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Synthetic approaches, modification ability and biological activity of 1,3,4-thiadiazole based [5+5] annelated heterosystems: Mini-review

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A B S T R A C T

Condensed bicyclic systems with thiadiazole core being annelated to other five-membered heterocycles such as 1,3-thiazole, imidazole or 1,2,4-triazole occupy prominent place in medicinal chemistry because of their broad spectrum of pharmacological activities. The combination of several heterocycles into a bicyclic system commonly provides much more interest in the enhanced activity profile of its analogs than their parent separate constituents. In this review, we summarized the literature data about the main approaches for obtaining and possible directions of structural modification of the most common 1,3,4-thiadiazole containing [5+5] annelated heterosystems as promising objects for modern medicinal chemistry.

1. Introduction

1,3,4-Thiadiazole core is one of the most promising construction motifs of many biologically active compounds and therapeutic agents. Thus, substituted 1,3,4-thiadiazoles had been reported to display a diverse range of pharmacological activities including anticancer, anti-inflammatory, antitubercular, antibacterial, antiviral, antifungal, insecticidal, antioxidant action[1-10] etc. The chemical features of 1,3,4-thiadiazoles were described in numerous reviews focusing on the main approaches to the synthesis, modification, and pharmacological potential.[11-13]

On the other hand, the condensed bicyclic systems based on 1,3,4-thiadiazole rings play vital roles in modern medicinal chemistry as the main structural components of a wide range of pharmacologically significant molecules. In particular, fused thiadiazoles have been reported as potential antitumor[14,15], antimicrobial[16-18], antiquorum-sensing[17,18], antifungal[19,20], antioxidant[21,22], antiviral[23], anti-inflammatory[24] and molluscicidal[24] agents.

There are quite a few different condensed derivatives based on conjugation of 1,3,4-thiadiazole ring with various five- or six-membered heterocycles. In most cases, they were obtained by annealing the corresponding heterocycle to a thiadiazole-based compound. In current research quantum-chemical calculations play an important role in the study of reaction mechanisms, reactivity of chemical compounds as well as biological aspects. In particular, a new theory for the study of reactivity in organic chemistry, named Molecular Electron Density Theory (MEDT), which is based on the idea that electron density distribution at the ground state is responsible for physical and chemical properties.of molecules. [25] This approach has been successfully realized in a number of synthetic protocols including [3+2] or [4+2] cycloaddition reactions and have been described in recent publications. [26-29]

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In the present review we highlight the main synthetic approaches to the construction and possible chemical modification methods of thiazolo[2,3-*b*][1,3,4]thiadiazoles, thiazolo[4,3-*b*][1,3,4]thiadiazoles, imidazo[2,1-*b*][1,3,4]thiadiazoles and triazolo[3,4-*b*][1,3,4]thiadiazoles as the most common 1,3,4-thiadiazole containing [5+5] annelated heterosystems (Fig. 1). This work can be considered as clear evidence that prove the importance of applied chemistry in different fields as reported before in different scientific papers.[30-34]

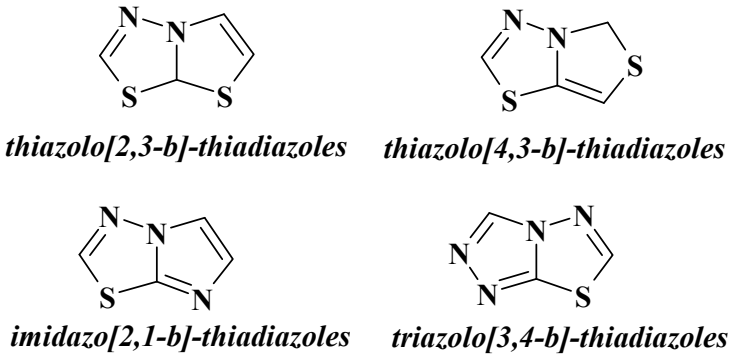


Fig. 1. Structures of the most common 1,3,4-thiadiazole based [5+5] bicyclic heterosystems.

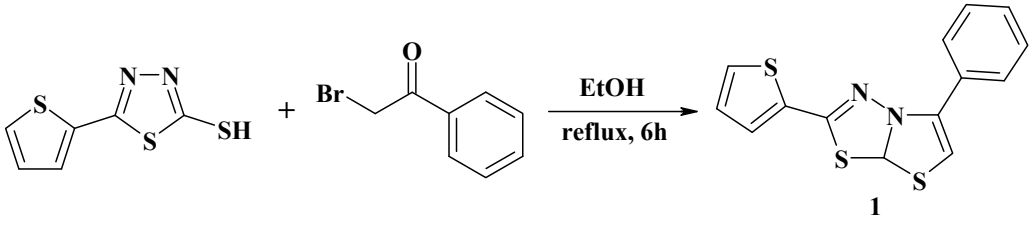
2. Materials and methods

Bibliosemantic and analytical methods were used in this work. During the literature review also were used bibliographic and abstract databases (Pubmed), as well as databases of chemical compounds (PubChem, Reaxys and SciFinder).

3. Synthetic approaches and possible directions of structural modification of [5+5] bicyclic heterosystems containing 1,3,4-thiadiazole ring

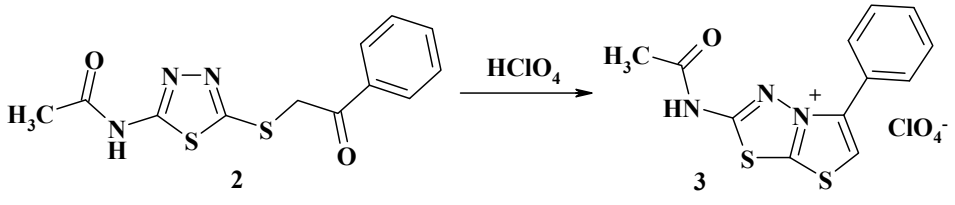
3.1. Synthesis of thiazolo[2,3-b][1,3,4]thiadiazoles

The synthesis of 2-(2-thienyl)-5-phenylthiazolo[2,3-*b*][1,3,4]thiadiazole **1** was carried out throught the reaction of 2-(2-thienyl)-5-thio-1,3,4-thiadiazole with phenacyl bromide in refluxing ethanol for 6h (**Scheme 1**). The diuretic activity of compound **1** was studied in male Sprague-Dawley rats (165-190 g) by the measurement of the effect of sodium and potassium on the volume of urine and the urinary output.[35]



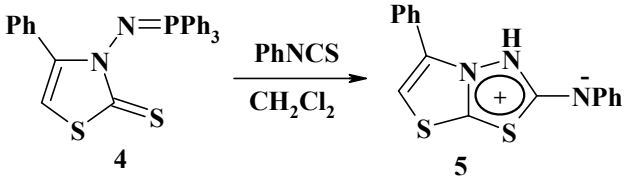
Scheme 1. Synthesis of 2-(2-thienyl)-5-phenylthiazolo[2,3-*b*][1,3,4]thiadiazole throught the reaction of 2-(2-thienyl)-5-thio-1,3,4-thiadiazole with phenacyl bromide.

Following the acid-promoted cyclization of 2-(acetylamino)-5-[(2-oxo-2-phenylethyl)-thio-1,3,4-thiadiazole **2** with perchloric acid the corresponding thiazolo[2,3-*b*][1,3,4]thiadiazolium salt **3** was formed in a high yield according to the **Scheme 2**:[36]



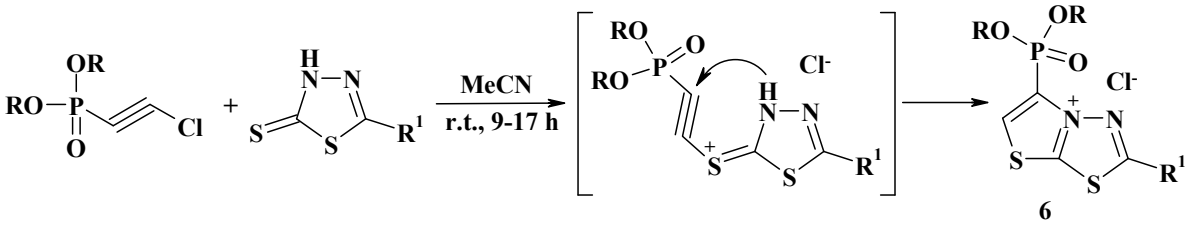
Scheme 2. Synthesis of thiazolo[2,3-*b*][1,3,4]thiadiazolium perchlorate by the acid-promoted cyclization of 2-(acetylamino)-5-[(2-oxo-2-phenylethyl)-thio[1,3,4]thiadiazole with perchloric acid.

Underwent an aza-Wittig-type reaction of iminophosphorane derivative from 3-amino-4-phenylthiazole-2(3H)-thione **4** with aromatic isothiocyanates leads to formation of thiazolo[2,3-*b*][1,3,4]thiadiazoles **5**, which display mesoionic character (**Scheme 3**):[37]



Scheme 3. Synthesis of thiazolo[2,3-*b*][1,3,4]thiadiazoles underwent an aza-Wittig-type reaction of iminophosphorane derivative with aromatic isothiocyanates.

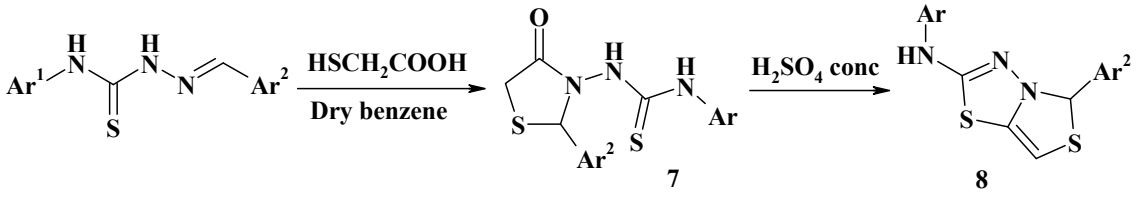
2-Substituted 5-(dialkoxyphosphoryl)thiazolo[2,3-*b*][1,3,4]thiadiazol-4-ylium chlorides **6** were obtained in good to excellent yields by reacting thiadiazole-2-thiones with 1-chloroacetylene-2-phosphonates in anhydrous acetonitrile (**Scheme 4**):[38]



Scheme 4. Synthesis of 2-substituted 5-(dialkoxyphosphoryl)thiazolo[2,3-*b*][1,3,4]thiadiazol-4-ylium chlorides by reacting thiadiazole-2-thiones with 1-chloroacetylene-2-phosphonates.

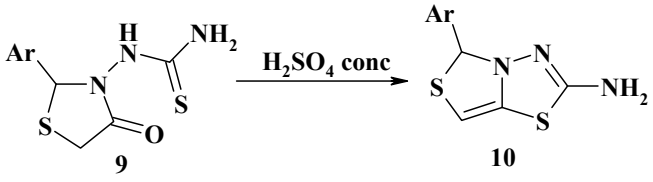
3.2. Synthesis of thiazolo[4,3-b][1,3,4]thiadiazoles

Addition condensation of 4-arylidenethiosemicarbazones to mercaptoacetic acid furnished the substituted 4-thiazolidinones **7**, which were cyclized with concentrated sulfuric acid to give the corresponding 2-arylamino-thiazolo[4,3-*b*][1,3,4]thiadiazoles **8** according to the **Scheme 5**. The obtained compounds **8** were compared with a commercial fungicide Dithane M-45 for their antifungal action against *Aspergillus flavus* and *Fusarium solani*.[39]



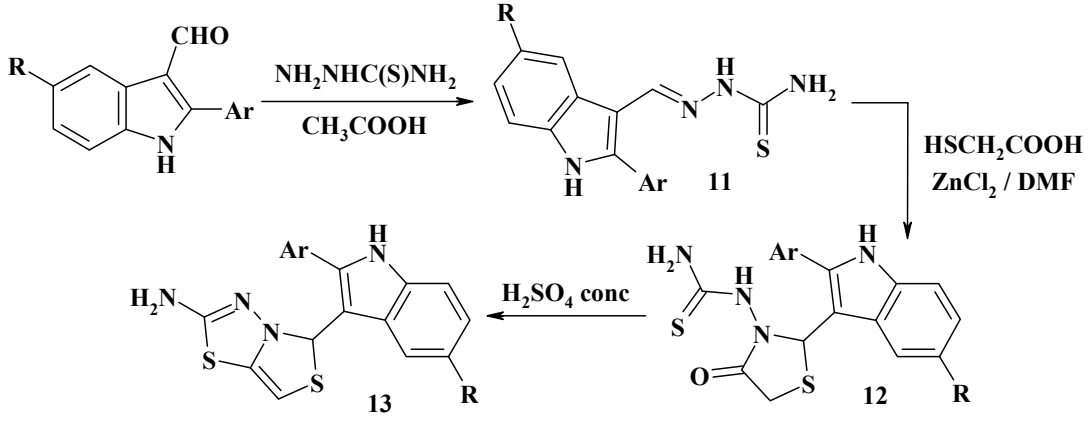
Scheme 5. Synthesis of 2-arylamino-thiazolo[4,3-*b*][1,3,4]thiadiazoles by cyclization of 3-substituted 4-thiazolidinones with concentrated sulfuric acid.

Similarly, following cyclodehydration of starting *N*-(2-aryl-4-oxothiazolidine-3-yl)thioureas **9** under the action of concentrated sulfuric acid the corresponding 5-aryl-2-aminothiazolo[4,3-*b*][1,3,4]thiadiazoles **10** have been synthesized (**Scheme 6**):[40]



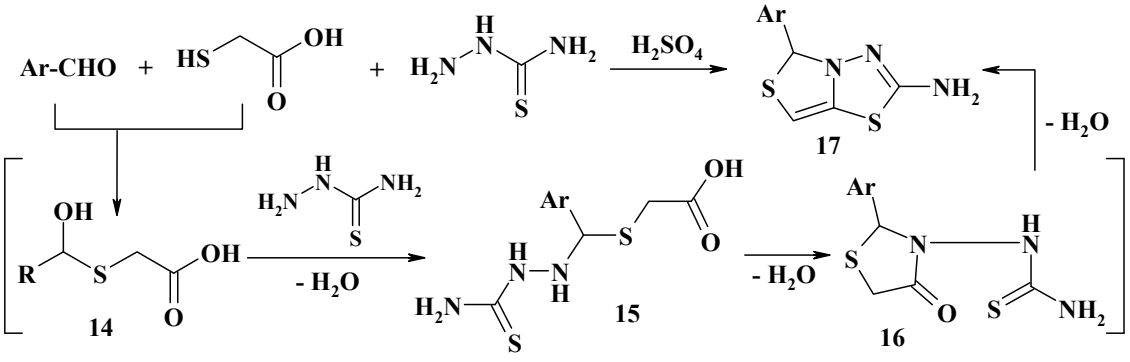
Scheme 6. Synthesis of 5-aryl-2-aminothiazolo[4,3-*b*][1,3,4]thiadiazoles by cyclodehydration of *N*-(2-aryl-4-oxothiazolidine-3-yl)thioureas.

A series of 5-indolyl substituted 2-amino 5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazoles **13** were synthesized by intramolecular chemoselective heterocyclization of the respective indolyl-thiazolidinones **12** with concentrated sulfuric acid (**Scheme 7**). Previously, compounds **12** were obtained on cyclocondensation of 2-arylindole based thiosemicarbazones **11** with thioglycolic acid in presence of anhydrous zinc chloride as a catalyst using *N,N*-dimethyl formamide as solvent under reflux condition. The investigation of antibacterial screening revealed that all compounds possessed moderate to good zone of inhibition against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*.[41]



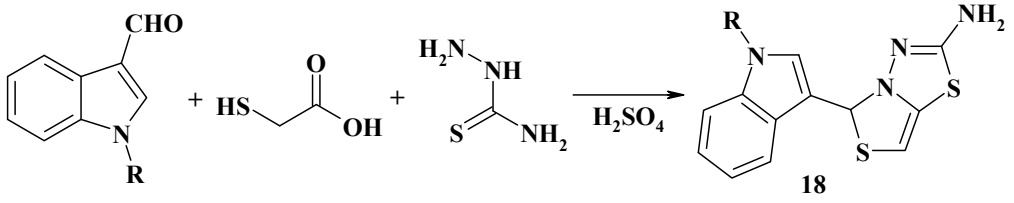
Scheme 7. Synthesis of 5-indolyl substituted 2-amino 5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazoles by intramolecular chemoselective heterocyclization of the respective indolyl-thiazolidinones.

A procedure for one-pot synthesis of 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazoles **17** (**Scheme 8**) from equimolar quantities of an aromatic aldehyde, thioglycolic acid, and thiosemicarbazide have been developed by Shukurov et al.[42] The specified transformations occur through the formation of intermediate semithioacetals of thioglycolic acid **14**, which further react with thiosemicarbazide giving the functionalized *N,S*-acetals **15**. Thioureas **16** were obtained as a result of cyclodehydration of compound **15** in concentrated H_2SO_4 medium and were transformed into the title compounds **17**:



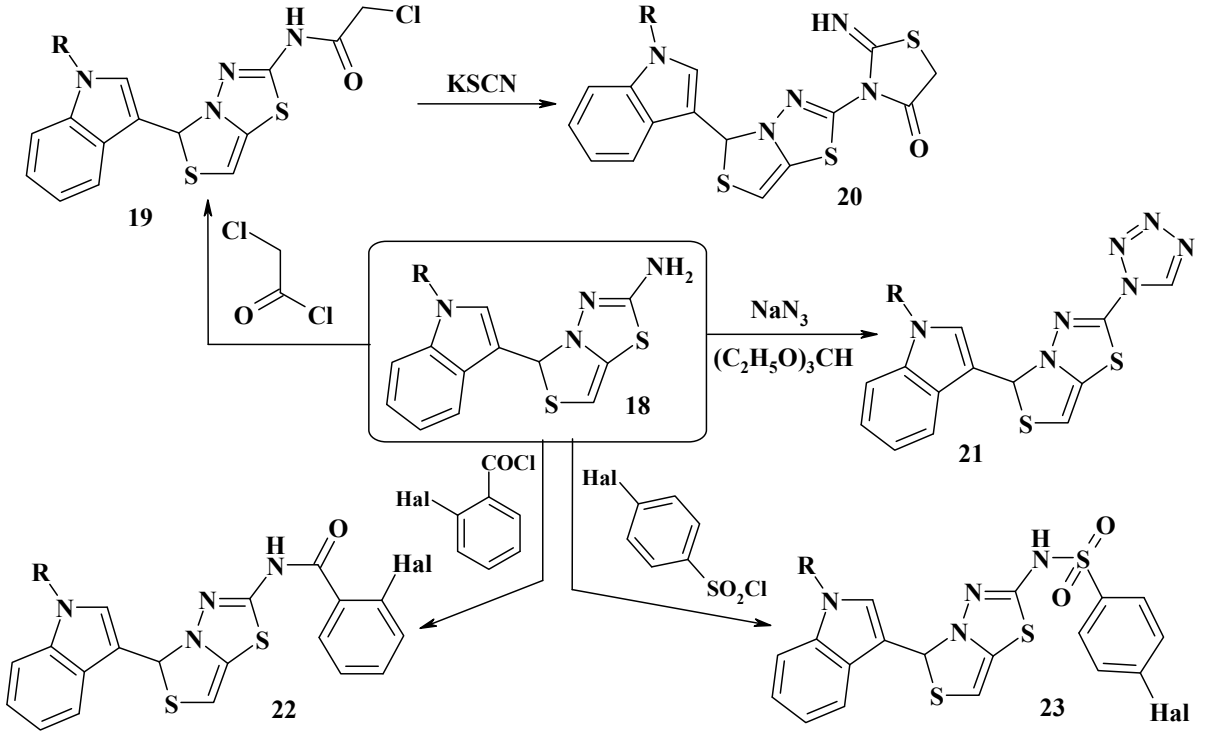
Scheme 8. A one-pot synthesis of 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazoles from equimolar quantities of an aromatic aldehyde, thioglycolic acid, and thiosemicarbazide.

Under the conditions of mentioned above one-pot reaction of *N*-substituted-1*H*-indol-3-carboxaldehydes with thioglycolic acid and thiosemicarbazide in concentrated sulfuric acid a novel 2-amino-5-(1*H*-indol-3-yl) substituted 5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazoles **18** were obtained (**Scheme 9**):[43]



Scheme 9. Synthesis of 2-amino-5-(1*H*-indol-3-yl) substituted 5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazoles under the reaction of *N*-substituted-1*H*-indol-3-carboxaldehydes with thioglycolic acid and thiosemicarbazide.

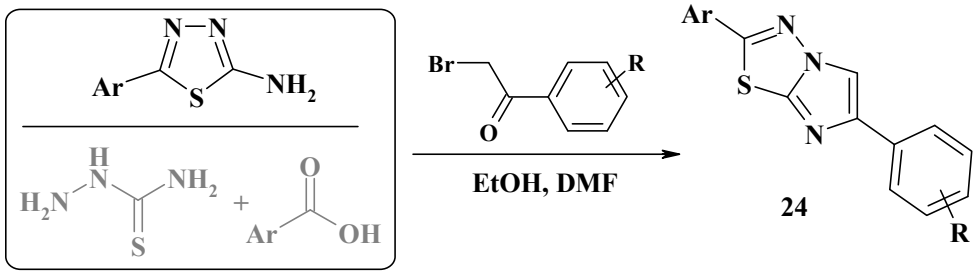
Further modification of compounds **18** was carried out throught the reaction with some benzenesulfonyl chlorides and/or benzoyl chlorides yielding sulfonamides **23** and benzamide **22** derivatives, respectively. The reaction of **18** with sodium azide yielded tetrazoles **21** according to the **Scheme 10**, whereas the reaction of **18** with chloroacetyl chloride yielded chloroacetamide derivatives **19**, which under cyclization with potassium thiocyanate yielded thiazolidinone derivatives **20** (**Scheme 10**). The preliminary DPPH radical-scavenging activity of the newly synthesized compounds was determined and the highly active derivative with IC_{50} of 69.14 mg/ml compared with ascorbic acid (IC_{50} of 6.50 mg/ml) was found.[43]



Scheme 10. Modification of 2-amino-5-(1*H*-indol-3-yl)-5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazoles throught the reaction with benzenesulfonyl chlorides, benzoyl chlorides, sodium azide or chloroacetyl chloride.

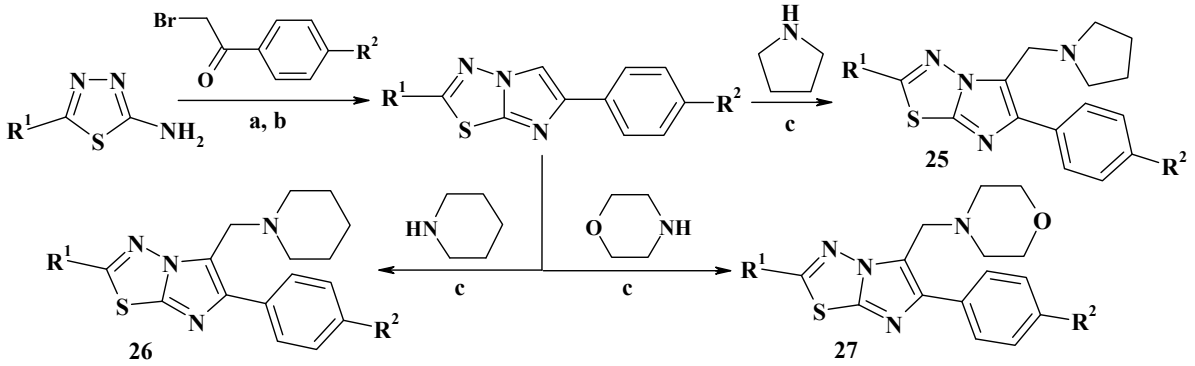
3.3. Synthesis of imidazo[2,1-b][1,3,4]thiadiazoles

The general synthetic approach, which leads to the formation of the imidazo[2,1-*b*][1,3,4]-thiadiazoles system, is the interaction of 2-amino-1,3,4-thiadiazoles with α-halocarbonyl compounds.[44,45] Thus, the 2,6-disubstituted imidazo[2,1-*b*][1,3,4]-thiadiazoles **24** were prepared by refluxing 5-aryl-1,3,4-thiadiazol-2-amine with corresponding α-bromoacetophenones in dry ethanol (**Scheme 11**):[46]



Scheme 11. Synthesis of 2,6-disubstituted imidazo[2,1-*b*][1,3,4]-thiadiazoles by interaction of 5-aryl-1,3,4-thiadiazol-2-amine with corresponding α-bromoacetophenones.

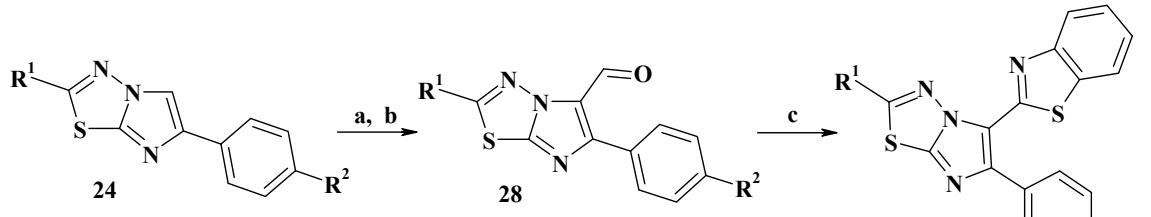
A series of aminomethylene derivatives (Mannich bases) **25-27** (**Scheme 12**) were obtained under the reaction of 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles with different cyclic secondary amines (pyrrolidine, piperidine and morpholine) and formaldehyde in methanol medium with catalytic amount of acetic acid. Among the tested Mannich bases a highly active compounds were identified which revealed excellent inhibition (97-99%) against *M. tuberculosis*.[44,45]



(a) dry ethanol, reflux, 8h; (b) aq. Na_2CO_3; (c) HCHO, AcOH / MeOH, reflux, 4h.

Scheme 12. Synthesis of aminomethylene derivatives by the reaction of 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles with different cyclic secondary amines and formaldehyde in methanol medium.

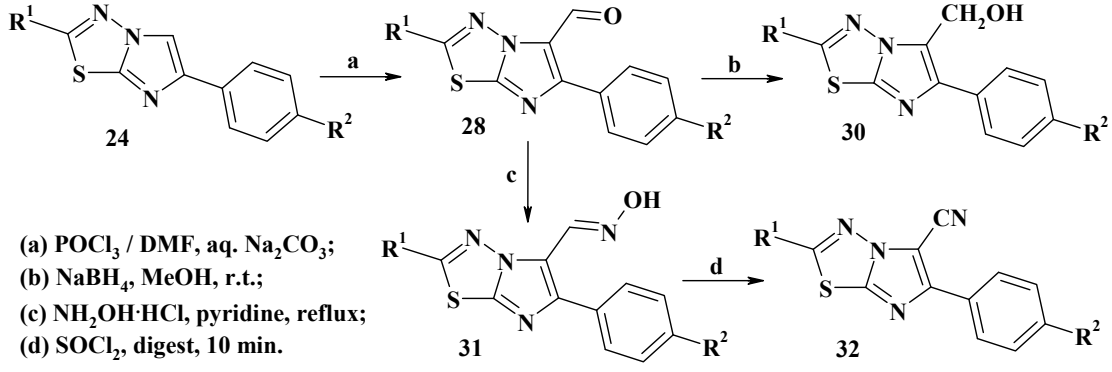
Obtained imidazo[2,1-*b*][1,3,4]thiadiazoles **24** were modified according to the Vilsmeier-Haack reaction procedure (refluxing DMF-$POCl_3$ mixture) with formation of 5-formyl derivatives **28**, which during the reaction with 2-aminothiophenol yielded imidazothiadiazole substituted benzothiazoles **29** (**Scheme 13**). In most cases, imidazothiadiazoles **24** retained their antitubercular activity after conversion to their formyl derivatives **28**, which, in turn lost their activity after further conversion to corresponding benzothiazoles derivatives **29**.[44]



(a) $POCl_3$ / DMF anhyd., 60°C, stirring, 2h; (b) aq. Na_2CO_3;
(c) 2-aminothiophenol, DMSO, 120°C, 4h

Scheme 13. Modification of imidazo[2,1-*b*][1,3,4]thiadiazoles according the Vilsmeier-Haack reaction procedure and further interaction with 2-aminothiophenol.

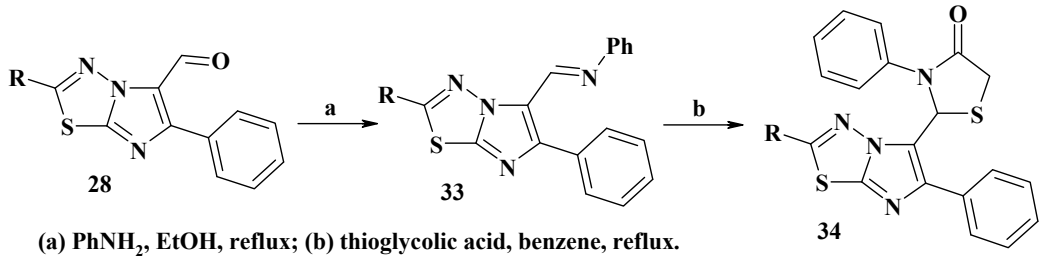
By reduction of 5-formylimidazo[2,1-*b*][1,3,4]thiadiazoles **28** with sodium borohydride in methanol medium at room temperature the respective carbinols **30** were obtained. The condensation of aldehyde **28** with hydroxylamine hydrochloride in pyridine gave corresponding oxime **31**, which under dehydration with thionyl chloride produced nitrile **32** in good yields (**Scheme 14**). Among the obtained compounds were found those that exhibited moderate antitubercular activity with percentage inhibition in a range 15-36%, respectively, at a MIC of > 6.25 μg/ml.[45]



(a) $POCl_3$ / DMF, aq. Na_2CO_3;
(b) $NaBH_4$, MeOH, r.t.;
(c) $NH_2OH{\cdot}HCl$, pyridine, reflux;
(d) $SOCl_2$, digest, 10 min.

Scheme 14. Reduction of 5-formylimidazo[2,1-*b*][1,3,4]thiadiazoles with sodium borohydride and it's condensation with hydroxylamine hydrochloride.

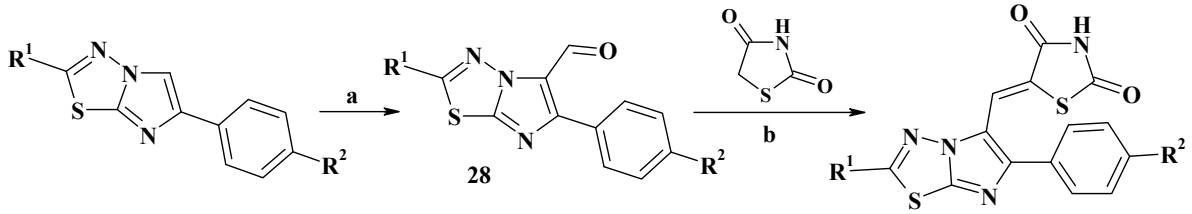
The interaction of imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydes **28** with aniline in ethanol medium at the presence of catalytic amounts of acetic acid yielded the corresponding Schiff bases **33**, which on refluxing with thioglycolic acid in benzene underwent heterocyclization to form 3-phenyl-4-thiazolidinone derivatives **34** according to the **Scheme 15**:[45]



(a) $PhNH_2$, EtOH, reflux; (b) thioglycolic acid, benzene, reflux.

Scheme 15. Synthesis of 3-phenyl-4-thiazolidinone substituted imidazo[2,1-*b*][1,3,4]thiadiazoles through the formation of intermediate Schiff bases.

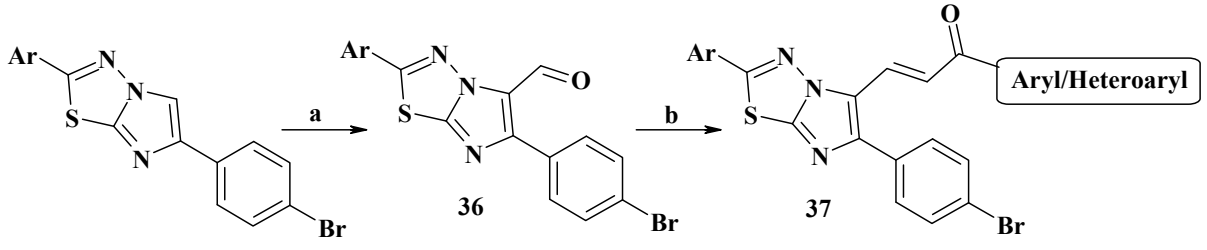
Therefore, the obtained imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydes **28** were successfully used following the Knoevenagel condensation with thiazolidine-2,4-dione in the presence of piperidinium acetate in refluxing toluene for the preparation of target imidazo[2,1-*b*][1,3,4]thiadiazole substituted 5-ylidene-4-thiazolidinones (**Scheme 16**). Newly synthesized compounds were tested for their *in vivo* hypoglycaemic and hypolipidemic activity. Further compounds that displad an interesting activity comparable with Pioglitazone were screened for PPARγ agonist activity.[47]



(a) $POCl_3$ / DMF, aq. Na_2CO_3; (b) piperidine acetate, toluene, reflux.

Scheme 16. Synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole substituted 5-ylidene-4-thiazolidinones following the Knoevenagel condensation of corresponding aldehydes with thiazolidine-2,4-dione.

The synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole based chalcones **37** was performed *via* Claisen-Schmidt condensation of corresponding aldehydes **36** with different aryl/heteroaryl ketones in ethanolic 10% NaOH (**Scheme 17**). The synthesized compounds displayed promising activity against tested fungal strains, in particular, for both normal and clinical isolated of *C. neoformans*. In addition, these chalcones **37** also showed moderate activity (MIC > 20 μg/mL) against M. tuberculosis $H_{37}Rv$.[48]



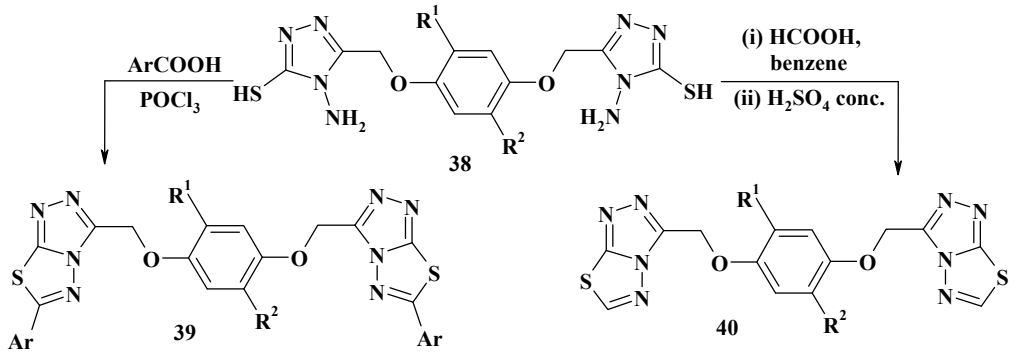
(a) DMF, $POCl_3$, 0°C, stir. / 90°C, 6h;
(b) Aryl/Heteroaryl ketones, EtOH, 10% NaOH, stir., r.t., 6-10h.

Scheme 17. Synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole based chalcones *via* Claisen-Schmidt condensation of corresponding aldehydes with different aryl/heteroaryl ketones.

3.4. Synthesis of triazolo[3,4-b][1,3,4]thiadiazoles

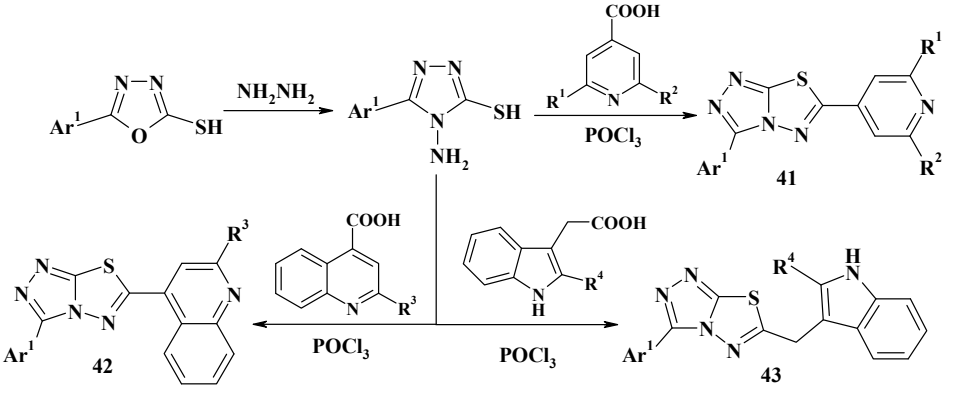
Another direction for obtaining of bicyclic systems based on thiadiazole is synthesis of condensed heterocycles combining a 1,3,4-thiadiazole ring with a 1,2,4-triazole, which can be considered as cyclic analogues of two pharmacologically important components – thiosemicarbazide and biguanide.

The condensation of symmetrical 1,4-bis-(4-amino-5-mercapto-1,2,4-triazol-3-ylmethoxy)-phenylenes **38** with various aromatic carboxylic acids in refluxing phosphorus oxychloride furnished a series of 1,4-bis-(6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-ylmethoxy)phenylenes **39**. The synthesis of 6-unsubstituted analogues **40** were obtained by reaction of starting bis-triazoles with formic acid in benzene followed by treatment with concentrated sulphuric acid (**Scheme 18**):[49]



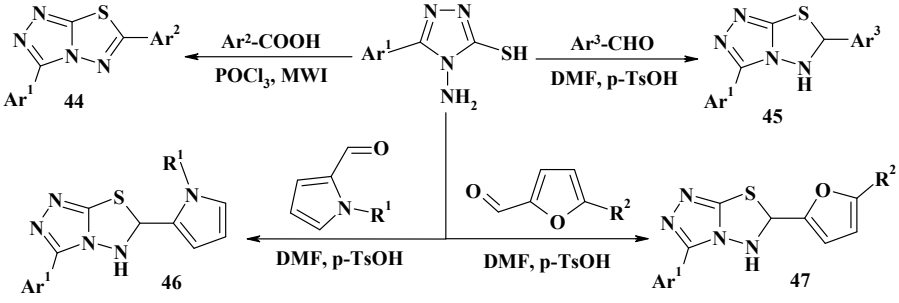
Scheme 18. Synthesis of 1,4-bis-(6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-ylmethoxy)phenylenes by condensation of symmetrical 1,4-bis-(4-amino-5-mercapto-1,2,4-triazol-3-ylmethoxy)-phenylenes.

Synthesis of novel 3,6-disubstituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles containing pyridine **41**, quinoline **42** and indole **43** moieties was carried out through the cyclization of 3-aryl/heteryl-4-aminotriazole-5-thiols with corresponding heterocyclic acids in refluxing phosphorus oxochloride (**Scheme 19**). Synthesized compounds were studied for their antibacterial, antifungal, anti-inflammatory and analgesic activities. Some of the tested compounds possessed significant pharmacological activities.[50,51]



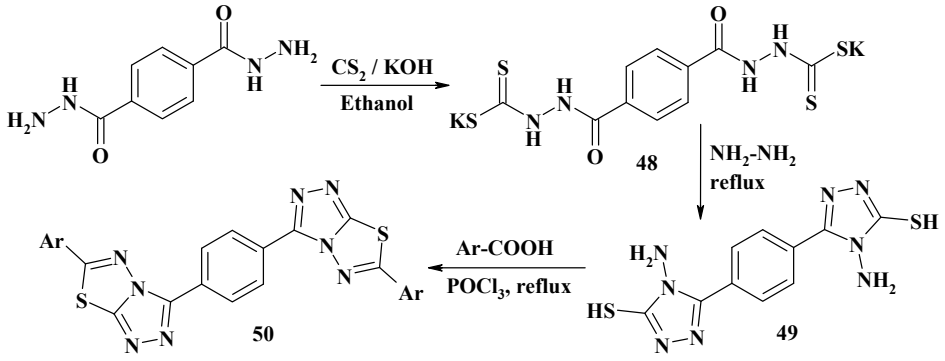
Scheme 19. Synthesis of 3,6-disubstituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles through the cyclization of 3-aryl/heteryl-4-aminotriazole-5-thiols with heterocyclic acids.

The similar 3,6-diaryl derivatives **44** were obtained by interaction of 4-aminotriazole-5-thiols with aromatic acids and phosphorus oxochloride under the microwave irradiation. Additionally, the synthesis of 5,6-dihydro analogues of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **45**-**47** was performed based on the reaction of starting 4-aminotriazole with aromatic aldehydes, furfural and pyrole-2-carbaldehyde derivatives in the presence of *p*-toluene sulfonic acid (**Scheme 20**):[50,51]



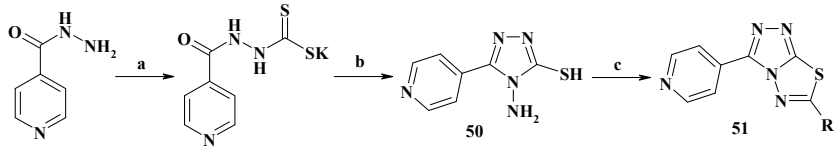
Scheme 20. Synthesis of 3,6-diaryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole and their 5,6-dihydro analologues by interaction of 4-aminotriazole-5-thiols with aromatic acids or aldehydes.

A series of 1,4-bis-(6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **50** have been synthesized from terephthalic dihydrazide through multistep reaction sequence according to the **Scheme 21**. It includes formation of an intermediate *bis*-dithiocarbazinate **48** and further underwent ring closure with an excess of hydrazine hydrate to give the 1,4-phenylene-*bis*(4-amino-4*H*-1,2,4-triazole-3-thiol) **49**. Finally, the resulted bis-triazole derivative **49** was converted into the title compounds **50** in a one-pot reaction by condensation with aromatic acids in phosphorus oxochloride medium:[52]



Scheme 21. Synthesis of 1,4-*bis*-(6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles by condensation of 1,4-phenylene-*bis*(4-amino-4*H*-1,2,4-triazole-3-thiol) with aromatic acids.

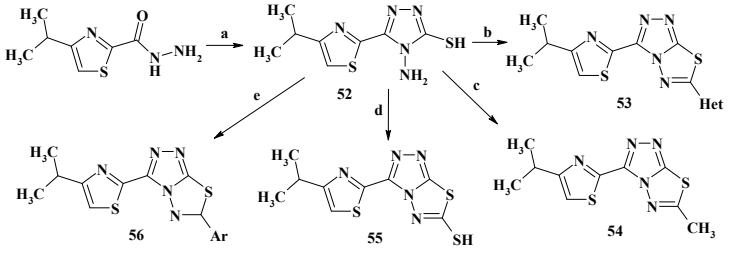
Based on isoniazid as starting material the synthesis of 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-thiol **50** was carried out. Further compound **50** was modified in a one-pot condensation with aromatic acids in the presence of $POCl_3$ with the formation of 1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazoles **51** containing pyridine fragment (**Scheme 22**). All compounds were further tested for their analgesic activity at the same oral dose and showed good to moderate analgesic activity in comparison to their respective standard and parent drugs. Compound having 4-nitrophenyl group at C-6 position of triazolo-thiadiazole ring showed the maximum activity (74.32 ± 1.20%), equivalent to that of the standard drug ibuprofen (73.52 ± 1.00%).[53]



(a) CS_2, KOH, EtOH, stirring, r.t.; (b) $NH_2NH_2{\cdot}H_2O$, reflux; (c) RCOOH, $POCl_3$, reflux, 5h.

Scheme 22. Synthesis of 1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazoles containing pyridine fragment in a one-pot condensation of 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-thiol with aromatic acids.

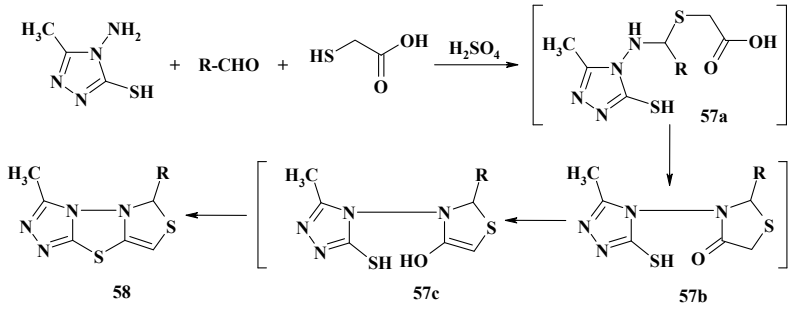
The synthesis of 6-heteryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole containing 4-isopropylthiazole moiety **53** was achieved by reacting 4-amino-5-(4-isopropyl-1,3-thiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol **52** with appropriate heteroaromatic acids in the presence of phosphorous oxychloride. Reaction of triazole **52** with phosphorus oxychloride and acetic acid in similar conditions produced 6-methyl analogue **54**. The transformation to 6-mercapto derivative **55** was achieved by treating compound **52** with carbon disulfide and potassium hydroxide. Whereas, the condensation of **52** with appropriate substituted aldehydes in presence of *p*-toluenesulphonic acid resulted in a series of 5,6-dihydro fused triazolothiadiazoles **56** according to the **Scheme 23**. Obtained compounds were evaluated for their preliminary *in vitro* antibacterial, antifungal and antitubercular activity against *Mycobacterium tuberculosis* H_37Rv strain by broth dilution assay method. All the compounds exhibited moderate to significant antibacterial and antifungal activities.[54,55]



(a) CS_2, $NH_2NH_2{\cdot}H_2O$, KOH, EtOH, reflux, 16h; (b) Het-COOH, $POCl_3$, reflux, 5h;
(c) CH_3COOH, $POCl_3$, reflux, 2h; (d) CS_2, KOH, MeOH, reflux, 6-7h;
(e) Ar-CHO, dry DMF p-TsOH, reflux, 10-12h.

Scheme 23. Synthesis of 6-substituted 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles by reacting 4-amino-5-(4-isopropyl-1,3-thiazol-2-yl)-4*H*-1,2,4-triazole-3-thiol with with aromatic/acetic acids or aldehydes.

An interesting method for the synthesis of 3-methyl-6*H*-thiazolo[4,3-*b*][1,2,4]triazolo[4,3-*d*][1,3,4]thiadiazoles **58** has been developed by the Kukaniev et al.,[56] which includes the one-pot reactor condensation of 4-amino-5-methyl-1,2,4-triazole-3(2*H*)-thione with aromatic aldehydes and thioglycolic acid in a sulfuric acid medium as its depicted at the **Scheme 24**:



Scheme 24. Synthesis of 3-methyl-6*H*-thiazolo[4,3-*b*][1,2,4]triazolo[4,3-*d*][1,3,4]thiadiazoles by condensation of 4-amino-5-methyl-1,2,4-triazole-3(2*H*)-thione with aldehydes and thioglycolic acid.

4. Conclusions

The chemistry of 1,3,4-thiadiazole and their fused heterocyclic derivatives has received considerable attention due to the synthetic and effective biological importance. A large number of ring systems containing 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. Among these fused heterosystems, thiazolo[2,3-*b*]thiadiazoles, thiazolo[4,3-*b*]thiadiazoles, imidazo[2,1-*b*]thiadiazoles and triazolo[3,4-*b*]thiadiazoles were the most widely studied but, lately, they have gain the interest of the researchers as is evidenced by the increase in the number of publications.

In the present review we performed the literature search and highlighted recent advances in the fast-growing research area of 1,3,4-thiadiazole containing [5+5] annelated heterosystems. The broad pharmacological profile of this class of compounds is evidenced by the numerous examples cited here. The variety of the synthetic approaches for obtaining of the mentioned structures and their widespread use in medicinal chemistry found a strong basis for the systematic research of these compounds. Publications in this field are continuously increasing and therefore new therapeutic applications involving members of this family of heterocycles could be discovered in the near future. All of the above can be considered as a background for further in-depth studies in the areas of chemistry and pharmacology of the mentioned heterocyclic systems with possible applications in medicine.

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