Review

Chemistry and Biological Activities of 1,2,4-Triazolethiones—Antiviral and Anti-Infective Drugs

Ashraf A. Aly 1,*, Alaa A. Hassan 1, Maysa M. Makhlouf 1 and Stefan Bräse 2,3,*

1 Chemistry Department, Faculty of Science, Minia University, El-Minia 61519, Egypt; alaahassan2001@mu.edu.eg (A.A.H.); maysaamahsoun@yahoo.com (M.M.M.)
2 Institute of Organic Chemistry, Karlsruhe Institute of Technology, 76131 Karlsruhe, Germany
3 Institute of Biological and Chemical Systems (IBCS-FMS), Karlsruhe Institute of Technology, 76344 Eggenstein-Leopoldshafen, Germany
* Correspondence: ashrafaly63@yahoo.com (A.A.A.); braese@kit.edu (S.B.)

Abstract: Mercapto-substituted 1,2,4-triazoles are very interesting compounds as they play an important role in chemopreventive and chemotherapeutic effects on cancer. In recent decades, literature has been enriched with sulfur- and nitrogen-containing heterocycles which are used as a basic nucleus of different heterocyclic compounds with various biological applications in medicine and also occupy a huge part of natural products. Therefore, we shed, herein, more light on the synthesis of this interesting class and its application as a biologically active moiety. They might also be suitable as antiviral and anti-infective drugs.

Keywords: 1,2,4-triazole ring; synthesis; reactions; biological activity

1. Introduction

Taribavirin (I) (Figure 1) is a triazole based clinically used as antiviral drugs (Figure 1). It is an active agent against a number of DNA and RNA viruses. It is indicated for severe respiratory syncytial virus (RSV) infection, hepatitis C infection, and other viral infections like the West Nile virus and dengue fever [1–3]. Taribavirin (also known as viramidine) is an antiviral drug in Phase III human trials, but not yet approved for pharmaceutical use [4].

AIDS is characterized by an abnormal host defense mechanism that predisposes to infections with opportunistic microorganisms [5]. It was reported [6] that compounds IIIa–d (Figure 1) have...
been proved as treatment for HIV-1. The viral enzymes, reverse transcriptase (RT), integrase (IN), and protease (PR) are all good drug targets. Two distinct types of RT inhibitors, both of which block the polymerase activity of RT, have been approved to treat HIV-1 infections, nucleoside analogs (NRTIs), and nonnucleosides (NNRTIs), and there are promising leads for compounds that either block the RNase H activity or block the polymerase in other ways. A better understanding of the structure and function(s) of RT and of the mechanism(s) of inhibition can be used to generate better drugs; in particular, drugs that are effective against the current drug-resistant strains of HIV-1.NNRTIs via high throughput screening (HTS) using a cell-based assay for inhibiting HIV-1 replication and promising activities against selected NNRTI-resistant mutants such as Y181L, Y181C, K103N, and L100I were observed.

Sulfanyltriazoles IIIa and IIIc (Figure 1) exhibited EC50 values of 182 and 24 nM, respectively, suggesting the potential of these sulfanyltriazoles to overcome the K103-related NNRTI-resistant mutants. These sulfanyltriazoles could serve as advanced lead structures promising great potential in overcoming these and other NNRTI-resistant mutants [7].

1,2,4-triazoles are a very important class of compounds which attracted the attention of many chemists and biologists in organic synthesis and medicinal and pharmaceutical fields due to their various biological activities such as anticancer [8,9], antimicrobial, anticonvulsant [10], anti-inflammatory [11], antitubercular [12], analgesic [13], antibacterial [14], and anti-HIV [15]. In addition, there are chemotherapeutically known drugs containing 1,2,4-triazole moiety, e.g., fluconazole (1) [16], (2-(2,4-difluorophenyl)-1,3-di-(1H-1,2,4-triazol-1-yl)propan-2-ol) and itraconazole (2) [17], (4-(4-(4-(((2S,4R)-2-(1H-1,2,4-triazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)phenyl)piperazin-1-yl)-phenyl)-1-((5)-sec-butyl)-1H-1,2,4-triazol-5(4H)-one), which are used as very effective antifungal drugs. In addition, prothioconazole (3) [18] is commercially available for the treatment of plant-pathogenic fungal infections, alprazolam (4) [18], (8-chloro-1-methyl-6-phenyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine), is used for treating of anxiety disorders, and anastrozole (5) [19] in addition to letrozole (6) is used for chemotherapeutic anticancer drugs [20] (Figure 2).

Incorporating of thione group either in 3- or 5-position (A and B, Figure 3) has been reported in numerous reports, leading to enhancement of biological activities related to triazole moiety [21]. Besides, the triazolethione system is considered as a cyclic analog of very important components like thiosemicarbazides and thiocarbohydrazides, which are widely spread as a reactive building block in many organic reactions leading to different heterocyclic rings and having effective biological applications. Many heterocyclic compounds are the main constituents of natural products; also, mercapto-1,2,4-triazole nucleus is found in many natural products and pharmaceuticals [22].
Mercapto-1,2,4-triazole also may be derived from natural products by applying some reactions to get the desired compounds [23].

$$\begin{align*}
1 & \quad \text{HN} \quad \text{NH} \\
2 & \quad \text{R} \quad \text{S} \\
3 & \quad \text{N} \\
4 & \quad \text{N} \\
\end{align*}$$

5-Substituted-1H-1,2,4-triazole-3(4H)-thiones  3-Substituted-1H-1,2,4-triazole-5(4H)-thiones

Figure 3. 1,2,4-Triazole thiones.

Triazolethione-thiols (Figure 4) have gained considerable importance in medicinal chemistry due to their potential anticancer [24,25], antimicrobial [26], antioxidant, antitumor [27], anti-tuberculosis [28], anticonvulsant [29], fungicidal [30], antiepileptic [31] and anti-inflammatory [32] activities.

$$\begin{align*}
\text{R}' & \quad \text{N} \quad \text{S} \\
\text{N} & \quad \text{R} \\
\end{align*}$$

Figure 4. Thione-thiol tautomeric forms.

1,2,4-triazolethiones have been prepared successfully by various methods. The most common classical method is the dehydrative cyclization of different hydrazinecarbothioamides in presence of basic media using various reagents such as sodium hydroxide [2,25,33], potassium hydroxide [34,35], sodium bicarbonate [36] or acidic ionic liquid [37] followed by neutralization either with acid or base for both cases, in addition to different other techniques including donor–acceptor interactions. Various synthetic routes and biological applications of spiro-1,2,4-triazolethiones were also discussed as main heterocyclic targets easily obtained from different hydrazinecarbothioamides [38,39].

Schiff bases of triazolethiones [40] have played vital roles in organic synthesis and they are obtained from triazolethiones using simple procedures; also, sometimes their structures possess biological and pharmaceutical activities other than triazolethione itself such as anti-inflammatory and anti-oxidant [41], anticancer [42], fungicidal activities [43], antibacterial [44], antiparasitic [45], antidepressant and antimicrobial [46]. Furthermore, many transition metal complexes of 1,2,4-triazolethione Schiff bases and their bioactivities were reported [47–49] along with nickel complexes of triazolethiones [50] showing high catalytic activity towards the synthesis of tetrahydrobenzo[b]pyrans [47].

Various reactions of mercapto-triazolethiones [25] were discussed depending on S and N nucleophilic sites and in presence of different reagents and conditions to afford other heterocyclic compounds, e.g., triazolothiadiazines [51,52], imidazothiadiazoles [51,53], bistriazolethione-1,4-dihydropyridines [54] and fused triazolethione pyrimidines [55].

2. Synthesis of 1,2,4-Triazole-3-thiones

Hydrazinolysis of ethyl-substituted benzoates 7a–c yielded the carbonylhydrazides 8a–c. Nucleophilic addition of carbon disulfide (CS₂) to 8a–c in basic media [22] gave the hydrazide oxadiazole-2-thiones 9a–c. The reaction of oxadiazoles 9a–c with hydrazine hydrate in ethanol afforded 4-amino-5-aryl-1,2,4-triazole-3-thiones 10a–c (Scheme 1) [22].
Alkaline cyclization of different substituted acylthiocarbohydrazides 12a–f, obtained from the reactions of acylhydrazides 11a–f with various isothiocyanates, gave the corresponding 4-alkyl-5-substituted-1,2,4-triazole-3-thiones 13a–f in 70–86% yields (Scheme 2) [23]. Screening of the anticonvulsant activity of the obtained compounds revealed that they are used as useful anticonvulsant drug candidates whose mode of action depends on voltage-gated sodium channels inhibition (VGSC) (Scheme 2) [23].

A series of 1,2,4-triazole-3-thiones 19a–d were successfully prepared through stepwise reaction starting from esterification of N-(4-hydroxyphenyl)acetamide (14) with ethyl bromoacetate (15) to give ethyl 2-(4-acetamido-phenoxy)acetate (16) [24]. The acetohydrazide 17 was then obtained through hydrazinolysis of compound 16 with hydrazine hydrate. The corresponding thiosemicarbazides 18a–d were synthesized by the reaction of 17 with different isothiocyanates in dry ethanol. Finally, thiosemicarbazide derivatives 18a–d were efficiently cyclized in basic media to give the desired 1,2,4-triazole-3-thiones 19a–d in 52–88% yields [24] (Scheme 3).
Reactions of thiosemicarbazide (20) with arylidene malononitrile afforded 5-(4-chlorophenyl)-1,2,4-triazolidine-3-thione 22a via the intermediate 21, whereas the reaction of 4-substituted thiosemicarbazides 23a,b with 4-chlorobenzaldehyde gave the corresponding 5-(4-chlorophenyl)-4-substituted-1,2,4-triazolidine-3-thiones 24a,b in 89% and 91% yield, respectively (Scheme 4) [50].

Thiosemicarbazide (20) reacted with 3,4-dichlorobenzyl chloride to give 2-(3,4-dichlorobenzyl)hydrazinecarbothioamide (25) which reacted with formic acid to form 1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3-thiol (27) in 82% yield through the formation of intermediate 26 (Scheme 5) [51].
The synthesis of 5-substituted phenyl-1,2,4-triazole-3-thiones 30a–c was done in high yields from the refluxing of arylidene derivatives and trimethylsilyl isothiocyanate using sulfamic acid as a catalyst via the intermediates 28a–c and 29a–c (Scheme 6) [52].

Scheme 6. Synthesis of triazolethiones 30a–c.

Substituted aryl hydrazides 12b–f reacted with CS2 in alcoholic potassium hydroxides and yielded potassium hydrazinecarbodithioate salts 31b–f. Refluxing of 31a–e with a dilute solution of hydrazine hydrate afforded the expected 4-amino-5-substituted-1,2,4-triazole-3-thiones 32a–e (Scheme 7) [29].

Scheme 7. Synthesis of triazolethiones 32a–c.

The reaction of diethyl 1-substituted-1H-1,2,3-triazole-4,5-dicarboxylates 33a–d with hydrazine hydrate yielded diacid hydrazides 34a–d. Hydrazinecarbothioamides 35a–d were obtained via refluxing of 34a–d with phenyl isothiocyanate. Dehydrative ring closure of compounds 35a–d under basic condition furnished the formation of bis-1,2,4-triazole-3-thiones 36a–d in 80–85% yields. Besides, the reaction of diacid hydrazides 34a–d with CS2 in basic solution followed by refluxing with hydrazine hydrate gave bis-4-amino-1,2,4-triazole-3-thiones 37a–d in 80–85% yields (Scheme 8) [28]. The resulting compounds were screened for their antimicrobial activities based on standard antimicrobial agents; compound 37d exhibited comparable antibacterial and antifungal activities against all the tested organisms [28].
Mycobacterium tuberculosis were screened against (Scheme 10) [54]. Screening of the synthesized compounds showed that they have good antifungal activity rather than antibacterial activity [56]. Compound 40f showed the highest inhibition (87%), and therefore, it was suggested to be as potentially active antituberculosis agent [53].

Thiocarbohydrazide (38) was heated with 2-(thiophen-2-yl)acetic acid to get 4-amino-1,2,4-triazole-3-thione (39). The reaction of 39 with different aryl aldehydes yielded the corresponding Schiff bases 40a–f in 52–61% yields (Scheme 9) [53]. All the synthesized compounds were screened against *Mycobacterium tuberculosis* H37Rv, and they proved to be less active than rifampicin (98%), used as reference drug. Compound 40f showed the highest inhibition (87%), and therefore, it was suggested to be as potentially active antituberculosis agent [53].

Scheme 8. Synthesis of bis-4-amino-triazolethiones 35a–d, 36a–d and 37a–d.

4-Methyl benzoylisothiocyanate was reacted with phenylhydrazine hydrate afforded 1-phenyl-5-(p-tolyl)-1H-1,2,4-triazole-3(2H)-thione (41). Schiff bases of triazolethione 42a–j were obtained via reaction of triazolethione 41 with formaldehyde and various aromatic amines (Scheme 10) [54]. Screening of the synthesized compounds 42a–j against different microorganisms showed that they have good antifungal activity rather than antibacterial activity [56].
Diflunisal (2′,4′-difluoro-4-hydroxybiphenyl-3-carboxylic acid) (43) was converted to its corresponding diflunisal ester 44. The desired diflunisal hydrazide 45 was obtained using hydrazine hydrate. The reaction of hydrazide 45 with various aryl isothiocyanates afforded substituted hydrazinecarbothioamides 46a–f. Cyclization of compounds 46a–f to the corresponding triazole-3-thiones 47a–f occurred in basic media (Scheme 11) [57]. The screening of compounds 47a–f against cancer cells revealed that compound 47f was found to be active against the colon carcinoma HCT-116 cancer cell line with a 6.2 μM IC50 value. In addition, compounds 47e and 47f were found active against the human breast cancer T47D cancer cell line with IC50 values of 43.4 and 27.3 μM, respectively [57].

Pyridine-2,5-dicarboxyhydrazide (49) was synthesized from the reaction of dimethylpyridine-2,5-dicarboxylic acid (48) with hydrazine hydrate, which reacted with different alkyl/aryl isothiocyanates to afford 2,2′-(pyridine-2,5-dicarboxylic acid)bis-(N-substituted hydrazinecarbothioamides) 50a–e. Ring closure of these hydrazine-carbothioamides 50a–e occurred in basic media to give bis-1,2,4-triazole-3-thiones 51a–e in 85–95% yields (Scheme 12) [58]. Biological activities of the synthesized compounds 51a–e were evaluated, and they showed high antioxidant activity. Moreover, all of the synthesized compounds efficiently inhibited some metabolic enzymes such as AChE (acetylcholinesterase I and II) and could be used as excellent candidate drugs in the treatment of some diseases such as mountain sickness, glaucoma, gastric and duodenal ulcers, epilepsy, osteoporosis, and neurological disorders [58].
with ethyl chloroacetate. The reaction of 53a–d with hydrazine hydrate gave the corresponding acylhydrazides 54a–d. Intramolecular cyclization of 54a–d with CS₂ in alkaline media resulted in oxadiazole-2-(3H)thiones 55a–d. 1,2,4-Triazolo-3-thiones 56a–d were synthesized from the reaction of compounds 55a–d with hydrazine hydrate. In addition, triazolothiadiazines 57a–d were synthesized from the reaction of 56a–d with phenacyl bromide [50]. The screening of compounds 55a–d and 57a–d revealed that they possess a higher antibacterial activity than antifungal activity; also, the halo-substituted compounds showed an increased growth inhibition activity higher than that of the reference drugs such as fluconazole and chloramphenicol (Scheme 13) [50].

Chlorosulfonation of ethyl 2-(3,4-dimethoxyphenyl)acetate (58) gave ethyl 2-(2-chlorosulfonyl)-4,5-dimethoxyphenyl)acetate (59) (Scheme 14). Sulfonamides 60a–e were readily obtained via reaction of 59 with secondary amines. The desired acid hydrazides 61a–e, which were obtained by reaction of 60a–e with hydrazine hydrate, were condensed with various isothiocyanates to

Scheme 12. Synthesis of bis-triazolethiones 51a–e.

Scheme 13. Synthesis of triazolethiones 57a–d.
yield the corresponding hydrazinecarbothioamides 62a–e. Further, 1,2,4-Triazole-3-thiones 63a–e were synthesized in 44–75% yields from the cyclization 62a–e in basic media (Scheme 14) [47]. Screening of compounds 63a–e for in vitro antifungal and antibacterial activity revealed that they have the best antifungal activity compared with the reference bifonazole in addition to the same bactericidal activity as streptomycin, except for Enterobacter cloacae and Salmonella species [47].

![Diagram](attachment:image.png)

Scheme 14. Synthesis of 1,2,4-triazole-3-thiones 63a–e.

Refluxing of thiocarbohydrazide (38) with acetic acid or trifluoroacetic acid gave 4-amino-5-substituted-4H-1,2,4-triazole-3-thiones 11d,e (Scheme 15) [42].

![Diagram](attachment:image.png)

Scheme 15. Synthesis of 4-N-amino-triazolethiones 11d,e.

Various thiosemicarbazide derivatives 65a–c were then synthesized from the reaction of acid hydrazides 64a–c with 3-fluorophenyl isothiocyanates. Further, 1,2,4-triazole-3-thiones 66a–c were obtained from alkaline cyclization of compounds 65a–c with 8% NaOH solution (Scheme 16) [40].
which on reacting with various aldehydes gave the Schiff bases (Scheme 18). The reaction produced, as a minor product, compound (Scheme 17) [30]. The synthesized compounds were screened for their cytotoxic activity against the cell line compared with cisplatin [59].

Treatment of oxadiazole thione 10a with hydrazine hydrate gave 4-amino-triazolethione (11a) which on reacting with various aldehydes gave the Schiff bases of triazolethiones 67a–d. The synthesis of 1,3,4-trisubstituted triazolethiones 69a–d was carried out from the reaction of triazolethiones 67a–d with (2-(acetoxymethyl)-6-bromotetrahydro-2H-pyran-3,4,5-triyl triacetate (68) in good yields (Scheme 17) [30]. The synthesized compounds were screened for their cytotoxic activity against human malignant cell lines (MCF-7 and Bel-7402). Interestingly, 69c showed more potent cytotoxic activity against MCF-7 cells compared with compound 67c. Compound 69b also was more active than compound 67b against MCF-7 and Bel-7402 cells [30].

A series of Pd complexes containing 1,2,4-triazole-3-thiones 71a–d [59] were synthesized from the reaction of different thiosemicarbazones 70a–d with diphenylphosphinopropane and K₂[PdCl₄] (Scheme 18). The reaction produced, as a minor product, compound 72 (Scheme 18) [59]. The in vitro cytotoxicity of 71a–d was evaluated against the MCF-7 cell line, with cisplatin as a reference. The complexes 71b and 71c showed significant cytotoxicity against the MCF-7 (human breast cancer) cell line compared with cisplatin [59].
Refluxing of 5-benzofuran-2-yl-1-phenyl-1H-pyrazole-3-carbohydrazides 73a–h with different aromatic isothiocyanates afforded the desired hydrazinecarbothioamides 74a–h. Ring closure of these compounds 74a–h occurred through refluxing with aqueous sodium hydroxide to give the target 1,2,4-triazole-3-thiones 75a–h in 78–88% yields. On the other side, when 2-bromoacetophenone was reacted with 75a–h, the reaction gave the corresponding benzothioates 76a–h in 74–86% yields (Scheme 19) [36]. Biological activity of compounds 74a–h and 76a–h showed that benzothioate 76a has a good antibacterial activity against all pathogenic bacteria compared with the standard chloramphenicol [36].

It was reported that the Eschenmoser coupling reaction was used as an efficient method to get 82–88% of diazenyl-1,2,4-triazole-5-thiones 79a–e via nucleophilic attack of disubstituted hydrazinecarbothioamides 77a–e on 2,3,5,6-tetrachloro-1,4-benzoquinone (78, p-CHL) which acted as a mediator [33] (Scheme 20).
The suggested mechanism based on initial CT-complexation formation of 80a–e, which losses chlorine molecule accompanies with the addition of another molecule of 77 would give the intermediate 81 (Scheme 21). Elimination of an arylamine equivalent from 81 would give the intermediate 82, which undergoes rearrangement to give 83. The addition of a Ph₃P molecule to 83 would give 84. The action of Ph₃P and Et₃N is to initiate the formation of triazolethione 85 via elimination of Ph₃P=S and triethylammonium. Dehydrogenation of 85 by a second molecule of 78 would give the expected final product 79 together with dichlorodihydroxybenzene (86) [33] (Scheme 21).

4-Amino-3-(4-methoxybenzyl)-1H-1,2,4-triazole-5(4H)-thione (88) was synthesized in 75% yield by refluxing of potassium 2-(2-(4-methoxyphenyl)acetyl)-hydrazinecarbodithioate (87) with hydrazine hydrate. Condensation of triazolethione 88 with different substituted aldehydes gave Schiff base derivatives 89a–c in 85–86% yields (Scheme 22) [43]. Screening of different Schiff bases 89a–c for anti-inflammatory and antioxidant activities showed that 89a and 89c were used as potent anti-inflammatory drugs. In addition, compound 89a was the most active antioxidant drug showing an IC₅₀ value of 7.2 ± 2.7 μg/mL compared with that of the reference ascorbic acid (2.61 ± 0.29 g/mL) [43].
multicomponent reaction of 96a amine)-3-(1-(4-isobutylphenyl)ethyl)-4 with hydrazine hydrate (Scheme 24) [60].

In addition, it is used as a building block for heterocyclization and synthesis of the desired (S)-3-(1-benzylpyrrolidin-2-yl)-4-butyl-1H-1,2,4-triazole-5-thiones (92a) in 56% yield (Scheme 23) [36].

Moreover, 4-amino-triazole-5-thiol (94) was obtained from two routes, i.e., from the fusion of substituted propanoic acid (93) with 38 or cyclization of potassium hydrazinecarbodithioate derivative (95) with hydrazine hydrate (Scheme 24) [60].

The reaction of triazolethione (94) with different aldehydes in acidic media afforded (E)-4-(substituted amino)-3-(1-(4-isobutylphenyl)ethyl)-4H-1,2,4-triazole-5-thiones (96a-f) in 44–85% yields [61]. One-pot multicomponent reaction of (96a-f), formaldehyde and secondary amines afforded 2,4,5-trisubstituted
triazolethiones 97a–f. Screening of the anti-inflammatory activity of the synthesized compounds revealed that Mannich bases (97b and 97e) exhibited the highest anti-inflammatory activity. Besides, the most potent anti-inflammatory molecules 97b, d–f were further examined for their analgesic activity in mice showing better analgesic activity compared to diclofenac [61].

Thiocarbohyrazide (38) was used efficiently as precursor of 4-amino-3-(1,2,3,4,5,6-hexahydroxyhexyl)-1H-1,2,4-triazole-5(4H)-thione (99) through refluxing with D-glucosporiic acid-1,4-lactone (98) [62]. Besides, the triazole-thione 99 was reacted with different substituted benzaldehydes to afford (E)-4-amino-3-(1,2,3,4,5,6-hexahydroxyhexyl)-1H-1,2,4-triazole-5(4H)-thiones 100a–f in good to moderate yields (50–70%). Introducing a glycosyl unit into triazolethiones Schiff bases 100a–f led to good water-solubility of these compounds and also improved their biological activities (Scheme 25) [62].

Scheme 25. Synthesis of triazolethiones 100a–f.

4-(Hydrazinylcarbonyl)-5-methyl-4,5-dihydro-1H-imidazole-3-oxides 101a–i reacted with different isothiocyanates (phenyl, t-butyl, and methyl) to give the corresponding hydrazinecarbothioamides 102a–i. Triazole-5-thiones 103a–i were obtained in 50–82% yields from the cyclization of substituted imidazole (carbonyl)hydrazinecarbothioamides 102a–i in basic media (Scheme 26) [63].

Scheme 26. Synthesis of imidazolyl-N-oxide-triazolethiones 103a–i.
The reaction of different carboxylic acids with thiocarbohydrazide 38 gave aminotriazolethiones 11d,f-j in 51–57% yields. In a different manner, the reaction of 38 with ethyl esters of γ-keto acids did not give the expected triazolethiones 104a,b but it gave 6-substituted phenyl-7,8-dihydro-[1,2,4]triazolo[4,3-b]pyridazine-3(2H)-thiones 105a,b in 35% and 39% yields. The reaction occurred via ring closure of triazole and intramolecular imine condensation of 104a,b (Scheme 27) [64]. The prepared compounds were tested for their inhibitory activities against Mycobacterium bovis BCG; compound 11d proved to be the most potent one against it, with MIC value of 31.25 µg/mL [64].

![Scheme 27. Synthesis of pyridazino-triazolethiones 105a,b.](image)

11: R = d = Methyl; f = H; g = Ethyl; h = (3-indolyl)methyl; i = hydroxy (phenyl)methyl,
          j = (2-thiophenyl)methanol

104, 105: R = a, H; b = 4-Cl

Reagents and conditions: A = heating at 150-160°C; B = NaOEt / MeOH

Scheme 27. Synthesis of pyridazino-triazolethiones 105a,b.

Natural products are used as staring materials for the synthesis of different mercapto triazoles. Hydrolysis by aqueous KOH of ((2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one) (106) gave 5-(benzo[d][1,3]dioxol-5-yl)penta-2,4-dienoic acid (107). (5-(Benzo[d][1,3]dioxol-5-yl)penta-2,4-dienehydrazide (108) was obtained after reacting the acid (107) with oxalyl chloride followed by hydrazine hydrate. Compounds 109a–n were prepared from reaction of the acid hydrazide 108 using different isothiocyanates. Basic hydrolysis of 109a–n efficiently gave the desired 3-(((E,3E)-4-(benzo[d][1,3]dioxol-5-yl)buta-1,3-dien-1-yl)-4-substituted-1H-1,2,4-triazole-5(4H)-thiones 110a–n in 32–51% yields (Scheme 28) [18]. The best trypanocidal activity was noted in case of 110g on proliferative forms of Trypanosoma cruzi [18].

![Scheme 28. Synthesis of triazolethiones 110a–n.](image)

105, 110: R = a, Methyl; b, Ethyl; c, Isopropyl; d, n-Butyl; e, n-Hexyl; g, C Cyclohexyl,
          h, Phenyl; i, Benzyl; j, 3,4,5-Trime-thexylenyl; k, tert-Butyl,
          l, 4-Methylthiophenyl; m, 3-Methoxyphenyl; n, 4-(Trifluoromethyl) phenyl

Reagents and conditions: A = KOH / EIOH / NaNH2; B = (COO)2, NaOH / H2O
          C = R-NCS / EIOH; D = (2N NaOH), HCl

Scheme 28. Synthesis of triazolethiones 110a–n.
Reaction of 2-(coumarin-4-yl)acetic acid with thiocarbohydrazide (38) in refluxing phosphoryl chloride yielded the target 4-((4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazole-3-yl)methyl)-2H-chromen-2-one (111) in 80% yield. Condensation of 111 with various aromatic aldehydes yielded (E)-4-((benzylideneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazole-3-yl)methyl)-2H-chromen-2-ones 112a–c (Scheme 29) [37]. The synthesized compounds were evaluated in vitro as anticancer agents in the human colon cancer (HCT 116) cell line. Compound 112c showed high anticancer activity (relative potency >50%) with IC₅₀ value of 4.363 μM compared to the potent anticancer drug doxorubicin, whereas compound 112a displayed moderate anticancer activity with IC₅₀ values 18.76 μM. The molecular docking studies of the active compounds revealed that these compounds might act via inhibition of tyrosine kinases (CDK2) [37].

\[ \text{H}_2\text{N} \quad \text{S} \quad \text{NH}_2 \quad \text{O} \quad \text{OH} \quad \text{A} \quad 111 \quad \text{B} \quad 112\text{a-c} \]

**Reagents and conditions:**
- **A:** POCl₃, Δ, 3h
- **B:** Ar-CHO / CH₃CH₂CH₂OH, AcOH

**Scheme 29.** Synthesis of chromen-2-ones derived by triazolethiones 112a–c.

Compound 2-(ethylthio)benzohydrazide (114) was obtained by refluxing ethyl 2-(ethylthio)benzoate (113) with hydrazine hydrate. Then, subjecting 114 with various aryl isothiocyanates yielded the thiosemicarbazides 115a–e. Compounds 115a–e were then cyclized to N-substituted triazolethiones 116a–e in 69–75% yields (Scheme 30) [65]. Compounds 115a,b and 116a, were effectively used as antioxidant agents with IC₅₀ values of 1.08, 0.74, and 0.22 μg/mL, respectively, compared to gallic acid (IC₅₀ = 1.2 μg/mL) [65].

\[ \text{113} \quad \text{A} \quad 114 \quad \text{B} \quad 115\text{a-e} \]

**Reagents and conditions:**
- **A:** N₂H₄ – H₂O / EtOH, Δ, 24h
- **B:** R-NCS, EtOH, Δ, 1-4h
- **C:** (4N NaOH), Δ, 3h

**Scheme 30.** Synthesis of triazolethiones 116a–e.

Phosphorylated triazolethione 119 was formed in 90% yield from the cyclization process of N-allyl-2-(2-(diphenylphosphoryl)acetyl)hydrazinecarbothioamide 118 (obtained from 2-(diphenylphosphoryl)acetohydrazide (117) with allyl isothiocyanate) in basic media (5%) NaOH [42]. Moreover, ethyl 2-((4-allyl-5-(diphenylphosphoryl)-methyl)-4H-1,2,4-triazole-3-ylthio)acetate (120) was synthesized in 68% yield by reacting 119 with ethyl bromoacetate. Hydrazinolysis of compound
120 gave 2-((4-allyl-5-((diphenylphosphoryl)methyl)-4H,1,2,4-triazole-3-yl)thio)acetohydrazide (121) in 43% yield (Scheme 31) [42].

Incorporating of triazolethiones into thiazole ring was the optimum pharmacophore model for anticonvulsant activities, thus condensation of ethyl thiazol-2-ylcarbamates 122a–d with 4-substituted thiosemicarbazides 123a–f afforded the corresponding hydrazinecarbothioamides 124a–d. Cyclization of the latter with aqueous sodium hydroxide gave 4-substituted phenyl-3-((4-aryl-4,5-dihydrothiazol-2-yl)amino)-1H-1,2,4-triazole-5(4H)-thiones 124a–d in 62–84% yields [66] (Scheme 32). The obtained compounds were screened for their anticonvulsant activity and showed that compounds 124d and 124e had a significant anticonvulsant activity compared with the standard drugs [66].

The condensation of (E)-1-(phenoxythiin-2-yl)-3-phenylprop-2-en-1-one (125) with malononitrile afforded 2-amino-6-((phenoxythiin-2-yl)-4-phenylnicotinonitrile (126). In addition, compound 126 reacted with triethyl orthoformate in acetic anhydride to give formimide 127, which upon hydrazinolysis with phenyl hydrazine yielded 4-imino-7-(phenoxythiin-2-yl)-5-phenylpyrido[2-
d]pyrimidin-3(4H)-amine (128). The reaction of the latter with CS₂ gave 16-phenyl-[1,2,4]triazolo-pyrimido[4-b]benzo[5,6][1,4]oxathiino[3,2-g]quinoline-2(3H)-thiones 129 (Scheme 33) [50].

![Scheme 33. Synthesis of [1,2,4]triazolo-pyrimido[4-b]benzo[5,6][1,4]oxathiino[3,2-g]quinoline-2(3H)-thiones 129.](image)

2-(Adamantanyl-1-carbonyl)-N-phenylhydrazincarbothioamide (130) was synthesized from the reaction of adamantane-1-carbohydrazide (9d) with phenyl isothiocyanate. Thereafter, 3-(adamantan-1-yl)-4-phenyl-1H,1,2,4-triazole-5(4H)-thione 131a was synthesized via basic hydrolysis of 130a with NaOH. Then, 3-(adamantan-1-yl)-1-((piperidin-4-yl)methyl)-4-phenyl-1H,1,2,4-triazole-5(4H)-thiones 132a-f were obtained from the reaction of compound 131a with 1-substituted piperazine and formaldehyde solution [34] (Scheme 34). The synthesized N-Mannich bases of triazolethiones 132b-f screened against Gram-positive and -negative bacteria in addition to some pathogenic fungus (Candida albicans) revealed that they had potent antibacterial activity [34].

![Scheme 34. Synthesis of 1,2,4-triazole-5(4H)-thiones 132a-f.](image)

Hydrolysis of disubstituted hydrazincarbothioamides 130b-d with aqueous sodium hydroxide gave 1,2,4-triazole-5-thiones 92b-d. Mannich reaction of 1,2,4-triazole-5-thiones 92b-d,
1-[(1R,2S)-2-fluorocyclopropyl]CPFX (133) and formaldehyde afforded 1-[(1R,2S)-2-fluorocyclopropyl]CPFX-1,2,4-triazole-5-thiones 134a–c in 52–57% yields (Scheme 35) [67].

\[
\begin{array}{c}
\text{\[1\text{H}-\text{thieno}[2,3-c]\text{pyrazole-5-carbonitrile (137) with triethyl orthoformate in the presence of acetic anhydride as catalyst gave (Z)-ethyl N-(5-cyano-3-methyl-1-phenyl-1H-thio}[2,3-c]\text{pyrazol-4-yl)formimidate (138). Hydrazinolysis of 138 with hydrazine hydrate yielded 7-imino-3-methyl-1-phenyl-1H-pyrazolo[3,2-d]pyrimidin-6(7H)-amine (139), whereas cyclization of pyrazolothienopyrimidines 139 with CS}_2\text{ afforded 7-methyl-9-phenyl-3,9-dihydro-2H-pyrazolo}[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine-2-thione (140) in 35\% yield (Scheme 37) [54].}
\end{array}
\]
The cyclization reaction of longer alkenyl/hydroxyl alkenyl acid hydrazides 9h–k CS₂/KOH followed by treatment with hydrazine hydrate yielded the corresponding 4-amino-3-substituted-1H-1,2,4-triazole-5(4H)-thiones 11k–n. 1,2,4-Triazolothiadiazines 141a–d were directly obtained from the reaction of amino triazolethiones 149a–e with phenacyl bromide in 62–90% yields (Scheme 38). In vitro screening of anticancer activity against three different cell lines, i.e., human hepatocellular carcinoma (Hep3B), human breast adenocarcinoma (MCF7), and human cervical carcinoma (HeLa), towards triazolethione and triazolothiadiazines showed that the nature of the long-chain on third position affected the potency of these drugs. Besides, fused triazolothiadiazines 141a–d were found to be potential anticancer agents [68].

Similarly, the reaction of acid hydrazides 142a–i with isothiocyanates afforded the acylhydrazides 143a–i (Scheme 39). The triazolethiones 144a–i were then obtained in 62–90% yields from the reaction of thiosemicarbazides 144a–i in NaHCO₃ in ethanol (Scheme 39) [69]. The 1,2,4-triazolethione 144g was found to be the best anti-inflammatory nucleus via inhibiting both COX-2 (IC₅₀ = 2.1 μM) and 5-LOX (IC₅₀ = 2.6 μM) enzymes, and this was supported via enzyme-ligand molecular modeling (docking studies), which gave favorable binding interactions in both COX-2 and 5-LOX active sites. It also has a superior gastrointestinal safety profile (ulcer index = 0.25) compared to the reference drug [69].
Scheme 40. Synthesis of triazolethiones 149a–e. Reaction of 2-((3,5,6-trichloropyridin-2-yl)oxy)acetic acid (150) with ... that 157c exhibited better antibacterial and antifungal activities than the other compounds (Scheme 41) [71].

Interestingly, esterification of 1H-benzimidazoles 145a–e with ethyl chloroacetate gave ethyl 2-(2-phenyl-1H-benzo[d]imidazol-1-yl)acetates 146a–e, which upon reacting with hydrazine hydrate gave the acid hydrazide 147a–e. Also, N-methyl-2-(2-(2-phenyl-1H-benzo[d]imidazol-1-yl)acetyl)hydrazinecarbothioamides 148a–e were formed by the reaction 147a–e with methyl isothiocyanate. Ring closure of hydrazine-carbothioamides 148a–e with aqueous NaOH afforded the biologically active triazolethiones 149a–e in 51–64% yields, with significant antioxidant properties (Scheme 40) [70].

Reaction of 2-((3,5,6-trichloropyridin-2-yl)oxy)acetic acid (150) with thionyl chloride gave 3,5,6-trichloropyridin-2-yl)hydrazine-carboxylate (152). When the acid hydrazide 152 was then subjected to aqueous potassium thiocyanate, 2-((3,5,6-trichloropyridin-2-yl)oxy)acetyl)hydrazine-carbothioamide (153) was obtained. Cyclization of 153 in basic media afforded 1H-1,2,4-triazole-5(4H)-thione 154) [71]. On the other side, various S-alkylated products 155a–e were obtained via reacting substituted benzyl chlorides with triazolethiones 154. However, the reaction of morpholine, formaldehyde, and compound 155a–e gave the N-alkylated morpholino-triazolethiones 156a–e, which
on oxidation with H$_2$O$_2$ in acidic media gave 3,4,5-trisubstituted-1,2,4- triazoles $157a$–$e$ in 54–69% yields [71]. The synthesized compounds $157a$–$e$ screened for their antimicrobial activity revealed that $157c$ exhibited better antibacterial and antifungal activities than the other compounds (Scheme 41) [71].

![Scheme 41. Synthesis of 3,4,5-trisubstituted-1,2,4-triazoles $157a$–$e$.](image)

On refluxing of 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde (158) with thiourea (20), the reaction proceeded to give the corresponding 3-(1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)-1H-1,2,4-triazole-5(4H)-thione (159) (Scheme 42). The bioassay of triazolethione 159 showed that it has significant anti-inflammatory activity [72].

![Scheme 42. Synthesis of triazolethione 159.](image)

Fusion of thiocarbohydrazide (38) with 2-(1,3-dioxoisoindolin-2-yl)acetic acid (160) gave the 2-((4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazole-3-yl)methyl)-isoindoline-1,3-dione (161) in 69% yield. The synthesis of triazolethione Schiff bases $162a$–$i$ was achieved, in 35–66% yield, by refluxing of 161 with different aromatic aldehydes. Besides, Mannich bases $163a$–$h$ were easily obtained from the reaction of Schiff bases $162a$–$i$ with formaldehyde and morpholine in 39–82% yields (Scheme 43) [73]. The antimicrobial bioassay of these compounds $163a$–$h$ showed that antimicrobial activity was increased by introducing azomethine group and also by the addition of morpholine group leading to prospective antimicrobial agents with $163a$–$b$, $163e$–$f$, and $163h$ [73].
Synthesis of Spiro-1,2,4-triazolethiones

Spiro-triazolethiones 165a–c were also obtained from donor–acceptor interactions in such as in case of reacting hydrazinecarbothioamides 23a,g–h with trinitrofluorenone (DTF) 164 in addition to 1,4-disubstituted hydrazine-carbothioamides 166a–c in 23–25% yields, respectively (Scheme 44) [74].

It was reported that thiosemicarbazide (20) reacted with dihydropyridazin-1(4H)-yl)acetate to get ethyl 2-(substituted phenyl)-3-thioxo-1,2,4,6,7-pentaazaspiroacetate (168) [75] (Scheme 45).

Patil et al. [32] reported the synthesis of a series of spiro-1,2,4-triazole-3-thiones 169a–g varied from good to excellent yields (55–95%) from thiosemicarbazide (20) and different cyclic ketones using different catalysts, the most effective catalyst was 1,1’-sulfinyldipyridinium bis(hydrogen sulfate) ionic liquid which gave high yield and short reaction time in alcohol at room temperature (Scheme 46).
The synthesis of 1-acetyl-5′-thioxospiro[indoline-3,3′-[1,2,4]triazolidin]-2-one (170), in 87% yield, was achieved by the reaction of 1-acetylindoline-2,3-dione with thiosemicarbazide 20 catalyzed by acidic ionic liquid (Scheme 47). Compound 170 showed good antibacterial activity [30].

Reactions of thiosemicarbazides 171a–j with various π-acceptors such as benzo- or naphthoquinones 78a,b led to different fused heterocyclic rings [76]. However, spiro-1,2,4-triazole-3-thiones 174a–j were obtained from the reaction of cycloalkanone-thiosemicarbazides 171a–j with benzo- or naphthoquinones 78a,b in 80–85% yields (Scheme 48) [76].

Scheme 46. A series of spiro-1,2,4-triazole-3-thiones 169a–g.

Scheme 47. Synthesis of 1-acetyl-5′-thioxospiro[indoline-3,3′-[1,2,4]triazolidin]-2-one (170).

Scheme 48. Synthesis of spiro-1,2,4-triazole-3-thiones 174a–j.
Substituted thiosemicarbazone 176 was cyclized to the corresponding spirotriazolethione 179 in 70–82% yields through the intermediates 177 and 178 (Scheme 49) [77].

Scheme 49. Synthesis of spirotriazolethione 179.

(1R,2R,4R,5S)-2,4-Disubstituted phenyl-3-azabicyclo[3.3.1]nonan-9-one hydro-chlorides 180a–g reacted with ammonia to give (1R,2R,4R,5S)-2,4-disubstituted phenyl-3-azabicyclo[3.3.1]nonan-9-ones 181a–g (Scheme 50) [31]. Condensation of compounds 181a–g with thiosemicarbazide 20 afforded compounds 182a–g, which upon cyclization in the presence of m-chlorobenzaldehyde efficiently gave spiro-1,2,4-triazoline-3′-thiones 183a–g in 50–70% yields (Scheme 50). Screening of these spiro-triazolethiones 183a–g for antibacterial and antifungal activities showed that compounds 183b–e had excellent antifungal activity against all the tested microorganisms. However, compounds 183d,e showed excellent antibacterial activity against β-H. streptococcus. Besides, compounds 183d,e showed varied activities toward the tested Gram-positive and -negative strains [31].

Scheme 50. Synthesis of spiro-triazolethiones 183a–g.

5-Substituted-5′-thioxospiro[indoline-3,3′-[1,2,4]triazolidin]-2-ones 185a–d (83–89% yields) successfully were obtained from the reaction of different 5-substituted indoline-2,3-diones 184a–d with 20 in water and catalyzed by using glycine nitrate. In the same manner, bis-spirotriazolethione 187 was synthesized from the reaction of 1,1′-(propane-1,3-diyl)bis(5-bromoindoline-2,3-dione) 186 with 20 in 89% yield (Scheme 51) [78].
Condensation of gonanone derivatives 188a–c with 20 in acidic media gave the corresponding thiosemicarbazones 189a–c. Oxidative cyclization of thiosemicarbazones 189a–c with hydrogen peroxide yielded the corresponding (5S)-10,13-dimethyl-17-octylhexadecahydrospiro-[cyclopenta[a]phenanthrene-6,3′-1,2,4triazolidine]-5′-thiones 190a–c in 66–78% yields (Scheme 52) [79].

Microwave irradiation was used as an efficient method to get good yields with a shorter time than the classical method for the synthesis of 6,6-dimethyl-phenyl-1,2,4,8-tetrazaspiro[4.5]decane-3-thiones 193a–e via formation of thiosemicarbazone intermediates 192a–e, which was obtained from the reaction of 3,3-dimethyl-phenylpiperidin-4-ones 191a–e with 20 (Scheme 53) [80].
Similarly, the reaction of 3-alkyl-2,6-diphenylpyran-4-ones 194a–f with 20 or 4-phenyl hydrazinecarbothioamides 23 gave thiosemicarbazones 195a–f. Oxidative cyclization of 195a–f with hydrogen peroxide led to the expected 7,9-diphenyl-8-oxa-1,2,4-triazaspiro[4.5]decane-3-thiones 196a–f. The synthesized compounds were tested for antimicrobial activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi, Aspergillus flavus, Aspergillus niger, Candida albicans, and Rhizopus sp. Compounds 196e and 196f showed potent antibacterial activity against E. coli and S. typhi. However, compounds 196d and 196f were potent against Rhizopus sp., whereas compound 196e gave significant antifungal activity against Aspergillus flavus (Scheme 54) [81].

Aly et al. [82] reported that reaction of equal equivalents of both N-substituted hydrazinecarbothioamides 23a,i with 2-(bis(methylthio)methylene)malononitrile (197) in dry ethanol catalyzed by few drops of Et$_3$N for 3 h afforded a colorless precipitate of 5-amino-4-cyano-3-(methylthio)-N-phenyl-1H-pyrazole-1-carbothioamide (198) as the major product in 65% yield together with 3,4-disubstituted amino-1H-1,2,4-triazole-5(4H)-thiones 199a,b and pyrazole carbonitrile 200 as minor products (Scheme 55) [82].
3. Reactions of 1,2,4-Triazolethiones

3.1. Synthesis of Open-Chain Compounds

The synthesis of mono and bipolar surfactants 201a–d and 202a–d was achieved by the reaction of 3-methyl-1H-1,2,4-triazole-5(4H)-thione (30c) and 3-phenyl-1H-1,2,4-triazole-5(4H)-thione (30d) with various alkyl bromides. However, in the case of n-dodecyl bromide, a mixture of two isomers 203 and 204 was obtained from the reaction of 201a–d and 202a–d with another molecule of alkyl bromide. In addition, bis-1,2,4-triazoles 205a,b were obtained from the reaction of linear dibromoalkanes with 3-methyl-1H-1,2,4-triazole-5(4H)-thione (30c) (Scheme 56) [83].

![Scheme 56. Synthesis of bis-1,2,4-triazoles 205a,b.](image)

Actylation of 3-substituted aminotriazolethione 206 by acetic anhydride afforded 4-substituted-1,2,4-triazole-5-thione 207 in 52% yield (Scheme 57). Additionally, ethyl 2-((4-amino-5-((6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyridin-3-yl)methyl)-4H-1,2,4-triazole-3-yl)thio)acetate (208) can be obtained in 50% yield upon reacting ethyl 2-bromoacetate with compound 206 (Scheme 57) [84].

![Scheme 57. Synthesis of 1,2,4-triazole-3-yl)thio)acetate (208).](image)
Reaction of various 1,2,4-triazolethiones 19a–g with alkyl or aryl isothiocyanates gave 1-substituted-3-(4-((4-substituted-5-thioxo-4,5-dihydro-1H-1,2,4-triazole-3-yl)-methoxy)phenyl)thioureas 209a–g (Scheme 58). All the synthesized compounds 209a–g evaluated against antiviral, anti-HIV, and anti-tuberculosis activity showed that compound 209g was the most active one with 79% inhibition against Mycobacterium tuberculosis H37Rv and also gave moderate protection against Coxsackievirus B4 with an MIC value of 16 mg/mL and a selectivity index of 5 [21].

Condensation of 4-amino-5-(pyridin-3-yl)-1,2,4-triazolidine-3-thione (11o) with 4-chlorobenzaldehyde yielded 4-chlorobenzylideneamino-5-(pyridin-3-yl)-1,2,4-triazolidine-3-thione (210). (E)-4-Chloro-benzylideneamino-5-(methylthio)-3-(pyridin-3-yl)-1,2,4-triazole 211 was synthesized form the reaction of 210 with methyl iodide. Finally, the trisubstituted 1,2,4-triazole 215 was synthesized in presence of iodide anion through the intermediates 212–214 (Scheme 59) [87].

The reaction of propargyl bromide with 5-(substituted phenyl)-1,2,4-triazolidine-3-thiones 21a,c–j yielded 3-substituted-5-(prop-2-yn-1-ylthio)-4,5-dihydro-1H-1,2,4-triazoles 216a–i in 62–77% yields. Besides, the reaction of compounds 216a–i with iodine afforded (E)-5-((2,3-diiodoallyl)thio)-3-(substituted phenyl)-1,2,4-triazoles 217a–i in 75–92% yields and traces of thiazolotriazoles 218a–i in 44–59% yields (Scheme 60) [88].
The synthesis of S- and N-alkylated products of triazolethiones 219 and 220 was achieved by the reaction of 1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3-thiol (27) with 1-bromooctane in basic media using tetrabutylammonium bromide (TBAB) as a catalyst in acetone for several minutes. Besides, 3-((2-bromoethyl)thio)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole (221) and 2-(2-bromoethyl)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (222) were prepared from the reaction of 27 with 1,2-dibromoethane as mentioned before. On the other hand, reacting 222 with 1,2,4-triazole afforded 2-(2-(1H-1,2,4-triazol-1-yl)ethyl)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (223), whereas reaction of 1,2,4-triazole with 221 gave 3-((2-(1H-1,2,4-triazol-1-yl)ethyl)thio)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole (224) [87]. The screening of antibacterial and antifungal activities showed that introducing a triazolium moiety in 223 and 224 would improve antibacterial and antifungal activities [87] (Scheme 61).
Reaction of 4-phenyl-5-(pyridin-3-yl)-1,2,4-triazole-3-thiol (92b) with ethyl bromoacetate gave 1,2,4-triazolthioacetate 225 which on reacting with hydrazine hydrate afforded the desired acetohydrazide 226. Moreover, the synthesis of various N-substituted-2-(2-((4-phenyl-5-(pyridin-3-yl)-4H-1,2,4-triazole-3-yl)thio)acetyl)hydrazinecarbothioamides 227a-f was achieved by reacting 226 with isothiocyanates (Scheme 62) [88].

![Scheme 62. Synthesis of 1,2,4-triazole-3-yl(thio)acetyl)hydrazinecarbothioamides 227a-f.](image)

Subjecting 4-substituted 3-((diphenylphosphoryl)methyl)-1H-1,2,4-triazole-5(4H)-thiones 119a,b with ethyl acrylate gave ethyl 3-((diphenylphosphoryl)methyl)-4-substituted-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanoates 228a-c [89] (Scheme 63).

![Scheme 63. Synthesis of triazolethiones 228a-c.](image)

The Schiff bases of 4-amino-3-((phenoxy)methyl)-1H-1,2,4-triazole-5(4H)-thiones 230a-e were synthesized upon reacting 4-aminotriazolethiones 229a-e with different aldehydes. Additionally, reaction of 230a-e with chloroacetic acid and catalyzation by pyridine gave 2-((4-(substituted benzylideneamino)phenoxy)methyl-4H-1,2,4-triazole-3-yl)thio)acetic acid derivatives 231a-e in 66–70% yields. The former compounds were screened for antimicrobial activities showing that compounds 231b and 231d have good antifungal activities against Aspergillus niger, Cryptococcus neoformans, and Aspergillus fumigatus at MIC of 0.25 μg/mL compared to the standard drug fluconazole with MIC of 1 μg/mL (Scheme 64) [90].
The reaction of 11o with compound 68 afforded disubstituted aminotriazolethiones 232 in 57% and 233 in 40%. Deamination of compounds 232 and 233 was achieved using nitrous acid in acidic media to afford 234 and 235 in 75% and 85% yield, respectively. In addition, deacetylation of 234 and 235 with methanolic ammonia gave the free nucleosides 236 and 237 in 70% and 88% yield, respectively [91]. Screening of antibacterial and antifungal activities of these compounds revealed that S-alkylated derivatives 232, 234, and 236 have a higher inhibitory effect against Aspergillus fumigatus, Syncephalastrum racemosum, and Staphylococcus aureus as well as a lower inhibitory effect against Penicillium italicum and Bacillus subtilis compared to N-alkylated derivatives 233, 235, and 237 (Scheme 65) [91].

Reagents and conditions: A = R'-CHO, B = CH₂CO₂H

Scheme 65. Synthesis of nucleosides 236 and 237.
Refluxing of 3-(adamantan-1-yl)-4-methyl-triazolethione 131b with 2-aminochloride derivatives afforded S-(2-aminomethyl) and N-(2-aminomethyl) derivatives 238 and 132g in 3:1 ratio, respectively [92]. Besides, 3-(adamantyl)-5-((2-methoxyethyl)thio)-4-phenyl-1,2,4-triazole 239 was obtained from the reaction of 1-bromo-2-methoxyethanone with 3-(adamantan-1-yl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione 131a. However, in the case of ethyl bromo acetate, two products were formed, ethyl 2-((5-(adamantan-1-yl)-4-phenyl-1,2,4-triazole-3-yl)thio)acetate 240 that converted to 2-((5-(adamantan-1-yl)-4-phenyl-1H-1,2,4-triazole-3-yl)thio)acetic acid 241. Moreover, reaction of aryl methyl halides with 3-(adamantan-1-yl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione 131a afforded 3-(adamantan-1-yl)-5-((substituted benzyl)thio)-4-phenyl-1,2,4-triazoles 242a–e (Scheme 66). The synthesized compounds were tested against anti-inflammatory and antimicrobial activities. Compounds 240 and 241 exhibited good anti-inflammatory activity, whereas compounds 240, 241, and 242c–e proved potent antibacterial activity against the tested microorganisms (Scheme 66) [92].

Scheme 66. Synthesis of thio-4-phenyl-1H-1,2,4-triazoles 242a–e.

The reaction of aminotriazolethiones 243a–i with different aldehydes afforded various arylidenes 244a–l, which upon reacting with 133 gave substituted triazoles 245a–i (Scheme 67). The bioassay of antibacterial and antifungal activities of 245a–i revealed that they have better antifungal than antibacterial activities; also, compounds 245b,c,f,j,k,l showed excellent antifungal activity against Candida albicans with an MIC of 16 μg/mL [93].
Mannich reaction of arylidene derivatives of triazolethiols 246 with formaldehyde and benzyl piperazine or 4-substituted pyrimidyl/phenyl/pyridylpiperazine in ethanol at room temperature led to new Mannich bases 247a–c and 248a–c in 67–74% and 72–83% yields, respectively [94] (Scheme 68). The bioassay of the synthesized compounds revealed that these compounds could be used as new fungicides, whereas compounds 247a–c exhibited higher and wider fungicidal activities comparable with that of control triadimefon (Scheme 68) [94].
oxo-5,8-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acid derivatives 251, which exhibited significant antimicrobial activities [95] (Scheme 69).

![Scheme 69. Reaction of triazolethione 249 with pipemidic acid 250.](image)

Schiff bases of triazolethiones 67a–c were obtained from the reaction of 4-substituted benzaldehyde with 4-amino-3-substituted-1,2,4-triazole-5-thiones 11a–c. Besides, the reaction of compounds 67a–c, formaldehyde, and 4-substituted piperazine gave the corresponding Mannich base 252a–c. In addition, bis-Mannich base derivatives 253a–c were synthesized in case of reaction of 67a–c with piperazine (Scheme 70) [52].

![Scheme 70. Synthesis of triazolethiones 252- and 253a–c.](image)

Reaction of 3,4-disubstituted triazolethiols 66a–c with 2-bromoacetophenones gave ((3,4-disubstituted-1,2,4-triazole-3-yl)thio)-1-phenyl-ethanones 254a–c in 70–82% yields and ((3,4-disubstituted-1,2,4-triazole-3-yl)thio)-1-(4-fluorophenyl)ethanones 255a–c in 72–85% yields [96]. The screening of the antioxidant activity using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method revealed that the corresponding hydrazinecarbothioamides showed excellent antioxidant activity, while 1,2,4-triazole-3-thiones showed good antioxidant activity (Scheme 71) [96].
Scheme 70. Synthesis of triazolethiones 252- and 253a–c. Reaction of 3,4-disubstituted triazolethioles 66a–c with 2-bromoacetophenones gave \((3,4\text{-disubstituted-1,2,4-triazole-3-yl})\text{thio})-1\text{-phenyl-ethanones} \(254a\text{–c}\) in 70–82% yields and \((3,4\text{-disubstituted-1,2,4-triazole-3-yl})\text{thio})-1\text{-}(4\text{-fluorophenyl})\text{ethanones} \(255a\text{–c}\) in 72–85% yields [96]. The screening of the antioxidant activity using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method revealed that the corresponding hydrazinecarbothioamides showed excellent antioxidant activity, while 1,2,4-triazole-3-thiones showed good antioxidant activity (Scheme 71) [96].

Scheme 71. Synthesis \(S\)-alkylated triazoles \(254a\text{–c}\) and \(255a\text{–c}\).

The reaction of 4-amino-5-((4-(bis(4-fluorophenyl)methyl)piperazin-1-yl)methyl)-4\(H\)-1,2,4-triazole-3-thiol (256) with benzyl bromide gave 3-(benzylthio)-5-((4-(bis(4-fluorophenyl)-methyl)piperazin-1-yl)methyl)-4\(H\)-1,2,4-triazole-4-amine (257) in 72% yield (Scheme 72) [97].

Scheme 72. Synthesis of triazolebenzylthiol 257.

3.2. Synthesis of Substituted Triazolethiones

Synthesis of Pyrazolo-1,2,4-triazoles

Compounds 4-Amino-5-(3-substituted pyrazolyl)triazolethiol 259a–d, 260a,b, and 261a–c in 61–78% yields were synthesized via reacting 4-aminotriazole-3-thiol (258), dimethoxy-\(N,N\)-dimethylmethanamine, and carbonyl compounds using acidic media (orthophosphoric acid) as catalyst [98] (Scheme 73). The mechanism describing the role of orthophosphoric acid is presented in Scheme 74.
3.2. Synthesis of Substituted Triazolethiones

**Synthesis of Pyrazolo-1,2,4-triazoles**

Compounds 4-Amino-5-(3-substituted pyrazolyl)triazolethiols 259a–d, 260a,b, and 261a–c in 61–78% yields were synthesized via reacting 4-aminotriazole-3-thiol (258), dimethoxy-N,N-dimethylmethanamine, and carbonyl compounds using acidic media (orthophosphoric acid) as catalyst [98] (Scheme 73). The mechanism describing the role of orthophosphoric acid is presented in Scheme 74.

**Scheme 73.** Synthesis of triazolethiols 259–261a–c.

Condensation of 5-chloro-1-phenyl-3-(substituted)-1H-pyrazole-4-carbaldehyde with amino-triazolethiones 11d,e furnished the corresponding Schiff bases 246a,b. Bis-aminotriazolethiones 262a,b can be obtained effectively in high yields (83–89% yields upon reaction of 246a,b with piperazine and formaldehyde in ethanol at room temperature) (Scheme 75) [61].

**Scheme 74.** Mechanism describes formation of triazolethiols 259a–c.

**Condensation of 5-chloro-1-phenyl-3-(substituted)-1H-pyrazole-4-carbaldehyde with amino-triazolethiones 11d,e furnished the corresponding Schiff bases 246a,b. Bis-aminotriazolethiones 262a,b can be obtained effectively in high yields (83–89% yields upon reaction of 246a,b with piperazine and formaldehyde in ethanol at room temperature) (Scheme 75) [61].**
3.3. Synthesis of Fused Triazoles

3.3.1. Synthesis of Fused Pyrazolotriazoles

The synthesis of pyrazolotriazoles 265a–d was easily established in 75–80% yields from the reaction of 4-amino-5-(substituted indole)-1,2,4-triazole-3-thiols 263a–d with N-arylhydrazonoacetates using basic media of triethylamine via the intermediate 264a–d. Desulfurization and ring contraction of compounds 264a–d gave the target compound 265a–d (Scheme 76) [99].

3.3.2. Synthesis of Thiazolotriazoles

The condensation reaction of 3-substituted-1,2,4-triazole 266a–c with chloroacetic acid in acidic media afforded thiazolotriazoles 267a–c in 65–69% yields. Interestingly, the synthesized compounds were screened for their antioxidant and antimicrobial activities [100] (Scheme 77). Compound 267a exhibited effective antimicrobial activity towards all the tested organisms.
Scheme 78. Synthesis of triazolo[1,3,4]-thiadiazoles 269a–e and 270. The reaction of different bromomalononitrile derivatives with 3-substituted triazolethiones 268 in 49–68% yields or (Z)-5-(1-acetyl-2-oxo-1H-indol-3(2H,3aH,7aH)-ylidene)thiazolo[3,2-b]-1,2,4-triazol-6(5H)-ones 270 were efficiently synthesized in 40% yield (Scheme 78) [101]. Screening of the obtained compounds for anticancer activity revealed that 5-arylidene-[1,3]thiazolo[3,2-b][1,2,4]triazol-6-ones 269a–e exhibited more potent anticancer activity than respective amides [101].

Scheme 79. Synthesis of thiazolotriazoles 267a–c.

However, in case of refluxing of 4H-1,2,4-triazole-3-thiol (268) with chloroacetic acid and different aldehydes or isatin derivatives in acidic media, various 5-substituted arylidene-thiazolotriazoles 269a–e in 49–68% yields or (Z)-5-(1-acetyl-2-oxo-1H-indol-3(2H,3aH,7aH)-ylidene)thiazolo[3,2-b]-1,2,4-triazol-6(5H)-ones 270 were efficiently synthesized in 40% yield (Scheme 78) [101]. Screening of the obtained compounds for anticancer activity revealed that 5-arylidene-[1,3]thiazolo[3,2-b][1,2,4]triazol-6-ones 269a–e exhibited more potent anticancer activity than respective amides [101].

Scheme 78. Synthesis of triazolo[1,3,4]-thiadiazoles 269a–e and 270.

The reaction of different bromomalononitrile derivatives with 3-substituted triazolethiones 30a–e produced the corresponding thiazolo-1,2,4-triazole carbonitriles 271a–e [102] (Scheme 79).

Scheme 79. Synthesis of thiazolo-1,2,4-triazole carbonitriles 271a–e.
The synthesis of $N$-aryl-2-(6-oxo-5,6-dihydrothiazolo[3,2-$b$][1,2,4]triazol-5-yl)acetamides 272 was achieved in 60–87% yields from the reaction of 268 with $N$-arylmaleimides in acidic media. It was established from the structure–activity relationship of these compounds that halo-substituted derivatives have a considerable increase in anticancer activities [103] (Scheme 80).

\[
\begin{align*}
268 + \text{Reagents and conditions: } A = H^+, \text{AcOH} \\
268, 272; \ a, X = H; \ b, X = \text{OCH}_3; \ c, X = \text{Cl}; \ d, X = \text{Br}; \ e, X = \text{CO}_2\text{Et}
\end{align*}
\]

Scheme 80. Synthesis of dihydrothiazolo[3,2-$b$][1,2,4]triazol-5-yl)acetamides 272a–e.

Shah et al. [104] have reported the synthesis of thiazolotriazoles 275 in 77–85% yields via refluxing of 5-phenyl-1,2,4-triazole-3-thiol (30d) with dibenzoylacetylene (273) through the intermediate 270 (Scheme 81).

Reagents and conditions: $A = \text{MeCN}$, r.t

Scheme 81. Synthesis of thiazolotriazole 275.

3.3.3. Synthesis of Triazolothiadiazoles

Triazolo[3,4-$b$][1,3,4]thiadiazoles 276a–g and 277a–e were obtained from refluxing of different aromatic carboxylic acids with 11o in the presence of phosphorous oxychloride [105]. Screening of the synthesized compounds against lung carcinoma (H157) and kidney fibroblast cell lines (BHK-21) showed that compound 277d has the highest inhibition activity of 74.0% for BHK-21 cells which is the same as that of standard drug vincristine (74.5%). Compound 276c,d,g showed less inhibition values, and triazolothiadiazole 276a was the most potent compound with inhibition value of 85.5%, whereas compounds 276b,f and 277a exhibited less inhibition values (Scheme 82) [105].
Scheme 83. Synthesis of triazolo[1,3,4]-thiadiazoles 278–281. When 3-substituted methylaminotriazolethione 11r was condensed with different aldehydes, aryldiene derivatives of triazoloethiones 282a–c were obtained in 54–66% yield, whereas triazolothiadiazoles 283a–c, in 48–74% yields, were synthesized from the reaction of compound 282a–c with iodine. In addition, 6-mercapto-1,2,4-triazolothiadiazoles 284 were synthesized upon reaction of 11r with CS₂ in pyridine. The synthesis of 4-((6-(ethylthio)-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)methyl)-2H-chromen-2-one 285 was occurred from reaction of 11r with methyl iodide in basic media in 55–75% yields. Moreover, 6-methylthio derivative 285 reacted with different aromatic amines to give triazolothiadiazoles 286a–c (in 55–75% yields). The obtained compounds were evaluated...
in vitro as anticancer agents in the human colon cancer (HCT 116) cell line where the aminosulfanyl derivative 286c exhibited high anticancer activity (Scheme 84) [37].

Scheme 83. Synthesis of triazolo[1,3,4]-thiadiazoles 278–281a–c. When 3-substituted methylaminotriazolethione 11r was condensed with different aldehydes, aryldene derivatives of triazolethiones 282a–c were obtained in 54–66% yield, whereas triazolothiadiazoles 283a–c, in 48–74% yields, were synthesized from the reaction of compound 282a–c with iodine. In addition, 6-mercapto-1,2,4-triazolothiadiazoles 284 were synthesized upon reaction of 11r with CS2 in pyridine. The synthesis of 4-((6-(ethylthio)-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)methyl)-2H-chromen-2-one 285 was occurred from reaction of 11r with methyl iodide in basic media in 55–75% yields. Moreover, 6-methylthio derivative 285 reacted with different aromatic amines to give triazolothiadiazoles 286a–c (in 55–75% yields). The obtained compounds were evaluated in vitro as anticancer agents in the human colon cancer (HCT 116) cell line where the aminosulfanyl derivative 286c exhibited high anticancer activity (Scheme 84) [37].

Scheme 84. Synthesis of chromone derived by triazolethiadiazines 283a–c and triazolo[3,4-b][1,3,4]thiadiazoles 286a–c.

3.3.4. Synthesis of 1,2,4-Triazolothiazines

The synthesis of triazolothiazines 287a–i (in 48–72% yields) was done from the reaction of compound 217a–i with CuI and tetramethylethlenediamine (TMEDA) using basic media (Scheme 85) [107].

Scheme 85. Synthesis of triazolothiadiazines 287a–i.

UV irradiation of disubstituted triazole-5(4H)-thione 288a–e under basic conditions gave a mixture of 3-substituted triazolothiazines 289a–e and 3,4-disubstituted-1,2,4-triazoles 290a–e according to the concentration of the base used. However, irradiation of 288a–e in presence of acetophenone and only compounds 290a–e was observed [108,109] (Scheme 86).
The antimicrobial activity of the synthesized compounds showed that triazolothiadiazines have significant antibacterial and antifungal activities against all the tested microorganisms [111].

3.3.5. Synthesis of 1,2,4-Triazolothiadiazines

Reaction of 92c with 2-chlorobenzoylketene 292 afforded 3-methyl-7-oxo-2,6-diphenyl-3,7-dihydro-[1,2,4]triazolo-[5,1-b][1,3]thiazin-8-ium-5-olate 293 in 66% yield [110] (Scheme 87).

Cyclocondensation of 4-amino-3-(4-(methylsulfonyl)benzyl)-1H-1,2,4-triazole-5(4H)-thione (294) with different substituted phenacyl bromide derivatives in ethanol afforded 6-substituted-3-(4-(methylsulfonyl)benzyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines 295a–i (Scheme 88). The antimicrobial activity of the synthesized compounds showed that triazolothiadiazines 295b,e,f,h have significant antibacterial and antifungal activities against all the tested microorganisms [111].

Refuxing of different carboxylic acids with thiocarbohydrazides 38 led to 4-amino-3-substituted-1,2,4-triazole-5-thiones 11s–v. Treatment of 11s–v with phenacyl bromide or chloride...
derivatives yielded triazolothiadiazines 296–299 [112] (Scheme 89). Interestingly, compounds 297b, 299b, and 299c, having either a chloride or fluoro substituent on the phenyl ring, gave better analgesic and anti-inflammatory activities and less ulcerogenic risk, along with minimum lipid peroxidation [112].

Various electrophilic reagents reacted with 206 to give different triazolothiadiazines 300, 302, and 304. Ethyl 2-((4-amino-5-((4-methyl-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl)methyl)-4H-1,2,4-triazole-3-yl)thio)acetate 301 was obtained from the reaction of 206 with ethyl bromoacetate which cyclized using sodium methoxide to give triazolothiadiazine 302. However, reacting 206 with ethyl bromoacetate and ethyl-2-chloroacetoacetate gave substituted triazolothiadiazine 300 and ethyl-substituted triazolo-[3,4-b][1,3,4]thiadiazine-7-carboxylate 304, respectively (Scheme 90) [113].
In a similar reaction, the reaction of (3-methylbenzofuran-2-yl)triazolethione 305 with either 2-bromoacetophenone or hydrazonyl halides produced the corresponding 3-(3-methylbenzofuran-2-yl)-triazolothiadiazine 306 and (2-arylhydrazono)triazolothiadiazine derivative 307, respectively [114] (Scheme 91).

\[
\begin{align*}
\text{305} & \xrightarrow{\text{EtOH/ Et3N}} \text{306} \\
\text{X} = \text{Br, Cl} & \quad \text{Reagents and conditions: A = MeOH/H \atop \Delta, 2-3h, B = H2O2/CHCl3}
\end{align*}
\]

Scheme 91. Synthesis of triazolothiadiazines 307.

It was reported that 1,2,4-triazole-3-thiol 11o reacted with various bromoacetophenone to yield the corresponding 3,6-disubstituted triazolothiadiazine 308a–h. The anticancer activity of these compounds was studied against H157 and BHK-21M cell lines showing that compound 308c was a potent inhibitor of H157 cells having 78.6% inhibition and compounds 308a and 308d were potent inhibitors in cancer therapy against BHK-21 cells with 73.3% and 72.6% inhibition, respectively [115] (Scheme 92).

\[
\begin{align*}
\text{11o} & \xrightarrow{\text{Ar \text{OAc} / \Delta}} \text{308a–h} \\
\text{Ar} = \text{a, 3-OMe-C6H4; b, 3-Cl-C6H4; c, 3-F-C6H4; d, 4-Me-C6H4; e, bipheny1; f, naphthyl; g, 3-NO2-C6H4; h, 3,4-dichloro-C6H3}
\end{align*}
\]

Scheme 92. Synthesis of triazolothiadiazines 308a–h.

4-Amino-5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazole-3-thiol (263) was successfully cyclized to give triazolo[3,4-b][1,3,4]thiadiazine (310) via reacting with 3-chloropentane-2,4-dione through the intermediate 309. Furthermore, diazotization occurred to compound 310 and chlorophenylidazene to give 311 (Scheme 93) [116].
4-Amino-5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazole-3-thiol (263) was successfully cyclized to give triazolo[3,4-b][1,3,4]thiadiazine (310) via reacting with 3-chloropentane-2,4-dione through the intermediate 309. Furthermore, diazotization occurred to compound 310 and chlorophenyldiazene to give 311 (Scheme 93) [115].

On reaction of 11a with N'-arylacetoxydrazonoyl halides 312 in the presence of sodium ethoxide, the reaction gave the corresponding 1,2,4-triazole-3-yl-2-(naphthalen-2-yl)-N'-arylethanehydrazonothioates 313. Cyclization of 313 in acidic media gave the target compound triazolothiadiazine 314 [116] (Scheme 94).

Refluxing of 11e with N-aryl-2-oxopropanehydrazonoylchloride 315a–e afforded (Z)-6-methyl-7-(2-aryllhydrazono)-3-(trifluoromethyl)-7H-[1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazine (317) via the formation of intermediate 316 [118]. Screening of the anticancer activities revealed that compounds 316a,e were the most active inhibitors against HEPG-2 cell line, whereas compound 316a was active against HCT cell line [118] (Scheme 95).
We also give spots on the biology of the target molecule as prospective antiviral drugs.

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4. Conclusions

In this review, we are trying to focus attention on the routes of triazole-thione synthesis. Since, triazolelethione-thiols have gained considerable importance in medicinal chemistry, due to their broad spectrum as antiviral, antibacterial, anticancer, etc. agents, their synthesis has become of great interest. We also give spots on the biology of the target molecule as prospective antiviral drugs.

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