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1,3-Thiazoles: Advances in Synthesis, Properties, and Comprehensive Biological Potential

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ABSTRACT

1,3-Thiazole compounds have garnered considerable interest due to their diverse biological activities and adaptable chemical structures. An extensive summary of 1,3-thiazole derivative synthesis, physicochemical characteristics, and biological uses is given in this review. A wide range of synthetic procedures is covered in depth, including metal-catalyzed and green chemistry techniques, as well as more contemporary approaches, such as the Hantzsch thiazole synthesis. The thiazole moiety is a useful scaffold in drug development because of its strong binding affinity to a variety of biological targets, which is facilitated by its structural flexibility and electrical properties. Additionally, the development of more potent thiazole-based treatments with enhanced selectivity and decreased toxicity has been directed by structure-activity relationship (SAR) research. 1,3-thiazole compounds have been investigated in agrochemicals, dyes, and materials science in addition to pharmacological uses. This review highlights recent advancements in developing thiazole-based heterocyclic compounds, emphasizing their role as a key scaffold in biological and medicinal applications

Keywords: Anti-Inflammatory, Antioxidant, Antiviral, Gewald Reaction, Hantzsch Synthesis.. ..

1. INTRODUCTION

Early in the 19th century, as organic chemistry advanced, a key subfield known as heterocyclic chemistry developed. Important turning points include Dobereiner's production of furfural from starch (1832), Runge's creation of "fiery oil" by bone distillation (1834), and Brugnatelli's isolation of alloxan from uric acid (1832). The discovery of the thiazole ring in vitamin B1 (thiamine) (1936) by Funk and collaborators underscored the biological importance of this heterocycle. Thiazole-containing peptides, such as thiostrepton and microcins, further expanded their role in natural product chemistry[1]. The significance of heterocyclic compounds was emphasized by Chargaff's laws (1951), which insisted on the function of purines and pyrimidines in the genetic code[2]. Heterocyclic compounds, or heterocycles, are organic molecules with a ring structure incorporating one or more heteroatoms[3]. Heterocyclic compounds incorporating sulfur, nitrogen, and oxygen are crucial in medicine and pharmaceuticals[4]. Heterocycles form a significant part of chemistry, particularly organic chemistry, and are key to medicinal chemistry. These biologically active compounds mimic natural molecules, making them vital in drug design and synthesis and ubiquitous in biological systems[5]. Numerous heterocyclic compounds with pharmacological activity are frequently employed in clinical settings[6]. Heterocyclic molecules are integral to organic chemistry and vital in synthesizing natural products, drugs, agrochemicals, and materials. They are defined by a ring structure containing heteroatoms like nitrogen, sulfur, oxygen, or occasionally phosphorus or boron[7]. Nitrogen and sulfur are key heteroatoms, imparting unique chemical reactivity and electrical properties that endow heterocycles with distinct chemical and biological functions[8]. The agricultural and pharmaceutical industries employ heterocyclic compounds. Heterocyclic molecules are the building blocks used to create organic molecules. Developers, sanitizers, corrosion inhibitors, anti-ordinates, plastics, dyes, and insecticides all include heterocyclic compounds[9]

Nitrogen-containing heterocycles, ranging from simple aromatics like pyridine to complex macrocycles, are crucial in medicinal chemistry and drug development. Found in DNA and RNA bases, alkaloids (e.g., caffeine, nicotine, morphine), and various drugs, they play key roles in treating diseases with antivirals (acyclovir), antibiotics (penicillin), and anticancer agents (imatinib). Sulfur-containing heterocycles, with distinct physicochemical properties and reactivity, are integral to many natural products, drugs, and bioactive compounds. Found in medications like thiazoles and thiophenes, they contribute to treatments for various conditions, including antipsychotics (thioridazine), antidiabetics (glimepiride), and antimicrobials (sulfamethoxazole)[8]. Essential aromatic molecules with distinct physicochemical characteristics and sulfur-nitrogen heterocycles are attracting interest due to their potential for creating cutting-edge materials like magnets and molecular conductors. These heterocycles, which are created by substituting nitrogen and sulfur for the carbon atoms in carbocycles, have a variety of structural heterogeneity and reactivity. Well-known sulfur-nitrogen heterocycles, such as thiazole and its derivatives, have shown notable pharmacological and biological effects despite difficulties in synthesis. They are useful targets for therapeutic applications because of their structural specificity, which permits efficient interactions with biological receptors[4].

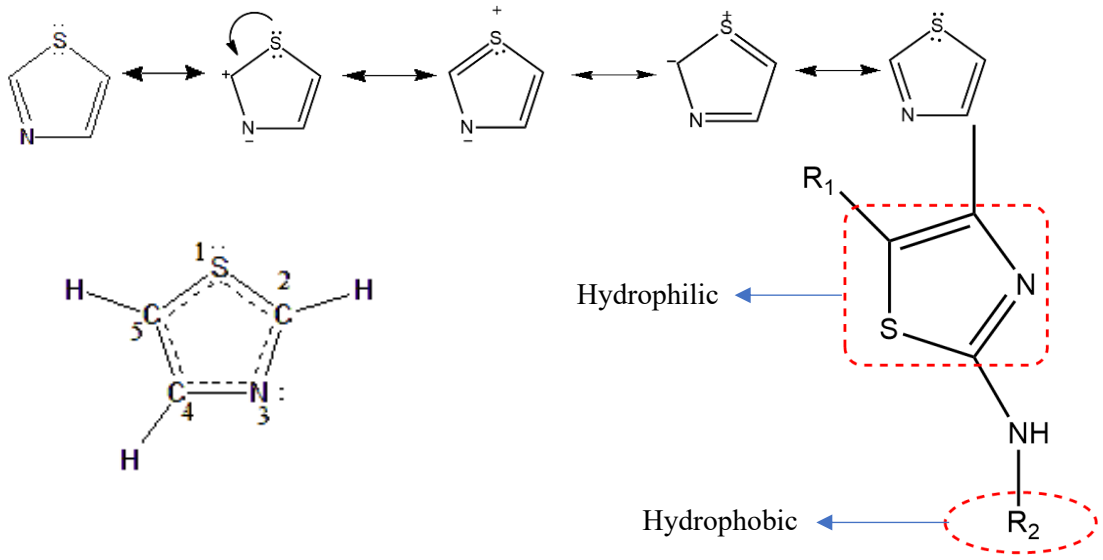
Thiazole

Regarding the five-membered heteroaryl ring systems, thiazole is a clear to light yellow liquid; a unique ring that comprises nitrogen and sulfur atoms, which makes it an unpredictable entity in actions and reactions. Thiazoles, which have five aromatic rings and a molecular weight of 85.13 gm^{n}mole1, are substances with the formula C_3H_3NS.

2.0 Chemistry of Thiazole:

A stable heterocyclic molecule is produced by thiazole's use of both an EDG (-S-) and an EWG (C=N)[10]. Other azole compounds, such as isothiazole, which contain similar atoms (sulfur and nitrogen) but different positions, can be isomeric with thiazole molecules. Thiazole is a translucent, pale yellow liquid that dissolves readily in ether and alcohol but remains insoluble in water. Its boiling temperature is between 116 and 118^{0} °C[11], [12]. Hückel's rule states that the heterocyclic structure of thiazole has six π electrons delocalized from the single pair of electrons on the sulfur atom[13]. Free thiazole is a pale yellow liquid with a pyridine-like odor. Although free thiazole is not found in nature, the ring of thiazole is present in a variety of natural molecules, such as cyclopeptides, metabolites, and peptide alkaloids. The 1H NMR spectroscopy, which shows a chemical shift of the protons between 7.27 and 8.77 ppm, was used to confirm the aromatic behavior of the thiazole ring[14].

The following are regarded as thiazole resonating structures. However, the d-orbitals of sulfur can also be involved in some resonant assemblies.



Thiazole gives reactions such as intramolecular nucleophilic substitution[15], donor-acceptor[16], photochemical reaction[17], [18], transformation, dimerization[19], arylation, cycloaddition, oxidation[20], etc. Depending on its molecular electrostatic potential (MEP), nitrogen is a more negatively charged atom in comparison to the neutral atoms of carbon and sulfur. Hantzsch and Weber initially reported the use of thiazoles in biological applications in 1887[16]. It had physical and chemical characteristics that were comparable to those of pyridine and pyrimidine. Yet, some of its derivatives exhibit characteristics that are comparable to those of furan and thiophene. Since the thiazole ring's somewhat acidic hydrogen at C-2 makes it extremely reactive, it has become an essential synthon for the synthesis of many novel chemical compounds. By

altering the thiazole ring at different places, a large number of new compounds with a variety of therapeutic potentials were created, including anti-tubercular, antibacterial, antioxidant, diuretic, antifungal, anti-inflammatory, and anti-cancer properties[21]. Thiazole is a crucial component of naturally produced antibiotics, which are penicillin-like drugs, either as a fused ring or as a solitary nucleus.

In recent decades, the thiazole moiety has drawn a lot of attention. The thiazole nucleus is crucial for the creation and improvement of more modern bioactive treatment options, according to several review papers[22], [23]. This review article aims to educate readers about several novel applications of thiazole platforms, such as thiazole-containing drug candidates in clinical studies or preliminary research stages, as well as drugs with thiazole rings that are currently being used to treat a variety of ailments. The current review article will be effective in encouraging medicinal chemists to seek out new leads that could be turned into new medications. One of the most important potentials in the primarily expanding chemical universe of substances is thiazole and correlation, with thiazoles exhibiting noteworthy pharmacological activities. This review broadly summarizes compounds' production and biological activity with a thiazole moiety[24].

3.0 Properties:

3.1 Physical Properties:

Thiazole is a pale yellow, flammable liquid with a pyridine-like odor. It has a boiling point of 116–118°C, a density of 1.2 g/cm³, and a dipole moment of 1.61 D. Its PKa (conjugated acid) is 2.5, and its ionization potential is 9.50 eV. Thiazole is fairly soluble in ether and alcohol but sparingly soluble in water. UV absorption in ethanol shows peaks at 207.5 nm (ε = 3.41) and 233.0 nm (ε = 3.57).

3.2 Chemical Properties:

3.2.1 Nucleophilic displacement reactions:

The preferred location for nucleophilic substitution is the electron-deficient C2, as seen by the electron density map. Sodium bromide and copper sulfate react with diazonium salt produced from amino thiazoles to produce 2-bromothiazole[25].

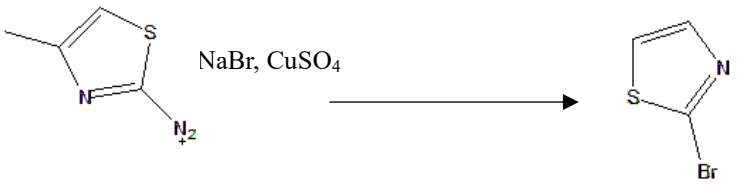


Figure 1: Sodium bromide and copper sulfate reaction with diazonium salt.

2-amino-4-methylthiazole is created when 3-methylthiazole reacts with highly nucleophilic substances such as $NaNH_2$.

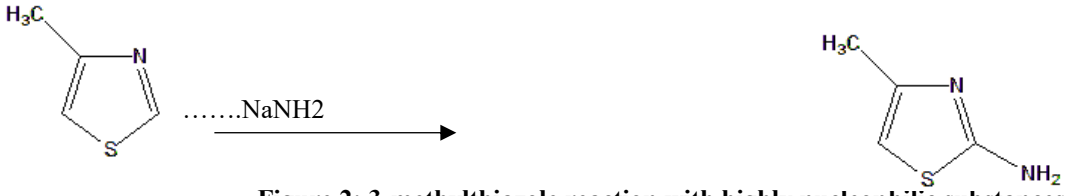


Figure 2: 3-methylthiazole reaction with highly nucleophilic substances

3.2.2 Electrophilic Substitution Reaction:

At Nitrogen: The electron density and substituent type of the thiazole nitrogen determine whether it is attacked electrophilically. Because of its low basicity and aromaticity, the sp2-hybridized nitrogen has a less reactive lone pair. It is alkylated/acylated and protonated to produce quaternary thiazolium salts and hydrochlorides.

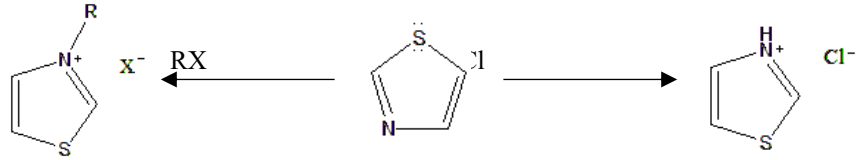


Figure 3: Electrophilic Substitution Reaction at N.

At Carbon: Electrophilic aromatic substitution at C_5 in 2-substituted thiazoles is facilitated by activating groups like methyl or amino. The delocalization of π-electrons from the electron-donating group at the 2-position to the 5-position, via the ring

nitrogen, follows the principle of vinylogy, enabling the reaction through the transient form (II)[26], [27], [28]. Strong electron-donating groups (e.g., NH_2, OH, SH) or their alkyl/acyl derivatives significantly enhance delocalization, as shown by the following structures.

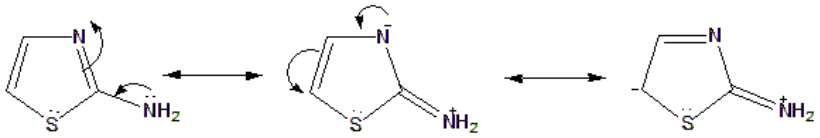


Figure 4: Electrophilic Substitution Reaction at C.

Electrophilic substitution in thiazole preferentially occurs at position 5th, or position 4th if occupied. The ring is deactivated for electrophilic substitution by protonation in an acidic environment. However, electron-donating substituents promote such reactions. For example, 2-aminothiazole undergoes nitration to yield 2-amino-5-nitrothiazole with HNO_3 and H_2SO_4. It reacts with concentrated H_2SO_4 to first form thiazol-2-ylaminoulfamic acid, which rearranges into 2-amino-5-sulfonic acid upon heating. Thiazole-5-sulfonic acid is produced by heating thiazole with fuming sulfuric acid and mercuric sulfate. Thiazol-2-yl-magnesium bromide and 2,4,5-tris(acetoxymercury)thiazole are the products of combinations with mercuric acetate and Grignard reagent, respectively. 2-Amino-5-bromothiazole is created when 2-aminothiazole is brominated using bromine. The following framework provides a summary of these reactions[29].

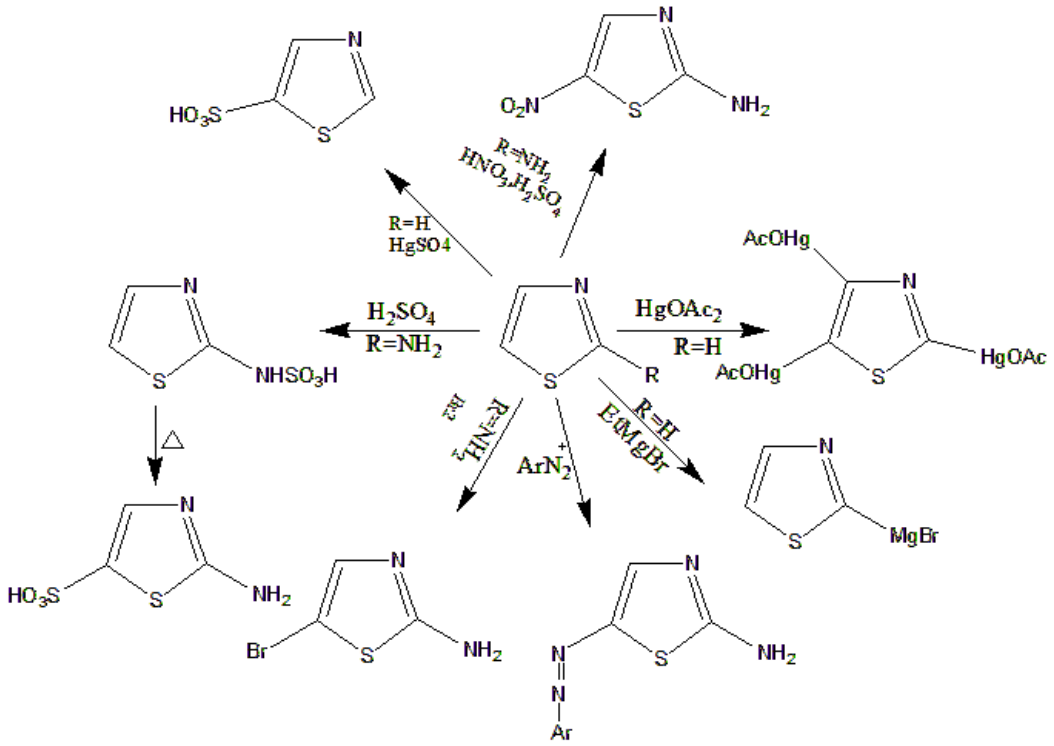
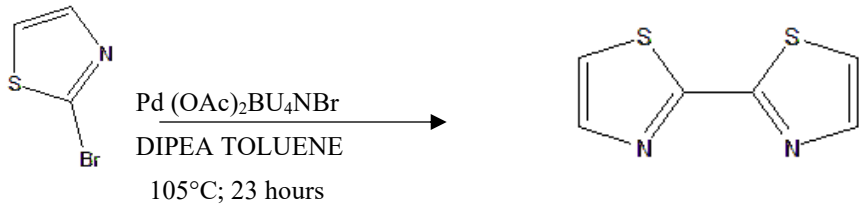


Figure 5: Summary of Electrophilic Substitution Reaction.

3.2.3 Dimer formation reactions:



2-bromothiazole 2,2'-bisthiazole (86%)

Figure 6: Dimer formation reaction of 2-bromothiazole.

3.2.4 Ring-forming reactions:

A bicyclic product was produced by [2 + 2 + 2] cycloaddition of 2- 2-isopropyl thiazole upon interaction with dichloro ketene[29].

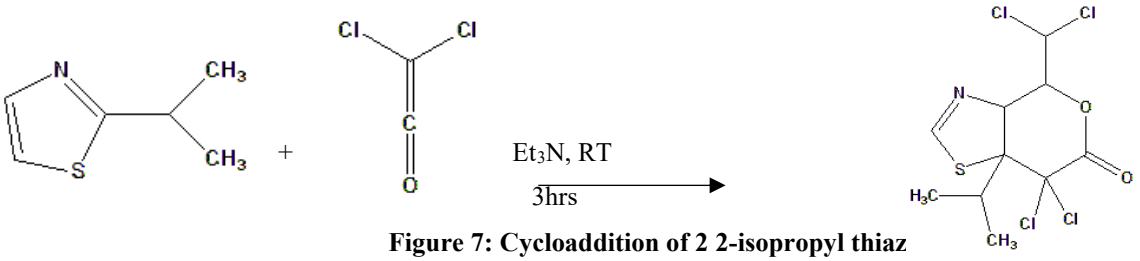


Figure 7: Cycloaddition of 2 2-isopropyl thiaz

3.2.5 Metal-catalyzed coupling reactions:

When 2-iodothiazole and 1-((phenylsulfonyl)-1Hindol 3yl) Zn Chloride are coupled, the result is 1H-lindol-3-yl-(1-(phenylsulfonyl)-2) Thiazole[29].

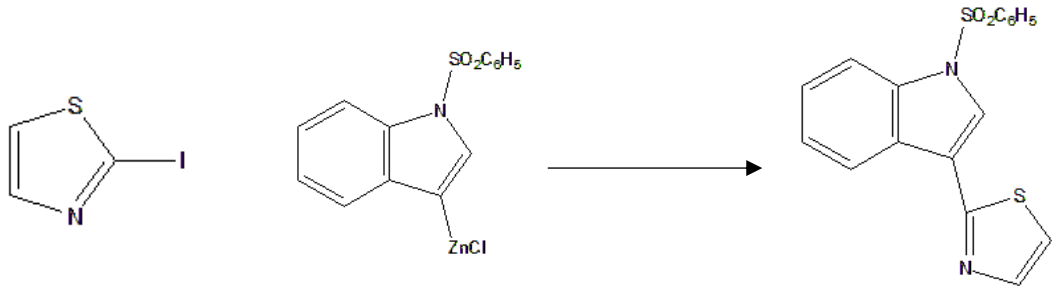


Figure 8: coupling reaction of 2-iodothiazole and 1-((phenylsulfonyl)-1Hindol 3yl) Zn Chloride

3.2.6 Oxidation:

The aromatic thiazole N-oxide is created by oxidation at nitrogen using substances like mCPBA and hypofluorous acid, which is created when fluorine and water are combined in acetonitrile. Sulfur undergoes some oxidation to produce non-aromatic sulfoxides or sulfones[30]. Palladium-catalyzed C-H arylations benefit from thiazole N-oxides because they can consistently alter reactivity to favor the 2-position and enable these reactions to occur under much milder conditions[31].

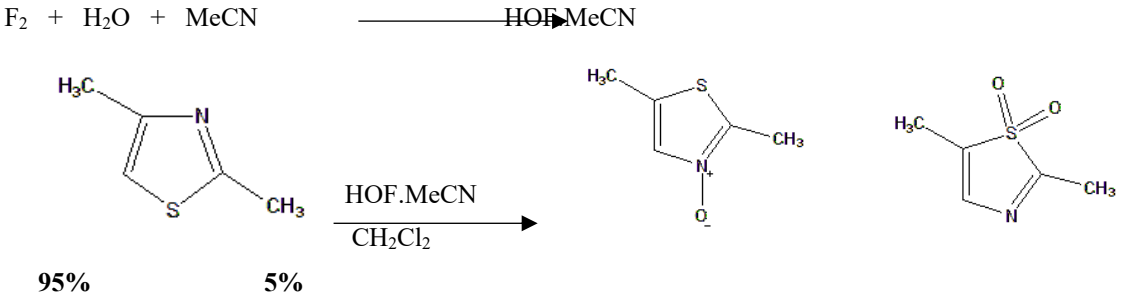


Figure 9: Creation of aromatic thiazole N-oxide by Oxidation.

3.2.7 Reduction:

Thiazole reduction, a useful method for preparing aldehydes, involves three steps: first, forming N-methyl thiazolium salt; second, reducing the thiazolium cation with $NaBH_4$; and finally, hydrolyzing the reduced thiazole intermediate with $HgCl_2$ to yield the aldehyde.

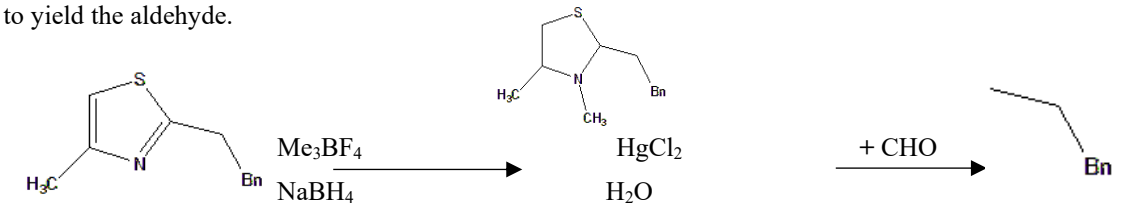


Figure 10: Preparation of aldehydes by Thiazole reduction.

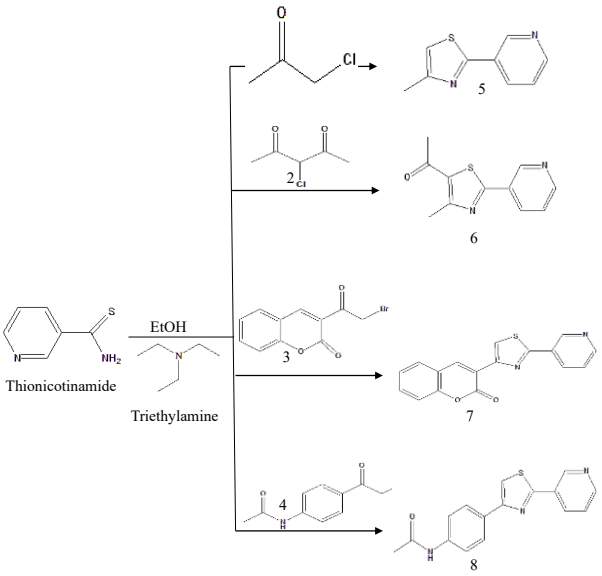
4.0 Strategies to Synthesize 1,3-Thiazole Derivatives:

The widely recognized techniques of Cook-Heilbron[32], Hantzsch and Gabriel made synthesizing thiazole ring systems simple. Numerous compounds, such as thiourea, thioamides, dithiocarbamate, ammonium thiocarbamate, and their derivatives, may operate as nucleophilic reagents in this reaction[33].

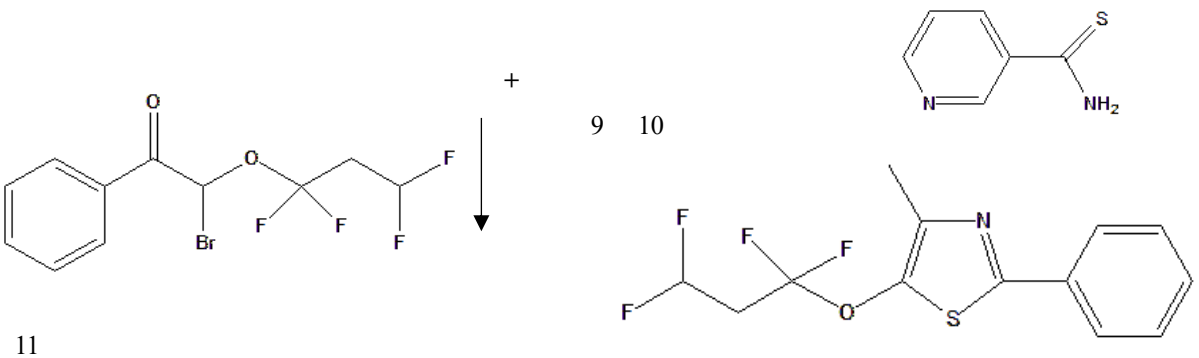
4.1 Hantzsch Synthesis:

The Hantzsch thiazole synthesis, introduced in 1887 by German chemist Arthur Hantzsch, is a renowned method for producing thiazoles. It involves the condensation of α-halo ketones with nucleophilic agents like thiourea, thioamides, ammonium thiocarbamate, or dithiocarbamate derivatives[34], [35], [36]. Additionally, it was suggested that Hantzsch thiazole synthesis was the best method for synthesizing thiazole compounds[37]. The Hantzsch reaction of thionicotinamide with four different forms of α-halo ketone—p-chloroacetylacetanilide (4), 3-chloroacetylacetone (2), 3-bromo acetyl-coumarin (3), and chloroacetone (1)—produced four thiazole derivatives in the presence of catalytic triethylamine. The 2-(3pyridyl) thiazole derivatives (5-8) produced by the procedure are shown in Scheme 1.

Various studies have highlighted notable drawbacks of this method, such as low yields, harsh reaction conditions, prolonged reaction times, and reliance on expensive catalysts. However, another researcher claims that dehalogenating the halo ketone during the procedure, this method delivers good results[38]. Because halide is an excellent leaving group, it has made the site more favorable for a nucleophilic assault, which will provide the reaction. By creating thiazole derivatives and directly attaching the tetrafluoroethoxy moiety to the heterocyclic ring's carbon atom, the Hantzsch cyclization technique was introduced. When α-Bromo-α-(tetrafluoroethoxy) acetophenone (9) and Phenylthioamide (10) were heated up to 60 °C in dioxane, they found that 2,4-diphenyl-5-(1,1,2,2-tetrafluoroethoxy) thiazole (11) was produced (Scheme 2). However, the yield percentage is low (18–20%) because thiobenzamide is unstable in acidic environments[39].



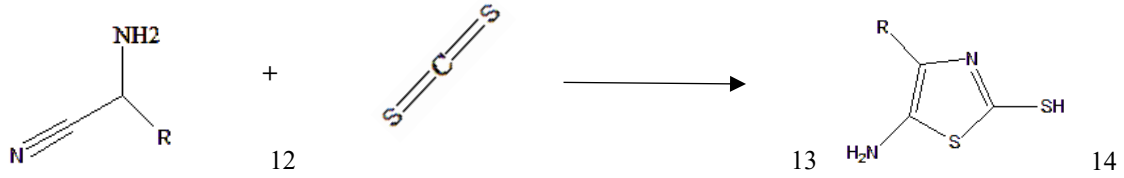
Scheme 1. Reaction synthesis of 2-(3-pyridyl) thiazole derivatives



Scheme 2. Hantzsch type synthesis of 2,4-diphenyl-5-(1,1,2,2-tetra fluor ethoxy)-thiazole

4.2 Cook-Heilbron Synthesis:

Additionally, Cook and Heilbron discovered the Cook-Heilbron synthesis, which uses carbon disulfide as the reactant and α-amino cyanides or α-aminoamides to generate the thiazole ring. The Cook-Heilbron procedure produced 5-amino thiazoles under mild conditions when aminonitrile reacted with salt and thioacid, carbon disulfide, or isothiocyanate esters to replace at position 2[40]. The reaction between α-aminonitriles (12) and carbon disulfide (13) to create 5-amino-2-mercaptothiazole (14) is illustrated in Scheme 3.

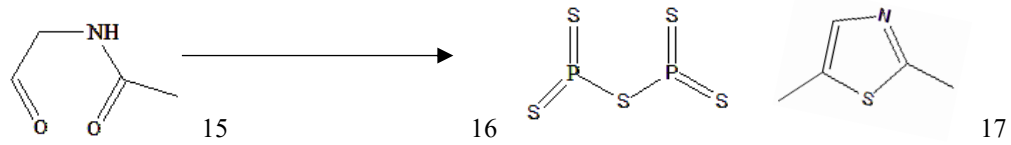


12 13 14

Scheme 3. The Cook-Heilbron thiazole synthesis

4.3 Gabriel Synthesis:

Another synthetic method for producing thiazole derivatives is the Gabriel synthesis. Reacting acylamino-ketone with P2S5 creates 2,5-disubstituted thiazole derivatives, which close the thiazole ring[40]. This study was corroborated by Kotadiya, which showed in Scheme 4 that 2,5-dimethyl-1,3-thiazole (17) was produced by heating acylamino compounds, namely N-(2-oxopropyl) acetamide (15) with (16)[41].



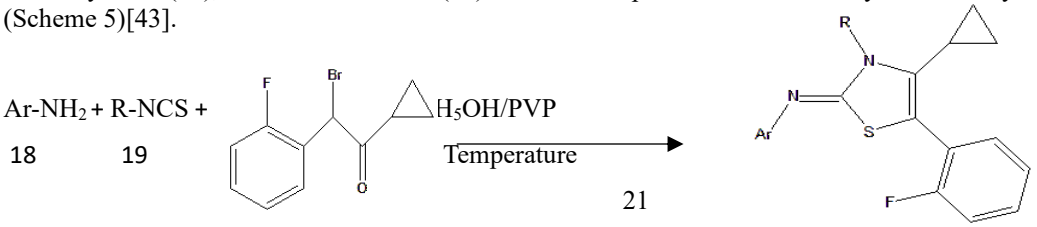
15 16 17

Scheme 4. Synthesis of thiazole compound *via* Gabriel reaction

4.4 Some novel approaches for Thiazole derivatives synthesis:

4.4.1 Multicomponent Methods for Synthesis of The Thiazole Ring:

Multicomponent reactions (MCRs) is novel synthetic techniques, in which three or more reactants can be combined without separating any intermediates, and are an efficient one-pot synthetic technique. They are better than ordinary replies because of their manageability and selectivity[13], [42]. Shiran and colleagues designed more environmentally friendly, one-pot, multicomponent reactions in which the desired thiazole derivatives (21) were obtained by stirring arylamine (18), alkyl isothiocyanate (19), and α-halo ketone (20) at room temperature with the recyclable catalyst polyvinyl pyridine (PVP) (Scheme 5)[43].

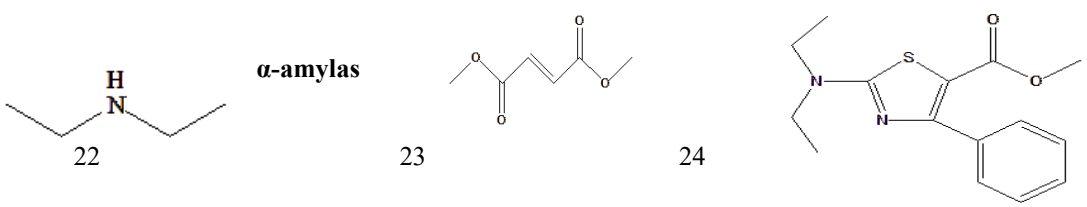


18 19 21

R= CH_3, C_2H_5, $CH_2CH{=}CH_2$; **Ar**= 4-$CH_3C_6H_4$, 4-$C_2H5C_6H_4$, 4-$OCH_3C_6H_4$, 4-$OC_2H_5C_6H_4$

Scheme 5. Multicomponent Synthesis of Thiazole Derivatives Using Polyvinyl Pyridine (PVP)

However, the Hantzsch cyclization, Cook-Heilbron, and Gabriel synthesis processes have serious drawbacks, including insufficient yield percentages and time consumption. The synthesis of thiazole derivatives with the use of chemoenzymatic organic processes is an example of the enzymatic synthesis of heterocyclic compounds. A one-pot multicomponent reaction was carried out in the study with medium chemoenzymatic conditions. Aspergillus oryzae produces α-amylase, which catalyzes the reaction of beginning materials like dimethyl acetylenedicarboxylate (24) in ethanol, secondary amine (22), and benzoyl isothiocyanate (23). (Scheme 6)[44].

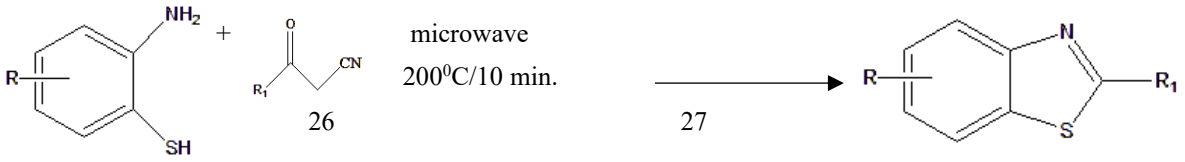


22 23 24

Scheme 6. One-pot multicomponent synthesis of thiazole derivatives using a derived enzyme

4.4.2 Green Chemistry Approaches to Thiazole Synthesis:

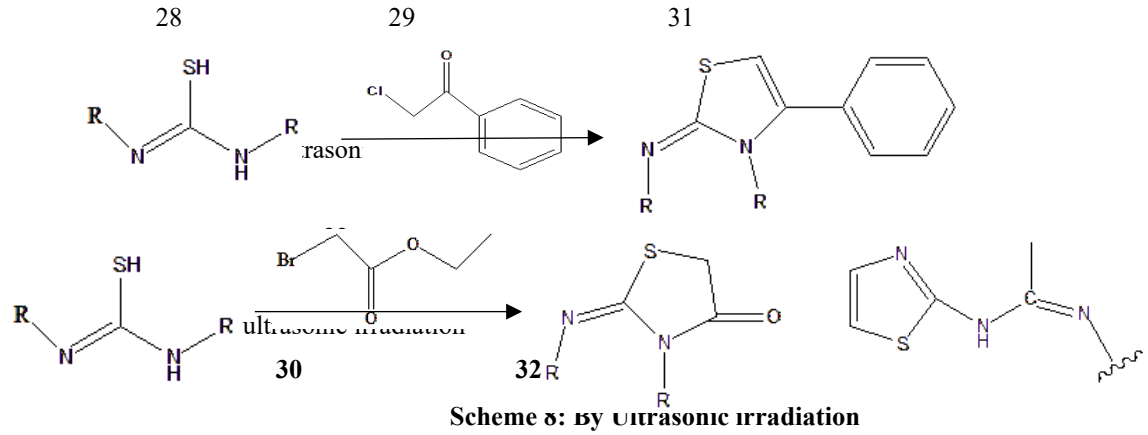
By subjecting a 1:1 mixture of alkyl/aryl/acyl acetonitriles (26) and o-amino thiophenol (25) to microwave irradiation (MWI) at 200 °C for 10 minutes, a benzothiazole (27) analog was created[45]. (Scheme 7) The yields (86%-95 %) varied from extremely good to exceptional.



R= H, Cl $R_{1=Alkyl, Aryl}$

Scheme 7: By Microwave irradiation:

According to a 2021 report, ultrasonic irradiation is a solvent-free, environmentally benign, and effective method for creating novel 1,3-thiazoles. Under ultrasonic circumstances, thiocarbohydrazones (28), α-Chloro ketone (29), or α-bromoester (30) interacted to produce 1,3-thiazoles 31 and 32 (Scheme 8)[46].

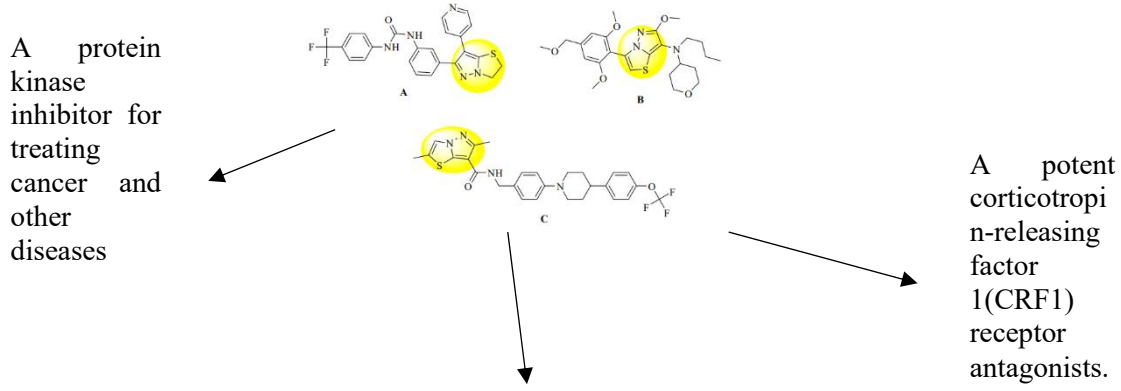


Scheme 8: By Ultrasonic irradiation

5.0 Hybrid Molecule Construction: The fusion of thiazole rings with other heterocycles, such as pyrazoles and thiadiazoles, has led to the development of novel compounds exhibiting enhanced biological activities.

5.1 Thiazole–Pyrazole Hybrids:

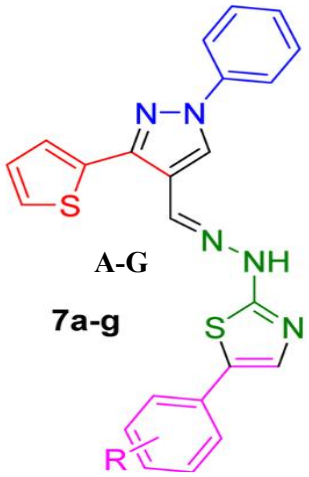
Pyrazolo[5,1-b]thiazole derivatives have been synthesized and evaluated for their antimicrobial and anticancer activities. These compounds demonstrated significant inhibitory effects against various bacterial strains and exhibited cytotoxicity against cancer cell lines, suggesting their potential as lead compounds in drug development[47].



5.2 Thiazole–Indole and Thiazole–Carbazole Hybrids:

Hybrid molecules combining thiazole with indole or carbazole moieties have shown enhanced antimicrobial properties. The incorporation of these heterocycles increases lipophilicity and electron-withdrawing characteristics, which can improve binding to biological targets.

5.3 Thiazole–Thiophene–Pyrazole Hybrids:



A: R= 4-OCH3
B: R= 4-NO2
C: R= 3-NO2
D: R= 4-F
E: R= 4-Cl
F: R= 4-Br
G: R= 4-CH3

b–g were evaluated against a panel of bacterial and fungal strains. The bacterial strains tested included Escherichia coli, Bacillus subtilis, Bacillus megaterium, and Staphylococcus aureus. The fungal strains tested included Aspergillus niger, Aspergillus oryzae, Rhizopus, and Candida albicans. Compounds **7c** and **7d** exhibited the highest antibacterial activity, particularly against *Bacillus subtilis* and *Bacillus megaterium*, with inhibition zones of 16 mm. **b–g** expressed as the percentage inhibition of DPPH and hydroxyl radicals. Higher percentages indicate stronger antioxidant activity[48].

5.4 Thiazole–Imidazole–Indole Hybrids with Anticancer and Antibacterial Activities:

Researchers synthesized novel thiazole–imidazole–indole hybrids using a microwave-assisted method, achieving yields between 68% and 85%. Compounds show significant anticancer activity against MCF-7 and SKVO3 cell lines. Additionally, some compounds exhibited notable antibacterial activity. Molecular docking studies indicated strong binding affinity to the EGFR active site, correlating with the observed biological activities[49].

6.0 Structure-Activity Relationships of Thiazole Ring Modifications:

Thiazole derivatives are useful scaffolds in drug creation because the cumulative impact of changes at these locations defines their overall physicochemical characteristics and biological activity[50].

Position	Modification	Effect on Activity	Examples of Beneficial Substituents
S_1	Oxidation	Decreased stability	Maintained as a thioether
2^{nd}	Electron-withdrawing groups	Enhanced kinase inhibition	-COOH, -CN, $-NO_2$
N_3	N-alkylation	Reduced activity	Generally avoided
4^{th}	Aromatic substitution	Improved metabolic stability	-Ph, -Pyridyl
5^{th}	Alkyl/aryl groups	Increased lipophilicity	$-CH_3$, $-CF_3$, -Ph
Thiazole Ring	Fusion with other heterocycles	Modified pharmacokinetics	Benzothiazole, Thiazolopyridine

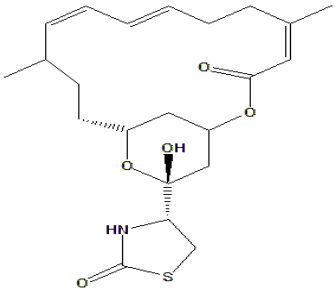
7.0 Biological Activities of Thiazole Derivatives:

Thiazole-containing compounds have shown promising potential in promoting good health and well-being through their therapeutic applications. Its derivatives, which include antibacterial, antifungal, and antimalarial agents, are among the most potent groups of chemicals with a wide range of action, antitubercular, antiviral, anti-inflammatory, anticonvulsant, antioxidant, anti-diabetic, anthelmintic, anticancer, and cardiovascular activities, and known novel bacterial DNA gyrase B inhibitors[51], [52].

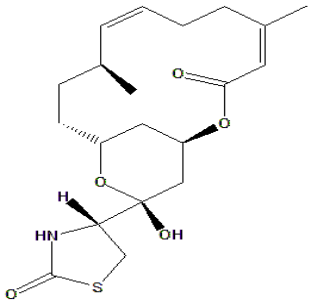
7.1 Marine Natural Products Containing Thiazole Moiety:

Chemical	**Activity**	**IC_{50} Values**	**Target Organism**
latrunculin Derivatives	prostate cancers breast tumors	50 nM to 1 µM 6.7 µM	HIF-1 inhibitors HIF-1 activators
bleomycin A2	testicular malignancies, neck carcinomas, and Hodgkin's lymphoma	≈ 65.8 Mm for Leukemia	DNA Binding and Cleavage, Cell Cycle Arrest

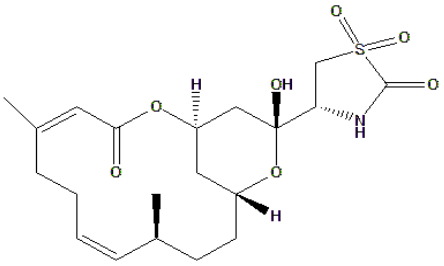
Thiazoles are found in a wide variety of natural substances, such as the secondary metabolites of aquatic life. The biological activities of these NPs have been evaluated and studied as essential ingredients for the creation of new drugs. According to biological measures, for example, derivatives of latrunculin (33,34,35) are inhibitors of HIF-1 for prostate cancers and activators of HIF-1 for breast tumors[53].



33. Latrunculin A



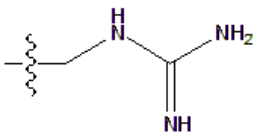
34. Latrunculin B



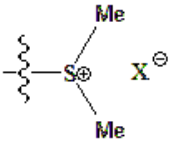
35. Oxalatrunculin B

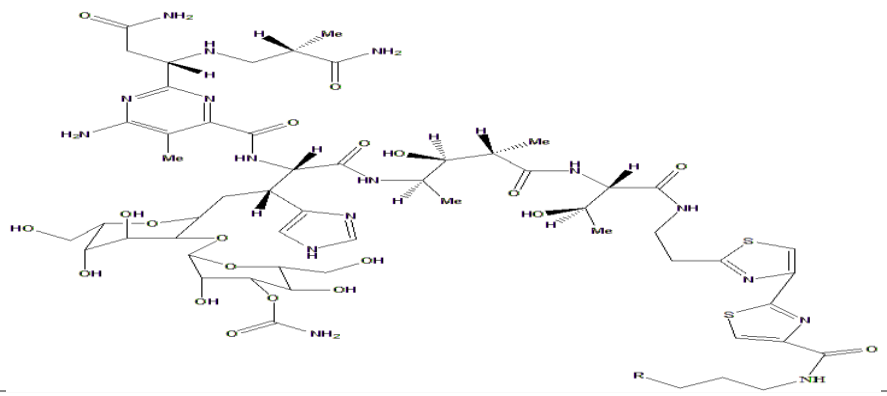
Umezawa and colleagues[54] identified a glycopeptide antibiotic called bleomycin (36,37) from the microbe Streptomyces verticillus. The main ingredient in the anticancer medication is bleomycin A2 (36), which is only different from other bleomycins in its C-terminus. Blenoxane (36) (trade name for bleomycin) has been used in conjunction with chemotherapy to treat testicular malignancies, cutaneous, head, and neck carcinomas, and Hodgkin's lymphoma[55].

36. Bleomycin A_2; R=



37. Bleomycin B_2; R=

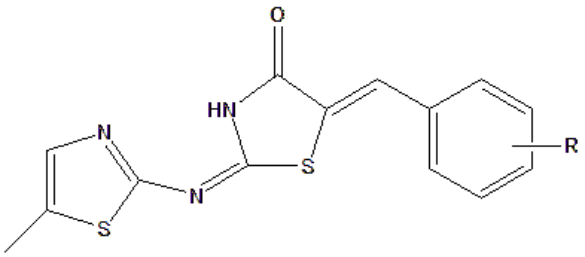




7.2 Antimicrobial Activity:

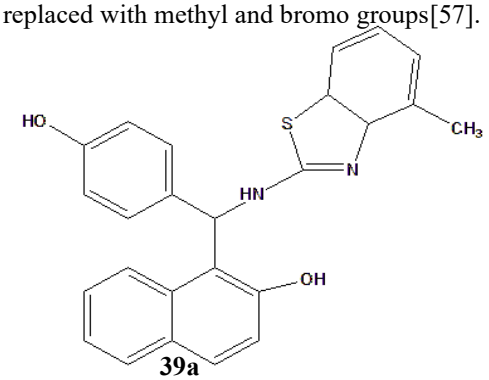
Chemical	Target Organism	Reference drug
38a, 38b, 38d, and 38f	B. cereus and E. coli	
38e	resistant varieties of MRSA, P. aeruginosa, and E. coli	Ampicillin and streptomycin
38c, 38f, and 38g	P. aeruginosa	

New thiazolidine derivatives based on methyl thiazole were synthesized by adding a solution of sodium carbonate and 2-amino-5-methylthiazole dropwise to chloroacetyl chloride in anhydrous DMF. The target compounds were obtained by undergoing multistep reactions with the resultant intermediate[56]. Several bacterial strains were used to test the antibacterial activity of recently synthesized benzothiazole derivatives. Among all studied strains, compounds 39a and 39b demonstrated the strongest antibacterial activity. Their strong activity is most likely due to a phenyl ring with hydroxy and nitro substitutions, as well as Dihydro-1,3-benzothiazole moieties replaced with methyl and bromo groups[57].

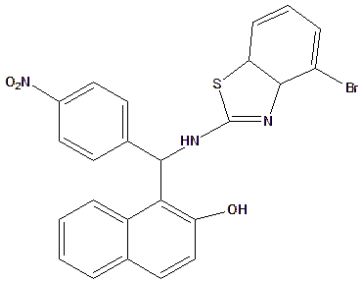


38

38a: R= H **38b** R= 4-OCH_3
38c: R= 3-F **38d:** R= 4-Cl
38e: R= 2,4-di Cl **38f:** R= 2,6-di Cl
38g: R= 3-Br



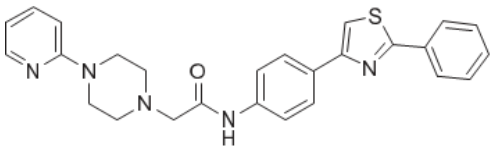
39a



39b

7.3 Antifungal Activity:

The biological activity of 2,4-Disubstituted Thiazole Derivatives 40 and 41 was assessed using various microorganisms[58].



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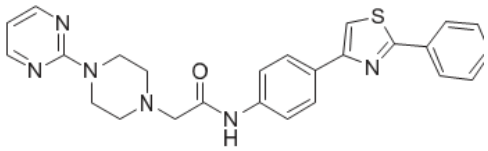
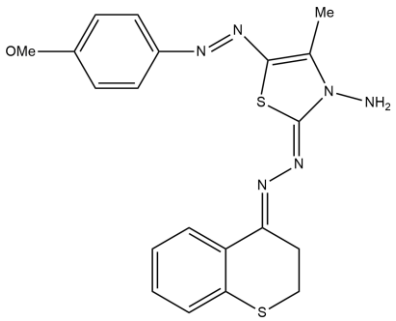


41

Compounds 42 and 43's biological characteristics were investigated by Farghaly et al. These exhibited antifungal effectiveness against *Syncephalastrum racemosum* (SR) comparable to that of gentamicin and greater than that of the well-known medication Amphotericin B[59].



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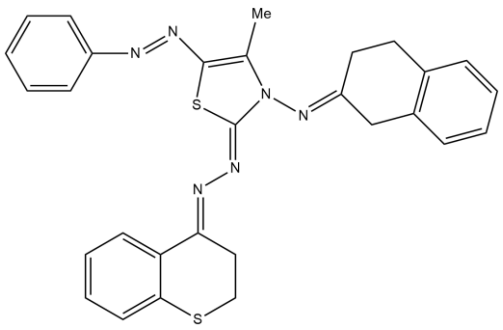


7.4 Antimalarial Activity:

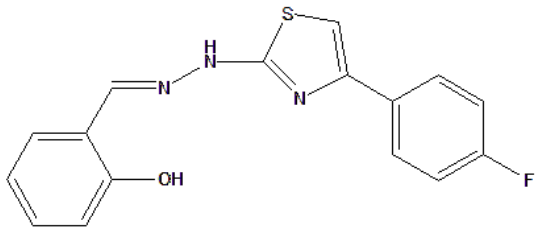
Chemical	IC_{50} Values	Target Organism
44	comparable to quinine	Plasmodium falciparum
45a and 45b	0.725 µM and 0.648 µM	*Plasmodium falciparum* NF54
46a, 46b	3.2, 2.7 µM 3.2, 3.2 µM	P. falciparum; chloroquine-active P. falciparum; chloroquine-inactive

Malaria remains a critical global health issue, with rising drug-resistant parasite strains posing a major challenge. The urgent need for new antimalarial drugs with novel mechanisms, broad applicability, and single-dose efficacy highlights the importance of thiazole derivatives in developing innovative treatments.

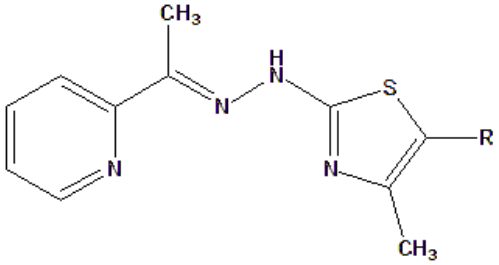
When 2-Hydroxybenzaldehyde or 5-chlorosalicylaldehyde was refluxed with Thiosemicarbamide in an environment of strong HCl in ethanol, certain novel thiazole hydrazine analogs(44) were created. According to the SAR study, the hydroxy and fluorine atoms that are substituted at the *p*-position of the phenyl ring are necessary to start the action[60].

In a related study, thiosemicarbazones were cyclized with aliphatic α-Halogenated carbonyl compounds to produce hydrazinyl thiazole derivatives 45a and 45b with varied substitutions. The activity was due to a 2-pyridyl hydrazinyl group at the thiazole ring's 2-position. Compound 45b, featuring an ethyl ester (COOC2H5) at the 5-position, showed strong efficacy, while substituting COOC2H5 with COCH3 in 45a further enhanced activity[61].

Utilizing a one-pot multicomponent technique, novel Thiazole-linked hydrazonic-thiazole amines 46a, 46b were synthesized with high yield utilizing 4-methyl-5-acetyl-2-aminothiazole, Thiourea-2-carbohydrazide, 2-Bromo-1-phenylethanone, or 3-(2-Bromoacetyl) coumarin. We evaluated their antimalarial activities in vitro. According to the structure-based study analysis, the thiazole ring's methoxy, bromo, and chloro groups must be substituted for the antimalarial activity to be shown[62].



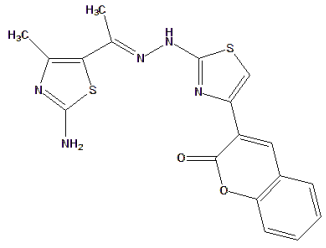
44



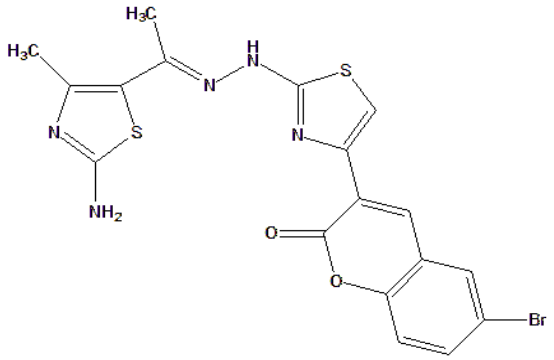
45

45a: R= $COCH_3$

45b: R= $COOC_2H5$



46a



46b

7.5 Anti-Tubercular Activity:

Despite being one of the leading causes of death globally, drug-resistant forms of tuberculosis (MDR-TB) render many treatments useless. There is an urgent need for better, more economical anti-TB treatments because existing medications like bedaquiline and linezolid have safety issues. Because of their safety and effectiveness, thiazole analogs hold promise as new options for creating potent anti-TB medications[51].

Recently, a copper-catalyzed [3 + 2] cycloaddition technique was used to synthesize some potential pyrazolyl thiazole compounds that showed efficacy against M. tuberculosis H37Ra (active and dormant strain). Significant efficacy was shown by compounds 47a–e against both the active and dormant strains of Mycobacterium TB H37Ra. The presence of several R and R1 groups (H, Cl, Br, F, hydroxymethyl, and methyl) connected to the phenyl ring is essential for the activity, according to the structure-based activity study[61].

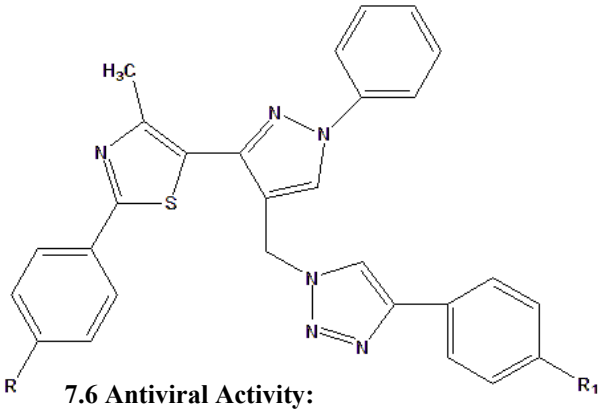
47a: R=H; R_1= H

47b: R=Br; R_1= F

47c: R=Br; R_1= CH_3

47d: R=Br; R_1=OCH_3

47e: R=Cl; R_1= F



47

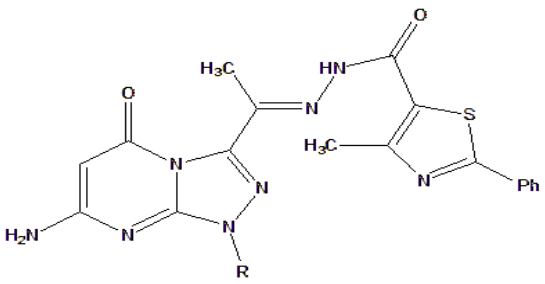
7.6 Antiviral Activity:

Chemical	Binding Energies	Target Organism	Reference drug
48a, 48b, and 48c	−8.1 0.33, −8.0 0.35, and 8.20.21 kilocal/mol	3C-like protease of coronavirus	
49b		Coxsackie Virus Type B (CVB3)	pirodavir or ribavirin
49a, 49d, and 49c		Enterovirus 71 (EV71)	pirodavir or ribavirin

Every year, a large number of individuals pass away from viral infections, which are among the most prevalent and deadly illnesses. In addition to recent developments in antiviral medication, there is an urgent need to discover more potent and effective agents. Numerous thiazole-based compounds were assessed and synthesized in this sector; some of them are reported below[62].

Many novel hydrazones containing a thiazole moiety, 48a, 48b, and 48c, have been synthesized, and current studies indicate that they have been computationally assessed for possible antiviral activity, specifically against the primary protease of the newly developed coronavirus (3C-like protease). According to the SAR analysis, particular groups, including triazole-substituted chloromethyl and phenyl aromatic rings, have to show antiviral properties[63].

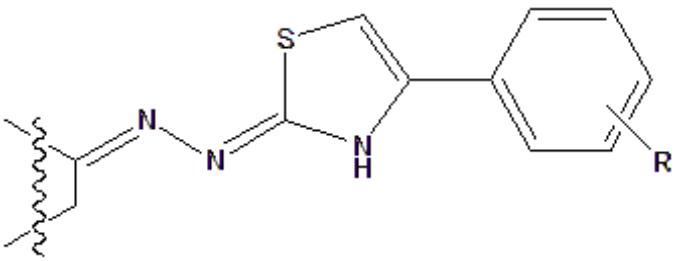
Using thiazoline heterocycles, several researchers created a range of steroid derivatives. Usually, N-substituted thiosemicarbazide has been added to DHEA in ethanol solution at the beginning. To find out, chemicals 49a-d are antiviral. A structure-based pharmacological activity investigation found that the addition of methoxy and nitro-substituted methyl and phenyl groups to thiazoles had the greatest impact on viral activity[64].



49

48

48a: R=C_6H_5
48b: R=4-$CH_3C_6H_4$
48c: R=4-ClC_6H_4



49a: R= 4-OCH_3
49b: R= 4-CN
49c: R=2-NO_2
49d: R= 4-CH_3

7.7 Anti-Inflammatory Activity:

Chemical	Target
50a, 50b, and 50c	COX-II Inhibitors
51a-e	Reducing inflammation
52a–h	Nitric oxide synthase (NOS) inhibitors

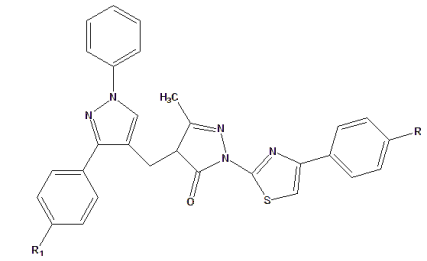
Inflammation is associated with various diseases like arthritis, cancer, infections, and asthma, with prostaglandins being a key marker. COX-1 and COX-2 are responsible for prostaglandin biosynthesis, and NSAIDs are commonly used to inhibit them. Recent research focuses on developing dual COX/LOX inhibitors, which may offer better therapeutic benefits, including improved anti-inflammatory effects and fewer side effects. The thiazole moiety, found in many drugs, has attracted attention for its potential in dual COX/LOX inhibition[54].

Many thiazole-bearing pyrazole analogs 50a, 50b, and 50c were developed for anti-inflammatory activity. Acetic acid was combined with 1-(2-bromophenyl) ethanone, Thiocarbohydrazide, and Ethyl acetoacetate at 60-80^{0}c. According to the structure-based study of the activity, to elicit the activity, the phenyl at position 4 has to be replaced by a methoxy and a chlorine group[65].

A novel anti-inflammatory medication showed, some of the molecules, 51a-e, were more successful in reducing inflammation than Celecoxib, the drug used as a base treatment[66].

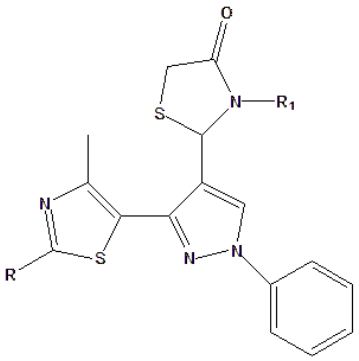
Novel compounds 5a and 52b exhibited significant activity because of the availability of oxadiazole and thiadiazole groups linked to the thiazole moiety, as well as phenyl and 2,2-bromophenyl connected to position 2 of the thiazole ring. Compounds 52a–h, on the other hand, have strong anti-inflammatory properties because of thiazoles attached to location 2 of substituted phenyl and at location 5 of substituted Thiosemicarbazide[67].

More anti-inflammatory and analgesic effectiveness was shown by derivative 53 when compared to indomethacin, the conventional medication. One possibility for the presence of 3-(Hydrazinomethyl)-4H-chromen-4-one is the enhanced activity that might occur[33].



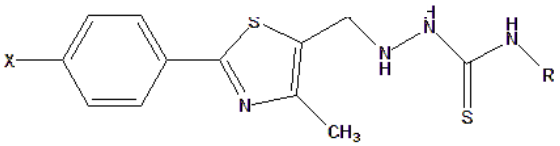
50

50a: R= Cl; R_1= H
50b: R= Cl; R_1= OCH_3
50c: R= H; R_1= H



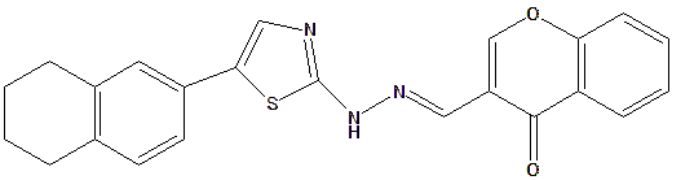
51

51a: R= C_6H_5; R_1= 4-FC_6H_4 **51b:** R= C_6H_5; R_1= 4-ClC_6H4 **51c:** R= CH_3; R_1= C_6H_5 **51d:** R= C_6H_5; R_1= 4-$CH_3C_6H_4$**51e:** R= CH_3; R_1= 4-FC_6H_4



52

52a: X= H; R= C_6H_5 **52b:** X= CH_3; R= C_6H_5 **52c:** X= Br; R= C_6H_5 **52d:** X= H; R= CH_3 **52e:** X= CH_3; R= CH_3 **52f:** X= Br; R= CH_3 **52g:** X=H; R= CH_2=CH-CH_2 **52h:** X= CH_3; R= CH_2=CH-CH_2



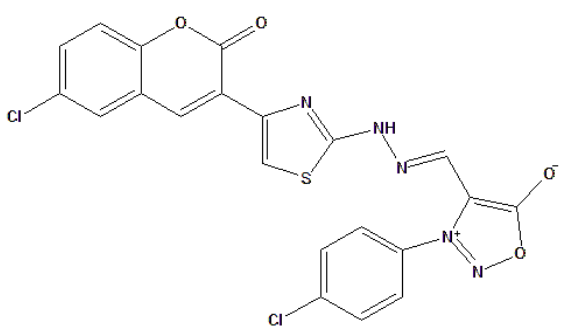
7.8 Anti-Diabetic Activity:

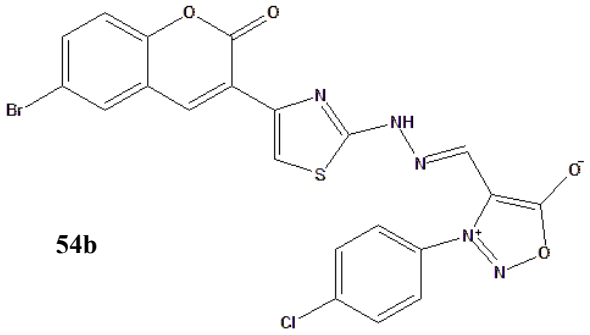
Chemical	Target
54a and 54b	α-amylase inhibitors
55a and 55b	Malonyl-CoA decarboxylase inhibitors
56	α-glucosidase and α-amylase inhibitors

Diabetes mellitus (DM) is characterized by chronic high blood sugar levels. Due to its structural similarity to thiazolidinediones, the thiazole nucleus holds significant potential for developing anti-diabetic drugs, making it a focus of research for effective diabetes treatments[68].

A novel one-pot thiazole-based synthesis of sydnones joined to coumarins was created. Treating 4-(Aryl) acetyl/4-(Aryl)formyl sydnone with thiosemicarbazide started the production of thiosemicarbazones. The resultant compounds 54a and 54b were analyzed for their DNA cleavage and α-amylase (antidiabetic) activities[69].

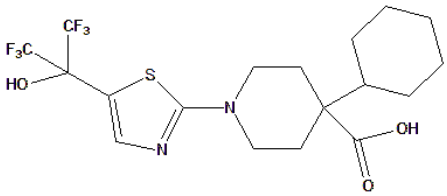
A novel family of hexafluoropropanols replaced with thiazoles was generated. The resulting substances were created by condensation with hexafluoroacetone hydrate, which started with 2-aminothiazole and resulted in 5-(2-Hydroxy-1,1,1,3,3,3-hexafluoropropan-2-yl)-2-aminothiazole. These recently created molecules, 55a and 55b, underwent MCD inhibitor testing. The end products are 3-(1H-indol-3-yl)-1-Phenyl-prop-2-en-1-one. The antihyperglycemic action of these analogs was evaluated by the enzymes α-glucosidase and α-amylase. This is likely due to compound 56's bromo group on the thiazole molecule's phenyl ring[70], [71].

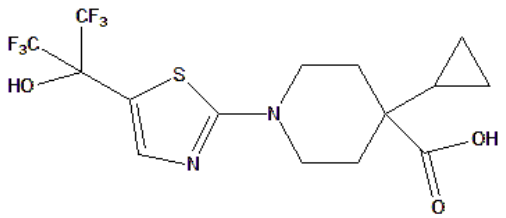




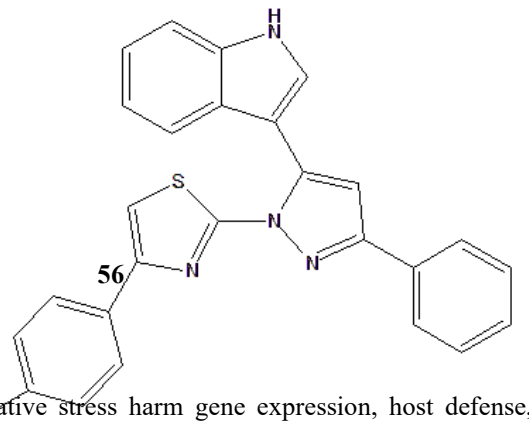
54b

55a





55b



56

7.9 Antioxidant Activity:

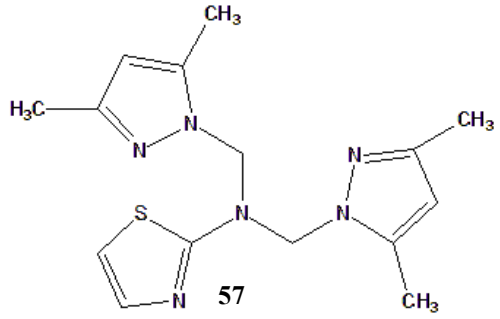
Elevated reactive oxygen species (ROS) during oxidative stress harm gene expression, host defense, and cell growth,

highlighting the importance of controlling free radicals to minimize cellular damage[72].

New heterocyclic compounds were created by linking the thiazole, pyrazole, and pyridine nuclei via condensing 4-pyridinamine or 1,3-thiazole derivatives with 3,5-dimethyl-1H-pyrazole,1,2,4-triazole, or 1H-pyrazole. Antioxidant (AO) properties were evaluated by DPPH scavenging. At 4.67 µg/mL, molecule 57 showed the highest level of antioxidant activity. The SAR analysis found that to show the action, substituting 2-aminothiazole was necessary[73].

Using various substituted isocyanates in acetone, an additional nucleophilic technique of (3-Chlorophenyl)-4-(2-chlorobenzoyl)-2-aminothiazole was used to synthesize a novel group of Selenocarbamide carrying a thiazole ring. It has been demonstrated that the selenourea compounds 58a, 58b, 58c, and 58d exhibit significant antioxidant action (AO) and have lower IC50 values than the reference drugs[74].

Production of 2-Thio-1,3,4-oxadiazol-5-(2-amino-5-methylthiazol-4-yl) analogs has antioxidant properties was investigated by the use of tests for OH, DPPH, NO, and superoxide radical scavenging. Compounds 59a, 59b, and 59c have been shown to have the ability to scavenge radicals; this may be because substituted aldehydes have an electron-donating substituent present[75].



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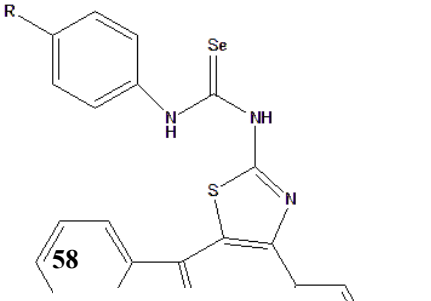
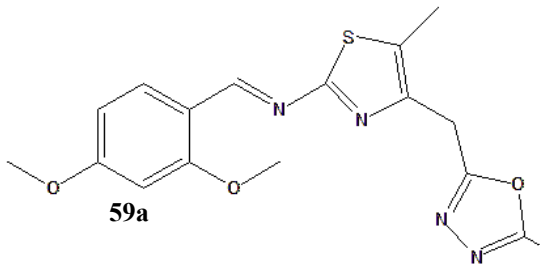
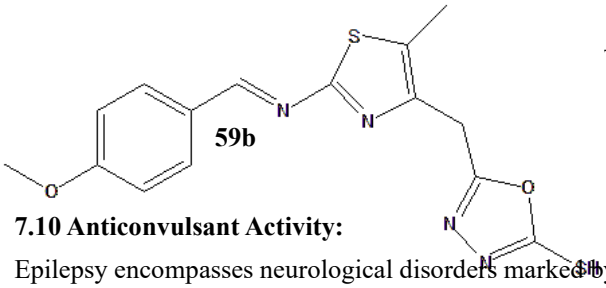


58

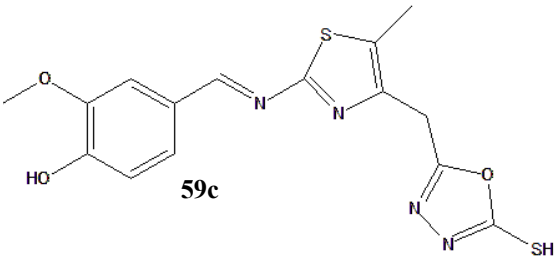
58a: R= CH_3 **58b:** R= OCH_3 **58c:** R= F **58d:** R= Br



59a



59b



59c

7.10 Anticonvulsant Activity:

Epilepsy encompasses neurological disorders marked by sudden, excessive neuronal activity causing seizures, often leading to unconsciousness or disorientation. Current anticonvulsant drugs control seizures in less than 70% of patients and frequently cause side effects like anemia, headaches, and ataxia. This underscores the need for new, selective, and less toxic antiepileptic drugs. Thiazole-based compounds have shown promise as anticonvulsants, with several examples detailed below[76].

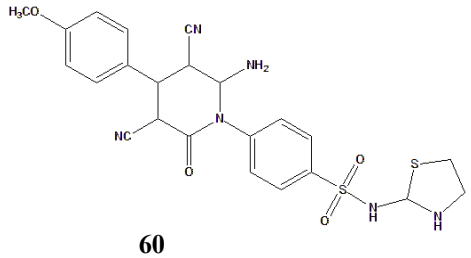
Farag et al. (2012) used 4-Amino-N-(2-thiazolyl) benzenesulfonamide as the starting molecule to create novel heterocyclic compounds. Numerous additional heterocyclic rings, such as pyrazole, thiazolidine, pyridine, and chromene, are present in the end products with the thiazole ring. Drug 60 was the most potent anticonvulsant medication, which completely stopped the tonic flexor period. Based on the SAR analysis, compound 80's highest activity might be linked to the Anisyl group that is bonded to the pyridine ring[77].

In MES and scope models, thiazole-containing compounds with 2,4-thiazolidinedione and thiazolidine-4-one nuclei have shown anticonvulsant efficacy. Using popular methods such as one-pot three-component, alkylation, and Knoevenagel

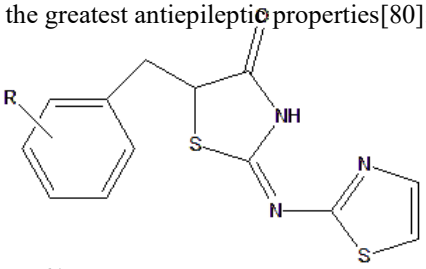
processes, the target compounds were synthesized. 61a and 61b were two of the analogues that were examined. 62 have a substantial anticonvulsant effect. Compound 61b's effectiveness was greater than that of sodium valproate, the reference medication[78].

A variety of novel amide-linked pyridazine-thiazole hybrids were compounded by Siddiqui et al. (2020). The derivative 63 is designated as N-(Thiazol-2-yl)-2-(4-chlorophenyl)-6-oxo-5,6-dihydropyridazin-1-yl acetamide in both the electroshock seizure test and Chemoconvulsant seizure test, showed best efficacy (effective dose=24.38 mg/kg & 88.23 mg/kg) respectively. When EWG such as F, Cl, and Br were identified at the phenyl ring connected at the 6th position of the pyridazine ring, higher seizure protection was shown in the SAR analysis of the synthesized compounds. The replacement of 4-chlorophenyl furthermore demonstrated the highest degree of activity[79].

Some newly synthesized thiazole-linked azoles that were evaluated exhibited anti-maximal electroshock seizure and anti-scPentylenetetrazol reactions. Analogs 64a and 64b in both seizure models give protection in the range from 33 to 100%. According to the SAR analysis, the 1,2,4-triazole moiety shows the greatest antiepileptic properties[80].



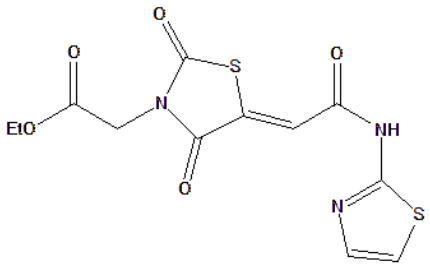
60

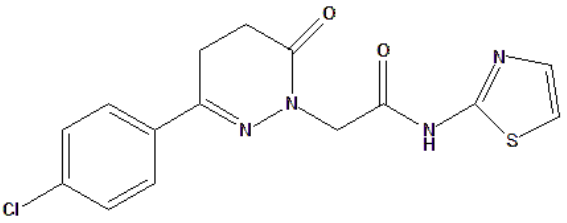


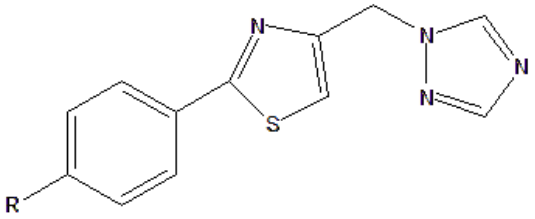
61

61a: R=3-NO_2 **61b:** R=3$CF_3C_6H_4NHCO$

63







64a: R= H **64b:** R=

64

7.11 Anticancer Activity:

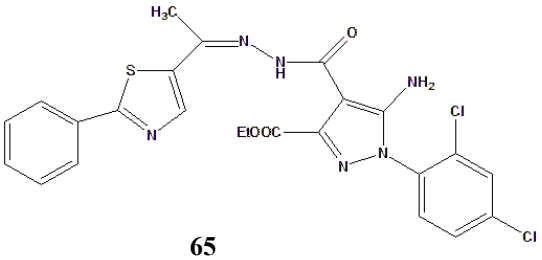
Significant advancements in anticancer drug discovery have led to the development of numerous innovative treatments. Several clinically used anticancer agents, such as dabrafenib, dasatinib, patellamide A, ixabepilone, and epothilone, feature a thiazole nucleus. Thiazole-based compounds have demonstrated potent antitumor activity, low toxicity, and the ability to target diverse biological pathways, including cell cycle regulation (microtubular inhibitors) and enzyme-linked receptors (polymerase inhibitors). This section highlights recent research on thiazole derivatives and their potential in anticancer drug development[81].

In a separate study, Gamma-Vinylpyridine, the chitosan-grafted polymer, was present when several new thiazole-bearing heterocycles were produced utilizing 1,3-dipolar cycloaddition techniques. Tests using (HCT-116) colorectal carcinoma, (HepG-2) human hepatocellular carcinoma, and (MCF-7) breast cancer cell lines revealed that all of the compounds had anti-proliferative activity. Compounds 65 and 66, which included chlorine, were the most powerful of them; nevertheless[82].

The newly created compounds were examined using ARPE-19, Bcl-2-Jurkat, and A-431 cultures. Several in vitro and silico experiments have been performed on each analog. Substitution in the phenyl ring by m, p-dimethyl proves the cytotoxic action of substance 87 as per the SAR study. The thiazole moiety's N, N-dimethyl group has to be changed to a phenyl ring

for Substance 68 to function. Substances 69 and 70 have an anticancer effect only if the p-chloro/p-methyl group of the ring of phenyl ring and the N, N-dimethyl group of the thiazole ring are substituted with a simple methyl group. Substance 71 requires substituting a methyl group form, p-dimethyl for the phenyl ring, and N, N-dimethyl for the thiazole ring to exhibit cytotoxic action[83].

In recent research, Sayed and colleagues (2020) described a three-component process that begins with 2-(2-benzylidene hydrazinyl)-4-methylthiazole and yields a variety of 1-(2-thiazol-2-yl) hydrazono-5-(2-ethylthiazole) analogs. Using the MTT colorimetric test, anticancer testing towards HepG2, HT-29, and HCT-116 was conducted. When analogs 72a, 72b, and 73 were pitted against cancer cell lines, they outperformed the common medications harmine and cisplatin. The thiazole ring was replaced on analogs 72a and 72b with 4-chlorophenyl and 2,4-chlorophenyl groups, respectively, resulting in notable effectiveness. In substance 73, thiazole-4-one is connected by a 2,4-chlorophenyl group[84].



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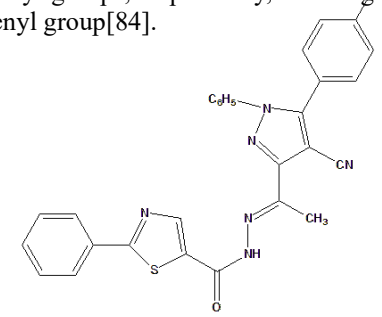

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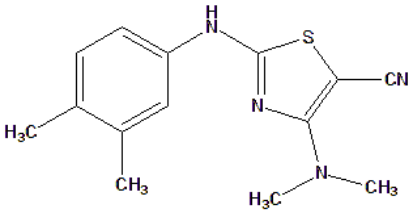

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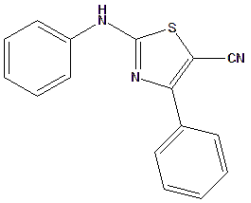
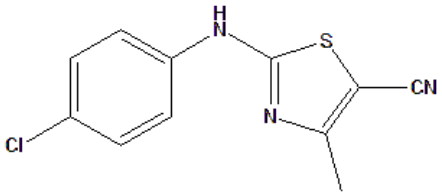


68



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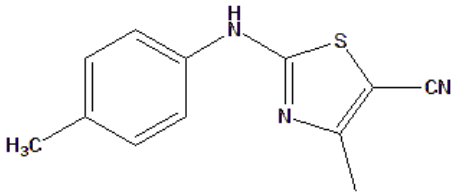

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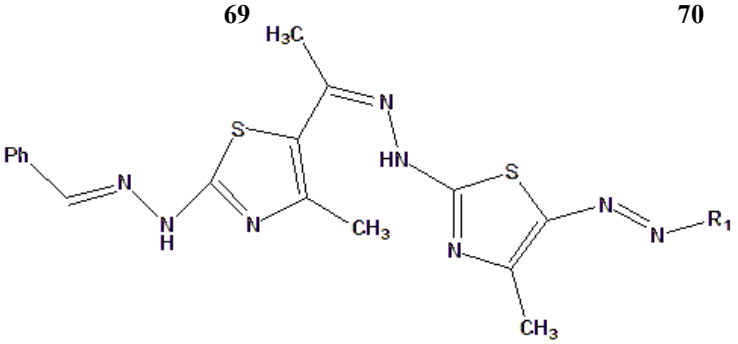
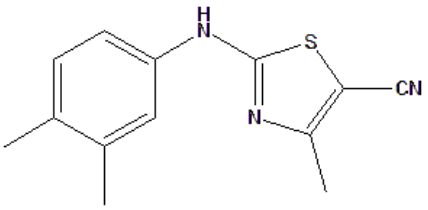


72

72a: R_1= 4-ClC_6H_4
72b: R_1= 2,4-ClC_6H_3



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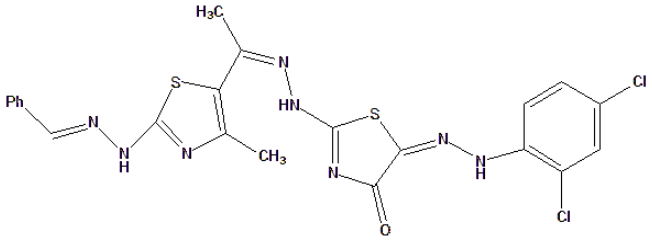


73

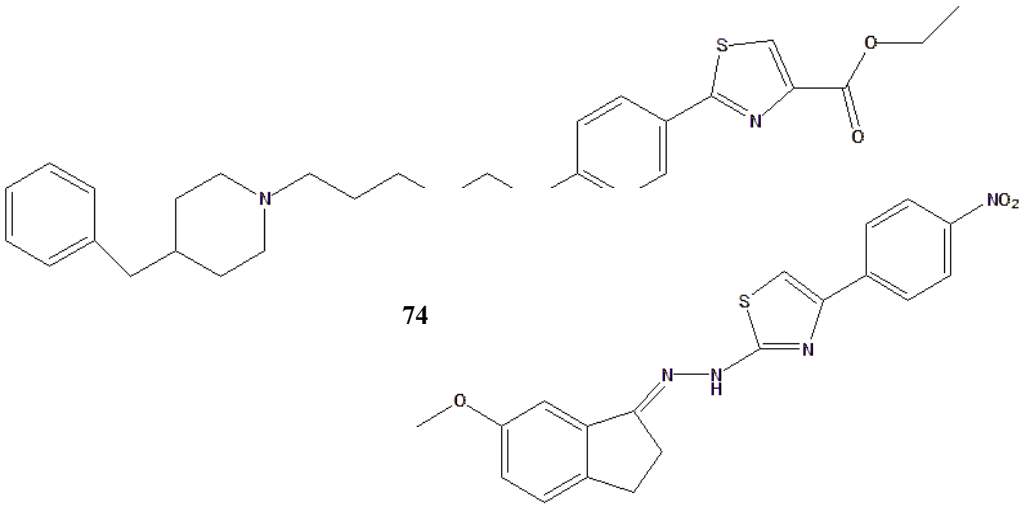
7.12 Anti-Alzheimer Activity:

Chemical	IC_{50} Values	Target
74	5.19 µM	Acetylcholinesterase inhibitors
74	5.83 µM	Butyrylcholinesterase inhibitors
75	0.026 µM	Cholinesterase (ChE) and beta-amyloid plaque inhibitors

Dementia, often associated with Alzheimer's disease (AD), is a neurological disorder that can result from various CNS conditions. Current treatment options are limited and fail to provide substantial relief or improve the quality of life for affected individuals, highlighting the urgent need for innovative, safe, and effective therapies. Many existing drugs are outdated and inadequate, prompting researchers to explore new possibilities. Given the success of thiazole-based compounds in treating various ailments, scientists are increasingly focusing on thiazole derivatives as potential anti-Alzheimer agents. Several promising candidates have shown significant efficacy against Alzheimer's disease[85].

Authors Shi et al. (2017) synthesized novel 2-phenylthiazole compounds to discover potent cholinesterase inhibitors. The first intermediate was created by combining Beta-Bromopyruvic acid ethyl ester and 4-Hydroxybenzothioamide with ethanol to create ethyl 2-(4-hydroxyphenyl) thiazole-4-carboxylate. The final compounds were then synthesized in several processes. Structure-activity analysis of 74 revealed that the primary prerequisite for demonstrating anti-Alzheimer's action was the presence of (5-Thiomorpholinopentyl) oxy groups[86].

Novel thiazol-2-ylhydrazine compounds were synthesized and created by the donepezil molecule. A p-nitrophenyl ring was shown to be available in compound 75 as per SAR investigations of anticholinesterase and anti-beta plaque amyloid behavior[87].



Applications Beyond Biology:

Fluorescent Probes and Sensors: Due to their aromaticity and conjugation.

Organic Electronics and Materials: Thiazole derivatives are used in OLEDs and solar cells.

Corrosion Inhibitors and Agrochemicals: Exploiting their strong coordination and biocidal properties[88].

8.0 Recent Developments:

Contemporary modifications to the Hantzsch synthesis incorporate solvent-free conditions and microwave assistance, which significantly improve reaction rates and yields while maintaining product quality[89]. The Lawesson's reagent methodology allows the synthesis of complex thiazole derivatives through selective thionation reactions under mild conditions with high functional group tolerance[90]. The thiochroman-based synthesis using thiocarbohydrazide has gained prominence due to its

one-pot multicomponent reactions, which offer improved atom economy and reduced waste generation. These synthetic strategies are still being developed, with current studies aiming to create thiazole synthesis techniques that are more effective, eco-friendly, and selective. Several variables, such as intended substitution patterns, scale needs, and resource availability, influence the choice of a particular synthetic pathway[91].

9.0 Future Perspectives:

Research is still being done to improve the medicinal potential of thiazole-based drugs using innovative, environmentally friendly synthesis techniques. The discovery of ideal candidates is being sped up by developments in computational chemistry, such as AI-driven drug design. Promising approaches to treating complex disorders include the creation of targeted drug delivery systems and multifunctional thiazole derivatives. These substances have the potential to become next-generation antibiotics and antivirals when drug resistance increases. Thiazoles will remain essential scaffolds in contemporary medicine thanks to interdisciplinary approaches that combine synthetic chemistry and biological sciences.

Submission Declaration:

This manuscript has not been published previously and is not being considered for publication elsewhere. The authors confirm that the work is original, and all authors have read and approved the final manuscript for submission.

Conflict Of Interest:

The authors, Vishnu Dev Verma, declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Credit Authorship Contribution Statement:

Vishnu: Writing- original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Amrita:** review & editing, Validation. **Himanshi:** Writing – review & editing, Conceptualization, Visualization. **Jay:** Writing – review & editing, Validation.

Declaration Of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Ethics Statement:

This review paper involves no experimental research, human subjects, or animal studies that need ethical approval; instead, it is based entirely on publicly available literature. For the sake of academic openness and integrity, all acknowledged sources have been appropriately referenced. I have done all in my power to provide an objective, accurate, and thorough literature review, free from any conflicts of interest that could affect the interpretation of the data. The development of this work has not involved any instances of scientific misconduct, data manipulation, or plagiarism. Let me know if you need any refinements!

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