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Review Article

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Synthesis and Biomedical Profile of Thiazole Derivatives & Hybrids

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Abstract
Thiazole represents a pivotal heterocycle in synthetic & medicinal chemistry. They are recognized for their structural diversity and significant biomedical activities such as antimicrobial, anticancer, anti-fungal, anti-diabetic, anti-convulsant, anti-viral, anti-inflammatory, herbicidal, etc. Their potential to function as biomimetics and reactive pharmacophores has piqued researchers' interest in the past few decades. This review consolidates the recent advances in synthetic methodologies of thiazole and its derivatives & hybrids, including classical and green approaches. The second section of the review focuses on the recent advances in biomedical applications of each of these thiazole moieties.

Keywords: Heterocycles, medicinal chemistry, pharmacophores, antimicrobial, anticancer, thiazole.

1. Introduction

The broadest and most diverse family of molecular fragments that chemists use for organic synthesis is perhaps heterocyclic compounds. Over two-thirds of the approximately 20 million chemical compounds known are wholly or partly aromatic, while around half are heterocyclic.[1] The most prevalent heteroatoms are nitrogen, oxygen, and sulphur. Still, there are also a few additional well-known heterocyclic compounds that contain tellurium, selenium, phosphorus, arsenic, silicon, boron, and other elements.[2] Numerous substances, both naturally occurring or not, consist of a heterocyclic skeleton such as alkaloids, vitamins, amino acids, hemoglobin, hormones, pigments, dyes, etc.[3] Heterocyclic compounds include several natural medications, including morphine, codeine, quinine, penicillin, papaverine, atropine, emetine, reserpine, procaine, etc.[4] Several synthetic drugs with heterocyclic rings have demonstrated therapeutic properties such as anti-tubercular, antidepressant, anti-bacterial, anti-fungal, anti-viral, anti-Alzheimer's, anti-inflammatory, anti-diabetic and anti-cancer, etc. making them a favored structure in medicinal chemistry.[5], [6], [7], [8], [9]

An important class of heterocycles with sulphur-nitrogen heteroatoms consists of aromatic compounds with various physicochemical characteristics. Aromatic carbocycles with two or more carbons or a complete CH=CH group replaced by both nitrogen (N) and sulphur (S) heteroatoms in the ring give rise to aromatic S-N-containing heterocycles. Carbon atoms offer stability to the cyclic skeleton according to the aromaticity and antiaromaticity principles while the sulphur-nitrogen score gives the compounds distinct characteristics due to their electron-rich p-excessive nature and the difference in electronegativity between carbon and heteroatoms.[10] As a result, the

physicochemical features and reactivity of the sulphur-nitrogen heterocycles differ from those of the precursor carbocyclic compounds. The structural heterogeneity and biological characteristics make them an intriguing class of heterocycles that are attracting the interest of researchers.

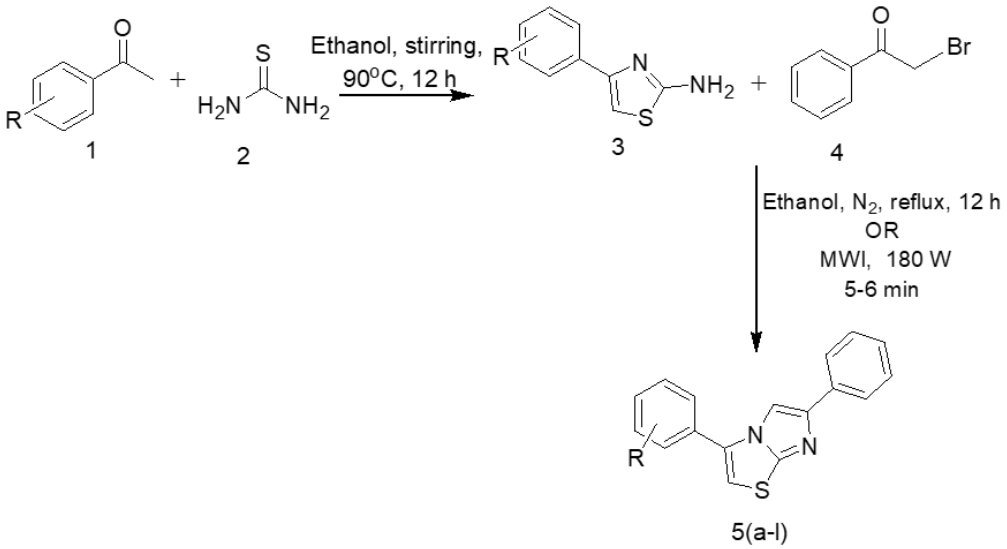
Thiazole is paramount among sulphur-nitrogen-containing heterocycles due to its broad synthetic versatility. The strategic modification of thiazole derivatives and hybrids opens up new avenues for drug discovery and development, allowing for creating compounds that better meet the needs of specific biomedical applications. Given the growing number of applications of thiazole, an updated exploration of this subject is required. Our goal is to present an overview of this heterocycle, including its chemistry, synthetic techniques, and biomedical applications that have led to its increased use in organic synthesis during the recent years.

2. Synthetic aspects of thiazoles

Synthetic routes for synthesizing thiazole compounds often involve various strategies to construct the desired ring structures. Some common methods are cyclization, cyclo-addition, metal-catalyzed transformations, etc. which facilitate the formation of five- or six-membered rings. Furthermore, microwave-assisted synthesis and ultrasound techniques have gained popularity for their ability to expedite reactions, improve yields, and simplify purification processes. Overall, the diversity of synthetic routes provides chemists with flexible options for creating a wide range of thiazole moieties. We have offered here a methodical mention of some of the major works in the previous decade.

Thiazole; the five-membered ring system with an alternate double bond and electronegative sulphur-nitrogen atoms undergoes resonance. This ability of delocalization of electrons across the ring influences the chemical behavior and reactivity of thiazole and its derivatives. Among all the heterocyclic compounds that contain S-N, it is one of the most frequently synthesized. A few notable syntheses of thiazole skeletons have been listed below:

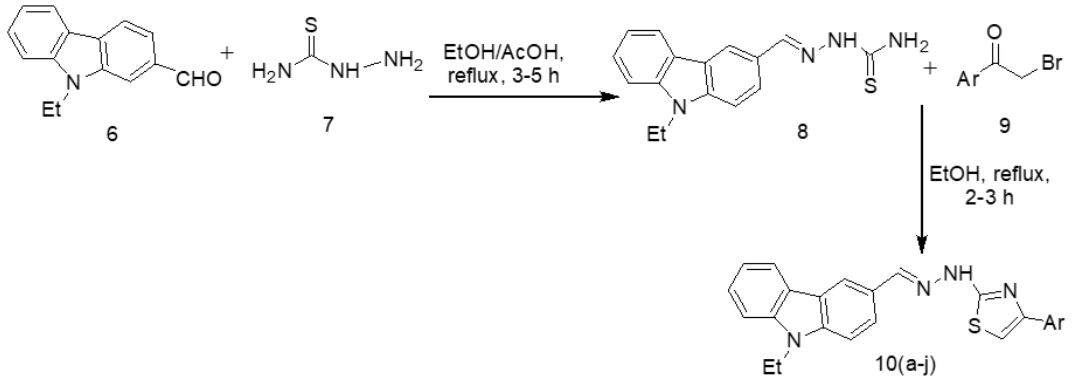
Koppireddi et al.[11] (Scheme 1) reported diphenyl-imidazole-thiazole derivatives in a two-step process. The synthetic route starts with a mixture of acetophenone and thiourea, stirred to obtain substituted aryl thiazole amines, which further reacts with 2-bromophenylethanone in ethanol under reflux to give the desired products. A quick microwave procedure was also conducted to successfully obtain a 75–90% yield of synthesized derivatives in less than 6 minutes. The major highlight of the synthesis is a systematic green approach that uses an eco-friendly solvent like ethanol and an energy-efficient MWI-enhanced pathway. However, the use of a complex setup that requires pressure tubes can be seen as a negative aspect of this method.



a; R = 4-F, b; R = 4-Cl, c; R = 4-Br, d; R = 2-Cl, e; R = 3-Cl, f; R = 2-F, g; R = 2-CH_3, h; R = 3-CH_3, i; R = 2-OCH_3, j; R = 3-CF_3, k; R = 4-CF_3, l; R = 4-Et

Scheme 1: Synthesis of imidazole-thiazole derivatives.

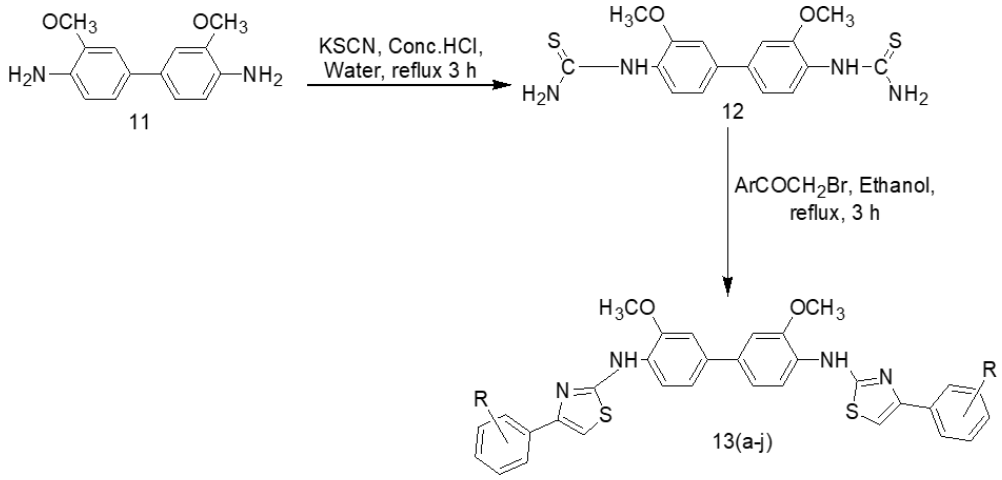
Nguyen et al.[12] (Scheme 2) developed a two-step synthetic procedure to create a series of thiazole-carbazole hybrids. The first phase of the reaction carried out the condensation of substituted carbaldehyde with thiosemicarbazide in ethanol with a catalytic quantity of acetic acid to create thiosemicarbazone. In the subsequent phase, the appropriate substituted thiazoles were produced by reacting thiosemicarbazone with different α-bromoketones in refluxing ethanol. The use of a non-reproducible catalyst like acetic acid and no discussion by the authors regarding the yields of derivatives can be seen as a limitation of this protocol.



Ar = a; Ph, b; 4-MePh, c; 4-OMePh, d; 4-OCF_3Ph, e; 4-ClPh, f; 4-BrPh, g; 4-NO_2Ph, h; 3-NO_2Ph, i; 4-CNPh, j; 2-Me-naphthalyl

Scheme 2: Synthesis of thiazole- carbazoles hybrids.

Zitouni et al.[13] (Scheme 3) synthesized bis-thiazole derivatives in a two-step method using simple reagents. The reaction took place between substituted biphenyl-diamine and KSCN in the presence of conc. HCl resulted in the formation of an intermediate that underwent ring closure with different substituted phenacyl bromides in ethanol to produce the desired products. Nearly all the derivatives synthesized with this procedure were in high yields (78-90%). One significant disadvantage of this pathway is the use of corrosive and toxic conc. HCl.

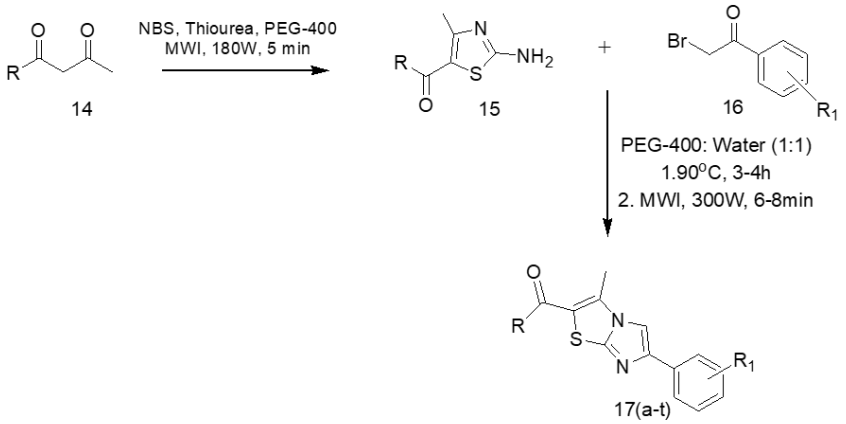


R = a;H, b;4-NO_2, c;4-CH_3, d;4-OCH_3, e;4-Br, f;4-Cl, g;3,4-diCl, h;2,4-diCl, i;2,5-diCl, j;2,5-diOCH_3

Scheme 3: Synthesis of bis-thiazole derivatives.

Vekariya et al.[14] (Scheme 4) reported conventional as well as microwave synthesis of imidazole-thiazole hybrids using α-bromo aralkyl ketones and 2-amino thiazoleis s in the presence of PEG-400, which exhibited a dual nature of solvent as well as catalyst. Initially, a green protocol was applied to produce 2-amino thiazoles via a reaction

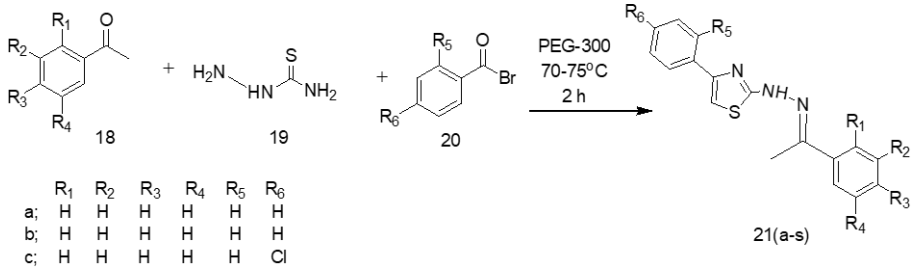
between substituted diketones, NBS, and thiourea in PEG-400. To optimize the reaction conditions the authors examined various solvents such as Tetrahydrofuran (THF), ethanol, methanol & brominating agents like KBr, KBrO3, HBr, Bromine (Br2), etc. but afforded poor product yield when compared with PEG-400 & NBS (82%-96% yield). While the use of inexpensive and non-toxic PEG-400 is a prominent merit of this protocol, however, no significant difference was noticed between the conventional and microwave yields.



a-j; R = Me, k-t; R = OEt
a,k; R_1 = Ph, b,l; R_1 = 2-ClPh, c,m; R_1 = 4-CH_3Ph, d,n; R_1 = 4-OCH_3Ph, e,o; R_1 = 4-BrPh,
f,p; R_1 = 4-ClPh, g,q; R_1 = 2,4diClPh,hr,; R_1 = 4-FPh, i,s; R_1 = 2-OCH_3Ph, j,t; R_1 = 4-NO_2Ph

Scheme 4: Synthesis of imidazole-thiazole derivatives.

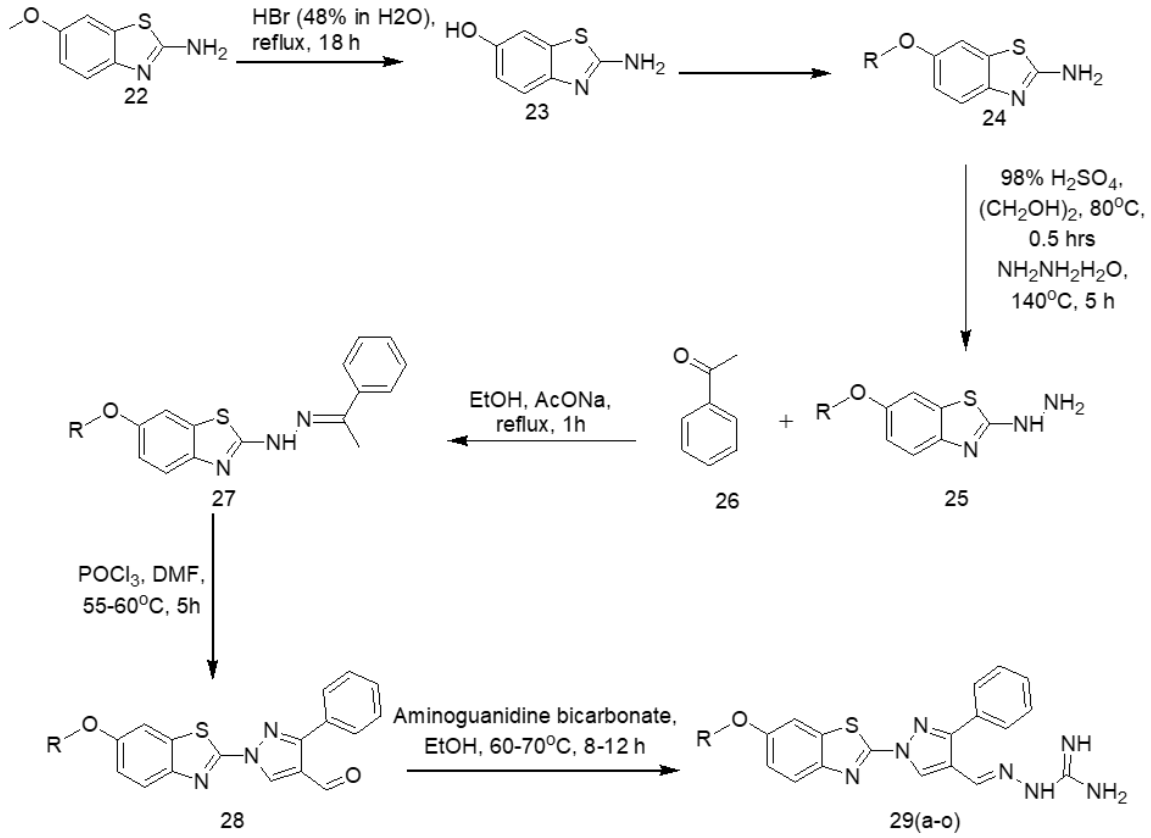
A one-pot PEG-mediated synthesis of hydrazine-thiazole derivatives was explored by Raut et al.[15] (Scheme 5). In this synthesis, PEG-300 was used as a reaction medium as well as a supportive catalyst. Substituted acetophenones and thiosemicarbazide were made to react through condensation in the presence of a catalytic amount of glacial acetic acid to produce thiosemicarbazone derivatives as intermediates, which subsequently reacted with the appropriate α-halo ketones to yield hydrazine-thiazole derivatives with 85-93% yields. The authors have provided a green aspect to the procedure by including PEG-300 and a good number of substituent groups are covered.



	R_1	R_2	R_3	R_4	R_5	R_6
a;	H	H	H	H	H	H
b;	H	H	H	H	H	H
c;	H	H	H	H	H	Cl
d;	H	H	H	H	H	H
e;	H	H	OH	H	Cl	Cl
f;	H	H	OH	H	H	CH_3
g;	H	H	OH	H	H	OCH_3
h;	H	H	OH	H	H	H
i;	H	NO_2	H	H	H	CH_3
j;	H	NO_2	H	H	H	OCH_3
k;	H	NO_2	H	H	Cl	Cl
l;	H	NO_2	H	H	H	Cl
m;	H	NO_2	H	H	H	H
n;	H	H	CH_3	H	H	H
o;	H	H	CH_3	H	H	CH_3
p;	H	H	CH_3	H	H	Cl
q;	H	H	CH_3	H	H	NO_2
r;	OH	H	H	Cl	H	H
s;	H	H	H	H	H	F

Scheme 5: Synthesis of hydrazine-thiazole derivatives

Through a series of steps, Liu et al.[16] (Scheme 6) created pyrazole-benzothiazole hybrids with aminoguanidine. To obtain the necessary derivatives, initially substituted amino-benzothiazole reacted with HBr under reflux. This was followed by a reaction with suitable alkyl bromides in acetone. The resultant compound was treated with hydrazine hydrate in sulfuric acid to produce hydrazine derivatives. In the presence of glacial acetic acid in ethanol, the hydrazine derivatives interacted with acetophenone to form hydrazone derivatives. In the presence of catalytic amounts of hydrochloric acid in ethanol, hydrazone derivatives reacted under Vilsmeier–Haack conditions (DMF–POCl3) to yield corresponding pyrazole-4-carbaldehyde derivatives, which in turn reacted with aminoguanidine bicarbonate to produce a series of novel pyrazole-benzothiazole moieties containing aminoguanidine units. The multistep method with a long reaction framework and moderate yields are negative aspects of this synthetic route.
this synthetic route.

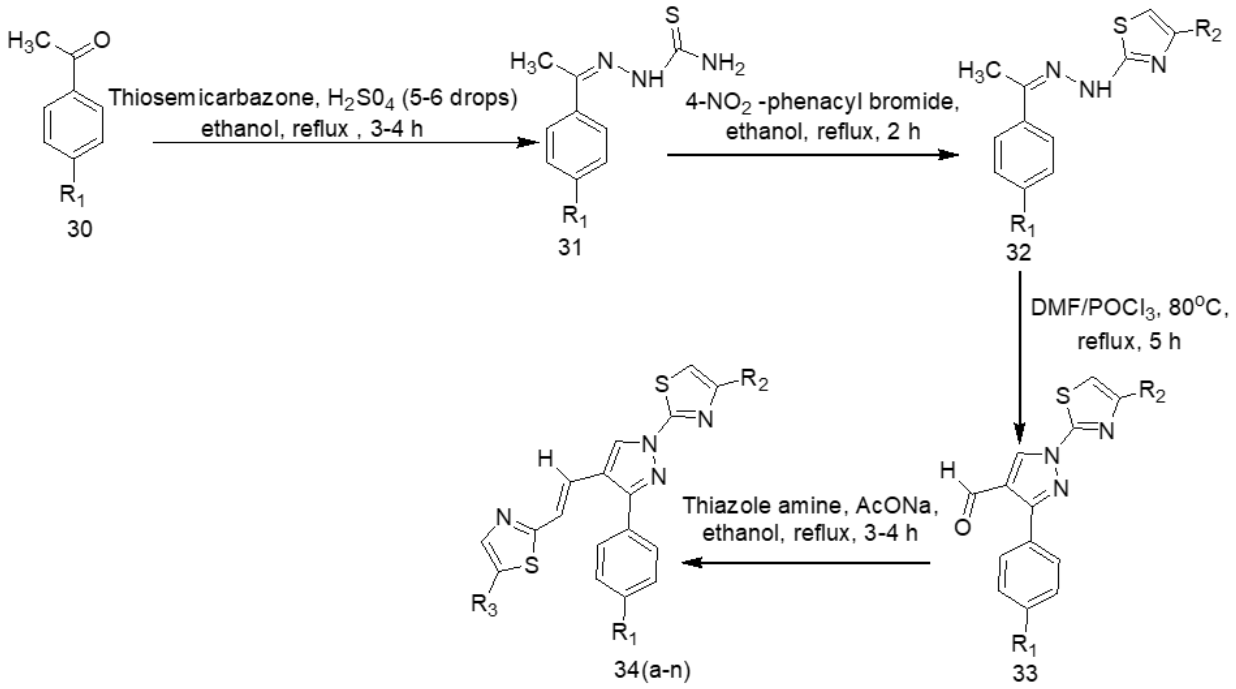


a;R = CH_3, b;R = C_3H_7, c;R = C_4H_9, d;R = C_5H_{11}, e;R = C_6H_{13}, f;R = C_7H_{15}, g;R = C_8H_{17}, h;R = C_9H_{19},
i;R = C_6H_5, j;R = 2F-C_6H_5, k;R = 3F-C_6H_4, l;R = 4F-C_6H_4, m;R = 2Cl-C_6H_4, n;R = 3Cl-C_6H_4,
o;R = 2,4diCl-C_6H_3

Scheme 6: Synthesis of pyrazole-benzothiazole hybrids with aminoguanidine.

Bansal et al.[17] (Scheme 7) efficiently synthesized a series of thiazole-clubbed pyrazole derivatives. The synthetic route starts with the reaction of substituted acetophenones with thiosemicarbazone in the presence of acid and ethanol. Further, Hantzsch thiazole synthesis was carried out using p-NO_2-phenacyl bromide in ethanol, later followed by a Vilsmeier-Haack cyclization reaction with DMF/$POCl_3$ as reagents to give substituted carbaldehydes. Later by refluxing appropriate substituted amino-thiazoles with carbaldehydes in ethanol and fused sodium acetate, a

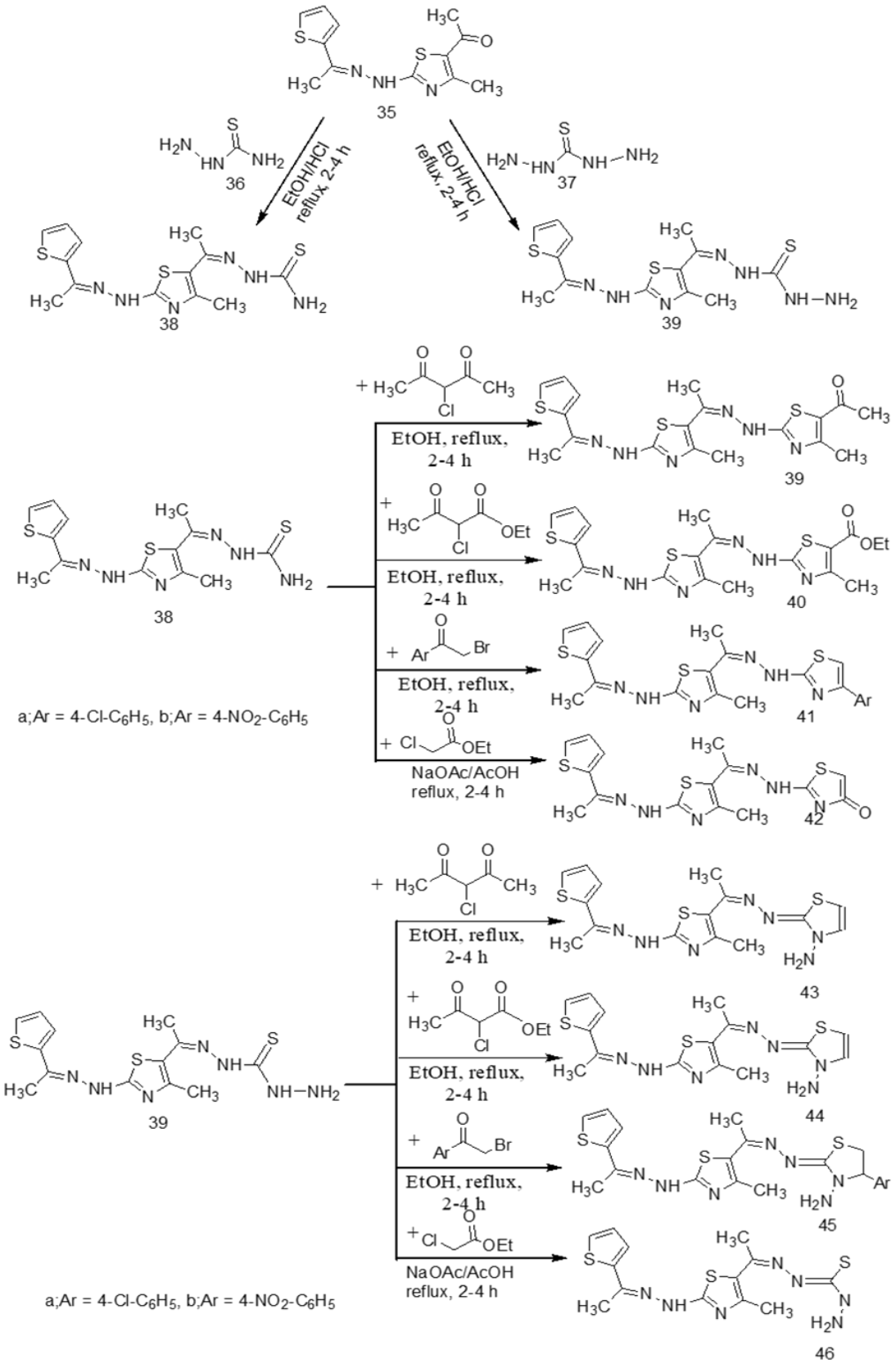
series of thiazole-pyrazole derivatives were obtained. The yields varied from moderate to good depending on the substituent attached.



a, h; R_1 = H, b, i; R_1 = NO_2, c, j; R_1 = F, d, k; R_1 = Br, e, l; R_1 = CH_3, f, m; R_1 = 2,6-diCl, g, n; R_1 = 2-OH
a-n; R_2 = 4-NO_2-C_6H_5
a-g; R_3 = H, h-n; R_3 = NO_2

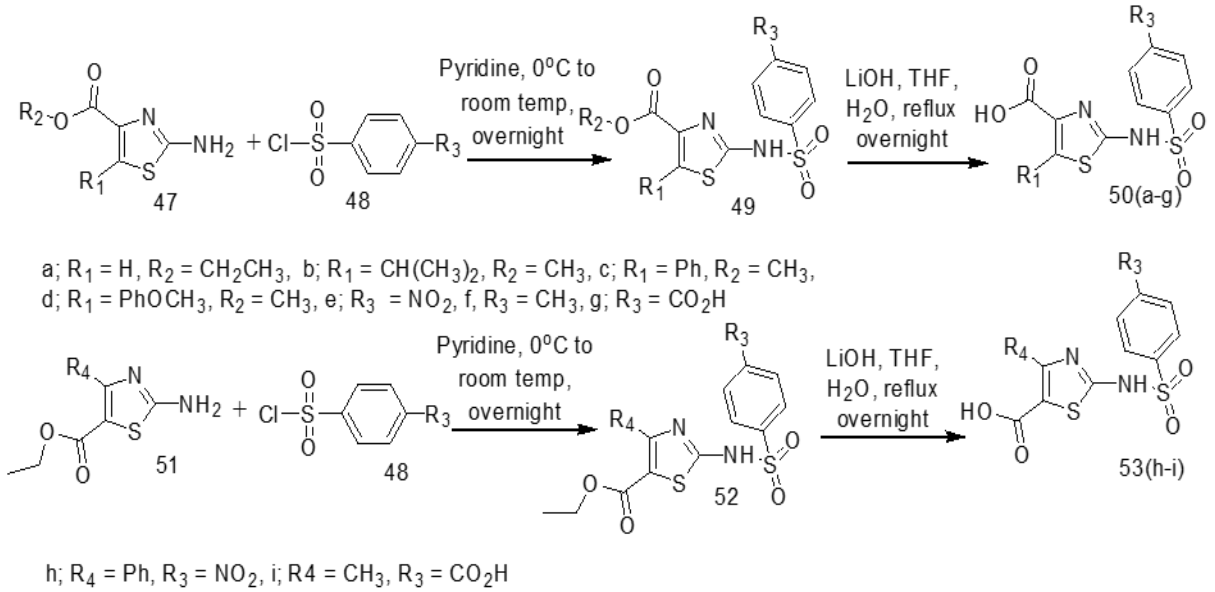
Scheme 7: Synthesis of thiazole clubbed pyrazole derivatives.

Gomha et al.[18] (Scheme 8) developed a multistep procedure for synthesis of new thiazole-thiosemicarbazones & thiazole-thiocarbohydrazone hybrids. Thiosemicarbazone & thiocarbohydrazone derivatives were prepared from the reaction of substituted thiazole with the respective thiosemicarbazide and thiocarbohydrazide in EtOH/ HCl under reflux. The chemical reactivity of resultant thiosemicarbazone & thiocarbohydrazone derivatives towards α-halo-compounds/ p-substituted phenacyl bromide derivatives/ ethyl 2-chloroacetate was investigated to synthesize a series of new thiazoles. The synthesis was limited to the usage of only two aryl substituents for compounds (41) and (45).



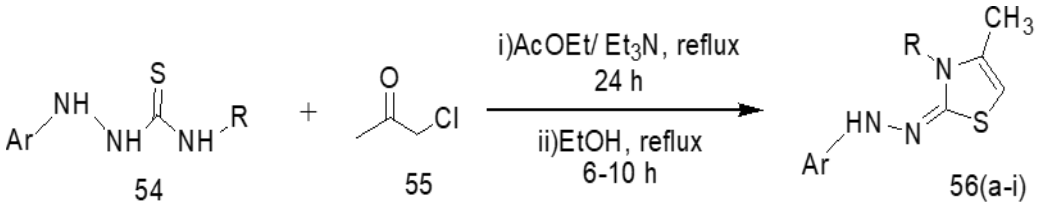
Scheme 8: Synthesis of thiazole-thiosemicarbazones & thiazole-thiocarbohydrazone hybrids.

Audat et al.[19] (Scheme 9) synthesized N-thiazole benzenesulfonamide moieties, during the course of reaction primary aromatic amines were converted to sulfonamide moieties via treatment with benzenesulfonyl chlorides in the presence of pyridine as a base. The crude was treated with HCl and later underwent a hydrolysis reaction utilizing lithium hydroxide under refluxing conditions to yield the desired compounds. The use of column chromatography for purification and very low yields for some derivatives is a drawback for this protocol.



Scheme 9: Synthesis of thiazole-benzenesulfonamide derivatives.

Al-Wahaibi et al.[20] (Scheme 10) worked on a mixture of substituted hydrazine-carbothioamides and chloroacetone in ethyl acetate as a solvent to synthesize a novel series of 2,3,4-trisubstituted thiazoles with a methyl group at position four in an outstanding yield of 78–99%. Et_3N successfully catalyzed the process and for recrystallization mixture of solvents such as ($AcOEt/Et_3N$: 98%) and (EtOH: 85%) were found suitable. The long time framework was the only drawback for this reaction.

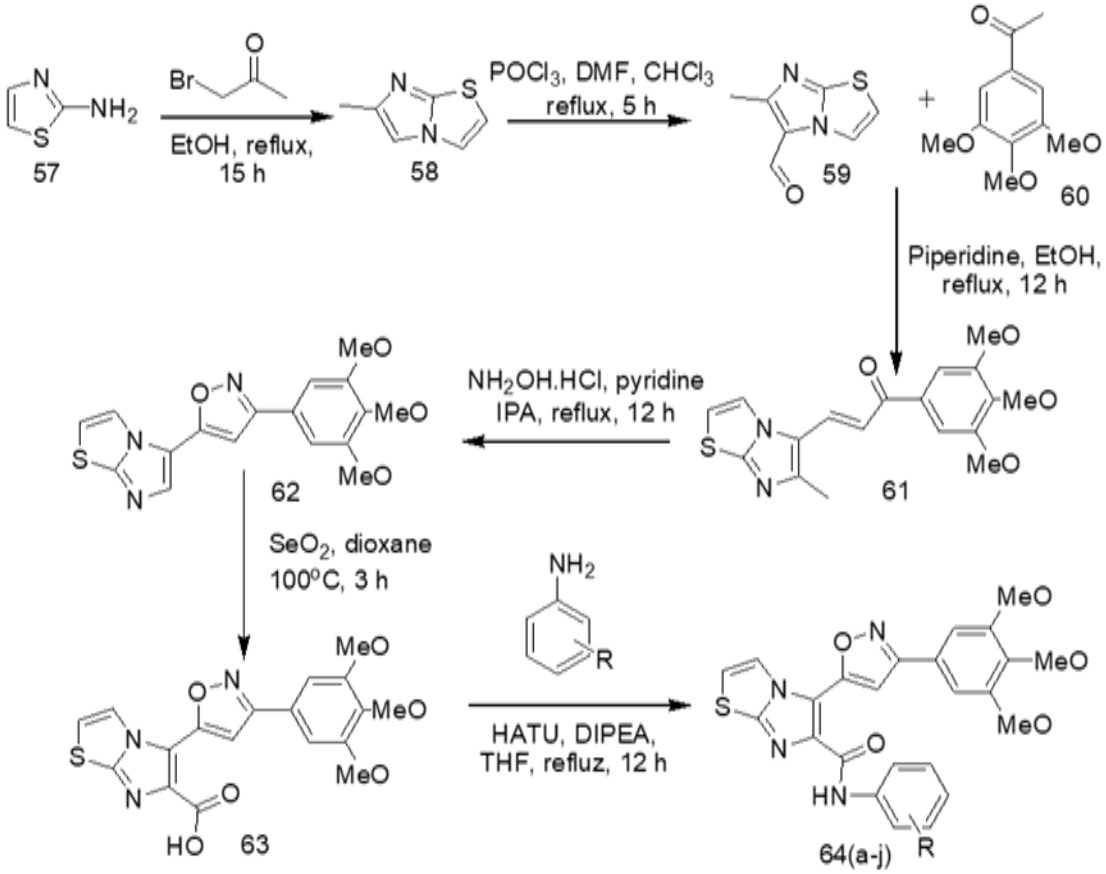


a-f;Ar = 2,4-di-NO_2Ph, g-i; Ar = p-CH_3Ph-SO_2-
a; R = CH_2Ph, b; R = CH_2CH_3, c; R = $CH_2CH{=}CH_2$, d; R = C_6H_{11}, e; R = C_6H_5, f; R = 4-CH_3Ph
g; R = Ph, h; R = $CH_2CH{=}CH_2$, i; R = CH_2CH_3

Scheme 10: Synthesis of 2,3,4-trisubstituted thiazoles.

Alapati et al.[21] (Scheme 11) synthesized a series of amide derivatives of thiazoles. The key intermediate was synthesized from the reaction between aminothiazole and bromo-propanone in ethanol under reflux. This was followed by a series of reactions including Claisen condensation with aryl ketone, and cyclization with NH2OH.HCl and pyridine in isopropyl alcohol thereby leading to a carboxylic acid intermediate formed using SeO2 in 1,4-

dioxane which was lastly, coupled with different types of aromatic amines to produce the desired derivatives. The derivatives were synthesized with good to excellent yields while the involvement of multiple steps with a large number of reagents is a limitation to this procedure.



Scheme 11: Synthesis of amide derivatives of thiazole.

Biomedical Applications: Thaizole nuclei provide a vast opportunity for new lead compounds for drug discovery and establishing activity relationships with biological targets to improve pharmacological effects. The diverse biological applications of thiazoles underscore their importance in drug development, agricultural chemistry, and biochemistry making them an inexhaustible resource of novel compounds. Several clinically approved drugs like, Dabrafenib, Cefotaxime, Isavuconazole, Ritonavir, Nitazoxanide, Pramipexole, Nizatidine etc. highlight the therapeutic potential of thaizoles in various medical fields.[22] Their diverse mechanisms of action make them important components of modern pharmacotherapy (Fig.3). We have highlighted the progress in developing thiazole compounds focusing it as a scaffold of biological and medical interest for past decade Table 1.

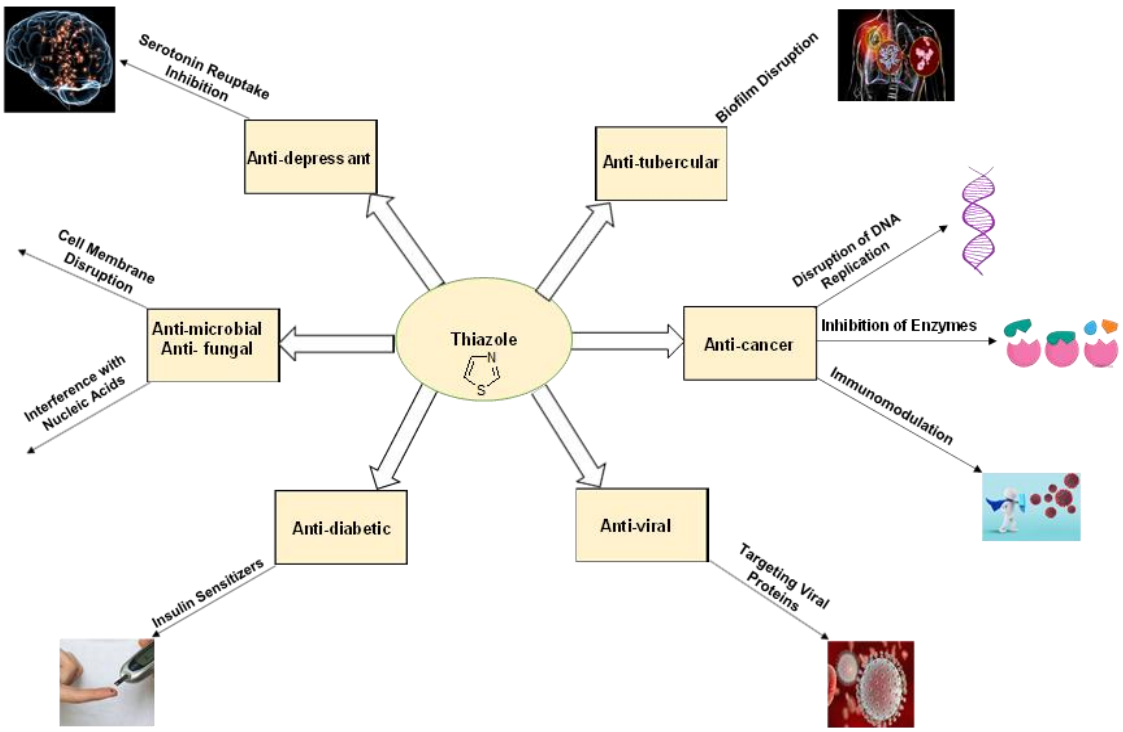
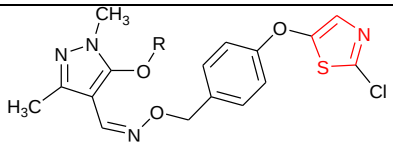
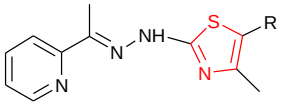
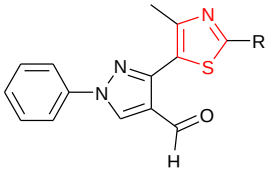
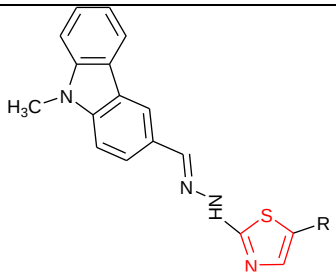
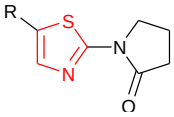
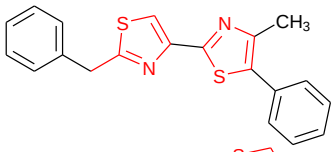
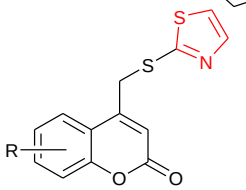
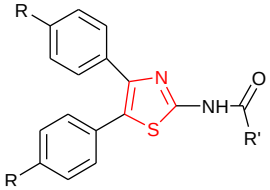
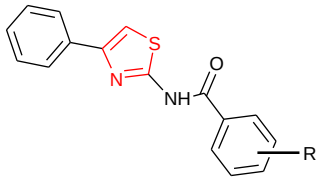
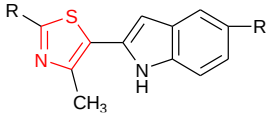


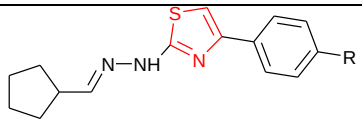
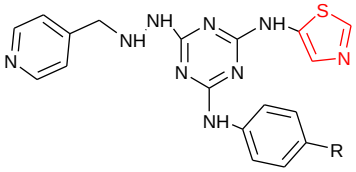
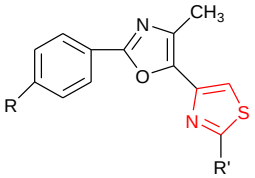
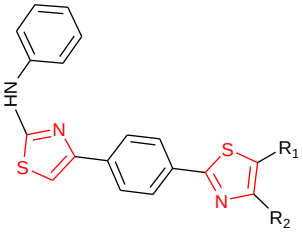
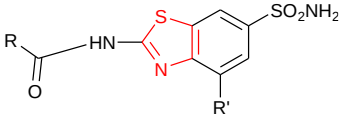
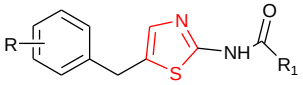
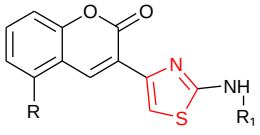
Figure 1: Diverse mechanism of action shown by Thiazoles.

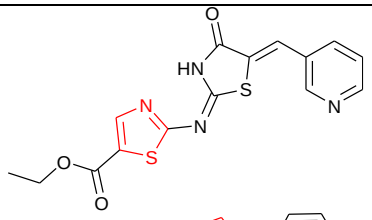
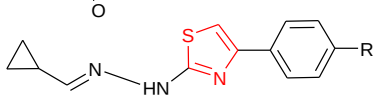
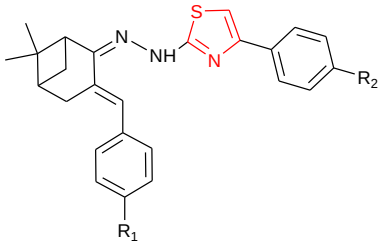
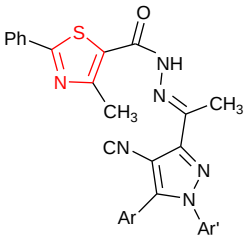
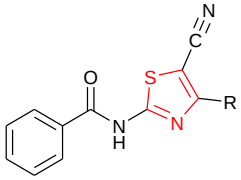
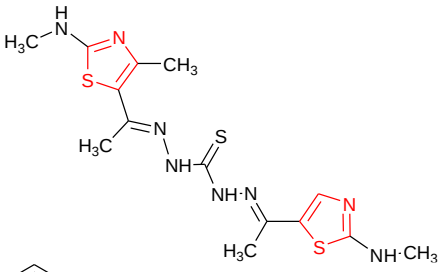
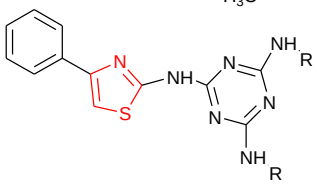
The number of publications related to thiazole biomedical activity has increased significantly, with over 200 articles published annually with promising pharmacological activities some of which are tabulated below.

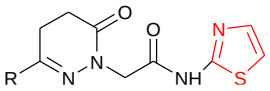
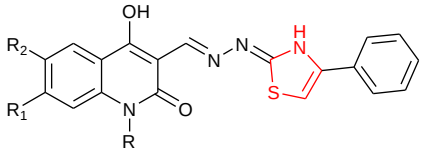
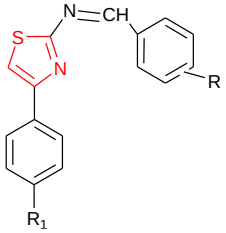
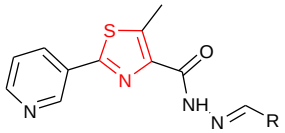
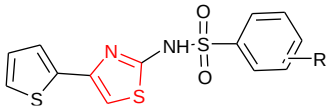
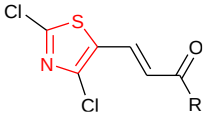
Table 1: Recent advances in biomedical activities of thiazole moiety:

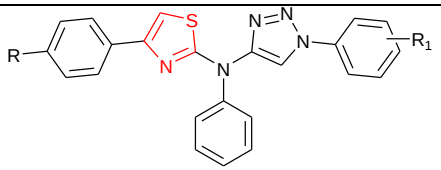
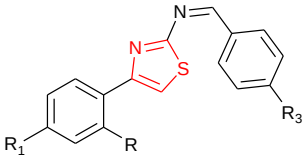
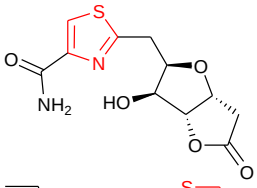
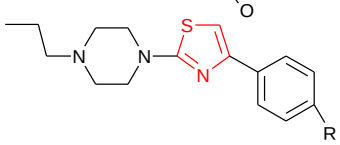
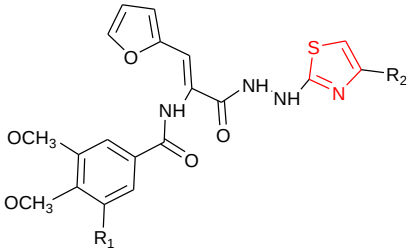
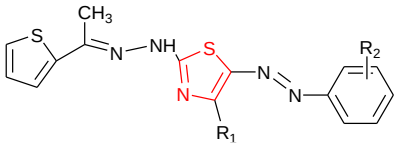
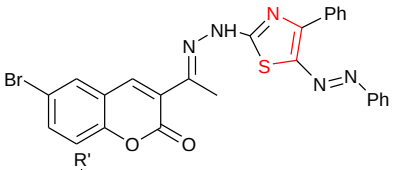
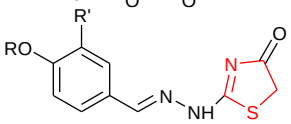
Year	Author	Type	Structure	Activity
2014	Dai *et al.*[23]	Thiazole-pyrazole hybrids	 R = Ph, 3-FPh, 4-FPh, 3-ClPh, 2-BrPh, 4-BrPh, 3-NO_2Ph, 2-CH_3Ph, 3-CH_3Ph, 4- CH_3Ph, 4-tbuPh, 6Cl-3CH_3Ph, 2,3-diCH_3Ph, 2,4-diFPh, 2-naphthyl	Insecticidal
2014	Makam *et al.*[24]	Thiazole derivatives	 R = phenyl, pyridyl and five-membered rings.	Anti-malarial
2014	Khillare *et al.*[25]	Thiazole-pyrazole hybrids	 R = phenyl or CH_3	Anti-inflammatory

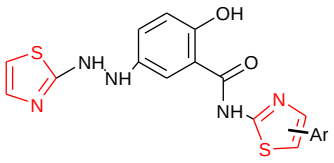
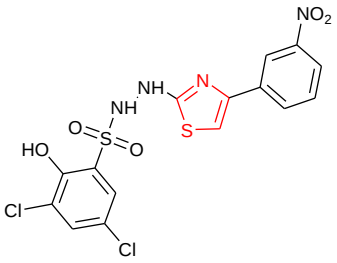
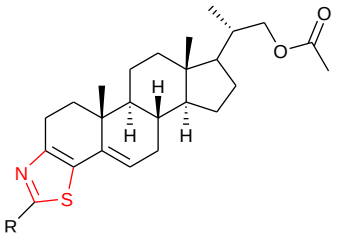
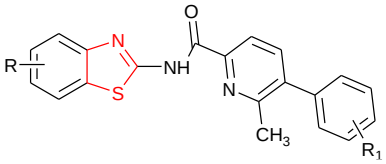
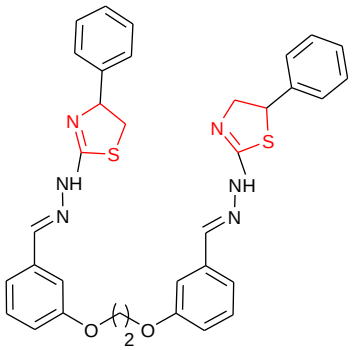
2014	Shaikh *et al.*[26]	Thiazole derivatives	 R = 4 Br-Ph, 4-Ph, 3,4diOCH_3-Ph, 4-ClPh, 4-NO_2Ph, 4-FPh, 4-p-tolyl,3-ClPh, 3-FPh, C_4H_4S, $C_9H_6O_2$, 6-Br$C_9H_6O_2$	Anti-mycobacterial
2015	Ghabbour *et al.*[27]	Thiazole-pyrrolidinone hybrid	 R = naphthyl	Anti-convulsant
2015	Abhale *et al.*[28]	Bithiazoles		Anti-tubercular & Anti-microbial
2015	Reddy *et al.*[29]	Thiazole-coumarin hybrids	 R = 6-CH_3, 6-Cl, 6-OCH_3, 5,6-Benzo, 7-CH_3, 7-Cl, 7-OCH_3, 5,7-diCH_3, 6-Br, 7-Br	Anti-tubercular
2015	Abdelazeem *et al.*[30]	Diphenyl thiazoles	 a: R = H, R’ = COOH; b: R = OMe, R’ = COOH; c: R = OMe, R’ = methylpiperazine	Anti-inflammatory
2016	Sun *et al.*[31]	Thiazole acetamide hybrids	 R = H, 4-CH_3, 2-CH_3 4-OCH_3, 2-OCH_3 4-F, 4-Cl, 2-Cl 4-NO_2 2-NO_2	Anticholinesterase agent
2016	Vaddula *et al.*[32]	Thiazole-indole hybrids	 R = 4-OCH_3Ph, 4-ClPh, CH_3, Indolyl, 3,4,5-$(OCH_3)_3$Ph	Anti-cancer

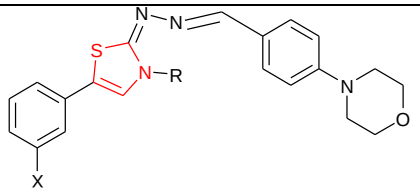
2016	Laczkowski *et al.*[33]	Thiazole derivatives	 R= F, Cl, Br, CH_3, NO_2, CN, OCH_3 , 3,4-diCl, CF_3	Anti-convulsant
2016	Desai *et al.*[34]	Thiazole-triazine hybrids	 R = H, 4-Br, 2-Cl, 3-Cl, 4-Cl, 2,5-Cl_2, 2,6-Cl_2, 4-F, 2-CH_3, 4-CH_3, 2-NO_2, 4-NO_2	Anti-microbial
2017	Abhale *et al.*[35]	Thiazole-oxazole hybrids	 R =H, 4-F; R' = Ph, 4-BrPh, 3-ClPh, 4-ClPh, 3-Cl-4-FPh, 4-FPh, 4-CH_3Ph, Bn, 3-ClBn, 4-ClBn, 4-FBn	Anti-mycobacterial
2017	Bikobo *et al.*[36]	Thiazole derivatives	 R_1 = H, H_3COO^-, $EtOCO^-$; R_2 = Ph, 4-OCH_3Ph, 4-NO_2Ph, 4-ClPh, 3-carbomyl-4-OHPh, 4-CNPh, Cl-CH_2, CH_3, $EtOCOCH_2$	Anti-microbial
2017	Abdoli *et al.*[37]	Benzothiazole derivatives	 R = C_6H_5COOH, CH_3; R' = Br, I	Carbonic anhydrase inhibitor
2017	Finiuik *et al.*[38]	Thiazole derivatives	 R = H, 4-Et, 3,4-Cl_2, 4-Br R_1 = phenoxy benzene, chromene, isothiochromene, benzofuran	Antineoplastic
2018	Osman *et al.*[39]	Thiazole-coumarin hybrids	 R = H, OMe; R_1 = Me, Et, Ph, 3,4-ClPh, 2-BrPh, 2-OMePh	Antibacterial

2018	Abo-Ashour *et al.*[40]	Aminothiazole-thiazolidinone hybrid		Anti-tubercular
2018	Laczkowski *et al.*[41]	Thiazole-cyclopropyl hybrids	 R = 4-F, 4-Cl, 4-p-tolyl, 4-Br, 4-CF_3, 4-OCH_3, 2,4-diF, CN, 4-N_3, 4-NO_2	Antifungal Anticonvulsant Antitoxoplasma
2018	Wang *et al.*[42]	β-pinene-based thiazole derivatives	 R_1 = CH_3, Cl; R_2 = H, F, OH, OCH_3,	Anticancer
2019	Abu Mehla *et al.*[43]	Thiazole derivatives	 Ar = Ph, 4-CH_3Ph; Ar' = Ph, 4-CH_3OPh, 4-ClPh	Anticancer
2019	Anuradha *et al.*[44]	Thiazole derivatives	 R = NMe_2, Ph	Anticancer
2019	Farghaly *et al.*[45]	Dithiazole		Anticancer
2019	Sahu *et al.*[46]	Thiazole-triazine hybrids	 R = cyclopropylamine, cyclohexylamine, phenylamine, o-toluidine, propylamine, benzylamine, piperidine, trimethylamine, dimethylamine	Antimalarial

			R_1 = 2,4-Cl, 3-NO_2	
2020	Siddiqui *et al.*[47]	Thiazole pyridazinone hybrids	 R = Ph, 4-FPh, 4-tolyl, 4-anisyl, 4-ClPh, 4-CH_3CH_2Ph, 3,4diCH_3Ph, 2,5diCH_3Ph, 2,4diCH_3Ph, 4-isobutylPh, 3,4diClPh, 4-benzylPh, 4-phenoxyPh, 4-propylPh, 4-biphenyl, 4-BrPh, 2-thienyl, naphthyl	Anticonvulsant
2020	Aly *et al.*[48]	Thiazole quinolone hybrids	 R = H, CH_2CH_3; R_1 = H, Cl, Br; R_2 = H, OCH_3, CH_3, Cl, Br	Anticancer
2020	Cordeiro *et al.*[49]	Aminothiazoles	 R = 3’4’5’- OCH_3, 2’-NO_2, 3’-Cl, 4’-OH; R1 = pyrrole-2,5-dione, isoindole-1,3-dione, benzamide	Antitubercular
2020	Kamat *et al.*[50]	Thiazole derivatives	 R = 4-ClPh, 3,4-diCH_3Ph, 4-CH_3Ph, Furan, 4-OHPh, 5-Br2-OHPh, benzyloxy-Ph, indole, 4-OH-3OCH_3Ph	Anti-inflammatory
2021	Meseli *et al.*[51]	Sulfathiazole-sulfonamide hybrids	 R = 4-Cl, 2,5-diCl, 4-Br, 4-OCH_3, 4-COCH, 4-t-Bu, 4-I, 4-NO_2,3-NO_2, 4-CH_3	Antibacterial
2021	Kasetti *et al.*[52]	Thiazole derivatives	 R = 2-ClPh, 3-CLPh, 4-ClPh, 2-3diClPh, 2-6diClPh, 2-5diClPh, 2-4diClPh, 3-4diCLPh, 2-FPh, 3-FPh, 4-FPh, 2-4diFPh, 2-5diFPh, 2-6diFPh, 3-4diFPh, 3-5diFPh, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-thiazolyl	Acetylcholinesterase Inhibitor

2021	Ankali *et al.*[53]	Thiazole-1,2,3-triazoles hybrids	 R = 4-Cl, 4-Br, R_1 =4-$CH_3$3-NO_2, 4-Cl, 4-NO_2, p-tolyl, 4-F, 2-NO_2, 4-OH, 4-OCH_3	Antianxiety & Anti inflammatory
2021	Lemilemu *et al.*[54]	Thiazole derivatives	 R = H; R_1 = H, NO_2; R_3 = NO_2	Antibacterial & Antioxidant
2022	Svircev *et al.*[55]	Thiazole bio-isostere of goniofufurone		Antiproliferative
2022	Pivovarova *et al.*[56]	Thiazole derivatives	 R = H, Cl, CH_3	Anticancer & Antimicrobial
2022	Al-Warhi *et al.*[57]	Thiazole Derivatives	 R_1 = H, OCH_3; R_2 = H, 4-Cl, 4-Br, 3NO_2, 3-OCH_3	Anticancer
2022	El-Naggar *et al.*[58]	Thiazole derivatives	 R_1 = CH_3, Ph, 4-NO_2Ph; R_2 = 4-OCH_3, 4-CH_3, 4-Cl, 2-COOH, 4-NO_2, primidine2,4-dione etc.	Anticancer & Antimicrobial
2023	Sayed *et al.*[59]	Thiazole-coumarin hybrid		Antimicrobial
2023	Al-Salmi *et al.*[60]	Thiazole derivatives		Anticancer

				R = H, $COCH_3$; R' = H, N=N-Ph, Br	
2023	Aziz *et al.*[61]		Thiazole derivatives		Antibacterial
2023	Khan *et al.*[62]		Thiazole derivatives		Alzheimer's Inhibitors
2024	Roy *et al.*[63]		Thiazole-fused Bisnoralcohol derivatives	 R = NPh, N-methyl, N-benzyl, CH_3-NPh, OCH_3-NPh, 3-OH-NpH, 4-OH-NpHl, 2-Cl-NPh, 4-Cl-NPh, 3-OCF_3-NPh, 2-F-NPh, 3-F-NPhl, 4-F-NPh, 2-pyridyl-NH, 3-pyridyl-NH, 5-CH_3-2-pyridyl-NH, 3-Cl-4-CH_3-NPh, 3,5-diCH_3-NPh, 2,4-diF-NPh, 4-OCH_3-6-CH_3-pyrimidinyl-NH, 6-Cl-2-pyridyl-NH, 4-Cl-2-pyridyl-NH, 5-F-2-pyridyl-NH, 6-CH_3-2-pyridyl-NH, naphthyl-NH, 3,5-diCF_3-NH, 3-CF_3-NH	Antibacterial & Antineoplastic
2024	Raju, Jha[64]		Benzothiazole picolinamide hybrid	 R = H, F; R_1 = CH_3, OCH_3	Anticancer
2024	Abdallah *et al.*[65]		Bisthiazole derivative		Antibacterial

2024	Tasleem *et al.*[66]	Thiazole-morpholine hybrid	 R = 3-cyclohexyl, 3-Ph, 3-Bn, 3-Phenethyl, 3-NO_2Ph, 4-OCH_3Ph, 3-naphthalenyl, 2-FPh, 2,6diCH_3Ph, 4-morpholinobenzylidene, 3-4-CH_3Bn X = H, Cl, Br, NO_2	Carbonic anhydrase-II inhibitors

4. Conclusion and Future Perspective

The synthesis and biological activity of thiomorpholine hybrids and derivatives are active research areas with important implications for medicinal chemistry and drug discovery. These compounds show a wide spectrum of biological activities, including antibacterial, anti-inflammatory, anticancer effects, etc. indicating their potential as therapeutic agents. Advances in synthetic techniques have made these heterocycles more accessible, allowing researchers to investigate structure-activity connections that will help them develop more effective molecules. Novel approaches, such as catalytic and green chemistry strategies have improved the efficiency and selectivity of these synthetic strategies. To further improve the qualities of these molecules, future studies should concentrate on investigating new synthesis pathways and clarifying the processes of reactivity. New applications and a better knowledge of chemistry will probably be made possible by the ongoing merging of computational techniques and experimental research. As this subject develops, interdisciplinary cooperation will be crucial to maximizing these adaptable compound's potential. Future research should also concentrate on enhancing the mechanisms of action, optimizing pharmacological profiles, and exploring the potential of thiomorpholine molecules in a variety of therapeutic settings. The continuous study of thiomorpholine promises to provide innovative drugs that can help address unmet medicinal needs. In our opinion, thiomorpholines are an intriguing class of organic synthesis. It is critical to recognize that their chemistry is still evolving, and their full potential remains untapped. More breakthroughs may occur as the specific properties of these heterocyclic moieties are more extensively exploited.

References

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[3]. E. Kabir and M. Uzzaman, "A review on biological and medicinal impact of heterocyclic compounds," Results Chem., vol. 4, p. 100606, Jan. 2022, doi: 10.1016/j.rechem.2022.100606.

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