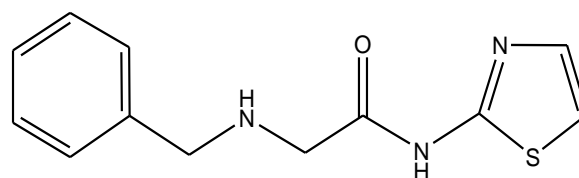


Antidiabetic activity

Bhagdev K. et al. synthesized and tested a variety of substituted benzothiazole derivatives for hypoglycemic (antihyperglycemic) activity. The ethoxybenzothiazole moiety in 2-(benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzothiazole was found to be crucial for enhancing glucose transport and AMPK activation in L6 myotubes. 2-(benzo[d]thiazol-2-ylmethylthio)-ethoxybenzo[d]thiazole significantly enhanced the rate of glucose absorption in L6 myotubes at pharmacologically applicable concentrations. The effect of 2-(benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzo[d]thiazole in on blood glucose levels in diabetic KKAy mice showed decrease in blood glucose level.¹⁷

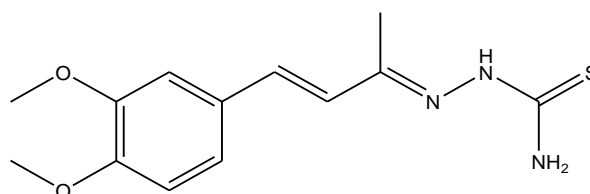


Abhishek K. et al. synthesised a series of thiazole-containing compounds as dipeptidyl peptidase IV (DPP-IV) inhibitors. The blood glucose level lowering activity of thiazole derivatives was investigated using a rat oral glucose tolerance test (OGTT).¹⁸

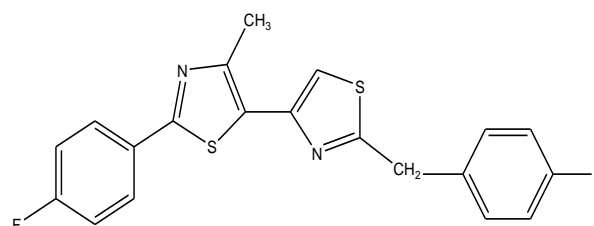


Anti-TB activity

Scarim C. et al. synthesized a novel styryl hydrazine thiazole hybrid, which was tested for anti-TB activity against five resistant clinical Mtb strains, including INH-R1 (Y155), INH-R2 (ATCC35822), RIF-R1 (S522L), RIF-R2 (ATCC35828), and FQ-R1 (fluoroquinolone-resistant strain-D94 N). The MIC values for anti-Mtb activity ranged from 3.2 M (INH-R1) to 1.5 M (INH-R2), 2.2 M (RIF-R1) to 6.3 M (RIF-R2), and 21.0 M (FQ-R1).¹⁹

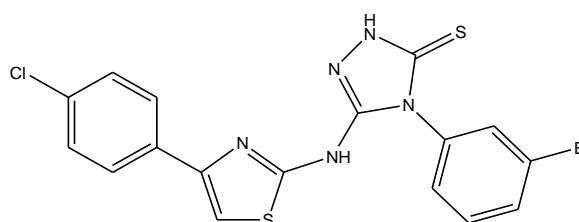


Arshad M. et al. synthesized a new bithiazolyl derivative and tested it for anti-TB activity. These novel analogues were tested against the *Mycobacterium smegmatis* MC2 155 strain. The analogue demonstrated strong anti-tubercular efficacy at a dose of 30 mM. The SAR studies revealed that the presence of a fluoro-substituted phenyl ring is critical for reducing the *M. smegmatis* surge.²⁰

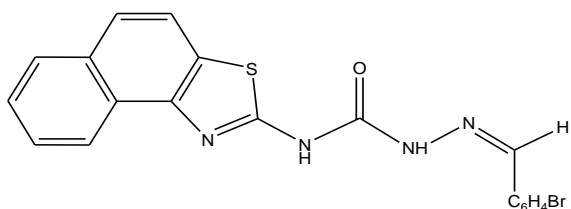


Anti-convulsant activity

Siddiqui N. et al. synthesized 3-[4-(substituted phenyl)-1,3-thiazol-2-ylamino] derivatives. 4-(substituted phenyl)-4,5-dihydro-1H-1,2,4-triazole-5-thione and tested for anticonvulsant efficacy in vivo using MES and scPTZ. Compounds showed strong anticonvulsant efficacy, with ED50 values of 23.9 mg/kg in the MES screen and 178.6 mg/kg in the scPTZ test.²¹

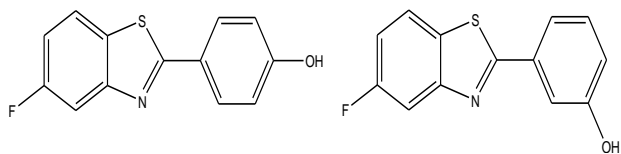


Shaikh A. et al. designed and synthesized a series of N4 (naphtha[1,2-d]thiazol-2-yl)semicarbazides and evaluated for their anticonvulsant and neurotoxicity studies. The compound showed efficacy against PTZ induced seizures.²²

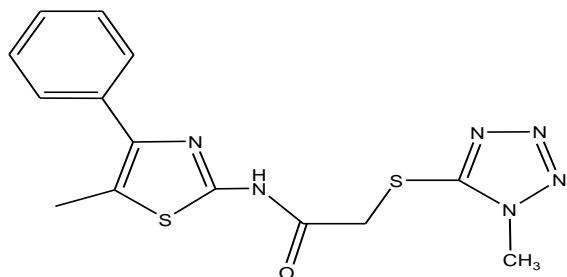


Anti-cancer activity

Kolageri S. et al. described the synthesis of fluorinated 2-aryl benzothiazole derivatives and their evaluation for anti-tumor activity against cancer cell lines MDA-MB-468 (mammary gland/breast tissues arising from metastatic site) and MCF-7 (human breast adenocarcinoma). The benzothiazole derivatives 4-(5-fluoro-1,3-benzothiazol-2-yl) phenol and 3-(5-fluoro-1,3-benzothiazol-2-yl)phenol with hydroxyl substituents on the third and fourth positions were more effective to those containing alkoxy, methyl sulphonyl, and ethyl substituents on the benzothiazole.²³

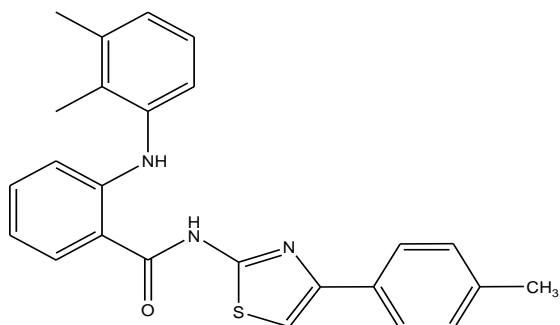


Petrou A. et al. synthesised novel N-(5-methyl-4-phenylthiazol-2-yl)-2-(1-methyl-1H-tetrazol-5-ylsulfanyl)acetamides and tested their anticancer activity against A549 and NIH/3T3 cell lines using MTT assay with cisplatin as the reference drug. The compound showed highest cytotoxic activity against A549 cells, but it was not toxic against NIH/3T3 cells.²⁴

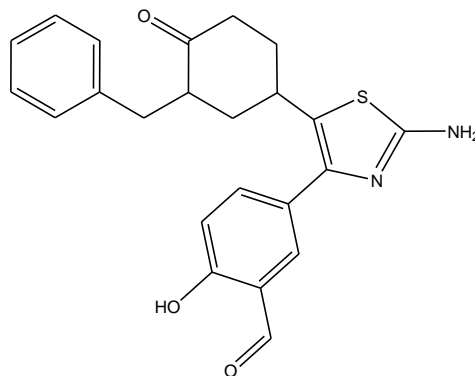


Anti-inflammatory activity

Krishnan G. et al. developed and synthesised a series of 2,4-disubstituted thiazole derivatives, which were tested for anti-inflammatory activity *in vitro* using the albumin denaturation method and compared to the standard medication diclofenac sodium.²⁵

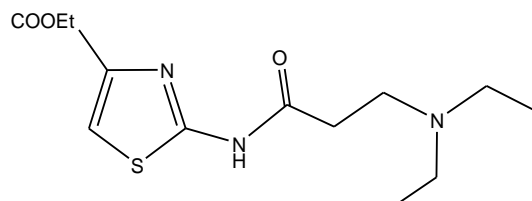


El-Achkar A. et al. synthesized amino thiazole derivatives and evaluated as *in vitro* and *in vivo* anti-inflammatory activity. The compounds exhibited anti-inflammatory effect in the dorsal air pouch model of inflammation as shown by inhibition of PGE₂ secretion.²⁶

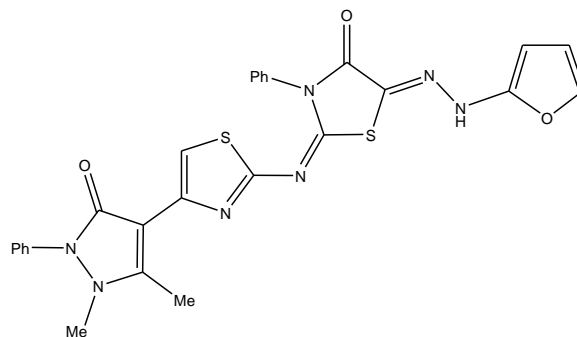


Anti-tumor activity

Alizadeh R. et al. synthesised and tested novel ethyl 2-substituted-aminothiazole-4-carboxylate derivatives for anticancer efficacy against 60 human tumour cell lines. Compound demonstrated strong activity against the RPMI-8226 leukaemia cell line (GI₅₀ = 0.08 M) and broad spectrum action against a group of 60 apart human cells with a GI₅₀ (MG-MID) value of 38.3 M.²⁷

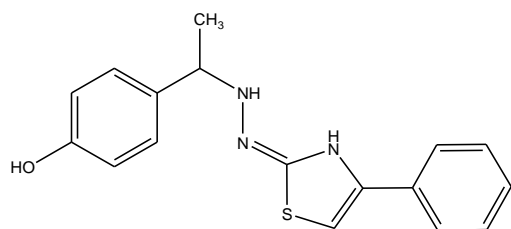


Kaur H. et al. synthesized 2-(4-(pyrazol-4-yl)thiazol-2-ylimino)-1,3,4-thiadiazole derivatives, which have been studied for anticancer efficacy against human hepatocellular carcinoma cells (HepG2), human breast cancer cells (MCF-7) and human lung cancer cells (A549) *in vitro*.²⁸

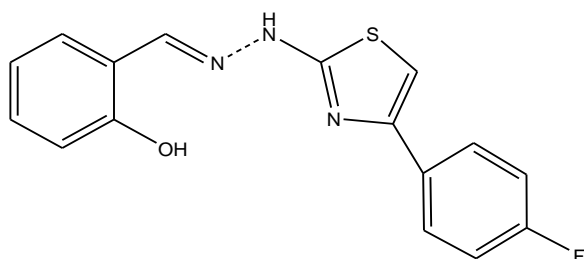


Antimalarial activity

Yadav A. et al. designed and synthesized thiazole compounds and tested them for antimalarial activity. The results have indicated that an electron-withdrawing group at the fourth position of the linked phenyl ring of thiazole derivatives is required for improved anti-malarial activity and a favourable drug-like profile, which can lead to the emergence of a possible therapeutic molecule in further development.²⁹

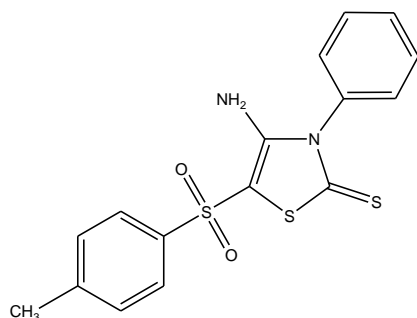


Rao Vallu V. et al. reported a new synthesis of novel thiazole hydrazine derivatives and their antimalarial activity screening. The antimalarial activity was conducted against *Plasmodium falciparum*, which is one of the species most responsible for malaria. The chemical demonstrated potent antimalarial action. The antimalarial activity of the compounds revealed that they were moderately active but less potent than standard quinine.³⁰

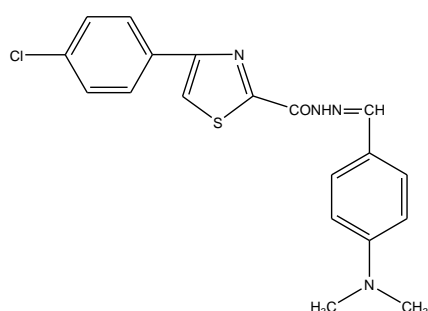


Antioxidant activity

Naminath H. et al. synthesized a new series of thiazole compounds and evaluated their antioxidant activities. When compared to conventional ascorbic acid, the molecule demonstrated significantly higher effectiveness against erythrocyte haemolysis (0.85%).³¹



Kashid G. et al. designed and synthesized a new thiazole derivative and evaluated the compound's antioxidant potential in-vitro free radical scavenging activity using the nitric oxide radical inhibition method. The antioxidant results of compounds with an aldehydic phenyl ring containing electron donating groups were more promising.³²



CONCLUSION

Thiazole compounds have been shown to exhibit a wide range of biological effects, including antidiabetic, anticonvulsant, antioxidant, antifungal, antimalarial, and antitumoral activities. Generally, thiazole compounds are recognized to have interesting biological features such as anticancer and antimicrobial activities.

It has been observed that changes to the thiazole moiety shown beneficial biological functions. More research is needed to evaluate thiazole's effectiveness against various disorders.

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