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A review on synthetic approaches for obtaining and chemical modification of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole based heterocyclic compounds

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C H R O N I C L E

Article history:
Received October 4, 2023
Received in revised form
January 10, 2024
Accepted March 23, 2024
Available online
March 23, 2024

Keywords:
1,2,4-Triazolo[3,4-b][1,3,4]thiadiazoles
Cyclocondensation
Oxidative cyclization

A B S T R A C T

Triazolo[3,4-*b*]thiadiazoles are a class of heterocyclic compounds, which have attracted great interest in medicinal chemistry owing to their wide range of pharmacological activities. A number of triazoles fused to thiadiazoles are incorporated into a wide variety of therapeutically important compounds possessing a broad spectrum of biological activities. Considering such a significant pharmacological potential, as well as wide synthetic possibilities triazolo-thiadiazoles have received considerable attention from scientific community and are extensively used for construction of prospective drug-likes molecules. In this review, we summarized the literature data about the main synthetic approaches for obtaining condensed heterocyclic compounds based on triazolo[3,4-*b*][1,3,4]thiadiazole scaffold as promising objects for modern bioorganic and medicinal chemistry.

1. Introduction

1,2,4-Triazoles and 1,3,4-thiadiazoles represent an important class of heterocyclic compounds possessing a wide spectrum of biological activities. In particular, triazoles have received much significant attention in last few decades on the field of medicinal chemistry because of their diversified biological properties like anticancer,[1] antibacterial,[2] antifungal,[3] antitubercular,[4] antitrypanosomal,[5] antiviral,[6] anti-inflammatory,[7] antioxidant,[8] and anticonvulsant[9] properties. Also, there are some known drugs containing 1,2,4-triazole moiety, e.g. Rizatriptan, Trapidil, Trazodone, Anastrozole, Letrozole, Ribavirin, and Loreclezole.[10]

On the other hand, different classes of thiadiazole compounds have been investigated, many of which have been found to be important scaffolds with a broad spectrum of pharmacological activities. Particularly, 1,3,4-thiadiazoles are much explored for their broad spectrum of biological activities including anticancer,[11] anti-inflammatory,[12] antitubercular,[13] antibacterial,[14] antifungal,[15] antiviral,[16] antitrypanosomal,[17] antioxidant,[18] antidiabetic,[19] anticonvulsant[20] action etc. Also, there are numerous reviews in the few last year's focusing on the chemical features, main approaches to the synthesis, modification, and pharmacological potential of 1,3,4-thiadiazole derivatives.[21-23]

Based on the conception of a hybrid-pharmacophore approach, it was observed that the combination of these two moieties into a single molecular scaffold may be a great value in designing and identification of new potent drug candidates. Thus, triazolo-thiadiazoles are an important class of fused heterocyclic ring system being studied for a wide range of pharmacological activities such as anticancer,[24] antibacterial,[25,26] antifungal,[26] anti-inflammatory,[27,28] analgesic,[28] anticonvulsant,[29] anti-diabetic,[30] cyclooxygenase inhibitory[31] action etc. It's considered that the triazoles fused to thiadiazoles exhibit various therapeutically important properties probably due to the existence of N-C-S fragments in the ring. Also, the condensed triazolothiadiazole system can be considered as a cyclic analogue of two very important components – thiosemicarbazide and biguanide which exhibit diverse biological activity.[32]

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doi: 10.5267/j.ccl.2024.3.007

In the present review, we summarized the literature data about the main synthetic approaches for oobtaining of heterocyclic compounds based on fused 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole system. Also, we made an attempt to structure the available data on the synthetic methodologies depending on the chemical structure of the starting reagents and, as a result, on the nature of the substituents in the target compounds. This work is a continuation of our numerous review studies, which provide a detailed analysis of synthetic methods of the obtaining and discourse of pharmacological significance for some oxa/thia-containing diazaheterocycles.[33-35]

2. Approaches for synthesis and structural modification of functionally substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives

4-Amino-3-mercapto-1,2,4-triazoles are versatile synthons for constructing various fused heterocycles including triazolo[3,4-*b*]thiadiazoles. The amino and mercapto groups of 1,2,4-triazoles serve as readily accessible nucleophilic centers for the preparation of *N*-bridged heterocycles. Possible synthetic routes of application of 5-substituted 4-amino-1,2,4-triazole-3-thiols for the obtaining various triazolo[3,4-*b*][1,3,4]thiadiazole derivatives are highlighted in **Fig. 1**.

In accordance to **Fig. 1**, depending on the chemical structure of the starting reagents and also on the nature of the substituent in position 5 of 4-aminotriazole-3-thiol a large variety of triazolo[3,4-*b*][1,3,4]thiadiazoles can be synthesized. Obtained as follows triazolo-thiadiazole derivatives may differ by various substituents in positions 3 and 6. Thus, a detailed review of synthetic protocols leading to the formation of triazolo-thiadiazole derivatives, as well as the structuring of the obtained results depending on the chemical structure of the target products, was the purpose of this work.

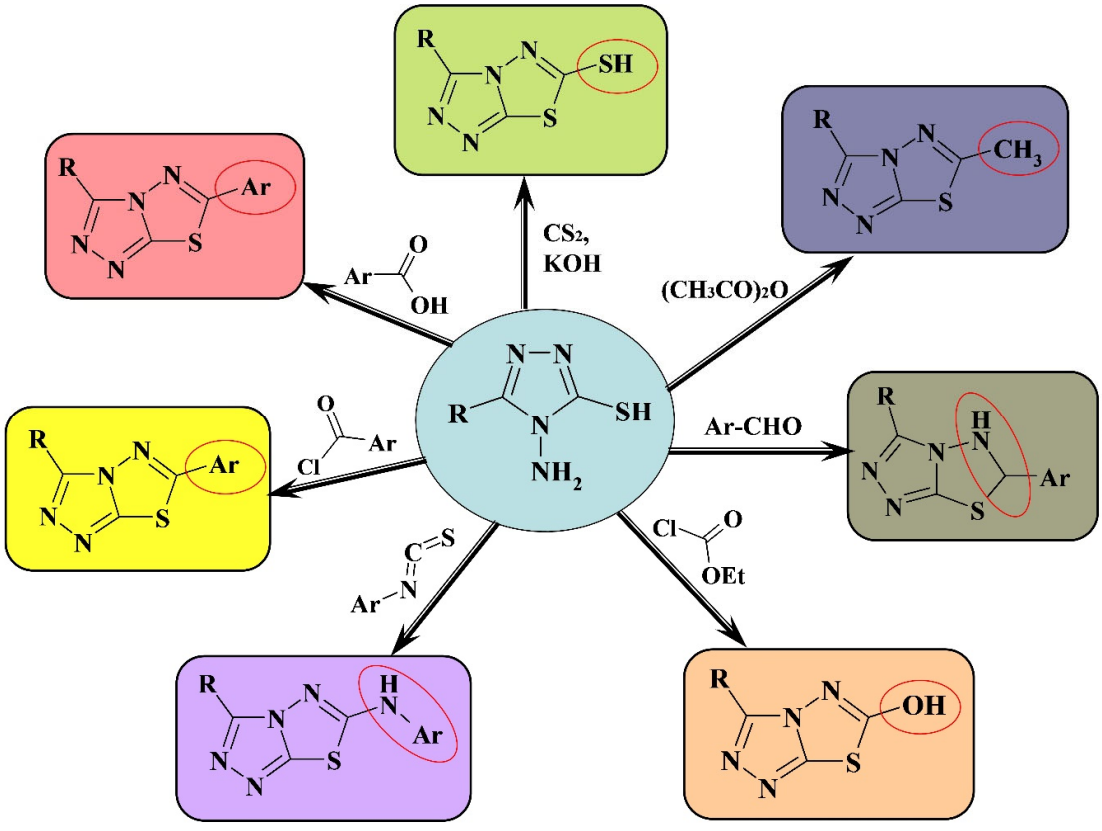
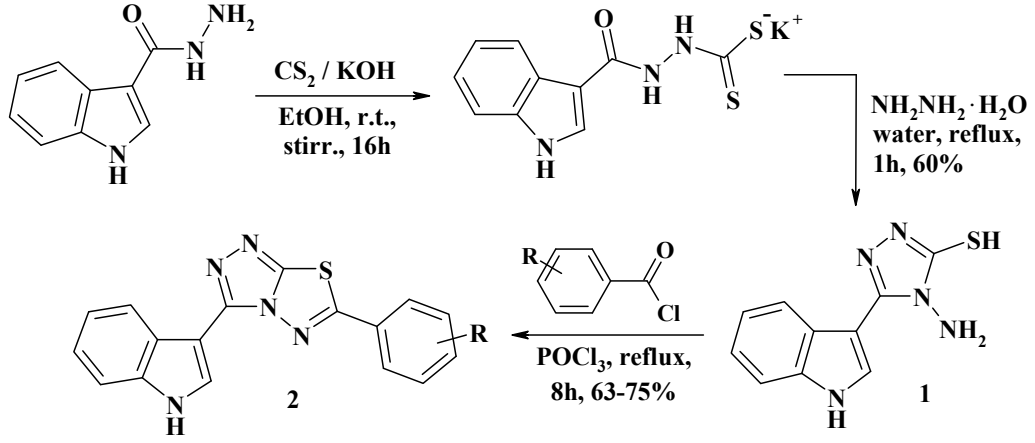


Fig. 1. Synthetic routes for obtaining triazolo[3,4-*b*][1,3,4]thiadiazole derivatives starting from 5-substituted 4-amino-1,2,4-triazole-3-thiols.

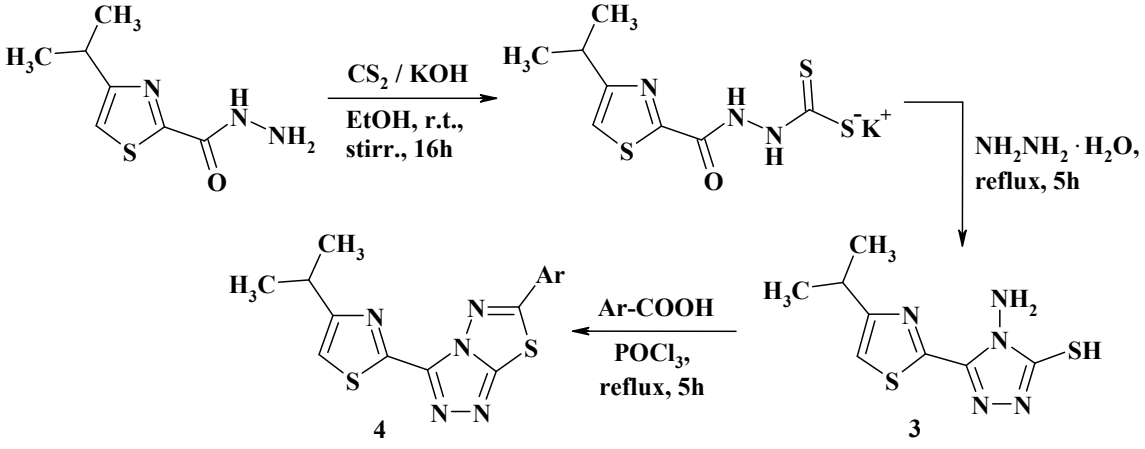
2.1. Condensation of 4-amino-4H-1,2,4-triazole-3-thiols with carboxylic acids or their chloroanhydrides in the presence of phosphorus oxochloride

The reaction of 1*H*-indole-3-carboxylic acid hydrazide with carbon disulphide and ethanolic KOH under reflux gave the corresponding potassium thiocarbamate salt (**Scheme 1**), which underwent cyclocondensation in the presence of excess hydrazine hydrate converted into indol-3-yl substituted 4-amino-1,2,4-triazole-3-thiol **1**. Further cyclization of **1** with substituted benzoyl chlorides in the presence of phosphorous oxychloride afforded the target 3-(indol-3-yl) substituted 6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **2**:[36]



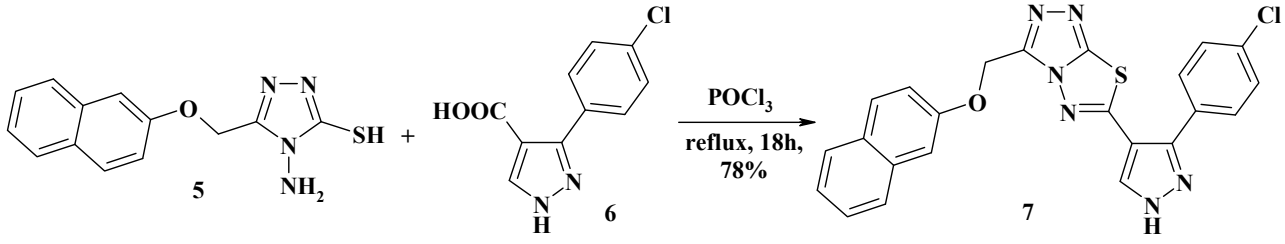
Scheme 1. Synthesis of 3-(indol-2-yl) substituted 6-aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles by cyclization of appropriate 4-amino-1,2,4-triazole-3-thiol with substituted benzoyl chlorides.

Kumar et. al.[37] reported the synthesis of 6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives containing 4-isopropylthiazole moiety **4** (**Scheme 2**) by reaction of 4-amino-5-(4-isopropyl-1,3-thiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol **3** with aromatic acids in the presence of phosphorous oxychloride:

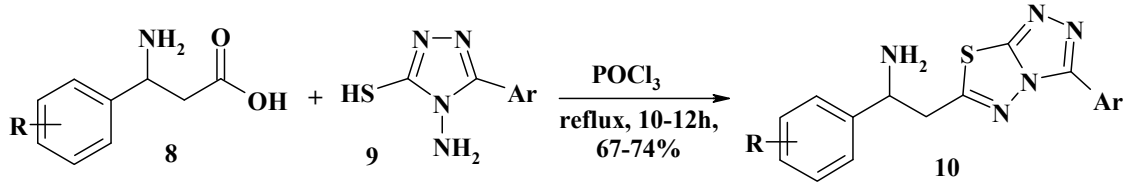


Scheme 2. Synthesis of 6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives containing 4-isopropylthiazole moiety by reaction of 4-amino-5-(4-isopropyl-1,3-thiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol with aromatic acid.

Following the interaction of 5-(naphthyl-2-oxymethyl)-4-amino-4*H*-1,2,4-triazole-3-thiol **5** with 3-(4-chlorophenyl)-pyrazole-4-carboxylic acid **6** in phosphorous oxychloride medium (**Scheme 3**) the synthesis of 3-(naphthyl-2-oxymethyl) substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **7** containing pyrazole moiety was carried out:[38]



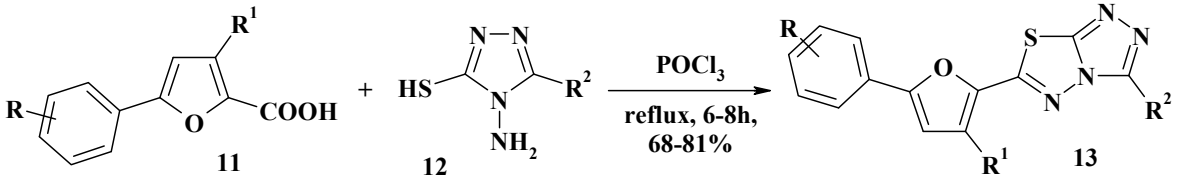
Scheme 3. Synthesis of 3-(naphthyl-2-oxymethyl) substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole containing pyrazole moiety by interaction of 4-amino-4*H*-1,2,4-triazole-3-thiol with 3-(4-chlorophenyl)-pyrazole-4-carboxylic acid.



Scheme 4. Synthesis of 6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives containing 2-phenyl-2-aminoethyl function by cyclocondensation of 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiols with β-amino acids.

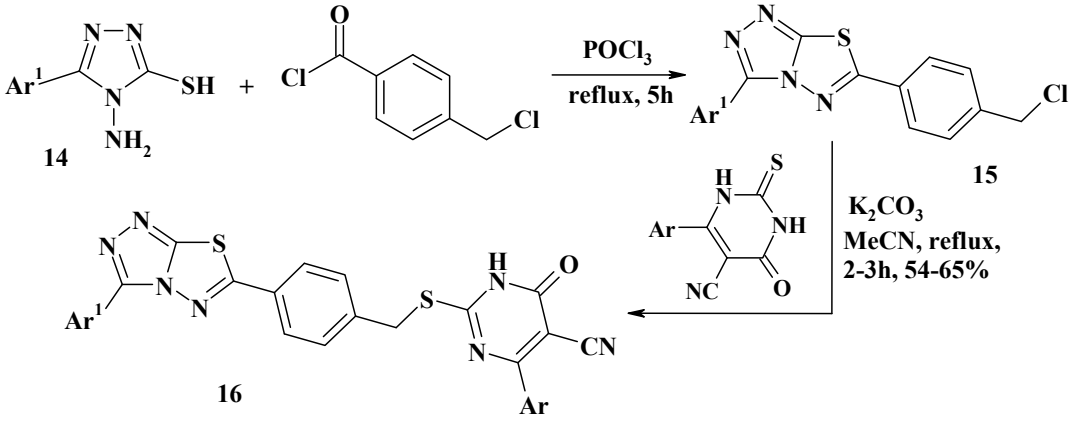
A series of 6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives containing 2-phenyl-2-aminoethyl function **10** (**Scheme 4**) were prepared by cyclocondensation of β-amino acids **8** with 4-amino-1,2,4-triazole-3-thiols **9** in the presence of phosphorous oxychloride under reflux condition:[39]

Myrko et al.[40] established that cyclization of 5-arylfuran-2-carboxylic acids **11** with 5-substituted 4-amino-4*H*-1,2,4-triazole-3-thiols **12** by heating in phosphorus oxochloride (**Scheme 5**) lead to the formation of 6-(5-arylfuran-2-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **13**:



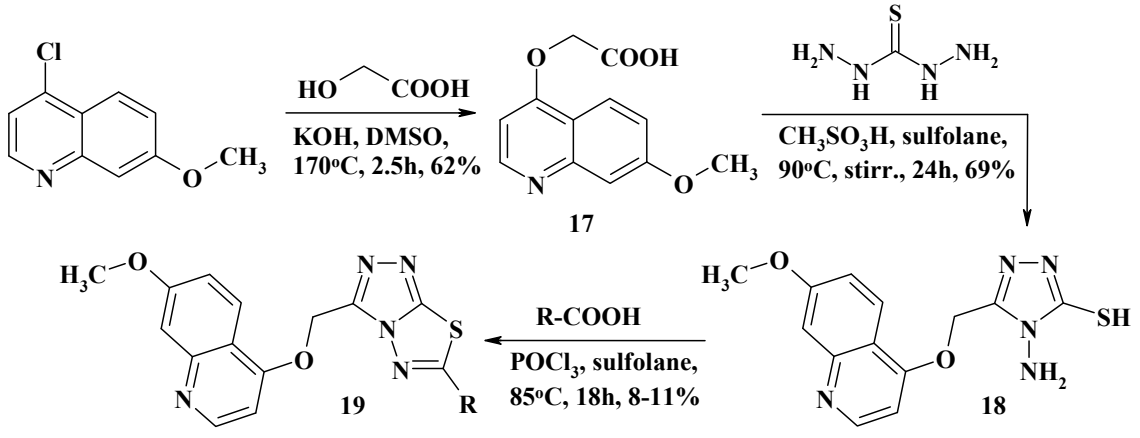
Scheme 5. Synthesis of 6-(5-arylfuran-2-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles by cyclization of 5-arylfuran-2-carboxylic acids with 5-substituted 4-amino-4*H*-1,2,4-triazole-3-thiols.

Design and synthesis of novel triazolo[3,4-*b*]thiadiazole derivatives containing thiouracil moiety **16** (**Scheme 6**) were suggested by Cui et al.[41] Initially, the starting 4-amino-5-aryl-4*H*-1,2,3-triazole-3-thiols **14** reacted with 4-(chloromethyl)benzoyl chloride in phosphorus oxochloride medium to give 3-aryl-6-(4-chloromethylphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **15**. The target compounds **16** were obtained by reacting **15** and thiouracil in acetonitrile at reflux temperature:



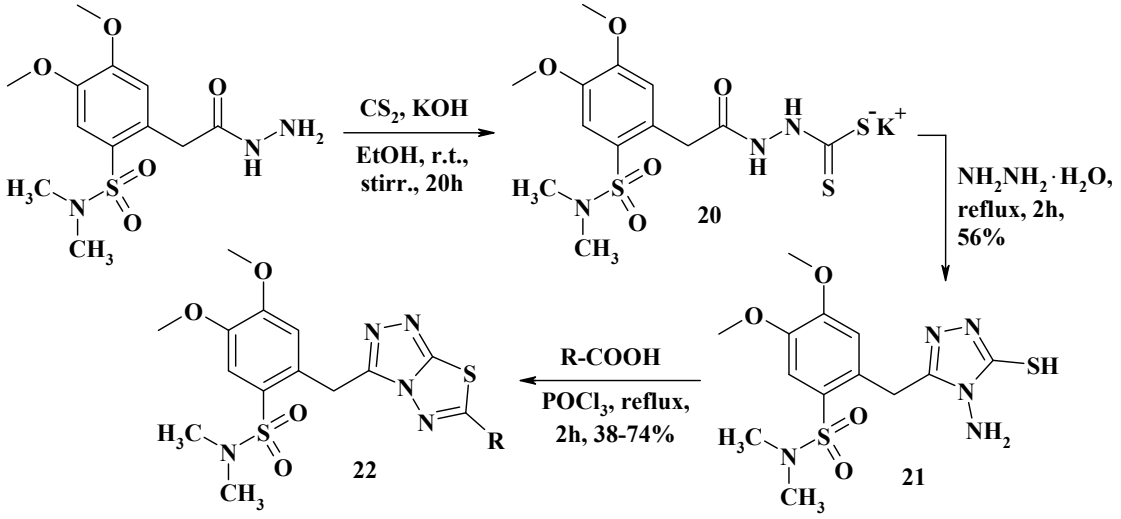
Scheme 6. Synthesis of 3-aryl-6-(4-chloromethylphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles containing thiouracil moiety by reaction of 4-amino-5-aryl-4*H*-1,2,3-triazole-3-thiols with 4-(chloromethyl)benzoyl chloride.

Interaction of (7-methoxyquinolin-4-yloxy)-acetic acid **17** with thiocarbohydrazide in the presence of methanesulfonic and sulfolane afforded the desired 4-amino-5-(7-methoxyquinolin-4-yloxymethyl)-4*H*-1,2,4-triazole-3-thiol **18** (**Scheme 7**). Further condensation of **18** with heteryl carboxylic acid under refluxing $POCl_3$ yielded the target 6-heteryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles containing methoxyquinolin-4-yloxymethyl moiety **19** in good yields:[42]



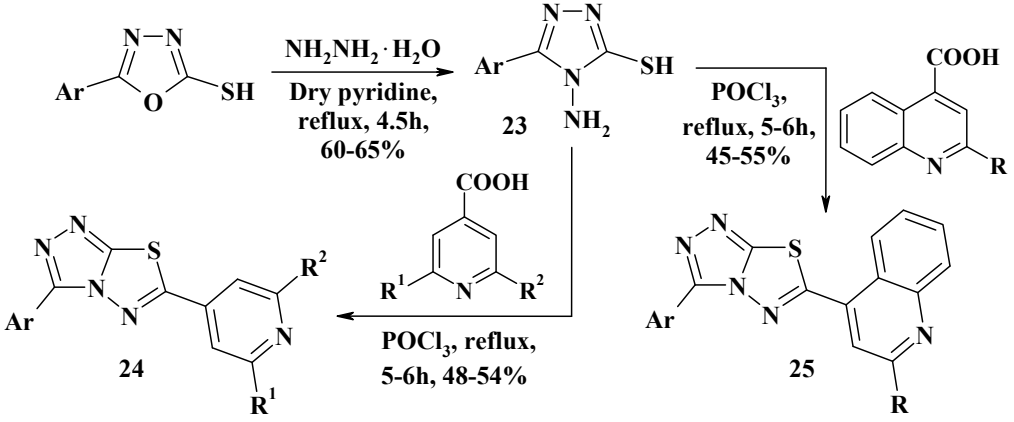
Scheme 7. Synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles containing methoxyquinolin-4-yloxymethyl moiety by reaction of 4-amino-5-(7-methoxyquinolin-4-yloxymethyl)-4*H*-1,2,4-triazole-3-thiol with heteryl carboxylic acid.

Based on starting 2-(*N*,*N*-dimethylsulfamoyl)-4,5-dimethoxy-phenylacetylacetylhydrazide by reaction with carbon disulfide in the presence of potassium hydroxide in ethanol the synthesis of corresponding potassium thiocarbamate **20** was carried out (**Scheme 8**). The obtained intermediate **20** underwent ring closure with excess of hydrazine hydrate to afford 5-[2-(*N*,*N*-dimethylsulfamoyl)-4,5-dimethoxybenzyl]-4-amino-4*H*-1,2,4-triazole-3-thiol **21**, which was further converted to 3,6-disubstituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **22** by condensing with various aromatic acids in the presence of phosphorus oxychloride:[43]



Scheme 8. Synthesis of 3,6-disubstituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles by reaction of 5-[2-(*N*,*N*-dimethylsulfamoyl)-4,5-dimethoxybenzyl]-4-amino-4*H*-1,2,4-triazole-3-thiol with various aromatic acids.

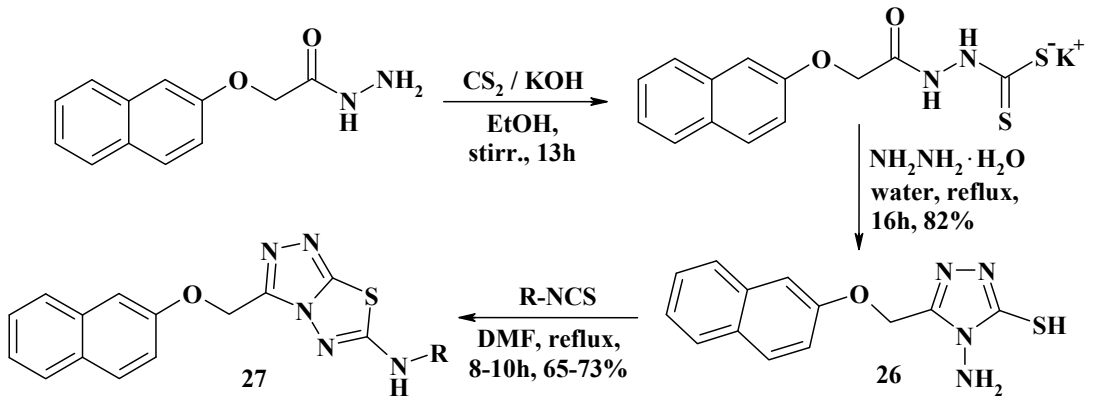
Heating of 2-aryl-5-mercapto-1,3,4-oxiadiazoles and hydrazine hydrate in dry pyridine expectedly resulted in 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiols **23** (**Scheme 9**), which on reaction with quinoline-4-carboxylic or pyridine-4-carboxylic acid derivatives at the presence of phosphorous oxychloride were modified into the 6-(quinolin-4-yl/pyridine-4-yl) substituted 3-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **24** and **25**:[44]



Scheme 9. Synthesis of 6-(quinolin-4-yl/pyridine-4-yl) substituted 3-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles by reaction of 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiols with quinoline-4-carboxylic or pyridine-4-carboxylic acid derivatives.

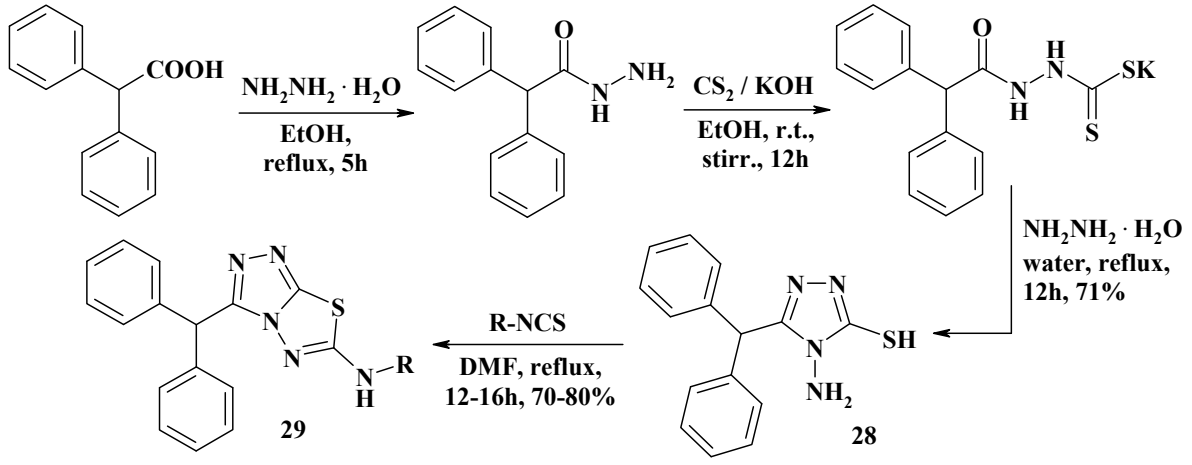
2.2. Synthesis of 6-alkyl(aryl)amino-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles by cyclization of 4-amino-4H-1,2,4-triazole-3-thiols with alkyl/aryl isothiocyanates

Modification of (naphthalen-2-yloxy)acetic acid hydrazide by reaction with carbon disulfide and potassium hydroxide in ethanol with following cyclization under the action of hydrazine hydrate (**Scheme 10**) gave 4-amino-5-[(naphthalen-2-yloxy)methyl]-4*H*-1,2,4-triazole-3-thiol **26**. Further interaction of **26** with aryl/alkyl isothiocyanates in the presence of DMF provided 6-aryl/alkylamino derivatives **27**:[45]



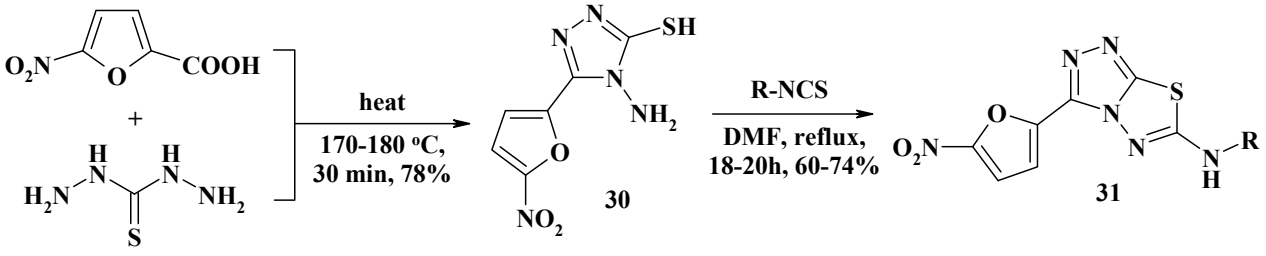
Scheme 10. Synthesis of 3-(naphthalene-2-oxy)methyl substituted 6-aryl(alkyl)amino-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles by interaction of 4*H*-1,2,4-triazole-3-thiol with aryl/alkyl isothiocyanates.

Starting from diphenylacetic acid following multistep sequence transformations the synthesis of intermediate key – 4-amino-5-diphenylmethyl-4*H*-1,2,4-triazole-3-thiol **28** was carried out (**Scheme 11**). Successive condensation of **28** with aryl/alkyl isothiocyanates in the presence of DMF afforded the target 3-diphenylmethyl substituted 6-aryl(alkyl)amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **29**:[46]



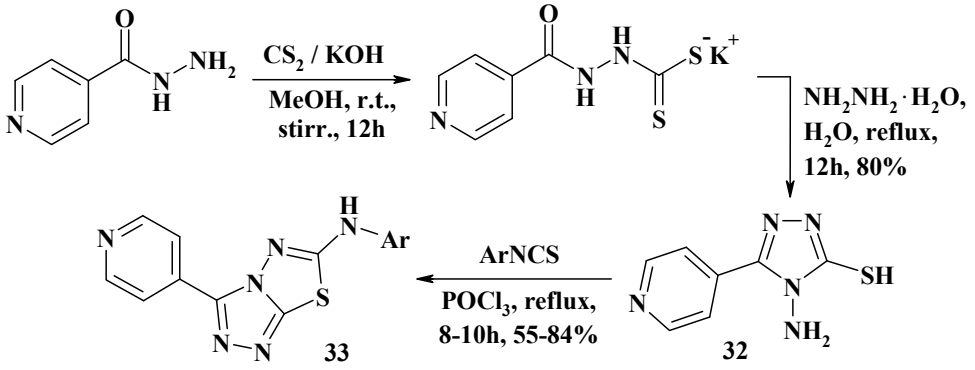
Scheme 11. Synthesis of 3-diphenylmethyl substituted 6-aryl(alkyl)amino-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles by condensation of 4-amino-5-diphenylmethyl-4*H*-1,2,4-triazole-3-thiol with aryl/alkyl isothiocyanates.

Obtained by a one-step condensation of 5-nitro-2-furoic acid with thiocarbohydrazide, 4-amino-5-(5-nitrofuran-2-yl)-4*H*-1,2,4-triazole-3-thiol **30** (**Scheme 12**) easily reacted with alkyl/aryl isothiocyanates in DMF medium to afford 6-alkyl(aryl)amino-3-(5-nitrofuran-2-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **31**:[47]



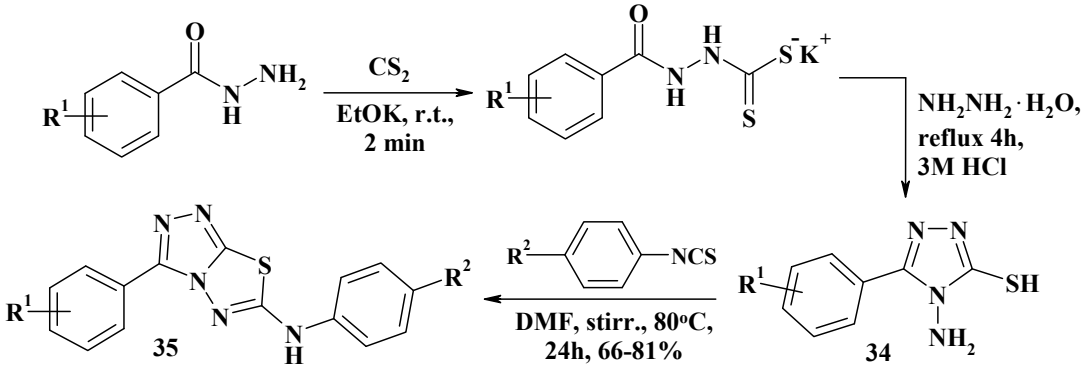
Scheme 12. Synthesis of 6-alkyl(aryl)amino-3-(5-nitrofuran-2-yl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-(5-nitrofuran-2-yl)-4*H*-1,2,4-triazole-3-thiol with alkyl/aryl isothiocyanates.

The synthesis of 6-arylamino-1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazoles containing pyridine fragment **33** (**Scheme 13**) was achieved through the reaction of 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-thiol **32** with various aryl isothiocyanates in refluxing pyridine for 2-3h:[48]



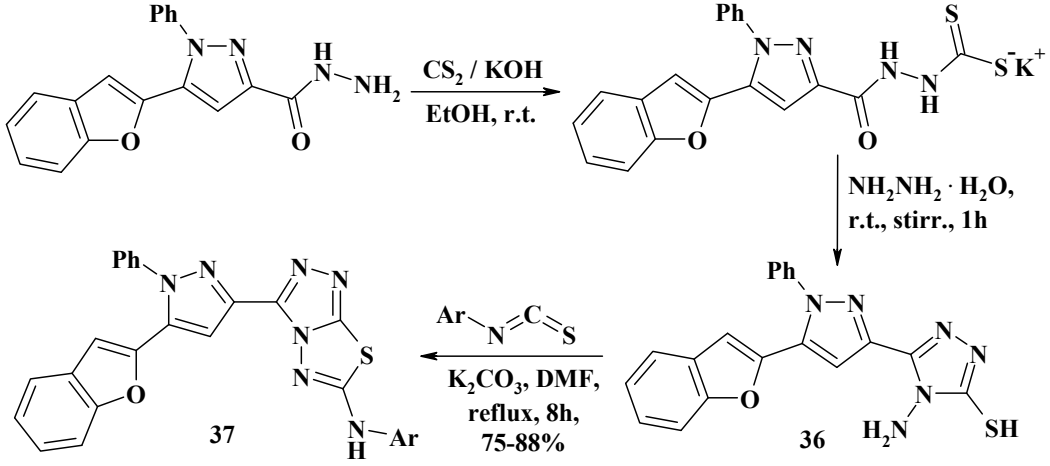
Scheme 13. Synthesis of 6-arylamino-1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazoles containing pyridine fragment by condensation of 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-thiol with various aryl isothiocyanates.

Reacting the obtained as shown at the Scheme **14** 4-amino-5-aryl-1,2,4-triazole-3-thiols **34** with 4-chloro(bromo)phenyl isothiocyanate in the anhydrous dimethylformamide environment to give the expected 3-aryl-6-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **35**:[49]



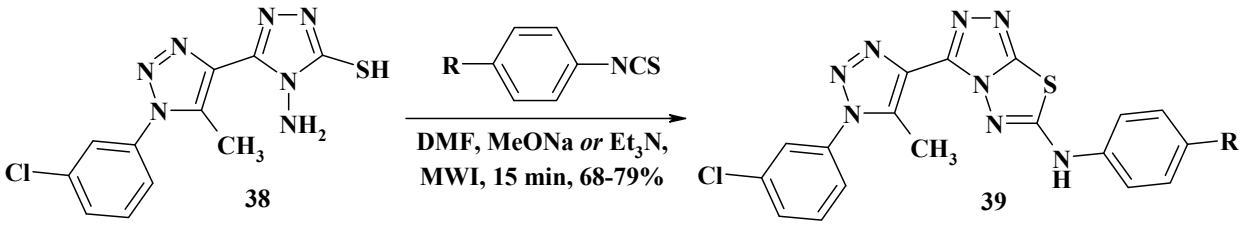
Scheme 14. Synthesis of 3-aryl-6-arylamino-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles heterocyclization by reacting of 4-amino-5-aryl-1,2,4-triazole-3-thiols with 4-chloro(bromo)phenyl isothiocyanate.

A simple efficient synthesis technique by one pot cyclocondensation reaction of 5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol **36** with substituted aryl isothiocyanates in DMF medium and K_2CO_3 presence (**Scheme 15**) afforded a series of benzofuran and pyrazole containing 6-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **37**:[50]



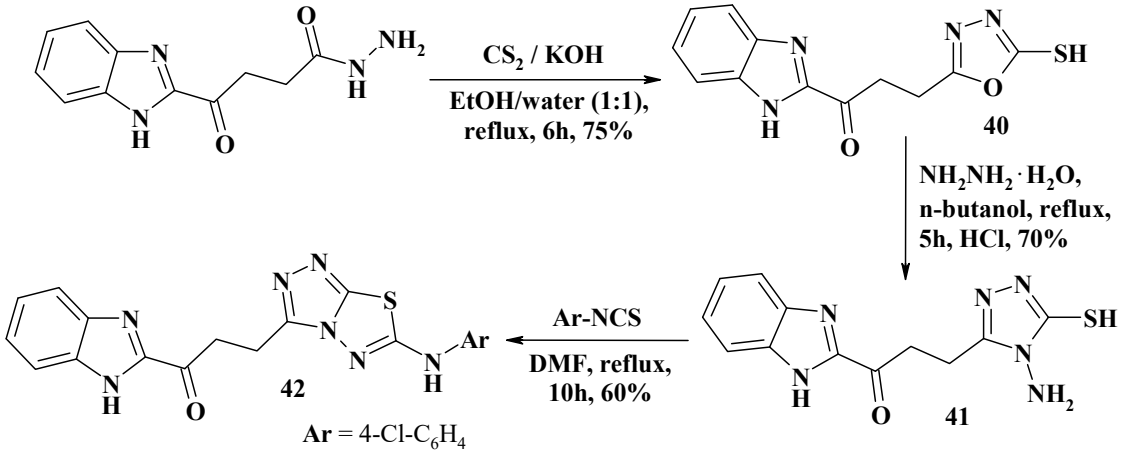
Scheme 15. Synthesis of benzofuran and pyrazole containing 6-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles by cyclocondensation of 5-substituted -4-amino-4*H*-1,2,4-triazole-3-thiol with aryl isothiocyanates.

Modification of 4-amino-1,2,4-triazole-3-thiol **38** *via* heterocyclization with aryl isothiocyanate in DMF medium without catalyst, or in the presence of a mild catalyst (e.g. sodium methoxide or triethylamine) under MWI (**Scheme 16**) afforded the desired 1,2,3-triazole substituted triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **39**:[51]



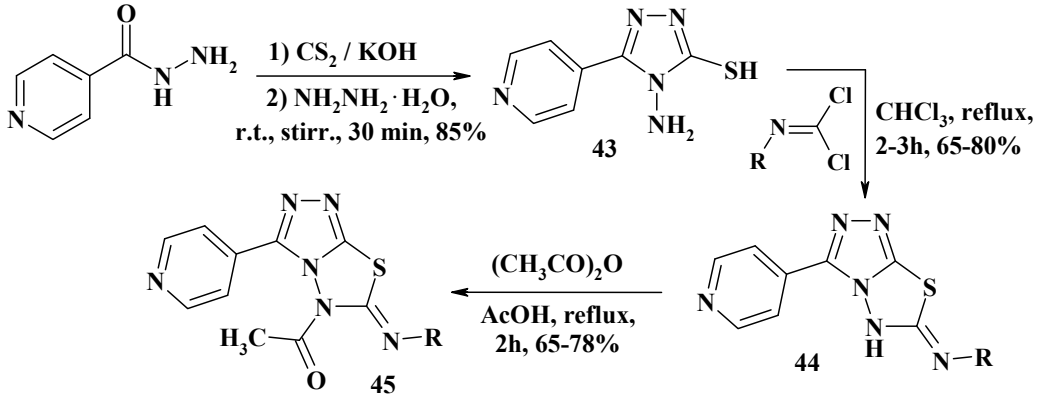
Scheme 16. Synthesis of 1,2,3-triazole substituted triazolo[3,4-*b*][1,3,4]thiadiazole derivatives *via* heterocyclization of 4-amino-1,2,4-triazole-3-thiol with aryl isothiocyanate in DMF medium.

Through the reaction of 3-(1*H*-benzo[*d*]imidazol-2-yl)-1,3,4-oxadiazole-5-thiol **40** with hydrazine hydrate Husain et al.[52] achieved the synthesis of intermediate 4-amino-4*H*-1,2,4-triazole-3-thiol **41** (**Scheme 17**). Further interaction of **41** with 4-chlorophenyl isothiocyanate in refluxing DMF provided the target benzo[*d*]imidazole containing 6-(4-chlorophenylamino)-1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazole **42**:



Scheme 17. Synthesis of benzo[*d*]imidazole containing 6-alkyl/aryl(amino)-1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazoles by interaction of 4-amino-4*H*-1,2,4-triazole-3-thiol with aromatic/aliphatic acids or 4-chlorophenyl isothiocyanate.

The synthesis of 6-arylimino-3-(pyridin-4-yl)-1,2,4-triazolo-[3,4-*b*]-[1,3,4]-thiadiazoles **44** was carried out by interaction 4-amino-3-mercapto-5-(pyridin-4-yl)-4*H*-1,2,4-triazole **43** with *N*-aryl isocyanodichlorides followed by the basification with dilute ammonium hydroxide (**Scheme 18**). Further acylation of **44** with acetic anhydride passes through the endocyclic nitrogen atom and afforded N^5-acetyl derivatives **45**:[53]

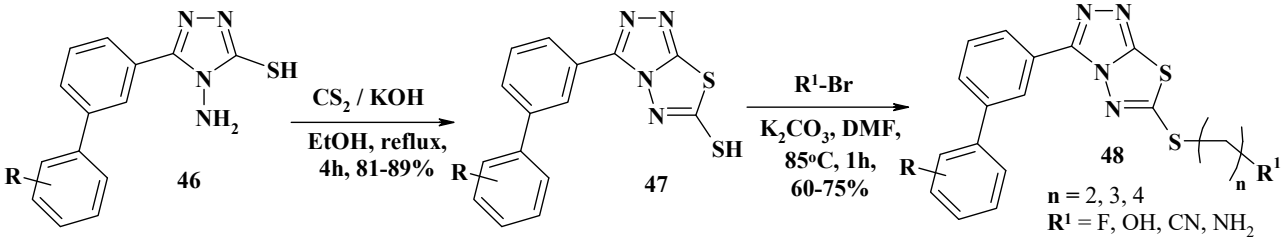


Scheme 18. Synthesis of 6-arylimino-3-(pyridin-4-yl)-1,2,4-triazolo-[3,4-*b*]-[1,3,4]-by condensation of 4-amino-3-mercapto-5-pyridin-4-yl-4*H*-1,2,4-triazole with *N*-aryl isocyanodichlorides.

2.3. Synthesis of 3-substituted 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole-6-thiols by condensation of 4-amino-4H-1,2,4-triazole-3-thiols with carbon disulfide under basic conditions

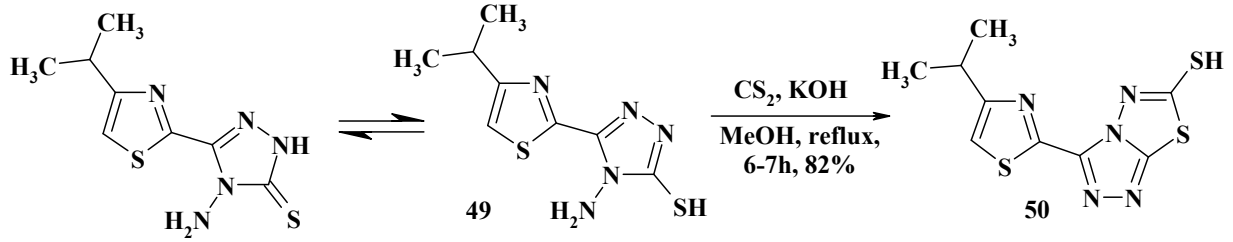
A series of 3-(1,1'-biphenyl)-3-yl substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiols **47** (**Scheme 19**) were prepared by reacting 4-amino-5-(substituted-(1,1'-biphenyl)-3-yl)-4*H*-1,2,4-triazole-3-thiols **46** with carbon disulfide, potassium hydroxide in ethanol as solvent. Further the regioselective synthesis of *S*-alkylated compounds **48** was performed

by heating compounds **47** with alkyl halides and potassium carbonate in *N,N*-dimethylformamide at 85°C for 2 h, while under microwave irradiation, it required shorter reaction time (5 min) and higher product yields making it superior method:[54]



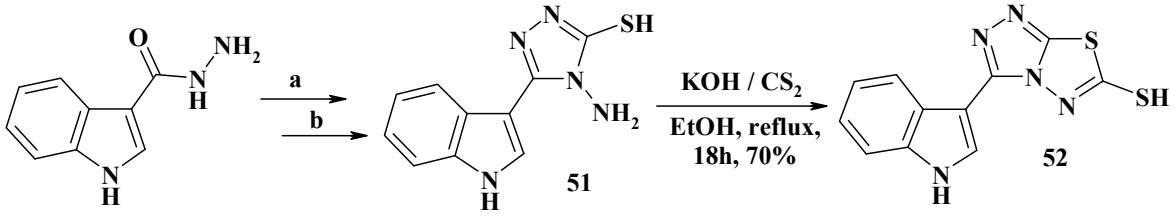
Scheme 19. Synthesis of 3-(1,1'-biphenyl)-3-yl substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiols by reaction of 4-amino-5-(substituted-(1,1'-biphenyl)-3-yl)-4*H*-1,2,4-triazole-3-thiols with carbon disulfide.

Modification of 4-amino-5-(4-isopropyl-1,3-thiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol **49** to 6-mercapto triazolo[3,4-*b*][1,3,4]thiadiazole derivative **50** (**Scheme 20**) was achieved by treating of **49** with carbon disulfide and potassium hydroxide:[55]



Scheme 20. Synthesis of 4-isopropylthiazole containing 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiol by reacting of 4-amino-5-(4-isopropyl-1,3-thiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol with aromatic acid.

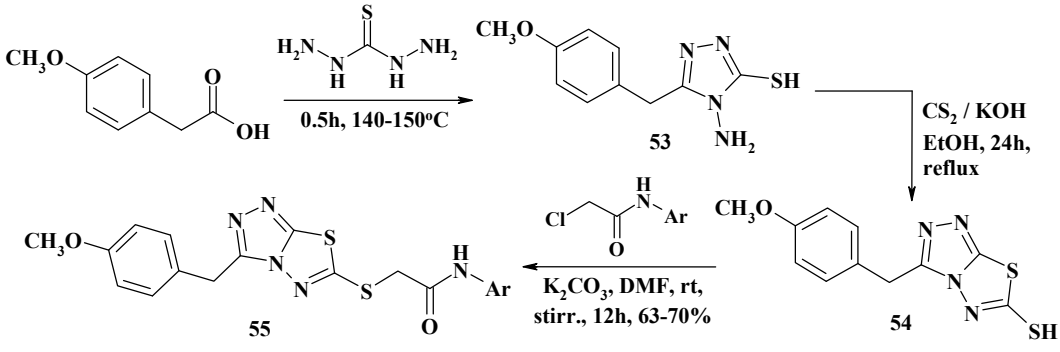
Starting from 1*H*-indole-3-carboxylic acid hydrazide Hamdy et al.[36] performed the synthesis of indol-3-yl substituted 4-amino-1,2,4-triazole-3-thiol **51** (**Scheme 21**), which further cyclized in the presence of carbon disulphide under basic conditions to provide the corresponding 3-(indol-3-yl) substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiol **52**:



a) CS_2, KOH, EtOH, stirring, 16h; b) $NH_2NH_2 \cdot H_2O$, water, reflux, 1h, 60%.

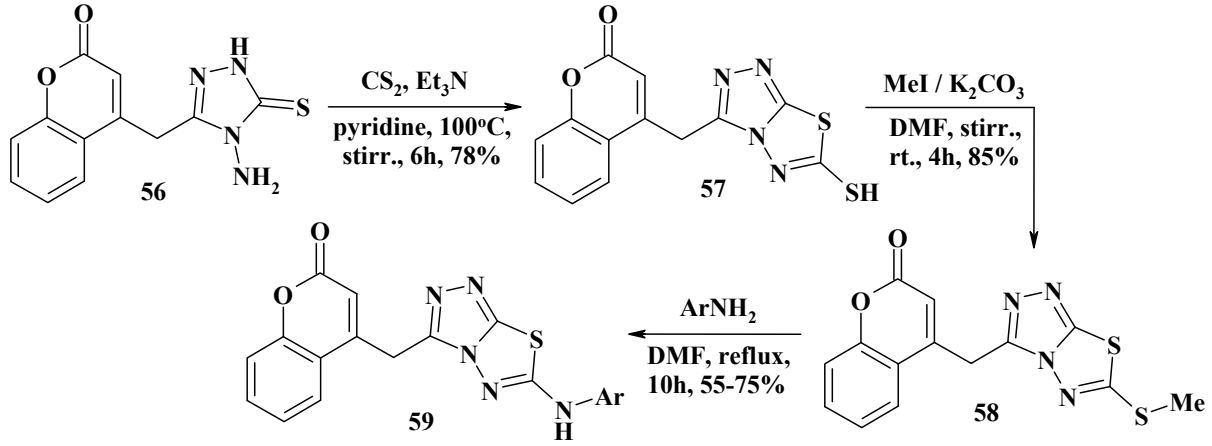
Scheme 21. Synthesis of 3-(indol-3-yl) substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiol by cyclization of 4-amino-4*H*-1,2,4-triazole-3-thiol in the presence of carbon disulphide under basic conditions.

Upon condensation of methoxyphenylacetic acid with thiocarbohydrazide in an oil bath at 140-150°C 5-(4-methoxybenzyl)-4-amino-4*H*-1,2,4-triazole-3-thiol **53** was prepared (**Scheme 22**).[56] Further, heating **53** with carbon disulfide in ethanol containing potassium hydroxide to give an appropriate triazolo[3,4-*b*]thiadiazole-6-thiol **54**. Finally, stirring **54** with 2-chloro-*N*-(4-substituted phenyl)acetamides in DMF containing potassium carbonate furnished the proposed *S*-alkyl 1,2,4-triazolo[3,4-*b*]thiadiazole derivatives **55**:



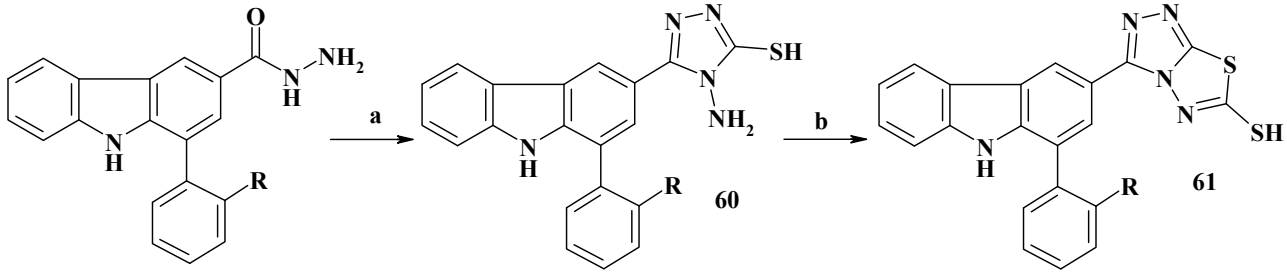
Scheme 22. Synthesis of 3-substituted 1,2,4-triazolo[3,4-*b*]thiadiazole-6-thiol by condensation of 5-(4-methoxybenzyl)-4-amino-4*H*-1,2,4-triazole-3-thiol with carbon disulfide.

The reaction of 3-[(coumarin-4-yl)methyl]-4-amino-1*H*-1,2,4-triazole-5(4*H*)-thione **56** with carbon disulfide in pyridine under reflux furnished 6-mercapto-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **57** (**Scheme 23**), which by reacting with iodomethane was converted into the methylthio analogue **58**.[57] Further interaction of **58** with primary aromatic amines *via* prolonged heating in DMF resulted in replacement of the methylthio group with an arylamino substituent leading to the 6-arylamino derivatives **59**:



Scheme 23. Synthesis of 2*H*-1-benzopyran-2-one substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiol by condensation of 3-[(coumarin-4-yl)methyl]-4-amino-1*H*-1,2,4-triazole-5(4*H*)-thione with carbon disulfide.

The synthesis of β-carboline derivatives bearing 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiol motif **61** (**Scheme 24**)[58] was achieved by treating the obtained by known metologies 4-amino-4*H*-1,2,4-triazole-3-thiol[59] **60** with carbon disulfide and potassium hydroxide:

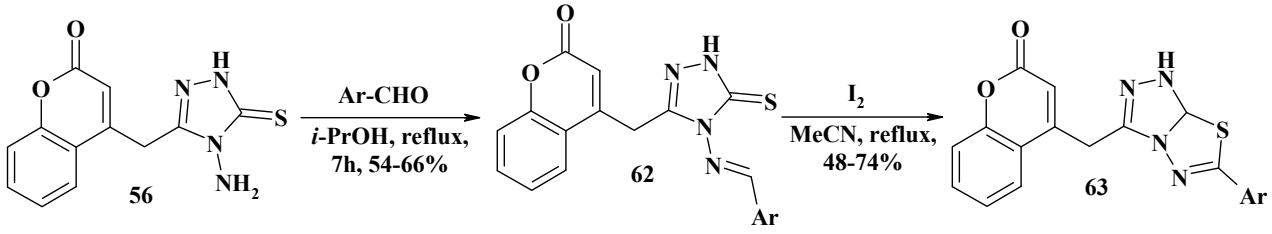


(a) i) CS_2, KOH, EtOH, reflux, 48h; ii) $NH_2NH_2 \cdot H_2O$, reflux, 4 days, 80-85%;
(b) i) CS_2, KOH, MeOH, 0-5°C, stirring; ii) then reflux, 48h, 54%.

Scheme 24. Synthesis of β-carboline substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiols by condensation of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol with carbon disulfide and potassium hydroxide.

2.4. Synthesis of 6-aryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles by oxidative cyclization of 4-(arylidene)amino-4H-1,2,4-triazole-3-thiones or N-thiadiazolyl substituted hydrazones

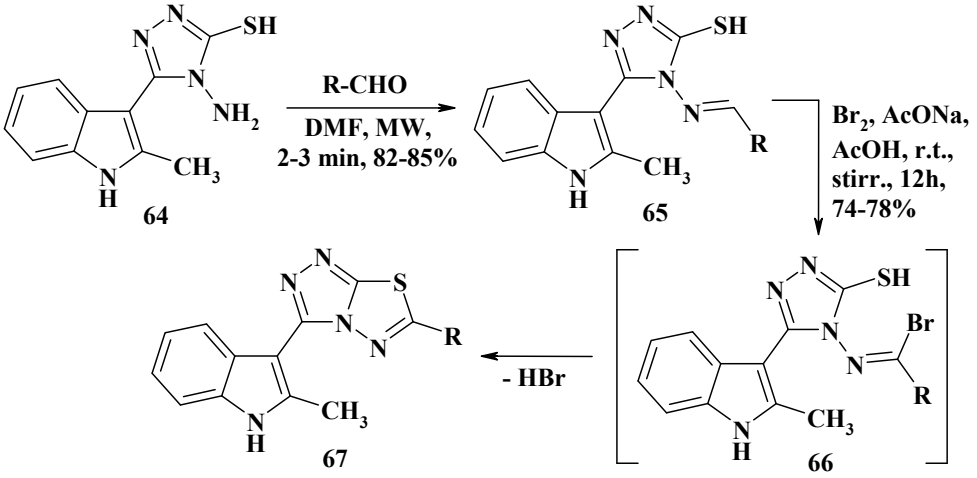
The reaction of 3-substituted 4-amino-1*H*-1,2,4-triazole-5(4*H*)-thione **56** (**Scheme 25**) with different aromatic aldehydes in propanol containing catalytic amount of acetic acid occurs with the formation of 4-(arylidene)amino derivatives **65**. After compounds **62** were subjected to undergo oxidative cyclization by the action of iodine in acetonitrile medium and successfully cyclized to 3-[(coumarin-4-yl)methyl]-6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **63**:[57]



Scheme 25. Synthesis of 2*H*-1-benzopyran-2-one substituted 6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles by oxidative cyclization of 3-[(coumarin-4-yl)methyl]-4-(arylidene)amino-1*H*-1,2,4-triazole-5(4*H*)-thione with iodine.

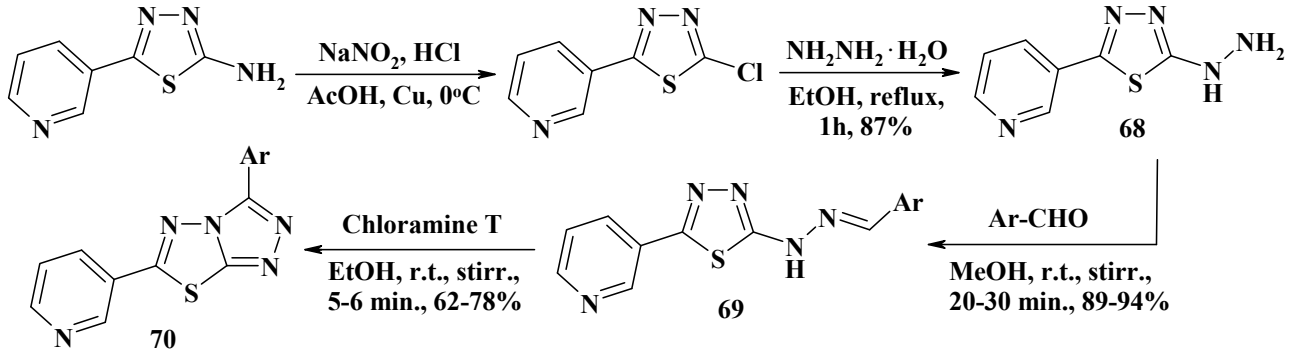
Condensation of 2-methyl-1*H*-indol-3-yl substituted 4-amino-5-mercapto-4*H*-1,2,4-triazol **64** with different aldehydes in dimethylformamide under microwave irradiation in the presence of catalytic amount of HCl to give the corresponding 4-

arylideneamino-1,2,4-triazole-5-thiol Schiff's bases **65** (**Scheme 26**).[60] Further bromination of **65** at room temperature in acetic acid in the presence of anhydrous sodium acetate afforded the respective 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **67** bearing indole moiety through the dehydrobromination stage of non-isolable intermediates **66**:



Scheme 26. Synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles containing indole moiety by bromination following cyclization of corresponding 4-arylideneamino-1,2,4-triazole-5-thiol Schiff's bases.

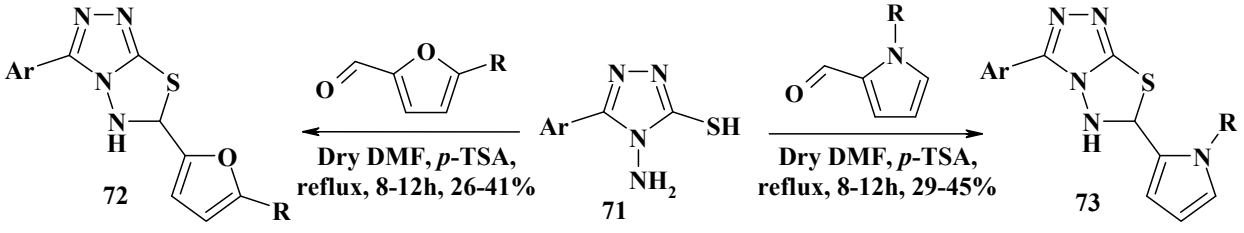
The required *N*-thiadiazolyl substituted hydrazones **69** were prepared in good yields by the condensation of 1-(5-(pyridine-3-yl)-1,3,4-thiadiazol-2-yl)hydrazine **68** with the appropriate aldehydes (**Scheme 27**).[61] The synthesis of 3,6-disubstituted triazolo[3,4-*b*][1,3,4]thiadiazoles containing pyridine moiety **70** was carried out by a rapid and convenient oxidative cyclization of **69** promoted by chloramine T trihydrate at ambient temperature:[61]



Scheme 27. Synthesis of 3,6-disubstituted triazolo[3,4-*b*][1,3,4]thiadiazoles containing pyridine moiety by oxidative cyclization of *N*-heteroaryl substituted hydrazones promoted by chloramine T trihydrate.

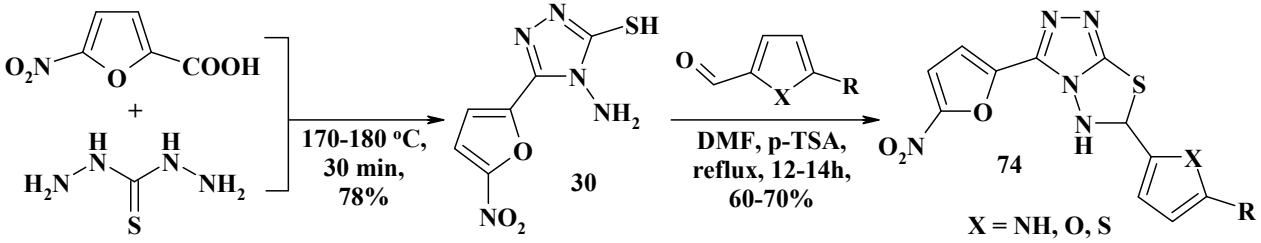
2.5. Synthesis of 3,6-disubstituted 5,6-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles by condensation of 4-amino-4H-1,2,4-triazole-3-thiols with aryl/heteryl carbaldehydes

The interaction of 4-amino-5-aryl-3-1,2,4-triazole-3-thiols **71** with furan- or pyrrole-2-carbaldehyde derivatives in the presence of p-toluene sulfonamides (*p*-TSA) (**Scheme 28**)[62] gives the corresponding 6-furan/pyrrole substituted 5,6-dihydro-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles **72** and **73**:



Scheme 28. Synthesis of 6-furan/pyrrole substituted 5,6-dihydro-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles by interaction of 4-amino-5-aryl-3-1,2,4-triazole-3-thiols with furan- or pyrrole-2-carbaldehydes.

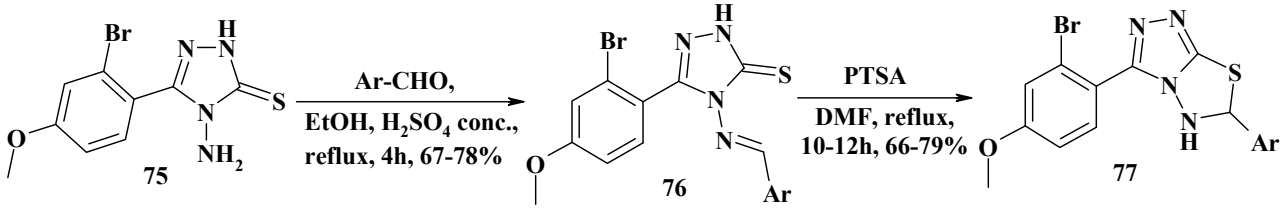
Following the reaction of 4-amino-5-(5-nitrofuran-2-yl)-4*H*-1,2,4-triazole-3-thiol **30** with hetero aromatic aldehydes (**Scheme 29**) in the presence of *p*-toluene sulfonic acid (p-TSA) as a catalyst the appropriate 6-heteryl substituted 3-(5-nitrofuran-2-yl)-5,6-dihydro-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **74** were obtained:[47]



Scheme 29. Synthesis of 6-heteryl substituted 3-(5-nitrofuran-2-yl)-5,6-dihydro-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-(5-nitrofuran-2-yl)-4*H*-1,2,4-triazole-3-thiol with hetero aromatic aldehydes.

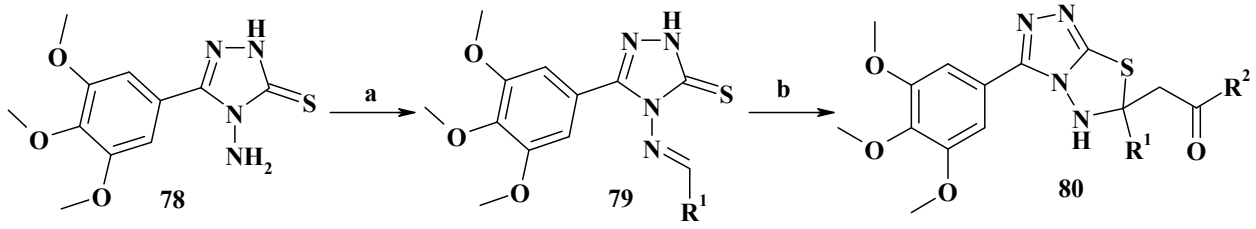
2.6. Synthesis of 3,6-disubstituted 5,6-dihydro-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles by intramolecular cyclization of 4-(arylidene)amino-5-aryl-4H-1,2,4-triazole-3-thiones

Interaction of 4-amino-5-(2-bromo-5-methoxyphenyl)-2,3-dihydro-3*H*-1,2,4-triazole-3-thione **75** with aromatic aldehydes in refluxing ethanol afforded the respective hydrazones **76** (**Scheme 30**),[63] which undergoes intramolecular cyclization in the presence of catalytic amount of *p*-toluene sulfonic acid to give corresponding 5,6-dihydro-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **77**:



Scheme 30. Synthesis of 5,6-dihydro-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives by intramolecular cyclization of 4-amino-2,3-dihydro-3*H*-1,2,4-triazole-3-thione based hydrazones in the presence of *p*-toluene sulfonic acid.

Through the condensation of 3-(3,4,5-trimethoxyphenyl)-4-amino-1*H*-1,2,4-triazole-5(4*H*)-thione **78** with substituted benzaldehydes the corresponding Schiff bases **79** were obtained (**Scheme 31**). Further interaction of **79** with phenacyl bromide or ethyl 2-bromoacetate in refluxing acetone leads to formation of the target 5,6-dihydrotriazolo[3,4-*b*][1,3,4]thiadiazoles **80** bearing 3,4,5-trimethoxyphenyl moiety:[64]



(a) R¹-CHO, AcOH, reflux; (b) phenacyl bromide or ethyl 2-bromoacetate, K_2CO_3, acetone, reflux, 67-78%.

Scheme 31. Synthesis of 5,6-dihydrotriazolo[3,4-*b*][1,3,4]thiadiazoles moiety by condensation of 4-amino-3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione Schiff bases with phenacyl bromide or ethyl 2-bromoacetate.

3. Conclusions

Triazolo[3,4-*b*][1,3,4]thiadiazoles are an important class of fused heterocyclic systems. It consists of two five-membered rings – 1,2,4-triazole and 1,3,4-thiadiazole, conjugation of which into a single molecular scaffold able to provide a synergistic effect and/or expansion of the pharmacological profile. The chemical features of triazolo[3,4-*b*][1,3,4]thiadiazoles were described in numerous research papers focusing on the main approaches for their synthesis and modification as well as their biological activity. The mentioned heterosystem can be considered as a cyclic analogue of two very important components – thiosemicarbazide and biguanide which exhibit diverse biological activity. Thus, 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole core have been incorporated into a wide variety of therapeutically interesting drug candidates including antitumor, antimicrobial, antifungal, antioxidant, antiviral, anti-inflammatory and analgesic agents etc.

In the present review we performed the literature search and highlighted the recent synthetic strategies for obtaining heterocyclic compounds based on fused triazolo[3,4-*b*]thiadiazole systems. The available synthetic protocols were divided and structured according to the chemical structure of the target products. All of these things, the wide synthetic capabilities and essential biological properties of triazolo[3,4-*b*][1,3,4]thiadiazole derivatives promote the scientists to further investigation and appliance of this heterocyclic system as a prospective building block for drug discovery.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

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