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Review

Appliance Features of 4-Amino-1,2,4-triazole-3-thiols in the Synthesis of 3,6-Disubstituted [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles

Maryan I. Lelyukh[1], Ivan O. Krukovskiy,[1] Zoryana M. Komarenska,[2] Nataliia V. Yelahina[3], Taras I. Chaban,[1,*] and Ihor G. Chaban[1]

[1] *Danylo Halytsky Lviv National Medical University, Pekarska St. 69, Lviv 79010, Ukraine*

[2] *Lviv Polytechnic National University, S. Bandery St. 12, Lviv 79013, Ukraine*

[3] *Lugansk State Medical University, 16 Lypnya St. 36, Rivne 33017, Ukraine*

* *Corresponding author: E-mail: chabantaras@ukr.net*
Tel. +38 098 942-79-56; Fax. +38 0322 75-77-34

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Abstract

4-Amino-5-substituted-4*H*-1,2,4-triazole-3-thiols are versatile synthons for the construction of various biologically active heterocycles. This is provided by the close proximity of the amino and mercapto groups, which serve as readily accessible nucleophilic centers for the preparation of *N*-bridged heterosystems. One of the possible and convenient directions of using 4-amino-4*H*-1,2,4-triazole-3-thiols in heterocyclic synthesis is based on their utilization in reaction with various carboxylic acids in the presence of dehydrating reagents, most often phosphorus oxychloride. Synthesized as follows, [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles may differ by various substituents in positions 3 and 6 such as alkyl-, aryl-, aryl(oxy)alkyl-, heteroaryl- etc. In this review, we present the synthetic strategies and subsequent chemical transformations of the resulting triazolo[3,4-*b*]thiadiazoles, providing certain important classes of functionalized compounds.

Keywords: 4-amino-1,2,4-triazole-3-thiols; [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles; organic synthesis; cyclocondensation; chemical transformations.

1. Introduction

The chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic application and effective biological importance as evidenced by numerous reports.[1–7] Currently, certain approved drugs that possess 1,2,4-triazole unit are available in medicine, e.g. Rizatriptan, Trapidil, Trazodone, Anastrozole, Letrozole, Ribavirin, and Loreclezole.[8]

On the other hand, 1,3,4-thiadiazole derivatives represent another important class of five-membered heterocycles with scientifically proven pharmacological efficacy that have been the subject of extensive studies in the recent years.[9] In particular, various substituted thiadiazoles are known to exhibit a diverse range of biological activities including anticancer,[10] antibacterial,[11] antifungal,[12] antitrypanosomal,[13] antitubercular,[14] antioxidant,[15] antiviral,[16] anti-inflammatory[17] action etc.

In view of that remarkable efficiency of triazole and thiadiazole derivatives, the conjugation of these two moieties into a single molecular scaffold may be considered as a perspective approach for drug-like molecules build-up. Especially, according to the hybrid pharmacophore approach concept, the combination of both pharmacologically significant templates can lead to shown synergistic effect and/or expansion of the pharmacological profile. In this regard, triazolothiadiazoles have received considerable attention from scientific community and are extensively used as scaffolds with diverse spectra of pharmacological activities including having anticancer,[18] antibacterial and antifungal,[19] anti-inflammatory,[20,21] antidiabetic,[21] antitubercular,[22] antioxidant,[23] and anticonvulsant[24] potential. Also, certain triazolothiadiazoles have been shown to possess potent alkaline phosphatase,[25] acetylcholinesterase,[26] SHP-2 protein tyrosine phosphatase,[27] dCTP pyrophosphatase 1,[28] heparanase,[29] cyclooxygenase,[30] and carbonic anhydrase hCA IX/XII[31] inhibitory action. It is considered that the triazoles fused to thiadiazoles exhibit various therapeutically important properties, probably

due to the existence of N–C–S fragment in their structures.

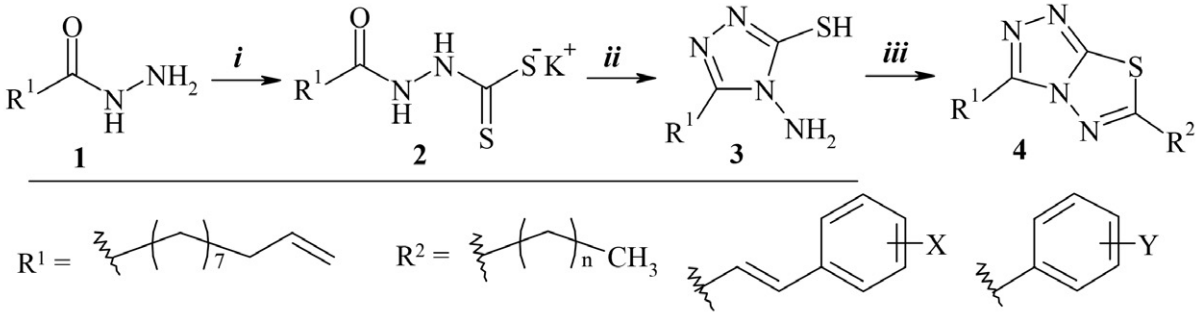
Herein, we have attempted to systematize the literature data on the synthetic methodologies leading to 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles involving cyclocondensation of 4-amino-1,2,4-triazole-3-thiols with various carboxylic acids. Also, all the provided data were structure-dependant on the chemical structure of the starting reagents and, as a result, on the nature of the substituents in the target compounds.

2. Synthetic Approaches for Obtaining [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole Based Heterocyclic Compounds

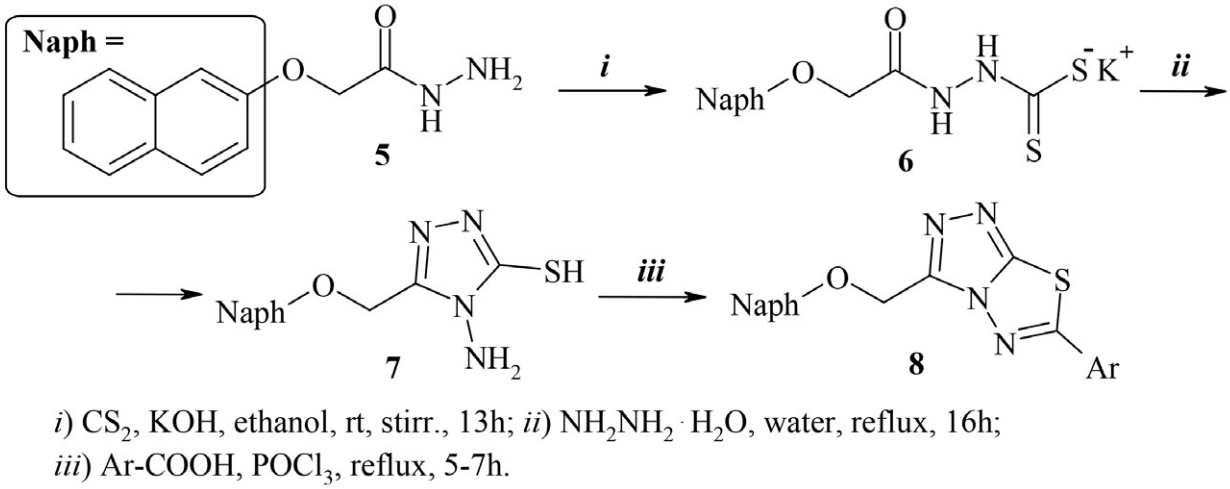
In general, there are several distinct approaches to building up [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole ring system, classified and described elsewhere.[32] However, the most convenient, efficient and commonly used of these involves the cyclocondensation of 4-amino-1,2,4-triazole-3-thiols with various carboxylic acids in the presence of phosphorus oxychloride. Phosphorous oxychloride was necessary for the cyclization of triazoles to triazolo[3,4-*b*] thiadiazoles, which activates the carbonyl group of carboxylic acids and increases its electrophilicity to enhance the addition of triazole to it. Using this approach, numerous different [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles can be obtained, which depends on the chemical structure of the respective carboxylic acid as well as from the nature of the substituent in position 5 of the starting 4-amino-1,2,4-triazole-3-thiol.

2. 1. Synthesis of 3,6-Disubstituted [1,2,4] Triazolo[3,4-*b*][1,3,4]thiadiazoles Containing Alkyl-, Aryl- or Aryl(Oxy) Alkyl- Substituents

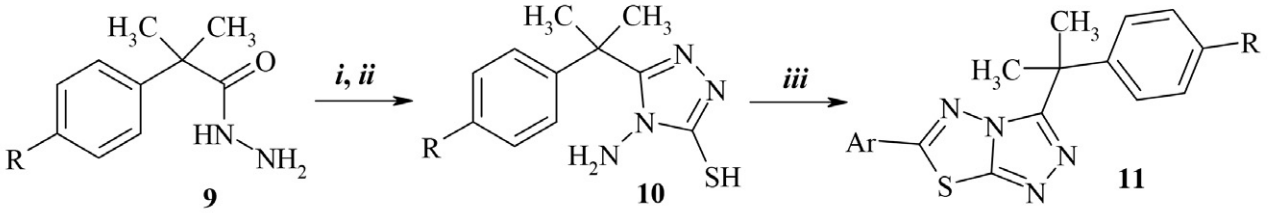
Based on undec-10-enehydrazide (**1**) through the stage of intermediate dithiocarbazinate formation **2** the synthesis of 5-(dec-9-en-1-yl) substituted 4-amino-4*H*-1,2,4-



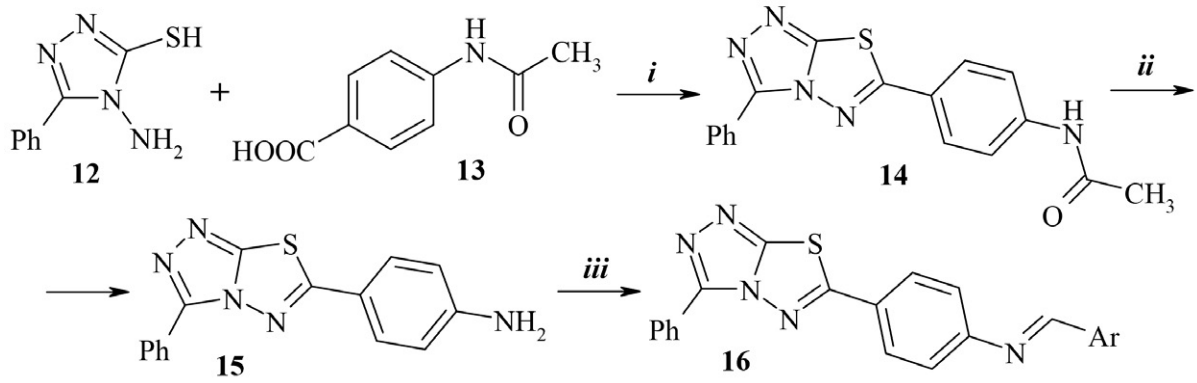
Scheme 1. The synthesis of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 5-(dec-9-en-1-yl) 4-amino-4*H*-1,2,4-triazole-3-thiol with aliphatic, cynnamic or aryl/heteryl carboxylic acids



Scheme 2. Synthesis of 3-(naphthalene-2-oxy)methyl-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



Scheme 3. Synthesis of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing *gem*-dimethyl benzyl moiety by condensation of 5-aralkyl-4-amino-4*H*-1,2,4-triazole-3-thiols with aromatic acids



Scheme 4. Synthesis of 3-phenyl-6-(4-*N*-acetylaminophenyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole by condensation of 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol with *N*-acetyl-*para*-aminobenzoic acid

triazole-3-thiols **3** was carried out (Scheme 1). Thereafter, a series of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole analogues **4** were synthesized by cyclocondensation of compound **3** with various aliphatic, cynnamic or aryl carboxylic acids in the presence of $POCl_3$.[33]

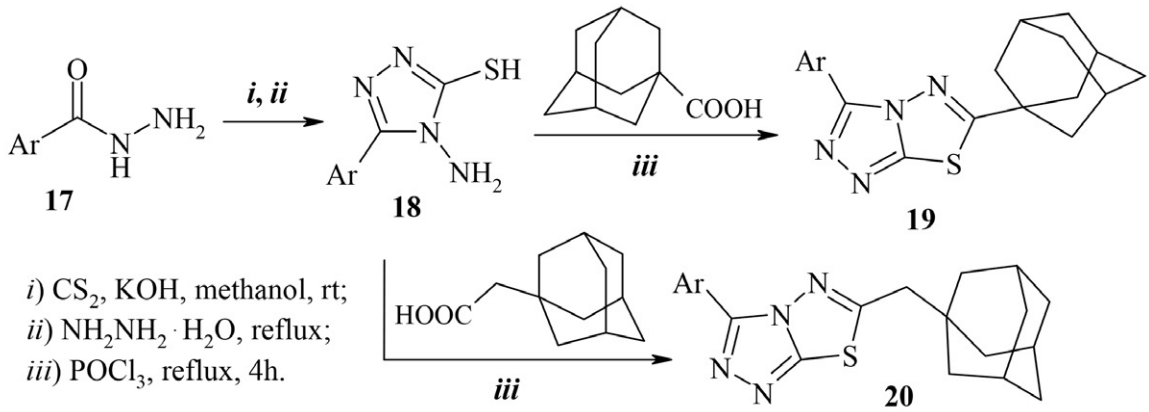
Following a similar transformations starting from 2-naphthoxyacetic acid hydrazide (**5**) Amir *et al.*[34] synthesized the corresponding 4-amino-5-[(naphthalen-2-yloxy) methyl]-4*H*-1,2,4-triazole-3-thiol (**7**) (Scheme 2). Further modification of compound **7** by treatment with substituted aromatic acids in the presence of phosphorus oxychloride resulted in target 3-(naphthalene-2-oxy)methyl substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **8**.

Modification of 2-methyl-2-aryl propanoic acid hydrazide **9** on sequential interaction with carbon disulfide in methanolic potassium hydroxide, followed by refluxing with hydrazine hydrate resulted in corresponding 5-substituted 4-amino-4*H*-1,2,4-triazole-3-thiols **10** (Scheme 3). 3,6-Disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing *gem*-dimethyl benzyl moiety **11** were prepared by condensation of compound **10** with fluoro substituted aromatic acids in the presence of refluxing $POCl_3$.[35]

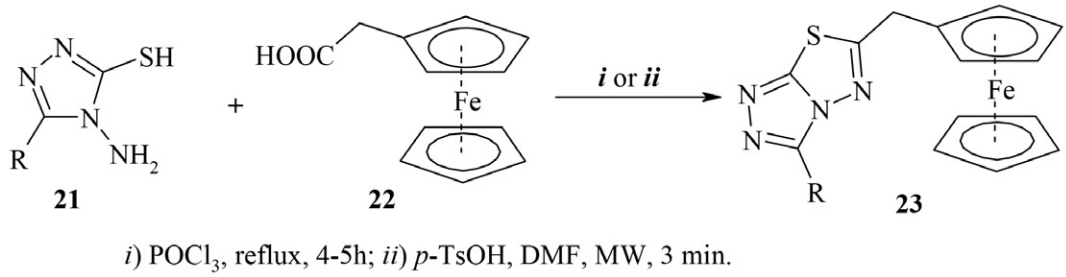
Kokila *et al.*[36] reported the efficient synthesis of 3-phenyl-6-(4-*N*-acetylaminophenyl)[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole **14** based on the reaction of starting 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**12**) with *N*-acetyl-*para*-aminobenzoic acid (**13**) in refluxing phosphorus oxychloride (Scheme 4). Further hydrolysis of compound **14** by refluxing with ethanol/concentrated HCl mixture to give an amino derivative **15**, which was converted into the corresponding Schiff bases **16** following the reaction with substituted benzaldehydes.

The interaction of 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiols **18** (previously obtained from appropriate aryl hydrazides **17**) with adamantyl-1-carboxylic or adamantyl-1-acetic acids in the presence of phosphorus oxychloride (Scheme 5), described by Khan *et al.*,[37] afforded the 3-aryl-6-adamantyl(methyl)[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles **19** and **20**.

A series of triazolo[3,4-*b*][1,3,4]thiadiazoles containing ferrocene **23** (Scheme 6) were synthesized following the condensation of 5-substituted 4-amino-1,2,4-triazole-3-thiols **21** with ferrocene acetic acid (**22**) in the presence of *para*-toluenesulfonic acid under microwave irradiation.[38]

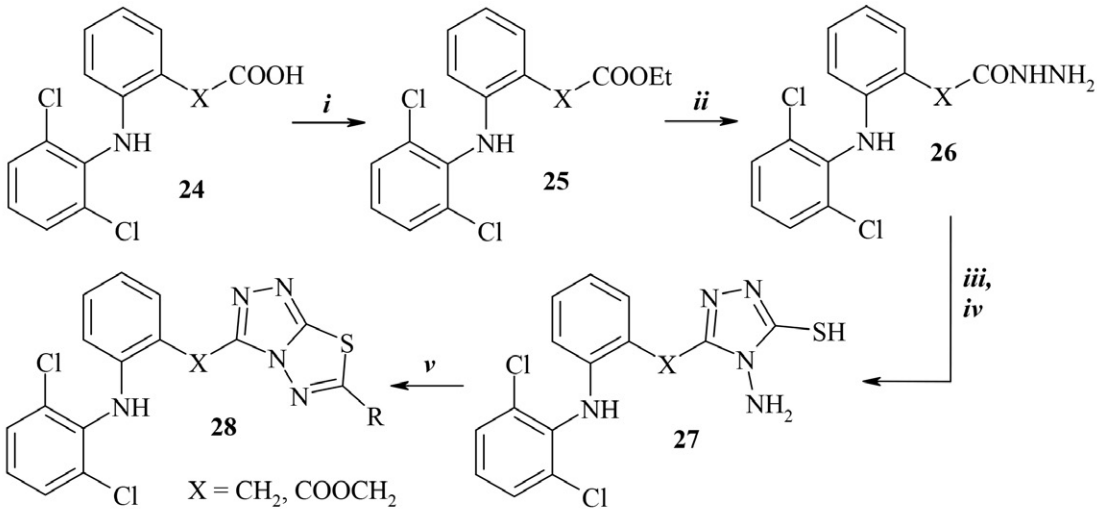


Scheme 5. Synthesis of 6-adamantyl(methyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-aryl-1,2,4-triazole-3-thiols with adamantyl-1-carboxylic or (adamant-1-yl)acetic acids

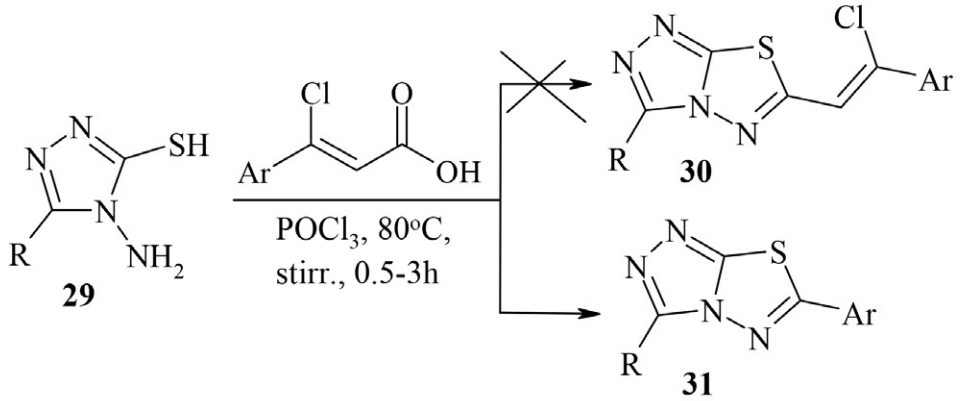


Scheme 6. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing ferrocene by condensation of 5-substituted 4-amino-1,2,4-triazole-3-thiols with ferrocene acetic acid

Modification of nonsteroidal anti-inflammatory drugs (NSAIDs) Diclofenac (**24**, X = CH_2) and Acelofenac (**24**, X = $COOCH_2$) according to the multi-step procedure by Ilango and Valentina[39] (Scheme 7) was accompanied by forming of 5-substituted 4-amino-4*H*-1,2,4-triazole-3-thiol **27**. As expected, the condensation of compounds **27** with various aromatic acids in the presence of phosphorus oxychloride allowed to obtain 3,6-disubstituted-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **28** hybridised with Diclofenac or Aceclofenac scaffolds.



Scheme 7. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles hybridised with Diclofenac or Aceclofenac scaffolds by condensation of corresponding 4-amino-4*H*-1,2,4-triazole-3-thiol with aromatic acid

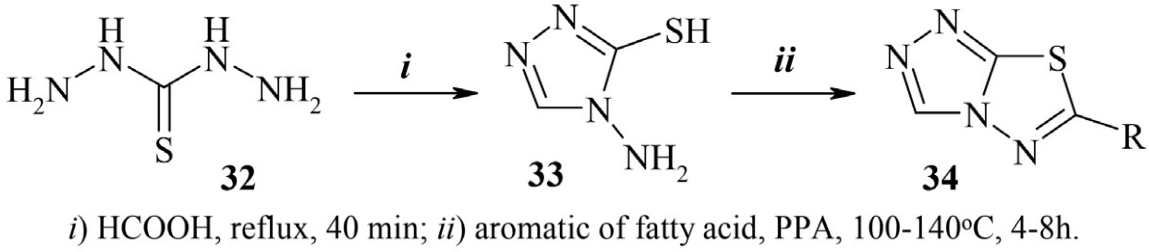


Scheme 8. Synthesis of 6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-aryl-1,2,4-triazole-3-thiols with (*Z*)-3-chloro-3-arylacrylic acids

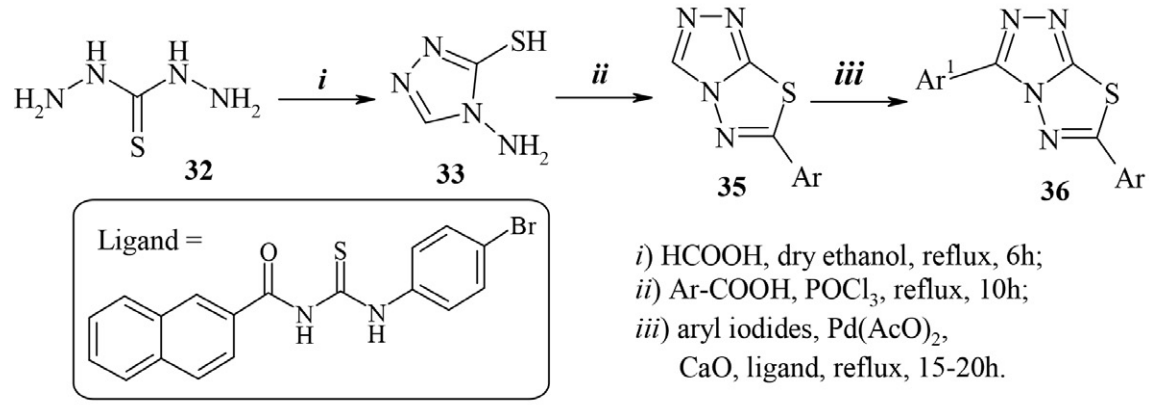
An unprecedented method for the conversion of (*Z*)-3-chloro-3-arylacrylic acids to corresponding benzoic acids in the process of their condensation with 4-amino-5-aryl-3-mercapto-1,2,4-triazoles **29** by stirring in $POCl_3$ at 80 °C (Scheme 8) was reported by Sahi *et al.*[40] Thus, instead of the expected (*Z*)-6-(chloro-2-(aryl)vinyl)-3-methyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **30**, only 6-aryl derivatives **31** were observed.

The synthetic protocol leading to the formation of 3-unsubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **34** described by Deng *et al.*[41] includes the previous interaction of thiocarbohydrazide **32** with formic acid under reflux conditions (Scheme 9). Further, the previously obtained 4-amino-4*H*-1,2,4-triazole-3-thiol (**33**), reacted with fatty acids or aromatic acids in polyphosphoric acid (PPA) yielding the target derivatives **34**.

Similarly to the above method, Saeed *et al.*[42] carried out the synthesis of 4-amino-1,2,4-triazole-3-thiole (**33**), and further reacted **33** with substituted aromatic acids in refluxing phosphorus oxychloride to afford the 3-unsubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **35** (Scheme 10). Finally, 3,6-diaryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **36** were obtained by C–H arylative cross-coupling of compound **35** with aryl iodides using 1-(2-naphthoyl)-3-(4-bromophenyl)thiourea as a ligand.



Scheme 9. Synthesis of 3-unsubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by reaction of 4-amino-4*H*-1,2,4-triazole-3-thiol with fatty or aromatic acids



Scheme 10. Synthesis of 3,6-diaryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by C–H arylative cross-coupling of 6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles with substituted iodoanilines

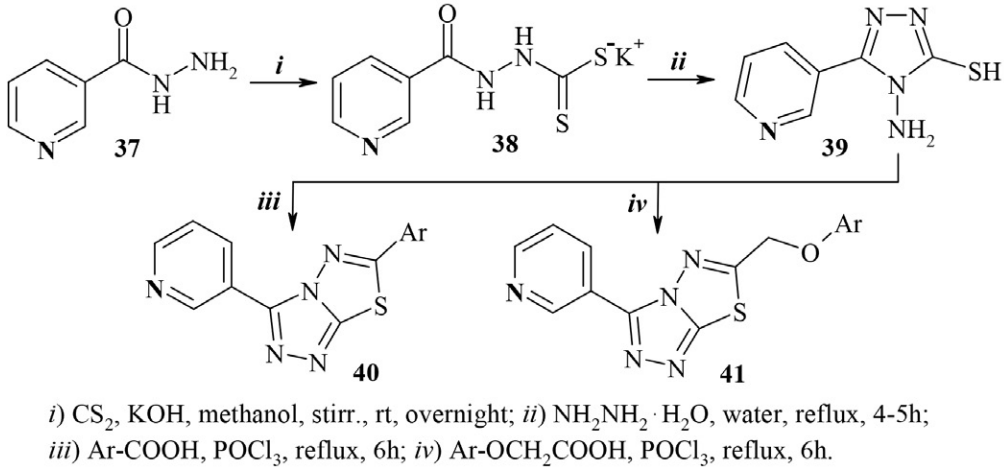
2. 2. Synthesis of 3-Heteroaryl Substituted [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles

The features of synthetic approaches leading to the formation of 3-heteroaryl substituted triazolo[3,4-*b*]thiadiazoles consist of applying the heterocyclic acids or their functional derivatives. Thus, the interaction of starting nicotinohydrazide (**37**) with carbon disulfide in methanolic potassium hydroxide gives the corresponding dithiocarbazinate **38**, which reacts with hydrazine hydrate to afford of 4-amino-5-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-thiol (**39**) (Scheme 11). Afterwards, compound **39** was modified in a one-pot condensation with various arylcarboxylic or phenyloxyacetic acids in the presence of $POCl_3$ with the formation of 3-(pyridine-3-yl) substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **40** and **41**.[43]

The using of isonicotinic acid hydrazide (**42**) as the starting material in similar two-step transformation resulted in 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-thiol (**43**), which upon reacting with aromatic acids in refluxing $POCl_3$ gave 3-(pyridine-4-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **44** (Scheme 12). Also, the synthesis of 6-methyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**45**) was achieved by heating compound **43** with acetic anhydride.[44]

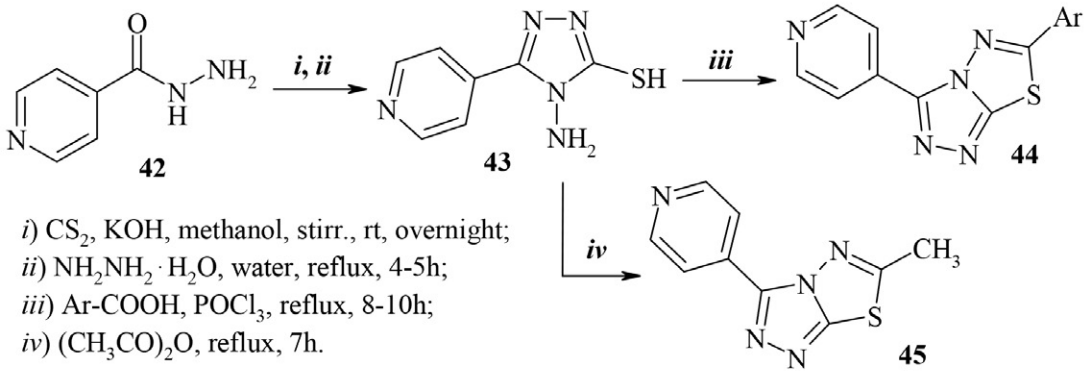
Following the reaction of 5-(1-phenyl-5-methylpyrazole) substituted 1,3,4-oxadiazole-2-thiol **46** with hydrazine hydrate Reedy *et al.*[45] performed the synthesis of corresponding 4-amino-4*H*-1,2,4-triazole-3-thiol **47** (Scheme 13). Further condensation of compound **47** with aromatic acids in the presence of $POCl_3$ in refluxing ethanol yielded the target 6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **48** containing 1-phenyl-5-methylpyrazole moiety.

Through a cascade of transformations starting from 4-methoxy-3-fluoro-acetophenone an intermediate 5-phenyl-1*H*-pyrazole-3-carbohydrazide **49** was obtained and then processed sequentially with carbon disulfide and ethanolic potassium hydroxide followed by hydrazine hydrate under reflux condition forming 5-(5-phenyl-1*H*-pyrazol-3-yl) substituted 4-amino-4*H*-1,2,4-triazole-3-thiols **50** (Scheme 14). Finally, the condensation of compound **50** with substituted carboxylic acids in phosphorus oxychloride medium resulted in a series of novel [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles bearing 5-phenyl-1*H*-pyrazole moiety **51**.[46]



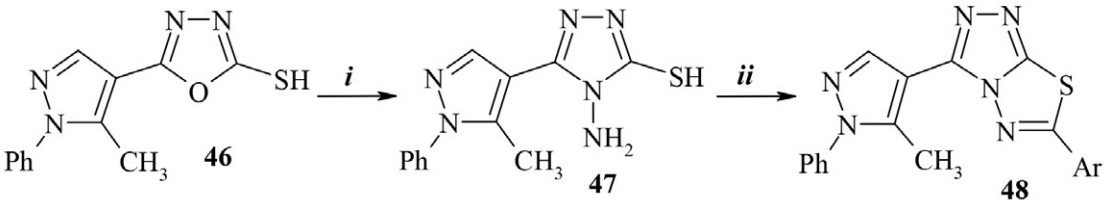
i) CS_2, KOH, methanol, stirr., rt, overnight; *ii*) $NH_2NH_2 \cdot H_2O$, water, reflux, 4-5h;
iii) Ar-COOH, $POCl_3$, reflux, 6h; *iv*) Ar-OCH_2COOH, $POCl_3$, reflux, 6h.

Scheme 11. Synthesis of 3-(pyridine-3-yl) substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-thiol with aromatic or phenyloxyacetic acids



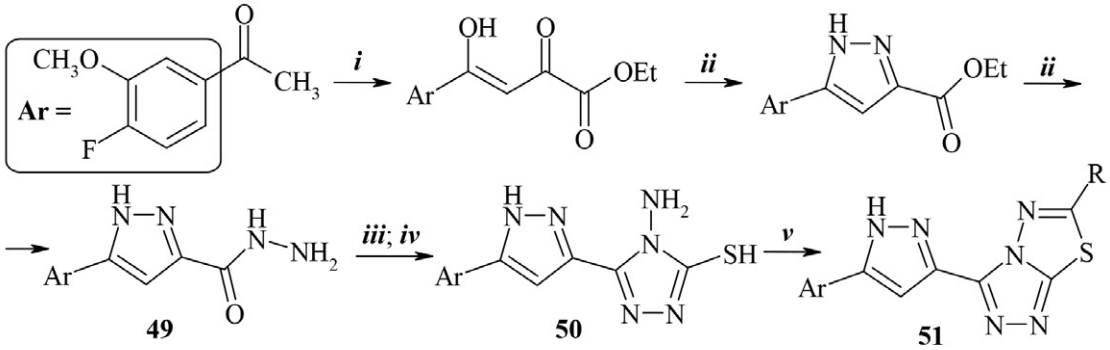
i) CS_2, KOH, methanol, stirr., rt, overnight;
ii) $NH_2NH_2 \cdot H_2O$, water, reflux, 4-5h;
iii) Ar-COOH, $POCl_3$, reflux, 8-10h;
iv) $(CH_3CO)_2O$, reflux, 7h.

Scheme 12. Synthesis of 3-(pyridine-4-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-thiol with aromatic acids or acetic anhydride



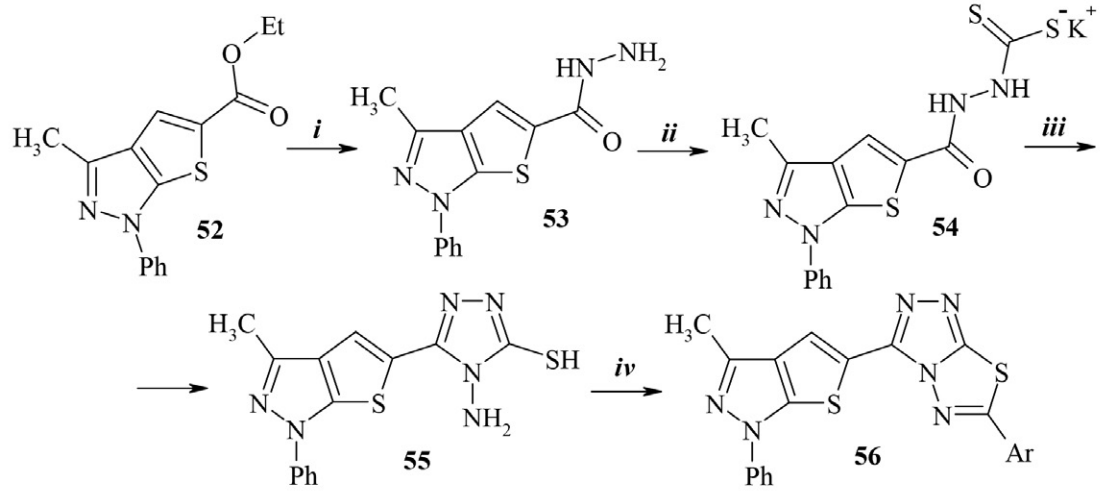
i) NH_2-$NH_2 \cdot H_2O$, ethanol, reflux; *ii*) Ar-COOH, $POCl_3$, ethanol, reflux, 12h.

Scheme 13. Synthesis of 3-(1-phenyl-5-methylpyrazol-4-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of corresponding 5-substituted 4-amino-4*H*-1,2,4-triazole-3-thiol with aromatic acids



i) diethyl oxalate, toluene, NaH, 25-30°C, stirr., 8h; *ii*) $NH_2NH_2 \cdot H_2O$, ethanol, reflux, 8h;
iii) CS_2, KOH, ethanol, reflux, 6h; *iv*) $NH_2NH_2 \cdot H_2O$, water, reflux, 12h;
v) substituted benzoic/pyridinyl acids, $POCl_3$, reflux, 8-10h.

Scheme 14. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles bearing pyrazole moiety by condensation of 5-(5-phenyl-1*H*-pyrazol-3-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol with substituted benzoic/pyridinyl acids



i) $NH_2NH_2 \cdot H_2O$, ethanol, reflux, 3h; [ii]) CS_2, KOH, ethanol, rt, 12h;
iii) $NH_2NH_2 \cdot H_2O$, water, reflux, 12h; *iv*) Ar-COOH, $POCl_3$, reflux, 4-5h.

Scheme 15. Synthesis of thieno[2,3-*c*]pyrazole substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of corresponding 5-substituted 4-amino-4*H*-1,2,4-triazole-3-thiol with aromatic acids

2. 3. Synthesis of 3-Heteroaryl(Condensed) [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles

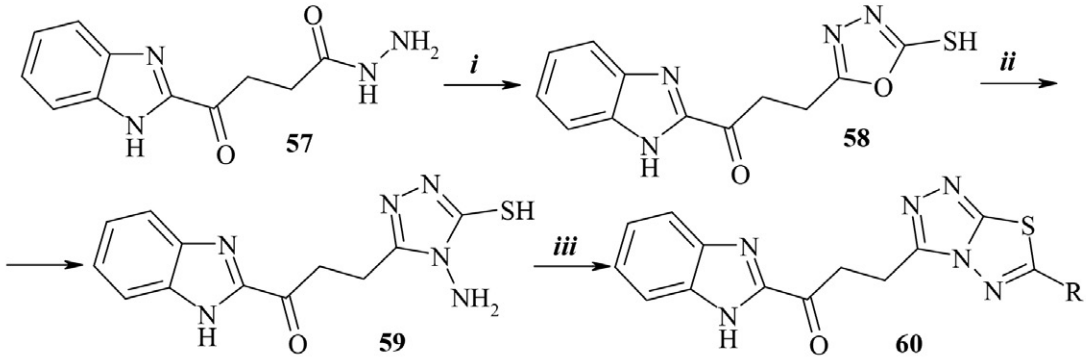
Following multi-step reaction sequence starting from ethyl thieno[2,3-*c*]pyrazole-5-carboxylate **52** through the formation of intermediate carbohydrazide **53** and potassium dithiocarbazinate **54** Patil *et al.*[47] achieved the synthesis of 5-(3-methyl-1-phenyl-1*H*-thieno[2,3-*c*] pyrazol-5-yl) substituted 4-amino-4*H*-1,2,4-triazole-3-

thiol **55** (Scheme 15). The resulting triazole **55** was further converted into [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **56** containing thieno[2,3-*c*]pyrazole by one-step condensation with aromatic acids in $POCl_3$.

Reacting 4-(1*H*-benzo[*d*]imidazol-2-yl)-4-oxobutanoic acid hydrazide (**57**) with carbon disulfide and potassium hydroxide in ethanol-water (1:1) mixture gives benzo[*d*]imidazole substituted 1,3,4-oxadiazole-2-thiol **58** (Scheme 16). Further reaction of compound **58** with hydrazine hydrate in refluxing ethanol yielded the corresponding 4-amino-4*H*-1,2,4-triazole-3-thiol **59**, which on reaction with different aromatic/aliphatic acids in the presence of $POCl_3$ afforded 6-alkyl/aryl[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazoles containing benzo[*d*]imidazole moiety linked by propan-1-one group **60**.[48]

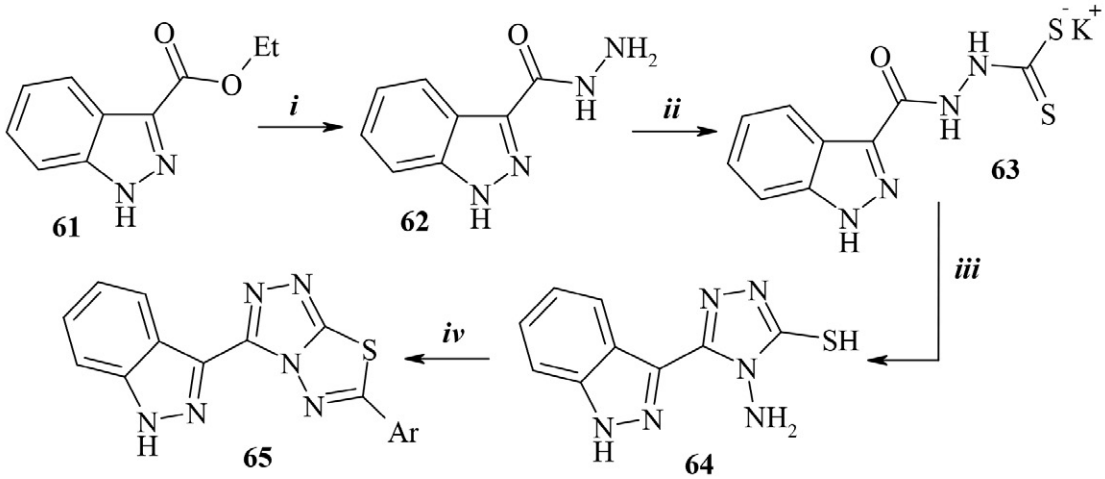
Based on the sequential interaction of 1*H*-indazole-3-carboxylic acid ethyl ester (**61**) with hydrazine hydrate, carbon disulfide in ethanolic potassium hydroxide and followed by cyclization upon heating with hydrazine hydrate, Raut *et al.*[49] performed the synthesis of 4-amino-5-(1*H*-indazol-3-yl)-4*H*-1,2,4-triazole-3-thiol (**64**) (Scheme 17). Finally, a series of 3-(1*H*-indazol-3-yl) substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **65** were obtained by condensation of **64** with substituted arylcarboxylic acids in refluxing $POCl_3$.

Gorgu *et al.*[50] reported an efficient synthetic procedure leading to [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing 2(3*H*)-benzoxazolone moiety as shown in Scheme 18. Thus, alkylation of starting 2-oxo-3*H*-benzoxazole (**66**) with ethyl bromoacetate followed by hydrolysis of the resulting ethyl ester **67** yielded 2-(2-oxo-3*H*-benzoxazol-3-yl)acetic acid (**68**). Heating the compound **68** with thiocarbohydrazide in an oil bath at 160–170 °C for 30 min resulted in 3-[(4-amino-5-thioxo-1,2,4-triazol-3-



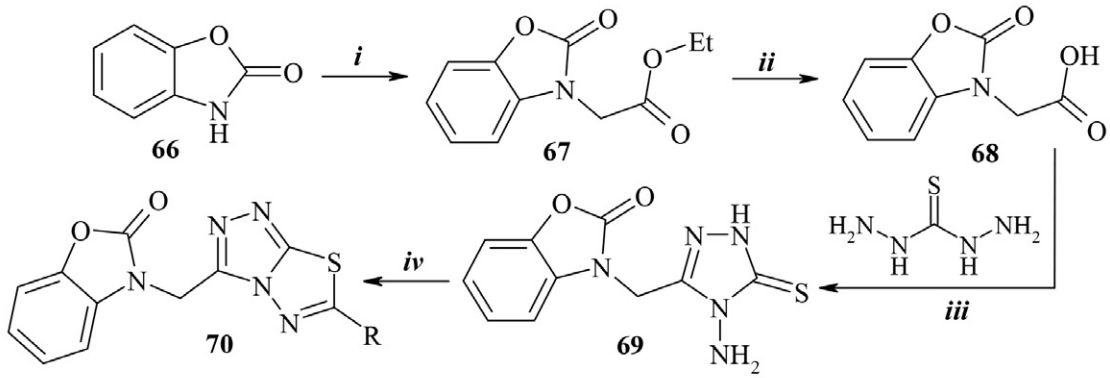
i) CS_2, KOH, ethanol-water (1:1), reflux, 6h; *ii*) $NH_2NH_2 \cdot H_2O$, ethanol, reflux, 5h;
iii) R-COOH, $POCl_3$, reflux, 5-6h.

Scheme 16. 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-thiols with aromatic/aliphatic acids

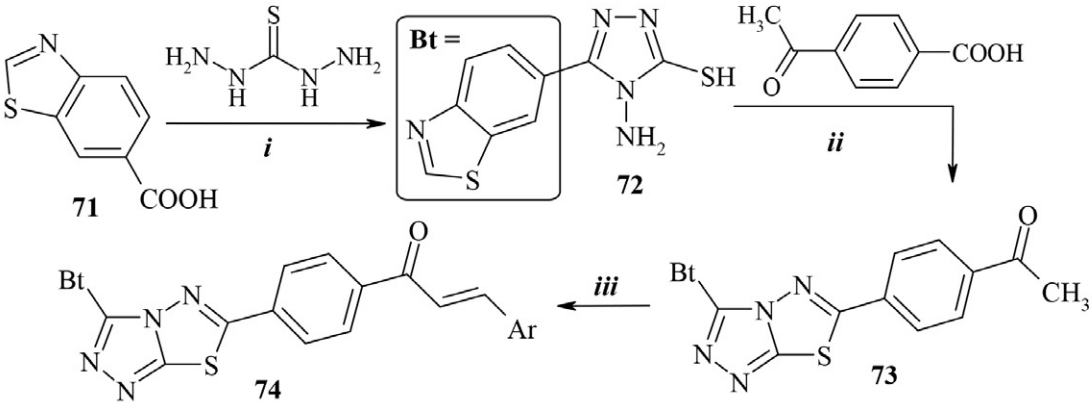


i) $NH_2NH_2 \cdot H_2O$, ethanol, reflux, 3h; *ii*) CS_2, KOH, ethanol, rt, stir., 14h;
iii) $NH_2NH_2 \cdot H_2O$, water, 90-95°C, 3-5h; *iv*) Ar-COOH, $POCl_3$, 90-95°C, 4-6h.

Scheme 17. 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 arylcarboxylic acids



Scheme 18. Synthesis of 2(3*H*)-benzoxazolone substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of corresponding 4-amino-4*H*-1,2,4-triazole-3-thiol with benzoic or phenylacetic acids



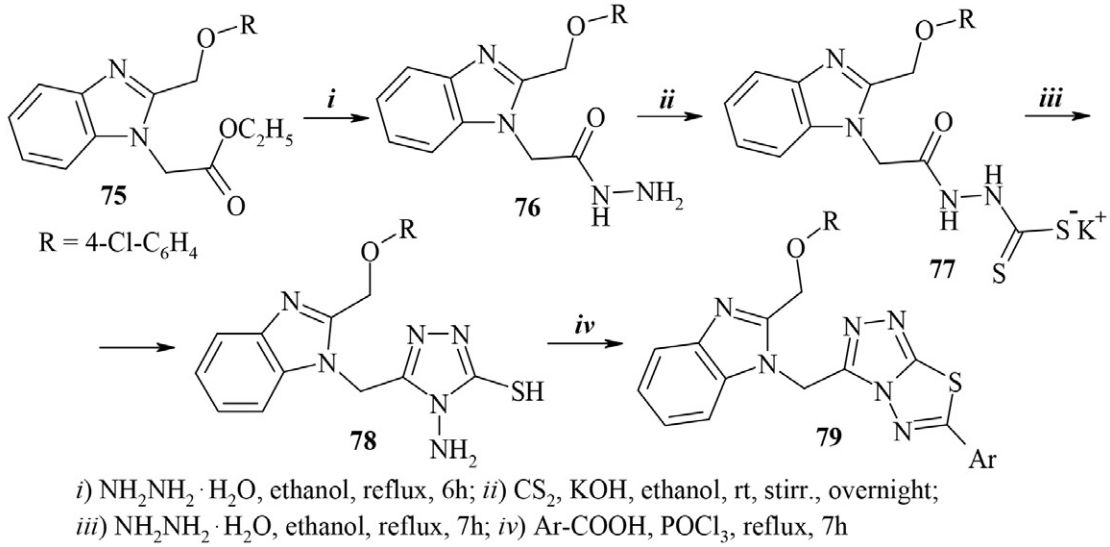
Scheme 19. Synthesis of 6-(4-acetylphenyl)[1,2,4]triazole[3,4-*b*][1,3,4]thiadiazole by condensation of 4-amino-5-(1,3-benzothiazol-6-yl)-4*H*-1,2,4-triazol-3-thiol with 4-acetylbenzoic acid

yl)methyl]-2(3*H*)-benzoxazolone (**69**), which was treated with substituted benzoic acid or phenylacetic acids using $POCl_3$ as cyclizing agent under microwave irradiation to give the expected [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **70**.

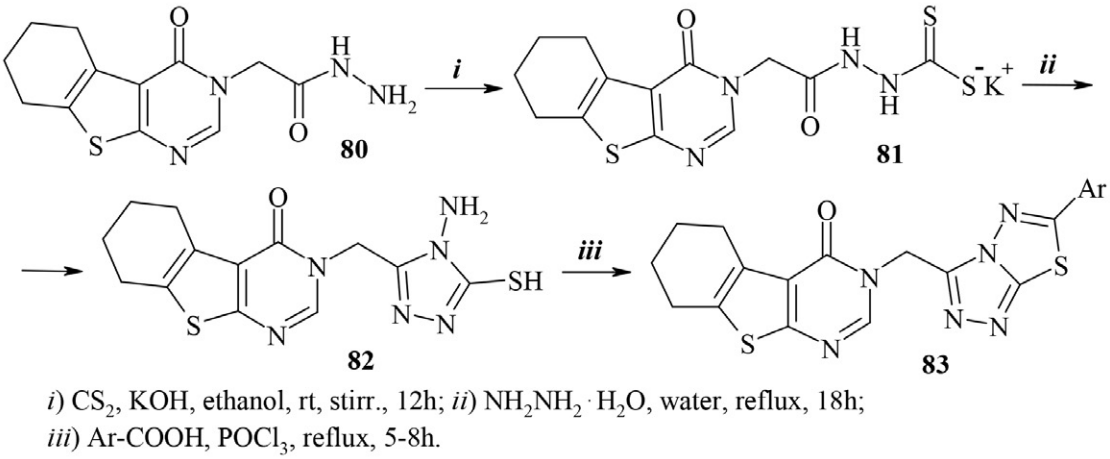
Condensation of 4-amino-5-(benzothiazol-6-yl)-4*H*-1,2,4-triazol-3-thiol (**72**), obtained by fusion of benzothiazole-6-carboxylic acid **71** with thiocarbohydrazide, with 4-acetylbenzoic acid in the presence of phosphoryl chloride and sulfolane at 85 °C for 18 hours gives benzothiazole containing 6-acetylphenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **73** (Scheme 19). Furhter interaction of compound **73** with different aromatic aldehydes using Claisen–Schmidt condensation procedure in the presence of catalytic amounts of piperidine as the base in ethanol under reflux conditions resulted in a series of novel triazolo[3,4-*b*][1,3,4]thiadiazole tethered chalcones **74**.[51]

Starting from 2-[2-(4-chlorophenoxymethyl)-1*H*-benzimidazole-1-yl]acetic acid ethyl ester (**75**) through intermediate stages of the corresponding hydrazide **76** and potassium dithiocarbazinate **77** formation, Li *et al.*[52] carried out the synthesis of 4-amino-1,2,4-triazole-3-thiol **78** (Scheme 20). Afterwards, compound **78** was allowed to react with (un)substituted aromatic acids in refluxing phosphorous oxychloride to afford the target 6-(benzimidazole-1-ylmethylene) substituted 3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **79**.

Nagaraju *et al.*[53] presented the synthesis of novel fused 6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-one moiety **83** through a multi-step reaction sequence starting from 2-(4-oxo-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-3-yl)acetic acid hydrazide (**80**) (Scheme 21). Thus, the initial interaction of compound **80** with carbon



Scheme 20. Synthesis of 6-(benzimidazole-1-ylmethylene) substituted 3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-4*H*-1,2,4-triazole-3-tiols with (un)substituted aromatic acids

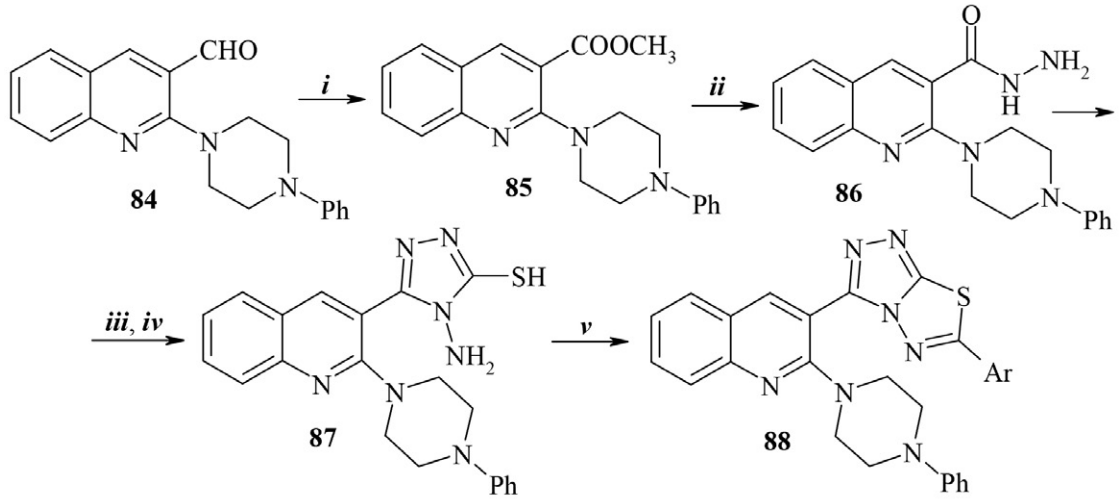


Scheme 21. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing thieno[2,3-*d*]pyrimidin-4-one moiety by condensation of corresponding 4-amino-4*H*-1,2,4-triazole-3-thiol with substituted aromatic acids

disulfide in ethanolic potassium hydroxide gave the corresponding potassium dithiocarbazinate **81**, which on treatment with an excess of 80% hydrazine hydrate expectedly provided the 4-amino-4*H*-1,2,4-triazole-3-thiol **82**. Finally, the compounds **83** were obtained by condensation of resulting 4-amino-4*H*-1,2,4-triazole-3-thiol **82** with various arylcarboxylic acids in the presence of phosphorus oxychloride.

Using the methyl 2-piperazinylquinoline-3-carboxylate (**85**), obtained by oxidation of 2-(4-phenylpiperazin-1-yl)quinoline-3-carbaldehyde (**84**) with iodine in methanol in the presence of potassium carbonate, *via* a three-step protocol including hydrazide **86**, salt formation with followed by cyclization allowing Tang *et al.*[54] to obtain the key intermediate – 4-amino-5-[2-(4-phenylpiperazin-1-y)quinolin-3-yl]-4*H*-1,2,4-triazole-3-thiol (**87**) (Scheme 22). Reaction of compound **87** with various aromatic carboxylic acids in refluxing phosphorus oxychloride yielded [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles bearing 2-(4-phenylpiperazin-1-yl)quinoline scaffold **88**.

The synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **95** containing quinazolin-4(3*H*)-one moiety according to the multi-stage procedure using methyl 2-aminobenzoate (**89**) as the starting material (Scheme 23) was proposed by Lv *et al.*[55] Thus, the initial interaction of methyl ester **89** with formamide under the reflux gave 3*H*-quinazolin-4-one (**90**), which was on reaction with ethyl 2-bromoacetate converted into ethyl 4-oxo-4*H*-quinazolin-3-acetate (**91**). Compound **91** through a sequential modifications including hydrazinolysis of **92**, potassium dithiocarbazinate formation (compound **93**) followed by cyclization with 80% hydrazine hydrate at reflux condition



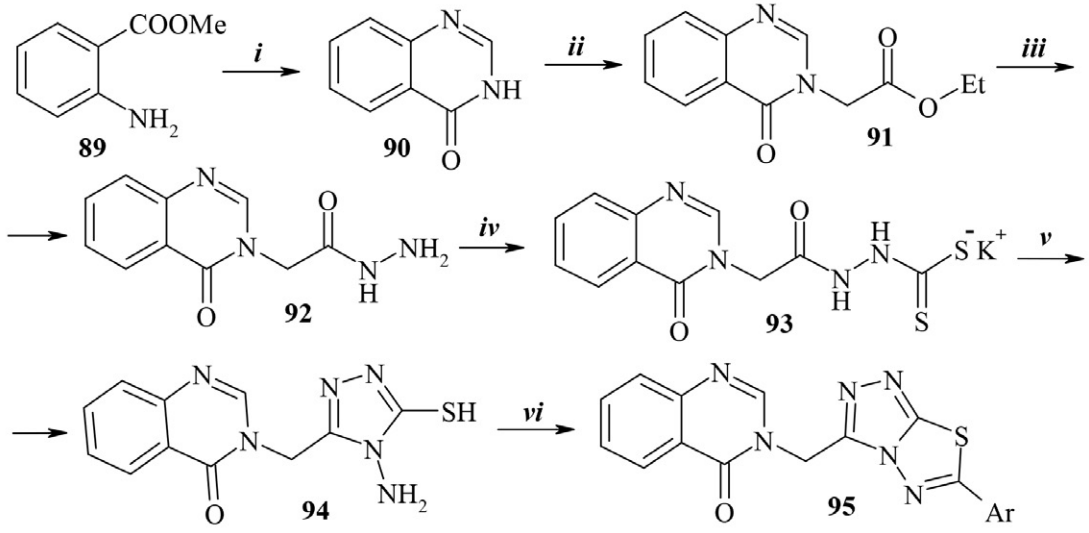
i) I_2, K_2CO_3, methanol, reflux, 5-6h; *ii*) $NH_2NH_2 \cdot H_2O$, reflux, 3h; *iii*) CS_2, KOH, ethanol, rt, stirr.; *iv*) $NH_2NH_2 \cdot H_2O$, water, reflux, 4-5h; *v*) Ar-COOH, $POCl_3$, reflux, 6-7h.

Scheme 22. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives by condensation of 4-amino-5-[2-(4-phenylpiperazin-1-yl)quinolin-3-yl]-4*H*-1,2,4-triazole-3-thiol with various aromatic acids

yielded the corresponding 4-amino-1,2,4-triazole-3-thiol **94**. Compound **94** then reacted with the substituted benzoic acids in refluxing phosphorus oxychloride to afford the target quinazolin-4(3*H*)-ones **95** containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles.[55]

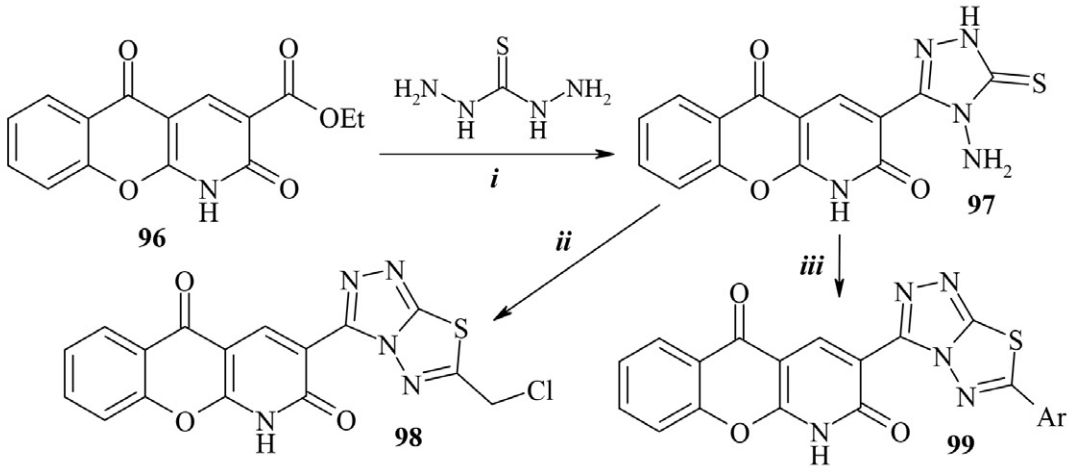
Following the reaction of ethyl 2,5-dioxo-1,5-dihydro-2*H*-chromeno[2,3-*b*]pyridine-3-carboxylate (**96**) with thiocarbohydrazide in DMF Ibrahim *et al.*[56] achieved the synthesis of chromeno[2,3-*b*]pyridine-2,5-dione based 4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole **97** (Scheme 24). Further heating of compound **97** with chloroacetyl chloride in pyridine under the reflux provided chromeno[2,3-*b*]pyridine substituted 6-chloromethyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **98**, whereas the reaction of **97** with benzoyl chloride or pyridine-4-carboxylic acid under similar conditions yielded 6-phenyl/pyridine-4-yl derivatives **99**.

Modification of 5-oxo-5*H*-indolo[3,2-*c*]isoquinoline-6(11*H*)-carbohydrazides **100** on reaction with carbon disulfide and ethanolic potassium hydroxide followed by



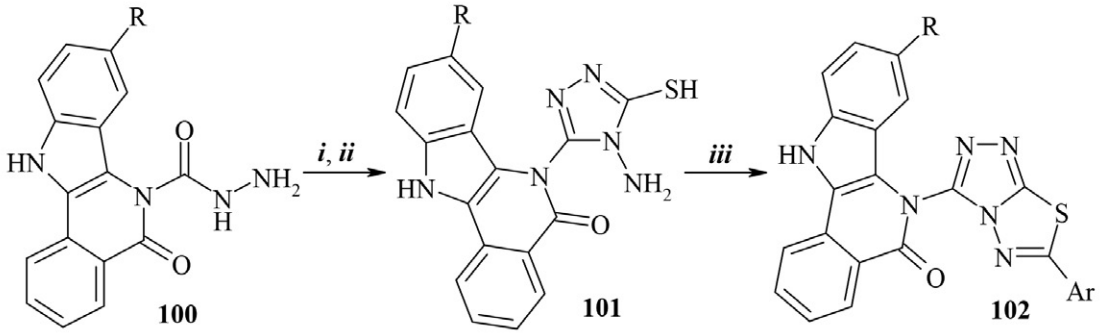
i) $HCONH_2$, reflux; *ii*) $BrCH_2COOEt$, K_2CO_3, acetone; *iii*) $NH_2NH_2 \cdot H_2O$, ethanol, reflux; *iv*) CS_2, KOH, ethanol, rt, stirr., 18h; *v*) $NH_2NH_2 \cdot H_2O$, reflux, 5h; *vi*) Ar-COOH, $POCl_3$, reflux, 5h.

Scheme 23. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing quinazolin-4(3*H*)-one moiety by condensation of corresponding 4-amino-1,2,4-triazole-3-thiol with substituted benzoic acids



i) DMF, reflux, 6h; *ii*) $ClCH_2COCl$, pyridine, reflux, 2h; *iii*) Ar-COCl, pyridine, reflux, 2h.

Scheme 24. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing chromeno[2,3-*b*]pyridine moiety by reaction of 4-amino-4*H*-1,2,4-triazole-3-thiol with chloroacetyl chloride or benzoyl chloride



i) CS_2, KOH, ethanol, rt, stirr.; *ii*) $NH_2NH_2 \cdot H_2O$, reflux; *iii*) Ar-COOH, $POCl_3$, reflux, 3-5h.

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

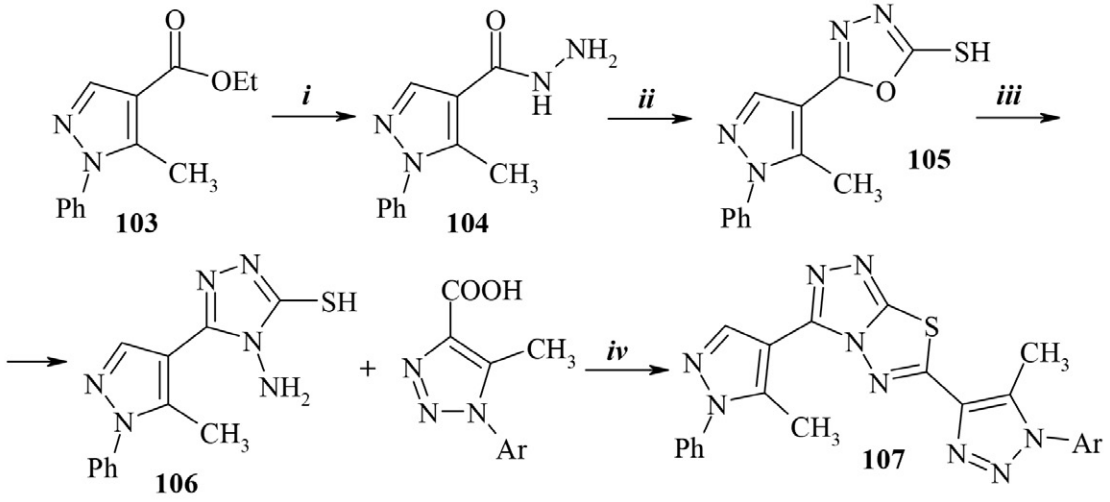
cyclization with hydrazine hydrate under the reflux allowed Verma *et al.*[57] to obtain indolo[3,2-*c*]isoquinolines-based 4-amino-4*H*-1,2,4-triazole-3-thiols **101** (Scheme 25). Compounds **101** were further utilized by heating with substituted aromatic acids in phosphorous oxychloride medium for 3–5 h for the formation of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **102** incorporating indolo[3,2-*c*]isoquinoline moiety.

2. 4. Synthesis of 6-Heteroaryl Substituted [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles

By reaction of starting ethyl 5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (**103**) with hydrazine hydrate followed by cyclization with carbon disulfide in ethanolic potassium hydroxide Reedy *et al.*[58] synthesized 5-(1-phenyl-1*H*-pyrazol-4-yl) substituted 1,3,4-triazole-2-thiol **106** (Scheme 26) as a key synthetic precursor for further transformations. Among them, following the hydrazinolysis of compound **105** the corresponding 5-(pyrazole-4-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol **106** was obtained, which on reaction with 1-aryl-5-methyl-1,2,3-triazole-4-carboxylic acids in the presence of $POCl_3$ in ethanol at reflux afforded the target pyrazole and 1,2,3-triazole **107** containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole moieties.

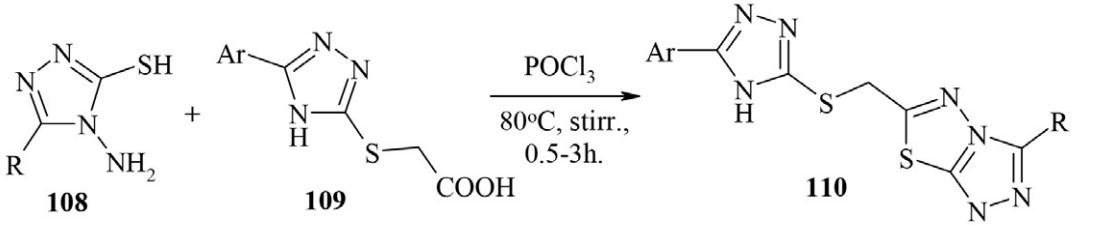
Sahi *et al.*[59] reported the synthesis of 6-(5-aryl-1,2,4-triazol-3-ylsulfanyl)methyl substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **110** (Scheme 27) by the one-pot condensation of corresponding 4-amino-1,2,4-triazoles-3-thiols **108** with 2-(5-aryl-4*H*-1,2,4-triazol-3-ylthio)acetic acids **109** by stirring in $POCl_3$ at 80 °C.

The synthetic protocol leading towards 6-(pyrazin-2-yl) substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **115** is provided by Mudgal *et al.*[60] Initially, it involves the preparation of 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiols **114** form corresponding arylcarboxylic acids **111** using



i) $NH_2NH_2 \cdot H_2O$, ethanol, reflux, 4h; *ii*) CS_2, KOH, ethanol, reflux, 12h;
iii) 80% NH_2NH_2 . H_2O, ethanol, reflux, 6h; *iv*) $POCl_3$, ethanol, reflux, 12h.

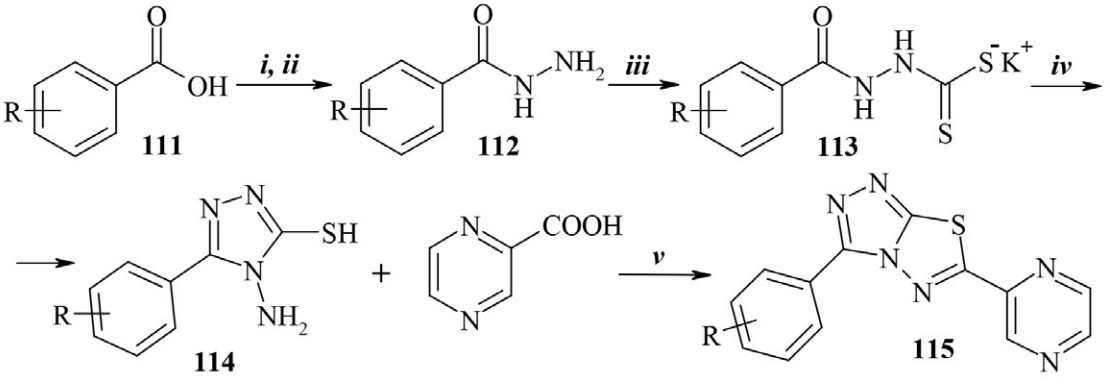
Scheme 26. Synthesis of 3,6-didubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 5-(pyrazole-4-yl)-4-amino-4*H*-1,2,4-triazole-3-thiol with 1-aryl-1,2,3-triazole-4-carboxylic acids



Scheme 27. Synthesis of 6-thiomethyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by the one-pot condensation of 4-amino-1,2,4-triazole-3-thiols with 2-(5-aryl-4*H*-1,2,4-triazol-3-ylthio)acetic acid

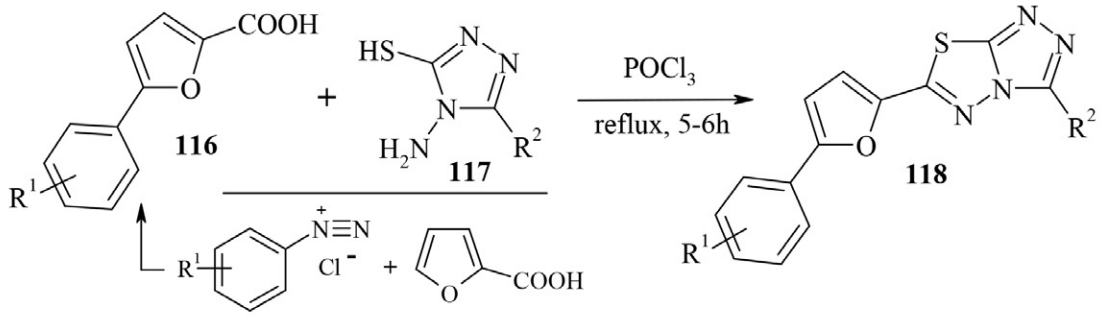
multi-step sequential procedure (Scheme 28). Eventually, condensation of compound **114** with pyrazine-2-carboxylic acid in phosphorus oxychloride medium yielded the desired 3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **115** containing pyrazine nucleus.[60]

Based on the reaction of 5-arylfuran-2-carboxylic acids **116**, obtained by arylation of corresponding heteroarylcarboxylic acids with arenediazonium salts, with 5-substituted 4-amino-4*H*-1,2,4-triazole-3-thiols **117** in refluxing $POCl_3$ (Scheme 29) Gorak *et al.*[61] prepared the

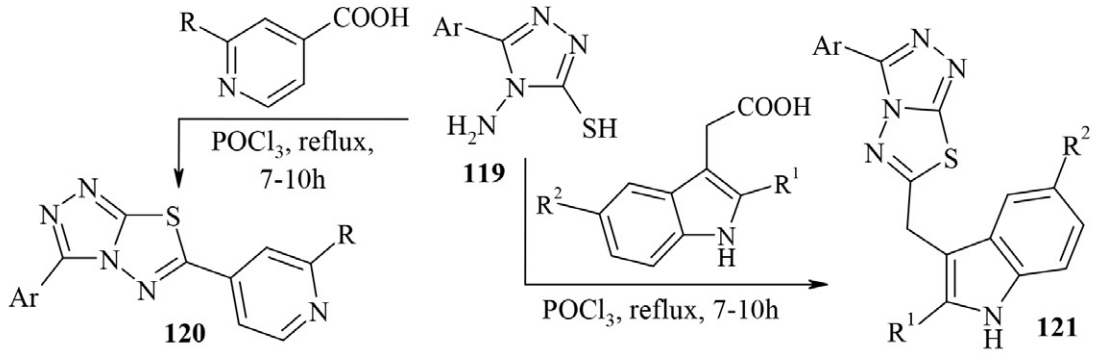


i) MeOH, H_2SO_4, reflux, 24h; *ii*) $NH_2NH_2 \cdot H_2O$, reflux, 5h; *iii*) CS_2, KOH, MeOH, stirr, 4h;
iv) $NH_2NH_2 \cdot H_2O$, reflux, 6-8h; *v*) $POCl_3$, reflux, 10h.

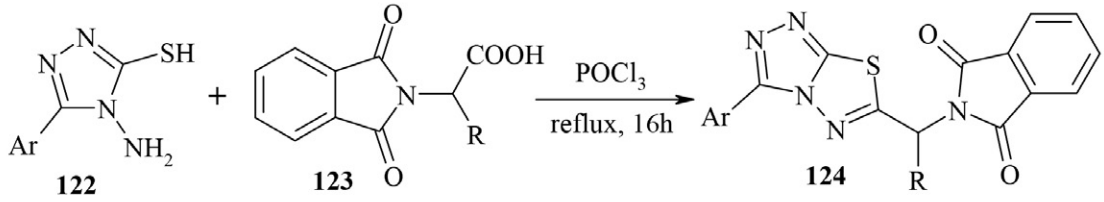
Scheme 28. Synthesis of 6-(pyrazin-2-yl) substituted 3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiols with pyrazine-2-carboxylic acid



Scheme 29. Synthesis of 6-(5-arylfuran-2-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 4-amino-4*H*-1,2,4-triazole-3-thiols with 5-arylfuran-2-carboxylic acids



Scheme 30. Synthesis of (pyridine-4-yl) or (indole-3-yl) substituted [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



Scheme 31. Synthesis of 3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles containing L-amino acid residues by one-pot reaction of 4-amino-4*H*-1,2,4-triazole-3-thiols with *N*-phthaloyl-L-amino acids

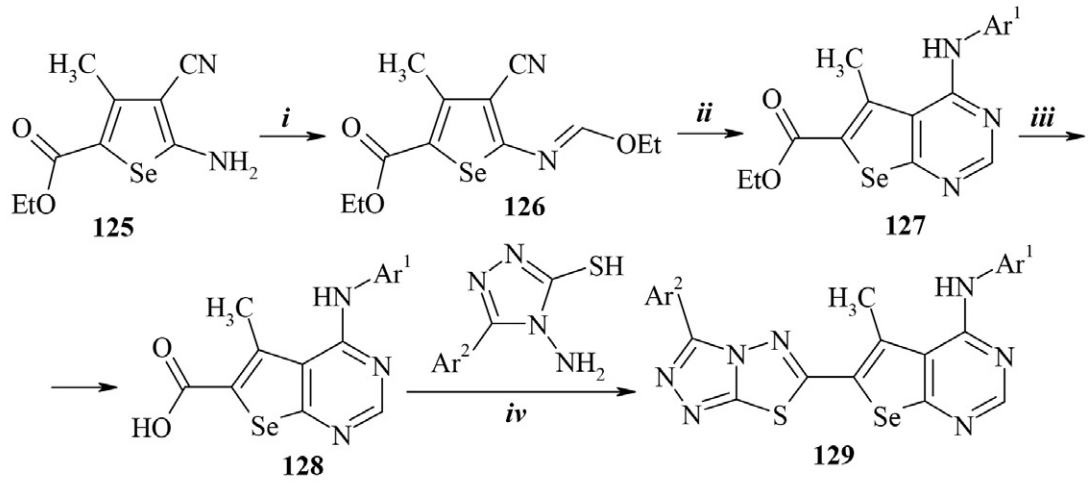
expected 6-(5-arylfuran-2-yl)[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles **118**.

Synthesis of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazoles containing pyridine or indole moieties (compounds **120** and **121**, respectively) (Scheme 30) was achieved by Mathew *et al.*[62] through the condensation of starting 4-amino-5-aryl-3-mercapto-1,2,4-triazoles **119** with isonicotinic or indol-3-ylacetic acid derivatives in the presence of phosphorous oxychloride.

Foroughifar *et al.*[63] implemented a one-pot preparation 3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **124** containing L-amino acid residues, starting from 4-amino-4*H*-1,2,4-triazole-3-thiols **122** and *N*-phthaloyl-L-amino acids **123** in the presence of phosphorus oxychloride (Scheme 31).

2. 5. Synthesis of 6-Heteroaryl(Condensed) [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles

Based on the molecular hybridization approach that involves combining multiple scaffolds in a single molecule, Kotaiah *et al.*[64] achieved the synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles incorporating selenopheno[2,3-*d*]pyrimidine (Scheme 32). Initially, the starting 5-amino-4-cyano-3-methylselenophene-2-carboxylic acid ethyl ester (**125**) by reaction with triethyl orthoformate was converted into 5-ethoxymethylenamino derivative **126**, which upon reaction with substituted anilines in acetic acid medium cyclized to 5-methyl-4-arylaminoselenopheno[2,3-*d*]pyrimidine-6-carboxylates **127**. Hydrolysis of compounds **127** with aqueous sodium hydroxide in methanol yielded the corresponding substituted carboxyl-



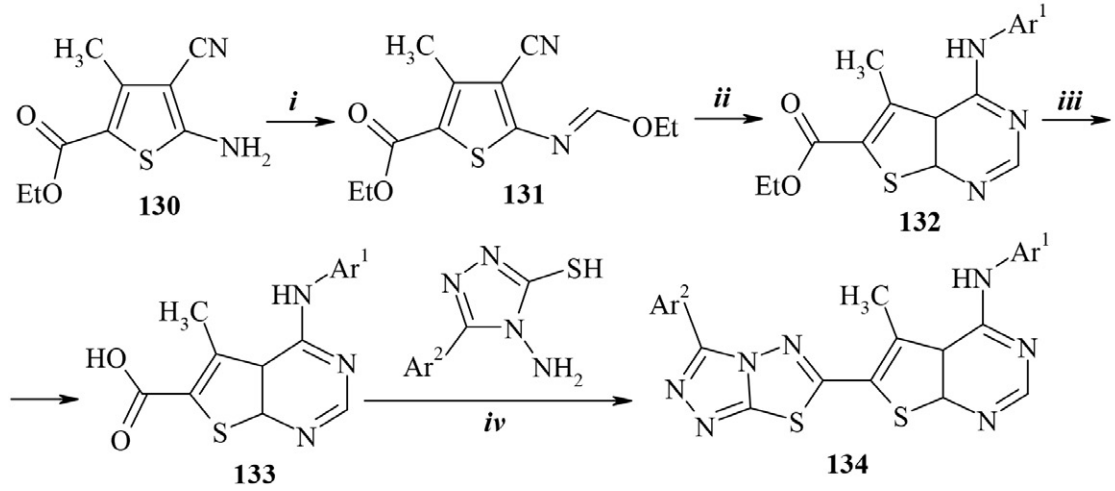
Scheme 32. Synthesis of selenopheno[2,3-*d*]pyrimidines containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by reaction of 4-amino-5-aryl-1,2,4-triazol-3-thiols with corresponding carboxylic acids

ic acids **128**, which further reacted with various 5-aryl-4-amino-4*H*-1,2,4-triazole-3-thiols in refluxing phosphorus oxychloride to afford 3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-6-yl selenopheno[2,3-*d*]pyrimidines **129**.

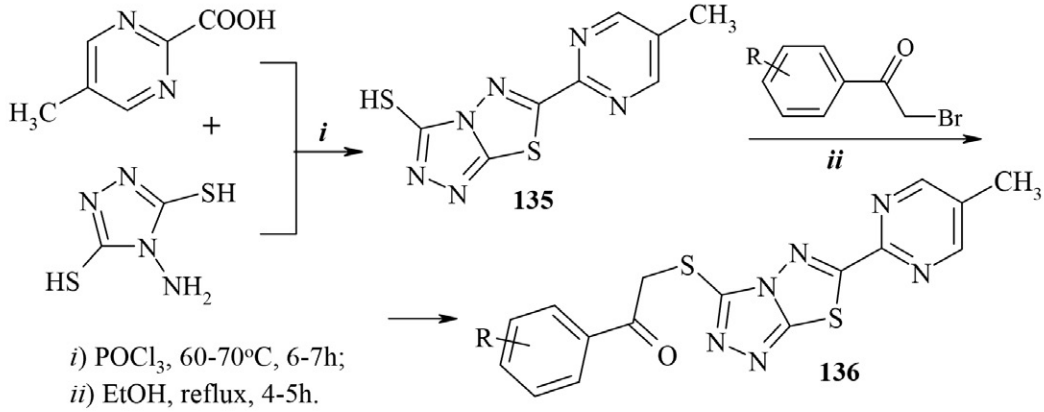
Settypalli *et al.*[65] proposed a similar synthetic approach for obtaining a new type of hybrids that combined both thieno[2,3-*d*]pyrimidine and [1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazole ring systems (Scheme 33). For this purpose, using ethyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate (**130**) on reaction with triethyl orthoformate followed by cyclization with substituted anilines in acetic acid and subsequent alkaline hydrolysis, the synthesis of 4-arylaminothieno[2,3-*d*]pyrimidine-6-carboxylic acids **133** was performed. The reaction of compounds **133** with 4-amino-5-aryl-1,2,4-triazole-3-thiols in the presence of $POCl_3$ yielded the target triazolo[3,4-*b*][thiadiazoles **134** containig thieno[2,3-*d*]pyrimidines.

2. 6. Synthesis of 6-Substituted [1,2,4] Triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiols

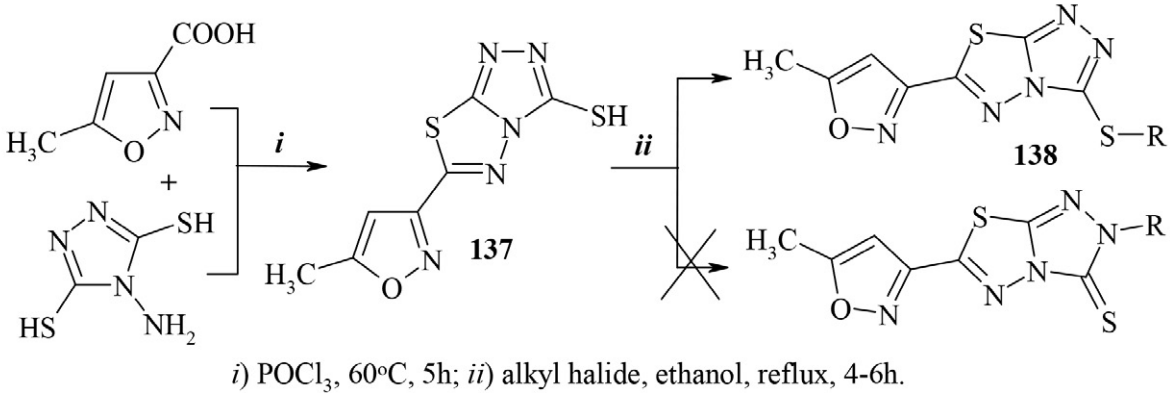
It was established that the reaction of various carboxylic acids with 4-amino-4*H*-1,2,4-triazole-3,5-dithiol under the action of dehydrating reagents leads to the for-



Scheme 33. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles hybridized by thieno[2,3-*d*]pyrimidine by interaction of 4-arylaminothieno[2,3-*d*] pyrimidine-6-carboxylic acids with 4-amino-4*H*-1,2,4-triazole-3-thiols



Scheme 34. Synthesis of pyrimidine-substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiols by condensation of 4-amino-4*H*-1,2,4-triazole-3,5-dithiol with 5-methylpyrimidine-2-carboxylic acid



Scheme 35. Synthesis of isoxazole substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles *via* condensation of 5-methylisoxazole-3-carboxylic acid with 4-amino-1,2-4-triazole-3,5-dithiol followed by alkylation

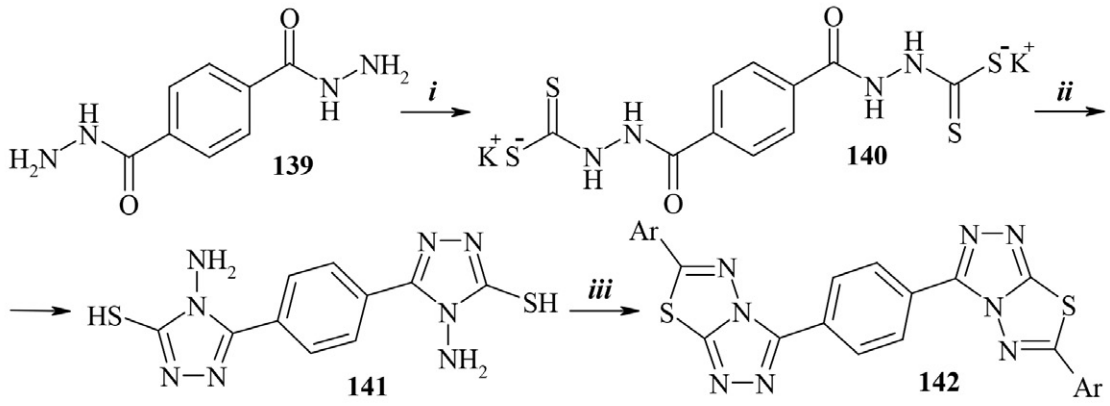
mation of 3-mercapto triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. Thus, the use of 5-methylpyrimidine-2-carboxylic acid in the above reaction in the presence of phosphorus oxychloride results in the formation of 6-(5-methylpyrimidin-2-yl) substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiol **135** (Scheme 34). Finally, the corresponding pyrimidine-containing [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)thio)-1-phenylethanones **136** were obtained by *S*-alkylation reaction of compound **135** with different phenacyl bromides in refluxing ethanol.[66]

According to Varla *et al.*[67], condensation of 5-methylisoxazole-3-carboxylic acid with 4-amino-1,2,4-triazole-3,5-dithiol using phosphorous oxychloride as a cyclizing reagent provided 6-(5-methylisoxazol-3-yl) substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiol **137** (Scheme 35). Also, it was emphasized that further reaction of the compound **137** with alkyl halides in ethanol medium occurs regioselectively with the formation of only *S*-alkylated products **138** in preference to *N*-alkylated, which can be explained by the high nucleophilicity of thiol group and was confirmed by spectral data.

2. 7. Synthesis of Bis[1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole Derivatives

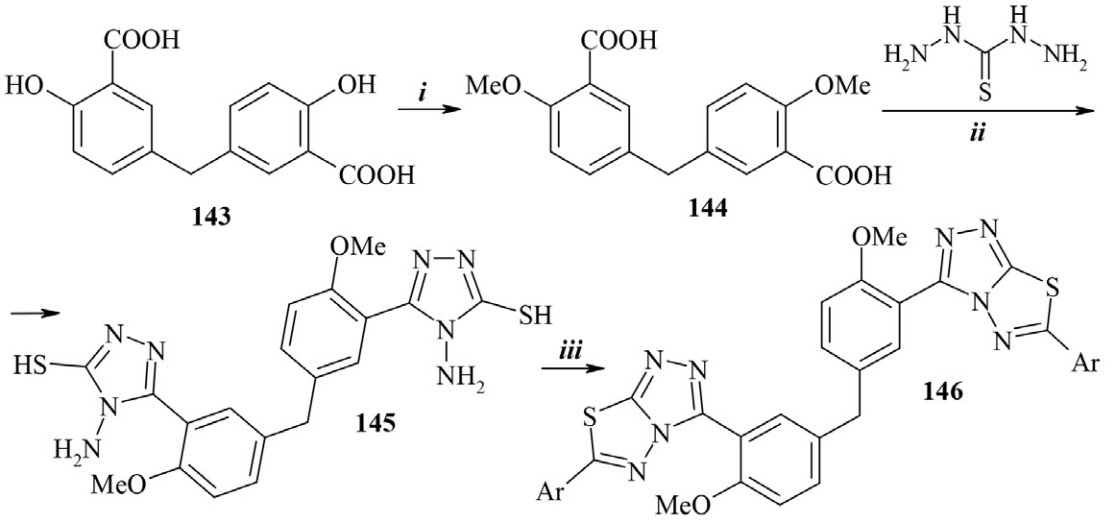
Palekar *et al.*[68] presented a multi-step synthetic approach for obtaining of 1,4-bis(6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole)phenylenes **142** starting from terephthalic acid hydrazide (Scheme 36). In particular, the reaction of hydrazide **139** with carbon disulfide and potassium hydroxide in ethanol gave the required bis-dithiocarbazinate **140**, which underwent ring closure with an excess of 99% hydrazine hydrate to afford the 1,4-phenylene-bis(4-amino-4*H*-1,2,4-triazole-3-thiol) **141**. After all, the synthesis of target 1,4-bis(6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)phenylenes **142** was achieved through the one-pot condensation of compounds **141** with aromatic acids in phosphorus oxychloride medium.

One more similar synthetic methodology leading to bis[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives (Scheme 37), which includes the initial interaction of starting 5-(3'-carboxy-4'-hydroxybenzyl)salicylic acid (**143**) with methyl iodide in dimethylformamide medium, was reported by Reddy *et al.*[69] Further, the resulting



i) CS_2, KOH, ethanol, rt, stirr., 12h; *ii*) $NH_2NH_2 \cdot H_2O$, water, reflux, 18-20h;
iii) Ar-COOH, $POCl_3$, reflux, 5h.

Scheme 36. 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



i) MeI, K_2CO_3, DMF, rt, stirr., 12h.; *ii*) heat, 3h; *iii*) Ar-COOH, $POCl_3$, reflux, 10h.

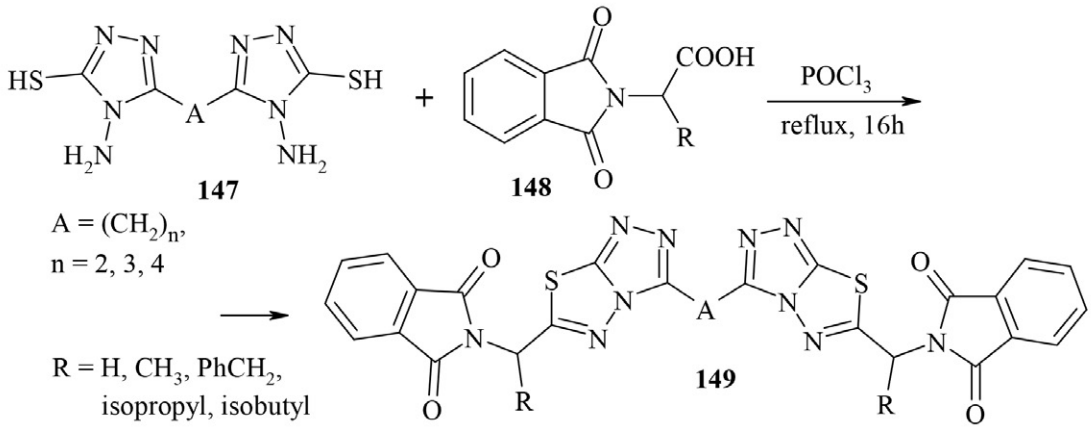
Scheme 37. Synthesis of bis-6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of bis[4-methoxy-3-[4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl]phenyl]methane with aryl/heteroaryl carboxylic acids

O-methylated derivative **144** on condensation with thiocarbohydrazide was converted into bis[4-methoxy-3-[4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl]phenyl]methane (**145**). Thereafter, a series of bis[3-(6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol)phenyl]methanes **146** were obtained by reaction of compound **145** with aryl/heteroaryl carboxylic acids in phosphorus oxychloride medium at reflux conditions.

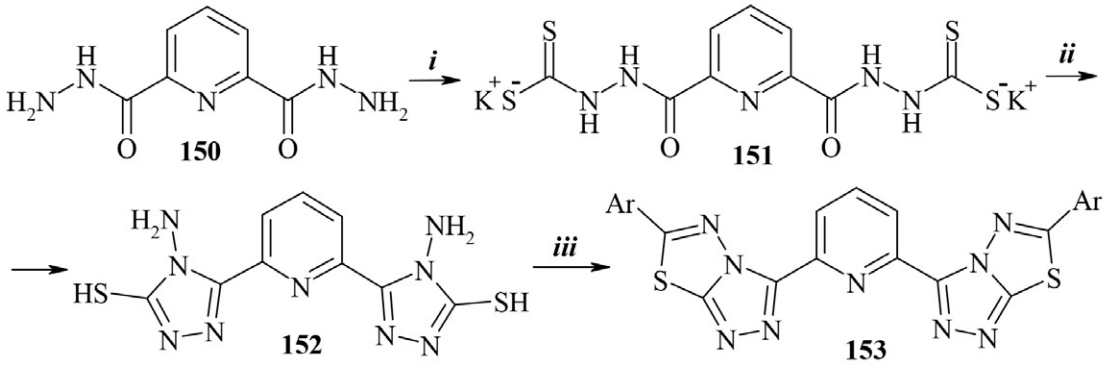
Synthesis of bis([1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-yl)alkanes **149** containing L-amino acid residues (Scheme 38) was described by Foroughifar *et al.*[70] Thus, the target derivatives **149** were obtained through a one-pot condensation of bis(4-amino-5-mercapto-4*H*-1,2,4-triazole-3-yl)alkanes **147** with *N*-phthaloyl-L-amino acids **148** in the presence of phosphorus oxychloride under the reflux for 16 h.

Xiao *et al.*[71] accomplished the synthesis of bis[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles linked by pyridine ring through a series of transformations (Scheme 39) using pyridine-2,6-dicarboxylic acid hydrazide (**150**) as the starting material. Reaction of **150** with carbon disulfide in the ethanolic potassium hydroxide yielded the corresponding potassium *N*,*N*'-(pyridine-2,6-dicarbonyl)dithiocarbazinate (**151**), which underwent ring closure with hydrazine hydrate to afford the intermediate bis(4-amino-5-sulfanyl-1,2,4-triazol-5-yl)pyridine (**152**). Compound **152** was allowed to react with various aryl carboxylic acids in phosphorus oxychloride to provide the target 2,6-bis([1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)pyridines **153**.

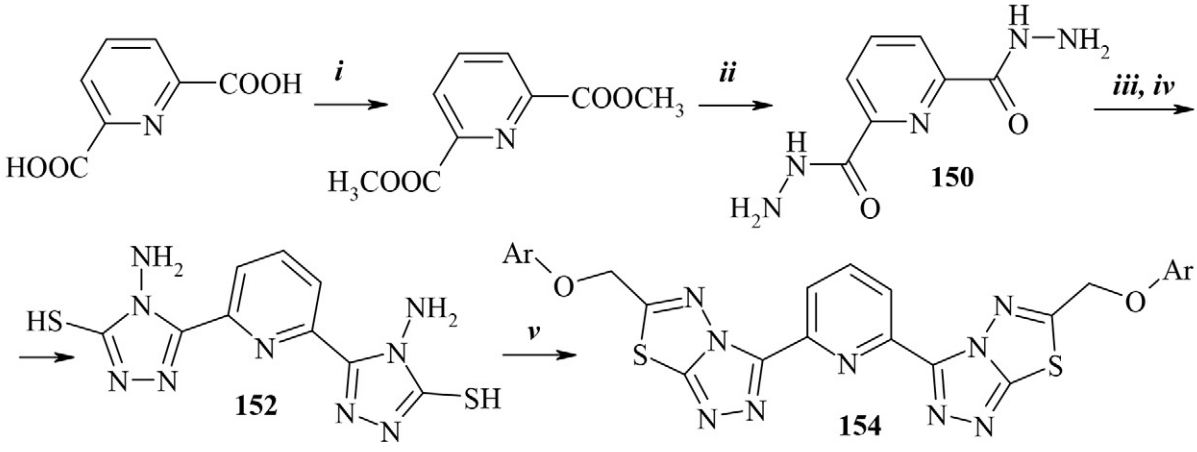
Similar transformation formed the basis of the strategy for the synthesis of bis[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives as ligands for preparation of their ter-



Scheme 38. Synthesis of bis([1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3-yl)alkanes containing L-amino acid residues by condensation of bis(4-amino-4*H*-1,2,4-triazole-3-thiols) with *N*-phthaloyl-L-amino acids



Scheme 39. Synthesis of 2,6-bis(6-substituted-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)pyridines by condensation of 5,5-(2,6-pyridyl)-bis(4-amino-5-thiol-1,2,4-triazole) with aryl carboxylic acids



Scheme 40. Synthesis of 2,6-bis(6-substituted-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)pyridines by condensation of 5,5-(2,6-pyridyl)-bis(4-amino-5-thiol-1,2,4-triazole) with phenoxyacetic acids

bium[72] or europium[73] coordination compounds. Thus, they were obtained by the multistep procedure starting from the pyridine-2,6-dicarboxylate (Scheme 40), bis(4-amino-5-thiol-1,2,4-triazol-5-yl)pyridine (**152**) reacting with phenoxyacetic acid derivatives in the presence of phosphorus oxychloride forming the expected 2,6-bis (6-aryloxymethyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole) pyridines **154**.

3. Conclusions

Currently, fused system bearing 1,2,4-triazole and 1,3,4-thiadiazole moieties represent an interesting class of heterocyclic compounds, which possess wide possibilities for chemical functionalization and versatile pharmacological potential. A survey of literature revealed that triazolo[3,4-*b*][1,3,4]thiadiazole derivatives have received much attention during recent years on account of their prominent utilization as anticancer, antifungal, antitubercular, anti-inflammatory, antidiabetic, antioxidant, and antibacterial agents etc.

This review summarizes the literature data about the main synthetic approaches for obtaining condensed heterocyclic compounds based on triazolo[3,4-*b*][1,3,4]thiadiazole scaffold. The simplicity and effectiveness of the synthetic procedures in the preparation 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 derivatives. Considering such a pharmacological significance as well as extensive synthetic possibilities triazolo[3,4-*b*] thiadiazoles proposes the scientists to further investigation of this heterocycle as a perspective building block for medicinal chemistry.

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Povzetek

4-Amino-5-substituirani-4*H*-1,2,4-triazol-3-tioli so vsestranski sintoni za pripravo različnih, biološko aktivnih, heterociklov, predvsem zaradi bližine aminske in merkapto skupine, ki delujeta kot lahko dostopna nukleofilna centra, kar je koristno pri sintezi *N*-premostenih heterosistemov. Ena izmed možnih in priročnih uporab 4-amino-4*H*-1,2,4-triazol-3-tiolov v sintezi heterociklov temelji na njihovi reaktivnosti z različnimi karboksilnimi kislinami v prisotnosti dehidacijskih reagentov, najbolj pogosto fosforjevega oksiklorida. Tako pripravljeni [1,2,4]triazolo[3,4-*b*][1,3,4]tiadiazoli se razlikujejo po substituentih na položajih 3 in 6, to so namreč lahko alkilni-, arilni-, aril(oksi)alkilni-, heteroarilni- in drugi substituenti. V tem preglednem članku predstavljamo sintezne strategije in sledeče kemijske pretvorbe triazolo[3,4-*b*] tiadiazolov, kar omogoča dostop do nekaterih pomembnih razredov funkcionaliziranih spojin.