

An Overview of Synthetic Derivatives of Thiazole and Their Role in Therapeutics

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SUMMARY

Thiazole derivatives have attracted much attention in medicinal chemistry due to their diverse pharmacological activities. This study provides an overview of the latest synthetic derivatives of thiazole and their therapeutic applications. Innovative methodologies have been adopted to enhance the structural diversity and optimize the pharmacological properties of thiazole-based compounds. These synthetic derivatives exhibit a broad spectrum of therapeutic activities, and understanding the essential features responsible for the observed pharmacological effects has been pivotal in structure-activity relationship studies. Drug development efforts have focused on modulating thiazole derivatives for improved bioavailability, selectivity, and reduced toxicity. This abstract highlights the potential of thiazole derivatives in targeting specific biological activity, paving the way for developing innovative therapeutic agents. Thiazole moiety as a heterocyclic compound was studied for its different pharmacological actions. The derivatives obtained from thiazole have diverse therapeutic actions along with antimicrobial activity, antitubercular activity, antidiabetic activity, anticonvulsant, anti-inflammatory actions, and antitumor activities. The mechanism of actions of all these activities is also studied by the researcher to provide scientific evidence and validation of their actions. Utilization of synthetic chemistry for exploration of various pharmacological potential of thiazole derivatives will lead the future pharmacologists to a newer dimension for new drug discovery and also these derivatives can be further optimized for the development of alternative options for the treatment of various diseases. The versatility of thiazole scaffolds presents promising opportunities for discovering new drugs with enhanced efficacy and improved pharmacokinetic profiles. As researchers continue to delve into the synthesis and pharmacological evaluation of thiazole derivatives, their significance in modern drug design and therapy becomes increasingly evident.

Key Words: Thiazole, heterocyclic, antitubercular, antimicrobial, anti-inflammatory.

Tiyazolün Sentetik Türevlerine ve Tedavideki Rollerine Genel Bir Bakış

ÖZ

Tiyazol türevleri, çeşitli farmakolojik aktivitelerinden dolayı medisinale kimyada büyük ilgi görmüştür. Bu çalışma, tiyazolün en yeni sentetik türevlerine ve bunların terapötik uygulamalarına genel bir bakış sunmaktadır. Tiyazol bazlı bileşiklerin yapısal çeşitliliğini artırmak ve farmakolojik özelliklerini optimize etmek için yenilikçi metodolojiler benimsenmiştir. Bu sentetik türevler geniş bir yelpazede terapötik aktivite göstermektedir ve gözlemlenen farmakolojik etkilerden sorumlu olan temel özelliklerin anlaşılması, yapı-aktivite ilişkisi çalışmalarında önemli bir rol oynamıştır. İlaç geliştirme çalışmaları, iyileştirilmiş biyoyararlanım, seçicilik ve azaltılmış toksisite için tiyazol türevlerinin modülasyonuna odaklanmıştır. Bu özet tiyazol türevlerinin spesifik biyolojik aktiviteyi hedeflemedeki potansiyelini vurgulayarak, yenilikçi terapötik ajanların geliştirilmesinin önünü açmaktadır. Heterosiklik bir bileşik olarak tiyazol, farklı farmakolojik etkileri açısından incelenmiştir. Tiyazolden elde edilen türevler, antimikrobiyal, antitüberküloz, antidiyabetik, antikonvülsan, antiinflamatuar ve antitümör aktiviteler dahil olmak üzere çeşitli terapötik etkilere sahiptir. Tüm bu aktivitelerin etki mekanizmaları, aktivitelerin bilimsel kanıtlarını ve geçerliliğini sağlamak için araştırmacılar tarafından da incelenmiştir. Tiyazol türevlerinin çeşitli farmakolojik potansiyellerinin araştırılması için sentetik kimyanın kullanılması, geleceğin farmakologlarını yeni ilaç keşfinde daha yeni bir boyuta taşıyacak ve ayrıca bu türevler, çeşitli hastalıkların tedavisi için alternatif seçeneklerin geliştirilmesi amacıyla daha da optimize edilebilecektir. Tiyazol halkasının çok yönlülüğü, etkinliği artırılmış ve farmakokinetik profilleri iyileştirilmiş yeni ilaçların keşfedilmesi için umut verici fırsatlar sunmaktadır. Araştırmacılar tiyazol türevlerinin sentezi ve farmakolojik değerlendirmesi üzerinde çalışmaya devam ettikçe, bunların modern ilaç tasarımı ve tedavisindeki önemi giderek daha belirgin hale gelmektedir.

Anahtar Kelimeler: Tiyazol, heterosiklik, antitüberküloz, antimikrobiyal, antiinflamatuar.

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INTRODUCTION

Thiazoles are a class of heterocyclic compounds that contain a unique aromatic pentagonal ring structure and are identified by the molecular formula C_3H_3NS . At room temperature, the unbound form of thiazoles appears as a pale yellow liquid. The thiazole nucleus serves as a fundamental structural component of vitamin B, highlighting the biological importance of this heterocyclic moiety. In synthetic chemistry, thiazoles are vital in the controlled generation of carbene entities. This is achieved by conjugating them with transition metals to form metal-thiazole complexes, which serve as catalysts in catalytic processes of considerable significance, such as the Stetter reaction and benzoin condensation. The strategic integration of thiazoles with transition metals permits the precise generation of free carbene species and imparts catalytic prowess to the resulting complexes, thus driving progress in synthetic methodologies in organic chemistry (Ali & Sayed, 2021; Alrazzak, 2018).

Compounds containing thiazole moieties, commonly referred to as thiazole derivatives, exhibit a broad range of biological activities encompassing antipsychotic, analgesic, anticancer, antiallergic, antihypertensive, antibacterial, anti-inflammatory, antimalarial, and antifungal properties. Thiazole-based scaffolds are essential due to their incorporation into the structural frameworks of FDA-approved drugs, highlighting their clinical relevance. Moreover, these thiazole-containing scaffolds are pivotal constituents in over 70 experimental drugs, indicating the ongoing exploration and potential therapeutic applications of thiazole-derived compounds in pharmaceutical research and development. Most naturally occurring thiazole rings are found in microbial and marine sources. Therefore, thiazoles or compounds containing them have several uses as pharmacological agents, making thiazole an effective nucleus (Rajiani & Ismail, 2019; Singh et al., 2020) analgesic, antibacterial, anticancer, antiallergic,

antihypertensive, antiinflammatory, antimalarial, antifungal and antipsychotic. The scaffold is present in more than 18 FDA approved drugs and also in more than 70 experimental drugs. Only a few reviews are available in the literature despite its great medicinal importance. During the course of time, this scaffold has been studied extensively for its antiviral activities and provided compounds with activity in the nM range. However, no focused review is available on the compilation of antiviral activities shown by this scaffold. Objective: In the present review, we have made an effort to compile antiviral literature of thiazoles reported from the year 2011 to till date. Methods: We searched the SciFinder database (excluding patent literature).

Thiazole, a unique heterocyclic ring of nitrogen and sulfur atoms, holds significant importance in chemistry. It is found in many heterocyclic compounds with antibacterial, anticancer, anti-inflammatory, anticonvulsant, and antibiotic properties. Thiazoles display diverse activities and are essential heterocyclic rings with five members. The thiazole derivative compounds in this category are classified as natural, semisynthetic, or synthetic. According to molecular orbital techniques, thiazole molecules are aromatic and contain some dienic character, as evidenced by the pi-bond ordering. The widespread presence of thiazole and its derivatives in various chemical, biological, and medicinal applications makes it an attractive area of research for scientists and chemists (Gartel & Kandel, 2008; Knott-Hunziker et al., 1979).

The boiling points of free thiazole lie between the range of 116°C to 118°C. Thiazole is characterized by its flammability and pale-yellow liquid form, emitting a fragrance similar to pyridine. Its aromatic properties are attributed to a single pair of electrons from the Sulphur atom that has delocalized and formed a 6π -electron system. Additionally, proton nuclear magnetic resonance demonstrates the strong aromaticity of the thiazole protons, where the chemical shift value of each thiazole ring proton falls between

7.27 and 8.77 ppm. The thiazole resonance structures are depicted in Figure 1. Electrophilic substitution occurs preferentially at the C₅ position, followed by the C₄ position, as indicated by the computed π -electron

density. On the other hand, nucleophilic substitution takes place at the C₂ position (Abdu-Rahem et al., 2021; Borcea et al., 2021).

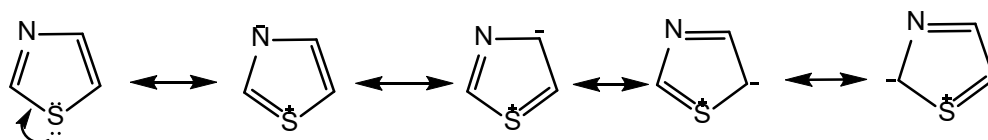


Figure 1. Resonance structures of thiazole

Biological Activities of Thiazole Derivatives

Antimicrobial Activity

Thiazole derivatives have been synthesized systematically as antimicrobial agents to combat the increasing challenge of multidrug-resistant bacterial strains. These derivatives have been specifically developed to target various highly resilient strains, including *E. species*, *A. baumannii*, *P. aeruginosa*, *E. cloacae*, *S. aureus*, and *Candida* species. These strains have demonstrated acquired resistance to fluconazole and are critical in the pathogenesis of numerous human diseases, such as pulmonary and urinary tract infections (Berkow & Lockhart, 2017). The absence of effective medications to combat resistant gram-negative bacteria is primarily attributed to several decades of inadequate innovative antimicrobial drug development. Consequently, novel medicines with distinct and relatively unique mechanisms of action are urgently required to target both susceptible and resistant strains. This calls for a concerted effort in the field of antimicrobial drug development to identify and develop new drugs with the potential to address the growing challenge of antibiotic resistance (Holmes et al., 2016).

A new set of chemical compounds known as 2-(4-arylpiperazine-1-yl)-N-[4-(2-(4-substituted phenyl)thiazol-4-yl)phenyl] acetamide derivatives were prepared and tested for their effectiveness in fighting against microorganisms (specifically 2a-2f) Figure 2. The reference medications ketoconazole and chloramphenicol were employed in the tests of the

compounds against both gram-positive and gram-negative bacteria and fungus, respectively. However, the compound's antibacterial activity was generally weaker than the reference drugs, with most compounds having a minimum inhibitory concentration (MIC) of between 100-400 $\mu\text{g/ml}$, while the reference drugs had a MIC of 25-50 $\mu\text{g/ml}$. For gram-positive *E. faecalis*, only two compounds (2b and 2c) in Figure 2. demonstrated marginally increased efficacy, with a MIC of 100 $\mu\text{g/ml}$ (Yurttas et al., 2015).

A newly developed compound called 2,4-disubstituted thiazole has promising potential as an antimicrobial agent against a gram-positive bacterial strain. The tube dilution technique was used to prepare this compound, and compounds 3a-c (Figure 3) were found equally effective against *S. aureus*. This result highlights the effectiveness of these particular derivatives as antimicrobial agents. The systematic analysis of the antimicrobial profiles of these newly developed thiazole derivatives provides valuable insights into their pharmacological attributes and paves the way for further investigations into their method of action and potential therapeutic applications (Arora et al., 2015; Testing, 2000).

New imidazolyl thiazole derivatives were synthesized, and two compounds (4a and 4b) were found to have the notable antibacterial activity when compared against standard drugs like fluconazole and ciprofloxacin. Their minimum inhibitory concentrations (MICs) were observed to range from 1.95 to 3.91 $\mu\text{g/ml}$ and 3.91 to 15.62 $\mu\text{g/ml}$ for 4a

and 4b (Figure 4), respectively, signifying significant efficacy, particularly against *Bacillus* species and *M. luteus* (Łączkowski et al., 2015; Testing, 2000).

Karale et al. synthesized a total of 24 molecules with antibacterial activity, among which compounds 5a and 5b (Figure 5) demonstrated moderate to low activity against *E. coli*, *S. typhi*, *B. subtilis*, and *S. aureus* and were found to be structurally similar to ciprofloxacin. However, compounds 5c to 5e (Figure 5) displayed the highest activity against *B. subtilis* (16-18 mm) and *S. aureus* (17 mm), highlighting their potential as effective antimicrobial agents. These findings provide valuable insights into developing novel antibacterial compounds with improved efficacy against commonly encountered bacterial pathogens (Karale et al., 2015).

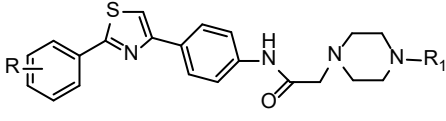
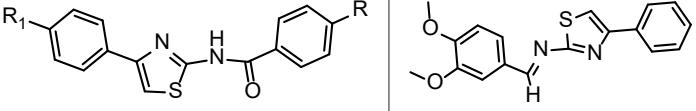
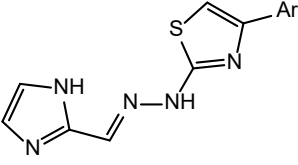
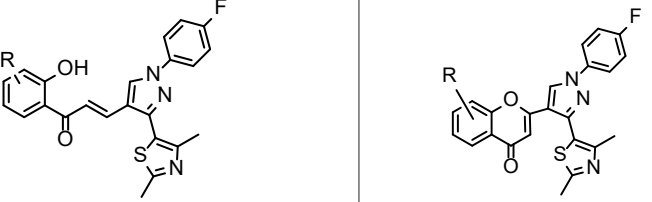
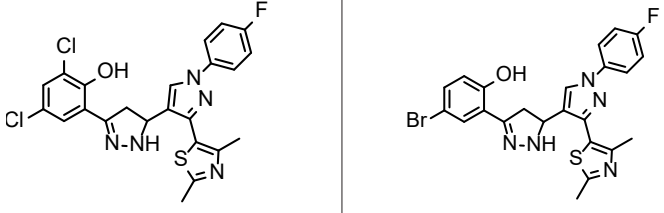
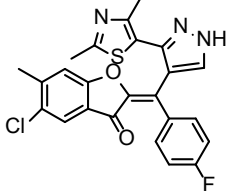
Assessment of synthetic compounds (6a and 6b) Figure 6 that contain thiazoles and thiazolidinediones were conducted to determine their antibacterial efficacy against a variety of gram-negative and gram-positive bacteria, including *B. subtilis*, *S. aureus*, and *S. epidermidis*. *P. aeruginosa*, *Proteus vulgaris*, and *Klebsiella pneumoniae*. Fungal strains were also included in the assessment. Compounds with electron-withdrawing groups demonstrated inhibition zones against *S. aureus*, *S. epidermidis*, and *B. subtilis*. Minimum inhibitory concentrations (MICs) for these gram-positive bacteria ranged from 0.98 to 3.9 µg/ml, while ampicillin displayed an MIC of 0.24 µg/ml. The antibacterial activity of the compounds varied,

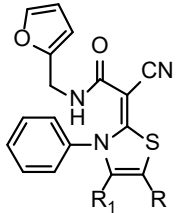
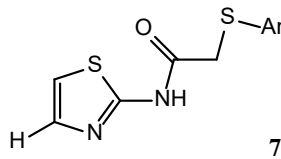
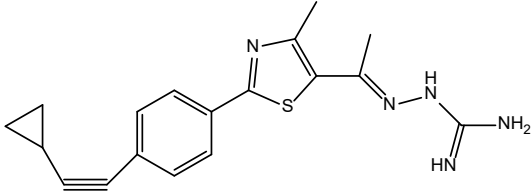
indicating the importance of structural characteristics and microbial targets when assessing efficacy across different species (Salem, 2017).

The antibacterial activity of 6-[(1/4-methyl imidazole/triazole/tetrazole-2/3/5-yl) thiol] derivatives was evaluated by Cankilic et al. against a diverse range of filamentous fungi, yeast, and bacteria. The N-(4-substituted thiazol-2-yl) acetamide analogs of compound 7 (Figure 7) exhibited antibacterial efficacies ranging from mild to moderate. Only compound 7 achieved 50% inhibition of *Listeria monocytogenes* among the tested compounds (Cankılıç & Yurttaş, 2017).

Elsebaei et al. examined a novel series of phenylthiazoles featuring alkynyl linkages, with compound 8 (Table 1) emerging as a promising candidate due to its efficacy in inhibiting the growth of antibiotic-resistant bacteria. The most potent compound exhibited exceptional activity against clinically relevant MRSA strains, with a minimal inhibitory concentration below 0.5 µg/ml. In terms of hepatic metabolism, compound 8 (Figure 8) demonstrated favorable stability, with a half-life ($t_{1/2}$) of 4.5 hours. Further, in a neutropenic mouse thigh infection model, this compound demonstrated comparable efficacy at low doses compared to vancomycin. These results indicate that phenylthiazoles have promise as a class of antibiotics with potent activity against drug-resistant bacteria (Elsebaei et al., 2018).

Table 1. Thiazole derivatives showing antimicrobial activity.

Activity	Compounds	Structures
Antimicrobial agents	<p>Compounds (2a-2f): aryl piperazine-1-yl)-N-[4-(2-(4-substituted phenyl)thiazol-4-yl)phenyl]acetamides derivatives</p>	 <p>2a: R=H, R₁=Ph-CH₂ 2b: R=H, R₁=C₅H₅N 2c: R=H, R₁=Pyrimidine 2d: R=4-OMe-Ph R₁=C₅H₅N 2e: R=4-Cl-Ph R₁=Ph-CH₂ 2f: R=4-F-Ph R₁=Ph-CH₂</p> <p>Figure 2. 2-(4-methyl piperazine-1-yl)-N-(4-(2-phenylthiazol-4-yl)phenyl)acetamide</p>
	<p>Compounds (3a-c): Structure of 2,4-disubstituted (E)-1-(3,4-methoxyphenyl)-N-(4-phenylthiazol-2-yl) methaniminederivatives</p>	 <p>3a: R=4-NO₂ R=H 3c: R=H R₁=4-OMe</p> <p>Figure 3(a,c). 4-methyl-N-(4-(p-tolyl)thiazol-2-yl)benzamide</p> <p>3b Figure 3b. (E)-N-(3,4-dimethoxybenzylidene)-4-phenylthiazol-2-amine</p>
	<p>Compounds (4a-b): structures of (E)-2-(2-((1H-imidazole-2-yl)methylene)hydrazinyl)-4-argiothiazole</p>	 <p>4a: Ar= 4-Br-C₆H₄ 4b: Ar= aamantyl</p> <p>Figure 4. (E)-2-(2-((1H-imidazole-2-yl)methylene)hydrazinyl)-4-argiothiazole</p>
	<p>Compounds (5a-e): structures of different (E)-3-(3-(2,4-dimethylthiazol-5-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one thiazole derivatives</p>	 <p>Figure 5a. (E)-3-(3-(2,4-dimethylthiazol-5-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one</p> <p>Figure 5b. 2-(3-(2,4-dimethylthiazol-5-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-4H-chromen-4-one</p>
		 <p>Figure 5c. 2,4-dichloro-6-(3'-(2,4-dimethylthiazol-5-yl)-1'-(4-fluorophenyl)-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-5-yl)phenol</p> <p>Figure 5d. 4-bromo-2-(3'-(2,4-dimethylthiazol-5-yl)-1'-(4-fluorophenyl)-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-5-yl)phenol</p>
		 <p>Figure 5e. (Z)-5-chloro-2-(((3-(2,4-dimethylthiazol-5-yl)-1H-pyrazol-4-yl)(4-fluorophenyl)methylene)-6-methylbenzofuran-3(2H)-one</p>

	<p>Compounds (6a-b): E-2-cyano-2-(4,5-dialkyl-3-phenylthiazol-2(3H)-ylidene)-N-(furan-2-ylmethyl)acetamide</p>	 <p>6a: R = COMe 6b: R = 4-Ph-NO₂</p> <p>Figure 6. (E)-2-cyano-2-(4,5-dimethyl-3-phenylthiazol-2(3H)-ylidene)-N-(furan-2-ylmethyl)acetamide</p>
Antimicrobial agents	<p>Compound 7: 2-(argiothio)-N-(thiazol-2-yl)acetamide</p>	 <p>Figure 7. 2-(argiothio)-N-(thiazol-2-yl)acetamide</p>
	<p>Compound 8: New (E)-2-(1-(2-(4-(cyclopropylethynyl)phenyl)-4-methylthiazol-5-yl)ethylidene)hydrazine-1-carboximidamide compounds</p>	 <p>Figure 8. (E)-2-(1-(2-(4-(cyclopropyl ethynyl)phenyl)-4-Methyl thiazole-5-yl)ethylidene)hydrazinecarboximidamide</p>

Antitubercular activity

Tuberculosis (TB) is a persistent global health concern, resulting in the loss of millions of lives annually. The severity of TB is amplified when drug-resistant strains of the pathogen *Mycobacterium tuberculosis* arise. In 2019, TB was responsible for the death of 1.4 million individuals, making it the leading fatal infectious health problem and one of the top ten causes of death globally. Although established treatments like pyrazinamide, rifampicin, ethambutol, and isoniazid have proved effective in treating the disease, TB's global incidence experiences a marginal annual decline of approximately 2%, according to the World Health Organization (WHO) data. However, the persistent challenge of drug-resistant tuberculosis, particularly the severe healthcare threat posed by multiple-drug-resistant tuberculosis (MDR-TB), requires rapid attention and innovative antitubercular agents to counteract the escalating prevalence of resistant strains. This imperative underscores the need to strengthen the therapeutic arsenal against this 608

formidable infectious disease (Fogel, 2015; Ran et al., 2016).

Bekker et al. conducted an *in vitro* investigation to assess a novel usnic acid derivative's capacity to suppress the development of *M. smegmatis* and *M. tuberculosis*. According to the study, for best results, specific configurations of amino acids inside the thiazole ring were required. The findings revealed notable protein kinase activity, especially against the strains of *S. lividans* and *M. smegmatis*. The kanamycin-resistant *M. smegmatis* strain exhibited enhanced susceptibility to (-) usnic acid thiazole compared to the (+) isomer, with 9a and 9b (Figure 9) demonstrating potent inhibitory activity. Both isomers exhibited a similar effect on *M. tuberculosis* H37Rv, with isomer 9b exhibiting greater efficacy than 9a (Bekker et al., 2015).

Researchers led by Guzeldemirci evaluated the antimycobacterial efficacy of a brand-new class of substances against *M. tuberculosis* H37Rv in culture. Derivatives of 2-[6-(4-bromophenyl)imidazo

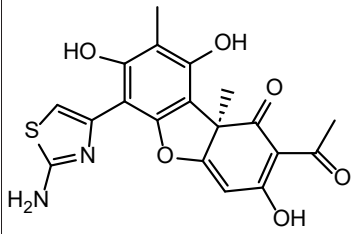
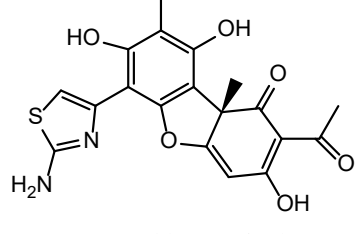
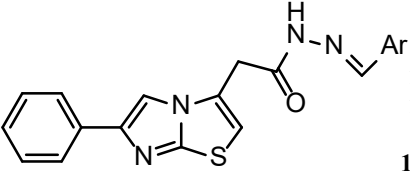
N-(arylidene) thiazol-3-yl acetohydrazides were produced. With an IC₅₀ greater than 1.6 mg/mL and 99% inhibition, compound 10a showed the greatest potency of all the compounds tested. Compound 10b, in contrast, had a comparatively lower inhibition rate (91%) and an IC₅₀ of 1.05 µg/mL than its counterparts. These results demonstrate these synthetic chemical's potential, especially compound 10b(Figure 10), as candidates with significant antimycobacterial activity (Ulusoy Güzeldemirci & Gürsoy, 2017).

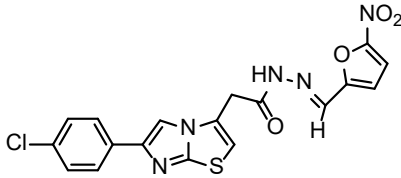
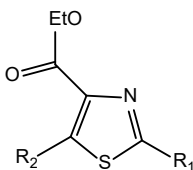
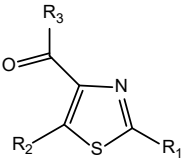
The antitubercular efficacy of arylidenehydrazide derivatives with an imidazo[2,1-b] thiazole moiety (compound 11) was studied by Guzeldemirci et al. against *M. tuberculosis* H37Rv. Using a broth microdilution assay in BACTEC 12B medium, the researchers evaluated the compound's antitubercular potential. The results showed that the compound had modest activity, with IC₅₀ values between 6.16 and 100 mg/ml. In contrast, rifampicin, the reference medication, exhibited an IC₅₀ value of 50 µg/ml. Compound 11(Figure 11) demonstrated the highest potency, equal to rifampicin, with an IC₅₀ value of

0.125 µg/ml. These findings suggest that compound 11 has the potential to be an effective antitubercular agent, warranting further investigation (Ulusoy Güzeldemirci et al., 2017).

Karale et al. conducted research utilizing the 2,4,5-trisubstituted thiazoles to assess their efficacy against *M. tuberculosis* H37Rv with the Microplate Alamar Blue Assay (MABA) test. The results showed that these thiazoles exhibited significant inhibitory effects against the bacterium, with compound 12a showing notable antitubercular activity (MIC values of 2.1 µg/mL and 1.8 µg/mL). The researchers further optimized the compounds by incorporating a third substituent, which resulted in promising outcomes. In particular, substances 12b-c (Figure 12) demonstrated the potential to reduce inactive *M. tuberculosis* H37Ra by over 90% at 10 µM, highlighting their potential as effective antitubercular agents. These findings suggest that 2,4,5-trisubstituted thiazoles, precisely compound 12b-c, may be promising candidates for developing new antitubercular agents (Karale et al., 2019).

Table 2. Thiazole derivatives showing antitubercular activity.

Activity	Compounds	Structures	
Antituberculosis agents	<p>Compounds (9a-b): structures of new (R)-2-acetyl-6-(2-aminothiazol-4-yl)-3,7,9-trihydroxy-8,9b-dimethyldibenzo[b,d]furan-1(9bH)-one derivatives</p>	 <p>Figure 9a. (R)-2-acetyl-6-(2-aminothiazol-4-yl)-3,7,9-trihydroxy-8,9b-dimethyldibenzo[b,d]furan-1(9bH)-one</p>	 <p>Figure 9b. (S)-2-acetyl-6-(2-aminothiazol-4-yl)-3,7,9-trihydroxy-8,9b-dimethyldibenzo[b,d]furan-1(9bH)-one</p>
	<p>Compounds (10a-b): structures of (E)-N'-(argiomethylene)-2-(6-phenylimidazo[2,1-b]thiazol-3-yl)acetohydrazide derivatives</p>	 <p>Figure 10. (E)-N'-(argiomethylene)-2-(6-phenylimidazo[2,1-b]thiazol-3-yl)acetohydrazide</p> <p>10a: Ar=2-NO₂-Ph 10b: Ar=2,4-di-NO₂-Ph 10b: IC₅₀ of 1.05 µg/mL</p>	

	<p>Compound 11: structure of (E)-2-(6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)-N'-((5-nitrofur-2-yl)methylene)acetohydrazide</p>	 <p>11:IC50 of 0.125 µg/mL</p> <p>Figure 11. (E)-2-(6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)-N'-((5-nitrofur-2-yl)methylene)acetohydrazide</p>	
<p>Antituberculosis agents</p>	<p>Compounds (12a-c): Structures of 2,4,5-trisubstituted 1-(2,5-dimethylthiazol-4-yl)ethan-1-one thiazole derivatives.</p>	 <p>12 a: R₁=isopropyl, R₂=benzoxonitrile</p> <p>Figure 12a. 1-(2,5-dimethylthiazol-4-yl)ethan-1-one</p>	 <p>12b: R₁=isopropyl, R₂=5methylbenzo[1,3]dioxole R₃=(S)N-methyl-1-phenylethamine 12c: R₁=isopropyl, R₂=5methylbenzo[1,3]dioxole R₃=(R)N-methyl-1-phenylethamine</p> <p>Figure 12(b,c). 1-(2,5-dimethylthiazol-4-yl)ethan-1-one</p>

Anticancer Activity

Cancer is a complex illness that develops when some cells accumulate genetic and epigenetic changes, with cells migrating to other tissues (Ch et al., 2021). A plethora of commercially available anticancer drugs exist, but the majority of them are quite hazardous and can become resistant, which means that the treatment would not work. As a result, there is a significant drive to develop novel, potential anticancer medication prototypes (Ghorab & Al-Said, 2012).

Braga et al. conducted a study to evaluate the potential cytotoxicity of a diverse range of thiazole molecules on cancer cell lines. The researchers identified that compound 13 showed potent efficacy against HL-60 promyelocytic leukemia cells with an IC₅₀ of 43 µM while exhibiting minimal toxicity towards normal Vero cells. However, MCF-7 breast cancer cells resisted most of the tested compounds. The selective cytotoxicity of compound 13 with its promising potential suggests that it could be further explored as an anticancer agent, especially in the treatment of breast cancer and promyelocytic leukemia (Braga et al., 2016; Küster et al., 2012)

to investigate their cytotoxic activity against three human cancers and normal (Vero) cells.

Gomha et al. conducted a study on the synthesis of arylazothiazoles and their efficacy against colorectal (HCT-116) and hepatic (HepG2) cancer cell lines using the MTT assay. The results were promising, with compounds such as 14b displaying potent anti-hepatocellular carcinoma effects (IC₅₀ = 4.9 ± 0.5 µM), surpassing cisplatin's effectiveness. In gastrointestinal cancer cell lines, 14a and 14b outperformed cisplatin (IC₅₀ = 3.1 ± 0.6 µM). As a result, compound 14b has shown promise as a subject for more research in anticancer drug development. Moreover, a novel class of pyridine thiazole hybrid compounds demonstrated potent cytotoxicity against stomach carcinoma MGC803 and colon cancer HCT-116. These results imply that these substances provide effective treatment options for these types of cancer (Islam et al., 2019).

Kantevari et al. examined the cytotoxicity of imidazole thiazole-linked compounds against four cancer cell lines: MCF-7, DU-145, MIA PaCa-2, and SK-N-SH. Among the substances examined, substance 15a (Figure 15) demonstrated the highest

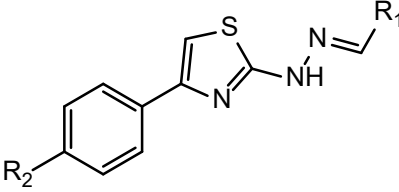
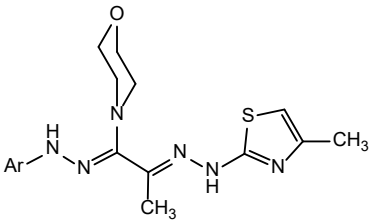
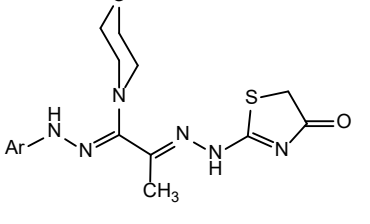
potency, with an IC_{50} value of $4.2 \pm 0.6 \mu M$. These findings suggest that certain derivatives, particularly compound 15a, show promise as potential cytotoxic agents against cancer cells and warrant further investigation (Nagireddy et al., 2019).

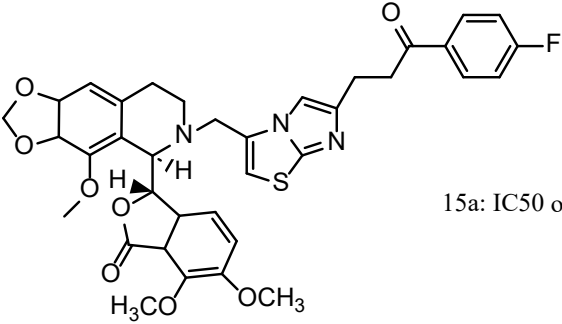
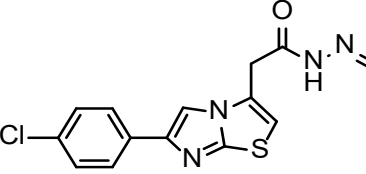
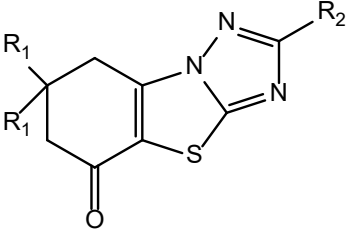
Güzeldemirci et al. conducted a study to evaluate the efficacy of arylidenehydrazide compounds containing imidazo[2,1-b] thiazole compound (16a and 16b) against various viruses such as HSV-1, influenza, coxsackie B4, feline coronavirus, parainfluenza-3, and Punta toro. The study revealed that compounds 16a and 16b (Figure 16) demonstrated notable antiviral activity. Moreover, compound 16a demonstrated effective antiviral activity against feline coronavirus ($IC_{50} 9 \mu M$) and HSV-1 (KOS) ($IC_{50} 7.5 \mu M$), indicating its potential for further development as diverse antiviral agents. These findings could be

significant in advancing the development of novel antiviral agents and contribute to managing viral infections (Ulusoy Güzeldemirci et al., 2017).

Galochkina et al. synthesized a few compounds based on investigated imidazo[2,1-b] thiazole as possible influenza virus inhibitors. They found that three derivatives (17a-c) Figure 17 with thiophene substitution were effective against the H1N1 influenza virus in MDCK cells. The IC_{50} values of these compounds ranged from 13 ± 3 to $49 \pm 6 \mu M$. Compound 17b had the highest activity with an IC_{50} of $13 \pm 3 \mu M$ and a selecting index (SI) of 77, better than the standard drug rimantadine. More research is needed to explore the antiviral potential of thiophene-substituted derivatives, especially compound 17b (Equine et al., 2009; Galochkina et al., 2019).

Table 3. Thiazole derivatives showing anticancer activity.

Activity	Compounds	Structures	
	<p>Compound 13: Structure of (E)-2-(2-ethylidenehydrazinyl)-4-(p-tolyl)thiazole derivatives</p>		<p>13: IC_{50} of $43 \mu M$ $R_1=4$-quinoline, $R_2=OMe$</p>
Anticancer agents	<p>Compounds (14a-b): Structures of 4-((1Z,2E)-1-(2-methylhydrazineylidene)-2-(2-(4-methylthiazol-2-yl)hydrazineylidene)propyl)morpholine derivatives</p>	 <p>14a: Ar = C_6H_5 14a: $IC_{50} = 4.9 \pm 0.5 \mu M$</p> <p>Figure 14a. 4-((1Z,2E)-1-(2argiohydrazono)-2-(2-(4-methylthiazol-2-yl)hydrazono)propyl)morpholine</p>	 <p>14b: Ar = 4-Cl-C_6H_4 14b: $IC_{50} = 3.1 \pm 0.6 \mu M$</p> <p>Figure 14b. 2-((E)-2-((Z)-1-(2-argiohydrazono)-1-morpholinopropan-2-ylidene)hydrazinyl)thiazol-4(5H)-one</p>

Anticancer agents	<p>Compound 15a: Structure of imidazo[2,1-b]thiazole-coupled noscapine derivatives.</p>	 <p>15a: IC₅₀ of 4.2±0.6 μM</p> <p>Figure 15a. (3S)-3-((5R)-6-((6-(3-(4-fluorophenyl)-3-oxopropyl)imidazo[2,1-b]thiazol-3-yl)methyl)-4-methoxy-3a,5,6,7,8,9a-hexahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6,7-dimethoxy-3,3a-dihydroisobenzofuran-1(7aH)-one</p>
	<p>Compounds (16a-b): Structures of imidazo[2,1-b]thiazole-coupled noscapine derivatives.</p>	 <p>16a: R=4-OH-C₆H₄ 16b: R=2,4-Cl₂-C₆H₃</p> <p>16a: IC₅₀ of 9 μM 16b: IC₅₀ of 7.5 μM</p> <p>Figure 16(a,b). 2-(6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)-N'-(propan-2-ylidene)acetohydrazide</p>
	<p>Compounds (17a-c): Structures of imidazol[2,1-b]thiazole-based 2,7,7-trimethyl-7,8-dihydrobenzo[4,5]thiazolo[3,2-b][1,2,4]triazol-5(6H)-one derivatives</p>	 <p>17a: IC₅₀ of 31 ± 3 μM 17b: IC₅₀ of 13 ± 3 μM 17c: IC₅₀ of 49 ± 6 μM</p> <p>17a: R₁=H, R₂=2- bromothiophene 17b: R₁=H, R₂=2- chlorothiophene 17c: R₁=Me, R₂=2- bromothiophene</p> <p>Figure 17(a-c). 2,7,7-trimethyl-7,8-dihydrobenzo[4,5]thiazolo[3,2-b][1,2,4]triazol-5(6H)-one</p>

Antidiabetic activity

Insulin-dependent diabetes mellitus, or diabetes, is a complicated metabolic disease identified by hyperglycemia. Hyperglycemia mainly results from abnormalities in either secretion or insulin actions. Diabetes shows a definite pattern of pathogenesis and diverse presentation of disease progression (Banday et al., 2021). About 10% of the world's population suffers from diabetes, a metabolic disease that is becoming more and more common (Karale et al., 2019).

Meng et al. synthesized a series of 2-imino-3-substituted-5-heterarylidene-1,3-thiazolidine-4-ones

and conducted a study to assess their efficacy as PTP1B inhibitors. The results of this study indicate that pyrrole substitutions at position 5, particularly exemplified by compound 18, exhibit superior inhibitory activity. Compound 18, in particular, demonstrated a significant PTP1B inhibitory activity with an IC₅₀ of 6.37 μM. Compound 18 presents itself as a promising candidate for further structural optimization, which could lead to the development of potent PTP1B inhibitors (Meng et al., 2016).

Ganou et al. synthesized a series of 4-thiazolinone derivatives and identified compound 19 as a potent

inhibitor of PTP1B, with an IC_{50} value of 0.92 μ M. Molecular docking studies revealed that compound 19 can form hydrogen bonds and establish non-covalent interactions with crucial catalytic residues, indicating its potential therapeutic efficacy in treating PTP1B-related conditions. These findings suggest that compound 19 holds promise as a candidate for developing novel PTP1B inhibitors (Ganou et al., 2018).

Wu et al. synthesized thiazole-5-carboxylates containing ethyl 4-(substituted phenoxymethyl) motifs, which were potent inhibitors of PTP1B. Among these, compound 20 showed an IC_{50} value of 4.46 μ M, making it the most potent inhibitor. The biological activity of these compounds was significantly influenced by structural modifications made to the benzene ring. These findings underscore the importance of such alterations in optimizing thiazole-5-carboxylates as inhibitors of PTP1B (Wu et al., 2020).

Patel et al. developed a series of thiazolidine-4-one derivatives, among which compound 21e demonstrated noteworthy inhibitory activity against PTP1B, with an IC_{50} of 5.88 ± 0.06 μ M. Molecular docking studies elucidated the mechanism of its action, revealing that it interacts with catalytic residues, Cys215, Ser216, and Gln262, acting as a potent antagonist. Moreover, compounds 21a–f also exhibited significant inhibitory efficacy, showcasing the potential for designing enhanced PTP1B inhibitors for therapeutic development. These findings suggest that the development of PTP1B inhibitors may hold promise for future therapeutic interventions (Patel et al., 2020).

Maezaki et al. have synthesized a diverse range of quinoline salts in combination with thiazole bases, including Substance 22, which exhibits potent Dipeptidyl peptidase-4 (DPP-4) inhibitory activity ($IC_{50} = 0.38$ μ M). The molecular docking study revealed a crucial salt bridge and hydrophobic contact with Tyr547, indicating that compound 22 and its

analogues hold great potential as therapeutic agents for DPP-4 inhibition in metabolic disorders. The findings of this study may contribute to the development of effective treatments for metabolic disorders (Maezaki et al., 2017).

Celestina and her colleagues have successfully synthesized two compounds, 23a and 23b (Figure 23), with a diverse range of substitutions such as nitro, fluorine, methyl, chlorine, and bromine. These compounds have displayed robust Aldose reductase (ALR2) inhibitory activity, as evidenced by their IC_{50} values of 40 and 60 μ M. Furthermore, docking studies have revealed that the hippuric acid chain present in the compounds has strong interactions with the crucial catalytic residues located in the ALR2 enzyme's anionic interaction zone. This finding highlights the potential of these compounds as a promising source of inhibitors for therapeutic applications (Celestina et al., 2020).

Sever et al. have synthesized N-(thiazolbenzothiazole-2-yl) acetamides, which demonstrate potent inhibitory activity against aldose reductase (AR), surpassing that of quercetin. The low K values of these compounds (0.04 ± 0.01 μ M and 0.08 ± 0.02 μ M) indicate superior AR inhibition with competitive behavior. Furthermore, cellular experiments have confirmed the safety of these compounds, and molecular docking studies have shown their potential as selective AR inhibitors, suggesting therapeutic promise. These findings demonstrate the potential of N-(thiazolbenzothiazole-2-yl) acetamides as a class of compounds (Figure 24) to be explored further for their therapeutic potential as AR inhibitors (Sever et al., 2020).

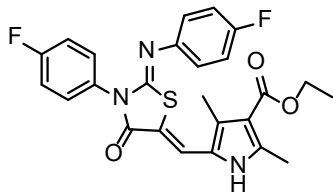
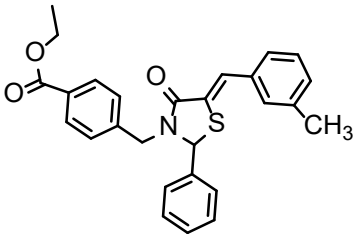
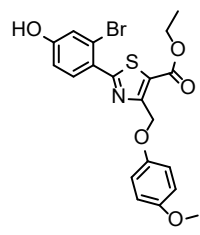
Sahu et al. created a library of twenty chemicals called thiazole-1,3,5-triazine and analyzed them using ADME. Viral antimalarial screening was carried out along with docking experiments on both natural and mutant Pf-DHFR (Dihydrofolate reductase) complexes. The findings indicated that compounds 26a-b were potent against trophozoites,

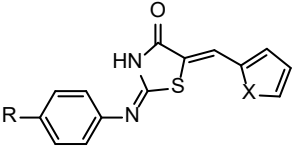
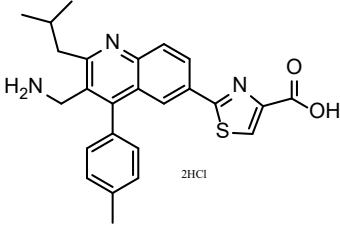
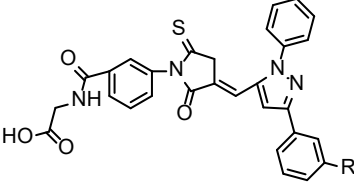
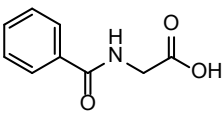
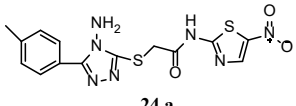
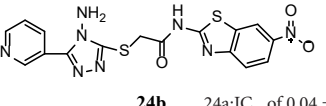
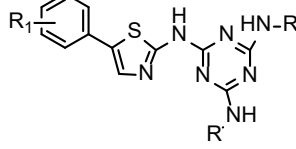
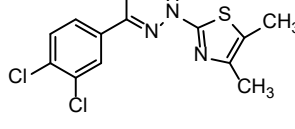
dead rings, and schizonts. These compounds exhibited noteworthy efficacy against chloroquine-resistant strains, with IC_{50} values of 12.48, 10.03, and 11.34 $\mu\text{g/ml}$. Chloroquine's reference compound had IC_{50} values of 0.7 and 1.2 $\mu\text{g/ml}$. Further investigation of 25a-b is recommended due to their promising antimalarial efficacy (Sahu et al., 2019).

Filho et al. conducted a study to evaluate the efficacy of a novel series of 1,3-thiazoles against *T. cruzi*. While several compounds demonstrated

toxicity in macrophages and rat cardiomyoblast cells at doses below 50 μM , molecule 26 exhibited the highest potency against *T. cruzi*, surpassing benznidazole and gentian violet. The compound showed an IC_{50} value of 0.37 μM , indicating its potential for developing anti-*T. Cruzii* agents. Therefore, compound 26 and other compounds in the series have displayed promising results that could be explored to create effective and safe anti-*T. cruzi* agents (de Oliveira Filho et al., 2017).

Table 4. Thiazole derivatives showing antidiabetic activity

Activity	Compounds	Structures
Antidiabetic agents	<p>Compound 18: Structure of 2-imino-3-substituted 5-heteroarylidene-1,3-thiazolidine-4-one derivatives.</p>	 <p>Figure 18. Ethyl 5-((Z)-((Z)-3-(4-fluorophenyl)-2-((4-fluorophenyl)imino)-4-oxothiazolidin-5-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate</p> <p>18:IC_{50} of 6.37 μM</p>
	<p>Compound 19: Structure of ethyl (Z)-4-((5-(3-methylbenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)methyl)benzoate</p>	 <p>Figure 19. (Z)-ethyl 4-((5-(3-methylbenzylidene)-4-oxo-2-phenylthiazolidin-3-yl)methyl)benzoate</p> <p>19:IC_{50} of 0.92 μM</p>
	<p>Compound 20: structure of ethyl 4-(substituted phenoxy methyl) thiazole-5-carboxylate derivatives</p>	 <p>Figure 20. Ethyl 2-(2-bromo-4-hydroxyphenyl)-4-((4-methoxyphenyl)methyl)thiazole-5-carboxylate</p> <p>20:IC_{50} of 4.46 μM</p>

<p>Compounds (21a-f): structures of thiazolidin-4-one 4-one derivatives</p>	 <p>21 a: x=S, R=CH₃ 21b: x=S, R=NO₂ 21c: x=S, R=Cl 21d: x=O, R=CH₃ 21e: x=S, R=NO₂ 21f: x=NH, R=NO₂</p> <p>21e:IC₅₀ of 5.88 ± 0.06 μM</p> <p>Figure 21. (2E,5Z)-5-(cyclopenta-1,3-dien-1-ylmethylene)-2-(p-tolylimino)thiazolidin-4-one</p>	
<p>Compound 22: structures of thiazole based 2-(3-(aminomethyl)-2-isobutyl-4-(p-tolyl)quinolin-6-yl)thiazole-4-carboxylic acid</p>	 <p>22:IC₅₀ of 0.38 μM</p> <p>Figure 22. 2-(3-(aminomethyl)-2-isobutyl-4-(p-tolyl)quinoline-6-yl)thiazole-4-carboxylic acid</p>	
<p>Compounds (23a-b): structures of 1,3-diarylpyrazol-rhodanine-3-hippuric acid derivatives</p>	 <p>23a: R=F 23b: R=CH₃</p> <p>23a:IC₅₀ of 40 μM 23b:IC₅₀ of 60 μM</p>  <p>hippuric acid</p> <p>Figure 23. (E)-2-(3-(2-oxo-3-((1-phenyl-3-(m-tolyl)-1H-pyrazole-5-yl)methylene)-5-thioxopyrrolidin-1-yl)benzamido)acetic acid</p>	
<p>Compounds (24a-b): structures of 2-[(4-amino-5-aryl-4H-1,2,4-triazol-3-yl)thio]-N-(thiazolbenzothiazol-2-yl)acetamides</p>	 <p>24 a</p> <p>Figure 24a. 2-[(4-amino-5-(p-tolyl)-4H-1,2,4-triazol-3-yl)thio]-N-(5-nitrothiazol-2-yl)acetamide</p>	 <p>24b</p> <p>24a:IC₅₀ of 0.04 ± 0.01 μM 24b:IC₅₀ of 0.08 ± 0.02 μM</p> <p>Figure 24b. 2-[(4-amino-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl)thio]-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide</p>
<p>Compounds (25a-b): structures of 5-isopropyl-2-(4-methylpiperazin-1-yl)-N-phenylthiazole-4-carboxamides and thiazole-1,3,5-triazines</p>	 <p>25a:IC₅₀ of 12.48 μM 25b:IC₅₀ of 11.34 μM</p> <p>25a: R₁=2,4-di-Cl, R=propyl 25b: R₁=2,4-di-Cl, R=Me</p> <p>Figure 25(a,b). N2,N4-dimethyl-N6-(5-phenylthiazol-2-yl)-1,3,5-triazine-2,4,6-triamine</p>	
<p>Compound 26: structure of (E)-2-(2-(1-(3,4-dichlorophenyl)ethylidene)hydrazineyl)-4,5-dimethylthiazole</p>	 <p>26:IC₅₀ of 0.37 μM</p> <p>Figure 26. (E)-2-(2-(1-(3,4-dichlorophenyl)ethylidene)hydrazineyl)-4,5-dimethylthiazole</p>	

Anti-inflammatory activity

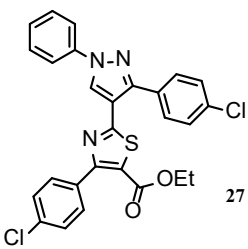
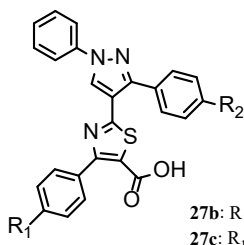
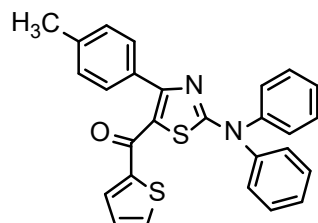
The response of the human body to various stimuli is characterized by inflammation. It is crucial to administer chronic or recurrent treatment for several inflammatory conditions, such as psoriasis, asthma, and arthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the primary treatment modalities to address symptoms such as fever, pain, and acute and chronic inflammation. However, their prolonged therapeutic usage is linked to severe adverse consequences, such as renal disease, unfavorable cardiovascular events, and gastrointestinal (GI) issues, as well as complications, such as bleeding and nephrotoxicity. These potential risks mandate meticulous consideration in the prolonged administration of NSAIDs for the management of inflammatory conditions (Bally et al., 2017; Cao et al., 2014; Goldstein & Cryer, 2014; Lucas et al., 2019; Rostom et al., 2002).

Khloya et al., have developed a novel class of pyrazolyl thiazole carboxylates and investigated the anti-inflammatory properties of their acid analogs

through carrageenan-induced rat paw edema. The synthesized ester compounds have demonstrated superior potency to their acid counterparts, with compounds 27a-c (Figure 27) exhibiting significant efficacy in the 93.66% to 89.59% range. The results indicate that the recently developed substances may be efficacious treatments that reduce inflammation. The study's findings may open the door to more investigation and advancement of anti-inflammatory drugs (Khloya et al., 2015).

Jakob et al. have reported the development of a green and efficient multi-component one-pot synthesis method for the preparation of 4-(substituted)-4-(4-(substituted phenyl) 2-carboxamide and 2-(substituted) thiazol-2(3H)-ylidene) thiophene-2thiazol-5-yl-4-(4-(substituted phenyl)) (diphenyl-2-yl) methanone. The synthesized 28 compounds (Figure 28) were evaluated for their inhibitory potential against lipoxygenase (LOX) and COX-1/COX-2 enzymes. The findings of this study are of significant value in developing new and potent drugs (Jacob & Manju, 2020).

Table 5. Thiazole derivatives with anti-inflammatory activity.

Activity	Compounds	Structures
Anti-inflammatory agents	<p>Compounds (27a-c): structure of ethyl 4-(4-chlorophenyl)-2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)thiazole-5-carboxylate</p>  <p>Figure 27a. Ethyl 4-(4-chlorophenyl)-2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)thiazole-5-carboxylate</p>	 <p>Figure 27(b,c). 2-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-4-(p-tolyl)thiazole-5-carboxylic acid 27b: R₁=F, R₂=H 27c: R₁=FOMe, R₂=Cl</p>
	<p>Compound 28: structure of N-(3-phenyl-4-(4-(substituted phenyl)thiazol-2(3H)-ylidene)thiophene-2-carboxamide</p>  <p>Figure 28 - (2-(diphenylamino)-4-(p-tolyl)thiazol-5-yl)(thiophen-2-yl)methanone</p>	

Antioxidant activity

Antioxidants are increasingly recognized for their potential as preventive and curative agents for various ailments. Reactive oxygen species (ROS) are continually produced due to extreme oxidative stress and routine organ activities. High concentrations of free radicals in the body can damage various biological macromolecules within cells and tissues, including DNA, lipids, proteins, and enzymes. Such damage poses a risk of mutations, which may lead to cancer. Additionally, heightened levels of free radicals are implicated in numerous inflammatory, autoimmune, cardiovascular, neurodegenerative, and metabolic disorders, as well as cellular aging. Given these associations, mitigating oxidative damage is an essential preventive and therapeutic strategy for various illnesses. Notably, recent years have witnessed significant advancements in developing novel antioxidant agents, particularly emphasizing the thiazole moiety within newly synthesized molecules. These developments hold great promise for the future of antioxidant therapy (Khan & Wang, 2018) including trichloroethylene (TCE).

Thota et al. have recently synthesized a novel class of molecules featuring thiazole- and indole-substituted coumarin moieties. These molecules have been found to possess potent antioxidant properties. Among them, compounds 29a-c (Figure 29) have demonstrated the highest efficacy, surpassing ascorbic acid in DPPH (2,2-diphenyl-1,1-picrylhydrazyl) scavenging. The IC_{50} values of the compounds 29a, 29b, and 29c were found to be 11.04 ± 0.18 , 11.28 ± 0.06 , and 12.16 ± 0.28 $\mu\text{g/ml}$, respectively. The compounds have shown commendable antioxidant activity, indicating their potential for therapeutic applications. Further investigation into their free radical scavenging properties is required (Thota et al., 2015).

Djukic et al. have synthesized a new class of 1,3-thiazole compounds, specifically 30a and 30c, demonstrating significant antioxidant activity in DPPH, FRAP (Ferric reducing antioxidant power),

and TBARS (Thiobarbituric acid reactive substances) assays. Compound 30b exhibited robust FRAP activity but lower efficacy in DPPH and TBARS tests. 30a and 30c showed potent antioxidant effects comparable to vitamin C in TBARS. These findings highlight the potential for diverse antioxidant capabilities among thiazolidinedione derivatives, underscoring the therapeutic promise of 30a and 30c (Figure 30). Further investigation is needed to explore these compounds' full potential (Djukic et al., 2018).

The antioxidant capacity of 2-alkylamino-4-(1-methylbenzimidazol-2-yl) thiazoles was assessed using the DPPH assay, which revealed exceptional scavenging abilities with a descending order of $31b > 31d > 31e > 31a > 31c$ (Figure 31). All synthesized compounds surpassed BHA (butylated hydroxyanisole) in antioxidant activity, as evidenced by HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energy levels. These results underscore the potential of the synthesized thiazole derivatives as promising antioxidants, suggesting their suitability for therapeutic interventions or industrial applications (Afifi et al., 2019).

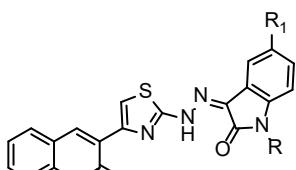
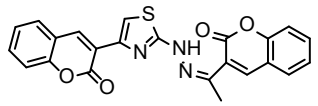
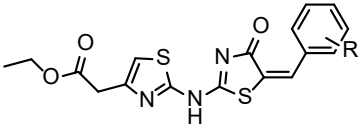
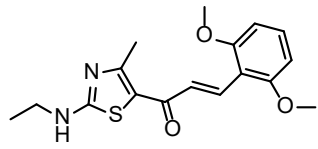
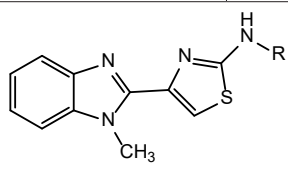
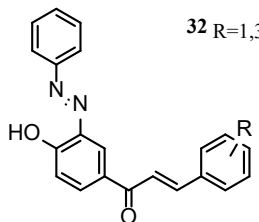
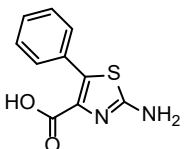
The findings of Mert et al. have revealed a novel class of sulfonamide derivatives that exhibit potent inhibition of cytosolic isoforms I and II of carbonic anhydrase (CA). These derivatives have a modified chalcone core, and compound 32 has shown the most promising performance among all compounds. Compound 32 (Figure 32) has a K_i value of 9.88 nm against hCA I, which is superior to the reference drug AZA. While all compounds have demonstrated action against hCA II (K_i range: 18.25 to 55.43 nm), compound 32 has emerged as a potent CA inhibitor, warranting further research to enhance its therapeutic selectivity (Mert et al., 2016).

Jaidi et al. produced many 2,4,5-trisubstituted thiazole compounds and assessed their effectiveness in inhibiting the cytosolic carbonic anhydrase (CA) III isoform using size exclusion high-performance dynamic light scattering chromatography. The results

indicated that Substance 33 (Figure 33) without any substituent was the most potent among the substituted compounds, showing an inhibitory constant (K_i) of 0.5 μ M. These observations suggest that a structural

relationship exists between the compounds and their activity, highlighting the potential of these substances as inhibitors of the CA III isoform (Al-Jaidi et al., 2020).

Table 6. Thiazole derivatives showing antioxidant activity.

Activity	Compounds		Structures
Antioxidant agents	<p>Compounds (29a-c): structures of (Z)-3-(2-(2-(1-(2-oxo-2H-chromen-3-yl)ethylidene)hydrazineyl)thiazol-4-yl)-2H-chromen-2-one derivatives</p>	 <p>29 a: R=H, R₁=F 29 b: R=H, R₁=I</p> <p>Figure 29 (a,b). (Z)-1,5-dimethyl 3-(2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)hydrazono)indolin-2-one</p>	 <p>29 c 29a: IC₅₀ of 11.04 ± 0.18 μM 29b: IC₅₀ of 11.28 ± 0.06 μM 29c: IC₅₀ of 12.16 ± 0.28 μM</p> <p>Figure 29c. (Z)-3-(2-(2-(1-(2-oxo-2H-chromen-3-yl)ethylidene)hydrazinyl)thiazol-4-yl)-2H chromen-2-one</p>
	<p>Compounds (30a-c): structures of 2-(2-((1H-indol-5-yl)methylene)-hydrazinyl)-thiazoles derivatives</p>	 <p>30 a: R=2-OCH₃ 30 b: R=3-OCH₃</p> <p>Figure 30(a,b). (E)-ethyl 2-(2-((5-benzylidene-4-oxo-4,5-dihydrothiazol-2-yl)amino)thiazol-4-yl)acetate</p>	 <p>30c</p> <p>Figure 30c. (E)-3-(2,6-dimethoxyphenyl)-1-(2-(ethylamino)-4-methylthiazol-5-yl)prop-2-en-1-one</p>
	<p>Compounds (31a-e): structures of 2-alkylamino-4-(1-methylbenzimidazol-2-yl)thiazole</p>	 <p>31 a: R=CH₃ 31 b: R=CH₂CH₃ 31 c: R=CH₂C(CH₃)₂ 31 d: R=CH(CH₃)₂ 31 e: R=(CH₂)₃CH₃</p> <p>Figure 31 (a-e). N-methyl-4-(1-methyl-1H-benzimidazol-2-yl)thiazol-2-amine</p>	
	<p>Compound 32: structures of (E)-1-(4-hydroxy-3-((E)-phenyldiazenyl)phenyl)-3-phenylprop-2-en-1-one derivatives</p>	 <p>32 R=1,3-dimethoxybenzene</p> <p>Figure 32. (E)-1-(4-hydroxy-3-((E)-phenyldiazenyl)phenyl)-3-phenyl prop-2-en-1-one</p>	
	<p>Compound 33: structure of 2-amino-5-phenyl thiazole-4-carboxylic acid derivatives</p>	 <p>Figure 33. 2-amino-5-phenyl thiazole-4-carboxylic acid</p>	

Anticonvulsant activity

Epilepsy, also known as convulsion, is a neurological disorder that affects approximately 67 million individuals worldwide, representing around 2-5% of the global population. The underlying cause of epilepsy is primarily attributed to the imbalance between inhibitory (GABAergic) and excitatory (glutamatergic) neurotransmitters at the synaptic level. This condition results in unpredictable seizures that can have varying intensities and durations. The impact of epilepsy on individuals and society at large is significant, as it can lead to disability, social stigma, and increased healthcare costs. Therefore, understanding the mechanisms underlying epilepsy and identifying effective treatment strategies is paramount (Chiroma et al., 2022).

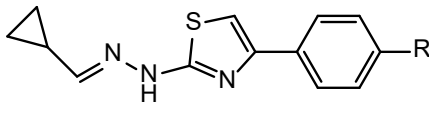
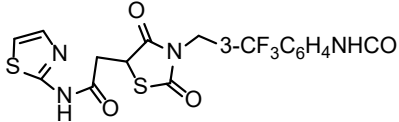
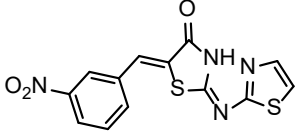
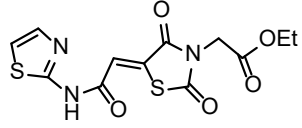
Epilepsy, a neurological disorder, is characterized by unexpected changes in behavior accompanied by rhythmic and synchronous firing of brain neurons. This condition is noteworthy for the abnormal synchronous activity of neurons in the brain that leads to seizures, which are often unpredictable and can vary in intensity and duration. Understanding the complex interplay of factors involved in epilepsy is critical for the development of effective treatments and interventions that can improve the quality of life for those affected by this disorder (Surineni et al., 2019).

Łączkowski and his team have synthesized ten new hydrazinylthiazole compounds, designated as

34a-j (Figure 34), which incorporate cyclopropyl moieties inspired by the growing use of such compounds in clinical trials. The compounds underwent rigorous evaluations to assess their anticonvulsant properties and demonstrated significant efficacy. In the maximal electroshock test, the trifluoromethyl and chloromethyl groups showed the most promise, while in the pentylenetetrazole (PTZ) test, the methoxy- and azido groups exhibited high efficacy. Significantly, none of the compounds adversely impacted motor coordination, as demonstrated by the rotarod test, suggesting their safety. These results underscore the potential of these cyclopropyl-containing thiazole derivatives as versatile agents with promising therapeutic applications, warranting further clinical investigation (Łączkowski et al., 2018).

Siddiqui and colleagues synthesized compound 35a-c (Figure 35.), a hybrid thiazole-pyridazine structure containing an amide linkage. The compound demonstrated potent anticonvulsant properties, with median effective doses of 88.23 mg/kg and 24.38 mg/kg in PTZ and Maximum electroshock (MES) tests, respectively. The GABA (γ -amino butyric acid) estimate test also revealed a significant increase in GABA levels, confirming compound 35a-c GABA modulatory action. Molecular docking studies that targeted the active site of the GABA receptor supported this mechanism. These results suggest that compound 35a-c has potential as an anticonvulsant intervention, warranting further exploration for clinical applications (Siddiqui et al., 2020).

Table 7. Thiazole derivatives showing anticonvulsant activity.

Activity	Compounds	Structures
Anticonvulsants	Compounds (34a-j): structures of (E)-2-(2-(cyclopropylmethylene)hydrazinyl)-4-(p-tolyl)thiazole derivatives	 Figure 34. (E)-2-(2-(cyclopropylmethylene)hydrazinyl)-4-(p-tolyl)thiazole 34a:R=F 34f:R=OCH ₃ 34b:R=Br 34g:R=2,4-diF 34c:R=Cl 34h:R=CN 34d:R=CH ₃ 34i:R=N ₃ 34e:R=CF ₃ 34j:R=NO ₂
	Compounds (35a-c): structures of (E)-5-((Z)-3-nitrobenzylidene)-2-(thiazol-2-ylimino)thiazolidin-4-one derivatives	 Figure 35a. (2E,5Z)-5-(3-nitrobenzylidene)-2-(thiazol-2-ylimino)thiazolidin-4-one
		<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  Figure 35b. 2-(3-methyl-2,4-dioxothiazolidin-5-yl)-N-(thiazol-2-yl)acetamide </div> <div style="text-align: center;">  Figure 35c. (Z)-ethyl 2-(2,4-dioxo-5-(2-oxo-2-(thiazol-2-ylamino)ethylidene)thiazolidin-3-yl)acetate </div> </div>

CONCLUSION

A fascinating class of chemical molecules, thiazole derivatives have attracted a lot of interest in the drug research community because of their remarkable pharmacological variety and adaptability. These compounds have demonstrated various therapeutic properties, including anti-inflammatory, antimicrobial, anticancer, antidiabetic, anticonvulsant, antioxidant, and antituberculosis effects. Researchers have conducted extensive studies to understand the precise molecular features that impact the pharmacological outcomes of thiazole derivatives. This has allowed for the rational design of novel compounds with low toxicity and higher potency. The ability of thiazole derivatives to modulate multiple biological pathways and molecular targets is a beacon of hope to develop the effective and safe therapeutic agents. A series of compounds can be synthesized and characterized to evaluate their biological actions, and studies have demonstrated that thiazole derivatives

hold great promise for targeting a range of diseases and conditions. These findings are not just exciting but also inspire us with the potential to develop novel drugs that can address unmet medical needs.

FUTURE PERSPECTIVES

Recent advancements in synthetic methodologies have allowed for modifying various thiazole derivatives addressing the challenges of bioavailability, selectivity, and toxicity. Thiazole-based compounds have shown immense potential to interfere with cellular processes involved in inflammation, microbial infections, cancer progression, and diabetes, paving the way for targeted therapeutic interventions. The broadening knowledge in this field contributes to a deeper understanding of the diverse pharmacological actions of thiazole derivatives, offering insights for future medicinal chemists. Given that the thiazole structure provides several sites for substitution with functional groups, many other compounds of biological interest are expected to be synthesized. Developing

new compounds with unique physicochemical, pharmacodynamic, and pharmacokinetic properties could be instrumental in future drug development. The remarkable therapeutic diversity demonstrated by synthetic thiazole derivatives underscores their significance as valuable contributors to the ongoing search for safe and effective pharmaceutical agents.

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AUTHOR CONTRIBUTION STATEMENT

Concept: M.K., M.U.M., Design: M.K., M.U.M., Software: M.K., Literature Search: M.K., M.U.M., Writing: M.K., M.U.M., P.P., A.T., Review & Editing: M.M., B.J.S.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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