

Synthesis of 3,6-Disubstituted [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazoles via Cyclocondensation of 4-Amino-1,2,4-triazole-3-thiols With Carboxylic Acids: A Review

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Abstract: Triazolo[3,4-*b*][1,3,4]thiadiazole core is the condensed thia/aza-containing bicyclic system combining 1,2,4-triazole and 1,3,4-thiadiazole rings, which represent an interesting class of heterocyclic compounds. Thus, functionalized derivatives incorporating triazolo[3,4-*b*]thiadiazole are of essential significance and particular interest for both the pharmaceutical and agrochemical industries due to their wide spectrum of biological properties. Considering the wide synthetic possibilities as well as a diverse range of pharmacological activities, triazolo[3,4-*b*][1,3,4]thiadiazoles have received considerable attention from the scientific community as a prospective structural scaffold for rational drug-like molecules build-up. In this review, we have attempted to summarize the literature data about the main synthetic approaches for obtaining triazolo[3,4-*b*][1,3,4]thiadiazole-based molecules as promising objects for modern bioorganic and medicinal chemistry.

Keywords: triazolo[3,4-*b*][1,3,4]thiadiazoles; fused heterocycles; synthesis; chemical modification; multistep transformation; cyclocondensation; molecular hybridization.

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1. Introduction

Heterocyclic compounds that possess nitrogen as a heteroatom are extensively found as therapeutic agents due to the diverse range of biological activities, low toxicity, and good pharmacokinetic and pharmacodynamic profiles. They exhibit a broad spectrum of chemical and pharmacological properties that make them highly valuable as a key structural motif for synthetic, pharmaceutical, and agrochemical fields [1-8]. In this context, special attention should be paid to five-membered diazaheterocycles, including oxa/thia-containing ones, such as pyrroles, pyrazolines, 1,3-thiazoles, oxadiazoles, and others. These heterocycles exhibit a wide range of biological and pharmacological activities, including anticancer, antitubercular, antibacterial, antihypertensive, anti-inflammatory, anticonvulsant, and antioxidant properties [9-16]. This is due to their unique electronic properties and structural stability, making them highly relevant in medicinal chemistry and target-oriented drug design.

1,2,4-Triazoles represent an important class of nitrogen-containing heterocyclic compounds that have displayed a broad spectrum of biological activities. The chemistry and pharmacology of 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention owing to their synthetic application and effective pharmacological efficiency as evidenced by numerous reports [17-24]. They own unique properties combining different weak interactions, a characteristic basicity, and several coordination modes [25].

1,3,4-Thiadiazoles are another newsworthy group of heterocyclic compounds with a five-membered ring composed of sulfur and two nitrogen atoms as heteroatoms. They are key scaffolds in a large number of molecular architectures that display antibacterial, antifungal, antitubercular, anti-protozoal, antioxidant, anticancer, antitrypanosomal, anti-inflammatory, or antiviral activities [26-34]. Also, there are numerous reviews in the last few years focusing on the chemical features, main approaches to the synthesis, and pharmacological potential of 1,3,4-thiadiazole derivatives [35-37]. In addition, 1,3,4-thiadiazoles are a versatile structural component for the synthesis of a large diversity of condensed polyheterocyclic systems [38].

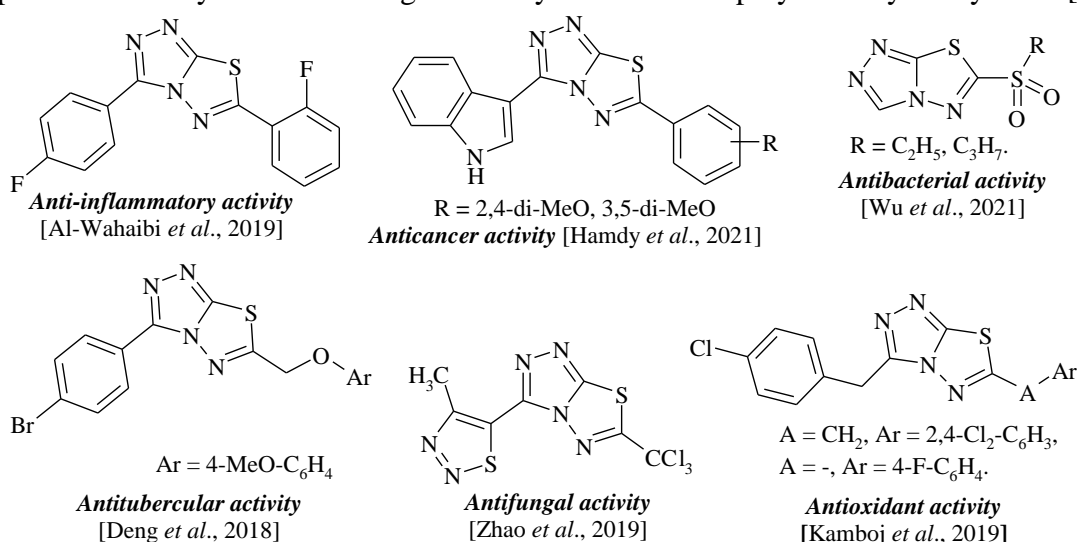


Figure 1. Pharmacological importance of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives.

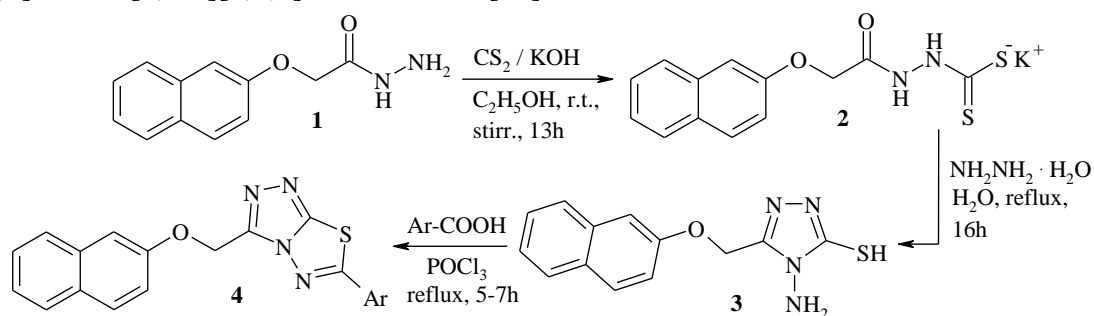
It is worth emphasizing that condensed heterocyclic systems are no less interesting and undeniably important compounds in organic chemistry. They are well-known for their excellent biological effects and are often of greater efficiency in terms of their biological activity than their individual monocyclic constituents. Thus, there are many works that confirm the pharmacological significance of polycyclic heterosystems [39-45]. In this regard,

triazolothiadiazoles are condensed heterosystems bearing 1,2,4-triazole and 1,3,4-thiadiazole moieties, which represent an interesting class of compounds possessing a wide spectrum of biological activities (Figure 1), as described elsewhere [46-53].

Continuing our interest in preparing sulphur and nitrogen-containing heterocyclic compounds and examining their various biological activities [54-64], this work presents a summary of the literature data about the recent strategies on the synthesis of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles based on one-pot cyclocondensation reaction of 4-amino-1,2,4-triazole-3-thiols with various carboxylic acids.

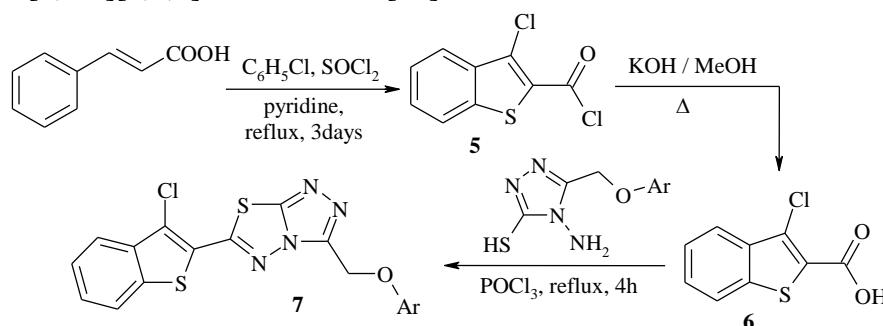
2. Synthetic Approaches for Obtaining and Chemical Modification of Heterocyclic Compounds Based on Condensed [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole System

Through a two-step transformation of starting 2-naphthoxyacetic acid hydrazide **1**, the corresponding 4-amino-5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazole-3-thiol **3** has been synthesized (Scheme 1). In the next stage, treating compound **3** with substituted aromatic acids in the presence of phosphorus oxochloride to afford 3-(naphthalene-2-oxy)methyl substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **4** [65].



Scheme 1. Synthesis of 3-(naphthalene-2-oxy)methyl substituted 6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by interaction of corresponding 4-amino-4*H*-1,2,4-triazole-3-thiol with aromatic acids.

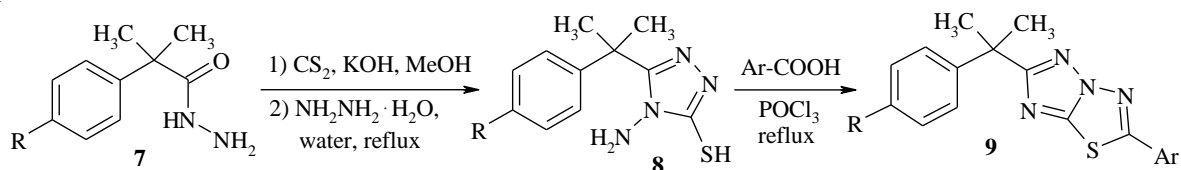
Following the hydrolysis of 3-chlorobenzo[*b*]thiophene-2-carboxyl chloride **5**, previously obtained from cinnamic acid and thionyl chloride in chlorobenzene medium, with methanolic potassium hydroxide, the corresponding benzo[*b*]thiophene-2-carboxylic acid **6** was formed (Scheme 2). Further interaction of **6** with various 5-aryloxymethyl substituted 4-amino-1,2,4-triazole-3-thiols leads to the formation of benzo[*b*]thiophene containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **7** [66].



Scheme 2. Synthesis of benzo[*b*]thiophene substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles following the interaction of 3-substituted-4-amino-1,2,4-triazoles with 3-chlorobenzo[*b*]thiophene-2-carboxylic acid.

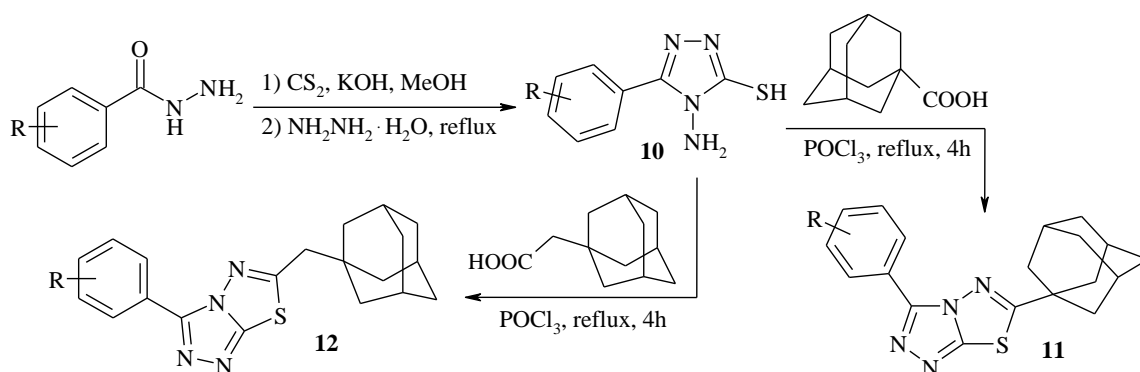
3,6-Disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing *gem*-dimethyl benzyl moiety **9** (Scheme 3) were prepared by condensation of 5-aryl/aralkyl substituted 4-

amino-4*H*-1,2,4-triazole-3-thiols **8** with corresponding fluoro substituted aromatic acids in the presence of POCl₃ [67].



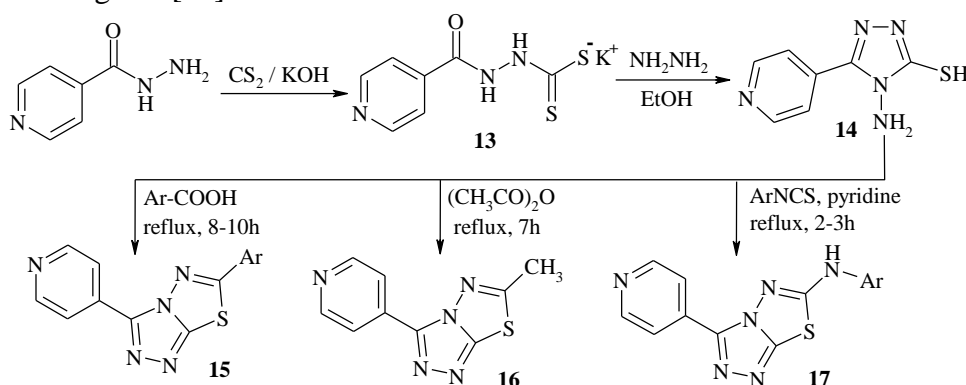
Scheme 3. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing *gem*-dimethyl benzyl moiety by condensation of 5-aryl/aralkyl-4-amino-4*H*-1,2,4-triazole-3-thiols with fluoro substituted aromatic acids.

The synthesis of 6-adamantyl(methyl) 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **11** and **12** was carried out (Scheme 4) by treatment of 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiols **10** with adamantyl-1-carboxylic [68] or adamantyl-1-acetic [69] acids, respectively, in the presence of refluxing phosphorus oxychloride.



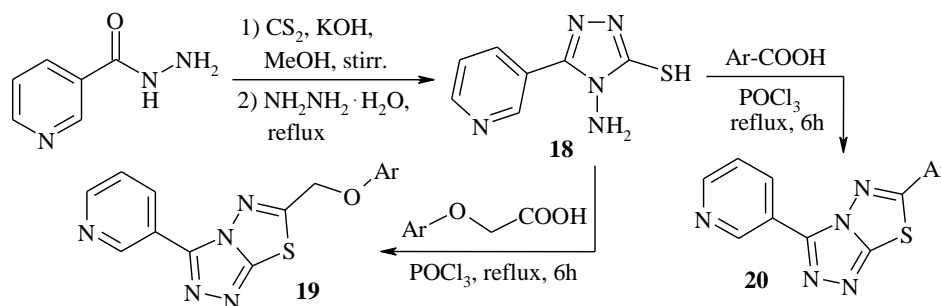
Scheme 4. Synthesis of 6-adamantyl(methyl) substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-aryl-1,2,4-triazole-3-thiols with adamantyl-1-carboxylic(acetic) acids.

The sequential modification of isoniazid with carbon disulfide in methanolic potassium hydroxide (**13**) followed by hydrazinolysis gives an intermediate 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-thiol **14** (Scheme 5). Further condensation of compound **14** with various aromatic carboxylic acids in phosphorus oxychloride medium yielded the corresponding 6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **15** [70,71]. In addition, the synthesis of 6-methyltriazolo[3,4-*b*]thiadiazole **16** was achieved *via* heating under reflux of **14** with acetic anhydride. Moreover, the reaction of **14** with various aryl isothiocyanates in pyridine for 2-3h until the complete evolution of H₂S (detected by lead acetate paper) afforded the cyclized 6-arylamino analogs **17** [71].



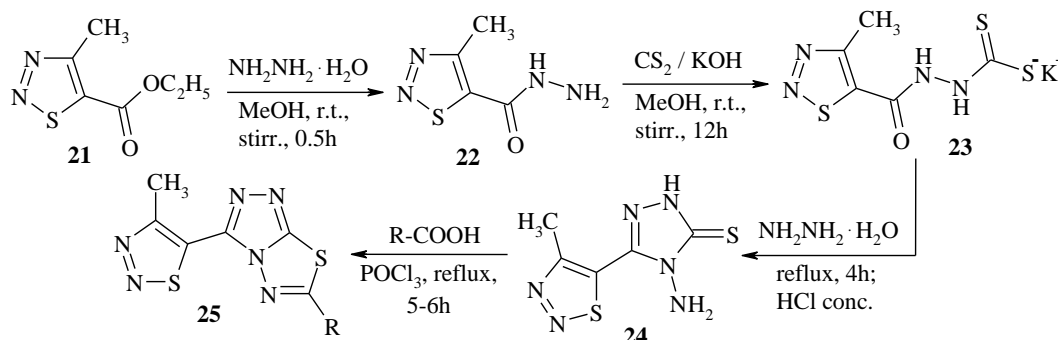
Scheme 5. Synthesis of 6-substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles from condensation of 4-amino-5-(pyridin-4-yl)-1,2,4-triazol-3-thiol with aromatic carboxylic acids, acetic anhydride, or aryl isothiocyanates.

Similarly, the synthesis of 4-amino-5-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-thiol **18** was carried out based on nicotinohydrazide as starting material (Scheme 6). Further, compound **18** was modified in a one-pot condensation with various aromatic or phenyloxyacetic acids in the presence of POCl₃, with the formation of 6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing pyridine moiety **19** and **20** [72].

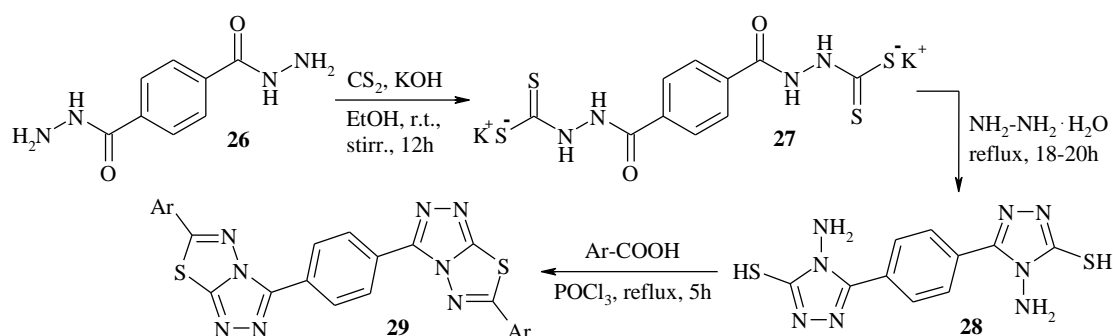


Scheme 6. Synthesis of 6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing pyridine fragment by condensation of 4-amino-5-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-thiol with aromatic or phenyloxyacetic acids.

Condensation of the 3-(1,2,3-thiadiazol-5-yl) substituted 4-amino-1,2,4-triazole-5-thione **24**, obtained from starting ethyl 4-methyl-1,2,3-thiadiazole-5-carboxylate **21** through the three-stage procedure (Scheme 7), with various carboxylic acids in the presence of phosphorus oxychloride under refluxing conditions, gave the expected 4-methyl-1,2,3-thiadiazole-containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **25** [73].



Scheme 7. Synthesis of 4-methyl-1,2,3-thiadiazole-containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 3-(4-methyl-1,2,3-thiadiazolyl)-4-amino-1,2,4-triazole-5-thione with carboxylic acids.

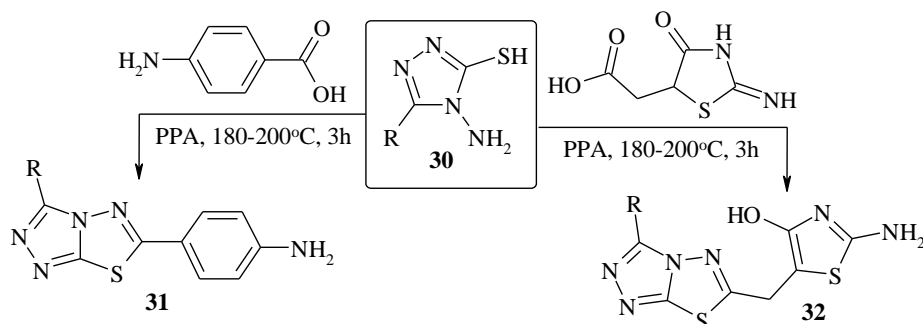


Scheme 8. Synthesis of 1,4-bis-(6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole)phenylenes by condensation of 1,4-phenylene-bis(4-amino-4*H*-1,2,4-triazole-3-thiol) with aromatic acids.

Following the multistep reaction sequence starting from terephthalic dihydrazide **26** through an intermediate stage of bis-dithiocarbamate potassium salt **27** formation, the corresponding 1,4-phenylene-bis-(4-amino-4*H*-1,2,4-triazole-3-thiol) **28** was obtained (Scheme 8). The synthesis of target 1,4-bis-(6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole)

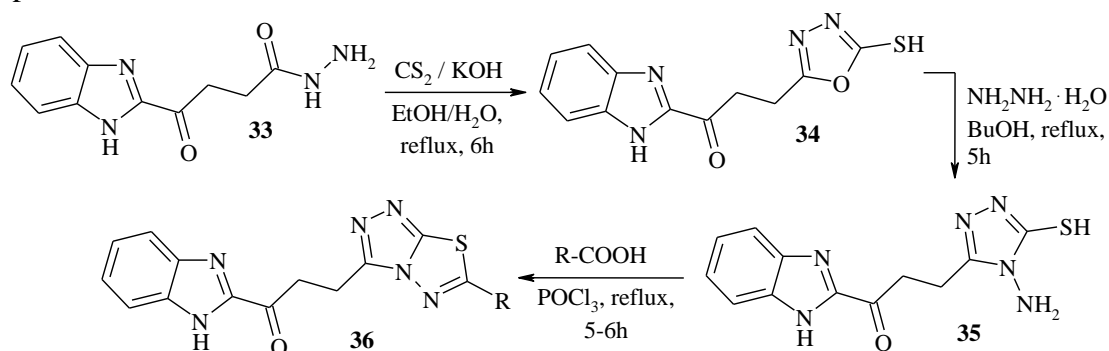
phenylenes 29 was achieved through the one-pot condensation of compound 28 with aromatic acids in refluxing phosphorus oxochloride [74].

Condensation of 5-substituted 4-amino-1,2,4-triazole-3-thiol 30 with 4-aminobenzoic or (2-iminothiazol-4-one-5-yl)acetic acids by heating in polyphosphoric acid afforded the target 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 31 and 32, respectively, as depicted in Scheme 9 [75].



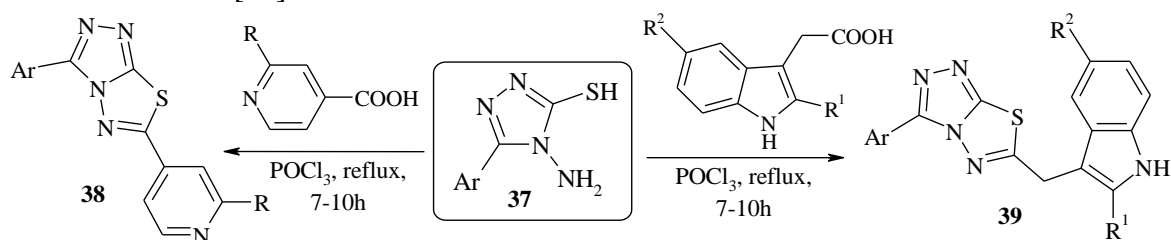
Scheme 9. Synthesis of 3,6-disubstituted triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 5-substituted 4-amino-1,2,4-triazole-3-thiol with 4-aminobenzoic acid or (2-iminothiazol-4-one-5-yl)acetic acid.

Starting from 4-(1*H*-benzo[*d*]imidazol-2-yl)-4-oxobutanoic acid hydrazide 33 through an intermediate stage of 1,3,4-oxadiazole-5-thiol 34 formation (Scheme 10), Husain et al. [76,77] performed the synthesis of benzo[*d*]imidazole substituted 4-amino-4*H*-1,2,4-triazole-3-thiol 35. Further interaction of compound 35 with different aromatic/aliphatic acids in the presence of POCl₃ occurs with the formation of 6-alkyl/aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 36 containing a benzo[*d*]imidazole moiety linked by a propan-1-one group.



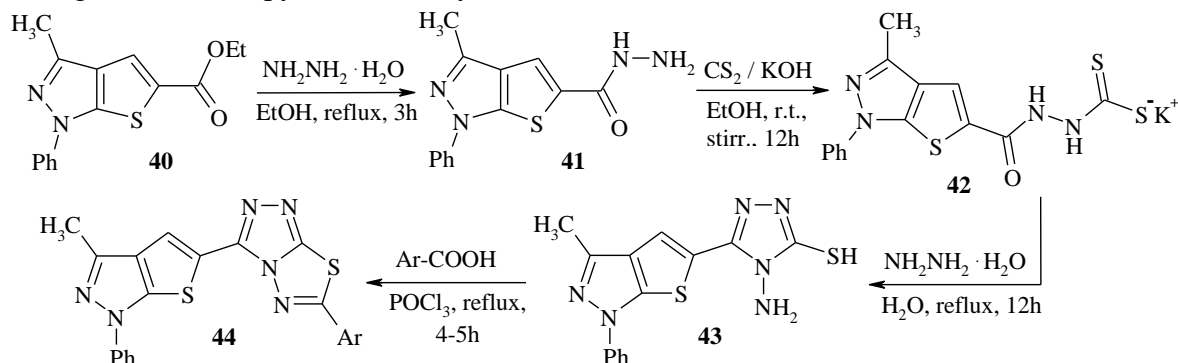
Scheme 10. Synthesis of 6-alkyl/aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing benzo[*d*]imidazole moiety by interaction of corresponding 4-amino-4*H*-1,2,4-triazole-3-thiol with aromatic/aliphatic acids.

Condensation of 4-amino-5-aryl-1,2,4-triazole-3-thiols 37 with isonicotinic or indol-3-ylacetic acid derivatives in the presence of phosphorus oxychloride (Scheme 11) resulted in the expected 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing pyridine 38 or indole 39 moieties [78].



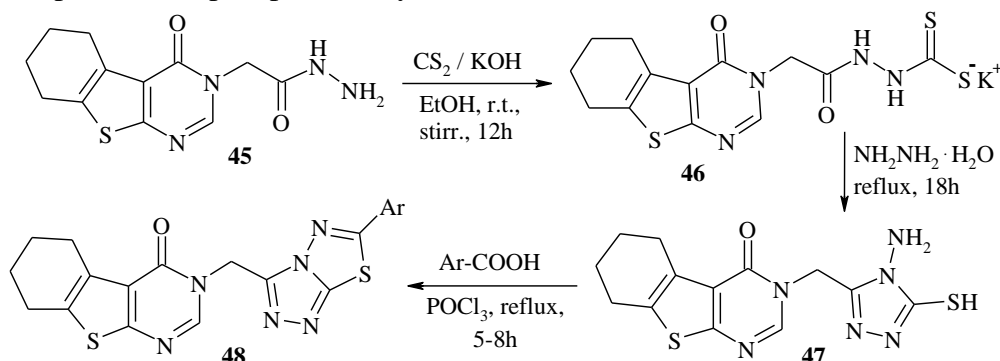
Scheme 11. Synthesis of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-aryl-1,2,4-triazole-3-thiols with substituted isonicotinic or indol-3-ylacetic acids.

Starting from 3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylic acid ethyl ester 40 through the multistep reaction sequence (Scheme 12), the synthesis of 4-amino-5-(thieno[2,3-*c*]pyrazol-5-yl)-substituted-4*H*-1,2,4-triazole-3-thiol 43 was carried out. Further one-pot condensation of the obtained 4-amino-4*H*-1,2,4-triazole-3-thiol 43 with aromatic acids in POCl₃ medium resulted in 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 44 bearing thieno[2,3-*c*]pyrazolo moiety [79].

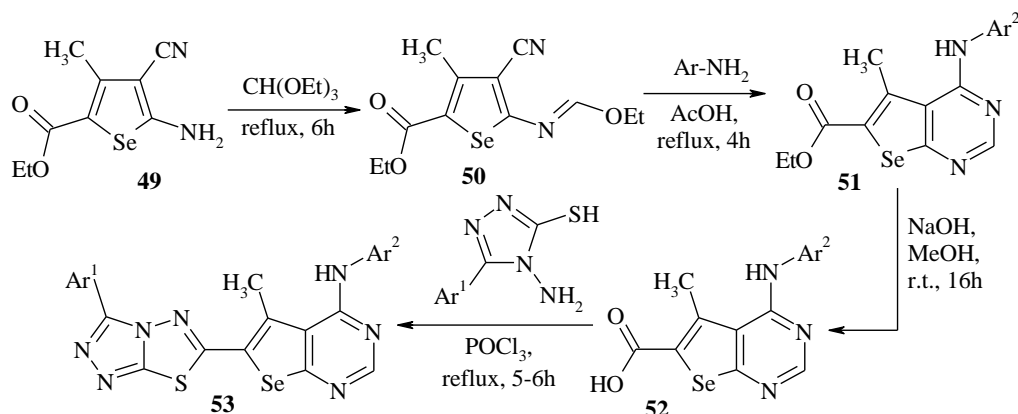


Scheme 12. Synthesis of thieno[2,3-*c*]pyrazole containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of corresponding 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol with aromatic acids.

The synthesis of thieno[2,3-*d*]pyrimidin-4-one containing 4-amino-4*H*-1,2,4-triazole-3-thiol 47 was performed starting from tetrahydrobenzo[*b*]thiophene-3-carbohydrazide 45, as shown in Scheme 13. Further, the title novel fused pentacyclic [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazolo thieno[2,3-*d*]pyrimidin-4-ones 48 were obtained on condensation of intermediate 4-amino-4*H*-1,2,4-triazole-3-thiol 47 with various substituted aryl carboxylic acids in the presence of phosphorus oxychloride [80].



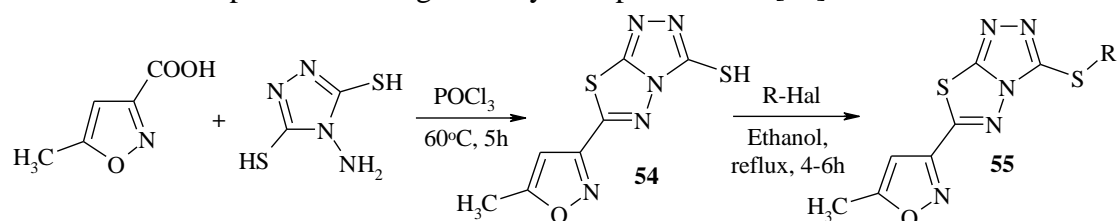
Scheme 13. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing thieno[2,3-*d*]pyrimidine by condensation of 4-amino-4*H*-1,2,4-triazole-3-thiols with substituted aromatic acids.



Scheme 14. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl selenopheno[2,3-*d*]pyrimidines from the reaction of 4-amino-5-aryl-1,2,4-triazol-3-thiols with corresponding carboxylic acids.

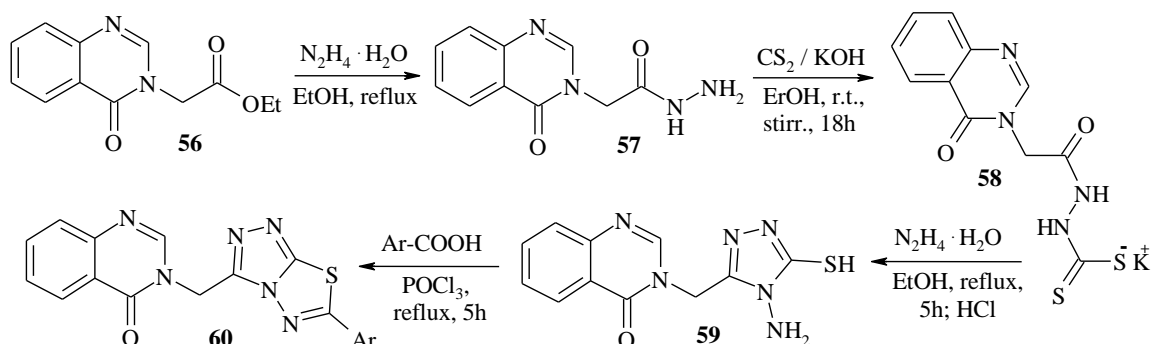
Modification of ethyl 5-amino-4-cyano-3-methylselenophene-2-carboxylate 49 with triethyl orthoformate (50), then substituted anilines in acetic acid (51), followed by hydrolysis of the corresponding 5-methyl-4-arylamino-selenopheno[2,3-*d*]pyrimidine-6-carboxylic acids 52 were obtained (Scheme 14). A series of title [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl selenopheno[2,3-*d*]pyrimidines 53 were synthesized from the reaction of carboxylic acids 52 with 4-amino-5-aryl-1,2,4-triazol-3-thiols in the presence of POCl₃ [81].

A new 5-methylisoxazole-3-yl substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiol 54 was synthesized *via* cyclocondensation of 5-methylisoxazole-3-carboxylic acid with 4-amino-1,2,4-triazole-3,5-dithiol using phosphorus oxychloride as a cyclizing reagent (Scheme 15). Further, compound 54 was modified on *S*-alkylation reaction with various alkyl halides in ethanol to provide the target *S*-alkylated products 55 [82].

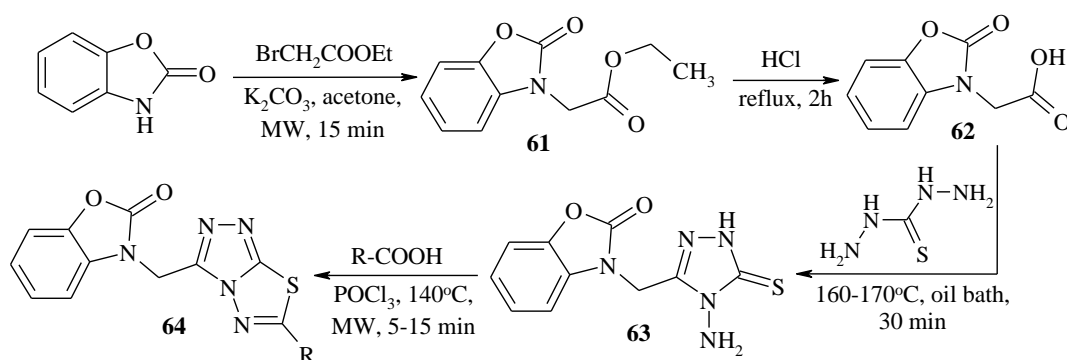


Scheme 15. Synthesis of isoxazole substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles *via* cyclocondensation of 5-methylisoxazole-3-carboxylic acid with 4-amino 1,2,4-triazole-3,5-dithiol followed by alkylation.

Upon the reaction of 4-oxo-4*H*-quinazolin-3-acetic acid hydrazide 57 with carbon disulfide in potassium hydroxide ethanolic solution, the potassium dithiocarbazate 58 was obtained and then treated with hydrazine hydrate to generate the corresponding 4-amino-1,2,4-triazole-3-thiol 59 (Scheme 16). Further condensation of 59 with the substituted benzoic acids in refluxing phosphorus oxochloride leads to the formation of quinazolin-4(3*H*)-one containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 60 [83].



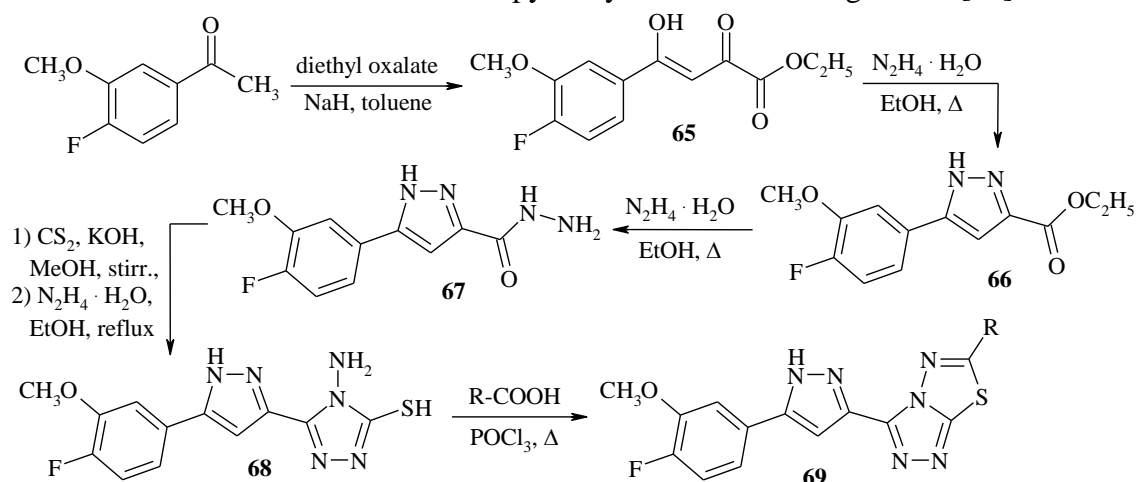
Scheme 16. Synthesis of quinazolin-4(3*H*)-one containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of corresponding 4-amino-1,2,4-triazole-3-thiol with substituted benzoic acids.



Scheme 17. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles having benzoxazolone moiety by condensation of 2(3*H*)-benzoxazolone substituted 4-amino-5-thioxo-1,2,4-triazole with benzoic or phenylacetic acids.

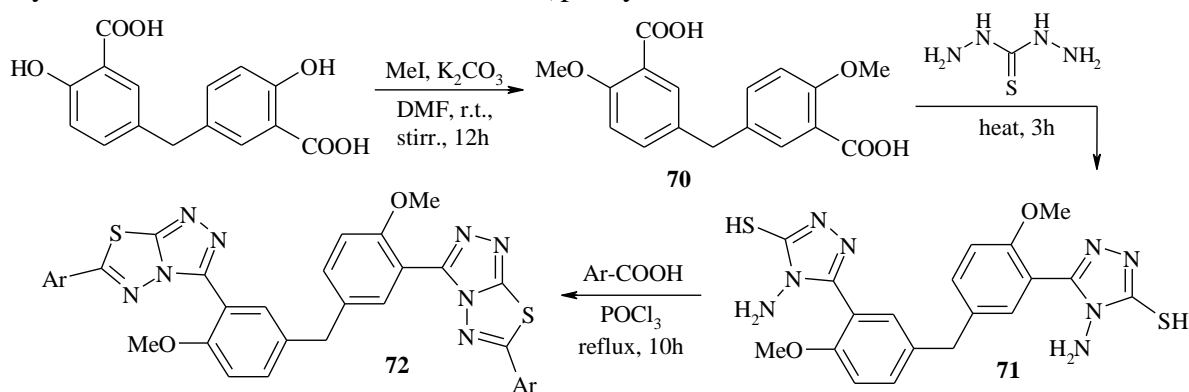
Following the interaction of 2-(2-oxo-3*H*-benzoxazol-3-yl)acetic acid 62, obtained by hydrolysis of the corresponding ethyl ester 61, with thiocarbosidrazide, the synthesis of 3-[(4-amino-5-thioxo-1,2,4-triazol-3-yl)methyl]-2(3*H*)-benzoxazolone 63 was performed (Scheme 17). A series of 2(3*H*)-benzoxazolone substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 64 were synthesized by condensation of compound 63 with substituted benzoic or phenylacetic acids in phosphorus oxochloride medium under microwave irradiation [84].

Sequential transformations of starting 4-methoxy-3-fluoro-acetophenone with diethyl oxalate (65), followed by cyclization with hydrazine hydrate (66), and hydrazinolysis of 5-aryl-1*H*-pyrazole-3-carbohydrazide 67 were obtained (Scheme 18). Then, intermediate 67 was processed with carbon disulfide in ethanolic potassium hydroxide and hydrazine hydrate, giving 5-pyrazolyl substituted 4-amino-4*H*-1,2,4-triazole-3-thiol 68. Finally, the synthesis of novel [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole bearing pyrazole moiety 69 was performed by interaction of 68 with substituted benzoic/pyridinyl acids in refluxing POCl₃ [85].



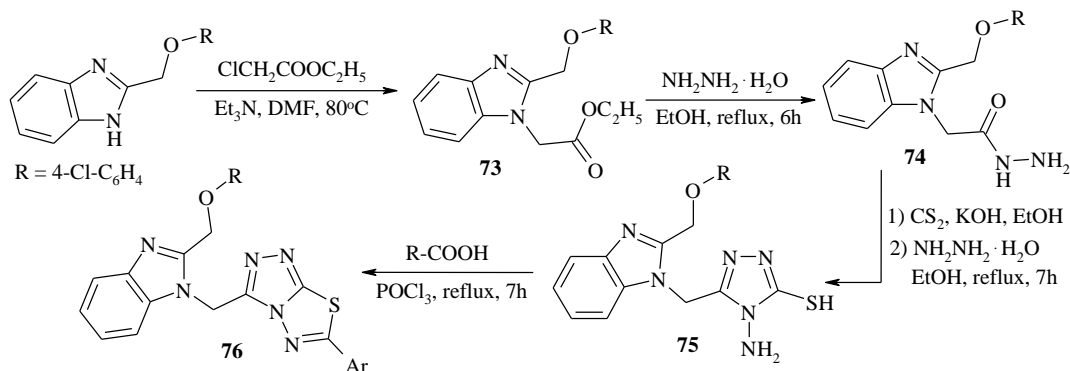
Scheme 18. Synthesis of 3-pyrazolyl substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-4*H*-1,2,4-triazole-3-thiol with benzoic/pyridinyl acids in phosphorus oxychloride.

By a two-step procedure, 5-(3-carboxy-4-methoxybenzyl)-2-methoxybenzoic acid 70 was synthesized and converted, upon reaction with thiocarbohydrazide, into bis[4-methoxy-3-[4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl]phenyl]methane 71, as shown in Scheme 19. Further, the interaction of 71 with the corresponding aryl/heteroaryl carboxylic acid in the presence of phosphorus oxychloride at reflux for 10 h afforded a novel bis[4-methoxy-3-(6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol)phenyl]methanes 72 [86].



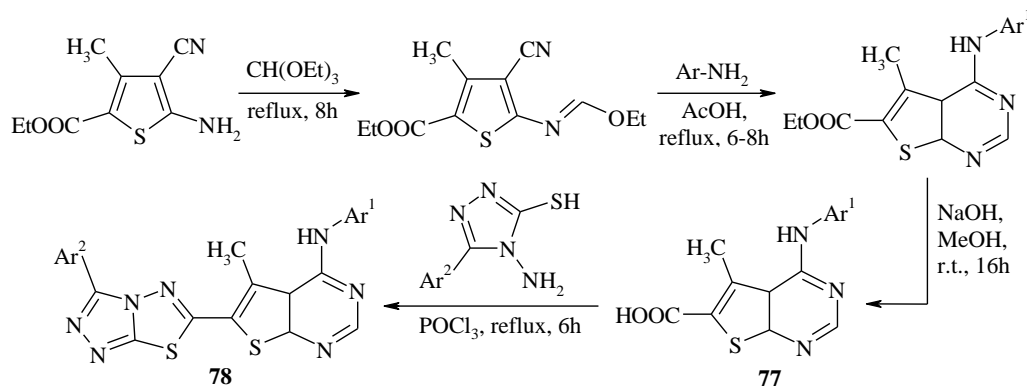
Scheme 19. Synthesis of bis[3-(6-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol)phenyl]methanes by condensation of bis[3-[4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl]phenyl]methane with aryl/heteroaryl carboxylic acids.

Using 2-[2-(4-chlorophenoxymethyl)-1*H*-benzimidazole-1-yl]-acetic acid ethyl ester 73 as starting material by sequential interactions with hydrazine hydrate (74) followed by cyclization with carbon disulfide in ethanolic potassium hydroxide, the synthesis of 4-amino-1,2,4-triazole-3-thiol 75 was carried out (Scheme 20). A series of 6-(benzimidazole-1-methylene) substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 76 were synthesized by condensation of 4-amino-3-mercapto-1,2,4-triazoles 75 with various (un)substituted aromatic acids in the presence of phosphorus oxochloride [87].

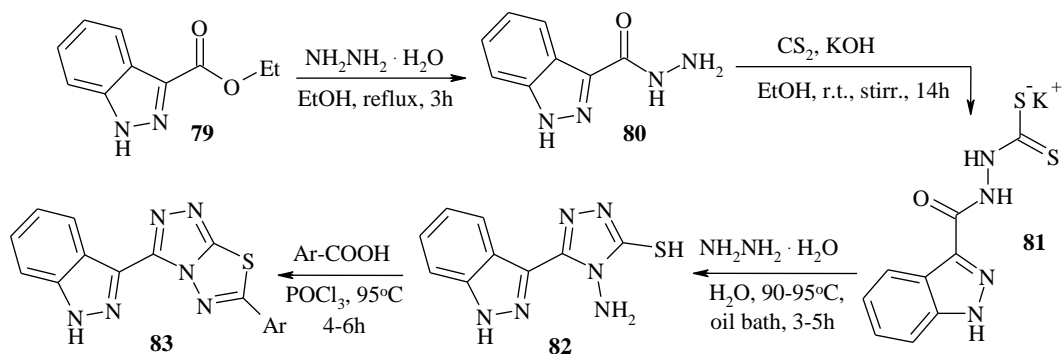


Scheme 20. Synthesis of benzimidazole-1-methylene substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-3-mercapto-4*H*-1,2,4-triazoles with (un)substituted aromatic acids.

Through the molecular hybridization approach, which includes the interaction of previously obtained 5-methyl-4-(substituted phenyl amino)thieno[2,3-*d*]pyrimidine-6-carboxylic acids 77 with 5-aryl substituted 4-amino-4*H*-1,2,4-triazole-3-thiols in refluxing phosphorus oxochloride (Scheme 21), a series of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole tagged thienopyrimidine hybrids 78 were obtained [88].



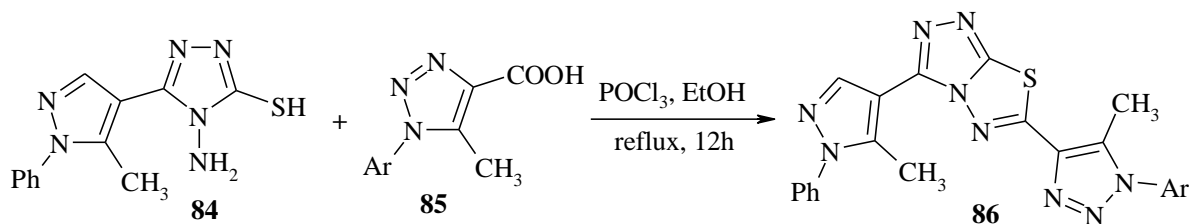
Scheme 21. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole tagged thienopyrimidine hybrids by interaction of 5-methylthieno[2,3-*d*]pyrimidine-6-carboxylic acids with 5-aryl-4-amino-4*H*-1,2,4-triazole-3-thiols.



Scheme 22. Synthesis of 1*H*-indazole substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-(1*H*-indazol-3-yl)-4*H*-1,2,4-triazole-3-thiol with substituted arylcarboxylic acids.

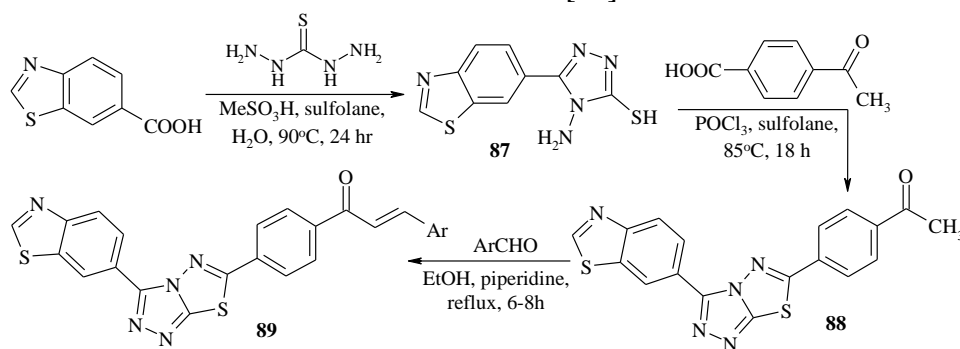
Starting from 1*H*-indazole-3-carboxylic acid ethyl ester 79 through an intermediate stage of the corresponding hydrazide 80 and potassium dithiocarbamate 81 formation, the synthesis of 4-amino-5-(1*H*-indazol-3-yl)-4*H*-1,2,4-triazole-3-thiol 82 was achieved (Scheme 22). Further, intermolecular condensation of compound 82 with substituted arylcarboxylic acids in refluxing POCl₃ provided a series of target 3-(1*H*-indazol-3-yl) substituted 3-aryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 83 [89].

Interaction of 5-(1-phenylpyrazole) substituted 4-amino-4*H*-1,2,4-triazole-3-thiol 84 with 5-methyl-1-aryl-1,2,3-triazole-4-carboxylic acids 85 in the presence of phosphorus oxochloride in ethanol medium at reflux conditions (Scheme 23) gave the expected pyrazole and 1,2,3-triazole having [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles 86 [90].

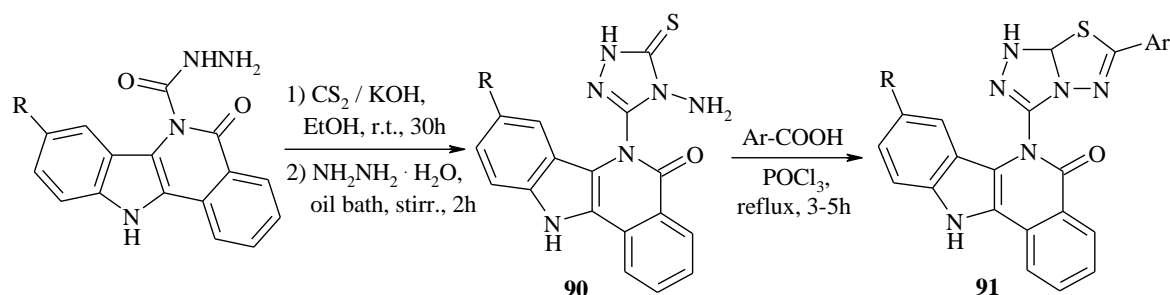


Scheme 23. Synthesis of pyrazole and 1,2,3-triazole having [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 5-substituted 4-amino-4*H*-1,2,4-triazole-3-thiol with 1-aryl-1,2,3-triazole-4-carboxylic acids.

The synthesis of 6-(4-acetylphenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole containing benzothiazole moiety 88 was carried out through the cyclocondensation of 4-amino-5-(1,3-benzothiazol-6-yl)-4*H*-1,2,4-triazol-3-thiol 87 with 4-acetylbenzoic acid in the presence of phosphoryl chloride and sulfolane at 85°C (Scheme 24). Then, interaction of 88 with different aryl aldehydes using Claisen-Schmidt procedure in the presence of catalytic amounts of piperidine base in ethanol under reflux conditions gives a series of titles 1,2,4[triazolo[3,4-*b*][1,3,4]thiadiazole tethered chalcone derivatives 89 [91].



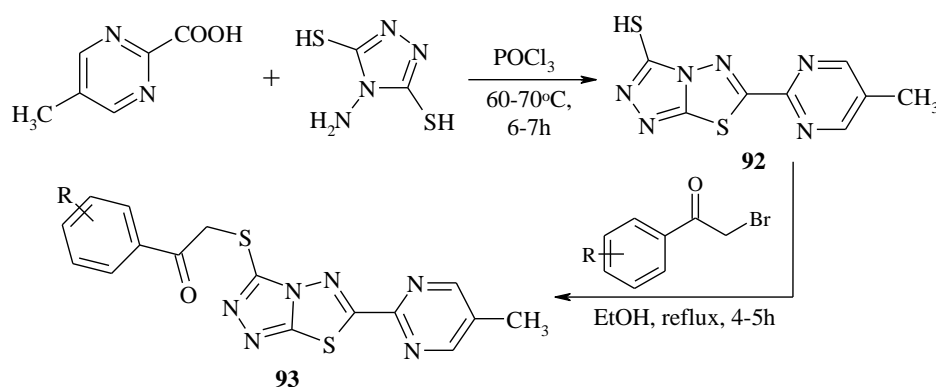
Scheme 24. Synthesis of benzothiazole containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole tethered chalcones by condensation of 4-amino-5-(1,3-benzothiazol-6-yl)-4*H*-1,2,4-triazol-3-thiol with 4-acetylbenzoic acid.



Scheme 25. Synthesis of indolo[3,2-*c*]isoquinolines incorporated with [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole moieties by condensation of corresponding 4-amino-1*H*-1,2,4-triazole-5-thiols with substituted aromatic acids.

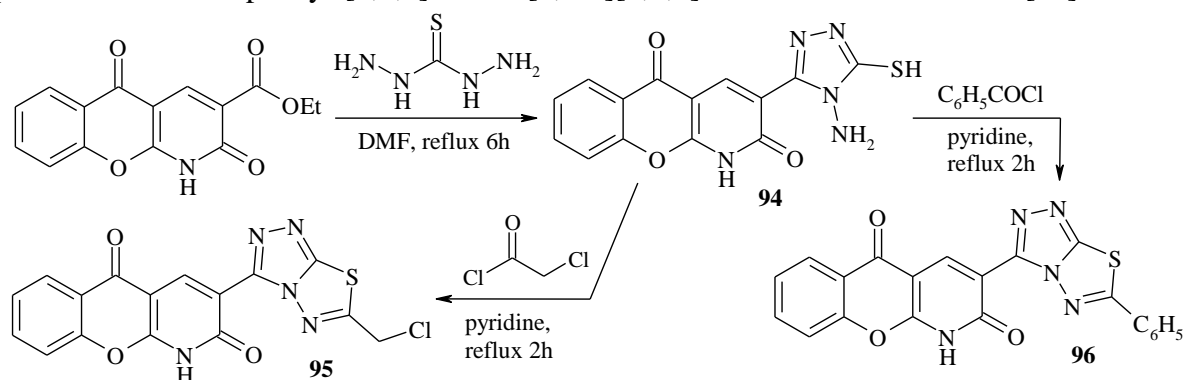
Reacting of starting 5-oxo-5*H*-indolo[3,2-*c*]isoquinoline-6(1*H*)-carbohydrazides with carbon disulfide and potassium hydroxide in ethanol medium to afford indolo[3,2-*c*]isoquinolin-5(1*H*)-one having 4-amino-1*H*-1,2,4-triazole-5-thiones 90 (Scheme 25). Then, a series of novel indolo[3,2-*c*]isoquinolines incorporated with [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole moieties 91 were synthesized by condensation of compound 90 with substituted aromatic acids in phosphorus oxychloride under reflux conditions [92].

The condensation between 5-methylpyrimidine-2-carboxylic acid and 4-amino-4*H*-1,2,4-triazole-3,5-dithiol in phosphorus oxochloride medium (Scheme 26) resulted in pyrimidine substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiol 92. Further interaction of 92 with different phenacyl bromides in ethanol gives the corresponding *S*-alkylated 2-thio-1-arylethanones having triazolo[3,4-*b*]thiadiazole scaffold 93 [93].



Scheme 26. Synthesis of 5-methylpyrimidine substituted triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiol by condensation of 4-amino-4*H*-1,2,4-triazole-3,5-dithiol with 5-methylpyrimidine-2-carboxylic acid.

Chromeno[2,3-*b*]pyridine containing 4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-thione 94 was obtained by boiling the appropriate ethyl ester with thiocarbohydrazide in DMF under reflux for 6 h. (Scheme 27). Further interaction of compound 94 with chloroacetyl chloride in pyridine medium yielded 6-chloromethyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazolyl chromeno[2,3-*b*]pyridine 95. Instead, the use in similar conditions of benzoyl chloride provided the title 6-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivative 96 [94].



Scheme 27. Synthesis of 6-chloromethyl/phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazolyl containing chromeno[2,3-*b*]pyridines by reacting 4-amino-1*H*-1,2,4-triazol-5-thione with chloroacetyl or benzoyl chloride.

3. Conclusions

Triazolo[3,4-*b*]thiadiazoles represent an important class of fused nitrogen and sulfur-containing heterocyclic compounds, which have attracted great interest in medicinal chemistry owing to their wide range of biological activities, such as antitumor, antibacterial, antifungal,

antitubercular, anticonvulsant, anti-inflammatory, neuroprotective, and antioxidant action. The presence of triazolo[3,4-*b*]thiadiazole system as a part of various therapeutically important molecules can be a determinant for its physicochemical and pharmacokinetic properties. The simplicity and effectiveness of the synthetic procedures in the generation of these compounds, together with the structural diversity of triazolo[3,4-*b*][1,3,4]thiadiazole derivatives, make them a convenient and efficient tool for obtaining various biologically active substances.

The significant pharmacological potential of triazolo[3,4-*b*]thiadiazole derivatives, as well as their wide synthetic possibilities, prompts scientists to further investigation of this heterocycle as a building block for medicinal chemistry. Thereby, in this review, we discuss the synthetic routes for obtaining the fused triazolo[3,4-*b*]thiadiazole heterosystem *via* a one-pot cyclocondensation procedure of 4-amino-1,2,4-triazole-3-thiols with various carboxylic acids as the most common and preparative one. We hope that this work will provide drug designers and medicinal chemists with comprehensive information for the development of novel therapeutically useful molecules based on functionally substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles.

Author Contributions

Conceptualization, M.L. and T.Ch.; methodology, O.K.; software, R.B.; validation, A.M., and A.V.; formal analysis, O.K.; investigation, S.H.; resources, R.S.; data curation, I.Ch.; writing—original draft preparation, M.L.; writing—review and editing, I.Ch., and T.Ch.; visualization, R.B., and A.M.; supervision, A.V.; project administration, T.Ch.; funding acquisition, R.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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