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Research Article

A Systematic Review On Thiazole Synthesis And Biological Activities

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ABSTRACT

Thiazole is a special heterocycle with nitrogen and sulfur atoms that plays a significant role in medicinal chemistry. It is a vital structural component found in numerous synthetic and naturally occurring medically significant substances, such as vitamin B1 (thiamine). The fact that the thiazole nucleus is a necessary component of the penicillin nucleus and some of its derivatives, which have been shown to have antimicrobial, antiretroviral, antifungal, antihistaminic, and antithyroid properties, illustrates the nucleus' versatility. The recent use of thiazole derivatives as anthelmintics, vulcanizing accelerators (mercaptobenzothiazole), anticancer agents (tiazofurin), and photographic sensitizers has significantly increased their synthetic significance. The chemistry of thiazoles has gradually advanced following the groundbreaking research of Hofmann and Hantsch. Significant contributions to the field's expansion were made by Bogert and associates. The significance of the thiazole ring in cyanine dyes, which is used as a photographic sensitizer, was established by Mills. A fused derivative of thiazole that has demonstrated commercial value is benzothiazole. The current review focuses on several synthetic methodologies and biological activities of thiazole.

Keywords: Thiazole, chemistry, synthetic pathway, biological activities

Introduction

Thiazole is a well-known five-membered heterocyclic compound. Various methods have been worked out for its synthesis. In the last few decades, a lot of work has been done on the thiazole ring to find new drugs with antioxidant, analgesic, anti-inflammatory, antimicrobial, antifungal, antiviral, diuretic, anticonvulsant, neuroprotective and antitumor or cytotoxic properties and fewer side effects. Thiazole is one of the leading heterocyclic five-membered ring compounds that contain sulphur atoms at position 1 and nitrogen atoms at position 3. Many of its natural and synthetic derivatives possess diverse biological activities. In drug research development, the substituent at thiazole ring was modified to generate new molecules with potent biological activities.

In medicinal chemistry, thiazolidinone is a frequently used pharmacophore with a variety of biological activities, including antifungal, antibacterial, antimycobacterial, antipsychotic, and anti-inflammatory properties. Furthermore, substituted thiazolidine derivatives are crucial intermediates in the synthesis of medications with pharmacological activity. It's common knowledge that thiazole compounds' biological activity has led to their recent growth. They have antifungal, antibacterial, and anticonvulsant properties. Some novel thiazole compounds have been used as anti-inflammatory drugs recently. Furthermore, morpholine is a straightforward heterocyclic compound that has significant industrial value. It has been discovered that numerous N-functionalized morpholines have a variety of pharmacological activities. It has been reported that they exhibit several significant physiological functions, including antidiabetic, antihyperlipo-proteinemics, antidepressants, bronchodilators, growth stimulants, and antiemetic platelet aggregation inhibitors. These were also used to treat pain, migraines, asthma, and inflammatory illnesses. In light of the aforementioned

information, there is increase in our research aimed at creating a novel, user-friendly, and effective process for the synthesis of heterocyclic compounds. It would be interesting to create new thiazole derivatives with a morpholine moiety. Studying the synthetic compounds' antibacterial and anti-inflammatory properties is another goal of research.(Naveena et al., 2013)(Helal et al., 2013)

Numerous physiologically active substances, such as pharmaceuticals and natural products, contain thiazoles.Because of the significance of thiazolines in both synthetic and biological contexts, these reduced forms of thiazoles have garnered significant attention as privileged scaffolds. It has been reported that compounds with thiazoline moiety display a variety of biological effects, including antimicrobial activity. Furthermore, hydrazides–hydrazones have drawn a lot of interest as significant pharmacophores in medicinal chemistry. Isoniazid is the first-line medication used to treat tuberculosis because it has a hydrazide moiety in its chemical structure. Nifuroxazide is a commonly used intestinal antiseptic. It is a nitrofuran antibacterial agent with a hydrazone moiety. The strong antimicrobial activity of isoniazid and other hydrazides' hydrazone derivatives has also been demonstrated by numerous investigations.(Altintop et al., 2014)(Mabkhot et al., 2019)

In the synthesis of pharmacologically active pharmaceuticals, 1-substituted-1H-tetrazole-5-thiol and 5-methyl-1,3,4-thiadiazole-2-thiol have become extremely important. Certain synthetic β-lactam antibiotics have as their side chain 5-thio-1-methyl-1H-tetrazole (MTT) or thio-linked thiadiazole. (G. L. Turan-Zitouni et al., 2018)Because of their enhanced safety profile and wide therapeutic range, triazole antifungal medications are highly effective in treating systemic fungal infections. For the treatment of systemic fungal infections, commonly used antifungal medications with a triazole ring include fluconazole, itraconazole, voriconazole, and posaconazole.

A great deal of research has also been done by medicinal chemists to find new antimicrobial agents with a pyrimidine moiety. Nowadays, pyrimidine-containing chemotherapeutic medications such as trimethoprim and sulfadiazine are used to treat infectious diseases.(Andreoli et al., 2013)(Pattan et al., 2004)

Techniques

The literature on thiazole derivatives and their use in biological processes was searched for and found from the databases of PUBMED, Science Direct, Scopus, Springer, and Google Scholar.

Thiazole chemistry

An electron-donating group (-S-) and an electron-accepting group (C=N) are both used by thiazole to produce a stable heterocyclic compound. Thiazole and its analogues, like oxazole, are regarded as a significant class of heterocycles with a variety of biological characteristics. An azole compound that has similar atoms (nitrogen and sulfur) arranged in a different position, such as isothiazole, is isomeric with thiazole compound. Thiazole is a transparent, pale yellow liquid that dissolves easily in ether and alcohol but only moderately in water.

The sulfur atom, which has a boiling point of 116–118 ºC, has a delocalization of six π electrons in its heterocyclic ring, which corresponds to Huckel's rule from the lone pair electrons. The resonance forms of thiazole (1) are depicted in Figure 1. The planar and smooth nature of thiazole derivatives makes them ideal model compounds for studies in chemistry.

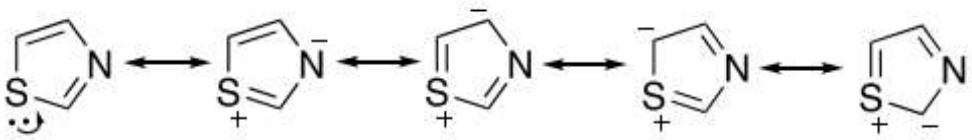


Figure 1. Resonance forms of thiazole compound

Compared to oxazole, aromatic structure shows greater π-electron delocalization .Using 1H NMR spectroscopy, the aromatic behavior of the thiazole ring was confirmed; the protons' chemical shift is visible between 7.27 and 8.77 ppm. The addition of distinct substituents at positions C-2, C-4, and C-5 caused strain in the thiazole derivatives ring's reactivity and may require additional structural consideration. For instance, the effect of the electron-donating group (methyl group) substituent was identified at any position of thiazole ring, increasing its basicity and nucleophilicity characteristics. However, when a powerful electron-withdrawing group, like a nitro group, is added to the molecule, basicity and nucleophilicity decrease.(Ansari et al., 2018)(Khan et al., 2016)(Abdel-Sattar et al., 2017)

Thiazole's versatile building blocks as bioactive compounds give its molecular structure uniqueness .Numerous research works have documented that the thiazole ring is found in the majority of synthetic and natural products, possessing a wide range of biological properties . One such instance is vitamin B1, also referred to as thiamine, which has a thiazole moiety and naturally supports the nervous system by linking to the synthesis of acetylcholine . Furthermore, because thiazole derivatives have both hydrophobic (lipophilic) and hydrophilic (lipophobic) parts, they have an amphiphilic quality as seen in Figure 2.

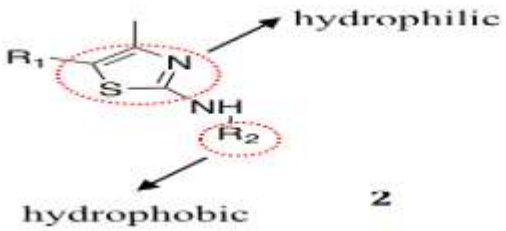


Figure 2. Structure of thiazole derivatives

This characteristic makes it more likely to easily diffuse into bacterial cell membranes to inhibit activity.(Weiß et al., 2011)(Weiß et al., 2011)(Farhan et al., 2023)(Rouf & Tanyeli, 2015a)(Al-Mathkuri et al., 2022)

Synthetic approaches

The Hantzsch thiazole synthesis, which was developed in 1887 by a German chemist by the name of Hantzsch, is the most well-known technique for synthesizing thiazoles This technique makes use of αhaloketone's condensation reaction with nucleophilic reagents like thioamide, thiourea, ammonia thiocarbamate, or derivatives of dithiocarbamate Furthermore, it was proposed that the most effective technique for synthesizing thiazole derivatives was Hatzsch thiazole synthesis. With this technique, four thiazole derivatives were made by using thionicotinamide (3)'s Hantzsch reaction with four different kinds of α-haloketone

In the presence of catalytic triethylamine (4), α-haloketone, specifically chloroacetone (5), 3-chloroacetylacetone (6), 3-bromoacetylcoumarin (7), and p-chloroacetylacetanilide (8), are produced. Scheme 1 illustrates the 2-(3-pyridyl) thiazole derivatives (9–12) that were produced by the reaction.

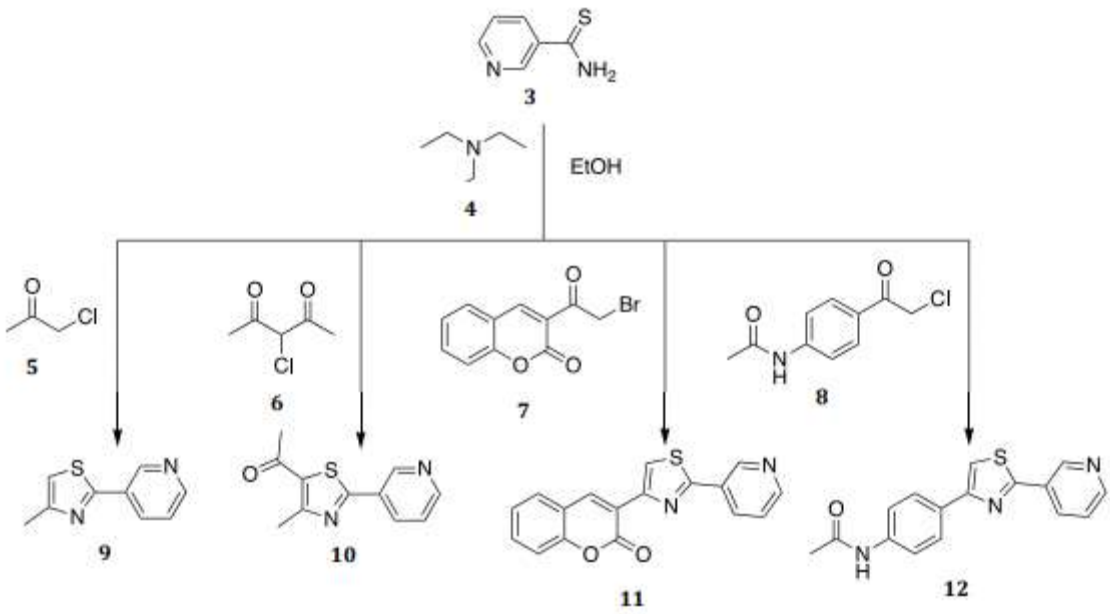


Figure 3 Scheme 1

Numerous investigations revealed that this approach has significant disadvantages, including low yield percentages, severe reaction conditions, extended reaction times, and the use of catalysts that are costly .However, according to a different study, this approach produces high yields by dehalogenating the haloketone during the reaction. Using the synthesis of thiazole derivatives, the Hantzsch cyclization method was developed, wherein the tetrafluroethoxy moiety was directly affixed to the heterocyclic ring's carbon atom In their investigation, they heated α-bromo-αtetrafluoroethoxyacetophenone (13) in dioxine at 60 °C with thiobenzamide (14) to form 2,4-diphenyl-5-(1,1,2,2-tetrafluoroethoxy)-thiazole (15) (Scheme 2). However, because thiobenzamide is unstable in an acidic medium, the yield percentage is low (18–20%). (Frija et al., 2016)

Cook-Heilbron

Furthermore, the thiazole ring can be synthesized using carbon disulfide and α-aminonitriles or α-aminoamides. as the reactants, a process that Cook and Heilbron discover and name Cook-Heilbron synthesis . Under mild conditions, the Cook-Heilbron method produced 5-aminothiazoles, where substitution happened at position 2 when ammonionitrile reacted with salt, esters of thioacids, carbon disulfide, or isothiocyanates. Scheme 3 shows how 5-amino-2-mercaptothiazole (18) is created when α-aminonitriles (16) react with carbon disulfide (17). Gabriel synthesis is an additional synthetic method for creating thiazole derivatives. This process

involves reacting acylamino-ketone with phosphorus pentasulfide to produce 2,5-disubstituted thiazole derivatives, which are then used to close the thiazole ring .
Kotadiya encouraged this study, in which the desired compound was synthesized by heating acylamino compounds, specifically N-(2-oxopropyl) acetamide (19) with phosphorus pentasulfide (20), as shown in Scheme 4.

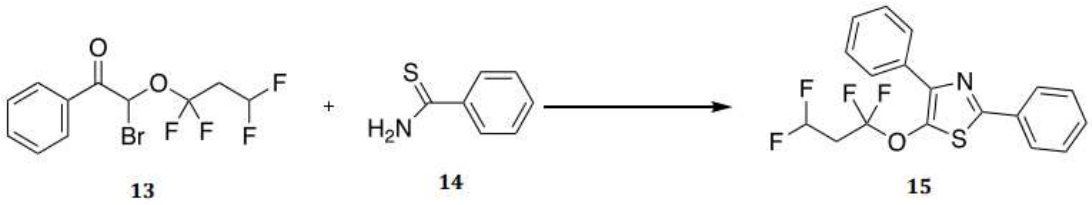


Figure 4 Scheme 2. Hantzsch type synthesis of 2,4-diphenyl-5-(1,1,2,2-tetrafluorethoxy)-thiazole

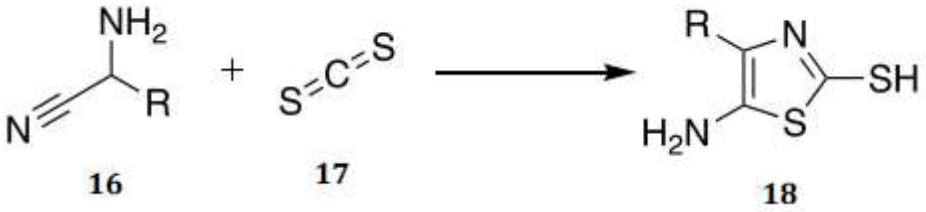


Figure 5 Scheme 3. The Cook-Heilbron thiazole synthesis

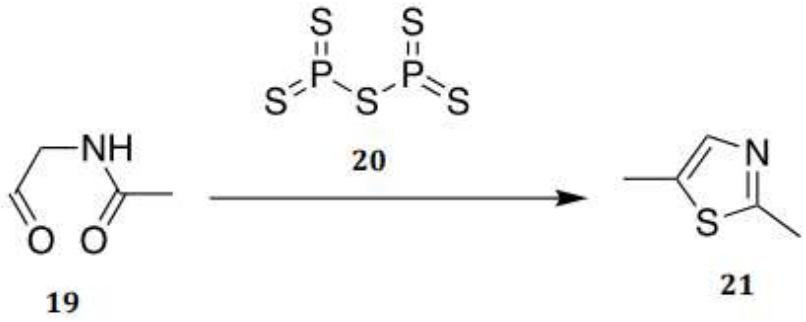


Figure 6 Scheme 4. Synthesis of thiazole compound via Gabriel reaction

Kaplancıkl et al assessed the antimicrobial activity and cytotoxicity of N′-(3,4-Diarylthiazol-2(3H)-ylidene)-2-(arylthio)acetohydrazides in NIH/3T3 cells. The most promising antibacterial agent against Pseudomonas aeruginosa was found to be compound 22 containing 1-phenyl-1H-tetrazole and p-chlorophenyl moieties, while compound 23 containing 1-phenyl-1H-tetrazole and p-bromophenyl moieties was the most promising antifungal agent against Candida albicans. The cytotoxicity of the most potent derivatives against C6 glioma cells was also assessed. The outcomes showed that compound 17 with nonsubstituted phenyl moieties and 1-phenyl-1H-tetrazole (IC50 = 8.3 ± 2.6 μg/mL) was more effective against C6 glioma cells than cisplatin (IC50 = 13.7 ± 1.2 μg/mL). On C6 cells, compound 17 also demonstrated inhibitory effects on DNA synthesis. Compound 17 also demonstrated minimal toxicity to NIH/3T3 cells (IC50 = 416.7 ± 28.9 μg/mL).(Altintop et al., 2014)
Berin Karaman et al synthesized New imidazo[2,1-b]thiazole derivatives and done biological assessment as anticancer agents. [6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl]acetic acid hydrazide was used to create a range of arylidenehydrazide compounds (3a–3j). The National Cancer Institute's in vitro disease-oriented antitumor screening was used to assess the antitumor activity of the newly synthesized compounds 3b and 3h. The most effective compound found, compound 3b, showed broad spectrum antiproliferative activity against every cell line tested, with log10GI50 values ranging from −4.41 to −6.44. With log10GI10 values of -6.44, -6.33, -6.11, -6.30, -6.13, and -6.22, respectively, the largest growth inhibitions were seen against the ovarian cancer cell line OVCAR-3, the colon cancer cell line HCT-15, the two renal cancer cell lines CAKI-1 and UO-31) and the two leukemia cell lines CCRF-CEM and SR.(Karaman & Ulusoy Güzeldemirci, 2016)(Başoğlu et al., 2021)(T. Chhabria et al., 2016)

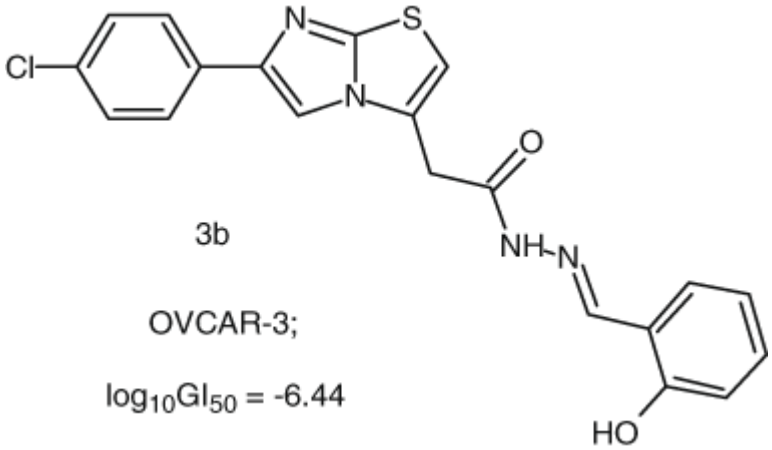


Figure 7 Compond 3b

Wen et al done the preparation and biological assessment of thiazole derivatives as new inhibitors of USP7. Herpesvirus-associated Ubiquitin-Specific Protease (HAUSP, also known as USP7) is one of the first examples of an enzyme that deubiquitinases oncogenic proteins; it interacts with and stabilizes Mdm2. One possible pharmacological target for USP7 in cancer treatment is thought to exist. It has recently been demonstrated that USP7 inhibitors inhibit both in vitro and in vivo tumor cell growth. In this research designing and synthesizing of a series of thiazole derivatives based on the well-known USP7 inhibitors P5091 and P22077 was done. The thiazole compounds demonstrated low micromolar inhibition activity against both the USP7 enzyme and cancer cell lines, according to the outcomes of in vitro assays. The substances both p53-dependently and p53-independently caused cell death. When considered collectively, this work may offer thiazole compounds as a novel class of inhibitors for USP7.(Chen et al., 2017).(Elwahy et al., 2023)

Xu et al Designd, synthesized and done biological evaluation of novel thiazole-based derivatives as human Pin1 inhibitors. A possible method of finding anti-tumor agents is to inhibit Pin1, which is a peptidyl prolyl cis-trans isomerase (PPIase). A series of thiazole derivatives with an alicyclic heterocycle on the 2-position were designed, synthesized, and tested against human Pin1 in an effort to find strong inhibitors of Pin1 with a novel scaffold. With an IC50 value of 0.95 μM, compound 9p—which carries a 2-oxa-6-azaspiro [3,3] heptane moiety on the thiazole scaffold—was found to be the most effective Pin1 inhibitor in this series. An alicyclic ring with an H-bond acceptor could be introduced to increase the binding affinity, according to the structure-activity relationship (SAR) and molecular modeling study. In many different physiological processes, proline-directed phosphorylation on Ser or Thr serves as a common regulatory mechanism. The only enzyme that acts as a conformational switch and isomerizes phosphorylated Ser/Thr- was Pin1 (protein interacting with NIMA1).Pro peptide bonds are found in many substrate proteins, and diseases like cancer and Alzheimer's are linked to its dysregulation. Pin1 has been found to be overexpressed in a variety of human cancer cells, including cancer cells from the breast, prostate, colon, and cervical regions. It has been reported that Pin1 both inactivates and activates a large number of growth-inhibitory or oncogenic proteins as well as tumor suppressors. Therefore, it is anticipated that blocking Pin1 will be a possible cancer treatment tactic. (Du et al., 2021)(Zhu et al., 2011)(Raghu et al., 2023)(Elsayed et al., 2022)

Rostom et al synthesised and biologically evaluated some 2,4,5-Trisubstituted Thiazole Derivatives as Potential Antimicrobial and Anticancer Agents. The synthesis and biological assessment of two series of 2,4,5-polysubstituted thiazoles that include some derived pharmacophores known to contribute to different chemotherapeutic activities and the acid hydrazide functionality is discussed in this research. Every recently created substance underwent in vitro antifungal and antibacterial screening. Thirteen of the compounds that were tested showed an inhibitory effect on the growth of three strains of Gram-positive bacteria, but they showed no effect on strains of Gram-negative bacteria. In addition, four substances demonstrated antifungal activity against Candida albicans. The thiosemicarbazide functions 6a–f and those substituted with both the thioureido and thiosemicarbazide moieties 12a–f were associated with possible antibacterial and antifungal activities. The compounds 6f and 12f (R = 4-F-C6H4) exhibit significant antibacterial activity against three different types of Gram-positive bacteria and significant antifungal activity against Candida albicans, making them potentially the most active participants in this study. When it came to B. subtilis, compounds 6d, 6f, and 12f were twice as effective as ampicillin. 50% less active than clotrimazole, compound 6d demonstrated the best antifungal activity. Using the NCI's current one-dose protocol, 17 compounds were chosen and their preliminary in-vitro anticancer activity was assessed. Three cell lines showed some sensitivity to most of the tested compounds: melanoma SK-MEL-2, ovarian cancer IGROV1, and non-small cell lung cancer Hop-92. With a broad spectrum of activity against the majority of the tested subpanel tumor cell lines, compound 12f emerged as the most potent anticancer member. As a result, 12f was kept for testing in the assay with five doses.(Al-Saadi et al., 2008)

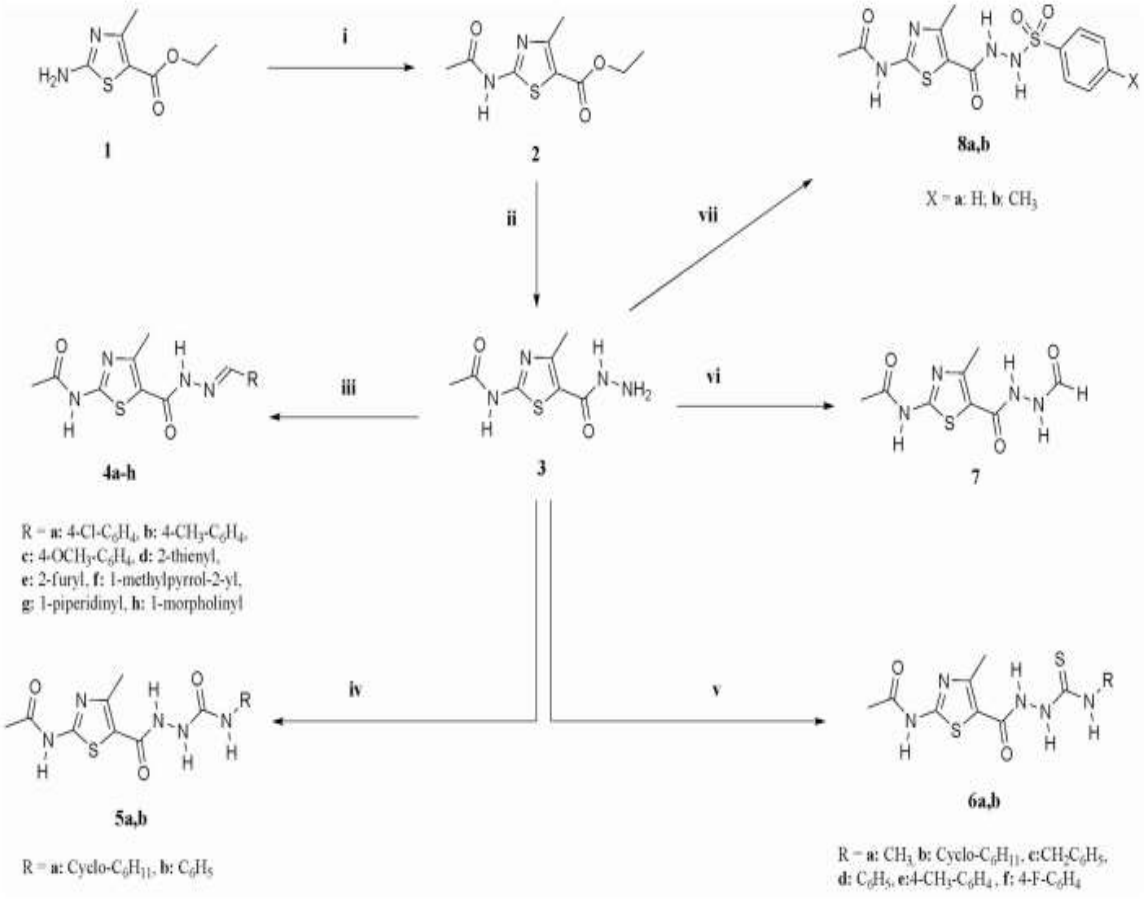


Figure 8 Scheme 5. Synthesis of the target compounds 2–8.

Reagents, conditions, and yields: i: (CH3CO)2O, warming, 83%; ii: H2NNH2.H2O, ethanol, reflux, 70%; iii: Aldehyde, acetic acid, reflux, 38 – 83%;iv: Substituted isocyanate, pyridine, reflux, 86 – 90%; v: Substituted isothiocyanate, pyridine, reflux, 38 – 82%; vi: HCOOH, reflux, 90%; vii: 4-substituted benzenesulfonyl chloride, pyridine, reflux, 39 – 61%.

Schemes 5 and 6 show the synthetic routes used in this study to produce the intermediate and target compounds. The ethyl 2-acetamido4-methylthiazole-5-carboxylate 2 in Scheme 5 was produced in a good yield by heating the initial ethyl 2-amino-4-methylthiazole-5-carboxylate 1 with acetic anhydride. The key intermediate in this section, 2-acetamido-4-methylthiazole-5-carboxylic acid hydrazide 3, was produced when 2 reacted with hydrazine hydrate. By condensing 3 with the suitable heterocyclic or aromatic aldehyde, the corresponding arylidine derivatives were produced. 4a–h.

The analogous 4-substituted thiosemicarbazides 6a–b and the corresponding 4-substituted 1-(2-acetamido-4-methylthiazole-5-carbonyl)semicarbazides 5a, b were produced by reacting the acid hydrazide 3 with various isocyanates and isothiocyanates in pyridine. in that order. Moreover, the target N-formyl-2-acetamido-4-methylthiazole-5-carboxylic acid hydrazide 7 was obtained by refluxing 3 in formic acid. Conversely, the N-substituted benzenesulfonyl-2-acetamido-4-methylthiazole-5-carboxylic acid hydrazides 8a, b were formed when 3 was reacted with benzenesulfonyl chloride or p-toluenesulfonyl chloride in the presence of pyridine. At this point, the plan was to use the initial thiazole ester 1 and hydrazine hydrate to synthesize the target carboxylic acid hydrazide 9. The compound N-acetyl-2-acetamido-4-methylthiazole-5-carboxylic acid hydrazide 10 was obtained by acetic anhydride-induced acetylation of 9. Ultimately, 4-substituted-1-(2-(N-substituted ureido)-4-methylthiazole-5-carbonyl)semicarbazides 11a, b and their isosteric Condensing the 12-a–f thiosemicarbazides 4-substituted-1-(2-(N-substituted thioureido)-4-methylthiazole-5-carbonyl)thiosamidine acid hydrazide 9 combined with two moles of the relevant isothiocyanates or isocyanates, as appropriate(Finiuk et al., 2017)(Mohanty et al., 2022)(Ravi Singh et al., 2023)(Biernasiuk et al., 2021).

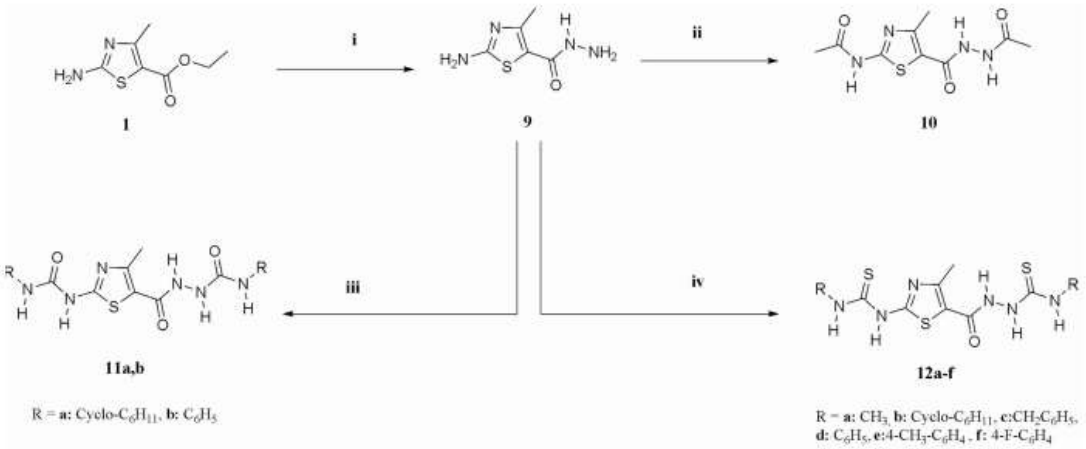


Figure 9 Scheme 6. Synthesis of the target compounds 9–12

Reagents, conditions, and yields: i: H2NNH2.H2O, ethanol, reflux, 67%; ii: (CH3CO)2O, warming, 73%; iii: Substituted isocyanate, pyridine,reflux,78 – 95%; iv: Substituted isothiocyanate, pyridine, reflux, 29-95%.
Kaplancikli et al synthesised and done biological evaluation of some thiazole derivatives as new cholinesterase inhibitors. In the current work, a number of thiazole derivatives were created by reacting different phenacyl bromides with 1-[2-(2-oxobenzo[d]thiazol-3(2H)-yl)acetyl]thiosemicarbazide in a ring closure reaction. The compounds chemical structures were clarified through elemental analyses, mass spectral data, 1H and 13C NMR, and other methods. A modified version of Ellman's spectrophotometric technique was used to assess each derivative's capacity to inhibit butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE). Using the MTT assay, the compounds' cytotoxic qualities were also examined. When compared to eserine (IC50 = 0.025 * 0.01 µg/mL), compounds 4e (IC50 = 25.5 * 2.12 µg/mL) and 4i (IC50 = 38.50 * 2.12 µg/mL), 4c (IC50 = 58.42 * 3.14 µg/mL), and 4g (IC50 = 68 * 2.12 µg/mL) were found to be the most potent AChE inhibitor. Compounds that were effective on AChE showed a weak inhibition of BuChE (IC50 > 80 µg/mL). The MTT assay revealed that compound 4e's cytotoxic dose (IC50 = 71.67 ± 7.63 µg/mL) was greater than its effective dose.

First, benzo[d]thiazol-2(3H)-one reacted with ethyl chloroacetate in the presence of potassium carbonate to produce ethyl 2-(2-oxobenzo[d]thiazol-3(2H)-yl)acetate (1). The corresponding hydrazide derivative (2) was then produced by converting this ester (1).
1-[2-(2-Oxobenzo[d]thiazol-3(2H)-yl)acetyl]thiosemicarbazide (3) was produced by reacting potassium thiocyanate and concentrated hydrochloric acid with the hydrazide derivative (2). Compound 3's ring closure utilizing phenacyl bromides resulted in the target compounds (4a–j). Scheme 7 summarizes these reactions, some of the compounds' characteristics. These compounds' (4a–j) structures were verified by elemental analyses, 1H and 13C NMR, mass spectral data, and mass spectral data.

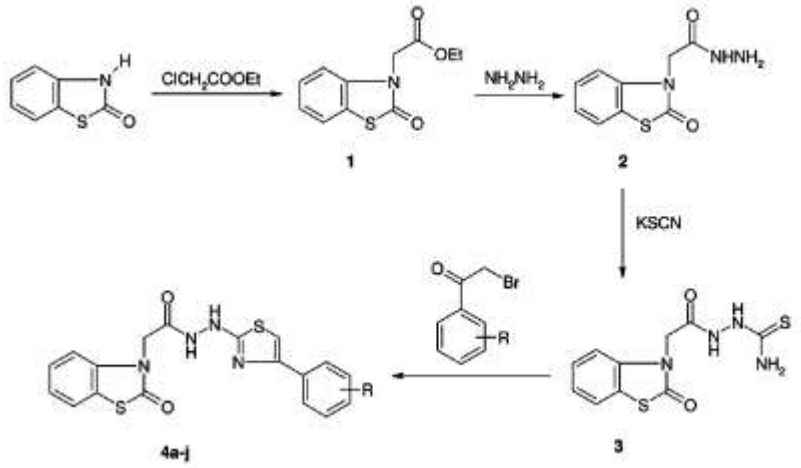
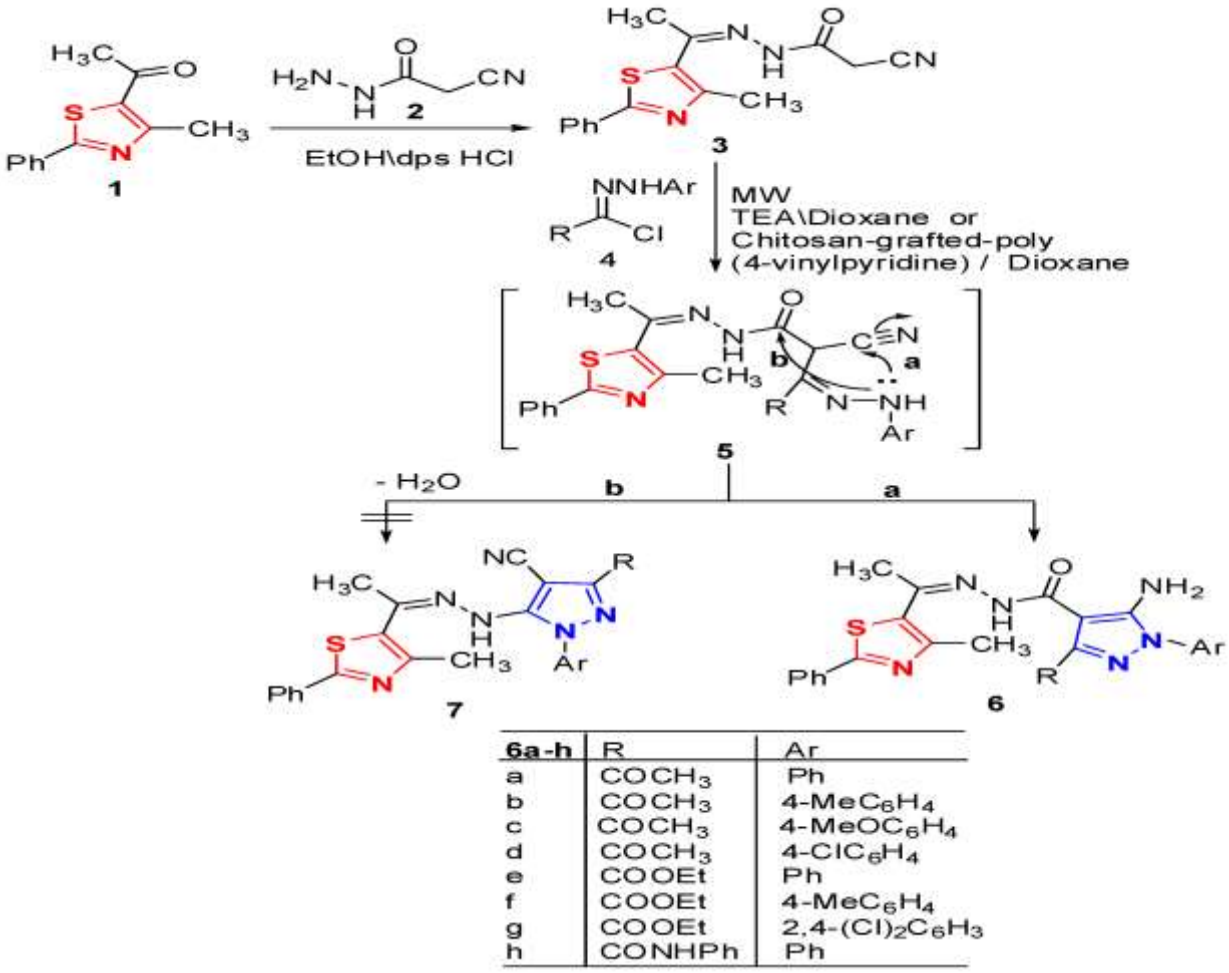


Figure 10 Scheme 7 Scheme of synthesis

With an IC50 value of 25.5 ± 2.12 µg/mL, compound 4e exhibits the most promising anticholinesterase agent among the compounds (4a–j). This is in contrast to eserine, which has an IC50 value of 0.025 ± 0.01 µg/mL. It is also mentioned in earlier research that galantamine had an IC50 value of 0.28 ± 0.04 µg/mL, indicating that

it had an inhibitory effect on AChE. Comparing compound 4e with galantamine, compound 4e also exhibited the highest AChE inhibitory effect. Despite having nitro substituents on their phenyl rings, compounds 4e and 4g exhibit varying degrees of anticholinesterase activity. The cytotoxicity of compounds 4e and 4g varies as well; their respective IC50 values are 71.67 ± 7.63 and 4.93 ± 0.11 µg/mL. These findings suggest that nitro substituent location on the phenyl ring plays a critical role in determining cytotoxicity and anticholinesterase activity. It is evident that the p-nitro group and anticholinesterase activity are positively correlated. AChE is inhibited by compound 4i, which has a 2,4-dichloro group on the phenyl ring, with an IC50 value of 38.50 ± 2.12 µg/mL, and compound 4c, which has a p-chloro group on the phenyl ring and an IC50 value of 58.42 ± 3.14 µg/mL. AChE is weakly inhibited by compounds 4d, 4f, 4h, and 4j (IC50 > 80 µg/mL), while compounds 4a and 4b show no activity.(El-Achkar et al., 2015)(Fouda et al., 2021)(G. Turan-Zitouni et al., 2013)(Ripain & Ngah, 2021)

Edrees et al synthesised and biologically evaluated Some Novel Thiazole-Based Heterocycles as Potential Anticancer and Antimicrobial Agents . Utilizing 1,3-dipolar cycloaddition reactions and chitosan-grafted poly(vinylpyridine) as an environmentally benign biopolymeric basic catalyst, a novel series of thiazole-based heterocycles was produced. Spectroscopic and elemental analysis provided an illustration of the synthetic compounds' molecular structure. The newly synthesized compounds were investigated for their possible antitumor, antimicrobial, and hepatoprotective properties using a variety of in vitro biological assays. All of the compounds demonstrated antitumor activities when tested against human hepatocellular carcinoma (HepG-2), colorectal carcinoma (HCT-116), and breast cancer (MCF-7) cell lines. The most effective compounds were those that contained chlorine, specifically 11c and 6g. Regarding the employed gram positive and gram negative bacterial species, most of the investigated thiazole derivatives demonstrated adequate antibacterial activity. (Abu-Melha et al., 2019)(Alsayari et al., 2021)



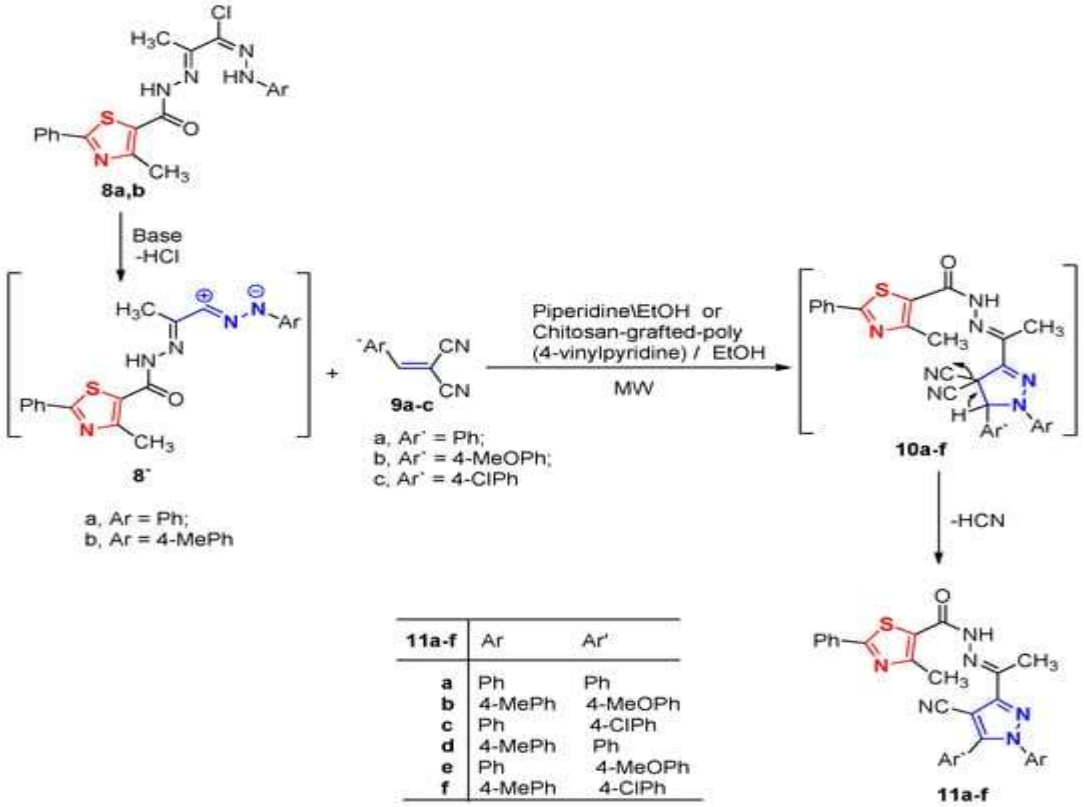
6a-h	R	Ar
a	$COCH_3$	Ph
b	$COCH_3$	$4\text{-}MeC_6H_4$
c	$COCH_3$	$4\text{-}MeOC_6H_4$
d	$COCH_3$	$4\text{-}ClC_6H_4$
e	COOEt	Ph
f	COOEt	$4\text{-}MeC_6H_4$
g	COOEt	$2,4\text{-}(Cl)_2C_6H_3$
h	CONHPh	Ph

Figure 11 Scheme 8. Synthesis of thiazolyl pyrazoles 6a–h.

2-cyano-N′-(1-(4-methyl-2-phenylthiazol-5-yl)ethylidene)- acetohydrazide (3, Scheme 8) was the sole product obtained from the refluxing of 5-acetyl-4-methyl-2-phenyl-thiazole (1) and 2-cyanoacetohydrazide (2) .

The same products, which are identified as the thiazole derivatives 6a–h rather than the other possible product 7 based on the spectral data (IR, MS, and 1H-NMR) of the isolated products, were obtained in each case of treating hydrazone derivative 3 with the appropriate hydrazonoyl halides 4a–h using triethylamine or chitosan as a basic catalyst and under the same experimental conditions. Based on the spectral analysis results, the two

potential products, 6 and 7, were distinguished. The absence of the nitrile absorption band was visible in the IR spectra. The thiazolyl pyrazoles 11a–f (Scheme 9) were formed by heating a mixture of hydrazonoyl halides 8a or 8b and the appropriate arylidine malononitriles 9a–c in ethanol containing piperidine under MW irradiation. Based on their elemental analysis and spectral data, the latter products' structure was determined .(Abu-Melha et al., 2019)



11a-f	Ar	Ar'
a	Ph	Ph
b	4-MePh	4-MeOPh
c	Ph	4-ClPh
d	4-MePh	Ph
e	Ph	4-MeOPh
f	4-MePh	4-ClPh

Figure 12 Scheme 9

Helal et al synthesised and biologicaly evaluated some novel thiazole compounds as potential anti-inflammatory agents. In this research, furo[2,3-d]Thiosemicarbazone derivative 2 reacted with diethyl acetylene dicarboxylate to yield thiazol-5(2H)-one 5. After treating thiosemicarbazone derivative 2 with suitable α-halogenated compounds, a set of newly synthesized 2-(hydrazinyl)thiazol-4(5H)-ones 6, 7, & 8 and 2-(4-(substituted)-thiazol-2-yl)hydrazono derivatives 9a, b & 10 were produced. Additionally, a three-component reaction of hydrazone derivative 11 with phenyl isothiocyanate and α-halogenated compounds catalyzed by DMF/KOH resulted in a one-pot synthesis of thiazole derivatives 13 & 15. The reaction of acetophenone derivative 1 with thiourea in the presence of iodine produced 4-(4-Morpholino phenyl) thiazol-2-amino 17. It was looked into how reactive 2-aminothiazole 17 was with certain electrophilic reagents. The newly synthesized compounds' structures were verified through elemental analysis and spectral data. The investigation focused on the antibacterial activity against two Gram positive (Staphylococcus aureus & Bacillus cereus) and two Gram negative (Proteus mirabilis & Serratia marcesens) bacteria. It was determined that these compounds inhibited the oedema caused by carrageenin and had anti-inflammatory properties.(Helal et al., 2013)(Naveena et al., 2013)(Bharti & Singh, 2014)(Azhari, 2020).

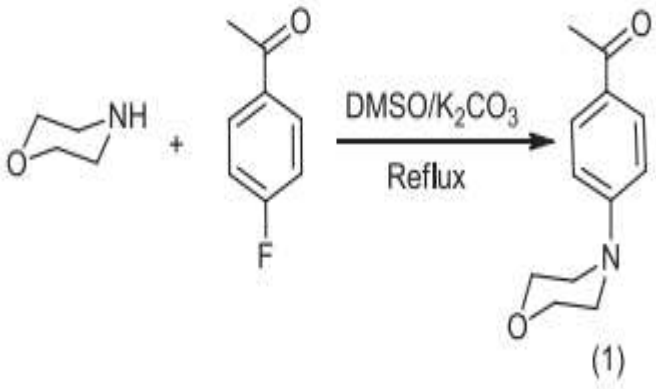


Figure 13 Scheme 10

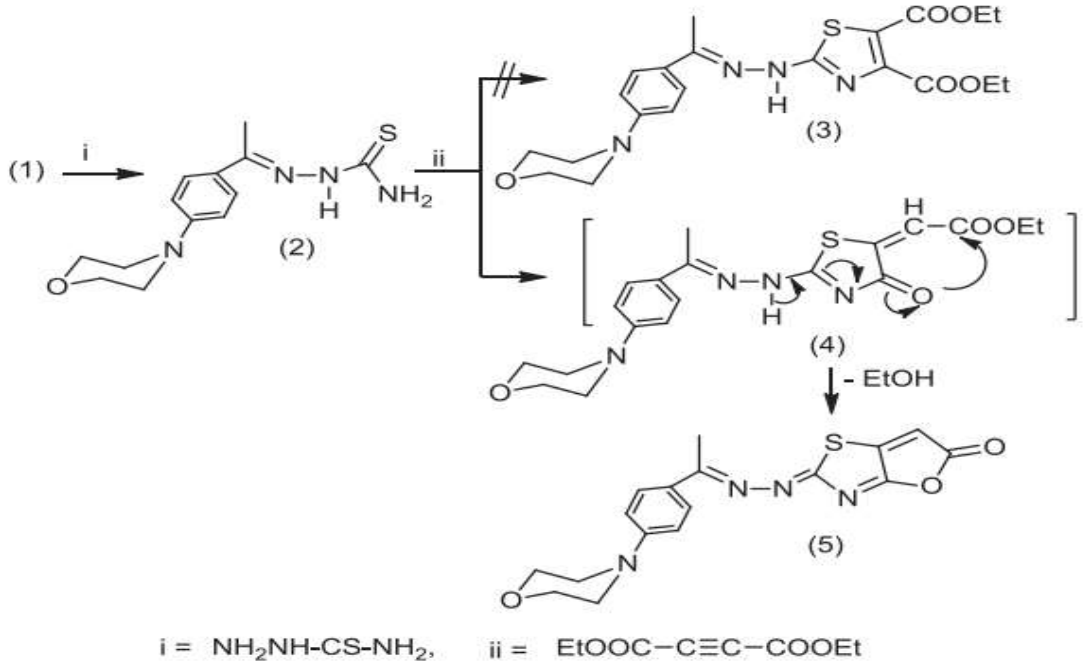


Figure 14 Scheme 11

By nucleophilically substituting the appropriate morpholine for 4-fluroacetophenone in dimethyl sulfoxide (DMSO) with potassium carbonate acting as a base under reflux, the starting 1-(4-morpholinophenyl)ethanone 1 was produced (Scheme 1). By condensing ethanone derivative 1 with thiosemicarbazide in the presence of a catalytic amount of concentrated HCl in ethanol as the solvent, thiosemicarbazone derivative 2 was produced, yielding a satisfactory yield of 70%. Compound 2's IR spectrum showed distinctive absorption bands at φ ¼ 3418, 3288, and 3167 cm1 that were assigned to (NH2 & NH), and its 1 HNMR spectrum (DMSO-d6) showed singlet signals for CH3, two triplets for morphonyl protons at 3.13, 3.73 ppm, and two singlets for NH and NH2 at 8.17 and 10.07 ppm, respectively. Additionally, signals at d 17.00 (CH3), 39.98 (C3, C5 of morpholine), 77.62 (C2, C6 of morpholine), 147.55 (C]N), and 178.28 (C]S) ppm were found by 13CNMR (DMSO-d6) of compound 2. On the basis of elemental analysis and spectral data, the treatment of thiosemicarbazone derivative 2 with diethyl acetylene dicarboxylate produced furo[2,3-d]thiazole derivative 5 and other expected structure 3.

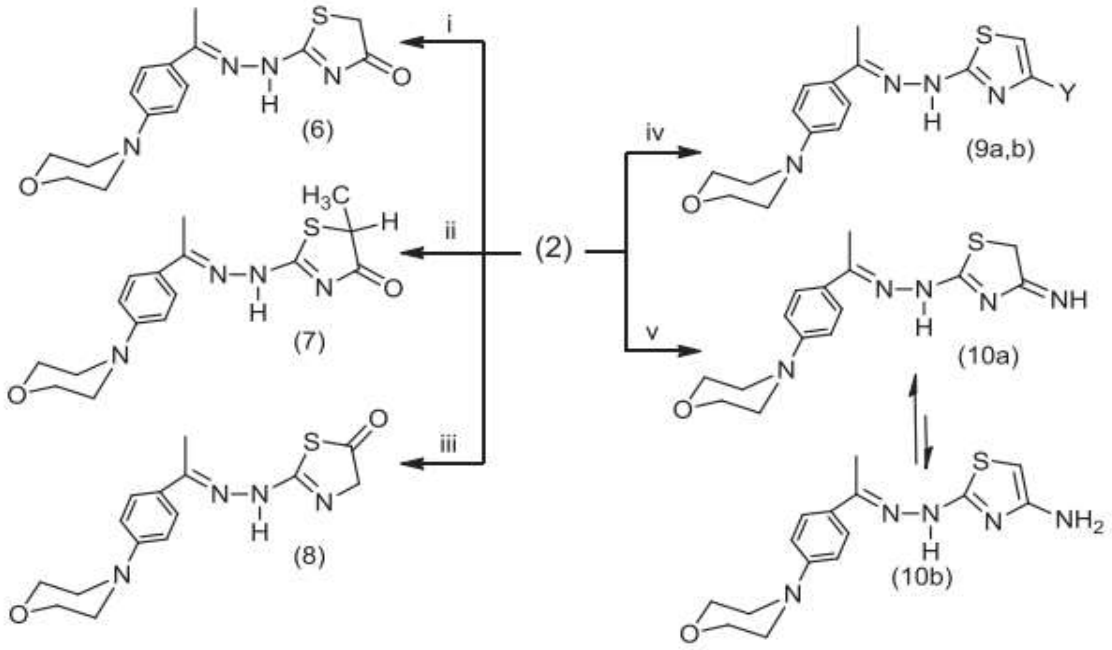


Figure 15 Scheme 12

It was assumed that compound 5 was formed by the nucleophilic attack of the SH group on the diethyl acetylene dicarboxylate's activated triple bond, which was followed by using non-isolable intermediate 4 and in situ heterocyclization with the removal of two ethanol molecules to produce compound 5 (Ayati et al., 2015b)(Rouf & Tanyeli, 2015b)

A versatile, previously unreported thiazole derivative was synthesized by examining the behavior of thiosemicarbazone derivative 2 toward certain halogenated compounds. Therefore, the corresponding 4-thiazolidinone derivative 6 was supported by the reaction of thiosemicarbazone derivative 2 with ethyl chloroacetate in glacial acetic acid that contained a catalytic amount of fused sodium acetate. Compound 6 was determined to have a molecular structure based on spectral data and elemental analysis.(Helal et al., 2013)(Naveena et al., 2013)(Bharti & Singh, 2014)

Application of thiazole derivatives in biologically

Both pharmacology and biology have made extensive use of thiazole derivatives. possessing a solid background in pharmaceuticals. Antimicrobial , antioxidant , anticancer, and antitubercular properties have been reported for them. Due to the presence of nitrogen and sulfur atoms in the molecules, thiazole compounds, specifically bis-(4-phenylthiazol-2-yl) amine and 1-(4-methyl-2-(2-(1-phenylidene) hydrazineyl)-4,5-dihydrothiazol-5-yl) ethenone as depicted have antiinflammatory properties .

In addition, a substance having thiazole as its fundamental structure showed antioxidant properties . The thiazole's antioxidant characteristics after synthesis was established.The 1,1-diphenyl-2-picyrylhydrazyl (DPPH) scavenging capacity test was used to assess derivatives (33, 34, and 35). According to the findings, compound 33 and compound 34 had DPPH radical inhibition rates of 18.73% and 15.62%, respectively. Compound 35 did not exhibit any antioxidant activity, which may be because it lacks a number of active atoms, which could reduce the structure's potential resonance.(Al-Mathkuri et al., 2022)(Liu et al., 2015)

Thiazole compounds have also been investigated as potential pharmaceutical candidates for antibacterial agents. The emergence of drug resistance to antibiotics against bacterial strains has piqued interest in the search and creation of a novel, effective antimicrobial medication. Research on thiazole derivatives as an antimicrobial agent has been actively undertaken since the thiazole moiety is well known for its biological activity. When different substituents were added to the thiazole's primary molecular structure, the tested bacterial strains responded favorably. Many investigations have been carried out to enhance the chemical structures of thiazole derivatives for antimicrobial applications. Specifically, trichlorophenyl thiazole compound demonstrated a significant inhibitory effect on a variety of Gram-positive and Gram-negative strains, including Pseudomonas fluorescens, Bacillus subtilis, Escherichia coli, and Staphylococcus aureus. Prolongation synthesis of active antimicrobial agents resulted in a series of 2,4-disubstituted-1,3-thiazole derivatives designation with identifiable invitro antimicrobial activities .The synthesized analogues of 36 and 37 comprising nitro group at phenyl substituents exhibited active results towards B. subtilis, S. aureus and E. coli with MIC values of 3.92-4.01, 3.39-4.11 and 3.59-4.23 μM/mL, respectively compared to compound 38

with values of 4.51, 4.60 and 4.32 μM/mL, respectively. Due to the nitro moiety's presence at the para position, which forms a potent hydrogen bond with the amino acid residue in the examined microbes. Thus, it can be said that both the optimization of the substituent at the ring and the inhibition of microorganism activity were significantly aided by the thiazole ring containing nitro at position 4.(Ayati et al., 2015b)(Ayati et al., 2015a)

Conclusion

In conclusion, a variety of techniques regarding the synthesis pathway of thiazole derivatives have been documented. It is possible to develop a novel, useful technique for thiazole synthesis. derivatives that yield a lot. To enhance the biological activities, a number of new structures were created and synthesized for use in biological applications by adding the appropriate substituent groups to the thiazole ring. Consequently, because of their unique qualities and potential, thiazole derivative research can serve as the main focus of future investigation.

References

1. Abdel-Sattar, N. E. A., El-Naggar, A. M., & Abdel-Mottaleb, M. S. A. (2017). Novel Thiazole Derivatives of Medicinal Potential: Synthesis and Modeling. *Journal of Chemistry*. https://doi.org/10.1155/2017/4102796
2. Abu-Melha, S., Edrees, M. M., Salem, H. H., Kheder, N. A., Gomha, S. M., & Abdelaziz, M. R. (2019). Synthesis and biological evaluation of some novel thiazole-based heterocycles as potential anticancer and antimicrobial agents. *Molecules*. https://doi.org/10.3390/molecules24030539
3. Al-Mathkuri, T. S. F., Sabti, A. B., & Raheem, A. A. (2022). Synthesis, characterization, and antimicrobial activity of some thiazole derivatives. *Egyptian Journal of Chemistry*. https://doi.org/10.21608/EJCHEM.2021.102830.4766
4. Al-Saadi, M. S., Faidallah, H. M., & Rostom, S. A. F. (2008). Synthesis and biological evaluation of some 2,4,5-trisubstituted thiazole derivatives as potential antimicrobial and anticancer agents. *Archiv Der Pharmazie*. https://doi.org/10.1002/ardp.200800026
5. Alsayari, A., Muhsinah, A. Bin, Asiri, Y. I., Al-Aizari, F. A., Kheder, N. A., Almarhoon, Z. M., Ghabbour, H. A., & Mabkhot, Y. N. (2021). Synthesis, characterization, and biological evaluation of some novel pyrazolo[5,1-b]thiazole derivatives as potential antimicrobial and anticancer agents. *Molecules*. https://doi.org/10.3390/molecules26175383
6. Altintop, M. D., Kaplancikli, Z. A., Çiftçi, G. A., & Demirel, R. (2014). Synthesis and biological evaluation of thiazoline derivatives as new antimicrobial and anticancer agents. *European Journal of Medicinal Chemistry*. https://doi.org/10.1016/j.ejmech.2013.12.060
7. Andreoli, F., Doukara, A. L., Mehdid, M. A., Vanthuyne, N., Roussel, C., Dessolin, J., & Kraus, J. L. (2013). Novel phenyl(thio)ureas bearing (thio)oxothiazoline group as potential BACE-1 inhibitors: Synthesis and biological evaluation. In *Journal of Enzyme Inhibition and Medicinal Chemistry*. https://doi.org/10.3109/14756366.2011.642375
8. Ansari, A., Ali, A., Asif, M., Rauf, M. A., Owais, M., & Shamsuzzaman. (2018). Facile one-pot multicomponent synthesis and molecular docking studies of steroidal oxazole/thiazole derivatives with effective antimicrobial, antibiofilm and hemolytic properties. *Steroids*. https://doi.org/10.1016/j.steroids.2018.04.003
9. Ayati, A., Emami, S., Asadipour, A., Shafiee, A., & Foroumadi, A. (2015a). ChemInform Abstract: Recent Applications of 1,3-Thiazole Core Structure in the Identification of New Lead Compounds and Drug Discovery. *ChemInform*. https://doi.org/10.1002/chin.201532298
10. Ayati, A., Emami, S., Asadipour, A., Shafiee, A., & Foroumadi, A. (2015b). Recent applications of 1,3-thiazole core structure in the identification of new lead compounds and drug discovery. In *European Journal of Medicinal Chemistry*. https://doi.org/10.1016/j.ejmech.2015.04.015
11. Azhari, P. (2020). Kritik Sosial Dalam Novel Laut Becerita Karya Leila S. Chudori dan Implementasinya Sebagai Bahan Ajar di SMA. *Molecules*.
12. Başoğlu, F., Ulusoy-Güzeldemirci, N., Akalın-Çiftçi, G., Çetinkaya, S., & Ece, A. (2021). Novel imidazo[2,1-b]thiazole-based anticancer agents as potential focal adhesion kinase inhibitors: Synthesis, in silico and in vitro evaluation. *Chemical Biology and Drug Design*. https://doi.org/10.1111/cbdd.13896
13. Bharti, S. K., & Singh, S. K. (2014). Design, synthesis and biological evaluation of some novel benzylidene-2-(4-phenylthiazol-2-yl) hydrazines as potential anti-inflammatory agents. *Medicinal Chemistry Research*. https://doi.org/10.1007/s00044-013-0708-z
14. Biernasiuk, A., Berecka-Rycerz, A., Gumieniczek, A., Malm, M., Łączkowski, K. Z., Szymańska, J., & Malm, A. (2021). The newly synthesized thiazole derivatives as potential antifungal compounds against Candida albicans. *Applied Microbiology and Biotechnology*. https://doi.org/10.1007/s00253-021-11477-7
15. Chen, C., Song, J., Wang, J., Xu, C., Chen, C., Gu, W., Sun, H., & Wen, X. (2017). Synthesis and biological evaluation of thiazole derivatives as novel USP7 inhibitors. *Bioorganic and Medicinal Chemistry Letters*. https://doi.org/10.1016/j.bmcl.2017.01.018
16. Du, L., Wang, X., Cui, G., & Xu, B. (2021). Design, synthesis and biological evaluation of novel thiazole-

based derivatives as human Pin1 inhibitors. *Bioorganic and Medicinal Chemistry*. https://doi.org/10.1016/j.bmc.2020.115878
17. El-Achkar, G. A., Jouni, M., Mrad, M. F., Hirz, T., El Hachem, N., Khalaf, A., Hammoud, S., Fayyad-Kazan, H., Eid, A. A., Badran, B., Merhi, R. A., Hachem, A., Hamade, E., & Habib, A. (2015). Thiazole derivatives as inhibitors of cyclooxygenases in vitro and in vivo. *European Journal of Pharmacology*. https://doi.org/10.1016/j.ejphar.2015.01.008
18. Elsayed, R. W., Sabry, M. A., El-Subbagh, H. I., Bayoumi, S. M., & El-Sayed, S. M. (2022). Thiazole-based SARS-CoV-2 protease (COV Mpro) inhibitors: Design, synthesis, enzyme inhibition, and molecular modeling simulations. *Archiv Der Pharmazie*. https://doi.org/10.1002/ardp.202200121
19. Elwahy, A. H. M., Ginidi, A. R. S., Shaaban, M. R., Farag, A. M., & Salem, M. E. (2023). Synthesis of novel bis-thiazoles, bis-thienopyridines, and bis-triazolothiadiazines linked to diphenyl ether core as novel hybrid molecules. *Synthetic Communications*. https://doi.org/10.1080/00397911.2023.2179405
20. Farhan, M. A., Ibrahim, W. A., & Ali, W. B. (2023). Synthesis, Evaluation of anticancer and antimicrobial activities of some Schiff bases derivatives. *Al-Kitab Journal for Pure Sciences*. https://doi.org/10.32441/kjps.07.02.p10
21. Finiuk, N. S., Hreniuh, V. P., Ostapiuk, Y. V., Matiychuk, V. S., Frolov, D. A., Obushak, M. D., Stoika, R. S., & Babsky, A. M. (2017). Antineoplastic activity of novel thiazole derivatives. *Biopolymers and Cell*. https://doi.org/10.7124/bc.00094B
22. Fouda, A. S., Abdel-Latif, E., Helal, H. M., & El-Hossiany, A. (2021). Synthesis and Characterization of Some Novel Thiazole Derivatives and Their Applications as Corrosion Inhibitors for Zinc in 1 M Hydrochloric Acid Solution. *Russian Journal of Electrochemistry*. https://doi.org/10.1134/S1023193521020105
23. Frija, L. M. T., Pombeiro, A. J. L., & Kopylovich, M. N. (2016). Coordination chemistry of thiazoles, isothiazoles and thiadiazoles. In *Coordination Chemistry Reviews*. https://doi.org/10.1016/j.ccr.2015.10.003
24. Helal, M. H. M., Salem, M. A., El-Gaby, M. S. A., & Aljahdali, M. (2013). Synthesis and biological evaluation of some novel thiazole compounds as potential anti-inflammatory agents. *European Journal of Medicinal Chemistry*. https://doi.org/10.1016/j.ejmech.2013.04.005
25. Karaman, B., & Ulusoy Güzeldemirci, N. (2016). Synthesis and biological evaluation of new imidazo[2,1-b]thiazole derivatives as anticancer agents. *Medicinal Chemistry Research*. https://doi.org/10.1007/s00044-016-1684-x
26. Khan, K. M., Qurban, S., Salar, U., Taha, M., Hussain, S., Perveen, S., Hameed, A., Ismail, N. H., Riaz, M., & Wadood, A. (2016). Synthesis, in vitro α-glucosidase inhibitory activity and molecular docking studies of new thiazole derivatives. *Bioorganic Chemistry*. https://doi.org/10.1016/j.bioorg.2016.08.010
27. Liu, C. B., Shan, B., Bai, H. M., Tang, J., Yan, L. Z., & Ma, Y. B. (2015). Hydrophilic/hydrophobic characters of antimicrobial peptides derived from animals and their effects on multidrug resistant clinical isolates. *Dong Wu Xue Yan Jiu = Zoological Research / "Dong Wu Xue Yan Jiu" Bian Ji Wei Yuan Hui Bian Ji*. https://doi.org/10.13918/j.issn.2095-8137.2015.1.41
28. Mabkhot, Y. N., Algarni, H., Alsayari, A., Muhsinah, A. Bin, Kheder, N. A., Almarhoon, Z. M., & Al-Aizari, F. A. (2019). Synthesis, X-ray analysis, biological evaluation and molecular docking study of new thiazoline derivatives. *Molecules*. https://doi.org/10.3390/molecules24091654
29. Mohanty, P., Behera, S., Behura, R., Shubhadarshinee, L., Mohapatra, P., Barick, A. K., & Jali, B. R. (2022). Antibacterial activity of thiazole and its derivatives: A review. In *Biointerface Research in Applied Chemistry*. https://doi.org/10.33263/BRIAC122.21712195
30. Naveena, C. S., Poojary, B., Arulmoli, T., Manjunatha, K., Prabhu, A., & Kumari, N. S. (2013). Synthesis and evaluation of biological and nonlinear optical properties of some novel 2,4-disubstituted [1,3]-thiazoles carrying 2-(aryloxymethyl)-phenyl moiety. *Medicinal Chemistry Research*. https://doi.org/10.1007/s00044-012-0195-7
31. Pattan, S. R., Sirajunisa, T., & Pattan, J. (2004). Synthesis and evaluation of some substituted mercaptothiazoles and their derivatives of biological interest. *Indian Journal of Chemistry - Section B Organic and Medicinal Chemistry*. https://doi.org/10.1002/chin.200422146
32. Raghu, M. S., Swarup, H. A., Shamala, T., Prathibha, B. S., Kumar, K. Y., Alharethy, F., Prashanth, M. K., & Jeon, B. H. (2023). Design, synthesis, anticancer activity and docking studies of novel quinazoline-based thiazole derivatives as EGFR kinase inhibitors. *Heliyon*. https://doi.org/10.1016/j.heliyon.2023.e20300
33. Ravi Singh, K., Lohith, T. N., Ananth Nag, T., Sridhar, M. A., & Sadashiva, M. P. (2023). Structure property relationship in two thiazole derivatives: Insights of crystal structure, Hirshfeld surface, DFT, QTAIM, NBO and molecular docking studies. *Molecular Crystals and Liquid Crystals*. https://doi.org/10.1080/15421406.2023.2194596
34. Ripain, I. H. A., & Ngah, N. (2021). A brief review on the thiazole derivatives: Synthesis methods and biological activities. *Malaysian Journal of Analytical Sciences*.
35. Rouf, A., & Tanyeli, C. (2015a). Bioactive thiazole and benzothiazole derivatives. In *European Journal of Medicinal Chemistry*. https://doi.org/10.1016/j.ejmech.2014.10.058
36. Rouf, A., & Tanyeli, C. (2015b). ChemInform Abstract: Bioactive Thiazole and Benzothiazole Derivatives. *ChemInform*. https://doi.org/10.1002/chin.201532306

37. T. Chhabria, M., Patel, S., Modi, P., & S. Brahmkshatriya, P. (2016). Thiazole: A Review on Chemistry, Synthesis and Therapeutic Importance of its Derivatives. *Current Topics in Medicinal Chemistry*. https://doi.org/10.2174/1568026616666160506130731
38. Turan-Zitouni, G. L., Yurttaş, L., Tabbi, A., Akalin Çiftçi, G. L., Temel, H. E., & Kaplancikli, Z. A. (2018). New thiazoline-tetralin derivatives and biological activity evaluation. *Molecules*. https://doi.org/10.3390/molecules23010135
39. Turan-Zitouni, G., Ozdemir, A., Kaplancikli, Z. A., Altintop, M. D., Temel, H. E., & Çiftçi, G. A. (2013). Synthesis and biological evaluation of some thiazole derivatives as new cholinesterase inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*. https://doi.org/10.3109/14756366.2011.653355
40. Weiß, K. M., Wei, S., & Tsogoeva, S. B. (2011). Novel one-pot process for the synthesis of 1,3-thiazoles via organocatalysed epoxidation of nitro-olefins. *Organic and Biomolecular Chemistry*. https://doi.org/10.1039/c10b05260h
41. Zhu, L., Jin, J., Liu, C., Zhang, C., Sun, Y., Guo, Y., Fu, D., Chen, X., & Xu, B. (2011). Synthesis and biological evaluation of novel quinazoline-derived human Pin1 inhibitors. *Bioorganic and Medicinal Chemistry*. https://doi.org/10.1016/j.bmc.2011.03.058